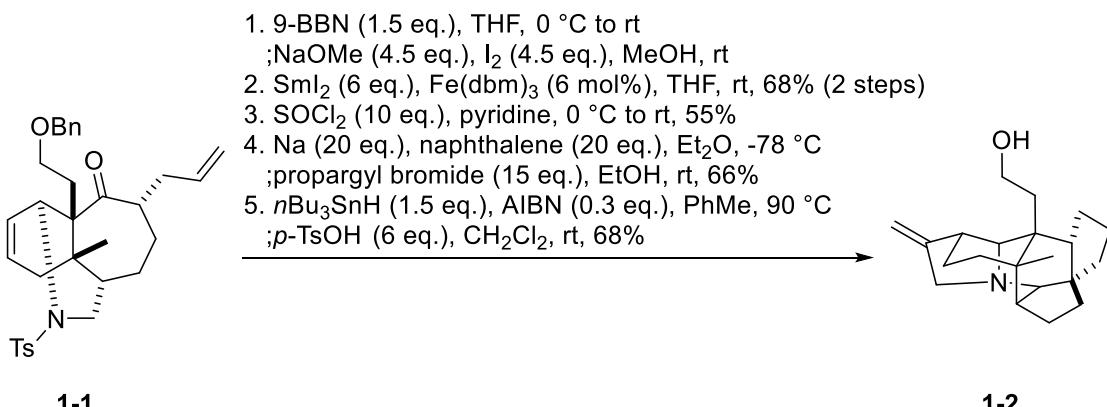


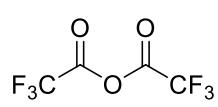
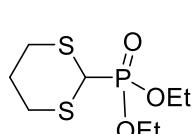
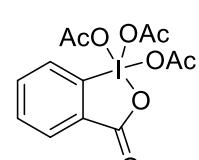
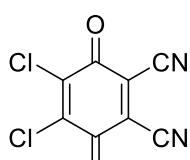
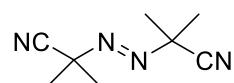
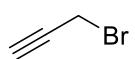
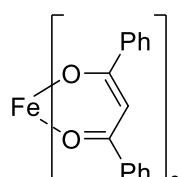
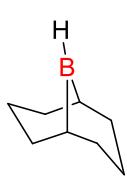
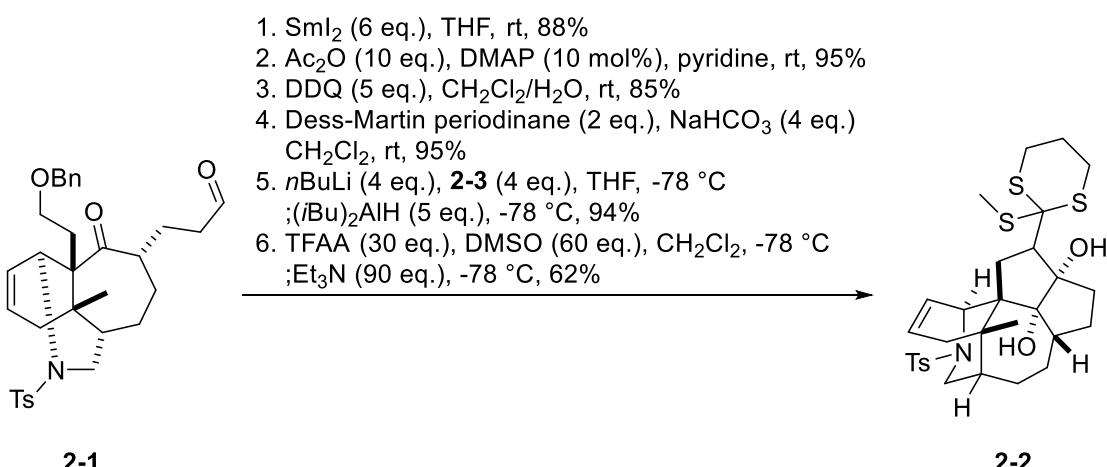
Problem Session (2)

2020.09.05. Itsuki Watanabe

(1) Please explain the reasonable reaction mechanisms.



(2) Please explain the reasonable reaction mechanisms.



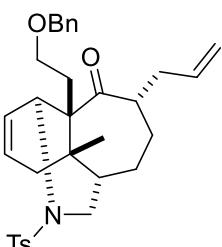
Problem Session (2) - Answer

2020.09.05 Itsuki Watanabe

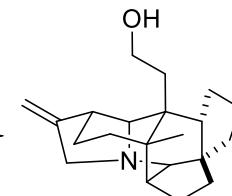
Topic: Total synthesis of Caldaphnidine

(1) Please explain the reasonable reaction mechanisms.

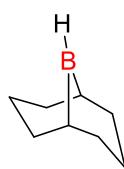
1. 9-BBN (1.5 eq.), THF, 0 °C to rt
;NaOMe (4.5 eq.), I₂ (4.5 eq.), MeOH, rt
2. SmI₂ (6 eq.), Fe(dbm)₃ (6 mol%), THF, rt, 68% (2 steps)
3. SOCl₂ (10 eq.), pyridine, 0 °C to rt, 55%
4. Na (20 eq.), naphthalene (20 eq.), Et₂O, -78 °C
;propargyl bromide (15 eq.), EtOH, rt, 66%
5. nBu₃SnH (1.5 eq.), AIBN (0.3 eq.), PhMe, 90 °C
;*p*-TsOH (6 eq.), CH₂Cl₂, rt, 68%



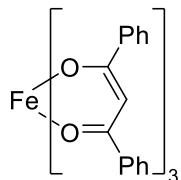
1-1



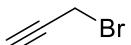
1-2



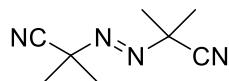
9-BBN



Fe(dbm)₃



propargyl bromide



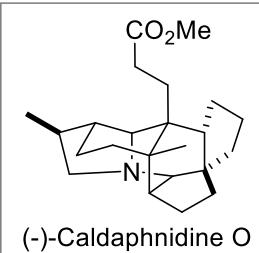
AIBN

Guo, L.; Hu, J.; Zhang, Y.; Tu, W.; Zhang, Y.; Pu, F.; Xu, J. *J. Am. Chem. Soc.* **2019**, 141, 13043.

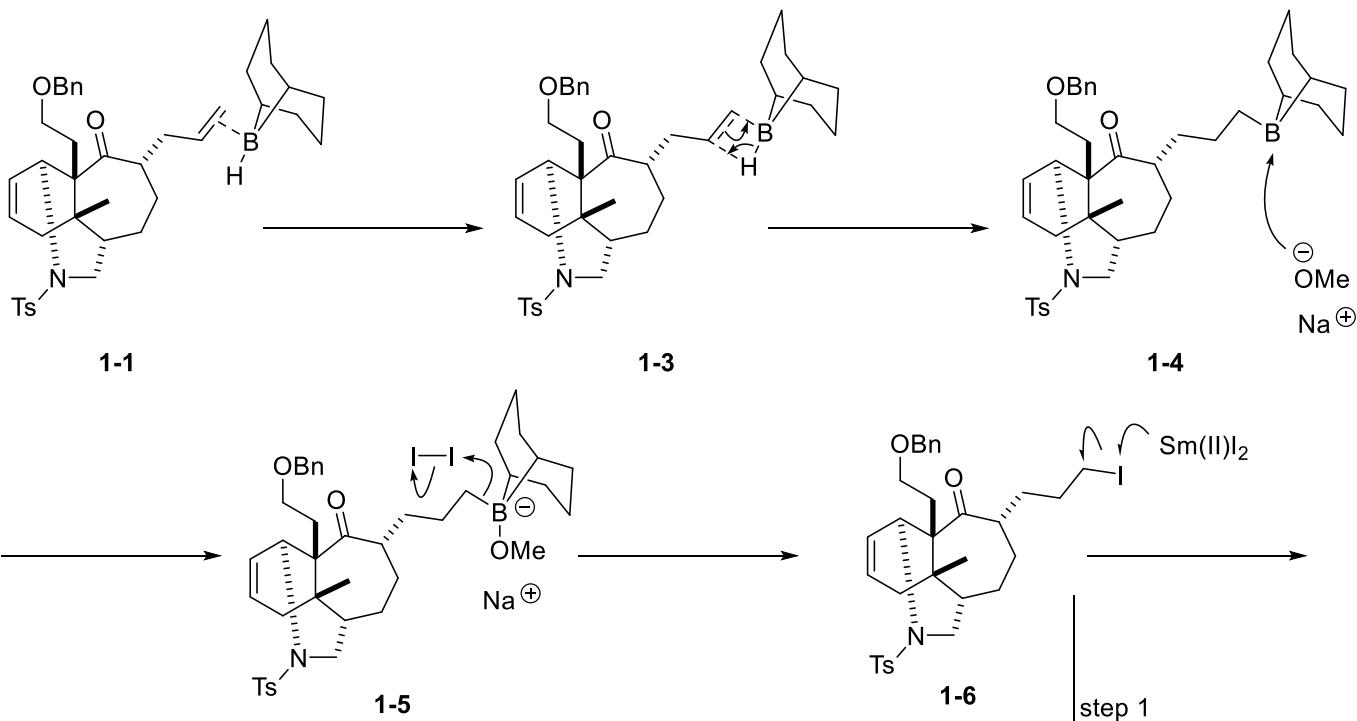
- **Total synthesis of (-)-Caldaphnidine O**

