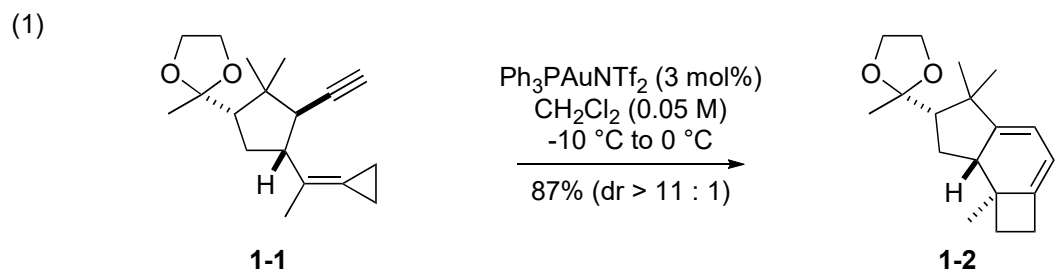# Problem Session (7)

2021.10.2   Haruka Fujino

Please privide the reaction mechanism.
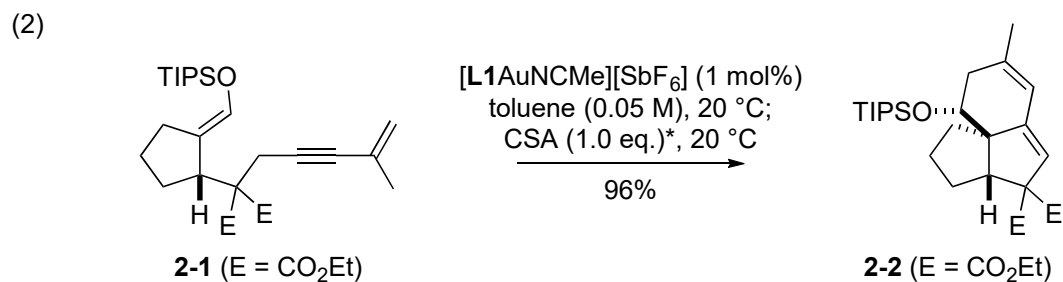
(1)

1-1 → Ph$_3$PAuNTf$_2$ (3 mol%)
CH$_2$Cl$_2$ (0.05 M)
-10 °C to 0 °C
87% (dr > 11 : 1) → **1-2**

(2)

2-1 (E = CO$_2$Et) → [**L1**AuNCMe][SbF$_6$] (1 mol%)
toluene (0.05 M), 20 °C;
CSA (1.0 eq.)*, 20 °C
96% → **2-2** (E = CO$_2$Et)

* CSA was added to the reaction mixture after all the starting material **2-1** was consumed.

(3)

3-1 → [**L2**AuNCPh][BAr$^F_4$]* (5 mol%)
CH$_2$Cl$_2$ (0.15 M), 25 °C
75% (dr 9 : 1) → **3-2**

*BAr$_4$$^{F-}$ = B(3,5-CF$_3$C$_6$H$_3$)$_4$$^-$
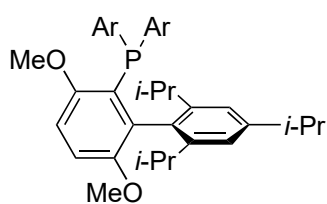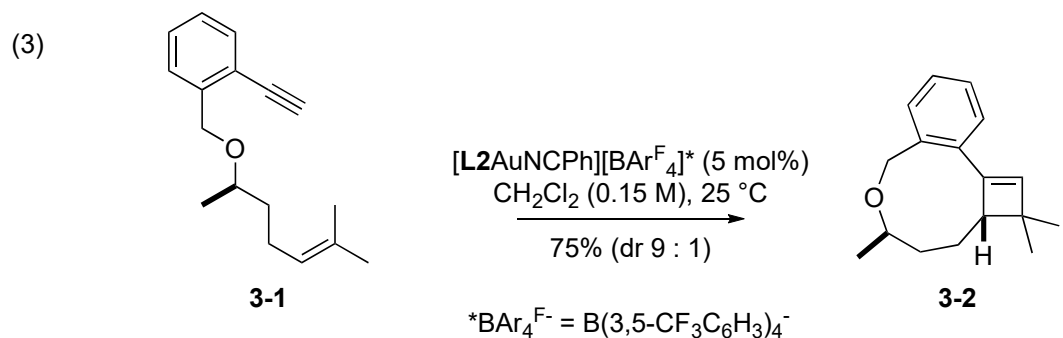
L1 (Ar = 3,5-CF$_3$C$_6$H$_3$)   CSA   **L2** (Ar = 2,6-i-PrC$_6$H$_3$)

Problem Session (7)

2021.10.2   Haruka Fujino
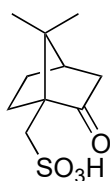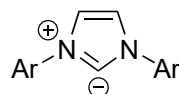
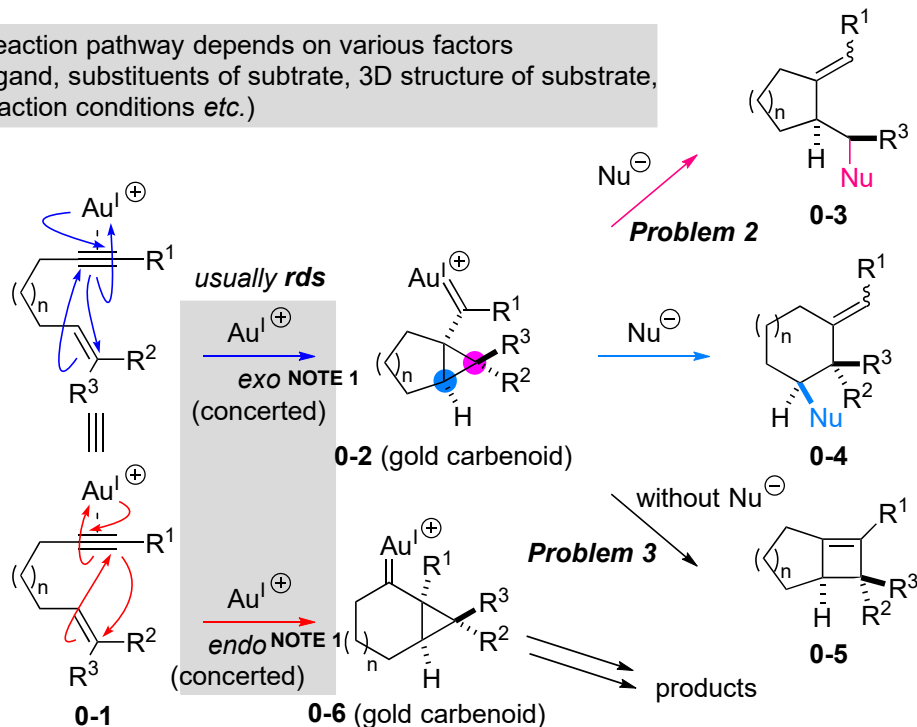**Topic**: Gold-Catalyzed Eneyne Cyclization

0. Introdution

0-1 Outline of the today's PS

General Scheme of Gold-Catalyzed Eneyne Cyclization

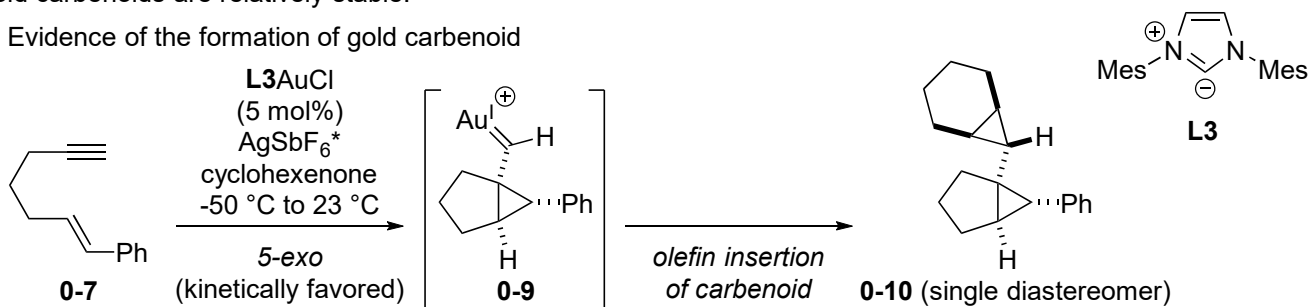 (For details on eneyne cyclization, see also: 200530_PS_Yusuke_Imamura.)

