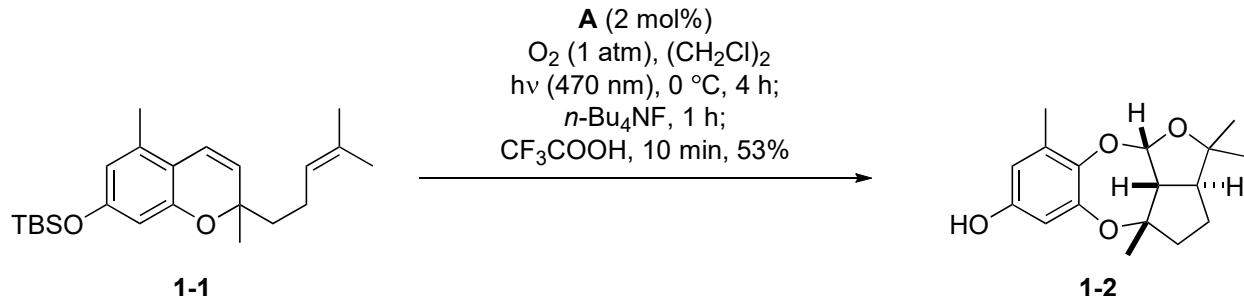


## Problem Session (4)

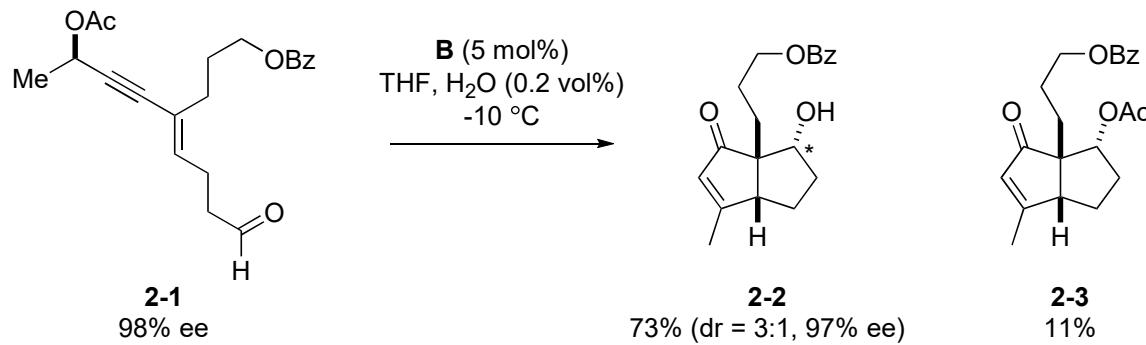
2019/4/13 Takumi Fukuda

Please provide the reasonable reaction mechanisms and explain the stereoselectivities.

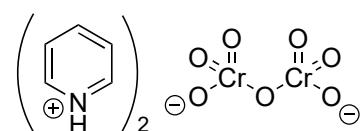
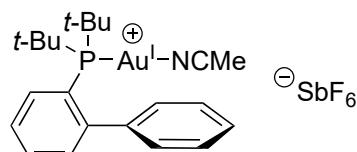
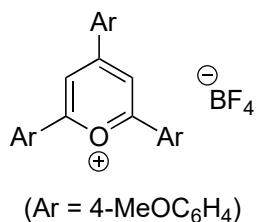
(1)



(2)



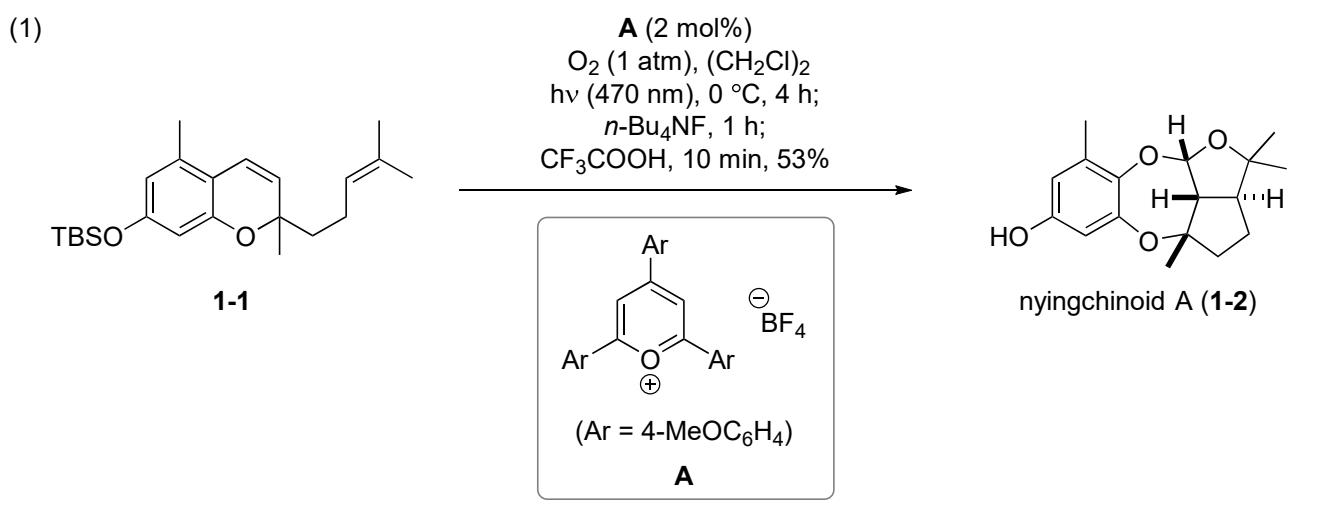
(3)



**Problem Session (4) Answer**  
**Topic: Recent total syntheses**

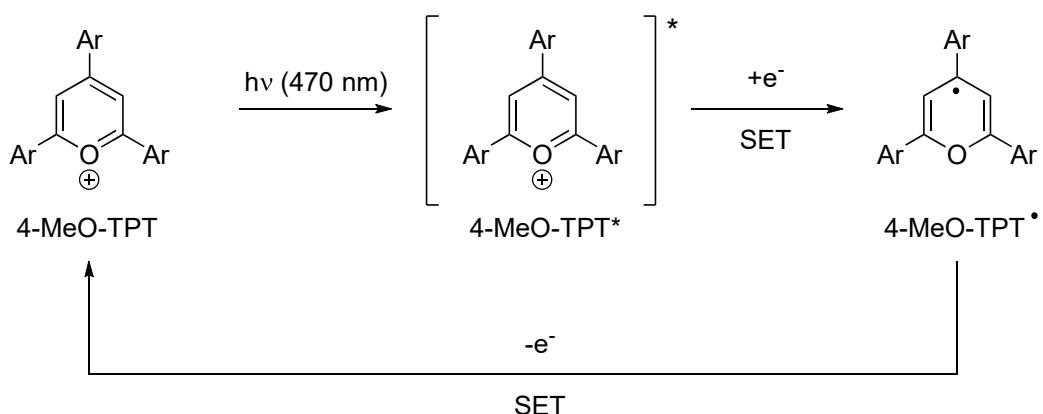
2019/4/13 Takumi Fukuda

1-1. Reaction mechanism



Hart, J. D.; Burchill, L.; Day, A. J.; Newton, C. G.; Sumby, C. J.; Haung, D. M.; George, J. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 2791.

