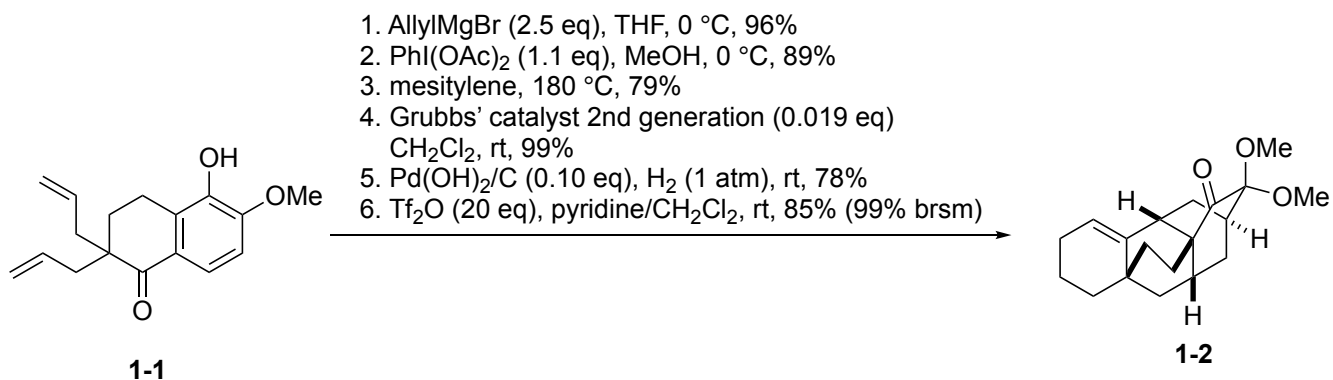


# Problem session (1)

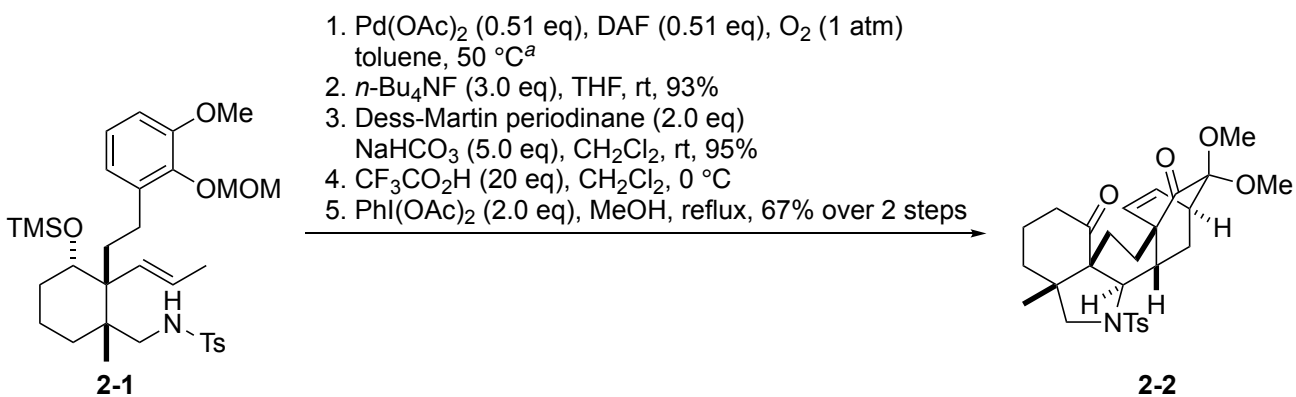
2022/12/17 Mizuki Sawada

Please provide the mechanisms for the following reactions.

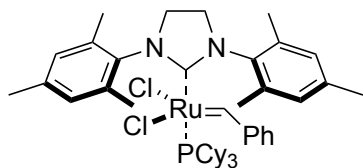
## Problem 1



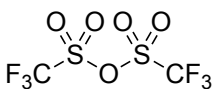
## Problem 2



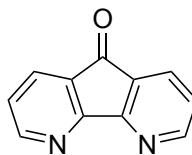
<sup>a</sup> Two diastereomers were obtained (major one: 54%, minor one: 22%).  
Only the major diastereomer was used for the next reaction.



