ORGANIC LETTERS

2012
Vol. 14, No. 12
2956–2959

Cyclization of 1,6-Enynes Catalyzed by Gold Nanoparticles Supported on TiO_2: Significant Changes in Selectivity and Mechanism, as Compared to Homogeneous Au-Catalysis

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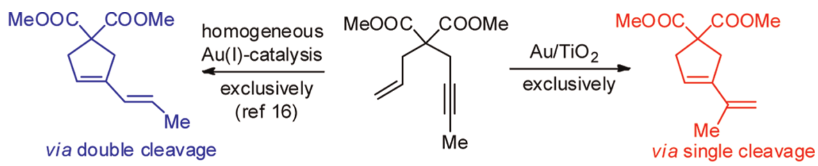
Received April 5, 2012

ABSTRACT



Gold nanoparticles supported on TiO_2 (1.2 mol %) catalyze, for the first time under heterogeneous conditions, the cycloisomerization of a series of 1,6-enynes in high yields. In several cases, the product selectivity differs significantly as compared to homogeneous Au(I)-catalysis. Based on product analysis and stereoisotopic studies it is proposed that the major or exclusive pathway involves a 5-exo cyclization mode to form stereoselectively gold cyclopropyl carbenes that undergo a single cleavage pathway, in contrast to homogeneous Au-catalysis where the double cleavage pathway operates substantially.

The homogeneous Au(I)-catalyzed cyclization of 1,6-enynes has been extensively studied during the past decade, revealing a variety of unprecedented modes of skeletal rearrangements.[1] The puzzling mechanistic peculiarity of cycloisomerizations and the discussions over the nature of the intermediates (carbenes or carbocations) continue to fascinate.[2] Under heterogenized conditions the reaction has been marginally studied. A specific example was recently presented using a gold(I) complex covalently bound on a polystyrene resin that provides the typical product selectivity of homogeneous Au(I) catalysts.[3] The identification of stabilized ionic gold species on metal oxide supported gold nanoparticles (Au NPs),[4] and the fact that epoxides[5] and silanes[6] are readily activated by Au NPs on titania (Au/TiO_2),[7] let us recently examine its catalytic

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(1) Recent review articles: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (b) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (c) Furstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (f) Echavarren, A. M.; Jimenez-Nunez, E. *Chem. Rev.* **2008**, *108*, 3326. (g) Soriano, E.; Marco-Contelles, J. *Acc. Chem. Res.* **2009**, *42*, 1026. (h) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075. (i) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. (j) Echavarren, A. M.; Jimenez-Nunez, E. *Top. Catal.* **2010**, *53*, 924.

(2) (a) Nieto-Oberhuber, C.; Lopez, S.; Jimenez-Nunez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916. (b) Cabello, N.; Jimenez-Nunez, E.; Bunuel, E.; Cardenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217. (c) Furstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (e) Seidel, G.; Mynott, R.; Furstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510. (f) Perez-Galan, P.; Herrero-Gomez, E.; Hog, D. T.; Martin, N. J. A.; Maseras, F.; Echavarren, A. M. *Chem. Sci.* **2011**, *2*, 141. (g) Perez-Galan, P.; Martin, N. J. A.; Campana, A. G.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Asian J.* **2011**, *6*, 482.

(3) Cao, W.; Yu, B. *Adv. Synth. Catal.* **2011**, *353*, 1903.

(4) (a) Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2006**, *348*, 1283. (b) Fierro-Gonzaleza, J. C.; Gates, B. C. *Chem. Soc. Rev.* **2008**, *37*, 2127. (c) Boronat, M.; Concepcion, P.; Corma, A. *J. Phys. Chem. C* **2009**, *113*, 16772. (d) Naya, K.; Ishikawa, R.; Fukui, K.-I. *J. Phys. Chem. C* **2009**, *113*, 10726. (e) Brown, M. A.; Fujimori, Y.; Ringleb, F.; Shao, X.; Stavale, F.; Nilius, N.; Sterrer, M.; Freund, H.-J. *J. Am. Chem. Soc.* **2011**, *133*, 10668.

