Problem Session (2) Answer

2022/05/07 Yuya Shiga

Topic: Total synthesis by Zhen Yang

0. Introduction

Prof. Zhen Yang

1982 : BS Shenyang College of Pharmacy
1986 : MS Shenyang College of Pharmacy (Prof. Qihuai Chen)
1992 : Ph. D. The Chinese University of Hong Kong (Prof. Henry N. C. Wong)
1992-1995 : Postdoc. The Scripps Research Institute
1995-1998 : Assistant Prof. The Scripps Research Institute
1998-2001 : Institute Fellow Harvard University
2002- : Professor Peking University

Research Topic:

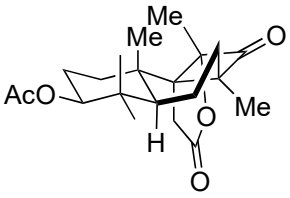
1. New Synthetic Methodology

2. Total Synthesis

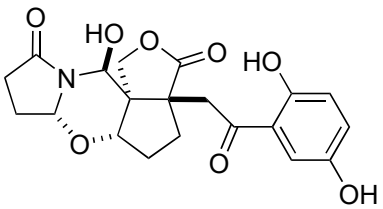
3. Chemical Genetics

Total Synthesis:

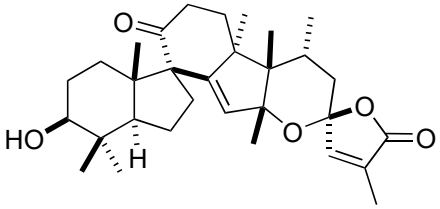
2021: (+)-Cyclobutastellettolide B (**Problem 1**), (±)-Cephanolide B, (-)-Spirochensilide A (210731_PS_Lin_Yuanqi),
2020: (+)-Haperforin G, (+)-Waihoensene, (-)-Guignardones A and B,(±)-Norascyrononones A and B, Pre-scchisanartanin C
2019: (−)-pavidolide B, hybocarpone
2018: insulicolide A, lancifodilactone G acetate, (±)-5-epi-cyanthiwigin, (±)-sinensilactam A (**Problem 2**), (−)-pavidolide B



cyclobutastellettolide B
(**Problem 1**)
J. Am. Chem. Soc. **2021**, *143,* 18287



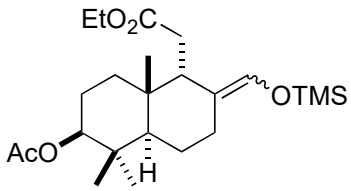
sinensilactam A
(**Problem 2**)
Org. Lett. **2018**, *20,* 1857



spirochensilide A
(210731_PS_Lin_Yuanqi)
J. Org. Chem. **2021**, *86*, 2158

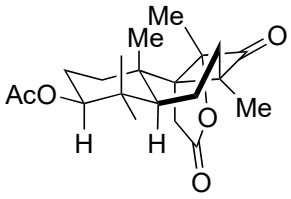
1-1. Reaction mechanism

(1)



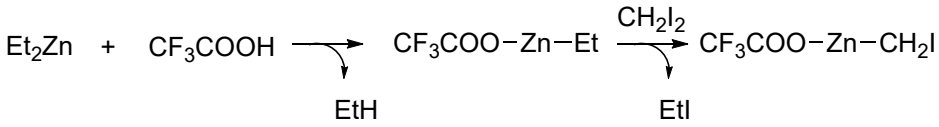
1-1
(Z/E=1:1)

1. CF_3COOH (8.0 eq), Et_2Zn (8.0 eq)
   CH_2I_2 (8.0 eq), CH_2Cl_2, 0 ºC to 25 ºC
2. conc. HCl (45 eq), acetone, reflux,
   85% (2 steps)
3. $EtPPh_3Br$ (3.0 eq), *n*-BuLi (2.9 eq),
   THF, 0 ºC, 94%
4. $K_2OsO_4 \cdot H_2O$ (10 mol%), NMO (10 eq)
   acetone/H_2O/*t*-BuOH=20/1/1, 25 ºC, 92%
5. $(COCl)_2$ (8.0 eq), DMSO (12 eq),
   Et_3N (24 eq), CH_2Cl_2, -78 ºC to rt, 97%
6. hv, $CHCl_3$, 25 ºC, 95%

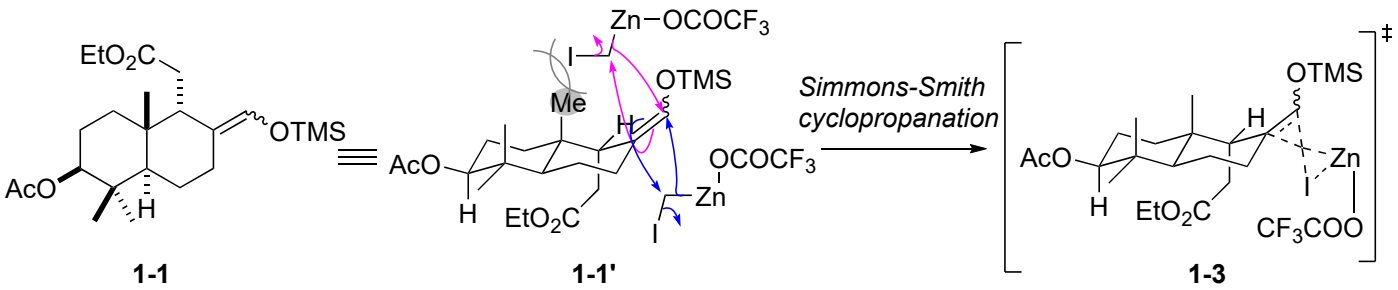


1-2

Zhang, Z.; Chen, S.; Tang, F.; Guo, K.; Liang, X.; Huang, J.; Yang, Z.*J. Am. Chem. Soc. 202*1, 14*3, 18*287



Yang, Z.; Lorenz, J.; Shi, Y. *tetrahedron*, **1998**, *39*, 8621.

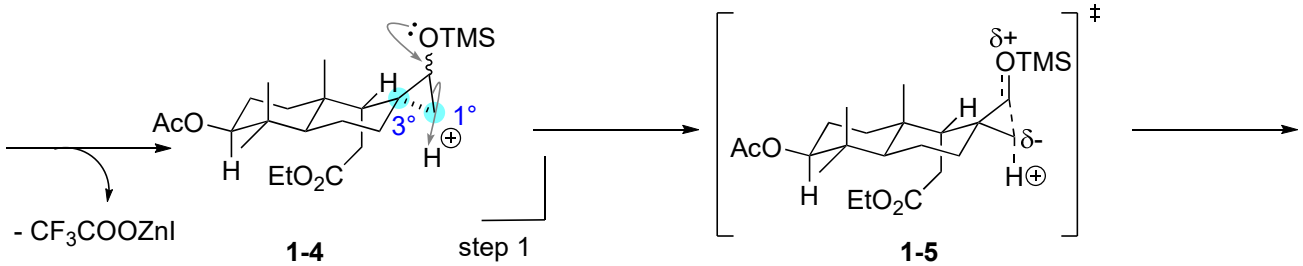


1-1

1-1'

Simmons-Smith cyclopropanation

1-3

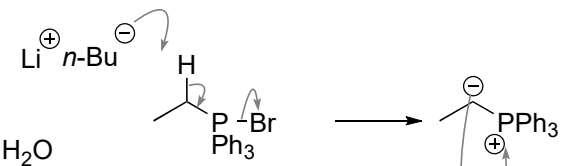


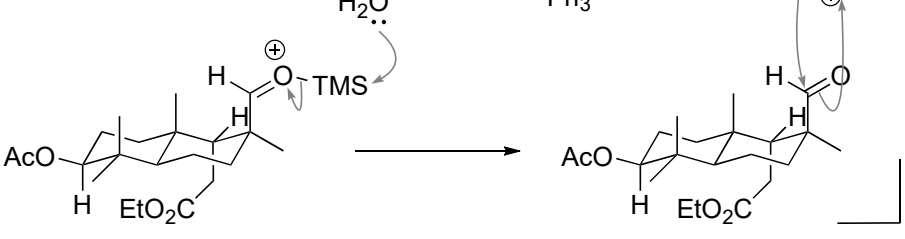
- $CF_3COOZnI$

1-4
(d.r.=1.1:1)

