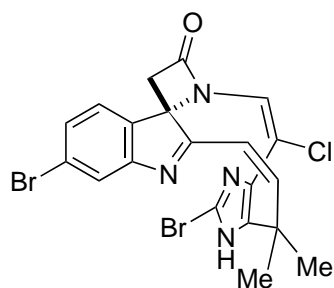


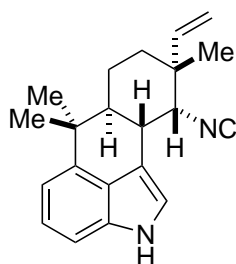
# Problem Session (1) - Answer

2017.7.1 Kohei Ogino

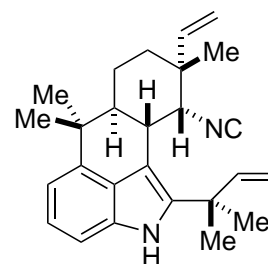
Topic: natural product including indole structure



(±)-Chartelline C  
2-5



(-)-hapalindole U  
3-3



(+)-ambiguine H  
3-5

## 0. Introduction

### 0.1. Isolation

Chartelline C

Isolated from the Marine Bryozoan *Chartella papyracea*

(Anthoni, U.; Chevolut, L.; Larsen, C.; Nielsen, Per. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709)

hapalindole U

Isolated from the Blue-Green Alga *Hapalosiphon fontinalis*

(Moore, R. E.; Cheuk, C.; Yang, X. Q.; Patterson, G. M. *J. Org. Chem.* **1987**, *52*, 3773.)

ambiguine H

Isolated from the Cyanobacterium *Fischerella* sp. Collected in Israel

Raveh, A.; Carmeli, S. *J. Nat. Prod.* **2007**, *70*, 196-201

### 0.2. Structural Feature

Chartelline C

composed of indolenine, imidazole, and  $\beta$ -lactam heterocycles arrayed in a dense  $\pi$ - $\pi$  stacking framework

hapalindole U, ambiguine H

tetracycle core

4 stereo centers

### 0.3. Total Synthesis

Chartelline C

Baran, Phil. S.; Shenvi, Ryan. A.; *J. Am. Chem. Soc.* **2006**, *128*, 14028.

hapalindole U

Muratake, H.; Natsume, M. *Tetrahedron* **1989**, *46*, 6331-6342.

Baran, P. S.; Thomas J. Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404-408.

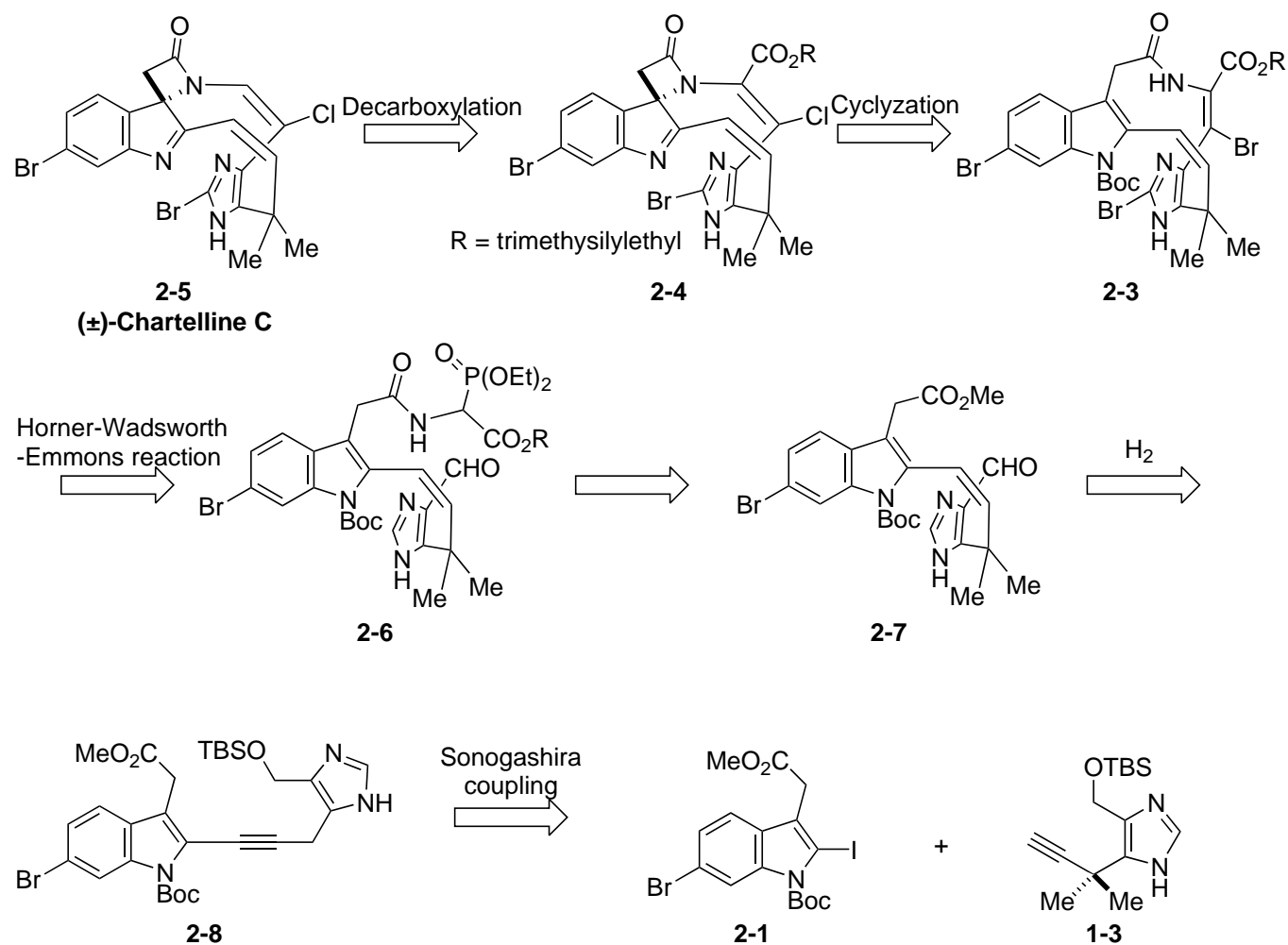
Ryan, J. R.; Robert, M. W.; *J. Org. Chem.* **2012**, *77*, 519-524.

ambiguine H

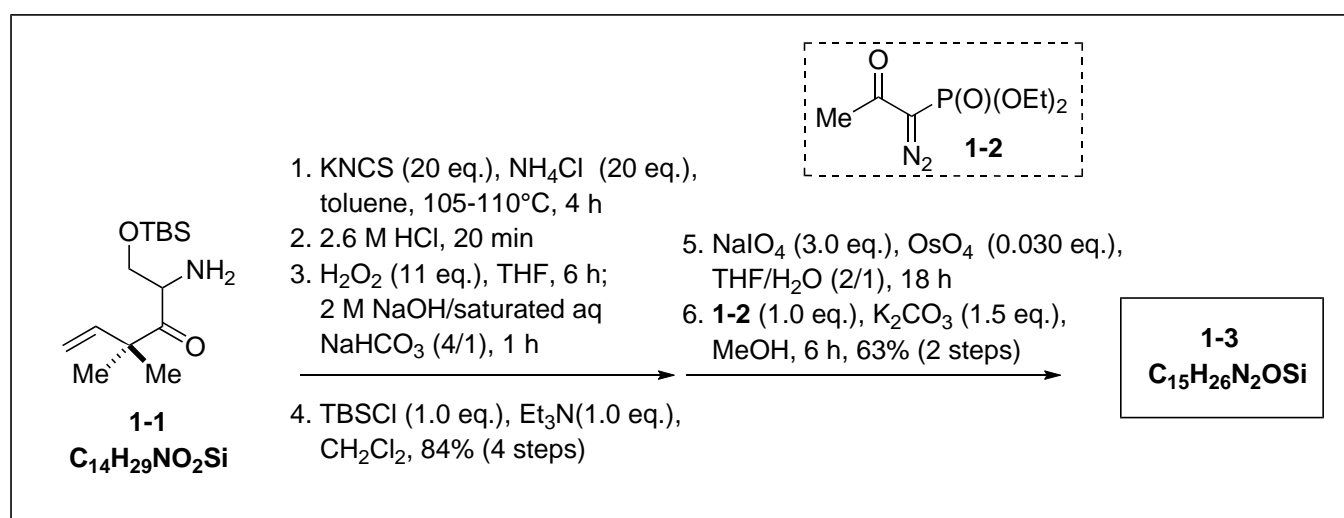
Baran, P. S.; Thomas J. Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404-408.

