DOI: 10.1002/cctc.201300695



## Very Small (3–6 Atoms) Gold Cluster Catalyzed Carbon– Carbon and Carbon–Heteroatom Bond-Forming Reactions in Solution

Judit Oliver-Meseguer, Antonio Leyva-Pérez,\* and Avelino Corma\*<sup>[a]</sup>

Gold catalysis has emerged in the last years as a powerful tool in organic synthesis for the construction of new bonds, and gold salts, complexes, and nanoparticles are used as efficient catalysts for many reactions.<sup>[1]</sup> In-depth mechanistic studies have confirmed that the catalytically active gold species are those added at the beginning of many reactions, and in some cases, organogold intermediates have been isolated and characterized.<sup>[2]</sup> However, if one looks into the literature, Au<sup>III</sup> salts, Au<sup>1</sup> salts, and gold complexes are indistinctly used as catalysts for a significant number of reactions, without substantial changes in the overall activity.<sup>[1b,f]</sup> The presence of a gold mirror at the end of the reaction is a common experimental observation that reflects the progressive reduction of gold to monoatomic gold and then to clusters, nanoparticles, and bulk gold and suggests the possibility that the gold(I)/(III) species could only be precatalysts, at least for a number of reactions. In those cases, the catalytic entities would be formed after reorganization and/or reduction of the starting gold species. The aim is then to determine which are the catalytically active gold species and how to synthesize them.<sup>[3]</sup> It was recently shown that gold clusters generated in situ from gold salts and complexes are able to catalyze reactions such as the ester-assisted hydration of alkynes and the bromination of arenes by using the gold clusters in only very small (parts-per-million) amounts.<sup>[4]</sup> Opposite to nanoparticles, these very small gold clusters are molecular entities having defined frontier orbitals, HOMO and LUMO, ready to interact with other molecules. It would then be of interest to investigate if gold clusters are also good catalysts for other representative carbon-carbon and carbon-heteroatom bond-forming reactions in solution that have been performed previously in the presence of gold salts and complexes.<sup>[5-8]</sup> Following this idea, herein we present gold clusters made up of 3-6 atoms that catalyze efficiently the phenol synthesis (C–C),<sup>[5]</sup> the  $\omega$ -bromination of terminal alkynes (C-Br),<sup>[6]</sup> the Conia-ene reaction (C-C),<sup>[7]</sup> and the hydration of alkynes (C–O).<sup>[8]</sup> The use of sub-nanometric gold particles in catalysis is generally restricted to solid-supported systems,<sup>[9]</sup> but here, the gold clusters are generated and stabilized

[a]	J. Oliver-Meseguer, Dr. A. Leyva-Pérez, Prof. A. Corma
	Instituto de Tecnología Química
	Universidad Politécnica de Valencia-Consejo Superior
	de Investigaciones Científicas
	Avda. de los Naranjos s/n, 46022, Valencia (Spain)
	E-mail: anleyva@itq.upv.es
	acorma@itq.upv.es
	Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300695.

in solution.<sup>[10]</sup> Remarkably, the clusters are generated from gold salts, complexes, and/or nanoparticles under the reaction conditions, and their reactivity is equivalent to that of gold clusters formed ex situ followed by their addition to the reaction.

#### **Phenol synthesis**

Hashmi et al. nicely showed that alkynylfurans rearrange to otherwise difficult to prepare phenol derivatives in the presence of gold salts or complexes<sup>[5,11]</sup> (typically 1–5 mol%). Figure 1 A shows that upon performing the reaction under similar conditions to those reported<sup>[5a]</sup> but with a lower amount of AuCl<sub>3</sub> (0.4 mol%), the corresponding product **2** was smoothly formed after an induction time, as evidenced by <sup>1</sup>H NMR spectroscopy at different times. Moreover, MALDI-TOF MS measurements showed that gold clusters were generated in the reac-



**Figure 1.** A) Phenol synthesis catalyzed by AuCl<sub>3</sub> (0.4 mol%). B) Yield-time plot for the phenol synthesis showed in scheme A above (——), and percentage of 3–4 atom gold clusters in solution according to MALDI-TOF MS measurements (----). For a complete set of measurements, see Figure S1. The inset shows a magnification of the induction period when clusters formed. C) Scheme for phenol synthesis by using AuCl as a catalyst in submolar amounts under two different reaction conditions. Compound  $\mathbf{3} = 2$ -methylbut-3-yn-2-ol,  $\mathbf{Ts} = para$ -toluenesulfonyl.

tion medium during the reaction induction period and that the reaction started only after the formation of gold clusters comprising 3–4 atoms (Figure 1B, see also Figure S1 in the Supporting Information).

