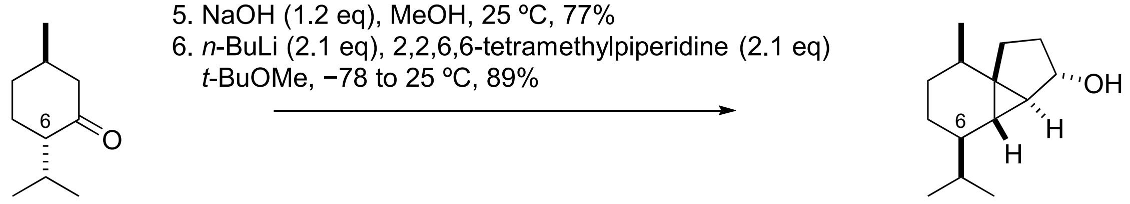
Problem Session (4) -Answer-

2024.10.7. Jaejoong Han

Topic: Construction of cyclopropane from epoxide

1.

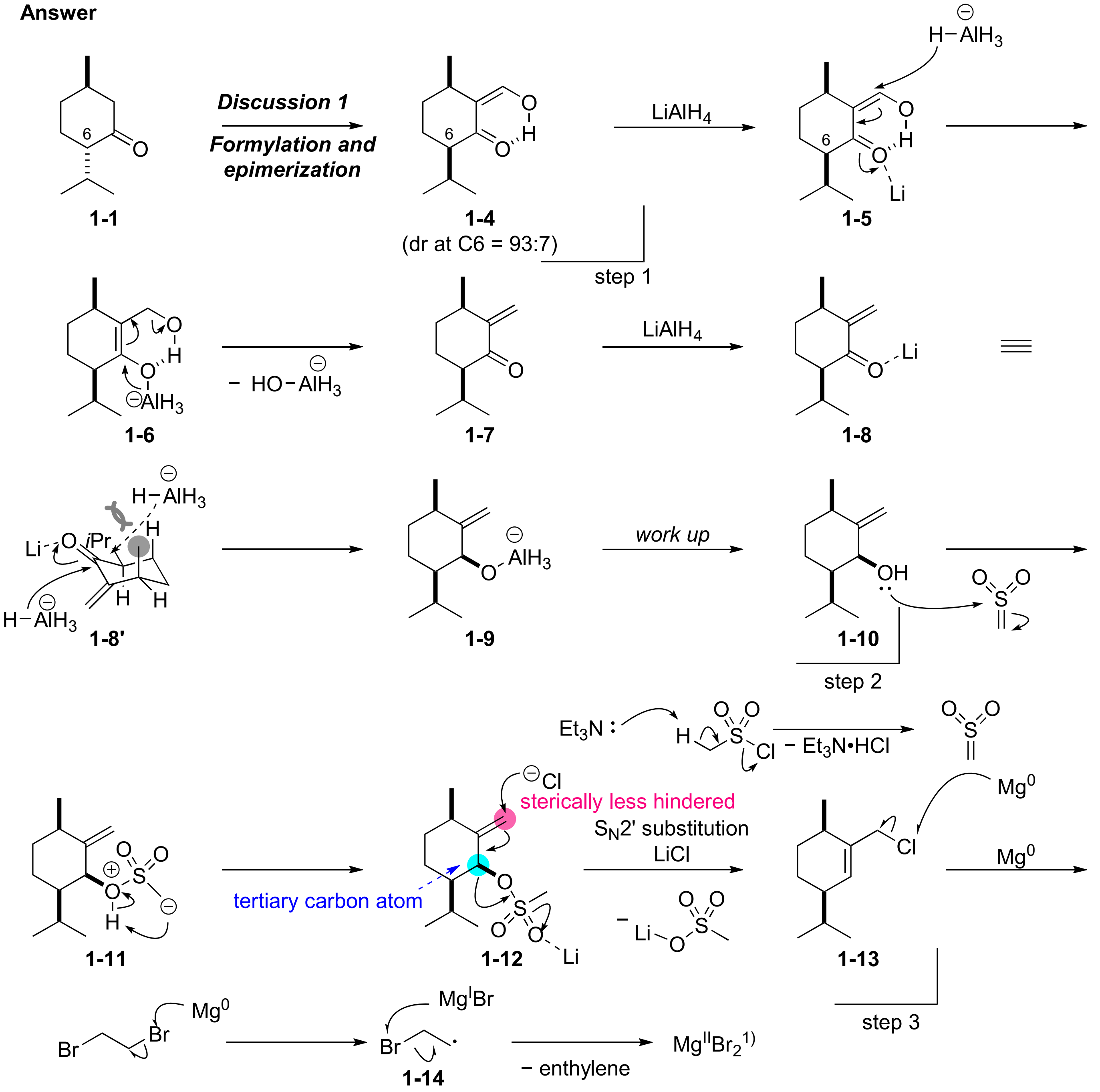
1. ethyl formate (3.0 eq), NaOMe (3.0 eq), toluene, 0 °C;
   1-1, toluene/THF, 25 °C, 82% (dr at C6 = 93:7)
2. $LiAlH_4$ (2.0 eq), Et_2O, reflux, 51%
3. Et_3N (2.0 eq), MsCl (2.0 eq), CH_2Cl_2, 0 °C;
   LiCl (10 eq), CH_2Cl_2/acetone, 0 °C, overnight, 76%
4. Mg (4.0 eq), THF, 25 °C, 1,2-dibromoethane (3 drops);
   1-3 (0.8 eq), CuI (10 mol%), THF, −78 to 0 °C, 50%
5. NaOH (1.2 eq), MeOH, 25 °C, 77%
6. *n*-BuLi (2.1 eq), 2,2,6,6-tetramethylpiperidine (2.1 eq)
   t-BuOMe, −78 to 25 °C, 89%

