

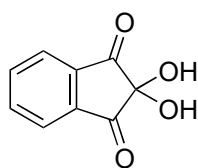
Problem Session (3)

2024.6.22. Shuji Toyama

Topic: Multicomponent reaction with ninhydrin

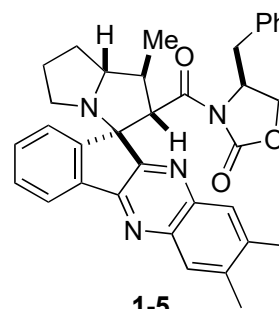
Please explain the reaction mechanisms and stereochemistry.

1.



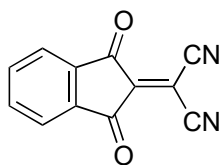
1-1

1-2 (1 equiv), EtOH (0.1 M), rt, 10 min
then 1-3 (1 equiv), 1-4 (1 equiv)
reflux, 20 h, 96%



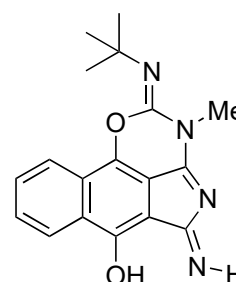
1-5

2.

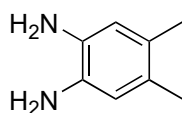
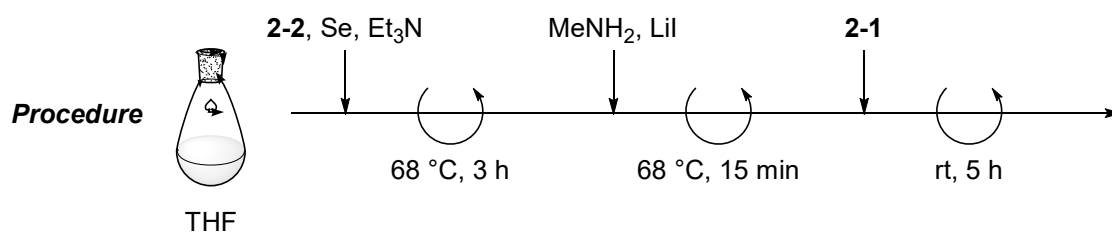


2-1

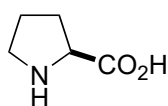
2-2 (1 equiv), MeNH₂ (1 equiv), Se (2 equiv)
Et₃N (1 equiv), Lil (30 mol%)
air, THF (0.3 M), **procedure**, 78%



