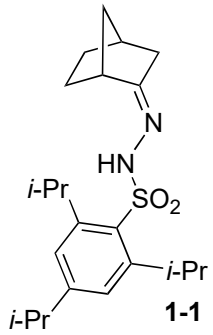
Problem Session (6)

2025/10/18 Kyohei Takaoka

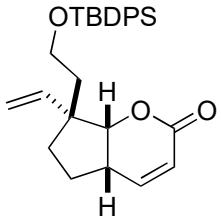
Please provide the reaction mechanisms.

1



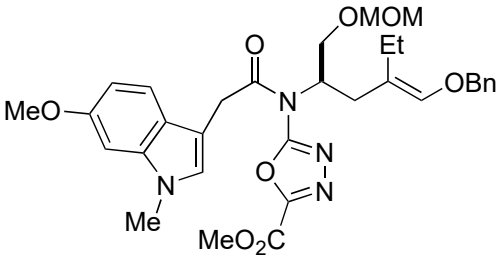
1-1

1. *s*-BuLi (2 eq), THF, −78 to 0 °C; ethylene oxide (2.3 eq) −78 to 0 °C; TBDPSCl (1.3 eq), 0 °C to rt, 79%
2. *m*-CPBA (1.1 eq), $NaHCO_3$ (2 eq), CH_2Cl_2, 0 °C, 93%
3. *o*-tolMgI (1.2 eq), Et_2O, reflux, 68%
4. acryloyl chloride (1.5 eq), *i*-Pr_2NEt (1.7 eq) CH_2Cl_2, rt, 96%
5. **A** (10 mol%), 1,6-heptadiene (20 mol%) benzene, 60 °C, 73%



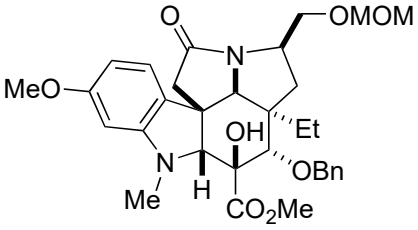
1-2

2



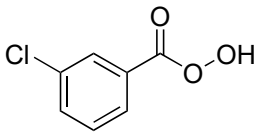
2-1

1. xylene, 130 to 175 °C
2. $NaBH_3CN$ (2 eq), AcOH/*i*-PrOH (1/4) 0 °C, 55% (2 steps)

