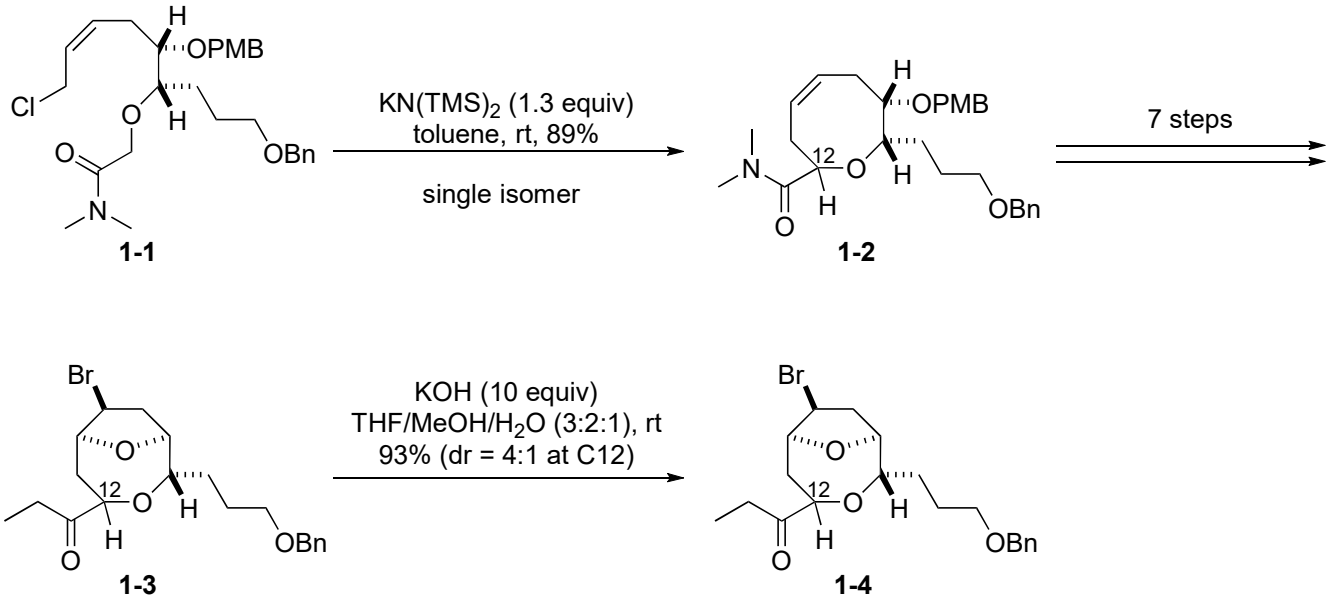
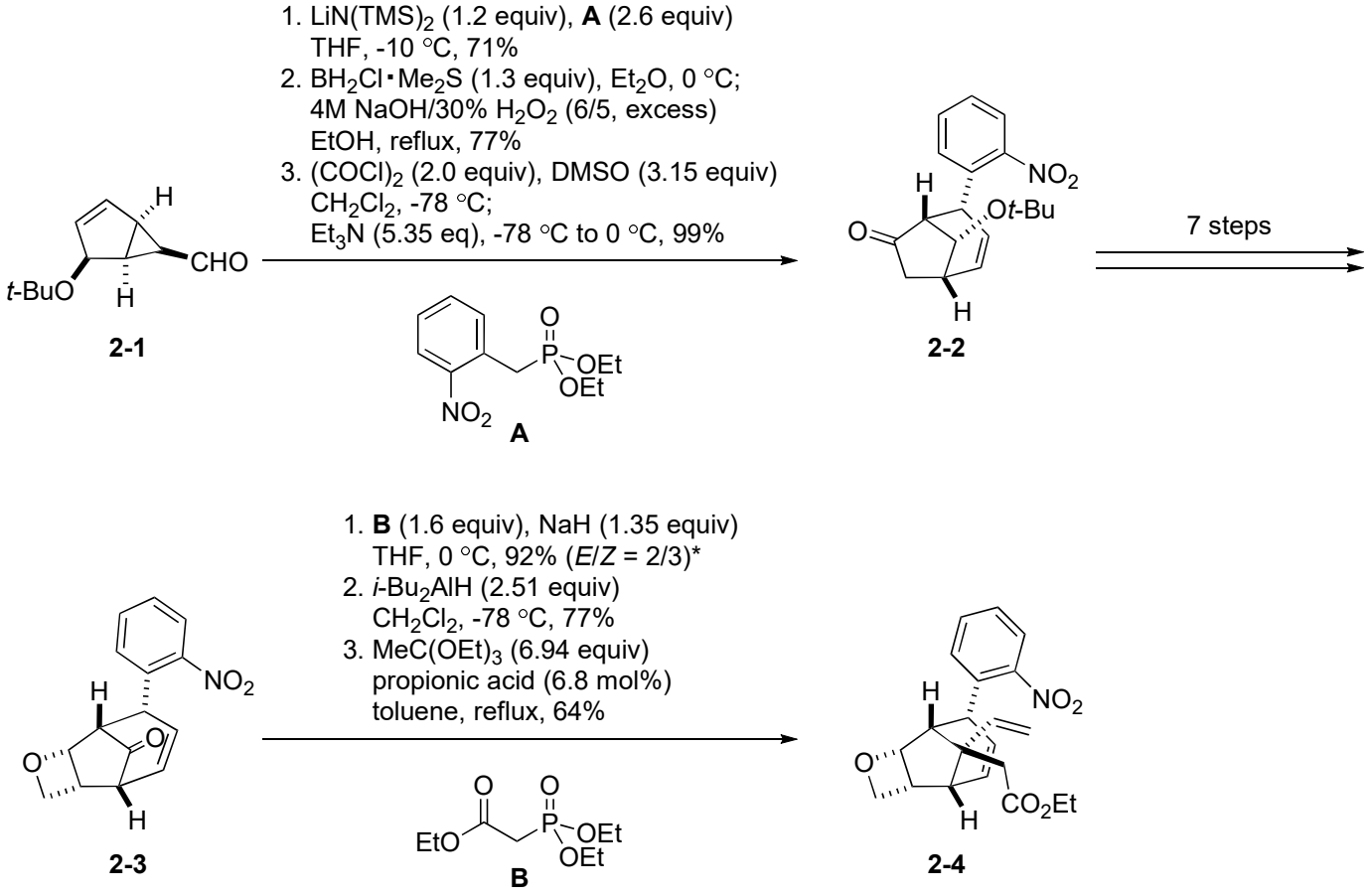
Problem Session (2)

2024.12.12 Yutaro Yamada

1 Please explain the reaction mechanism and determine the stereochemistry at C12 of **1-2** and **1-4**.
(The stereochemistry at C12 of **1-3** is the same as that of **1-2**.)



2 Please explain the reaction mechanism.



* Two isomers were used in the following reactions without separation.

