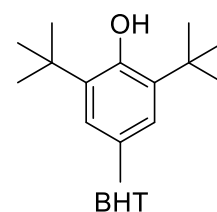
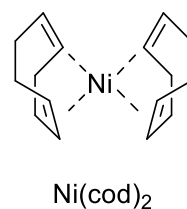
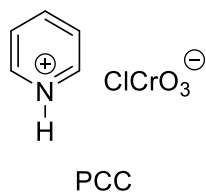
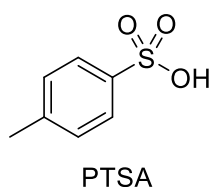
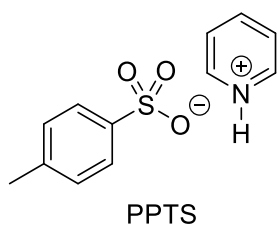
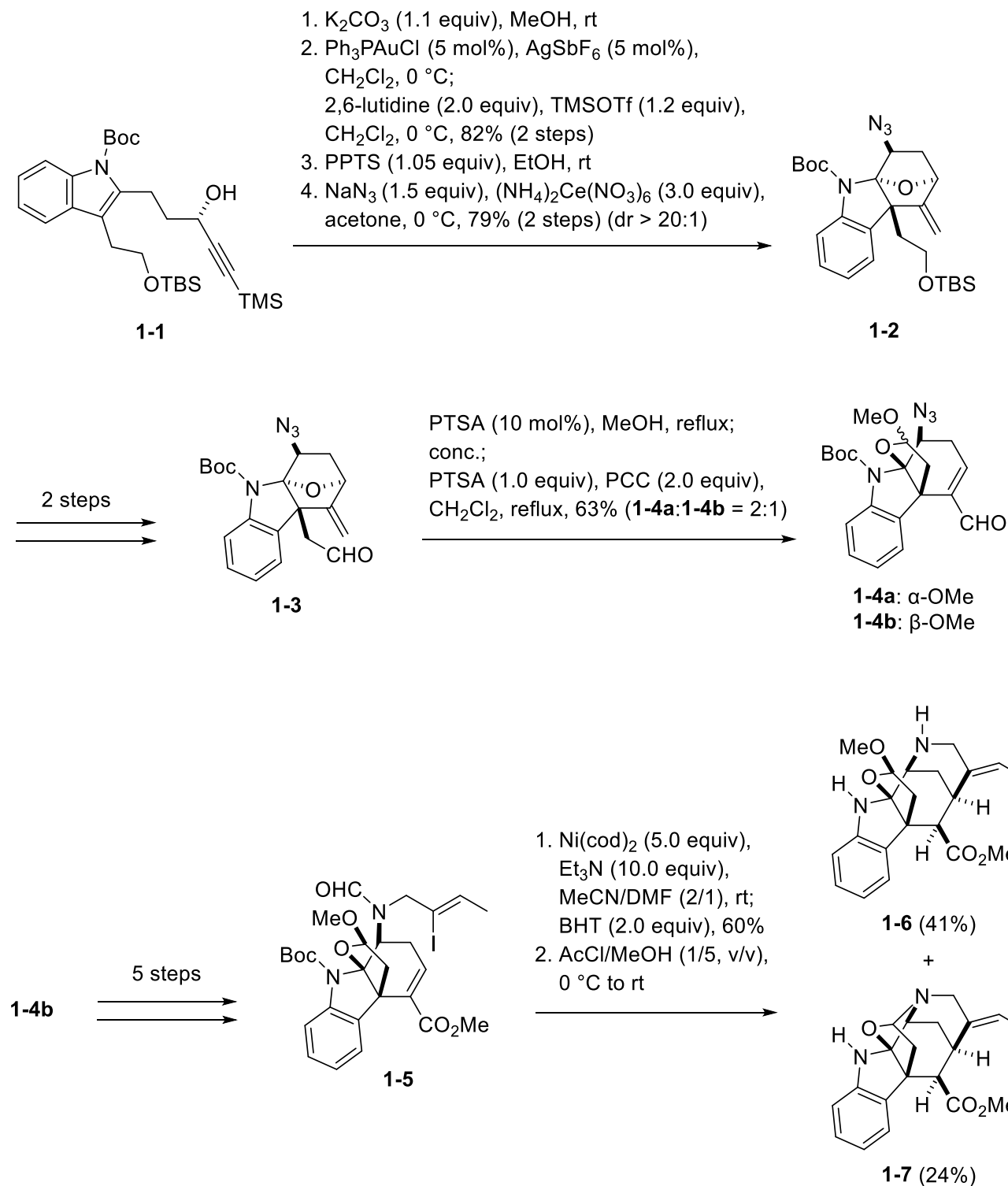
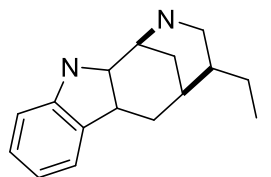


Please provide the reaction mechanism and stereoselectivity.



## Topic: Total synthesis of (-)-Picrinine and (-)-Scholarisine C

### Introduction



core structure of  
akuammiline alkaloids

**Isolation:** *Apocynaceae*

**Bioactivity:**

anticancer, antibacterial, anti-inflammatory, and antimalarial activity,  
inhibition of SGLT, inhibition of NF- $\kappa$ B<sup>1</sup>

**Structure features:** indoline, 2-Azabicyclo[3.3.1]nonane

**Total synthesis:**

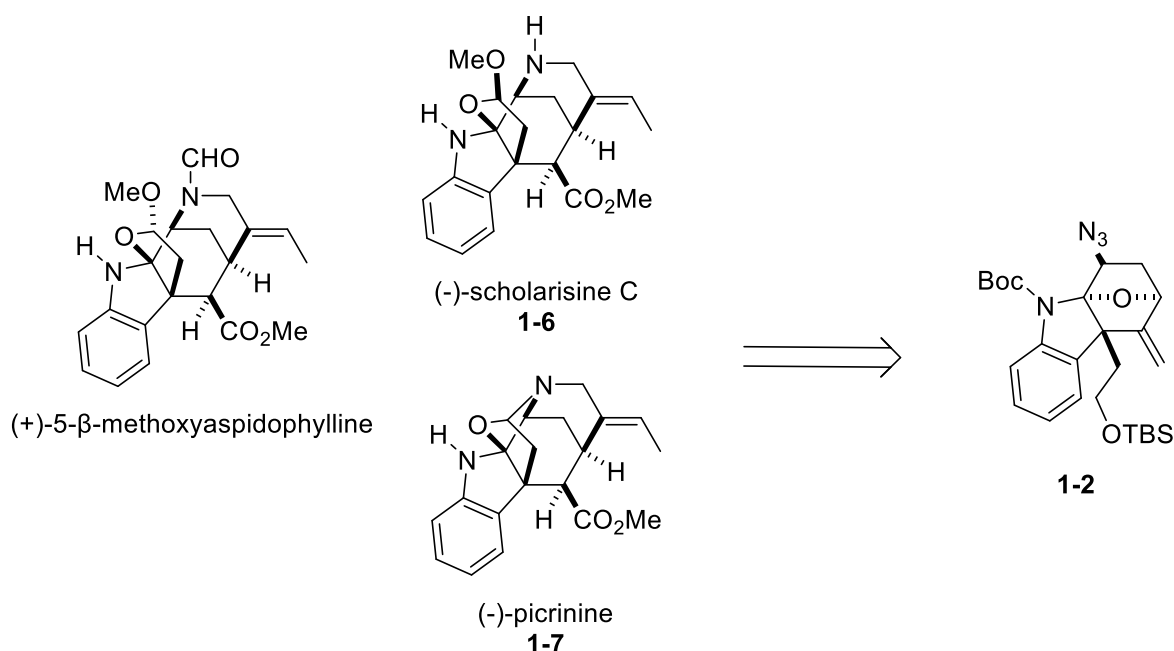
(-)-scholarisine C

• Zhai (asymmetric, *Org. Lett.* **2021**, 23, 17, 6836–6840)

