

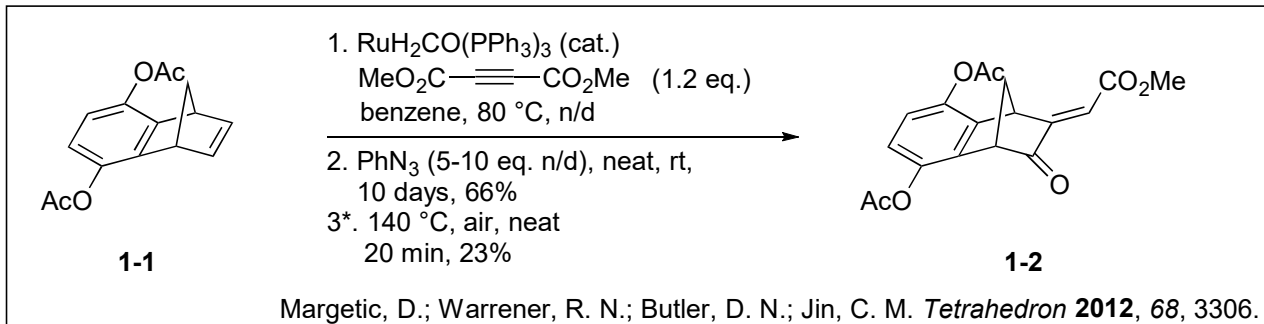
Problem Session (2) -Answer-

2017. 6. 3. Tsukasa Shimakawa

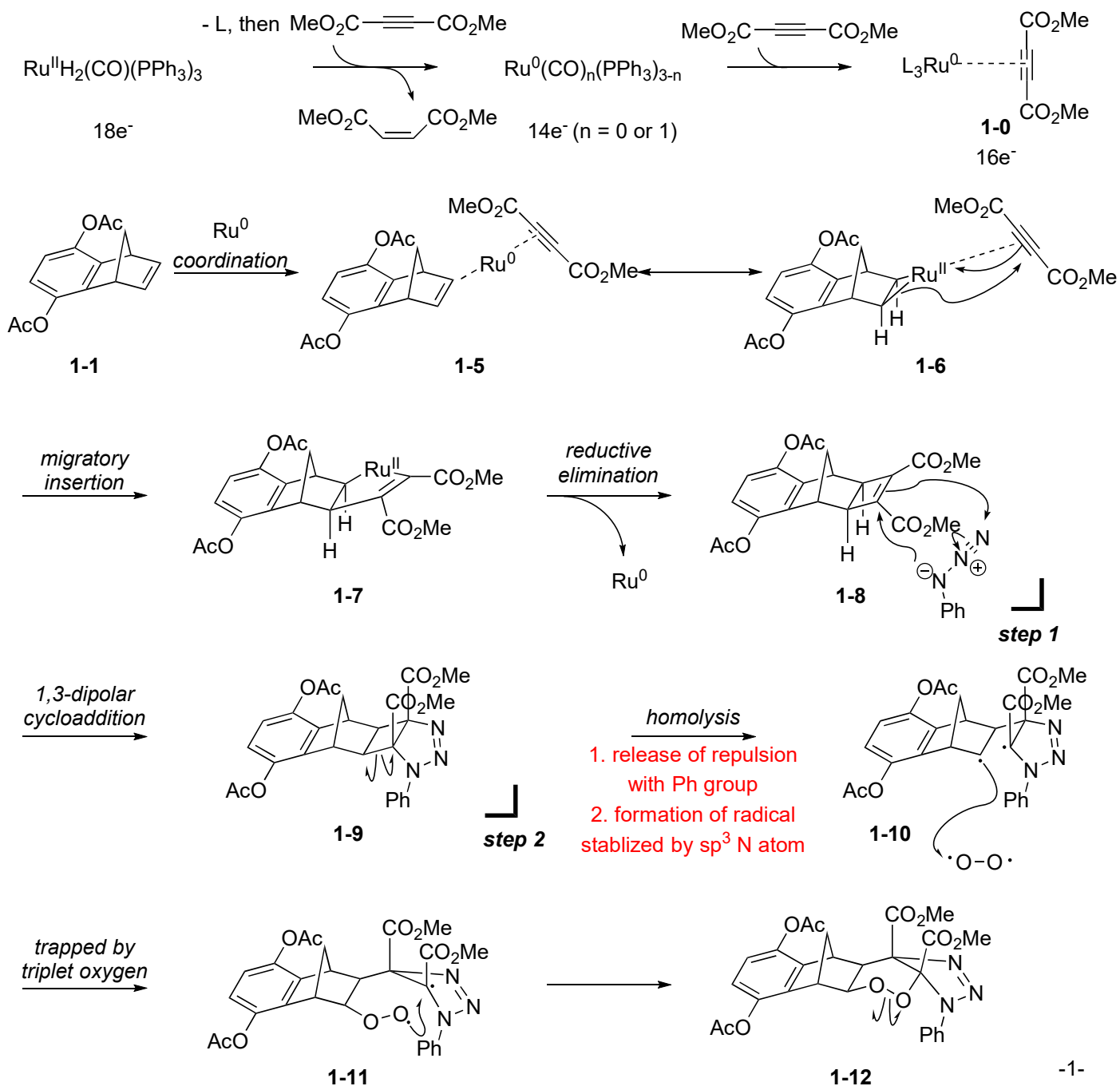
Topic: cyclobutane and cyclobutene derivatives in skeletal rearrangement

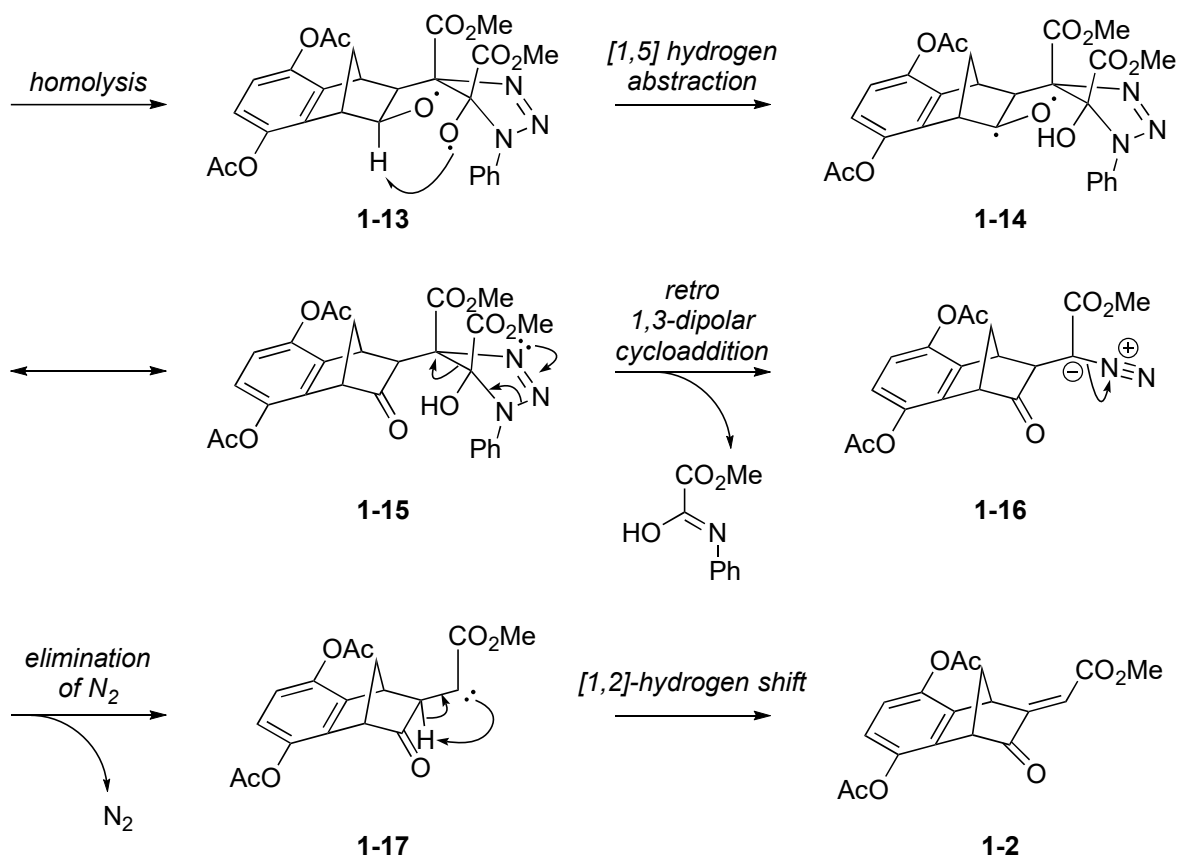
1. Cascade thermal isomerization of cyclobutane derivatives

1-1. Reaction mechanism



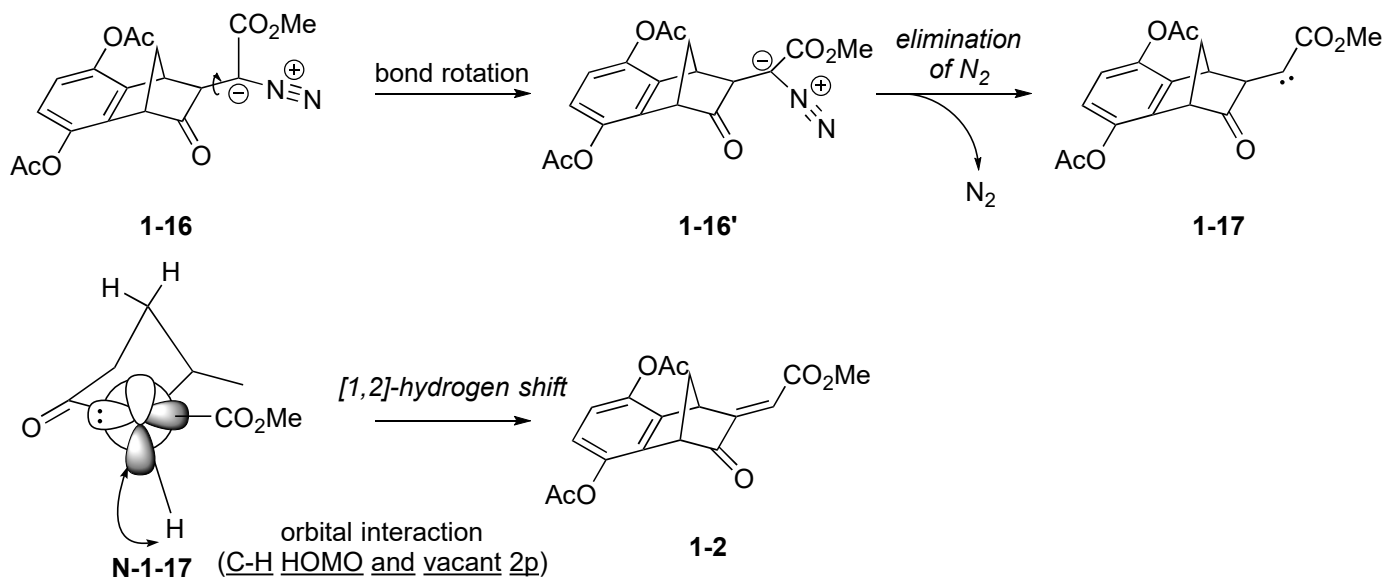
Key Point: autoxidation, [1,5] hydrogen abstraction, [1,2] hydrogen shift





