Problem Session (4) Answer

2024/06/01 Hisahiro Morozumi

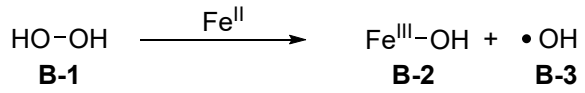
Topic: Cleavage of week O-O bond by Fe^{II}

Main review: Dworkin, J. H.; Denhart, B. W.; Kwon, O. *Trends*. *Chem*. **2023**, *5*, 174.

Brief introduction: Cleavage of peroxides in organic synthesis.

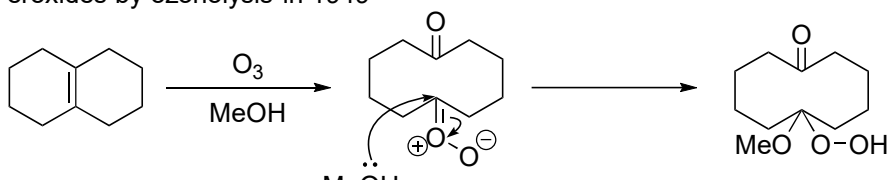
The weakness of the O-O bond of peroxides provides an opportunity for alkoxy radical formation through homolysis or reduction.

1. Historical background and reaction mechanism



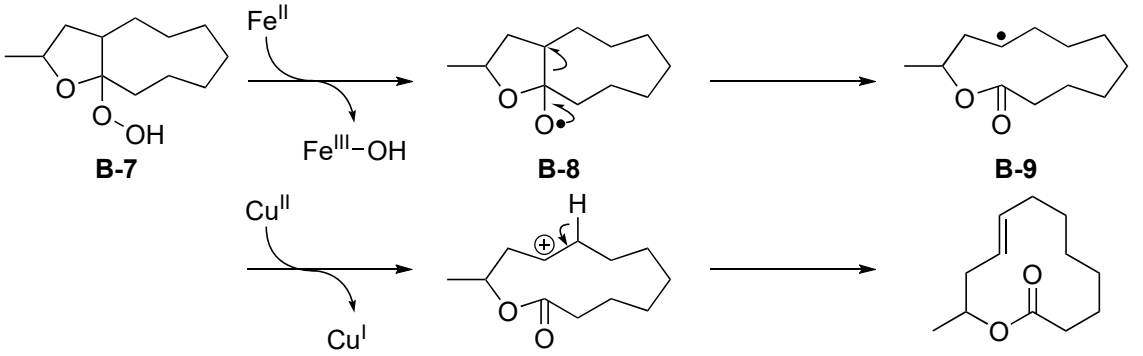
B-1 **B-2** **B-3**

1-2. Peroxides by ozonolysis in 1949[2)]



B-4 **B-5** **B-6**

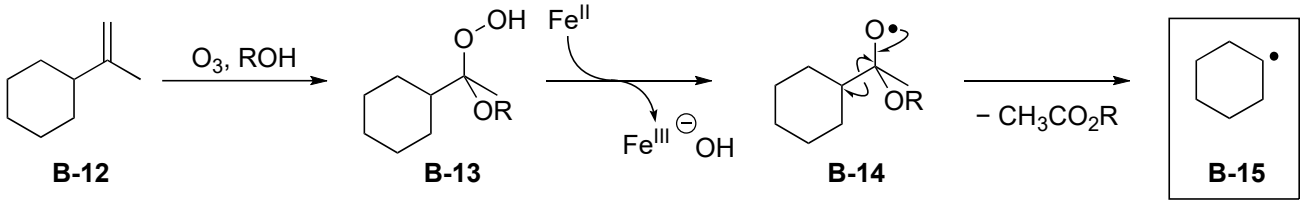
1-3. First application in total synthesis by Shreiber in 1980[3)]



B-7 **B-8** **B-9** **B-10** (±)-recifeiolide (**B-11**)

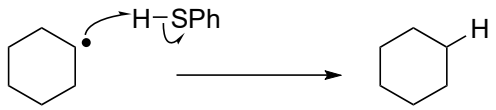
Since then, total synthesis and reaction development using cleavage of peroxides by iron has been developed. In particular, ozone has been widely used as a complete peroxide introduction method.

2. Radical reaction using isopropenyl group



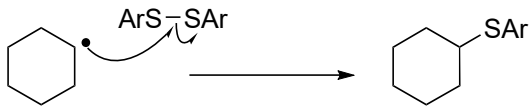
B-12 **B-13** **B-14** **B-15**

(a) Hydrogenation (**problem 2**)[4)]



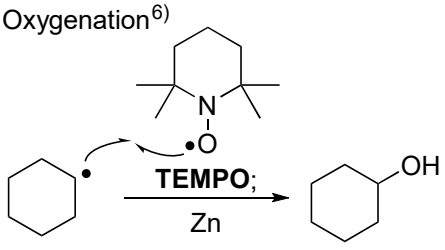
B-15 **B-16**

(b) Thiylation[5)]



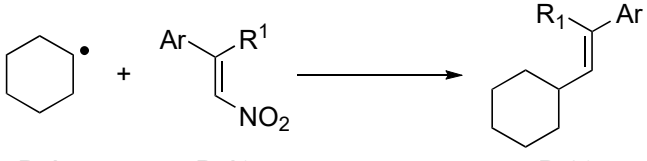
B-15 **B-17**

(c) Oxygenation[6)]

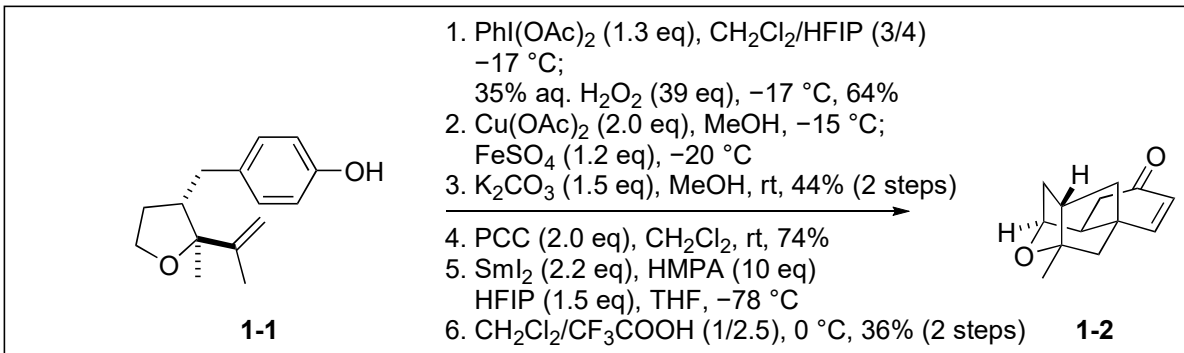


B-15 **B-18**

(d) Introduction of substituted olefin[7)]

