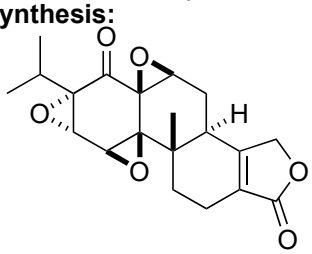
Problem Session (2) -Answer-

2022.5.14. Jaejoong Han

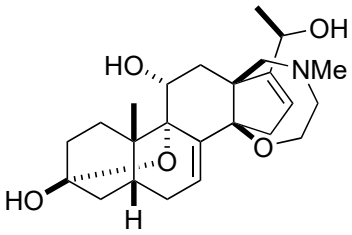
Topic: Recent total synthesis by Prof. Tuoping Luo

2005 :B.S. in Chemistry, College of Chemistry and Molecular Engineering, Peking University (Prof. Zhen Yang)
2005-2011 :Ph.D. in Chemistry, Department of Chemistry and Chemical Biology, Harvard University;
Chemical Biology Program, Broad Institute (Prof. Stuart L. Schreiber)
2011-2013 :Postdoctoral Fellow, H3 Biomedicine Inc., (Dr. John Yuan Wang)
2013-2019 :Assistant professor, College of Chemistry and Molecular Engineering, Peking University
2019- :Associate professor, College of Chemistry and Molecular Engineering, Peking University

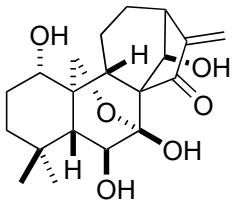
Total synthesis:



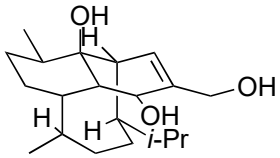
(-)-triptonide
J. Am. Chem. Soc. **2022**, *144*, 2292−2300.



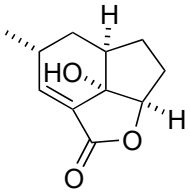
(-)-batrachotoxinin A
J. Am. Chem. Soc. **2020**, *142*, 3675−3679.



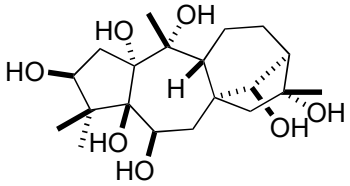
(-)-oridonin
J. Am. Chem. Soc. **2019**, *141*, 20048−20052.
200613_PS_Shimizu_Shinzuke



(-)-vinigrol
J. Am. Chem. Soc. **2019**, *141*, 3440-3443.
191207_LS_Yuto_Hikone_(-)-Vinigrol

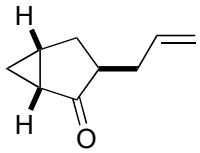


(-)-4-*epi*-Galiellalactone
Org. Biomol. Chem. **2019**, *17*, 1886−1892.
problem 1



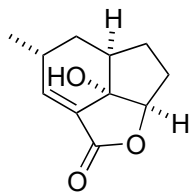
(-)-Grayanotoxin III
J. Am. Chem. Soc. **2022**, *144*, 5268−5273.
problem 2

1.

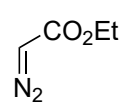


1-1

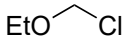
1. BF_3•Et_2O (1.5 eq), **1-2** (1.5 eq), toluene, 0 to 25 ºC, 43%
   (2 steps from previous alkylation)
2. NaH (1.5 eq), **1-3** (1.5 eq), THF, 0 to 25 ºC, 63%
3. 9-BBN (3 eq), THF, 0 to 25 ºC
   then EtOH, 6 M aq. NaOH, H_2O_2, 0 ºC
4. DMP (1.5 eq), $NaHCO_3$ (4 eq), CH_2Cl_2, 0 to 25 ºC, 74% (2 steps)
5. TMS_3SiH (2 eq), AIBN (0.25 eq), toluene, 85 ºC, 86%
6. *hv* (254 nm), MeOH, 25 ºC, 9 h then additional 12 h without irradiation, 63%



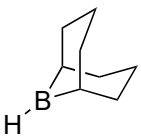
1-4
((-)-4-*epi*-Galiellalactone)



