

Problem Session (2) -Answer-

2020/09/19 Yuma Komori

Topic: Total synthesis of Waihoensene

Introduction

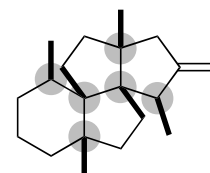
Isolation: *Podocarpus totara* var *waihoensis* (1997*)

Structural features: highly congested *cis*-fused tetracycle, six contiguous stereogenic centers

Total synthesis: (±)-Waihoensene...Lee (2017) **Problem 1**

(+)-Waihoensene...Yang (2020) **Problem 2**

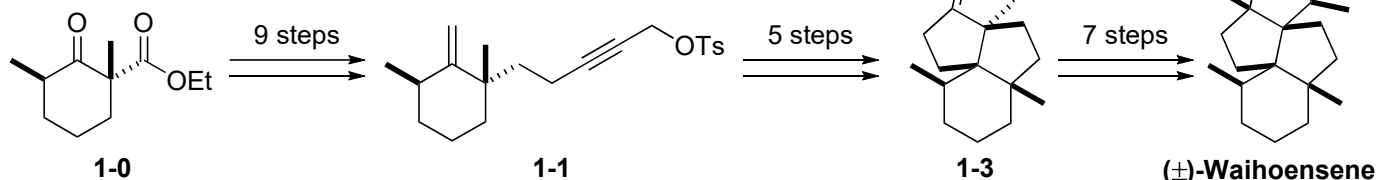
Snyder (2020)



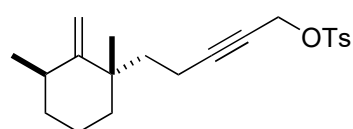
(+)-Waihoensene

*Clarke, D. B.; Hinkley, S. F. R.; Weavers, R. T. *Tetrahedron Lett.* **1997**, 38, 4297.

Introduction of problem 1: Lee's synthetic route

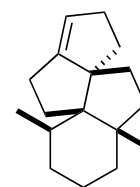


Problem 1

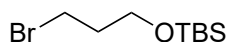


1-1

- 1-2 (3.0 eq.), Mg (3.3 eq.), 1,2-dibromoethane (0.1 eq.), CuCN (0.3 eq.), THF, 0 °C
 - TBAF (2.0 eq.), THF, 0 °C to rt, 95% (2 steps)
 - (COCl)₂ (1.5 eq.), DMSO (2.5 eq.), Et₃N (5.0 eq.), CH₂Cl₂, -78 °C to rt, 94%
-
- H₂NNHTs (1.1 eq.), MeOH, 0 °C to rt
 - NaH (1.2 eq.), toluene, 0 °C to 110 °C, 82%(2steps)
(1-3 : other isomers = 3.3 : 0.79 : 0.21)