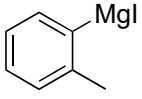


2-2

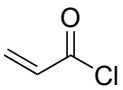
ethylene oxide



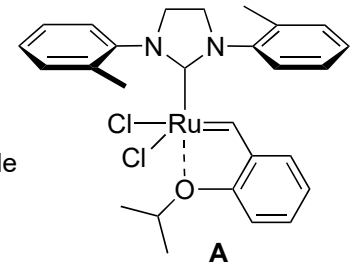
m-CPBA



o-tolMgI



acryloyl chloride



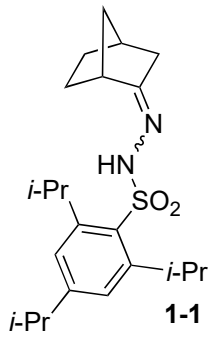
A

Problem Session (6) Answer

2025/10/18 Kyohei Takaoka

Topic: Tamdem ring opening/closing in total synthesis

1



1-1

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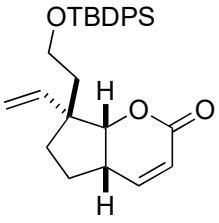
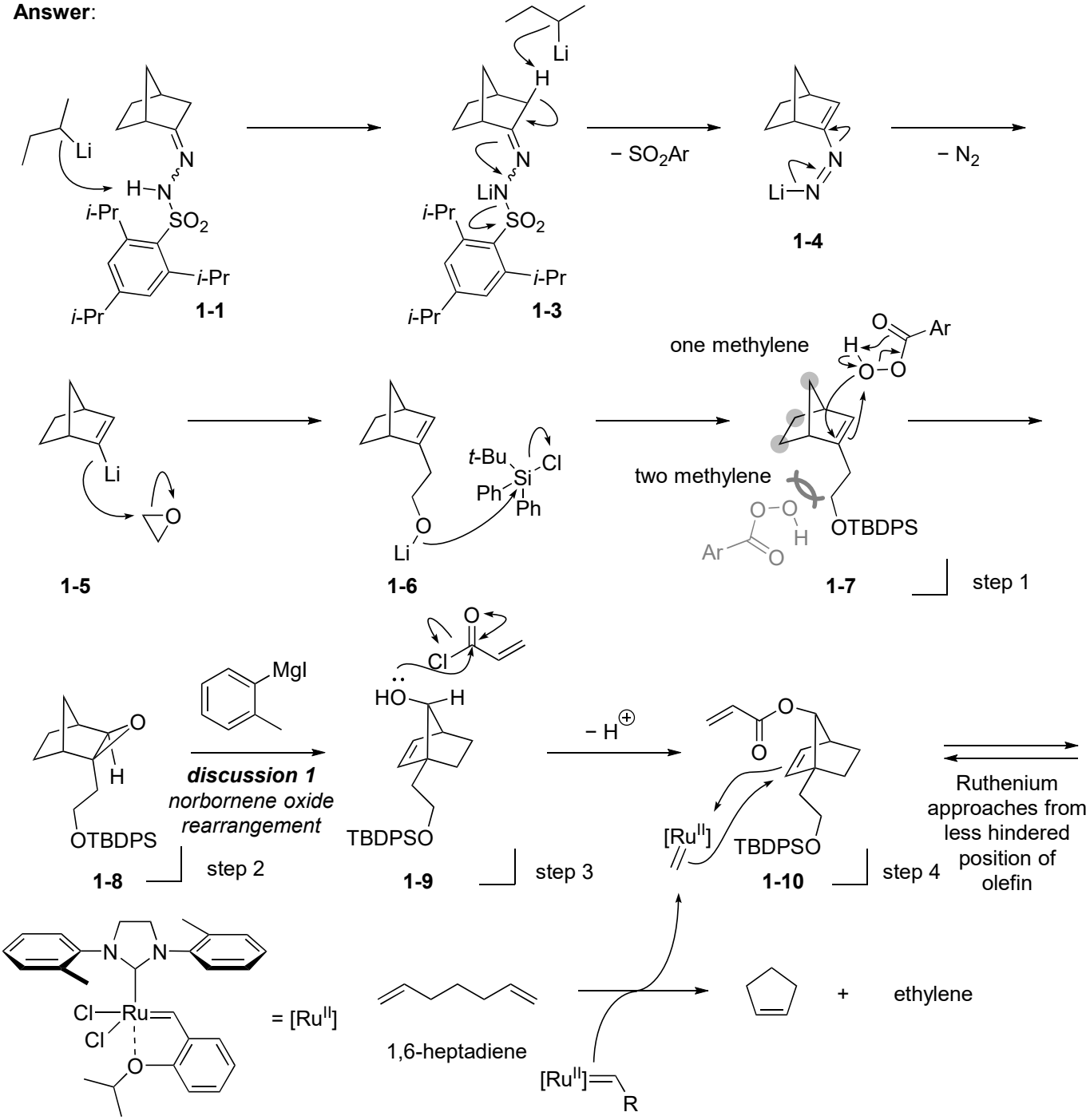
5. **A** (10 mol%), 1,6-heptadiene (20 mol%) benzene, 60 °C, 73%



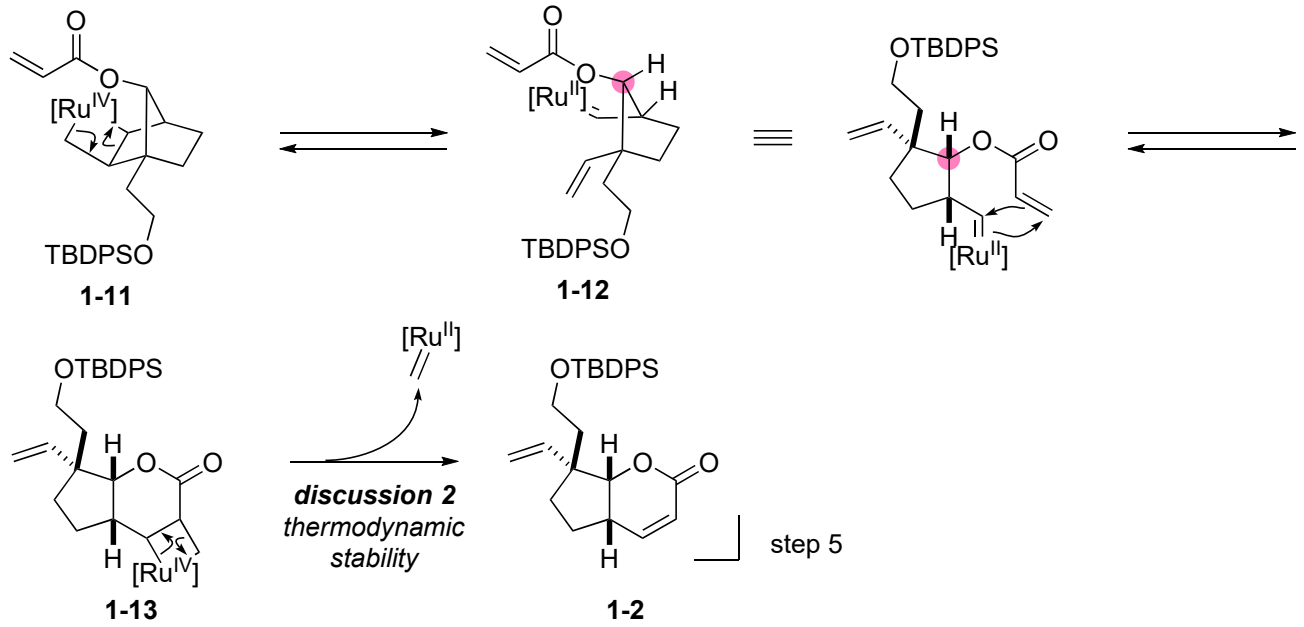
1-2

Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2012**, *134*, 11995.