step 1

1-5



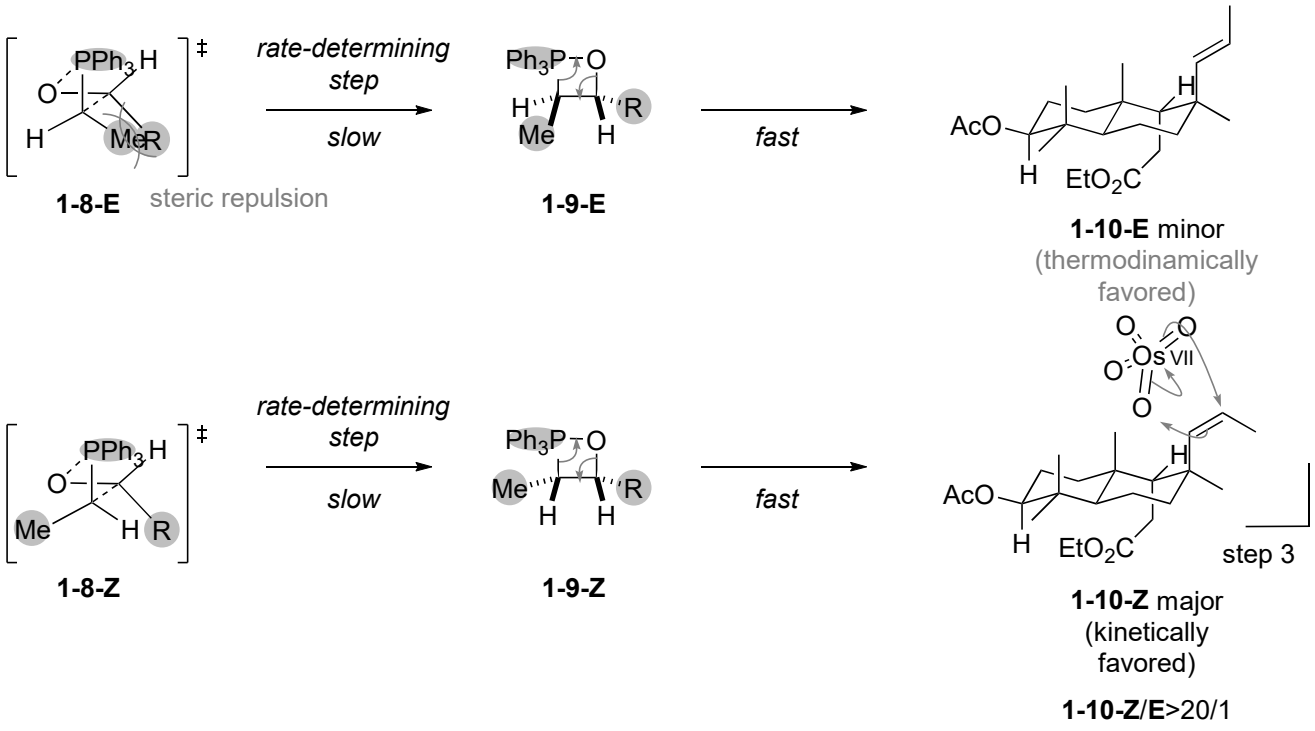


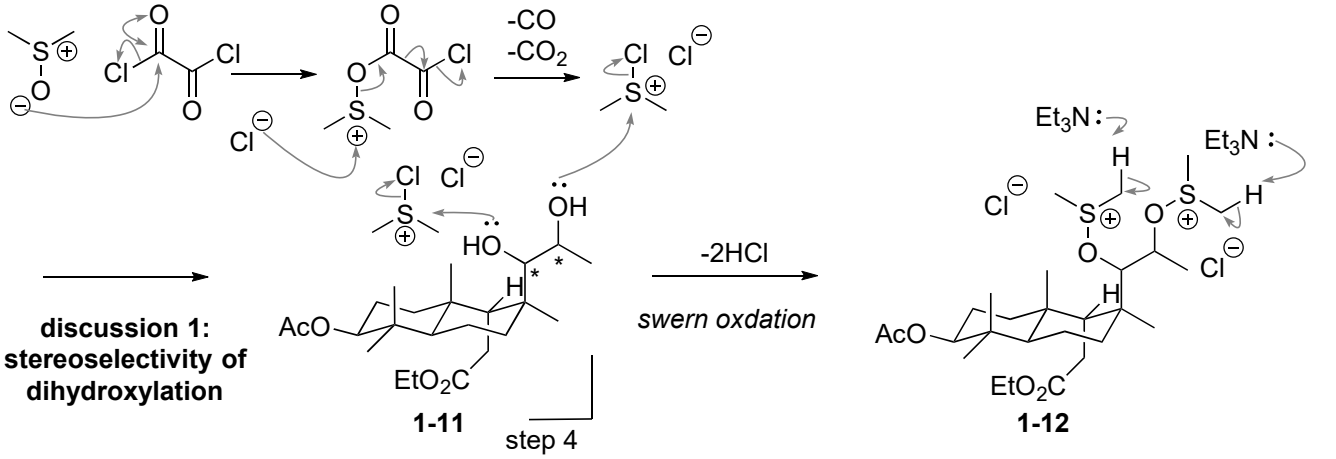
1-6

1-7

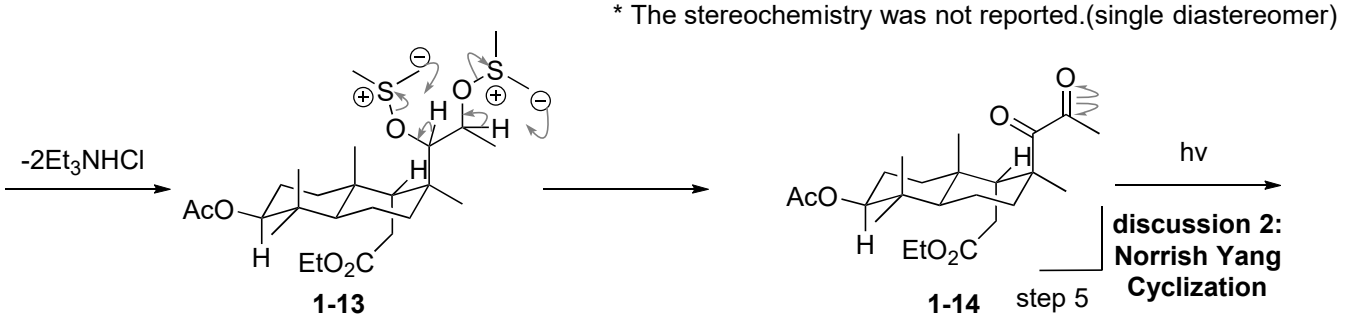
step 2

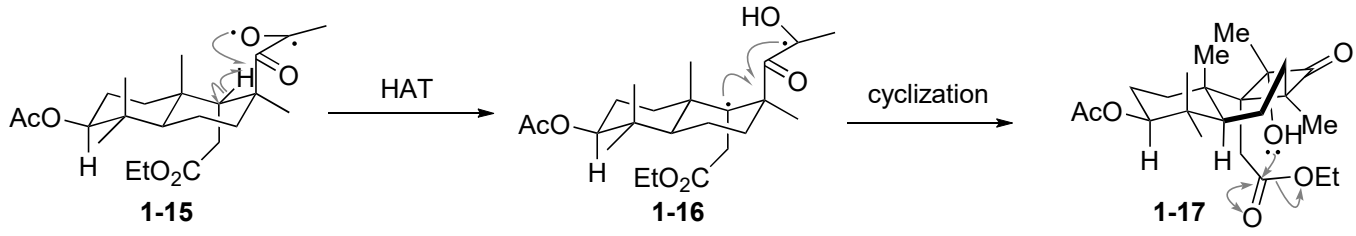
wittig-reaction

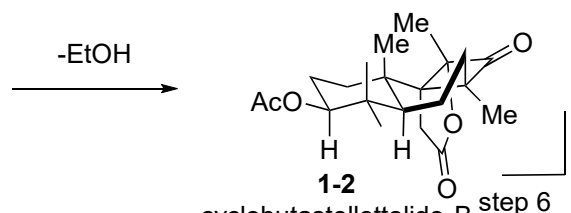




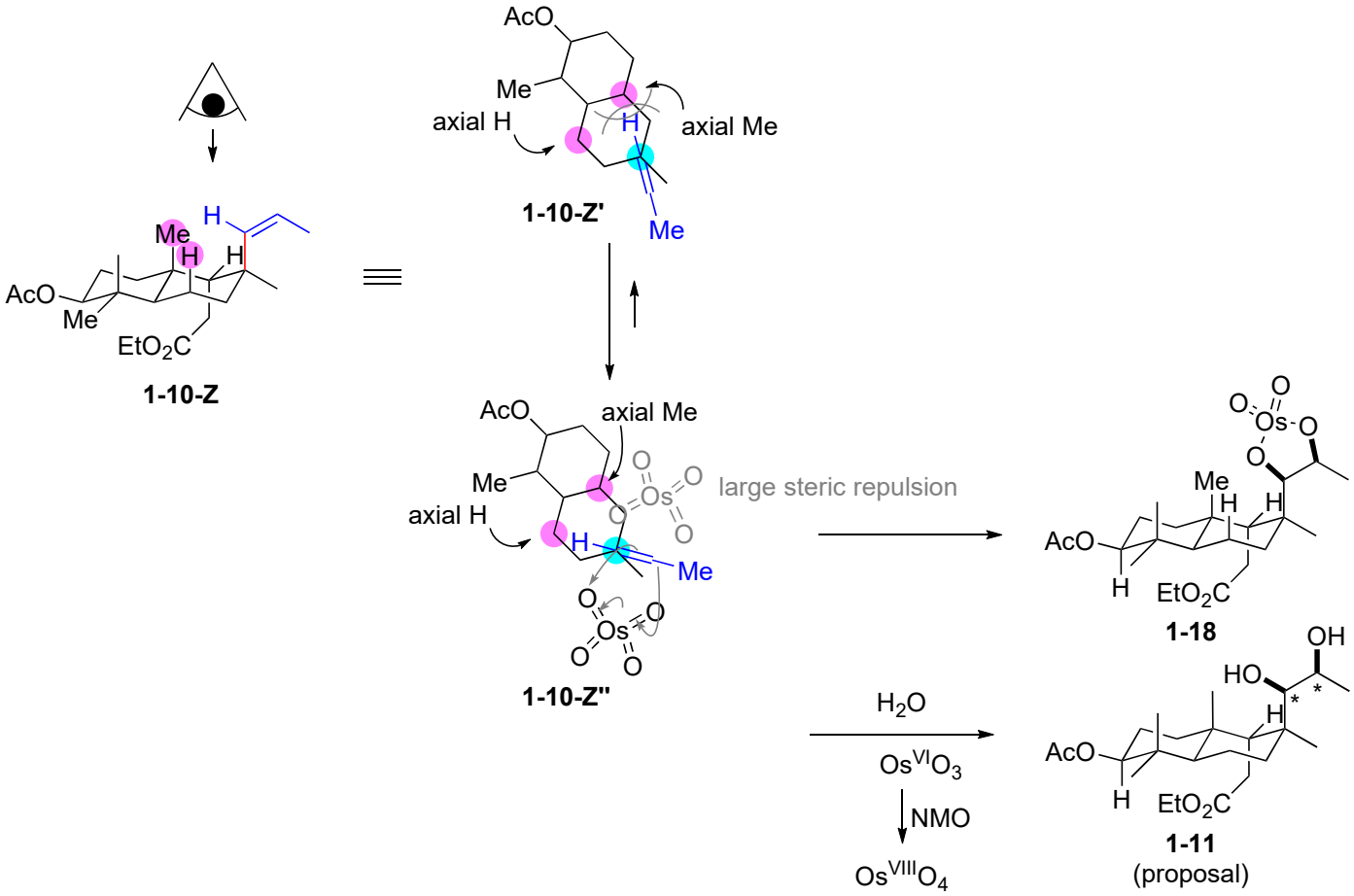
* The stereochemistry was not reported.(single diastereomer)







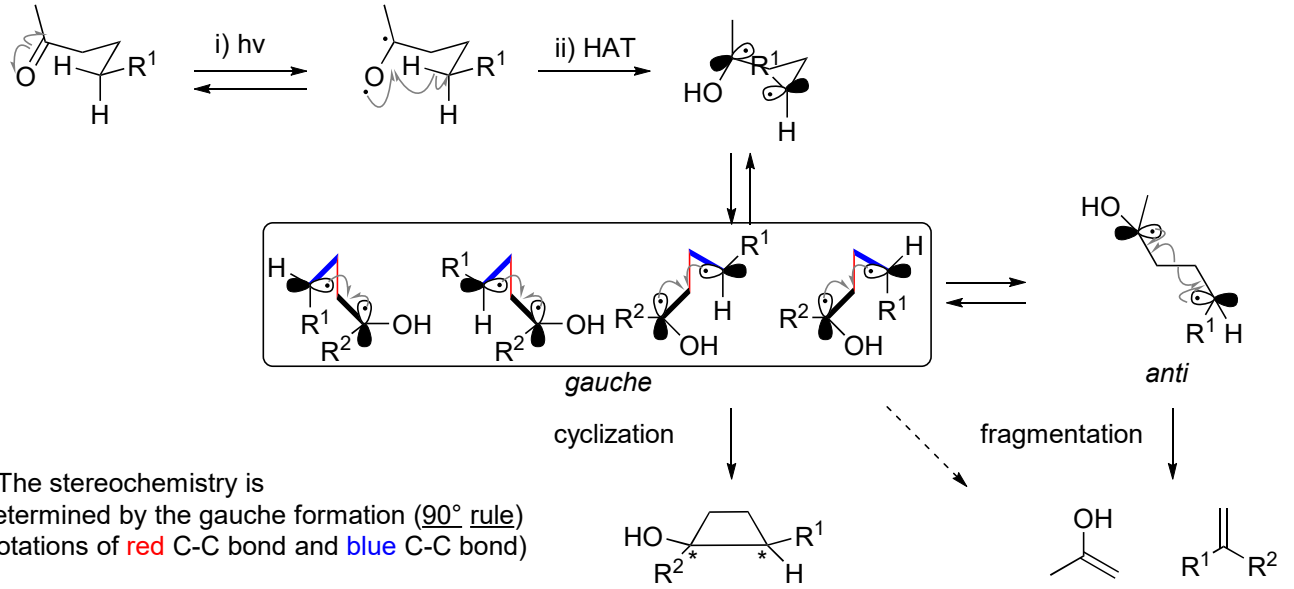
1-2. discussion 1: stereoselectivity of dihydroxylation



** The stereochemistry was not reported. (single diastereomer)

1-3. discussion 2: Norrish-Yang cyclization

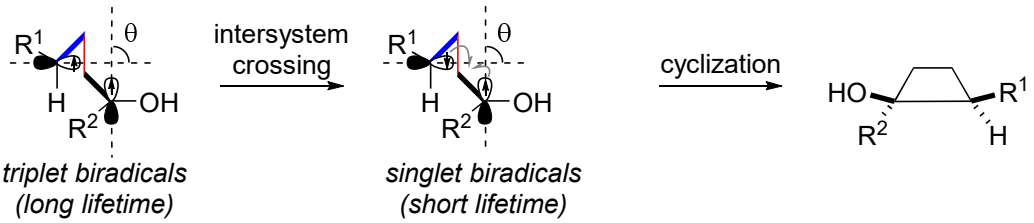