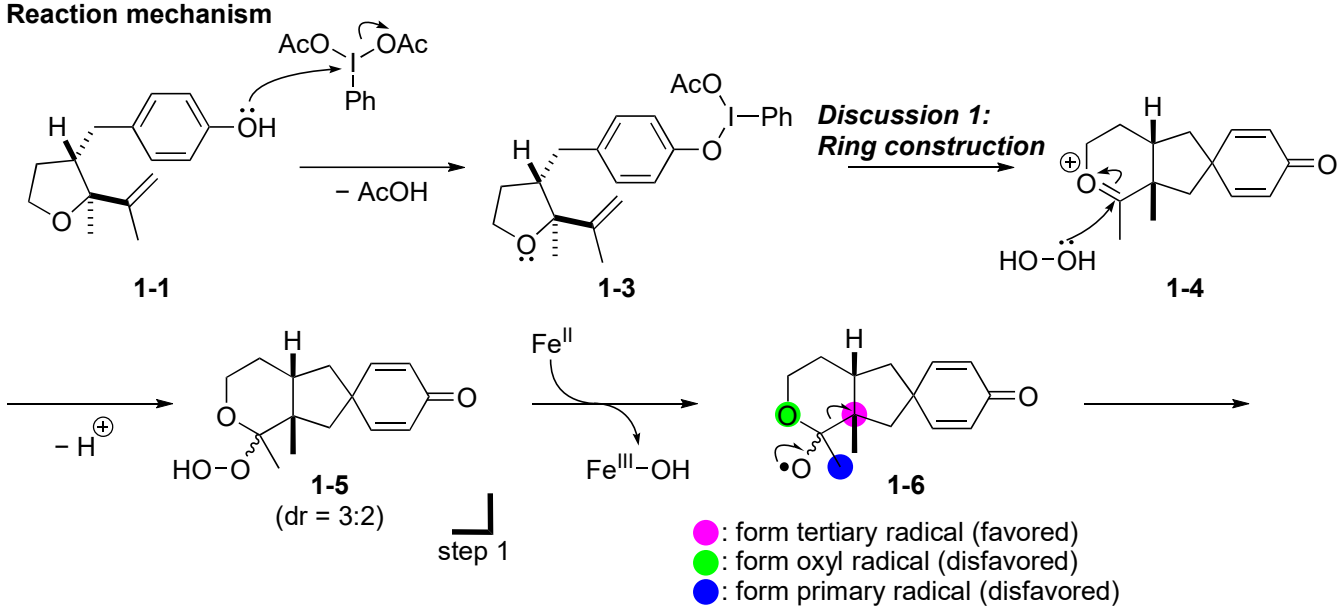


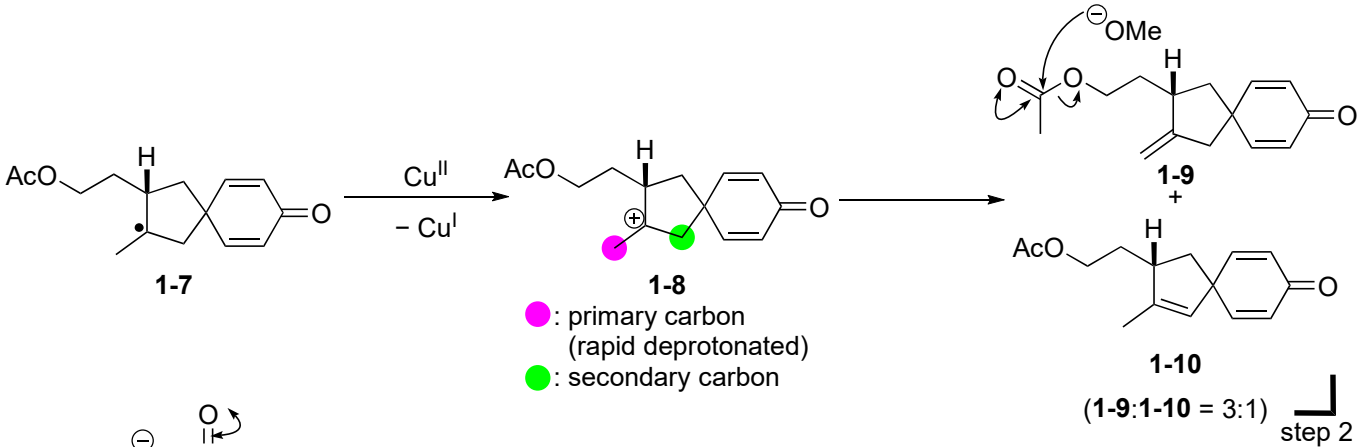
B-15 **B-19** **B-20**

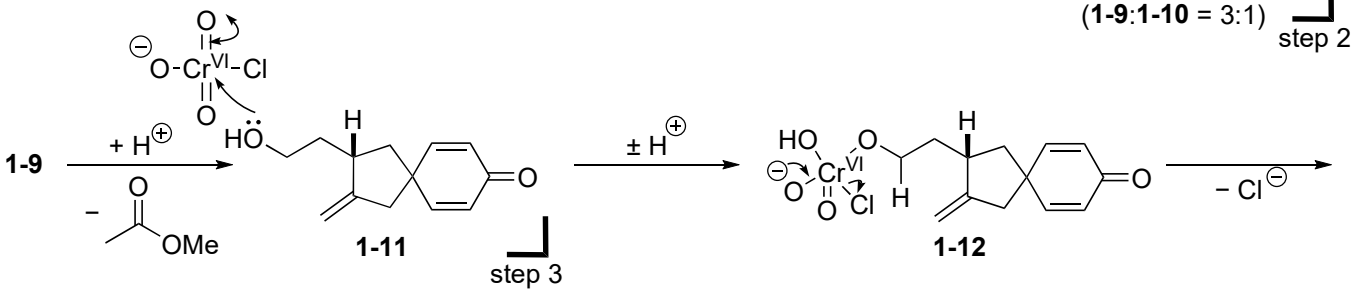


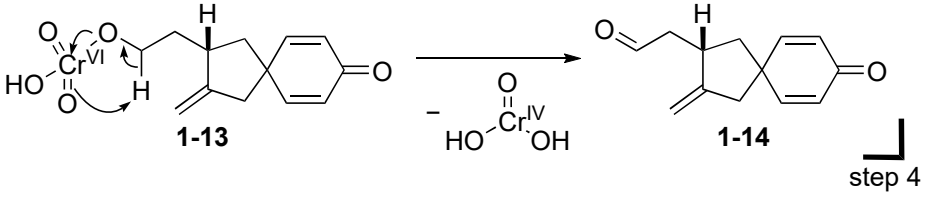
Beaulieu, M.-A.; Sabot, C.; Achache, N.; Guérard, K. C.; Cansei, S. *Chem. Eur. J.* **2010**, *16*, 11224.