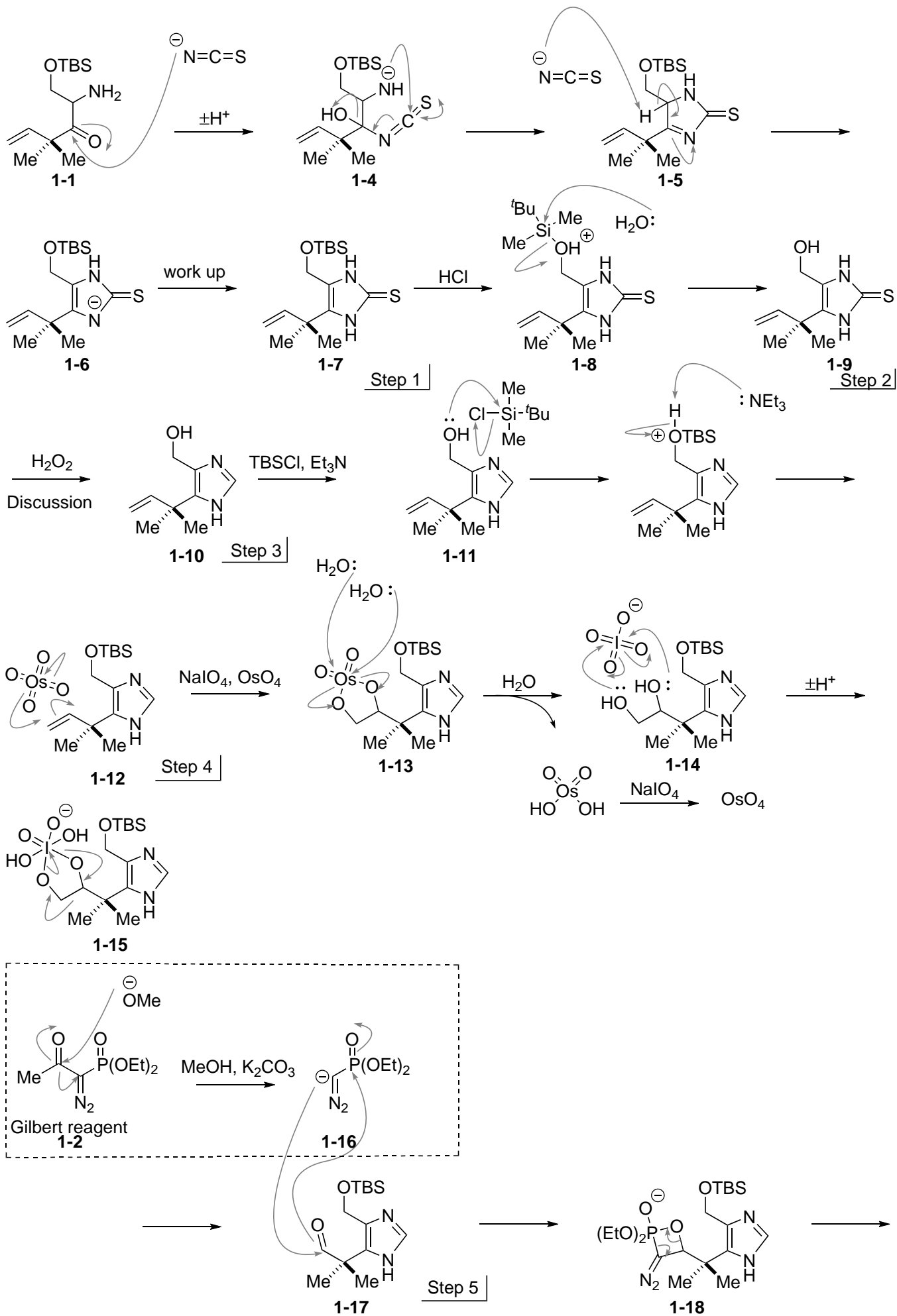
1. Total synthesis of (±)-Chartelline C by Baran, P. S. et al. [*J. Am. Chem. Soc.* **2006**, *128*, 14028.]

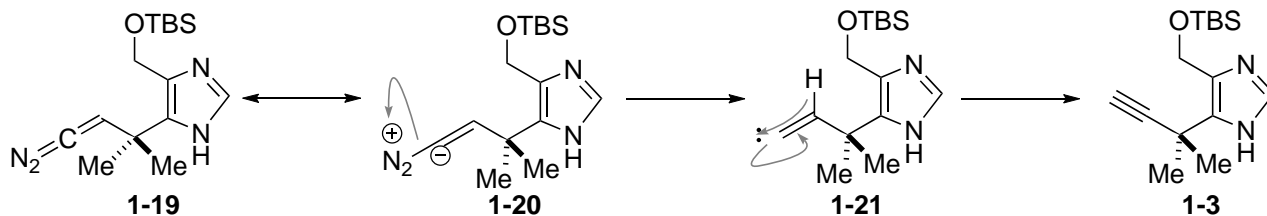
1.1 Retrosynthesis



1.2 Answer of (1)

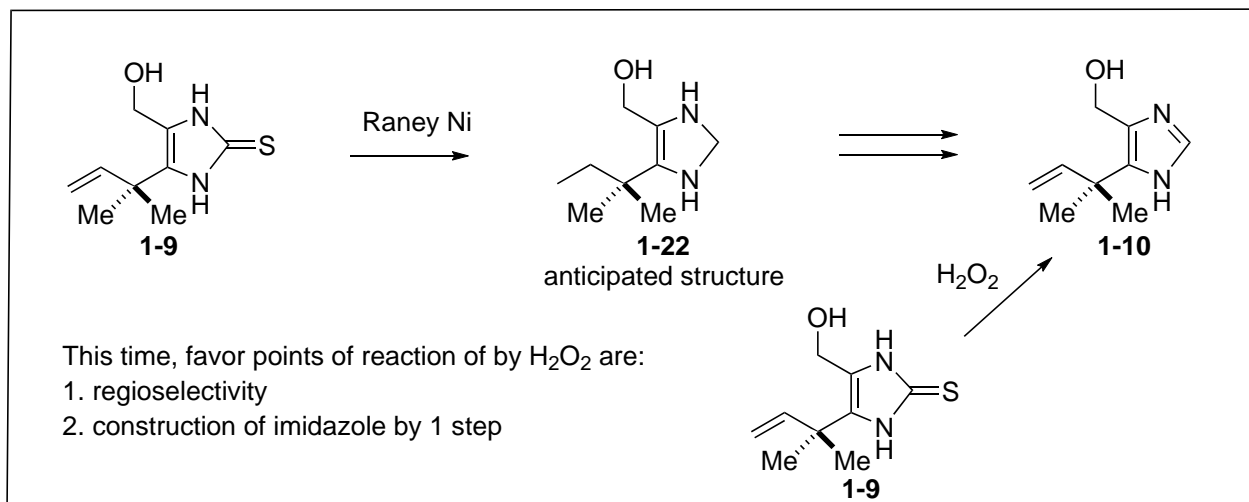




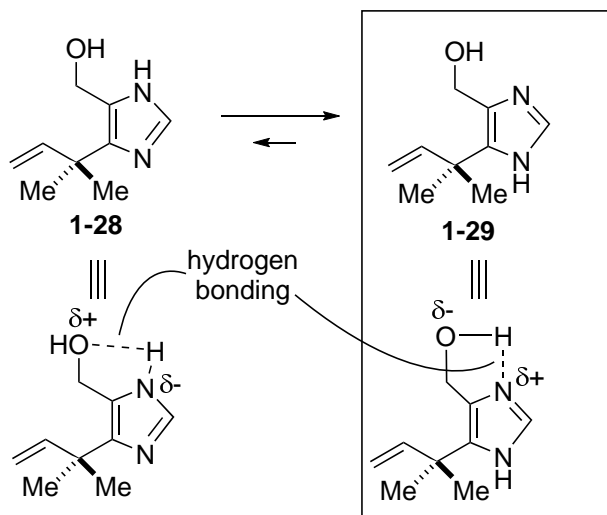
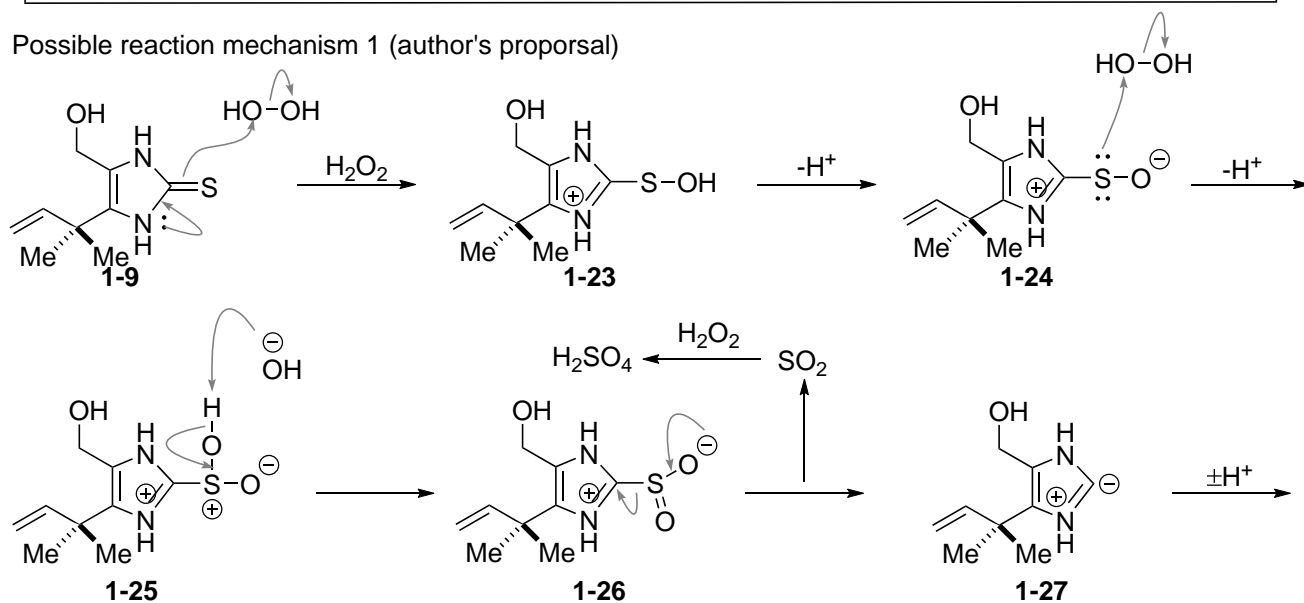


