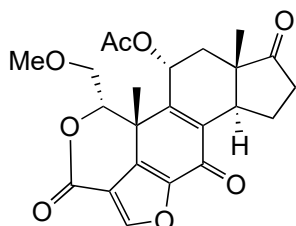


Problem session (1) Answer

2017/07/08 Yun-wei Xue

Topic: total synthesis of wortmannin

0. Introduction



wortmannin (0-1)

0-1. Isolation

from *penicillium wortmanni*

(Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Norris G. L. F. *Trans. Brit. Mycol. Soc.* **1957**, *40*, 365-368.)

0-2. Pharmacological activity

a. A potent and specific PI3K (phosphoinositide 3-kinase) inhibitor with a low nanomolar IC₅₀ value (Stephene, L. *Biochem. Soc. Trans.* **1995**, *23*, 207-221.)

b. A potent inhibitor of PLK1 (Polo-like kinase)

(Liu Y.; Shreder K. R.; Gai W.; Corral S.; Ferris D. K.; Rosenblum J. S. *Chem. Biol.* **2005**, *12*, 99-107.)

0-3. Structural feature

a. An allylic quaternary carbon center

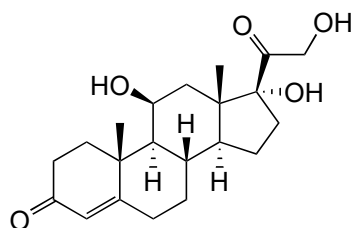
b. A furanovyclohexadienone lactone unit

0-4. Total synthesis

(±)-Wortmann from Hydrocortisone (0-2): Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Letters* **1996**, *37*, 6141-6144.

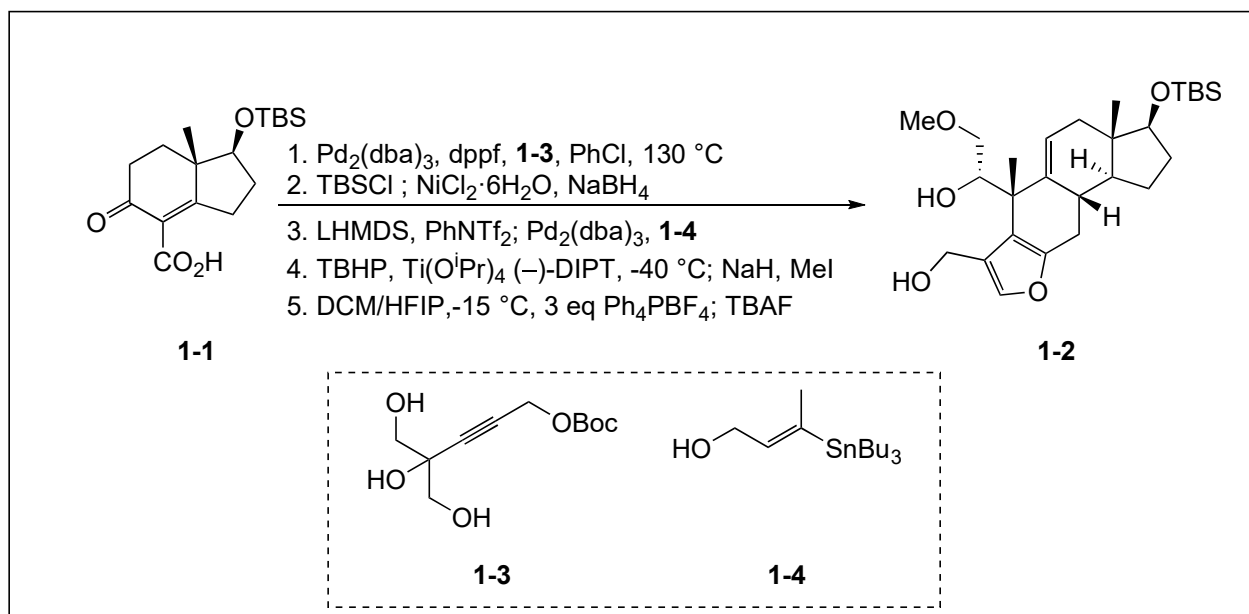
(±)-Wortmann: Mizutani, T.; Honzawa, S.; Tosaki S.-y.; Shibasaki M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4680-4682.

(+)-Wortmann: Guo, Y.; Quan, T.; Lu, Y.; Luo, T. *J. Am. Chem. Soc.* **2017**, *139*, 6815-6818.

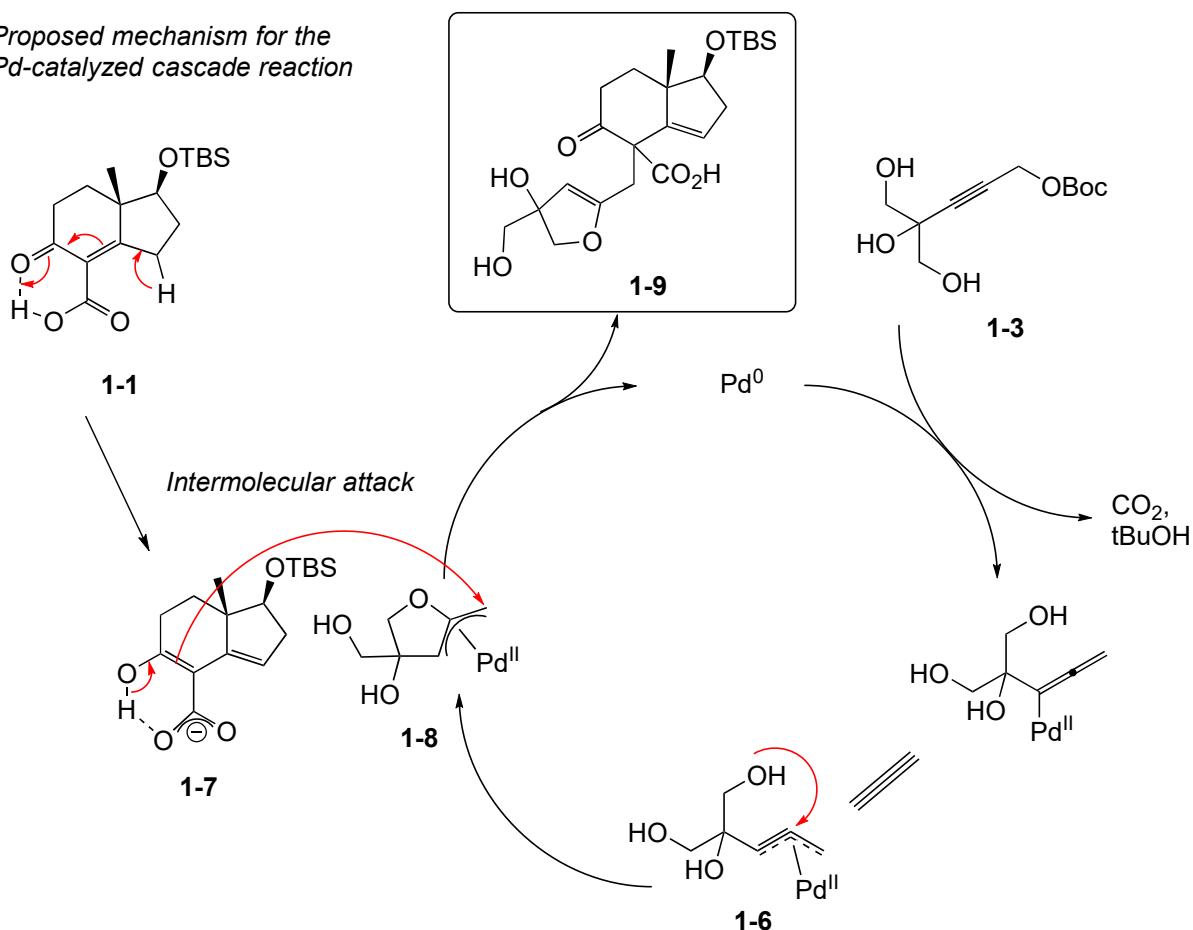


hydrocortisone (0-2)

