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Tuan-Anh Nguyen, E. Daiann Sosa Carrizo, H el ene Cattey, Paul Fleurat-Lessard, Julien Roger, et al.. Tetranuclear Dicationic Auophilic Gold(I) Catalysts in Enyne Cycloisomerization: Cooperativity for a Dramatic Shift in Selectivity. *Chemistry - A European Journal*, In press, 10.1002/chem.202200769 . hal-03610938

**HAL Id: hal-03610938**

**<https://hal.science/hal-03610938v1>**

Submitted on 16 Mar 2022

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# Tetranuclear Dicationic Auophilic Gold(I) Catalysts in Enyne Cycloisomerization: Cooperativity for a Dramatic Shift in Selectivity

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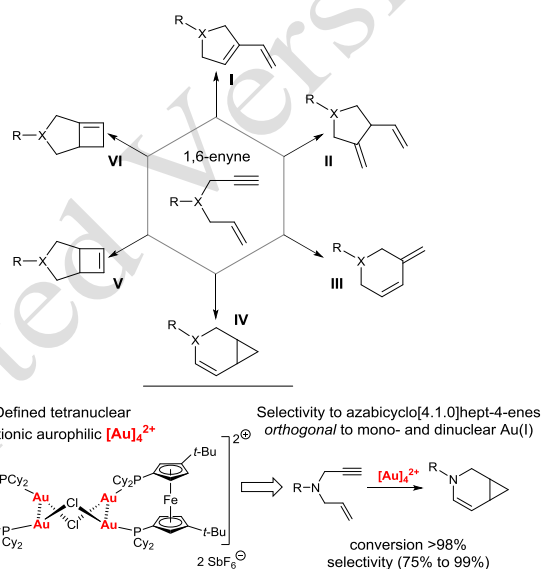
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**Abstract:** In comparison to mononuclear gold Lewis-acid catalysts, digold complexes and dual-gold catalysis have illustrated a distinct and powerful potential for the activation of carbon-carbon multiple bonds. Herein, we pushed this concept further by designing novel tetranuclear gold(I) dicationic complexes structurally supported by strongly stabilizing constraint diphosferocenyl ligands and attractive closed-shell Au...Au aurophilic interactions. The use of a molecularly-defined tetranuclear dicationic aurophilic gold(I) precatalyst for the selectivity-challenging cycloisomerization of low-substituted 1,6-enynes favors the formation with high selectivity of strained azabicyclo[4.1.0]hept-4-enes –even in the complete absence of activating/orienting substituents on alkyne and olefin reactive functions. This selectivity is not achieved by the reported phosphine- and carbene-stabilized mono- and dinuclear cationic gold(I) complexes, including the ones formed from the same ligands. More importantly this selectivity differs also from nanoparticles and heterogeneous gold catalysts reported to date. DFT studies correlated to experimental mechanistic investigations support an unprecedented “cluster-like” reactivity from polynuclear cooperation at the origin of this peculiar selectivity where the aurophilic interactions preexist, and pre-organize, gold cluster reactive intermediates.

## Introduction

Transition metal-catalyzed enyne cycloisomerization is a powerful strategy for the synthesis of functionalized cyclic and polycyclic structures.<sup>[1–5]</sup> The building of structural complexity starting with fairly simple acyclic subunits containing alkyne and olefin moieties has motivated this success (Figure 1, top). Accordingly, gold(I) species are very powerful for the construction of complex molecular architectures under very mild conditions and in short reaction time<sup>[6–21]</sup> via skeletal rearrangement of enynes by Lewis-acidic induced cyclization.<sup>[22–26]</sup> The outcome of the cycloisomerization reaction and its selectivity is strongly influenced by the substitution pattern of the starting enyne and the nature of the catalyst used. On the other hand, digold complexes and dual-gold catalysis have recently illustrated a distinct and powerful potential for the activation of carbon-carbon multiple bonds.<sup>[27–39]</sup> This gave the impetus for designing novel digold(I) complexes based on strongly stabilizing ligands such as tertiary mono- and diphosphines or heterocyclic carbenes,<sup>[27,37–41]</sup> while the attractive closed-shell interactions between d<sup>10</sup>–d<sup>10</sup> pairs of gold atoms – known as Au...Au aurophilic interaction<sup>[42]</sup> might further assist the structuring of digold complexes.<sup>[40]</sup>

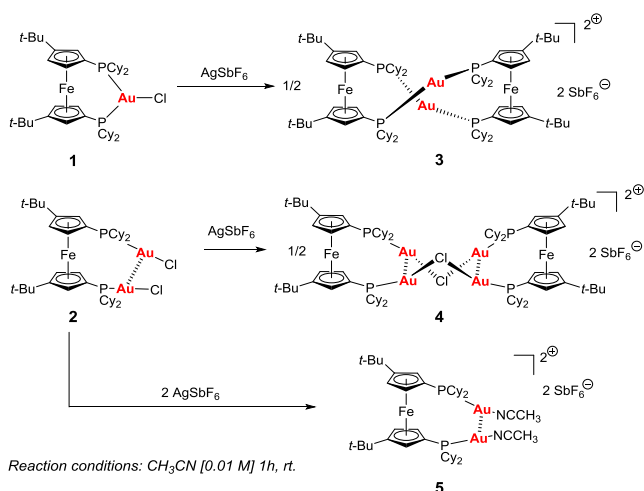


**Figure 1.** Top: general five- or six-membered ring dienes and bicyclic core-structures achievable by 1,6-enyne cycloisomerization. Bottom: unique selectivity to challenging strained azabicyclo[4.1.0]hept-4-ene promoted by tetranuclear Au<sub>4</sub><sup>2+</sup> complexes (this work).

