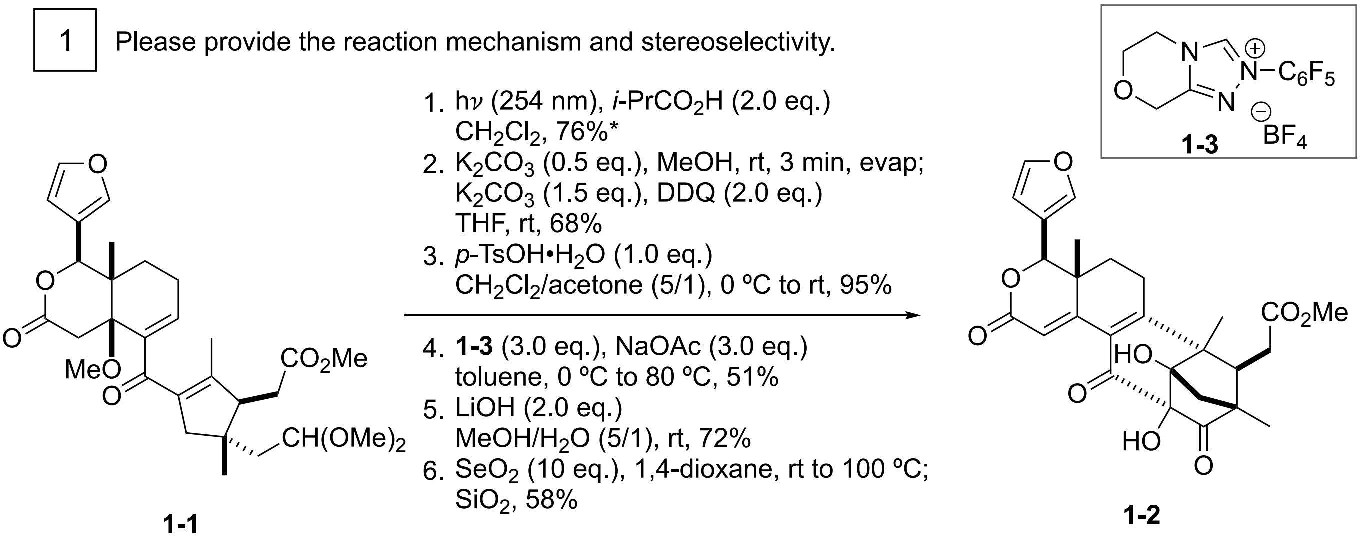
Problem Session (1) -Answer-

2025/02/08 Ryo Nishikawa

topic: Nazarov cyclization

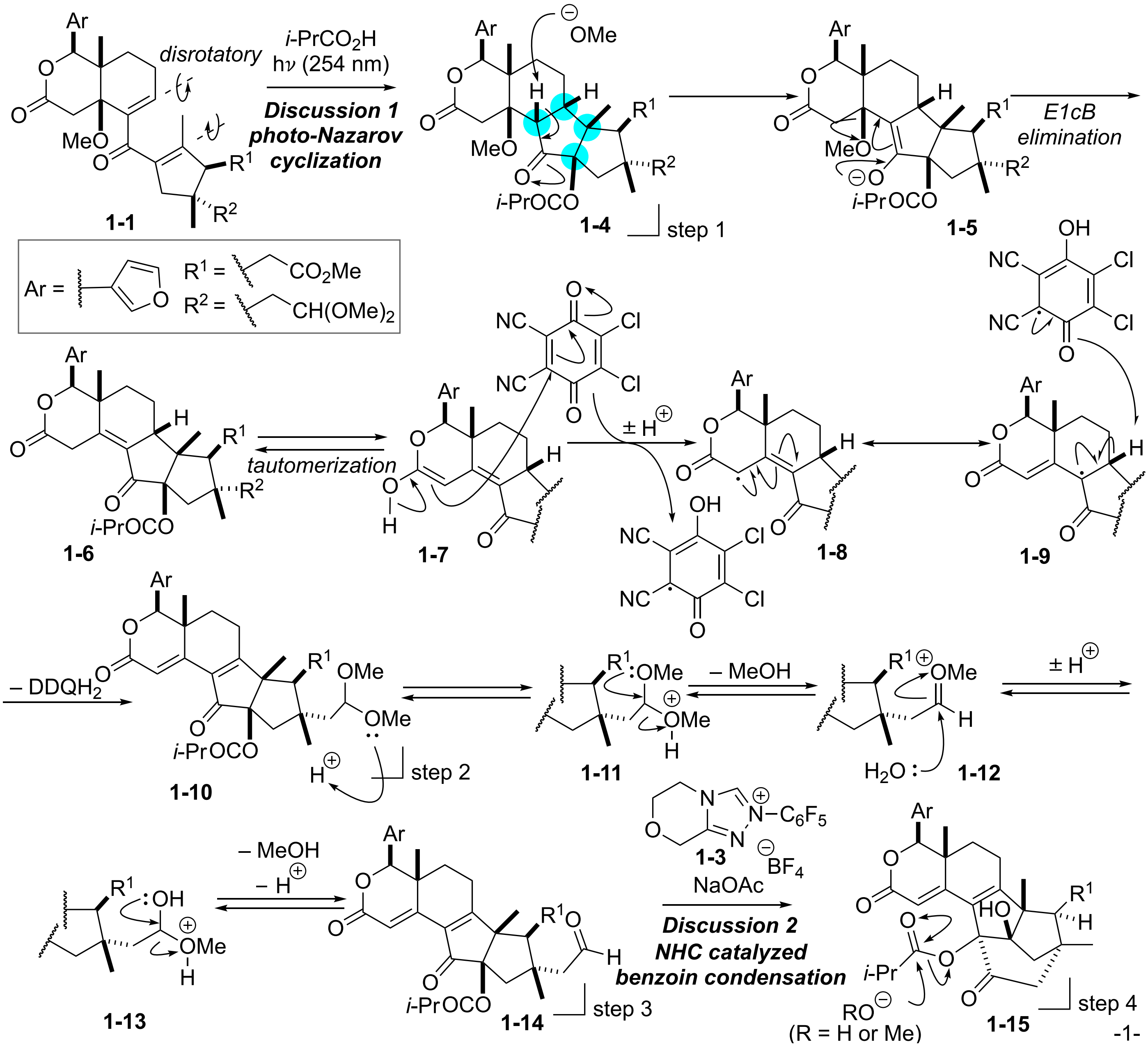
Problem 1: Total synthesis of Phragmalin and Khayanolide-type Limonoid.

