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A Formal [3+3+1] Reaction of Enyne-Methylenecyclopropanes through Au(I)-Catalyzed Enyne Cycloisomerization and Rh(I)-Catalyzed [6+1] Reaction of Vinylspiropentanes and CO

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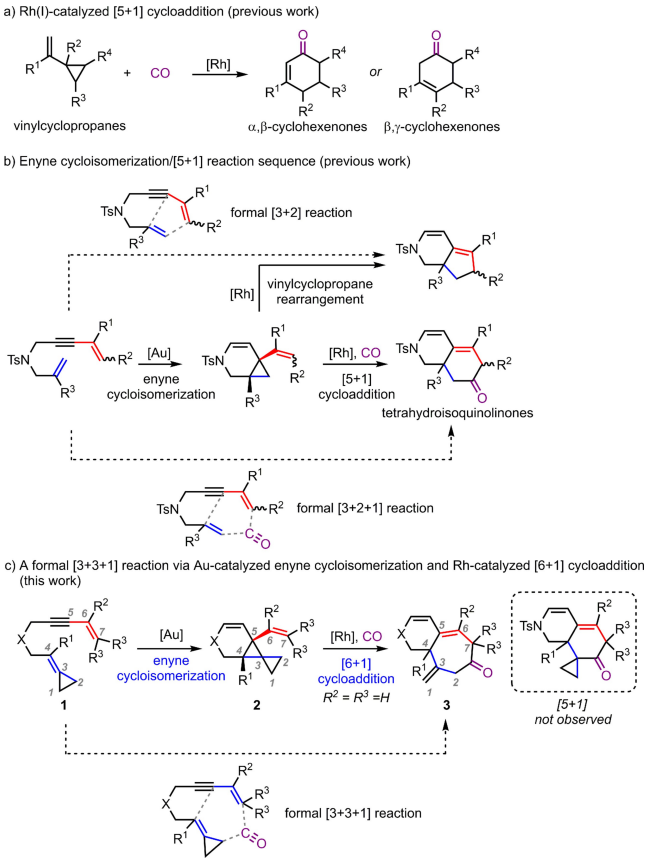
Abstract: A formal [3+3+1] reaction through gold(I)-catalyzed enyne cycloisomerization of enyne-methylenecyclopropanes and rhodium(I)-catalyzed [6+1] reaction of vinylspiropentanes and CO has been developed to synthesize aza-6/7 bicyclic compounds, hexahydrocyclohepta[*c*]pyridinones. DFT calculations reveal that four steps are involved in the [6+1] cycloaddition of vinylspiropentanes and CO, including oxidative addition of cyclopropane to Rh, β–C elimination, CO insertion and reductive elimination.

Introduction

Transition-metal-catalyzed cycloadditions using carbon monoxide (CO) as one component have been widely utilized to construct various ring skeletons.[1] This field has been attracting many leading chemists to develop new reactions that could become tools for chemists in their pursuit of atom- and step-economical synthesis of molecules of interest. Our group is also very active in this research frontier. So far, we have developed [3+2+1],[2] [4+2+1],[3] [5+1],[4] [5+2+1][5] and [7+1][6] reactions, some of which have been used in total synthesis of natural products.[2,4b,5b,7] Among these reactions, Rh(I)-catalyzed [5+1] cycloaddition of vinylcyclopropanes (VCPs) and CO (Scheme 1a) can be used to synthesize α,β- or β,γ-cyclohexenones (asymmetric version can also be realized when chiral vinylcyclopropanes were used).[4a,d] The utility of this cycloaddition was successfully demonstrated in the shortest asymmetric synthesis of (-)-mesembrine.[7d] In order to obtain important perhydroisoquinoline skeletons that are widely found in natural products and pharmaceuticals, an Au-catalyzed enyne cycloisomerization/Rh-catalyzed [5+1] reaction sequence was developed (Scheme 1b),[8] which was also named as a formal [3+2+1] reaction. Without adding CO, the reaction can provide 6/5 bicyclic molecules through Rh-catalyzed vinylcyclopropane rearrangement.[8] With these, we envisioned that if the original 2π component of enynes was replaced by a methylenecyclopropane (MCP) group, the corresponding enyne-methylenecyclopropanes (enyne-MCPs) **1** could undergo Au-catalyzed cyclopropanation to give vinylspiropentanes **2**,[9] which could then undergo some unforeseeable cycloadditions with CO to give molecules with new skeletons.[10,11] We were not sure what the exact products from this reaction would be generated when we had such an idea, but we thought that the additional cyclopropane in **2** compared to vinylcyclopropane could have some C–C bond cleavage reactions and these could have some surprising and useful results for us. To our delight, experimentally, the enyne-MCPs can be converted to vinylspiropentanes by using gold catalyst, which then, under



Scheme 1. Previous [5+1] reaction and its further development, and the present formal [3+3+1] reaction.

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rhodium catalysis and in the presence of CO, underwent a [6+1] reaction to deliver a molecule with the 6/7 skeleton (Scheme 1c).[12] A proposed mechanism for the key [6+1] reaction of vinylspiropentanes and CO is given in Scheme 2, which includes the distal C1–C2 bond oxidative addition to Rh, C3–C5 bond cleavage, CO insertion and reductive elimination. We name the present enyne cyclopropanation/[6+1] reaction as a formal [3+3+1] reaction,[13] in which both enyne and MCP serve as the 3 C synthons and CO acts as a 1 C synthon. Considering the challenges in the synthesis of seven-membered rings, together with the easy preparation of enyne-MCPs reported here, we believe that the present [3+3+1] reaction can serve as an efficient way to access molecules with 6/7 bicyclic rings. Here we present the development of this reaction and the mechanism of the [6+1] reaction revealed through DFT calculations.

