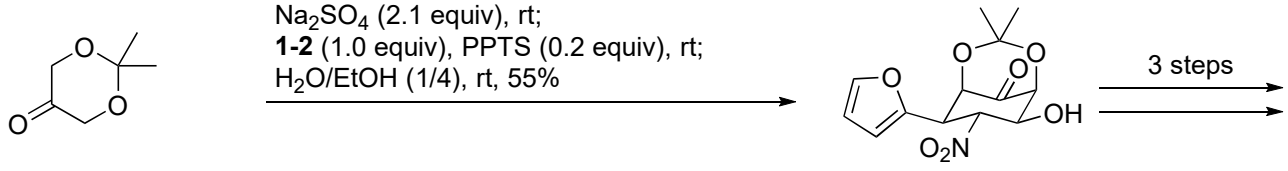
Problem Session (3)

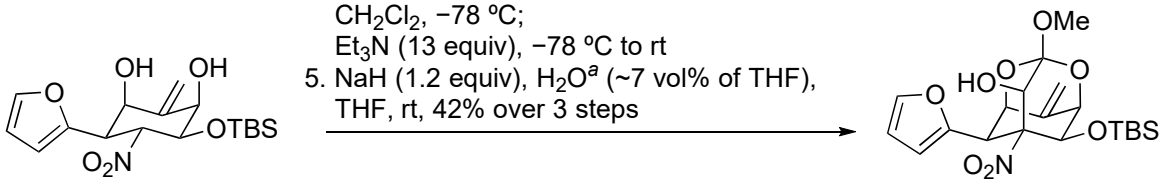
2022.8.6 Junichi Taguchi

Please provide the reaction mechanisms.

(1)



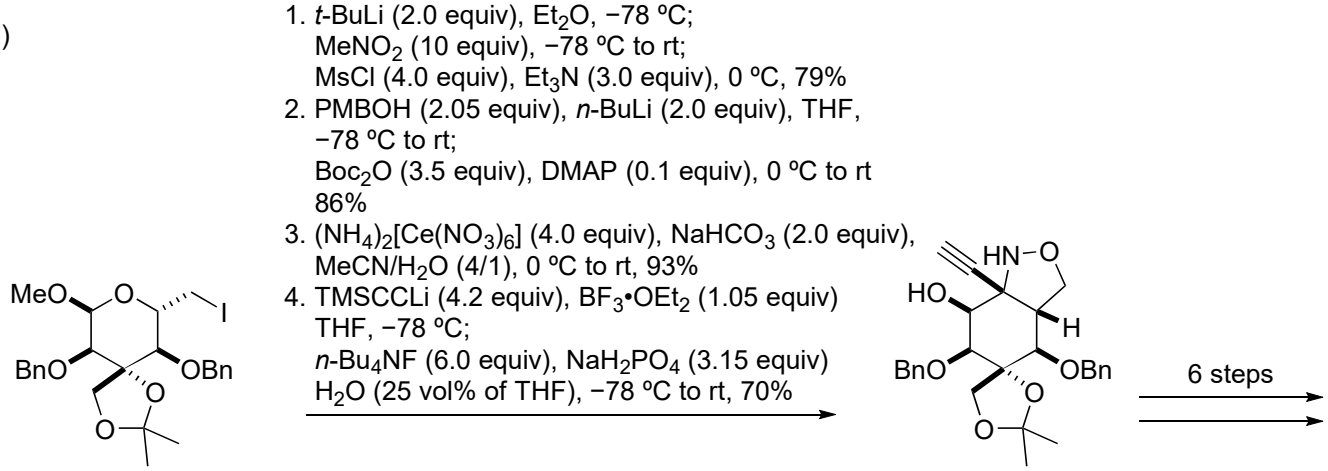
1-1 **1-3**



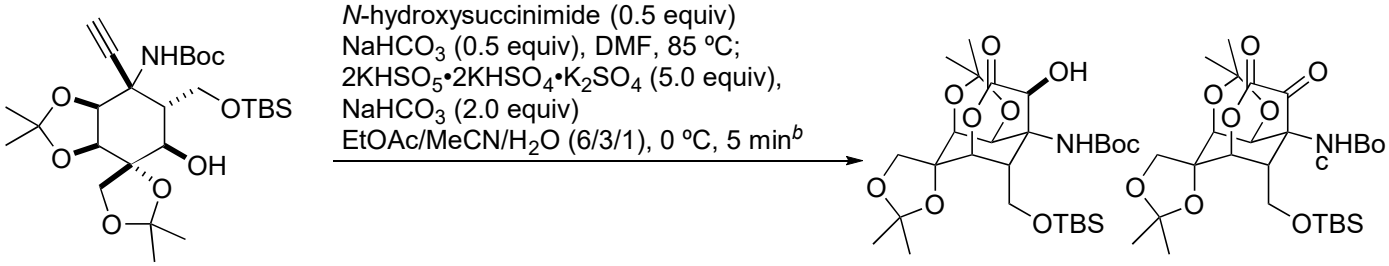
1-4 **1-6**

a) H_2O was added portionwise via syringe until the complete consumption of the starting material.

(2)

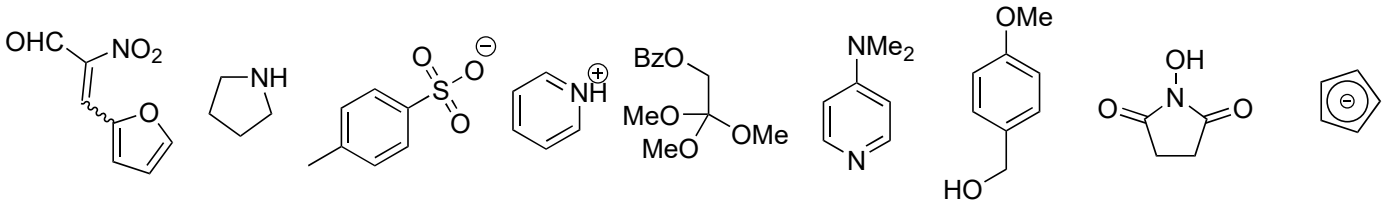


2-1 **2-2**



2-3 **2-4** (71%) **2-5** (11%)

b) The reaction time is critical. Longer reaction times result in higher ratios of **2-5** over **2-4**.



1-2* pyrrolidine PPTS **1-5** DMAP PMBOH *N*-hydroxysuccinimide Cp

***1-2** is easy to isomerize.

Problem Session -Answer- (3)

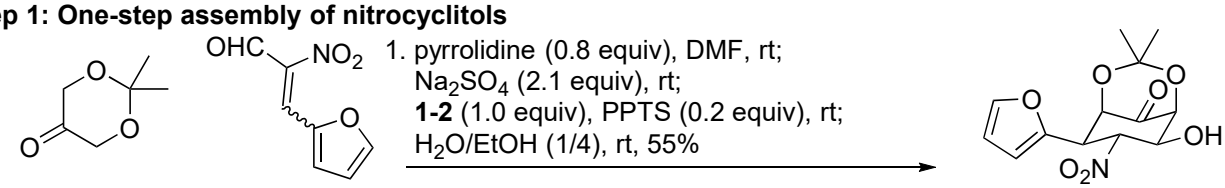
2022.8.6 Junichi Taguchi

topic: Strategy for the Construction of the Dioxaadamantane Unit of Tetrodotoxin and its Analogues

See also: 130803_LS_Ken_MUKAI, 170930_LS_Takahiro_Watanabe, 200527_PS_Ayumu_Watanabe

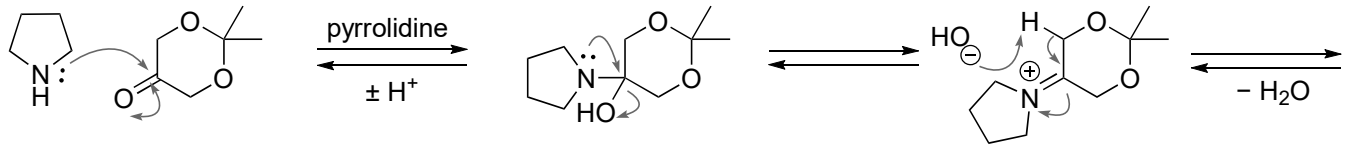
1. Problem 1:

step 1: One-step assembly of nitrocyclitols



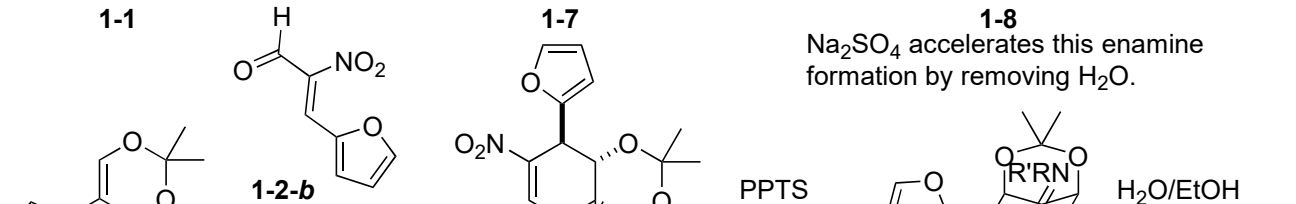
1-1 **1-2** **1-3**

Cagide-Fagín, F.; Alonso, R. *Eur. J. Org. Chem.* **2010**, *2010*, 6741.



1-1 **1-7** **1-8**

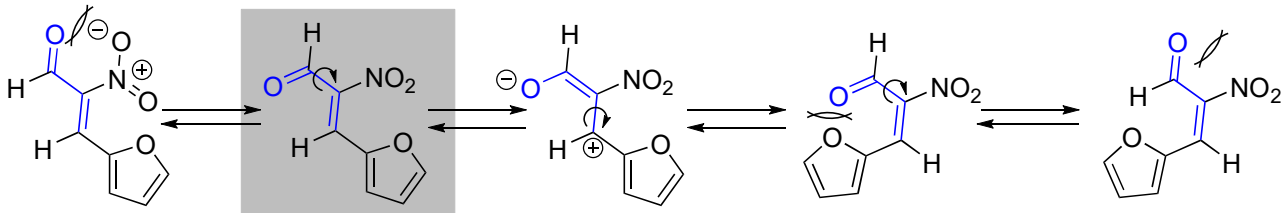
Na_2SO_4 accelerates this enamine formation by removing H_2O.



