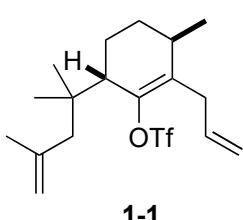


Problem session (3)

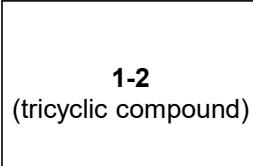
Daiki Kuwana

Please fill in the blank and explain reaction mechanisms and stereoselectivities.

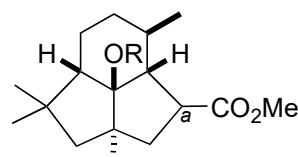
1.



1. $\text{Pd}(\text{OAc})_2$ (10 mol%), DPEphos (20 mol%)
Et₃N, toluene, 90 °C
2. OsO_4 (14 mol%), NMO; NaIO₄
acetone/H₂O (3/1), rt
3. *m*-CPBA, NaHCO₃, CH₂Cl₂, rt
4. LiN(TMS)₂, -78 to 0 °C; MeOH, -78 °C to rt;
Stryker's reagent (0.4 eq.), rt, 28% (4 steps)

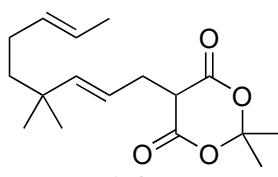


5. TMSOTf, Et₃N, CH₂Cl₂, rt
6. *p*-ABSA, DBU, CH₃CN, 95% (2 steps)
7. 125W Hg-lamp, MeOH, Et₃N, 83%

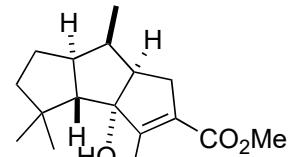
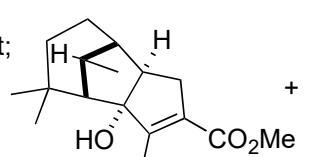


a. Stereochemistry of this position was not determined.

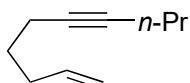
2.



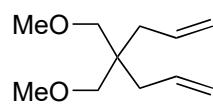
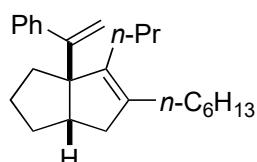
1. KH(TMS)₂, **2-2**, THF, 0 °C to rt;
2. *m*-CPBA, CH₂Cl₂, rt
3. Cu (12.5 mol%)
pyridine/MeOH(10/1), reflux



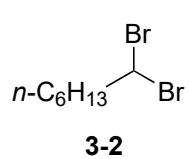
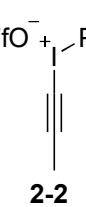
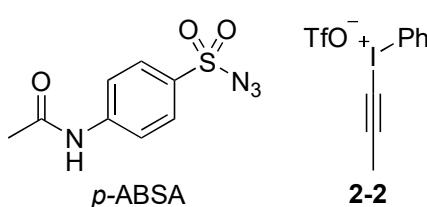
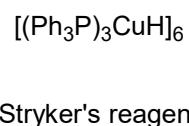
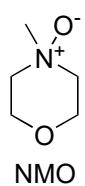
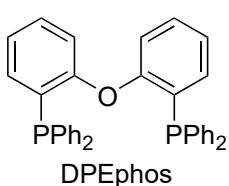
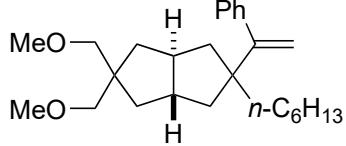
3. (i)



- Cp₂ZrCl₂, *n*-BuLi, THF, -78 °C;
3-1, -78 °C to rt;
3-2, LDA, -78 °C;
Ph-C≡CLi (3.0 eq), -78 °C;
MeOH, NaHCO₃ aq. rt, 82%



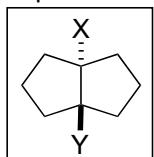
- Cp₂ZrCl₂, *n*-BuLi, THF, -78 °C;
3-4, -78 °C to rt;
3-2, LDA, -78 °C;
Ph-C≡CLi (3.0 eq), -78 to -55 °C;
MeOH, NaHCO₃ aq. rt, 77%



Problem Session (3) - Answer

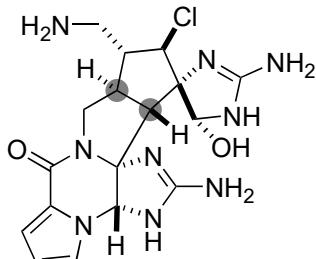
2017.11.25 Daiki Kuwana

Topic: *trans*-fused 5,5-ring

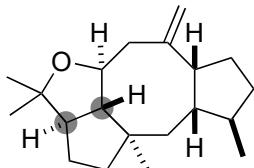


0. Introduction

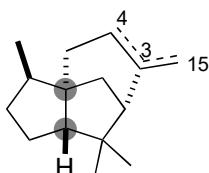
0-1. Natural products including *trans*-fused 5,5-ring



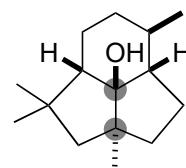
Palau'amine



(+)-epoxydictymene



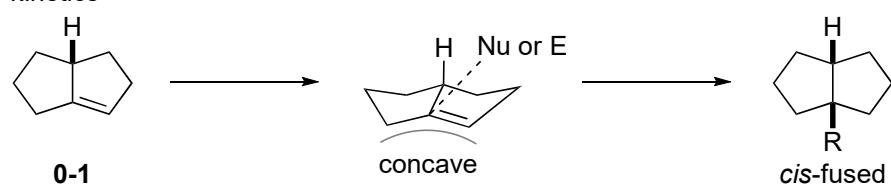
α -funebrene ($\Delta^{3,4}$)
 β -funebrene ($\Delta^{3,15}$)



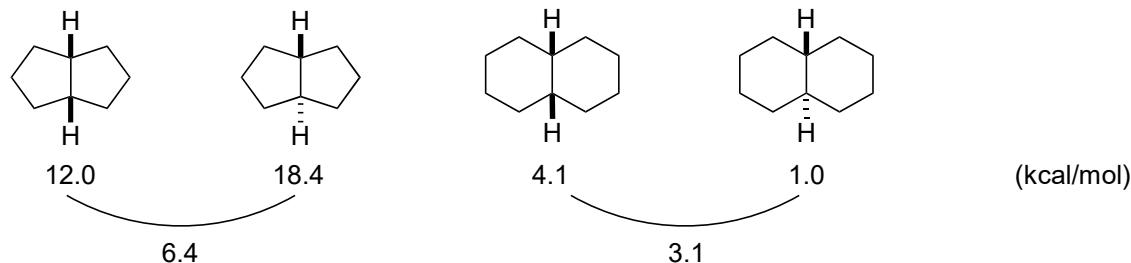
(-)-presilphiperfolan-8-ol
(Problem 1)

0-2. Difficulty of formation of *trans*-fused 5,5-ring

kinetics



thermodynamics

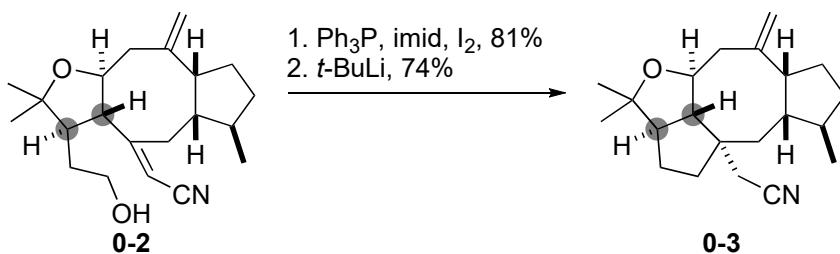


Richard, H., B. et al. *J. Am. Chem. Soc.* **1970**, 92, 3109.

trans-fused 5,5-ring is less stable than *cis*-fused both kinetically and thermodynamically.

0-3. Methods to construct *trans*-fused 5,5-ring

0-3-1. Connection of two alkyl chains



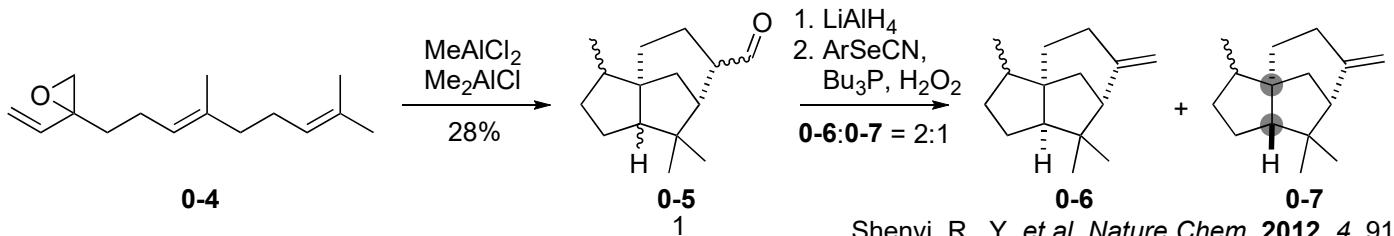
0-3

Schreiber, S., L. et al. *J. Am. Chem. Soc.* **1994**, 116, 5505.

0-3-2. Ring contraction (Problem 1)

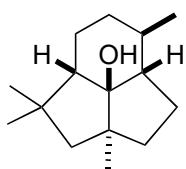
0-3-3. Zirconacyclopentane (Problem 3)

0-3-4. Generation as byproduct (Problem 2)



1. Total synthesis of (-)-presilphiperfolan-8-ol

1-1. Brief introduction



(-)presilphiperfolan-8-ol
(1-0)

Isolation

Bohlmann F. et al. *Phytochemistry* **1981**, 20, 2239.

