Heterogeneous Tandem Catalysis

DOI: 10.1002/ange.200900802

Gold Supported on Hydroxyapatite as a Versatile Multifunctional Catalyst for the Direct Tandem Synthesis of Imines and Oximes**

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Tandem catalysis that enables one-pot multistep reactions holds great potential for increasing the efficiency of chemical synthesis.[1] Performing multiple reactions simultaneously in a single reaction vessel offers possibilities for reduced waste and increased safety as well as manipulation of equilibria.[2] Although many transition-metal-based catalysts have been developed, the focus has been largely on homogeneous rather than heterogeneous catalysis.[3] Indeed, several heterogeneous multifunctional processes involving different synthetic transformations in the context of one-pot multistep catalysis have been reported.[4] However, relevant reports are limited to a few heterogenized homogeneous metal complexes, which generally suffer from product contamination and limited recyclability.[5] In general, truly heterogeneous systems capable of catalyzing two or more mechanistically different reactions in tandem are scarce.[6] Moreover, most of these systems require the use of large excesses of reagents or expensive activators and are not effective for the construction of complex organic compounds.[7] In this respect, the development of a single heterogeneous multitask catalyst that is highly effective for sustainable tandem synthesis still remains a great challenge.

Imines and oximes are versatile synthetic intermediates for dyes, fragrances, pharmaceuticals, fungicides, and agricultural chemicals.[8] Although several oxidation procedures that use stoichiometric amounts of reagents for the synthesis of imines and oximes from amines are known, only a few catalytic procedures have been reported. A number of ruthenium or palladium complexes have been used for the oxidation of amines with dioxygen,[9] iodosylbenzene,[10] or persulfate ions[11] as oxidants. However, these systems are not generally useful because of their low turnover numbers (TONs) and frequencies (TOFs), the formation of significant amounts of by-products, severe deactivation of the catalysts, and narrow applicability to a limited number of amines. Recently, a tandem catalytic process to produce imines directly from alcohols and amines with manganese octahedral molecular sieves (OMS-2) was reported.[6c] However, the reaction requires elevated temperatures (above 100°C) and prolonged reaction times (up to 24 h) to achieve high yields of the products (greater than 90%).

Application of supported gold nanoparticles as catalysts for organic transformations is of growing interest.[12] Although catalytic tandem reactions for efficient organic synthesis are recognized as an atom-economical route to sustainable chemistry, the possibilities offered by supported gold catalysts have scarcely been explored to date.[13] Very recently, we reported the design of a versatile bifunctional Au/β-Ga_2O_3 catalyst that is highly effective for direct one-step oxidative esterification of a range of alcohols, aldehydes, and acetals.[14] The benefit of utilizing gallium oxide as a support has been attributed to a unique cooperative interaction between gold and surface Lewis acidic sites on the β-Ga_2O_3 support. Herein, we report that gold nanoparticles supported on hydroxyapatite[15] possessing a unique amphoteric character are efficient multifunctional catalysts for rapid direct synthesis of imines and oximes from amines under mild conditions by a facile tandem oxidation–condensation pathway. Prior to this work, there have been no examples in the literature of recyclable multitask gold catalysts for the direct tandem synthesis of imines or oximes.

Hydroxyapatite (HAP, $Ca_{10}(PO_4)_6(OH)_2$) was synthesized according to literature procedures.[16] Surface acidity and basicity measurements by NH_3- and CO_2-TPD and pyridine adsorption coupled with FTIR measurements (see details in the Supporting Information, Table S1, Figure S1 and S2; TPD = temperature-programmed desorption) reveal an abundance of basic surface sites of medium strength and a limited number of Lewis acid sites in the as-synthesized HAP material. When gold nanoparticles were deposited onto the HAP (see Supporting Information for the detailed preparation procedure), X-ray photoelectron spectroscopy (XPS) of the Au $4f_{7/2}$ core level showed a contribution from metallic Au^0 at a binding energy of 83.9 eV. Almost identical XRD patterns were obtained for Au/HAP and HAP, indicating a good maintenance of the crystallinity of hydroxyapatite. TEM analysis of the Au/HAP catalyst reveals randomly dispersed particles, and energy-dispersive X-ray (EDX) analyses confirm that the particles corresponded to gold with an average diameter of about 3.6 nm. The introduction of gold nanoparticles significantly modifies the acid–base distribution (Table S1 in the Supporting Information), increasing the overall number of both acidic and basic sites on HAP.

