

Problem Session (1) -Answer-

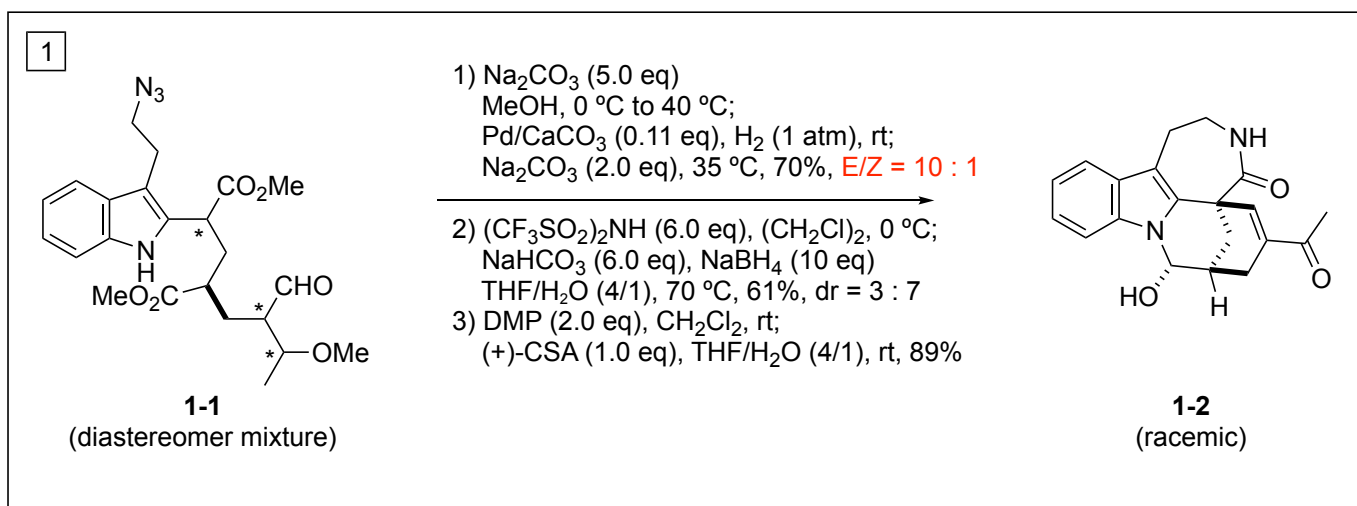
Topic: Tandem cyclization

Problem 1 Total synthesis of Tronocarpine

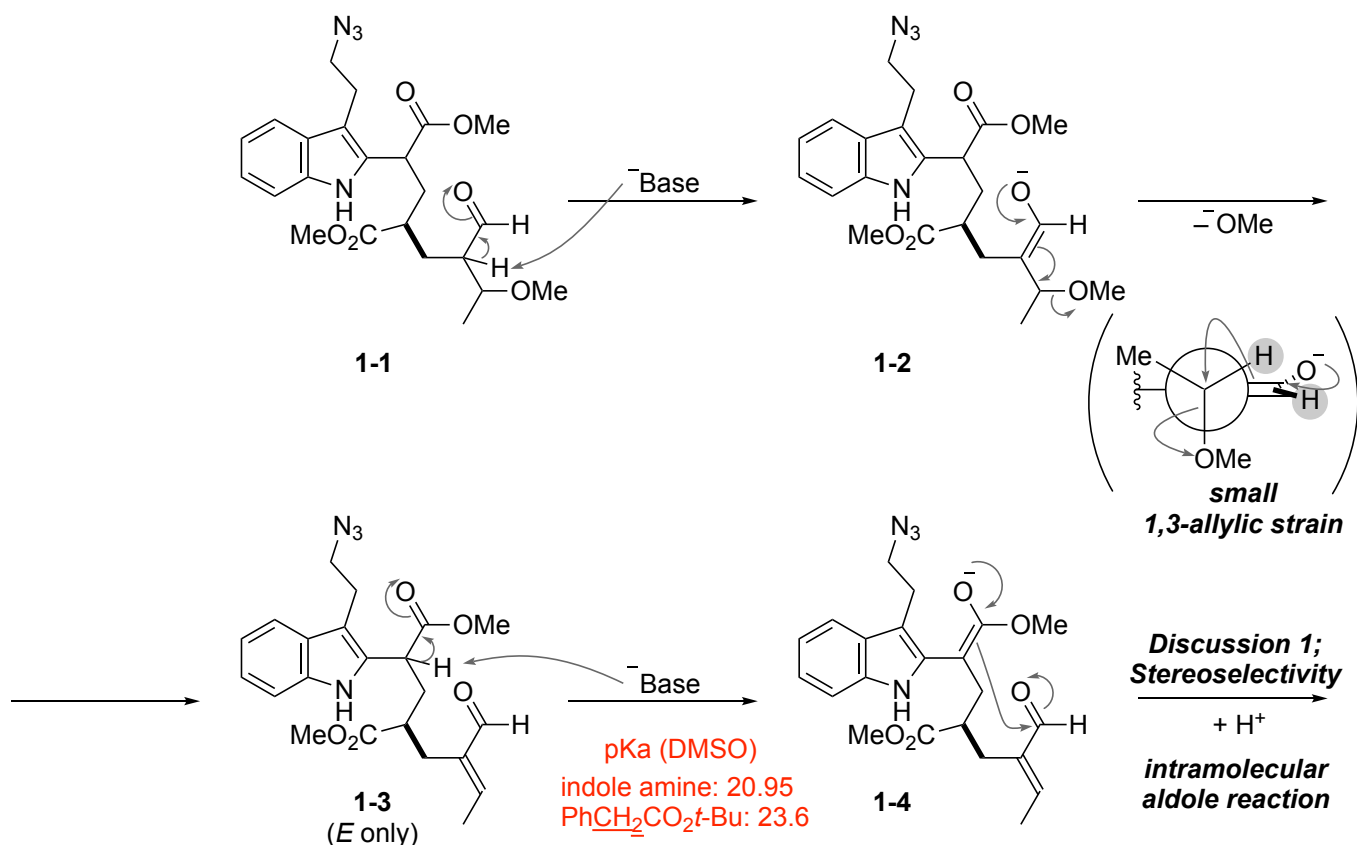
1-1. reaction mechanism

2021.12.11

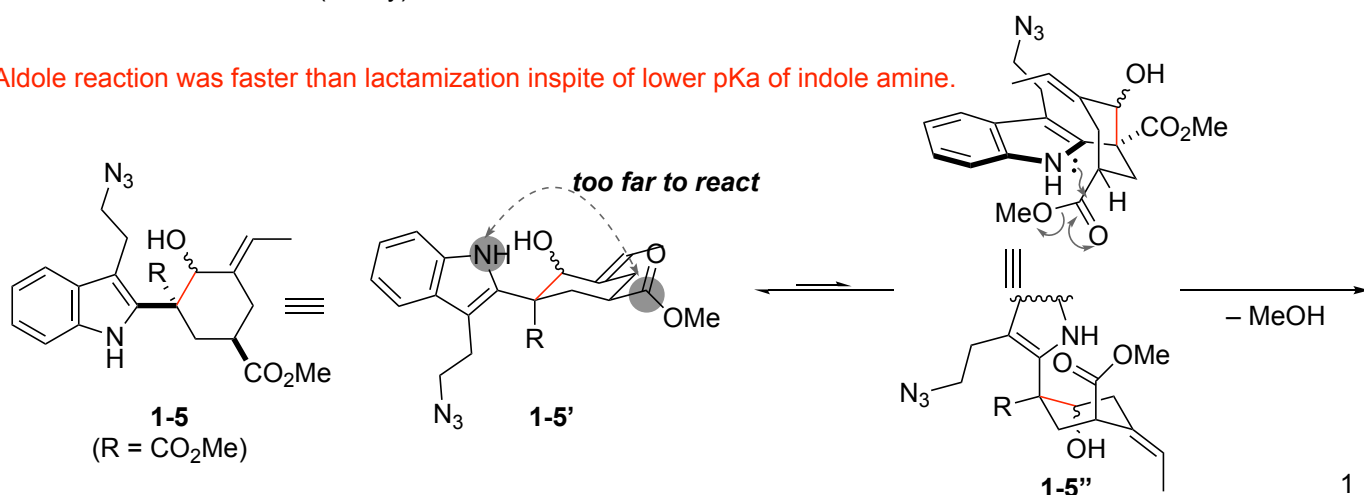