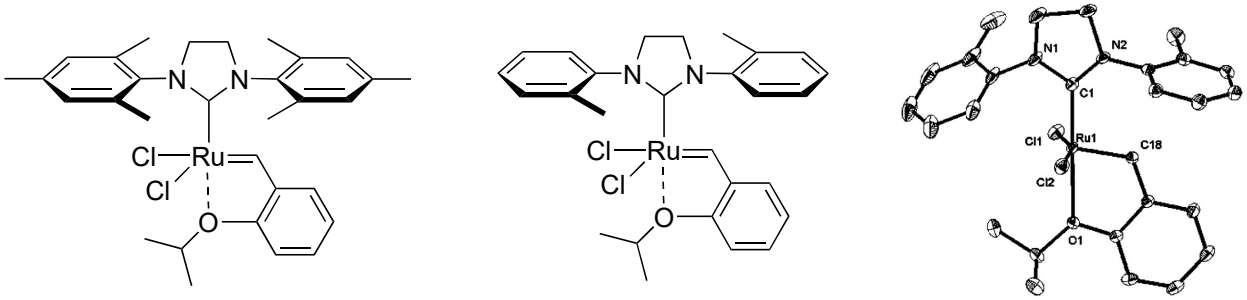
Answer:



A (Stewart-Grubbs catalyst)



Regarding the reactivity of ruthenium catalyst:
The yield of the step 5 dropped to 24% when catalyst **B** (Hoveyda-Grubbs 2nd) was used. (73% in **A**)
Higher reactivity of **A** can be attributed to more open steric environment around the ruthenium center.
In fact, crystal structure of **A** indicates that two methyl groups of NHC ligand are in syn relationship (syn/anti = 91:9), therefore olefin can easily reacted with catalyst **A**.

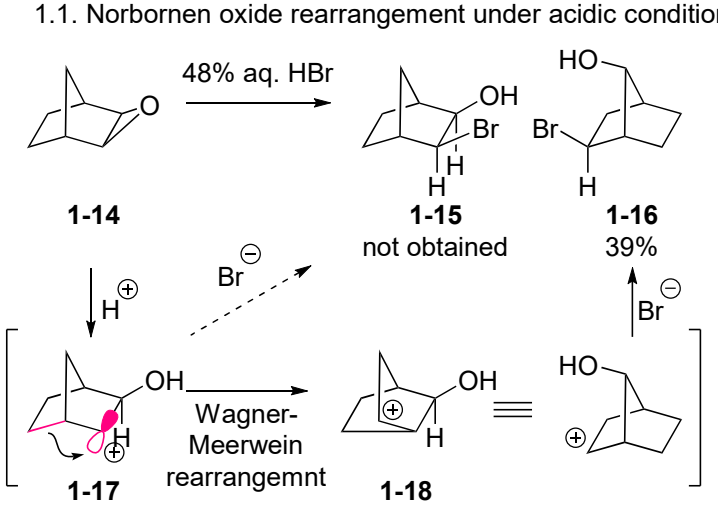


B (Hoveyda-Grubbs 2nd) **A** (Stewart-Grubbs catalyst) crystal structure of **A**

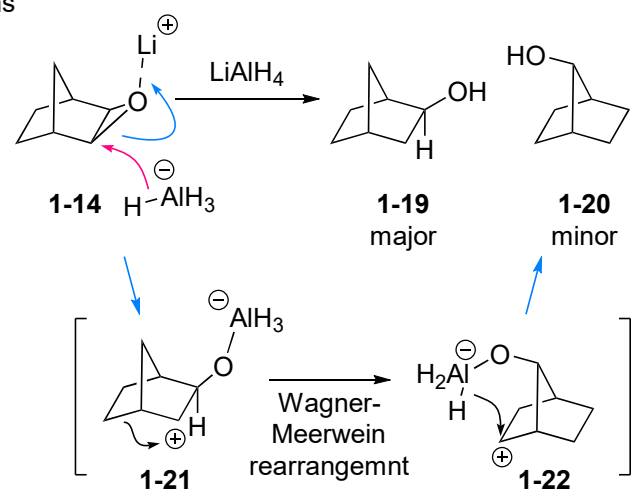
Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.