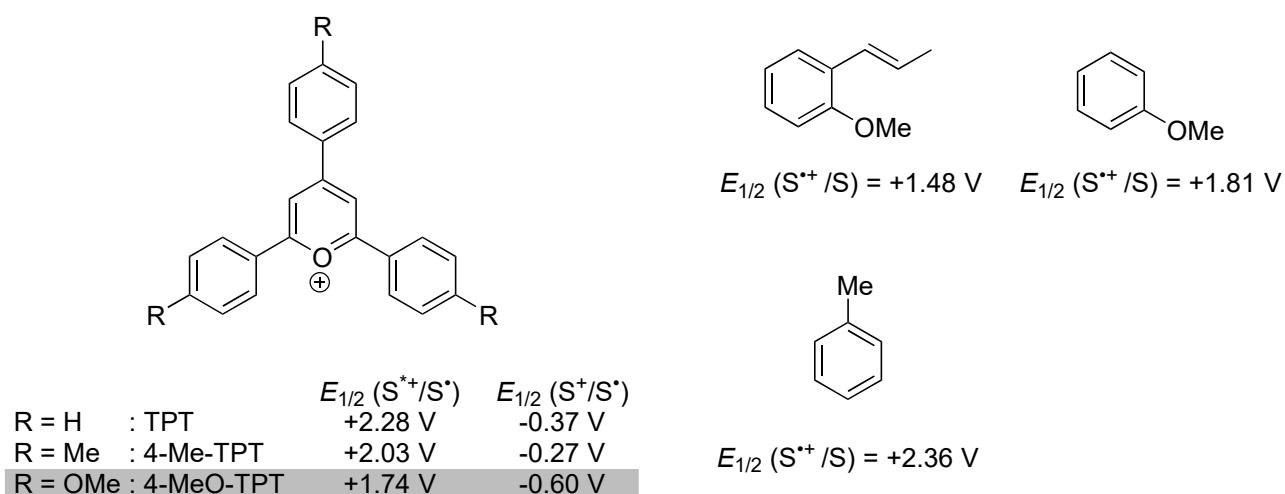
Catalytic cycle of photocatalyst

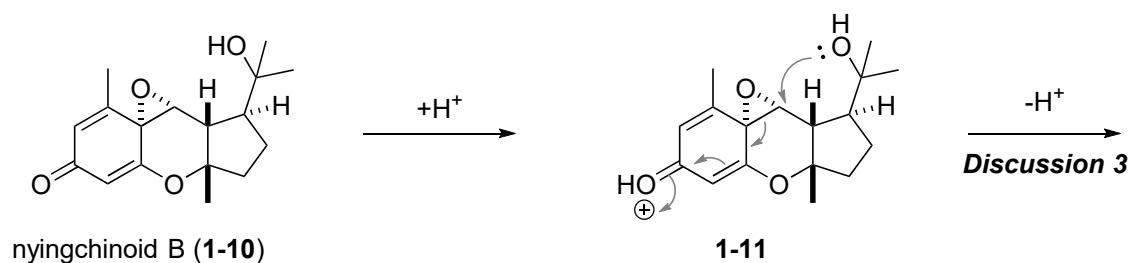
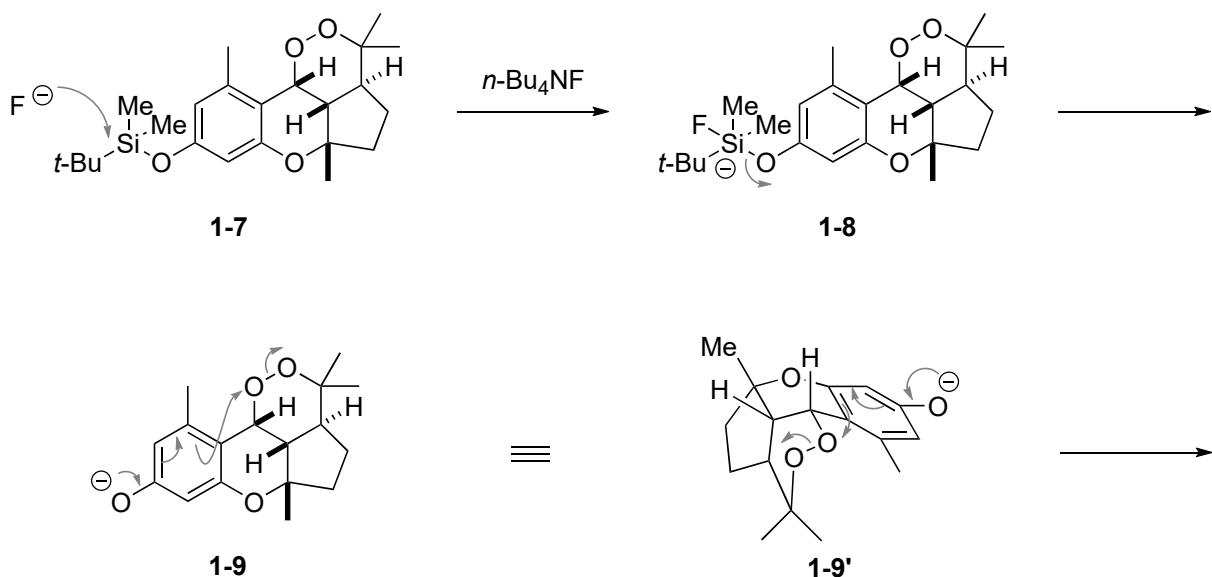
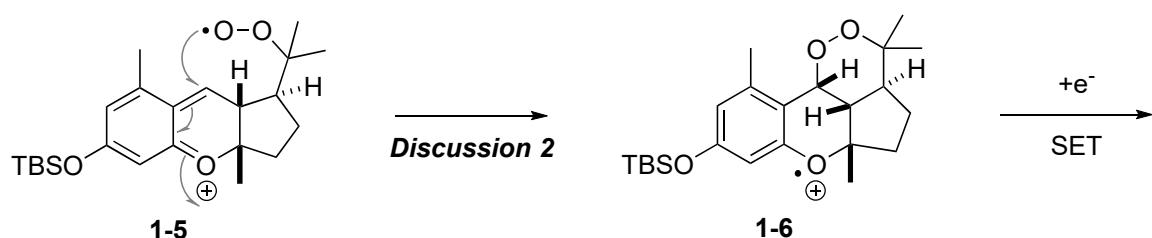
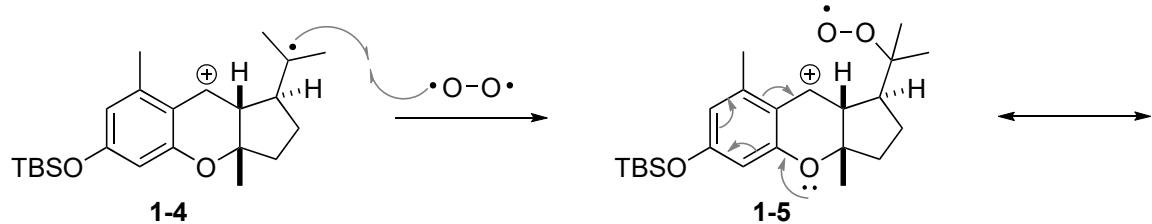
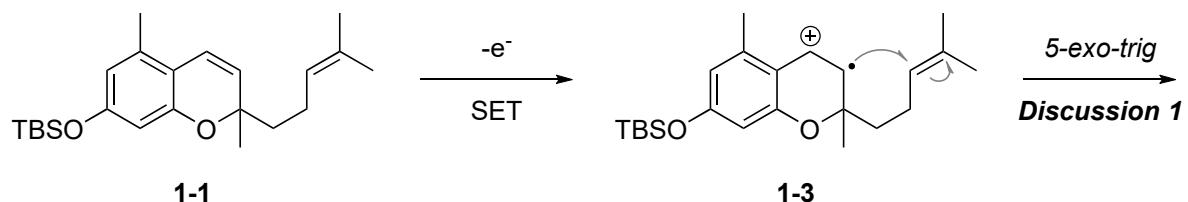


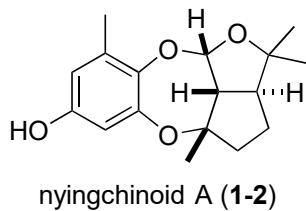
Reduction potential vs. SCE

Martiny, M.; Steckhan, E.; Esch, T. *Chem. Ber.* **1993**, *126*, 1671.

Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett*, **2016**, 27, A-J.