Initially, benzyl alcohol and aniline (1:1 molar ratio) were used as model substrates to study the activity of various catalysts, including previously reported solid catalysts (Table 1). Among various catalysts tested, Au/HAP showed

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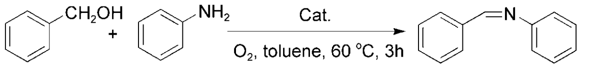
[**] The authors thank the NSF of China (20633030, 20721063, and 20873026), the State Key Basic Research Program of PRC (2003CB615807), Science & Technology Commission of Shanghai Municipality (08DZ2270500, 07QH14003), and Shanghai Education Committee (06SG03) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900802.

the highest catalytic activity for the direct tandem synthesis of benzylimine (Table 1, entry 1). Compared to palladium or ruthenium nanoparticles supported on HAP[17] as reference catalysts, gold is far superior to other noble metals for the tandem oxidation (Table 1, entries 2, 3). The tandem reaction hardly proceeded in the absence of catalysts (Table 1, entry 11) or in the presence of parent HAP (Table 1, entry 12). In the presence of Au/CeO_2,[18] the selectivity for benzylimine was very low, and benzaldehyde was obtained as a main by-product (Table 1, entry 4). Gold supported on β-Ga_2O_3 (Au/β-Ga_2O_3) and gold reference catalysts (Au/TiO_2, Au/Fe_2O_3, and Au/C) supplied by the World Gold Council were not effective for the tandem oxidation reaction (Table 1, entries 5–8). In the case of Au/TiO_2, the undesired formation of appreciable amounts of azobenzene as a consequence of the direct aerobic oxidation of aniline was observed.[19] Previously reported solid catalysts such as K-OMS-2[6c] showed only very little activity under otherwise identical conditions (Table 1, entry 9).

Table 1: Direct tandem synthesis of benzylimine from benzyl alcohol and aniline by various catalysts.[a]

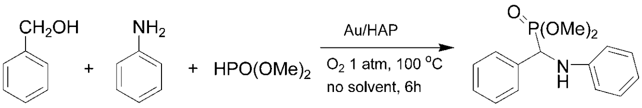


Entry	Catalyst	Conv. [%]	Sel. [%]	
			Imine	Aldehyde
1	Au/HAP	99	>99	<1
2	Ru/HAP[b]	49	99	<1
3	Pd/HAP[b]	15	90	10
4	Au/CeO_2[b]	53	74	25
5	Au/Fe_2O_3	10	99	<1
6	Au/TiO_2	36	88[c]	10
7	Au/C	1	99	<1
8	Au/β-Ga_2O_3[b]	13	97	3
9	K-OMS-2[d]	8	58	42
10	Au/HAP[e]	99	96	4
11	none	n.r.	–	–
12	HAP	n.r.	–	–

[a] Reaction conditions: alcohol (1 mmol), amine (1 mmol), catalyst (metal: 1 mol%), toluene (10 mL), 60 °C, O_2 bubbling (20 mL min^{-1}), 3 h. Selectivity based on the conversion of alcohol to imine. Main by-product was aldehyde. n.r. = no reaction. [b] Au/β-Ga_2O_3,[14] Ru/HAP,[17a] Pd/HAP,[17b] and Au/CeO_2[18] were prepared according to literature procedures. [c] As noted by Grirrane et al.,[19] in the case of Au/TiO_2, aniline also underwent the oxidative reaction, leading to the formation of azobenzene. We confirmed that in the present case, the yield of the azo compounds is ca. 23% based on aniline conversion. [d] K-OMS-2 (50 mg) prepared according to reference [6c]. [e] Reaction conditions: 10 mmol each substrate, Au/HAP (Au: 0.23 mol%), no solvent, 100 °C, O_2 bubbling (20 mL min^{-1}), 5 h.

To gain insight into the origin of the enhanced activity achieved using HAP as support, we examined the course of the tandem conversion of benzyl alcohol over time along with the corresponding oxidation in the absence of aniline. The time course plot for the alcohol oxidation alone over Au/HAP closely resembles that for the tandem reaction (Figure S6 in the Supporting Information). Conversely, a significantly retarded conversion has been identified for other supported gold systems.[20] Furthermore, Au/HAP was also found to be unique in terms of its ability to significantly accelerate the direct condensation of benzaldehyde with aniline under mild conditions (Table S2 in the Supporting Information), which is a process known to be catalyzed by Lewis acids.[21] On the basis of these observations, a delicate cooperation between metallic gold and the acid/base sites of the hydroxyapatite surface may play a key role in determining the efficiency and compatibility of the Au/HAP catalyst for not only the rate-determining alcohol oxidation but for the subsequent condensation step of the tandem reaction (Scheme S1 in the Supporting Information). The later process would be catalyzed by the acid sites on Au/HAP. This scenario is reinforced by the fact that the dehydrative condensation reaction was strongly inhibited when Au/HAP was impregnated with a basic oxide such as MgO.