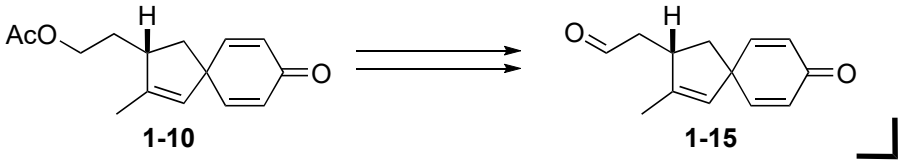
Reaction mechanism







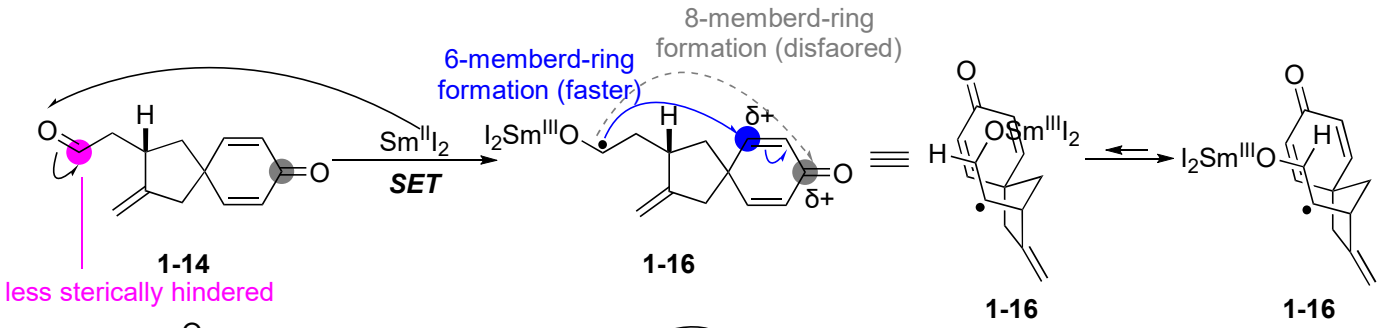




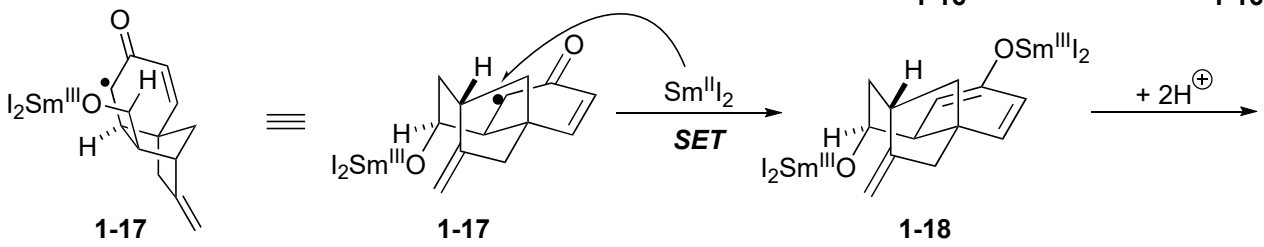
1-10 **1-15**

step 3, 4

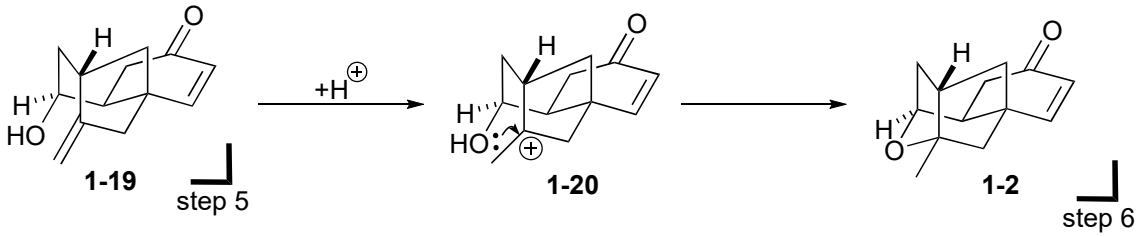
The mechanism of **1-10** to **1-15** is similar to that of **1-9** to **1-14**, so it is omitted here.