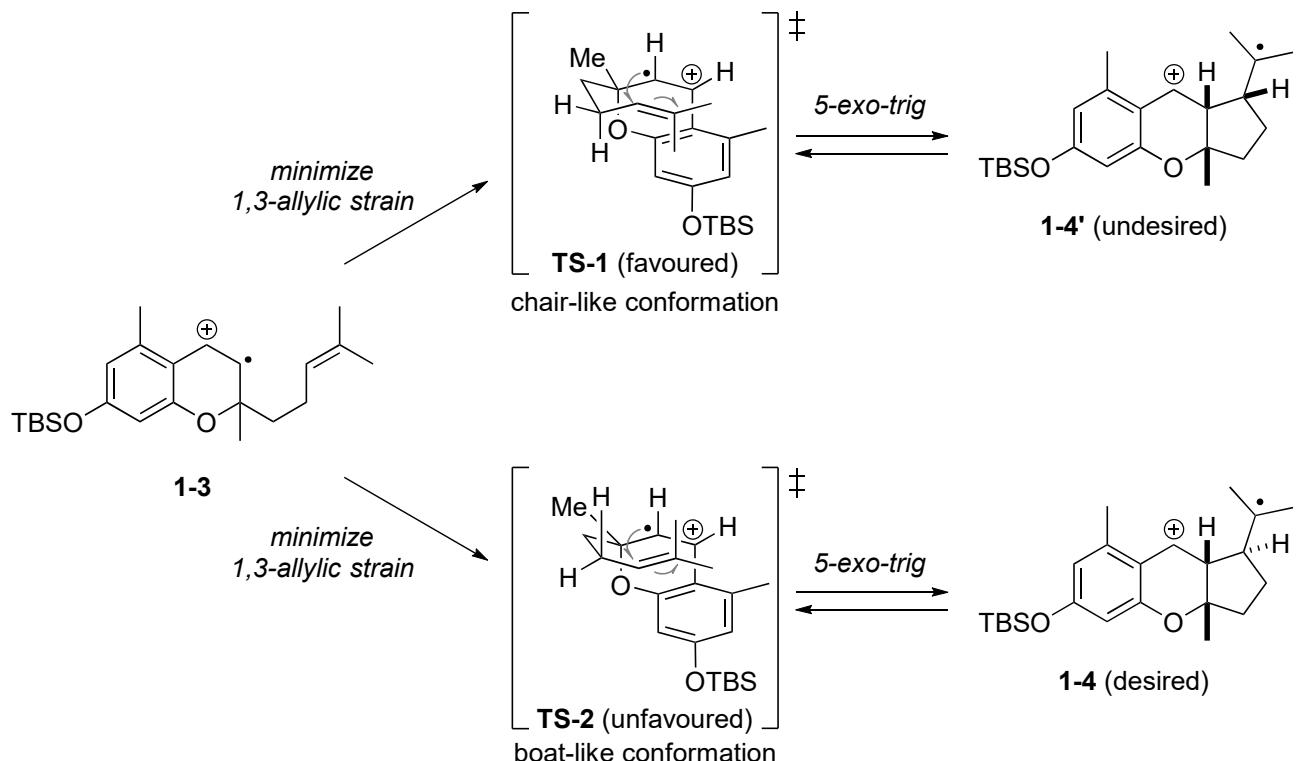




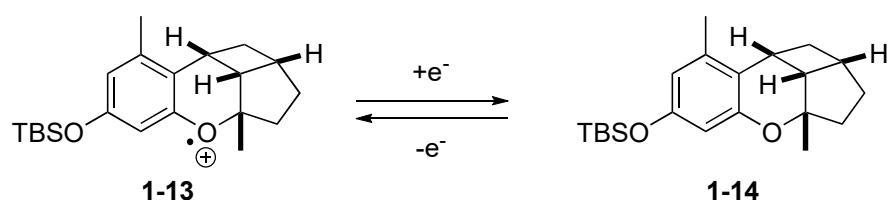
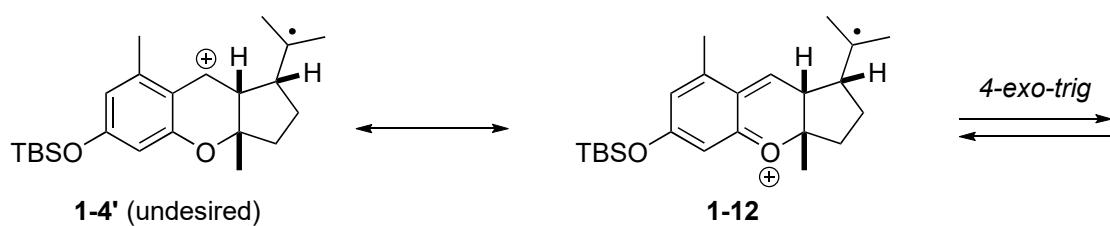


## 1-2. Discussion

### 1-2-1. Stereoselectivity of 5-exo-trig cyclization (**Discussion 1**)

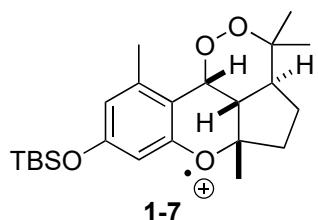
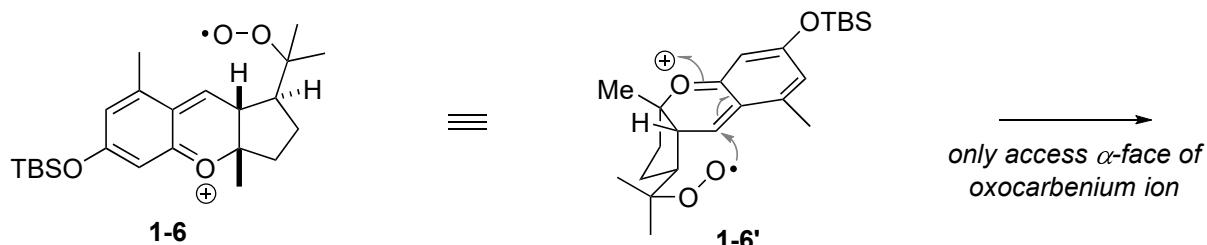


**TS-2** is unfavoured due to the boat-like transition state.



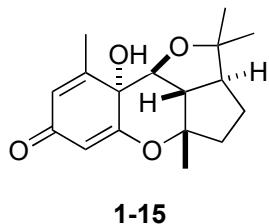
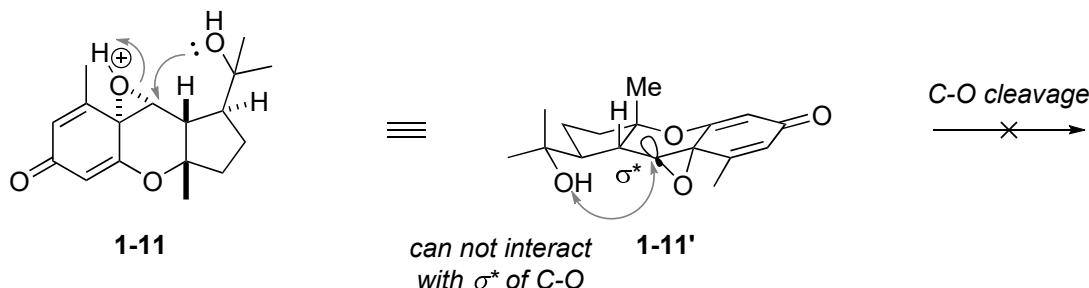
Re-oxidation of **1-14** by the excited photocatalyst (**4-MeO-TPT<sup>\*</sup>**) could regenerate radical cation **1-3**. Therefore, the kinetic **1-14** could be recycled to give **1-7** via radical cation **1-4**.

1-2-2. Stereoselectivity of 1,2-dioxane formation (***Discussion 2***)

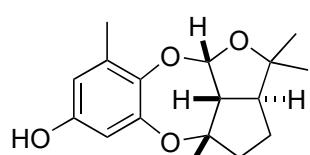
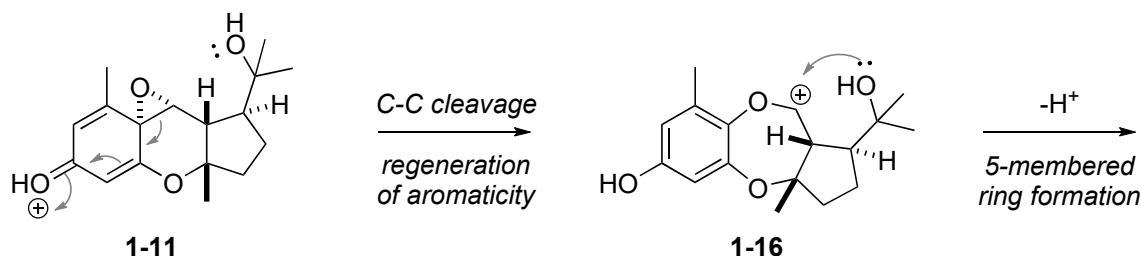


1-2-3. Ring opening of epoxide and regeneration of aromaticity (***Discussion 3***)

