

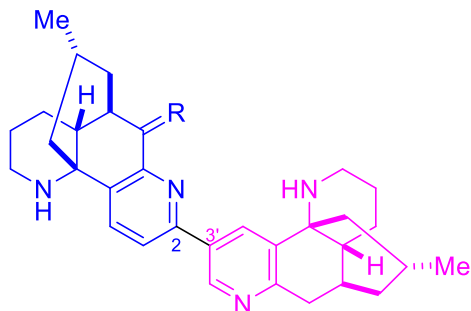
# Problem Session (2) -Answer-

2021/11/20 Yosuke Nakata

Topic : pyridine-containing *Lycopodium* alkaloids

## 0. Introduction

### 0-1. Complanadine A and B



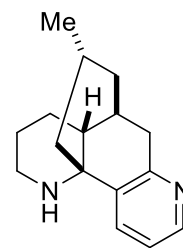
complanadine A<sup>1)</sup> : R = H,H

complanadine B<sup>2)</sup> : R = O

isolated from *Lycopodium complanatum*

bioactivity : nerve growth factor (NGF) enhancer

structure : unsymmetrical dimer of lycodine with C2-C3' linkage



lycodine<sup>3)</sup>

isolated from *L. annotinum*

structure : bicyclo [3,3,1] nonane, pyridine

### 0-2. Total synthesis

Siegel's group: complanadine A (2010)<sup>4)</sup>

Sarpong's group: complanadine A (2010)<sup>5)</sup>, complanadine B (2013)<sup>6)</sup>

→About total synthesis of complanadine A by Siegel and Sarpong, see also 100501\_LS\_Satoshi\_KASUYA.

Hirama's group: complanadine A and B (2013)<sup>7)</sup> -> problem 1

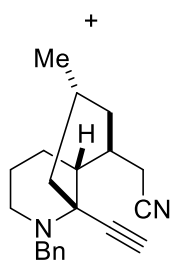
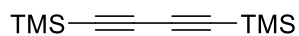
Dai's group: complanadine A (2021)<sup>8)</sup> -> problem 2

### 0-3. Synthetic route

#### 0-3-1. Construction of lycodine structure

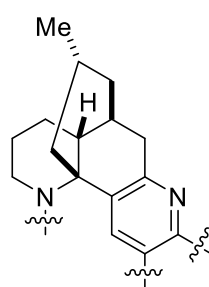
Siegel's group

Sarpong's group



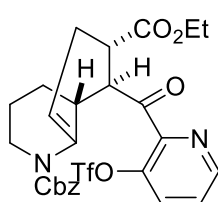
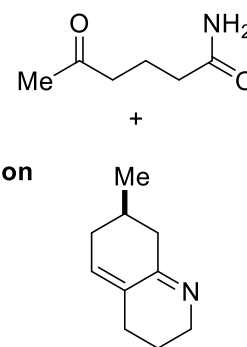
CpCo(CO)<sub>2</sub>

[2+2+2] cyclization



lycodine structure

Mannich reaction & amide-ketone cyclization

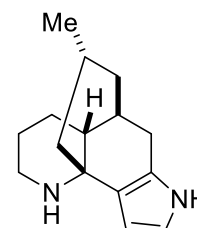


Heck reaction

Pd cat.

Ciamician-Dennstedt rearrangement

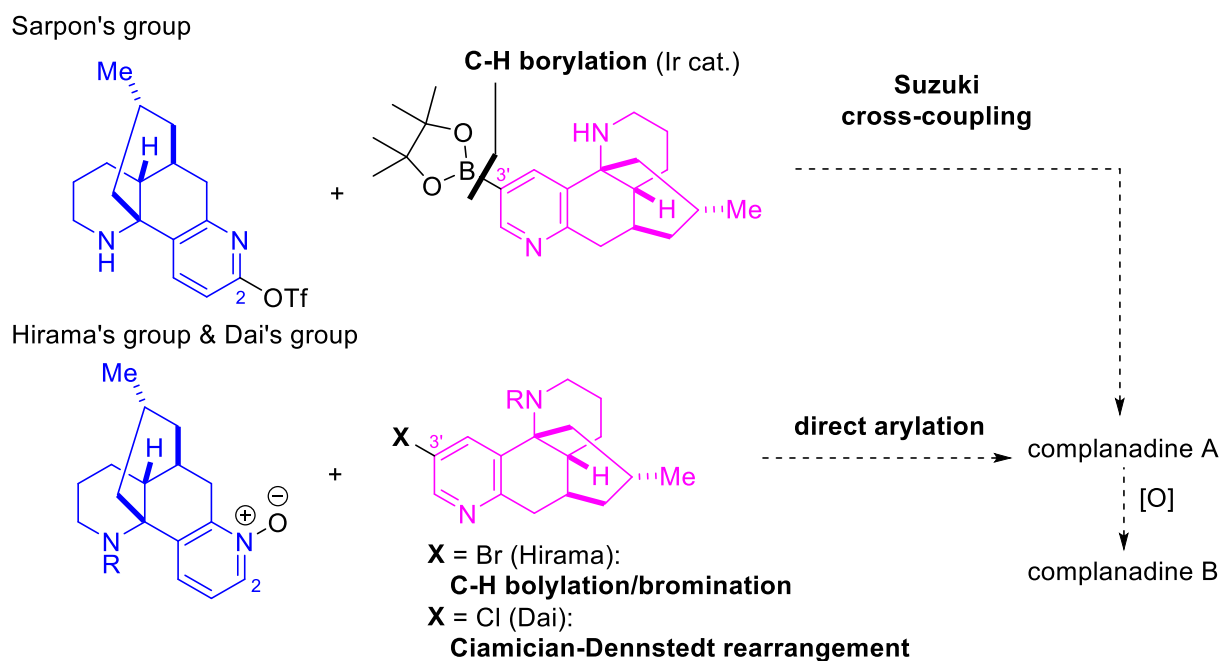
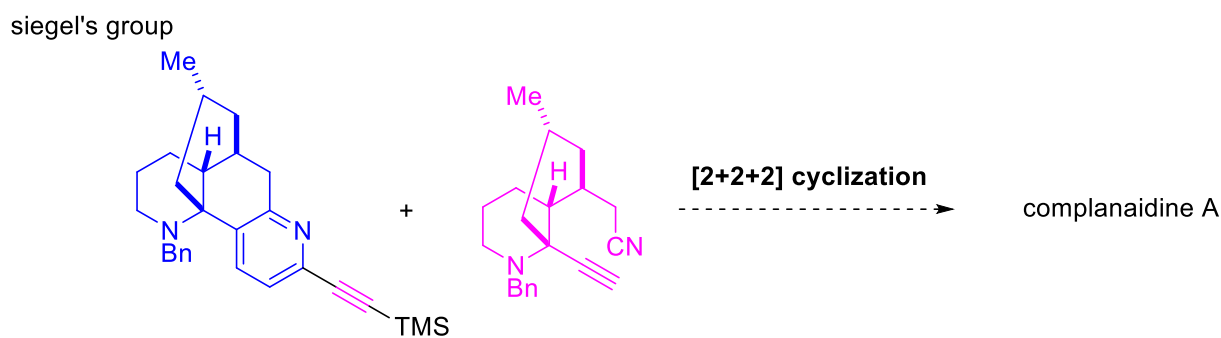
: CCl<sub>2</sub>



