Potential of Gold Nanoparticles for Oxidation in Fine Chemical Synthesis

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Abstract

In recent years supported gold nanoparticles have emerged as efficient catalysts with considerable synthetic potential for liquid-phase oxidation reactions based on molecular oxygen as oxidant. Here we critically review the most attractive applications related to the selective oxidation of functional groups containing O, N, or Si heteroatoms. The reactions include the oxidation of alcohols, aldehydes, and organosilanes; the diverse transformations of amines; benzylic oxidations; and some one-pot multistep reactions starting with alcohol or amine oxidation. In complex liquid-phase transformations relying on bifunctional catalysis, appropriate choice of the support is frequently more important than the size of the gold particles. In some oxidation reactions gold nanoparticles outperform the traditional platinum-group metal catalysts, but the latest results indicate the superiority of bimetallic particles containing gold and platinum, palladium, or rhodium. The environmentally benign nature of the transformations is discussed.

INTRODUCTION

TOF: turnover frequency

After a long history of minor interest in catalysis by the noblest metal, gold, Haruta et al.'s discovery (1, 2) of the exceptional activity of nanosized gold in CO oxidation in the late 1980s initiated exponential growth in this field. Intensive research by numerous groups revealed that the application range of gold nanoparticles is remarkably broad and goes well beyond the gas-phase oxidation of small molecules (3–9). Aerobic oxidation—that is, the use of molecular oxygen as the only oxidant—is the most-studied application of nanogold catalysts in fine chemical synthesis.

Numerous efficient methods for the preparation of gold nanoparticles have been put forward in past decades. Some recent reports provide a good overview of the different concepts and also techniques useful for characterization of the catalysts (4, 10, 11).

We consider here all nanoparticles stabilized by either a capping agent or a solid surface. Both approaches have advantages and disadvantages, but the key point is that the nanoparticle-stabilizer system determines the catalytic properties. Gold particles supported on a solid surface are well suited for catalyst separation and recycling, and the metal-support interaction may improve the catalytic properties dramatically (12–15). In the other approach, colloid stabilizers allow the precise tuning of the size and shape of gold nanoparticles (16); they cover a significant fraction of the surface metal sites and may control the outcome of the chemical transformation (17, 18). Naked gold nanoparticles are highly active but impractical, as in the absence of a stabilizer particle growth occurs over a timescale of less than 100 s (19). Surface science studies on single gold crystals avoid this complication and offer new insight into the reaction mechanism (20–22), but the properties of an extended metal surface deviate strongly from those of tiny nanoparticles.

A fundamental aspect of gold catalysis is the critical importance of small particle size of less than 5 nm. Feasible explanations for the phenomenon include the outstanding contribution of low-coordination surface atoms (corners, edges) (23), a change in the oxidation state and electronic structure of the metal with the particle size (24–26), the sensitivity of O_2 dissociation to the surface arrangement of gold atoms (27), charge transfer and oxygen spillover between the gold particles and the support (28, 29), and support-induced strain (30). It is widely accepted that in the case of reducible oxides (Fe_2O_3, CeO_2, TiO_2), the gold/support interface plays a major role in the activation of oxygen (23, 31).

The necessity of small particle size for the catalytic activity of gold has been questioned recently. Relatively big particles (7–25 nm) (32), or even gold powder (approximately 1,000 nm) (33), can catalyze the oxidation of amines. The latter observation corrects the common misbelief that bulk gold does not exhibit catalytic activity. Nevertheless, the synthetic value of catalysis by bulk gold is negligible owing to its extremely low surface area and reaction rate; its turnover frequency (TOF), the moles of substrate converted by 1 mol of loaded gold per unit time, is approximately 0.001 h^{-1}.

In the following, we present a short overview of the potential of gold nanoparticles in catalytic aerobic oxidations for the synthesis of fine chemicals. The most promising area is the transformation of functional groups containing an O, N, or Si heteroatom. **Figure 1** provides an overview of the aerobic oxidations in which supported gold nanoparticles have been found to be efficient. Our discussion focuses on the synthetic, engineering, and environmental aspects of these reactions.

OXYGEN-CONTAINING FUNCTIONAL GROUPS

Oxidation of Alcohols

The first report by Prati & Rossi (34) on the selective aerobic oxidation of diols to hydroxy acids in 1997 introduced a new, highly successful application of gold in liquid-phase aerobic oxidations. Several reviews (3–5) have summarized the impressive development in the oxidation