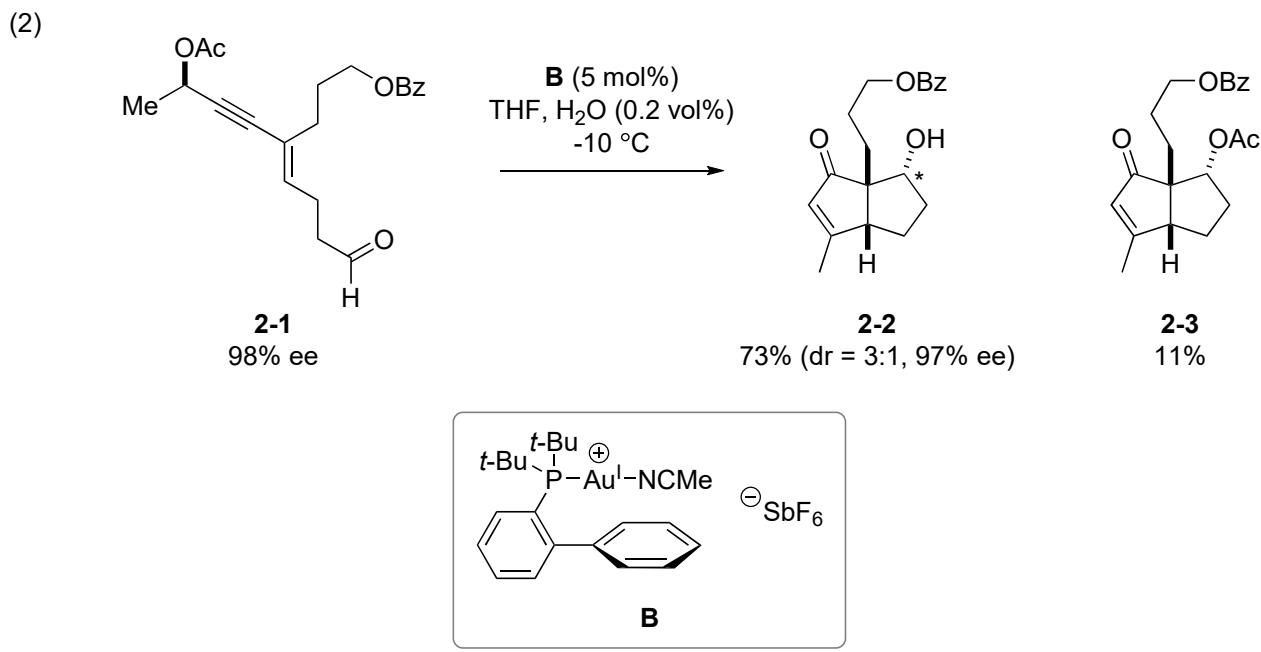
(1) C-C cleavage vs. C-O cleavage



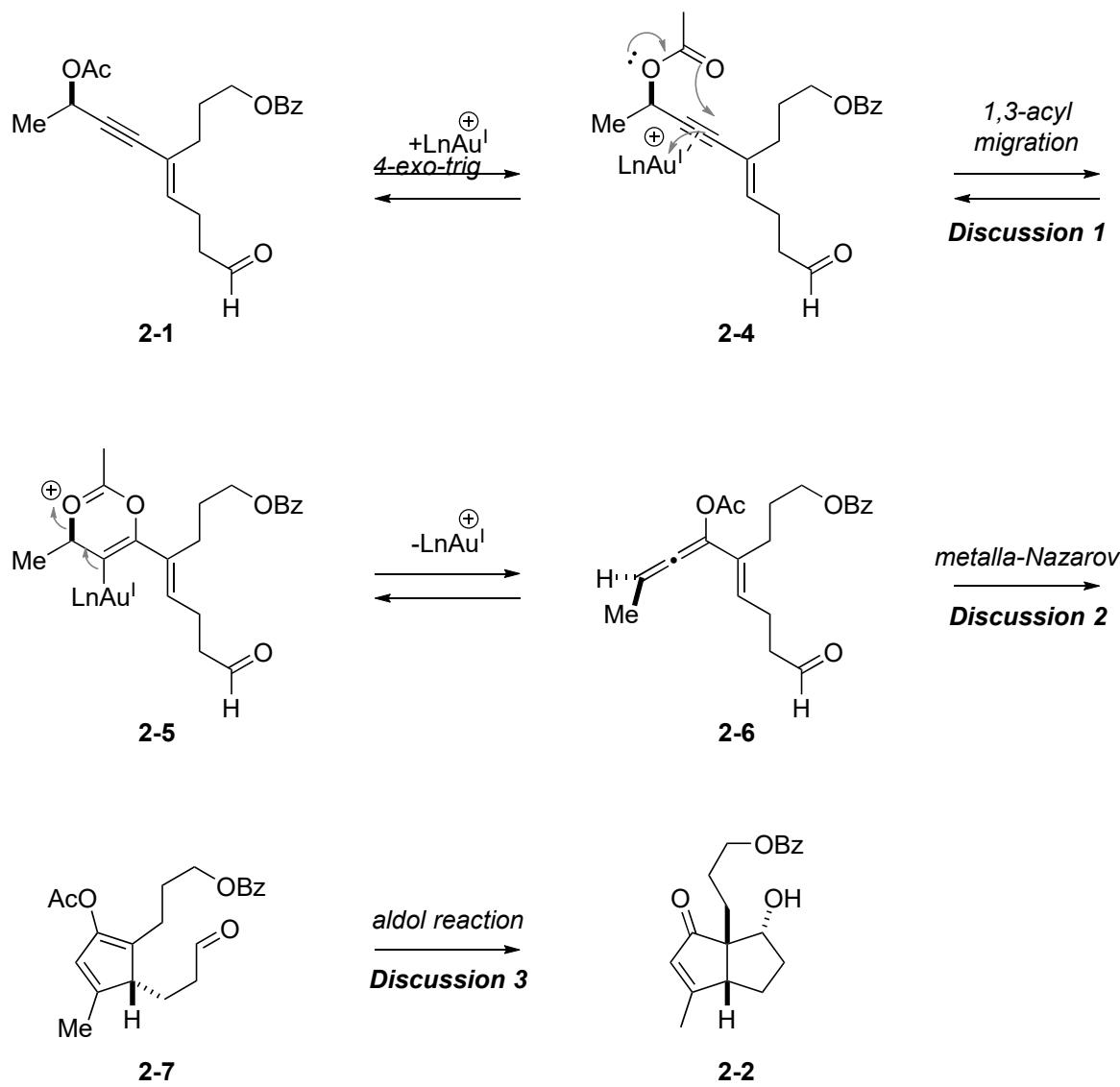
(2) Stepwise mechanism



2-1. Reaction mechanism



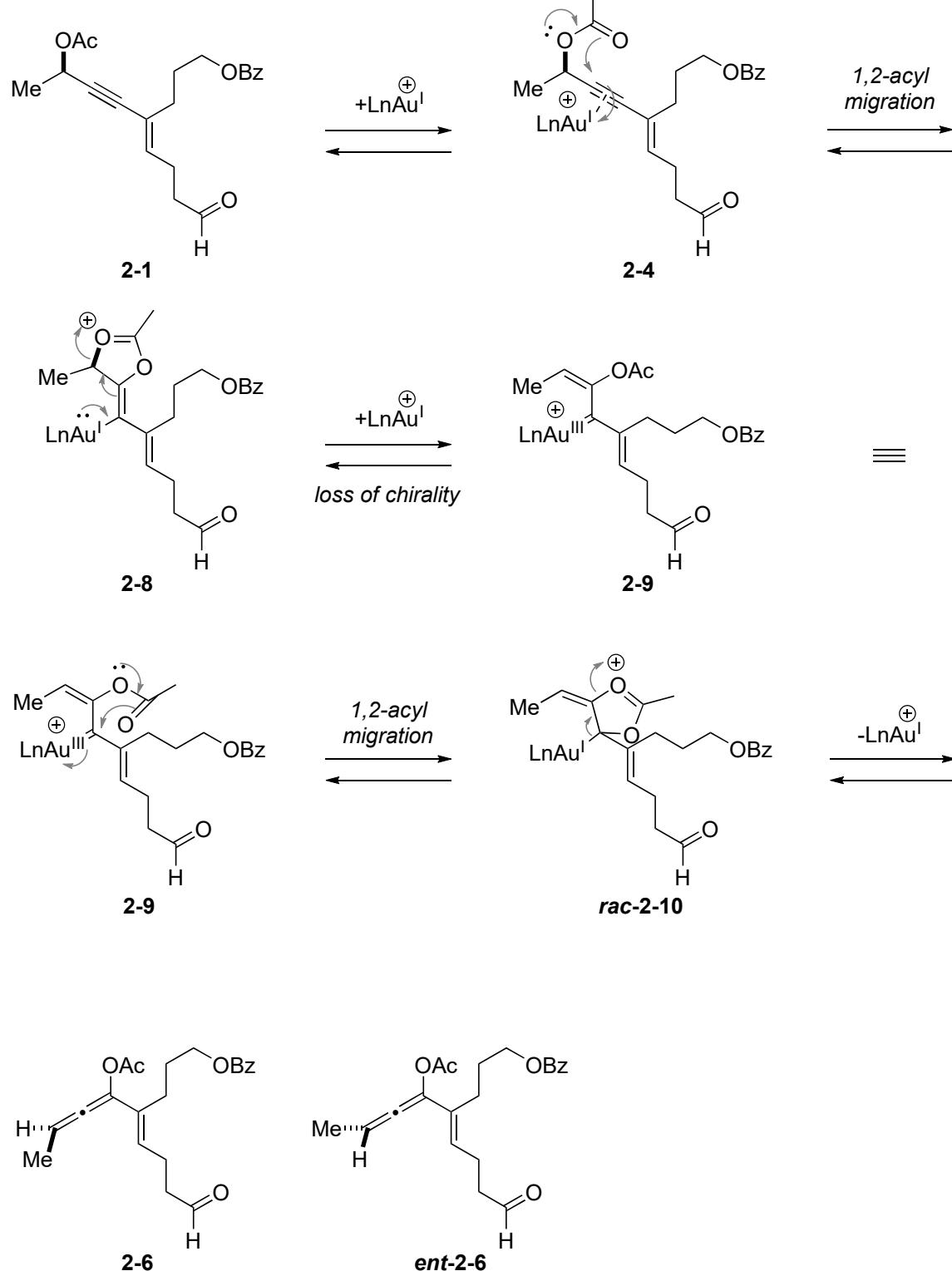
Branstetter, M; Freis, M.; Huwyler, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2490.