Hirama's group

Dai's group

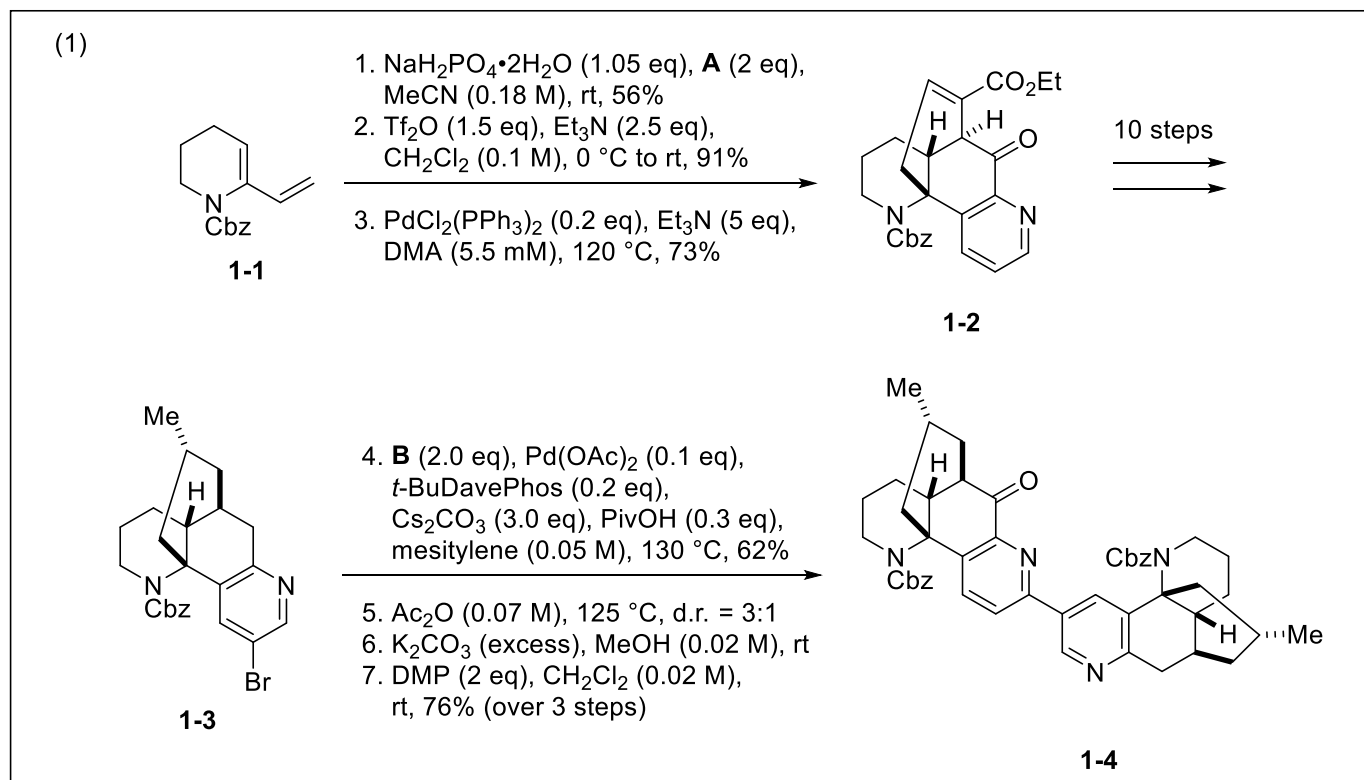
### 0-3-1. Dimerization



- 1) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *Tetrahedron Lett.* **2000**, *41*, 9069.
- 2) Morita, H.; Ishiuchi, K.; Haganuma, A.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2005**, *61*, 1955.
- 3) Anet, L. A. F.; Eves, R. C. *Can. J. Chem.* **1958**, *36*, 902.
- 4) Yuan, C.; Chang, C.-T.; Axelord, A.; Siegel, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924.
- 5) Fischer, F. D.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926.
- 6) Newton, N. J.; Fischer, F. D.; Sarpong, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 1726.
- 7) Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1722.
- 8) Ma, D.; Martin, S. B.; Gallagher, S. K.; Siato, T.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 16383.

