

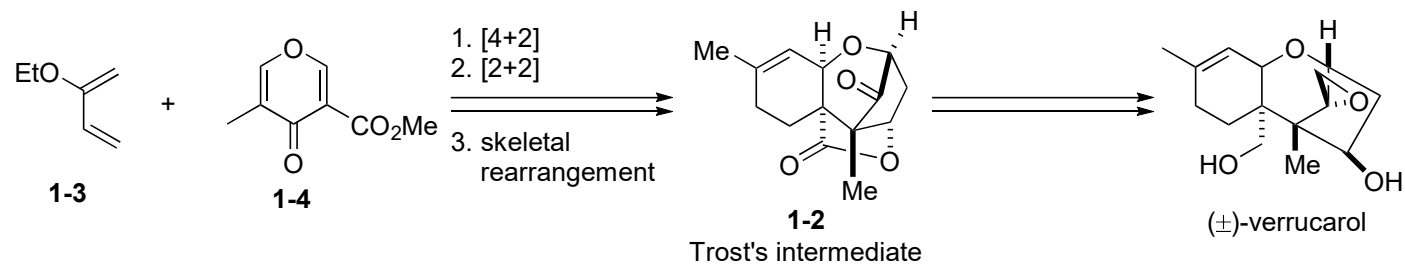
## Problem Session (4)

2019. 6. 22. Tsukasa Shimakawa

**Topic:** Construction of bicyclo [3.2.1] octane skeleton

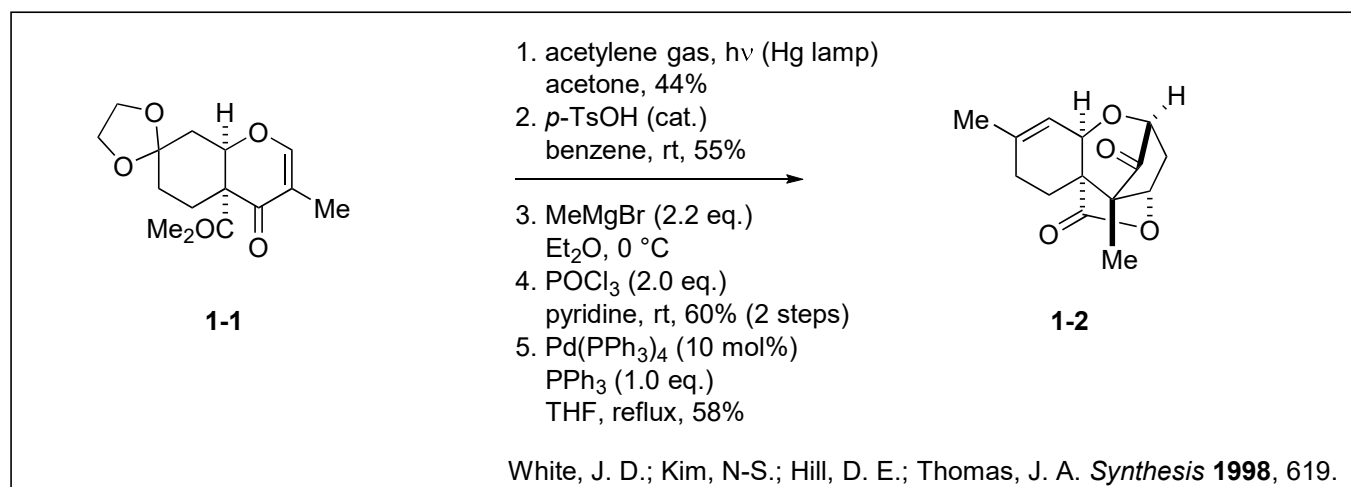
### 1. Formal total synthesis of ( $\pm$ )-verrucarol

