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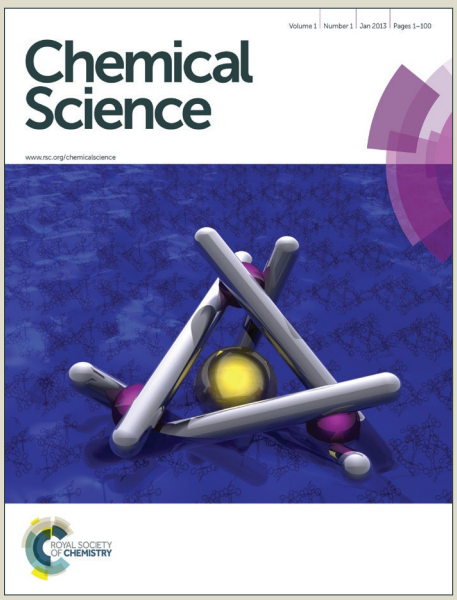

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ARTICLE TYPE

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*

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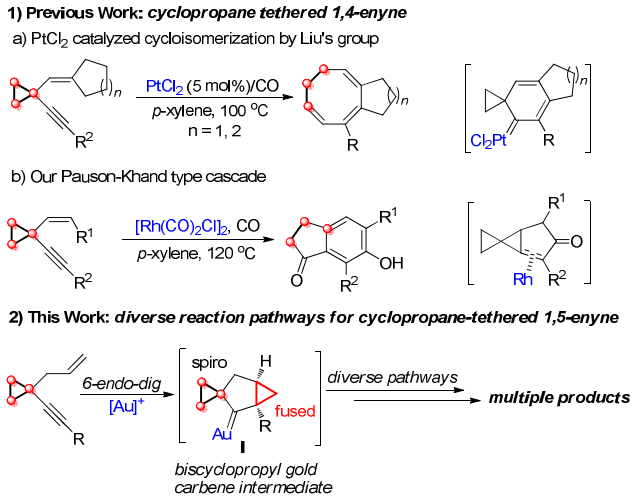
A gold(I)-catalyzed cycloisomerization of easily available 1,5-enynes containing a cyclopropane has been developed, efficiently providing cyclobutane fused 1,4-cyclohexadiene, tricyclic cyclobutene, biscyclopropane, 1,3-cyclohexadiene derivatives in moderate to excellent yields. When the phenyl group 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[1] is one of the most important strategies for the construction of cyclic structures from simple acyclic enyne substrates, of which 1,4-,[2] 1,5-,[3] 1,6-[4] and 1,7-enynes[4k, 5] 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.[6a, b] Reports on homogeneous gold catalysis have been increasing explosively during the last decade[6-7] and 1,5-enyne has always been the trial ground for gold catalysis. In 2004, Malacria[3o] and Fürstner[3p] 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 $PtCl_2$ or gold(I), respectively. Subsequently, Toste's group found that gold(I)-catalyzed isomerization of 1,5-enynes could produce bicyclo[3.1.0]hexane[3q] or tetracyclic[3h] compound efficiently. Kozmin[3j, 3n] and Zhang's[3k] group disclosed that cyclohexadiene derivatives could be synthesized from siloxy 1,5-enynes or 3-carboxy 1,5-enynes under gold(I) catalysis.

On the other hand, cyclopropanes are versatile building blocks in organic synthesis.[8] The unique structure and its intrinsic strain endow cyclopropanes with high reactivity. Thus far, it has been well known that cyclopropyl group can effectively stabilize carbocations adjacent to it due to its π-character;[9] and cyclopropylmethyl carbocation is a stable non-classical carbocation, which has several resonance structures: homoallyl carbocation, cyclobutyl carbocation and etc.[9a,10,11] In 2010, Liu's group disclosed a novel $PtCl_2$ catalyzed cycloisomerization of cyclopropyl group tethered 1,4-enynes, providing eight-membered carbocycles efficiently (Scheme 1, eq 1a).[2h] Subsequently, we found that cyclopropyl tethered 1,4-enynes could undergo a tandem Pauson-Khand type reaction in the presence of Rh(I) catalyst under CO atmosphere (Scheme 1, eq 1b).[2c] However, reaction of 1,5-enynes tethered by a cyclopropane has been rarely reported to the best of our knowledge (Scheme 1, eq 2).[3c]



Scheme 1. Previous work and this work.