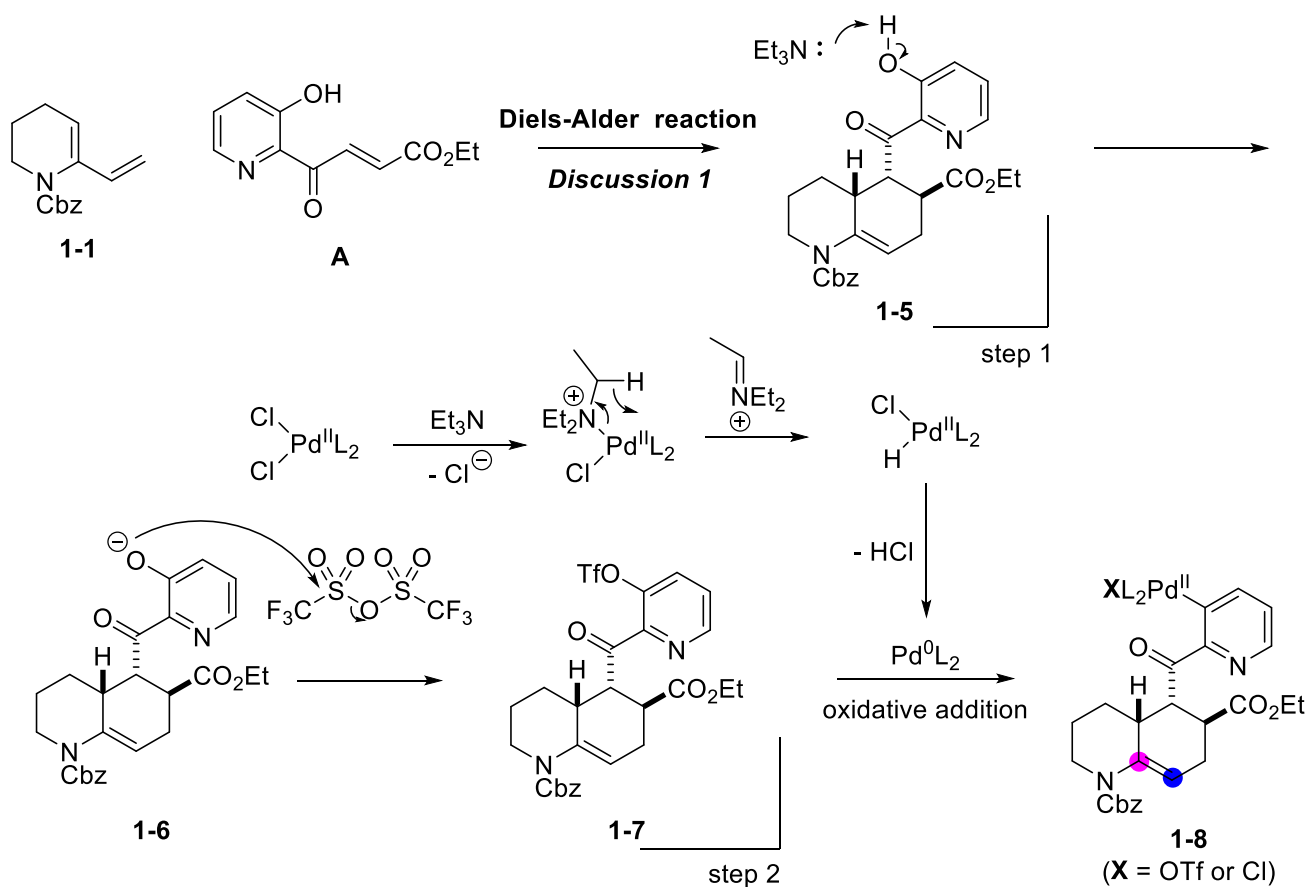
1. Problem 1

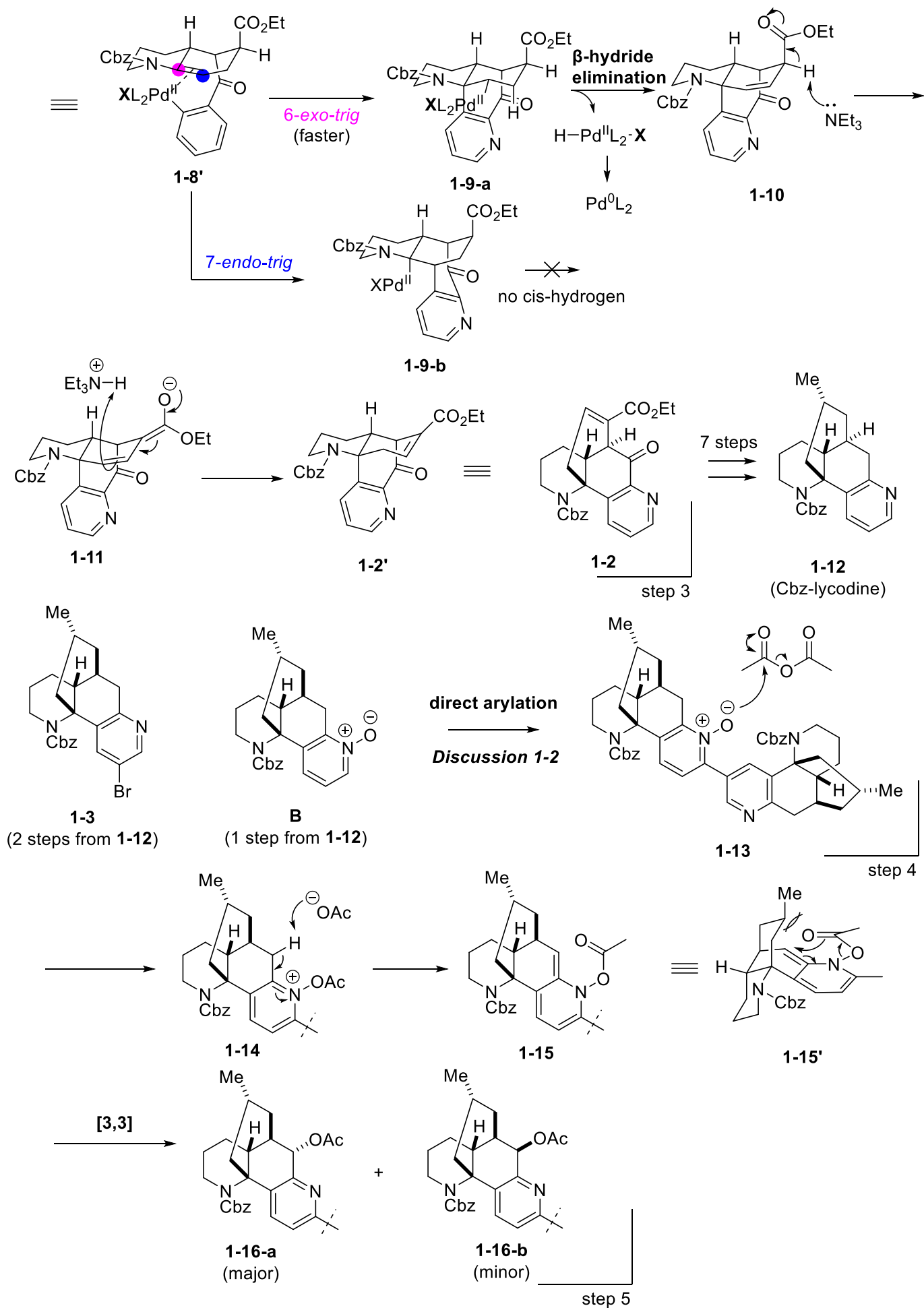
1-1. Answer for problem 1

