

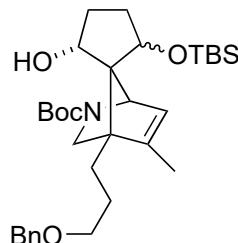
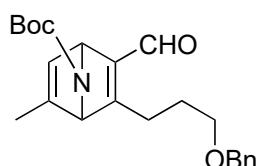
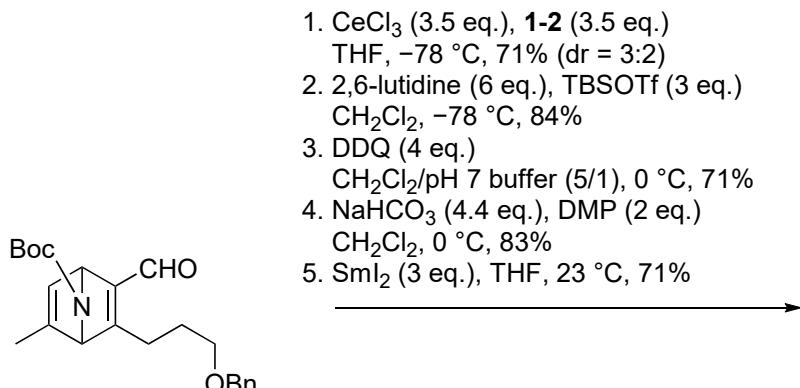
## Problem Session (5)

2023.7.29. Shu Nakamura

**Topic:** Use of Diels-Alder adduct

Please explain the reaction mechanism.

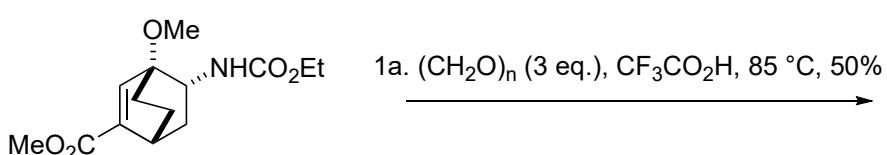
1.



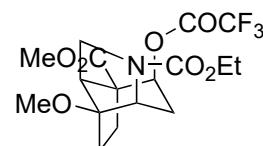
**1-1**

**1-3**  
( $\text{dr} = 3:2$ )

2.a)

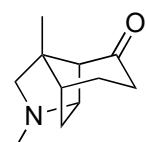
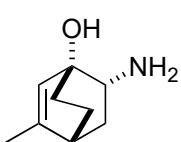
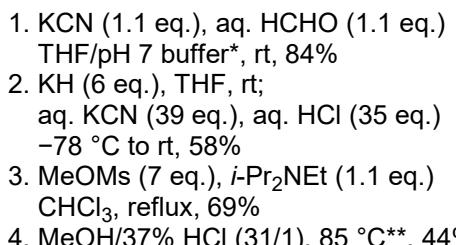


**2-1**



**2-2**

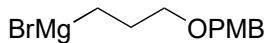
b)



