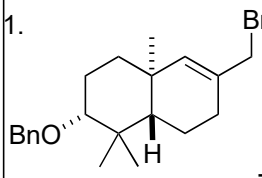
Problem Session (1) 2022.10.22 Yuyan Liang

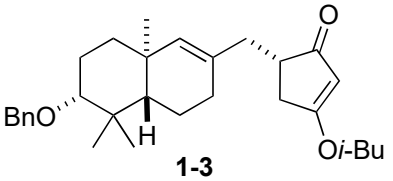
Topic: Problem 1. Interconversions of *ent*-kaurane, ent-trachylobane, ent-atiserane diterpenoids via a common precusor.
Problem 2. Synthesis of Spiromeroterpenoids: chermesin B

1.



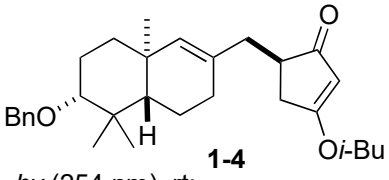
1-1

1. $LiN(i\text{-}Pr)_2$ (1.5 eq.), **1-2** (1.5 eq.), -78 °C;
HMPA (1.7 eq.), **1-1** (1.0 eq.),
-78 °C to 0 °C to rt, THF
87% (**1-3**:**1-4** = 3:2)



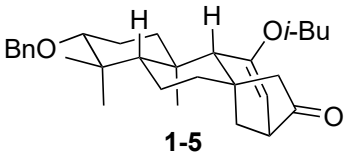
1-3

+



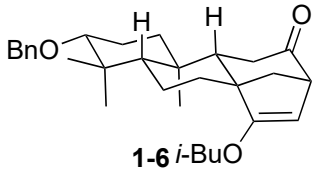
1-4

2. *hv* (254 nm), rt;
$BF_3 \cdot 2AcOH$ (3.0 eq.), 0 °C to rt
CH_3CN/acetone (10/1)

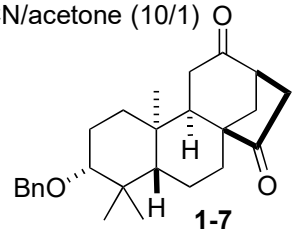


1-5
18% from the 3:2 isomers
(=30% from **1-3**)
ent-kaurane-type

+



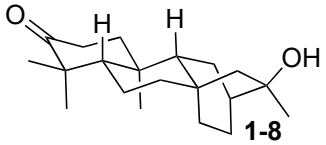
1-6 *i*-BuO
7% from the 3:2 isomers
(=12% from **1-3**)
ent-trachylobane



1-7
21% from the 3:2 isomers
(=52% from **1-4**)

1-5

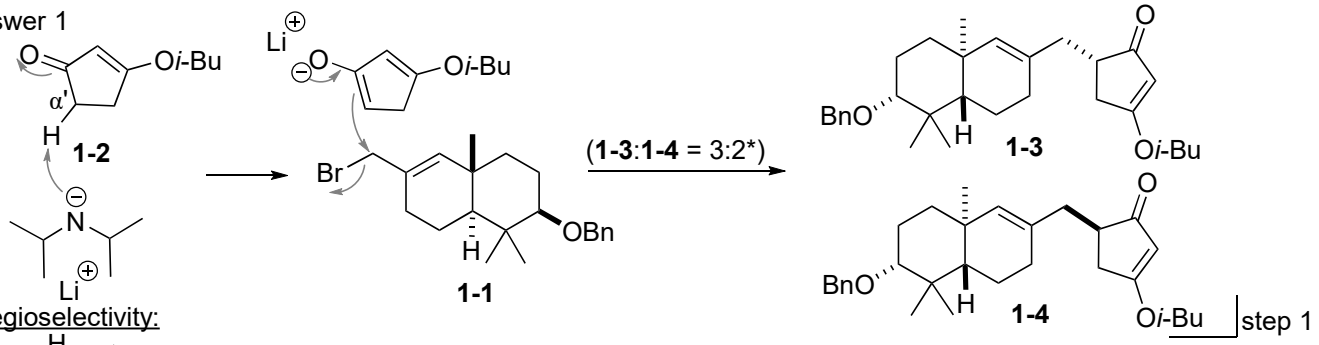
3. CH_3PPhBr (5.0 eq.), $NaN(TMS)_2$ (4.5 eq.), THF, 0 °C to rt, 90%
4. 1 M aq. HCl (0.6 eq.), acetone, 20 °C, 5 h, 87%
5. NH_2NH_2, KOH (150 eq.), diethyl glycol, 210 °C
6. H_2, Pd/C, MeOH, 62% for 2 steps
7. Dess-Martin periodinane (1.5 eq.), $NaHCO_3$ (3.0 eq.), CH_2Cl_2, rt, 82%
8. CF_3CO_2H (1.1 eq.), benzene, rt; NaOH, $EtOH/H_2O$ (9:1), rt, 51%



1-8
***ent*-16α-hydroxy-atisane-3-one**

Xu, Z.; Zong, Y.; Qiao, Y.; Zhang, J.; Liu, X.; Zhu, M.; Xu, Y.; Zheng, H.; Fang, L.; Wang, X.; Lou, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 19919.

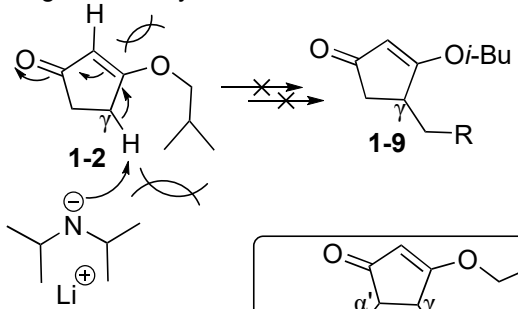
Answer 1



(**1-3**:**1-4** = 3:2*)

step 1

Regioselectivity:

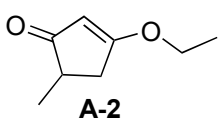


This is a kinetically-controlled deprotonation reaction with LDA.
The branched conjugated enolate is formed faster and irreversibly.
Another explanation is that to avoid the interaction of vinyl proton and *iso*-butyl group, the orientation of iso-butyl group may make Hγ hindered and block the deprotonation by bulky base LDA.
Thus no γ-alkylated procduct generated.

2.67-2.55, m
2.48-2.41, m

A-1

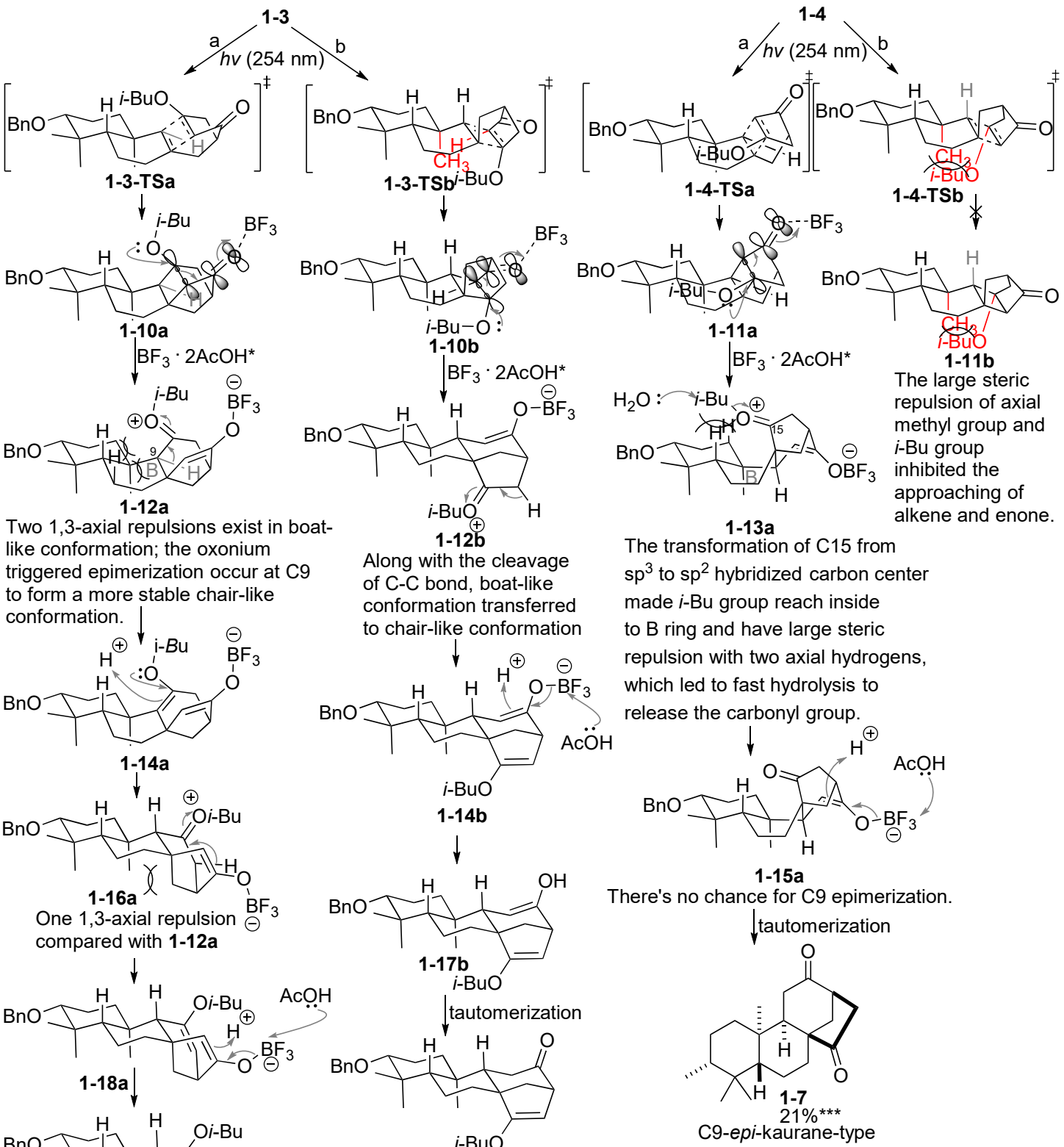
$LiN(i\text{-}Pr)_2$ (1.37 eq.), **A-1** (1.0 eq.), -78 °C;
HMPA (2.0 eq.), **MeI** (1.5 eq.),
-78 °C to rt, THF, 80%



A-2

Johnson, T.; Pultar, F.; Menke, F.; Lautens, M. *Org. Lett.* **2016**, *18*, 6488−6491.