On the basis of the research work of Liu's group as well as gold catalyzed cyclopropane chemistry from Schmalz[12j] and other groups[12] and our long-term exploration on cyclopropane

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: weiyin@sioc.ac.cn; siocxiangying@mail.sioc.ac.cn; mshi@mail.sioc.ac.cn.

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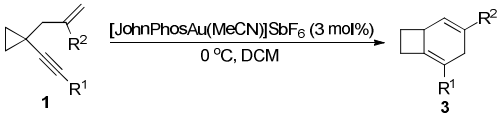
chemistry,[13] we envisaged that when the 1,5-enyne was tethered with a cyclopropane moiety, the reaction should be different. We postulate that a biscyclopopane gold carbene intermediate **I** can be produced in the presence of gold catalyst. The intermediate **I** has a spiro and a fused cyclopropane moiety adjacent to the carbene center, and this unique structure makes it undergo diverse reaction pathways, affording multiple kinds of products (Scheme 1, eq 2).

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 $[PPh_3AuCl]/AgSbF_6$, product **3a** could be afforded in 82% NMR yield. After further optimization of the reaction conditions, we found that when [JohnPhosAu·MeCN]SbF_6 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)$_3$PAu·MeCN]SbF_6, [(*p*-CF_3-Ph)$_3$PAu·MeCN]SbF_6, [P(OAr)$_3$Au·MeCN]SbF_6, [(*t*-Bu)$_3$PAu·MeCN]SbF_6, [JackiePhosAu·MeCN]SbF_6, [XPhosAu·MeCN]SbF_6, and [IPrAu·MeCN]SbF_6 were also evaluated, but no better result was obtained. Therefore, [JohnPhosAu·MeCN]SbF_6 was identified as the best catalyst for the current reaction (see Table SI-1 in the Supporting Information for the detailed optimization of the reaction conditions).

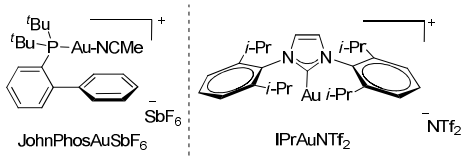
With the optimal reaction conditions in hand, we next turned our efforts to examine the substrate scope of the reaction. We found that when R^1 were aromatic groups with electron-donating or electron-withdrawing substituents (Table 1, entries 1-9), the corresponding products could be obtained in good to excellent yields. Only when a strongly electron-withdrawing group CF_3 or NO_2 was introduced (R^1 = *p*-CF_3-Ph or *p*-NO_2-Ph), the reaction went sluggishly and elevation of temperature was required for the complete conversion (Table 1, entry 10, 11). When the substituents were heteroaromatic groups such as thienyl 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-methoxyl-2-naphthyl group (Table 1, entries 14 and 15). In addition, R^2 could also be an alkyl group, and the corresponding product **3p** could be obtained in 69% yield in the presence of $IPrAuNTf_2$[14] (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**.



entry[a]	R^1, R^2	Time (h)	Yield (%)[b]
1	**1a**, R^1 = Ph, R^2 = H	20	**3a**, 92
2	**1b**, R^1 = *p*-Me-Ph, R^2 = H	17	**3b**, 90
3	**1c**, R^1 = 3,5-*di*-Me-Ph, R^2 = H	14	**3c**, 91
4	**1d**, R^1 = *p*-MeO-Ph, R^2 = H	12	**3d**, 93
5	**1e**, R^1 = *m*-MeO-Ph, R^2 = H	17	**3e**, 88
6	**1f**, R^1 = *p*-Ph-Ph, R^2 = H	16.5	**3f**, 92
7	**1g**, R^1 = *p*-Br-Ph, R^2 = H	18	**3g**, 85
8	**1h**, R^1 = *p*-Cl-Ph, R^2 = H	20	**3h**, 84
9	**1i**, R^1 = *p*-F-Ph, R^2 = H	19	**3i**, 82
10[c]	**1j**, R^1 = *p*-CF_3-Ph, R^2 = H	19	**3j**, 82
11[d]	**1k**, R^1 = *p*-NO_2-Ph, R^2 = H	36	**3k**, 72
12	**1l**, R^1 = 2-thienyl, R^2 = H	14	**3l**, 86
13	**1m**, R^1 = 1-Boc-5-indoly, R^2 = H	14	**3m**, 95
14	**1n**, R^1 = 2-Naphthyl, R^2 = H	14	**3n**, 87
15	**1o**, R^1 = 6-MeO-2-naphthyl, R^2 = H	18	**3o**, 94
16[e]	**1p**, R^1 = 9-Phen, R^2 = Me	12	**3p**, 69

[a] 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 catalyst solution was added to the Schlenk tube. The reaction was allowed to stir at indicated temperature until TLC indicated complete conversion of **1**. [b] Isolated yield. [c] The reaction was conducted at 10 °C. [d] The reaction was conducted at 60 °C for 36 h, and the product contains about 20% of 1,3-cyclohexadiene **9k** and the total yield was 91%. [e] $IPrAuNTf_2$ was used as catalyst instead of JohnPhosAuSbF_6.