Kyohei Oga

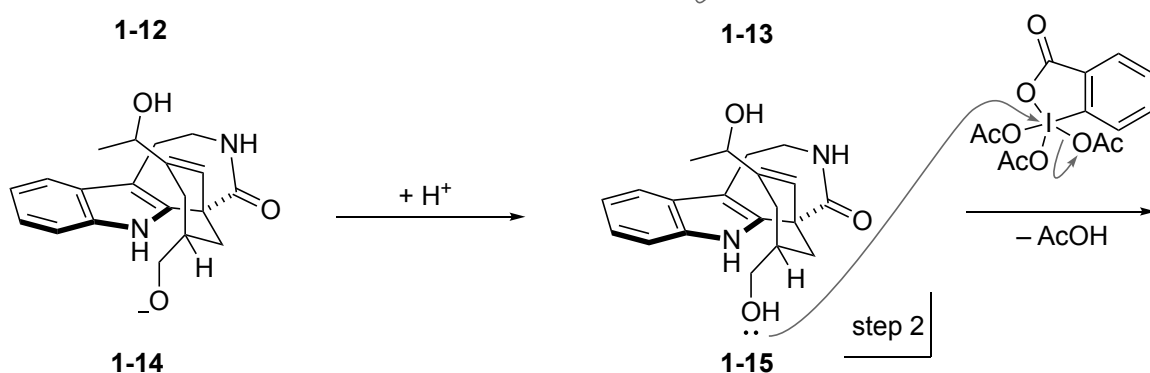
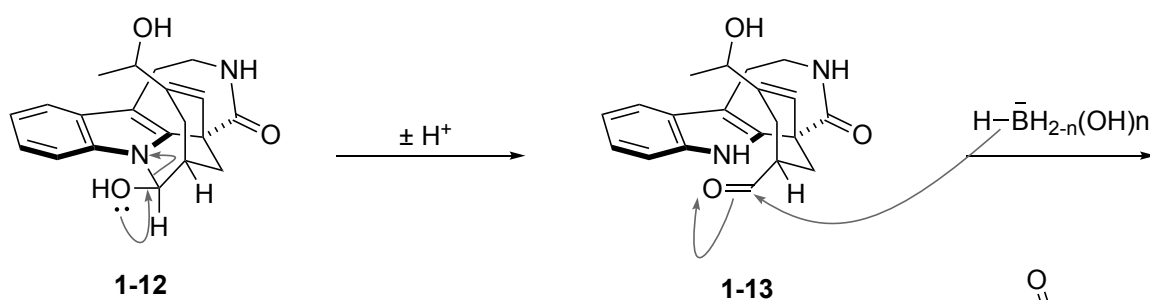
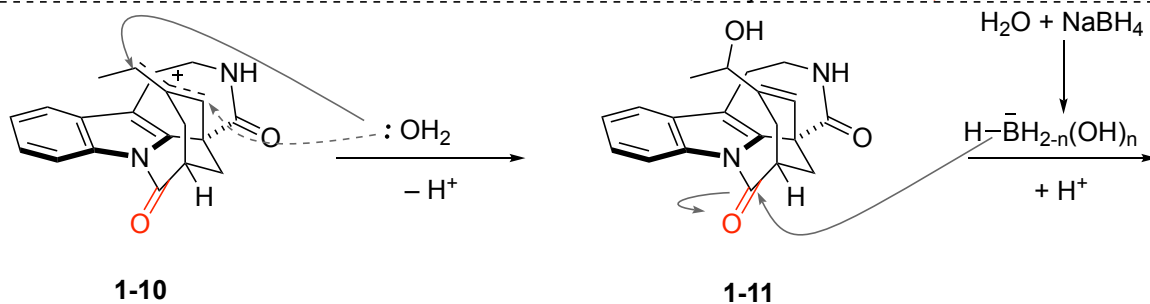
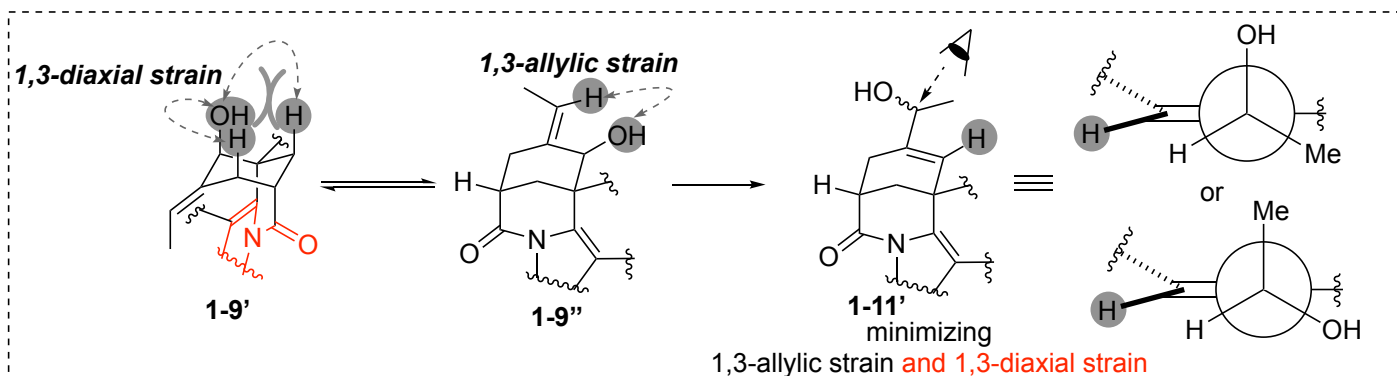
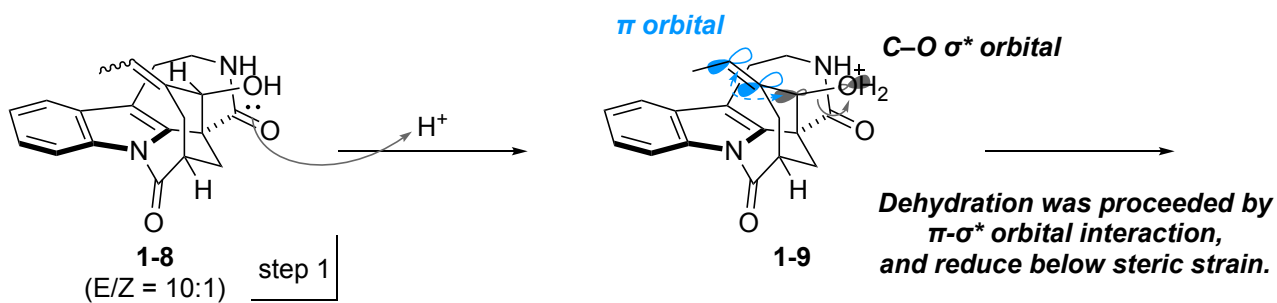
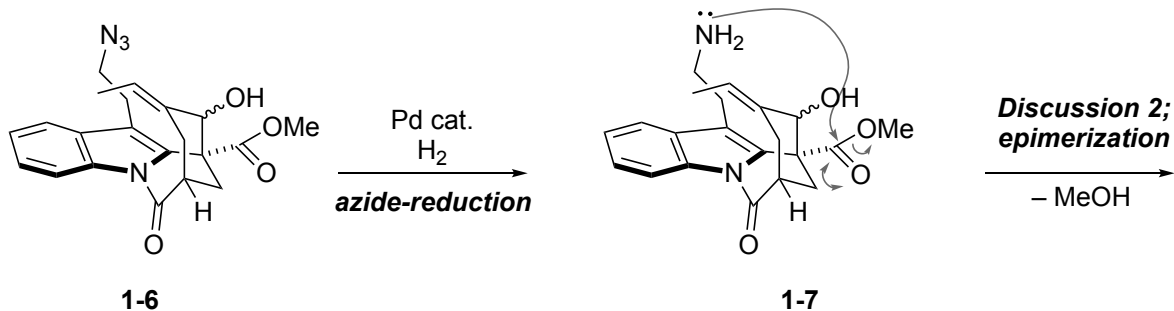


