ACS Catalysis

Research Article

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Reactivity of Electron-Deficient Alkynes on Gold Nanoparticles

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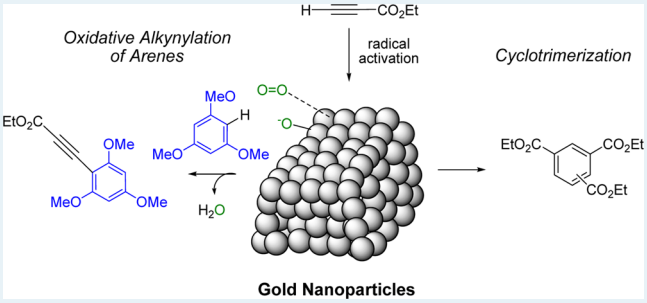
Supporting Information

ABSTRACT: Propiolates cyclotrimerize in the presence of catalytic amounts of gold nanoparticles to give aryl benzoates in high yields and with turnover frequencies of thousands per hour. Types of alkynes other than propiolates do not react, and, if molecular oxygen is present and dissociated by the gold nanoparticles, electron-rich arenes engage with the propiolate to form a new C−C bond. The activation of propiolates and electron-rich arenes to form C−C bonds, beyond gold-catalyzed Michael additions, constitutes a new example of how and where gold nanoparticles modify the electronic density of unsaturated C−C bonds and opens the door to future transformations.



KEYWORDS: *gold catalysis, supported nanoparticles, oxidative alkynylation of arenes, cyclotrimerization, C−H activation*

INTRODUCTION

Gold catalysis has become a trending topic in current research due to the continuous discovery of new transformations and unexpected reaction pathways.[1−3] Different solid-supported and homogeneous gold catalysts have been reported, and although the latter allows a fine-tuning of the electronic/steric properties of the metal through ligand interactions, the former is preferred by economical, practical, and environmental reasons.[4−7] The electronic nature of gold nanoparticles as a function of size, shape, and interaction with the support has been studied for particular reactions, and some structure−activity relationships (SARs) have been made[8−10] though a complete switch of reactivity for a single molecule by fine-tuning the catalytic activity of the nanoparticle is rarely presented. In this regard, the use of additives on the nanoparticle to reach a better reactivity control can offer new opportunities.[11] As illustrated in Scheme 1, we will show that (a) propiolates react selectively on gold nanoparticles to form aryl rings, (b) electron-rich arenes seem to enhance the cyclotrimerization, and (c) both molecules finally engage if the gold nanoparticle is partially oxidized with molecular oxygen.

RESULTS AND DISCUSSION

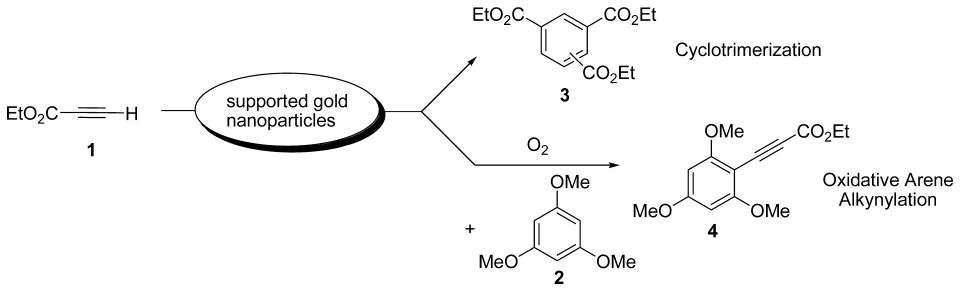
Nature of the gold catalyst. If ethyl propiolate **1** is heated with a catalytic amount of Au−TiO_2 in 1,2-dichlorobenzene under air, the cyclotrimerization reaction occurs in good yields and selectivity, as shown in Figure 1.[12,13] The reaction rate is not improved in nitrogen atmosphere, and no reaction occurs in the presence of other gold-supported catalysts such as Au−CeO_2, Au−Fe_2O_3, Au−Al_2O_3, or Au−carbon, and very little with Au−ZnO (see Supporting Information, Table S1, entries 6−10) under these reaction conditions. A sample of Au−TiO_2 was further reduced with phenylethanol under nitrogen atmosphere and tested in situ for the cyclotrimerization of **1**, and no catalytic differences were found when compared with the H_2-reduced sample (Figure S1 in the Supporting Information).[13] With Au(I) chloride as a catalyst only minor amounts of product were obtained after prolonged times, and Au(III) salts were completely inactive for the cyclotrimerization (entries 11 and 12 in Table S1 in the Supporting Information). A literature search showed that there is only one precedent for the gold-catalyzed cyclotrimerization of alkynes.[14] There, trisalkynegold(I) complexes decompose into cyclotrimerization products after heating in a hexane/dichloromethane (DCM) mixture, and a catalytic amount of $AuSbF_6$ is also able to accomplish the cyclotrimerization of the raw alkyne, but in both cases the yields are <50%.

