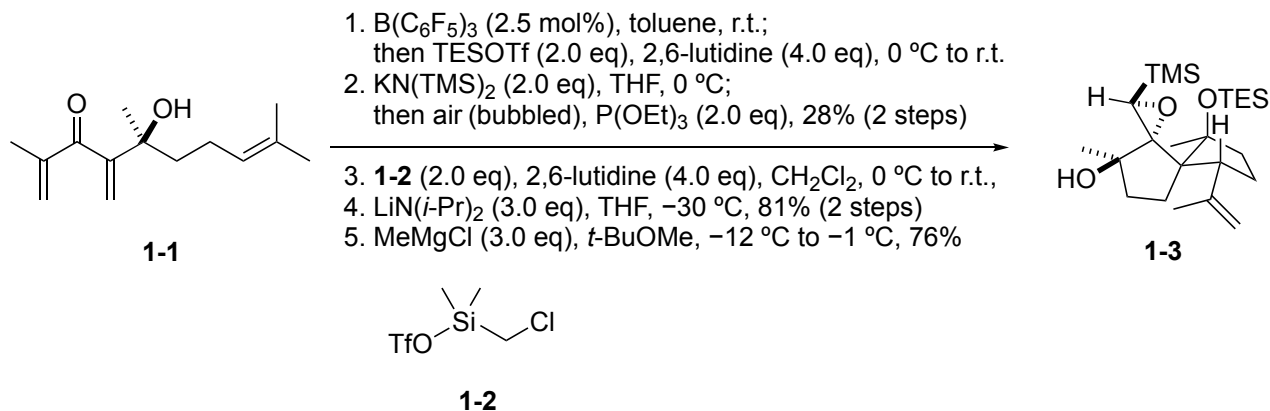


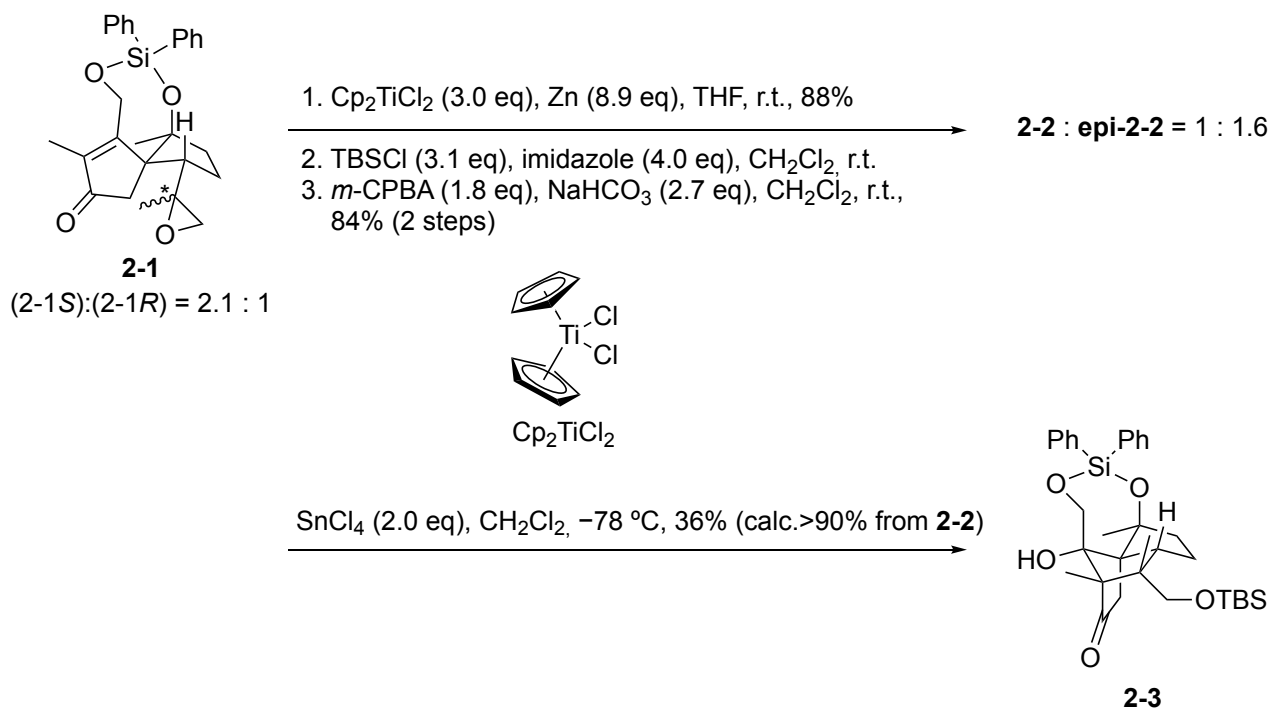
# Problem session (1)

2023/09/09 Takuya Ishii

(1) Please provide the reaction mechanism and explain the stereoselectivity



(2) Please provide the reaction mechanism and explain the stereoselectivity



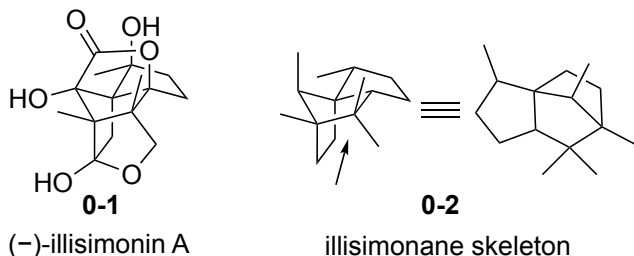
# Problem Session (1) -Answer-

2023/09/09 Takuya Ishii

Topic: Asymmetric Total Synthesis of Illisimonin A  
Etling, C.; Tedesco, G.; Di Marco, A.; Kalesse, M.  
*J. Am. Chem. Soc.* **2023**, *145*, 7021-7029.

