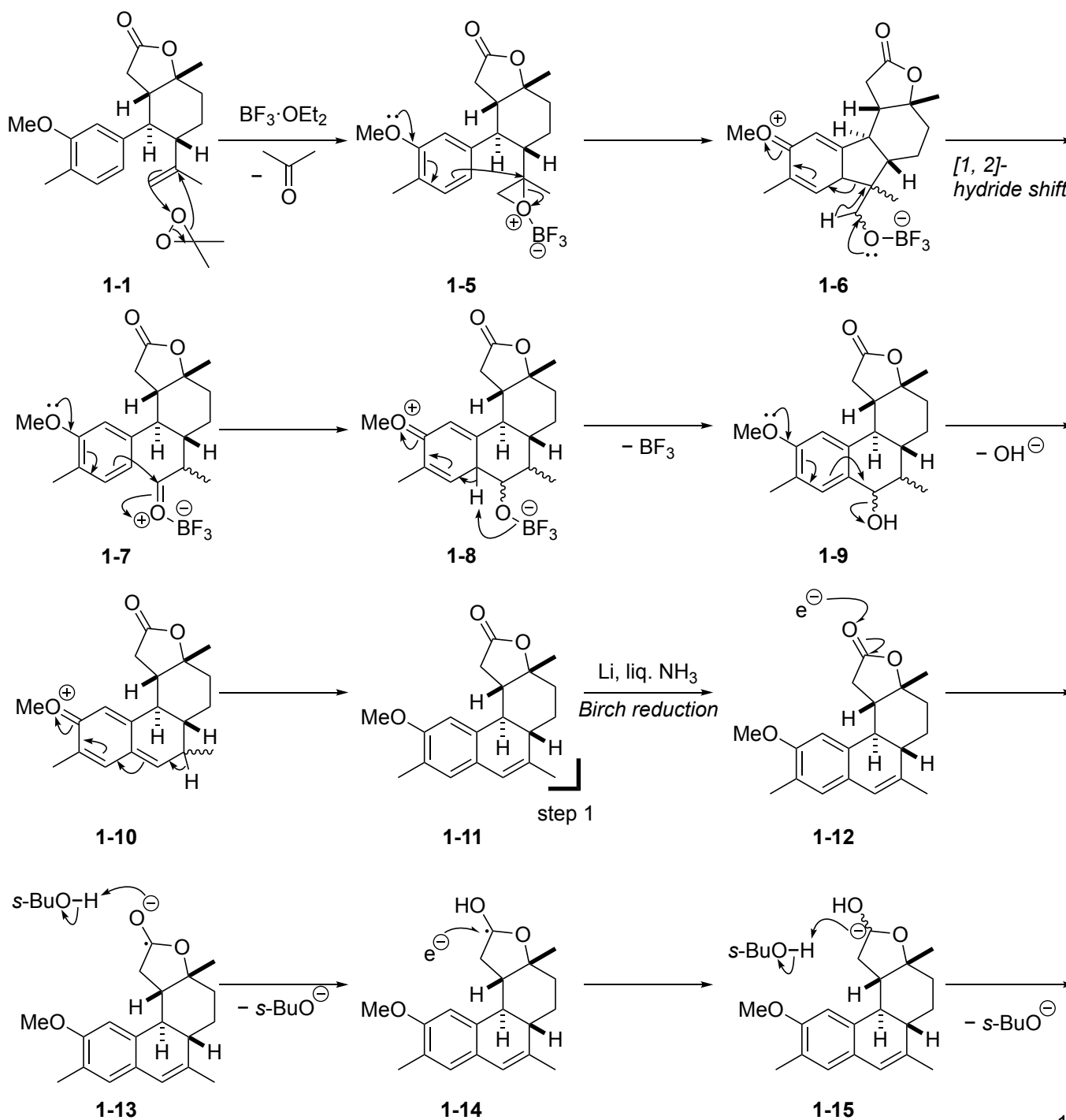
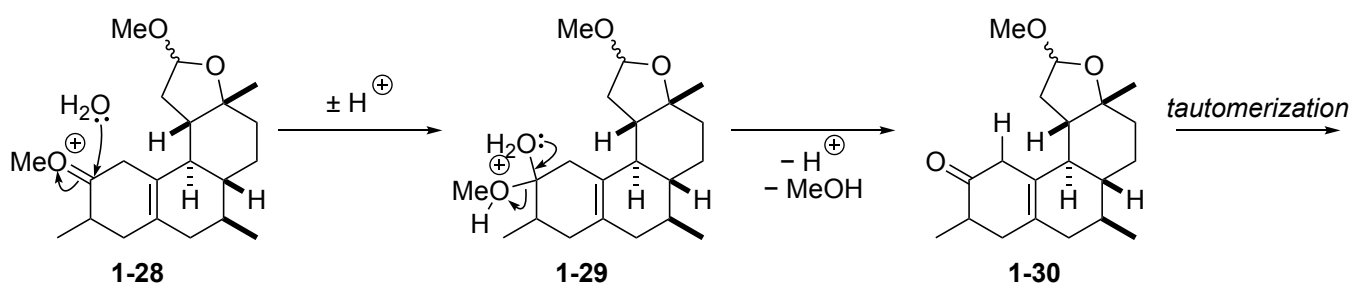
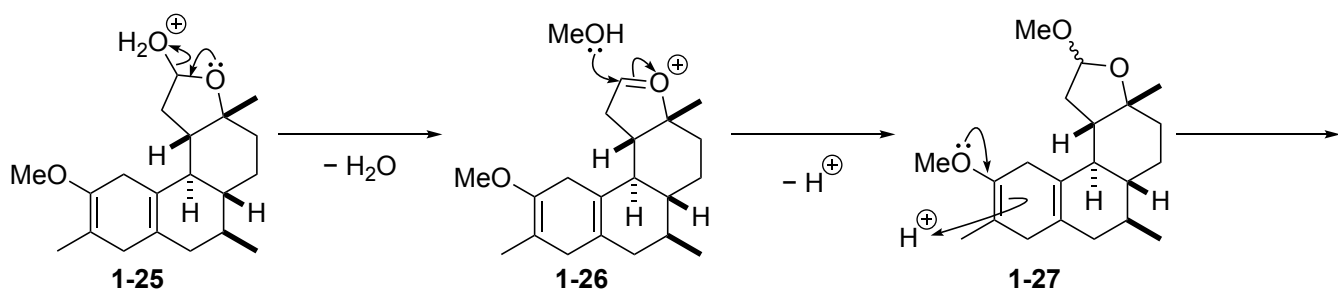
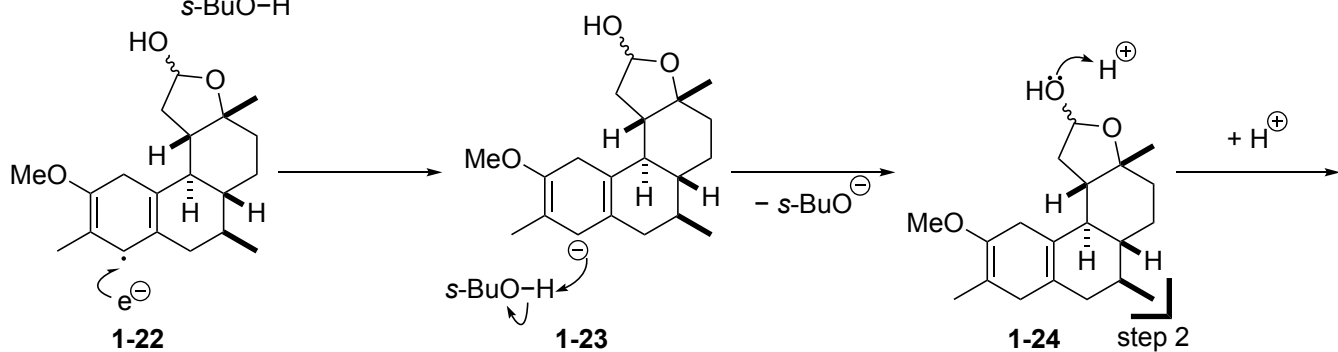
