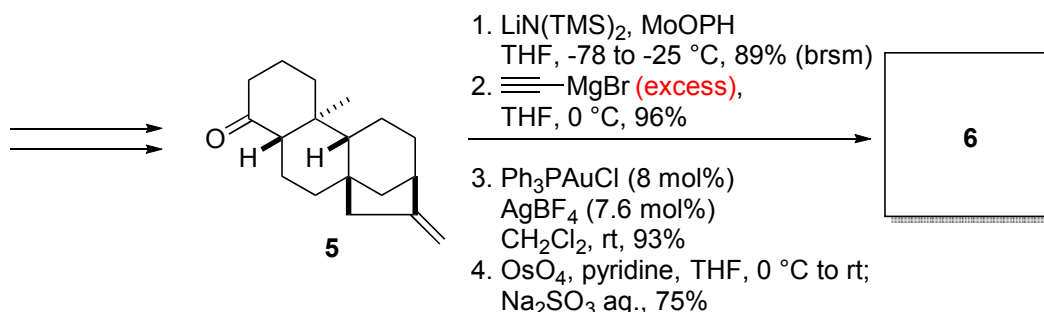
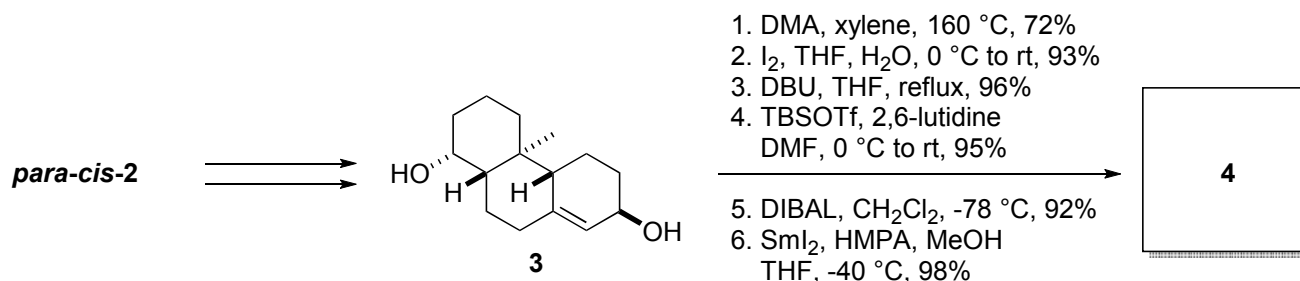
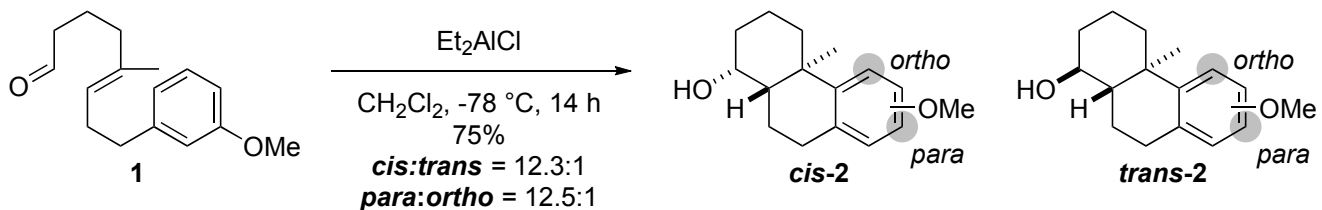


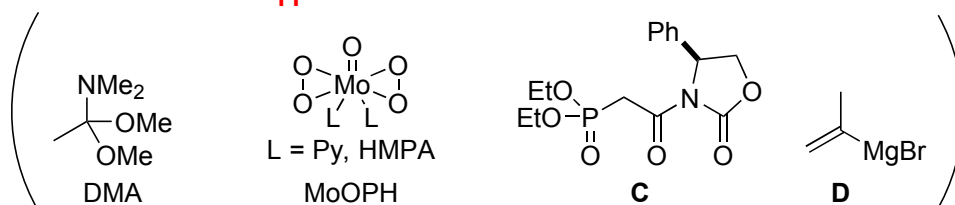
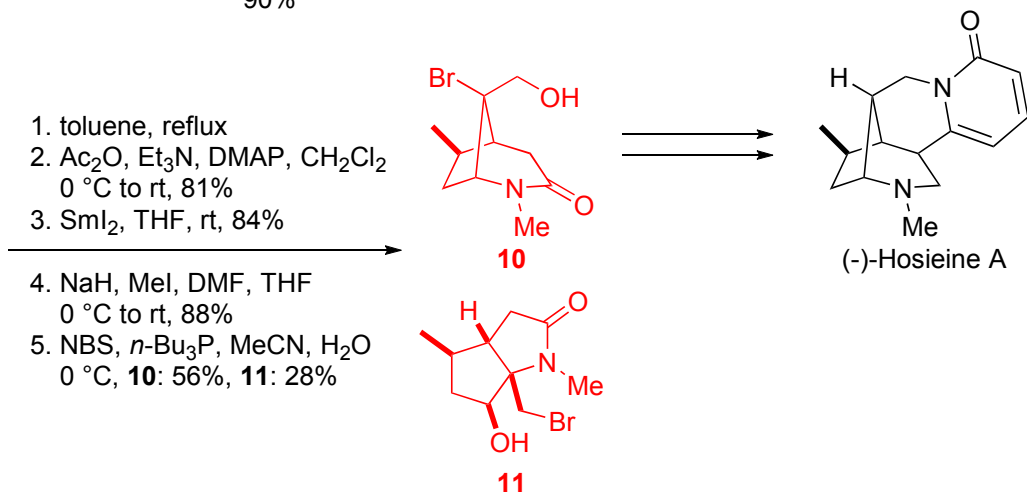
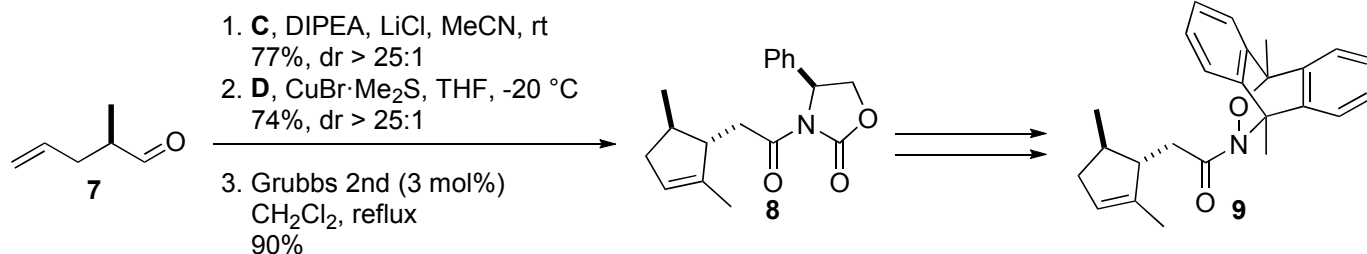
# Problem Session (3)

