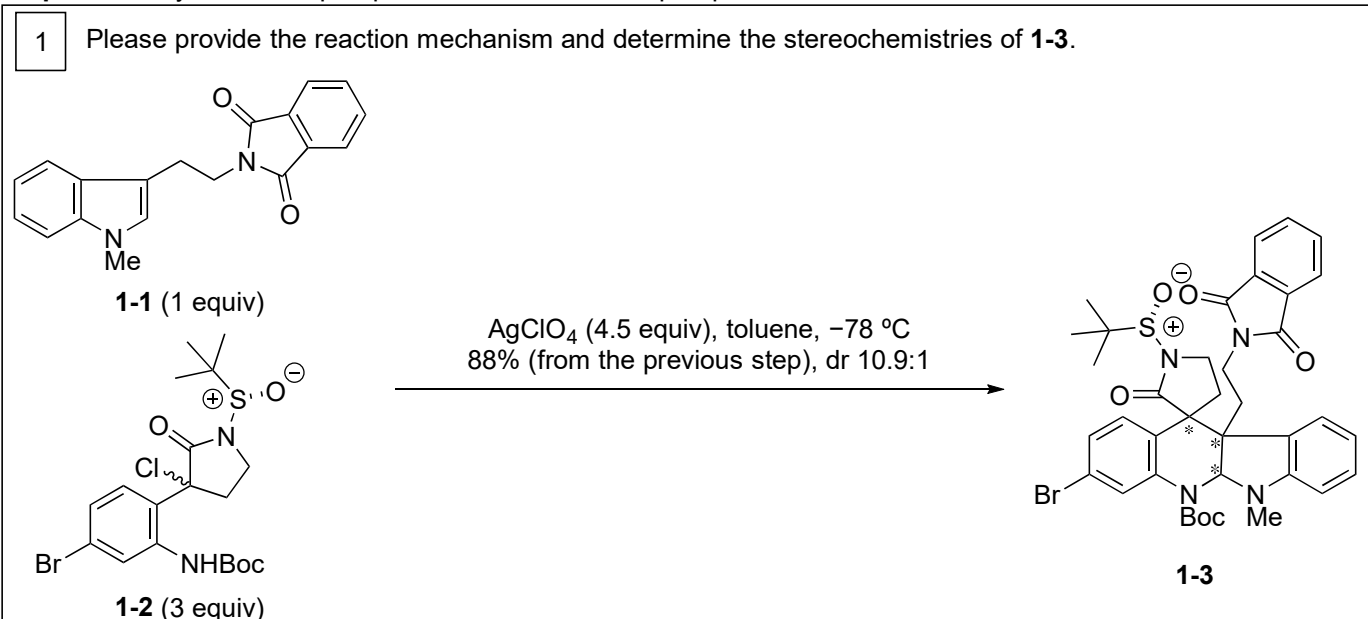


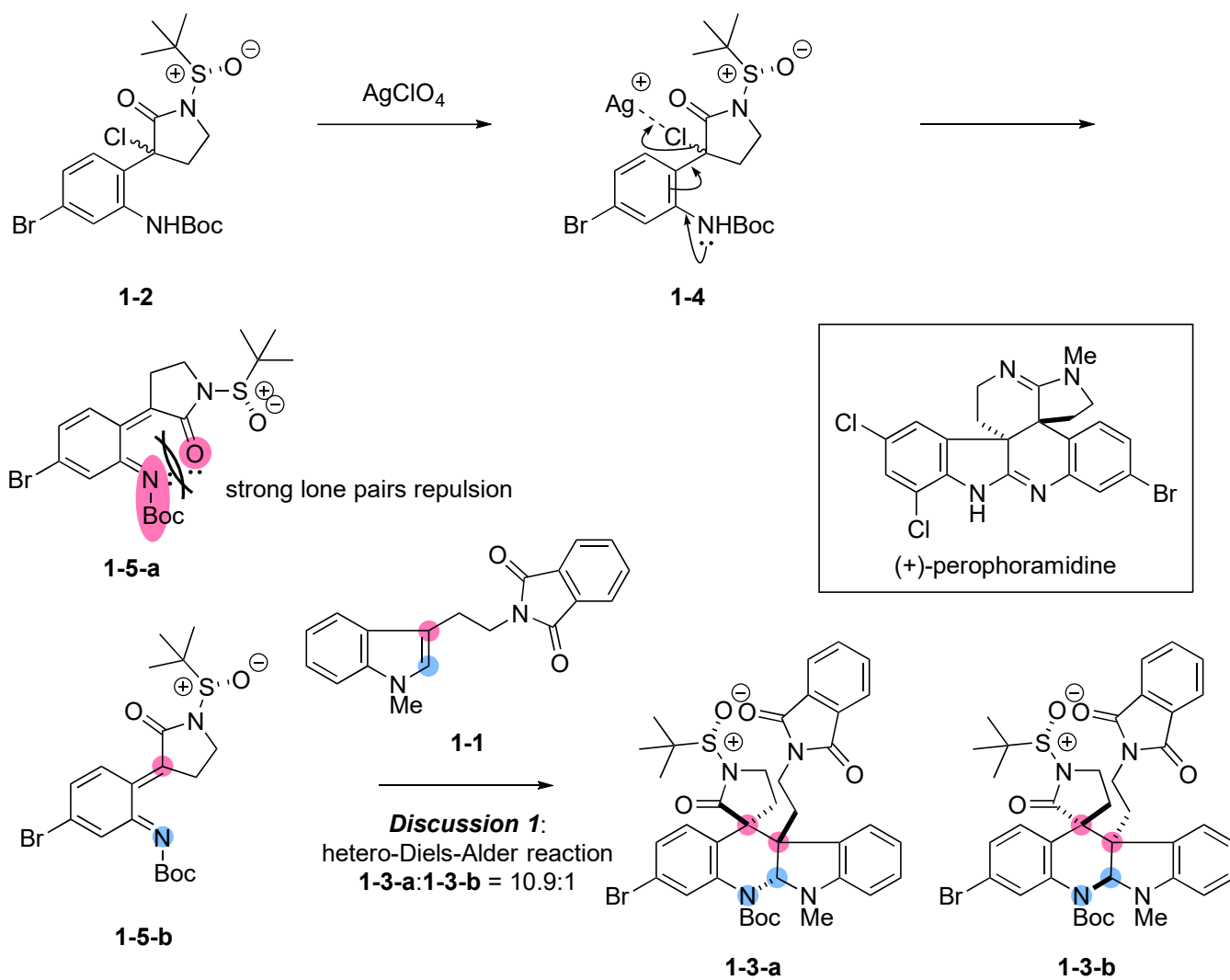
Problem Session (5) -Answer-

2024/04/27 Wataru Shigematsu

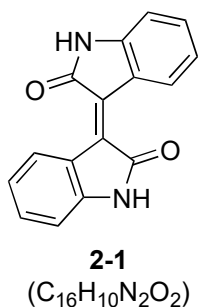
Topic: Total syntheses of perophoramidine and dehaloperophoramidine



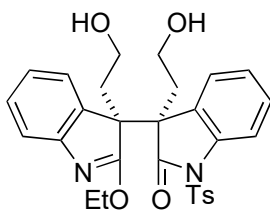
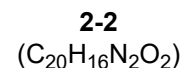
Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052.



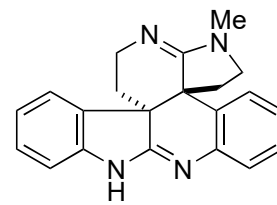
2 Please provide the reaction mechanisms.



