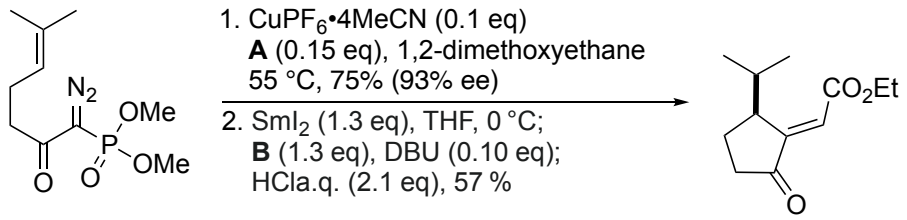
Problem Session (2) -Answer-

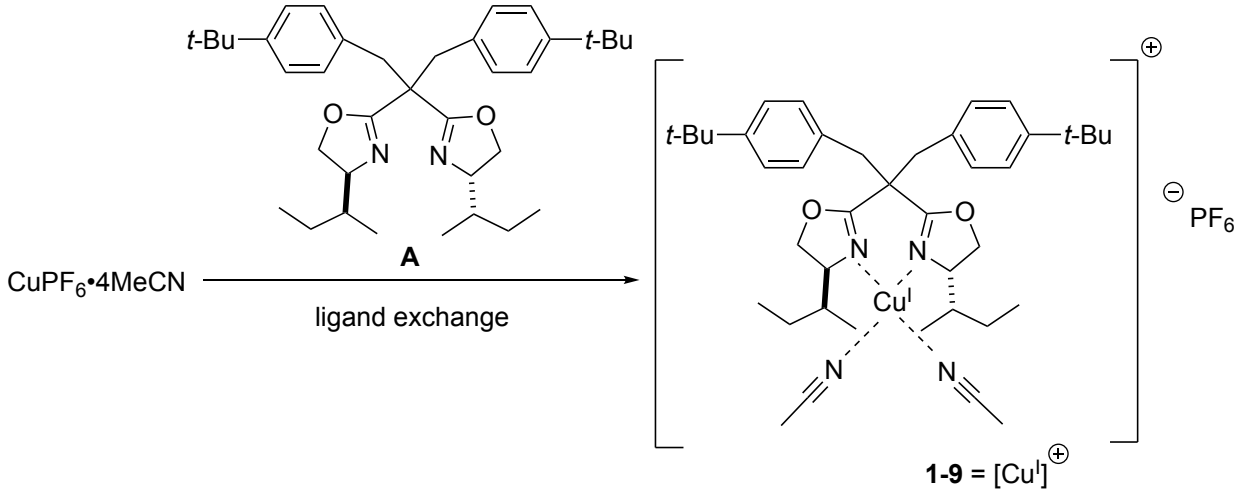
2023/11/18 Takahiro Migita

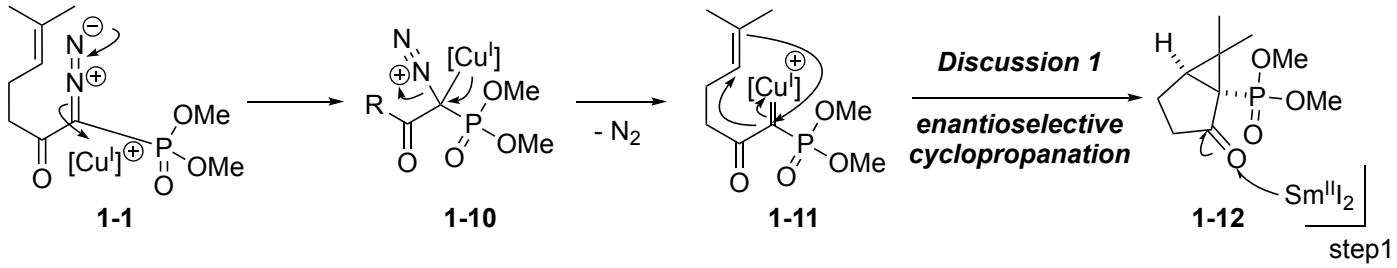
Topic: Total Syntheses of Vulgarisins

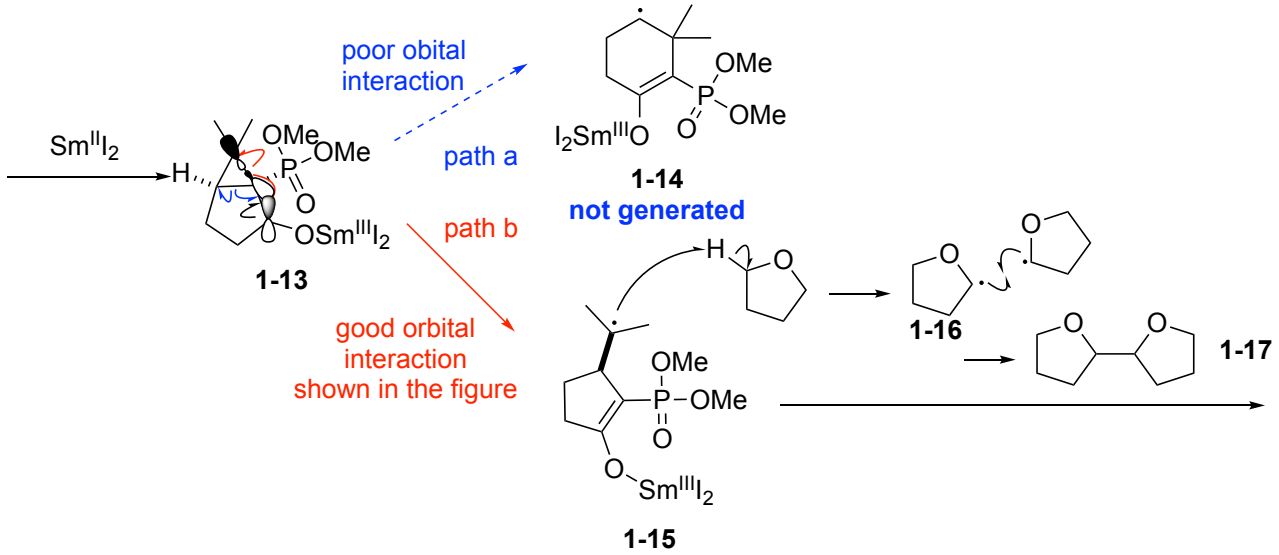
Xu, K.; Mu, S.; Rao, H.; Hu, J.; Ding, H. *Angew. Chem. Int. Ed.* **2023**, e202303668.