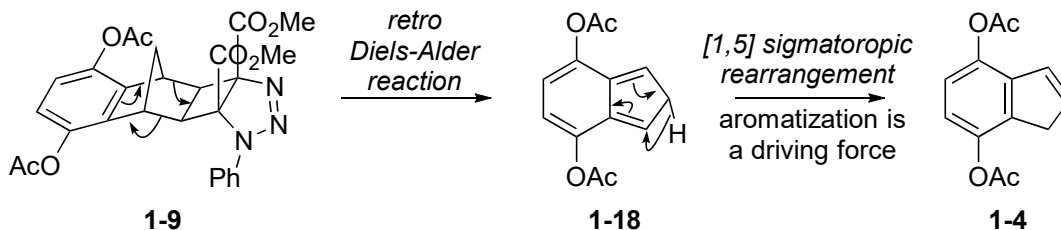
1-2. Discussion

1-2-1. Explanation of geometric isomers

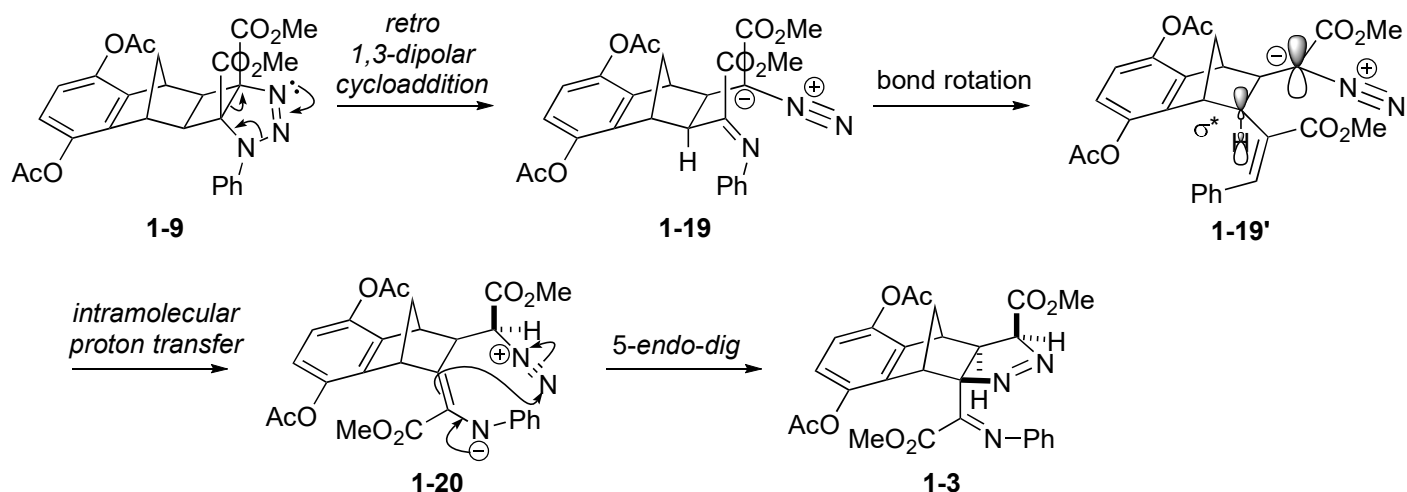


1-2-2. Reaction mechanism for **1-3** and **1-4**

1-2-2-1. transformation from **1-9** to **1-4**

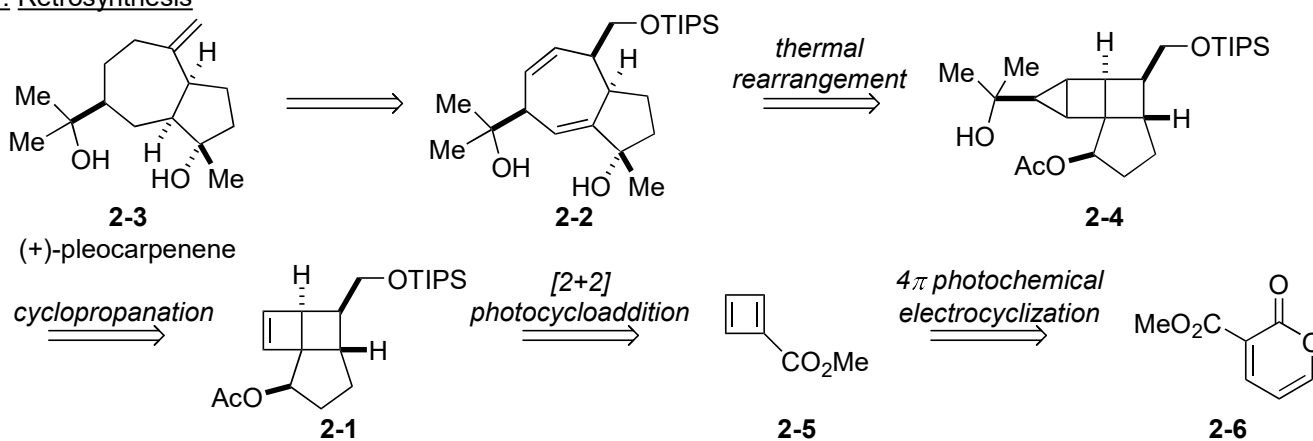


1-2-2-2. transformation from 1-9 to 1-3

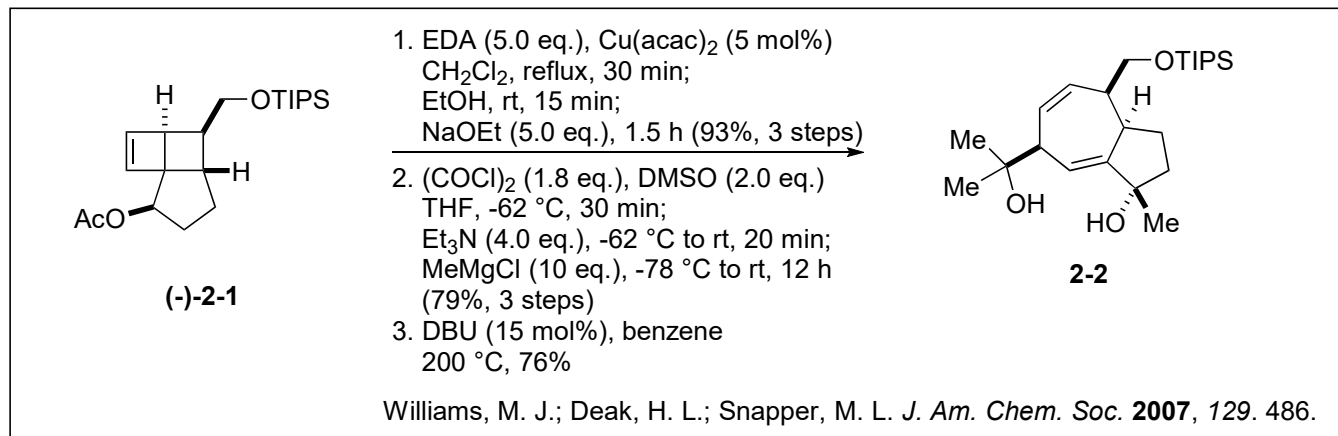


2. Asymmetric total synthesis of (+)-pleocarpenene by Snapper group

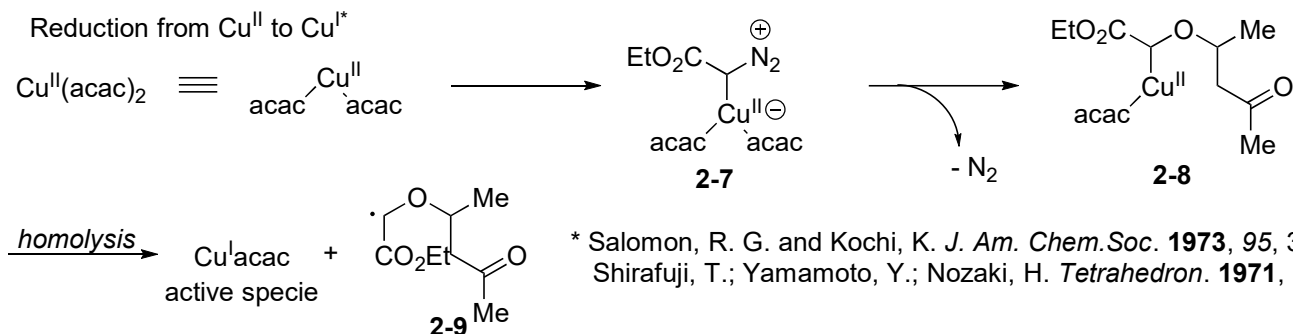
2-1. Retrosynthesis

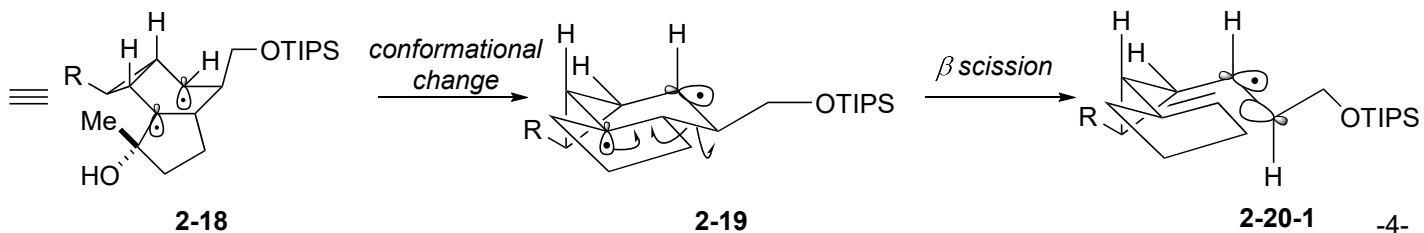
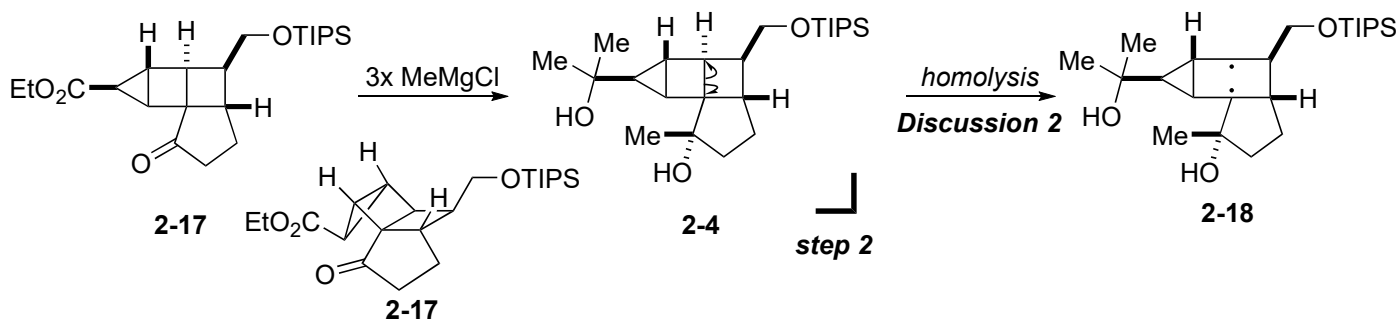
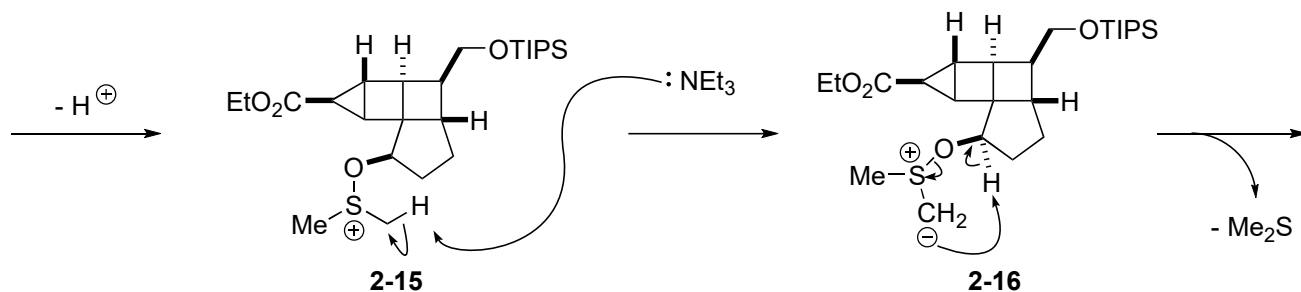