Regarding gold-catalyzed cycloisomerization of 1,6-enynes, mostly mononuclear cationic species have been reported as being useful, whereas the performances of well-defined aurophilic digold(I) complexes have been only recently illustrated.<sup>[41]</sup> To the best of our knowledge, the competence of molecularly-defined higher rank polynuclear complexes, and clusters has never been reported in cycloisomerization of 1,6-enynes, despite the conceivable benefit of pre-organizing gold centers in a constrained environment regarding selectivity outcome in such reactions. This issue is all the more pertinent that, surprisingly, very high but divergent selectivity is also achieved at the surface of heterogeneous gold catalysts and from nanoparticle catalysts.<sup>[43–45]</sup> Herein, we report the use of a molecularly-defined tetranuclear dicationic aurophilic gold(I) catalyst for the selectivity-challenging cycloisomerization of low-substituted 1,6-enynes (Figure 1, bottom). We show that such tetranuclear Au(I) species specifically favors the formation of strained azabicyclo[4.1.0]hept-4-enes with high selectivity –even in the complete absence of activating/orienting substituents on alkyne and olefin reactive functions–, which is usually hardly achieved by phosphine- and carbene-stabilized mono- and dinuclear cationic gold(I) complexes or heterogeneous gold catalysts.

## Results and discussion

The bis(dicyclohexyl)phosphino-ferrocene ligand *rac* **L1** displays a versatile coordination chemistry with gold(I) salts that we exploited in order to synthesize the well-defined complexes **1-5** (Scheme 1) having various gold nuclearity, generally stabilized by aurophilic interactions, and being either neutral or cationic.



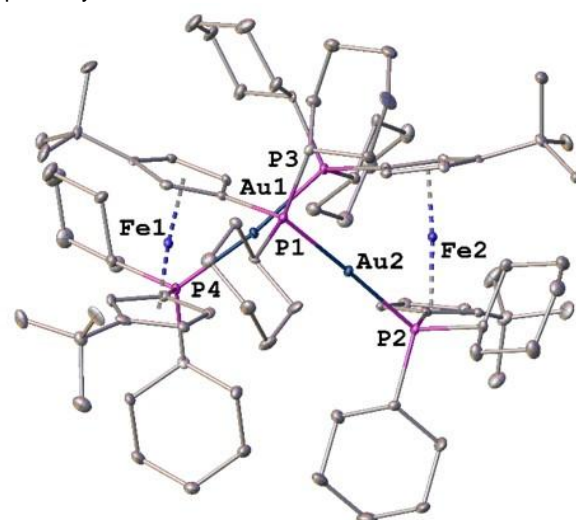
**Scheme 1.** Neutral and polynuclear cationic gold(I) complexes of bis(dicyclohexylphosphino)-ferrocene *rac* **L1**.

From complexes **1** and **2**,<sup>[41]</sup> the straightforward formation of cationic gold complexes **3** and **4** was respectively achieved by total or partial chloride abstraction using one equivalent of  $\text{AgSbF}_6$  in acetonitrile [0.01 M] at rt for 1 h. The complexes **3** (<sup>31</sup>P NMR 53.7 ppm) and **4** (46.1 ppm) crystallized as pure orange solid in 97% and 65% yield, respectively. The formation of the related dicationic digold complex **5** was achieved by reacting dinuclear complex **2** with 2 equiv of  $\text{AgSbF}_6$  in  $\text{CH}_3\text{CN}$  (Scheme 1). Comparatively to **3** and **4**, the complex **5** that is isolated as a dark orange solid (86% yield, <sup>31</sup>P NMR 41.3 ppm) was found to be less stable and degraded in solution overtime, forming gold mirror.

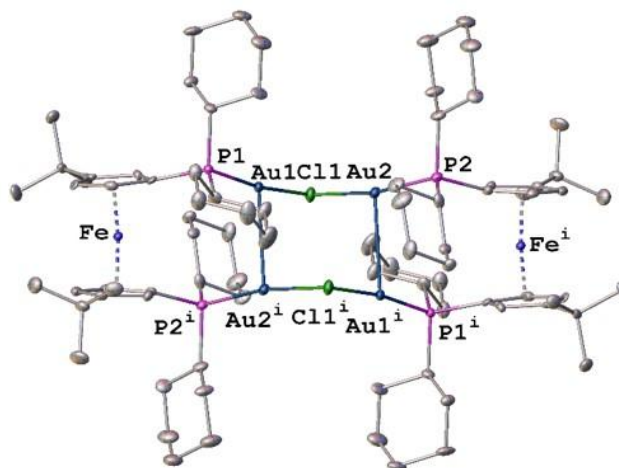
Single crystal X-ray diffraction analysis of the cationic **3-5** complexes was conducted (Figure 2). Gold tetranuclear bis-chloride-bridged structure organized such as complex **4** was rarely reported.<sup>[27]</sup> Complex **4** is structurally related to tetranuclear species recently reported by the van der Vlugt group from a tridentate diarylamino-bisphosphine ligand ( $\text{PN}^{\text{H}}\text{P}^{\text{Pr}}$ , Figure S1),<sup>[37]</sup> and by the Tamm group from N-heterocyclic carbene-phosphinidene species ( $\text{IPr}\cdot\text{PPh}$ , Figure S2).<sup>[46]</sup> Interestingly, the  $\text{PN}^{\text{H}}\text{P}^{\text{Pr}}$ -complex was suggested to be in equilibrium with its neutral dinuclear counterpart that is a precursor for a digold cationic species catalytically active in dual  $\sigma,\pi$ -alkyne activation.<sup>[37]</sup> More importantly, the tetranuclear cationic complex  $[(\text{IPr}\cdot\text{PPh})_2\text{Au}_4\text{Cl}_2][\text{BARF}]_2$  that was directly tested in enyne cycloisomerization was found to promote the formation of five- or six-membered ring dienes of I and III type (Figure 1), with a moderate selectivity (66% to 75%).