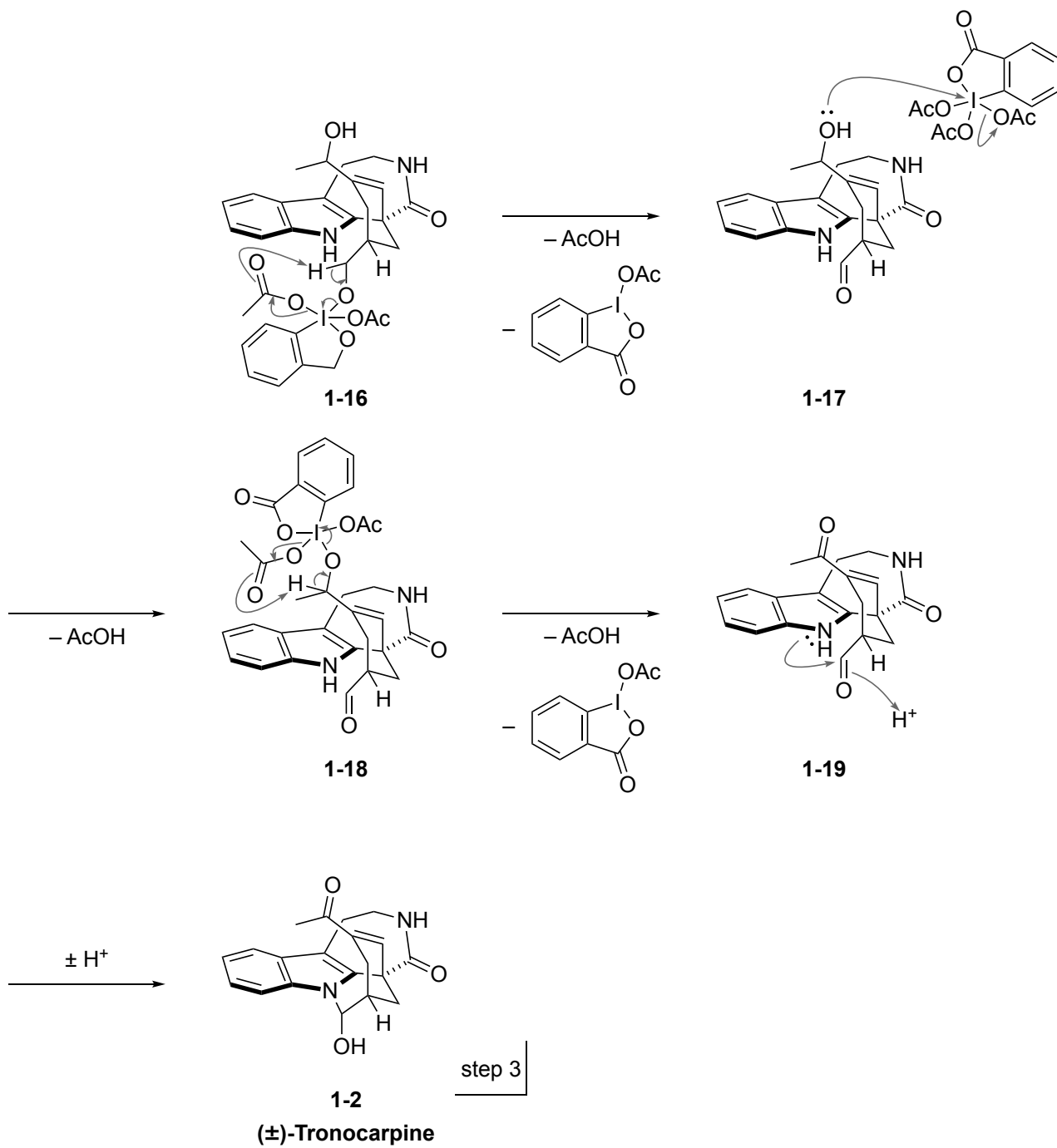
Nakayama, A.; Nakamura, T.; Zaima, T.; Fujimoto, S.; Karanjit, S.; Namba, K. *Angew. Chem. Int. Ed.* **2021**, *60*, 635



Aldole reaction was faster than lactamization inspite of lower pKa of indole amine.