If 3–4 atom gold clusters are the true active species for the gold-catalyzed phenol synthesis, other gold sources that could evolve with time to form these clusters in situ should also show some activity.<sup>[2a]</sup> We selected AuCl as an alternative starting source of gold, as it has been reported that it catalyzes the synthesis of phenol very poorly at >1 mol% amounts.<sup>[5b]</sup> Figure 1C shows that upon adding a submolar amount (0.2–0.4 mol%) of AuCl to the substrate, the phenol product was obtained in a yield that was not far from that obtained with the use of AuCl<sub>3</sub>, provided that a strong Brønsted acid was also added. MALDI-TOF MS measurements showed that Au<sub>3–4</sub> clusters were formed immediately after acidification of the AuCl solution and that without acid no clusters were formed; accordingly, the phenol synthesis did not proceed.

One can also attempt the reaction with gold nanoparticles either in solution or supported on TiO2. Thus, we performed the phenol synthesis with gold nanoparticles with an average size of 3 nm (Figure S2, Supporting Information); no reaction was observed and gold clusters were not detected in solution. If we leached out the gold nanoparticles from the support and then added the Brønsted acid, Au<sub>3-4</sub> clusters were generated, and the reaction then proceeded. It is believed that gold supported on TiO<sub>2</sub> is not in the form of small clusters but in the form of nanoparticles.<sup>[12]</sup> From these results, we concluded that although 3-4 atom clusters are active, the nanoparticles are not able to catalyze the phenol synthesis. However, it was reported<sup>[13]</sup> that if gold is deposited on CeO<sub>2</sub>, besides the nanoparticles, gold clusters comprising 3-5 atoms could be stabilized. If this is so, then Au-CeO<sub>2</sub>, unlike Au-TiO<sub>2</sub>, should be active in the absence of added acid, and no induction period should be observed. Indeed, it was reported that gold on nanoceria (Au-CeO<sub>2</sub>) is able to catalyze the phenol synthesis,<sup>[11a]</sup> and we observed that with a sample of Au-CeO<sub>2</sub> prepared by following a mild reductive process<sup>[11a]</sup> no induction period occurred. These results are consistent with the possibility that the gold clusters that form on the surface of nanocrystalline CeO<sub>2</sub> are the active species. Thus, taking into account all of the above results, we could conclude that the phenol synthesis reaction proceeds with gold clusters formed in solution or with gold clusters present on the solid catalysts.

#### **ω**-Bromination of alkynes

The activation of alkynes by Lewis acid gold catalysts not only proceeds through a  $\pi$  fashion, as for phenol synthesis and many other examples,<sup>[1f]</sup> but also in a  $\sigma$  fashion through slippage mechanisms. The  $\omega$ -bromination of terminal alkynes catalyzed by gold complexes in solution is a representative example of the  $\sigma$  activation of alkynes.<sup>[6]</sup> Figure 2A shows that upon performing the reaction in the presence of AuPtBu<sub>3</sub>NTf<sub>2</sub> (Tf= trifluoromethanesulfonyl) and by systematically decreasing the amount of gold from 2 to 0.1 mol%, a reaction induction time appeared. Excellent yields of **5** were obtained in all cases. Mon-



Figure 2. A) Conversion-time plot for the  $\omega$ -bromination of phenylacetylene (4) with different amounts of the gold(I) AuPtBu<sub>3</sub>NTf<sub>2</sub> complex catalyst. The inset maximizes the initial time. B) Fluorescence emission spectra of the reaction with 1-dodecyne (6) before (a), during (b), and after (c) the induction time; irradiated at 350 nm. NBS = *N*-bromosuccinimide. DCM = CH<sub>2</sub>Cl<sub>2</sub>.

itoring the reaction by <sup>31</sup>P NMR spectroscopy showed the progressive degradation of the gold complex during the reaction, whereas <sup>19</sup>F NMR spectroscopy showed the concomitant formation of free triflimidic acid (HNTf<sub>2</sub>). According to these spectroscopic measurements, the degradation of AuPrBu<sub>3</sub>NTf<sub>2</sub> provides the two elements needed for the formation and stabilization of the gold clusters: ligand-free gold species and a strong Brønsted acid.

