Supported Catalysts

Supported Gold(III) Catalysts for Highly Efficient Three-Component Coupling Reactions**

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Over the past few years gold has emerged as a source of effective heterogeneous^[1] and homogeneous catalysts,^[2] represented by supported gold nanoparticles and gold salts/ complexes, respectively. Both these types of catalyst have their advantages and disadvantages.^[2,3] Attempts to bridge the gap between homogeneous and heterogeneous gold catalysis will lead to more efficient and environmentally friendly methods for chemical synthesis.^[4] Our group has recently been carrying out comparative studies on homogeneous and heterogeneous gold catalysts for a series of reactions.^[1e,4b,5] This methodology, combined with theoretical calculations,^[5f] has allowed us to design effective gold catalysts and rationalize the nature of different catalytic sites present on supported gold nanoparticles. We have noticed, however, that although catalytic multicomponent reactions for efficient organic synthesis are recognized as an atom-economic route to green chemistry, the possibilities offered by supported gold catalyst have scarcely been explored to date.^[6] We show herein that the appropriate choice of heterogeneous gold catalysts offers unique possibilities for multicomponent reactions.

Propargylamines are versatile synthetic intermediates in organic synthesis and are also important structural elements in natural products and therapeutic drug molecules.^[7a-c] These compounds have traditionally been synthesized by nucleophilic attack of lithium acetylides or Grignard reagents on imines or their derivatives.^[7d,e] However, these reagents must be used in stoichiometric amounts, are highly moisturesensitive, and require strictly controlled reaction conditions. An alternative atom-economical approach to their synthesis is to perform this type of reaction by a catalytic coupling of alkyne, aldehyde, and amine (A³ coupling) by C-H activation, where water is the only theoretical by-product.^[8] Recent progress in this area has been reported using homogeneous catalysts such as gold salts (AuBr₃ or AuCl),^[9a] organic gold complexes,^[9b] silver salts,^[10] copper salts,^[11a-c] Hg₂Cl₂,^[11d] and a Cu/Ru^{II} bimetallic system,^[11e] among which the cationic gold species showed the highest catalytic activity.^[9] However, besides the potential limitations of homogeneous catalysis for

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achieving a sustainable catalytic process, the rapid reduction of cationic gold species into inactive metallic atoms is unavoidable when gold salts activate alkynes/alkenes.^[2b,c,3] Heterogeneous catalysts may therefore be an attractive solution to this problem, although the very limited number of examples reported for the A³ coupling thus far show very low activity (turnover number (TON) \leq 33).^[6,12] Since catalysis with gold salts/complexes indicates that Au^{III} and Au^I could be the most active species,^[9] we have prepared supported gold catalysts in which partially charged and electron-deficient gold atoms are stabilized and show that Au nanoparticles supported on nanocrystalline ZrO₂ and CeO₂ are highly active, selective, and recyclable catalysts for the A³ coupling reaction with water as solvent. The direct synthesis of functionalized indoles by three-component coupling and cyclization is also presented.

Benzaldehyde, piperidine, and phenylacetylene were used as model substrates to study the catalytic activity of the different supported gold catalysts. The results of these studies (Table 1) show that gold supported on SiO₂ or carbon leads to low conversion ($\leq 13\%$). The Au/TiO₂ and Au/Fe₂O₃ catalysts supplied by the World Gold Council show moderate activity, while gold (2–5 nm) supported on nanocrystalline CeO₂ (approx. 5 nm) and ZrO₂ (5–10 nm) give the highest conversion ($\geq 95\%$), with yields of isolated product of between 93 and 100%. No conversion was found in the absence of catalyst under identical conditions.

In a first approximation, the differences in the catalytic activity observed might appear to be correlated with the

Table 1: Three-component coupling of benzaldehyde, piperidine, and phenylacetylene with supported gold catalysts.^[a]