Discussion 1: Norbornene oxide rearrangement

1.1. Norbornen oxide rearrangement under acidic conditions



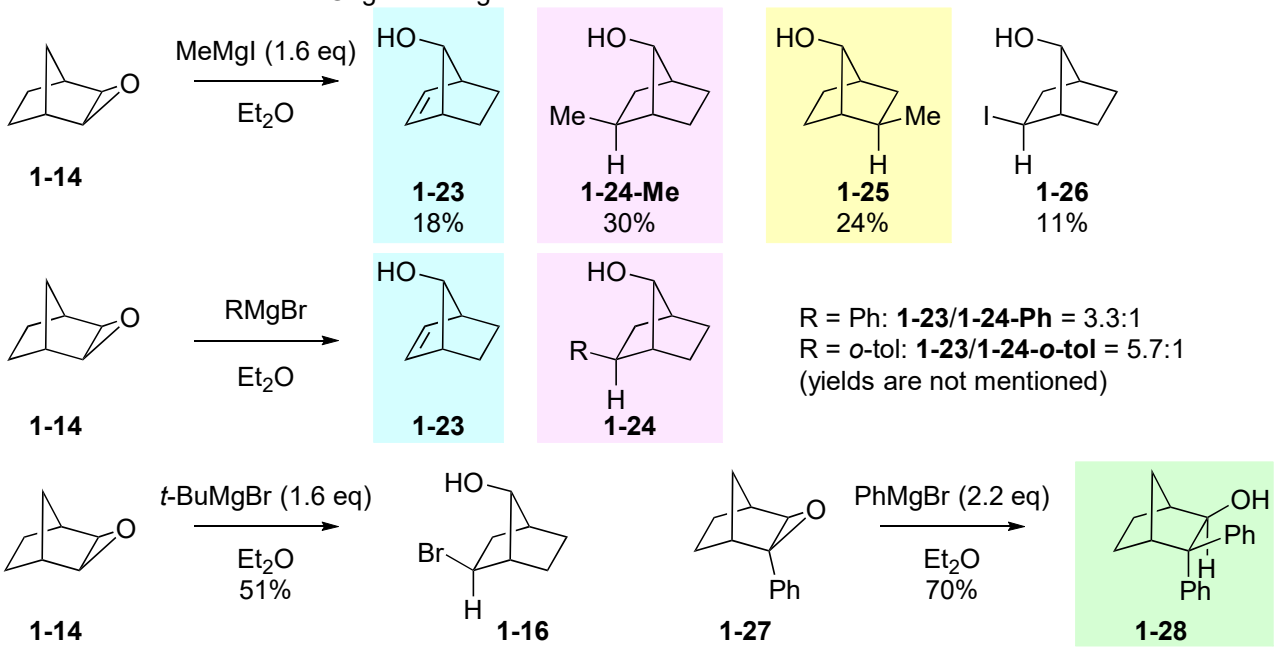
Walborsky, H. M.; Lonerini, D. F. *J. Org. Chem.* **1957**, *22*, 1117.



Kwart, H.; Takeshita, T. *J. Org. Chem.* **1962**, *28*, 670.

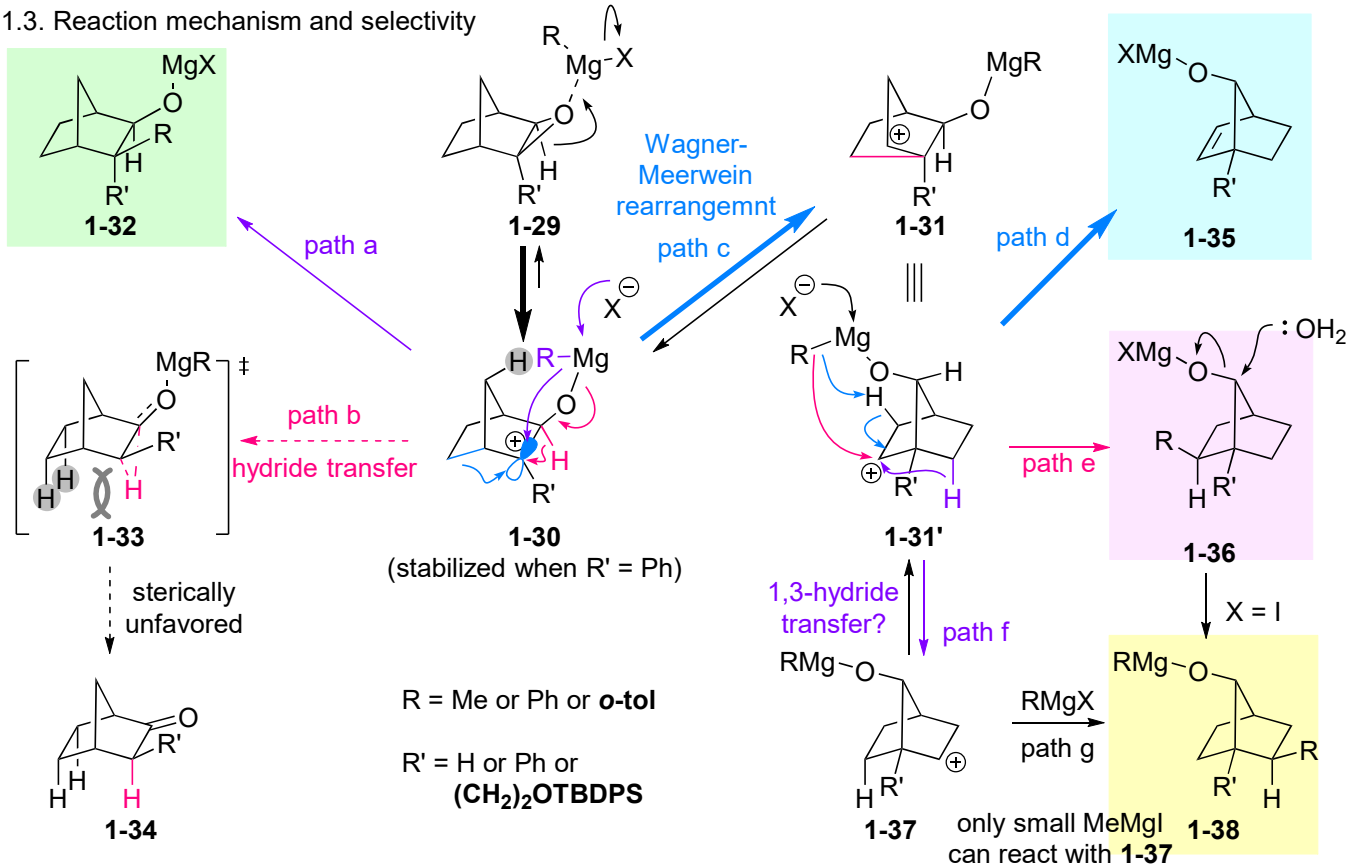
Under Brønsted/Lewis acidic conditions, epoxide **1-20** opens to generate secondary cation **1-17** or **1-21**. Proximal hydroxy groups make cations of **1-17** and **1-21** unreactive to nucleophiles. Instead, Wagner-Meerwein rearrangement proceed to give **1-18** and **1-22**, respectively. Further reactions only proceed from these less hindered cations.

