

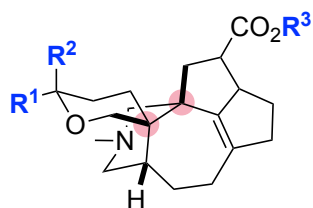
Problem Session (3)

22/11/19 Junhao Fu

Topic: total synthesis of yuzurine-type alkanoid daphgraciline



Daphniphyllum gracile



yuzurine-type alkanoid
~ 50 members

isolation:

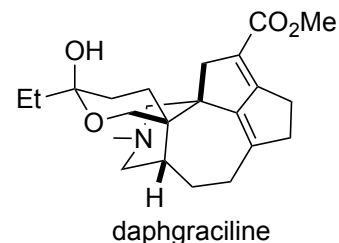
the bark of *Daphniphyllum gracile* Gage

structural features:

- [6-7-5-5-6] pentacyclic core
- azabicyclo[4.3.1] system
- spiro ring system
- 2 adjacent quaternary carbons

bioactivities:

- cytotoxic activity
- pesticidal activity



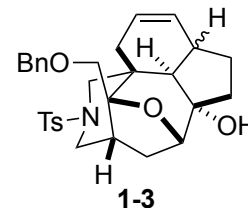
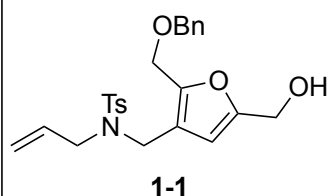
daphgraciline

total synthesis:

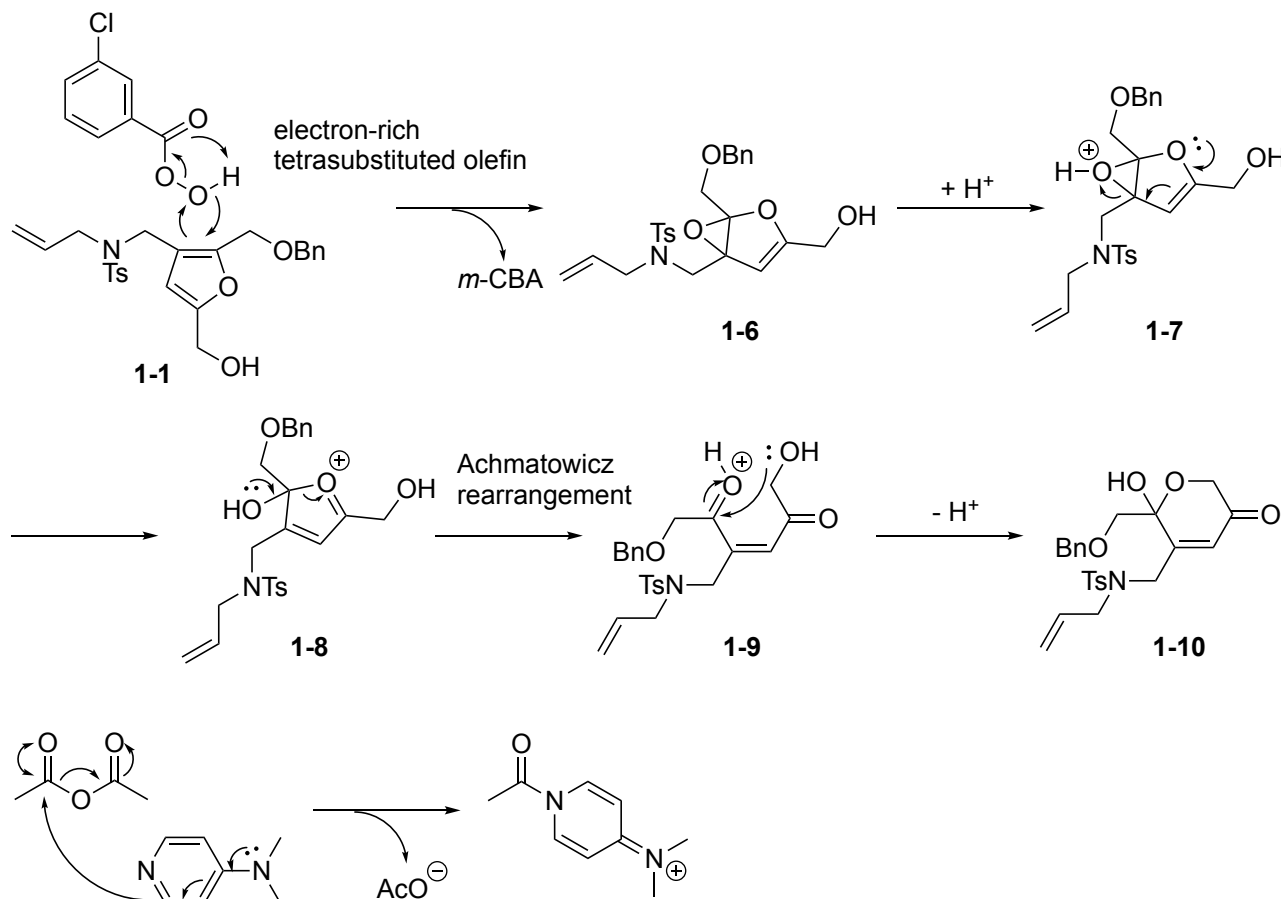
only one example reported: racemic synthesis of daphgraciline ~ C.-C. Li, 2022

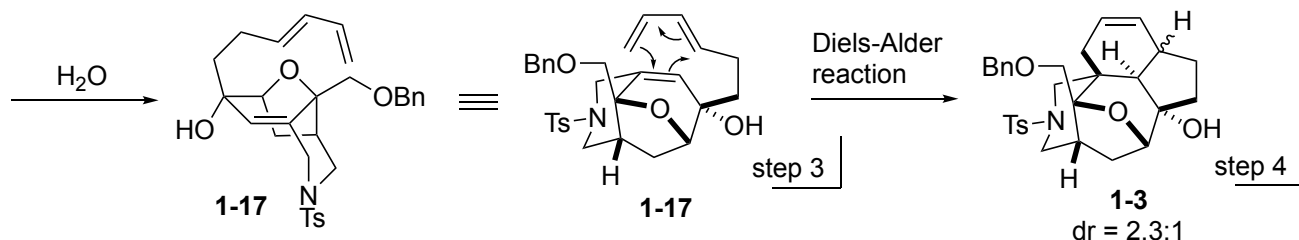
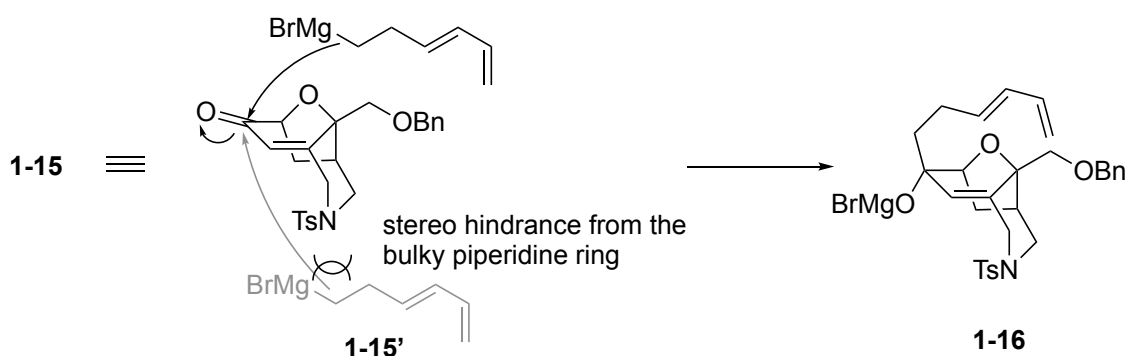
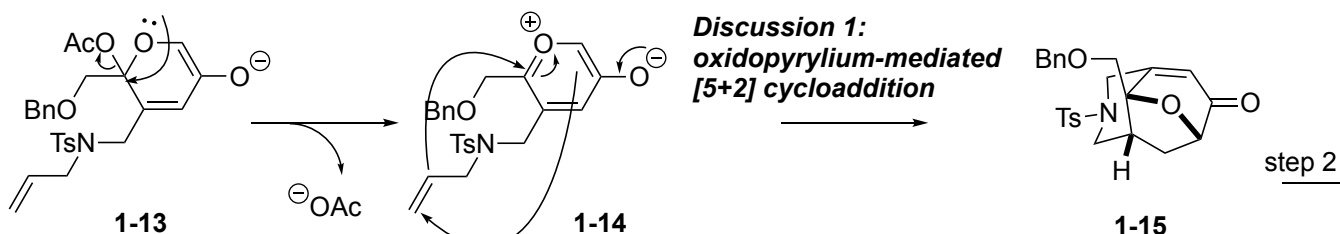
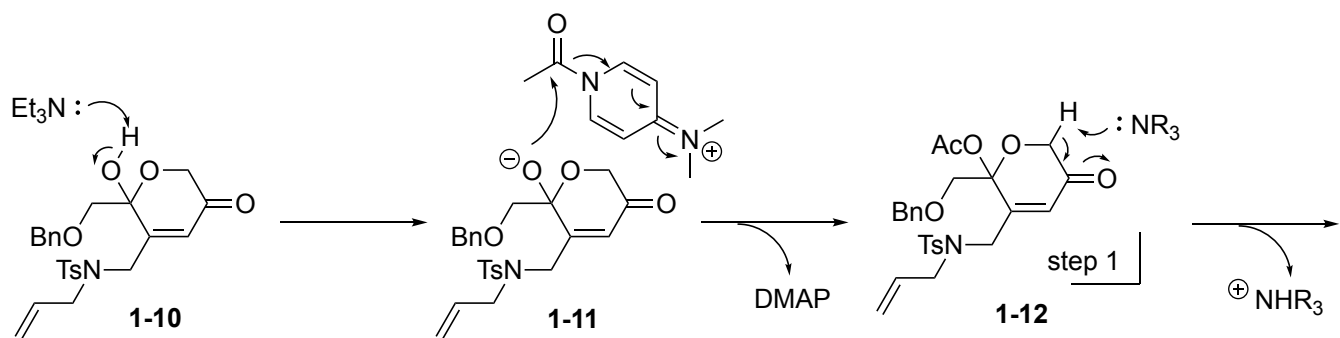
Problem 1-1