Reaction pathway depends on various factors
(ligand, substituents of subtrate, 3D structure of substrate,
reaction conditions *etc.*)

usually rds

Au^I $^{\oplus}$
exo **NOTE 1**
(concerted)

Au^I $^{\oplus}$
endo **NOTE 1**
(concerted)

0-1

0-2 (gold carbenoid)

Nu$^{\ominus}$
Problem 2

0-3

Nu$^{\ominus}$

0-4

without Nu$^{\ominus}$
Problem 3

0-5

0-6 (gold carbenoid)   products

Echavarren, A. M. et al.
Chem. Rev. **2021**, *121*, 8613
and references herein.

NOTE 1: The formation of gold carbenoids **0-2** or **0-6** generally proceeds in a concerted manner because *E/Z* geometry of **0-1** is basically transferred to the cyclopropane stereochemistry of **0-2** or **0-6**.
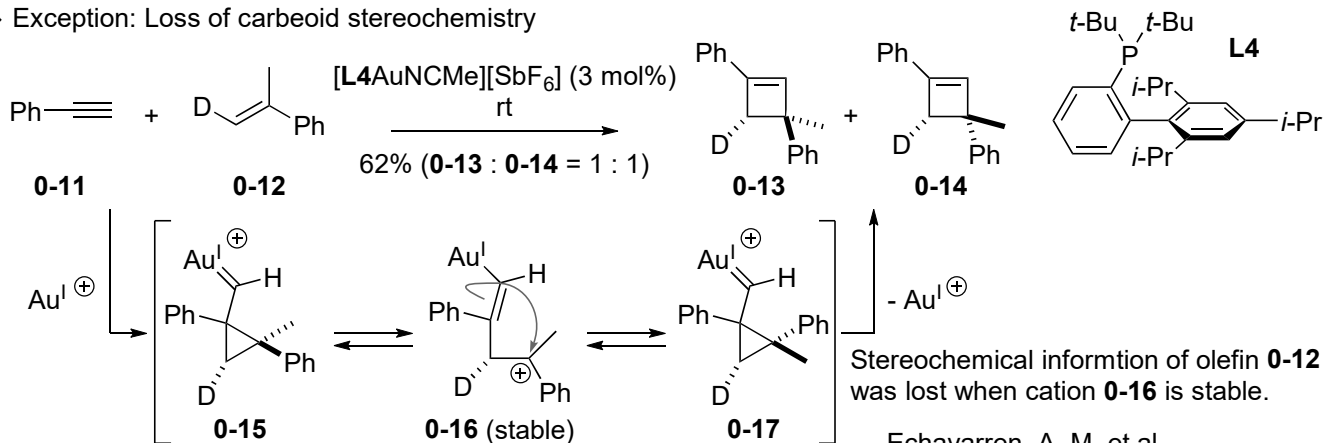Gold carbenoids are relatively stable.

♦ Evidence of the formation of gold carbenoid

L3AuCl
(5 mol%)
AgSbF$_6$*
cyclohexenone
-50 °C to 23 °C

5-exo
(kinetically favored)

0-7

0-9

*olefin insertion
of carbenoid*

0-10 (single diastereomer)

L3

* **L3**AuCl + AgSbF$_6$ -> **L3**AuSbF$_6$ (more cationic) +AgCl [in situ formation of more reactive species]

Echavarren, A. M. et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029.

♦ Exception: Loss of carbeoid stereochemistry

[**L4**AuNCMe][SbF$_6$] (3 mol%)
rt

62% (**0-13** : **0-14** = 1 : 1)

0-11   **0-12**

0-13   **0-14**

L4

Au^I $^{\oplus}$

0-15   **0-16** (stable)   **0-17**

- Au^I $^{\oplus}$

Stereochemical informtion of olefin **0-12**
was lost when cation **0-16** is stable.

Echavarren, A. M. et al.
*J. Am. Chem. Soc.* **2017**, *139*, 10302.

NOTE 2: Valency of gold is kept one throughout the reaction based on the definition that neutral ligands including carbene do not affect the oxidation number of the gold (cf.「有機合成のための遷移金属触媒反応」 辻二郎著).
So, the valency of gold (I) is omitted in this handout.

0-2 Characteristics of gold: Reletivistic effect and "alkynophilicity"
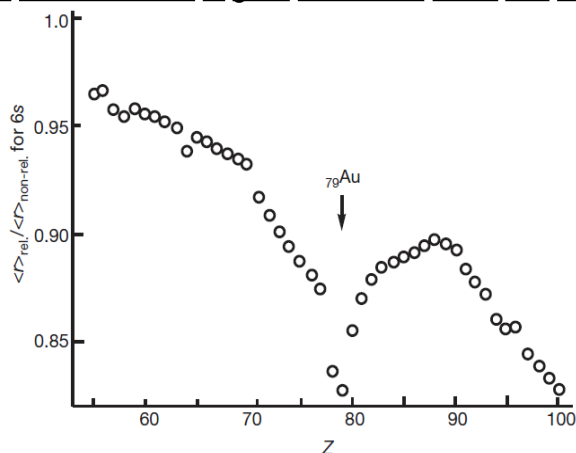
Box 1 Figure 1 | Calculated relativistic contraction of the 6s orbital. The relativistic and non-relativistic 6s orbital radii were determined computationally[100]. Notably, Pt, Au and Hg are markedly influenced. (Reprinted from ref. 4, with permission from the American Chemical Society.)

$[Au^0] = [Xe]4f^{14}5d^{10}6s^1$
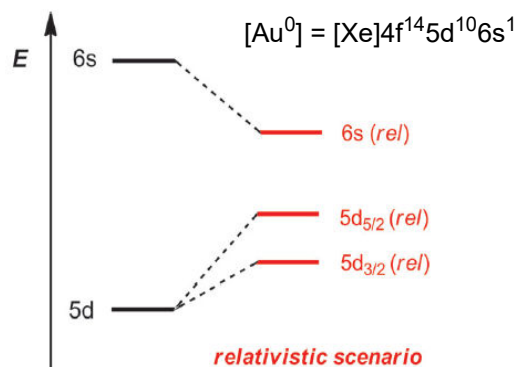
Scheme 1. Relativistic effects alter the energy levels of the 6s and 5d orbitals.

Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573.
Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

Due to the strong reletivistic effect of gold,
 1. gold is relatively redox-stable and has high ionixation energy. (6s orbital energy is very low.)
 2. the resultant lowering energy gap between the filled 5d and the empty 6s shells favors rehybridization and entails the strong preference of Au^I complexes for a linear dicoordinate ligand environment (See below figure).

$$Ph_3P{-}{-}Au{-}{-}NCMe \quad^{\oplus} \quad^{\ominus}SbF_6$$
0-18
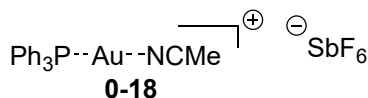
angle of P-Au-N: 177.10 (determined by X-ray analysis)
Echavarren, A. M. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 5455.

♣ Au(I) catalysts favor ligation of a single π-system, which make themselves highly reactive.

♣ Also, the diffuse nature of the valence orbitals referred to above explains the "soft" character of large and polarizable Au^+ cation and also explains its high affinity to π-bonds of all sorts.

-> But, if so, why can Au(I) selectively activate alkyne (i.e. "alkynophilicity"), not alkene?

♦ Actually, the corrdination energy of Au(I) to alkyne and olefine is comparable. Therefore, "alkynophilicity" should be explained by kinetic reasons (i.e. Activation energy of alkyne should be smaller than that of olefine. ***Reason 1***) and the thermodinamic stability of the activated product (***Reason 2***).

Reason 1.
 As shown in Figure 4, the energy gap between LUMO of Au-acetyle complex and HOMO of ethylene is smaller than LUMO of Au-ethylene complex and HOMO of acetylene. That is why Au(I) can selectively activate alkyne in eneyne cyclization.