1.2. The reaction with other Grignard reagents



Gerteisen, T. J.; Kleinfelter, D. C. *J. Org. Chem.* **1971**, *36*, 3255.

1.3. Reaction mechanism and selectivity



All rearrangement reactions (paths c and f) are reversible, so there is an equilibrium among **1-29**, **1-30**, **1-31** and **1-37**. Path b is unfavorable because of steric repulsion with the highlighted hydrogen atoms.

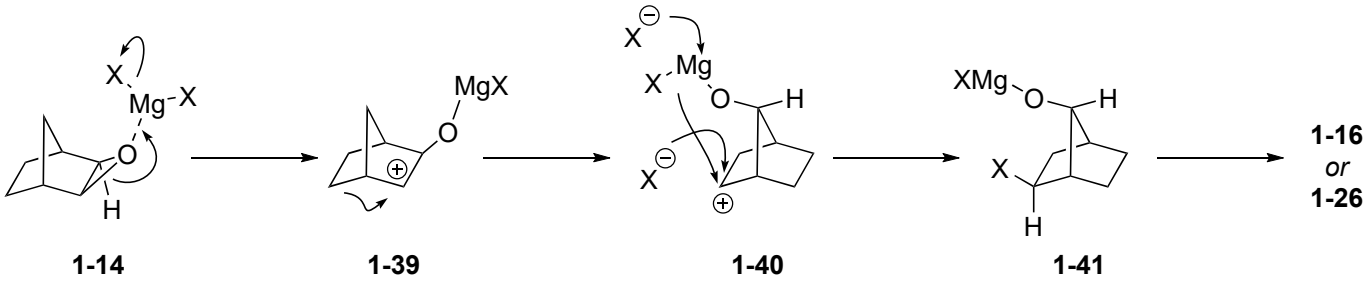
In case of R' = Ph: **1-30** becomes benzyl cation and much more stable than others. As a result, the reaction proceeds from **1-30** to generate **1-32** via path a. Otherwise, almost the same amount of intermediates exist, so the reaction is supposed to be kinetically controlled.

In case of R = Ph, ***o*-tol**: They are relatively bulky, so intramolecular reactions (paths a, d, and e) are preferable. Among them, path d is the most favorable reaction for bulkier reagent, because the most accessible proton is the reaction point. As a result, **1-35** is a major product. Path e is the second most favorable, because there is a steric repulsion in path a (highlighted in gray in **1-30**).
Especially in case of R' = **$(CH_2)_2$OTBPDS**: Paths a and e are unfavorable because of steric hindrance of alkyl chain. Therefore, the reaction occurred selectively.

In case of R = Me: Due to small size of Me, three paths (d, e, f) competed with each others.

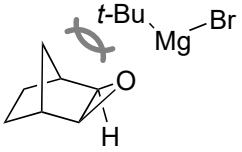
For halogenation:

2 RMgX $\rightleftharpoons$ MgR_2 + MgX_2



1-14 **1-39** **1-40** **1-41**

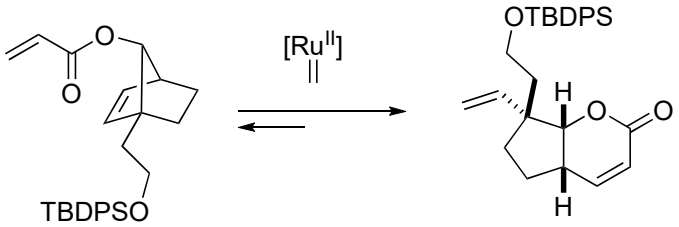
Due to Schlenk equilibrium, some amount of MgX_2 exists in the reaction mixture.
When **1-14** reacts with MgX_2, halogenated product is obtained.
The population of MgX_2 differs in the alkyl group, and formation of $MgMe_2$ would be more favorable than formation of $MgPh_2$ or Me(*o*-tol)$_2$ because of steric repulsion.
Therefore, in case of MeMgI, **1-26** was generated.
In case of *t*-BuMgBr, only MgX_2 can react with **1-14** because of bulky *t*-Bu group, yielding **1-16** in moderate yield.



1-14

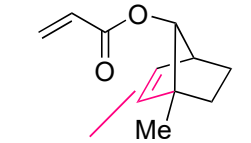
Discussion 2: Thermodynamic stability

The entire reaction process is reversible, thus the reaction is thermodynamically controlled.