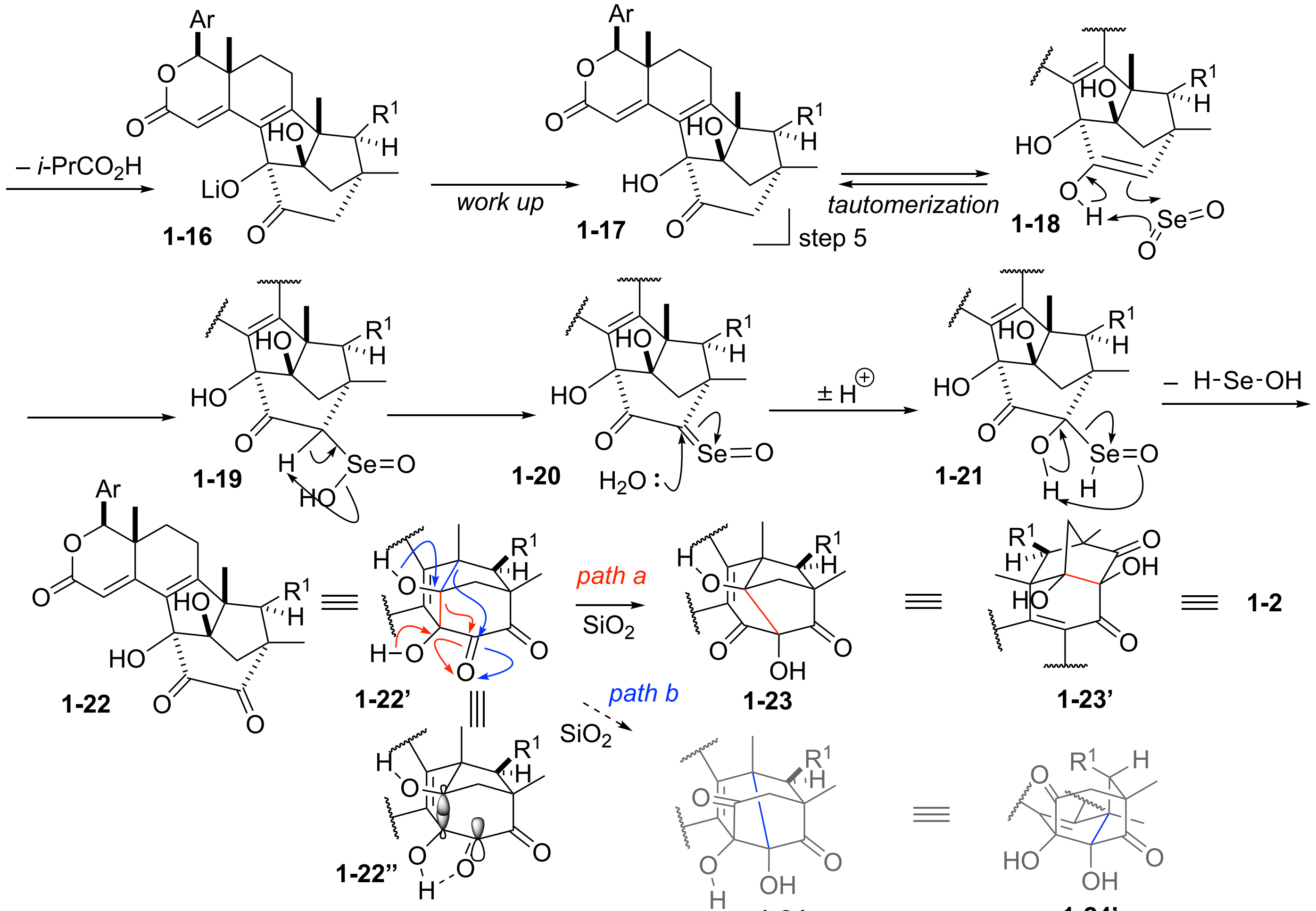
1 Please provide the reaction mechanism and stereoselectivity.



*The reaction temperature is not mentioned in the paper.

Rao, P.; Tang, D.; Xia, Q.; Hu, J.; Lin, X.; Xuan, J.; Ding, H. *J. Am. Chem. Soc*. **2025**, *147*,, 3003.