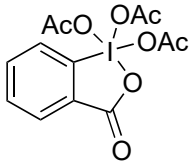
1-2



1-3



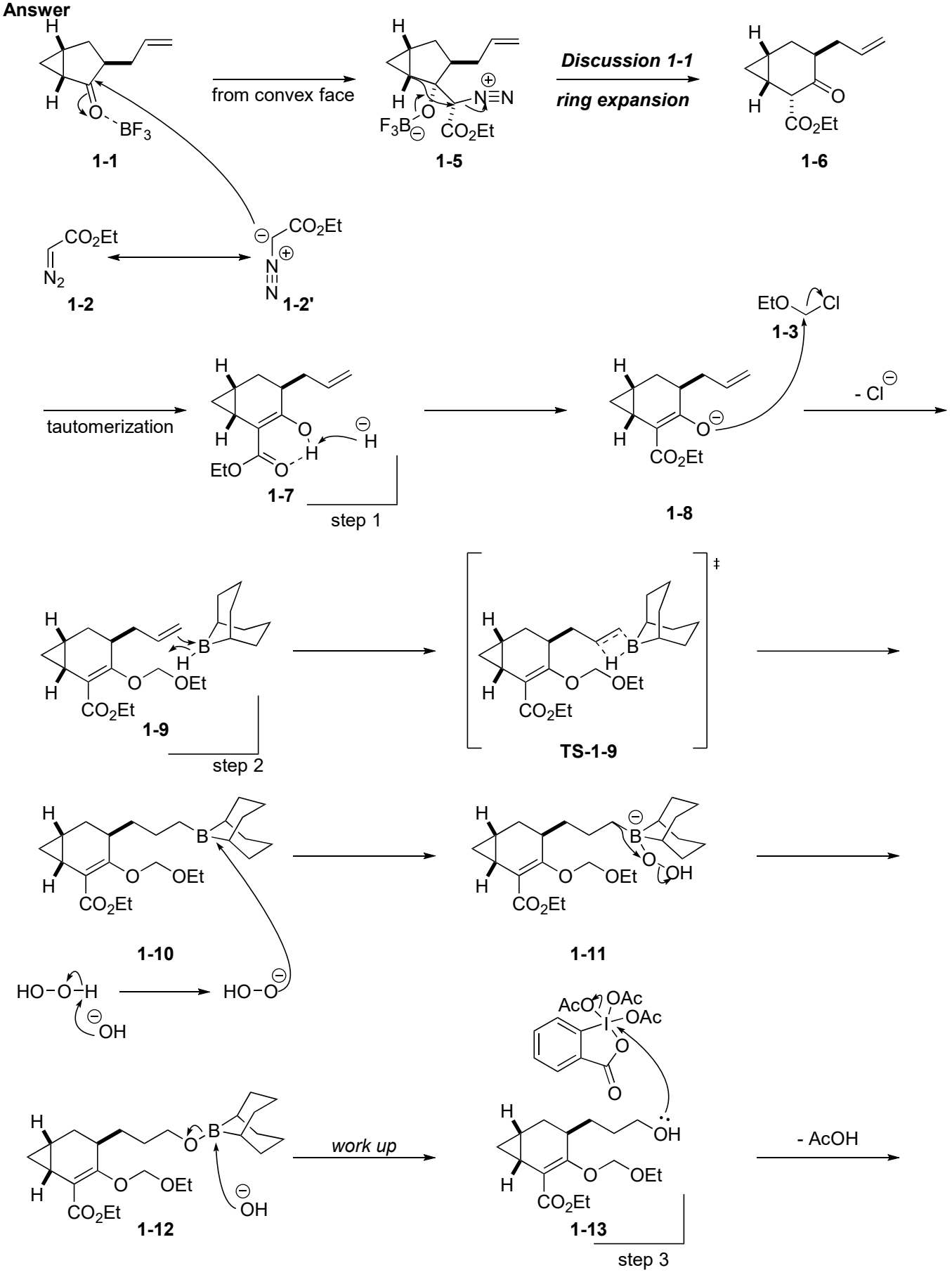
9-BBN

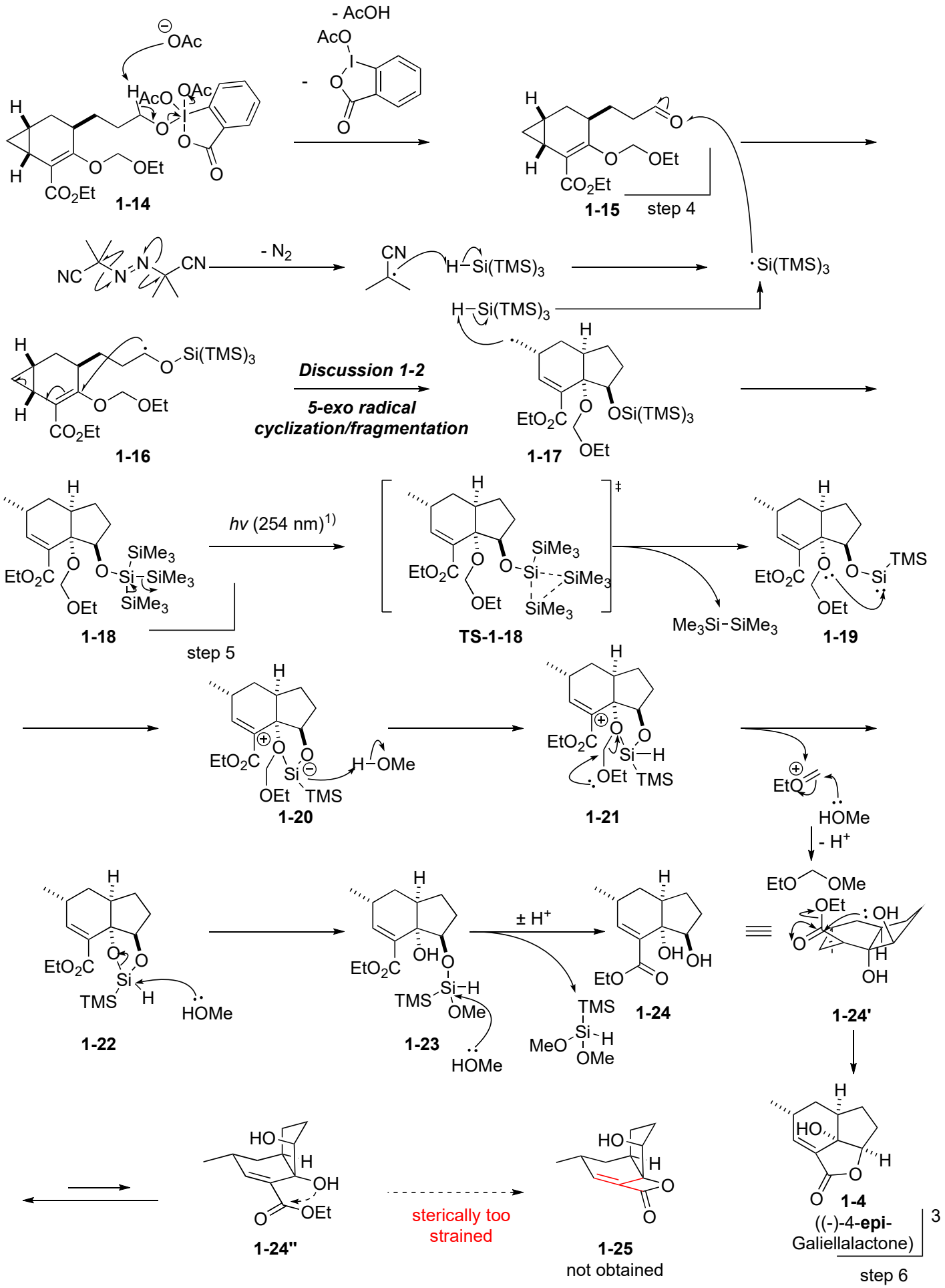


DMP

Lu, Y.; Zhao, S.; Zhou. S.; Chen, S.-C.; Luo, T. *Org. Biomol. Chem*. **2019**, *17*, 1886−1892.