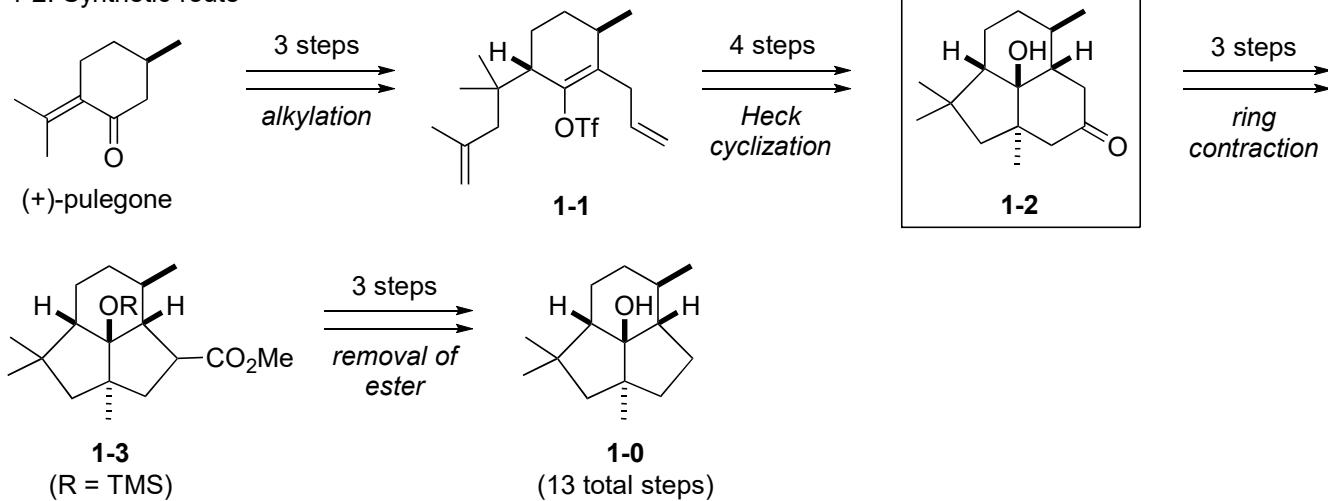
X-ray structure determination

Wilson, S. et al. *J. Am. Chem. Soc.* **1996**, 118, 9249.