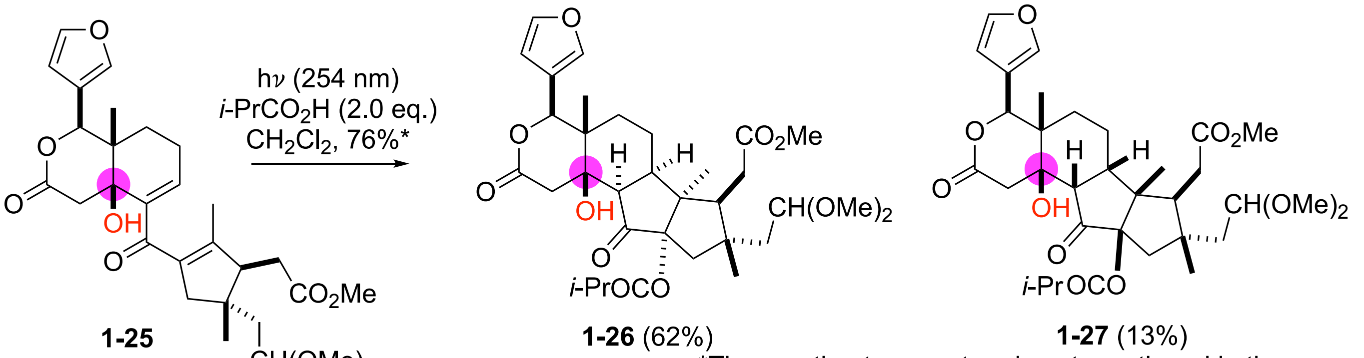




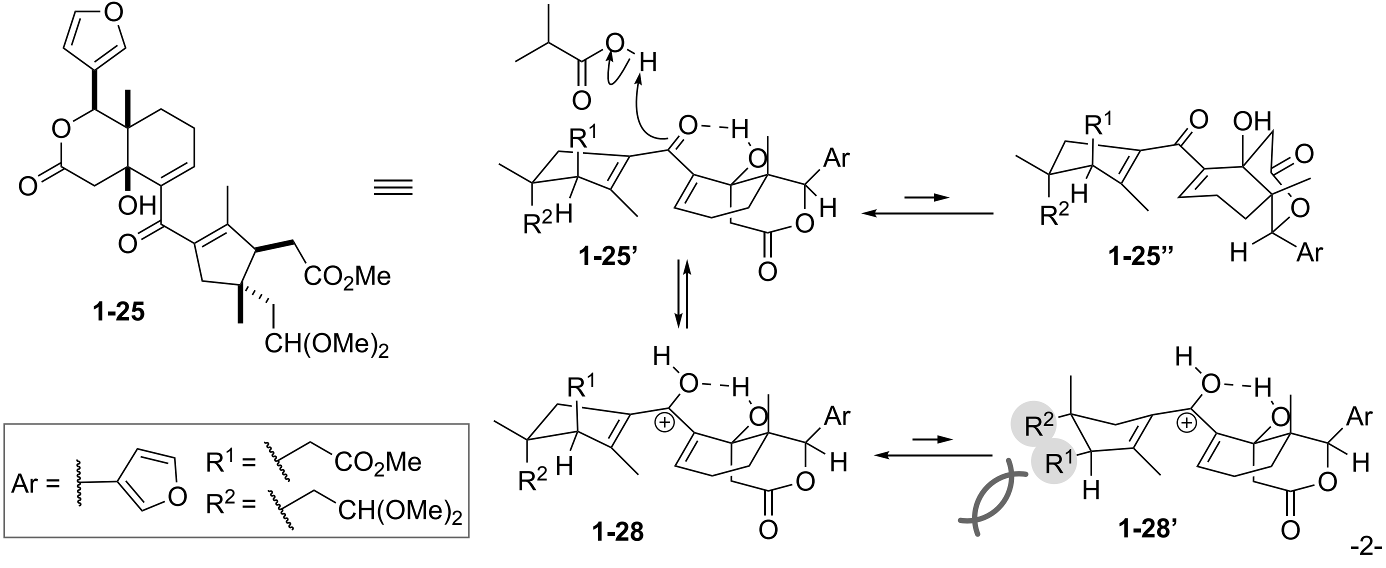
Discussion 1: photo-Nazarov cyclization

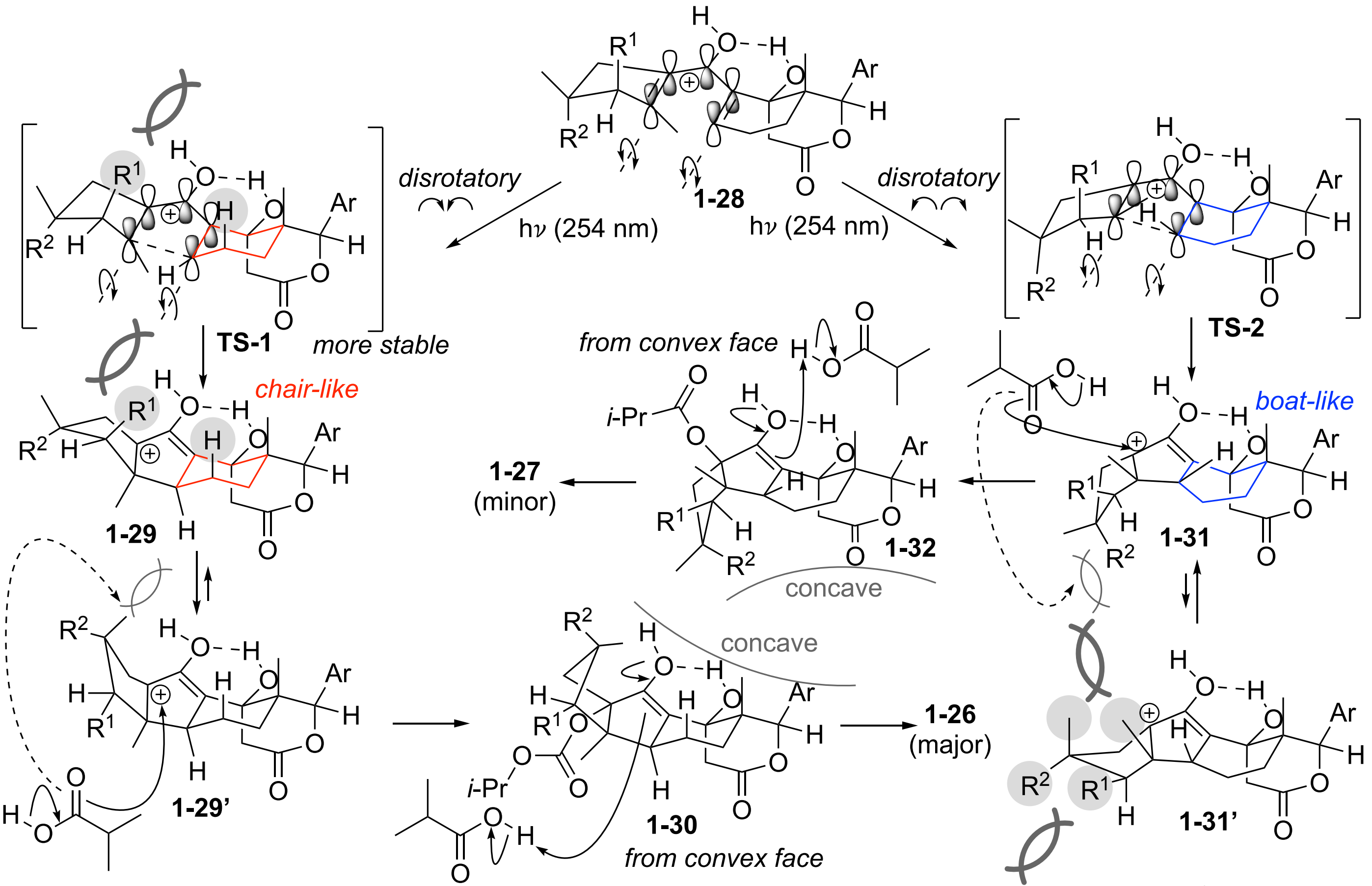