1-3-0. introduction



* The stereochemistry is determined by the gauche formation (90° rule) (rotations of red C-C bond and blue C-C bond)

Griesbeck, A.; Heckroth, H. *J. Am. Chem. Soc.* **2002**, *124*, 396.

90° rule



At θ=90°, SOC (spin-orbit coupling) value is the largest.

↓

Triplet biradicals undergo intersystem crossing.

Carlacci, L.; Doubleday, C.; Furlani, T.; King, H.; McIver, J. *J. Am. Chem. Soc.* **1987**, *109*, 5323.

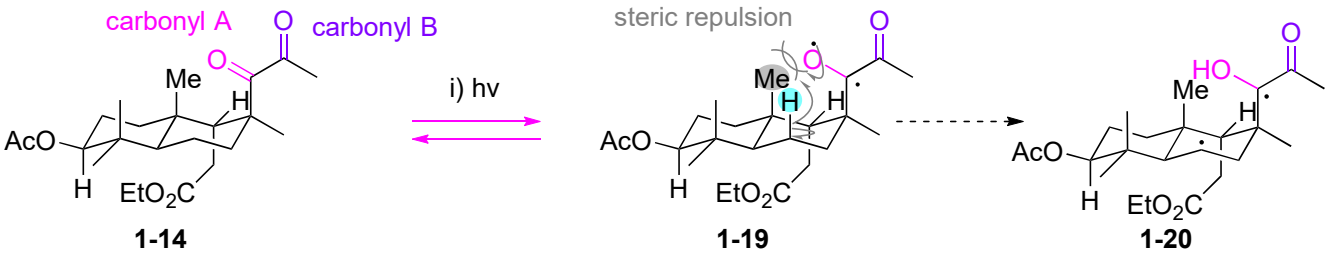
Problems of Norrish Yang cyclization

i) chemoselectivity of carbonyl
ii) HAT selectivity
iii) cyclization or fragmentation
iv) stereoselectivity

