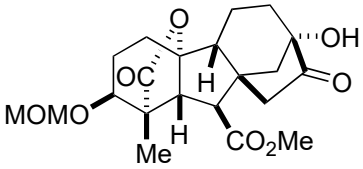
Problem Session (6)

2021. 5. 29. Tsukasa Shimakawa

Please provide reasonable mechanisms of each steps and answer the question Q1.

(1)

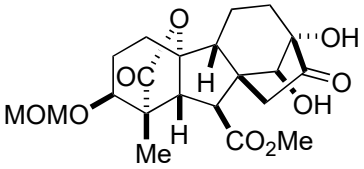


1-1

1. NaH (60 wt%, ~2 eq.)
   CH_2Cl_2, 25 °C, 82%
2. Ac_2O (2.6 eq.), Et_3N (3.6 eq.)
   DMAP (cat.)
   CH_2Cl_2, rt, 96%
3. TBSOTf (2.1 eq.), Et_3N (4.3 eq.)
   CH_2Cl_2, rt, 70%

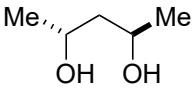
→

4. DMDO (in acetone, 7.0 eq.)
   CH_2Cl_2, -40 °C to 25 °C; evp.
   ; *n*-Bu_4NF (10 eq.)
   THF, 25 °C, 80%
5. NaH (60 wt%, ~5.3 eq.)
   MeOH (one drop)
   CH_2Cl_2, 25 °C, 84%



1-2

(2)

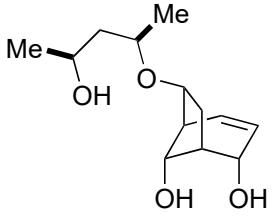


2-1
(2*R*, 4*R*)-pentanediol

1. phenol (1.1 eq.)
   DIAD (1.2 eq.), PPh_3 (1.2 eq,)
   THF, rt
2. $Hg(OAc)_2$ (20 mol%)
   ethyl vinyl ether (solvent), 45 °C
   55% (2 steps)
3. hν (254 nm)
   pentane, 25 °C, 27 h, 67%

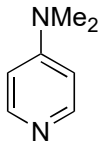
→

4. *m*-CPBA (1.0 eq.)
   CH_2Cl_2, 0 °C to rt;
   2 M HCl aq. (4.0 eq.), 79%
5. $NaBH_4$ (1.2 eq.), $CeCl_3 \cdot 7H_2O$ (1.5 eq.)
   MeOH, -78 °C, 89%



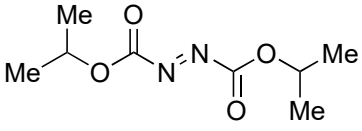
2-2

Q1. Explain the roles of chiral pentanediol motief in these transformations.

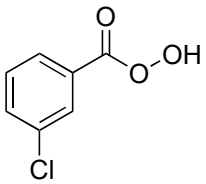


DMAP

DMDO



DIAD



m-CPBA

Problem Session (6)

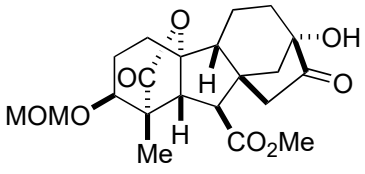
2021. 5. 29. Tsukasa Shimakawa

Topic: Skeletal reorganization in organic syntheses

Answer:

1. Hydroxylation of C14 position in gibberellins by Mander's group (Review: *Nat. Prod. Rep.* **2003**, *20*, 49.)

1-1. Reaction mechanism



1-1

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   CH_2Cl_2, rt, 96%
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4. DMDO (in acetone, 7.0 eq.)
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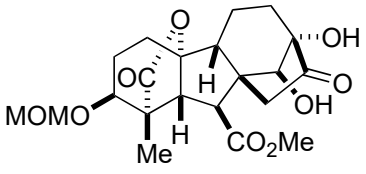
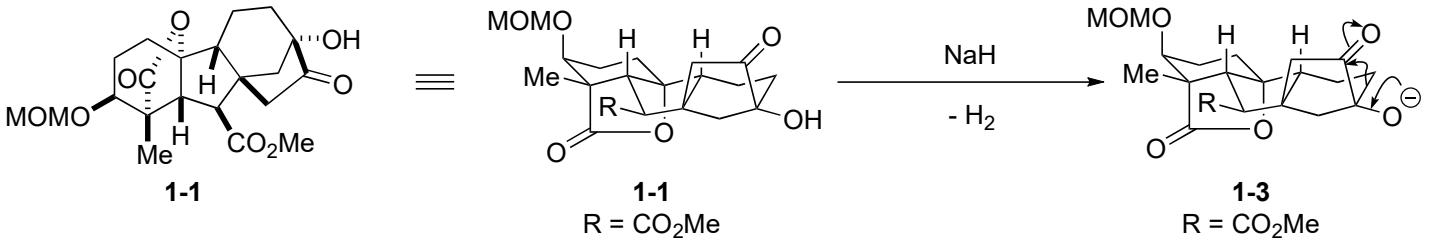
5. NaH (60 wt%, ~5.3 eq.)
   MeOH (one drop)
   CH_2Cl_2, 25 °C, 84%



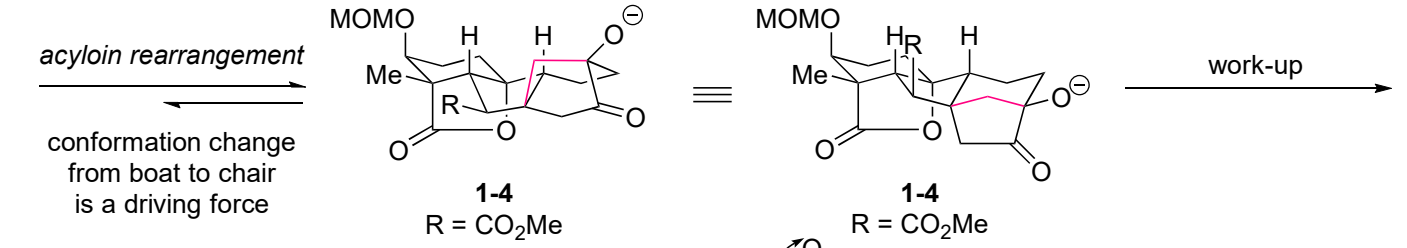
1-2

Liu, J.; Mander, L. N.; Willis, A. C. *Tetrahedron* **1998**. *54*. 11637.