## 0. Introduction

### 0-1. Outline of Illisimonin A



Isolation: the fruits of *illicium simonsii*

Structural features:

unprecedented illisimonane skeleton

bridged tricyclo[5.2.1.0<sup>1,5</sup>]decane ring system

*trans*-pentalene

norbornane substructure

cage-like 5/5/5/5/5 pentacyclic structure

Ma, S.-G.; Li, M.; Lin, M.-B.; Li, L.; Liu, Y.-B.; Qu, J.; Li, Y.; Wang, X.-J.; Wang, R.-B.; Xu, S.; Hou, Q.; Yu, S.-S.  
*Org. Lett.* **2017**, *19*, 6160–6163.

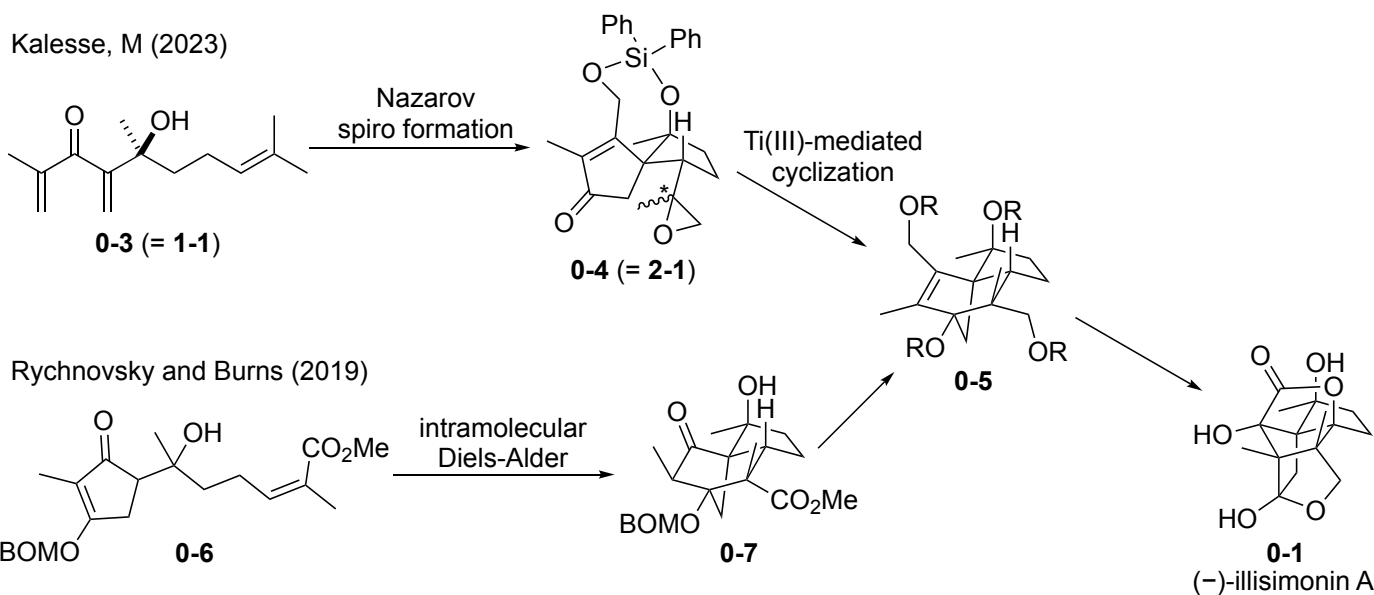
### 0-2. Previous Total Synthesis

Burns, A. S.; Rychnovsky, S. D.

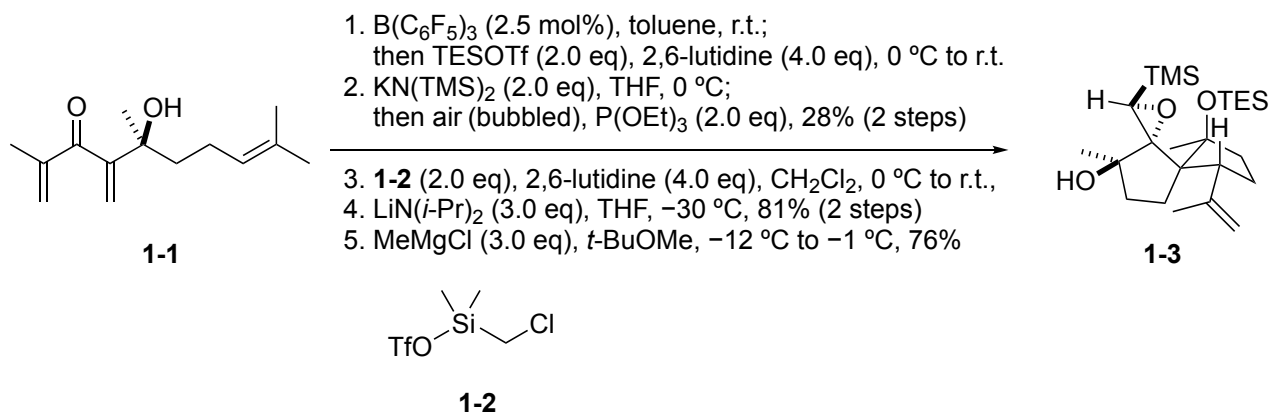
*J. Am. Chem. Soc.* **2019**, *141*, 13295–13300.