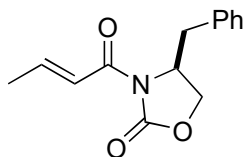
2-3



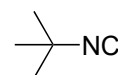
1-2



1-3



1-4

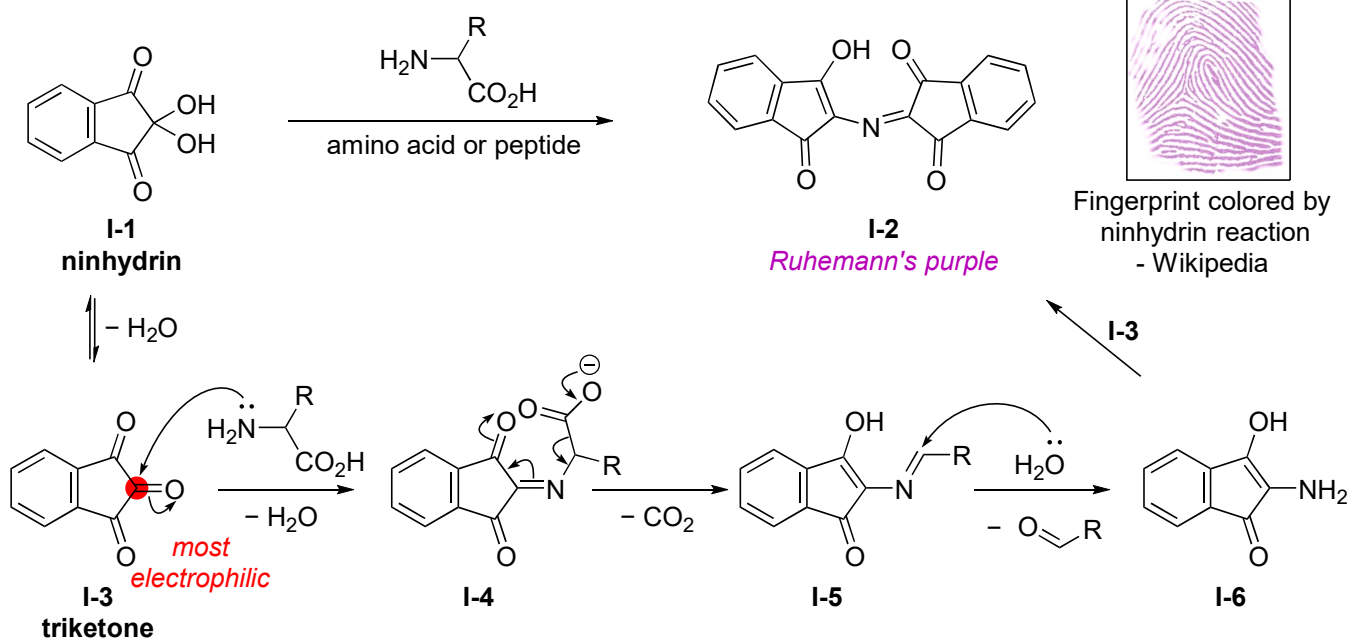


2-2

Problem Session (3) - Answer -
Topic: Multicomponent reactions with ninhydrin

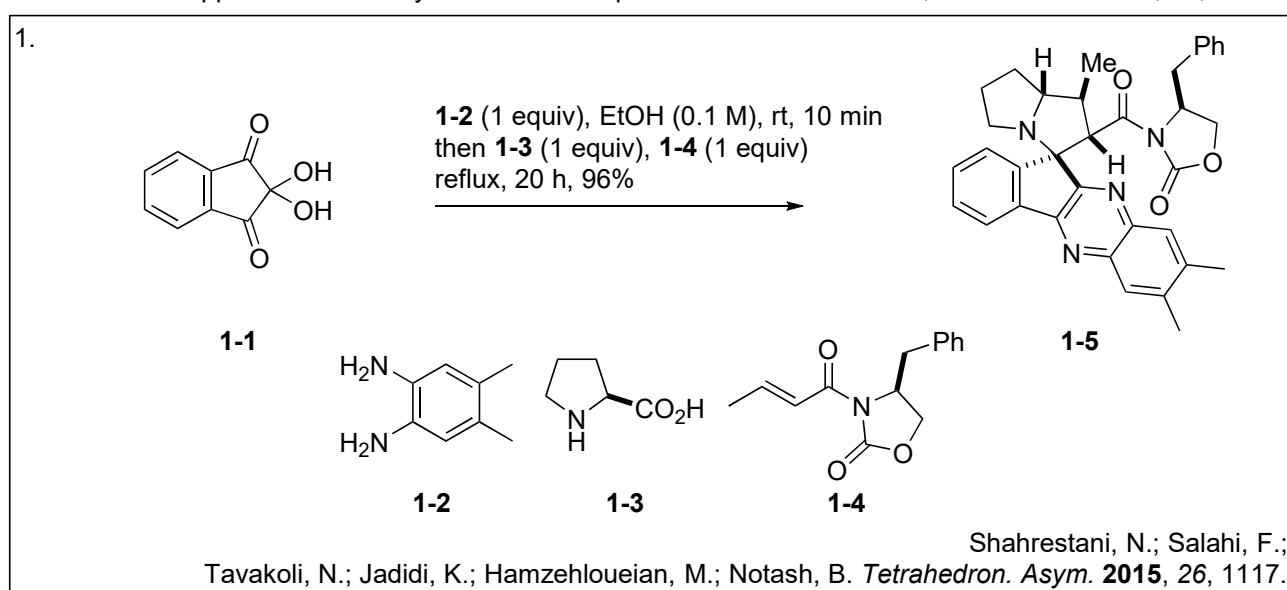
2024.6.22. Shuji Toyama

Introduction: Ninhydrin reaction

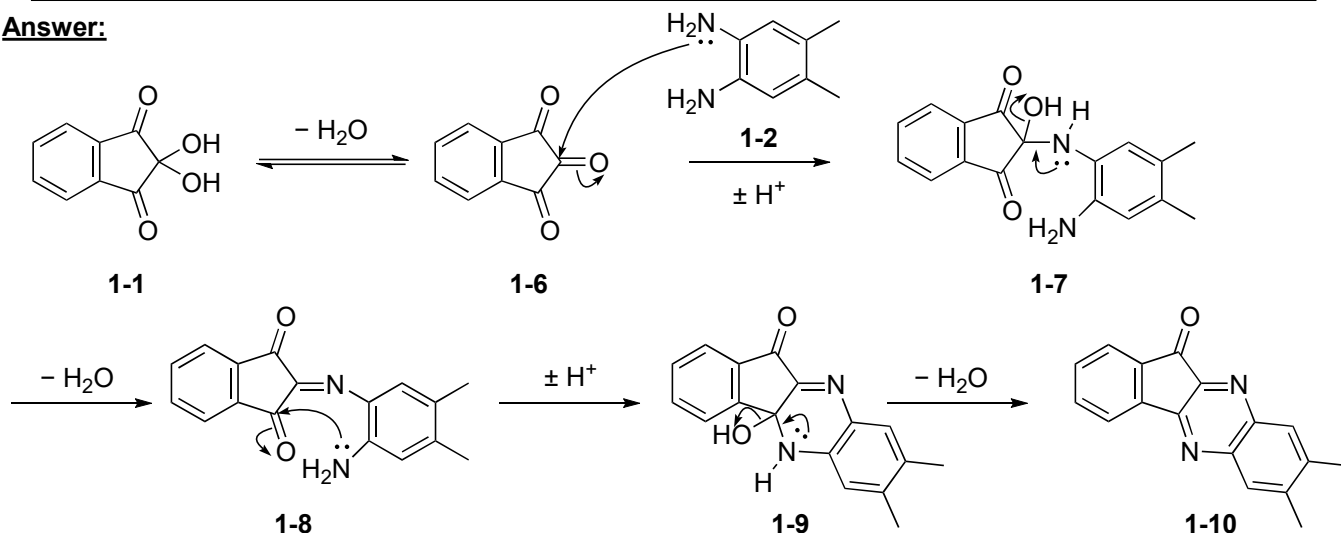


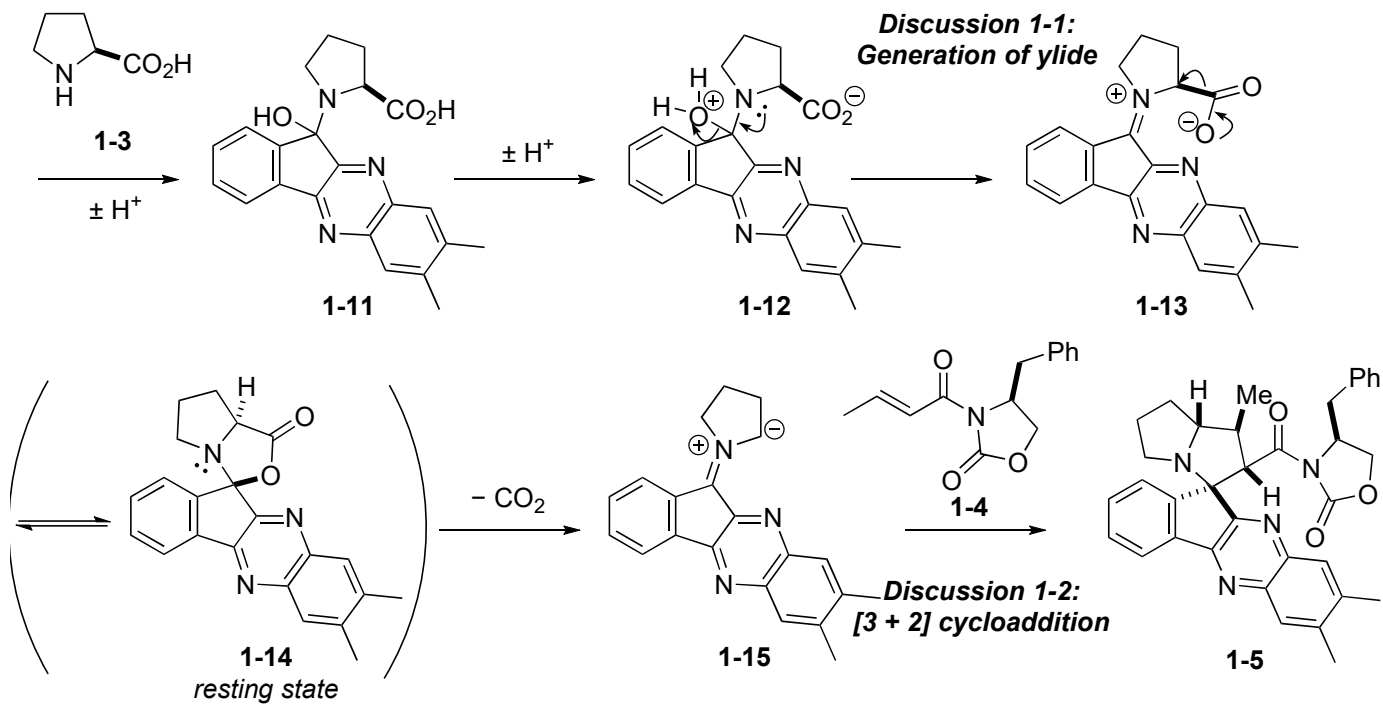
Ruhemann, S. *J. Chem. Soc. Trans.* **1911**, 99, 1486.

Ninhydrin reaction is a well-known reaction applied in fingerprint identification in the field of forensic science. Recent review of applications of ninhydrin in multicomponent reactions: → Das, S. *RSC Adv.* **2020**, 10, 18875.