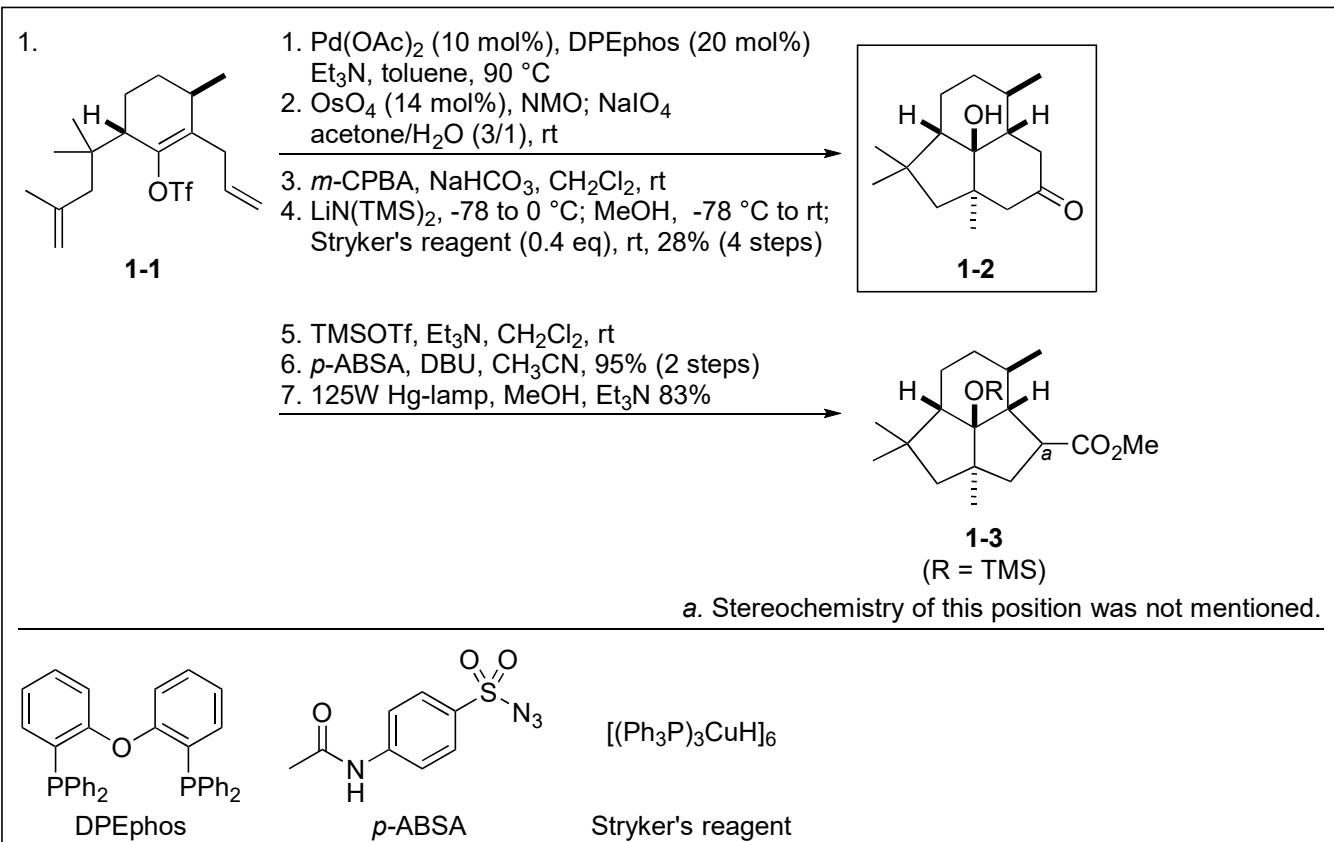
Structural features

5 stereocenters
trans-fused 5,5-ring

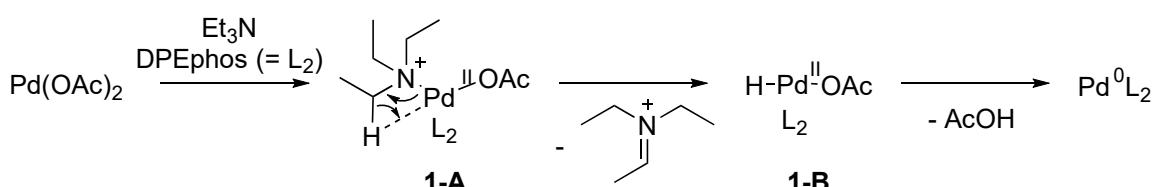
1-2. Synthetic route

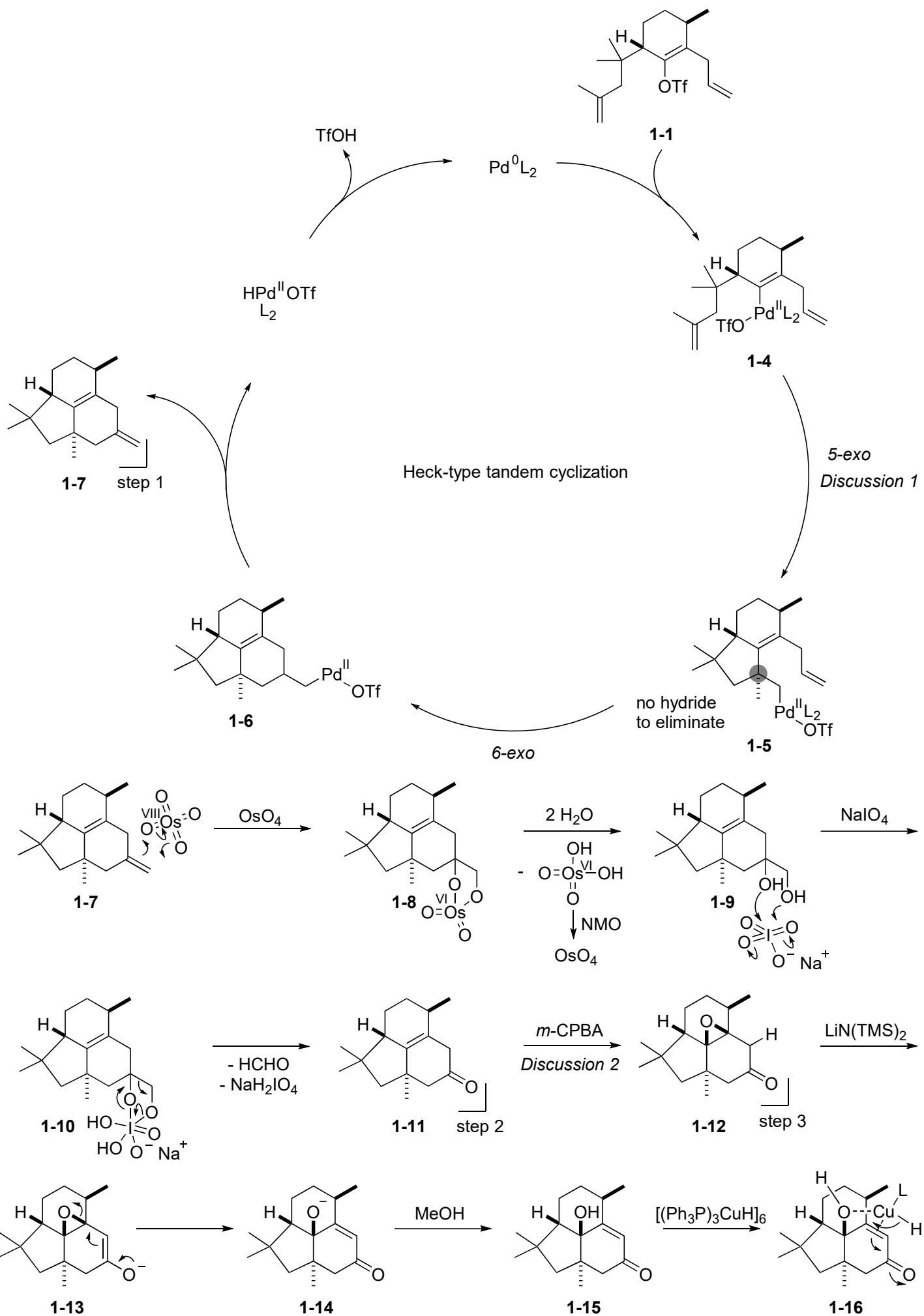


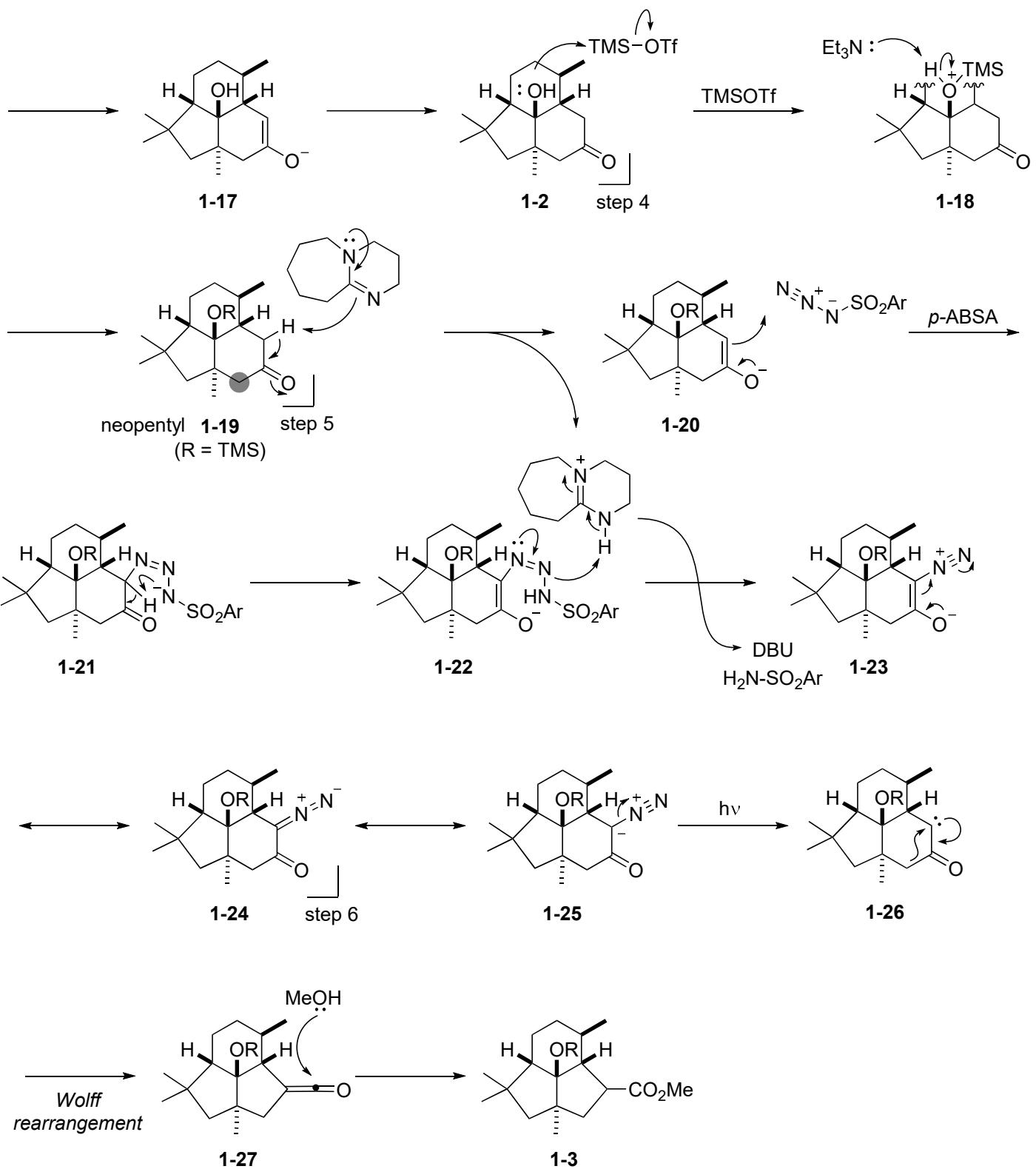
1-3. Answer



Answer

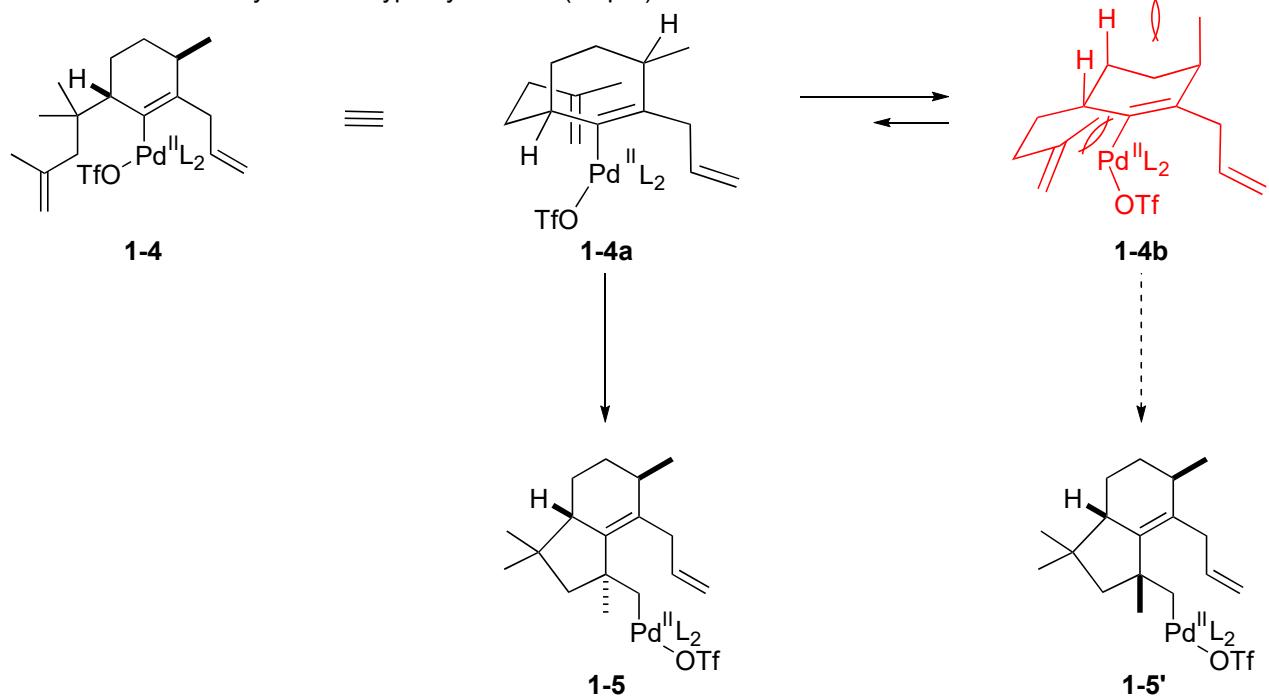