### 0-3. Their Approaches

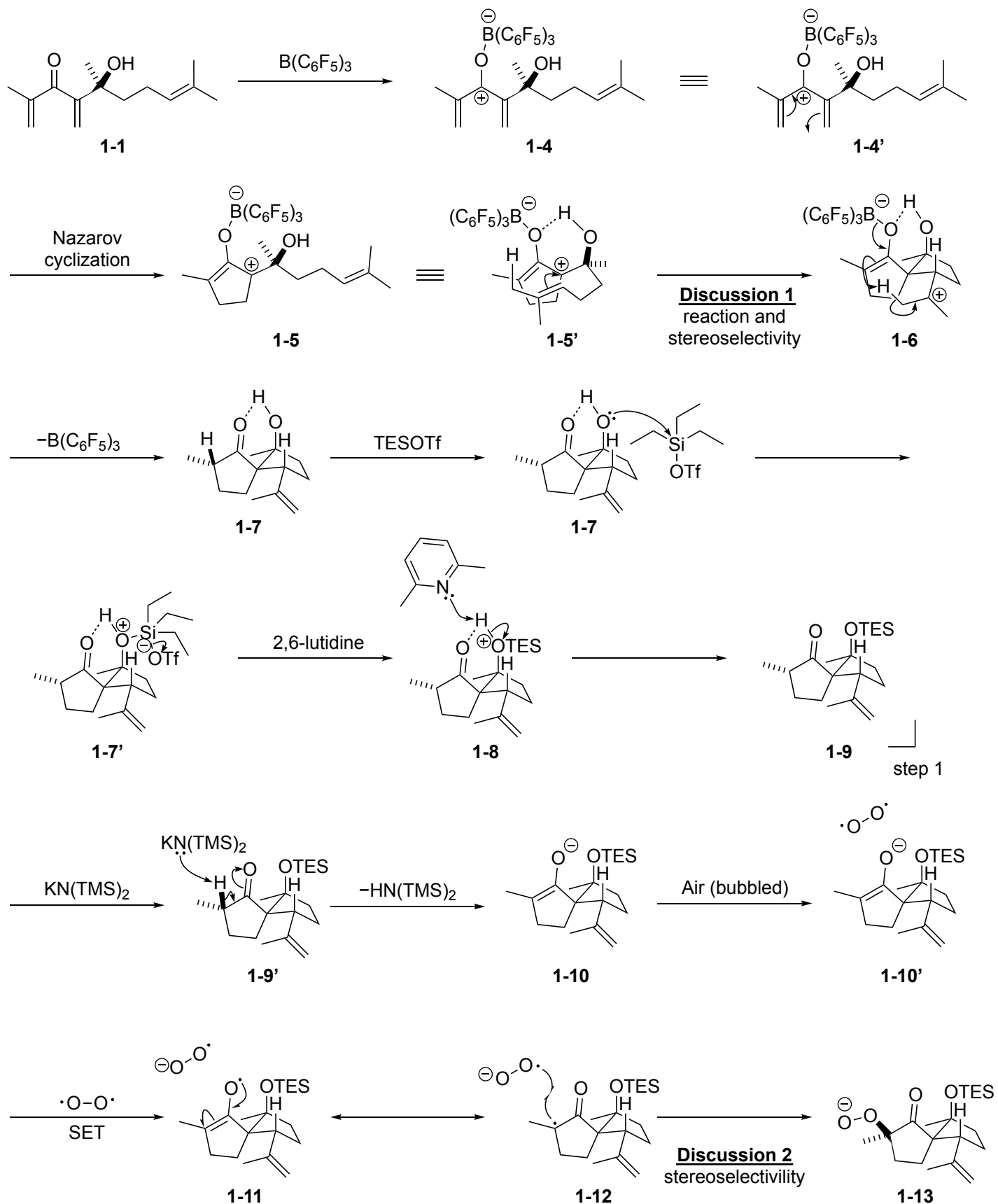
Kalesse, M (2023)