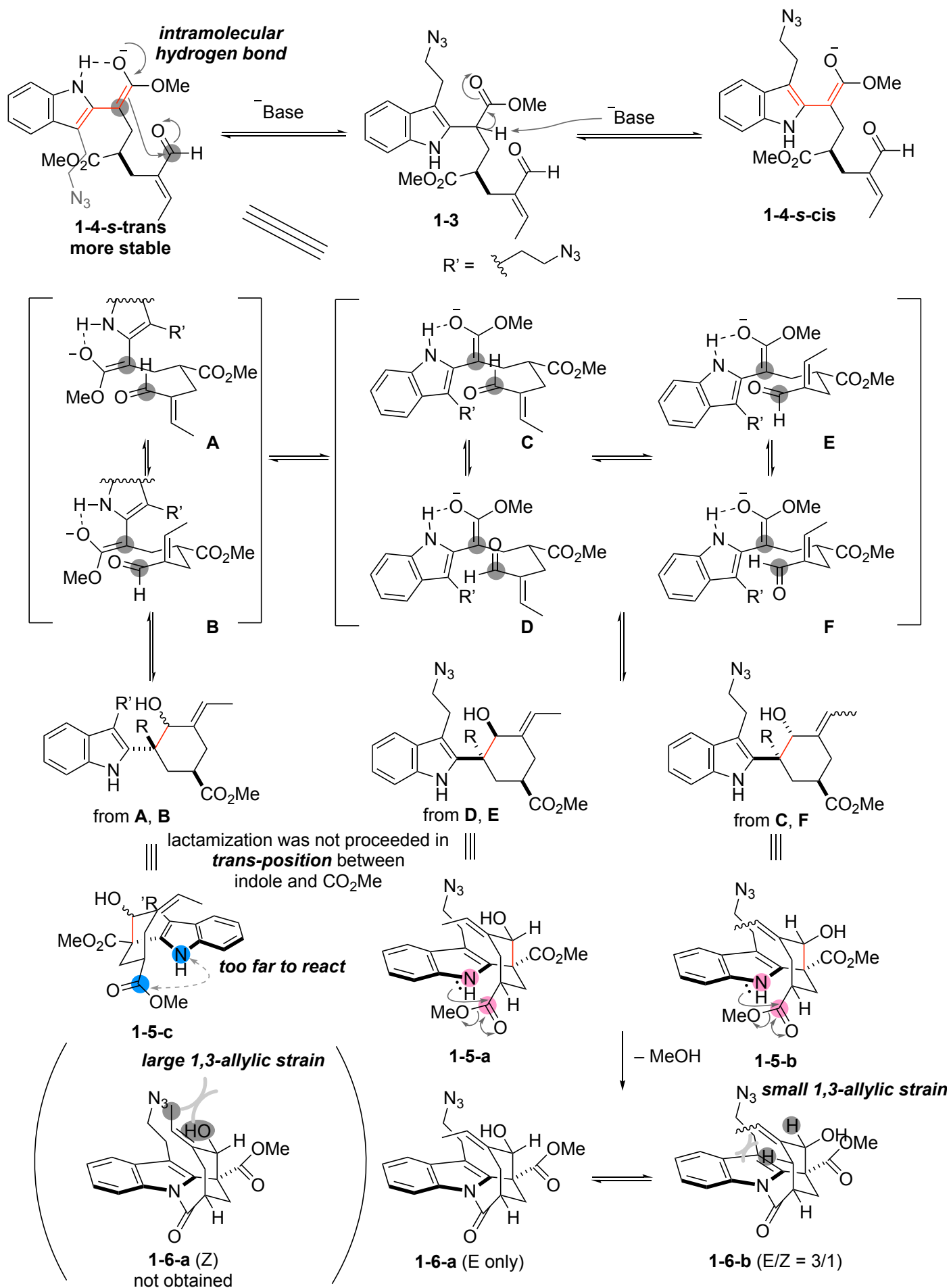






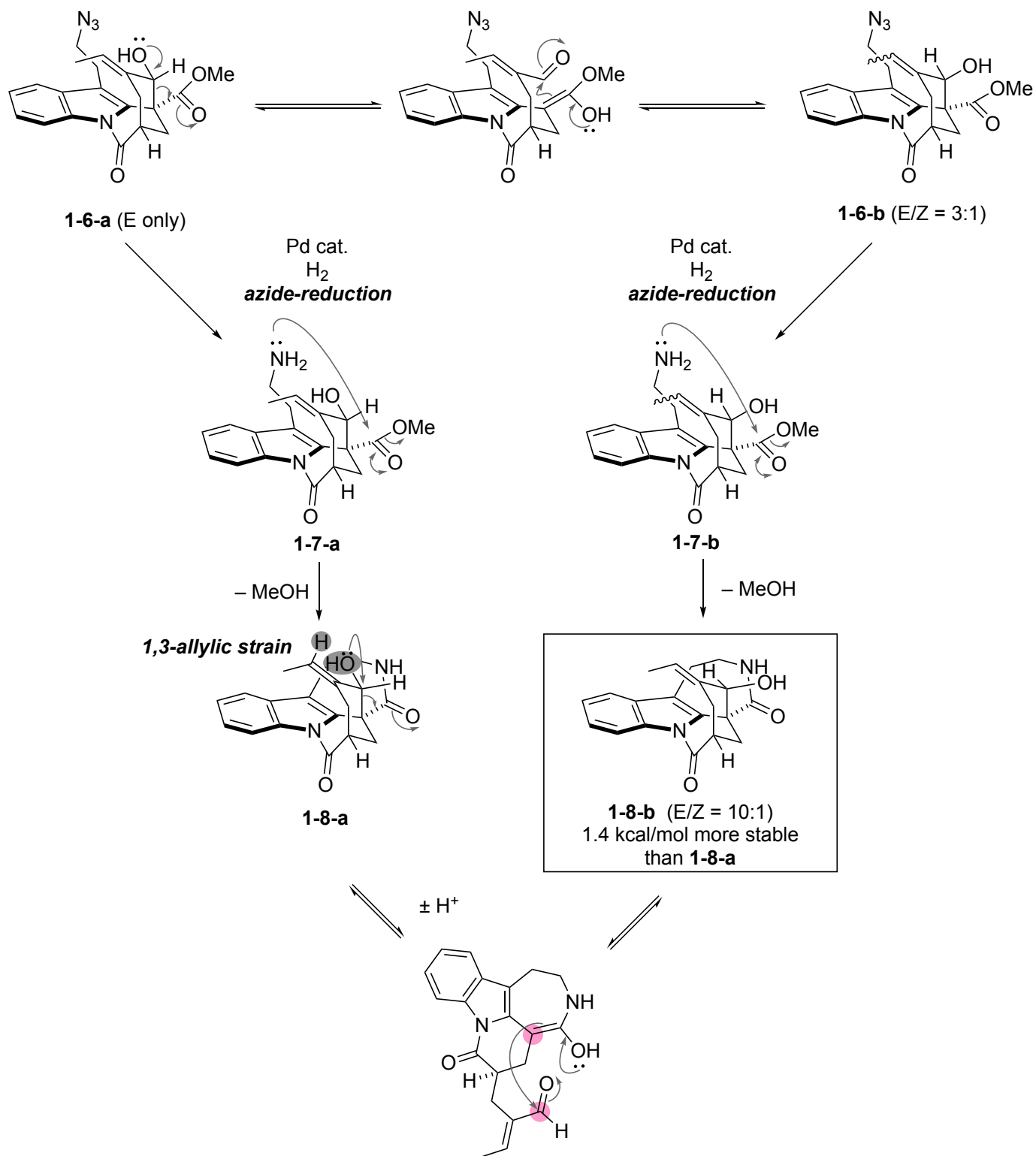
1-2. Discussion

1-2-1. equilibrium of aldole and retro-aldole reaction (*Discussion 1*)