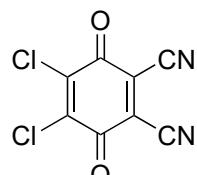
**2-3**

\* aq.  $\text{HCl}$  was slightly added to keep pH 7.  
\*\* in a sealed ampule

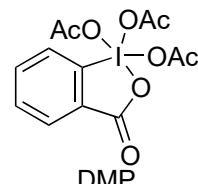
**2-4**



**1-2**



**DDQ**

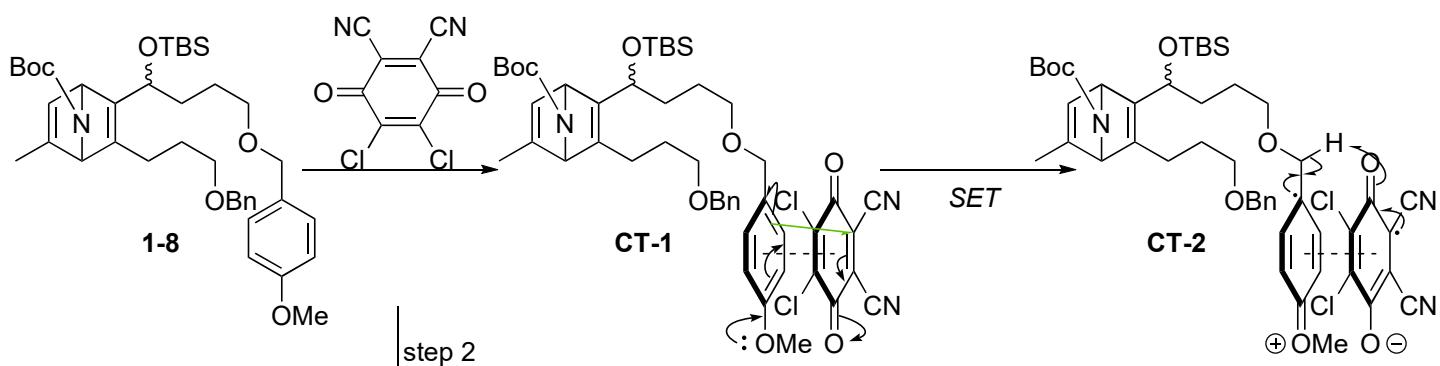
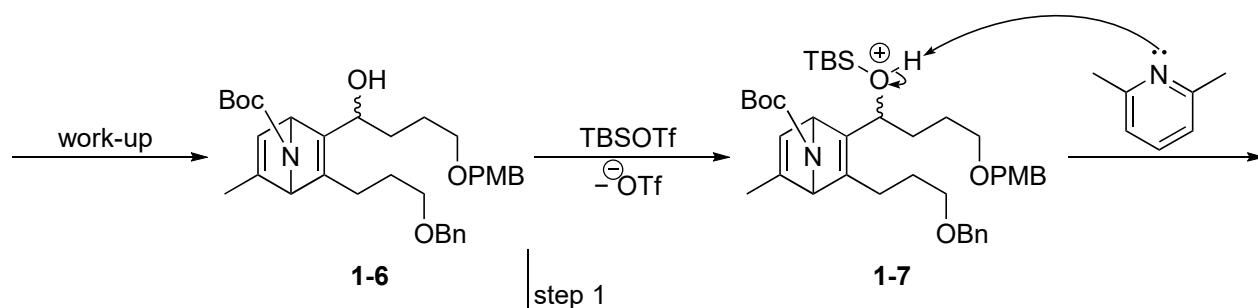
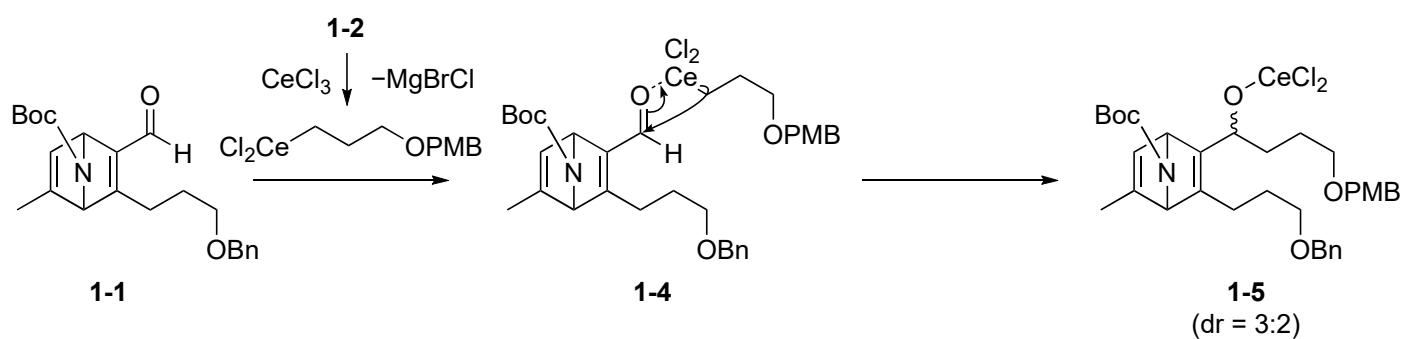
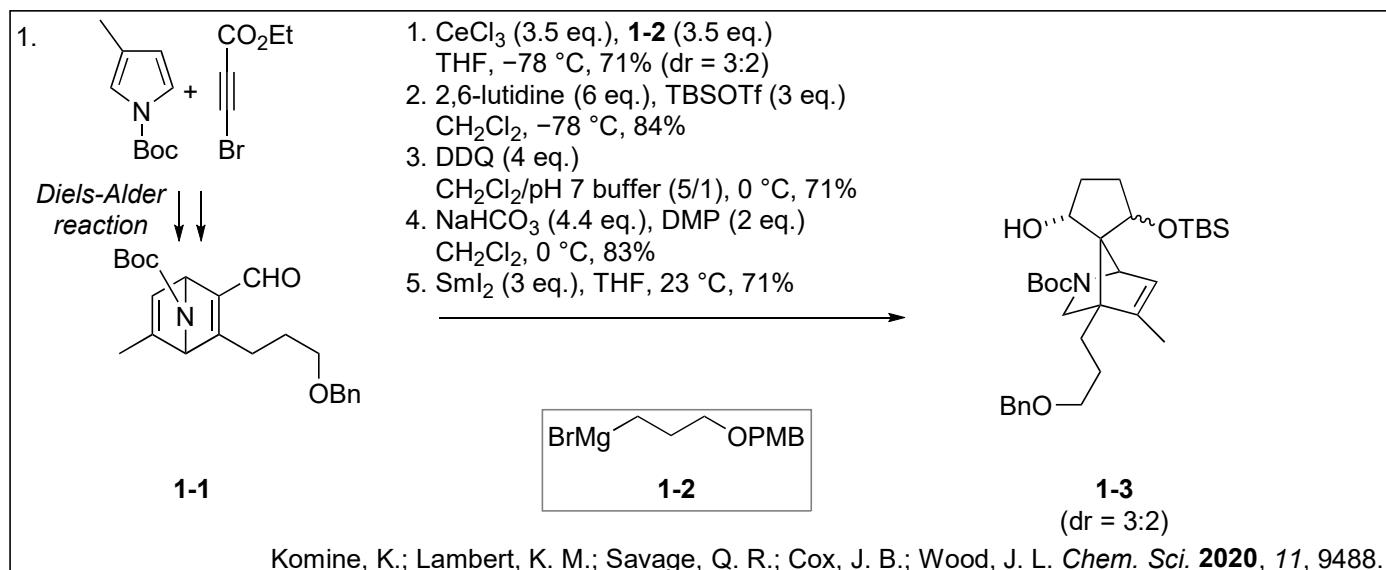


