

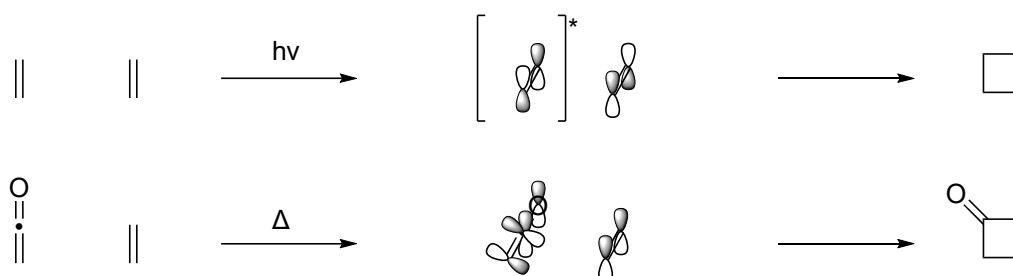
Problem Session (4) -Answer-

2022/11/05 Yuma Komori

Topic: Total synthesis using [2+2] cycloaddition

Introduction

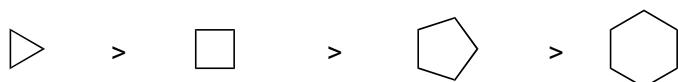
[2+2] cycloaddition



Some natural compounds have cyclobutane moiety.

strain energy

Chickos, J. S.; Hesse, D. G.; Panshin, S. Y.; Rogers, D. W.; Saunders, M.; Uffer, P. M.; Liebman, J. F. *J. Org. Chem.* **1992**, *57*, 1897.



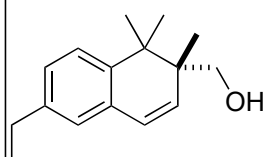
27.5 kcal/mol 26.4 kcal/mol 6.3 kcal/mol 0 kcal/mol

Highly hused ring.

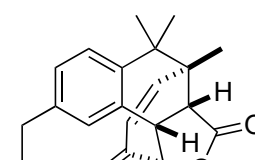
->Good precursor for ring expansion or bond cleavage.

Problem 1 (Total synthesis of salimabromide)

1. Dess–Martin periodinane (2.0 equiv.), K_2CO_3 (2.0 equiv.), CH_2Cl_2 , 0 °C, 96%
2. **1-2** (1.5 equiv.), $NaN(TMS)_2$ (1.7 equiv.), THF, -78 °C to 23 °C, 85%
3. pyrrolidine (15 equiv.), 100 °C, 99%
4. Tf_2O (1.2 equiv.), 2,4,6-collidine (1.2 equiv.), $(CH_2Cl)_2$, 80 °C; concentrated; CCl_4 , H_2O , 80 °C, 89%
5. SeO_2 (10 equiv.), SiO_2 (19 equiv.), 1,4-dioxane, 120 °C, 47% (5 cycles)
6. *t*-BuCHO (5.0 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv.), O_2 (1 atm), $(CH_2Cl)_2$; Dess–Martin periodinane (2.0 equiv.), $NaHCO_3$ (5.0 equiv.), 79% (**1-3**:**1-4** = 3.2:1)

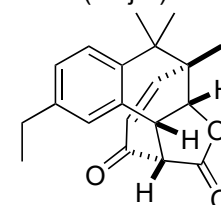


1-1



1-3

(major)

