This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Divergent Reaction Pathways in Gold Catalyzed Cycloisomerization of 1,5-enynes Containing a Cyclopropane: Dramatic Ortho Substituent and Temperature Effects

Gen-Qiang Chen, Wei Fang, Yin Wei, Xiang-Ying Tang,* and Min Shi*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A gold(I)-catalyzed cycloisomerization of easily available 1,5-enynes containing a cyclopropane has been developed, efficiently providing cyclobutane fused 1,4-cyclohexadiene, tricyclic cyclobutene, biscyclopropane, 1,3-cyclohexadiene derivatives in moderate to excellent yields. When the phenyl group was not ortho substituted, 1,4-cyclohexadienes could be produced. With an ortho-substituent, three different products could be synthesized selectively by control of the temperature and the used gold(I) catalyst. The 1,5-enyne substrate first undergoes a classical enyne cycloisomerization to form a tricyclic cyclobutene key intermediate, which undergoes subsequent transformation to produce the desired products.

A plausible reaction mechanism was proposed according to the deuterium labeling experiments and the intermediate trapping experiments as well as DFT calculations. In our current reaction, the ortho substituent on the phenyl group controls the reaction outcome and the ortho substituent effect was found to originate from steric and electronic factors.

Transition metal catalyzed enyne cycloisomerization is one of the most important strategies for the construction of cyclic structures from simple acyclic enyne substrates, of which 1,4- and 1,5-enynes have been extensively examined. Among a range of transition metal catalysts for enyne cycloisomerization, gold(I) complexes were the most active and selective catalysts probably due to relativistic effects. Reports on homogeneous gold catalysis have been increasing explosively during the last decade and 1,5-enyne has always been the trial ground for gold catalysis. In 2004, Malacria and Fürstner reported their pioneering work on 1,5-enyne cycloisomerization, affording bicyclo[3.1.0]hexenes from 1,5-enynes with hydroxy or acyloxy groups at propargylic position in the presence of PtCl2 or gold(I). Subsequently, Toste’s group found that gold(I)-catalyzed isomerization of 1,5-enynes could produce bicyclo[3.1.0]hexane or tetracycl[8h] compound efficiently.
The cyclopropane tethered 1,5-enyne substrate 1a was synthesized and its reactivity was examined. We screened various gold catalysts to find the optimal catalyst. In the presence of [PPh₃AuCl]₆AgSbF₆, product 3a could be afforded in 82% NMR yield. After further optimization of the reaction conditions, we found that when [JohnPhosAu-MeCN]SbF₆ was used as the catalyst, product 3a could be produced in 92% isolated yield after 20 h at 0 °C in DCM (dichloromethane). Other gold catalysts such as [(p-F-Ph)₂PAu-MeCN]SbF₆, [(p-CF₃-Ph)₂PAu-MeCN]SbF₆, [P(OAr)₂PAu-MeCN]SbF₆, [(t-Bu)₂PAu-MeCN]SbF₆, [JackiePhosAu-MeCN]SbF₆, [XPhosAu-MeCN]SbF₆ and [IPrAu-MeCN]SbF₆ were also evaluated, but no better result was obtained. Therefore, [JohnPhosAu-MeCN]SbF₆ was identified as the best catalyst for the current reaction (see Table S1-1 in the Supporting Information for the detailed optimization of the reaction conditions).

With the optimal reaction conditions in hand, we next turned our efforts to examine the substrate scope of the reaction. We found that when R¹ was aromatic groups with electron-donating or electron-withdrawing substituents (Table 1, entries 1-9), the corresponding products could be obtained in good to excellent yields. Only when a strongly electron-withdrawing group CF₃ or NO₂ was introduced (R¹ = p-CF₃-Ph or p-NO₂-Ph), the reaction went sluggishly and elevation of temperature was required for the complete conversion (Table 1, entry 10). When the substituents were heteroaromatic groups such as thieryl or 5-indolyl group, the reaction went smoothly to produce 3l and 3m in excellent yields (Table 1, entries 12 and 13). The reaction also worked very well when the substituent was a 2-naphthyl group or 6-methoxy-2-naphthyl group (Table 1, entries 14 and 15). In addition, R² could also be an alkyl group, and the corresponding product 3p could be obtained in 69% yield in the presence of IPrAuNTf₂ (Table 1, entry 16). The structure of 3 was unambiguously determined by the X-ray diffraction of compound 3o.¹⁵

Table 1. Au(I) catalyzed cycloisomerization of 1 leading to 3.