| 0.2% Au/SiO ₂ | 0.013 | < 5 | - | - |
|--|--|--|--|---|
| 3.0% Au/C | 0.081 | 13 | n.d. | 161 |
| 1.5 % Au/TiO ₂ | 0.075 | 35 | n.d. | 464 |
| 4.5 %Au/Fe ₂ O ₃ | 0.247 | 40 | n.d. | 162 |
| 2.8% Au/ZrO ₂ | 0.142 | 95 | 93 | 668 |
| 2.5 % Au/CeO ₂ | 0.127 | 100 | >99 | 788 |
| | 0.2% Au/SiO ₂ 3.0% Au/C 1.5% Au/TiO ₂ 4.5%Au/Fe ₂ O ₃ 2.8% Au/ZrO ₂ 2.5% Au/CeO ₂ | 0.2% Au/SiO2 0.013 3.0% Au/C 0.081 1.5% Au/TiO2 0.075 4.5%Au/Fe2O3 0.247 2.8% Au/ZrO2 0.142 2.5% Au/CeO2 0.127 | $\begin{array}{cccc} 0.2\% \; Au/SiO_2 & 0.013 & < 5 \\ 3.0\% \; Au/C & 0.081 & 13 \\ 1.5\% \; Au/TiO_2 & 0.075 & 35 \\ 4.5\% Au/Fe_2O_3 & 0.247 & 40 \\ 2.8\% \; Au/ZrO_2 & 0.142 & 95 \\ 2.5\% \; Au/CeO_2 & 0.127 & 100 \\ \end{array}$ | $\begin{array}{cccccc} 0.2\%Au/SiO_2 & 0.013 & < 5 & - \\ 3.0\%Au/C & 0.081 & 13 & n.d. \\ 1.5\%Au/TiO_2 & 0.075 & 35 & n.d. \\ 4.5\%Au/Fe_2O_3 & 0.247 & 40 & n.d. \\ 2.8\%Au/ZrO_2 & 0.142 & 95 & 93 \\ 2.5\%Au/CeO_2 & 0.127 & 100 & > 99 \end{array}$ |

[a] Reaction conditions: benzaldehyde (1.0 mmol), piperidine (1.2 mmol), and phenylacetylene (1.3 mmol), H_2O (MiliQ, 1.0 mL), 6 h, 100 °C. [b] The number (e.g. 0.2%) is the mass weight of gold loaded on the support (e.g. SiO₂). [c] Determined by GC analysis based on aldehyde. [d] Yields of isolated product based on benzaldehyde; n.d. not determined. [e] Calculated on the basis of total weight of gold.



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nano-size effect of the gold. This effect can easily be ruled out with our catalysts since, although the gold particles supported on TiO₂, Fe₂O₃, carbon, ZrO₂, and CeO₂ supports are similar in size (2–5 nm; see Figure S1 and Table S1 in the Supporting Information), their catalytic activity is quite different. It must therefore be concluded that there is no direct correlation between the size of the gold particles of the supported catalysts and the activity observed for the A³ coupling reaction. This conclusion agrees very well with the work of Kidwai et al.,^[12a] who found that unsupported gold nanoparticles with average sizes of 10, 20, or 30 nm gave very similar conversions (approx. 90%).

In an attempt to explain the catalytic activity of the different supported gold catalysts, we considered that cationic gold could be the active species, as is the case with homogeneous gold catalysis. If this is so, and taking into account that XPS, FTIR, and EXAFS studies and theoretical calculations have indicated that cationic gold species can be stabilized on $\text{CeO}_2^{[5,13]}$ and $\text{ZrO}_2^{[14,15]}$ but not on silica, carbon (NaBH₄ reduction of a gold precursor), or the gold reference catalysts (calcination at 400 °C in air results in the reduction of cationic gold species to the metal),^[16] it can be assumed that the high catalytic activity observed for Au/ZrO₂ and Au/CeO₂ is due to the presence of positively charged gold species.

To check the validity of this assumption, we prepared a series of Au/CeO₂ and Au/ZrO₂ samples in which the Au^{III}/Au^T (Au^T: total amount of gold) and Au^I/Au^T ratios were varied by reducing the sample with H₂ at 100 and 300 °C for 3 h, respectively. The results, which are presented in Figure 1 a and Table S2 in the Supporting Information, show a direct correlation between the concentration of Au^{III} species and the catalytic activity; no clear correlation was found between the catalytic activity and the concentration of Au^I or Au⁰ (Table S2). Although it is not possible to discard some catalysis by Au^I and Au⁰, their catalytic activity should be much lower than that of Au^{III}.