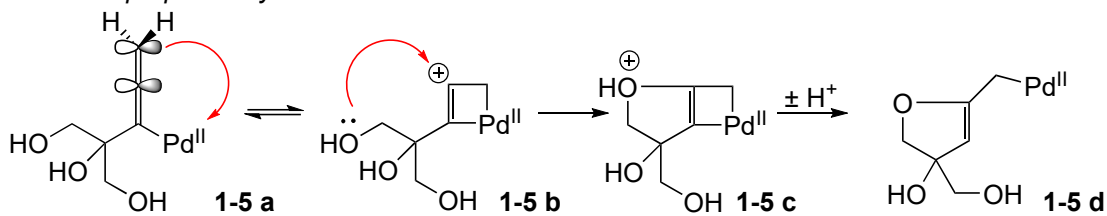
1-1. Reaction and mechanism

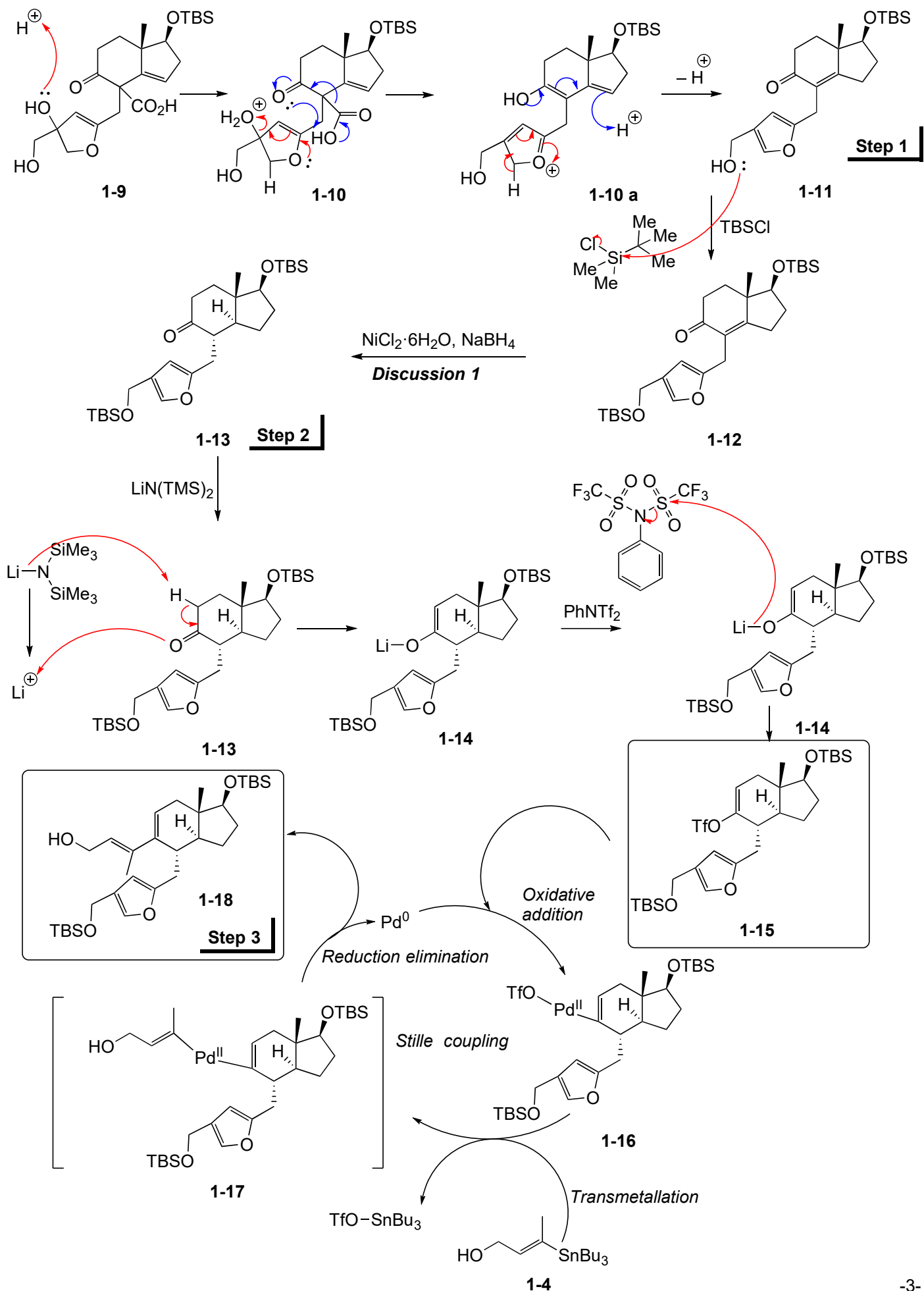


Proposed mechanism for the Pd-catalyzed cascade reaction

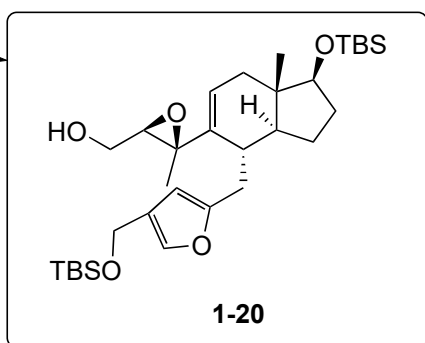
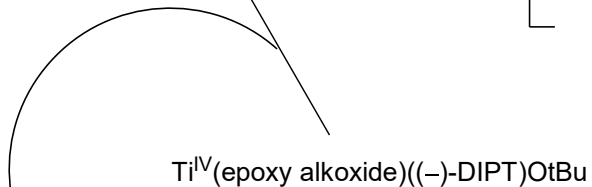
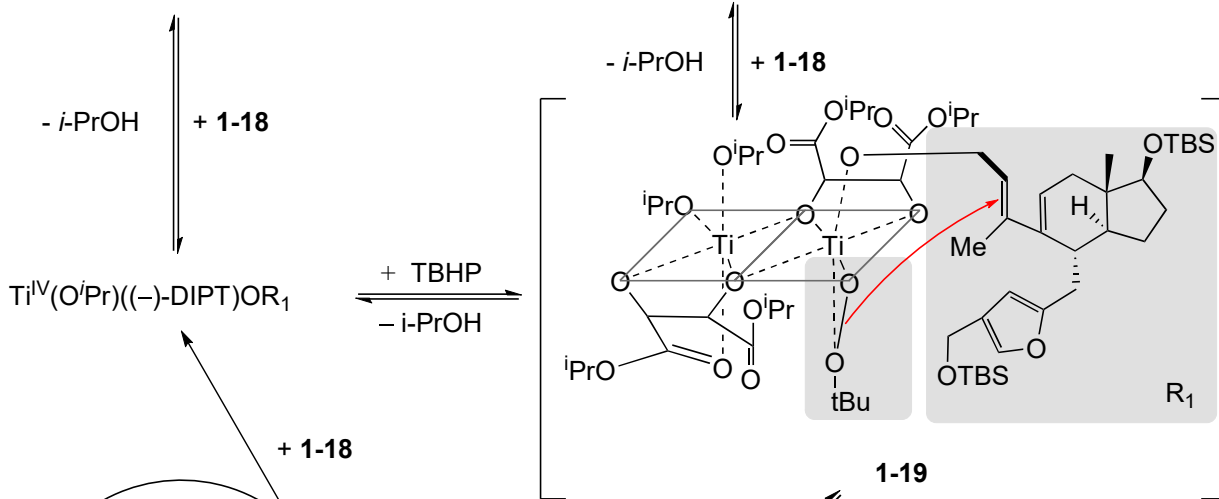
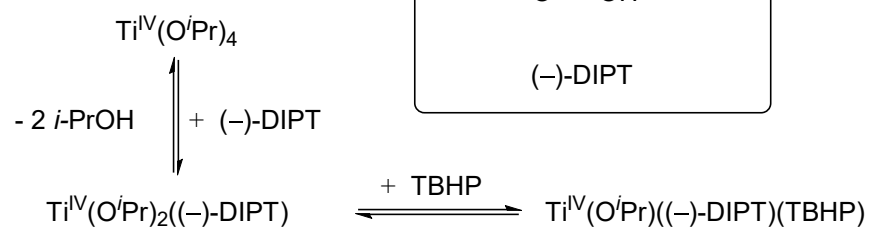
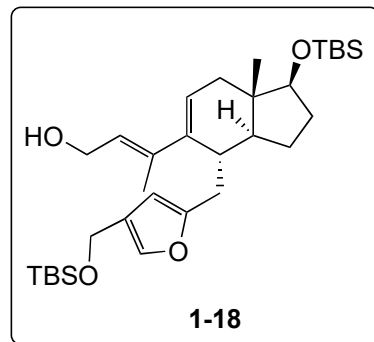
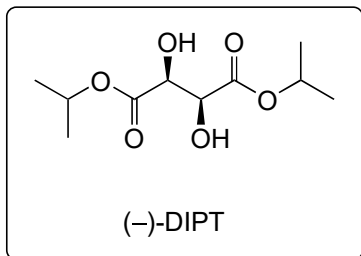