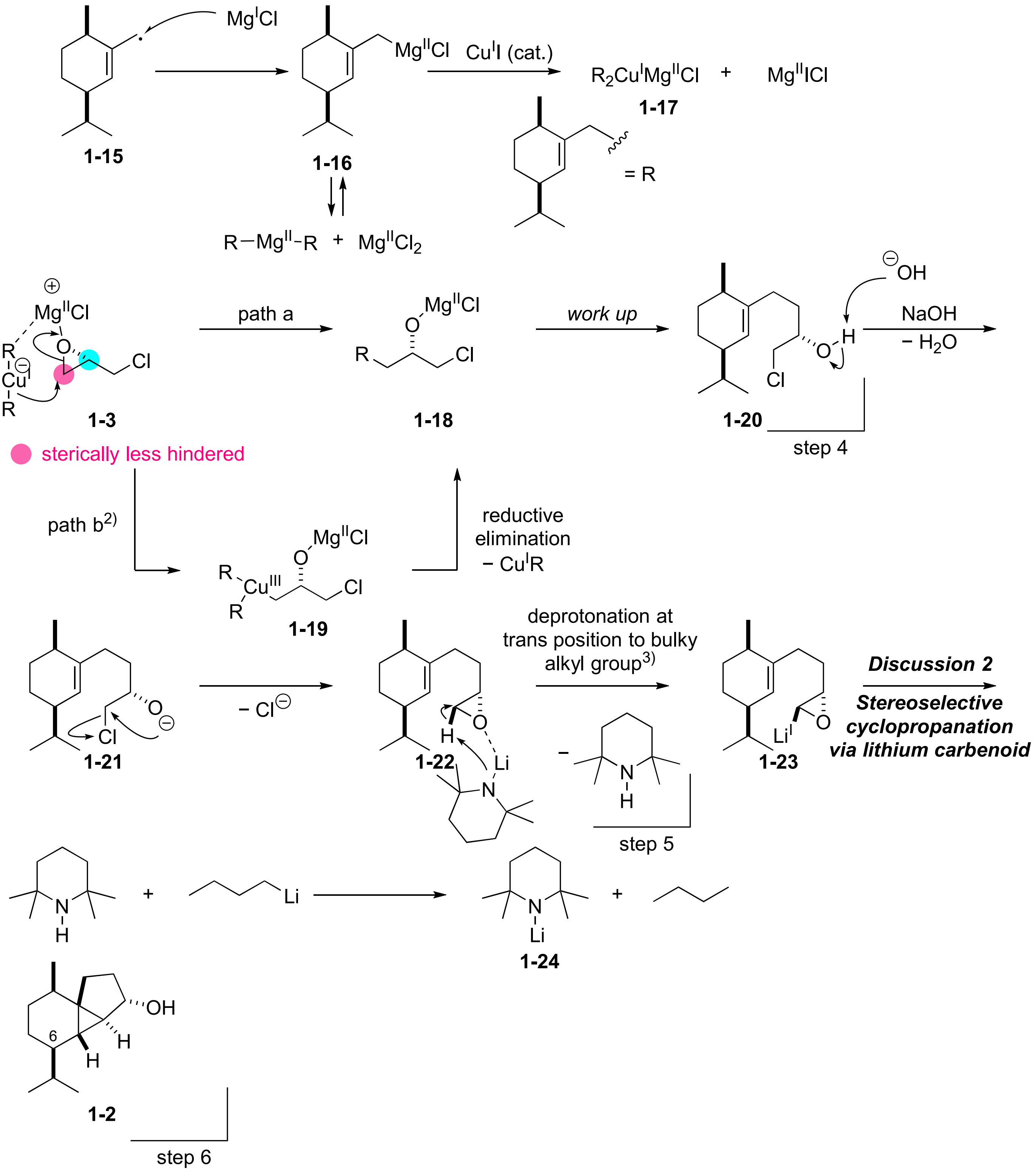


1-1 **1-2**

Hodgson, D. M.; Salik, S.; Fox, D. J. *J. Org. Chem.* **2010**, *75*, 2157.

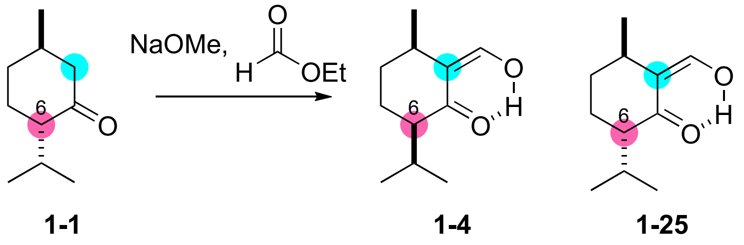
Answer





DIscussion 1: Formylation and epimerization

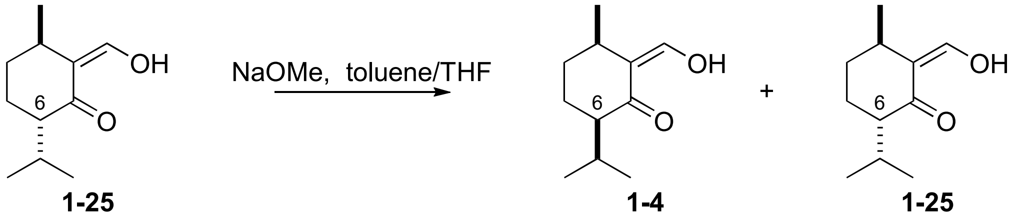
1-0. Reaction overview



1-4:**1-25** = 93:7

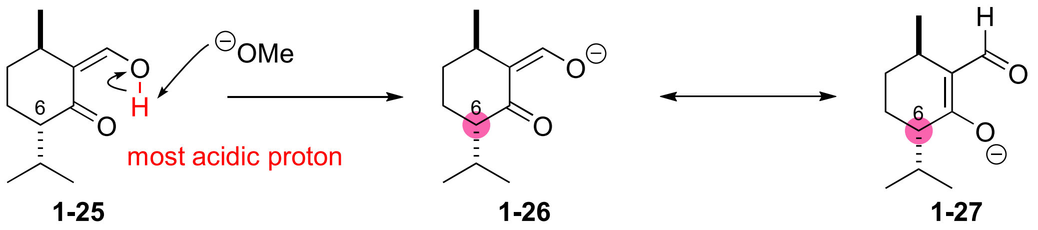
Under these conditions, formylation and epimerization at C6 occurs.
The order of these reactions and stereoselectivity will be discussed below.

