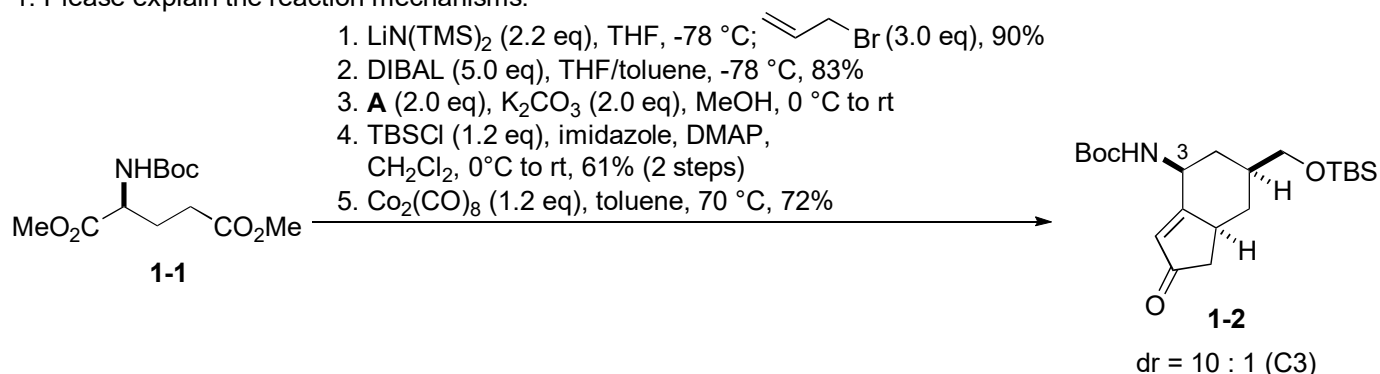
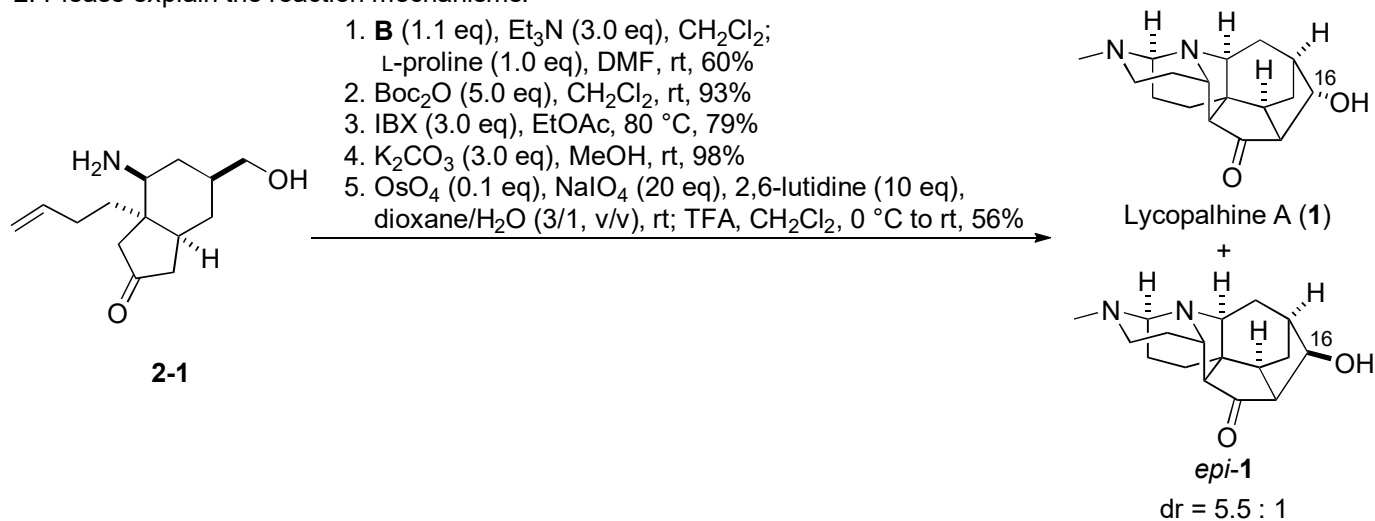


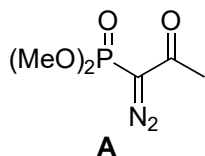
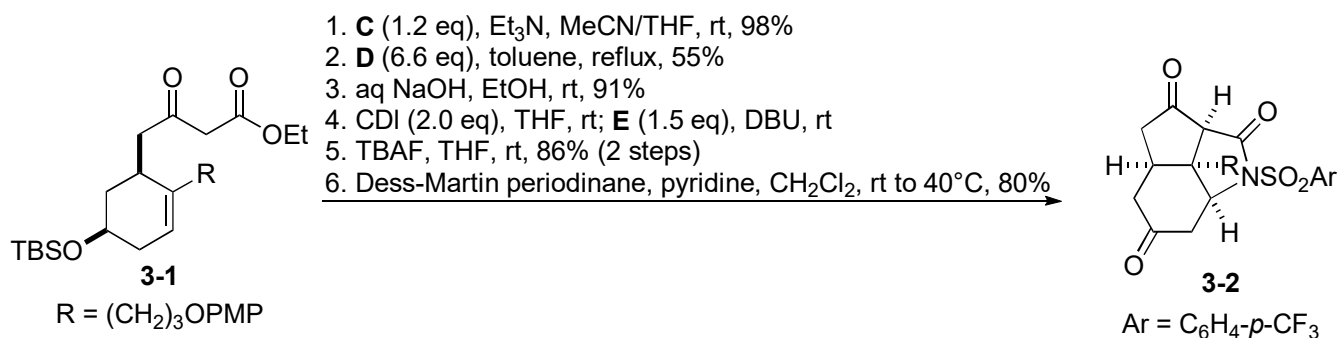
1. Please explain the reaction mechanisms.



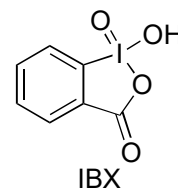
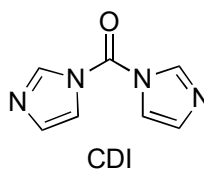
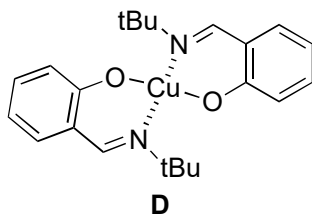
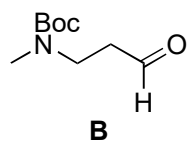
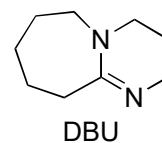
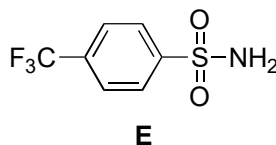
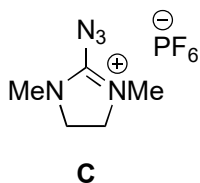
2. Please explain the reaction mechanisms.



