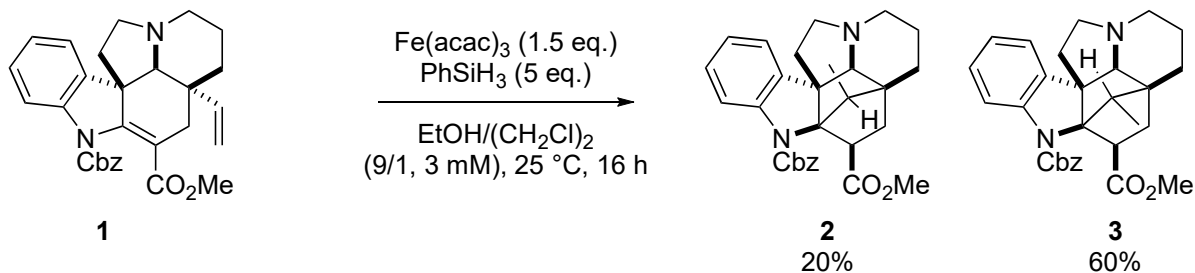


# Problem Session (5)

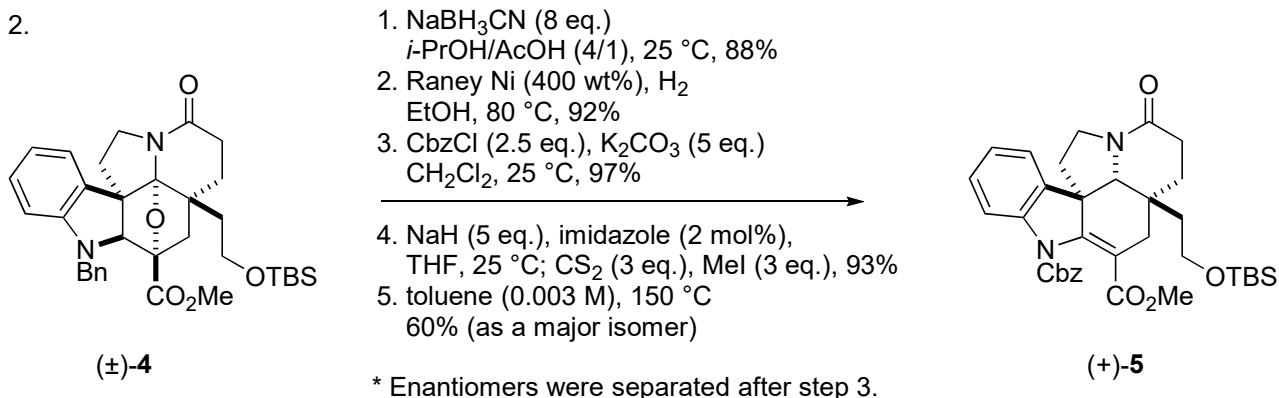
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Please provide each reaction mechanisms and explain the stereoselectivities.

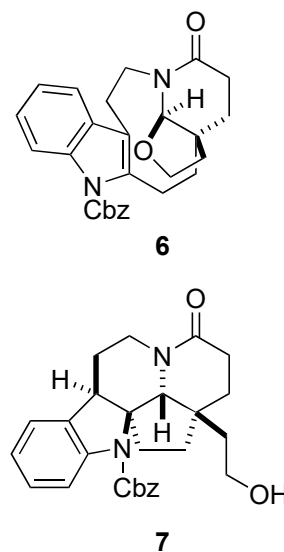
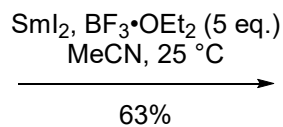
1.



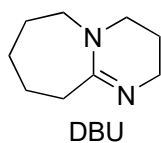
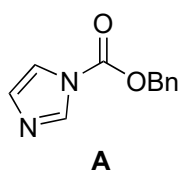
2.



1. KOH (10 eq.)  
 THF/MeOH/ $\text{H}_2\text{O}$  (1/1/1), 70 °C  
 2. toluene, 108 °C, 2 steps 95%  
 3. **A** (10 eq.), DBU (3 eq.), MeCN  
 25 °C, 73% (brsm 92%)



\*  $\text{Sml}_2$  was added until **6** was consumed and its equivalent was not mentioned.