1-1. Torquoselectivity

1-1-1. *Another result in similar compound*

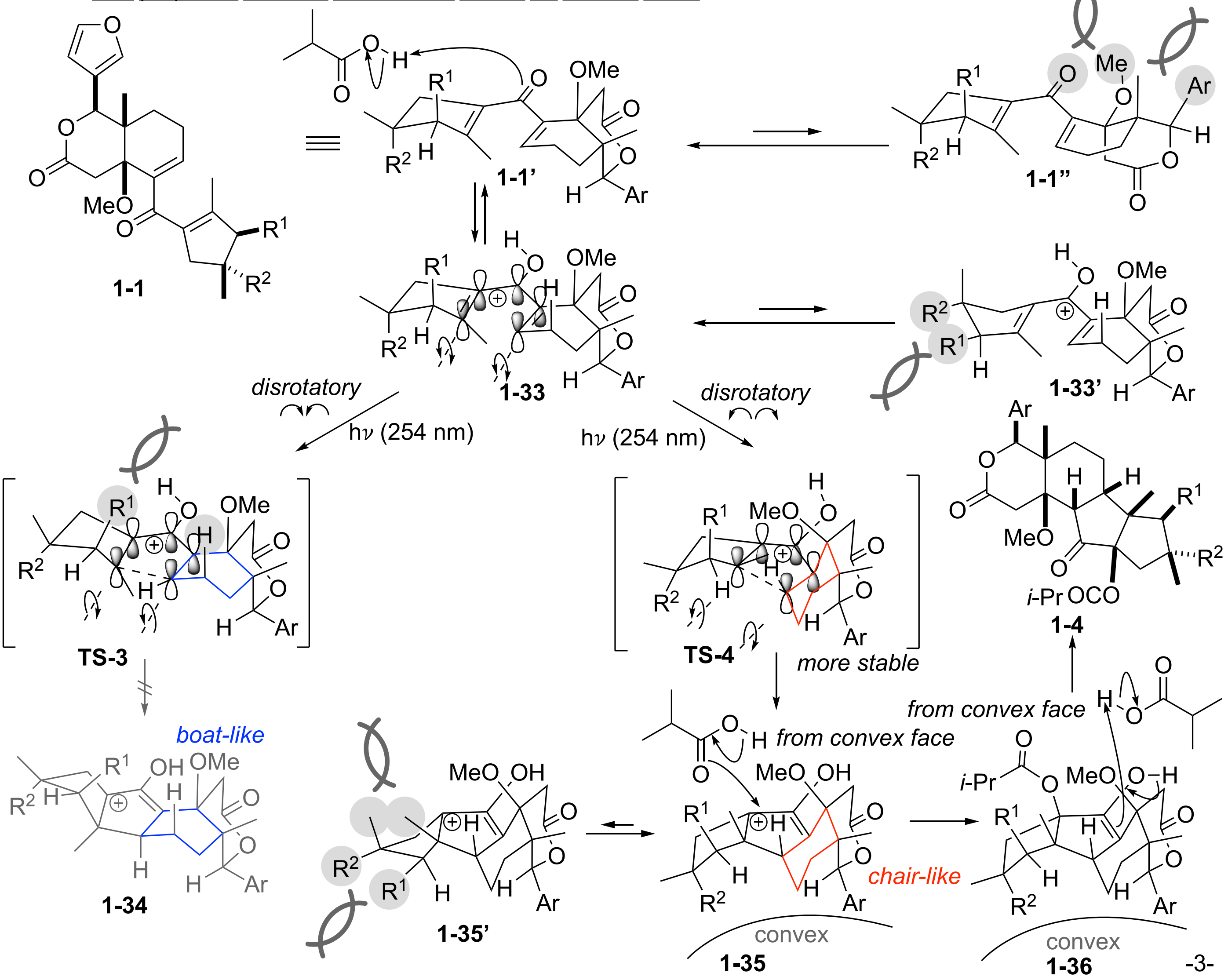


*The reaction temperature is not mentioned in the paper.