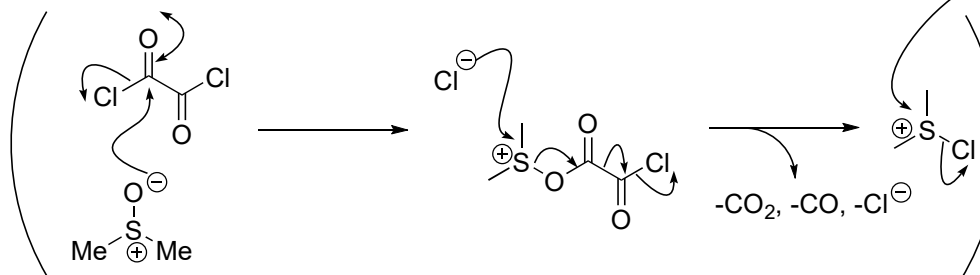
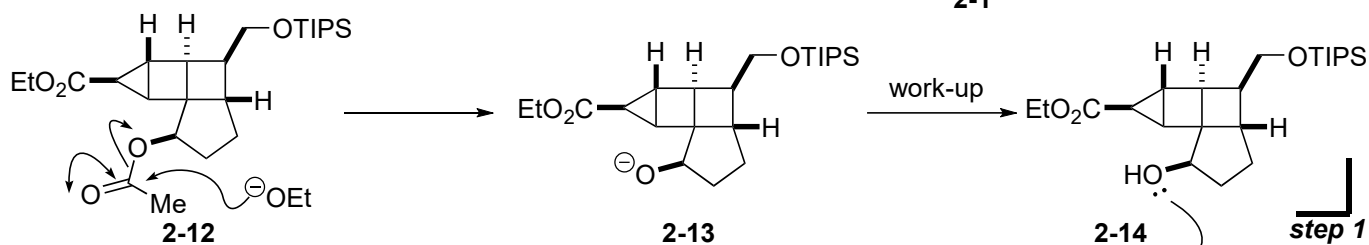
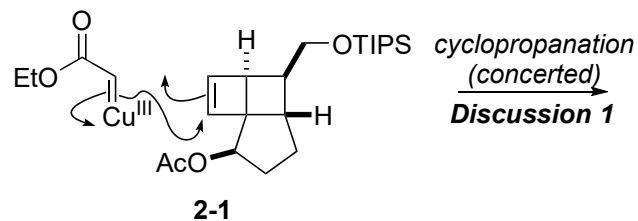
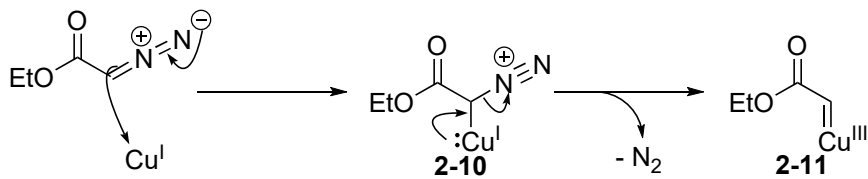


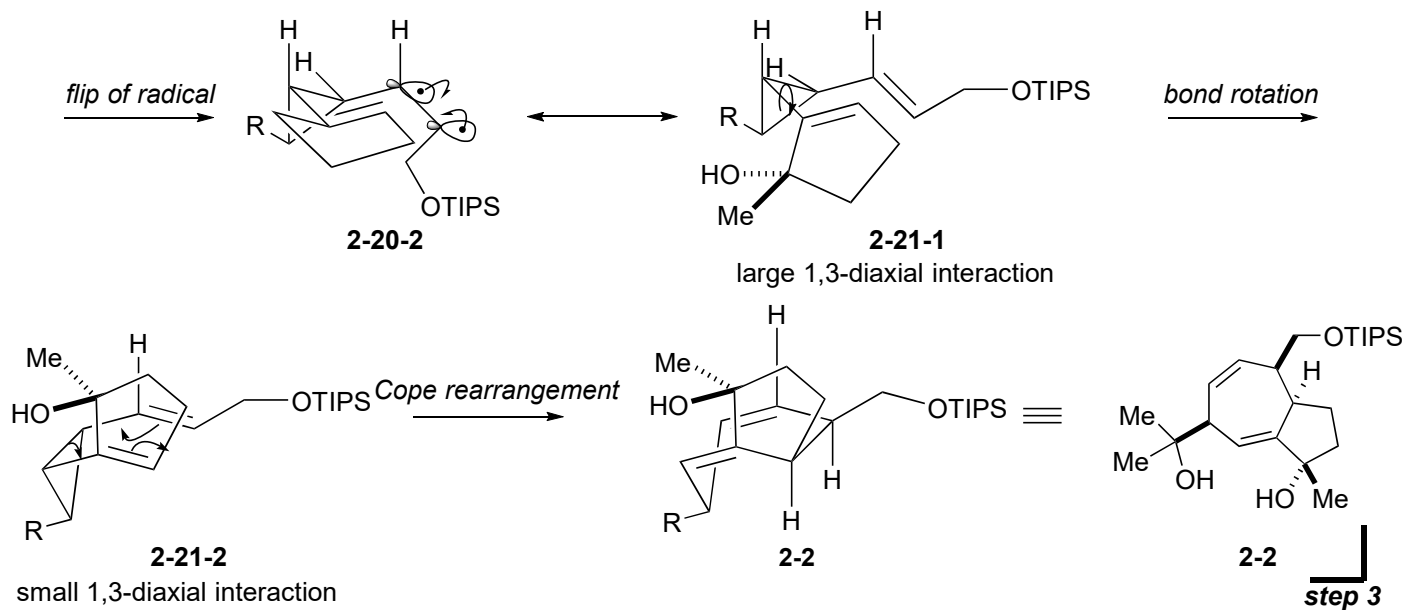
2-2. Reaction mechanism



Key Point: Thermal rearrangement (fragmentation and Cope rearrangement)

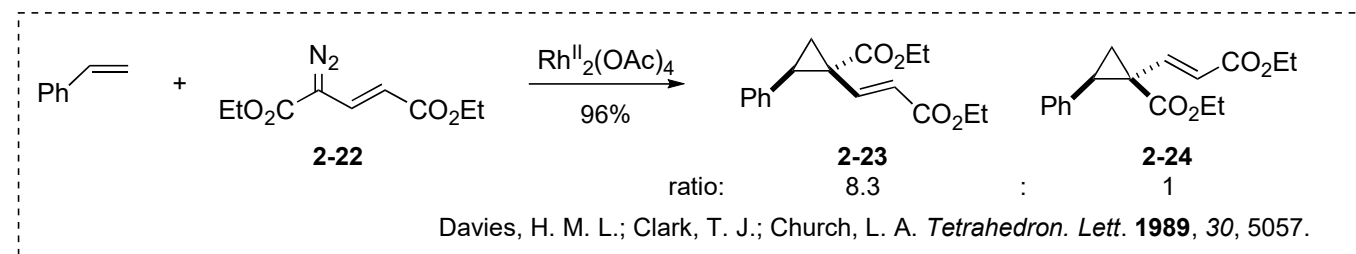






2-3. Discussion

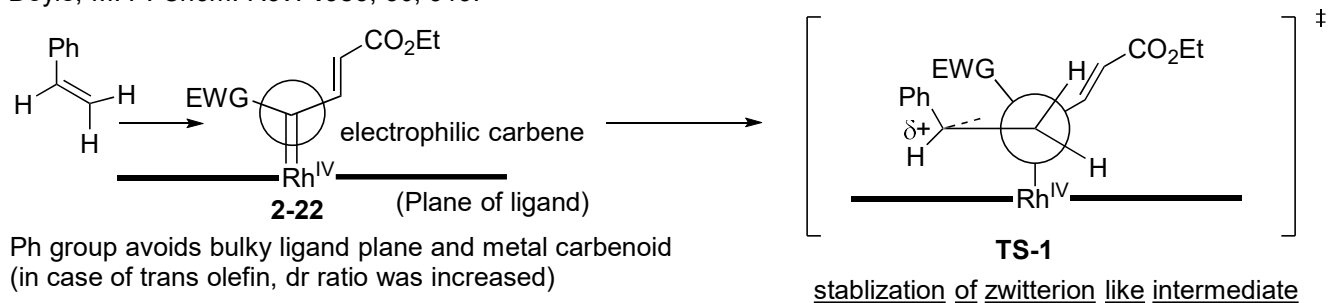
2-3-1. Diastereoselectivity of cyclopropanation via metalcarbenoid



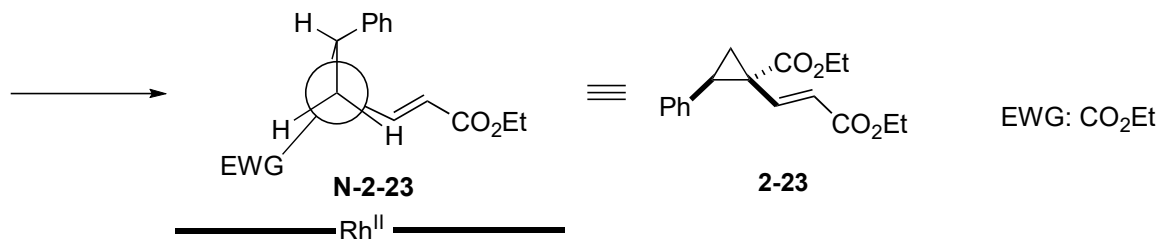
Explanation of diastereoselectivity by Davies group

Davies, H. M. L. *et al.*, *J. Am. Chem. Soc.* **1996**, 118, 6897.