1. SmI₂ (2.5 equiv), LiCl (11 equiv), THF, rt;
Cl-CH=CH-Cl (1.4 equiv), THF, 0 °C, 68%

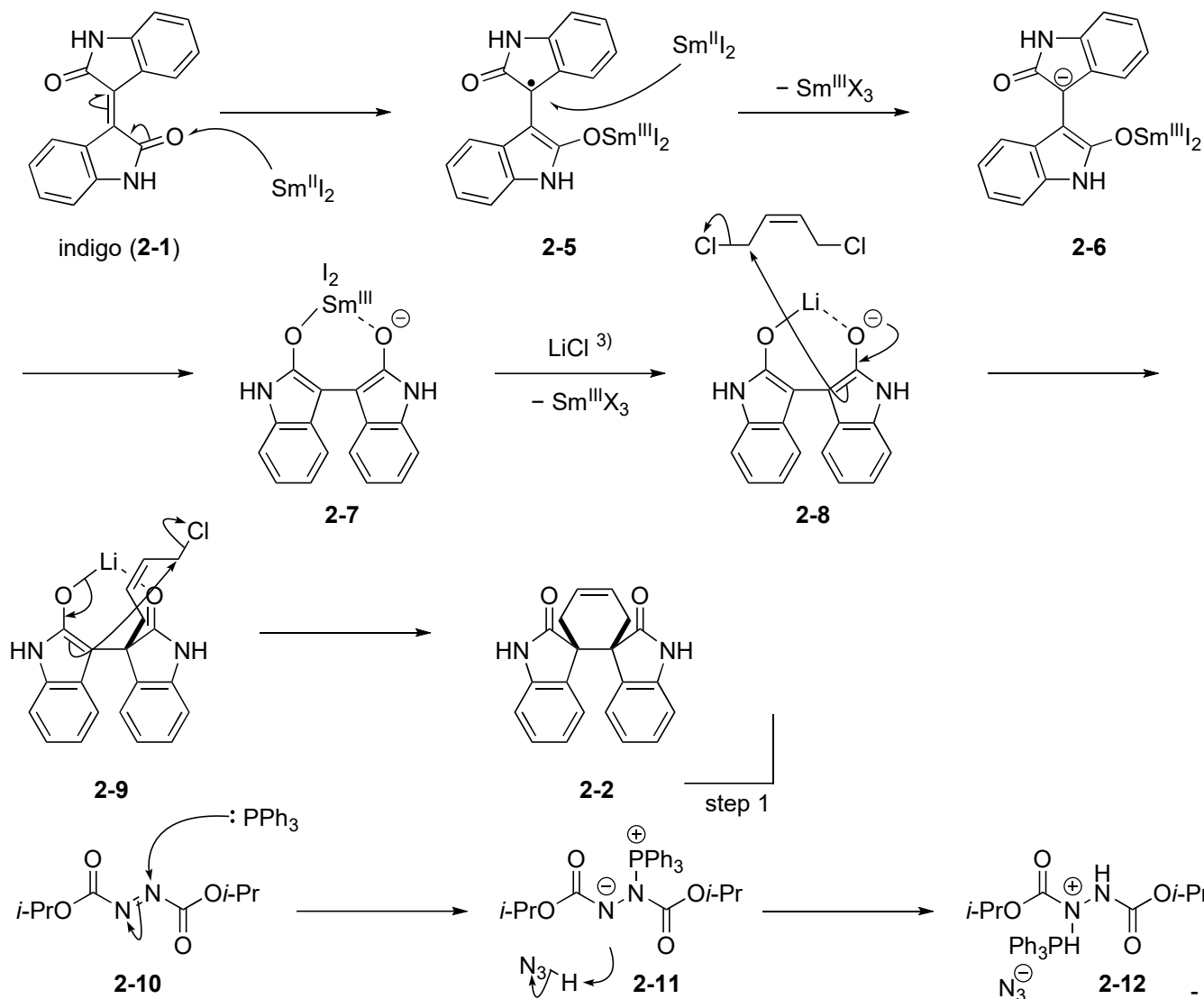


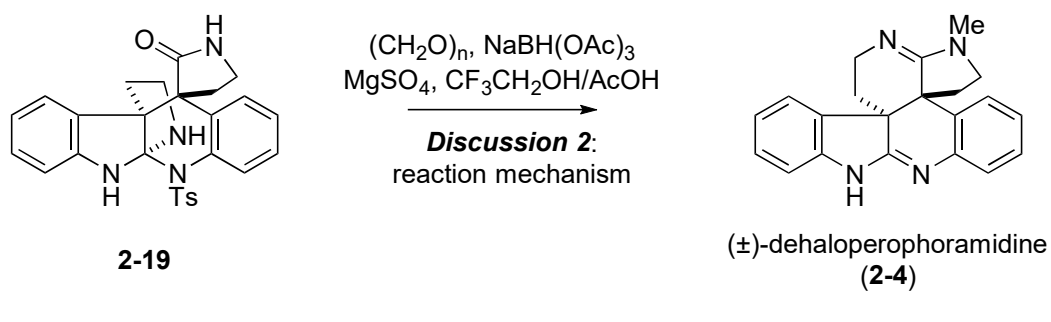
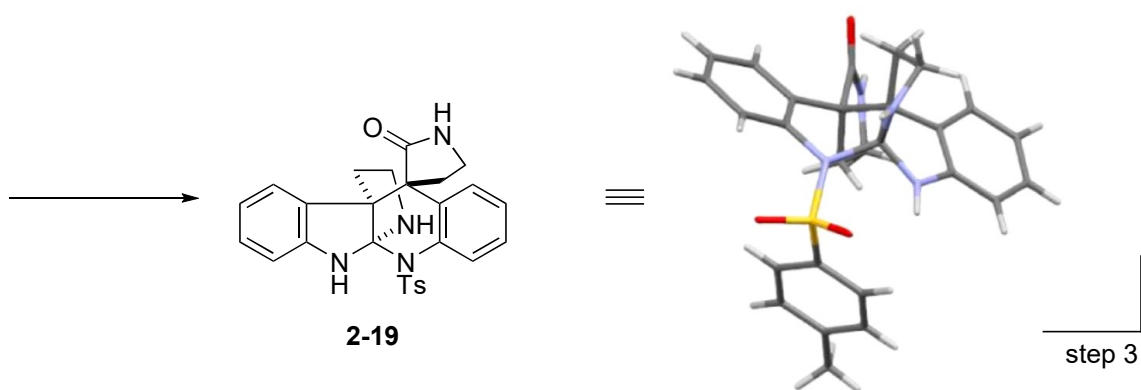
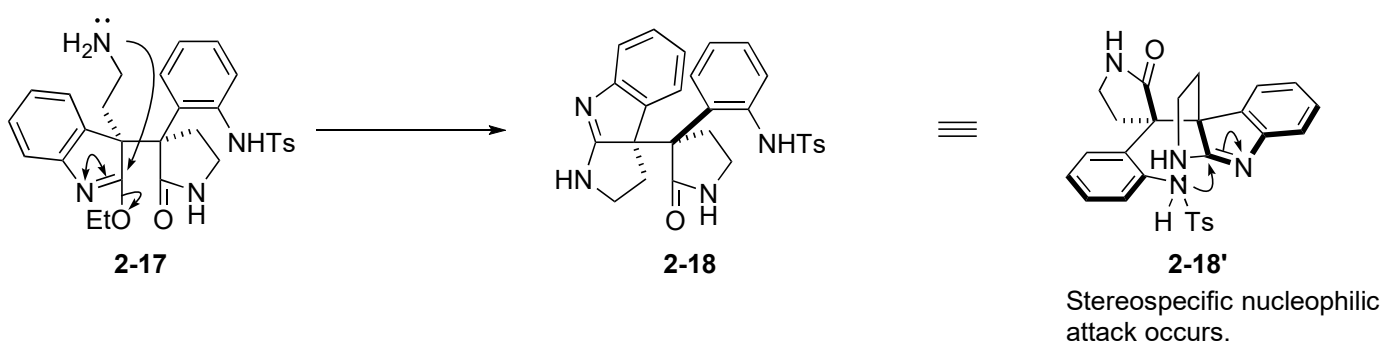