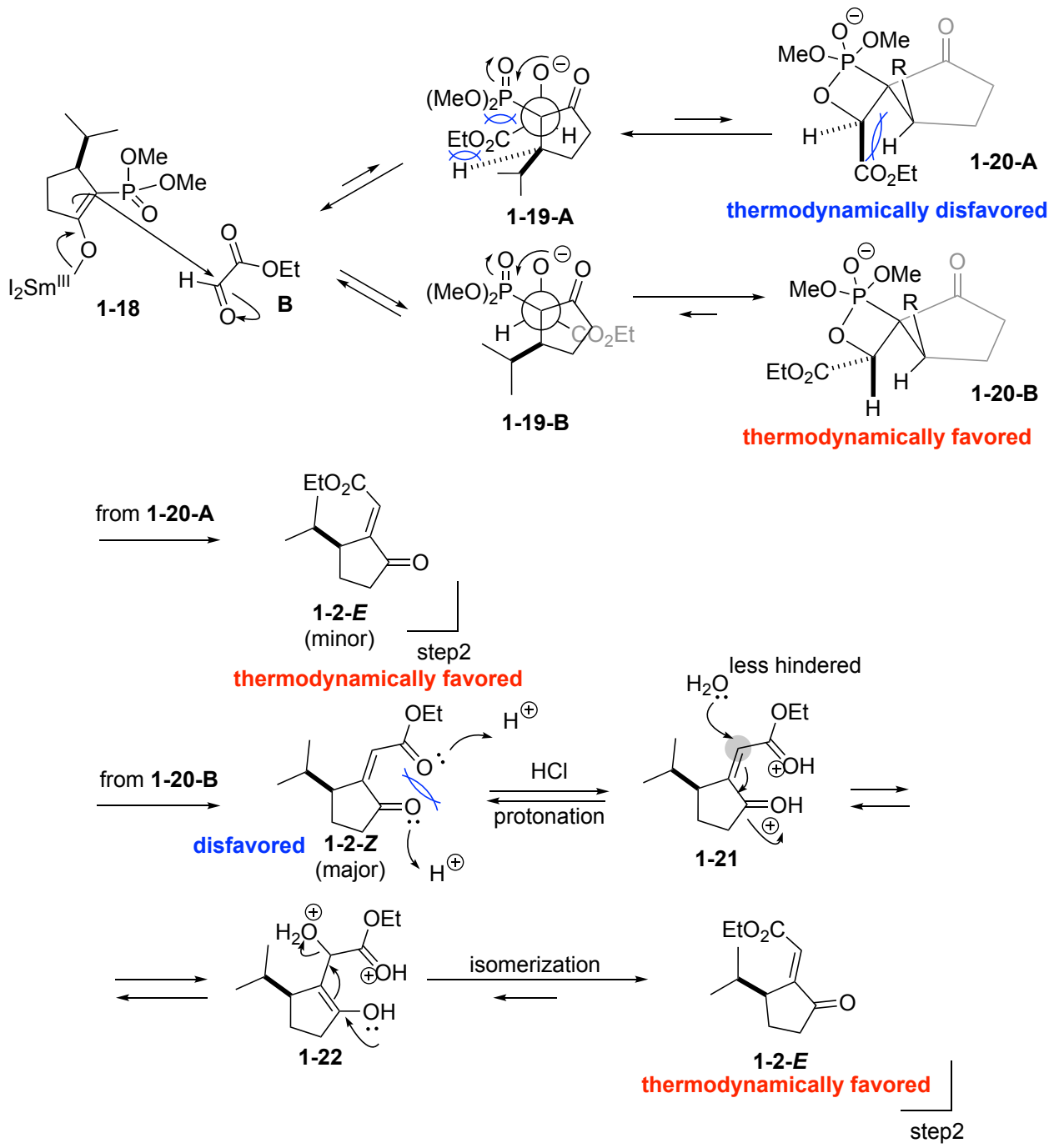
1. Intramolecular enantioselective cyclopropanation



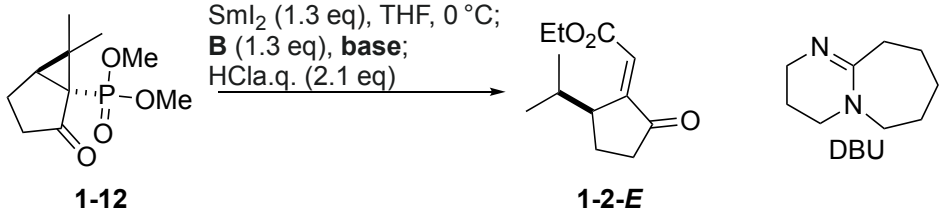








***Role of DBU**: DBU catalytically inhibited the protonation of enolate **1-16** during HWE reaction.

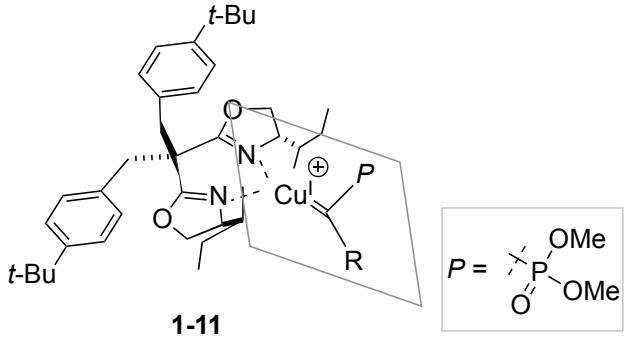


base	yield
none	25%
DBU (0.1 eq)	57%

The reaction proceeded even without DBU, which indicates DBU was not essential, but it helps the reaction progress.

