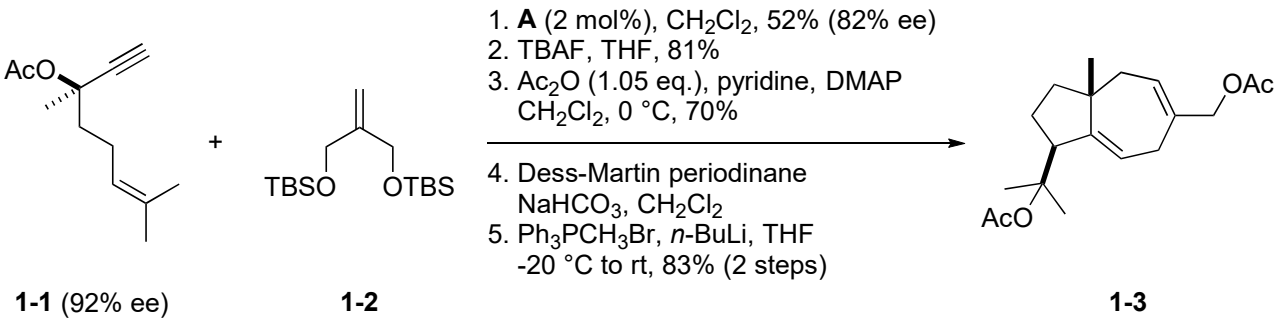
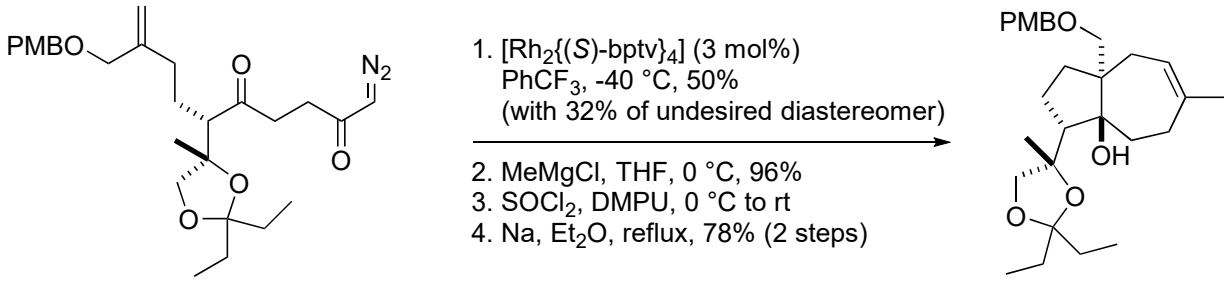
Problem Session (3)

2018/11/17 Takehiro Kato

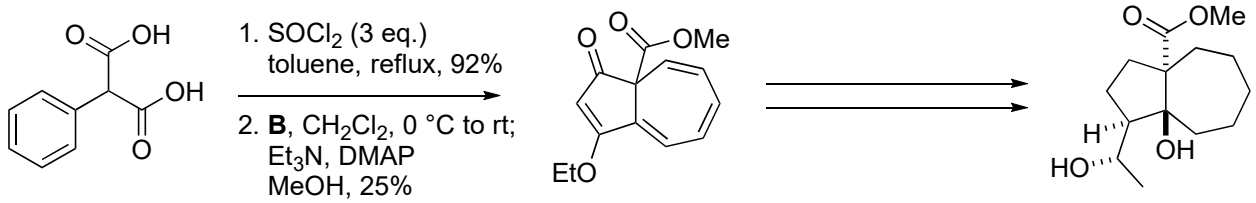
Please provide the reaction mechanisms.



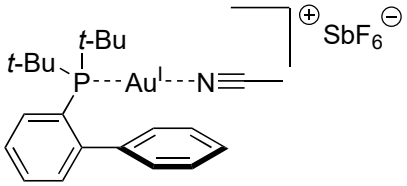
1-1 (92% ee) **1-2** **1-3**



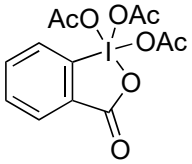
2-1 **2-2**



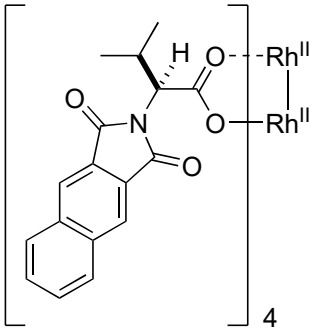
3-1 **3-2** **3-3**



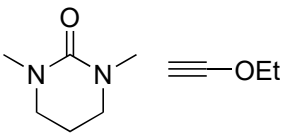
A



Dess-Martin periodinane



$[Rh_2\{(S)\text{-bptv}\}_4]$

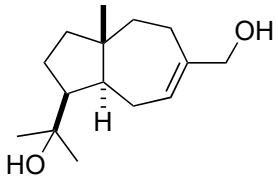


DMPU **B**

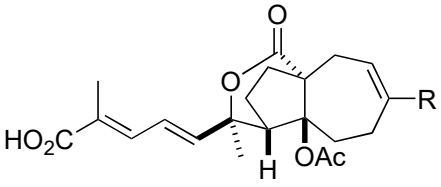
Problem Session (3) -Answer-

2018/11/17 Takehiro Kato

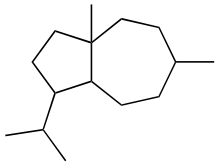
Topic: Synthetic approaches to the *trans*-fused carotane skeleton



(+)-schisanwilsonene A (**0-1**)

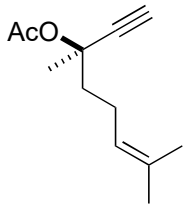


pseudolaric acid A (R = Me, **0-2**)
pseudolaric acid B (R = CO_2Me, **0-3**)

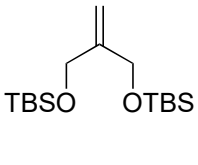


carotane (daucane) skeleton

Problem 1. Total synthesis of (+)-schisanwilsonene A by Echavarren's group

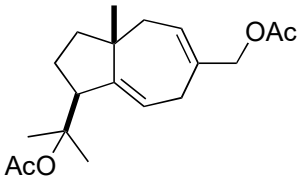


1-1 (92% ee)

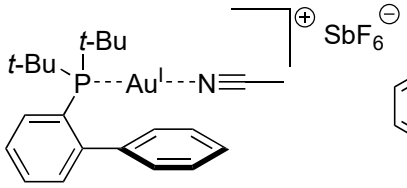


1-2

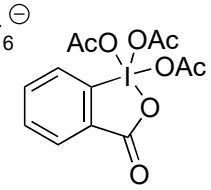
1. **A** (2 mol%), CH_2Cl_2, 52% (82% ee)
2. TBAF, THF, 81%
3. Ac_2O (1.05 eq.), pyridine, DMAP CH_2Cl_2, 0 °C, 70%
4. Dess-Martin periodinane $NaHCO_3$, CH_2Cl_2
5. Ph_3PCH_3Br, *n*-BuLi, THF -20 °C to rt, 83% (2 steps)



1-3



A

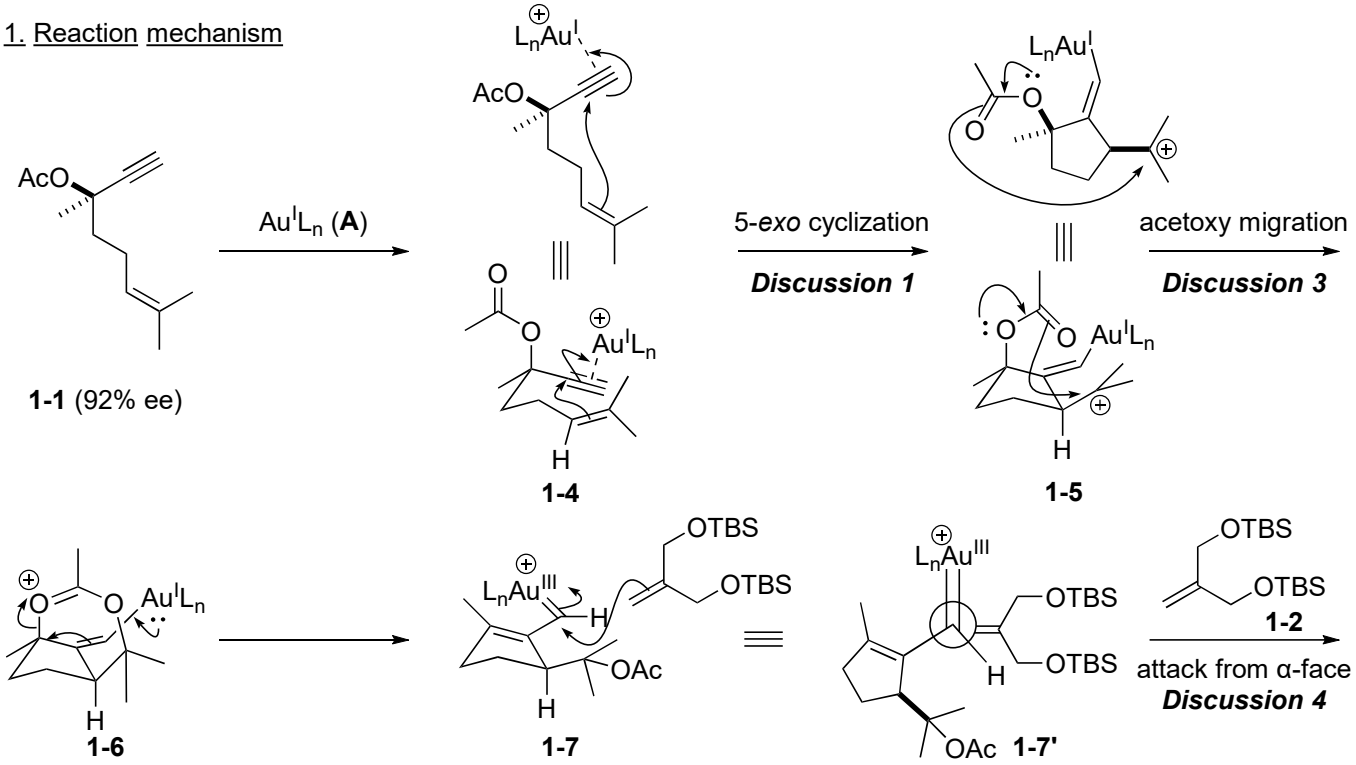


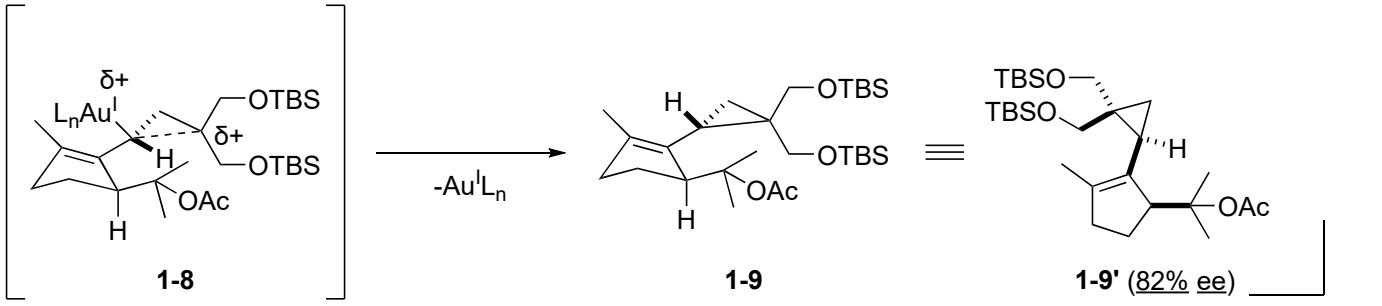
Dess-Martin periodinane

Gaydou, M.; Miller, R. E.; Delpomt, N.; Ceccon, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.,* **2013**, *125*, 6524.