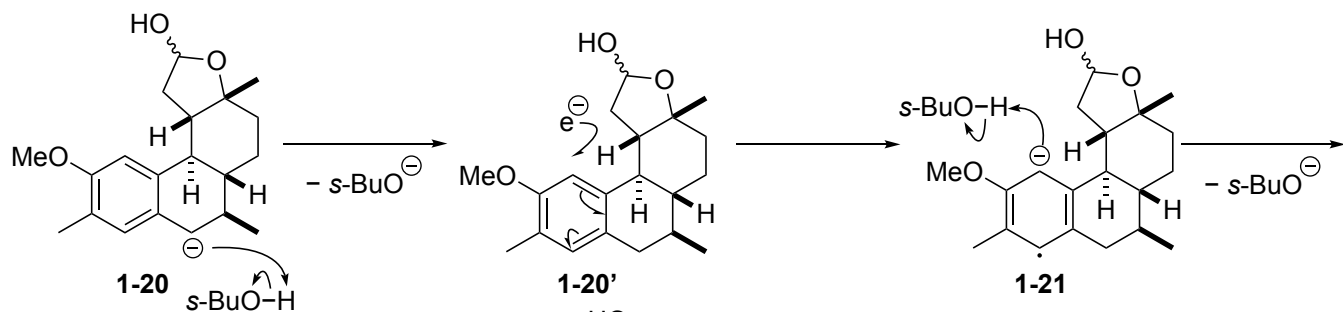
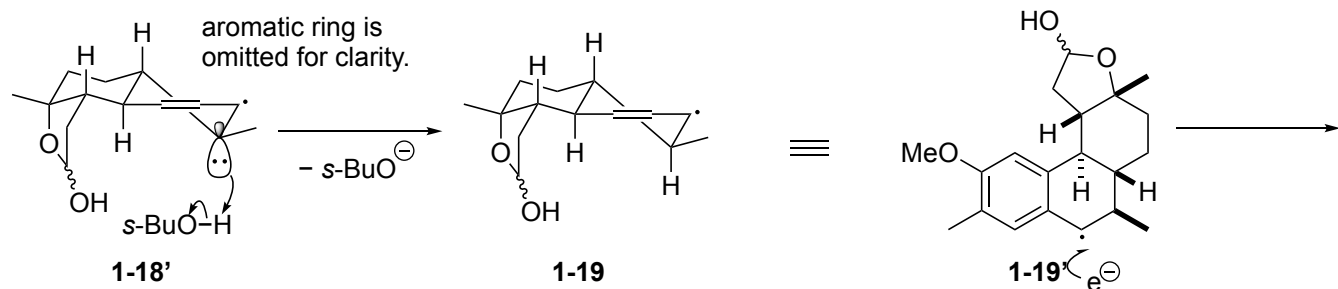
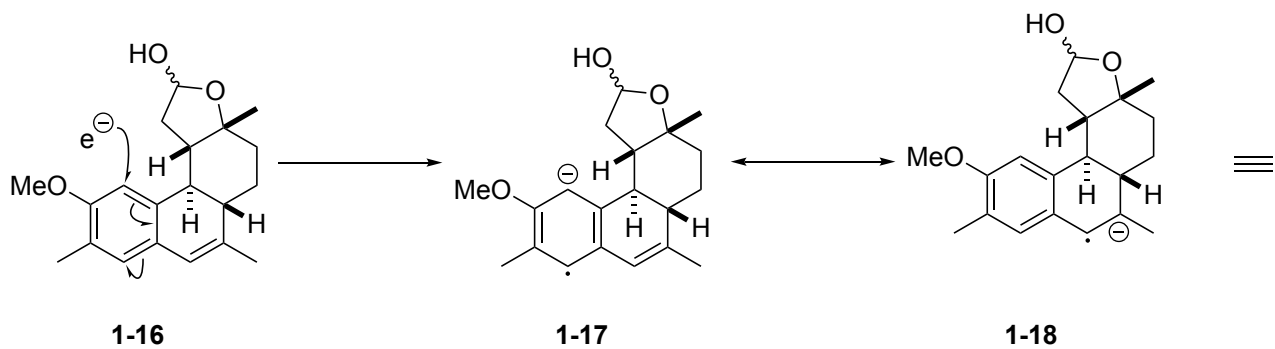