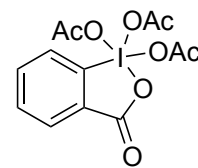
Grubbs' catalyst  
2nd generation



Tf<sub>2</sub>O



DAF

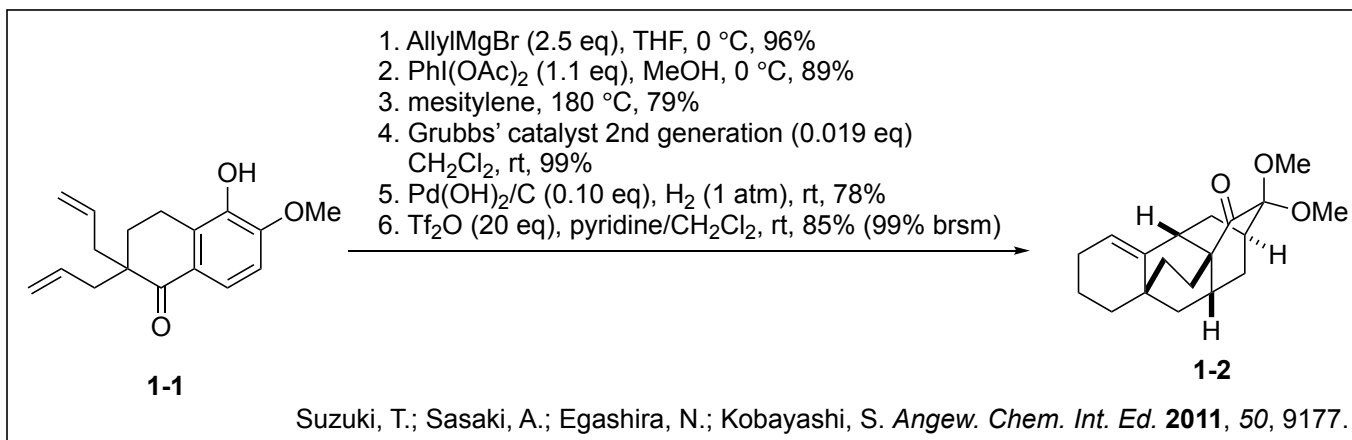


Dess-Martin periodinane

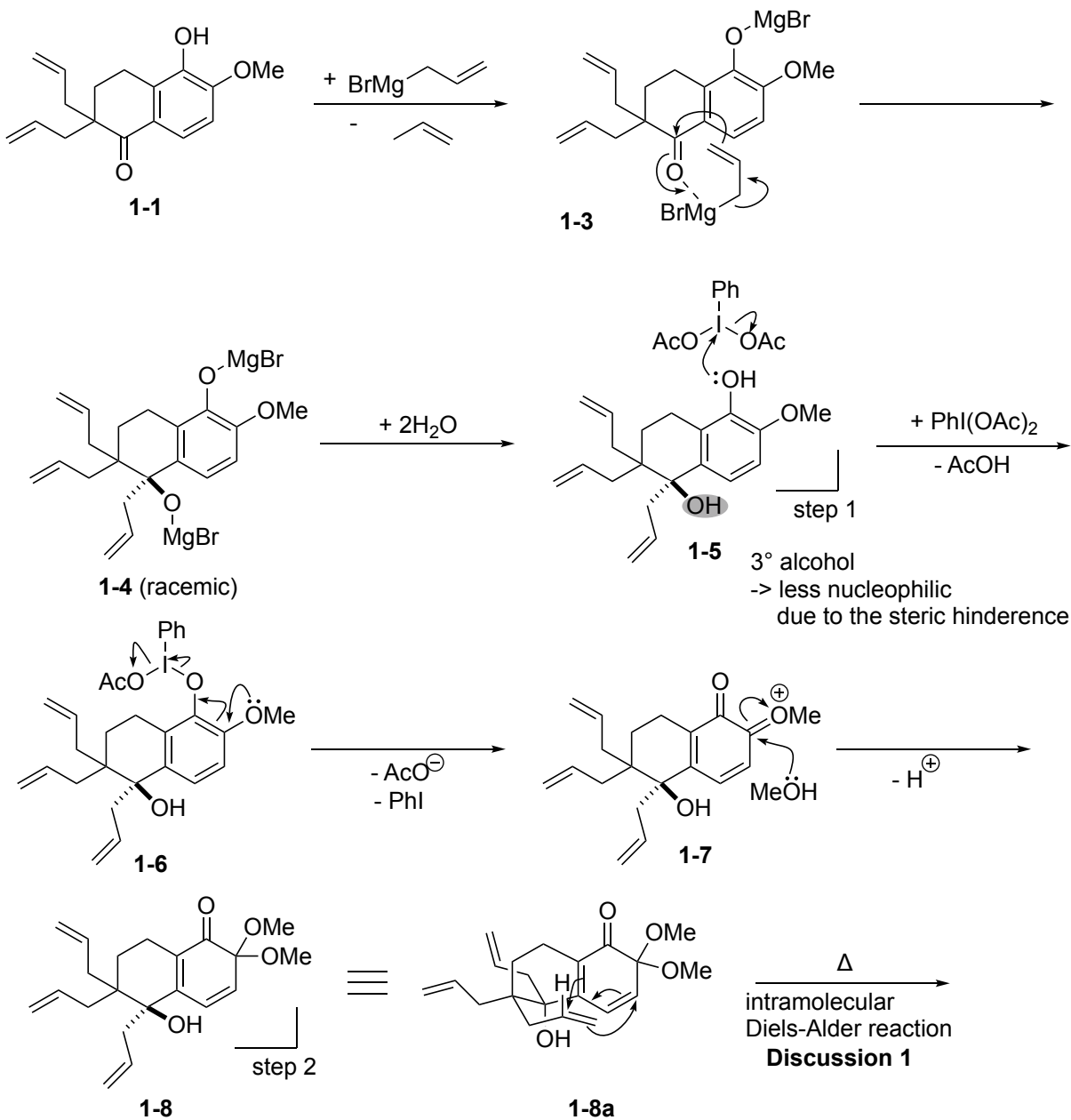