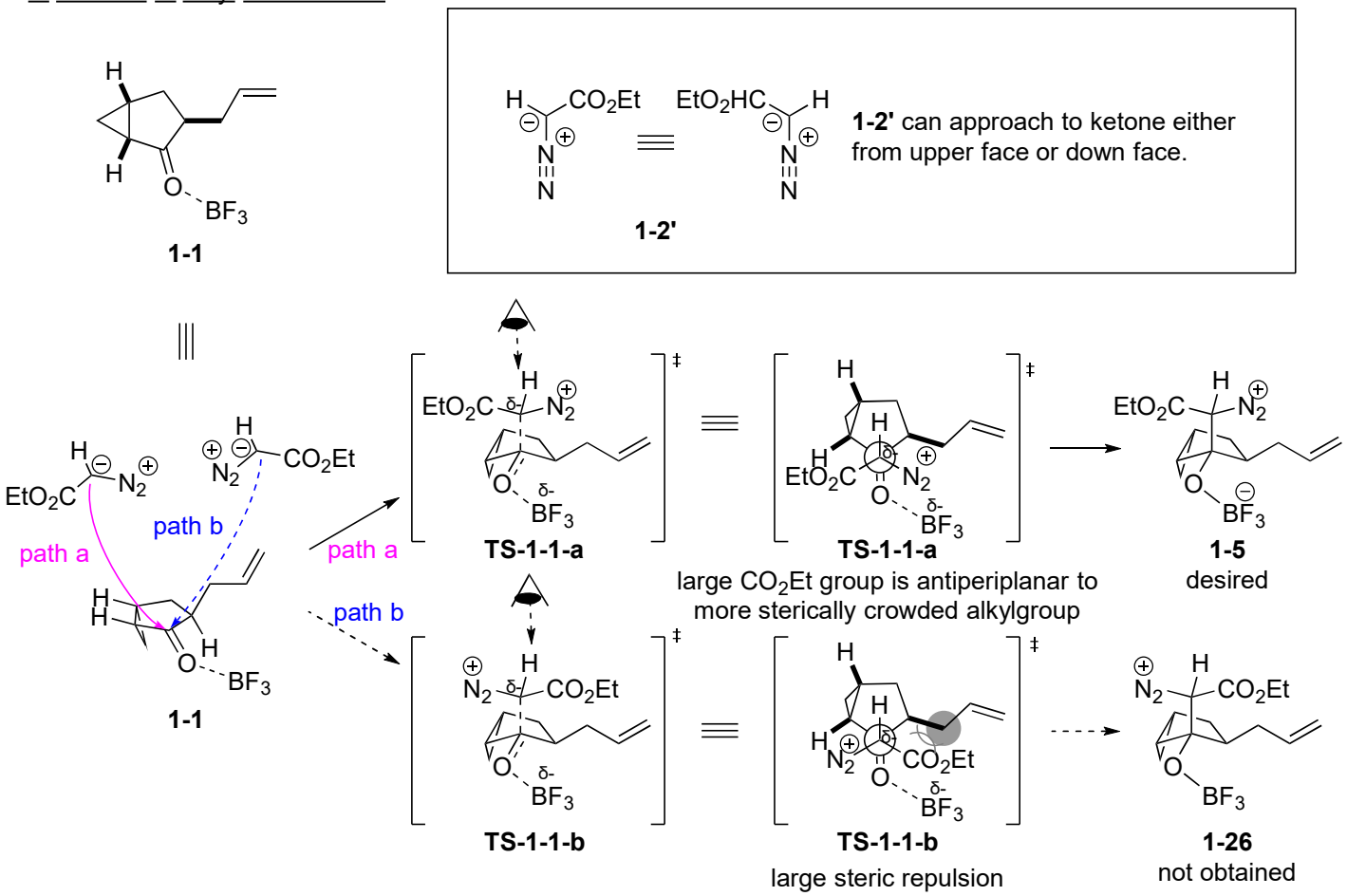
Answer


from convex face
Discussion 1-1
ring expansion
1-1
1-5
1-6
1-2
1-2'
1-3
tautomerization
1-7
step 1
1-8
- Cl
1-9
step 2
TS-1-9
1-10
1-11
work up
1-12
1-13
step 3
- AcOH


- AcOH
1-14
1-15
step 4
- N2
Si(TMS)3
1-16
Discussion 1-2
5-exo radical
cyclization/fragmentation
1-17
hv (254 nm)1)
1-18
step 5
TS-1-18
Me3Si-SiMe3
1-19
1-20
1-21
HOMe
- H+
1-22
± H+
1-23
1-24
1-24'
1-24"
sterically too
strained
1-25
not obtained
1-4
((-)-4-epi-
Galiellalactone)
step 6
3

