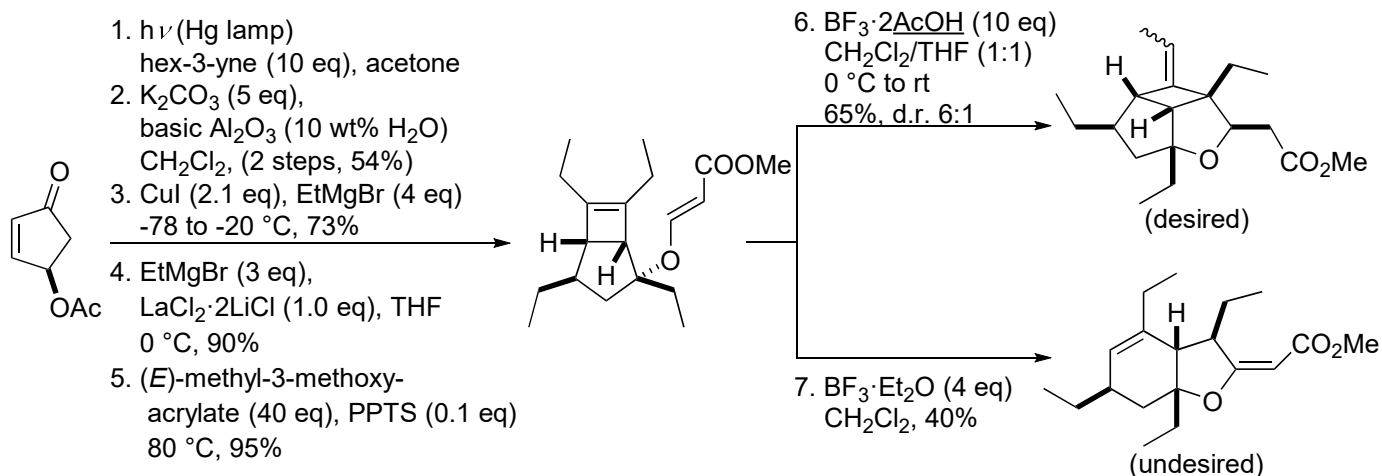
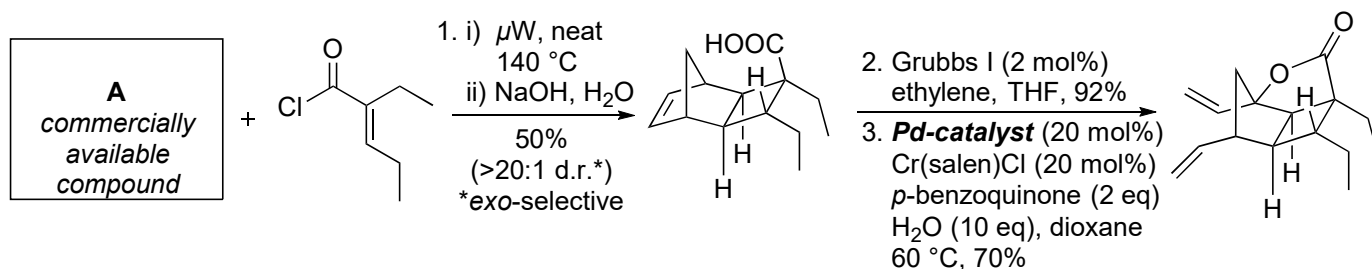


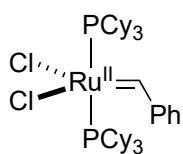
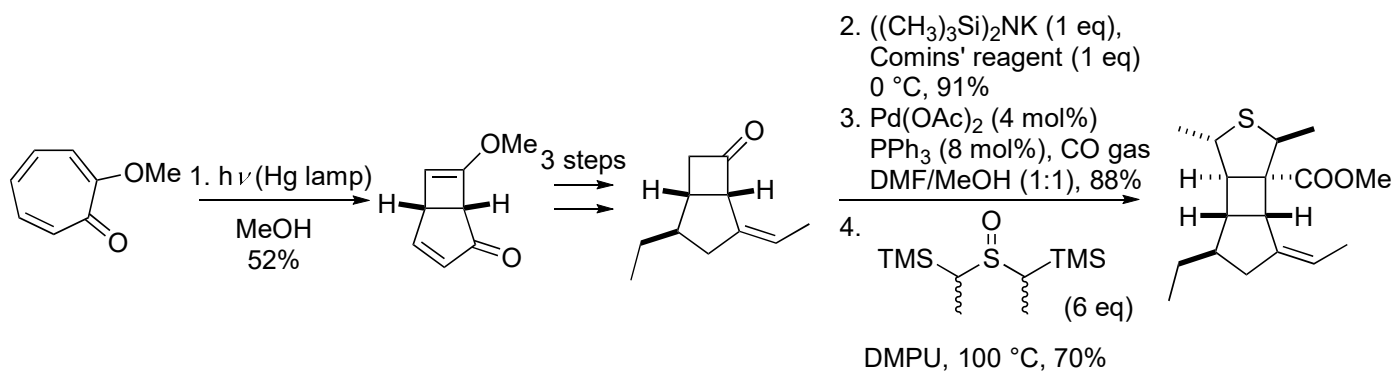
**Problem 1:** Provide plausible mechanisms of the following reactions, 1-7, and consider a possible role of AcOH in reaction 6.



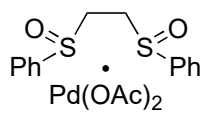
**Problem 2:** Fill in the blank **A** and provide plausible mechanisms of the following reactions, 1-3.



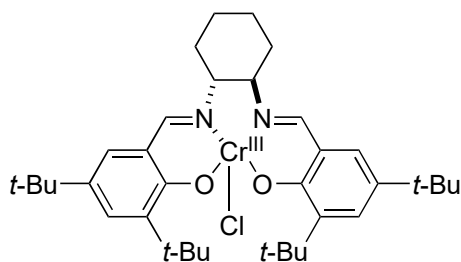
**Problem 3:** Provide plausible mechanisms of the following reactions, 1-4.



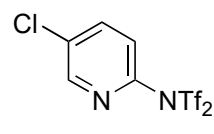
Grubbs I



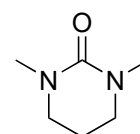
**Pd-catalyst**



$Cr(salen)Cl$



Comins' reagent

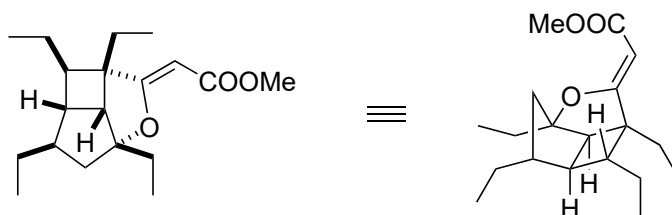


DMPU

Total Synthesis of Hippolachnin A

0. Introduction (*Org. Lett.* **2013**, *15*, 3526)

0-1. Hippolachnin A



Hippolachnin A (1)

*Isolation:* South china marine sponge *Hippospongia lachne* in 2013 (5.1 mg from 3.6 kg sponge)

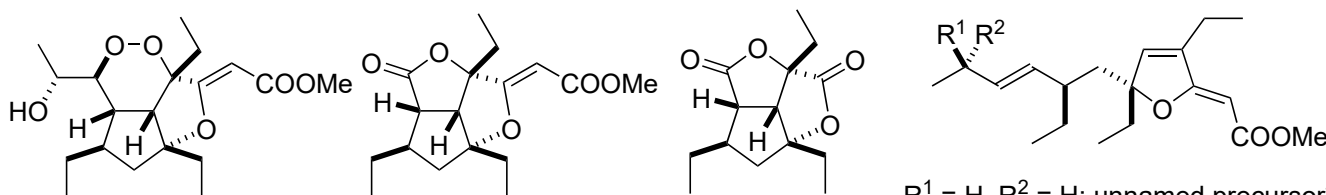
*Biological activity:* Antifungal activity against pathogenic fungi and no toxicity against human cancer cell lines (preliminary data)

*Structural feature:* Congested and compact tricyclic core bearing six contiguous stereocenters (one quaternary center)

*Total synthesis:*

1. Carreira's group (racemic, *Angew. Chem. Int. Ed.* **2015**, *54*, 2378) = **Problem 1**
2. Wood's and Brown's groups (collaborative/racemic, *J. Am. Chem. Soc.* **2016**, *138*, 2437) = **Problem 2**
3. Trauner's group (racemic, *J. Am. Chem. Soc.* **2017**, *139*, 11706) = **Problem 3**

0-2. Related natural products



gracilioether A (2)

gracilioether E (3)

gracilioether F (4)