# Problem session (1) -answer-

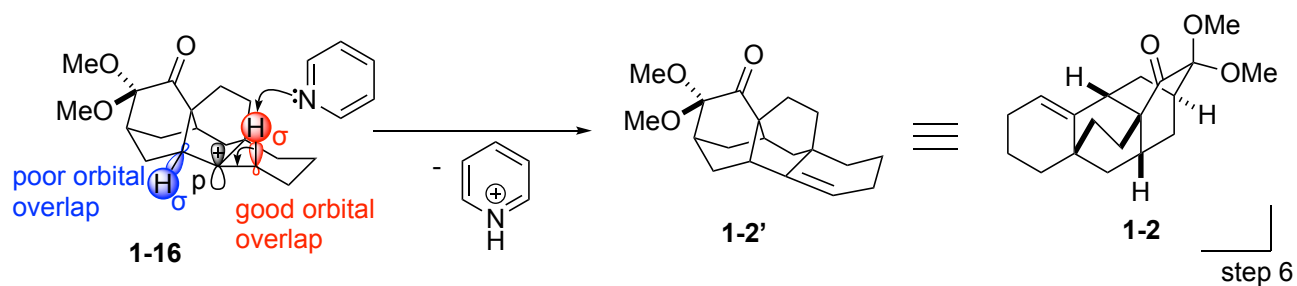
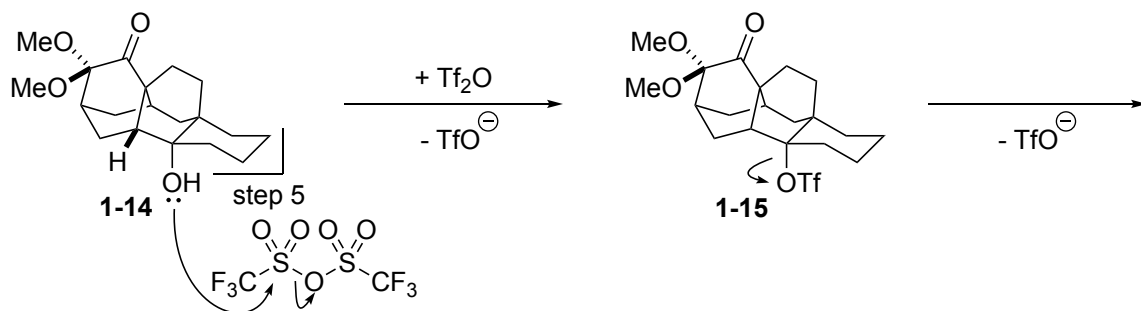
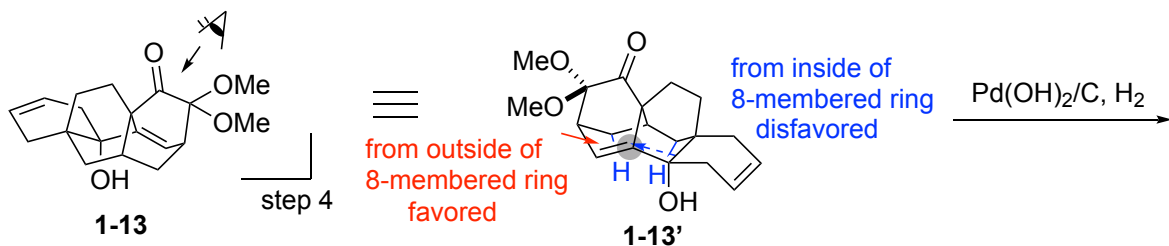
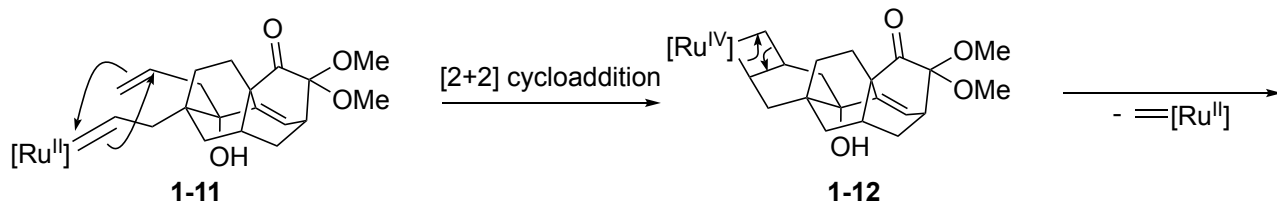
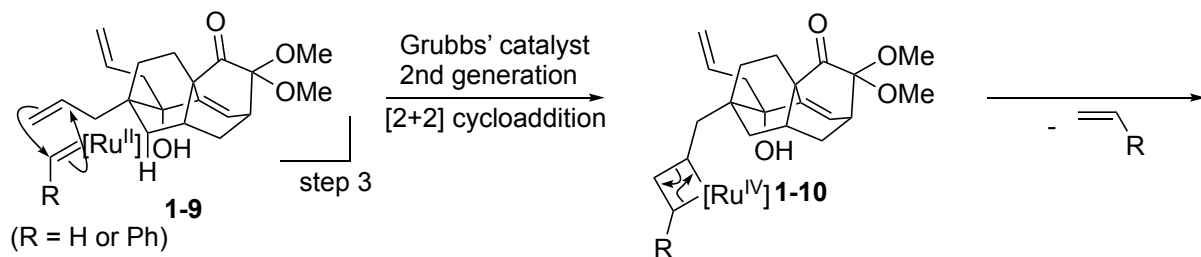
2022/12/17 Mizuki Sawada