1. *m*-CPBA (1.2 eq), CH₂Cl₂, 25 °C, 1 h;
then Et₃N (6.0 eq), Ac₂O (2.5 eq), DMAP (1.0 eq)
0 °C, 1 h, 83%;
2. DHQD (0.5 eq), MeCN, 55 °C, 12 h, 75%;
3. **1-2** (4.0 eq), CH₂Cl₂, 25 °C, 1 h, 85%;
4. BHT (0.2 eq), toluene, 140 °C, 12 h, 85% (dr = 2.3:1);

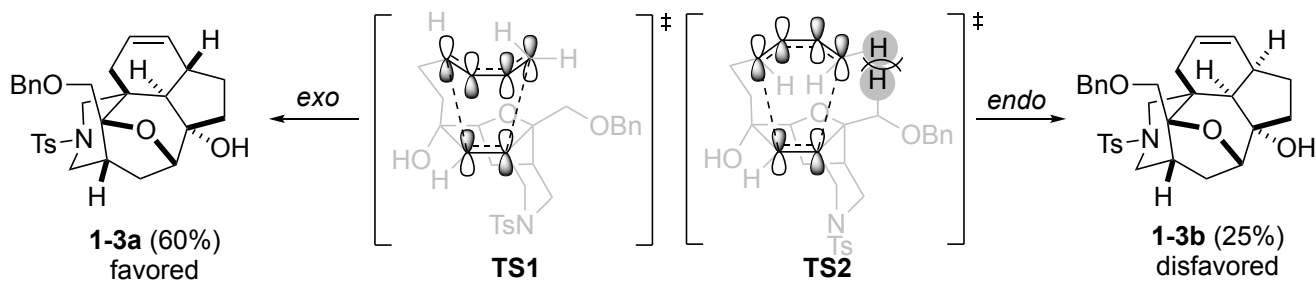


Li, L.; Min, L.; Yao, T.; Ji, S.; Qiao, C.; Tian, P.; Sun, J.; Li, C. *J. Am. Chem. Soc.* **2022**, *144*, 18823.

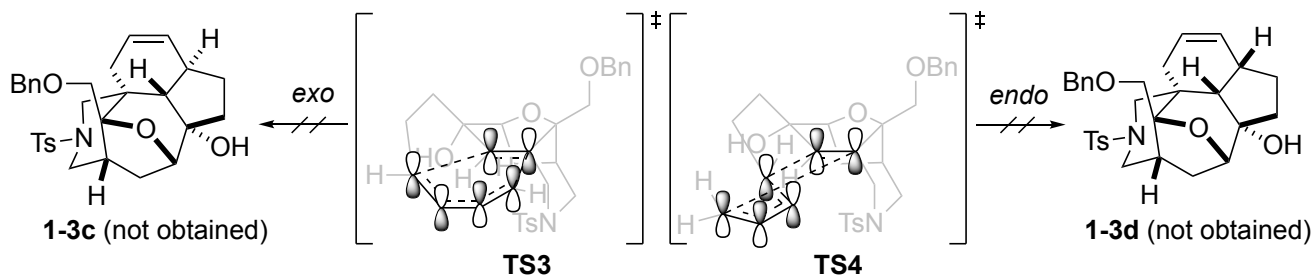


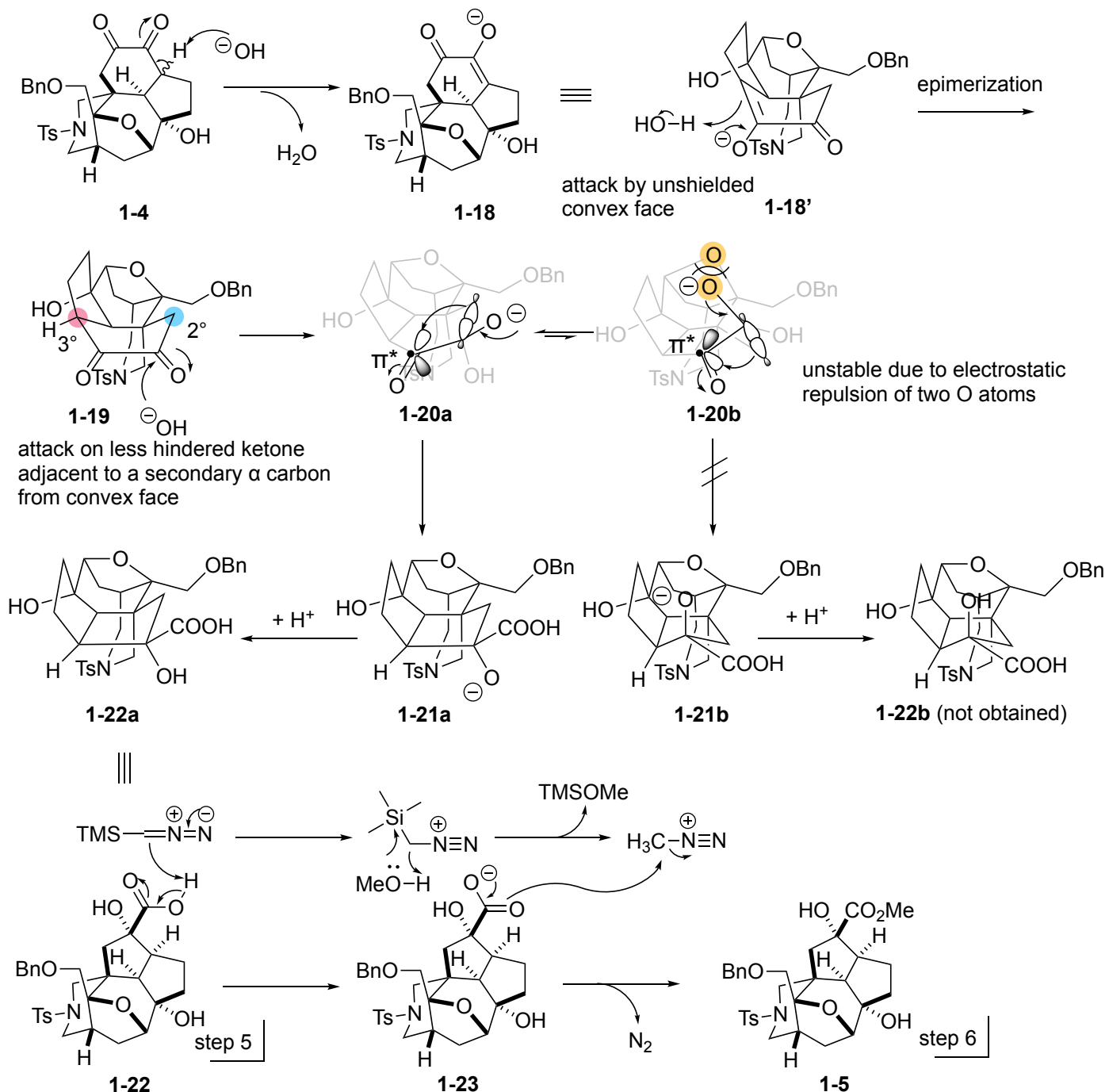
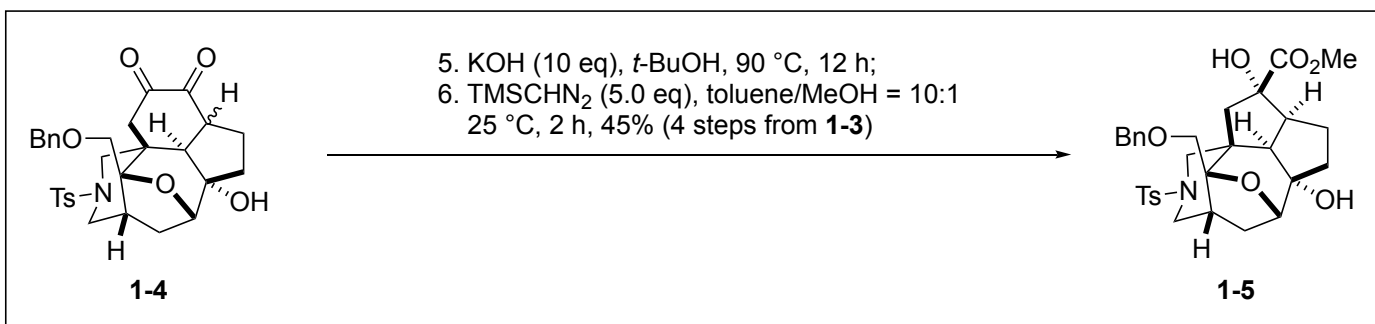