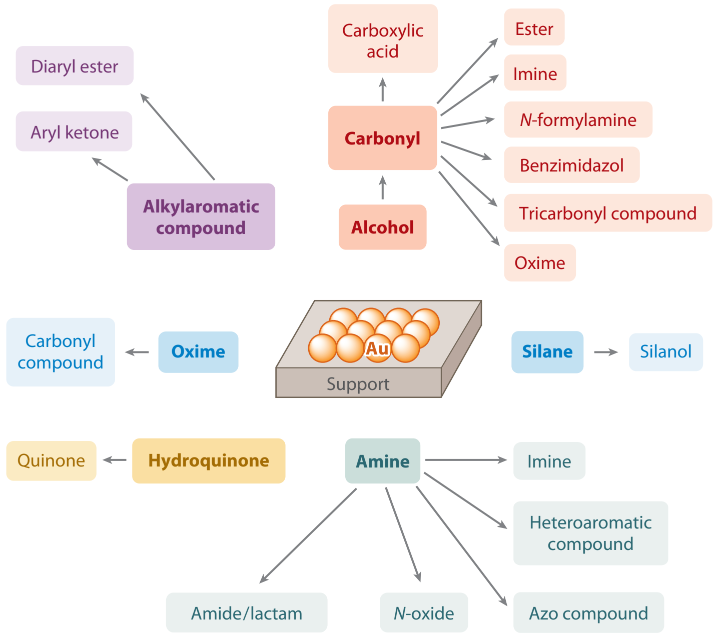

Figure 1

The most important aerobic oxidations in fine chemical syntheses catalyzed by supported gold nanoparticles.

of alcohols and polyols. Secondary aromatic alcohols can be transformed (almost) quantitatively to ketones, whereas most catalysts are less active and selective in the oxidation of cycloaliphatic and heteroaromatic alcohols (35–39). Partial oxidation of primary alcohols to aldehydes is also demanding, because gold is active in the subsequent undesired reaction step to carboxylic acid. Oxidation of aldehydes to carboxylic acids is discussed below.

With membrane-occluded Au-Pd bimetallic nanoparticles, 94–99% aldehyde yields were obtained in the oxidation of 1-octanol, 1-octene-3-ol, and benzyl alcohol, and in the last case the TOF was 16,520 h^{-1} (at 413 K) (40). Even higher rates were measured by numerous authors at 433 K and elevated pressure in the transformation of 1-phenylethanol to acetophenone. The product distribution is, however, usually not mentioned, and the usefulness of these forcing conditions for the synthesis of complex, thermolabile molecules is doubtful.

The reactions are usually carried out in organic solvents (38), but water in the presence of a base (5, 36) or solvent-free conditions (40) are also appropriate. The oxidation of benzyl alcohol was faster in single-phase dense CO_2 than in the absence of solvent (41).

The preparation method, including the nature of the gold precursor and the reducing agent, and the support have a dramatic and not always understood influence on the performance of gold, and generalization of the effect of reaction conditions is difficult. Several catalysts are active at approximately ambient temperature and pressure, and they provide excellent yields of carbonyl compounds using only oxygen or air as oxidant (35, 37). Addition of a base may increase the reaction rate several hundredfold, with the drawback that in the oxidation of primary alcohols the base favors the formation of carboxylic acids from the intermediate aldehyde (42). The necessary base additive may be omitted by deposition of gold onto a basic support such as Cs_2CO_3 (43). This catalyst does not catalyze the further oxidation of benzylic aldehydes to carboxylic acids, which is a rare feature of gold (and Pt-group metal) catalysts. Further possibilities to improve

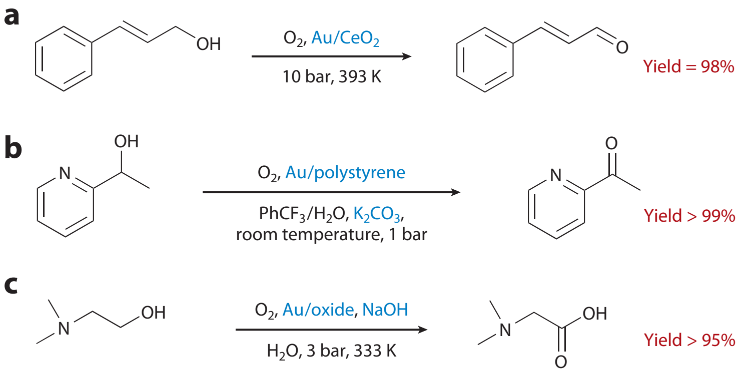

Figure 2

Representative examples of the selective oxidation of bifunctional alcohols (35, 50, 51): (*a*) cinnamyl alcohol, (*b*) pyridineethanol, and (*c*) 2-dimethylaminoethanol.

the performance of gold include the use of special, collaborating support ceria (44, 45) and the application of bimetallic nanoparticles containing Pd or Pt (3, 46–49).

For practical application in the synthesis of fine chemicals, selective oxidation of a single OH group of bi- and polyfunctional compounds is important. Ceria-supported gold allowed 72–99% selectivity in the oxidation of allylic alcohols to α,β-unsaturated aldehydes under solvent-free conditions (**Figure 2*a***) (50). Heteroaromatic alcohols containing N or S were oxidized with 94–99% yield at room temperature in the presence of three equivalents of base (**Figure 2*b***) (35). The alcoholic OH function can be selectively oxidized in the presence of a tertiary amino group, although tertiary amines can also be converted to *N*-oxides on gold (see below). More than 95% yield was achieved in the oxidation of 2-dimethylaminoethanol to dimethylamino-acetic acid in alkaline water (**Figure 2*c***) (51). Selective oxidation of ethanolamine and 2-methylaminoethanol failed owing to competing imine formation and catalyst deactivation.

