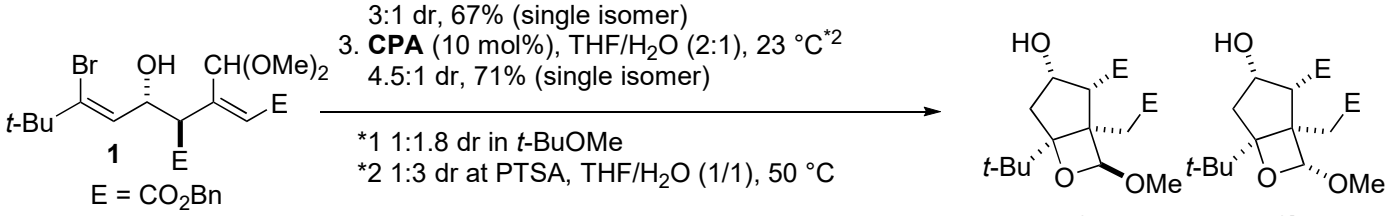
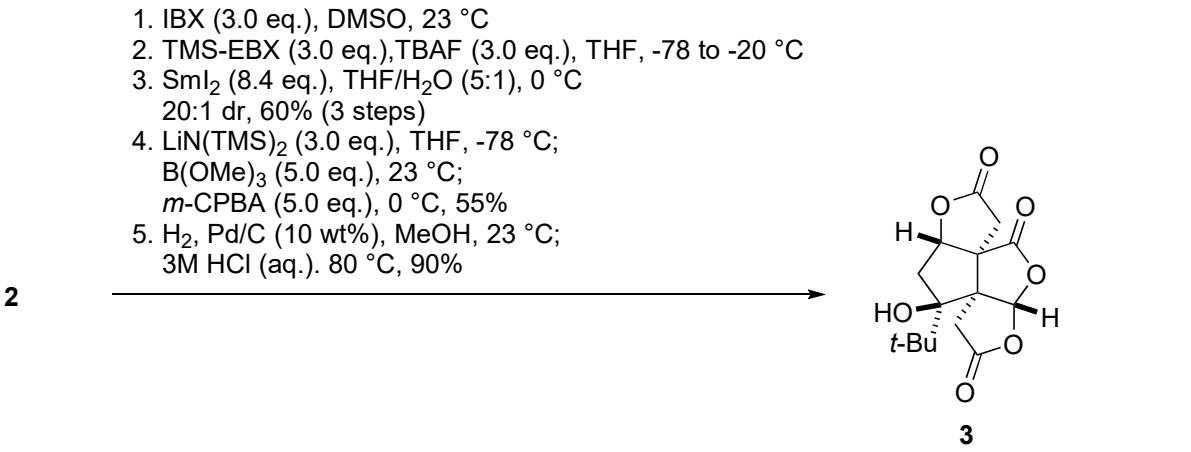
Problem Session (4) - Problem

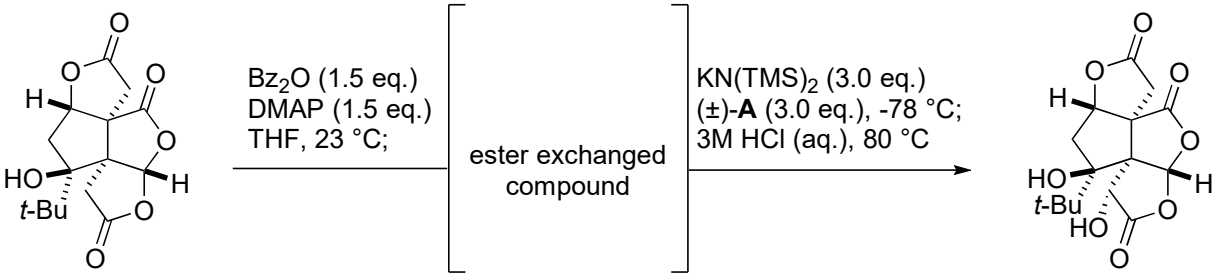
2019.11.2 Yusuke Imamura

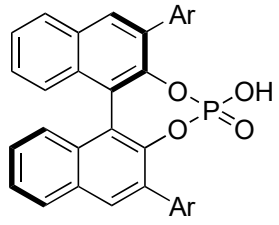
Please explain the reaction mechanisms.



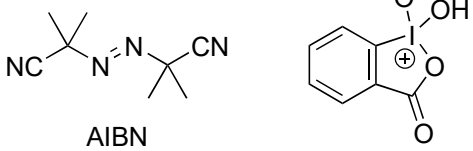


Please explain the reaction mechanisms and the reason of tentative benzoyl protection.





CPA (Ar = phenanthryl)



Problem Session (4) - Answer

2019.11.2 Yusuke Imamura

Topic: Total synthesis of bilobalide by Shenvi group[ref1]

0. Introduction

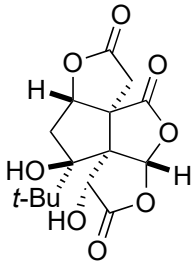
0.1. bilobalide

♣isolation: leaves of *ginko biloba*

♣bioactivity: Down syndrome treatment for model mouse (by antagonism of GABAa receptors)

♣structural features: • tetra cyclic tri-lactone • bowl-like structure with buried OH

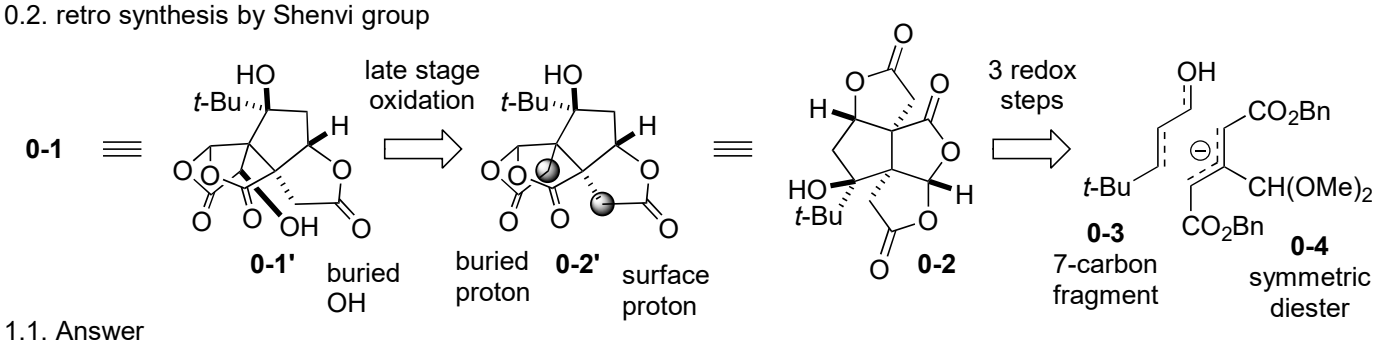
♣syntheses: Corey (1987, racemic), Crimmins (1993, racemic), Corey (1988, asymmetric)