3. Please explain the reaction mechanisms.



(Ohira-Bestmann reagent)



0. Introduction

Isolation

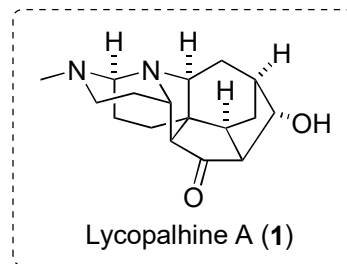
Isolated from *Palhinhaea cernua* (Dong, L.-B. *et. al. Chem. Commun.* **2012**, 48, 9038-9040)

Biological activity

Acetylcholinesterase and butyrylcholinesterase inhibitory activities (Dong, L.-B. *et. al. Chem. Commun.* **2012**, 48, 9038-9040)

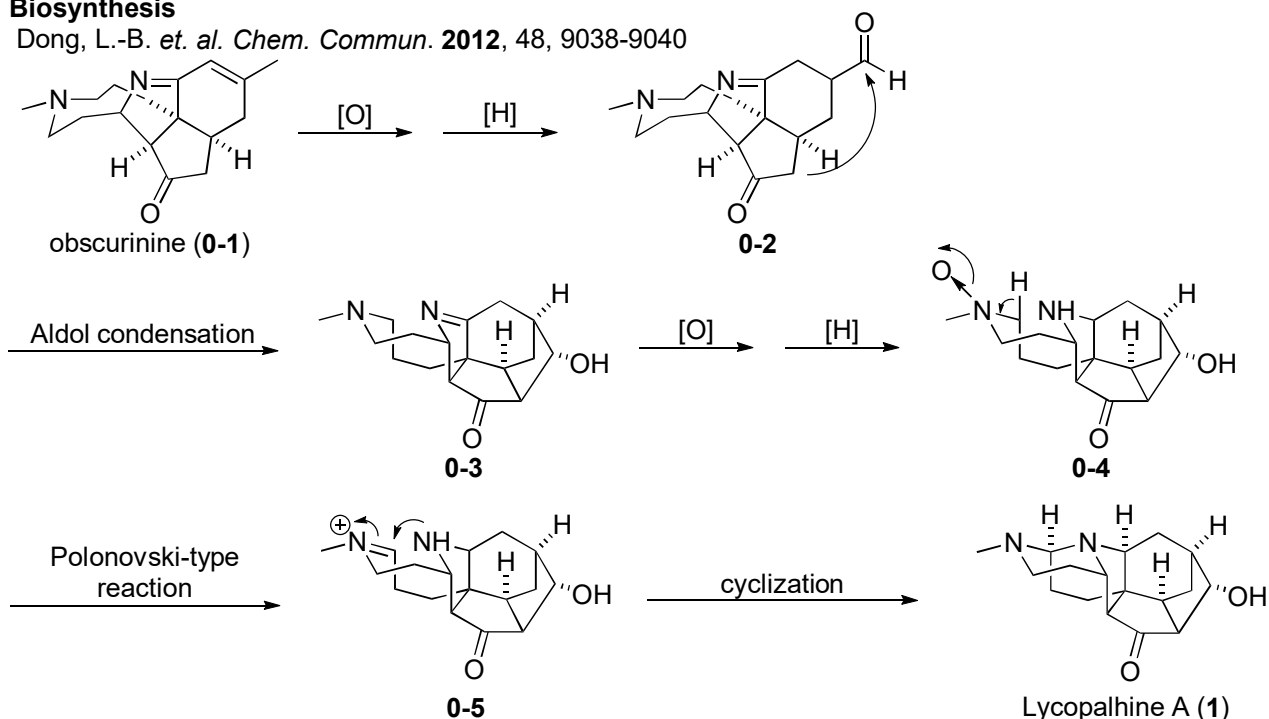
Structure

Belongs to Lycopodium alkaloids
 One six-membered and two five-membered carbocycle
 A piperidine and a hexahydropyrimidine heterocycle
 A densely substituted pyrrolidine core



Biosynthesis

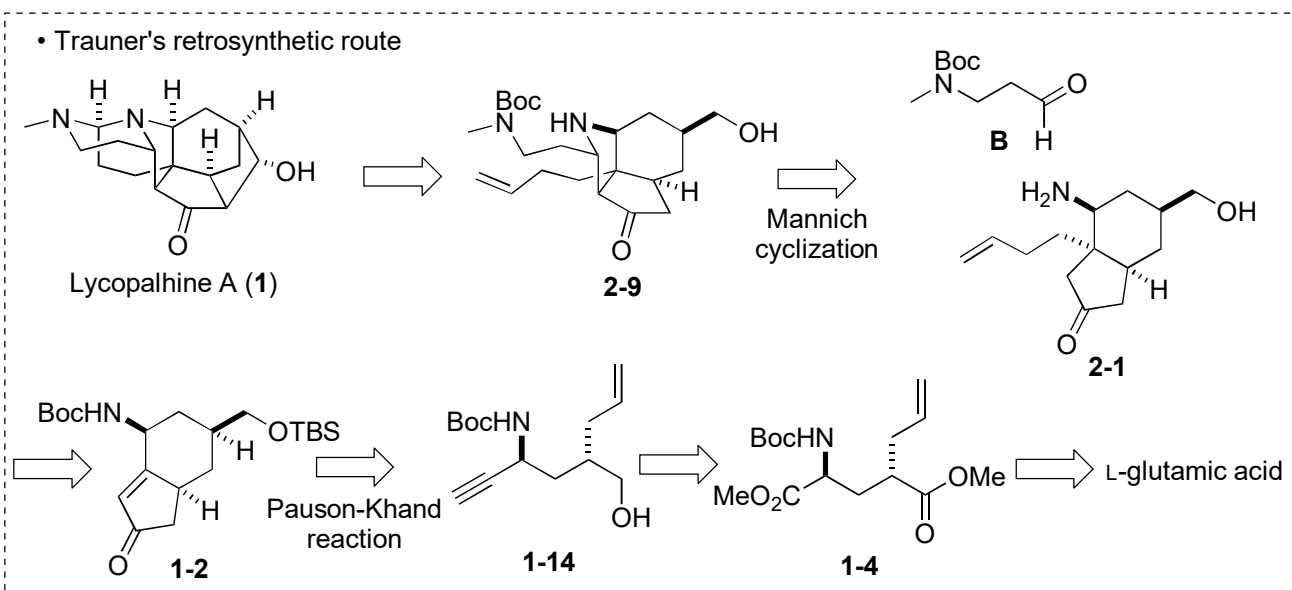
Dong, L.-B. *et. al. Chem. Commun.* **2012**, 48, 9038-9040