2016.1.23. Hiroaki Matoba

1. Please fill in the blanks and provide reaction mechanism.



2. Please fill in the blanks and provide reaction mechanism.

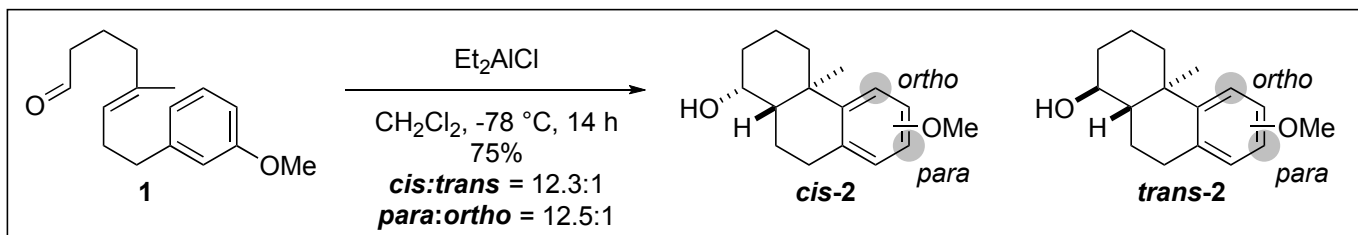


# Problem Session (3) Answer

2016.1.23. Hiroaki Matoba

Topics: Total syntheses by Prof. R. Hong group

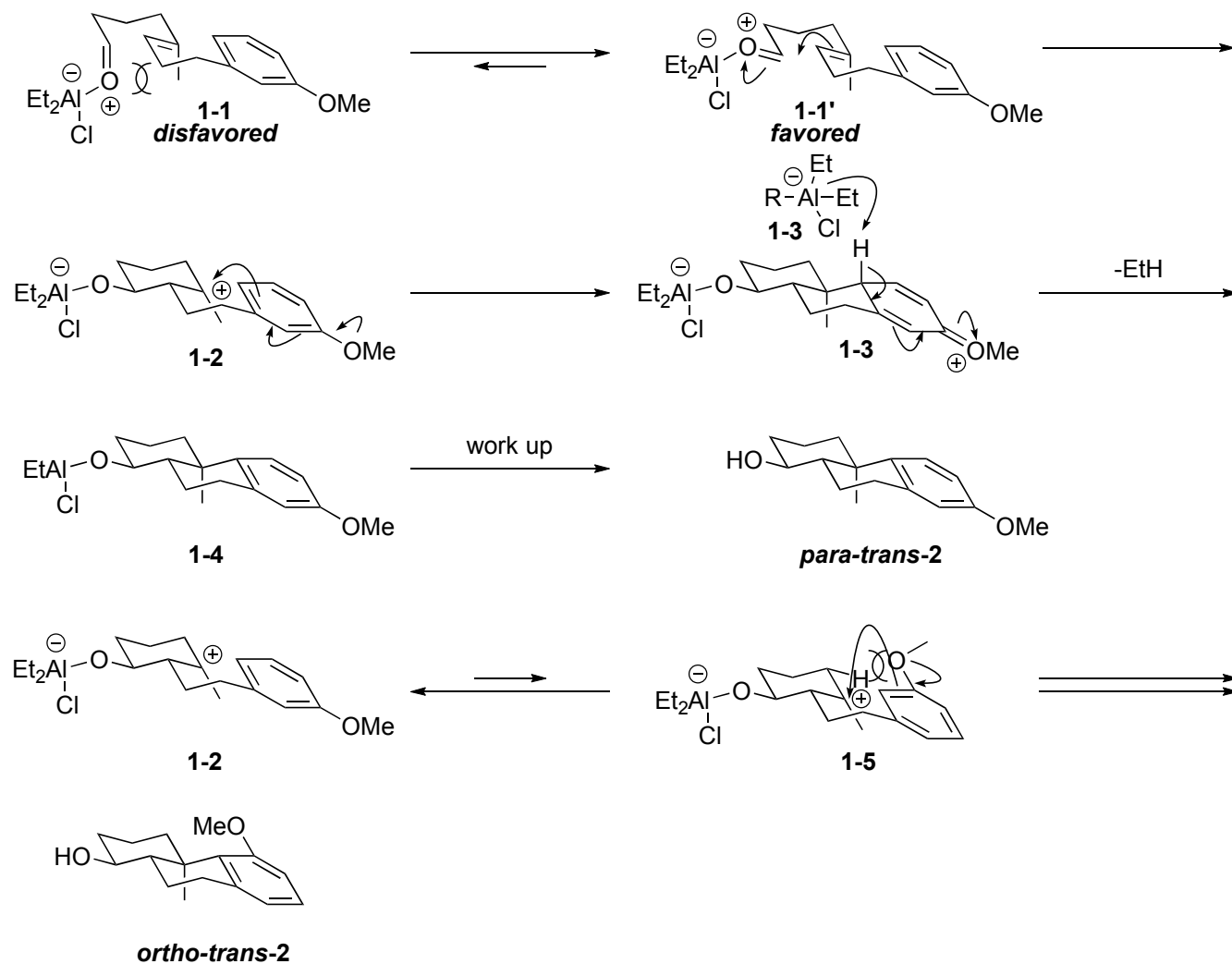
Problem 1. Total synthesis of cafestol *OL*, 2014, 16, 2162.



