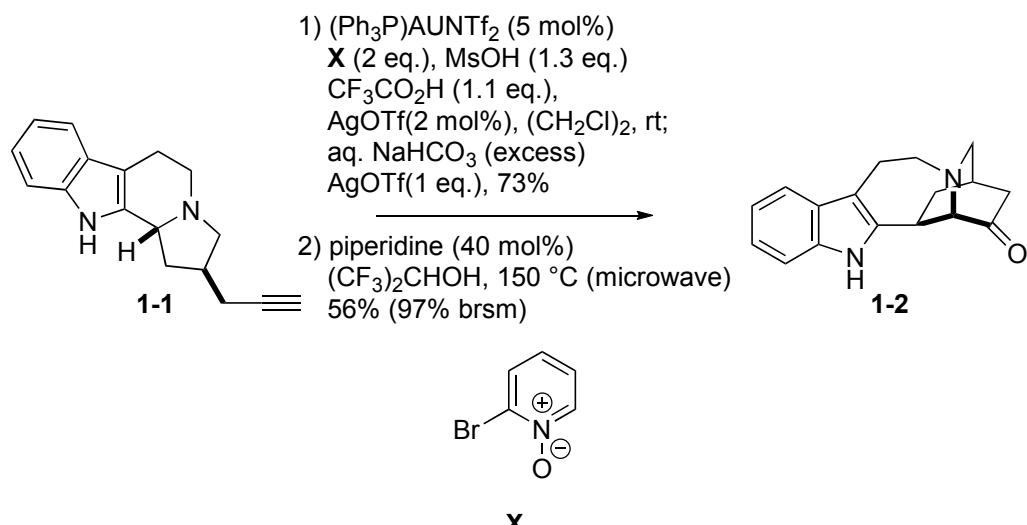


Problem Session (8)

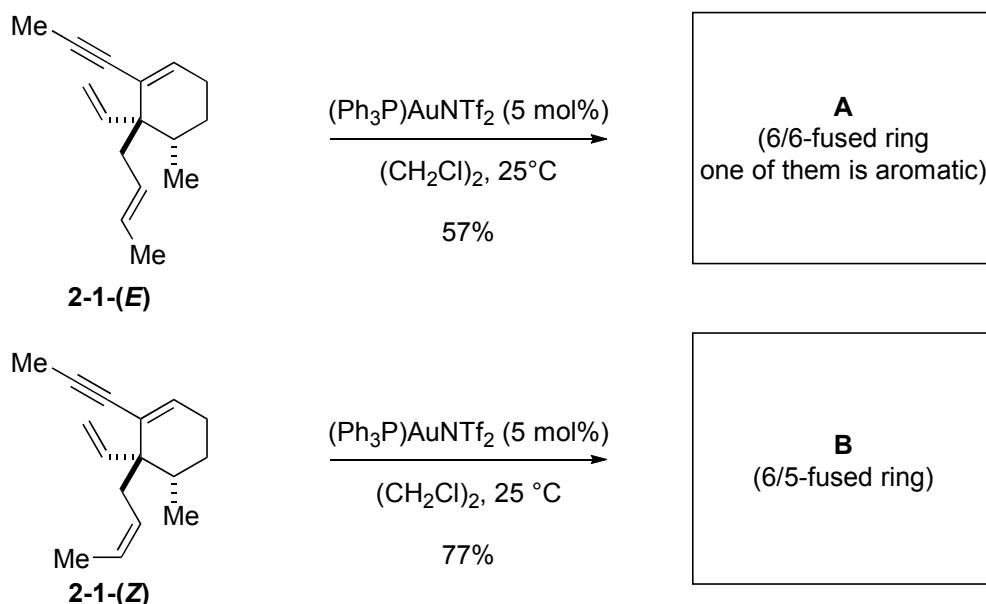
2019/11/30 Koichi Hagiwara

All problems are from works by Prof. Tuoping Luo.

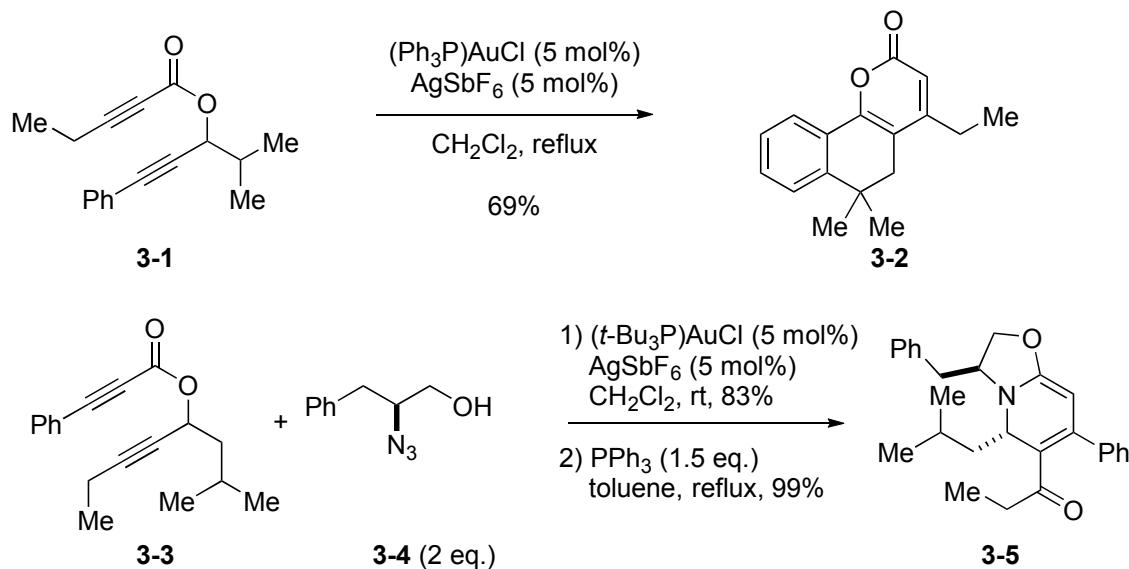
(1) Please explain the reasonable reaction mechanisms.



(2) Please fill in the blanks, **A** and **B**.



(3) Please explain the reasonable reaction mechanisms.



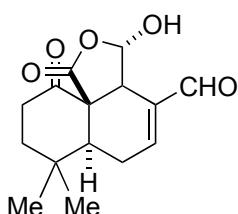
Topic: Works by Prof. Tuoping Luo

2005 B.S. in Chemistry, College of Chemistry and Molecular Engineering, Peking University (Prof. Zhen Yang)
 2005-2011 Ph.D. in Chemistry, Department of Chemistry and Chemical Biology, Harvard University;
 Chemical Biology Program, Broad Institute (Prof. Stuart L. Schreiber)
 2011-2013 Postdoctoral Fellow, H3 Biomedicine Inc., (Dr. John Yuan Wang)
 2010-2013 Designed and managed natural product total synthesis projects in collaboration
 with Prof. Zhen Yang and Prof. Yefeng Tang
 2013-present Provisional Principal Investigator, Peking University-Tsinghua University Joint Center for Life Sciences
 2013-present Principal Investigator, College of Chemistry and Molecular Engineering, Peking University



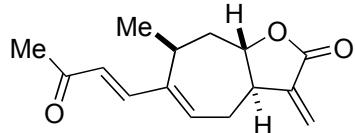
Prof. Schreiber's lab: 1. Synthesized HDAC inhibitors in collaboration with Dr. Weiping Tang
 2. **Developed novel gold-catalyzed cascade reactions**
 3. Screened and developed potent STK33 kinase inhibitors
 for probing KRAS-dependent cancer cells (with Prof. Todd R. Golub)

Selected synthesized natural product



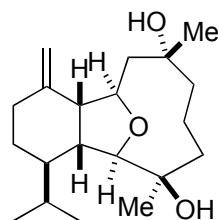
kuehneromycin A
 and other 3 related compounds
 (with Prof. Yang and
 Prof. Chuang-chuang Li)

Au-catalyzed tandem reaction
J. Am. Chem Soc. **2011**, 133, 14944.



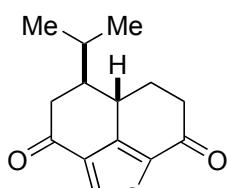
xanthatin
 and other 6 related compounds
 (with Prof. Yang and Prof. Tang)

dyotropic rearrangement of *cis*- β -lactone
Angew. Chem. Int. Ed. **2012**, 51, 6984.



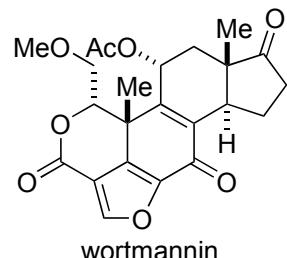
Sclerophytin A
 and other 8 related compounds
 (with Prof. Yang)

Au-catalyzed cascade reaction
 of 1,7-diyne
Angew. Chem. Int. Ed. **2014**, 53, 1837.

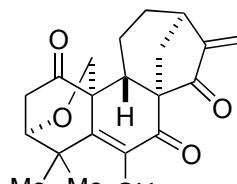


hibiscone C

radical fragmentation of cyclobutane
Org. Lett. **2017**, 19, 620.