Pathes from 1,4-biradicals depends on the conformations (gauche or anti)

from *gauche*....only cyclization proceeds.
(fragmentation is kinetically disfavored)
from *anti*.....only fragmentation proceeds

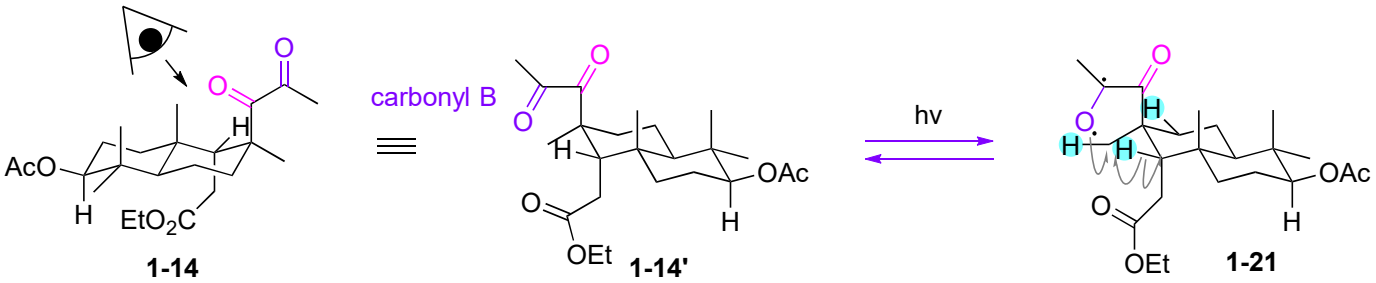
1-3-1. Chemoselectivity of carbonyl (pathway from triplet states of carbonyl A)



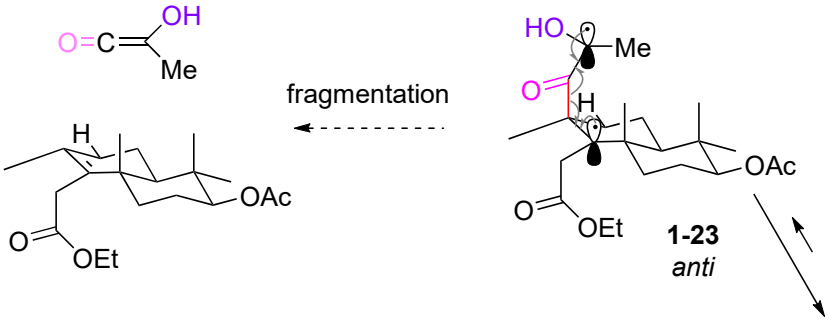
1-14 **1-19** **1-20**

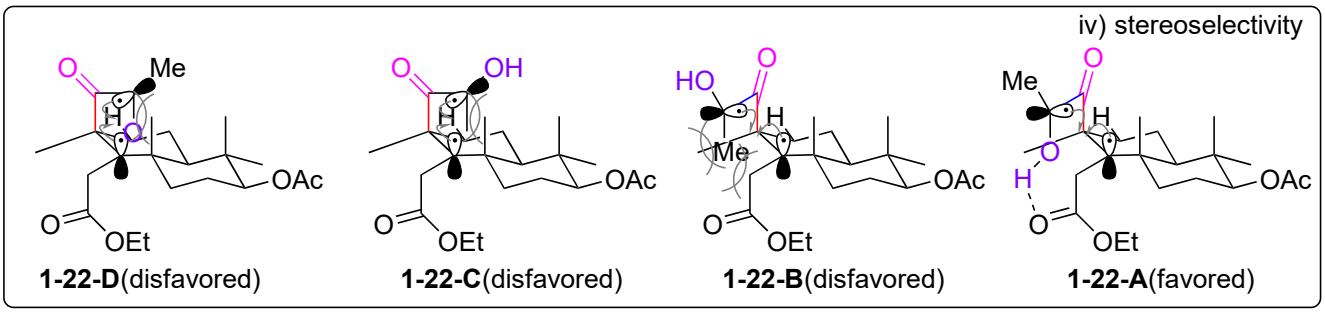
i) chemoselectivity of carbonyl→ From the triplet states of carbonyl A, HAT did not proceed.

1-3-2. pathway from triplet states of carbonyl B



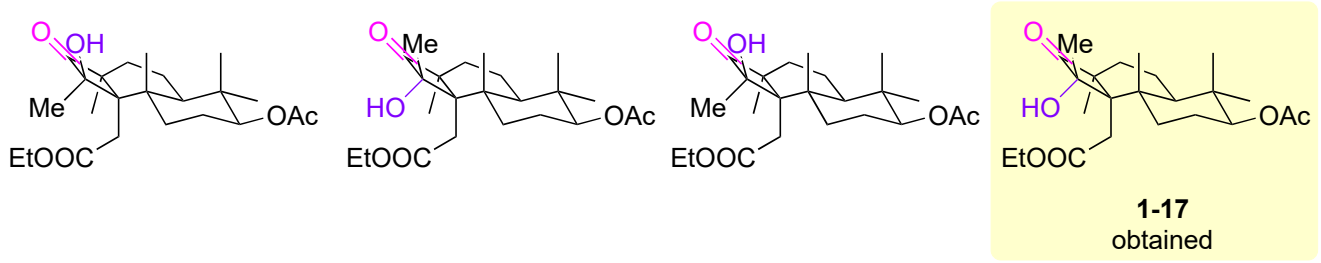
At *anti* conformation, **1-23**, p orbital of radical and ketone are orthotal to each other. So it's unstable.