1-9 **1-10** **1-11**

Discussion: Cascade annulation

Phase 1: hetero Diels–Alder reaction

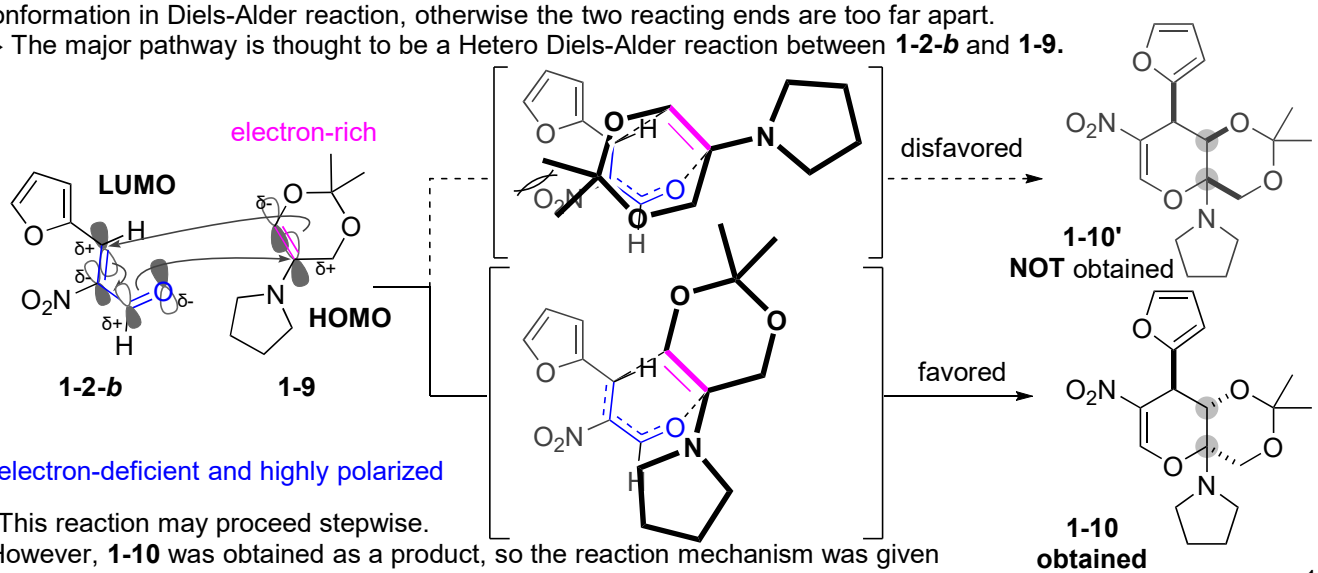


1-2-*a* ***s-trans*** | **1-2-*b*** ***s-cis*** | **1-2'** | **1-2-*c*** ***s-cis*** | **1-2-*d*** ***s-trans***

▸**1-2** is easy to isomerize. Judging from the steric and electronic factors, **1-2-*b*** seems to be easy to react with **1-9**. (In the case of **1-2-*c*** and **1-2-*d***, the carbonyl group and the olefin are not conjugated. **1-2-*a*** seems to be an unstable isomer due to the dipole minimization.)

▸In this reaction, there is a good complementarity of electronic density of **1-9** (the electron-rich double bond) and **1-2** (the electron-deficient and highly polarized enal moiety). Furthermore, it's important that the diene be in the "*s–cis*" conformation in Diels-Alder reaction, otherwise the two reacting ends are too far apart.

→ The major pathway is thought to be a Hetero Diels-Alder reaction between **1-2-*b*** and **1-9.**



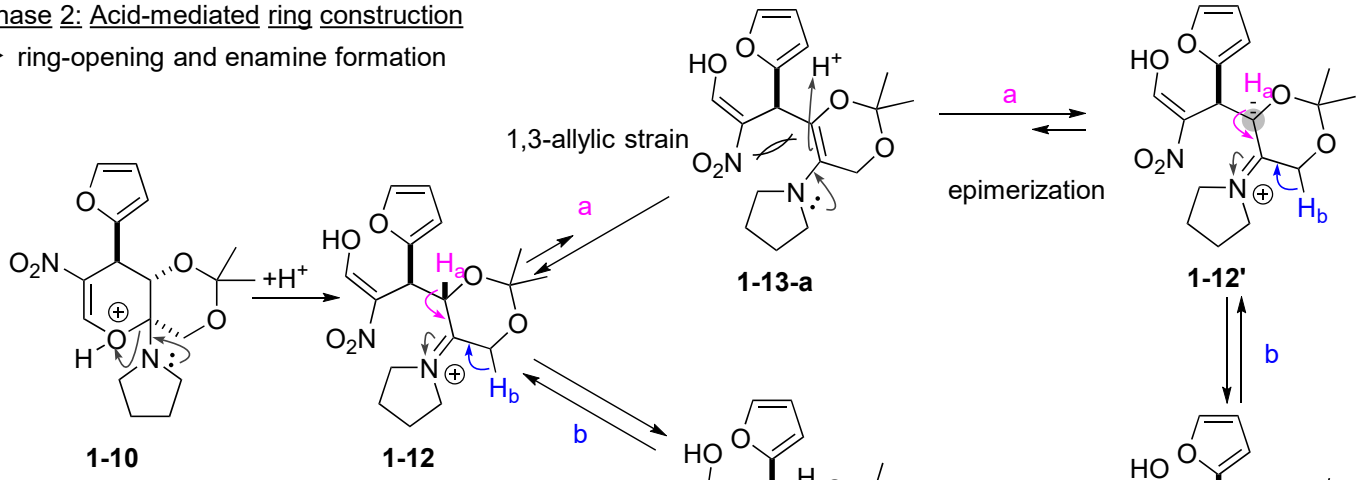
1-2-*b* **1-9**

electron-deficient and highly polarized

*This reaction may proceed stepwise. However, **1-10** was obtained as a product, so the reaction mechanism was given as a concerted pathway.**This reaction is racemic.

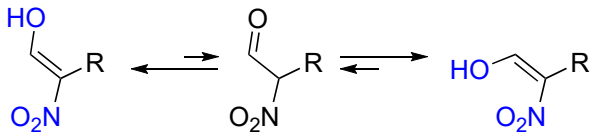
Phase 2: Acid-mediated ring construction

▸ ring-opening and enamine formation



○ The geometric isomers of the nitroenal

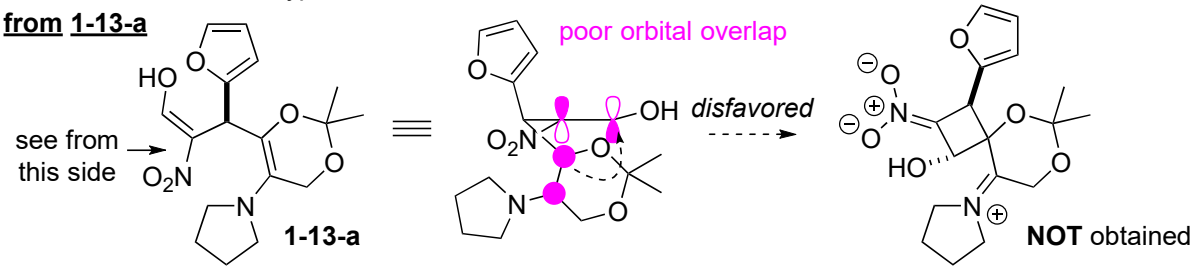
It would be easy to isomerize under an acidic condition.