1-1. Epimerization of 1-25

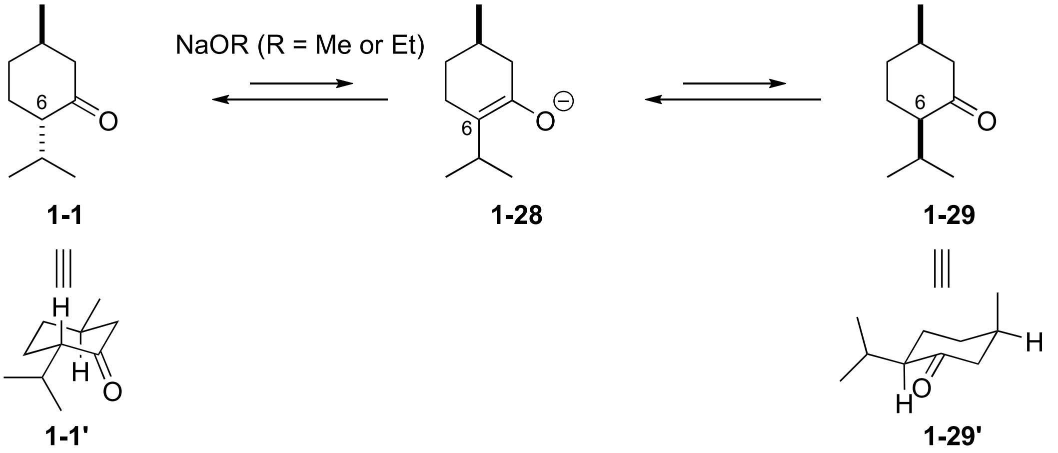


1-4:**1-25** = 1:4

*The temperature was not mentioned, though it is likely room temperature.
Epimerization of **1-25** under the same conditions as this problem's formylation step was attempted.
Epimerization partially occurred, though **1-4** wasn't the major product.
This may be because deprotonation at C6 is slow due to reduced acidity at C6.
From this result, epimerization at C6 should occur before the formylation reaction.

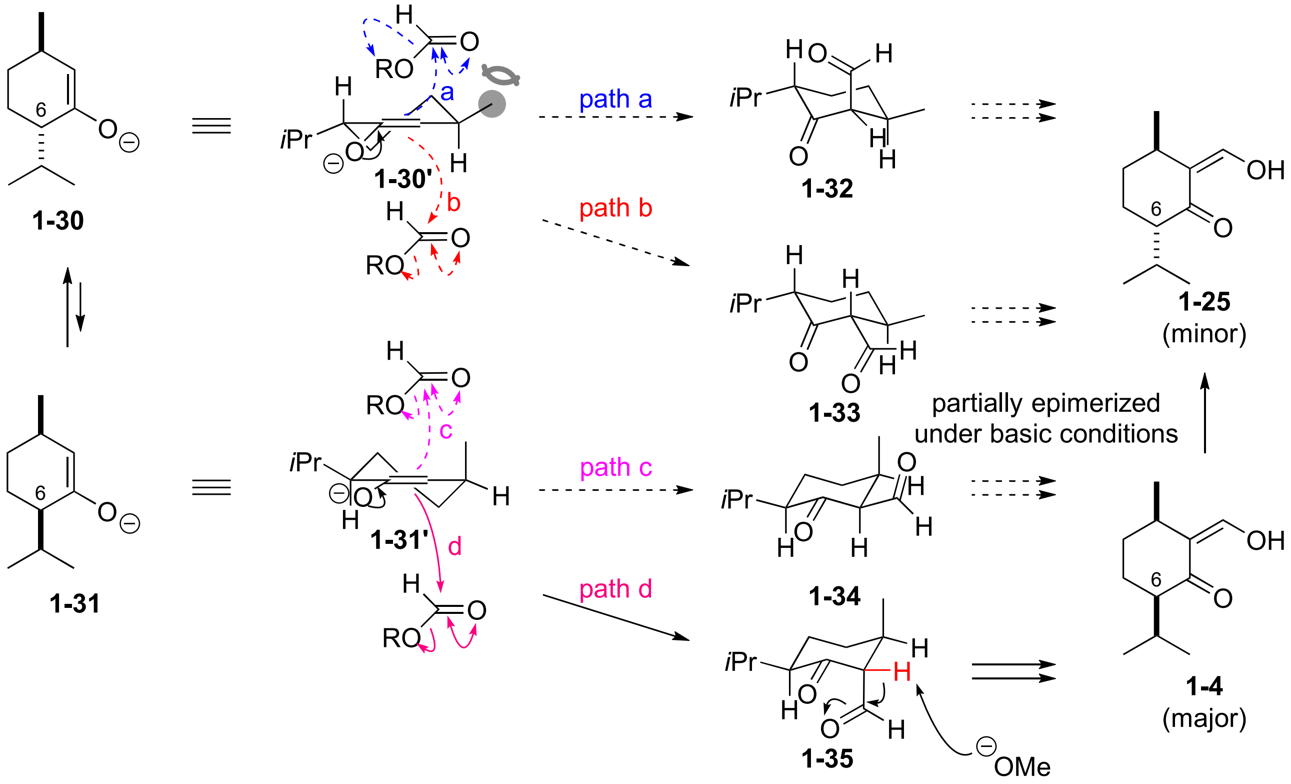


1-2. Equilibrium of starting material



The equivalent favours **1-1** because both isopropyl group and methyl group are equatorial-oriented.
Thus, thermodynamical stability of **1-1'** and **1-29'** cannot explain the ratio of **1-4** and **1-25**.

1-3. Rationale of stereoselectivity of epimerization



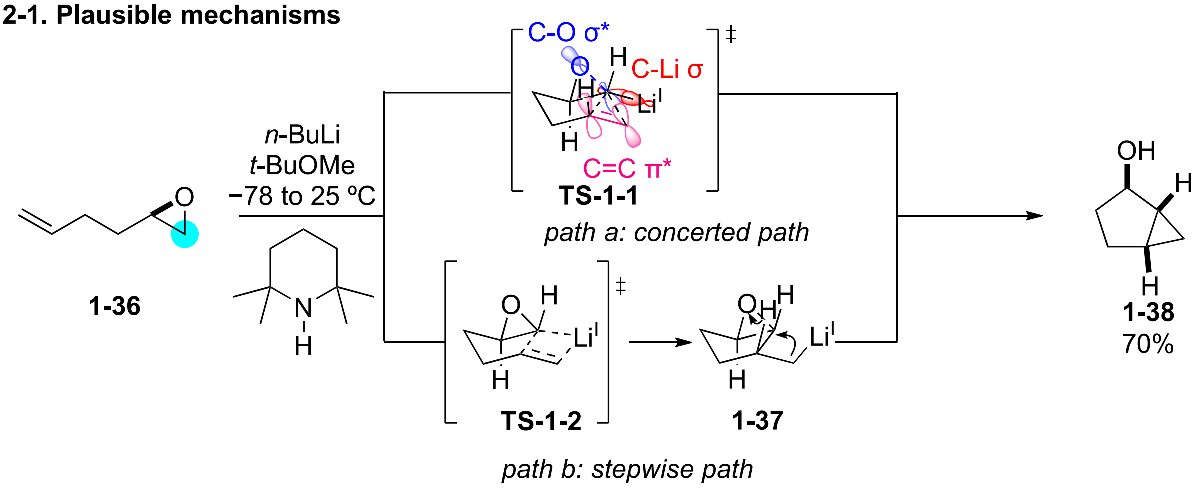
As the reaction solvent is MeOH, this aldol reaction proceeds via open transition state rather than Zimmerman-Traxler transition state.