If we start with the hypothesis that the active gold species are formed from the initial gold complex, then those active gold species should be detected if the reaction starts and proceeds, that is, after the induction time. To check this, the bromination of the aliphatic, nonchromophoric alkyne 1-dodecyne (**6**) was performed and followed by GC–MS and absorption and emission UV/Vis spectroscopy. According to the jellium model, gold clusters absorb and emit in a particular wavelength as a function of their size.<sup>[14]</sup> Figure 2B shows the fluorescence emission spectra of the reaction mixture irradiated at 350 nm before, during, and after the induction time. The formation of gold clusters is clearly observed when the bromina-

<sup>© 2013</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tion of 1-dodecyne (**6**) starts but not before, and the size of the clusters formed was calculated to be 3–5 gold atoms according to the jellium model.<sup>[13]</sup> Furthermore, MALDI-TOF MS experiments confirmed the presence of chemical entities with m/z = 1060, which corresponds to Au<sub>5</sub> species (Figure S3, Supporting Information).

CHEMCATCHEM COMMUNICATIONS

Figure 3 shows that colloidal gold nanoparticles (10 $\pm$  2.5) nm in size were also able to catalyze the  $\omega$ -bromination of phenylacetylene provided that HCl was added to the aqueous colloidal solution. UV/Vis spectroscopy and fluorescence measurements confirmed the formation of 5 atom gold clusters



**Figure 3.** A) Bromination–hydration cascade with  $(10\pm2.5)$  nm gold colloidal aqueous solution (0.25 mM, 0.1 mol%) treated with concentrated HCl (1 mol%). B) Photograph and corresponding absorption UV/Vis spectra of the Au colloid before and after the addition of HCl.

after the addition of HCl to the gold nanoparticles and the complete absence of the original plasmon band at approximately 550 nm, as shown in Figure 3B (see also Figure S4, Supporting Information, for the fluorescence and MALDI-TOF MS measurements). An excess amount of NBS together with water present in the reaction medium allowed the in situ gold-catalyzed hydration of the bromoalkyne to give  $\alpha, \alpha'$ -dibromoketone **8** in a single step in reasonable yield after two consecutive gold-catalyzed reactions, one involving  $\sigma$  activation and the other involving  $\pi$  activation.<sup>[6]</sup> Note that product **8** was obtained under the same reaction conditions upon starting directly from bromoalkyne **5** and not from acetophenone **9**, which confirmed that the  $\omega$ -bromination proceeds before hydration.

The photograph in Figure 3 B show that, visually, the red gold colloidal solution turns transparent after acid treatment. Zeta-potential measurements (Figure S5, Supporting Information) revealed that the typical negative potential of stable colloidal solutions ( $\approx -10$  meV) changed to positive values after the addition of the acid. It is well accepted that alkyne  $\sigma$  or  $\pi$  activation by gold involves Lewis species, so it is not surprising

ChemCatChem 0000, 00, 1–7

that the catalytically active gold clusters are cationic in nature, as previously assessed by experimental and computational methods.<sup>[15]</sup>

To confirm the above results, we tested the  $\omega$ -bromination of **4** with different Au clusters prepared by an external laboratory.<sup>[16]</sup> The results show that Au<sub>3-5</sub> and Au<sub>5-7</sub> clusters are active species not only for the bromination but also for the hydration of the triple bond (Figure S6a, Supporting Information), whereas the 2–3 atom gold clusters show an induction period. Fluorescence measurements unveiled that this induction period corresponds to the agglomeration of the Au<sub>2-3</sub> clusters to form catalytically active Au<sub>3-7</sub> clusters (Figure S6b, Supporting Information).

# Ester-assisted hydration of alkynes with HCI-treated gold colloids

If 3–5 atom gold clusters are formed from gold nanoparticles after the addition of HCl, acid-treated gold colloids should be able to catalyze other Lewis acid catalyzed reactions involving the same gold clusters such as the ester-assisted hydration of alkynes that has been reported to be catalyzed by 3–5 atom gold clusters in parts-per-billion amounts.<sup>[7]</sup> Figure 4 shows that HCl-treated gold colloids approximately 5 and 10 nm in size catalyze the formation of **10** without an induction time



**Figure 4.** Yield-time plot for the ester-assisted hydration reaction catalyzed by gold clusters generated from different colloidal solutions after HCl treatment.

with an excellent turnover number and turnover frequency (TON = 10100 and TOF = 5930 h<sup>-1</sup>, respectively), whereas gold colloidal nanoparticles alone do not catalyze the ester-assisted hydration of alkynes. The absence of an induction time indicates that gold salts (chloride) are not formed after the addition of HCl to the colloidal nanoparticles, because in the presence of AuCl or AuCl<sub>3</sub>, an induction time before the reaction should be observed.<sup>[4a]</sup> Notably, the reaction rate was faster for smaller ( $\approx$  5 nm) colloids than for larger ( $\approx$  10 nm) colloids. Additional UV/Vis spectrophotometric and MALDI-TOF MS measurements together with  $\zeta$ -potential values showed that the

<sup>© 2013</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

formation of the clusters depends on the nanoparticle size, as smaller nanoparticles formed clusters more rapidly.