#### 1-1. Synthetic plan

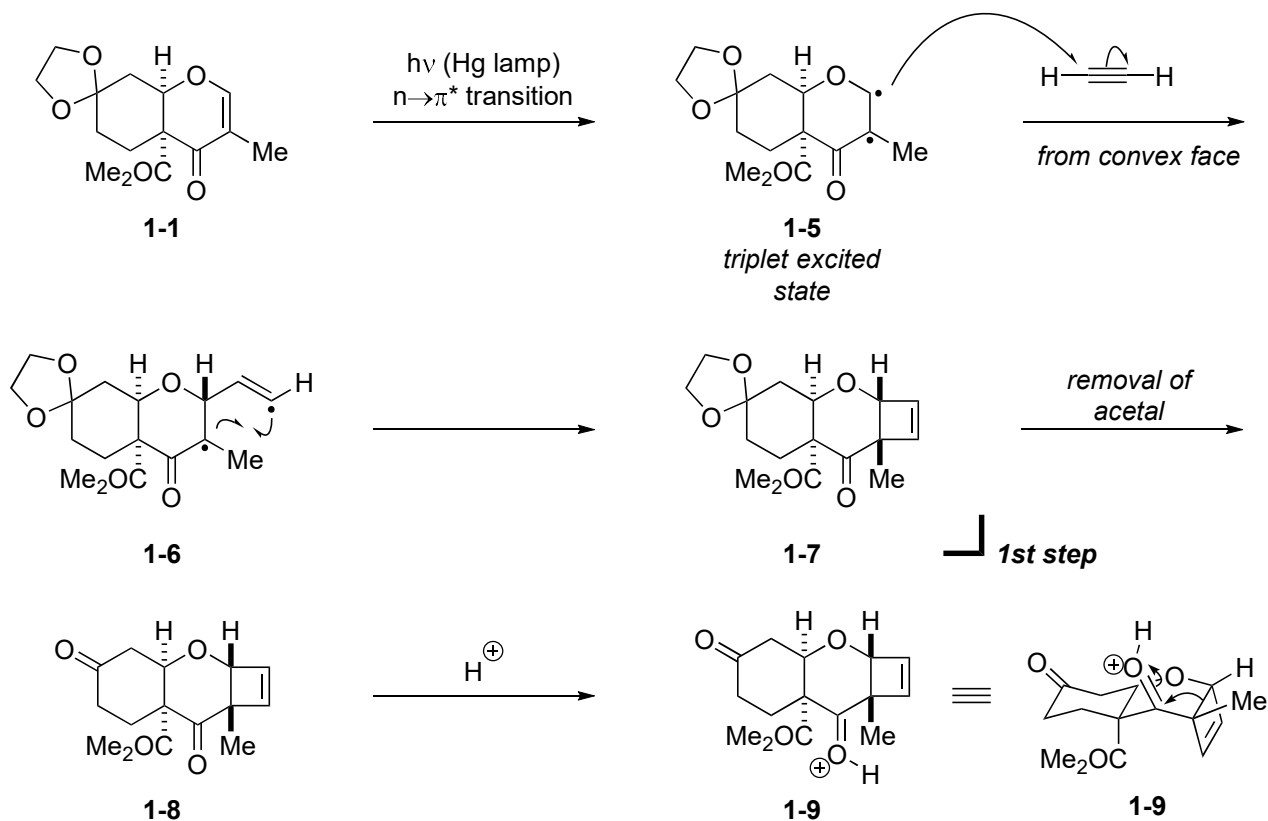


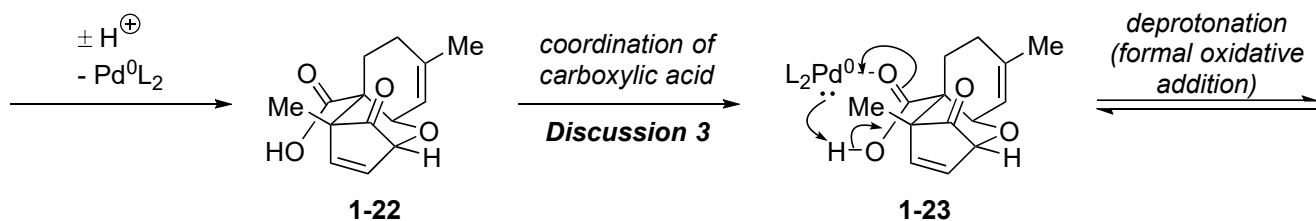
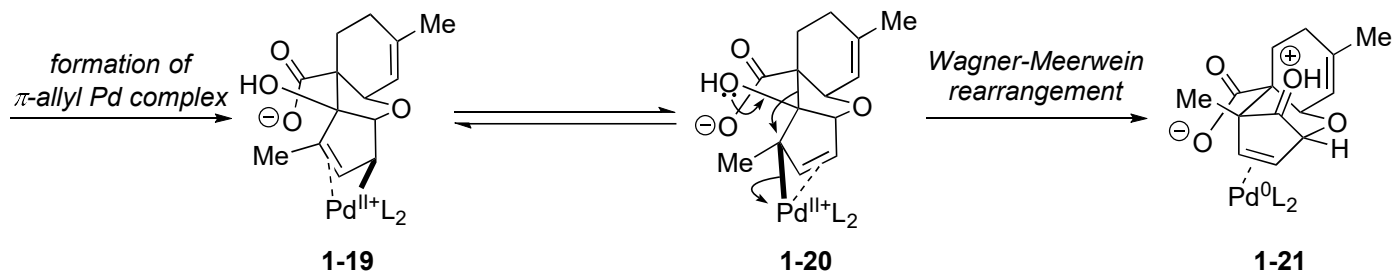
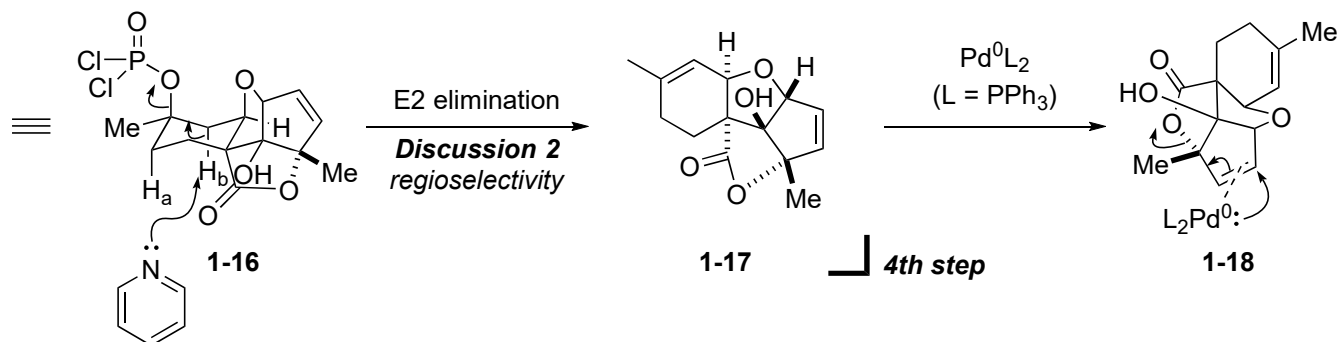
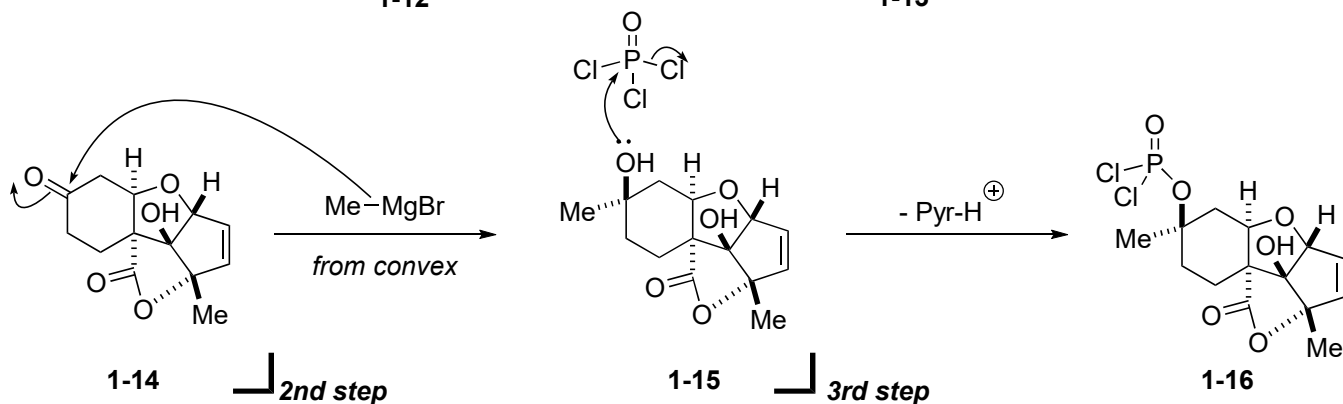
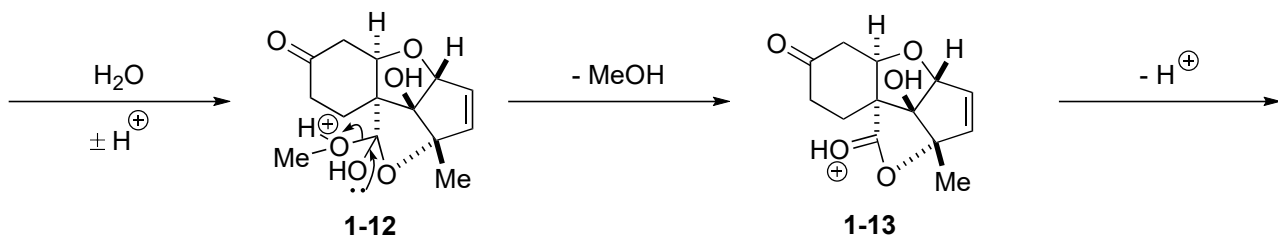
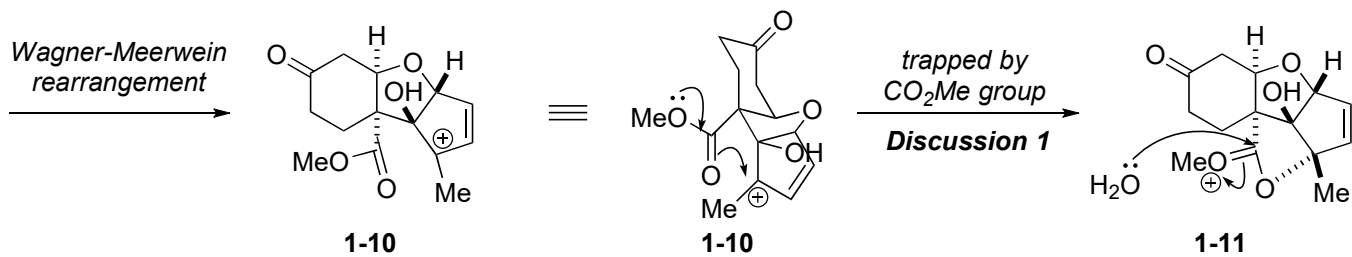
Trost, B. M. et al. *J. Am. Chem. Soc.* **1984**, *106*, 383.