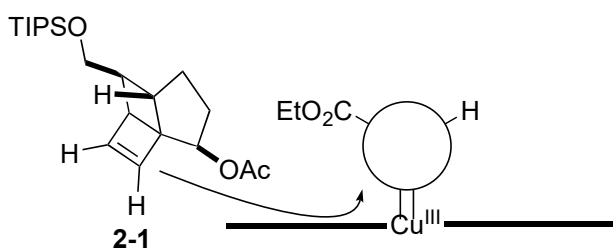
Doyle, M. P. *Chem. Rev.* **1986**, 86, 919.



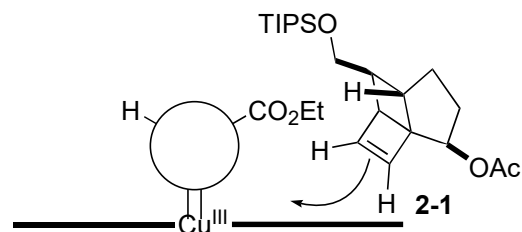
Ph group avoids bulky ligand plane and metal carbenoid (in case of trans olefin, dr ratio was increased)

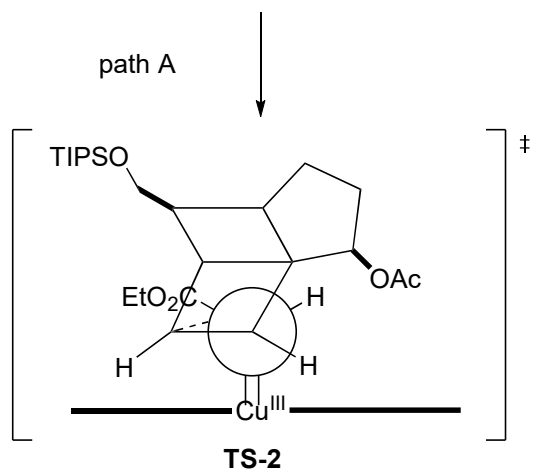


1. Path A (favored)

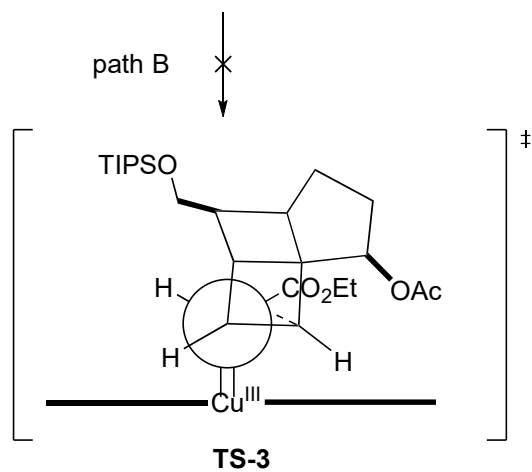


2. Path B (disfavored)

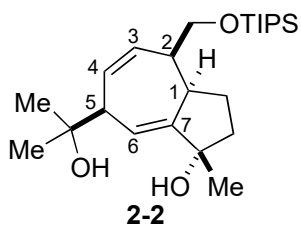
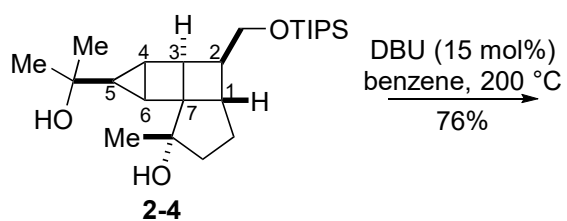
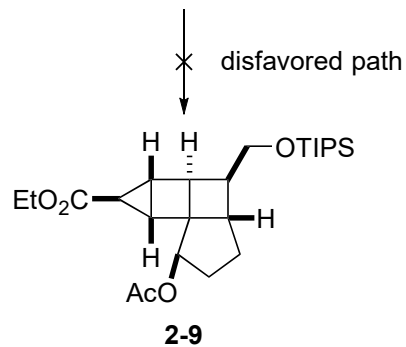
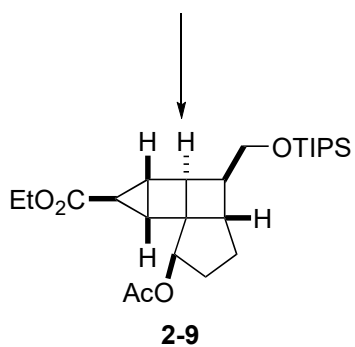




small steric repulsion between ethyl ester and five membered ring



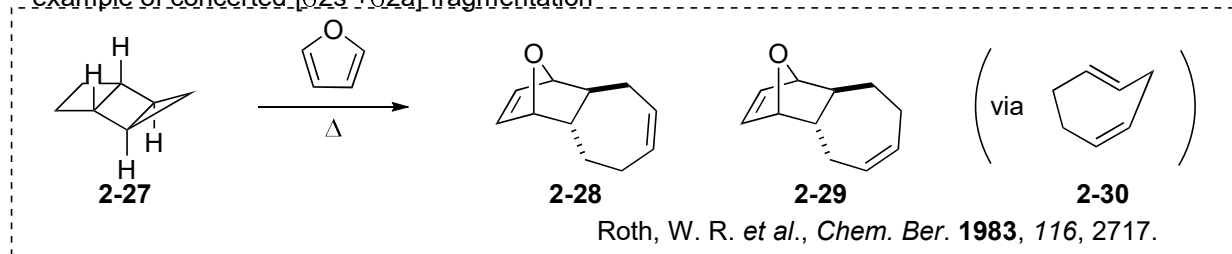
large steric repulsion between ethyl ester and five membered ring



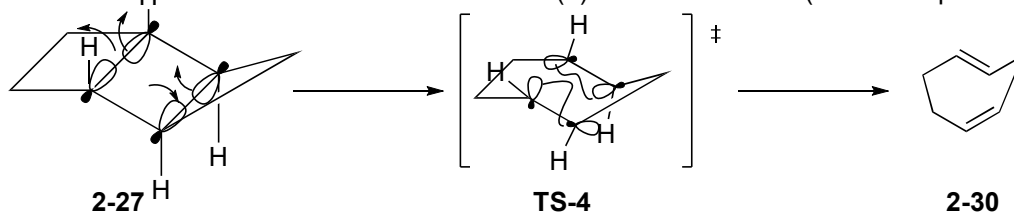
2-3-2. Reaction mechanism of thermal rearrangement

(1) Concerted path ($[\sigma 2s + \sigma 2a]$ fragmentation)

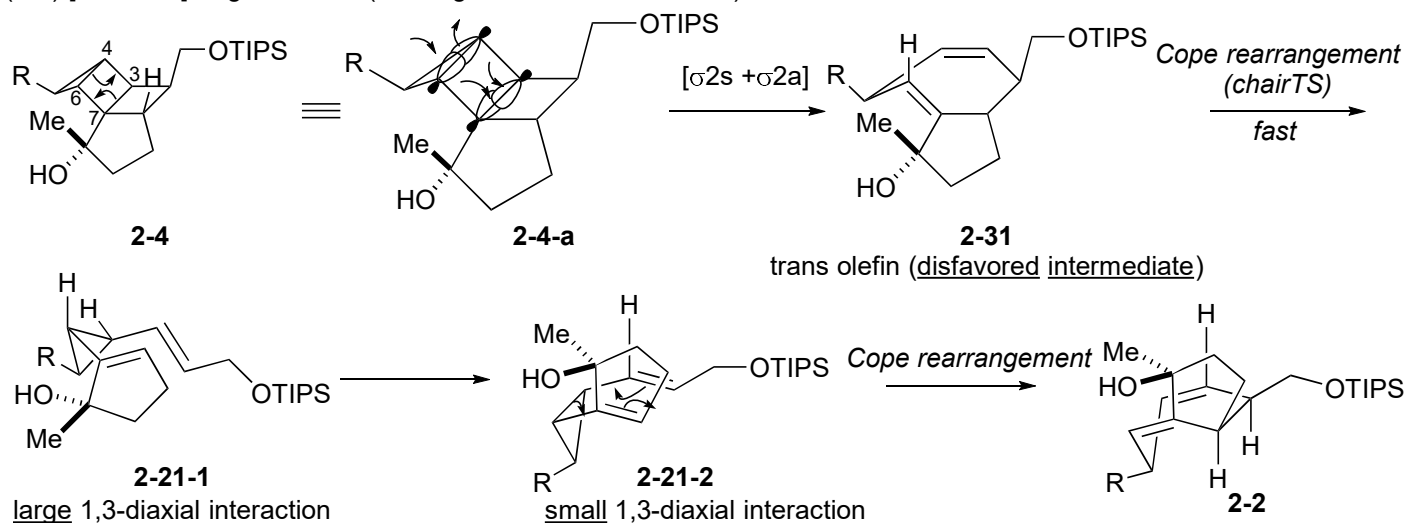
example of concerted $[\sigma 2s + \sigma 2a]$ fragmentation



Reaction mechanism (from **2-27** to **2-30**): $4q+2 (s) = 1$
 $4r (a) = 0$ \Rightarrow consistent with Woodward-Hoffmann rule (concerted pathway)