1-10 ($C_{28}H_{34}O_3Si$) **1-12** ($C_{28}H_{34}O_3Si$)

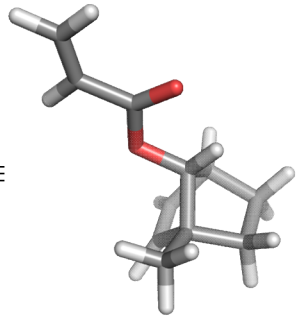
bicyclo [2.2.1] hept-2-ene



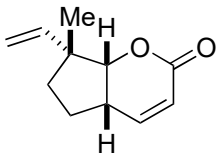
bond angle: 108 °

M1
(+6.0 kcal/mol)

≡

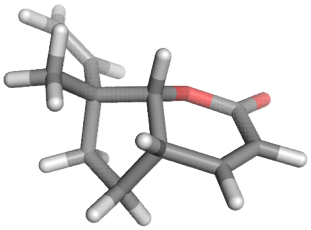


5/6-*cis* fused ring system



M2
(0.0 kcal/mol)

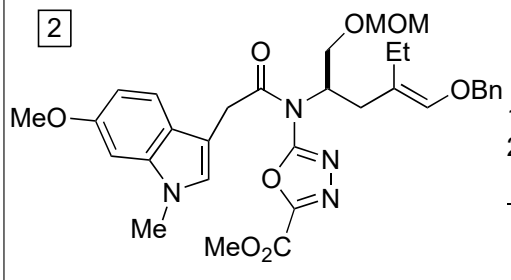
≡



relative Gibbs free energy calculated at B3LYP/STO-3G (298 K, 1 atm, gas phase)

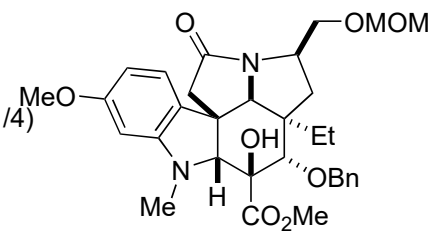
Calculation of model substrate **M1** and **M2** implied that **M2** is thermodynamically stable isomer, which accrods with the experimental result. Olefin highligheted in pink induces significant ring strain, so **M1** becomes less stable.

2



2-1

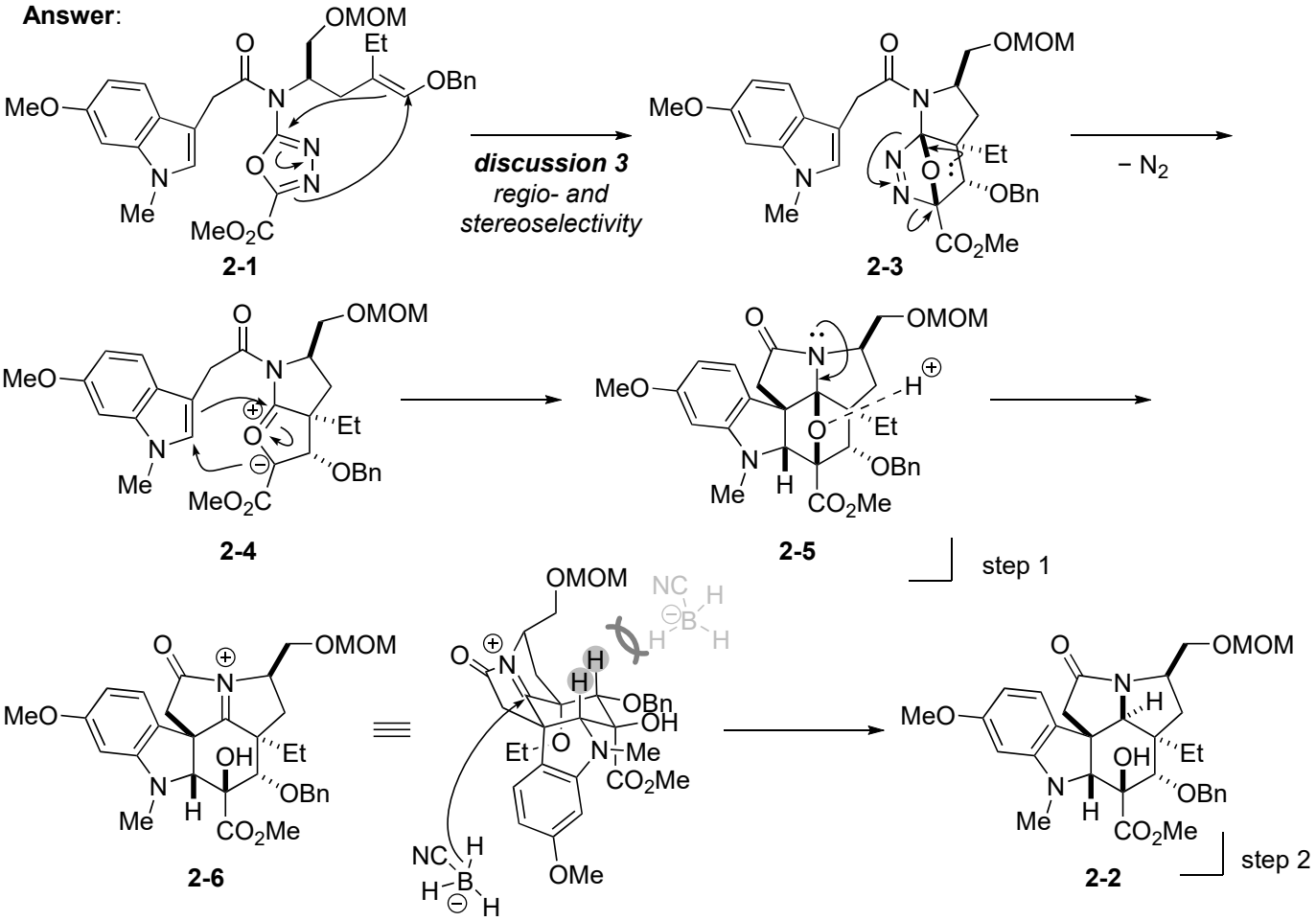
1. xylene, 130 to 175 °C
2. NaBH3CN (2 eq), AcOH/i-PrOH (1/4)
   0 °C, 55% (2 steps)