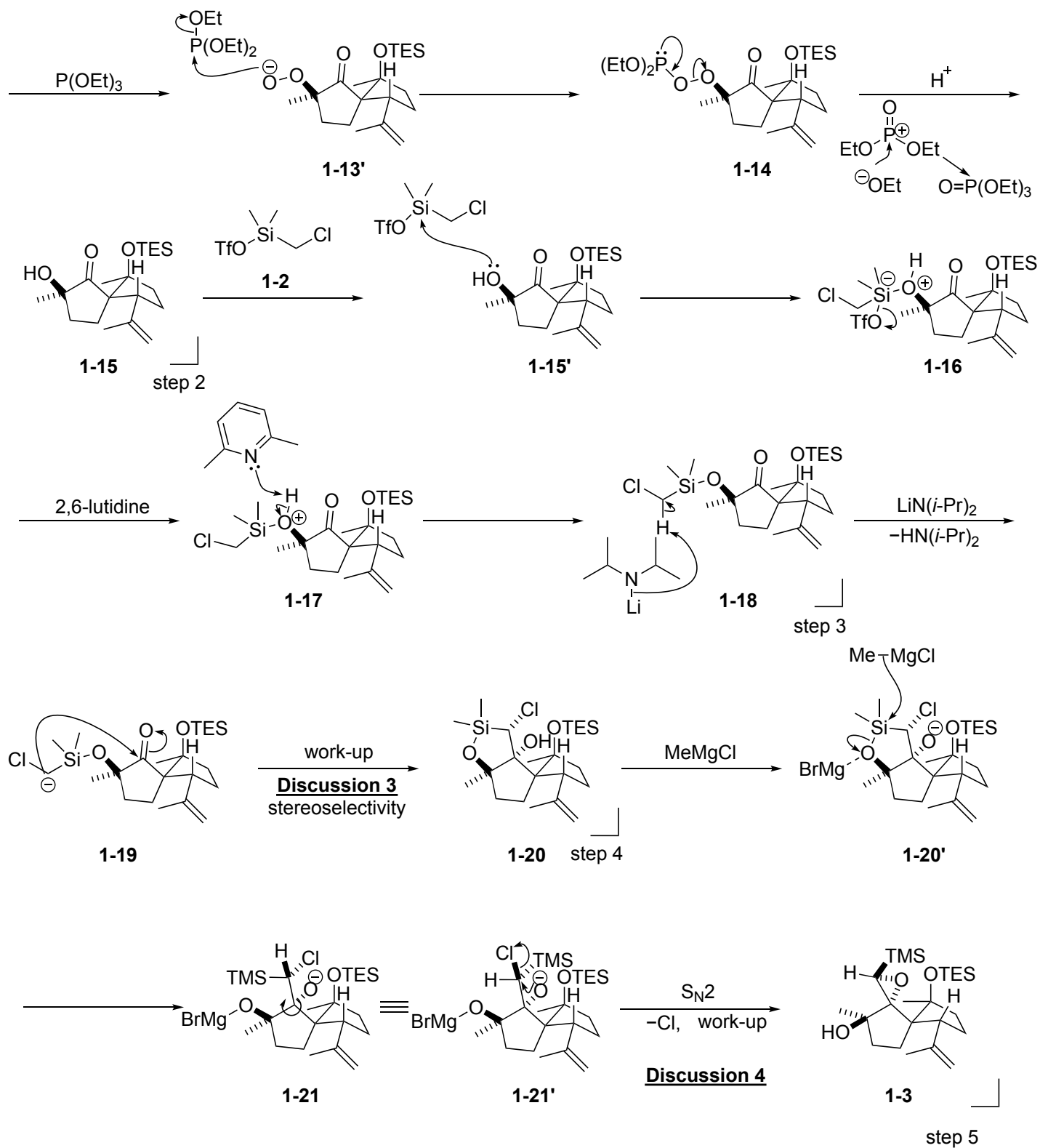


(1) Please provide the reaction mechanism and explain the stereoselectivity



Answer:



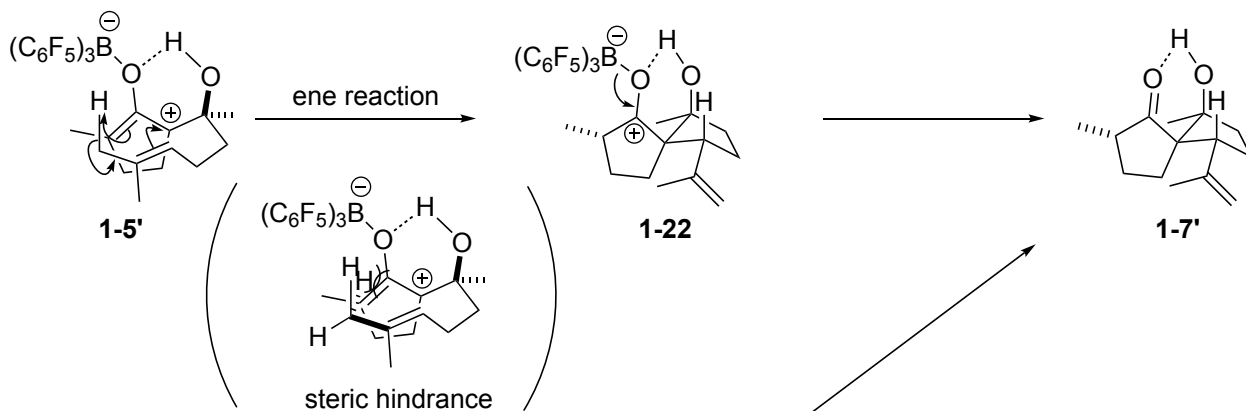


## Discussion 1

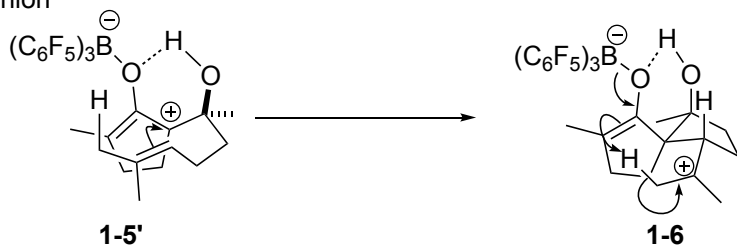
<reaction mechanism>

The author insisted that the ene reaction (concerted pathway) was occurred. In my opinion, the stepwise pathway is more feasible because of the steric repulsion between alkene and H atom during the ene reaction.