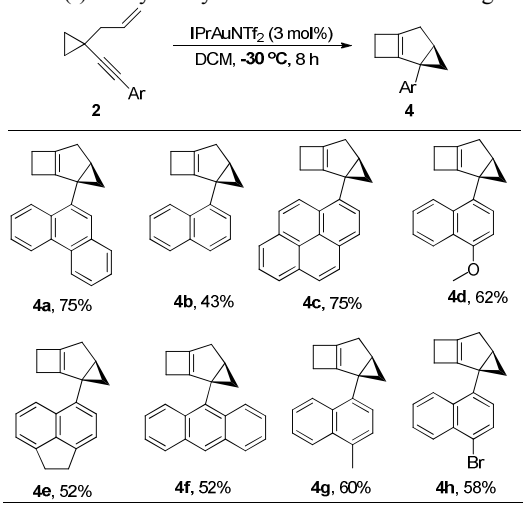
It was a great surprise that compound **2a**, in which Ar is a 9-phenanthrenyl group, could not produce **3a** in the presence of [JohnPhosAu·MeCN]SbF_6 and two new compounds **5a** and **6a** were obtained in 37% and 54% yields, respectively (Table 2, entry 1). Inspired by this discovery, we optimized 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]SbF_6 (Table 2, entry 3). By elevation of the reaction temperature, compound **6a** could be obtained in higher yield in the presence of $IPrAuNTf_2$ or [JohnPhosAu·MeCN]SbF_6 (Table 2, entries 4 and 5) in DCE. When the reaction of **2a** was conducted at -20 °C using [JohnPhosAu·MeCN]SbF_6 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 $IPrAuNTf_2$, **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**.

entry	catalyst (3 mol%)	solvent	temperature (°C)	yield[a] (%)		
				4a	5a	6a
1[b]	[JohnPhosAu(MeCN)]SbF_6	DCM	rt	N.D.	37	54
2	JohnPhosAuOAc	DCE	rt		N.R.	
3[b]	***[JohnPhosAu(MeCN)]SbF$_6$***	***DCM***	***0***	***trace***	***84***	***< 5***
4	IPrAuNTf$_2$	DCE	80	N.D.	N.D.	90
5	***[JohnPhosAu(MeCN)]SbF$_6$***	***DCE***	***60***	***N.D.***	***N.D.***	***95***
6[b]	[JohnPhosAu(MeCN)]SbF_6	DCM	-20	5[d]	trace	N.D.
7[b,c]	***IPrAuNTf$_2$***	***DCM***	***-30***	***75***	***trace***	***N.D.***

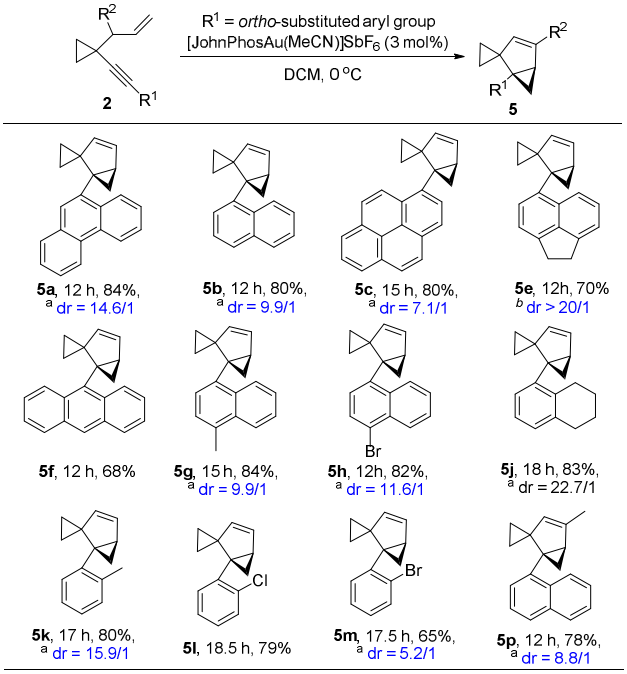
[a] Isolated yield. [b] The reaction was quenched with DMS (dimethyl sulfide). [c] The reaction was conducted for 8 hours. [d] NMR yield.