Considering that Au^{III} is the most active catalytic species when the A^3 coupling reaction is carried out in a homogeneous phase, we compared the catalytic activity of Au/CeO_2 and $AuCl_3$ under the same reaction conditions. It can be seen from Figure 1b and Table S3 that benzaldehyde conversion with $AuCl_3$ is higher than with Au/CeO_2 in the first 2 h and the maximum conversion (80%) is obtained at 2 h, while



Figure 1. A) Correlation between the $Au^{|||}/Au^{T}$ ratio of Au/CeO_{2} (**A**) and Au/ZrO_{2} (**B**) and the TON calculated on the basis of total gold. b) Comparison of the catalytic activity of $AuCl_{3}$ (**•**) and Au/CeO_{2} (**□**) catalysts under identical reaction conditions (benzaldehyde (2.0 mmol), piperidine (2.4 mmol), and phenylacetylene (2.6 mmol), H₂O (1.0 mL), 100°C; Au/CeO_{2} : 5 mg; $AuCl_{3}$: 1.8 mg).

benzaldehyde conversion increases continuously up to 99% with Au/CeO₂ over 12 h. This result indicates that AuCl₃ is deactivated in the first 2 h and is decomposed or reduced into metallic gold,^[2b,c,3] whereas no significant deactivation of Au/ CeO₂ is found. The turnover frequencies (TOFs) calculated on the basis of total gold (1645 h^{-1}) and Au^{III} ions (5674 h^{-1}) are significantly higher than that of AuCl₃ (635 h^{-1}) when working at low levels of benzaldehyde conversion (<31 % at 0.17 h); the maximum TONs calculated on the basis of total gold (3120) and Au^{III} ions (10760) of Au/CeO₂ are one and two orders of magnitude higher than that of $AuCl_3$ (273), respectively (see Table S3). Although 100% conversion has also been reported with much larger amounts of AuBr₃ under similar reaction conditions,^[9a] our results indicate that the TON and TOF obtained with Au/ZrO2 and Au/CeO2 are much higher than those of gold salts/complexes, copper/silver salts, and others (TON ≤ 100).^[9-11] It has also been reported that unsupported Au and Ag nanoparticles (TON \leq 10),^[12a,b] gold on layered double hydroxide (LDH-AuCl₄, TON < 33),^[6] or hydroxyapatite-supported Cu $(TON < 8)^{[12c]}$ are active catalysts for the A³ coupling reaction. However, the results presented above clearly show that the activity of our Au/ZrO₂ and Au/CeO₂ catalysts is two orders of magnitude higher than those of these previously reported solid catalysts.^[6,12]

It should be noted that these Au/ZrO₂ and Au/CeO₂ catalysts can work in a variety of organic solvents (methanol and tetrahydrofuran), where they lead to more than 80% conversion. Nevertheless, the reaction in water is very clean and this is the solvent of choice. In contrast to homogeneous gold, silver, copper, or unsupported Au nanoparticles,^[9-12] Au/CeO₂ and Au/ZrO₂ do not require an inert atmosphere.

To examine the scope of the A³ coupling reaction with Au/ CeO₂ and Au/ZrO₂, we extended our studies to different combinations of aldehydes, amines, and alkynes. As depicted in Table 2, aromatic aldehydes give excellent yields in the A³ coupling reaction (entries 1-7). Benzaldehydes with electrondonating groups react smoothly (entries 2-4), while substitution of electron-withdrawing groups on the benzene ring decreases the reactivity (entries 5-7). High yields are still generally obtained in the latter case except for with 4nitrobenzaldehyde, which contains a strongly electron-withdrawing group (entry 8), although longer reaction times are needed. Notably, aliphatic aldehydes such as cyclohexanecarboxaldehyde, butylaldehyde, and octylaldehyde also display very high activity, with yields of 99, 85, and 95%, respectively (entries 9-11). While unwanted trimerization of aliphatic aldehydes is a major limitation of the A³ coupling reactions catalyzed by homogeneous catalysts,^[9-11] no trimer could be detected with the supported gold catalyst.

The reaction with secondary amines proceeded smoothly to afford the corresponding propargylamines (Table 2, entries 12–15). The reactions with piperidine and pyrrolidine resulted in complete benzaldehyde conversion with a yield higher than 99%. The A³ coupling reactions with chiral amines were also successful, with yields of more than 97% and excellent diastereoselectivities (up to 99:1) obtained with (S)-(+)-2-pyrrolidinemethanol and (S)-(+)-2-(methoxymethyl)pyrrolidine (entries 16–18). (S)-(+)-2-methylpiperidine afforded up to 87% yield with good diastereoselectivity