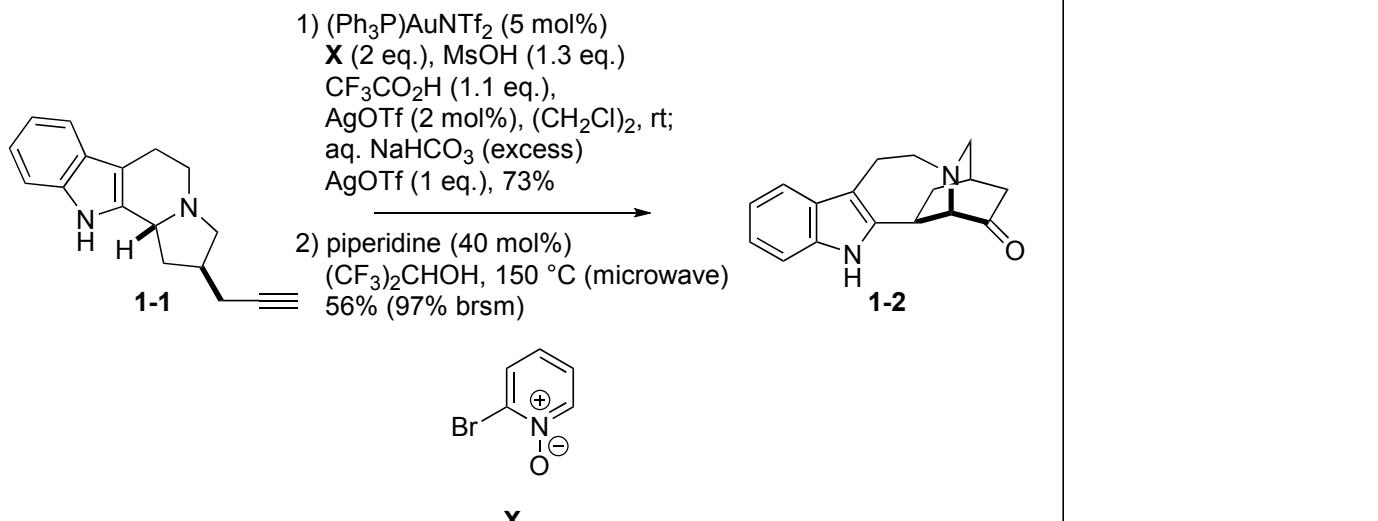
Pd-catalyzed cascade reaction
J. Am. Chem Soc. **2017**, 139, 6815.



carbonyl-alkene
 reductive coupling

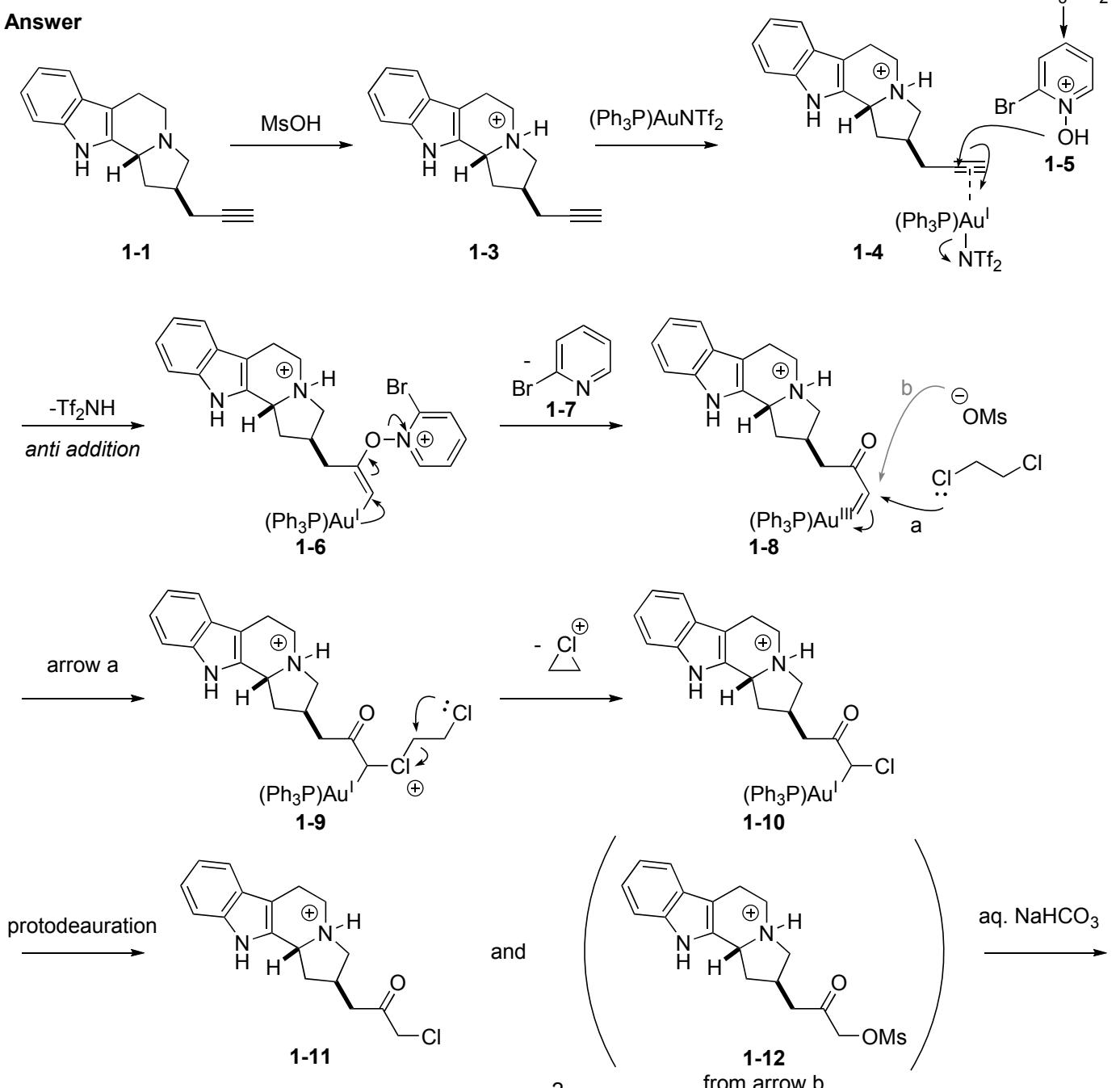
Angew. Chem. Int. Ed. **2018**, 57, 760.

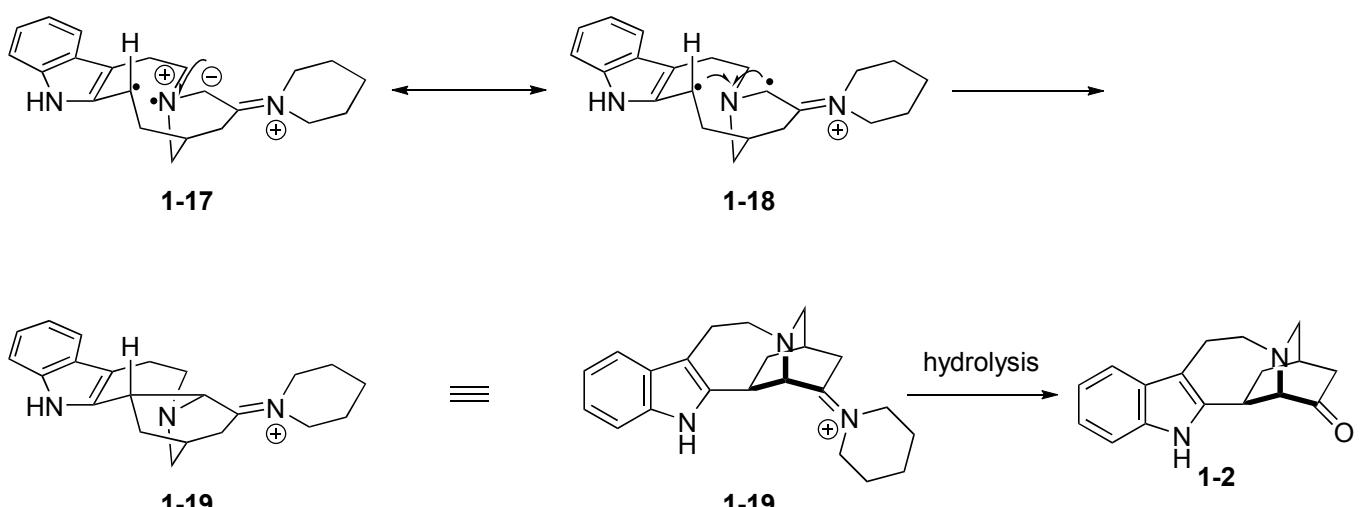
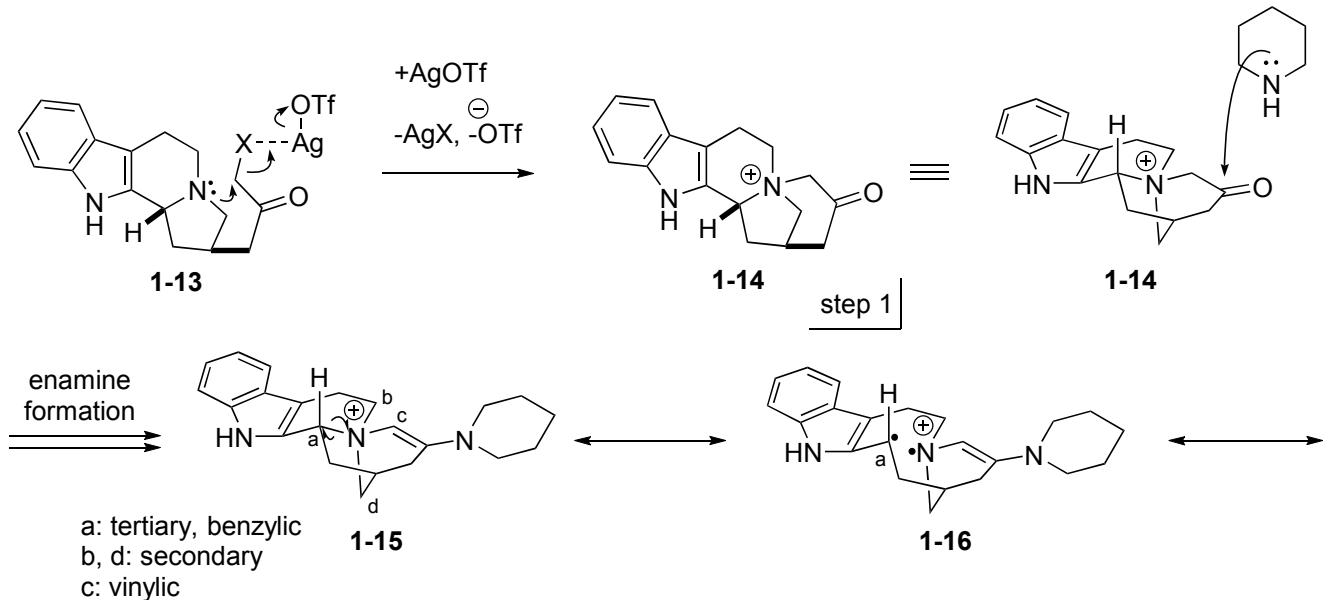
(1) Please explain the reasonable reaction mechanisms.