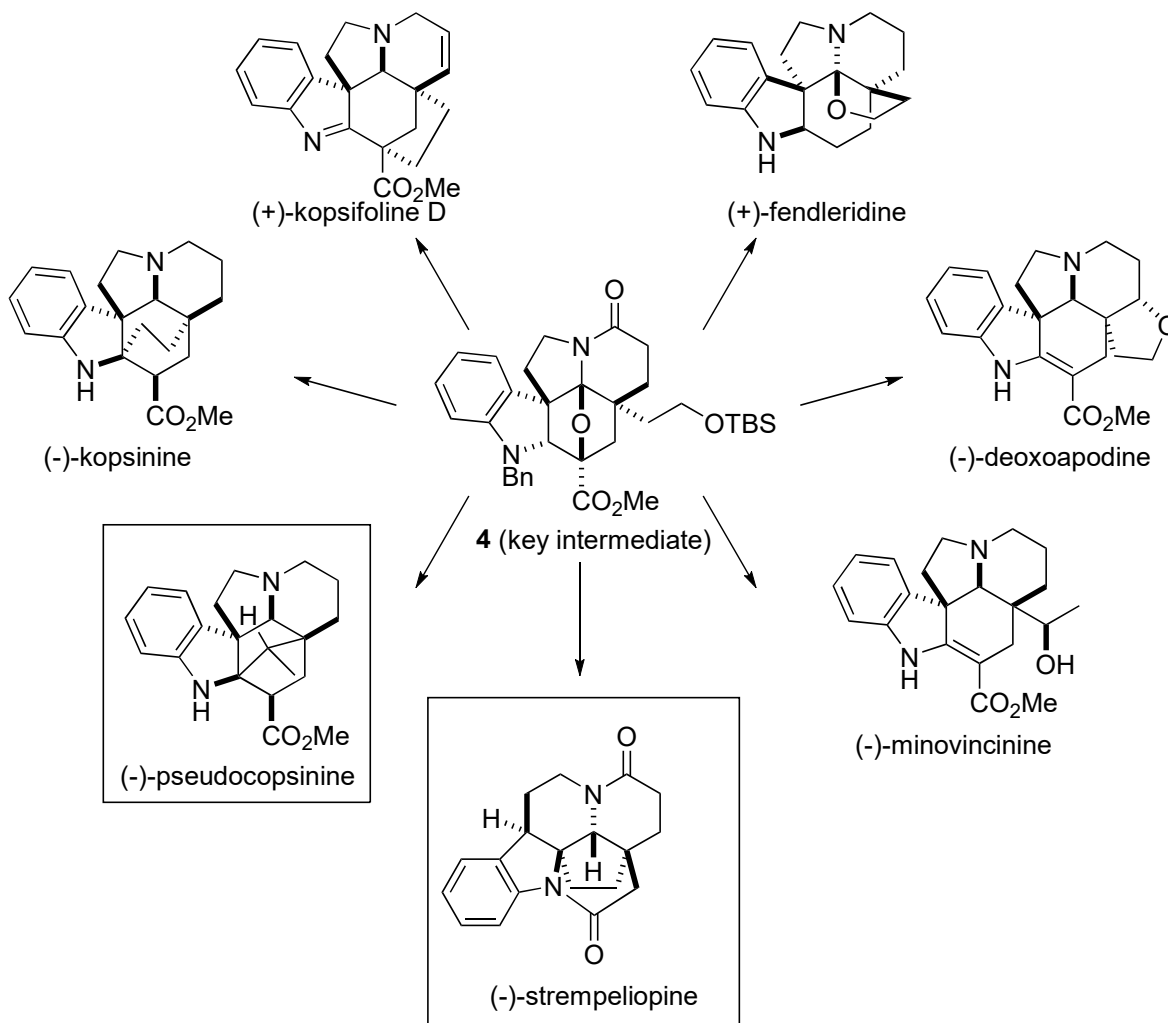
# Problem Session (5)-Answer-

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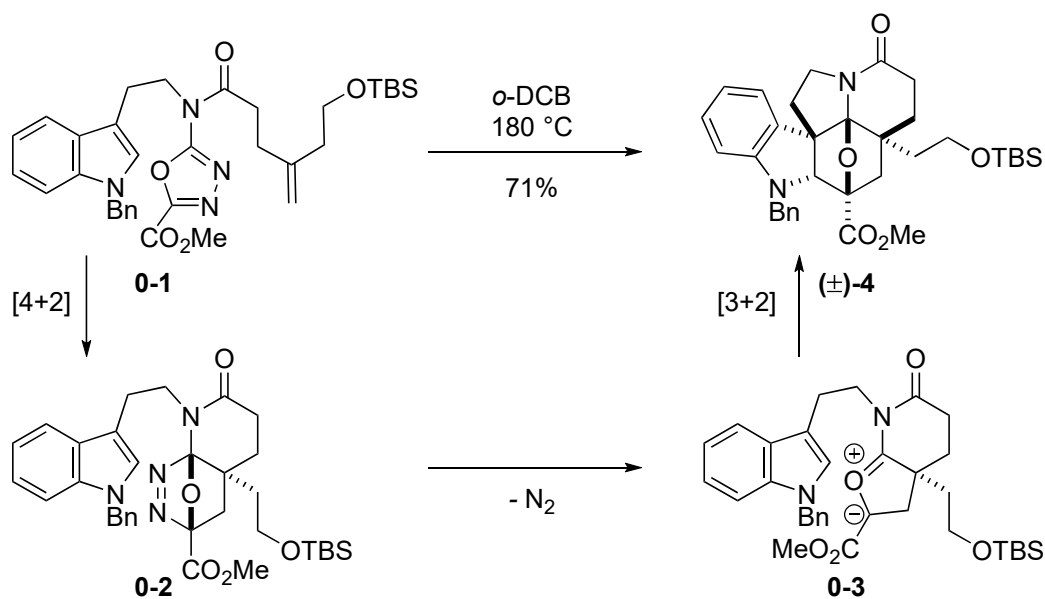
Topic: Total synthesis of (-)-pseudocopsinine and (-)-strempeleine by Boger's group

## 0. Introduction

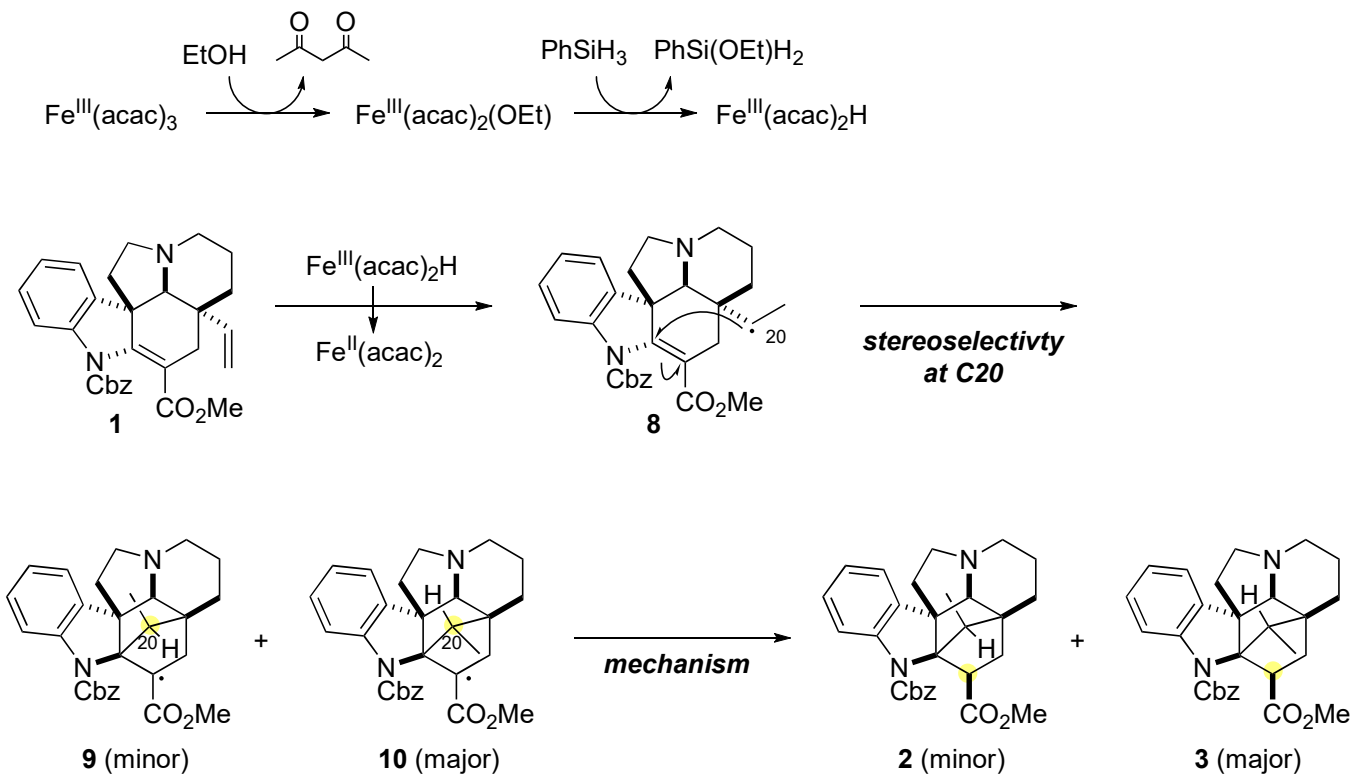
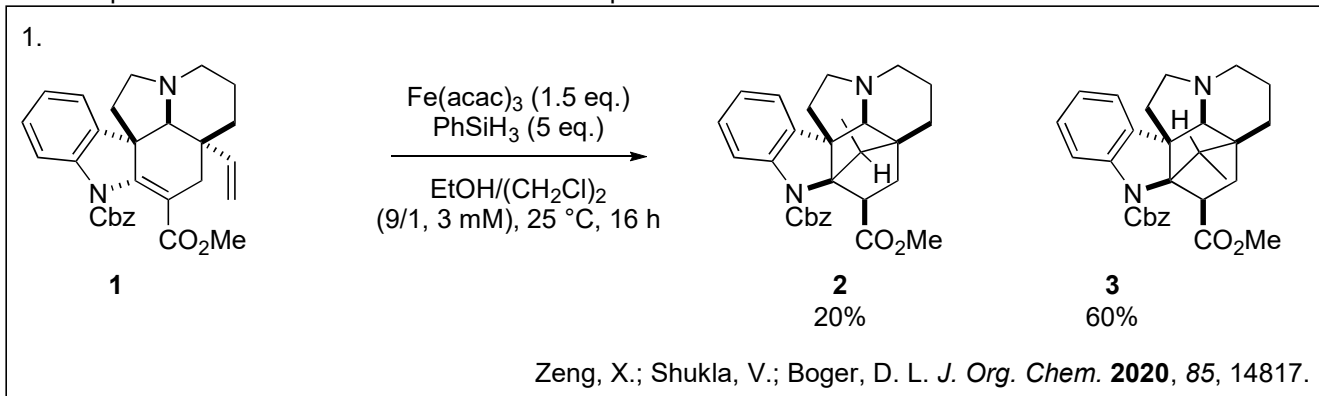
Boger group has achieved divergent total synthesis from common intermediate **4**.