Formylation can undergo from **1-30** via path a-b, from **1-31** via path c-d.
There is a steric repulsion of hilighted methyl group in path a, so this path is less favourable than path d.
Formylation proceeds via twisted-boat conformation in path b and c, so these paths are unfavourable.
So, I think path d is most favourable.
(The author calculated the free energies of transition state of path a and d, and the activation energy of path a is 2.1 kcal/mol higher than that of path d).

In my opinion, formylayion occures exclusively via path d to afford only **1-4**.
And then, partial epimerization occured from **1-4** to afford **1-25** as a minor diastereomer.
If formylation from **1-28** proceeds, retro-aldol reaction would generate **1-28** again.

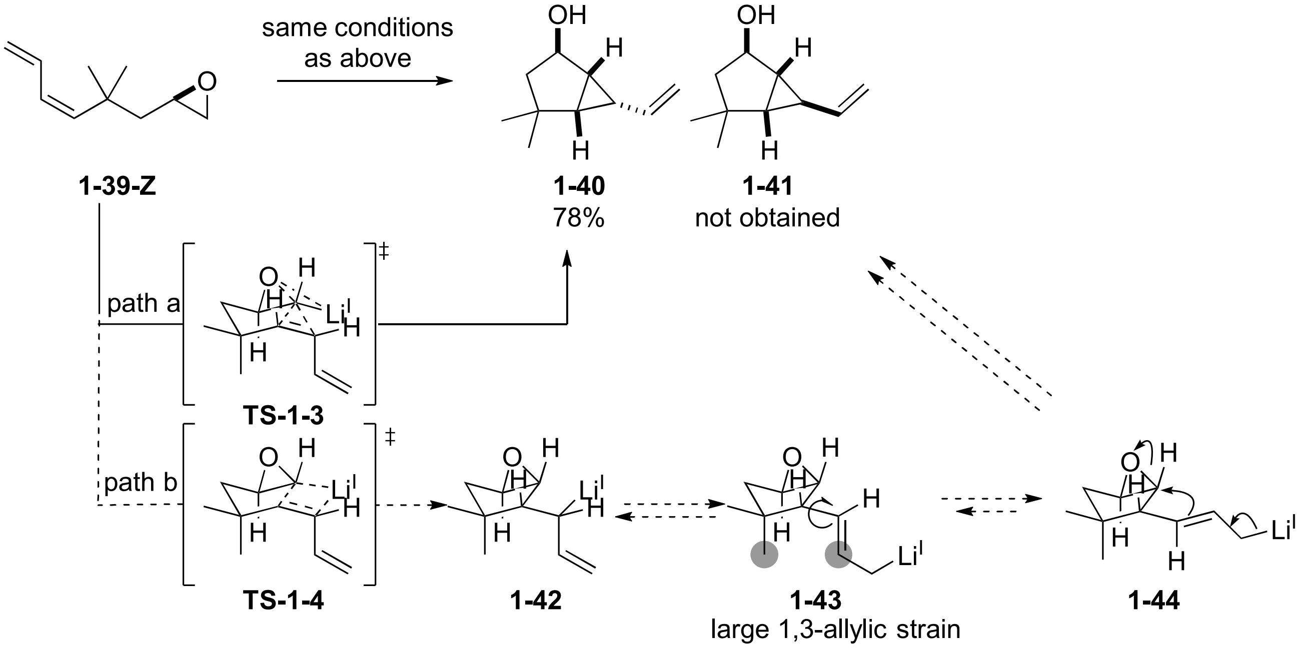
DIscussion 2: Stereoselective cyclopropanation via lithium carbenoid

2-1. Plausible mechanisms



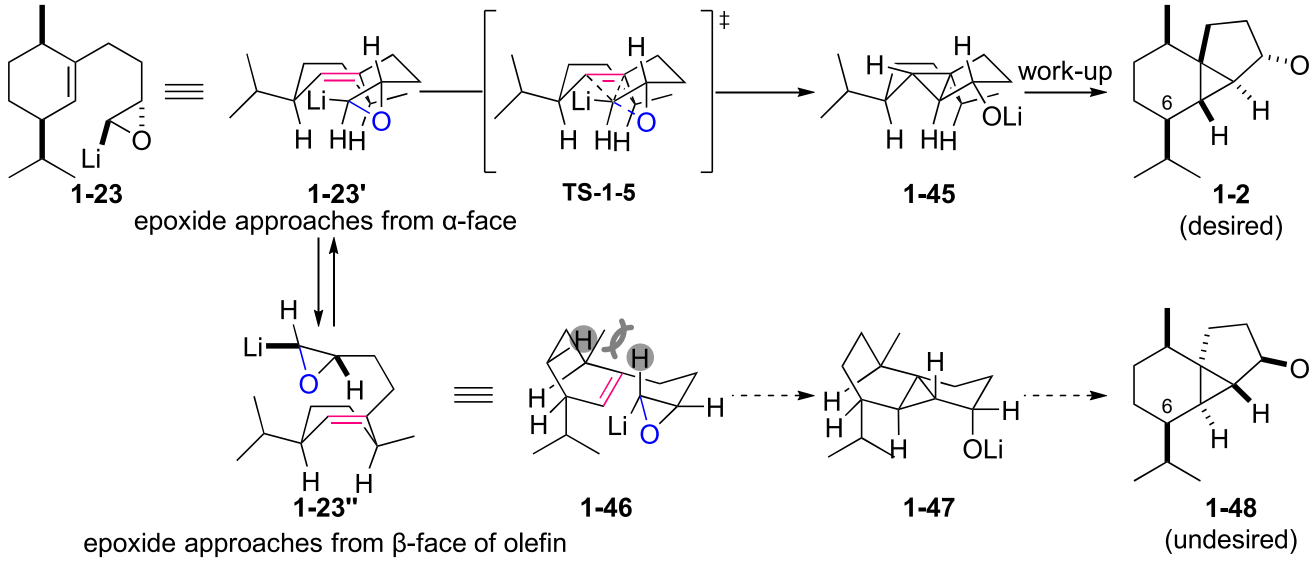
The auther proposed **TS-1-1** via chair-like transition state[4], in which C-O σ* and C=C π orbitals are pararel[5]. Take orbital interations into account, the mechanism should be someweher between path a and path b.