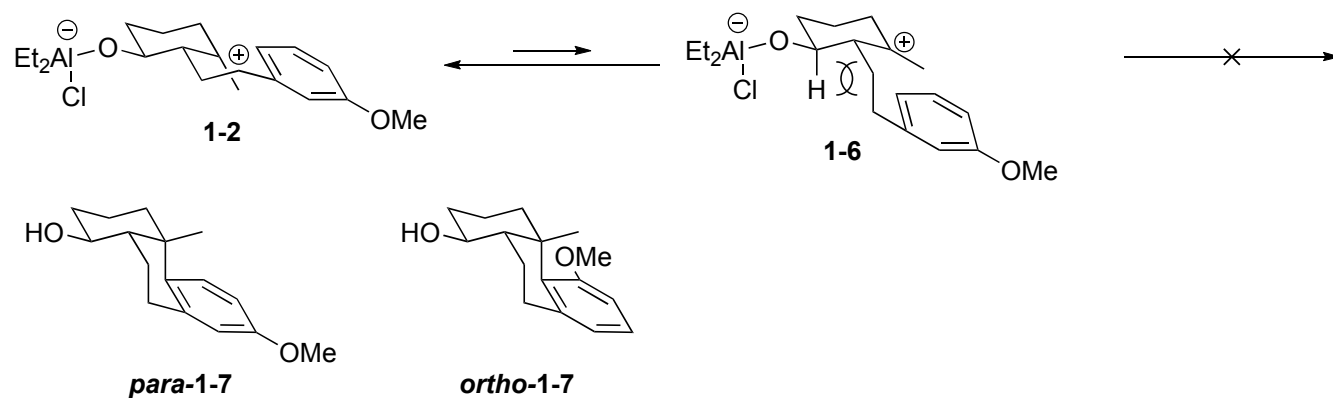
## Lewis acid mediated cyclization

### Proposed mechanism

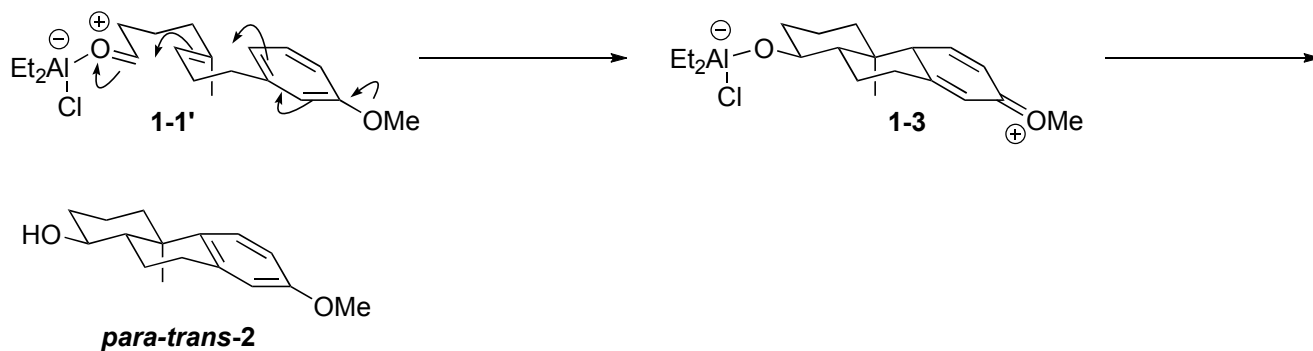
#### Path A cationic cyclization



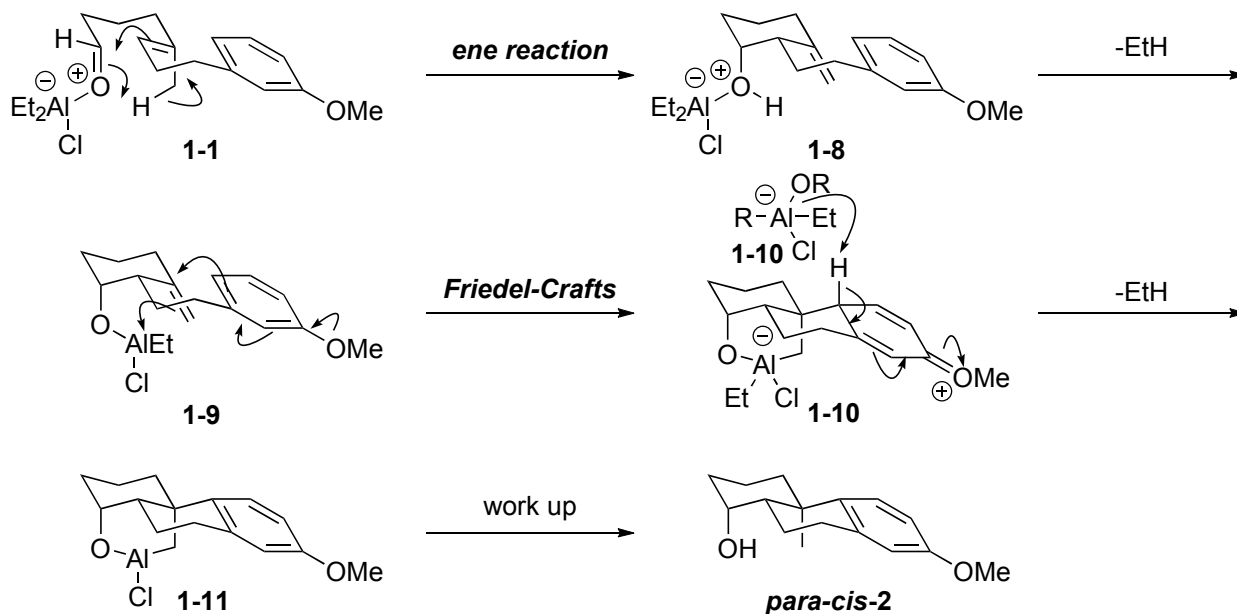
#### Stereoselectivity of methyl group



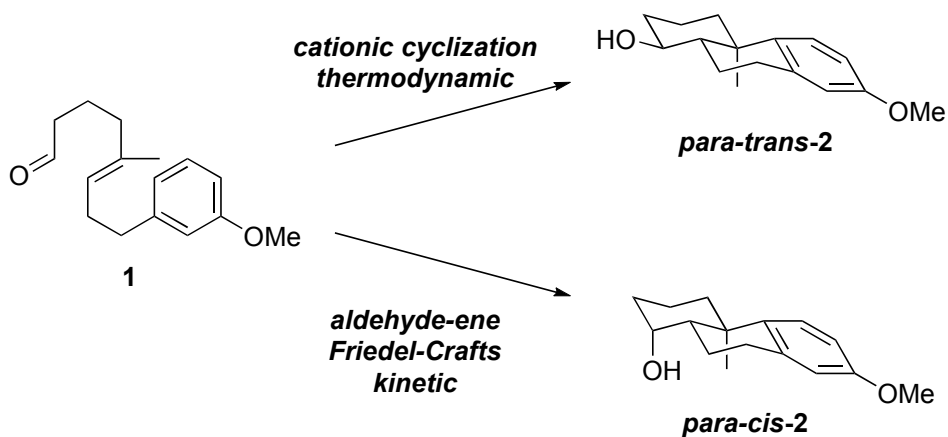
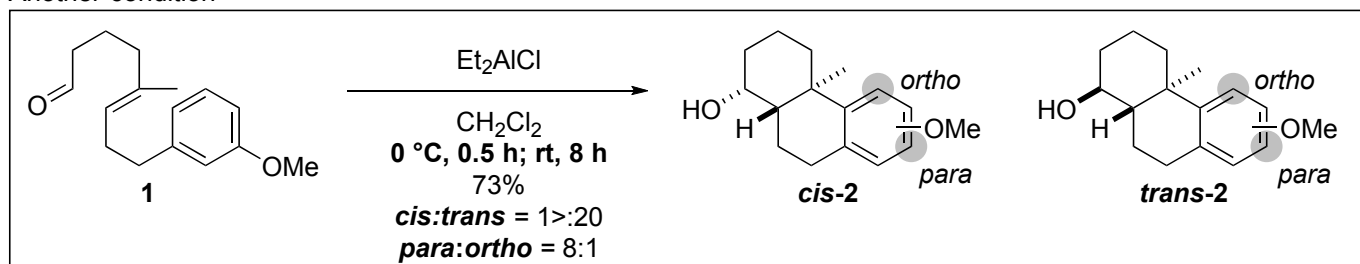
Another pathway to **trans-2**