Zhang, Y.; Xue, Y.; Li, G.; Yuan, H.; Luo, T. *Chem. Sci.* **2016**, 7, 5530.

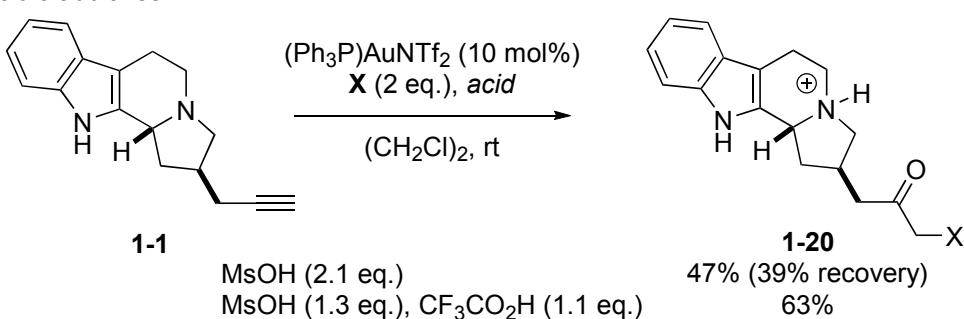
Answer



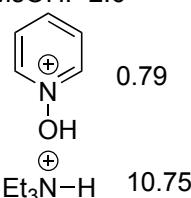


Product **1-2** was provided in stereoselective manner.
The presence of a solvent cage was proposed.

• Acidic additives

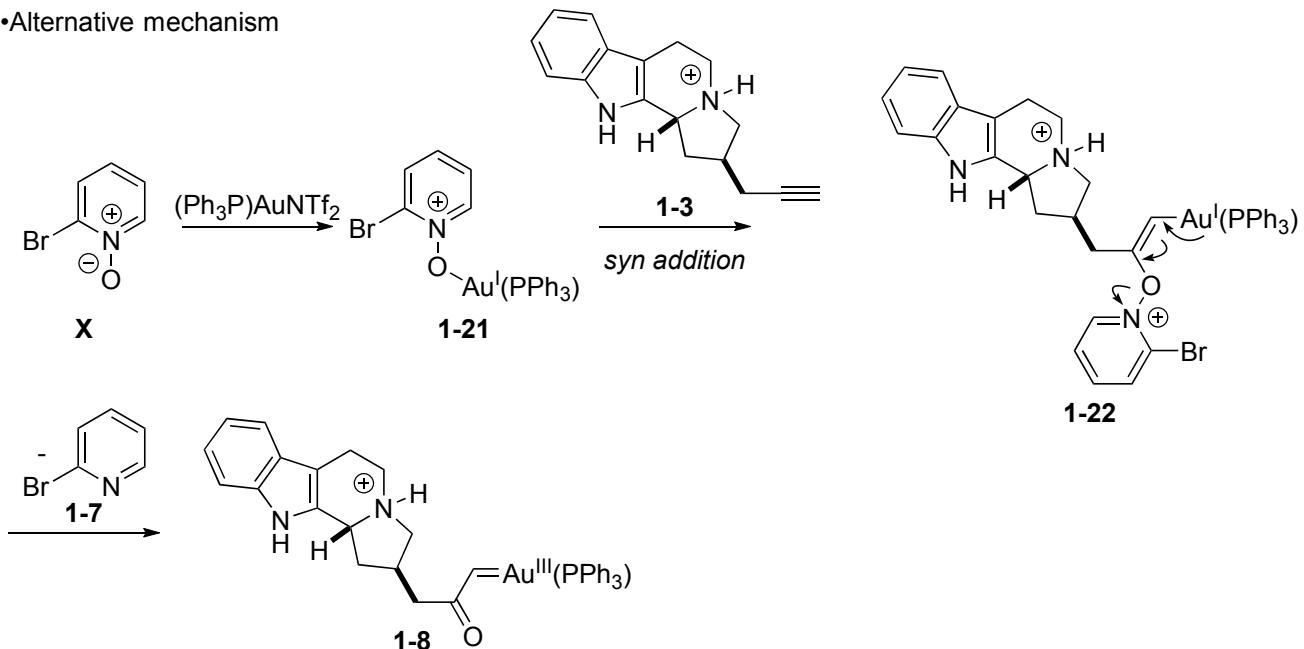


pKa: CF_3CO_2H : -0.25
 $MsOH$: -2.6

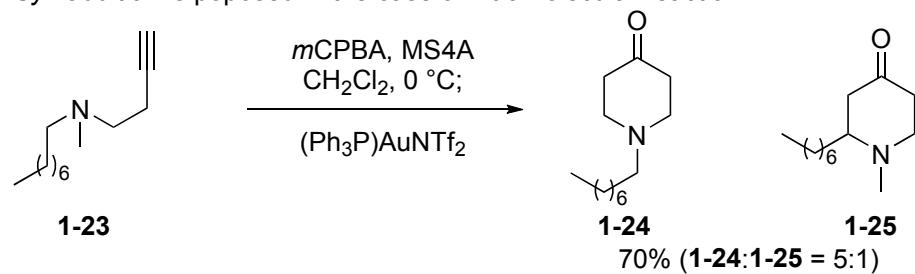


lower nucleophilicity than N-oxide
→ The cause of low conversion in the case of $MsOH$?

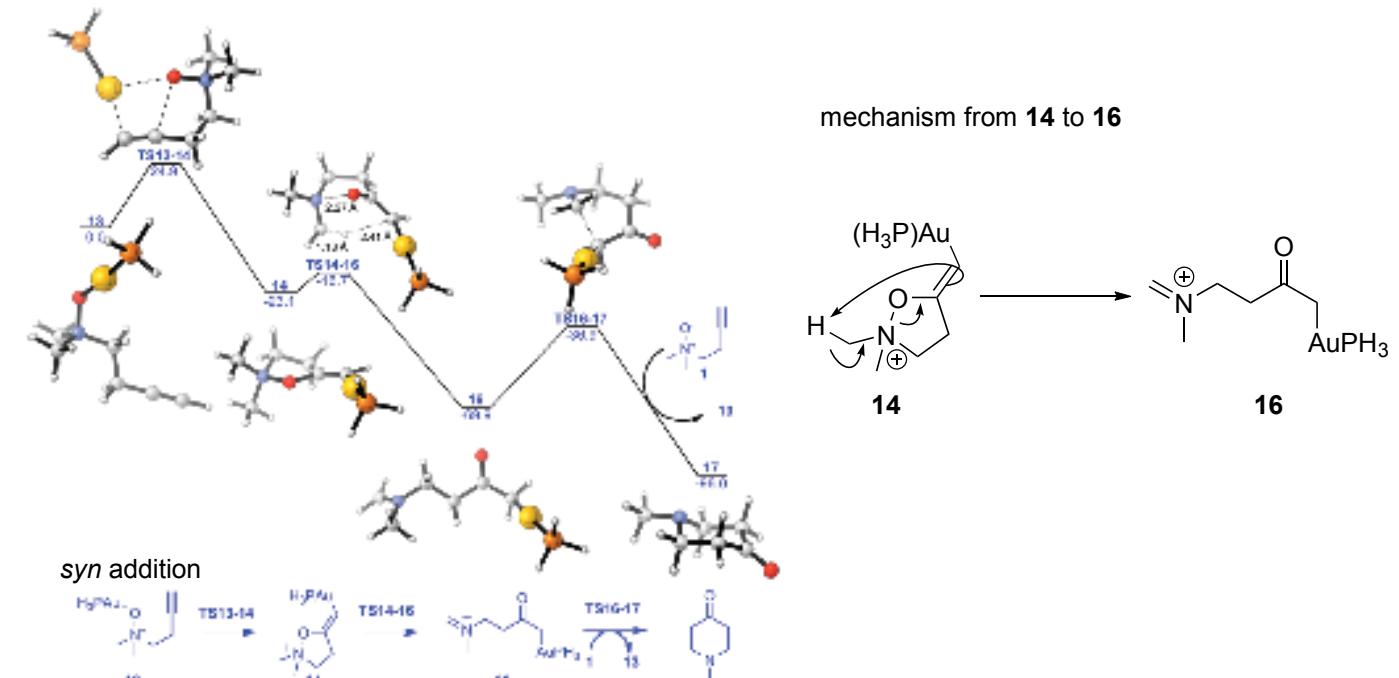
• Alternative mechanism



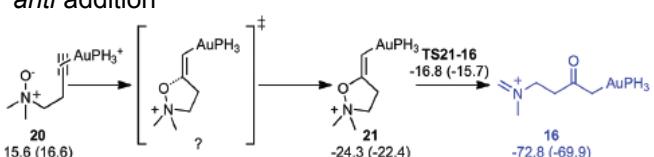
• Syn addition is proposed in the case of intramolecular reaction.



Zhang, L. et al. *J. Am. Chem. Soc.* **2009**, 131, 8394.

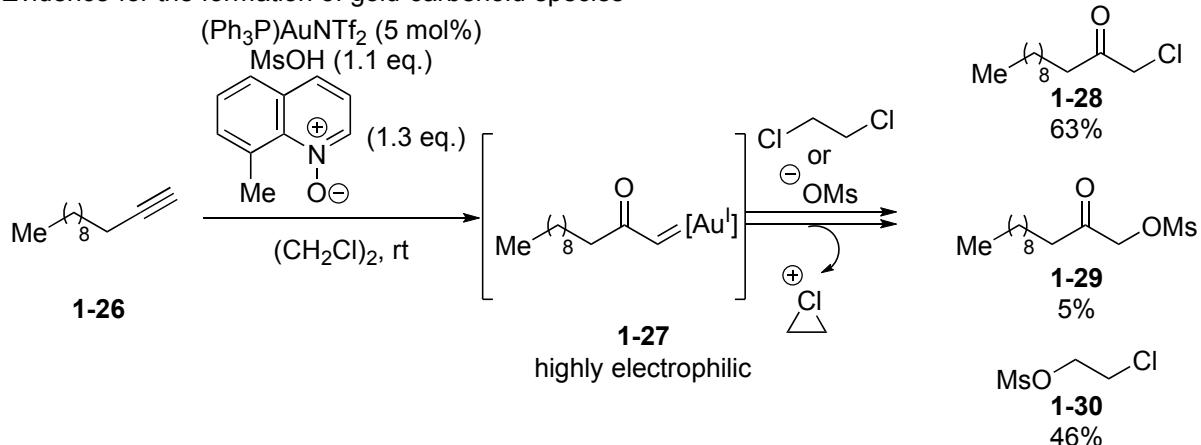


anti addition

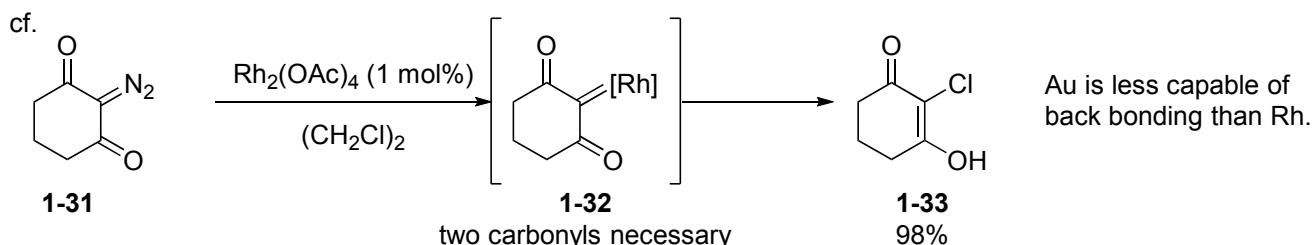


Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, 134, 1078.