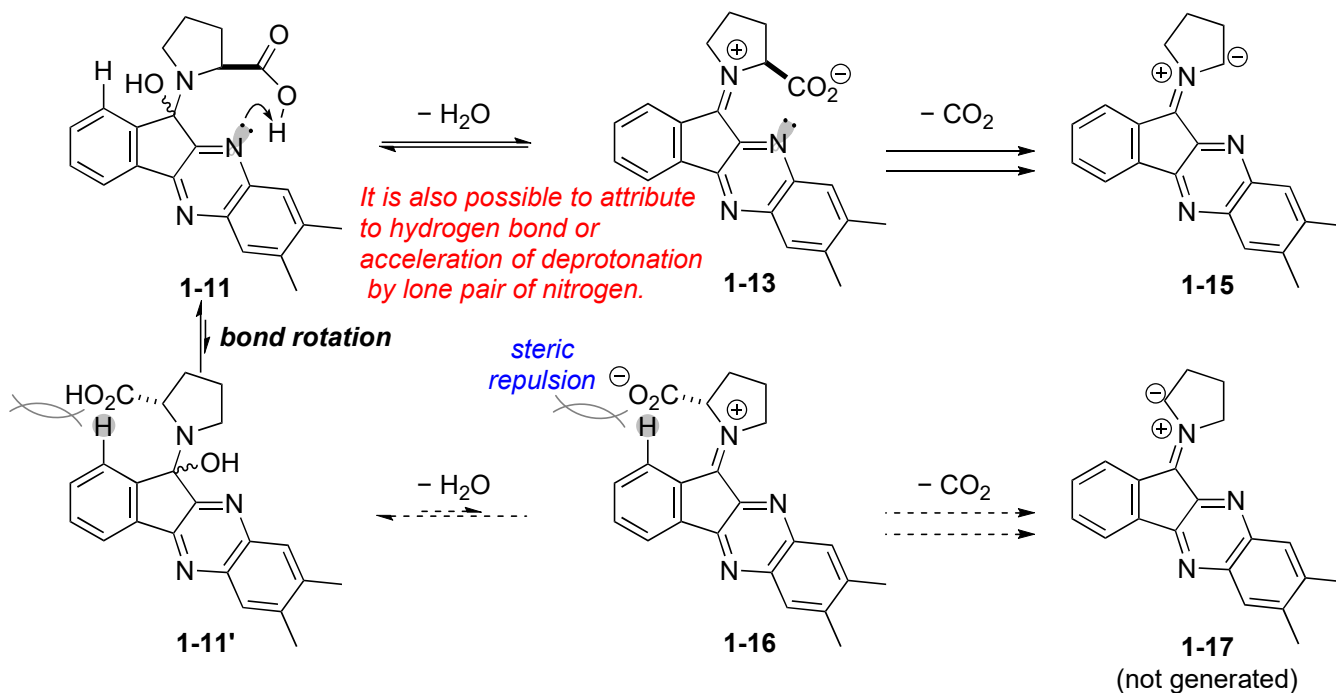


Answer:



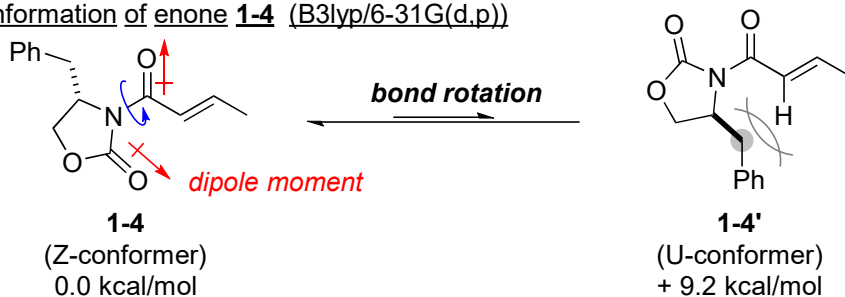


Discussion 1-1: Generation of ylide



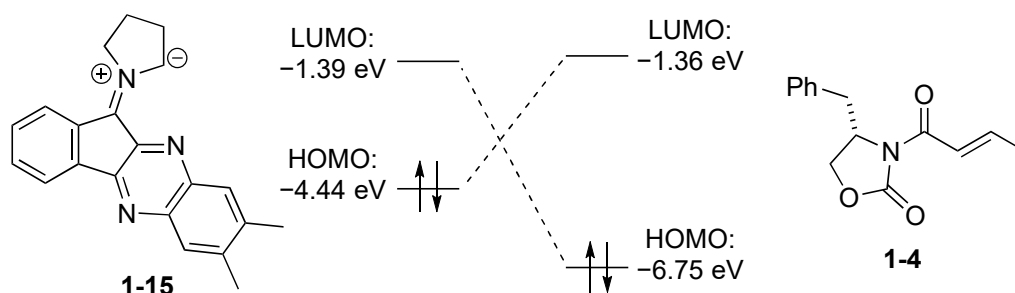
Discussion 1-2: [3 + 2] cycloaddition

1. Conformation of enone **1-4** (B3lyp/6-31G(d,p))



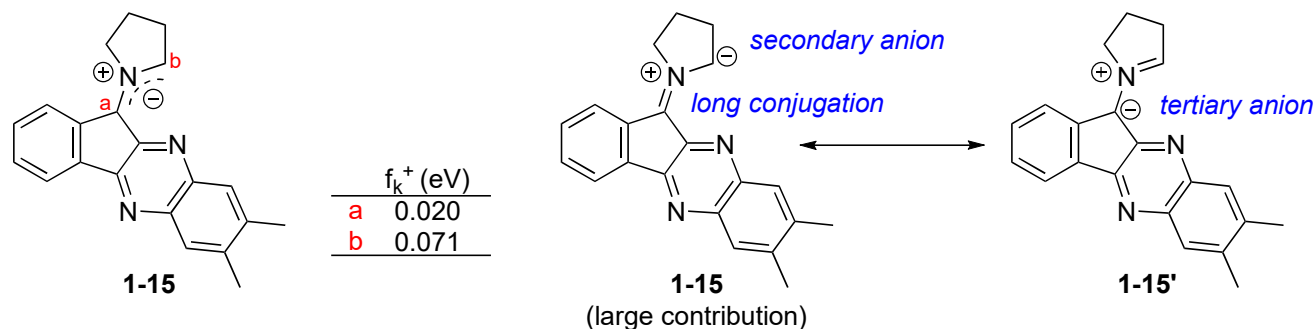
Z-conformer **1-4** is favored in 9.2 kcal/mol than U-conformer **1-4'**, maybe because there is the steric repulsion in **1-4'** between methylene group and proton of enone α position. Therefore, only Z-conformer **1-4** will be discussed in the following section.

2. HOMO, LUMO calculation of azomethine ylide **1-15** and enone **1-4** (B3lyp/6-31G(d,p))



The energy gap between HOMO₁₋₁₅ and LUMO₁₋₄ (Δ 3.08 eV) is lower than that of HOMO₁₋₁₅ and LUMO₁₋₄ (Δ 5.36 eV). Therefore, this cycloaddition reaction is controlled by HOMO_{dipole}-LUMO_{dipolarophile} interaction (normal electron demand reactions).