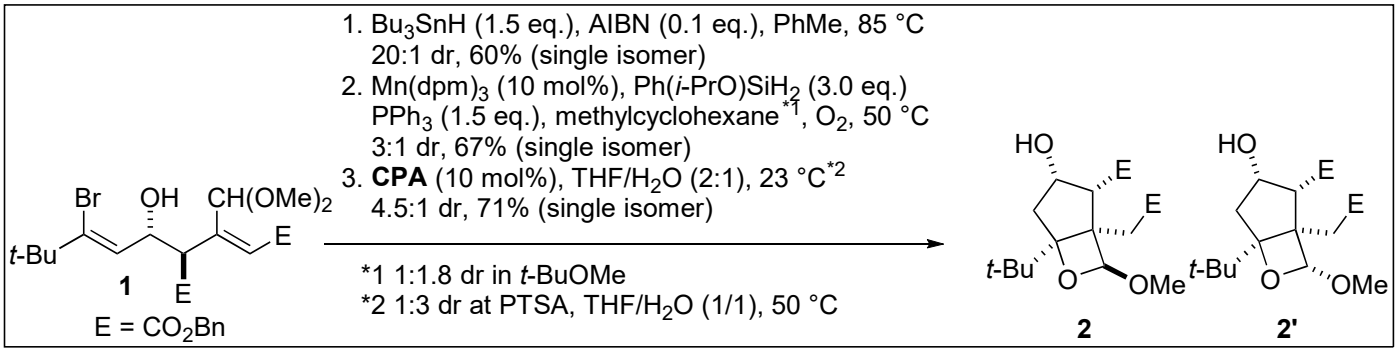
0-1 (bilobalide)

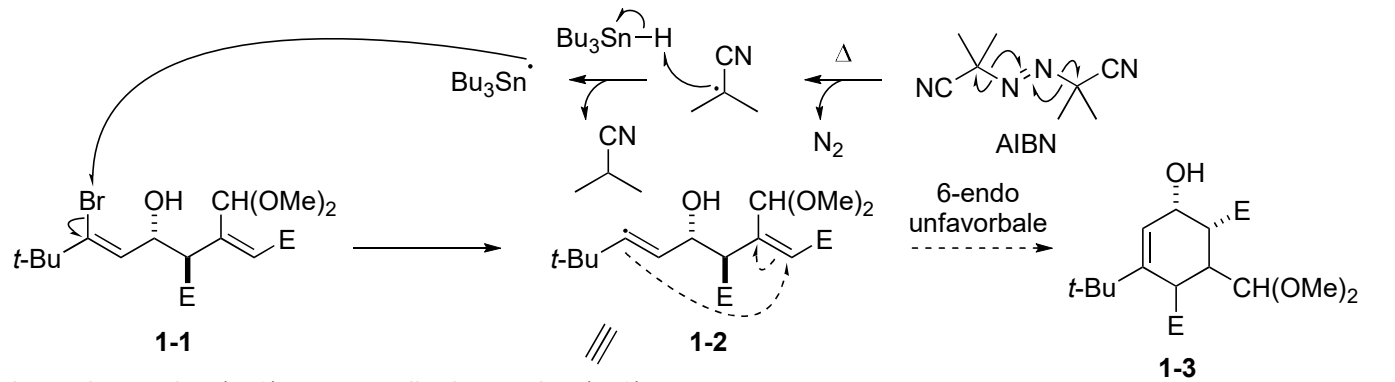
For more detail about bilobalide, please refer to
"180901_Nonpublic_PS_Masanori_NAGATOMO_Synthetic_Plan_of_Bilobalide_.pdf"