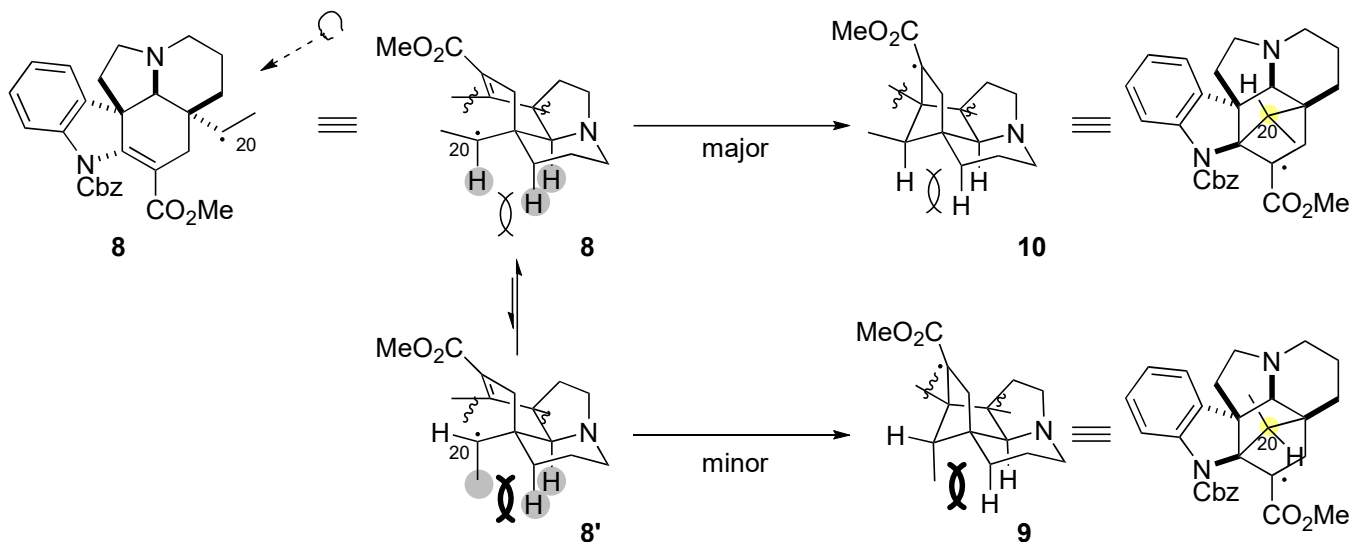
Synthesis of common intermediate: [4+2]/[3+2] cycloaddition cascade <sup>1)</sup>



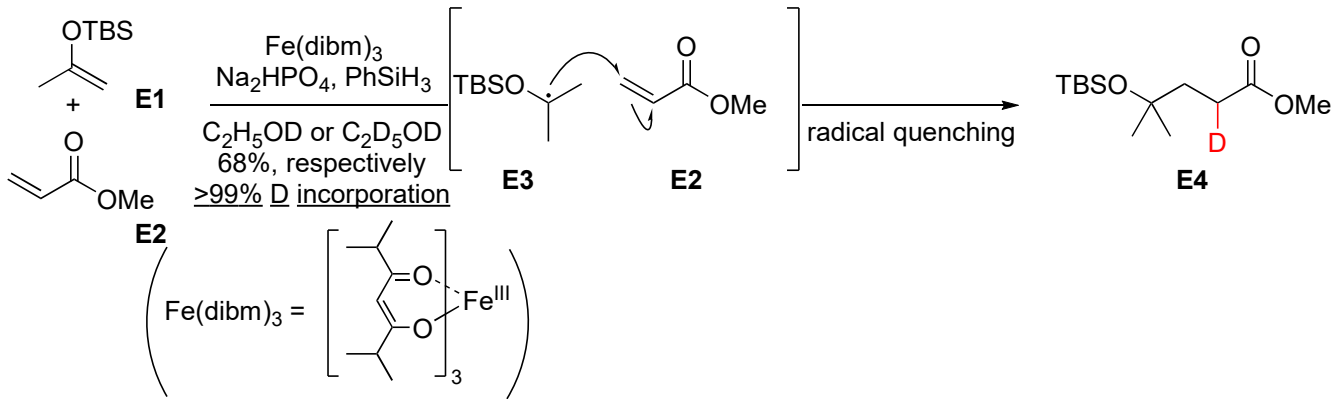
Please provide each reaction mechanisms and explain the stereoselectivities.



discussion 1-1. stereoselectivity at C20 (indoline ring is omitted.)



discussion 1-2. mechanism of quenching the generated radical



The proton derives from ethanol. <sup>2)</sup>

-> three possibilities for quenching the product radical are conceivable.

Mechanism (a): stepwise ET/PT pathway



Mechanism (b): CPET pathway



Mechanism (c): protonation from an organometallic complex

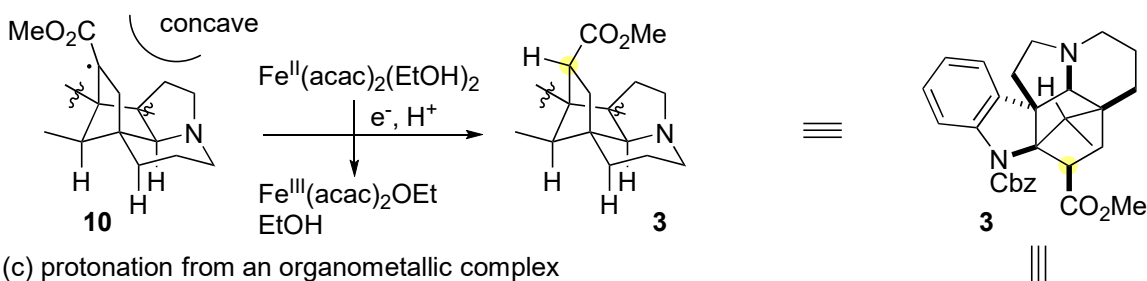


Holland et al. mentioned (a) was unlikely.

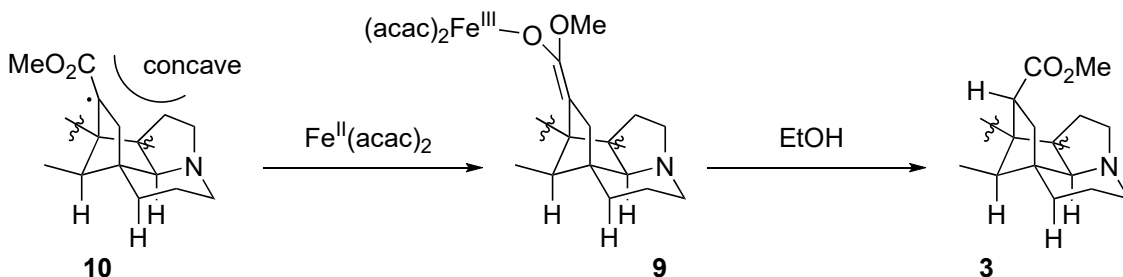
$[\text{Fe}^{\text{III}}(\text{acac})_2]^+ + e^- \rightarrow \text{Fe}^{\text{II}}(\text{acac})_2$ ;  $E_{\text{Fe(III)/Fe(II)}} = -0.48 \text{ V}$  (in EtOH, measured by cyclic voltammetry)  
 $\text{MeCH}^+(\text{CO}_2\text{Me}) + e^- \rightarrow \text{MeCH}^-(\text{CO}_2\text{Me})$ ;  $E_{\text{Fe(III)/Fe(II)}} = -1.04 \text{ V}$  (in MeCN) <sup>3)</sup>

$\therefore \text{Fe}^{\text{II}}(\text{acac})_2 + \text{MeCH}^+(\text{CO}_2\text{Me}) \rightarrow [\text{Fe}^{\text{III}}(\text{acac})_2]^+ + \text{MeCH}^-(\text{CO}_2\text{Me})$ ;  $E_{\text{total}} = \sim -0.56 \text{ V}$  (13 kcal/mol) -> uphill  
 Though solvents are different, electron transfer from  $\text{Fe}^{\text{II}}$  to the generated radical will be kinetically unfavorable. (They conducted DFT calculation and predicted it is more uphill (35.0 kcal/mol) in EtOH)  
 In contrast, activation barriers in (b) and (c) were calculated as 9.4 kcal/mol and 11.0 kcal/mol, respectively, so path (b) or (c) is more likely than path (a).