(5) Raptis, C.; Garcia, H.; Stratakis, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3133.

(6) Lykakis, I. N.; Psyllaki, A.; Stratakis, M. *J. Am. Chem. Soc.* **2011**, *133*, 10426.

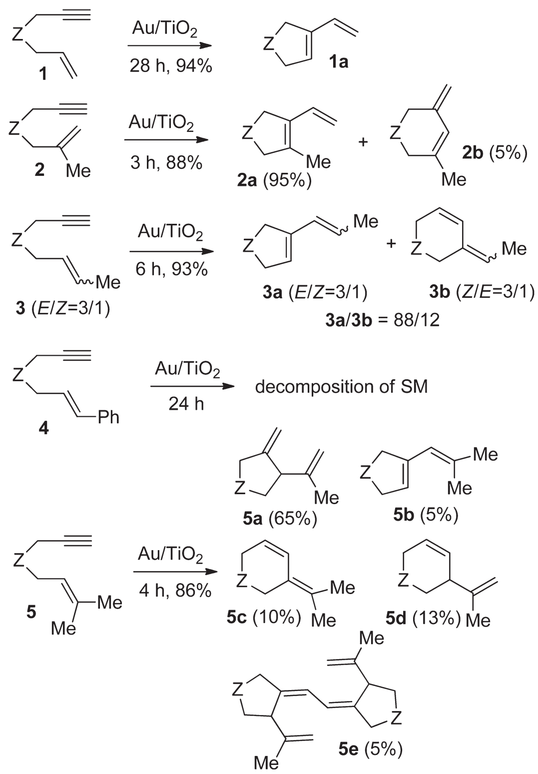
(7) Au/TiO_2 (~1 wt % in Au) is commercially available.

10.1021/ol301212j
Published on Web 06/05/2012

efficiency in heterogeneous alkyne activation. Thus, we found that Au/TiO_2 catalyzes the cycloisomerization of aryl propargyl ethers into (2*H*)-chromenes.[8] Byproducts from oxidative dimerization promoted by molecular oxygen were also formed. It was postulated that formation of (2*H*)-chromenes is catalyzed by positively charged Au species, whereas dimeric 2*H*,2′*H*-3,3′-bichromenes derive via a redox $Au^{III}-Au^{I}$ catalytic cycle. Although Au/CeO_2 have reported to be inactive against 1,6-enyne cyclization,[9] we were prompted to test Au/TiO_2 as a catalyst for such a purpose and develop the first heterogeneous gold-catalyzed approach in this well-studied under homogeneous conditions reaction.

To our delight, gold nanoparticles (1.2% mol in overall Au content) catalyze in high yields the cyclization of a series of 1,6-enynes in refluxing DCE, which provides once more proof for the existence of ionic gold species on Au/TiO_2 as the potent catalytic sites. However, on many occasions the observed product selectivity differs significantly from that under homogeneous Au(I) conditions. The initial examples using 1,6-enynes bearing a simple propargyl moiety are presented in Scheme 1. Parent enyne **1** provides exclusively the five-membered ring carbocycle **1a** in 94% isolated yield. This selectivity resembles its Pd(II)-, Pt(II)-, Ir(I)-, In(III)-, or Ru(II)-catalyzed cyclization[10] in contradiction to homogeneous Au(I)-catalysis,[11] which provides primarily a six-membered ring cyclization product, with **1a** being a minor one. For the case of **2**, diene **2a** is formed as occurs under homogeneous conditions,[12] accompanied by ~5% of **2b**. Crotyl-substituted **3** (E/Z = 3/1) not only led primarily to product **3a**[11] ($E/Z \approx 3/1$) but also formed a minor amount (12%) of the six-membered **3b** ($Z/E \approx 3/1$). Product **3b** had been reported as a minor one in the In-catalyzed cyclization of **3**[10d] and as major in the Ru-catalyzed[13] cyclization. Cinnamyl-substituted **4** decomposes under the reaction conditions suffering oxidative cleavage of the double bond. Enyne **5** mainly affords the nonconjugated diene **5a** (65% relative yield), conjugated diene **5b** (5%), a minor fraction of two six-membered ring isomers **5c** and **5d** (total 23%), oxidative dimerization product **5e**[14] (5%) as an equimolar mixture of diastereomers (*meso* and *dl*), and a small fraction (~2%) of two other dimers (isomeric to **5e**) as revealed by GC-MS analysis. Diene **5a** is produced in the $PtCl_2$-catalyzed cyclization of **5**.[15] Under homogeneous Au(I)-conditions **5a** was seen only if the reaction solvent is polar DMSO,[11] while in DCM **5b** (a minor product under our reaction conditions) is exclusively formed.