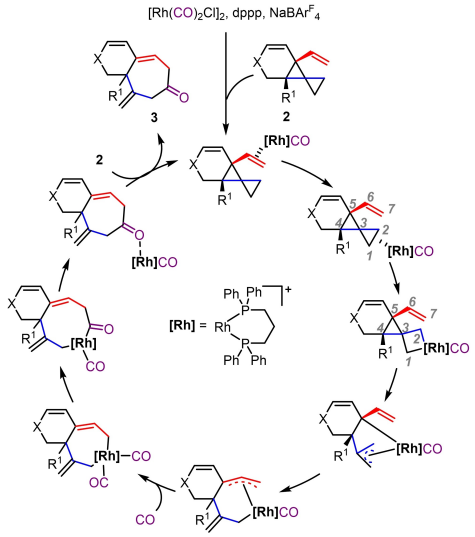
Results and Discussion

We divide our results and discussion here into two parts. In part I, we describe the reaction development of both cycloisomerization and [6+1] reactions, including the study of the scope of the cyclopropanation of enyne-MCPs under the gold catalysis, preliminary attempts to achieve an asymmetric version of this reaction, screening the reaction conditions and studying the scope of the [6+1] reaction of vinylspiropentanes and CO. In part II, we present our DFT calculation results of the [6+1] reaction to understand the details of the reaction mechanism.

Reaction development of formal [3+3+1] reaction

Scope of the Au(I)-Catalyzed Enyne Cycloisomerization

We previously found that, substrates of enyne-methylenecyclopropanes **1** with R^1=Ar, can be converted to azepine-fused cyclobutanes via a cyclization/rearrangement pathway when they were subjected to cationic Au catalyst.[14] Under the same conditions, substrate **1a** with R^1=H was converted to cyclopropanation product **2a** in 56% (Table 1). We then studied the scope of this reaction using the same reaction conditions applied in previous study.[14] Substrates **1b**–**1d** (R^1= Me, ^{n}Bu, Bn) were easily transformed into their corresponding products (**2b**–**2d**) in moderate yields (Table 1, entries 2–4). Substrate **1e** with an electron-deficient aryl group can also undergo the cyclopropanation in 46% yield (Table 1, entry 5), in contrast to similar substrates with R^1=electron-neutral and electron-rich aryl groups. Substrates with different substituents at alkene parts (**1f**–**1h**) gave rise to their corresponding products (**2f**–**2h**) in good yields (76% to 90%, Table 1, entries 6–8). We also found that enyne-MCPs with other nitrogen protecting groups (**1i**–**1k**) provided desired tricyclic compounds (**2i**–**2k**, Table 1, entries 9–11). However, the oxygen-tethered enyne-MCP **1l** only gave a complex mixture (Table 1, entry 12).

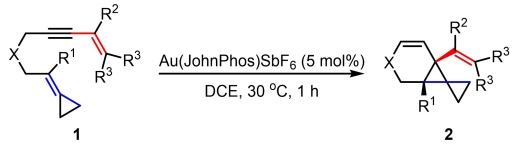


Scheme 2. Proposed mechanism of [6+1] reaction.

Optimization of Au(I)-Catalyzed Enantioselective Cycloisomerization

We then tried to develop an asymmetric version of this Au(I)-catalyzed cycloisomerization. As shown in Table 2, several gold

Table 1. Synthesis of vinylspiropentanes.[a]

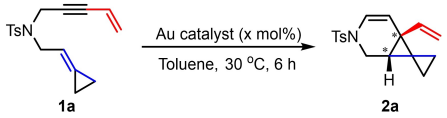


1 2

Entry	Substrate	Product[b]
1	**1a**, R^1=H	**2a**, 56%
2	**1b**, R^1=Me	**2b**, 48%
3	**1c**, R^1=^{n}Bu	**2c**, 50%
4	**1d**, R^1=Bn	**2d**, 52%
5[c]	**1e**, R^1=4-$CF_3C_6H_4$	**2e**, 46%
6[d]	**1f**, R^2=Me, R^3=H	**2f**, 90%
7[d]	**1g**, R^2=Ph, R^3=H	**2g**, 76%
8	**1h**, R^2=H, R^3=Me	**2h**, 82%
9[d]	**1i**, X=NNs	**2i**, 64%
10	**1j**, X=NSO_2Ph	**2j**, 60%
11	**1k**, X=NBs	**2k**, 60%
12	**1l**, X=O	complex mixture

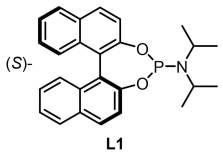
[a] Reaction conditions: 0.2 mmol **1**, 5 mol% Au(JohnPhos)SbF_6, DCE (0.1 M), 30 °C, 1 h; [b] average yield of two runs; [c] 17 h; [d] 12 h.