Keypoint: Au^I-catalyzed 5-exo cyclization/acetoxy migration/cyclopropanation cascade

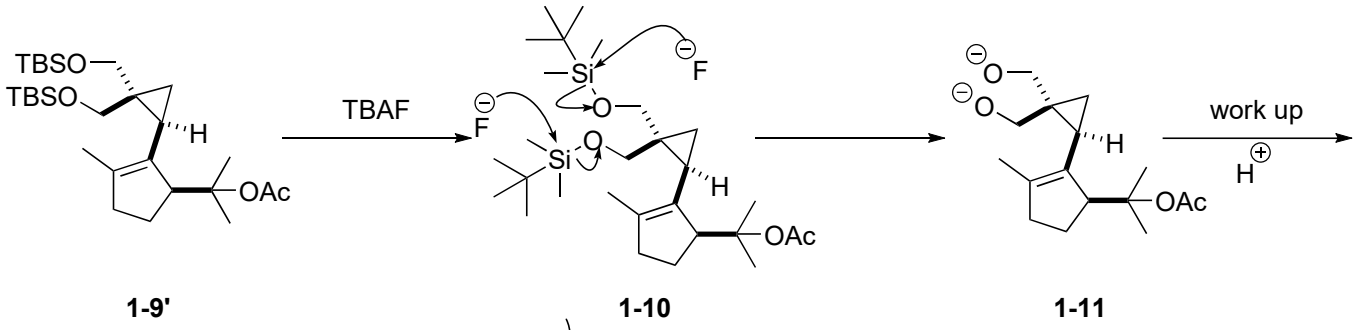
1. Reaction mechanism

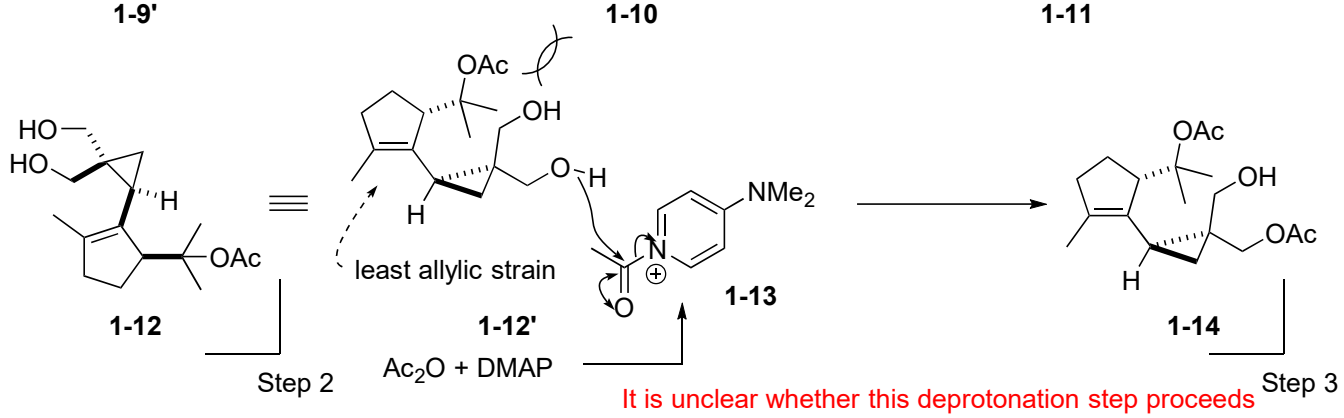




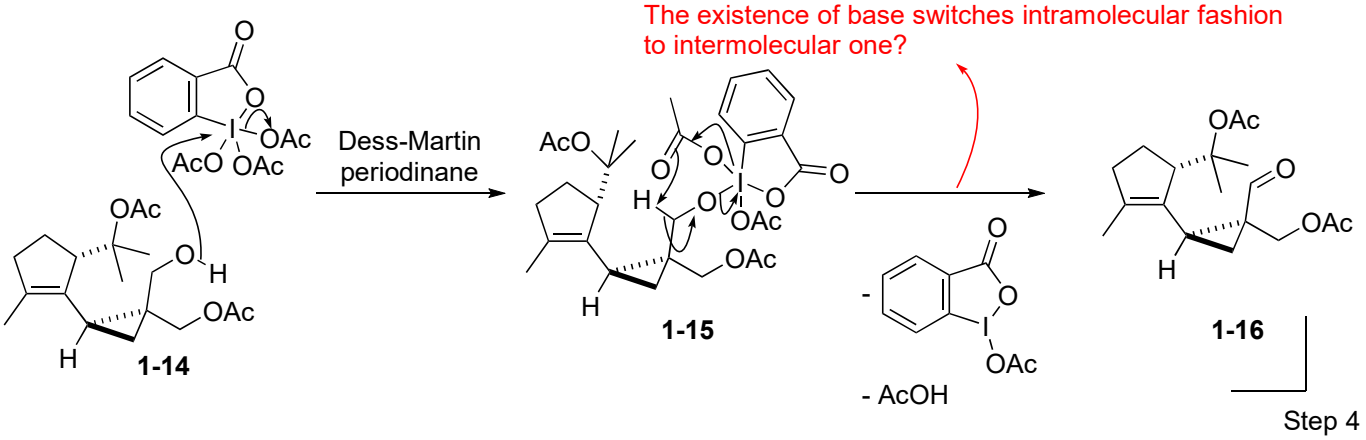
concerted transition state

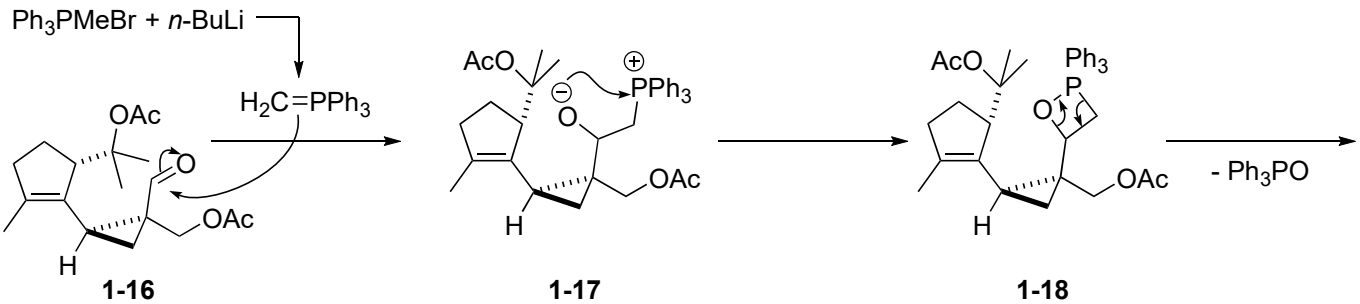
Note: Partial racemization occured in step 1. -> ***Discussion 2***

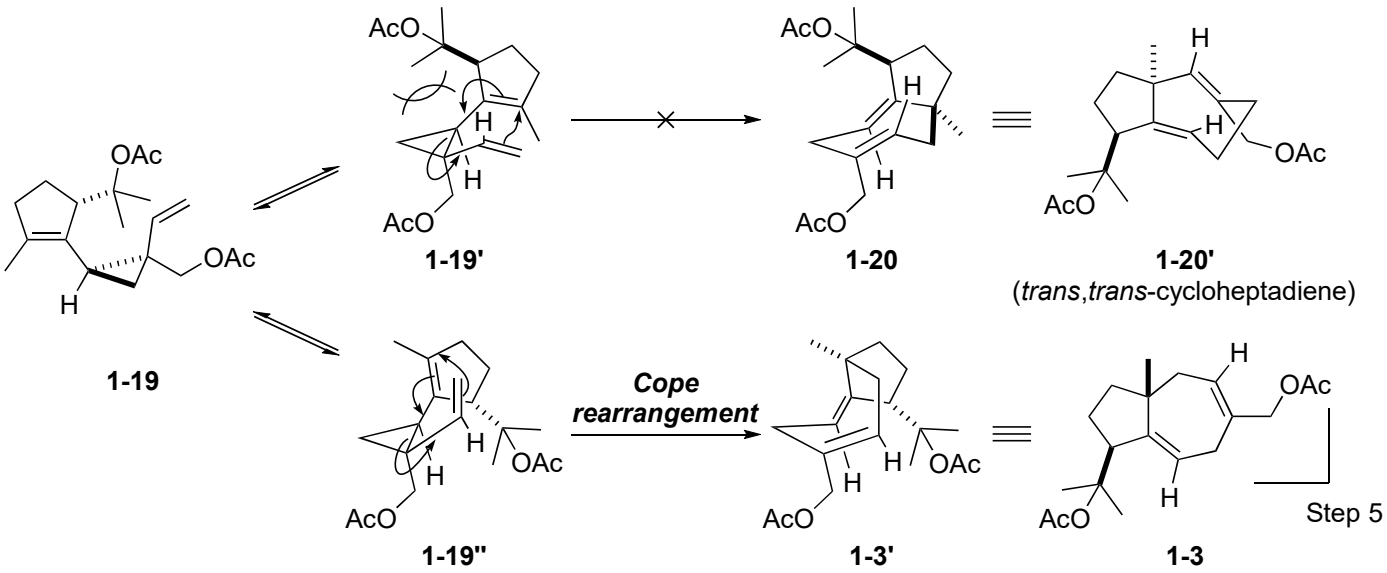




It is unclear whether this deprotonation step proceeds intermolecularly by AcO^- or intramolecularly.
The existence of base switches intramolecular fashion to intermolecular one?

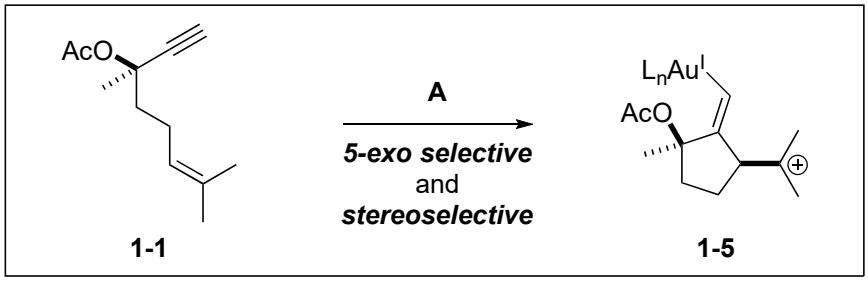


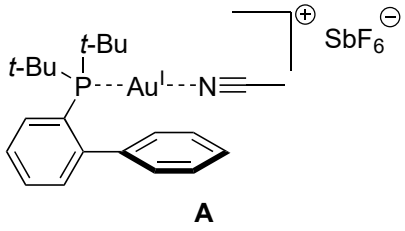




2. Discussion

Discussion 1: Au^{I}-catalyzed cyclization

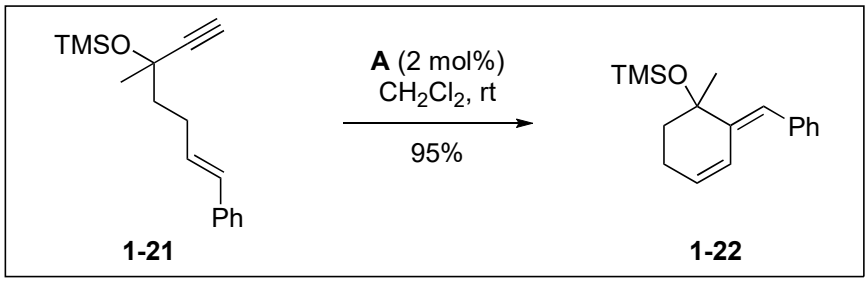




1-A. 5-*exo* vs. 6-*endo*

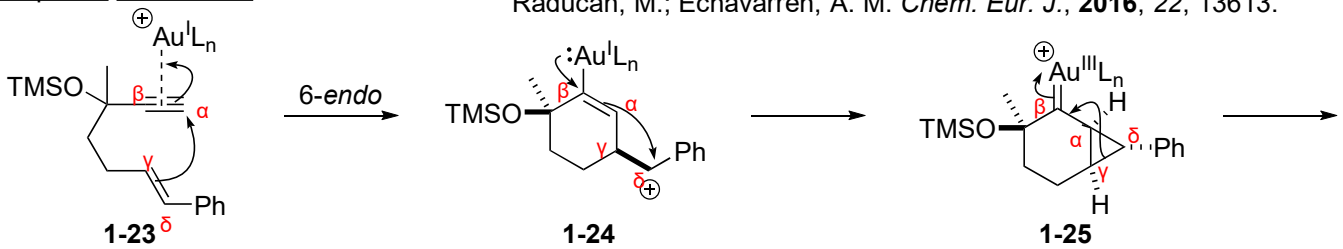
1-A-1. 6-*endo* selective cyclization of related substrate