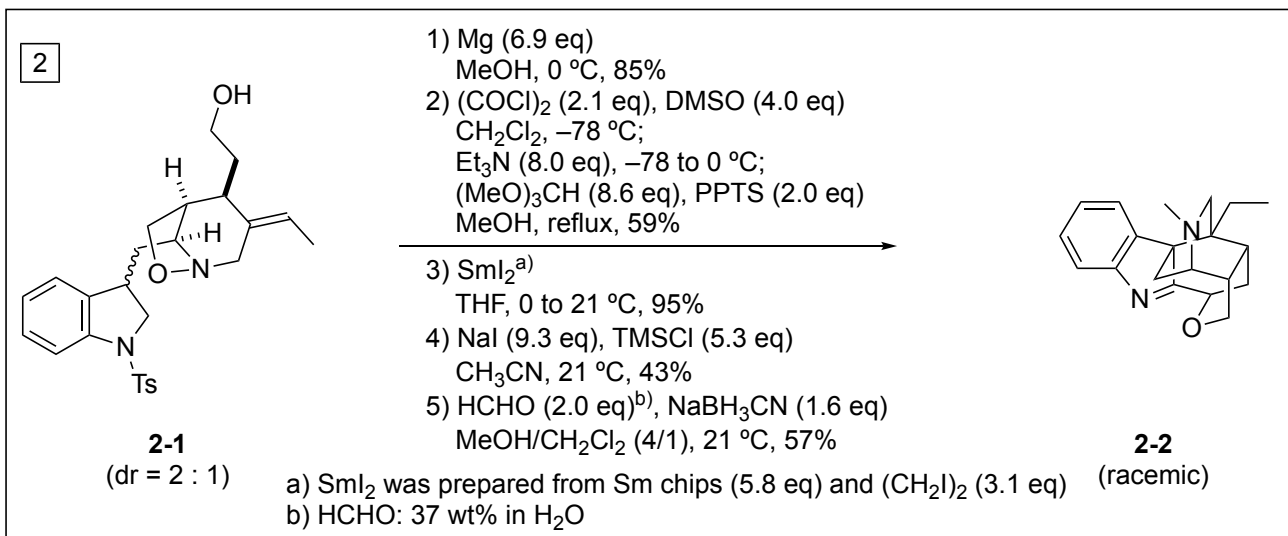
• Both *E* and *Z* were obtained in **1-6-b** because of small 1,3-allylic strain than **1-6-a**

1-2-2. epimerization (*Discussion 2*)

