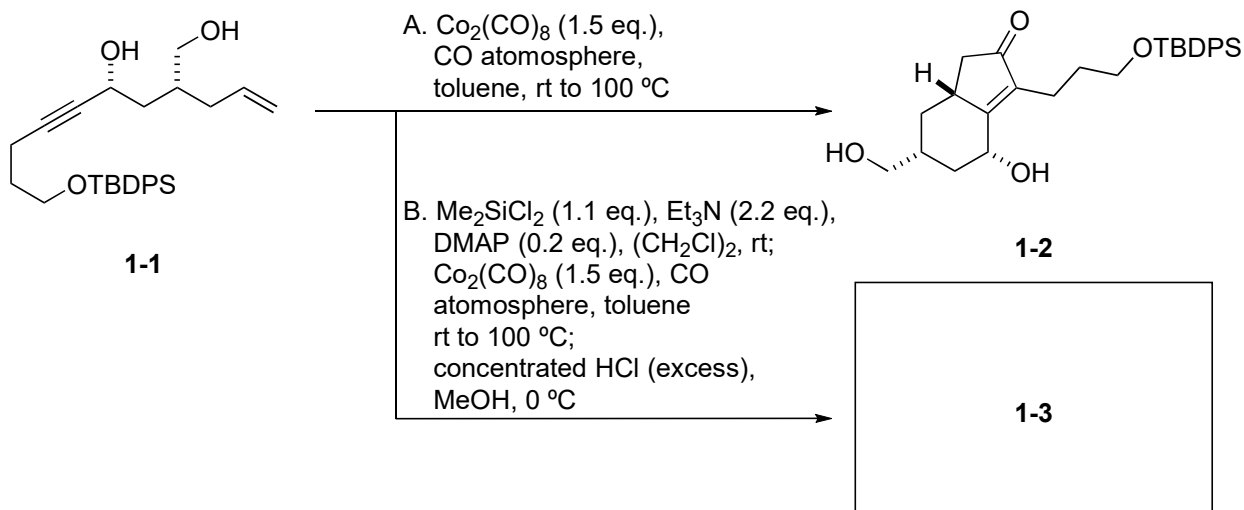


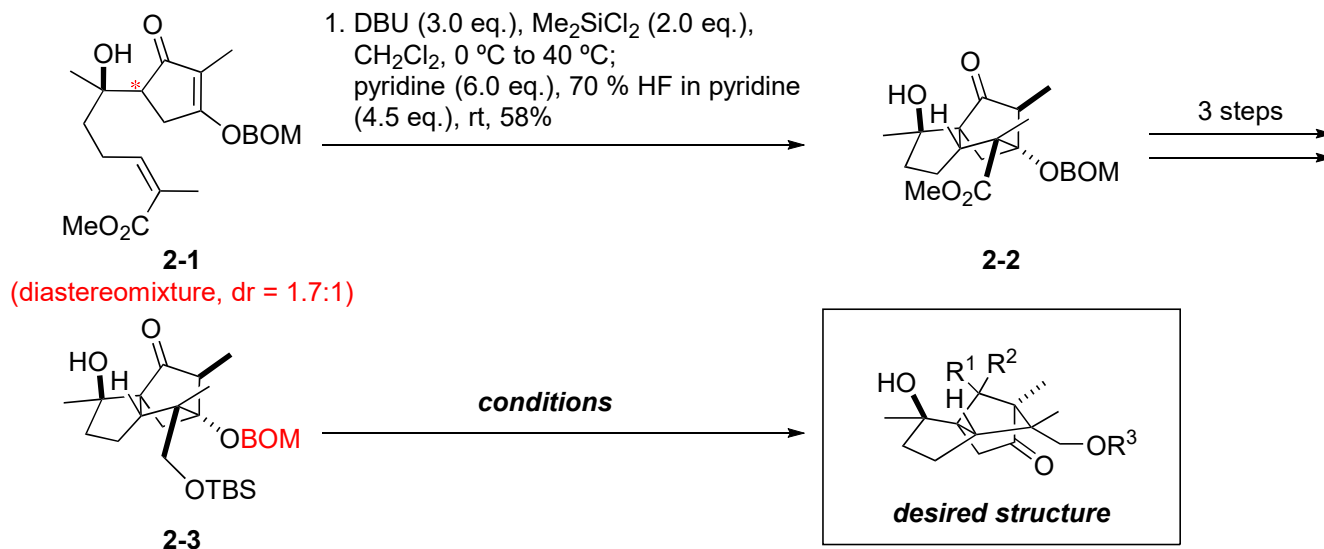
Problem Session (2)

2021.12.3 Junichi Taguchi

(1) Please provide the structure of **1-3** and explain the role of Me_2SiCl_2 .



(2) Please provide the reaction mechanism and choose the proper reaction condition in order to obtain the desired structure (Under one of the two conditions, an overreaction occurred).

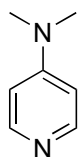


condition A:

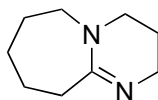
1. AcCl/MeOH (1/5), 0 °C, 72%
2. Br_2 (1.7 eq.), AcOH (3.2 eq.), $\text{THF}/\text{Et}_2\text{O}$ (3/1), 0 °C
3. AgClO_4 (2.4 eq.), THF , rt, 54% (2 steps)

condition B:

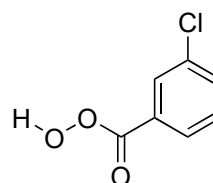
1. $(\text{NH}_2)_2\cdot\text{H}_2\text{O}$ (3.1 eq.), AcOH (8.5 eq.), EtOH , reflux
2. DBU (9.8 eq.), I_2 (3.9 eq.), THF , rt, 72% (2 steps)
3. $i\text{-PrMgCl}$ (2 M in Et_2O , 2.0 eq.), THF , 0 °C; $n\text{-BuLi}$ (2.25 M in hexane, 3.0 eq.), -78 °C; DMF (6.0 eq.), -78 °C to rt; NaBH_4 (8.0 eq.), MeOH , rt
4. $m\text{-CPBA}$ (ca. 70% with H_2O , ca. 2.0 eq.), CH_2Cl_2 , rt, 83% (2 steps)
5. $\text{CF}_3\text{CO}_2\text{H}$ (0.89 eq.), CHCl_3 , rt, 57%



DMAP



DBU



m-CPBA

Problem Session (2) -Answer-

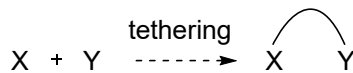
2021.12.3 Junichi Taguchi

Topic: Silicon tether approaches for regio- and stereoselectivity

0. Introduction (For more details: Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev.* **2010**, *39*, 4114.)

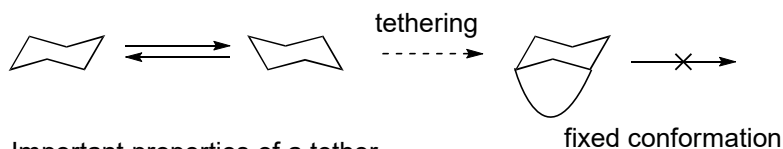
0-1. The advantage of the use of tethering

► intermolecular reaction → intramolecular reaction



- **higher effective concentration** of the reacting partners
- **lower entropic demand** on the free energy of activation

► greater regio- and stereoselectivity



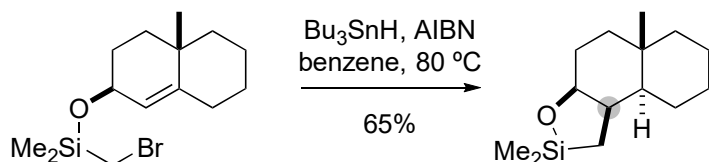
- inevitable increase in conformational restriction of the reaction state

0-2. Important properties of a tether

- readily introduced in high yields
 - stable to the reaction conditions
 - easily removed or converted into other functional groups
- **Silicon-based functionalities** are ideal.