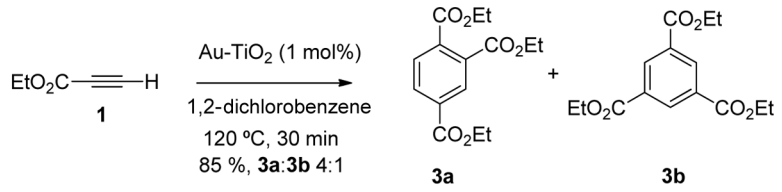
A solvent screening showed that only alkyl hydrocarbons or chlorinated compounds are good solvents for the reaction while coordinating solvents such as dioxane, toluene, or ethyl acetate inhibit the reaction (Table S2 in the Supporting Information). These observations connect with the feasibility of the reaction in hexane/DCM mixtures after decomposition of gold(I) complexes[14] and reflect that gold nanoparticles present a high sensitivity to external coordinating groups when activating alkyne **1** for the cyclotrimerization reaction.

Received: May 15, 2013
Revised: July 3, 2013
Published: July 5, 2013

   dx.doi.org/10.1021/cs400362c | ACS Catal. 2013, 3, 1865−1873

Scheme 1. Different Reaction Pathways for Ethyl Propiolate 1 on Supported Gold Nanoparticles





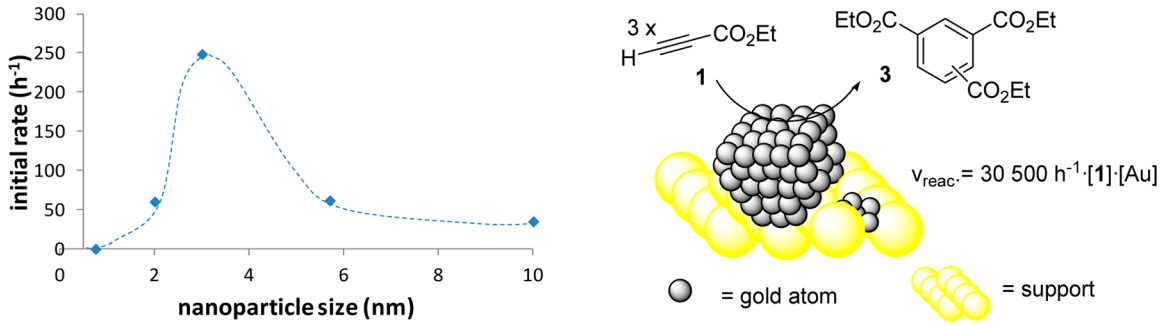


Figure 1. Top: Au−TiO_2-catalyzed cyclotrimerization of **1**. Reaction conditions: **1** (25.3 μL, 0.25 mmol), Au−TiO_2 (1 wt %, 45 mg, 1 mol %), 1,2-dichlorobenzene (0.5 mL, 0.5 M). Mass balances >95%, no other byproducts found. Middle: Initial rate for the cyclotrimerization of **1** as a function of the crystal size for samples containing 1.0−1.5 wt % Au on TiO_2 (left) and schematic drawing on the mechanism including the calculated equation rate (right). Bottom: Initial rate for the cyclotrimerization of **1** as a function of the concentration of Au−TiO_2 catalyst (left) and alkyne **1** (right). Dodecane was used as an external standard.

If the higher catalytic activity found for gold on titania compared to ceria comes from a more pronounced metallic character of gold on the former support, as assessed by X-ray photoelectron spectroscopy (XPS, Figure S2 in the Supporting Information), gold nanoparticles with metallic character should catalyze the cyclotrimerization reaction independently of the support employed. This was confirmed after fully reducing a sample of Au−CeO_2 with phenylethanol in order to generate a more metallic gold (Figure S2 in the Supporting Information), and the catalytic performance of this reduced Au−CeO_2 sample increased for the cyclotrimerization of **1** with respect to that of hydrogen-reduced Au−CeO_2 (Table S1 in the Supporting Information, entry 13). On the other hand, gold subnanoparticles (<1 nm) are quasi-molecular species with a tendency to stabilize positive charges, thus accordingly they should be inactive for the reaction. When a sample of Au−TiO_2 was treated with methyl iodide,[15] the diffuse reflectance ultraviolet−visible (DR-UV−vis) spectrum (Figure S3 in the Supporting Information) showed that only small gold clusters remain on the solid and that the plasmonic gold nanoparticles are absent. When this sample of <0.75 nm gold particle size was submitted to reaction conditions, no cyclotrimerization occurred, suggesting the catalytic activity of metallic gold nanoparticles.