Reason 2.
 When Au(I) activate gold, **0-19** is delocalized with **0-20**. This stabilization effect could not be found in case of **0-22**.
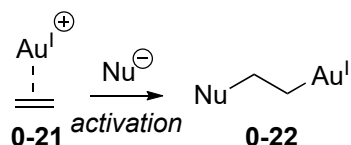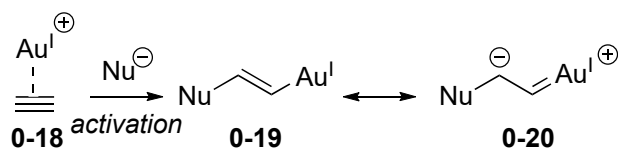
B3LYP/6-31G(d,p)//LANL2DZ
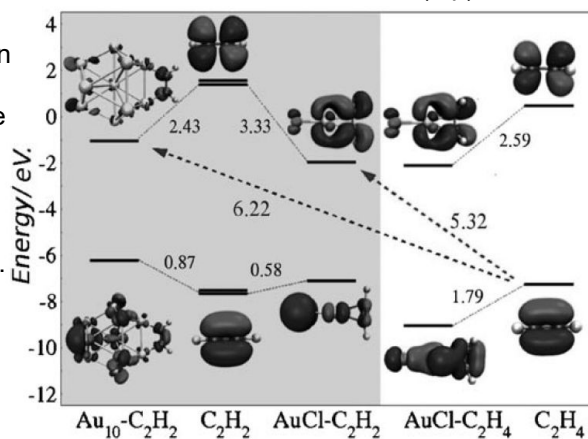
Figure 4. Molecular orbital diagram showing the corresponding HOMO and LUMO orbitals for C_2H_2 and C_2H_4 free and coordinated to AuCl and Au_{10}.

Lopez, N. et al. *Chem. Phys. Chem.* **2008**, *9*, 1624.

- powerful catalyst (Au(I) salt can promote chemical transformations at room temperature)
- air and moisture tolerance
- redox-stable
- generation of only environmentally-benign byproduct
- more abundant than platinum, palladium, rhodium and other metals
- biocompatible (stable under physiological-like conditions)

1. Problem 1
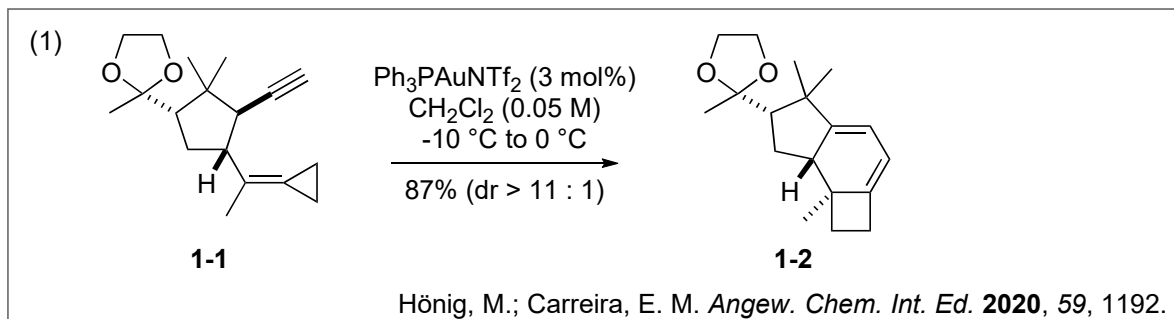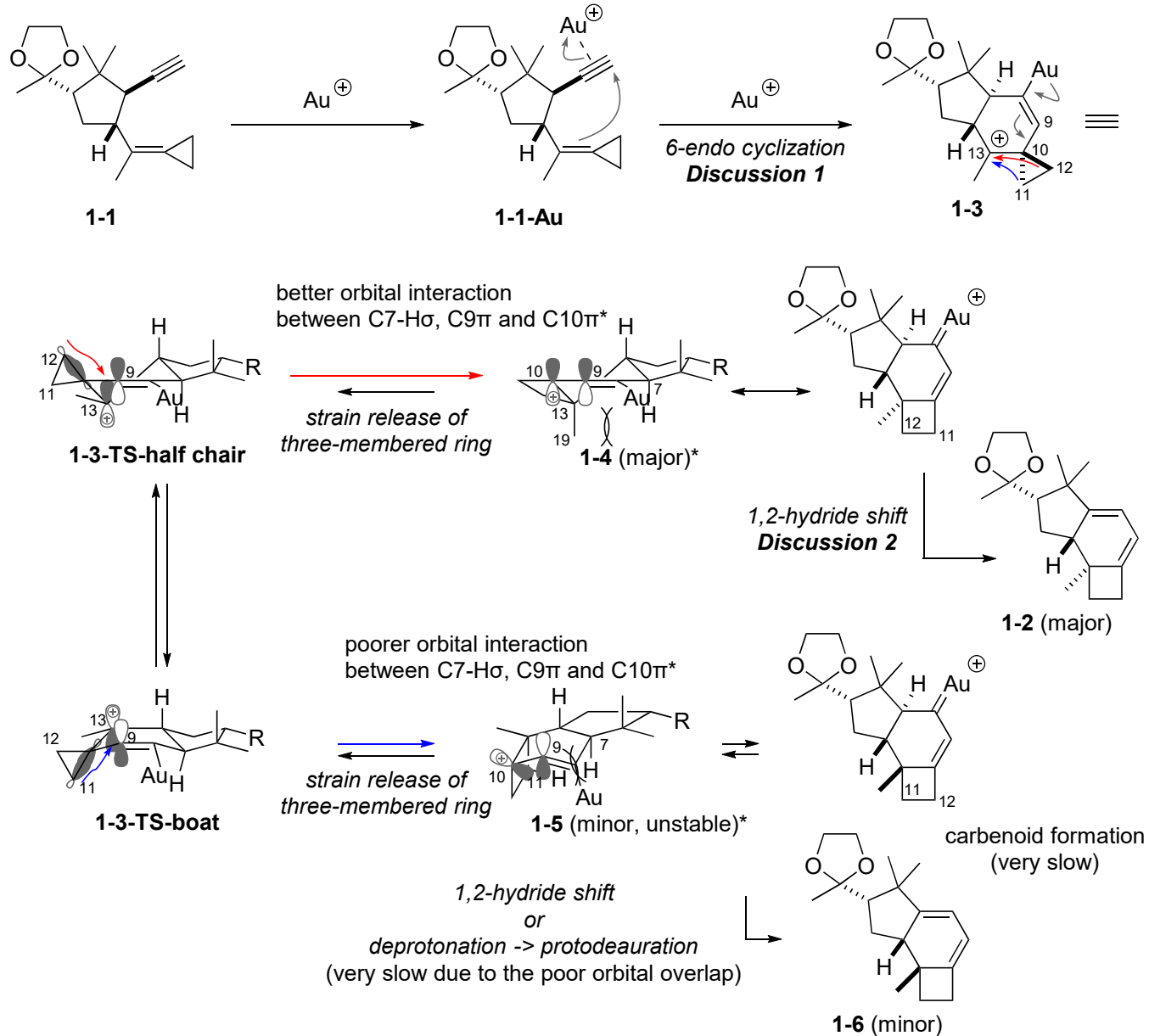
(1)

Ph$_3$PAuNTf$_2$ (3 mol%)
CH$_2$Cl$_2$ (0.05 M)
-10 °C to 0 °C

87% (dr > 11 : 1)

1-1 → **1-2**

Hönig, M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 1192.

1.0 Answer

1-1 → Au⊕ → **1-1-Au** → Au⊕ *6-endo cyclization* **Discussion 1** → **1-3**

better orbital interaction
between C7-Hσ, C9π and C10π*

1-3-TS-half chair → *strain release of three-membered ring* → **1-4 (major)***

1,2-hydride shift **Discussion 2** → **1-2 (major)**

poorer orbital interaction
between C7-Hσ, C9π and C10π*

1-3-TS-boat → *strain release of three-membered ring* → **1-5 (minor, unstable)***

1,2-hydride shift
or
deprotonation -> protodeauration
(very slow due to the poor orbital overlap)

carbenoid formation
(very slow)