### 1.3 Discussion: reaction (1-9 to 1-10)

A representative reduction method of thioether is using Raney Ni. But Raney Ni maybe conduct reduction of olefin.

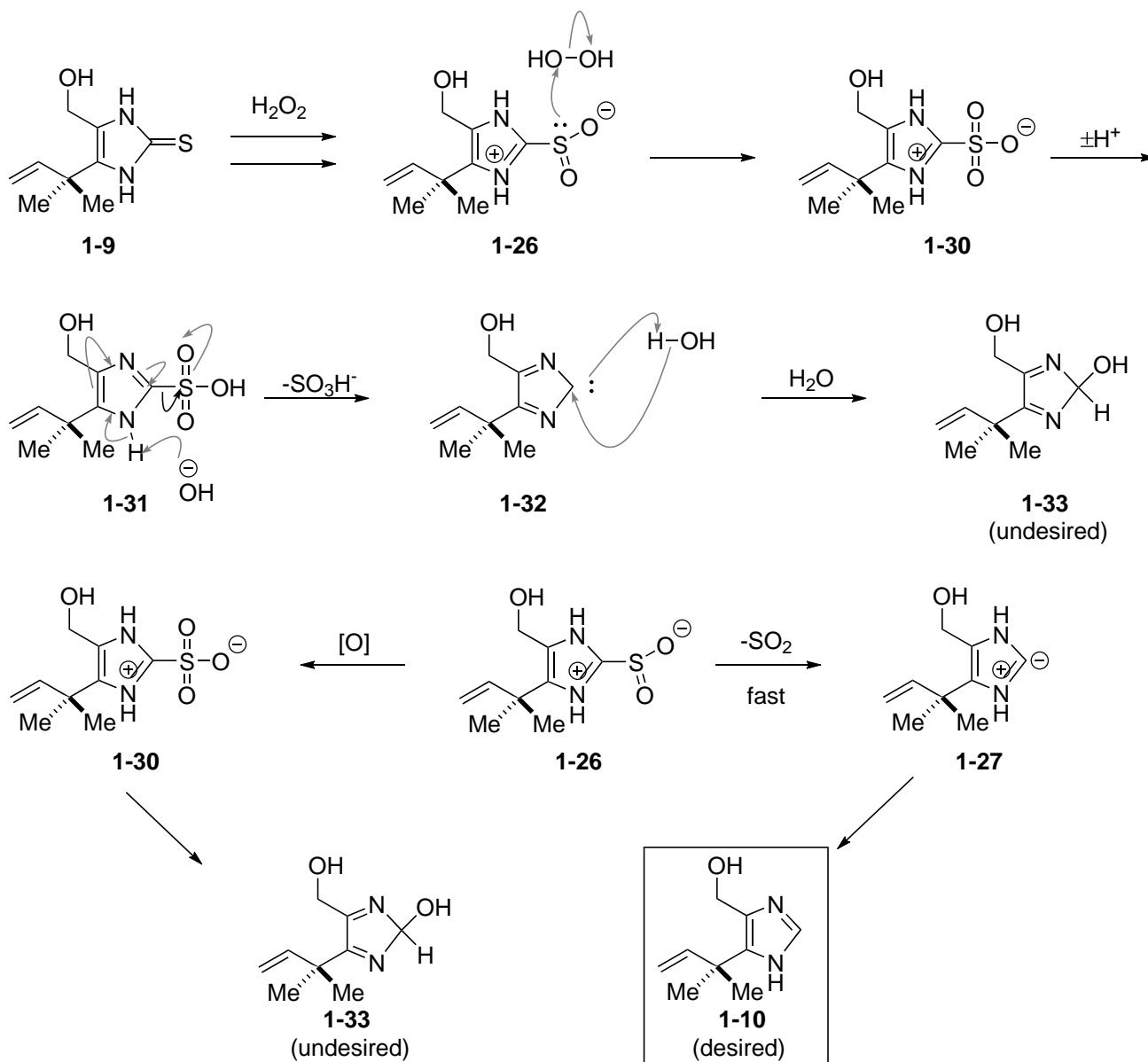


Possible reaction mechanism 1 (author's proposal)