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹, R²</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a, R² = Ph, R² = H</td>
<td>20</td>
<td>3a, 92</td>
</tr>
<tr>
<td>2</td>
<td>1b, R² = p-MePh, R² = H</td>
<td>17</td>
<td>3b, 90</td>
</tr>
<tr>
<td>3</td>
<td>1c, R² = 3,5-dimethylPh, R² = H</td>
<td>14</td>
<td>3c, 91</td>
</tr>
<tr>
<td>4</td>
<td>1d, R² = p-MeO-Ph, R² = H</td>
<td>12</td>
<td>93, 63</td>
</tr>
<tr>
<td>5</td>
<td>1e, R² = p-MeO-Ph, R² = H</td>
<td>17</td>
<td>3e, 88</td>
</tr>
<tr>
<td>6</td>
<td>1f, R² = p-MeO-Ph, R² = H</td>
<td>165</td>
<td>3f, 92</td>
</tr>
<tr>
<td>7</td>
<td>1g, R² = p-BnPh, R² = H</td>
<td>18</td>
<td>3g, 85</td>
</tr>
<tr>
<td>8</td>
<td>1h, R² = p-CF₃-Ph, R² = H</td>
<td>20</td>
<td>3h, 94</td>
</tr>
<tr>
<td>9</td>
<td>1i, R² = p-CF₃-Ph, R² = H</td>
<td>19</td>
<td>3i, 92</td>
</tr>
<tr>
<td>10</td>
<td>1j, R² = CF₃-Ph, R² = H</td>
<td>19</td>
<td>3j, 62</td>
</tr>
<tr>
<td>11</td>
<td>1k, R² = p-NH₂-Ph, R² = H</td>
<td>36</td>
<td>3k, 72</td>
</tr>
<tr>
<td>12</td>
<td>1l, R² = p-NH₂-Ph, R² = H</td>
<td>36</td>
<td>3l, 95</td>
</tr>
<tr>
<td>13</td>
<td>1m, R² = p-NO₂-Ph, R² = H</td>
<td>14</td>
<td>3m, 87</td>
</tr>
<tr>
<td>14</td>
<td>1n, R² = p-NO₂-Ph, R² = H</td>
<td>14</td>
<td>3n, 95</td>
</tr>
<tr>
<td>15</td>
<td>1o, R² = p-NH₂-Ph, R² = H</td>
<td>18</td>
<td>3o, 94</td>
</tr>
<tr>
<td>16</td>
<td>1p, R² = p-Hen, R² = Me</td>
<td>12</td>
<td>3p, 69</td>
</tr>
</tbody>
</table>

To a 25 mL flame and vacuum dried Schlenk tube was added 1 (0.2 mmol), then the tube was evacuated and backfilled with Ar. The catalyst (3 mol%) was dissolved in 2.5 mL DCM and then the solution was degassed with Ar. The catalyzed solution was added to the Schlenk tube. The reaction was allowed to stir at indicated temperature until TLC indicated complete conversion of 1. Isolated yield. The reaction was conducted at 0 °C. The reaction was conducted at 60 °C for 36 h and the product contains about 20% of 1,3-cyclooctadiene 8k and the total yield was 91%. IPrAuNTf₂ was used as catalyst instead of [JohnPhosAu-MeCN]SbF₆.