1-6 (minor)
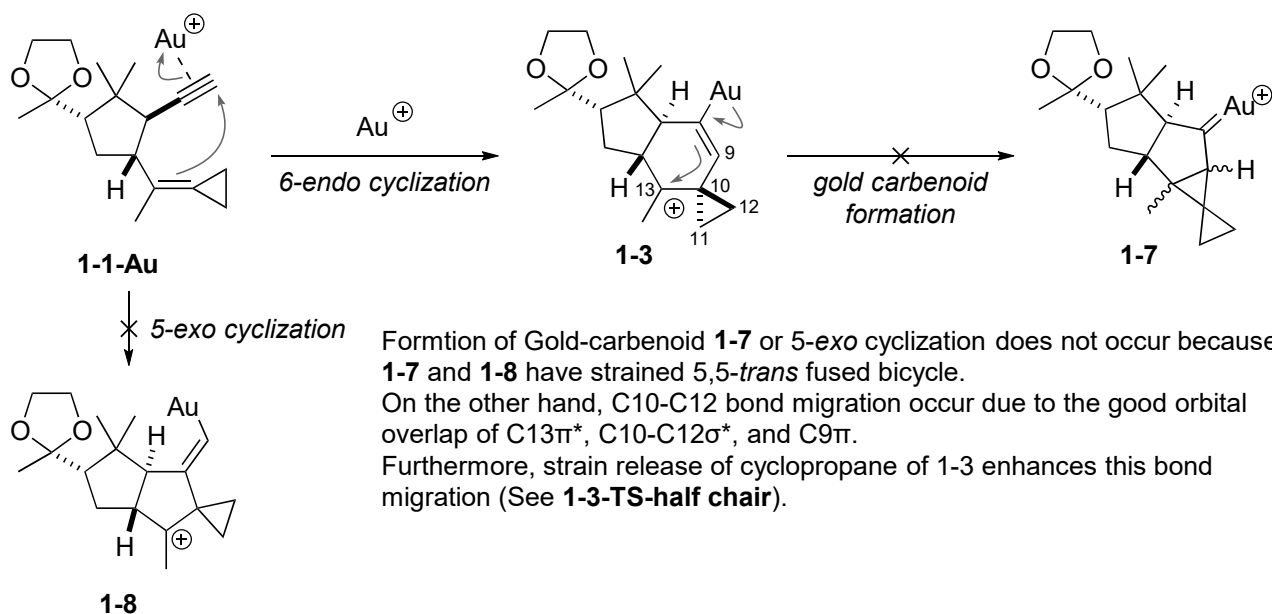
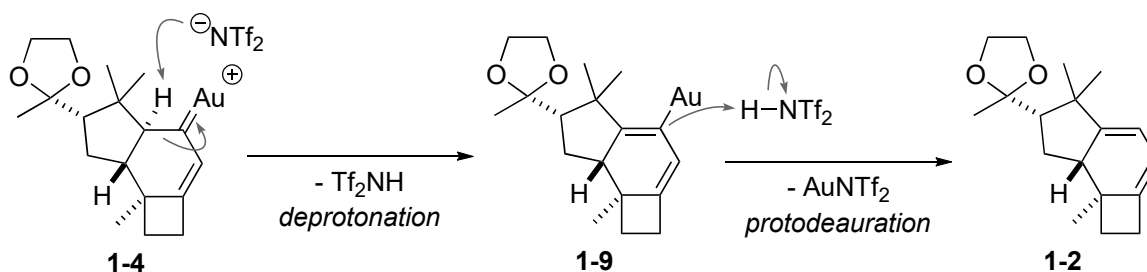*While both six-membered rings of **1-4** and **1-5** have 1,3-diaxial repulsion (H7 and H19 for **1-4**, H7 and H10 for **1-5**), steric repulsion of **1-5** looks larger because H11 is fixed inside the bicycle due to the rigid four-membered ring.
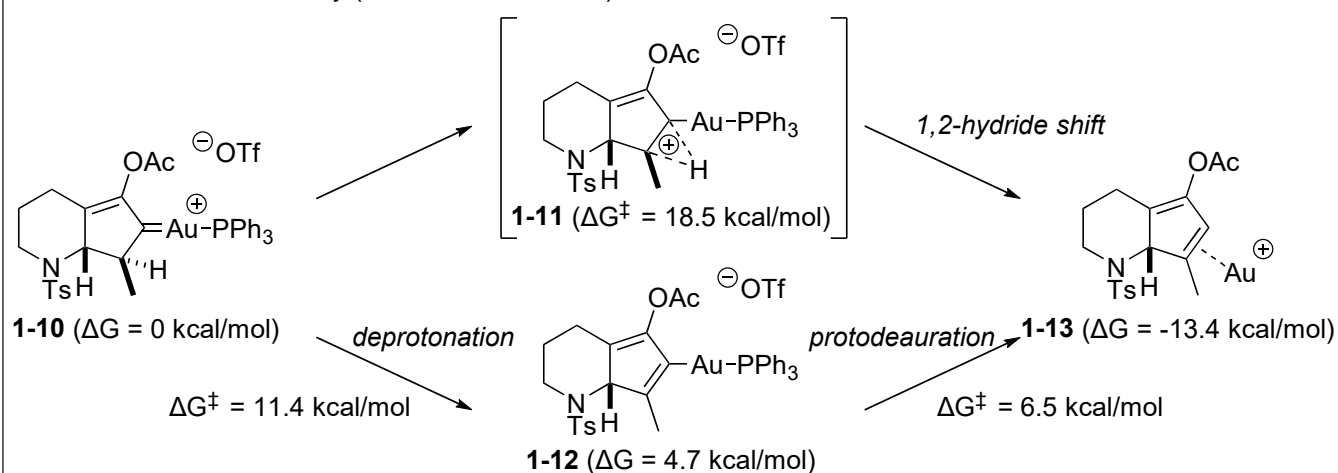
1.2 *Disussion 1*: 6-endo cyclization of **1-1-Au**

1-1-Au

6-endo cyclization → **1-3**

gold carbenoid formation ✗ → **1-7**

5-exo cyclization ✗ → **1-8**

Formtion of Gold-carbenoid **1-7** or 5-*exo* cyclization does not occur because **1-7** and **1-8** have strained 5,5-*trans* fused bicycle.
On the other hand, C10-C12 bond migration occur due to the good orbital overlap of C13π*, C10-C12σ*, and C9π.
Furthermore, strain release of cyclopropane of 1-3 enhances this bond migration (See **1-3-TS-half chair**).

1.3 *Disussion 2*: 1,2-hydrogen shift from gold carbenoid

1-4 → *- Tf₂NH* *deprotonation* → **1-9** → *- AuNTf₂* *protodeauration* → **1-2**

Instead of 1,2-hydride shift, the above-mentioned two-step sequence consisting of deprotonation and protodeauration is also possible.
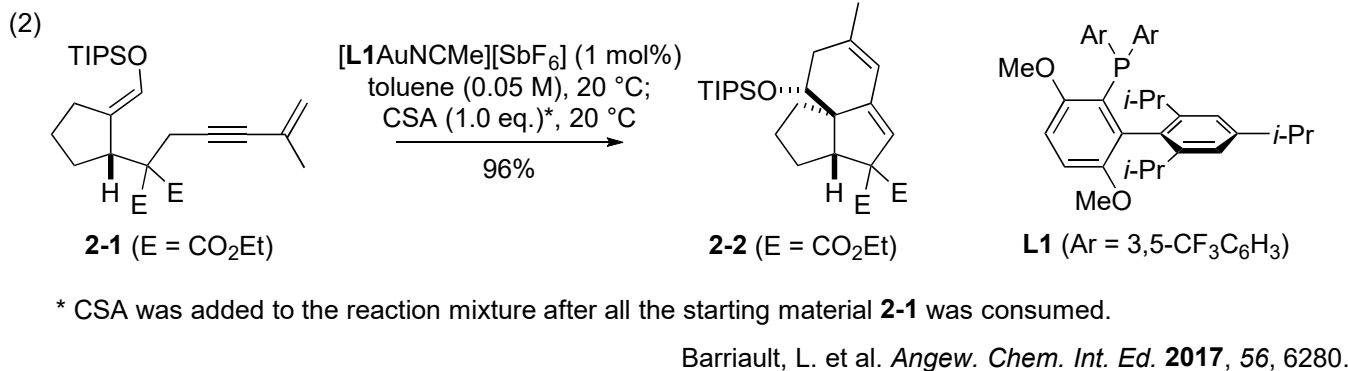
cf. related mechanistic study (counter anion = TfO⁻)

1-10 (ΔG = 0 kcal/mol)

1-11 (ΔG‡ = 18.5 kcal/mol)

1,2-hydride shift

deprotonation   ΔG‡ = 11.4 kcal/mol

1-12 (ΔG = 4.7 kcal/mol)

protodeauration   ΔG‡ = 6.5 kcal/mol

1-13 (ΔG = -13.4 kcal/mol)

B3LYP/6-31G(d,p)//SDD

Gómez-Bengoa, E. et al. *Beistein J. Org. Chem.* **2020**, *16*, 3059.