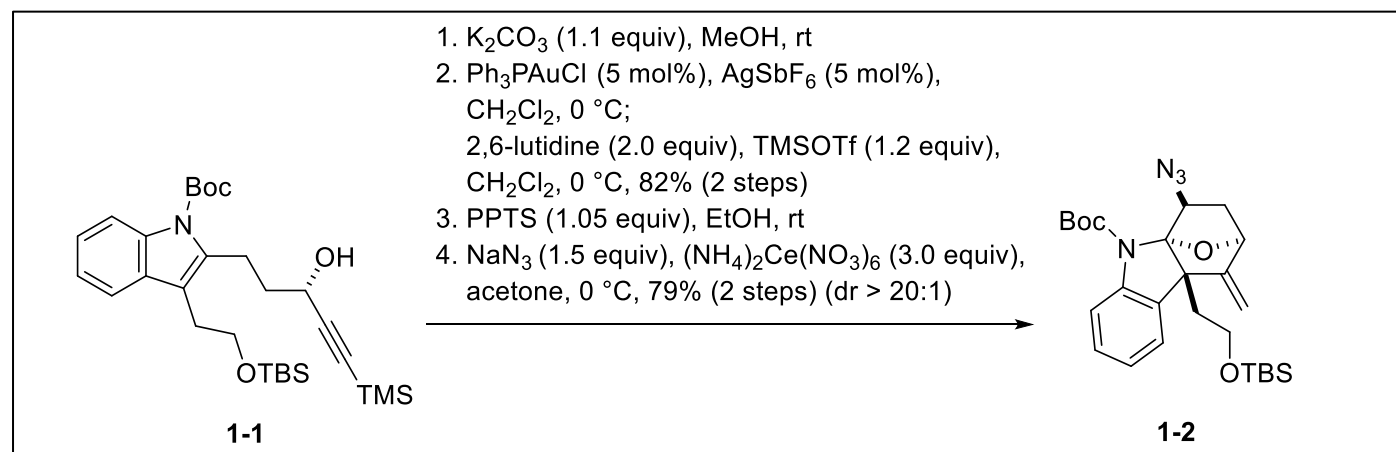
(-)-picrinine

• Garg (reacemic, *J. Am. Chem. Soc.* **2014**, 136, 12, 4504–4507)

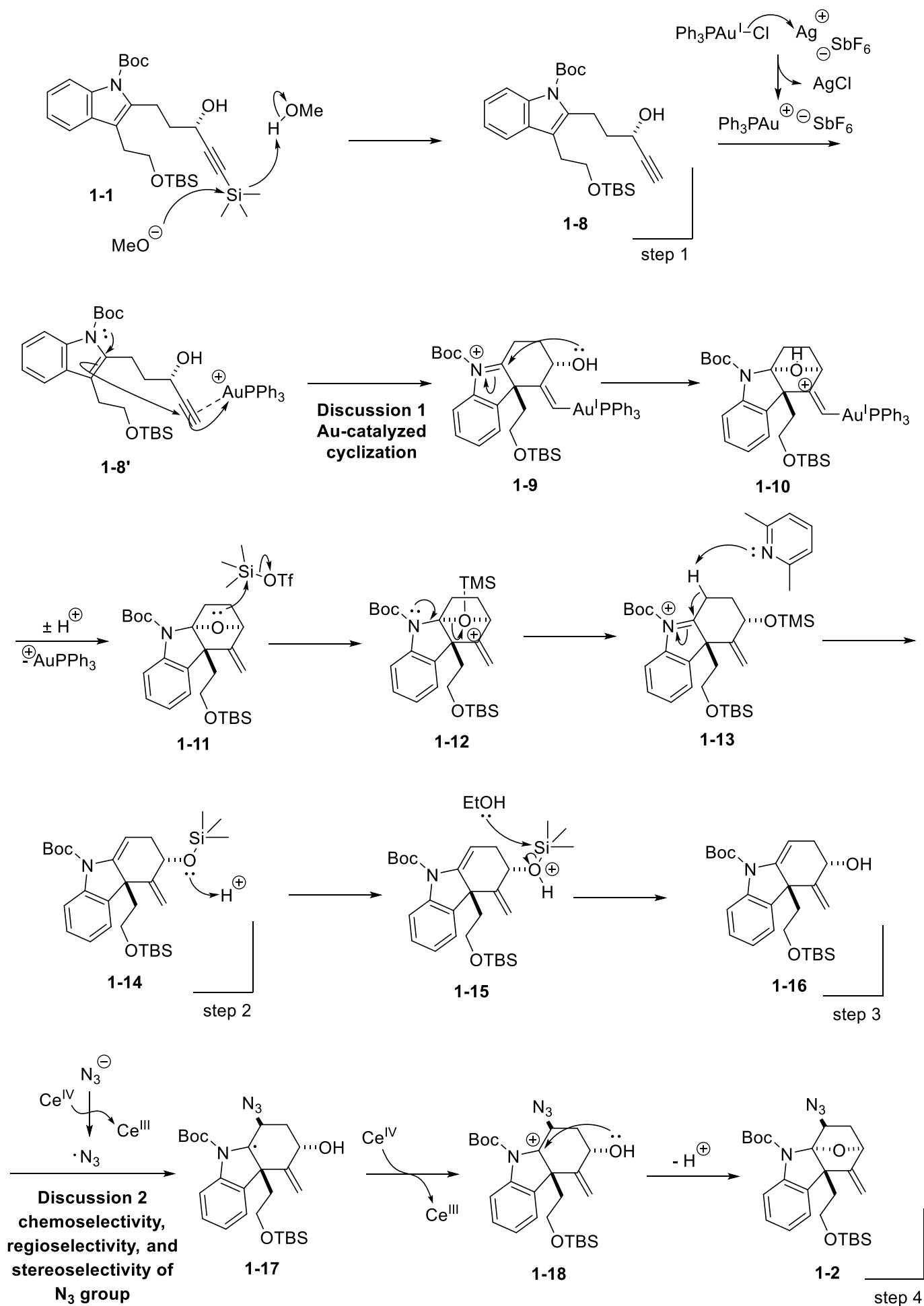
• Zhai (asymmetric, *Org. Lett.* **2021**, 23, 17, 6836–6840)