It was a great surprise that compound 2a, in which Ar is a 9-phenanthryl group, could not produce 3a in the presence of [JohnPhosAu-MeCN]SbF₆ and two new compounds 5a and 6a were obtained in 37% and 54% yields, respectively (Table 2, entry 1). Inspired by this discovery, we optimized the reaction conditions for the gold catalyzed cycloisomerization of compound 2a. With JohnPhosAuOAc, the reaction could not proceed at all (Table 2, entry 2). When the temperature was lowered to 0 °C, compound 5a was obtained in 84% yield combined with trace amount of compound 4a and small amount of compound 6a in the presence of [JohnPhosAu-MeCN]SbF₆ (Table 2, entry 3). By elevation of the reaction temperature, compound 6a could be obtained in higher yield in the presence of IPrAuNTf₂ or [JohnPhosAu-MeCN]SbF₆ (Table 2, entries 4 and 5) in DCE. When the reaction of 2a was conducted at -20 °C using [JohnPhosAu-MeCN]SbF₆ as catalyst, 4a could be afforded in 5% yield combined with trace amount of 5a (Table 2, entry 6). When the reaction was conducted at -30 °C in the presence of IPrAuNTf₂, 4a was produced as major product in 75% yield along with trace amount of 5a and 6a could not be detected at all (Table 2, entry 7). Entries 3, 5 and 7 were identified as the optimal conditions for the formation of 5a, 6a and 4a, respectively.

Table 2. Optimization of reaction conditions for the gold catalyzed cycloisomerization of 2a.
Table 3. Au(I) catalyzed cycloisomerization of 2 leading to 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (3 mol%)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[JohnPhosAuMeCN]BF$_3$</td>
<td>DCM</td>
<td>rt</td>
<td>N.D. 37</td>
</tr>
<tr>
<td>2</td>
<td>JohnPhosAuMeCN</td>
<td>DCE</td>
<td>rt</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>[JohnPhosAuMeCN]BF$_3$</td>
<td>DCM</td>
<td>0</td>
<td>trace 84</td>
</tr>
<tr>
<td>4</td>
<td>IPA/1N$_3$</td>
<td>DCE</td>
<td>80</td>
<td>N.D. N.D. 90</td>
</tr>
<tr>
<td>5</td>
<td>[JohnPhosAuMeCN]BF$_3$</td>
<td>DCE</td>
<td>60</td>
<td>N.D. N.D. 95</td>
</tr>
<tr>
<td>6</td>
<td>IPA/1N$_3$</td>
<td>DCM</td>
<td>50</td>
<td>9' trace  N.D.</td>
</tr>
</tbody>
</table>

* Isolated yield. \(^{a}\) The reaction was quenched with DMS (dimethyl sulfide). \(^{b}\) The reaction was conducted for 8 hours. \(^{c}\) NMR yield.

The substrate scope for the formation of 4 was also explored. When the aryl group was a substituted naphthyl group or its derivative such as pyrene or anthracene, the products 4 could be produced in moderate to good yields, ranging from 43% to 75% (Table 3, 4a-4h). The structure of 4a was determined by its 2D-NMR spectroscopy (for details see the Supporting Information).

Table 4. Au(I) catalyzed cycloisomerization of 2 leading to 5.

The substrate generality for the formation of the bicyclopropane product 5 was also examined. When the alkynyl substituent was a naphthyl or substituted naphthyl group or its derivatives, the reaction went smoothly to produce products 5 in high yields (Table 4, 5a-5h); H$_2$-naphthyl substrate 2 also worked well (Table 4, 5i); the desired products 5 could also be produced in moderate to high yields when the phenyl group was substituted at the ortho position (Table 4, 5k-5m). In the case that the substituent on the allylic position was a methyl group, the reaction also proceeded efficiently to produce the desired product 5p in 78% yield. The structure of 5a was unambiguously determined by X-ray diffraction.\(^{15}\) Interestingly, the product 5 was detected as mixtures of two diastereomers. Due to the following reasons, we believe that compound 5 exists as a pair of rotamers: 1) compounds 5f and 5l had no dr value; 2) four peaks could be found in the chiral HPLC resolution (for the details see the Supporting Information); 3) when the bromine atom in compound 5m was removed, the dr value disappeared (Scheme 11); 4) when the $^1$H-NMR spectrum of compound 5m was recorded at 65 °C in CDCl$_3$, the two peaks converged into one peak, indicating that the dr value disappeared at higher temperature (for details, see the Supporting Information).