0.2. retro synthesis by Shenvi group

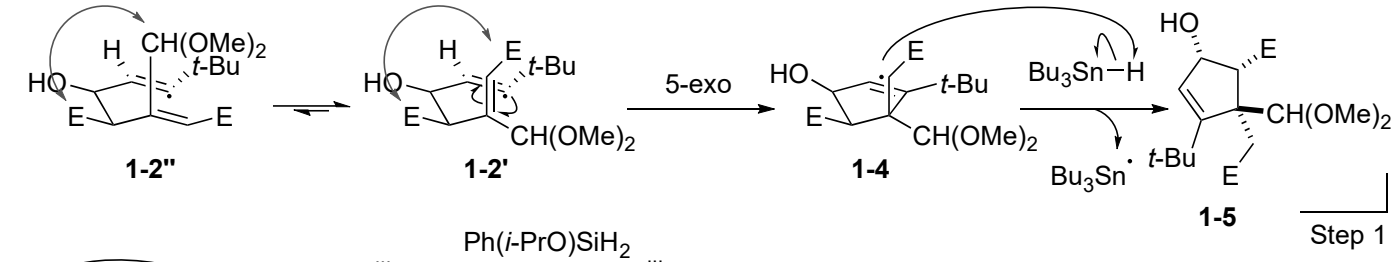


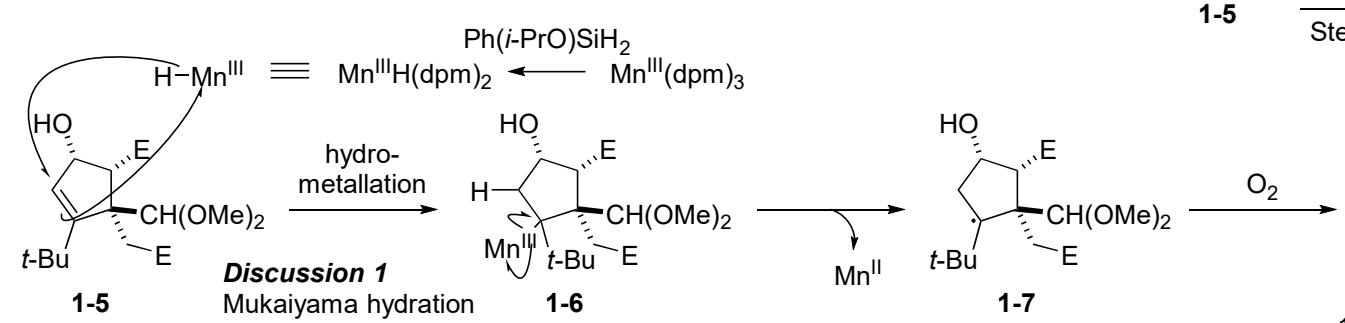
1.1. Answer





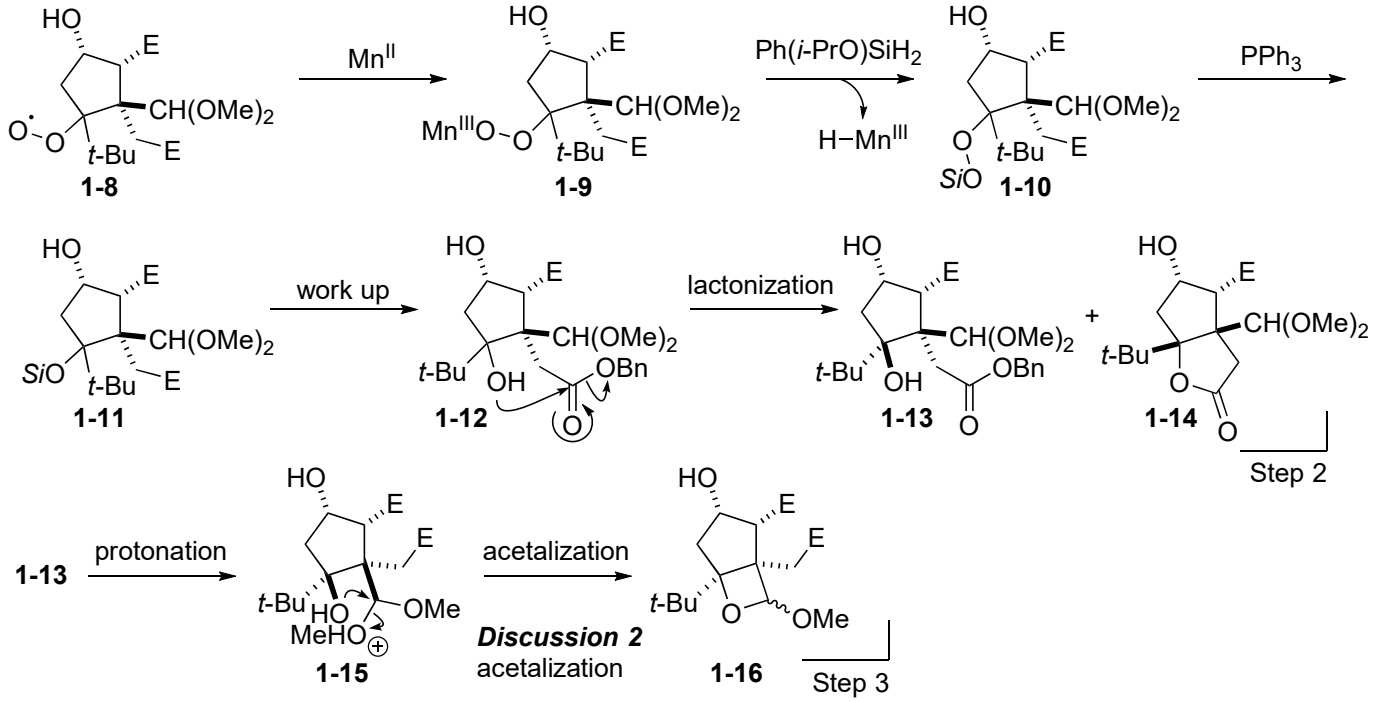
larger interaction (sp3) smaller interaction (sp2)





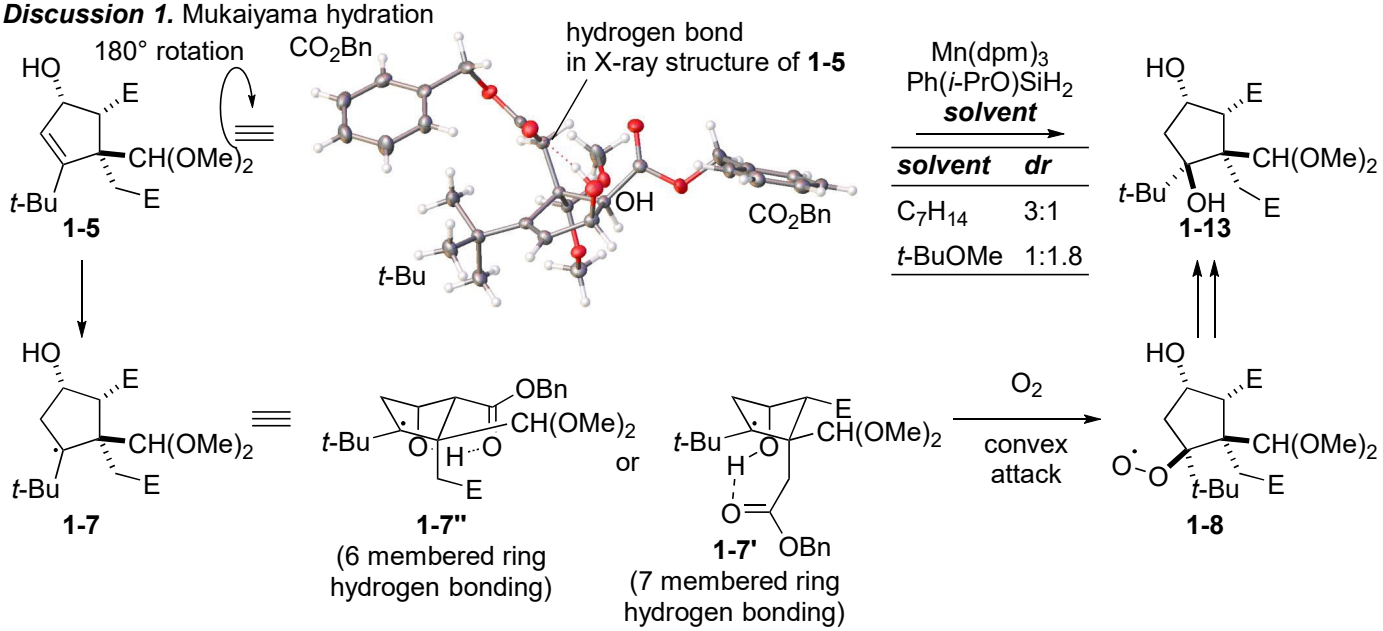
Discussion 1

Mukaiyama hydration



1.2. Discussion

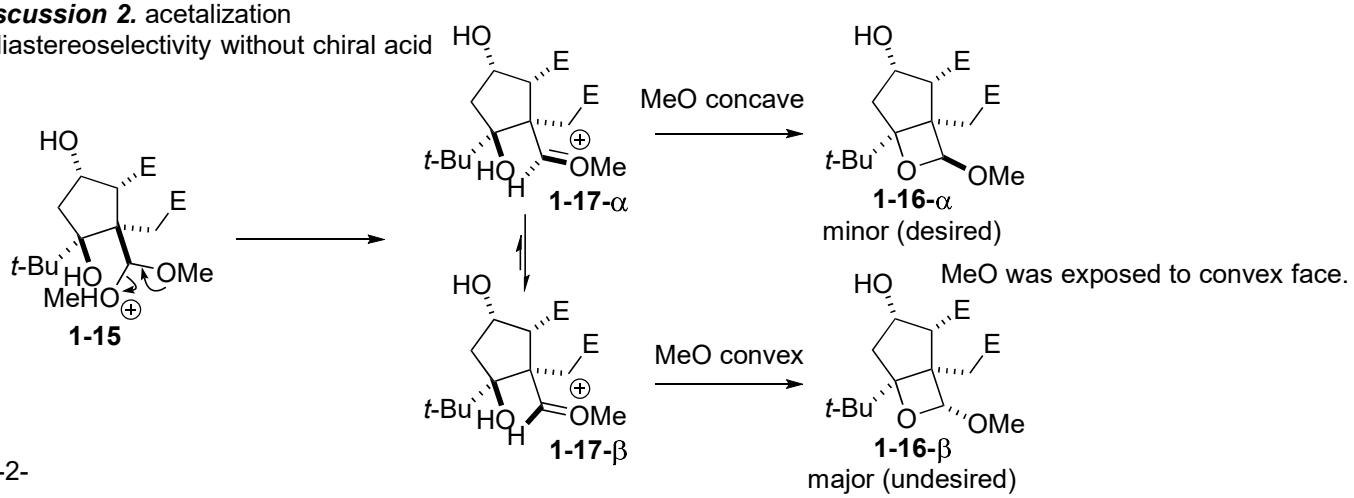
Discussion 1. Mukaiyama hydration



Hydrogen bonding was observed in crystal structure of **1-5**.
Polar solvent (*t*-BuOMe) decreased diasteromeric ratio.
It is because hydrogen bonding was weakened.
The reverse selectivity arose from adjacent tetrasubstituted carbon. ($CH(OMe)_2$>CH_2CO_2Bn?)

