Efficient and chemoselective reduction of carbonyl compounds with supported gold catalysts under transfer hydrogenation conditions†

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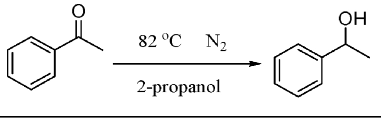
A new heterogeneous catalytic transfer hydrogenation (CTH) system, consisting of a non-flammable supported Au catalyst along with 2-propanol as the hydrogen donor, was proven to be effective for chemoselective reduction of a wide range of aromatic ketones and aldehydes to the corresponding alcohols.

The reduction of carbonyl compounds to the corresponding alcohols is a synthetically important transformation, both in the laboratory and industry.[1] Although a number of methods have been developed, the search for new facile, cost-effective and ecofriendly procedures that avoid the use of stoichiometric reducing reagents or hazardous molecular hydrogen (H_2) has attracted substantial interest.[2] An attractive alternative is the catalytic transfer hydrogenation (CTH) employing hydrogen donors, *e.g.*, 2-propanol, which is operationally simple and can avoid the use of molecular hydrogen.[3] Both homogeneous as well as heterogeneous catalysts for CTH are known.[4] From a practical point of view, it is more desirable to develop a heterogeneous catalyst that is efficient for this transformation.[5] Nevertheless, these processes require flammable or moisture-sensitive catalysts such as using Raney Ni, Pd/C and PtO_2 *etc.*,[6–8] which presents additional handling problems. Although CTH reactions are generally very facile over these catalysts, they are, however, not selective toward functional groups such as –CO, –CX and $–NO_2$ moieties, and almost all labile functional groups undergo reduction under the reaction conditions. In the continued search for more effective catalysts for the CTH process, there is a definite need for new easily-handled heterogeneous catalysts that allow convenient and efficient transfer reduction under mild conditions.

Supported gold nanoparticles[9] have recently emerged as excellent catalysts for a broad range of organic transformations under mild conditions.[10] Despite appreciable work that has been conducted in several oxidation reactions,[11] a number of recent reports have demonstrated that supported gold nanoparticles can be highly chemoselective for the direct hydrogenation of C=O groups of α,β-unsaturated aldehydes.[12] Very recently, Corma and Serna have established that the regioselective direct hydrogenation of a nitro group in the presence of other reducible functions can be achieved by using supported gold catalysts.[13] In view of the microscopic reverse nature of the key step (*i.e.*, formation of a metal hydride complex) of the transfer hydrogenation with respect to direct hydrogenation, it is conceivable that the supported gold catalysts may also provide an attractive alternative for transfer hydrogenation. Herein, we report for the first time a very efficient, highly selective and rapid method for the reduction of carbonyl compounds using a supported gold catalyst. To the best of our knowledge, this study also presents the first chemoselective reduction of nitro compounds in the presence of carbonyl groups by transfer hydrogenation using gold catalysts.

First of all, a comparative study of Au/support (1.5 wt% Au/TiO_2, 4.5 wt% Au/Fe_2O_3 and 0.8 wt% Au/C, all provided by the World Gold Council) and Pd/C (5 wt%, Fluka) catalysts was carried out with acetophenone as a substrate. The CTH reactions were carried out as per standard procedures using 2-propanol as the hydrogen donor.† As can be seen from Table 1, excellent selectivities towards phenyl ethanol can be attained for all Au catalysts, with the order of the catalysts with respect to the corresponding yield of acetophenone being $Au/TiO_2 > Au/Fe_2O_3 > Au/C$. Furthermore, there is no reaction on using Au-free TiO_2 catalysts, illustrating that the presence of gold was indispensable for high catalytic activity. The reason for the high catalytic activity of Au/TiO_2 is probably the high dispersion of Au nanoparticles in combination with a beneficial synergetic interaction with the TiO_2 support.[14,15] A clear advantage of the supported gold catalyst over Pd/C was also noticed when acetophenone was reduced using Pd/C under otherwise identical conditions. Note that this behaviour is in contrast to