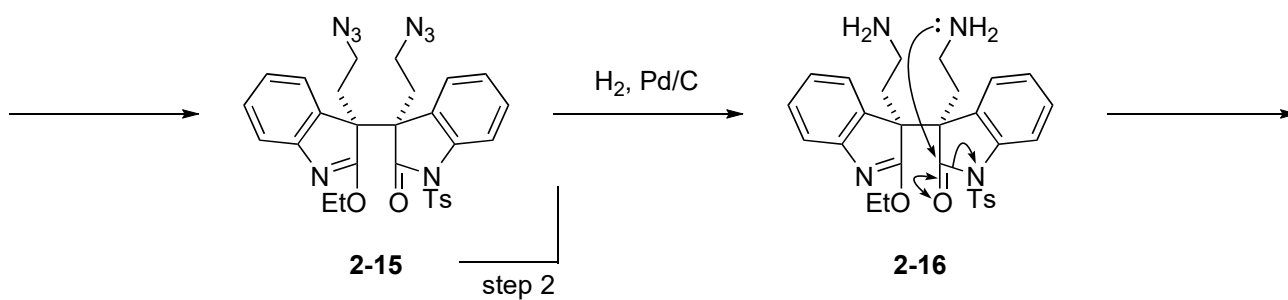
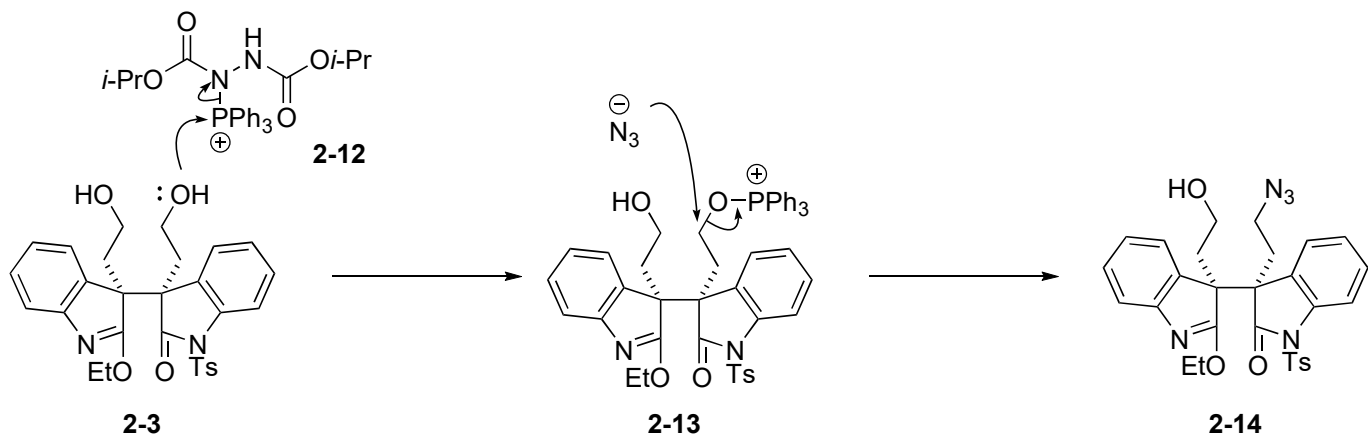
2. HN₃ (5 equiv), PPh₃ (4 equiv), DIAD (4 equiv)
THF, 0 °C, 92%
3. H₂ (1 atm), Pd/C (10 wt%), EtOAc, rt, 99%
4. (CH₂O)_n (1 equiv), NaBH(OAc)₃ (2 equiv)
MgSO₄ (50 wt%), CF₃CH₂OH/AcOH
80 °C, 52%