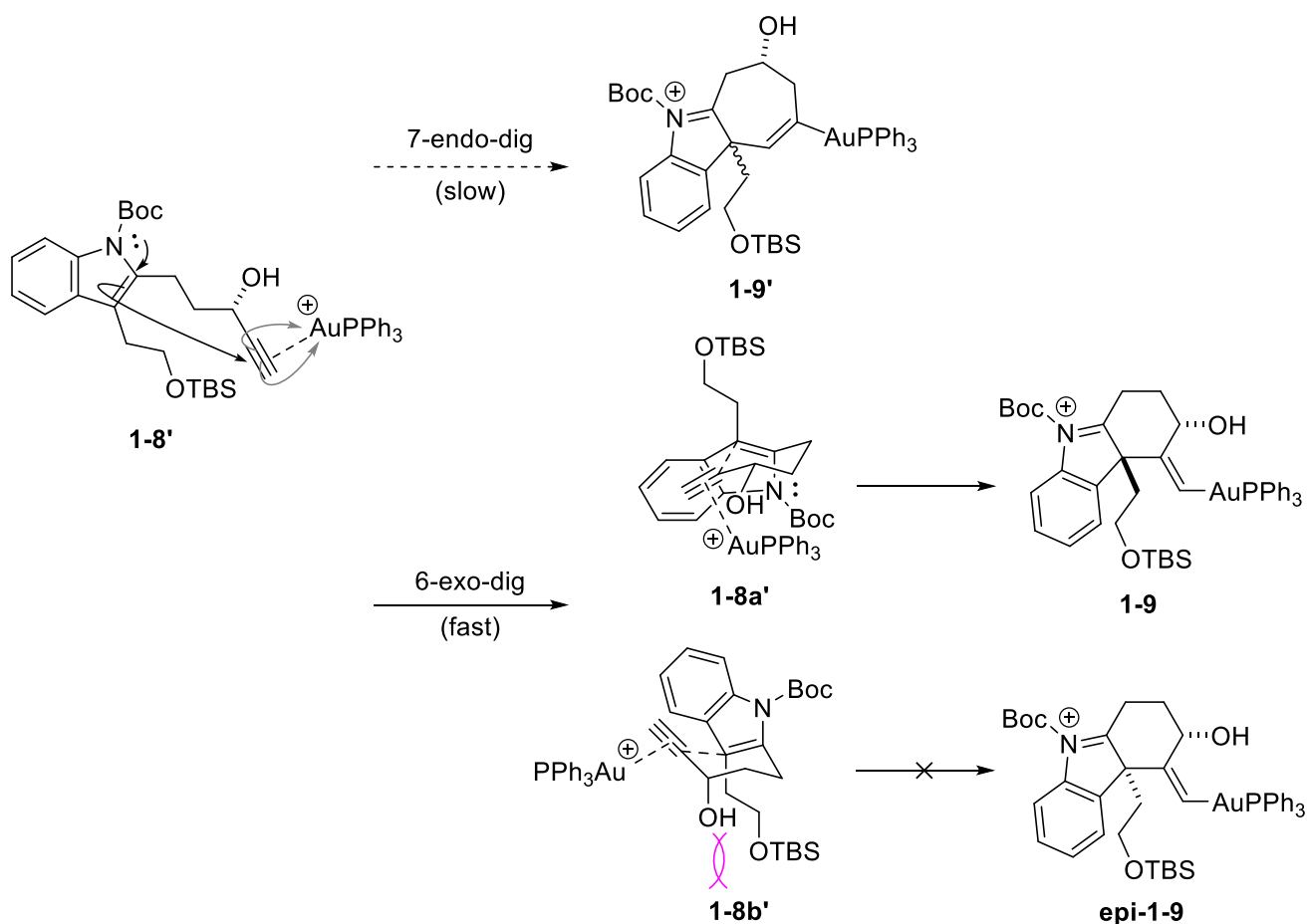
### Problem



# Answer



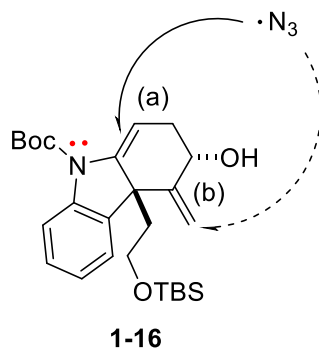
## Discussion 1: Au-catalyzed cyclization



This reaction would proceed under kinetic control. Therefore, 6-exo cyclization proceeded faster than 7-endo cyclization. Also, in the transition state of 6-exo cyclization, **1-8b'** was less favored than **1-8a'** due to the steric repulsion between OH group and alkyl chain with TBS group.

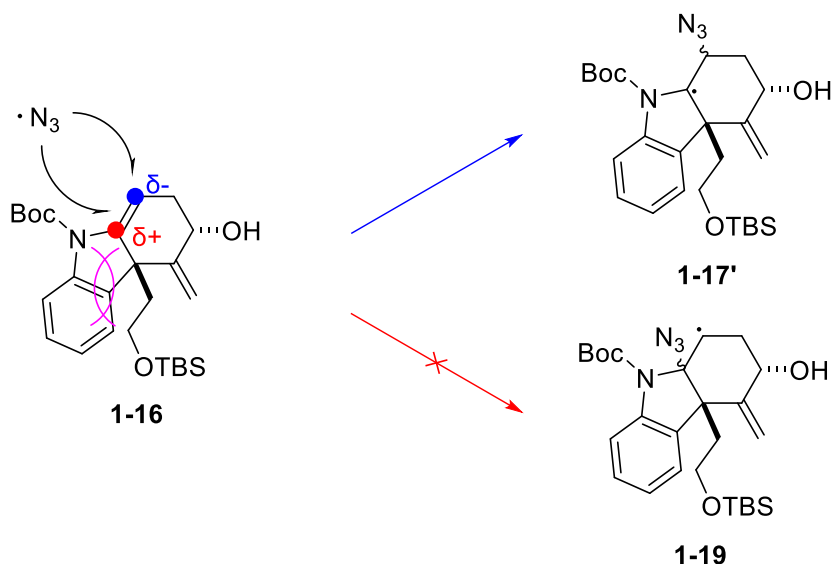
## Discussion 2: chemoselectivity, regioselectivity, and stereoselectivity of $\text{N}_3$ groups