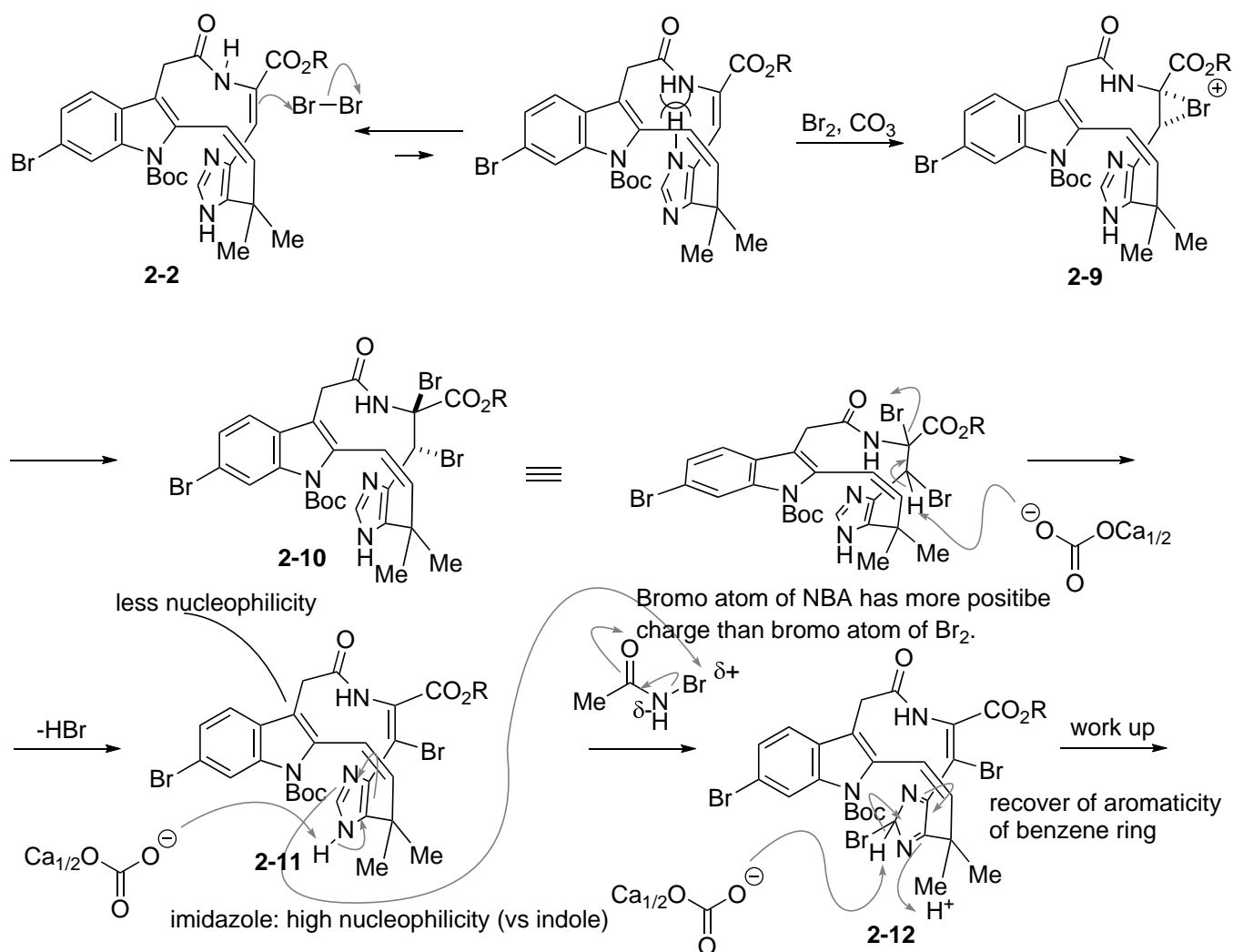
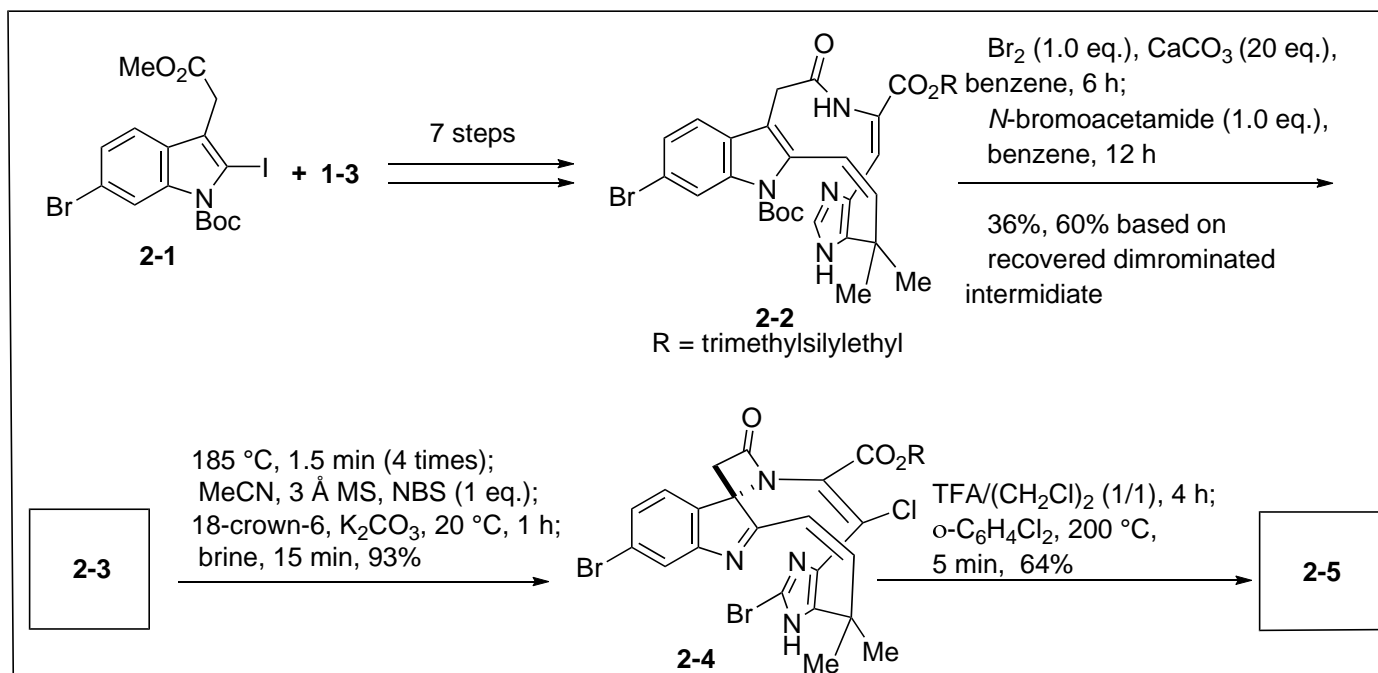
Positive charge is on oxygen atom of 1-28 and nitrogen atom of 1-29. But positive charge of 1-29 is delocalized. So 1-29 is more stable than 1-28.

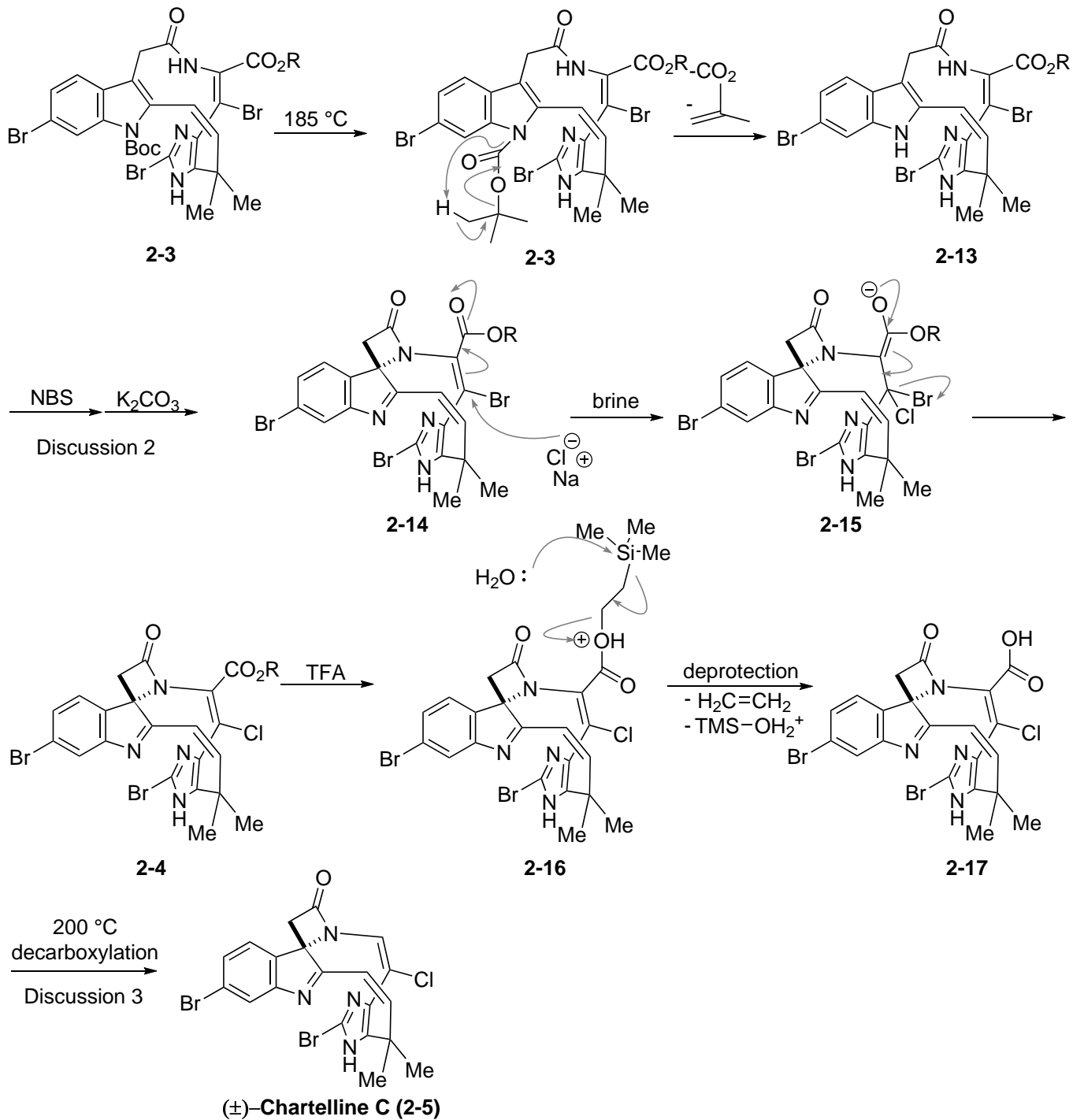
Possible reaction mechanism 2



Leaving of  $\text{SO}_2$  is faster than oxidation of sulfur dioxide because  $\text{SO}_2$  is stable gas.