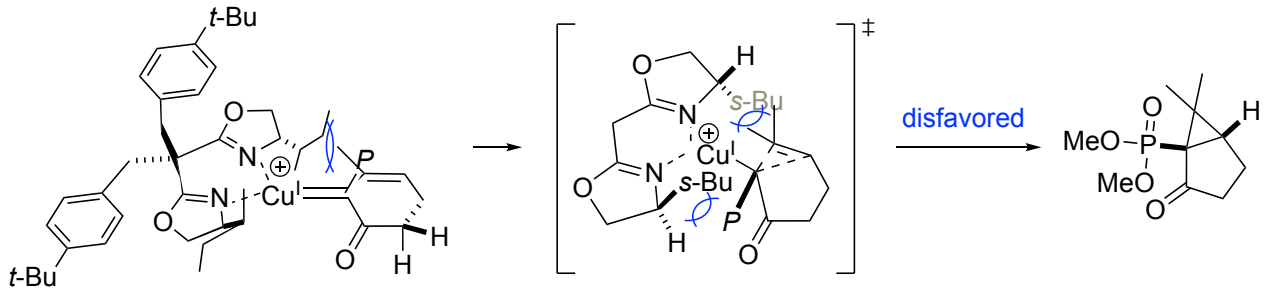
Discussion 1: Intramolecular enantioselective cyclopropanation[ref1]

In order to avoid steric repulsion, the conformation of **1-11** should be the one shown below.