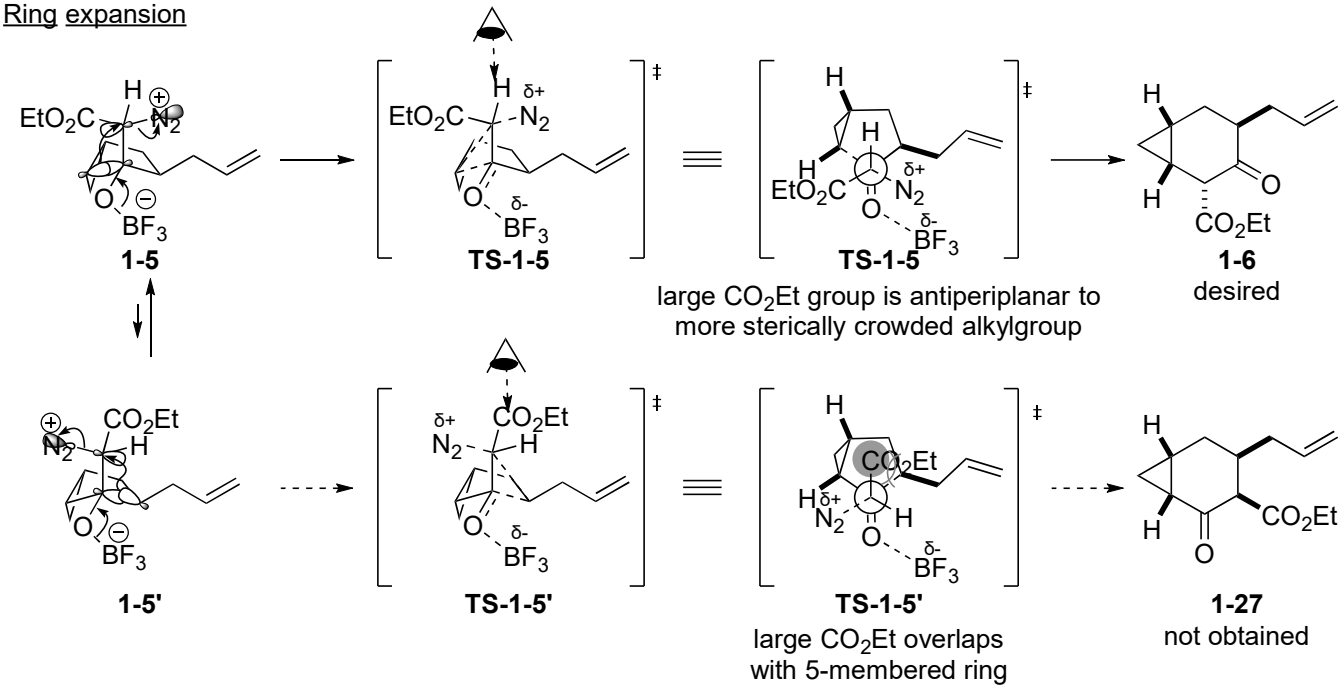
Discussion 1-1: ring expansion

1. Addition of ethyl diazoacetate



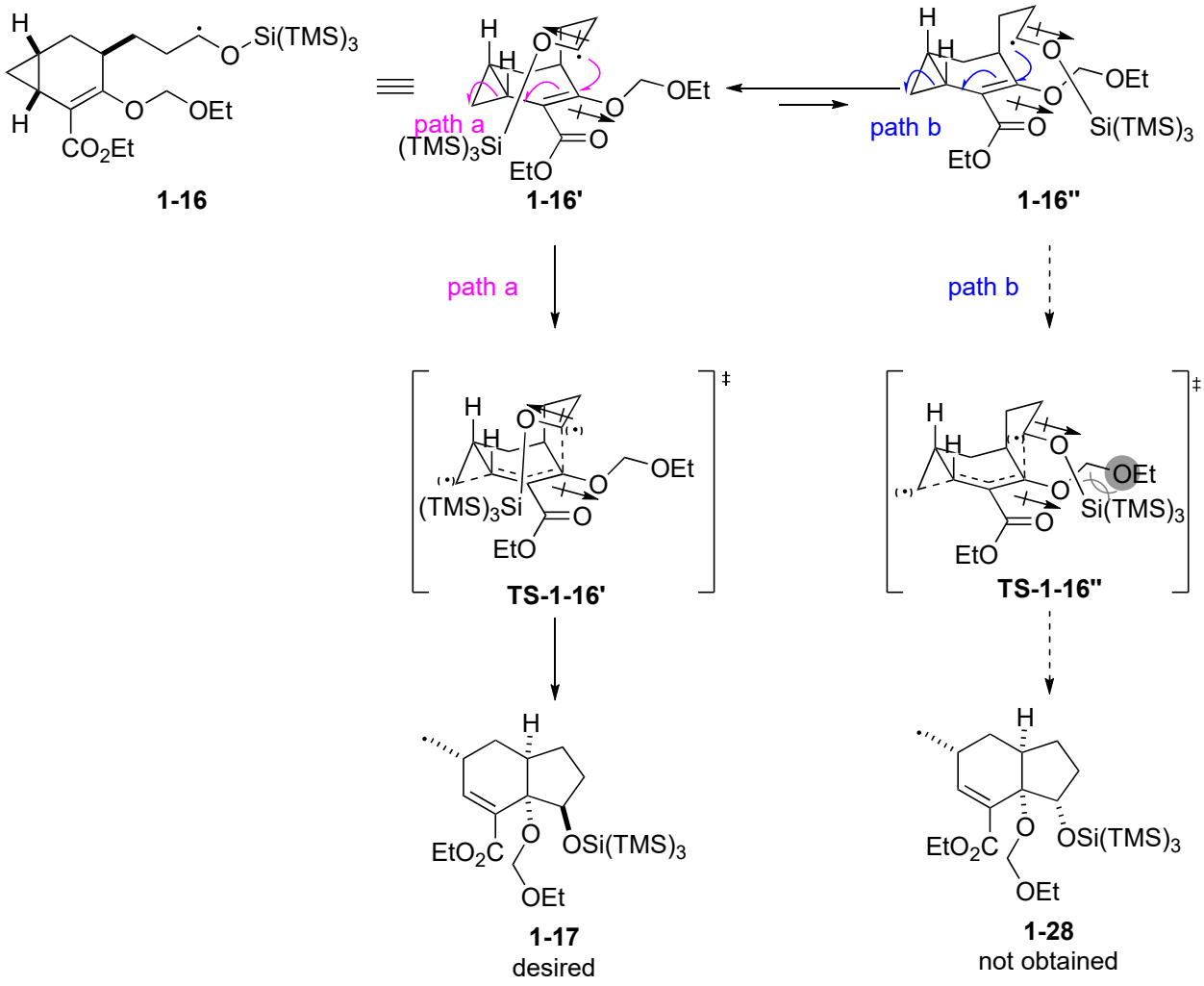
1-2' approaches to ketone with minimizing gauch interaction in the transition states. So, H is antiperiplanar to O atom. The energy of **TS-1-1-b** is higher than **TS-1-1-a** because of large steric repulsion between CO_2Et and alkyl group.

2. Ring expansion



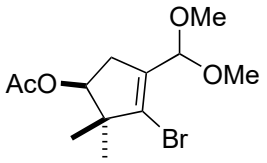
Rearrangement might occur either by **1-5** and **1-5'**, of which orbital orverlap are good.
The energy of **TS-1-5'** is higher than **TS-1-5** because large CO_2Et overlaps with 5-membered ring in **TS-1-5'**.

Discussion 1-2: 5-exo radical cyclization/fragmentation



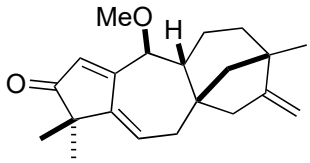
TS-1-16' is more favourable because dipole interaction is smaller than the other.
And also, there is large steric repulsion between ethoxy methyl group and silyl group in **TS-1-16''**.

2.

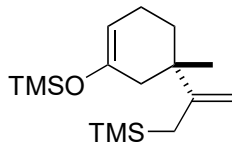


2-1

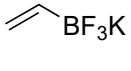
1. **2-2** (1.3 eq), **(+)-A** (0.15 eq), TMSOTf (0.15 eq), *t*-BuOMe, -78 ºC
   then $EtAlCl_2$ (2 eq), *t*-BuOMe/CH_2Cl_2, 0 ºC, 58%
2. **2-3** (7 eq), $Pd(PPh_3)_4$ (0.25 eq), Na_2CO_3 (10 eq)
   EtOH/H_2O/toluene, reflux
   then NaOH (10.7 eq), MeOH/H_2O, 50 ºC, 90%
3. DMP (2 eq), $NaHCO_3$(10 eq), CH_2Cl_2, 0 ºC
4. Tf_2O (1.5 eq), pyridine (3 eq), CH_2Cl_2, 0 to 25 ºC
   then *i*-PrOH (3 eq)
   then 4-phenylpyridine (1.5 eq), $(CH_2Cl)_2$, 80 ºC, 44% (2 steps)



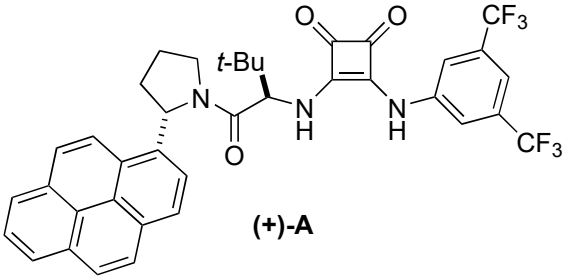
2-4



2-2



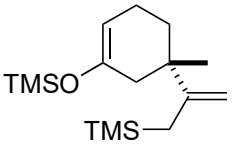
2-3



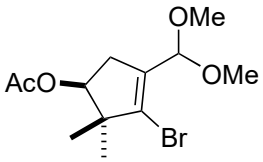
(+)-A

Kong, L.; Yu, H.; Deng, M.; Wu, F.; Jiang, Z.; Luo, T. *J. Am. Chem. Soc.* **2022**, *144*, 5268−5273.

Answer



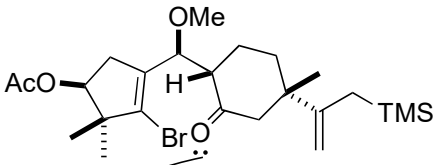
2-2
(+)-A



2-1

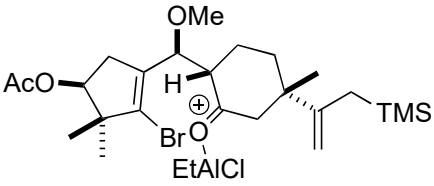
Discussion 2-1

asymmetric Mukaiyama aldol reaction



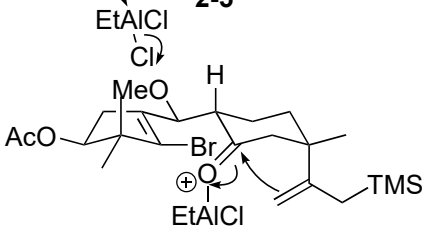
2-5

- $Cl^{\ominus}$

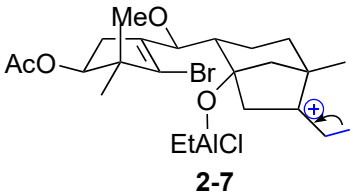


2-6

≡

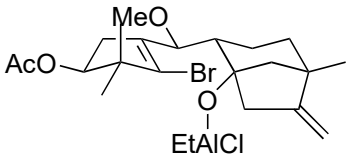


2-6'