Table 2. Optimization of ligands for Au-catalyzed asymmetric enyne cycloisomerization.[a]

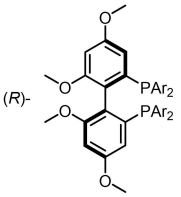


1a 2a

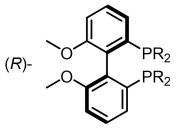
entry	Au catalyst	x	yield	e.e.
1	**L1**$AuSbF_6$	5	complex mixture	–
2	**L2**$(AuSbF_6)_2$	**2.5**	**58%**	**78%**
3	**L3**$(AuSbF_6)_2$	2.5	N.R.[b]	–
4	**L4**$(AuSbF_6)_2$	2.5	mixture[c]	–
5	**L5**$(AuSbF_6)_2$	2.5	mixture[d]	–
6	**L6**$(AuSbF_6)_2$	2.5	mixture[e]	–
7	**L7**$(AuSbF_6)_2$	2.5	N.R.[f]	–
8	**L8**$(AuSbF_6)_2$	2.5	N.R.[g]	–
9	**L9**$(AuSbF_6)_2$	2.5	mixture[h]	–
10[i]	**L9**$(AuSbF_6)_2$	2.5	41%	56%
11	**L10**$(AuSbF_6)_2$	2.5	mixture[j]	–



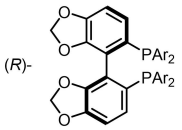
L1



L9, Ar = 4-MeO-3,5-(^{t}Bu)$_2$C$_6$H$_2$



L2, R = 4-MeO-3,5-(^{t}Bu)$_2$C$_6$H$_2$
L3, R = 3,4,5-MeOC$_6$H$_2$
L4, R = 4-NMe$_2$-3,5-(^{i}Pr)$_2$C$_6$H$_2$
L5, R = 3,5-(Me)$_2$C$_6$H$_3$
L6, R = 4-MeC$_6$H$_4$
L7, R = Ph
L8, R = ^{i}Pr



L10, Ar = 4-MeO-3,5-(^{t}Bu)$_2$C$_6$H$_2$

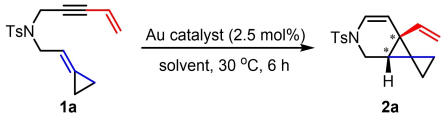
[a] 0.1 mmol **1a**, 2.5 or 5 mol% Au catalyst, Toluene (0.05 M), 30 °C, 6 h; [b] substrate was recovered in 80%; N.R. = no reaction; [c] a mixture of the substrate and product with a ratio of 1/0.48; [d] a mixture of the substrate and product with a ratio of 1/0.13; [e] a mixture of the substrate and product with a ratio of 1/0.1; [f] substrate was recovered in 79%; [g] substrate was recovered in 93%; [h] a mixture of the substrate and product with a ratio of 1/4.45; [i] 12 h; [j] a mixture of the substrate and product with a ratio of 1/0.36.

catalysts with different chiral ligands were tested. Gold catalyst with phosphoramidite ligand **L1** (*O*,*O*′-(*S*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*-di-^{i}propyl-phosphoramidite) was firstly used in the reaction of **1a**, and unfortunately only complex mixture was generated (Table 2, entry 1). Then, we tried the cycloisomerization of **1a** with MeOBIPHEP type ligands **L2**–**L8** (Table 2, entries 2–8). The desired product **2a** was obtained in 58% yield and 78% e.e. when **L2** ((*R*)-4-MeO-3,5-(^{t}Bu)$_2$-MeOBIPHEP) was employed (Table 2, entry 2). But to our disappointment, no reaction of **1a** took place by using **L3** and **L7**–**L8** (Table 2, entries 3 and 7–8), and a mixture of **1a** and **2a** was produced by using **L4**–**L6** (Table 2, entries 4–6). A mixture of **1a** and **2a** was also obtained when **L9** ((*R*)-DTBM-Garphos) was tested (Table 2, entry 9). We could get **2a** in 41% yield and 56% e.e. by elongating the reaction time to 12 h (Table 2, entry 10). However, the reaction also provided a mixture of **1a** and **2a** when **L10** ((*R*)-DTBM-SEGPHOS) was employed (Table 2, entry 11). Therefore, we decided to use **L2** in entry 2 to do further optimizations of solvents and counter anions (Table 3). Unfortunately, all test solvents such as DCE or THF were found to be inferior than toluene (Table 3, entries 1 to 5). We also tested several different counterions, finding that either the starting material of **1a** remained (Table 3, entries 6, 8 and 10) or a mixture of **1a** and **2a** was observed (Table 3, entries 7 and 9). In addition, substrate **1a** could be transformed into product **2a** in a comparable yield of 55% and the same 78% e.e. in 0.2 mmol scale (Table 3, entry 11). Considering that product **2a** can only be synthesized in modest yield (58%) and e.e. (78%), we decided to just disclose a racemic version of this cycloisomerization/[6 + 1] reaction by using racemic vinylspiropentanes.

Rh(I)-Catalyzed [6 + 1] Reaction of Vinylspiropentanes and CO

Table 4 lists our study of optimizing the [6 + 1] cycloaddition reaction of **2a** and CO. We firstly applied the standard reaction conditions of our previous [5 + 1] cycloaddition, finding that the desired **3a** can be produced in 19% yield (Table 4, entry 1). By raising the CO pressure to 1 atm, the yield of **3a** was increased to 64% (Table 4, entries 1–3). However, no reaction took place without CO, and in this case, substrate **2a** was recovered in a high yield. To our disappointment, changing either ligands or solvents could not improve the outcome of the [6 + 1] reaction (Table 4, entries 3–9). Through screening various counter anions (Table 4, entries 3 and 10–12), we found that tetrakis(3,5-bis (trifluoromethyl)phenyl)borate (BAr^F_4) was the best one, and **3a** can be obtained in 75% yield in this case. Neither increasing Rh catalyst loading nor decreasing reaction temperature gave better results (Table 4, entries 12–14). But to our surprise, the reaction yield decreased to 21% under a higher CO pressure of 5 atm (Table 4, entries 12 and 15). When this reaction was

Table 3. Optimization of solvents and counterions for Au-catalyzed asymmetric enyne cycloisomerization.[a]