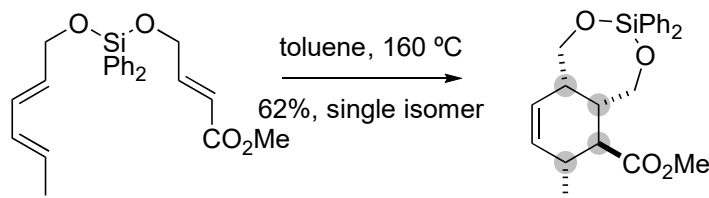
0-3. Examples of applications of temporary silicon tethers

0-3-1. Radical cyclization



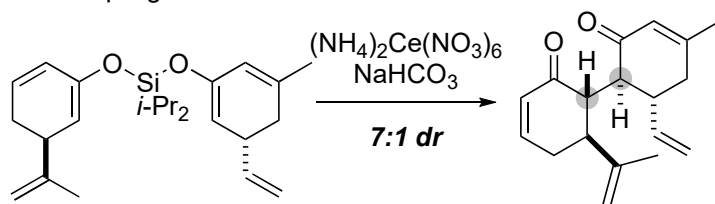
Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.

0-3-2. Cycloaddition



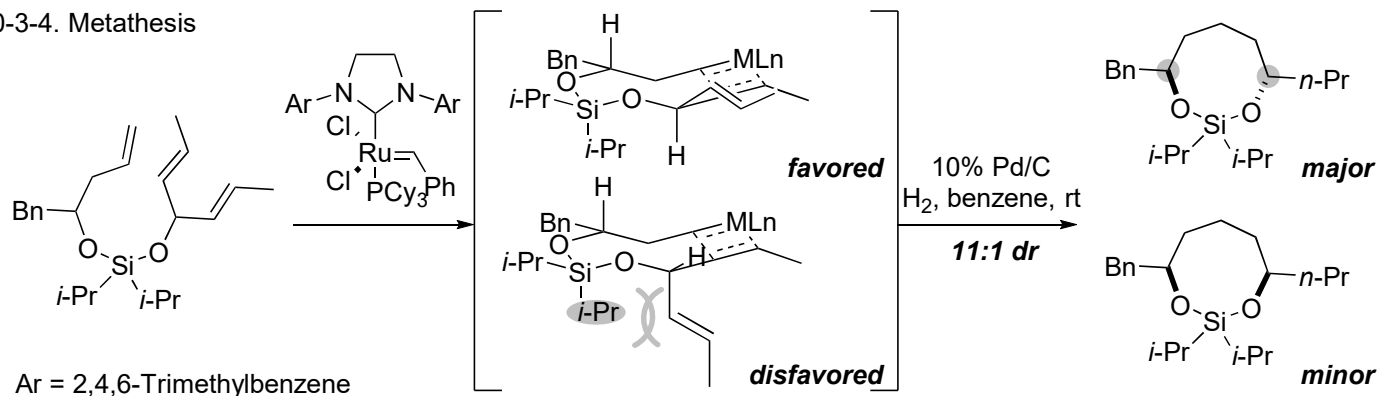
Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585.

0-3-3. Coupling reaction



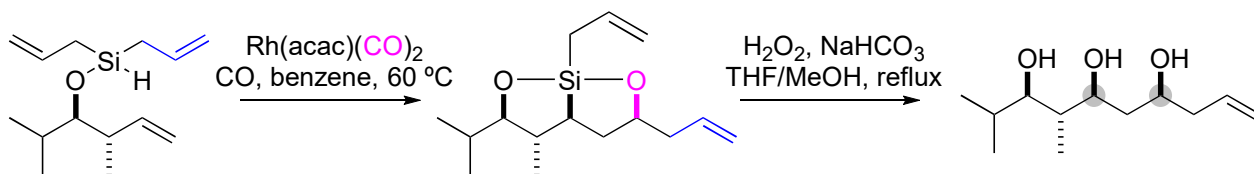
Robinson, E. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2018**, *140*, 1956.

0-3-4. Metathesis



Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734.

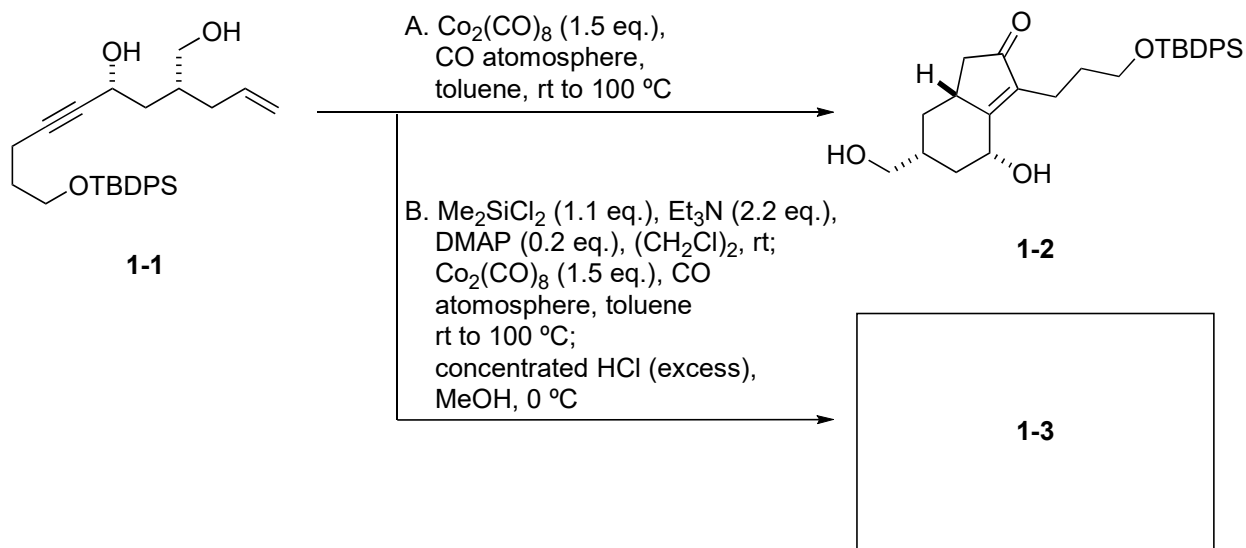
0-3-5 Hydrosilylation and carbosilylation



See also 151128_PS_Masaki_Koshimizu
Zacuto, M.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