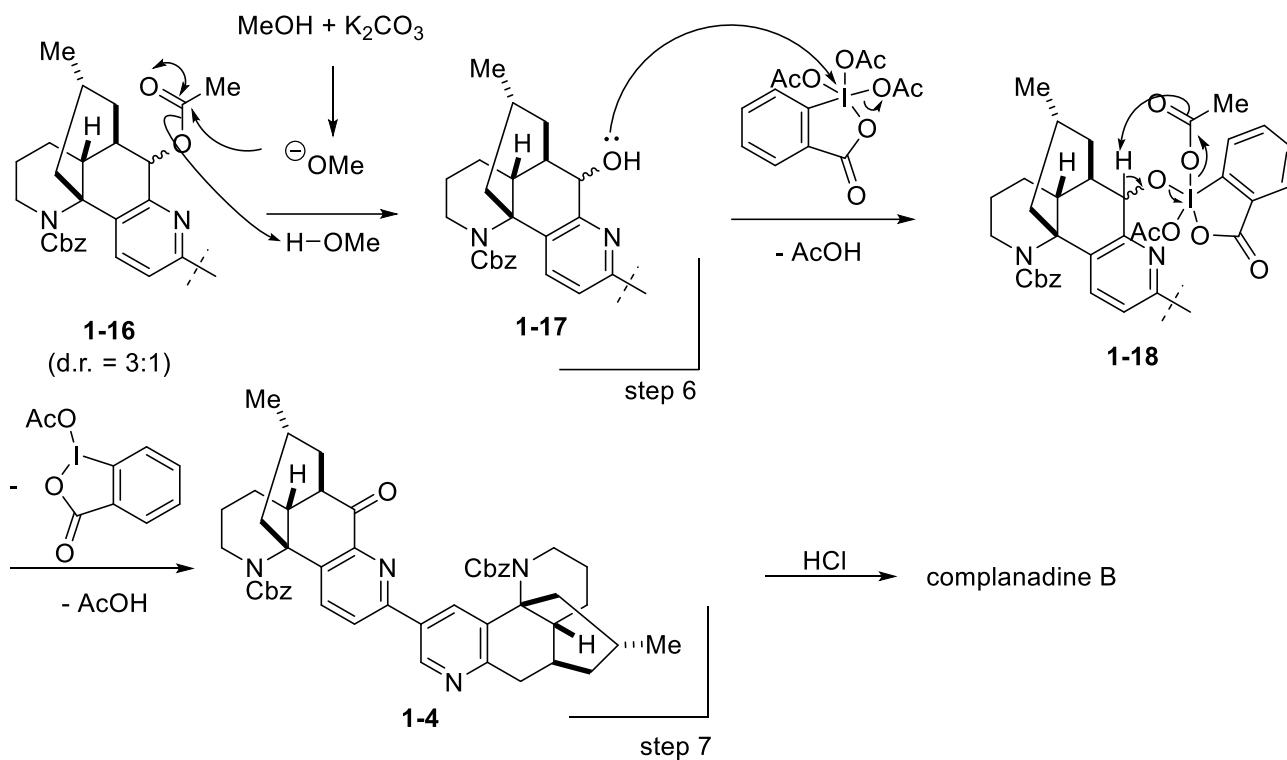


Tsukano, C.; Zhao, L.; Takemoto, Y. Hirama, M. *Eur. J. Chem.* **2010**, 4198.

Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirma, M. *Angew. Chem. Int. Ed.* **2013**, 52, 1722.



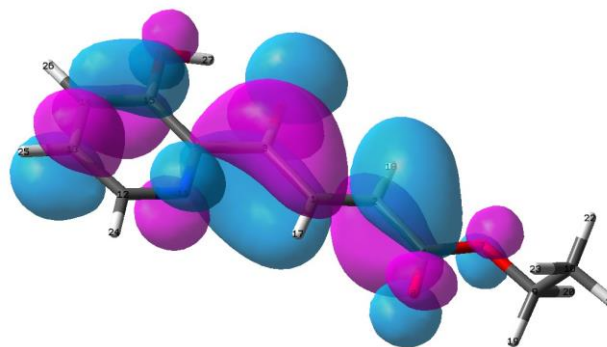
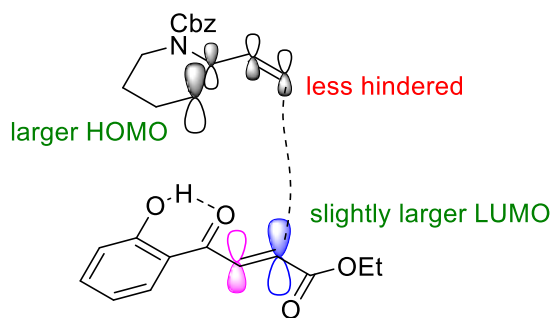




## 1-2. Discussion 1: Diels-Alder reaction

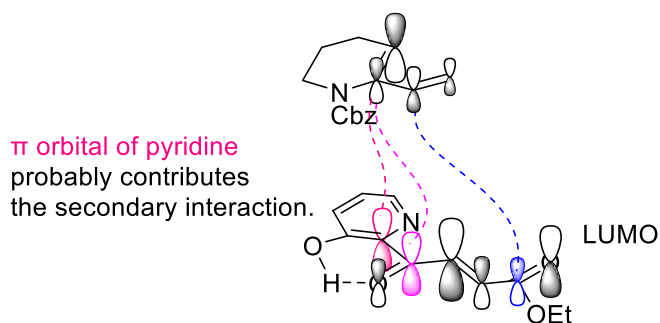
Zhao, L.; Tsukano, C.; Kwon, E.; Shirakawa, H.; Kaneko, S.; Takemoto, Y.; Hirama, M. *Chem. Eur. J.* **2017**, *23*, 802.

### 1-2-1. Regioselectivity



contribution to LUMO:  
 ethyl ester side was almost same as pyridyl ketone side  
 $\Rightarrow$  steric effect > orbital interaction

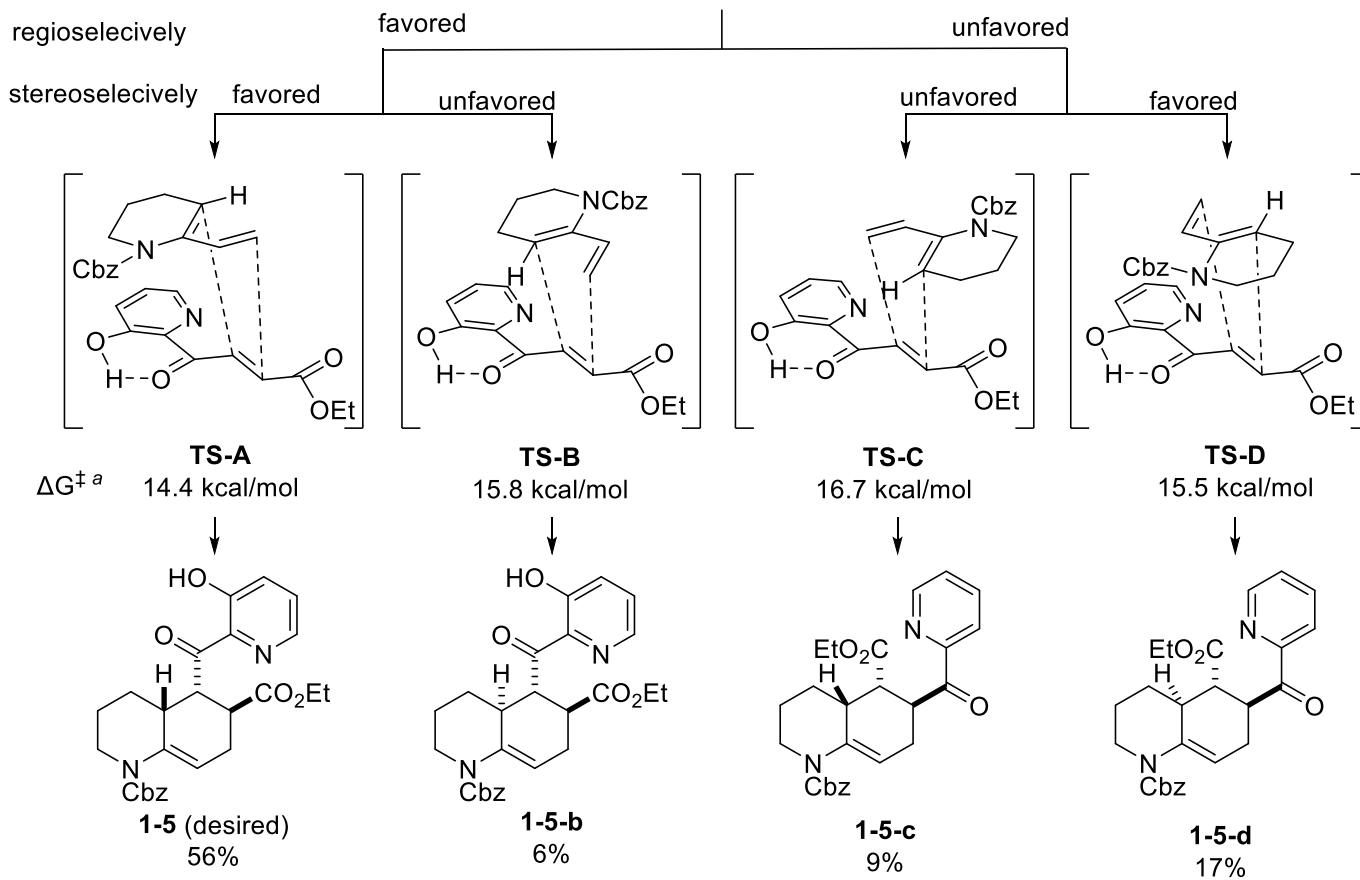
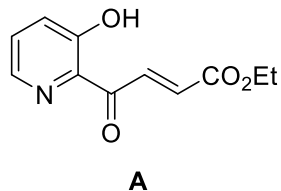
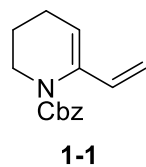
### 1-2-2. Stereoselectivity