Mechanism proposed by Mutoh-san:

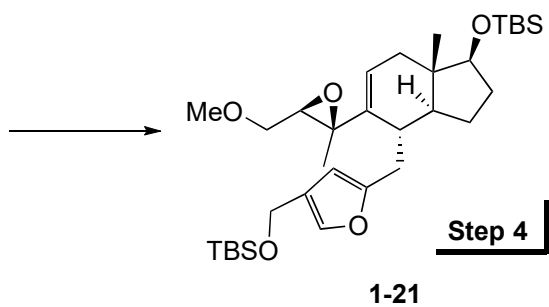
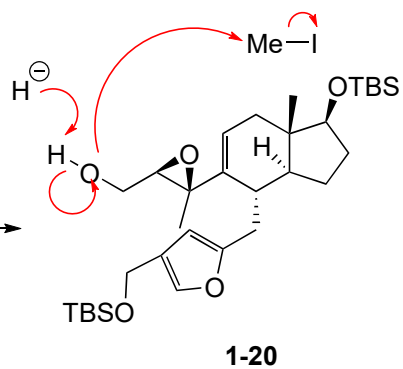


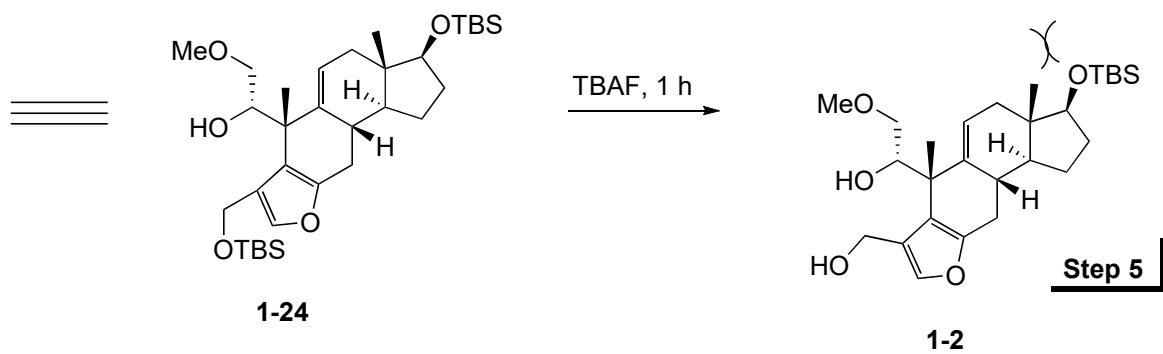
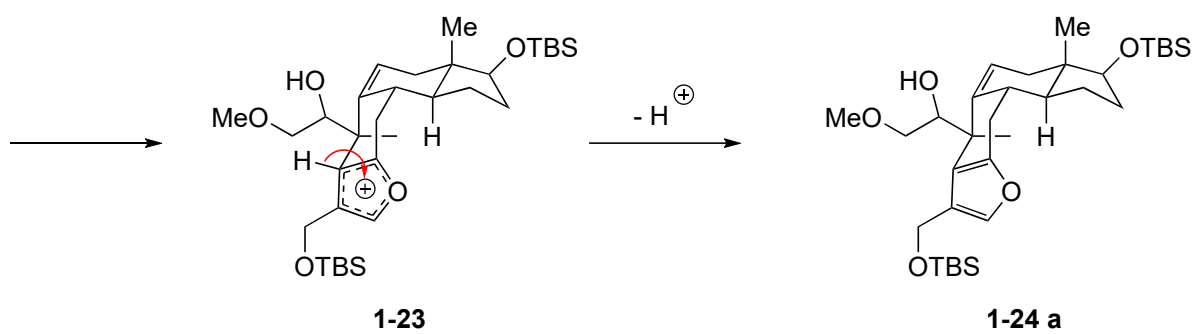
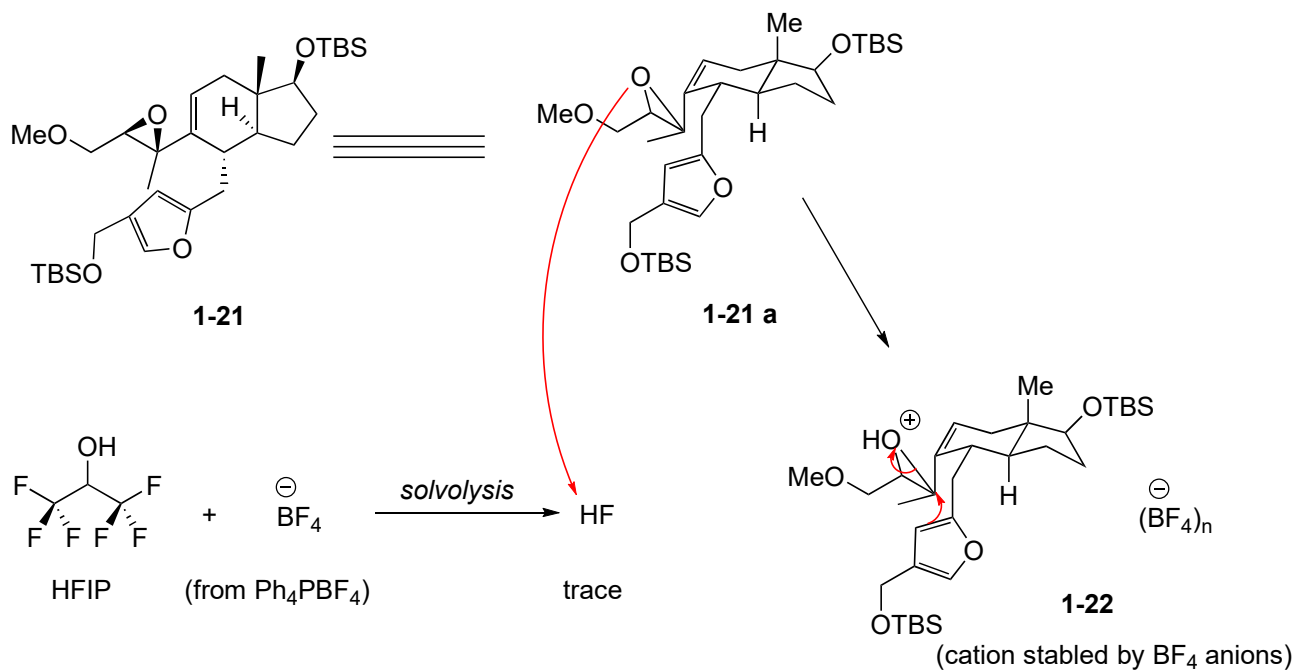