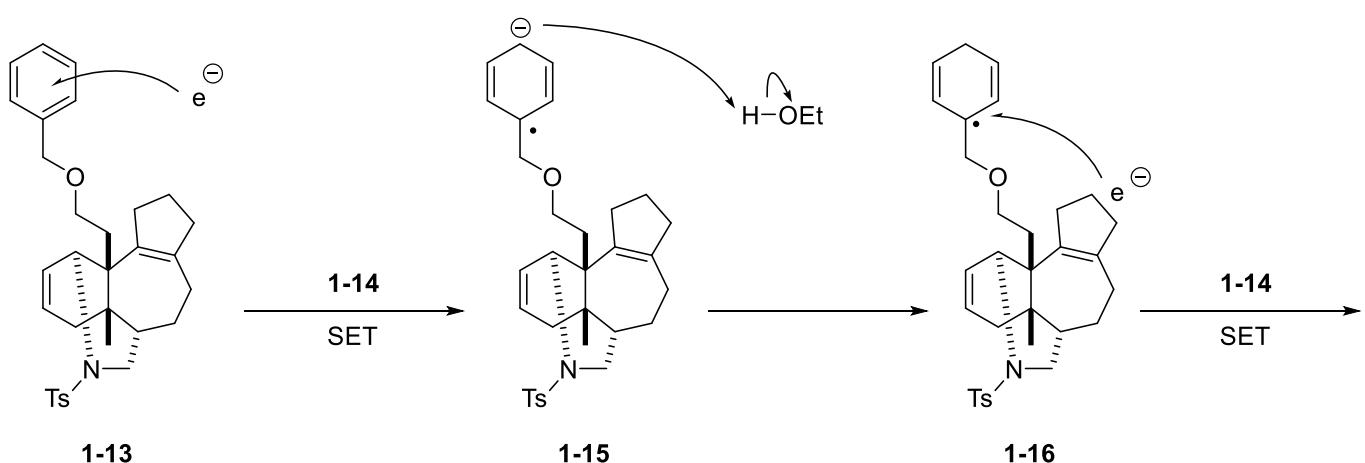
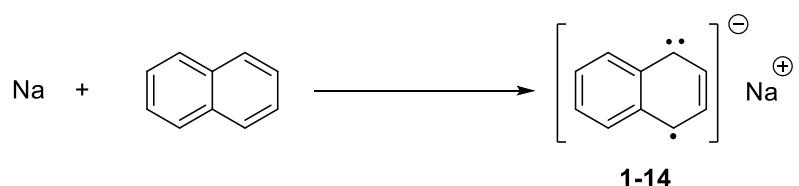
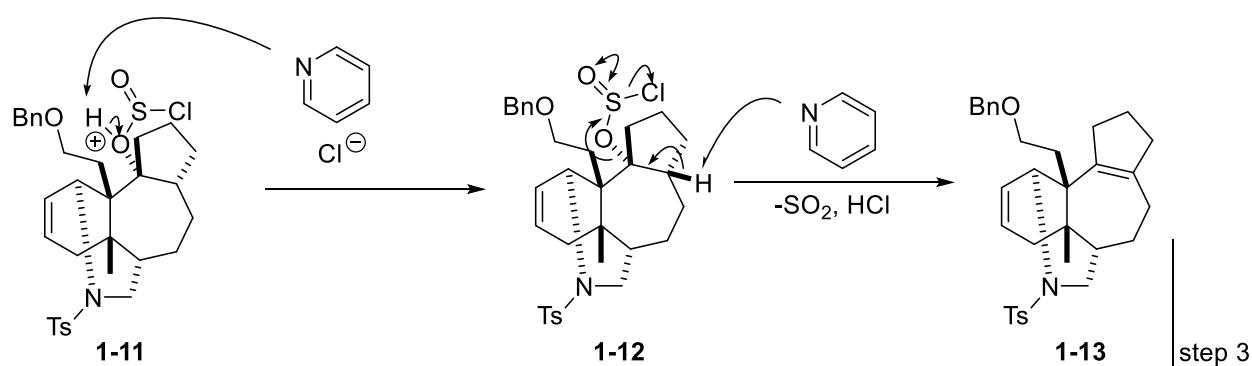
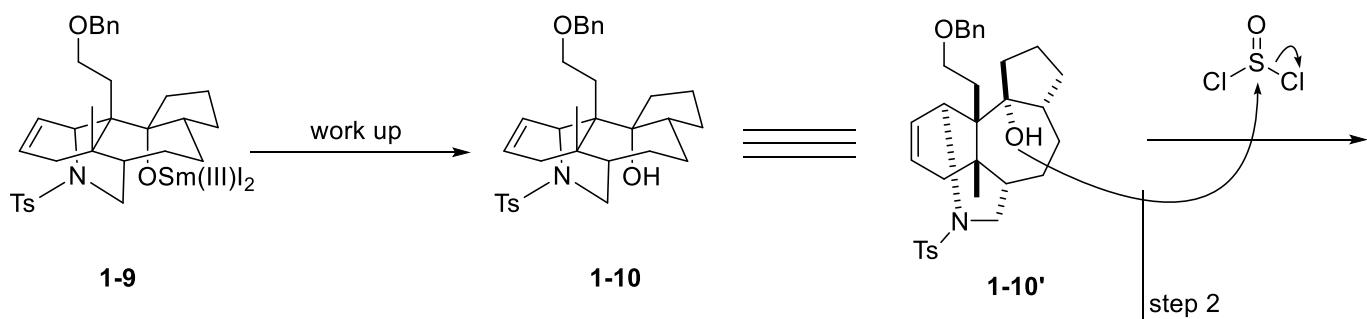
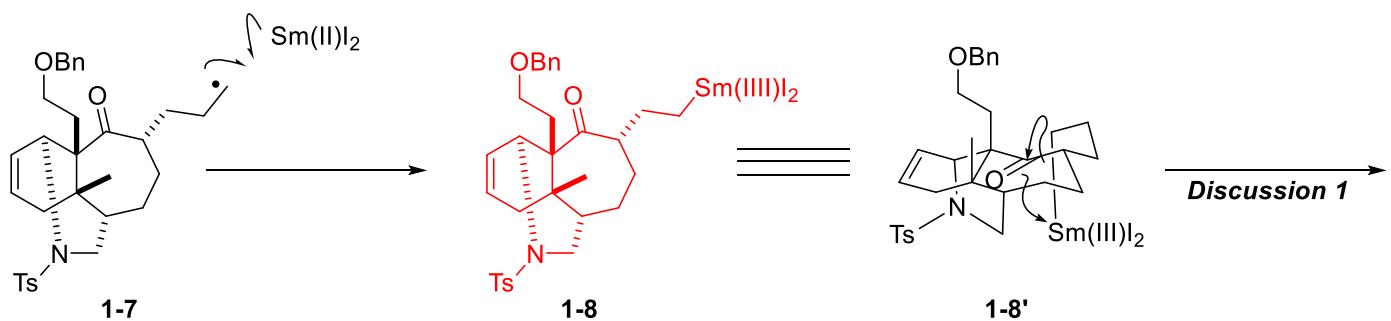
This paper is the first and enantioselective synthesis.