2-3
(4 steps from 2-2)

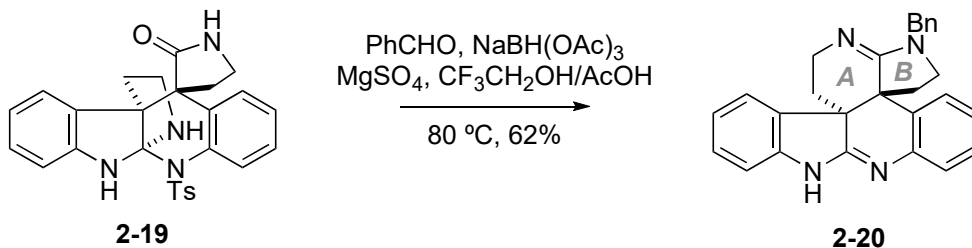
Popov, K.; Hoang, A.; Somfai, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 1801.
Hoang, A.; Popov, K.; Somfai, P. *J. Org. Chem.* **2017**, *82*, 2171.



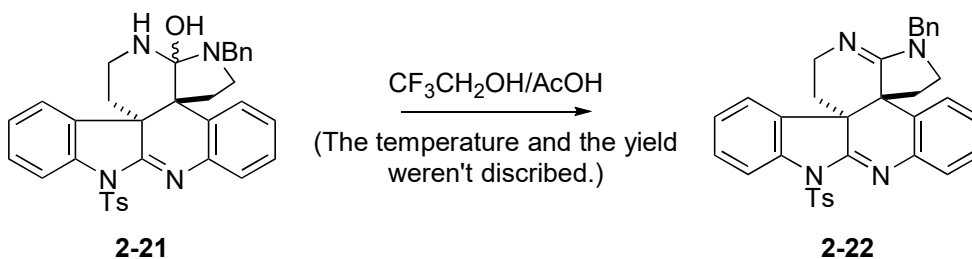
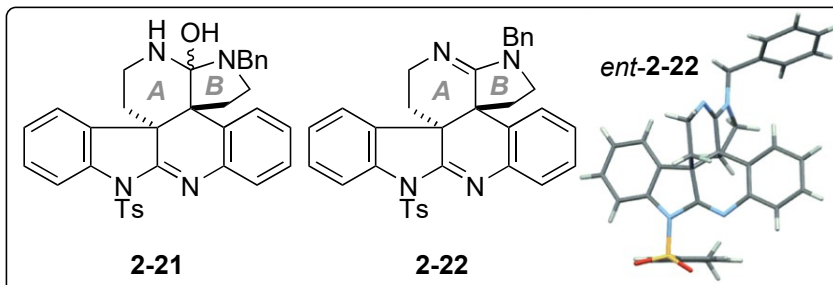