Preferential oxidation of a primary OH function in the presence of a secondary OH group is typical for gold (52). Transformation of ethylene glycol to glycolate and propylene glycol to lactate in alkaline water gave 98–100% selectivity even at high conversion (**Figure 3*a***) (53). In a comparison, Au/C proved to be less active but more selective than Pd/C or Pt/C catalysts (53).

Partial oxidation of glycerol is one of the most-studied transformations on gold (54–58). Despite extensive research, only one route allows greater than 90% selectivity to a single product, glyceric

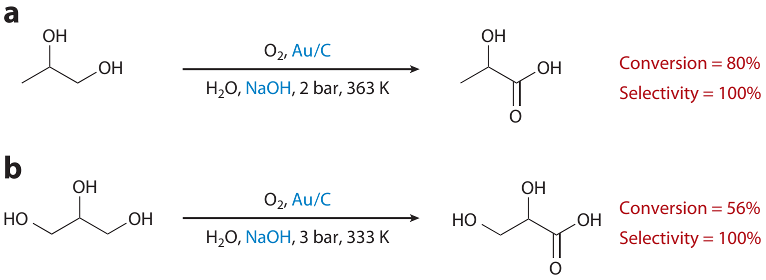

Figure 3

Selective oxidation of the primary OH function in (*a*) 1,2-propylene glycol (53) and (*b*) glycerol (59).

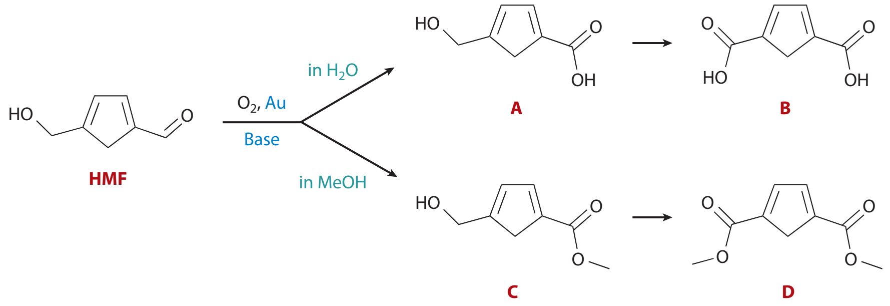

Figure 4

Oxidation of 5-hydroxymethylfurfural (HMF) into valuable chemicals. HMF can be transformed into dicarboxylic acid B on hydrotalcite-supported Au in water at 368 K. In aqueous NaOH and at room temperature, only the aldehyde function of HMF is oxidized to give the corresponding monocarboxylic acid A on Au/C. Replacement of water with methanol results in the formation of dimethyl ester D over Au/TiO_2 at 403 K. At room temperature, only the aldehyde function of HMF is converted to produce the monoester C.

acid (**Figure 3*b***) (59). High NaOH concentration enhanced the reaction rate and selectivity, whereas no reaction was observed in neutral solution. H-abstraction from a primary OH group was assumed to be the rate-determining step. Another interesting feature is the structure sensitivity: The reaction is much faster on small, approximately 5-nm particles, but big particles ($\geq$20 nm) are more selective (60). On small particles the rate of H_2O_2 formation is also higher, and the peroxide favors glycolic acid formation via C–C bond cleavage.

A key intermediate from the conversion of biomass (61, 62) is 5-hydroxymethylfurfural (HMF; **Figure 4**). This heteroaromatic hydroxyaldehyde can efficiently be transformed into dicarboxylic acid B (**Figure 4**) with more than 99% yield on hydrotalcite-supported Au in water at 368 K (63). Quantitative yield in this reaction was achieved 20 years ago with Pt/Al_2O_3 in aqueous medium at a controlled pH of 9 (64). The new development in the gold-catalyzed reaction is that the necessary base catalysis is provided by the basic support of the bifunctional catalyst. In aqueous NaOH and at room temperature, only the aldehyde function of HMF is oxidized to give the corresponding monocarboxylic acid A on Au/C (93% yield; **Figure 4**) (65). Replacement of water with methanol results in the formation of dimethyl ester D (**Figure 4**) in 98% yield over Au/TiO_2, and in this case only a catalytic amount of base ($NaOCH_3$) is necessary (66). (For oxidative esterification see also the next section.) When the reaction temperature is decreased from 403 K to room temperature, only the aldehyde function of HMF is converted, and high yield is achieved to the monoester C (**Figure 4**). The synthesis of the diester D has been further improved by using an Au/CeO_2 catalyst in the absence of any base additive (67).