dx.doi.org/10.1021/cs400362c | ACS Catal. 2013, 3, 1865−1873

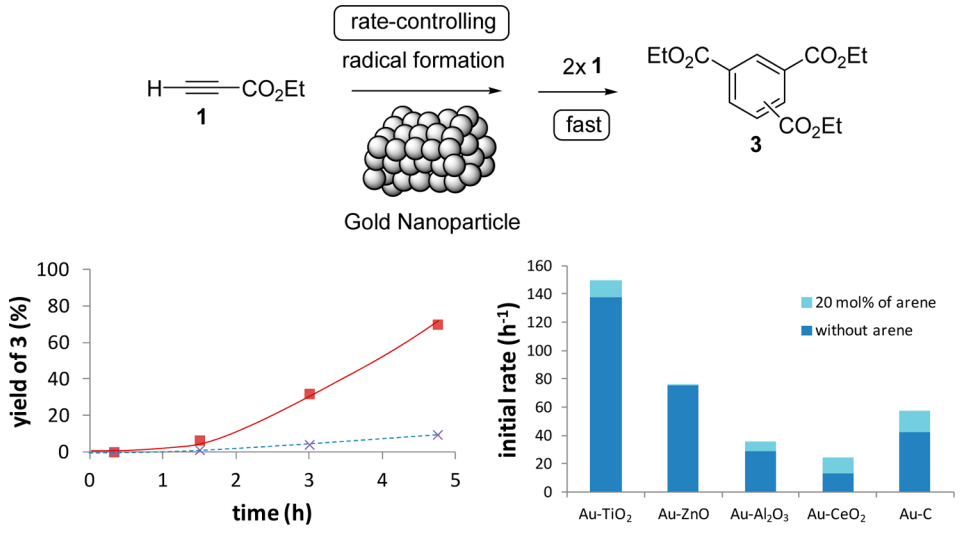


Figure 2. Top: Possible mechanism for the gold-catalyzed cyclotrimerization reaction. Bottom left: Au−CeO_2-catalyzed cyclotrimerization of **1** in the presence (×) or not (□) of 50 mol % of 2,6-di-*tert*-butylcatechol. Bottom right: Initial rate for the Au-supported-catalyzed cyclotrimerization of **1** in the presence or not of 20 mol % of 1,3,5-trimethoxybenzene **2**. Reaction conditions: **1** (67.4 μL, 0.66 mmol), catalyst (0.5 mol %), 1,2-dichlorobenzene (0.66 mL, 1 M), 120 °C. Dodecane was used as an external standard.

With these results in hand, we have to accept that the catalytic activity for the cyclotrimerization of **1** is related to electron-rich Au^0 crystals, and it could very well occur that there is an optimum size of the gold nanoparticle for catalyzing the trimerization reaction. To check this, we prepared and tested different Au−TiO_2 solids with particle sizes ranging from <1 to ∼10 nm,[16,17] and Figure 1 shows that the initial catalytic activity peaks at gold nanoparticles of ∼3 nm and levels off for shorter and larger crystallite sizes. These results indicate that the surface gold atoms on the nanoparticles facilitate the reaction and that crystallites of 3 nm suppose a good compromise between atoms exposed and metallic nature.

Reaction Mechanism. The accepted general mechanism for the cyclotrimerization of alkynes involves the formation of a five-membered organometallic ring that inserts a third alkyne unit to finally collapse into the benzene ring and regenerate the catalyst.[18−26] However, in the case of gold nanoparticles, these crowded organometallic rings are very improbable since gold prefers mono- or bis-coordinated linear structures. Therefore, we may think about an alternative mechanism. For doing that, we decomposed the global reaction process into the elementary steps of the reaction (Figure S4 in the Supporting Information). It is clear that, depending on which is the controlling step, a different kinetic equation could be written. For instance, if the activation of the first alkyne molecule is the rate-limiting step (see Figure 1), then the rate equation will involve the concentration of the alkyne and gold, and a linear correlation between the initial reaction rate and the initial concentration of the alkyne and gold should be observed. Results in Figure 1 show that this is indeed what occurs, confirming that the first step is the rate-limiting. The calculated kinetic rate constant indicates that ∼30 000 catalytic cycles per hour are made in a 1 M solution of gold and alkyne. Dodecane was used as an external standard during the catalytic experiments.

To shed more light on the mechanism, deuterated ethyl propiolate **1**-d^1 was prepared[27a] and used as substrate. The results (also in Figure S4 in the Supporting Information) showed a kinetic isotopic effect (KIE) of 4.2. The observed KIE denotes that the terminal C−H bond is somehow broken during the catalytic cycle and, together with the kinetic equation, gives a possible mechanism for the cyclotrimerization reaction in which the rate-determining step would consist of the σ-activation of **1** on gold, joining a second molecule of alkyne to finally cyclize with the third unit, as shown in Figure 2. In accordance with this rate equation, none of the intermediates were detected during reaction, indicating that the attack to the second alkyne and the final trimerization are much faster than the rate of activation of the first alkyne molecule.

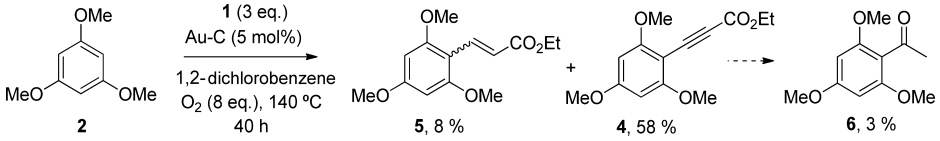
Since the metallic gold atoms present an electron unpairing $6s^1$ configuration that gives a possibility to radical catalysis,[18] the radical inhibitor 2,6-di-*tert*-butylcatechol was introduced in the reaction medium in order to check if the cyclotrimerization on gold is a radical reaction, and the results in Figure 2 show that the reaction was indeed inhibited, which confirms that radical intermediates are present during the catalytic cycle.[27b]

It is not surprising that nanosized gold with metallic character catalyzes the cyclotrimerization of alkynes since other metals reported as catalysts for this reaction lie in low-oxidation states.[19−26] In many cases, arene-type ligands have been employed as electron-donors to stabilize the metal charge.[19b,22−24] We added electron-rich arenes in the reaction medium to test a possible enhancement of the cyclotrimerization reaction, and the results in Figure 2 show that Au supported solids become in general more active for the cyclotrimerization of **1** in the presence of methoxy-substituted arenes. It was also found that this catalytic enhancement is maximized for catalytic amounts of the arene (Figure S5 in the Supporting Information) and decreases as the arene additive becomes less electron-rich, and finally a complete inhibition of the reaction occurs for neutral arenes such as mesitylene.