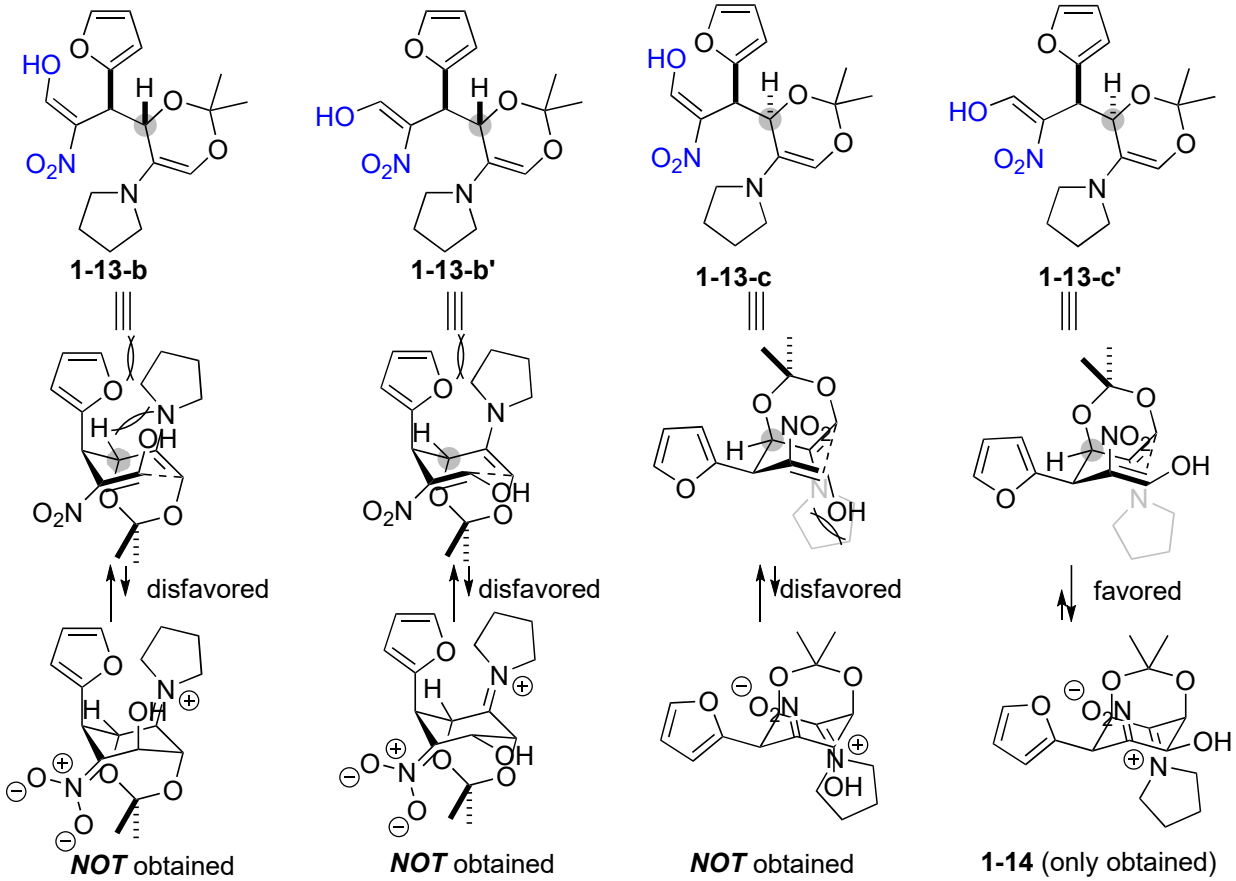
▸ring-reconstruction

intramolecular Michael-type addition

from 1-13-a

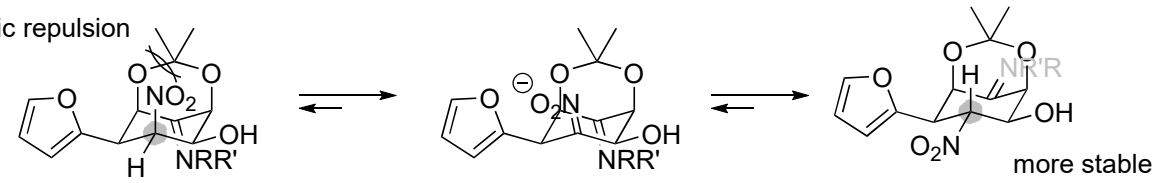


from 1-13-b, 1-13-c: Due to the six-membered cyclic acetal group, we only need to consider one chair-type transition state for each isomer.



Protonation:

steric repulsion



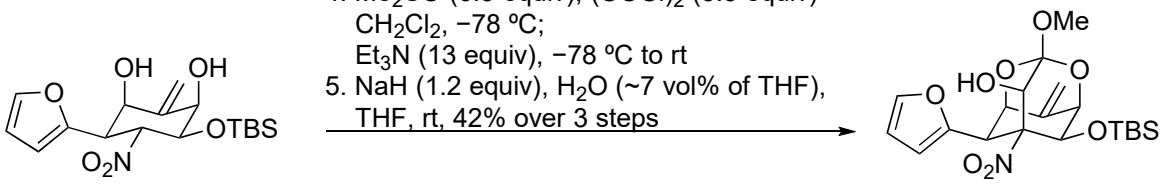
1-11' **1-14** **1-11** more stable

Nucleophilic addition to aldehydes :

The transition states are almost the same as ones of the intramolecular Michael-type addition (and the same product can be obtained). However, retro-aldol type reaction would occur rapidly. So, pathways via nucleophilic addition to aldehydes are thought to be minor.

step 2-5: Stereocontrolled orthoesterification and water-promoted intramolecular Henry addition

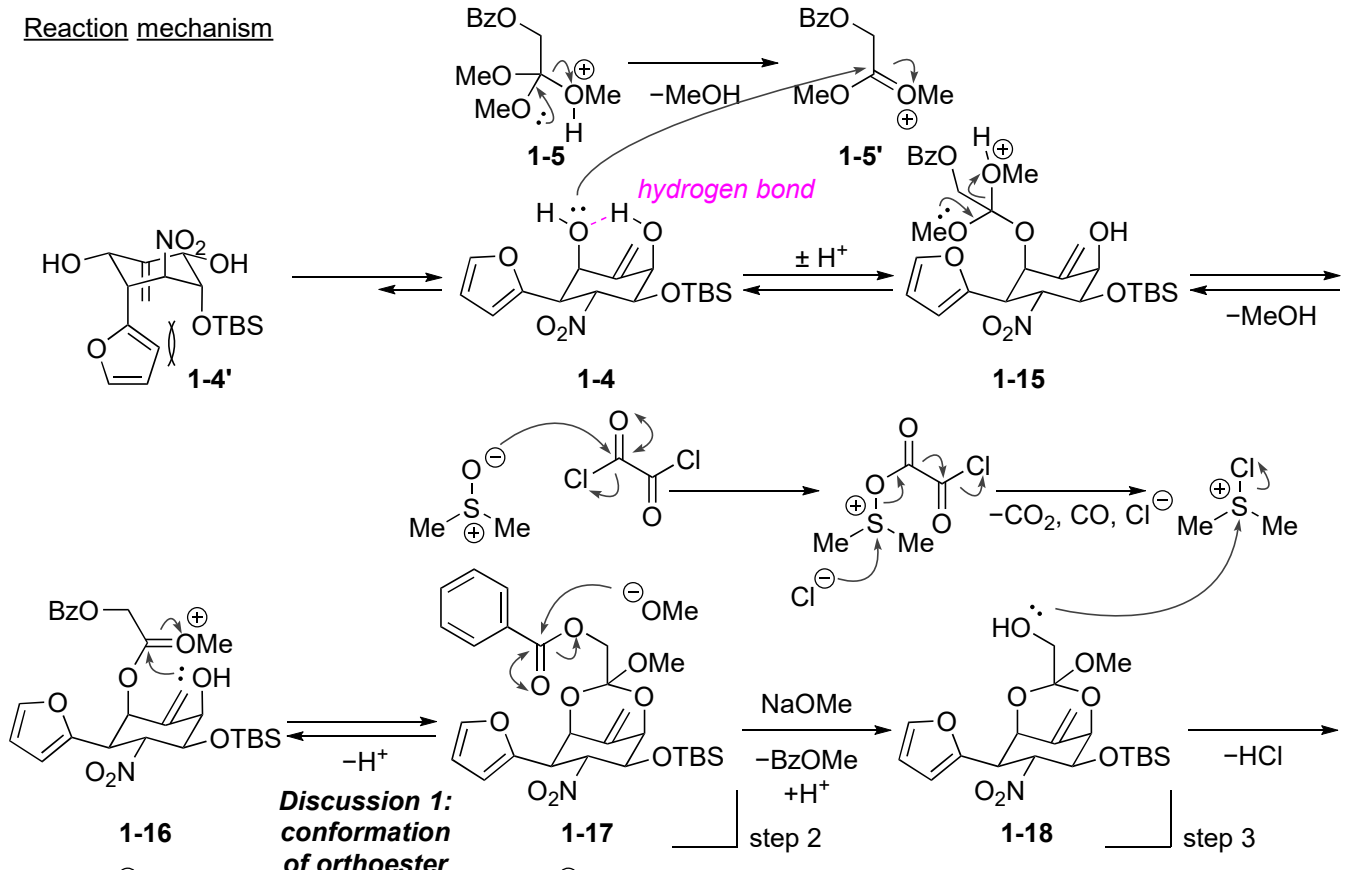
2. **1-5** (15 equiv), $TsOH•H_2O$ (2.0 equiv)
   100 ºC, 67%
3. NaOMe in MeOH (3% w/v, 4.1 equiv), rt
4. Me_2SO (6.5 equiv), $(COCl)_2$ (3.3 equiv)
   CH_2Cl_2, −78 ºC;
   Et_3N (13 equiv), −78 ºC to rt
5. NaH (1.2 equiv), H_2O (~7 vol% of THF),
   THF, rt, 42% over 3 steps



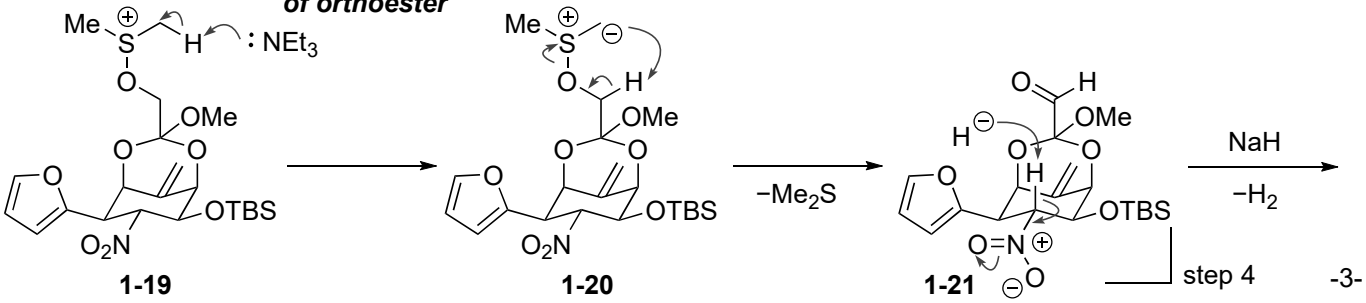
1-4 **1-6**

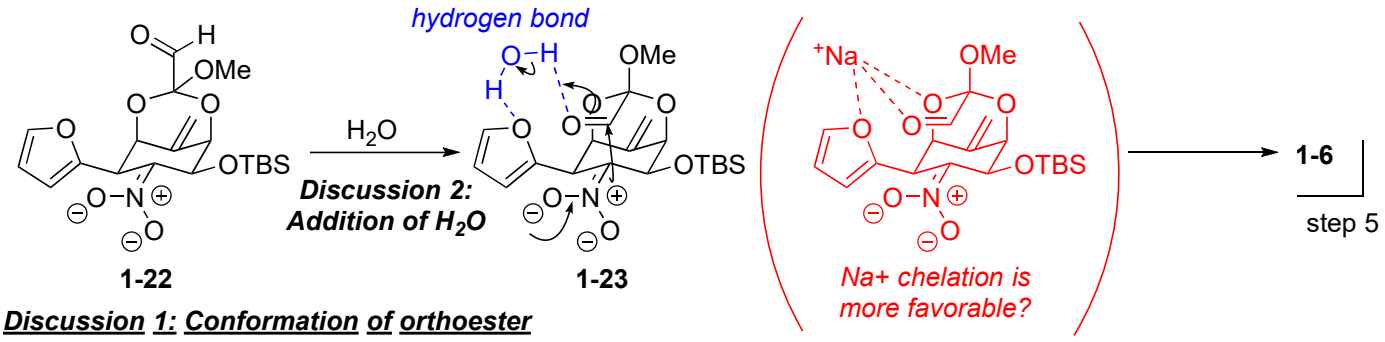
Lago-Santomé, H.; Meana-Pañeda, R.; Alonso, R. *J. Org. Chem.* **2014**, *79*, 4300.