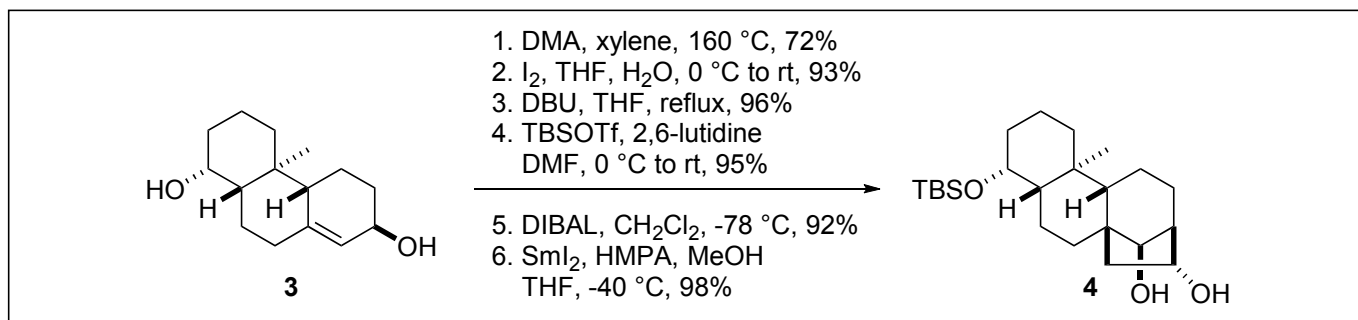


**Path B aldehyde-ene reaction -> Friedel-Crafts reaction**



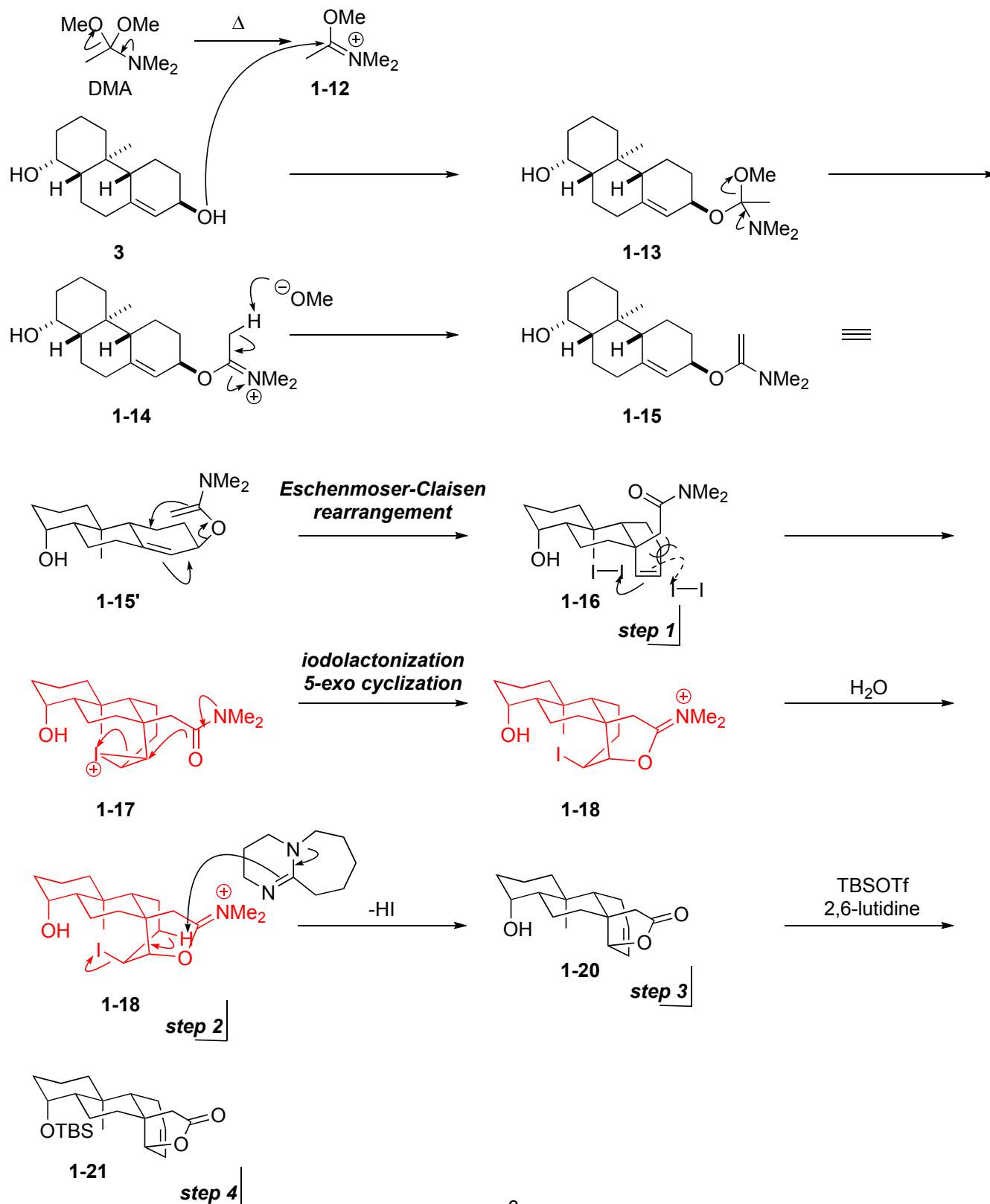
Another condition

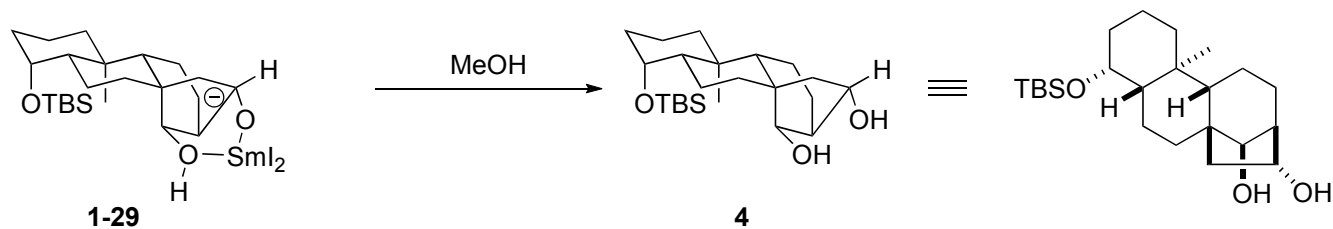
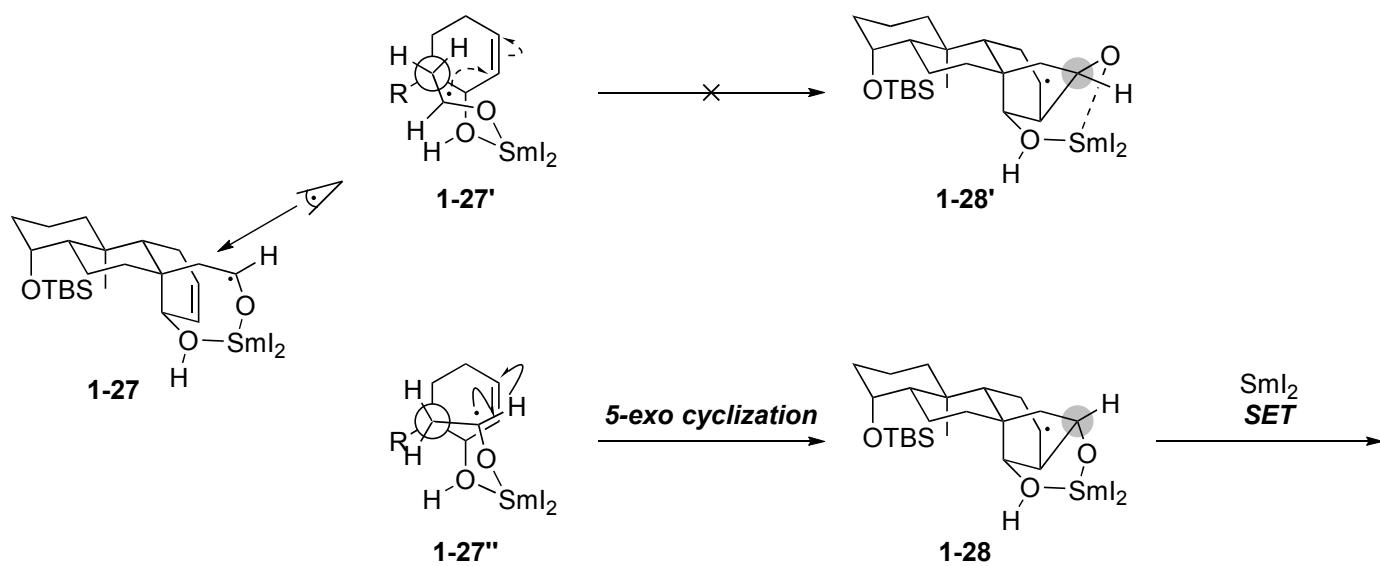
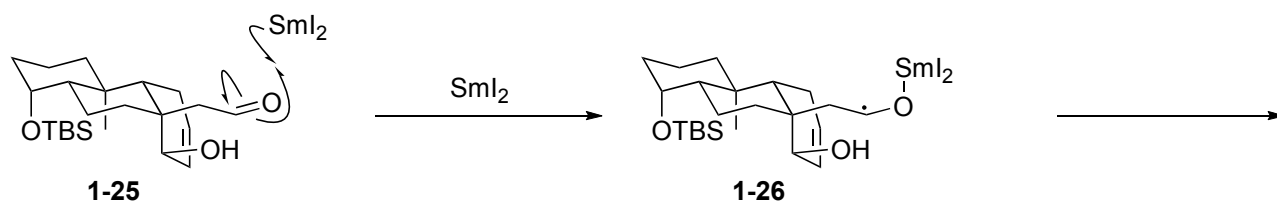
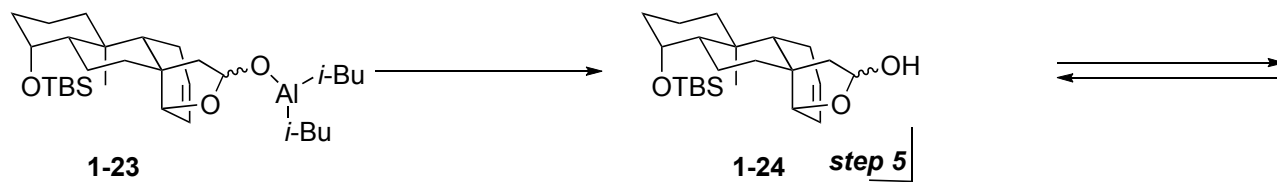
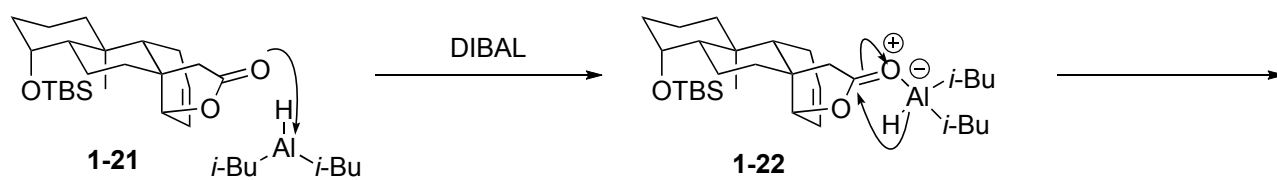


