

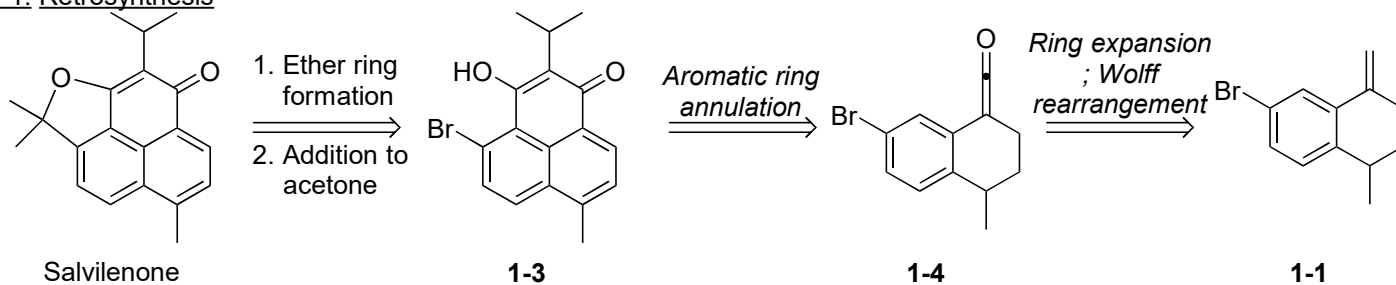
Problem Session (3) -Answer-

2018. 10. 6. Tsukasa Shimakawa

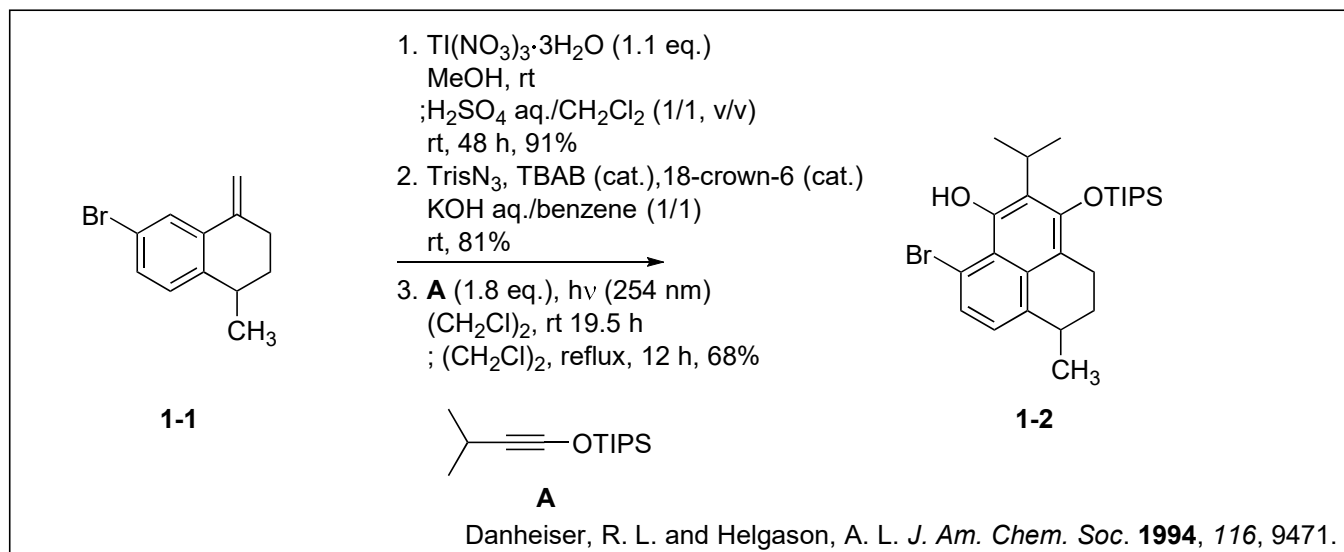
Topic: Reactions including singlet carbene intermediate