Reaction mechanism



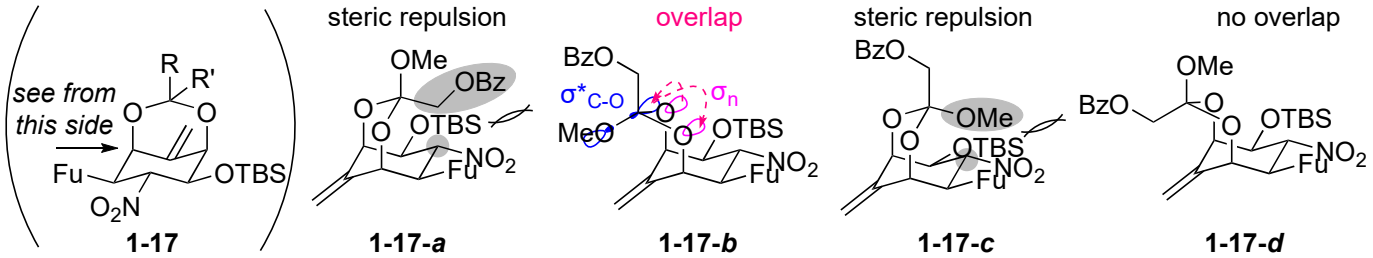
Discussion 1: conformation of orthoester





Discussion 1: Conformation of orthoester

Four possible orthoesters are shown below (Fu = 2-furyl group).



Because the orthoester fomation is an equilibrium reaction, the most thermodynamically stable compound would be obtained in this reaction.

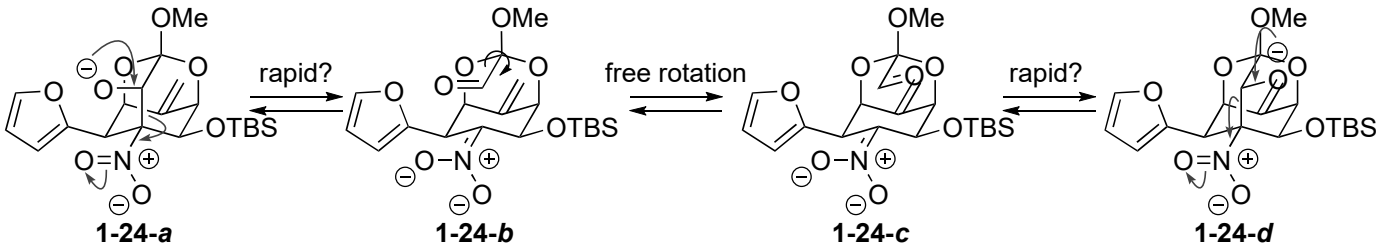
→ **1-17-*b*** would be a major product.

Discussion 2: Addition of H_2O

"Besides base (NaH in dry THF), the key intramolecular nitroaldol reaction required the addition of very small amounts of water to the reaction mixture until disappearance of the starting material."

▸The role of H_2O

1. Protonation (Inhibition of reverse reaction)
2. Orienting the carbonyl oxygen away from the OTBS group (stereocontrol)

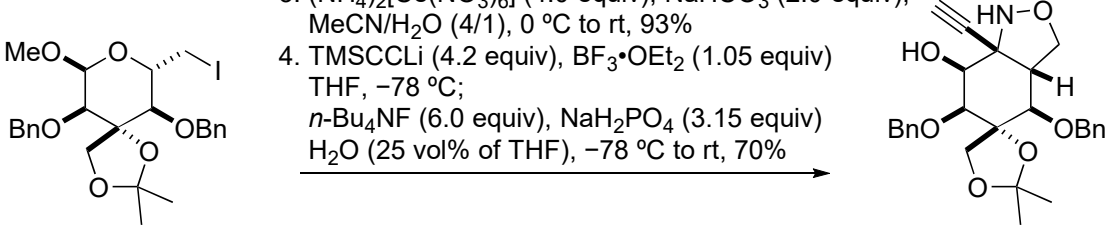


2. Problem 2

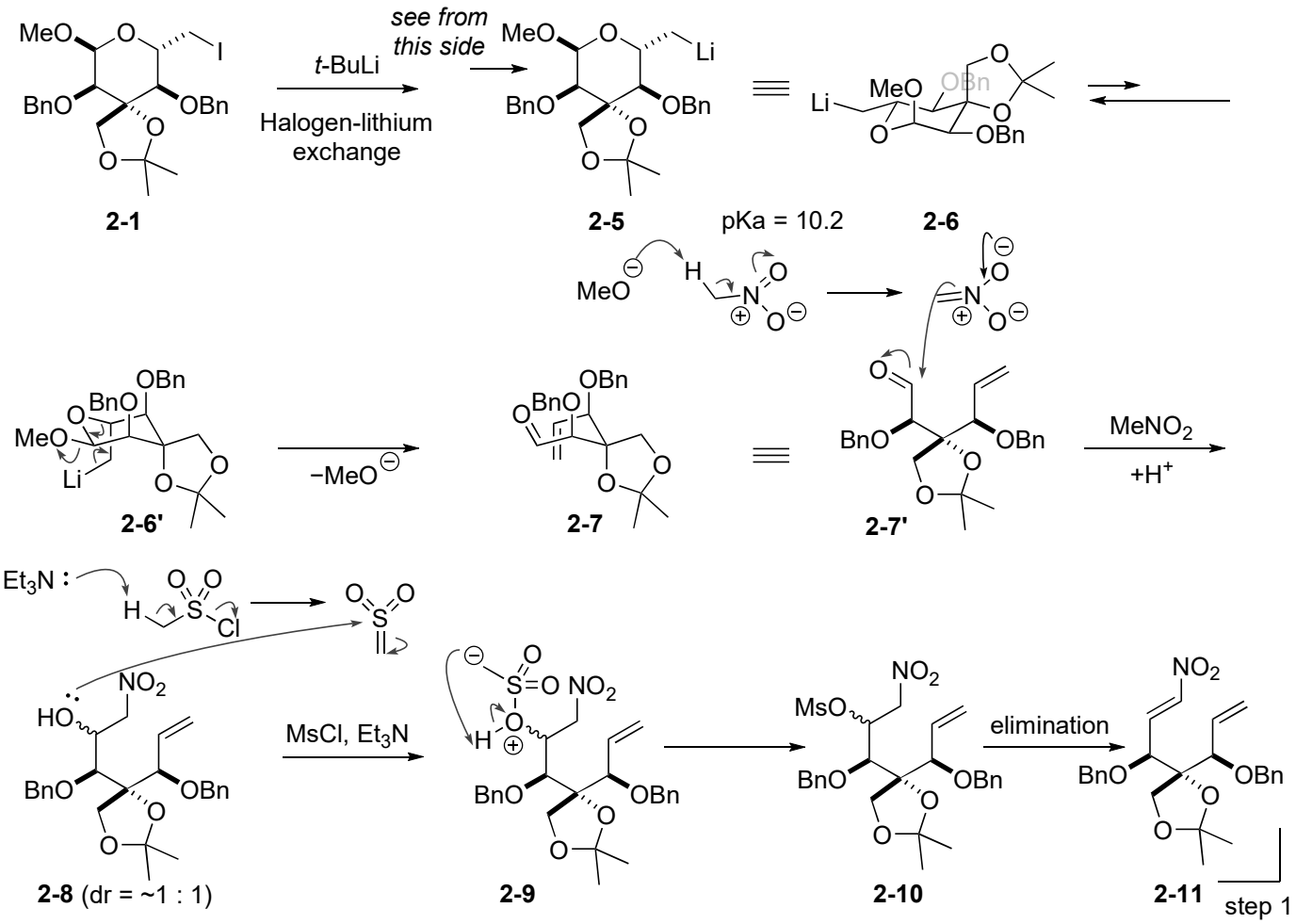
Konrad, D. B.; Rühmann, K. -P.; Ando, H.; Hetzler, B. E.; Strassner, N.; Houk, K. N.; Matsuura, B. S.; Trauner, D. *Science* **2022**, *377*, 411.

step 1-4: Development of a diastereoselective route to the cyclohexane core and installation of the α-tertiary amine