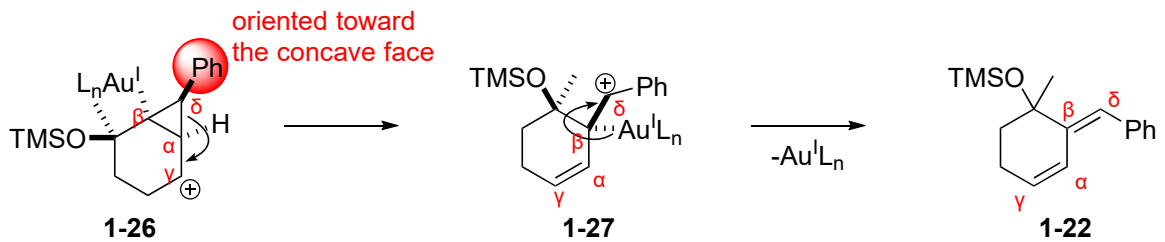
- Generally, Au^{I}-catalyzed enyne cyclization prefers 5-*exo* fashion.
  But some substrates undergo 6-*endo* cyclization under same conditions.



Proposed mechanism

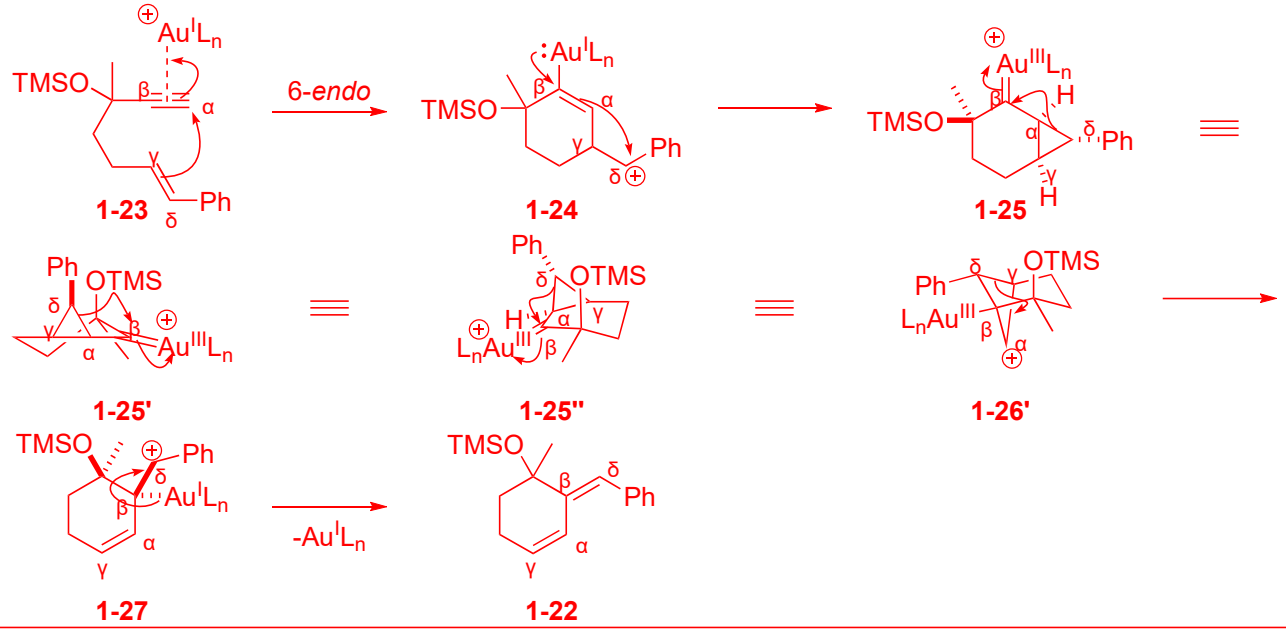
Calleja, P.; Pablo, Ó.; Ranieri, B.; Gaydou, M.; Pitaval, A.; Moreno, M.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.*, **2016**, *22*, 13613.





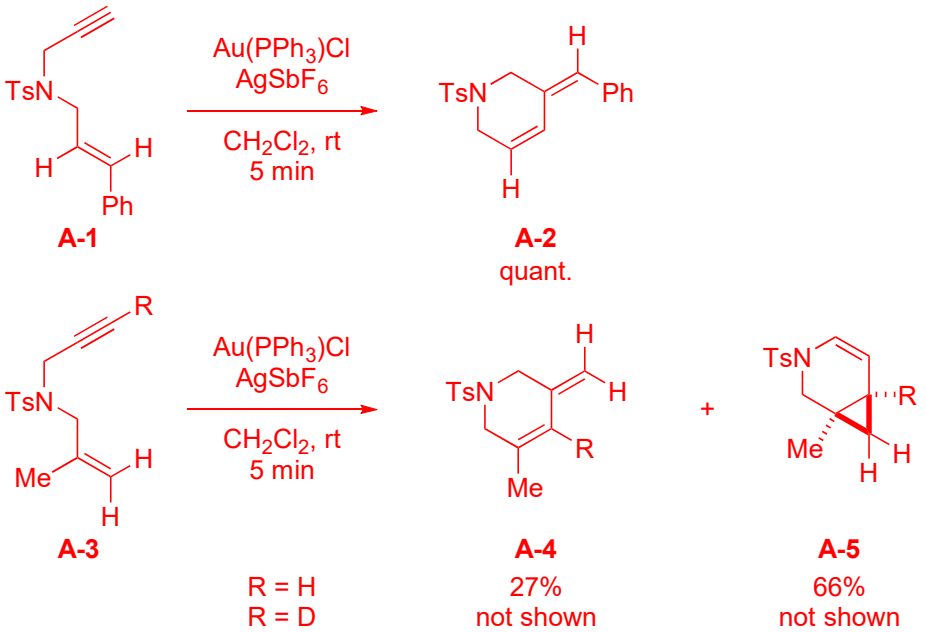
-> Authors don't mension the origin of this 6-*endo* selectivity.

Another possible route

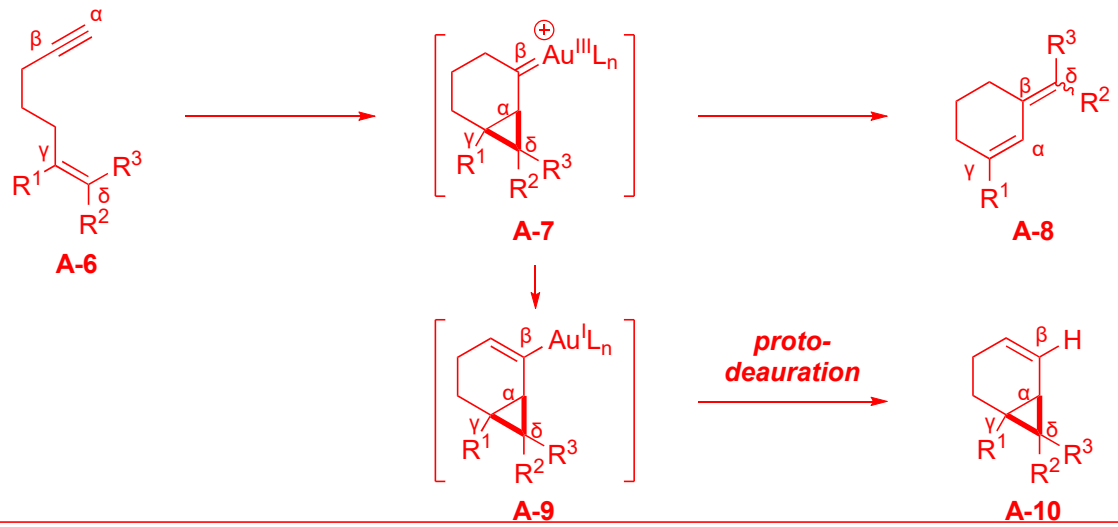


Isotope/substituent labeling experiments (see below) suggests both pathways are possible, but from the view of orbital interaction and steric repulsion, the pathway via four-membered ring is more plausible.

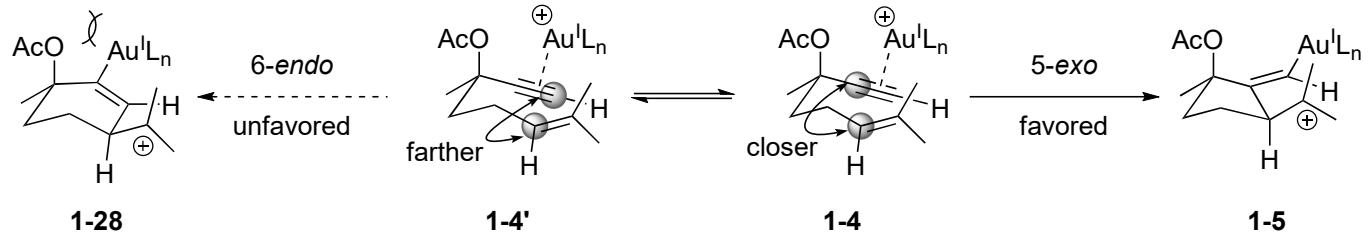
Labeling experiment



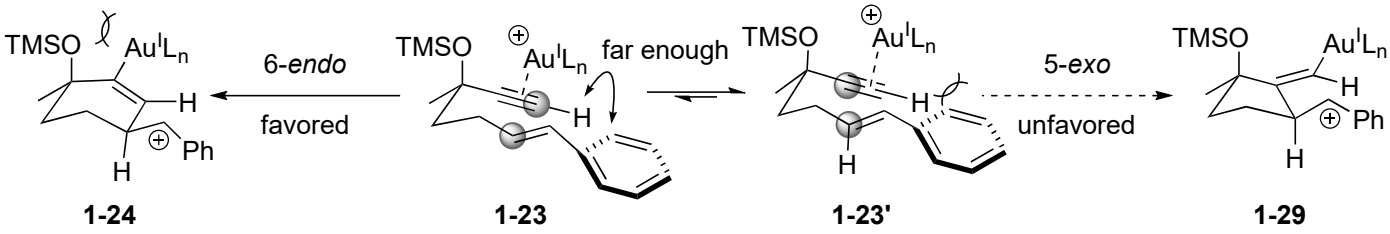
Proposed gereral mechanism



1-A-2. Rationale for 5-*exo*/6-*endo* selectivity (my proposal)



-> 5-*exo* cyclization dominantly proceeds due to the matter of the distance between two reaction centers.
Furthermore, adduct **1-28** has some steric repulsion among bulky ligand on Au atom and adjacent substituents.