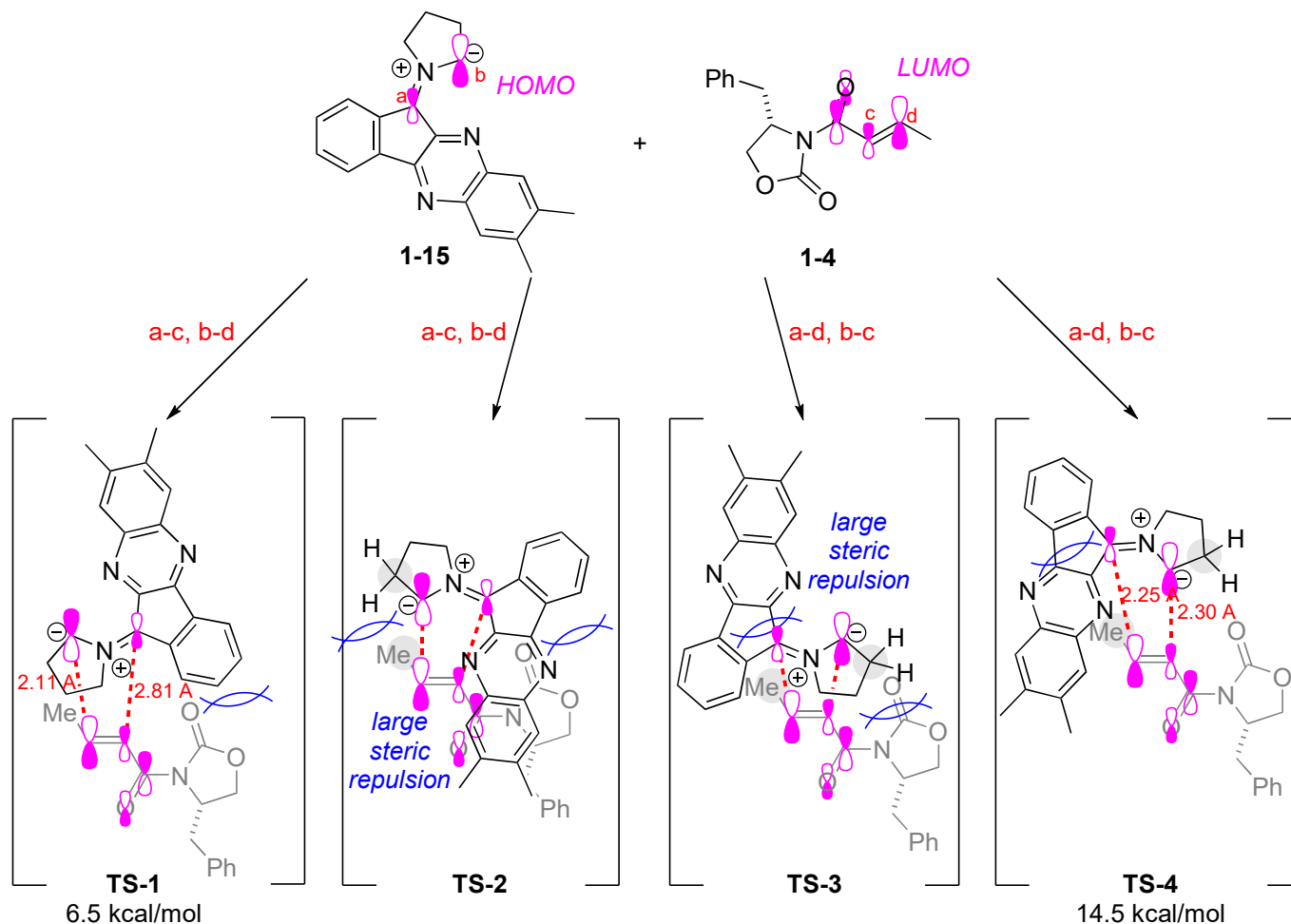
3. Localization of charge in azomethine ylide **1-15** (B3lyp/6-31G(d,p))



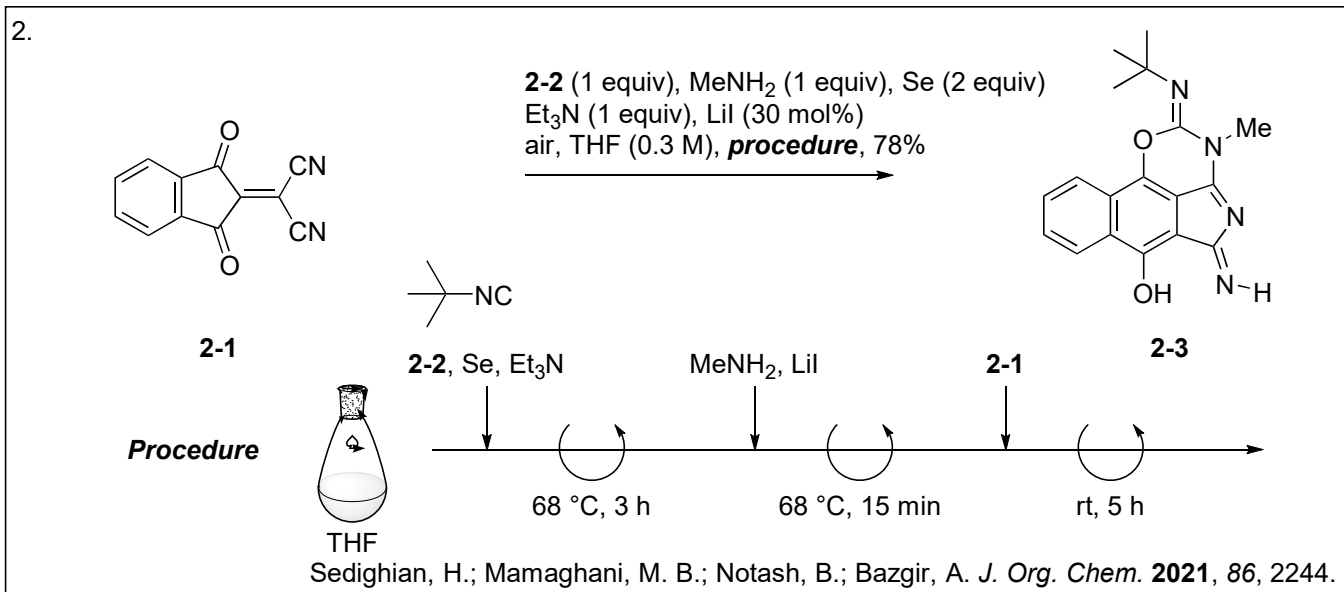
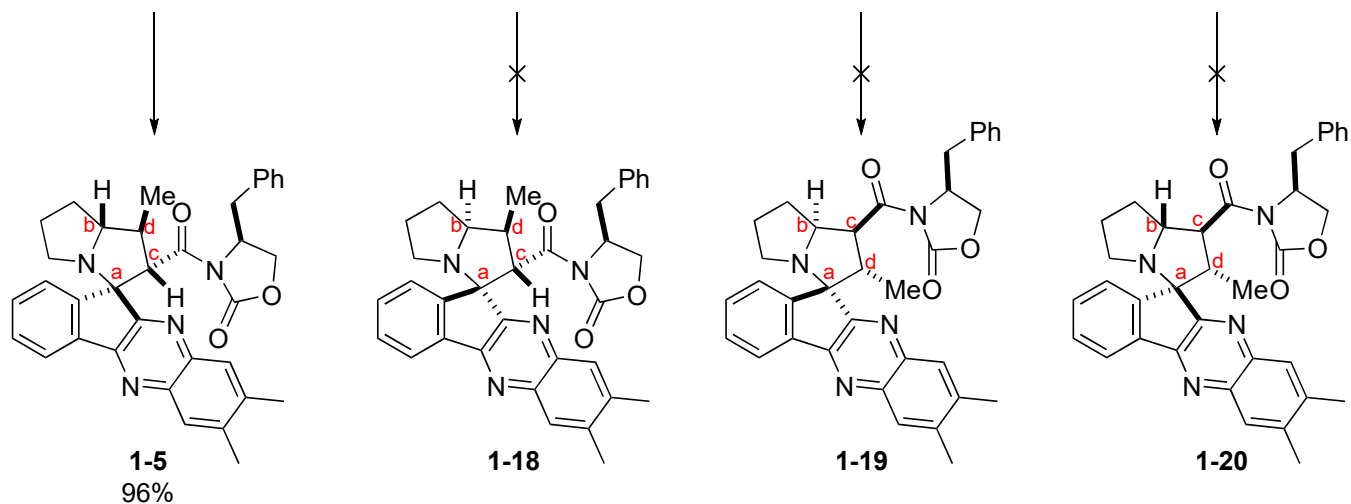
f_k^+ : Fukui function for nucleophilic attack