1. Total synthesis of Salvilenone by Danheiser's group

1-1. Retrosynthesis

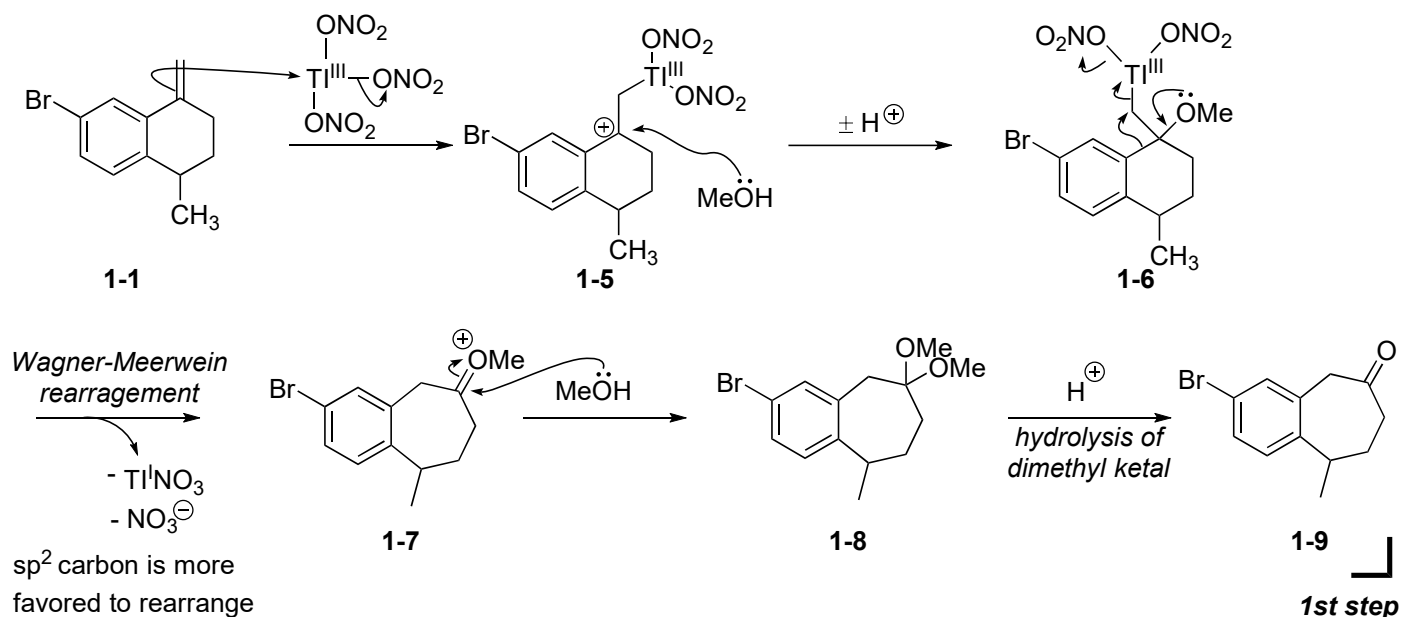


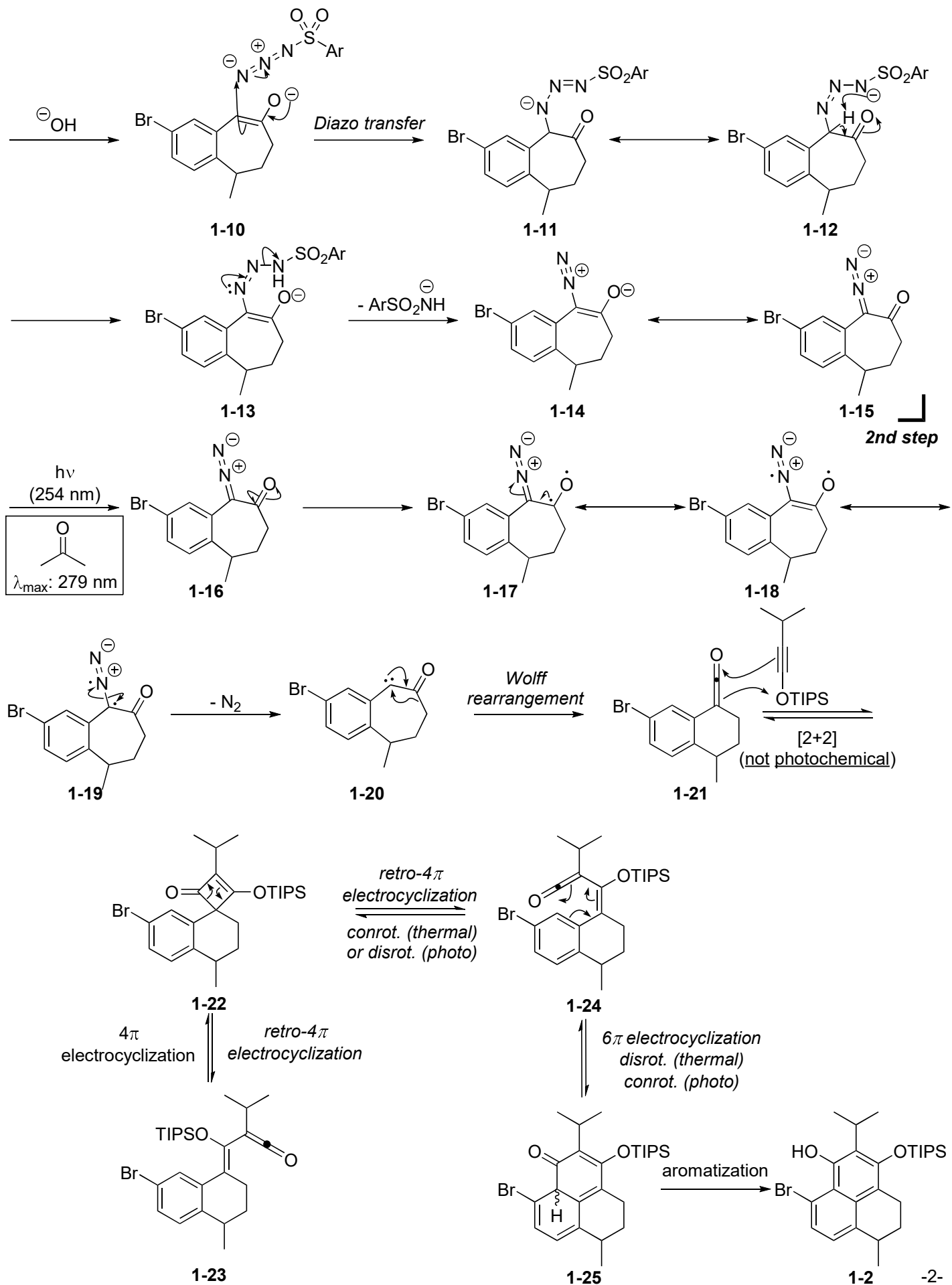
1-2. Reaction mechanism



Key Point: 1. Ring expansion using $\text{Ti}^{\text{III}}(\text{NO}_3)_3$

2. Wolff-rearrangement and successive Danheiser benzannulation

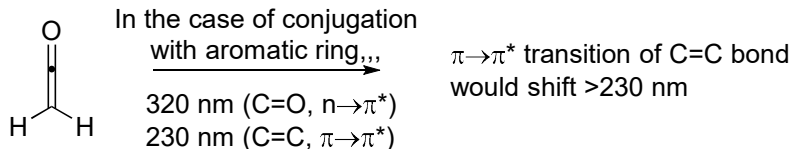




Discussion:

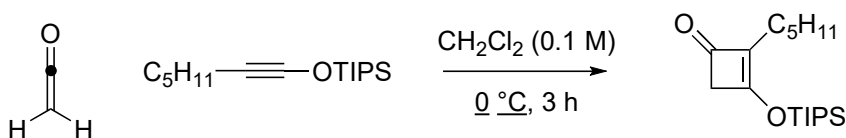
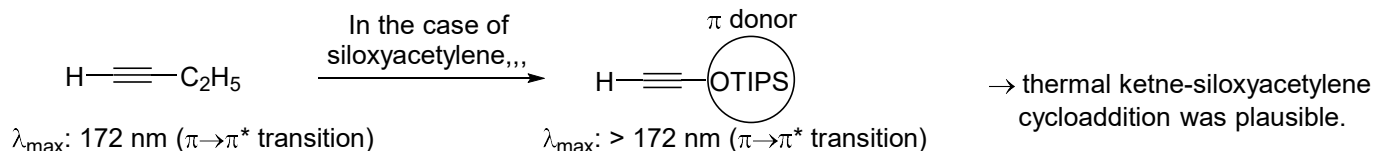
1. [2+2] cycloaddition

1-1. Absorption wavelength of ketene and siloxyacetylene



Dixon, R. N. and Kirby, G. H. *Trans. Faraday Soc.*, **1966**, 62, 1406.