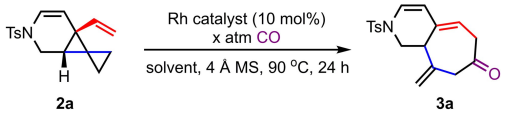


1a 2a

entry	Au catalyst	solvent	yield	e.e.
1	**L2**$(AuSbF_6)_2$	**Toluene**	**58%**	**78%**
2	**L2**$(AuSbF_6)_2$	DCE	complex mixture	–
3	**L2**$(AuSbF_6)_2$	DCM	complex mixture	–
4	**L2**$(AuSbF_6)_2$	THF	N.R.[b]	–
5	**L2**$(AuSbF_6)_2$	MeCN	N.R.[c]	–
6	**L2**$(AuBAr^F_4)_2$	Toluene	N.R.[d]	–
7	**L2**$(AuBF_4)_2$	Toluene	mixture[e]	–
8	**L2**$(AuOTf)_2$	Toluene	N.R.[f]	–
9	**L2**$(AuNTf_2)_2$	Toluene	mixture[g]	–
10	**L2**$(AuPF_6)_2$	Toluene	N.R.[h]	–
11[i]	**L2**$(AuSbF_6)_2$	Toluene	55%	78%

[a] 0.1 mmol **1a**, 2.5 mol% Au catalyst, solvent (0.05 M), 30 °C, 6 h; [b] substrate was recovered in 100%; N.R. = no reaction; [c] substrate was recovered in 92%; [d] substrate was recovered in 79%; [e] a mixture of the substrate and product with a ratio of 1/0.45; [f] substrate was recovered in 90%; [g] a mixture of the substrate and product with a ratio of 1/0.09; [h] substrate was recovered in 90%; [i] 0.2 mmol scale, 4 mL solvent.

Table 4. Optimization of [6+1] cycloaddition.[a]

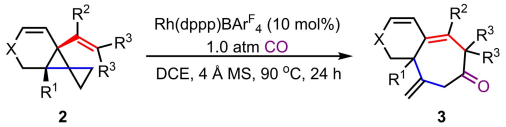


2a 3a

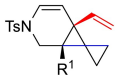
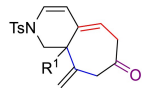
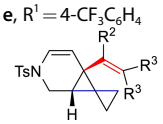
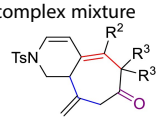
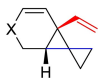
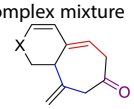
entry	Rh catalyst	x	solvent	yield
1	Rh(dppp)SbF_6	0.2	DCE	19%
2	Rh(dppp)SbF_6	0.5	DCE	20%
3	Rh(dppp)SbF_6	1.0	DCE	64%
4	Rh(dppb)SbF_6	1.0	DCE	9%
5	Rh(dppe)SbF_6	1.0	DCE	12%
6	Rh(dppf)SbF_6	1.0	DCE	13%
7	Rh(L)SbF_6	1.0	DCE	trace
8	Rh(dppp)SbF_6	1.0	PhMe	5%
9	Rh(dppp)SbF_6	1.0	1,4-dioxane	27%
10	Rh(dppp)OTf	1.0	DCE	39%
11	Rh(dppp)NTf_2	1.0	DCE	57%
12	Rh(dppp)BAr^F_4	1.0	DCE	75%
13[b]	Rh(dppp)BAr^F_4	1.0	DCE	67%
14[c]	Rh(dppp)BAr^F_4	1.0	DCE	40%
15	Rh(dppp)BAr^F_4	5.0	DCE	21%
16[d]	**Rh(dppp)BAr^F_4**	**1.0**	**DCE**	**80%**

[a] Reaction conditions: 0.1 mmol **2a**, 10 mol% Rh catalyst, solvent (0.05 M), 0.06 g 4 Å MS, x atm CO, 90 °C, 24 h; [b] 15 mol% Rh catalyst; [c] 80 °C; [d] 0.2 mmol **2a**, 0.1 M; L = 1,3-bis(dicyclohexylphosphino)propane; BAr^F_4 = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

Table 5. Study of reaction scope of [6+1] cycloaddition.[a]



2 3

entry	substrate	product[b]
		
1	**2a**, R^1 = H	**3a**, 80%
2	**2b**, R^1 = Me	**3b**, 58%
3	**2c**, R^1 = ^{n}Bu	**3c**, 38%
4	**2d**, R^1 = Bn	**3d**, 24%
5	**2e**, R^1 = 4-$CF_3C_6H_4$	complex mixture
		
6	**2f**, R^2 = Me, R^3 = H	complex mixture
7	**2g**, R^2 = Ph, R^3 = H	complex mixture
8	**2h**, R^2 = H, R^3 = Me	complex mixture
		
9[c]	**2i**, X=NNs	**3i**, 62%
10	**2j**, X=NSO_2Ph	**3j**, 73%
11	**2k**, X=NBs	**3k**, 72%

[a] Reaction conditions: 0.2 mmol **2**, 10 mol% Rh(dppp)BAr^F_4, DCE (0.1 M), 0.06 g 4 Å MS, 1.0 atm CO, 90 °C, 24 h; [b] average yield of two runs; [c] 26 h.

conducted in a higher concentration (0.1 M) and a larger scale (0.2 mmol), **3a** was obtained in the highest yield of 80% (Table 4, entry 16). Based on these results, we chose entry 16 of Table 4 as the optimal reaction conditions for the [6+1] reaction.