## 2-2. Discussion

### 2-2-1. 1,3-acyl migration vs. 1,2-acyl migration (***Discussion 1***)

(1) 1,2-acyl migration and sequential 1,2-acyl migration (formal 1,3-acyl migration)



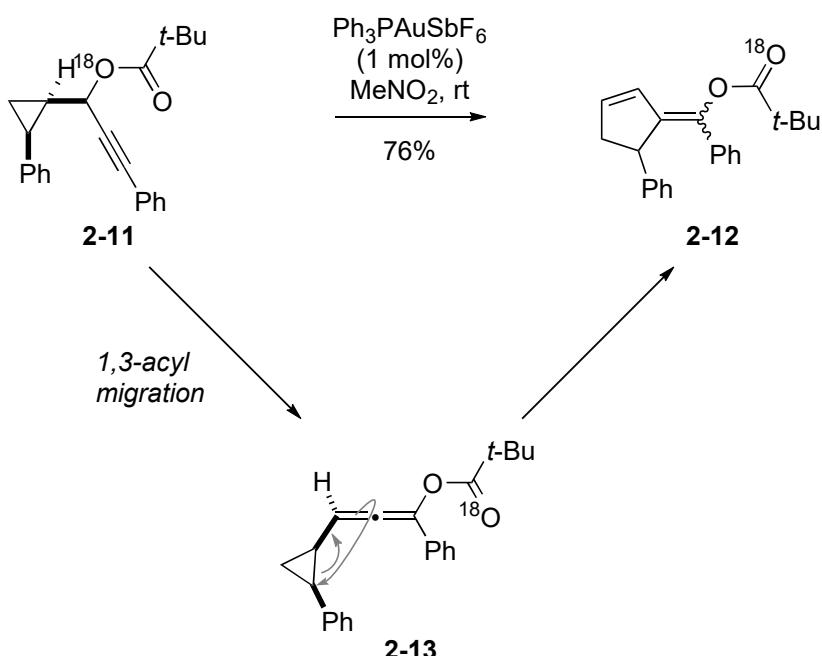
1,3-acyl migration product **2-6** can be formed from 1,2-acyl migration product **2-9** via additional 1,2-acyl migration.

Both 1,2-acyl migration and 1,3-acyl migration were considered as reversible reaction. (Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718. see Appendix)

In contrast to 1,3-acyl migration, the chirality of **2-1** is lost after 1,2-acyl migration. Therefore, 1,3-acyl migration only occurred in this case. For the same reason, sequential 1,2-acyl migration did not occur.

The isotope labelling study conducted by Toste's group support 1,3-acyl migration route.

Mauleon, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, 131, 4513.



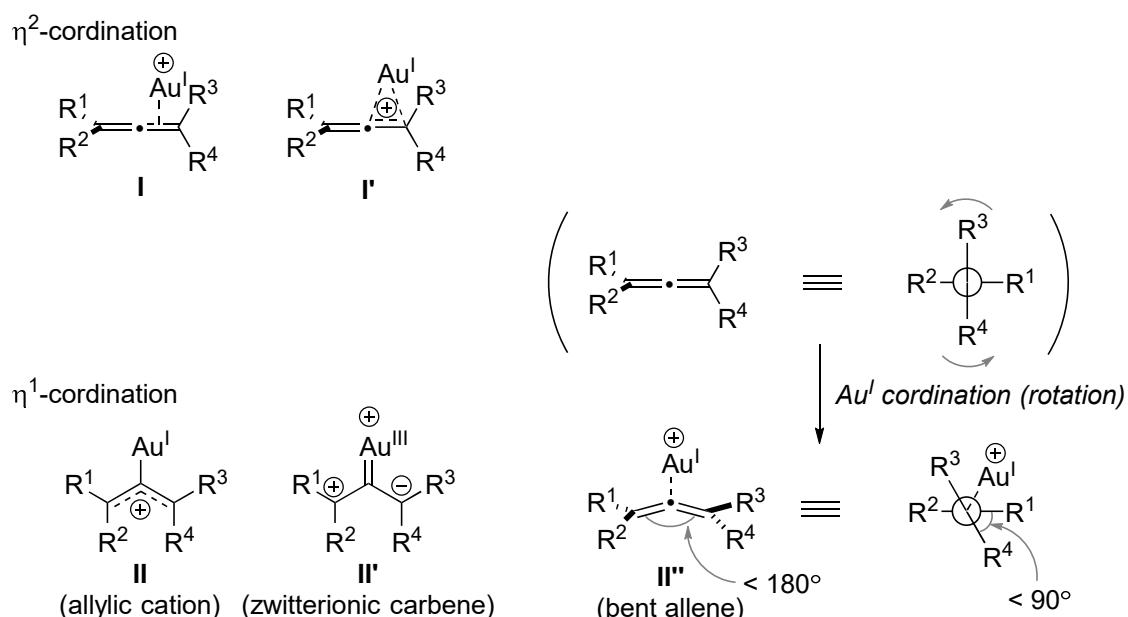
$^{18}\text{O}$  label resided exclusively at the carbonyl oxygen of **2-12**. It suggested that the sequential 1,2-acyl migration did not occur.

## 2-2-2. metalla Nazarov cyclization (*Discussion 2*)

### (1) $\eta^1$ -coordinated bent allene

Gandon, V.; Lemiere, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2008**, 47, 7534.

Various coordination modes of allenes are known.



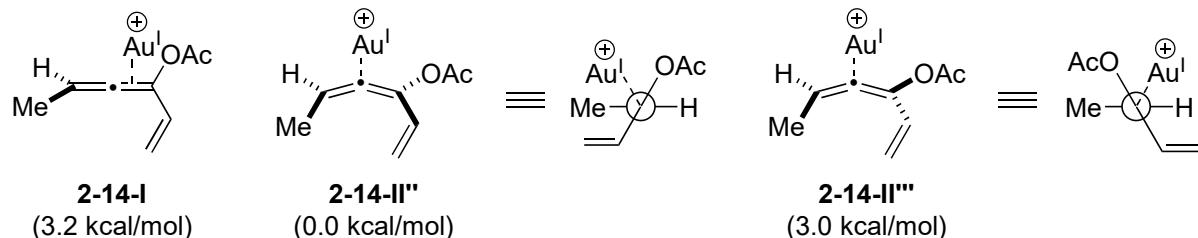
The orbital interactions between the unfilled  $5p$  orbital of  $\text{Au}^{\text{I}}$  and the  $\pi^*$  orbitals of allene and the occupied  $5d$  orbital of  $\text{Au}^{\text{I}}$  and the  $\pi$  orbitals of allene exists. (Chenier, J. H. B.; Howard, J. A.; Mile, B. *J. Am. Chem. Soc.* **1985**, 107, 4190.)