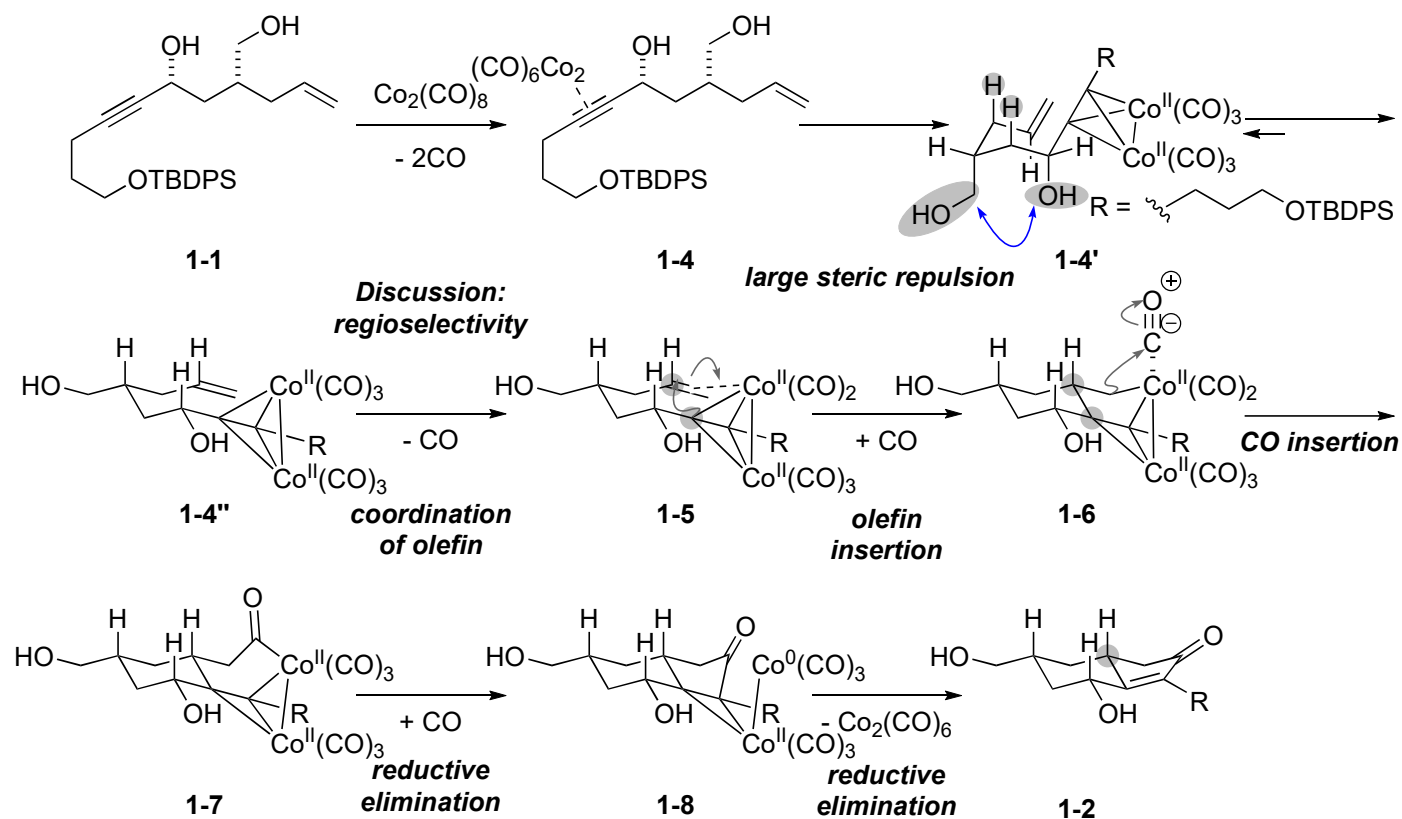
1. Problem 1

(1) Please provide the structure of **1-3** and explain the role of Me_2SiCl_2 .

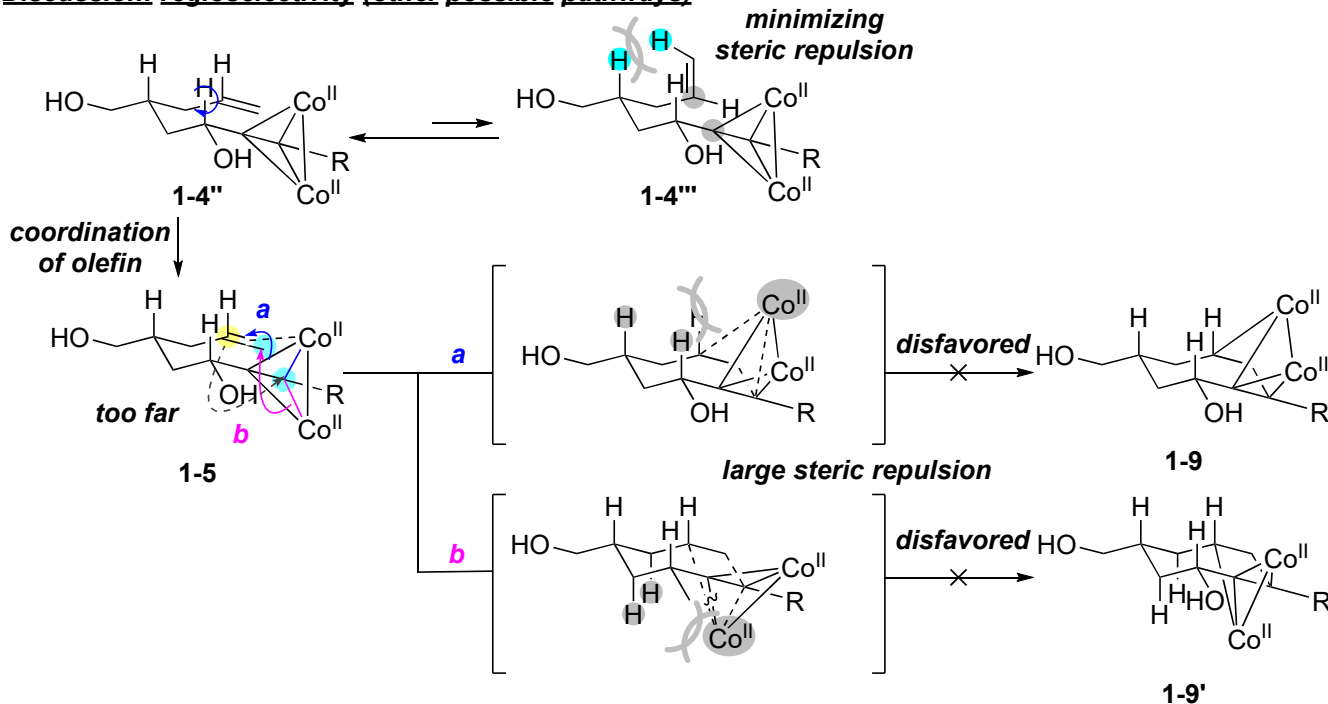


Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8025.