Problem Session (2) -Answer-

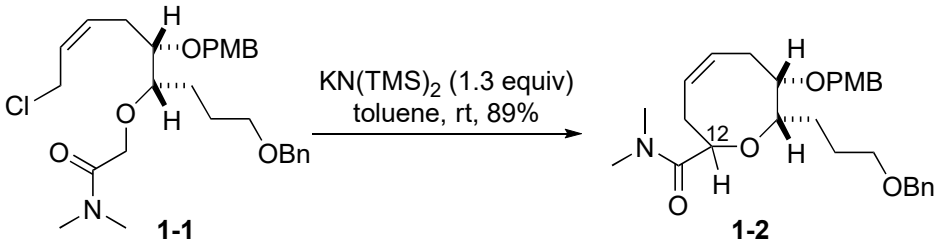
2024.12.12 Yutaro Yamada

topic: Electrostatic effect

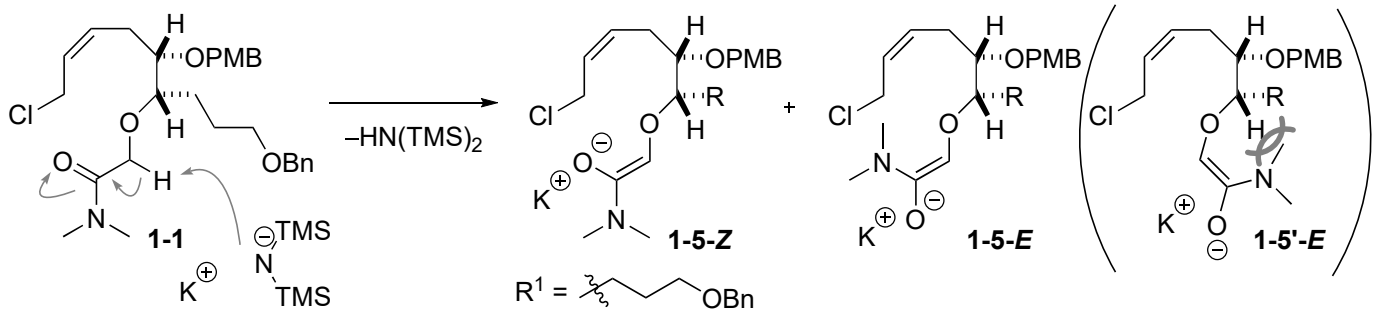
1 Theme: Isomerization controlled by lone pair-lone pair interaction

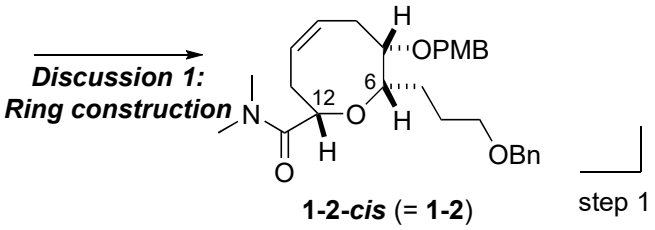
main paper: Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269.

1. Construction of an 8-membered ether ring



Reaction mechanism:



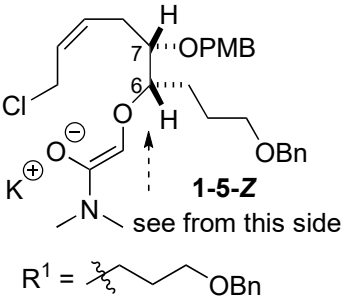


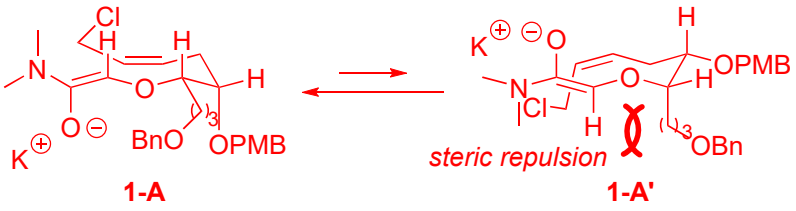
The stereochemistry at C12 of **1-2** was *cis* relative to C6.

Discussion 1*: *Ring construction

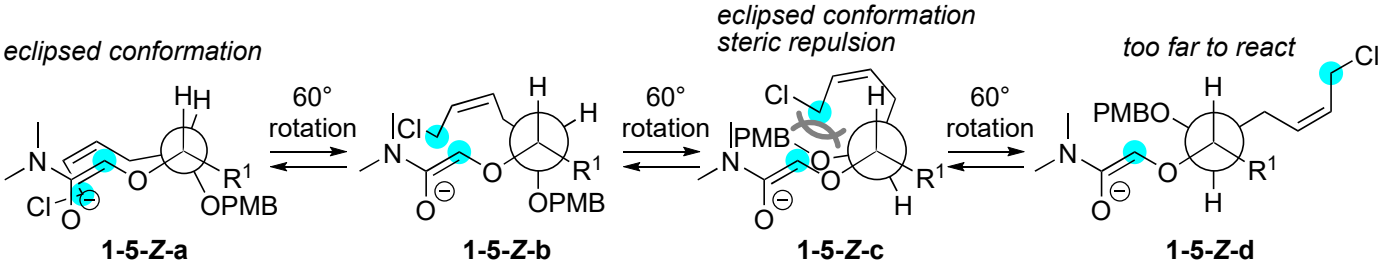
1. Bond rotation of C6-C7

The enolate **1-5-*Z***, an intermediate for cyclization, contains multiple bulky substituents at C6 and C7 position. The steric interactions among these groups are thought to control the conformation of an 8-membered ring construction. Therefore, the bond rotation of C6-C7 was considered first.