Carbon−Carbon Bond Forming Reaction. In view that ethyl propiolate **1** and 1,3,5-trimethoxybenzene **2** are probably coadsorbed onto gold nanoparticles, we considered the possibility that both could be engaged in C−C bond forming reactions. On one hand, He and Shi have reported that aromatic rings and propiolates give Michael-type additions after C−H activation of the ring in gold-catalyzed homogeneous conditions.[28] On the other hand, Nevado and de Haro have

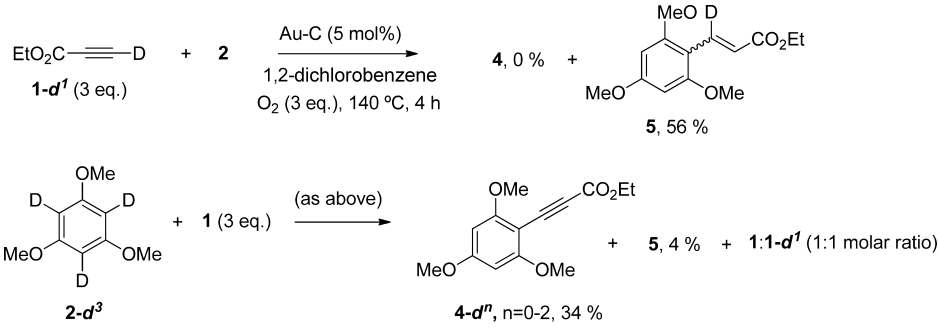
dx.doi.org/10.1021/cs400362c | ACS Catal. 2013, 3, 1865−1873

Scheme 2. Results for the Reaction between Trimethoxybenzene 2 and Ethyl Propiolate 1 in the Presence of Au−C (5 mol %) and Molecular Oxygen[a]

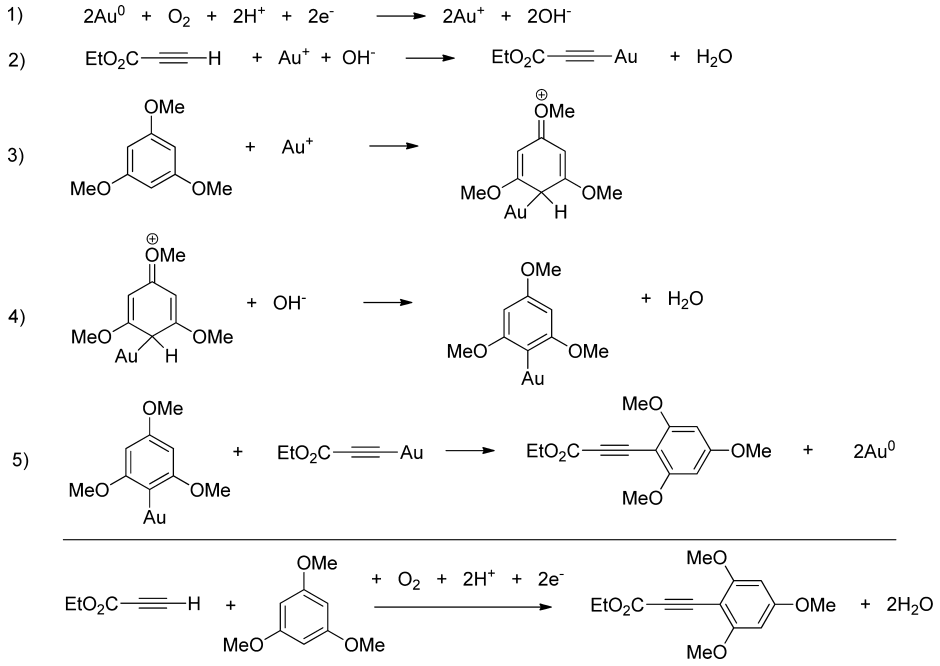


[a]Reaction conditions: **2** (21.0 mg, 0.125 mmol), **1** (38.0 μL, 0.375 mmol), 1,2-dichlorobenzene (0.5 mL). Percentages refer to GC yields. Complete mass balance for the arene and ~80−99% for the alkyne. Reaction stops after **1** is transformed into **3** (not shown).

Scheme 3. Isotopic Experiments for the Oxidative Alkynylation between Trimethoxybenzene 2 and Ethyl Propiolate 1 in the Presence of Gold-Supported Nanoparticles and Molecular Oxygen



Scheme 4. Tentative Mechanism for the Oxidative Alkynylation between Trimethoxybenzene 2 and Ethyl Propiolate 1 in the Presence of Gold-Supported Nanoparticles and Molecular Oxygen



recently reported that gold phosphine complexes catalyze the oxidative alkynylation of electron-rich rings in solution through Au(I)/(III) redox cycles after treatment with strong iodine oxidants and base.[29] Since it has been reported that gold nanoparticles dissociate molecular oxygen on unsaturated atoms to form oxygen reactive species (ORS),[30] it was envisaged that the oxidative alkynylation of the arene may occur on the gold nanoparticle provided that gold could act as a bifunctional catalyst that activates the organic molecules and molecular oxygen at the same time. The ORS released after oxygen dissociation would act as the base needed to quench the protons generated during the reaction. If this was so, it would represent, to our knowledge, the first example of a homogeneous reaction catalyzed by Au(I)/Au(III) redox cycles that is also catalyzed by a gold heterogeneous system.[31] The result in Scheme 2 shows that the oxidative propiolation of **2** to give **4** indeed occurs in reasonable yields with Au−carbon as a catalyst, after optimization (see also Table S3 in the Supporting Information), and that the Michael-type addition reaction does not compete. Minor amounts of product **6**, coming from either the oxidative cleavage of the triple bond or a hydration/retroaldolic sequence in **4**, were observed in some cases.