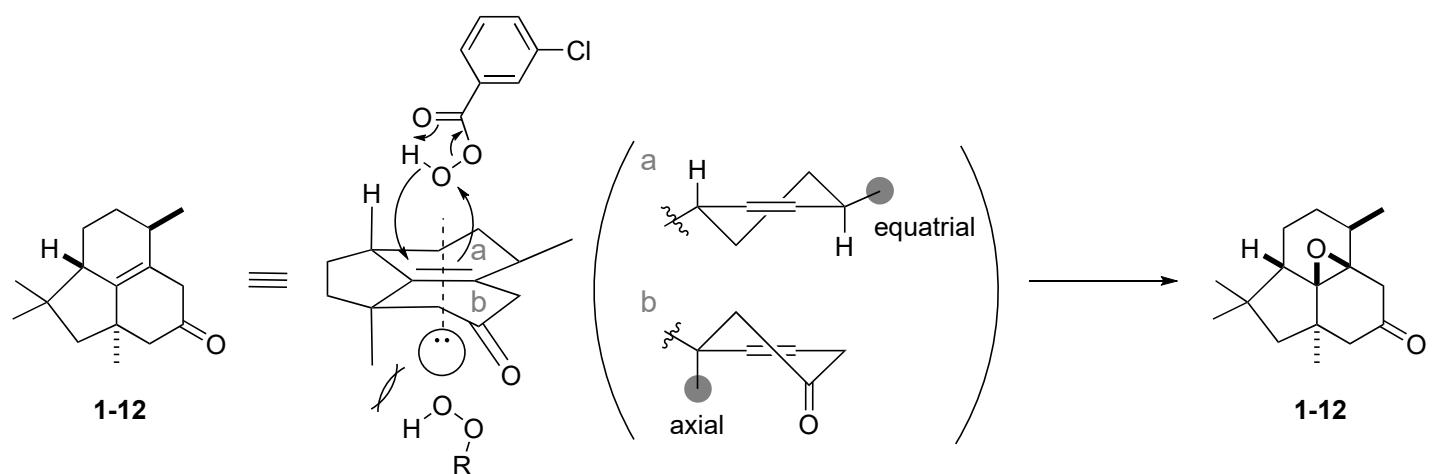


1-4. Discussion

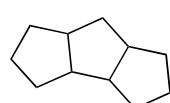
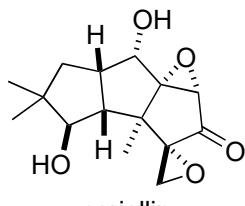
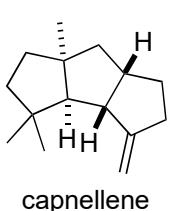
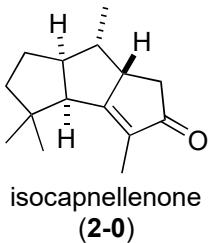
1-4-1. Stereoselectivity of Heck-type cyclization (step 1)