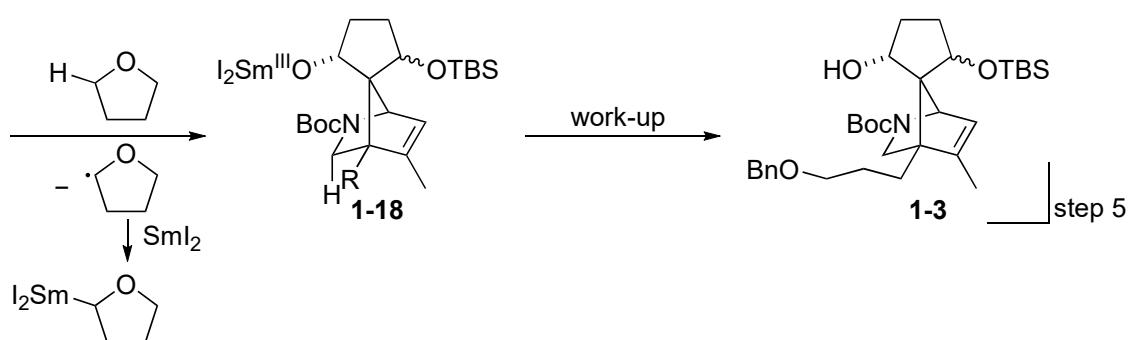
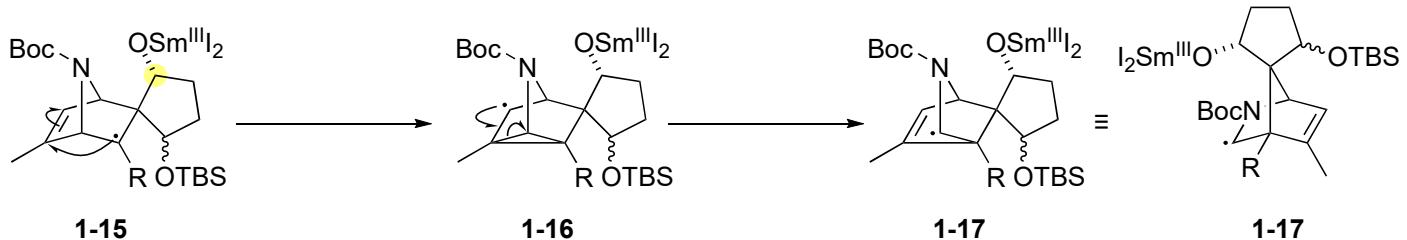
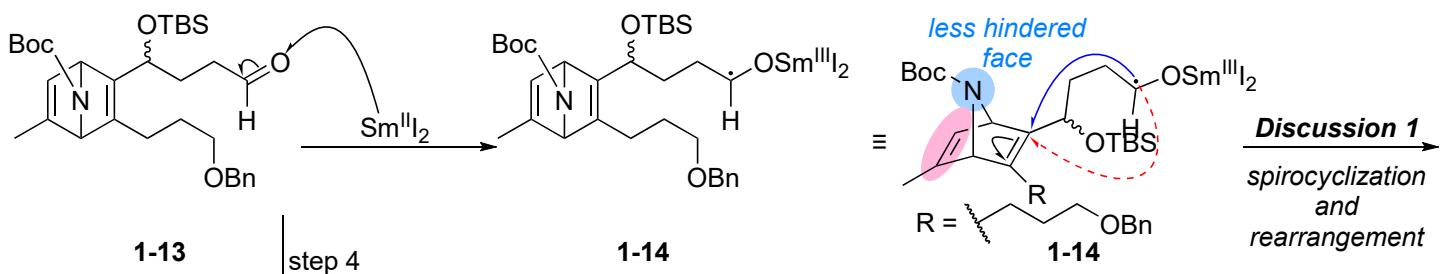
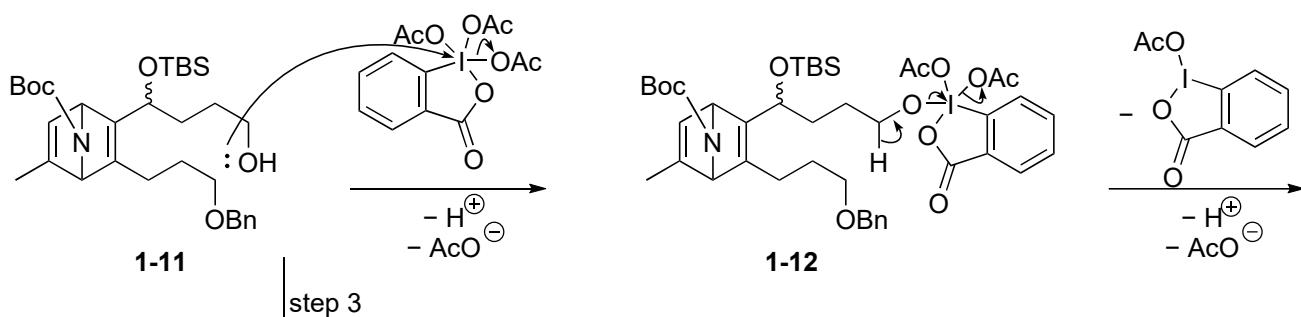
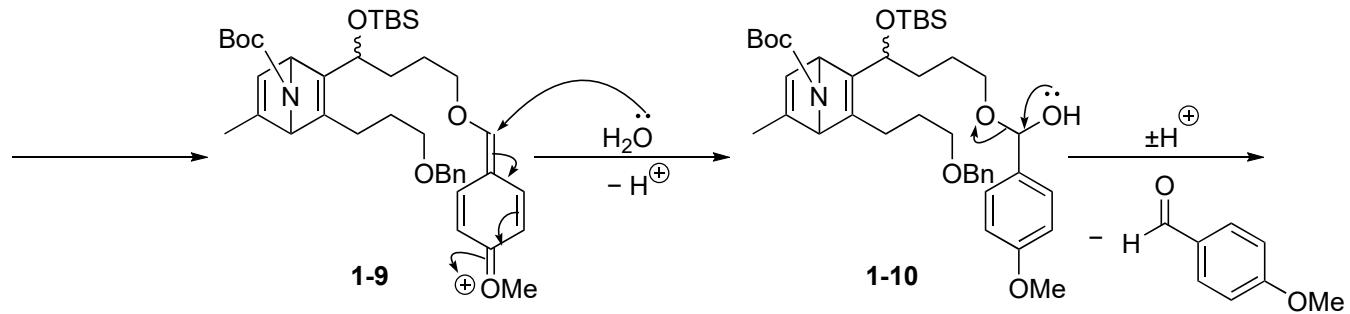
DMP  
(Dess-Martin Periodinane)