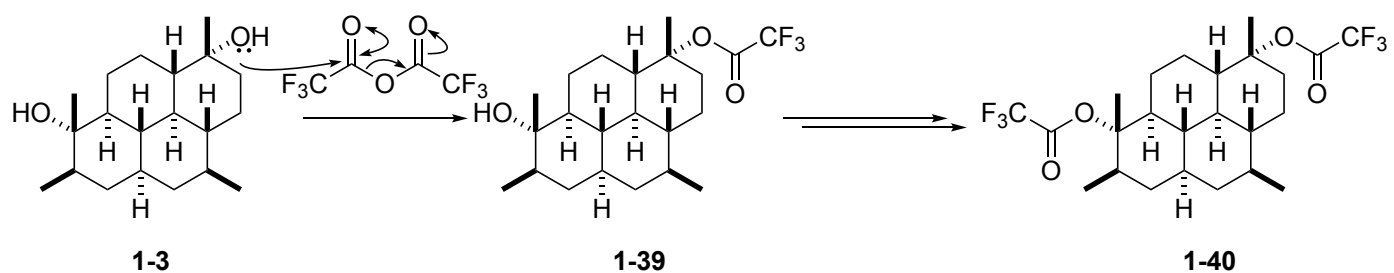
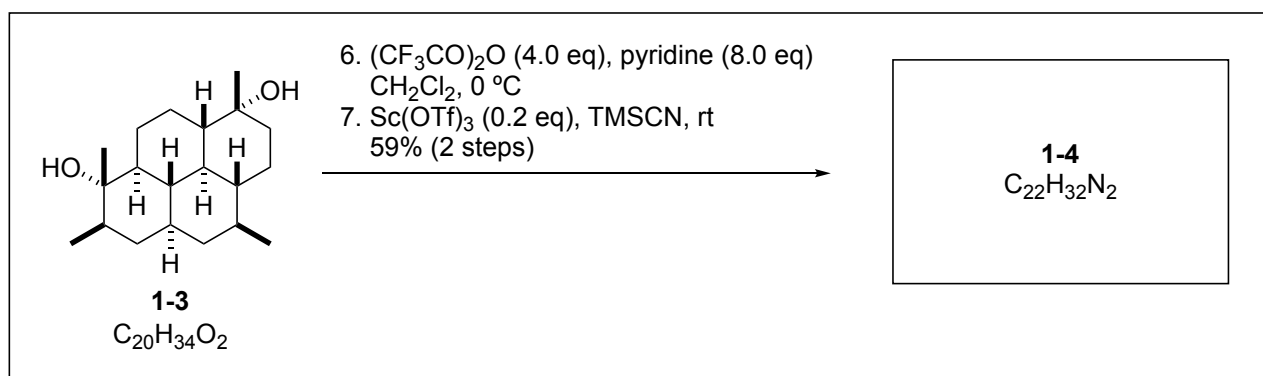
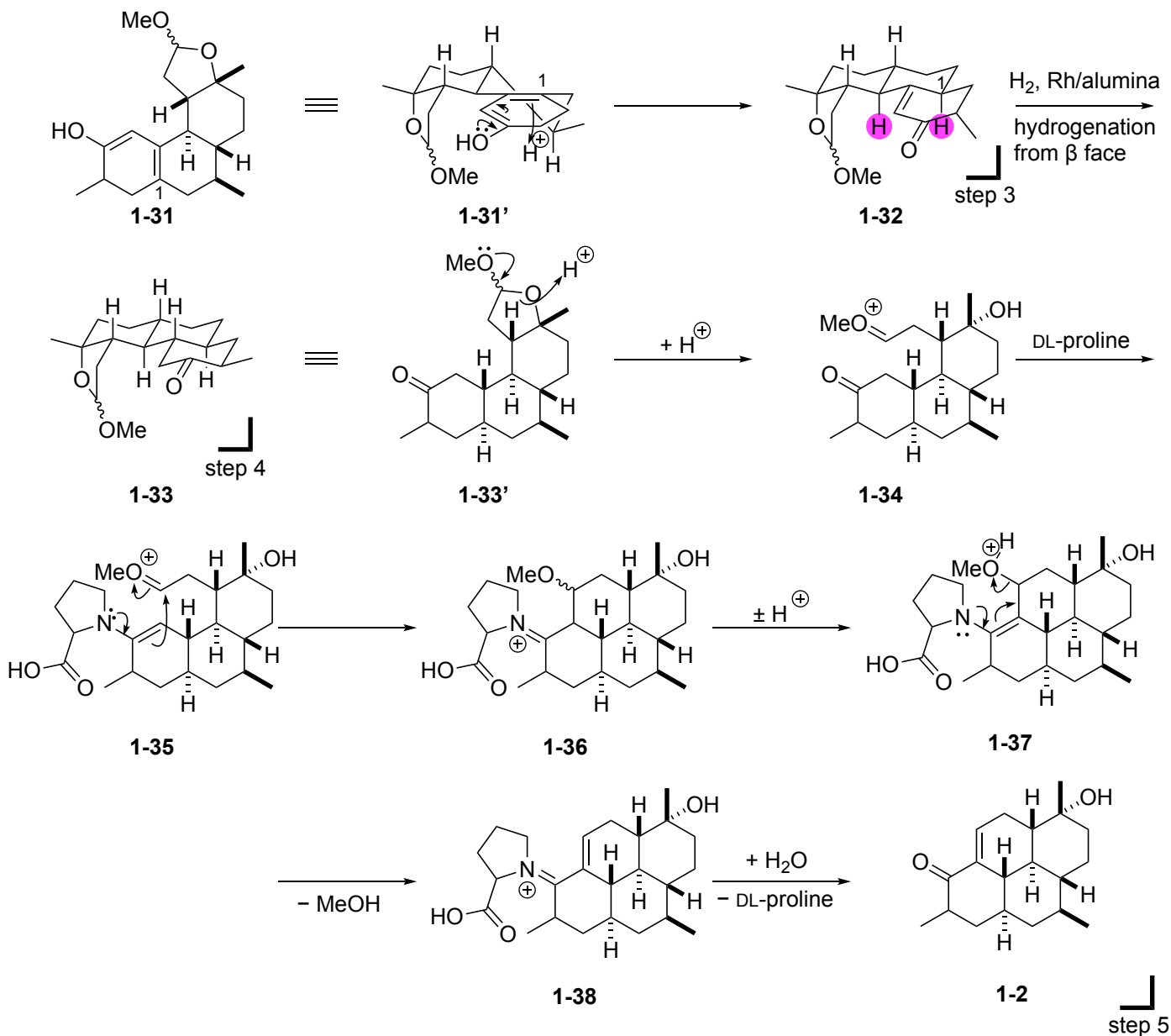
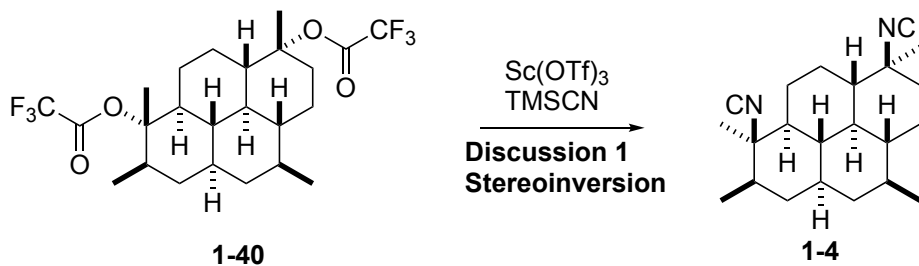