Discussion 2: Reaction mechanism

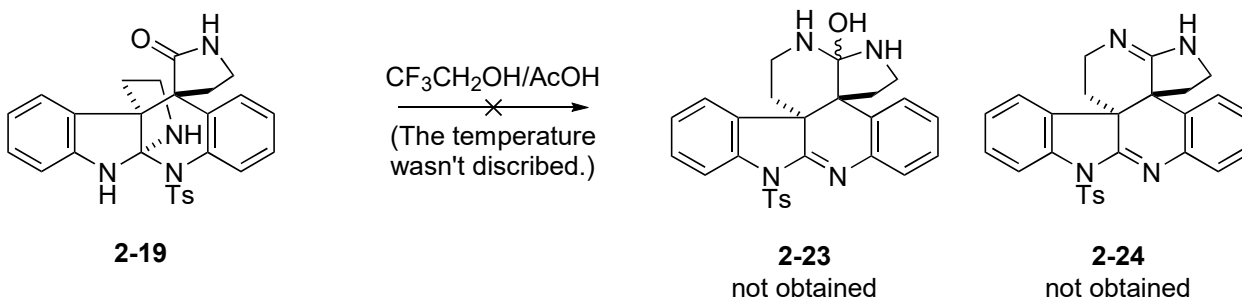
2-1. Initial trial for construction of hexacycle using PhCHO



Using benzaldehyde instead of paraformaldehyde, hexacycle **2-20** was obtained. In this reaction, Ts-shifted intermediate **2-21** and **2-22** were able to be isolated. As **2-21** was able to be converted to **2-22** in acidic conditions, the reductive amination seemed to take place before the formation of amidine in AB-ring.

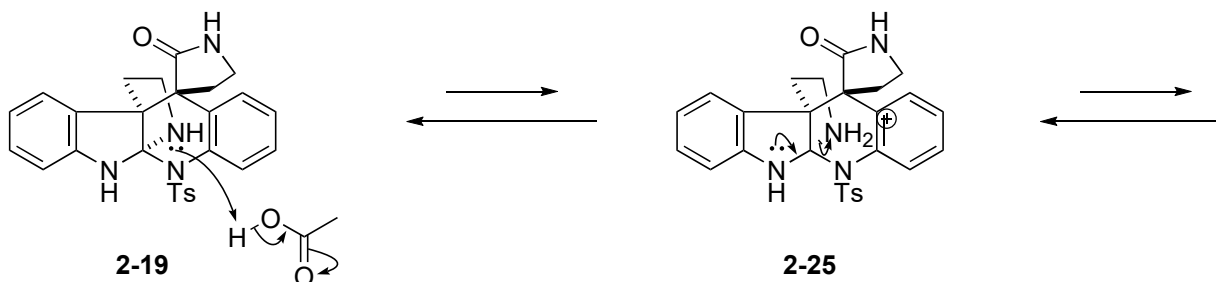


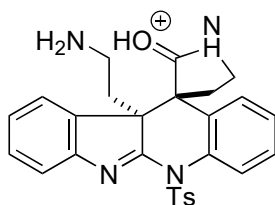
2-19 was completely recovered when it was subjected to the acidic conditions. This result also suggested the sequence of the reaction (amidine formation -> reductive amination).



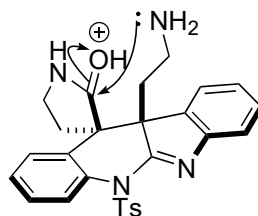
From these experimental results, I think that the reaction mechanism of reductive amination and hexacyclic ring formation can be described as the below.

