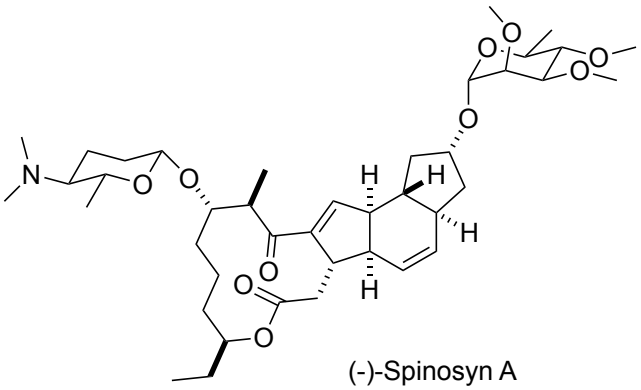
Problem session (1) -answer-

2021/12/25 Hiromu Kakizawa

Topic: Total synthesis of (-)-Spinosyn A by Mingji Dai's group

1. Introduction



(-)-Spinosyn A

Isoration:
in 1990, from Saccharopolyspora spinosa
by Eli Lilly and company researchers

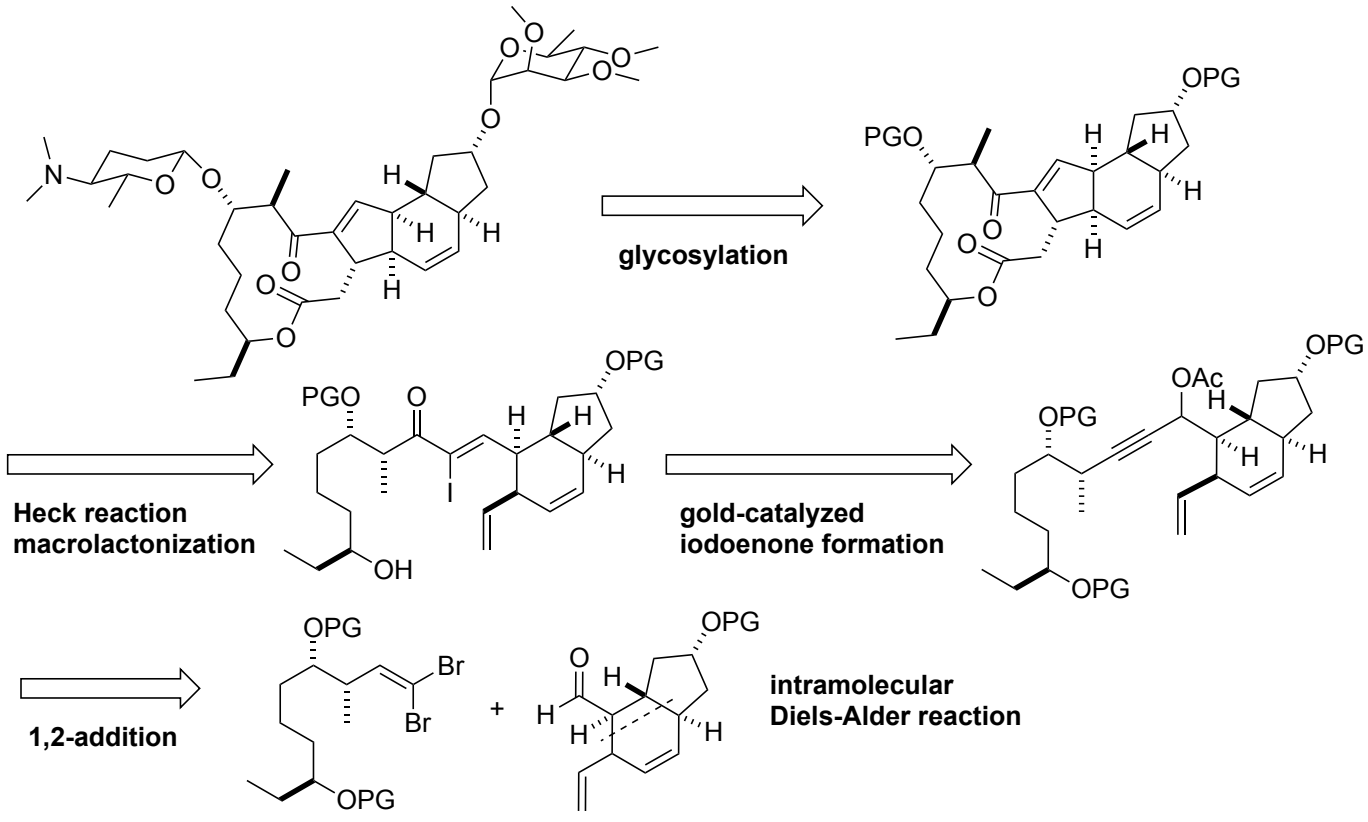
Use:
Insecticide (owing to its high toxicity to insects
by affecting the neurotransmission)

Structural feature:
5,6,5,12-fused tetracyclic ring system

4 total synthesis reported so far:

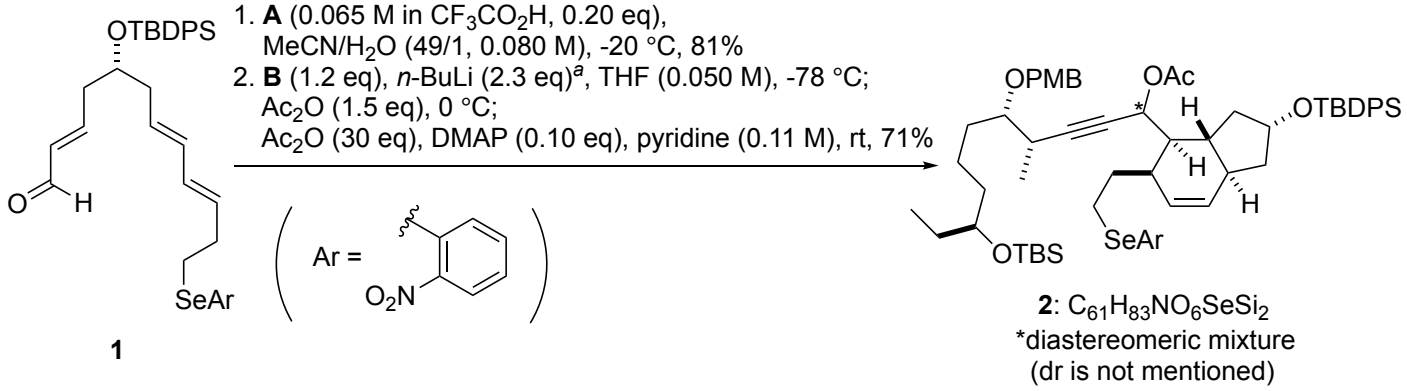
- Evans's group (1993)[1], 31 steps in LLS
- Paquette's group (1998)[2], 35 steps in LLS
- Roush's group (2004)[3], 23 steps in LLS
- Dai's group (2016)[4], 15 steps in LLS -> this problem

Synthetic plan by Dai's group



Reference:
1) W. C. Black; D. A. Evans, *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513
2) Z. Gao; Z. Ni; G. F. Smith; L. A. Paquette. *J. Am. Chem. Soc.* **1998**, *120*, 2543-2552
3) D. J. Mergott; S. A. Frank; W. R. Roush. *Proc. Natl. Acad. Sci. USA.* **2004**, *101*, 11955-11959
4) Y. Bai; X. Shen; Y. Li; M. Dai. *J. Am. Chem. Soc.* **2016**, *138*, 10838-10841

2. Mechanisms for steps 1 and 2



[a] Product of the previous step was added to pre-mixed **B** and *n*-BuLi.