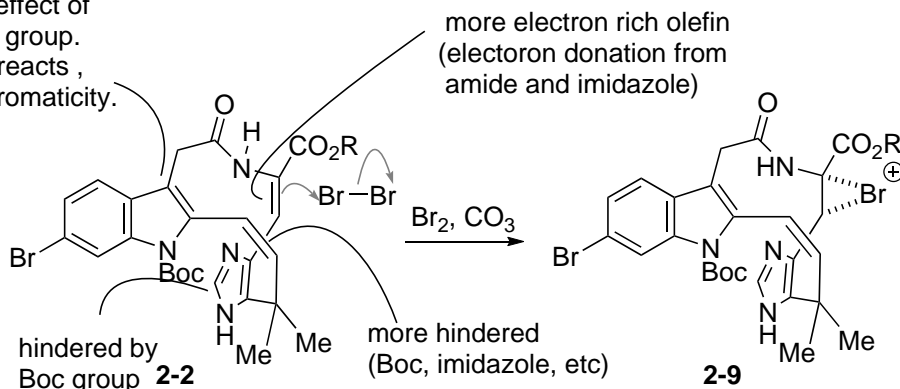
1.4. Answer of (2)





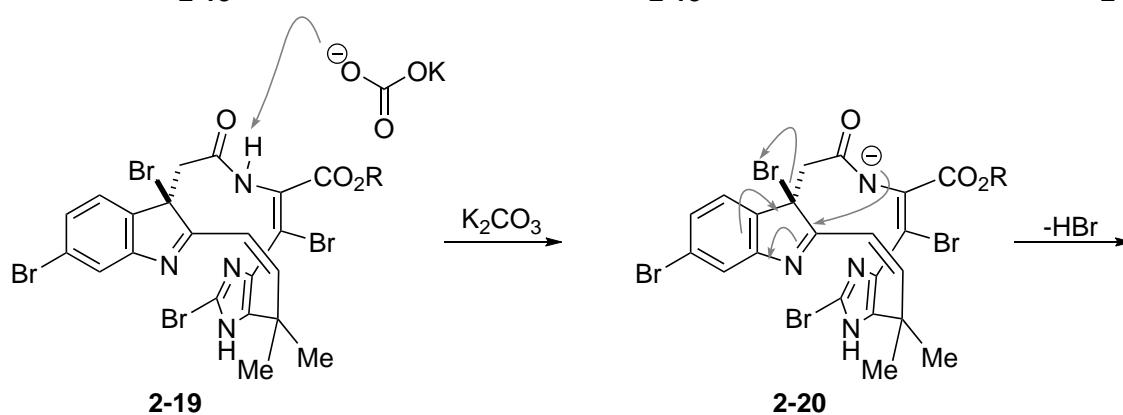
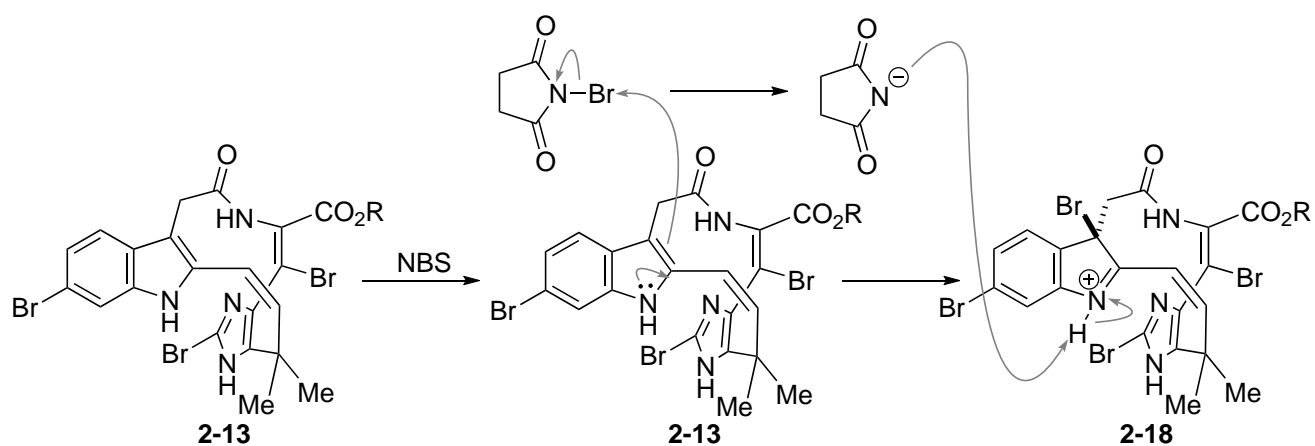
### 1.6 Discussion 2 : regioselectivity (2-2 to 2-3)

Nucleophilicity is weak because of electron withdrawing effect of Boc group and amide group. Then, if this position reacts, indole ring loses an aromaticity.

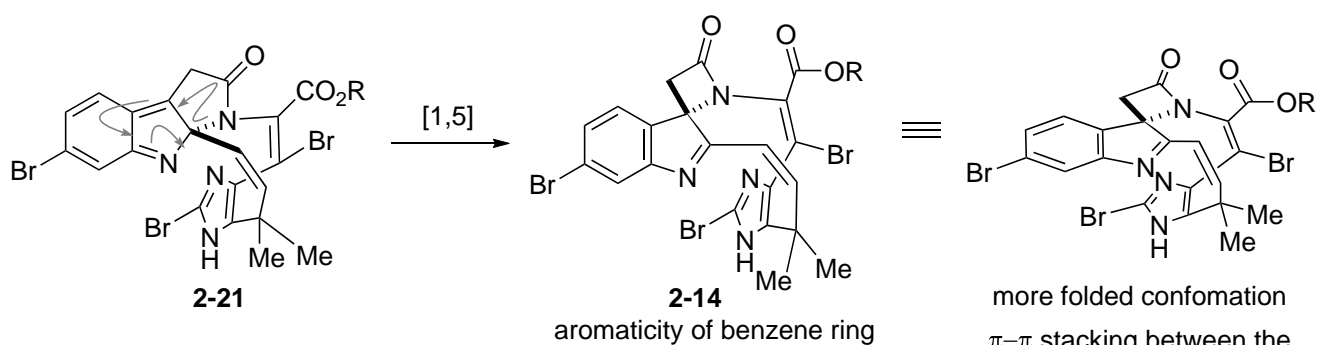


### 1.6 Discussion 3 : reaction mechanism (2-13 to 2-14)

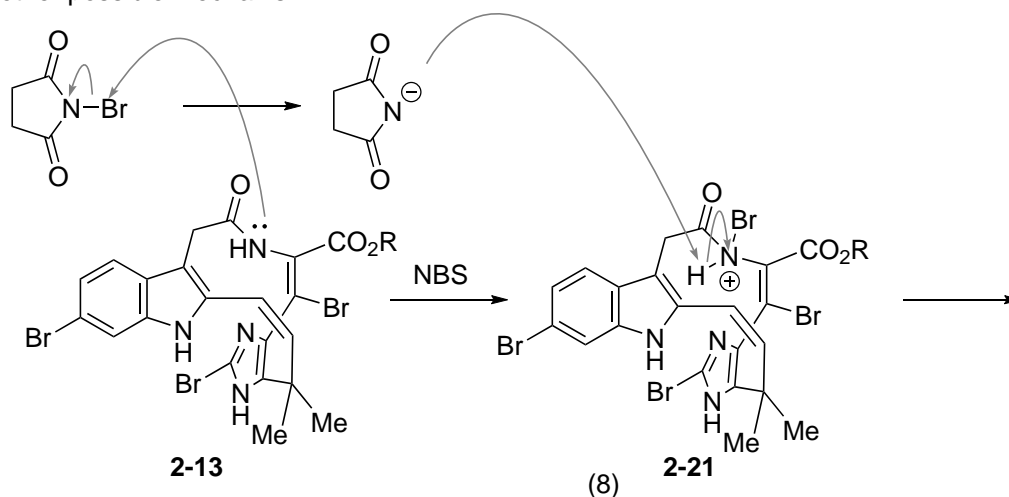
#### 1.6.1 author's proposal



I think that losing aromaticity of benzene ring is unfavor.

