

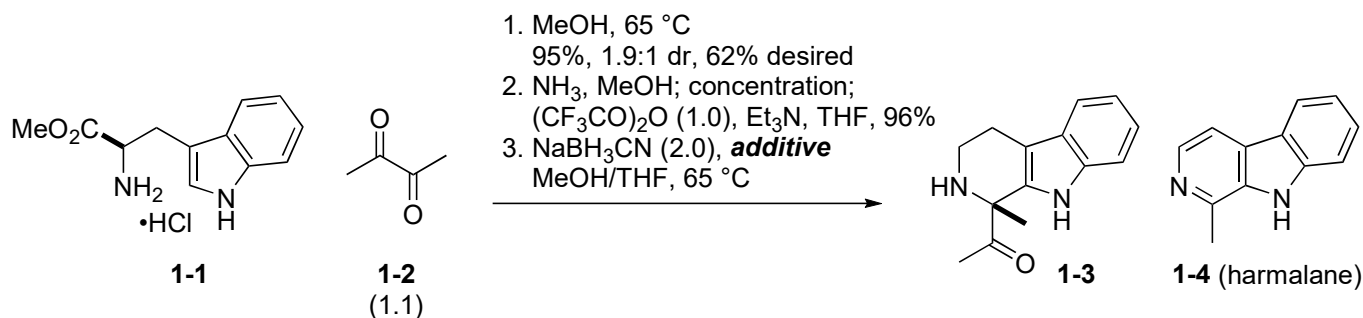
## Problem Session (6) - Problem

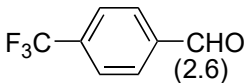
2021.4.10. Yusuke Imamura

Please provide the reaction mechanisms. Values in the parentheses are the amount (eq.) of the reagent.

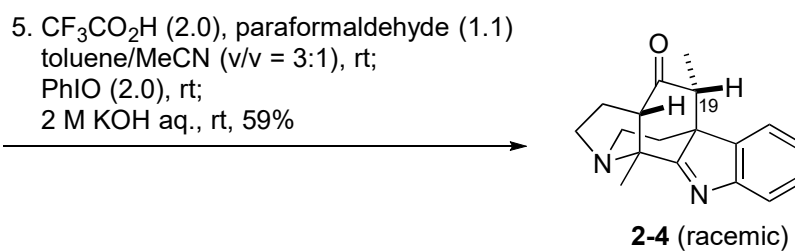
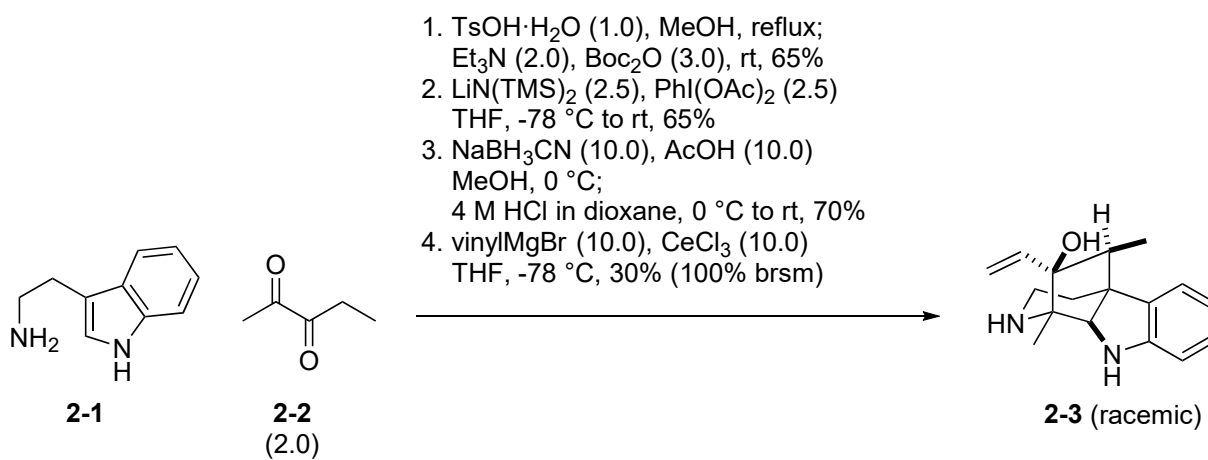
In 3rd reaction of problem 1, please provide each reaction mechanism w/ or w/o the additive and explain the effect of the additive.

### • problem 1



<b>additive</b>	<b>1-3</b>	<b>1-4 (harmalane)</b>
none	<20%	major
 (2.6)	71%	not mentioned