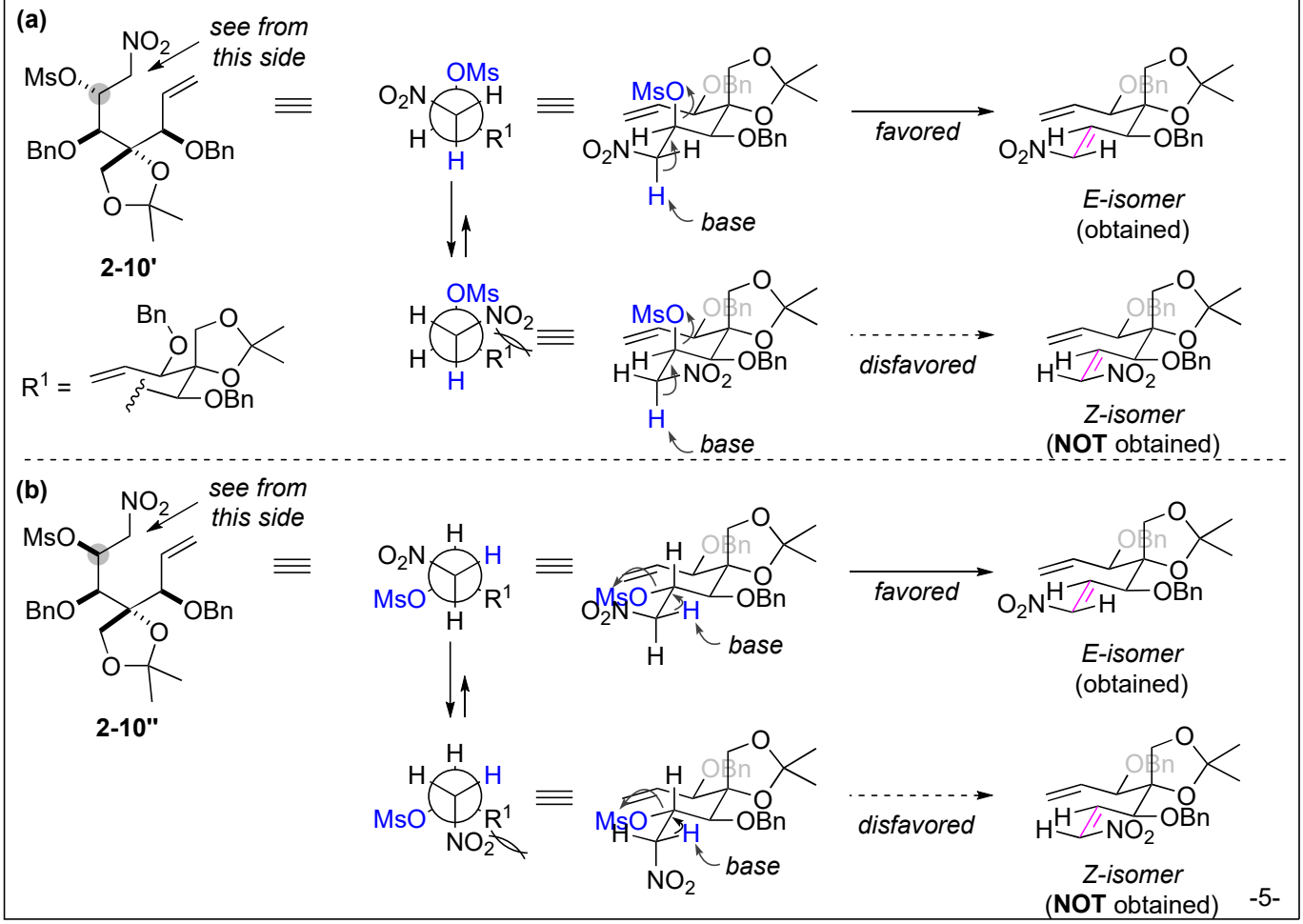
1. *t*-BuLi (2.0 equiv), Et_2O, −78 ºC;
   $MeNO_2$ (10 equiv), −78 ºC to rt;
   MsCl (4.0 equiv), Et_3N (3.0 equiv), 0 ºC, 79%
2. PMBOH (2.05 equiv), *n*-BuLi (2.0 equiv), THF,
   −78 ºC to rt;
   Boc_2O (3.5 equiv), DMAP (0.1 equiv), 0 ºC to rt
   86%
3. $(NH_4)_2[Ce(NO_3)_6]$ (4.0 equiv), $NaHCO_3$ (2.0 equiv),
   $MeCN/H_2O$ (4/1), 0 ºC to rt, 93%
4. TMSCCLi (4.2 equiv), BF_3•OEt_2 (1.05 equiv)
   THF, −78 ºC;
   n-Bu_4NF (6.0 equiv), NaH_2PO_4 (3.15 equiv)
   H_2O (25 vol% of THF), −78 ºC to rt, 70%