*The lithium counterpart of **1-2** is a planar structure and the electrophilic reaction site of **1-1** is methylene group, which led to a poor selectivity (3:2). HMPA can solvate $K^{\oplus}$, enabling oxygen anion more nucleophilic.

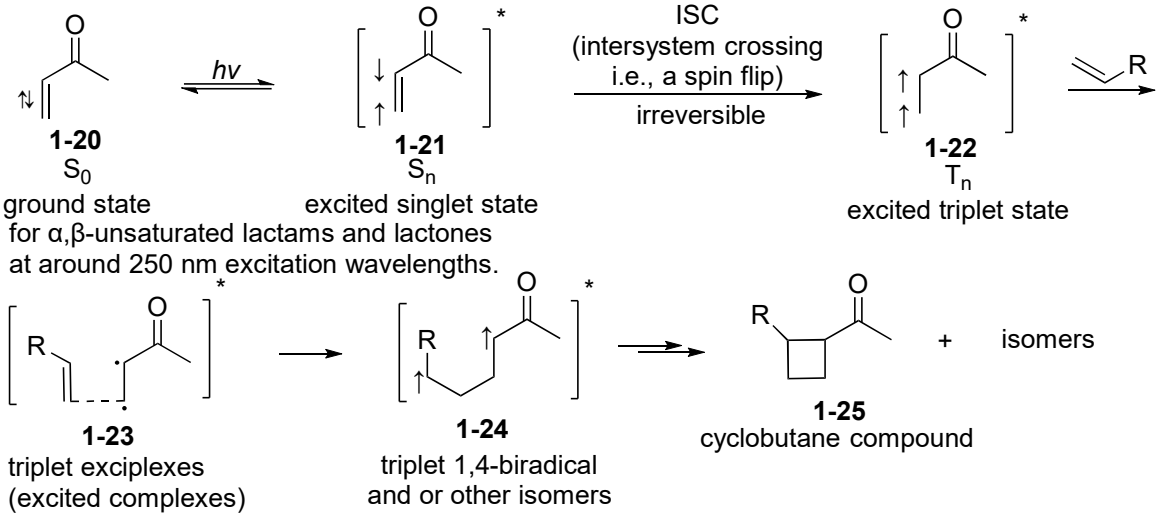


*The De Mayo reaction is reckoned as a stepwise cycloaddition reaction (page 3). Herein I draw the concerted transition state just for easy looking of the conformations. The stereochemical result won't be different in this ring system.

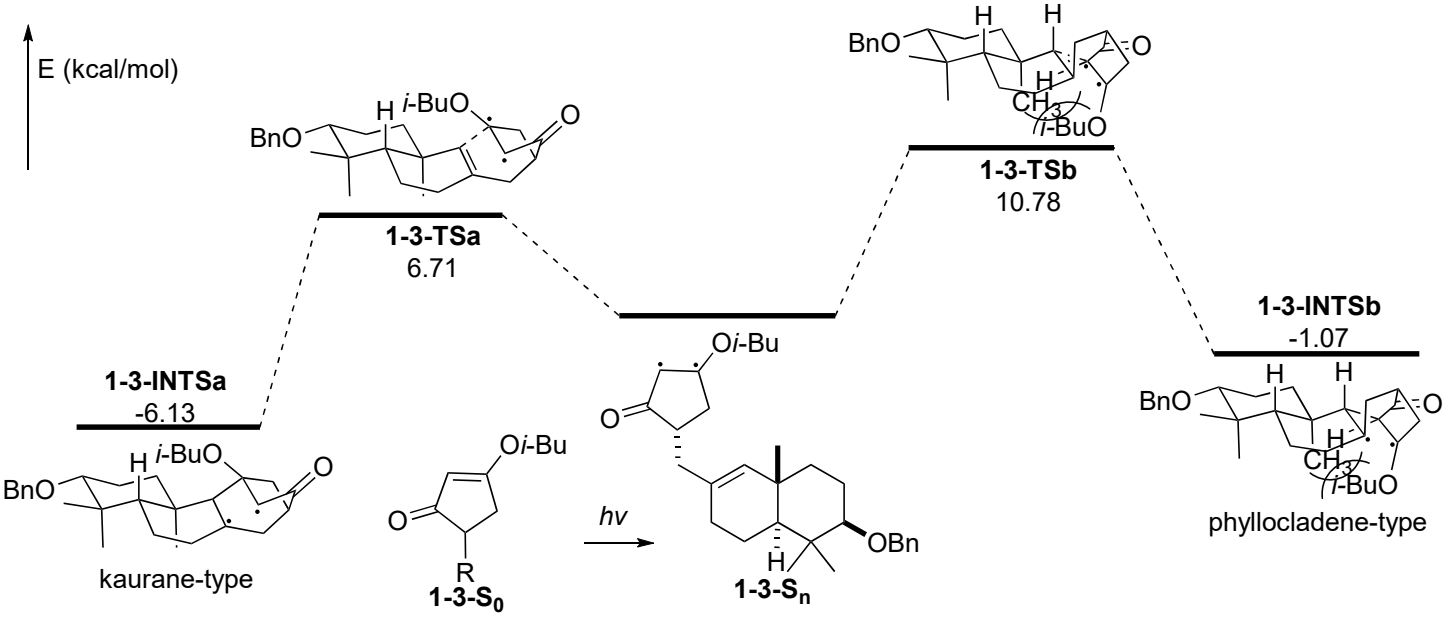
**In this step, Lewis acid catalyzed retro-aldol reaction occurred. Because the newly formed tricyclo-system is too rigid for cyclopentanone to adopt typical envelope conformation, which might cause inadequate overlap of π orbital and σ orbital.

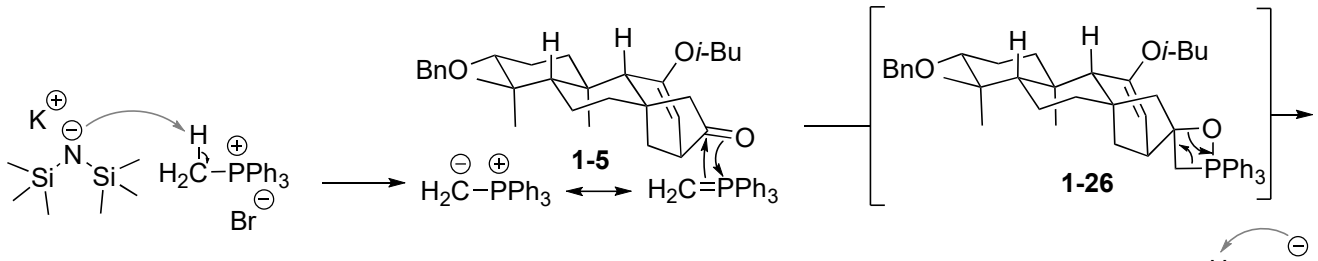
***Yields from 3:2 mixtures of **1-3** and **1-4**

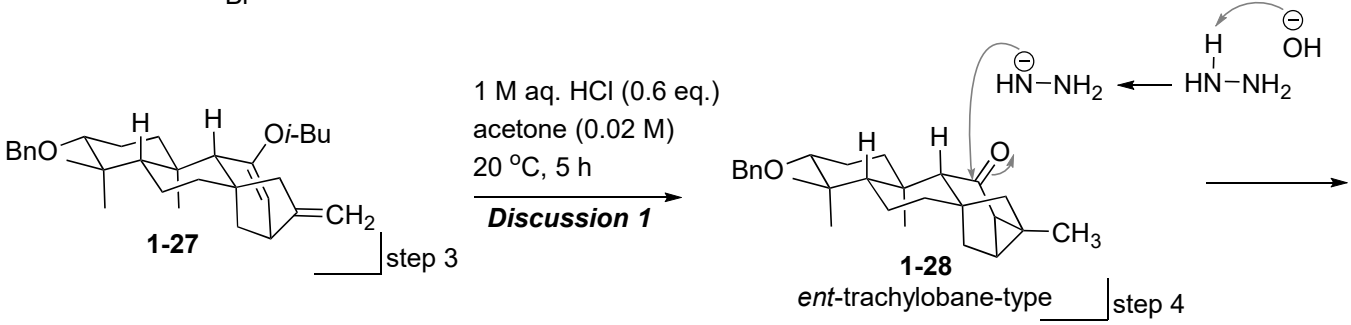
Brief mechanistic introduction of De Mayo reaction.