Table 5 shows our study of the scope of the [6+1] reaction. It was found that reaction of **2b** (R^1 = Me), and CO delivered hexahydrocyclohepta[*c*]pyridinone **3b** with a quaternary center at its bridgehead carbon, in a modest yield of 58% (Table 5, entry 2). However, for substrates **2c** and **2d** with bulky R^1 groups (R^1 = ^{n}Bu, Bn), yields of **3c** and **3d** were decreased to 38% and 24%, respectively (Table 5, entries 3 and 4). We only found a complex mixture by applying the standard [6+1] cycloaddition conditions for substrate **2e** which has a CF_3 substituted aryl group (Table 5, entry 5). To our disappointment, we got complex mixtures for substrates with substituents on their alkene moiety (**2f**–**2h**, Table 5, entries 6–8). Tricyclic compounds with other nitrogen protecting groups (**2i**–**2k**) can be successfully converted to their corresponding products (**3i**–**3k**) in modest to good yields (62% to 73%, Table 5, entries 9–11). Furthermore, the 6/7 bicyclic structure of [6+1] product **3i** was confirmed by its X-ray crystallography.[15] We must comment here that, even though the scope of the present [6+1] reaction is of limitation, the obtained products are useful substrates for further transformations, considering that there are several functional groups (enamine, alkene, ketone) in the final [3+3+1] cycloadducts.

Computational Investigation

To rationalize the mechanism of the [6+1] reaction for the formation of hexahydrocyclohepta[*c*]pyridinones **3** from **2**, density functional theory (DFT) calculations at the SMD(DCE)/M06/6-311G(d,p) (SDD for Rh)//B3LYP/6-31G(d) (LANL2DZ for Rh) level[16–21] had been carried out (the cycloisomerization step from **1** to **2** was studied previously[22]). In order to reduce the computational costs without influencing the understanding of the reaction mechanism, the model substrate for our DFT calculations is **2a'**, which differs from the real substrate **2a** by changing the *para*-toluenesulfonyl protecting group in **2a** into a smaller methanesulfonyl group. In addition, four phenyl groups in the dppp ligand in the catalyst are replaced by four methyl groups. Figure 1 is the computed energy profile based on the relative Gibbs free energies computed in DCE solution (ΔG_{sol}). Other computed values such as enthalpies in the gas phase are given in the Supporting Information for reference. In substrate **2a'**, we name one cyclopropyl group with the vinyl substitution as the "activated cyclopropane" and the other group as a "non-activated cyclopropane",[1,23] considering that vinyl group can help the cleavage of cyclopropane.

The [6+1] reaction starts from a 16e intermediate **Int1**, a complex formed by Rh and the C6–C7 double bond of **2a'** (see Figure 1 for atom labelling). Then, this intermediate is converted into a 16e complex **Int2**, which uses the non-activated cyclopropane in the substrate as a coordinating ligand. This change of coordination modes is endergonic by 12.5 kcal/mol. Then a