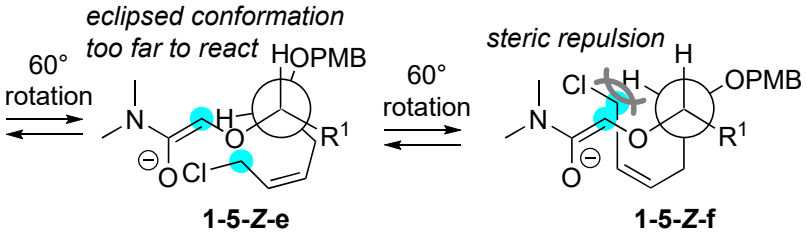




Cyclization would occur from **1-A.**

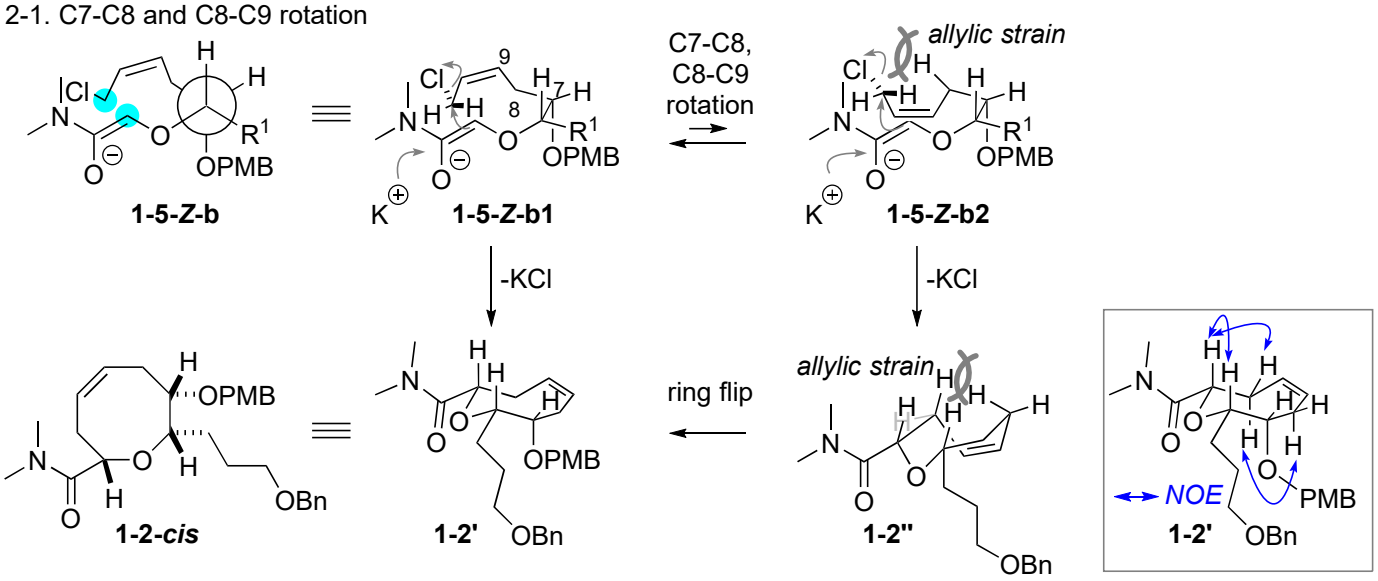


most favorable

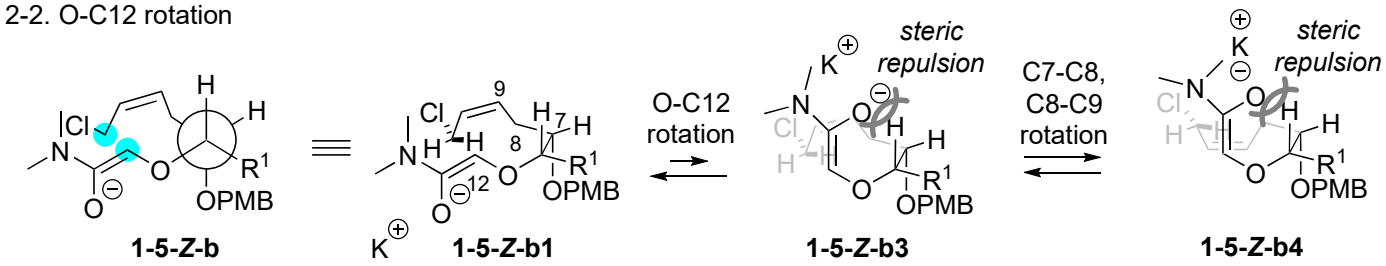


Construction of an 8-membered ring would occur between highlighted positions.
1-5-*Z*-d and **e** –> Highlighted positions are too far to react.
1-5-*Z*-a, b, c and **f** –> Highlighted positions are appropriate for cyclization so cyclization would occur. However, **1-5-*Z*-a** and **c** are unfavorable conformations for cyclization at room temperature compared to **1-5-*Z*-b** due to torsional strain. **1-5-*Z*-c** and **f** are also unfavorable because of steric repulsion between the chlorine-substituted allylic methylene and other substituents.
–> Conformation of **1-5-*Z*-b** was mainly considered.

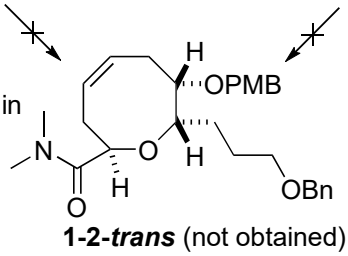
2. Other bond rotation
2-1. C7-C8 and C8-C9 rotation



2-2. O-C12 rotation



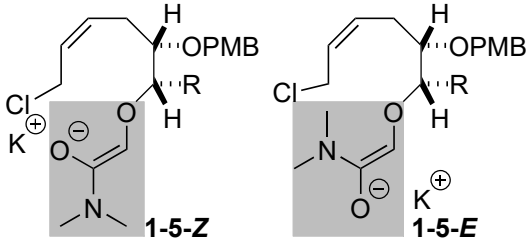
Due to the steric repulsion between the enolate oxygen and proton located in α-position of ether, **1-2-*trans*** was not obtained.



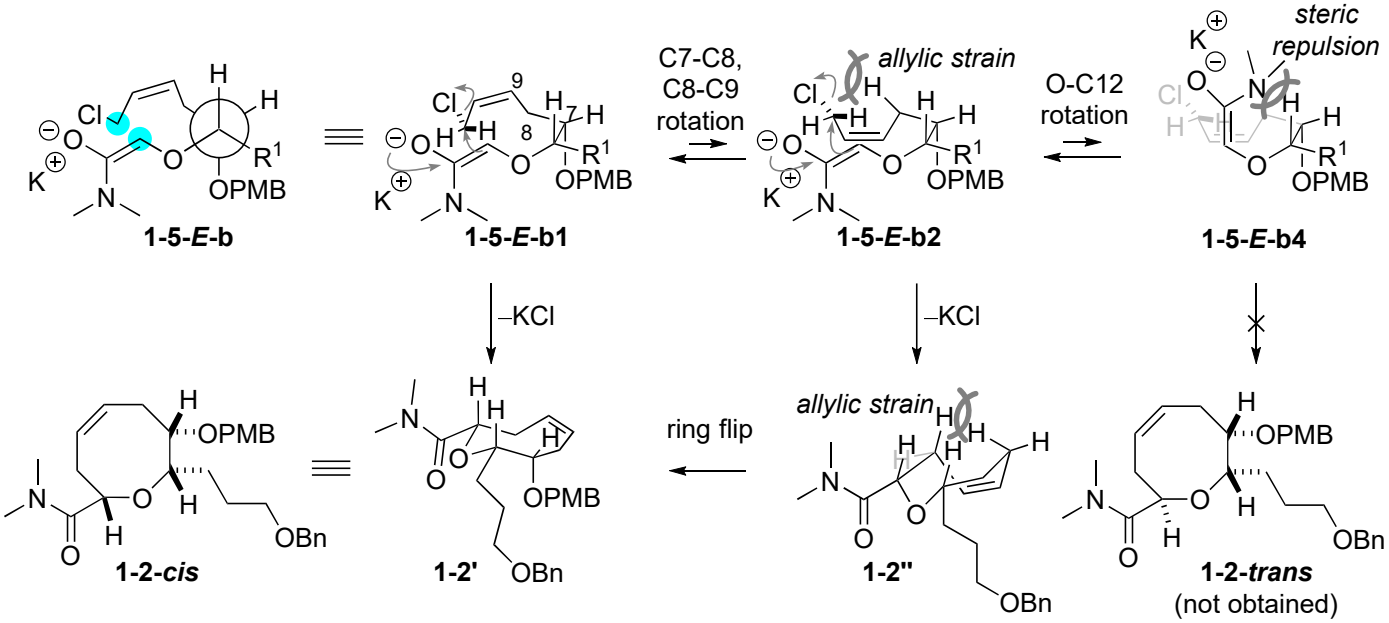
1-2-*trans* (not obtained)

3. In the case of **1-5-*E***

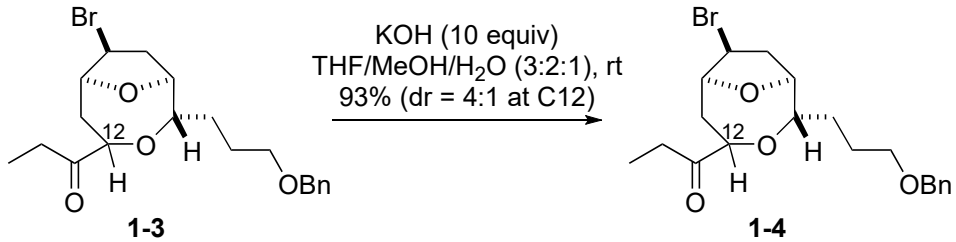
When discussing the cyclization conformation of **1-5-*Z*** in discussion 1-1, steric hindrance around the enolate part was disregarded because it is highly planar (highlighted in ■). Therefore, the same discussion regarding the conformation for cyclization in discussion 1-1 can be extended to **1-5-*E***.