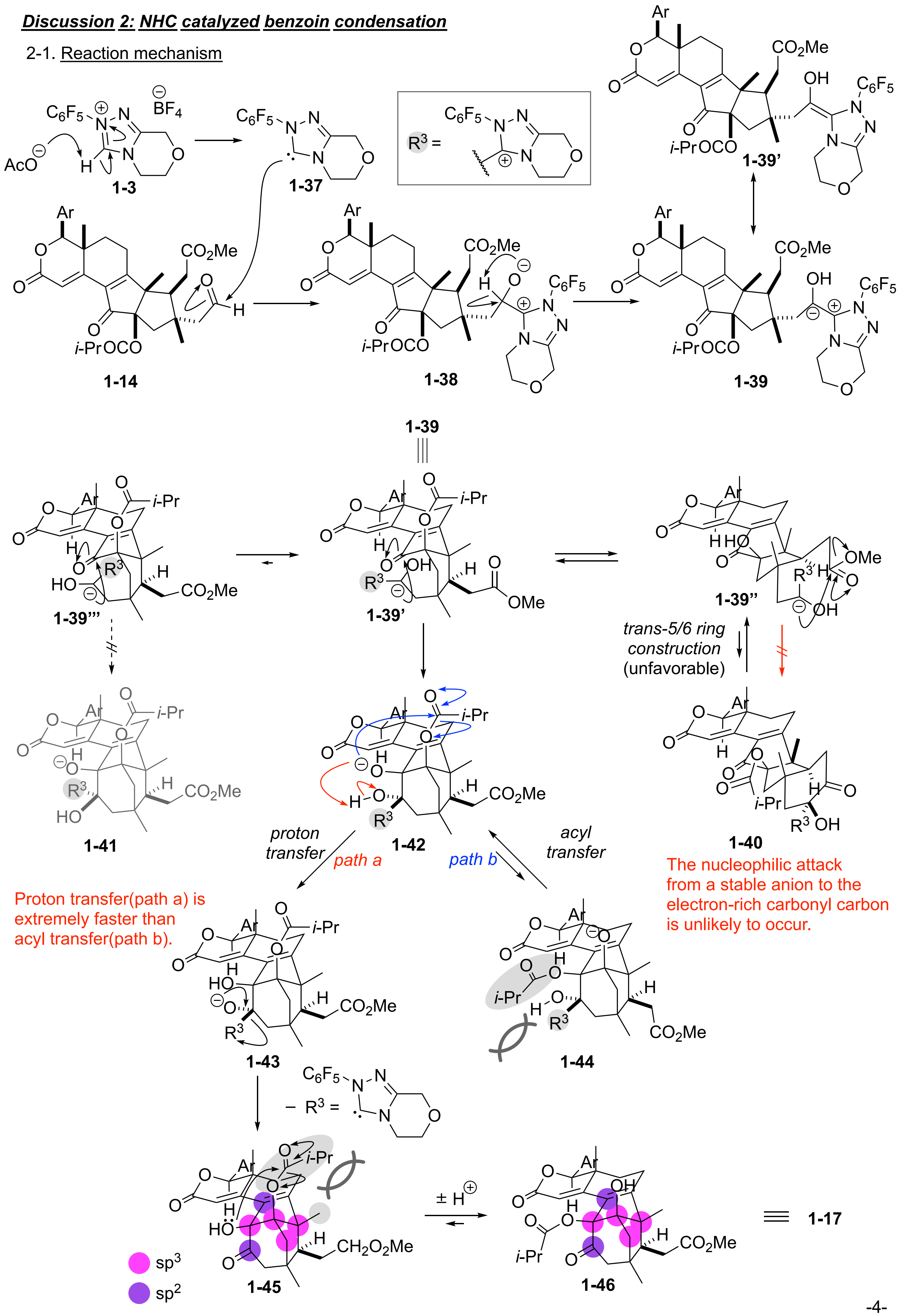


1-1-2. The proposed reaction mechanism based on section 1-1-1



Discussion 2: NHC catalyzed benzoin condensation

2-1. Reaction mechanism

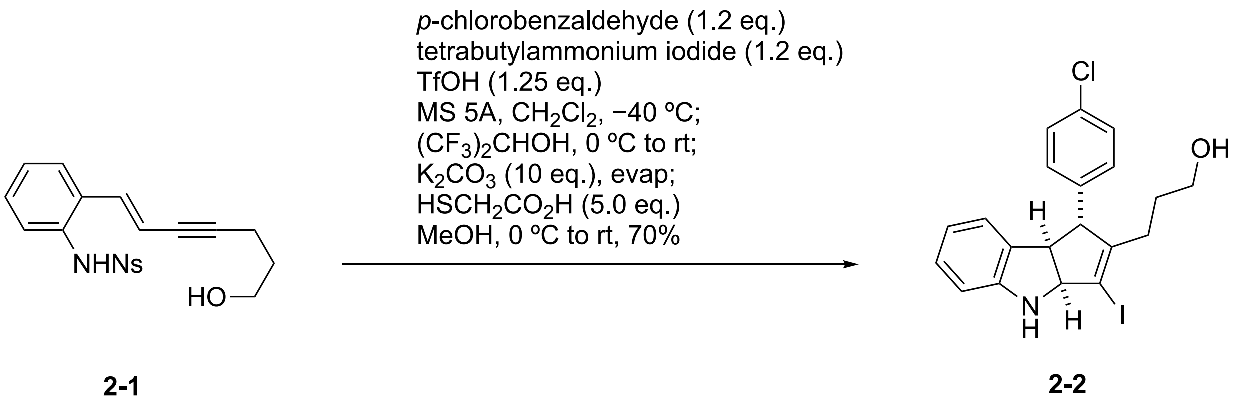


Proton transfer(path a) is extremely faster than acyl transfer(path b).

The nucleophilic attack from a stable anion to the electron-rich carbonyl carbon is unlikely to occur.

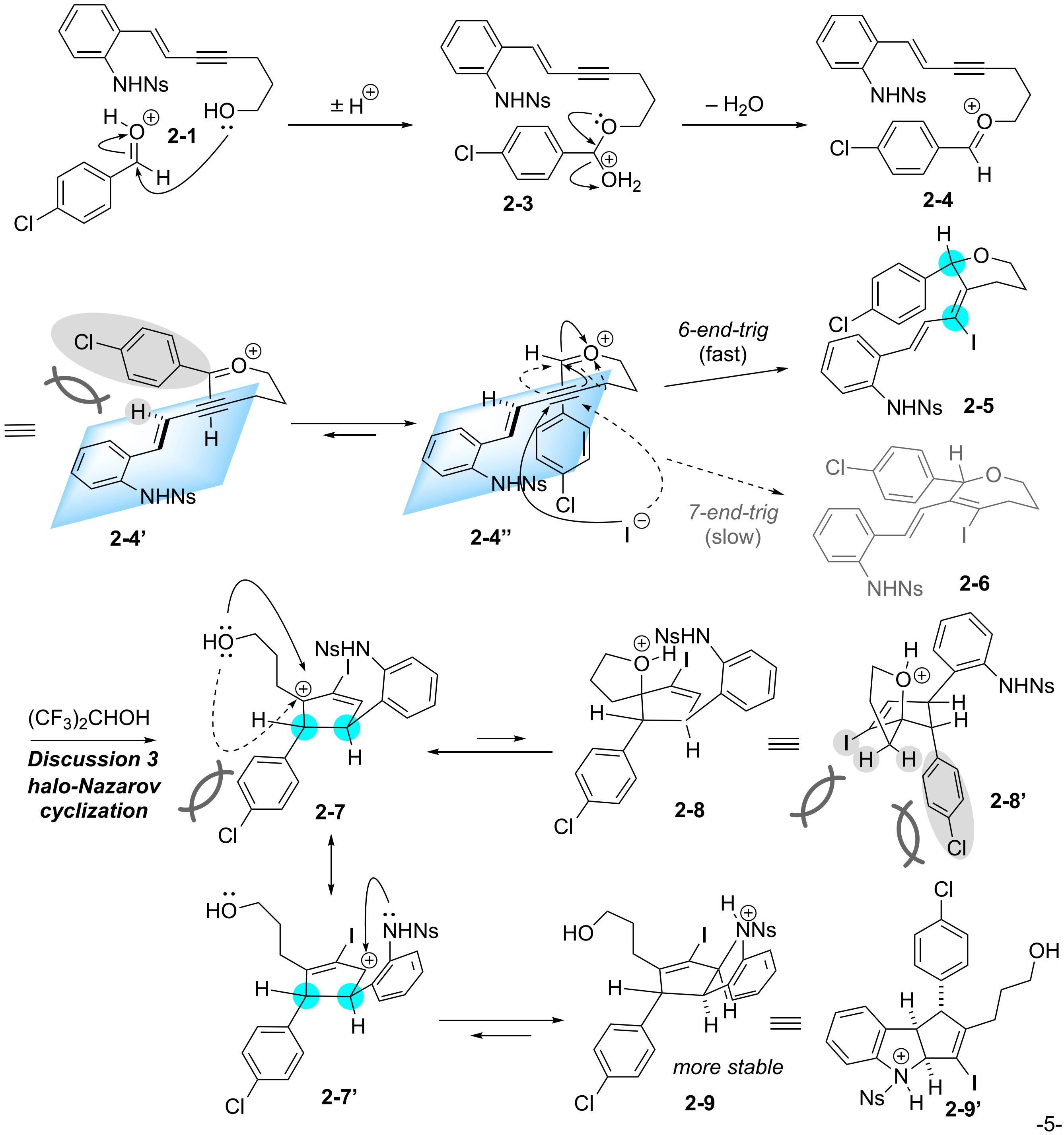
Problem 2: Nitrogen-interrupted halo-Prins/halo-Nazarov coupling cascade