### 2-1. chemoselectivity



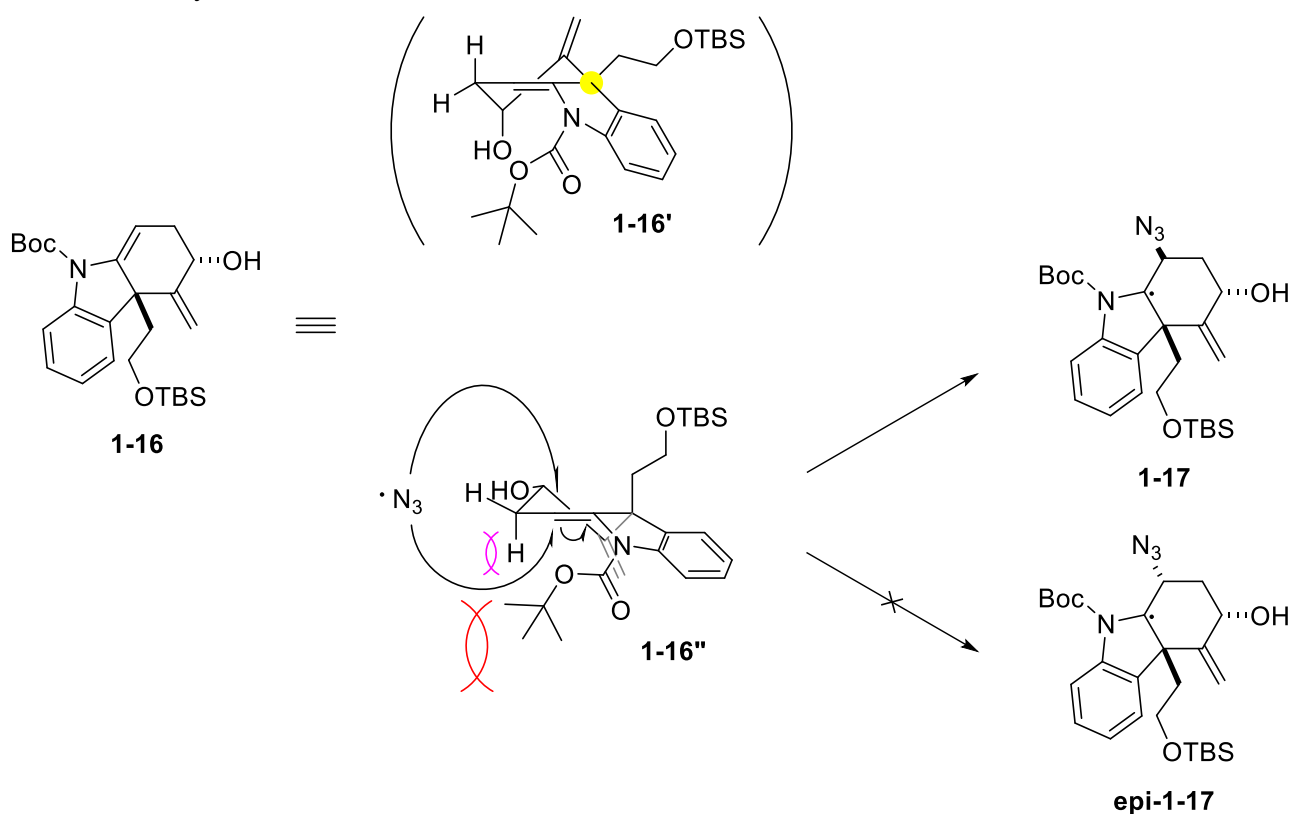
Azido radical is electrophilic radical. Olefin (a) is more electron-rich than olefin (b) because olefin (a) is adjacent to nitrogen. Therefore, azido radical added to olefin (a).

## 2-2. regioselectivity

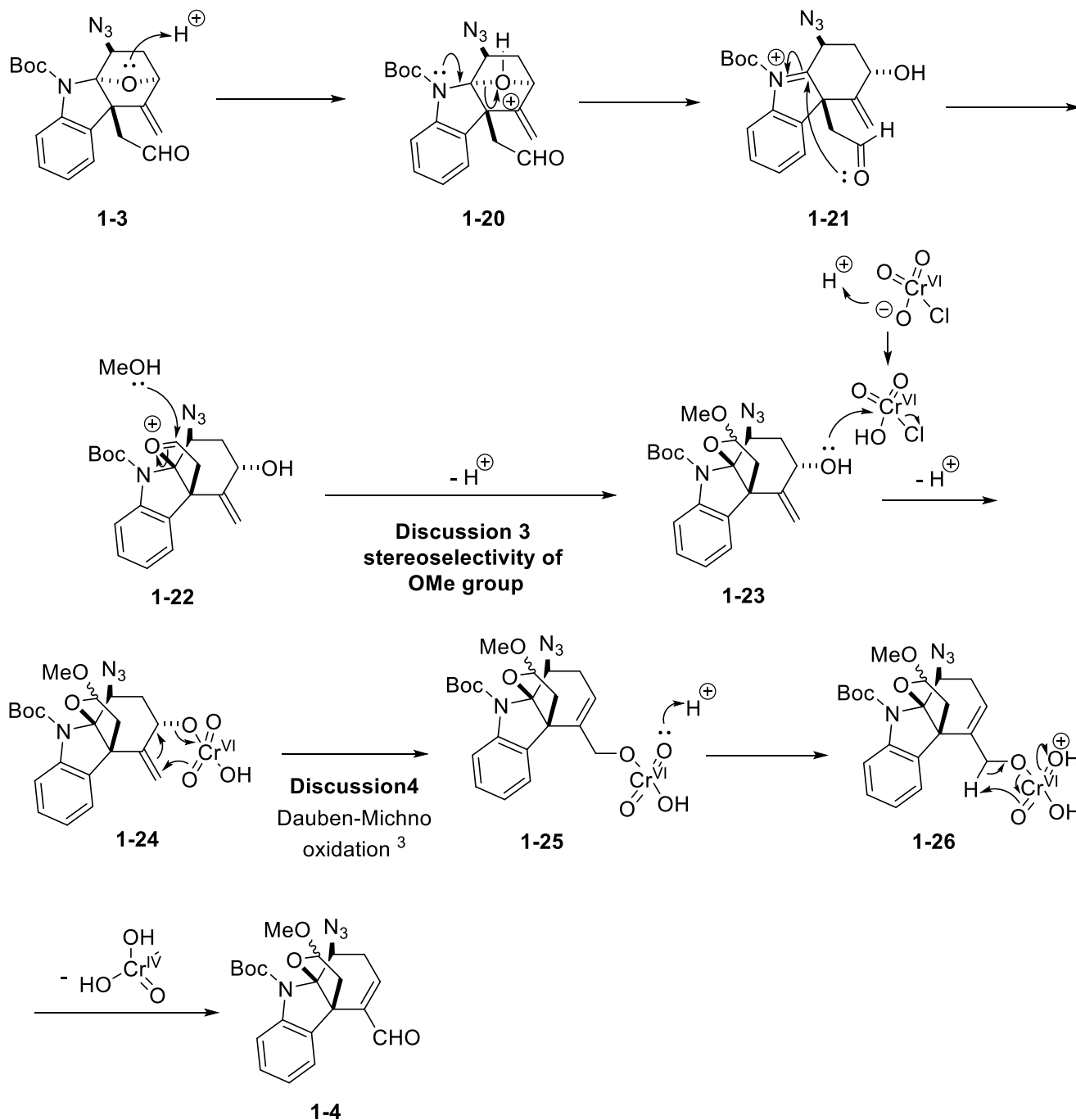
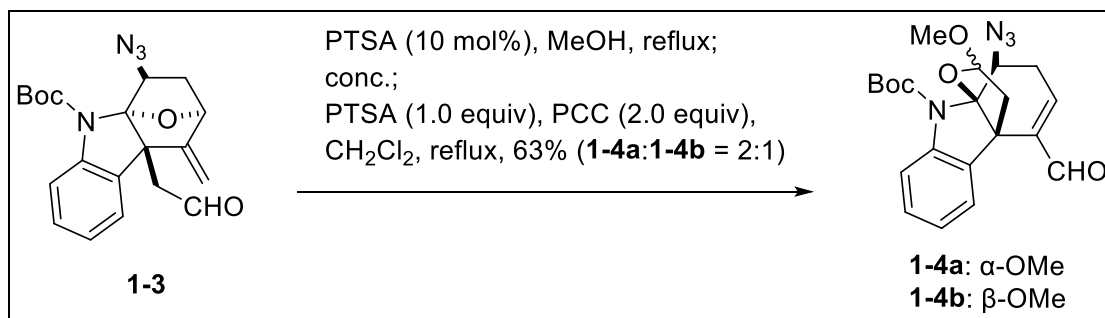