## Problem Session (5) -Answer-

2023.7.29. Shu Nakamura

Topic: Skeletal rearrangement from Diels-Alder adduct



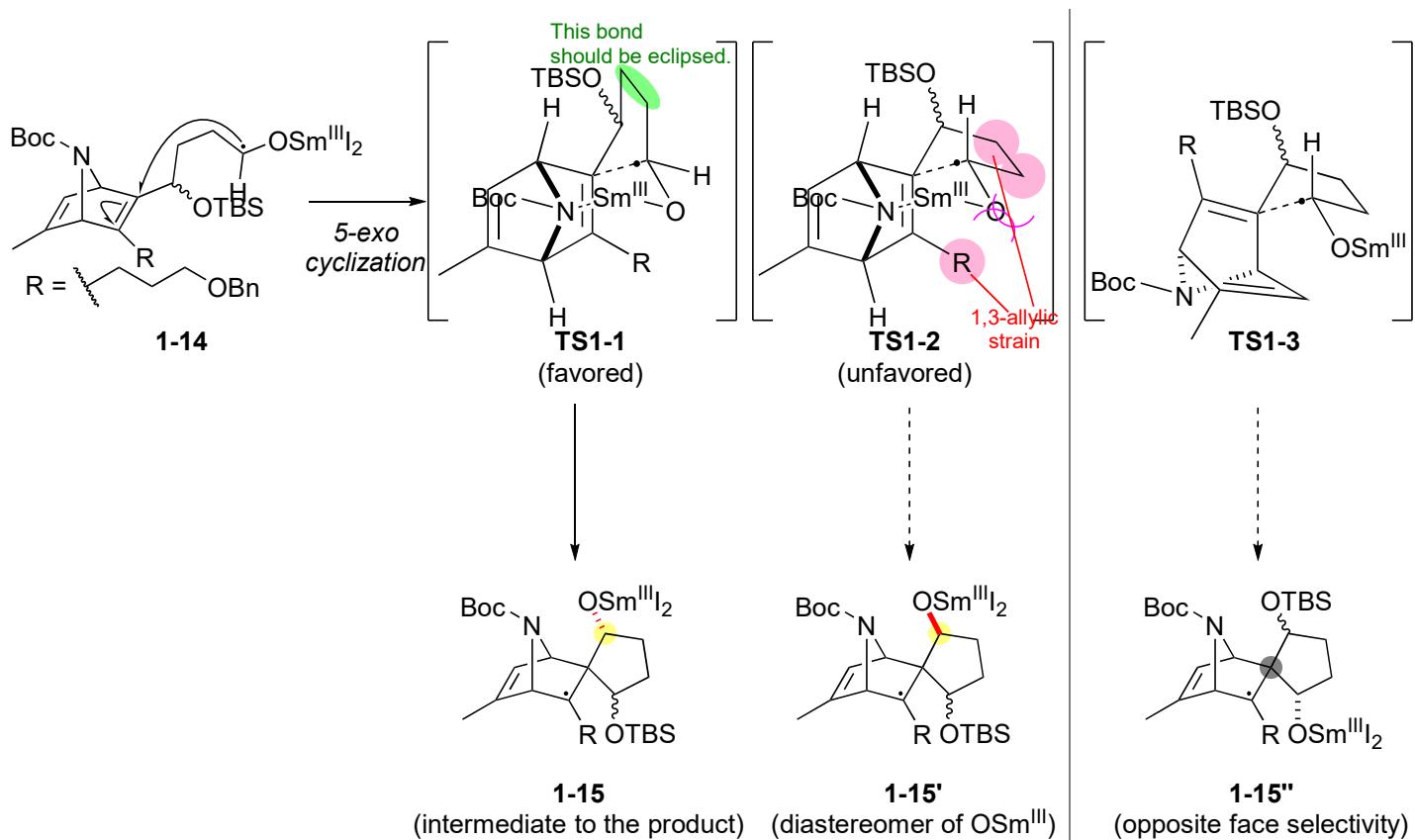


## Discussion 1: Spirocyclization and rearrangement cascade

### 1-1. Spirocyclization - stereoselectivity

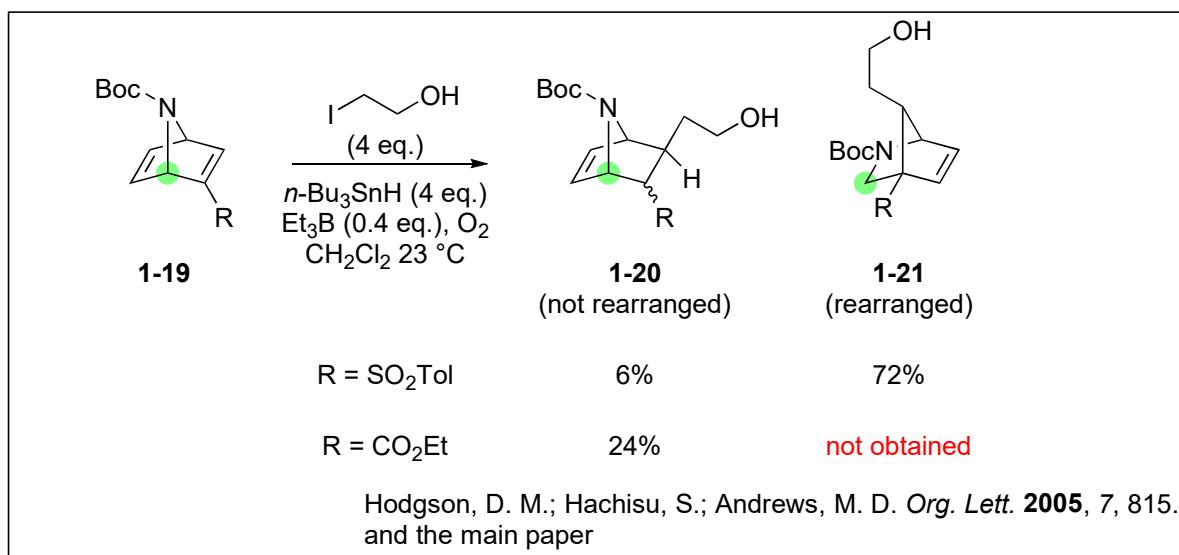
From proper face, nitrogen atom can coordinate to Sm(III).

(Nitrogen in carbamate is thought to be pyramidal at the ground state<sup>1)</sup>, which would enable the coordination.)

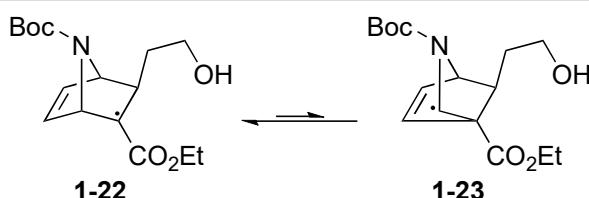


### 1-2. Rearrangement

BDEs are important for this rearrangement considering the following results of model intermolecular addition.