• Evidence for the formation of gold-carbenoid species



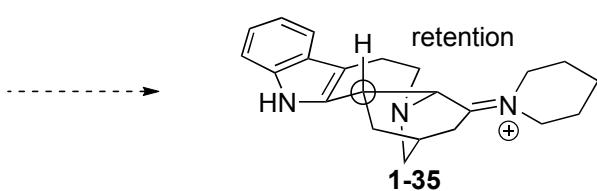
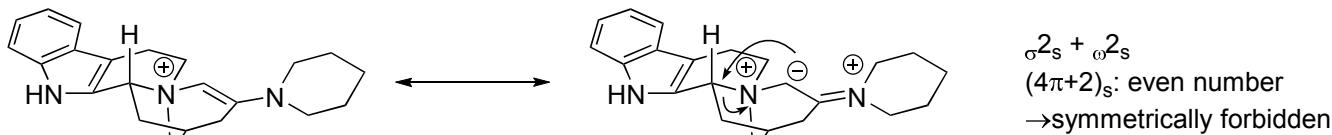
Xiang, J.; Zhang, L. et al. *Org. Biomol. Chem.* **2012**, *10*, 3168.



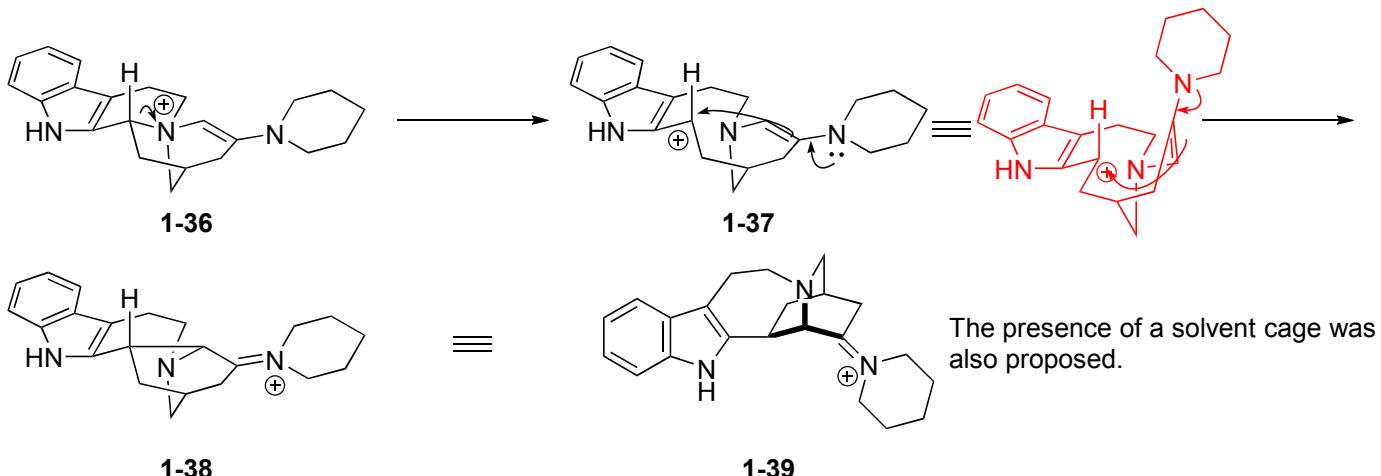
Pirrung, M. C. et al. *J. Org. Chem.* **1995**, *60*, 2112.

• Stevens rearrangement

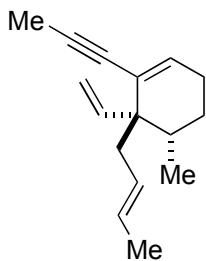
Concerted mechanism is symmetrically forbidden.



cationic mechanism (proposed by author)



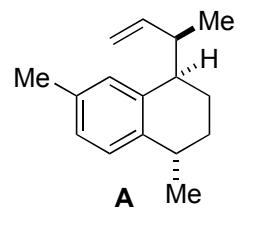
(2) Please fill in the blanks, A and B.



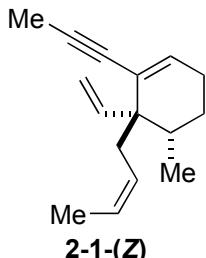
$(\text{Ph}_3\text{P})\text{AuNTf}_2$ (5 mol%)

$(\text{CH}_2\text{Cl})_2$, 25°C

57%



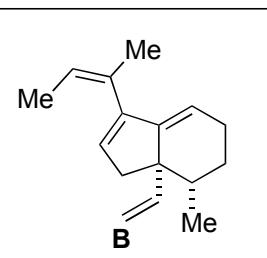
2-1-(E)



$(\text{Ph}_3\text{P})\text{AuNTf}_2$ (5 mol%)

$(\text{CH}_2\text{Cl})_2$, 25 °C

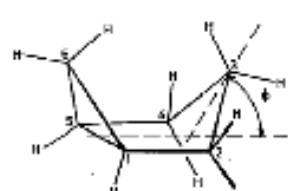
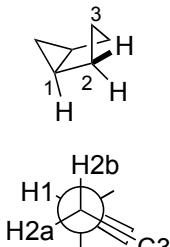
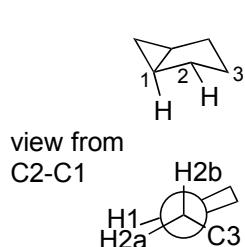
77%



2-1-(Z)

Yu, X.; Su, F.; Liu, C.; Yuan, H.; Zhao, S.; Zhou, Z.; Quan, T.; Luo, T. *J. Am. Chem. Soc.* **2016**, 138, 6261.