#### **Conia-ene reaction**

Figure 5A shows the Conia–ene reaction, an early example of gold-catalyzed carbon–carbon bond formation.<sup>[7]</sup> In pioneering work, Toste et al. showed that the gold(I) AuPPh<sub>3</sub>OTf complex (3 mol%) catalyzed the intramolecular formation of **12**, whereas AuCl<sub>3</sub> was a very unselective catalyst, and only 30% of **12** 



**Figure 5.** A) Results of the gold-catalyzed Conia–ene reaction of alkyne **11** with different gold catalysts. B) Initial rate dependence on the concentration of the initial AuPPh<sub>3</sub>OTf complex catalyst. C) Initial rate dependence on the concentration of initial AuCl treated with HOTf. Lines are a guide for the eye.

was obtained with a higher loading (10 mol %) of the gold salt after complete conversion.  $\ensuremath{^{[7]}}$ 

Upon changing the amount of AuCl and AuCl<sub>3</sub> introduced to 0.02 mol%, no conversion was observed. However, good yields were obtained if 0.2 mol% of HOTf was added to the gold-containing reaction. Fluorescence analysis showed emission bands corresponding to 3–6 atom gold clusters as soon as the gold(III) salt and the acid were mixed, and if AuCl was em-

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ployed instead of AuCl<sub>3</sub>, a similar result was obtained. MALDI-TOF MS measurements showed the instantaneous and preferential formation of Au<sub>5</sub> species from AuCl and AuCl<sub>3</sub>, provided that HOTf was present in the reaction mixture (Figure S7, Supporting Information). Our results strongly suggest that gold clusters are also able to catalyze the Conia–ene reaction with TON=3500, which is two orders of magnitude higher than that previously reported by using AuPPh<sub>3</sub>OTf under the same reaction conditions.<sup>[7]</sup>

In more specific experiments, it was studied whether the gold AuPPh<sub>3</sub>OTf complex acted merely as a source of the gold clusters or was stable under the reaction conditions. Kinetic experiments with the use of AuPPh<sub>3</sub>OTf as the catalyst did not show any induction time, and Figure 5B shows that a clear first-order dependence of the reaction with respect to the AuP-Ph<sub>3</sub>OTf catalyst was observed upon plotting the initial reaction rate versus the amount of gold complex. In situ <sup>31</sup>P NMR and <sup>19</sup>F NMR spectroscopy measurements of the AuPPh<sub>3</sub>OTf-catalyzed reaction showed that the original signals of the complex remained unaltered after the reaction (Figure S8, Supporting Information) and that a mixture of HOTf, PPh<sub>3</sub>, and AuCl<sub>3</sub> dissolved in CD<sub>2</sub>Cl<sub>2</sub> showed different signals to those obtained with the gold complex. Both the kinetic and spectroscopic results indicated that AuPPh<sub>3</sub>OTf does not decompose under the reaction conditions and that it acts as a Lewis acid species by itself. In any case, as shown above, gold clusters are also active in this reaction, and their TON is two orders of magnitude higher than that of AuPPh<sub>3</sub>OTf.

#### Hydration of alkynes

The use of gold catalysts in amounts lower than 0.1 mol% is rarely reported for gold-catalyzed organic reactions except for reactions involving the formation of carbon-oxygen bonds.<sup>[16]</sup> For instance, Nolan et al. nicely showed that the hydration of alkynes could be catalyzed by a gold(I)-carbene complex in parts-per-million amounts, and this is one of the most efficient gold-catalyzed processes reported so far.<sup>[8]</sup> Upon performing a kinetic study of the gold(I)-carbene-catalyzed hydration of diphenylacetylene (13), we observed a clear induction time, as shown in Figure 6A, B. This result suggests that the gold-carbene complex may not be the actual active species but a very efficient precursor. It was reported that strong acids or silver salts are responsible for the formation of catalytically active gold species form the original gold source, which supports our results.<sup>[17]</sup> Upon following the hydration of nonchromophoric 1-octyne (15) by GC-MS in combination with UV/Vis spectroscopy, it was found that the reaction started only after 3-5 atom clusters were formed and not before, as shown in Figure 6C.