Sharpless asymmetric epoxidation



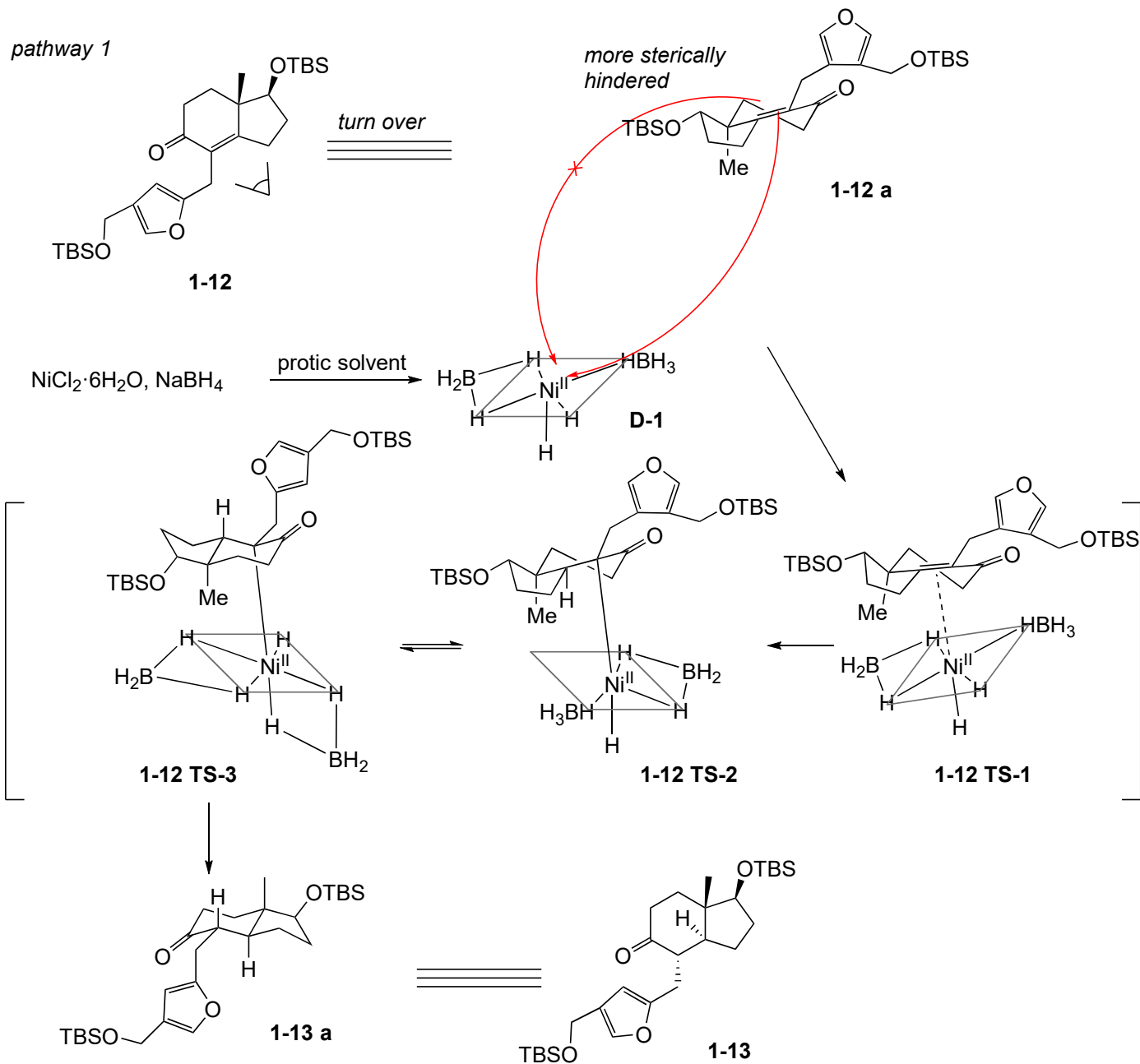
NaH, MeI



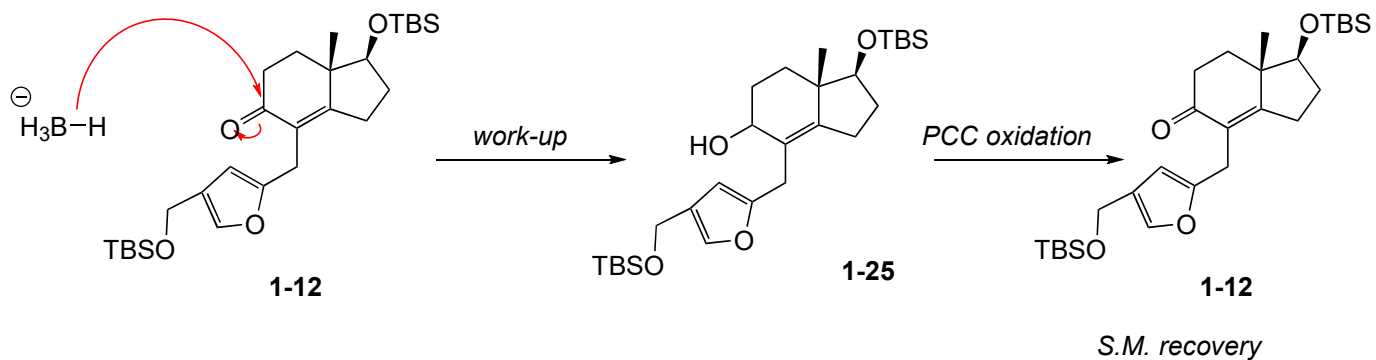


selectivity due to kinetic control and steric hindrance

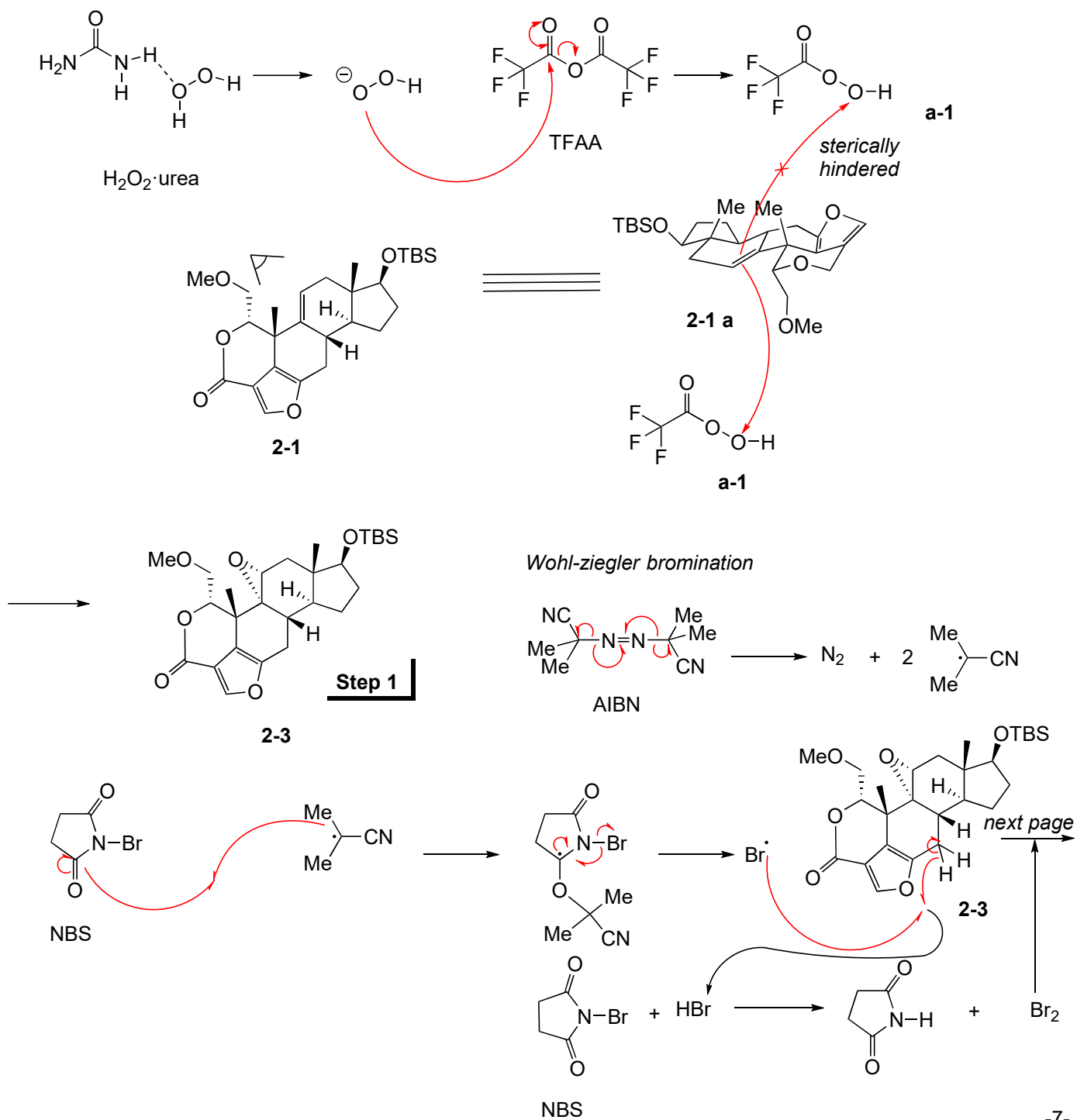
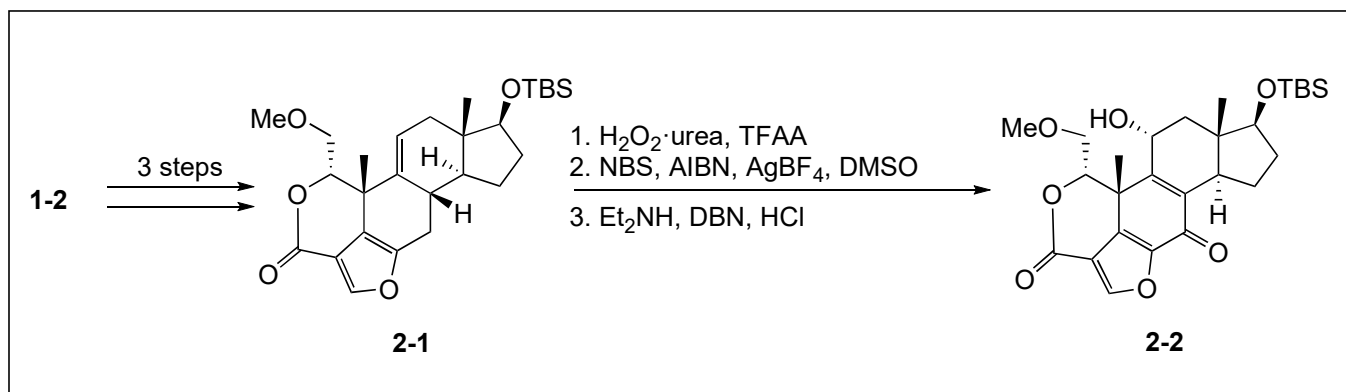
1-2 Discussion 1 Stereoselective reduction