Scheme 1. Cyclization of Enynes **1**–**5**[a] Catalyzed by Au/TiO_2[b,c]



[a] Z = $C(COOMe)_2$. [b] 1.2 mol % of catalyst. [c] DCE, 70 °C.

For further exploration we examined the cyclization of internal enynes **6**–**11** (Scheme 2). Generally, their reaction rates are lower; however with one exception high yields were obtained. The cyclization of **6** provides a striking difference among homogeneous and heterogeneous gold catalysis. In the presence of Au/TiO_2, diene **6a** (single cleavage product) is exclusively formed, in contrast to homogeneous Au(I)-conditions, where the isomeric (*E*)-**3a** is formed via a double cleavage rearrangement mechanism.[16] An identical cyclization mode was found in the case of **7** which selectively provides the acid-sensitive carbocycle **7a** in 75% yield. Enyne **8** affords primarily a mixture of five-membered ring allene **8a** (major), the six-membered nonconjugated diene **8b** (minor), and a mixture of three dimeric products (GC-MS) in an approximately 6% relative ratio, which could not be separated and characterized properly. The formation of allenes in the gold-catalyzed cyclization of some benzyl-substituted

(8) Efe, C.; Lykakis, I. N.; Stratakis, M. *Chem. Commun.* **2011**, *47*, 803.

(9) Garcia-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Perez-Ramirez, J.; Lopez, N. *ChemPhysChem.* **2008**, *9*, 1624.

(10) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (c) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433. (d) Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155. (e) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049.

(11) Nieto-Oberhuber, C.; Paz Munoz, M.; Lopez, S.; Jimenez-Nunez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677.

(12) Nieto-Oberhuber, C.; Paz Munoz, M.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

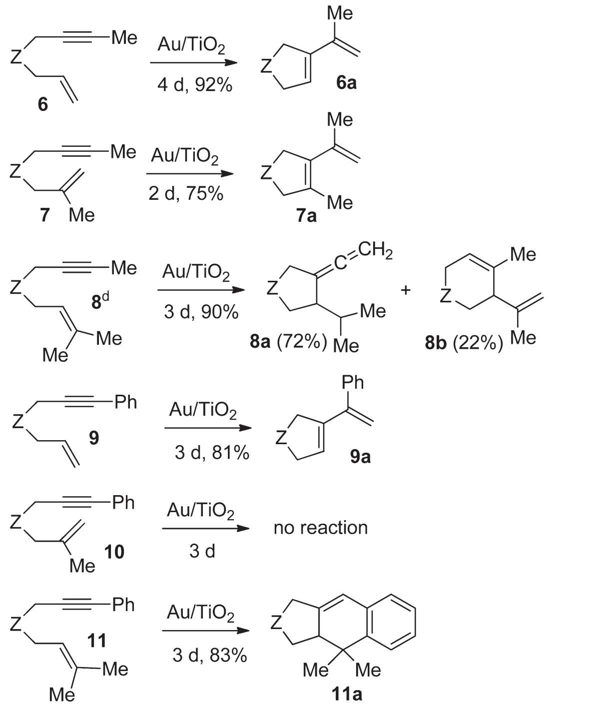
(13) Faller, J. W.; Fontaine, P. P. *J. Organomet. Chem.* **2006**, *691*, 1912.