1-1. Reaction mechanism¹⁾



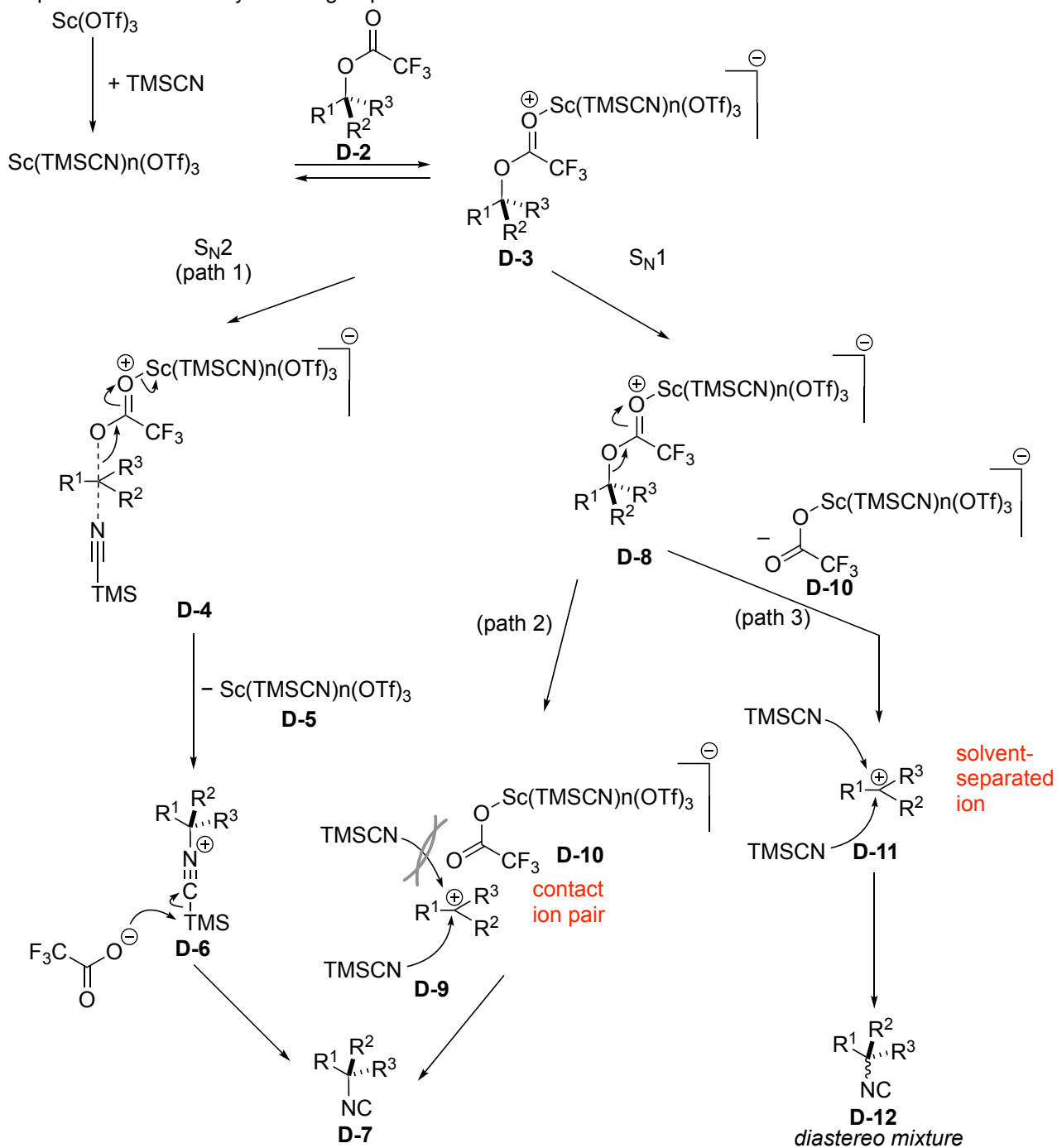






1-2. Discussion 1: Stereoinversion of tertiary alcohol

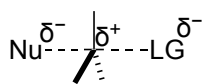
1-2-1. Proposed mechanism by Shenvi group²⁾



1-2-2. Stereoconversion via intramolecular cyclization

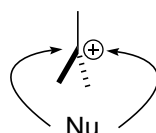
1-2-2-1. S_N2 reaction and S_N1 reaction

• S_N2 reaction



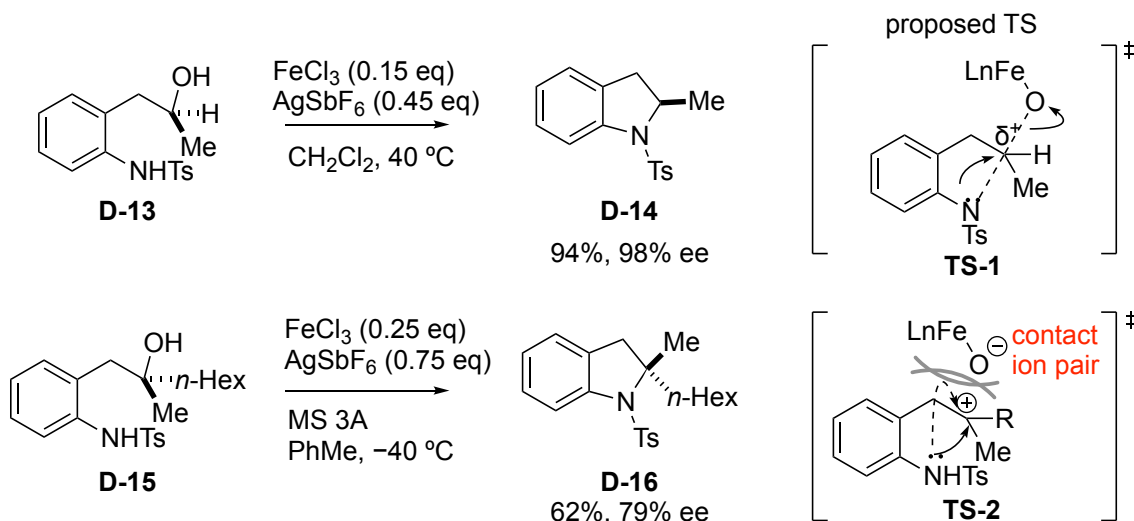
Stereoinvertive reaction

• S_N1 reaction



Stereoablative reaction

1-2-2-2. Stereoconversion via intramolecular cyclization by Cook's group³⁾

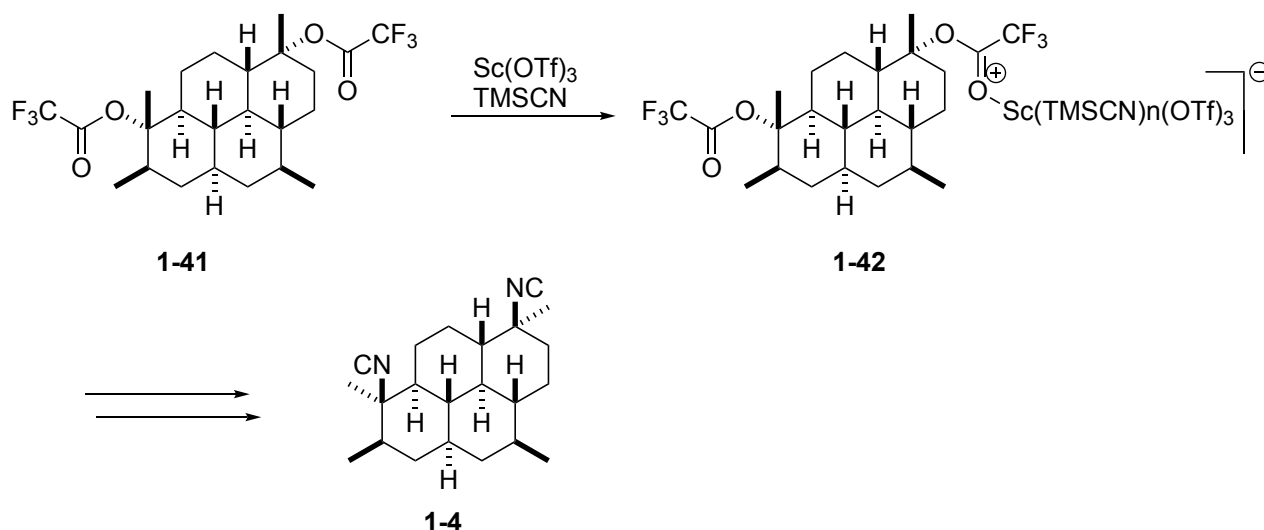


In the case of secondary alcohol, stereochemistry was almost completely inverted.