2-2

Kato, D.; Sasaski, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *162*, 3685-3687.

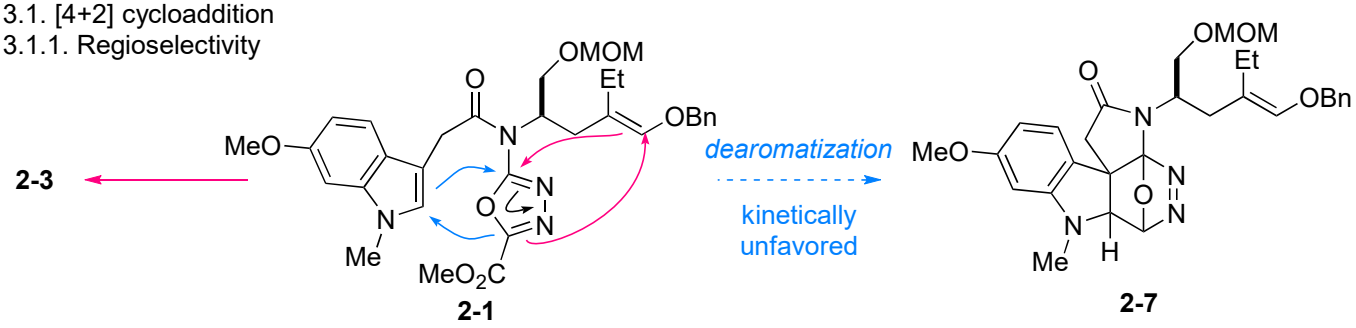
Answer:



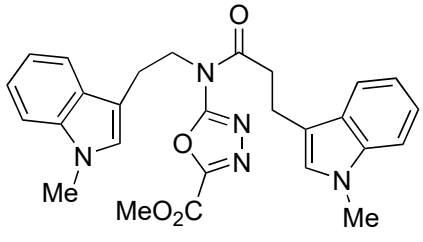
Discussion 3: Regio- and stereoselectivity

3.1. [4+2] cycloaddition

3.1.1. Regioselectivity



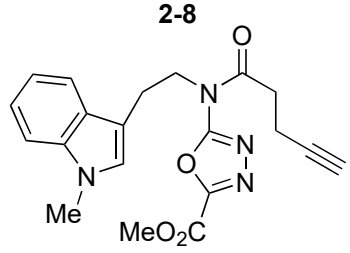
Dearomatization of indole is unfavorable, so the reaction from indole ring did not proceed.



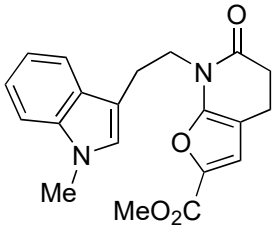
180 to 230 °C
>96 h

no reaction

These two experiments also support that indole ring is inactive to [4+2] cycloaddition.



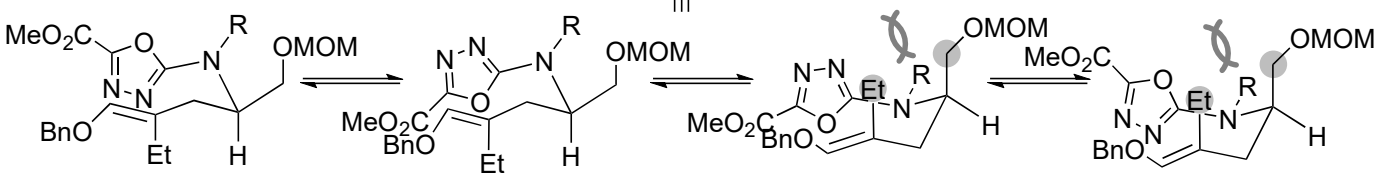
o-dichlorobenzene
175 °C, 63%



Wilkie, G. D.; Elliott, G. I.; Blagg, E. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292.