### • problem 2

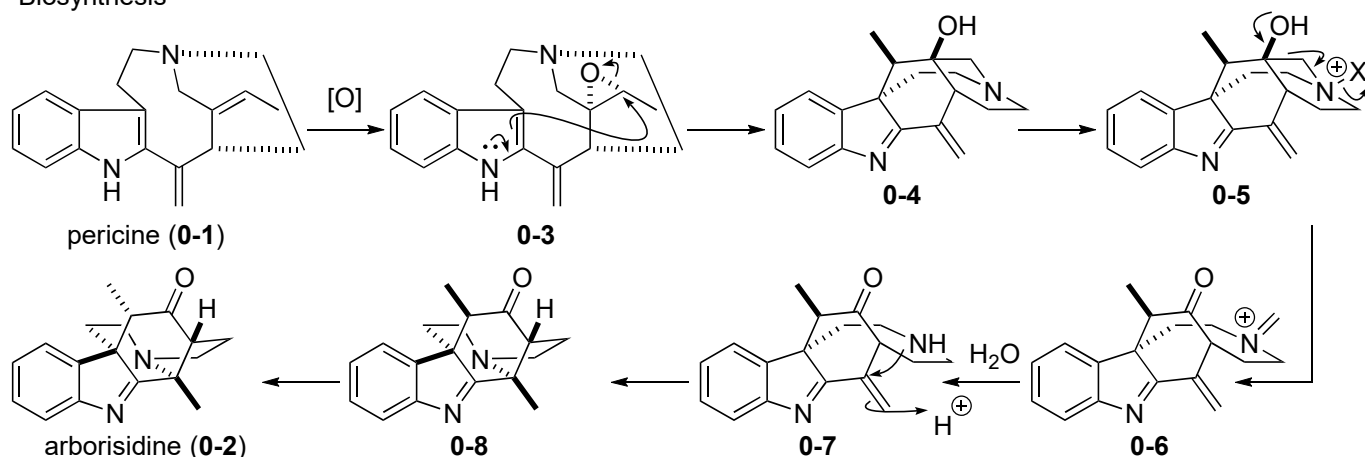


## Problem Session (6) - Answer

Topic: Total Synthesis of Arborisidine

### 0. Introduction of Arborisidine

- Isolation: from Malayan *K. arborea* Blume by Kam and co-workers (Wong, S.-P.; Chong, K.-W.; Lim, K.-H.; Lim, S.-H.; Low, Y.-Y.; Kam, T.-S. *Org. Lett.* **2016**, *18*, 1618–1621.)
- Biosynthesis

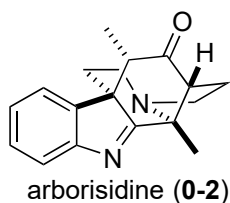


- Biological activities

Arborisidine inhibits gastric cancer in vivo when used in combination with pimelautide.

(Chinese Patent CN106540237 A, 2016.)

- Total syntheses of related Monoterpene Indole Alkaloids

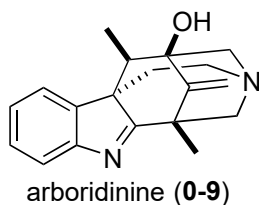


(+)-arborisidine: (problem 1)

Zhou, Z.; Gao, A. X.; Snyder, S. A. *J. Am. Chem. Soc.* **2019**, *141*, 1650.

(-)-arborisidine (enantiomer): (problem 2)

Andres, R.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2020**, *142*, 14276.



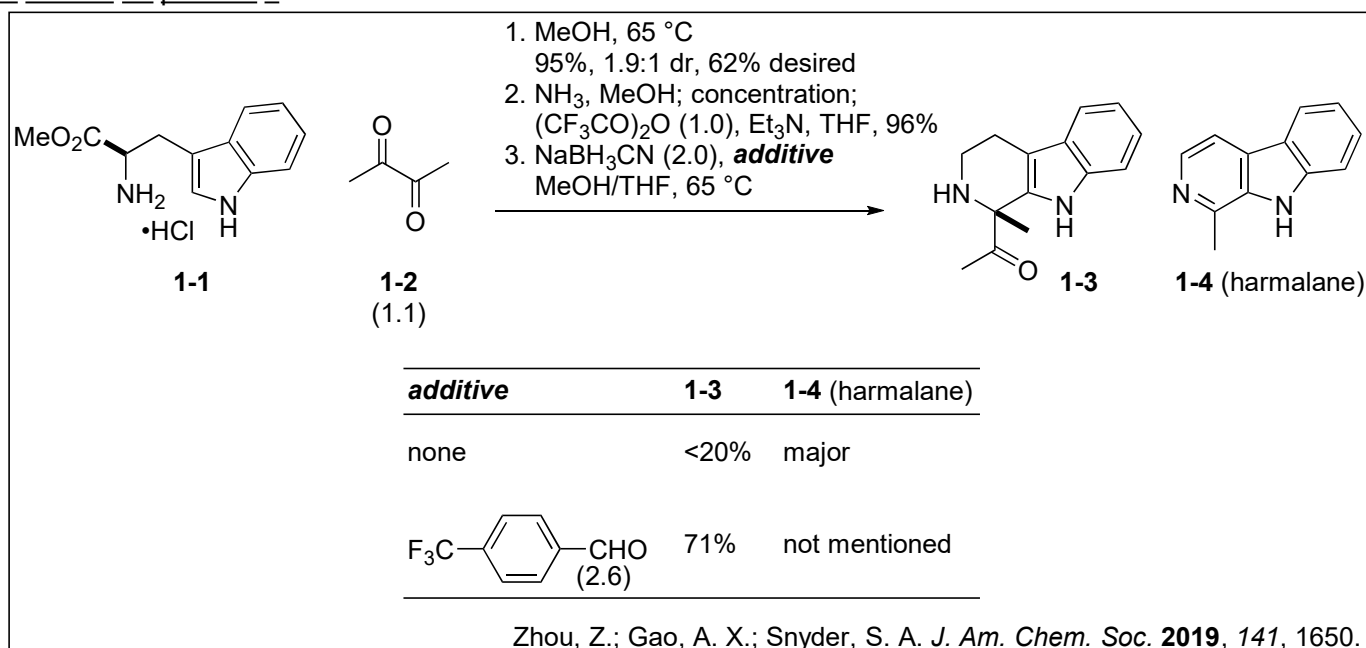
(?)-arboridinine:

Gan, P.; Pitzen, J.; Qu, P.; Snyder, S. A. *J. Am. Chem. Soc.* **2018**, *140*, 919.