The present system was applicable to larger-scale production (10 mmol for both substrates, heating at reflux, bath temperature 100 °C) in the absence of solvent, and the corresponding imine could be isolated in 95% yield after 5 h (Table 1, entry 10). The efficient tandem oxidation of benzyl alcohol catalyzed by Au/HAP in the presence of aniline, together with the synthetic utility of the product imines,[22] prompted us to develop a one-pot three-component approach as an alternative catalytic route for the tandem synthesis of α-aminophosphonates. These compounds are currently obtained by a number of multistep synthetic approaches[23] involving nucleophilic addition of phosphites to imines. Interestingly, when a mixture of benzyl alcohol (10 mmol), aniline (10 mmol), and dimethyl phosphite (10 mmol) was stirred under dioxygen (1 atm) at 100 °C for 6 h in the presence of multifunctional Au/HAP under solvent-free conditions, the corresponding α-aminophosphonate product was isolated in 86% yield (Scheme 1). Given that α-aminophosphonates are prominent core scaffolds in biologically active compounds,[24] this atom-economical route opens up new possibilities for the application of supported gold catalysts to the green synthesis of pharmaceutically important compounds.



Scheme 1. Three components form α-aminophosphonates with Au/HAP in a solvent-free system. The product is isolated in 86% yield.

To demonstrate the general applicability of the Au/HAP catalyst for direct imine synthesis and the scope of the process, various alcohols and amines were investigated. As depicted in Table 2, various aromatic alcohols react with aniline to give the desired products in excellent yields. Benzyl alcohols with electron-donating groups react smoothly (Table 2, entries 2, 3), while substitution with electron-withdrawing groups on the benzene ring decreases the reactivity (Table 2, entries 4, 5). High yields are still generally obtained in the latter case except for with 4-nitrobenzyl alcohol, which contains a strongly electron-withdrawing group (Table 2,

Table 2: Tandem synthesis of imines from various alcohols and amines using Au/HAP.[a]

$$R^1CH_2OH \;+\; R^2NH_2 \xrightarrow[O_2,\ \text{toluene},\ 60\,^{\circ}C]{\text{Au/HAP}} R^1CH{=}NR^2$$

Entry	R^1	R^2	*t* [h]	Conv. [%][b]	Sel. [%][b]
1	Ph	Ph	3	99	>99
2	4-MeC_6H_4	Ph	4	98	97
3	4-$MeOC_6H_4$	Ph	4.5	97	95
4	4-ClC_6H_4	Ph	7	99	97
5[c]	4-$NO_2C_6H_4$	Ph	12	76	97
6	cinnamyl	Ph	7.5	95	96
7[d]	*n*-heptyl	Ph	16	75	99
8	Ph	$PhCH_2$	3	99	99
9	Ph	4-MeC_6H_4	2.5	97	98
10	Ph	4-$MeOC_6H_4$	2.5	99	99
11[d]	Ph	4-$NO_2C_6H_4$	9	99	90
12	Ph	*n*-hexyl	1.5	99	98
13	Ph	*n*-butyl	1	95	97
14	Ph	cyclohexyl	3	99	99
15	Ph	(+)-α-methylbenzyl	2.5	95	97
16[e]	4-$HOCH_2C_6H_4$	*n*-butyl	3	95	99
17[f]	Ph	Ph	3	95	98

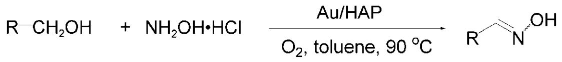
[a] Reaction conditions: alcohol (1 mmol), amine (1 mmol), Au/HAP (Au: 1 mol%), toluene (10 mL), 60 °C, O_2 bubbling (20 mL min^{-1}). [b] Determined by GC using 1,3,5-trimethylbenzene as an internal standard and confirmed by GC-MS; conversion (%) and selectivity (%) based on the conversion of alcohols to imines. [c] 0.5 mmol substrates (Au: 2 mol%). [d] 0.25 mmol substrates (Au: 4 mol%). [e] 1 mmol alcohol (Au: 1 mol%), 2.5 mmol butylamine. [f] Result for the fifth run using the same catalyst material.

entry 5), although longer reaction time is needed. Au/HAP also displays high activity in the tandem oxidation of allylic alcohols for imine synthesis. For example, cinnamyl alcohol was selectively oxidized to the corresponding imine with 95% conversion in 7.5 h (Table 2, entry 6). Furthermore, unactivated aliphatic alcohols, which are notoriously difficult to oxidize, could also be smoothly oxidized to the corresponding imines in high yield (Table 2, entry 7). However, the catalytic activity for most aliphatic alcohols was significantly lower than for benzylic and allylic alcohols (Table 2, entries 2–7).