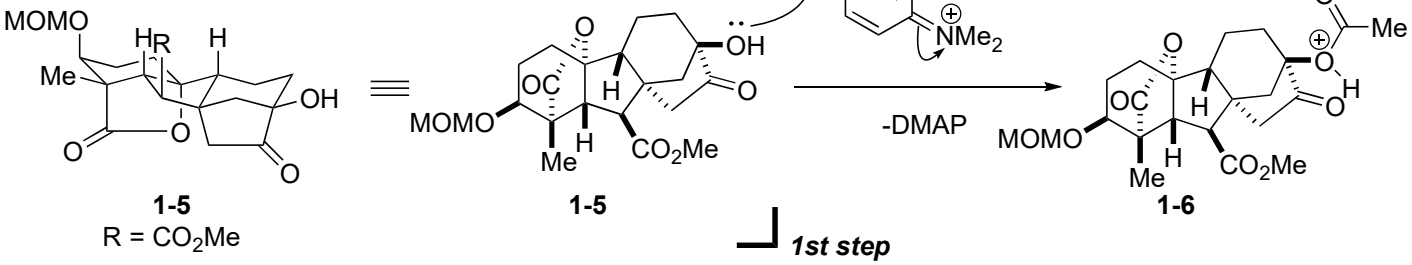
Key point: 1) acyloin rearragement (step 1 and 5) 2) three dimensional conformation of polycyclic compound



1-1 ≡ **1-1** (R = CO_2Me) —NaH, - H_2→ **1-3** (R = CO_2Me)

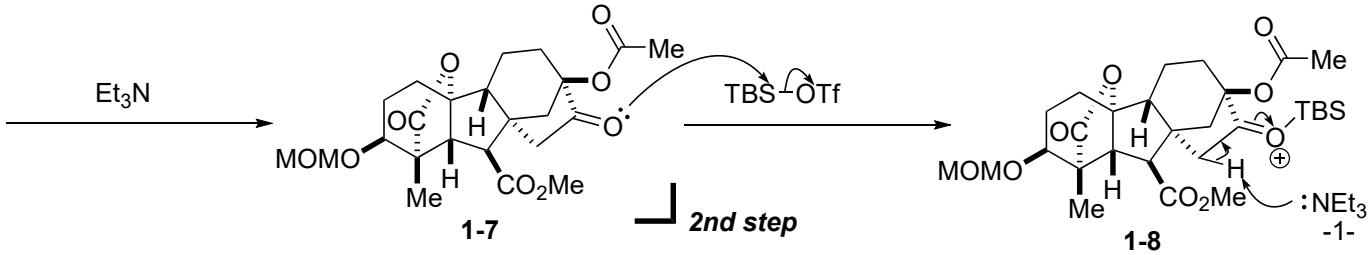


acyloin rearrangement (conformation change from boat to chair is a driving force): **1-4** (R = CO_2Me) ≡ **1-4** (R = CO_2Me) —work-up→



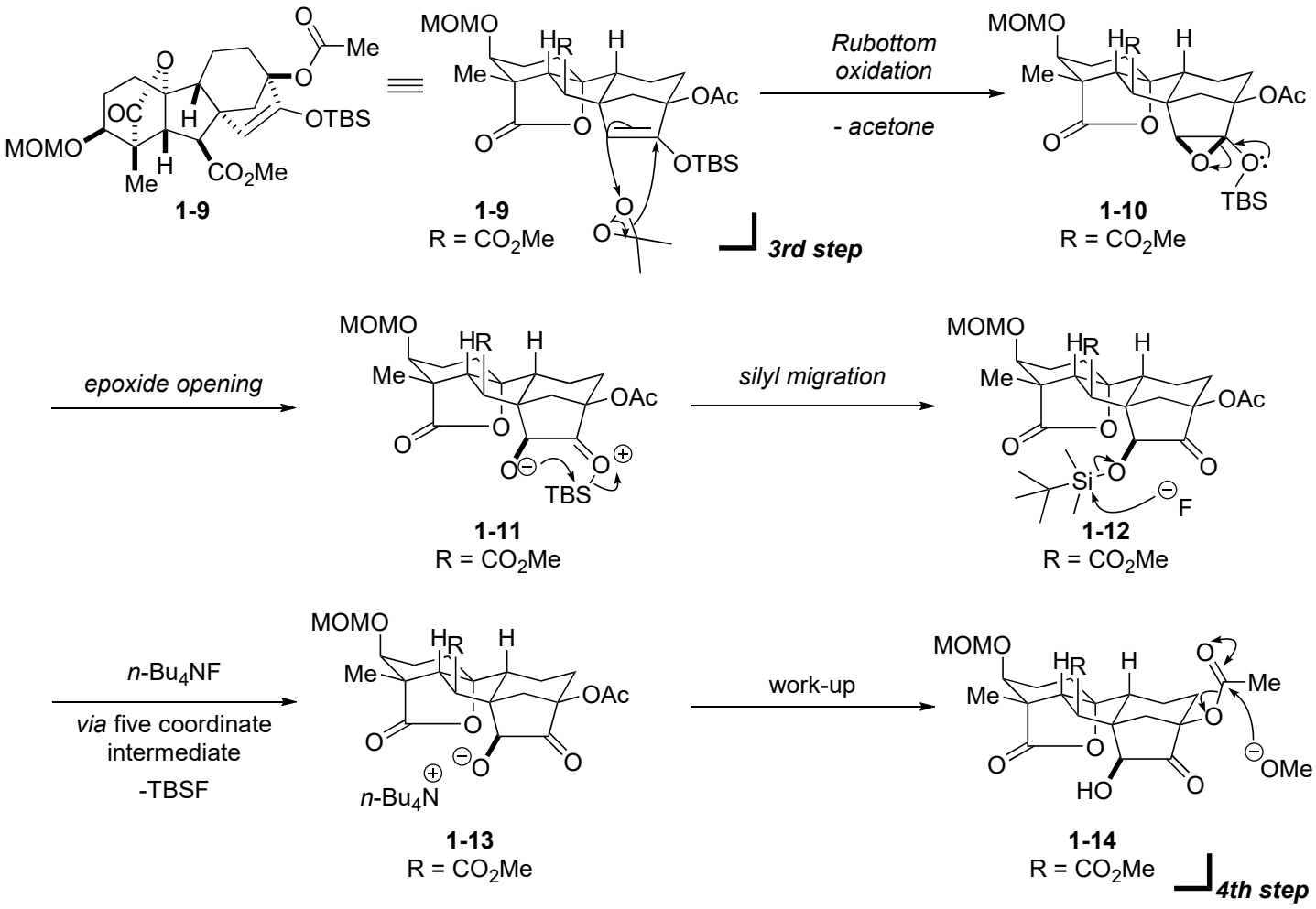
1-5 (R = CO_2Me) ≡ **1-5** —-DMAP→ **1-6**