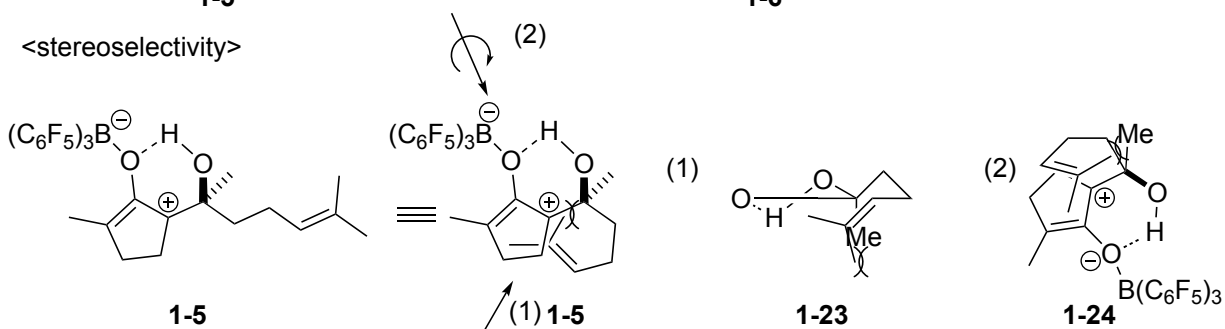
author



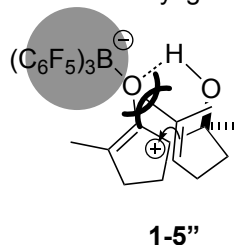
my opinion



<stereoselectivity>

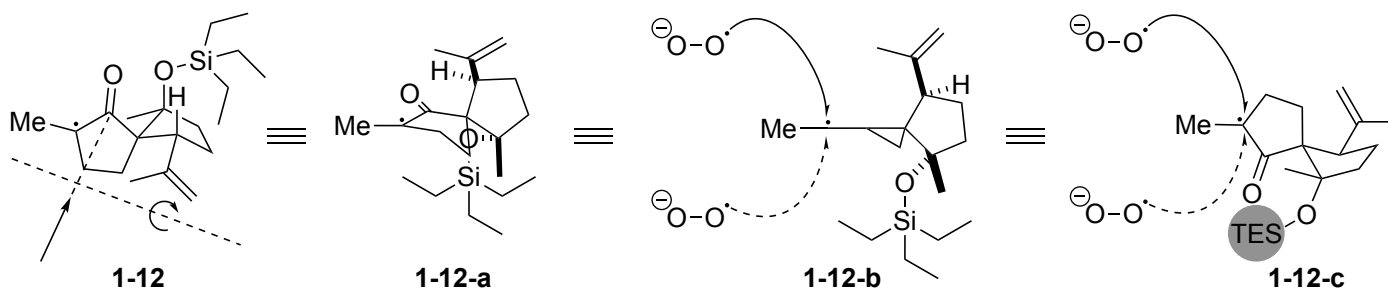


The steric repulsion between two methyl groups prevents the reaction from the back side of 5-membered ring.



The steric repulsion between isopropenyl and borate prevent the reaction.

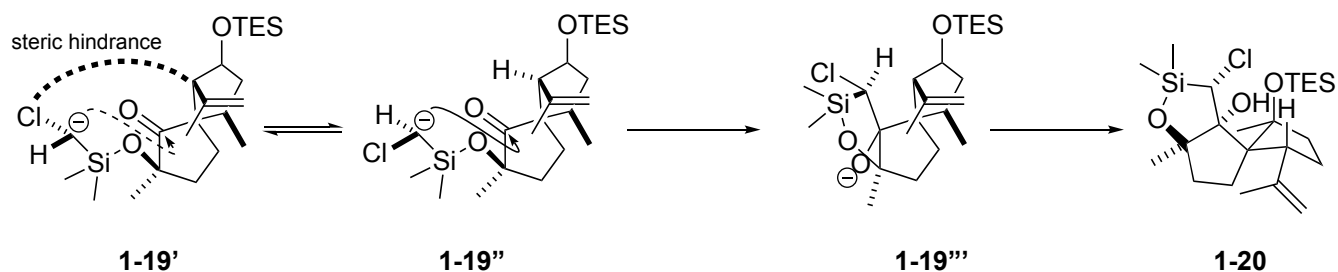
## Discussion 2



The bulky OTES group prevented the reaction of **1-12** and the oxyl radical from the back side.

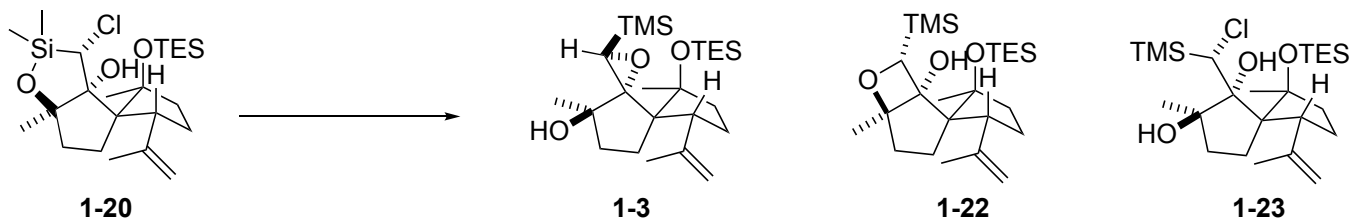
The steric repulsion between the isopropenyl group and the oxyl radical seemed not to be problematic.

### Discussion 3

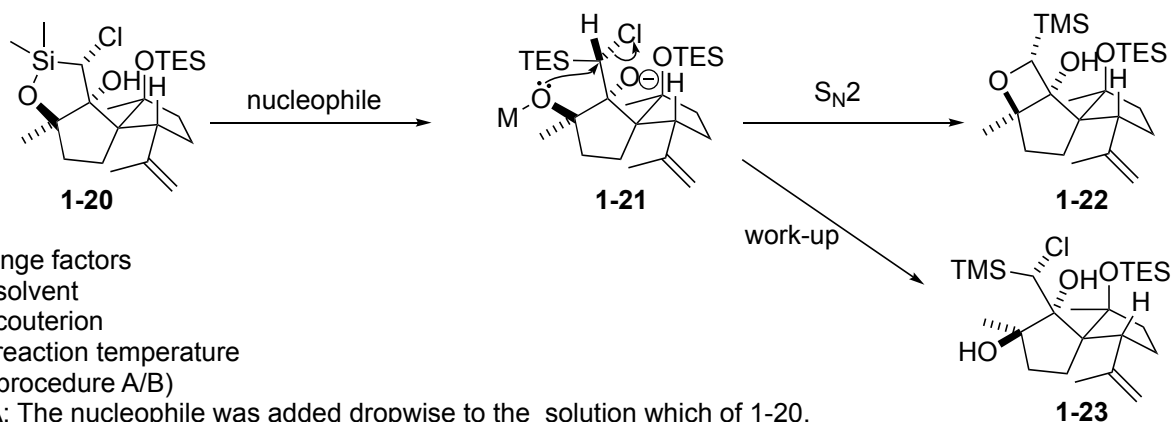


In **1-19'**, the steric hindrance between Cl and 5-membered ring prevented the nucleophilic attack.