Diels-Alder reaction: release of strain of bridgehead double bond even without activation of dienophile by EWG cycloaddition from β face of dienophile:



cycloaddition from α face of dienophile: too far, kinetically disfavored

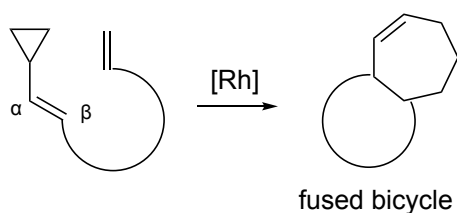




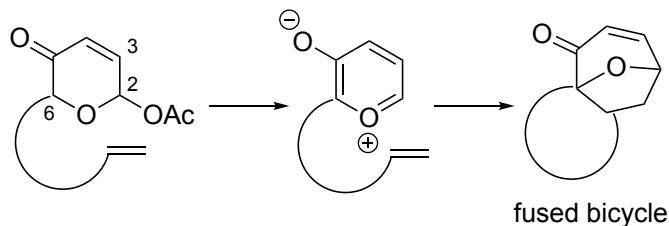
Discussion 1: oxidopyrylium-mediated intramolecular type II [5+2] cycloaddition
— a direct access to bridged cycloheptane bicyclic system

(A) intramolecular type I [5+2] cycloaddition

(1) vinylcyclopropane-mediated

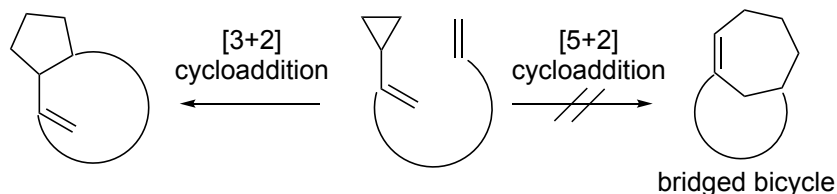


(2) oxidopyrylium-mediated



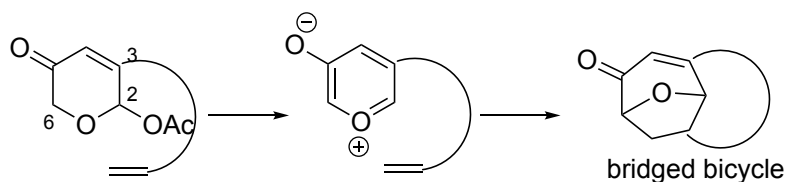
(B) intramolecular type II [5+2] cycloaddition

(1) vinylcyclopropane-mediated

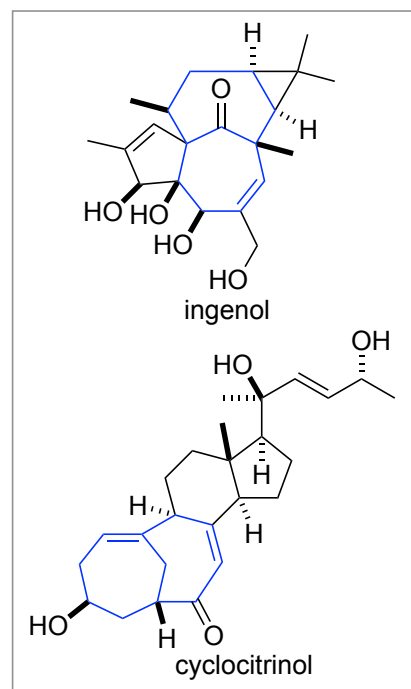


Unactivated vinylcyclopropane acts as a three-carbon synthon rather than a five-carbon synthon.

(2) oxidopyrylium-mediated



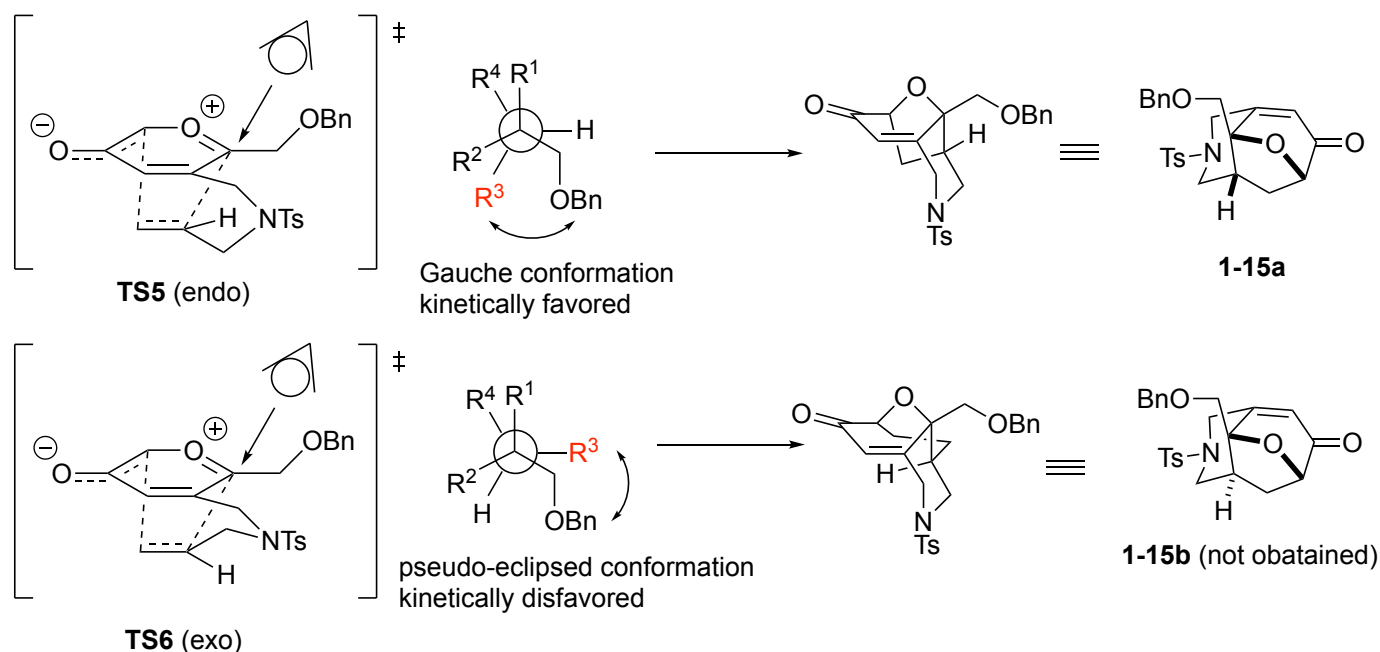
Oxidopyrylium is capable of constructing 7-membered bridged bicycles, as well as other medium rings by varying the length of tether.