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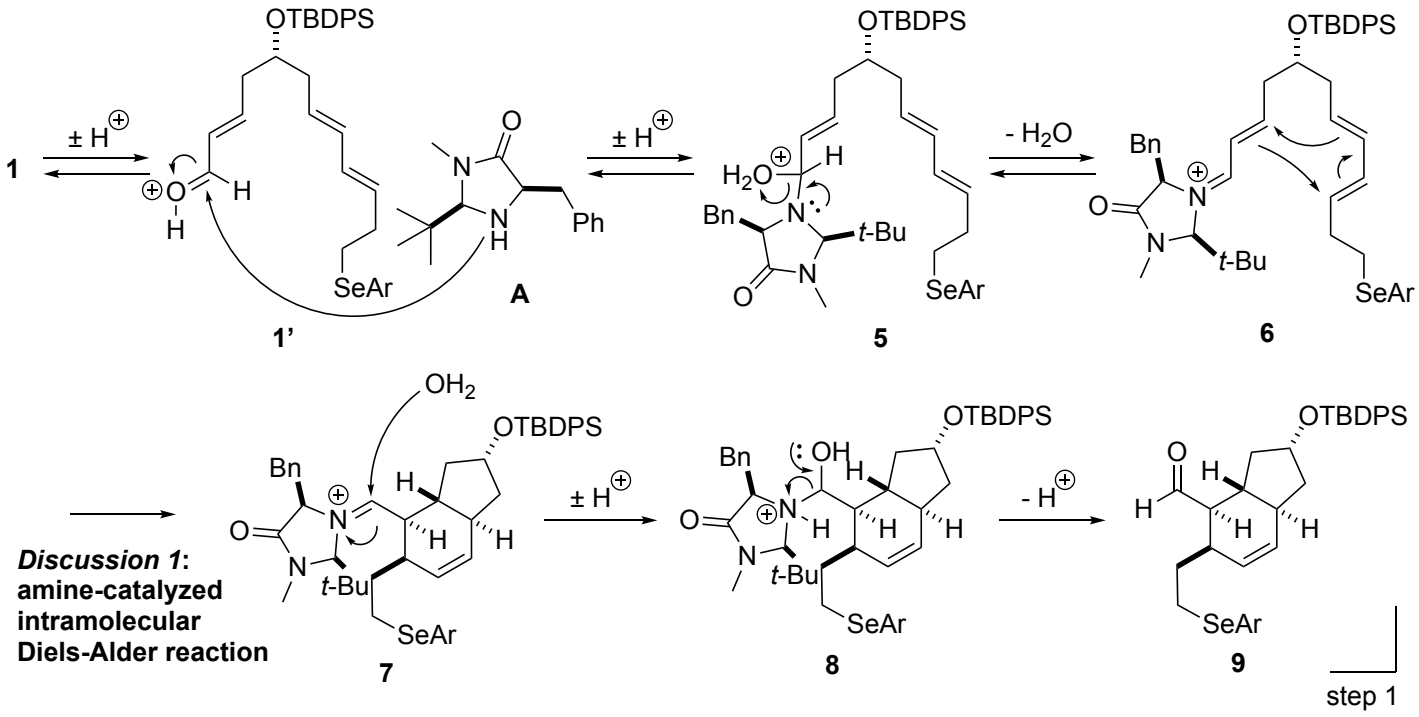
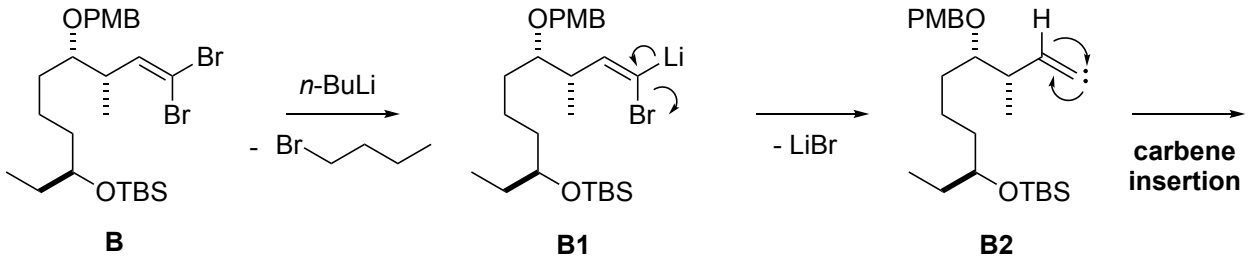