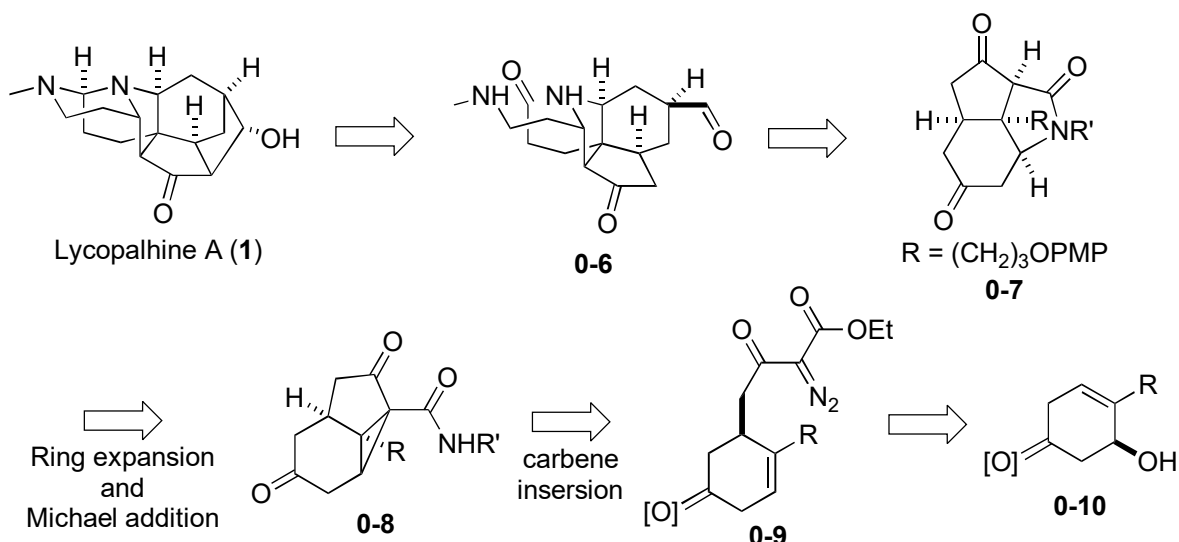
Total synthesis

Williams, B. M.; Trauner, D. *Angew. Chem. Int. Ed.* **2016**, 55, 2191-2194 (Problem 1 and 2)

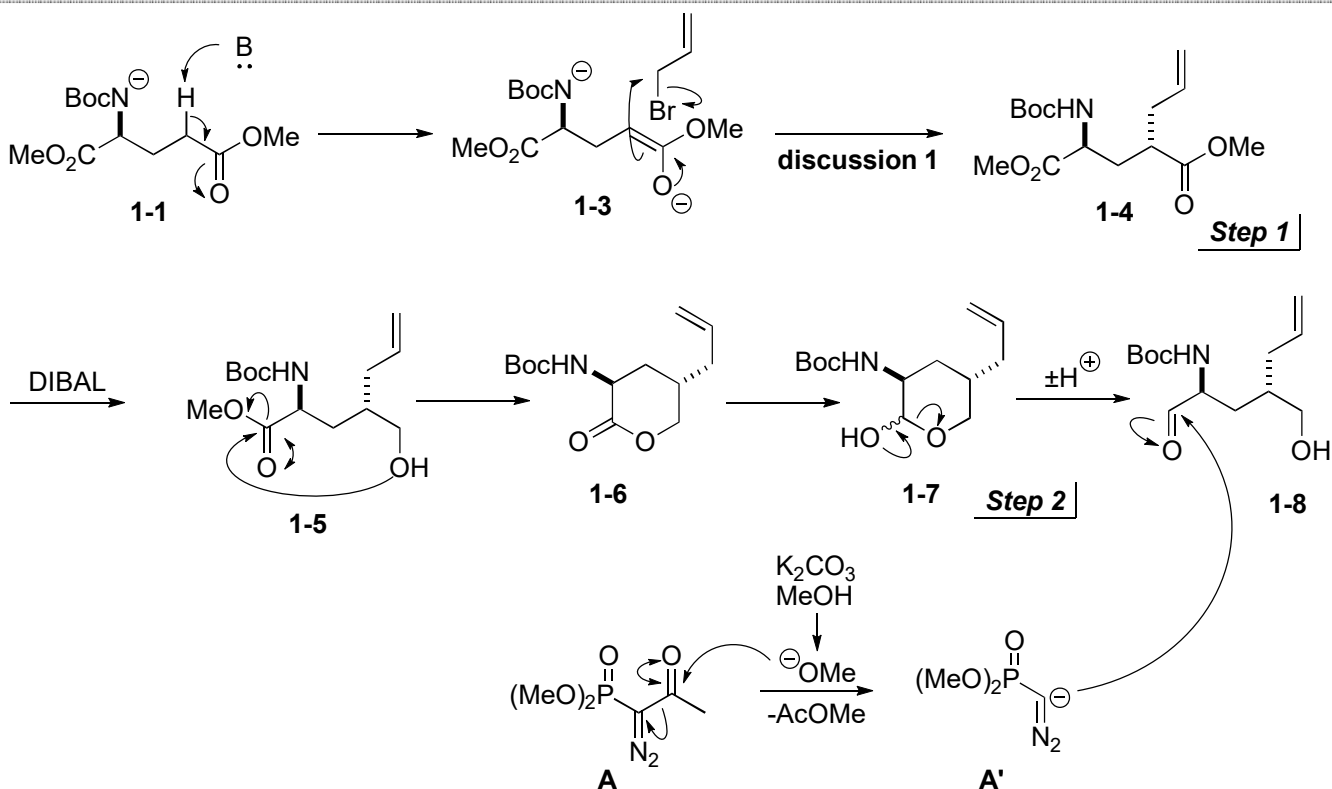
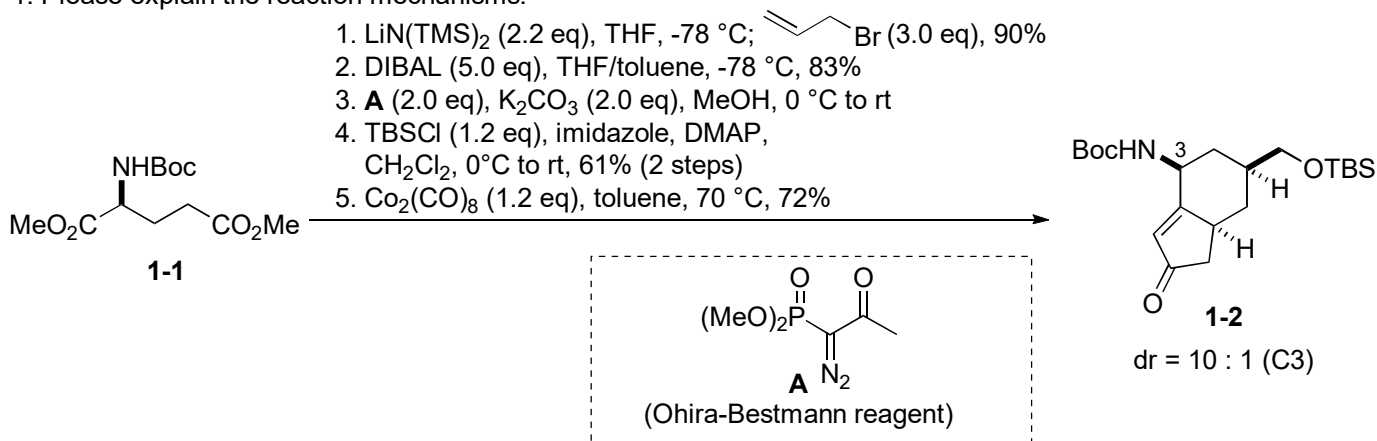
Ochi, Y.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2016**, 18, 1494-1496 (Problem 3)