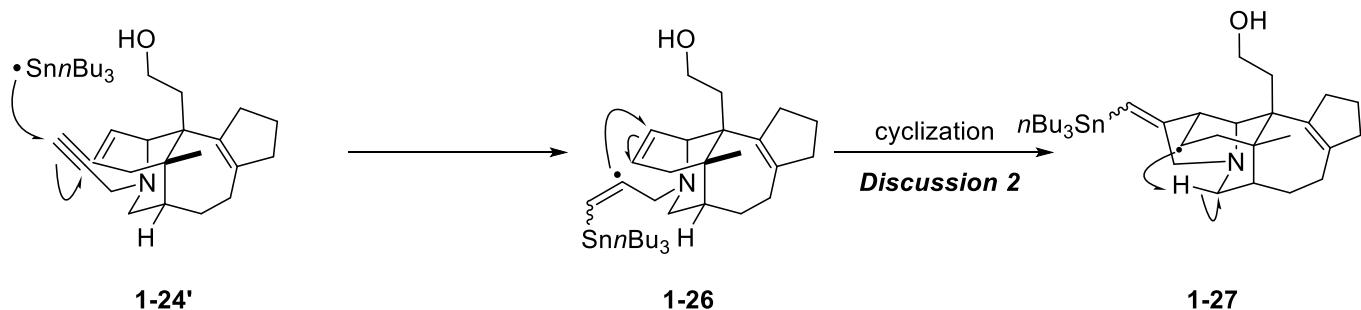
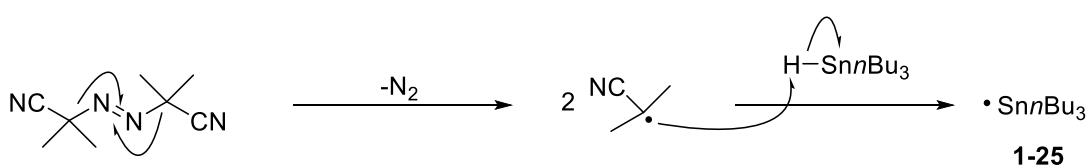
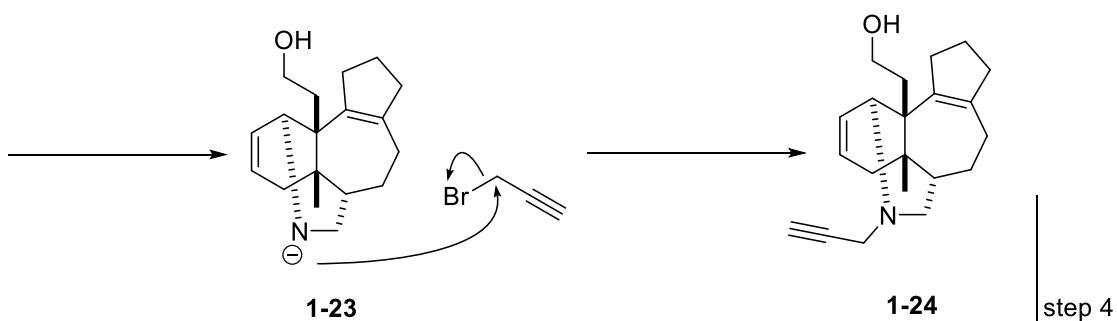
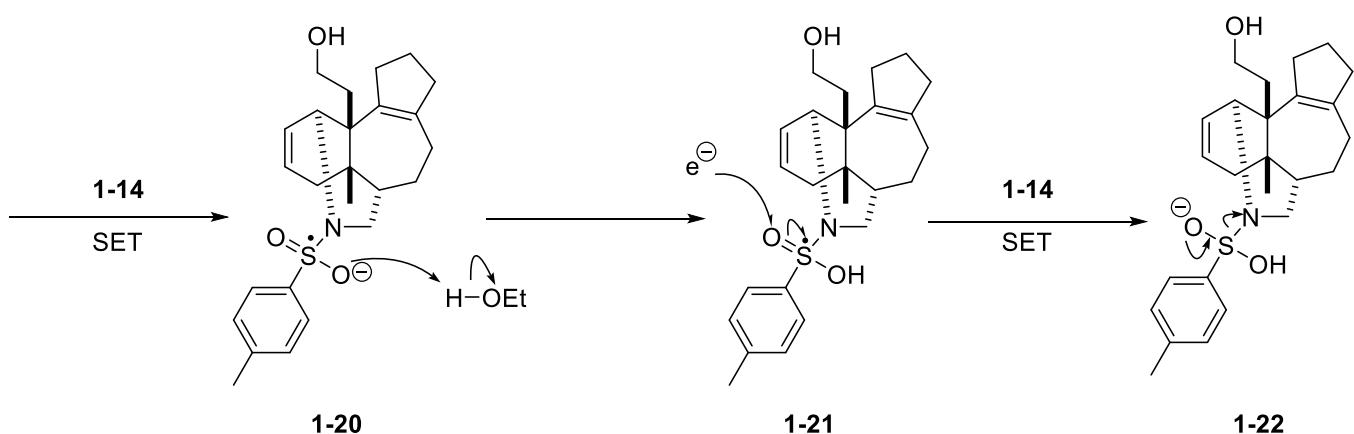
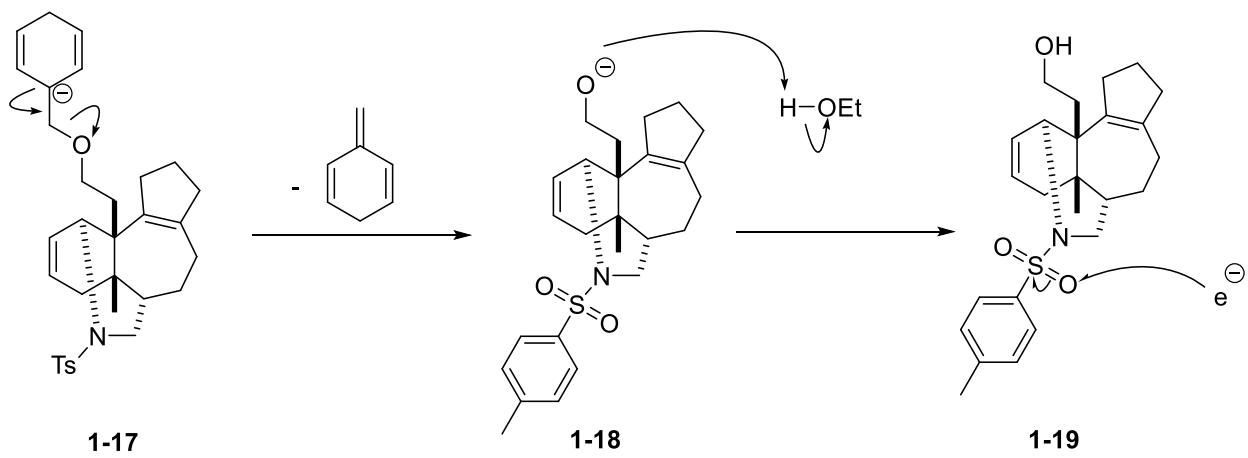
- **Key reaction: radical cyclization cascade (step 5)**

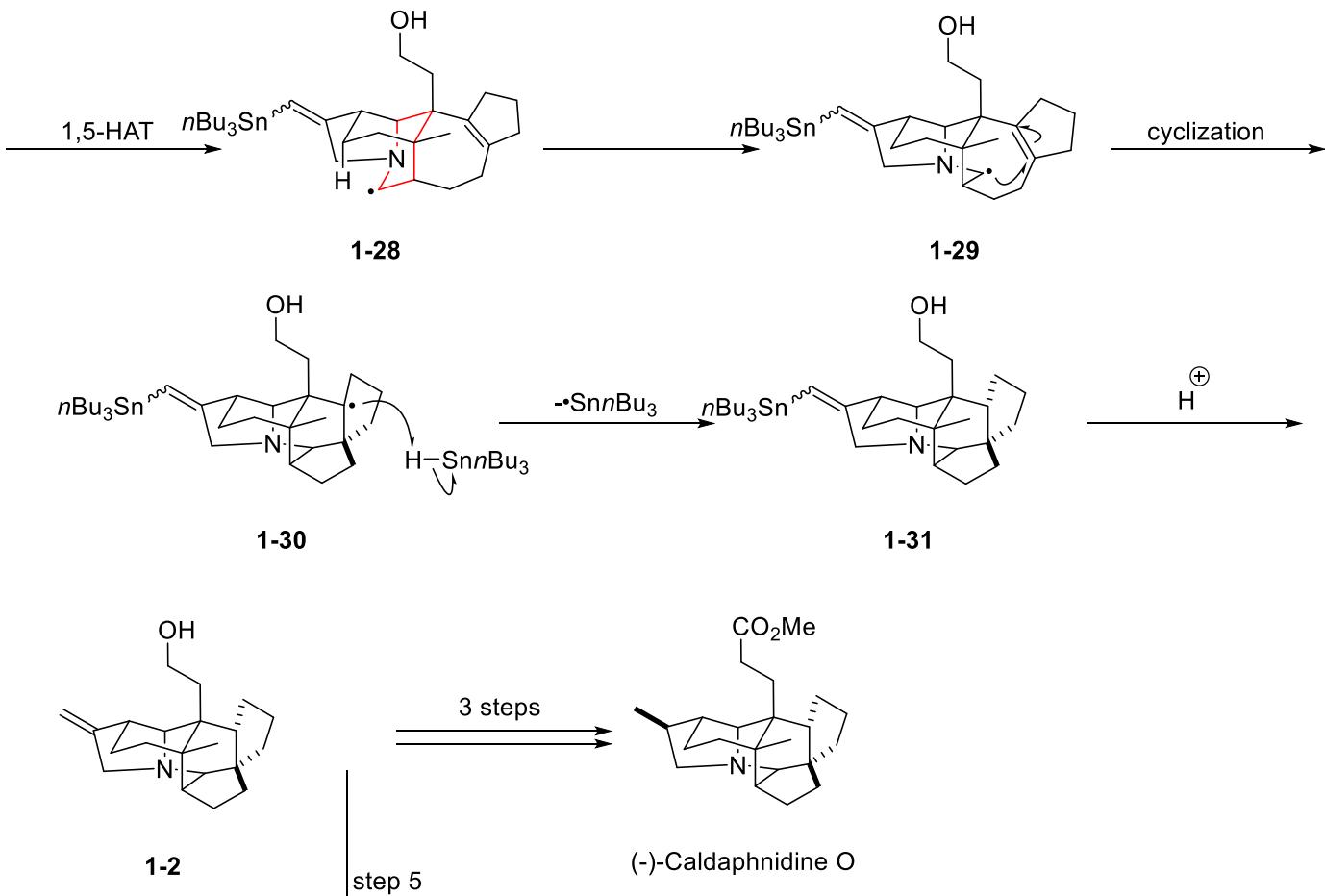


Answer:



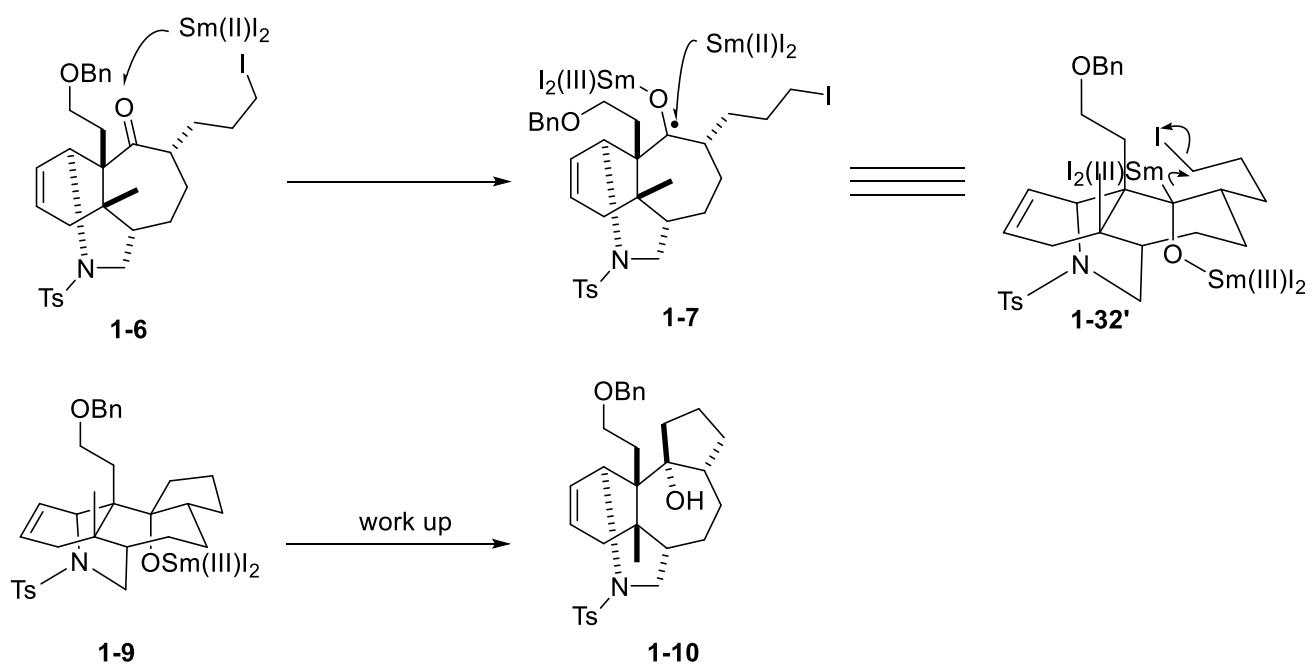


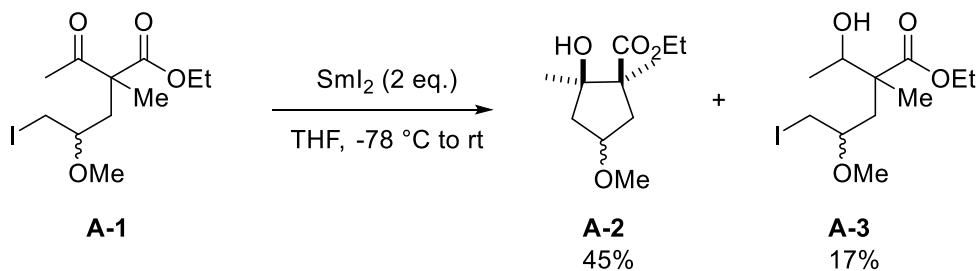




Discussion 1: Kagan-Molander coupling (step 2)

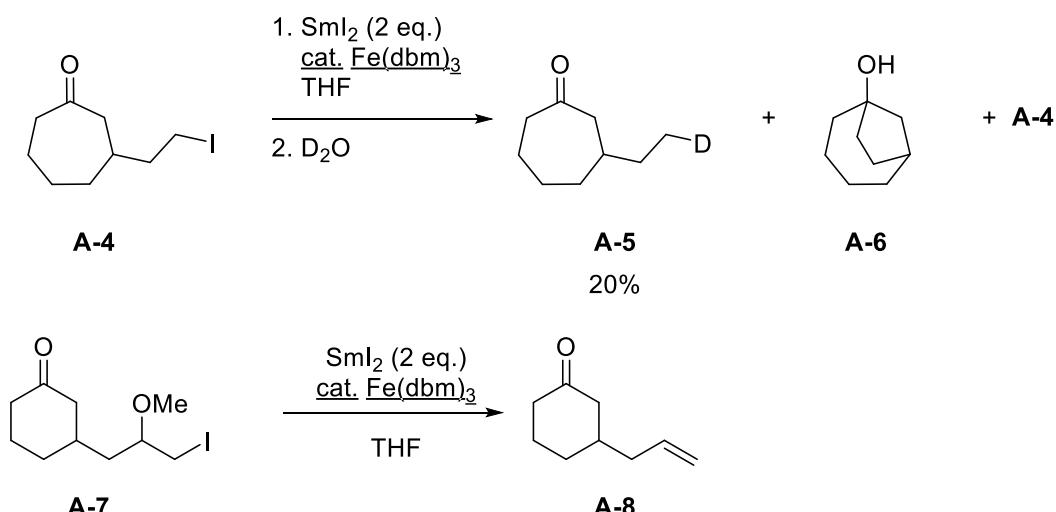
another path: **ketyl radical attack to alkyl halide**





Cooke, M. P.; Houpis, I. N. *Tetrahedron, Lett.* **1985**, 26, 4987.

This result showed that ketyl radical might be produced before alkyl radical.

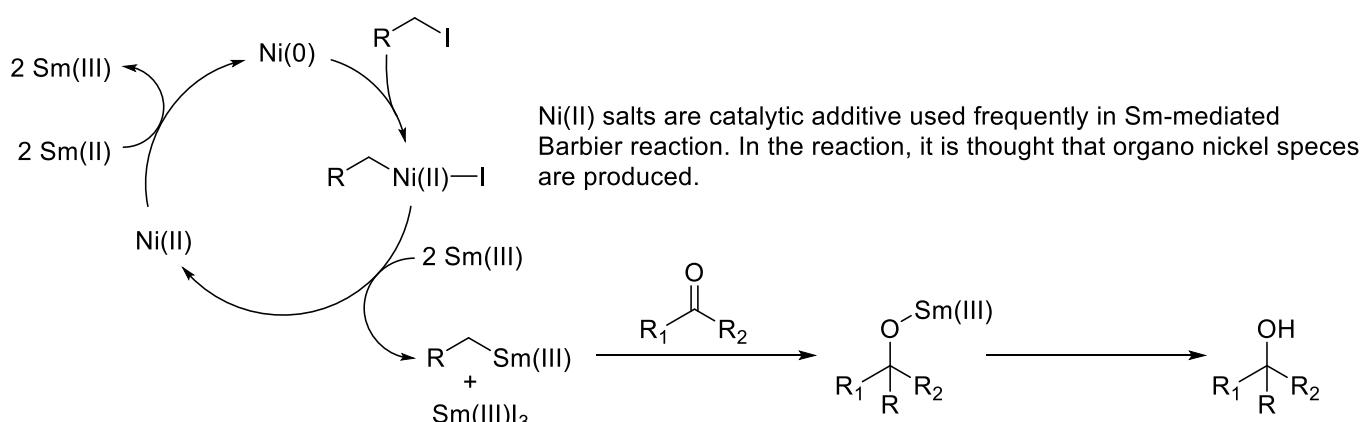


Molander, A. G.; McKie, A. J. *J. Org. Chem.* **1991**, 56, 4113.