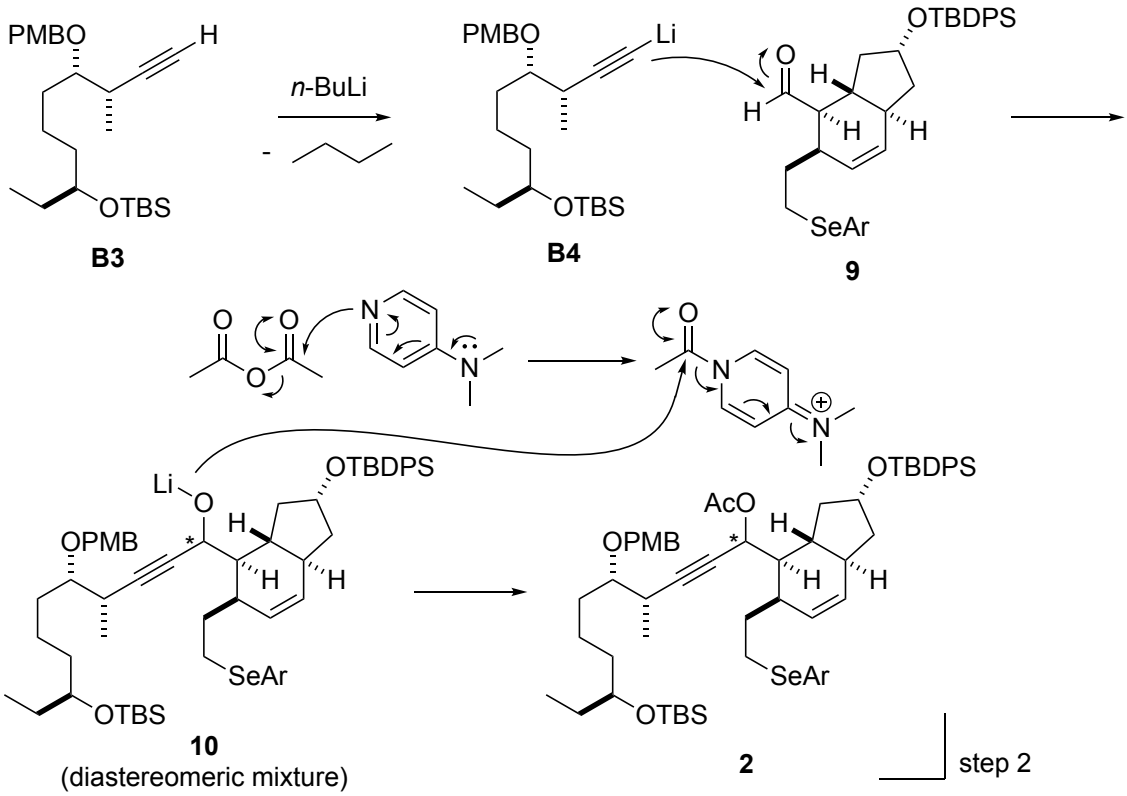
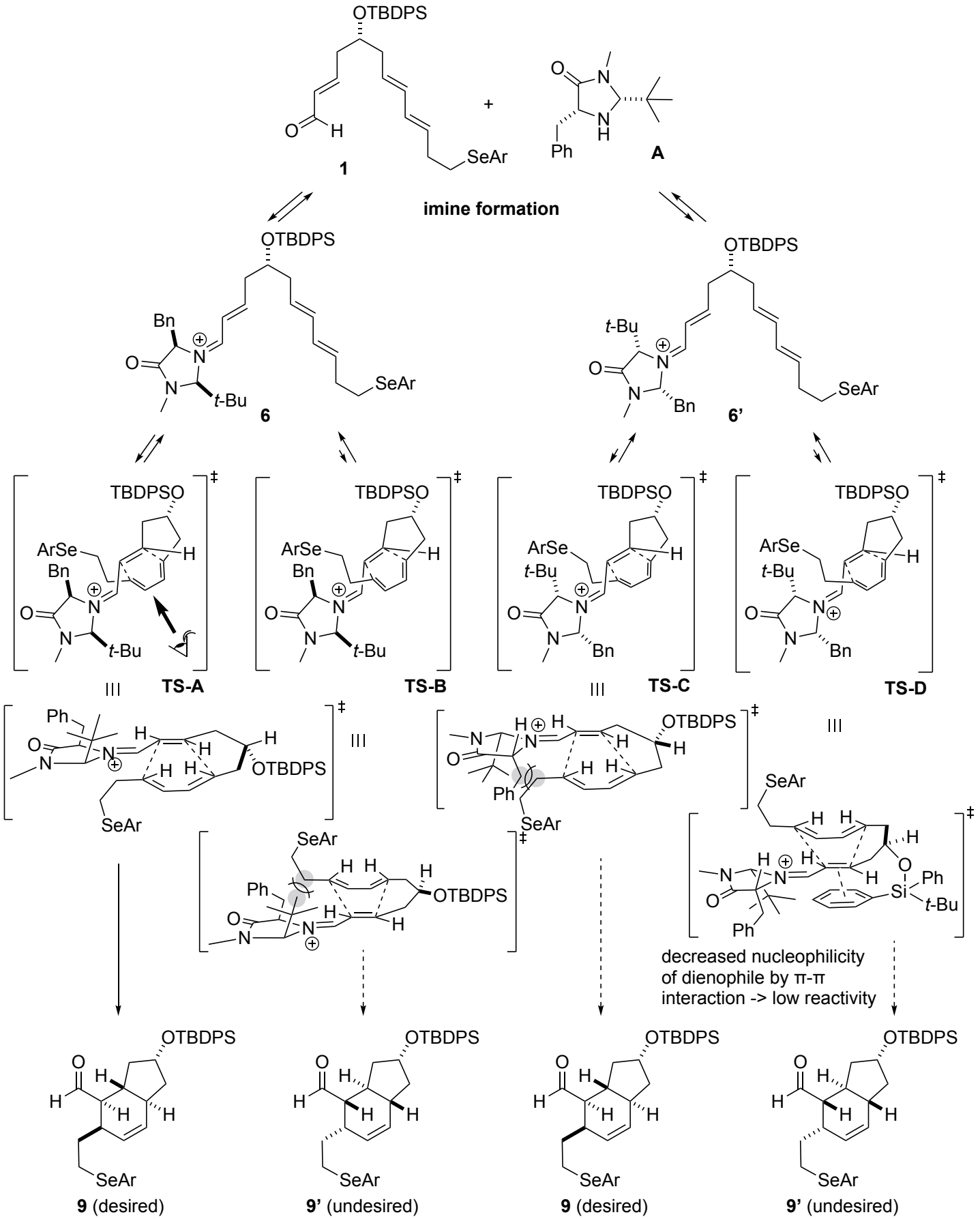
2-1. Reaction mechanisms