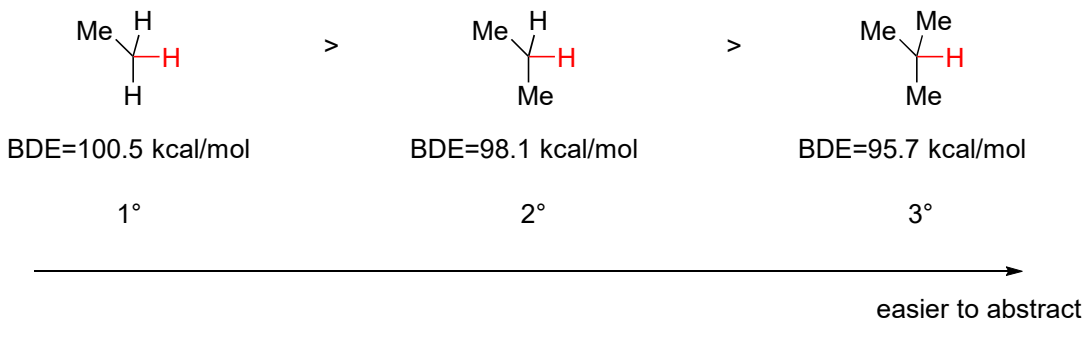


gauche

iii) cyclization



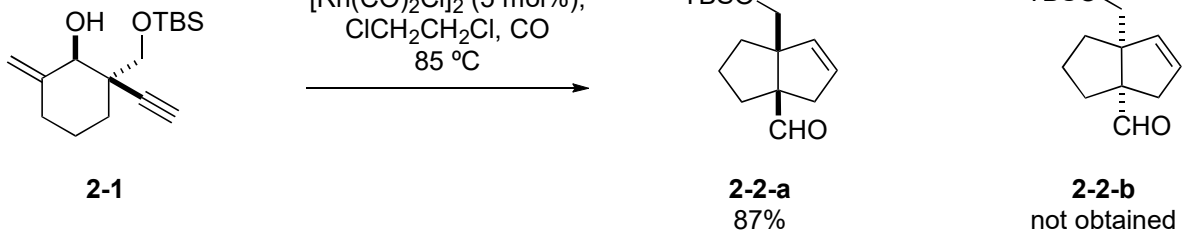
ii) HAT selectivity



2-1-1. reaction mechanism

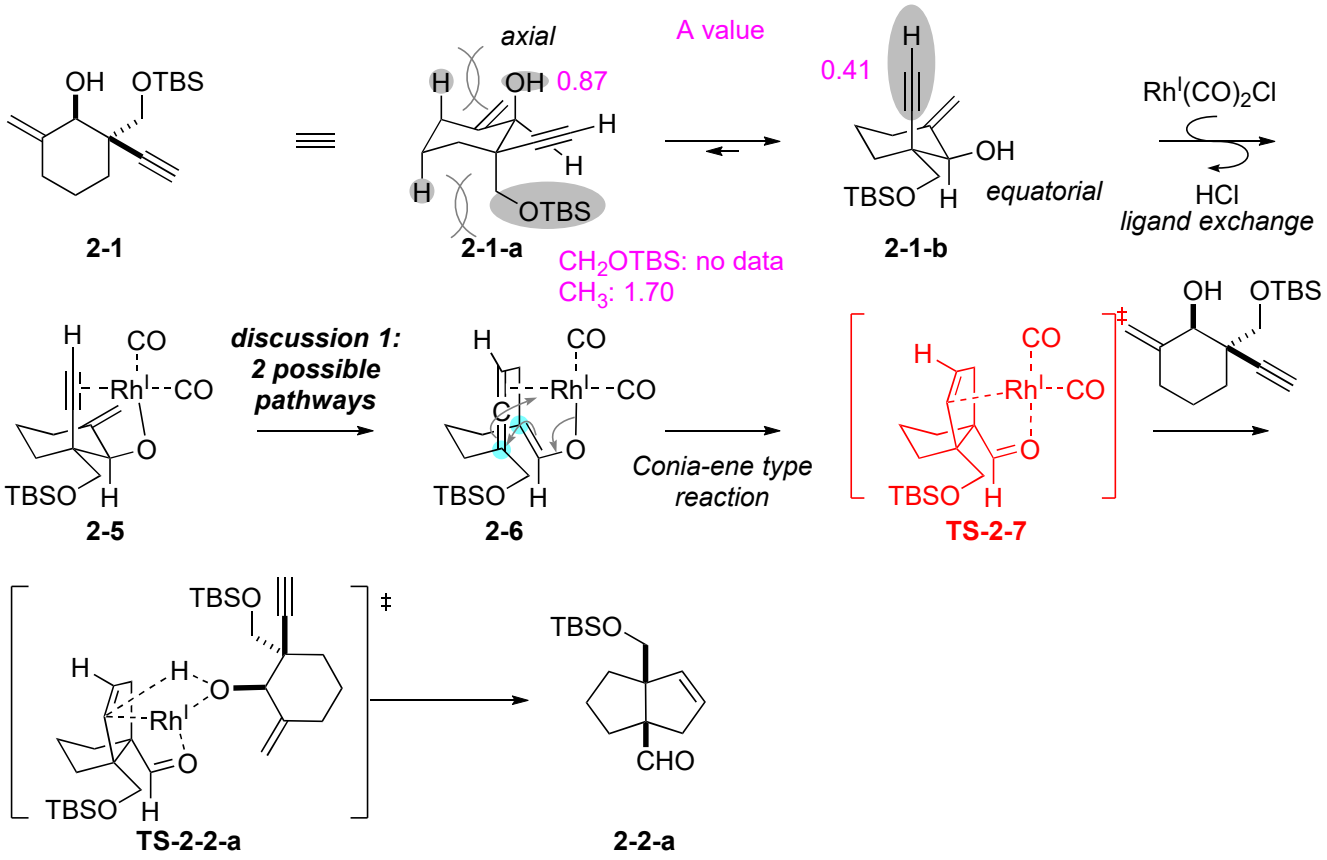
2

(1)



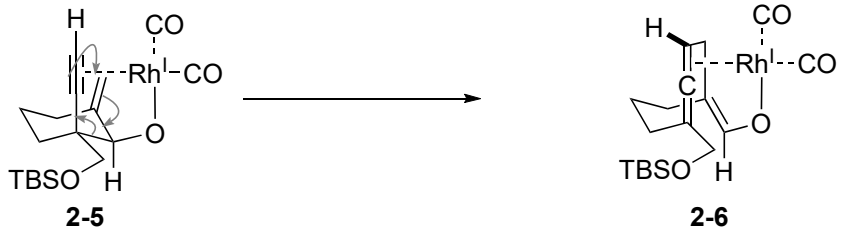
2-1 | **2-2-a** 87% | **2-2-b** not obtained

Qi, X.; Liu, S.; Zhang, T.; Long, R.; Huang, J.; Gong, J.; Yang, Z.; Lan, Y. *J. Org. Chem.* **2016**, *81*, 8306.

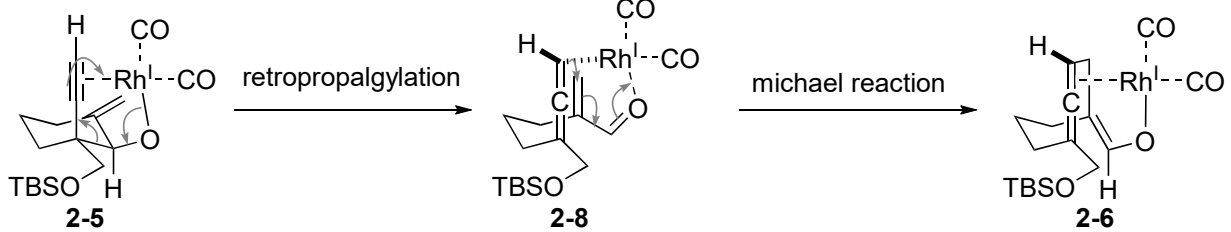


2-1-2. discussion 1: 2 possible pathways ([3,3]-sigmatropic rearrangement or retropropargylation, michael reaction)

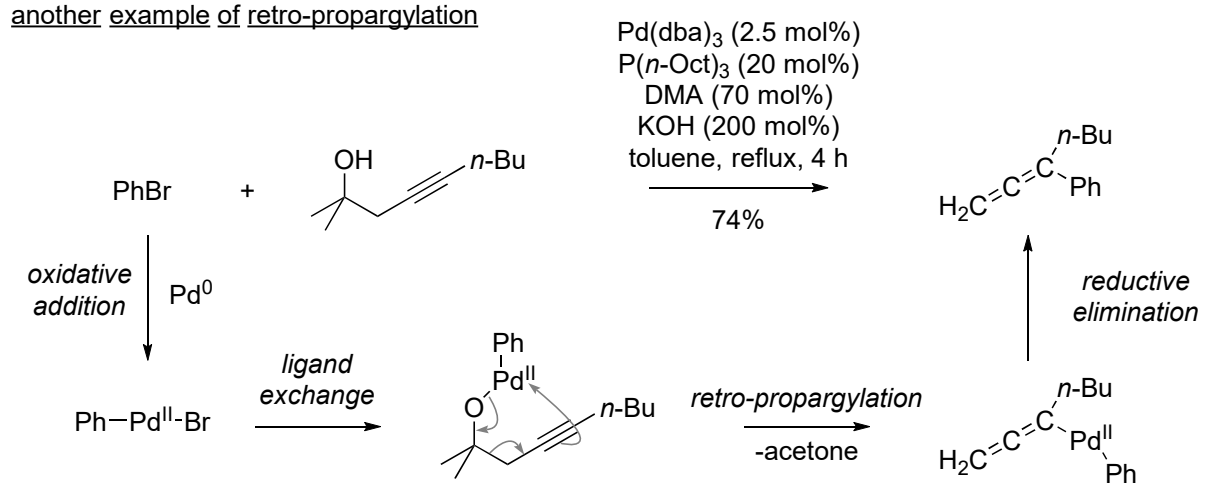
pathway A:[3,3]sigmatropic rearrangement