Diffusion-ordered NMR Spectroscopy (DOSY <sup>1</sup>H NMR) experiments conducted for **2** and **4** in  $\text{CD}_2\text{Cl}_2$  solution at 298 K, correlated the dinuclear and tetranuclear structure of the

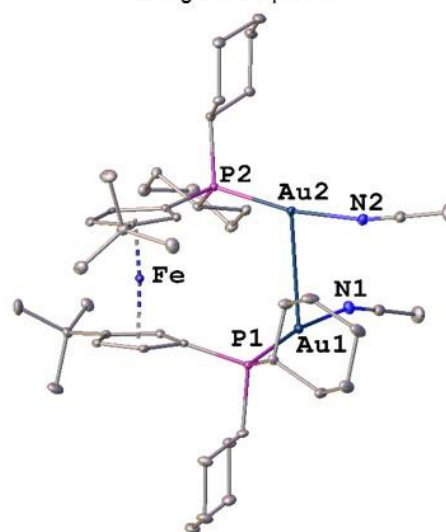
complexes with coefficients of  $8.57 \times 10^{-10}$  and  $6.92 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ , respectively.



Digold complex **3**.



Tetragold complex **4**.



Digold complex **5**.

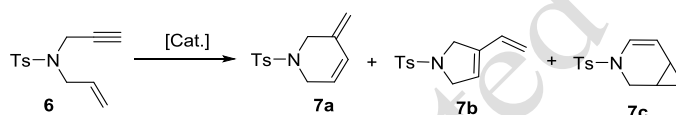
**Figure 2.** Molecular views of XRD structures of the cationic part of gold(I) complexes **3-5** (counter anions, solvent and hydrogen atoms are omitted for clarity). For **4**, two cyclohexyl groups are disordered over two positions with occupation factors converged to 0.71:0.29 (details in Supporting Information); symmetry code: (i) 1-x, 1-y, 1-z.

**1,6-Enyne cycloisomerization from aurophilic cationic tetranuclear complexes.** The Echavarren group reported that gold-based catalysts were very effective for accomplishing a series of 1,6-enyne cycloisomerization.<sup>[22]</sup> The catalyst was generated by treatment of Au(PPh<sub>3</sub>)Cl with AgSbF<sub>6</sub>, which resulted in the formation of highly reactive cationic Au(PPh<sub>3</sub>)<sup>+</sup> species. With the gold catalyst, various 1,6-enynes were converted into five-membered dienes (type **I**, Figure 1) at rt; this completed the known reactivity of palladium, platinum, and ruthenium, previously identified for such cyclopentenes formation.<sup>[47–49]</sup> Following this milestone work, mononuclear cationic gold complexes have been shown to promote mostly the formation of either five and/or six-membered dienes (type **I-III**, Figure 1), sometimes with a troublesome selectivity.<sup>[23,50–61]</sup> Au(I) catalytic systems are occasionally able to form bicyclic strained structures such as bicyclo[4.1.0]hept-4-enes (type **IV**, Figure 1) and cyclobutenes (type **V-VI**, Figure 1). In these cycloisomerization reactions using 1,6-enyne substrates, a high substrate-dependence is observed for the final selectivity. In particular, alkyl groups at the olefin function,<sup>[22,41,53,62]</sup> and/or bulky aromatic groups at the alkyne<sup>[63–65]</sup> assist the cyclopropyl

formation. However, while Pt-based catalysts promote the formation of bicyclo[4.1.0]hept-4-enes **IV** (Figure S3),<sup>[66]</sup> for gold catalysts the competition to form isomeric dienes is conversely found very strong in the absence of such substituents on the enyne.<sup>[67]</sup>

Since the vast majority of defined cationic gold complexes tested in 1,6-enyne cycloisomerization are preformed mononuclear species, we were eager to screen the activity and selectivity obtained from the well-defined complexes **1-5**, among which cationic aurophilic di- and tetranuclear species, unexploited to date, are present. We performed this preliminary approach using the low-substituted *N*-propargyl-*N*-allyl-toluene-4-sulfonylamine **6** (unsubstituted at the olefin and terminal alkyne, Table 1), assuming that this simple 1,6-enyne *a priori* does not strongly influence the cycloisomerization selectivity outcome by its own structure. Our starting conditions had been previously optimized to form selectively **7a** from the dinuclear aurophilic complex **2** (Table 1, entry 2),<sup>[41]</sup> by *in situ* cationization with 2.5 equiv of [AgSbF<sub>6</sub>], while the same operation on the mononuclear counterpart **1** was mostly unproductive (Table 1, entry 1).

**Table 1.** Intramolecular cycloisomerization of 1,6-enyne **6**.<sup>a</sup>



Entry	Catalyst ([Au] 4 mol%)	[AgSbF <sub>6</sub> ] (mol%)	Solvent [0.067 M]	Temp. (°C)	Time (h)	Conversion in <b>7a,b,c</b> (%)	Selectivity <b>7a / 7b / 7c</b>
1	<b>1</b>	10	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	6	—
2	<b>2</b>	10	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	72	86% / 14% / 0%
3	<b>3</b>	0	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	0	—
4	<b>4</b>	0	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	13	0% / 0% / 100%
5	<b>5</b>	0	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	37	83% / 11% / 6%
6	<b>4</b>	0	DCE	60 °C	3	56	10% / 7% / 83%
7	<b>4</b>	0	DCE	85 °C	3	98	8% / 17% / 75% <sup>b</sup>
8	<b>2</b>	10	DCE	85 °C	3	99	82% / 18% / 0%
9	<b>1</b>	10	DCE	85 °C	3	90	71% / 18% / 11%
10	<b>3</b>	0	DCE	85 °C	3	0	—
11	<b>5</b>	0	DCE	85 °C	3	99	71% / 15% / 14% <sup>c</sup>
12	<b>4</b>	2	DCE	85 °C	3	99	59% / 13% / 28% <sup>d</sup>
13	<b>4</b>	2	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	31	79% / 0% / 21%
14	<b>4</b>	4	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	54	81% / 6% / 13%
15	<b>4</b>	10	CH <sub>2</sub> Cl <sub>2</sub>	20 °C	3	64	79% / 10% / 11%

<sup>a</sup> Conditions: enyne **6** (0.1 mmol), [Au] (4 mol%), 1.5 mL solvent [0.067 M in enyne], <sup>1</sup>H NMR conversion are given from triplicate experiments. DCE: dichloroethane. <sup>b</sup> Triplicate experiments insured this result, notably, at the end of these reactions using tetranuclear complex **4** a limpid solution is obtained without any precipitation of gold. <sup>c</sup> Freshly prepared complex **5** is used in these conditions, while storage during one day or one week progressively reduced both the conversion and selectivity, confirming the weaker stability of **5**. <sup>d</sup> Experiments performed for 15, 30, and 60 min showed that the same products distribution is conserved along the reaction, which achieves 85% conversion after 15 min.