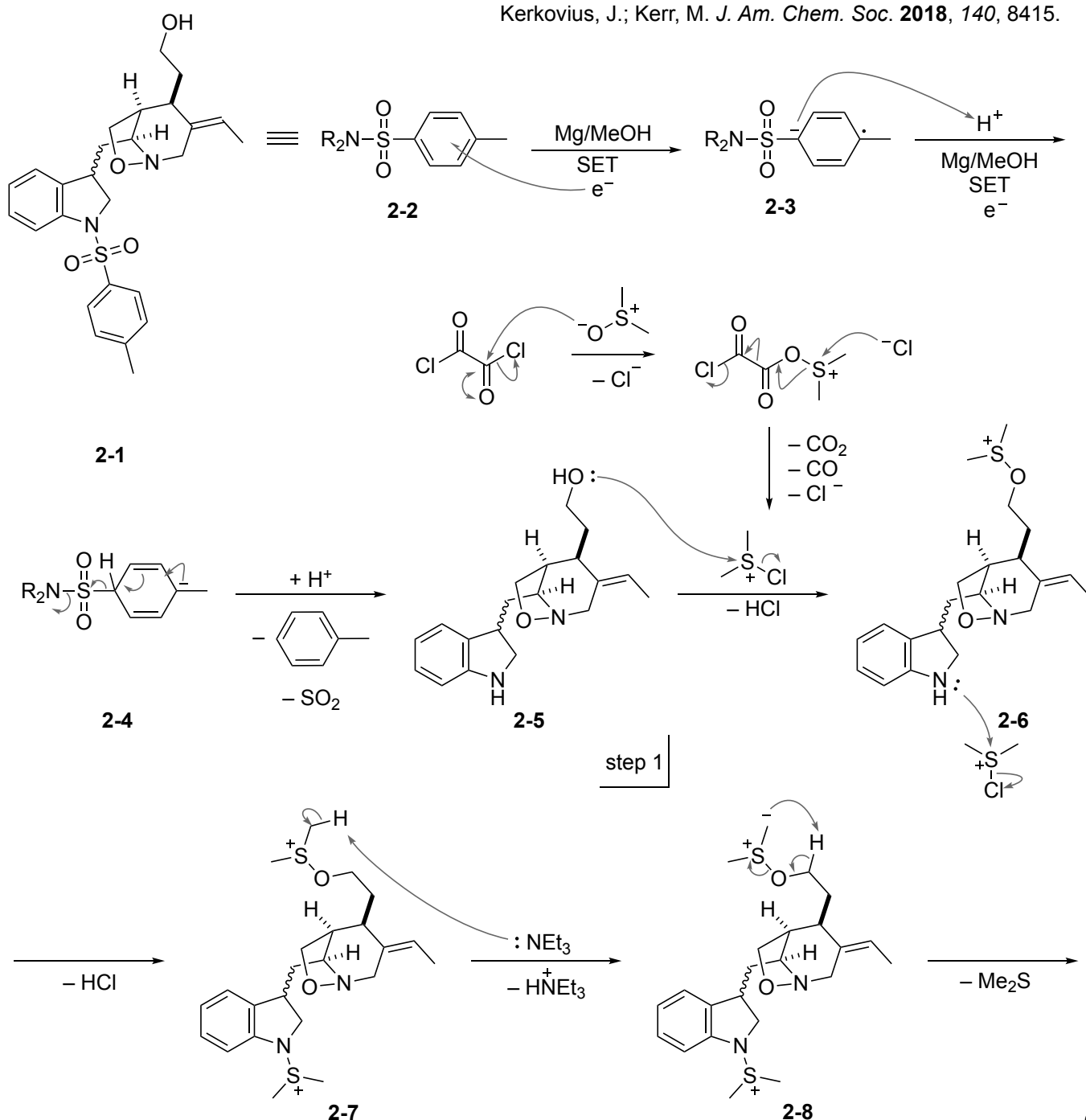


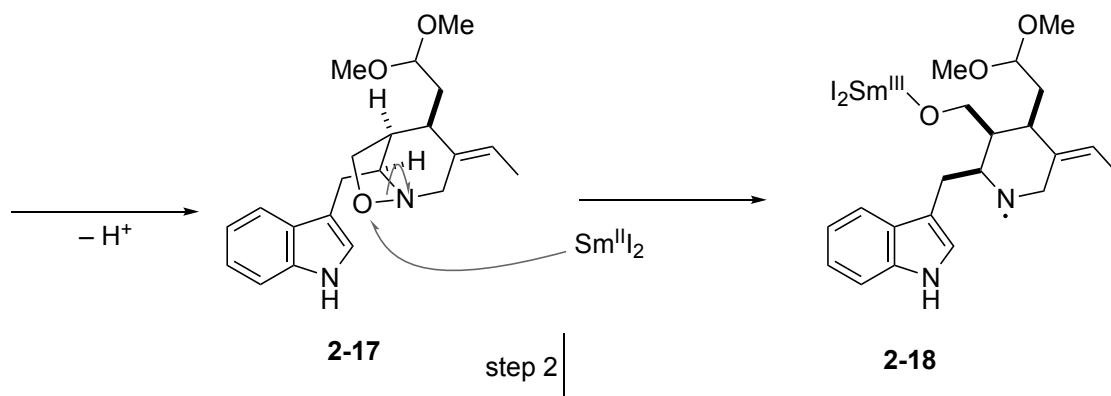
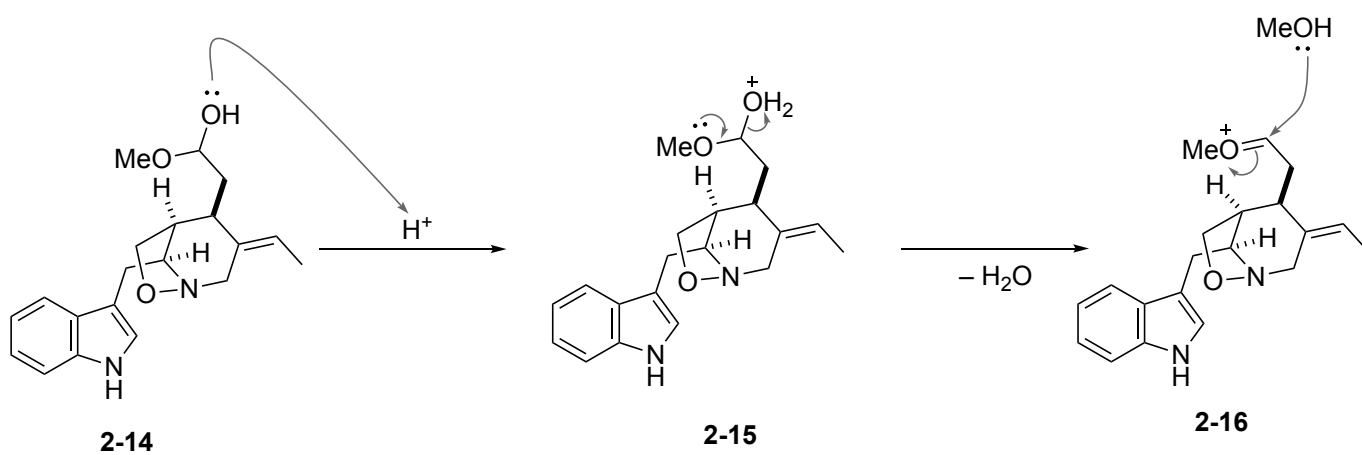
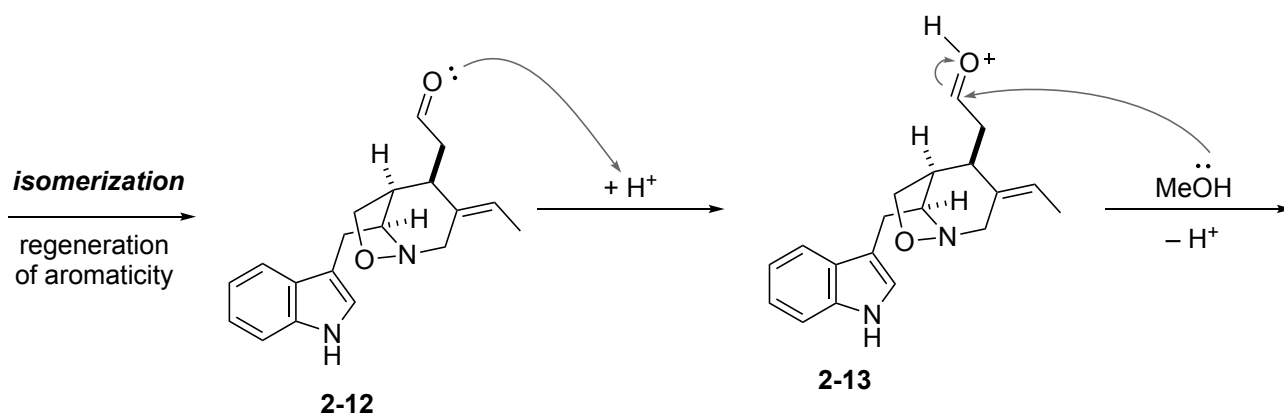
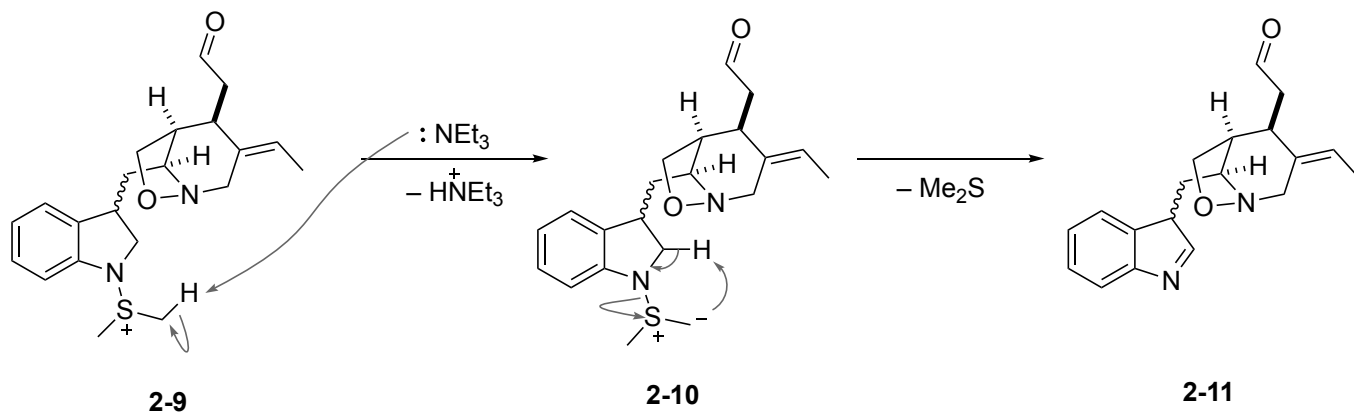
Problem 2. Total synthesis of isodihydrokoumine