### Discussion 4



reaction mechanism



change factors

1. solvent
2. counterion
3. reaction temperature
4. procedure A/B

A: The nucleophile was added dropwise to the solution which of 1-20.

B: MeMgCl was added quickly to the solution of 1-20.

#### 1. solvent (procedure A)

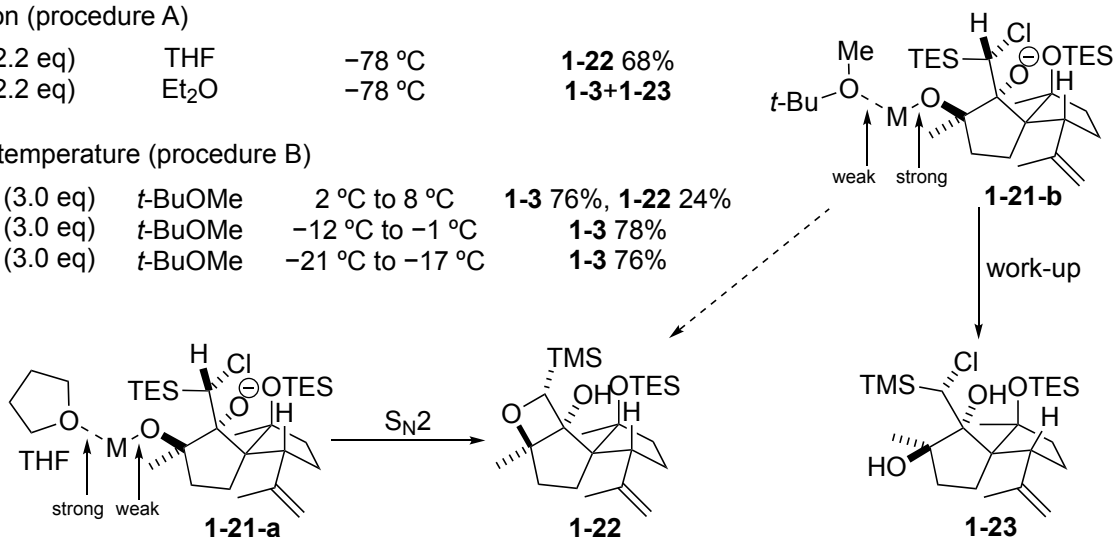
MeMgBr (3.0 eq)	THF	0 °C	<b>1-22</b> main
MeMgBr (3.0 eq)	Et <sub>2</sub> O	0 °C	<b>1-3</b> 50%
MeMgBr (3.0 eq)	<i>t</i> -BuOMe	0 °C	<b>1-3</b> 62%

#### 2. counterion (procedure A)

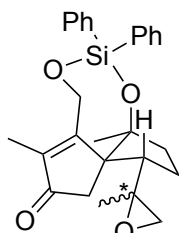
MeLi (2.2 eq)	THF	-78 °C	<b>1-22</b> 68%
MeLi (2.2 eq)	Et <sub>2</sub> O	-78 °C	<b>1-3+1-23</b>

#### 3. reaction temperature (procedure B)

MeMgCl (3.0 eq)	<i>t</i> -BuOMe	2 °C to 8 °C	<b>1-3</b> 76%, <b>1-22</b> 24%
MeMgCl (3.0 eq)	<i>t</i> -BuOMe	-12 °C to -1 °C	<b>1-3</b> 78%
MeMgCl (3.0 eq)	<i>t</i> -BuOMe	-21 °C to -17 °C	<b>1-3</b> 76%



(2) Please provide the reaction mechanism and explain the stereoselectivity



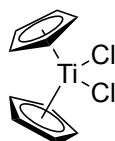
(2-1S):(2-1R) = 2.1 : 1

1.  $\text{Cp}_2\text{TiCl}_2$  (3.0 eq), Zn (8.9 eq), THF, r.t., 88%

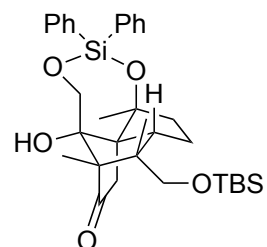
2. TBSCl (3.1 eq), imidazole (4.0 eq),  $\text{CH}_2\text{Cl}_2$ , r.t.

3. *m*-CPBA (1.8 eq),  $\text{NaHCO}_3$  (2.7 eq),  $\text{CH}_2\text{Cl}_2$ , r.t., 84% (2 steps)