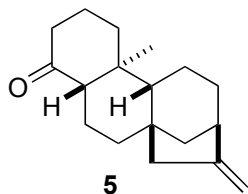


Eschenmoser-Claisen rearrangement -> iodolactonization -> radical cyclization

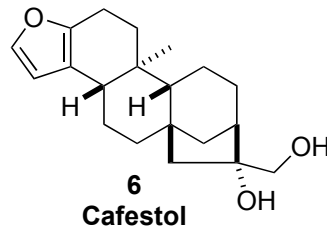
Proposed mechanism





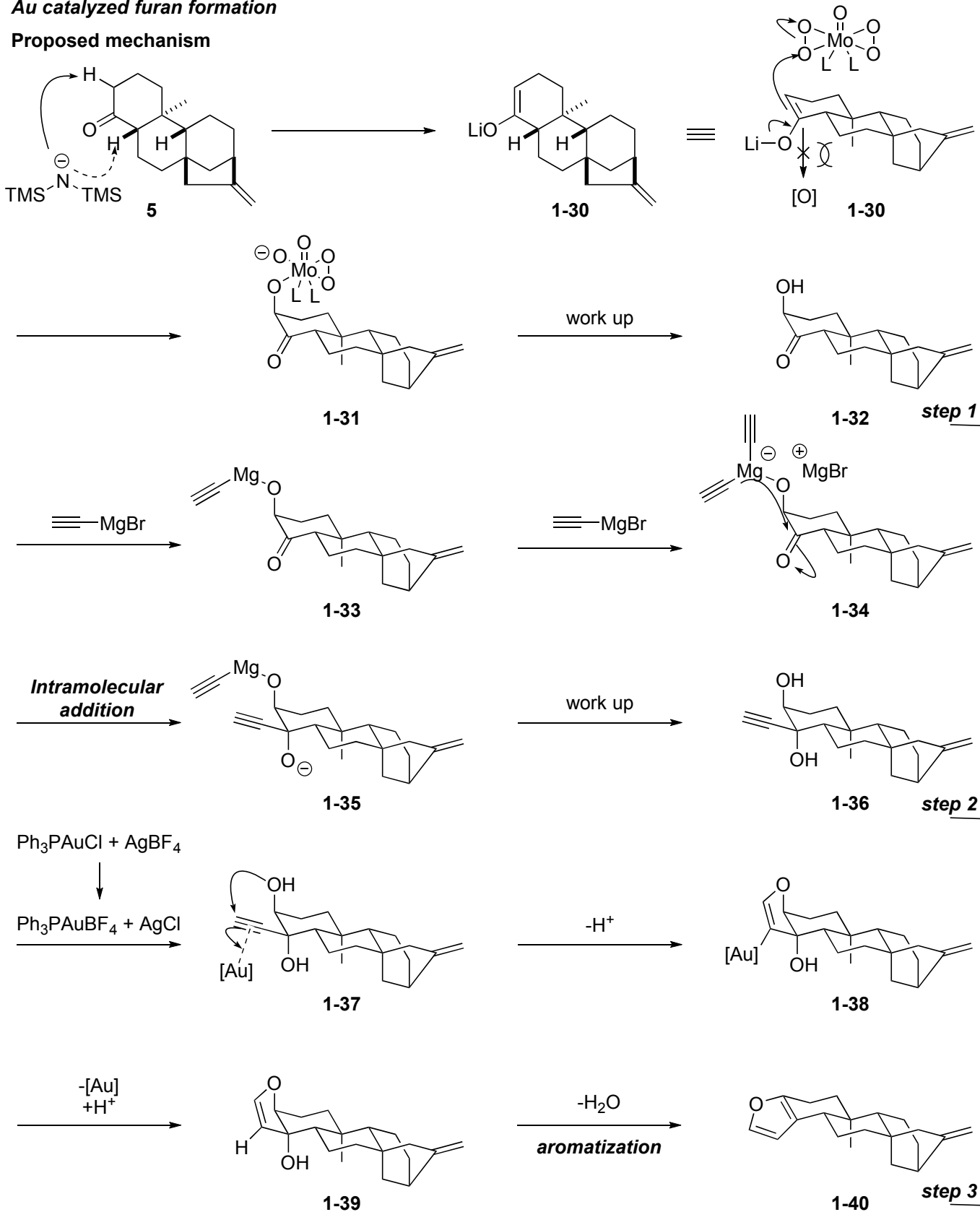


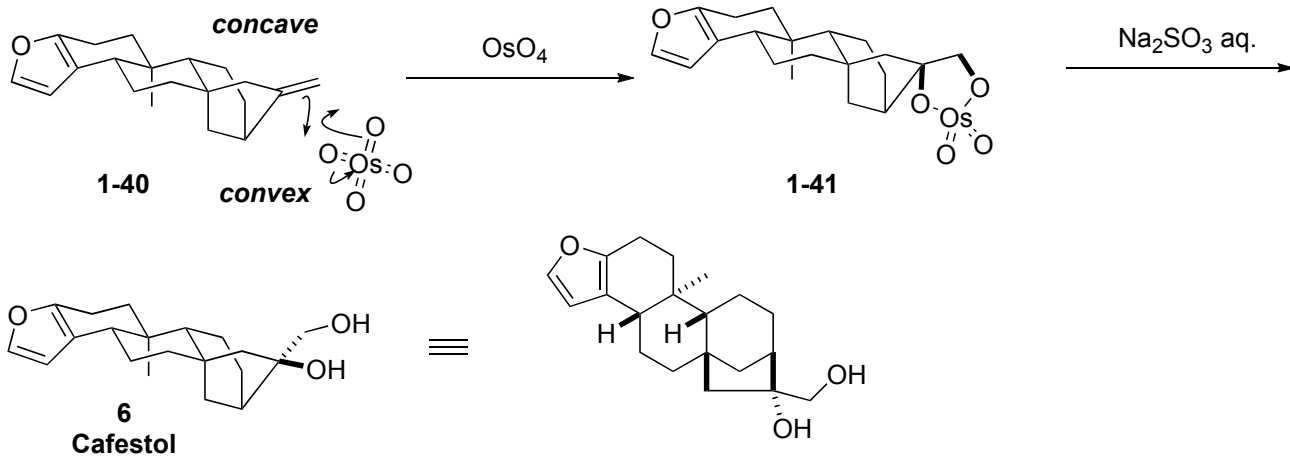
1.  $\text{LiN}(\text{TMS})_2$ , MoOPH  
THF,  $-78$  to  $-25$  °C, 89% (brsm)
  2.  $\equiv\text{MgBr}$ , THF,  $0$  °C, 96%
- 
3.  $\text{Ph}_3\text{PAuCl}$  (8 mol%)  
 $\text{AgBF}_4$  (7.6 mol%)  
 $\text{CH}_2\text{Cl}_2$ , rt, 93%
  4.  $\text{OsO}_4$ , pyridine, THF,  $0$  °C to rt;  
 $\text{Na}_2\text{SO}_3$  aq., 75%



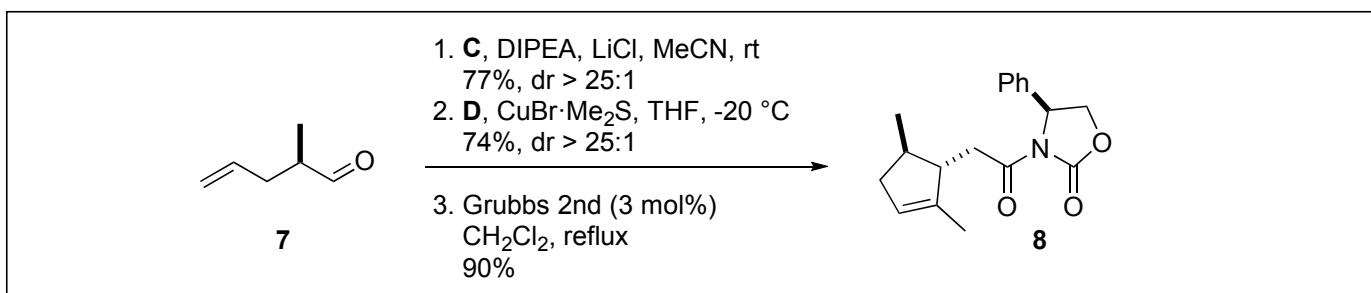
### Au catalyzed furan formation

#### Proposed mechanism



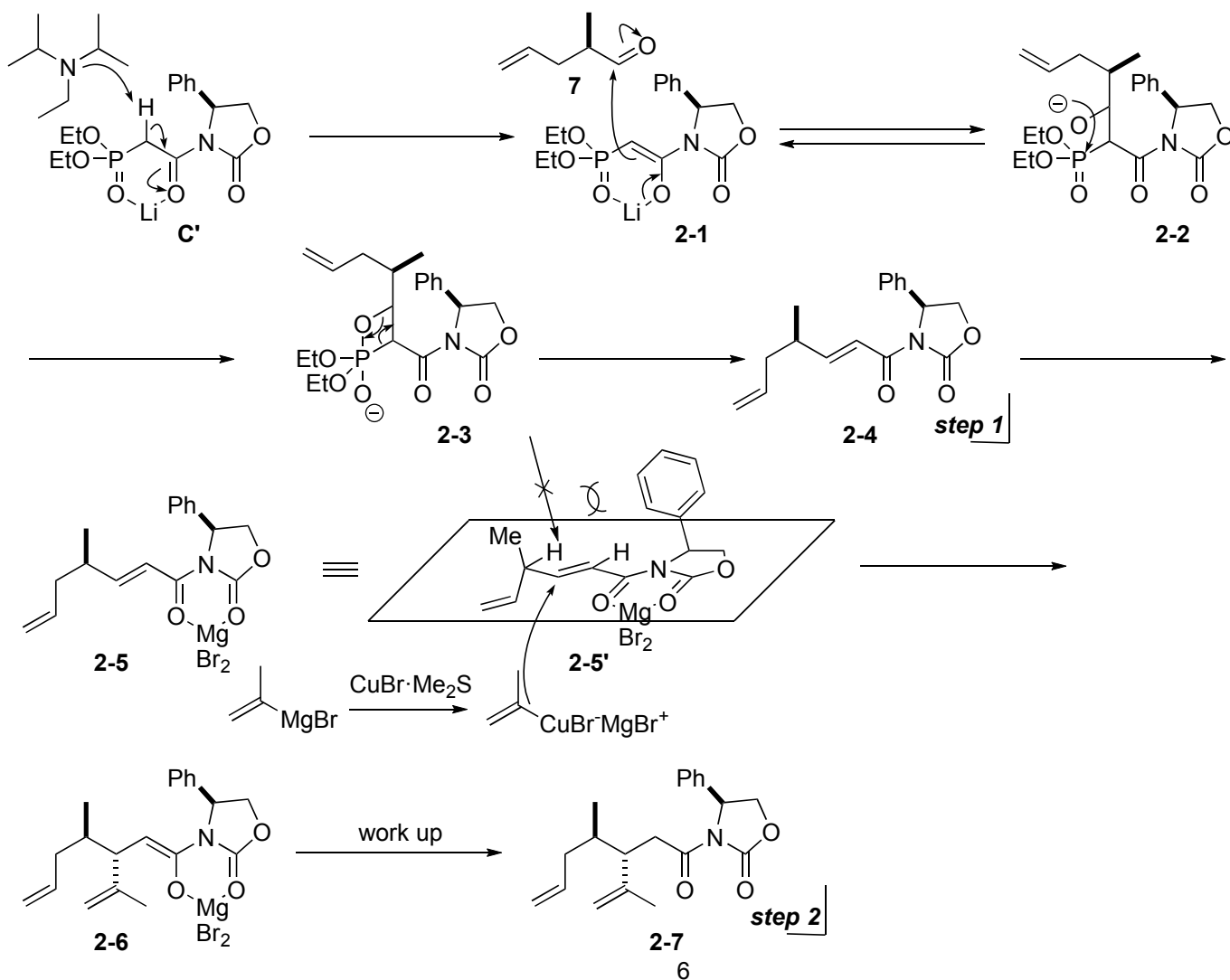


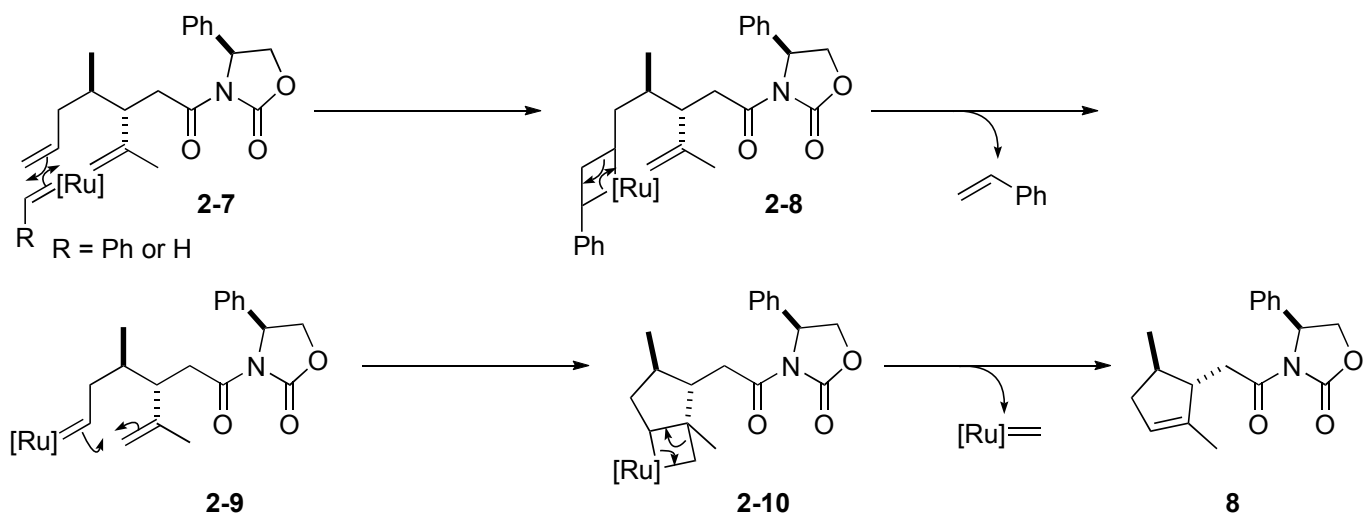
**Problem 2. Total synthesis of (-)-hosieline A *ACIE*, 2015, 54, 10940.**