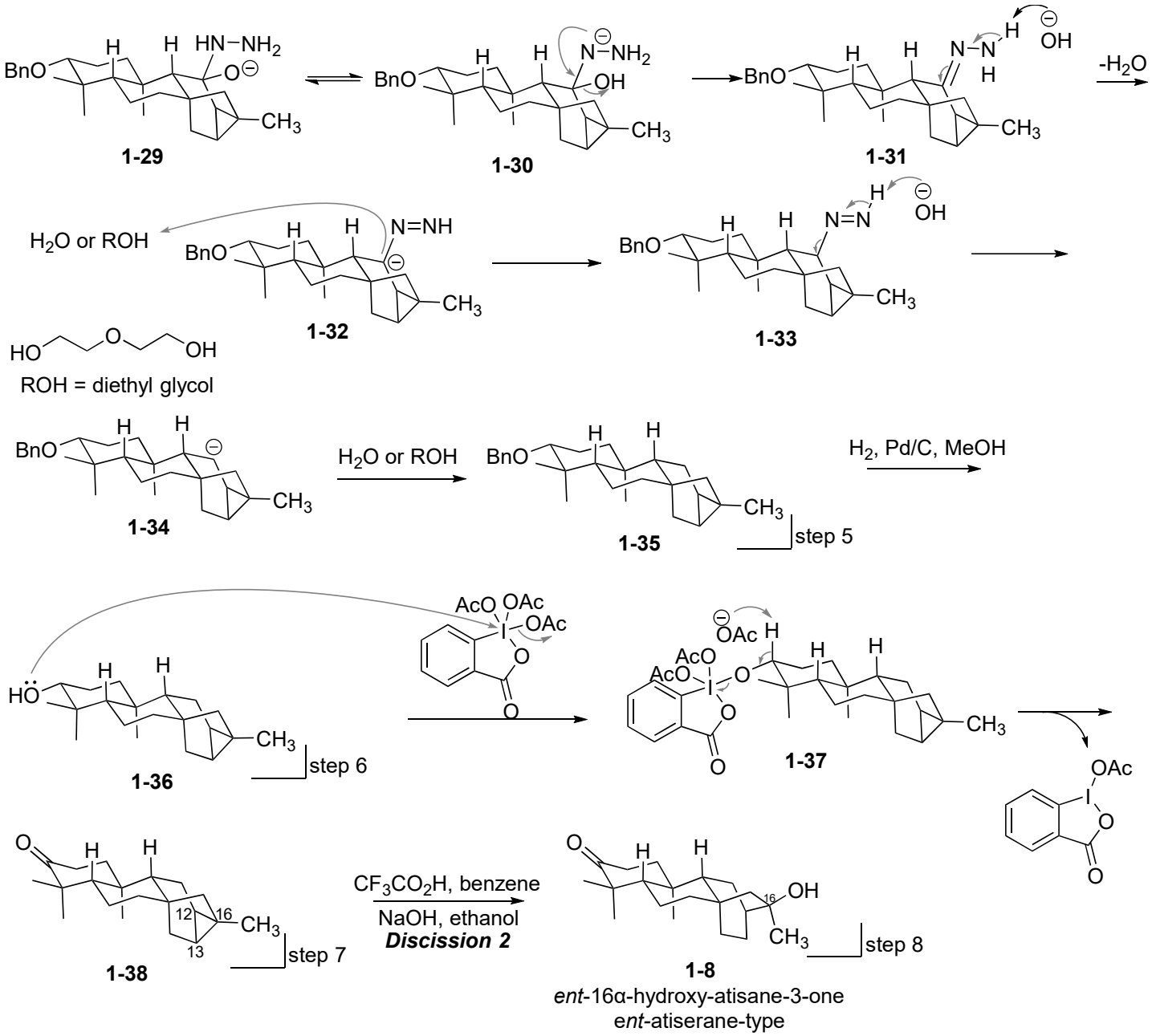


Evidence for regioselectivity of olefin [2+2] photocycloaddition reaction (De Mayo reaction).
DFT calculations (B3LYP/6-31G(d)) demostrates that the intermediate **1-3-TSa** with kaurane-type skeleton is favored both kinetically and thermodynamically compared to the phyllocladene-type skeleton intermediate.









Discussion 1: Nucleophilic cyclopropanation

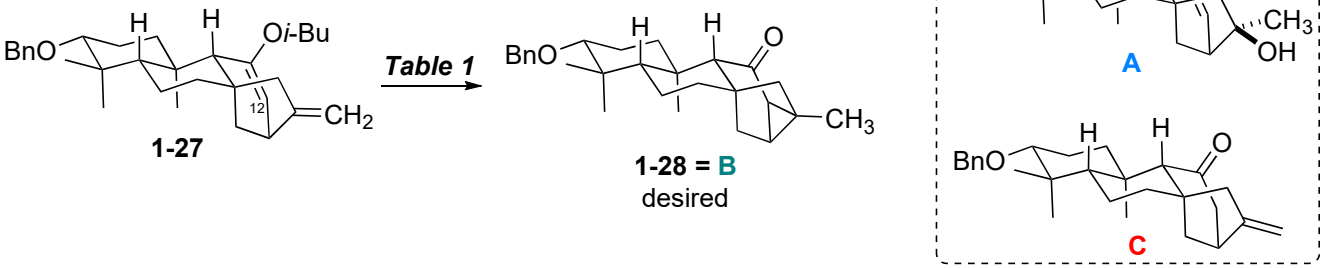
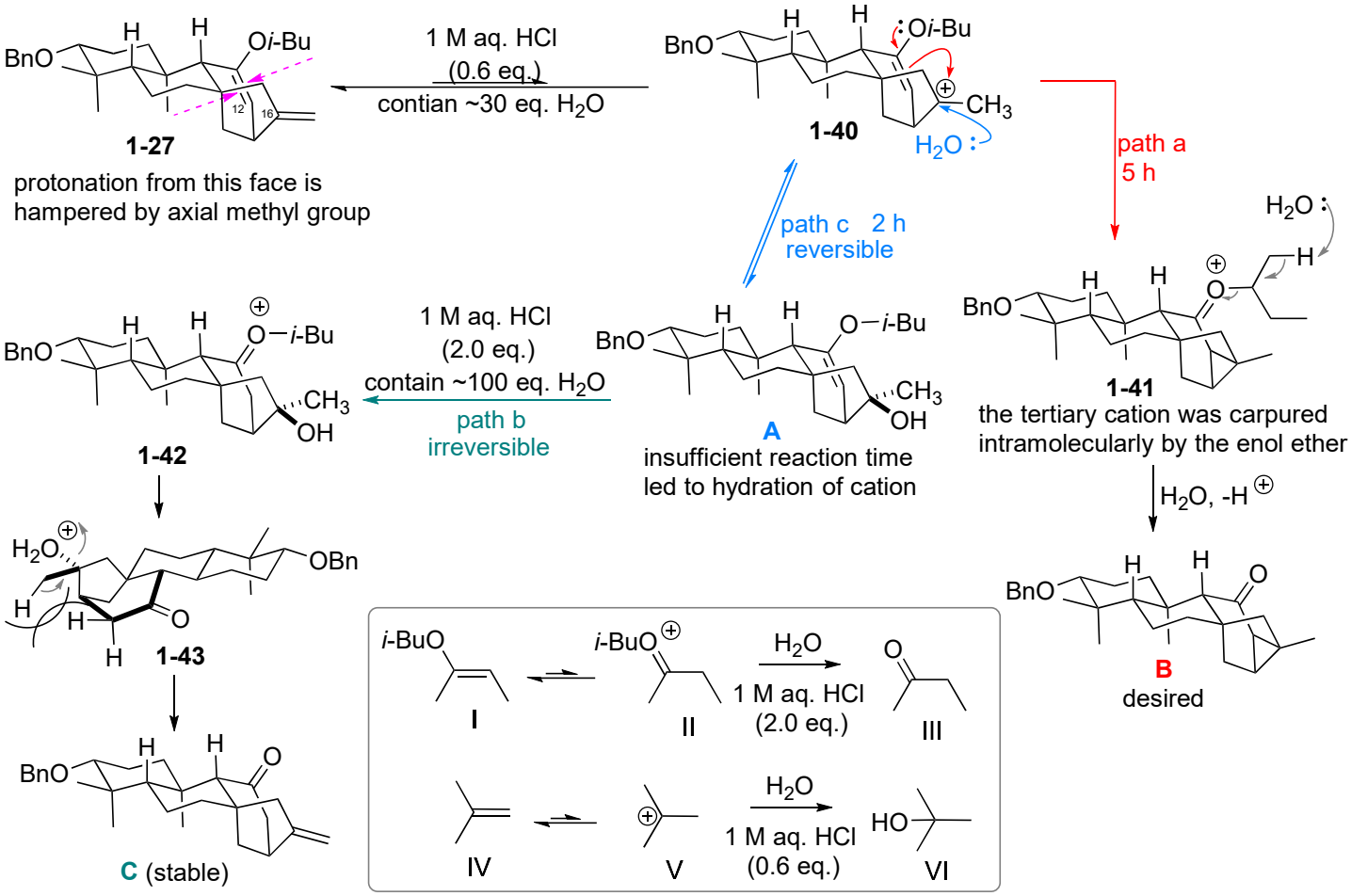


Table 1

entry	Conditions	yields		
		A	B	C
1	1 M aq. HCl (2.0 eq.), acetone (0.02 M), 20 °C, 5 h		43%	38%
2	1 M aq. HCl (0.6 eq.), acetone (0.02 M), 20 °C, 2 h	69%	20%	
3	1 M aq. HCl (0.6 eq.), acetone (0.02 M), 20 °C, 5 h		87%	

proton can hardly approach from concave face

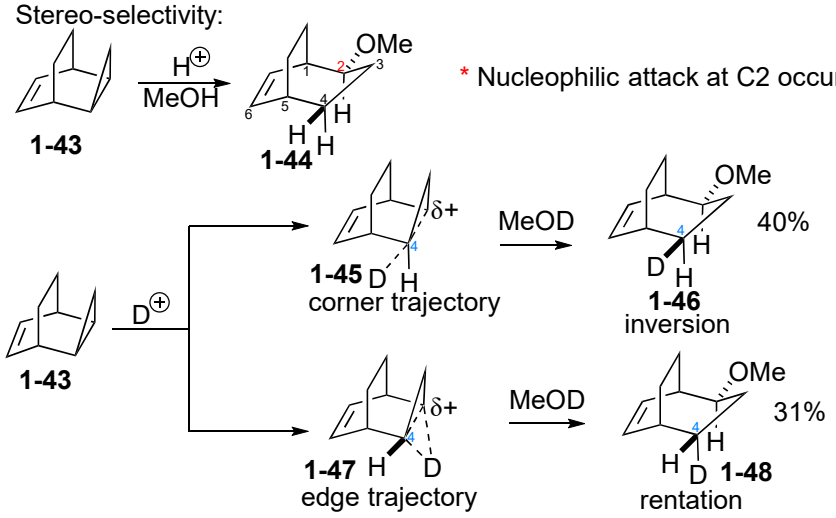


H_2O plays a key role in the selectivity of reaction pathway.
In the acidic condition, there are always equilibrium between I and II, IV and V.
More equivalent aq. HCl increases the oppotunity of enol ether hydrolysis.
Less anount of aq. HCl allowed enol ether to act as nucleophile toward cation.