Table 5. Au(I) catalyzed cycloisomerization of 2 leading to 6.
After further exploration of the substrate scope for the formation of 6, we found that when the substituent on the alkyne group was 1-naphthyl or substituted 1-naphthyl group or its derivatives, the corresponding products 6b-6i could be obtained in good to excellent yields. The reaction also proceeded smoothly when the phenyl group was substituted at the ortho position (Table 5, 6j-6n). In the case that the substituent on the alkyne was a benzyl group, the reaction also went efficiently to produce the desired product 6o in 83% yield. As for the substrate in which the allylic position was substituted with an alkyl group, the corresponding product 6p could also be obtained in 91% yield (Table 5). If the alkenyl unit was substituted at the terminal position, the desired product 6q was produced as a mixture of two diastereomers (dr = 6.4/1) in 90% yield (Table 5). The structure of compound 6 was further confirmed by the X-ray diffraction of compound 6c.\[15\]

\textbf{Deuterium Labeling Experiments.} The deuterium labeling experiment was conducted to gain further insights into the reaction mechanism. For deuterium-labeled substrates \([D_2]_1-1a\) and \([D_1]_1-1n\), the corresponding products \([D_2]_1-3a\) and \([D_1]_1-3n\) were obtained without deuterium shift, suggesting that there is no carbon rearrangement of allyl group during the reaction (Scheme 2, eqs 1 and 2). When the allylic hydrogen atoms were deuterated, compound \([D_1]_1-3a^+\) was produced in 80% yield along with one deuterium shift (Scheme 2, eq 3).

The deuterium-labeled compounds \([D_2]_1-2b\) and \([D_1]_1-2b\) were also synthesized and subjected to the standard reaction conditions for the formation of products 4b, 5b and 6b. The corresponding products \([D_2]_1-4b\), \([D_2]_1-5b\), \([D_2]_1-6b\) and \([D_1]_1-4b\), \([D_1]_1-5b\), \([D_1]_1-6b\) were produced in high yields with retention of the deuterium content (Scheme 3 and Scheme 4). As can be seen from the deuterium labeling experiment, the deuterated C-H bond was not disturbed during the reaction process. Apparently, for the formation of 4b, only carbon skeleton was rearranged and all the hydrogen atoms were not altered during the reaction process; an allylic hydrogen shift was involved during the formation of 5b and 6b.

\textbf{Scheme 2. Deuterium labeling experiment for formation of 3.}
Scheme 5. Capture of compound 7j.

It appears that the reactions leading to 3 and 5 or 6 are controlled by the nature of substituent R. The inherent relationship between them stimulated our further investigations. Fortunately, by quenching the reaction of substrate 1j with DMS after 1 h at room temperature, we were able to capture 7j in 6% yield, indicating that 7j was a key intermediate for the reaction that leads to 1,4-cyclohexadiene 3j (Scheme 5, for the details, see the Supporting Information).

Furthermore, the control experiment showed that 5a could be afforded from 4a at 0 °C in the presence of [JohnPhosAu⋅MeCN]SbF₆ (Scheme 6, eq 1). Under the standard reaction conditions, both compounds 4a and 5a could be transformed to product 6a in almost quantitative yields, indicating that both compounds 4a and 5a are the intermediates for the formation of product 6a (Scheme 6, eqs 2 and 3).

Scheme 6. Reactions of 4a and 5a under standard conditions.

Proposed Reaction Pathways. Based on the deuterium labeling experiments, intermediate trapping experiments and theoretical investigations (Schemes 9 and 10), some possible reaction pathways are ruled out and the most reasonable mechanism is proposed in Scheme 7 (for details, see Schemes S9 and S10 in the Supporting Information). Product 4 is formed through a classical 1,5-enyne cyclization. Coordination of gold(I) to the alkyne moiety of substrate 1 or 2 forms intermediate A. Nucleophilic attack of the alkyne by the alkene unit gives intermediate B or its resonance structure B'. Gold(I) carbenoid initiated ring expansion produces intermediate C, which probably has other resonance structures illustrated as C' and C''. Release of the catalyst from intermediate C affords tricyclic cyclobutene 4 (Scheme 7, cycle I). An equilibrium probably exists between tricyclic cyclobutene 4 and gold catalyst to give intermediate C', which can further undergo subsequent transformations to generate other products. As for substrates having aryl group without ortho substituent, the corresponding intermediate C' undergoes the cleavage of the cyclopropyl ring to form cationic intermediates D and D', which are in resonance with each other. Subsequent 1,2-H shift followed by release of the cationic Au(I) species results in product 3 (Scheme 7, cycle II). On the other hand, as for the substrates having aryl group with ortho substituent or having a benzyl group, the corresponding intermediate C' probably has another resonance structure depicted as cationic intermediate C'', which is probably more favorable. The cationic intermediate C'' undergoes the ring contraction to form carbenoid intermediate E. 1,2-H shift of intermediate E produces intermediate F, which is in equilibrium with compound 5. Carbocation initiated cyclopropane ring opening of intermediate F forms intermediate G. Finally, compound 6 is obtained after the ring expansion process (Scheme 7, cycle III).
Scheme 7. A plausible mechanism for the formation of 3, 4, 5 and 6.