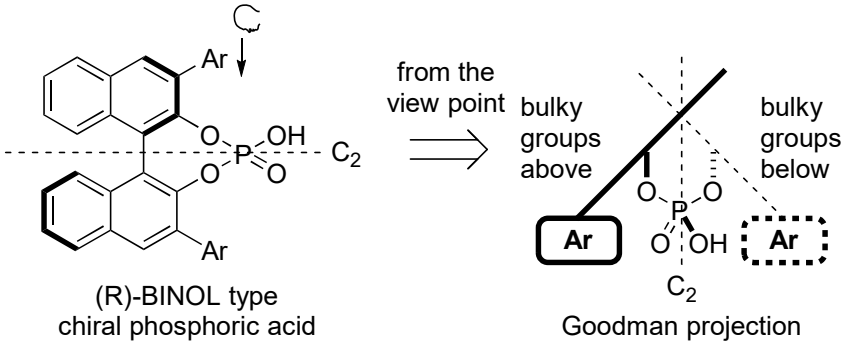
Discussion 2. acetalization

i) diastereoselectivity without chiral acid



ii) Goodman projection[ref2]

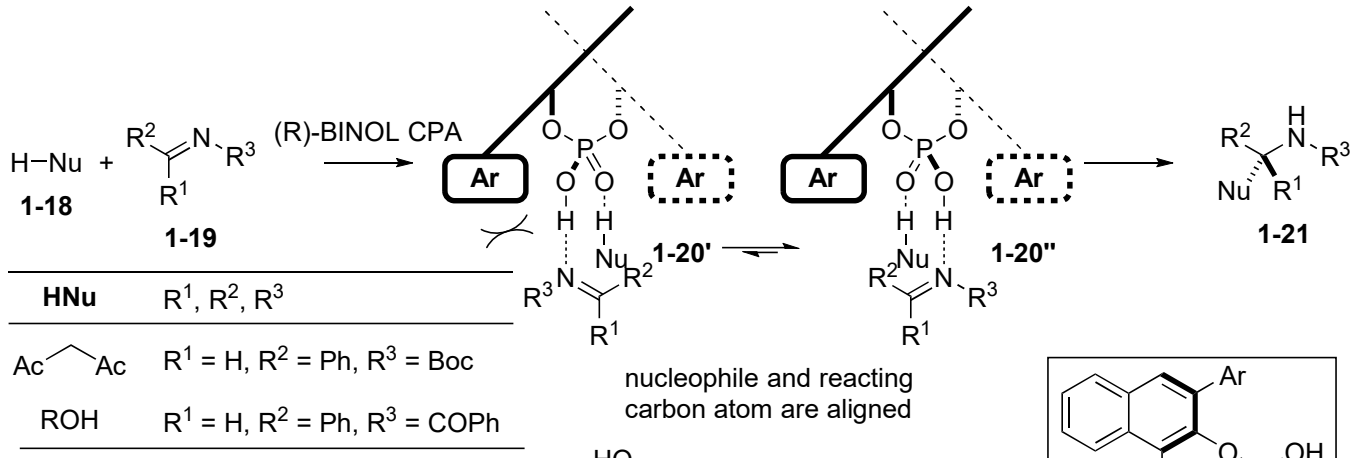
♦ prediction of enantioselectivity of chiral phosphoric acid mediated imine-nucleophile reaction



(R)-BINOL type chiral phosphoric acid

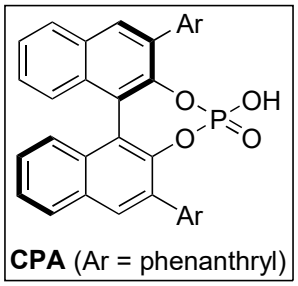
Goodman projection

♦ General explanation of enantioselectivity in imine nucleophile reaction



HNu	R^1, R^2, R^3
Ac Ac	R^1 = H, R^2 = Ph, R^3 = Boc
ROH	R^1 = H, R^2 = Ph, R^3 = COPh

nucleophile and reacting carbon atom are aligned



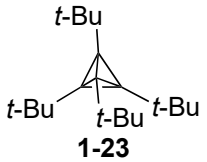
CPA (Ar = phenanthryl)

iii) diastereoselectivity with chiral acid

H^+ coordinated MeO positioned away from OH.

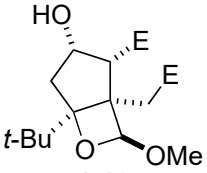
In this explanation, S_N2 reaction is assumed in acetalization.[ref3]
It is because, reaction positions were pre-coordinated by chiral phosphoric acid and "corset effect".
The speed of the reaction can also be confirmed by the fact that the methyl acetal didn't hydrolyzed even in the presenece of H_2O as solvent.

iv) corset effect[ref4]



1-23

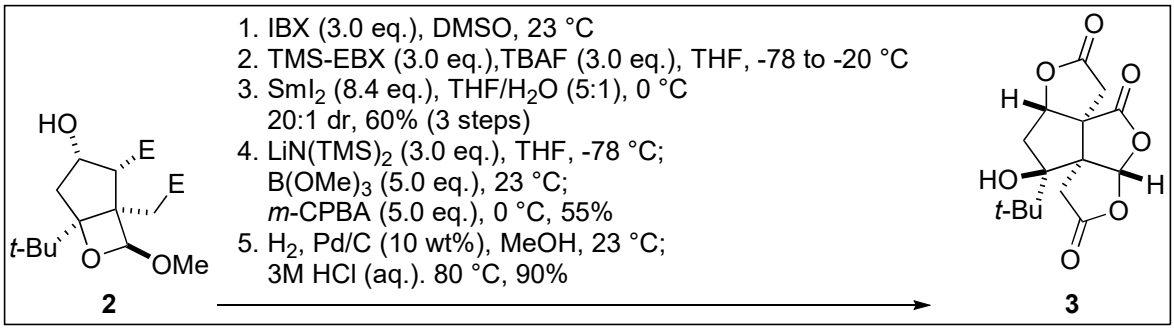
Tetrahedrane is highly strained compound and many chemist have tried to synthesize it.
Its drivertive, tetra-*tert*-butyl-tetrahedrane (**1-20**) are synthesized by Maiier G. in 1978.
The compound is unexpectedly stable.
They assumed the reason is that fully substituted bulky *t*-Bu group pushed back togather and inside core became more rigid.
-> "corset effect"