## 1. Problem 1

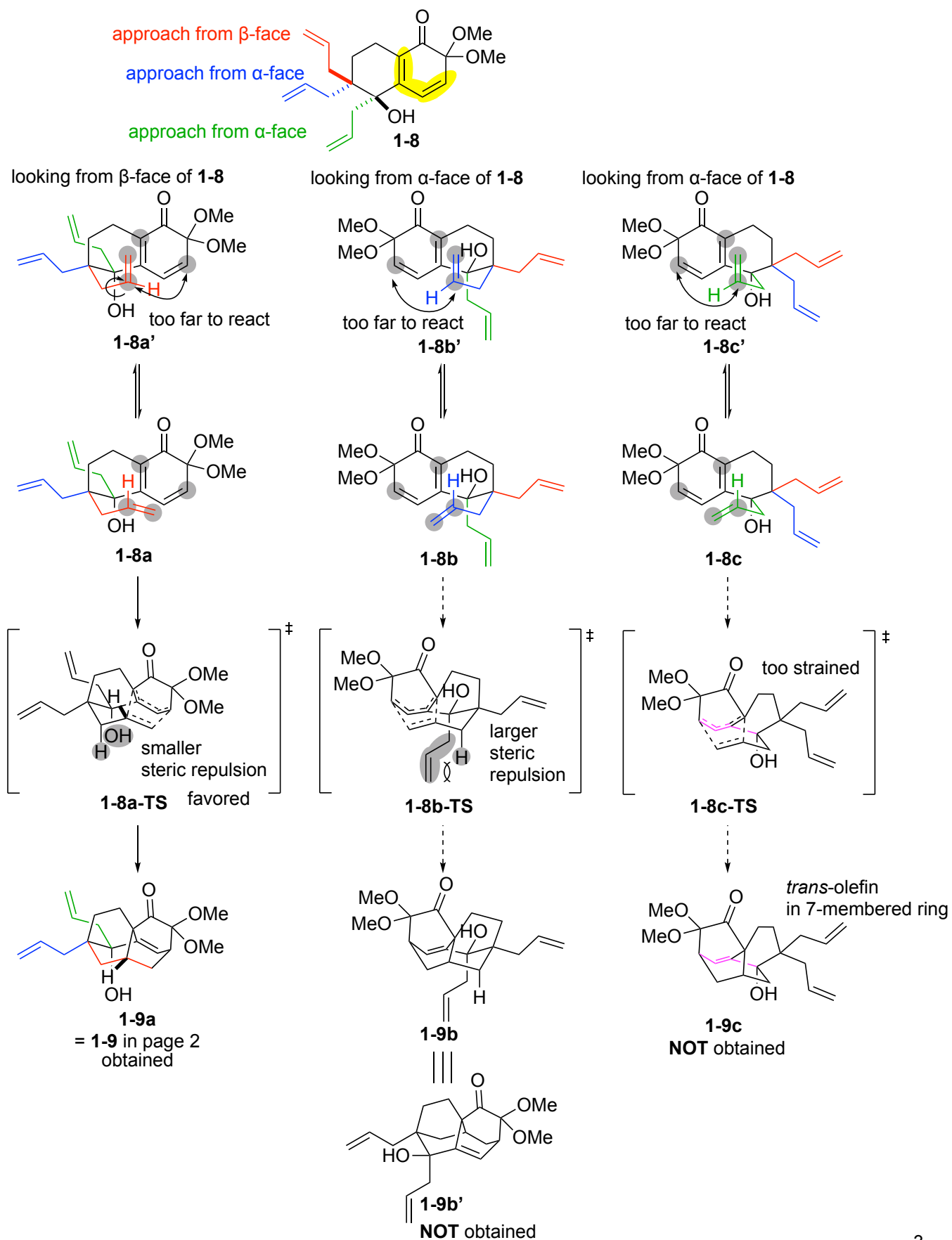


### 1-1. Reaction mechanisms

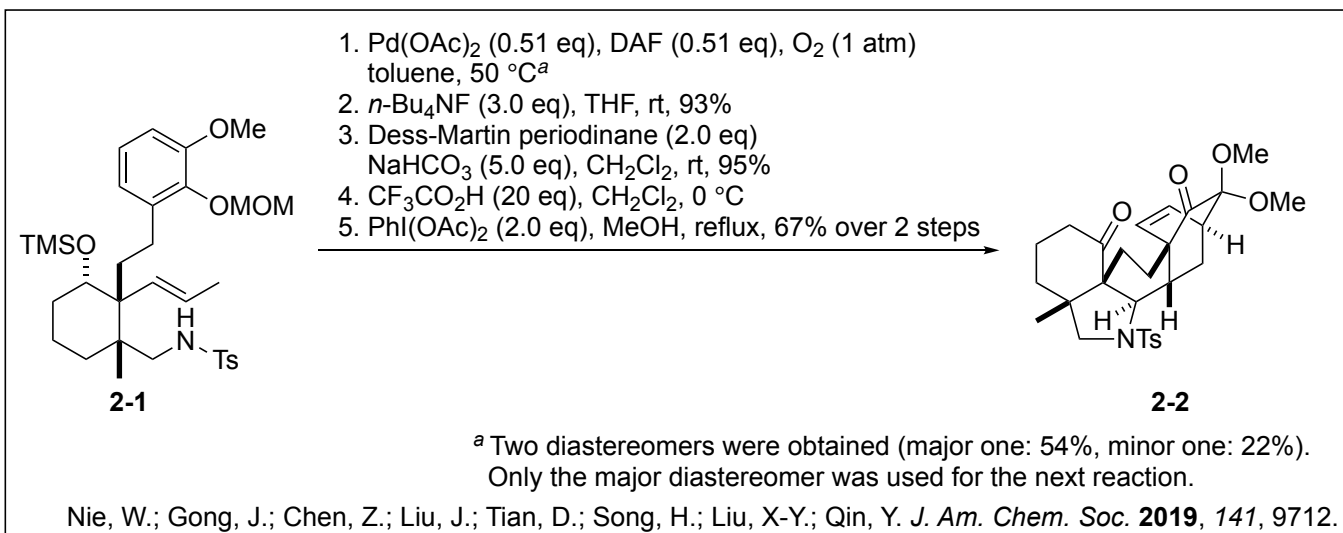




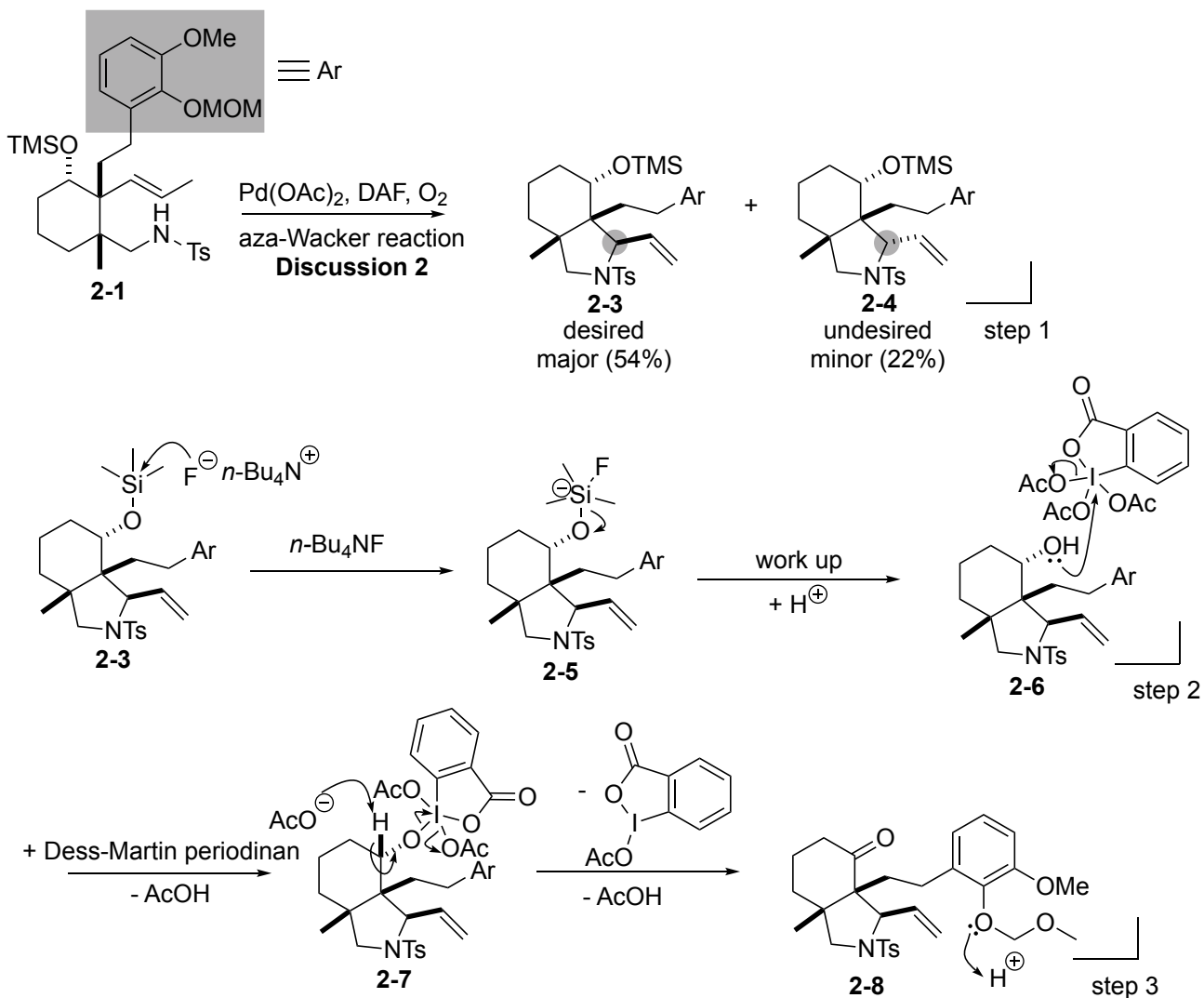
1-2. **Discussion 1:** Chemoselectivity and diastereoselectivity of intramolecular Diels-Alder reaction