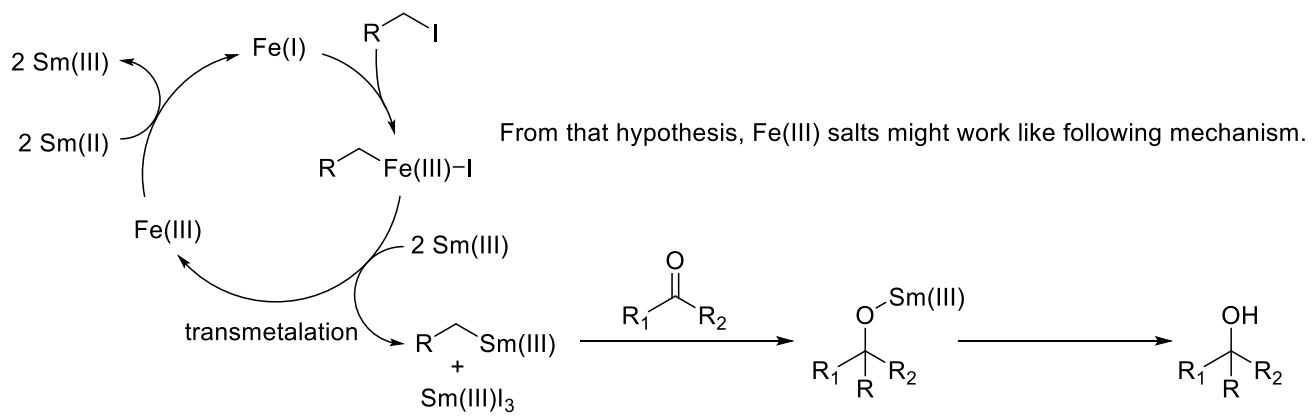
On the other hand, these results showed that alkyl radical might be produced before ketyl radical.

The role of Fe(III) catalyst

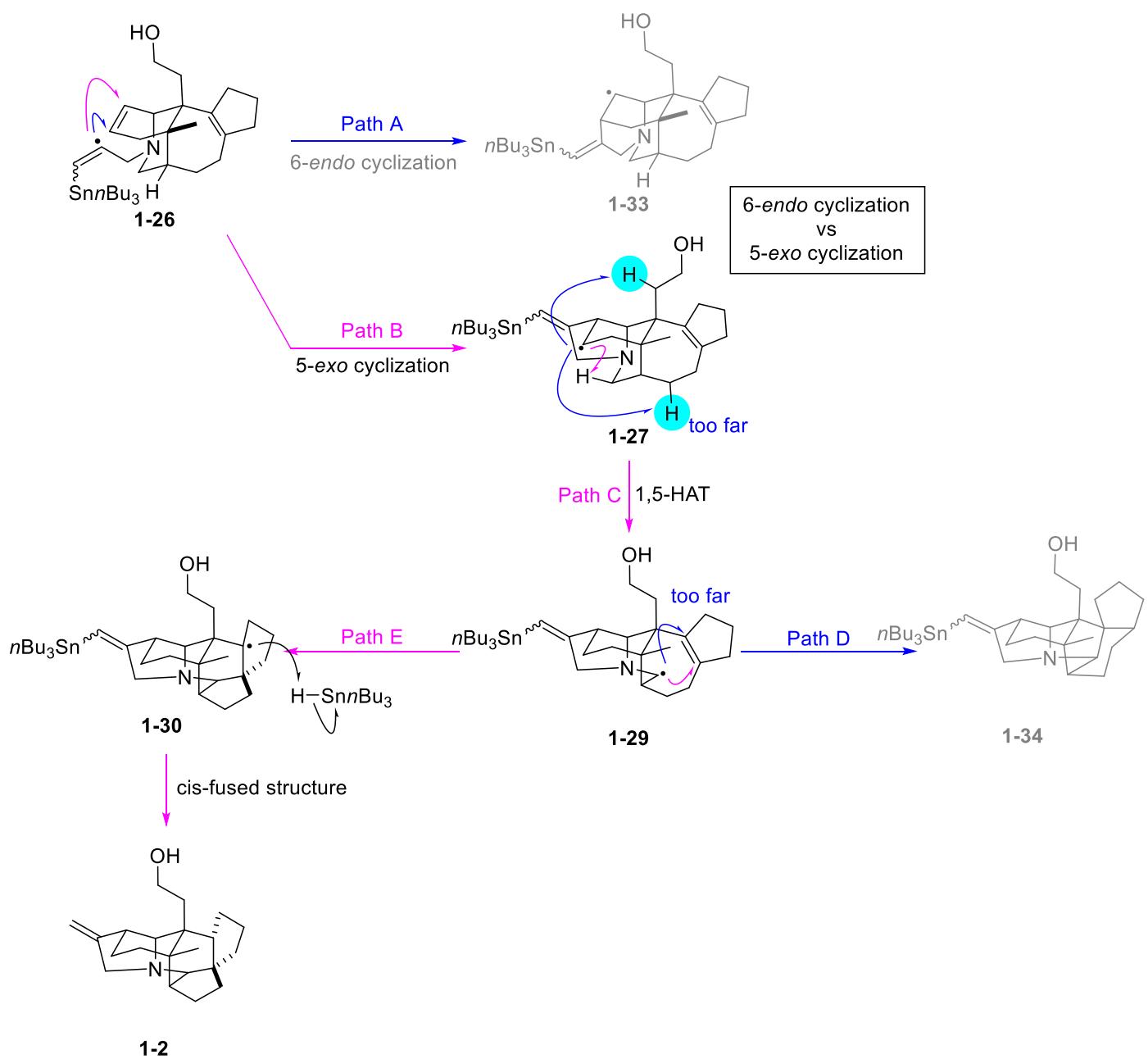
The role of Fe(III) catalyst was not known.. .



Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A. *J. Am. Chem. Soc.* **2013**, 133, 10655.

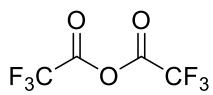
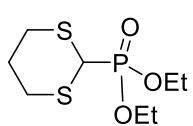
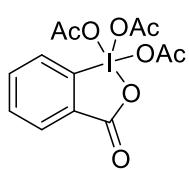
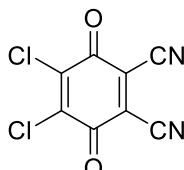
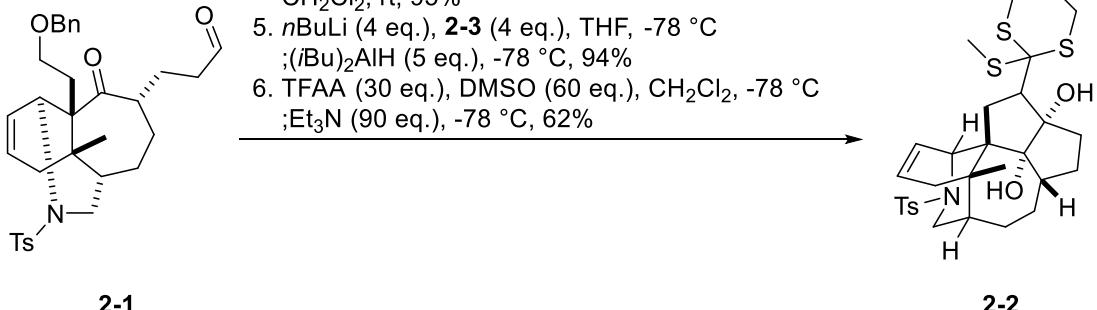


Discussion 2: Each selectivities of radical cyclization cascade (step 5)



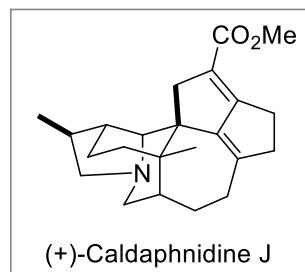
(2) Please explain the reasonable reaction mechanisms.