3.1.2. Stereoselectivity

2-1

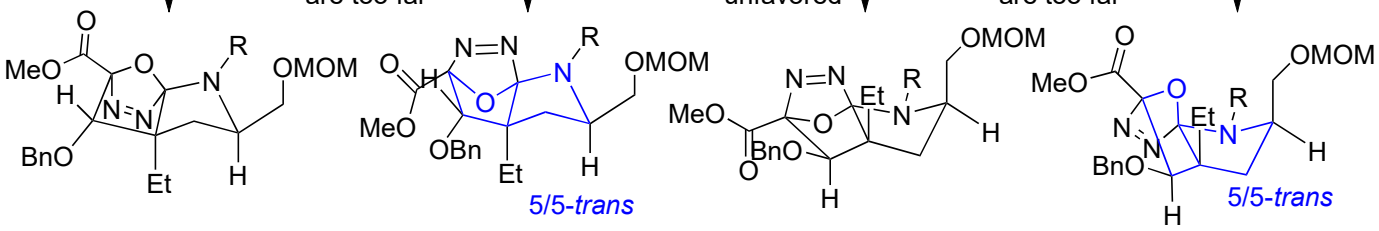


2-1-a **2-1-b** **2-1-c** **2-1-d**

the reaction points are too far

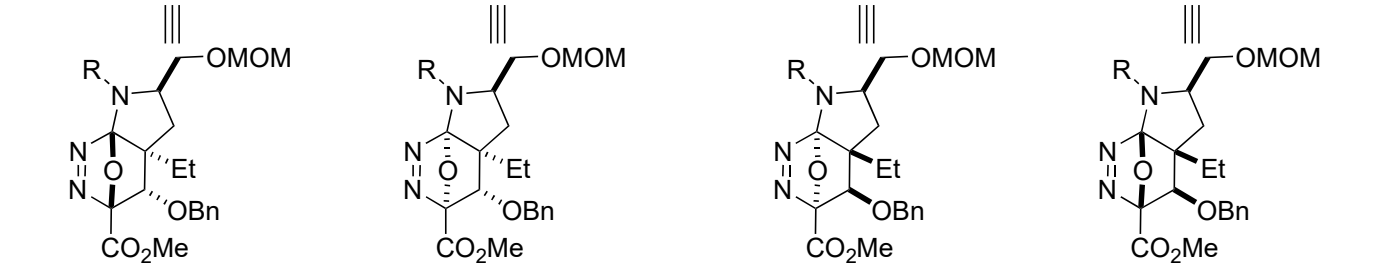
sterically unfavored

the reaction points are too far



5/5-*trans*

5/5-*trans*



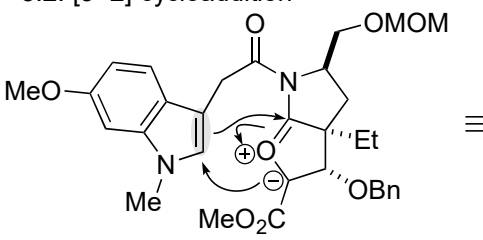
2-3
generated

2-11
not generated

2-12
not generated

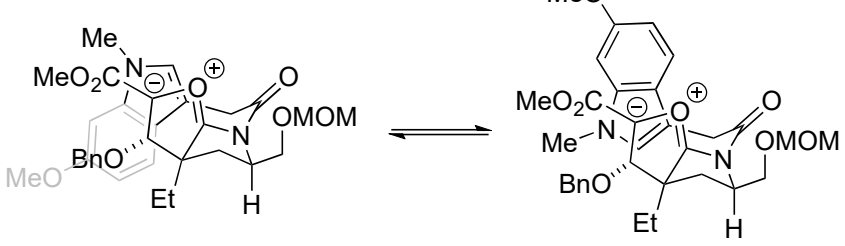
2-13
not generated

3.2. [3+2] cycloaddition



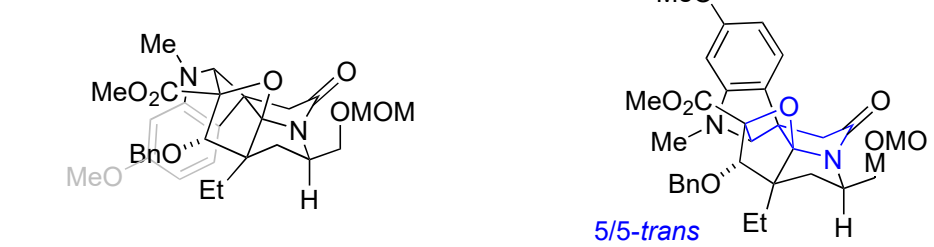
2-4

indole ring reacts with 1,3-dipole from convex face of 5/5-*cis* fused ring

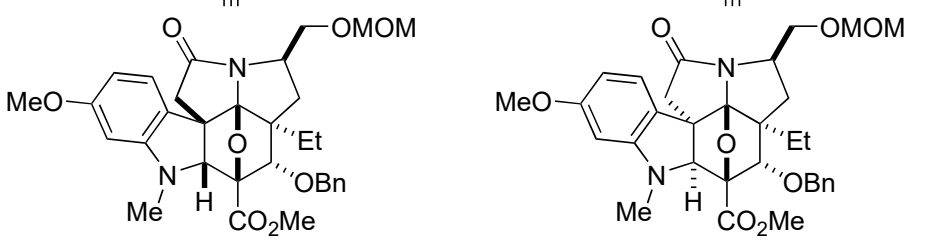


2-4-a **2-4-b**

the reaction points are too far



5/5-*trans*



2-5
obtained

2-14
not obtained