The calculation of Fukui function shows C_b is more nucleophilic than C_a . This result suggests that C_b is better to connect enone β position based on frontier orbital theory that explain the bond formation at the site of the largest LUMO of nucleophile and the largest HOMO of electrophile.

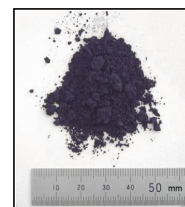
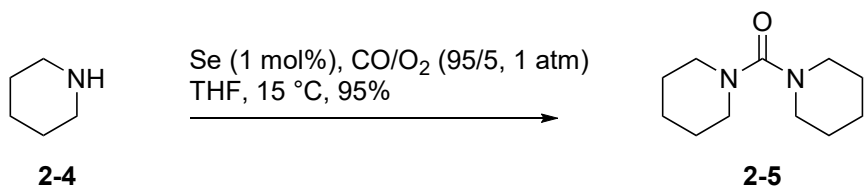
4. Explanation of regio- and stereoselective [3 + 2] cycloaddition



Steric factor: **TS-1** > **TS-4** >> **TS-2**, **TS-3**
Orbital interaction: **TS-1**, **TS-2** > **TS-3**, **TS-4**



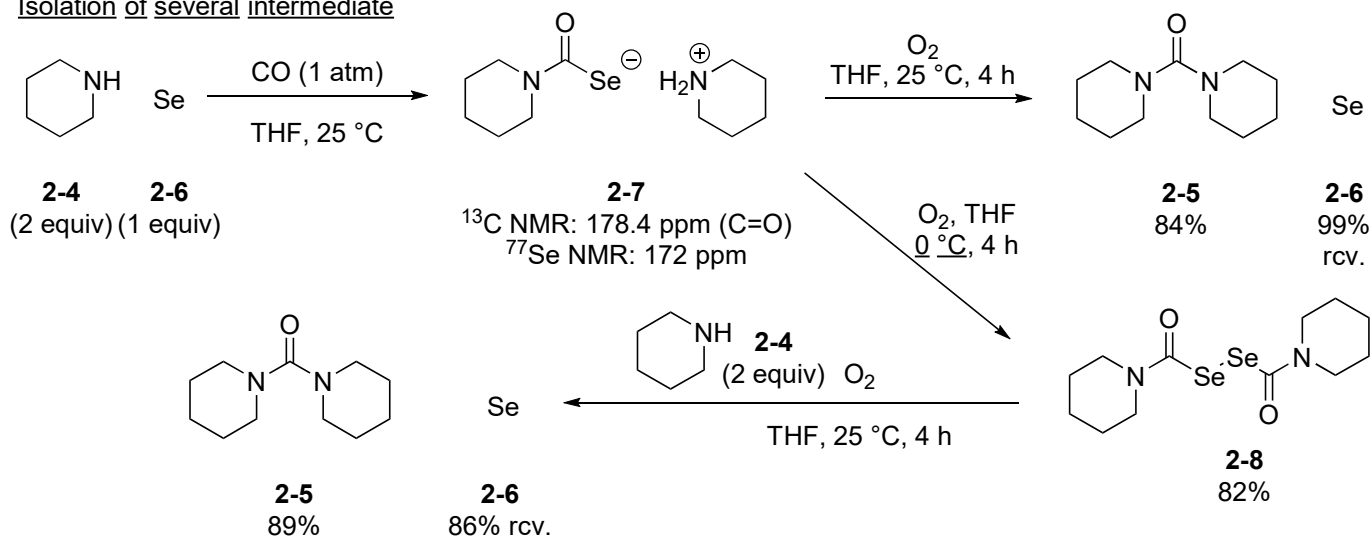
Introduction: The use of elemental Se. <Se/CO system>



Se powder
dark red, black
- e-nacalai

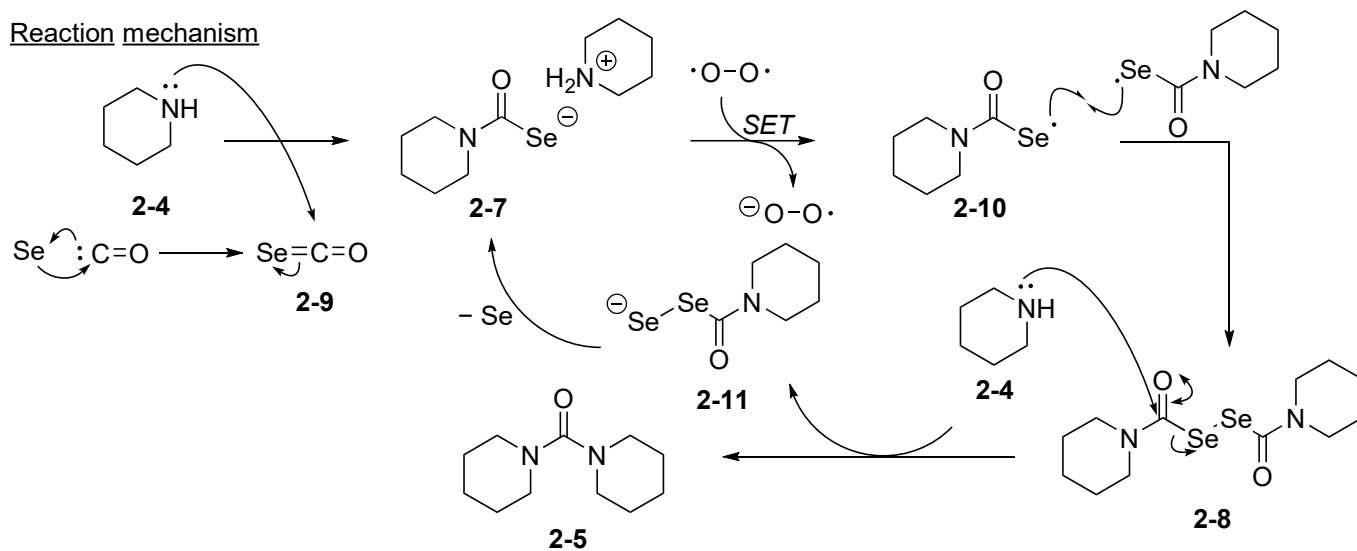
Sonoda, N. *Pure & Appl. Chem.* **1993**, *65*, 699.