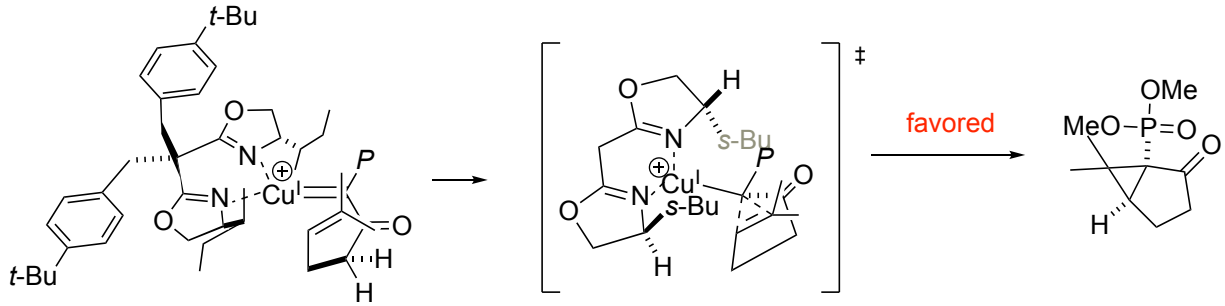


1-11

<generation of **1-12**>

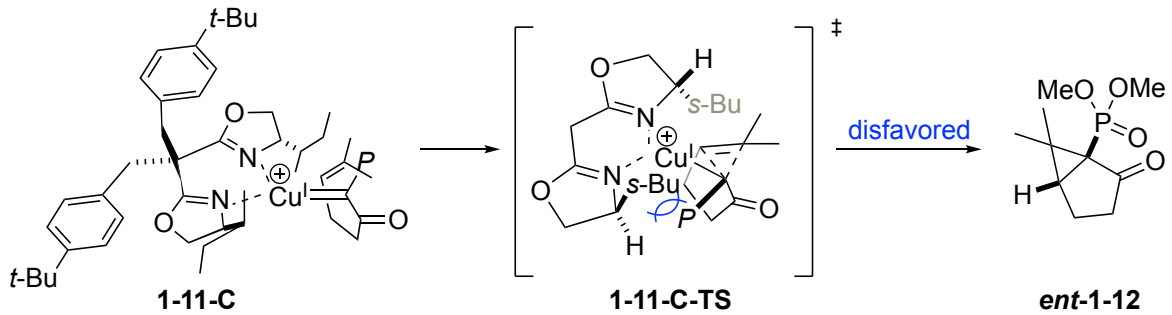


1-11-A **1-11-A-TS** **1-12**

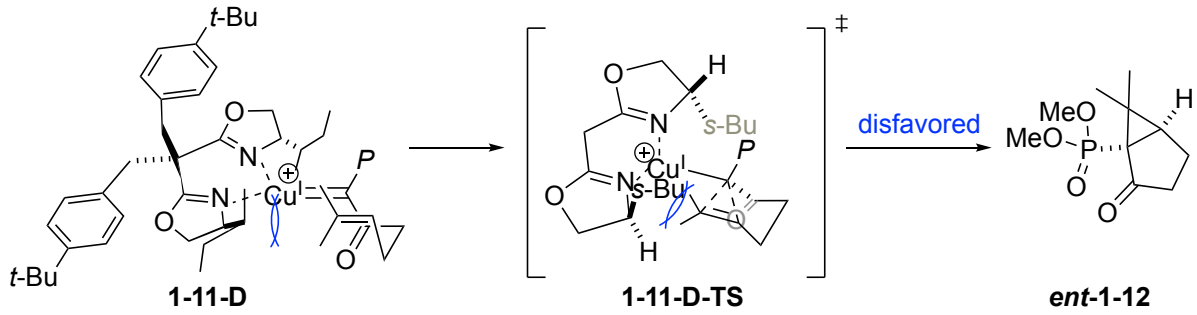


1-11-B **1-11-B-TS** **1-12**

<generation of ***ent*-1-12**>

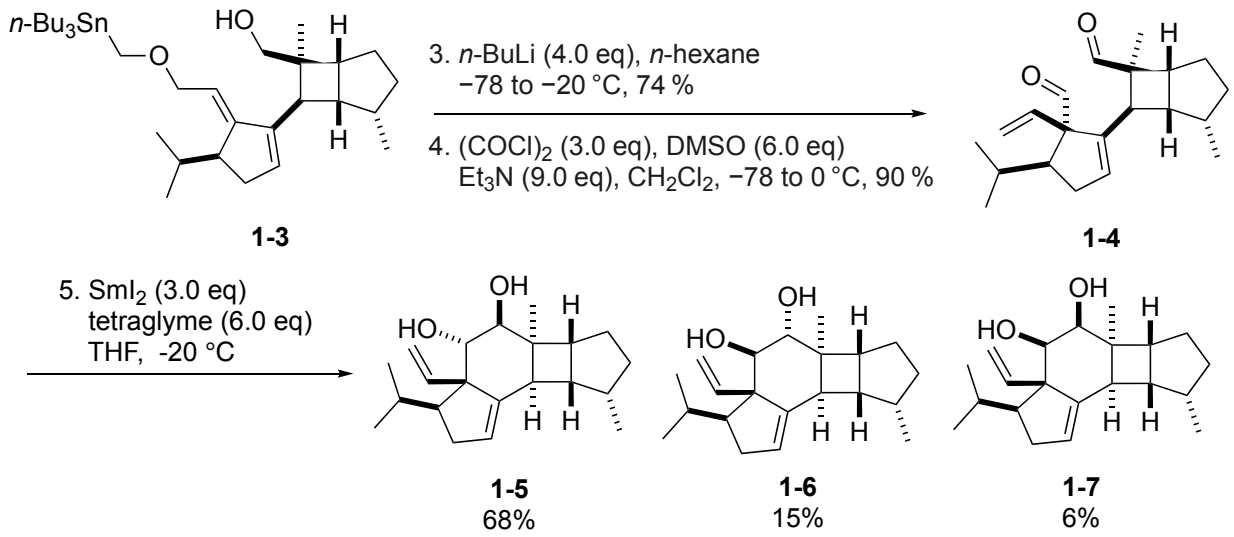


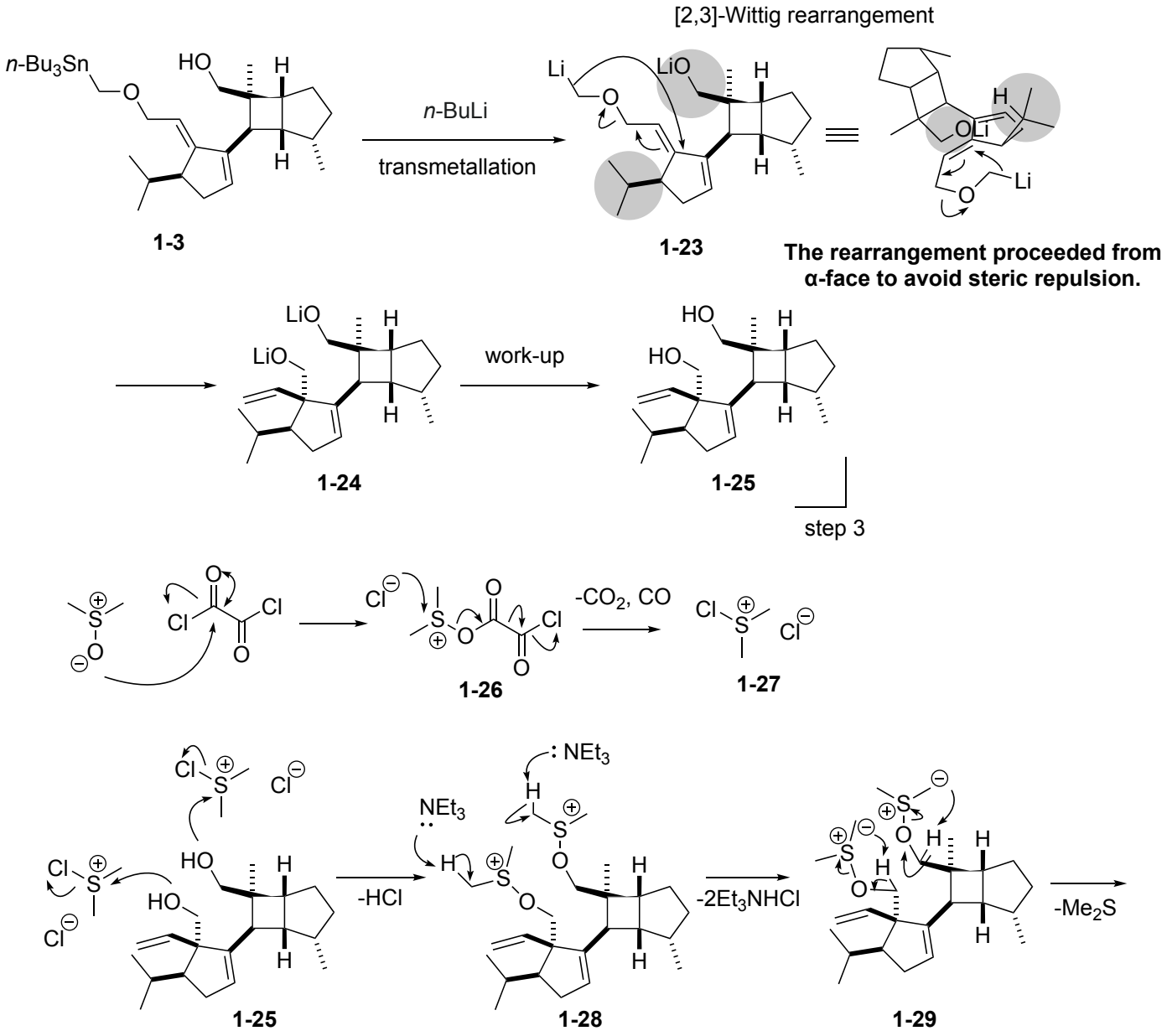
1-11-C **1-11-C-TS** ***ent*-1-12**

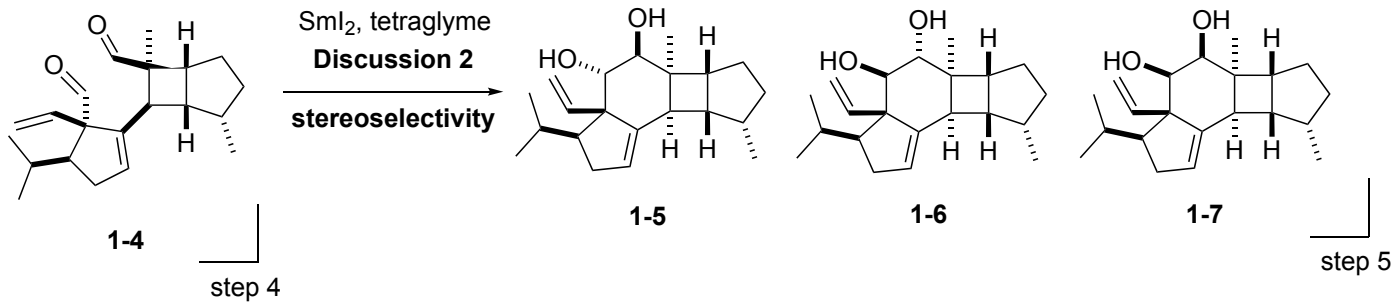


1-11-D **1-11-D-TS** ***ent*-1-12**

2. Pinacol coupling



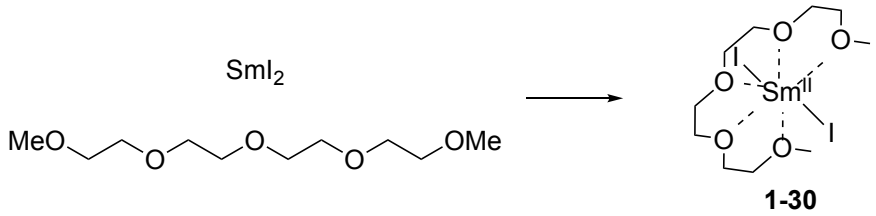




Discussion 2: Stereoselectivity of pinacol coupling [ref 2]