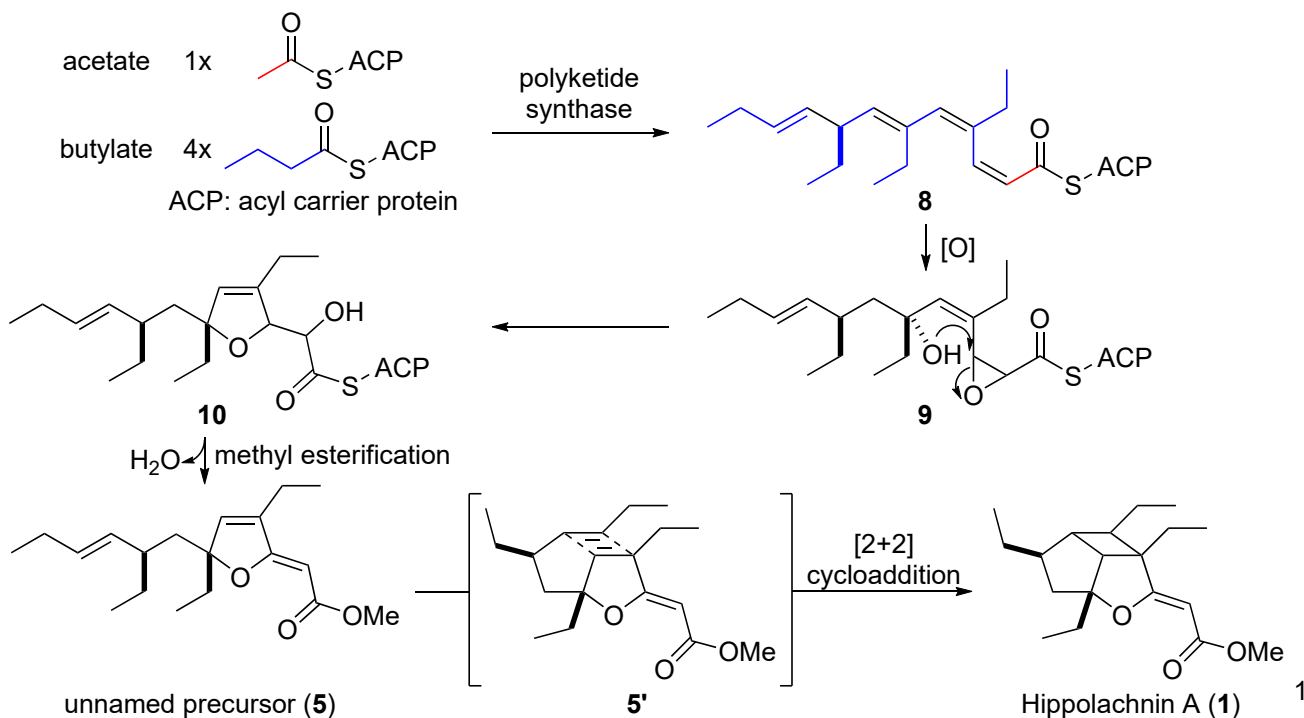
$R^1 = H, R^2 = H$ : unnamed precursor\* (5)

\*isolated with hippolachnin A (1)

$R^1 = R^2 = O$ : gracilioether B (6)

$R^1 = H, R^2 = OH$ : gracilioether C (7)

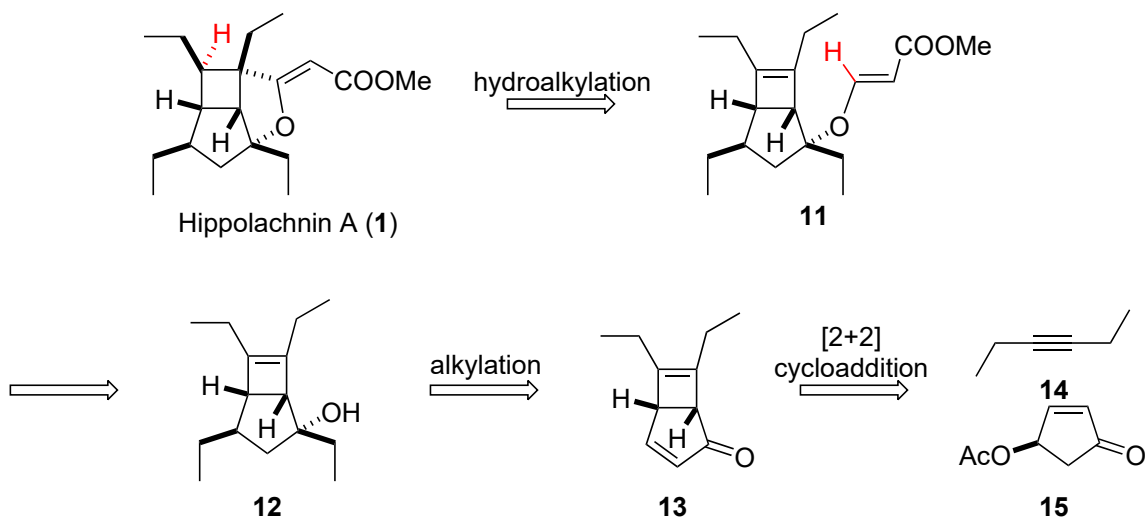
0-3. Plausible biosynthetic pathway



1. **Problem 1** (Carreira's synthesis, *Angew. Chem. Int. Ed.* **2015**, *54*, 2378)

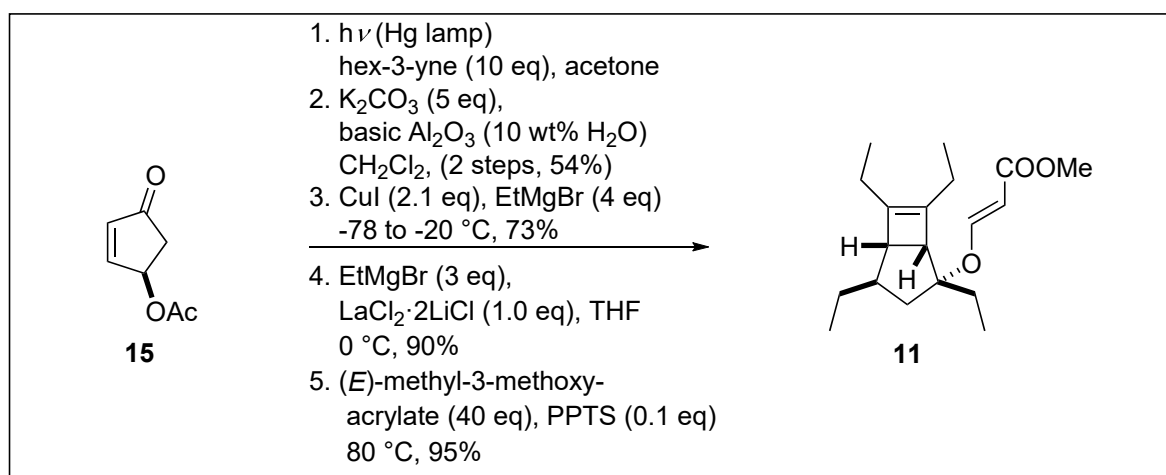
1-1. Introduction

1-1-1. Retrosynthesis

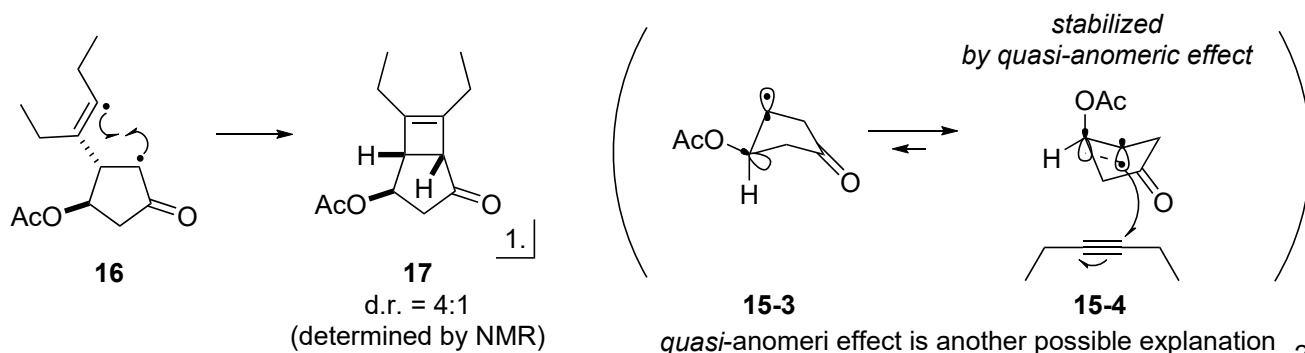
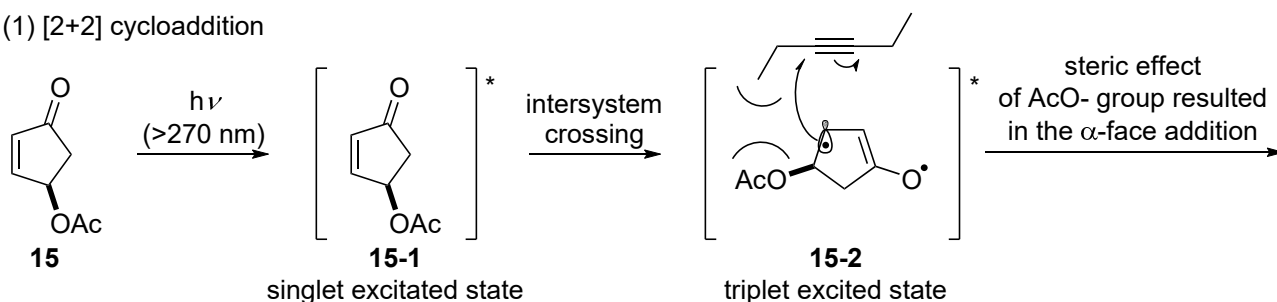