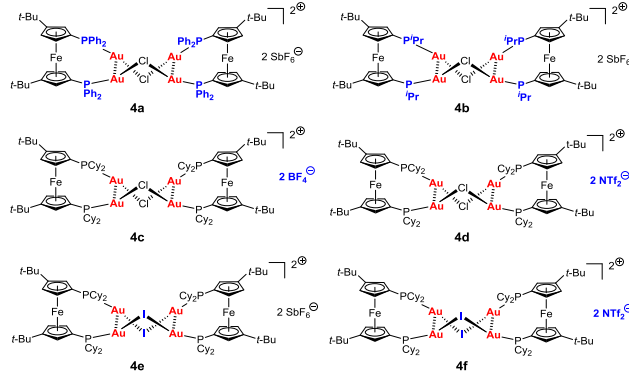
When using the tetranuclear dicationic complex **4**, we observed a dramatic shift in selectivity to the full formation of the strained azabicyclo[4.1.0]hept-4-ene **7c** (99%, entry 4), albeit with low conversion, providing thus from cycloisomerization of **6** a selectivity neither observed previously using any ferrocenylphosphine stabilized mononuclear and dinuclear complexes.<sup>[41]</sup> This selectivity was not observed using the defined cationic complexes **3** and **5** (Table 1, entries 3 and 5). A solvent change to dichloroethane (DCE) allowed us to access higher temperatures of activation, and enhanced the conversion while conserving a high selectivity in **7c** (entries 6 and 7). These changes in solvent and temperature were applied with the other

complexes **1-3** (entries 8-10), and led to the loss of either the activity or the selectivity to bicyclo[4.1.0]hept-4-ene **7c**. This confirmed the specific activity and selectivity of tetranuclear dicationic complex **4**. Beside the fact that the well-defined dinuclear cationic complex **5** does not favor a good selectivity to **7c** (entry 11), we observed that the addition of 2 to 10 mol% of [AgSbF<sub>6</sub>] to gold tetranuclear **4** induced the progressive disappearance of **7c** in favor of the formation of the five and six-membered dienes **7a** and **7b** (entry 12, and comparison of entry 4 with entries 13-16). This was presumably attributed to the breakdown of the tetranuclear motif due to further chloride abstraction. To further challenge this hypothesis, we achieved



the synthesis of the analogous tetranuclear compounds **4a-4f** (XRD analyses and molecular structures of **4b-4f** are provided in Supporting Information), and we tested those well-defined complexes similarly into the cycloisomerization of **6** (Table 2).

**Table 2.** Effect of tetranuclear complexes **4a-4f** in Intramolecular cycloisomerization of 1,6-enyne **6**.



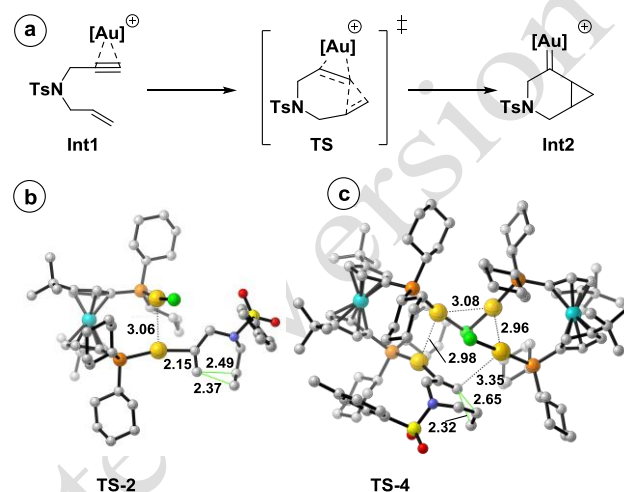
Entry	Catalyst ([Au] 4 mol%)	Conversion in <b>7a,b,c</b> (%)	Selectivity <b>7a</b> / <b>7b</b> / <b>7c</b>
1	<b>4</b>	98	8% / 17% / 75%
2	<b>4a</b>	93	12% / 26% / 62%
3	<b>4b</b>	92	12% / 20% / 69%
4	<b>4c</b>	52	11% / 13% / 76%
5	<b>4d</b>	67	6% / 15% / 79%
6	<b>4e</b>	11	22% / 0% / 78%
7	<b>4f</b>	4	0% / 0% / 100%

<sup>a</sup> Conditions: enyne **6** (0.1 mmol), [Au] (4 mol%), 1.5 mL DCE [0.067 M in enyne], 85 °C, 3 h, <sup>1</sup>H NMR conversion are given from duplicate experiments.

The cycloisomerization results all confirmed that the tetranuclear scheme is essential in the formation of **7c** with a selectivity above 60% (Table 2, entries 1-7). However, the structure changes operated with **4a-f**, regarding the cousin structure of **4**, deserve some comments. Despite a slight selectivity loss, a high activity in the conversion from **6** to **7c** was conserved when the phosphino substituents introduced on the ferrocene ligand were phenyl (**4a**, entry 2, 93%) and *i*-propyl groups (**4b**, entry 3, 92%). This remarkable activity is strongly in favor of the conservation of the gold centers in a constrained pre-organized environment. Indeed, mono- and dinuclear cationic gold complex counterparts provided with these ferrocenylphosphine ligands very different synthetic issues.<sup>[68]</sup> Conversely, a noticeable drop of activity was due to the counter-anion change from SbF<sub>6</sub><sup>-</sup> (**4**, entry 1, 98%) to NTf<sub>2</sub><sup>-</sup> (**4d**, entry 5, 67%) and BF<sub>4</sub><sup>-</sup> (**4c**, entry 4, 52%) while a high selectivity in **7c** is conserved above 75%. The presence of the  $\mu$ -chloro bridges was found to be even more determining for the activity of the complexes since their replacement for  $\mu$ -iodo in **4e** (entry 6, 11%) and **4f** (entry 7, 4%) provided unproductive catalysts. The question of the structural advantage of a smaller bridge size and higher strength of the separation bridge is thus open.