When counter anion of Au(I) catalyst is TfO⁻, two-step sequence (deprotonation -> protodeauration) is more likely pathway due to the modest basicity of TfO⁻ (pK_{BH} of TfO⁻ in MeCN = 0.70, ΔG_{acid} of TfOH = 299.5 kcal/mol*). Given that the basicity of Tf₂N⁻ is comparable with TfO⁻ (pK_{BH} of Tf₂N⁻ in MeCN = -0.10, ΔG_{acid} of Tf₂NH = 286.5 kcal/mol*), both pathways are plausible in the case of Problem 1.

* Leito, I. et al. *J. Phys. Org. Chem.* **2013**, *26*, 162.
  Ishihara, K. *Fluorous Topics* **2014**, 1, 1.

2. Problem 2

(2)

2-1 (E = CO₂Et) → 2-2 (E = CO₂Et)

[**L1**AuNCMe][SbF₆] (1 mol%)
toluene (0.05 M), 20 °C;
CSA (1.0 eq.)*, 20 °C
96%

L1 (Ar = 3,5-CF₃C₆H₃)

* CSA was added to the reaction mixture after all the starting material **2-1** was consumed.

Barriault, L. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 6280.

2.1 answer

2-1 (E = CO₂Et) → 2-1-Au → *5-exo cyclization* **Discussion 1*** → gold carbenoid 2-3

(step-wise mechanism)

gold carbenoid 2-3 ≡ → 2-16-1 ⇌ 2-16-2

2-17 (unstable) 2-4 → 2-10 2-17

2-4 → - Ha⁺ → 2-6 → *protodeauration* → 2-8
no selectivity **2-8** : **2-2** = 1 : 1
- Hb⁺ → 2-7 → *protodeauration* → 2-2 (E = CO₂Et, thermodinamically stable)

; CSA

- 5 -

2.2 *Discussion 1:* *5-exo* cyclization

gold carbenoid **2-3**
(thermodinamically stable
= Carbenoid is stabilized by
the conjugated olefin.)

kinetically favored
(Cyan carbon is
closer to enol ether)

5-exo

6-endo

kinetically disfavored
(Magenta carbon
is far from enol ether)

2-1-Au (E = CO₂Et)

gold carbenoid **2-9**

rearrangement
; CSA

2-2 (major)

rearrangement
; CSA

2-10 (minor)

2-2 : **2-10** > 20 : 1
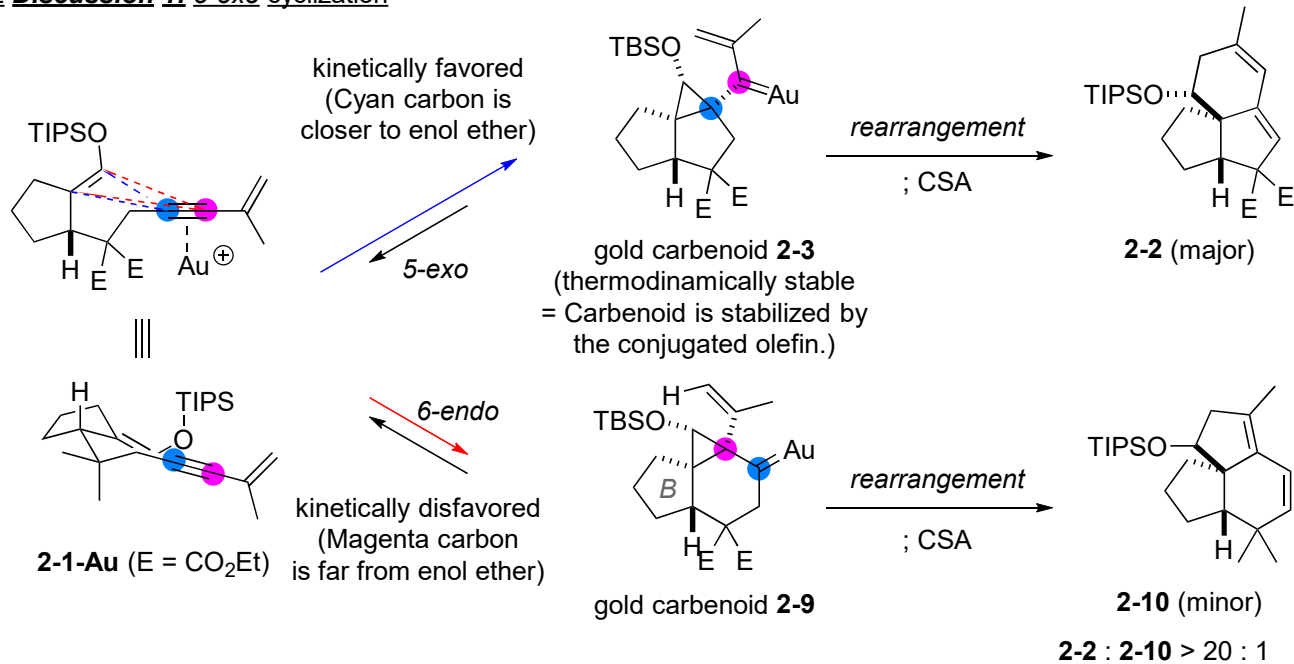
2.2 *Discussion 2:* concerted vs step-wise