Discussion 2: Mechanism of acid catalyzed cyclopropane ring opening

Regio-stereoselectivity: acid-catalyzed rupture of cyclopropane results in the cleavage of the most substituted carbon-carbon bond in preference to form more substituted carbon cation (Markovnikov rule).

Stereo-selectivity:

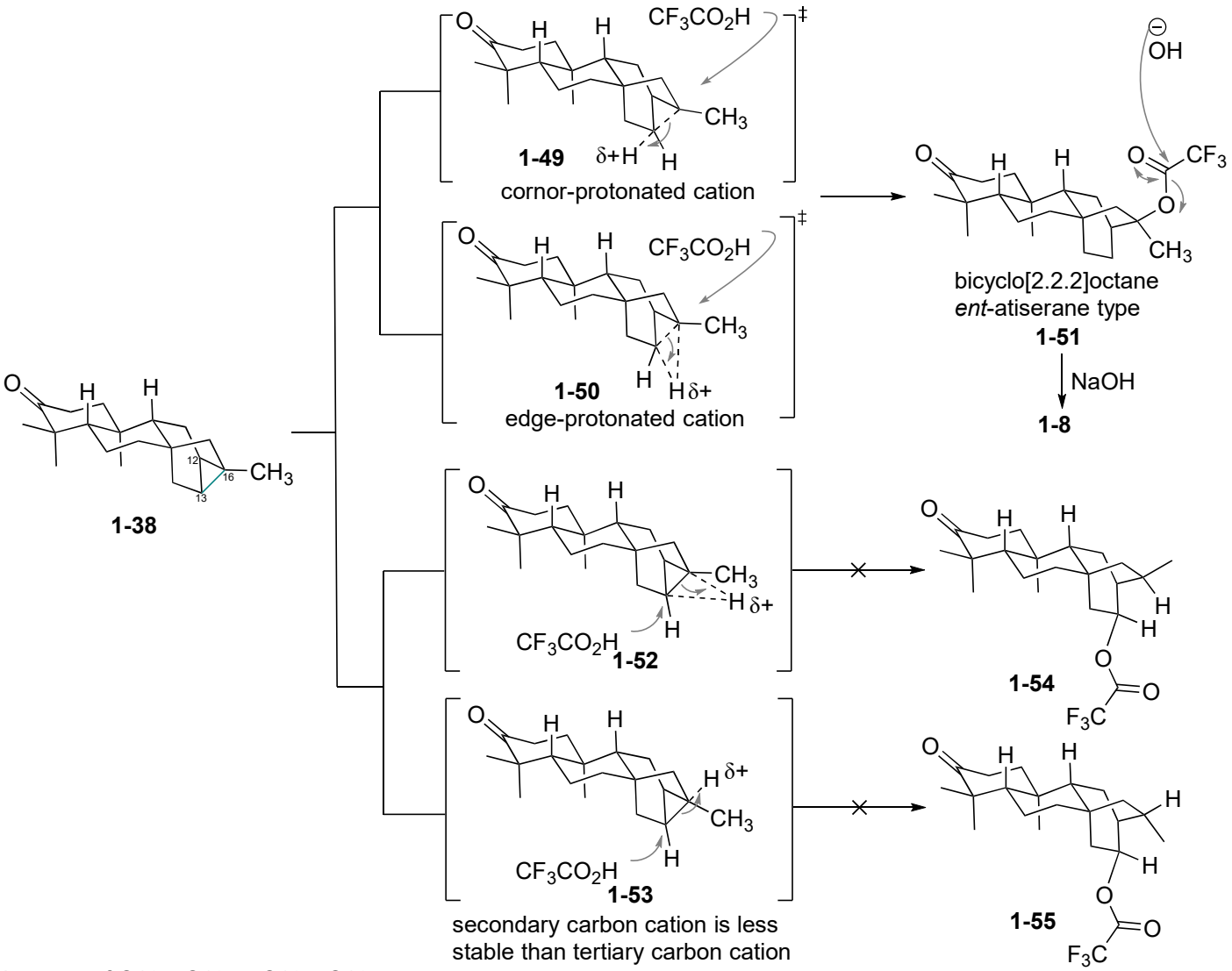


* Electrophilic attack at C4 occurs with both inversion and retention (1.3 : 1.0), indicating facile competiton.

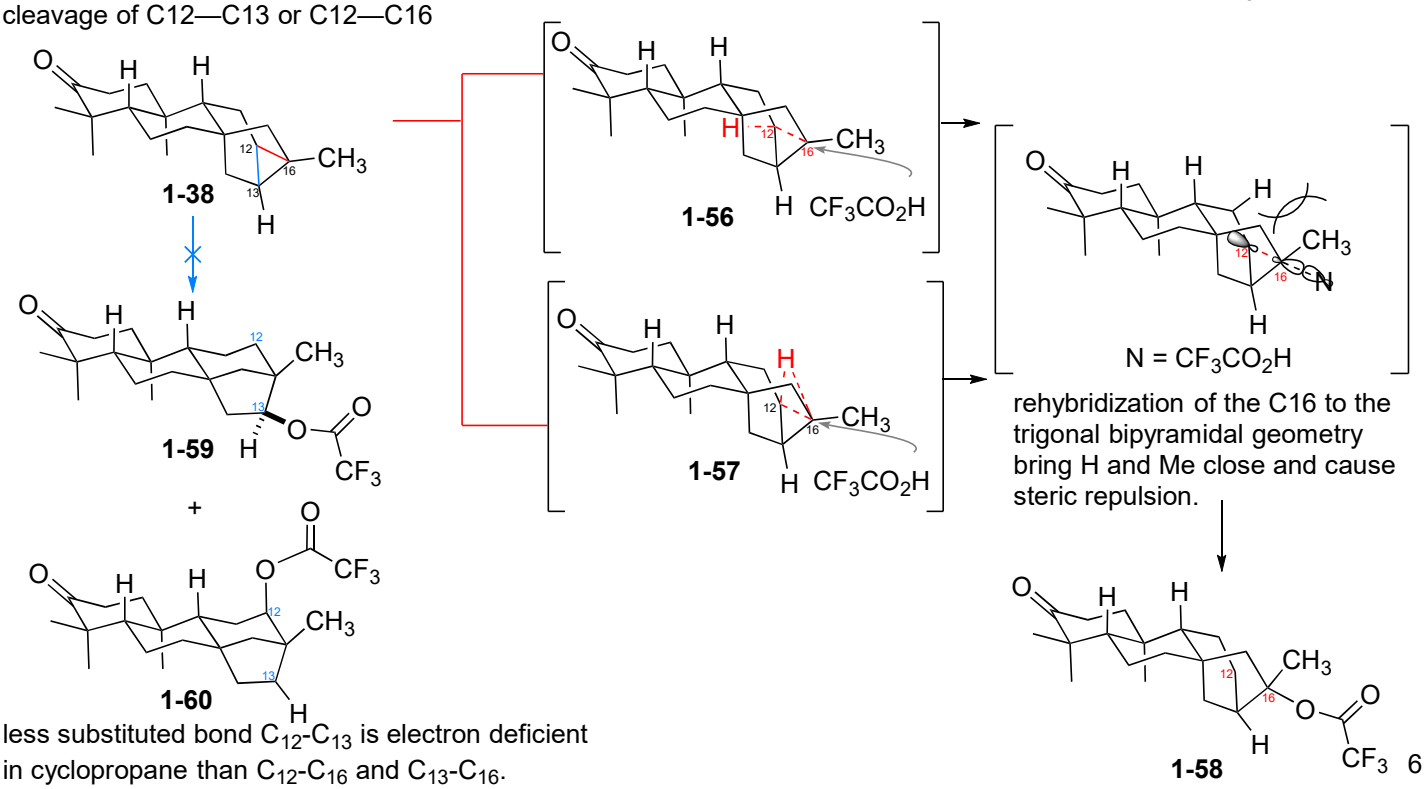
The protonated intermediate **1-45** and **1-46** do not further relax to classical secondary cation probably because no rearrangement product was obtained.