2-2. Stereoselectivity of cyclopropanation of other substrate[4]



In this case, if path b dominates over path a, and also the equivalent between **1-42** and **1-43** is fast, **1-41** could be obtained via allyl lithium intermediate **1-44**.
So, I think path a is more favourable than path b

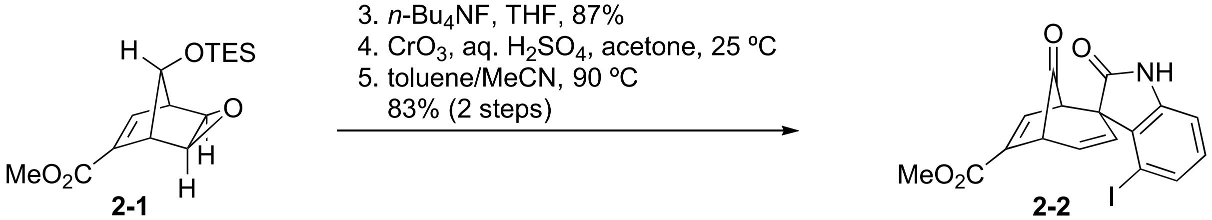
2-3. Rationale of stereoselectivity of cyclopropanation



Due to steric repulsion between H atoms, the reaction proceeds from conformation **1-1** rather than **1-2**.

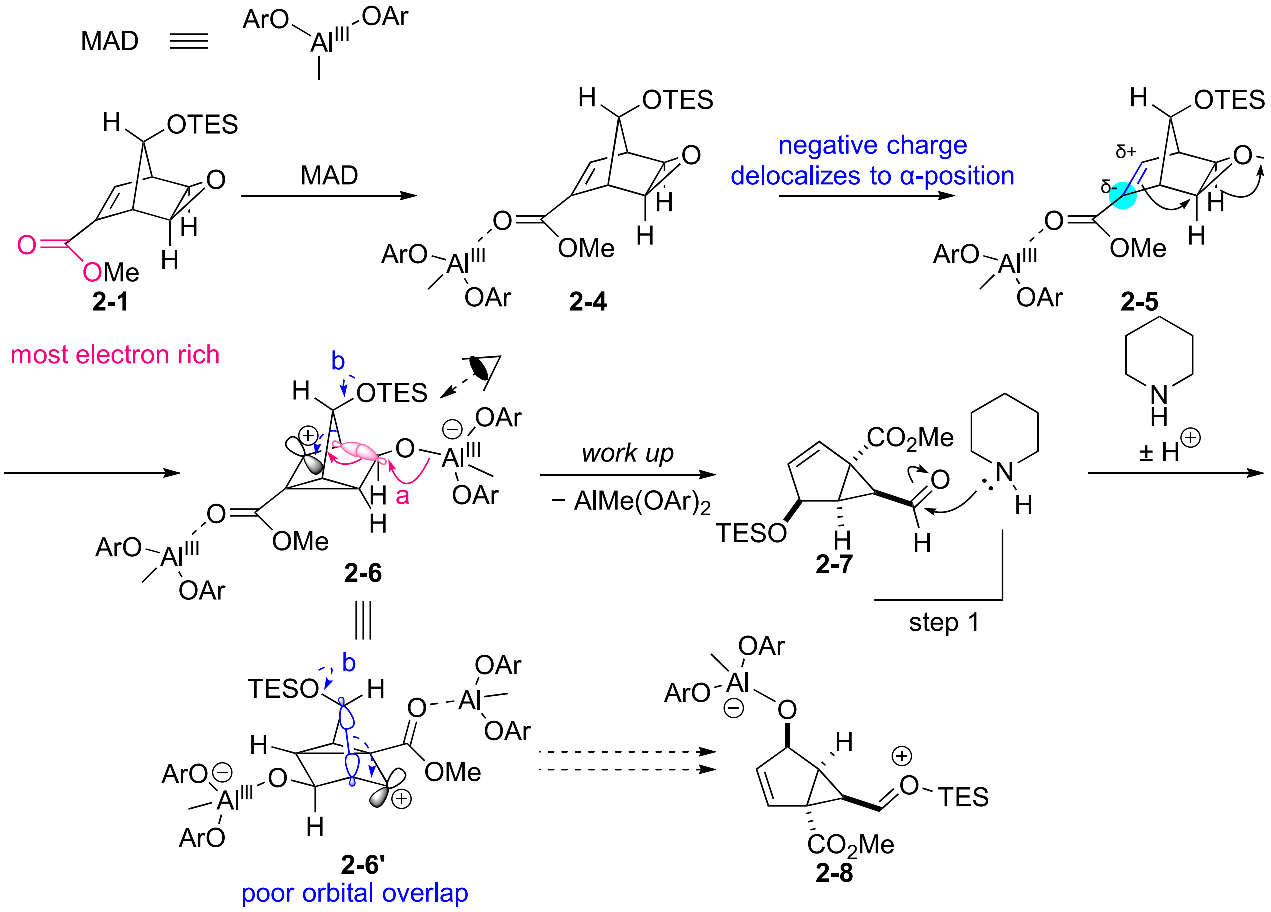
2.