Table 3. Au(I) catalyzed cycloisomerization of **2** leading to **4**.



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).

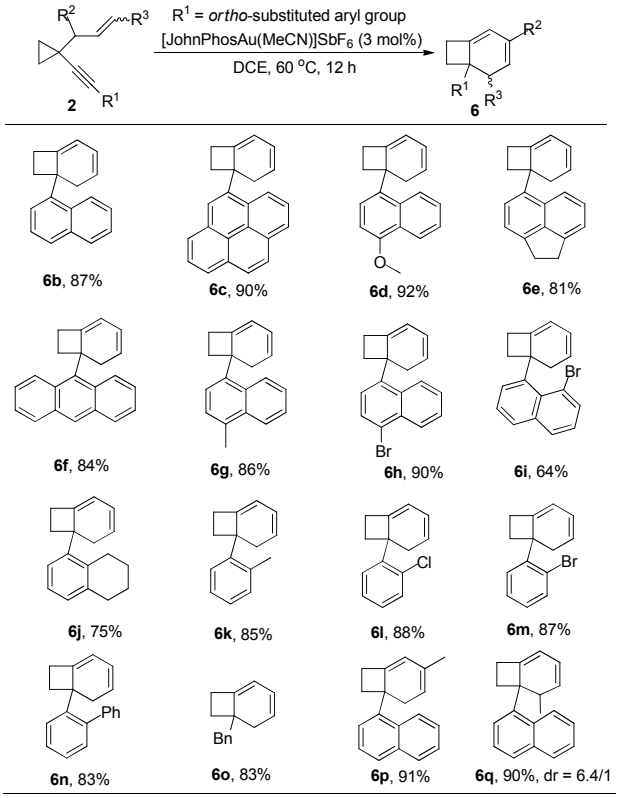
Table 4. Au(I) catalyzed cycloisomerization of **2** leading to **5**.



[a] The dr value was determined by ^{1}H-NMR spectroscopy in $CDCl_3$. [b] The dr value was determined by ^{1}H NMR spectroscopy in $CDCl_3$ as well as HPLC resolution.

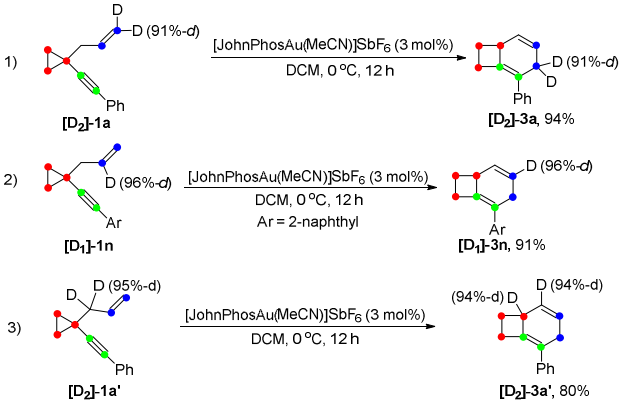
The substrate generality for the formation of the biscyclopropane product **5** was also examined. When the alkynyl substituent was a naphthyl or substituted naphthyl group or its derivatives, the reaction went smoothly to produce products **5** in high yields (Table 4, **5a**-**5h**); H_4-naphthyl substrate **2j** also worked well (Table 4, **5j**); 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 the 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**.



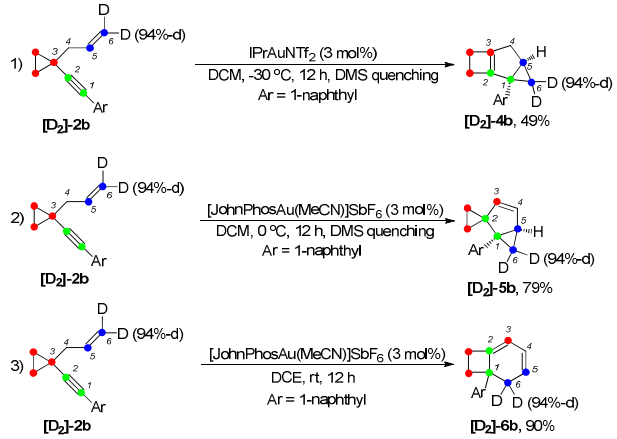
After further exploration of the substrate scope for the formation of **6**, we found that when the substituent on the alkyne group was 1-naphthyl or substituted 1-naphthyl group or its derivatives, the corresponding products **6b**-**6i** could be obtained in good to excellent yields. The reaction also 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 alkene 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]

Deuterium Labeling Experiments. The deuterium labeling experiment was conducted to gain further insights into the reaction mechanism. For deuterium-labeled substrates **[D$_2$]-1a** and **[D$_1$]-1n**, the corresponding products **[D$_2$]-3a** and **[D$_1$]-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$_2$]-3a**' was produced in 80% yield along with one deuterium shift (Scheme 2, eq 3).