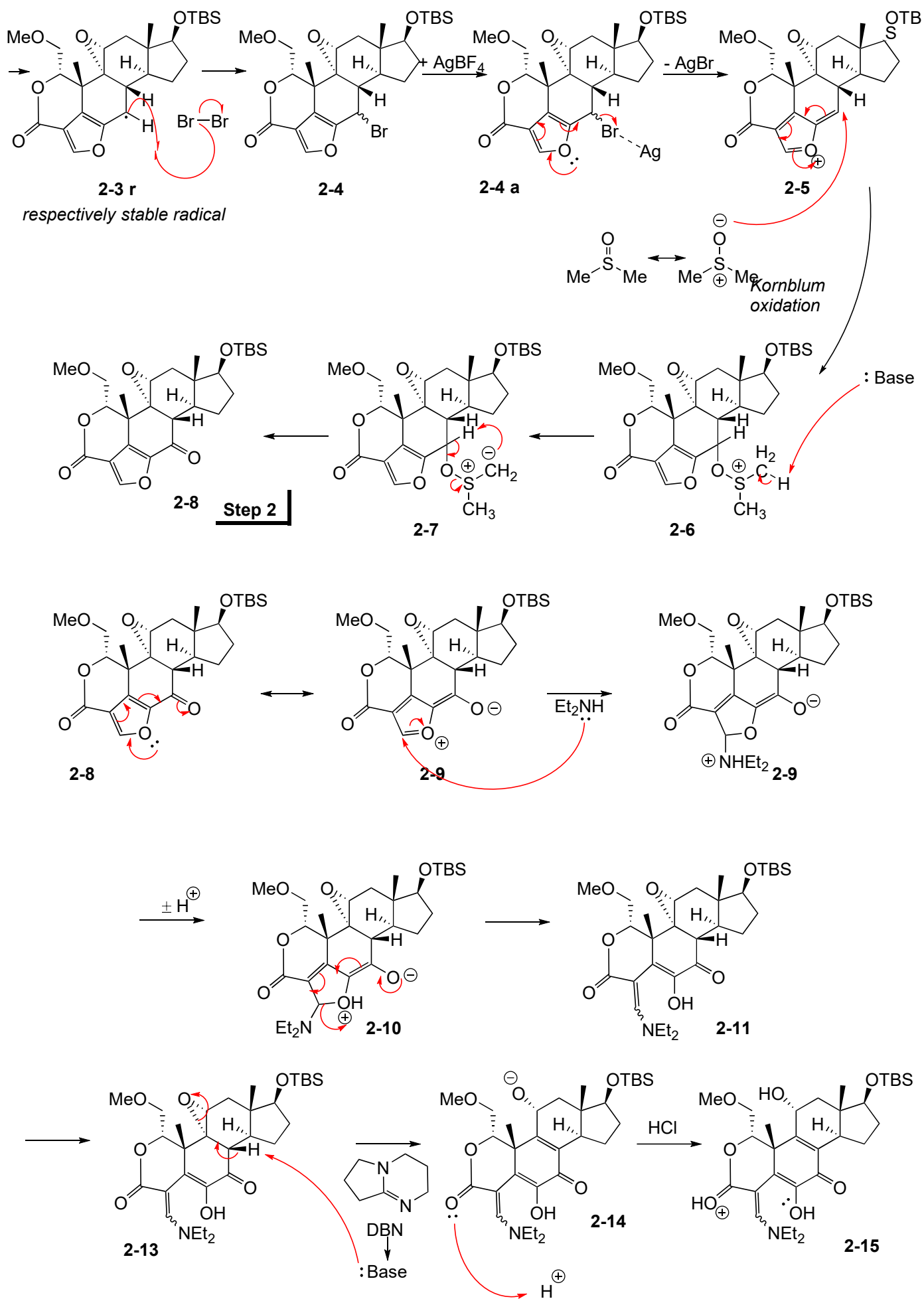


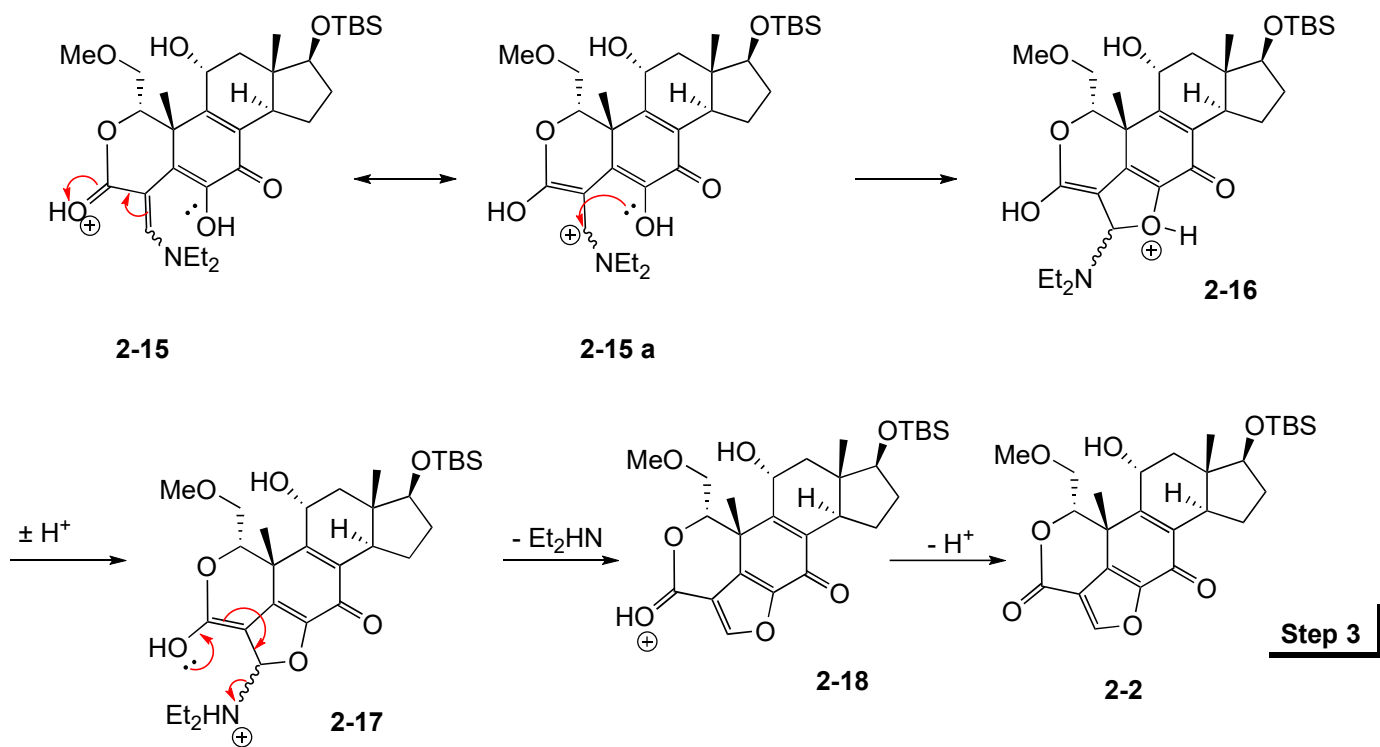
pathway 2 (1,2-reduction)