1st step



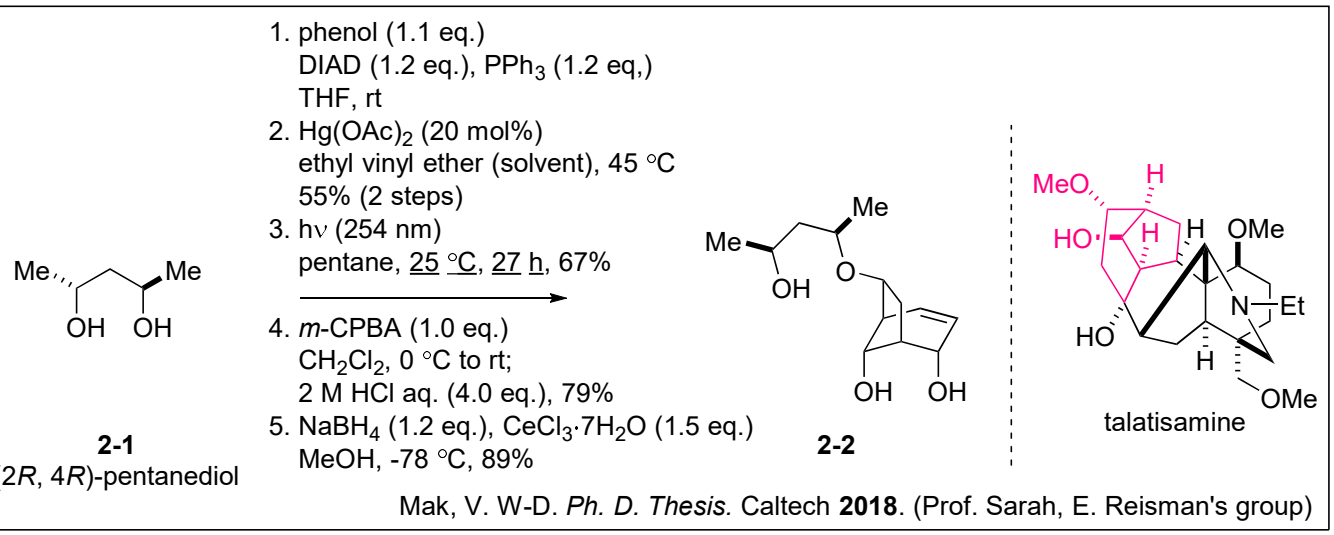
—Et_3N→ **1-7** —TBS-OTf→ **1-8**

2nd step


MOMO
Me
OTBS
CO2Me
1-9
R = CO2Me
Rubottom oxidation
- acetone
OAc
TBS
1-10
3rd step
epoxide opening
silyl migration
1-11
1-12
n-Bu4NF
via five coordinate intermediate
-TBSF
n-Bu4N
1-13
work-up
OMe
HO
1-14
4th step
NaOMe
(from NaH and MeOH)
acyloin rearrangement
1-15
1-16
MeOH
1-2
2 x intramolecular hydrogen bonds
5th step
cf.
1 x intramolecular hydrogen bond
1-17

2. Construction of CD-ring fragment of C19-diterpenoid alkaloid talatisamine by Reisman's group

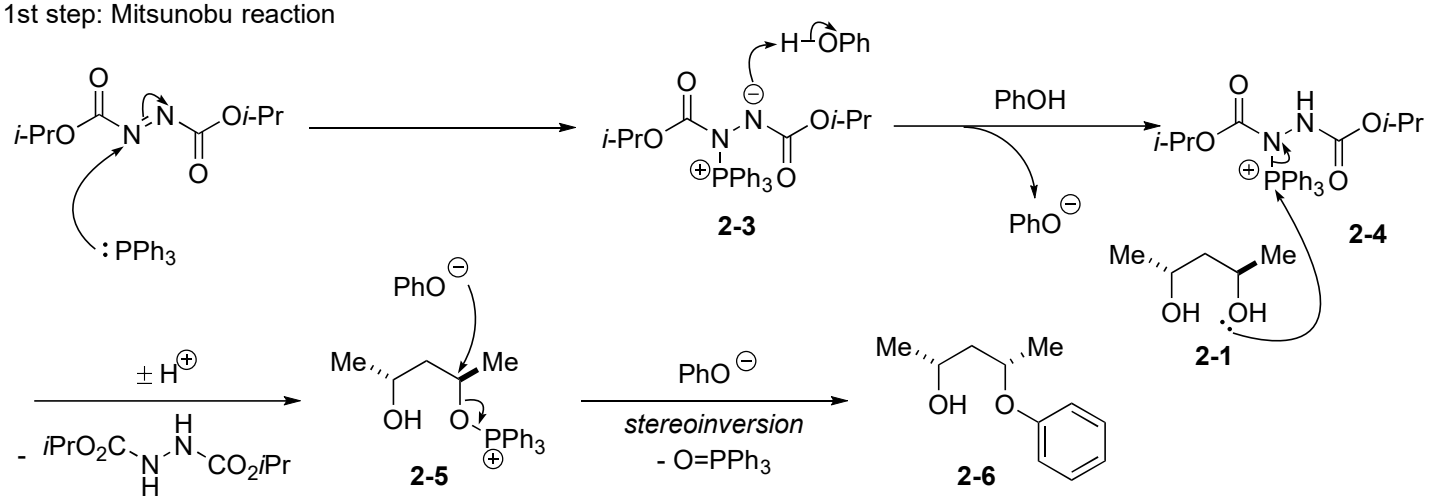
2-1. Reaction mechanism



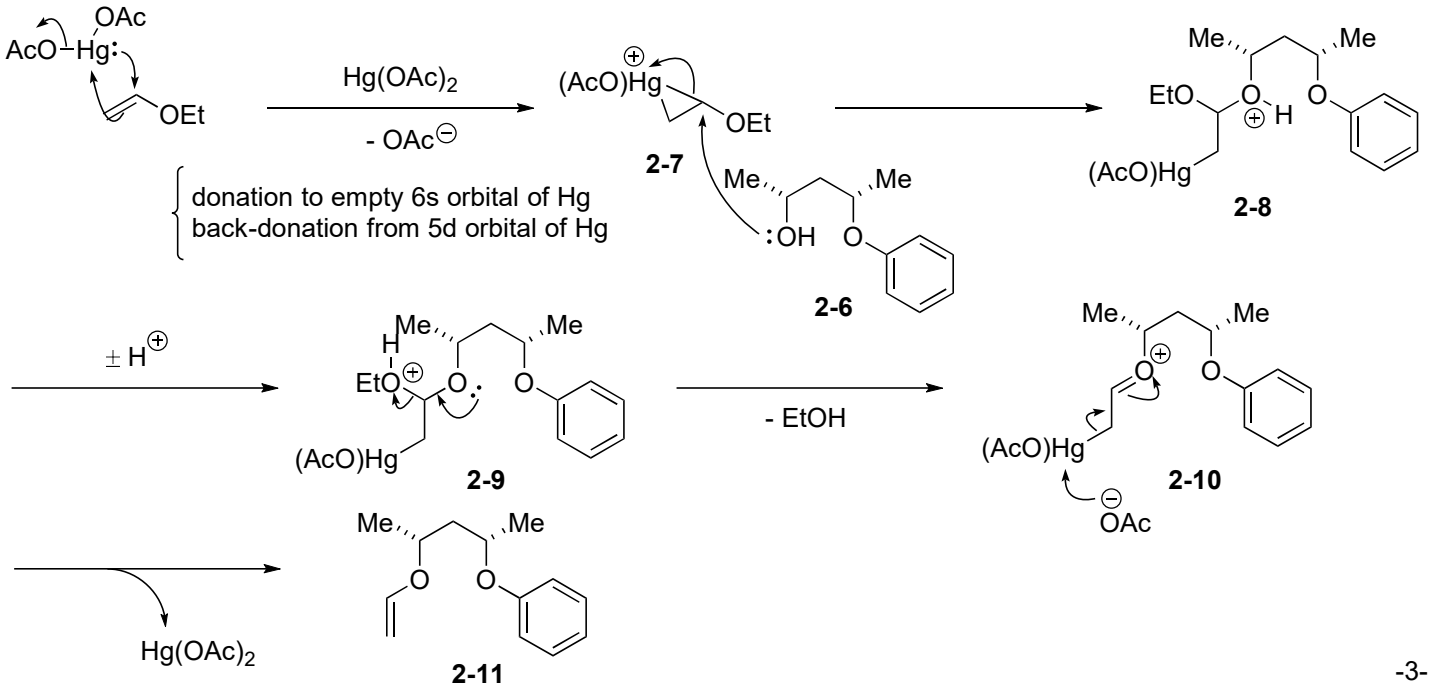
Mak, V. W-D. *Ph. D. Thesis.* Caltech **2018**. (Prof. Sarah, E. Reisman's group)