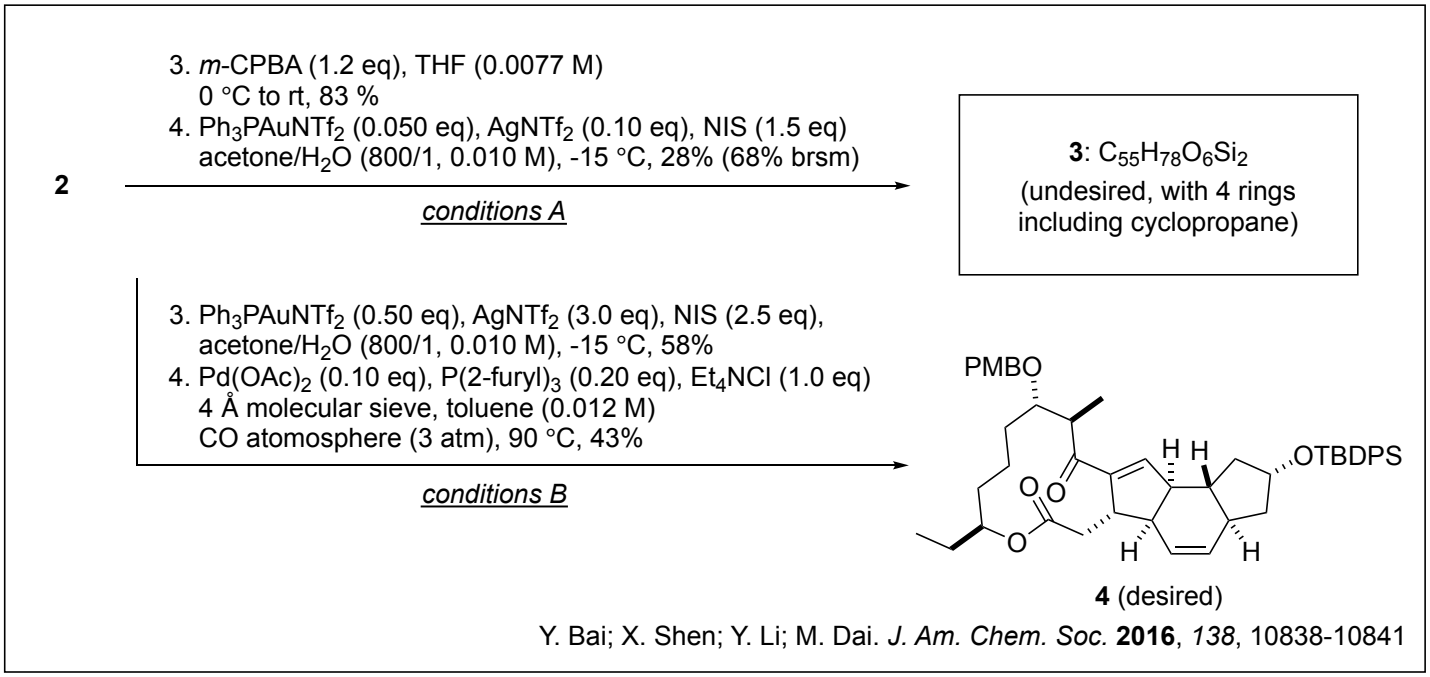



PMBO
H
OTBS
B3
n-BuLi
-
PMBO
Li
OTBS
B4
O
H
H
H
H
OTBDPS
SeAr
9
O
O
O
N
N
O
N
N
Li
O
OTBDPS
OPMB
*
H
H
H
SeAr
OTBS
10
(diastereomeric mixture)
AcO
OPMB
*
H
H
H
OTBDPS
SeAr
OTBS
2
step 2

2-2. ***Discussion* 1: intramolecular Diels-Alder reaction using amine catalyst**