(14) Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2672.

(15) Mendez, M.; Paz Munoz, M.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511.

(16) Nieto-Oberhuber, C.; Lopez, S.; Paz Munoz, M.; Cardenas, D. J.; Bunuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146.

Scheme 2. Cyclization of Enynes **6**–**11**[a] Catalyzed by Au/TiO_2[b,c]



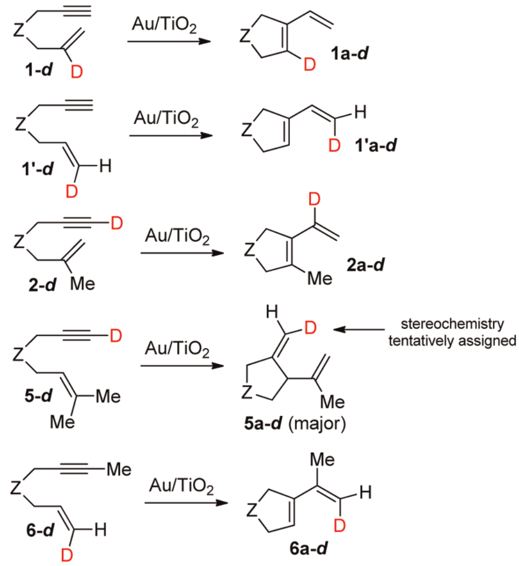
[a] Z = $C(COOMe)_2$. [b] 1.2% mol of catalyst. [c] DCE, 70 °C. [d] A mixture of three products from an oxidative dimerization pathway was also formed in ~6% relative yield (GC-MS analysis).

internal enynes has been recently demonstrated.[17] Concerning phenyl substituted internal enynes, **9** lead to the five-membered ring carbocycle **9a** in 81% isolated yield, in contrast to homogeneous Au(I)-catalysis where a fused bicyclic cyclobutene derivative[18] is primarily formed. It is also known that **9** mainly cyclizes into **9a** yet under Rh(II) catalysis conditions.[19] Substrate **10** was unreactive even under prolonged refluxing conditions, while **11** afforded the fused tricycle **11a** in 83% yield, in accordance to the homogeneous gold catalysis conditions.[2f,18]

Useful mechanistic information was acquired upon studying the Au/TiO_2-catalyzed cycloisomerization of some deuterium labeled 1,6-enynes, presented in Scheme 3. Generally, sp-C deuterium labeled terminal alkynes suffer gradual isotopic depletion under our reaction conditions; thus for substrates requiring a prolonged time to cyclize, mechanistic conclusions could not be drawn.

(17) Harrak, Y.; Simonneau, A.; Malacria, M.; Gandon, V.; Fensterbank, L. *Chem. Commun.* **2010**, *46*, 865.
(18) Nieto-Oberhuber, C.; Perez-Galan, P.; Herrero-Gomez, E.; Lauterbach, T.; Rodriguez, C.; Lopez, S.; Bour, C.; Rosellon, A.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.
(19) Ota, K.; Chatani, N. *Chem. Commun.* **2008**, 2906.
(20) Odabachian, Y.; Le Goff, X. F.; Gagosz, F. *Chem.—Eur. J.* **2009**, *15*, 8966.
(21) (a) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, *2*, 2417. (b) Grirrane, A.; Garcia, H.; Corma, A.; Alvarez, E. *ACS Catal.* **2011**, *1*, 1647. (c) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644.