• Conformation of bicyclo[3.1.0]hexane

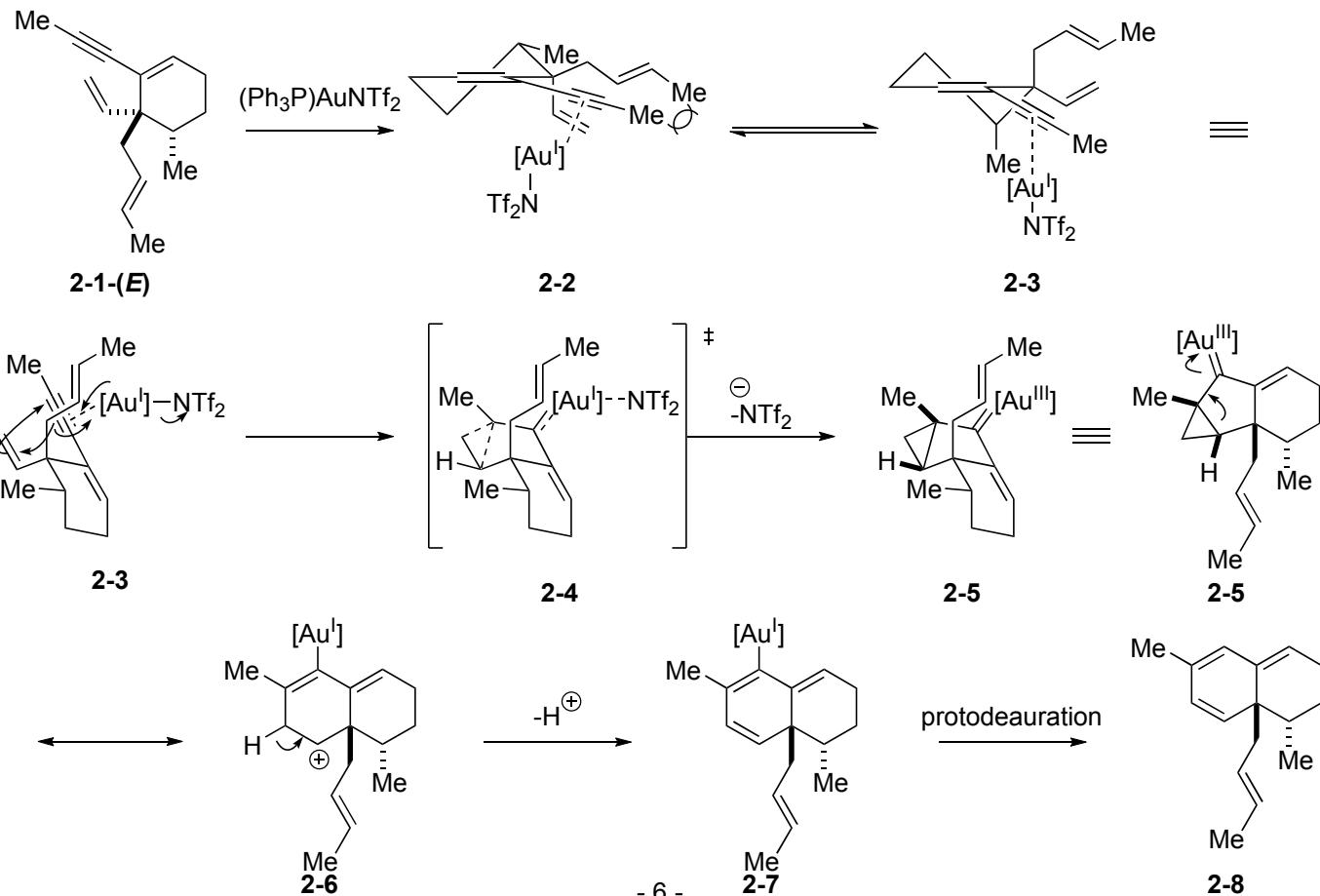


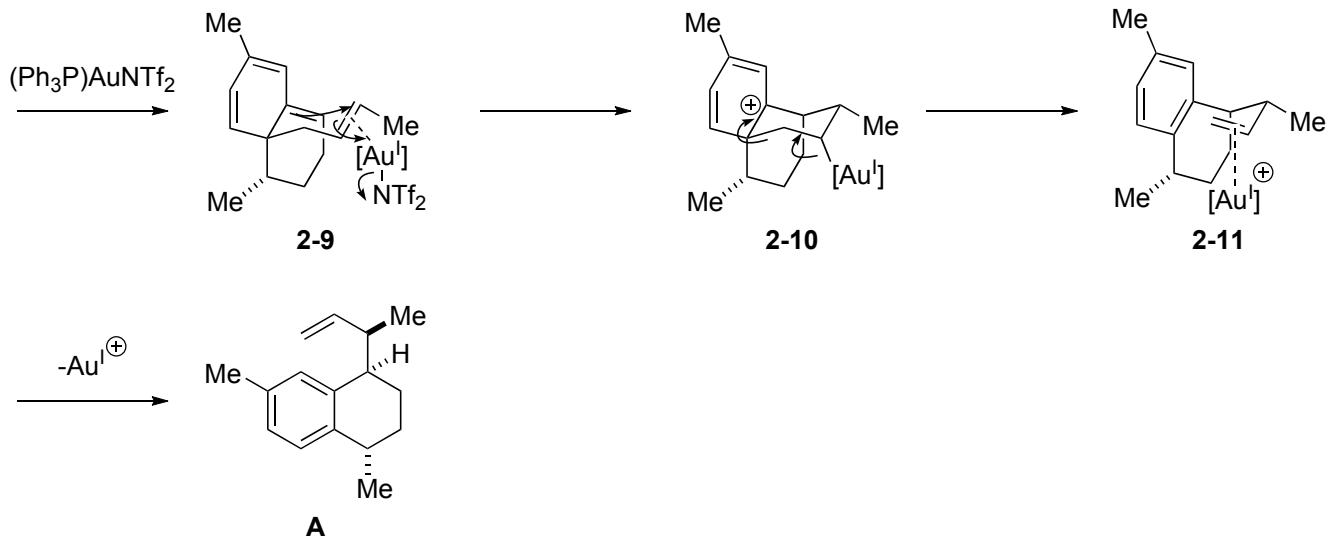
view from
C2-C1

Mjöberg, P. J.; Almlöf, J. *Chem. Phys.* **1978**, 29, 201.

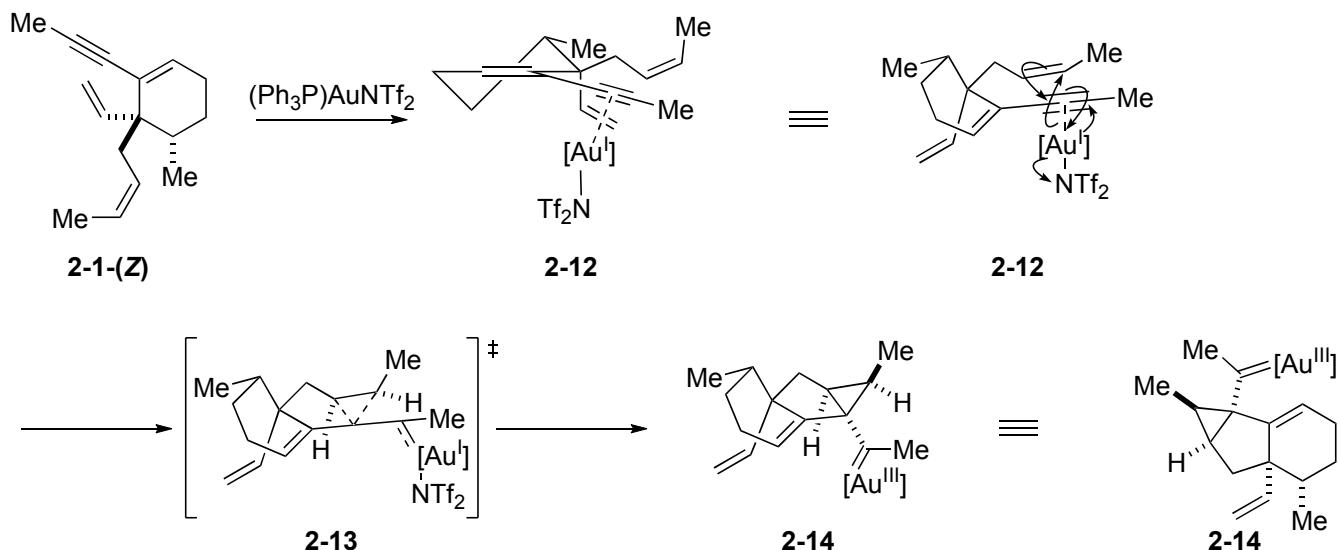
boat conformation is more stable.