Electrophilic azido radical could attack to the less substituted carbon of the olefin (highlighted in blue) because the less substituted carbon is less sterically hindered and more electron-rich.

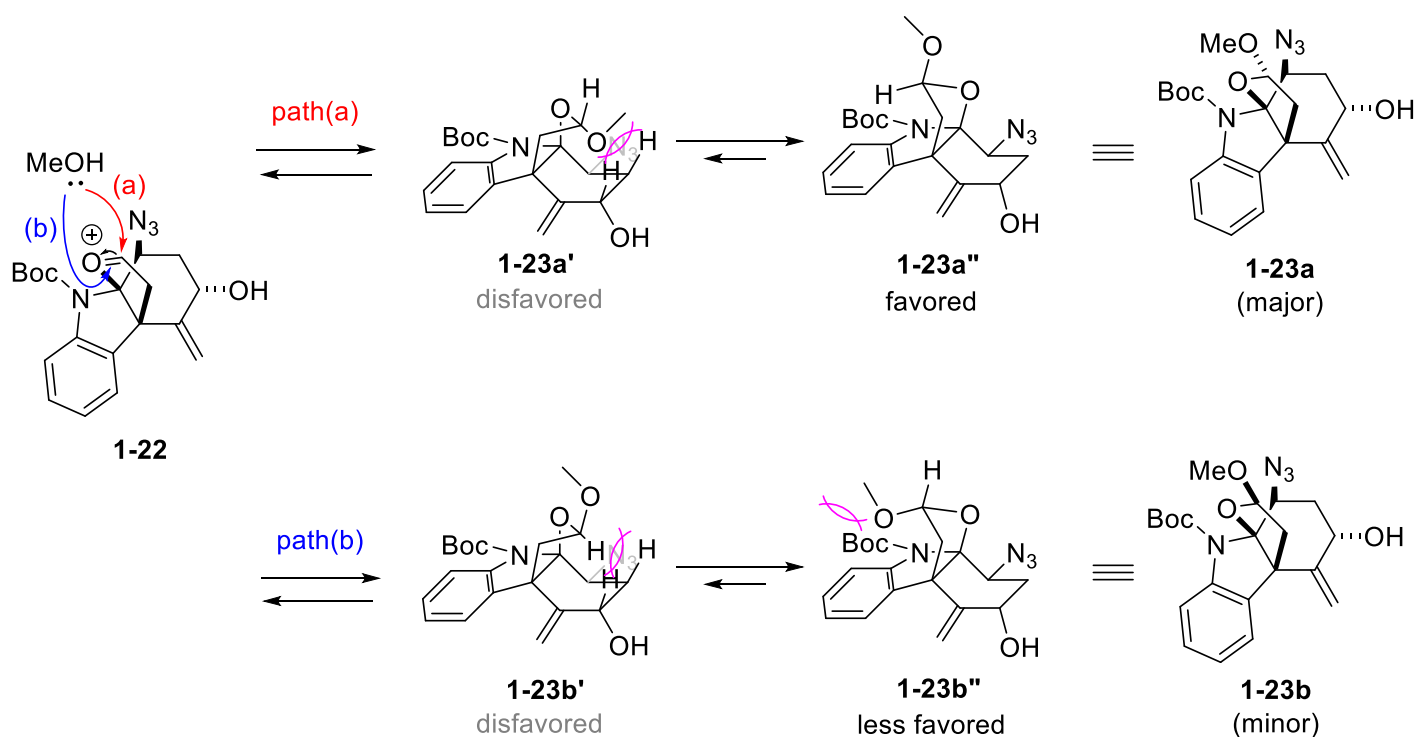
## 2-3. stereoselectivity



**1-16** can take two conformations above. The conformation of **1-16'** would be disfavored because steric strain is too large due to alkyl chain with TBS group and olefin existing in the same direction and the planarity of indoline ring. Therefore, the most stable conformation of **1-16** seems to be like **1-16''**. It is difficult for azido radical to approach from downside because the olefin is hindered by bulky Boc group and pseudo-axial hydrogen on the downside.