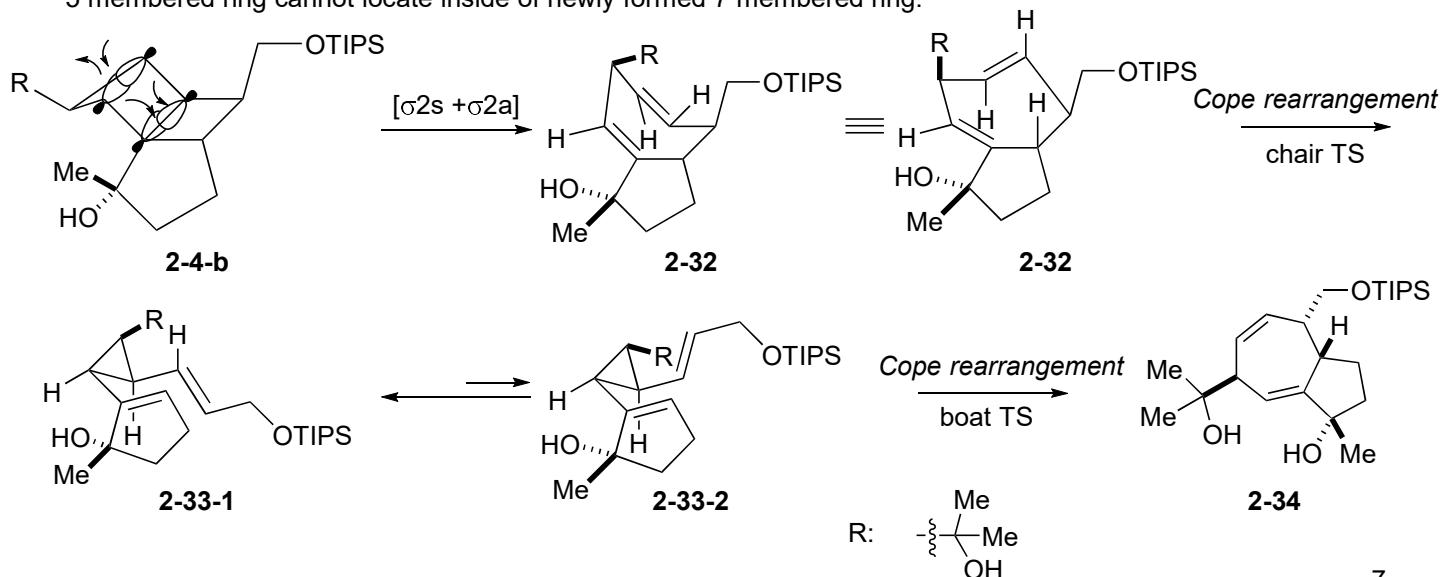


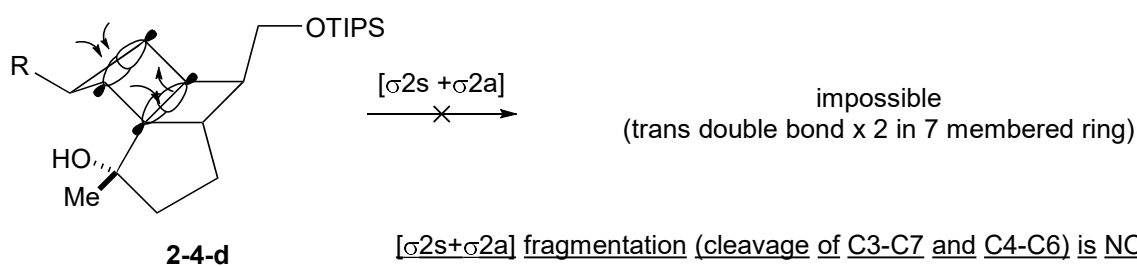
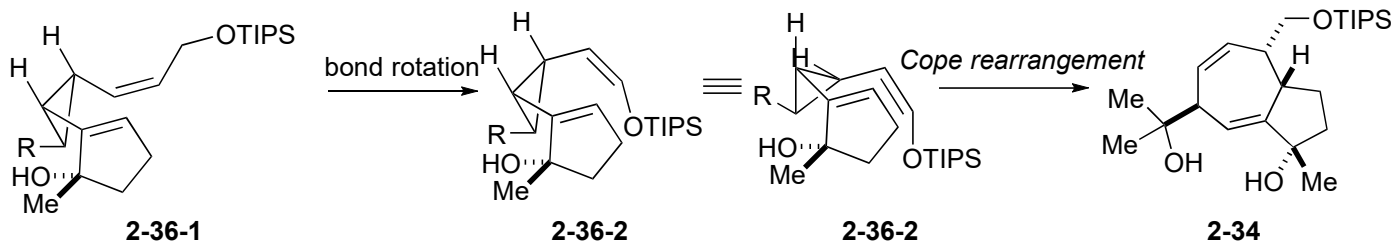
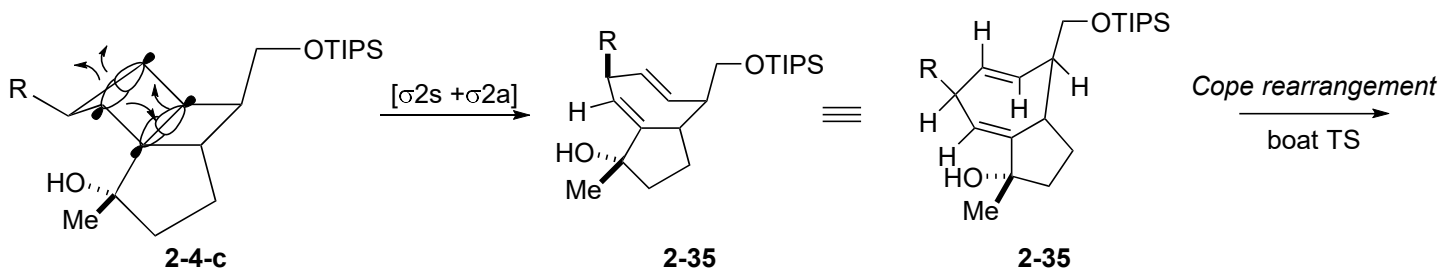
(1-1) $[\sigma 2s + \sigma 2a]$ fragmentation (cleavage of C3-C7 and C4-C6)



Other possibilities of $[\sigma 2s + \sigma 2a]$ fragmentation (3 types)

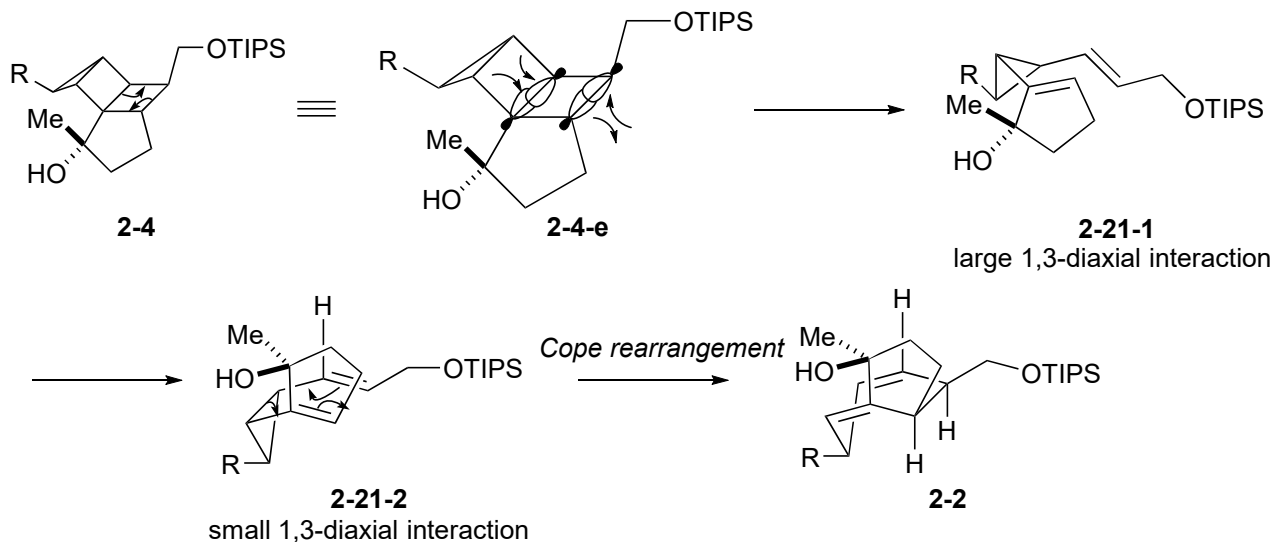
* 5 membered ring cannot locate inside of newly formed 7 membered ring.



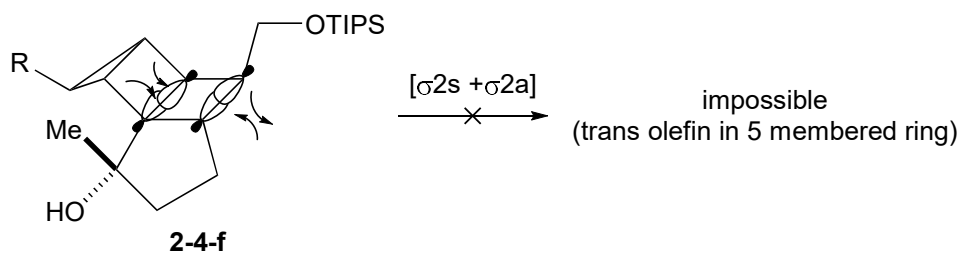


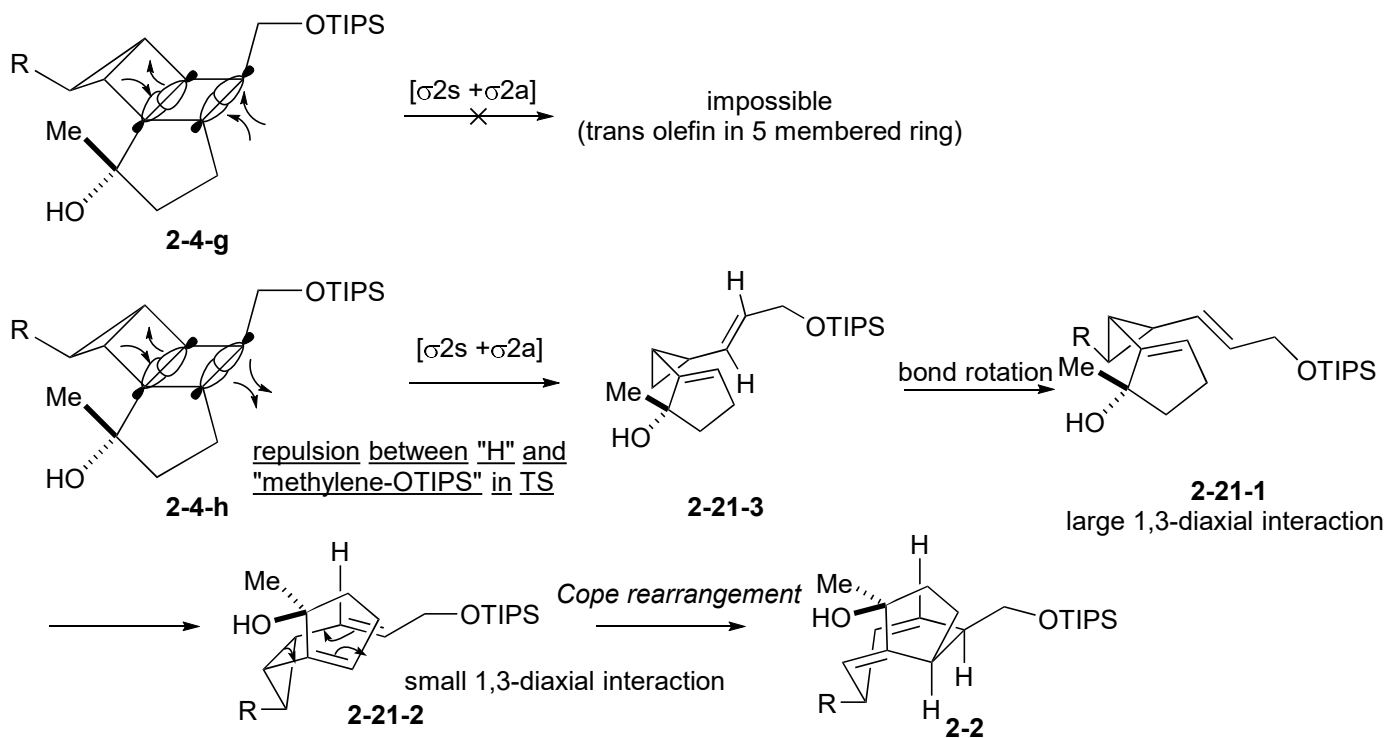
$[\sigma 2s + \sigma 2a]$ fragmentation (cleavage of C3-C7 and C4-C6) is NOT a reasonable path
 ← 1. via trans olefin included in 7 membered ring intermediate
 2. Possibility of generating diastereomer **2-34**