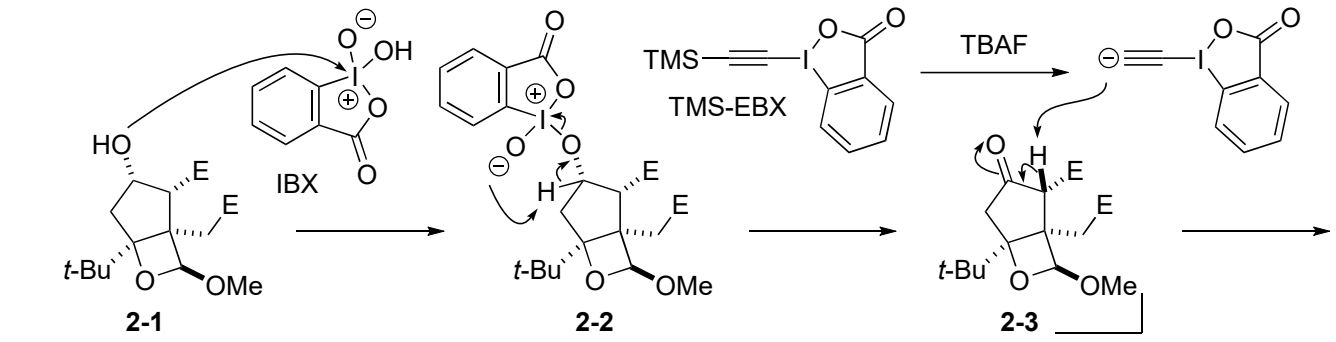


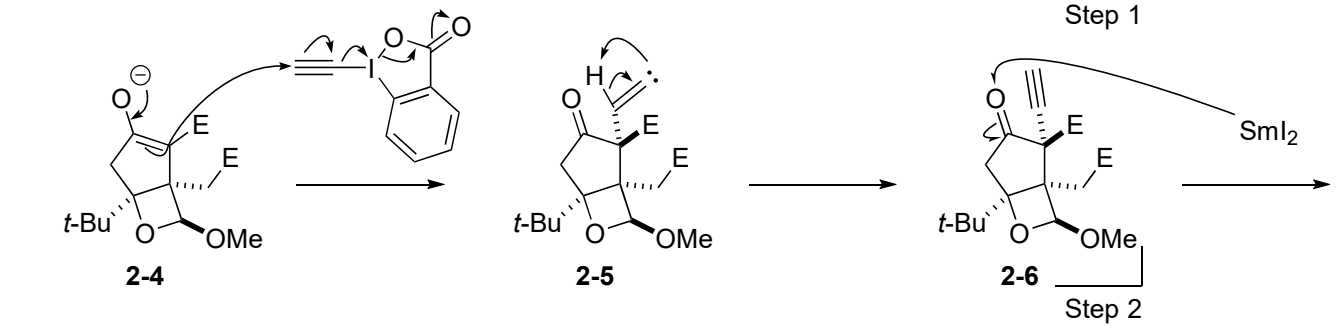
1-16

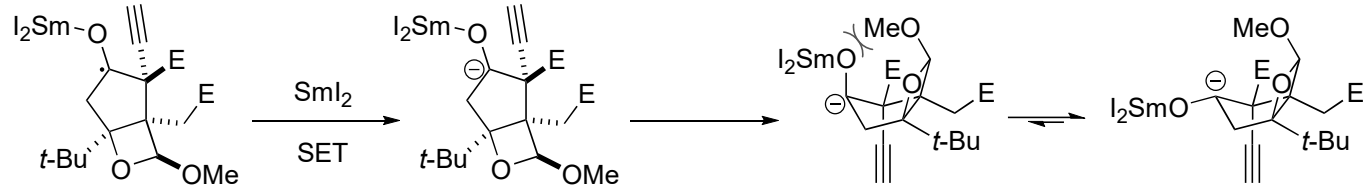
Oxetane acetal of **1-15** is assumed to be unstable.
However, the structure is stabilized by poly-substitution.

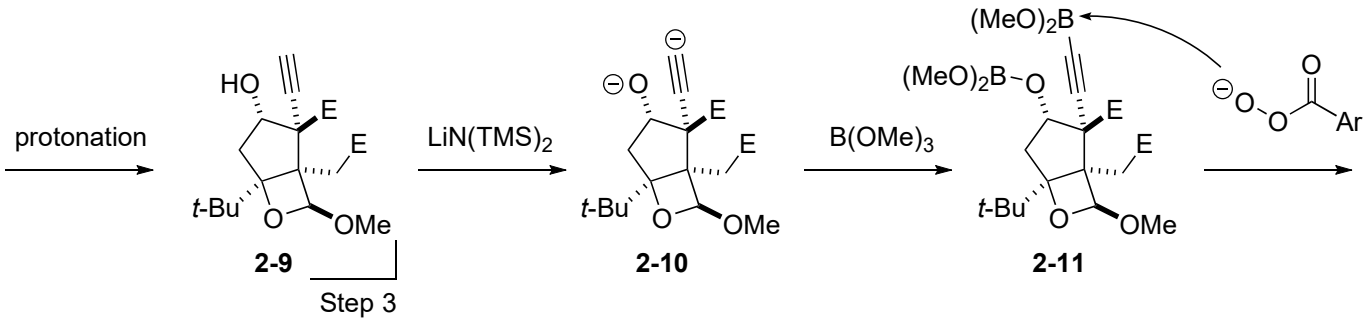
2.1. Answer

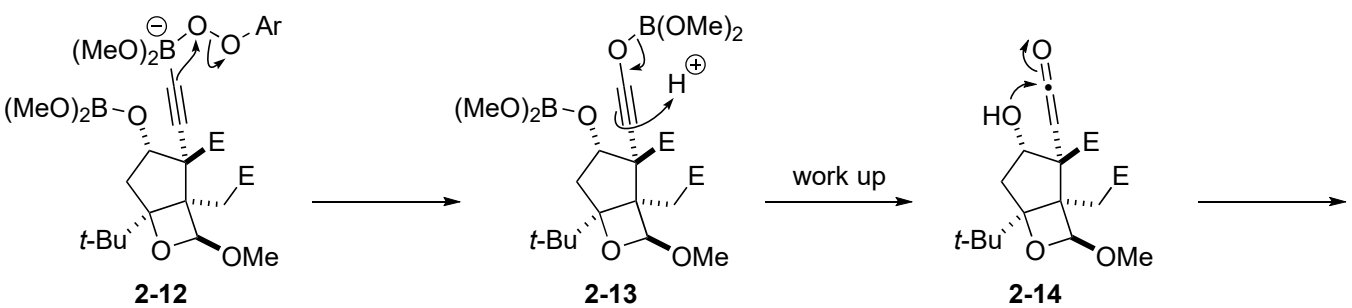

1. IBX (3.0 eq.), DMSO, 23 °C
2. TMS-EBX (3.0 eq.),TBAF (3.0 eq.), THF, -78 to -20 °C
3. SmI2 (8.4 eq.), THF/H2O (5:1), 0 °C
20:1 dr, 60% (3 steps)
4. LiN(TMS)2 (3.0 eq.), THF, -78 °C;
B(OMe)3 (5.0 eq.), 23 °C;
m-CPBA (5.0 eq.), 0 °C, 55%
5. H2, Pd/C (10 wt%), MeOH, 23 °C;
3M HCl (aq.). 80 °C, 90%
2
3