• Answer from 2-1-(E) to A

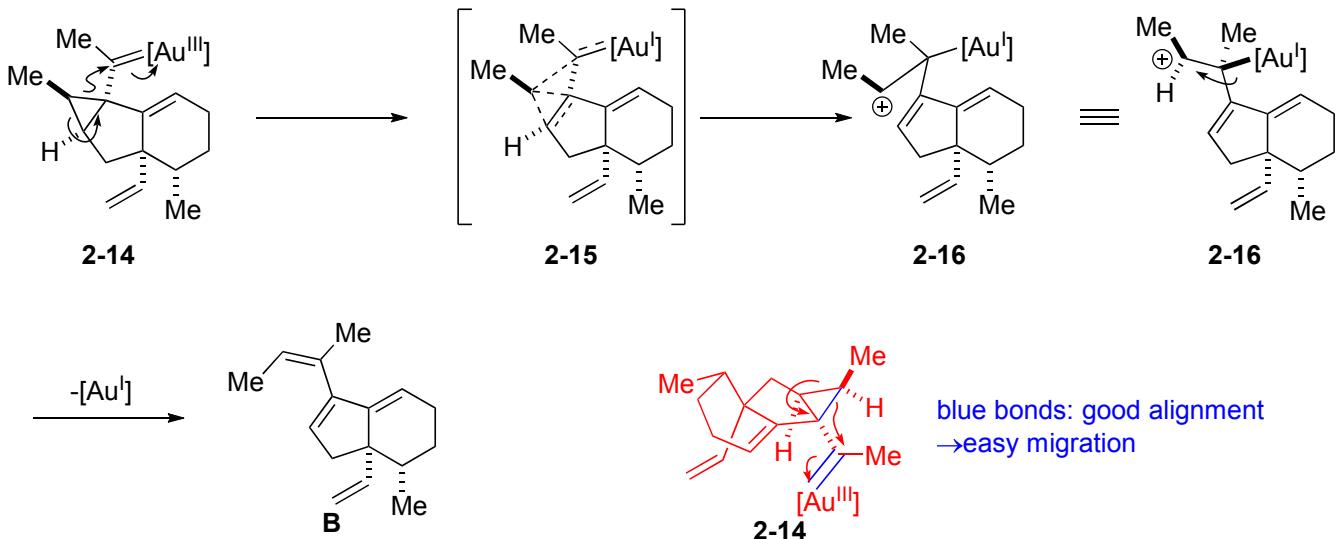




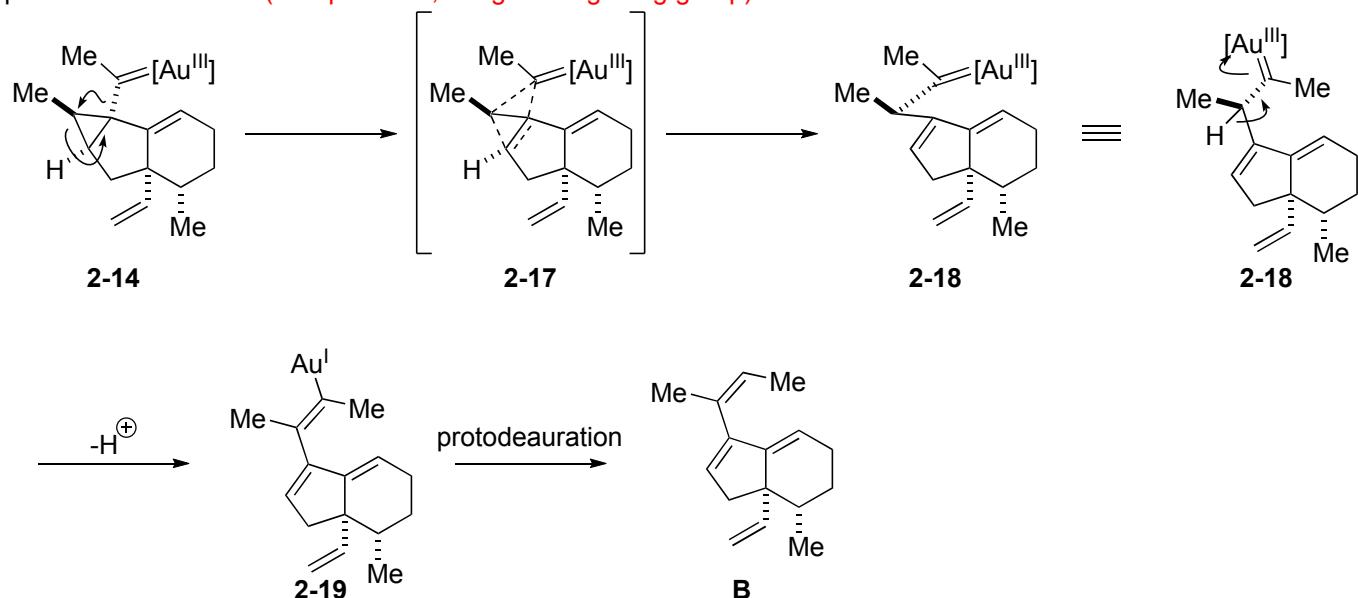
•Answer from 2-1-(Z) to 2-14



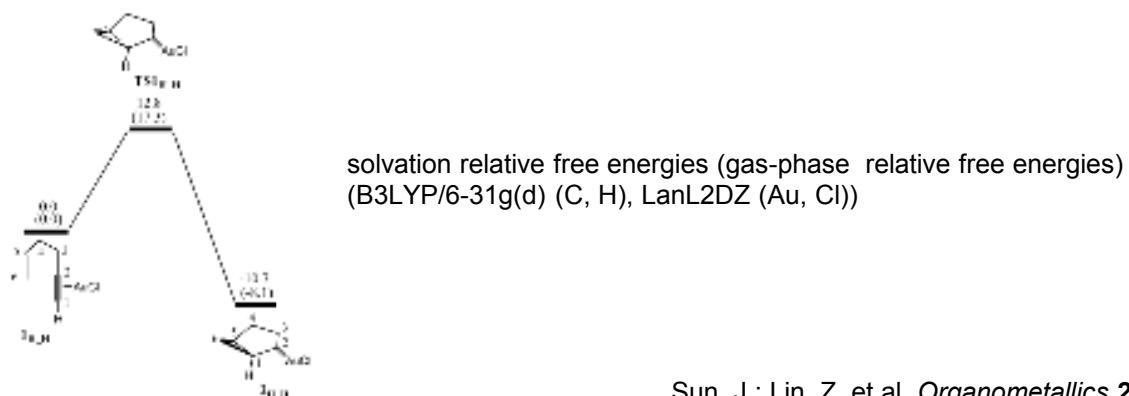
path a from 2-14 to B



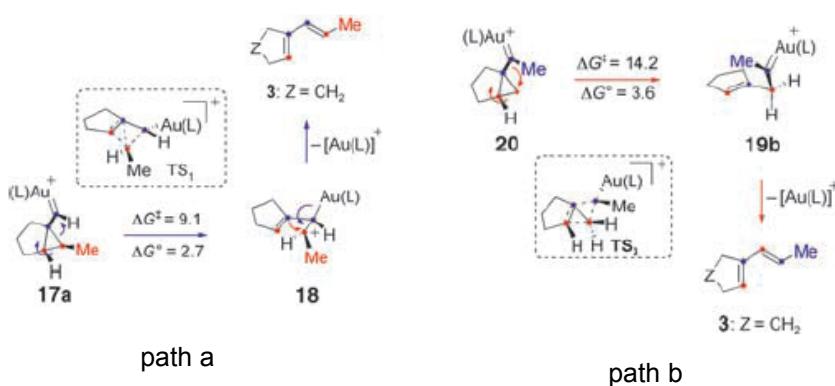
path b from **2-14** to **B** (less probable, not good migrating group)



• 1,5- or 1,6-enyne cycloisomerization by Au-catalyst is proposed to proceed by concerted mechanism.



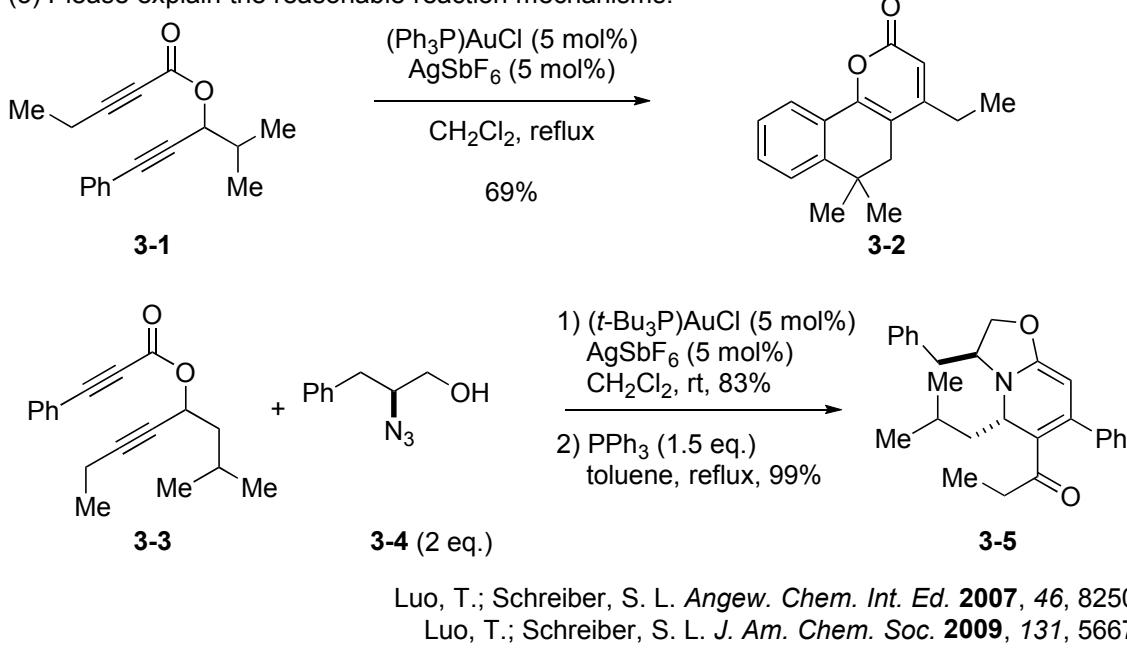
• From **X** to **B**, both reaction mechanisms are possible by calculations.



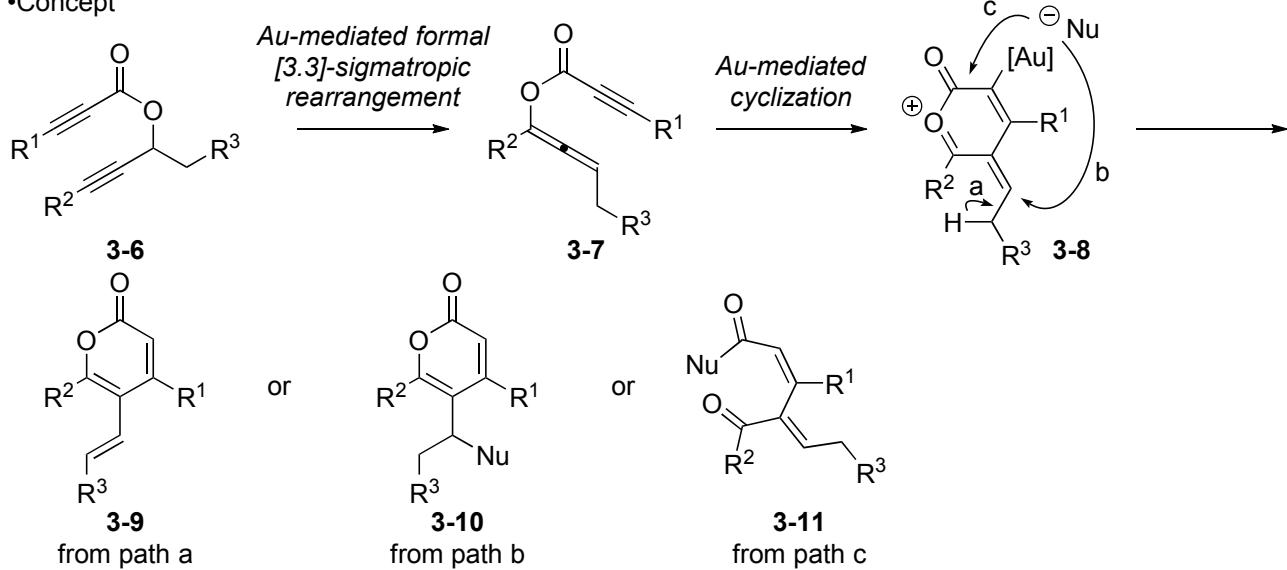
B3LYP/6-31g(d) (C, H, P), LanL2DZ (Au)

Echavarren, A. M. et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

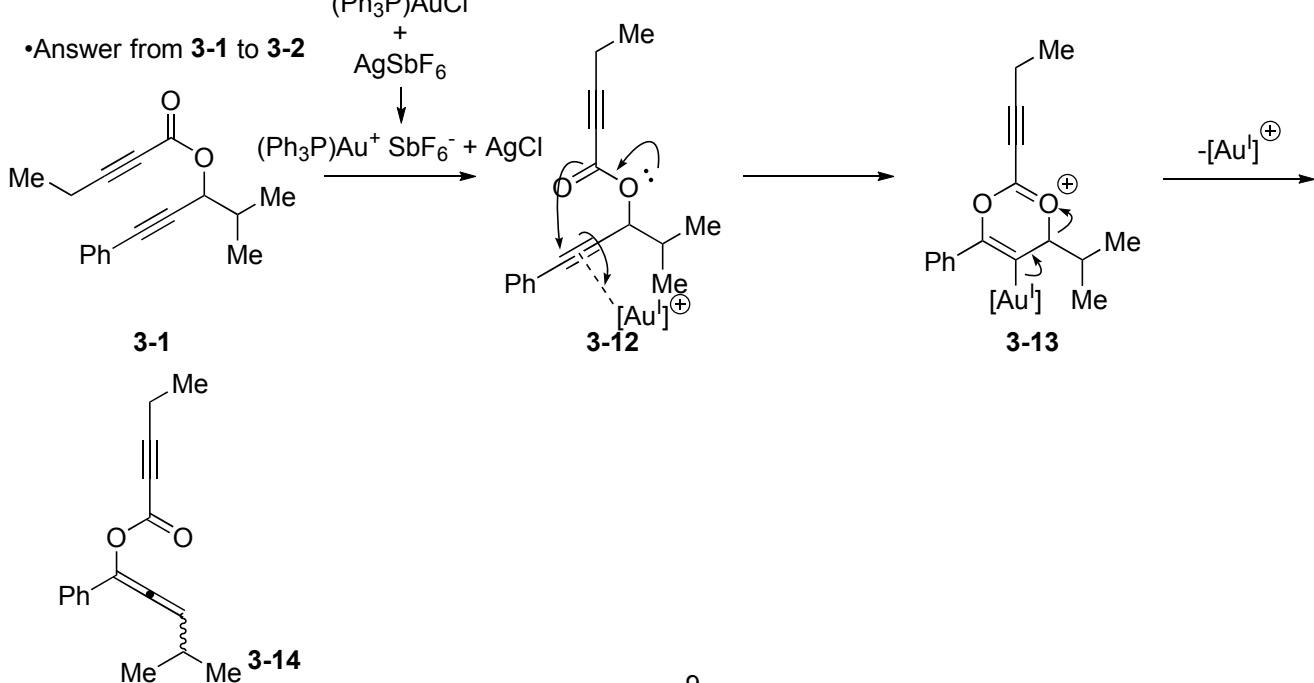
(3) Please explain the reasonable reaction mechanisms.