1-4-2. Stereoselectivity of epoxydation (step 3)



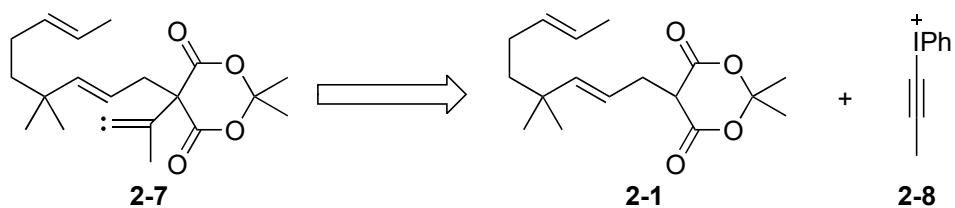
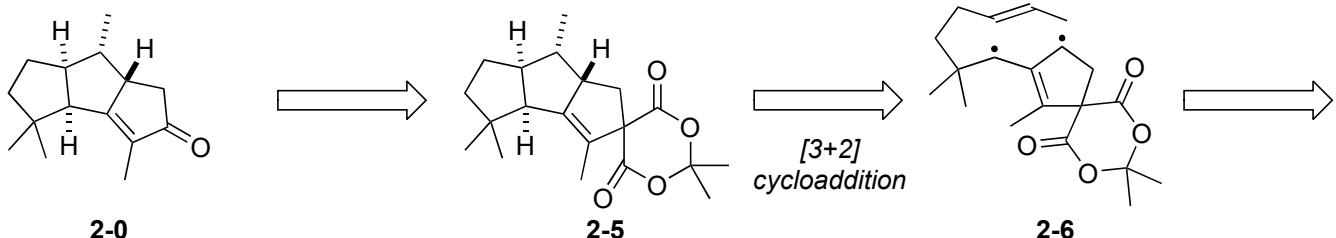
2. Attempted synthesis of isocapnelleneone using trimethylenemethane



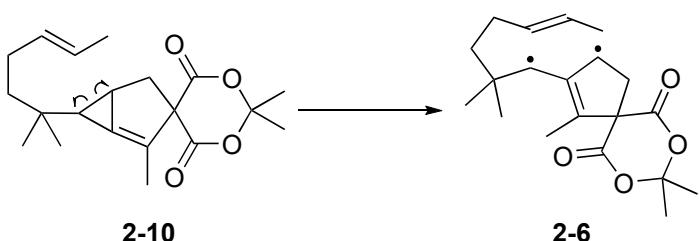
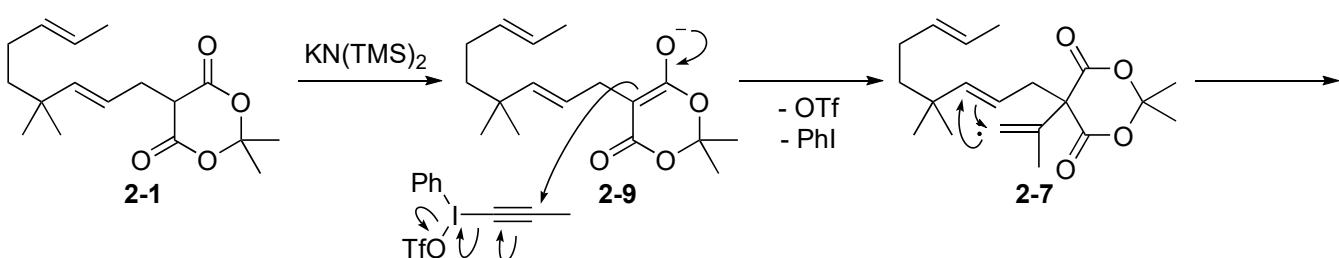
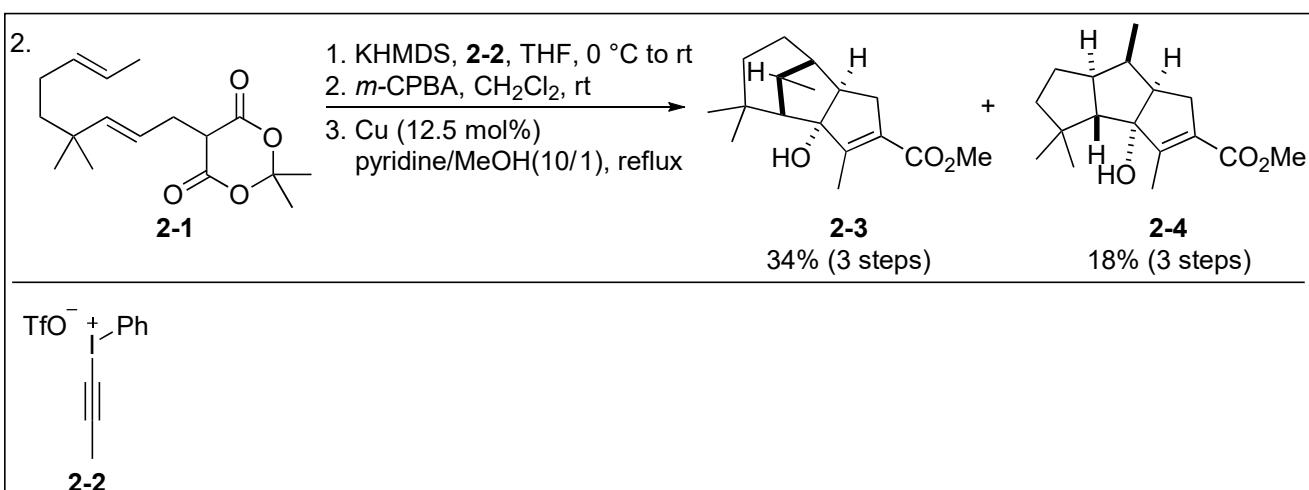
linear triquinane skeleton

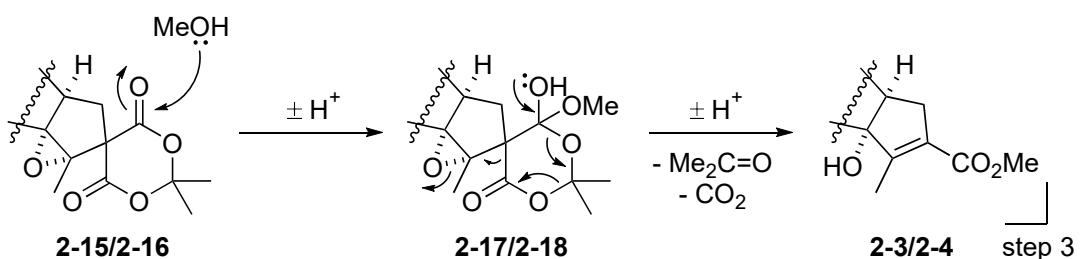
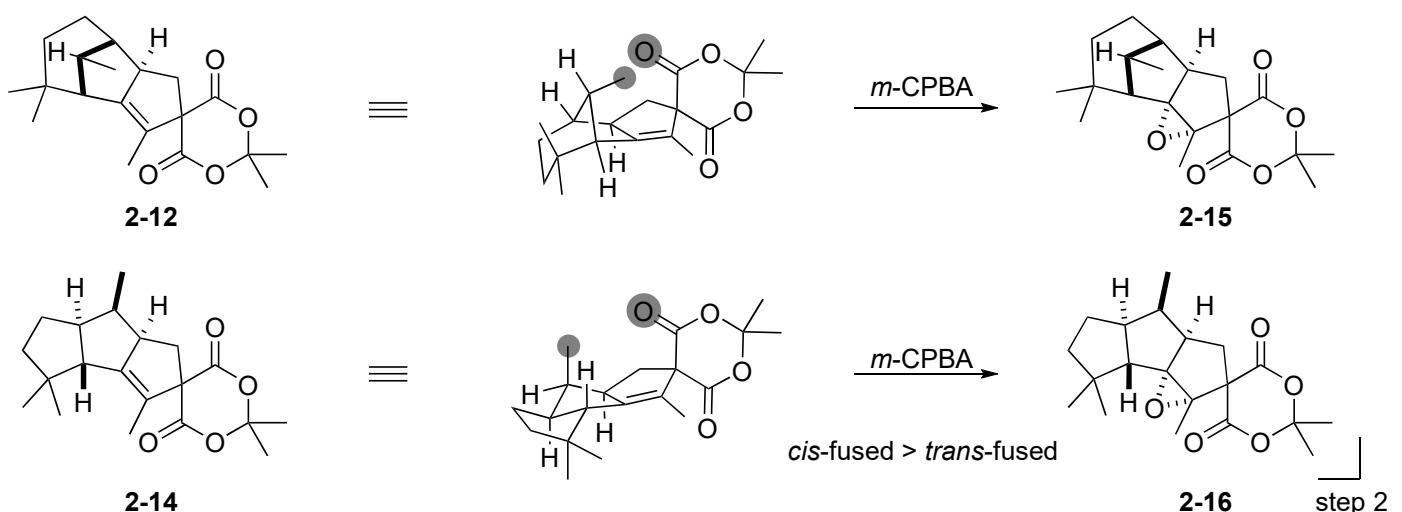
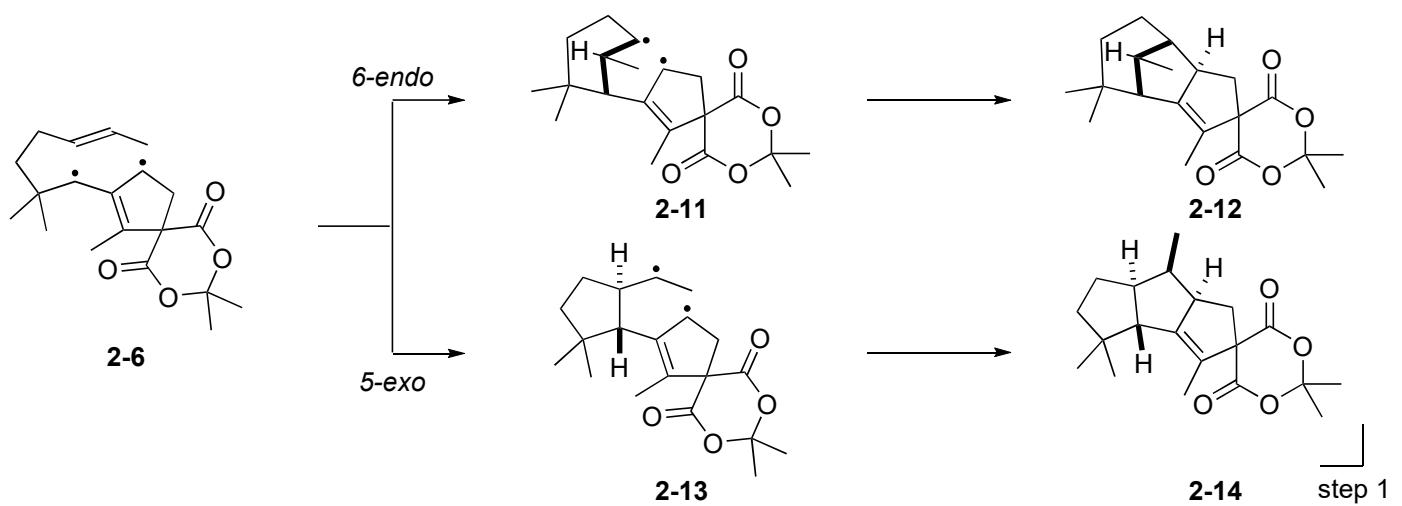
for total synthesis of coriollin : 160827_PS_Yuki_NAKAGAWA