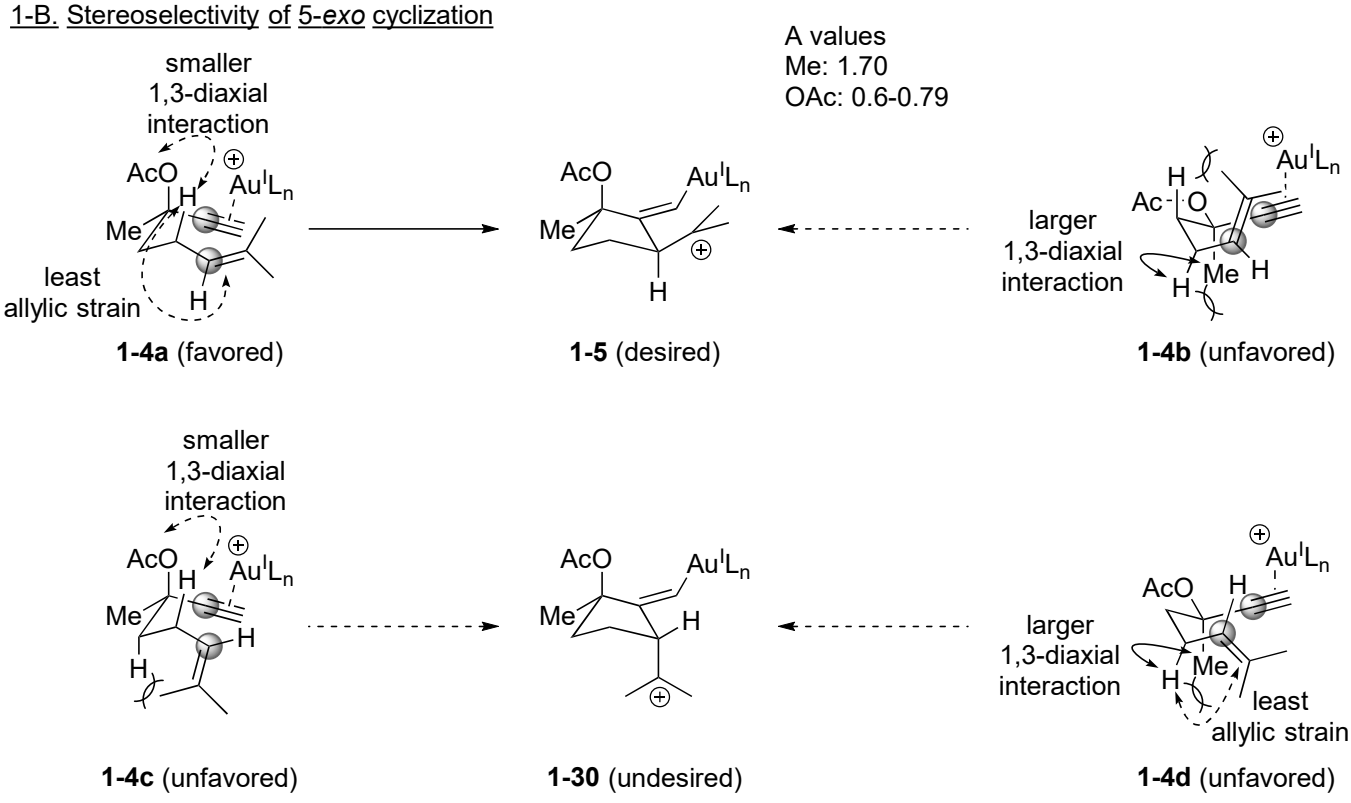


-> In this case, steric repulsion between H atom of acetylene and Ph group is the dominant factor of selectivity.

C-C triple bond of alkyne is bent by the coordination to Au^{I} atom.
See also: 170617_PS_Takumi_Fukuda_Total_Synthesis_of_Lundurines
Wu, J.; Kroll, P.; Dias, H. V. R. *Inorg. Chem.*, **2009**, *48*, 423.

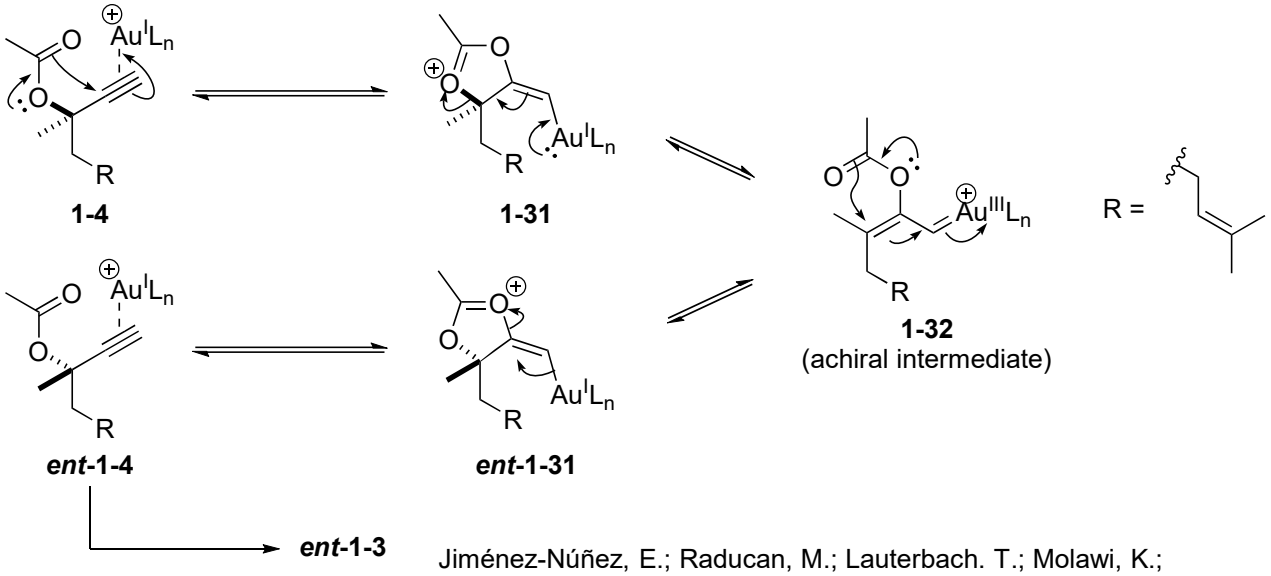
More reactive olefin can react with alkyne from farther distance (and thus needs weaker coordination of alkyne to Au)?
If so, reactivity (electron density?) of olefin affects the selectivity of cyclization.

1-B. Stereoselectivity of 5-*exo* cyclization



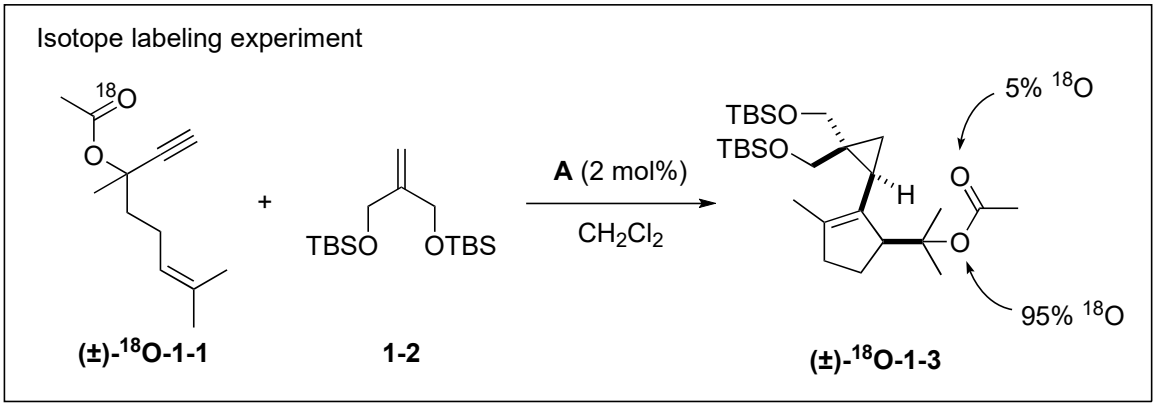
Discussion 2: Partial racemization

• Since 5-*exo* cyclization proceeds stereoselectively, racemization proceeds **before** cyclization.



Jiménez-Núñez, E.; Raducan, M.; Lauterbach. T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6152.

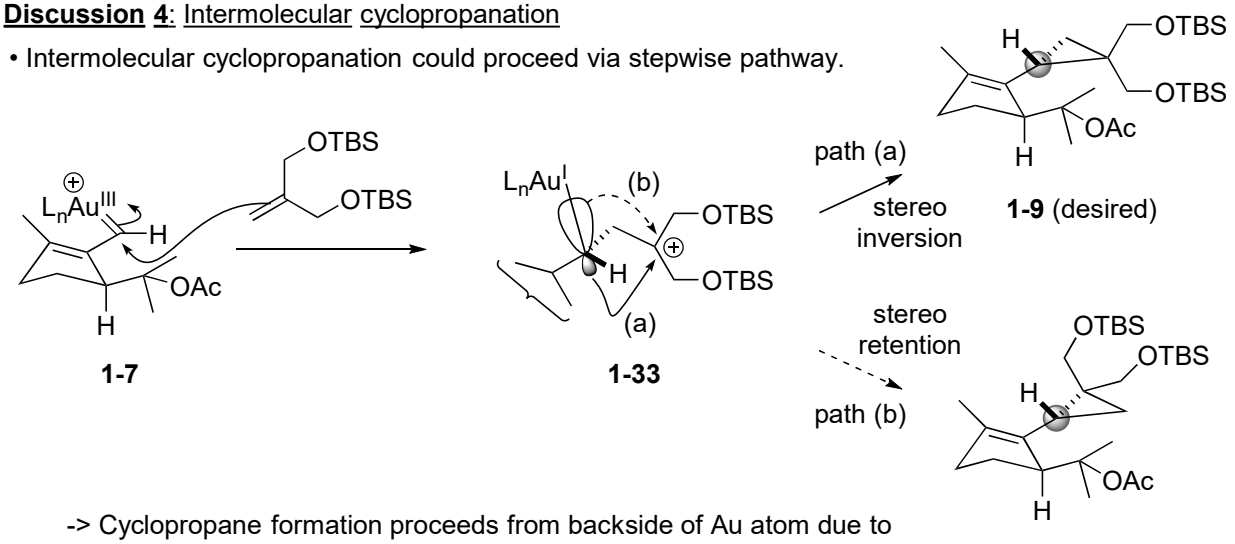
Discussion 3: Acetoxy group migration



-> Acetoxy group is mainly transferred intramolecularly, without elimination.

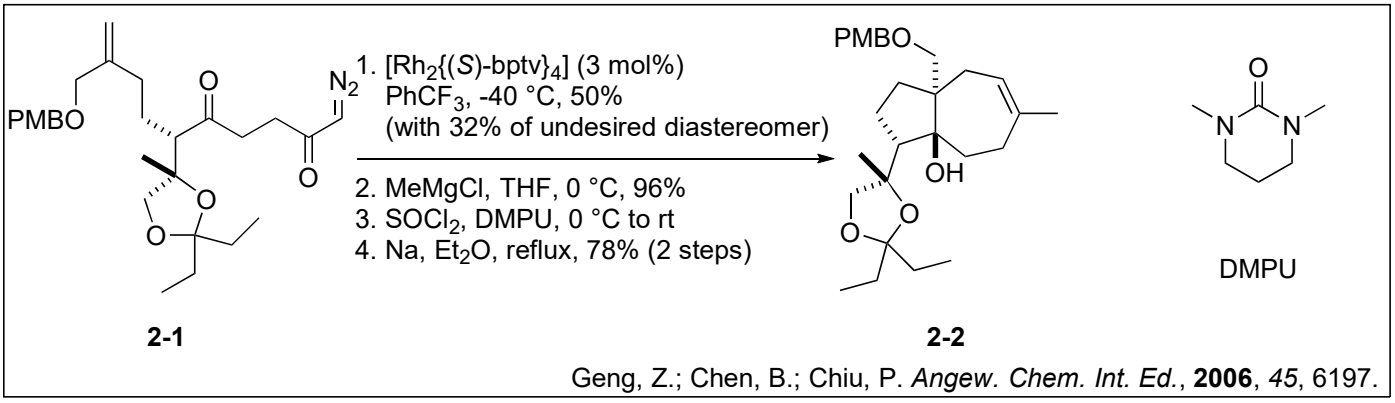
Discussion 4: Intermolecular cyclopropanation

• Intermolecular cyclopropanation could proceed via stepwise pathway.