Key point: 1. Diastereoselective *meta*-photocycloaddition (step 3), 2. epoxidation induced fragmentation (step 4)
3. Stereoselective reduction of ketone (step 5)

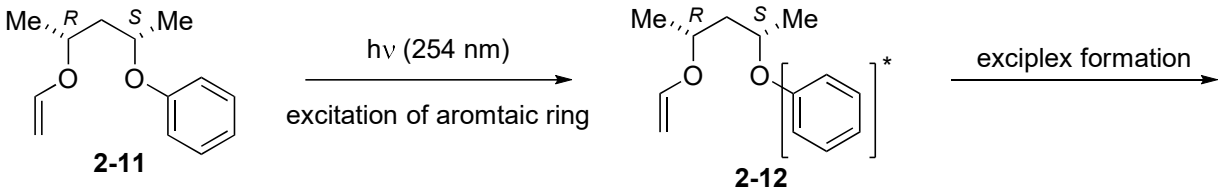
1st step: Mitsunobu reaction

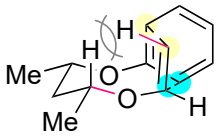


2nd step: vinyl etherification



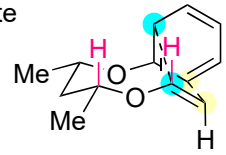
3rd step: diastereoselective *meta*-photocycloaddition





2-13-A
aromatic ring from *Si face* of vinyl ether

or



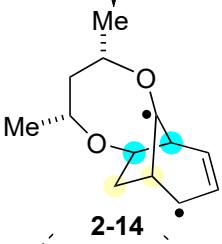
2-13-B
aromatic ring from *Re face* of vinyl ether

× *slower*

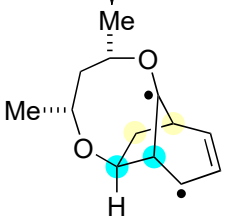
faster

X *endo*/*exo* selectivity
O facial selectivity

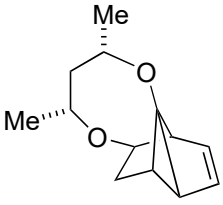
For mode and regio selectivities, see discussion sections.



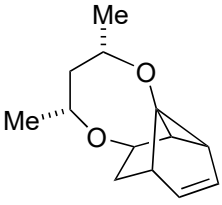
2-14



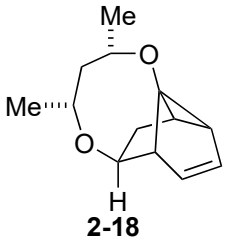
2-17



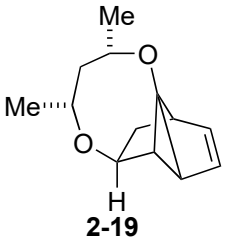
2-15



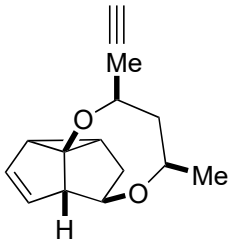
2-16



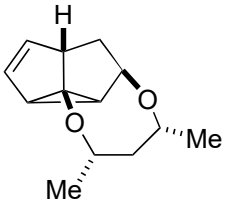
2-18



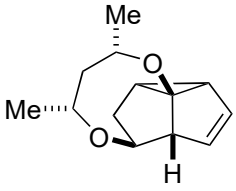
2-19



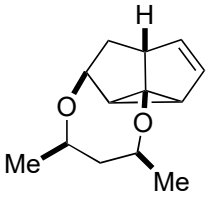
2-15
not obtained
(kinetically disfavored)



2-16
not obtained
(kinetically disfavored)

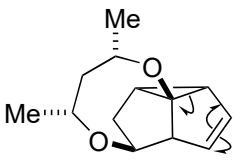


2-18
initially obtained



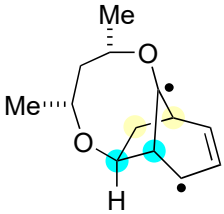
2-19
initially obtained

Once **2-18** and **2-19** are generated in the reaction system, **2-17** , **2-18**, and **2-19** are under the equilibrium via vinyl cyclopropane rearrangement.