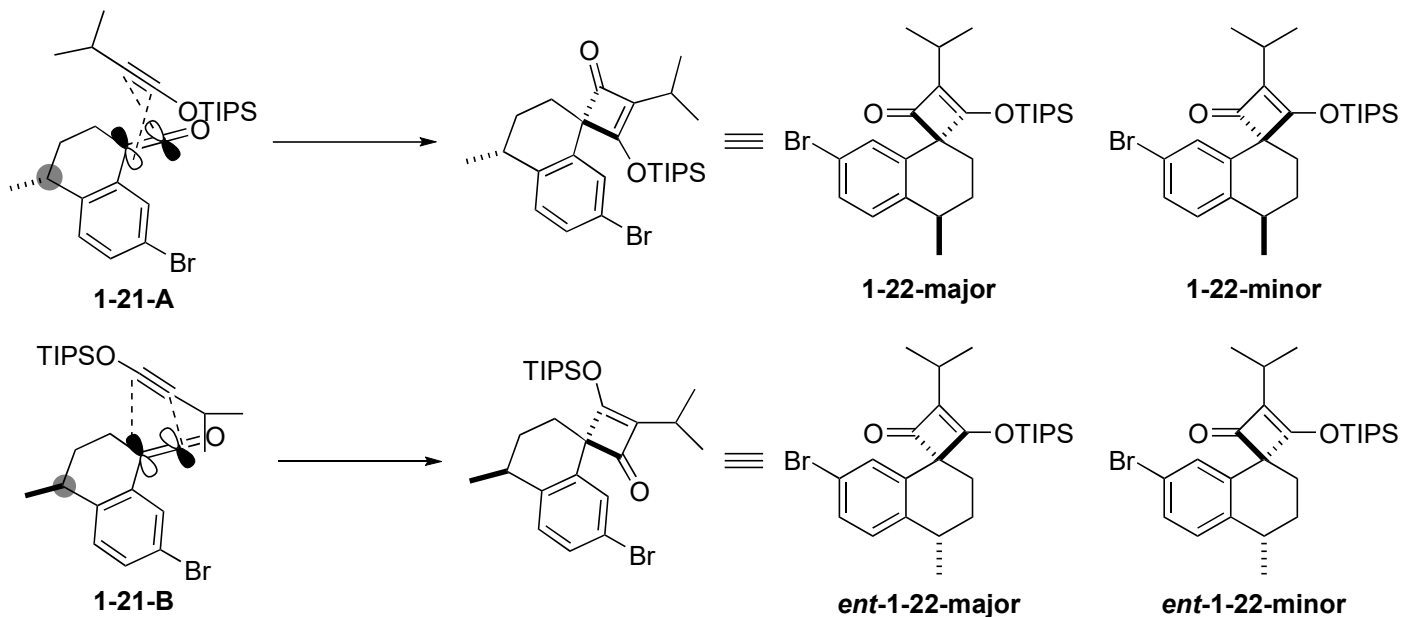
Berg, O. and Ewing, G. E. *J. Phys. Chem.* **1991**, 95, 2908.



Kowalski, C. J. and Lal, G. S. *J. Am. Chem. Soc.* **1988**, 110, 3693.

1-2. Plausible diastereoselectivity of [2+2] cycloaddition

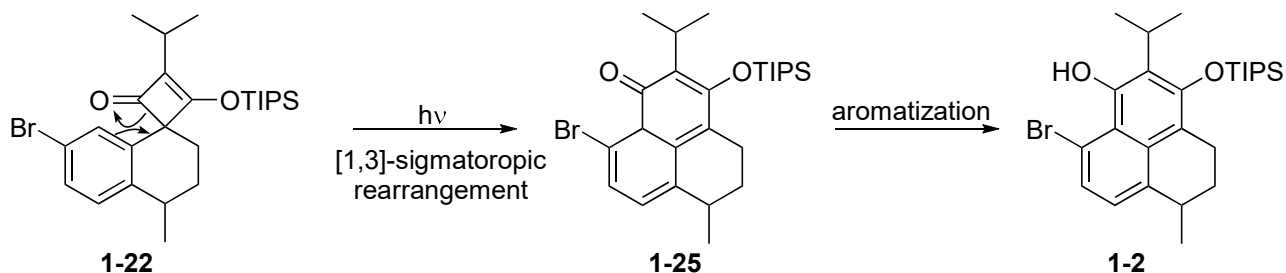
· α face was shielded by aromatic ring → ketenophile approaches from β face.



Author said cyclobutenone intermediate present as a mixture of two diastereomers from TLC analysis

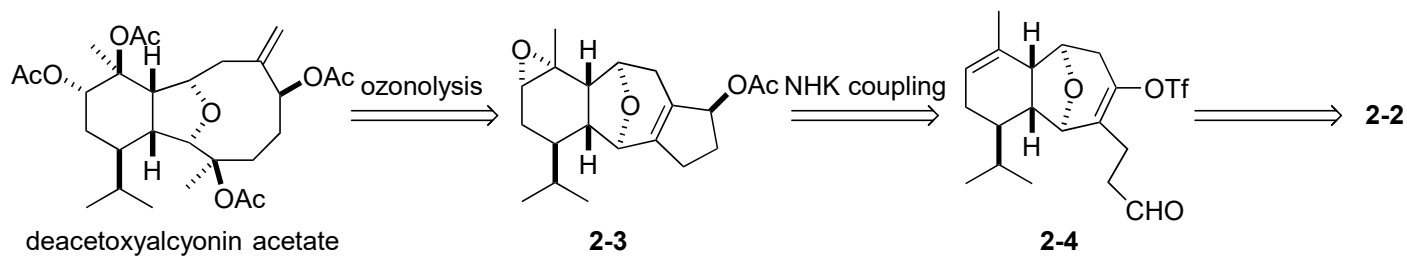
2. Another plausible reaction mechanism from cyclobutenone to tricyclic phenol