(1-2) $[\sigma 2s + \sigma 2a]$ fragmentation (cleavage of C1-C2 and C3-C7)



· Other possibilities of $[\sigma 2s + \sigma 2a]$ fragmentation (3 types)

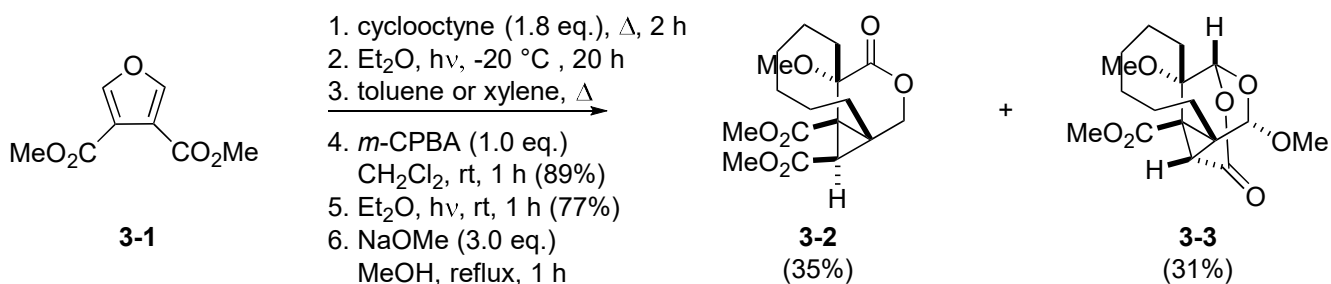




1. via diradical (Homolysis of C3-C7 bond) or 2. $[\sigma_{2s} + \sigma_{2a}]$ fragmentation of C1-C2, C3-C7 bond

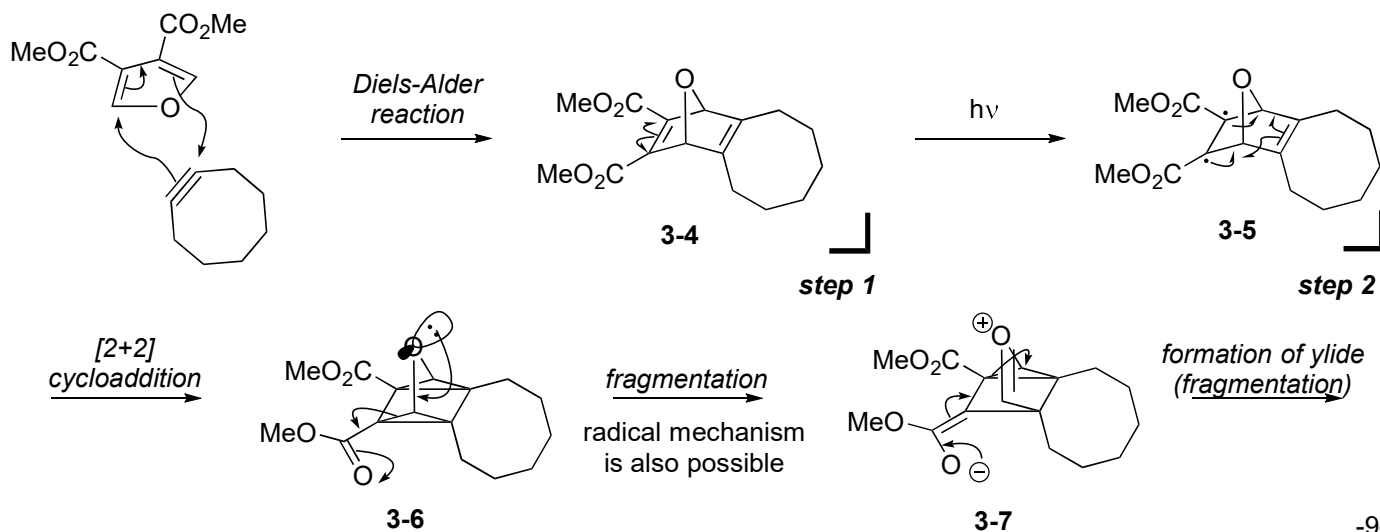
3. Synthesis of bridged cyclopropane derivative

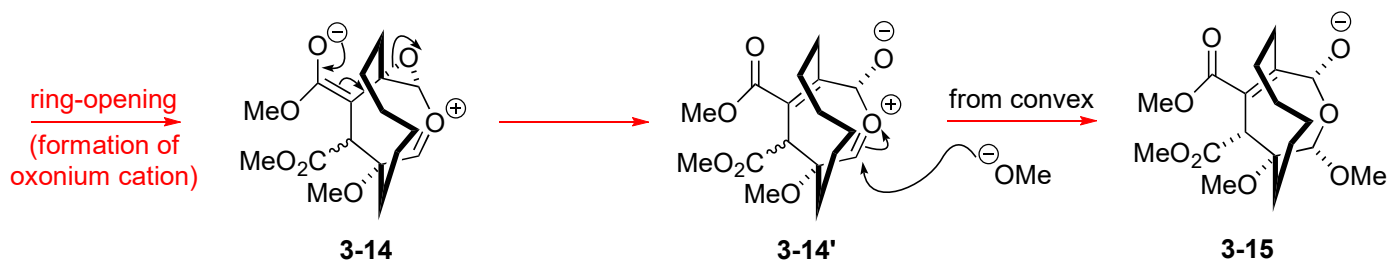
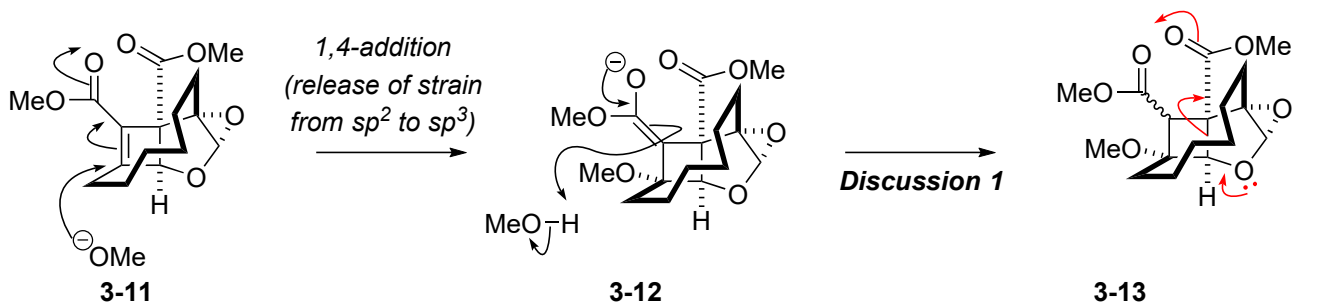
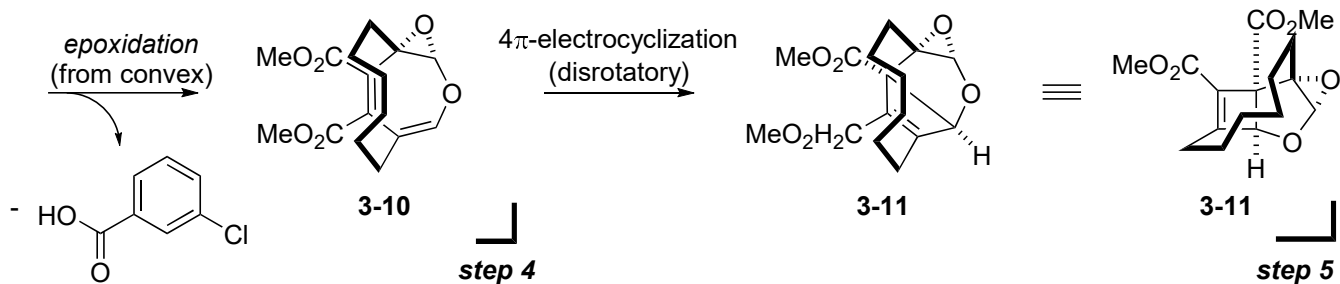
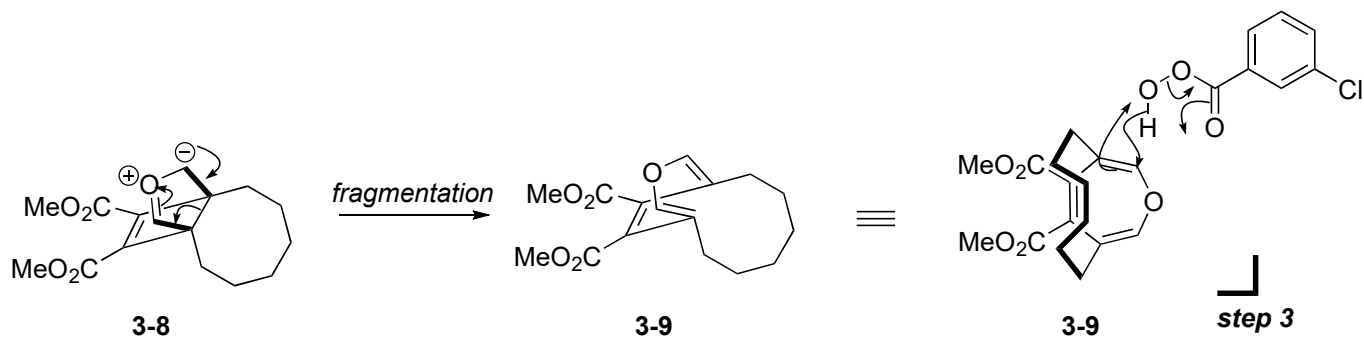
3-1. Reaction mechanism



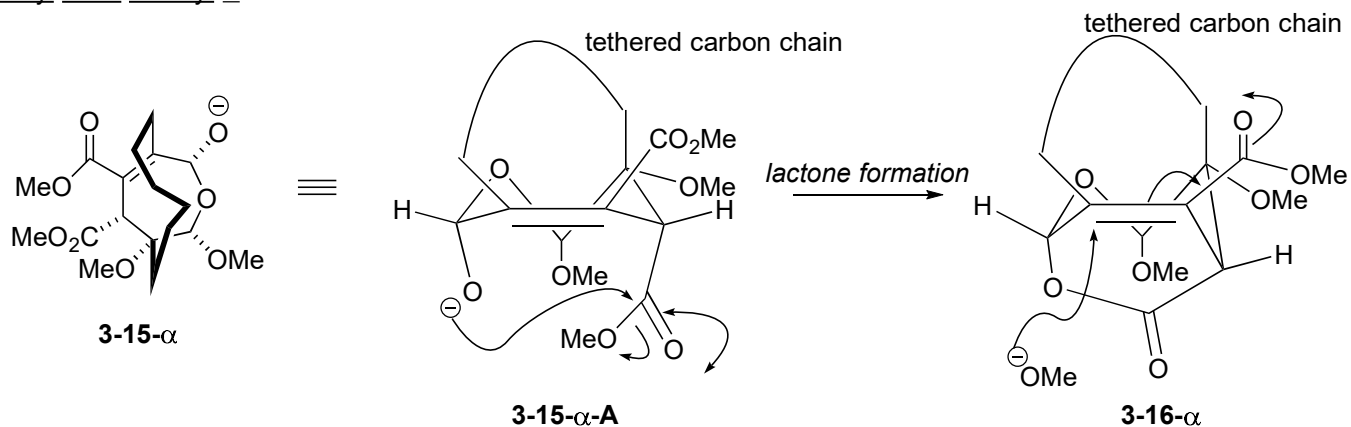
Glaser, R.; Neumann, M.; Ott, F.; Peters, E. M.; Peters, K.;
 Schnering, H. G. V.; Tochtermann, W. *Tetrahedron*, **2001**, 57, 3927.
 Tochtermann, W. and Rosner, P. *Chem. Ber.* **1981**, 114, 3725.