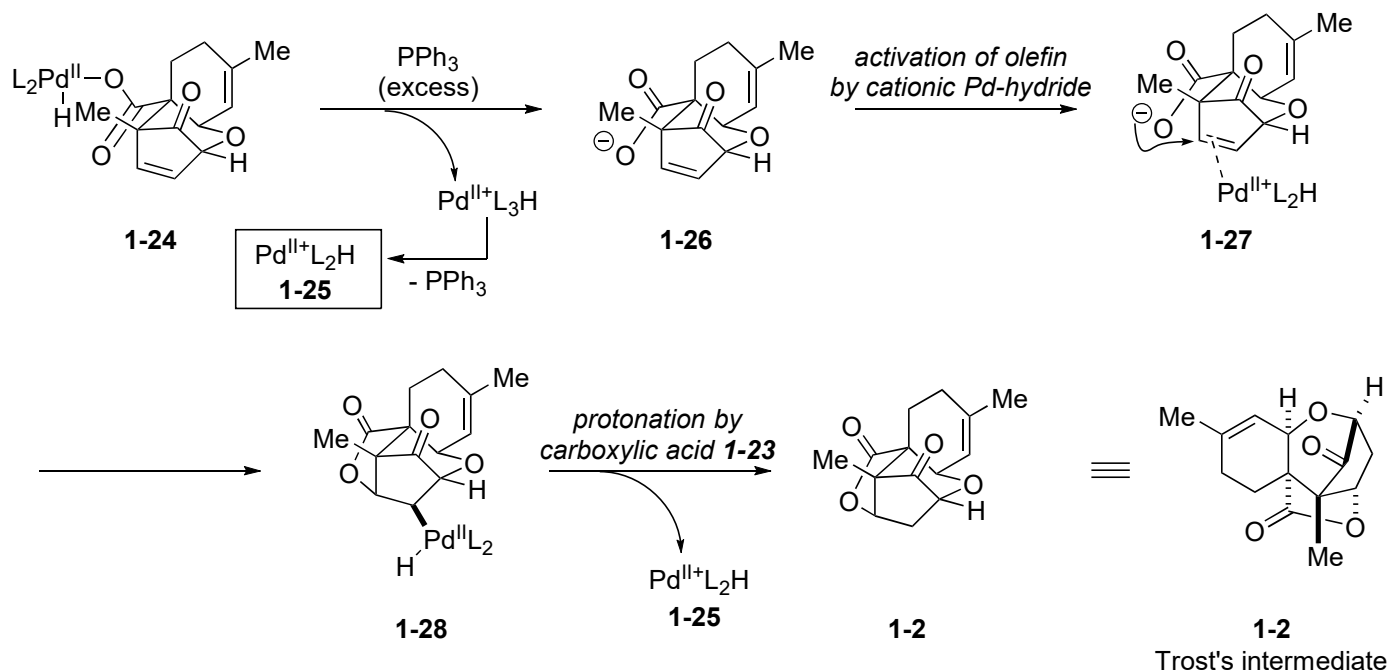
#### 1-2. Reaction mechanism



**Key reaction:** Pd(0) catalyzed skeletal rearrangement-lactonization



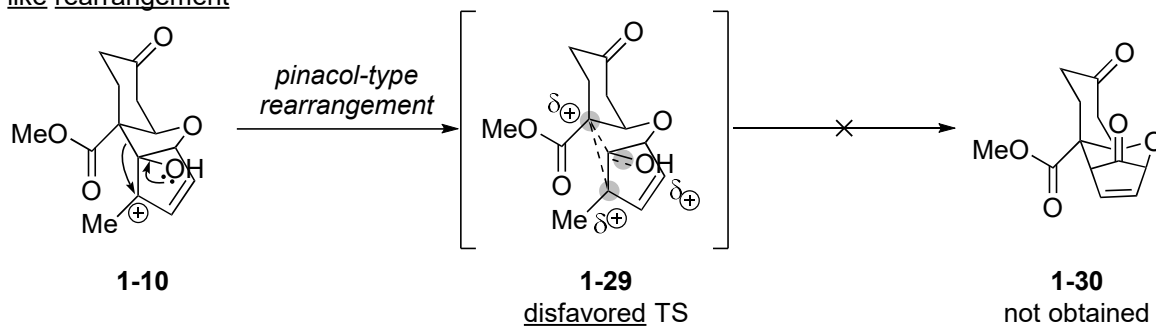




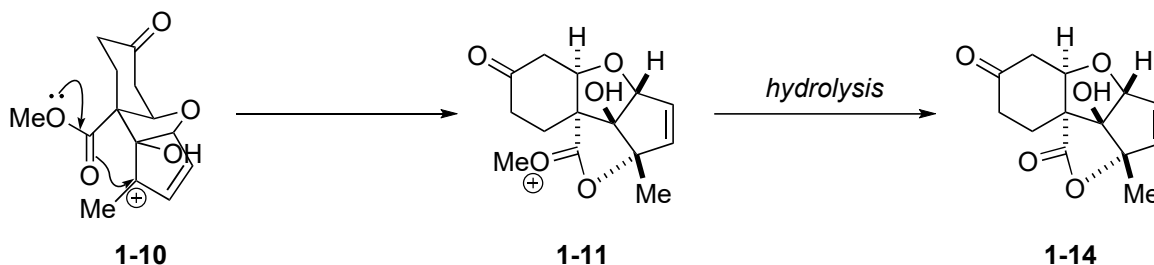
### 1-3. Discussion

#### 1-3-1. Pinacol like rearrangement vs interruption by methoxycarbonyl group

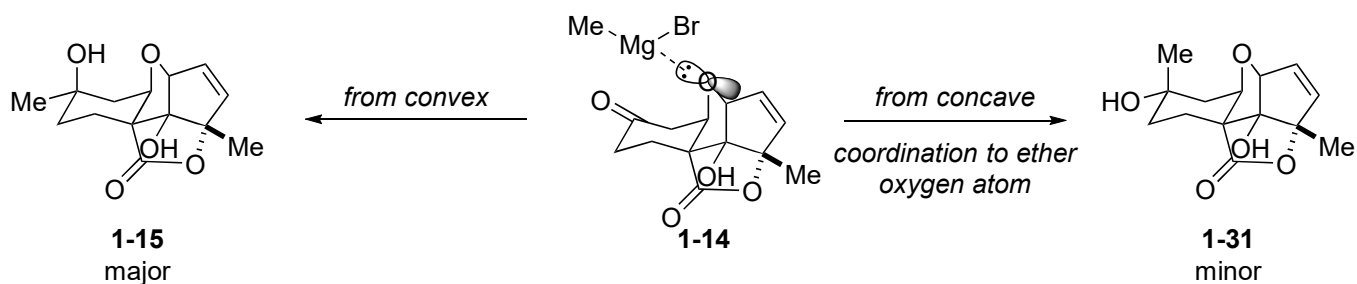
##### A) Pinacol like rearrangement



##### B) Interrupted pinacol type rearrangement



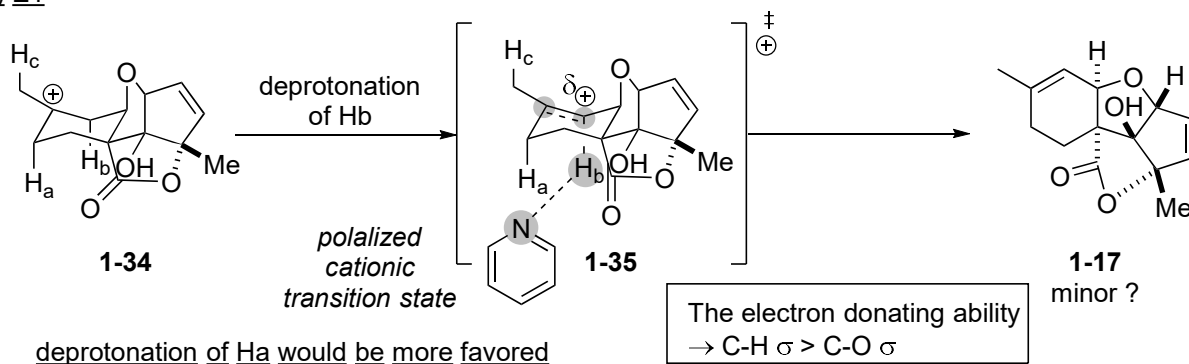
#### 1-3-2. Addition of methyl magnesium bromide and dehydration



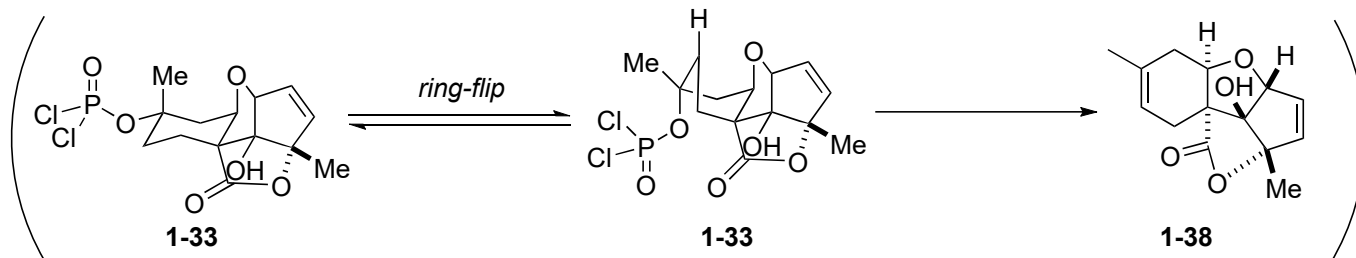
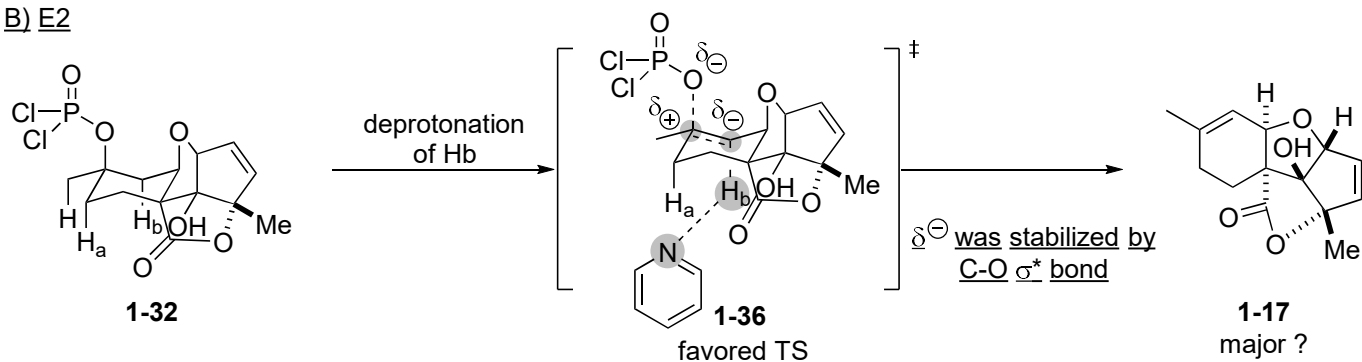
In the original article, the diastereomeric ratio was not mentioned.