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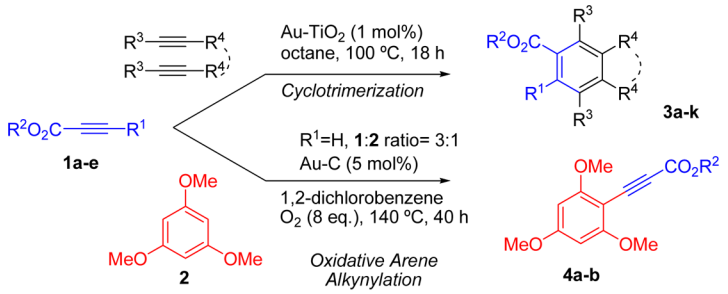


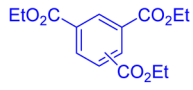
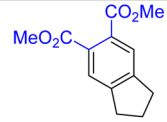
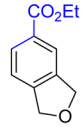
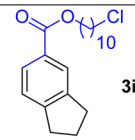
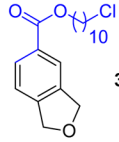
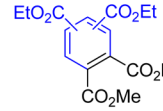
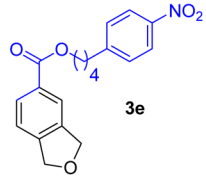
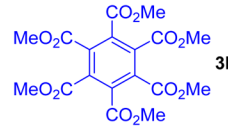
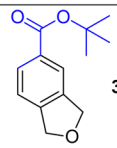
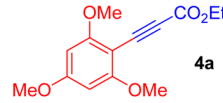
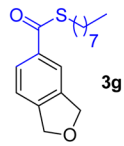
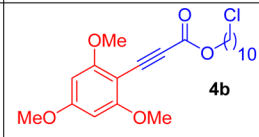
Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 3a-b	90 [85][b]	7	 3h	65[c,d]
2	 3c	[59][c]	8	 3i	75[c]
3	 3d	[85]	9	 3j-k	[75][c,e,f]
4	 3e	53[c]	10	 3l	[64][g]
5	 3f	66[c]	11	 4a	58
6	 3g	62[c]	12	 4b	52

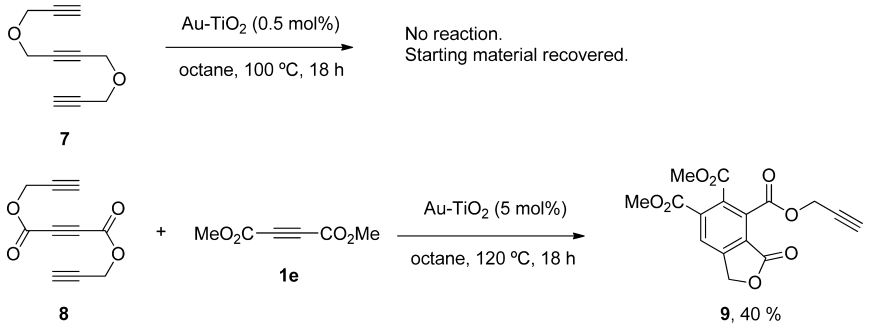
Figure 3. Scope for the cyclotrimerization and oxidative alkynylation of different propiolates **1a−e** and trimethoxybenzene **2** in the presence of gold-supported nanoparticles and oxygen. [a]GC yields, between brackets isolated yields. [b]Ratio isomers 4:1; with 0.015 mol % Au, 77% yield; TON, 5000. [c]3 equiv of propiolate. [d]2 mol % Au. [e]5 equiv of **1a**. [f]Ratio of isomers 1:1. [g]Reaction temperature 120 °C.

Experiments with AuCl and $HAuCl_4$ (Table S3 in the Supporting Information, entries 1−2) showed that, as expected,[28] the Lewis-catalyzed Michael addition to form **5** occurs in moderate yields with neat cationic gold, and cationic gold stabilized on CeO_2 and Fe_2O_3 also gave the addition product **5** preferentially to **4** (entries 5−7). These results confirm that the unsaturated gold atoms on the nanoparticles, having a cationic character, catalyze the Michael-type addition, as salts do. To check this, a new experiment was performed in the absence of oxygen (entry 12) and no product **4** was found but only **5** and **3**, which confirms that the oxidative alkynylation only occurs under the action of oxygen and that, otherwise, the Michael-type addition proceeds on the cationic gold present. In order to further check that the oxidative coupling product **4** does not come from the Michael product, the cinnamylic ester **5** was prepared independently[28] and introduced under oxidative conditions. No reaction was observed in that case. With these results in hand, in principle, cationic supported gold remains aside of the oxidative process. Oxygen dissociation on small gold nanoparticles has been proved elsewhere,[31] and electrovoltammetry of the Au−carbon solid confirmed the feasibility of the redox process.[32,33]

Deuterated ethyl propiolate **1**-d_1 was prepared and Scheme 3 shows that the oxidative alkynylation is inhibited when this was used as a reactant, only Michael addition occurring. Notice that **1**-d_1 also retards the cyclotrimerization reaction (KIE observed), and these results suggest that the deprotonation of the propiolate occurs before the oxidative coupling. If this is so,

dx.doi.org/10.1021/cs400362c | ACS Catal. 2013, 3, 1865−1873

Scheme 5. Failed Cyclotrimerization Reaction of Triyne 7 (Top) and Selective Intermolecular Cyclotrimerization of 8 and 1e (bottom) under Au−TiO_2 Catalyzed Conditions[a]



[a]GC yields.