L5AuCl (2 mol%)
AgSbF6

76%

2-11

2-12

L5AuCl (2 mol%)
AgSbF6

64%

2-13

2-14

via

2-15

Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.
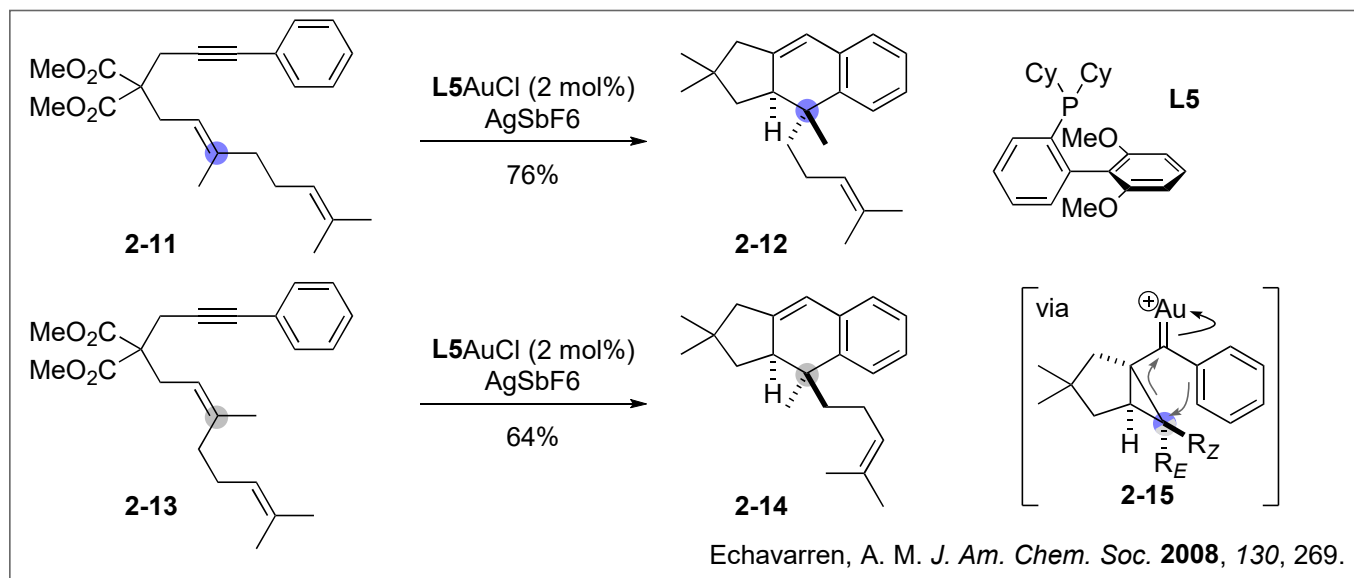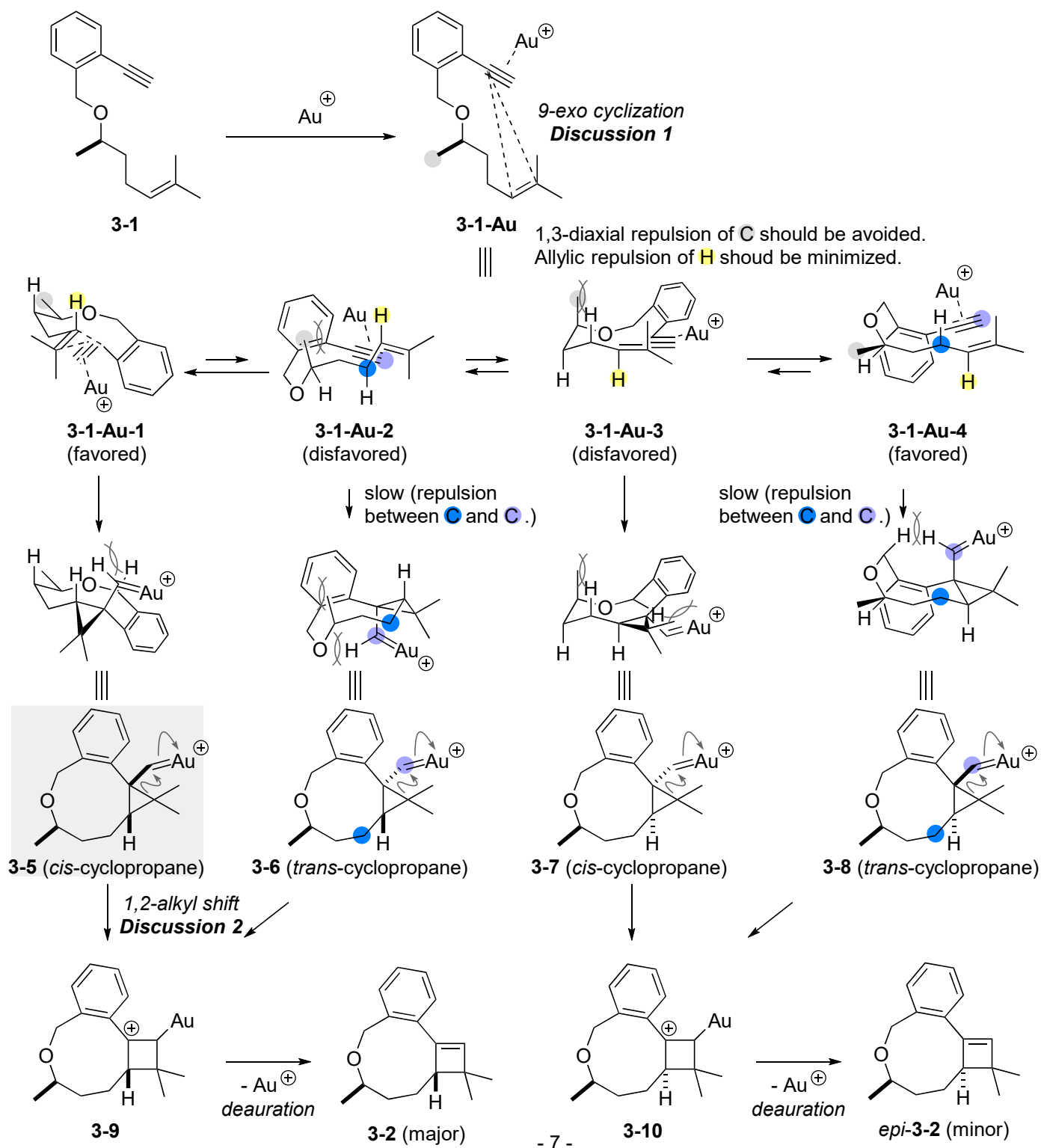
Based on the above results, the present reaction is likely to go in a cencerted fashion.
However, the step-wise mechanism can not be denied given the stability of α-alkoxy cation **2-16**.

3. Problem 3

(3)

[L2AuNCPh][BArF4]* (5 mol%)
CH2Cl2 (0.15 M), 25 °C

75% (dr 9 : 1)

*BAr4F- = B(3,5-CF3C6H3)4-

3-1

3-2

L2 (Ar = 2,6-i-PrC6H3)

Echavarren, A. M. et al. *Org. Lett.* **2016**, *18*, 1614.

3.1 answer

3-1

3-1-Au

9-exo cyclization
Discussion 1

1,3-diaxial repulsion of C should be avoided.
Allylic repulsion of H shoud be minimized.

3-1-Au-1
(favored)

3-1-Au-2
(disfavored)

3-1-Au-3
(disfavored)

3-1-Au-4
(favored)

slow (repulsion
between C and C.)

slow (repulsion
between C and C.)

3-5 (*cis*-cyclopropane)

3-6 (*trans*-cyclopropane)

3-7 (*cis*-cyclopropane)

3-8 (*trans*-cyclopropane)

1,2-alkyl shift
Discussion 2

3-9

- Au⊕
deauration

3-2 (major)

3-10

- Au⊕
deauration

*epi-***3-2** (minor)

- 7 -

3.2 *Discussion 1:* 9-*exo* cyclization

◆ Theoretcally, **3-2** can be obtained via 10-*endo* cyclization product **3-7**.

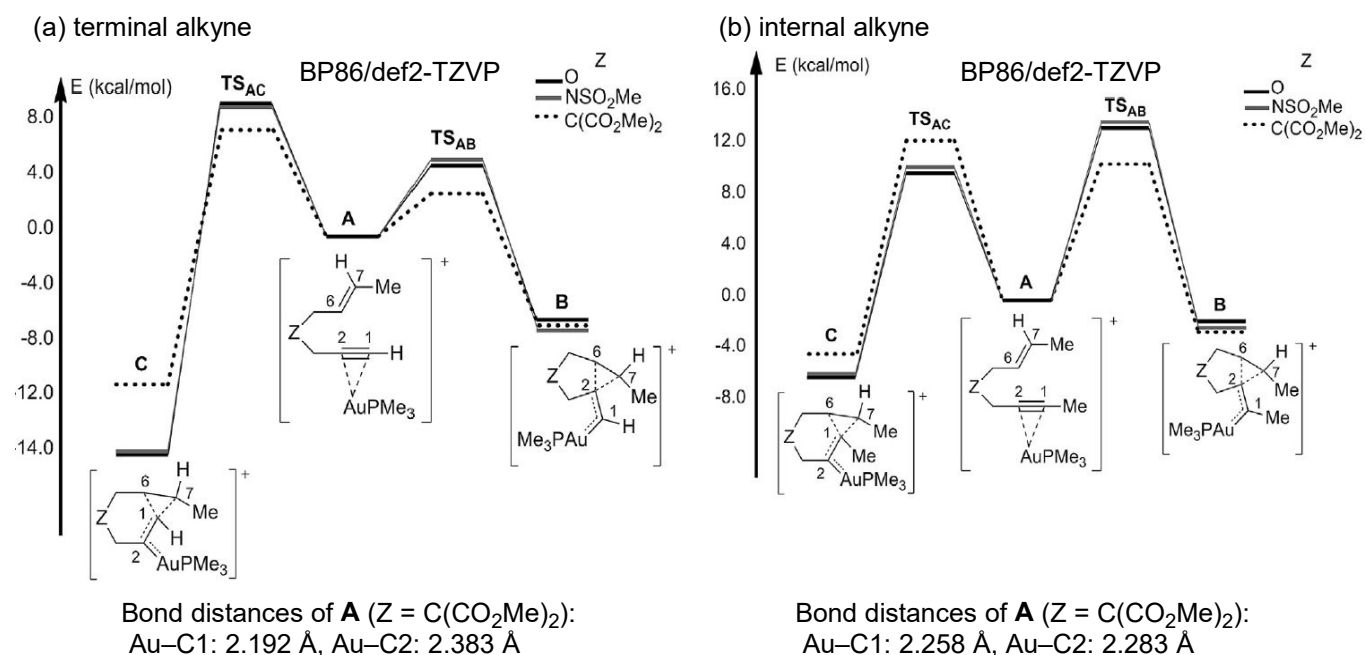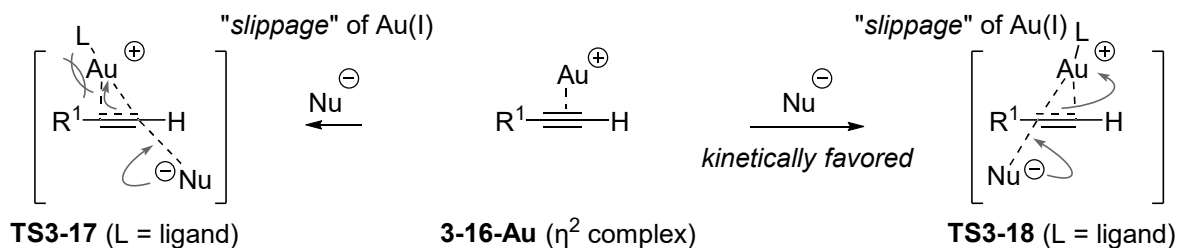**3-1-Au** → (10-endo cyclization) → **3-11** → (1,2-alkyl shift) → **3-2** and *epi*-**3-2**
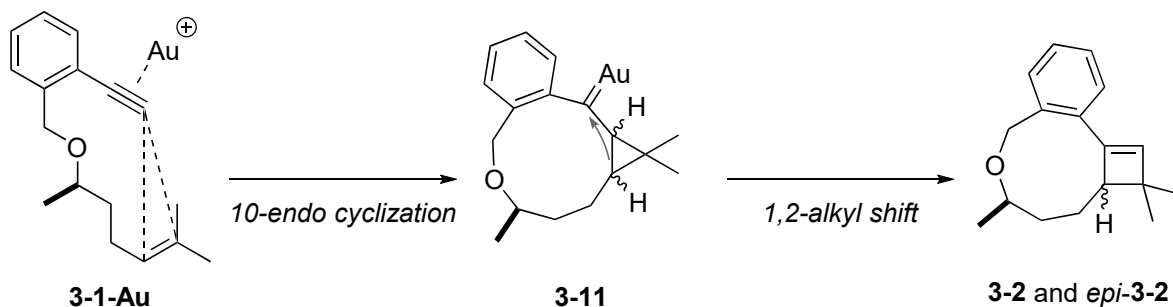
However, in case of eneyne having terminal alkyne such as **3-1**, *exo* cyclization is more likely pathway as shown below.