Burritt, A.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1995**, *60*, 7670-7673

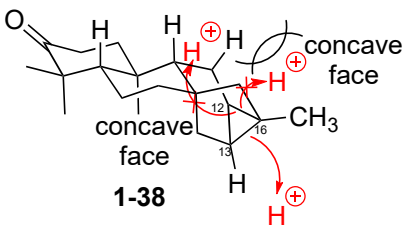
cleavage of C13—C16



cleavage of C12—C13 or C12—C16

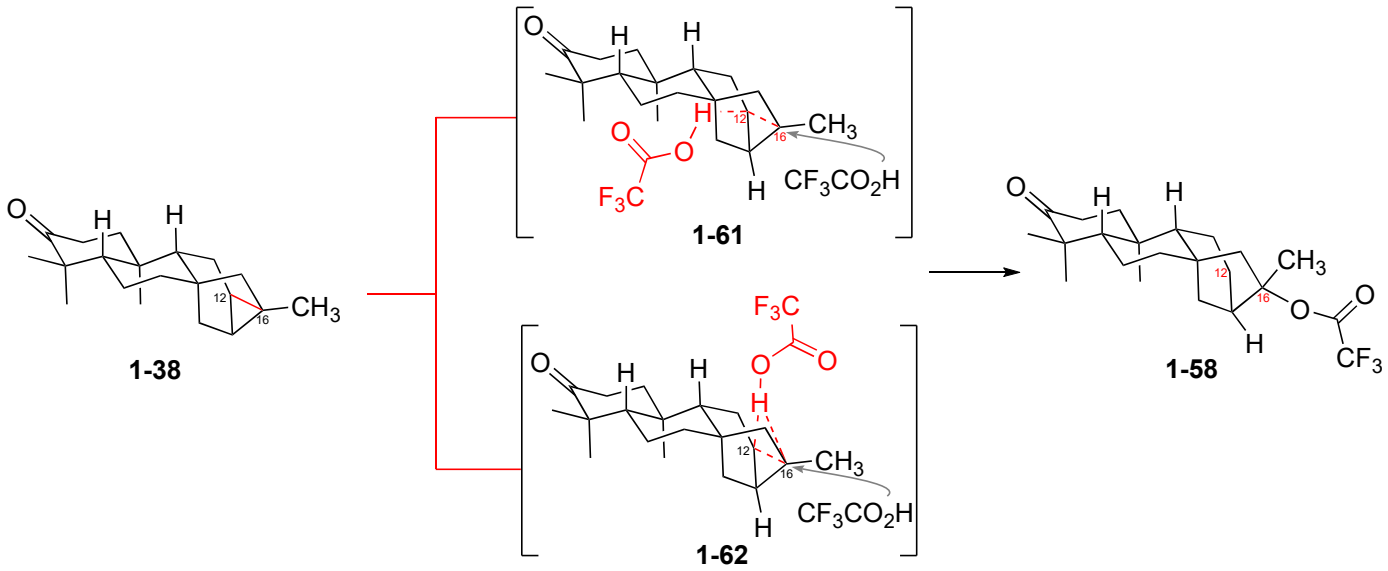


less substituted bond C_{12}-C_{13} is electron deficient in cyclopropane than C_{12}-C_{16} and C_{13}-C_{16}.



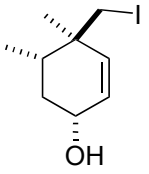
Carbon bonds C_{12}-C_{16} and C_{13}-C_{16} are more basic than C_{12}-C_{13} due to more substituted Methyl group at C_{16}.
Protonation of C_{13}-C_{16} is more favorable because the paths for C12-C16 protonation would encounter steric repulsion of concave face.

CF_3CO_2H can also act as a whole for the protonation of cyclopropane.



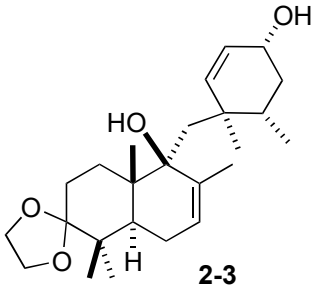
Large steric repulsion exists when CF_3CO_2H approaches from the concave faces to cyclopropane.

2.



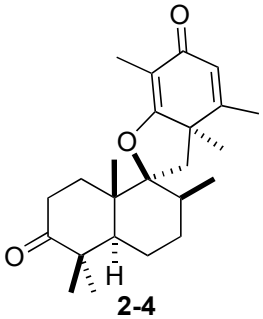
2-1
(1.2 eq.)

1. *n*-BuLi (1.0 eq.), -78°C, 2 min;
   t-BuLi (2.2 eq.), rt; **2-2**
   pentane/ether (3:2), rt
   83%



2-3

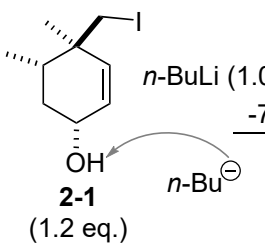
2. MnO_2 (10 eq.), CH_2Cl_2,rt, 67-75% *)
3. $Fe(acac)_3$ (0.2 eq.), $PhSiH_3$ (2 eq.), EtOH, 60 °C, 88-95% *)
4. IBX (3.0 eq.), Na_2HPO_4 (1.2 eq.), MS 4A, DMSO, 80 °C, 72%
5. I_2 (1.1 eq.), $(NH_4)_2[Ce(NO_3)_6]$ (1.1 eq.), MeCN, 0 °C, 84%
6. $Pd(OAc)_2$ (0.1 eq.), SPhos (0.2 eq.), K_3PO_4 (4.0 eq.), $MeB(OH)_2$ (5 eq.), H_2O (10 eq.), toluene, 80 °C, 95%
7. $(PhSeO)_2O$ (2.0 eq.), $NaHPO_4$ (3.0 eq.), MS 4A, PhCl, 100 °C; HCl, 86%



2-4
chermesin B

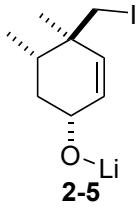
Yang, F.; Jr, J. A. P. *J. Am. Chem. Soc.* **2022**, *144*, 12970−12978.

Answer 2



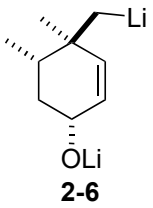
2-1
(1.2 eq.)