Table 1 Catalytic results of the transfer hydrogenation of acetophenone over different catalysts[a]



Entry	Catalysts	Time/h	Conversion (%)	Selectivity (%)
1	Au/TiO_2	4	99	100
2	TiO_2	6	—	—
3	Au/Fe_2O_3	4	35.3	99
4	Au/C	4	13.9	98
5	Pd/C	4	63	98
6[b]	Au/TiO_2	4	98.5	100

[a] Reaction performed under an N_2 atmosphere at 82 °C using 2-propanol (10 ml) as the solvent and hydrogen source, 1 mmol substrate, 0.78 mol% metal and 0.3 equiv. KOH. Conversion and selectivity was determined by GC using *o*-xylene as the internal standard. [b] Results for the fifth run.

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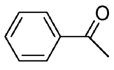
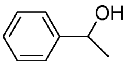
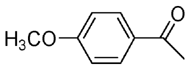
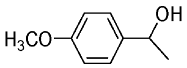
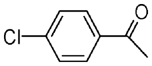
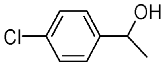
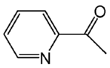
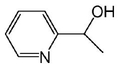
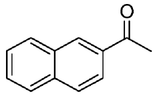
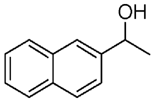
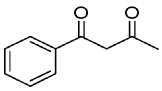
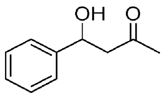
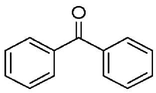
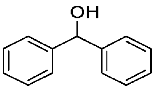
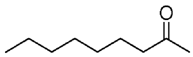
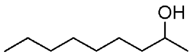
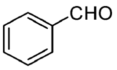
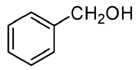
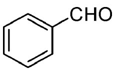
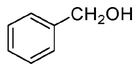
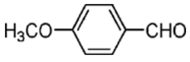
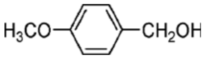
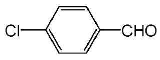
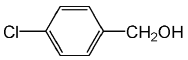
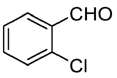
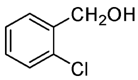
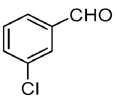
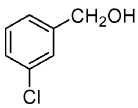
Table 2 Catalytic transfer hydrogenation of ketones over Au/TiO_2[a]

Entry	Substrate	Product	Time/h	Conversion (selectivity) (%)
1			4	99 (100)
2			6	98 (99)
3			3.5	92 (99)
4			8	93 (98)
5			10	60 (98)
6			8	70 (86)
7			9	44 ($>$99)
8			8	31 (98)

[a] Reaction performed under an N_2 atmosphere at 82 °C using 2-propanol (10 ml) as the solvent and hydrogen source, 1 mmol substrate, 0.78 mol% Au and 0.3 equiv KOH. Conversion and selectivity was determined by GC using *o*-xylene as the internal standard.

Table 3 Catalytic transfer hydrogenation of aldehydes over Au/TiO_2[a]

Entry	Substrate	Product	Time/h	Conversion (selectivity) (%)
1			4	90 (99)
2[b]			6	94 (99)
3			9	98 (98)
4			2	92 (99)
5			8	99 (94)
6			2.5	$>$99 (99)

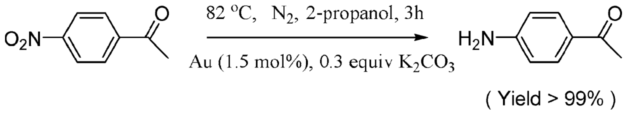
[a] Reaction performed under an N_2 atmosphere at 120 °C using 2-propanol (10 ml) as the solvent and hydrogen source, 1 mmol substrate, 0.78 mol% Au and 0.3 equiv. K_2CO_3. Conversion and selectivity was determined by GC using *o*-xylene as the internal standard. [b] Reaction performed at 150 °C with no addition of base.

recent liquid phase direct hydrogenation studies where Au is found to be much inferior to Pd as a hydrogenation catalyst.[12,13] Although the origin of this exceptional activity is not clear, a possible explanation might be that under these hydrogen transfer conditions the presence of a strong base can greatly facilitate the hydrogen-delivery rates of the Au catalyst.