1-1-2. Step count and yield: 9 steps (linear), 9% overall yield

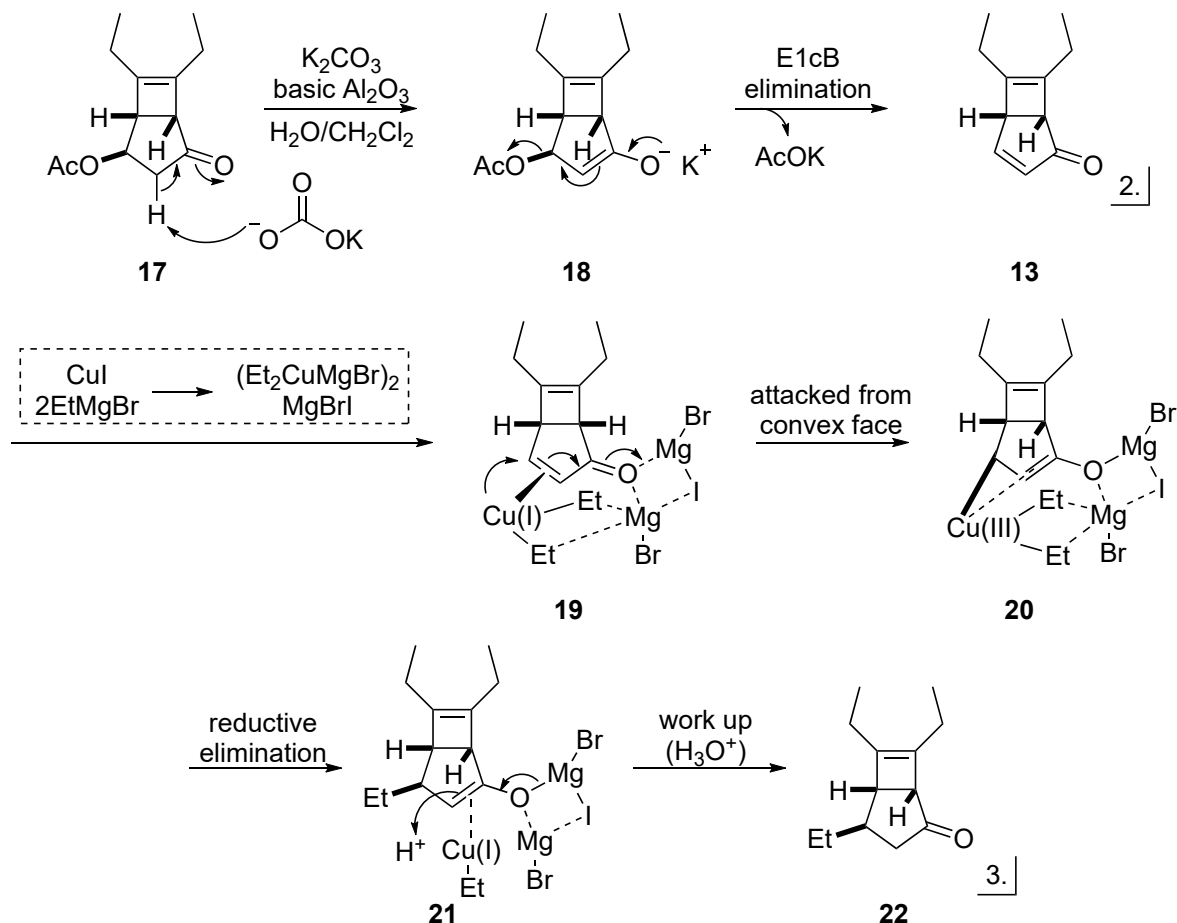
1-2. Plausible reaction mechanisms



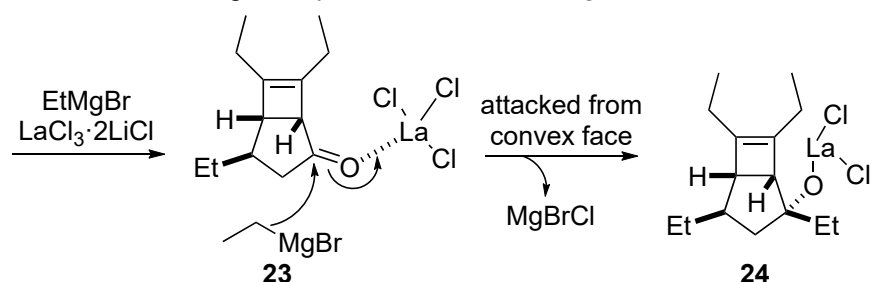
(1) [2+2] cycloaddition



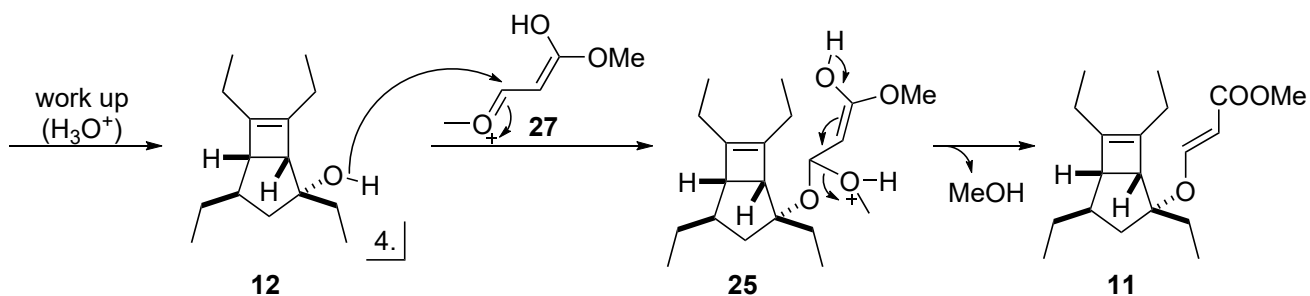
(2-5) E1cB elimination, stereoselective 1,4-addition, stereoselective 1,2-addition and enol ether formation



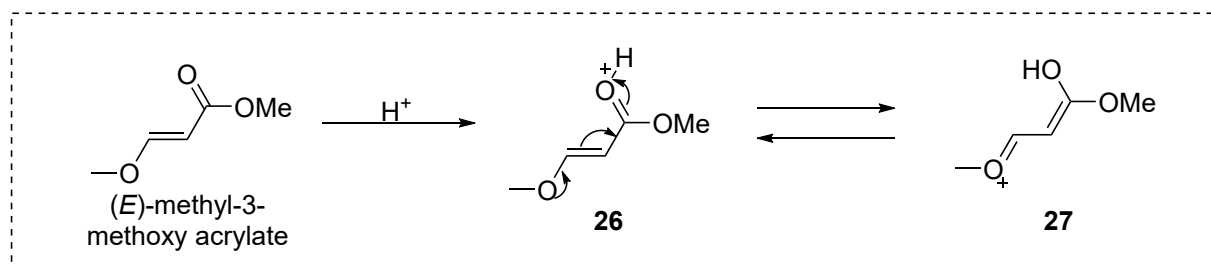
\*For this reaction mechanism of organocuprate addition, see: *Angew. Chem. Int. Ed.* **2000**, 39, 3750.

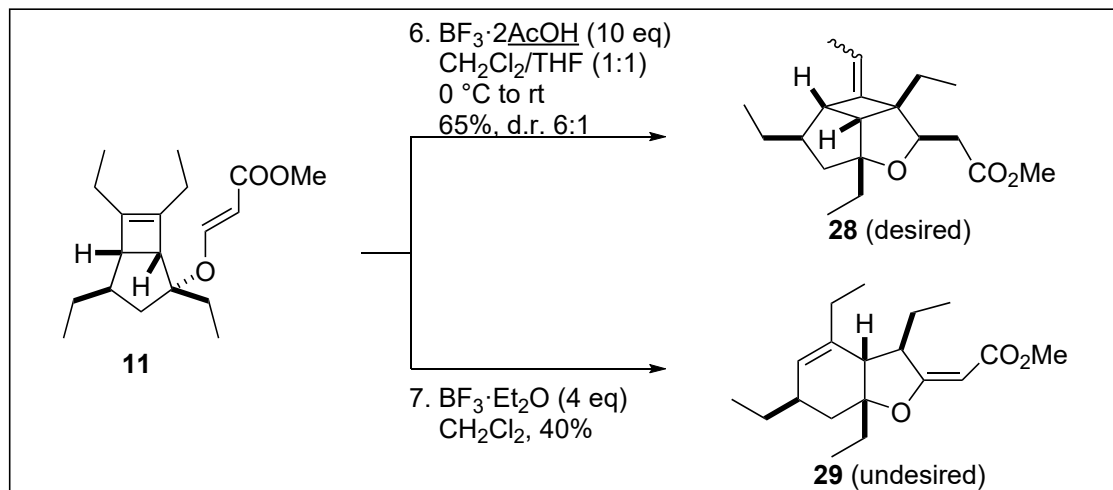


\*\*Oxophilic nature of lanthanide salts made the 1,2-addition reaction favored over competitive reactions such as reduction (by  $\beta$ -hydride transfer)