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Table 2: Coupling of an aldehyde, alkyne, and amine catalyzed by Au/ CeO₂ and Au/ZrO₂ in water.^[a]

| | | т D4 | Au/CeO ₂ , Au/Z | ZrO ₂ | \downarrow | |
|-------|--------------------------------------|------------------------|-----------------------------------|------------------|-------------------------|----------------------|
| к -сп | | - K — — – | H ₂ O | F | R1 1 | |
| | | | | | | |
| Entry | R ¹ | $R^2 R^3 N H^{[b]}$ | R ⁴ | <i>T</i> [h] | Yield ^[c] (e | d.r.) ^[d] |
| 1 | Ph | piperidine | Ph | 6 | >99% | |
| 2 | $4-MeC_6H_4$ | piperidine | Ph | 6 | 90 % | |
| 3 | $4-MeOC_6H_4$ | piperidine | Ph | 8 | 93 % | |
| 4 | 3,4-MeOC ₆ H ₄ | piperidine | Ph | 12 | 90 % | |
| 5 | 4-CNC ₆ H ₄ | piperidine | Ph | 12 | 99 % | |
| 6 | 2-BrC ₆ H₄ | piperidine | Ph | 12 | 95 % | |
| 7 | $4-CIC_6H_4$ | piperidine | Ph | 12 | 97% | |
| 8 | $4-NO_2C_6H_4$ | piperidine | Ph | 14 | 26% | |
| 9 | Cyclohexyl | piperidine | Ph | 6 | > 99% | |
| 10 | Propyl | piperidine | Ph | 14 | 85 % | |
| 11 | Heptyl | piperidine | Ph | 14 | 95 % | |
| 12 | Ph | pyrrolidine | Ph | 6 | > 99% | |
| 13 | Ph | R^2 , $R^3 = PhCH_2$ | Ph | 6 | 92 % | |
| 14 | Ph | R^2 , $R^3 = Allyl$ | Ph | 8 | 93 % | |
| 15 | Ph | morpholine | Ph | 12 | 83 % | |
| 16 | Cyclohexyl | M1 | Ph | 6 | 99 % | (99:1) |
| 17 | Heptyl | M1 | Ph | 6 | 97% | (99:1) |
| 18 | Heptyl | M2 | Ph | 6 | 99 % | (99:1) |
| 19 | Cyclohexyl | M3 | Ph | 6 | 82 % | (82:18) |
| 20 | Heptyl | M3 | Ph | 6 | 87% | (84:16) |
| 21 | Ph | piperidine | $4-MeOC_6H_4$ | 6 | 99 % | |
| 22 | Ph | piperidine | 4-ClC ₆ H ₄ | 6 | 77% | |
| 23 | Ph | piperidine | (CH ₃) ₃ C | 6 | 25 % | |
| 24 | Cyclohexyl | piperidine | (CH ₃) ₃ C | 4 | 85 % | |
| 25 | Heptyl | piperidine | (CH ₃) ₃ C | 4 | 95 % | |
| 26 | Heptyl | piperidine | butyl | 4 | 90 % | |
| 27 | Cyclohexyl | piperidine | butyl | 4 | 99 % | |
| 28 | Cyclohexyl | piperidine | (CH₃)₃Si | 4 | 88% | |

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.2 mmol), and alkyne (1.3 mmol), Au/CeO₂ (gold: 0.00127 mmol for entries 1–15 and 21–23; 0.0025 mmol for entries 16–20), Au/ZrO₂ (gold: 0.0025 mmol for entries 24–28) H₂O (MilQ, 1.0 mL), 100°C (120°C for entries 24–28). [b] Chiral amines denoted as M1, M2, M3 are (S)-(+)-2-pyrrolidinemethanol, (S)-(+)-2-(methoxymethyl)pyrrolidine, and (S)-(+)-2-methylpiperdine, respectively. [c] Yields of isolated product based on aldehyde. [d] Determined by ¹H NMR spectroscopy and/or GC; the absolute configuration was not determined.

(entries 19 and 20). Considering that chiral propargylamines are present in many important bioactive compounds,^[7] these results open up new possibilities for the application of supported gold catalysts to the synthesis of chiral compounds.

Good to excellent yields were generally obtained for aryl alkynes (Table 2, entries 1–22), although the reactivity is a little lower in the case of aliphatic alkynes. Yields of 85-95%were obtained using cyclohexanecarboxaldehyde and octylaldehyde at 120 °C, and excellent yields can also be obtained with *n*-hexyne and (trimethylsilyl)acetylene in combination with octylaldehyde and cyclohexanecarboxaldehyde at 120 °C (Table 2, entries 24–28).