**Computational approach of the selectivity induced by aurophilic cationic tetranuclear complexes.** To decipher the origin of this unexpected selectivity from tetragold catalysts, we used computational chemistry to investigate the formation of azabicyclo[4.1.0]hept-4-ene. Previous studies have shown that **7c** is mainly formed from the 6-*endo*-dig cyclization, while **7b**

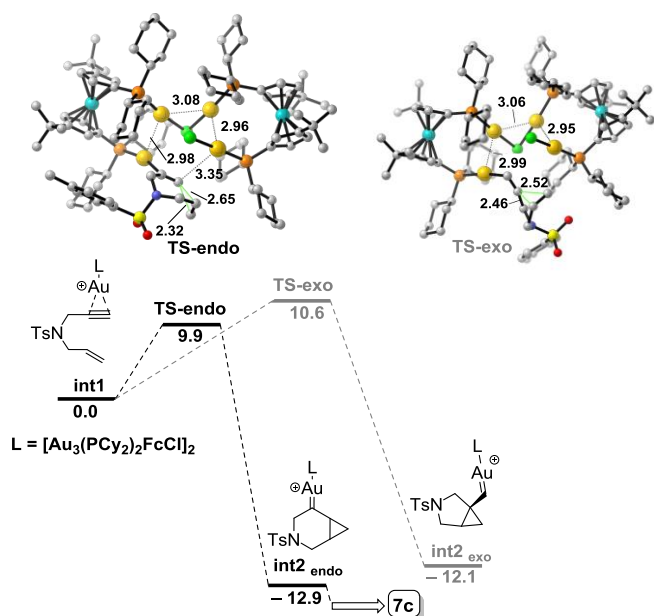
mainly comes from the 5-*exo*-dig cyclization and **7a** can be formed from both intermediates.<sup>[22a,69]</sup> Electronic structure and non-covalent interactions (NCI) were analyzed at the DFT level (AIM and NCI analyses in Supporting Information) for the 6-*endo*-dig transition states with aurophilic pre-catalysts dinuclear **2** and tetranuclear **4** (Figure 3). Consistent with experimental XRD data, we identified a stabilizing aurophilic interaction between the two gold atoms in **2** and **TS-2**. This aurophilic interaction is also present in **4** and **TS-4** between the paired gold atoms Au1...Au2 and Au3...Au4 (NCI analysis in Figure Sth1).



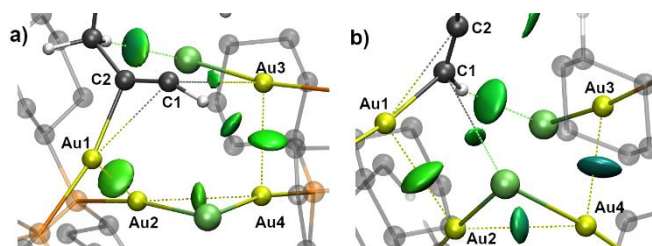
**Figure 3.** (a) General mechanism of the 6-*endo*-dig cyclization step. (b) Transition state DFT geometry with catalyst **2**. (c) Transition state geometry with catalyst **4**. Geometries were optimized at the BP86-D3(BJ)/def2SVP level in CH<sub>2</sub>Cl<sub>2</sub> (internuclear distances are given in Å).

Computing the Gibbs free energies for the cyclization steps, we found that the -TsN- enyne linker favors the formation of the 5-*exo*-dig cycle with digold **2** (Figure Sth2), in agreement with previous reports.<sup>[22a,69,15,70]</sup> Conversely, with tetragold **4**, the 6-*endo*-dig cyclization leading to **7c** (Figure 4) is favored both from kinetic and thermodynamic perspective (TS-*endo* found at 9.9 kcal mol<sup>-1</sup> and **int2 endo** stabilized at -12.9 kcal mol<sup>-1</sup>). The Gibbs free energy difference between the *endo* and the *exo* TS (10.6 kcal mol<sup>-1</sup>) we identified corresponds to a 70:30 **7c**:(**7b,a**) ratio, in good agreement with our experiments for tetragold catalysts (Table 2).

Electronic structure and non-covalent interactions were analyzed more in depth in **TS-4 endo** and **exo** (Figure 5) regarding this inversion of stability. Actually, in addition to the stabilizing aurophilic interactions between the gold atoms Au1...Au2 (2.98 Å) and Au3...Au4 (2.96 Å), the supplementary interaction which takes place between the gold atoms Au2 and Au3 (in addition to chlorine bridge, Au2...Au3 = 3.08 Å, Figure 3) leads to the formation of a metallic structure as a folded tetranuclear linear chain solidarizing the two moieties of the catalyst. In addition, the analysis of the non-covalent interactions reveals an Au3-alkyne interaction that stabilizes the 6-*endo*-dig TS with respect to the 5-*endo*-dig one. One can also note a strong interaction of one chlorine atom with the substrate. The set of weak interactions evidenced from **TS-4** highlights a polynuclear cooperative behavior that is not achievable from lower rank mono- and dinuclear systems.



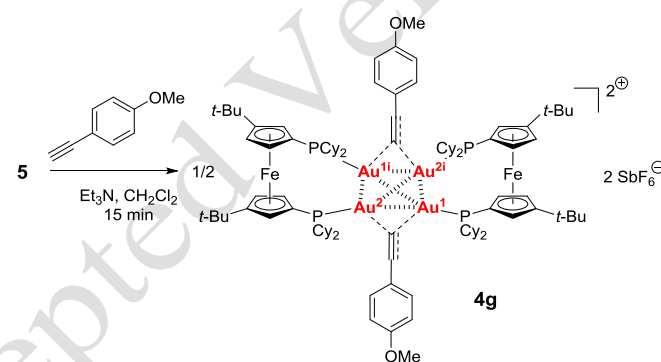
**Figure 4.** Gibbs free energies for the cyclization steps from tetragold **4**. Geometries were optimized at the BP86-D3(BJ)/def2SVP level in  $CH_2Cl_2$ , internuclear distances are given in Å.