1. SmI_2 (6 eq.), THF, rt, 88%
2. Ac_2O (10 eq.), DMAP (10 mol%), pyridine, rt, 95%
3. DDQ (5 eq.), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, rt, 85%
4. Dess-Martin periodinane (2 eq.), NaHCO_3 (4 eq.)
 CH_2Cl_2 , rt, 95%
5. $n\text{BuLi}$ (4 eq.), **2-3** (4 eq.), THF, -78°C
 $;(i\text{Bu})_2\text{AlH}$ (5 eq.), -78°C , 94%
6. TFAA (30 eq.), DMSO (60 eq.), CH_2Cl_2 , -78°C
 $;\text{Et}_3\text{N}$ (90 eq.), -78°C , 62%



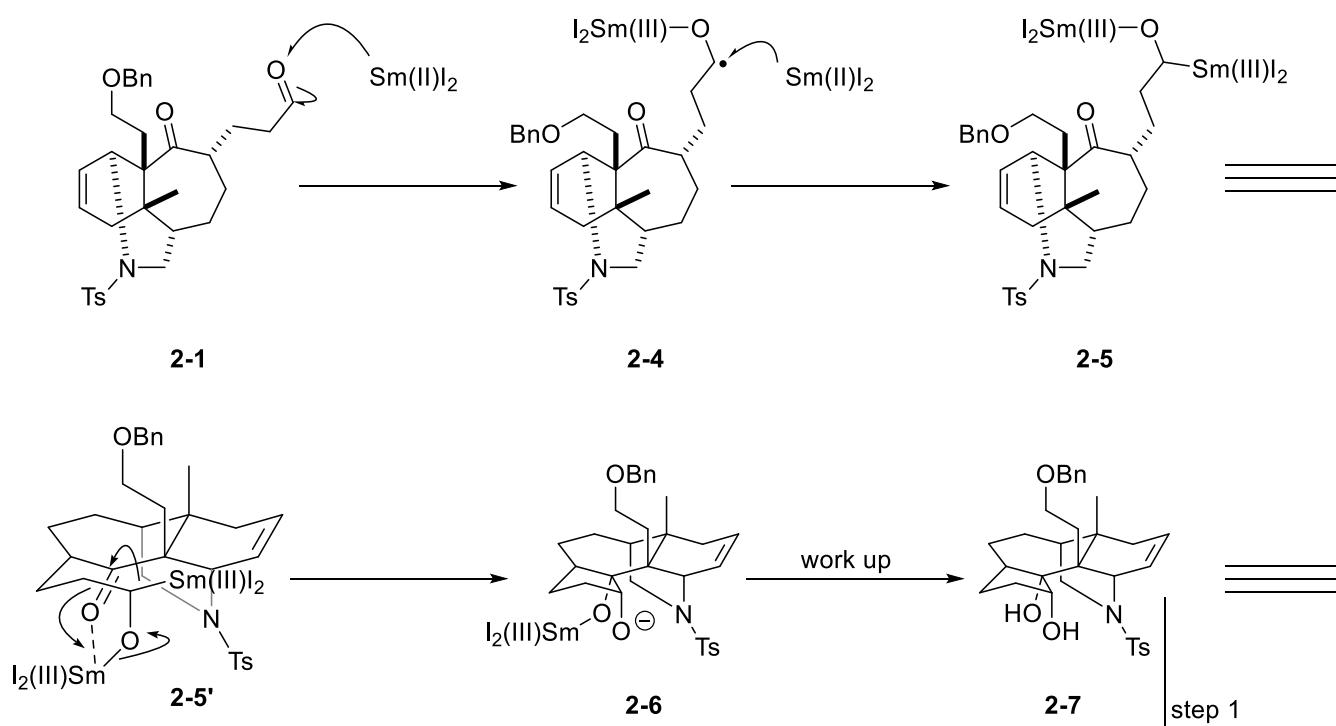
Guo, L.; Zhang, Y.; Hu, J.; Ning, C.; Fu, H.; Chen, Y.; Xu, J.; *Nat. Comm.* **2020**, 11, 3538.

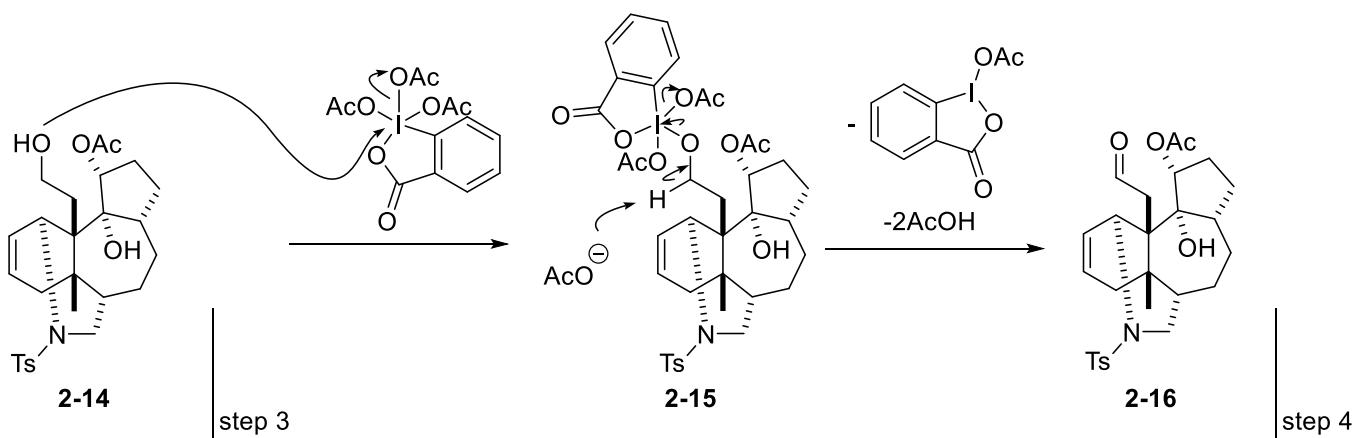
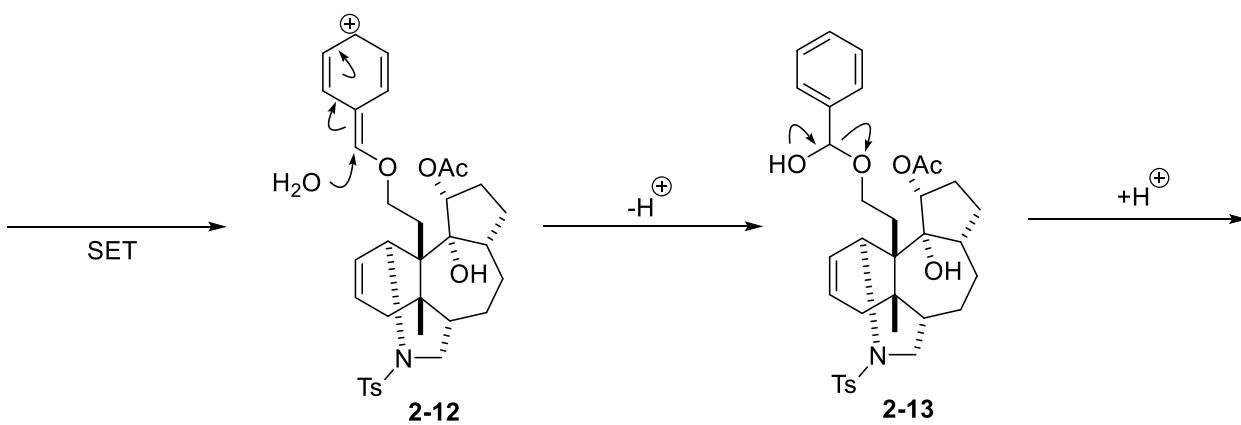
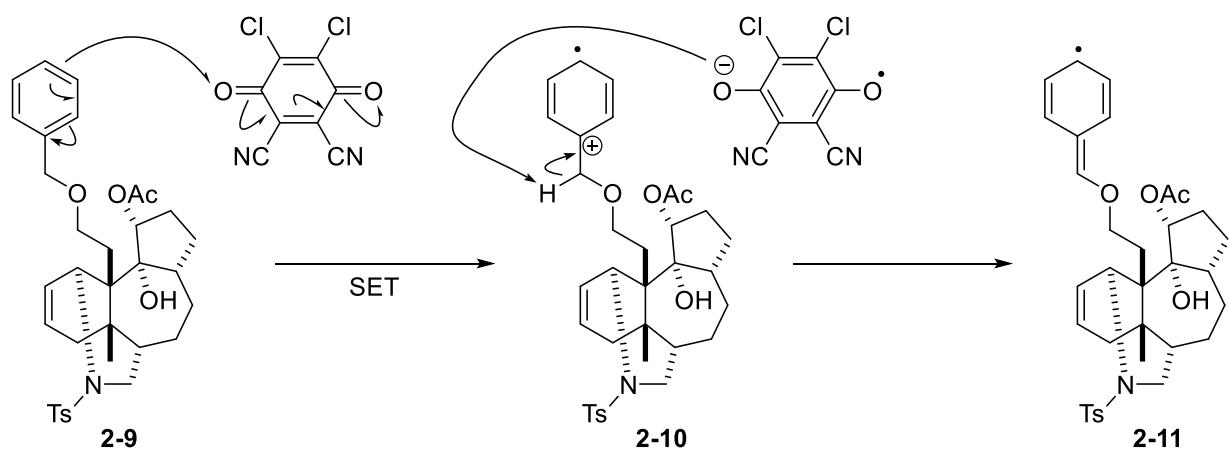
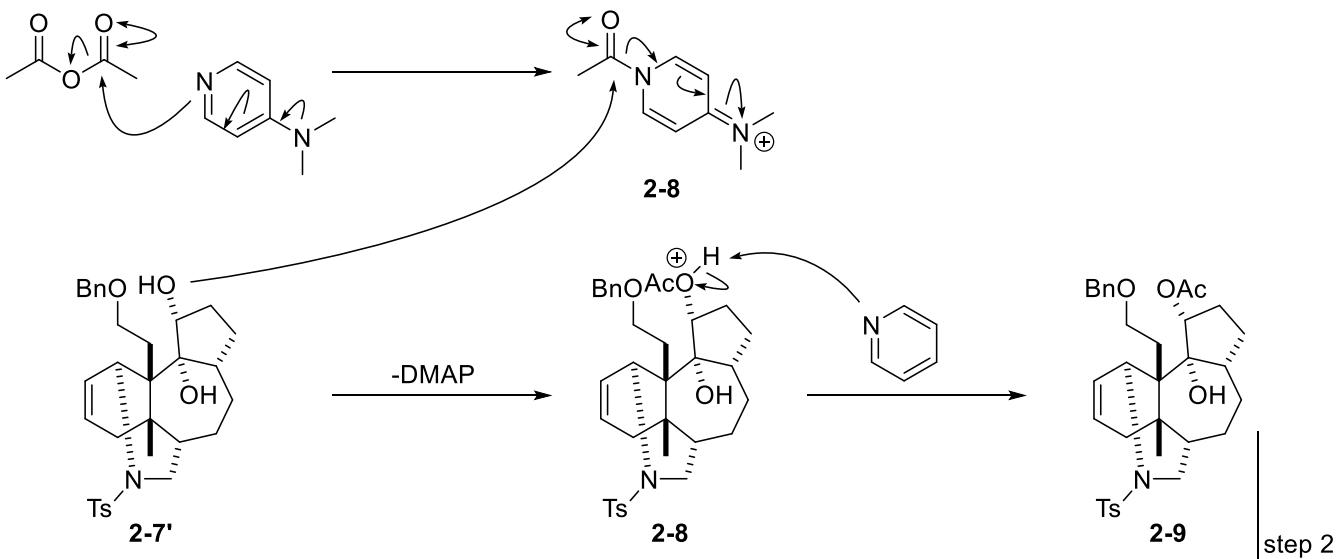
• Total synthesis of (+)-Caldaphnidine J
This paper is the first and enantioselective synthesis.