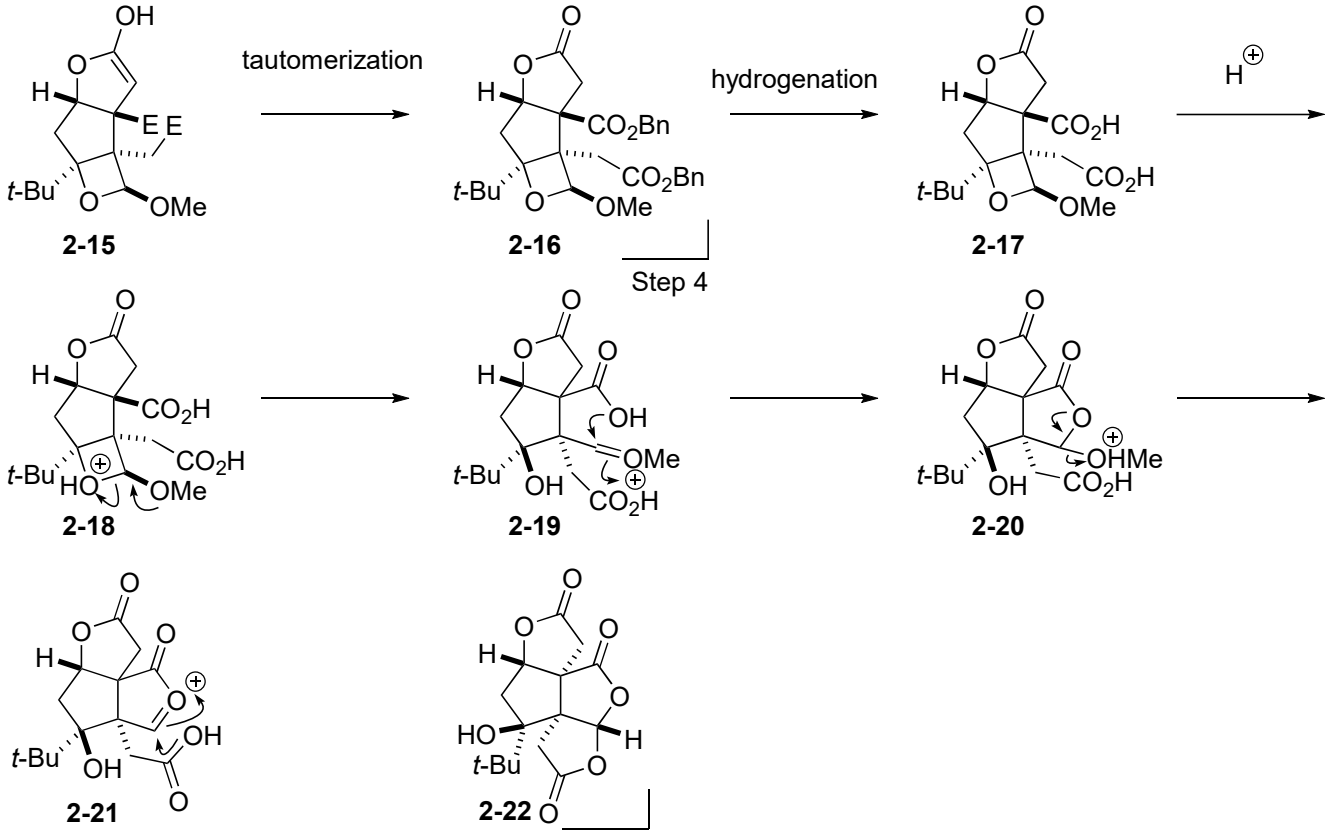

IBX
TMS-EBX
TBAF
2-1
2-2
2-3
Step 1


SmI2
2-4
2-5
2-6
Step 2


SmI2
SET
2-7
2-8
2-8'
2-8''


protonation
LiN(TMS)2
B(OMe)3
2-9
2-10
2-11
Step 3

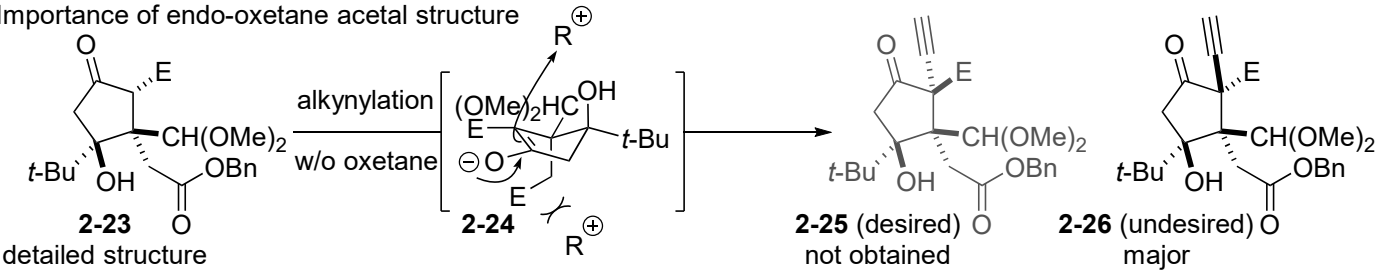

work up
2-12
2-13
2-14



Step 5

2.2. Discussion

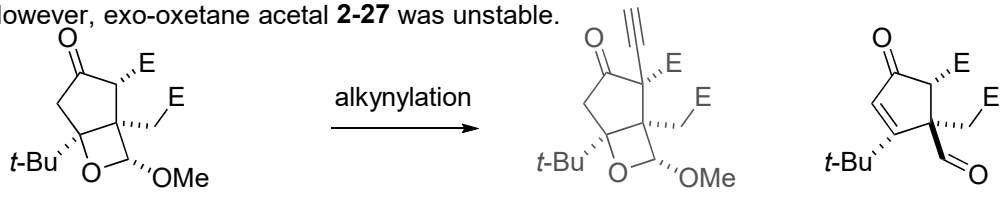
Importance of endo-oxetane acetal structure



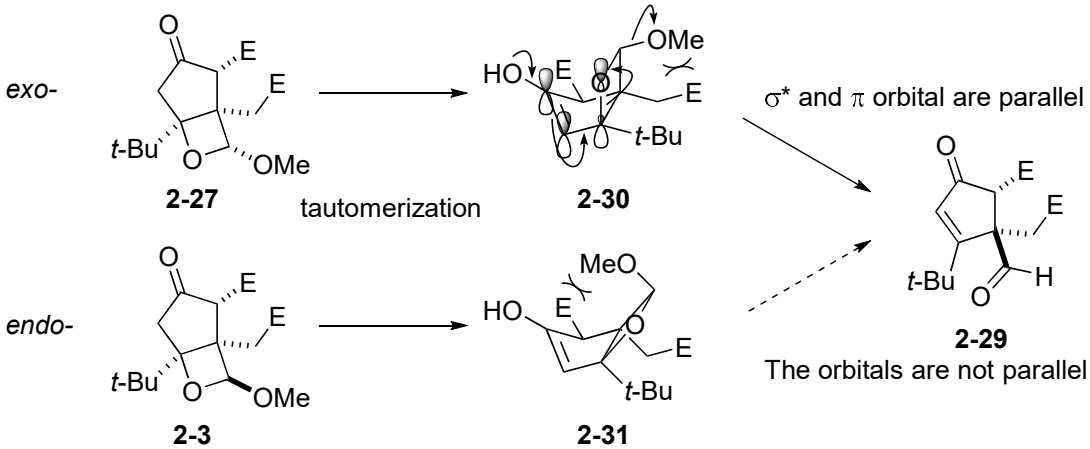
t-Bu and $CH(OMe)_2$ are oriented equatorial.