Furthermore, the reaction also proceeds successfully with other structurally diverse amines. The use of (+)-α-methylbenzylamine gave the expected amine with no loss of optical activity ($[\alpha]_D = 60.1$ deg cm^3 g^{-1} dm^{-1} ($c = 0.5$ g cm^{-3}, EtOH); $[\alpha]_D$[25] $= 54.4$ deg cm^3 g^{-1} dm^{-1} ($c = 0.5$ g cm^{-3}, EtOH); Table 2, entry 15). Diols can be converted efficiently into bis(imines) (Table 2, entry 16). The results in Table 2 (entries 9, 10) also indicate that the presence of electron-donating substituents on the benzene rings have a positive effect on the tandem oxidation–imine formation reaction. Moreover, a surprising increase in formation rate could be achieved when aliphatic amines were used instead of aniline (Table 2, entries 12, 13). For example, when the reaction proceeds with *n*-butylamine and benzyl alcohol, it is complete after only 1 h (Table 2, entry 13). These results suggest that the high basicity of alky amines can provide an environment that facilitates the proton abstraction step in the oxidation of alcohols,[26] thus further confirming that the preliminary alcohol oxidation is the rate-determining step in the direct tandem synthesis of imines from alcohols and amines.

It is essential to verify that the observed catalytic conversion is caused by solid Au/HAP rather than leached gold species; to this end, control experiments were carried out. Catalytic transformation of benzyl alcohol and aniline was performed under the conditions in Table 2. After completion of the reaction, Au/HAP was removed by filtration. When further substrate was added to the filtrate and the mixture was again heated at 60 °C, no further formation of benzylimine was detected. Inductively coupled plasma (ICP) analysis showed that the amount of Au species present in the filtrate was below the detection limit (2.5 ppb). TEM and XPS analysis of the surface of the catalyst reveal no change in the Au dispersion before and after use (see Table S3 and Figure S7 in the Supporting Information). Furthermore, the Au/HAP catalyst could be reused with almost the same catalytic performance (Table 2, entry 17). These findings rule out any contribution to the observed catalytic conversion from soluble leached gold species.

Table 3: Tandem synthesis of oximes by using Au/HAP.[a]



Entry	R	*t* [h]	Yield [%][b]
1	Ph	3.5	95 (89)
2	4-$MeOC_6H_4$	2.5	97
3	4-ClC_6H_4	5	92
4	cinnamyl	6.5	94
5[c]	furfuryl	5	93

[a] Reaction conditions: alcohol (0.5 mmol), hydroxylamine (0.5 mmol), Au/HAP (Au: 2 mol%), solvent (10 mL), 90 °C, O_2 bubbling (20 mL min^{-1}). The number in the parenthesis is the yield for the third run using the same catalyst under identical reaction conditions. [b] Determined by GC using 1,3,5-trimethylbenzene as an internal standard and confirmed by GC-MS. [c] 0.25 mmol substrates (Au: 4 mol%).

The Au/HAP catalyst was also applied to the tandem synthesis of oximes from alcohols and hydroxylamine. Various kinds of alcohols, including aromatic (Table 3, entries 1–3), unsaturated (Table 3, entry 4), and heterocyclic (Table 3, entry 5) alcohols, could be converted into the corresponding oximes in high yields in the presence of only one equivalent hydroxylamine. This reaction is also catalyzed heterogeneously, and the Au/HAP catalyst could be reused without significant loss of catalytic activity. Although the tandem one-pot synthesis of oximes is very useful, stoichiometric amounts of reagents such as Na_2SO_4 (10 equiv with respect to substrates) and ZnO (2 equiv) have generally been used with an excess of hydroxylamine (more than 3 equiv).[27] While Taylor and co-workers have reported an efficient one-step synthesis of oximes from alcohols in the presence of activated manganese dioxide,[28] this system only gives high yields of oximes in the presence of an additive, such as 4 Å molecular sieves as the dehydrating agent. In contrast, the present system has the following significant advantages: 1) It needs only one equivalent of hydroxylamine. 2) It functions without any additives or promoters. 3) It requires only simple workup, namely catalyst/product separation by filtration. 4) The Au/HAP catalyst can be reused. 5) The Au/HAP catalyst is easily prepared and easy to handle.

In conclusion, we report herein the noteworthy features of the multitask Au/HAP reagent for the heterogeneously catalyzed tandem oxidation of alcohols and amines to imines (or oximes) as well as the one-pot three-component syntheses of α-aminophosphonates in solvent-free conditions. Further extensions of this multifunctional catalyst to a variety of functional transformations, as well as studies to clarify other factors that control tandem reactions, are currently under investigation.

Received: February 10, 2009
Revised: March 12, 2009

Keywords: gold · heterogeneous catalysis · hydroxyapatite · imines · oximes

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[20] The retarded conversion can be attributed to the higher affinity of the acidic-oxide-supported gold catalysts for amine adsorption, which blocks their activity relative to Au/HAP. On the other hand, the pronounced surface basicity (Table S1 in the Supporting Information) may account for the superior activity of Au/HAP for alcohol oxidation in the absence or presence of aniline.

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