-> Cyclopropane formation proceeds from backside of Au atom due to steric repulsion between AuL_n group and OTBS groups.

Problem 2. Total synthesis of Pseudolaric acid A by Chiu's group

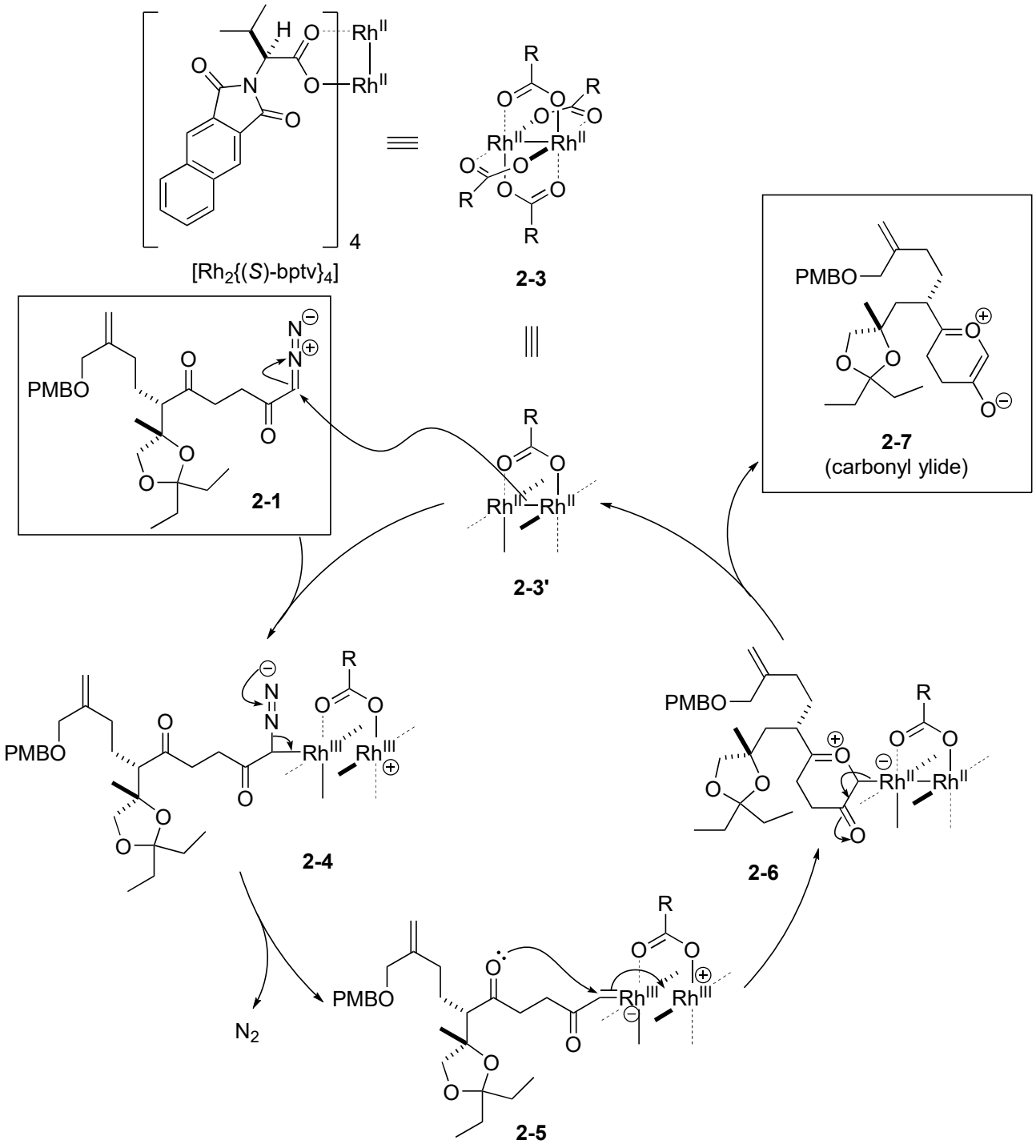


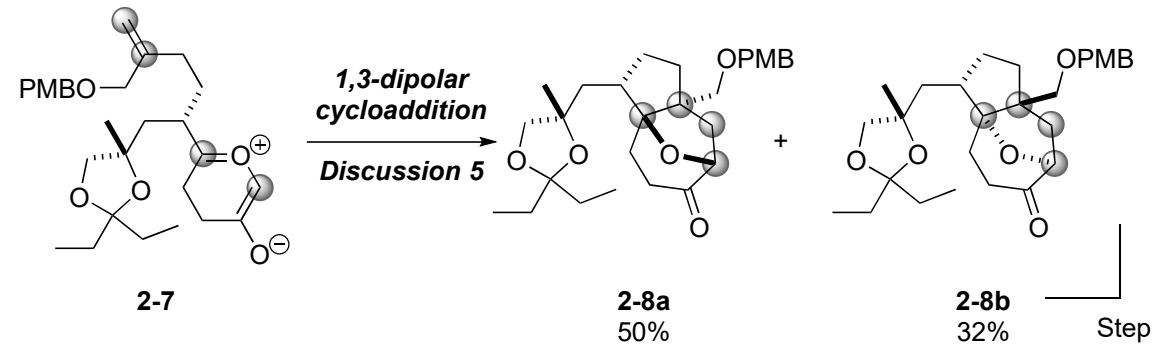
2-1 **2-2**

Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem. Int. Ed.*, **2006**, *45*, 6197.

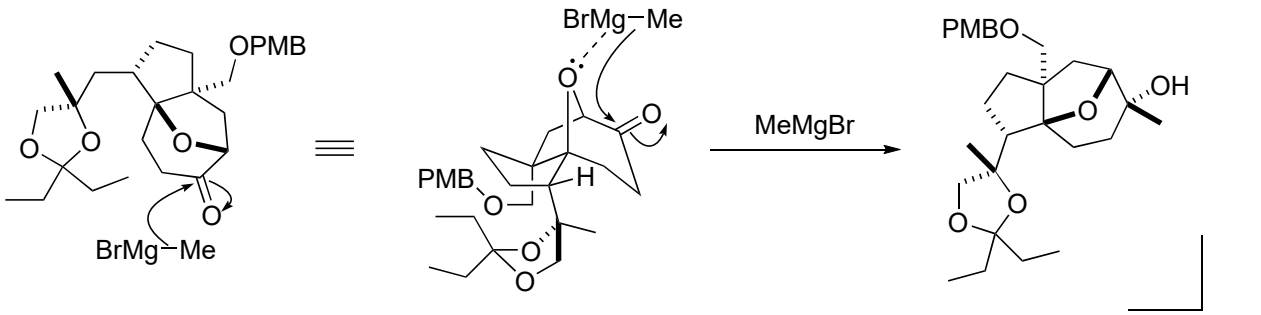
Keypoint: Rh^{II}-catalyzed carbonyl ylide formation/1,3-dipolar cycloaddition
For the total synthesis of pseudolaric acid B by Trost's group, see:
130706_PS_Yuuki_Amaoka_synthesis_pseudolaric_acidB