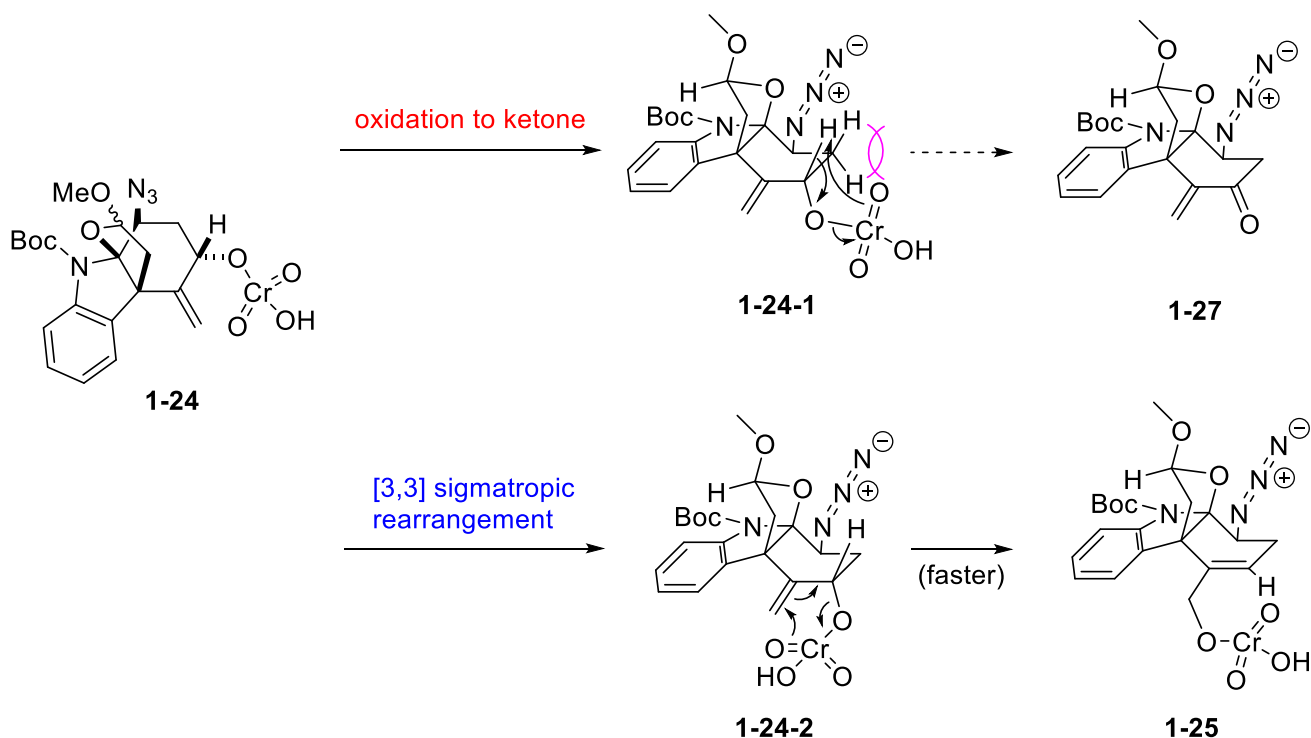


### Discussion 3: stereoselectivity of OMe group

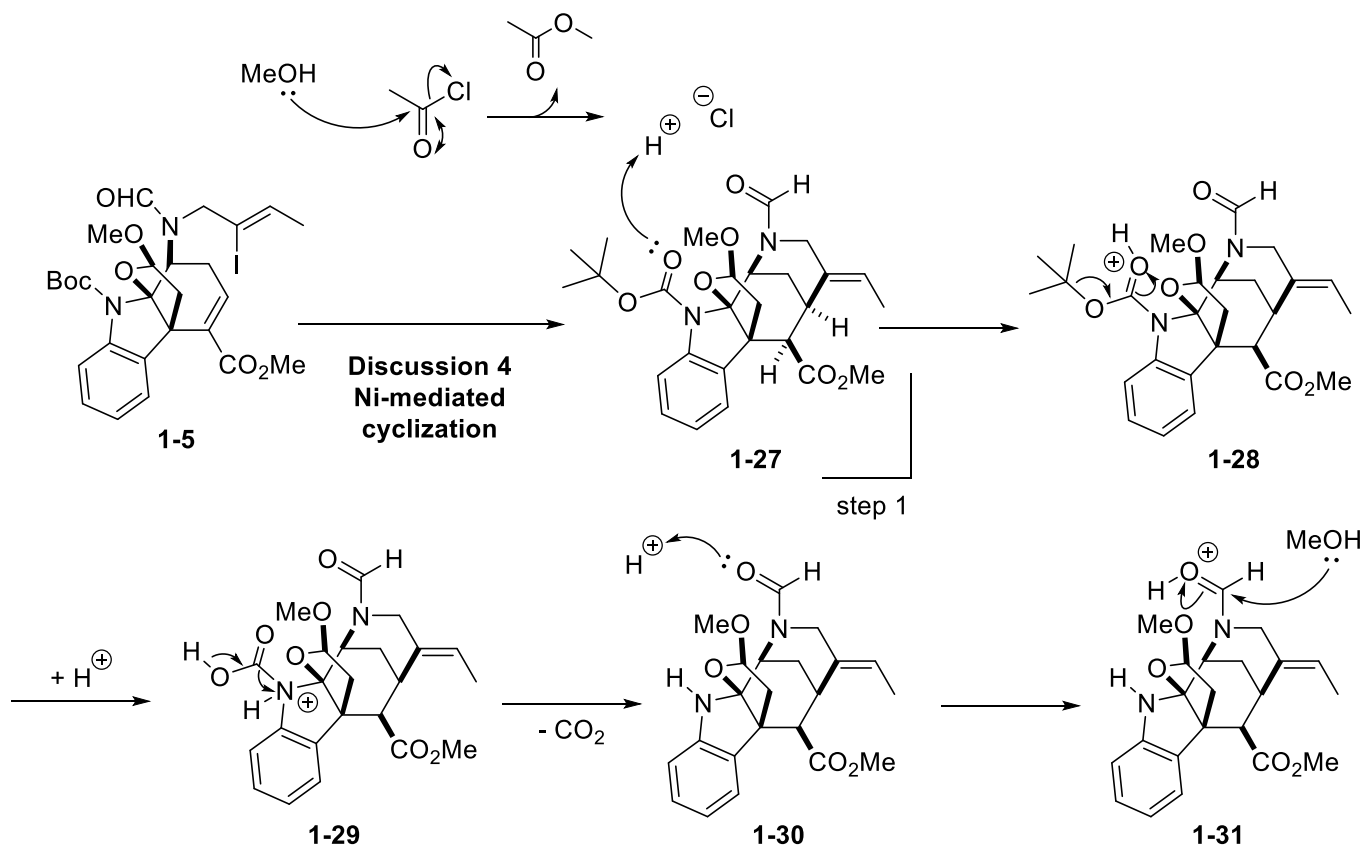
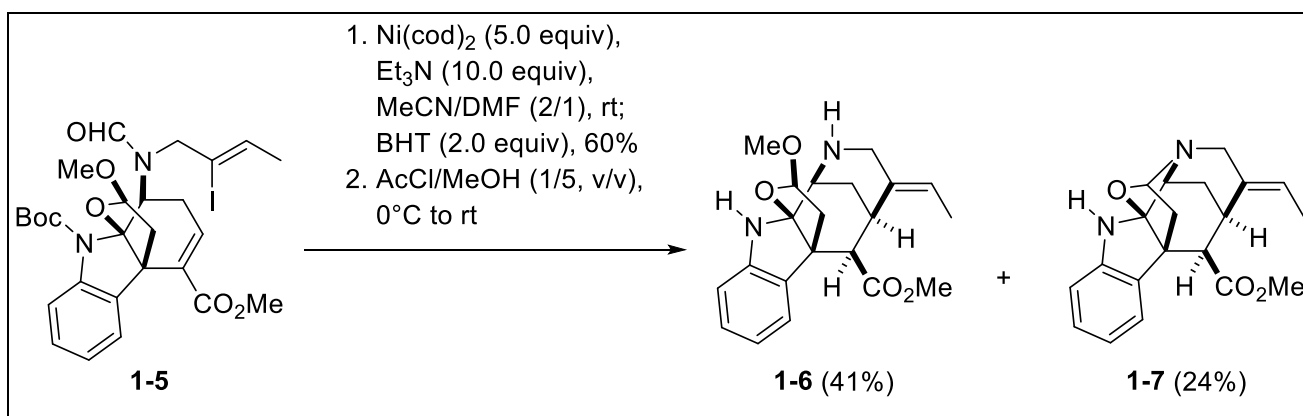


This reaction would proceed under thermodynamic control. After methanol attacked on **1-22**, there are four conformations above. In both paths, the conformations where tetrahydrofuran ring leans to cyclohexane ring (**1-23a'** and **1-23b'**) would be disfavored due to the steric repulsion between methoxy group (**1-23a'**) or hydrogen (**1-23b'**) and pseudo-axial hydrogen. **1-23b''** would be less favored than **1-23a''** because larger methoxy group sticks to the indoline ring in **1-23b''**.