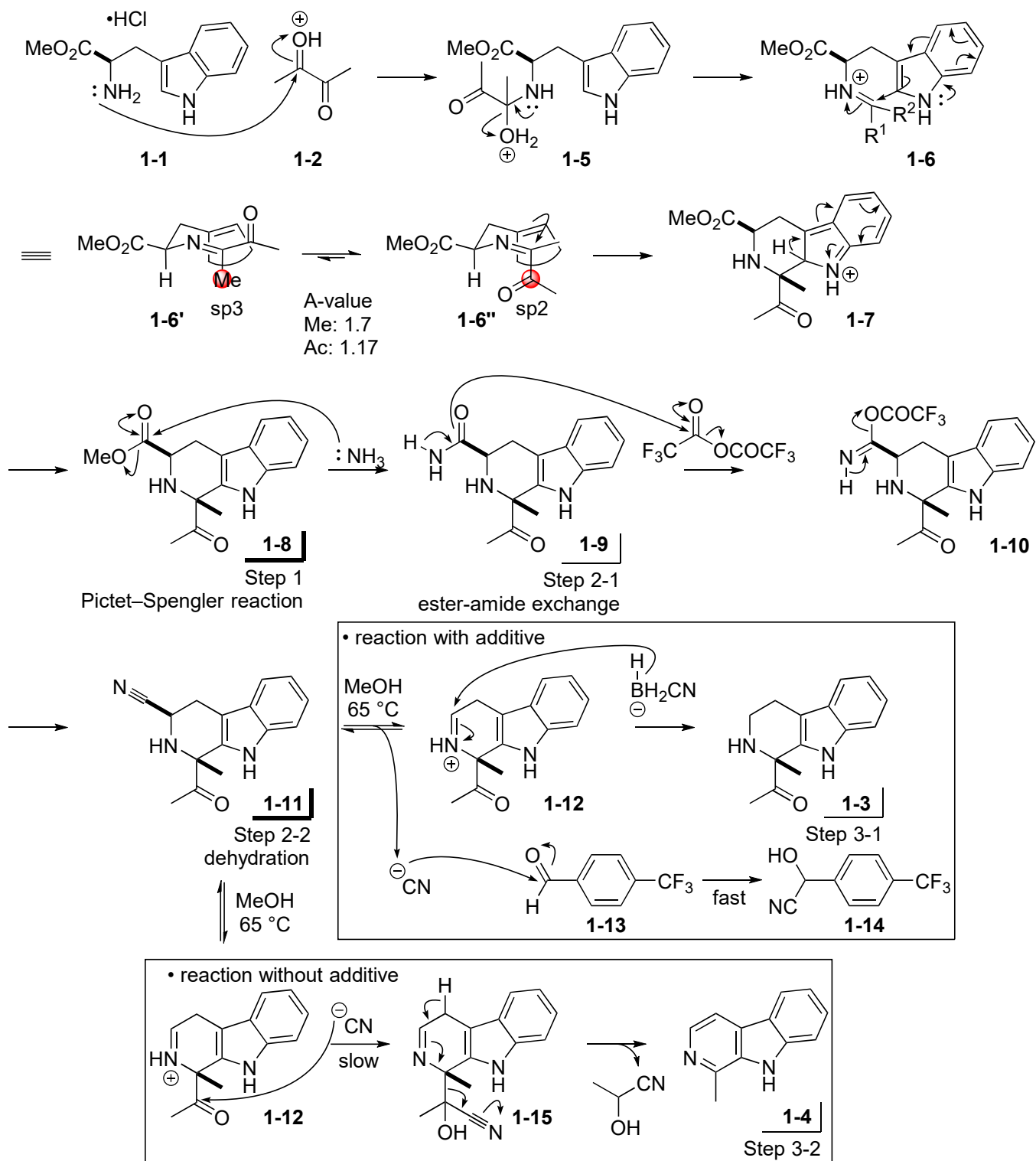
(+)-arboridinine:

Zhang, Z.; Xie, S.; Cheng, B.; Zhai, H.; Li, Y. *J. Am. Chem. Soc.* **2019**, *141*, 7147.