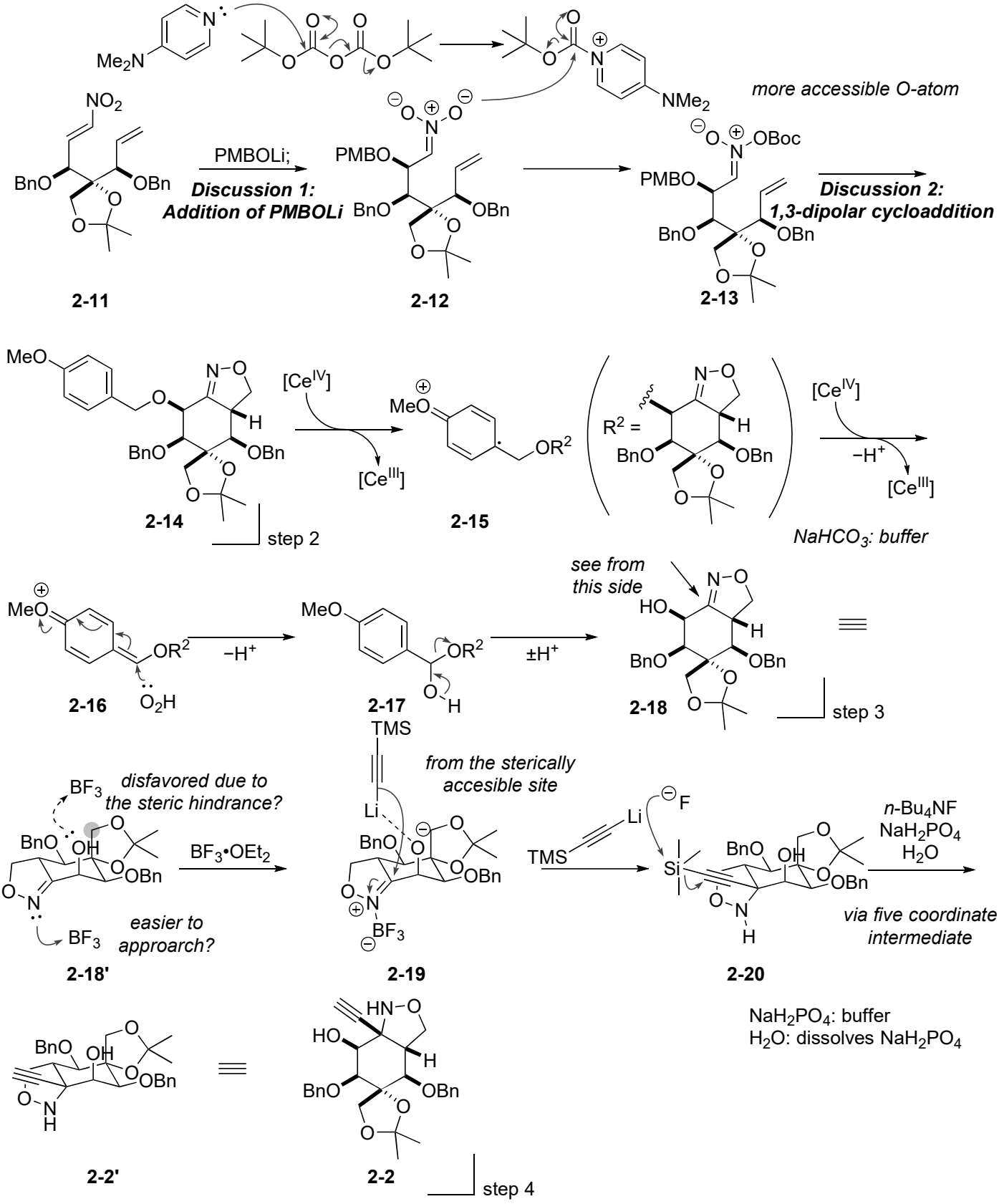


Reaction mechanism



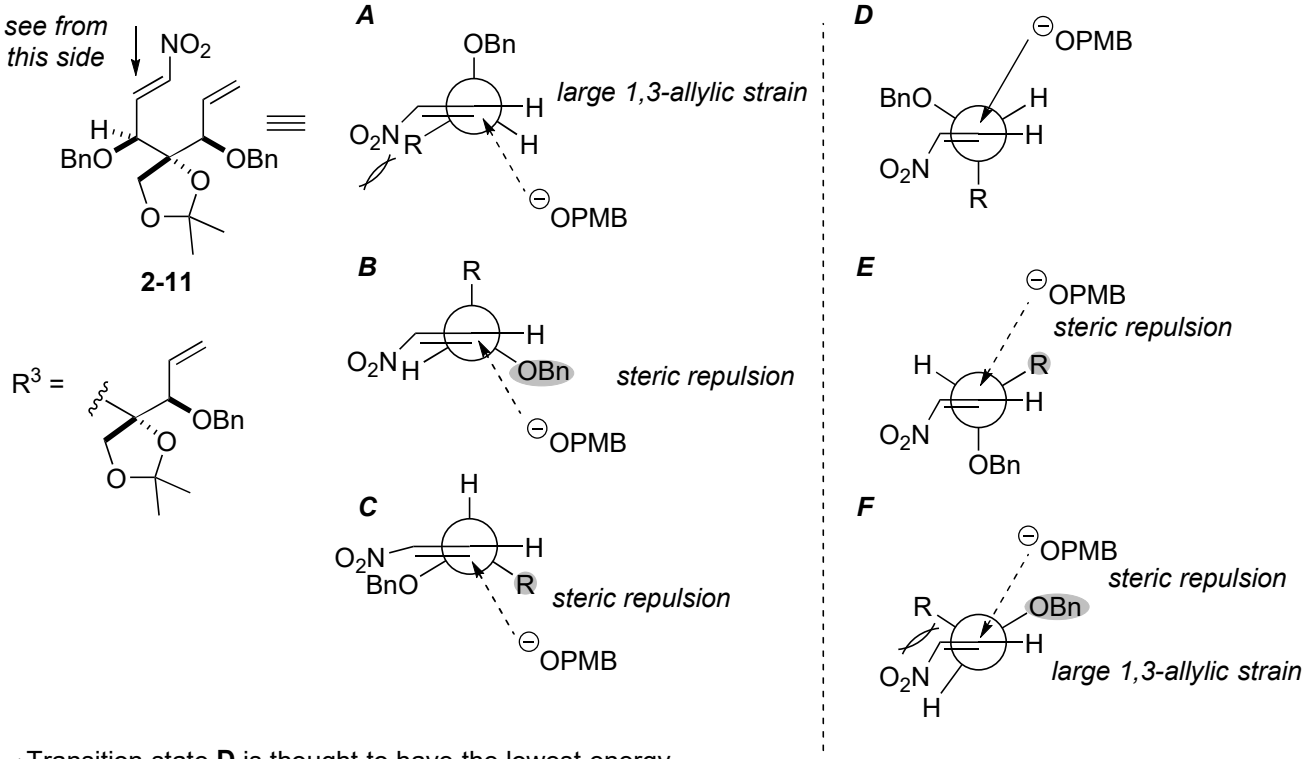
2-10→2-11



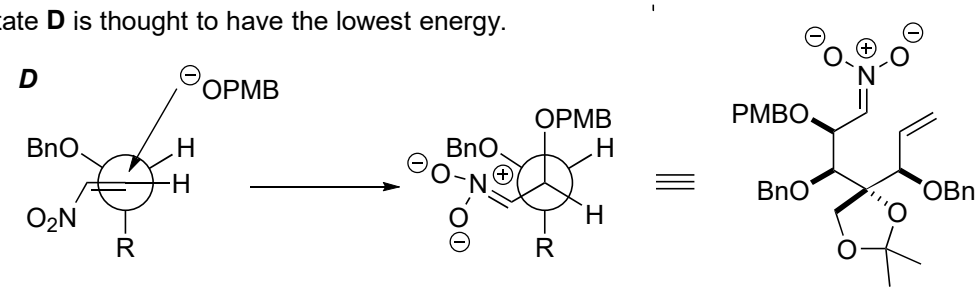

Me2N
NMe2
more accessible O-atom
NO2
BnO
OBn
PMBOLi;
Discussion 1:
Addition of PMBOLi
PMBO
OBoc
Discussion 2:
1,3-dipolar cycloaddition
2-11
2-12
2-13
MeO
[CeIV]
[CeIII]
R2 =
−H+
2-14
step 2
2-15
NaHCO3: buffer
see from
this side
HO
OR2
O2H
2-16
2-17
±H+
2-18
step 3
TMS
from the sterically
accesible site
BF3
disfavored due to
the steric hindrance?
BF3•OEt2
Li
F
n-Bu4NF
NaH2PO4
H2O
Si
easier to
approarch?
via five coordinate
intermediate
2-18'
2-19
2-20
NaH2PO4: buffer
H2O: dissolves NaH2PO4
HN−O
2-2'
2-2
step 4

Discussion 1: Addition of PMBOLi

The selectivity of this reaction can be explained by the steric effect.
There are six possible diastereomeric transition states.



→Transition state **D** is thought to have the lowest energy.

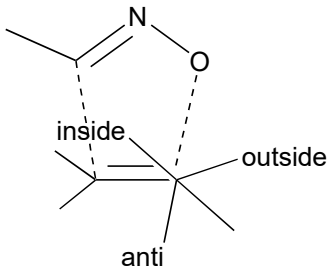


2-12
major intermediate

▸The authors said that this selectivity can be explained by "*inside alkoxy effect*".

inside alkoxy effect [ref. 10]

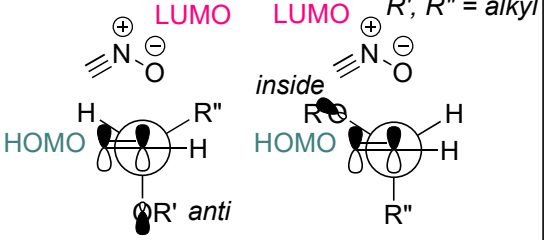
The *inside alkoxy effect* is useful for predicting the stereoselectivity of nitrile oxide cycloaddition reactions with chiral allylic ethers. The hypothesis states that allylic ethers adopt the inside position and alkyl substituents prefer the sterically less-crowded anti conformation in transition states for these electrophilic cycloadditions.



transition state of 1,3-dipolar addition

In **electrophilic** attack upon an allylic ether, the π bond becomes electron deficient. Electron-donor substituents on the alkene stabilize the transition state, while electron-withdrawing substituents destabilize the transition state.

→ When the allylic ether is *anti*, the $\sigma^*_{C\text{-}O}$ orbital overlaps with, and withdraws electron density from, the alkene π orbital.
When the allylic ether is *inside*, it is near the plane, and overlap of $\sigma^*_{C\text{-}O}$ orbital with $\pi_{C=C}$ is minimized.
When the allylic ether is *outside*, there is an electrostatic repulsion between the two oxygens, one on the allylic stereocenter and one on the nitrile oxide.

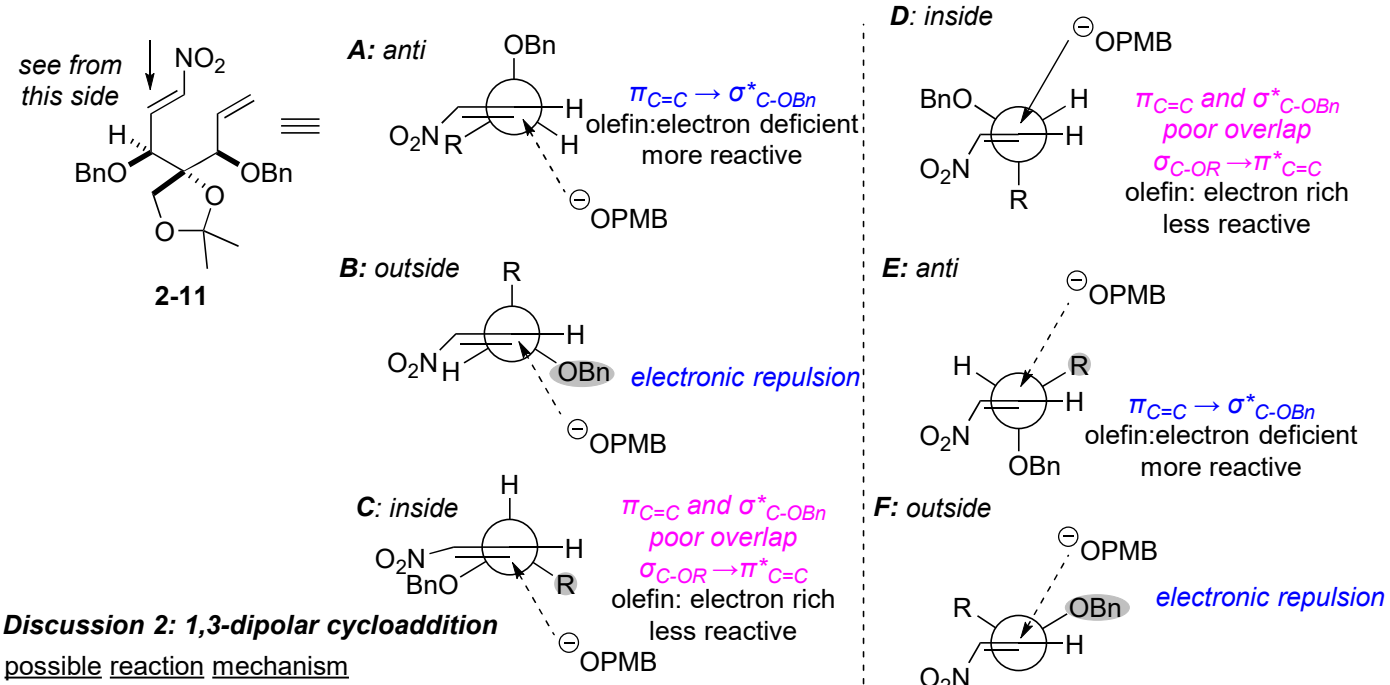


$\pi_{C=C} \rightarrow \sigma^*_{C\text{-}OR'}$: *destabilization*

$\pi_{C=C}$ *and* $\sigma^*_{C\text{-}OR'}$: *poor overlap*
$\pi_{C=C}$ *and* $\sigma_{C\text{-}R''}$: *stabilized*

In the case of this reaction, a **nucleophilic addition** occurred.→ The LUMO of the olefin would react. **So, an electron deficient olefin is thought to be favorable.**

In my opinion, this rule cannot be used for the explanation of this selectivity.



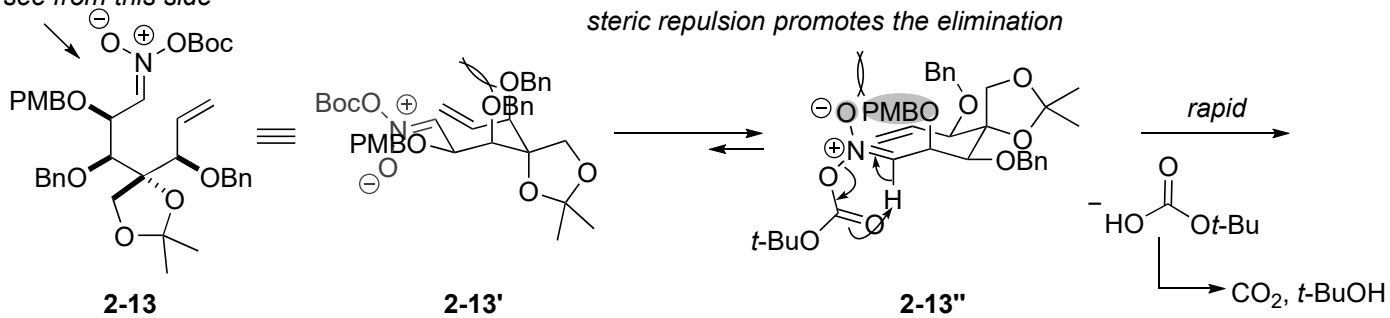
Discussion 2: 1,3-dipolar cycloaddition

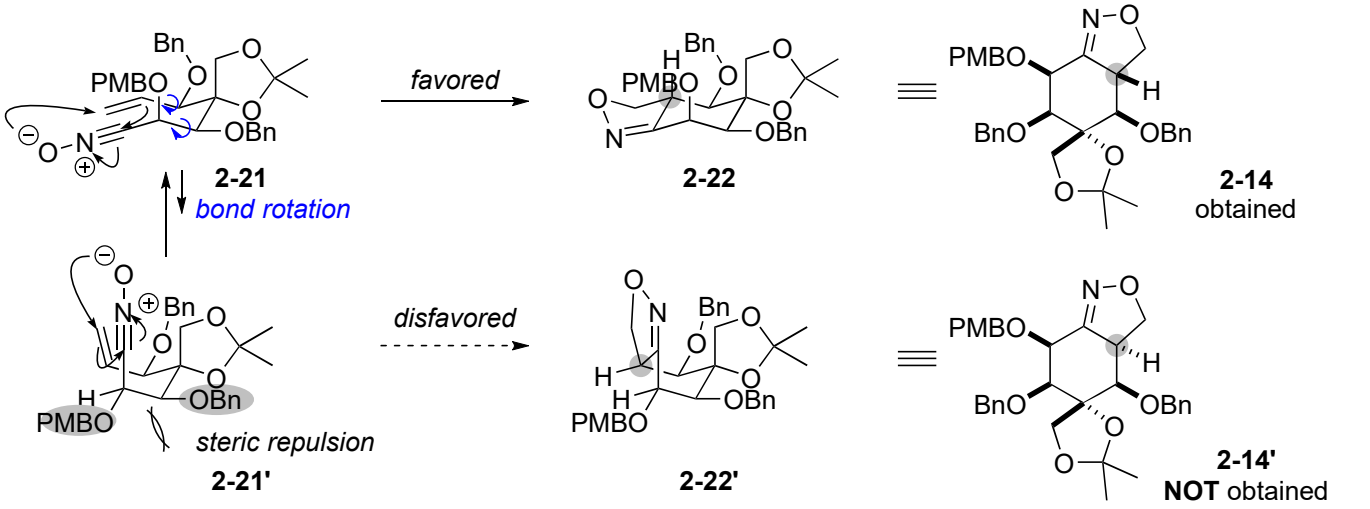
possible reaction mechanism

Path A: elimination → 1,3-dipolar addition (favorable)