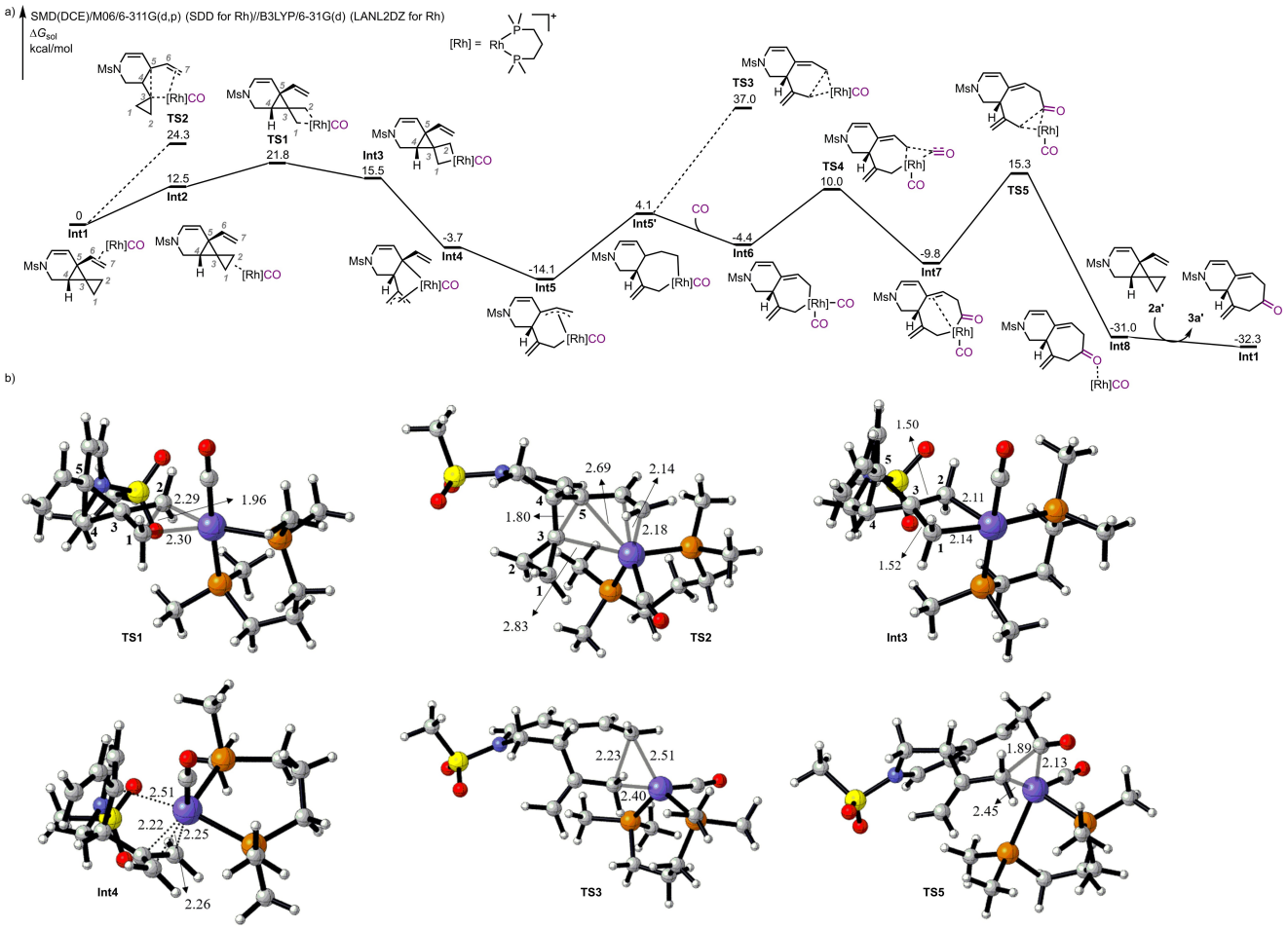


Figure 1. a) Energy profile for the [6 + 1] reaction of **2a'**, and b) the key computed structures (bond distances in angstrom).

direct oxidative addition of Rh catalyst to the C1–C2 bond of the non-activated cyclopropane takes place via **TS1**, affording a 16e intermediate **Int3**. This step is endergonic by 15.5 kcal/mol and requires an activation free energy of 21.8 kcal/mol (from **Int1**). Another possible oxidative addition of Rh catalyst to the C3–C5 bond (via **TS2**) of the activated cyclopropane with a computed activation free energy of 24.3 kcal/mol from **Int1** can also be found. The higher barrier of **TS2** (24.3 kcal/mol of **TS2** vs. 21.8 kcal/mol of **TS1**) indicates that C3–C5 bond cleavage is disfavored. A transition state of the β–C elimination (C3–C5 bond cleavage) from **Int3** to 18e complex **Int4** cannot be located by us, with many trials. Later on, we found that this step is barrierless, as indicated by energy scan calculations through elongating the C3–C5 distance in **Int3** (see the Supporting Information for details).

The newly formed 18e complex **Int4** from **Int3** can isomerize to a more stable $^{3}\eta$-allylic 18e complex **Int5** (this step is exergonic by 10.4 kcal/mol). **Int5** can then isomerize to another $^{1}\eta$-allylic 16e complex **Int5'**, which via CO coordination is converted to $^{1}\eta$-allylic 18e complex **Int6**. Then CO coordination to the Rh atom in **Int5** gives rise to an $^{1}\eta$-allylic 18e complex **Int6**. After that, CO insertion into the Rh–C bond via **TS4** converts **Int6** to an 18e intermediate **Int7**, in which there is an intramolecular alkene coordination to the Rh. This step is endergonic by 4.3 kcal/mol and needs an activation free energy of 24.1 kcal/mol (from **Int5**). A direct reductive elimination (via **TS3**) from **Int5** and **Int5'** with an activation free energy of 51.1 kcal/mol can be excluded for further consideration (see Supporting Information).

The last step of the [6 + 1] reaction is the reductive elimination via **TS5**, needing an activation free energy of 25.1 kcal/mol and delivering a 16e complex **Int8**. Finally, through a ligand exchange reaction between **Int8** and **2a'**, the desired **3a'** is obtained and **Int1** is regenerated for the next catalytic process. This step is exergonic by 1.3 kcal/mol. Overall, in the [6 + 1] reaction, the rate-determining step is the reductive elimination step (via **TS5**) and the overall activation free energy is 29.4 kcal/mol (from **Int5** to **TS5**).

Conclusion

In summary, we developed a Au(I)-catalyzed cycloisomerization/Rh(I)-catalyzed [6 + 1] cycloaddition sequence to obtain hexahydrocyclohepta[*c*]pyridinones from easily prepared enyne-methylenecyclopropanes (enyne-MCPs) **1**. This method, which is

named as a formal [3+3+1] reaction, can be applied to construct aza-compounds that have 6/7 bicyclic skeleton. Detailed DFT calculations have also been performed to reveal the reaction mechanism of this new [6+1] cycloaddition, finding a direct oxidative addition to the distal C1–C2 bond in the non-activated cyclopropane without a vinyl substitution in **2** is preferred over the proximal C3–C5 bond of activated cyclopropane with a vinyl substitution. This step is then followed by a barrierless β–C elimination, CO insertion and reductive elimination. The present study unveils a new C–C cleavage mode and could inspire further development of new reactions involving C–C bond activation.[24]

Experimental Section

Preparation of solution of cationic Au(I) catalyst

Anhydrous DCE (2.0 mL) was added to a mixture of Au(JohnPhos)Cl (5.3 mg, 10.0 μmol) and $AgSbF_6$ (4.1 mg, 11.9 μmol) under nitrogen. The mixture was stirred at room temperature for 30 min. The resulting suspension was left to stand until the formed AgCl precipitated. The supernatant was used in Au(I)-catalyzed cycloisomerization reactions as the catalyst precursor.

General procedure of Au(I)-catalyzed cycloisomerization

Under nitrogen, the above $Au(I)^+$ solution (2.0 mL, 10.0 μmol) was added to a flame-dried glassware containing **1a** (60.6 mg, 0.2 mmol) at 30 °C. The reaction was monitored by TLC. Upon completion, **2a** (33.9 mg) was obtained in 56% yield after flash column chromatography on silica gel (eluted with PE/EA, 20:1).

Preparation of solution of cationic Rh(I) catalyst

Anhydrous DCE (2.0 mL) was added to a mixture of $[Rh(CO)_2Cl]_2$ (3.9 mg, 10.0 μmol), $NaBAr^F_4$ (21.2 mg, 23.9 μmol), dppp (8.2 mg, 19.9 μmol), and the newly activated 4 Å MS (0.06 g) under nitrogen. The mixture was stirred at room temperature for 30 min. The resulting suspension was filtered to afford the supernatant, which was further used in Rh(I)-catalyzed [6+1] cycloaddition reactions as the catalyst precursor.