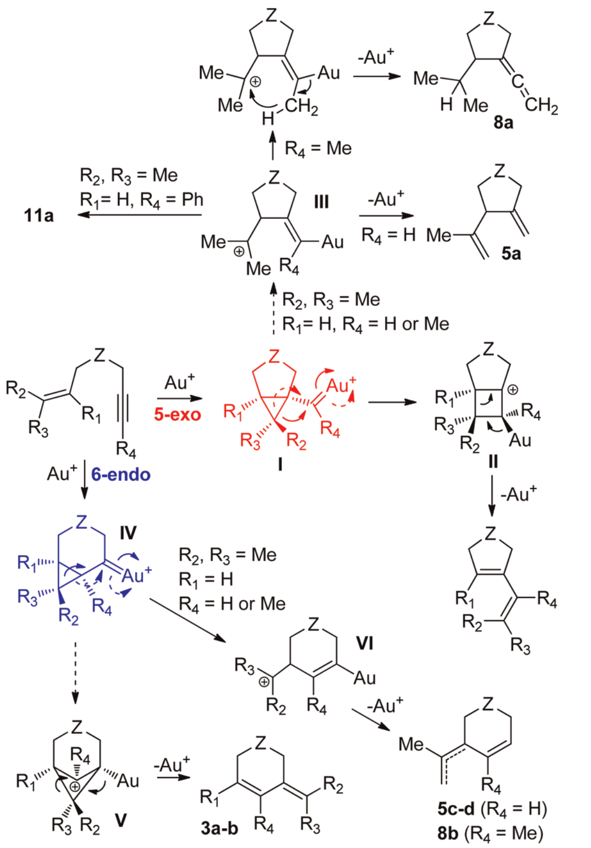
Scheme 3. Cyclization of Some Deuterium Labelled 1,6-Enynes



Partial deuterium exchange in terminal alkynes is also known under homogeneous Au(I)-conditions[20] and most likely involves the reversible formation of Au-acetylides.[21] Despite the partial deuterium depletion[22] on the starting materials for the case of enynes **2-*d*** and **5-*d***, tentative conclusions regarding the disposition of the D-atom were acquired. Thus, in product **2a-*d***, deuterium resides on the exocyclic secondary sp^2-carbon of the pentacycle. In the cyclization of **5-*d***, deuterium is stereoselectively attached on the exocyclic double bond of the major product **5a-*d*** (tentative assignment due to the 70% isotopic depletion in cyclization product; see Supporting Information). An identical stereochemical conclusion has been reported in the cyclization of **5-*d*** catalyzed by a homogeneous Au(I) complex in DMSO.[11] This stereoselective deuterium disposition excluded the participation of an Alder ene- type process. Additionally, the stereoselective introduction of D in the side allyl chain of enynes 1 and 6, either by $LiAlD_4$ addition to propargyl alcohol[23] (synthesis of **1-*d***) or by $LiAlH_4$ addition to propargyl alcohol followed by quenching with D_2O (synthesis of **1′-d** and **6-*d***), was achieved.[24] Regarding the cyclization of **1-*d***, the D-atom appeared exclusively on the endocyclic secondary sp^2-carbon, whereas, for **1′-*d*** and **6-*d***, stereospecific disposition of the stereochemical integrity of the terminal olefinic carbon atom was found in cyclized products **1′a-*d*** and **6a-*d***, respectively.

(22) sp-Deuterium labeled enyne **1** undergoes complete isotopic depletion under the prolonged reaction time of cyclization, not allowing thus any mechanistic conclusions. For labeled **2-*d*** and **5-*d***, approximately 60% and 90% depletion of D respectively was seen on unreacted starting materials at ~90% consumption. After reaction completion, 44% isotope depletion was seen in **2a-*d*** and 70% in **5a-*d***.
(23) Minsek, D. W.; Chen, P. *J. Phys. Chem.* **1993**, *97*, 13375.
(24) The deuterium-content in **1′-*d*** and **5-*d*** was 60%, while, in **1-*d***, it was 95%.