1-5-*Z* **1-5-*E***

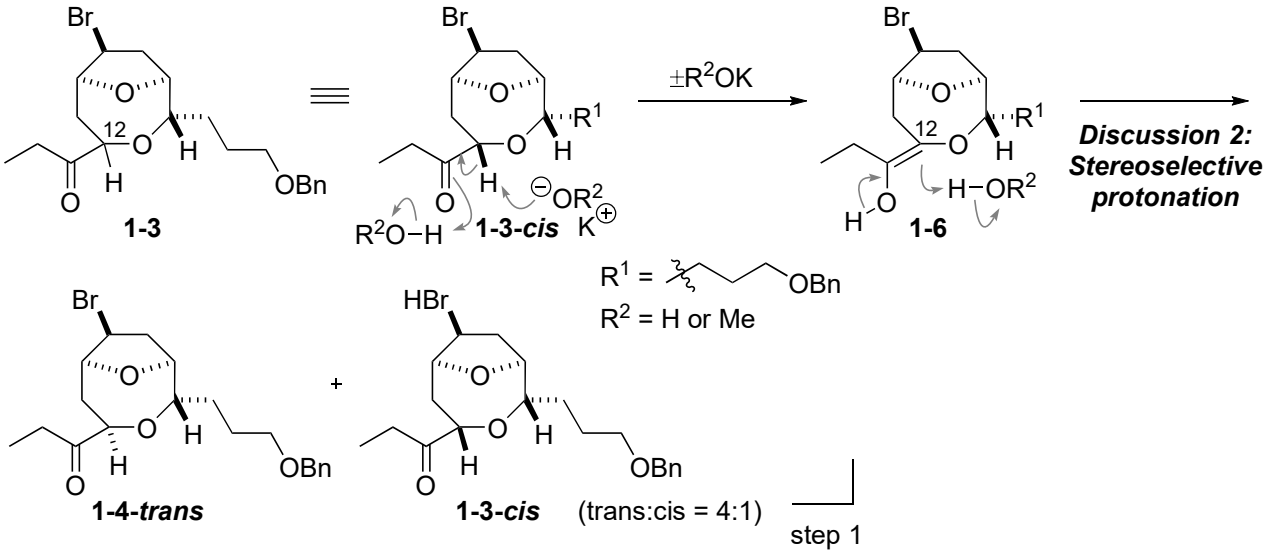


2. Isomerization



The stereochemistry of C12 of **1-3** is the same as that of **1-2-cis**.

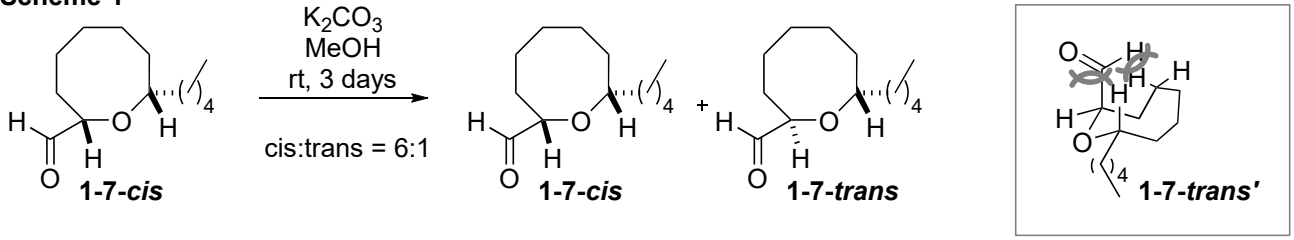
Reaction mechanism:



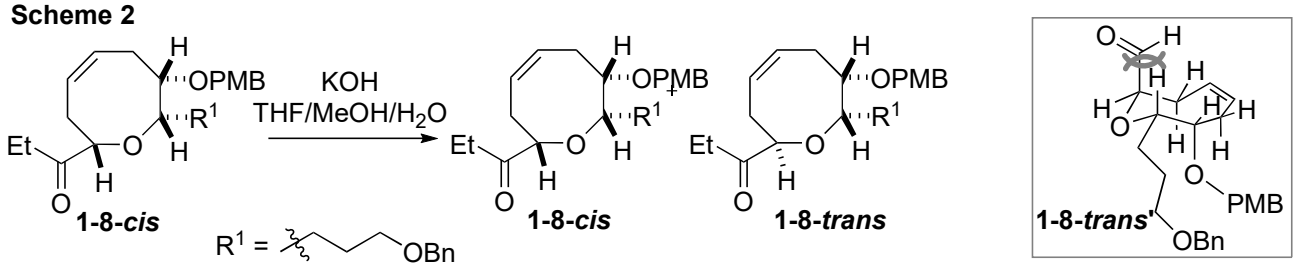
Discussion 2*: *Stereoselective protonation