General procedure of Rh(I)-catalyzed [6+1] cycloaddition

Under nitrogen, the above $Rh(I)^+$ solution (2.0 mL, 20.0 μmol) was added to a flame-dried glassware containing **2a** (60.6 mg, 0.2 mmol) and the newly activated 4 Å MS (0.06 g) at room temperature. Then, the reaction mixture was bubbled with CO (1.0 atm) for 10 min. The glassware was immersed into an oil bath at 90 °C and reacted under the atmospheric pressure of CO. The reaction was monitored by TLC. Upon completion, **3a** (52.7 mg) was obtained in 80% yield after flash column chromatography on silica gel (eluted with PE/EA, 5:1).

Computational Methods

All calculations were performed with the Gaussian 09 program.[25] Geometry optimizations of all minima and transition structures in the gas phase were carried out using the hybrid B3LYP functional[16] with the LANL2DZ basis set[17] and pseudopotential for Rh and the 6-31G(d) basis set[18] for the other atoms. The keyword "5D" was used to specify that five d-type orbitals were used for all elements in the calculations. Frequency calculations at the same level were performed to confirm that each stationary point was either a minimum or a transition structure and to evaluate its zero-point energy and the thermal corrections at 298 K. To improve the calculation accuracy, single-point energy calculations were carried out using the M06 functional[19] with the SDD basis set[20] and pseudopotential for Rh and the 6-311G(d,p) basis set[18] for the other atoms. Solvation energies ($\Delta G_{solvation}$) were single-point energy differences in DCE from those in the gas phase. Single-point energies in DCE ($\varepsilon = 10.125$) were evaluated by SMD[21] calculations. Gibbs free energies in solutions were obtained from sums of the large basis set gas-phase single-point energies, solvation energies ($\Delta G_{solvation}$), and the gas-phase Gibbs free energy corrections (at 298 K). The energy profile was drawn according to Gibbs free energies in the DCE solution (ΔG_{sol}), Gibbs free energies, and enthalpies in the gas phase (ΔG_{gas} and ΔH_{gas}) have been all given in the Supporting Information. Standard state concentrations of 5.5 mM[26] and 1.0 M at 298 K were used for CO and the other species, respectively. The computed structures were illustrated using CYLview.[27]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: gold · enyne cycloisomerization · rhodium · [6+1] cycloaddition · DFT calculations

[1] For selected reviews, see: a) L. Jiao, Z.-X. Yu, *J. Org. Chem.* **2013**, *78*, 6842; b) Y. Gao, X.-F. Fu, Z.-X. Yu, *Top. Curr. Chem.* **2014**, *346*, 195; c) P.-H. Chen, B. A. Billett, T. Tsukamoto, G. Dong, *ACS Catal.* **2017**, *7*, 1340; d) G. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.* **2017**, *117*, 9404; e) J. Liu, R. Liu, Y. Wei, M. Shi, *Trends Chem.* **2019**, *1*, 779; f) J. Wang, S. A. Blaszczyk, X. Li, W. Tang, *Chem. Rev.* **2021**, *121*, 110.
[2] L. Jiao, M. Lin, L.-G. Zhuo, Z.-X. Yu, *Org. Lett.* **2010**, *12*, 2528.
[3] a) Z.-Y. Tian, Q. Cui, C.-H. Liu, Z.-X. Yu, *Angew. Chem.* **2018**, *130*, 15770; *Angew. Chem. Int. Ed.* **2018**, *57*, 15544; b) Q. Cui, Z.-Y. Tian, Z.-X. Yu, *Chem. Eur. J.* **2021**, *27*, 5638.
[4] a) G.-J. Jiang, X.-F. Fu, Q. Li, Z.-X. Yu, *Org. Lett.* **2012**, *14*, 692; b) C.-H. Liu, Z.-X. Yu, *Org. Biomol. Chem.* **2016**, *14*, 5945. For a formal [5+1]/[2+2+1] cycloaddition, see: c) M. Lin, F. Li, L. Jiao, Z.-X. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 1690. For the asymmetric version involving chiral vinylcyclopropanes, see: d) R. Wu, K. Chen, J. Ma, Z.-X. Yu, S. Zhu, *Sci. China Chem.* **2020**, *63*, 1230.
[5] a) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 10060; b) L. Jiao, C. Yuan, Z.-X. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 4421; c) F. Huang, Z.-K. Yao, Y. Wang, Y. Wang, J. Zhang, Z.-X. Yu, *Chem. Asian J.* **2010**, *5*, 1555.
[6] a) Z.-K. Yao, J. Li, Z.-X. Yu, *Org. Lett.* **2011**, *13*, 134; b) X.-F. Fu, Y. Xiang, Z.-X. Yu, *Chem. Eur. J.* **2015**, *21*, 4242.
[7] a) Y. Feng, Z.-X. Yu, *J. Org. Chem.* **2015**, *80*, 1952; b) S. Bose, J. Yang, Z.-X. Yu, *J. Org. Chem.* **2016**, *81*, 6757; c) J. Yang, W. Xu, Q. Cui, X. Fan, L.-N. Wang, Z.-X. Yu, *Org. Lett.* **2017**, *19*, 6040; d) L.-N. Wang, Q. Cui, Z.-X. Yu, *J. Org. Chem.* **2016**, *81*, 10165; e) X. Fan, M.-X. Tang, L.-G. Zhuo, Y. Q. Tu, Z.-X. Yu, *Tetrahedron Lett.* **2009**, *50*, 155; f) X. Fan, L.-G. Zhuo, Y. Q. Tu,