Although the stereochemical information is maintained in species **I**, **I'** and **II''**, the axial chirality of the allene <sup>7</sup> seems to be lost in **II** and **II'**.

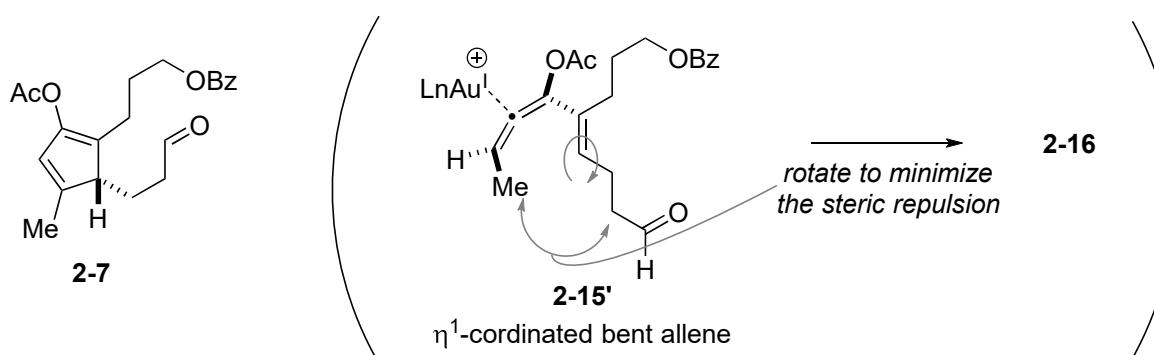
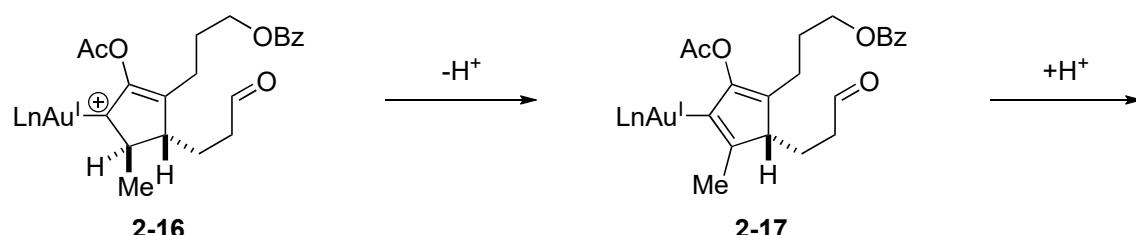
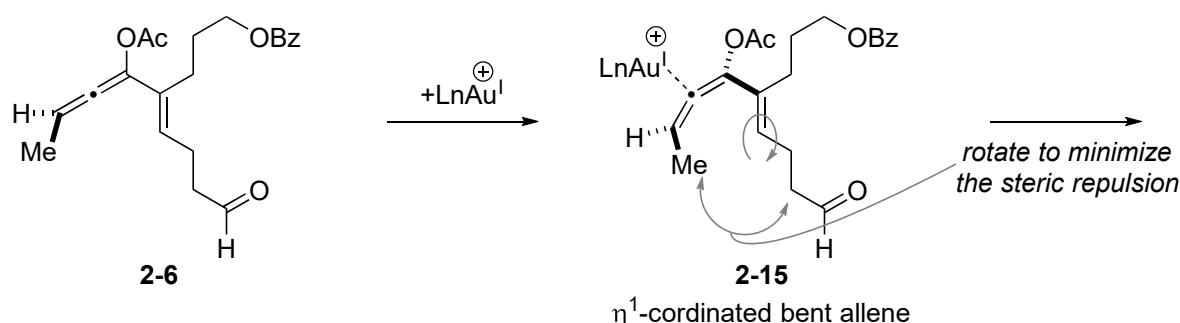
Malacia's group calculated the energies of  $\eta^2$ -coordinated complex **2-14-I** and  $\eta^1$ -coordinated bent allene **2-14-II''** and **2-14-II'''** and found that **2-14-II''** was more stable.

Therefore, Nazarov cyclization via  $\eta^1$ -coordinated bent allene **II''** was proposed, but the cyclization might occur from chiral  $\eta^2$ -coordinated complex **I** and **I'**.

Gandon, V.; Lemiere, G.; Hours, A.; Fensterbank, L.; Malacia, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7534.

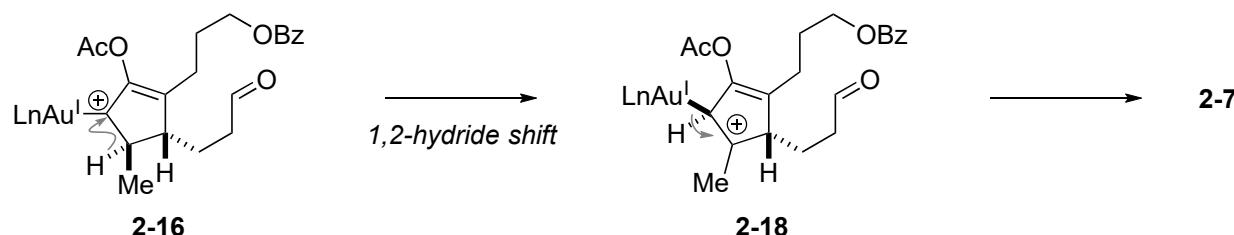


## (2) reaction mechanisms

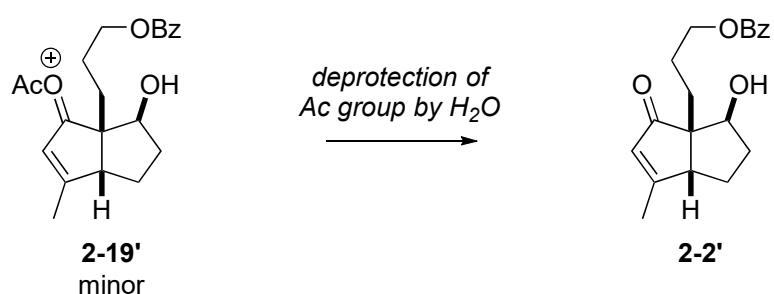
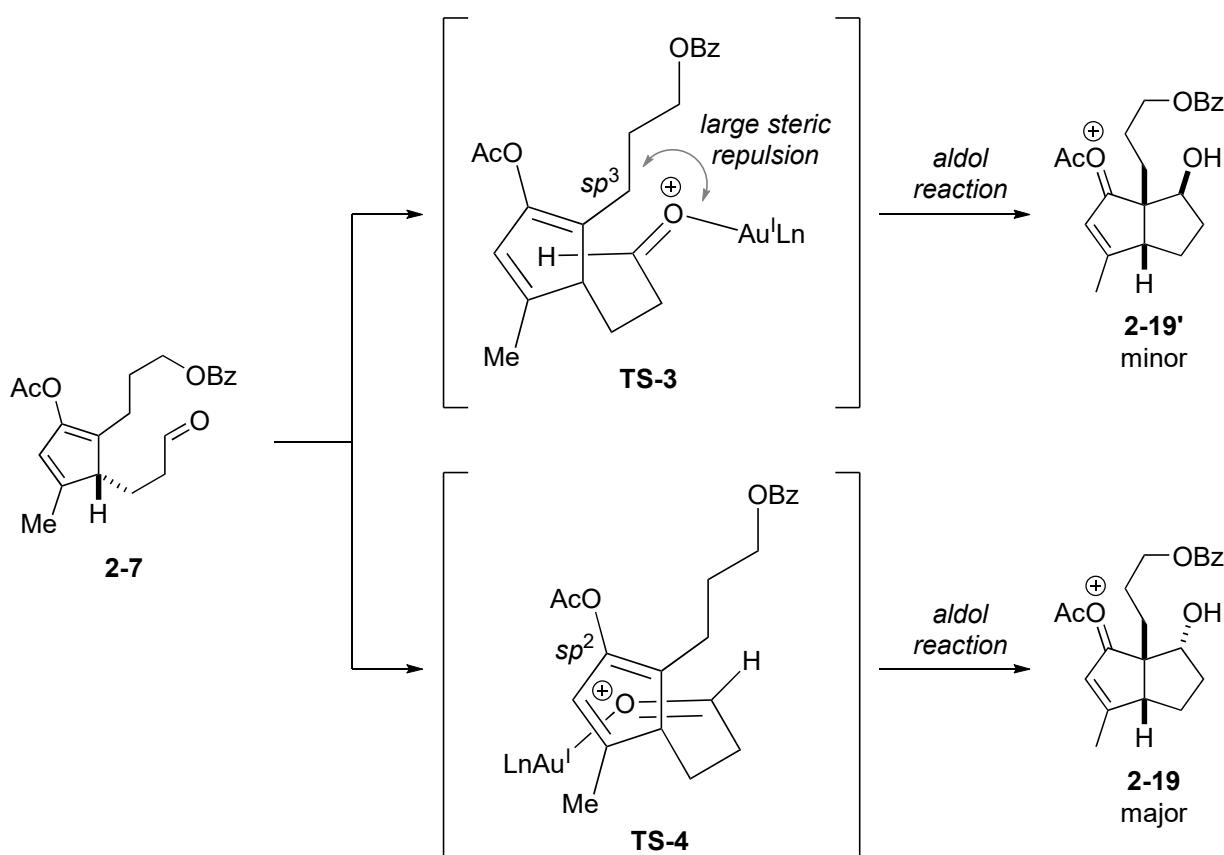