pathway B:retropropalgylation, michael reaction

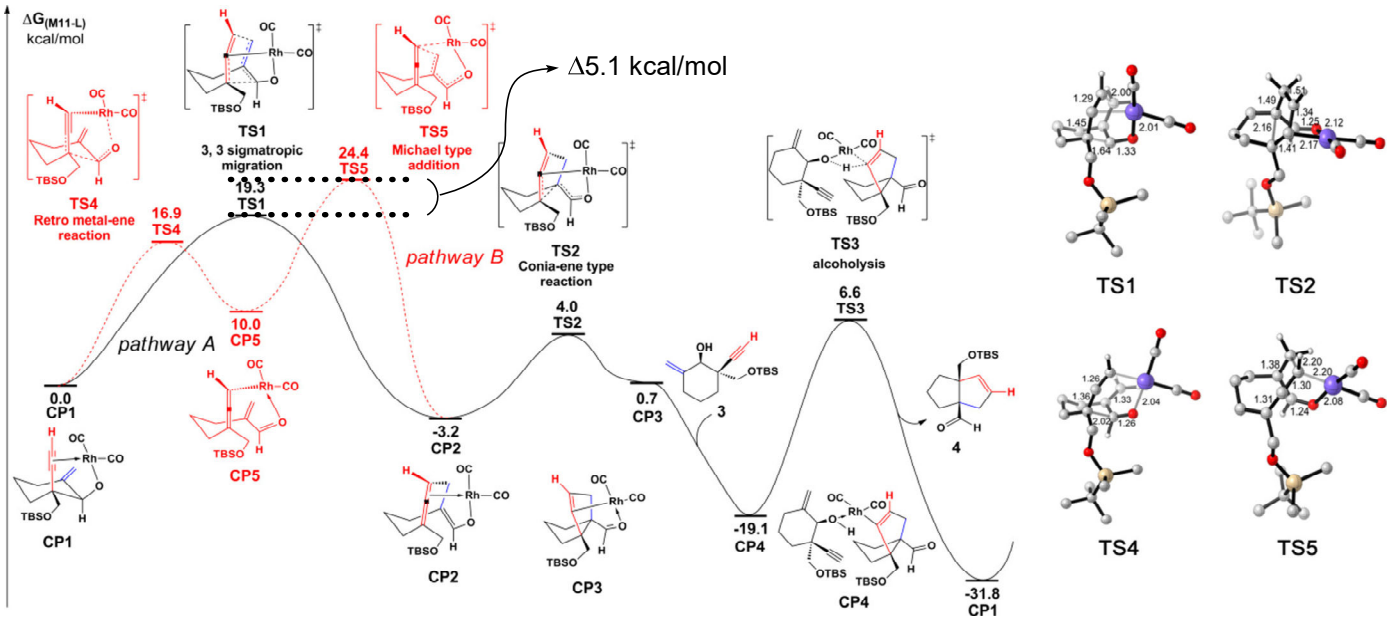


another example of retro-propargylation



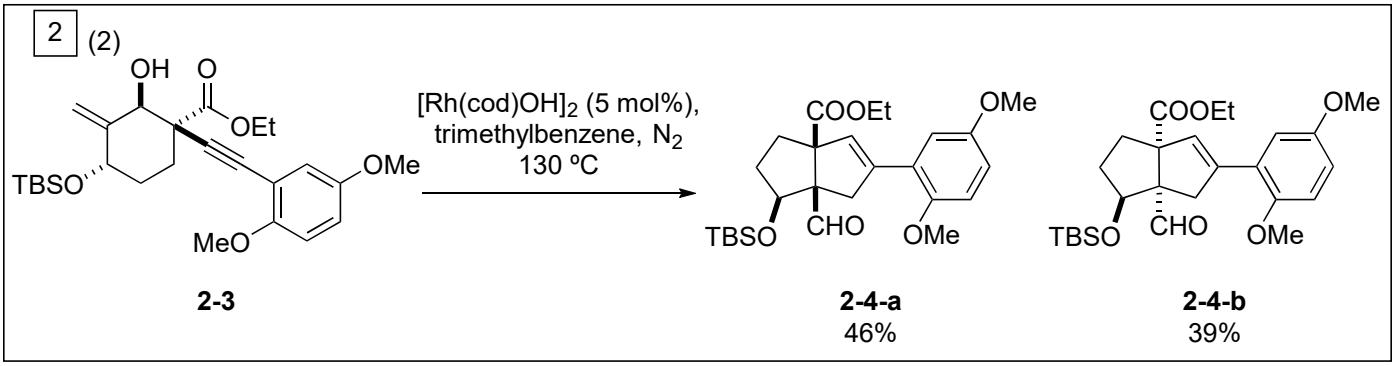
Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem.* **2008**, *130*, 5048.

Calcurated TS by author



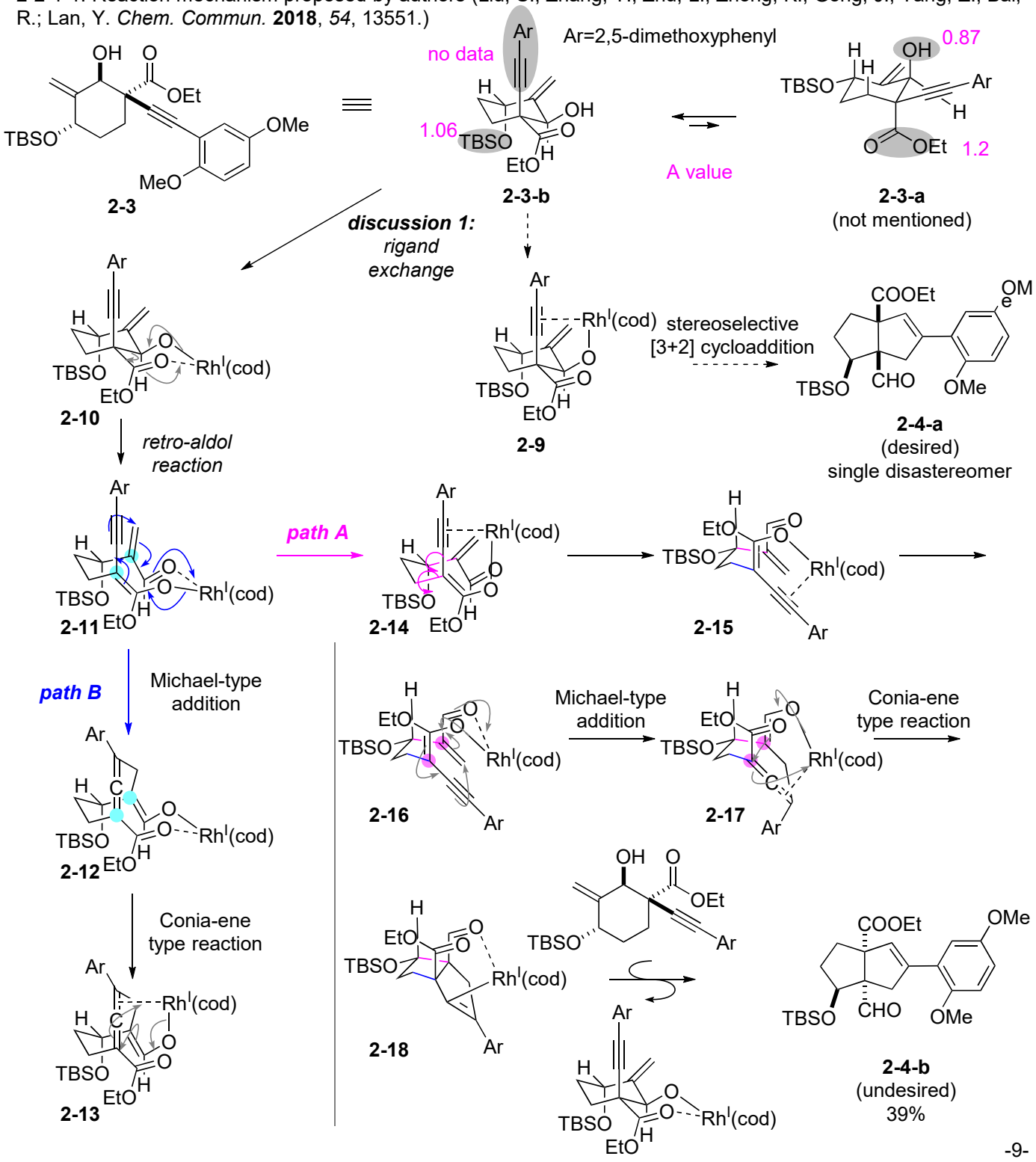
M11-L//M11-L and M11-L//B3LYP

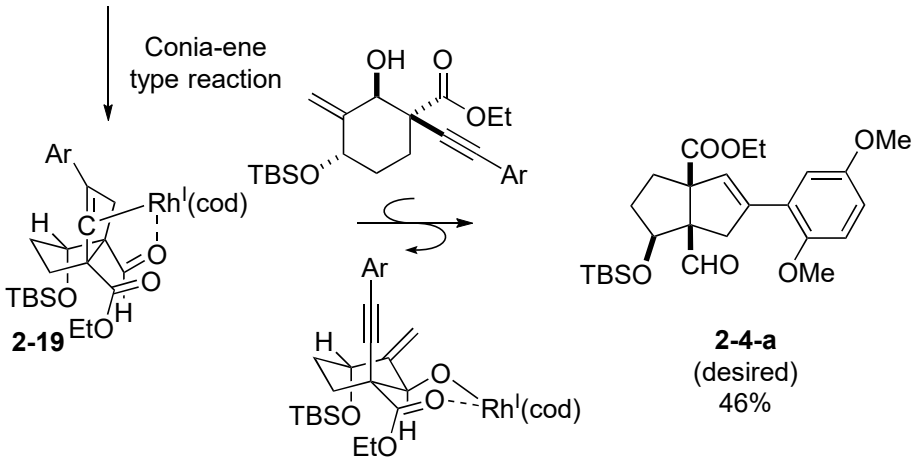
Author's opinion
→The mechanism of 3,3-sigmatropic is favorable.