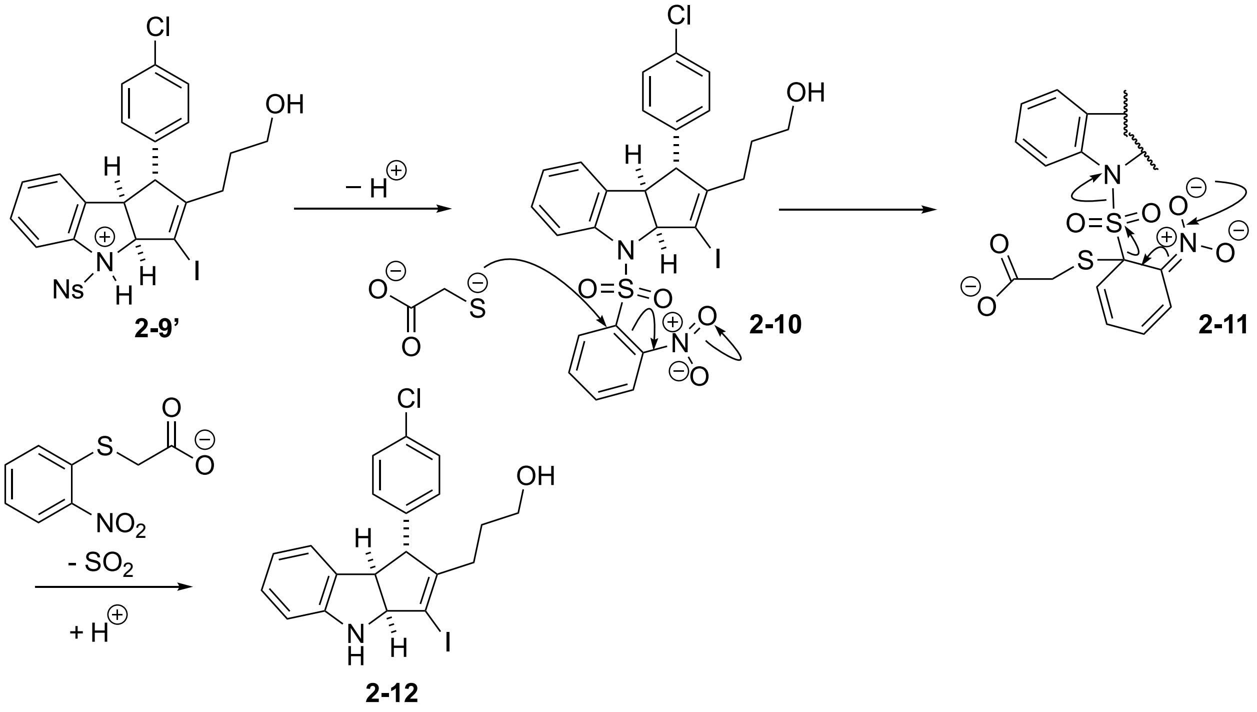
2 Please provide the reaction mechanism and stereoselectivity.



2-1 **2-2**

Milosavljevic, A.; Holt, C.; Frontier A. J. *Chem. Sci.* **2023**, *14*, 5431.