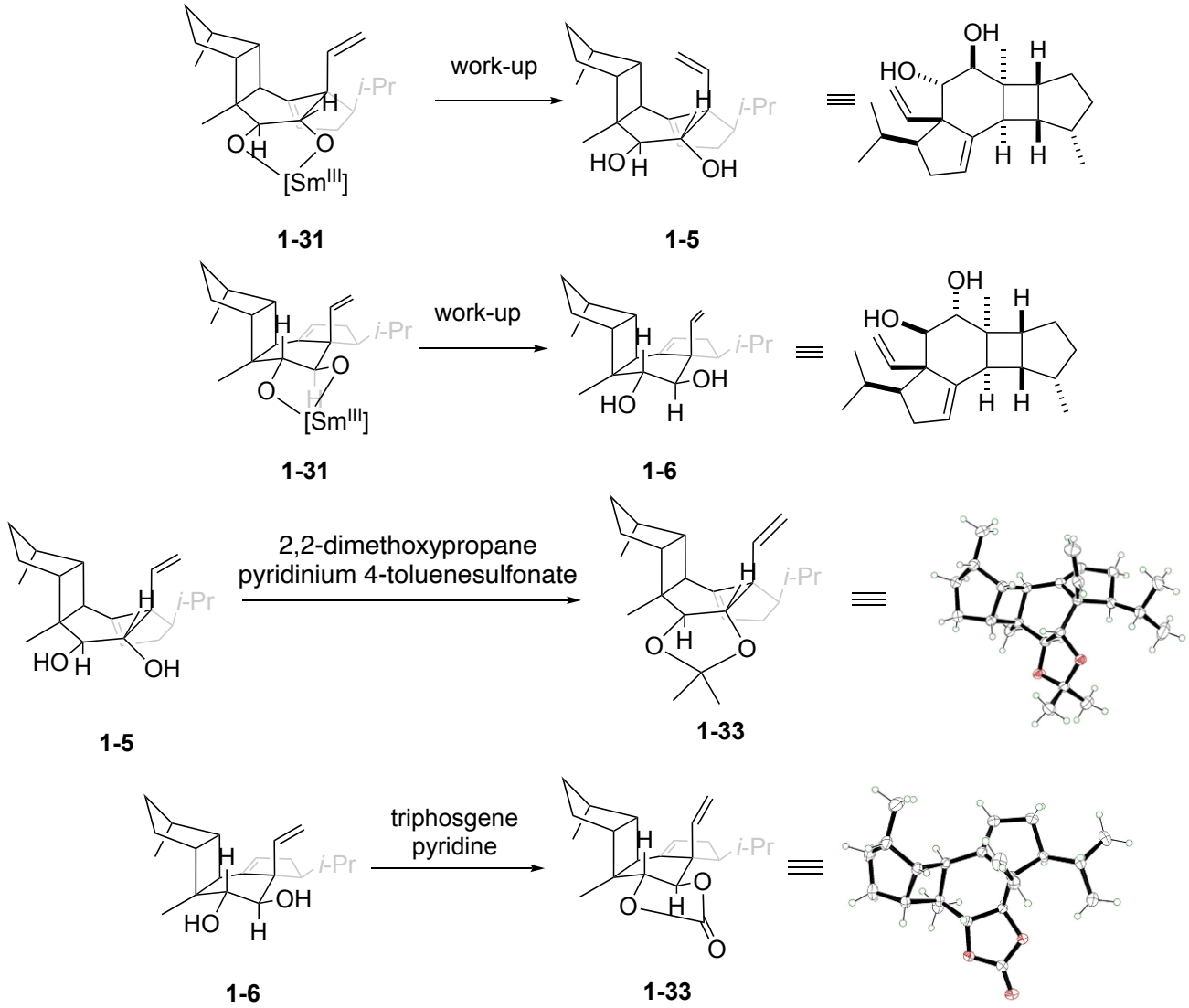
- Role of tetraglyme

Tetraglyme is utilized as a ligand to achieve stereoselectivity by forming bulky complex **1-30** with SmI_2.

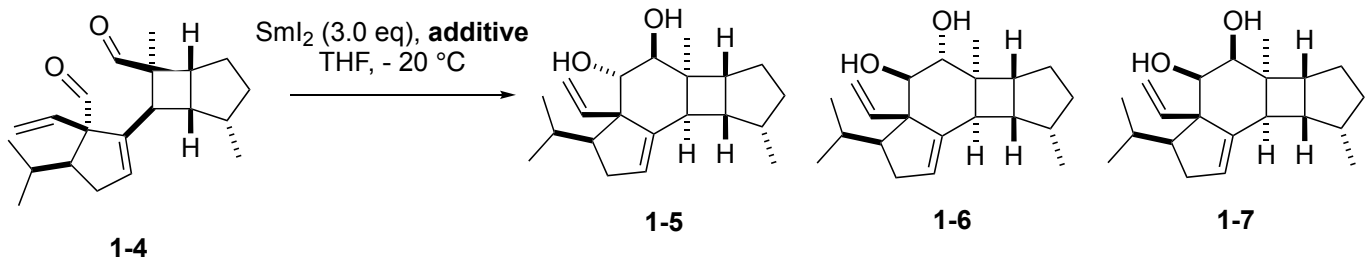


- Stereoselectivity

The authors' opinion: **1-5** was produced through half-chair like conformation **1-31** and **1-6** generated via chair-like conformation **1-32** based on the X-ray structure of **1-33** and **1-34**. The selectivity is controlled by the steric repulsion between Sm complex and *i*-Pr group.