secondary interaction  
 pyridyl ketone > ethyl ester

pyridyl ketone : endo  
 ethyl ester : exo

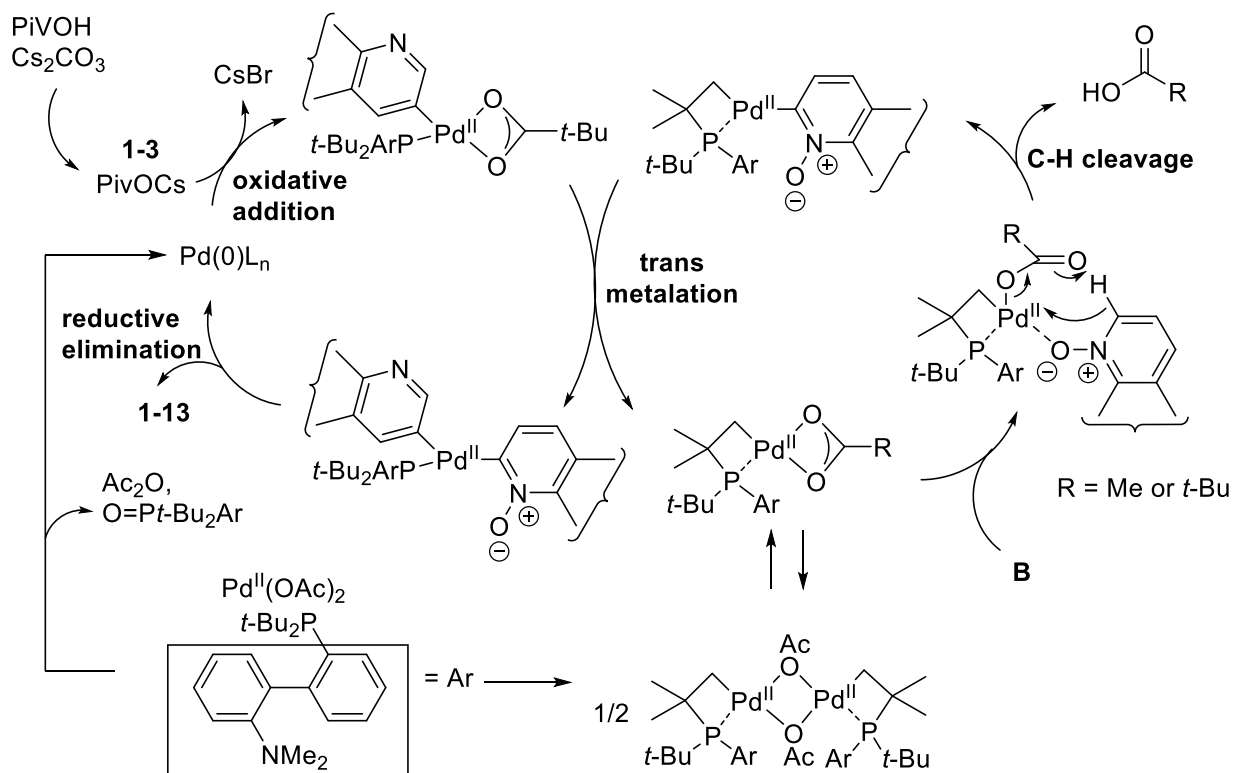
### 1-2-3. Results



<sup>a</sup> DFT calculation at the B3LYP/6-31G(d) level

### 1-3. **Discussion 1-2:** direct arylation

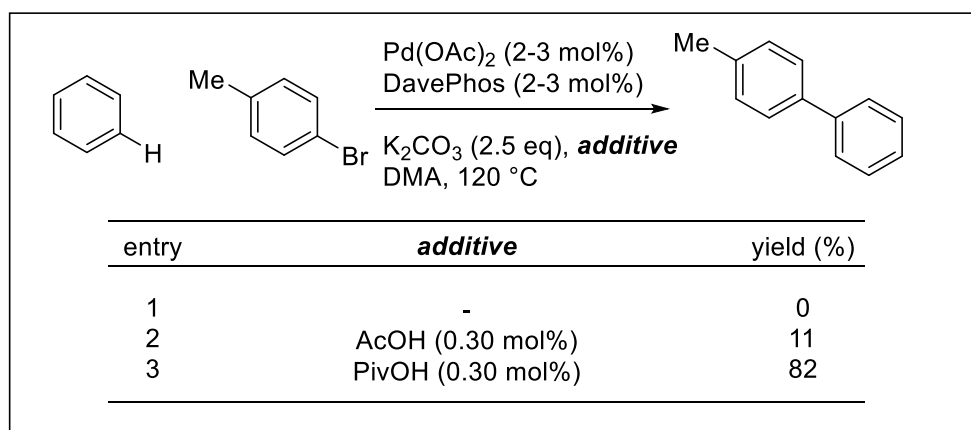
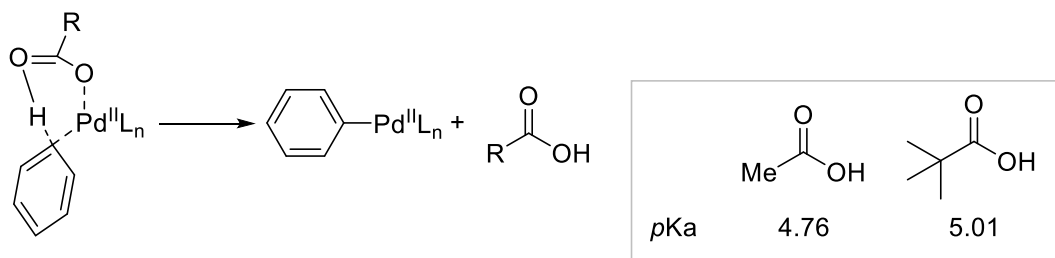