The selective synthesis of functionalized indoles by using N-protected ethynylaniline instead of phenylacetylene and paraformaldehyde as the aldehyde, in dioxane, gave the 2-(aminomethyl)indole derivative in 95% yield with no formation of the expected propargylamines (Table 3, entry 1). Paraformaldehyde can be exchanged for aldehydes such as

Table 3: Three-component coupling and cyclization of an aldehyde, amine, and N-protected ethynylaniline.^[a]

| | | Au/ZrO ₂ | N I Ts | $<_{R^1}^{NR^2R^3}$ |
|-------|----------------------|---------------------|--------------|----------------------|
| Entry | R ¹ -CHO | R^2R^3NH | <i>T</i> [h] | Yield ^[b] |
| 1 | $(HCHO)_n (R^1 = H)$ | piperidine | 6 | 95 |
| 2 | Heptyl | piperidine | 6 | 97 |
| 3 | Cyclohexyl | piperidine | 6 | 75 |
| 4 | $(HCHO)_n (R^1 = H)$ | pyrrolidine | 6 | 87 |
| 5 | $(HCHO)_n (R^1 = H)$ | morpholine | 6 | 70 |
| 6 | $(HCHO)_n (R^1 = H)$ | diethylamine | 6 | 90 |

[a] Aldehyde (0.20 mmol), amine (0.24 mmol), and N-protected ethynylaniline (0.26 mmol), gold (0.0007 mmol), dioxane (1.0 mL); Ts = toluene-4-sulfonyl. [b] Yields of isolated product based on aldehyde.

octylaldehyde and cyclohexanecarboxaldehyde to give the appropriate three-component coupling and cyclization products in good to excellent yields (Table 3, entries 2 and 3). The reaction with pyrrolidine, morpholine, and diethylamine using paraformaldehyde also goes smoothly to give the respective functionalized indoles in up to 90% yield (Table 3, entries 4–6). Considering that functionalized indoles are prominent core frameworks in biologically active compounds,^[17] this atom-economical strategy towards functionalized indoles opens up a new application for supported gold catalysts that is clearly superior to previously reported reactions using homogeneous Cu and Pd catalysts,^[17] at least from a catalyst separation and reuse point of view.

The stability of Au/CeO₂ was studied by separating and recycling the Au/CeO₂ catalyst. After three successive cycles with intermediate extensive washing with acetone and water, the catalyst activity decreases by around 20%. This decrease is mainly due to the leaching of a small portion of the gold that interacts only weakly with the nanocrystalline CeO₂ support. Further recycling does not produce any further decrease in activity (see the Supporting Information).

We speculate that the reaction mechanism of these supported gold catalysts (Scheme 1) could be the same as that with cationic gold and/or copper under homogeneous conditions.^[9,11b,17d] Thus, the C–H bond of the alkyne is activated by a Au^{III} species stabilized by nanocrystalline CeO₂ or ZrO₂ to give a gold acetylide intermediate (A), which reacts with the immonium ion (B) generated in situ from the aldehyde and secondary amine to give the corresponding propargylamine (C) or indole (D), in the case of alkyne and



Scheme 1. Tentative mechanism for the direct synthesis of functionalized propargylamines (C) and indoles (D) by nanocrystalline CeO_2 or ZrO_2 -stabilized Au^{III}-catalyzed three-component coupling reactions.

N-protected ethynylaniline, respectively, and regenerate the catalytically active site.

In conclusion, a heterogeneous catalyst based on gold supported on nanocrystalline CeO_2 and ZrO_2 has been successfully developed for the A^3 coupling reaction. The catalytic activity (TON and TOF) of Au/CeO₂ and Au/ZrO₂ is the highest reported so far for this reaction and the catalysts are air stable and can readily be recovered and reused. The process is simple and general and produces propargylamines (with high diastereoselectivities for chiral amines) and functionalized indoles in good to excellent yields from alkynes and N-protected ethynylaniline, respectively.

Experimental Section

Catalyst preparation: Au/CeO₂ was prepared by precipitation of HAuCl₄ with NaOH following a procedure described elsewhere.^[5c] Details of the preparation and characterization of the supported gold catalysts are given in the Supporting Information.

General procedure for the three-component coupling reaction: All commercially available reagents were purchased from Aldrich and used as received. The desired amount of supported gold catalyst was added to a mixture of aldehyde (1 mmol), amine (1.2 mmol), and alkyne (1.3 mmol) in 1.0 mL of H₂O (MilQ) with *n*-octane as an internal standard. The A³ coupling reaction was performed in a closed glass reactor (2.0 mL, SUPELCO) with rapid stirring (approx. 1000 rpm) at 100 °C in air. After a given reaction time, the product mixtures were cooled to room temperature and centrifuged. The separated oil was analyzed by GC (the water phase was also analyzed) to determine the aldehyde conversion. The pure product was obtained by flash chromatography and identified by GC-MS and ¹H NMR spectroscopy (see Supporting Information).

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