2-7

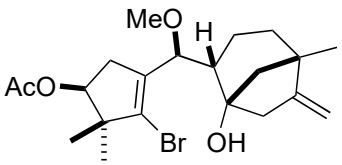
$-Me_3Si-Cl$



2-8

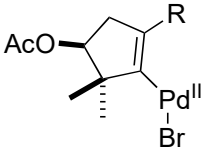
work up

cation is stabilized by β-silicon effect

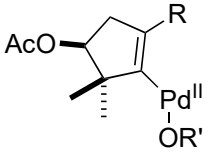


2-9

Pd^0
oxidative addition



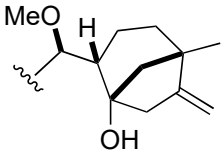
$OR'^{\ominus}$ $Br^{\ominus}$
ligand exchange
R' = H or Et



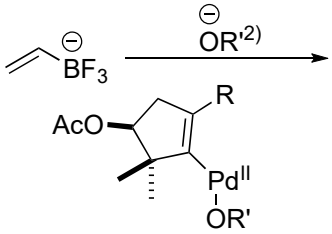
2-11

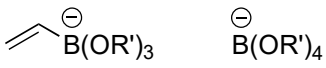
step 1

R =

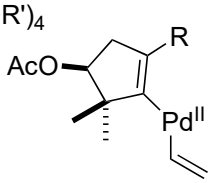


2-10

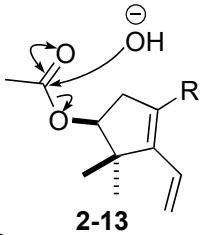




transmetalation



- Pd^0
reductive elimination

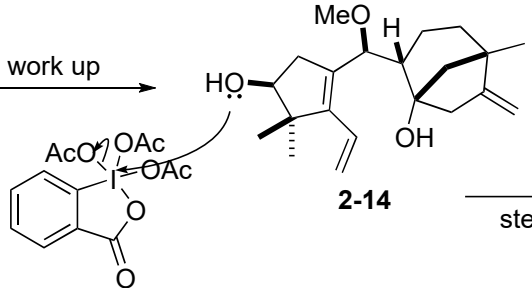


2-11