♣ "slippage mechanism" in Au(I)-catalyzed alkyne functionalization

"*slippage*" of Au(I)

3-12   **3-12-Au** (η^2 complex)   **TS3-14**   **3-15** (η^1 complex)
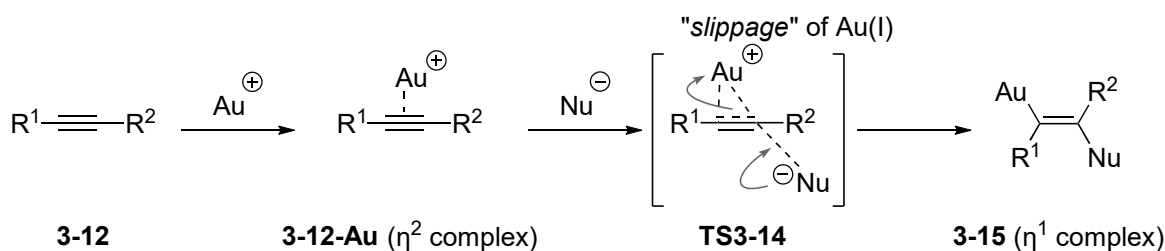
Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308.
Senn, H. M.; Blöchl, P. E.; Togni, A. *J. Am. Chem. Soc.* **2000**, *122*, 4098.

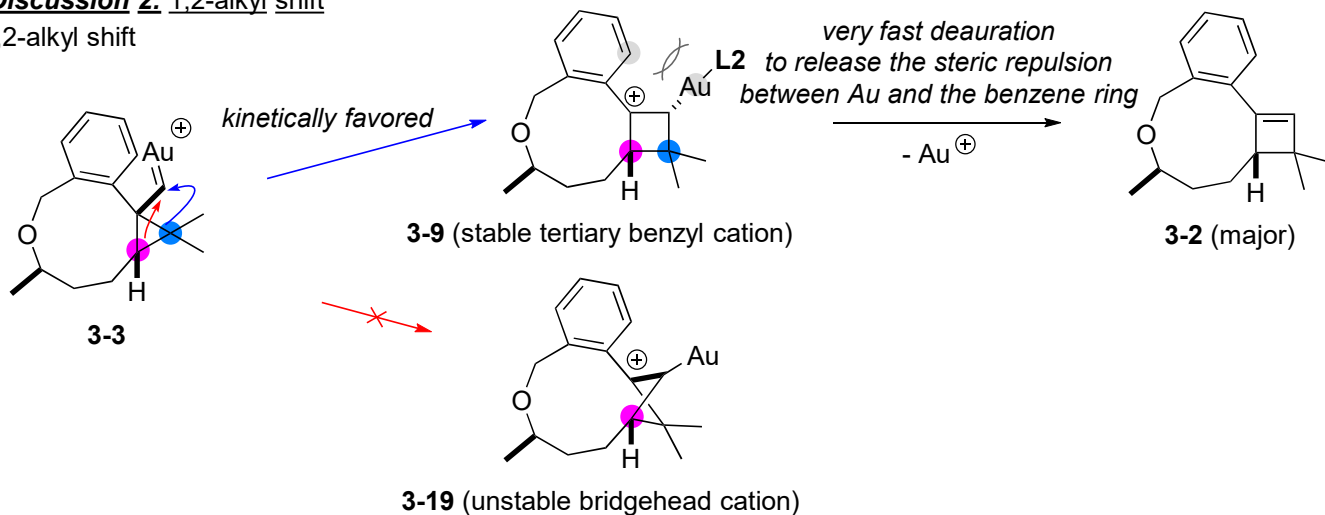In case of terminal alkynes, the effct of "slippage mechanism" is remarkable.

"*slippage*" of Au(I)   "*slippage*" of Au(I)

TS3-17 (L = ligand)   **3-16-Au** (η^2 complex)   **TS3-18** (L = ligand)

kinetically favored

(a) terminal alkyne

BP86/def2-TZVP

Bond distances of **A** (Z = C(CO$_2$Me)$_2$):
Au–C1: 2.192 Å, Au–C2: 2.383 Å

(b) internal alkyne

BP86/def2-TZVP

Bond distances of **A** (Z = C(CO$_2$Me)$_2$):
Au–C1: 2.258 Å, Au–C2: 2.283 Å

Mattalia, J.-M.; Nava, P. *J. Organometal. Chem.* **2014**, *749*, 335.

In case of eneyne compomund having terminal alkyne moiety, *exo* cyclization is kinetically favored.
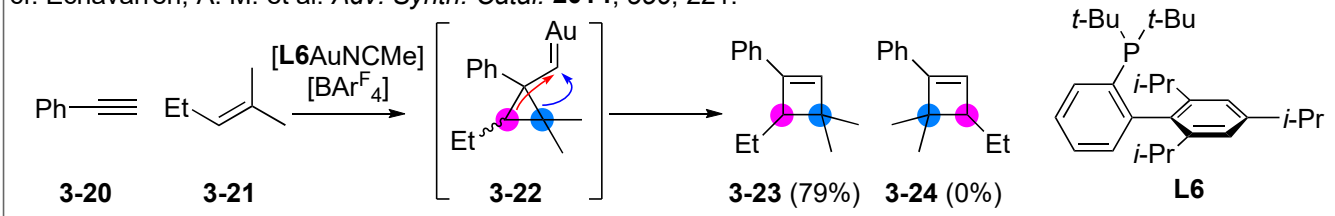
♦ 1,2-alkyl shift

kinetically favored

3-3

3-9 (stable tertiary benzyl cation)

very fast deauration to release the steric repulsion between Au and the benzene ring