In many alcohol oxidation reactions, gold appears to be a better choice than supported Pt-group metal catalysts (68), but contrary examples also exist (69). In some enthusiastic reports on the superiority of gold, however, the comparisons are not convincing. In the oxidation of cinnamyl alcohol to cinnamaldehyde, for example, the performance of Au/CeO_2 was considered outstanding with a TOF of 538 h^{-1} (50) because the next best catalyst found in the literature, a Bi-promoted Pt/Al_2O_3, afforded a TOF of only 144 h^{-1} (70). However, gold was used at 393 K and 1 bar in oxygen, whereas the supposedly less active bimetallic catalyst was tested at 313 K and 0.2 bar oxygen partial pressure. Another frequent issue with many of the comparisons is that the conditions selected for the comparison are optimized for Au but not for Pt and Pd. Furthermore, comparisons between gold nanoparticles prepared by a highly sophisticated technique and randomly selected,

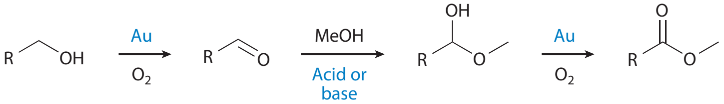

Figure 5

Oxidative esterification of alcohols to methyl esters via aldehyde and hemiacetal intermediates.

commercially available Pt or Pd catalysts are also not conclusive. These issues markedly reduce the significance of the comparisons.

One-Pot Synthesis Starting with Alcohol Oxidation

The basic idea behind this one-pot but two (or more) reaction steps approach is the formation of a reactive aldehyde intermediate by the oxidation of an alcohol. The aldehyde reacts in situ with a second substrate added at an appropriate time. The method is particularly advantageous when the aldehyde is unstable or not easily available.

A simple, well-known one-pot route to methyl esters is the oxidative esterification of a reactive primary alcohol in the less reactive methanol as solvent (**Figure 5**). The rate-determining step is the formation of the intermediate aldehyde by gold-catalyzed aerobic oxidation. In the absence of water, the aldehyde is not hydrated and oxidized to carboxylic acid. Rather, the hemiacetal is formed with methanol, which is further oxidized to the ester. The acetal formation is catalyzed by an added base (71) or by the acidic (72) or basic (73, 74) sites on the catalyst support. Typical side reactions are ester formation with the reactive alcohol instead of methanol as well as the competing oxidation of methanol to formic acid, methyl formate, and CO_2. Direct formation of methyl glycolate from ethylene glycol and methanol (75) is of industrial interest.

In those instances in which the aldehyde is easily available, the slow oxidation of alcohol to aldehyde may be omitted. The base-catalyzed oxidation of aldehydes to methyl esters proceeds smoothly even at room temperature on Au/TiO_2 (76). This method has been extended to the facile synthesis of 1,2- and 1,3-diol monoesters from aldehydes using polymer-incarcerated gold nanoparticles and 0.5 equivalents of base (K_2CO_3) (77).

Another version of oxidative esterification is lactone synthesis by oxidative cyclization of α,ω-diols (78). Kaneda and colleagues (73) have reported many examples of the synthesis of lactones in high yields using Au nanoparticles deposited onto a basic hydrotalcite.

Oxidation of aromatic (reactive) alcohols in the presence of primary amines provided the corresponding imines via the intermediate aldehyde with up to 98% yield at only 333 K (79). Cooperation between gold and the amphoteric hydroxyapatite support was critical: Gold on other supports or Pd and Ru on hydroxyapatite were ineffective. The method could be extended to the synthesis of oximes from aromatic alcohols and hydroxylamine.

An analogous reaction is the *N*-formylation of *N*-methylbenzylamine with methanol via formaldehyde and the hemiaminal intermediate (80). However, the method has no significant advantage compared with the direct use of aqueous formaldehyde, which is considerably faster.

Benzimidazoles were synthesized from *o*-phenylenediamines starting with the aerobic oxidation of an alcohol (81). The diamine was added to the reaction mixture after high conversion of benzyl alcohol, because the amine poisoned the oxidation to benzaldehyde (**Figure 6**). Schiff base formation was followed by cyclization, and further oxidation gave the final product. In the alcohol oxidation step Pd/C was more active than Au/CeO_2, leading to a lower overall yield with gold. The new, environmentally friendly procedure was extended to several other alcohols and amines using Au/CeO_2 (yield = 13–91%). Electron-withdrawing substituents on the alcohol or the diamine reduced the reaction rates and the overall yields. Poor results were obtained only with aliphatic

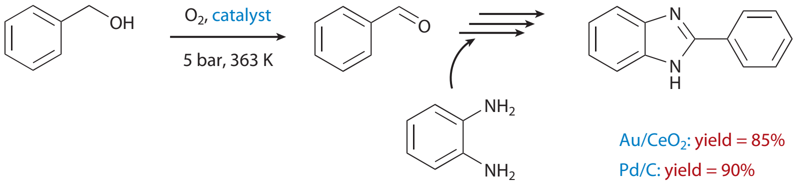

Figure 6

One-pot oxidative synthesis of benzimidazoles from alcohols and diamines (81).

alcohols. The sluggish oxidation of aliphatic alcohols is a known limitation of gold and Pt-group metal catalysts (5, 68).

A recent innovation is the aerobic oxidation of allylic alcohols followed by the Michael addition of 1,3-dicarbonyl compounds over a unique bifunctional catalyst (82). The first step to the corresponding α,β-unsaturated ketone is catalyzed by Au-Pd nanoparticles under mild conditions (**Figure 7**). Next, the ketone reacts with the 1,3-dicarbonyl compound on the immobilized boron sites. These Lewis acid sites are formed by addition of $NaBH_4$ to the polymeric catalyst support. Immobilization of boron as a tetravalent complex probably occurs through esterification with the OH functions of the polymer. This multicomponent catalyst has a broad application range and can be recycled with only a minor loss in its performance.