To assess the evolution of the carbene–gold complex, we followed the reaction by in situ <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>19</sup>F NMR spectroscopy in  $[D_8]$ -1,4-dioxane, and the loss of the original signals corresponding to the complex, together with the appearance of new signals corresponding to the free carbene, was observed as the reaction evolved under typical heating conditions (120°C; Figure S9, Supporting Information). These



**Figure 6.** A) Hydration of diphenylacetylene (**13**) in the presence of the gold(I)–carbene AuIPrCI complex (50 ppm) and a silver salt as the catalyst. B) Kinetic profile. The inset shows a magnification of the induction period. C) Absorption UV/Vis and the corresponding emission (inset) spectra for the AuIPrCI-catalyzed hydration of 1-octyne (**15**) just after the induction time.

results suggest that the gold(I) carbene decomposes under the reaction conditions, and as 3-5 atom gold-alkyne clusters are formed after an induction time, the latter could be the catalytically active gold species. If this is so, the gold(I) carbene complex should be an excellent precatalyst for other reactions catalyzed by Au clusters, provided that they decompose in a similar way. In accordance, phenol synthesis was recently performed by using gold carbenes.[17b, 18b] Figure 7 shows that upon using this carbene complex as a catalyst for the Coniaene reaction (Figure 7 A) and for the  $\omega$ -bromination of alkynes (Figure 7 B) good yields of the product were obtained. In all cases, the reaction started just after the gold carbene had decomposed and the gold clusters had formed (Figure S10, Supporting Information). These results strongly suggest the formation of catalytically active 3-5 atom gold clusters from the gold(I) carbene AulPrCl [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] complex under acidic conditions.<sup>[4, 16]</sup> The decomposition of carbene metal complexes under a variety of reaction conditions has been previously reported.<sup>[18]</sup>

In summary, small gold clusters containing 3–6 atoms (submolar) catalyze different carbon–carbon and carbon–heteroatom bond-forming reactions. They can be formed in situ from gold salts, complexes, and nanoparticles under acidic conditions. A sound determination of possible clusters in solution



Figure 7. A) Conia–ene reaction catalyzed by AulPrCl (2 mol%) and HOTf (10 equiv.) at 30 °C. B)  $\omega$ -Bromination of alkynes catalyzed by AulPrCl (2 mol%) and HOTf (10 equiv.) at 30 °C.

for previously reported reactions can only be assessed after accurate kinetic studies, in situ and ex situ spectroscopic measurements, and comparison with preformed gold clusters, as the stability of gold salts and complexes can vary depending on the type of catalyst and the experimental conditions. The results here reported could be expanded not only to other gold-catalyzed reactions but also to other catalytic metal systems.

### **Experimental Section**

Synthesis of 2,3-dihydro-5-methyl-2-[(4-methylphenyl)sulfonyl]-1*H*-isoindol-4-ol (2) by using AuCl<sub>3</sub>: Alkyne 1 (72.3 mg, 0.25 mmol) was added to a solution of the AuCl<sub>3</sub> catalyst (0.4 mol%) in CD<sub>3</sub>CN at room temperature. The reaction was followed by <sup>1</sup>H NMR spectroscopy until a conversion of 56% was reached. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.76 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.52 (q, *J* = 2.4 Hz, 2H), 2.45 (s, 3H), 2.22 (s, 3H), 2.10 ppm (t, *J* = 2.4 Hz, 1H).

Synthesis of 2,3-dihydro-5-methyl-2-[(4-methylphenyl)sulfonyl]-1*H*-isoindol-4-ol (2) by using AuCl and acid: Alkyne 1 (37 mg, 0.125 mmol) was added to a solution of AuCl/HCl or  $HNTf_2$  (0.2 mol%) in CD<sub>3</sub>CN at room temperature. The reaction was followed by <sup>1</sup>H NMR spectroscopy until a conversion of 42 or 30% was reached, respectively.

**ω-Bromination**: AuPtBu<sub>3</sub>NTf<sub>2</sub> (13.6 mg, 0.02 mmol) and NBS (355.6 mg, 2 mmol) were placed in a vial equipped with a magnetic stir bar. The vial was closed with a septum cap and then anhydrous CH<sub>2</sub>Cl<sub>2</sub> (DCM, 2 mL) and the corresponding alkyne, phenylacetylene (**4**; 220 μL, 2 mmol) or dodecyne (**6**; 428 μL, 2 mmol), were added. The resulting suspension was placed in a preheated oil bath at 30 °C and stirred. Aliquots were periodically taken and diluted for GC and UV/Vis analysis in diethyl ether by using dodecane as an external standard. For analysis by NMR spectroscopy, the reaction was performed in CD<sub>3</sub>CN. Product characterization was performed by comparison with pure compounds.