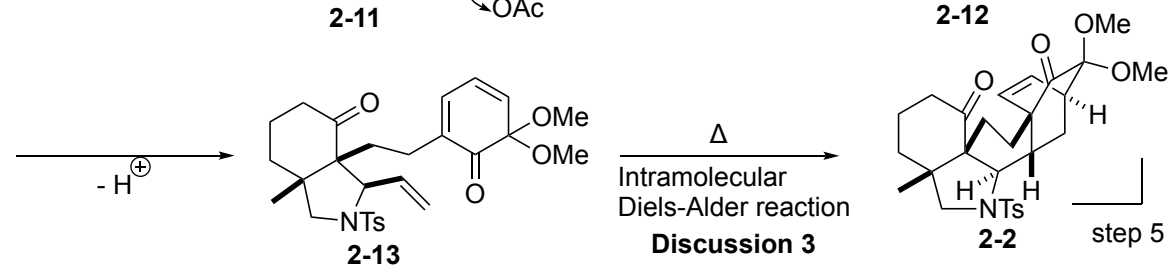
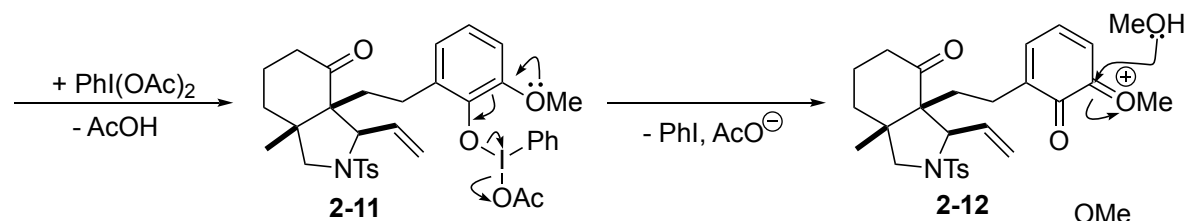
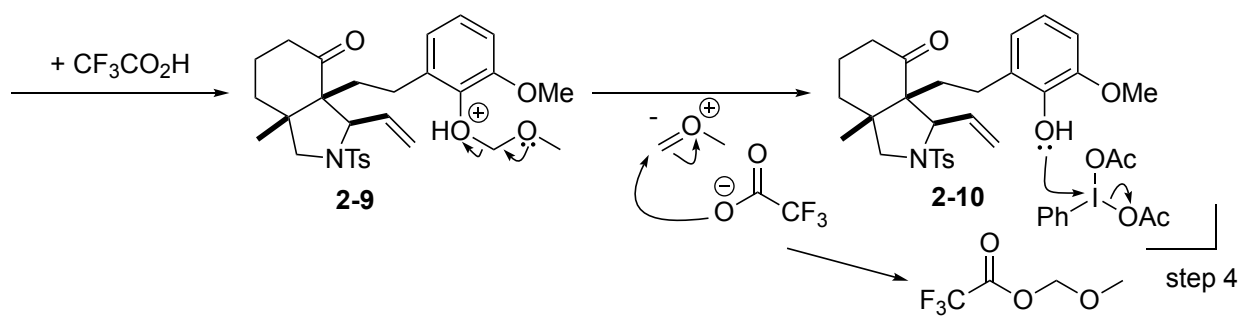