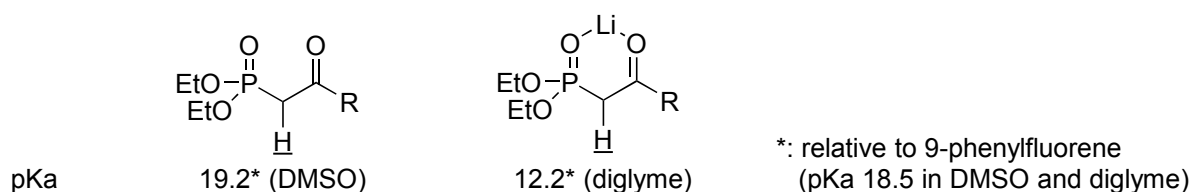
**HWE-reaction (Roush-Masamune condition) -> Stereoselective 1,4-addition**

**Proposed mechanism**



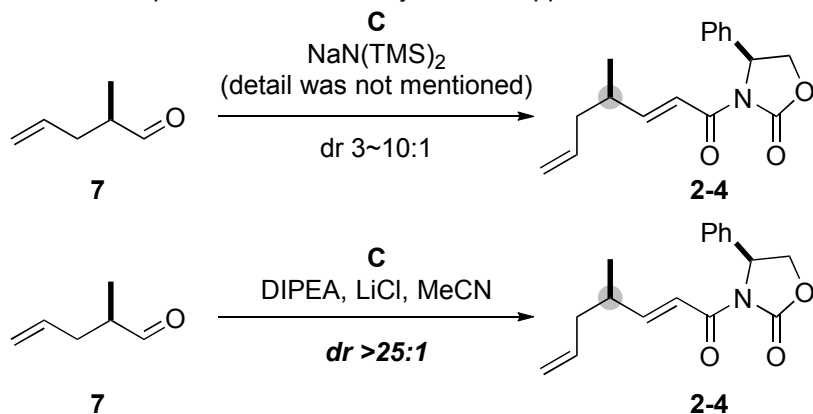


**HWE-reaction (Roush-Masamune condition) TL, 1984, 25, 2183.**



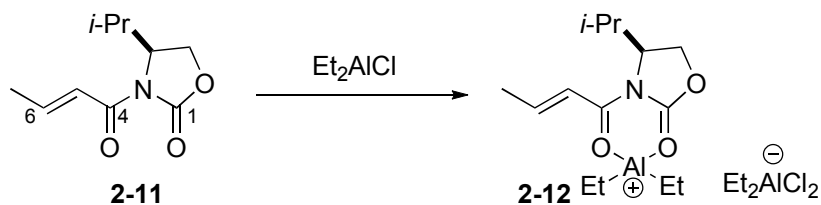
In HWE-reaction, strong base such as NaH (pKa 35) and  $\text{NaN}(\text{TMS})_2$  (pKa 25.8) in the presence of a lithium salt, phosphonates can be easily deprotonated with an amine (pKa DBU 11.6, DIPEA 10.5)

In this case, epimerization of aldehyde was suppressed.



**Stereoselective 1,4-addition TL, 1998, 39, 8593.**

NMR experiment JACS, 1993, 115, 2986.



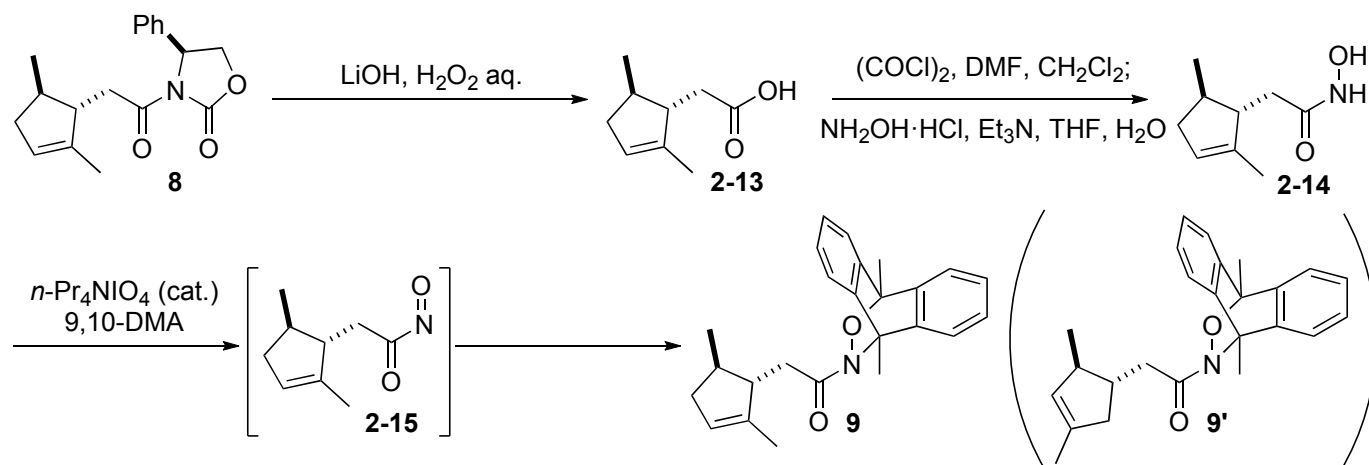
$^{13}\text{C}$  NMR chemical shift

C	2-11	2-12
C-1	154.6	161.0
C-4	165.2	171.1
C-6	146.5	169.2

C-1, C-4 and C-6 experience downfield shifts. This result indicates that chelate **2-12** was formed.



### Transformation of 8 -> 9

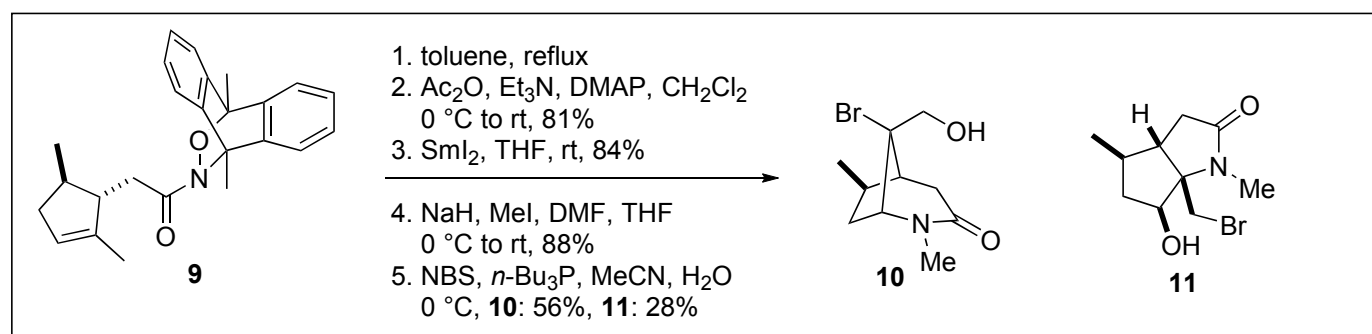


Authors described 9' instead of 9.

They only mentioned nitroso 2-15 was revealed from 9' through retro Diels-Alder reaction.

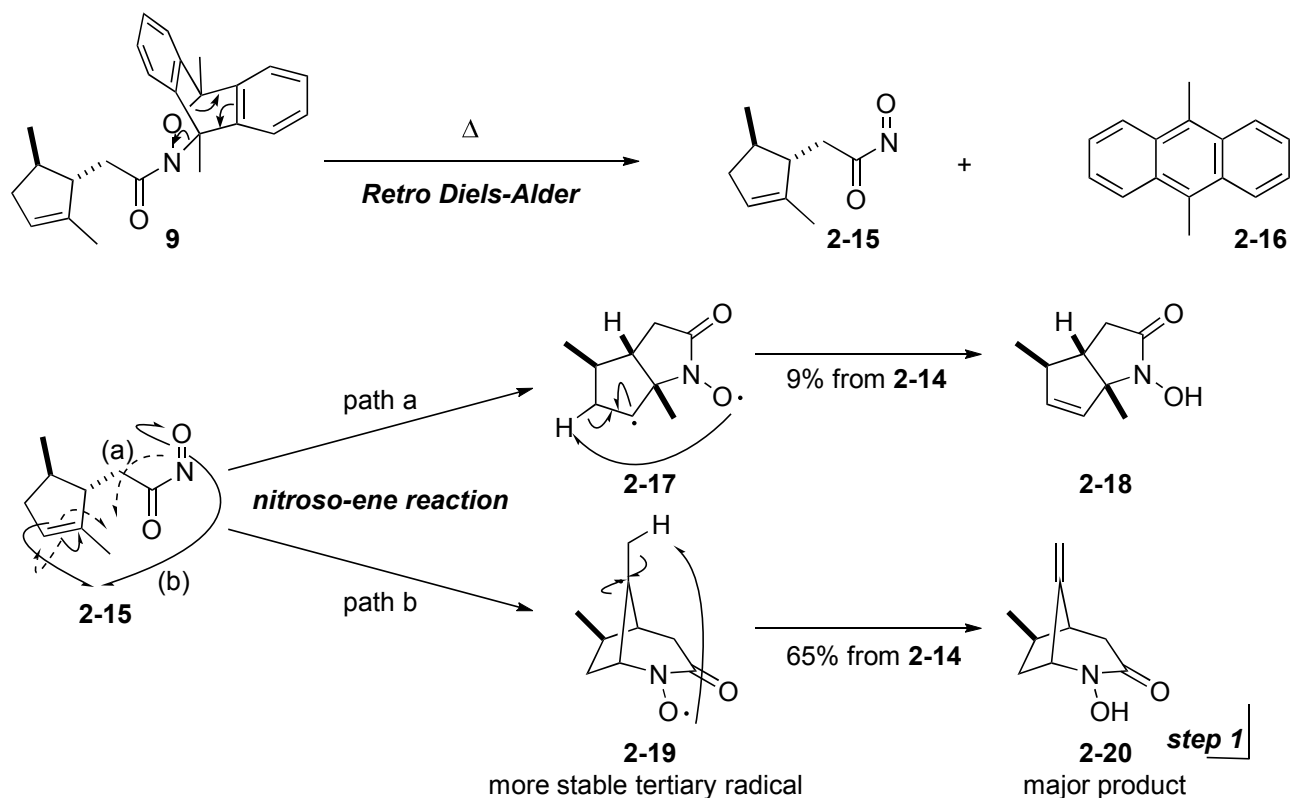
There is no NMR data of 9' in the paper, I could not confirm the true structure of 9'.