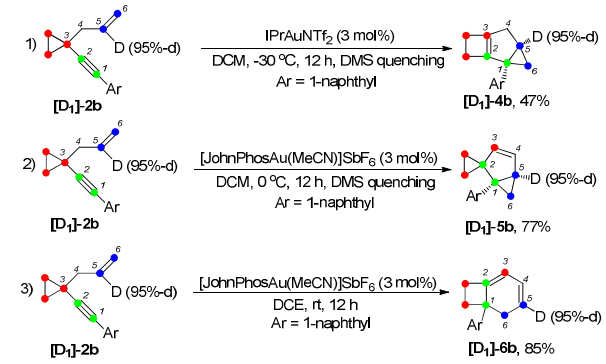


Scheme 2. Deuterium labeling experiment for formation of **3**.

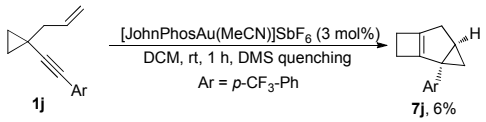
The deuterium-labeled compounds **[D$_2$]-2b** and **[D$_1$]-2b** were also synthesized and subjected to the standard reaction conditions for the formation of products **4b**, **5b** and **6b**. The corresponding products **[D$_2$]-4b**, **[D$_2$]-5b**, **[D$_2$]-6b** and **[D$_1$]-4b**, **[D$_1$]-5b, [D$_1$]-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**.



Scheme 3. Deuterium labeling experiment (**[D$_2$]-2b**).



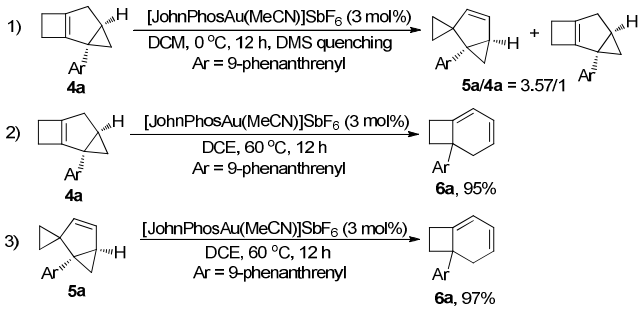
Scheme 4. Deuterium labeling experiment (**[D$_1$]-2b**).



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^1. 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]SbF_6 (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).[17] 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[16] 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.[20] The cationic intermediate **C**" undergoes the ring contraction to form carbenoid intermediate **E**.[4p,18] 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).

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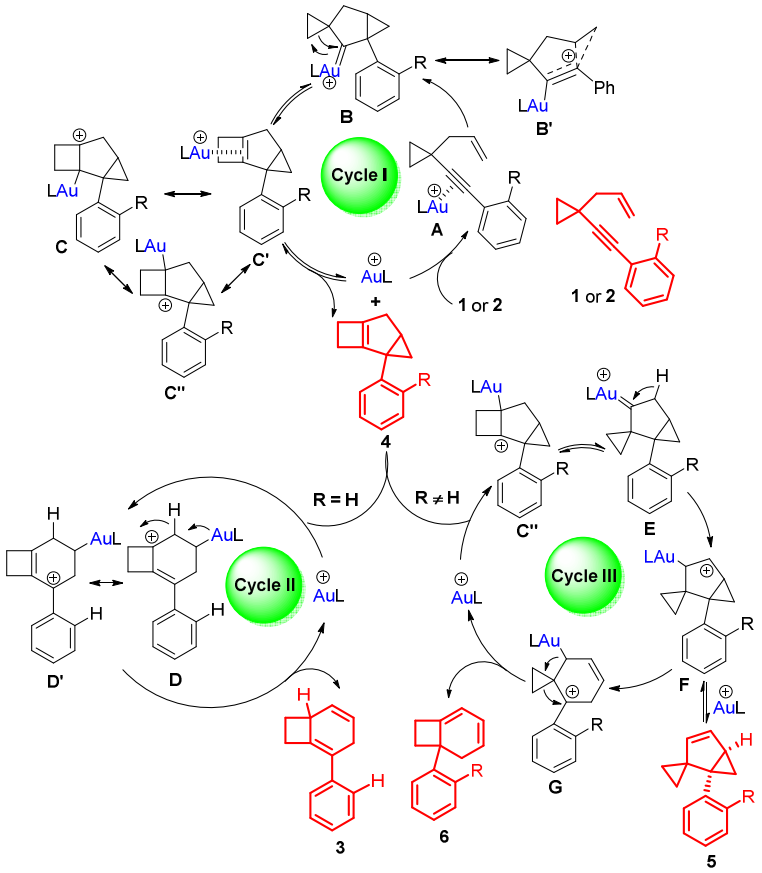