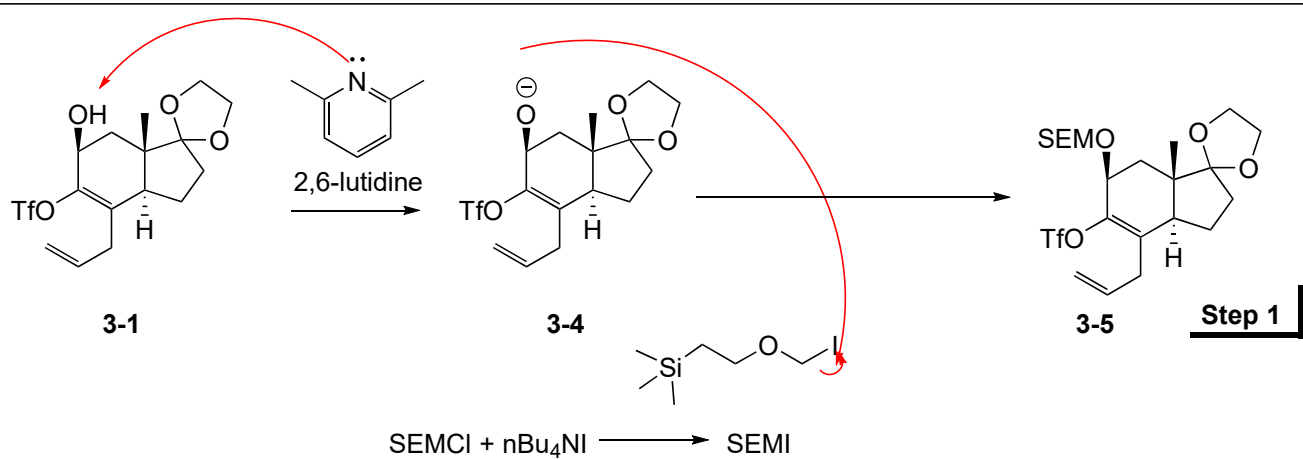
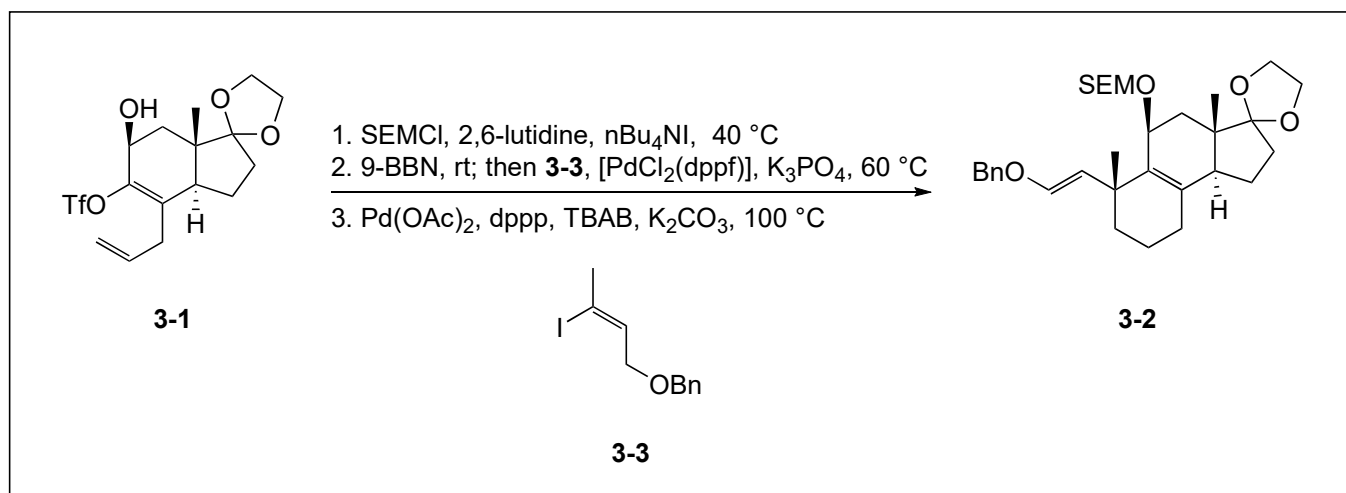
2-1. Reaction and mechanism