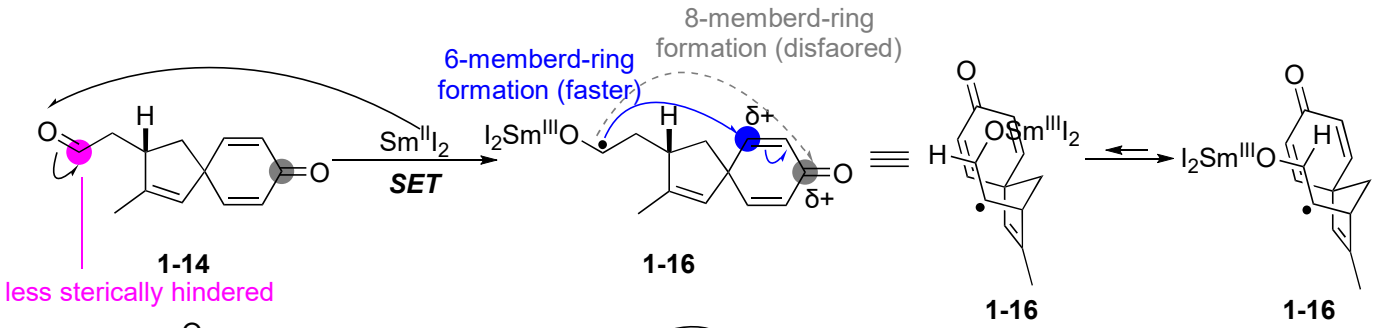
1-14 **1-16** **1-16** **1-16**



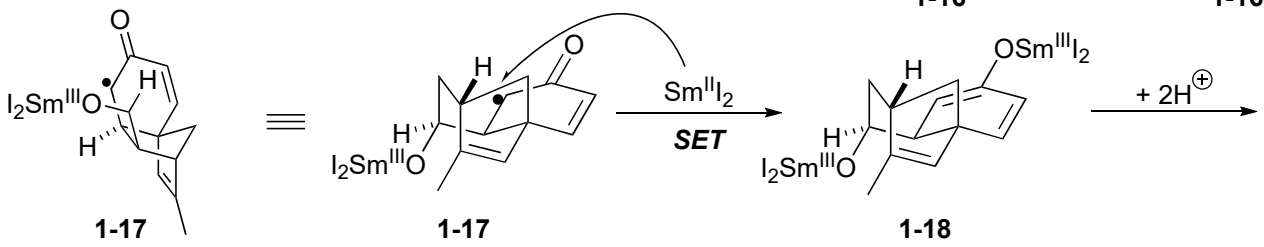
1-17 **1-17** **1-18**



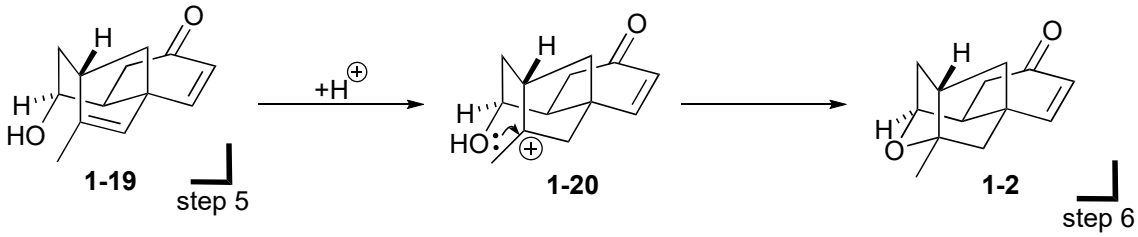
1-19 step 5 **1-20** **1-2** step 6



1-14 **1-16** **1-16** **1-16**



1-17 **1-17** **1-18**

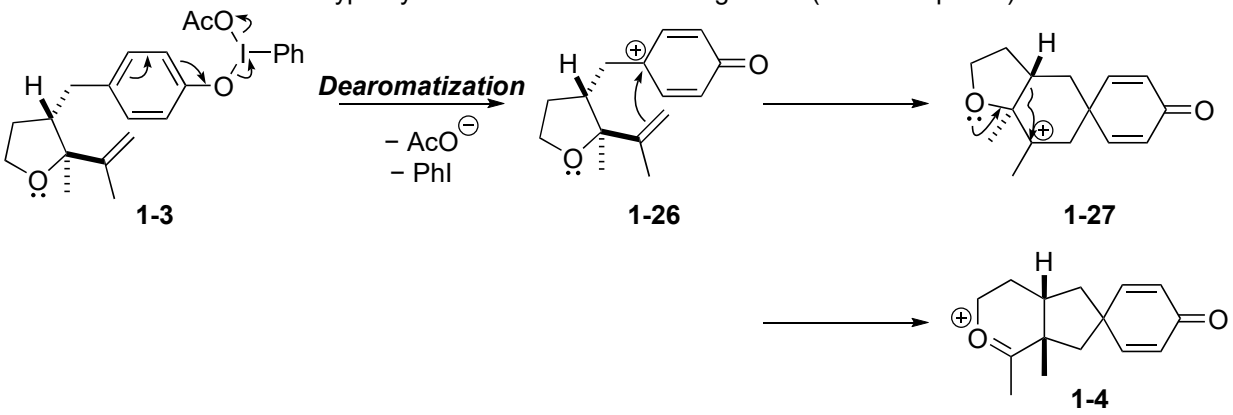


1-19 step 5 **1-20** **1-2** step 6

Discussion 1: Ring construction

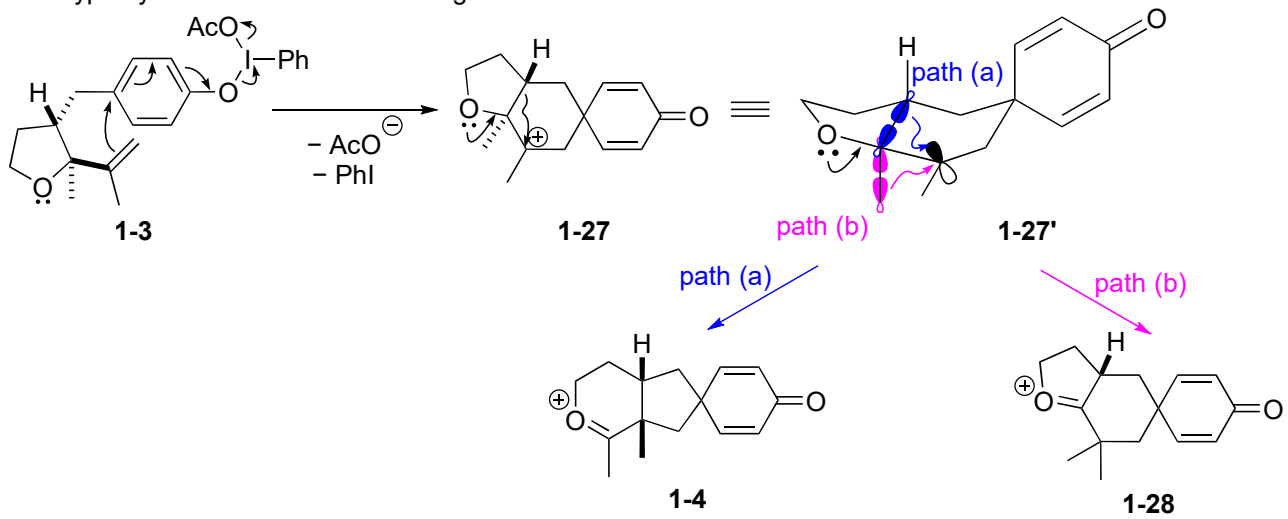
1. Possibe mechanistic pathways

1-1. Dearomatization->Prins-type cyclization->Pinacol rearrangement (author's opinion)



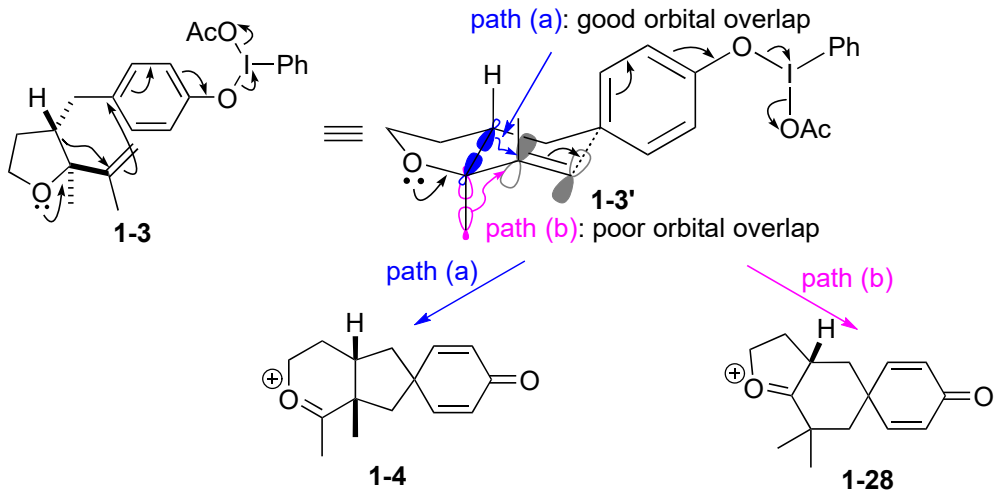
Aromatic rings cannot stabilize the cation of **1-26** as they lack electron-donating groups, thus there is no driving force to generate unstable carbocation **1-26** through de-aromatization.