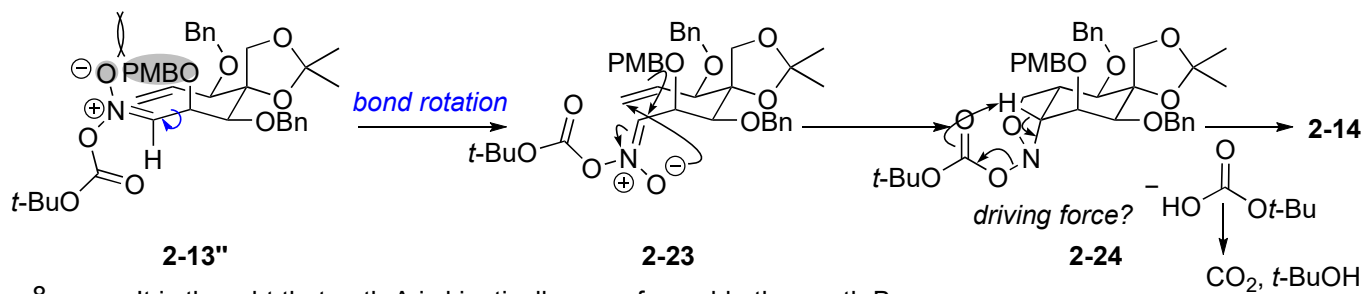
see from this side

steric repulsion promotes the elimination





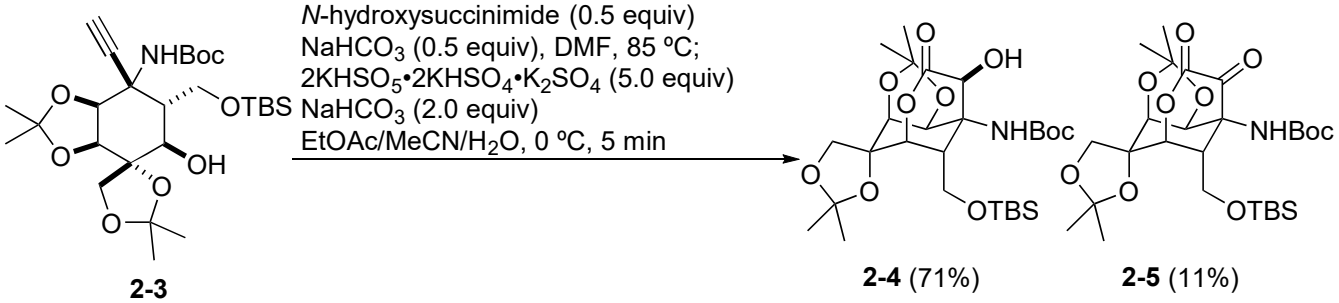
Path B: 1,3-dipolar addition → elimination



It is thought that path A is kinetically more favorable than path B.

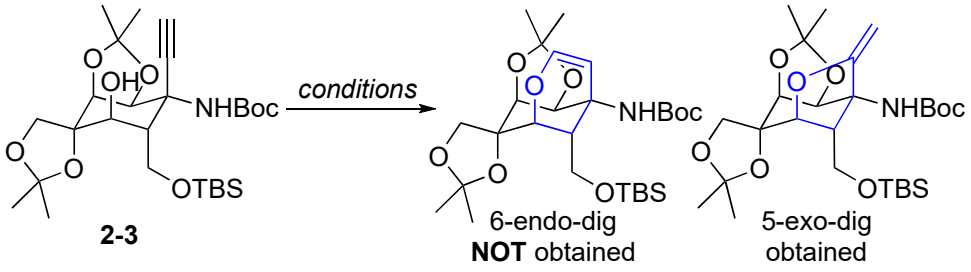
step 5: Ru-mediated hydroxylactonization

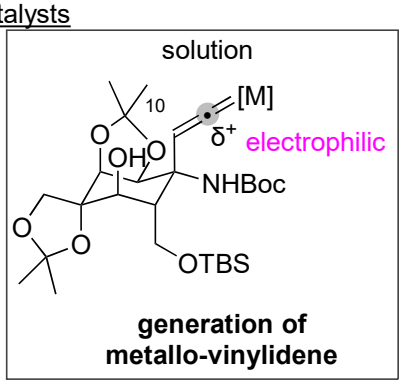
5. $CpRu(PPh_3)_2Cl$ (8 mol%), PPh_3 (16 mol%)
n-Bu_4NPF_6 (13 mol%)
N-hydroxysuccinimide (0.5 equiv)
$NaHCO_3$ (0.5 equiv), DMF, 85 ºC;
$2KHSO_5•2KHSO_4•K_2SO_4$ (5.0 equiv)
$NaHCO_3$ (2.0 equiv)
EtOAc/MeCN/H_2O, 0 ºC, 5 min



Background

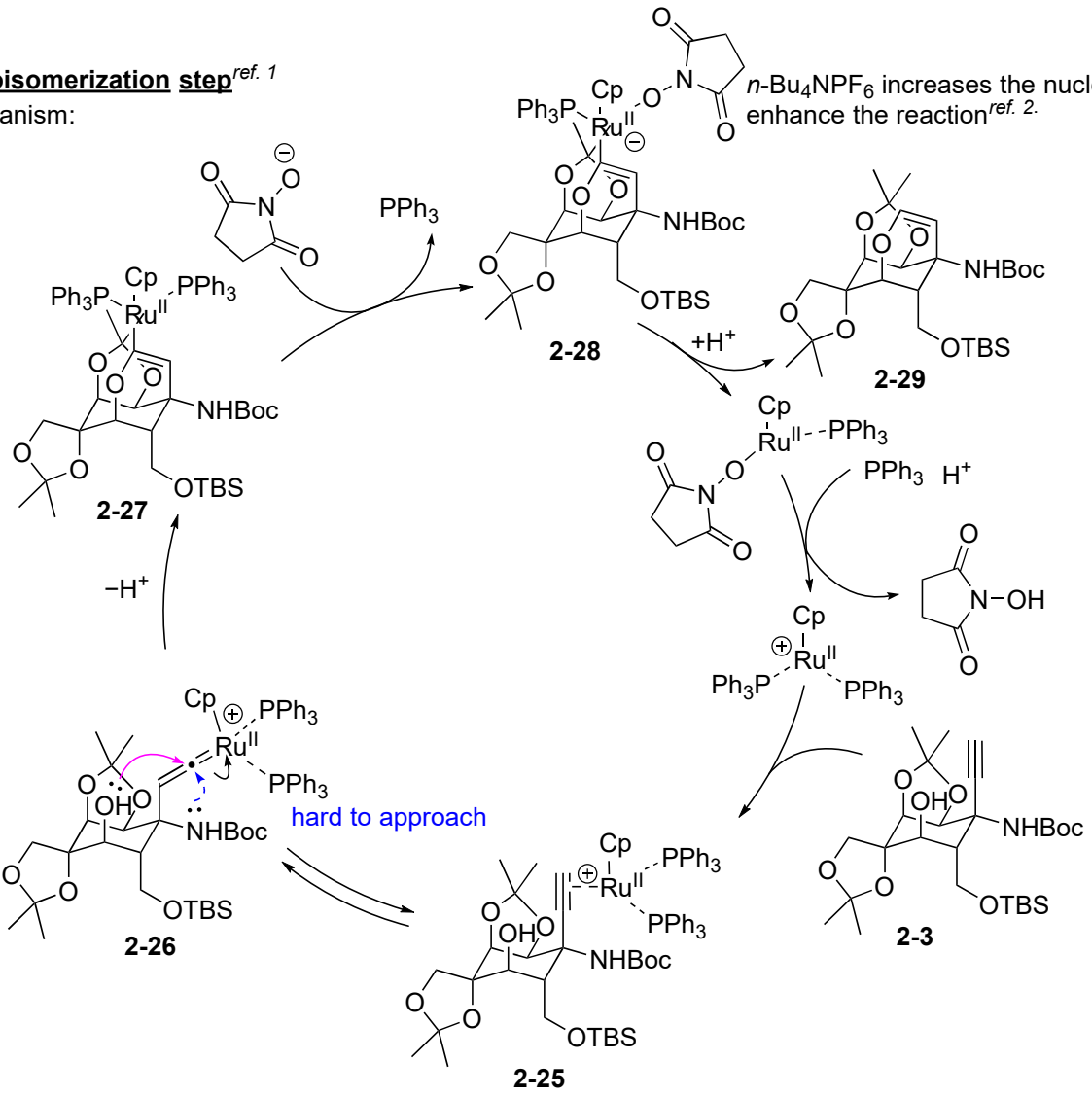
▸Attempted 6-endo-dig cyclization conditions with gold- or silver-based π-acid catalysts





Cycloisomerization step[ref. 1]
mechanism:

n-Bu_4NPF_6 increases the nucleophilicity and enhance the reaction[ref. 2].