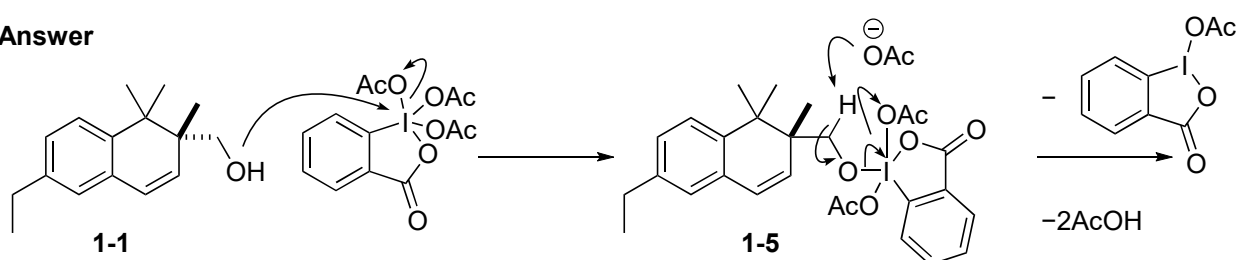


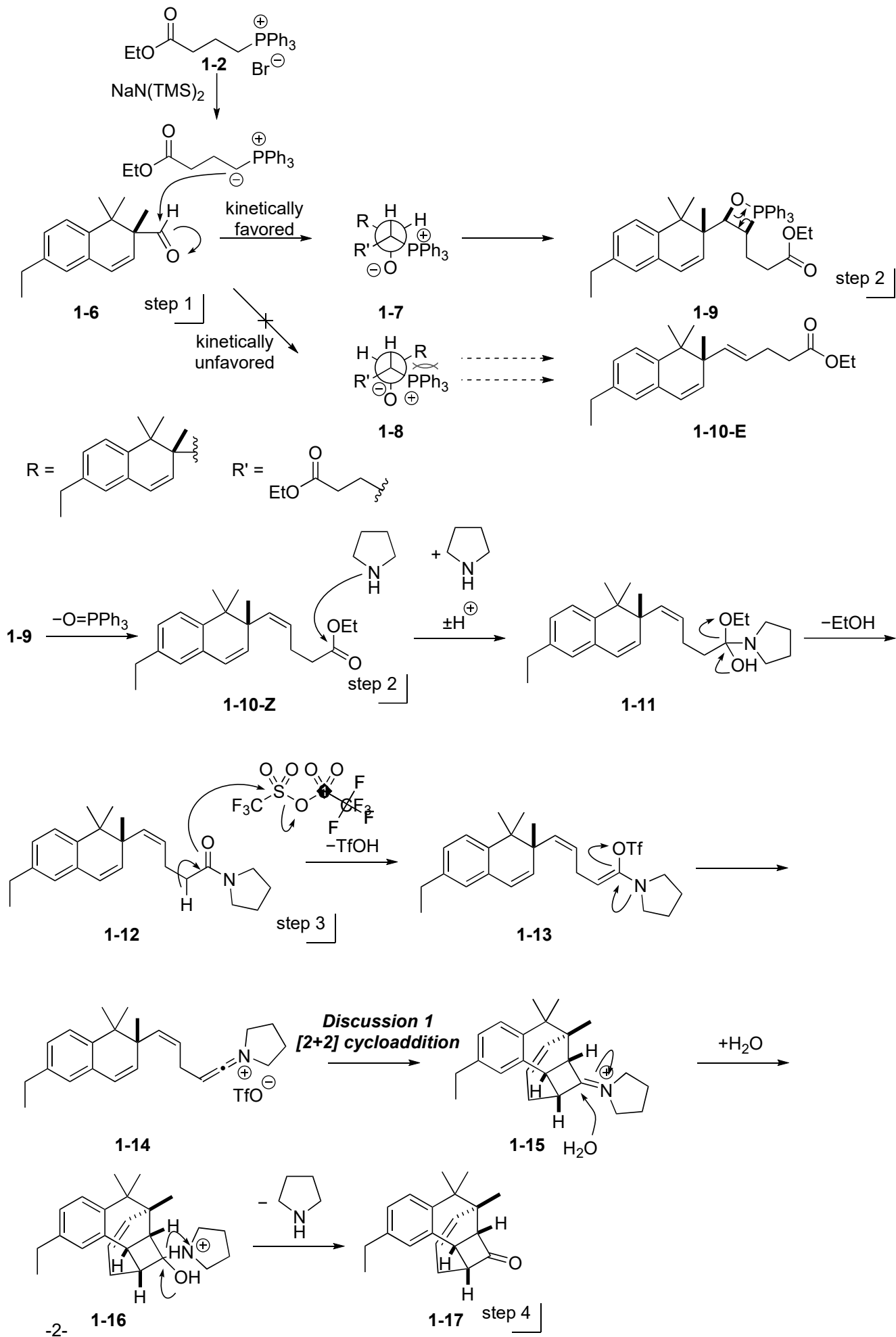
1-4