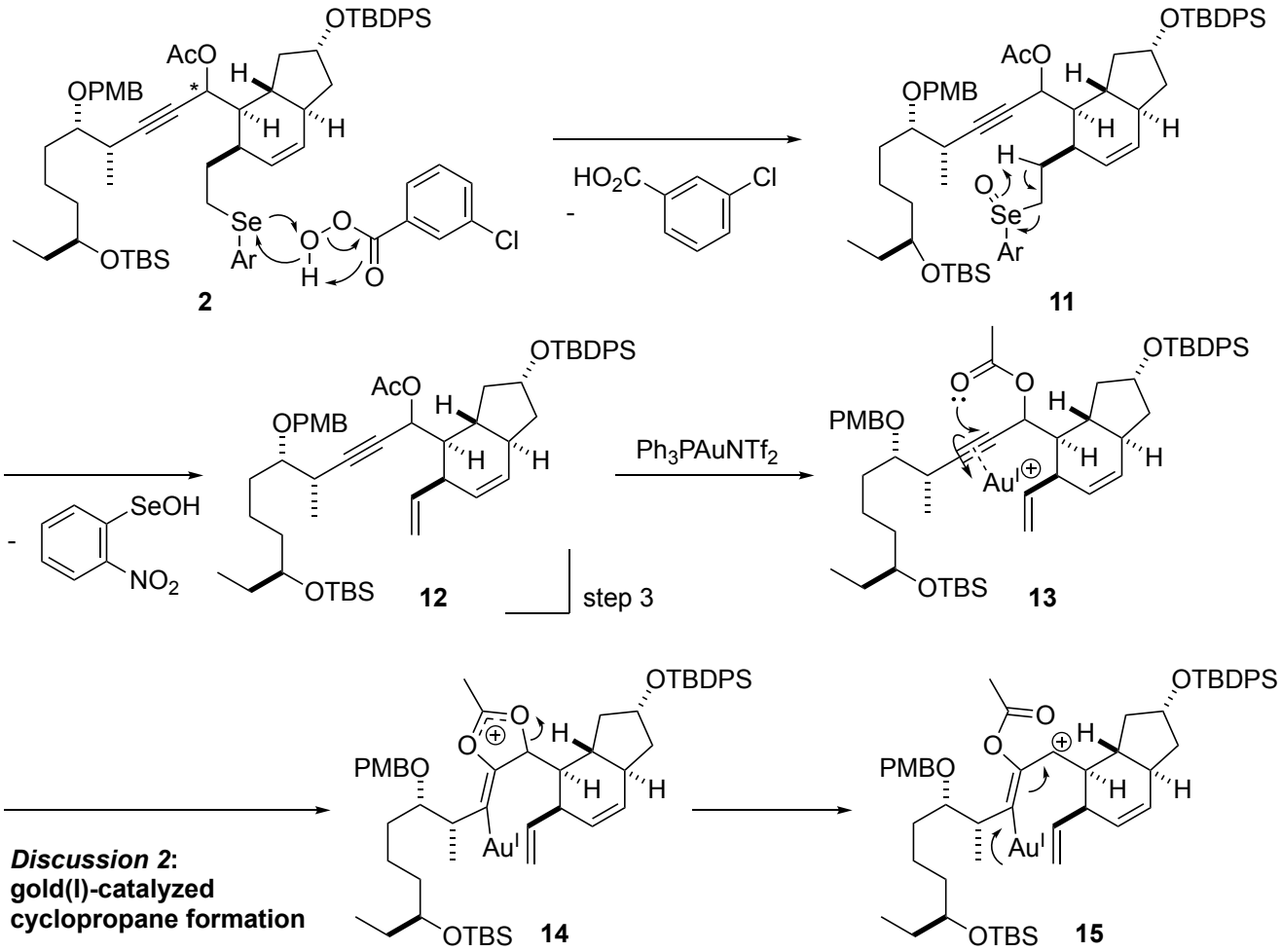


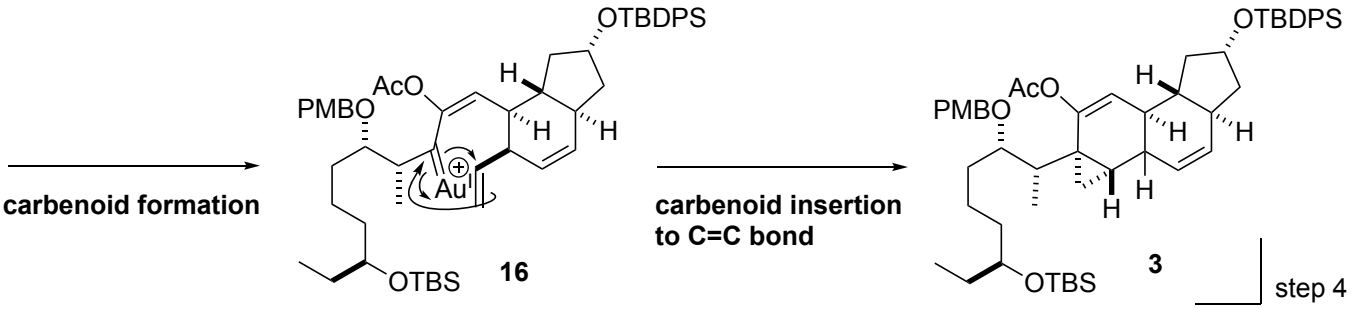
3. Mechanisms for steps 3 and 4



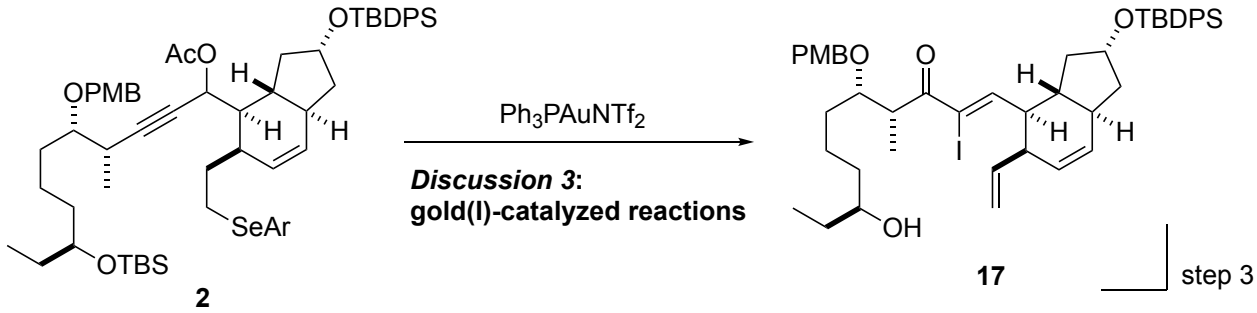
Y. Bai; X. Shen; Y. Li; M. Dai. *J. Am. Chem. Soc.* **2016**, *138*, 10838-10841