Oxidation of Aldehydes

As mentioned previously, in the transformation of primary alcohols to carboxylic acids the rate-limiting step is the formation of the aldehyde intermediate. Accordingly, further oxidation of aldehydes is usually a facile reaction under mild conditions, and the yields are typically high. Surprisingly, there are some aldehydes, such as *o*- and *p*-hydroxybenzaldehyde and glyoxal, which resist oxidation by the gold-oxygen system (5). Gold catalyzes mainly C–C bond breakage in glyoxal to yield formic acid (83), whereas gold is a promoter of palladium in the conversion of glyoxal to glyoxalic acid (84).

Another unexplained phenomenon is the strong inhibitory effect of acetonitrile solvent in the oxidation of some aliphatic and aromatic aldehydes. In the oxidation of benzaldehyde, 96% yield was obtained in CCl_4 and 24% in water, which is a poor solvent of the substrate; addition of acetonitrile to water surprisingly diminished the yield to 5% (85). We assume that the catalyst inhibition is linked to the radical mechanism of aldehyde oxidation involving peroxo radicals or H_2O_2 as a coproduct (55, 86–88). Nitriles are certainly not inert in oxidation reactions in the presence of H_2O_2 or hydroperoxides as intermediates (89–91), as discussed in a recent review on reactions in sacrificial solvents (92). Acetonitrile can consume H_2O_2, and the adduct peroxycarboximidic acid may also react with the substrate as a chemical oxidizing agent (**Figure 8**). A general conclusion is that solvents, which are easily converted by peroxides [e.g., nitriles, amides, sulfoxides, ethers (92)] should not be used in the oxidation of aldehydes (and primary alcohols) to

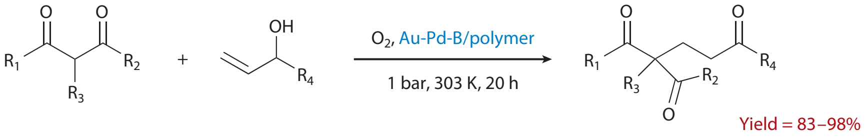

Figure 7

One-pot aerobic oxidation of allylic alcohols followed by Michael addition of 1,3-dicarbonyls (82).

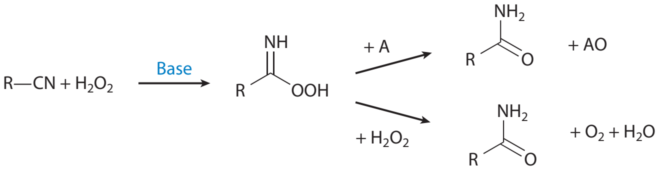

Figure 8

Involvement of nitriles in oxidation reactions in the presence of H_2O_2. Abbreviation: A, oxidizable substrate (92).

carboxylic acids. These side reactions diminish the atom economy (93) of the overall process and eliminate the environmentally friendly character of gold-catalyzed aerobic oxidations.

Oxidation of D-glucose to D-gluconate is a broadly investigated, industrially relevant transformation in this reaction class. Early studies by Rossi and colleagues (94) have revealed that supported gold nanoparticles are more appropriate catalysts than the previously preferred promoted Pt-group metals (95–97). Gold provides an extremely high reaction rate and selectivity under very mild conditions (98). Useful information for the design of novel active catalysts is that in this simple transformation, efficient control of the small particle size is more critical than the choice of the support (98). In a continuous flow reactor study lasting 70 days (at 313 K, 1 bar, and pH 9), no loss of activity or selectivity of the Au/Al_2O_3 catalyst was observed (99). From an engineering point of view, the limited stability and recyclability are the biggest drawbacks of Pt- and Pd-based catalysts in carbohydrate oxidations.

In many respects, the heterogeneous gold-catalyzed aerobic oxidation process is a real alternative to the biochemical route (100). A common problem to be solved is that not D-gluconic acid but rather a dilute aqueous solution of sodium gluconate is the primary product of D-glucose oxidation (5). The subsequent transformation via calcium gluconate using sulfuric acid is definitely not an environmentally friendly process. The rate of the biochemical process at low pH is too low, and the activity of Au, Pd, and Pt catalysts is also insufficient in the presence of free gluconic acid.

The efficient route developed for the production of D-gluconate can be applied to the synthesis of many other aldonic acids starting from mono- and disaccharides (101). Here again, comparison of Au-, Pt-, and Pd-based catalysts has revealed the superiority of gold with respect to activity and selectivity.

Oxidation of Hydroquinones

Researchers discovered that polymer-incarcerated gold nanoparticles are good catalysts for the synthesis of quinones from hydroquinones and their derivatives (102). The reactions proceeded smoothly under mild conditions, and the yields were particularly high with hydroquinones substituted with an electron-releasing (alkyl or methoxy) functional group. Subsequently, the same Japanese research group found that a similar polymer-incarcerated platinum catalyst was remarkably more active than gold (103). This catalyst provided TOFs up to 1,000 h^{-1} and afforded excellent yields. In addition, platinum was effective in the demanding oxidation of hydroquinones substituted with electron-withdrawing groups; in this transformation gold was poorly active even after addition of an equivalent amount of a base catalyst.