2-1. Photochemical [1,3]-sigmatropic rearrangement

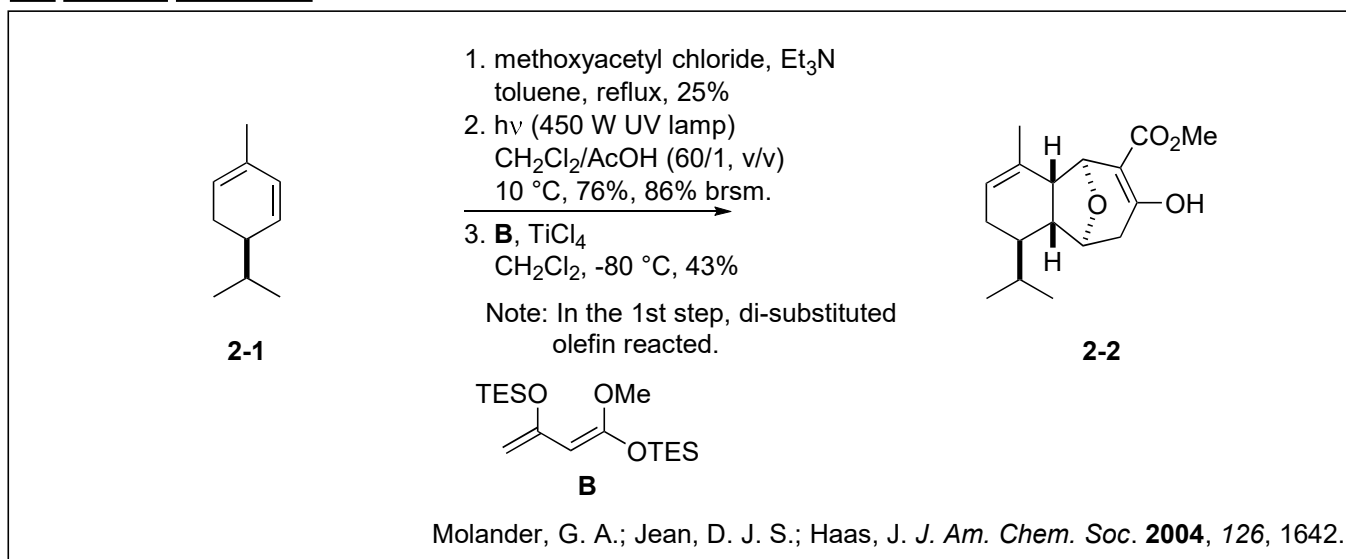


2. Asymmetric total synthesis of Deacetoxyalcyonin acetate by Molander's group

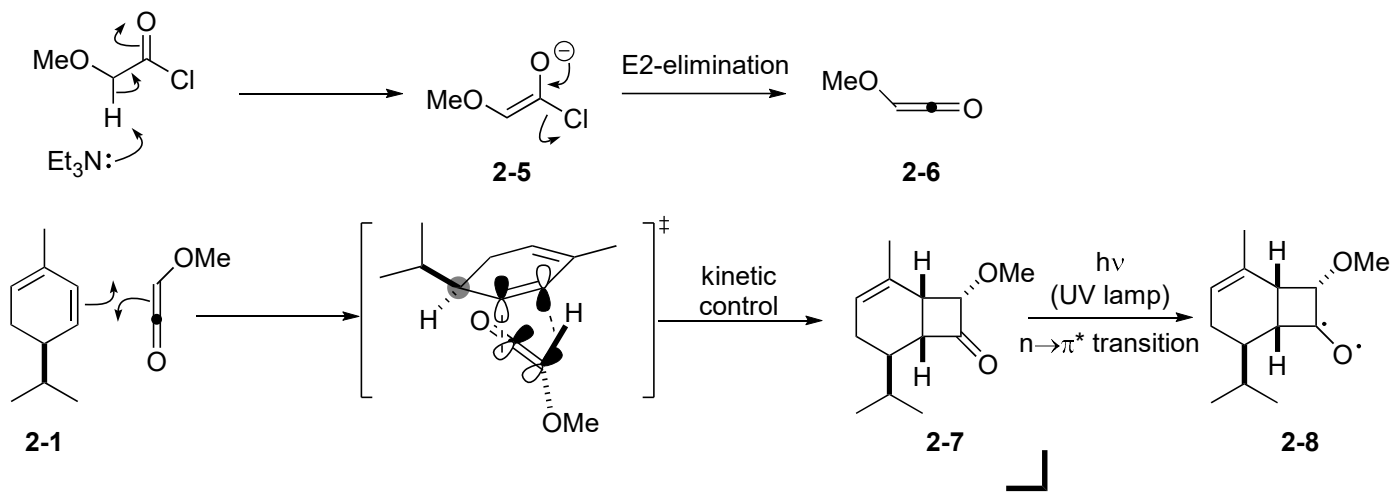
2-1. Retrosynthesis



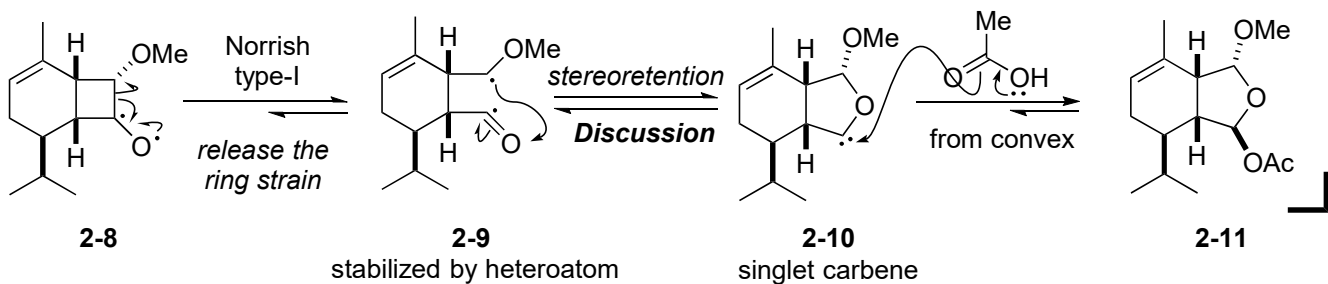
2-2. Reaction mechanism

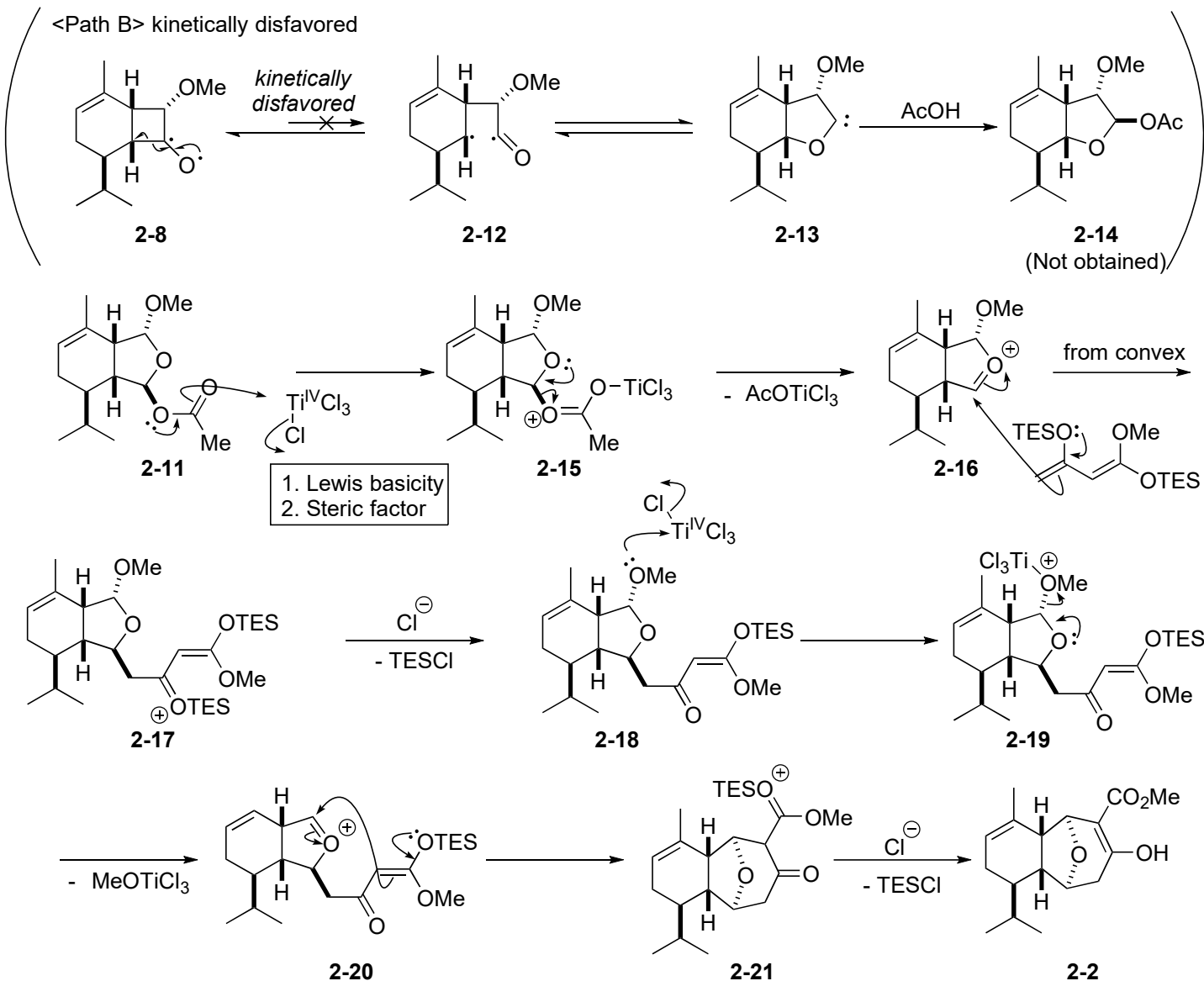


Key Point: Ring expansion following formation of oxacarbene



<Path A> kinetically favored

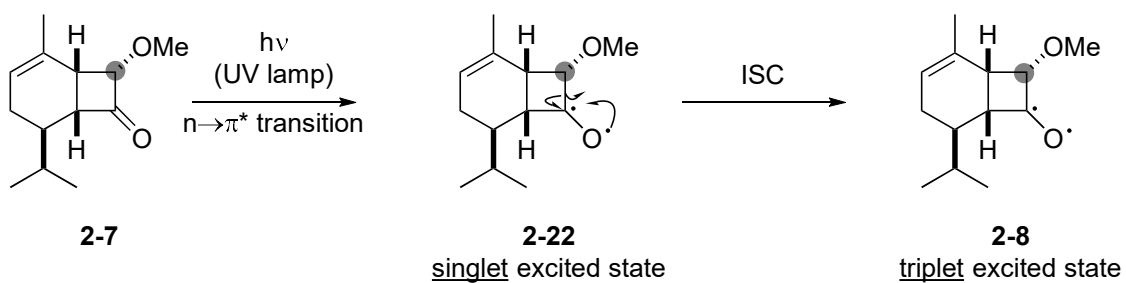




Discussion:

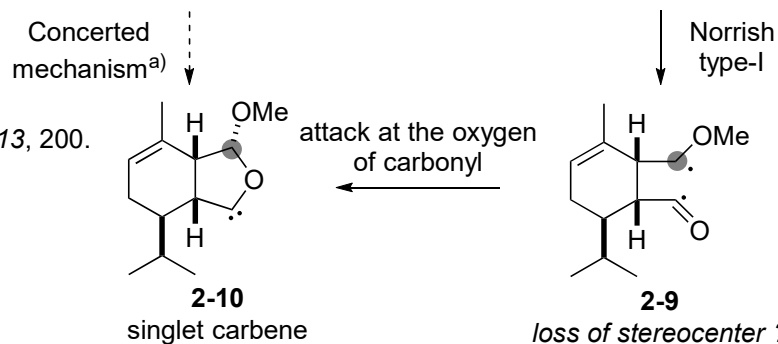