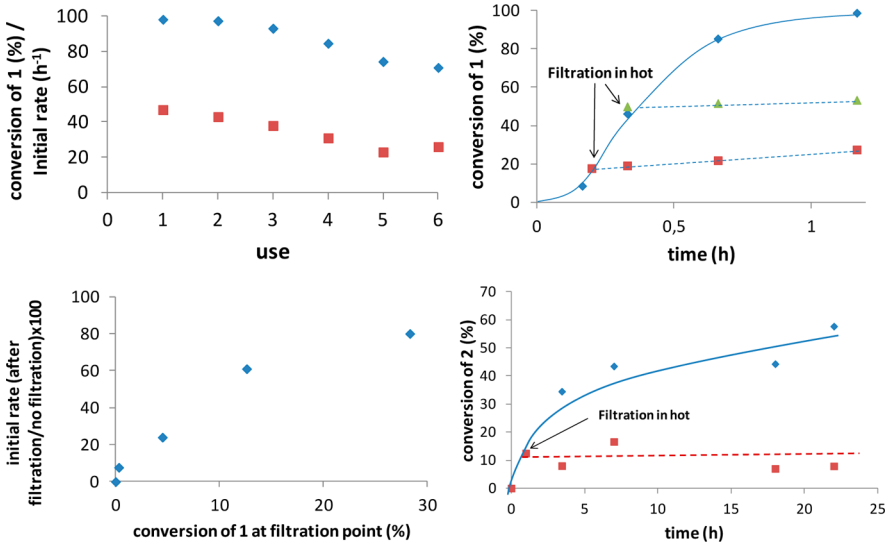


Figure 4. Top left: Reusability of Au−TiO_2 in the cyclotrimerization of **1**, in terms of final yield (◇) and initial rate (□). Top right: Hot filtration test for the cyclotrimerization of **1** by filtering at 20% (□) and 50% (Δ) conversion of **1**. Bottom left: Percentage of contribution in the reaction rate for the cyclotrimerization of **1** of the leached species after filtration of Au−CeO_2. Au−TiO_2 gave similar results. Bottom right: Hot filtration test by filtering at 10% (□) for the oxidative alkynylation of **1** and **2**. Reaction conditions for the cyclotrimerization: **1** (67.4 μL, 0.66 mmol), catalyst (1 mol % left, 0.5 mol % right), *n*-decane (0.66 mL, 1 M), 120 °C. Reaction conditions for the oxidative alkynylation: **1** (38.0 μL, 0.375 mmol), **2** (21 mg, 0.125 mmol), 1,2-dichlorobenzene (0.5 mL), catalyst (5 mol %), 120 °C, molecular oxygen (6 bar, ∼1 mmol, ∼8 equiv). Dodecane was used as an external standard.

the cyclotrimerization should compete with the alkynylation, and this is indeed observed (see Table S3 in the Supporting Information). The results would explain the moderate conversion of arene **2** since propiolate consumption occurs even in high excess.

Trimethoxybenzene **2**-d_3 was also prepared and tested in reaction, and Scheme 3 shows that hydrogen exchange was also observed, even in the absence of the gold catalyst. Deuterium scrambling between **2**-d_3 and **1** confirms somehow the interaction of the arene with gold. Nevertheless, none of these two processes are the rate-limiting step of the reaction since the H-exchange rate is much faster than the coupling rate (seven times faster for the arene), so it must be assumed that the final coupling constitutes the rate-limiting step.

A tentative mechanism for the alkynylation of trimethoxybenzene **2** on Au−carbon is depicted in Scheme 4. The different steps proposed are supported by kinetic, isotopic, and spectroscopic experiments. Overall, small gold nanoparticles dissociate molecular oxygen, probably only in the presence of the reactants, to give basic ROS that neutralize the protons released by the alkyne and the arene after gold activation, and a final reductive elimination process engages both molecules into a new C−C bond and regenerates the metallic gold sites. This reaction pathway is in accordance with one proposed by Nevado and de Haro in solution.[29]

Scope of the Reactions. Now it seems possible to control the reactivity of propiolates toward the cyclotrimerization reaction or the oxidative alkynylation of arenes by using the appropriate gold-supported nanoparticles under oxygen or not. A brief scope of the reactions was evaluated after preparing different propiolates,[34] and the results in Figure 3 reveal that the propiolates engage intermolecularly with different diynes for the cyclotrimerization reaction and also with the arene **2** for the oxidative coupling in good yields. Remarkably, a turnover number (TON) of 5000 can be obtained for the cyclotrimerization of **1** which constitutes, as far as we know, the highest recorded for an intermolecular cyclotrimerization of alkynes.