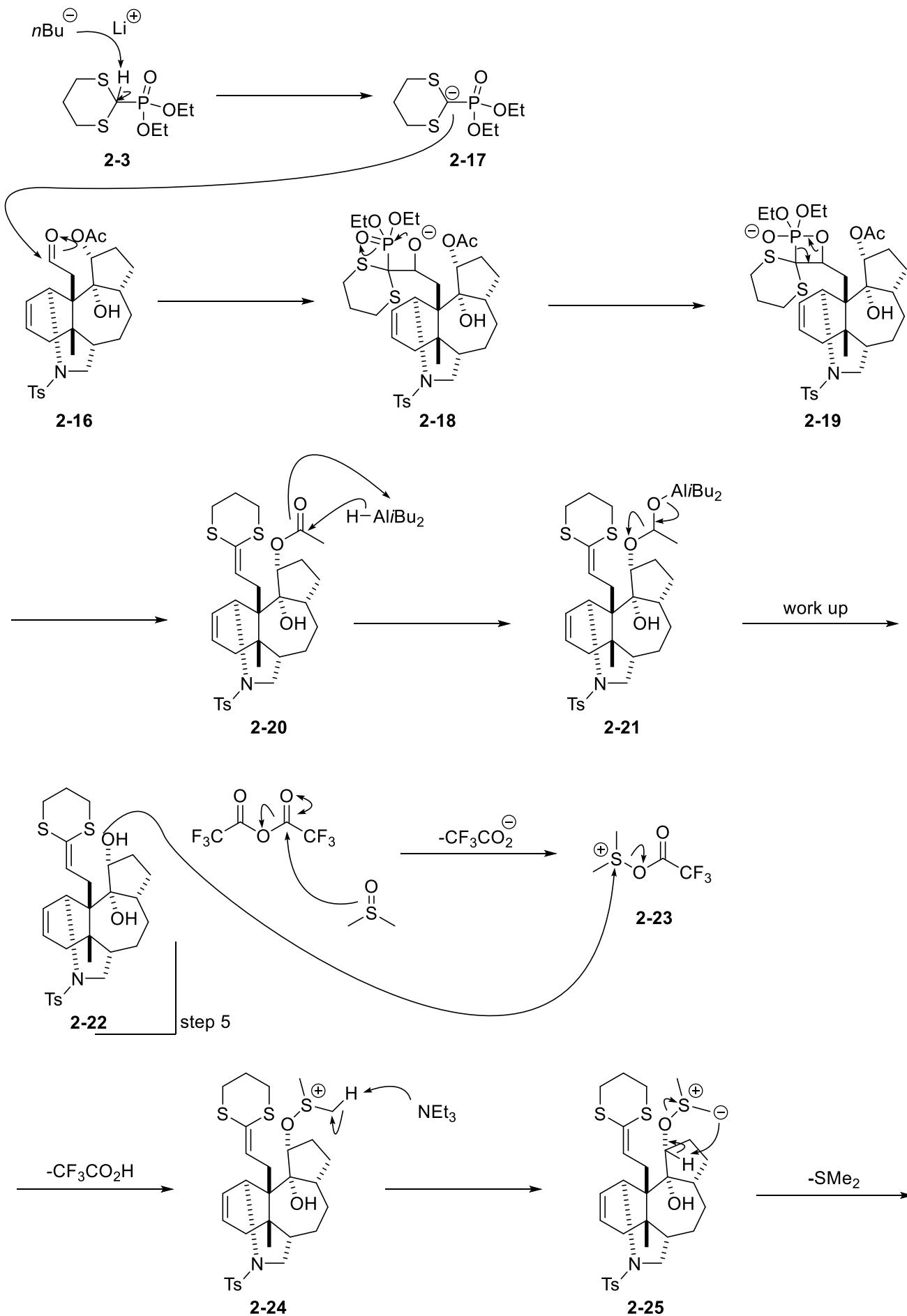


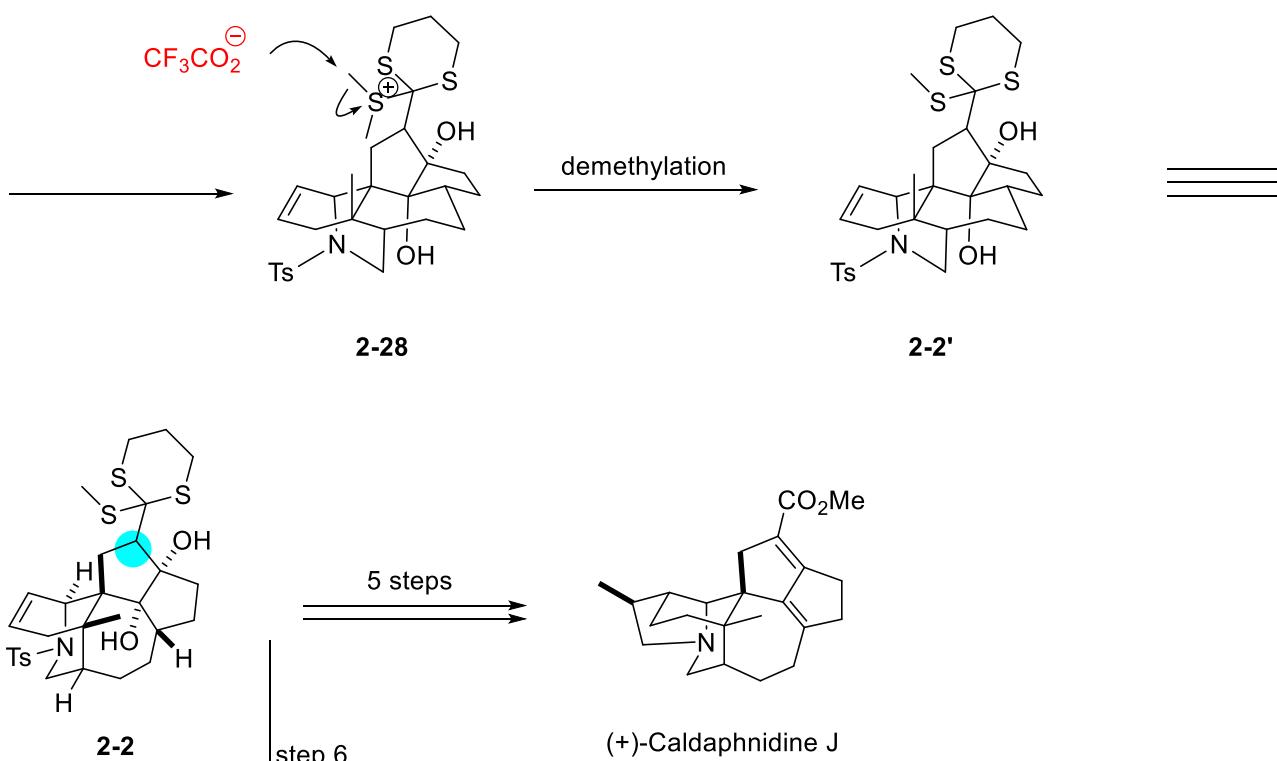
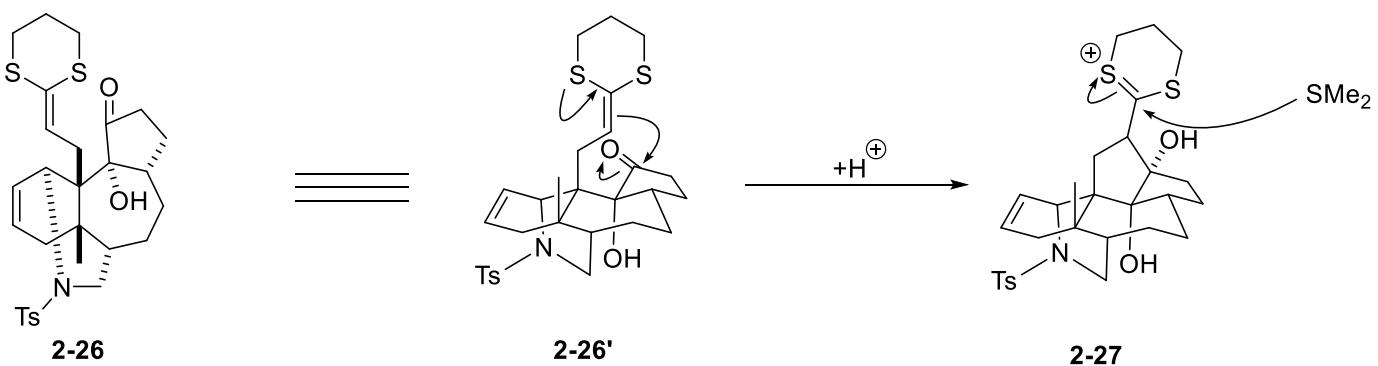
• Key reaction: one pot Swern oxidation and ketene dithioacetal Prins reaction (step 6)