1. Photochemical generation of oxacarbene intermediate

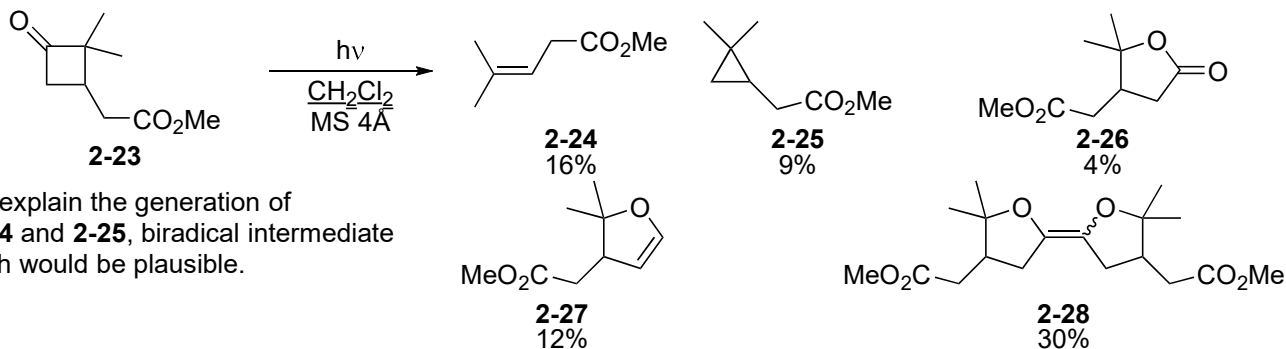
1-1. Concerted mechanism or biradical coupling mechanism



a) Quinkert, G. et al.

Angew. Chem. Int. Ed. **1974**, 13, 200.

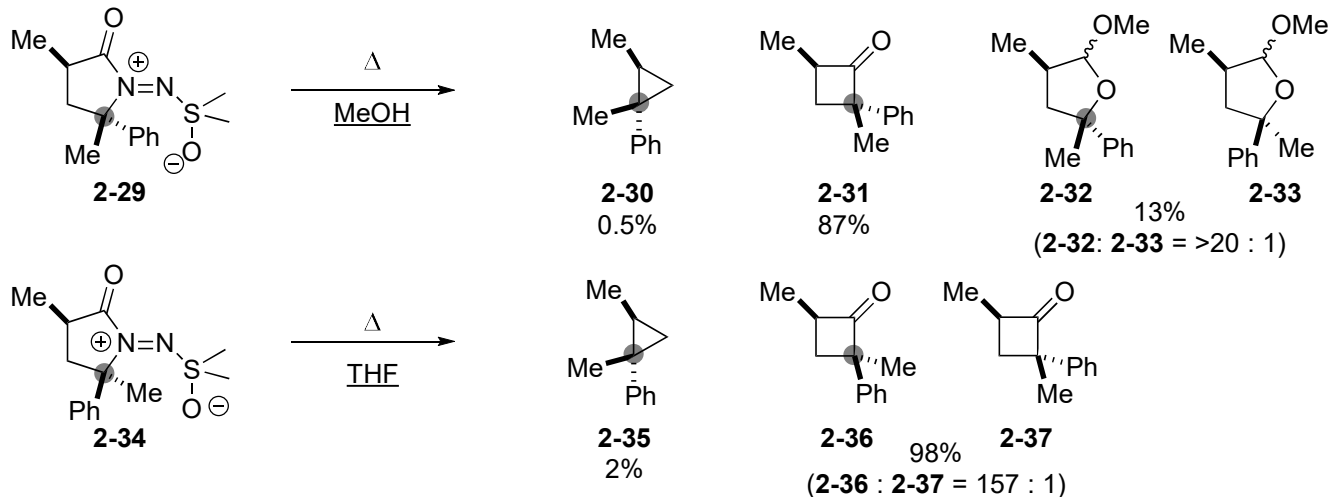




To explain the generation of **2-24** and **2-25**, biradical intermediate path would be plausible.

Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824.

1-2. Evidence for singlet carbene intermediate



Miller, R. D.; Golitz, P.; Janssen, J.; Lemmens, J. *J. Am. Chem. Soc.* **1984**, *106*, 7277.