#### 1-3-1. Catalytic cycles



Tan, Y.; B-Landeros, F.; Hartwig, F. J. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

#### 1-3-2. The role of PivOH

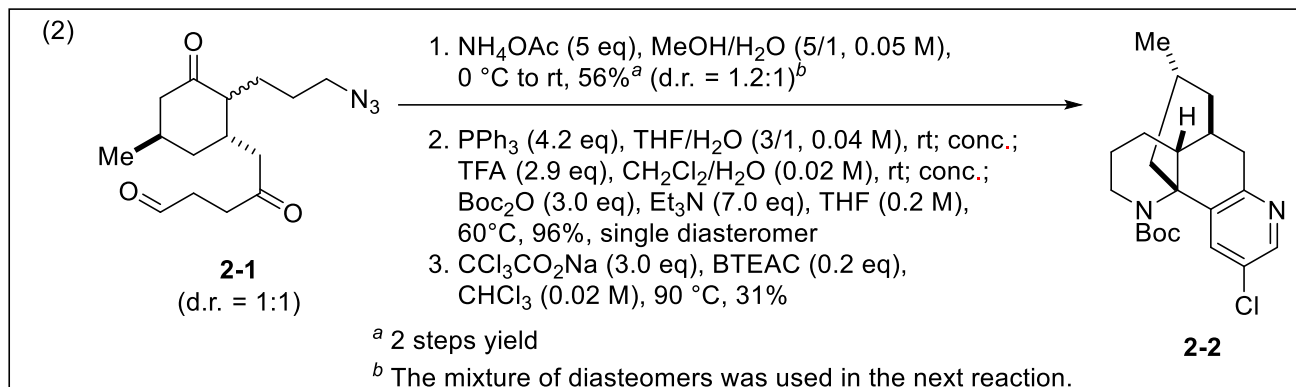
pivalate accelerates aryl C-H cleavage.



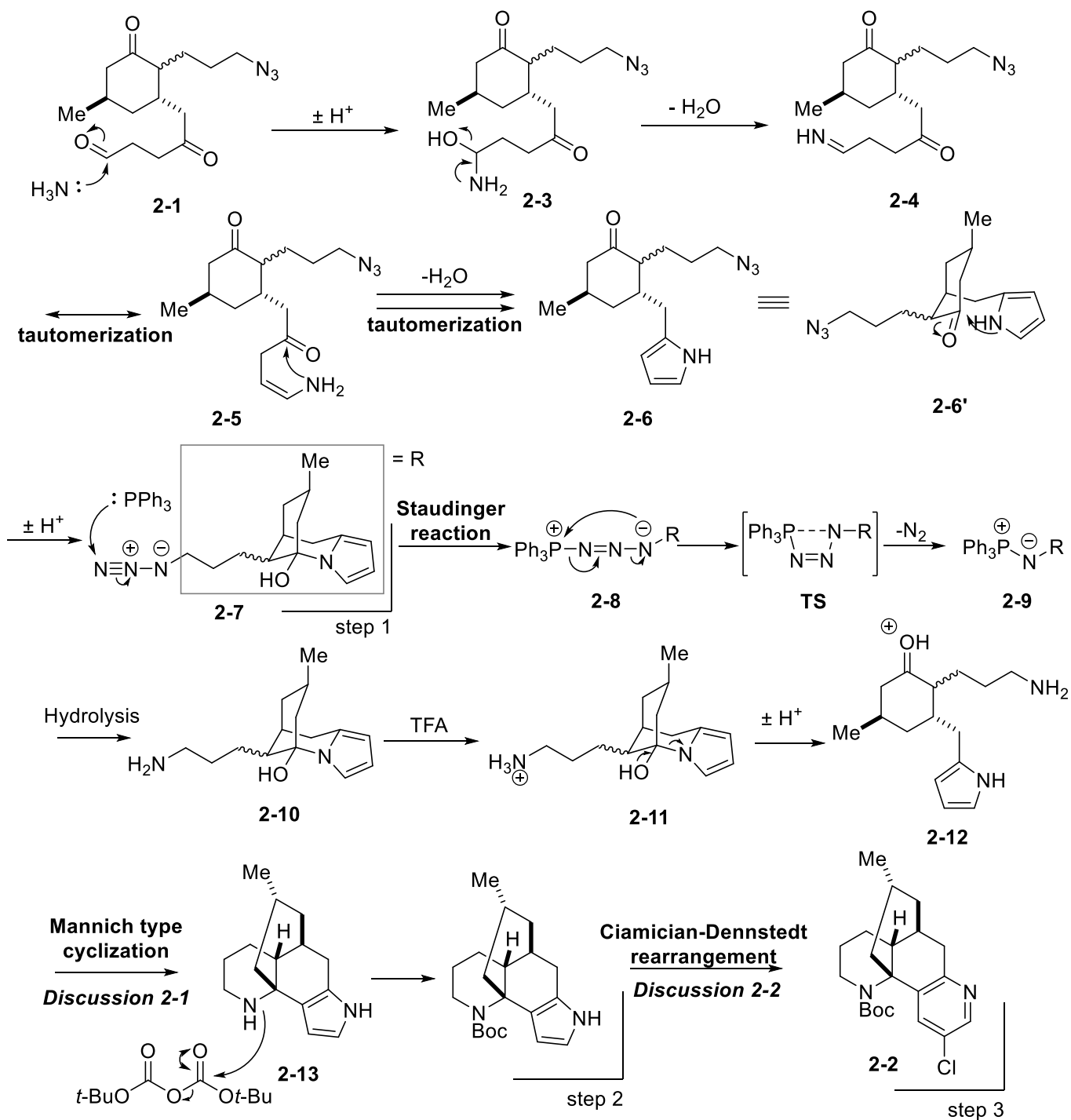
Lafrance, M.; Fangou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