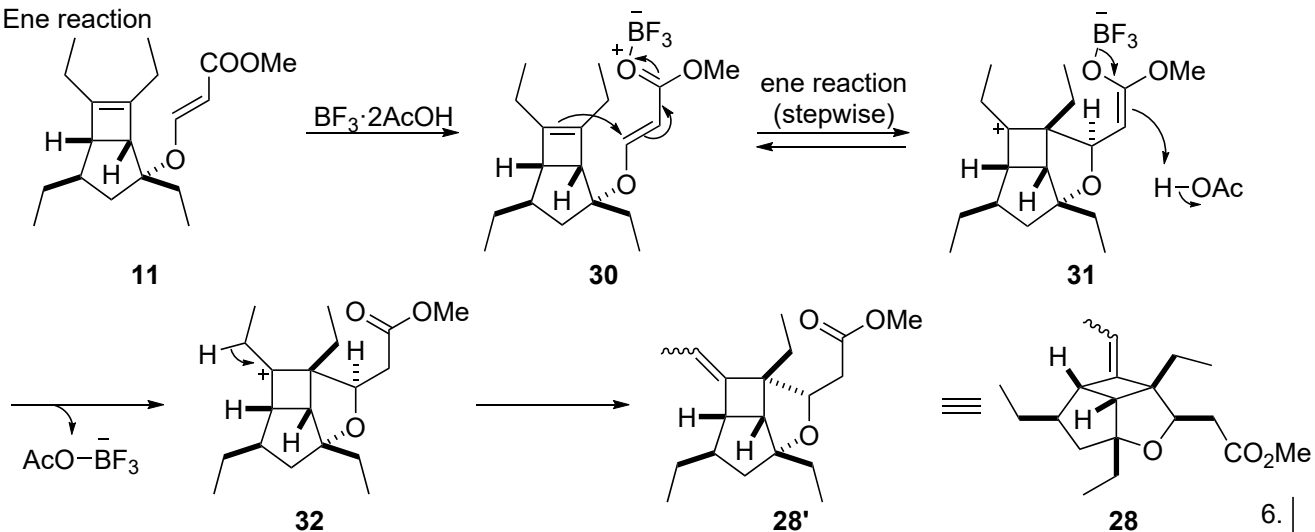


\*\*\*(*Z*)-product (**Z-11**) can be formed in this mechanism, but it converged on stabler (*E*)-product in this thermodynamic condition via acid-catalyzed tautomerization.



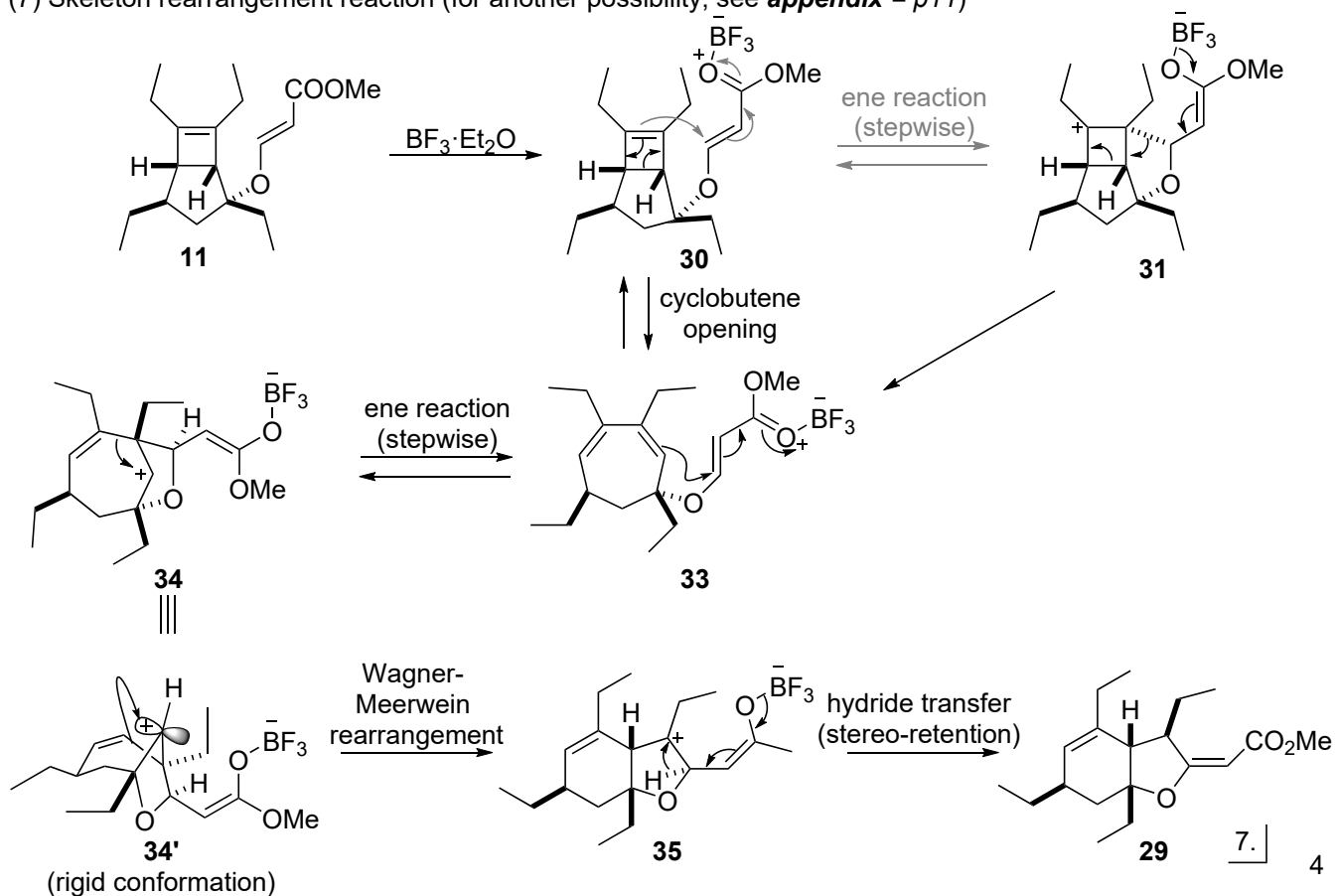


(6) Ene reaction



AcOH immediately quenches enolate **X** to inhibit ring-opening of cyclobutene and byproduct production.

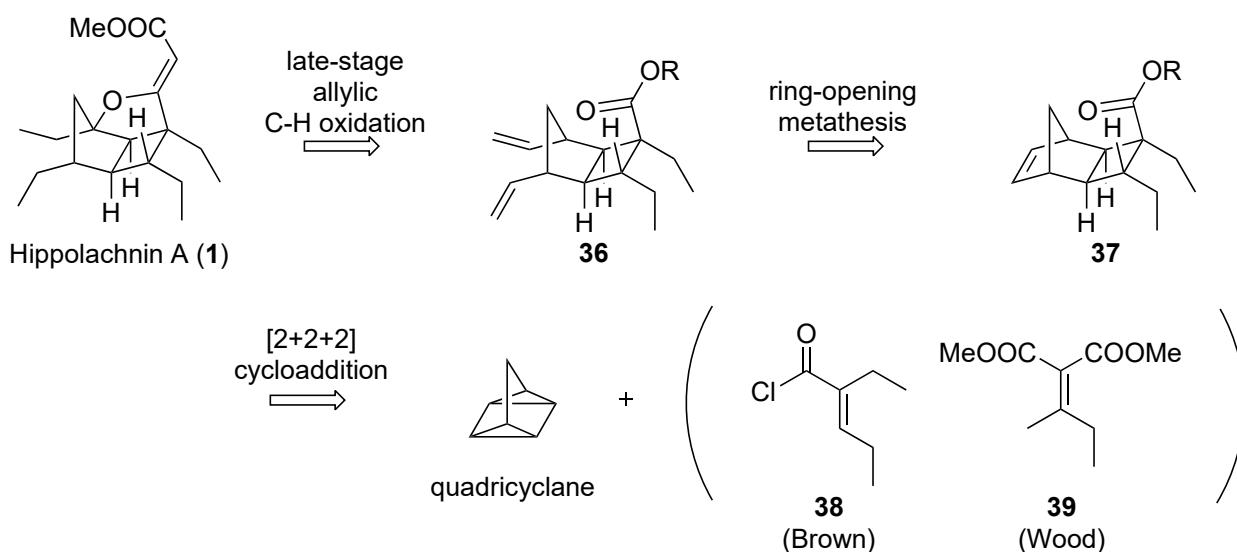
(7) Skeleton rearrangement reaction (for another possibility, see **appendix = p11**)



2. **Problem 2** (Wood and Brown's collaborative synthesis, *J. Am. Chem. Soc.* **2016**, *138*, 2437)

2-1. Introduction

2-1-1. Common retrosynthesis



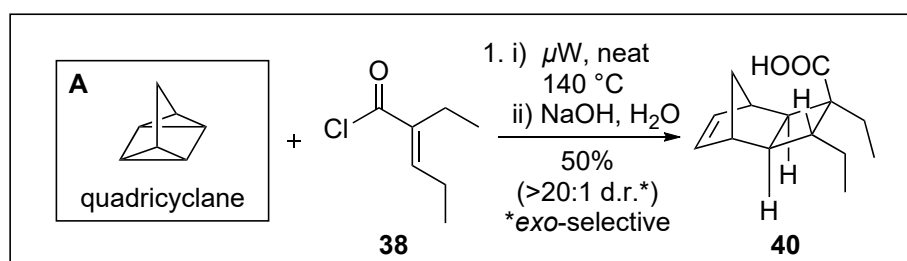
2-1-2. Step count and yield:

Brown's synthesis: 10 steps (linear), 6.4% overall yield

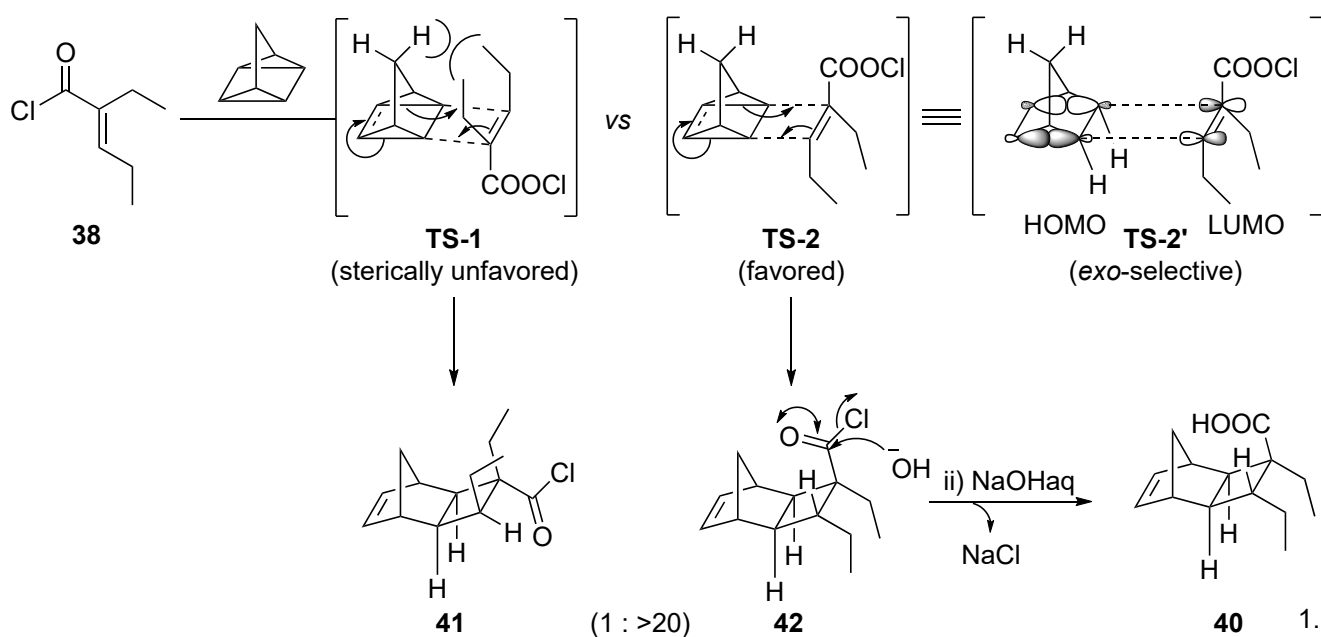
Wood's synthesis: 9 steps (linear), 1.3% overall yield

Collaborative synthesis: 6 steps (linear), 4.8% overall yield

2-2. Plausible reaction mechanisms

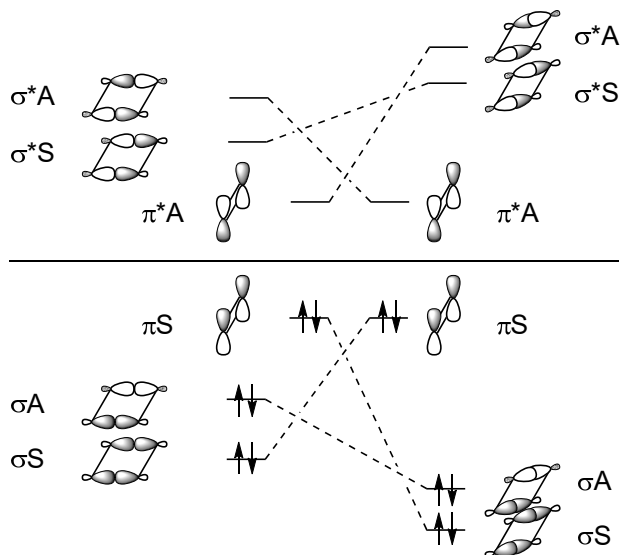
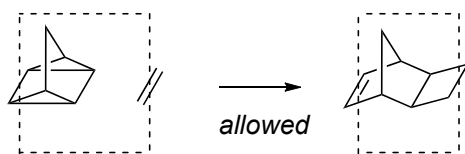


(1) Concerted  $[2\pi+2\sigma+2\sigma]$  cycloaddition reaction (*J. Am. Chem. Soc.* **1972**, *94*, 787)

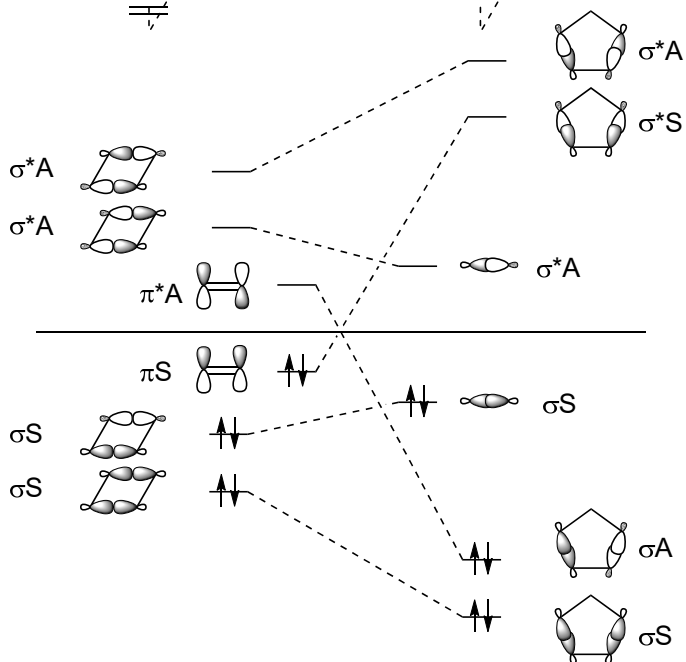
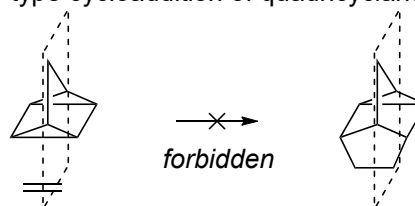


**Discussion:** Orbital correlation diagrams of thermal cycloaddition of quadricyclane and norbornadiene

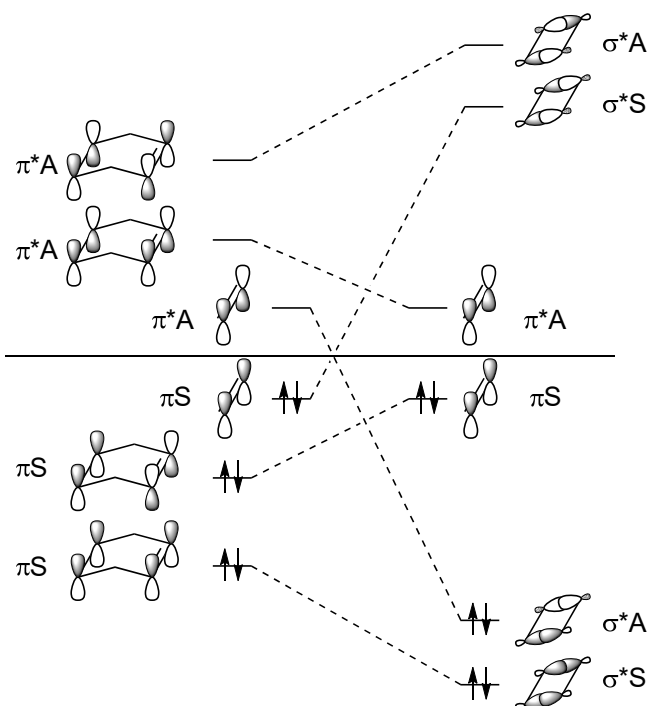
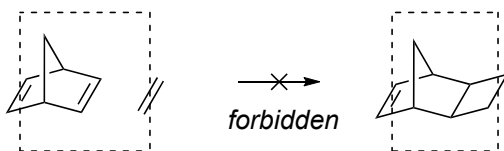
(a) *exo*-type cycloaddition of quadricyclane



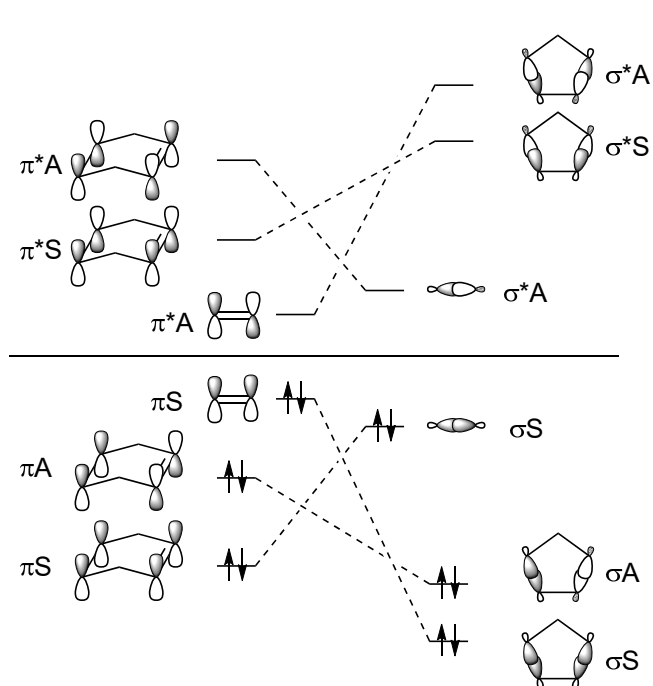
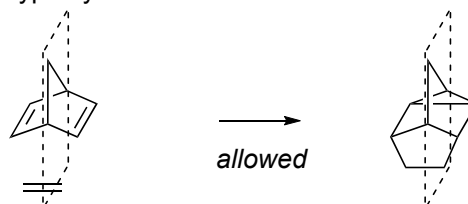
(b) *endo*-type cycloaddition of quadricyclane