### 1. Answer for problem 1

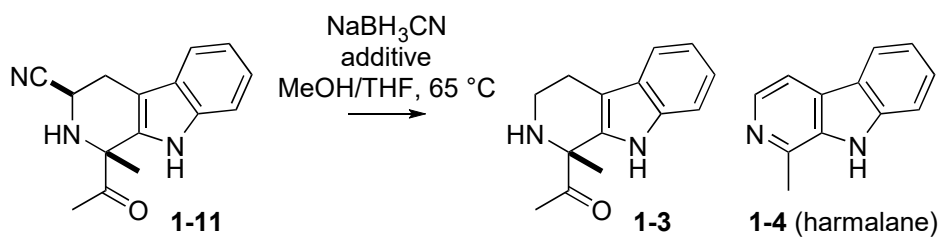


## 1.1. mechanisms



## 1.2. discussion

### • Screening of benzaldehyde derivative

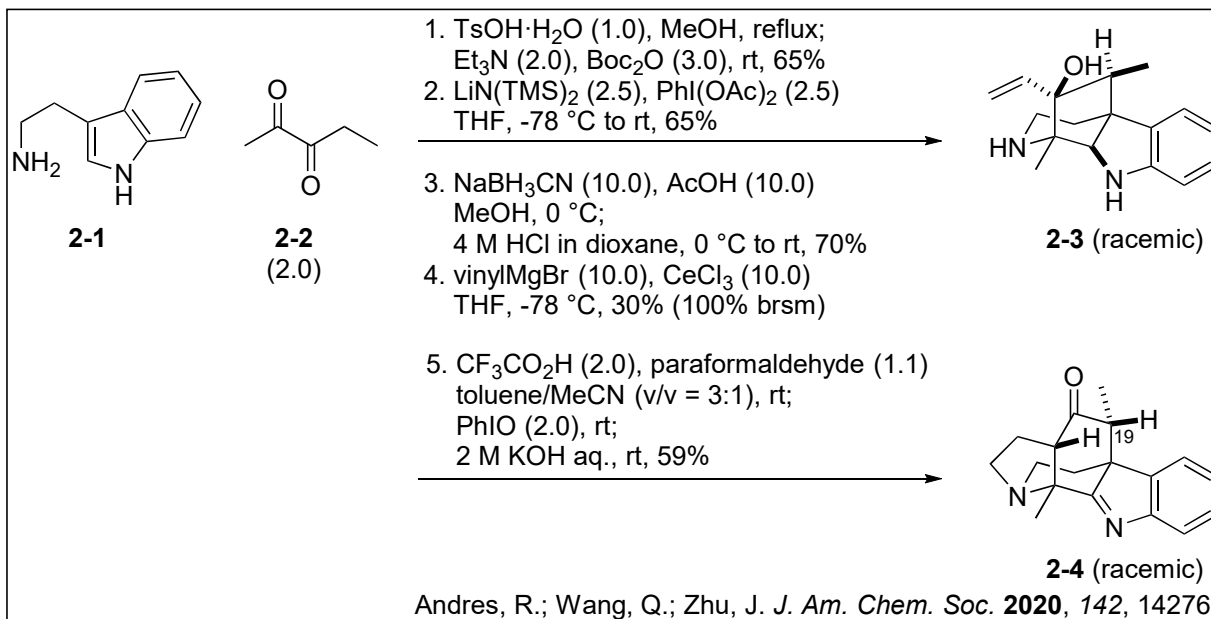


additive	<b>1-3</b>
none	<20%
$\text{C}_6\text{H}_5\text{CHO}$	56%
4-MeOC <sub>6</sub> H <sub>4</sub> CHO	42%
4-ClC <sub>6</sub> H <sub>4</sub> CHO	46%
4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	69%

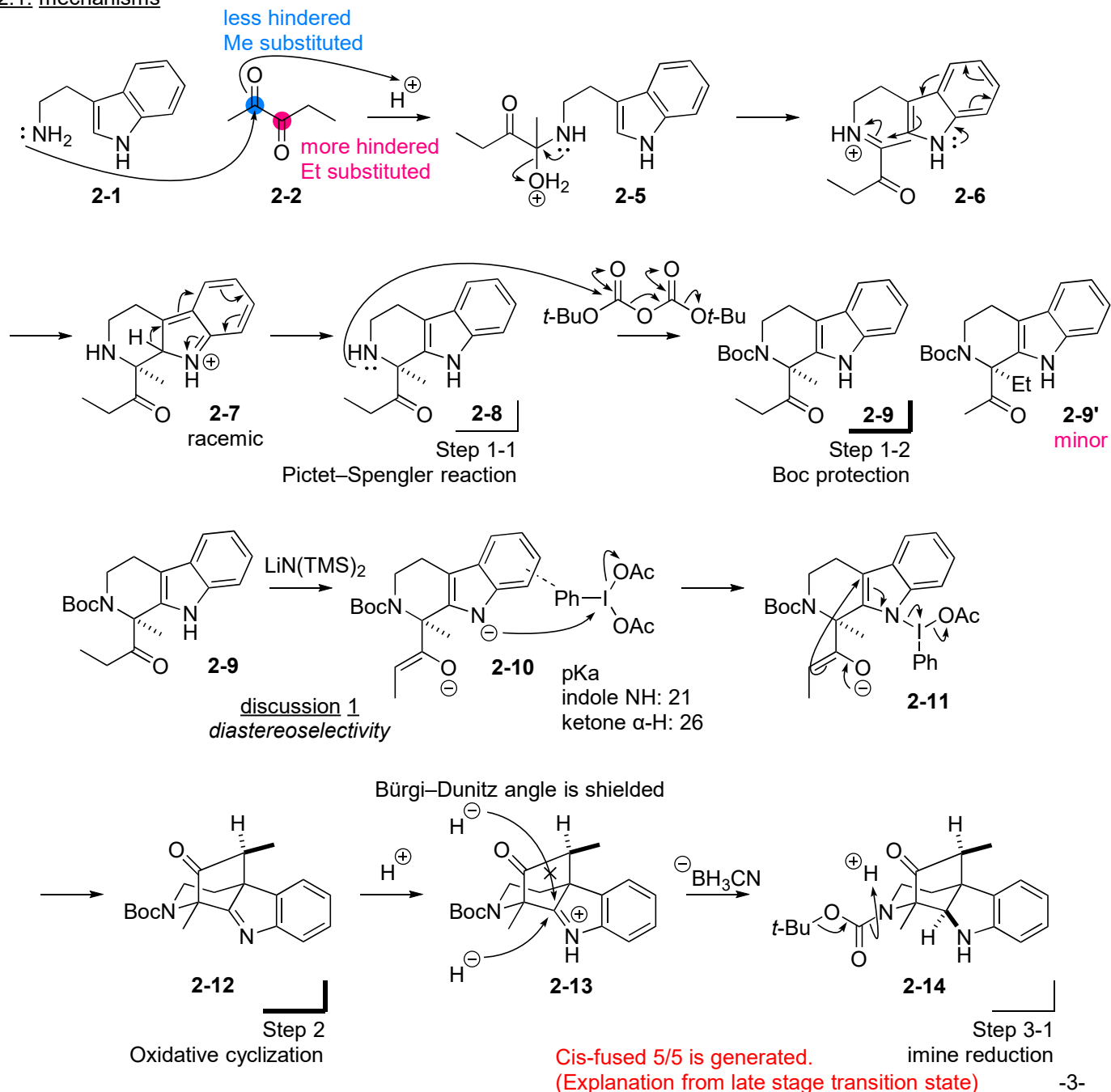
Benzaldehydes were added as a cyanide scavenger.