1. Results of monocyclic ether ring

Scheme 1 *ref. 1*

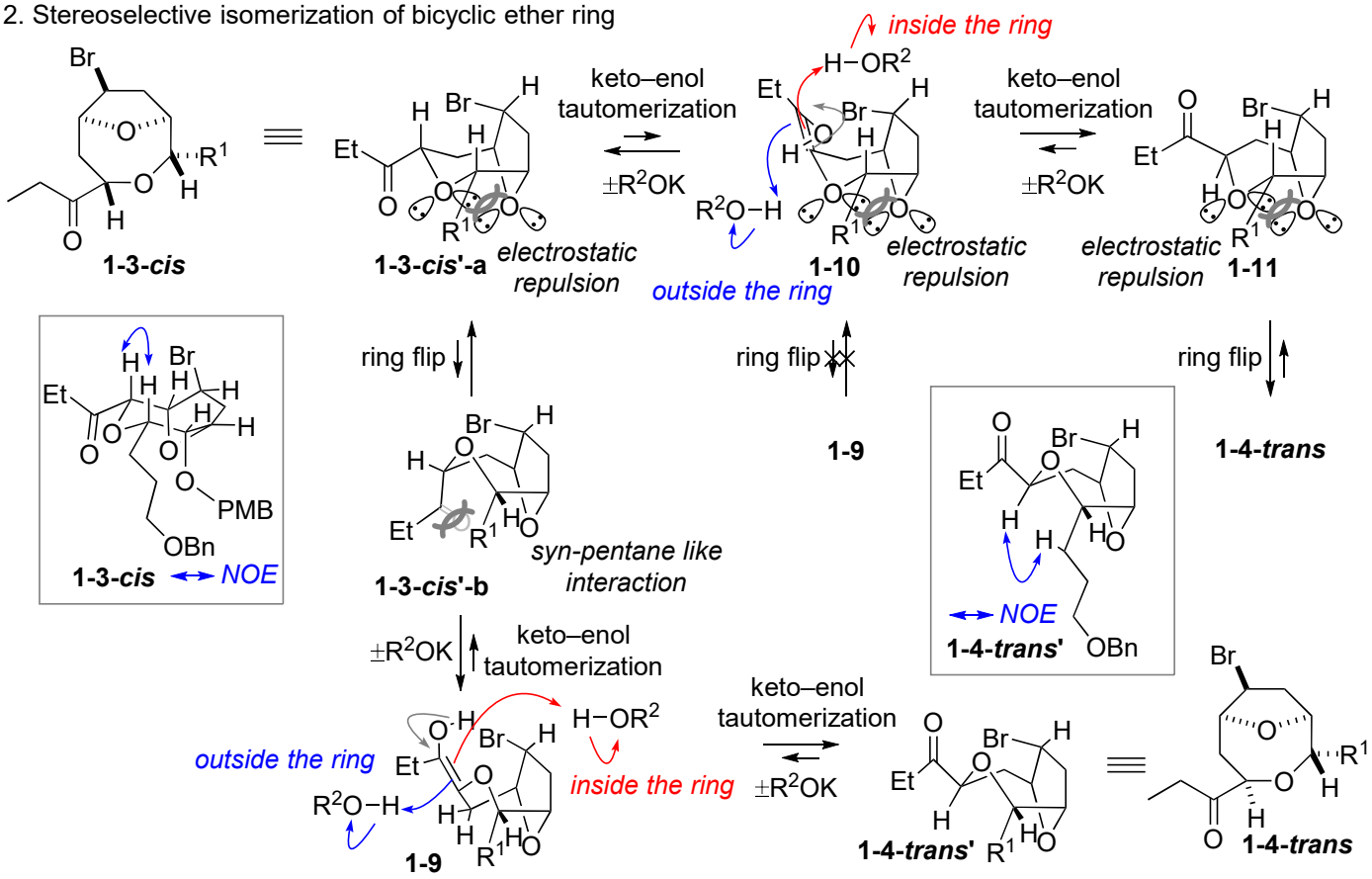


Scheme 2



Although the detail of the reaction was not mentioned, **1-8-*cis*** was obtained as a mojor product.

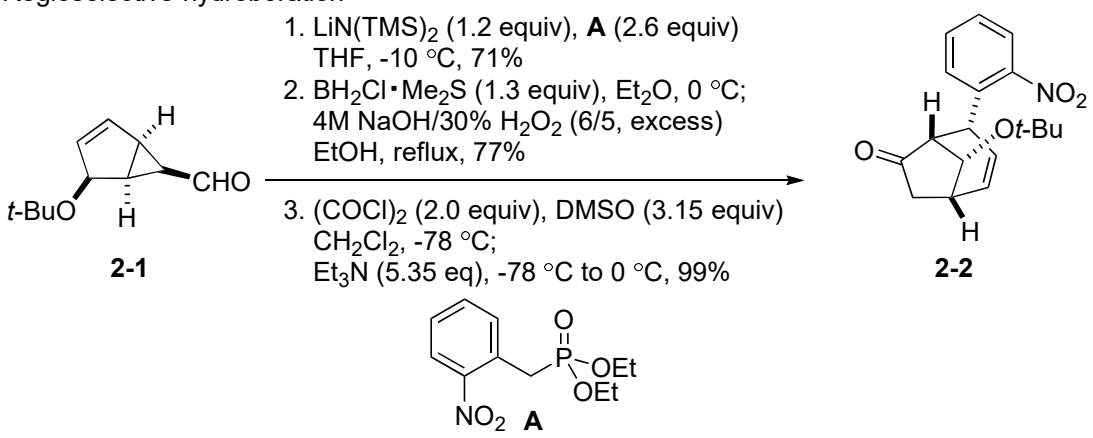
2. Stereoselective isomerization of bicyclic ether ring



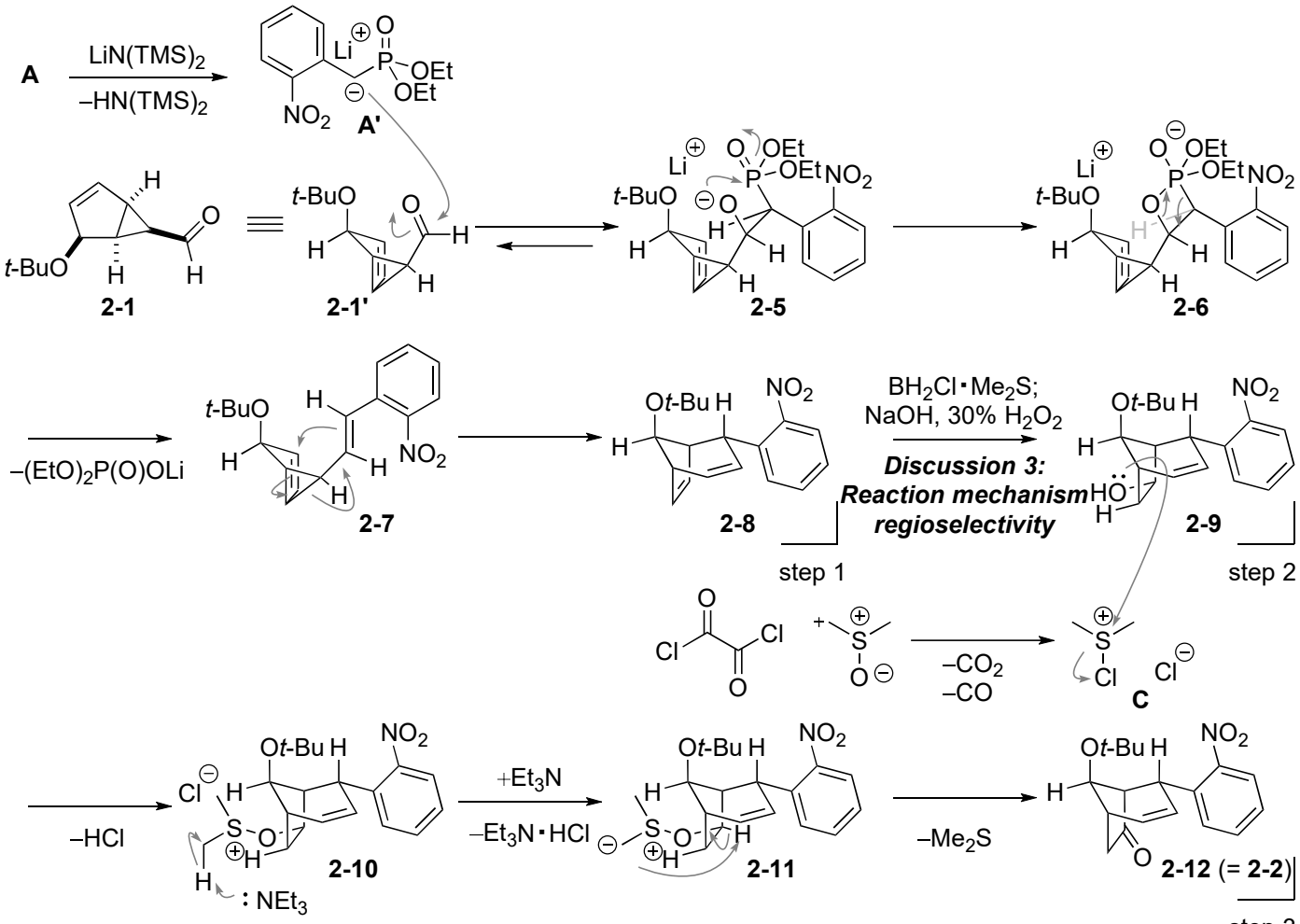
In **1-3-*cis*'-a**, the lone pairs of two oxygen atoms face each other, resulting in electrostatic repulsion. To alleviate this repulsion, ring flip occurs, and **1-3-*cis*'-b** is formed. However, **1-3-*cis*'-b** has a large steric hindrance. This is minimized through keto-enol tautomerization, leading to the formation of **1-4-*trans***.
Alternatively, if keto-enol taumerization occurs before the ring flip of **1-3-*cis*'-a**, **1-11** is generated via **1-10**. Because of electrostatic repulsion in **1-11**, ring flip occurs, resulting in formation of **1-4-*trans*.** The ring flip of **1-10** was not considered because the half-life of this enol is assumed to be shorter than the time required for the ring flip.