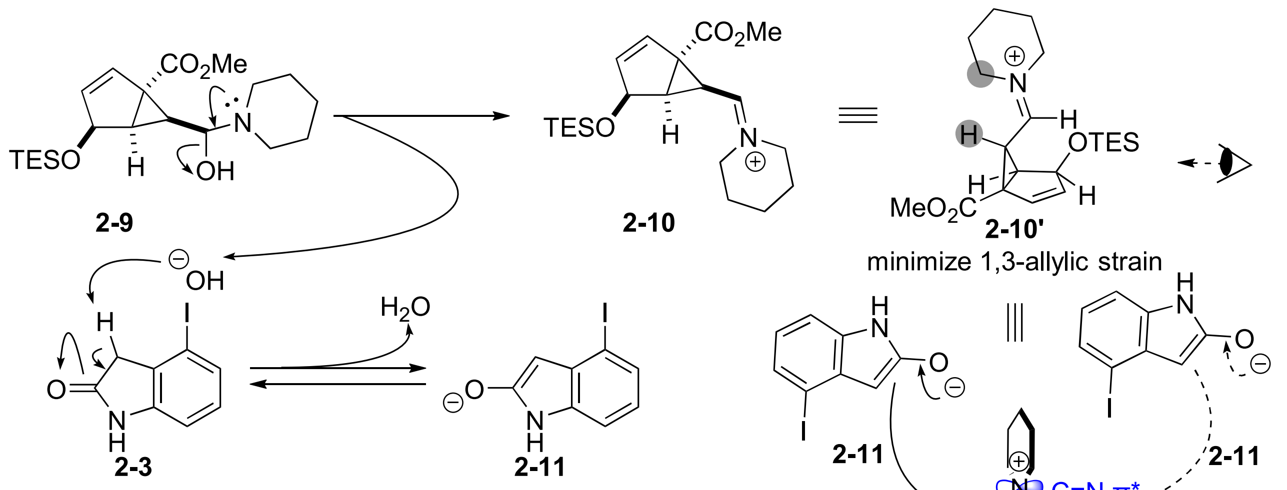
1. MAD, toluene, −20 ºC
2. **2-3**, piperidine (cat.), MeOH
   60% (2 steps)
3. n-Bu_4NF, THF, 87%
4. CrO_3, aq. H_2SO_4, acetone, 25 ºC
5. toluene/MeCN, 90 ºC
   83% (2 steps)



Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4073.

Answer

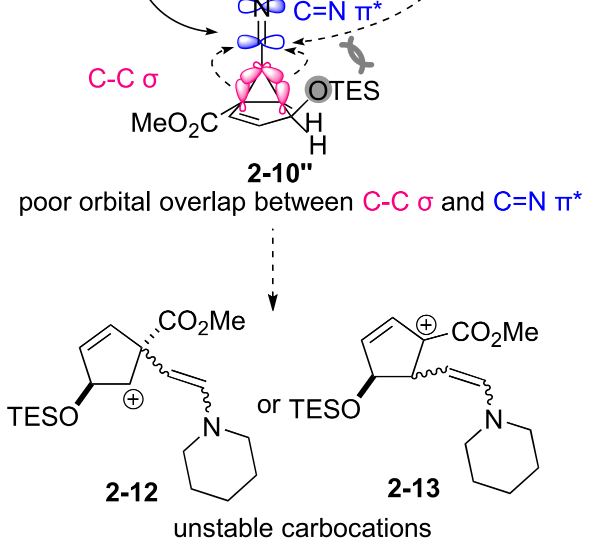




2-9 **2-10** **2-10'**

minimize 1,3-allylic strain

2-3 **2-11**



2-11 **2-11**

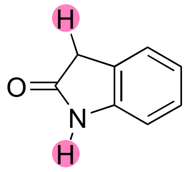
2-10''

poor orbital overlap between C-C σ and C=N π*

2-12 **2-13**

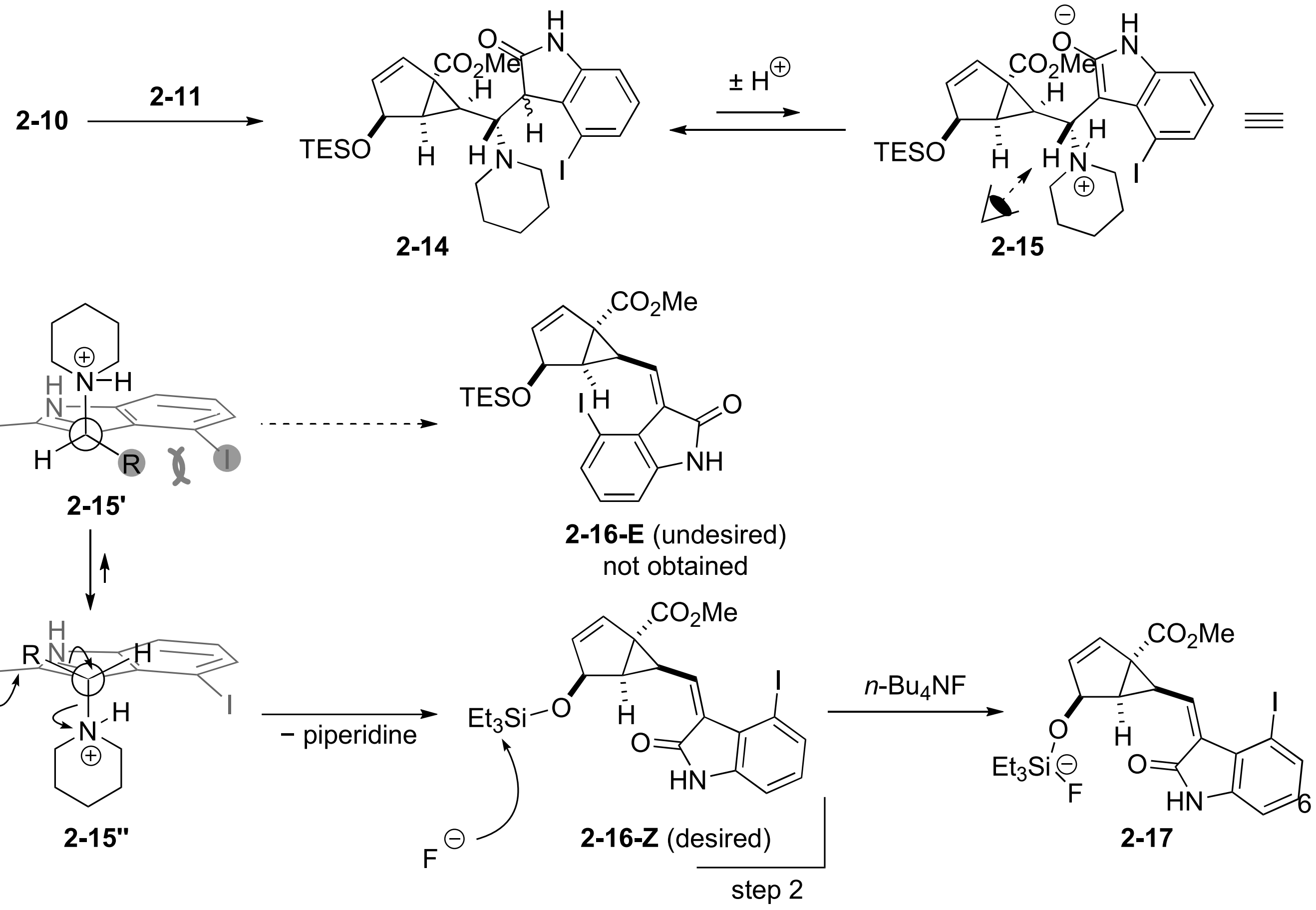
unstable carbocations

pKa Value:

	in DMSO	in H_2O
H_2O	31.4	14.0
 oxindole	18.2	n.d.