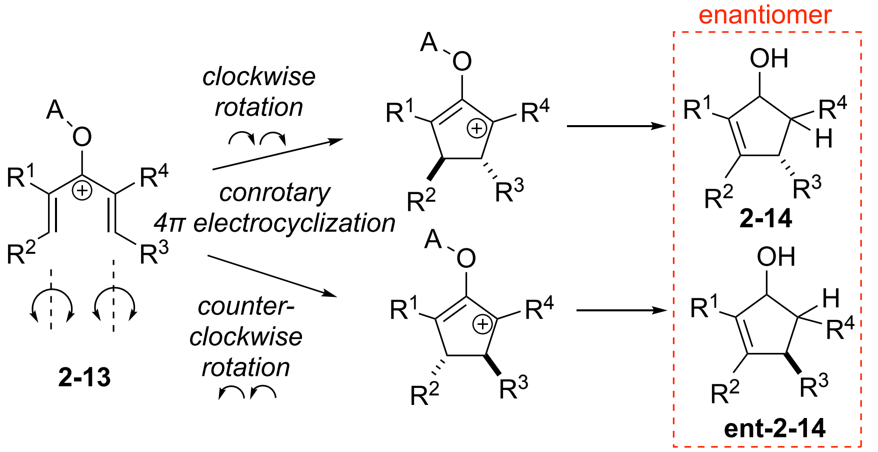


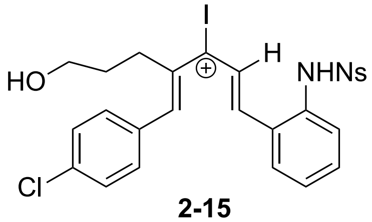


Discussion 3: halo-Nazarov cyclization

3-1. Reaction mechanism

3-1-1. Enantiomericity in Nazarov cyclization of achiral compound

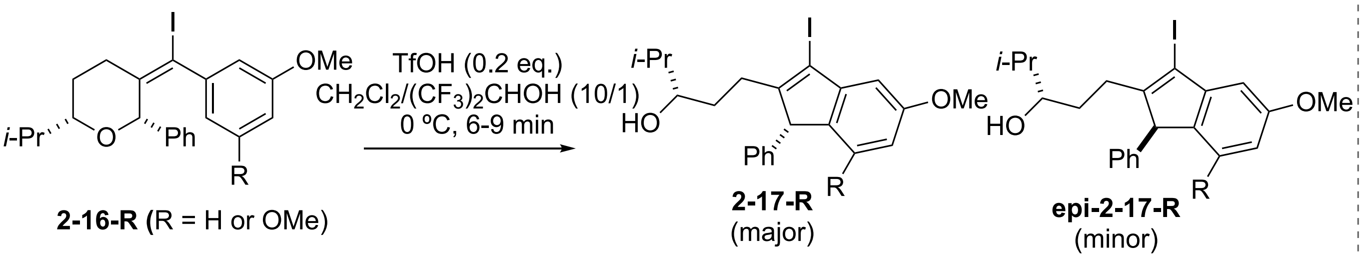




2-15

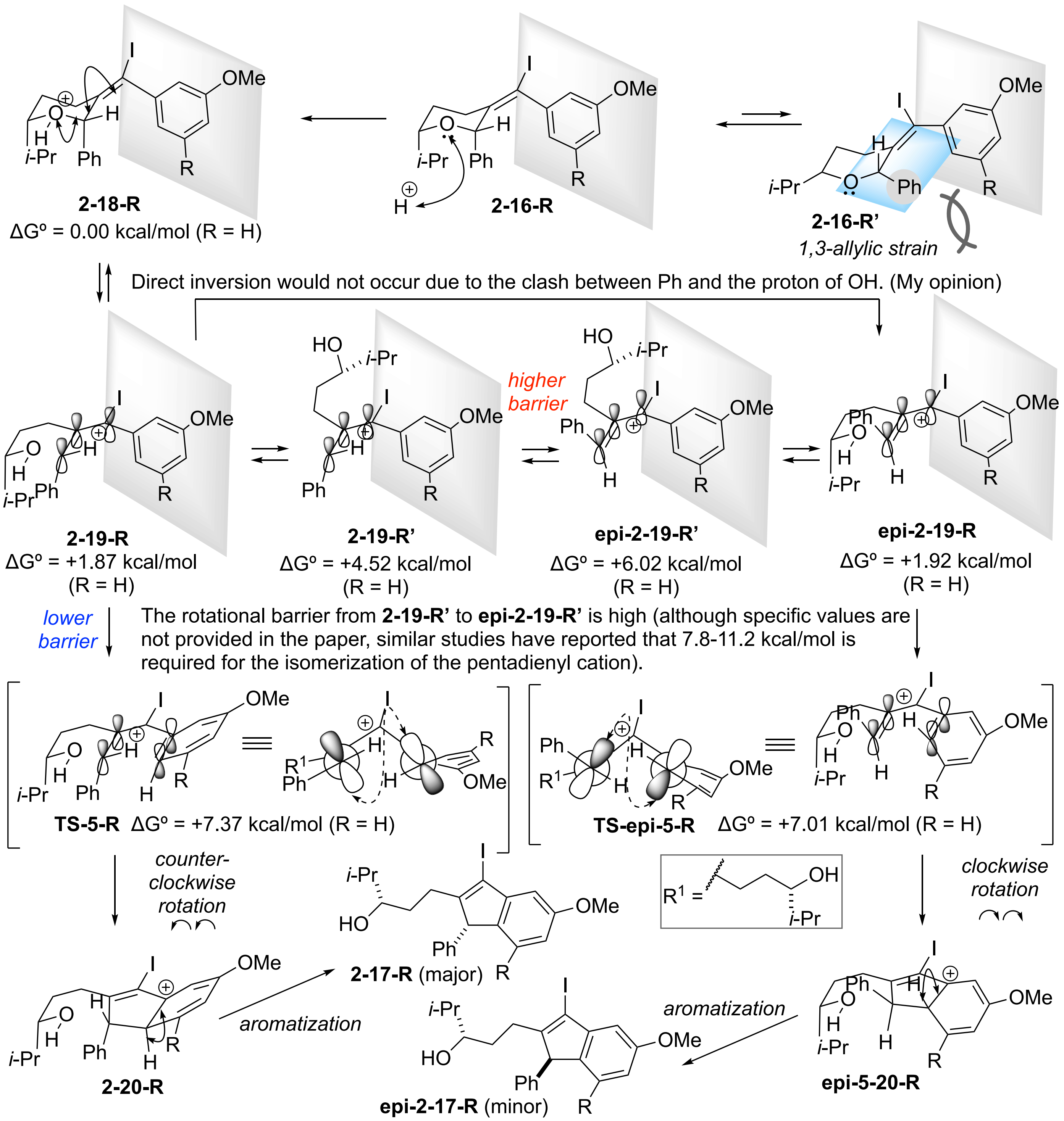
Generally, Nazarov cyclization of achiral compound is enantiomeric.
In problem 2, the Nazarov cyclization proceeds from the reaction intermediate 2-15, and enantiomers are obtained.
The reaction mechanism will be analyzed in detail based on the experimental results.

3-1-2. *Other results in similar compound and analysis of its pathways*



2-17-H:**epi-2-17-H** = 2.5:1 (92% yield)
2-17-OMe:**epi-2-17-OMe** = 6:1 (77% yield)

Alachouzos, G.; Holt, C.; Frontier, A. J. *Org. lett.* **2020**, *22*, 4010.



2-18-R ΔG° = 0.00 kcal/mol (R = H)

2-16-R

2-16-R’ *1,3-allylic strain*

Direct inversion would not occur due to the clash between Ph and the proton of OH. (My opinion)

2-19-R ΔG° = +1.87 kcal/mol (R = H)

2-19-R’ ΔG° = +4.52 kcal/mol (R = H)

epi-2-19-R’ ΔG° = +6.02 kcal/mol (R = H)

epi-2-19-R ΔG° = +1.92 kcal/mol (R = H)

The rotational barrier from **2-19-R’** to **epi-2-19-R’** is high (although specific values are not provided in the paper, similar studies have reported that 7.8-11.2 kcal/mol is required for the isomerization of the pentadienyl cation).

TS-5-R ΔG° = +7.37 kcal/mol (R = H)

TS-epi-5-R ΔG° = +7.01 kcal/mol (R = H)

2-20-R

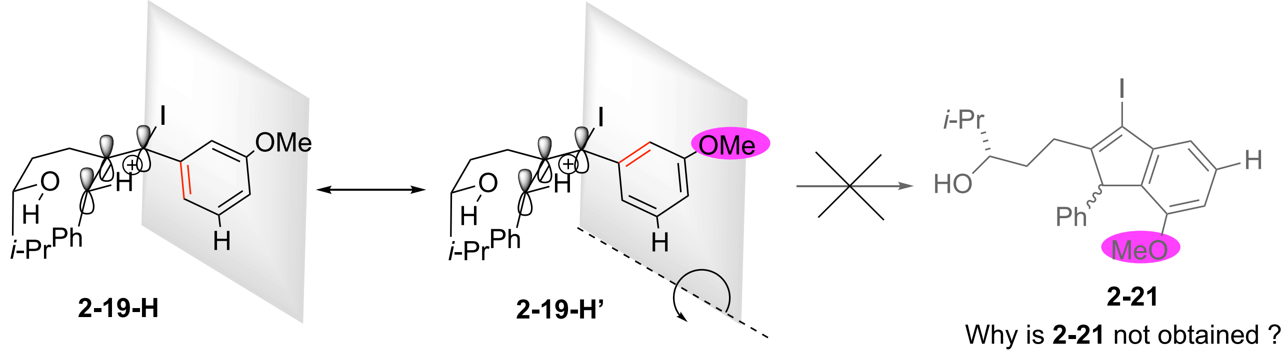
2-17-R (major)

epi-2-17-R (minor)

epi-5-20-R

- The reason **2-17-R** can be obtained as a major product is that the energy of the transition state **TS-5-R** is lower than that required for the isomerization from **2-19-R** to **epi-2-19-R**. (Author’s opinion)
- In the case of R = OMe, the improvement in the diastereomeric ratio is due to the stabilization of the transition state of **TS-5-R** through electron donation from OMe. (My opinion)