-my proposal of the reaction mechanism of step 4-

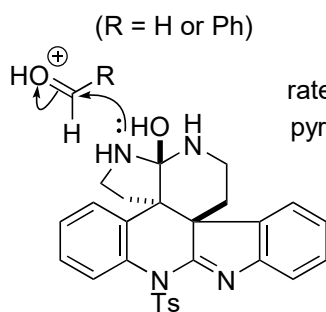
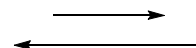




2-26

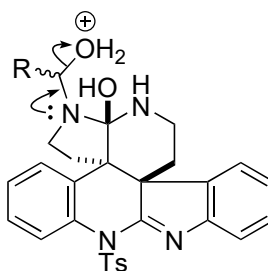
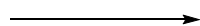


2-27

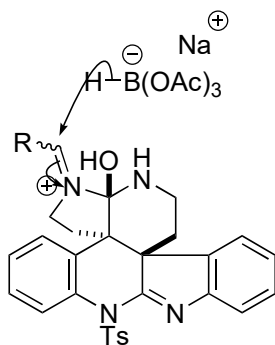


2-28

rate of iminium formation:
pyrrolidine > piperidine ⁴⁾



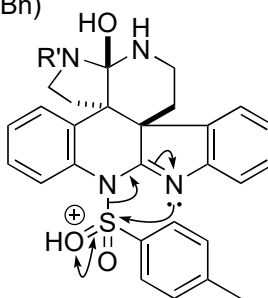
2-29



2-30



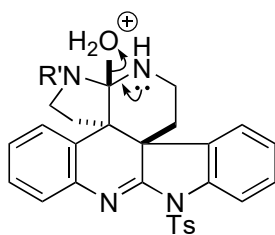
(R' = Me or Bn)



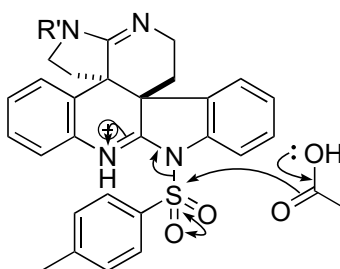
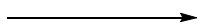
2-31 (R' = Me)

2-21 (R' = Bn)

1,3-sulfur shift ⁵⁾



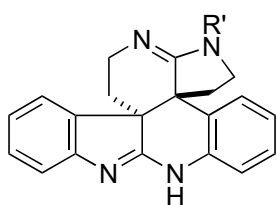
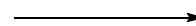
2-32



2-33 (R' = Me)

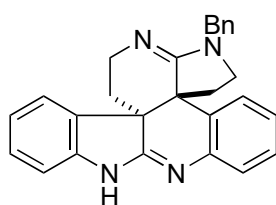
2-22 (R' = Bn)

hydrolysis ⁶⁾



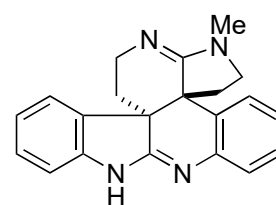
2-34

isomerization



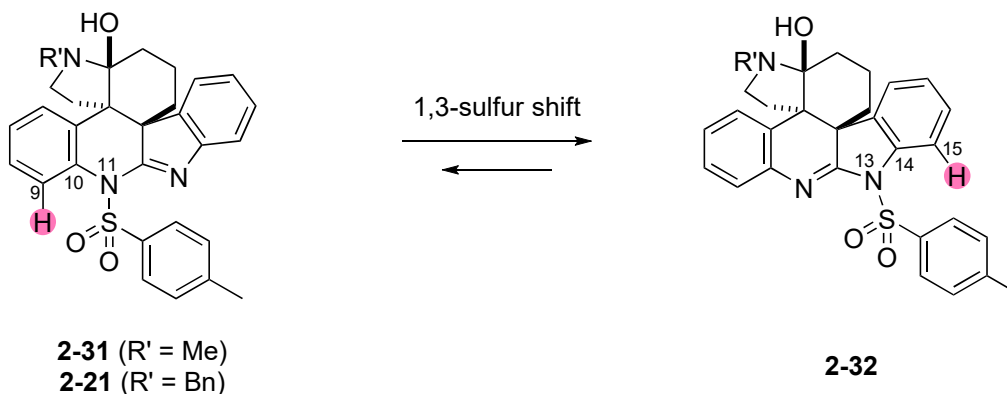
2-35

or



(±)-dehaloperophoramidine
(2-4)

The rearrangement of tosyl group should reflect the thermodynamic preference between the two isomers.