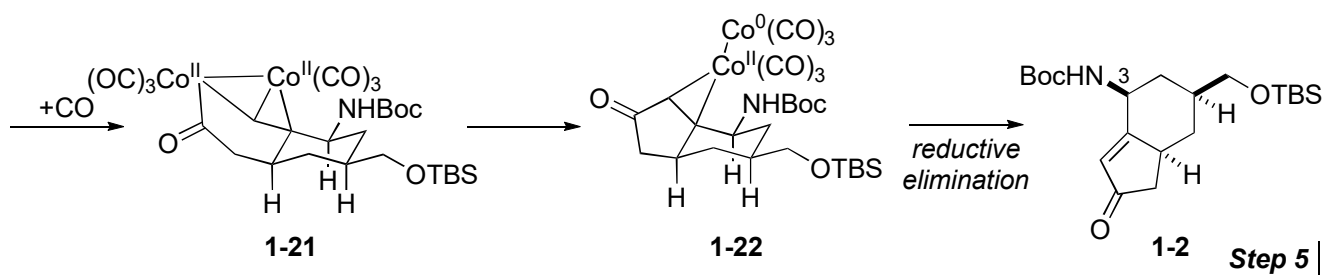
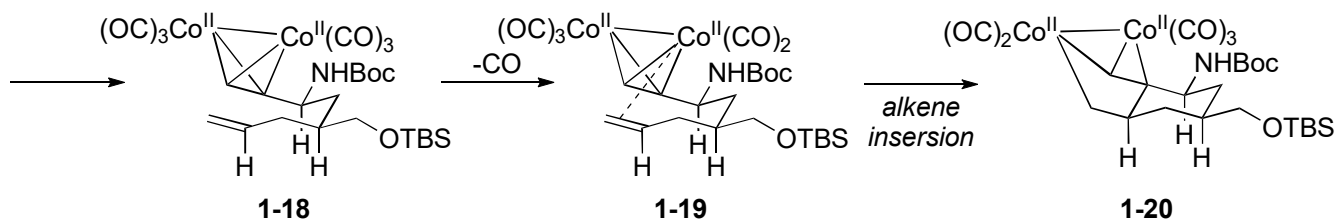
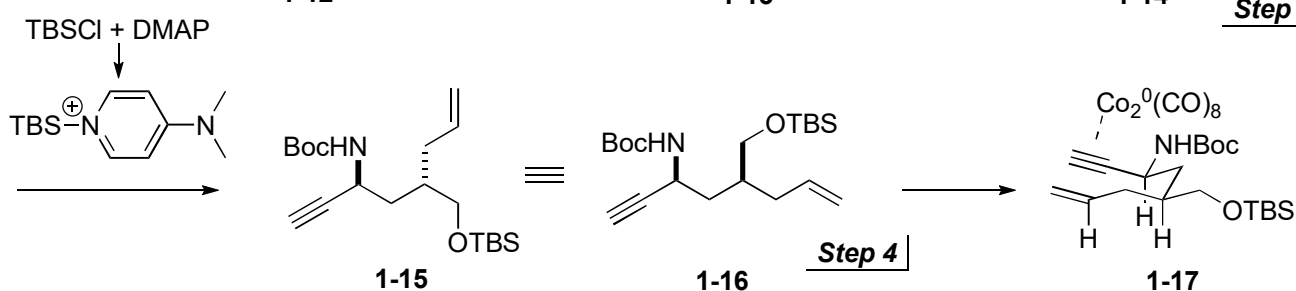
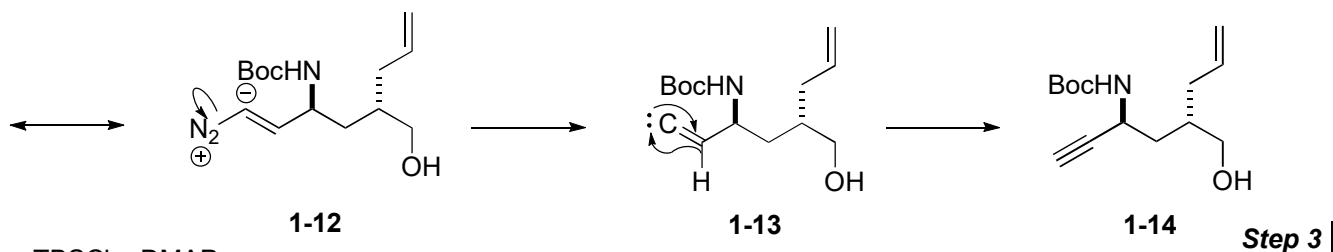
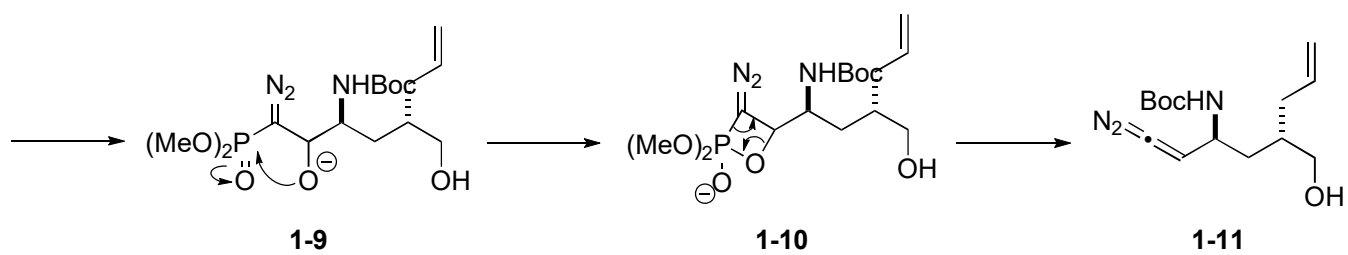


• Fukuyama's retrosynthetic route



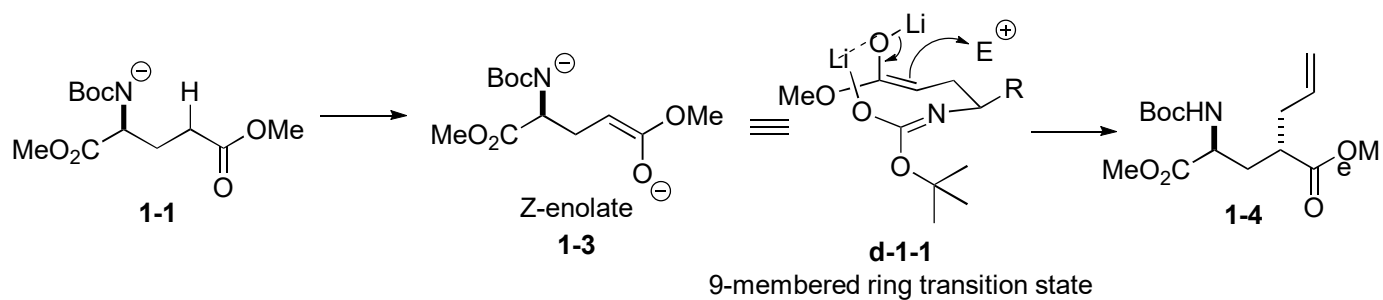
1. Please explain the reaction mechanisms.





• **discussion 1**

- The mechanism of stereo selectivity



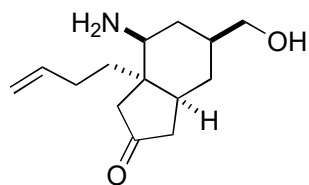
E-enolate also construct 9-membered ring transition state and generate **1-4**.