2. Problem 2

2-1. Answer for problem 2



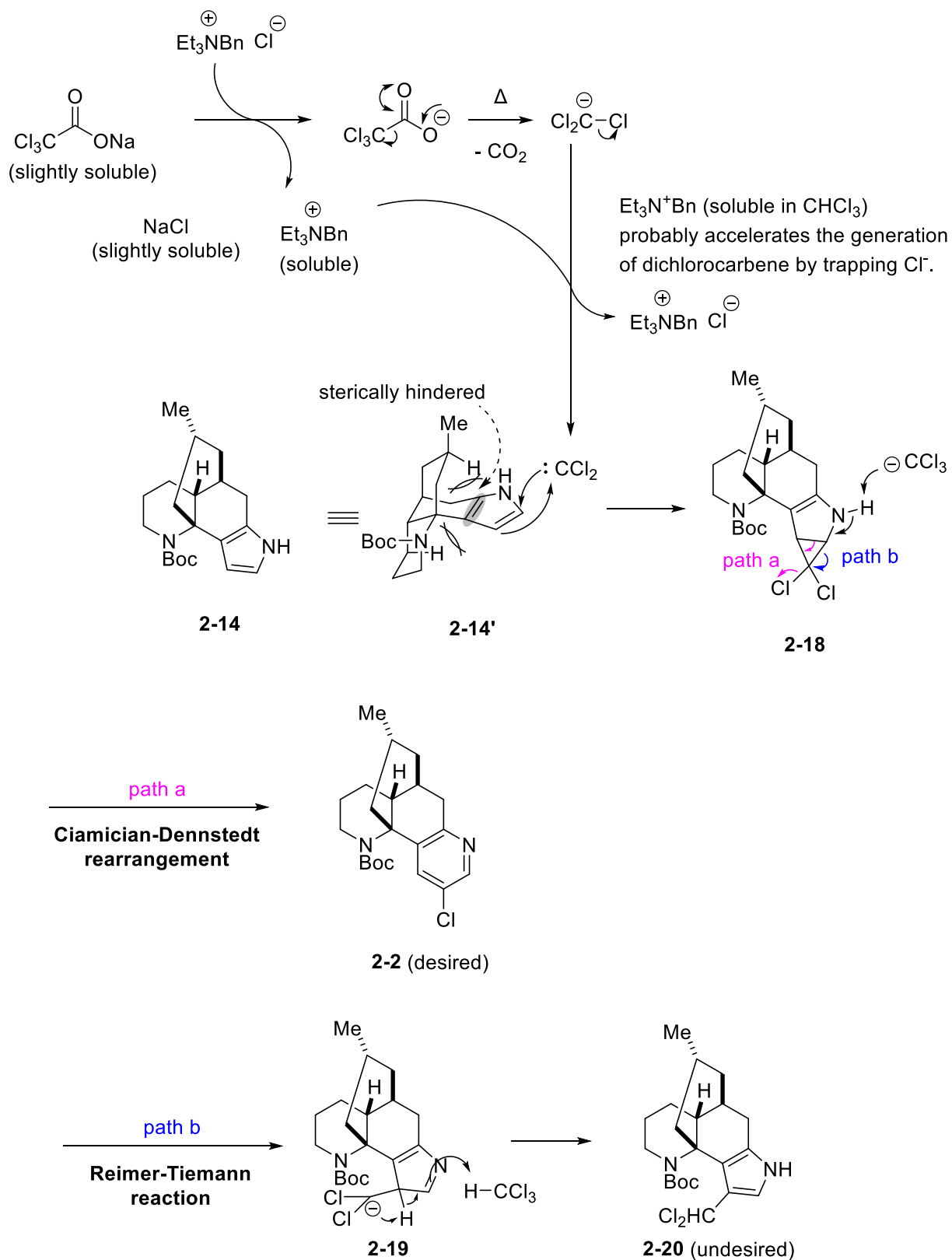
Ma, D.; Martin, S. B.; Gallagher, S. K.; Siato, T.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 16383.







### 2-3. Discussion 2-2: Ciamician-Dennstedt rearrangement



The low yield of **2-2** is caused by the generation of **2-20** via Reimer-Tiemann reaction.