1.1 Reaction mechanism (condition A)

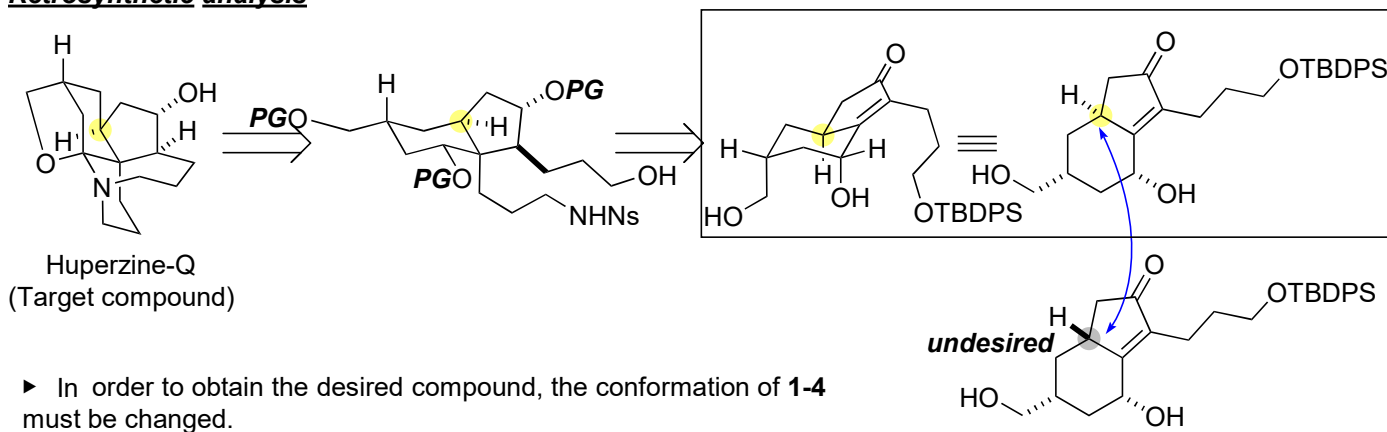


Discussion: regioselectivity (other possible pathways)

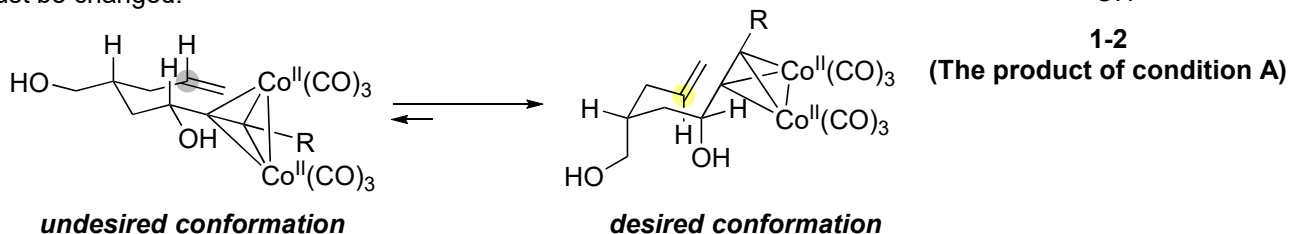


1.2 Background

Retrosynthetic analysis

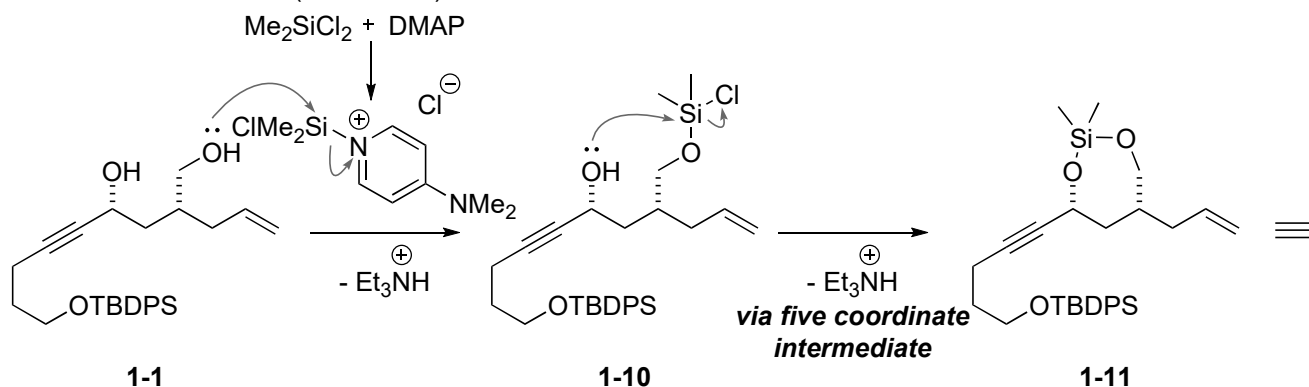


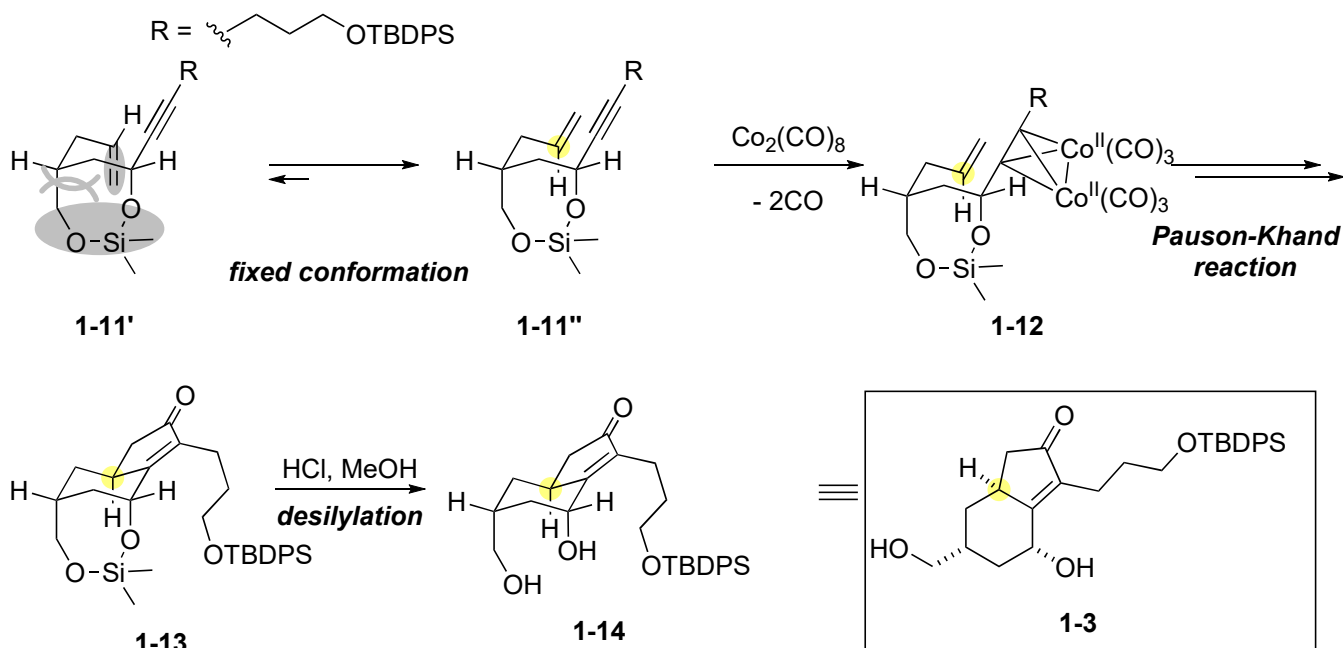
► In order to obtain the desired compound, the conformation of **1-4** must be changed.