Cascade bromination-hydration reaction with different sizes of Au clusters: NBS (22.5 mg, 0.125 mmol) was placed in a vial equipped with a magnetic stir bar. The vial was closed with a septum cap and then DCM (0.25 mL) and phenylacetylene (4; 14  $\mu$ L, 0.125 mmol) were added. Then, an aqueous solution of Au clusters (100 ppm from a commercial aqueous dilution of 0.1 mm

<sup>© 2013</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

for Au<sub>2-3</sub>, 0.15 mM for Au<sub>3-5</sub>, and 0.05 mM for Au<sub>5-7</sub>) was added, and the mixture was stirred in a preheated oil bath at 30 °C. Direct analysis by GC–MS by using dodecane as an external standard was performed, and product characterization was performed by comparison with pure compounds.

Ester-assisted hydration of 2-methylbut-3-yn-2-yl heptanoate (9) with gold colloids: Alkyne 9 (50 mg, 0.25 mmol) and 2-methylbut-3-yn-2-ol (3; 1 mL, 10 mmol) were placed in a 2 mL vial equipped with a magnetic stir bar. The vial was sealed, and the resulting mixture was stirred for 30 min at room temperature. After 30 min, the Au colloid solution (50 ppm from a commercial aqueous dilution of  $2.5 \times 10^{-4}$  M) was added, and the resulting mixture was stirred at room temperature. Aliquots of 25 µL were periodically removed, diluted in *n*-hexane, and analyzed by GC to follow the progress of the reaction by using dodecane as an external standard. Product 10 was characterized by GC-MS and <sup>1</sup>H NMR, <sup>13</sup>C NMR, and DEPT spectroscopy, and the corresponding spectra agree with those previously reported.<sup>[2]</sup> R<sub>f</sub>=0.65 (n-hexane/ethyl acetate, 8:2); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 2.26$  (dd, J = 9.6, 9.6 Hz, 2 H), 2.04 (s, 3 H), 1.61-1.51 (m, 2H), 1.39 (s, 6H), 1.24 (m, 6H), 0.84-0.80 ppm (m, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.7 (C), 173.0 (C), 83.3 (C), 34.2 (CH<sub>2</sub>), 31.2 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 23.4 (2 CH<sub>3</sub>), 23.2 (CH<sub>3</sub>), 22.3 (CH<sub>2</sub>), 13.8 ppm (CH<sub>3</sub>); GC–MS: *m/z* (%): 215 (1) [*M*+H]<sup>++</sup>, 171 (17), 130, (1), 113 (100), 85 (29), 57 (9), 43 (23).

Conia-ene reaction: A solution of the corresponding catalyst (20 mm, 2 μL, 0.02 mol%) in acetonitrile (for AuCl or AuCl<sub>3</sub>) or DCM (for AuPPh<sub>3</sub>OTf, prepared by metathesis between AuPPh<sub>3</sub>Cl and AgOTf) and a solution of triflic acid (200 mm, 2  $\mu L,$  0.2 mol%) in acetonitrile were added to a sealed vial equipped with a magnetic stir bar. The vial was placed in a preheated oil bath at 30  $^\circ\text{C}$  and a solution of alkyne 11 (18.2 mg, 0.1 mmol) in anhydrous DCM  $(250 \ \mu\text{L}, 0.4 \ \text{m})$  was added. The resulting mixture was stirred at that temperature and aliquots of 10 µL were periodically removed, diluted in diethyl ether, and analyzed by GC-MS to follow the progress of the reaction by using dodecane as an external standard. Methyl 1-acetylcyclopentanecarboxylate (12) was characterized by GC-MS and <sup>1</sup>H NMR, <sup>13</sup>C NMR, and DEPT spectroscopy after purification by column chromatography, and the corresponding spectra agree with those previously reported.<sup>[4]</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta =$  5.29 (t, J=2.4 Hz, 1 H), 5.22 (t, J=2.4 Hz, 1 H), 3.74 (s, 3 H), 2.43 (m, 3 H), 2.21 (s, 3 H), 2.16 (s, 1 H), 1.71 ppm (m, 2 H);  $^{13}\mathrm{C}\ \mathrm{NMR}$ (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 203.5 (C), 171.7 (C), 148.7 (C), 112.2 (CH<sub>2</sub>), 70.4 (C), 52.6 (CH<sub>3</sub>), 35.0 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 26.6 (CH<sub>3</sub>), 24.1 ppm (CH<sub>2</sub>). NMR reaction experiments were performed in CD<sub>2</sub>Cl<sub>2</sub>.