2. Problem 2



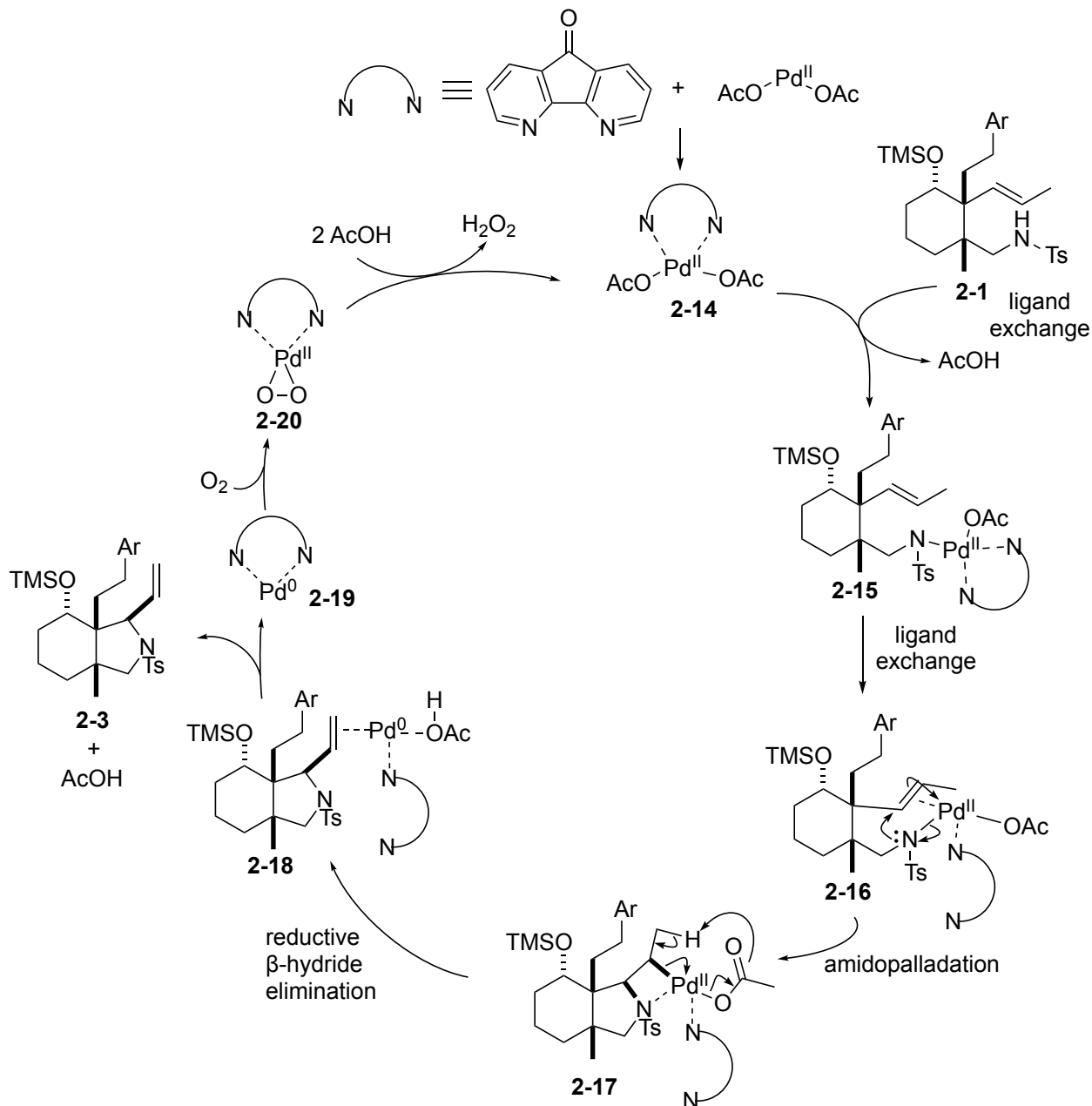
2-1. Reaction mechanisms





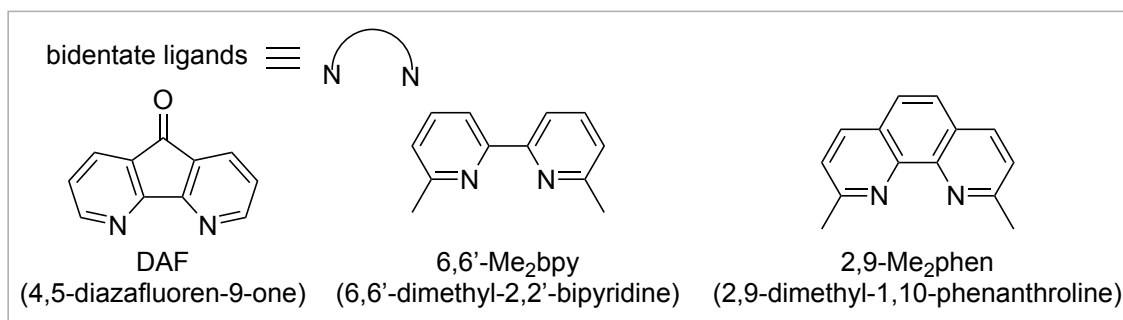
## 2-2. Discussion 2: Reaction mechanism and diastereoselectivity of aza-Wacker reaction

### 2-2-1. Reaction mechanism (only major product **2-3** is described)



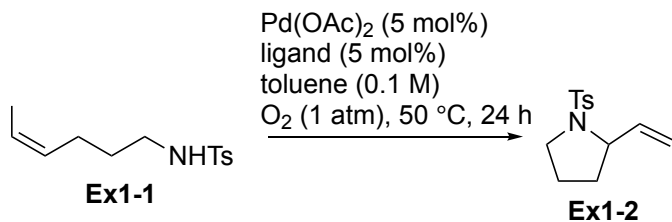
Amidopalladation occurs in the *syn* fashion due to the coordination of N to Pd.

### 2-2-2. Proposed reaction pathway and the advantage of using DAF as a ligand



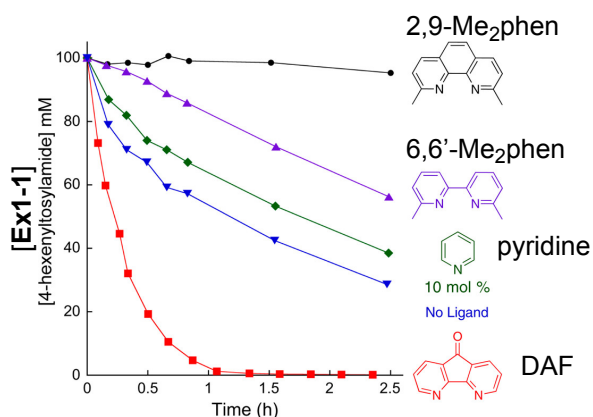
### Experiment 1: Comparison of ligands effect on aza-Wacker reactivity

(White, P. B.; Jaworski J. N.; Zhu G. H.; Stahl, S. S. *ACS Catal.* **2016**, *6*, 3340.)



**Table 1.** Effect of ligands on aza-Wacker reactivity

entry	ligand	yield
1	none	66%
2	6,6'-Me <sub>2</sub> bpy	81%
3	6,6'-Me <sub>2</sub> bpy (24 °C)	40%
4	DAF	97%
5	DAF (24 °C)	97%

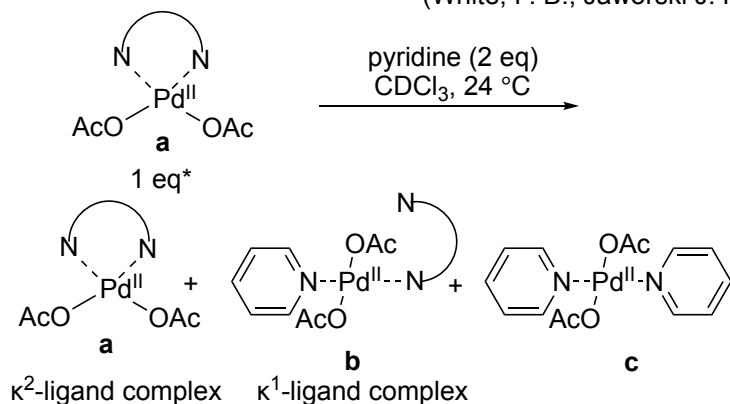


**Figure 1.** Rates of consumption of Ex1-1 during aza-Wacker reaction with various ligand

→ DAF extremely accelerated aza-Wacker reaction.

### Experiment 2: Assessment of relative ligand binding strengths of bidentate ligands

(White, P. B.; Jaworski J. N.; Zhu G. H.; Stahl, S. S. *ACS Catal.* **2016**, *6*, 3340.)