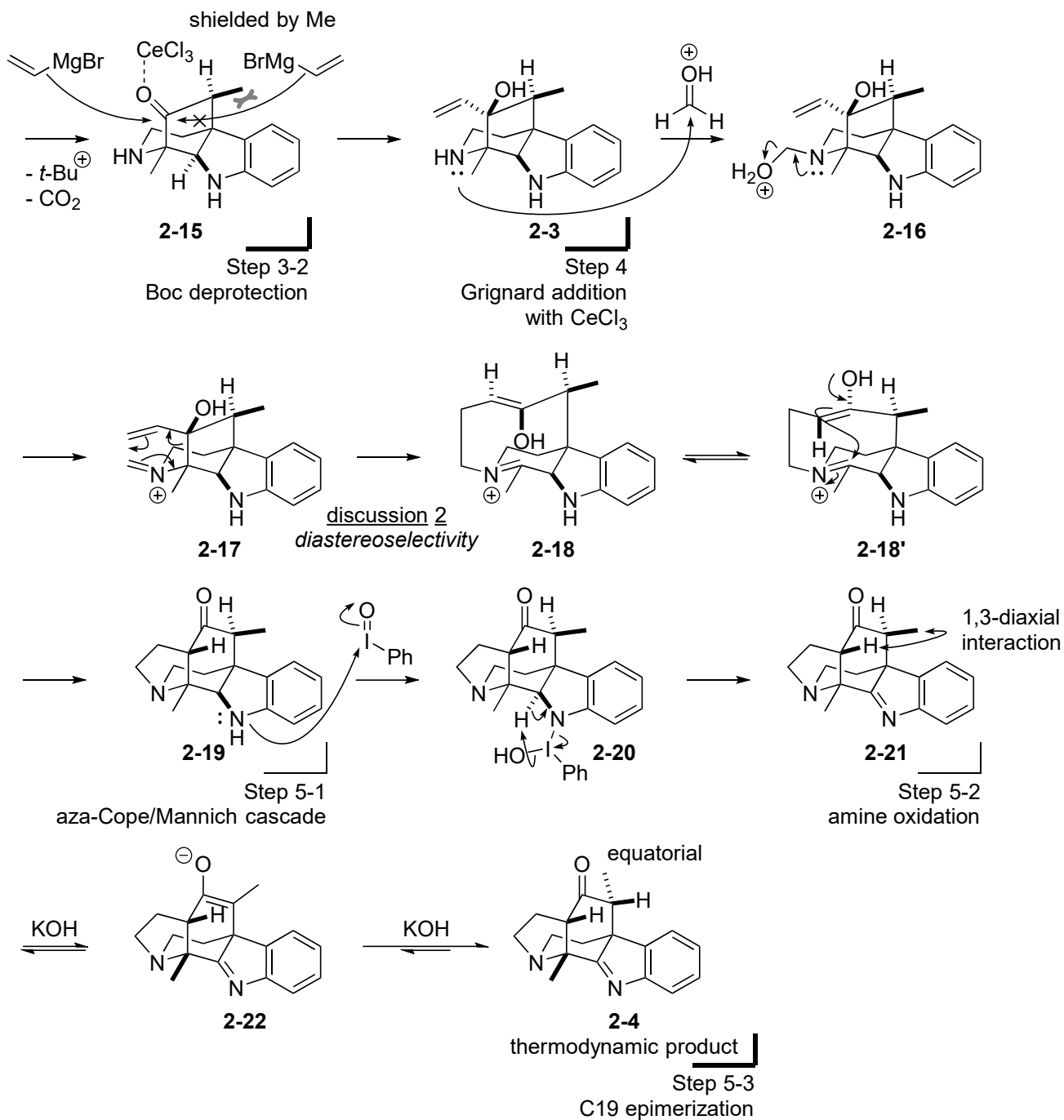
More electron-deficient aldehydes were effective, because it made the nucleophilic addition of cyanide faster.