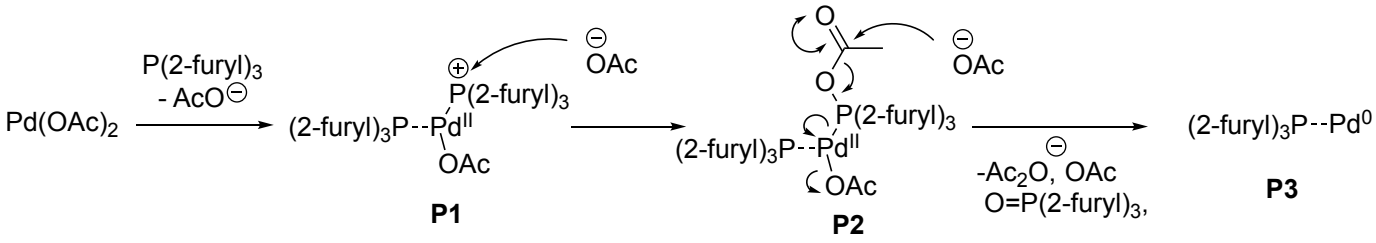
3-1. Mechanisms for *conditions A*

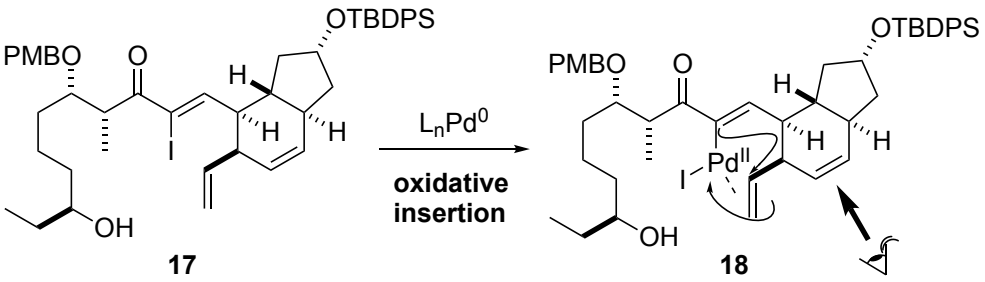


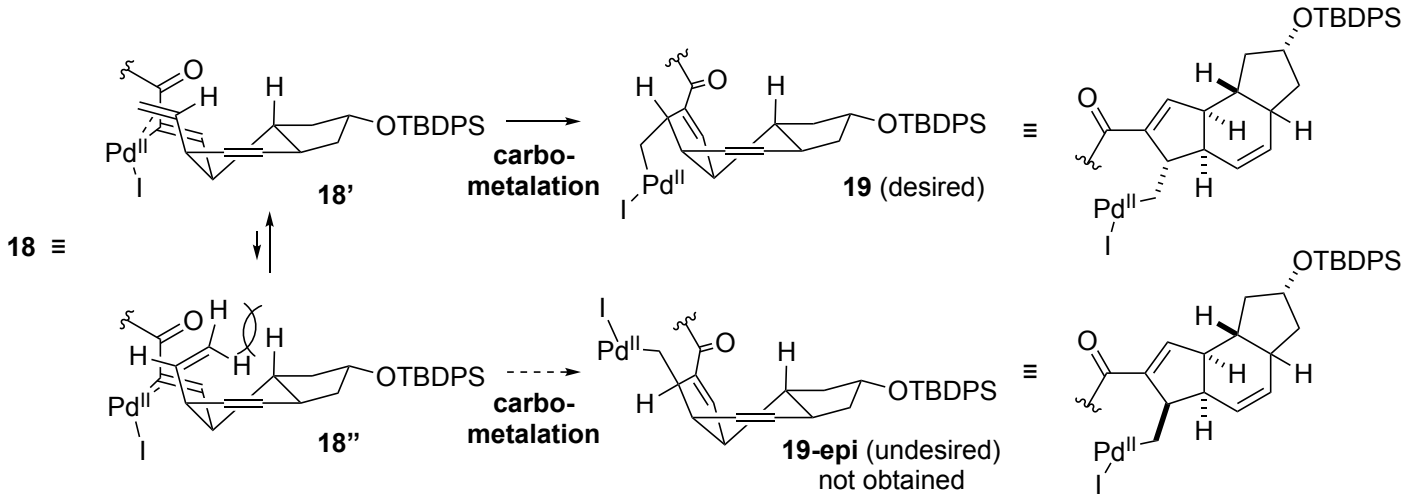


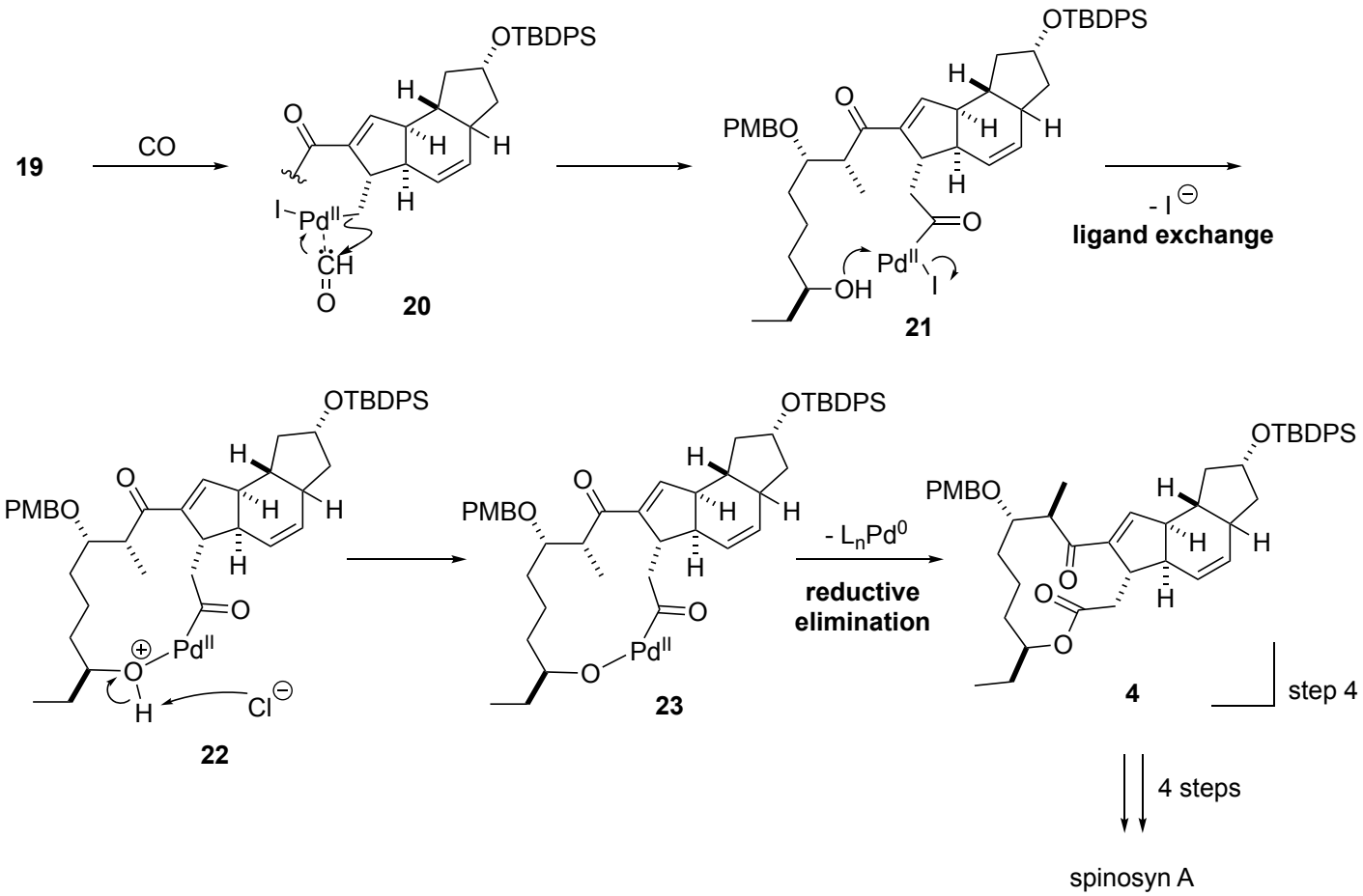
3-2. Mechanisms for *conditions B*





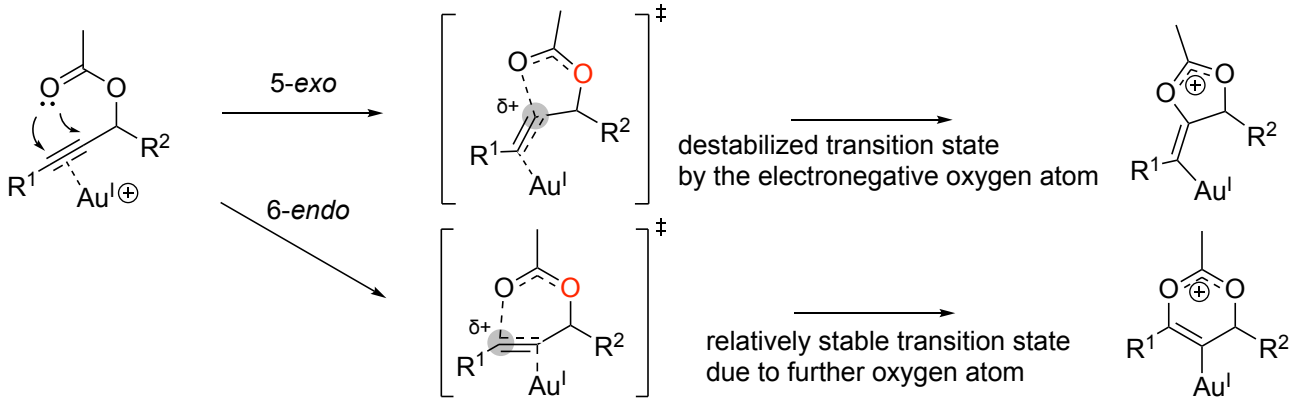




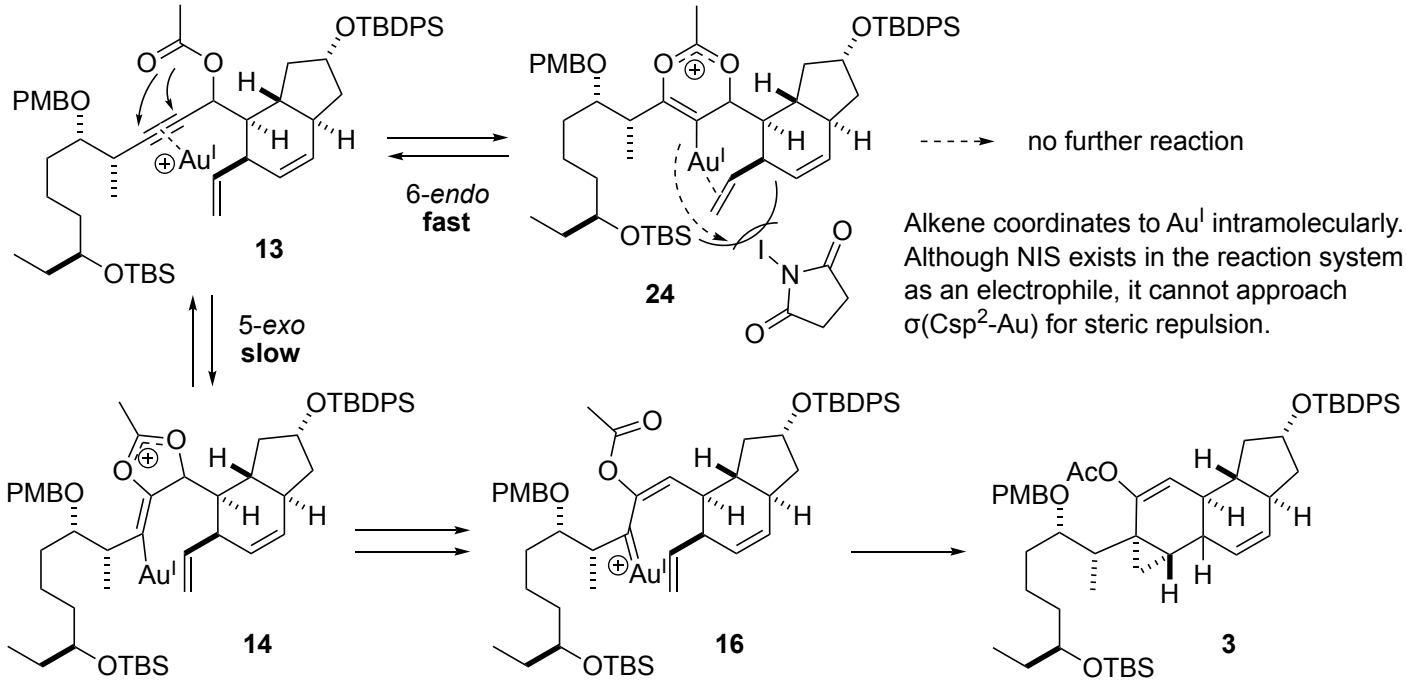


3-3. ***Discussion 2*: gold(I)-catalyzed cyclopropane formation**

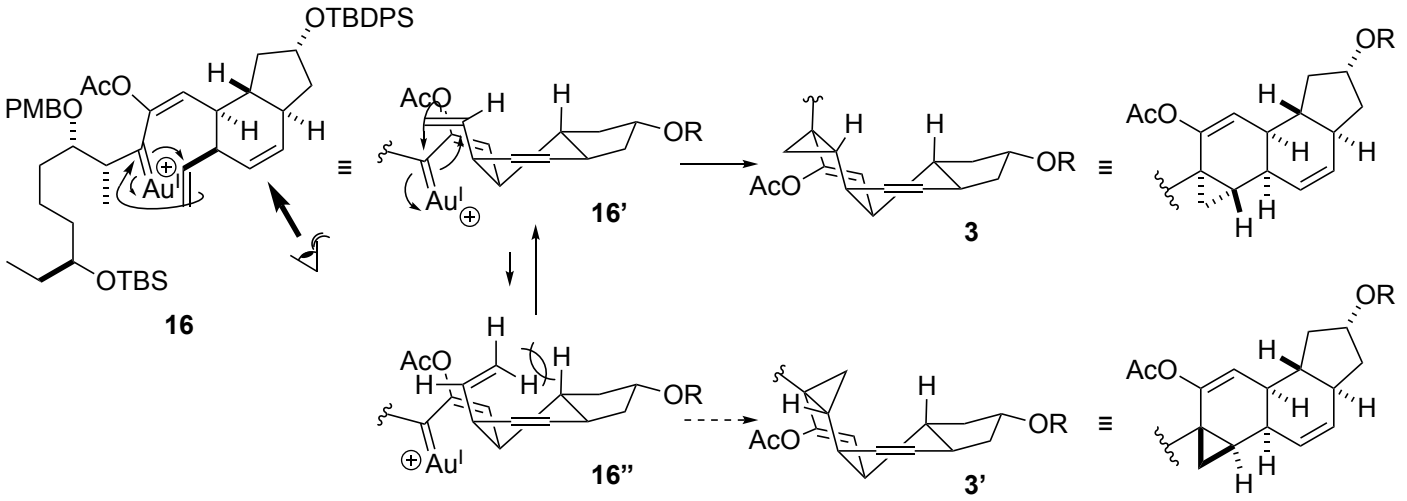