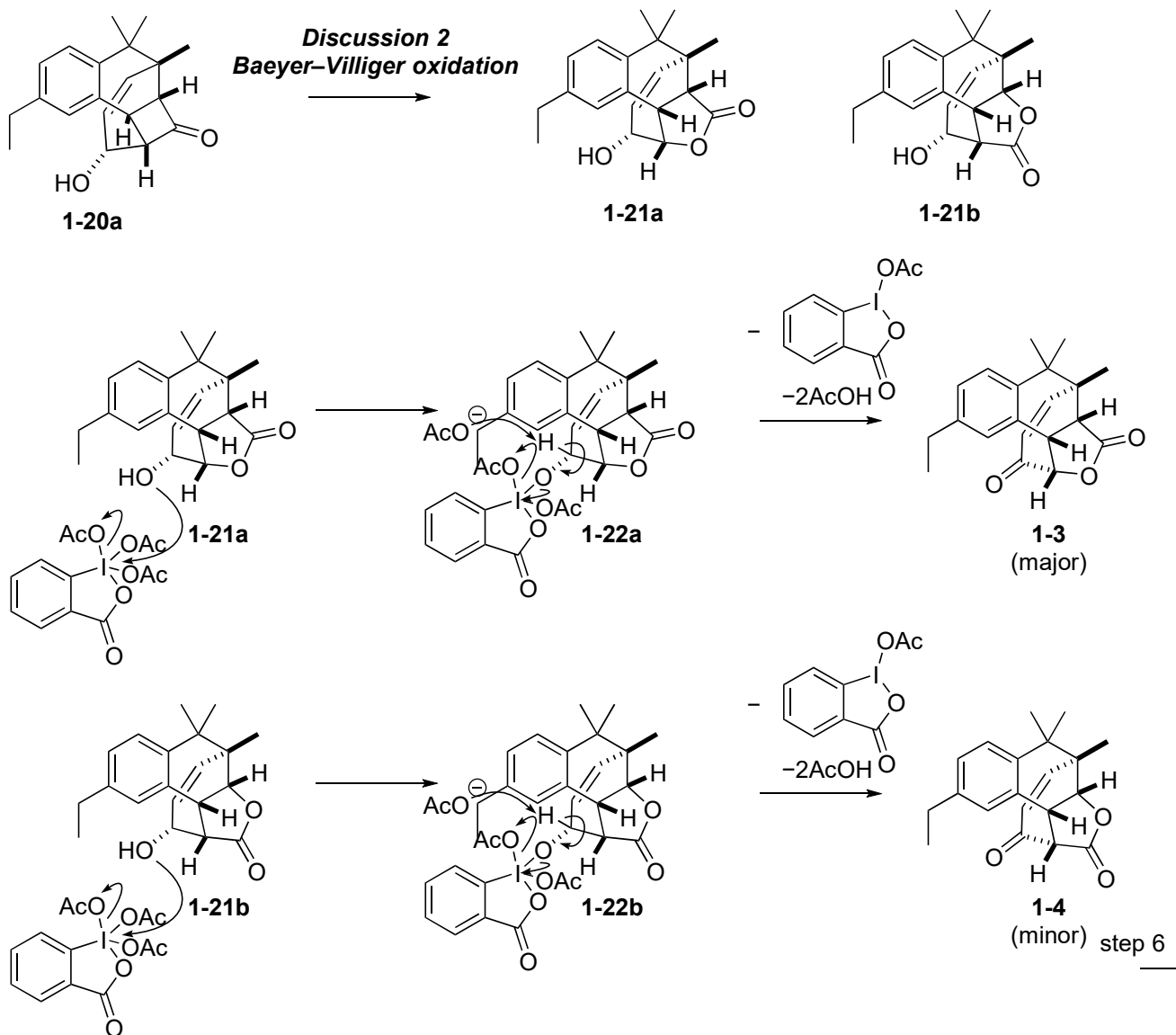
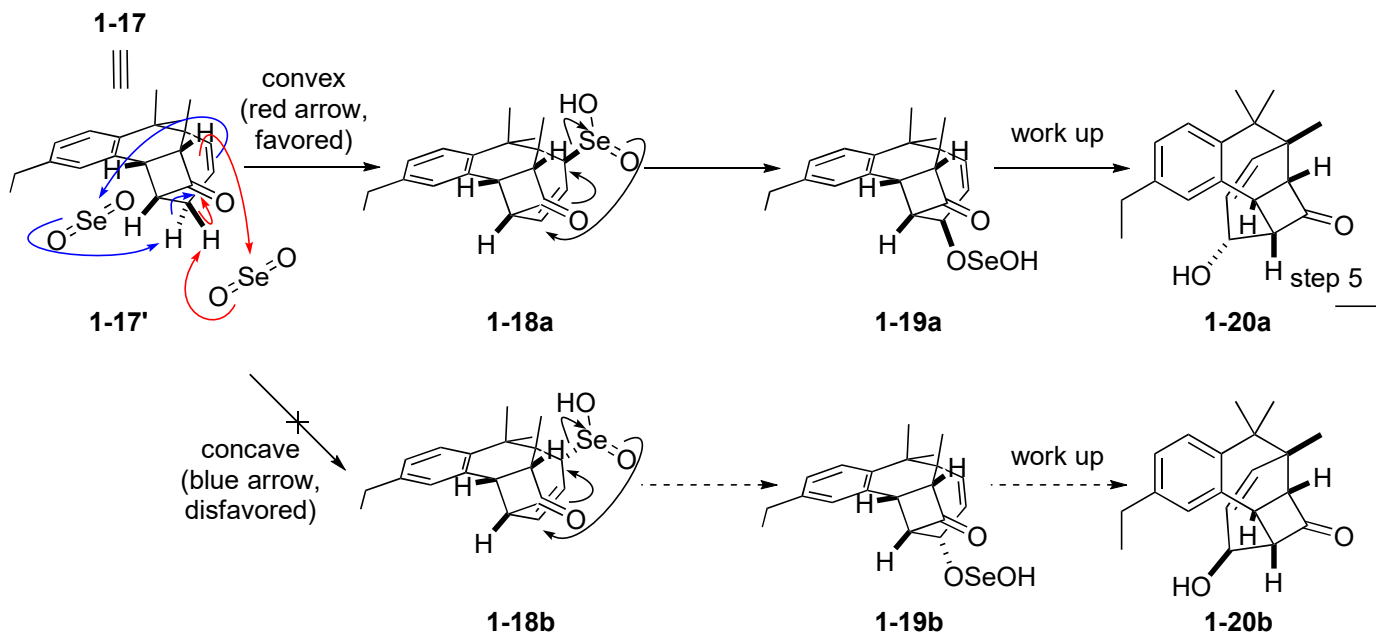
(minor)