1. cyclobutanone formation

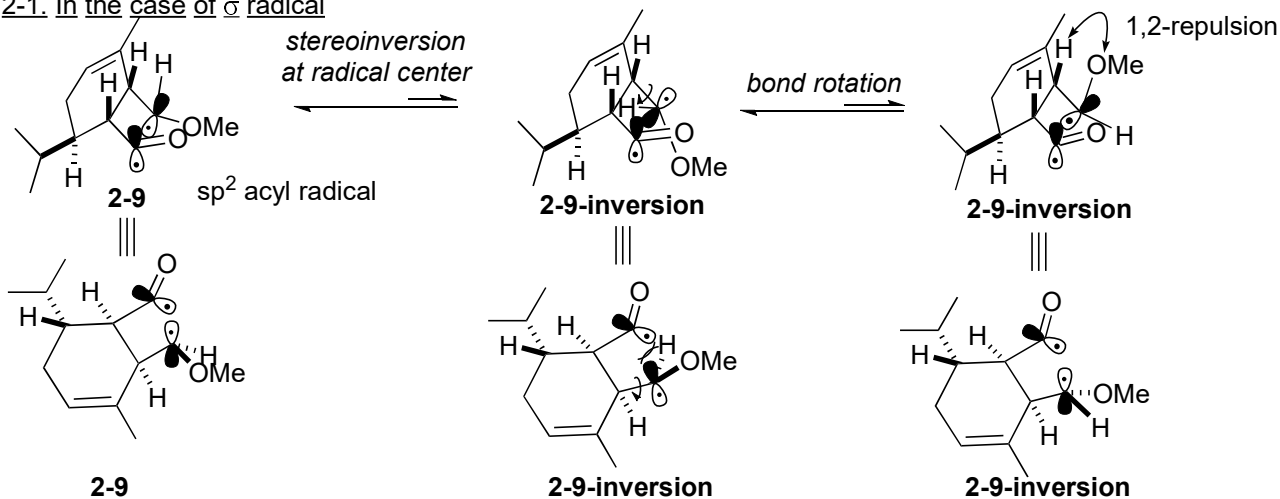
♣ No need of orbital re-hybridization (from low energy sp^2 acyl radical to sp acyl radical)

2. Oxacarbene formation

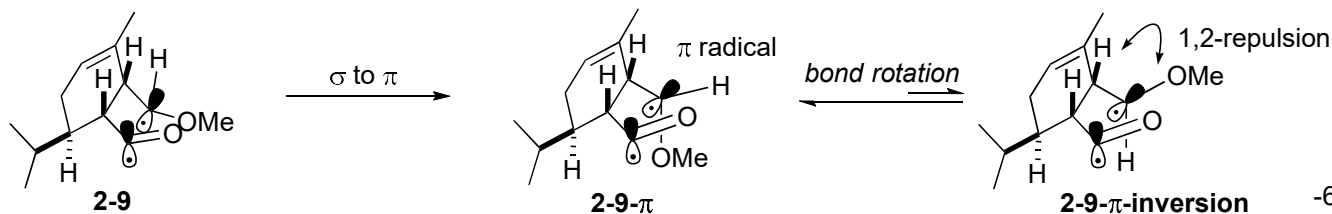
♣ orbital re-hybridization was necessary. \rightarrow low stereoretention ratio than cyclobutanone formation ??

2. Explanation of stereoretention mechanism in radical recombination

2-1. In the case of σ radical

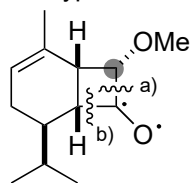


2-2. In the case of π radical



3. Explanation of regioselectivity

Norrish type I → electrophilic oxyl radical (SOMO) and C-C (HOMO) interaction



2-8

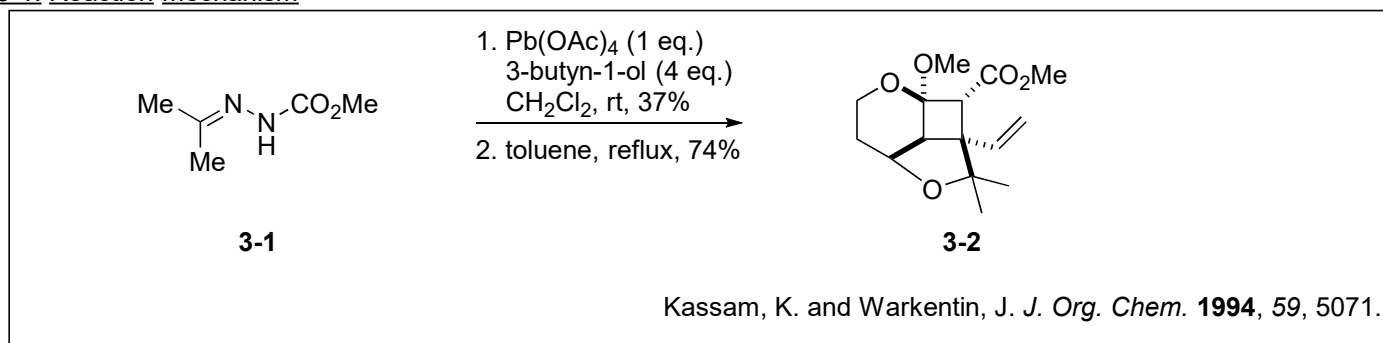
triplet excited state

type a) → Orbital interaction between C-C σ and lone pair of O atom
= Increase the energy level of HOMO of C-C

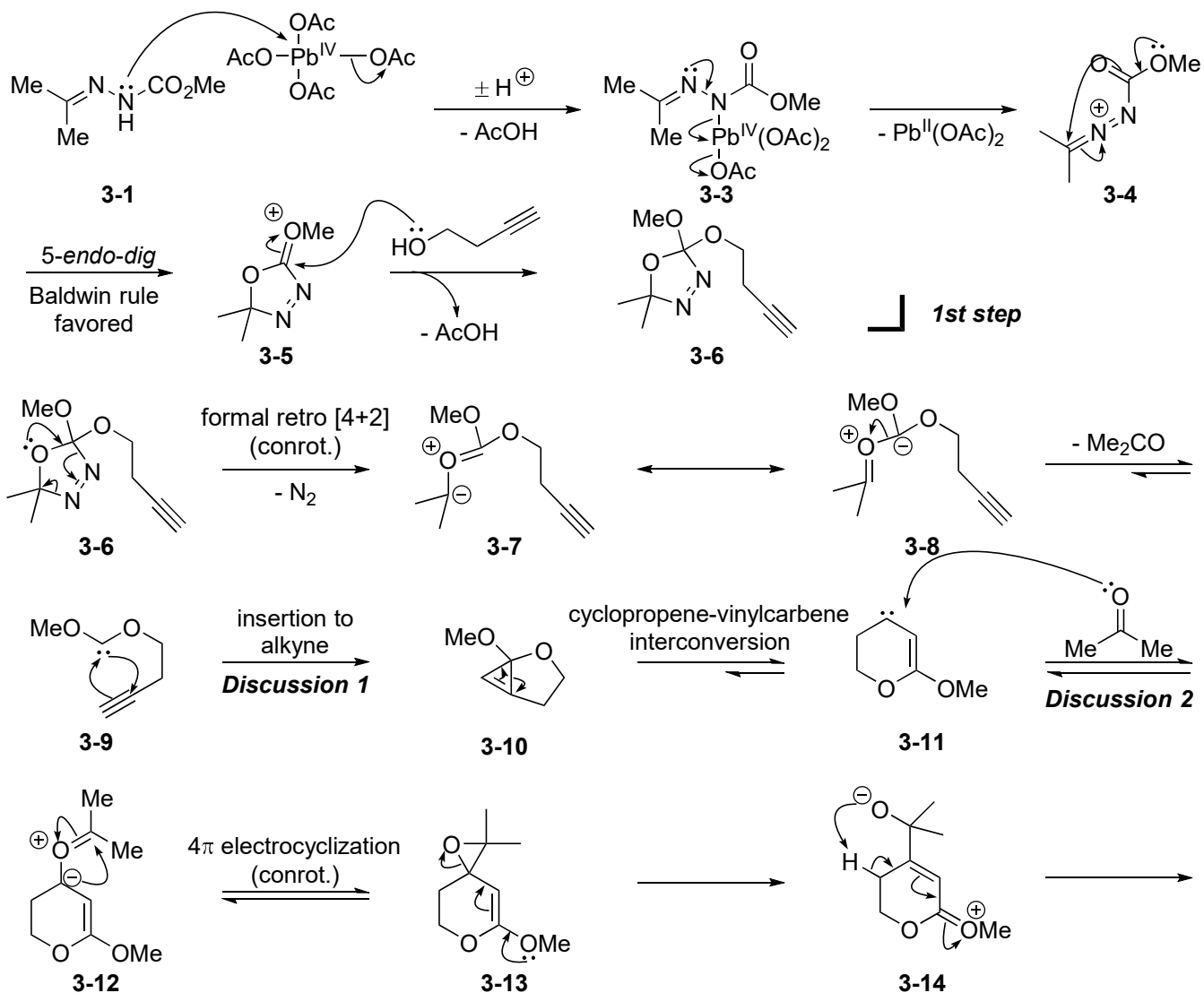
type b) → No orbital interaction with lone pair of heteroatom