Key Point: Pericyclic reaction ($[4+2]$, $[2+2]$, 4π electrocyclization), 3σ - 3π isomerization, $[1,3]$ -hydride shift

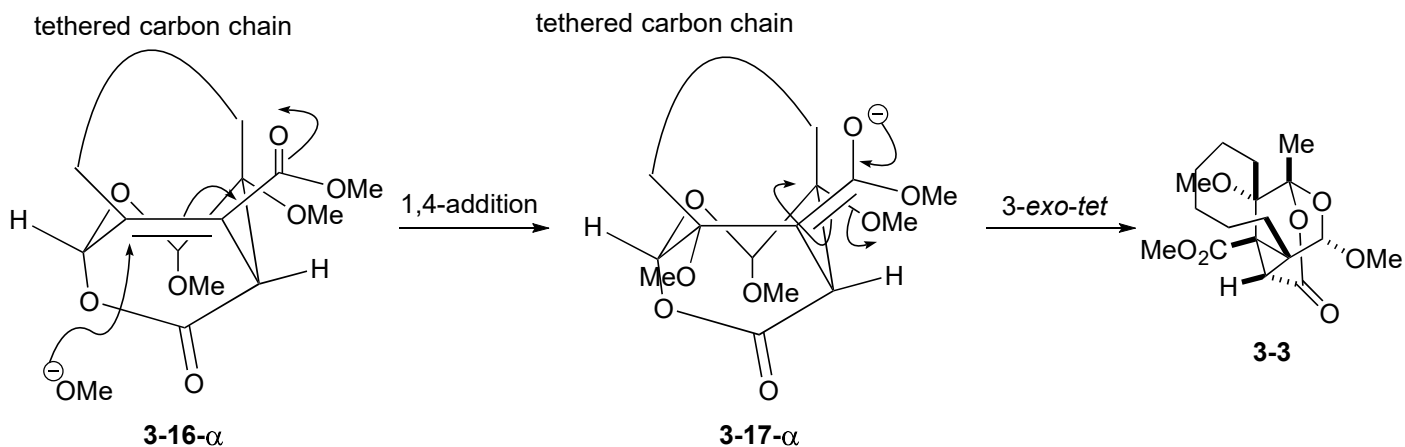
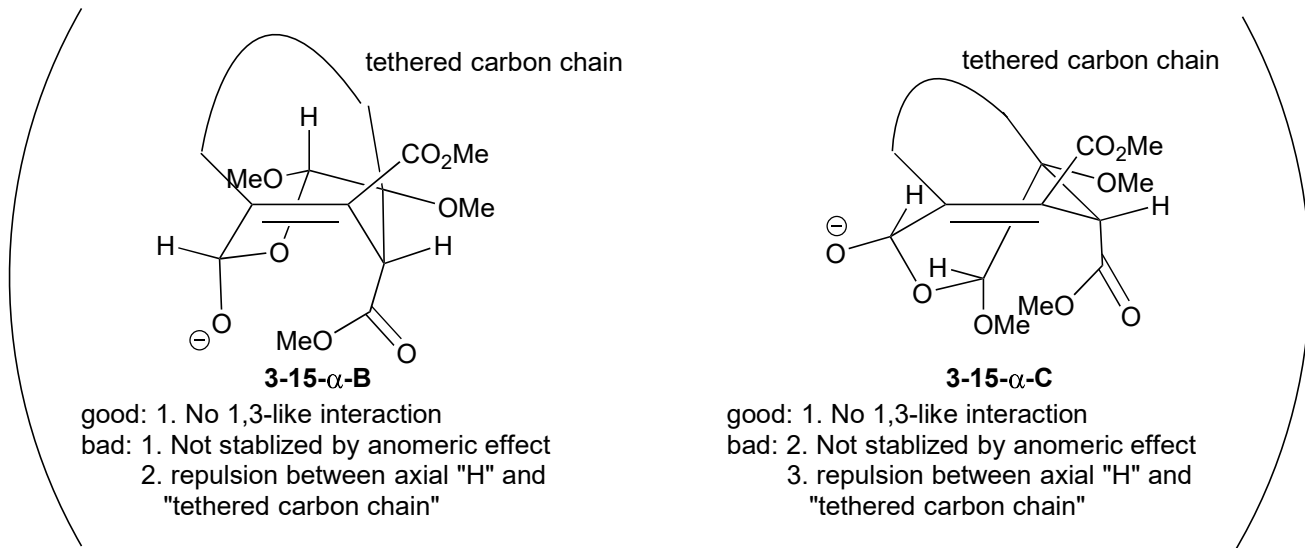




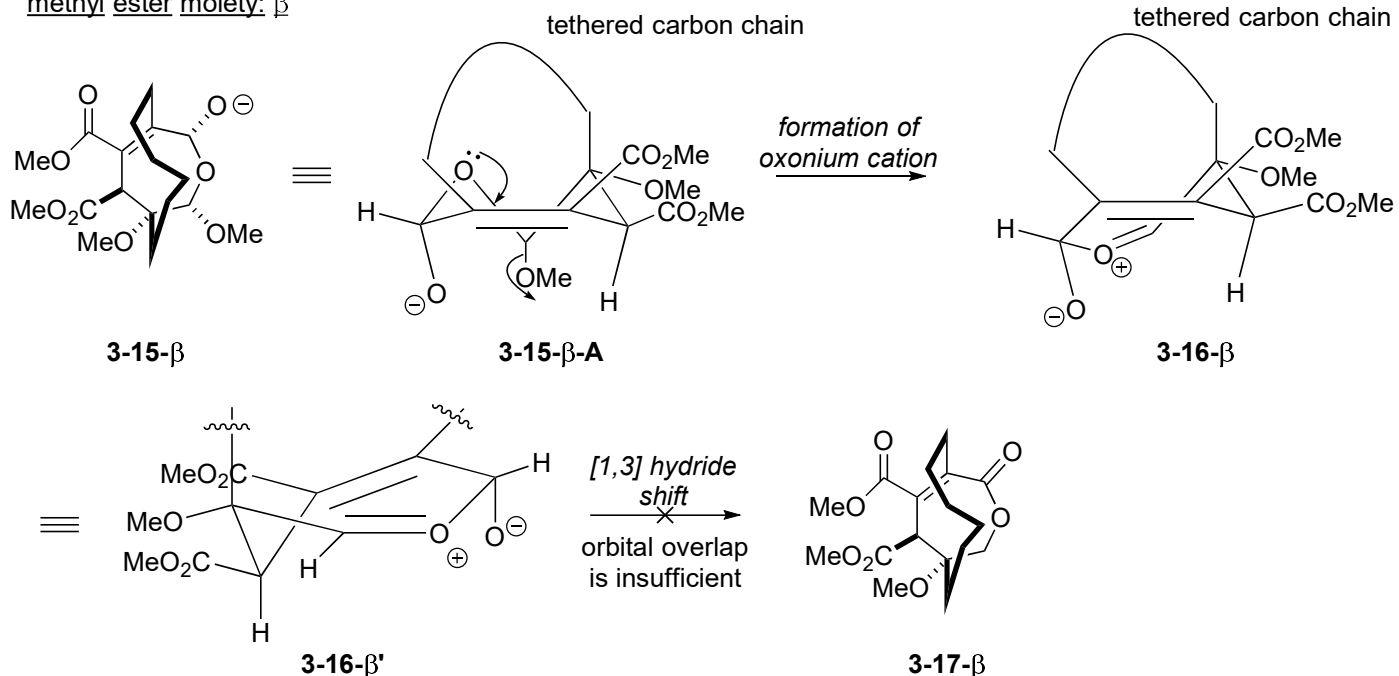
methyl ester moiety: α



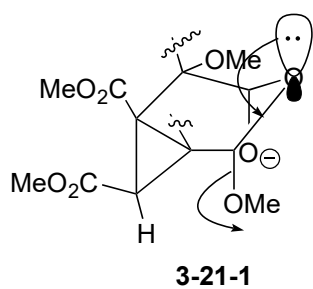
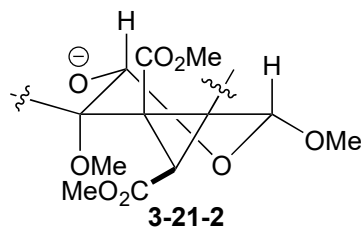
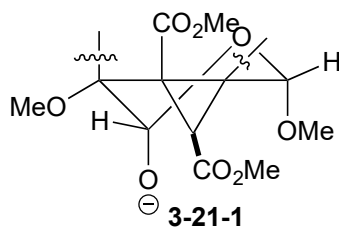
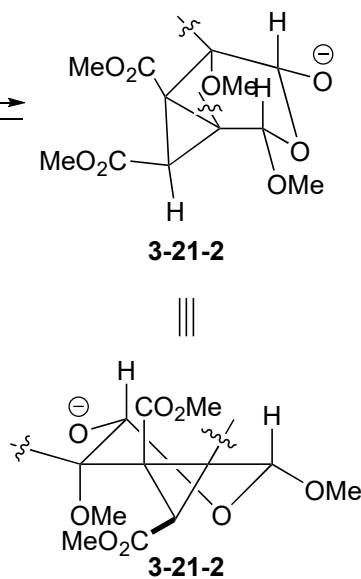
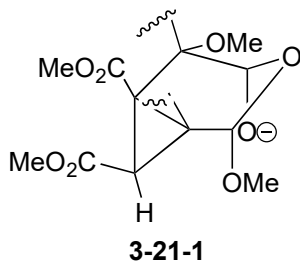
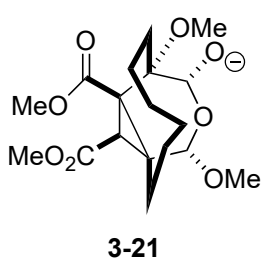
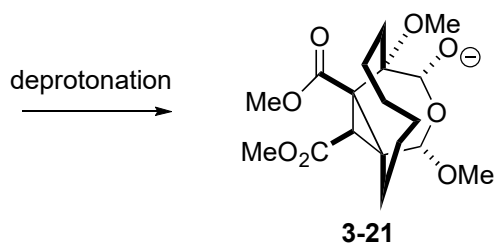
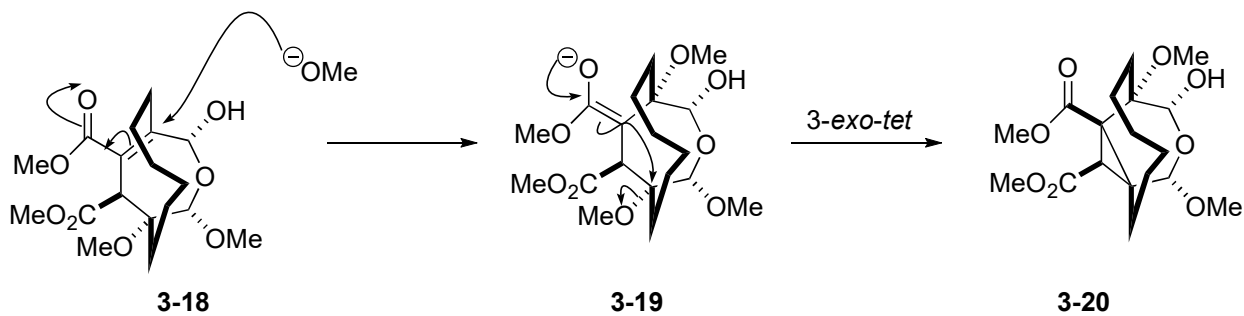
- good: 1. stabilized by anomeric effect
 2. No repulsion with tethered carbon chain
 bad: 3. 1,3 like interaction