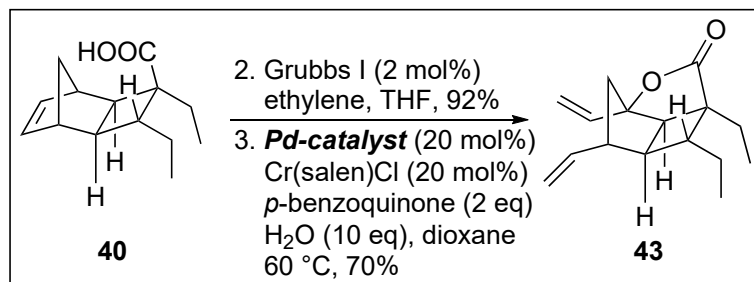
(c) *exo*-type cycloaddition of norbornadiene



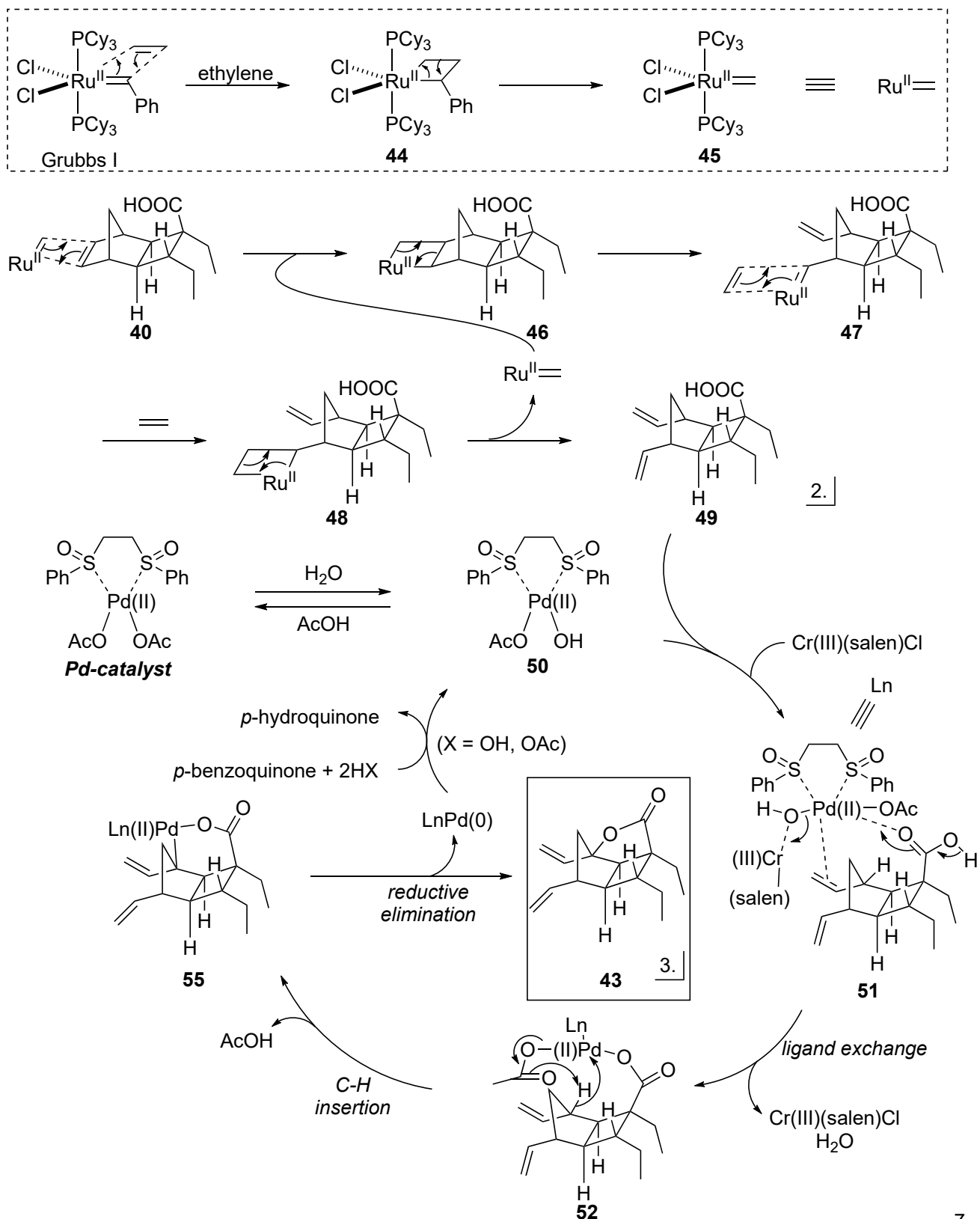
(d) *endo*-type cycloaddition of norbornadiene



\* S = symmetry, A = Antisymmetry



(2-3) Ring-opening metathesis and Pd(II)-bissulfide catalyzed allylic C-H activation



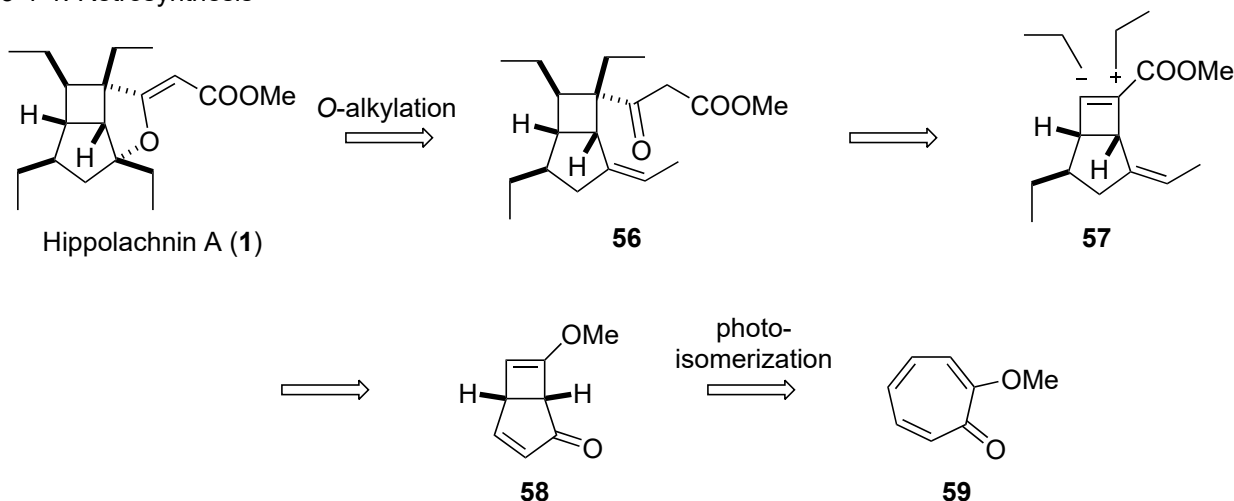
\* For White's catalyst, Pd(II)-bissulfoxide, see *J. Am. Chem. Soc.* **2004**, *126*, 1346.



3. **Problem 3** (Trauner's synthesis, *J. Am. Chem. Soc.* **2017**, *139*, 11706)