Isolation of several intermediate

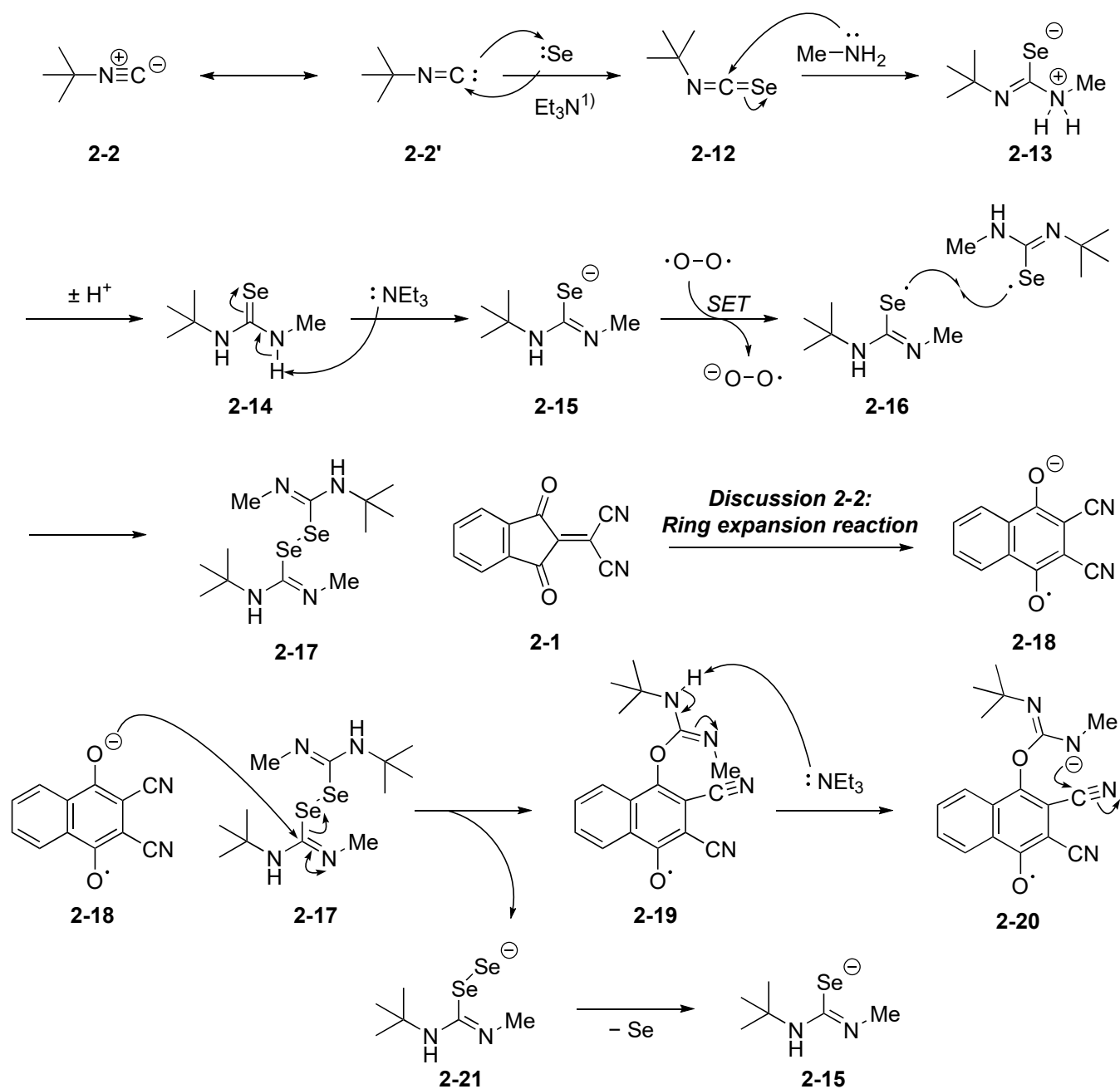


Fujiwara, S.; Miyoshi, N.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Phys. Org. Chem.* **1989**, *2*, 359.