3-1-3. The direction of rotation of the surface painted in gray (My opinion)

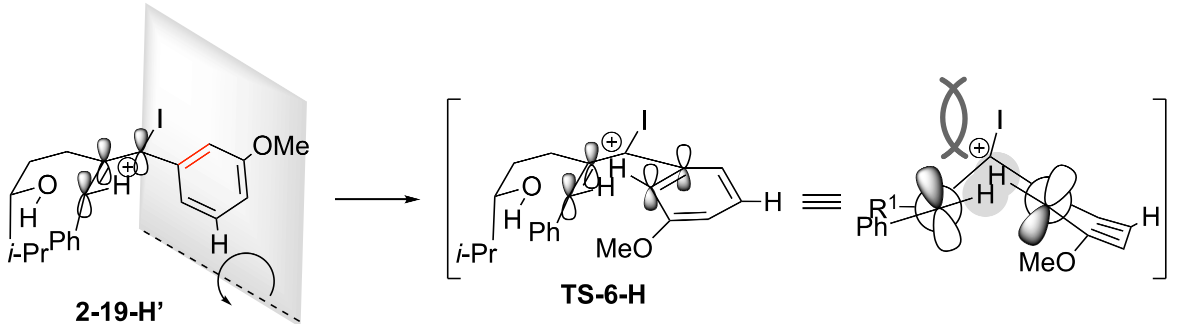


2-19-H

2-19-H’

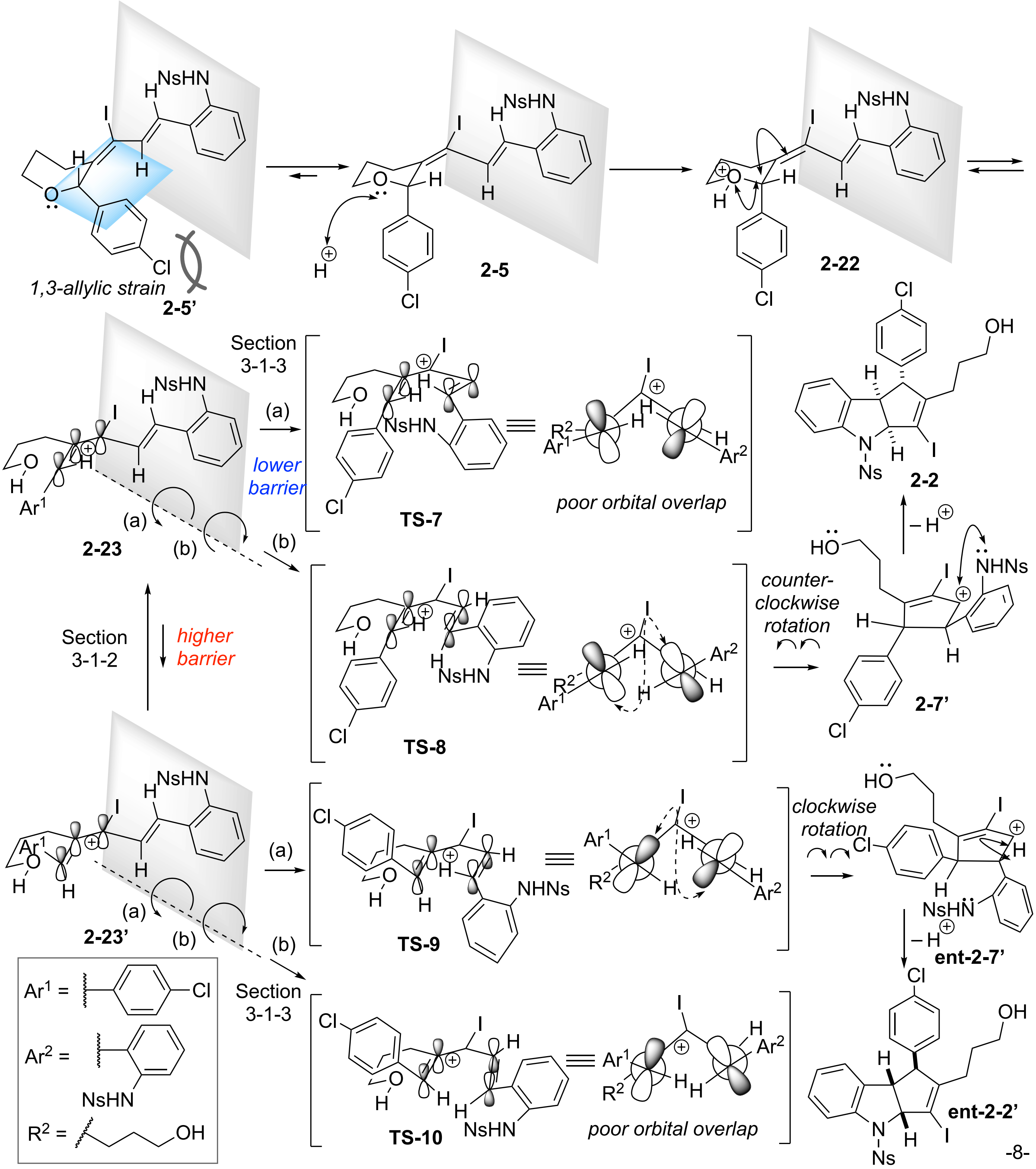
2-21

Why is **2-21** not obtained ?



The orbital overlap is poor due to steric repulsion between the hydrogen atoms.

3-1-4. The proposed reaction mechanism based on section 3-1-2 and 3-1-3 (My opinion)



More appropriate structures of the cationic intermediates and the transition states in page 7.