Z.-X. Yu, *Tetrahedron* **2009**, *65*, 4709; g) Y. Liang, X. Jiang, Z.-X. Yu, *Chem. Commun.* **2011**, *47*, 6659; h) Y. Liang, X. Jiang, X.-F. Fu, S. Ye, T. Wang, J. Yuan, Y. Wang, Z.-X. Yu, *Chem. Asian J.* **2012**, *7*, 593.
[8] Z. Zhuang, C.-L. Li, Y. Xiang, Y.-H. Wang, Z.-X. Yu, *Chem. Commun.* **2017**, *53*, 2158.
[9] D.-H. Zhang, Y. Wei, M. Shi, *Chem. Eur. J.* **2012**, *18*, 7026.
[10] For cycloadditions of spiropentanes or vinylspiropentanes with CO, see: a) T. Kurahashi, A. de Meijere, *Angew. Chem.* **2005**, *117*, 8093; *Angew. Chem. Int. Ed.* **2005**, *44*, 7881; b) T. Kurahashi, A. de Meijere, *Synlett* **2005**, *2005*, 2619; c) T. Matsuda, T. Tsuboi, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12596.
[11] For selected reviews about reactions of methylenecyclopropanes, see: a) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213; b) L. Yu, R. Guo, *Org. Prep. Proced. Int.* **2011**, *43*, 209; c) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2014**, *114*, 7317; d) D.-H. Zhang, X.-Y. Tang, M. Shi, *Acc. Chem. Res.* **2014**, *47*, 913; e) L. Yu, M. Liu, F. Chen, Q. Xu, *Org. Biomol. Chem.* **2015**, *13*, 8379.
[12] For a [6+1] reaction, see: P. A. Wender, N. M. Deschamps, R. Sun, *Angew. Chem.* **2006**, *118*, 4061; *Angew. Chem. Int. Ed.* **2006**, *45*, 3957.
[13] For a [3+3+1] reaction, see: S. Y. Kim, S. I. Lee, S. Y. Choi, Y. K. Chung, *Angew. Chem.* **2008**, *120*, 4992; *Angew. Chem. Int. Ed.* **2008**, *47*, 4914.
[14] C.-L. Li, Z.-X. Yu, *J. Org. Chem.* **2019**, *84*, 9913.
[15] For X-ray structure of **3 i**, see Supporting Information. The CCDC number of **3 i** is 2105972.
[16] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.
[17] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.
[18] W. J. Hehre, L. Radom, P. v R Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986**.
[19] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[20] a) L. V. Szentpaly, P. Fuentealba, H. Preuss, H. Stoll, *Chem. Phys. Lett.* **1982**, *93*, 555; b) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* **1987**, *86*, 866; c) P. Schwerdtfeger, M. Dolg, W. H. E. Schwarz, G. A. Bowmaker, P. D. W. Boyd, *J. Chem. Phys.* **1989**, *91*, 1762.
[21] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.
[22] For recent reviews containing Au-catalyzed cycloisomerizations of the 1,6-enynes, see: a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; b) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889; c) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028; d) D. Qian, J. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 677; e) W. Zi, F. D. Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567; f) Y. Li, W. Li, J. Zhang, *Chem. Eur. J.* **2017**, *23*, 467; g) Y. Hu, M. Bai, Y. Yang, Q. Zhou, *Org. Chem. Front.* **2017**, *4*, 2256.
[23] For selected reviews, see: a) Y. Wang, Z.-X. Yu, *Acc. Chem. Res.* **2015**, *48*, 2288; b) V. Ganesh, P. R. Sridhar, S. Chandrasekaran, *Isr. J. Chem.* **2016**, *56*, 417; c) E. M. Budynina, K. L. Ivanov, I. D. Sorokin, M. Y. Melnikov, *Synthesis* **2017**, *49*, 3035; d) D. K. Brownsey, E. Gorobets, D. J. Derksen, *Org. Biomol. Chem.* **2018**, *16*, 3506.
[24] *C–C Bond Activation, Vol. 346* (Ed.: G. Dong), Springer, Berlin, **2014**, pp. 1–257.
[25] *Gaussian 09*, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2013**.
[26] F. W. Skirrow, *Z. Phys. Chem., Stoechiom. Verwandtschaftsl.* **1902**, *41*, 139.
[27] C. Y. Legault, *CYLview*, 1.0b; Universitéde Sherbrooke, **2009**. http://www.cylview.org.

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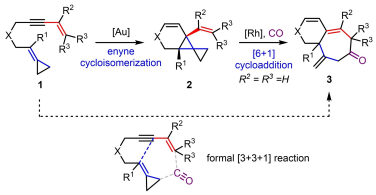
FULL PAPER

A formal [3 + 3 + 1] reaction of enyne-methylenecyclopropanes and CO, which is combined by Au(I)-catalyzed enyne cycloisomerization and Rh(I)-catalyzed [6 + 1] reaction, has been developed to synthesize hexahydrocyclohepta[*c*]pyridinones. The 6c synthon in the [6 + 1] reaction is vinylspiropentanes, generated from Au-catalyzed cycloisomerization of enyne-methylenecyclopropanes. DFT study reveals that the [6 + 1] reaction starts from oxidative addition at the distal bond of non-activated cyclopropane (rather than the proximal bond of activated cyclopropane with a vinyl substitution) in vinylspiropentanes, followed by β–C elimination, CO insertion and reductive elimination.



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A Formal [3 + 3 + 1] Reaction of Enyne-Methylenecyclopropanes through Au(I)-Catalyzed Enyne Cycloisomerization and Rh(I)-Catalyzed [6 + 1] Reaction of Vinylspiropentanes and CO