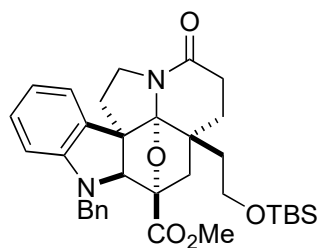
(b) concerted proton-coupled electron transfer path



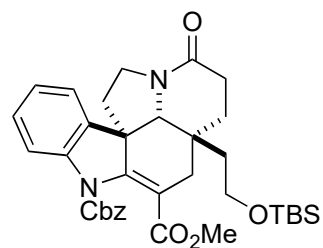
(c) protonation from an organometallic complex



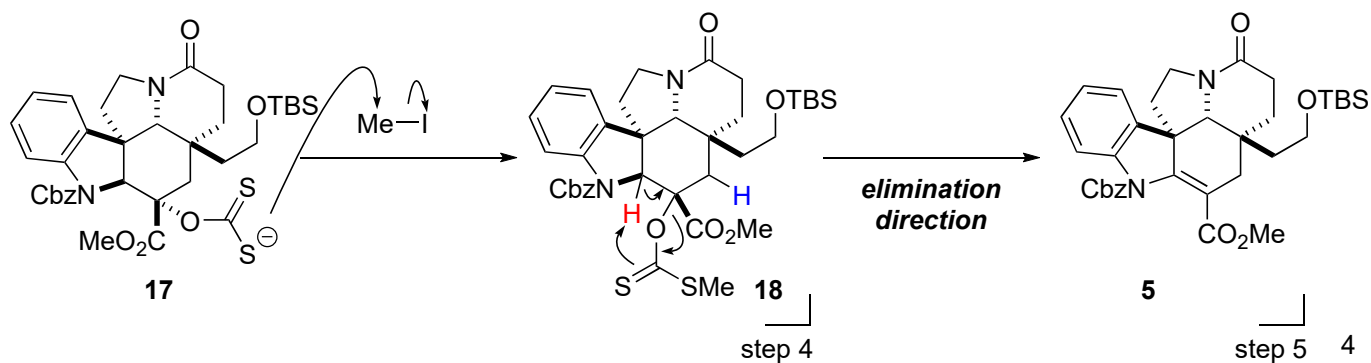
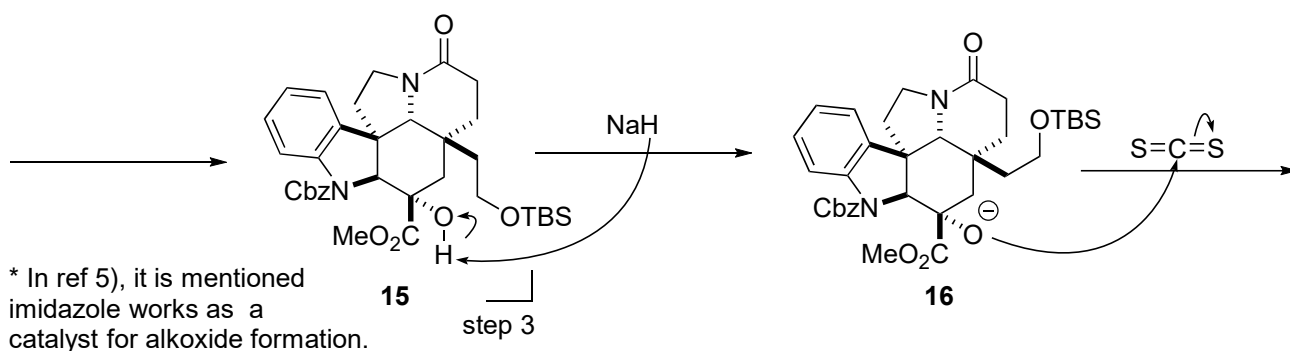
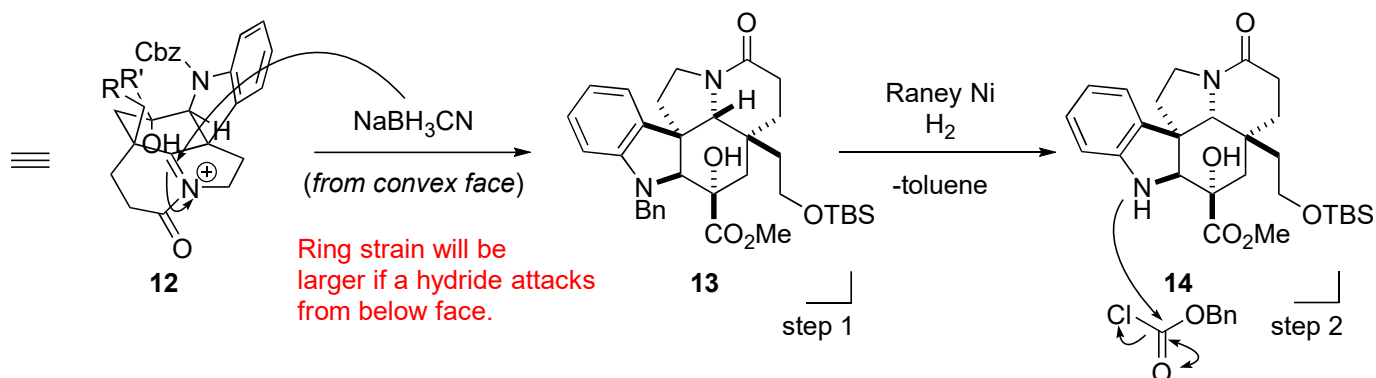
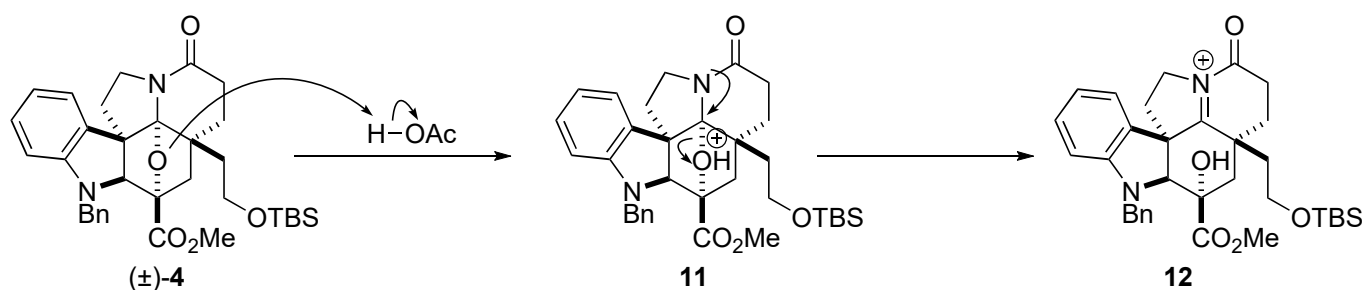
2.