3-3-1. Acetyl migration: 5-*exo* vs 6-*endo*



Considering the electronic destabilization of transition state,
the reaction rate is predicted to be 6-*endo* > 5-*exo* in general.



3-3-2. Stereoselectivity of cyclopropane formation



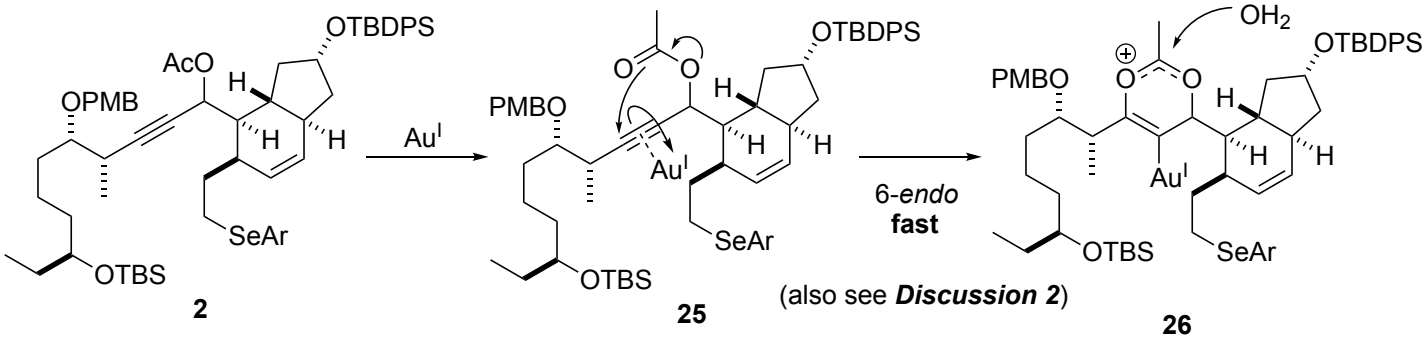
Although the stereochemistry of the cyclopropane was not determined by the authers,
it is proposed that **3** would be the observed structure, with the cyclopropane ring fused downwards.