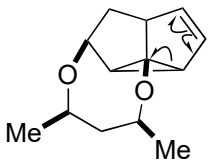
2-18
initially obtained

vinyl cyclopropane rearrangement

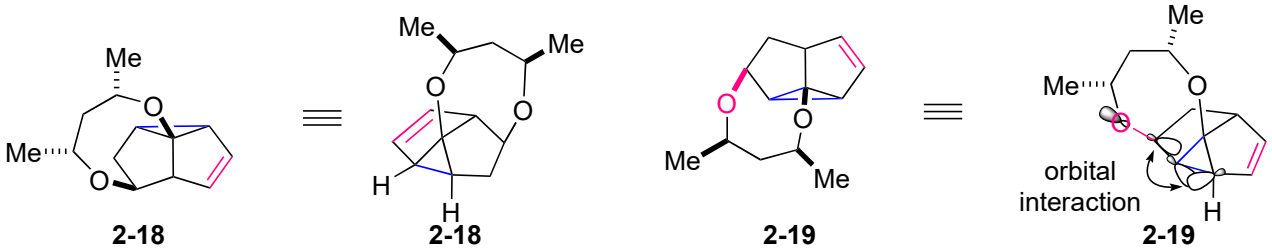


2-17

vinyl cyclopropane rearrangement



2-18
thermodynamically more stable



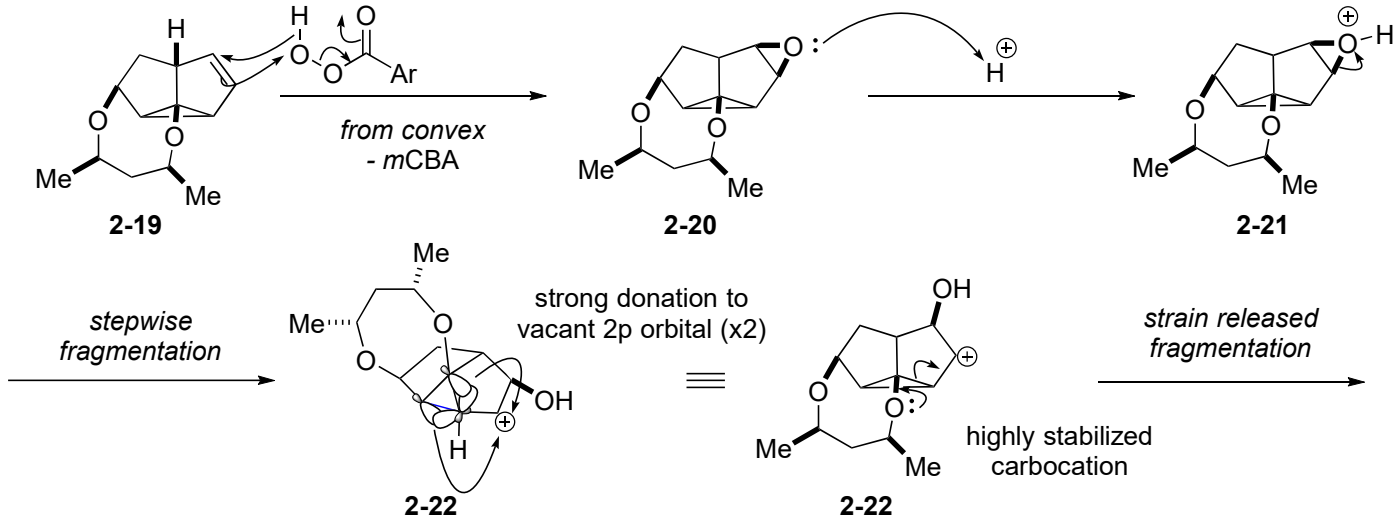
2-18 **2-18** **2-19** **2-19**

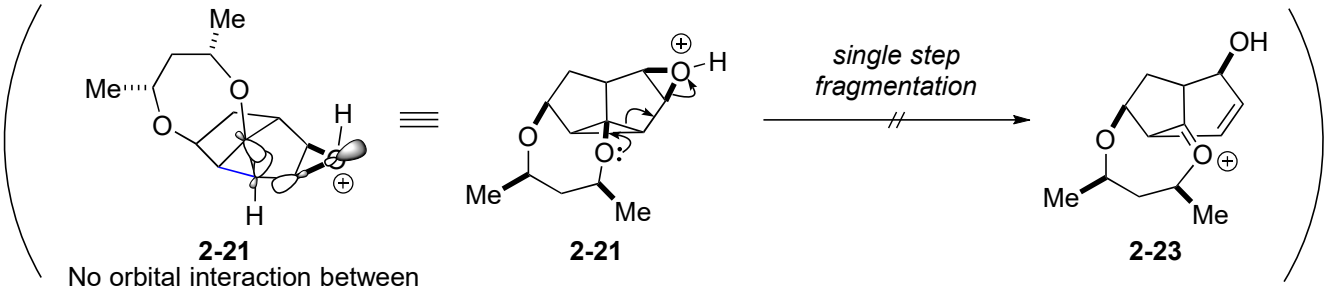
No additional orbital interaction between cyclopropane and chiral tether

orbital interaction between C-C σ of cyclopropane and C-O σ* of chiral tether

Fifer, N. L.; White, J. M. *Org. Biomol. Chem*. **2005**, *3*, 1776.

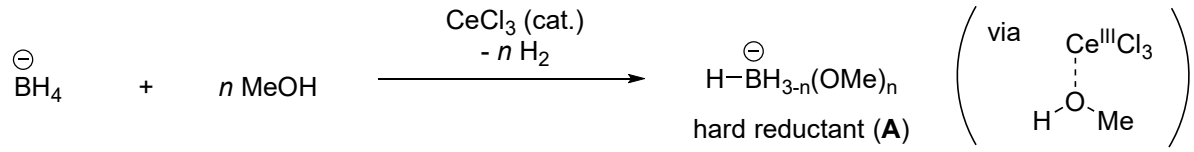
4th step: epoxidation induced fragmentation



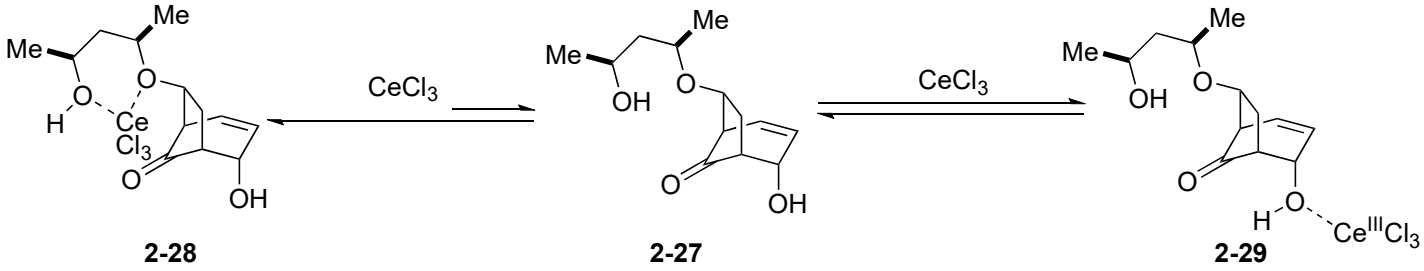


No orbital interaction between C-C σ of cyclopropane and C-O σ*of epoxide

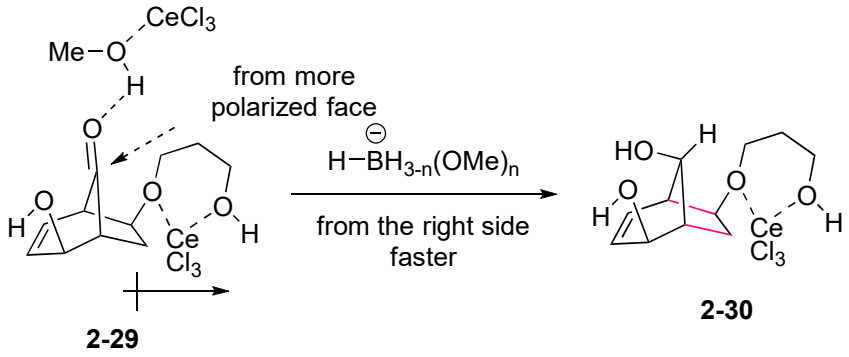
5th step: Stereoselective Luche reduction