Schmid, M.; Grossmann, A. S.; Wurst, K.; Magauer, T. *J. Am. Chem. Soc.* **2018**, *140*, 8444.

Answer

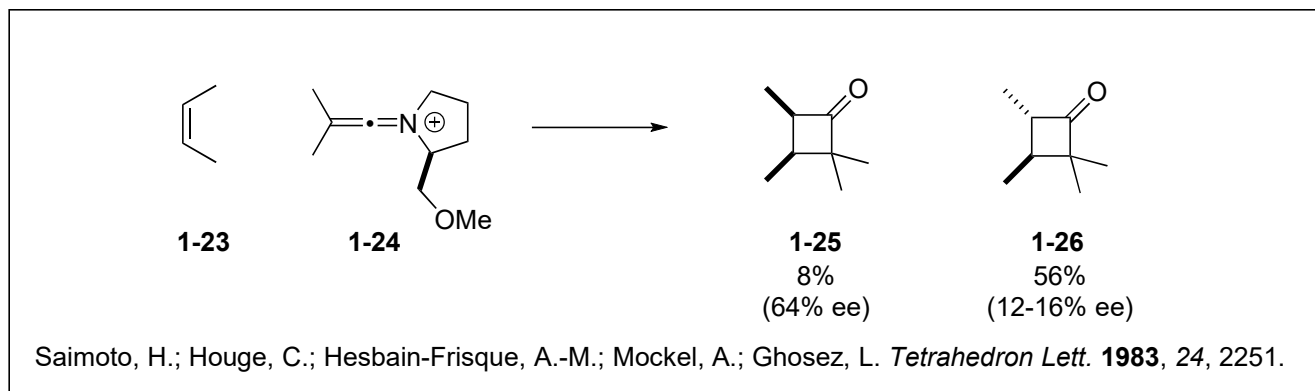




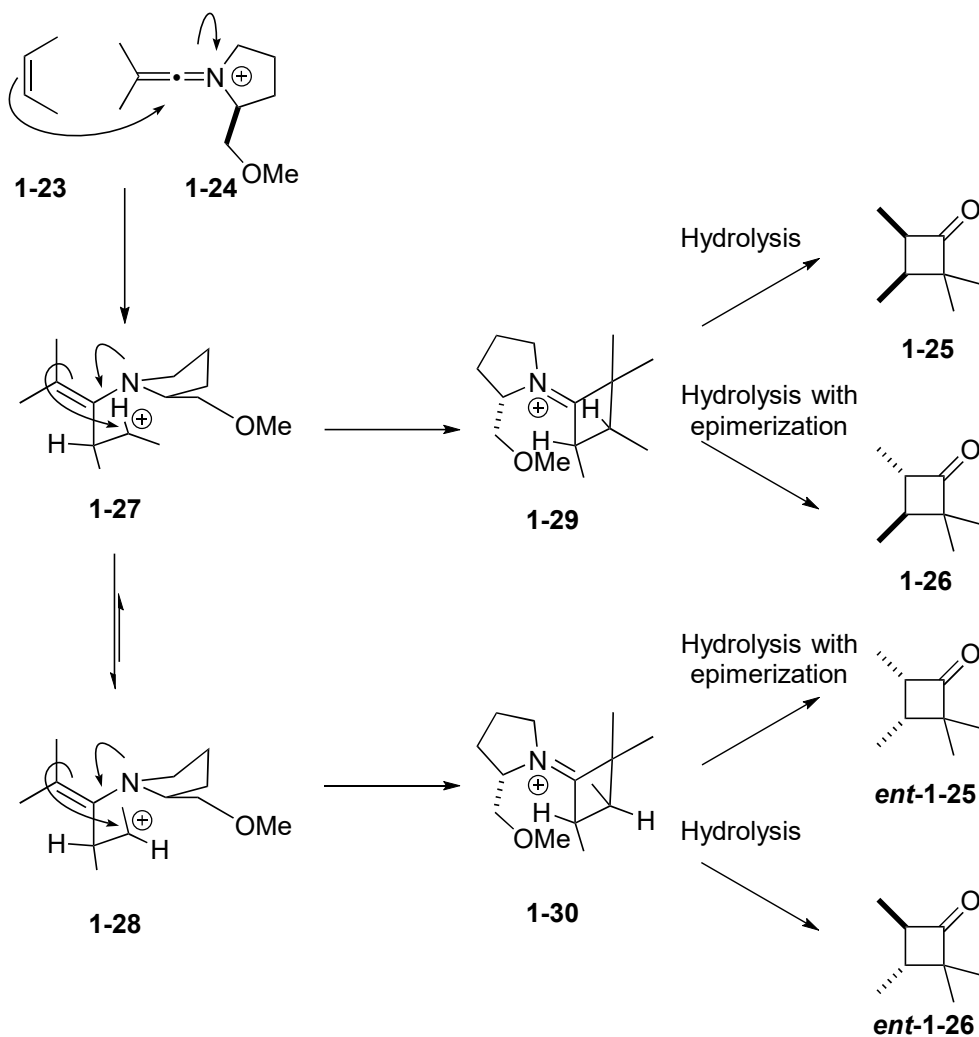


Discussion 1: [2+2] cycloaddition

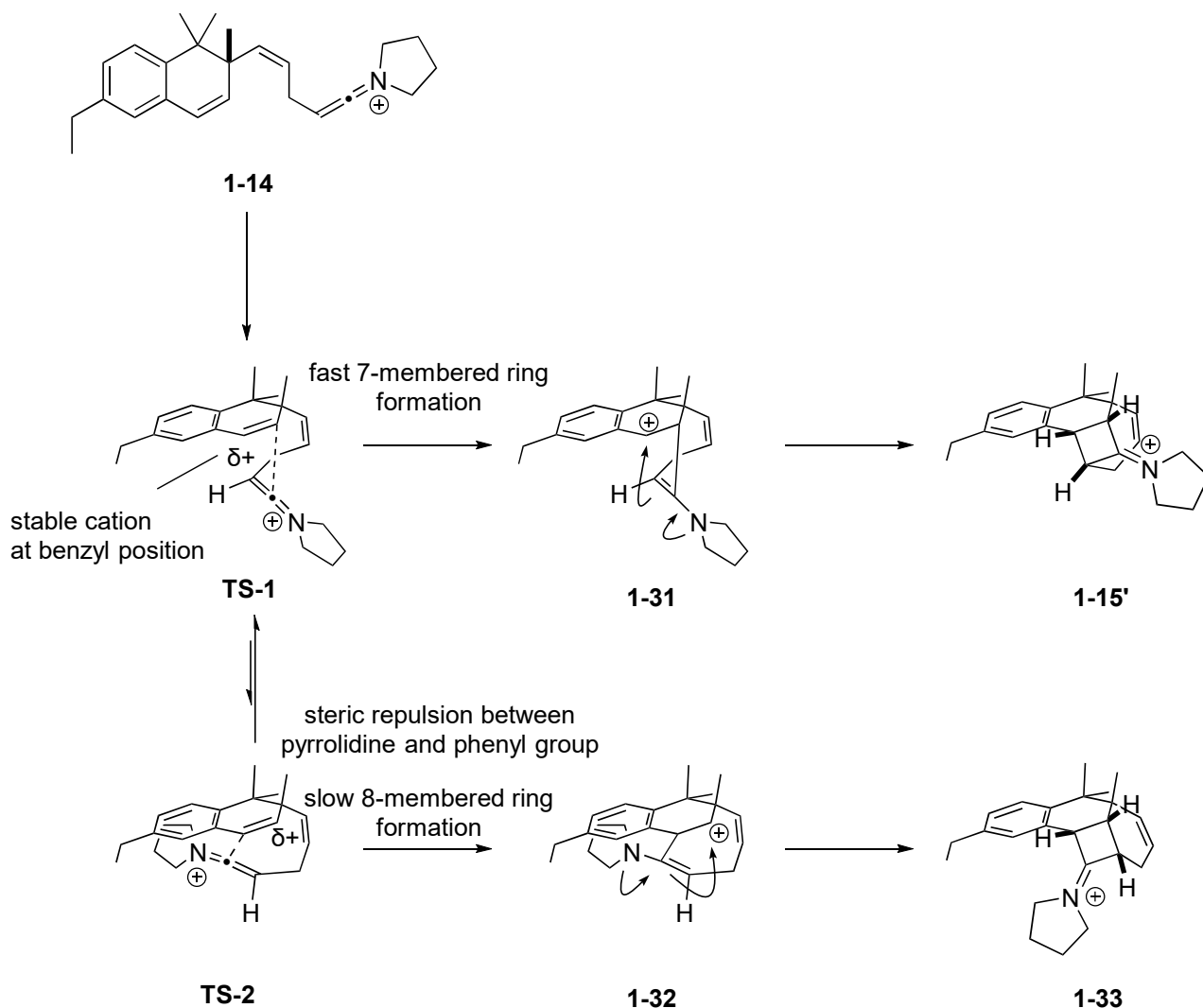
1. Mechanism of [2+2] cycloaddition using keteneiminium salt



Enantio excess decreased. This would be caused by bond rotation during cycloaddition.

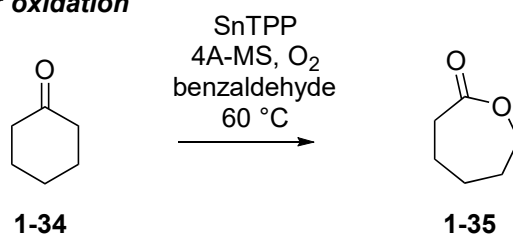


This result indicates that cycloaddition proceeds stepwise.