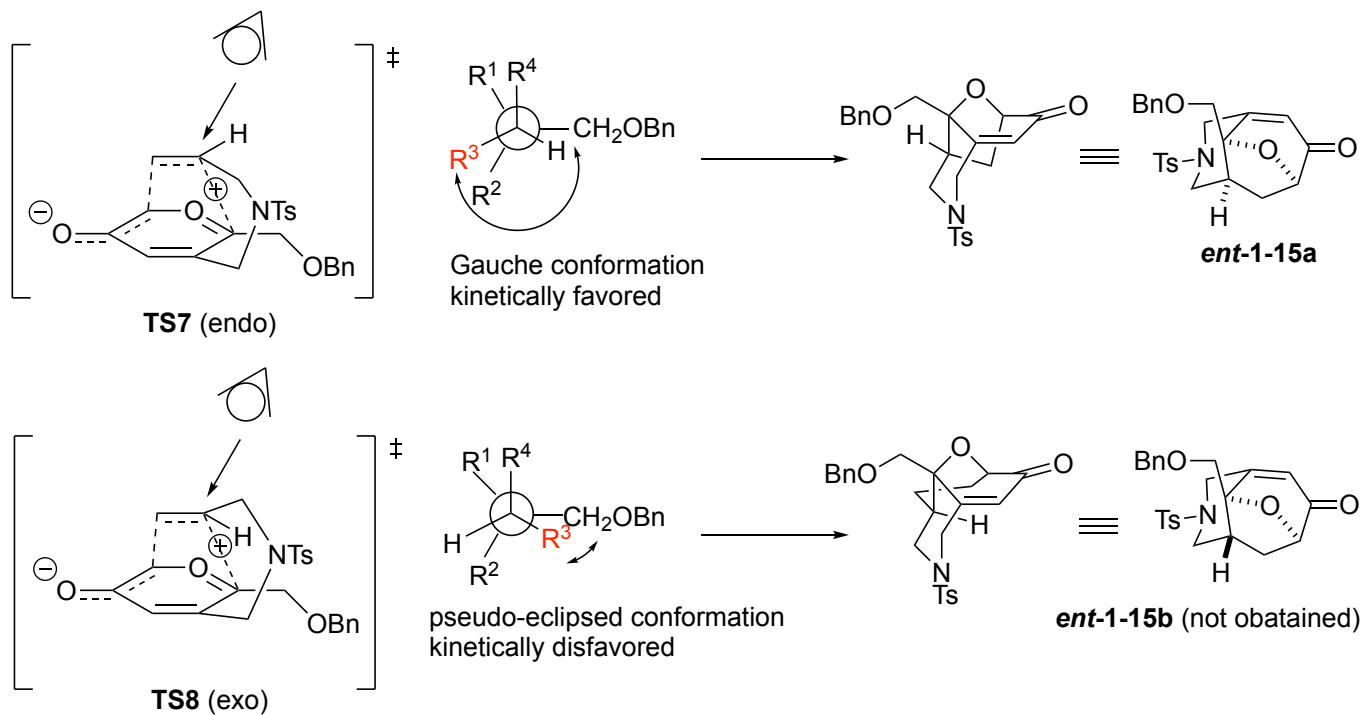
Mei, G.; Liu, X.; Qiao, C.; Chen, W.; Li, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1754