*the acidity of 2 protons are almost the same

The reaction solvent is MeOH, so pKa value in H_2O seems to reflect the actual reaction system than that in DMSO. pKa Value of oxindole in H_2O is not reported, though the value could be similar to that of H_2O in the analogy to other active methylene compounds like diethyl malonate (16.4 in DMSO, 12.9 in H_2O).



2-10 → **2-11** → **2-14** ⇌ ± H⁺ **2-15**

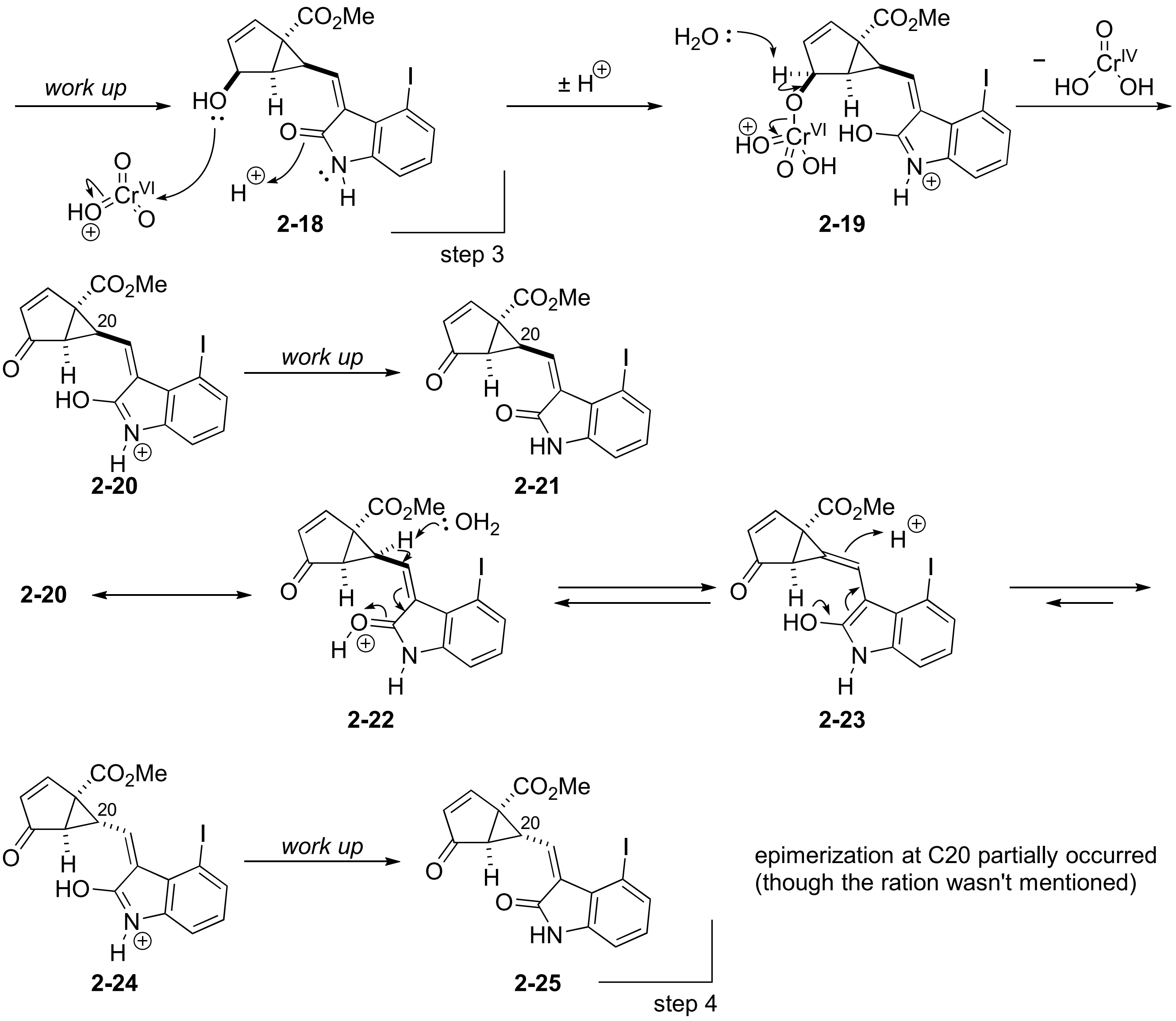
2-15' **2-15''**

2-16-E (undesired)
not obtained

2-16-Z (desired)