**Table 2.** Coordination of pyridine and various bidentate ligands to Pd<sup>II</sup>

entry	bidentate ligand	a : b : c
1	2,9-Me <sub>2</sub> phen	5 : - : 1
2	6,6'-Me <sub>2</sub> bpy	1 : - : 4.3
3	DAF	- : 1 : 5.4

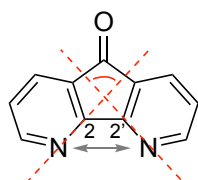
\* DAF was added as pre-mixed 1/1 mixture with Pd(OAc)<sub>2</sub>

Albeit lower affinity than pyridine, DAF preferred to form a κ<sup>1</sup>-ligand complex.

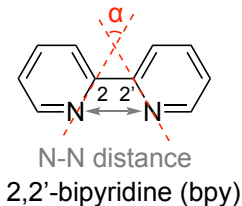
### Rationale of the results in Experiment 2

(White, P. B.; Jaworski J. N.; Fry, C. G.; Dolinaar, B. S.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2016**, *138*, 4869.)

unligated ligands



DAF  
 angle α  
 73°  
 N-N distance  
 3.10 Å

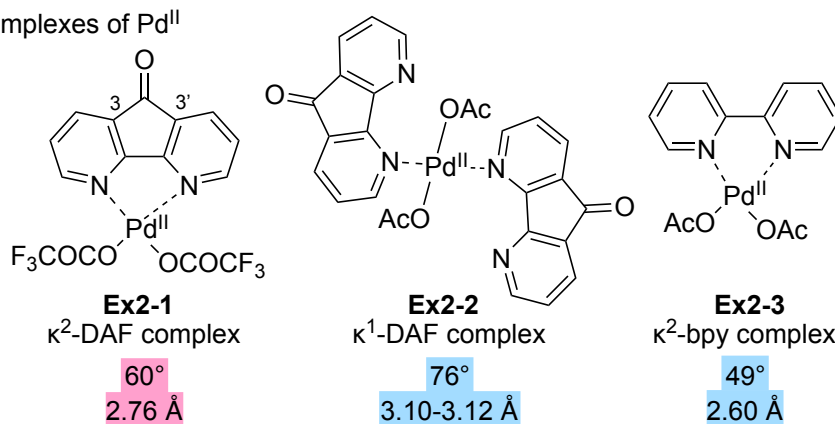


2,2'-bipyridine (bpy)  
 angle α  
 53°  
 N-N distance  
 2.66 Å

\*angle α: defined by C2-N and C2'-N bond vectors of the two pyridine ring



ligand complexes of Pd<sup>II</sup>



DAF (with one atom linker between 3- and 3'- positions of 2,2'-bipyridine)

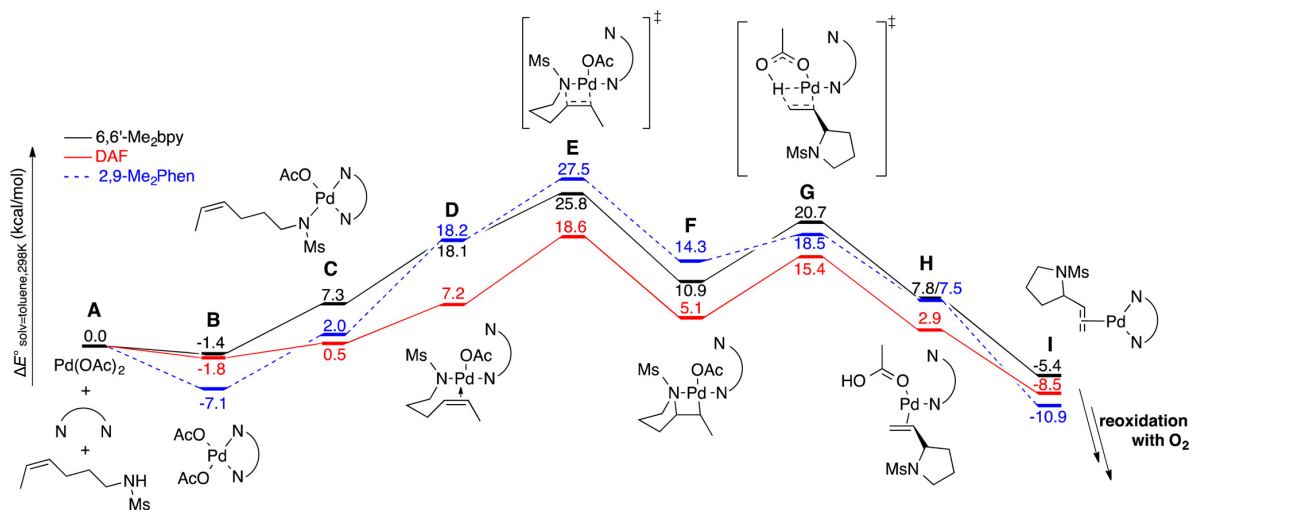
: The κ<sup>2</sup>-DAF complex of Pd<sup>II</sup> **Ex2-1** requires contraction of angle α, but κ<sup>1</sup>-DAF complex **Ex2-2** does not.  
-> κ<sup>1</sup>-DAF complex is more favored than κ<sup>2</sup>-DAF complex.

6,6'-Me<sub>2</sub>bpy and 2,9-Me<sub>2</sub>phen (without one atom linker between 3- and 3'- positions of 2,2'-bipyridine, probably showing the similar angle α to 2,2'-bipyridine)

: The angle α of κ<sup>2</sup>-bpy complex of Pd<sup>II</sup> **Ex2-3** is similar to that of unligated bpy.  
-> κ<sup>2</sup>-ligand complex is favored.

### Computational study: DFT calculation of aza-Wacker reaction pathway with three bidentate ligands

(White, P. B.; Jaworski J. N.; Zhu G. H.; Stahl, S. S. *ACS Catal.* **2016**, *6*, 3340.)



DFT calculation (298 K, gas phase)  
geometry optimization calculations: rB3LYP/6-31+G(d)  
single point energy calculations: rB3LYP/6-311+G(d,p)

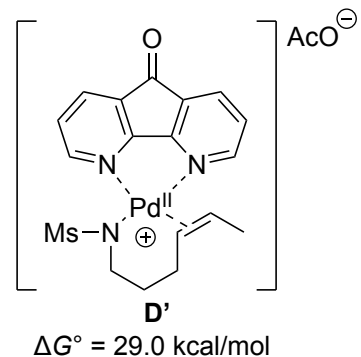
Cationic complex **D'** is unstable in toluene.