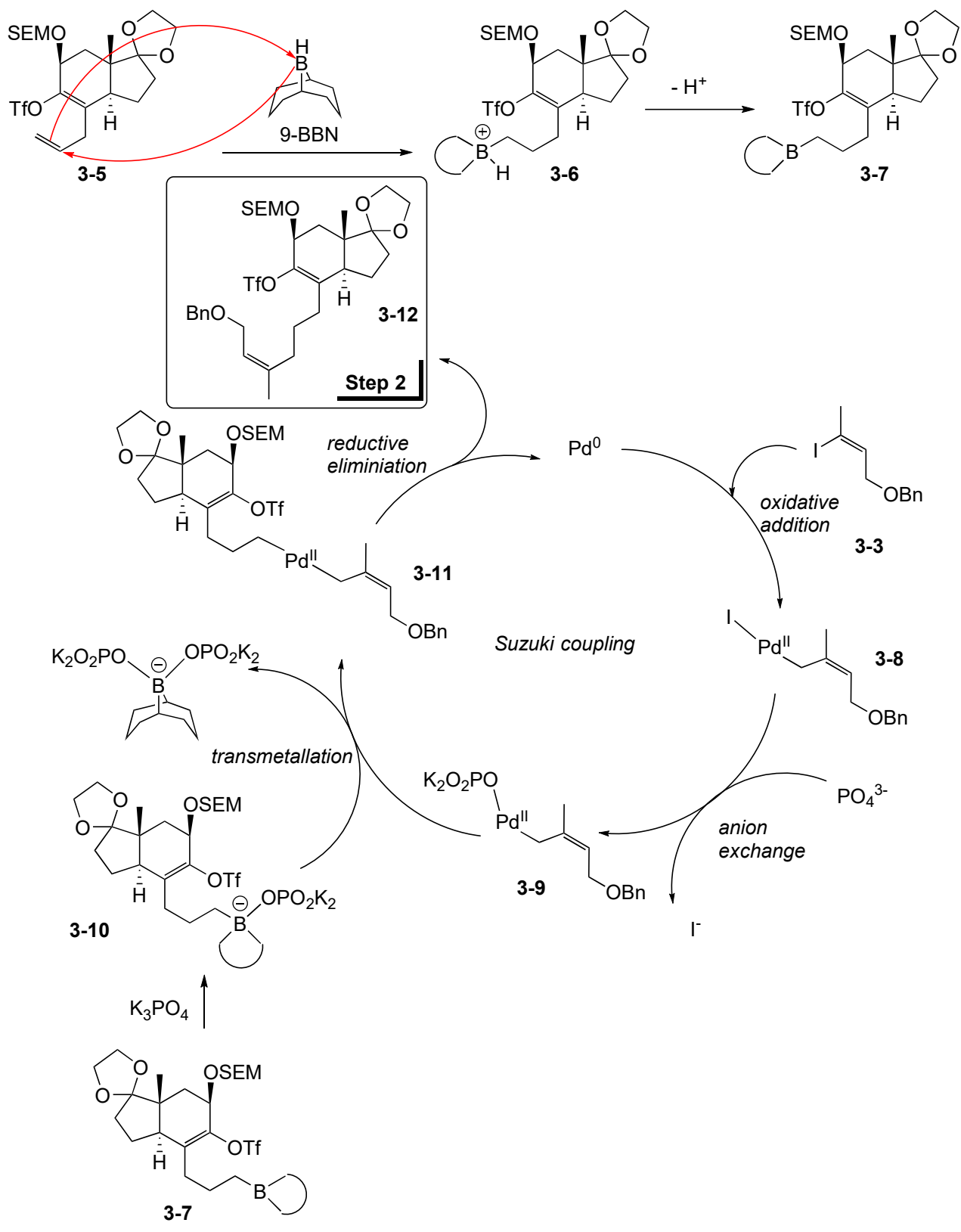


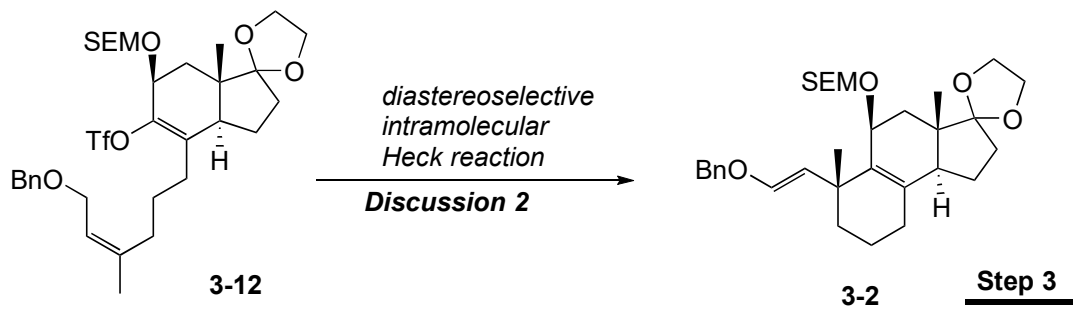




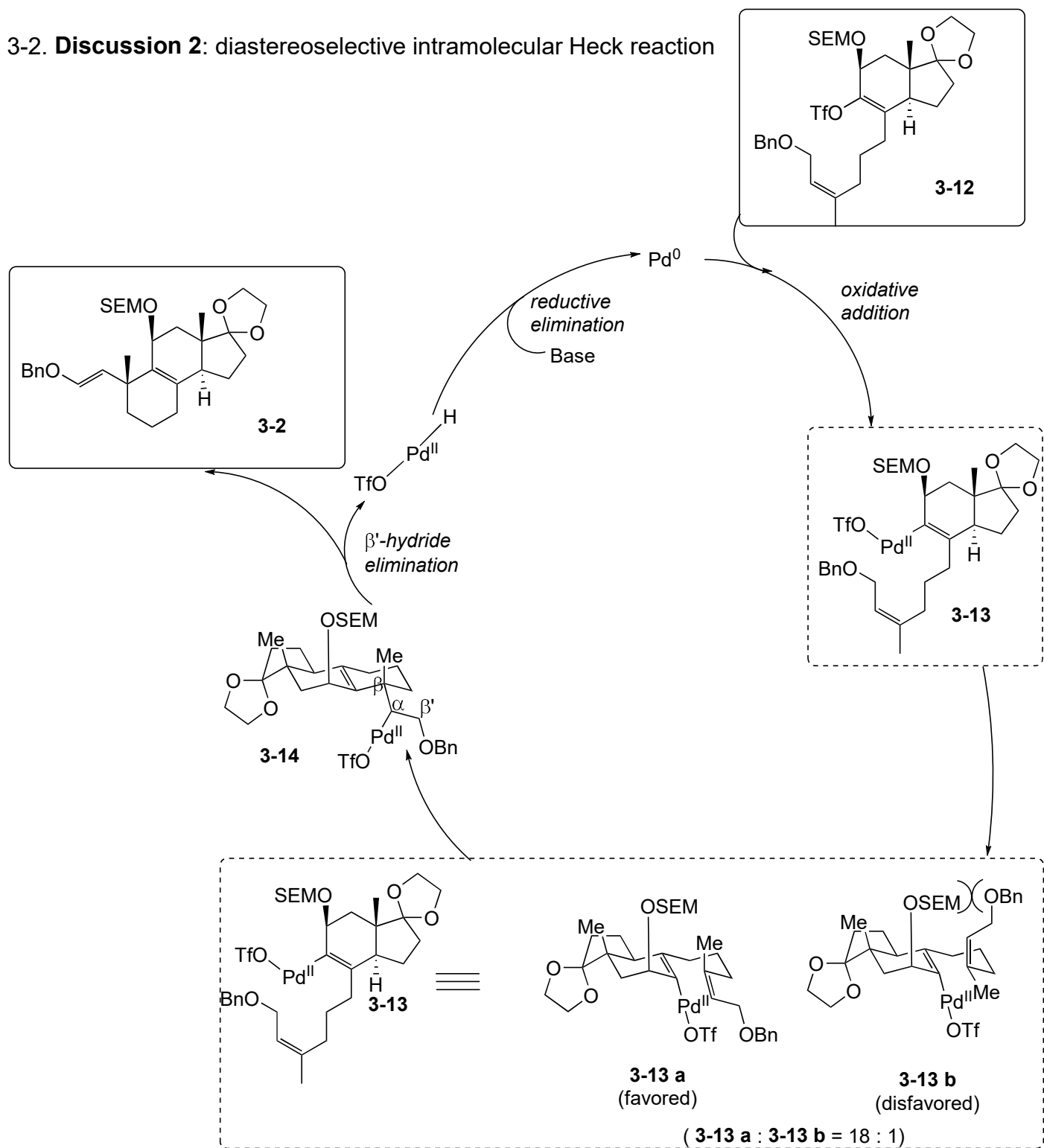
3-1. Reaction and mechanism





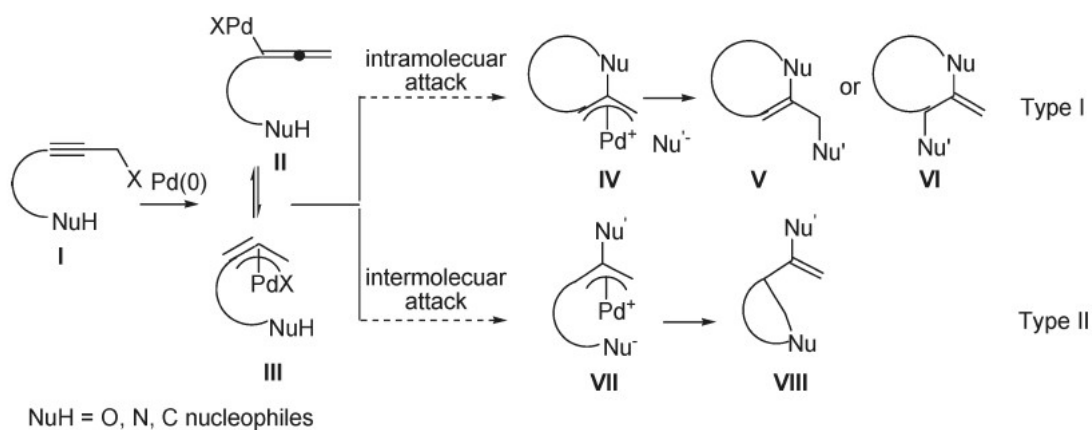


3-2. **Discussion 2**: diastereoselective intramolecular Heck reaction



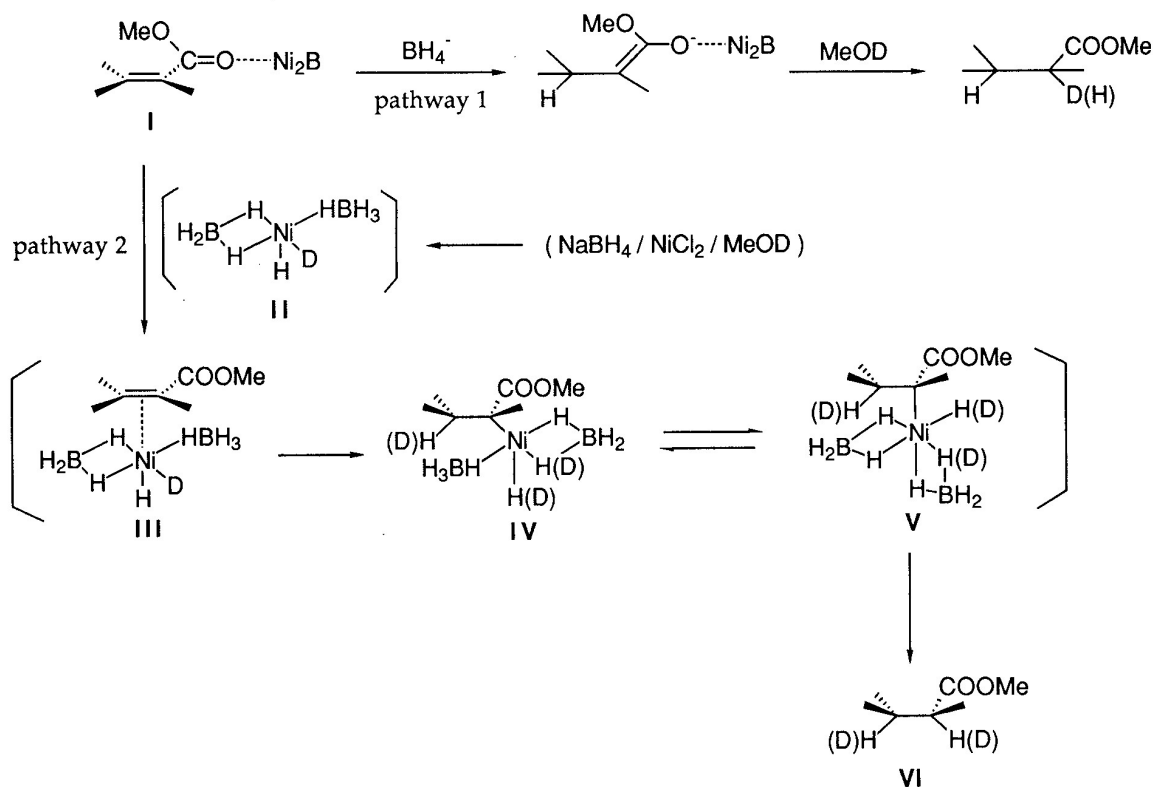
4. Appendix

4-1. The cyclization of functionalized propargylic compounds with nucleophile

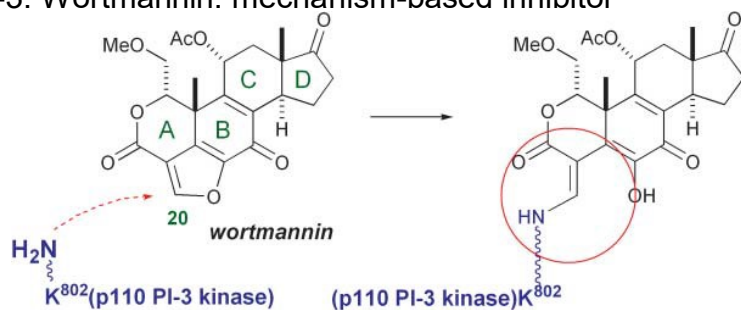


(Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111.)

4-2. Reduction with the $\text{Ni}^{2+}/\text{BH}_4^-$ system



4-3. Wortmannin: mechanism-based inhibitor



(Wipf, P.; Halter, J. H. *Org. Biomol. Chem.* **2005**, *3*, 2053.)