→ From the result of next dehydration step, **1-15** would be the major product.

A) E1



B) E2

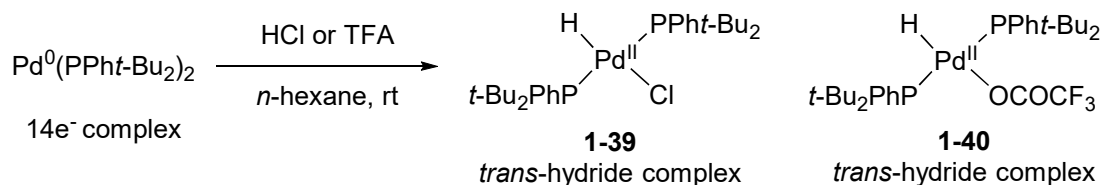


From **1-33**, undesired **1-38** would be the major product.

1-3-2. Lactonization catalyzed by Pd(0) specie

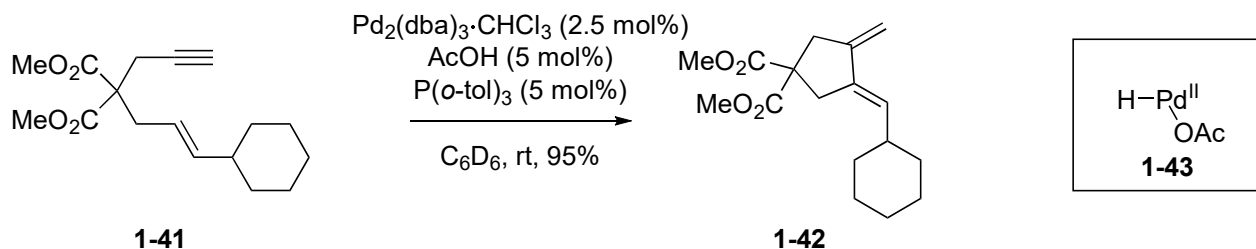
Pd(II)-hydride catalyzed mechanism would be rational.

a) Example for oxidative addition of strong acid



Yoshida, T. and Otsuka, S. *J. Am. Chem. Soc.* **1977**, 99, 2134.

b) Pd(0) and AcOH catalyzed cycloisomerization reaction reported by Trost's group

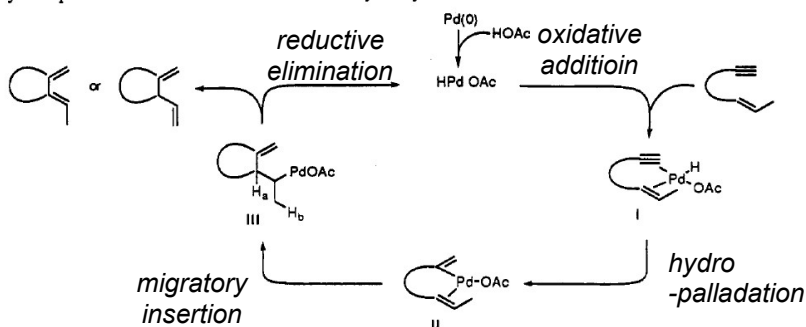


This cycloisomerization was found to proceed via Pd<sup>II</sup> specie **1-43**.

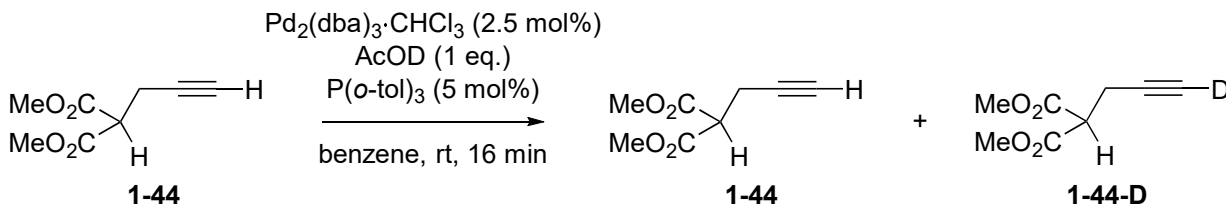
Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, 116, 4268.  
See also PS\_170617\_Takumi\_Fukuda

Proposed mechanism for AcOH mediated cycloisomerization

**Scheme 1.** Hydridopalladium Acetate Mechanism for Enyne Cycloisomerization

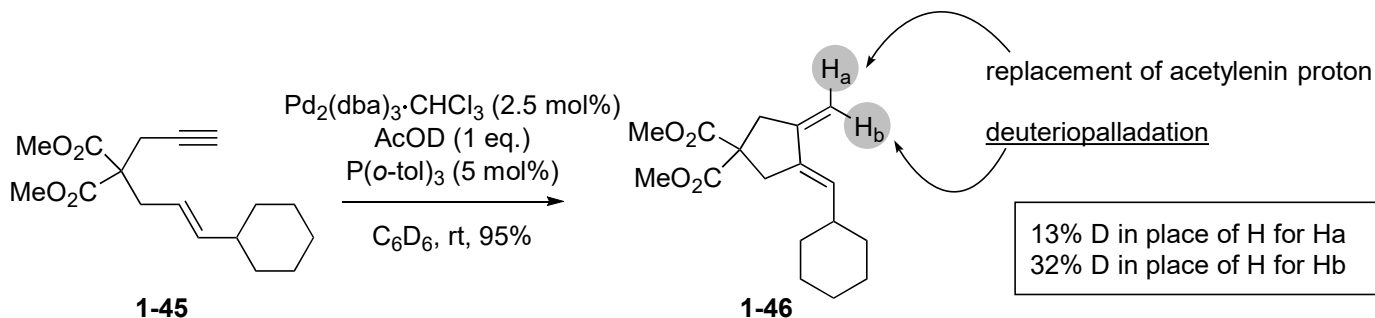


Deuterium experiment

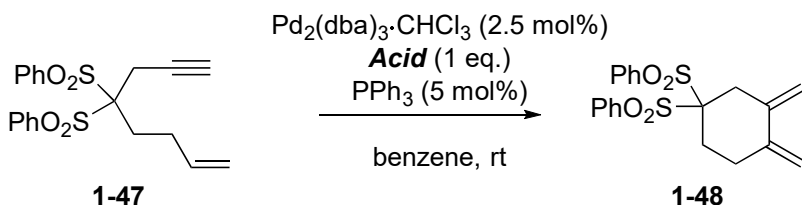


replacement of acetylenin proton was observed

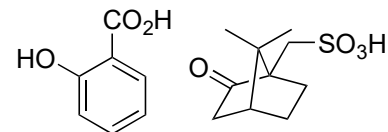
$1\text{-44}/1\text{-44-D} = 33/66$



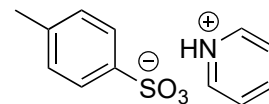
Effect of acid



entry	Acid	result	entry	Acid	result
1	AcOH (pKa: 4.76)	62%	4	mandelic acid (pKa: 3.85)	60-63%
2	$\text{CF}_3\text{CO}_2\text{H}$ (pKa: -0.25)	60-63%	5	PPTS (pKa: 5.21)	failed
3	$\text{HCO}_2\text{H}$ (pKa: 3.77)	60-63%	6	CSA (pKa: 1.2)	failed



mandelic acid CSA



PPTS

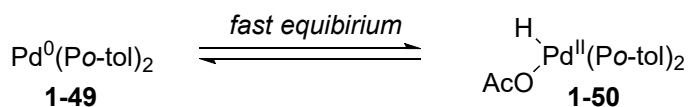
No  $\text{pK}_a$  matter for oxidative addition of acid to Pd(0) specie