Different functionalities including ether, chloride, and nitro groups are tolerated under the reaction conditions. Dimethy-

dx.doi.org/10.1021/cs400362c | *ACS Catal.* 2013, 3, 1865−1873

lacetylene dicarboxylate (DMAD) **1e** reacts with other alkynes (**3h**, **3j**−**k**) and with itself (**3l**) when forcing the reaction conditions. The reactivity of internal alkynes strongly supports a radical mechanism. In any case, the cyclotrimerization does not proceed unless one of the partners is a propiolate. For instance, a benchmark substrate for the cyclotrimerization reaction[12] such as the entropic and sterically favored triyne **7** was prepared[35a] and tested under Au−TiO_2 catalyzed conditions, and the result in Scheme 5 shows that no reaction occurs. However, if the nonreactive internal alkyne is converted in a propiolate such as triyne **8**,[35b] it does react with DMAD **1e** to give the cyclotrimerization product **9** having a free, unreacted, terminal alkyne. Other common cyclotrimerization partners such as nitriles[12] do not react either. These results illustrate the high specificity of Au−TiO_2 toward propiolates.

Catalyst Stability and Reusability. At this point, an extensive study on the reusability and stability of the catalyst under reaction conditions was carried out. As shown in Figure 4, Au−TiO_2 could be reused up to six times for the cyclotrimerization of **1** in *n*-decane after filtering the solid just at complete conversion (22 min), but a slight decrease in both the initial rate and final conversion was observed.

Hot filtration tests revealed that no active species are present in solution, but inductively coupled plasma atomic emission spectroscopy analysis of the filtrates and X-ray fluorescence measurements of the reused solid showed that ∼5% of the total gold in the solid was leached to the solution during reaction, which explains the gradual loss of activity. After this result, the possible leaching and activity of gold species in 1,2-dichlorobenzene was scrutinized by filtering the solid at different times and comparing the initial rate before and after filtration. The results in Figure 4 show a progressive contribution of leached species to the catalytic activity, but this contribution is only significant at conversions of **1** >20%, even at long reaction times, which denotes that the initial rate measurements reflect only catalytically active supported gold species. The filtration hot test was also carried out for the oxidative alkynylation of **1** and **2** and revealed that no active species are present in solution with 1,2-dichlorobenzene as a solvent, which confirms that the catalytic process occurs onto the solid. The presence of inactive gold in solution during the reaction fits well with the lack of catalytic activity of uncoordinated atoms on the solid since the latter are easily leached into the solution. A similar effect has been observed for gold-catalyzed Sonogashira reactions.[4a,b]

■ CONCLUSIONS

Propiolates give different reactions on supported gold nanoparticles depending on the nature of the particle and the amount of oxygen present: cyclotrimerization products on metallic nanoparticles, Michael additions with 1,3,5-trimethoxybenzene on cationic gold species, and oxidative alkynylation of 1,3,5-trimethoxybenzene for terminal propiolates if enough molecular oxygen dissociates on the gold nanoparticle.

■ EXPERIMENTAL SECTION

Preparation of the Solid Catalysts. Au−TiO_2[16,17] and Au−CeO_2[4a,6] solids were prepared according to a reported procedure. In some cases gold was incorporated onto the solids by the incipient wetness methodology with a solution of AuCl in acetonitrile, drying in an oven at 100 °C after impregnation and reducing under H_2 at the specified temperature. XPS showed that no chlorides remain on the solid after treatment under hydrogen at high temperature. Alternatively, neat phenylethanol (5 mL per gram of solid) was used as reducing agent in a preheated oil bath at 160 °C for 1 h, washing with acetonitrile and diethyl ether and drying under vacuum. The commercial samples used were supplied by the following: Strem, Aurelite (Au−TiO_2 1 wt %, Au−ZnO, 1 wt %, Au−Al_2O_3 1 wt %); and Johnson-Matthey, Au−CeO_2 (1 wt %) and Au−carbon (2.3 wt %).

Preparation of Propiolates. Ethyl (**1a**, referred to as **1** throughout the text for simplification), *tert*-butyl (**1d**), and dimethyl (**1e**) were supplied by Aldrich. The chloro- and nitro-substituted ones were prepared according to a modified standard procedure[34] as follows. *Synthesis of functionalized terminal propiolates **1b** and **1c**:* A mixture of DCC (2.32 g) and DMAP (0.090 g) in DCM/Et_2O (5/25 mL) was added dropwise over 20 min to a solution of the corresponding alcohol (10.0 mmol) and propiolic acid (0.678 mL, 11.0 mmol) in Et_2O (5 mL) at −30 °C. The reaction mixture was stirred overnight at room temperature and quenched with saturated NH_4Cl (15 mL), and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over magnesium sulfate, concentrated under reduced pressure, and purified by column chromatography to give the corresponding terminal propiolate.