(Hanessian, S.; Schaum, R. *Tetrahedron. Letters*. **1997**, 38, 163-166)

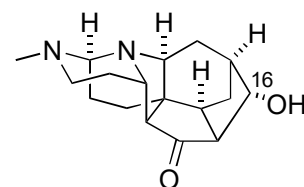
(Hanessian, S.; Margarita, R. *Tetrahedron. Letters*. **1998**, 39, 5887-5890)

2. Please explain the reaction mechanisms.

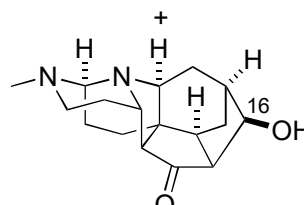
- B** (1.1 eq), Et₃N (3.0 eq), CH₂Cl₂; L-proline (1.0 eq), DMF, rt, 60%
- Boc₂O (5.0 eq), CH₂Cl₂, rt, 93%
- IBX (3.0 eq), EtOAc, 80 °C, 79%
- K₂CO₃ (3.0 eq), MeOH, rt, 98%
- OsO₄ (0.1 eq), NaIO₄ (20 eq), 2,6-lutidine (10 eq), dioxane/H₂O (3/1, v/v), rt; TFA, CH₂Cl₂, 0 °C to rt, 56%



2-1

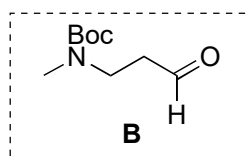


Lycopalhine A (1)

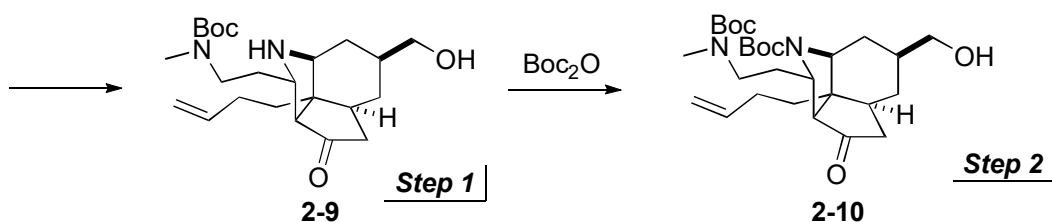
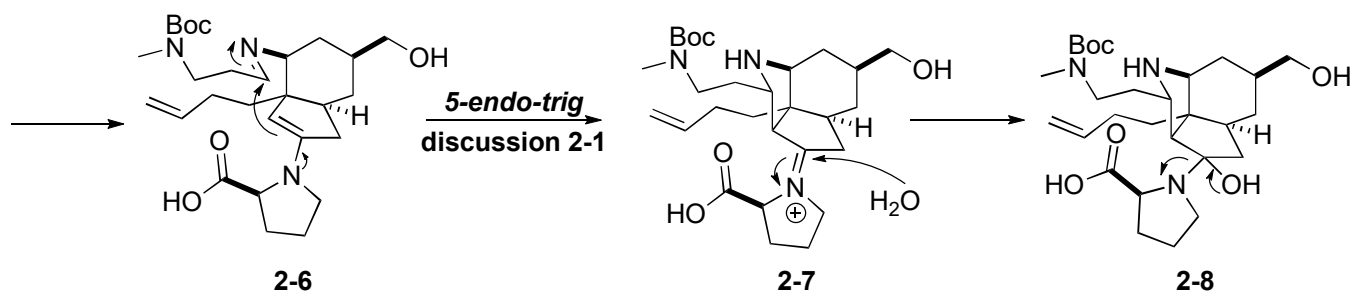
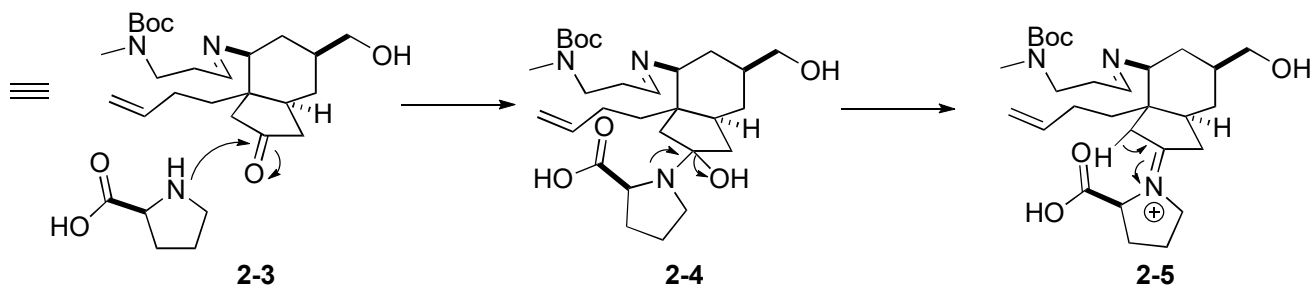
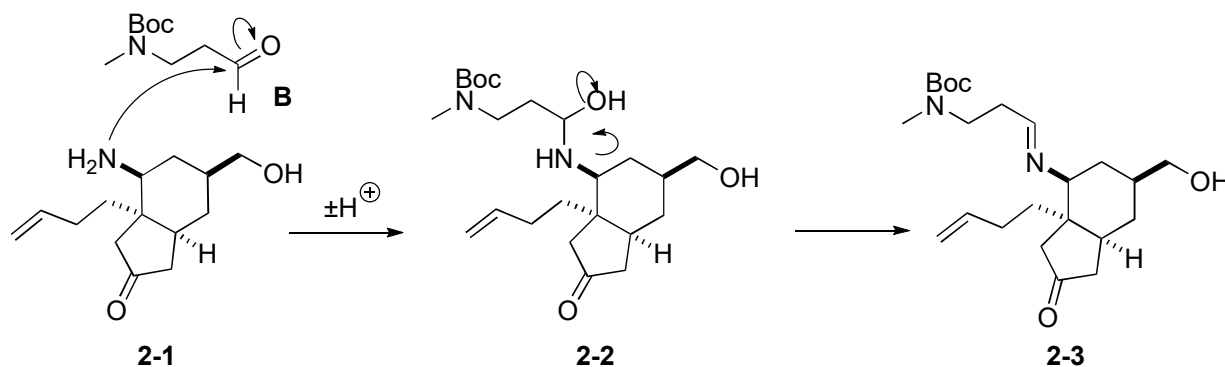