1-2. Prins-type cyclization->Pinacol rearrangement

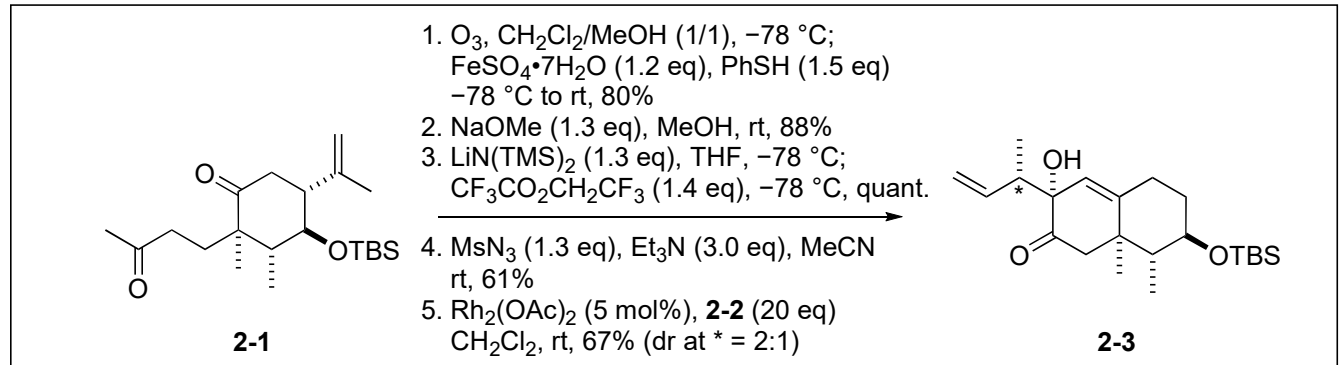


The $\sigma_{C\text{-}C}$ bond highlighted in blue is much electron-rich than the $\sigma_{C\text{-}C}$ bond in pink.
However, the orbital interaction with the empty p orbital of the cation is the same in path (a) and (b).
Therefore, there is also the possibility of the rearrangement of the methyl group.

1-3. Semipinacol type rearrangement (my opinion)