NITROGEN-CONTAINING FUNCTIONAL GROUPS

Interest in the gold-catalyzed oxidation of *N*-containing functional groups is quite recent, limited to the past five years. Nevertheless, studies have already revealed the remarkable potential of gold nanoparticles in these transformations.

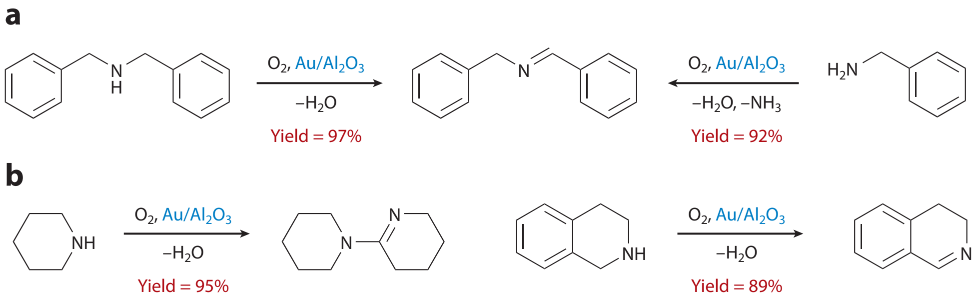

Figure 9

Representative examples of the selective oxidation of amines to imines on Au/Al_2O_3: (*a*) comparison of the oxidation of dibenzylamine and benzylamine; (*b*) comparison of the oxidation of piperidine and 1,2,3,4-tetrahydroisoquinoline (1 bar, 373 K, toluene) (113).

Amine oxidations have two unique features. Because amines are good reducing agents, active gold nanoparticles may be produced in situ from the precursor by interaction with the substrate (104, 105). A practically important consequence is that leaching of gold and homogeneous catalysts is highly unlikely in amine oxidation, as evidenced by in situ X-ray absorption spectroscopy (106). Additionally, contradictory reports have appeared on the influence of gold particle size on the reaction rate (107–109). Clearly, small particle size, preferably less than 5 nm, is not a requirement for good oxidation activity; rather, the metal-support interactions seem to be critical. For example, in benzylamine oxidation, decreasing the average particle size from 25 to 3.5 nm increased the TOF of Au/TiO_2 from 0 to 70 h^{-1}, but Au/C with 10-nm particle size was more active (TOF $=$ 280 h^{-1}) than any of the titania-supported catalysts (107). In several instances the acidic or basic sites on the support play a decisive role in the transformation (bifunctional catalysis), as will be illustrated below.

Oxidation of Amines to Imines

Amines (and isocyanides) can take part in a variety of oxidation reactions on the gold surface, as first discovered by Angelici and colleagues (110–112) five years ago using gold powder. A highly selective transformation is the oxidative dehydrogenation of amines to imines with the coformation of water. Acyclic secondary amines, such as dibenzylamine, afford the corresponding imines in high yield on alumina-supported gold (**Figure 9*a***) (113). Dehydrogenation of primary amines is accompanied with dimerization via the imine intermediate, followed by a second dehydrogenation to imine. Accordingly, *N*-benzylidene benzylamine is the product from both benzylamine and dibenzylamine (**Figure 9*a***). Starting from cyclic secondary amines, the major product depends on the substrate structure and thus on the stability of the imine (**Figure 9*b***) (113). In general, steric effects and the relative position of an aryl group are important in controlling the product distribution in the oxidation of secondary amines (107). For example, carbon-supported gold transformed a broad range of aryl-substituted acyclic and cyclic benzylic amines to imines with up to 99% yields, although at low rates (TOF $\approx$ 1 h^{-1}) (114). Gold on ceria is more active in amine oxidation; it gave up to 100% yield and a TOF of 92 h^{-1} in the oxidation of indoline to indole (105, 108).

Oxidation of tribenzylamine on Au/TiO_2 affords *N*-benzylidene benzylamine and benzaldehyde (107). An analogous debenzylation reaction is the recovery of aryl- and alkylamines via oxidative removal of the *p*-methoxybenzyl protecting group (109). Interestingly, in that case oxidation of secondary amines gave approximately 90% yield to primary amines, but neither the product

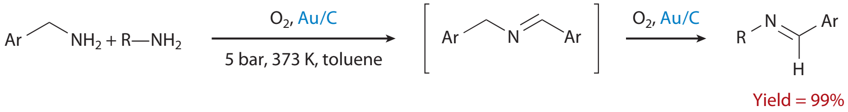

Figure 10

Oxidative cross-condensation of benzylamines and amines possessing no α-H (107). Abbreviation: Ar, aromatic moiety.

primary amines nor tertiary amines possessing a *p*-methoxybenzyl protecting group reacted on the polymer-supported gold.

Corma and colleagues (15) utilized the unique activity spectrum of carbon-supported gold in the oxidative cross-condensation of benzylamines and amines possessing no α-H atom (107). Outstanding yields to imines were obtained for several combinations of amines (**Figure 10**).