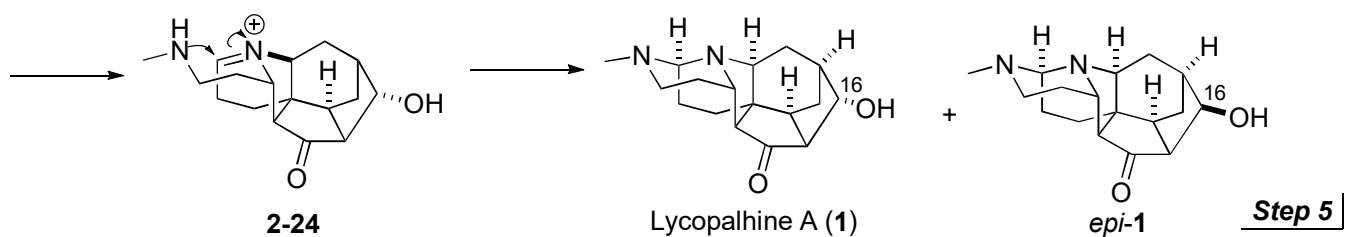
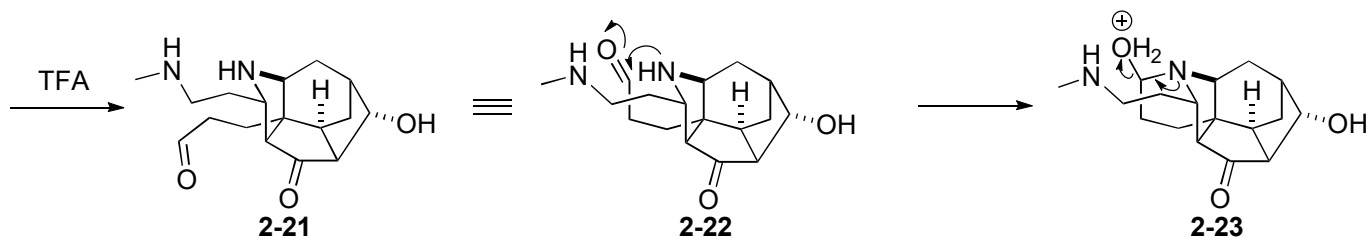
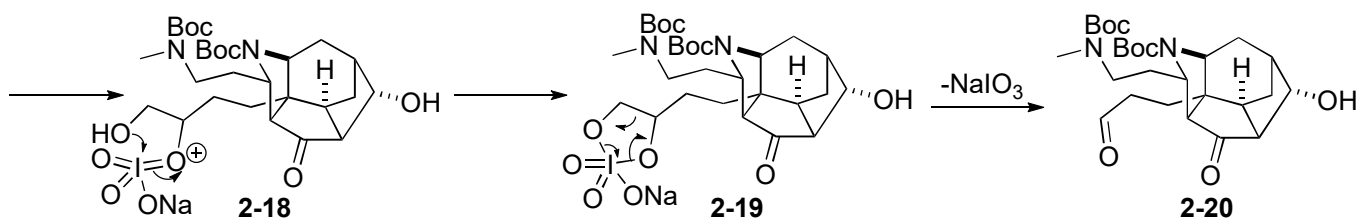
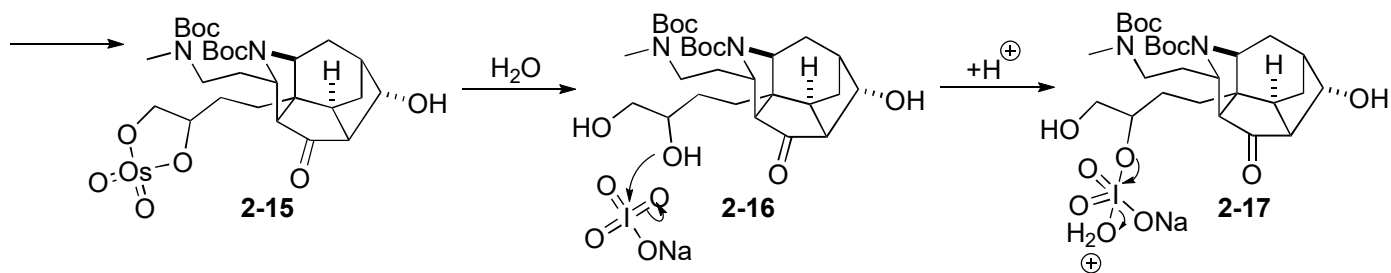
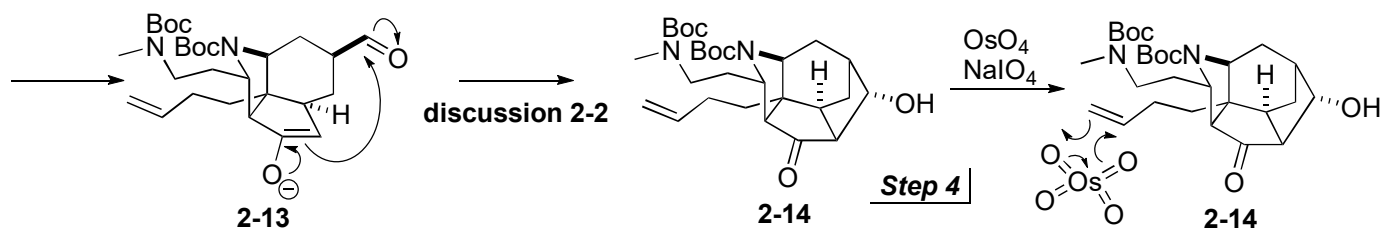
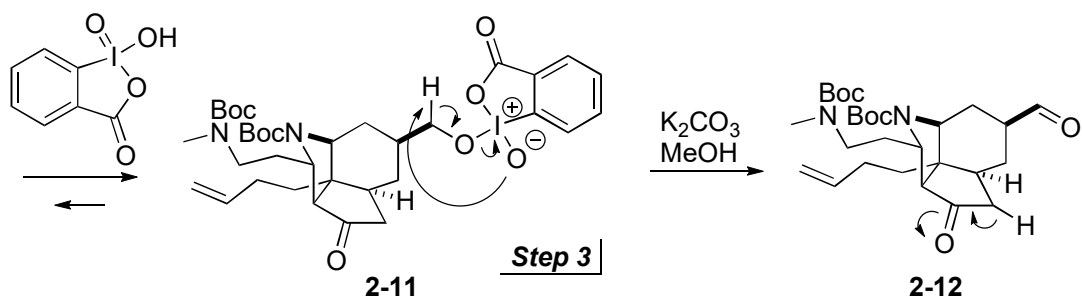
epi-1

dr = 5.5 : 1



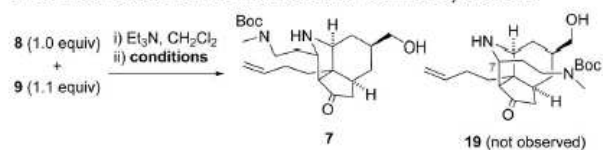
B





• discussion 2-1

Table 1: Conditions for the intramolecular Mannich cyclization.