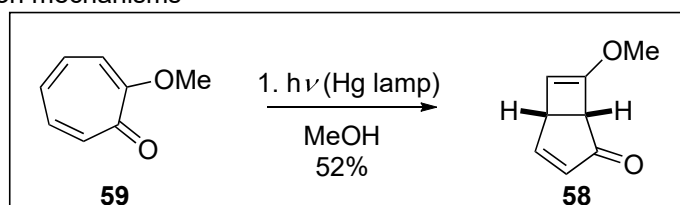
3-1. Introduction

3-1-1. Retrosynthesis

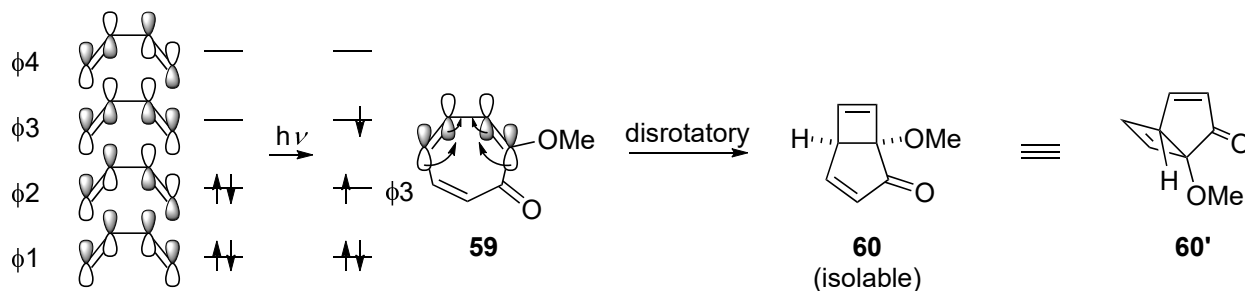


3-1-2. Step count and yield: 13 steps (linear), 4.9% overall yield

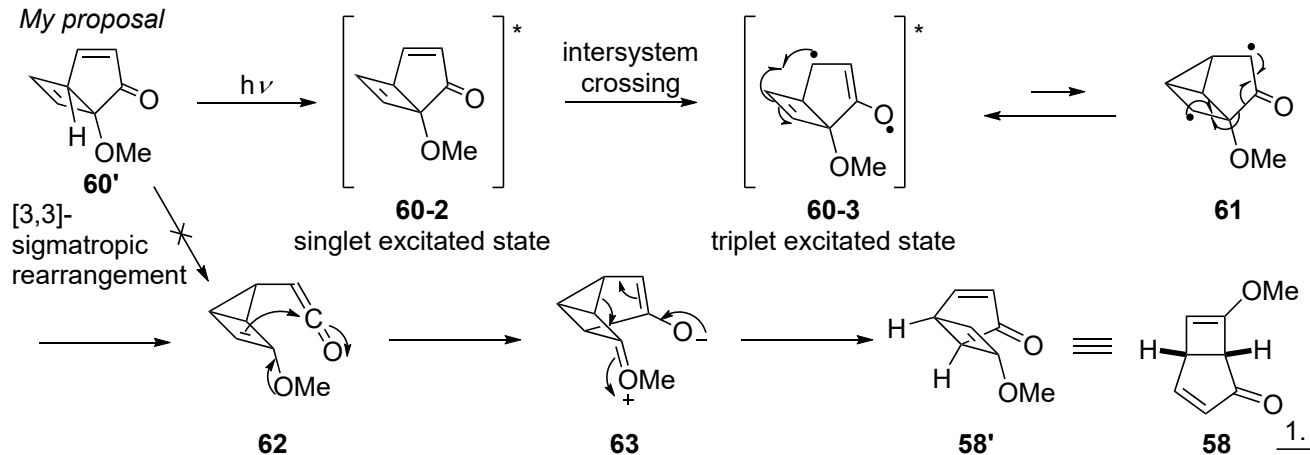
3-2. Plausible reaction mechanisms



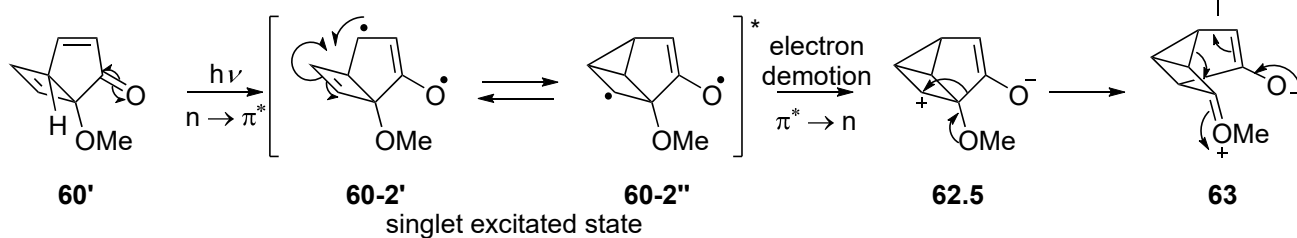
(1) Photo-isomerization reaction of  $\alpha$ -tropolone methyl ether (*J. Am. Chem. Soc.* **1963**, *85*, 2616.)



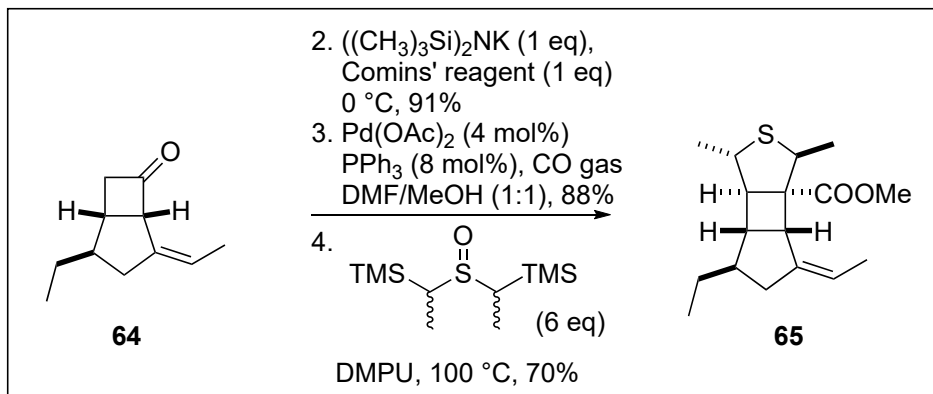
My proposal



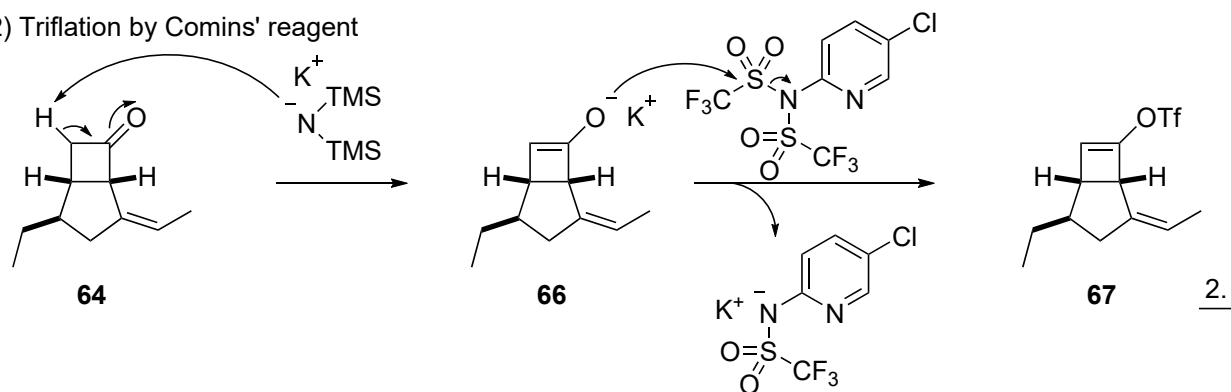
Reported mechanism (*J. Am. Chem. Soc.* **1962**, *84*, 4527)



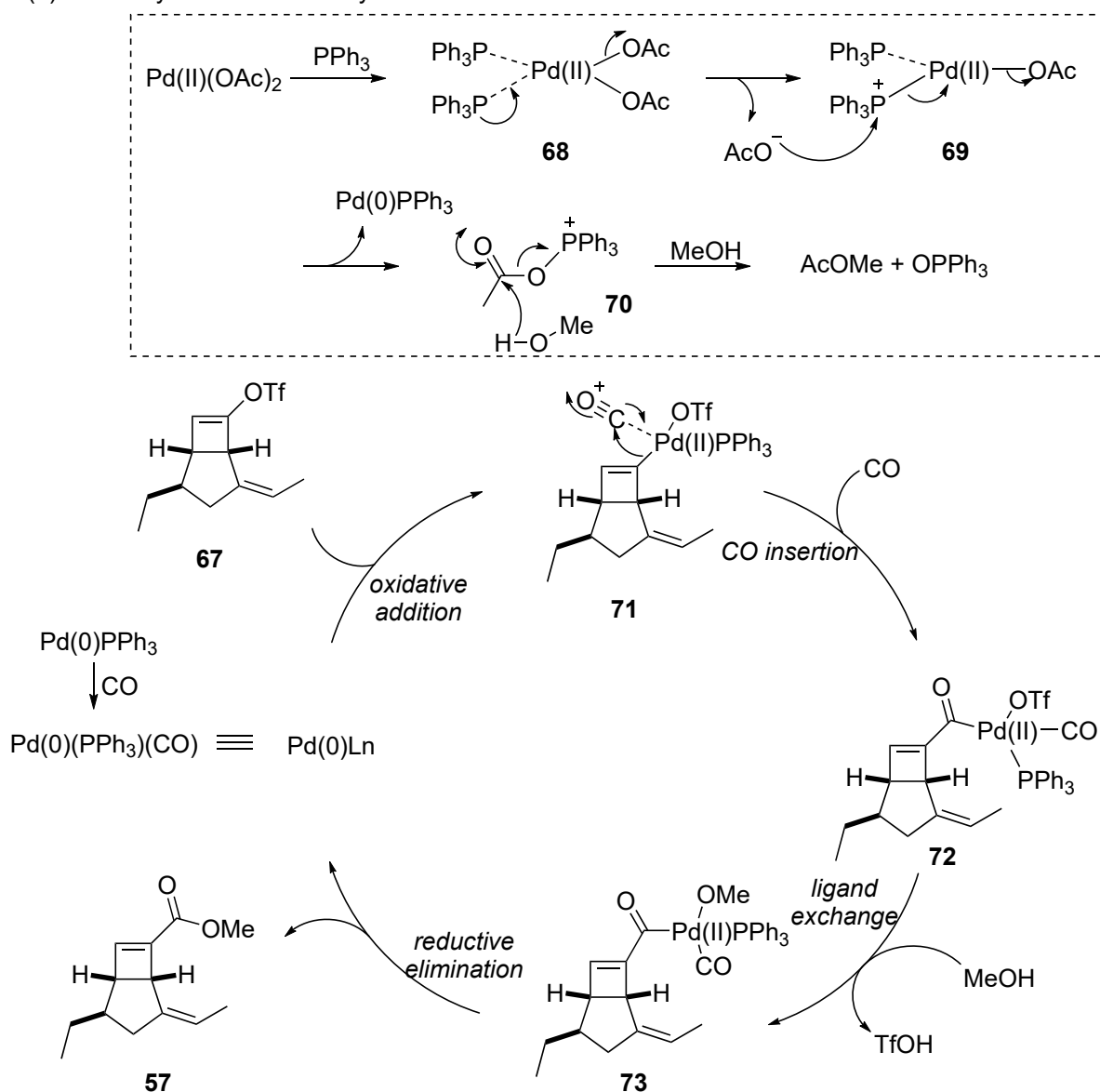
\*Reported mechanism is more reasonable, because 62 wasn't isolated.