→ coordination to Pd(0) complex would be important in this oxidative addition

O coordination → deprotonation mechanism

X deprotonation → coordination mechanism

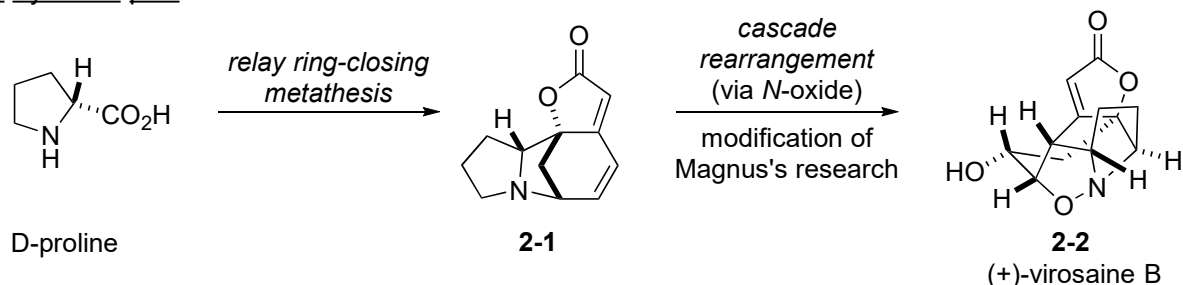
c) The role of excess amount of  $\text{PPh}_3$  ligand



This oxidative addition was known to be fast and reversible from  $^1\text{H}$  NMR experiment

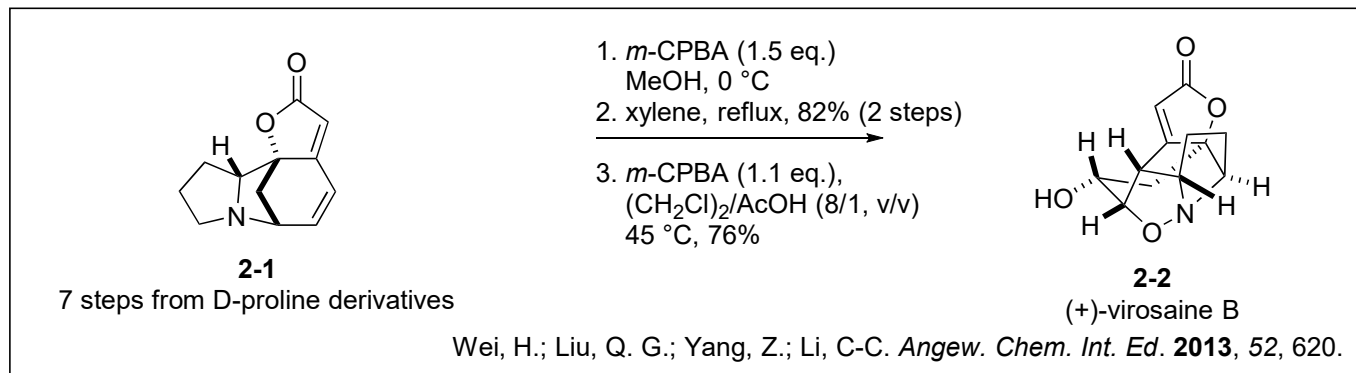
## 2. Total synthesis of (+)-virosaine B by Chuang-chuang Li's group