2-1. Synthetic plan

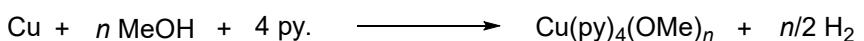


2-2. Answer

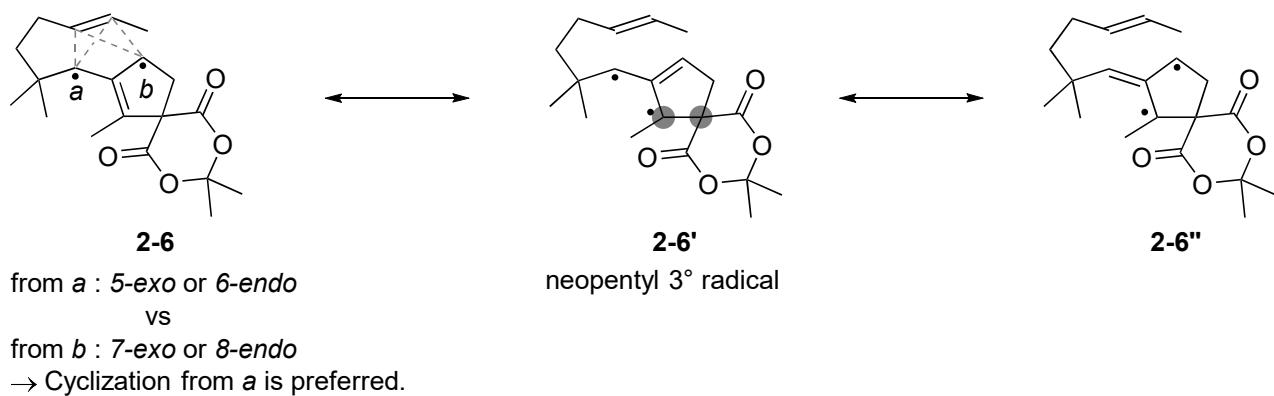




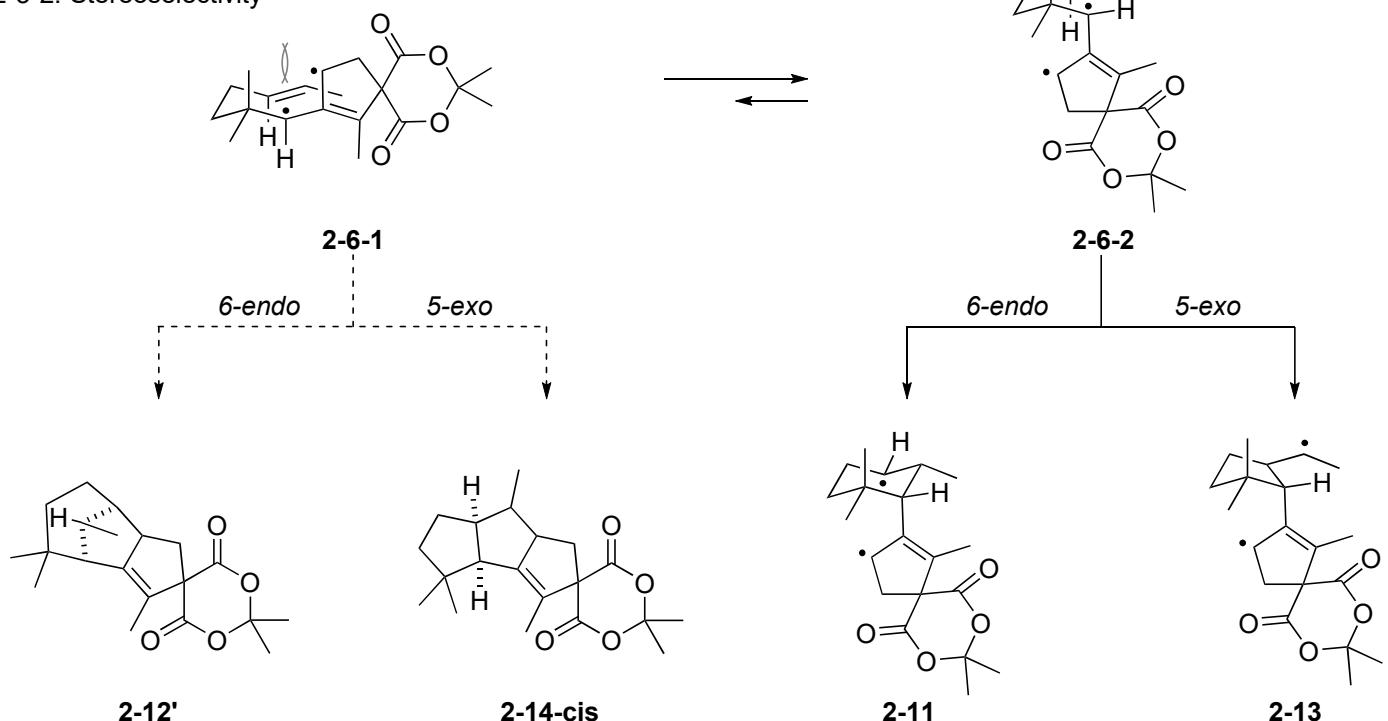
Cu accelerates solvolysis. \rightarrow Methoxide anion is generated?



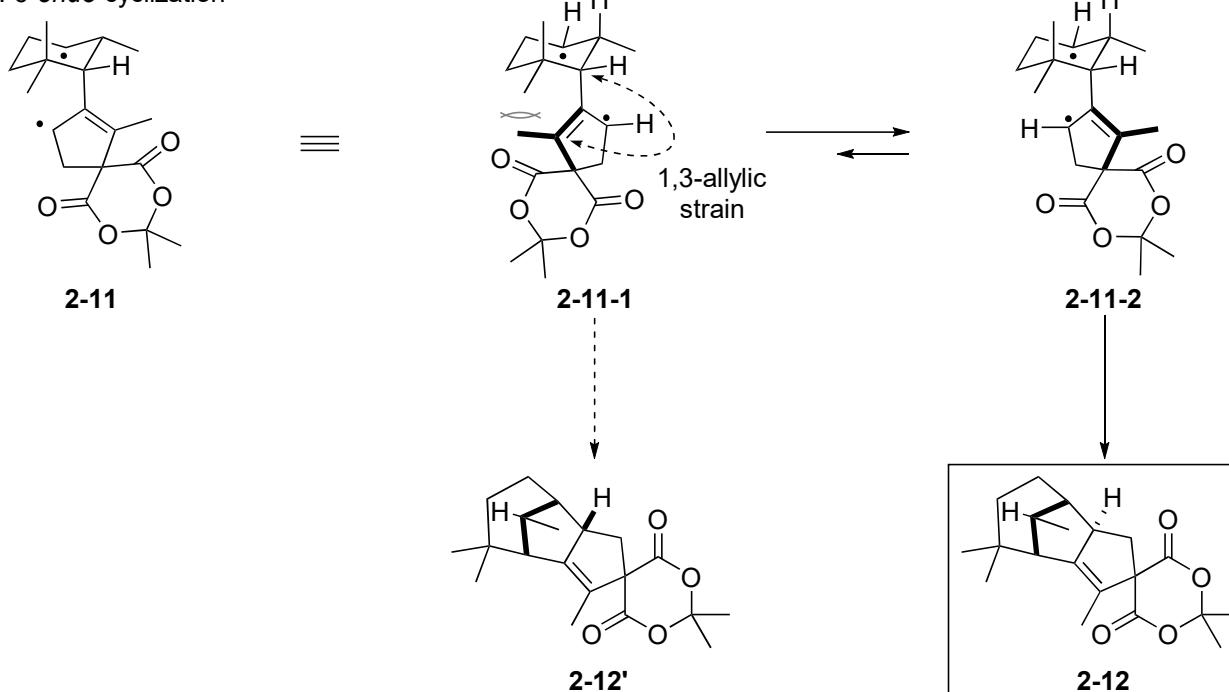
2-3. Discussion: selectivity of [3+2] addition
 2-3-1. Regioselectivity