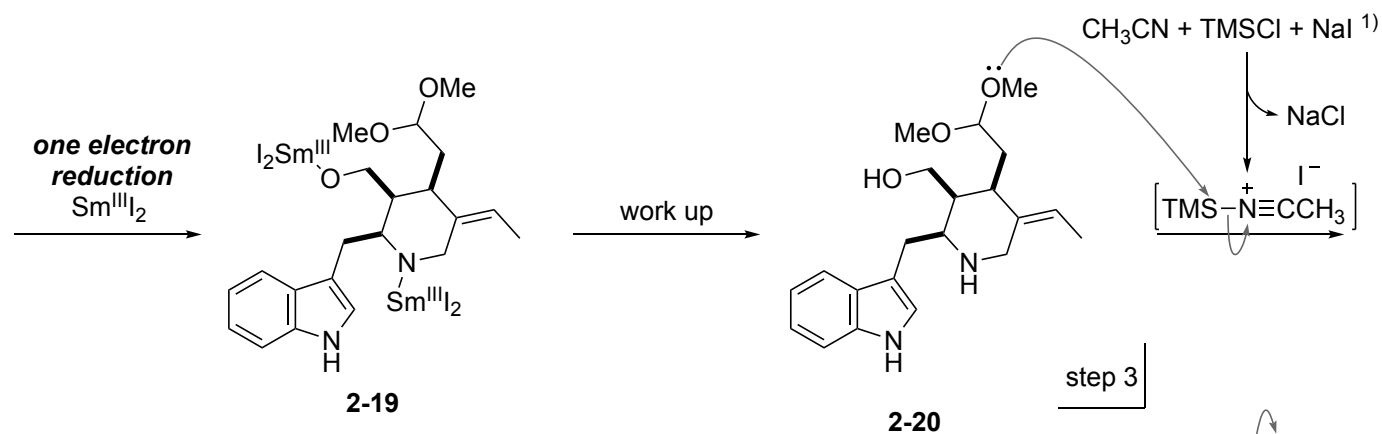
2-1. Reaction mechanism



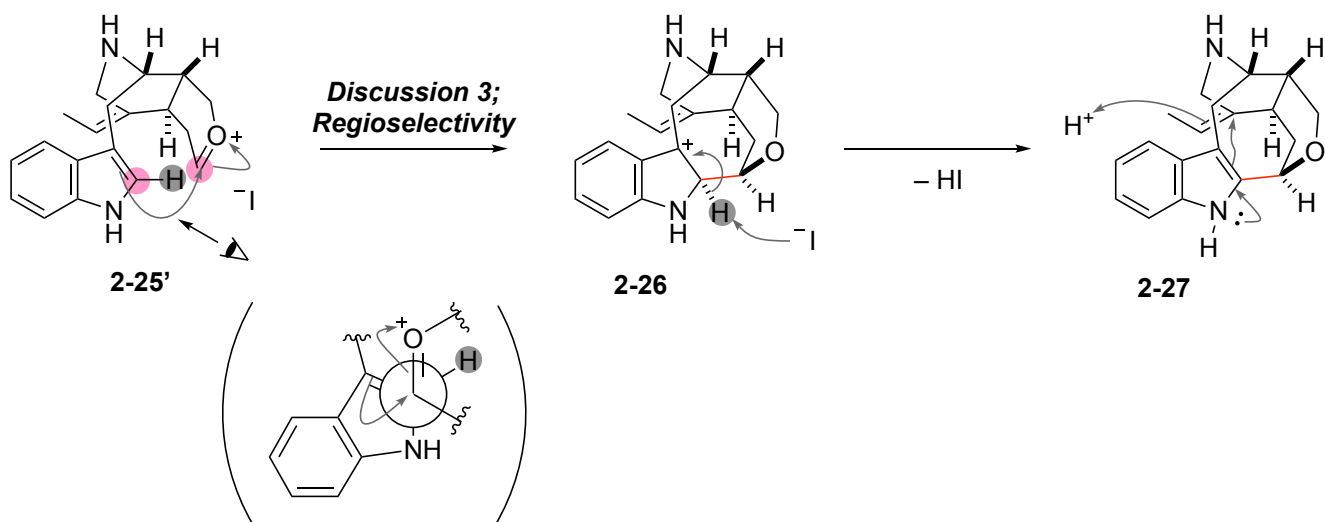
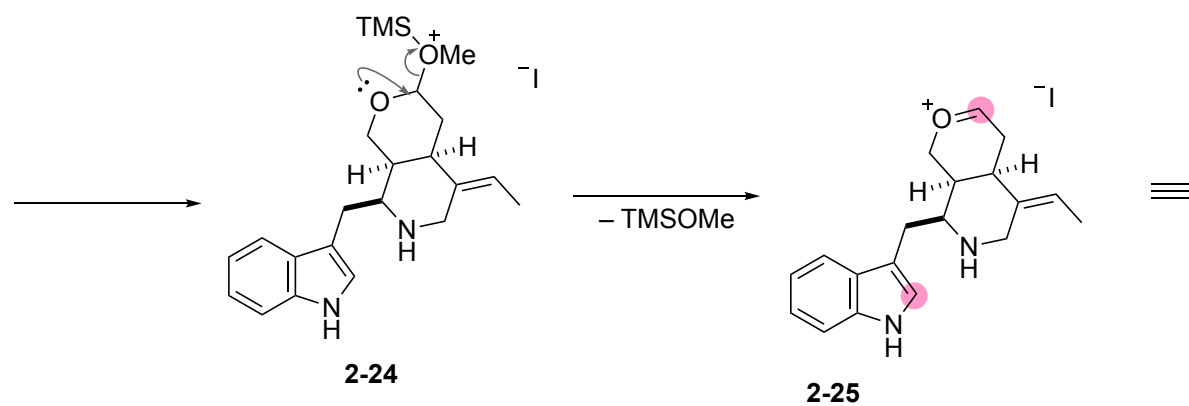
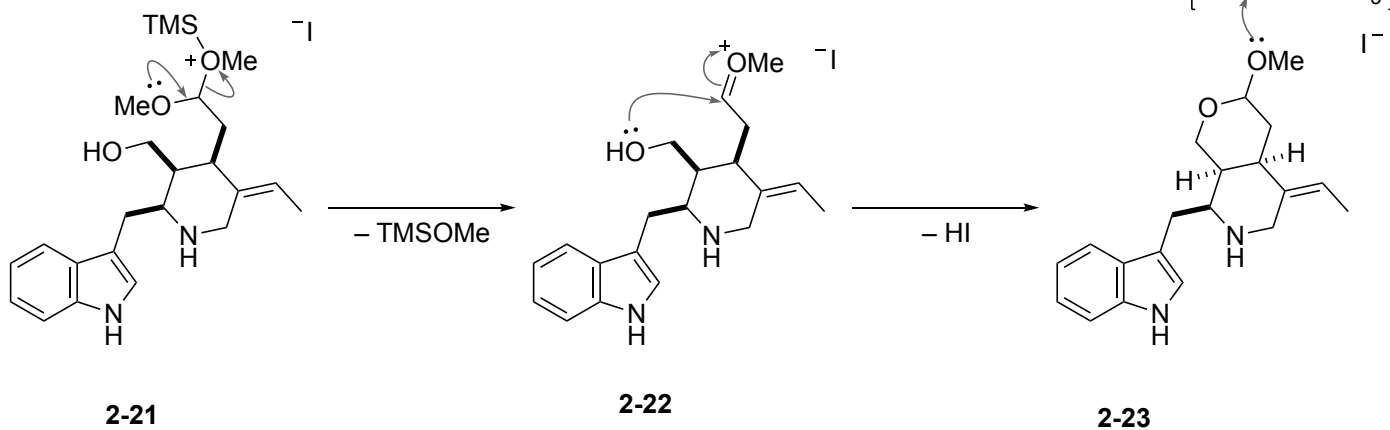
Kerkovius, J.; Kerr, M. *J. Am. Chem. Soc.* **2018**, *140*, 8415.





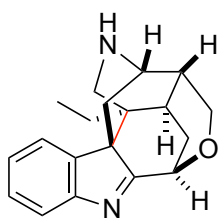


1) Provot, O. et al. *Eur. J. Org. Chem.* **2020**, 5775



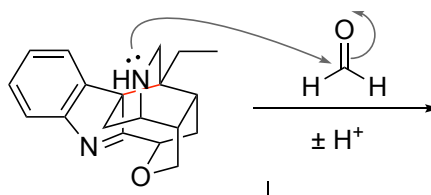
**Discussion 4;
Cyclization**

$\pm H^+$



2-28

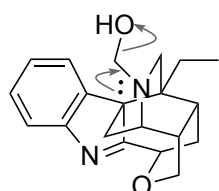
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2-28'