1. Reaction mechanism

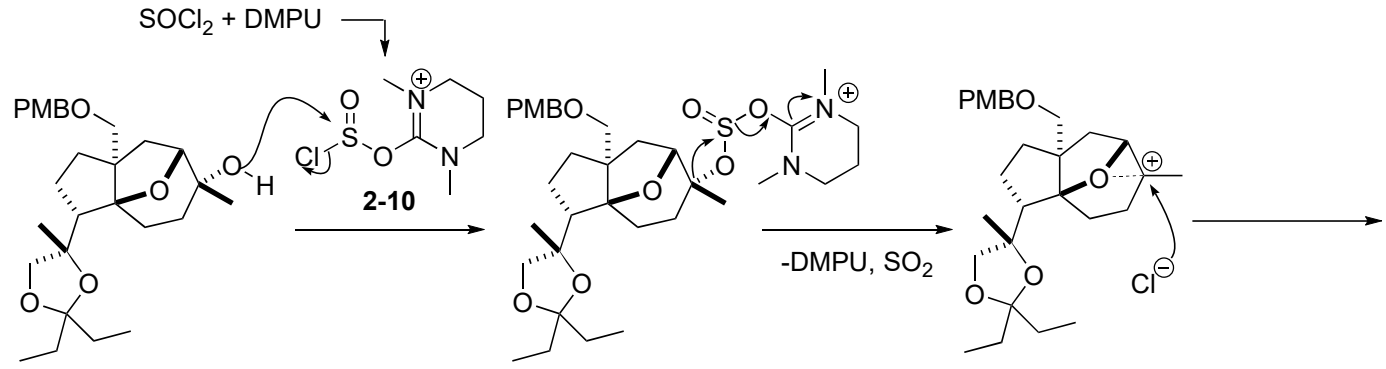




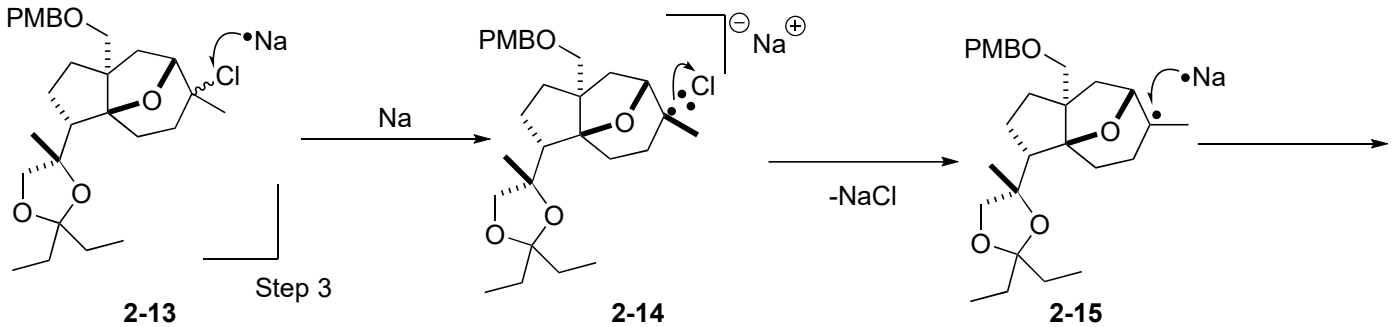
2-7 **2-8a** 50% **2-8b** 32% Step 1



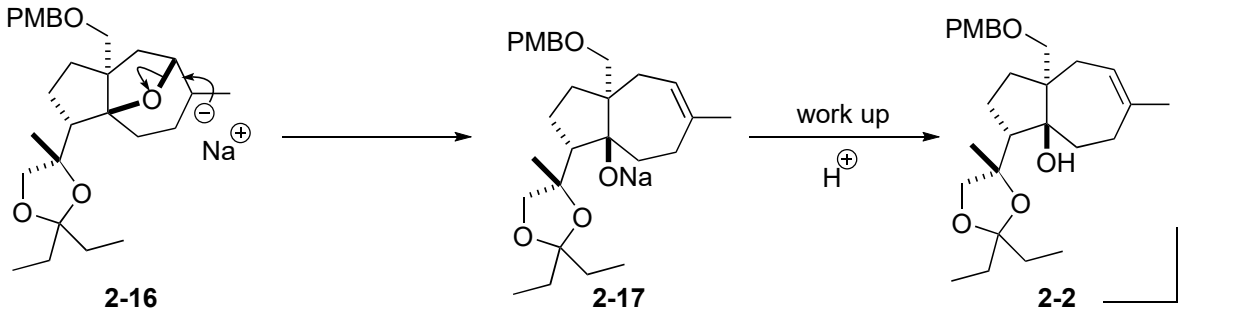
2-8a **2-8a'** **2-9** Step 2



2-9 **2-11** **2-12**



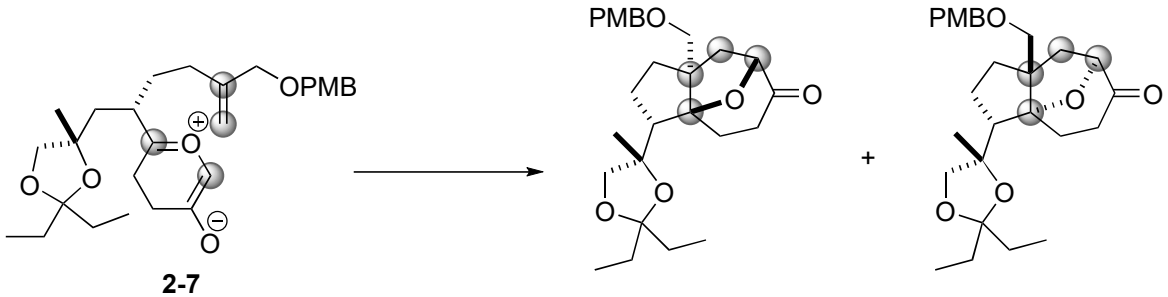
2-13 Step 3 **2-14** **2-15**



2-16 **2-17** **2-2** Step 4

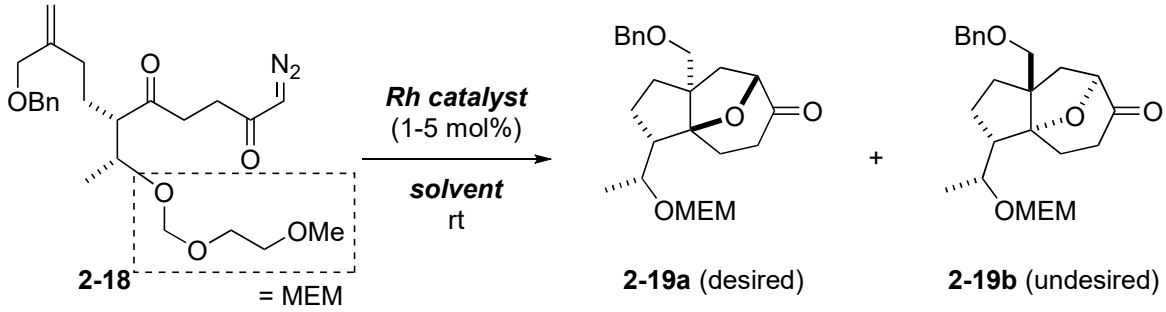
2. Discusssion

Discussion 5: 1,3-dipolar cycloaddition



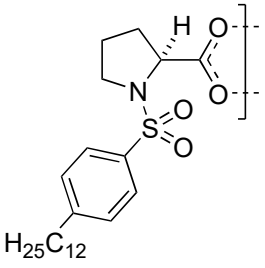
-> The diastereoselectivity of this cycloaddition is highly influenced by Rh-catalyst.
Other two possible diastereomers are omitted since they have *trans*-5/5 bicycle.

5-A. Investigation on the stereoselectivity in the cycloaddition of related substrate **2-18**

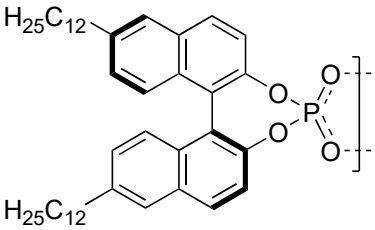


entry	***Rh catalyst***	***Solvent***	yield (**2-19a**+**2-19b**)	ratio (**2-19a**:**2-19b**)
1	$Rh_2(OAc)_4$	CH_2Cl_2	61%	1 : 1.3
2	$Rh_2(OCOCF_3)_4$	CH_2Cl_2	61%	1 : 1.9
3	Rh_2(*R*-dosp)$_4$	CH_2Cl_2	53%	1 : 1.3
4	Rh_2(*S*-dosp)$_4$	CH_2Cl_2	62%	1 : 1.7
5	Rh_2(*S*-ddbnp)$_4$	CH_2Cl_2	54%	1 : 1.6
6	Rh_2(*S*-bptv)$_4$	CH_2Cl_2	67%	1.3 : 1

Chiu, P. *Pure Appl. Chem.*, **2005**, *77*, 1183.



S-dosp

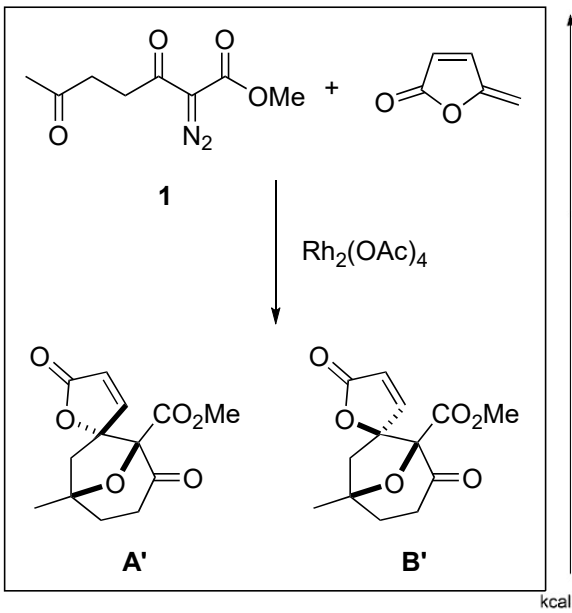


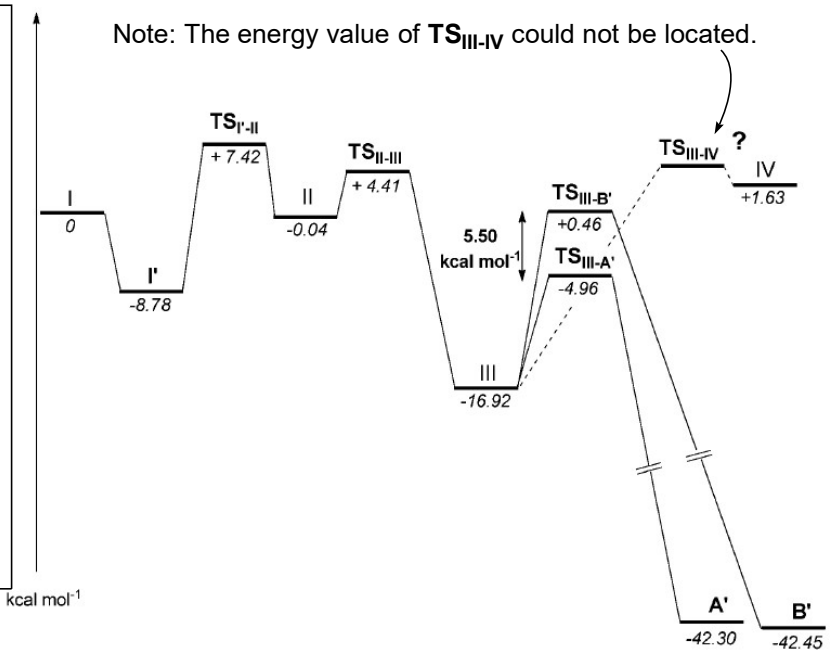
S-ddbnp

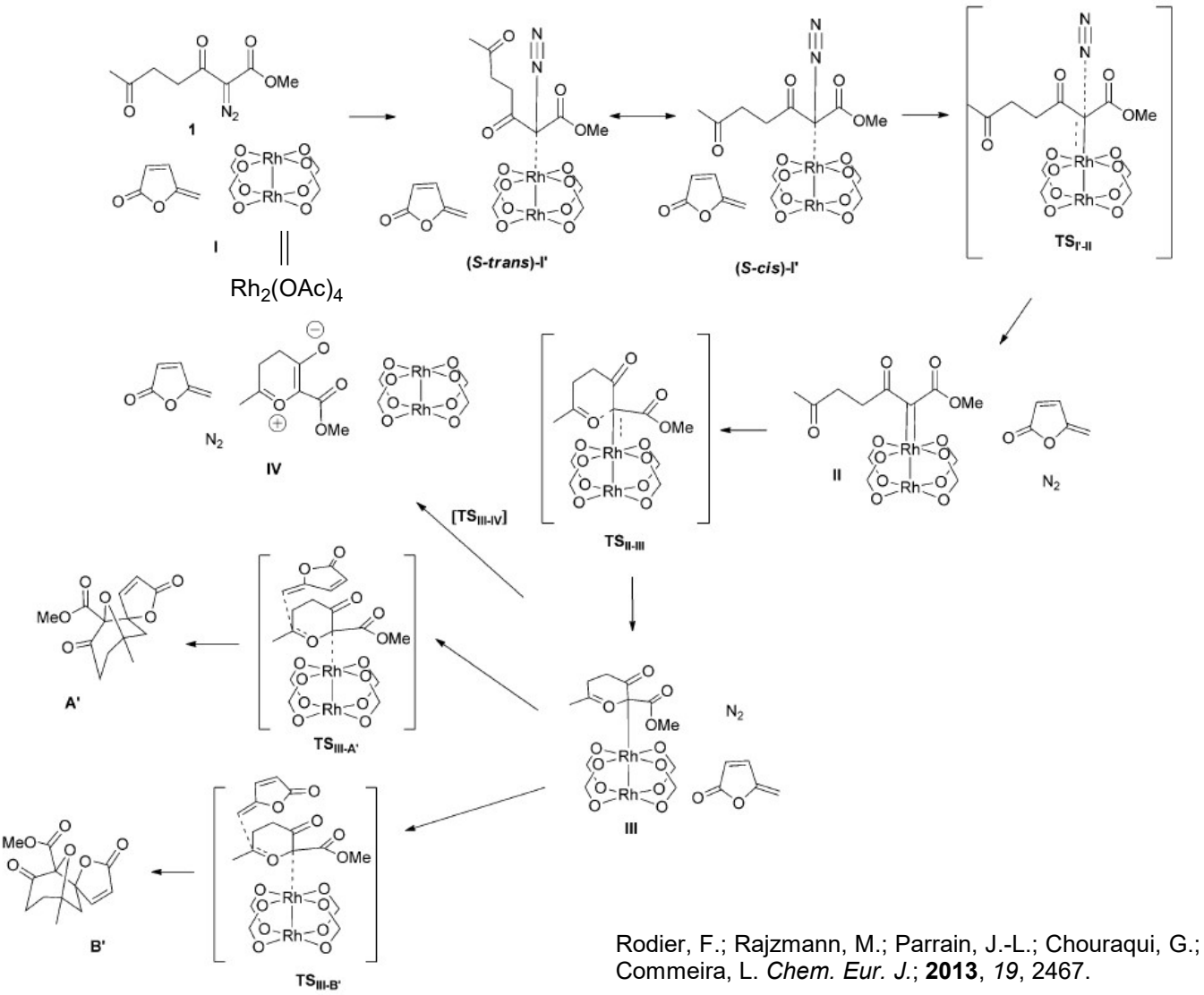
In the case of substrate **2-18**, diastereomeric ratio inverted only when Rh_2(*S*-bptv)$_4$ was used as catalyst.