Oxidation of Tertiary Amines to *N*-Oxides

Gold supported on carbon or alumina is an efficient catalyst in the quantitative transformation of pyridine and 3-dimethylamino-1-propanol to the corresponding *N*-oxides (115). The reactions were complete in 2 h at 1–2 bar and 343–363 K. In the more demanding oxidation of triethylamine, Pt/C outperformed gold, but an Au-Rh/C catalyst was the best with 100% yield.

Oxidation of Amines to Amides and Lactams

It has been shown recently that the bifunctional catalyst Au/TiO_2 is able to transform selectively *n*-hexylamine to hexanoic acid *N*-hexylamide, although the conversion under solvent-free conditions was slow even at 403 K (116). The gold-catalyzed synthesis of cyclic amides (lactams) from heterocyclic tertiary amines is more promising (**Figure 11**) (114). The cumulative yield to various amides and enamides via oxidation at the benzylic C atom reached 90–99%. Addition of saturated aqueous $NaHCO_3$ to the reaction mixture in toluene increased the amide/enamide ratio up to 93:4.

1,2,3,4-Tetrahydroisoquinoline was oxidized quantitatively in a strongly basic aqueous medium to the corresponding lactam on poly(*N*-vinyl-2-pyrrolidone)-stabilized gold (117). In another reaction series with the same catalyst, oxidation of tetrahydroquinoline at the α-C atom gave a 91% yield to the lactam at only 300 K. Variation of the size of the heterocyclic ring, however, diminished the reactivity of the amines. The probable reaction route involves the imine and hemiaminal intermediates (117).

Oxidation of Anilines to Azo Compounds

A novel and practically relevant application of gold is the synthesis of aromatic azo compounds from amines, as discovered recently by Corma and colleagues (15). The environmentally friendly

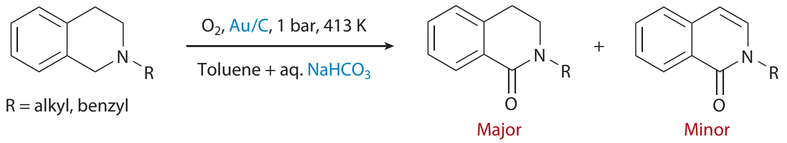

Figure 11

Synthesis of amides from heterocyclic tertiary amines (*N*-alkyl- and *N*-aryl-1,2,3,4-tetrahydroisoquinolines) (114).

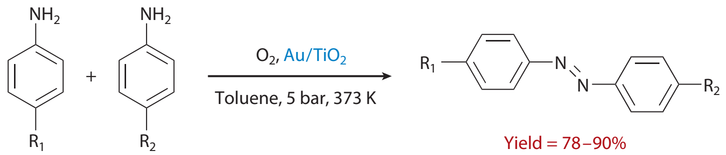

Figure 12

Synthesis of azo compounds from anilines (in toluene at 373 K and 5 bar) (15).

process allows the oxidation of two different amines to mixed azo compounds (**Figure 12**). When only one aniline derivative is applied as substrate (**Figure 12**, $R_1 = R_2$), the yields increase to 99%.

Oxidative Cyclization of Aromatic Amines with Aldehydes

Aromatic amines react smoothly over Au/silica with aliphatic aldehydes to give polyheterocyclic compounds with up to five fused aromatic rings (**Figure 13**) (118). Although the selectivities achieved are attractive, the method suffers from relatively slow reaction rates (TOF $< 4\ h^{-1}$). This is understandable considering the large average gold particle size of approximately 28 nm, the large active site ensemble required at the metal surface for the transformation, and the probably strong adsorption (poisoning effect) of aromatic amines. The multistep reaction necessitates Lewis acid sites for catalyzing the electrophilic aromatic substitution and dehydration to give 1,2-dihydroquinolines, and the subsequent dehydrogenation to quinolines occurs on metallic sites.

Oxidation of Oximes to Carbonyl Compounds

In the transformation of oximes to the corresponding ketones, Au/TiO$_2$ and Pt/C were poorly active and selective, respectively, but both metals performed excellently when they were supported on ceria (119). In the industrially relevant synthesis of carvone, only the C=N bond of the oxime was oxidized with complete selectivity to the C=O group even at 99% conversion; the two C=C bonds in the substrate were not attacked. Control experiments revealed a remarkable cooperation between the metal and the support as well as the high activity of ceria alone. The presence of water in the solvent mixture was important because of a hydrolysis step in the reaction route.

MIXED OXIDATION REACTIONS

Benzylic Oxidations

A recent example of the outstanding performance of bimetallic gold-based catalysts is the oxidation of toluene and its aryl-substituted derivatives on Au-Pd/C (120). Up to 80% yield to benzoyl benzoate was achieved under solvent-free conditions at 433 K and 10 bar. The transformation resembles the oxidative esterification of alcohols (**Figure 5**) with the unique advantage that the alcohol is produced in situ from a cheap hydrocarbon.

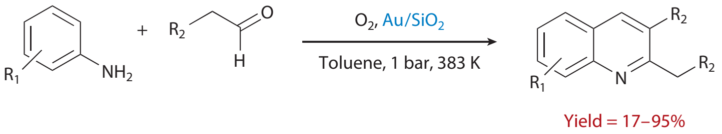

Figure 13

Oxidative cyclization of aryl-substituted anilines with aldehydes (118).