racemic synthesis of 1-15: endo selectivity

approach from α face

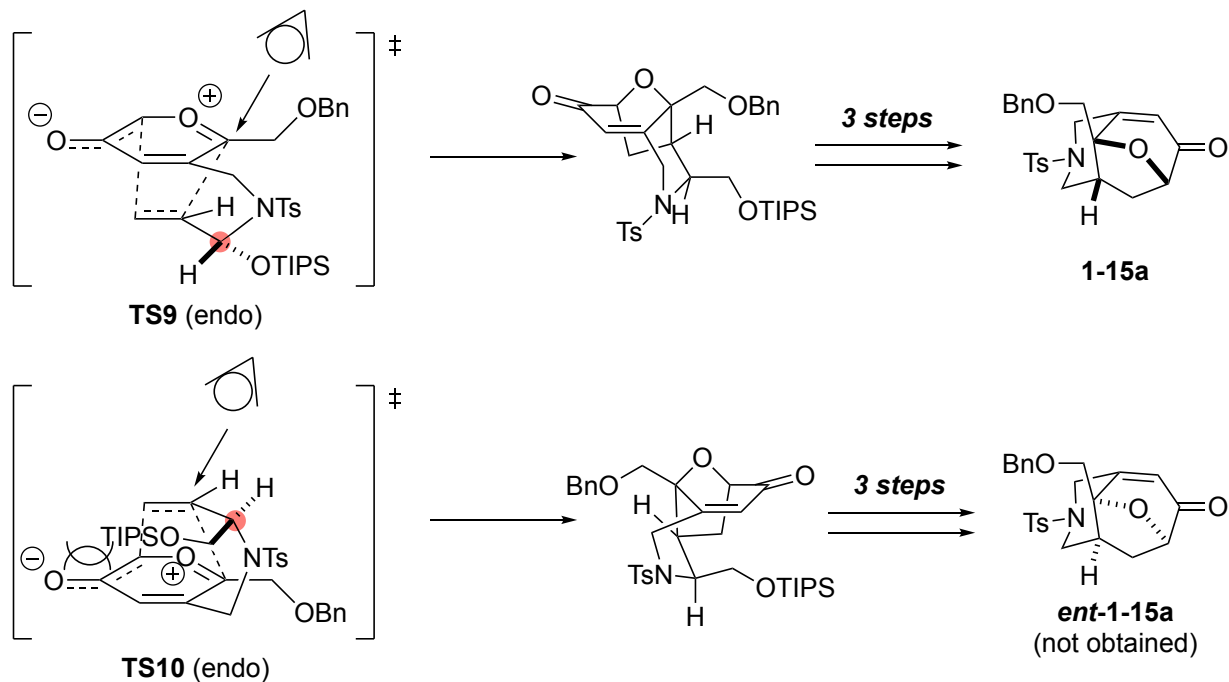


approach from β face

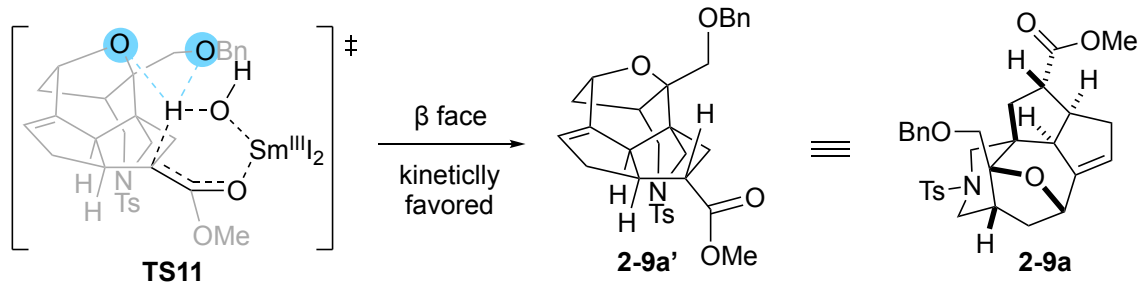
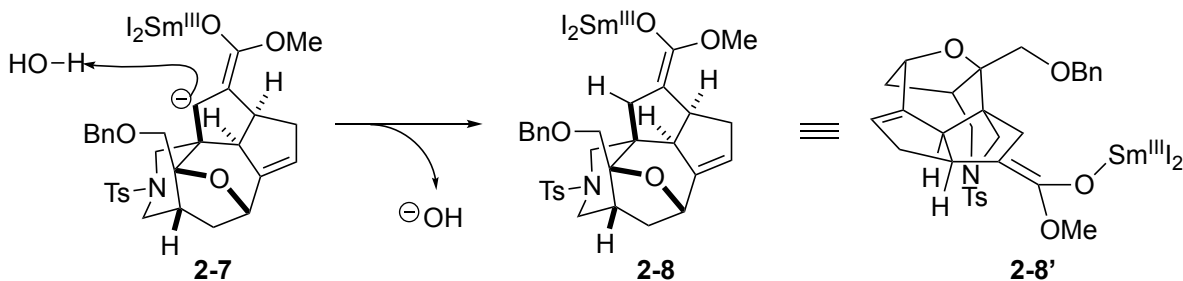
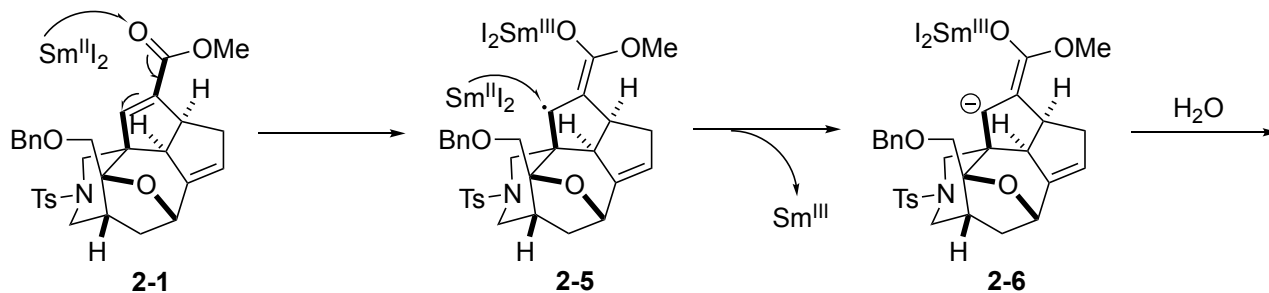
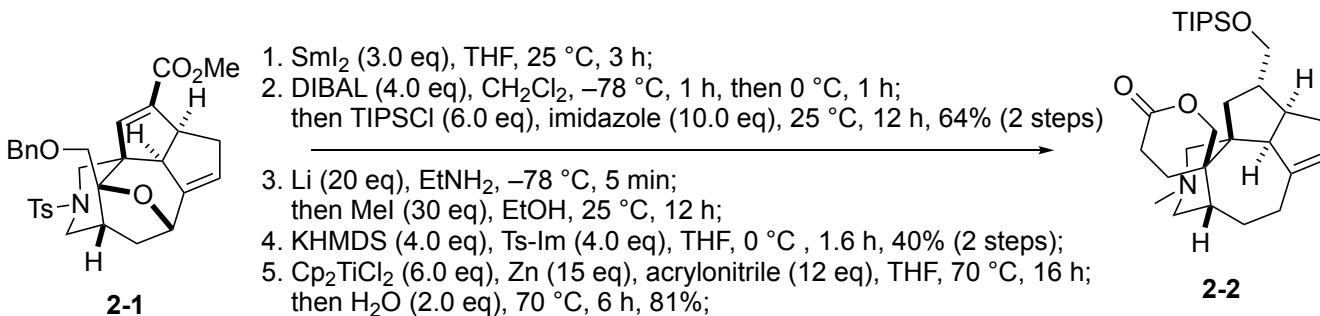


asymmetric synthesis of (+)-1-15

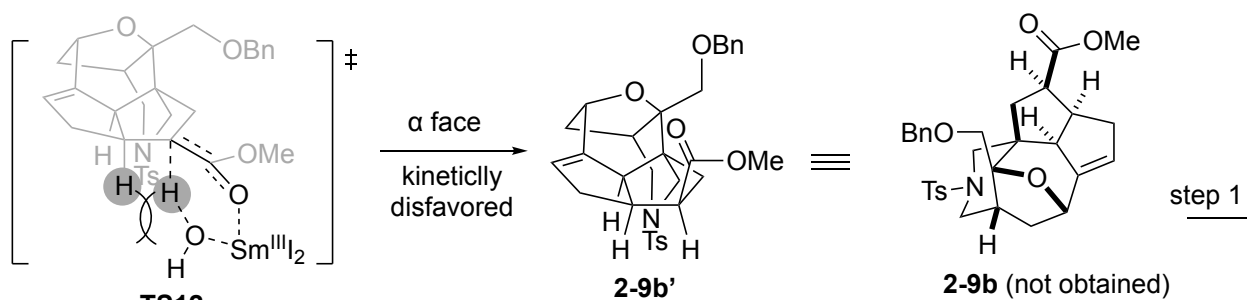
Introduction of chiral center in allylic position of the terminal olefin enhances the diastereo selectivity of this reaction