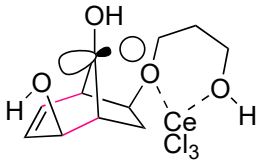
* $CeCl_3$ can coordinate to the hydroxyl group on the substrate **2-27**



1. anionic reductant approaches from the more polarized face = favored



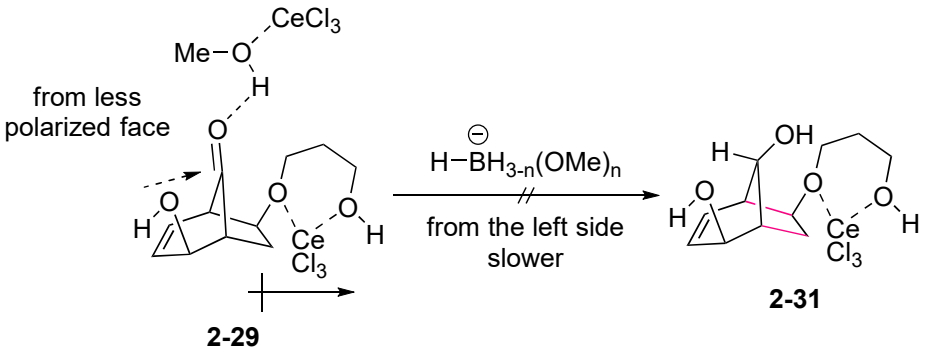
<TS analysis>



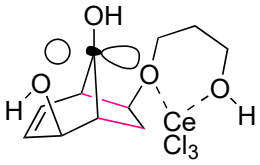
TS-1
donation from 2 x C-C σ bond
to newly formed C-H σ*

Vaidyanathan, R. *et al. Org, Process. Res. Dev*. **2019**, *23,* 2754.

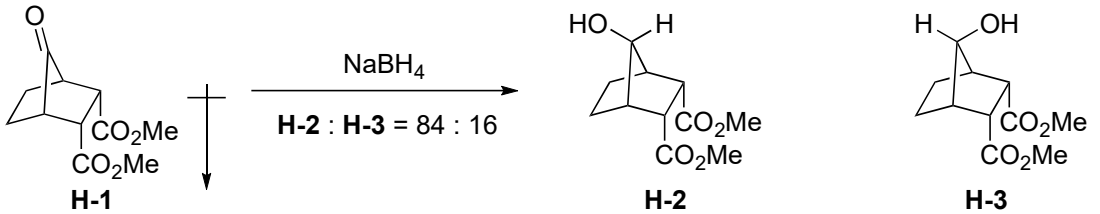
2. anionic reductant approaches from the less polarized face = disfavored



<TS analysis>



TS-2
donation from 2 x C-C σ bond
to newly formed C-H σ*
the energy of C-C σ decreases
due to the coordination of $CeCl_3$



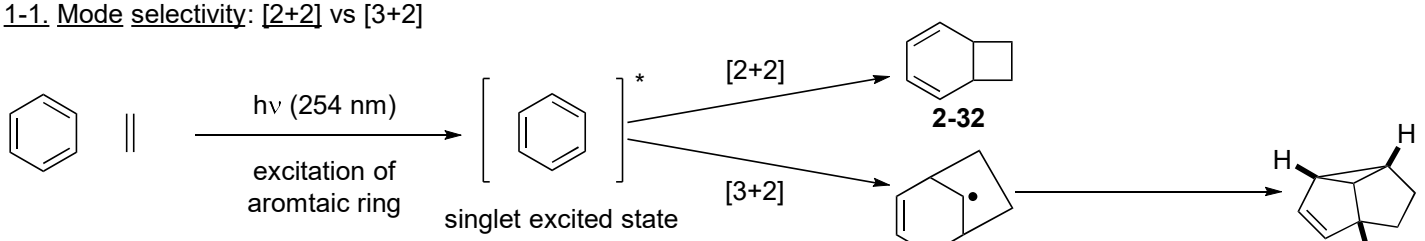
Remote polar substituents can control the stereoselectivity of nucleophilic addition to cyclic ketones **H-1**.

Mehta, G.; Khan, F. A. *J. Am. Chem. Soc*. **1990**, *112*, 6140.
Paddon-Row, M. N.; Wu, Y. -D.; Houk, K. N. *J. Am. Chem. Soc*. **1992**, *114*, 10638.

Discussion:

1. arene-alkene photocycloaddition

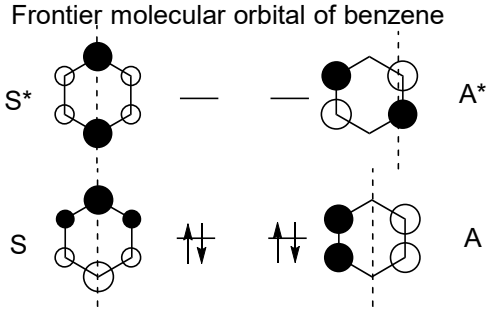
1-1. Mode selectivity: [2+2] vs [3+2]



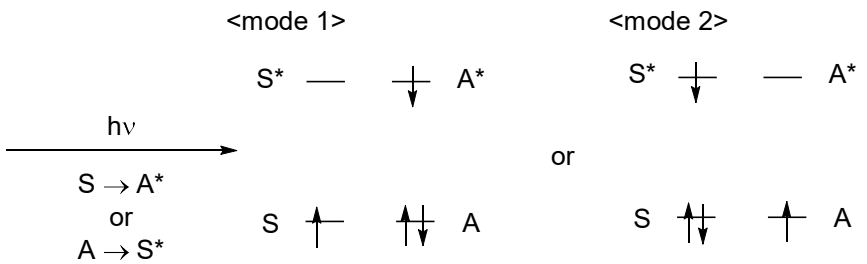
Which factors determine the mode selectivity ?

Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem*. **2011**, *7*, 525.