The triynes **7** and **8** were prepared according to reported procedures.[35]

Typical Procedure for the Cyclotrimerization of 1. The solid catalyst (1 mol % of metal respect to **1**) was placed in a 2 mL vial equipped with a magnetic stirrer. 1,2-Dichlorobenzene, *n*-decane, or *n*-octane (0.66 mL) and ethyl propiolate **1** (67.6 μL, 0.66 mmol) were added, and the vial was sealed. The resulting mixture was placed in a preheated oil bath at 120 °C and magnetically stirred for the corresponding time. Aliquots were periodically taken, poured into diethyl ether or CH_2Cl_2 (1.0 mL), filtered through a 0.2 μm PTFE filter syringe if needed, and submitted to GC and GC−MS analysis after dodecane (5.6 μL, 0.05 mmol) was added as external standard. In some cases dodecane (14.6 μL, 0.066 mmol) was added to the reaction as internal standard. At the end of the reaction, diethyl ether or CH_2Cl_2 (1 mL) was added after cooling the vial and the mixture was stirred for a few minutes at room temperature, solids were filtered off, and the resulting filtrates were analyzed as the aliquots. For reusing, *n*-decane (1 mL) was used as a solvent and the solid was washed twice with decane (1 mL) before the next run. The resulting solid after six uses was washed with CH_2Cl_2 (3 mL, 3 times) and dried under vacuum before analyses. Isolation of the products was performed by column chromatography or preparative TLC (15% AcOEt/hexane) to give **3** as a mixture of triethyl benzene-1,2,4-tricarboxylate (**3a**, major) and triethyl benzene-1,3,5-tricarboxylate (**3b**, minor) in a 4:1 ratio. The reaction could be scaled up to 5 mmol without loss of efficiency. Triethyl benzene-1,2,4-tricarboxylate **3a**: colorless oil (40 mg, 60%). R_f (20% AcOEt/hexane): 0.42. GC−MS (*m*/*z*, $M^{+\bullet}$ 294), major peaks found: 294 (11%), 249 (100%), 221 (100%), 193 (90%). IR (cm^{-1}): 2982, 1727, 1307, 1283, 1245, 1110. ^1H NMR (δ, ppm; *J*, Hz): 8.31 (1H, dd, *J* = 1.6, 0.5), 8.10 (1H, dd, *J* = 8.1, 1.6), 7.67 (1H, dd, *J* = 8.0, 0.5), 4.32 (6H, q, *J* = 7.1), 1.32 (9H, t, *J* = 7.1). ^{13}C NMR (δ, ppm): 167.0 (C), 166.4 (C), 164.8 (C), 136.1 (C), 132.5 (C), 132.0 (C), 131.9 (CH), 129.9 (CH), 128.7 (CH), 61.8 (CH_2), 61.7 (CH_2), 61.5 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 13.9 (CH_3). HRMS (ESI) [(M + H)$^+$;

dx.doi.org/10.1021/cs400362c | ACS Catal. 2013, 3, 1865−1873

calculated for $C_{11}H_{15}O_3$: 195.1021] found m/z 195.1014. Triethyl benzene-1,3,5-tricarboxylate **3b**: white solid (10 mg, 15%). R_f (20% AcOEt/hexane): 0.52. GC−MS (m/z, M^+ 294), major peaks found: 294 (27%), 266 (36%), 249 (100%), 238, (24%), 221 (66%), 210 (26%), 193 (31%). IR (cm^{-1}): 2996, 1726, 1718, 1239. ^{1}H NMR (δ, ppm; J, Hz): 8.77 (3H, s), 4.37 (6H, q, J = 7.1), 1.36 (9H, t, J = 7.1). ^{13}C NMR (δ, ppm): 165.0 (C × 3), 134.4 (CH × 3), 131.4 (C × 3), 61.7 (CH_2 × 3), 14.3 (CH_3 × 3). HRMS (ESI) [$(M + H)^+$; calculated for $C_{11}H_{15}O_3$: 195.1021] found m/z 195.1014.

Typical Procedure for the Oxidative Alkynylation. The solid catalyst (5 mol % of metal respect to **2**) and trimethoxybenzene **2** (21 mg, 0.125 mmol) were placed in a double-walled glass 2 mL reactor equipped with a magnetic stirrer and a manometer. 1,2-Dichlorobenzene (0.5 mL) and ethyl propiolate **1** (38.0 μL, 0.375 mmol) were added, and the reactor was closed. Molecular oxygen (6 bar, ∼ 0.9 mmol) was introduced at room temperature, and the resulting mixture was magnetically stirred in a preheated oil bath at 120 °C for the required time. Aliquots were periodically taken, poured into CH_2Cl_2 (1 mL), filtered through a 0.2 μm PTFE filter syringe, and submitted to GC and GC−MS analysis after dodecane (5.6 μL, 0.025 mmol) was added as an external standard. At the end of the reaction, CH_2Cl_2 (1 mL) was added after cooling the reactor and the mixture was stirred for a few minutes at room temperature, solids were filtered off, and the resulting filtrates were analyzed as the aliquots.

Hot Filtration Tests. Two parallel reaction mixtures were followed by GC, taking aliquots periodically, under typical reaction conditions, and one of them was filtered hot at a determined conversion through a 0.2 μm PTFE filter. The resulting filtrates were placed under the same conditions (stirring and temperature) as the original reaction and also followed by GC.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, syntheses and characterization of catalysts, substrates, and products, reaction procedures, additional tables and figures, and NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.L.-P. thanks CSIC for a contract. J.O.-M. thanks ITQ for a postgraduate scholarship. J.R.C.-A. and P.R.-M. thank MECD for the concession of a FPU contract. Financial support by the Severo Ochoa program and Consolider-Ingenio 2010 (proyecto MULTICAT) from MICIINN is acknowledged, and also the King Saud University. P.S. thanks European Union Seventh Framework programme (PIOF−GA−2009−253129).

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