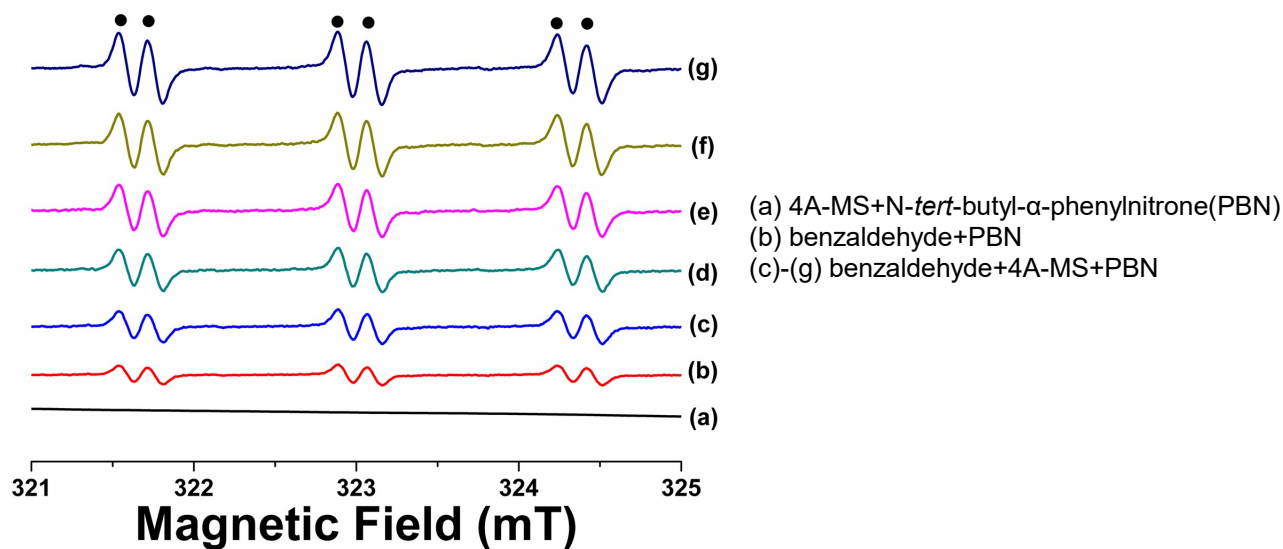
Discussion 2: Baeyer–Villiger oxidation

2.1. Mechanistic study



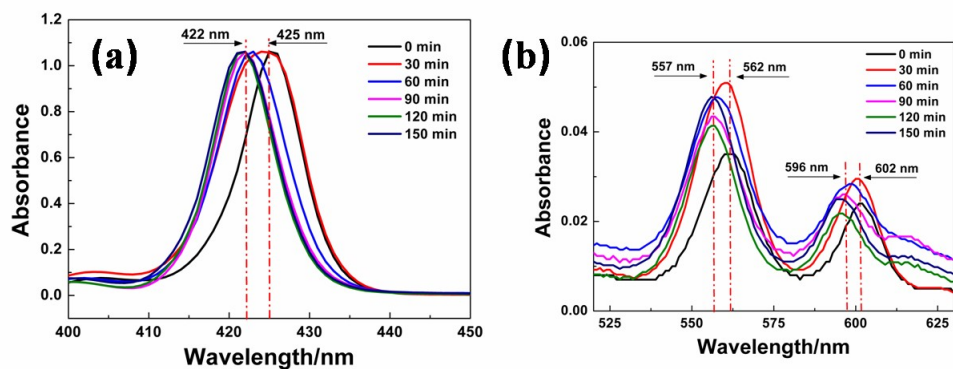
Chen, S.-Y.; Zhou, X.-T.; Ji, H.-B.
Catal. Today **2016**, 264, 191.

Electron paramagnetic resonance shows radical species generated from aldehyde.

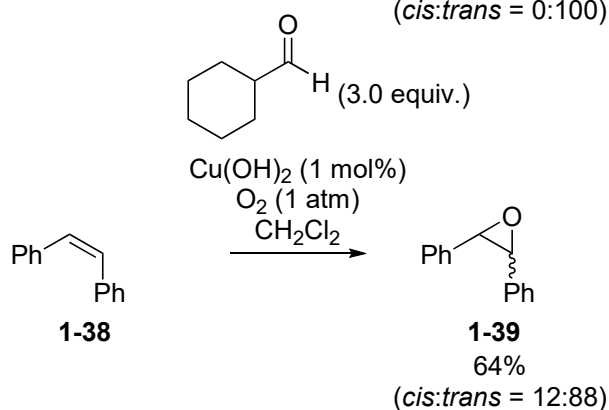
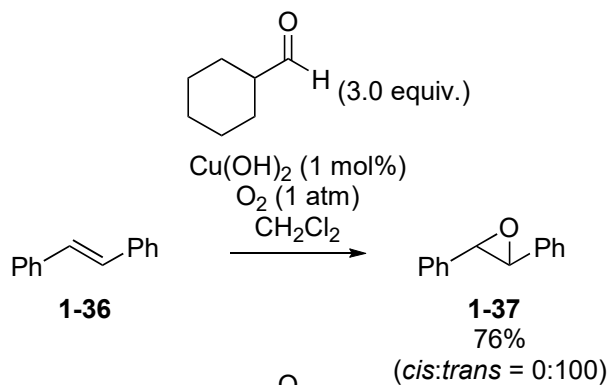


Also, reaction was inhibited when 2,6-*tert*-butyl-4-methyl-phenol was used as a radical trap.

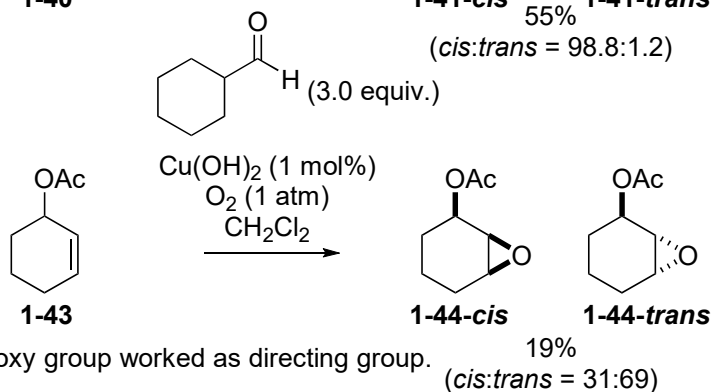
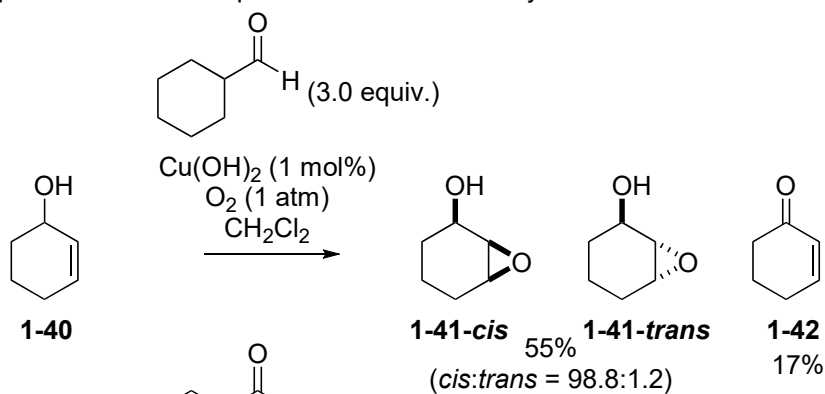
Sn was oxidized to $\text{PorSn}^{\text{IV}}=\text{O}$ under reaction conditions, judging from UV-vis spectrum.



Komiya, N.; Naota, T.; Oda, Y.; Murahashi, S.-I. *J. Mol. Catal. A: Chem.* **1997**, *117*, 21.