## 2. Answer for problem 2



### 2.1. mechanisms

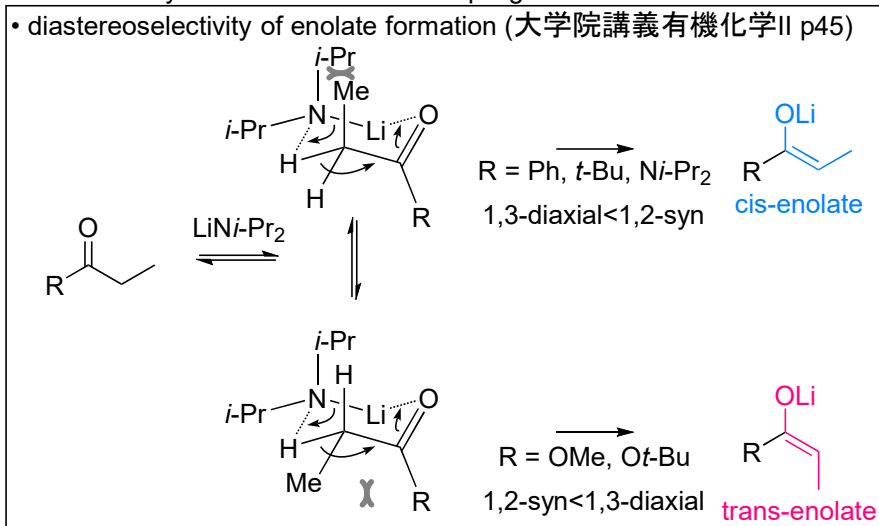


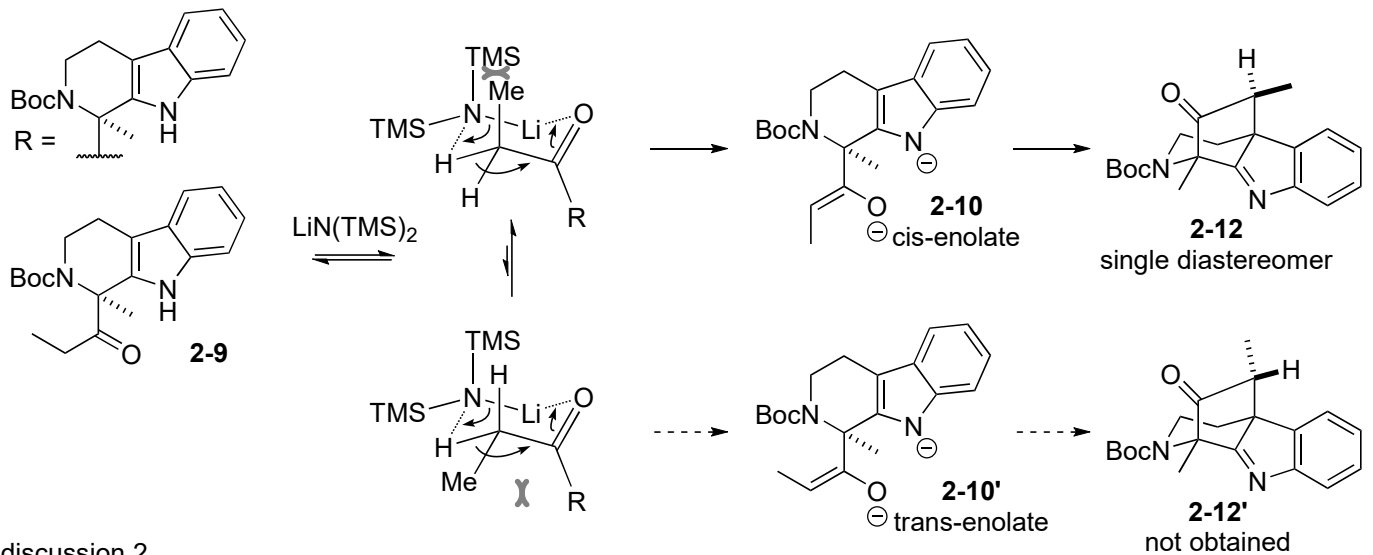


## 2.2. discussions

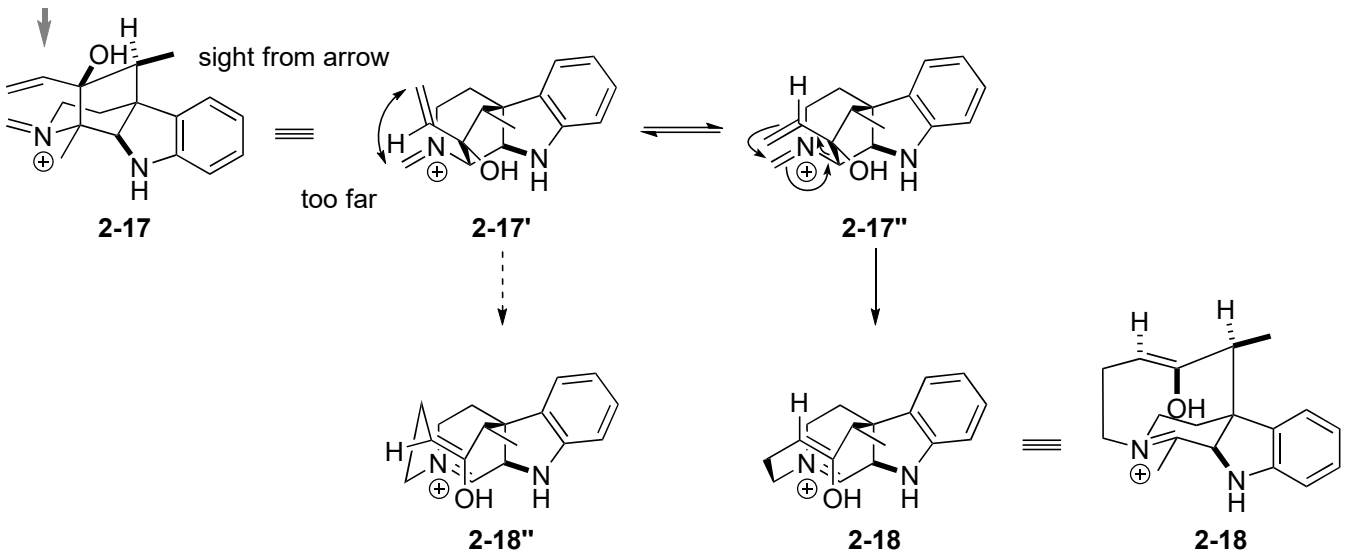
### • discussion 1

#### diastereoselectivity of oxidative enolate coupling

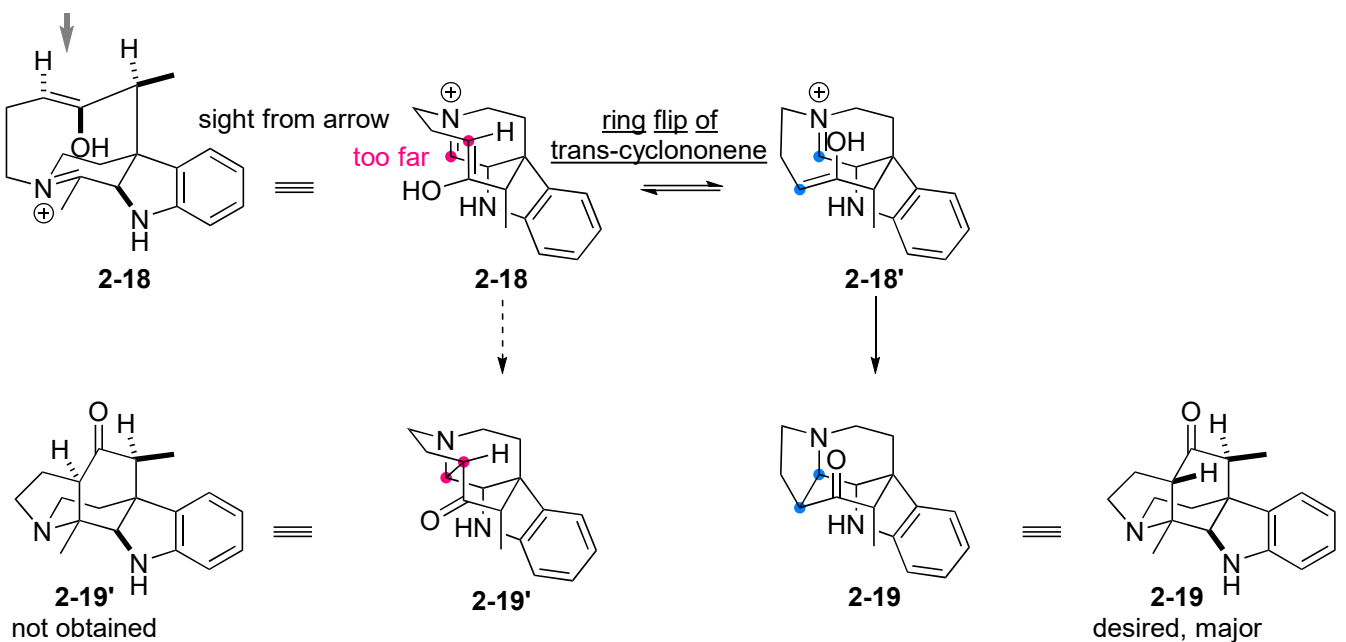




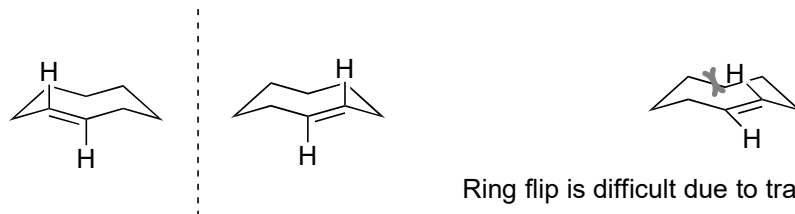
• discussion 2  
 diastereoselectivity of aza-Cope/Mannich cascade  
 ♣ diastereoselectivity in aza-Cope reaction



♣ diastereoselectivity in Mannich reaction



♣ molecular asymmetry of trans-cycloalkene (ring flip of trans-cycloalkene)

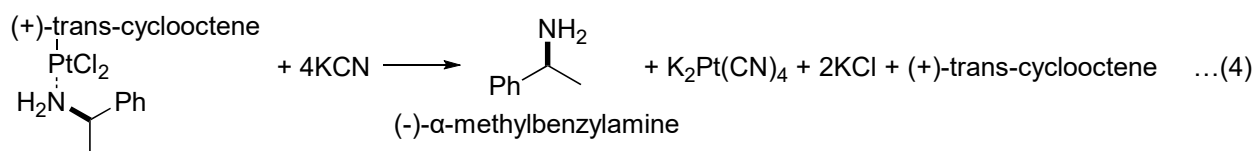
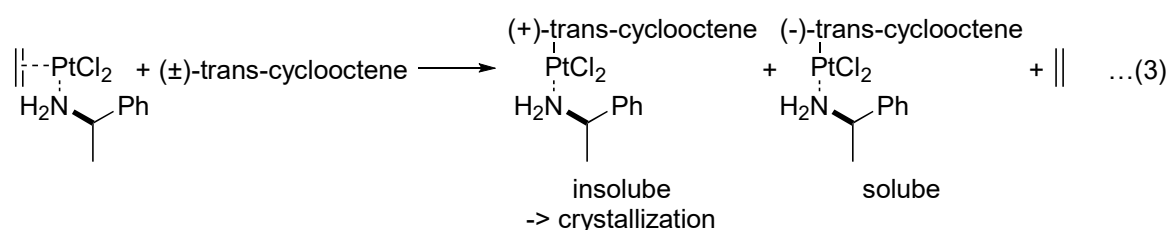