-> Authors propose electroneutral κ<sup>1</sup>-ligand complex **D** as an intermediate.

Using DAF as a bidentate ligand, κ<sup>2</sup>-ligand complex **B** and **C** is less stable, and κ<sup>1</sup>-ligand complex **D** - **H** is more stable.

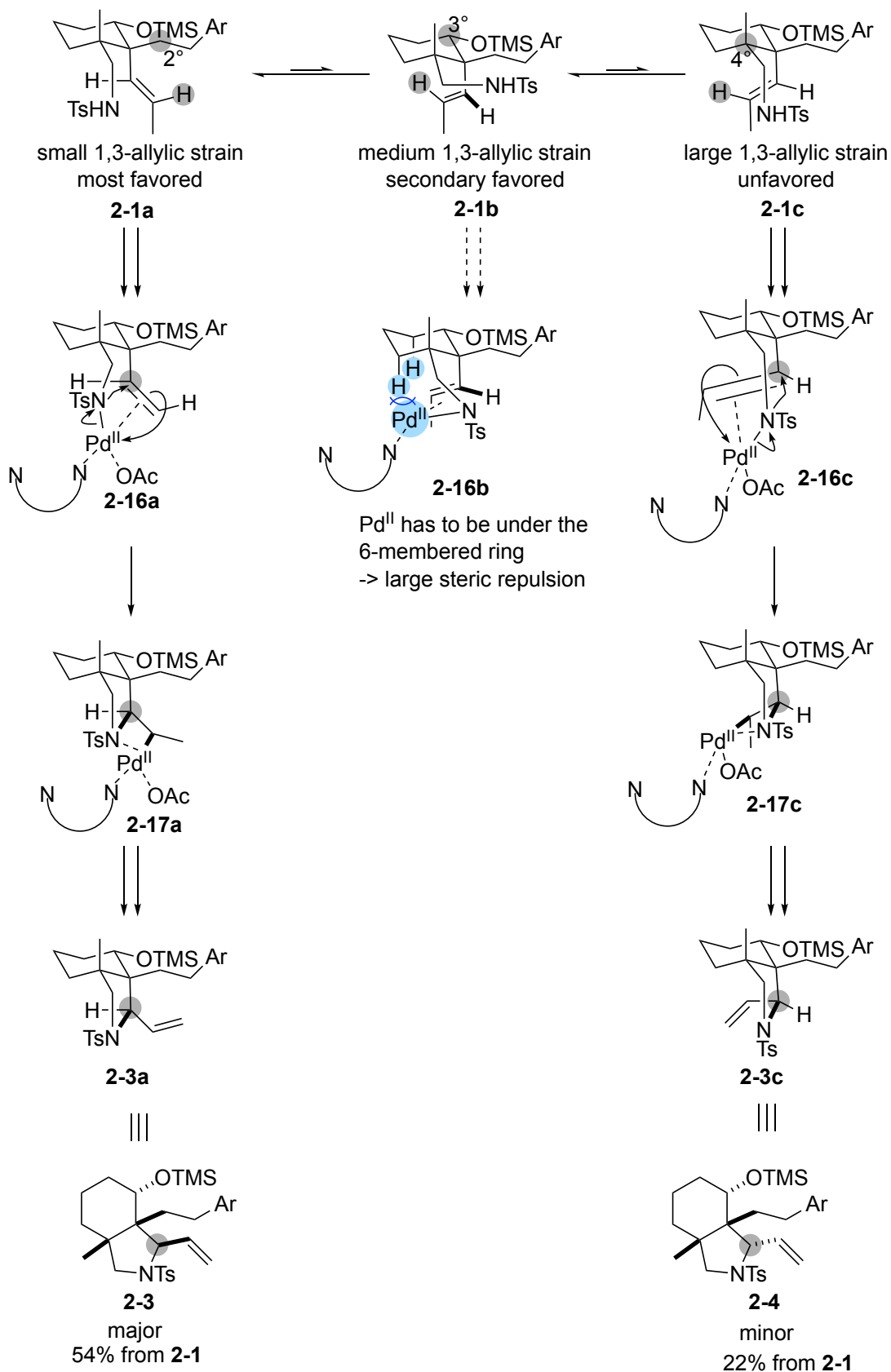
-> DAF promotes transition from **C** to **D**, and lowers ΔE° in TS **E** and **G**.

-> DAF extremely accelerates aza-Wacker reaction.



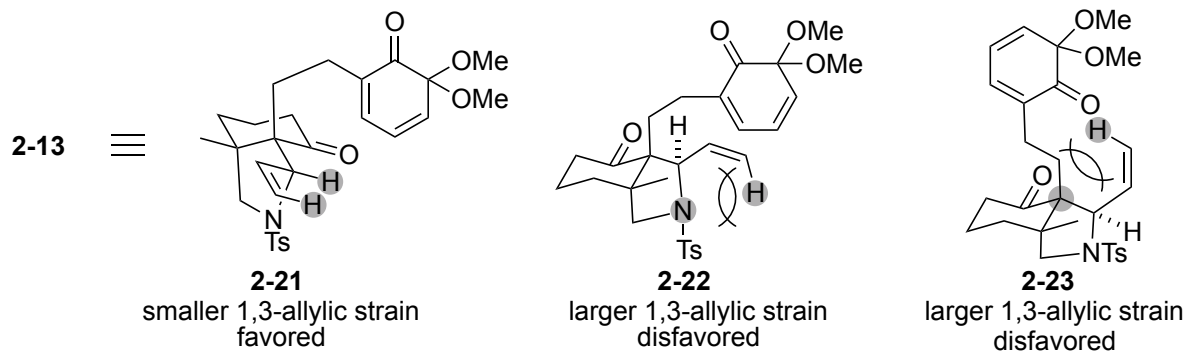
## 2-2-3. Diastereoselectivity

The orientation of allyl group is determined by 1,3-allylic strain.



### 2-3. Discussion 3: Diastereoselectivity of intramolecular Diels-Alder reaction

Orientation of dienophile is determined by 1,3-allylic strain.



Diene is placed at the  $\beta$ -side of the dienophile, so approach of diene from the  $\beta$ -face is favored.

-> Stereochemistry at highlighted carbon is determined.