– Au⊕

3-2 (major)
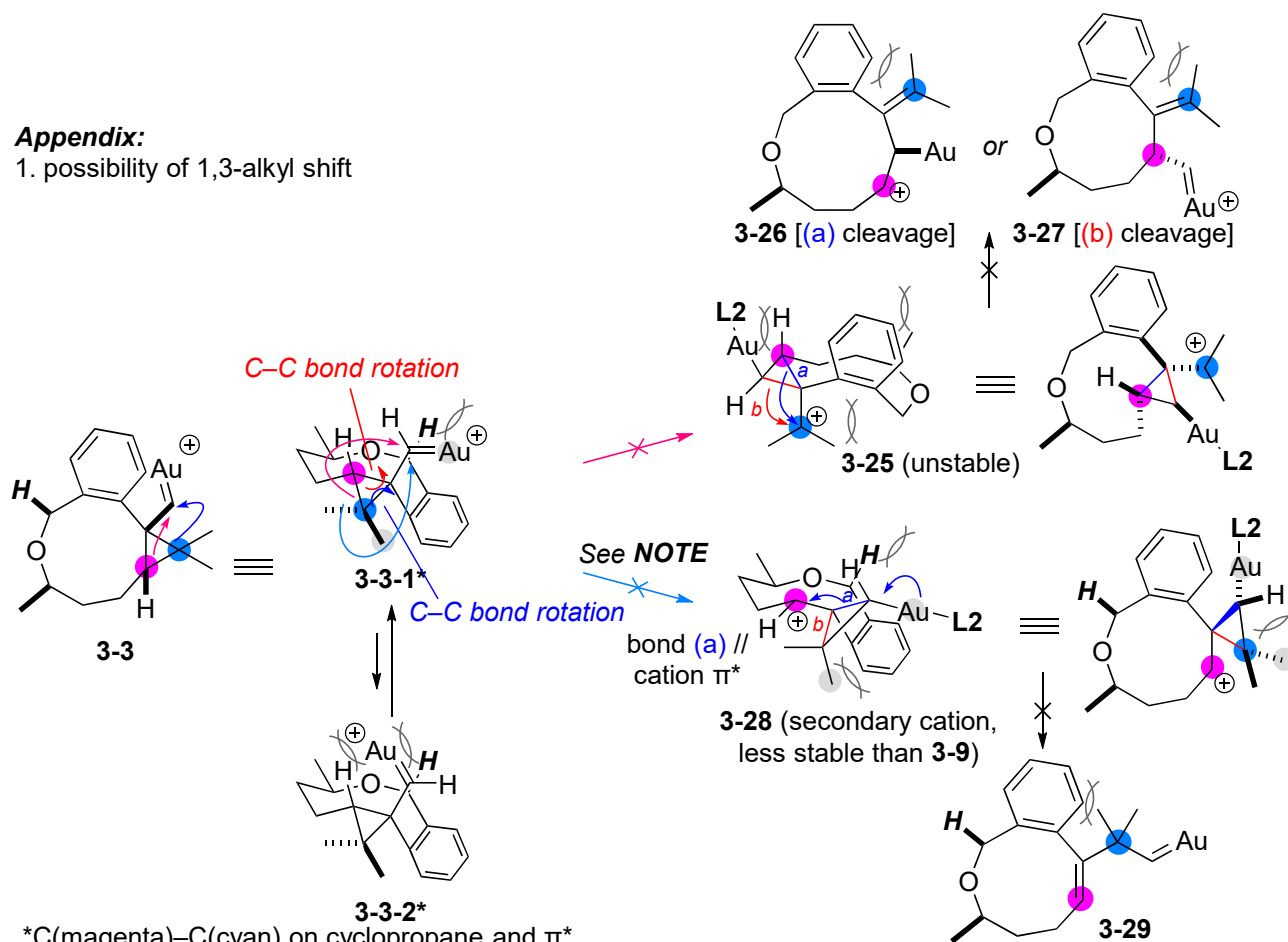
3-19 (unstable bridgehead cation)

Rearrangement of multi-substituted carbon is kinetically favored (cyan carbon > magenta carbon) because multi-susbstituted carbon easily localize the cation charge. (cf. Baeyer-Villiger oxidation)

cf. Echavarren, A. M. et al. *Adv. Synth. Catal.* **2014**, *356*, 221.

Ph≡ **3-20**   Et **3-21**   [**L6**AuNCMe][BAr$^F_4$]   **3-22**   **3-23** (79%)   **3-24** (0%)   **L6**

Appendix:
1. possibility of 1,3-alkyl shift

3-26 [(a) cleavage]   *or*   **3-27** [(b) cleavage]

3-25 (unstable)

C–C bond rotation

3-3

3-3-1*

C–C bond rotation

3-3-2*

*See **NOTE***

bond (a) // cation π*

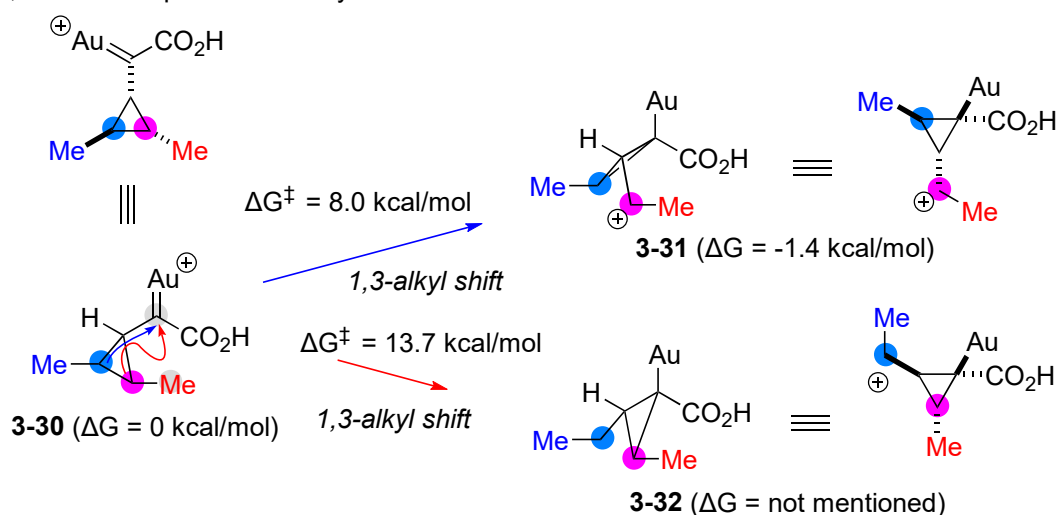**3-28** (secondary cation, less stable than **3-9**)

3-29

C(magenta)–C(cyan) on cyclopropane and π
carbenoid carbon shoud be parallel in 1,3-alkyl shift.

NOTE:
In forming the new C–C bond of **3-28**, there is severe steric repulsion between two gray carbons. As a result, the activation energy from **3-3-1** to **3-28** would be high.
(See the next page.)

cf, related computational study

ΔG‡ = 8.0 kcal/mol

1,3-alkyl shift

3-31 (ΔG = -1.4 kcal/mol)

3-30 (ΔG = 0 kcal/mol)

ΔG‡ = 13.7 kcal/mol

1,3-alkyl shift

3-32 (ΔG = not mentioned)

Yu, Z.-X.; Shin, S. et al. *J. Am. Chem. Soc.* **2012**, *134*, 208.

2. the structure of Au-alkyne complex

bending
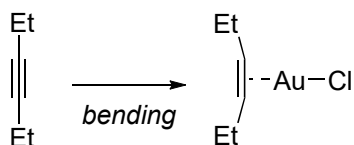
Table 1. Selected Bond Lengths (A) and Angles (deg) of Au(EtC≡CEt)Cl[a]

Parameter	experimental	computed
C3≡C4	1.224(6)	1.247
Au−C4	2.152(4)	2.206
Au−C3	2.172(5)	2.231
Au−Cl	2.2703(11)	2.304
C4−C3−C2	166.9(5)	165.7
C3−C4−C5	163.0(5)	163.0

[a] See Figure 2 for the atom numbering scheme. The calculated C≡C distance of free 3-hexyne is 1.215 Å.
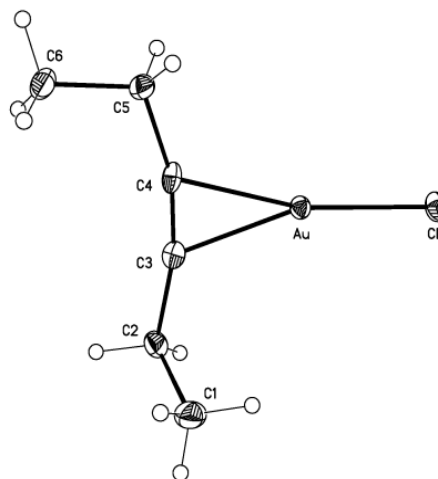
Figure 2. Molecular structure of Au(EtC≡CEt)Cl. Selected bond lengths (Å) and angles (deg): Au−C4 2.152(4), Au−C3 2.172(5), Au−Cl 2.2703(11), C1−C2 1.530(7), C2−C3 1.472(7), C3−C4 1.224(6), C4−C5 1.470(6), C5−C6 1.526(6); C4−Au−C3 32.88(17), C4−Au−Cl 167.13(13), C3−Au−Cl 159.99(12), C3−C2−C1 112.4(4), C4−C3−C2 166.9(5), C4−C3−Au 72.7(3), C2−C3−Au 120.3(3), C3−C4−C5 163.0(5), C3−C4−Au 74.4(3), C5−C4−Au 122.6(3), C4−C5−C6 111.6(4).