n-BuLi (1.0 eq. relative to **2-1**),
-78°C, 2 min

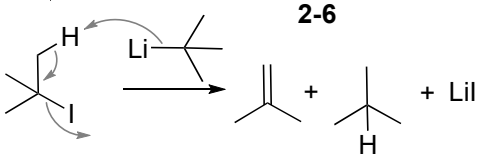


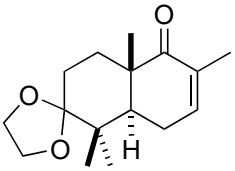
2-5

t-BuLi (2.2 eq.relative to **2-1**),
-78 °C, 10 mins; rt, 15 mins

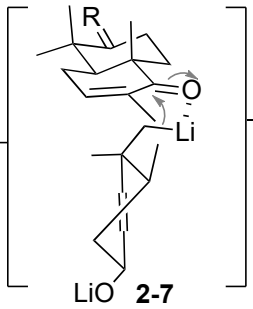


2-6

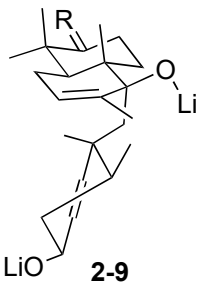




2-2

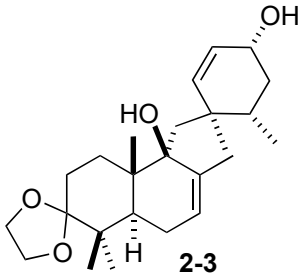


2-7

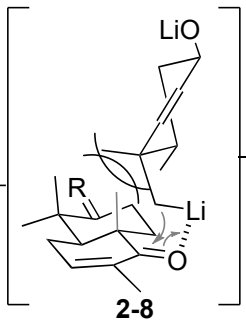


2-9

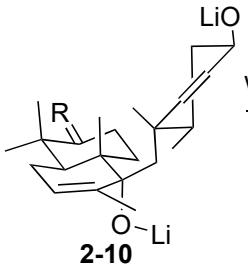
work up



2-3
obtained

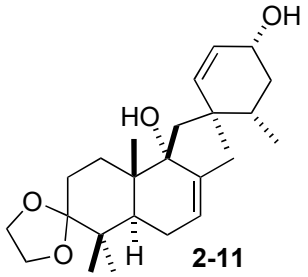


2-8



2-10

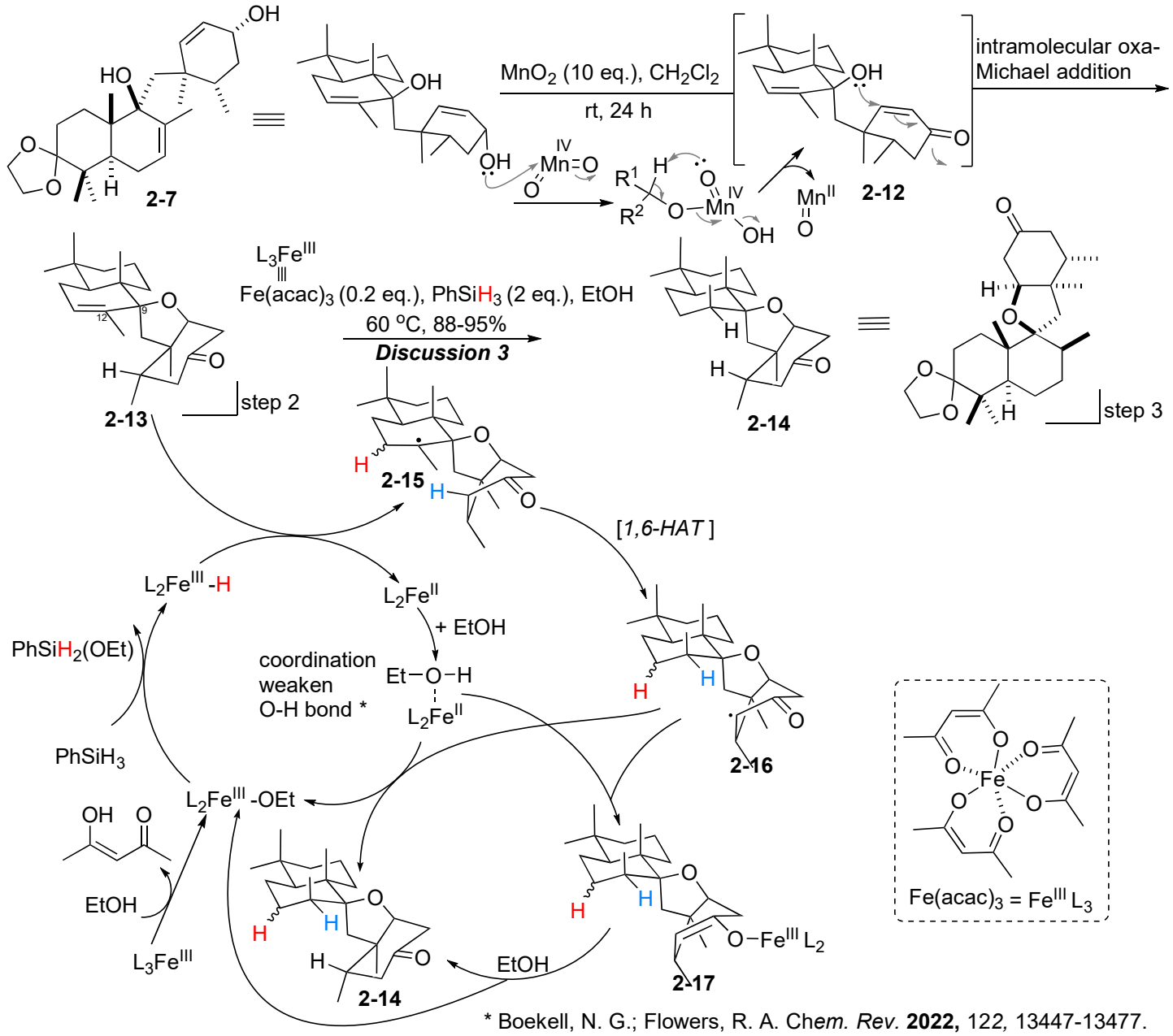
work up



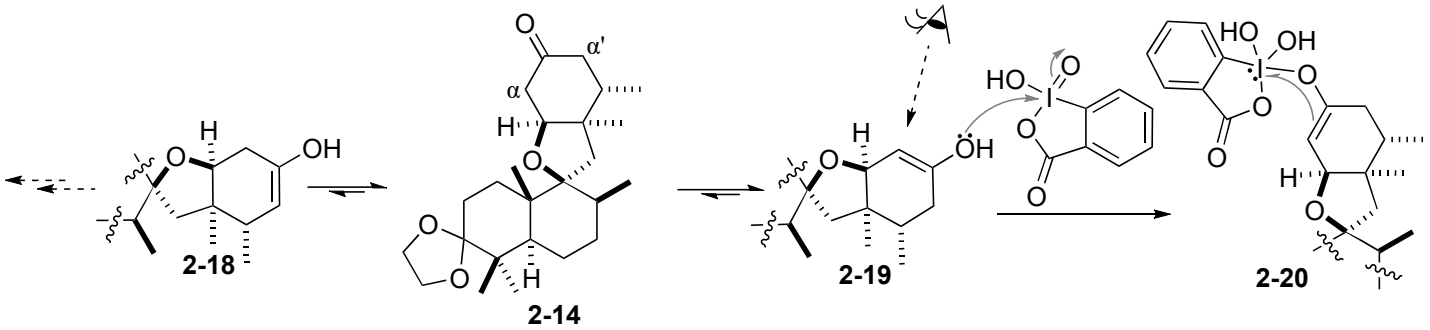
2-11
NOT obtained

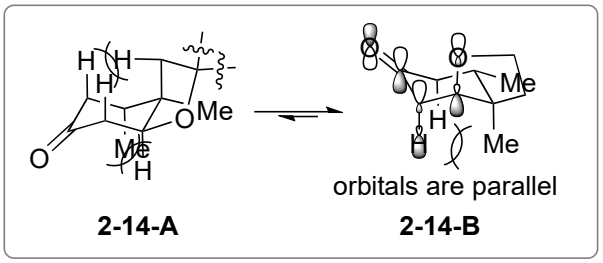
The axial methyl group inhibit the approaching of lithium species from up face.

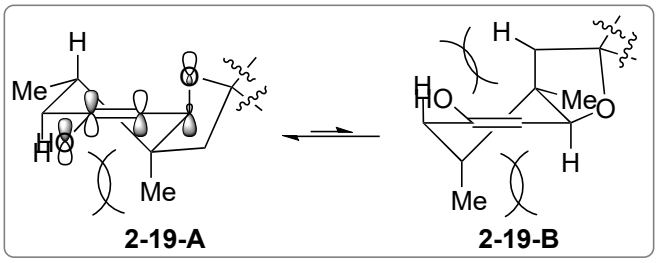
step 1

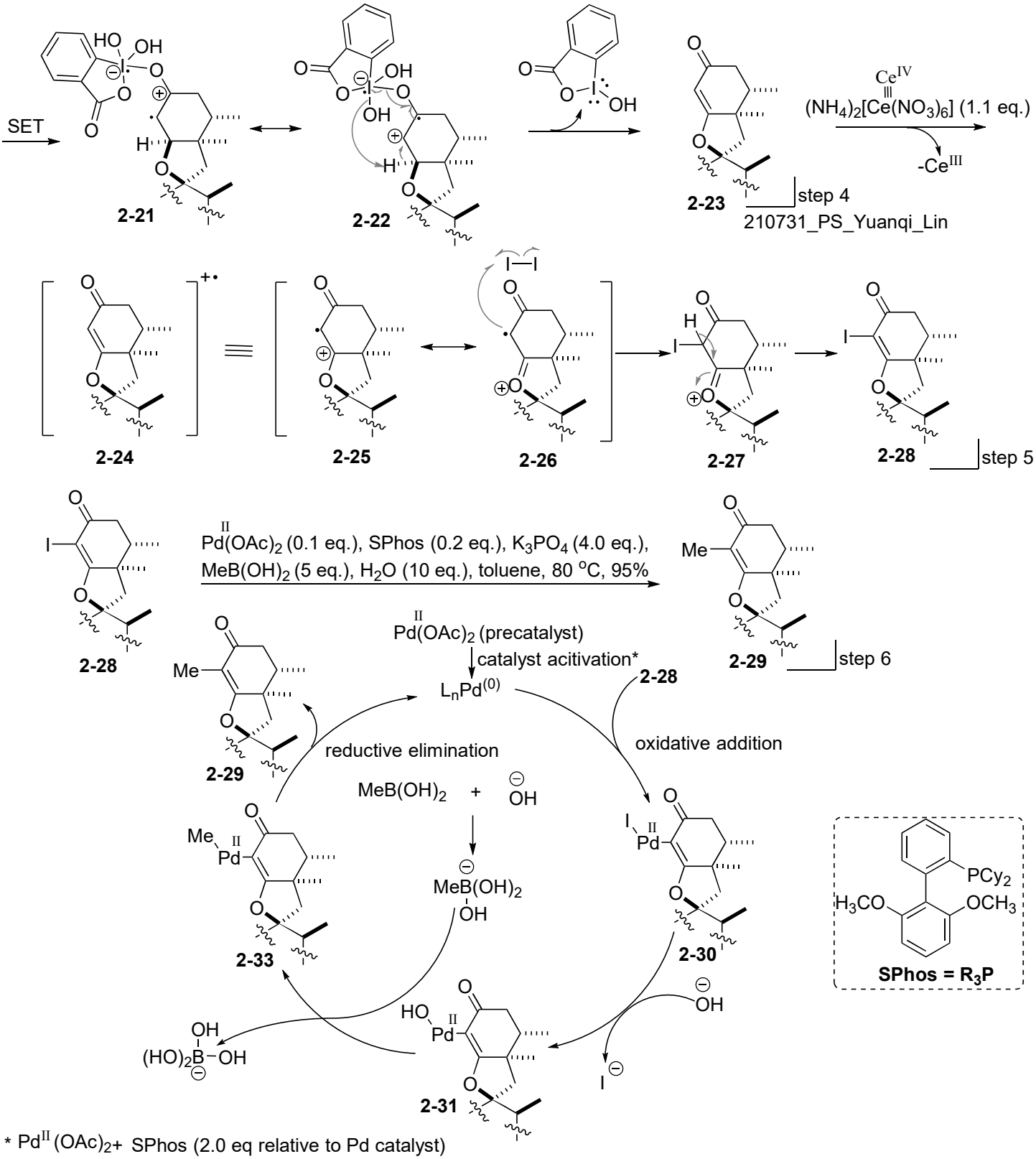


* Boekell, N. G.; Flowers, R. A. Ch*em. Rev.* **2022,** 122, 13447-13477.
Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland P. L. *J. Am. Chem. Soc.* **2019**, *141*, 7473−7485.