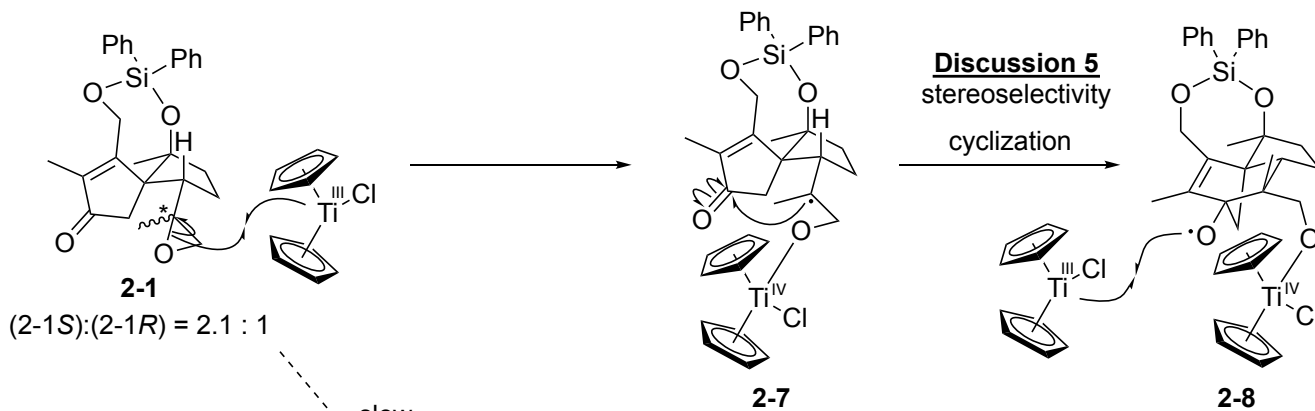
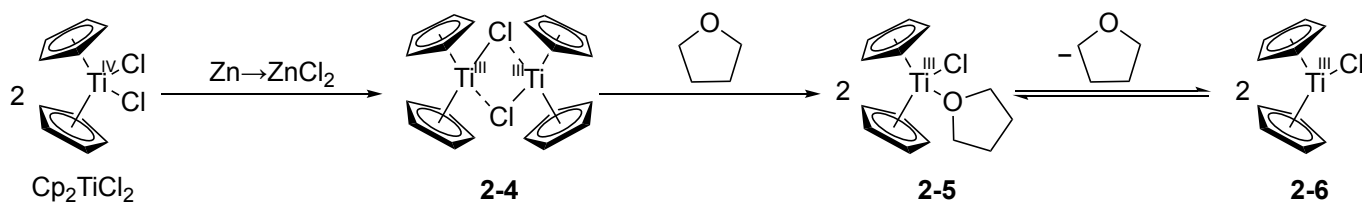
**2-2** : epi-**2-2** = 1 : 1.6



$\text{SnCl}_4$  (2.0 eq),  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 36% (calc. >90% from **2-2**)