2-12

2-13

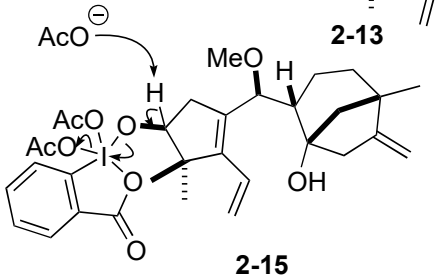
work up



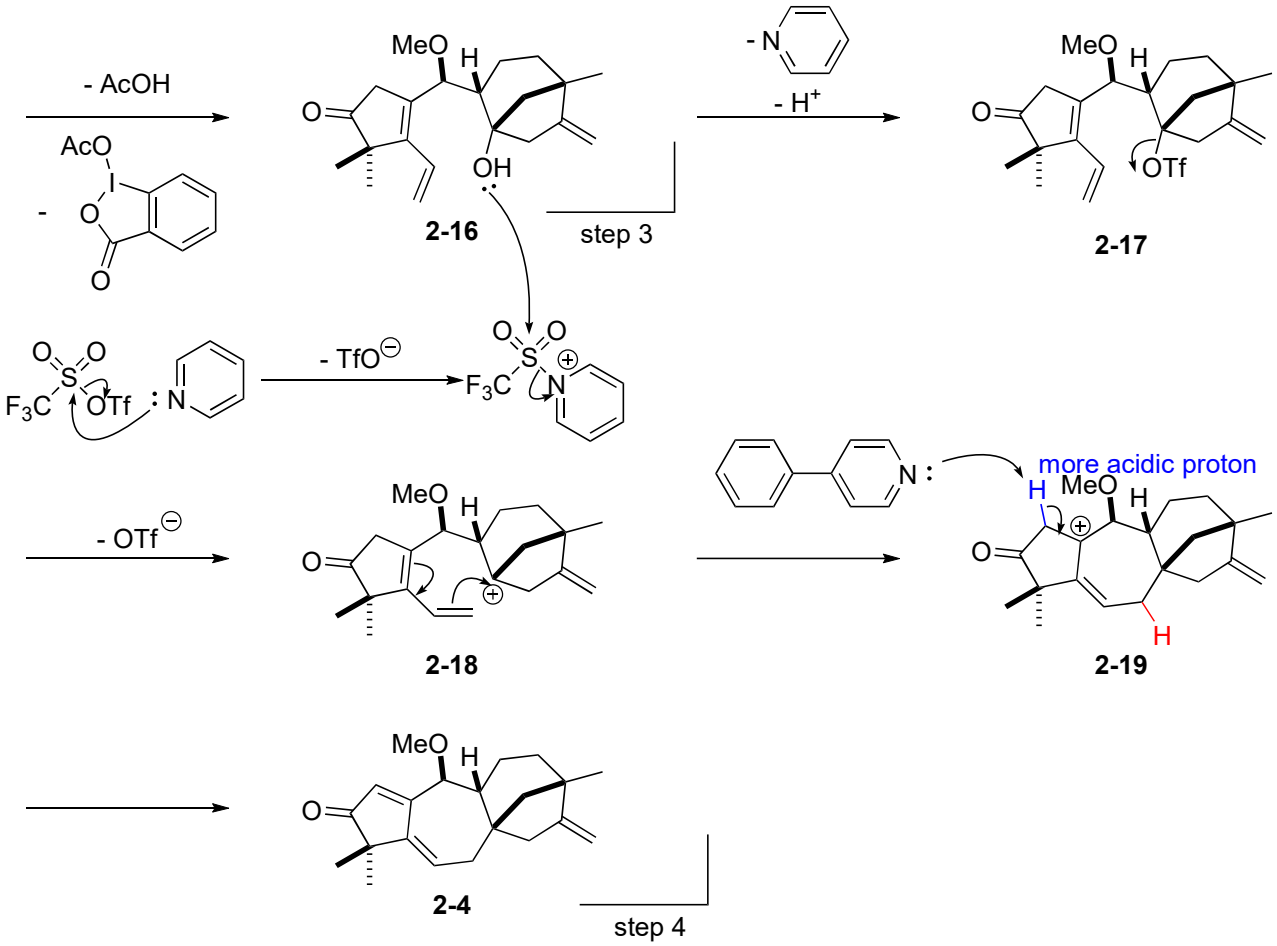
2-14

step 2

- AcOH

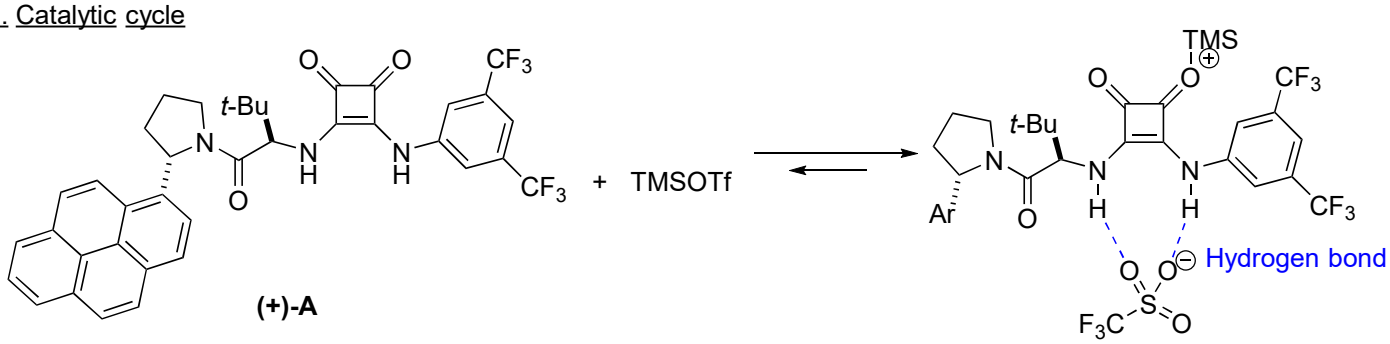


2-15

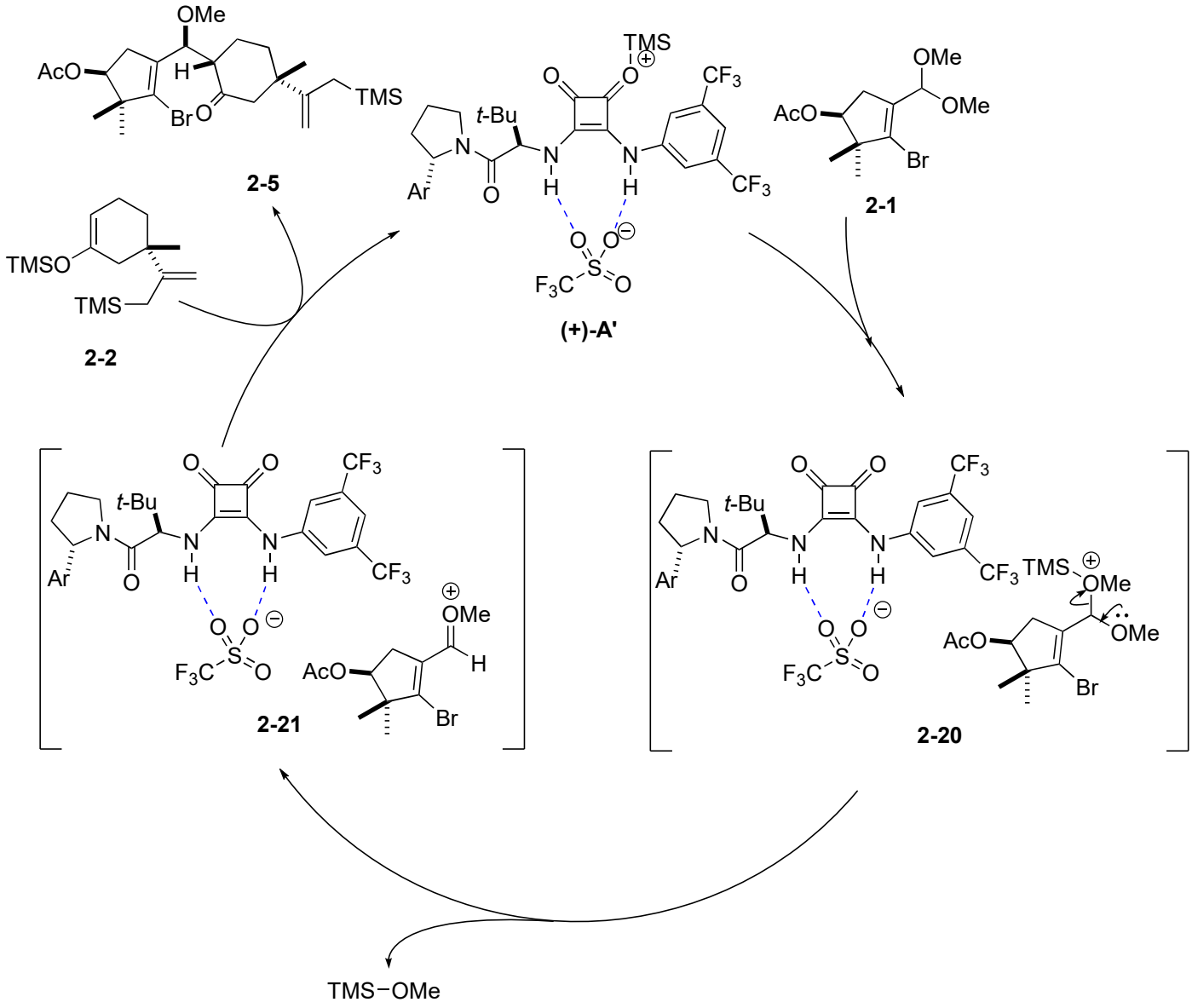

- AcOH
AcO
I
O
O
-
MeO
H
O
OH
2-16
step 3
- N
- H+
MeO
H
O
OTf
2-17
O
O
S
F3C
OTf
: N
- TfO⊖
O
O
S
F3C
N
- OTf⊖
MeO
H
O
2-18
N :
more acidic proton
H
MeO
H
O
H
2-19
MeO
H
O
2-4
step 4

Discussion 2-1: asymmetric Mukaiyama aldol reaction

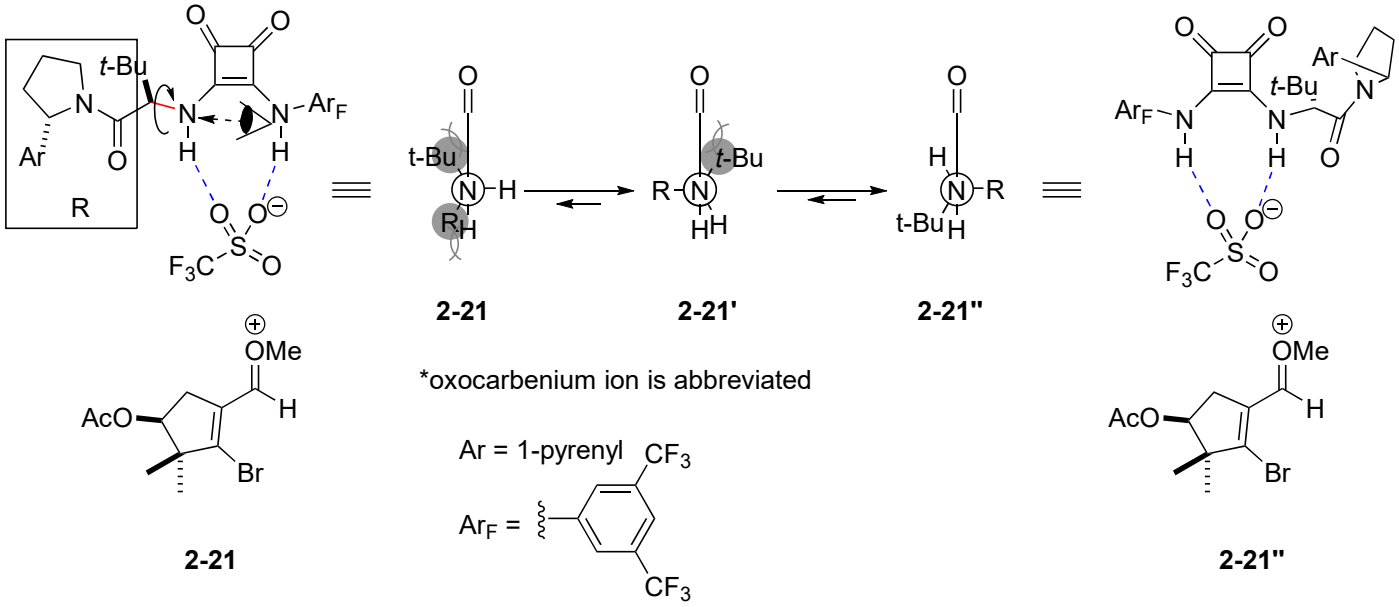
1. Catalytic cycle



(+)-A is highly reactive Lewis acid complex due to the hydrogen bond between the catalyst and triflate anion.[3)]