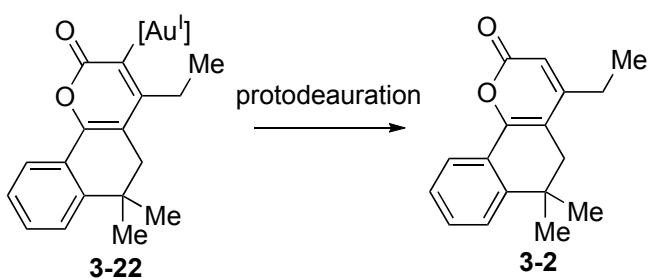
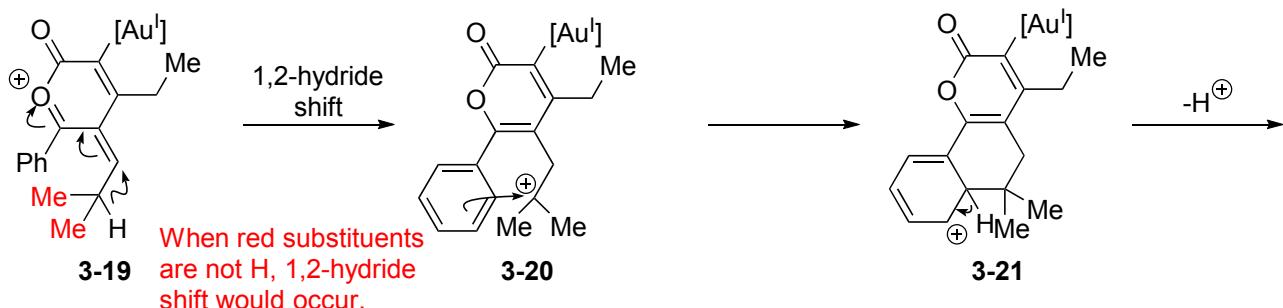
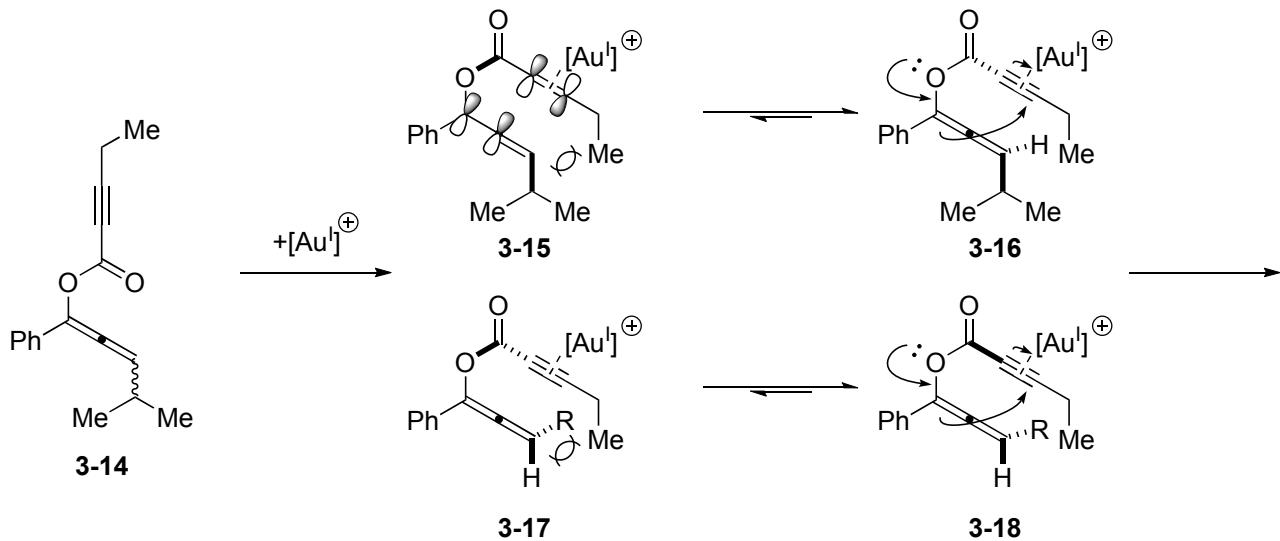