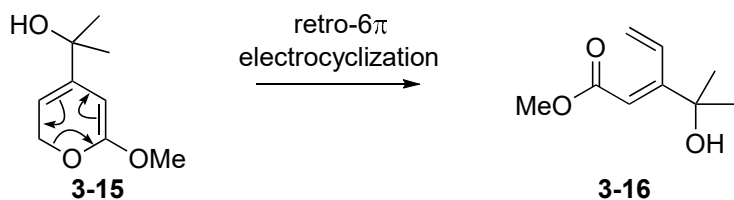
3. Preparation of oxadiazoline and thermal cascade reaction

3-1. Reaction mechanism

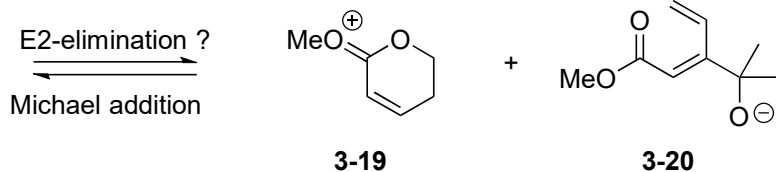
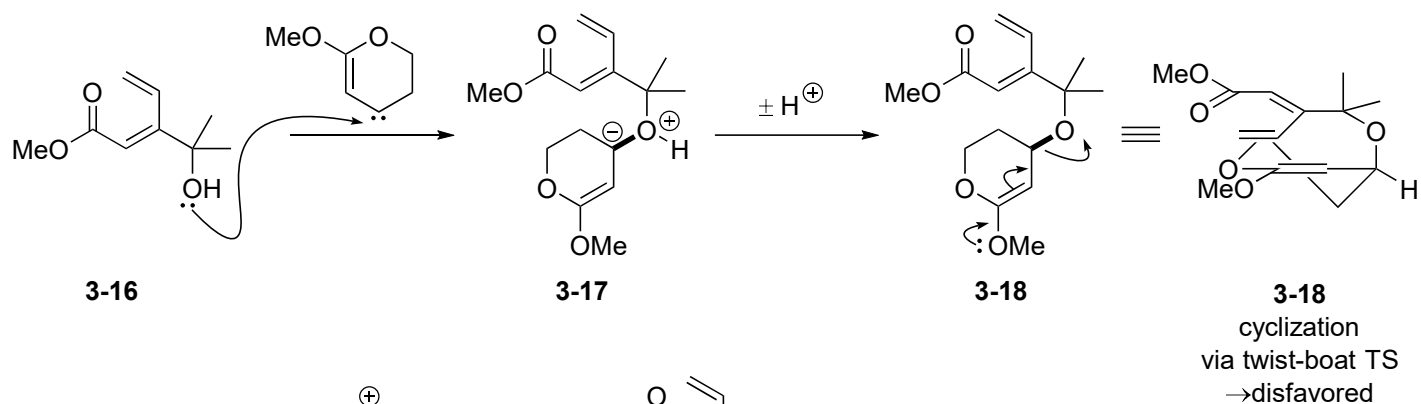


Key Point: 1. Oxadiazoline formation 2. Thermal cascade (pericyclic rxn.) 3. Character of singlet carbene