### 2-1. Synthetic plan

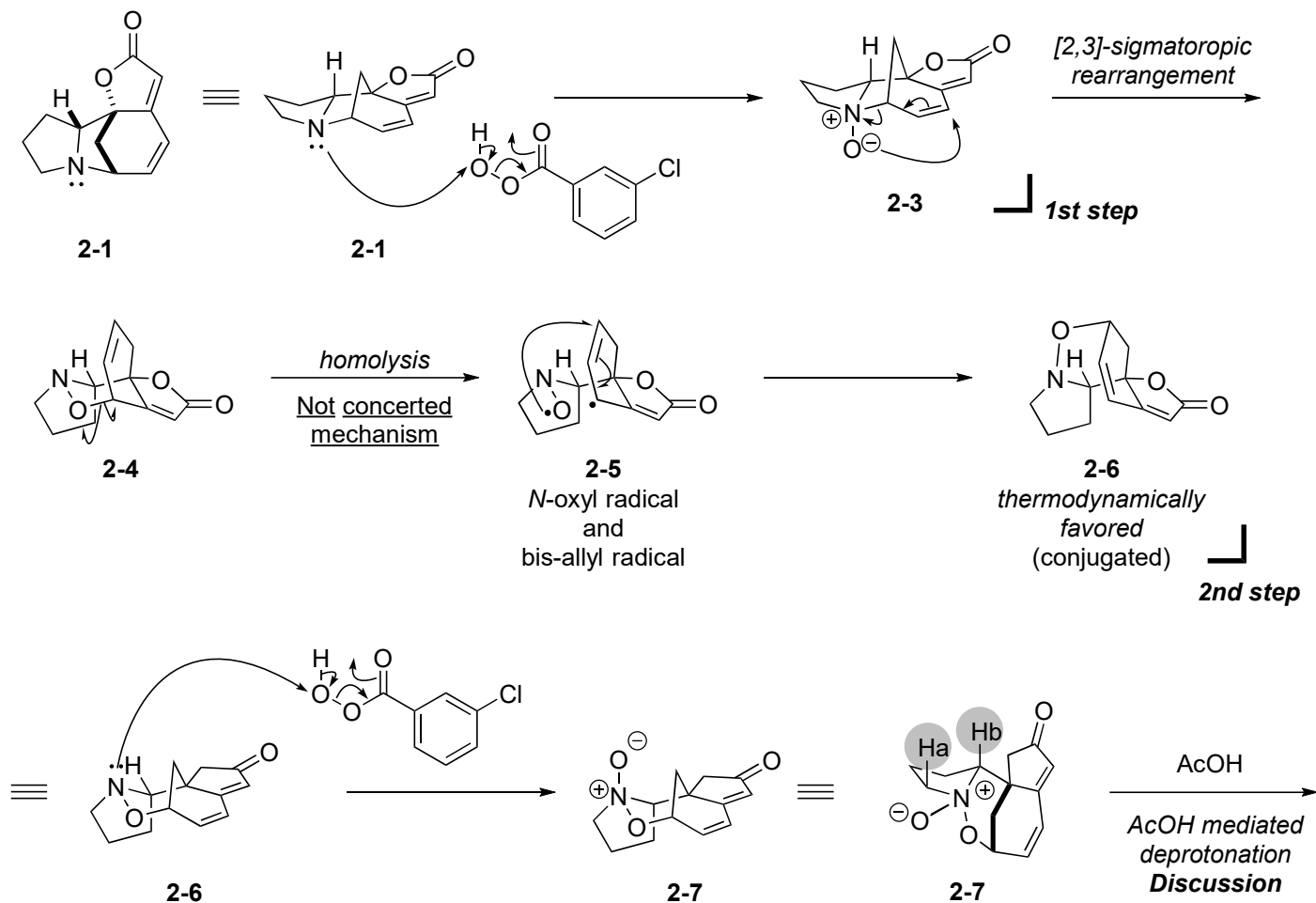


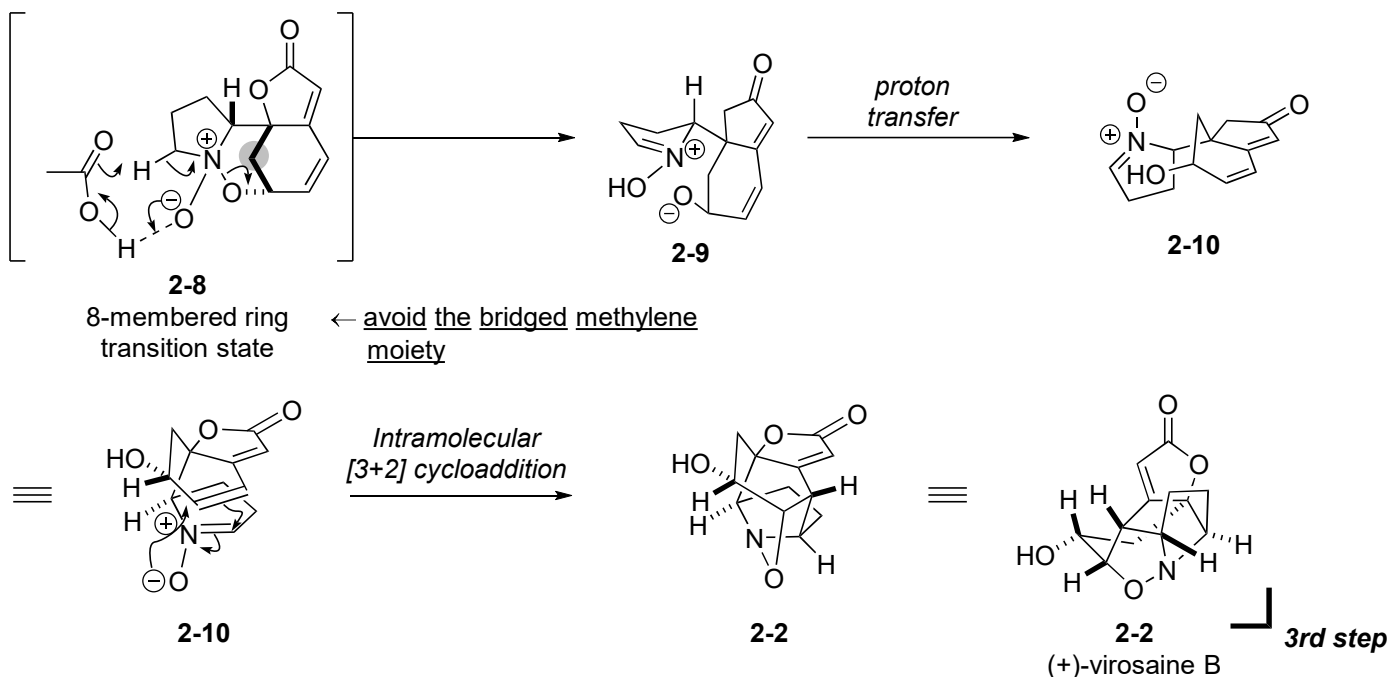
Magnus, P. et al. *Tetrahedron* **1993**, 49, 8059.

### 2-2. Reaction mechanism



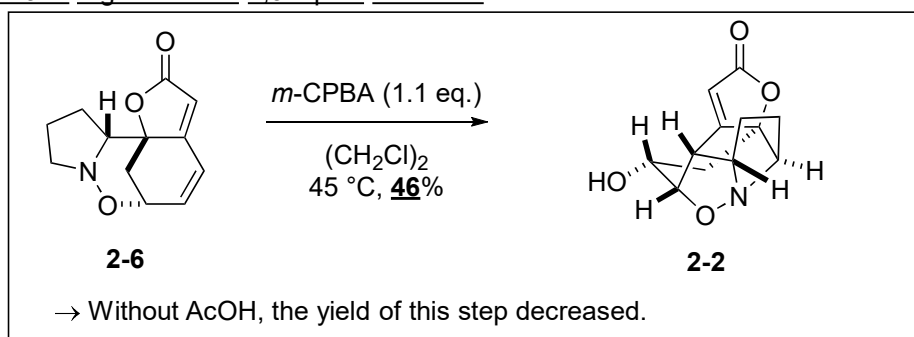
**Key reaction:** tandem sigmatropic rearrangement ([2,3] and formal [1,3] rearrangement)



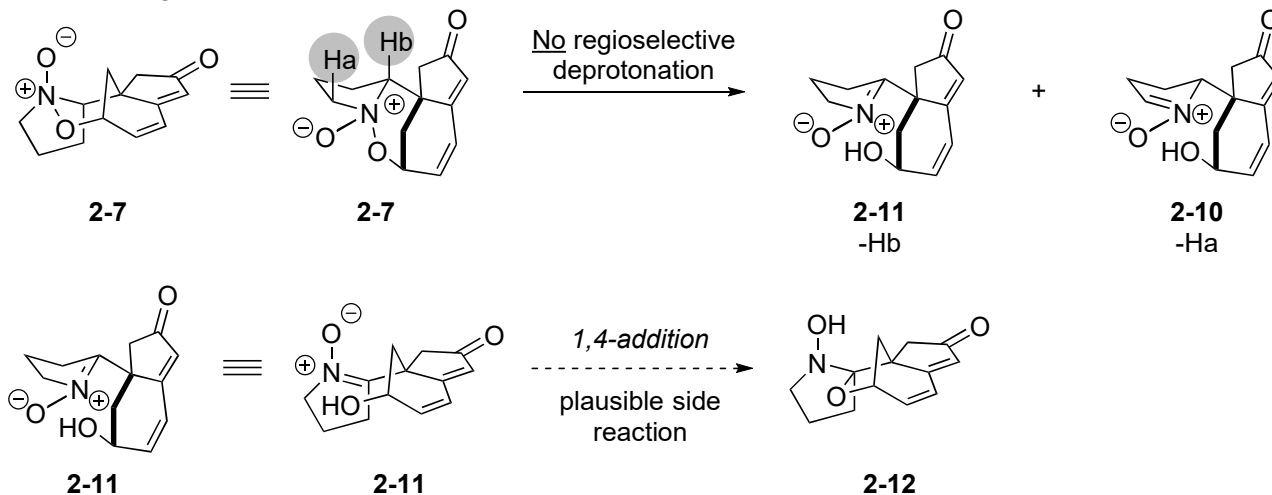


### 2-3. Discussion

#### 2-3-1. regioselective 1,3-dipole formation



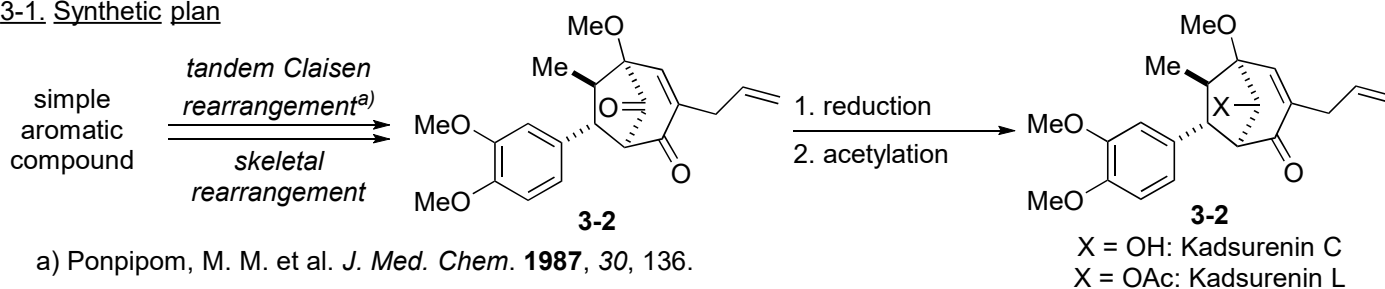
<Without AcOH>



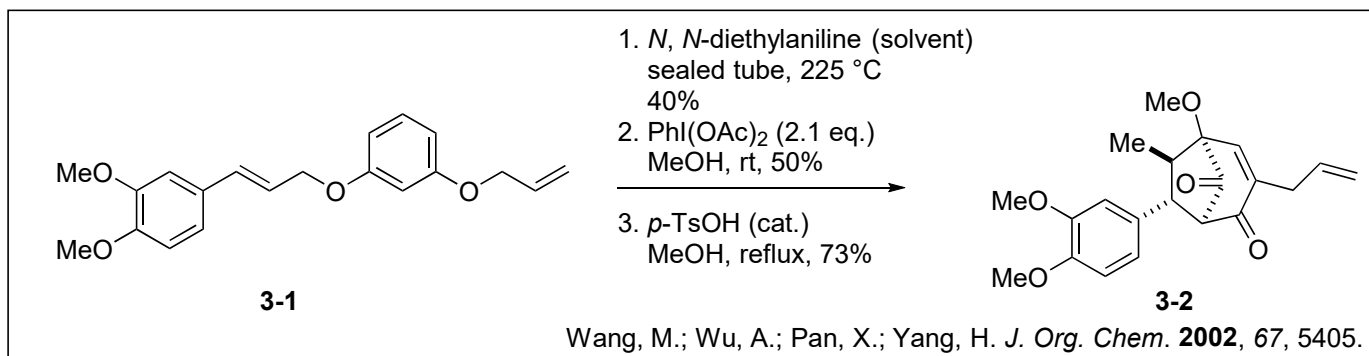
One of the plausible side reactions is 1,4-addition to afford **2-12** (Magnus, P. et al. *Tetrahedron Lett.* **1993**, 49, 8059.)