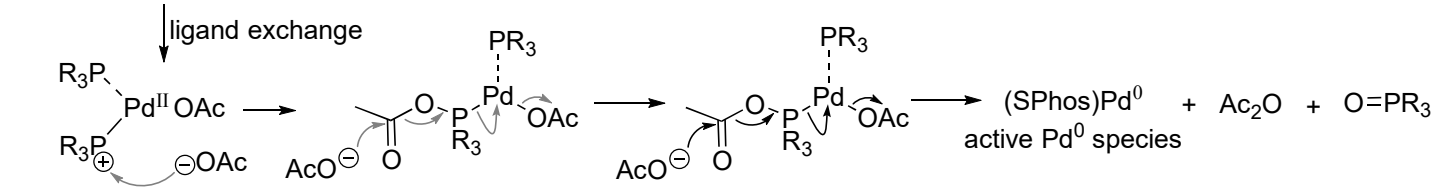




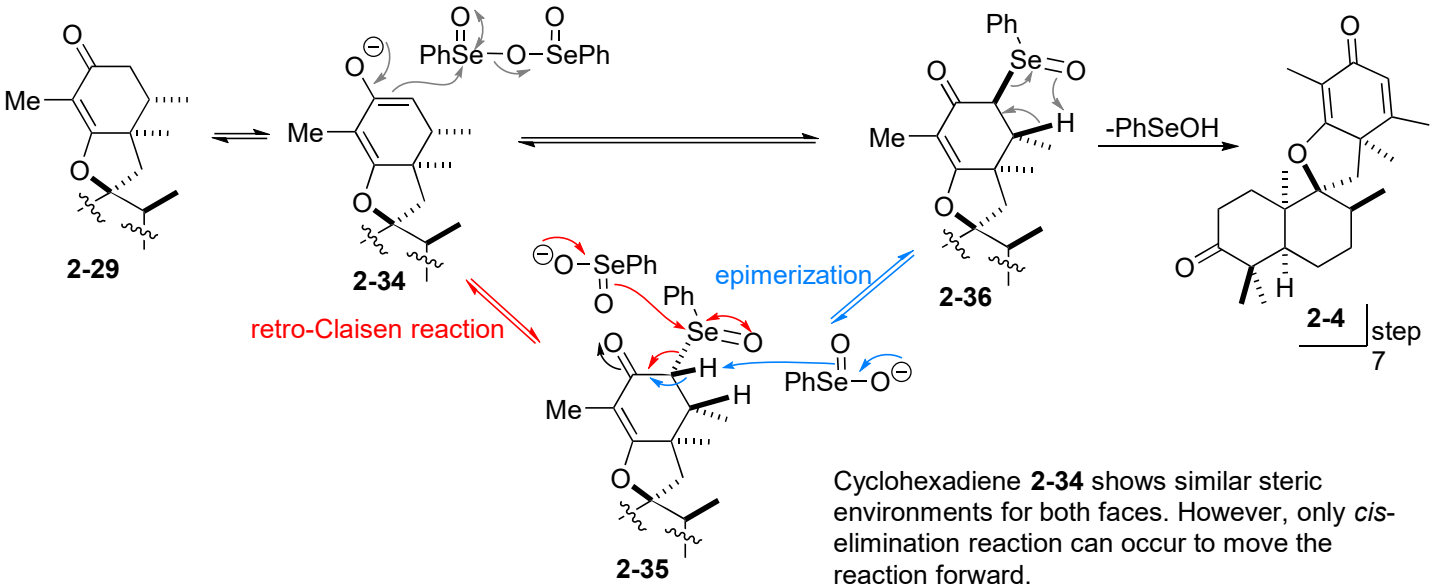




* $Pd^{II}(OAc)_2$+ SPhos (2.0 eq relative to Pd catalyst)



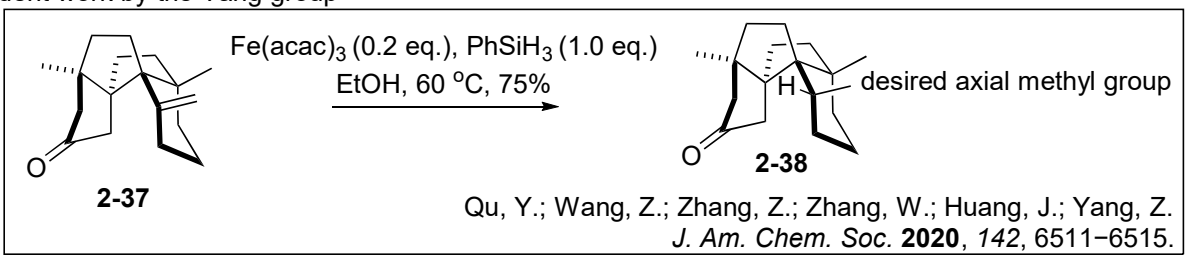
Wei, C. S.; Davies, G. H. M.; Soltani, O.; Albrecht, J.; Gao, Q.; Pathirana, C.; Hsiao, Y.; Tummala, S.; Eastgate, M. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 5822 –5826.



Cyclohexadiene **2-34** shows similar steric environments for both faces. However, only *cis*-elimination reaction can occur to move the reaction forward.

Discussion 3: Selectivities of intramolecular HAT reaction

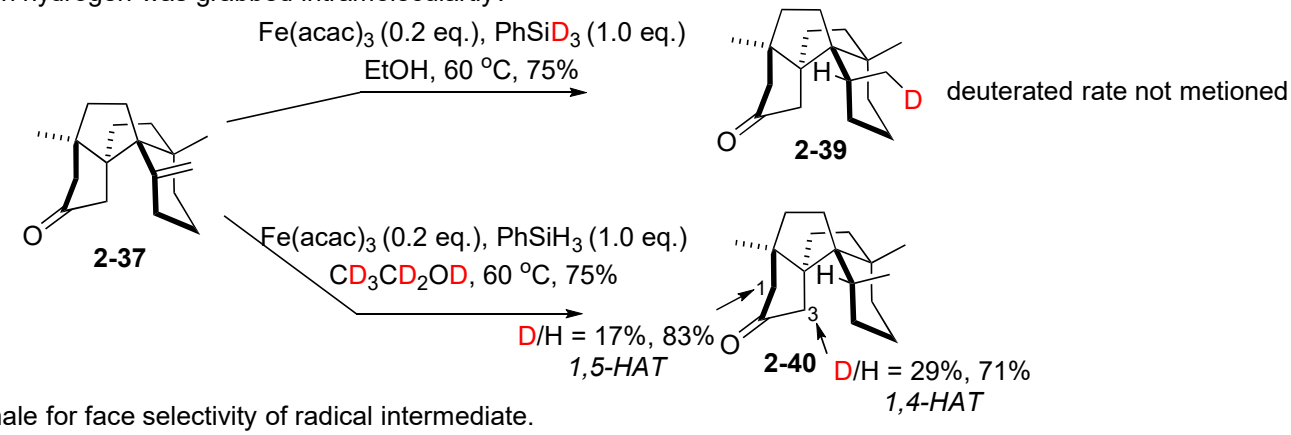
2.1 Precedent work by the Yang group



Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511−6515.

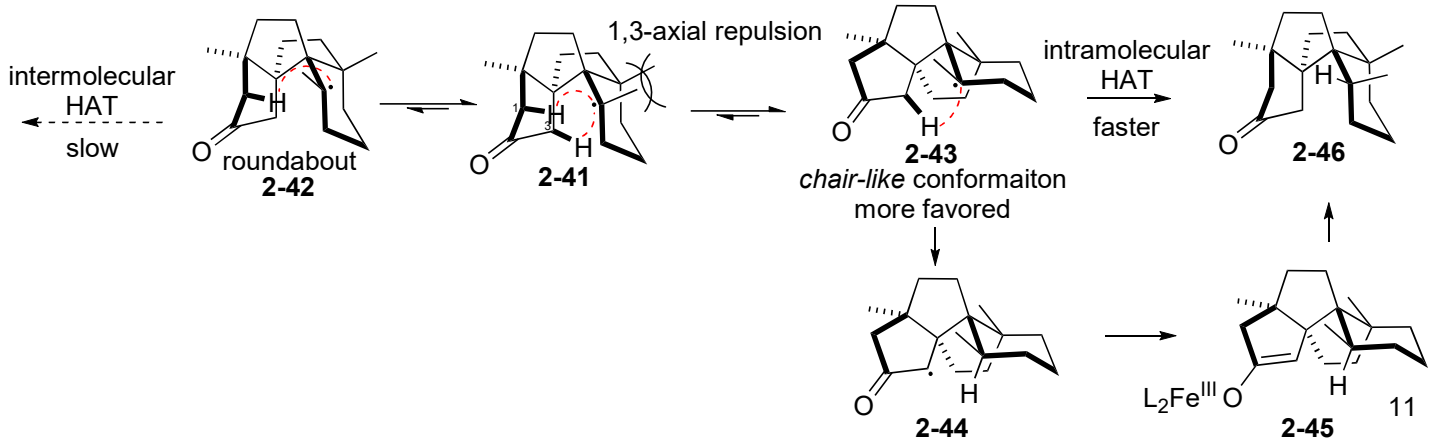
2.1.1 Deuterium labeling studies

Which hydrogen was grabbed intramolecularly?



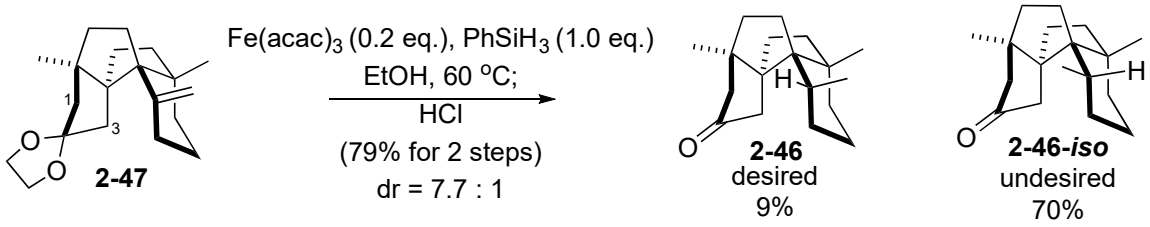
2.1.2 Rationale for face selectivity of radical intermediate.