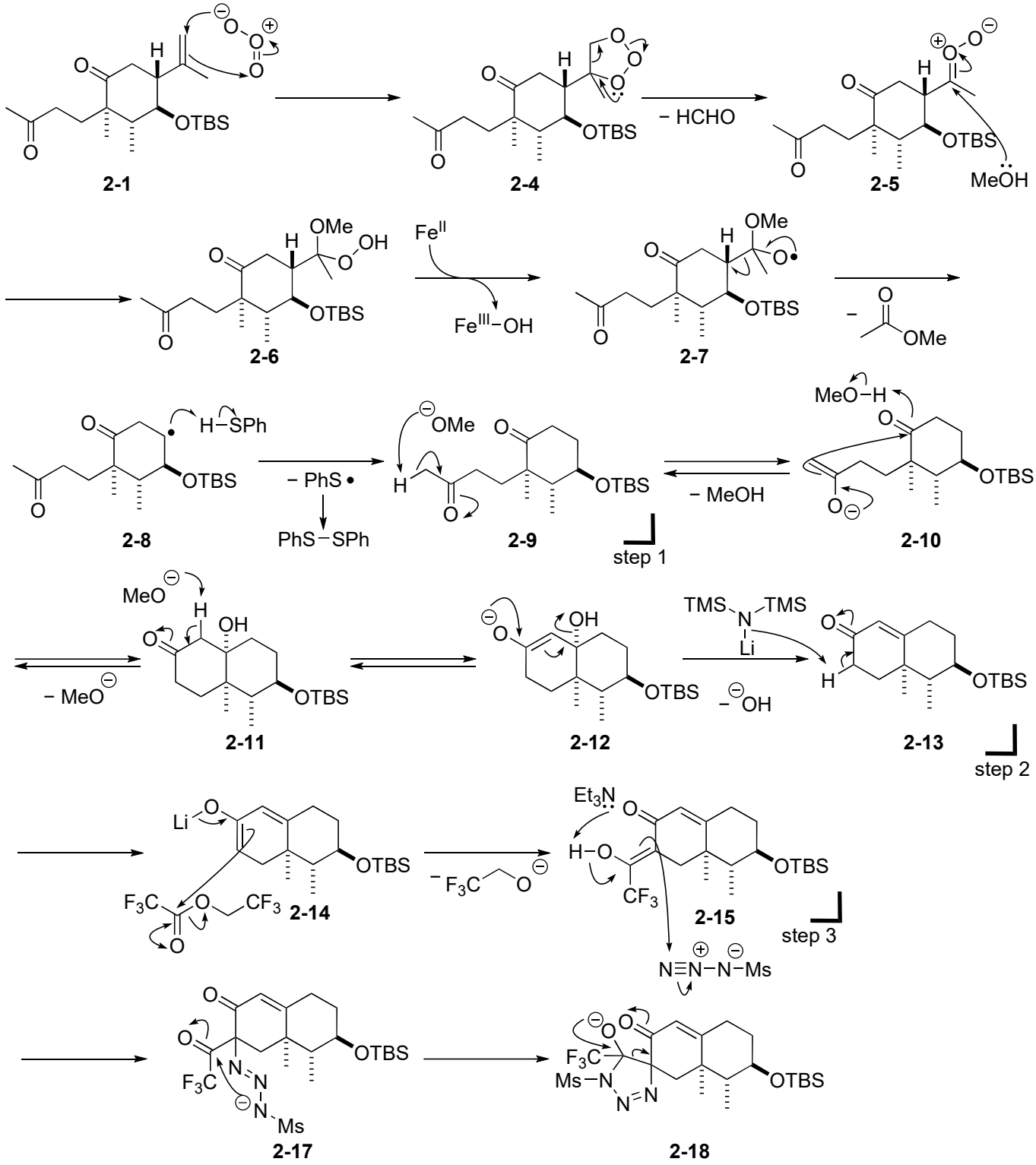


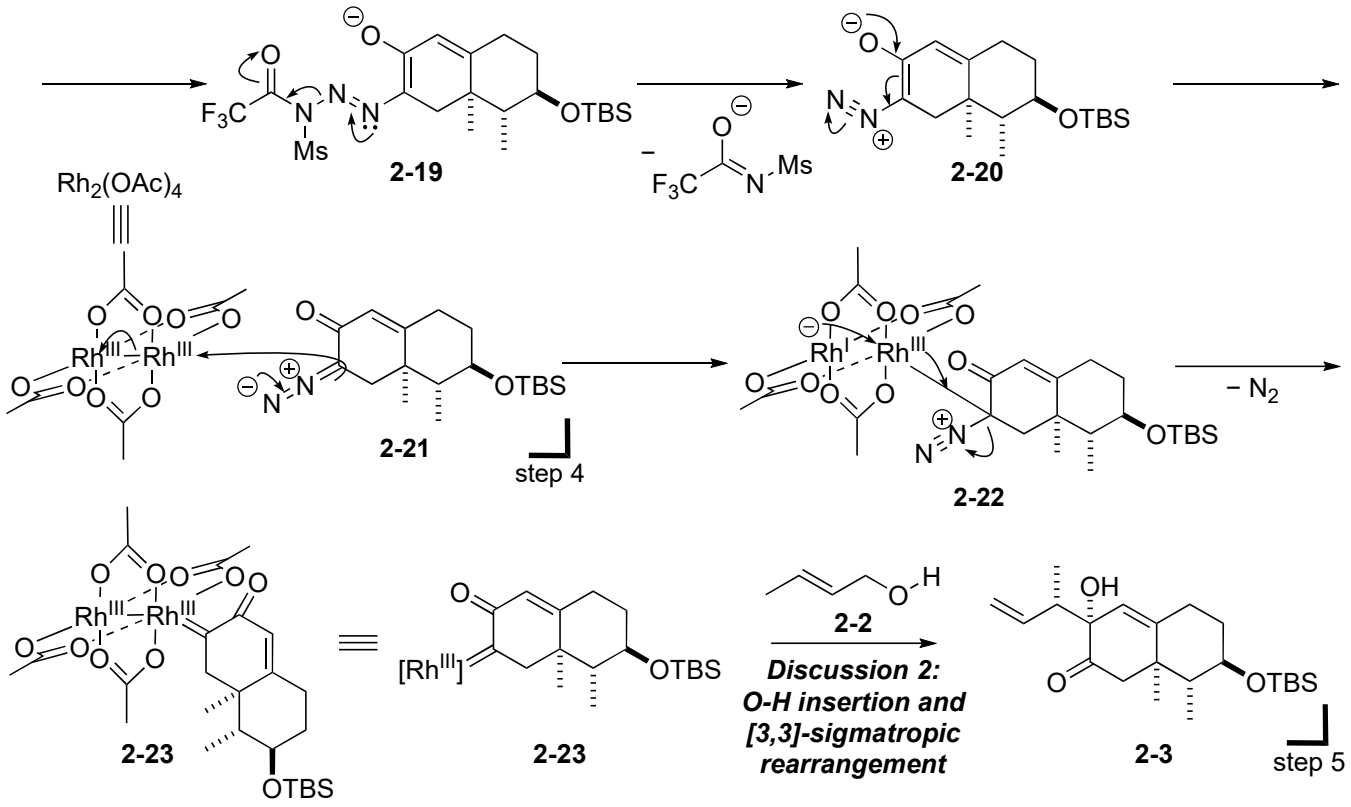
Alternatively, in a pathway where bond rearrangement is driven by electron push from the oxygen atom, the orbital interaction between the blue $\sigma_{C\text{-}C}$ bond and π^* bond is large. Therefore, considering the favorable orbital overlap and the electron-rich nature, I thought that the blue bond rearranged.
Since the reaction proceeded via the chair-like transition state shown in the figure above, the 6,5-cis fused ring system formed.



step 1: Smaligo, A. J.; Swain, M.; Quintana, J. C.; Tan, M. F.; Kim, D.; A. Kwon, O. *Science* **2019**, *364*, 681.
step 2-5: Liffert, R.; Linden, A.; Godemann, K. *J. Am. Chem. Soc.* **2017**, *139*, 16096.

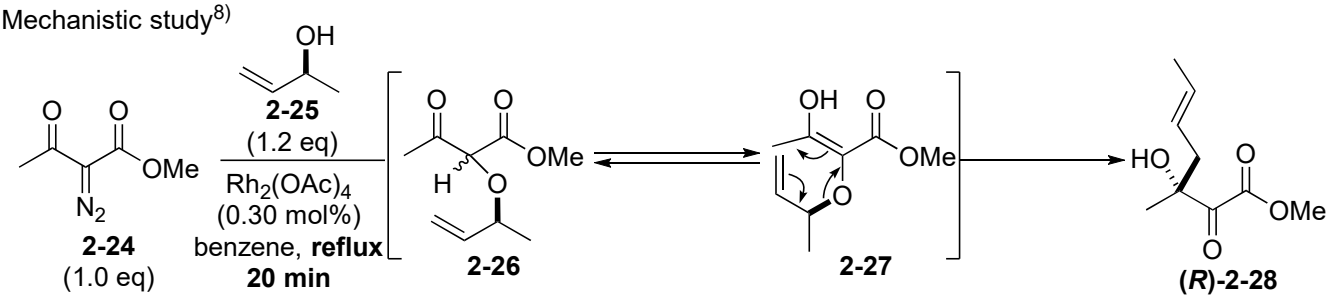
Reaction mechanism





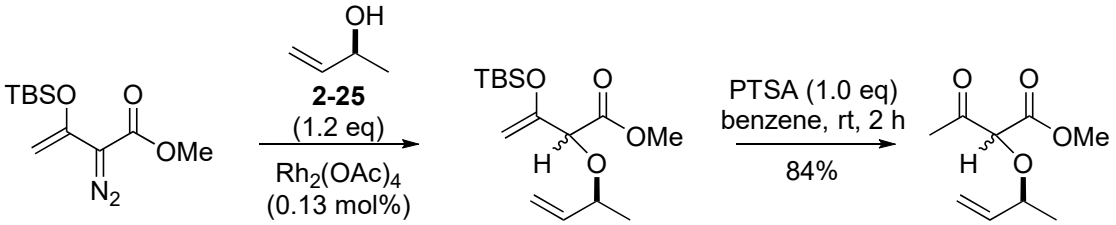
Discussion 2: O-H insertion and [3,3]-sigmatropic rearrangement

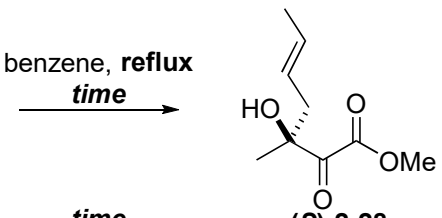
1. Mechanistic study[8)]



2-26 was not obtained and only (***R***)-**2-28** was obtained as a enantiopure product.
Initially, it was thought that the generated **2-26** rapidly teutomerized and then underwent [3,3]-sigmatropic rearrangement.