Scheme 7. A plausible mechanism for the formation of **3**, **4**, **5** and **6**.

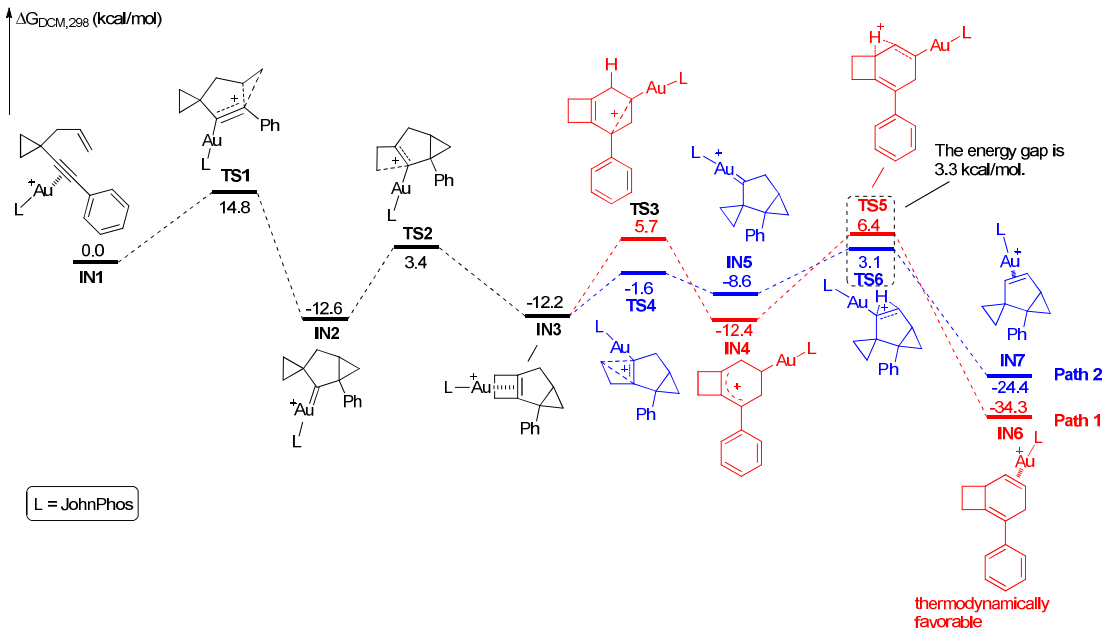
Rationalization of Ortho-substituent Effects. As for substrate **1** having aryl group without ortho-substituent, 1,4-cyclohexadienes **3** could be produced. In contrast, substrate **2** having aryl group with ortho-substituent afforded three different products. Based on the proposed reaction mechanism, 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.