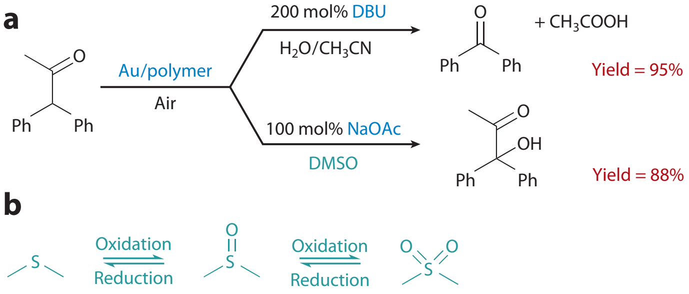

Figure 14

(*a*) Control of the selectivity in the oxidation of benzylic ketones at 300 K (123). Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMSO, dimethylsulfoxide; Ph, phenyl group. (*b*) The involvement of DMSO in redox reactions as a sacrificial solvent (92).

The benzylic methylene groups are easily transformed to ketones on some more reactive substrates, such as ethylbenzene (121), indan, diphenylmethane, and tetraline (122). The radical oxidation on gold nanowires (121) and Au/TiO_2 (122) is feasible and highly selective at only 373 K, but the yields are low.

An interesting application of gold is the mild oxidation of benzylic ketones (123). In a protic solvent mixture in the presence of excess strong base, the major products are benzophenone and the corresponding carboxylic acid (**Figure 14*a***). When a weak base in the aprotic solvent dimethylsulfoxide (DMSO) is applied, the dominant reaction switches from C–C bond cleavage to α-hydroxylation. The initial product is an α-peroxide, and gold accelerates its formation. Although the method may be attractive for laboratory application, we do not agree with the authors that it represents an environmentally friendly catalytic process (123). We have mentioned (**Figure 8**) that in the presence of peroxides the solvent acetonitrile is involved in the oxidation process. DMSO also belongs to the group of sacrificial solvents (92); it takes part in the transformation as a reductant (in the present case) and produces dimethyl sulfone as a coproduct, or it act as an oxidant with the coformation of dimethyl sulfide (**Figure 14*b***).

Oxidation of Silanes to Silanols

Gold supported on hydroxyapatite is an outstanding catalyst for the aerobic oxidation of organosilanes (R_3SiH) to silanols (R_3SiOH) (124). The method reported by Kaneda and colleagues (124) offers 92–99% yield for a broad range of silanols; formation of disiloxane condensation products is negligible. The yields dropped when hydroxyapatite was replaced by other supports. Platinum and ruthenium on hydroxyapatite were also quite selective but far less active catalysts. The facile reaction under mild conditions (353 K, 1 bar) in water is an attractive, environmentally friendly process. An alternative approach is the use of nanoporous gold in the absence of oxygen (125). In this case the yields to silanols are even better, but a technological drawback of the process is the evolution of the coproduct hydrogen.

CONCLUSIONS

In this overview of the state of art in catalytic aerobic oxidations by gold, we focused on the emerging new possibilities in fine chemical synthesis. Some reaction classes are characterized by unusually high rates and almost quantitative yields. An important aspect is the excellent stability and reusability of supported gold in practically relevant oxidation reactions. Leaching of gold into the liquid phase during oxidation reactions is not favored owing to its highest oxidation potential among all metals. Leaching is even less likely in the transformation of good reducing agents such as alcohols (126) and amines (106). In contrast, gold is unstable in the presence of a good ligand, and homogeneous catalysis becomes feasible owing to a shift in the redox potential. Practically relevant examples are halide anions (127) and cyanide (128, 129).

In most liquid-phase transformations described here, the closest competitors of Au are Pt and Pd. Frequently, gold nanoparticles are superior to Pt-group metal catalysts, which have been and still are widely used under similar conditions. A more recent development is the application of Au-Pt, Au-Pd, and Au-Rh bimetallic catalysts, which in several applications show superior performance compared with any of the metals alone.

Many sophisticated transformations rely on the presence of acidic and basic sites on the support, and thus the development of efficient gold-support catalyst systems is highly beneficial. Importantly, for some gold-catalyzed reactions, such as the oxidation of functional groups containing N or Si heteroatoms, development is in an early stage, and significant further improvements may be foreseen.

From a technological point of view, an interesting aspect is that the explosion-like development in gold catalysis in the past decade has been accompanied by similar growth in the price of gold (+650% since 1999). Based on data from August 2011, gold (approximately $1,800/oz) is already more than twice as expensive as palladium (approximately $800/oz) and matches the price of platinum (approximately $1,800/oz). Continuation of this trend may restrain industrial interest in introducing new gold-based technologies, at least in those applications in which catalyst costs are considerable. This unpredictable development does not change our positive attitude toward gold catalysis. In the past, the traditionally high price of Pt could not prevent the widespread application of various Pt-based catalysts, although it increased the general requirements concerning process efficiency and precious metal regeneration and recovery.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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