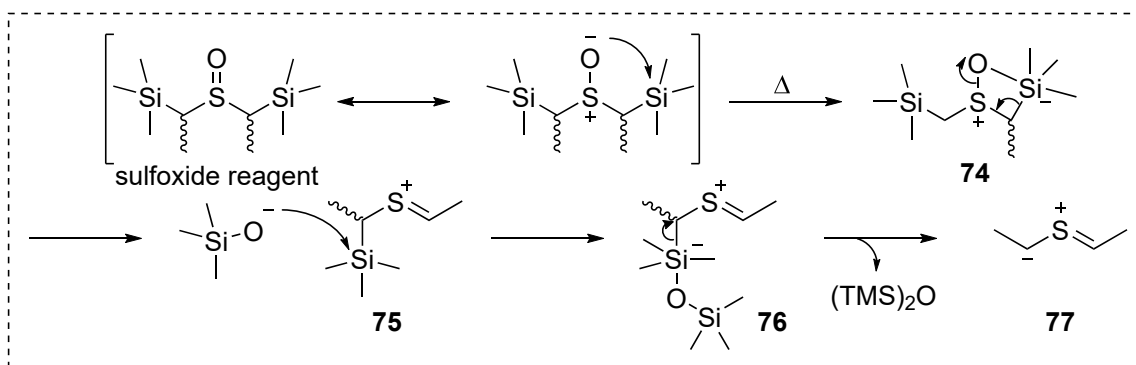
(2) Triflation by Comins' reagent



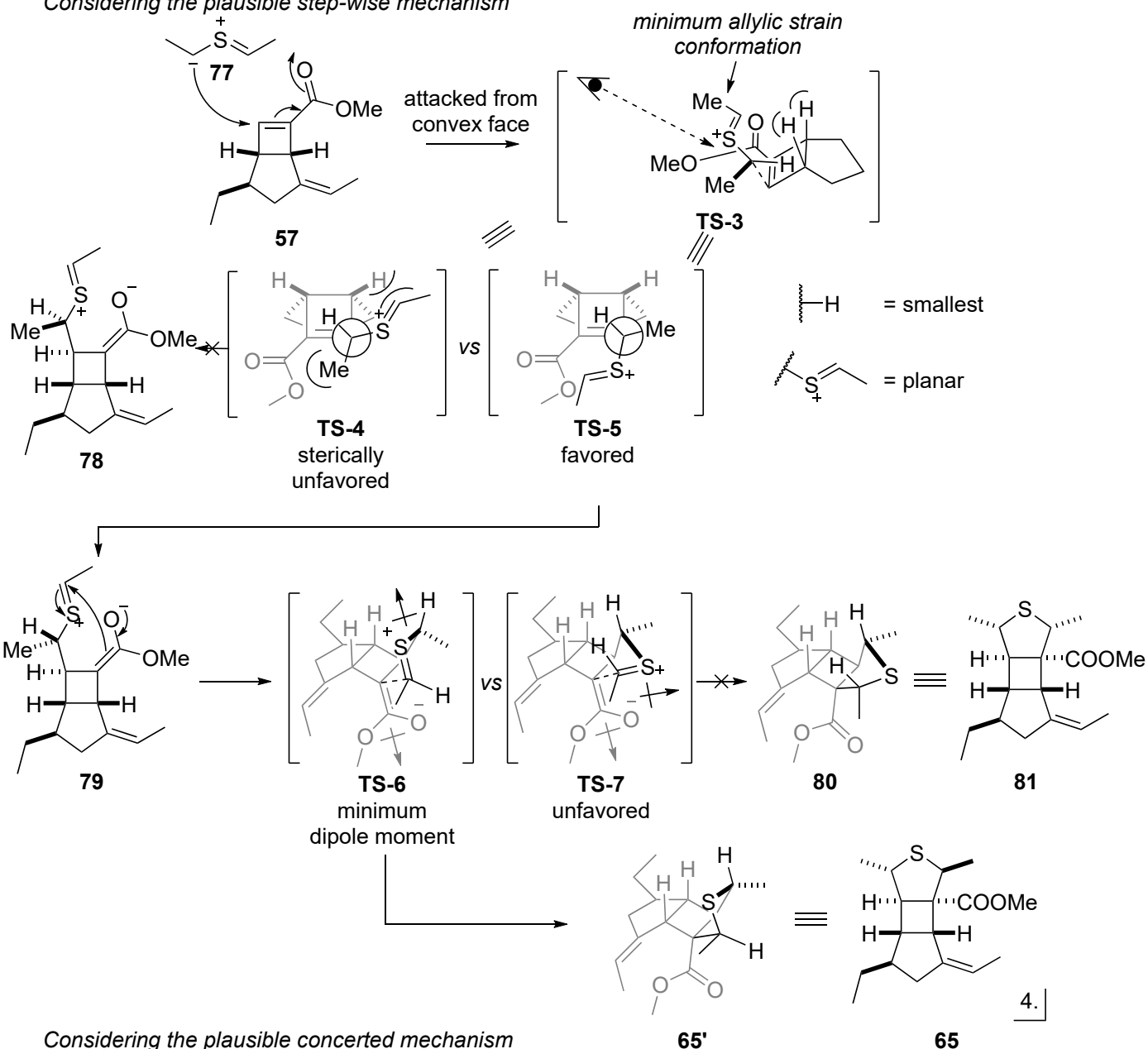
(3) Pd-catalyzed carbomethoxylation



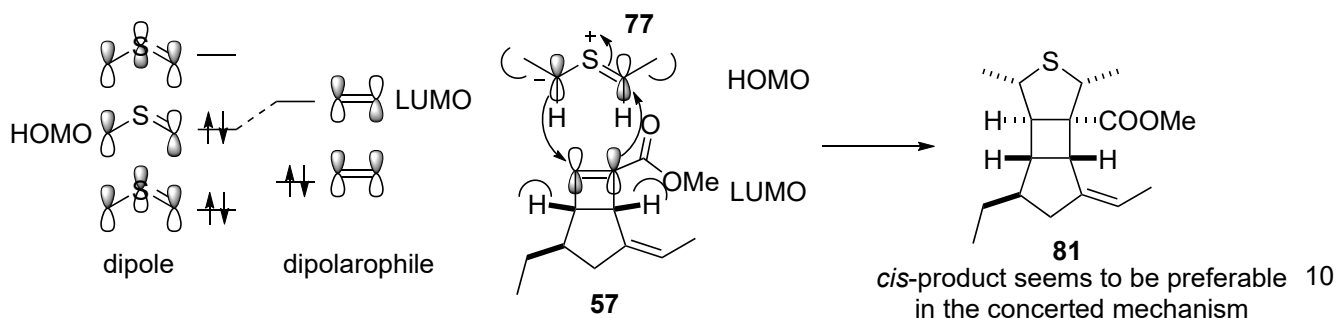
(4) Thiocarbonyl ylide cycloaddition reaction (*Heterocycles* **1995**, 40, 249.)



Considering the plausible step-wise mechanism



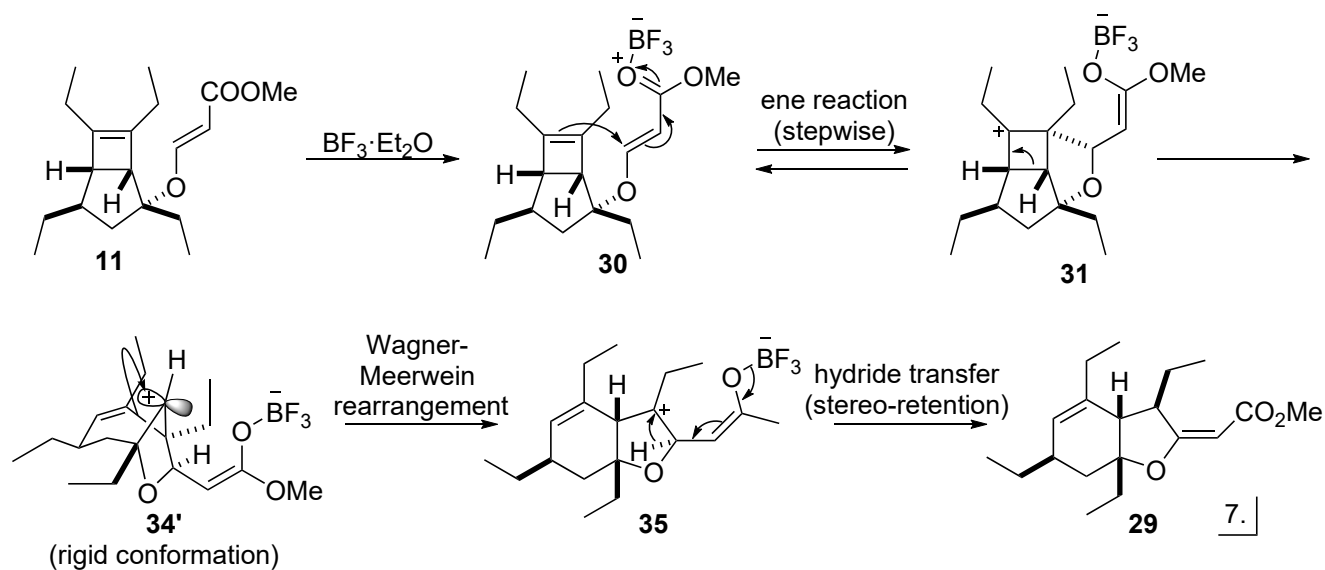
Considering the plausible concerted mechanism



**Appendix**

**Problem 1-reaction 7: discussion of other possibilities**

-A mechanism where enolate isn't involved in opening of cyclobutane



In this case, AcOH seems to play an important role as a base to accelerate formation of olefin 28 as shown below:

(6) Ene reaction