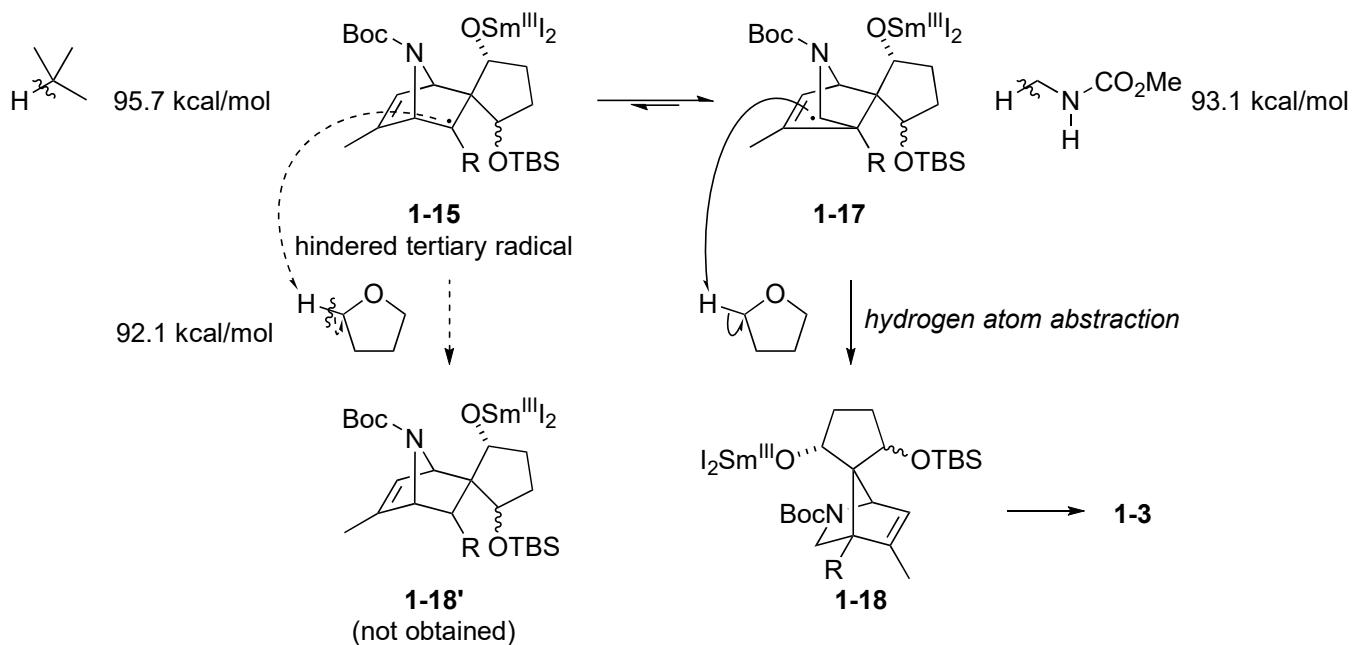


BDEs <sup>2)</sup>	
	92.6 kcal/mol
	99.0 kcal/mol
	93.1 kcal/mol



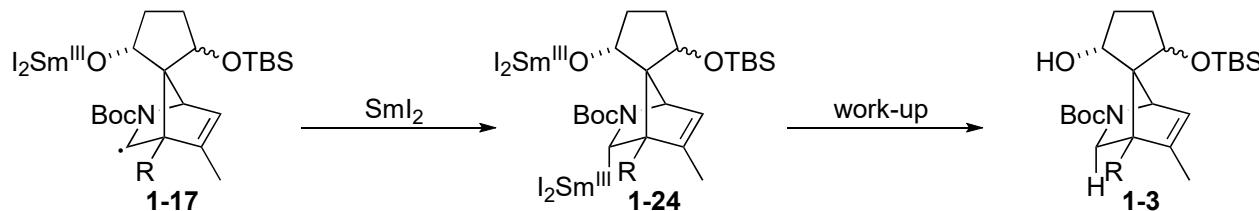
Rearranged radical **1-23** seemed not to be so favored over **1-22** based on BDEs, resulting in no generation of **1-21**.

As for this problem, rearranged radical **1-17** seemed to be more stabilized than **1-15**.

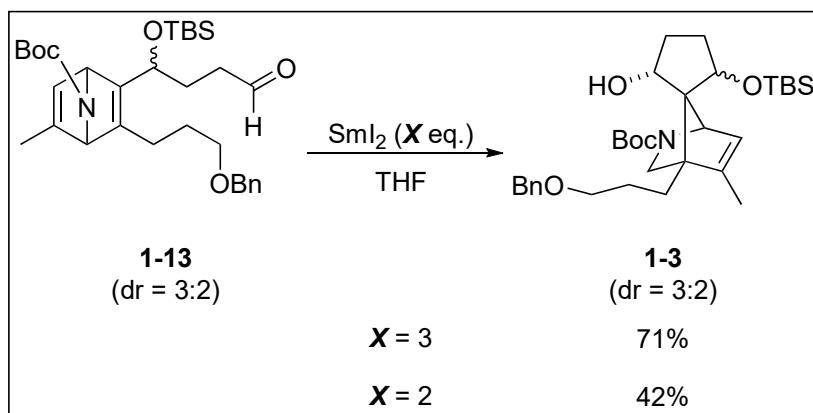


### 1-3. Termination of the cascade

Another possible pathway



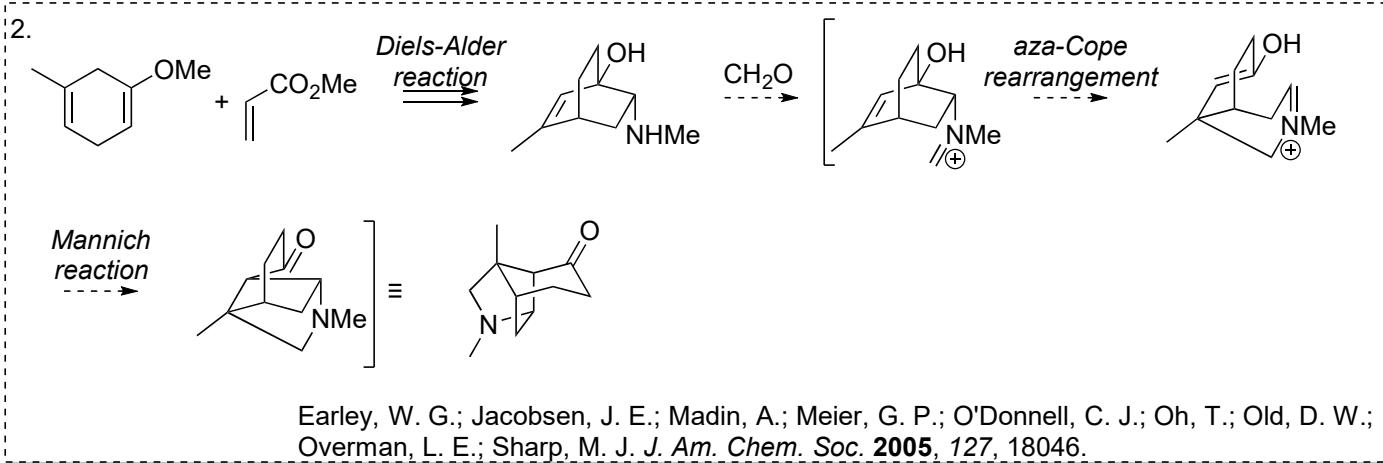
However, no deuterated product was obtained when the reaction was quenched by D<sub>2</sub>O and MeOD. Therefore, radical **1-17** should be quenched by hydrogen atom abstraction from THF.