Rationalization of Ortho-substituent Effects. As for substrate 1 having aryl group without ortho-substituent, 1,4-cyclohexadienes 3 could be produced. In contrast, substrate 2 having aryl group with ortho-substituent afforded three different products. Based on the proposed reaction mechanism, we speculate that the stability of intermediate D is the key point to affect the reaction path. As depicted in Scheme 8, when the phenyl group was substituted at the ortho position, it cannot effectively stabilize the cationic intermediate since the steric hindrance makes coplanar conformation of the phenyl ring and the allylic carbocation become unfavorable in energy. Furthermore, benzyl group is also not good enough to stabilize the carbocation intermediate. Thus, in all these cases, the energy level of intermediate D is high and the reaction probably prefers to undergo the cycle III.

Scheme 8. Our speculation for the reaction path divergence.

To understand these ortho-substituent effects, we performed DFT calculations on the possible reaction pathways using substrates 1a and 2m. For substrate 1a, the reaction energy profile is depicted in Scheme 9. Initially, coordination of Au(I) catalyst to the alkyne moiety of substrate 1a generates gold complex IN1. The gold complex IN1 undergoes a 6-endo-dig cyclization to give a gold carbene intermediate IN2 via transition state TS1 with an energy barrier of 14.8 kcal/mol. Subsequently, the intermediate IN2 undergoes ring enlargement via transition state TS2 with an energy barrier of 16.0 kcal/mol, producing another intermediate IN3. The intermediate IN3 can undergo two possible reaction pathways to obtain products 3 and 5. In Path 1, the cleavage of cyclopropane ring via TS3 with an energy barrier
of 17.9 kcal/mol, leading to the carbocation intermediate \text{IN}4. Subsequently, 1,2-H shift of intermediate via TS5 is leading to intermediate \text{IN}6, which undergoes deauration to give product 3. Transition state TS5 is located 18.6 kcal/mol above intermediate \text{IN}3 and 0.7 kcal/mol above transition state TS3, indicating that the 1,2-H shift step is rate-limiting step for Path 1. Another possible reaction pathway (Path 2) for the carboxylation intermediate \text{IN}3 is skeletal rearrangement via TS4 with energy barrier of 10.6 kcal/mol, leading to gold carbene intermediate \text{IN}5. Intermediate \text{IN}5 also undergoes 1,2-H shift via TS6, affording intermediate \text{IN}7, which undergoes deauration to give product 5. Transition state TS6 is located 15.3 kcal/mol above intermediate \text{IN}3 and 4.7 kcal/mol above transition state TS4, indicating that the 1,2-H shift step is also rate-limiting step for Path 2. Transition state TS5 is higher than transition state TS6 in energy by 3.3 kcal/mol, and intermediates \text{IN}4 and \text{IN}6 along the Path 1 are thermodynamically more stable than those intermediates \text{IN}5 and \text{IN}7 along the Path 2 by 3.8 kcal/mol and 9.9 kcal/mol, respectively. These calculation results indicate that the Path 1 is thermodynamically favorable and the reaction of 1a is thermodynamically controlled, which may account for that product 3 is experimentally obtained as the major product if using 1a as substrate. For comparison, we switched the ligand to PPh3, and also investigated the possible reaction pathways of substrate 1a (for details, see Scheme S11 in the Supporting Information).