2 Theme: Regioselectivity and stereoselectivity controlled by electrosteric effect
main paper: Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812.

1. Regioselective hydroboration



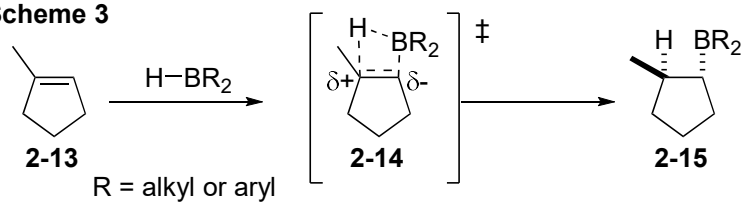
Reaction mechanism:



Discussion 3*: *Reaction mechanism and regioselectivity of hydroboration

1. Hydroboration

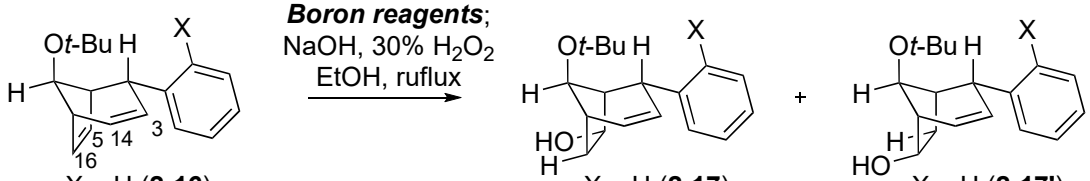
Scheme 3



Generally, regioselectivity of hydroboration is controlled by steric and electronic effect.

1. Boron adds to the less substituted end (steric effect).
2. The partial positive charge that arises in the transition state is generated at the more substituted end (electronic effect).

2. Regioselective hydroboration [ref. 2]

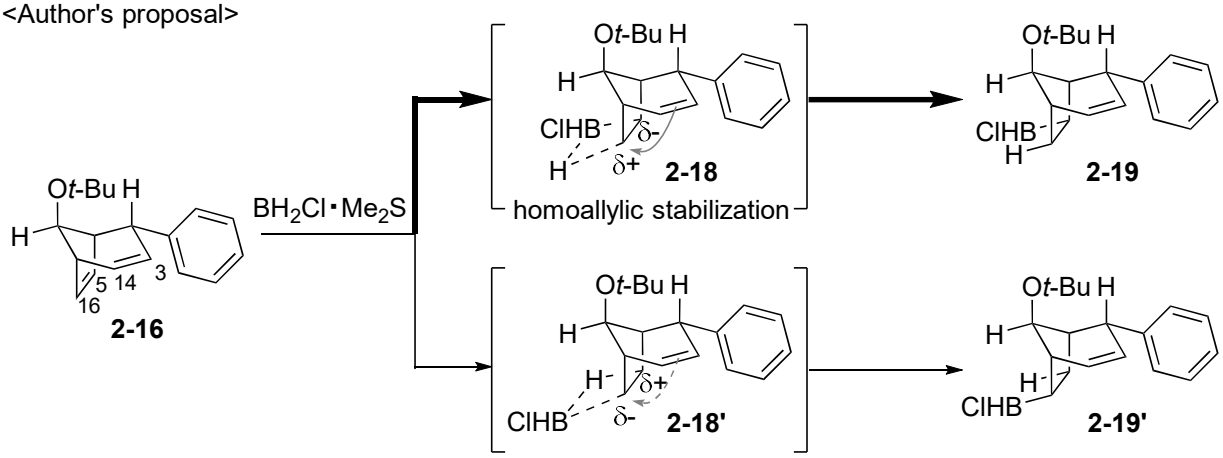


Table

entry	***Boron reagents***	ratio (**2-17**:**2-17'** or **2-9**:**2-9'**)
1. **2-16**	**BH_3·THF** (1.11 eq) THF, 0 °C	4:1
2. **2-16**	**9-BBN** (1.15 eq) THF, rt	6:1
3. **2-16**	**BH_2Cl·Me_2S** (1.12 eq) Et_2O, 0 °C	16:1
4. **2-8**	**BH_2Cl·Me_2S** (1.3 eq) Et_2O, 0 °C	11:1

entry 1 to 3 −> The higher the electrophilicity of borane might enhance the electro-deficient in transition state, resulting in a better regioselectivity.
entry 3 and 4 −> Electron withdrawing NO_2 group on the phenyl ring decreased regioselectivity.

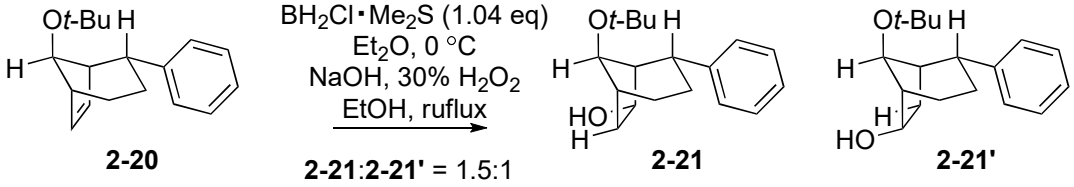
<Author's proposal>



In the case of **2-18**, C3-C14 olefin stabilizes partial positive charge in transition state. The homoallylic stabilization effect could be more pronounced when a more electrophilic borane is used due to larger partial positive charge. On the other hand, inductive effect on aryl group results in less electron rich of C3-C14 olefin so stabilized effect is weaker.

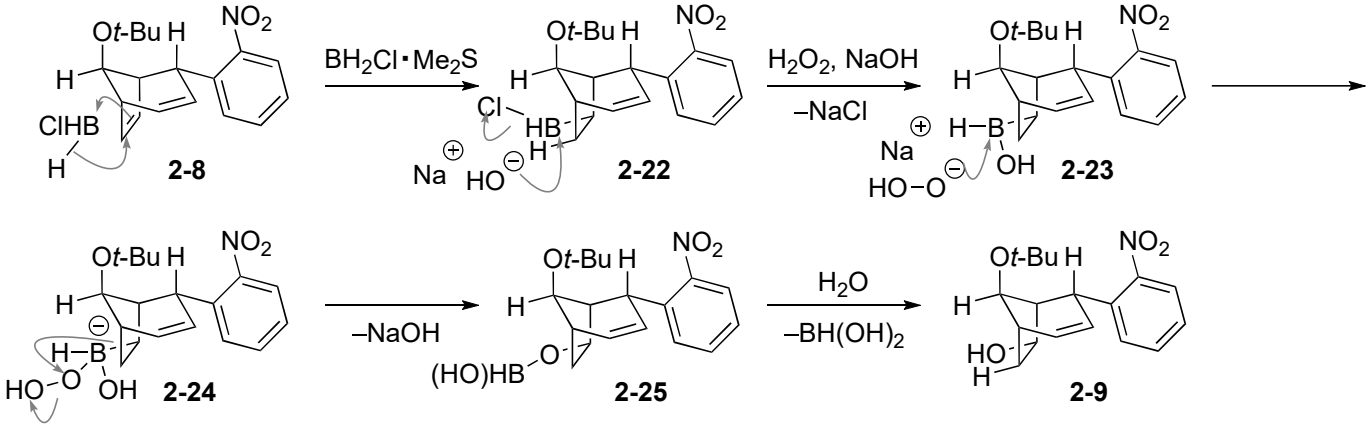
3. Confimation of homoallylic stabilization effect