→ **By tethering two hydroxy groups using disposable silicon linkers, it would be possible to change the conformation.**

1.3 Reaction mechanism (condition B)

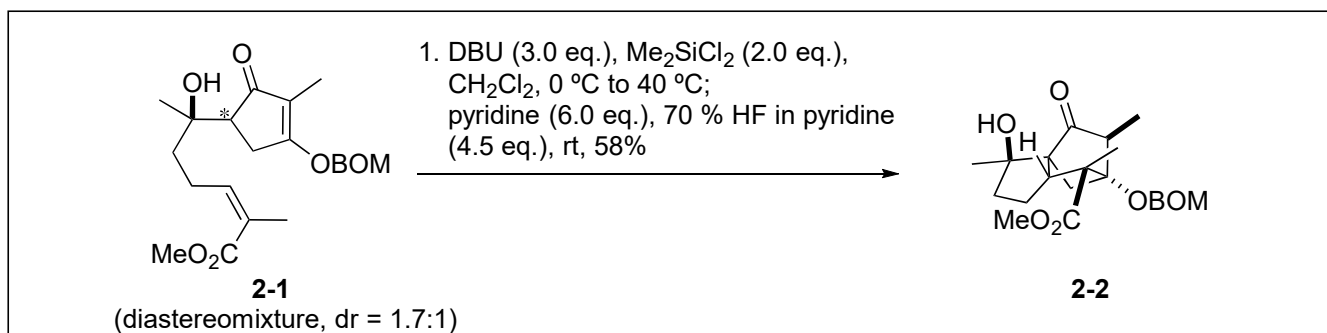




2. Problem 2

Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295.

2.1 Silicon-tethered intramolecular Diels-Alder reaction



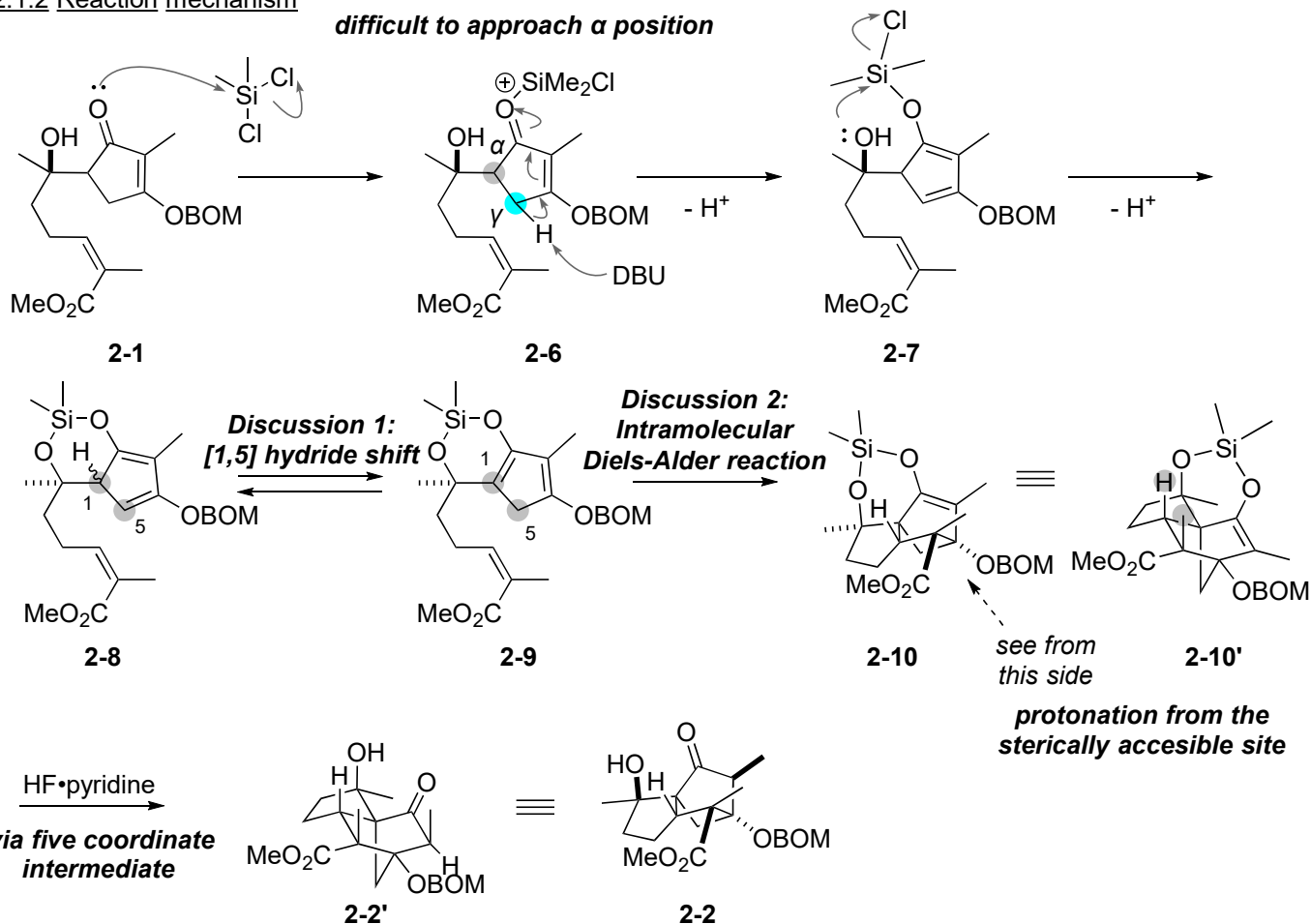
2.1.1 Background

Without Me_2SiCl_2 (ex. Lewis acid catalyzed Diels-Alder reaction, My opinion)