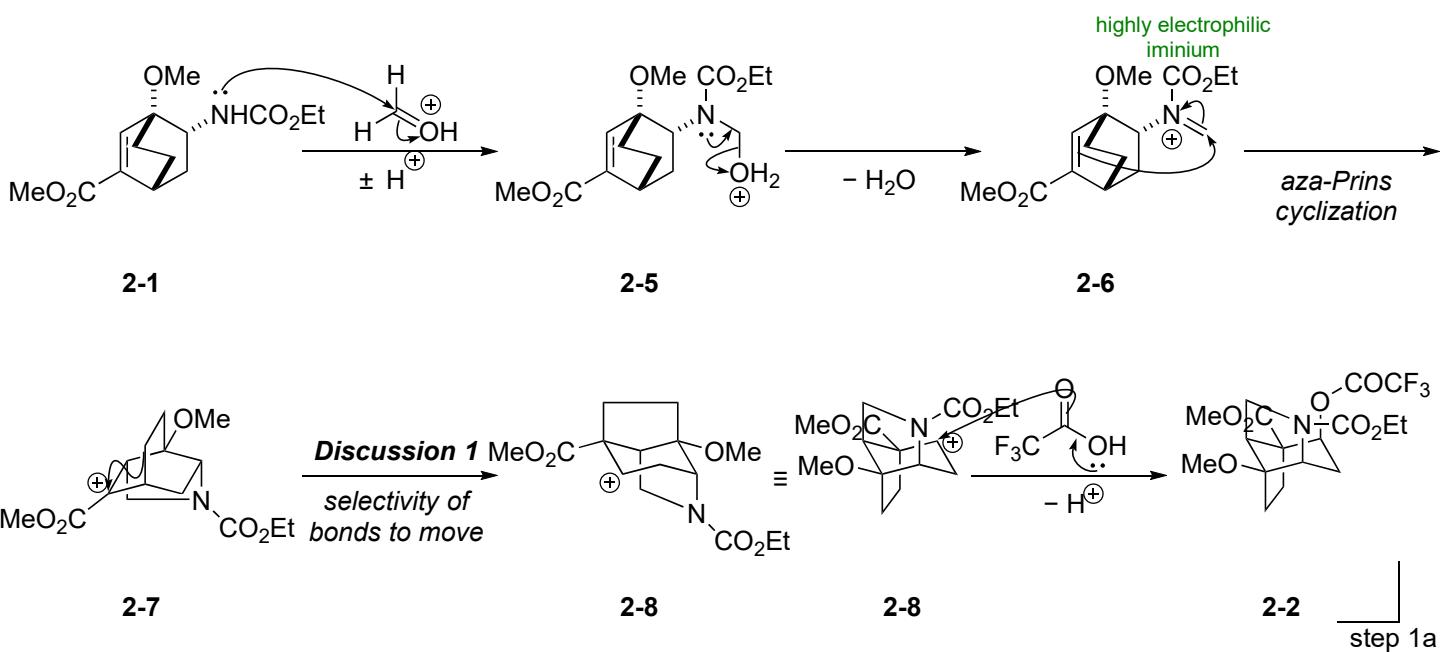
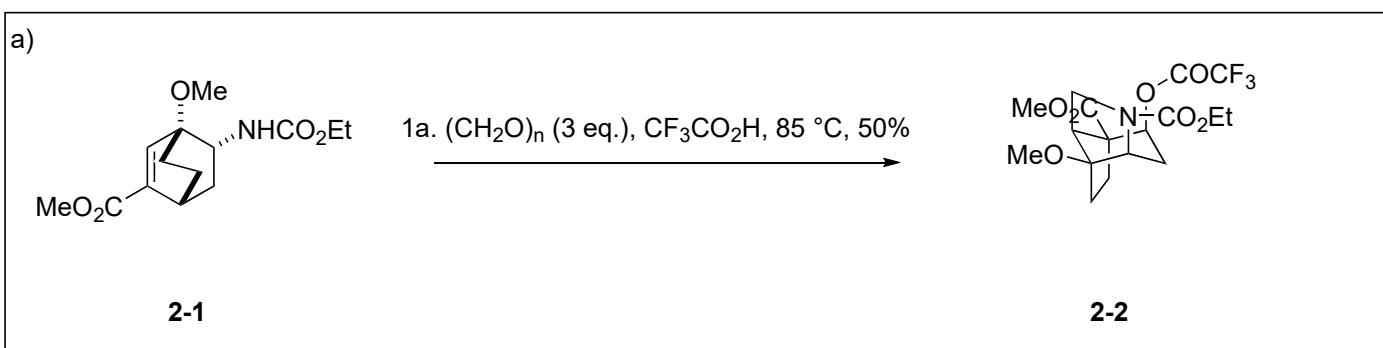
Authors also reported that the yield of **1-3** decreased as the amount of SmI<sub>2</sub> was reduced. That observation may be attributed to the reduced efficiency to quench the generated radical from THF.