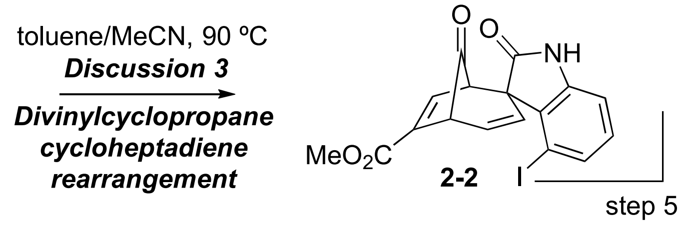
step 2

2-17



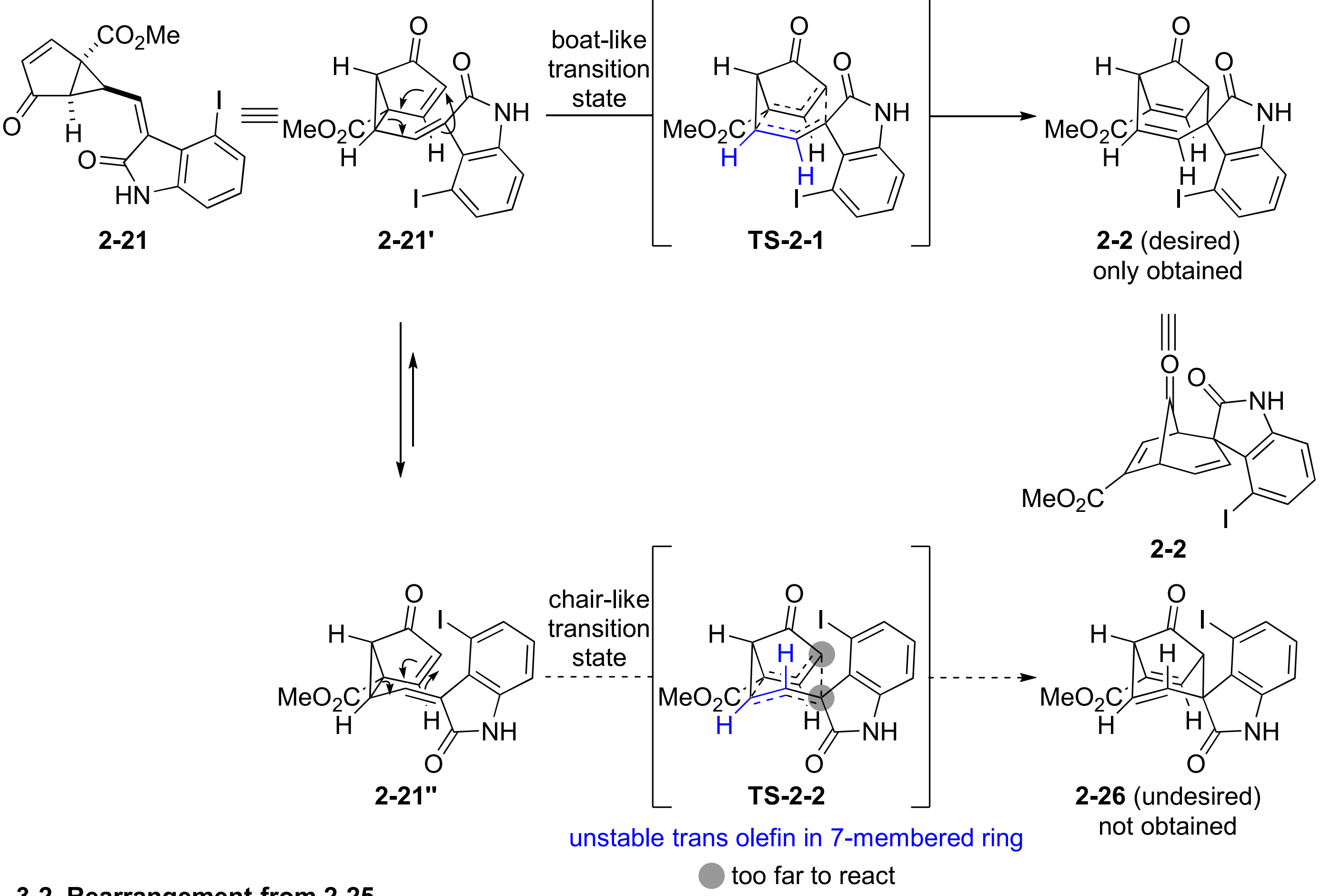
epimerization at C20 partially occurred (though the ration wasn't mentioned)

mixture of **2-21** and **2-25**

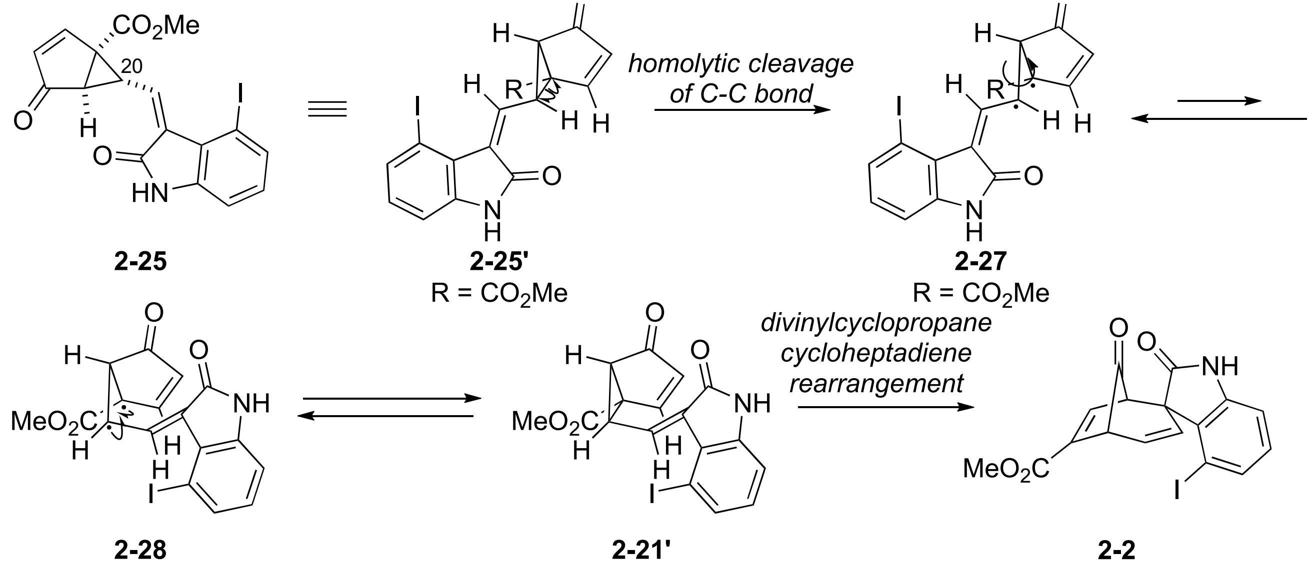


DIscussion 3: Divinylcyclopropane cycloheptadiene rearrangement

3-1. Rearrangement from 2-21



3-2. Rearrangement from 2-25



Usually, this *cis-trans* isomerization via diradical species occurs at high temperature above 200 ºC6).
However, both vinyl radicals of **2-28** are stabilized by neighbouring electron withdrowing groups.
So, this isomerization occurred at 90 ºC.

Reference

1) Lai, Y.-H. *Synthesis*, **1981**, *8*, 585.
2) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294.
3) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc. Commun.* **1994**. 2103.
4) Hodgson, D. M.; Chung, Y. K.; Nuzzo, I.; Freixas, G.; Kulikiewics, K. K.; Cleator, E.; Paris, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4456.
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