Scheme 4. A General Mechanistic Scenario for the Cyclization of 1,6-Enynes Catalyzed by Au/TiO_2



Prior to the mechanistic discussion, we propose that the stereoselective disposition of H and D in product **5a-*d*** indicates catalysis by monodentate to the enynes, gold(I) bearing, oxidized nanoclusters.[25] Based on the product analysis of Schemes 1−2, and the stereoisotopic results in Scheme 3, we present in Scheme 4 a general mechanistic scenario for the Au/TiO_2-catalyzed cycloisomerization of 1,6-enynes, considering catalysis by Au(I) species. It is clear that in all cases the major pathway is a 5-exo cyclization to form stereoselectively cyclopropyl carbene **I**, as proposed earlier.[1f] Depending on the substituents, **I** may undergo ring expansion to cyclobutyl tertiary carbocation **II** or isomerize to monocyclic **III** (typical example, the cyclization of **5**). Carbocation **II** in turn eliminates Au^+ in a conrotatory fashion[26] (typical examples, the cyclization of **1′-*d*** and **6-*d***). If R_1 = H and R_2, R_3, and R_4 = Me, carbocation **III** undergoes an intramolecular hydride shift[17] to form allene **8a**. A single cleavage pathway (especially in the cyclization of **1** and **6**) forming an exocyclic carbocation, as suggested[2a,b] under homogeneous Au(I)-catalysis conditions, is less likely to participate under our heterogeneous conditions due to the requirement for the formation of a pseudoprimary carbocation (see Supporting Information, p S38). Analogously, the most likely fate of the minor 6-endo cyclization mode is to form stereoselectively cyclopropyl carbene **IV**, which depending on the substituents may lead either to fused bicyclic carbocation **V** or to monocyclic **VI**. The minor products of oxidative dimerization (cyclization of enynes **5** and **8**) more likely arise via a redox $Au^{III}–Au^{I}$ catalytic cycle primarily from deprotonated intermediate **III**, as postulated earlier in the case of aryl propargyl ethers.[8] Therefore, Au/TiO_2 catalyzes the cyclization of non-prenyl-substituted 1,6-enynes exclusively via a single skeletal rearrangement of gold cyclopropyl carbenes into cyclobutyl carbocations, in contrast to homogeneous catalysis by Au(I) and Au(III) complexes or salts that proceed via mixed single and double cleavage pathways.[27] It is possible that the polar support plays a crucial role in our case, through stabilizing the transformation of cyclopropyl carbenes into rearranged cyclobutyl carbocations or, alternatively, their opening into carbocation **III** for the case of prenyl-substituted enynes.

In conclusion, we have presented for the first time a heterogeneous gold-based catalytic approach regarding the cyclization of 1,6-enynes. Product analysis and stereoisotopic studies reveal that the main pathway involves an initial 5-exo cyclization by Au(I) species to form stereoselectively gold cyclopropyl carbenes. Isomerization of carbenes into bicyclic cyclobutyl carbocations via a single cleavage pathway, followed by conrotatory ring opening, results in the stereoselective disposition of the terminal olefinic bond of reacting enynes. Depending on the substituents, ring opening of cyclopropyl carbenes into open carbocations may also take place. By contrast, based on the literature data, in the homogeneous Au-catalyzed cyclization of 1,6-enynes, the double cleavage pathway operates substantially. The current work exemplifies the unique nature of Au nanoparticles in catalysis.[28]

Acknowledgment. This work was supported by the project "IRAKLEITOS II - University of Crete" of the Operational Programme for Education and Lifelong Learning 2007-2013 (E.P.E.D.V.M.) of the NSRF (2007-2013), which is cofunded by the European Union (European Social Fund) and National Resources.

Supporting Information Available. Copies of ^{1}H, ^{13}C NMR of all products and key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) $PtCl_2$ which is bidentate to alkyne and alkene provides opposite stereochemical H/D disposition during the cyclization of enyne **5-*d***. See refs 1g and 15.

(26) (a) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (b) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371.
(27) Nakai, H.; Chatani, N. *Chem. Lett.* **2007**, *36*, 1494.
(28) Zhang, Y.; Cui, X.; Shi, F.; Deng, Y. *Chem. Rev.* **2012**, *112*, 2467.

The authors declare no competing financial interest.