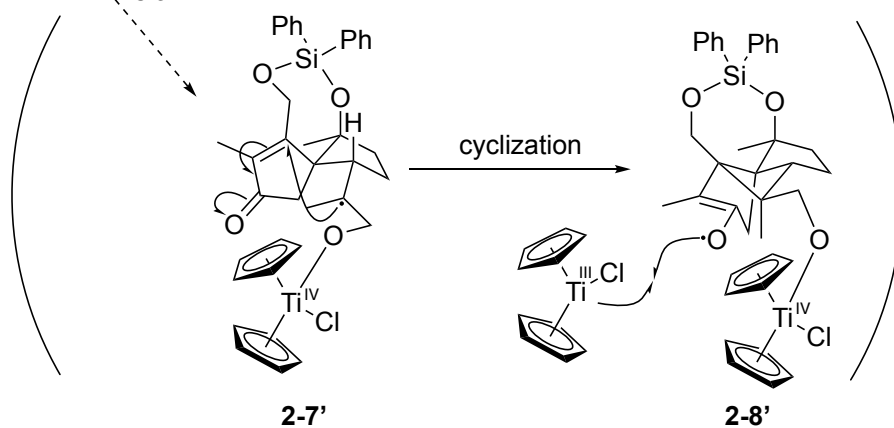


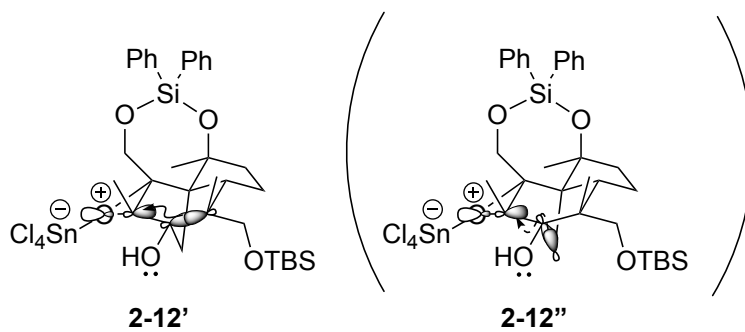
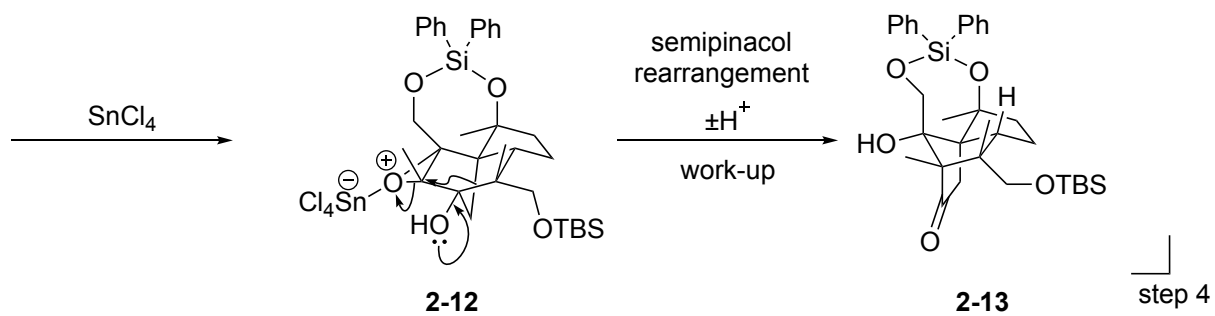
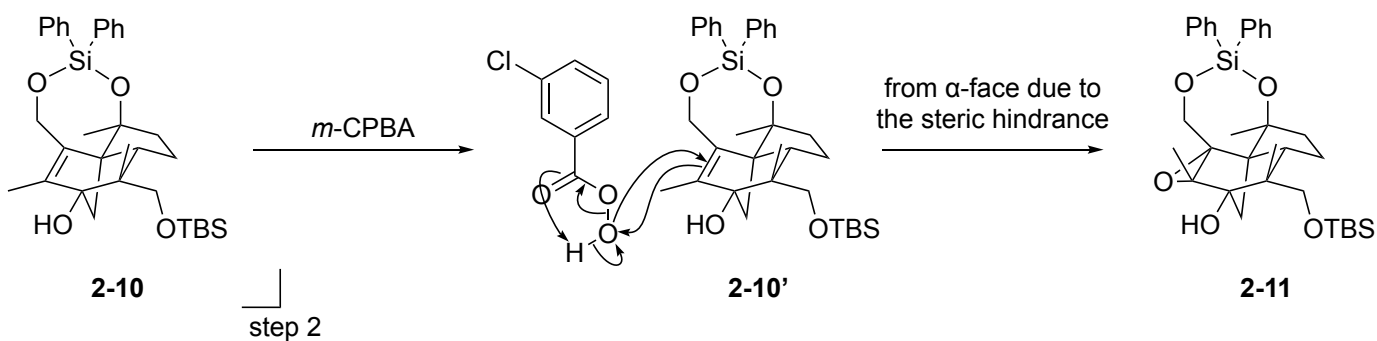
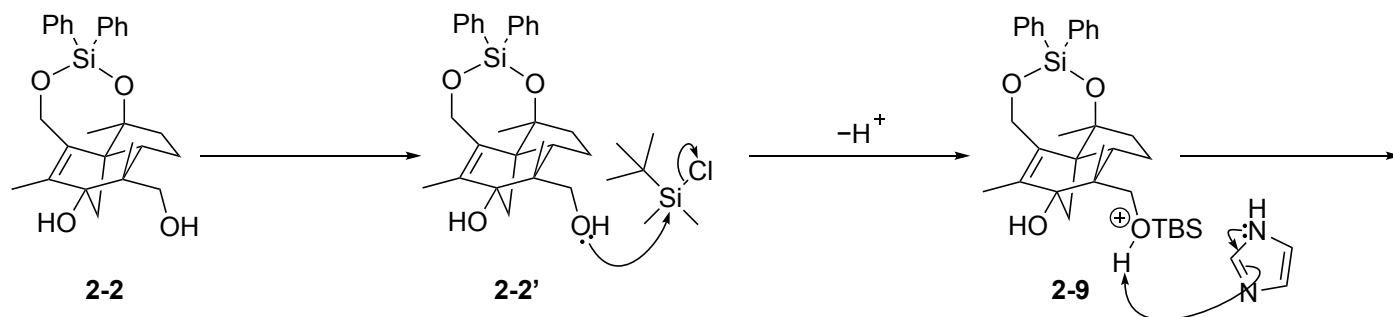
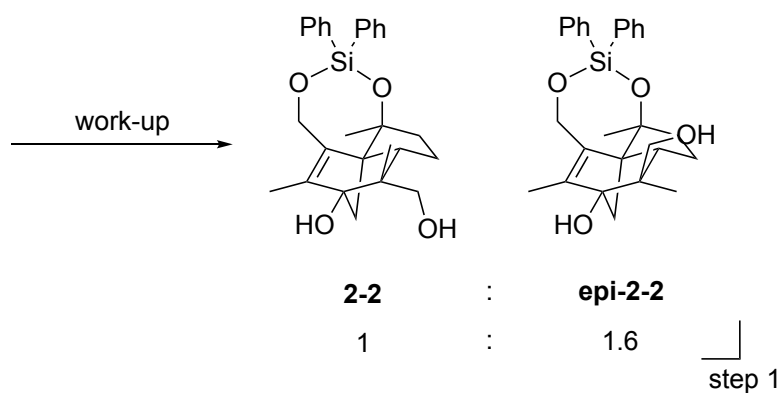
**Answer:**



(2-1S):(2-1R) = 2.1 : 1

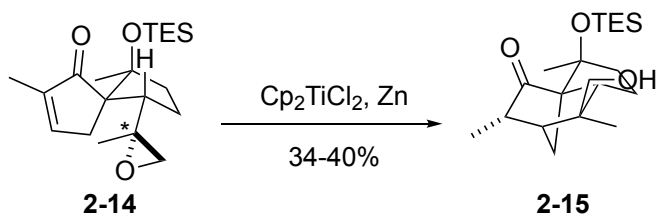
slow



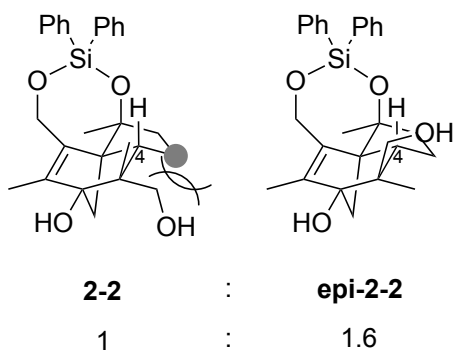




## Discussion 5



Author investigated the reaction conditions. Most of that resulted in undesired diastereomer such as **2-15**. The optimized condition, using Ti(III)-mediated cyclization of epoxy enone, was found.



Author insisted that the factor of low yield of desired diastereomer observed under most conditions is minimization of steric interactions between OR (R = TBS or  $\text{Cp}_2\text{TiCl}$ ) and methine proton at C4. They prefer an orientation *syn*, result in **epi 2-2**.

Addition of epoxide solution to  $\text{Cp}_2\text{TiCl}_2$  solution were the best condition. Catalytic condition failed in their hand. Coordination of titanium complex to both the epoxide oxygen and the carbonyl oxygen let epoxide oxygen be oriented to the carbonyl oxygen, result in **2-2**.

However, The steric hindrance may get larger by titanium species than OR. These factors may result in ratio of 1:1.6.