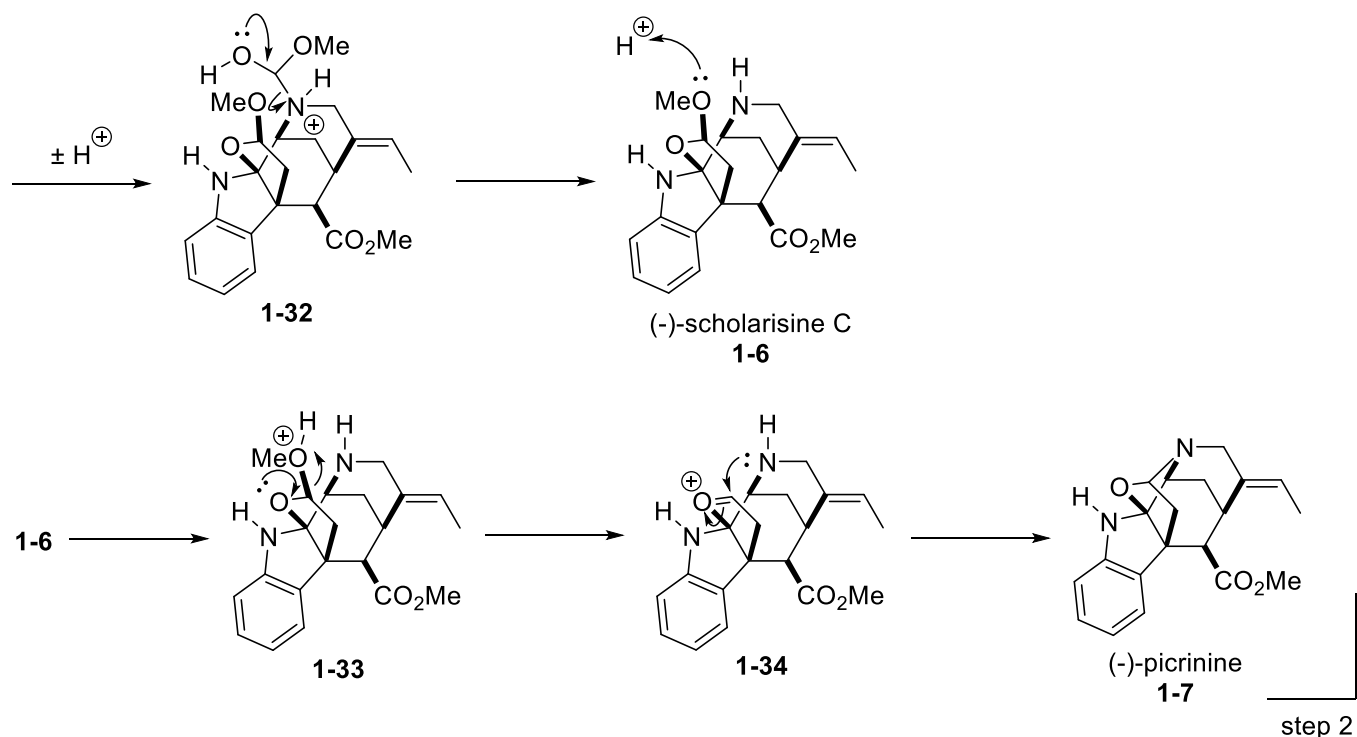
### Discussion 4: Dauben-Michno oxidation



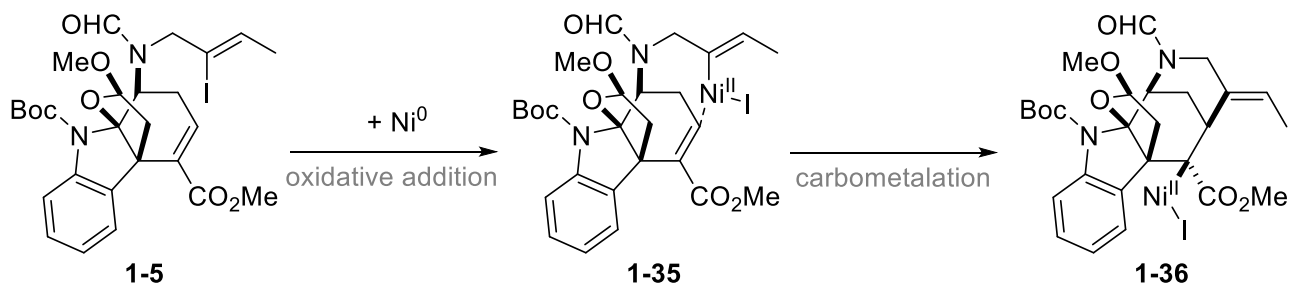
Usually, secondary alcohol is oxidized to ketone by PCC reagent. However, in this case, [3,3] sigmatropic rearrangement would occur after chromate ester was generated. If **1-24** would generate ketone, chromium has to approach pseudo-axial hydrogen. However, this conformation would be disfavored due to the steric repulsion like 1,3-diaxial interaction between chromate ester and pseudo-axial hydrogen of methylene group. On the other hand, **1-24** can take the conformation like **1-24-2**, in which chromate ester is close to olefin and steric repulsion of chromate ester is minimized. Therefore, [3,3] sigmatropic rearrangement from this conformation proceeded faster.