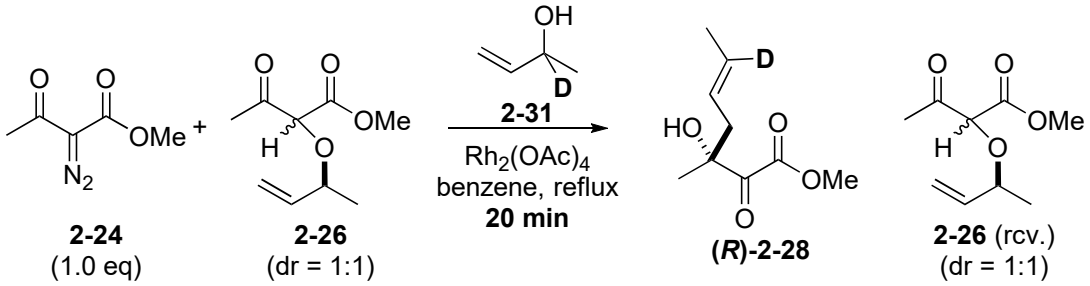
(***R***)-**2-28**: 77% (95%ee)
2-26: 0%





time	(***S***)-**2-28**
20 min	(***S***)-**2-28**: trace
18 h	(***S***)-**2-28**: 75% (47%ee)

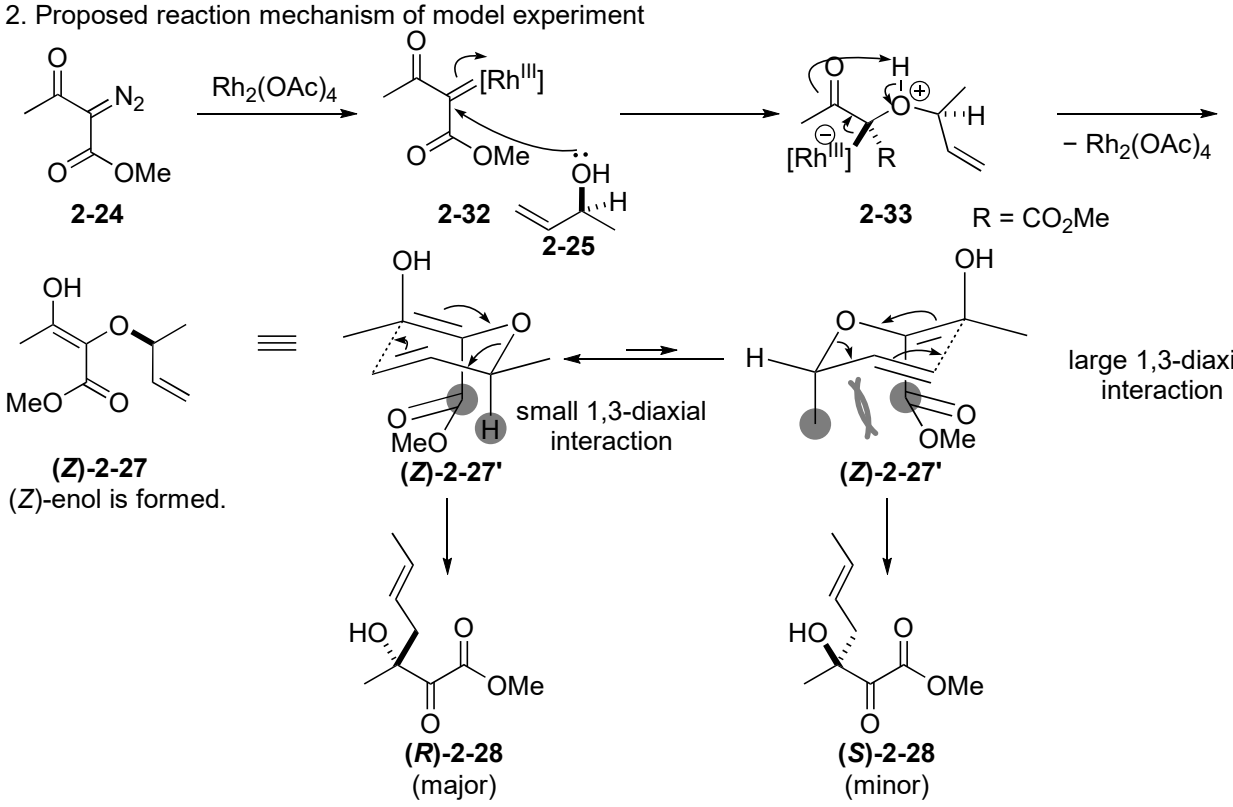
Next, **2-26** was isolated and subjected to the same reaction conditions, but the reaction didn't proceed very much in 20 minutes and required very long time.
Furthermore, the stereoselectivity of the reaction was reversed.



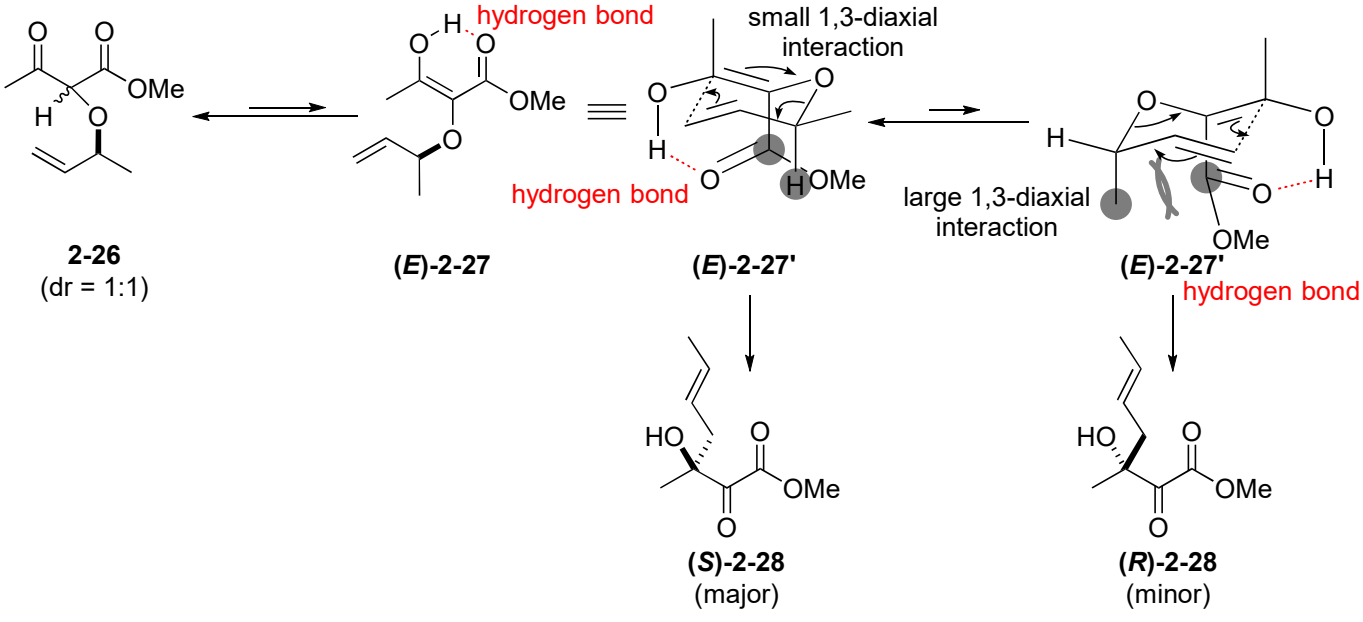
Only **2-24** reacted quickly and converted to **(*R*)-2-28**, whereas **2-26** didn't.