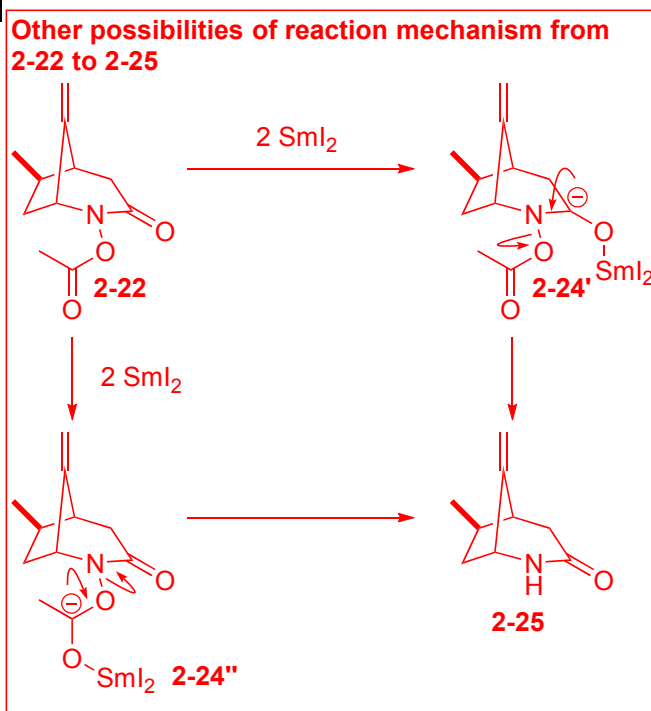
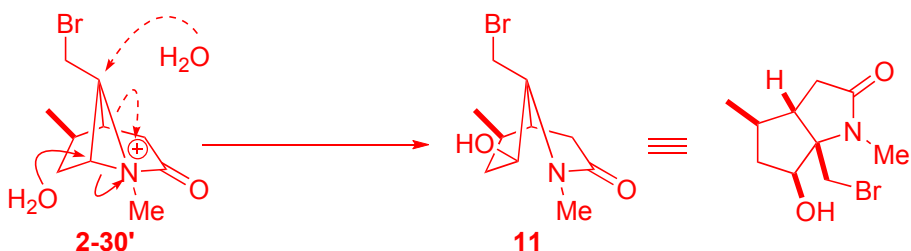
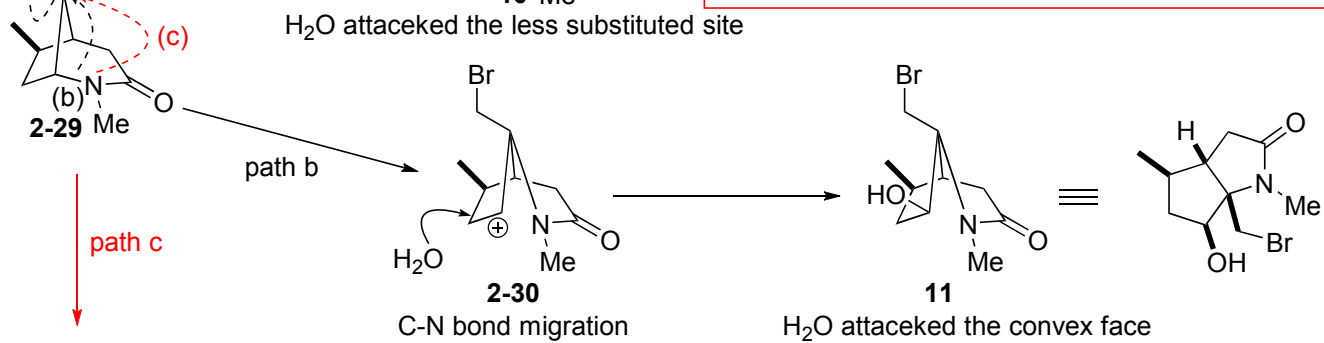
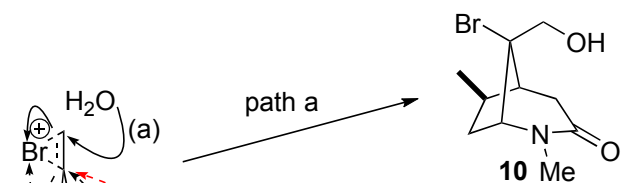
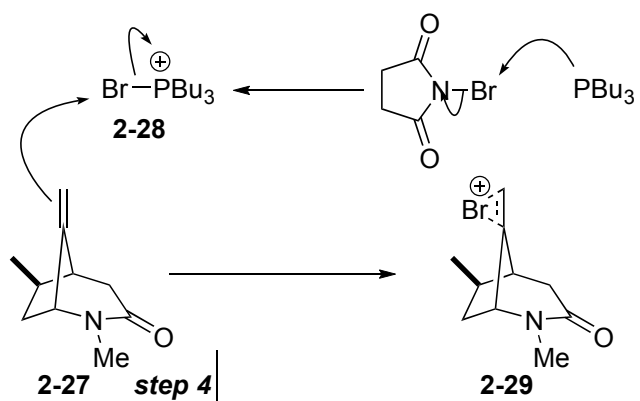
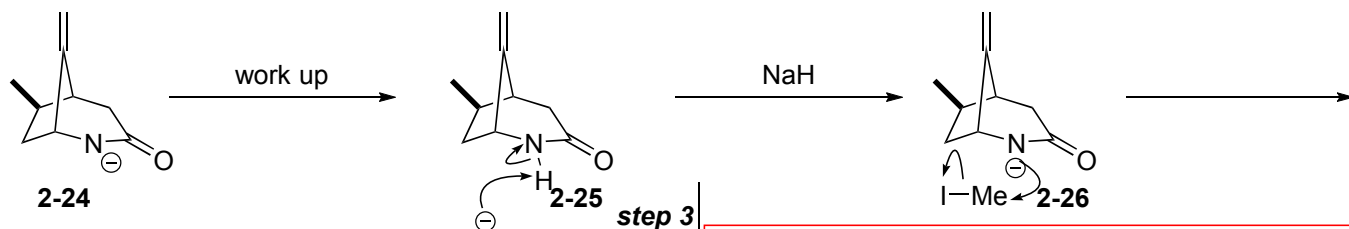
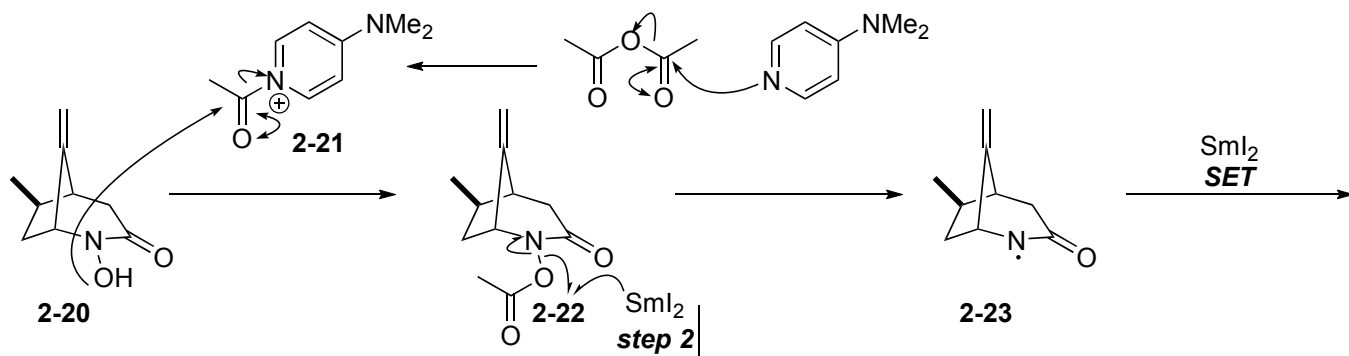
But I thought 9 was plausible product of the last reaction.