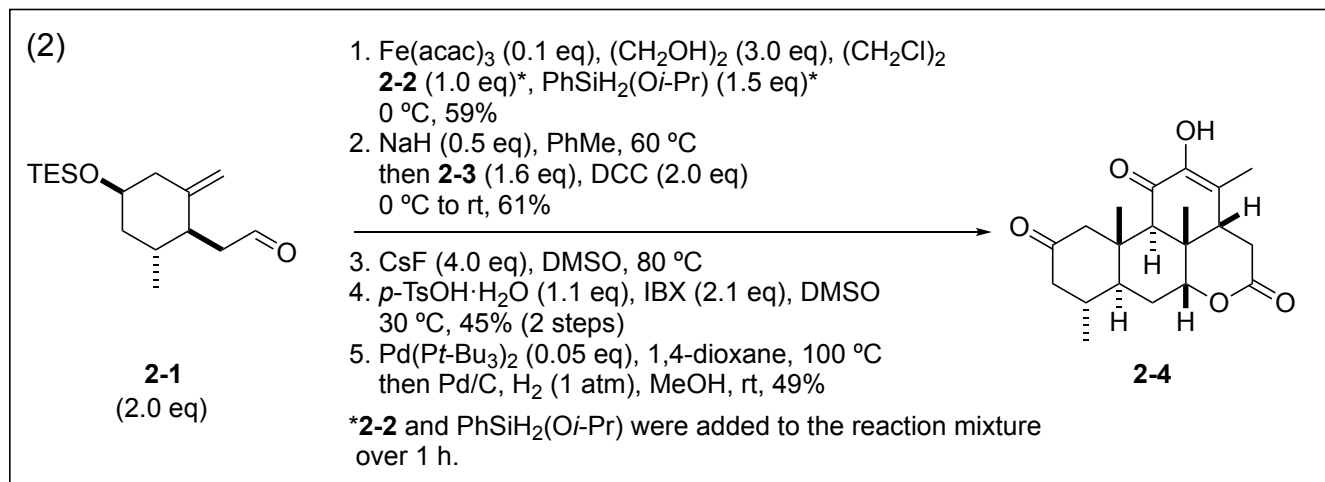
It is suggested that S_N2 -type reaction proceeded.

On the other hand, when tertiary alcohol was used as a reactant, racemization partially occurred and the ee was relatively lower, which indicated that S_N1 -type reaction should be considered.

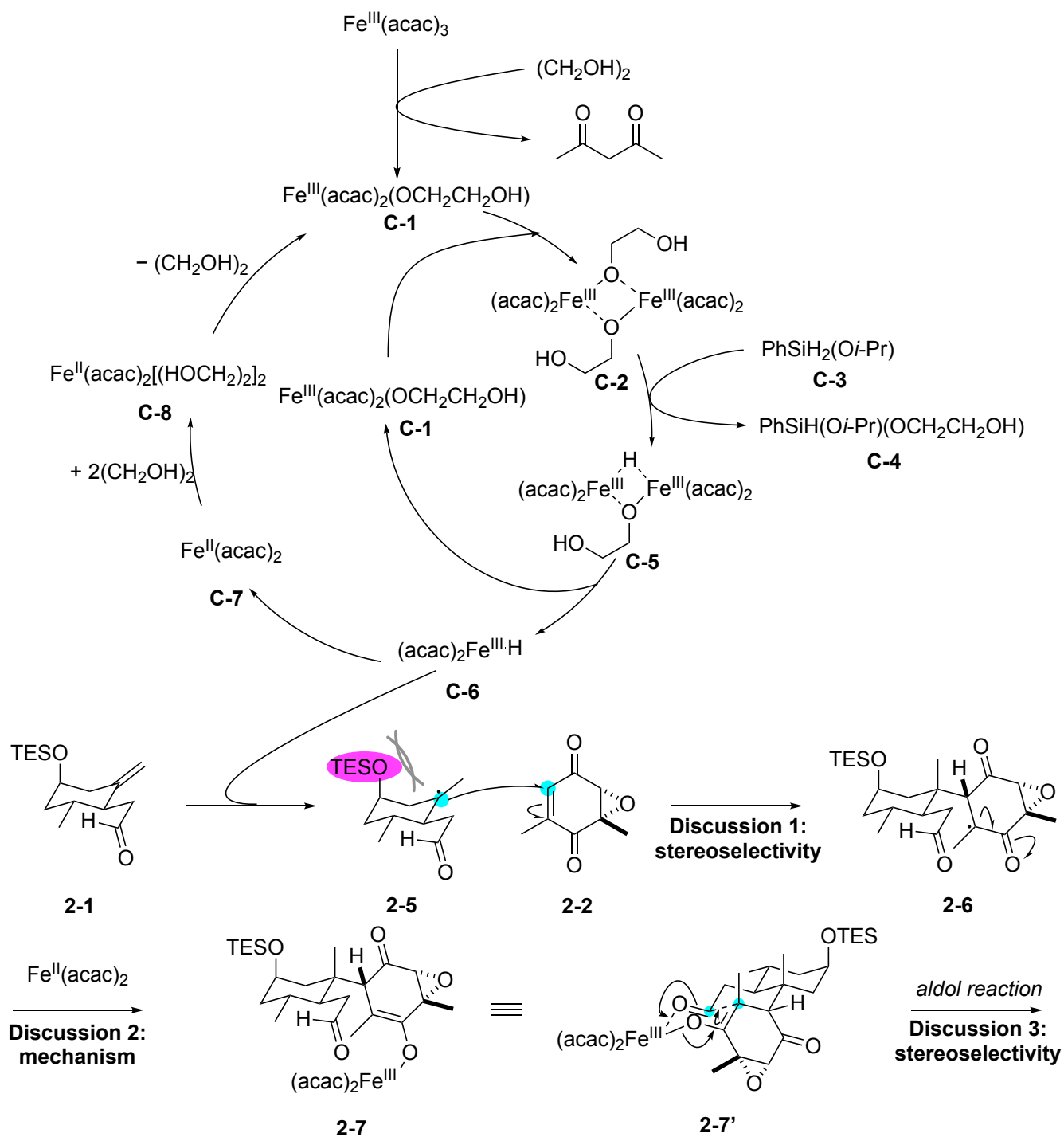
In this reaction, when the contact ion pair was generated, the intramolecular 5-exo-type cyclization would proceed faster than the ion pair dissociated. Therefore, **D-16** was synthesized with good enantioselectivity.