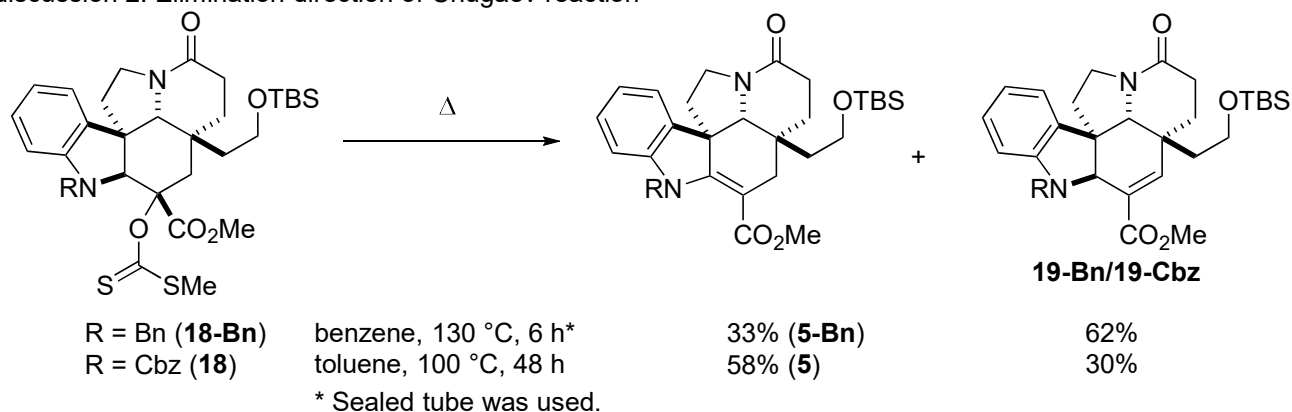
1.  $\text{NaBH}_3\text{CN}$  (8 eq.)  
*i*-PrOH/AcOH (4/1), 25 °C, 73%
2. Raney Ni (1300 wt%),  $\text{H}_2$   
EtOH, 80 °C, 92%
3. CbzCl (2.5 eq.),  $\text{K}_2\text{CO}_3$  (5 eq.)  
 $\text{CH}_2\text{Cl}_2$ , 25 °C, 92%
4. NaH (13 eq.), imidazole (2 mol%),  
THF, 25 °C;  $\text{CS}_2$  (19 eq.), MeI (19 eq.), 90%
5. toluene (0.003 M), 150 °C  
58% (as a major isomer)



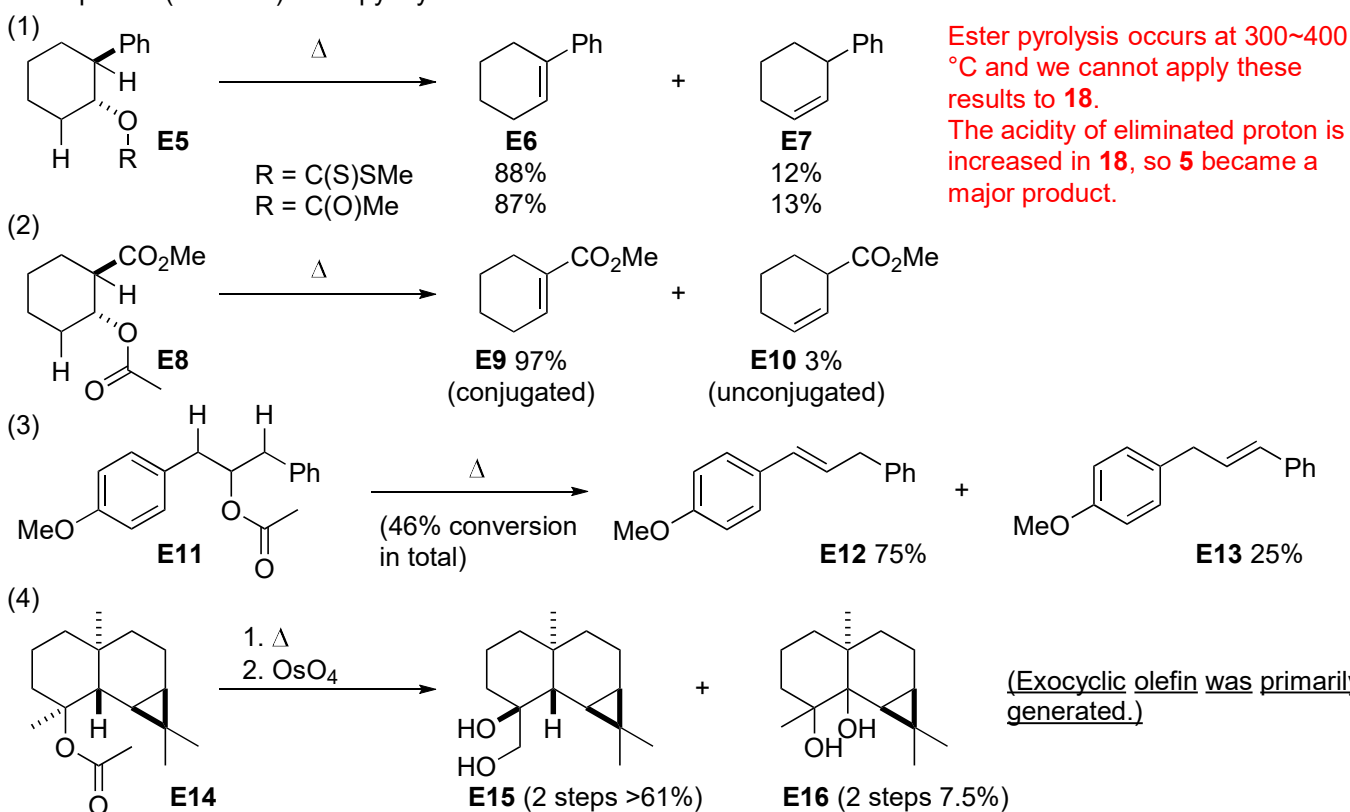
\* Enantiomers were separated after step 3.



discussion 2. Elimination direction of Chugaev reaction

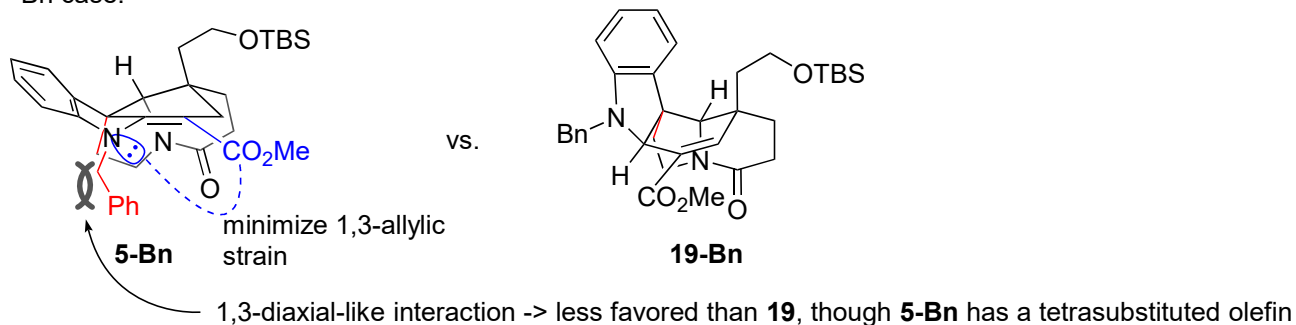


Examples of (xanthate) ester pyrolysis<sup>4)</sup>:

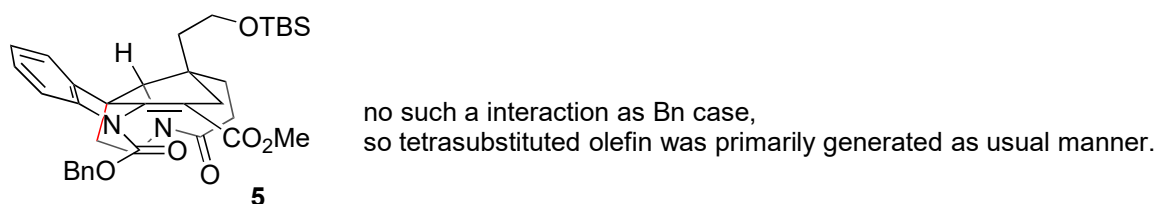


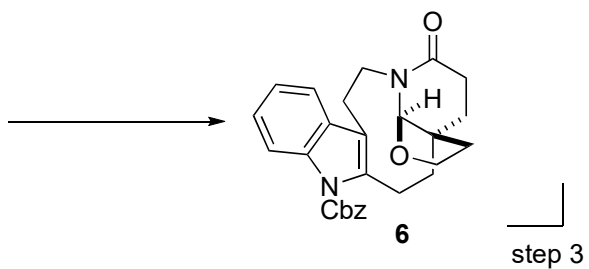
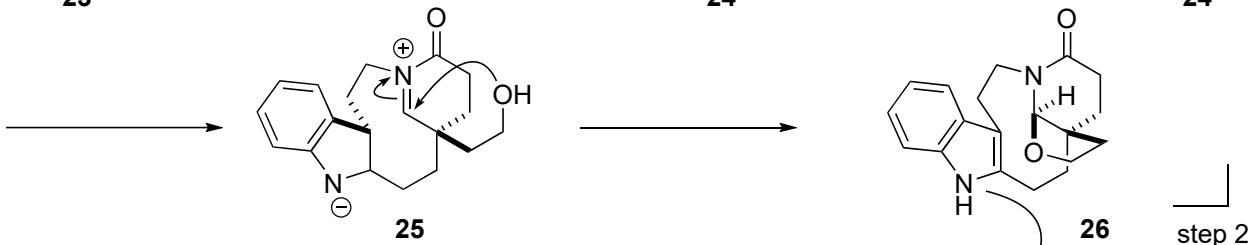
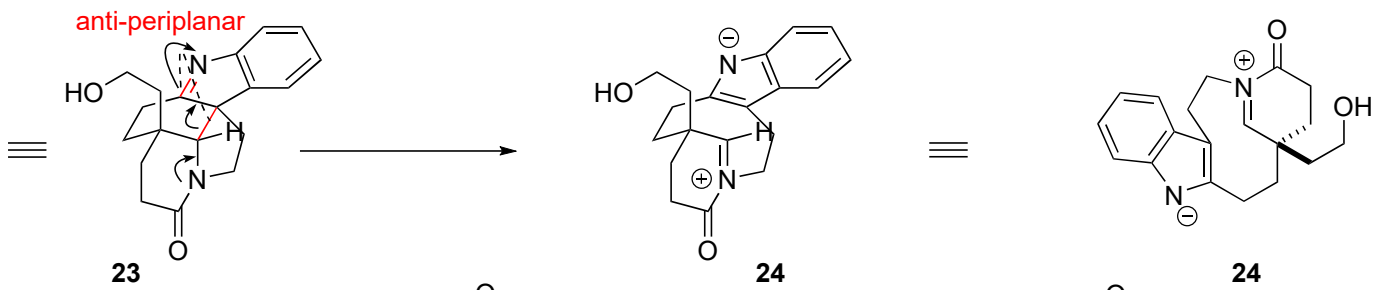
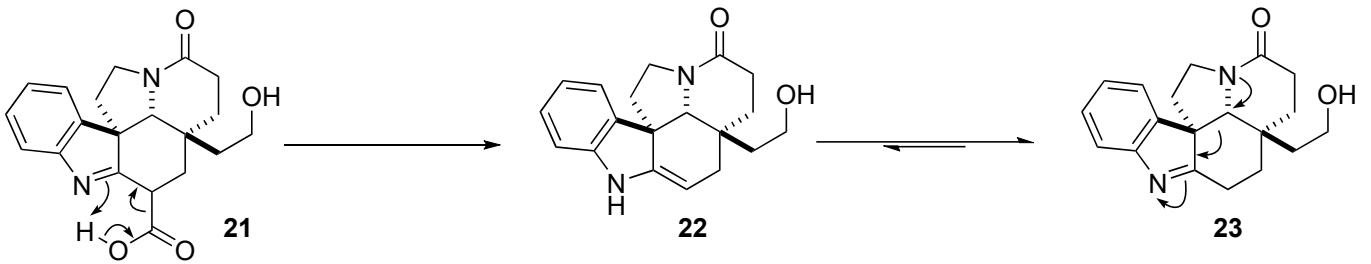
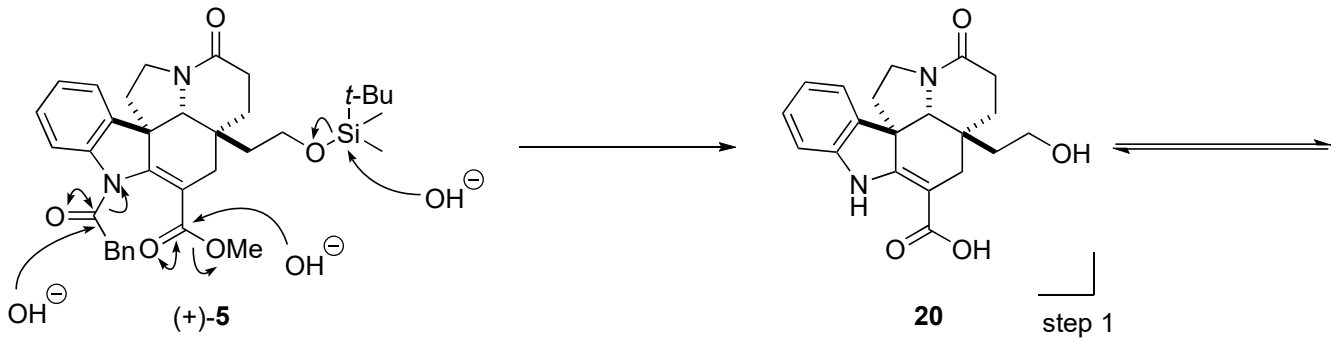
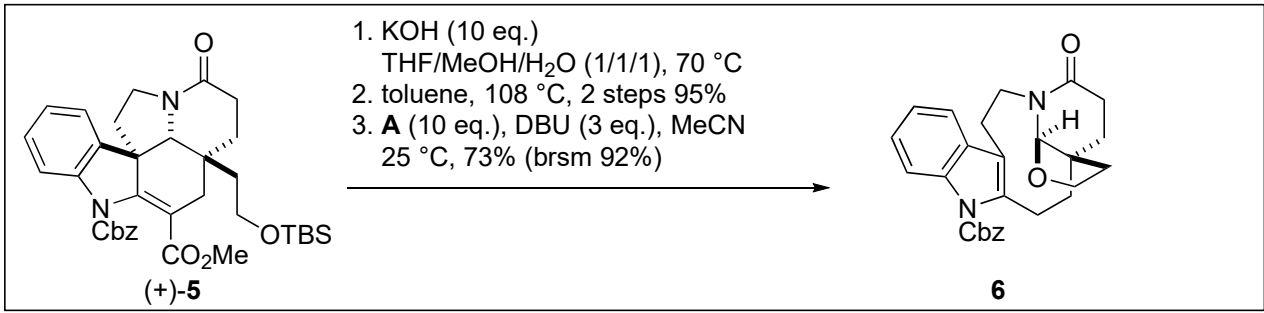
-> In general, the influence of functional groups has been mainly attributed to their effect on the stability of the resultant olefin ((1)~(3)). Exocyclic olefin was primarily generated in (4), and internal olefin would be unfavored in the entire molecule due to the strain (1,3-allylic strain, for example).