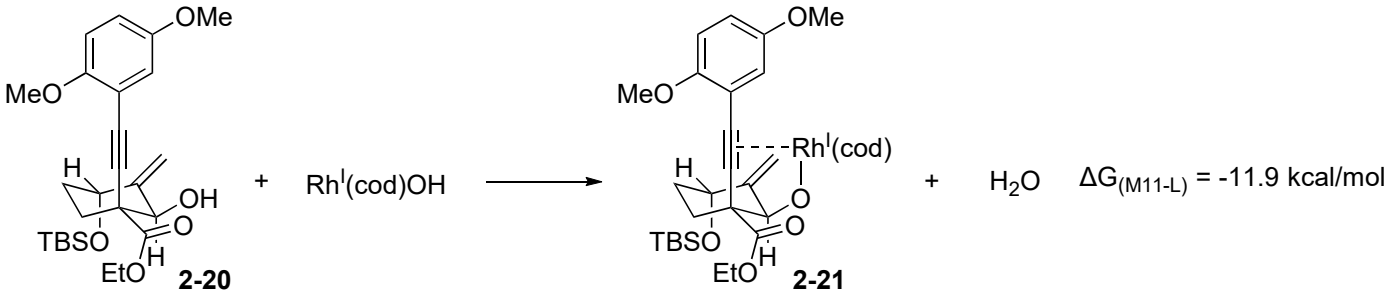
Shao, W.; Huang, J.; Guo, K.; Gong, J.; Yang, Z. *Org. Lett.* **2018**, *20*, 1857.

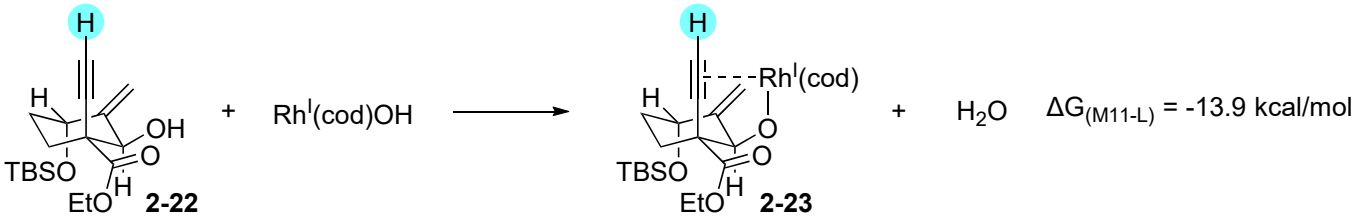
2-2-1-1. Reaction mechanism proposed by authors (Liu, S.; Zhang, T.; Zhu, L.; Zhong, K.; Gong, J.; Yang, Z.; Bai, R.; Lan, Y. *Chem. Commun.* **2018**, *54*, 13551.)



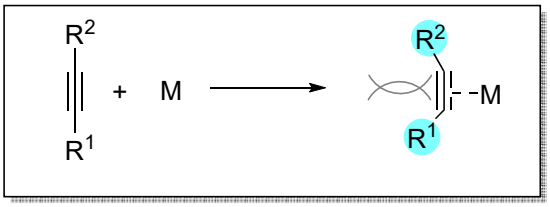


2-2-1-2. discussion 1: rigand exchange

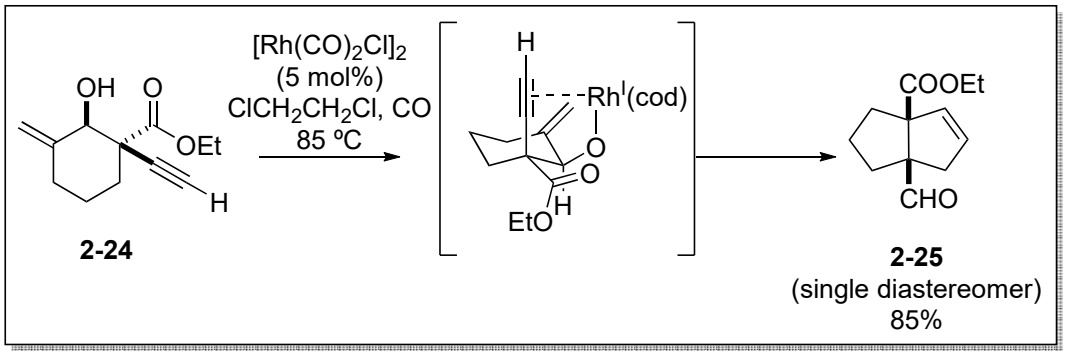




The lower coordination capability of **2-20** is due to the steric repulsion of the alkyne complex.



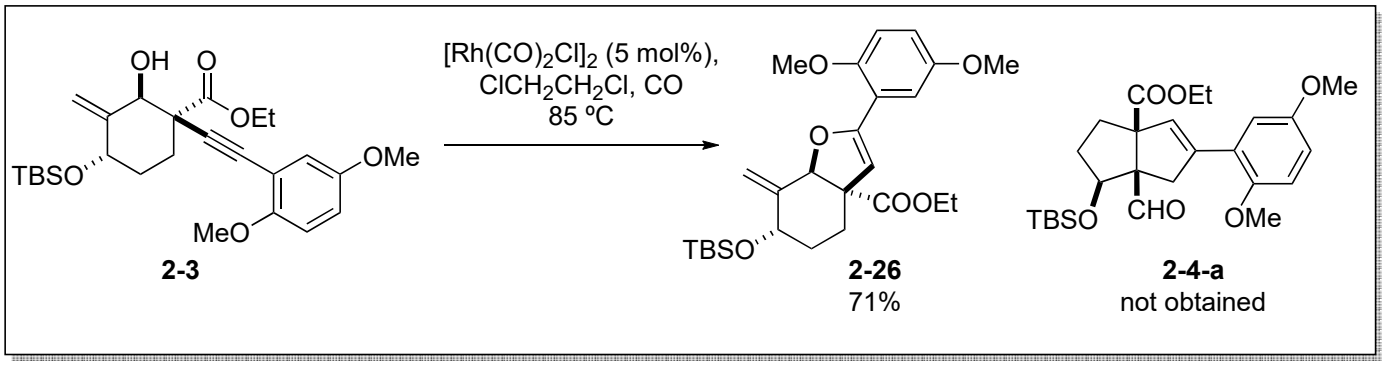
ハートウィグ有機遷移金属化学



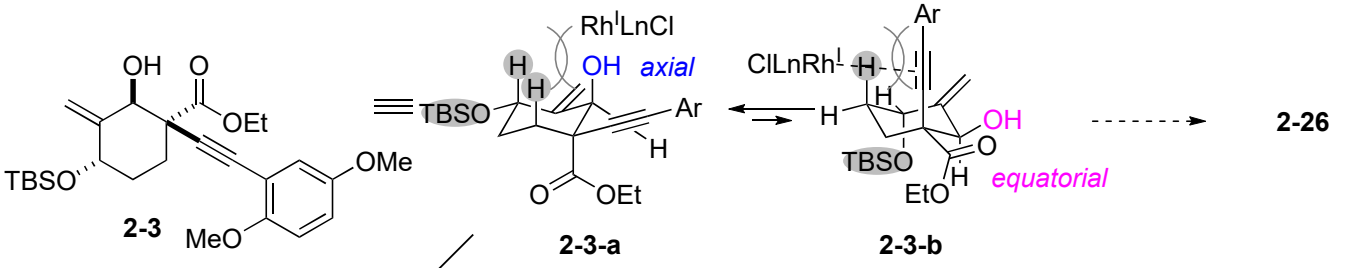
Long, R.; Huang, J.; Shao, W.; Liu, S.; Lan, Y.; Gong, J.; Yang, Z. *Nat. Commun.* **2014**, *5*, 5707.

The explaination of the effect of alkyne substituent is plausible and consistent with the above experimental result.

2-2-2. The etherification proceeded.

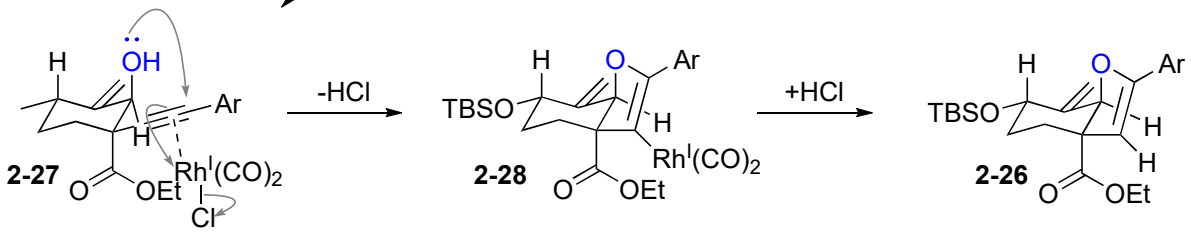


2-2-2-1. The reaction mechanism. Shao, W.; Huang, J.; Guo, K.; Gong, J.; Yang, Z. *Org. Lett.* **2018**, *20*, 1857.