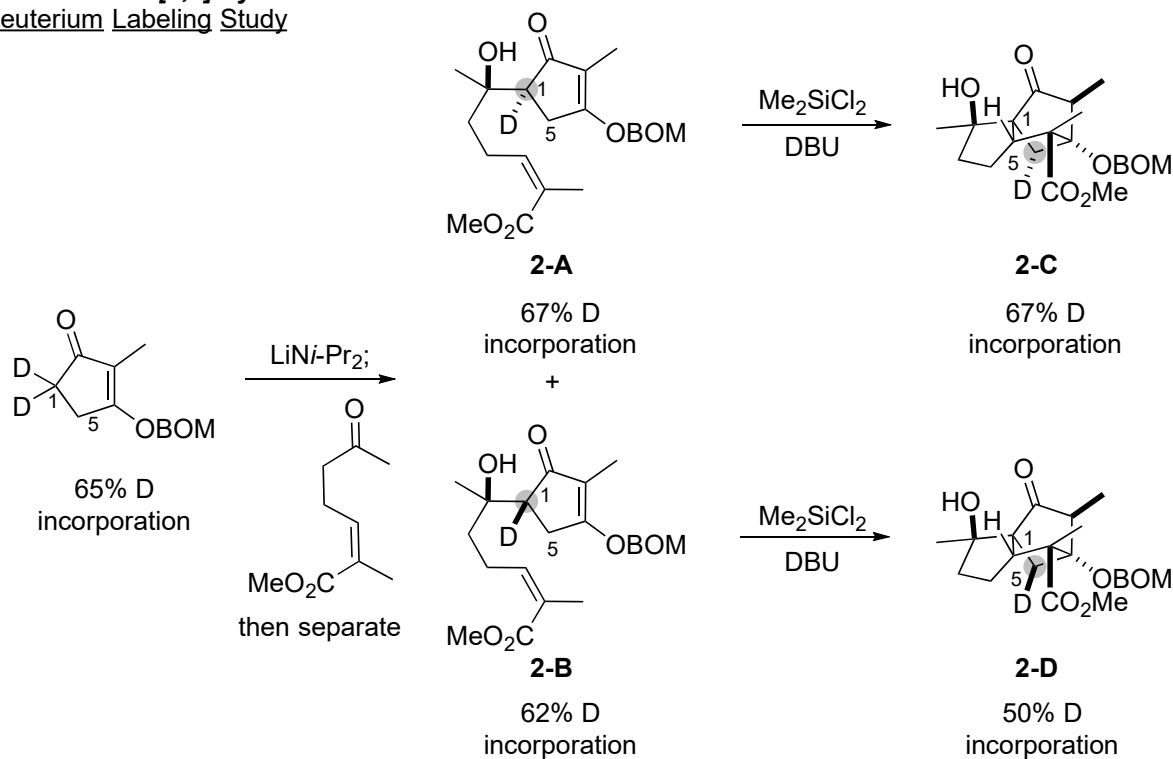


2.1.2 Reaction mechanism

difficult to approach α position

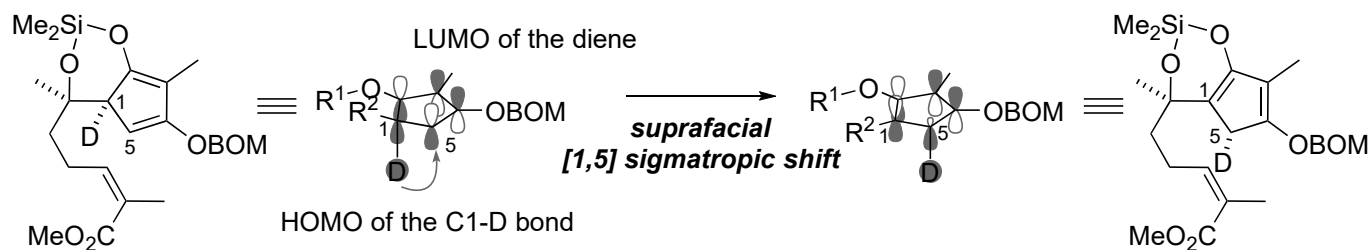


Discussion 1: [1,5] hydride shift
Deuterium Labeling Study



Subjecting **2-A** and **2-B** to the intramolecular Diels-Alder reaction conditions gave **2-C** and **2-D**, respectively, with near-quantitative deuterium migration to the γ -position.

→ **The mechanism of formation for the reactive diene proceeds primarily through γ -deprotonation and [1,5] hydride shift.**

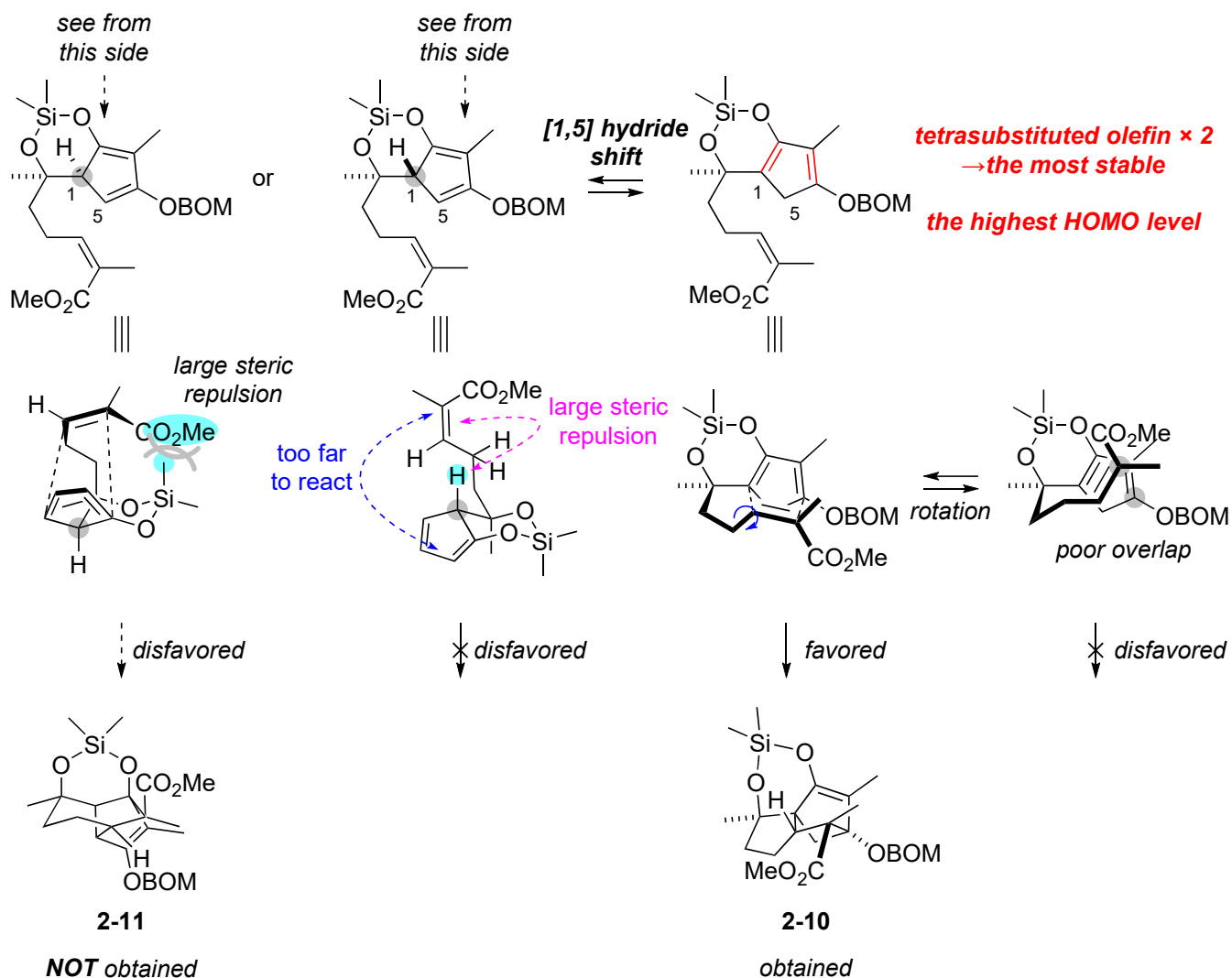


Furthermore, the diastereospecific migration between the two diastereomers strongly suggests that the migration occurs via a suprafacial [1,5] sigmatropic shift.