3-4. ***Discussion 3*: gold(I)-catalyzed reactions avoiding cycloisomerization**

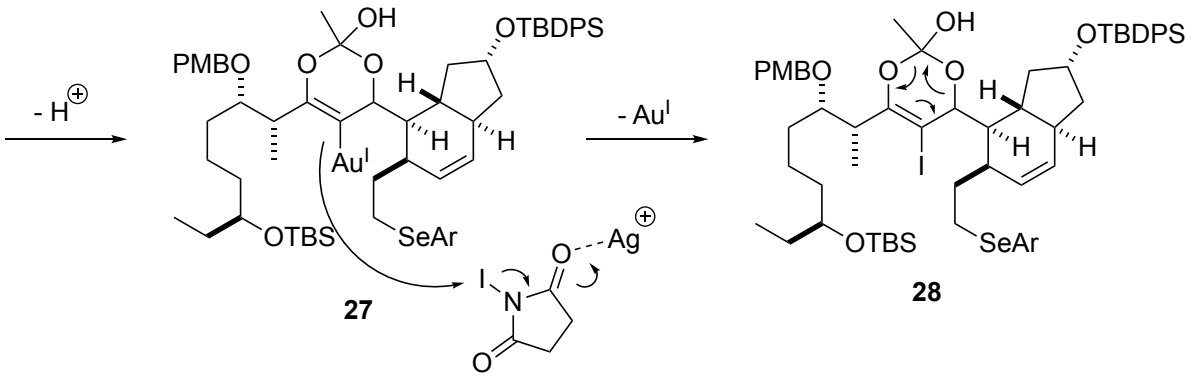
Three reactions occur in a single step;
- *Z*-selective α-iodoenone formation catalyzed by gold(I)
- formation of terminal C=C double bond via the elimination of selenium
- TBS deprotection (deprotected hydroxyl group is necessary in the next macrolactonization step)

Based on the observation that the existence of terminal alkene inhibited the formation of α-iodoenone and formed undesired cyclopropane via carbenoid generation (transformation **2** -> **3**), iodization should have occured before the alkene formation.

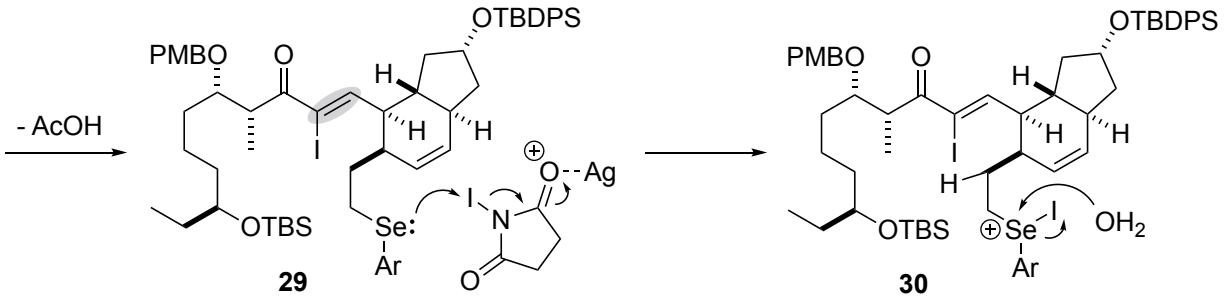
Reaction mechanisms:



2 **25** **26**

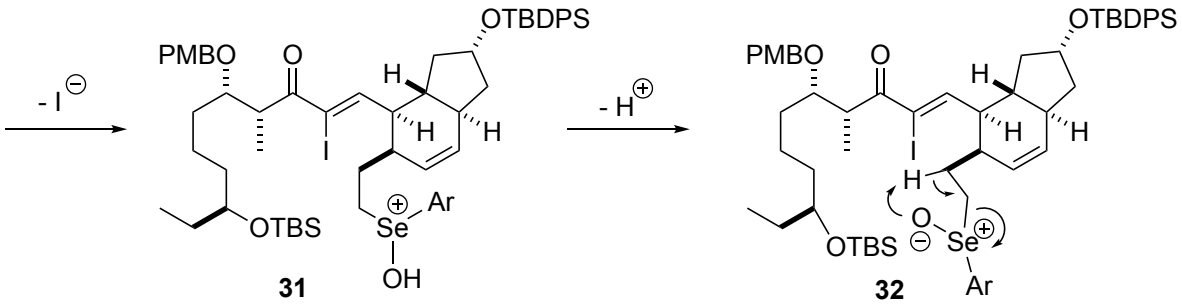


27 **28**

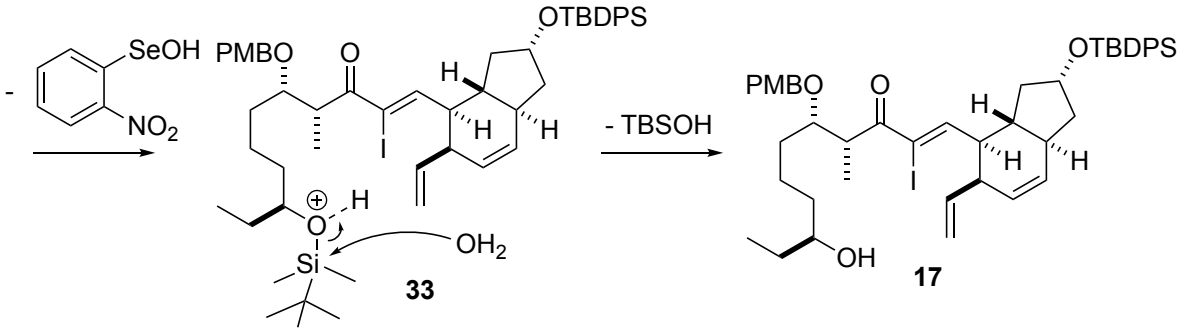


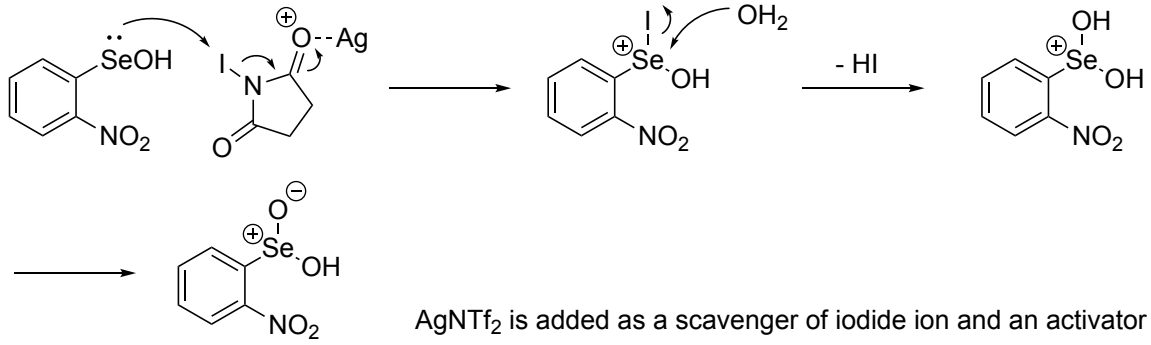
29 **30**

Z-isomer is formed selectively.



31 **32**





$AgNTf_2$ is added as a scavenger of iodide ion and an activator of NIS.