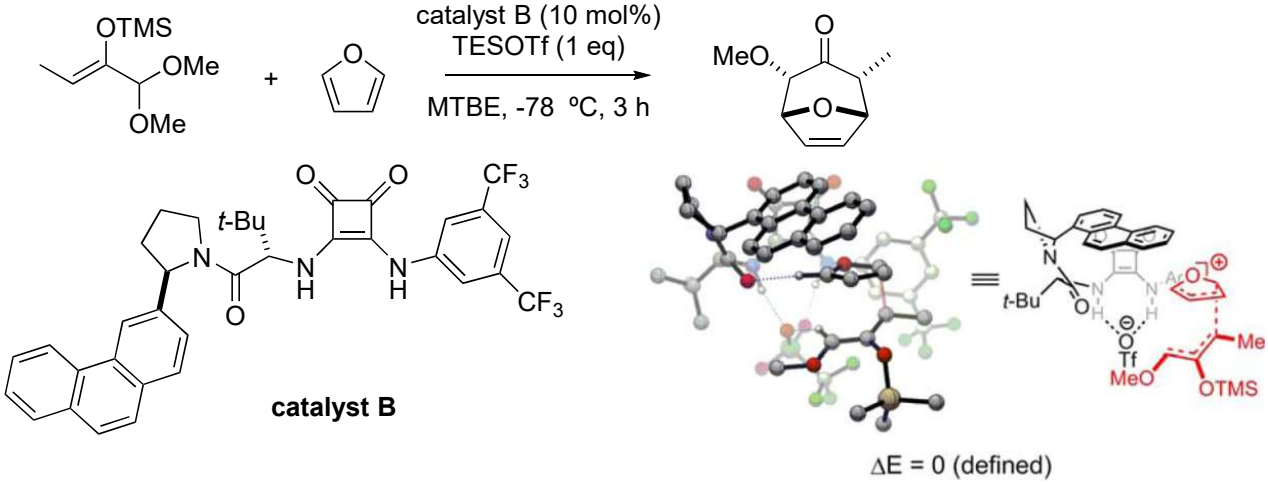


2. Conformation of the catalyst during Mukaiyama aldol reaction



The largest R group should be vertical to C-N and N-H bond of the catalyst, so conformation **2-21'** or **2-21"** are more stable than other conformations.
Among **2-21'** and **2-21"**, **2-21'** is less stable due to large steric repulsion.
So the reaction proceeds by **2-21"**.

3. Stereoselectivity

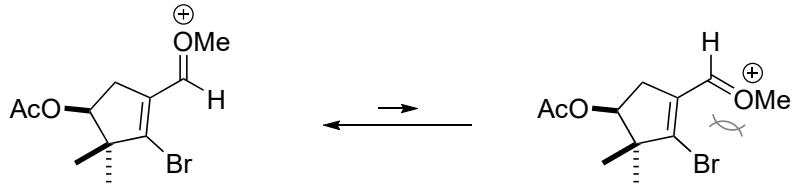


The lowest energy transition state of [4+3] cycloaddition catalyzed by **catalyst B**, according to DFT calculation. Hydrogen bond between furan and amide moiety of the catalyst, and also between oxyallyl fragment and triflate anion are associated.

Banik, S. M.; Levina, A.; Hyde, A. M.; Jacobsen, E. N. *Science.* **2017**, *358*, 761−764.

In this reaction,CH-O interaction between oxocarbenium ion and electron rich amide moiety[4)] of the catalyst, and cation-π interaction between oxocarbenium ion and 1-pyrenyl group seems to play an important role.
*CH-O interaction is classified as one of weak hydrogenbonds.

- conformation of oxocarbenium ion

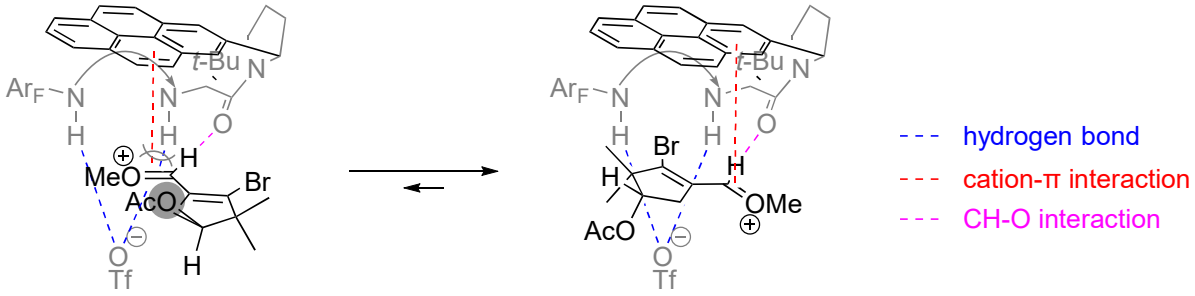


2-22 **2-22'**

large 1,3-allylic strain

Among **2-22** and **2-22'**, **2-22** is more favourable because of large 1,3-allylic strain in **2-22'**.