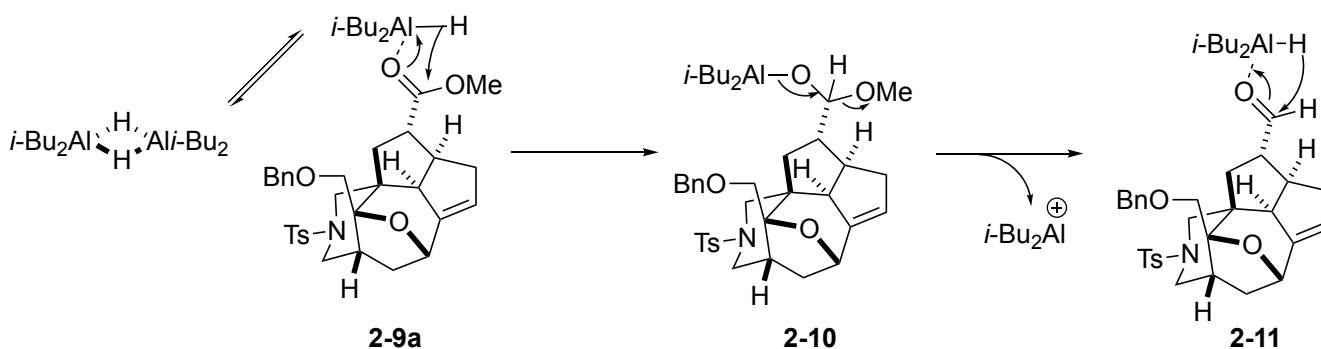
Problem 2

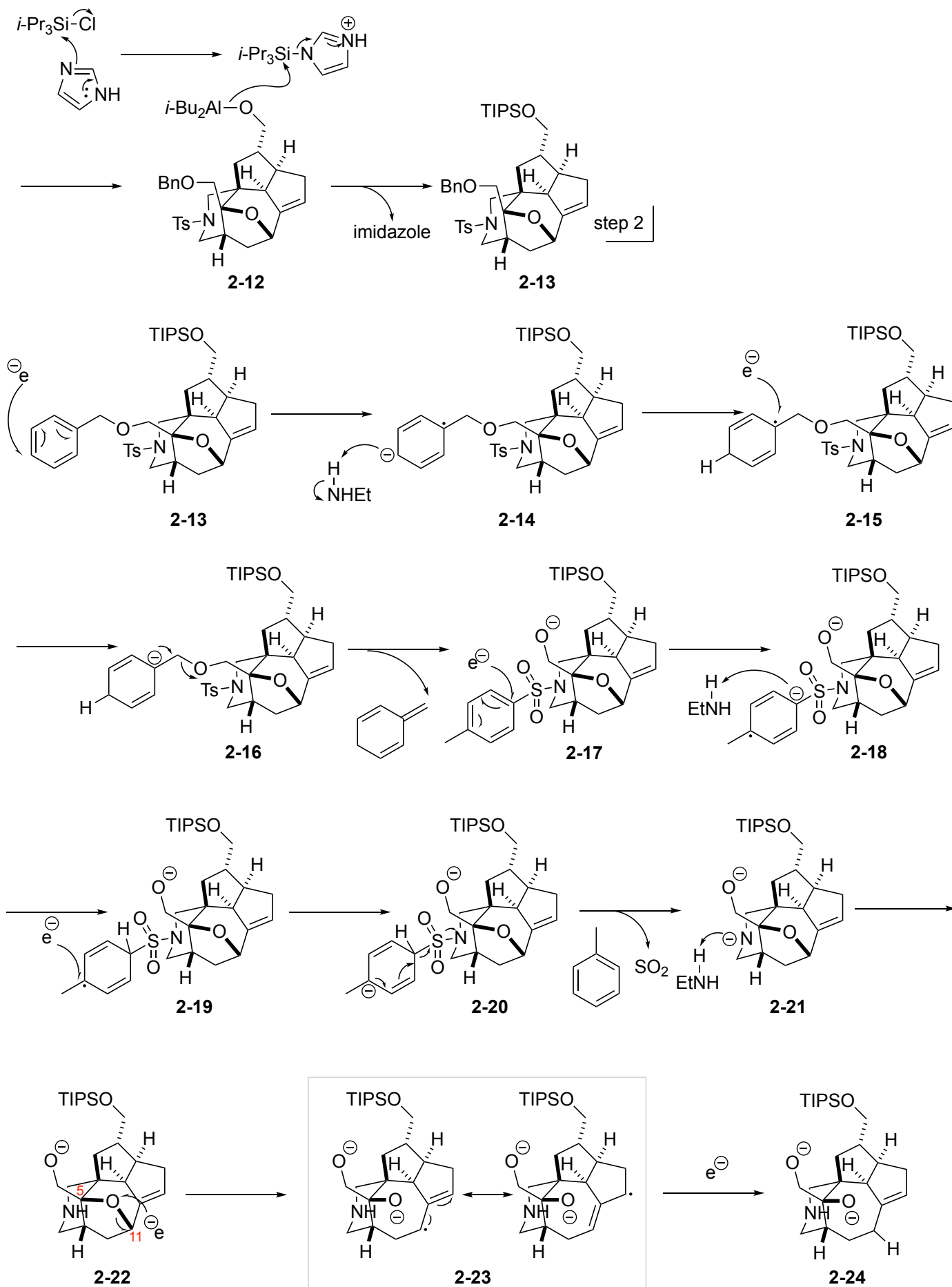


TS stabilized by possible hydrogen bonding with adjacent O atom?

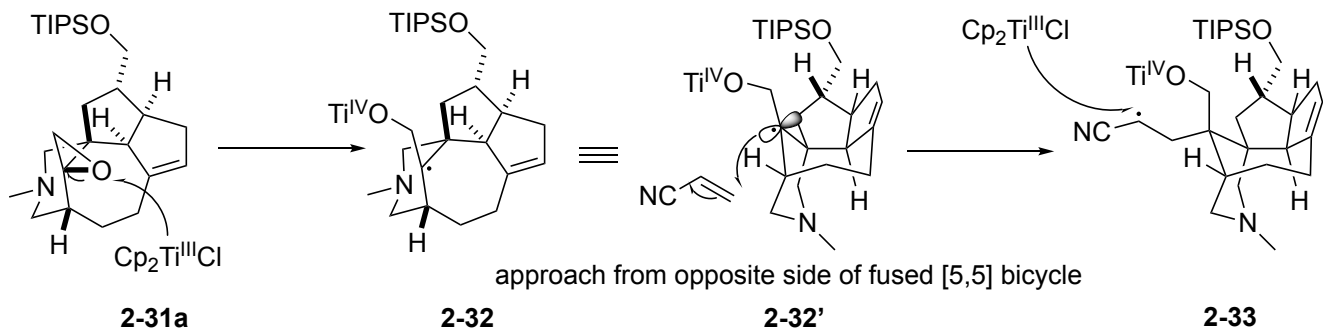
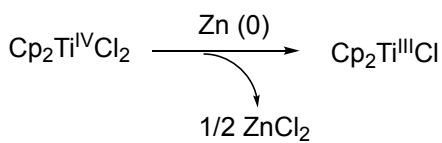
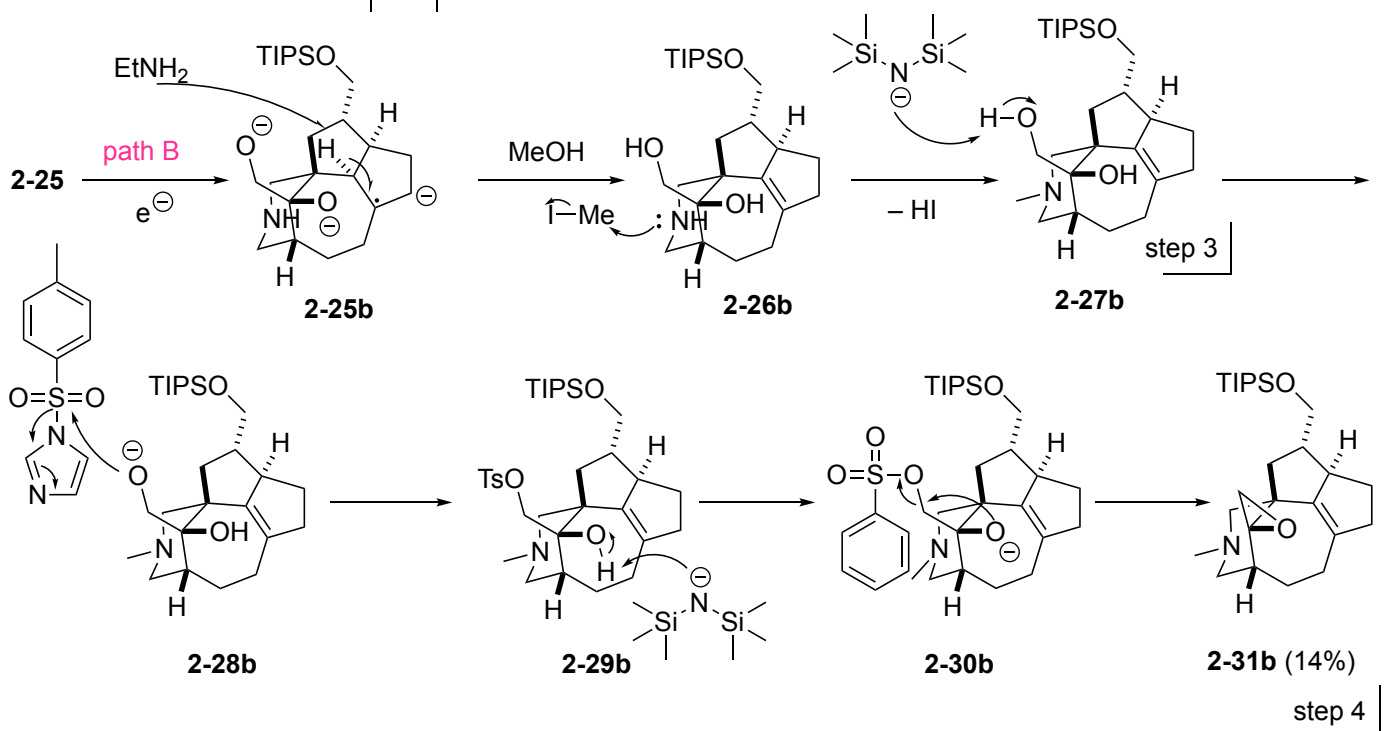
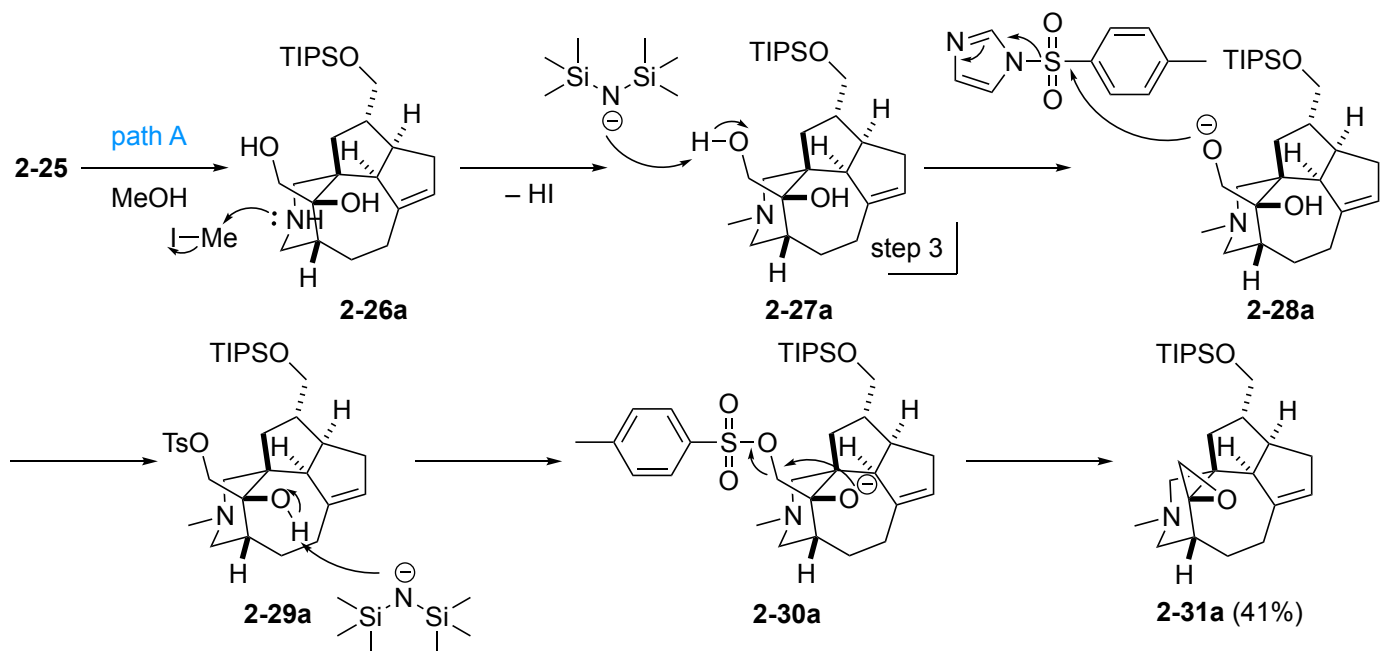