However, **1-31** and **1-32** does not seem to have differences in their steric repulsion to explain the stereoselectivity, which does not match the result of experiment conducted without tetraglyme.

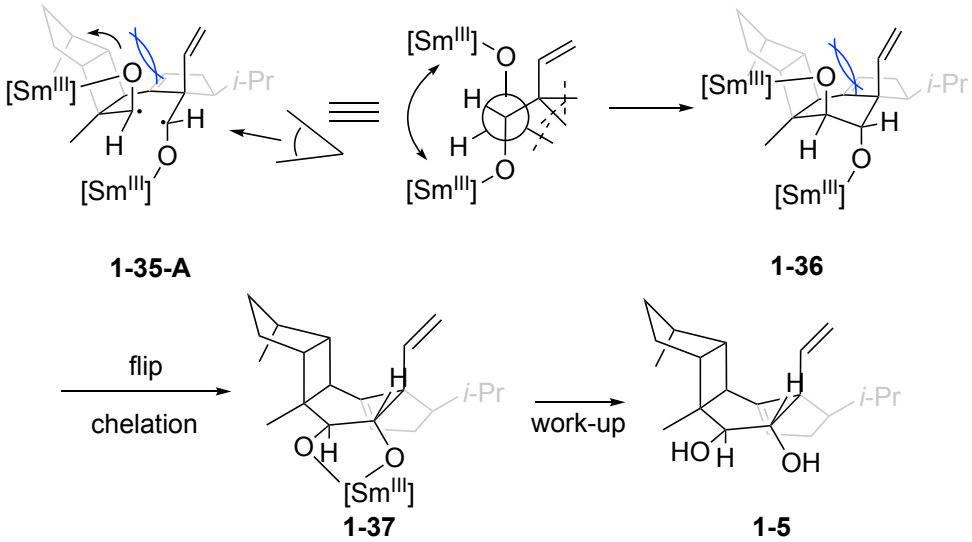


additive	yield of **1-5**	yield of **1-6**	yield of **1-7**
none	33%	24%	11%
tetraglyme (6.0 eq)	68%	15%	6%

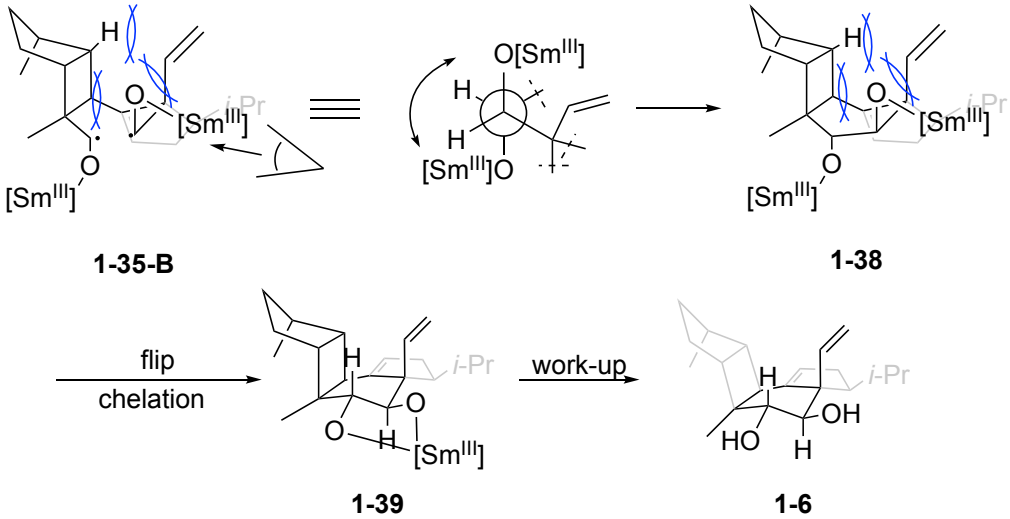
Thus, I propose that the reaction would begin with no-chelation species **1-35** (this mechanism is supported by the results of intermolecular pinacol coupling in ref2).

My opinion:

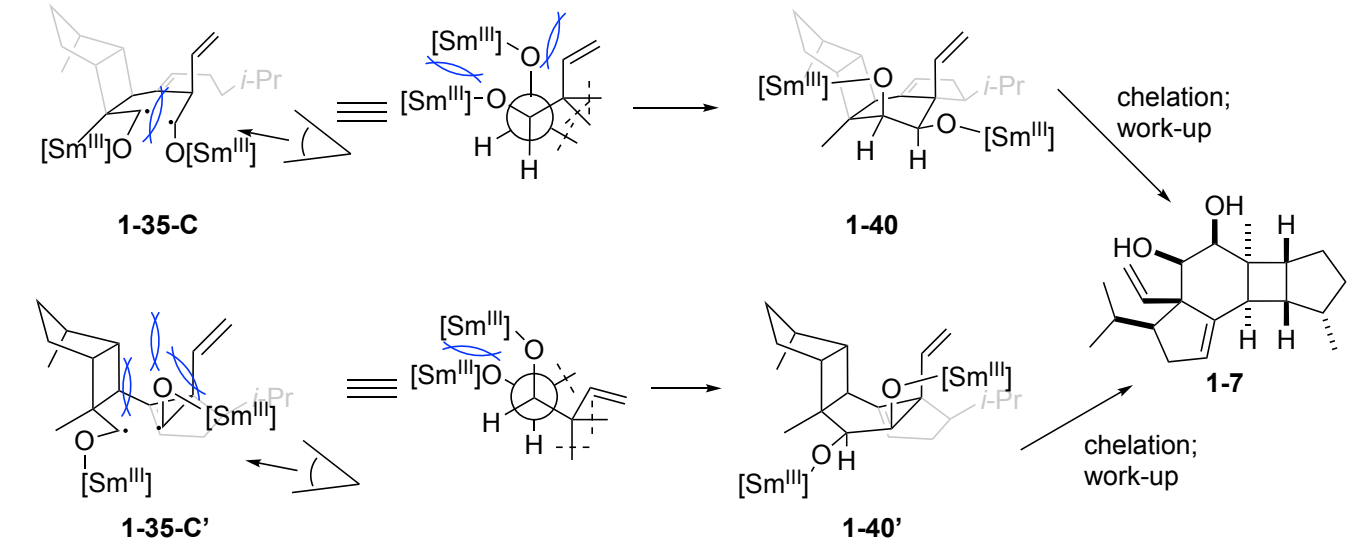
1-5 (major product): The cyclobutane ring is tilted to the outside, which leads to relatively small steric repulsion between the four-membered ring and neighbor Sm complex.