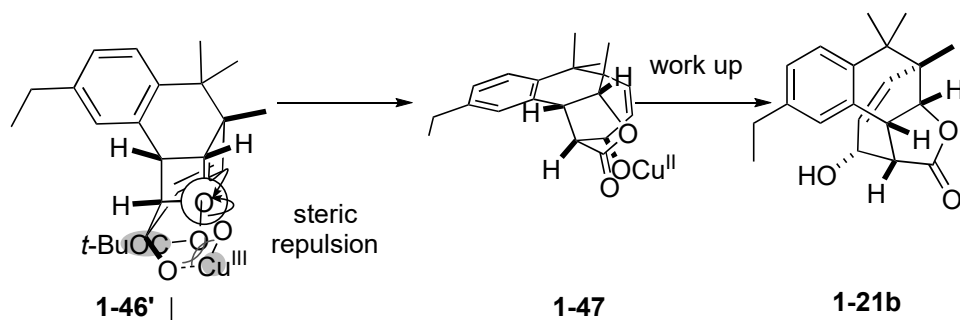
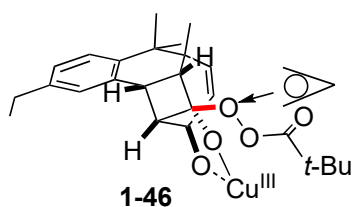
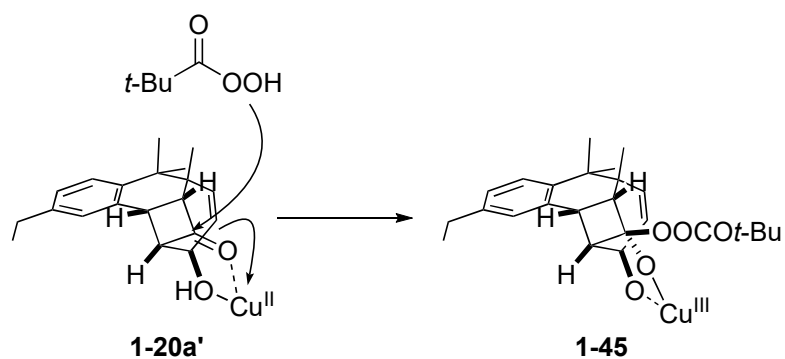
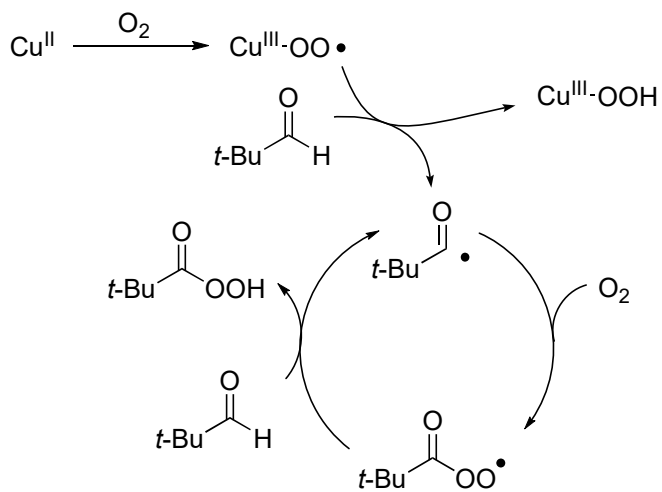


This isomerization indicates that epoxidation does not proceed in concerted way.



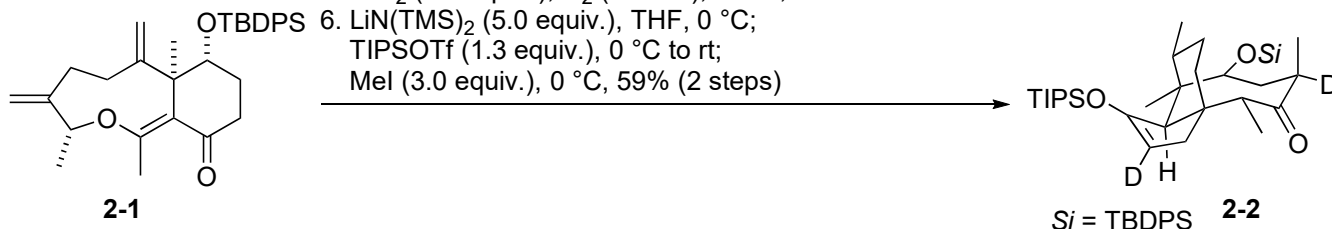
When copper was used, free hydroxy group worked as directing group.

2.2. Proposed mechanism



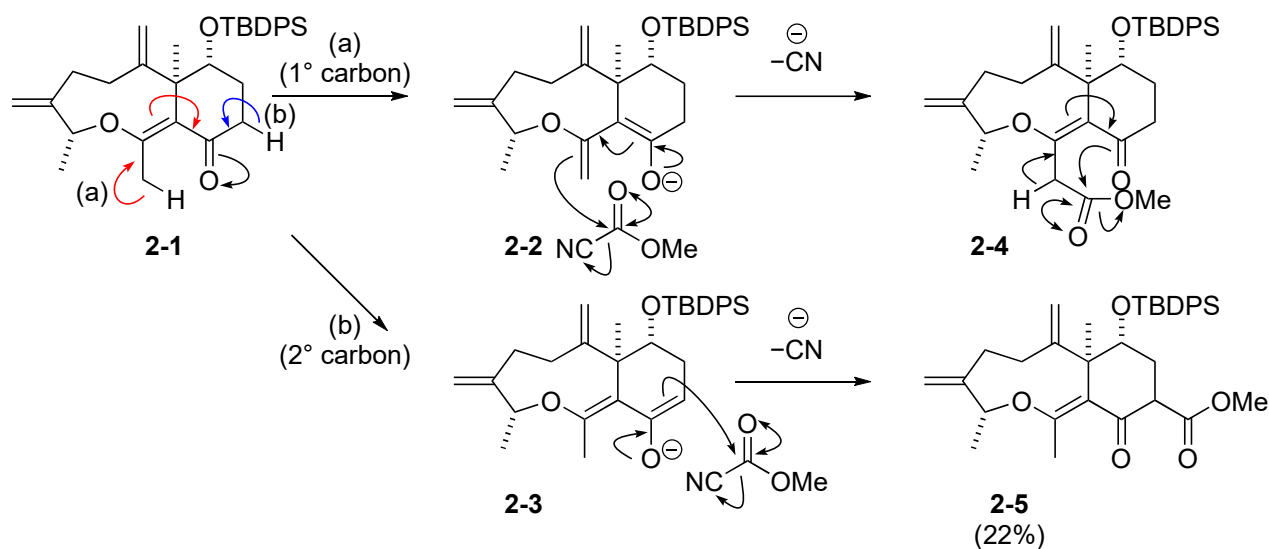
Problem 2 (Total synthesis of (+)-mutilin)

1. $\text{LiN}(\text{TMS})_2$ (1.1 equiv.), NCCO_2Me (1.5 equiv.), THF, 45% (60% brsm)
2. toluene, reflux; concentrated; NaOH (1.2 equiv.), D_2O , MeOD, 65 °C, 64%
3. TBSOTf (1.4 equiv.), 2,6-lutidine (2.1 equiv.), CH_2Cl_2 , 0 °C, 97%
4. $h\nu$ (365 nm), toluene; concentrated; HF-pyridine (30 equiv.), pyridine (7.5 equiv.), THF, 30 °C, 47%
5. PtO_2 (0.1 equiv.), H_2 (1 atom), EtOH, 30 °C
6. $\text{LiN}(\text{TMS})_2$ (5.0 equiv.), THF, 0 °C; TIPSOTf (1.3 equiv.), 0 °C to rt; MeI (3.0 equiv.), 0 °C, 59% (2 steps)