bond angle (C9-C10-N11): 120°
(C10-N11-S): 120°

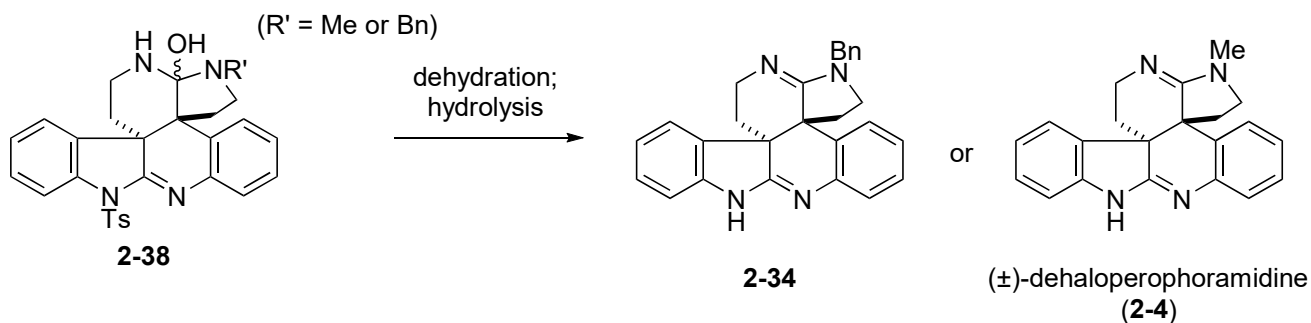
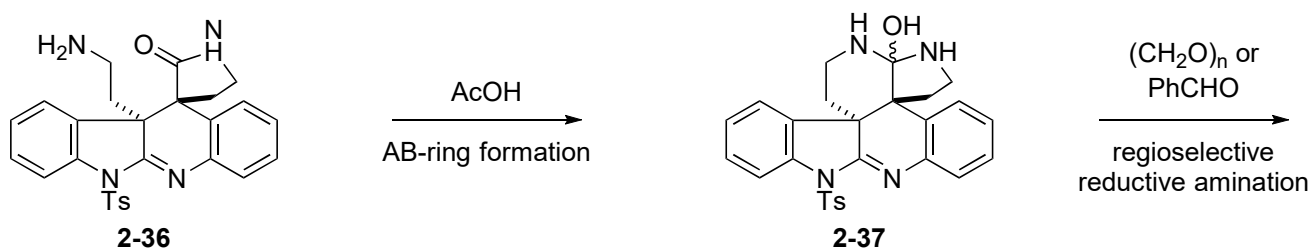
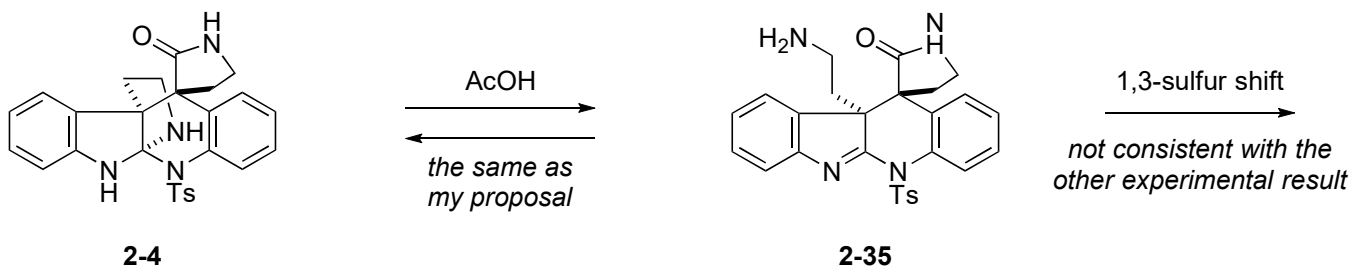
bond angle (C15-C14-N13): 130°
(C14-N13-S): 125°

The nearest proton to tosyl group is highlighted. As the highlighted proton can be away from tosyl group, **2-32** is thermodynamically favorable.

The authors proposed the mechanism as below.

First, as my proposal, elimination of the aliphatic moiety proceeds. Then, the rearrangement of tosyl group occurs. Finally, the target compound is formed by AB-ring formation, reductive amination, and hydrolysis.

-the authors' proposal of the reaction mechanism of step 4-



1,3-Sulfur shift must occur in acidic conditions. This proposal is not consistent with the experimental result that **2-4** recovered completely in acidic conditions.

References

- 1) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052.
- 2) a) Popov, K.; Hoang, A.; Somfai, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 1801.
b) Hoang, A.; Popov, K.; Somfai, P. *J. Org. Chem.* **2017**, *82*, 2171.
- 3) Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166.
- 4) Brown, H. C. *J. Am. Chem. Soc.* **1956**, 1248.
- 5) Lin, P.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1102.
- 6) Javorskis, T.; Orentas, E. *J. Org. Chem.* **2017**, *82*, 13423.