Chair-like conformation radical intermediate dominated.



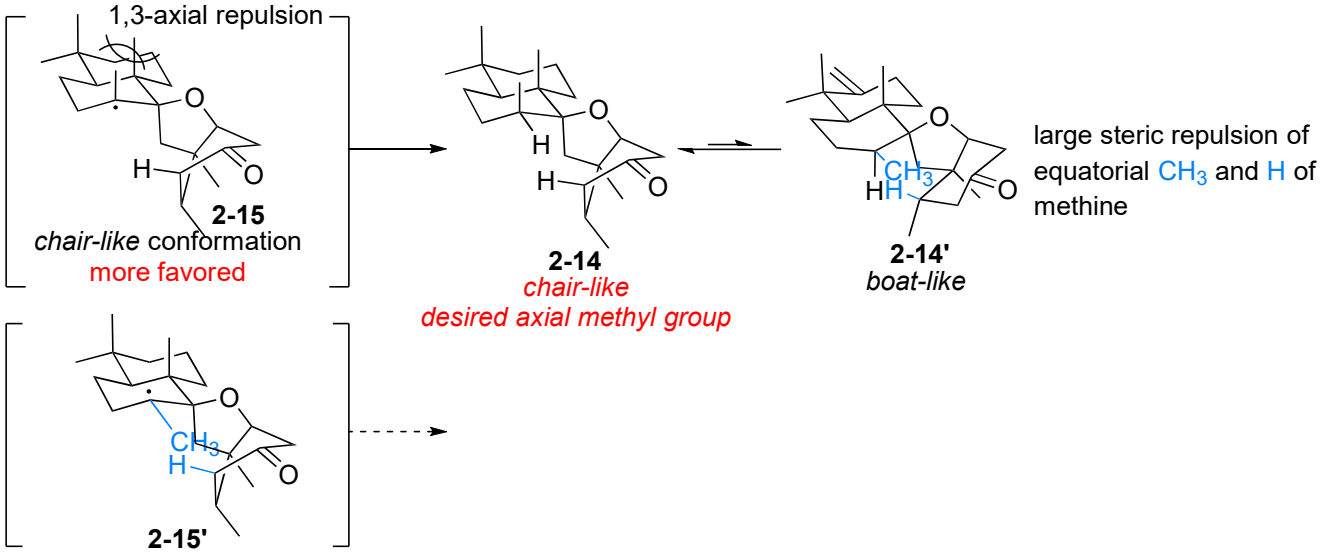
2.1.3 Control experiment

The protons at the C1 and C3 positions can be abstracted intramolecularly largely due to the acitivation of **carbonyl group**.



2.2 Applicable to this case.

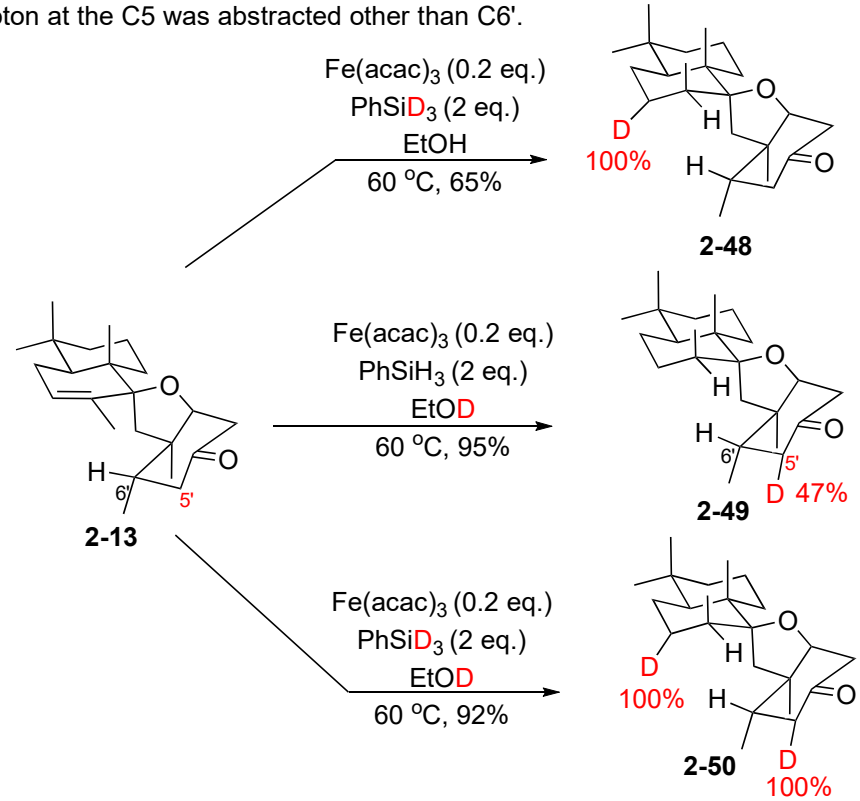
2.2.1 Consideration of transitions state and product conformations



Methyl group hinders the H to be seized

2.2.2 Deuterium labeling studies

Only proton at the C5 was abstracted other than C6'.



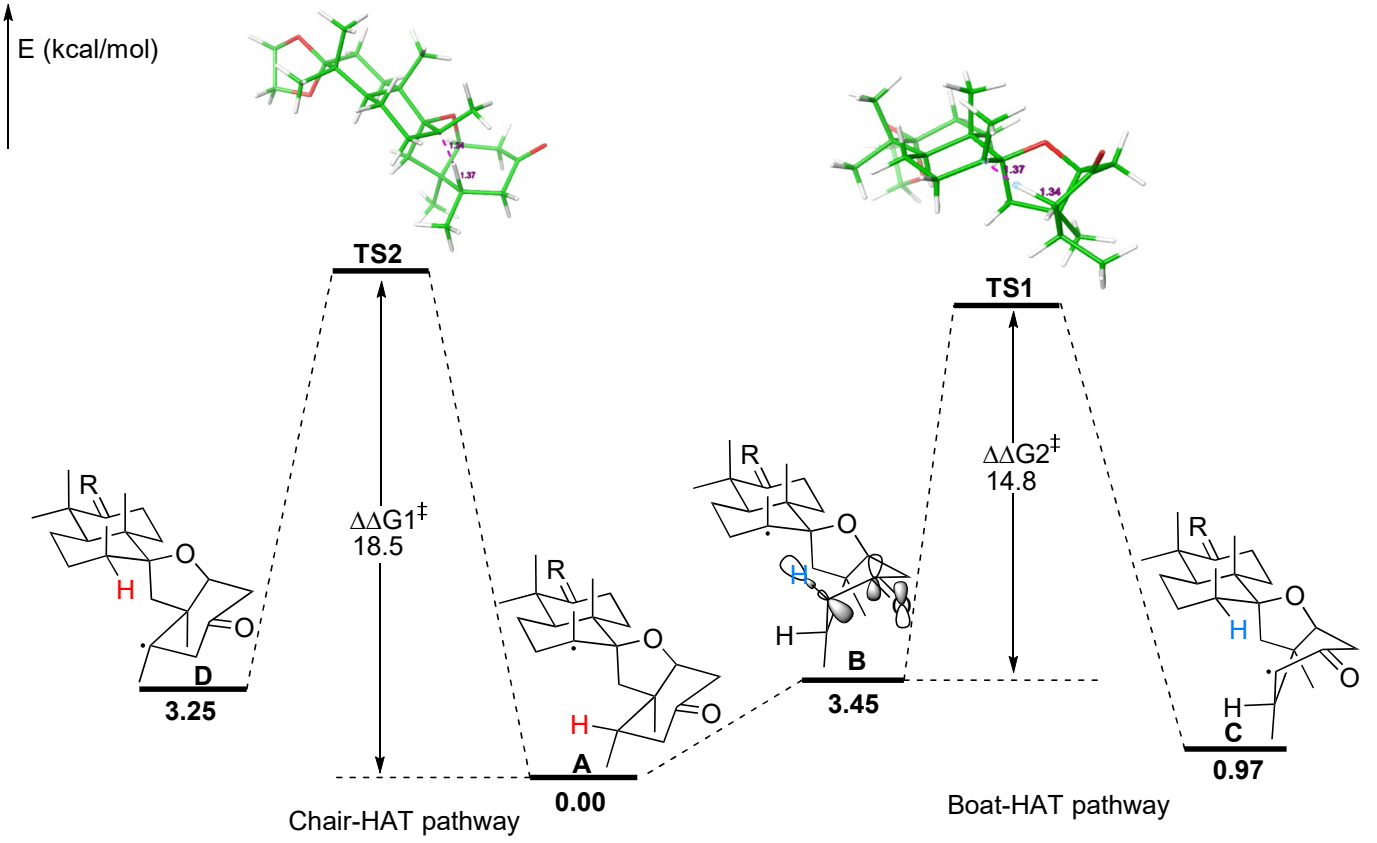
2.2.3 Rationale for hydrogen selectivity

Less stable conformer led to the major product: the reaction rates are much slower than the rate of interconversion, (ΔGAB is small relative to ΔΔG1 and ΔΔG2);

The lower energy of boat-like pathway product than chair-like pathway product might explain the exclusive abstraction of proton 5'.

The selective proton 5' transfer might also benefit from the activation of carbonyl group.

The radical in C might have characteristic of electrophilic radical which might be the reason why it is more stable than D, it might be stabalized by the adajecent carbonyl group.



DFT calculations at (M06-2X/6-31G(d,p)/PBF.