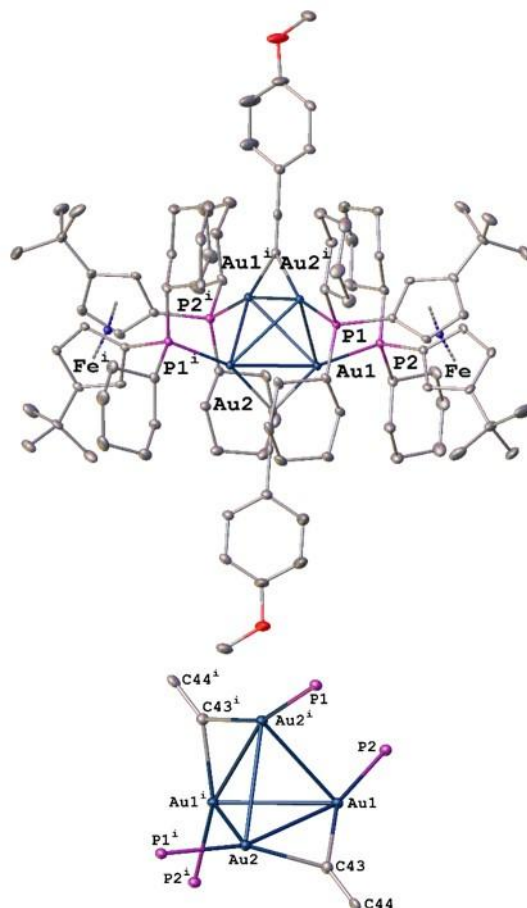
**Figure 5.** Non-covalent interactions (NCI) analysis in a) TS-4 endo, b) TS-4 exo for catalyst **4**. Contour plots of the reduced density gradient isosurfaces (density cutoff of 0.04 au for Au...Au interactions and 0.02 for all others). The green surfaces indicate weak attractive interactions (NCI). The visualization is focused on interactions near to the Au atoms, complete views are given in SI.

**Alkyne bridging-interaction within gold tetranuclear motif – formation of a gem gold cluster.** From the computational results and the experiments gathered in Table 2 (and notably the tests using dinuclear **4** in the presence of  $AgSbF_6$  as halide extractor, entries 12-15 in Table 1), the selectivity towards low-substituted azabicyclo[4.1.0]hept-4-enes is clearly attributed to the persistence of the gold tetranuclear motif. To further assess the structural role of the tetragold catalysts, we experimentally examined the interaction of tetranuclear motif with a model alkyne 4-methoxyphenylacetylene. The isolation of pertinent alkyne (or enyne) intermediate species from direct reaction with the precatalyst **4** was found to be difficult, presumably because of the high reactivity of the intermediates. However, we first observed that dicationic complex **5** can be obtained from fragmentation of **4** by adding  $AgSbF_6$  for chloride bridge removal. Then, after Cl abstraction, **5** reacted with one equiv of 4-methoxyphenylacetylene and quantitatively formed a new tetragold organometallic cluster **4g** bridged by two alkynes (Scheme 2). The presence of a base for alkyne deprotonation is needed to form this very stable species that was characterized by XRD in the solid state (Figure 6 bottom). This species differ from the dinuclear van der Vlugt intramolecular  $Au_2(\sigma,\pi\text{-acetylide})$  complex with a diphosphine ligand [ $d Au^1...Au^2 =$

$3.1110(2)$ ],<sup>37</sup> since each acetylide is equally shared for bridging gold pairs, inducing very close distances [ $d Au^1...Au^2 = d Au^2...Au^1 = 2.9525(2)$  Å]. Very interestingly, the change from chloride to carbon bridging induces a contraction of the tetranuclear motif in which additional shorter aurophilic interactions are observed with  $d Au^1...Au^2 = d Au^1...Au^2^i = 3.0561(2)$  Å,  $d Au^2...Au^2^i = 3.0888(3)$  Å,  $d Au^1...Au^1^i = 3.1015(3)$  Å. Notably, these internuclear distances fully matches the computed values for enyne activation above reported. Further crystallographic details of **4g** are given in SI. Beside its unique and very original bis(diphosphine)polyaurophilic cluster structure, compound **4g** illustrates that tetranuclear gold preorganization can be potentially conserved upon interaction with alkyne. This definitely establish the interest of constraint diphosphine ligands for assembling tetra gold complexes. Such cluster formation would be also structurally advantageous for promoting polynuclear cooperativity and lead to selectivity alterations from mono- or digold catalysis.



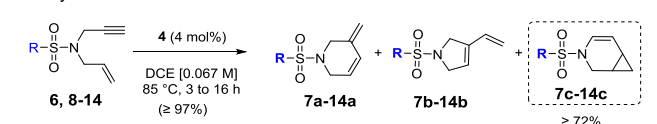
**Scheme 2.** Dialkyne-bridged diphosphine tetragold cluster **4g** formation.



**Figure 6.** Molecular structure (top) and cluster core (bottom) of the dialkyne-bridged diphosphine tetragold cluster **4g**. Symmetry Code: (i) 1-x, y, 3/2-z.

**Synthesis of low-substituted azabicyclo[4.1.0]hept-4-enes.** Having confirmed the propensity of these tetranuclear Au(I) catalysts to form the bicyclic strained structure **7c** with a high and unexpected selectivity, we further examined the activity of complex **4** on variously aryl-substituted *N*-propargyl-*N*-allyl-aryl-sulfonylamines **8-14** (Table 3).