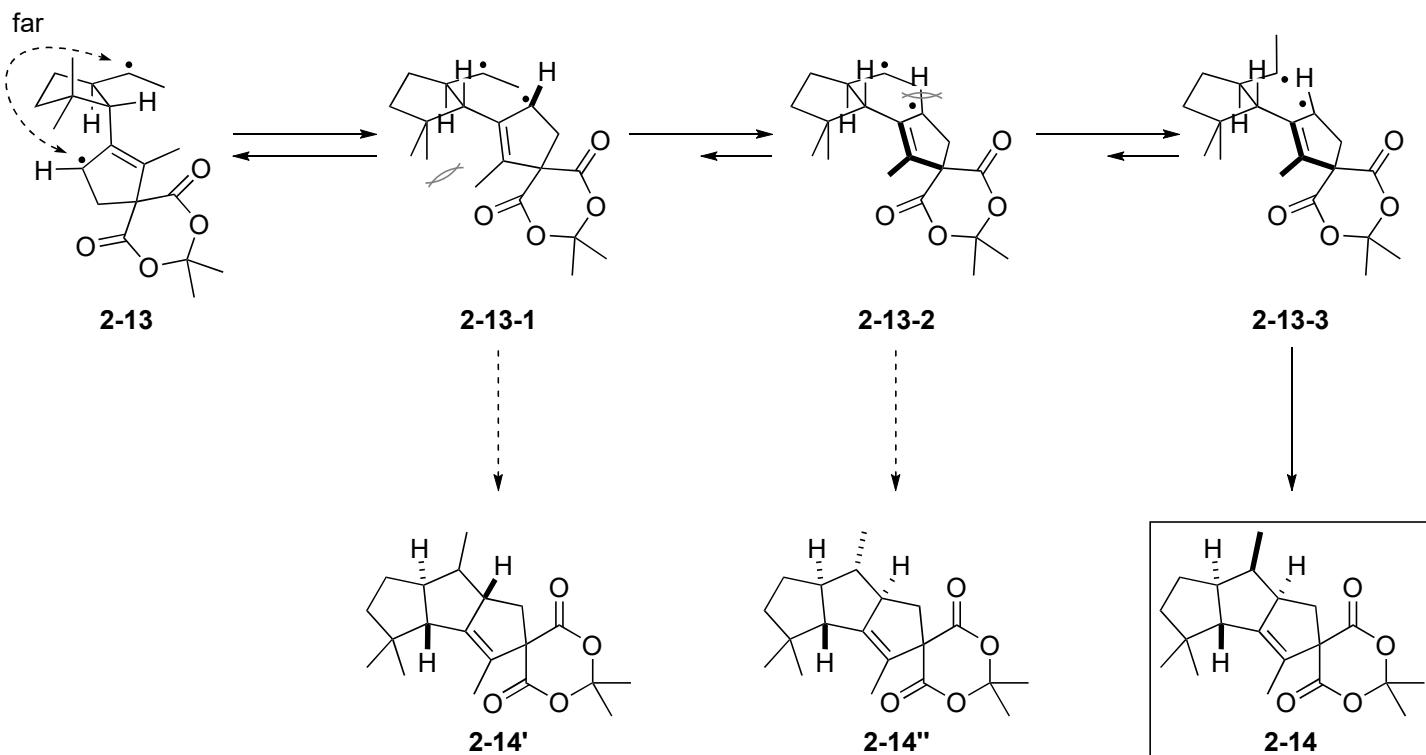
2-3-2. Stereoselectivity



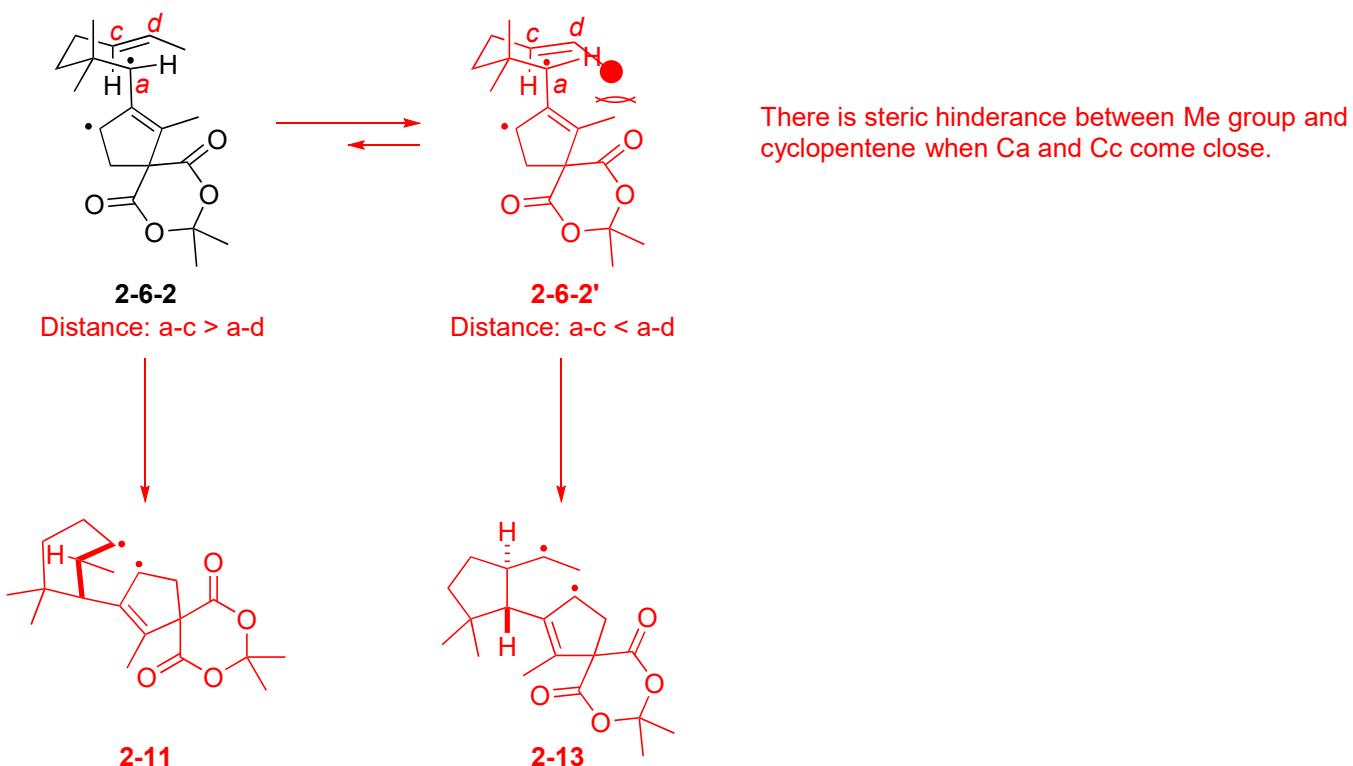
2-3-2-1. 6-*endo* cyclization



2-3-2-2. 5-exo cyclization

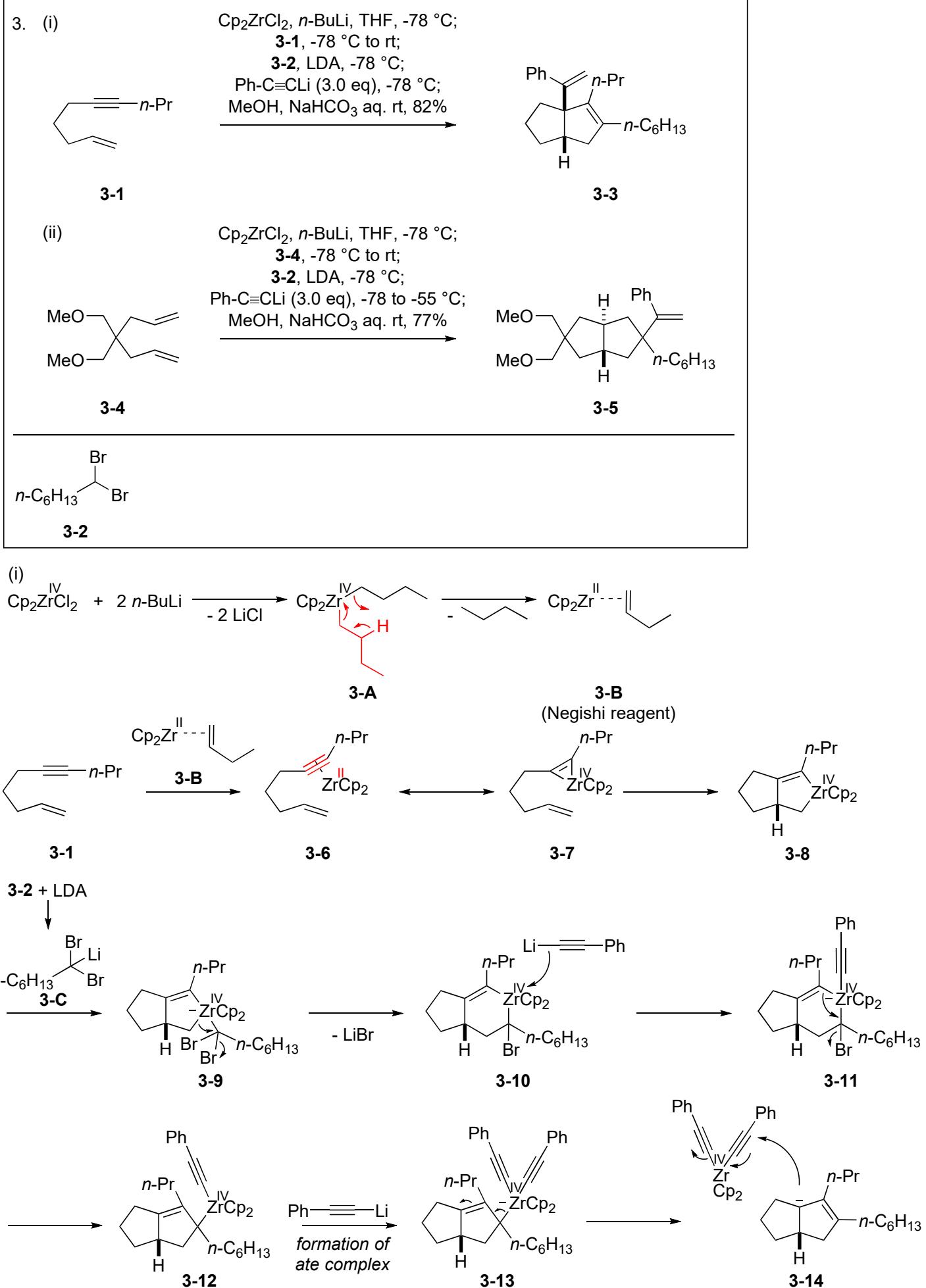


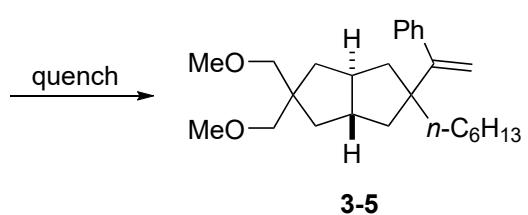
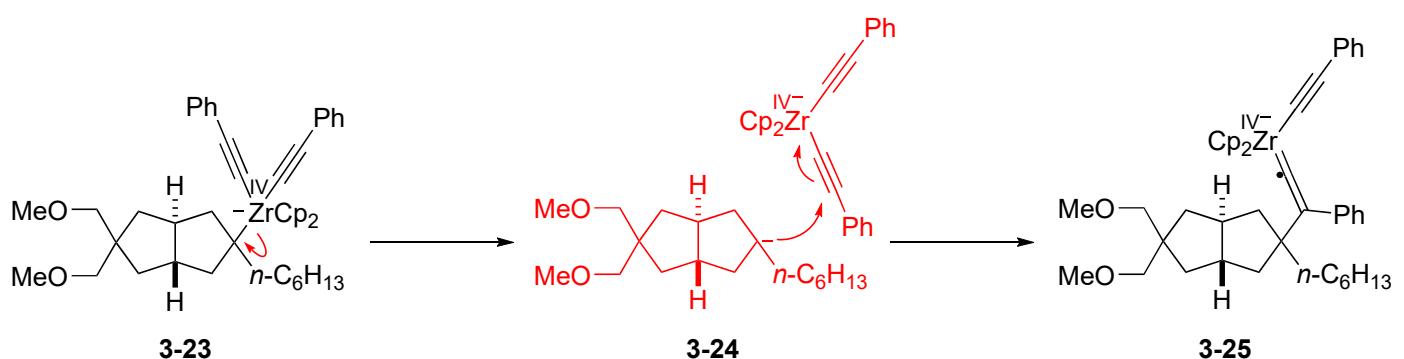
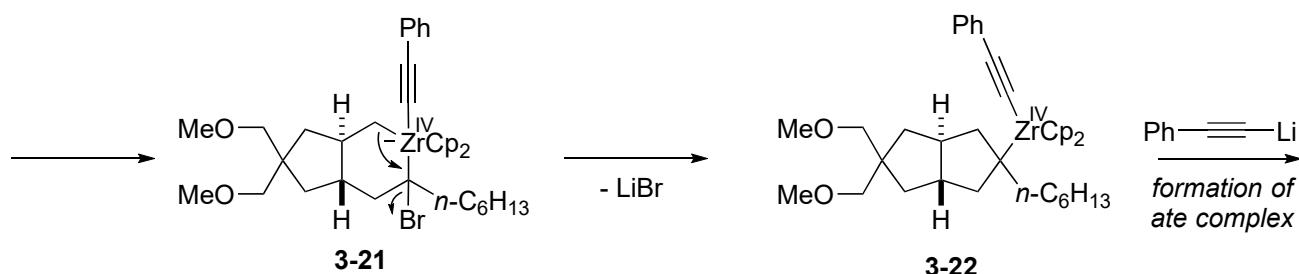
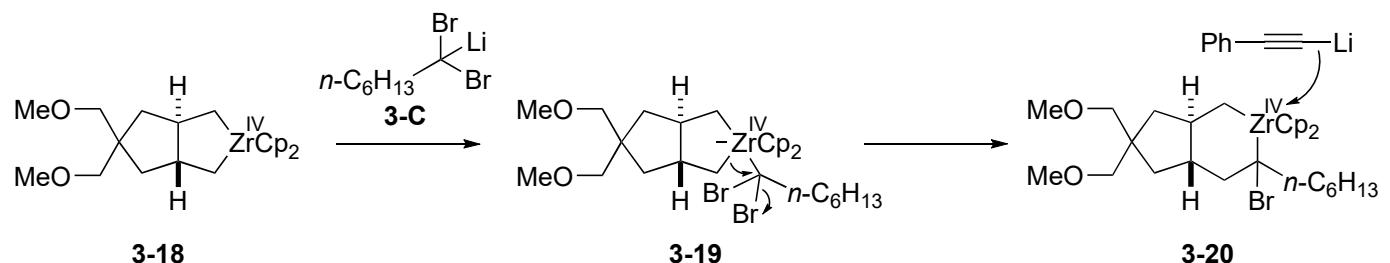
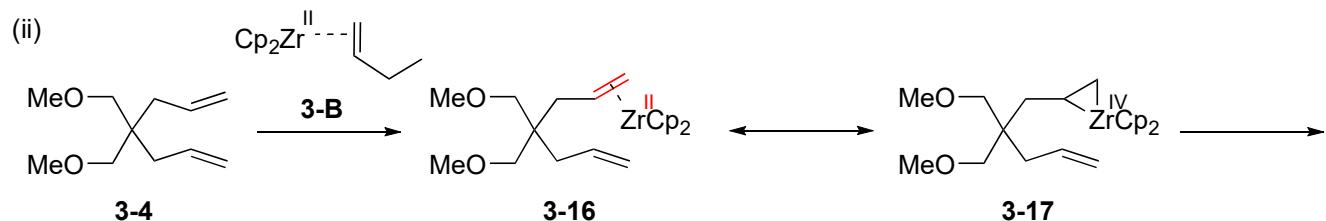
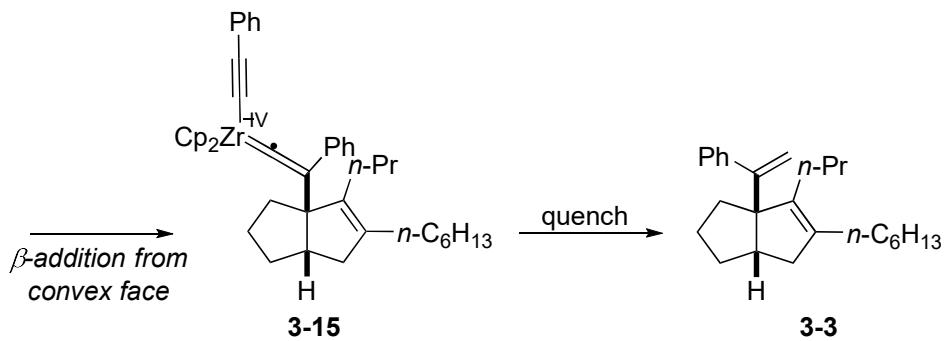
2-3-3. 5-exo vs 6-endo