Reaction mechanism

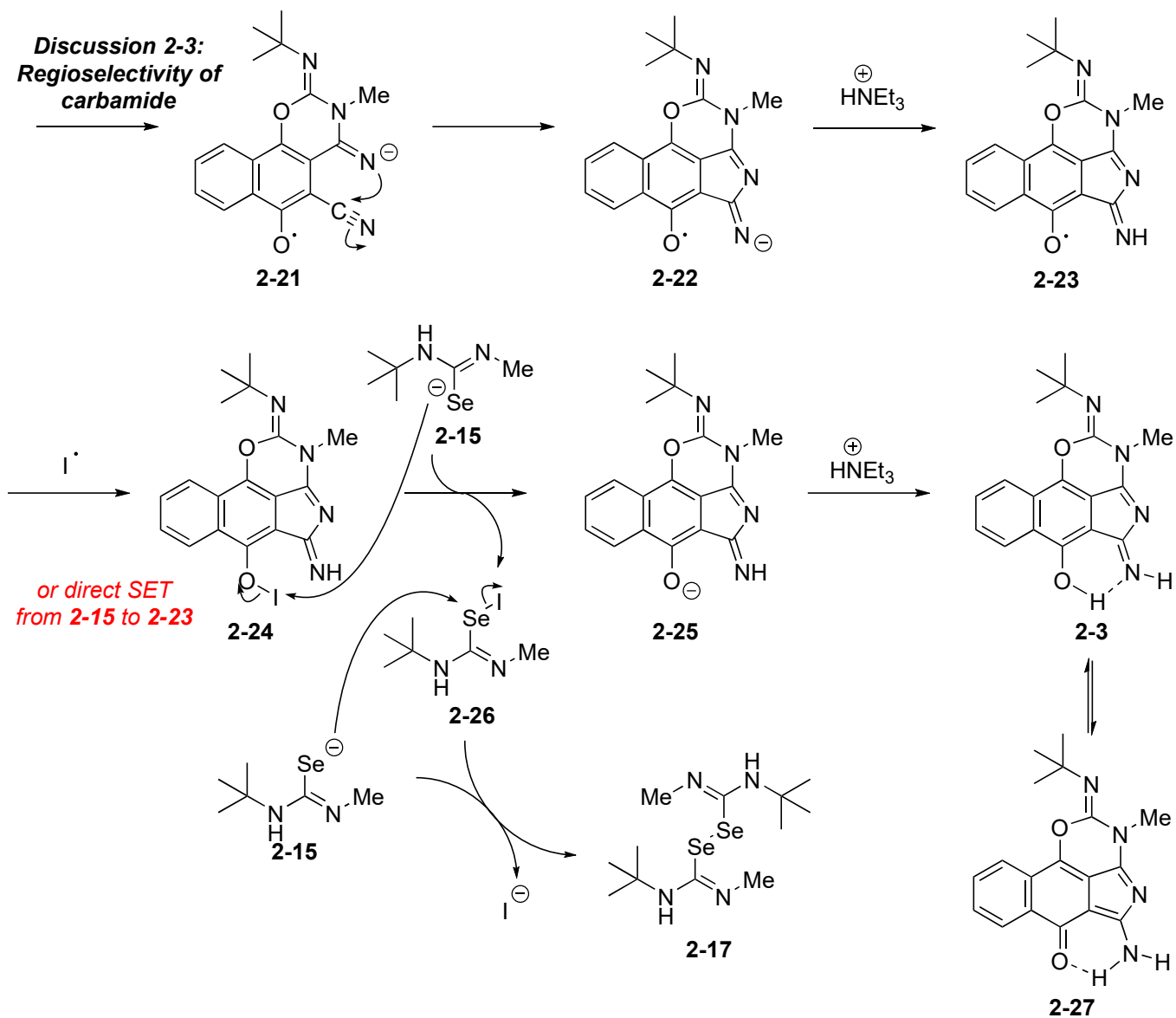


Answer: Discussion 2-1: Optimization and control experiment

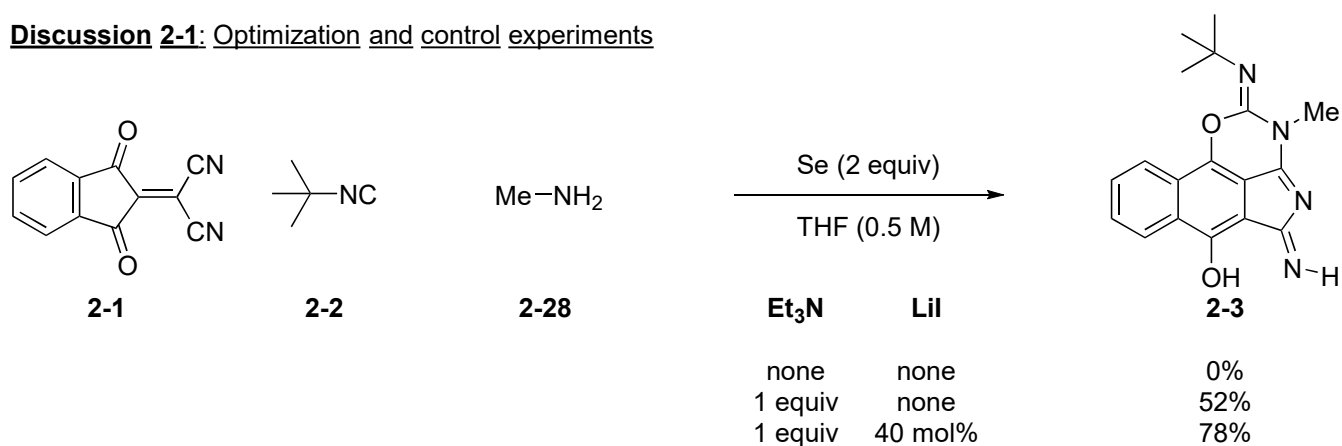


1) Sonoda, N.; Yamamoto, G.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* **1972**, *46*, 2937.

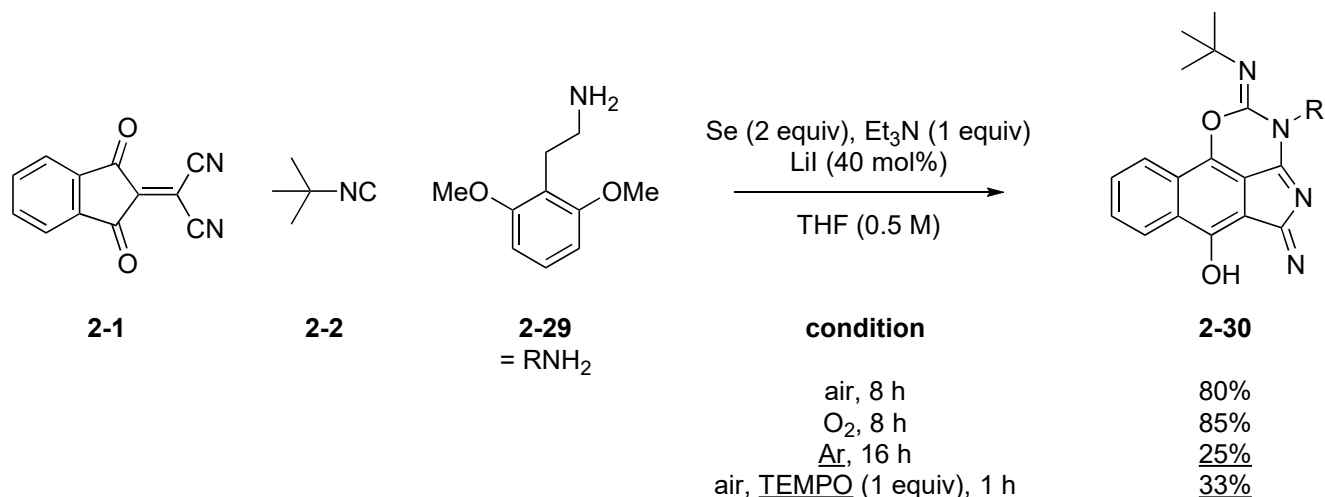
Discussion 2-3: Regioselectivity of carbamide



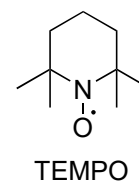
Discussion 2-1: Optimization and control experiments



Et₃N was necessary for the reaction. Lil promoted the reaction, although 2-3 was obtained in moderate yield without Lil.

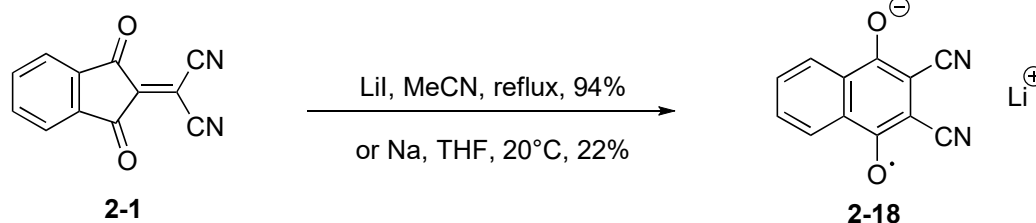


O₂ promoted the reaction. The yield got low when TEMPO was added as a radical scavenger, so radical intermediates should be involved in the reaction.