Answer:



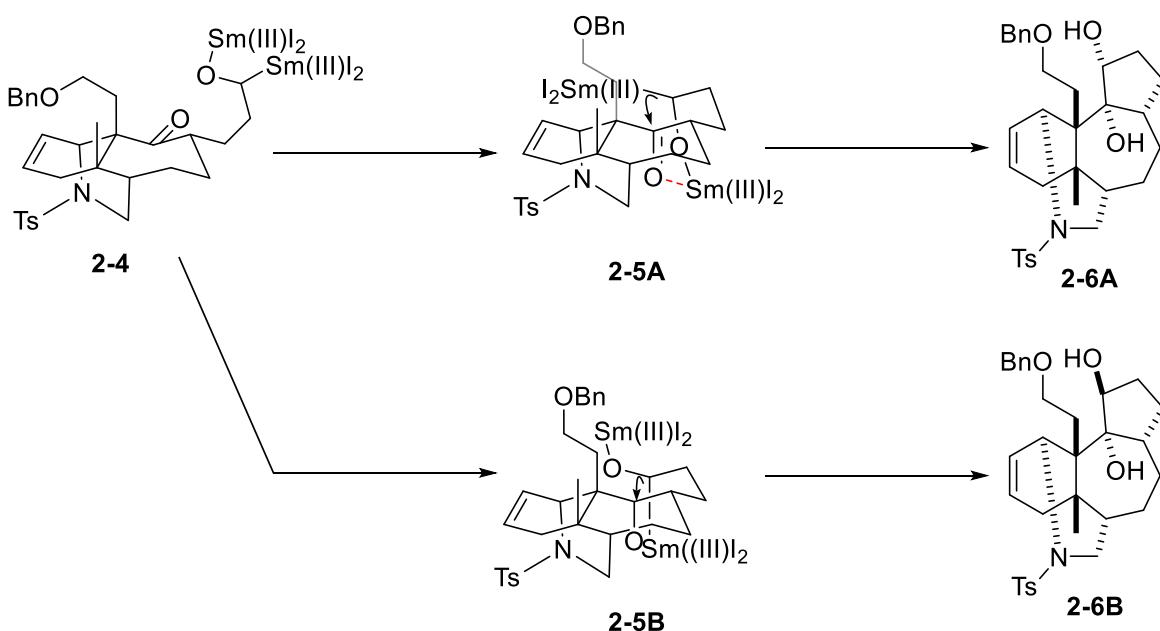


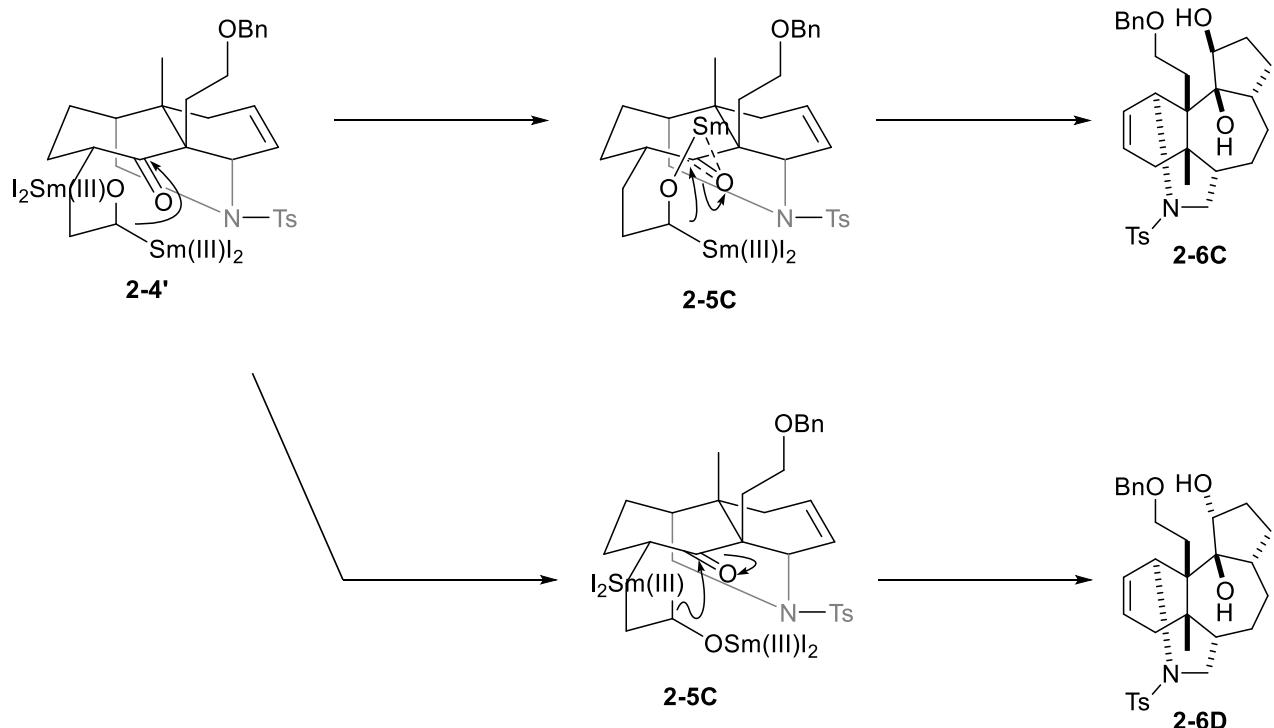




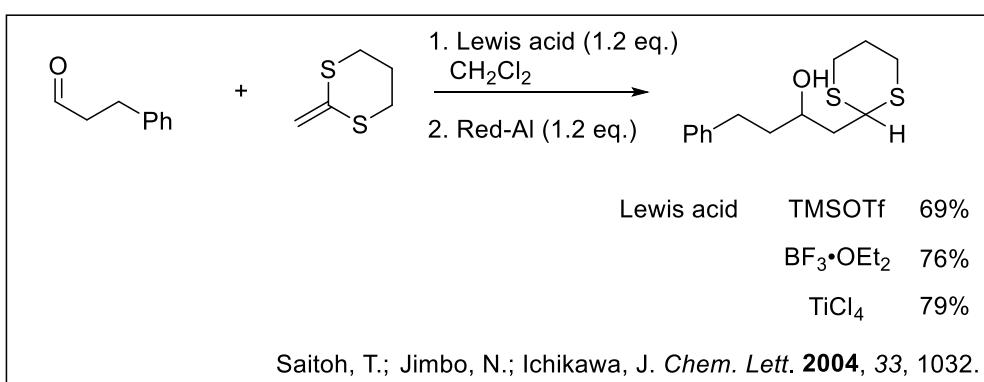
Steric constitution of this position was not reported.

Discussion1: pinacol coupling





Discussion 2: intramolecular Prins reaction (step 6)



In intermolecular Prins reaction, strong Lewis acid is needed. In this case, strong Lewis acid may not be needed because of intramolecular reaction.

- demethylation

another path: like pummerer rearrangement