Scheme 4

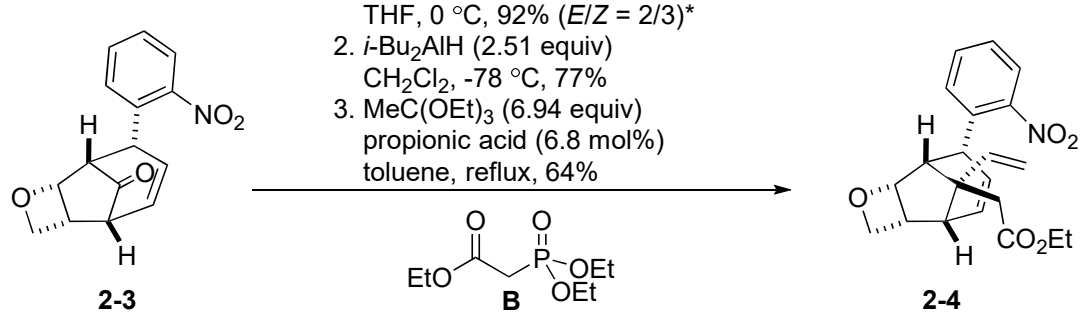


If C3-C14 olefin is reduced, regioselectivity of hydroboration drastically decreases.

4. Reaction mechanism

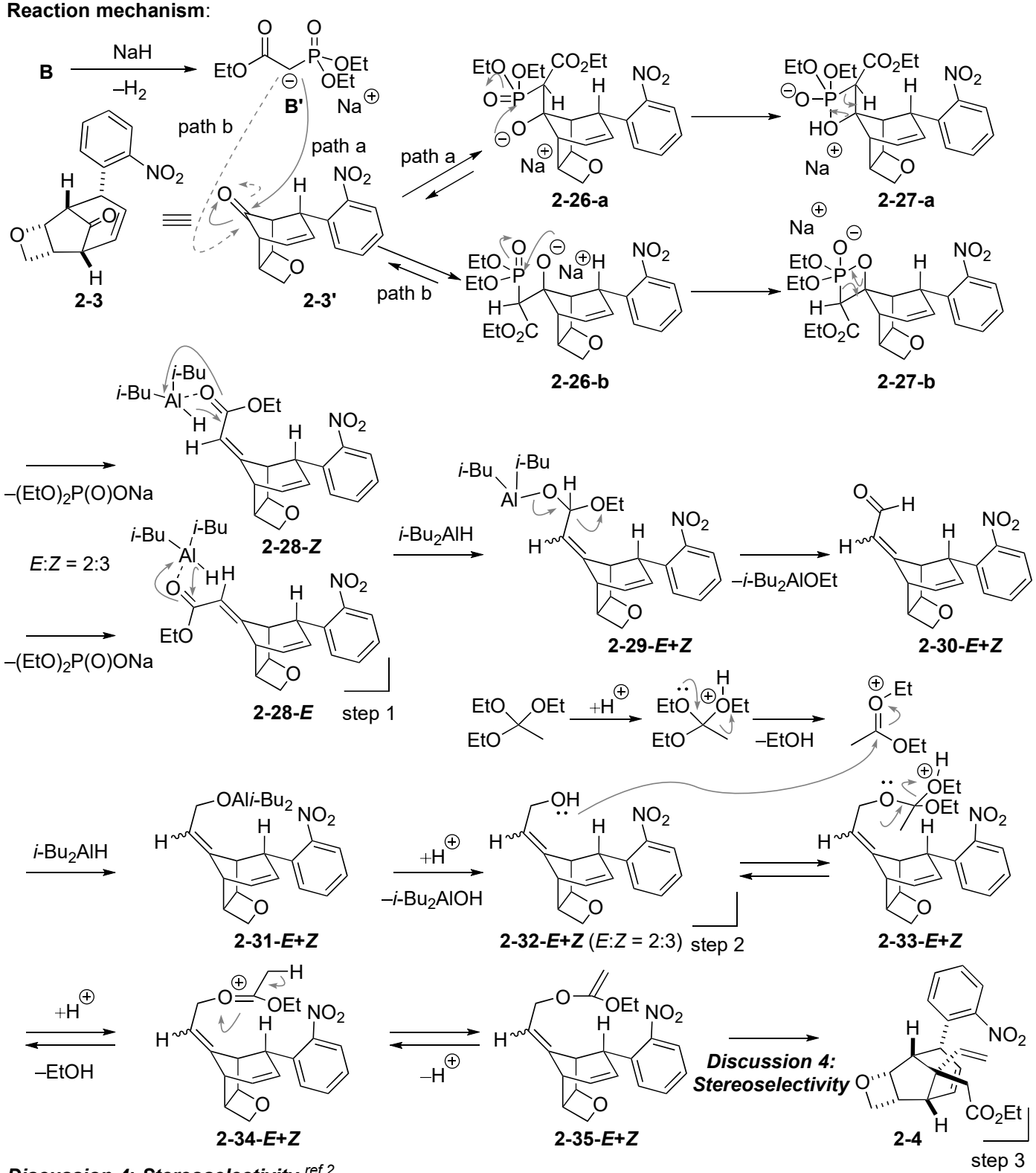


2. [3,3]-sigmatropic rearrangement controlled by electrostatic effect



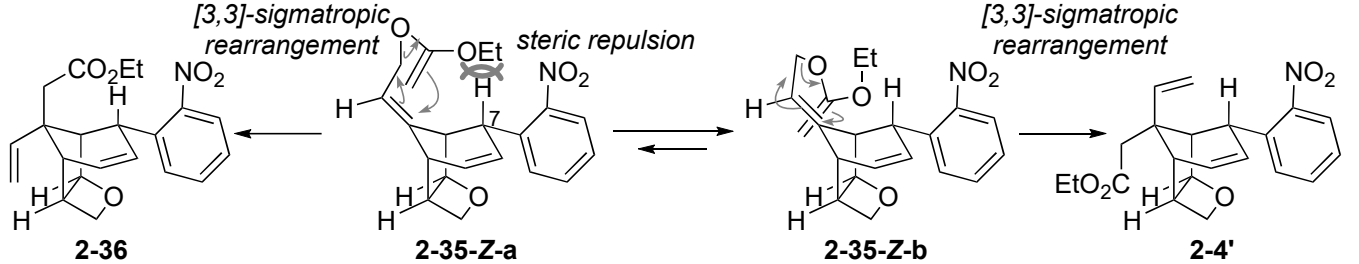
* Two isomers were used in the following reactions without separation.