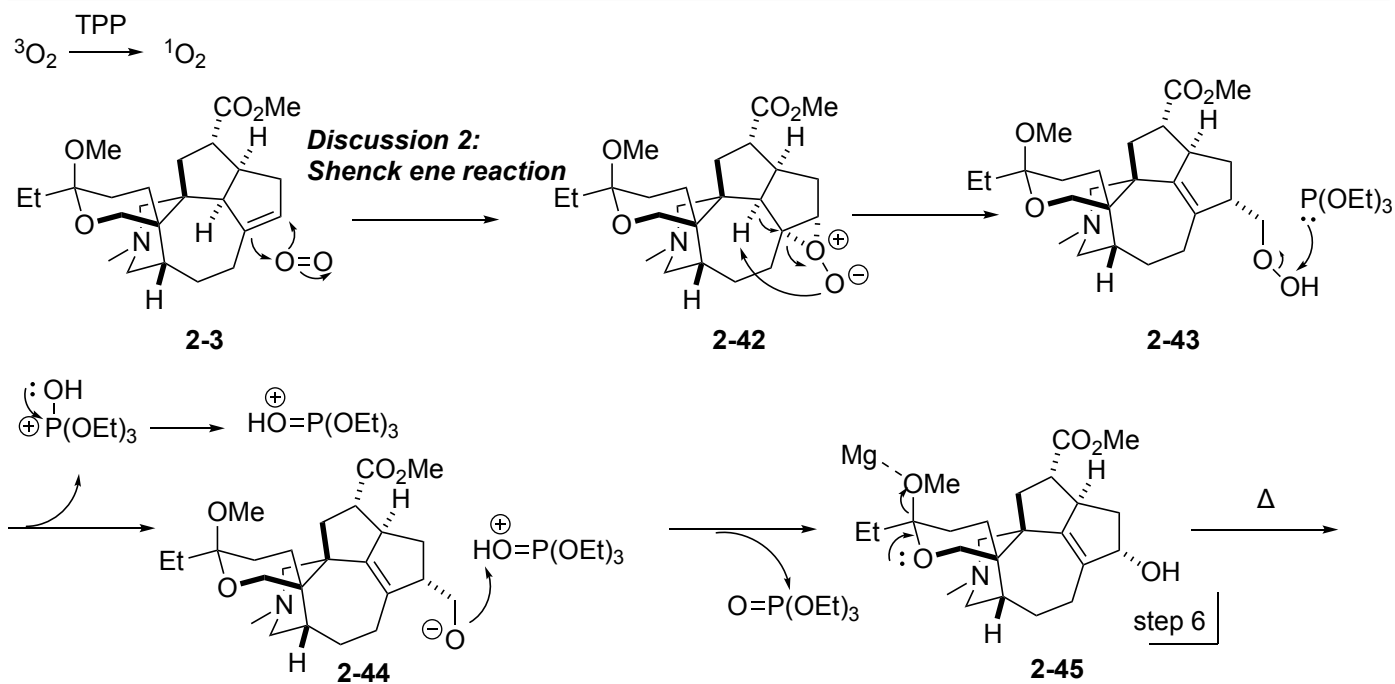
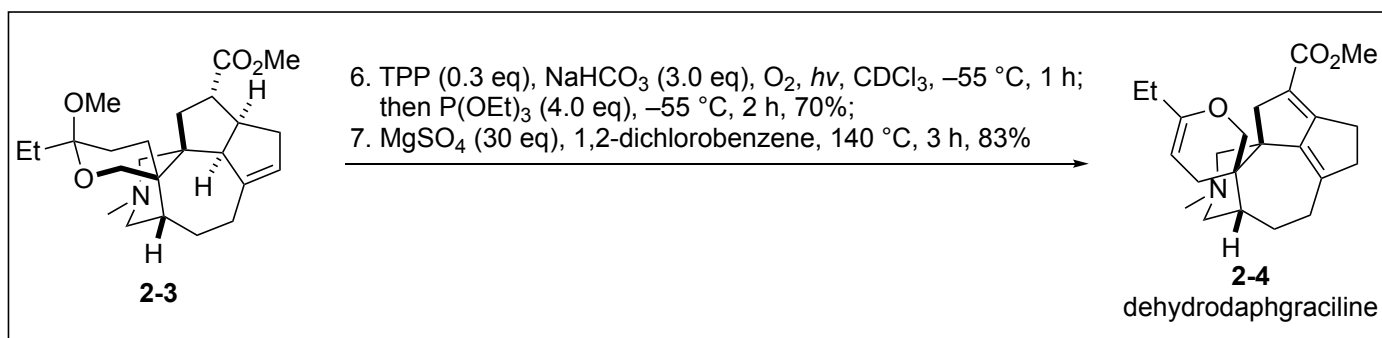
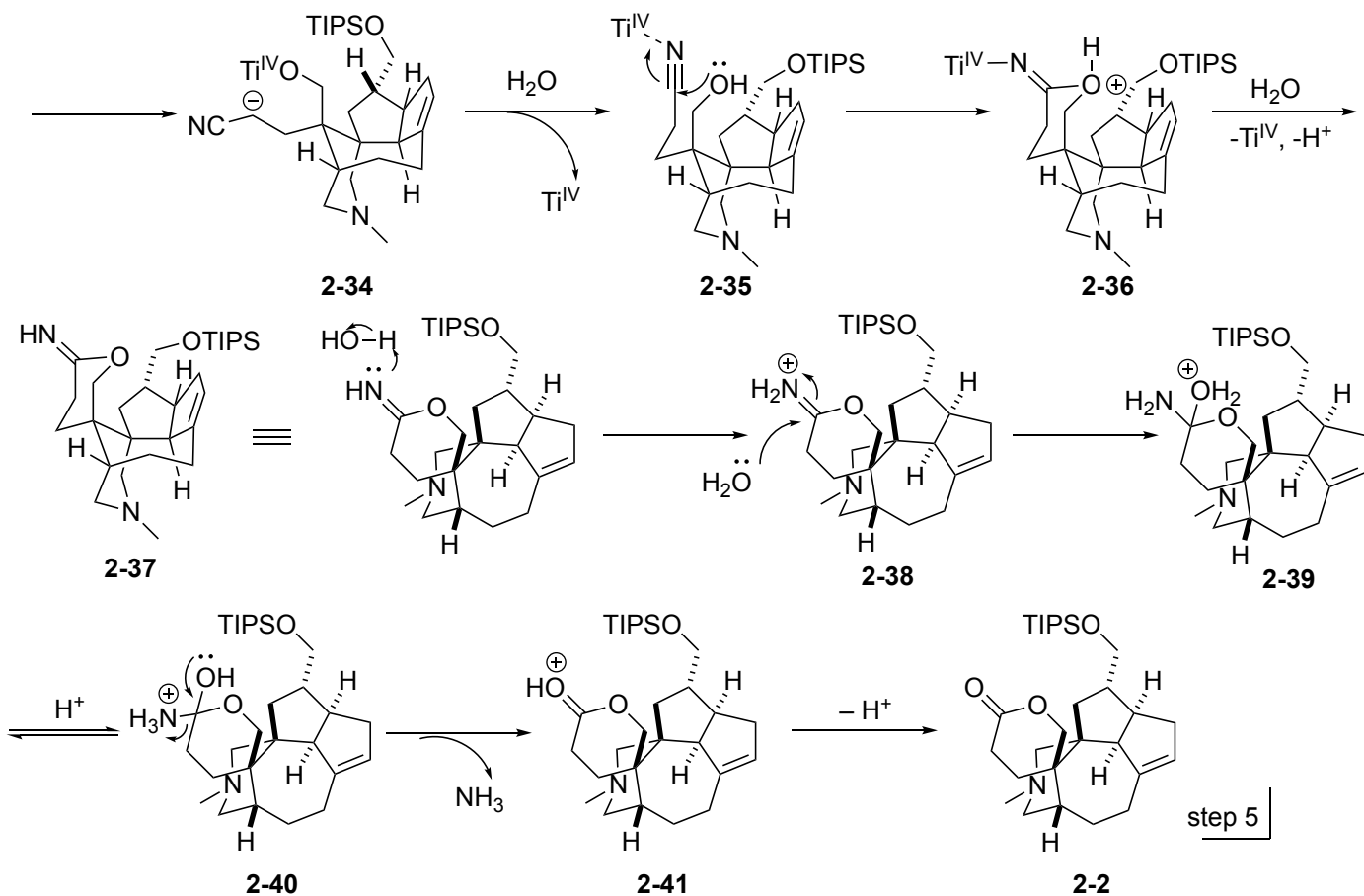
less stable TS due to steric repulsion