**2-15** and **2-15'** give the same enantiomer **2-16** after the cyclization.

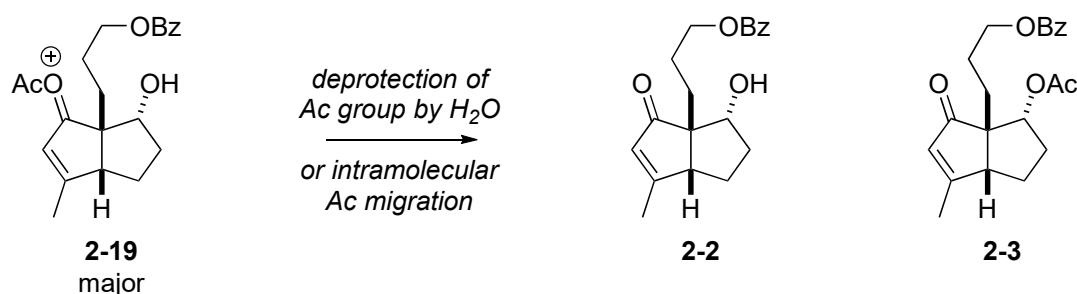
◆ another possible mechanism from **2-16** to **2-7**



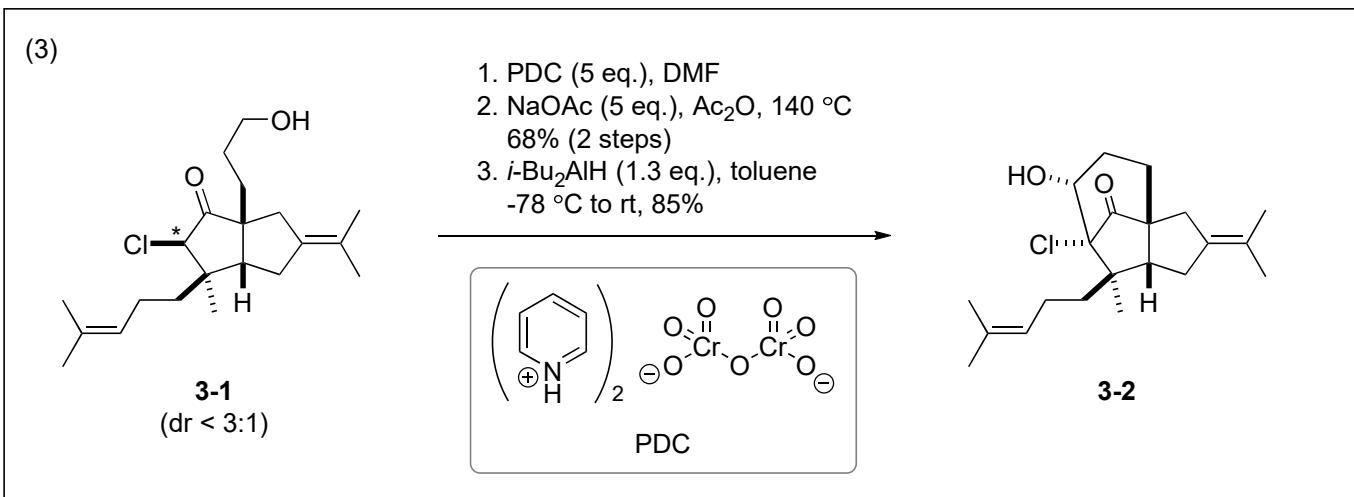
2-2-3. aldol reaction (***Discussion 2***)



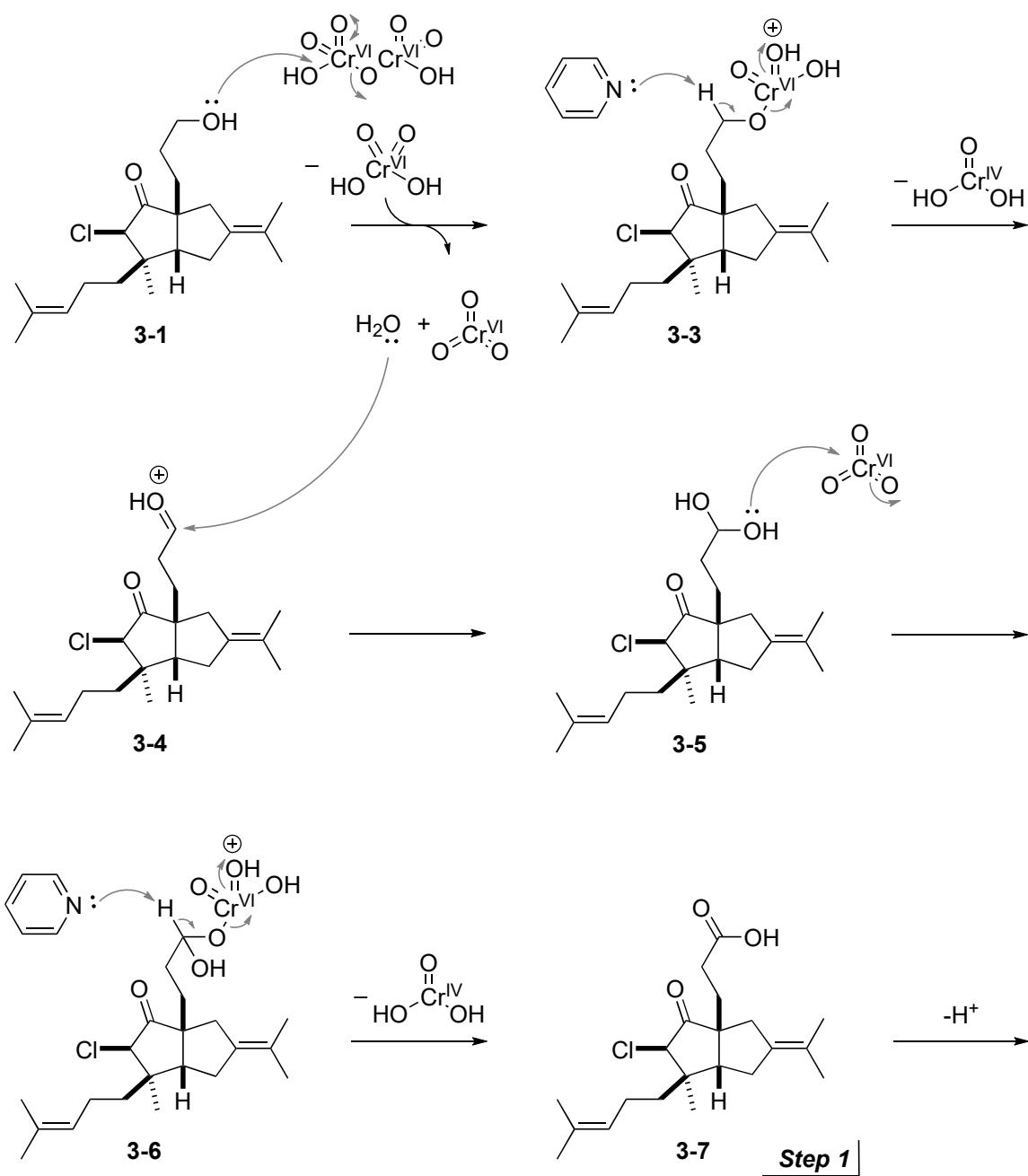
The Intramolecular Ac migration did not occurred due to the long distance between hydroxy group and Ac group.