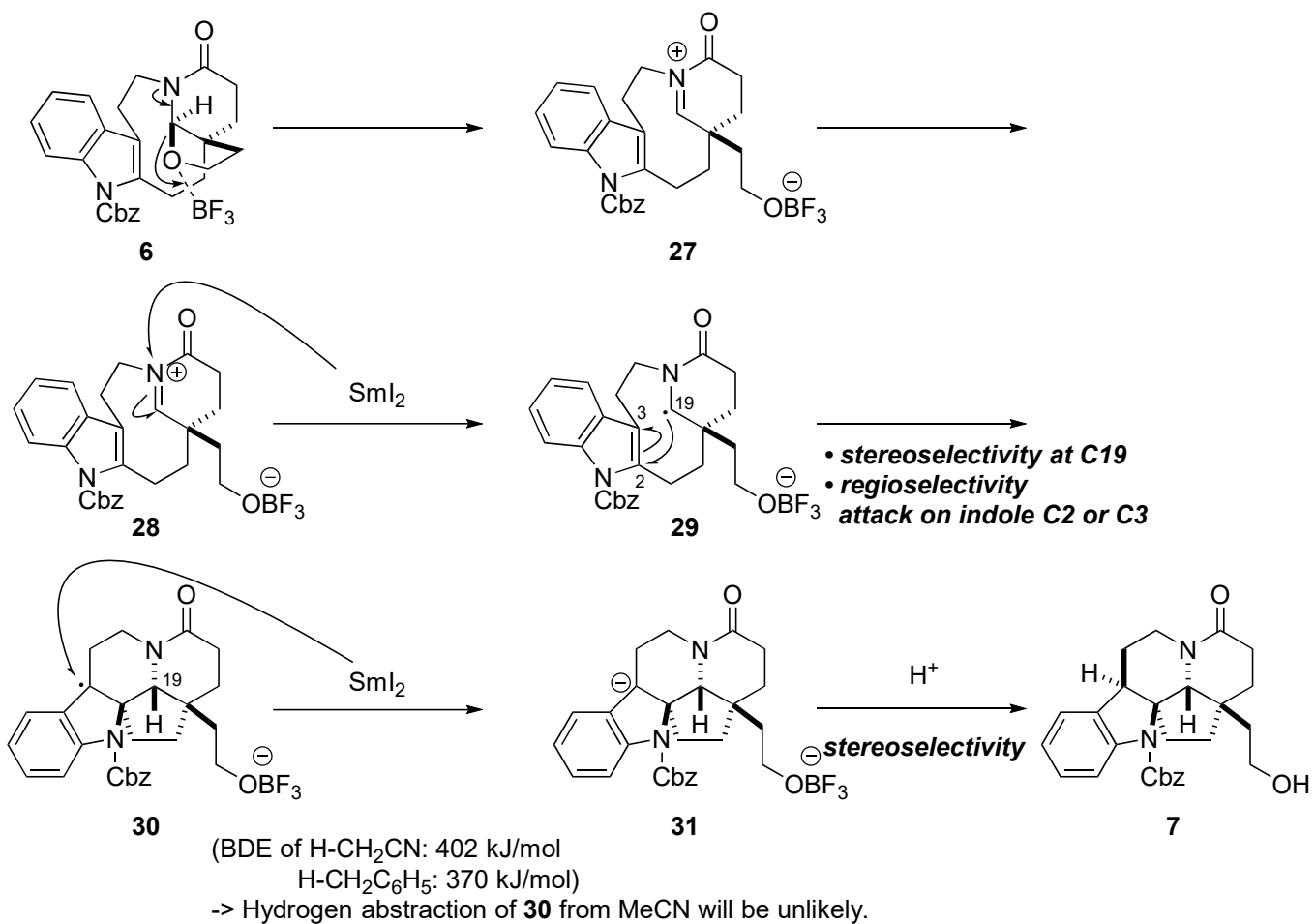
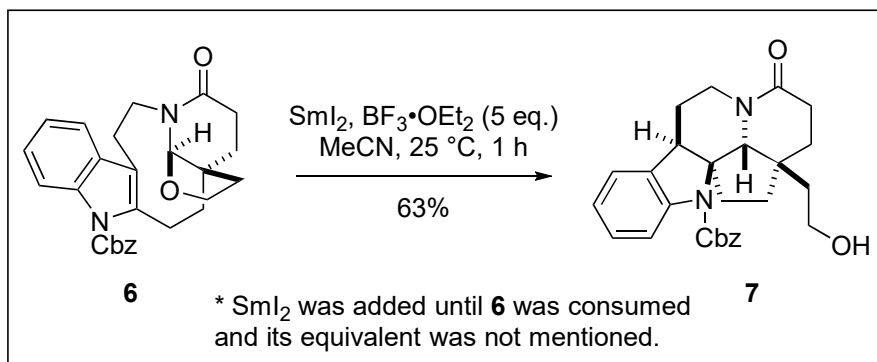
- Bn case:



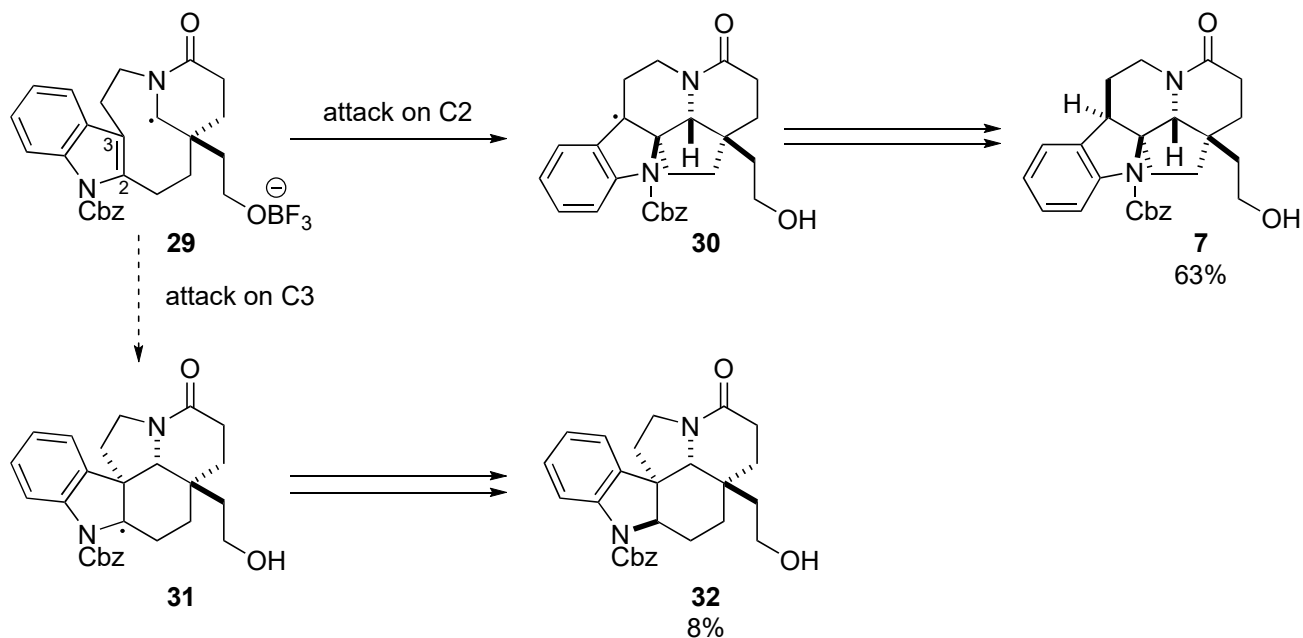
- Cbz case:





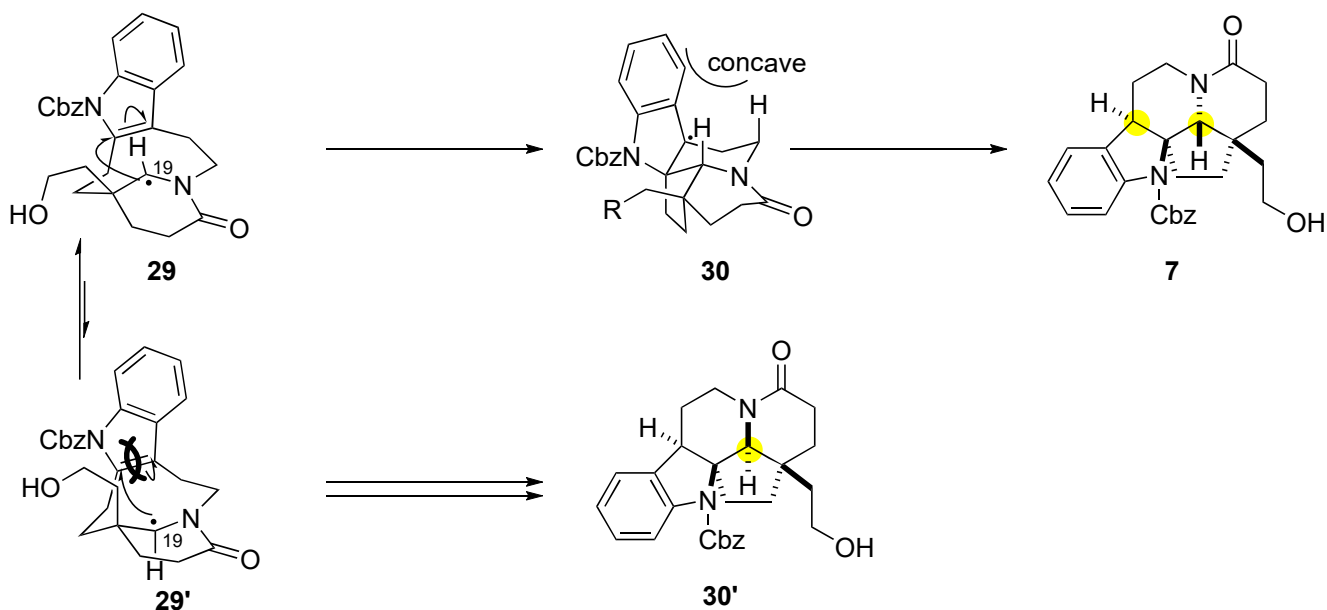


discussion 2. Radical addition to C2 or C3 of indole

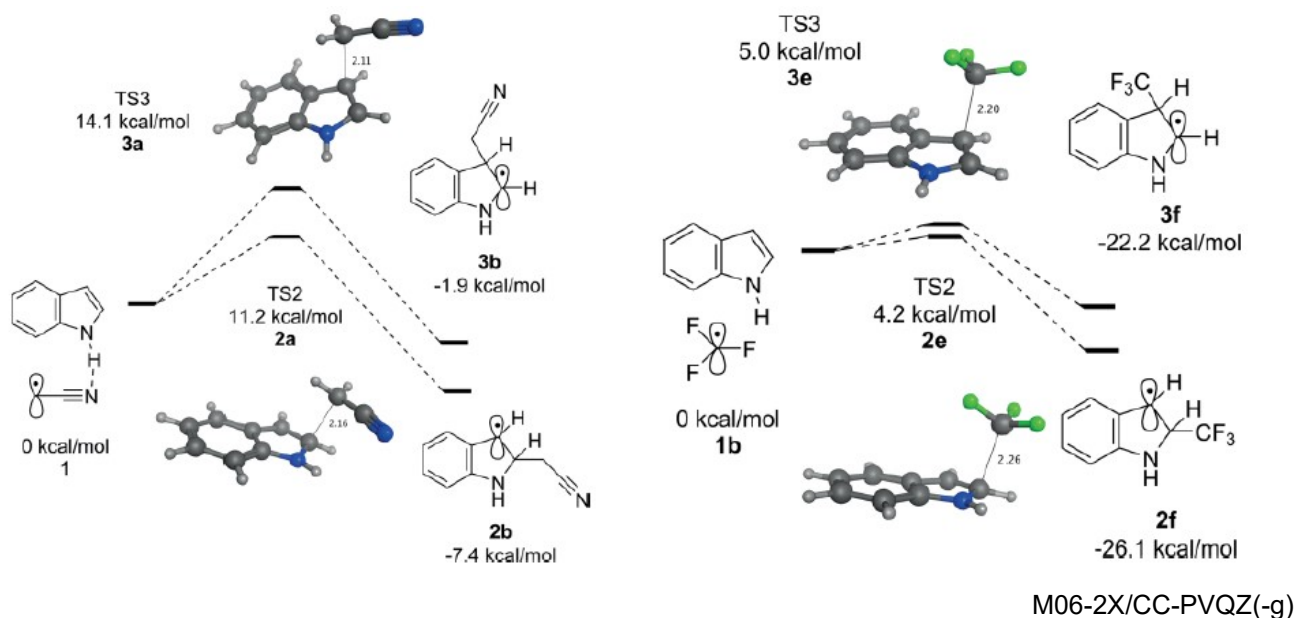




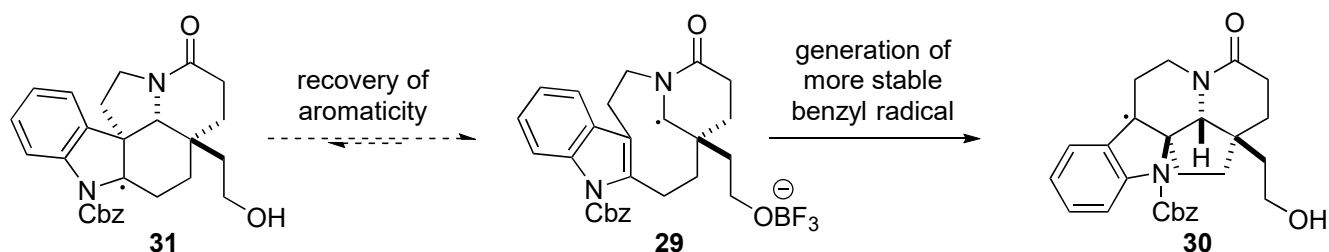
Stereoselectivity at C19:



Regioselective addition of electron-deficient radicals on indole C2<sup>6)</sup>:



-> Intermolecular attack on indole C2 is kinetically and thermodynamically favored. The equilibrium between **31** and **29** will be conceivable.



## Reference

- 1) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009.
- 2) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C. M.; Baran, P. S. *Nature* **2014**, *516*, 343.
- 3) Bortolamei, M.; Isse, A. A.; Gennaro, A. *Electrochim. Acta* **2010**, *55*, 8312.
- 4) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.
- 5) Barton, D. H.; McCombie, S. W. *J. Chem. Soc. Perkin Trans 1* **1975** 1574
- 6) Li, Y.; Vaz, R. J.; Olson, S. H.; Munson, M.; Paras, N. A.; Conrad, J. *Eur. J. Org. Chem.* **2020**, 5828.