-> Rh catalyst binds to the carbonyl ylide throughout the cycloaddition, and chiral ligands on Rh atom affect the diastereoselectivity. But the detailed mechanism is still unclear.

5-B. Energy calculation of carbonyl ylide formation (other substrate)



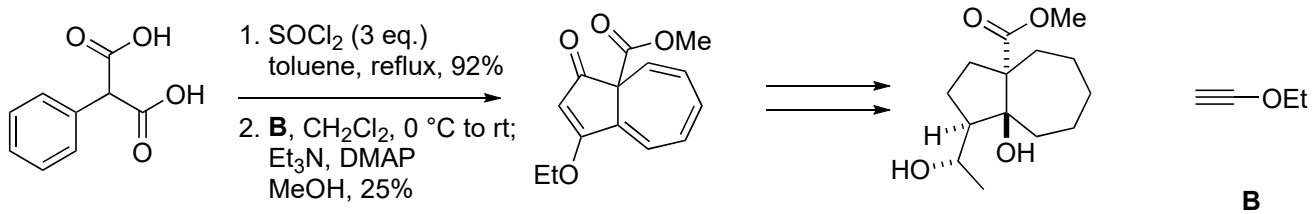




Rodier, F.; Rajzmann, M.; Parrain, J.-L.; Chouraqui, G.; Commeira, L. *Chem. Eur. J.*; **2013**, *19*, 2467.

-> At least in this system, it is more favorable for the cycloaddition to proceed via Rh-binding intermediate **III** than to proceed via free ylide **IV**.

Problem 3. Synthetic approach toward hydroazulene core of pseudolaric acid by Chen's group

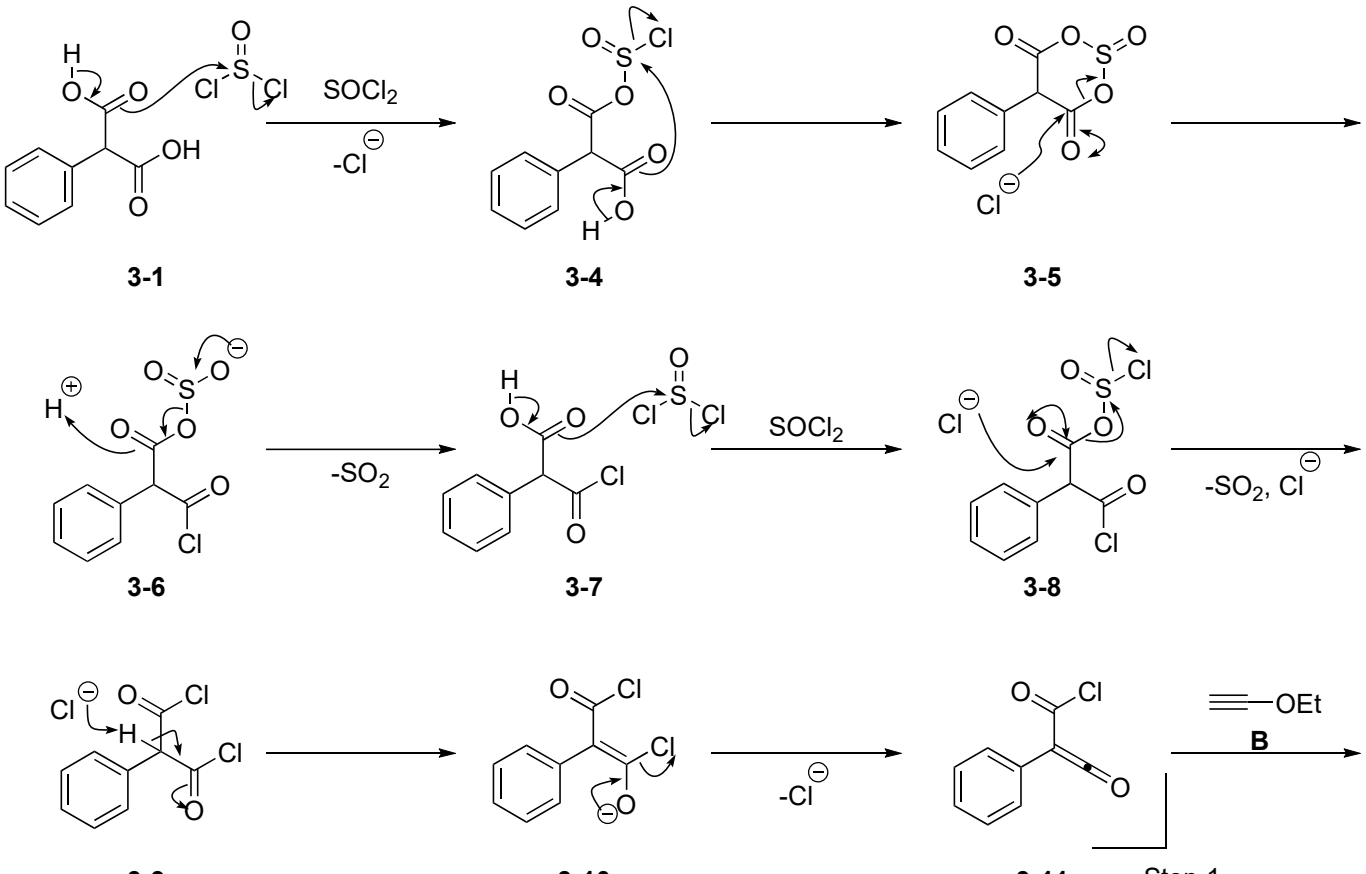


3-1 **3-2** **3-3**

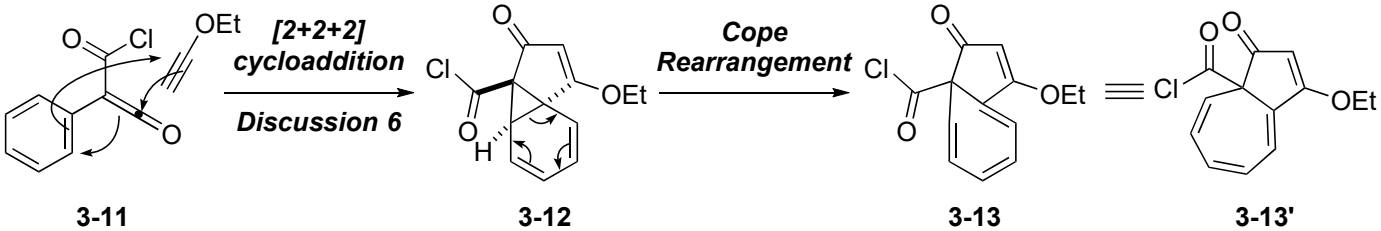
3-1 to **3-2**:
Nakanishi, S.; Bulter, K. *Org. Prep. Proc. Intl.*, **1975**, *7*, 155.
Brown, D. G.; Hoye, T. R.; Brisbois, R. G. *J. Org. Chem.*, **1998**, *63*, 1630.
3-2 to **3-3**:
Yue, X.-D.; Chen, L.; Li, W.-D. Z. *Tetrahedron*, **2014**, *70*, 5505.

Keypoint: peculiar [2+2+2] cycloaddition of phenylketene and ethoxyacetylene

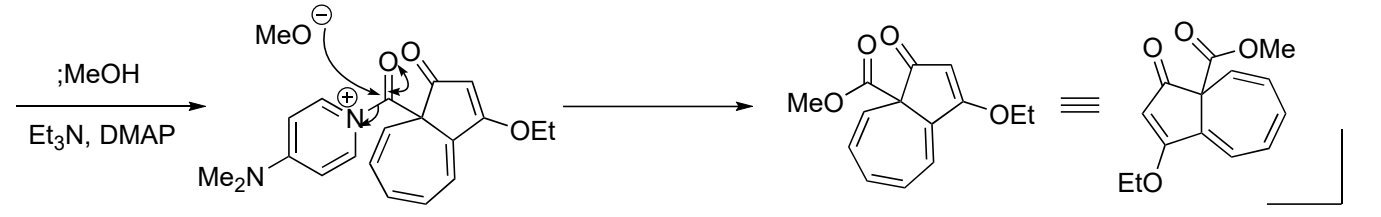
1. Reaction mechanism



3-1 **3-4** **3-5** **3-6** **3-7** **3-8** **3-9** **3-10** **3-11** Step 1



3-11 **3-12** **3-13** **3-13'**

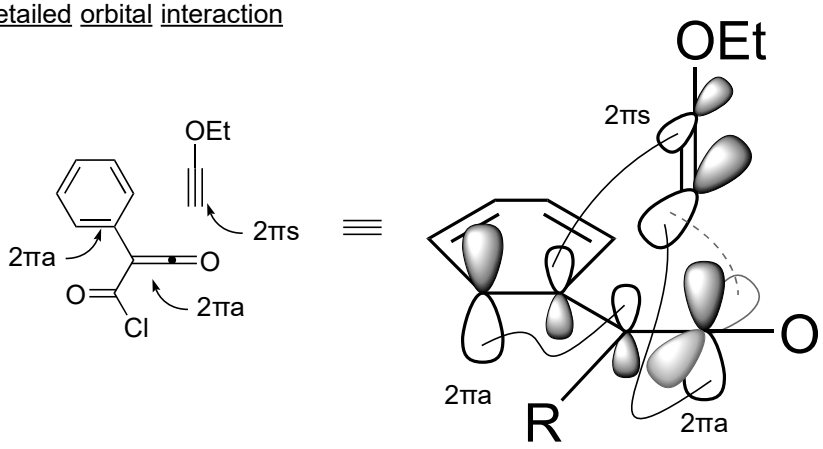


3-14 **3-2'** **3-2** Step 2

2. Discussion

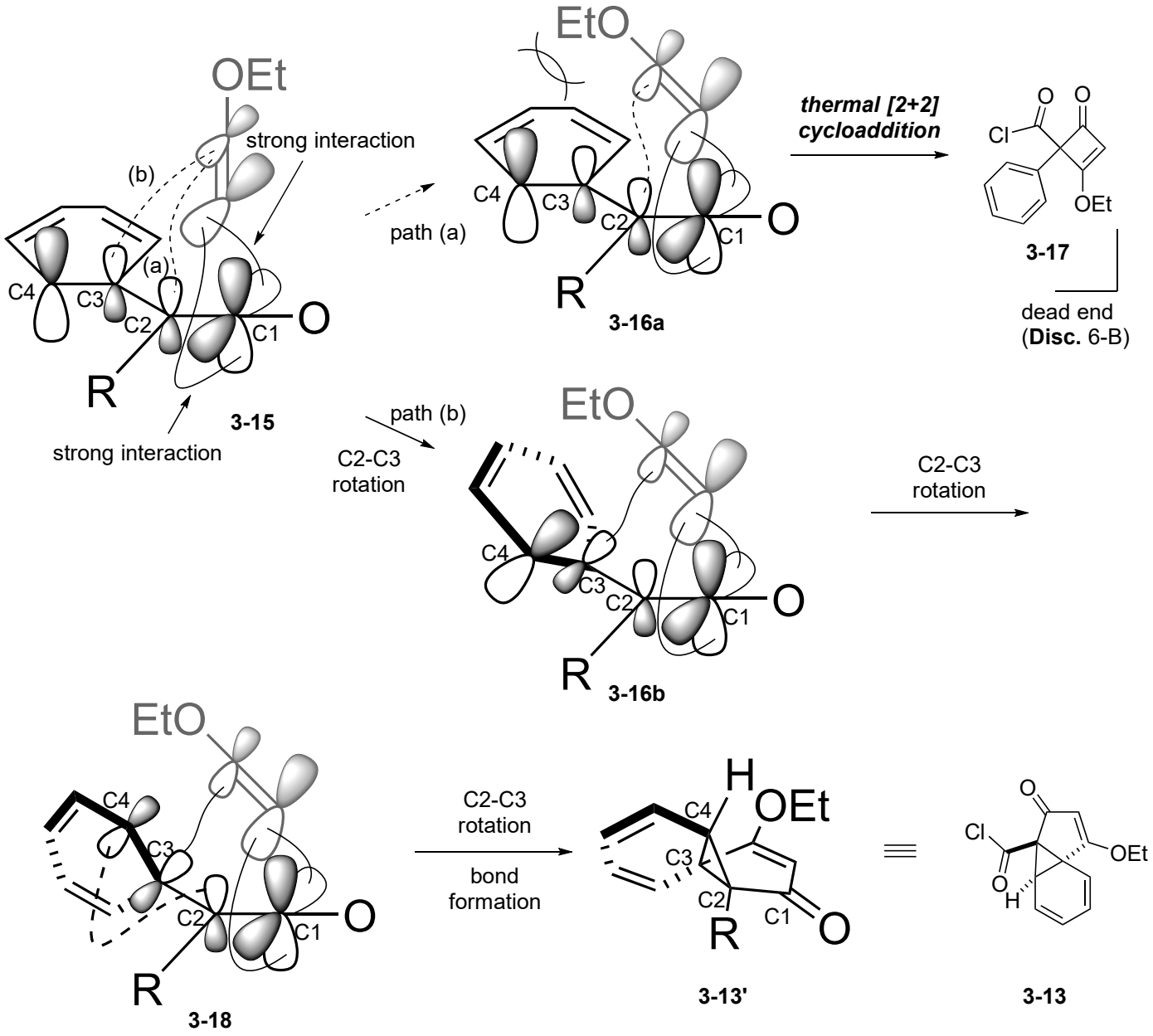
Discussion 6: Cycloaddition between phenylketene and ethoxy acetylene