**Hydration of diphenylacetylene (13)**: According to a modified literature procedure,<sup>[5]</sup> [(IPr)AuCl] (31  $\mu$ L of a 1 mg mL<sup>-1</sup> solution in THF, 0.05  $\mu$ mol, 50 ppm) was added to 1,4-dioxane (660  $\mu$ L) in a sealed 2 mL reaction vial equipped with a magnetic stir bar. Then, AgSbF<sub>6</sub> (tip of a spatula) was added, and the reaction mixture was stirred for 1 min. Alkyne **13** (1 mmol, 1 equiv.) was added, followed by the addition of distilled H<sub>2</sub>O (330  $\mu$ L). The reaction mixture was heated for 30 h at 120 °C. Aliquots of 25  $\mu$ L were periodically removed, diluted in DCM, and analyzed by GC–MS to follow the progress of the reaction by using dodecane as an external standard. *R*<sub>f</sub> = 0.63 (*n*-hexane/EtOAc, 8:2).

### Acknowledgements

Financial support by the Severo Ochoa program and Consolider-Ingenio 2010 (proyecto MULTICAT) from Ministerio de Ciencia e Innovación (MCIINN) is acknowledged. J. O.-M. thanks Instituto de Tecnología Química (ITQ) for a postgraduate scholarship. A. L.-P. thanks Consejo Superior de Investigaciones Científicas (CSIC) for a contract.

Keywords: carbon–carbon bond formation  $\cdot$  carbon– heteroatom bond formation  $\cdot$  gold  $\cdot$  molecular clusters  $\cdot$ nanoparticles

- [1] a) A. S. K. Hashmi, G. J. Hutchings, Angew. Chem. 2006, 118, 8064–8105; Angew. Chem. Int. Ed. 2006, 45, 7896–7936; b) A. S. K. Hashmi, Chem. Rev. 2007, 107, 3180–3211; c) D. J. Gorin, F. D. Toste, Nature 2007, 446, 395–403; d) D. J. Gorin, B. D. Sherry, F. D. Toste, Chem. Rev. 2008, 108, 3351–3378; e) S. P. Nolan, Acc. Chem. Res. 2011, 44, 91–100; f) A. Corma, A. Leyva-Pérez, M. J. Sabater, Chem. Rev. 2011, 111, 1657–1712; g) A. Leyva-Pérez, A. Corma, Angew. Chem. 2012, 124, 636–658; Angew. Chem. Int. Ed. 2012, 51, 614–635.
- [2] a) G. Seidel, C. W. Lehmann, A. Fuerstner, Angew. Chem. 2010, 122, 8644–8648; Angew. Chem. Int. Ed. 2010, 49, 8466–8470; b) A. S. K. Hashmi, Angew. Chem. 2010, 122, 5360–5369; Angew. Chem. Int. Ed. 2010, 49, 5232–5241; c) A. Gómez-Suárez, S. P. Nolan, Angew. Chem. 2012, 124, 8278–8281; Angew. Chem. Int. Ed. 2012, 51, 8156–8159; d) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, Organometallics 2012, 31, 644–661; e) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph, F. Rominger, Angew. Chem. 2012, 124, 4532–4536; Angew. Chem. Int. Ed. 2012, 51, 4456–4460.
- [3] a) A. Grirrane, A. Corma, H. García, *Science* 2008, *322*, 1661–1664; b) A. Corma, P. Serna, *Science* 2006, *313*, 332–334.
- [4] a) J. Oliver-Meseguer, J. R. Cabrero-Antonino, I. Domínguez, A. Leyva-Pérez, A. Corma, *Science* 2012, *338*, 1452–1455. For the recent observation of a very high turnover number, see: b) M. C. Blanco-Jaimes, C. R. N. Böhling, J. M. Serrano-Becerra, A. S. K. Hashmi, *Angew. Chem.* 2013, *125*, 8121–8124; *Angew. Chem. Int. Ed.* 2013, *52*, 7963–7966.
- [5] a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, J. Am. Chem. Soc. 2000, 122, 11553–11554; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, Org. Lett. 2001, 3, 3769–3771.
- [6] A. Leyva-Pérez, P. Rubio-Marqués, S. S. Al-Deyab, S. I. Al-Resayes, A. Corma, ACS Catal. 2011, 1, 601–606.
- [7] J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, J. Am. Chem. Soc. 2004, 126, 4526-4527.
- [8] N. Marion, R. S. Ramón, S. P. Nolan, J. Am. Chem. Soc. 2009, 131, 448– 449.
- [9] a) A. A. Herzing, C. J. Kiely, A. F. Carley, P. Landon, G. J. Hutchings, *Science* 2008, *321*, 1331–1335; b) S. Chretien, S. K. Buratto, H. Metiu, *Curr. Opin. Solid State Mater. Sci.* 2007, *11*, 62–75; c) H. Tsunoyama, T. Tsukuda, *J. Am. Chem. Soc.* 2009, *131*, 18216–18217; d) L. Alves, B. Ballesteros, M. Boronat, J. R. Cabrero-Antonino, P. Concepción, A. Corma, M. A. Correa-Duarte, E. Mendoza, *J. Am. Chem. Soc.* 2011, *133*, 10251–10261; e) J. Lu, C. Aydin, N. D. Browning, B. C. Gates, *Angew. Chem.* 2012, *124*, 5944–5948; *Angew. Chem. Int. Ed.* 2012, *51*, 5842–5846; f) Q.-Y. Bi, X.-L. Du, Y.-M. Liu, Y. Cao, H.-Y. He, K.-N. Fan, *J. Am. Chem. Soc.* 2012, *134*, 8926–8933.
- [10] Y. Shichibu, K. Konishi, Small 2010, 6, 1216-1220.
- [11] a) S. Carrettin, M. C. Blanco, A. Corma, A. S. K. Hashmi, *Adv. Synth. Catal.* 2006, *348*, 1283–1288; b) A. S. K. Hashmi, T. Hengst, C. Lothschuetz, F. Rominger, *Adv. Synth. Catal.* 2010, *352*, 1315–1337; c) A. S. K. Hashmi, M. Ghanbari, M. Rudolph, F. Rominger, *Chem. Eur. J.* 2012, *18*, 8113–8119. Recently, better turnover numbers have been reported for a more difficult substrate type: d) A. S. K. Hashmi, A. Loos, S. Doherty, J. G. Knight, K. J. Robson, F. Rominger, *Adv. Synth. Catal.* 2012, *112*, 4469–4506.