▸ The importance of *N*-hydroxysuccinimide[ref.2]
Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680.

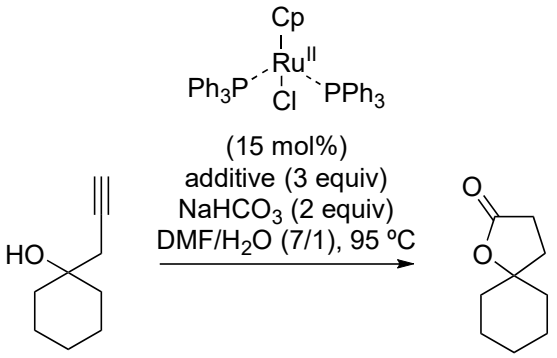
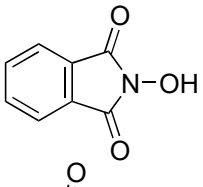
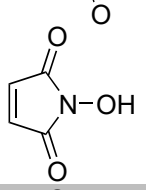
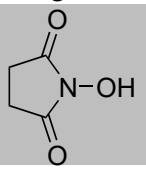


***Table* 1**

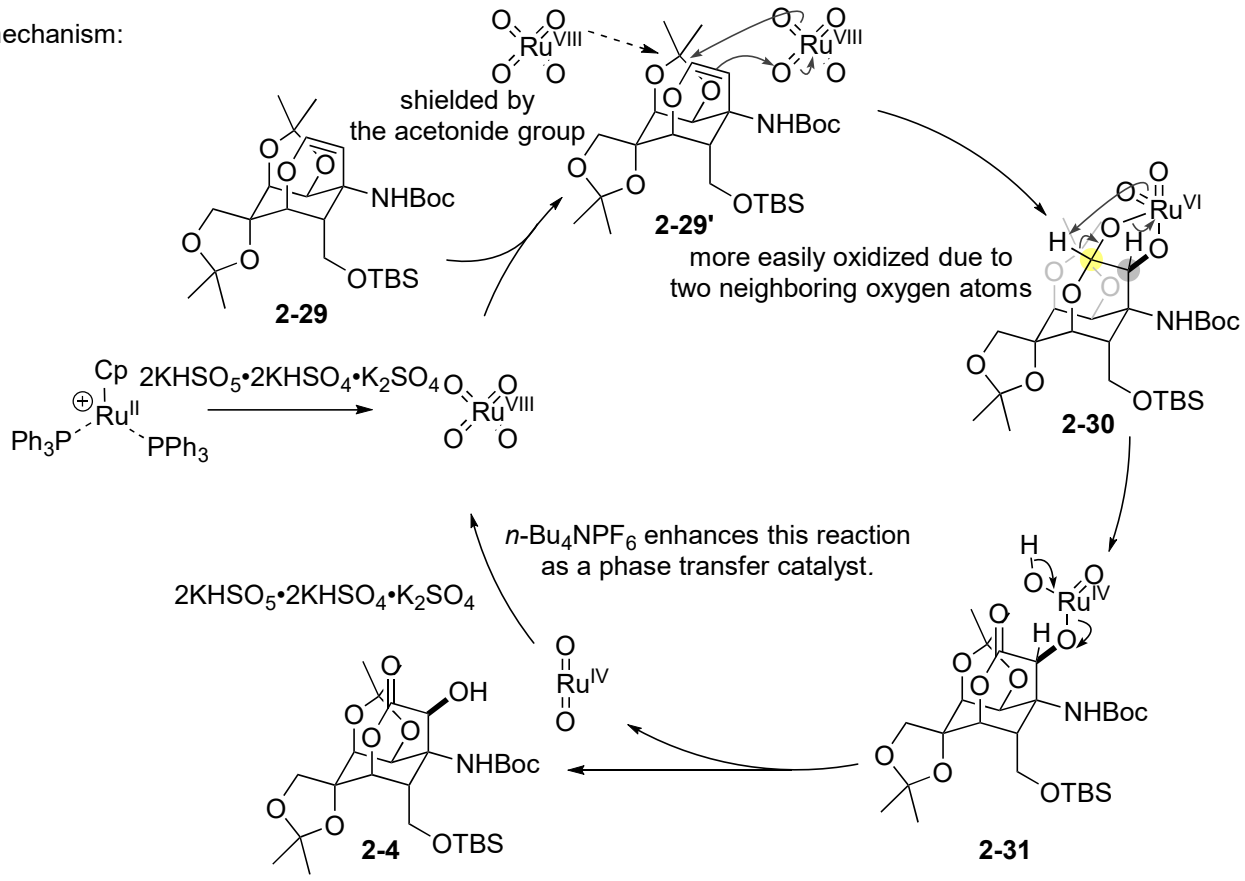
additive	result (target compound)
H_2O_2 *t*-BuOOH *m*CPBA pyridine *N*-oxide Me_2SO	no reaction
	17%
	38%
	61%

An addition of oxidants and noncoordinating bases[ref. 3] (such as Et_3N and $NaHCO_3$, not shown in ***Table* 1**) only led to recovery of the starting material.
The use of coodinating bases to promote ligand exchange in cycloisomerization pathway is thought to be crucial.

Hydroxylactonization step

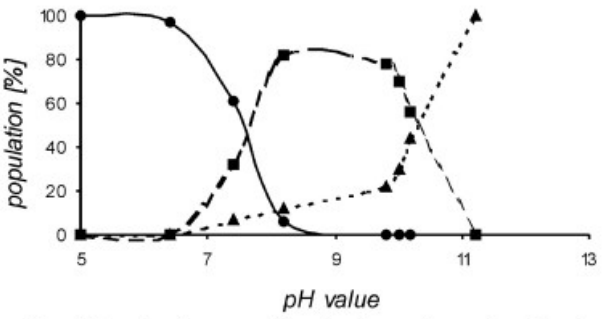
▸The oxidation of $CpRu(PPh_3)_2Cl$ was able lead to the use of a single catalyst for more than one chemical transformation in a single synthetic operation.
(A variety of ruthenium sources, such as $RuCl_3$[ref. 4], RuO_2[ref. 5], and $[RuCl_2(PPh_3)_2]$[ref. 6] have been used for the formation of the oxidative species RuO_4 in different oxidation reactions. The authors would expect that the oxidation of Ru catalyst would be easy to perform.)

mechanism:



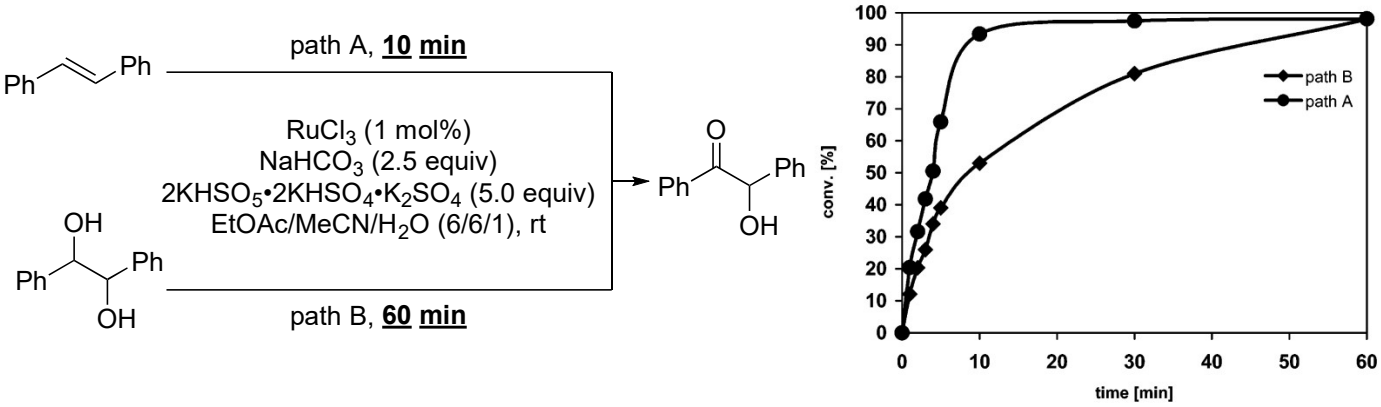
Active species: RuO_4 *ref. 7*

This reaction is carried out in an acidic condition.
So, RuO_4 would catalyze this reaction.



Population of various oxoruthenates depending on the pH-value
(RuO_4 (●), $[RuO4]^-$ (■) and trans-$[Ru(OH)_2O_3]^-$ (▲).

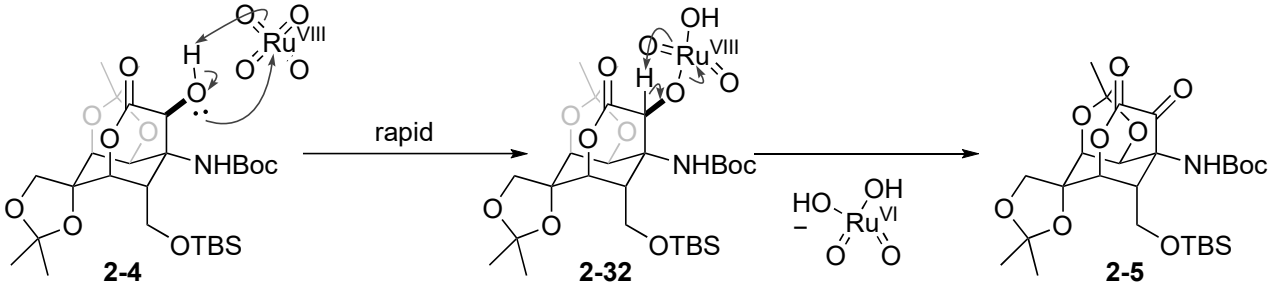
Two-step process of *syn*-dihydroxylation or concomitant mono oxidation of the resulting diol *ref. 8*



Considering this result, **two-step process of *syn*-dihydroxylation would be more favorable.**

▸overoxidation *ref. 9*

It is thought that the overoxidation is also performed by RuO_4. The reaction rate would be also rapid, so the reaction time need to be shortened in order to surpress the overoxidation.



2-4 **2-32** **2-5**

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