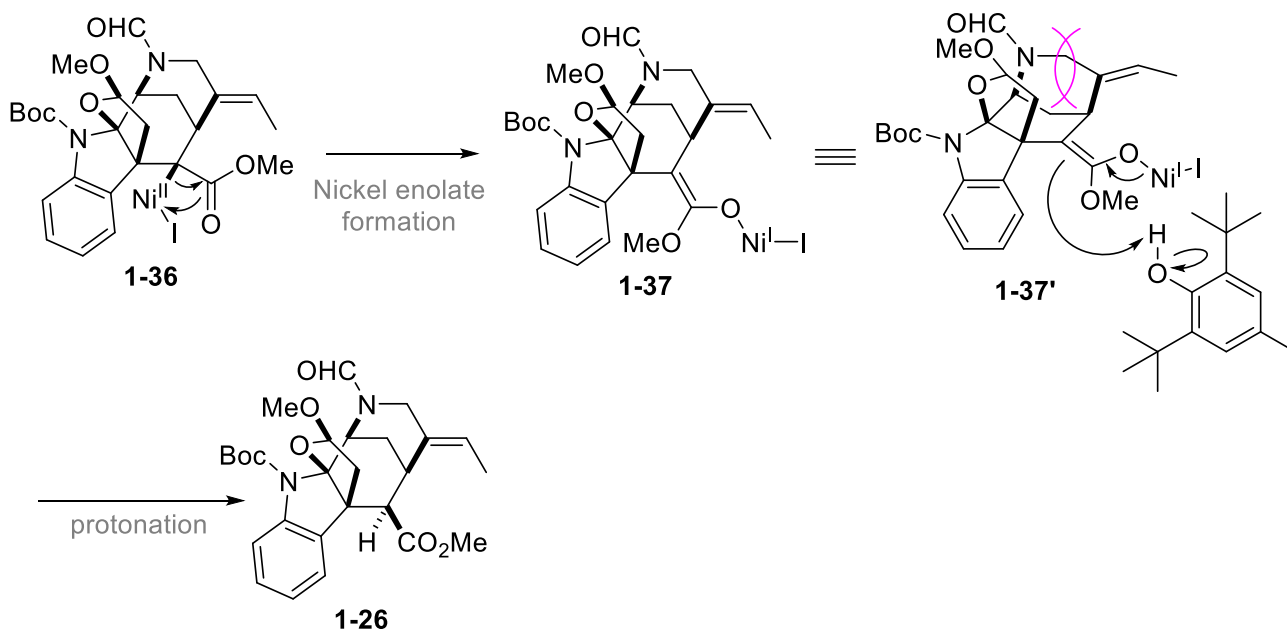


#### Discussion 5: Ni-mediated cyclization



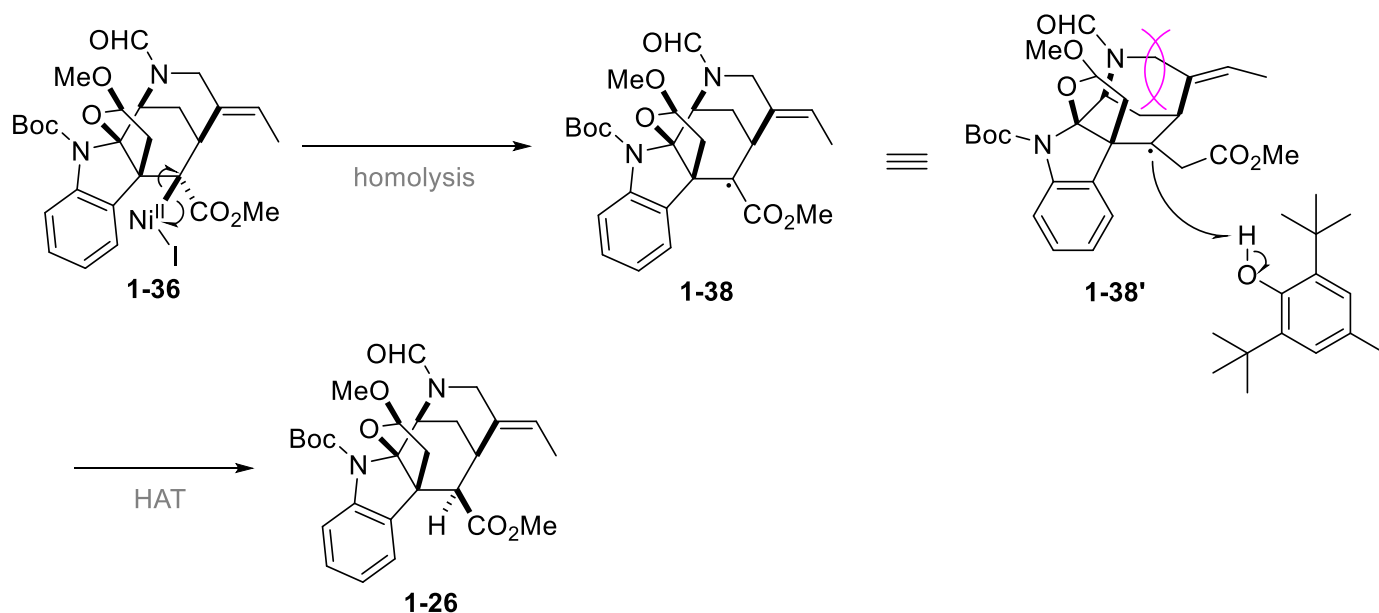
The authors proposed that nickel promoted reductive Heck reaction type cyclization. The reaction mechanism of cyclization is estimated as above. Then, there are two possible pathways for **1-26** to be generated.

#### Path (a)



**1-36** is likely to form nickel O-enolate **1-37** because O-enolate is more stable than C-enolate at room temperature.<sup>4</sup> Then protonation occurs from sterically less hindered  $\alpha$ -face of **1-37**, which leads to desired **1-26**. I think the path (a) is more reasonable than path (b).

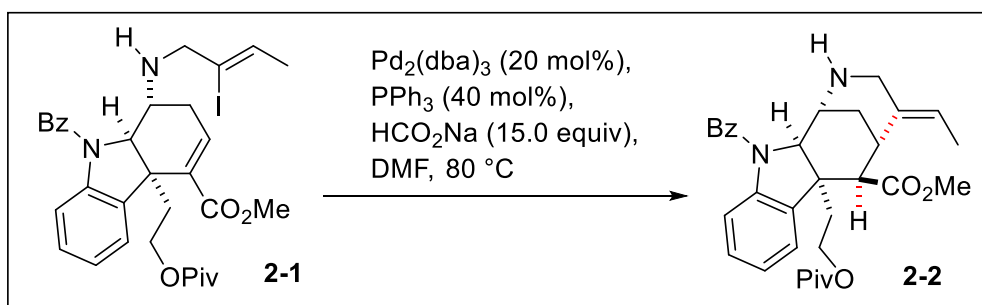
#### Path (b)



There is a possibility that homolysis of C-Ni bond occurs. The tertiary radical **1-38** withdraws hydrogen of BHT from sterically less hindered  $\alpha$ -face of **1-38** in the same way as path (a). Then **1-26** would be generated.

Nickel is thought to be used in this reaction because it promotes the reaction that goes through mechanisms such as path (a) and path (b) and gives the desired product **1-26**. Indeed, Pd-catalyzed reductive Heck cyclization of similar compound gave the different stereoselectivity from **1-26**. Though **epi-1-26** can epimerize to **1-26**, it's unlikely to happen because piperidine ring and tetrahydrofuran ring exist on the upside causing large steric repulsion.

e.g. Pd-catalyzed reductive Heck cyclization<sup>5</sup>



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- 1) Eckermann, R.; Gaich, T. *Synthesis* **2013**, 45, 2813–2823
- 2) Fujimoto, K.; Tokuda, Y.; Matsubara, Y.; Maekawa, H.; Mizuno, T.; Nishiguchi, I. *Tetrahedron Lett.* **1995**, 36, 7483-7486
- 3) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, 42, 4, 682–685

- 4) Juan, C.; Celia M. M.; Pilar P.; Ernesto C.; Enrique G. P.; Caridad R. *Journal of the American Chemical Society* **2003**, 125 (6), 1482-1483
- 5) Xiang Z.; Badrinath N. K.; Rui G.; Sonyabapu Y.; Yucheng G. Ang L. *Angewandte Chemie* **2019**, 131 (18), 6114-6119