<sup>© 2013</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

- [13] C. Jeyabharathi, S. S. Kumar, G. V. M. Kiruthika, K. L. N. Phani, Angew. Chem. 2010, 122, 2987–2990; Angew. Chem. Int. Ed. 2010, 49, 2925– 2928.
- [14] M. Walter, J. Akola, O. Lopez-Acevedo, P. D. Jadzinsky, G. Calero, C. J. Ackerson, R. L. Whetten, H. Gronbeck, H. Hakkinen, *Proc. Natl. Acad. Sci.* USA 2008, 105, 9157–9162.
- [15] a) H. Sakurai, I. Kamiya, H. Kitahara, Pure Appl. Chem. 2010, 82, 2005 2016; b) M. Boronat, A. Corma, J. Catal. 2011, 284, 138 – 147.
- [16] Three different aqueous solutions containing: a) 2–3 Gold atom clusters; b) 3–5 gold atom clusters; c) 5–7 gold atom clusters, were purchased from NANOGAP. See M. J. Rodríguez-Vázquez, C. Vazquez-Vazquez, J. Rivas, M. A. Lopez-Quintela, *Eur. Phys. J. D* 2009, *52*, 23–26.
- [17] a) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, J. Am. Chem. Soc. 2012, 134,

9012–9019; b) A. Gómez-Suárez, Y. Oonishi, S. Meiries, S. P. Nolan, *Organometallics* **2013**, *32*, 1106–1111; c) S. G. Weber, F. Rominger, B. F. Straub, *Eur. J. Inorg. Chem.* **2012**, 2863–2867.

[18] a) A. S. K. Hashmi, *Science* 2012, *338*, 1434; b) M. Albrecht, *Science* 2009, *326*, 532–533; c) R. Lalrempuia, N. D. McDaniel, H. Müller-Bunz, S. Bernhard, M. Albrecht, *Angew. Chem.* 2010, *122*, 9959–9962; *Angew. Chem. Int. Ed.* 2010, *49*, 9765–9768; d) V. Lavallo, R. H. Grubbs, *Science* 2009, *326*, 559–562.

Received: August 20, 2013 Published online on

## COMMUNICATIONS

J. Oliver-Meseguer, A. Leyva-Pérez,\* A. Corma\*

## 

Very Small (3–6 Atoms) Gold Cluster Catalyzed Carbon–Carbon and Carbon–Heteroatom Bond-Forming Reactions in Solution

**Clusters get the gold:** Atomic gold clusters Au<sub>n</sub> (n = 3–6) are very active species (sub-mol%) for gold-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions of interest in organic synthesis. The gold clusters can be formed in situ or generated ex situ and introduced into the reaction media. Salts, complexes, and nanoparticles (NPs) can be used as a starting source of gold. Ts = para-toluenesulfonyl.