•Concept

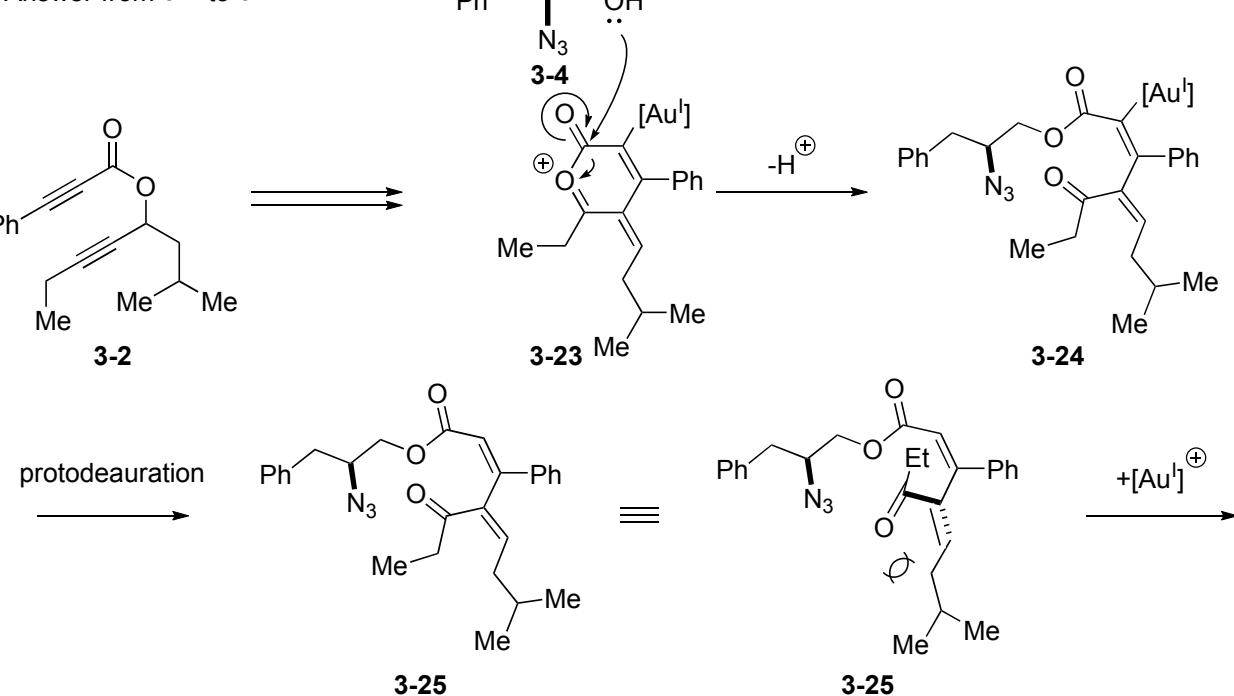


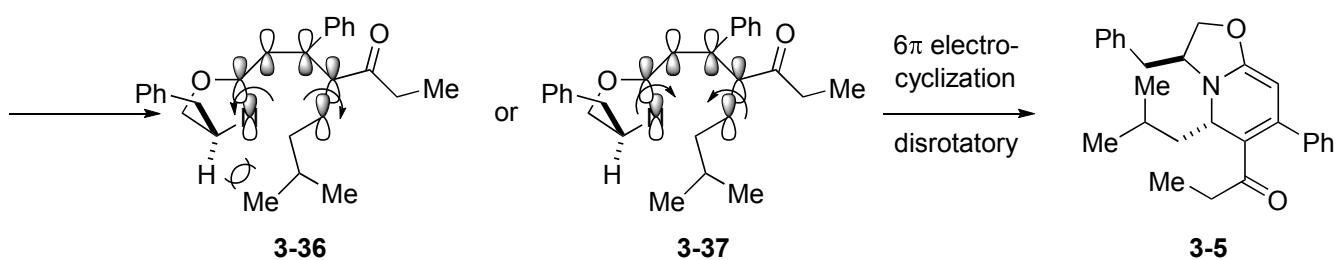
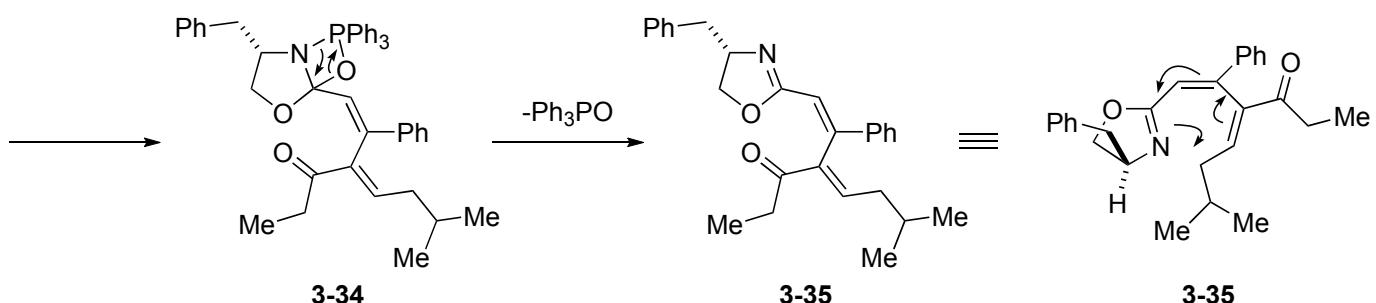
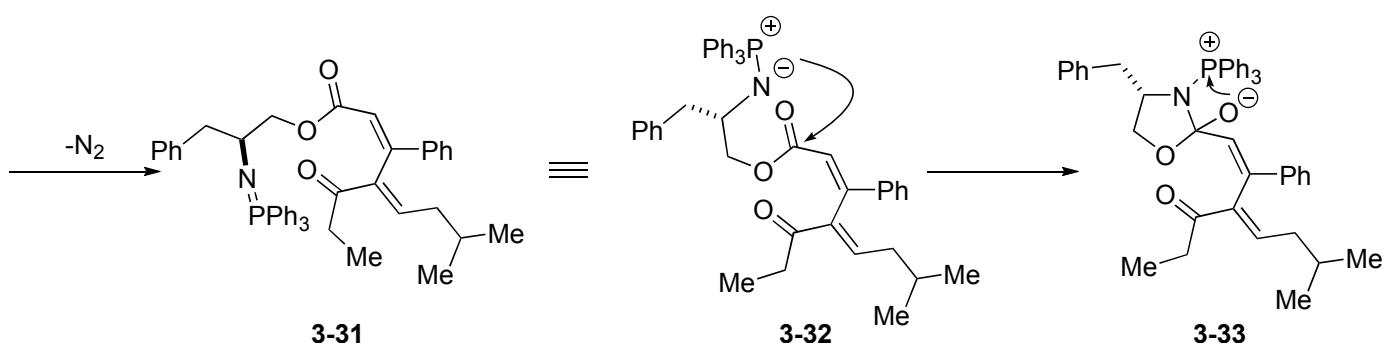
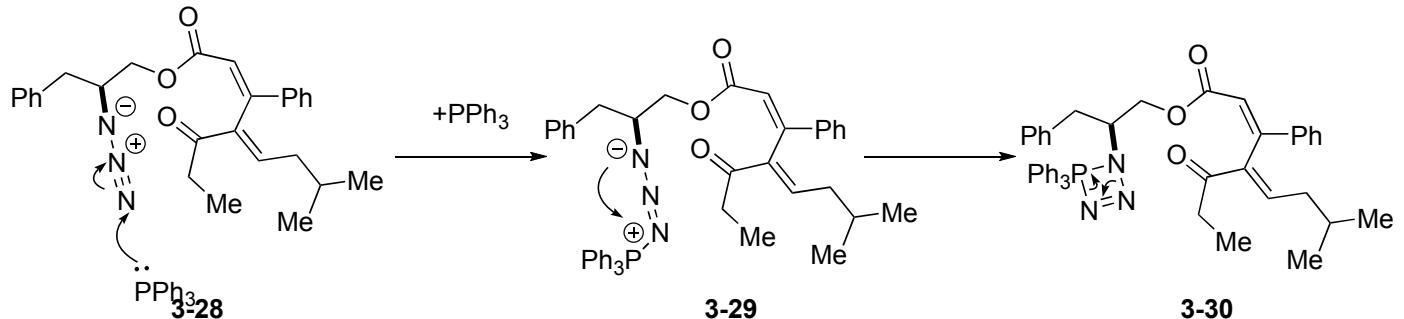
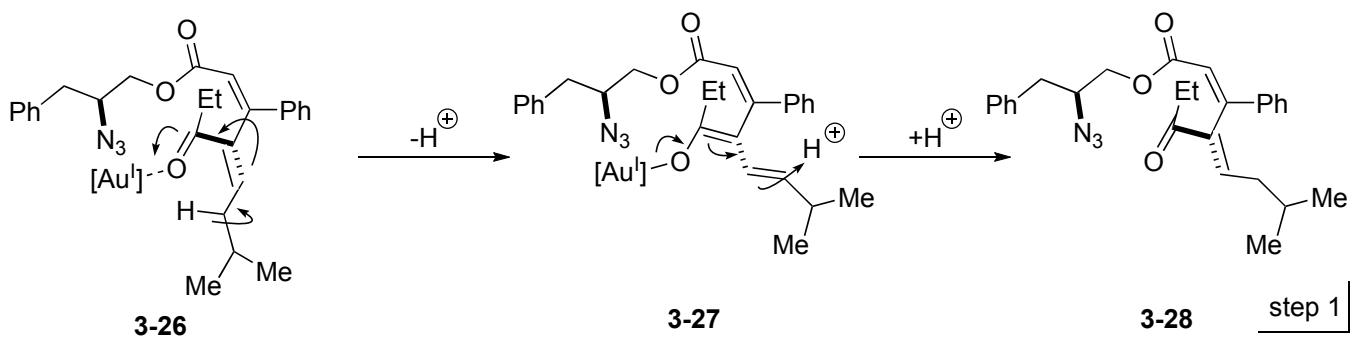
•Answer from 3-1 to 3-2



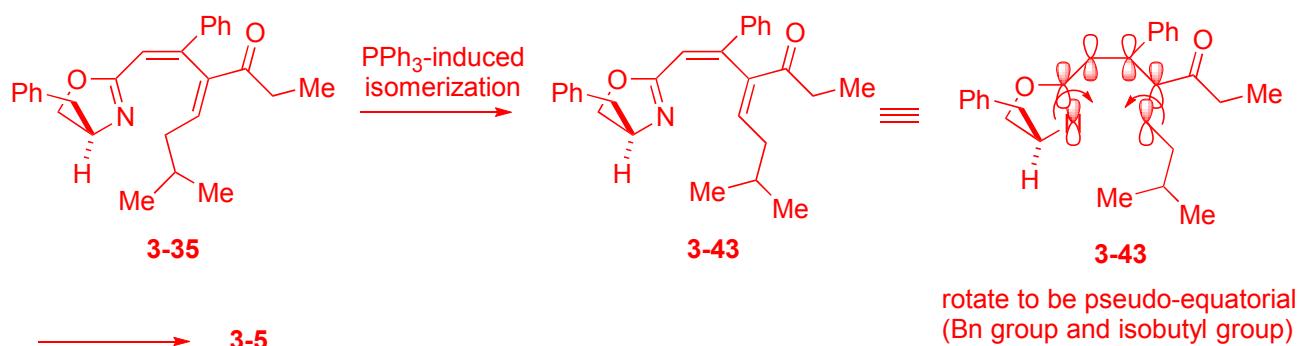


•Answer from 3-1 to 3-2

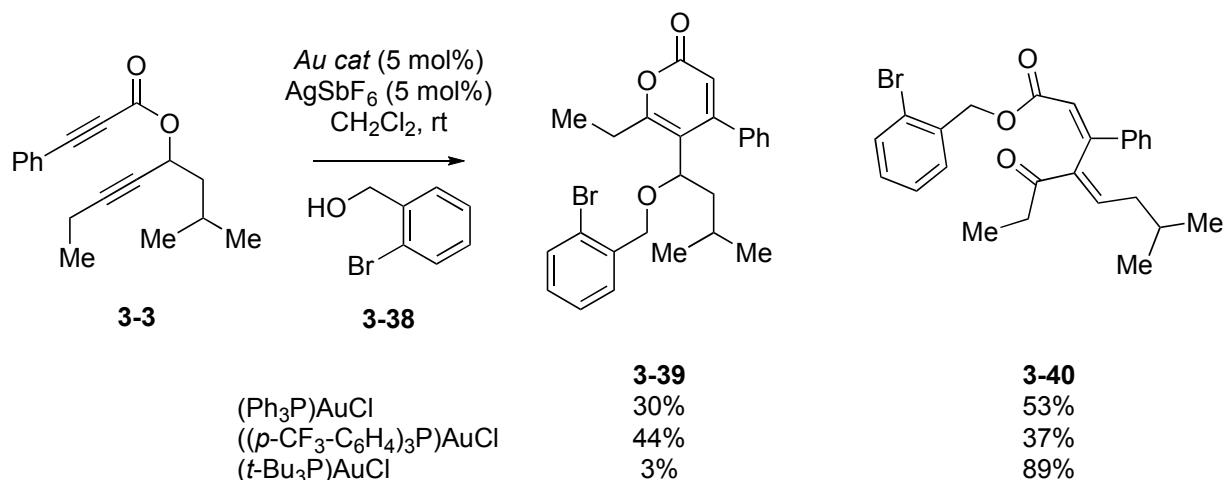
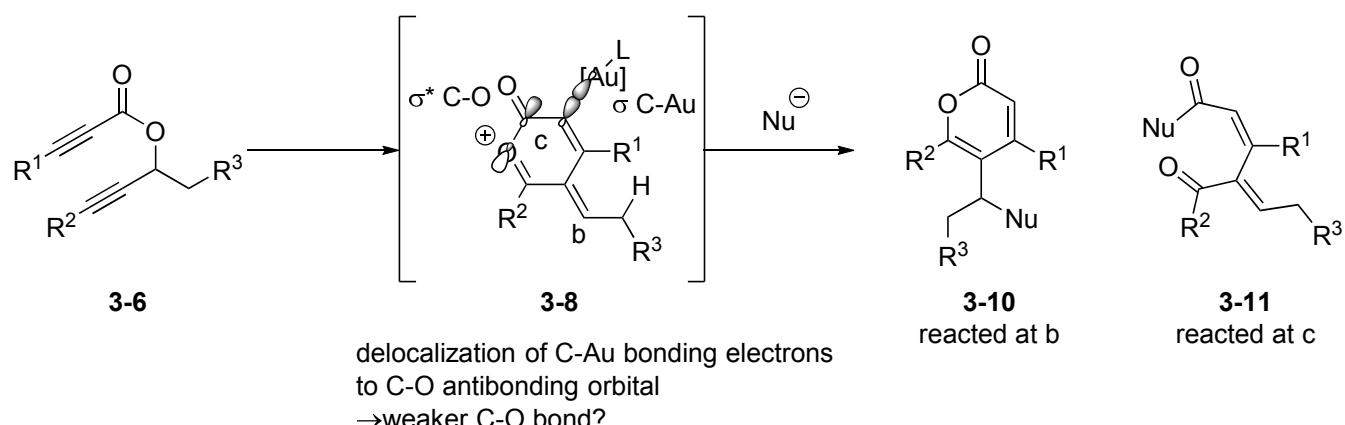




•another possibility



•Electron density of ligand on Au is important for reaction outcomes.



Electron rich ligand promoted the nucleophilic attack at c.

Softer nucleophile tends to attack at b position.