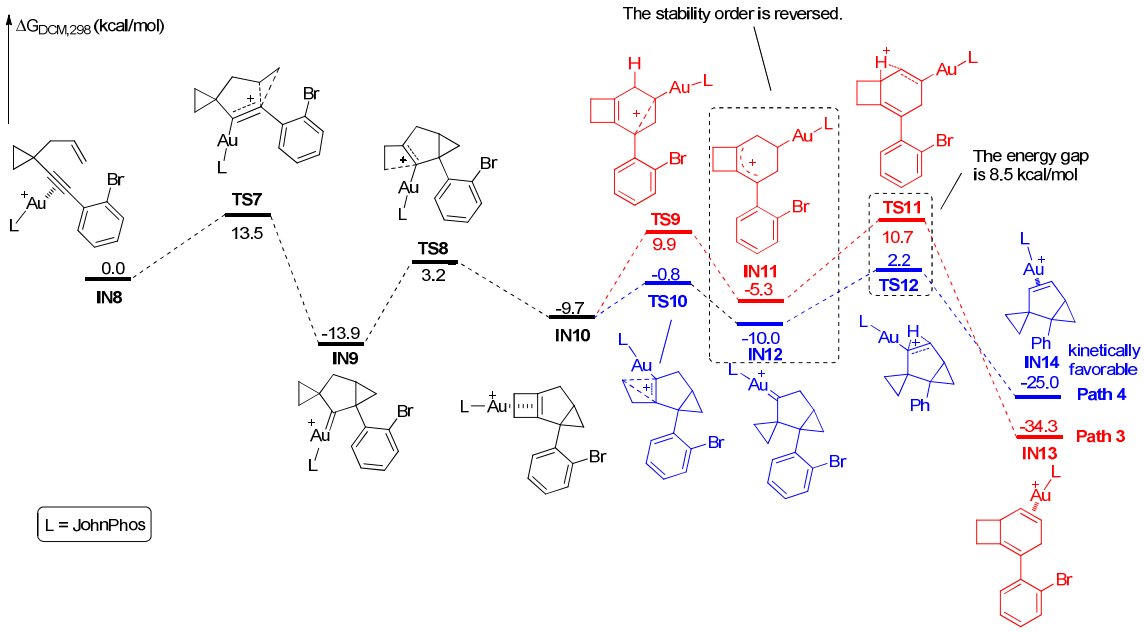
To understand these ortho-substituent effects, we performed DFT calculations on the possible reaction pathways using substrates **1a** and **2m**. For substrate **1a**, the reaction energy profile is depicted in Scheme 9. Initially, coordination of Au(I) catalyst to the alkyne moiety of substrate **1a** 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 **IN4**. Subsequently, 1,2-H shift of intermediate via **TS5** is leading to intermediate **IN6**, which undergoes deauration to give product **3**. Transition state **TS5** is located 18.6 kcal/mol above intermediate **IN3** 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 carbocation intermediate **IN3** is skeletal rearrangement via **TS4** with energy barrier of 10.6 kcal/mol, leading to gold carbene intermediate **IN5**. Intermediate **IN5** also undergoes 1,2-H shift via **TS6**, affording intermediate **IN7**, which undergoes deauration to give product **5**. Transition state **TS6** is located 15.3 kcal/mol above intermediate **IN3** 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 **IN4** and **IN6** along the **Path 1** are thermodynamically more stable than those intermediates **IN5** and **IN7** 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 PPh_3, 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 $[PPh_3AuCl]/AgSbF_6$. 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.