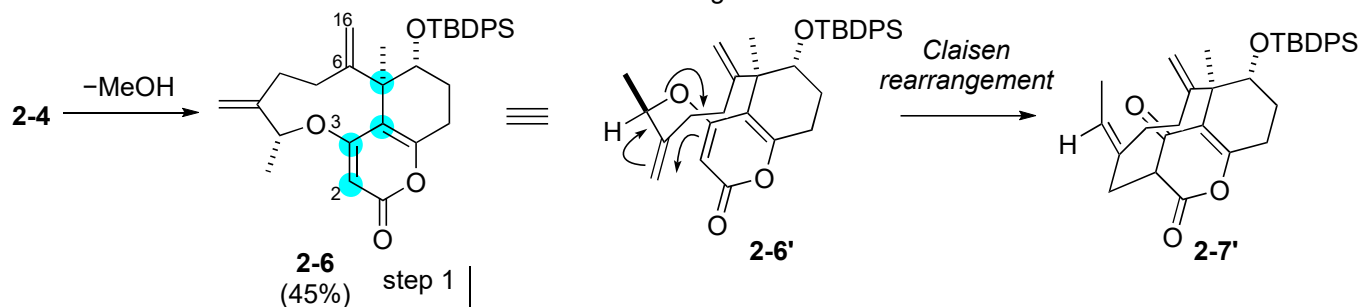


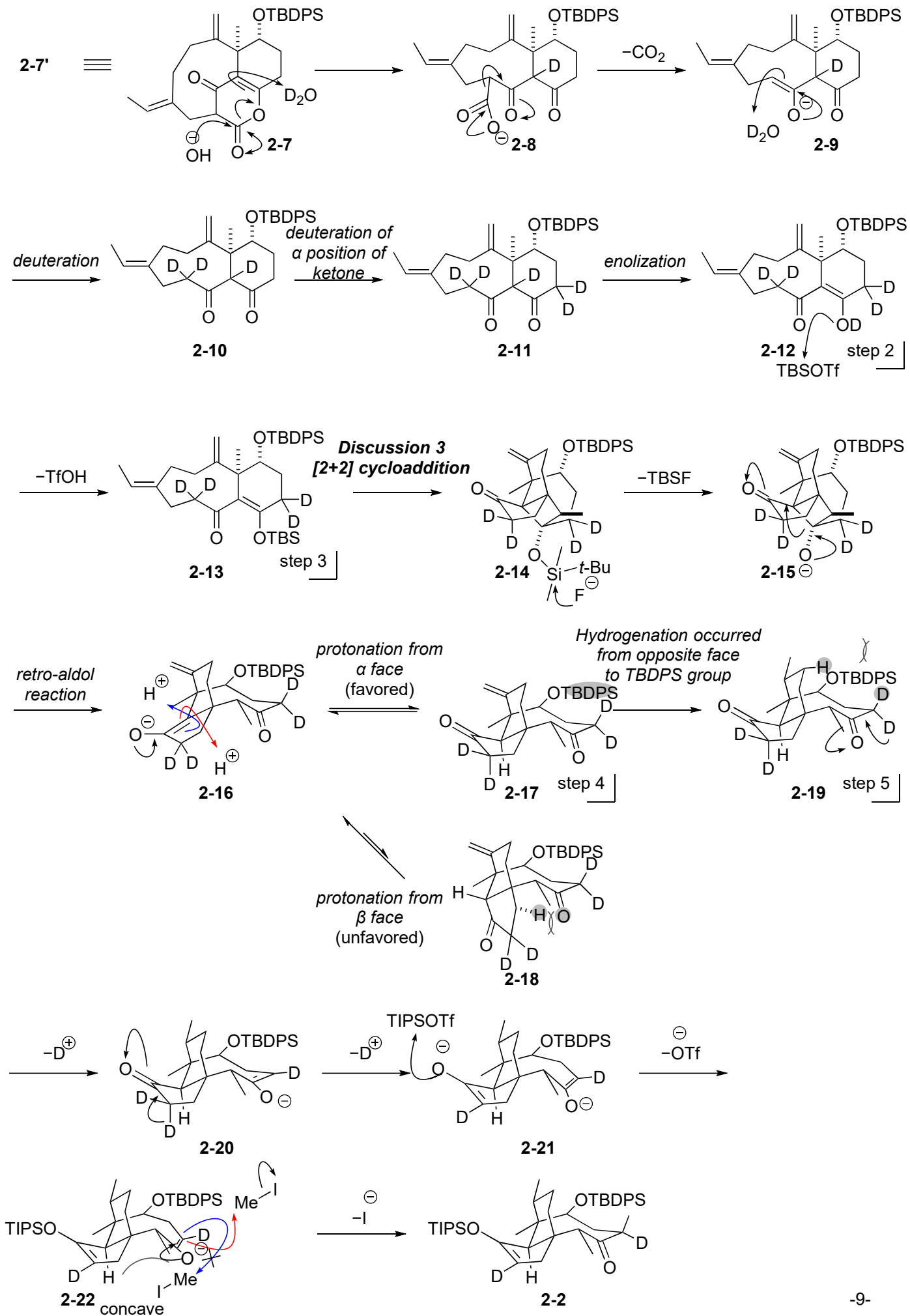
Chen, H.; Li, Z.; Shao, P.; Yuan, H.; Chen, S.-C.; Luo, T. *J. Am. Chem. Soc.* **2022**, *144*, 15462.