-> Definition of concave/convex face by acetal formation is needed.

However, exo-oxetane acetal **2-27** was unstable.

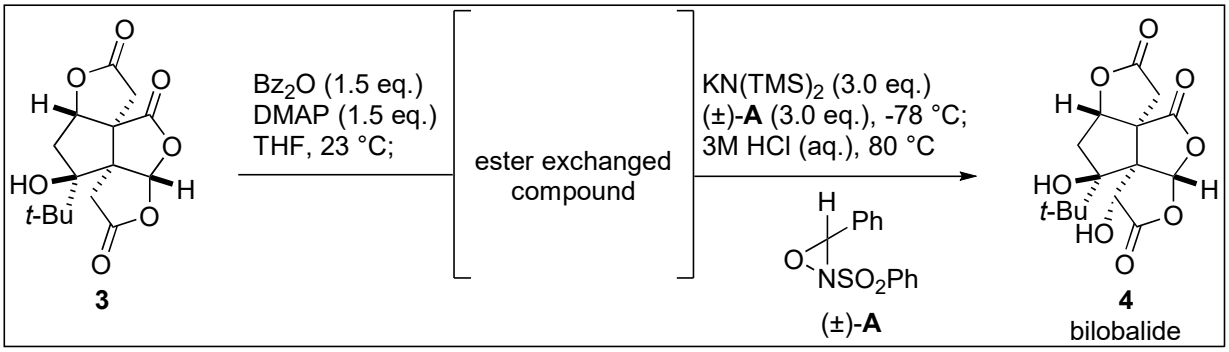


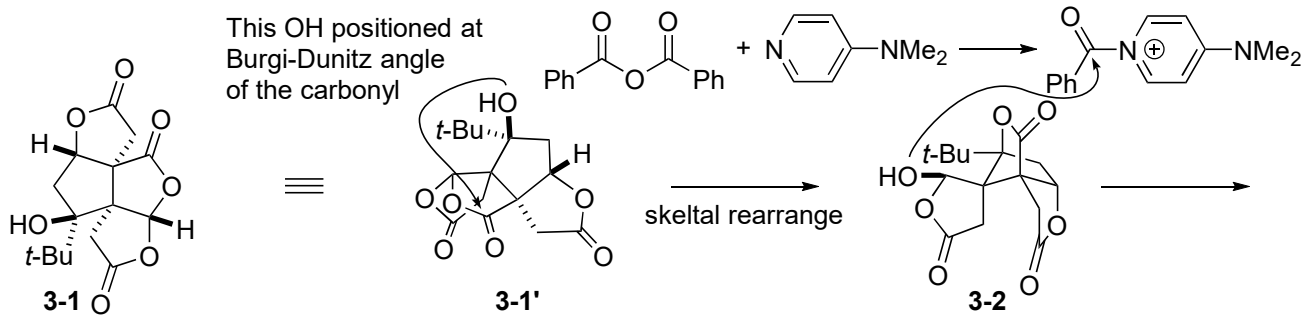
♦ Rationale for instability of exo-oxetane acetal **2-27**

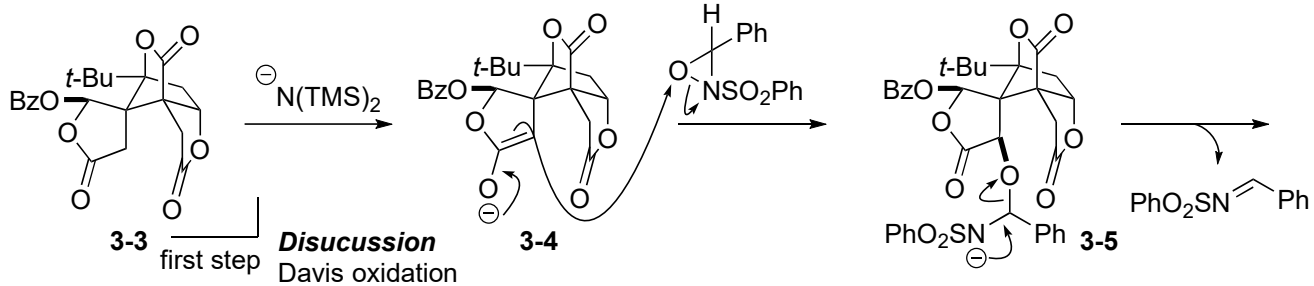


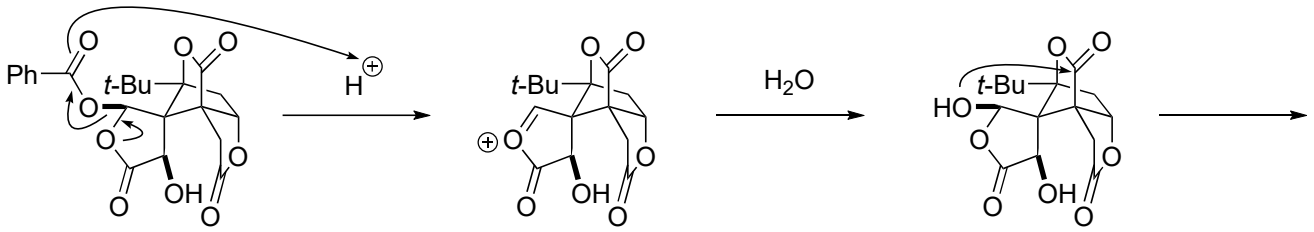
Diastereoselective acetal formation was conducted.

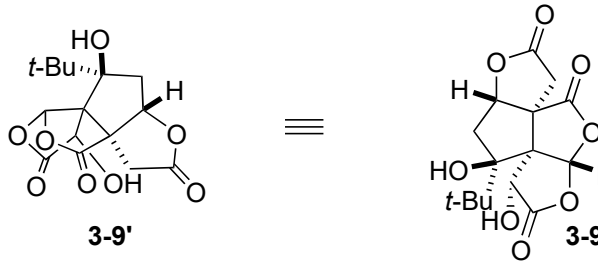
3.1. Answer


Bz2O (1.5 eq.)
DMAP (1.5 eq.)
THF, 23 °C;
ester exchanged compound
KN(TMS)2 (3.0 eq.)
(±)-A (3.0 eq.), -78 °C;
3M HCl (aq.), 80 °C
3
(±)-A
4
bilobalide


This OH positioned at Burgi-Dunitz angle of the carbonyl
skeltal rearrange
3-1
3-1'
3-2