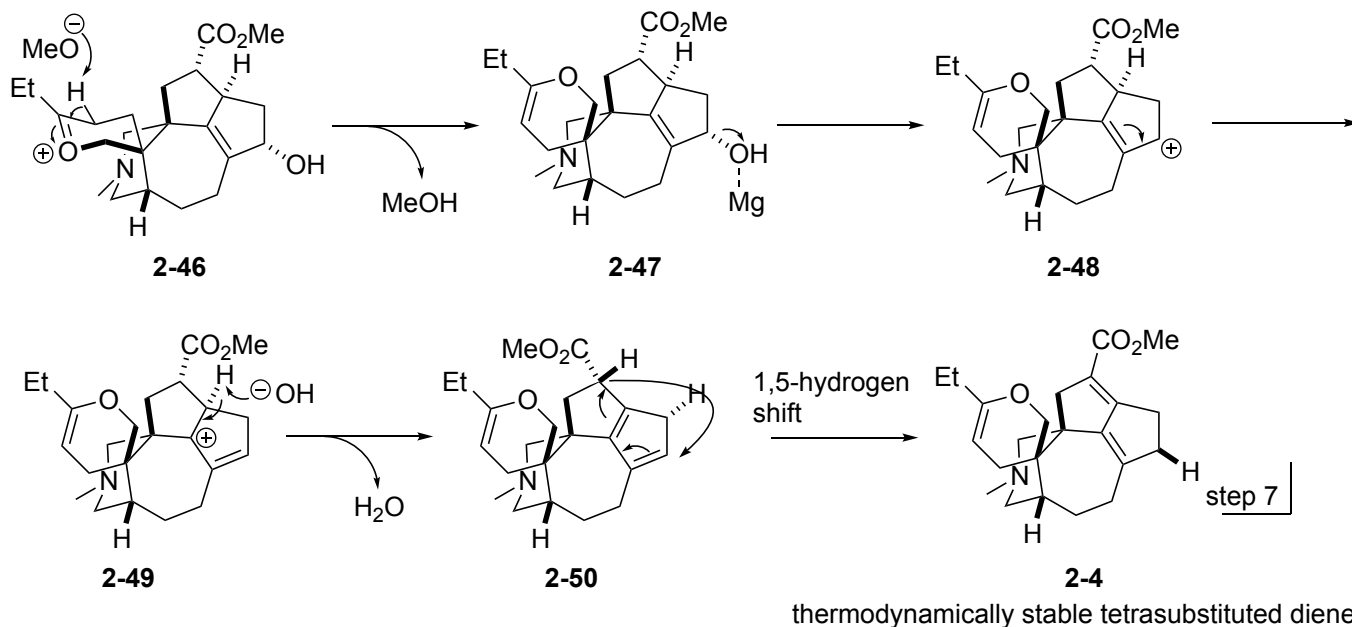




selective cleavage of C11-O over C5-O:
resonance stabilization effect



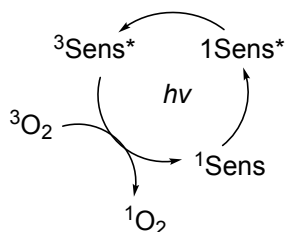




Discussion 2: Shenck ene reaction

generation of singlet oxygen:

energy transfer from photosensitizer excited by visible light



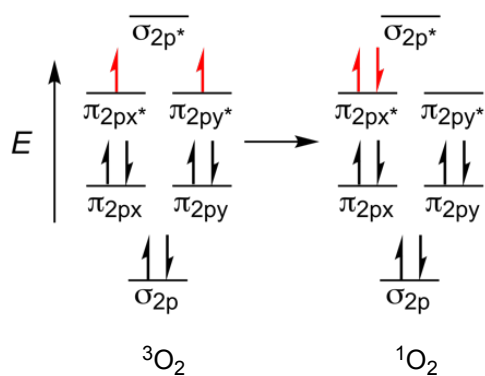
lifetime of 1O_2 :

gas phase: ~ ms

solution phase: ~ μ s, solvent dependent,

affected by **deuterium isotope effects**

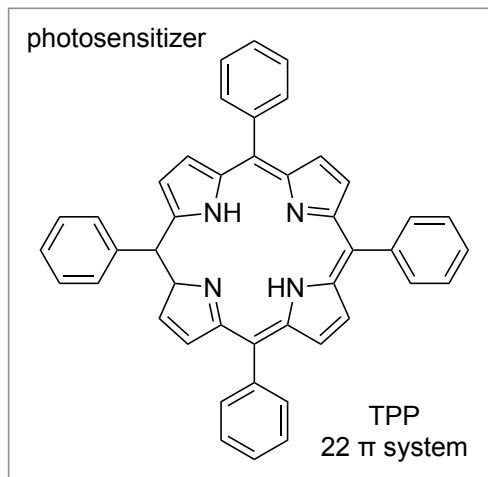
molecular orbitals:



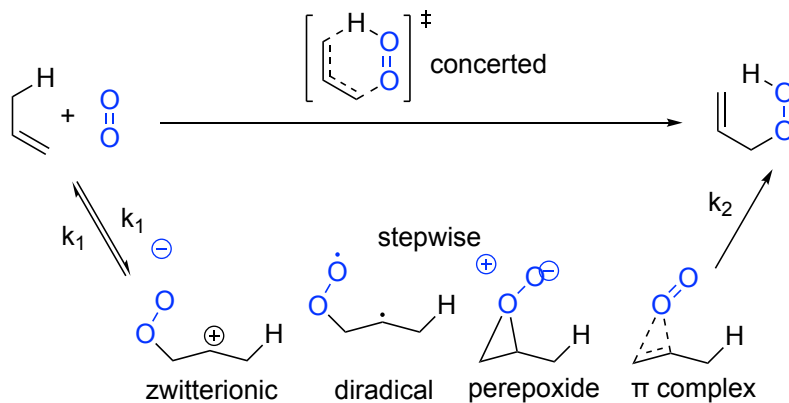
3O_2 : $\dot{O}-\dot{O}$
shows properties as biradical

1O_2 : $O=O$

active in sigmatropic reactions (ene reactions, [2+2] cycloaddition, [4+2] cycloaddition, etc.)



proposed mechanism:



Prein, M.; Adam, W. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477.