Discussion 2-2: Ring expansion reaction

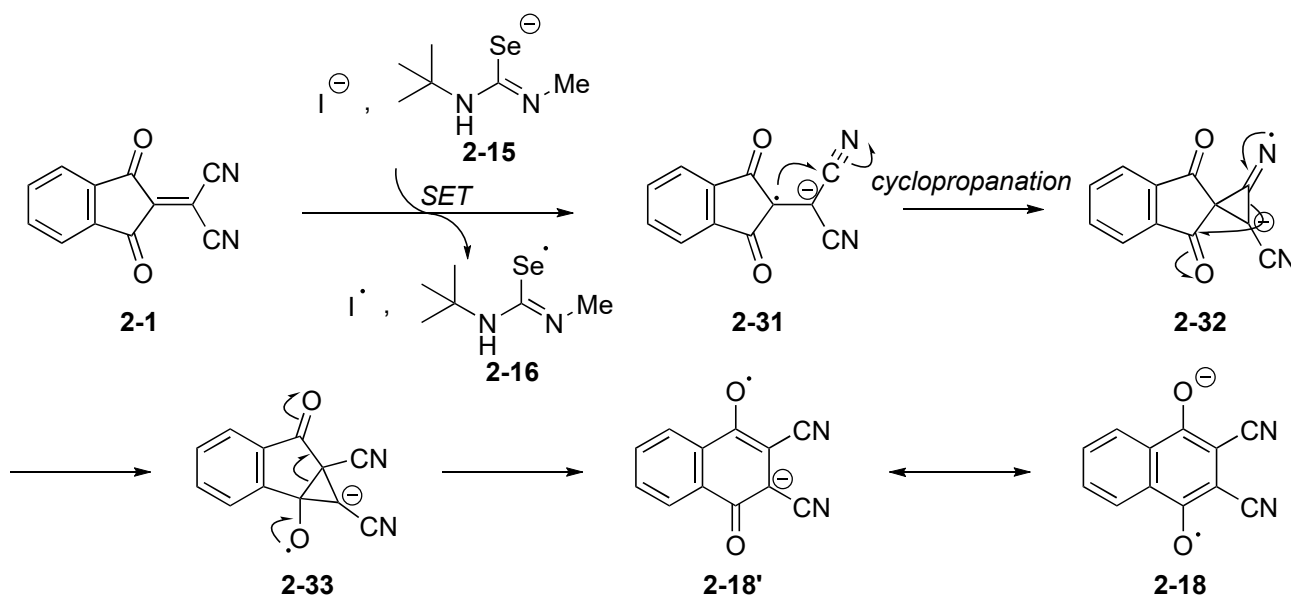
1. Isolation of radical anion 2-18



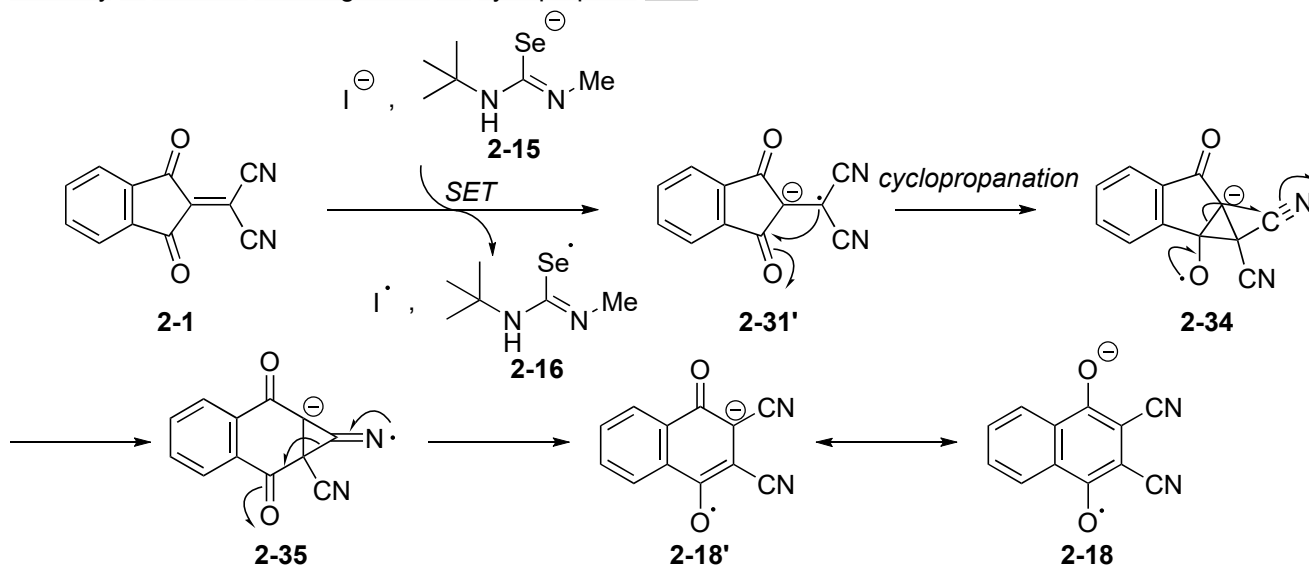
Ashwell, G. J.; Bryce, M. R.; Davies, S. R.; Hasan, M. *J. Org. Chem.* **1988**, *53*, 4585.
 Bryce, M. R. S.; Davies, R.; Hasan, M.; Ashwell, G. J.; Szablewski, M.; Drew, M. G. B.; Short, R.; Hursthouse, M. B. *J. Chem. Soc. Perkin. Trans.* **1989**, *2*, 1285.

2. Possible reaction mechanisms

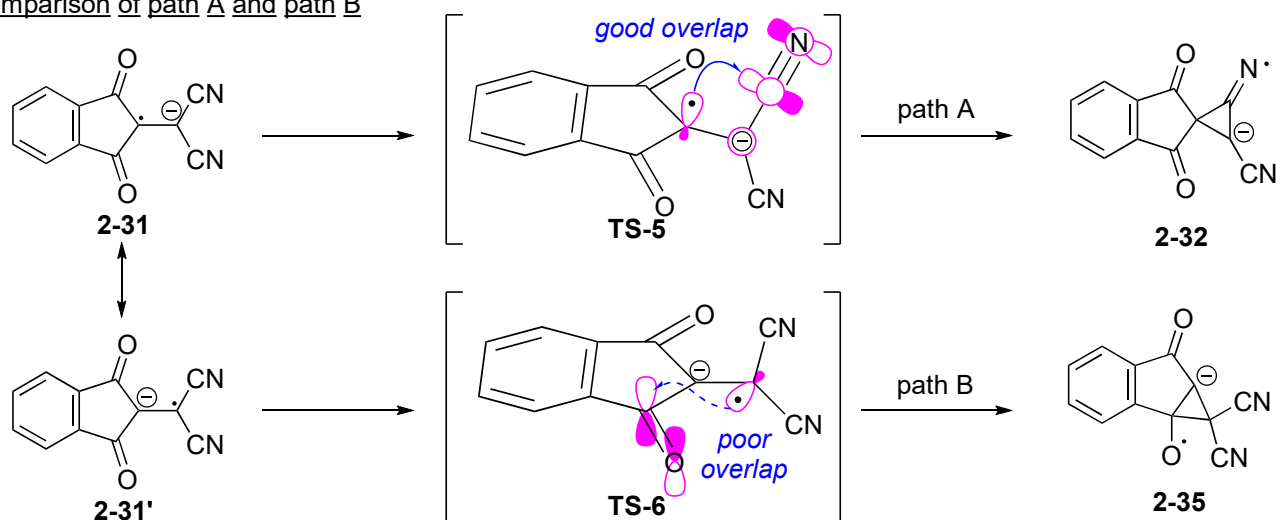
Pathway A: Skeletal rearrangement via cyclopropane 2-32 (proposed by author)



Pathway B: Skeletal rearrangement via cyclopropane **2-34**



3. Comparison of path A and path B



Carbanion and π^* orbital of nitrile show good overlap in **TS-5**. Therefore, I think path A is the most reasonable reaction pathway.

Discussion 2-3: Regioselectivity of carbamide