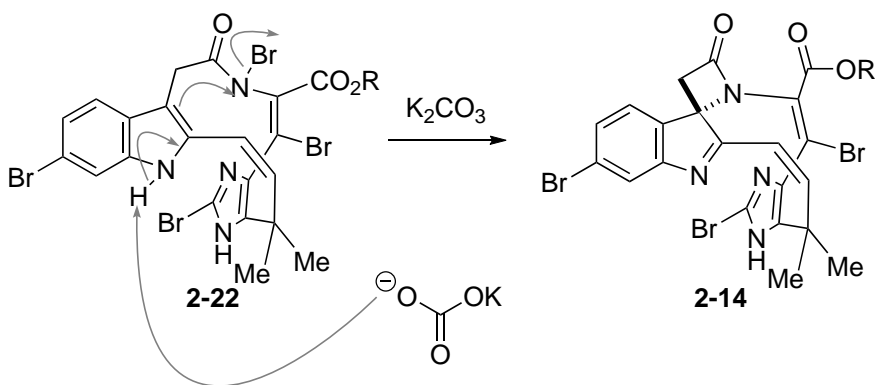


#### 1.6.2 other possible mechanism

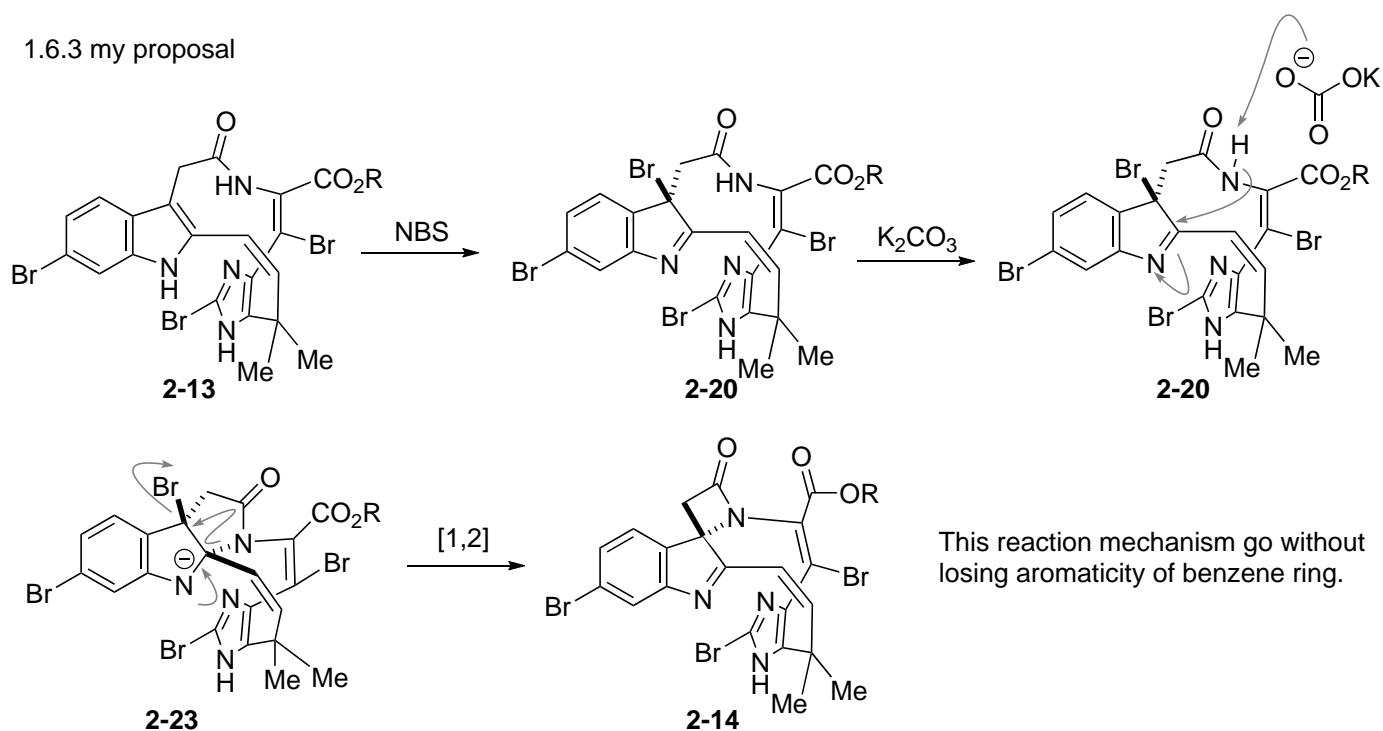


(8)

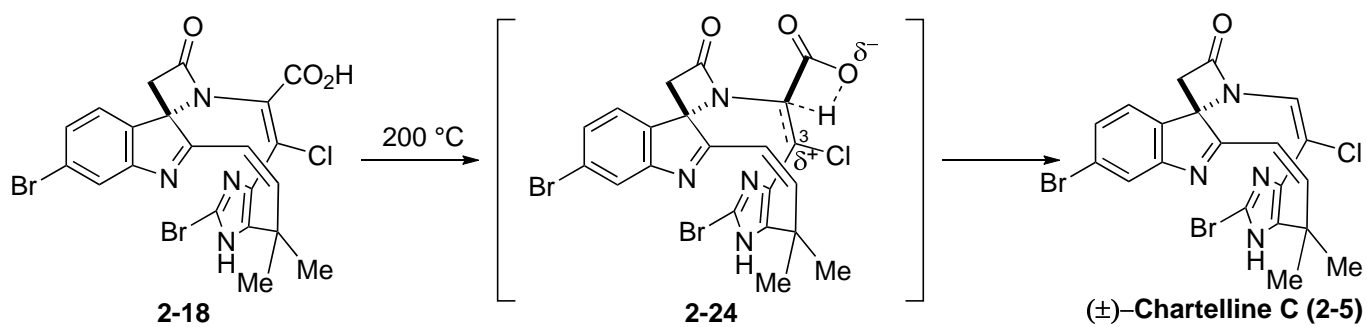




### 1.6.3 my proposal



### 1.6. Discussion 4: decarboxylation

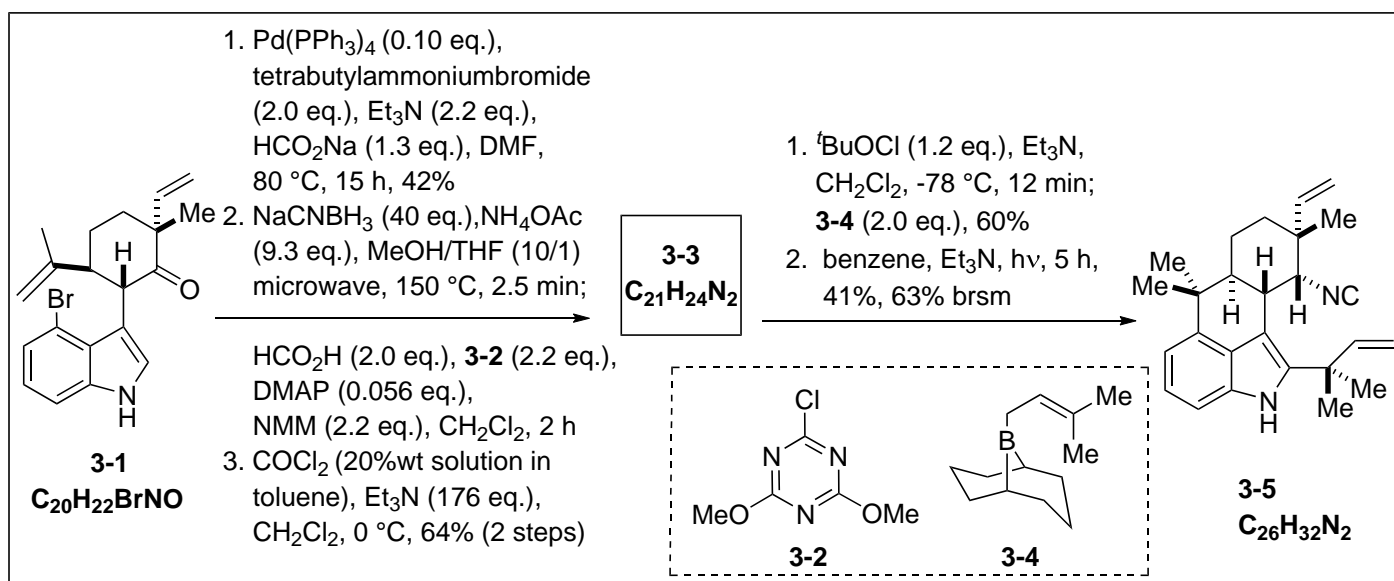
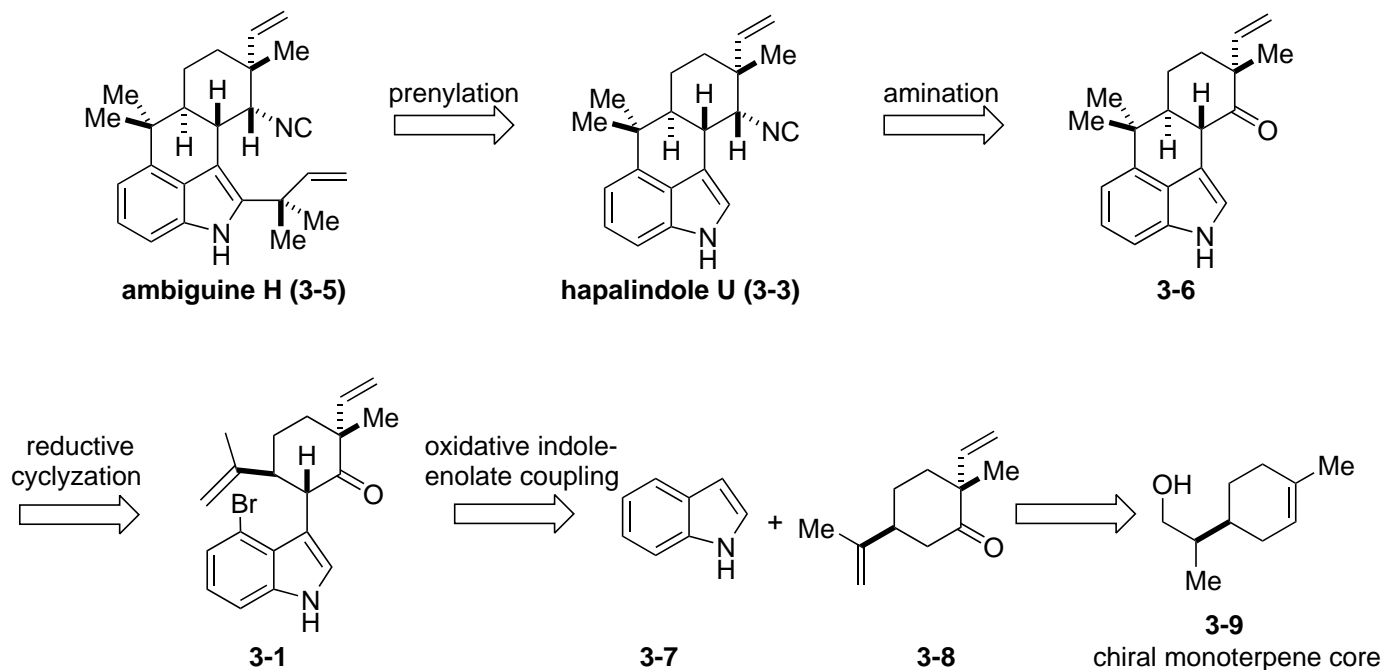