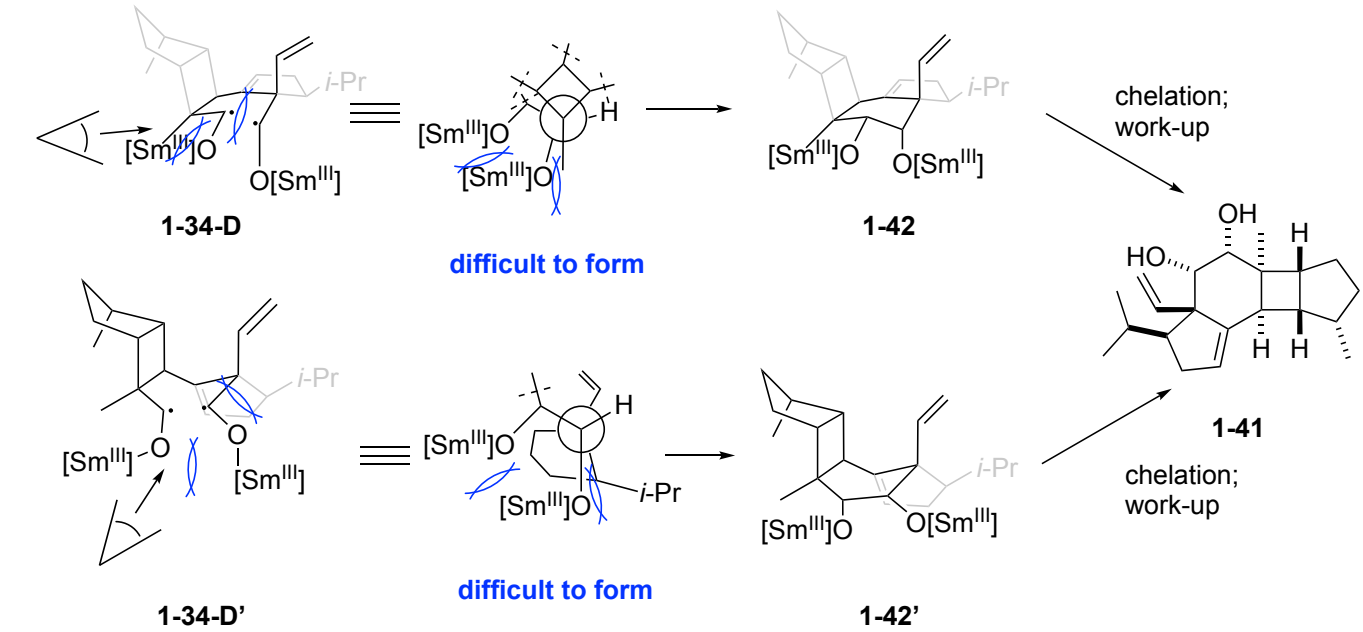
1-6 (minor product): The cyclobutane ring in **1-34-B** is closer to the vinyl group of the molecule than **1-34-A**, which generates larger steric repulsion.