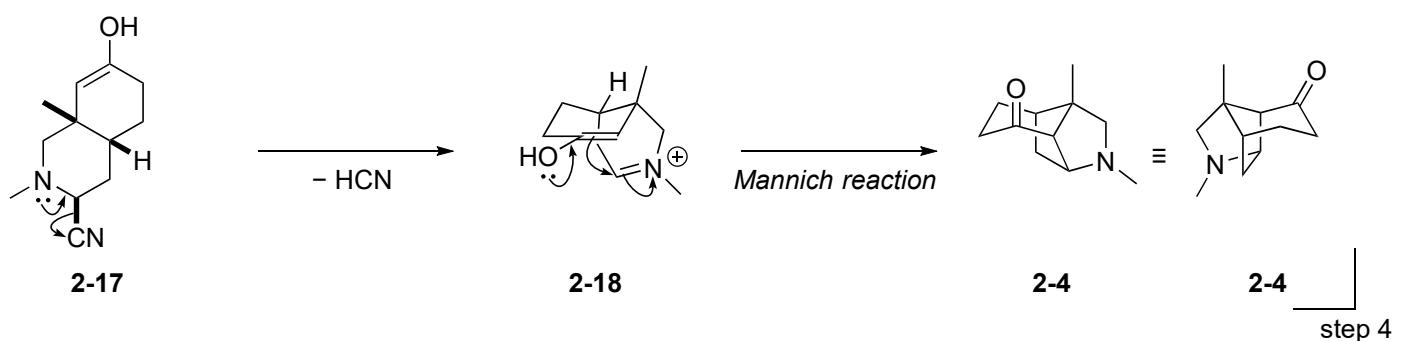
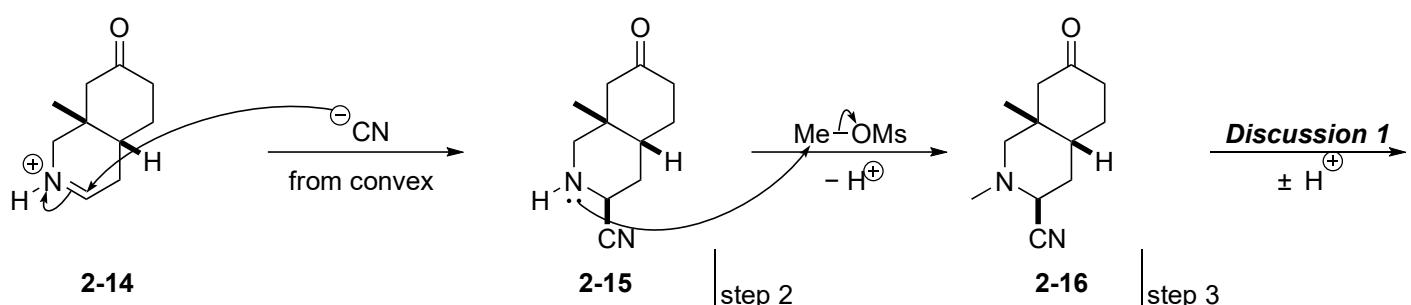
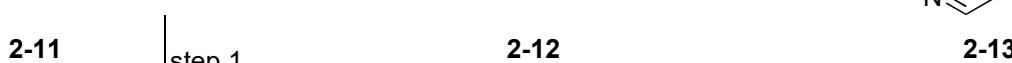
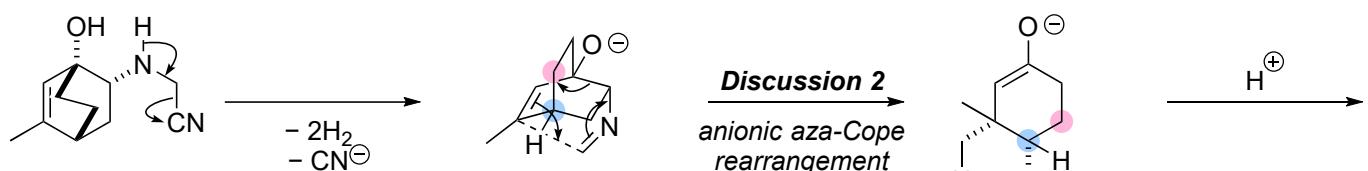
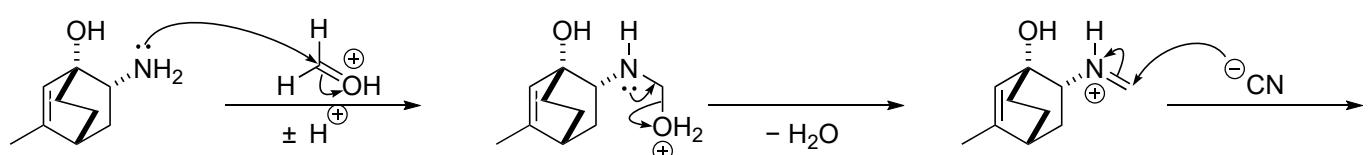
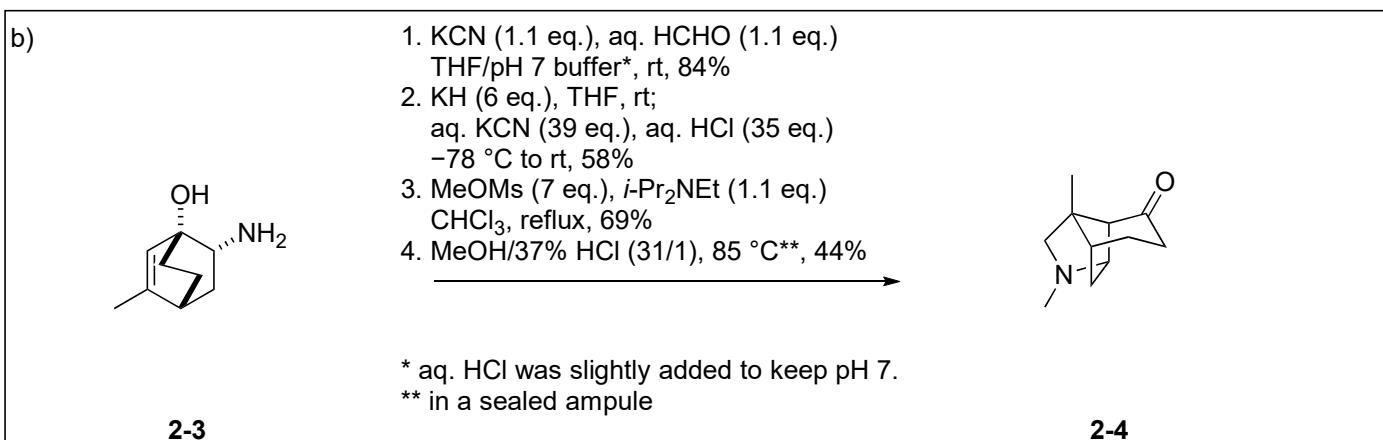
### References:

- 1) Kydd, R. A.; Rauk, A. *J. Mol. Struct.* **1981**, 77, 227.
- 2) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; Luo, Y.-R., Ed.; CRC Press: Boca Raton, 2007; pp 1-1688.



For more about aza-Cope/Mannich cascade, see: 080628\_PS\_Tamaki\_HOSHIKAWA





## Discussion 1: Tricyclodecanes - isomers of adamantane

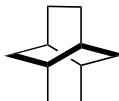
Many of  $\Delta H_f^\circ$  (heats of formation) of tricyclodecanes are reported<sup>3)</sup>, suggesting the strain energy of each skeleton. (Adamantane is most stable among these tricyclic skeletons.)