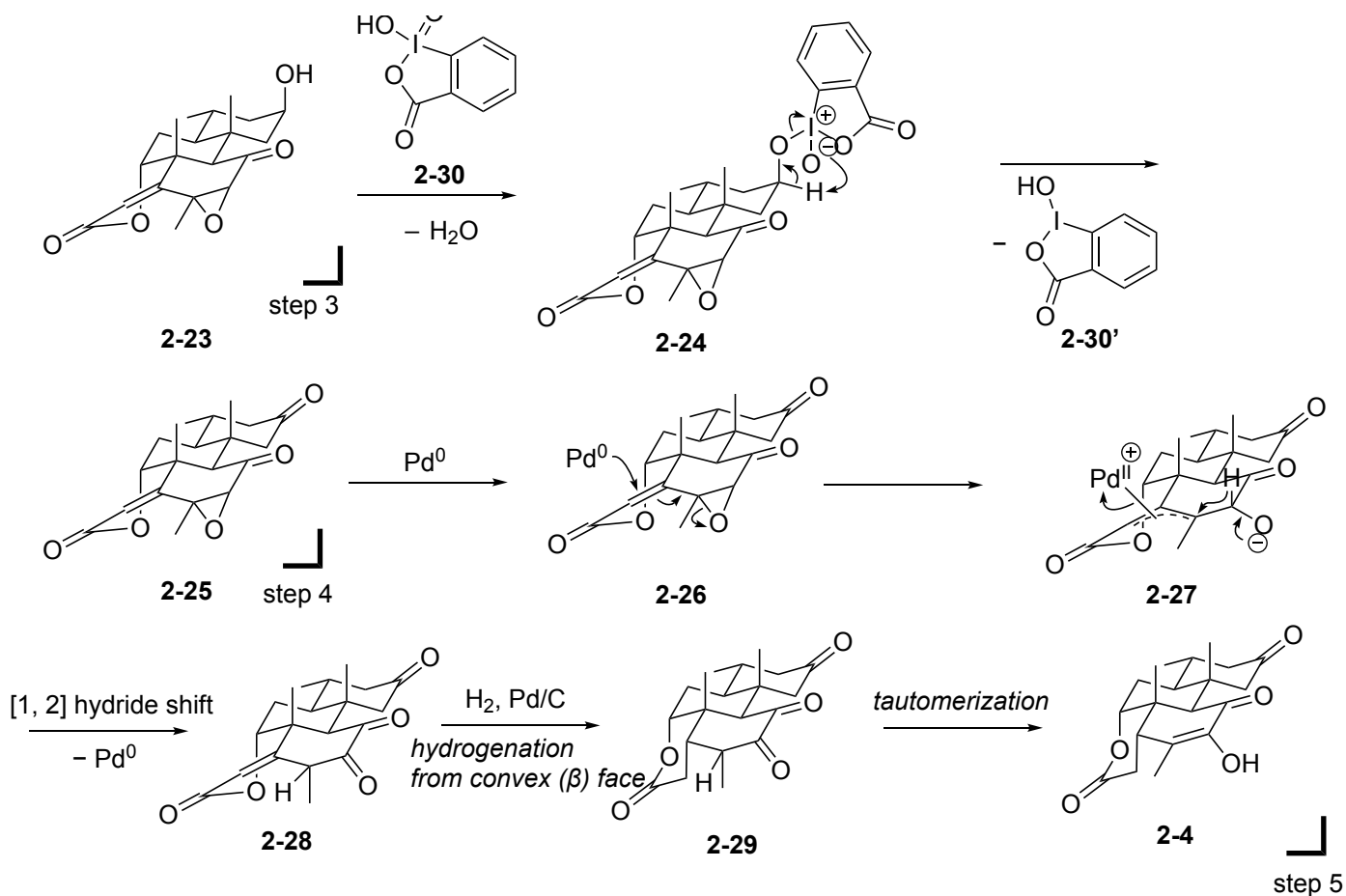


In this conversion of tertiary alcohol to isonitrile, S_N1 -type reaction from contact ion pair should be dominant. Solvent amount of TMSCN would be important for the fast nucleophilic attack to achieve the stereoconversion.

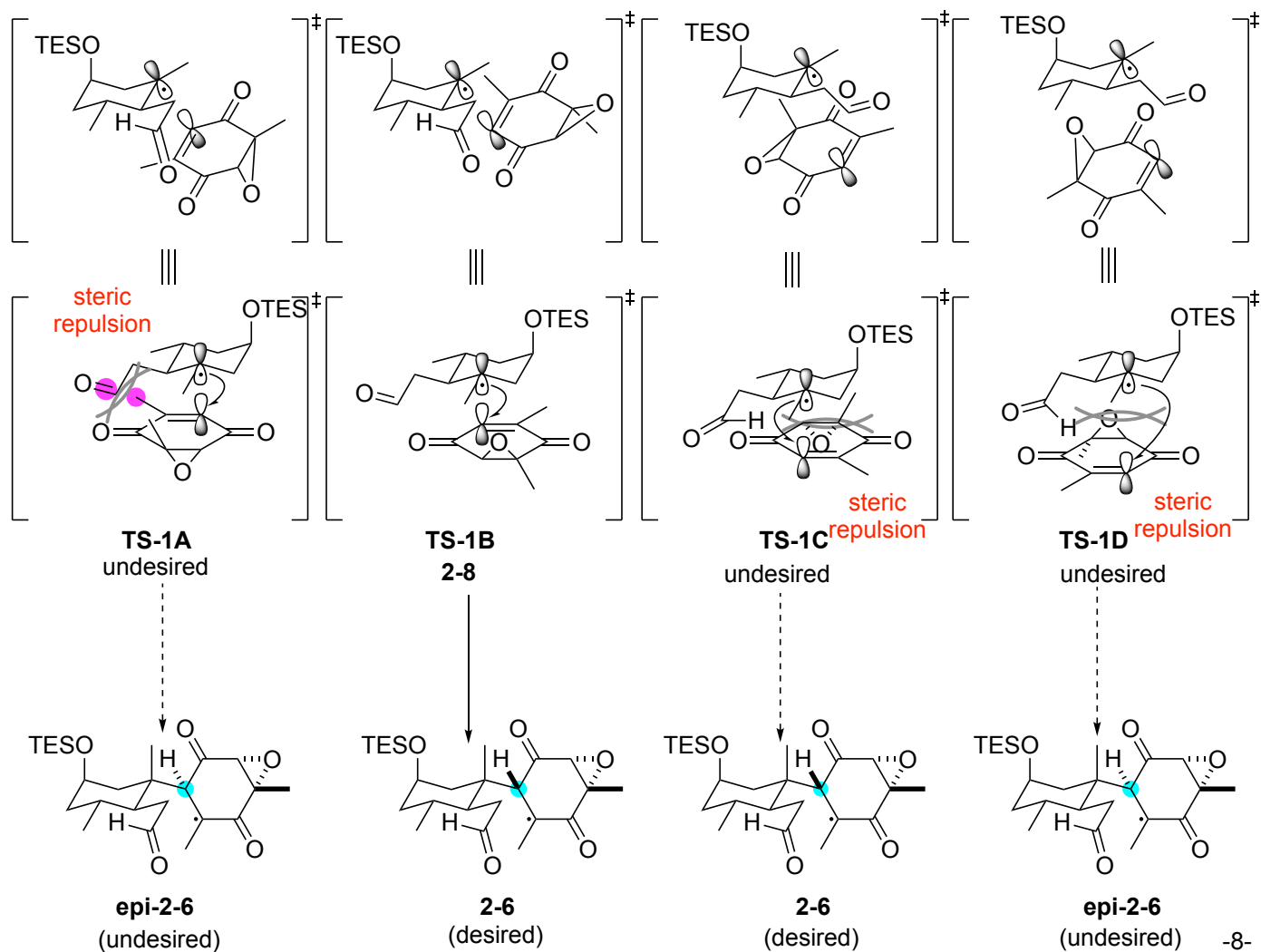


2-1. Reaction mechanism⁴⁾



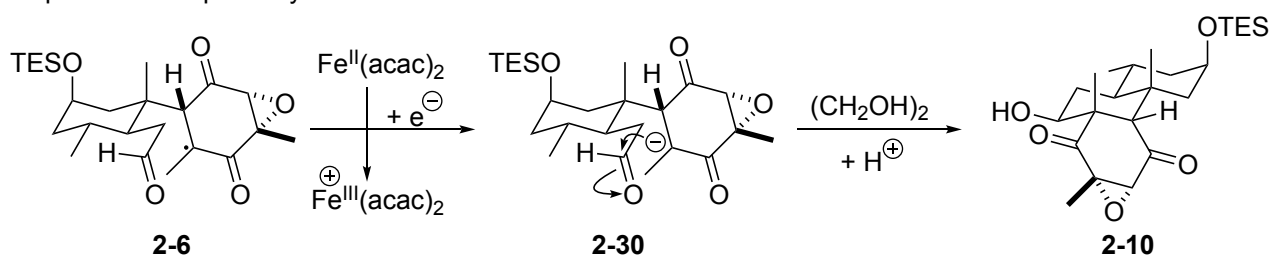


2-2. Discussion 1: stereoselectivity

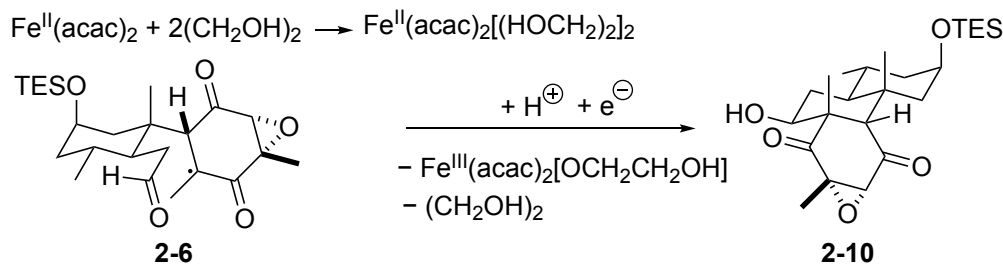


2-3. **Discussion 2:** mechanism of further reduction of **2-6** (see also 210911_PS_Takahiro_Watanabe⁵⁾)
 Based on Holland's report⁶⁾, there are 3 proposed pathways.