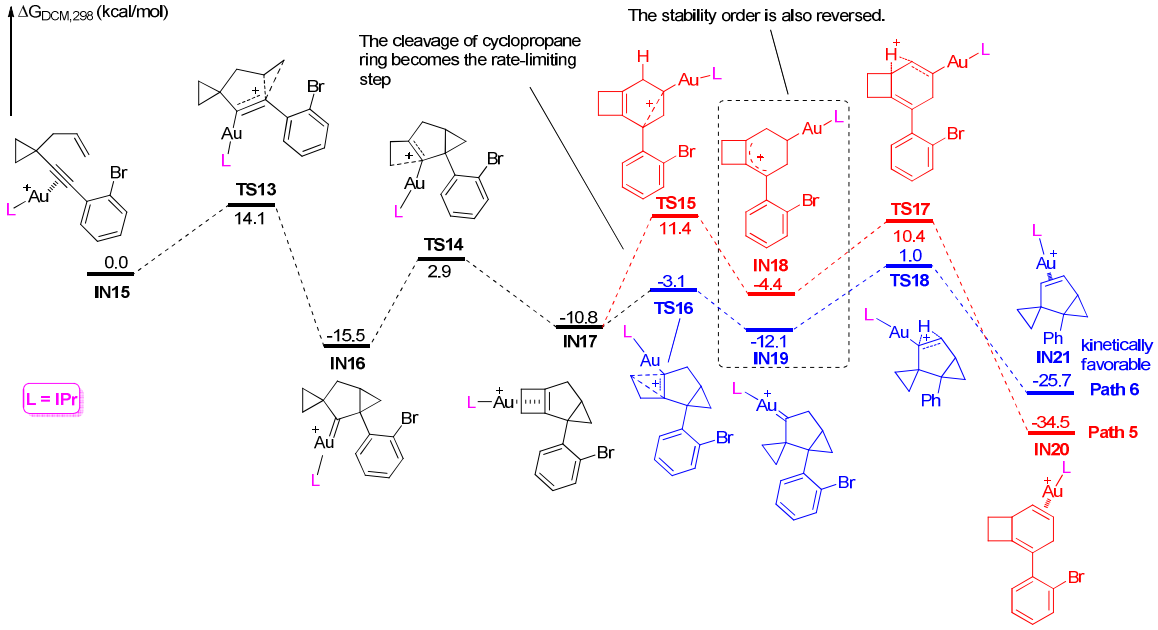
We further investigated the reaction energy profiles for the reaction of substrate **2m** having aryl group with ortho-substituent Br, and the results are shown in Scheme 10. In the similar manner, coordination of Au(I) catalyst to the alkyne moiety of substrate **2m** generates gold complex **IN8**. The gold complex **IN8** undergoes a 6-*endo*-dig cyclization to give a gold carbene intermediate **IN9** via transition state **TS7** with an energy barrier of 13.5 kcal/mol. Subsequently, the intermediate **IN9** undergoes ring enlargement via transition state **TS8** with an energy barrier of 17.1 kcal/mol, producing another intermediate **IN10**. The intermediate **IN10** 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 carbocation intermediate **IN11**. Subsequently, 1,2-H shift of intermediate via **TS11** is leading to intermediate **IN13**, which undergoes deauration to give product **3**. Transition state **TS11** is located 20.4 kcal/mol above intermediate **IN10** 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 carbocation intermediate **IN10** is skeletal rearrangement via **TS10** with energy barrier of 8.9 kcal/mol, leading to gold carbene intermediate **IN12**. Intermediate **IN12** also undergoes 1,2-H shift via **TS12**, affording intermediate **IN14**, which undergoes deauration to give product **5**. Transition state **TS12** is located 11.9 kcal/mol above intermediate **IN10** and 3.0 kcal/mol ab ove 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 carbocation intermediate **IN11** is less stable than the gold carbene intermediate **IN12** 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 **IN11** 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 carbocation intermediate **IN18** is less stable than the gold carbene intermediate **IN19** by 7.7 kcal/mol, which is similar to their analogues **IN11** and **IN12**, 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.

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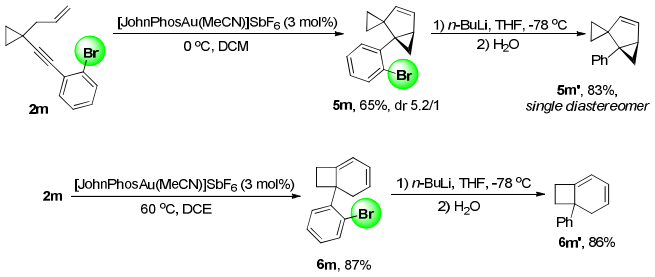
ARTICLE TYPE

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 $IPrAuNTf_2$ 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 **4** 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,[19] 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 biscyclopropane derivatives can be selectively synthesized in high yields. A plausible mechanism has been proposed according to the deuterium 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.[21] The geometries of all minima and transition states have been optimized using PBE1PBE functional.[23] 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 unscaled vibrational frequencies obtained at this same level. The solvent effect was estimated by the IEFPCM method[22] with radii and nonelectrostatic terms for SMD salvation model[24] 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.

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[15] The crystal data of **3n** have been deposited in CCDC with number 1048653. The crystal data of **5b** have been deposited in CCDC with number 1033827. The crystal data of **6c** have been deposited in CCDC with number 1036129.

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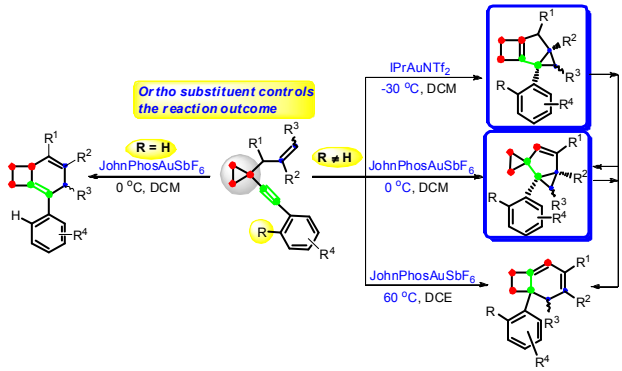
Divergent Reaction Pathways in Gold Catalyzed Cycloisomerization of 1,5-enynes Containing a Cyclopropane: Dramatic Ortho Substituent and Temperature Effects



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 biscyclopropane derivatives.

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