The DFT calculation results indicate that the phosphorus ligand does not affect the reaction energy profile significantly. This is line with the experimental findings that the product 3 can be obtained in acceptable yield in the presence of [PPh3AuCl]/AgSbF6. From practical use point of view, the JohnPhos ligand is more stable due to its steric bulkiness in our reaction conditions for gold catalysis. Moreover, for the comparison with the substrates having ortho-substituent, JohnPhos ligand is chosen as the primary ligand for the gold catalysis.

We further investigated the reaction energy profiles for the reaction of substrate 2m having aryl group with ortho-substituent Br, and the results are shown in Scheme 10. In the similar manner, coordination of Au(I) catalyst to the alkyne moiety of substrate 2m generates gold complex \text{IN}8. The gold complex \text{IN}8 undergoes a 6-endo-dig cyclization to give a gold carbene intermediate \text{IN}9 via transition state TS7 with an energy barrier of 13.5 kcal/mol. Subsequently, the intermediate \text{IN}9 undergoes ring enlargement via transition state TS8 with an energy barrier of 17.1 kcal/mol, producing another intermediate \text{IN}10. The intermediate \text{IN}10 can also undergo two possible reaction pathways to obtain products 3 and 5. In Path 3, the cleavage of cyclopropane ring via TS9 with an energy barrier of 19.6 kcal/mol, leading to the carboxylation intermediate \text{IN}11.

Subsequently, 1,2-H shift of intermediate via TS11 is leading to intermediate \text{IN}13, which undergoes deauration to give product 3. Transition state TS11 is located 20.4 kcal/mol above intermediate \text{IN}10 and 0.8 kcal/mol above transition state TS9, indicating that the 1,2-H shift step is rate-limiting step for Path 3. Another possible reaction pathway (Path 4) for the carboxylation intermediate \text{IN}10 is skeletal rearrangement via TS10 with energy barrier of 8.9 kcal/mol, leading to gold carbene intermediate \text{IN}12. Intermediate \text{IN}12 also undergoes 1,2-H shift via TS12, affording intermediate \text{IN}14, which undergoes deauration to give product 5. Transition state TS12 is located 11.9 kcal/mol above intermediate \text{IN}10 and 3.0 kcal/mol above transition state TS10, indicating the 1,2-H shift step is also rate-limiting step for Path 4. Due to the ortho substituent effect, the carboxylation intermediate \text{IN}11 is less stable than the gold carbene intermediate \text{IN}12 by 4.7 kcal/mol; the energy gap between transition states TS11 and TS12 is increased to 8.5 kcal/mol, which is significantly larger than that between TS5 and TS6 (3.3 kcal/mol), indicating that the intermediate \text{IN}11 is more difficult to cross over this energy barrier. The reaction using substrate 2m is probably kinetically controlled, thus the kinetically favorable product 5 is obtained. The calculation results can explain why using substrate having aryl group with ortho-substituent can obtain product 5 as major product in experiments. For comparison, we switched the ligand to IPr, and also investigated the possible reaction pathways of substrate 2m, and the results are shown in Scheme 11. In general, the calculated reaction energy profiles using IPr as ligand are similar to those using JohnPhos as ligand. The carboxylation intermediate \text{IN}18 is less stable than the gold carbene intermediate \text{IN}19 by 7.7 kcal/mol, which is similar to their analogues \text{IN}11 and \text{IN}12, indicating that the key intermediates’ stabilities are hardly influenced by phosphorus ligand. It is notable that the cleavage of cyclopropane ring via TS15 with an energy barrier of 22.2 kcal/mol, which is slightly higher than that of 1,2-H shift step via TS17 in Path 5, thus the cleavage of cyclopropane ring becomes the rate-limiting step. Moreover, the energy barrier (22.2 kcal/mol) of the rate-limiting step along Path 5 is higher than that (20.4 kcal/mol) of the rate-limiting step along Path 3, indicating that it is more difficult to obtain product 3 using IPr as ligand. This result partially agrees with the experimental finding that the poor yield of product 3 was obtained using IPr as ligand. There is no significant difference between the reaction energy profile along Path 4 and that along Path 6. The experimental results in Table 2 show that the catalysts affect the product selectivity, probably mainly due to the temperature effect, not significantly influenced by the ligand effect.
Scheme 9. Calculated reaction pathway for the reaction of 1a having aryl group without ortho substituent.