**Table 3.** Intramolecular cycloaddition of *N*-propargyl-*N*-allyl-aryl-sulfonylamines **8-14**.<sup>a</sup>



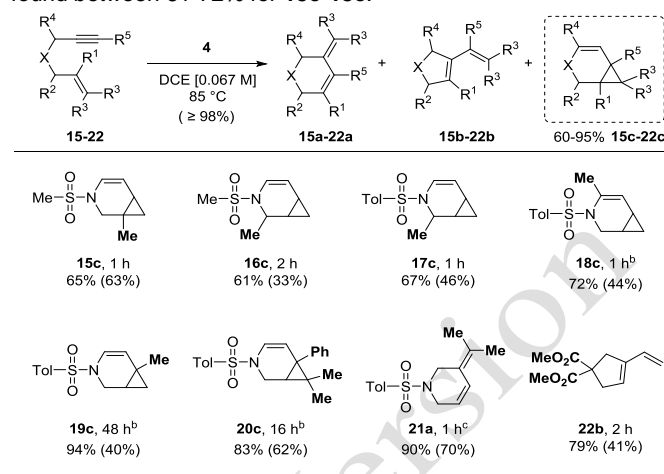
Entry	1,6-Enyne / R group	Enyne Conversion (%)	7c-14c/ Selectivity (%)	Isolated Yield of 7c-14c (%)
1	<b>6</b> /(C <sub>6</sub> H <sub>4</sub> )-4-Me	98	<b>7c</b> /75	46
2	<b>8</b> /C <sub>6</sub> H <sub>5</sub>	97	<b>8c</b> /78	48
3	<b>9</b> /(C <sub>6</sub> H <sub>4</sub> )-4- <i>t</i> -Bu	99	<b>9c</b> /75	50
4	<b>10</b> /(C <sub>6</sub> H <sub>4</sub> )-4-OMe	99	<b>10c</b> /72	37
5	<b>11</b> /(C <sub>6</sub> H <sub>4</sub> )-4-CF <sub>3</sub>	99 <sup>b</sup>	<b>11c</b> /85	74
6	<b>12</b> /(C <sub>6</sub> H <sub>4</sub> )-4-NO <sub>2</sub>	99 <sup>b</sup>	<b>12c</b> /78	57
7	<b>13</b> /CH <sub>2</sub> (C <sub>6</sub> H <sub>5</sub> )	97	<b>13c</b> /76	49
8	<b>14</b> /CH <sub>3</sub>	99 <sup>b</sup>	<b>14c</b> /72	62

<sup>a</sup> Conditions: enyne **6**, **8-14** (0.2 mmol), **4** (1 mol%, *i.e.* [Au] = 4 mol%), 3 mL dichloroethane (DCE, 0.067 M in enyne), 85 °C, 3 h, conversion from NMR yield. <sup>b</sup> 16 h. Isolated yields averaged from triplicate experiments.

These low-substituted substrates are of particular interest to examine since with current gold catalysts cyclopropyl formation from 1,6-enynes cycloisomerization is generally reported using enynes holding substituents at the olefin,<sup>[10,22,41,53,62]</sup> or at the alkyne moiety.<sup>[10,63-65]</sup> The current state-of-the art, whatever the conditions, including Rh, Ru, Ir or nonmetal, does not describe high-yield general synthesis of low-substituted azabicyclo[4.1.0]hept-4-enes.<sup>[58,71-74]</sup> We were glad to observe high conversion, above 97%, and consistent selectivity, above 72%, for the formation of 3-phenylsulfonyl-3-azabicyclo[4.1.0]hept-4-ene **8c** (Table 3, entry 2) and variously phenyl-substituted new sulfonyl-3-azabicyclo[4.1.0]hept-4-enes **9c-12c** (entries 3-6). These were isolated in moderate to good yields (37-74%). The catalytic system tolerated electron-donating and electron-withdrawing substituents: 3-[(4-*tert*-butylphenyl)sulfonyl]-3-azabicyclo[4.1.0]hept-4-ene **9c** and 4-(methoxyphenyl)sulfonyl analogue **10c** were isolated in 50% and 37%, respectively. 4-Trifluoromethylphenylsulfonyl-substituted **11c** and 4-nitrophenylsulfonyl **12c** were isolated in 74% and 57% yield, respectively. Alkylsulfonyl-3-azabicyclo[4.1.0]hept-4-enes were equally accessible with the benzyl-substituted **13c** isolated in 49% yield and the methyl-substituted **14c** isolated in 62% yield.

Besides the formation of these previously undescribed azabicyclo[4.1.0]hept-4-enes, we assessed the performances of the gold tetranuclear **4** in the cycloisomerization of more classical alkyl-substituted 1,6-enynes (Scheme 3). Using enyne substrates methylated at various positions, an excellent activity with conversions above 98%, was conserved for reactions

achieved within 1 to 40 h. The faster cycloisomerization reactions were accompanied with a slight loss in selectivity, found between 61-72% for **15c-18c**.



**Scheme 3.** Intramolecular cycloaddition of 1,6-enyne **15-22**.<sup>a</sup> Conditions: enyne **15-22** (0.2 mmol), Au(I) tetranuclear cationic complex **4** (1 mol%), 3.0 ml DCE [0.067 M in enyne], 85 °C, <sup>1</sup>H NMR conversion and isolated yield (in brackets) are given from triplicate experiments. <sup>b</sup> **4** (2 mol%). <sup>c</sup> **4** (0.5 mol%).

We were glad to observe the major formation of azabicycloheptenes **19c** and **20c**,<sup>[56,62,75,76]</sup> albeit in slower reaction with the need to increase gold catalyst loading for optimized conversions. The preferential formation of the six-membered ring **21a** isolated in 70% yield (90% selectivity, 99% enyne conversion) is consistent with a fast reactivity (0.5 mol% of **4**, 1 h) and a strong influence of *gem*-methyl groups on the olefin; it has been repeatedly reported.<sup>[52,56,60]</sup> From dimethyl allyl(propargyl)malonate the five-membered **22b** was isolated in 41% yield (79% selectivity, 99% enyne conversion). The selective cycloisomerization of dimethyl allyl(propargyl)malonate is usually challenging, and gold homogeneous catalysts often achieved mixtures of six and five-membered cyclic dienes.<sup>[22,26,45]</sup> Notably, very high selectivity from this malonate precursor to the five-membered **22b** has been recently achieved at the surface of ultra-small gold nanoparticles (NPs, sizing 1.3 nm, > 99% selectivity in **22b**).<sup>[45]</sup> It is tempting to hypothesize some structural relationship between the reactivity at the surface of ultra-small gold NPs and the present gold polynuclear species in this substrate case.