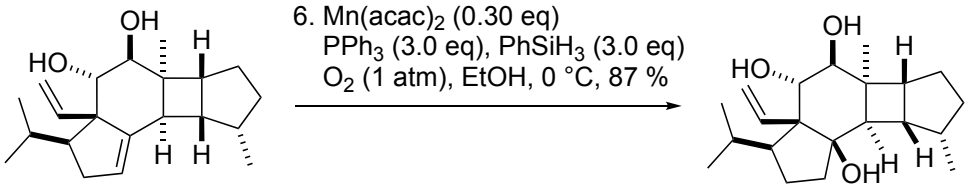
<1-7 (minor product)>

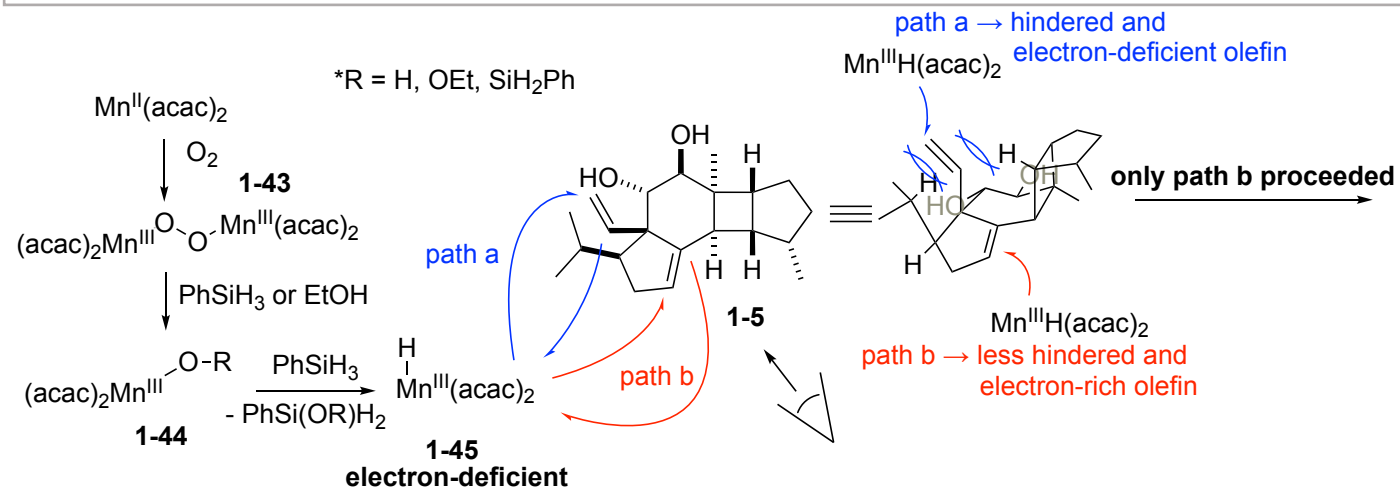


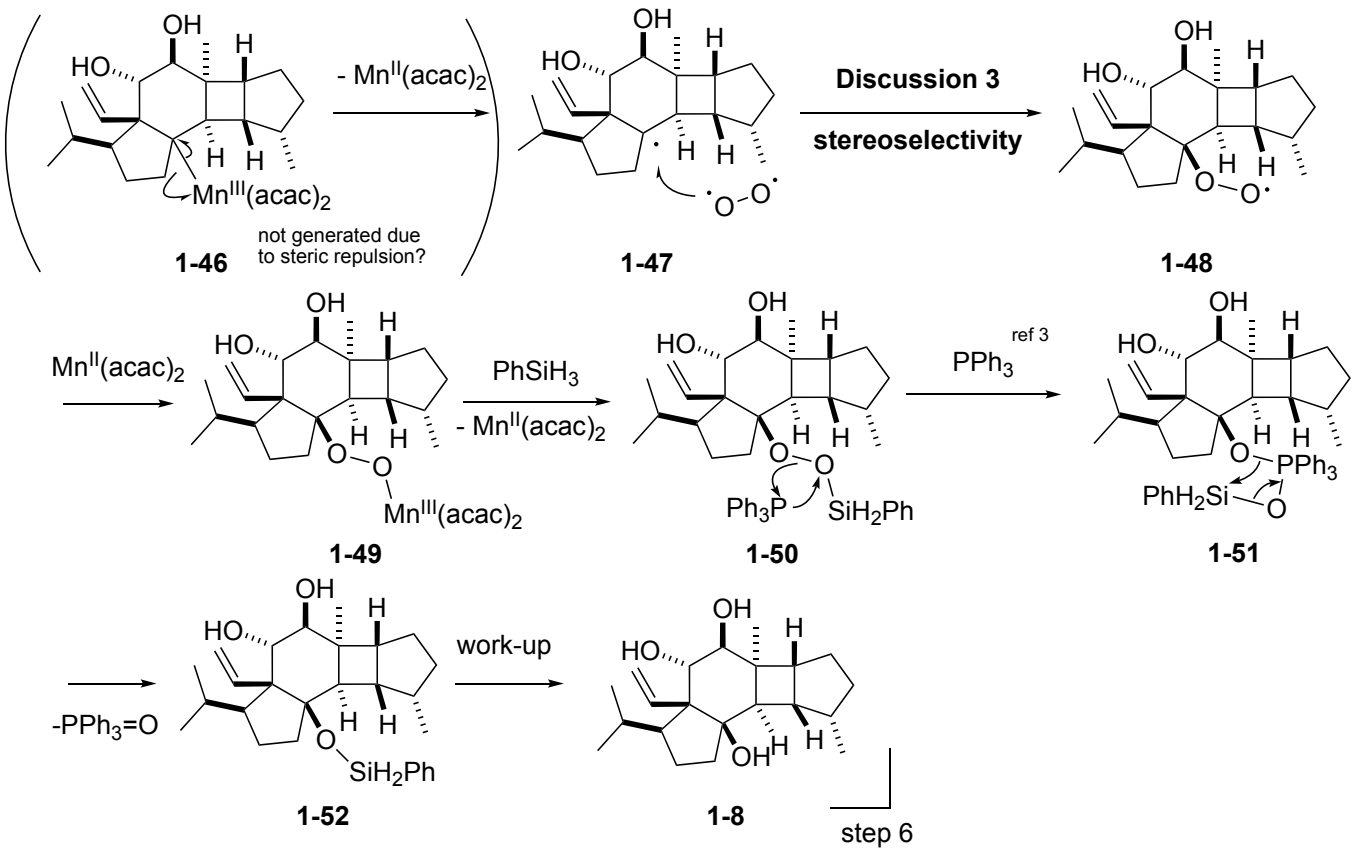
<1-41 (not observed)>



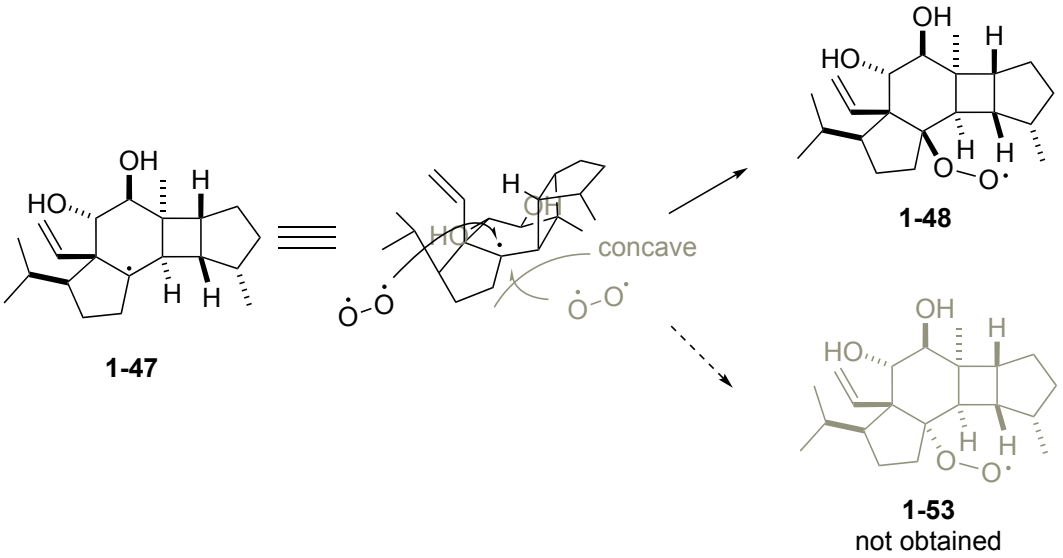
3. Mukaiyama hydration







Discussion 3: Stereoselectivity



References: (1) (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860. (b) Fraile, J. M.; García, J. I.; Martínes-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616. (2) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919. (3) Harris, J. R.; Haynes, M. T.; Thomas, A. M.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 5083.