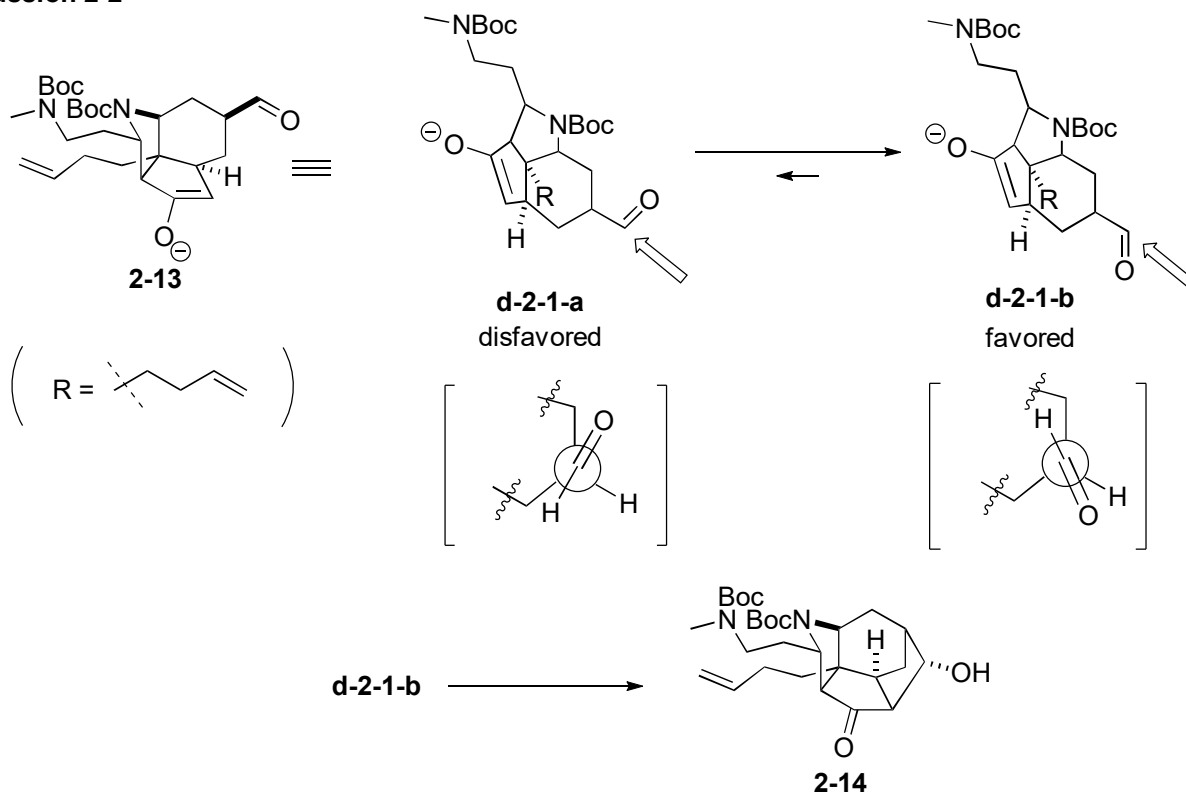
Entry ^[a]	Additives (equiv)	Solvent	T [°C]	Yield ^[b] [%]
1	Yb(OTf) ₃ (1.0)	MeCN	0–RT	–
2	TiCl ₄ (2.0) / Et ₃ N (4.0)	CH ₂ Cl ₂	–30–RT	–
3	K ₂ CO ₃ (3.0)	MeOH	RT	–
4 ^[c]	Et ₃ N (3.0)	PhMe	RT–80	–
5	pyrrolidine (1.0)	DMF	RT	11
6	pyrrolidine (1.0) / AcOH (1.0)	DMF	RT	10
7	D-proline (1.0)	DMF	RT	20
8	L-proline (1.0)	DMF	RT	60
9 ^[c]	L-proline (0.5)	DMF	RT	39
10	L-phenylalanine (1.0)	MeCN	RT	30

[a] Reactions conducted under nitrogen atmosphere for 18–24 h.

[b] Yield of isolated product. [c] Reaction performed without preformation of imine by treatment with Et₃N.

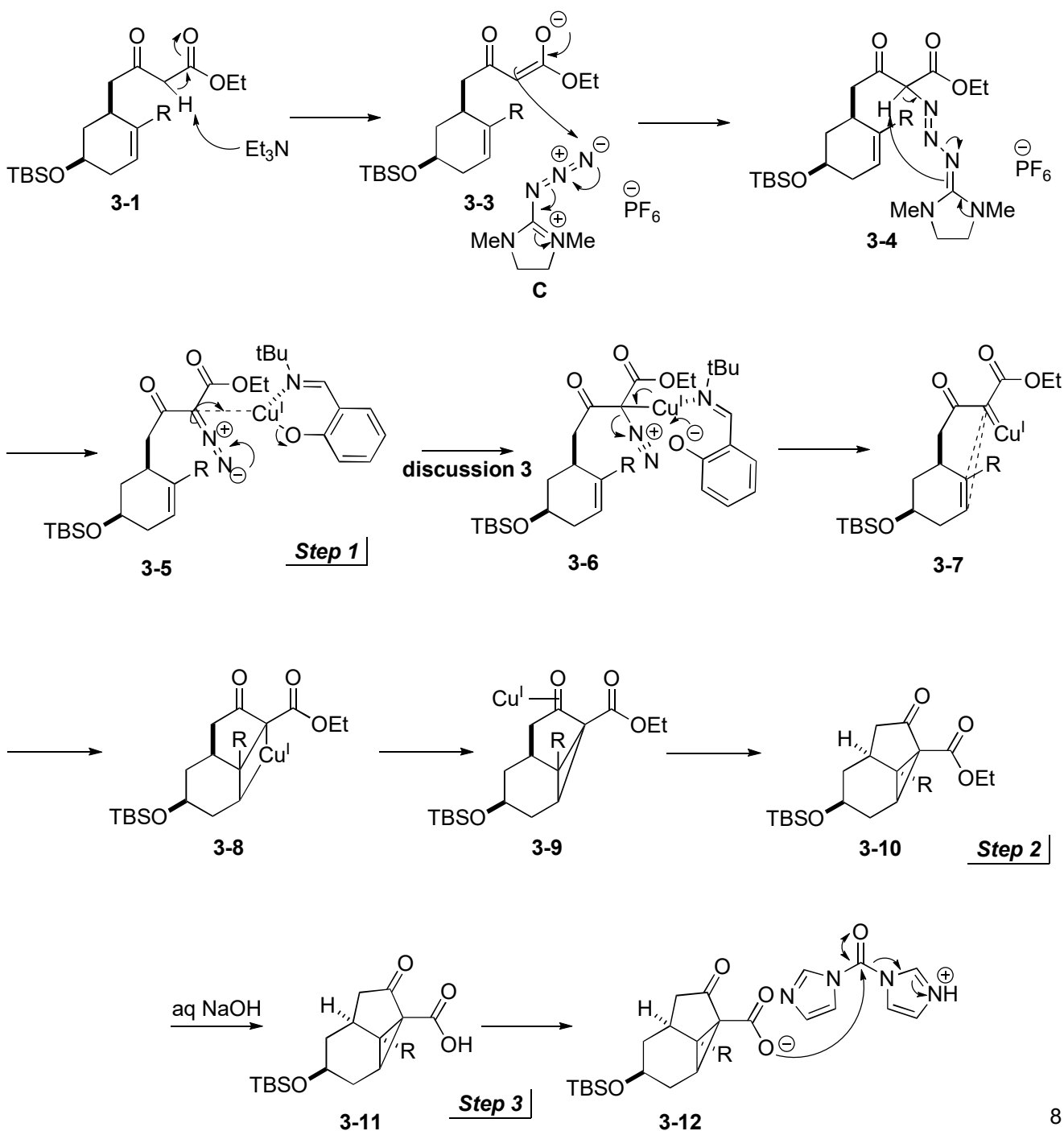
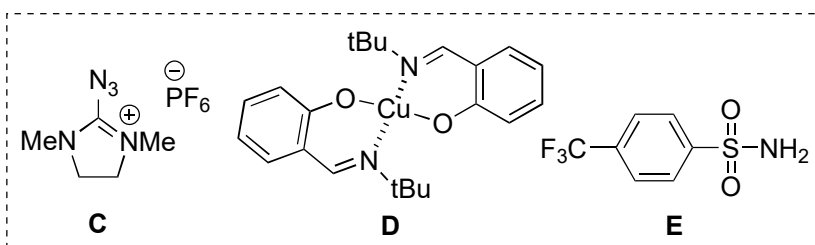
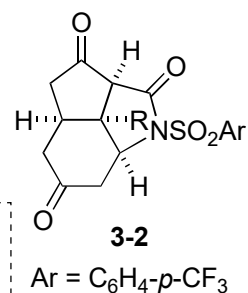
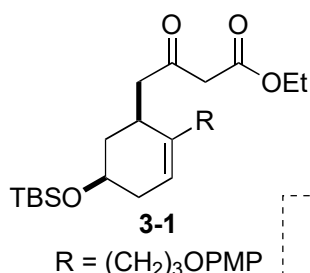
(Ochi, Y.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2016**, 18, 1494–1496)