Scheme 10. Calculated reaction pathway for the reaction of 2m having aryl group with ortho substituent.
Scheme 11. Calculated reaction pathway for the reaction of 2m having aryl group with ortho substituent using IPr as the ligand.
Rationalization of the Temperature Effect: the steric bulky and electron-rich IPr ligand was crucial for the selective formation of product 4 at -30 °C because the gold complex IPrAuNTf₂ also becomes steric bulky and electron-rich and thus will be less reactive to activate the alkene unit in 4. On the other hand, Johnphos is a bulky phosphine ligand as well, however, it is not as electron-rich as IPr. Thus, the compound could be transformed into compound 5 at 0 °C. At higher temperature, compound 6 was produced as the final product.

Compounds 5m and 6m could be transformed to compounds 5m' and 6m' by halogen-lithium exchange and subsequent quenching with water, indicating that the bromine atom at the ortho position can serve as a removable directing group to control the reaction pathway, and it can be easily removed when the reaction was complete (Scheme 12).

Scheme 12. Removable bromine atom controls the reaction outcome.

In conclusion, a novel gold(I) catalyzed cycloisomerization of 1,5-enynes containing a cyclopropane has been developed. The cyclopropane functionality in substrates has a great influence on the reaction pathway, and the suggested gold carbene intermediate I involving two cyclopropyl moieties is critical to result in the divergent reaction pathways. With this methodology, cyclobutane fused 1,4-cyclohexadiene, 1,3-cyclohexadiene derivatives, tricyclic cyclobutene derivatives and bis cyclopropane derivatives can be selectively synthesized in high yields. A plausible mechanism has been proposed according to the deuteration labeling, the intermediate trapping experiments and theoretical investigations. The dramatic ortho-substituent effects have been investigated by DFT calculations, which rationalized the experimental findings. Further efforts to expand application of this novel gold(I) catalyzed reaction are underway, and the results will be published in due course.

Computational methods. All DFT calculations were performed with Gaussian 09 program. The geometries of all minima and transition states have been optimized using PBE1PBE functional. The SDD basis set and pseudopotential were used for the gold atom, and the 6-31G(d) basis set was used for other atoms. The subsequent frequency calculations on the stationary points were carried out at the same level of theory to ascertain the nature of the stationary points as minima or first-order saddle points on the respective potential energy surfaces. All transition states were characterized by one and only one imaginary frequency pertaining to the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory to further authenticate the transition states. The conformational space of flexible systems has first been searched manually. Thermochemical corrections to 298.15 K have been calculated for all minima from unscalled vibrational frequencies obtained at this same level. The solvent effect was estimated by the IEFPCM method with radii and non-electrostatic terms for SMD salvation model in dichloromethane (ε = 8.93). Solution-phase single point energy calculations (SDD basis set and pseudopotential used for the gold atom, and the 6-31+G(d,p) basis set used for other atoms) were performed based on the gas phase optimized structures.

Acknowledgement: We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, and the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21421091, 21372250, 2112062, 21302203, 20732008, and 21572052).

Notes and references


[15] The crystal data of 2 has been deposited in CCDC with number 1033827. The crystal data of 2a has been deposited in CCDC with number 1036129.

When the cyclopropane was replaced with two methyl groups, the reaction outcome was different. See ref. 3p.


Divergent Reaction Pathways in Gold Catalyzed Cycloisomerization of 1,5-Enynes Containing a Cyclopropane: Dramatic Ortho Substituent and Temperature Effects

Gold catalyzed cycloisomerization of 1,5-enynes containing a cyclopropane provides an efficient synthetic protocol for the construction of cyclobutane fused 1,4-cyclohexadiene, 1,3-cyclohexadiene derivatives, tricyclic cyclobutene derivatives and bicyclop propane derivatives.

Gen-Qiang Chen, Wei Fang, Yin Wei,* Xiang-Ying Tang,* and Min Shi*