Frontier molecular orbital of benzene



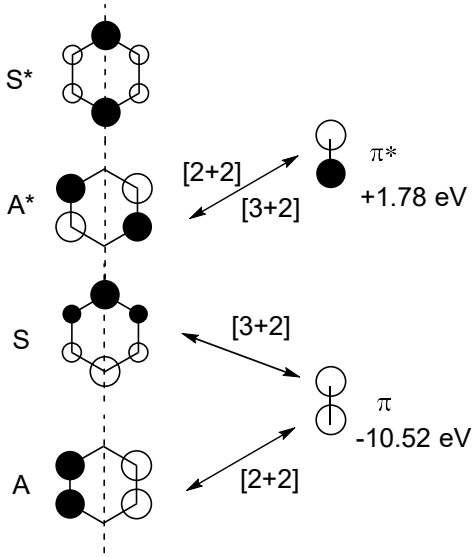
S: symmetric A: antisymmetric



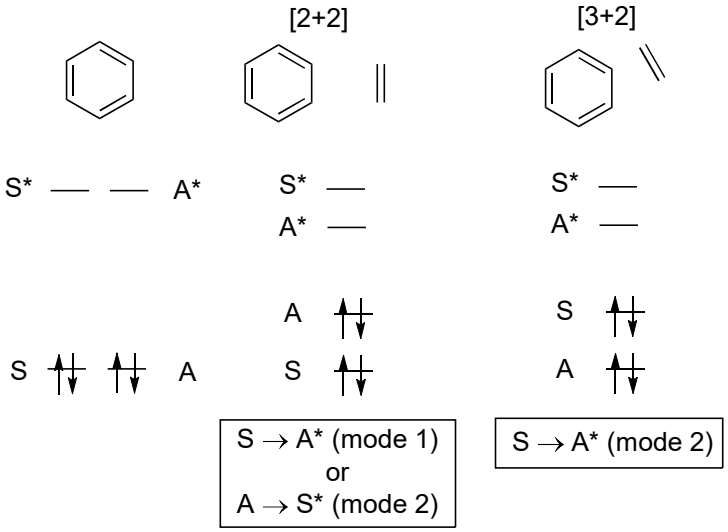
Houk, K. N. *Pure. Appl. Chem*. **1982**, *54*, 1633.

π orbital of benzene is degenerated, so four orbitals should be incorporated to describe singlet excited state of benzene

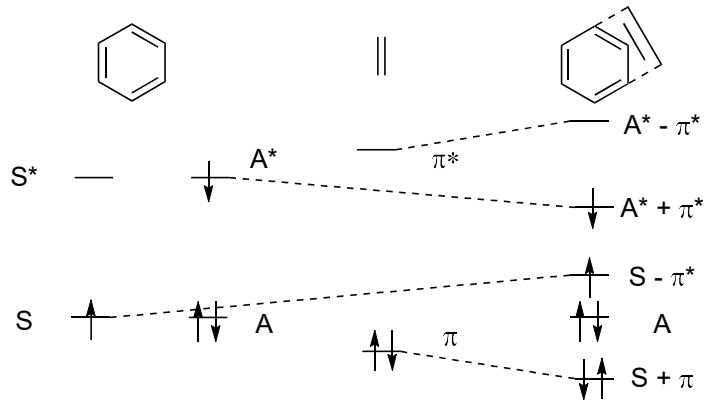
benzene-ethylene orbital interactions (independently)

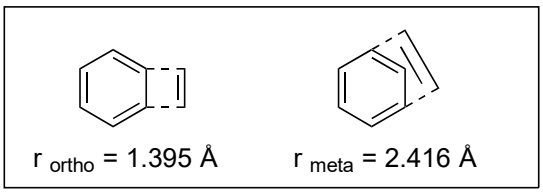


ground-state orbital energy change



Meta-photocycloaddition ([3+2] cycloaddition)





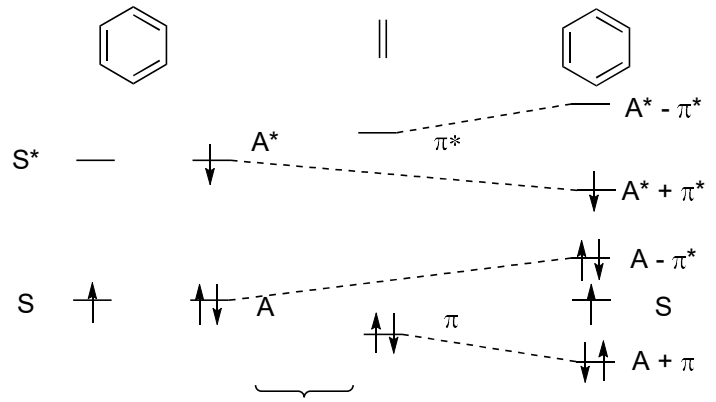
1. S → A* transition is highly stabilized
(2 x orbital interactions)

→These stabilization overcomes the diasfavored orbital overlapping in [3+2] cycloaddition.

Houk, K. N. *Pure. Appl. Chem*. **1982**, *54*, 1633.

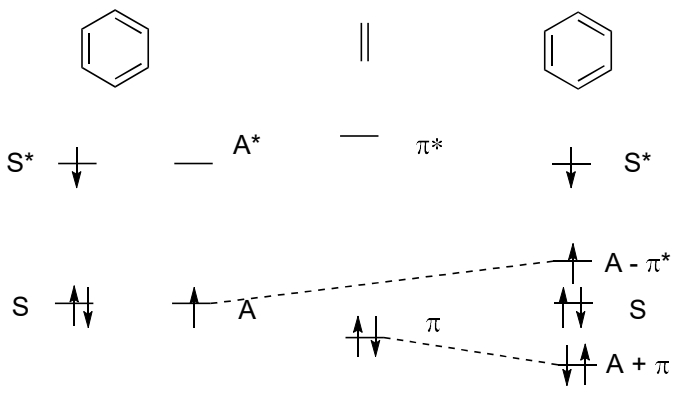
[2+2] cycloaddition

1. S → A*



four electrons in two orbitals
→ total = destabilized

2. A → S*

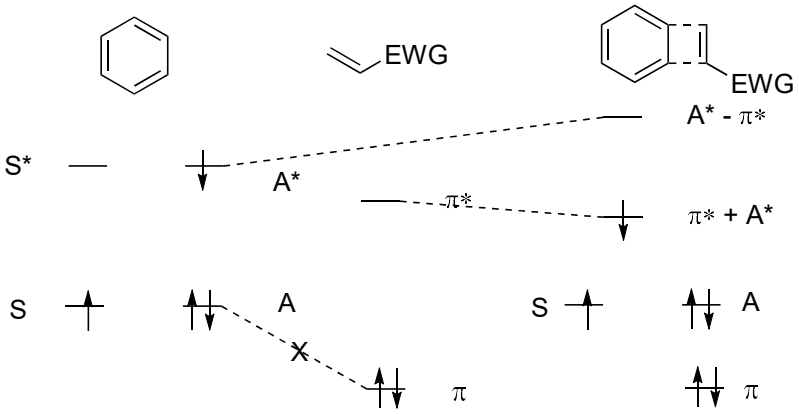


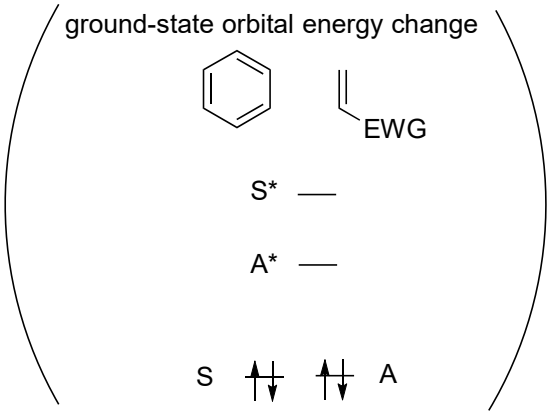
1. single orbital interaction

When the HOMO and LUMO of an aromatic compound are at approximately the same energy level as that of olefin, the [3+2] cycloaddition reaction is favored.