Positive charge at C3 is stabilized by chlorine lone pairs.

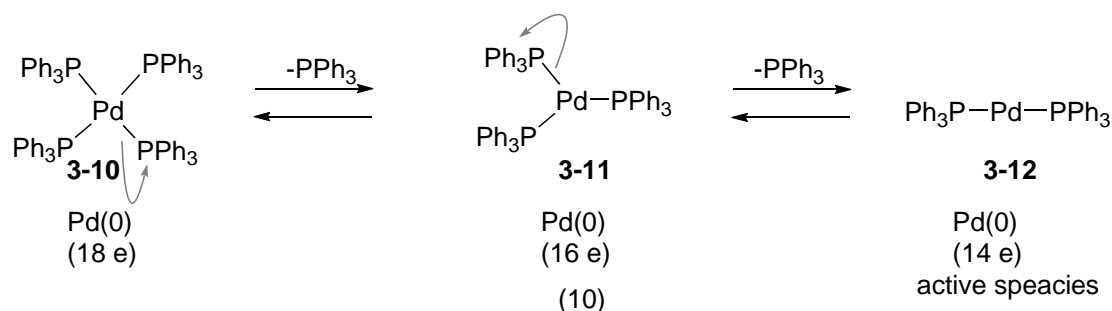
If substrates do not have the vinyl chloride, decarboxylation is not possible.

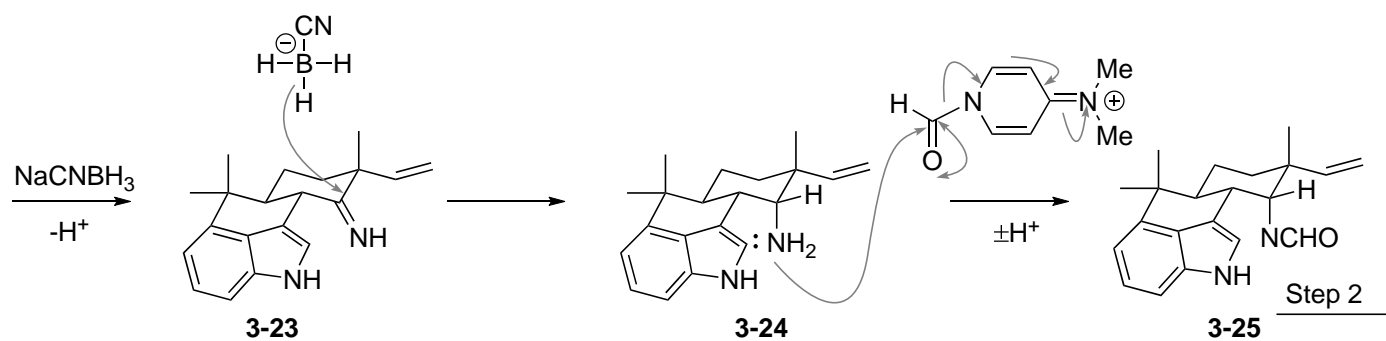
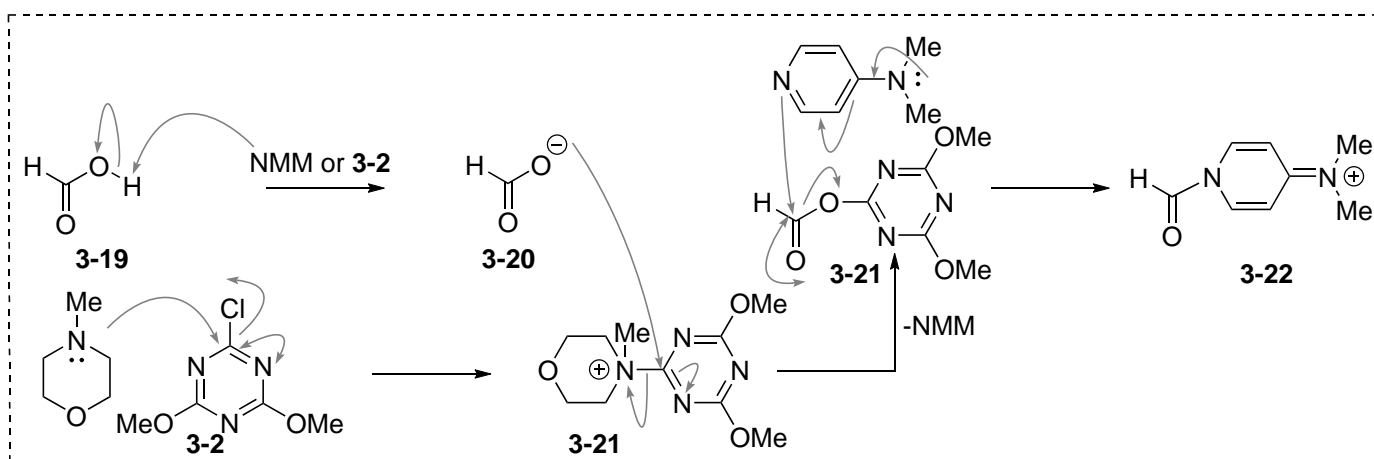
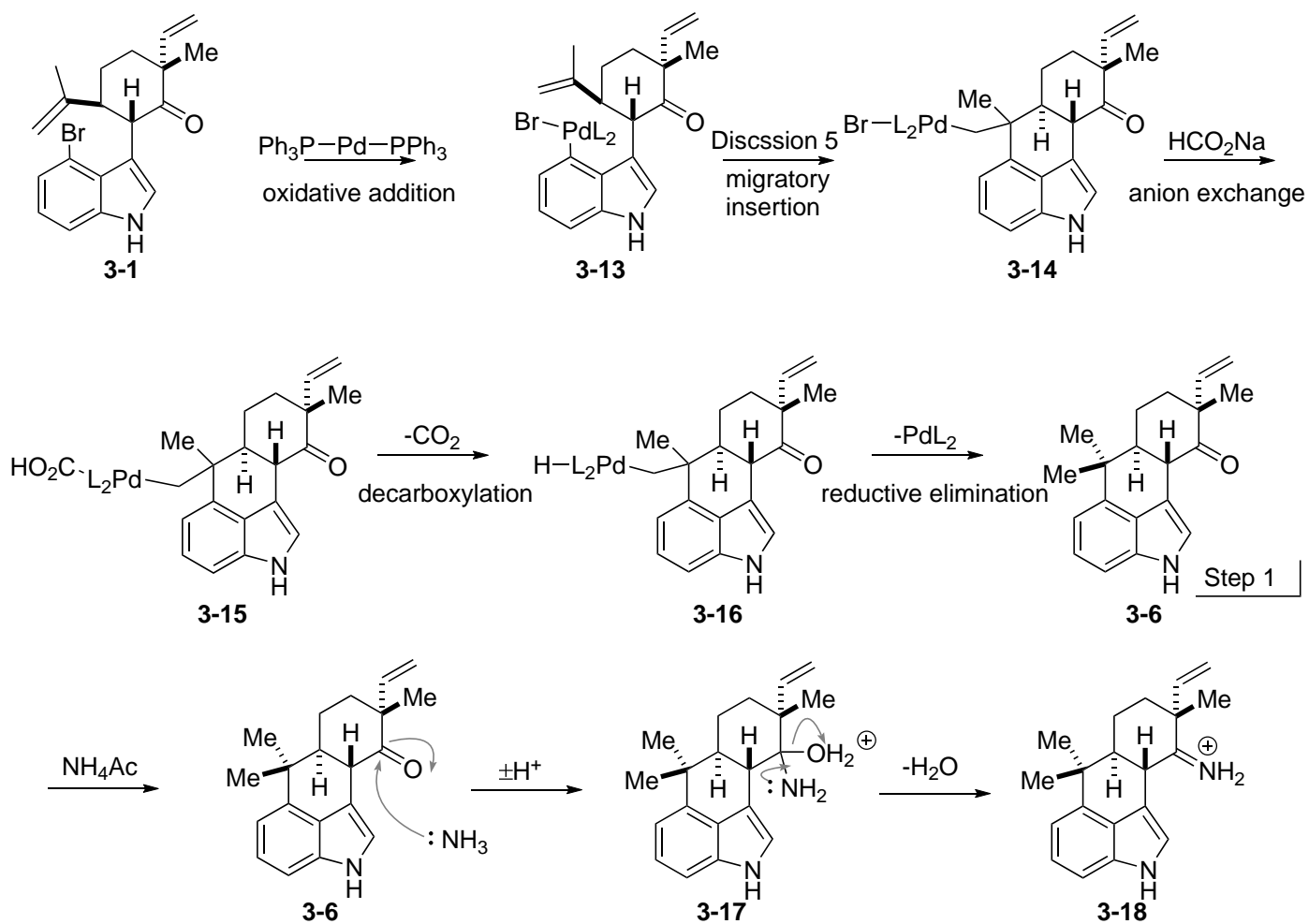
2. Total synthesis of (-)-hapalindole U and (+)-ambiguine H by Baran, P. S. et al. (*Tetrahedron* 2015, 71, 3652.)