It is thought that rhodium-initiated reaction dose not proceed via **2-26**. I think that [3,3]-sigmatropic rearrangement is vely slow because tautomerization of **2-26** is vely slow and **2-24** directly converted to the enol **2-27** and easily took chair-like transition state.

2. Proposed reaction mechanism of model experiment

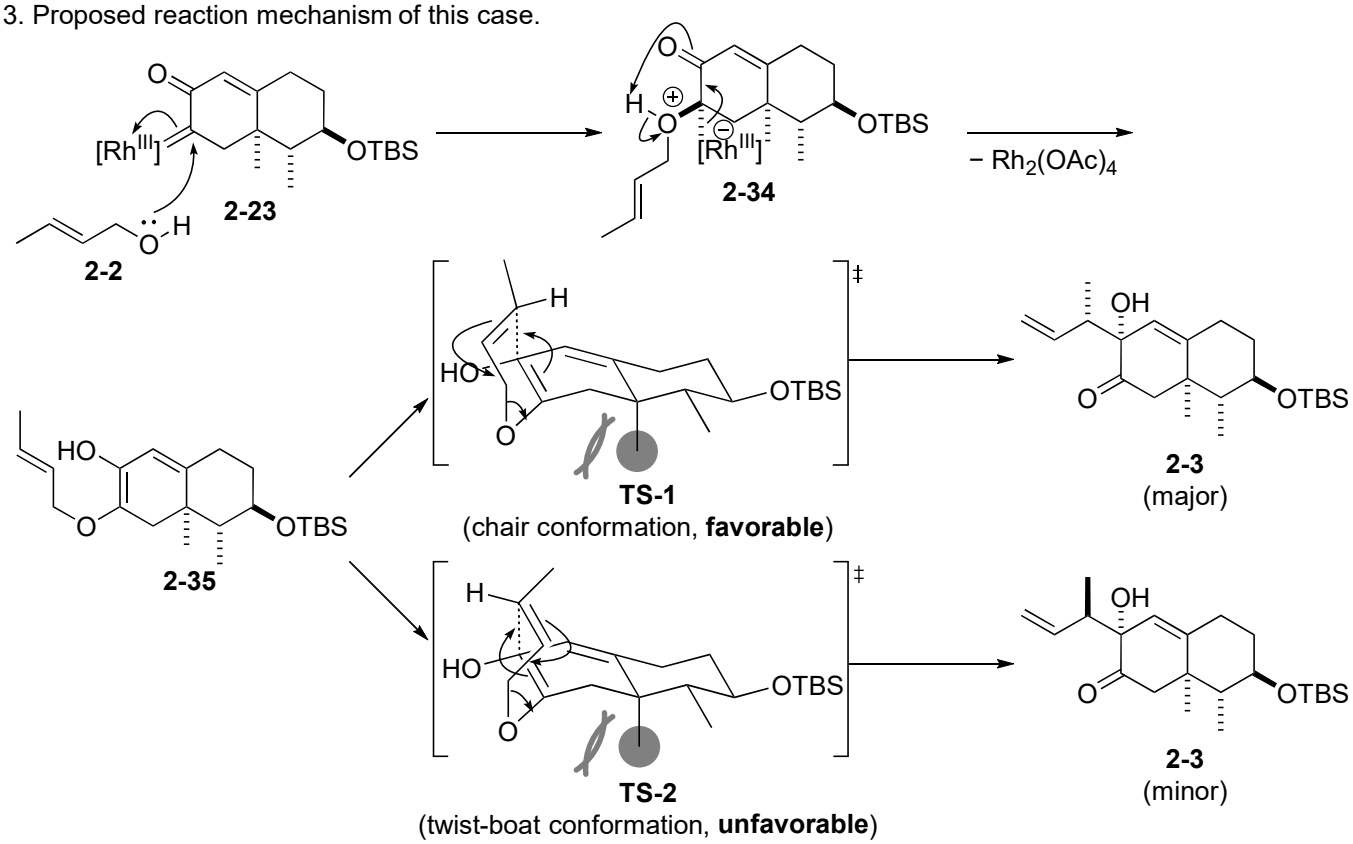


To avoid steric repulsion, the carbonyl group is not the same plane as the olefin and the enone is not conjugated. Therefore, olefin has much electron and [3,3]-sigmatropic rearrangement proceeded fast.



Since hydrogen bond colud be formed, [3,3]-sigmatropic rearrangement mainly proceeded via **(*E*)-2-27**. However, olefin has less electron due to the conjugation and [3,3]-sigmatropic rearrangement proccede slowly.

3. Proposed reaction mechanism of this case.



Since the α-face is sterically crowded by methyl groyp, the reaction proceeded from the α-face.

References

1) Häber, F.; Weiss, J. *Die Naturwissenschaften* **1932***,* 20, 948.
2) Criegee, R.; Wenner, G. *Justus Liebigs Ann. Chem.* **1949***, 564*, 9.
3) Shreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163.
4) Smaligo, A. J.; Swain, M.; Quintana, J. C.; Tan, M. F.; Kim, D.; A. Kwon, O. *Science* **2019**, *364*, 681.
5) Smaligo, A. J.; Kwon, O. *Org. Lett.* **2019**, *21*, 8592.
6) Smaligo, A. J.; Wu, J.; Burton, N. R.; Hacker, A. S.; Shaikh, A. C.; Quintana, J. C. Wang, R.; Xie, C.; Kwon, O. *Angew. Chem. Int. Ed.* **2020**, *59*, 1211.
7) Swain, M.; Sedykhov, G.; Wang, R.; Kwon, O. *Angew. Chem. Int. Ed.* **2020**, *59*, 17565.
8) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.