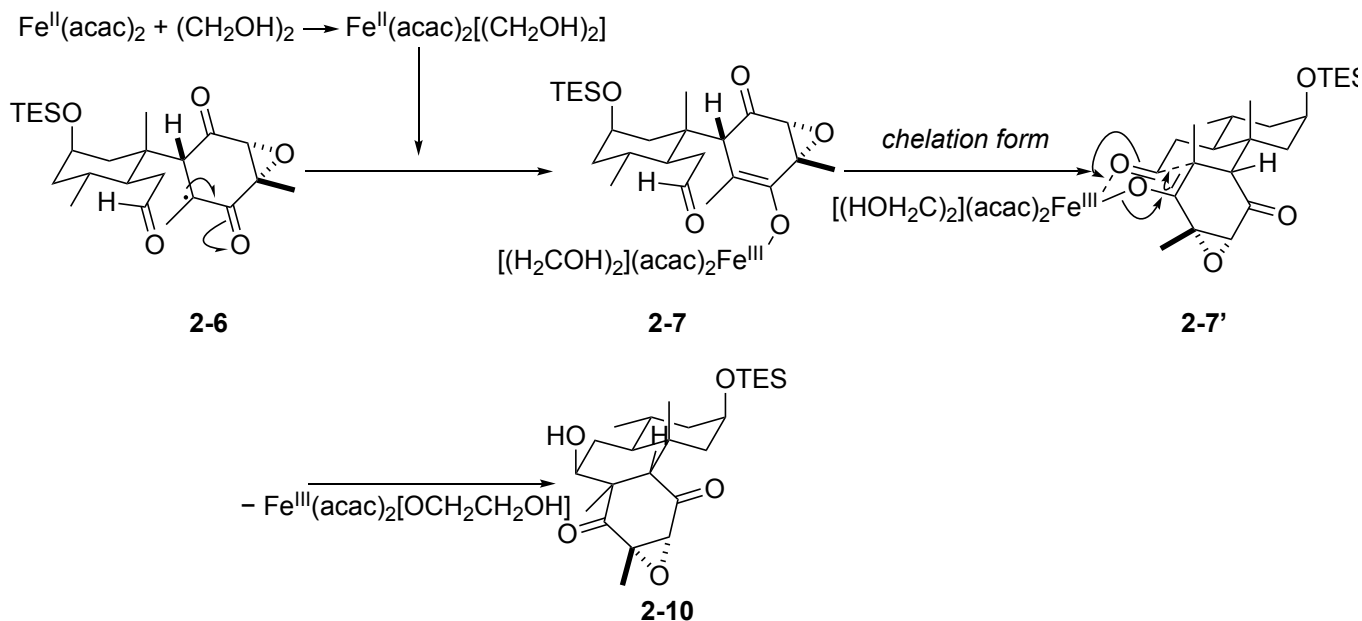
(a) stepwise ET/PT pathway



(b) Concerted Proton-coupled Electron Transfer (CPET) pathway



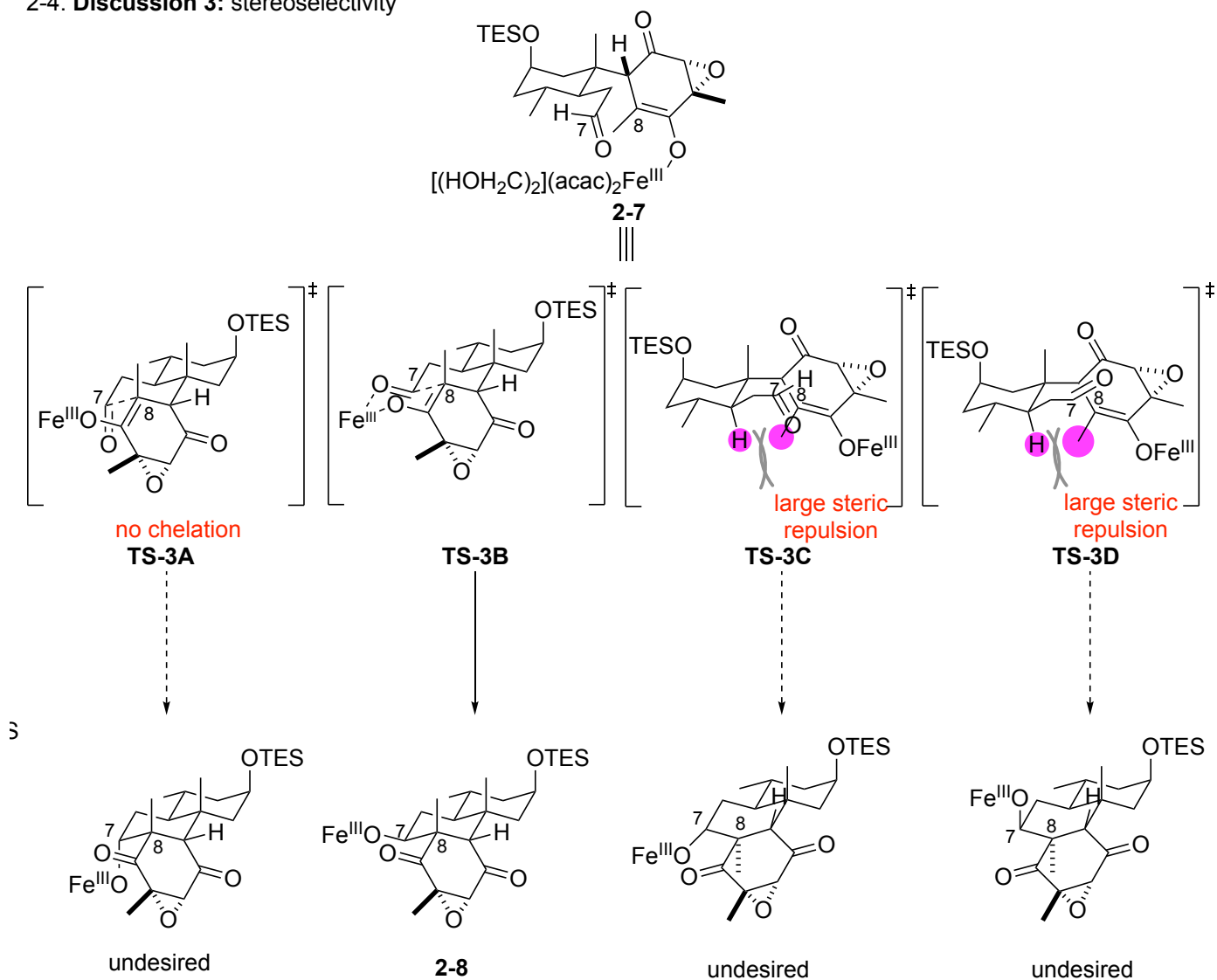
(c) Intramolecular proton transfer to O-bond ester enolate pathway