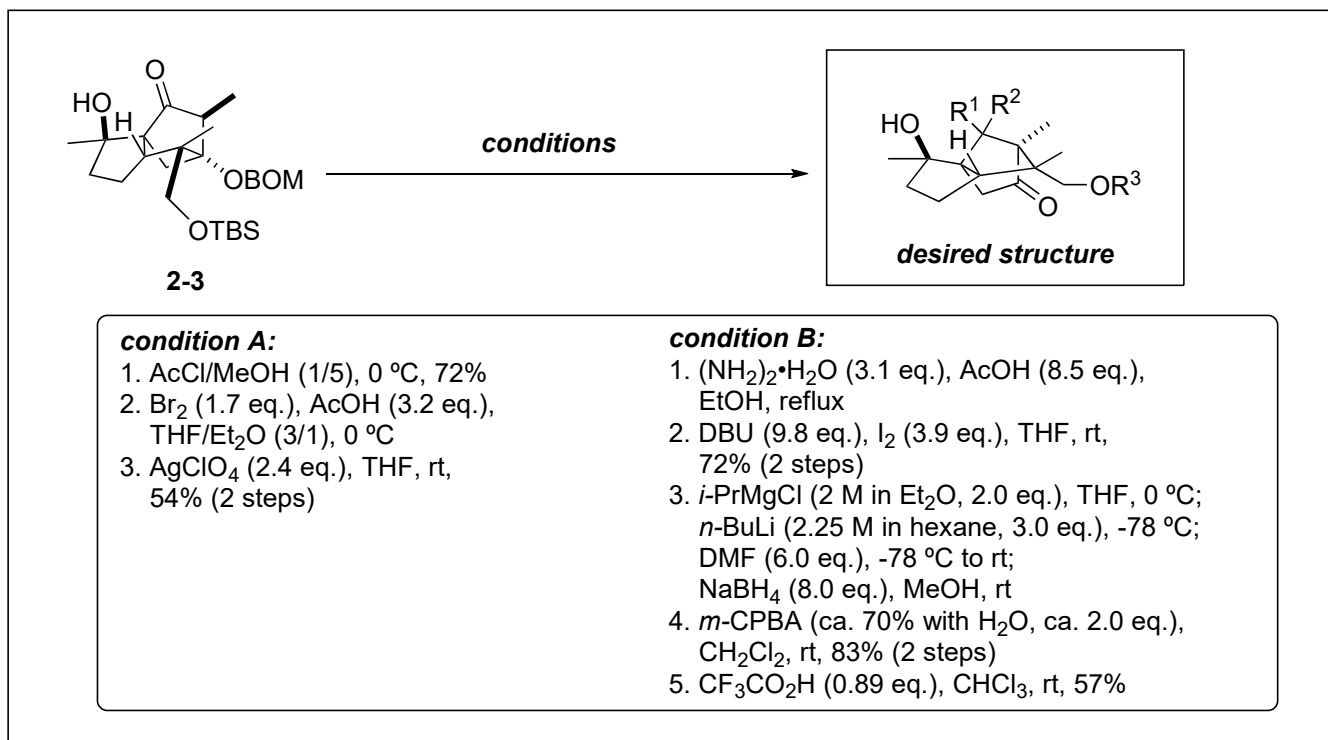
Carlson, P. R.; Burns, A. S.; Shimizu, E. A.; Wang, S.; Rychnovsky, S. D. *Org. Lett.* **2021**, 23, 2183.

Discussion 2: Intramolecular Diels-Alder reaction

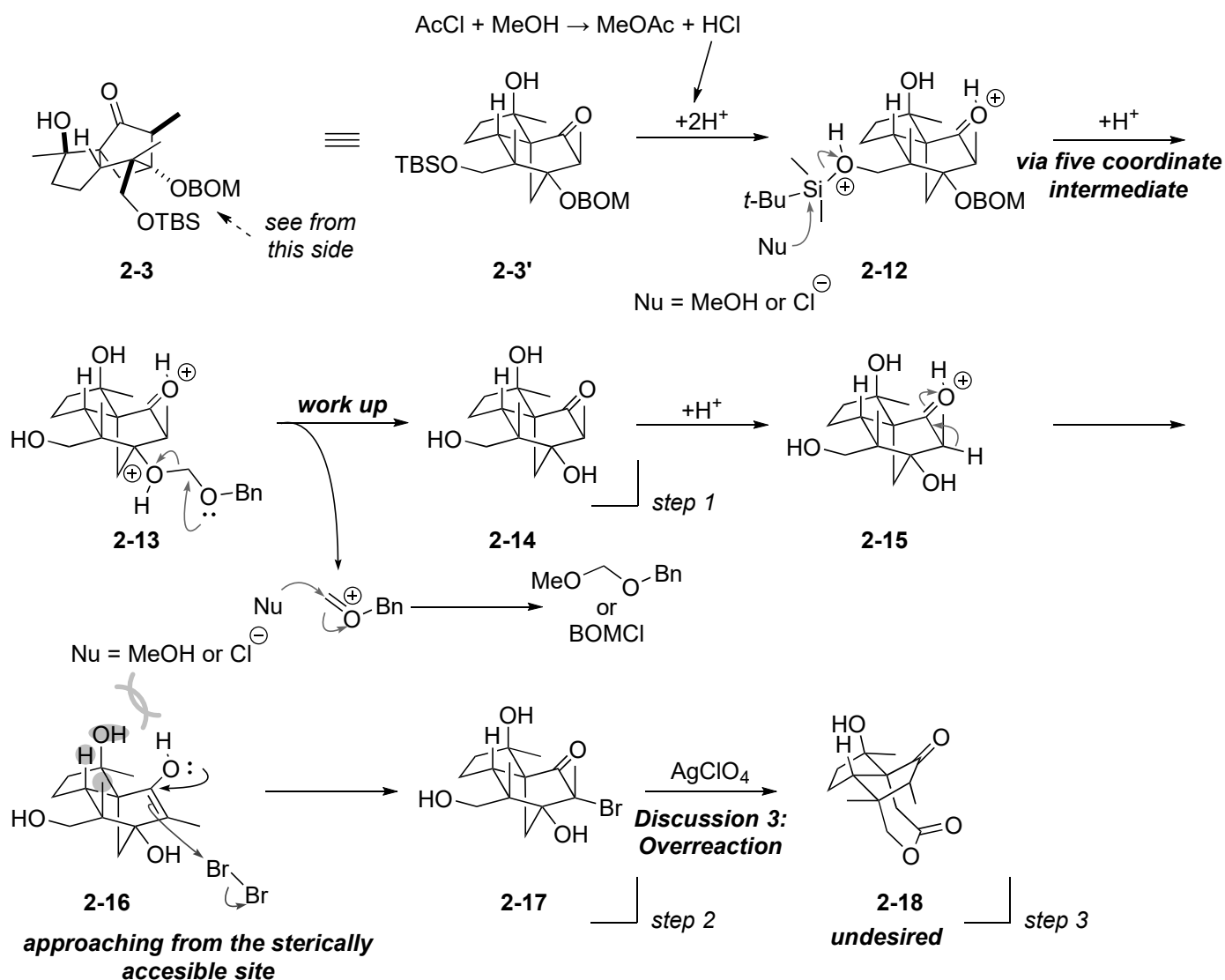
Due to the rigid silicon-containing 6-membered ring, the conformations are strictly determined.