**adamantane**

$\Delta H_f^\circ = -32.6 \text{ kcal/mol}$

### 1-1. Selectivity of Wagner-Meerwein rearrangement (step 1a)

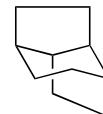


All rings are **twisted-boat**.  
→ High energy isomer

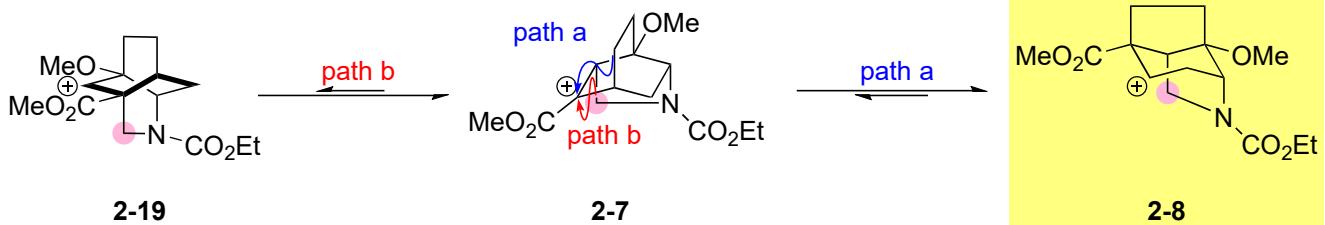


**2-19'** (twistane)  
 $\Delta H_f^\circ = -13.3 \text{ kcal/mol}$

**2-7'**  
 $\Delta H_f^\circ = -18.7 \text{ kcal/mol}$

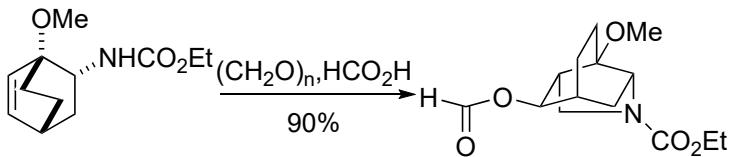


**2-8'**  
 $\Delta H_f^\circ = -18.7 \text{ kcal/mol}$



**2-19** has a less stable skeketon, so this rearrangement should convert **2-7** to **2-8** not to **2-19**.

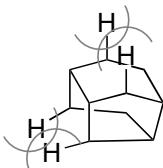
Also, electron-withdrawing group is necessary for this rearrangement to **2-8** by increasing reactivity of cation **2-7**.



**2-20**

**2-21**

### 1-2. Regioselectivity of Mannich reaction (step 4)



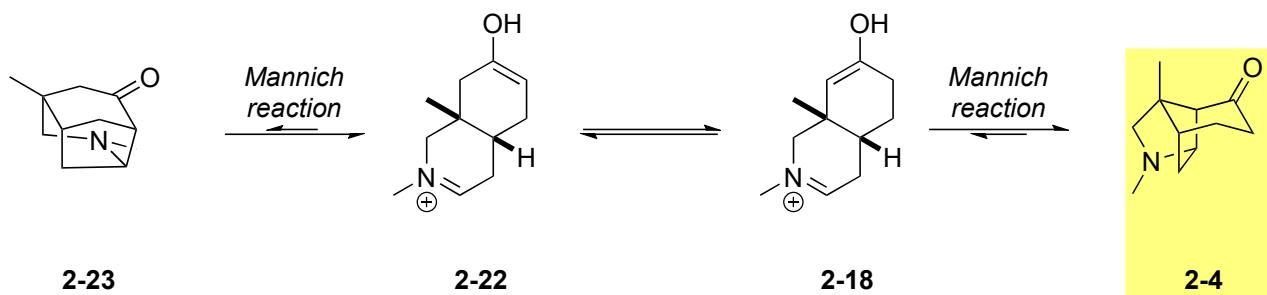
Both six-membered rings  
are boat form.  
→ Unstable isomer



**2-23'**  
 $\Delta H_f^\circ = -8.5 \text{ kcal/mol}$

**2-4'**

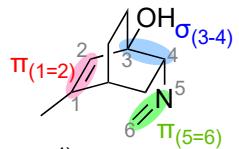
$\Delta H_f^\circ = -15.8 \text{ kcal/mol}$



Therefore, most stable **2-4** was obtained.

## Discussion 2: Anionic aza-Cope rearrangement

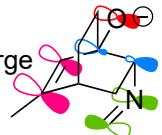
Some atoms and orbitals are named as shown in the right figure for this section.



Negative charge of alkoxide is known to delocalize to  $\sigma^*$  orbital of a position through hyperconjugation.<sup>4)</sup>

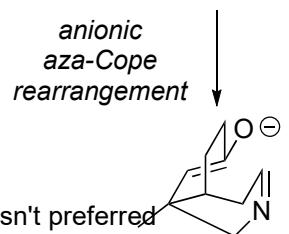
Therefore, anion of alkoxide **2-12** should delocalize to  $\sigma^*(3-4)$ , which would accelerate aza-Cope rearrangement by weakening C3-C4 bond to dissociate in the desired aza-Cope rearrangement.

(Also, delocalization to  $\sigma^*(3-4)$  might increase nucleophilicity of  $\pi_{(1=2)}$ , especially at C1 (due to the charge repulsion between C2 and C3))



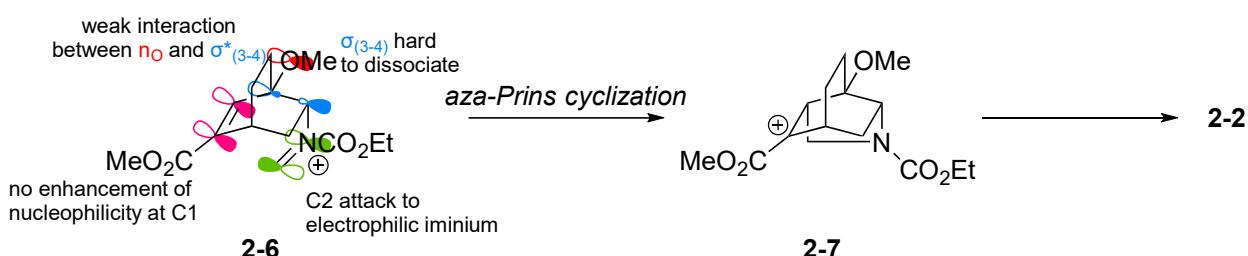
→Aza-Cope rearrangement (dissociation of C3-C4 bond) proceeded.

**2-12**



Due to the weak hyperconjugation from neutral oxygen atom, aza-Cope rearrangement wasn't preferred to aza-Prins cyclization (nucleophilic attack of C2).

**2-13**



## References:

- 3) a) Vanderbilt, J. J. Doctor Thesis, The University of Michigan, 1978.
- b) Fort, R. C., Jr. *Adamantane: The Chemistry of Diamond Molecules*; Marcel Dekker: New York, 1976.
- 4) Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, 101, 1994.