Answer

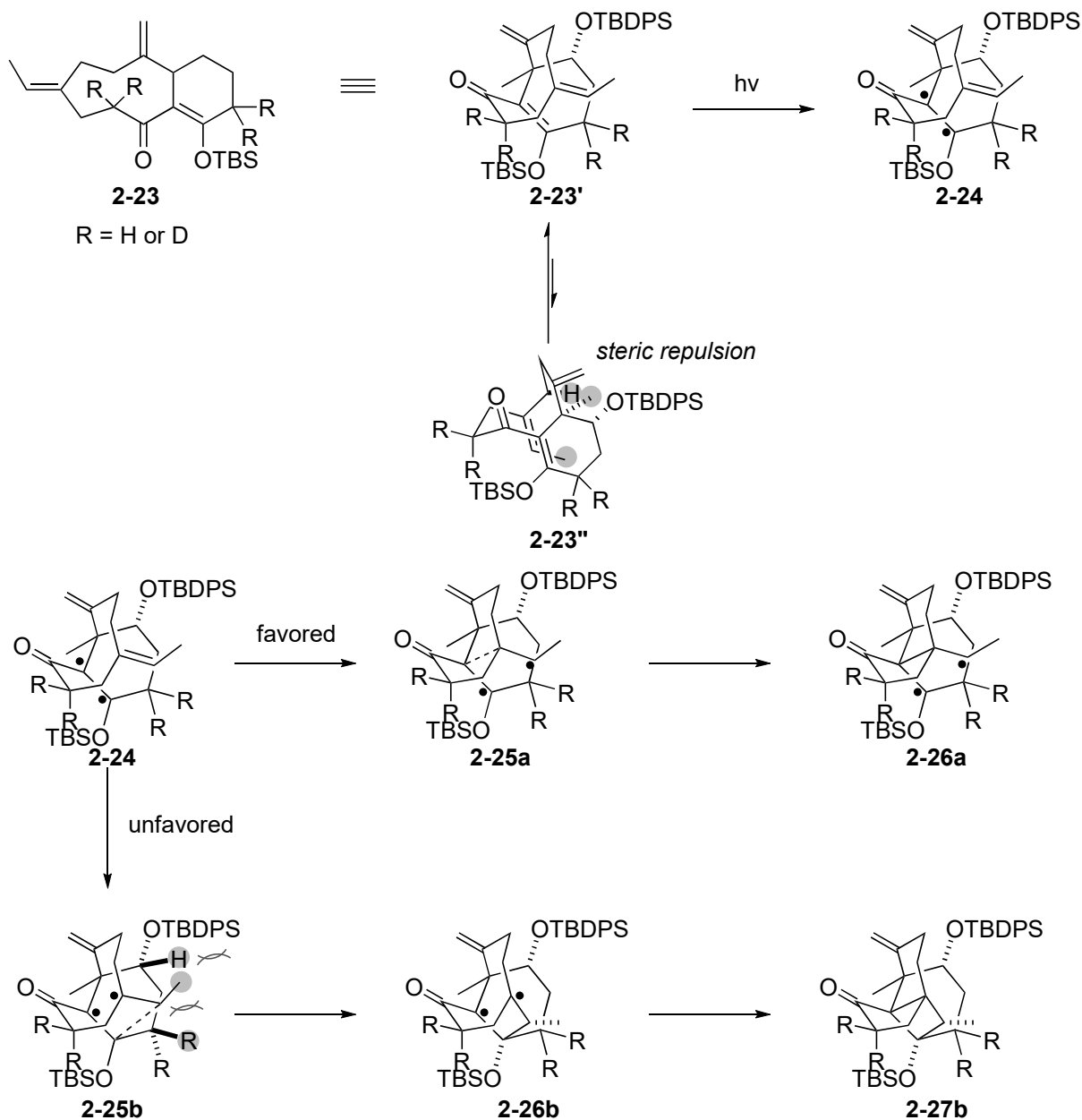


Highlighted four carbons are on a same plane, so C6-C16 olefin cannot construct six-membered ring with C2-C3 olefin.



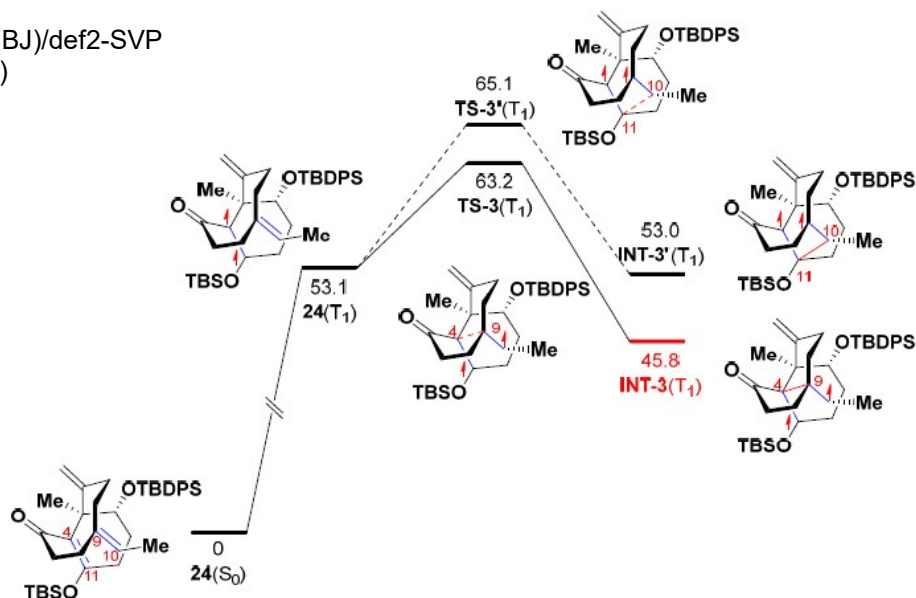


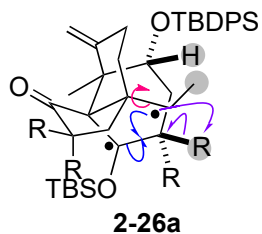
Discussion 3: [2+2] cycloaddition



DFT calculation shows **2-25a** is more favorable than **2-25b**.

B3LYP-D3(BJ)/def2-SVP
(gas phase)

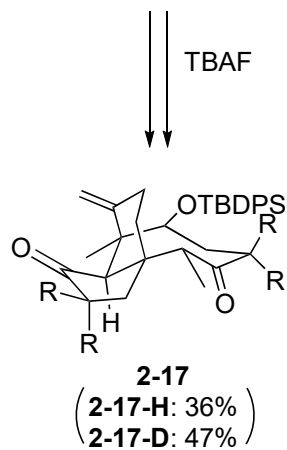
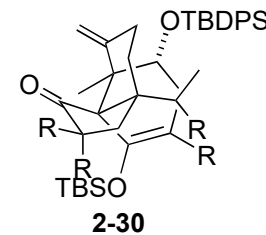
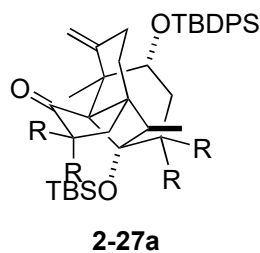
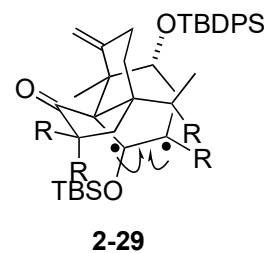
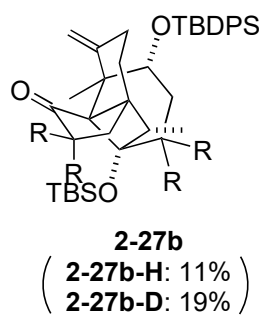
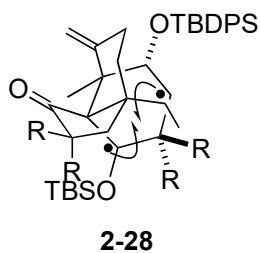




(a) bond rotation
(red arrow)

(b) recombination
(blue arrow)

(c) 1,5-HAT
(purple arrow)



When R = D, HAT was suppressed by kinetic isotope effect.

(After treatment by TBAF)
2-30-H+2-31: 30%
2-30-D: 19% (calcd.)