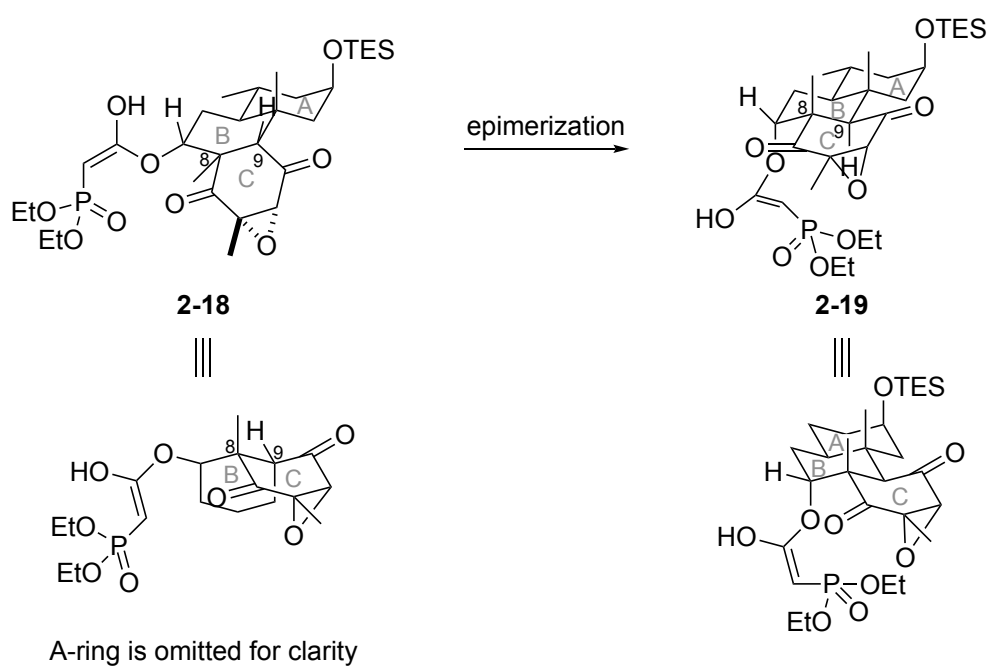
According to the DFT calculation by Holland et al., the activation energy of path (a) is much greater than that of path (b) and path (c). Therefore, path (b) and (c) should be considered.

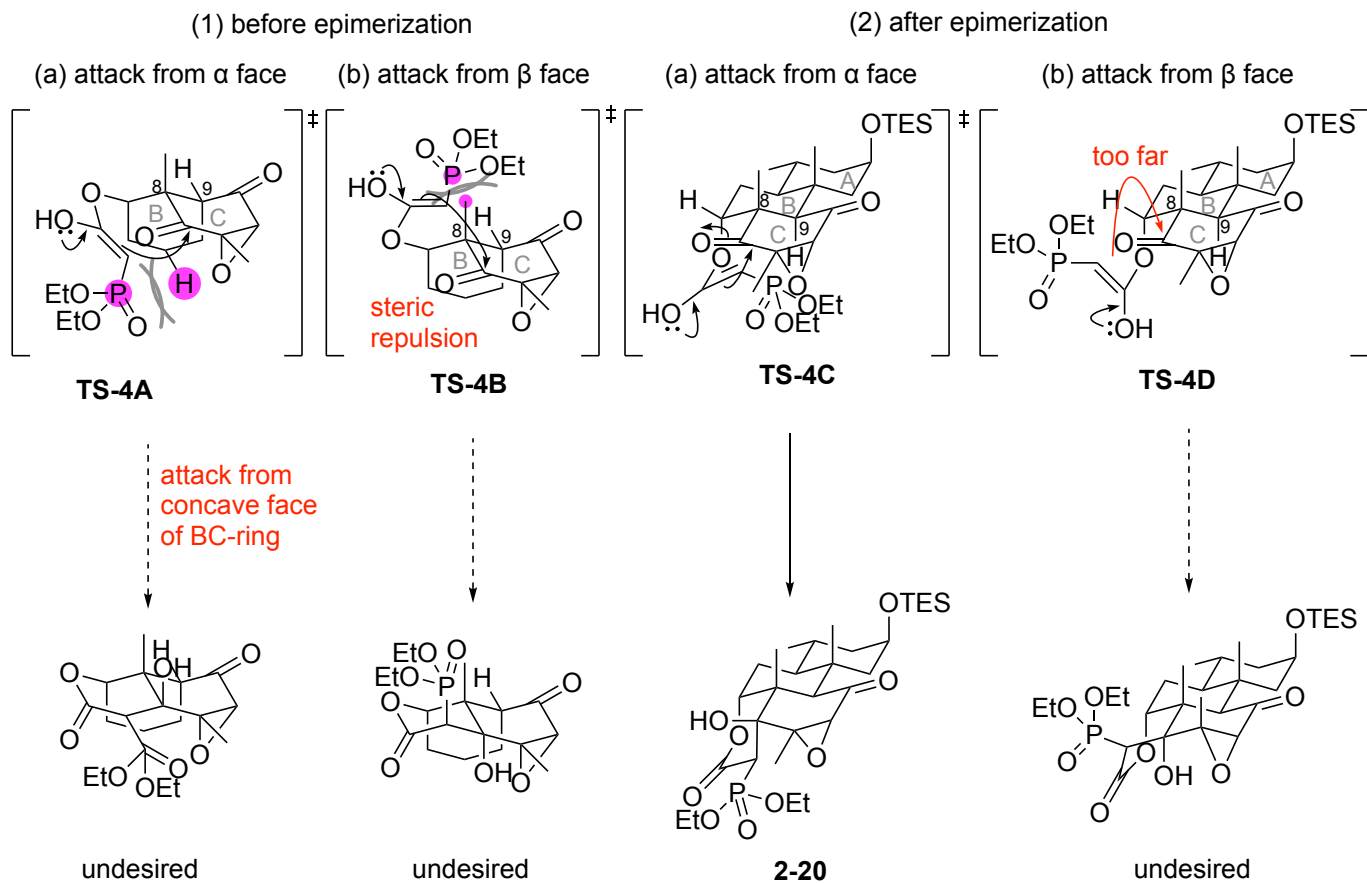
Considering the chelation of Fe to the aldehyde, path (c) should be more plausible.

2-4. Discussion 3: stereoselectivity



2-5. Discussion 4: epimerization at C9





Reference

- 1) Karns, A. S.; Ellis, B. D.; Roosen, P. C.; Chahine, Z.; Roch, K. G. L.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2019**, *58*, 13749-13752.
- 2) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature*. **2013**, *501*, 195-199
- 3) Marcyk, P. T.; Jefferies, L. R.; AbuSalim, D. I.; Pink, M.; Baik, M. H.; Cook, S. P. *Angew. Chem., Int. Ed.* **2019**, *58*, 1727-1731.
- 4) Thomas, W. P.; Pronin, S. V. *J. Am. Chem. Soc.* **2022**, *144*, 118-122
- 5) 210911_PS_Takahiro_Watanabe_total_synthesis_of_pseudocopsinine
- 6) Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. *J. Am. Chem. Soc.* **2019**, *141*, 7473-7485