Reaction mechanism:



Discussion 4*: *Stereoselectivity [ref.2]

1. [3,3]-sigmatropic rearrangement using **2-35-*Z*** as a substrate

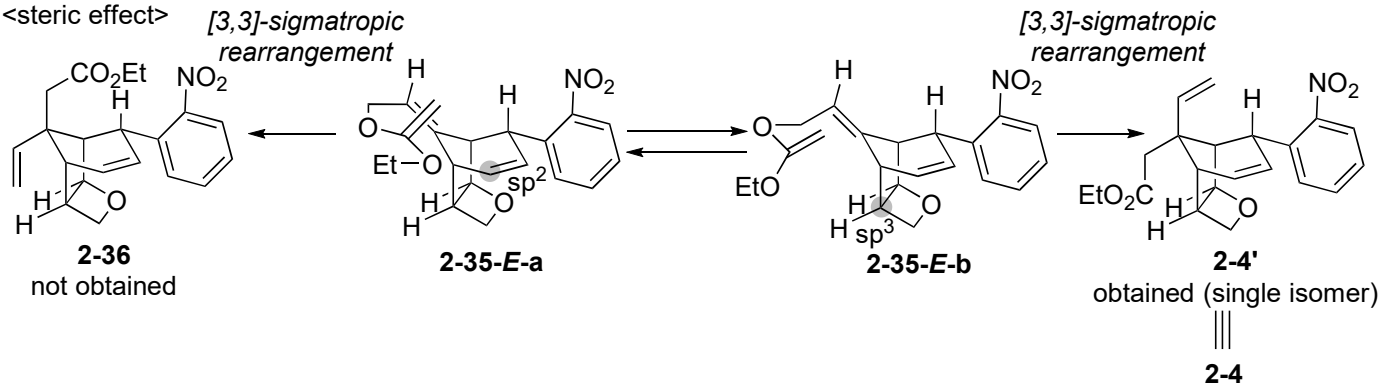


Because of the steric repulsion between proton of C7 and ketene acetal part in **2-35-*Z*-a**, **2-36** would not be obtained.

2-4

2. [3,3]-sigmatropic rearrangement using **2-35-*E*** as a substrate

<steric effect>



2-36 not obtained

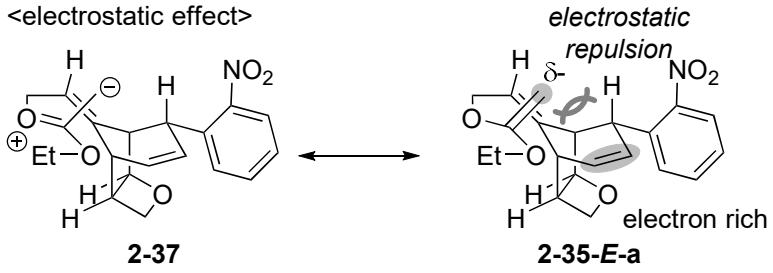
2-35-*E*-a

2-35-*E*-b

2-4' obtained (single isomer) ≡ **2-4**

The highlighted proton in gray, potentially causing steric repulsion with the ketene acetal, is sp² hybridized in **2-35-*E*-a** and sp³ hybridized in **2-35-*E*-b**. Therefore, based on steric factors, **2-36** would be expected to form selectively. However, **2-4'** was isolated as the sole product instead of **2-36**.

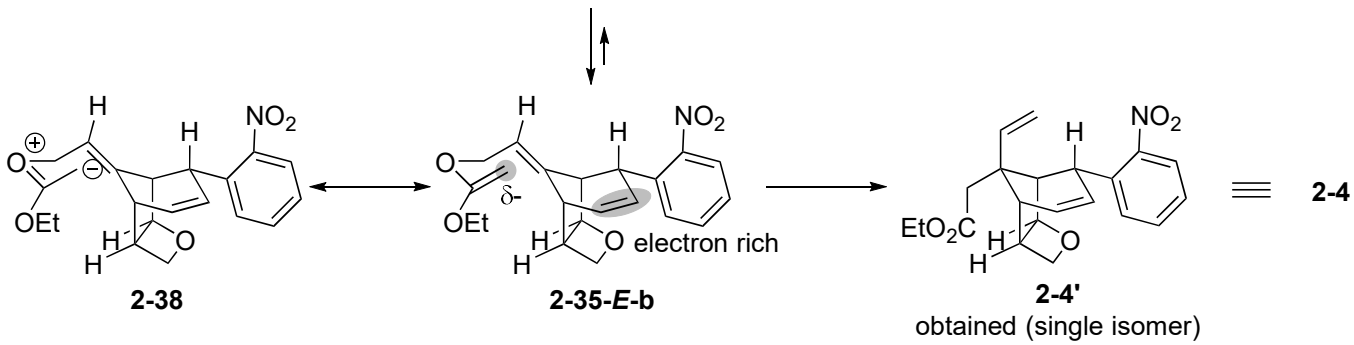
<electrostatic effect>



2-37

2-35-*E*-a

In **2-35-*E*-a**, unfavorable interaction between the polarized carbon of ketene acetal with a higher electron density and π-electrons of endocyclic olefin. On the other hand, these parts are far away in **2-35-*E*-b**.



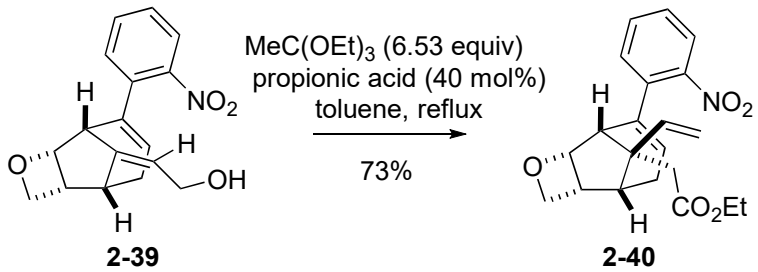
2-38

2-35-*E*-b

2-4' obtained (single isomer) ≡ **2-4**

3. Confirmation of electrostatic interaction

Scheme 5

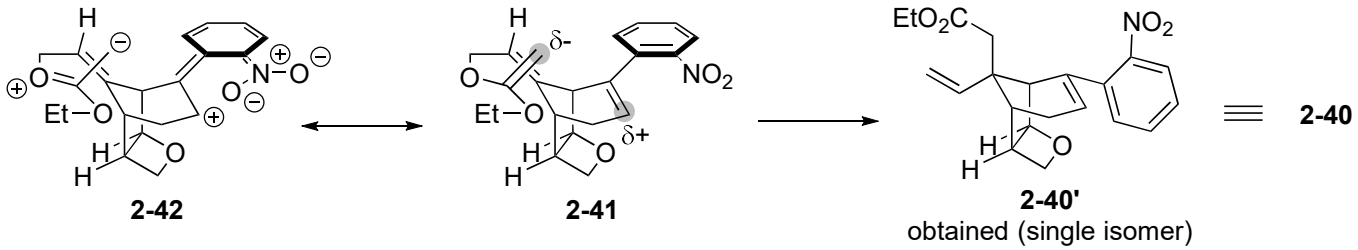


2-39

2-40

If endocyclic olefin is conjugated with *o*-nitrophenyl, face selectivity reversed due to the change in the mode of electrostatic inteaction.

<explanation of stereochemistry>



2-42

2-41

2-40' obtained (single isomer) ≡ **2-40**

reference

1. Carking, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 83.
2. (a) Ng, F. W.; Chiu, P.; Danishefsky, S. J. *Tetrahedron Lett.* **1998**, 767.
   (b) Ng, F. W. Ph.D. Thesis, Columbia University, 1997.