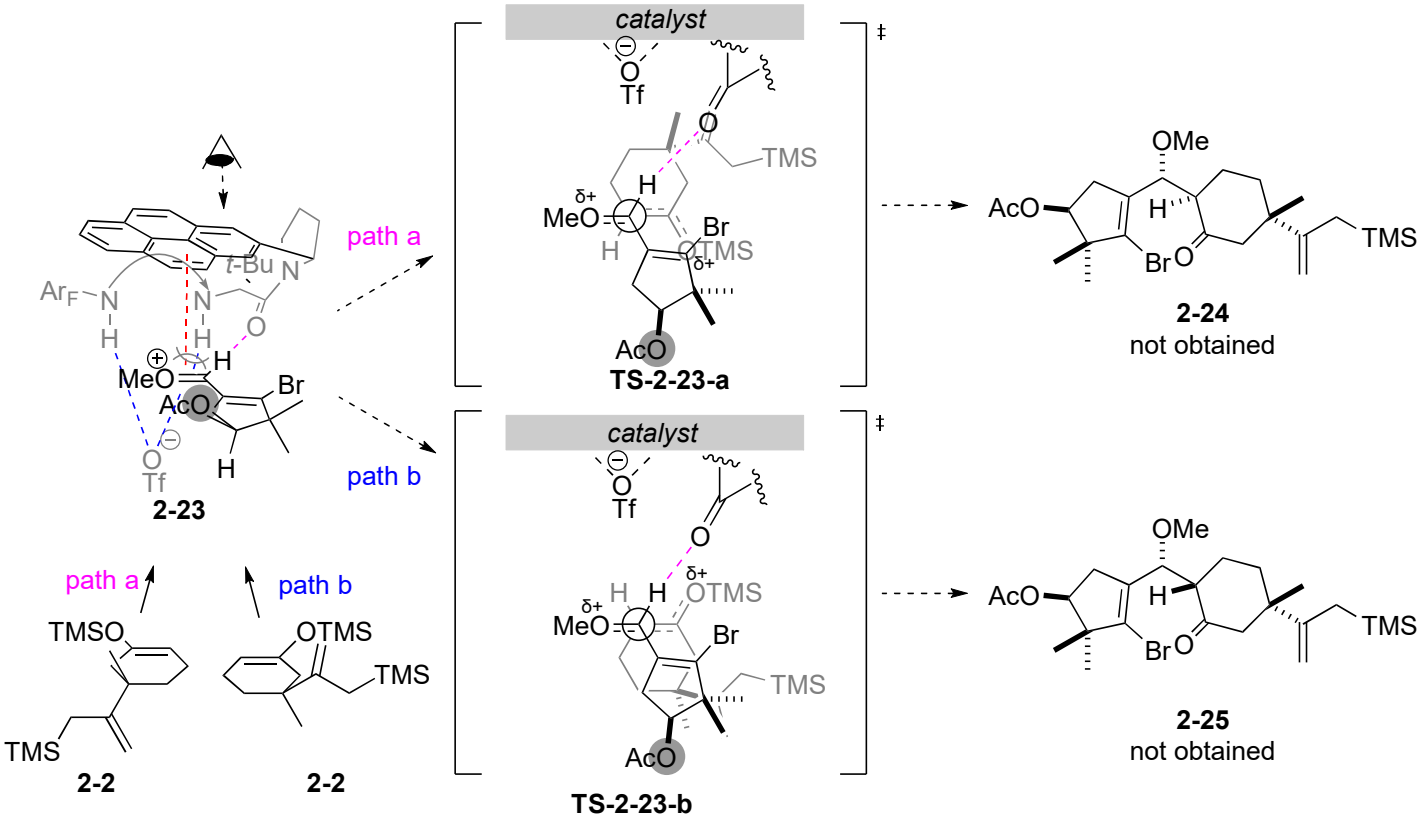
- spacial arrangement of the catalyst and oxocarbenium ion

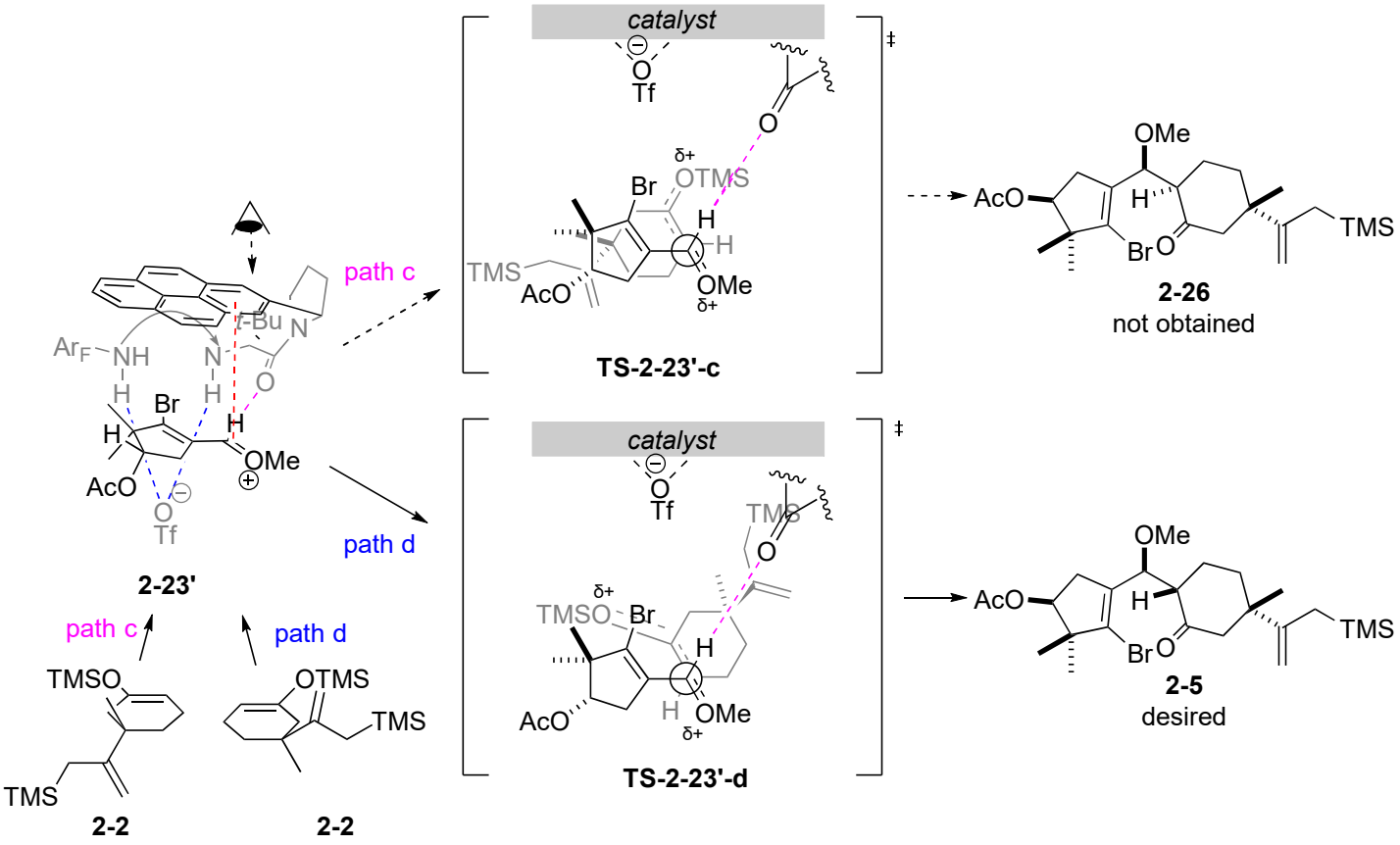


2-23 **2-23'**

Due to cation-π interaction and CH-O interaction between oxocarbenium ion and the catalyst, spacial arrangement of oxocarbenium ion and the catalyst is fixed either of **2-23** and **2-23'**.
There is large steric repulsion between 1-pyrenyl group and acetyl group, so **2-23** is less favourable than **2-23'**.
Because β-face of oxocarbenium ion is shielded by 1-pyrenyl group, silyl enol ether approaches from α-face.

- aldol reaction





Silyl enol ether can't form a chelate, so 6-membered ring transition state doesn't need to be considered.
Path b and path c is unfavourable because5-membered ring of oxocarbenium ion overlaps with 6-membered ring of silyl enol ether in **TS-2-23-b B** and **TS-2-23'-c.**
Among path a and path d, path d is more favourable because there is large steric repulsion between 1-pyrenyl group and acetyl group in **TS-2-23-a**.

Reference

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3. Banik. S. M.; Levina. A.; Hyde. A. M.; Jacobsen. E. N. *Science.* **2017**, *358*, 761−764.
4. Strassfeld. D. A; Algera. R. F.; Wickens. Z. K.; Jacobsen. E. N. *J. Am. Chem. Soc*. **2021**, *143*, 9585−9594.