3. formation of *trans*-fused 5,5-ring via zirconacyclopentane

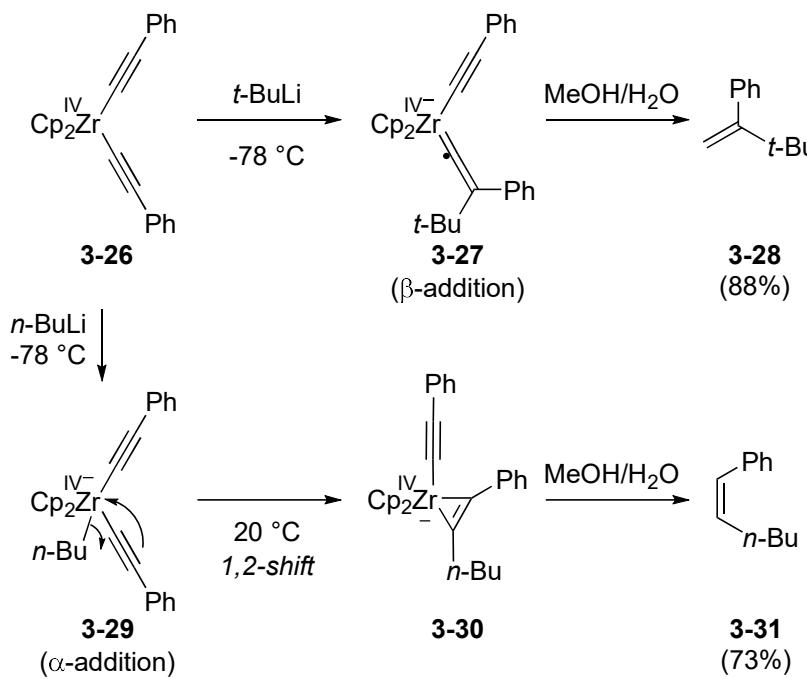
3-1. Answer





3-2. Discussion

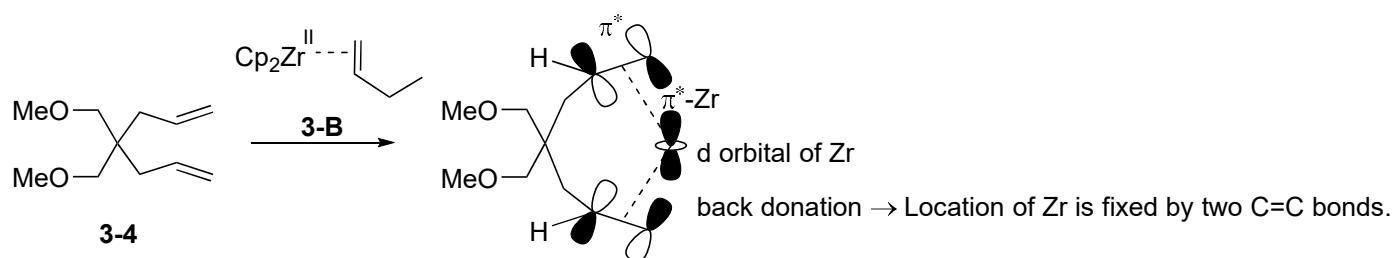
3-2-1. Selectivities of β -addition



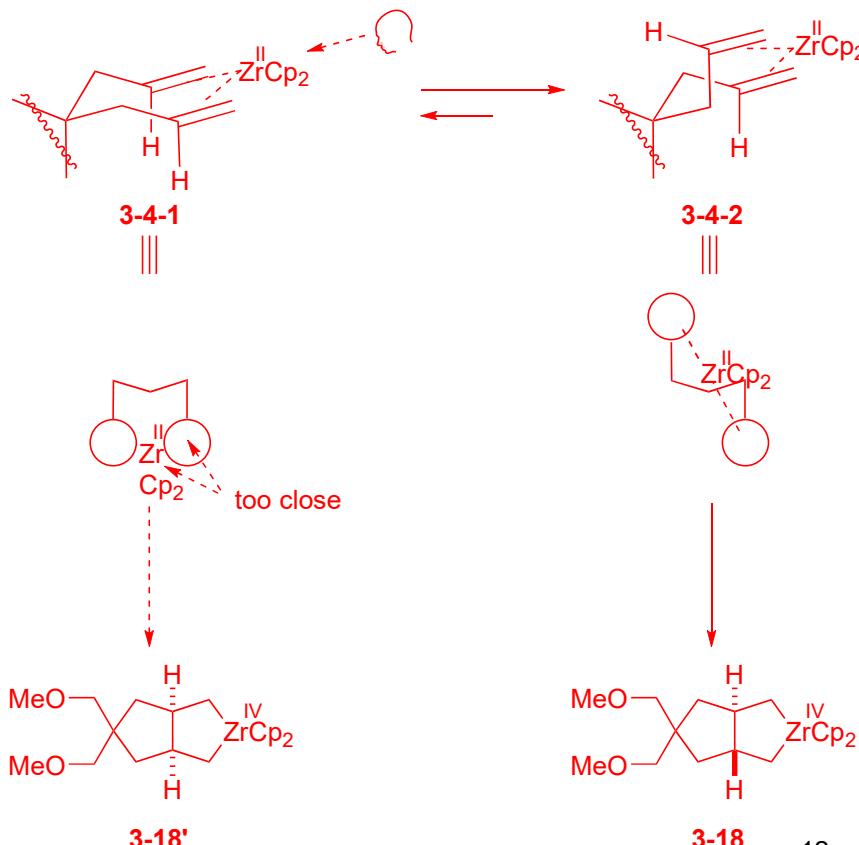
β -selective addition occurs when bulky nucleophile is used.

3-2-2. Selectivity of formation of zirconacyclopentane

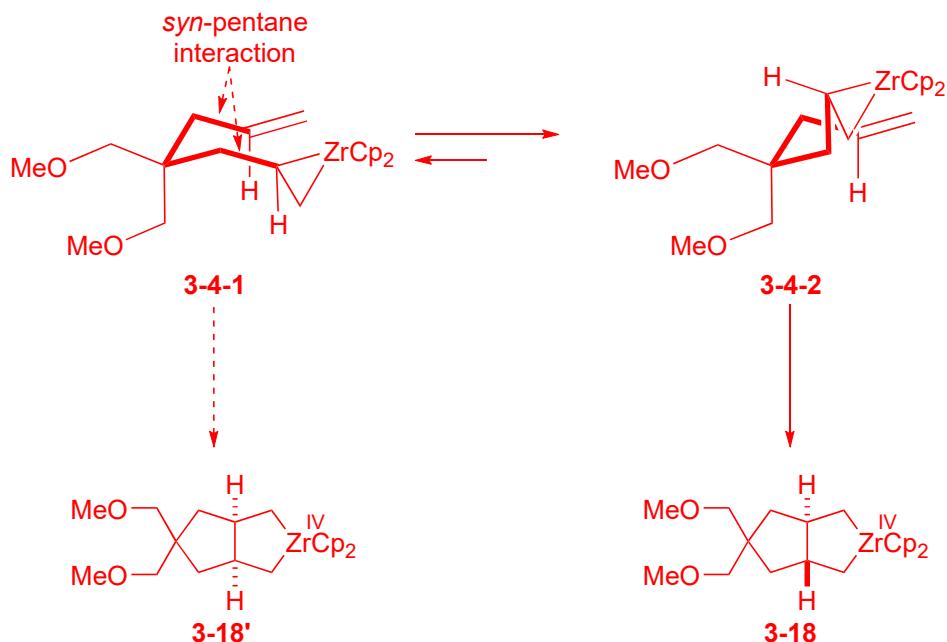
3-2-2-1. Proposal 1



Nakamura, A. et al. *Polyhedron* **1991**, *10*, 1.



3-2-2-2. Proposal 2



3-3. Appendix: metal vinylidenes vs metal alkynes

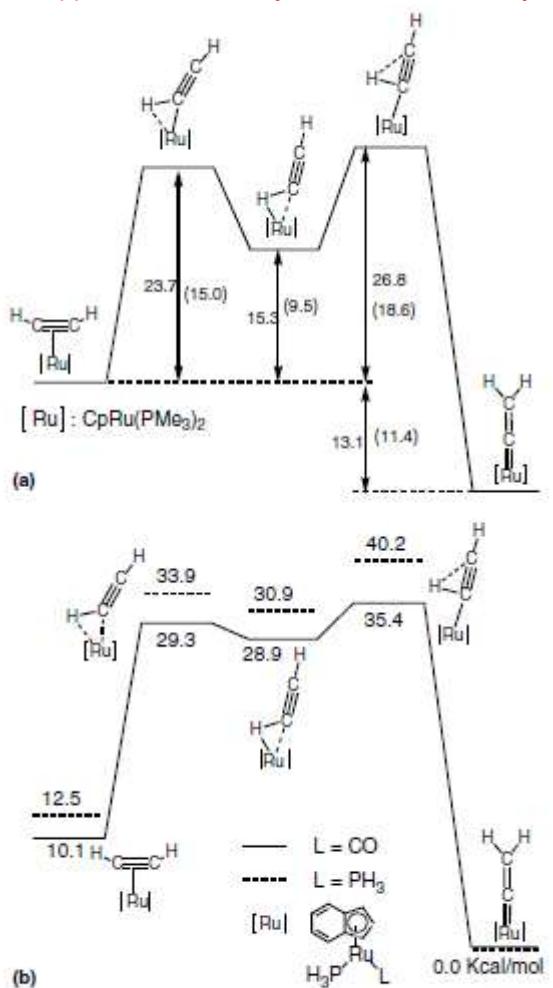


Fig. 7. (a) Tautomerization of C_2H_2 and C_2HMe (values in parenthesis). (b) Tautomerization in (Indenyl)ruthenium complexes.

Metal vinylidenes seem to more stable than metal alkynes.

Wakatsuki, Y. J. Organomet. Chem. **2004**, 689, 4092.

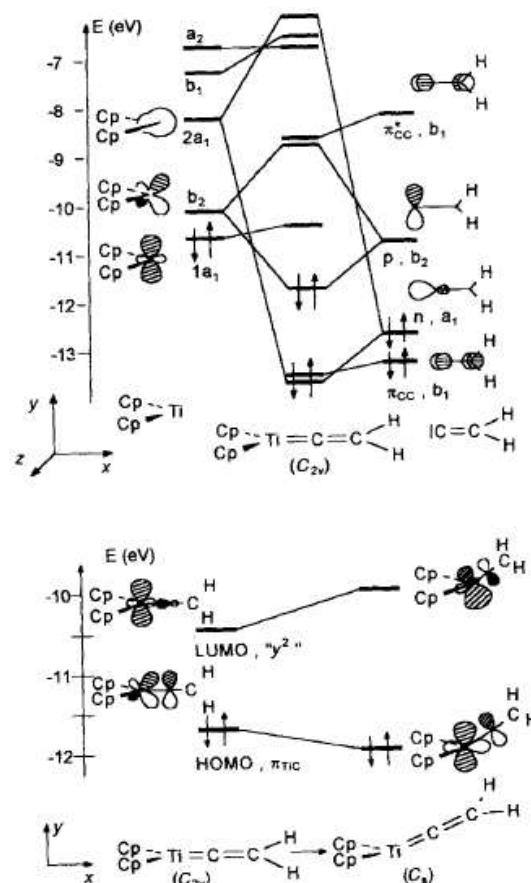


Figure 1. Top: Correlation diagram for a $[\text{Cp}_2\text{Ti}]$ fragment (C_{2v}) and vinylidene (C_{2v}) for "trigonal planar" $[\text{Cp}_2\text{Ti}=\text{C}=\text{CH}_2]$ (C_{2v}) (only relevant valence MOs are shown). Bottom: Decrease in energy for C_4 -symmetrical **8**.

There is back-donation from d-orbital of metal to empty p-orbital of carbene.

Beckhaus, R. Angew. Chem. Int. Ed. **1997**, 36, 686.