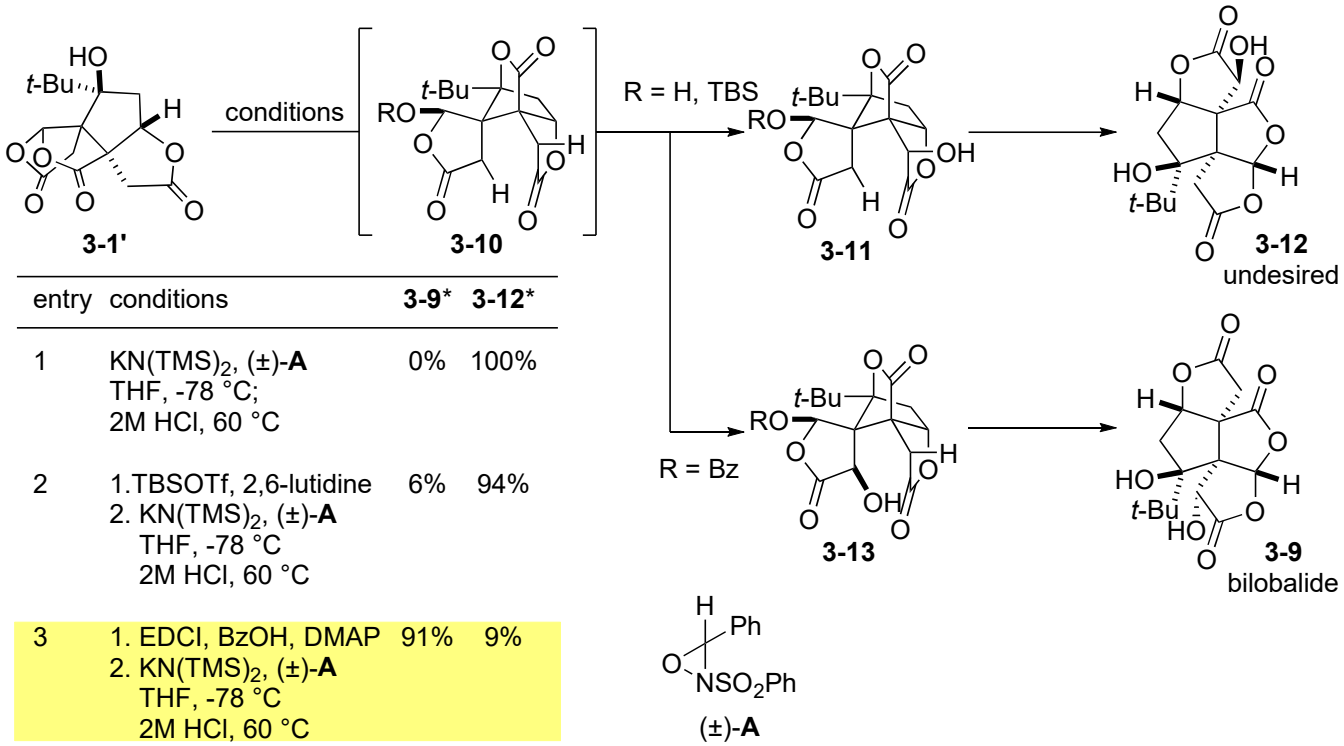

N(TMS)2
3-3
3-4
3-5
first step
Disucussion
Davis oxidation


H2O
3-6
3-7
3-8


3-9'
3-9

3.2. Discussion

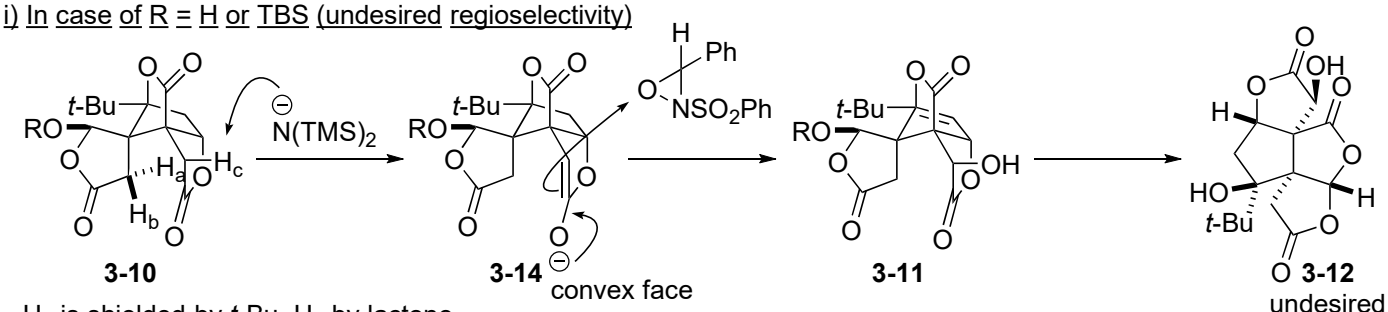
regio- and stereo- selectivity of Davis oxidation



entry	conditions	3-9*	3-12*
1	$KN(TMS)_2$, (±)-**A** THF, -78 °C; 2M HCl, 60 °C	0%	100%
2	1.TBSOTf, 2,6-lutidine 2. $KN(TMS)_2$, (±)-**A** THF, -78 °C 2M HCl, 60 °C	6%	94%
3	1. EDCI, BzOH, DMAP 2. $KN(TMS)_2$, (±)-**A** THF, -78 °C 2M HCl, 60 °C	91%	9%

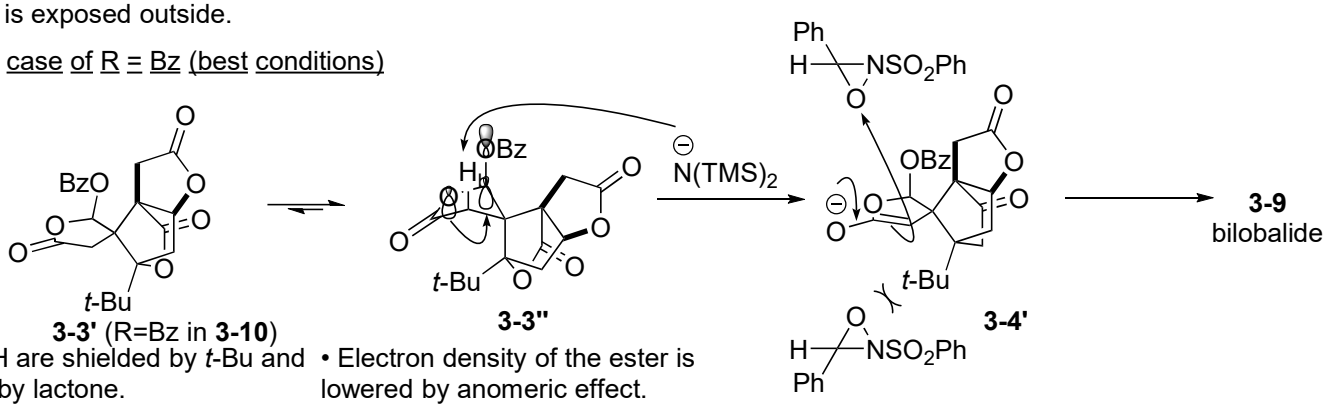
* Yield based on conversion.

i) In case of R = H or TBS (undesired regioselectivity)



H_a is shielded by *t*-Bu, H_b by lactone.
H_c is exposed outside.

ii) In case of R = Bz (best conditions)



- α-H are shielded by *t*-Bu and β-H by lactone.
- No anomeric effect
- Electron density of the ester is lowered by anomeric effect.
- β-H are less shielded.

Benzoyl protection made anomeric effect stronger and equibillium moved right side.

Reference

1. Baker, M. A.; Demoret, R. M.; Ohtawa, M.; Shenvi, R. A. *Nature* **2019**, DOI:10.1038/s41586-019-1690-5
1. Simon, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.
2. Coric, L.; Vallalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536.
3. Maier, G.; Pfriem, S.; Schafer, U.; Matusch, R. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 520.