### 3. Total synthesis of (+)-Kadsurenin C and (+)-Kadsurenin L

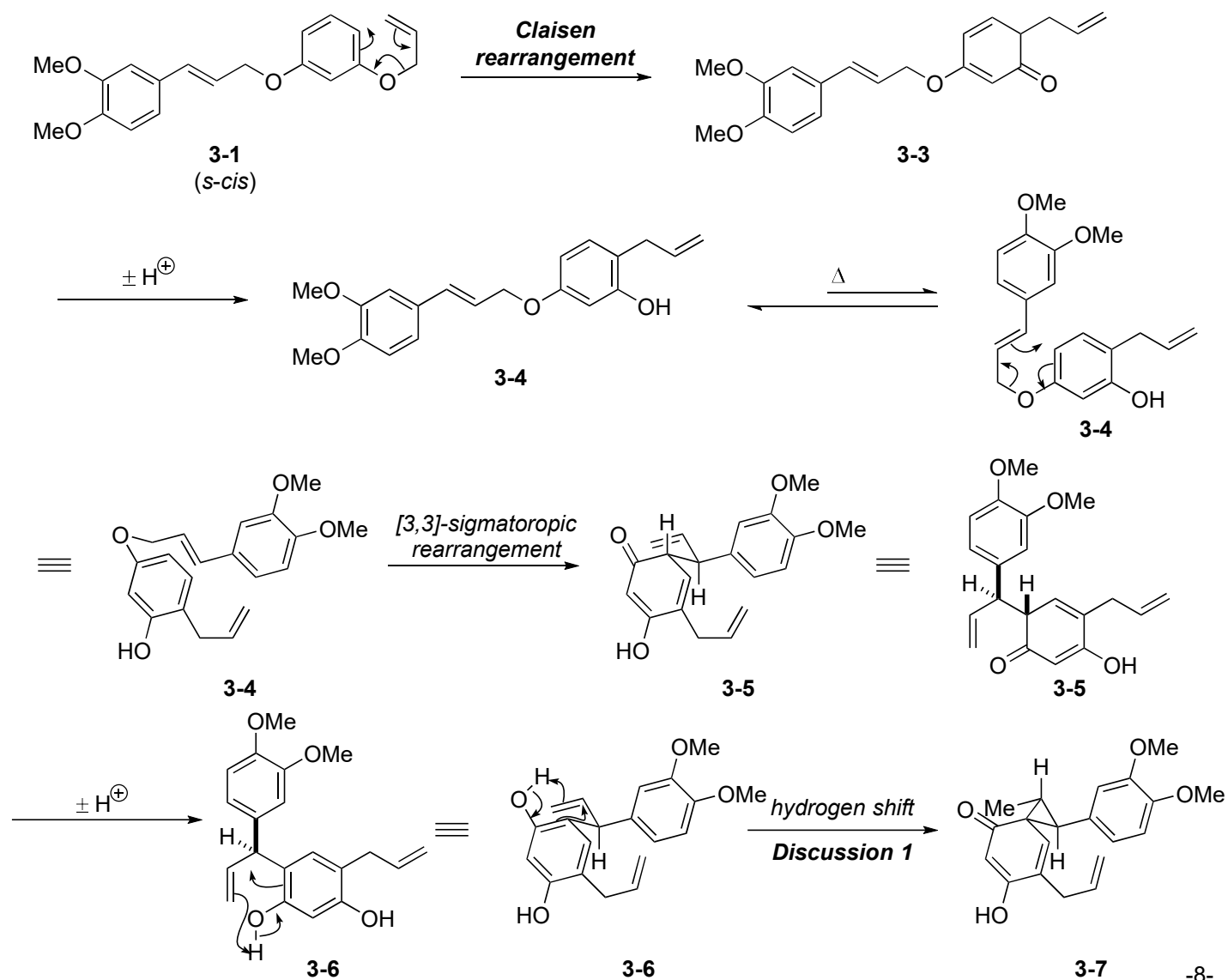
#### 3-1. Synthetic plan



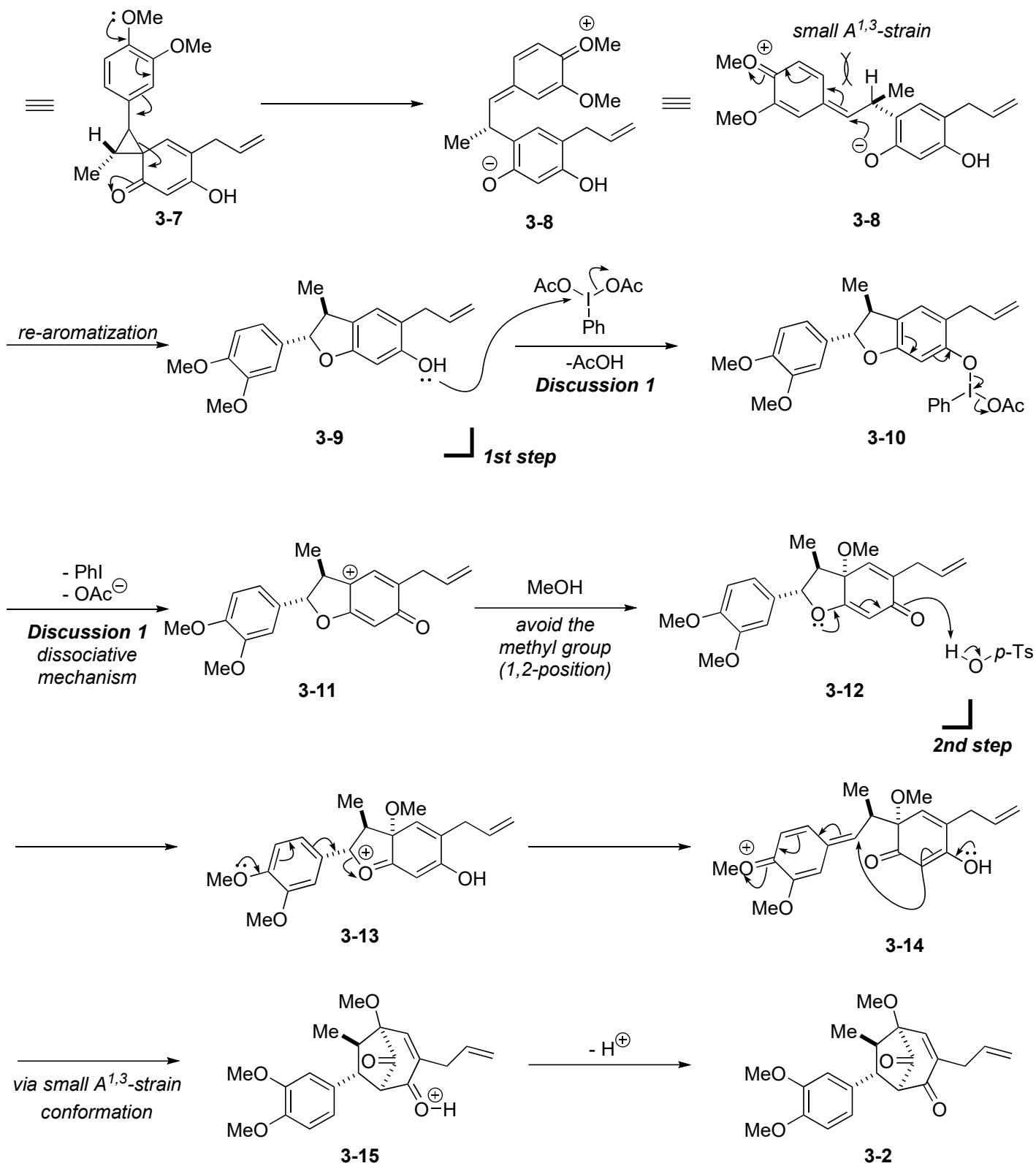
#### 3-2. Reaction mechanism



**Key reaction:** Interrupted abnormal Claisen rearrangement



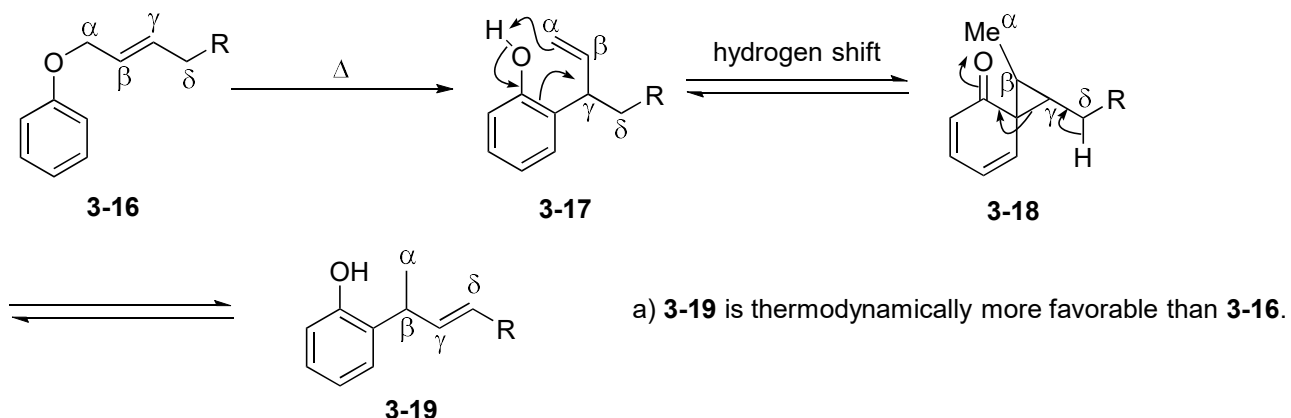




### 3-3. Discussion

#### 3-3-1. Abnormal Claisen rearrangement

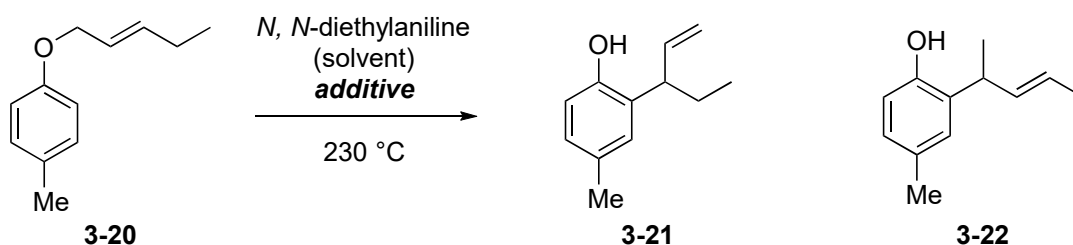
Claisen rearrangement bearing  $\gamma$ -alkyl substituent



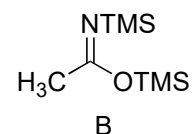
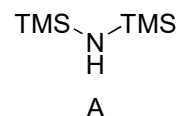
Stepwise mechanism including "hydrogen-shift" is widely accepted

Roberts, R. M.; Landolt, R. G.; Greene, R. N.; Heyer, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 1404.

#### Support for the hydrogen-shift including stepwise mechanism



entry	additive	time	result
1	none	5.5 h	63% <b>3-21</b> : <b>3-22</b> = 58 : 42
2	A	8.0 h	70% <b>3-21</b> : <b>3-22</b> = >99 : <1