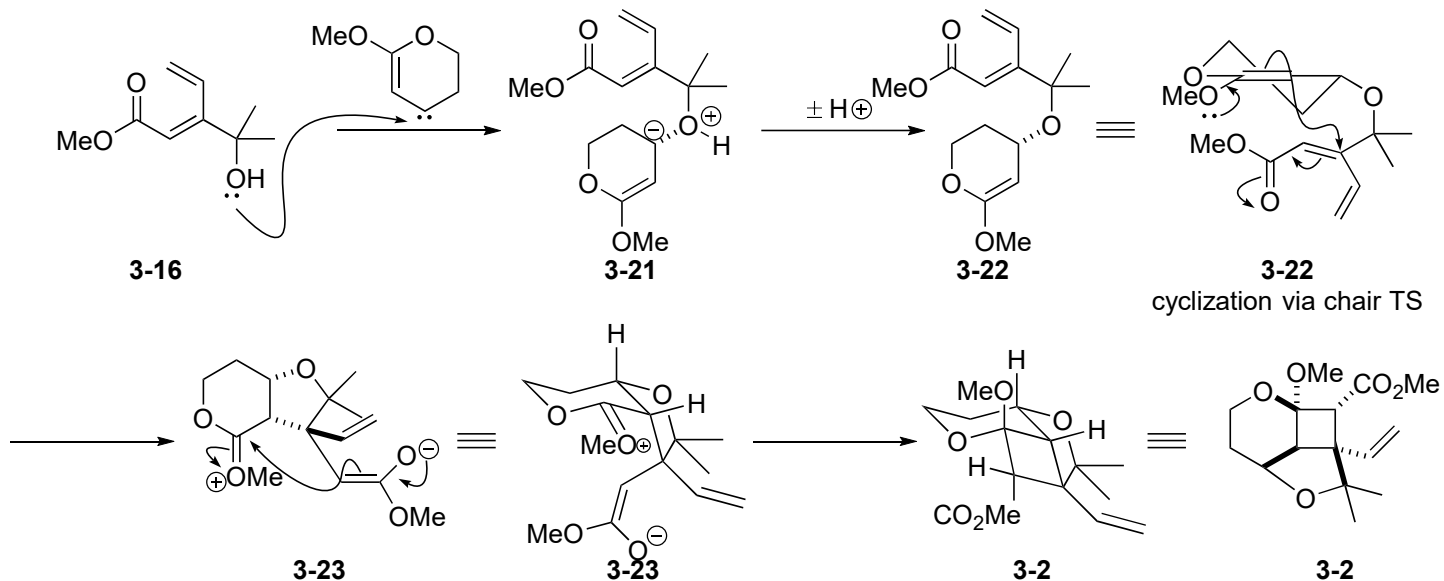




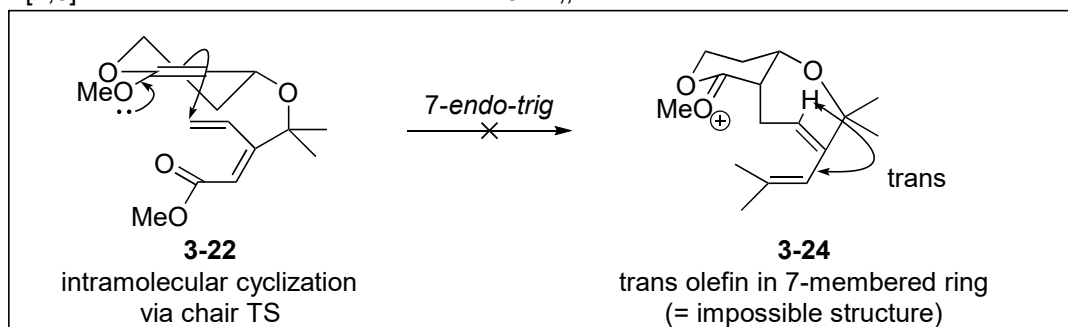
<Path A>



<Path B>



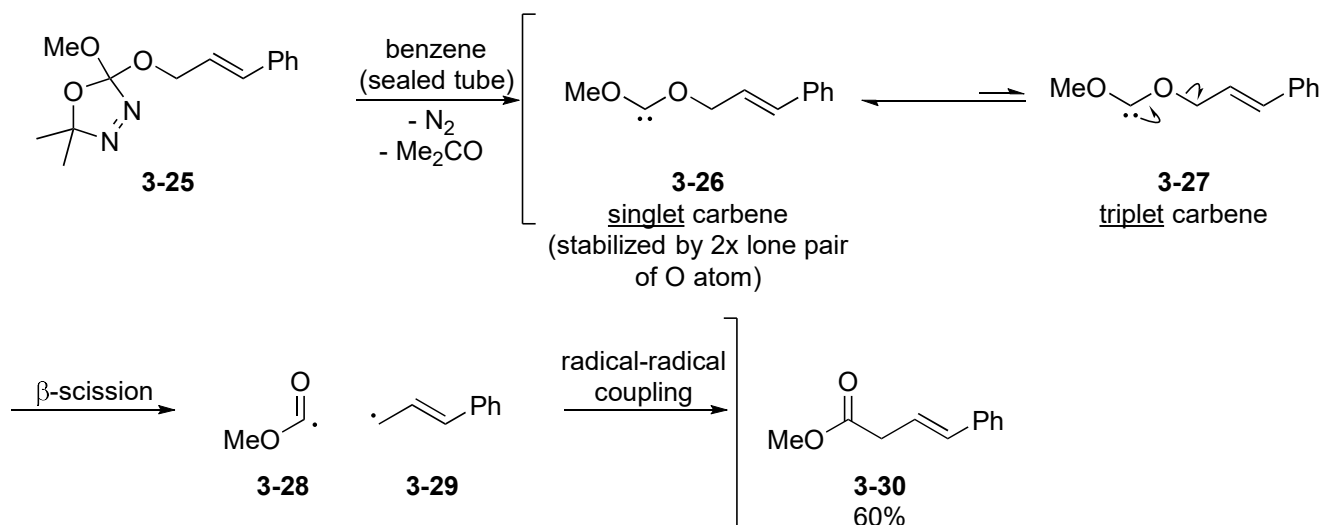
If [1,6]-addition occurred from intermediate **3-22**,



Discussion:

1. Dialkoxycarbene intermediate **3-9**

a). Insertion to alkyne b). Homolysis of carbene (See, **Problem 2**)



Venneri, P. C. and Warkentin, J. *J. Am. Chem. Soc.* **1998**, *120*, 11182.

In the case of dimethoxycarbene, Energy difference between the planar singlet carbene and nonplanar triplet carbene was calculated about 76 kcal/mol^a.

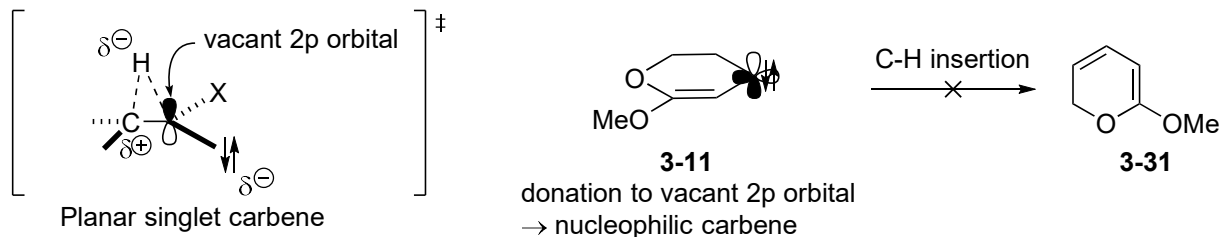
→ Intramolecular insertion to alkyne occurred.

Moss, R. A. et al. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

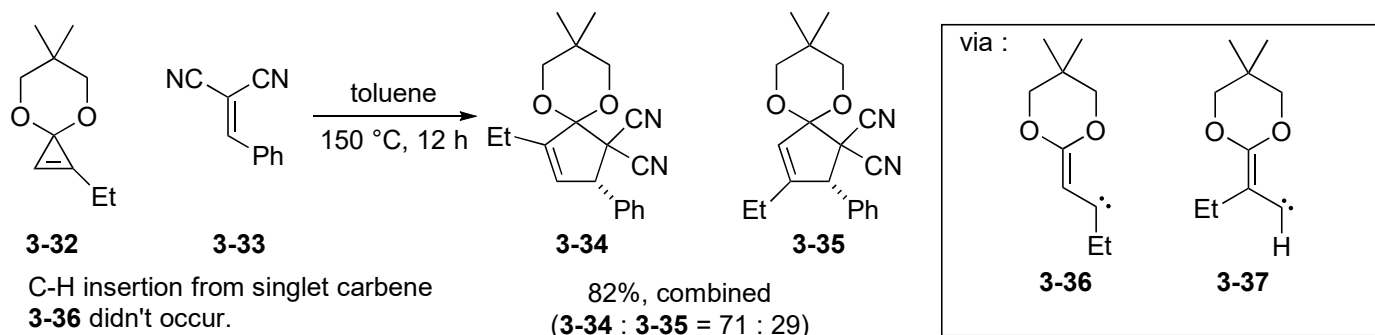
2. Intermediate of singlet carbene **3-11**

a). Intramolecular C-H insertion, b). Intermolecular trapping by acetone, c) Intermolecular trapping by alcohol

<Mechanism of C-H insertion> Moss, R. A.; Liu, W.; Ge, C-S. *J. Phys. Org. Chem.* **1993**, *6*, 376.



eg. Thermal reaction of cyclopropanone acetal



Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523.