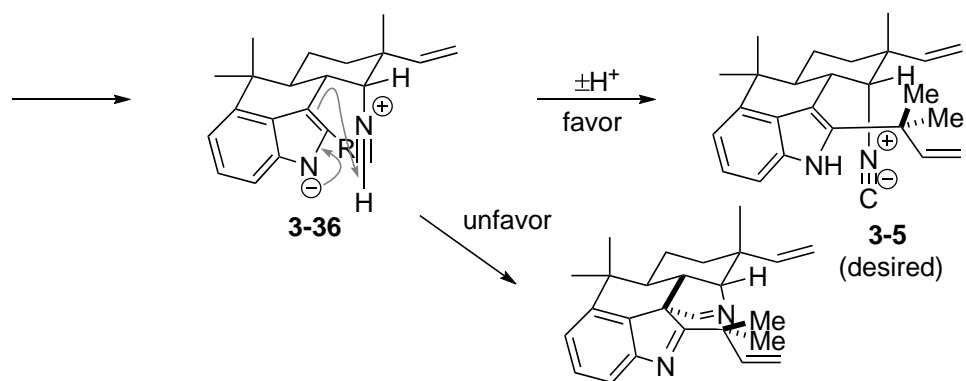
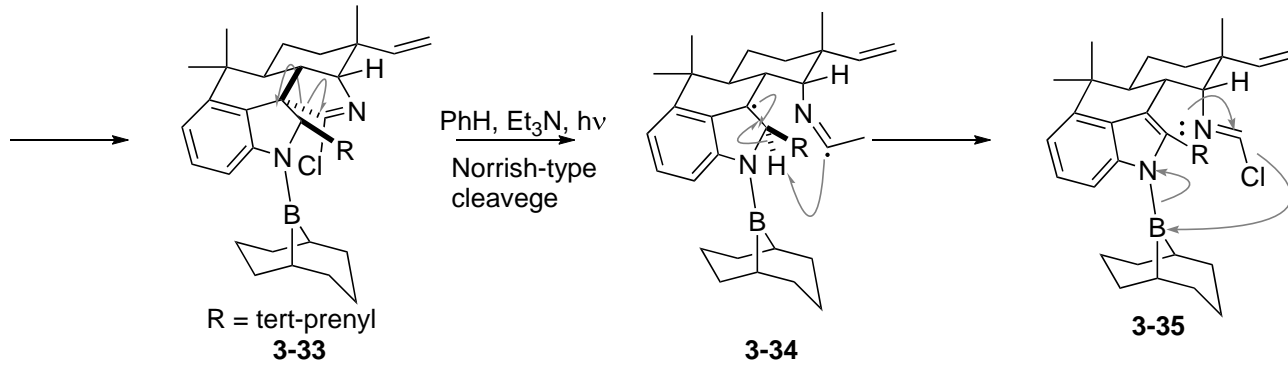
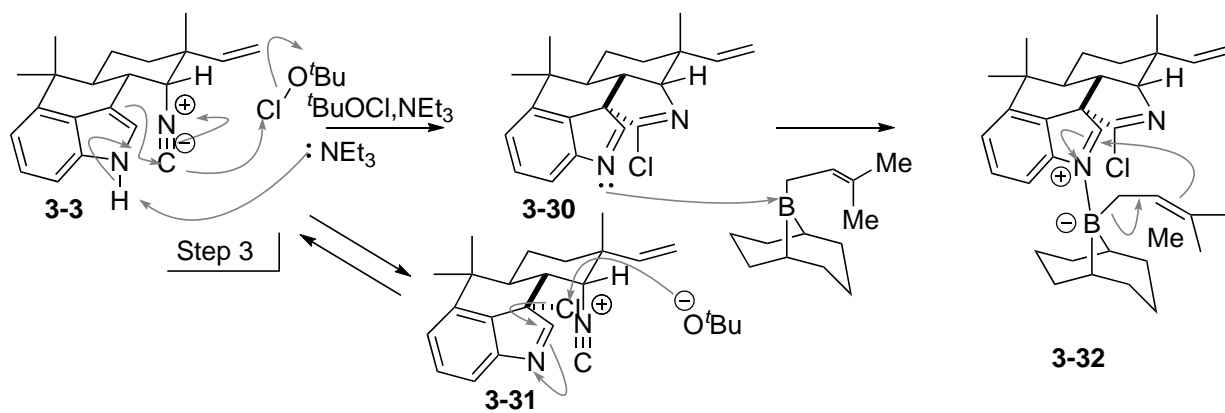
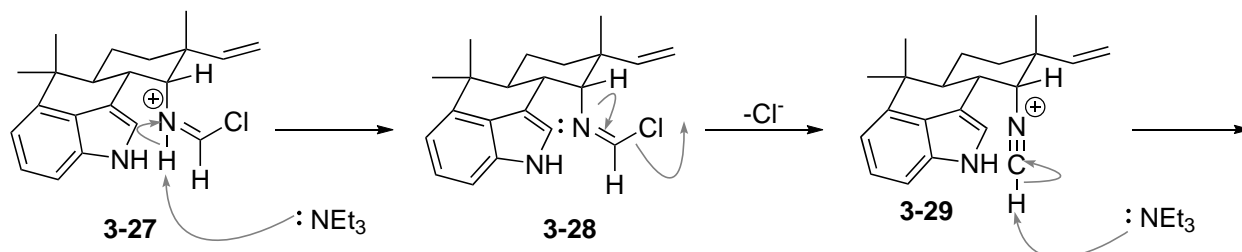
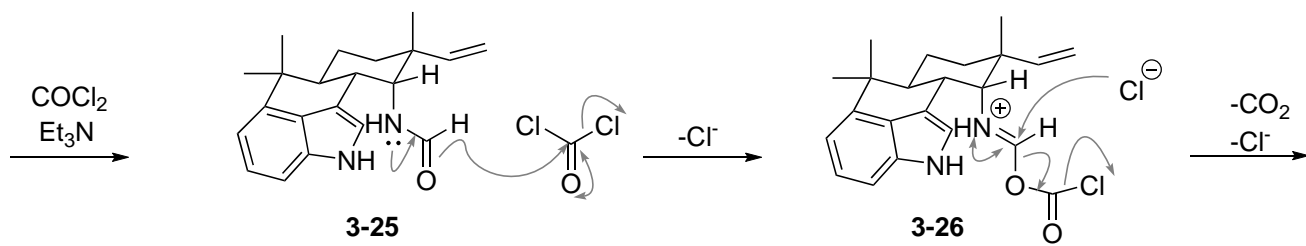
2.1 Retrosynthesis



2.1 Answer of (3)







steric repulsion between  
 indole's substituent and  
 new 5-membered-ring

2.3 Discussion 5 : reductive Heck reaction