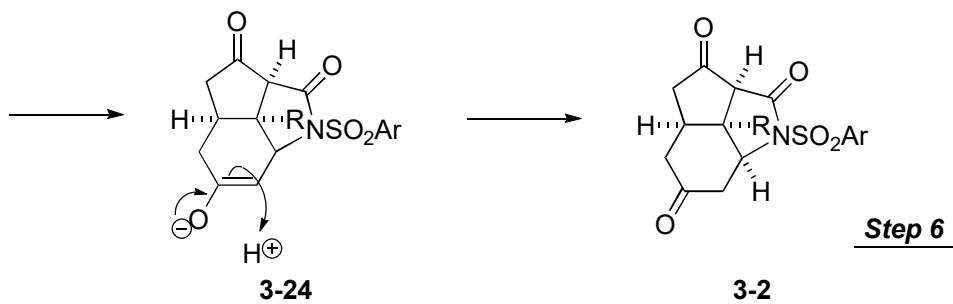
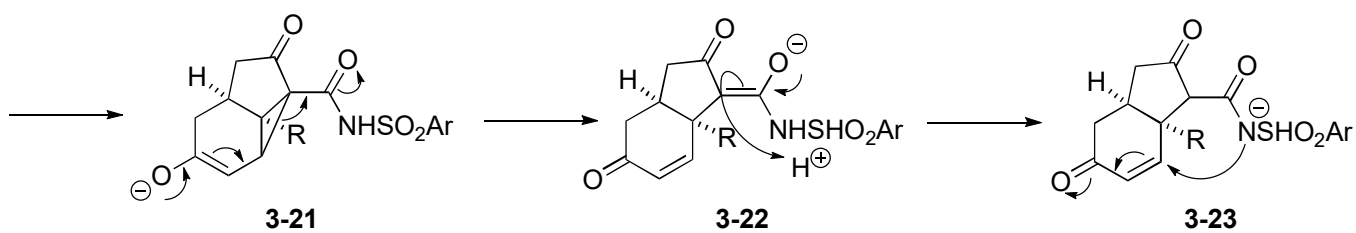
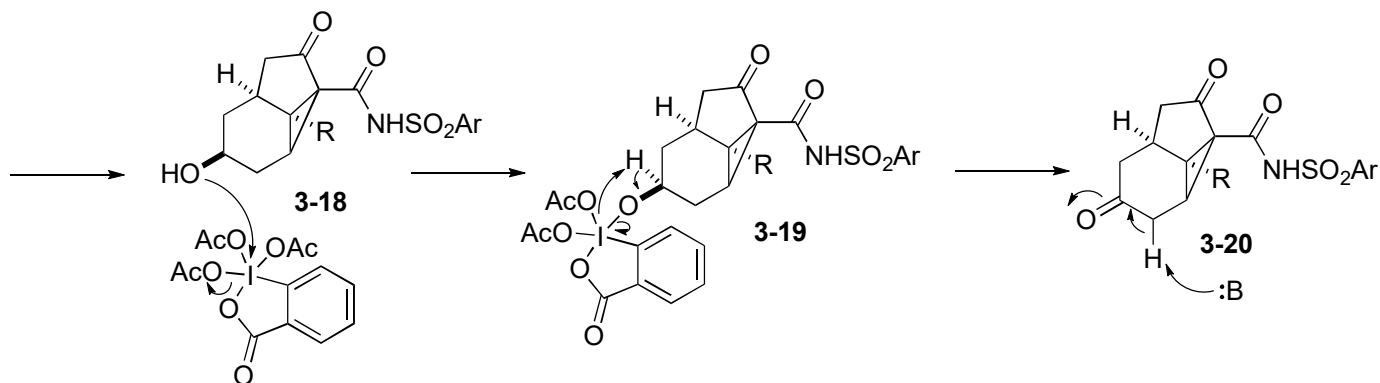
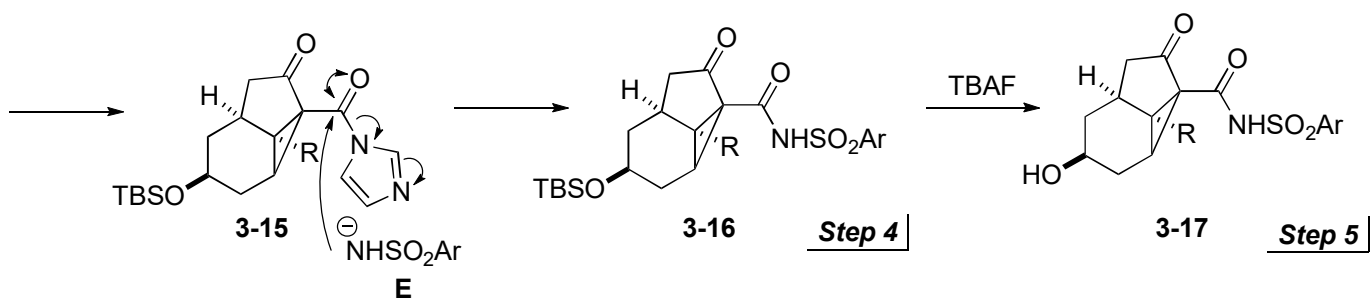
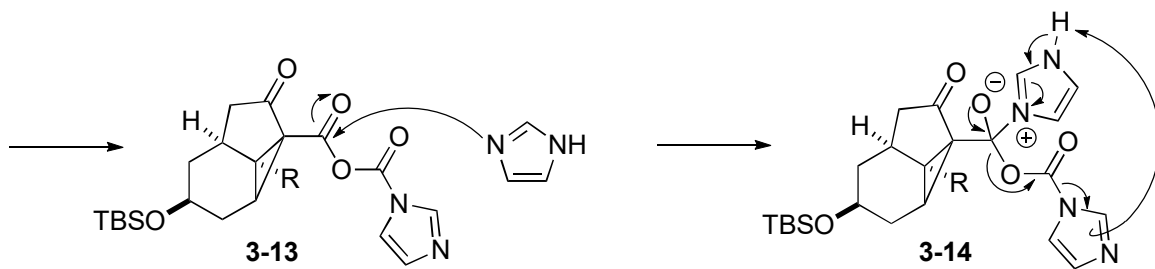
• discussion 2-2



3. Please explain the reaction mechanisms.

- C** (1.2 eq), Et₃N, MeCN/THF, rt, 98%
- D** (6.6 eq), toluene, reflux, 55%
- aq NaOH, EtOH, rt, 91%
- CDI (2.0 eq), THF, rt; **E** (1.5 eq), DBU, rt
- TBAF, THF, rt, 86% (2 steps)
- Dess-Martin periodinane, pyridine, CH₂Cl₂, rt to 40°C, 80%





• **discussion 3**

The way to generate Cu^I

The mechanism bellow was suggested.

(Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, 95, 3300-3310)