6-A. Detailed orbital interaction



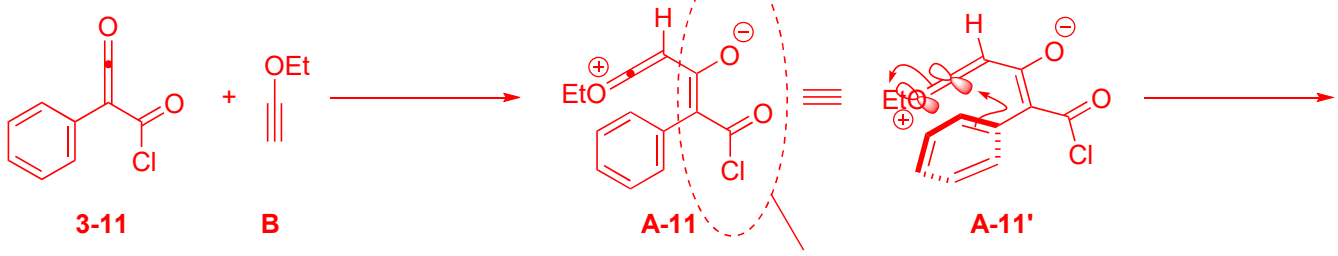
Teufel, H.; Jenny, E. F. *Tetrahedron Lett.*, **1971**, *21*, 1769.

This cycloaddition to produce very distorted tricycle is supposed to proceed via peculiar thermally allowed **2πs+2πa+2πa** fashion.



"Concerted" pathway shouldn't involve bond rotation.
This serial sequence of orbital interactions should be described as stepwise pathway.

Stepwise formation of the tricycle



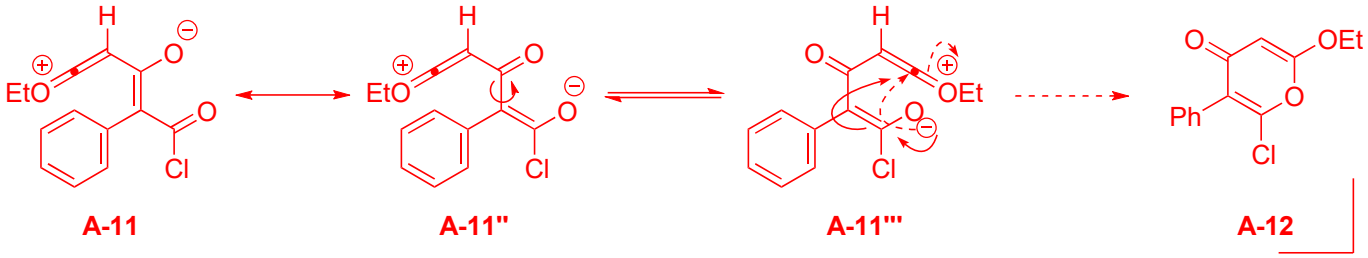
3-11 **B** **A-11** **A-11'**

Nucleophilicity is attenuated due to charge delocalization.
-> Formal [2+2] and pyrone formation is suppressed? (see below)

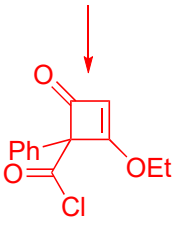
A-12 **3-12**

C=O π* orbital of ketene is on the same plane with the enolate.
On cyclization, phenyl group should rotate to interact with it and thus break the conjugation with the enolate.
-> Electron density of each carbon on phenyl group is not affected by the anion, and the closest *ipso*-carbon undergoes Friedel-Crafts type of cyclization.

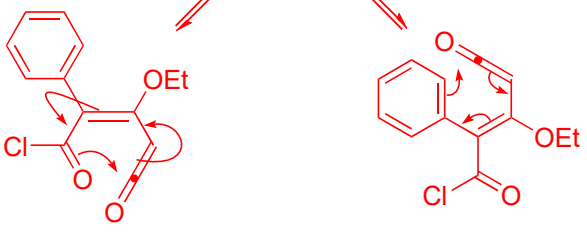
Pathways toward other possible byproducts



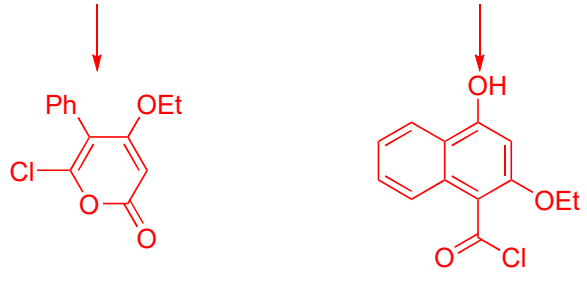
A-11 **A-11"** **A-11'''** **A-12**



A-13



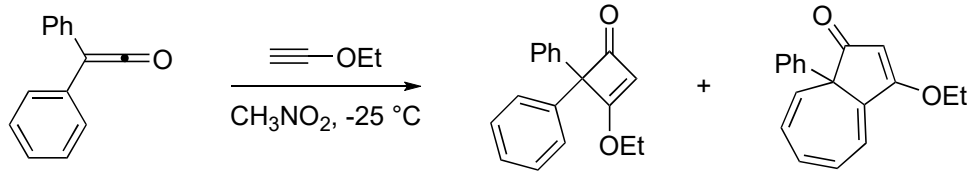
A-13' **A-13"**



A-14 **A-15**

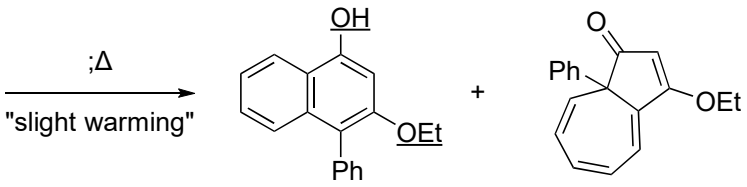
6-B. Investigation with related compounds

6-B-1. Thermal decomposition

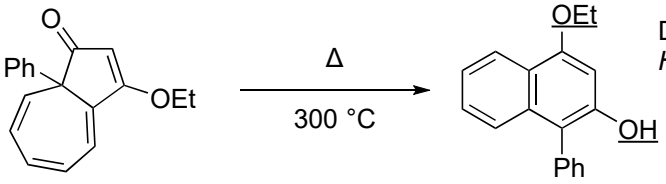


3-19 **3-20** **3-21**

~ 1:1



3-22 **3-21**

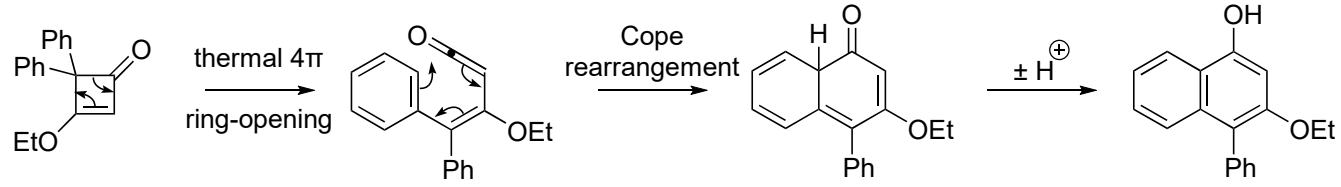


3-21 **3-23**

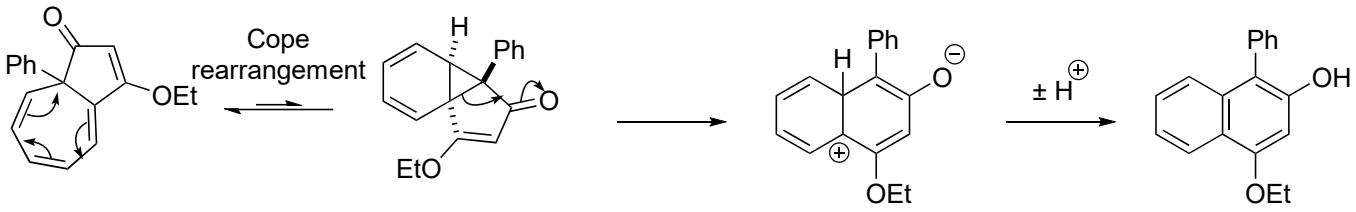
Druey, J.; Jenny, E. F.; Schenker, K.; Woodward, R. B. *Helv. Chim. Acta*, **1962**, *71*, 600.

Cyclobutenone **3-20** readily decomposes into naphtol **3-22**, while **3-21** decomposes only under harsh conditions into naphtol **3-23**.
-> **3-20** is **not** the intermediate of the formation of **3-21**.

Proposed mechanisms

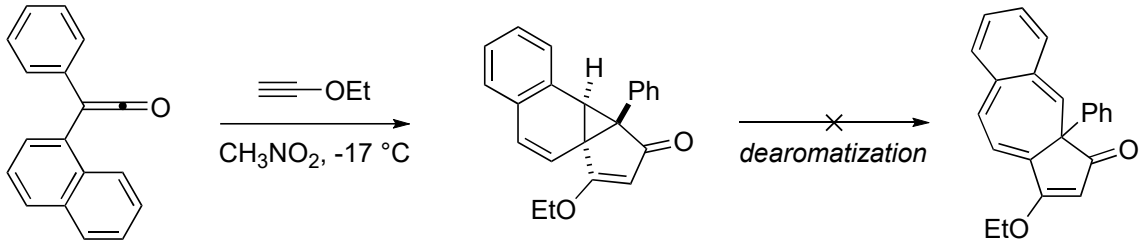


3-20 **3-24** **3-25** **3-22**



3-21 (dihydroazulenone structure) **3-26** (norcaradiene structure) **3-27** **3-23**

6-B-2. Isolation of stable intermediate



3-28 **3-29** (norcaradiene structure) **3-30** (*o*-quinodimethane structure)

26% (stable on alumina PTLC)

Wuest, J. D. *Tetrahedron*, **1980**, *36*, 2291.

-> Dihydroazulenones **3-14** and **3-21** would rise from norcaradienes **3-13** and **3-26**, respectively.