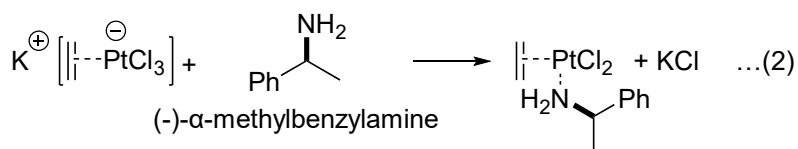


Ring flip is difficult due to transannular interaction.

These cyclooctenes are enantiomers and could be separated.

(Cope, A. C.; Ganellin, C. R.; Johnson, Jr., H. W.; Van Auken, T. V.; Winkler, H. J. S.

*J. Am. Chem. Soc.* **1963**, *85*, 3276.)



These procedures were applied for trans-cyclononene and trans-cyclodecene.

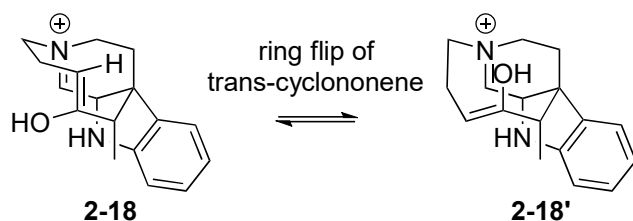
However, several optimizations to suppress the racemization were needed for the isolation of optically active trans-cyclononene, and trans-cyclodecene was not able to be isolated.

And also, thermal stability of isolated trans-cyclooctene and trans-cyclononene were tested.

(Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649.

Cope, A. C.; Banholzer, K.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644.)

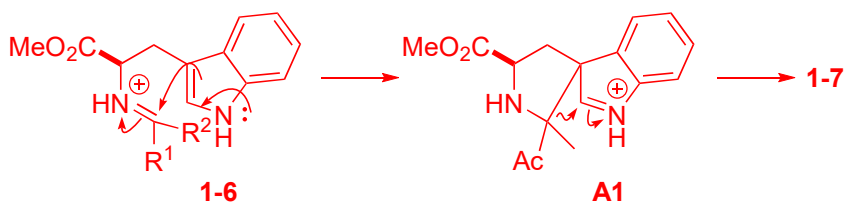
	activation energy	half-life time
cyclooctene	35.6 $\pm$ 0.9 kcal/mol	122 h (132.7 °C), 15 h (156.4 °C), 1 h (183.9 °C)
cyclononene	20 $\pm$ 2 kcal/mol	4 min (0 °C), 20 s (20 °C), 6 s (30 °C)



The ring flip of **2-18** is fast enough for the aza-Cope/Mannich cascade reaction.

## Appendix

### • Pictet-Spengler reaction from C2 or C3



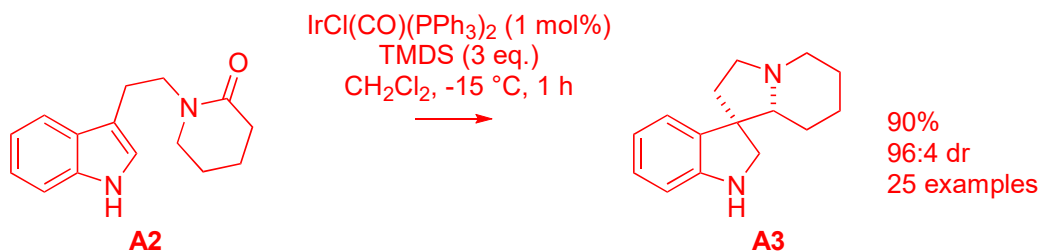
Nucleophilic attack from indole C3 position can be possible.

However, construction of adjacent tetrasubstituted olefin seems to be difficult in this situation.

In different situation, C3 attack are reported.

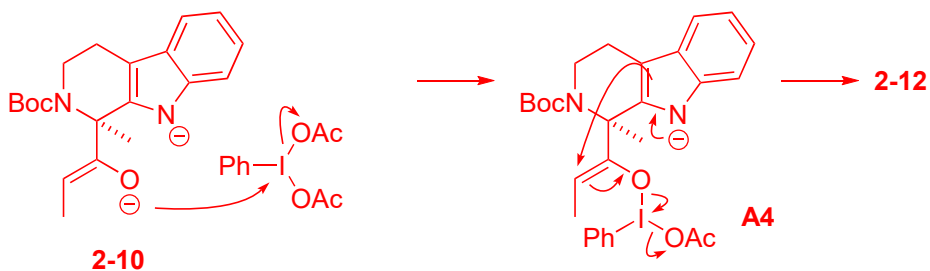
ref. Zheng, C.; Xia, X.-L.; You, S. L. *Chem.* **2018**, *4*, 1952. (mechnistic study)

Gabriel, P.; Gregory, A. W.; Darren, D. J. *Org. Lett.* **2019**, *21*, 6658. (selective example of interrupted P-S reaction)



Construction of continuous tetrasubstituted carbon was not reported.

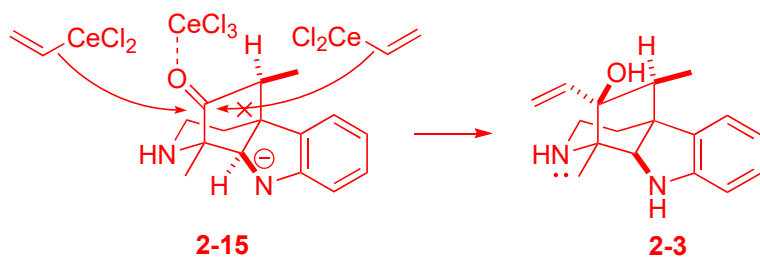
### • Alternative mechanism for oxidative cyclization



Aromatic interaction between indole and PIDA might not such large.

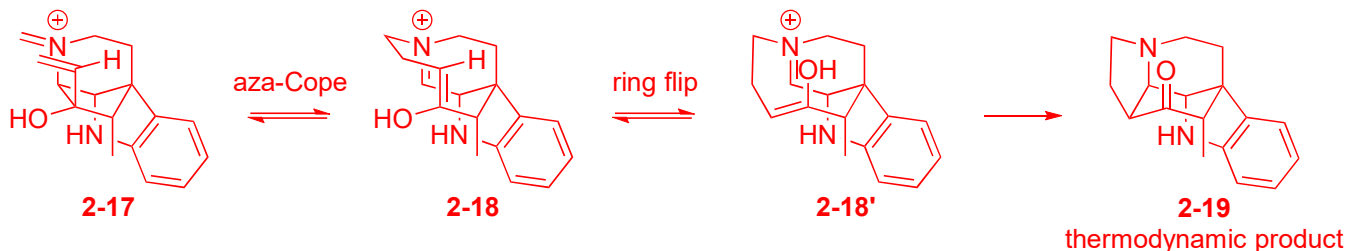
More nucleophilic oxygen might react with PIDA.

### • Vinyl Grignard addition



Electrostatic repulsion might also exist.

### • Thermodynamic explanation of aza-Cope/Mannich cascade



**2-19** might be thermodynamically yielded from **2-17**.

i.e. **2-17**, **2-18**, **2-18'** are in equilibrium and reaction from **2-18'** to **2-19** is irreversible.