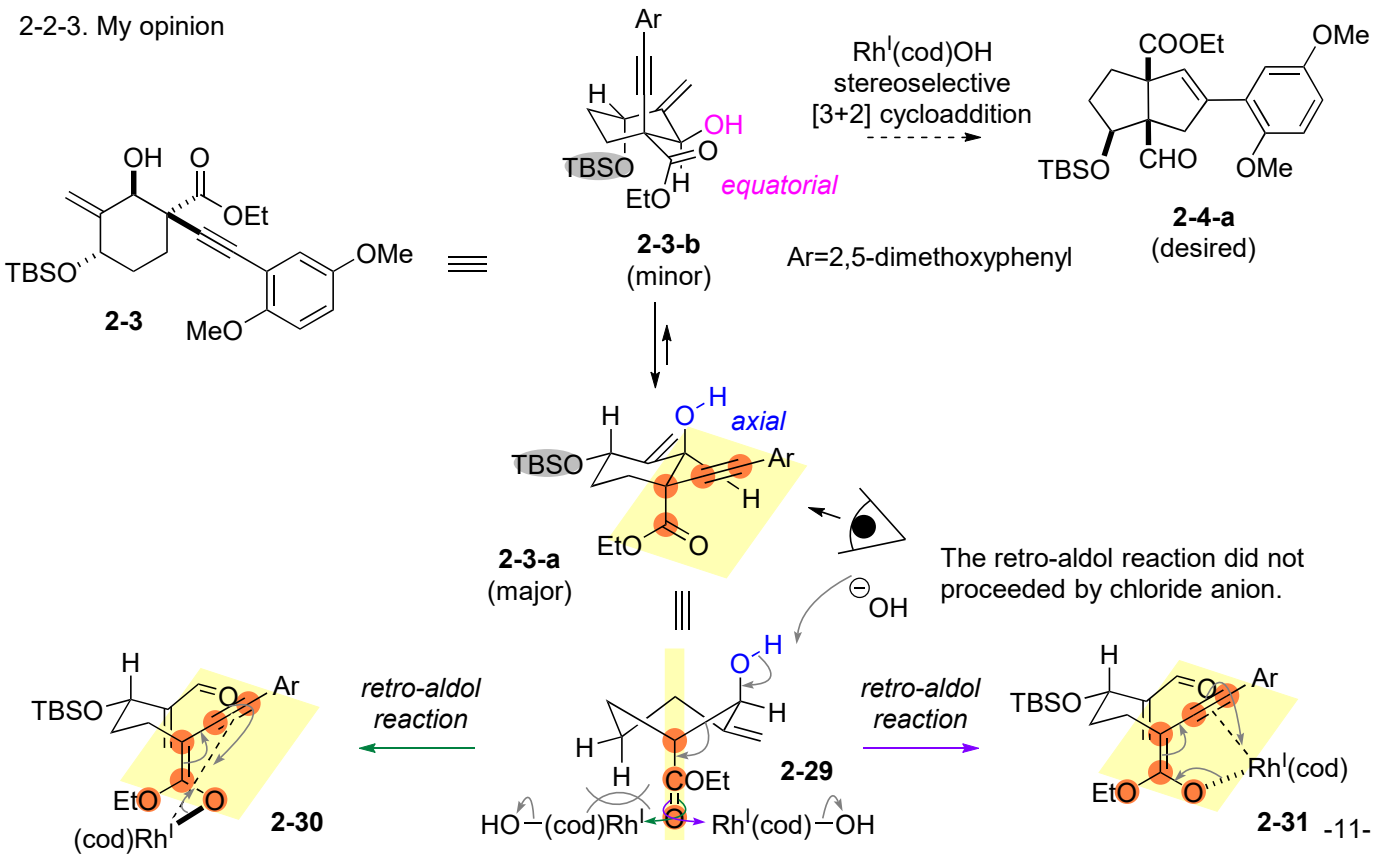
rigand exchange did not proceeded at axial OH

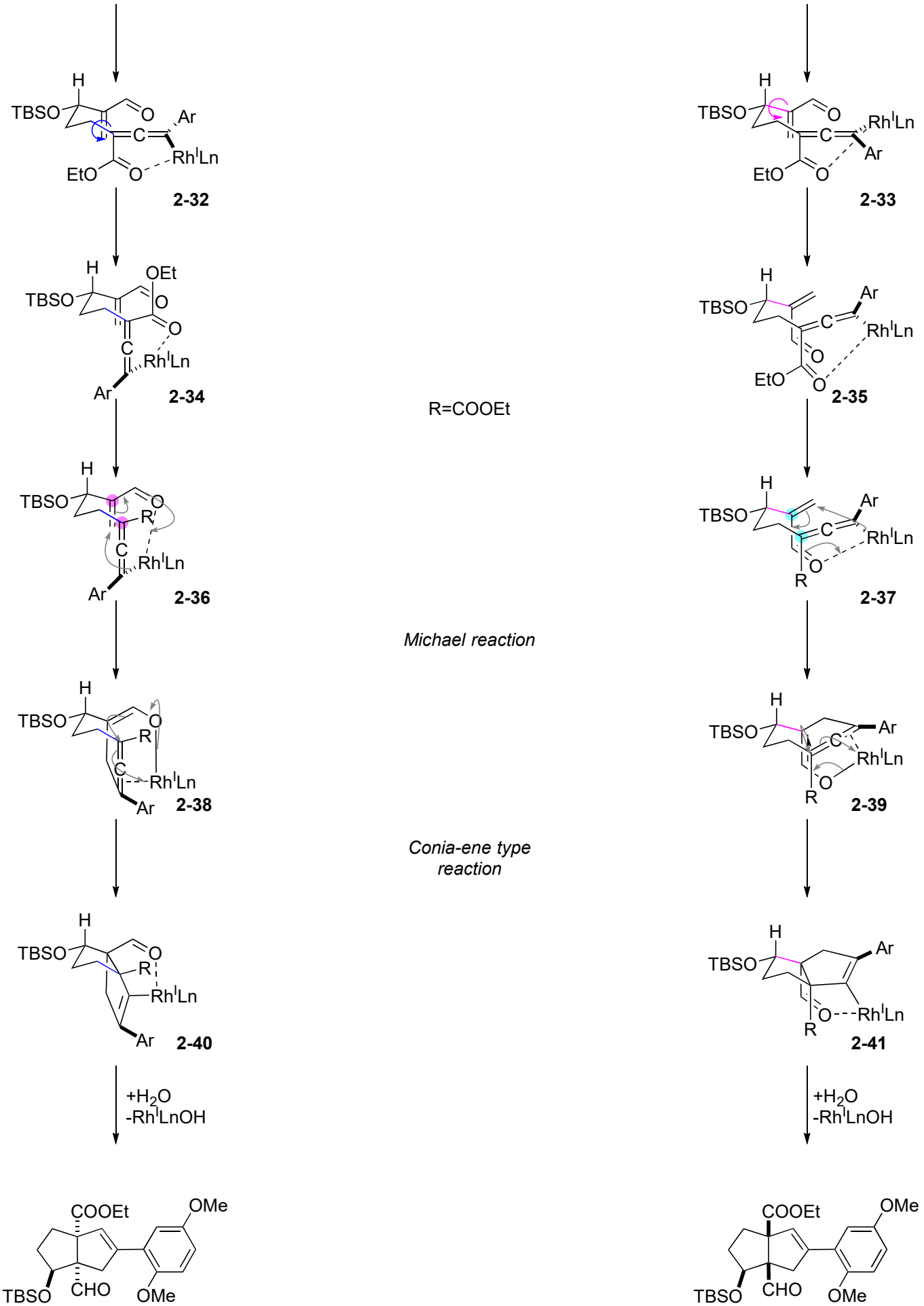
Ar=2,5-dimethoxyphenyl



- The major conformation of **2-3** is **2-3-a**?
- The rigand exchange did not proceeded at axial OH?

2-2-3. My opinion




H
TBSO
O
Ar
C
Rh^lLn
EtO
O
2-32
2-33
OEt
2-34
2-35
R=COOEt
R
2-36
2-37
Michael reaction
2-38
2-39
Conia-ene type reaction
2-40
2-41
+H2O
-Rh^lLnOH
COOEt
OMe
CHO
2-4-b
39%
2-4-a
46%