The Au/TiO_2 was stable, reusable and not flammable and thus could be easily handled or stored under ambient conditions. After the first transfer reduction reaction, the catalyst was filtrated and washed with acetone, then reused for the second reaction. The catalytic results indicate that there is no difference in either activity or selectivity between the first and fifth runs (Table 1, entries 1 and 6). Au leaching was negligible during the above recycles. In addition, no change in the Au particle structure was observed by TEM.† These results demonstrate that highly dispersed gold nanoparticles retain their properties even after completion of the reaction and that the catalyst is active for several cycles.

The scope of the catalyst was established by using a wide range of aromatic ketones and in many cases the reaction was completed within 4–10 h with exceedingly high yields (Table 2). As illustrated in Table 2, selective reduction of 4-methoxyacetophenone (entry 2) is possible to afford the corresponding alcohol in excellent yield albeit with a longer reaction time. Moreover, high yields can also be attained for 4-chloroacetophenone reduction (entry 3), with no evidence of hydrodechlorination or ring reduction. It is worth noting that a hetero-aromatic ketone can also be reduced in almost quantitative yields (entry 4). On the other hand, the reductions of compounds containing substituents present either on the aromatic ring or in the α-position (entries 5–7) revealed that the activity is largely influenced by the presence of an α-bulky group due to steric hindrance. Such a limitation was also observed in the reduction of 2-nonanone (entry 8), for which the observed activity is significantly lower than all other substrates.

Further, for the transfer reduction of aldehydes, we examined the catalytic activity of Au/TiO_2 for the selective reduction of various substrates and the results are presented in Table 3. To avoid undesirable Cannizzaro reactions that may take place in the presence of strong bases, transfer hydrogenation of aldehydes was carried out in the presence of K_2CO_3. Although it is well known that aldehydes are difficult to reduce by catalysts commonly used for CTH,[16] transfer hydrogenation of aromatic aldehydes (entries 1, 3–6) could afford complete conversion to the benzyl alcohols. Moreover, much higher rates for *para* and *meta* isomers relative to the *ortho* isomer reveal a tremendous steric effect for *p*-, *o*-, or *m*-chloroacetaldehyde isomer reductions. It is also important



Scheme 1 Catalytic transfer hydrogenation of 4-nitroacetophenone over Au/TiO_2.

to note that the transfer hydrogenation of benzaldehyde can also proceed efficiently under base-free conditions (entry 2), although a higher reaction temperature is required. This indicated that the presence of a base is helpful to form the Au–H complex[17] *via* interaction with the hydrogen donor, which is believed to be the key active intermediate for transfer hydrogenation.

The selective and rapid reduction of nitro groups in the presence of carbonyl functionalities is also a highly valuable transformation in organic synthesis.[18] The development of an efficient catalytic system to achieve this goal has attracted considerable effort recently.[13,19] Therefore it was decided to investigate whether Au/TiO_2 could provide a viable solution to this challenge. The result showed that Au/TiO_2 mediated transfer hydrogenation can afford highly efficient reduction of nitro groups in the presence of carbonyl functionalities (Scheme 1). It is remarkable that 100% chemoselectivity in terms of $-NO_2$ reduction can be achieved for 4-aminoacetophenone production. Such reaction exclusivity, notably the absence of any carbonyl group or ring reduction, is unique when compared with the conventional catalytic systems.[5e,20]

In summary, we have demonstrated that the non-flammable Au/TiO_2 regent has great potential for catalytic transfer hydrogenation. This catalyst has been proven to be highly efficient and chemoselective in the reduction of carbonyl and nitro groups. The efficiency and stability of the catalyst has also been demonstrated convincingly by conducting five successive runs without any drop in the reaction rate. Further application of the Au-based catalytic system to many other key transformations is currently being explored.

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