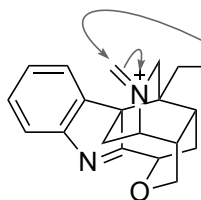
step 4

$\pm H^+$



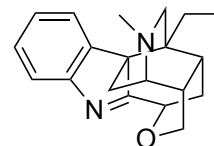
2-29

$-OH^-$



2-30

Na^+
 $H-\bar{B}H_2CN$

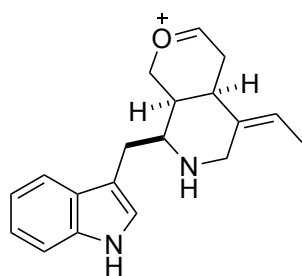


2-2

isodihydrokoumine

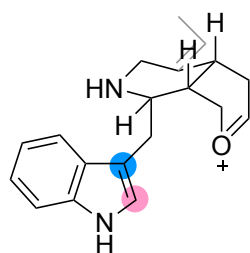
2-2. Discussion

2-2-1. Intramolecular Friedel-Crafts reaction (**Discussion 3**)



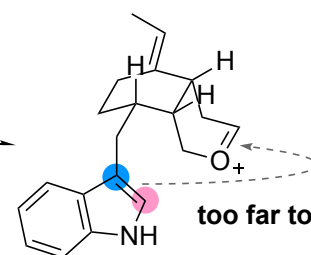
2-25

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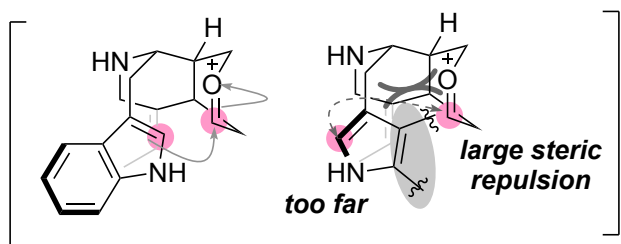


2-25'

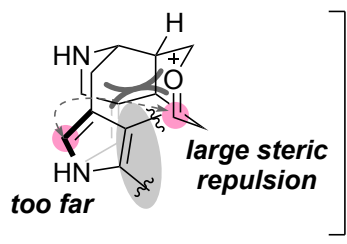
\rightleftharpoons



too far to react

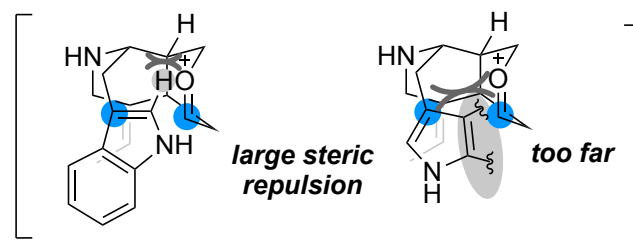


TS-2-1
favored



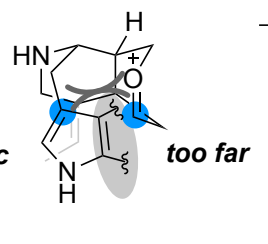
TS-2-2
disfavored

large steric repulsion

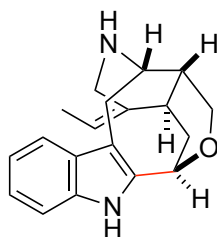
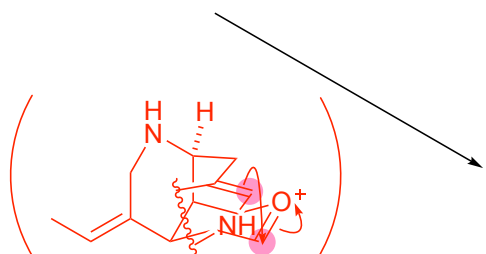


TS-2-3
unfavored

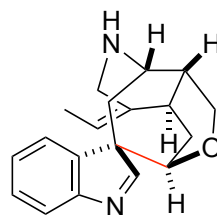
large steric repulsion



TS-2-4
disfavored



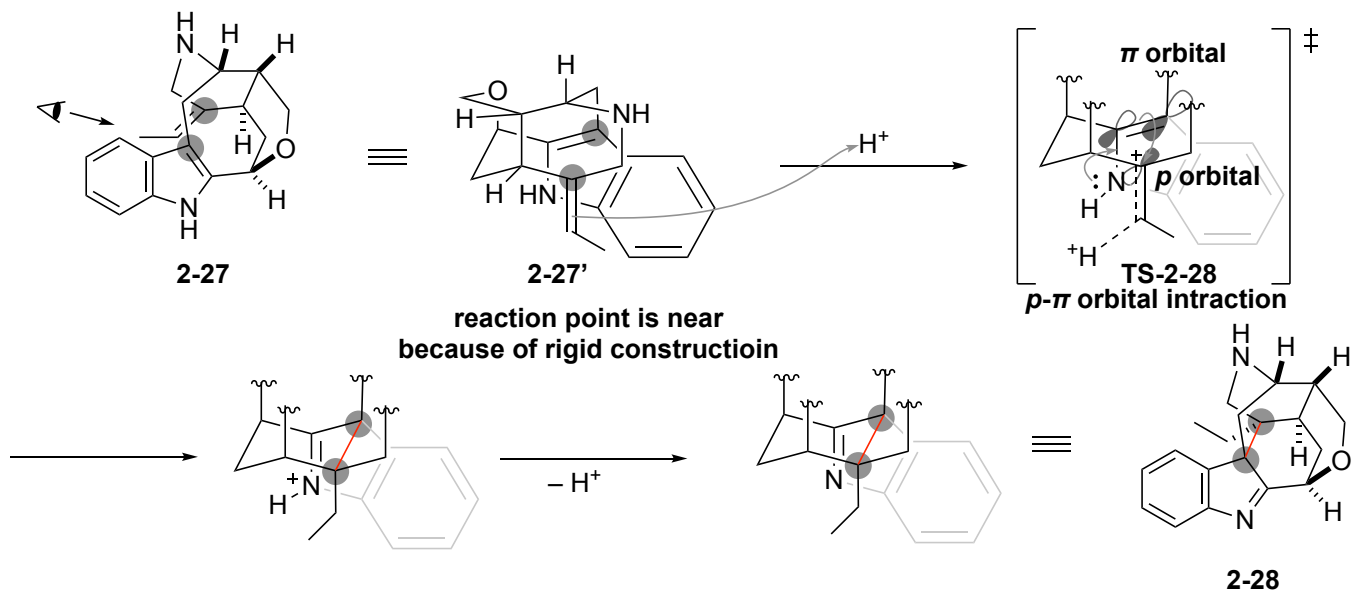
2-27
obtained



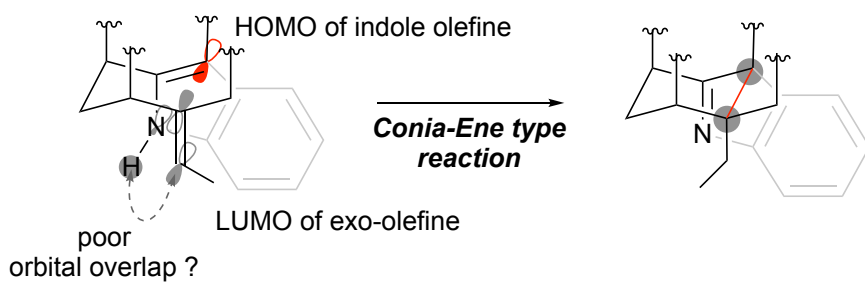
not obtained

2-2-2. Cyclization (**Discussion 4**)

path A: stepwise (my opinion)



path B: concerted (proposed mechanism by the author)



- I consider path A is more appropriate than path B.