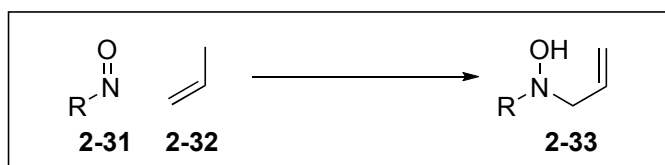
### nitroso-ene reaction -> stereoselective bromohydrination

#### Proposed mechanism

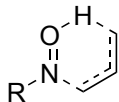




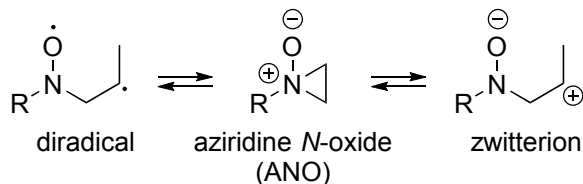
## nitroso-ene reaction



possible mechanisms  
concerted pathway

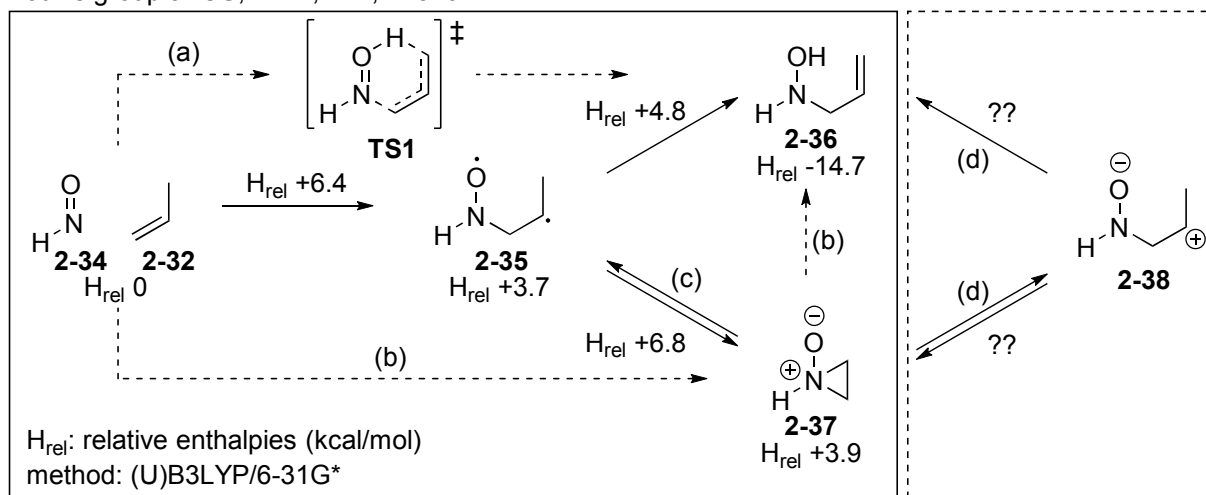


intermediates of stepwise pathway



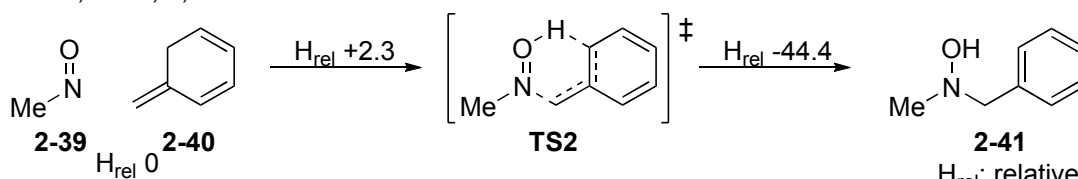
Computational study

Houk's group *JACS*, **2002**, 124, 14820.



- (a) The authors were unable to locate a concerted transition state for the ene reaction.  
 (b) There is no direct path linking the ANO to either reactant or product.  
 (c) Both of the steps from ANO to reactant and product could only be achieved by passing through a local minimum, diradical intermediate.  
 (d) They didn't mention about zwitterion intermediate.

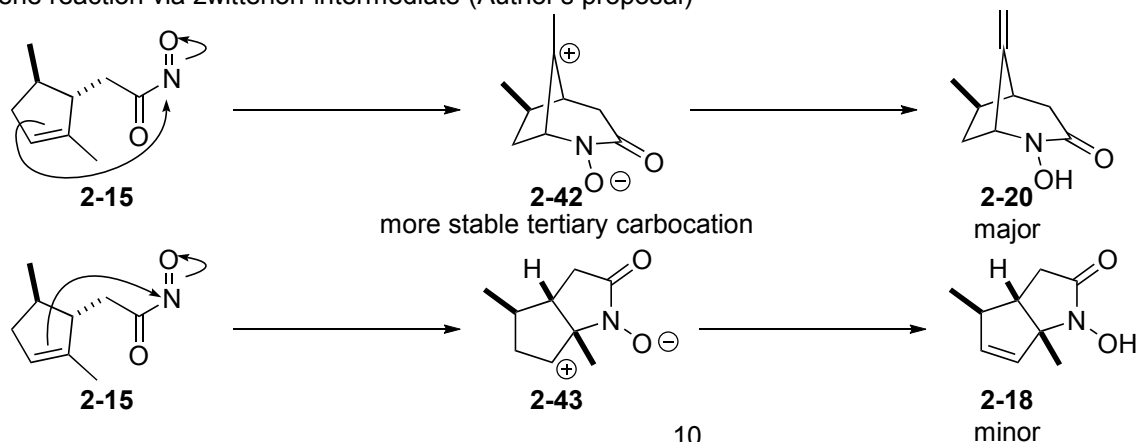
Lu *OL*, **2004**, 6, 2813.



It is the first report of the concerted nitroso ene reaction.

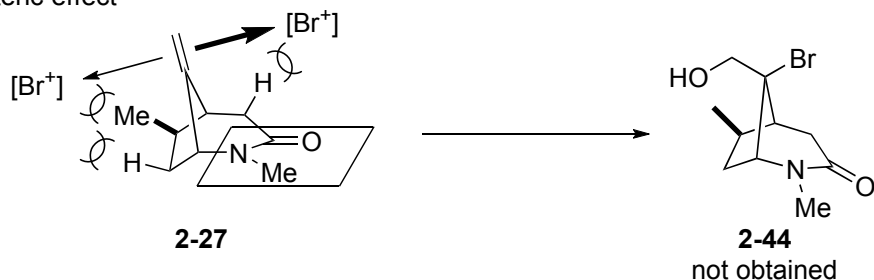
According to these results, nitroso ene reaction is usually stepwise mechanism via diradical intermediate.

ene reaction via zwitterion intermediate (Author's proposal)



## Stereoselective bromohydrination

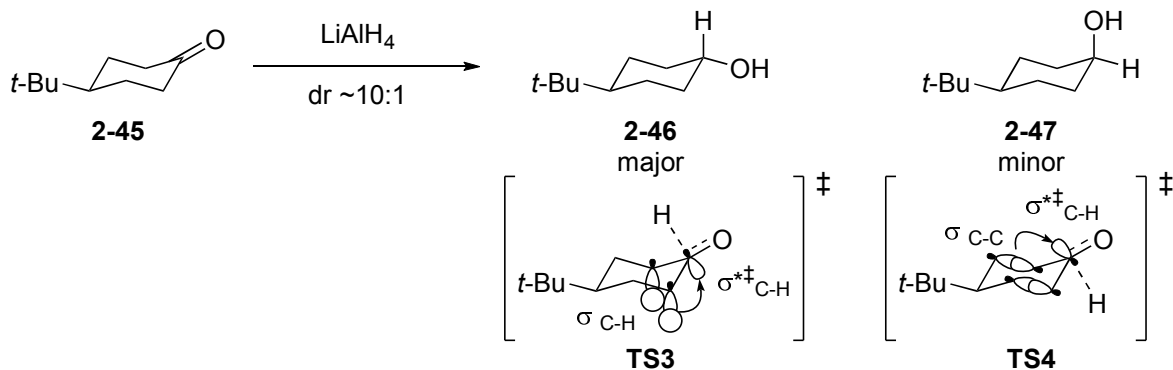
steric effect



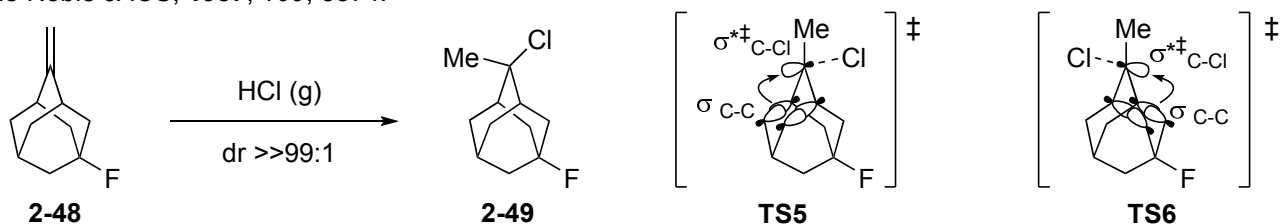
Bromination reagent approached more hindered face.

hyperconjugation

Cieplak *JACS*, **1981**, *103*, 4540.



le Noble *JACS*, **1987**, *109*, 5874.



Both nucleophiles and electrophiles approach trigonal carbon from the direction anti parallel to the electron richest single bond.

These results can be explained that there are hyperconjugation between  $\sigma$  orbitals of single bond and  $\sigma^*$  orbital of forming bond.

In this case, the selectivity of bromination was derived from the difference of bond angle.

In **TS7**,  $\sigma$  orbitals are directed parallel to  $\sigma^*$  orbital, but in **TS8**,  $\sigma$  orbitals are directed toward more inside than in **TS7**.