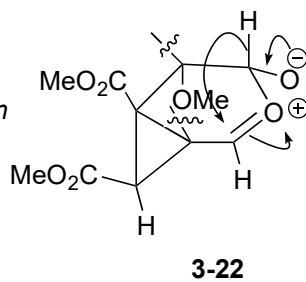
methyl ester moiety: β



conformation is fixed due to double bond (x2)

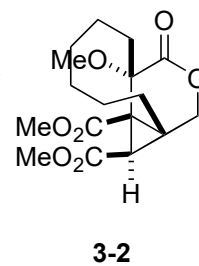


formation of
oxonium cation



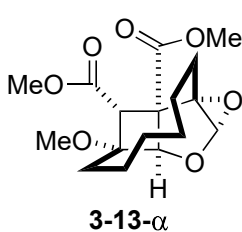
[1,3]-hydride shift

overlap of orbital
is sufficient

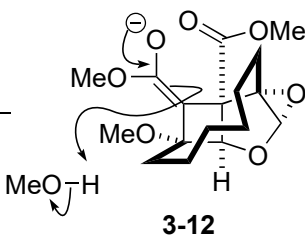


3-2. Discussion

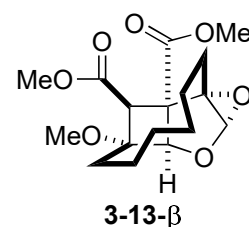
3-2-1. Facial selectivity of protonation



thermodynamically favored

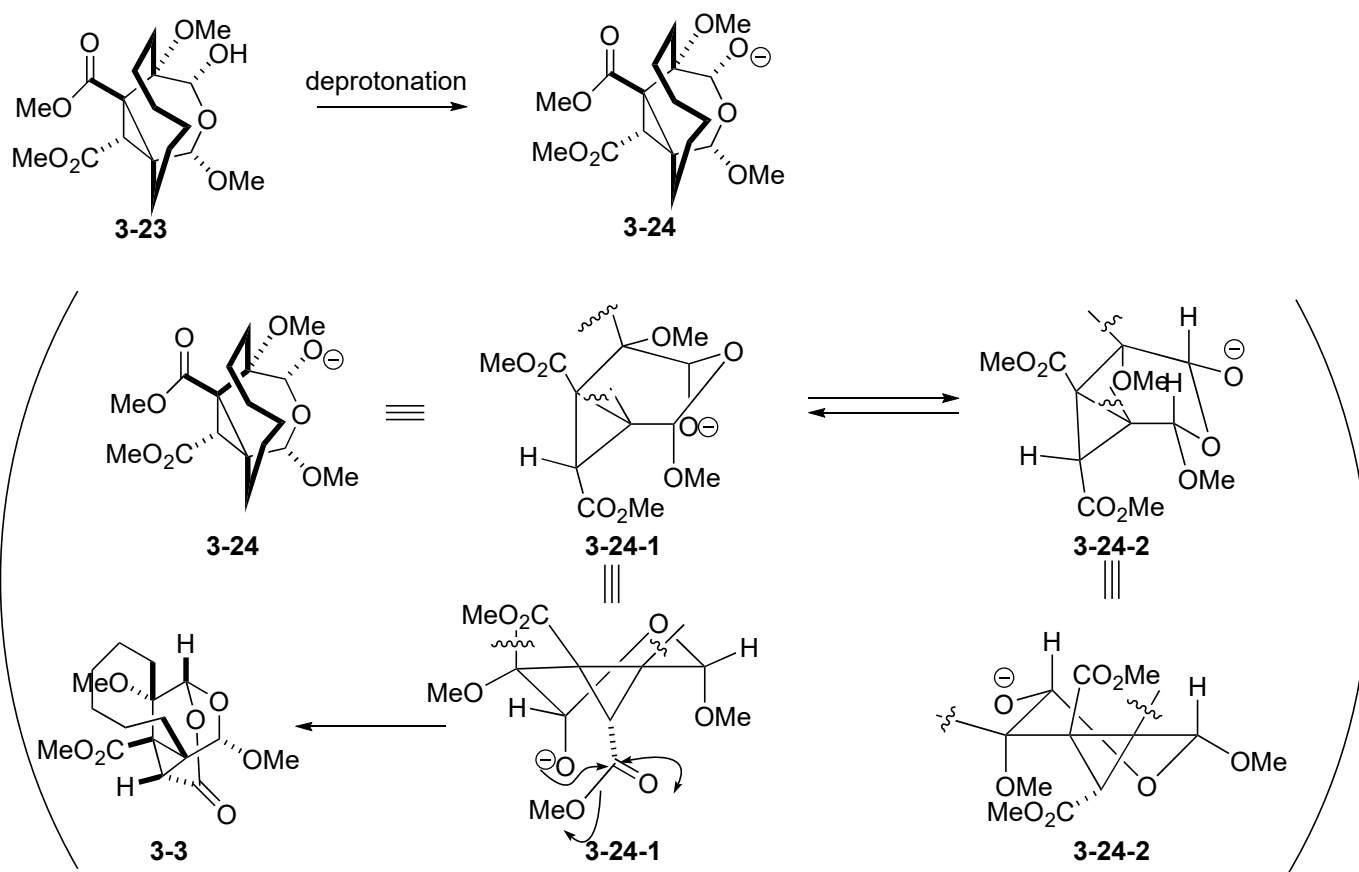


from convex

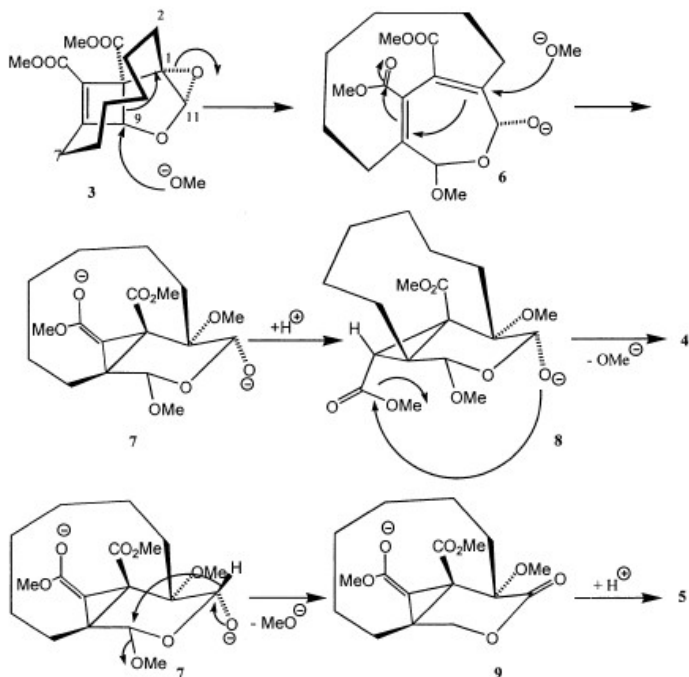


kinetically favored

3-2-2. Another mechanism of final step



3-3. Appendix (Proposed mechanism by author)

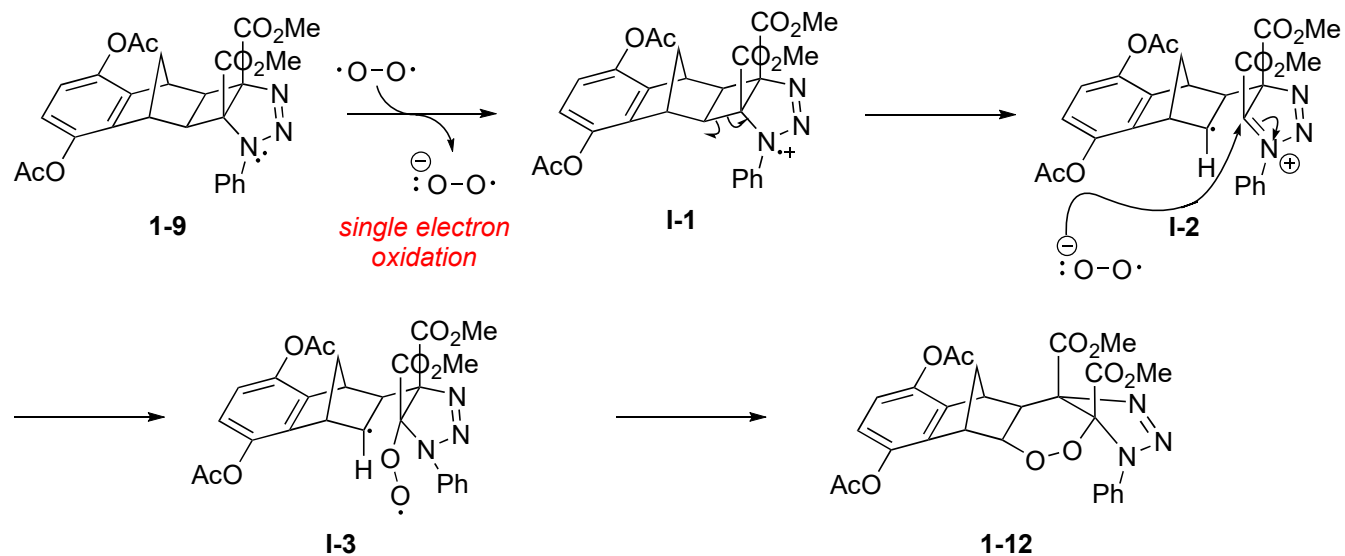


1. anti Baldwin's rule (3-endo-trig)

Appendix

1. **Problem 1**

1-1. Another reaction mechanism to form 1-12 (Proposed by Prof. Inoue)



If single electron oxidation occurs, regioselectivity of this reaction is explained.