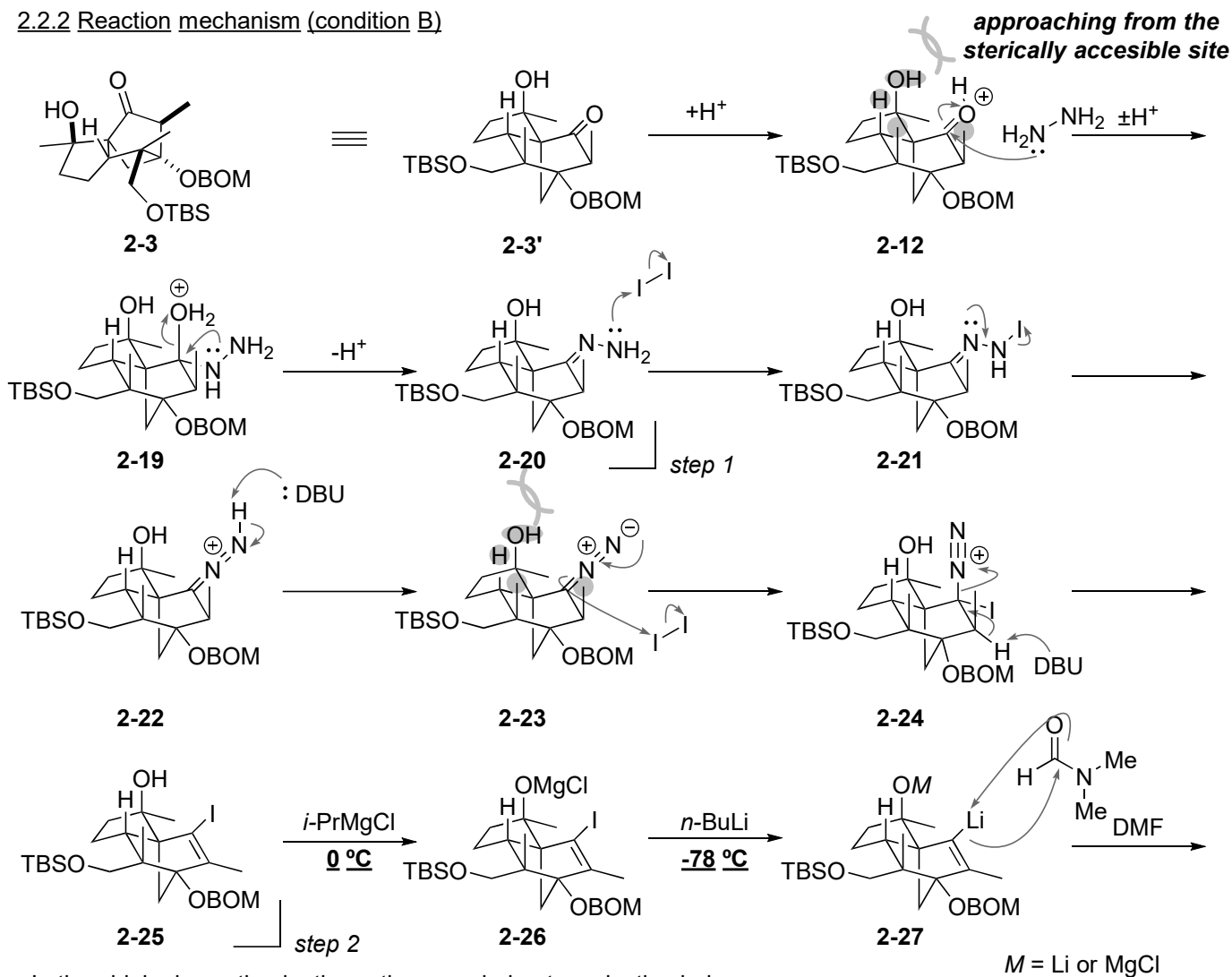
2.2 Generation of the desired trans 5,5-ring system



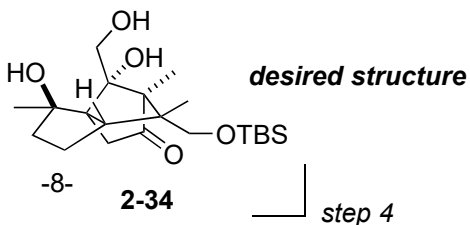
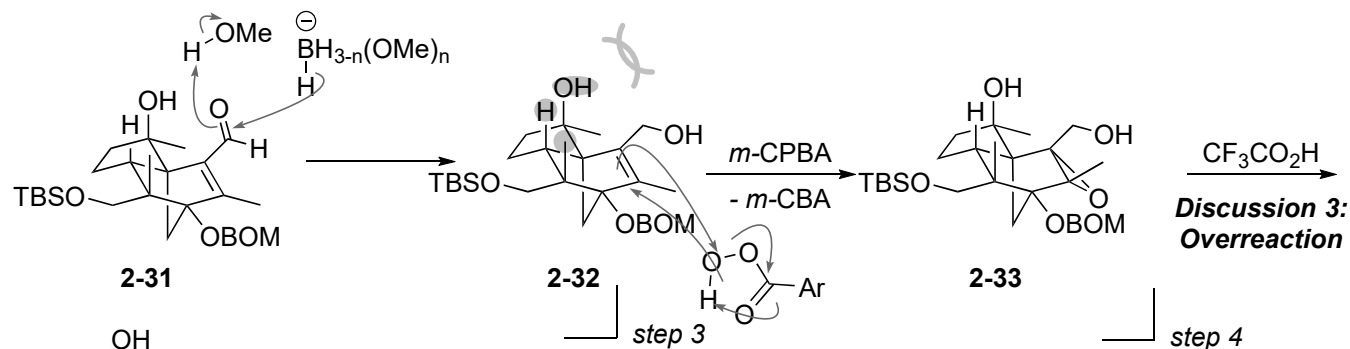
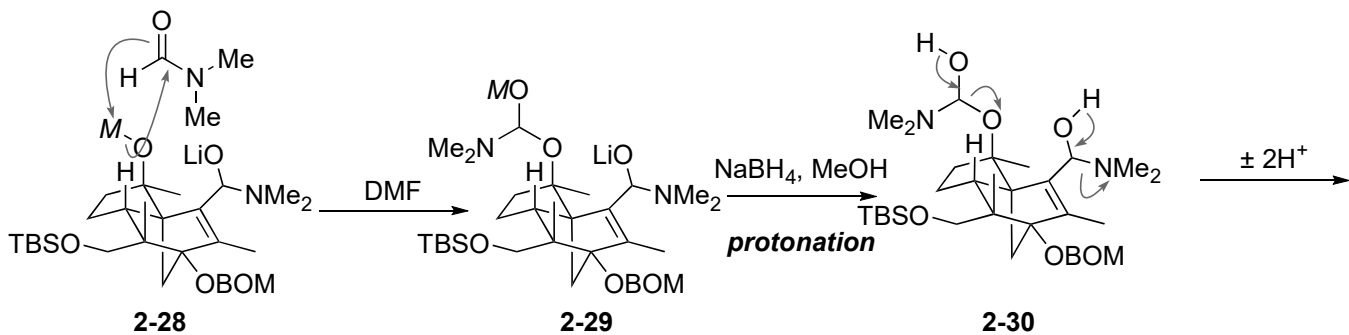
2.2.1 Reaction mechanism (condition A)



2.2.2 Reaction mechanism (condition B)



In the aldehyde synthesis, the authors carried out a selective halogen-metal exchange by using *i*-PrMgCl and *n*-BuLi.



Condition B