## Conclusion

Molecularly-defined tetranuclear dicationic aurophilic gold(I) precatalysts used in cycloisomerization of 1,6-enynes favors the formation with high selectivity of strained azabicyclo[4.1.0]hept-4-enes, even in the absence of activating or orienting substituents on alkyne and olefin functions. The bis(dicyclohexyl)phosphino-ferrocene supporting ligand **1** for tetragold complex is the most efficient for a general high cycloisomerization yield and selectivity. Strained azabicyclo[4.1.0]hept-4-enes are not formed by mono- and dinuclear neutral or cationic gold(I) complexes stabilized with the same class of phosphine ligands, evidencing for the first time the importance of a gold tetranuclear scheme in this selectivity. DFT studies correlated to experimental mechanistic investigations support an unprecedented "cluster-like" reactivity from

polynuclear cooperation at the origin of this peculiar selectivity. Herein, the aurophilic interactions preexist, and pre-organize, gold cluster reactive intermediates. Accordingly, and more importantly, the selectivity observed also differ from nanoparticles and heterogeneous gold catalysts reported to date.

Crystallographic data deposition numbers: 2128908 (for **3**), 2128909 (for **4**), 2128910 (for **5**), 2128911 (for **4g**), as well as 2144186 (for **4b**), 2144187 (for **4c**), 2144188 (for **4d**), 2144189 (for **4e**), and 2144190 (for **4f**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

## Acknowledgements

This work was supported by the CNRS, the Université de Bourgogne, the Conseil Régional de Bourgogne–Franche-Comté (CHIMENE project, PhD grant for T.-A. N.), the PIA-excellence ISITE-BFC program (COMICS: Chemistry of Molecular Interactions Catalysis and Sensors, for JCH), ANR JCJC 2018 FITFUN (ANR-18-CE07-0015, for RJ) and the Fonds Européen de Développement Régional (FEDER). Calculations were performed using HPC resources from CCUB (Université de Bourgogne). This work was granted access to the HPC resources of CINES under the allocation A0090807259 made by GENCI, for PFL.

## Conflict of interest

The authors declare no conflict of interest.

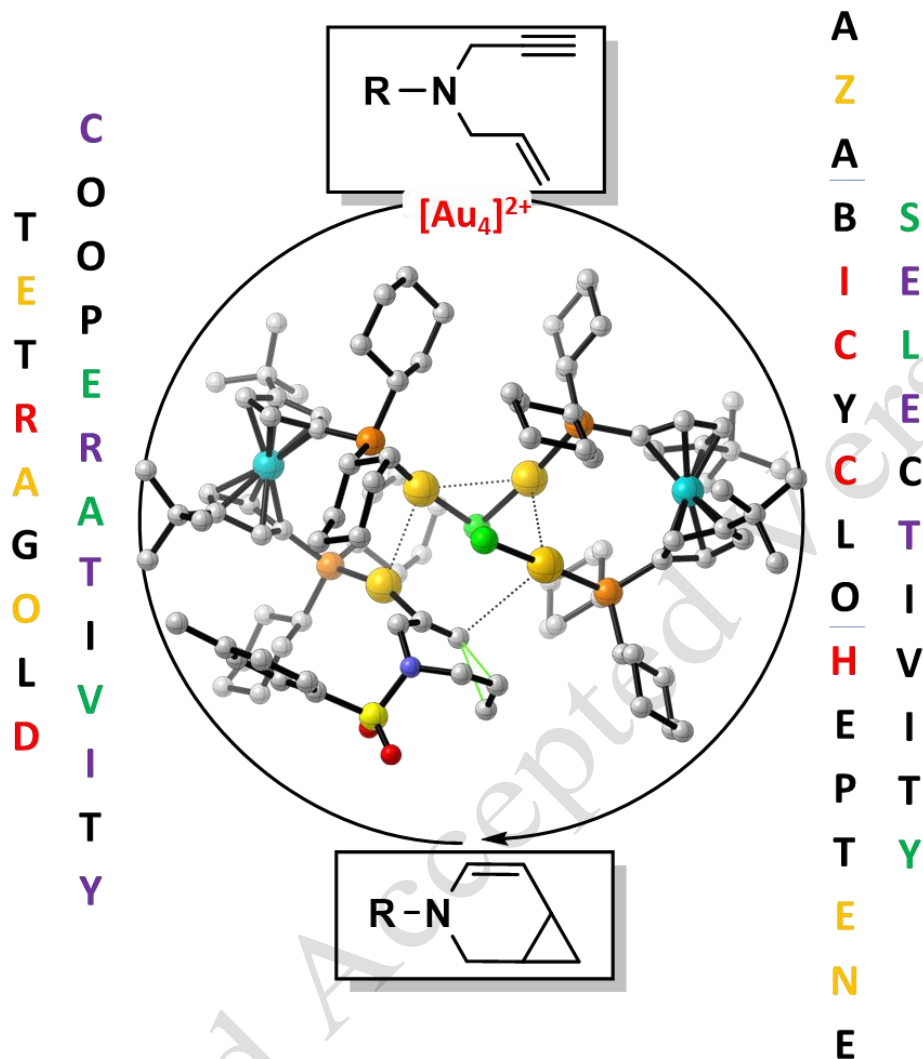
**Keywords:** Gold catalysis • polynuclear complexes • alkyne activation • gold cluster • azabicyclo-hept-4-enes

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## Entry for the Table of Contents



**Towards specific “cluster-like” reactivity?** Ligands pre-organizing gold centers in a constrained environment, assisted with aurophilic interactions, push further the selectivity not achieved by mono- and digold complexes from previously unseen cooperative tetragold catalysis.

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