[2+2] photocycloaddition

a. with electron deficient olefin





Houk, K. N. *Pure. Appl. Chem*. **1982**, *54*, 1633.

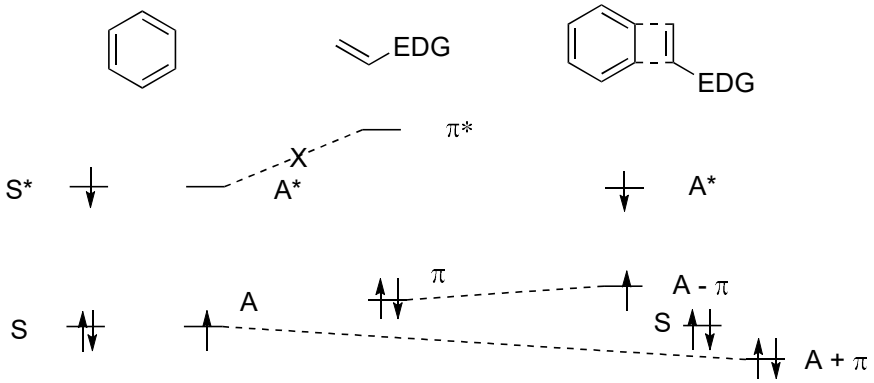
1. From the ground-state analysis, S → A* transition is favored.

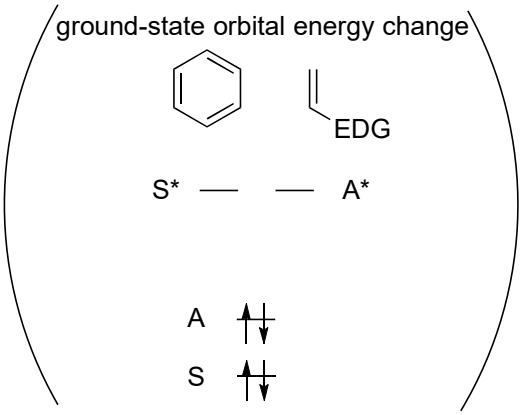
2. Interaction between A* and π* is possible

From the point of overlapping of the orbital [2+2] cycloaddition is favored.

3. Orbital interaction between A and π is impossible

b. with electron rich olefin





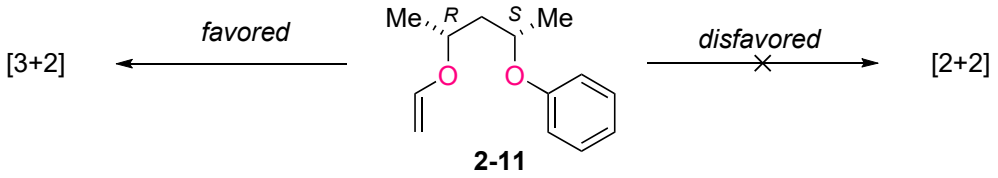
Houk, K. N. *Pure. Appl. Chem*. **1982**, *54*, 1633.

1. From the ground-state analysis, A → S* transition is possible.

2. Interaction between A* and π* is impossible

3. Interaction between A and π is possible

In this problem, cycloaddition between electron rich aromatic ring and electron rich olefin proceeds.

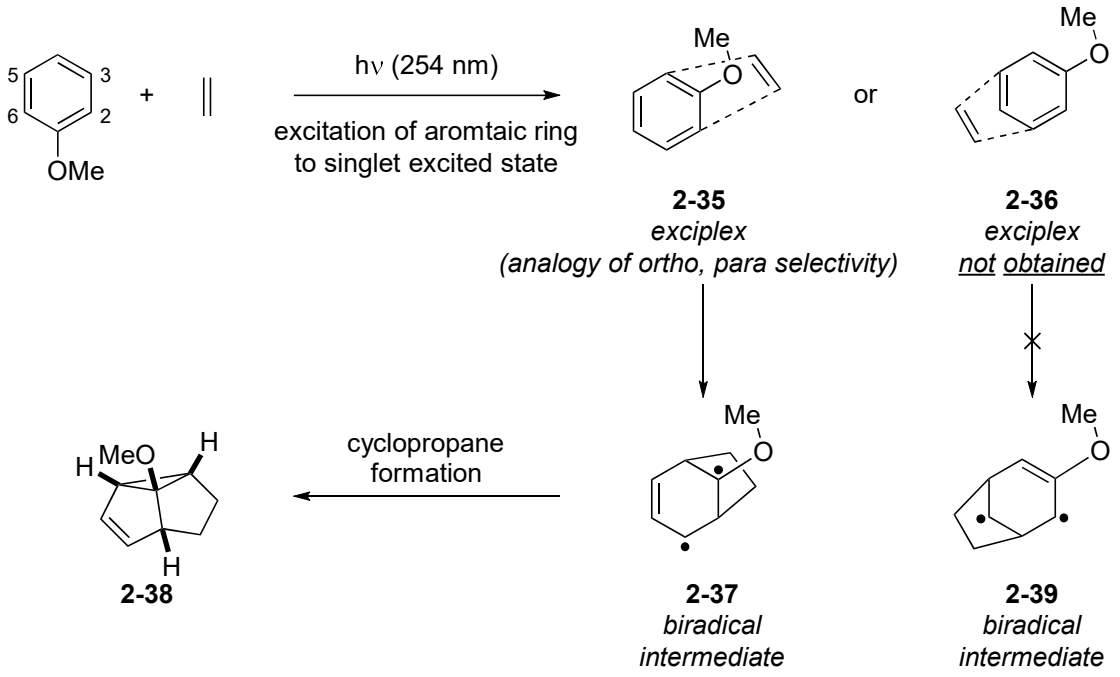


2-11

1. Olefins having electron-donor and electron-acceptor abilities preferentially afford [2+2] cycloadducts.

2. If olefin lacks good electron donor or electron acceptor, the reaction affords [3+2] cycloadducts.

1-2. Regioselectivity in *meta*-photocycloaddition using elecron rich aromatic ring



2-35
exciplex
(analogy of ortho, para selectivity)

2-36
exciplex
not obtained

2-38

2-37
biradical intermediate

2-39
biradical intermediate