3	B	4.5 h	81% <b>3-21</b> : <b>3-22</b> = >99 : <1



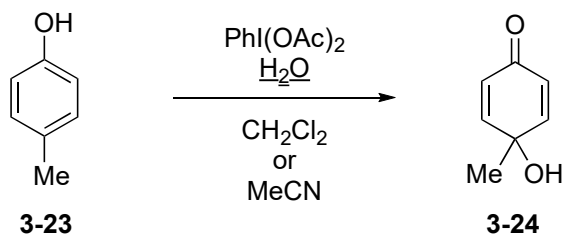
silylating reagent A and B can trap the intermediate **3-21** by silylation  
 → prevent the hydrogen shift and block abnormal Claisen rearrangement

Fukuyama, T.; Li, T.; Peng, G. *Tetrahedron Lett.* **1994**, *35*, 2145.

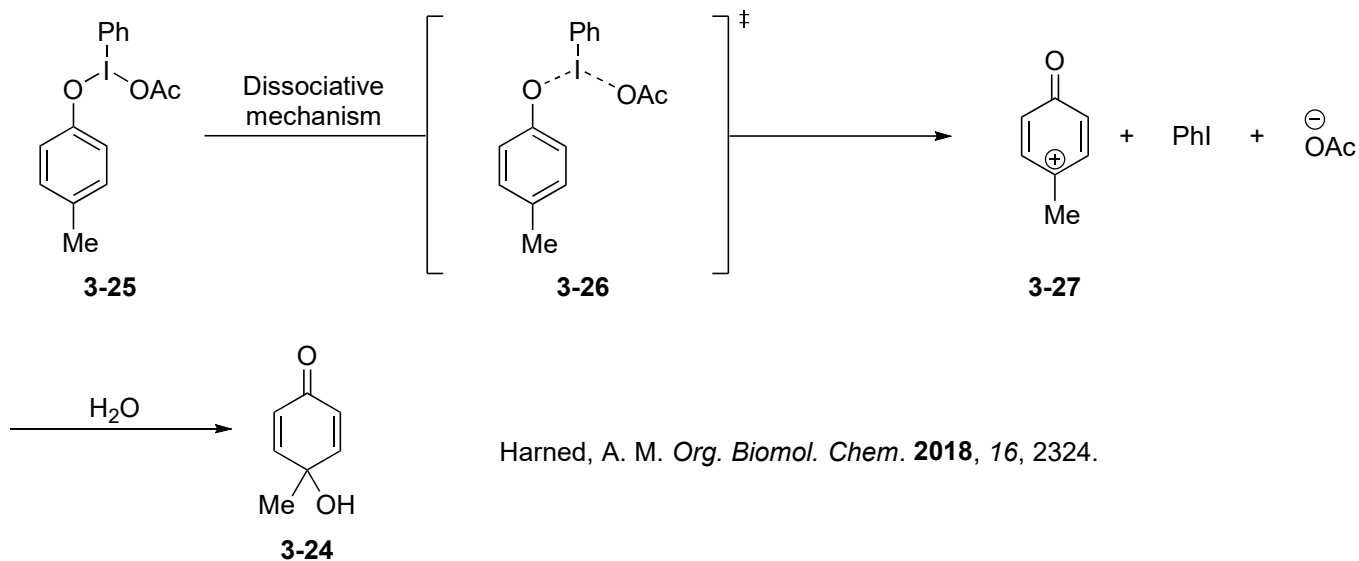
#### 3-3-2. Oxidative dearomatization

##### a) in case of phenol

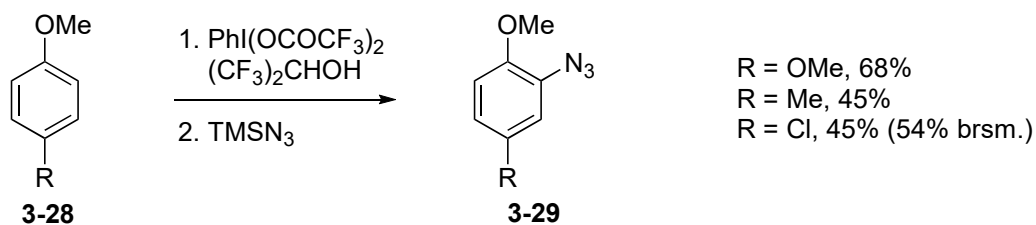
In case of phenol, phenolic OH group first react to an iodine center (ligand exchange of iodine center).  
 (Formation of CT complex vs reaction of phenolic OH group)



Dissociative mechanism was found to be more favorable by Harned group → generation of cationic intermediate



cf. Oxidative dearomatization of phenol ethers



Kita reported this hypervalent iodine-induced nucleophilic substitution occurred via the radical cation intermediate.