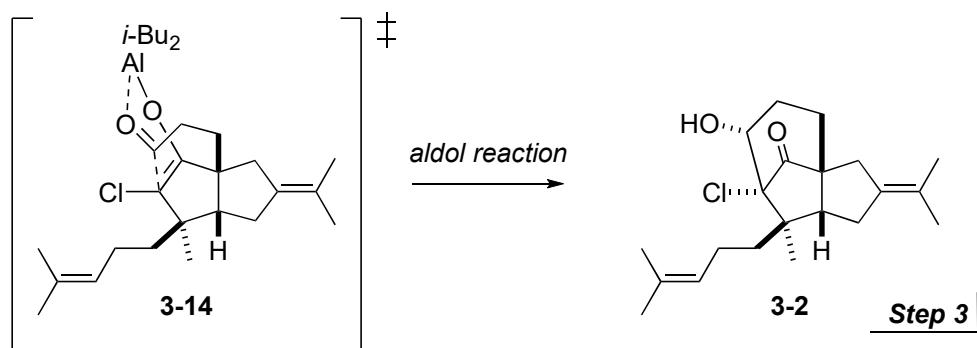
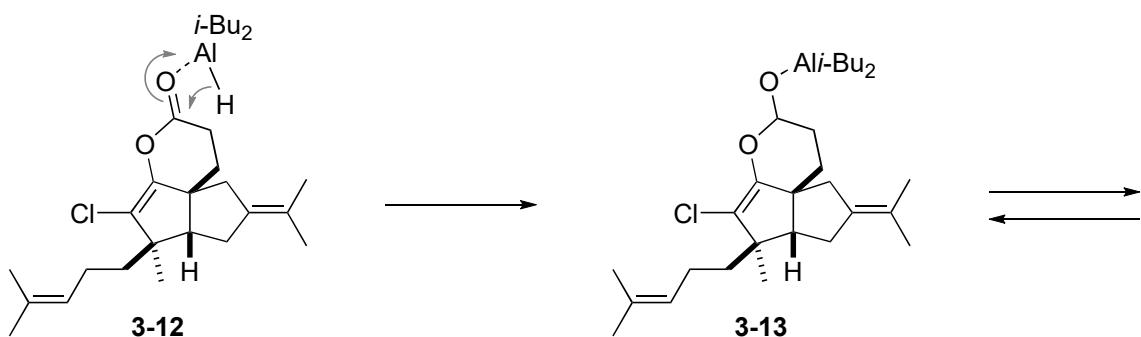
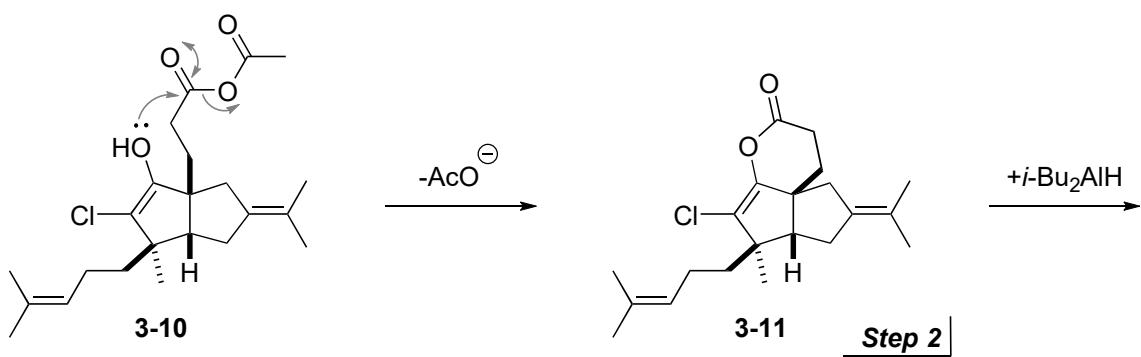
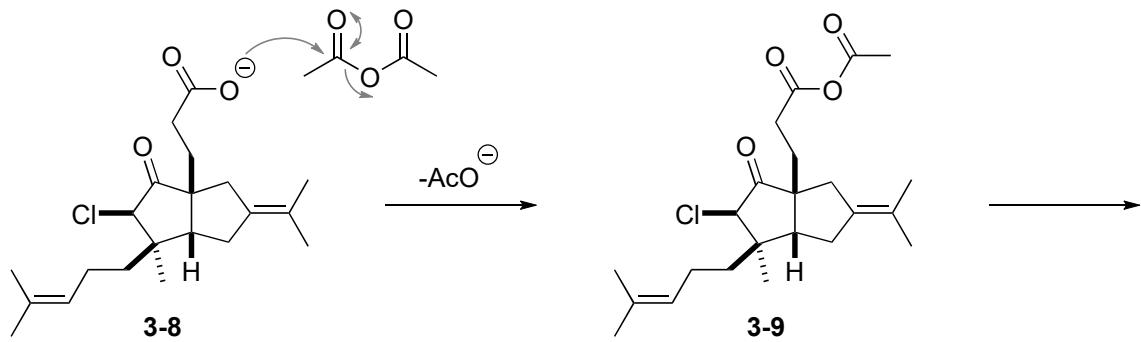


### 3-1. Reaction mechanism



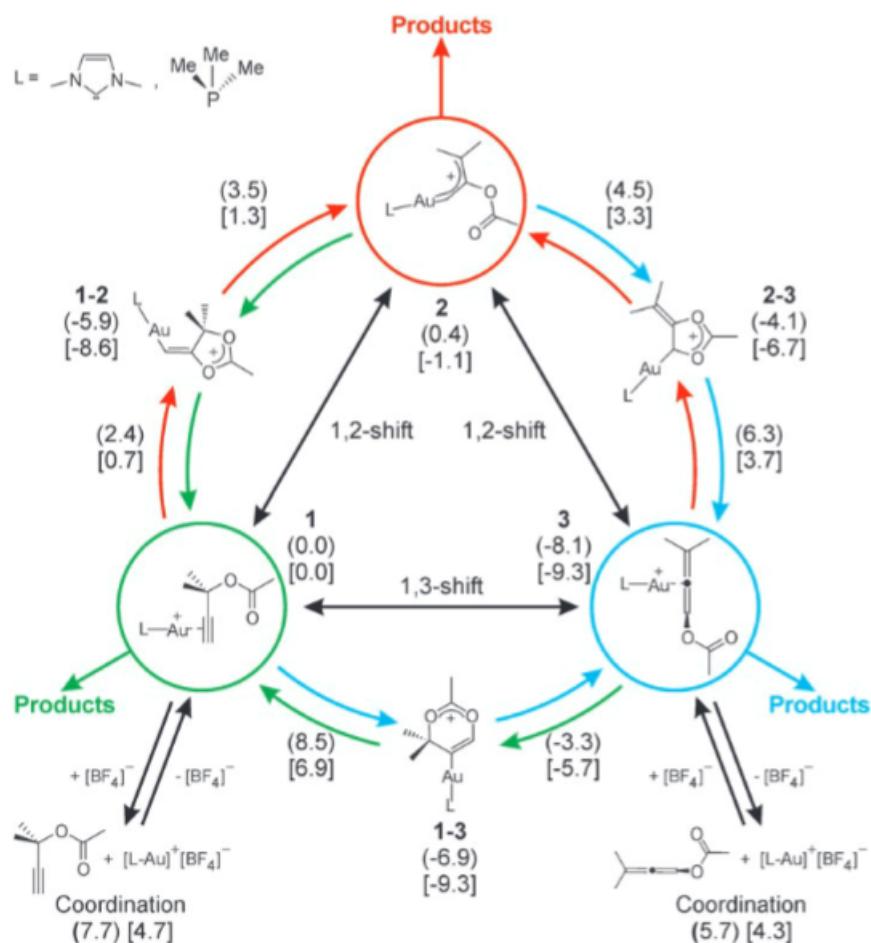
Branstetter, M; Freis, M.; Huwyler, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2019**, 58, 2490.





Appendix

Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718.



**Figure 2.** Schematic representation of the thermodynamics associated with the  $1 \rightleftharpoons 2 \rightleftharpoons 3 \rightleftharpoons 1$  equilibrium. Energies in  $\text{kcal mol}^{-1}$  (in round/square brackets for  $L = \text{IMe}$  and  $\text{PMe}_3$ , respectively) are calculated relative to **1**. Numbers close to the arrows represent the energy of the transition state associated with that reaction step.