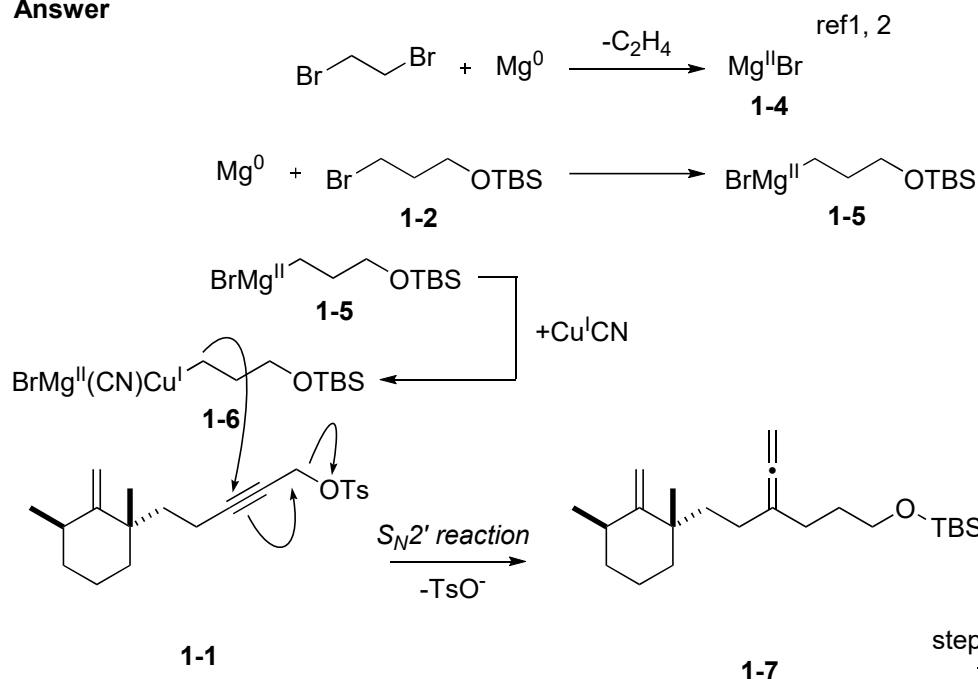
1-3

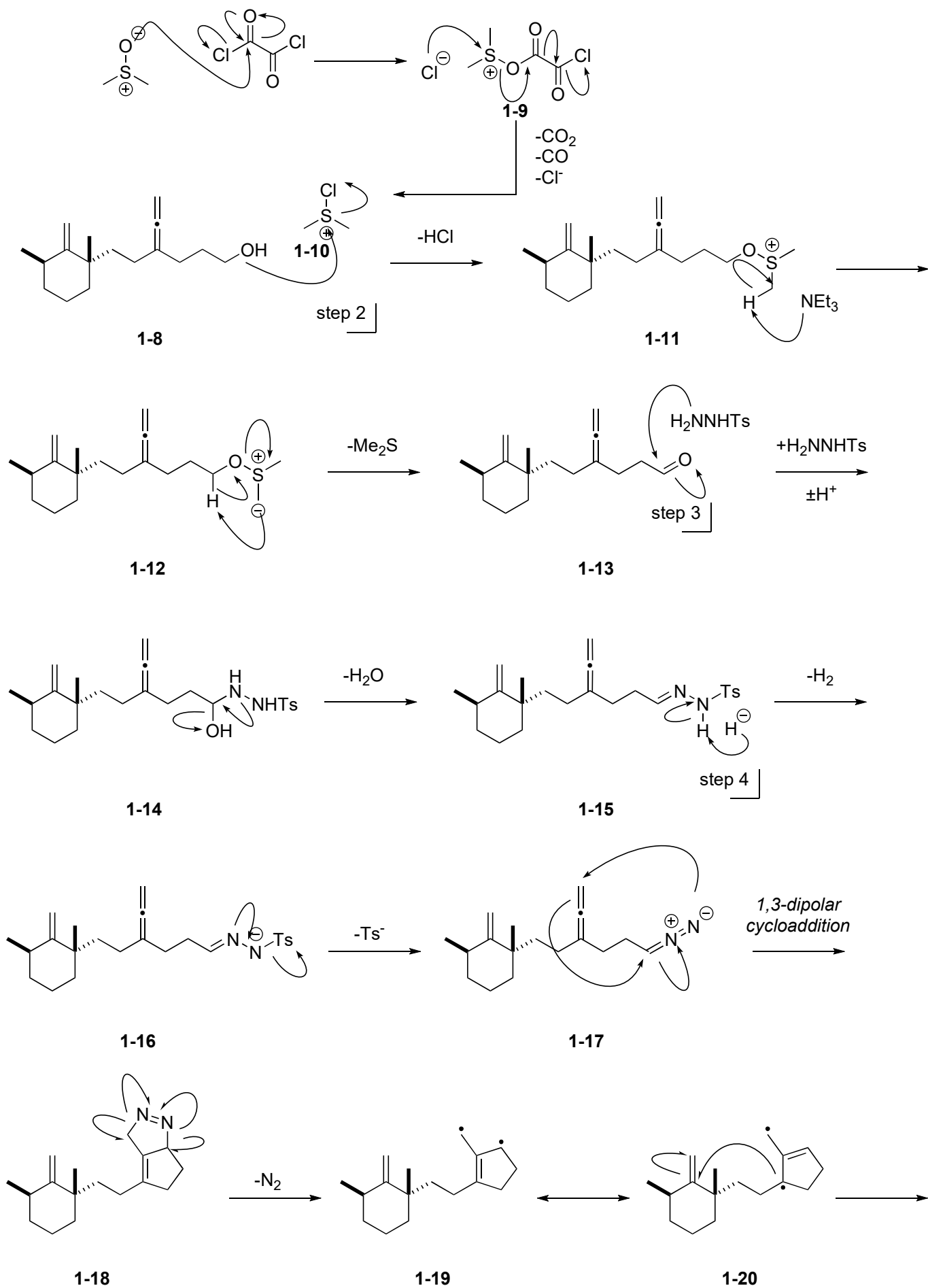


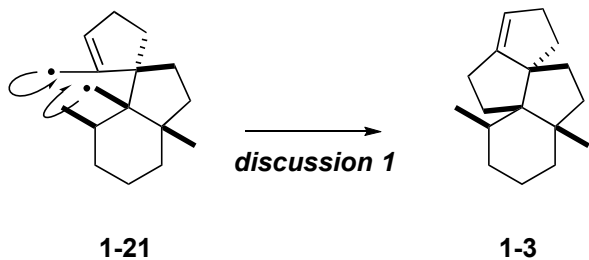
1-2

Lee, H.; Kang, T.; Lee, H.-Y. *Angew. Chem. Int. Ed.* **2017**, 56, 8254.

Answer



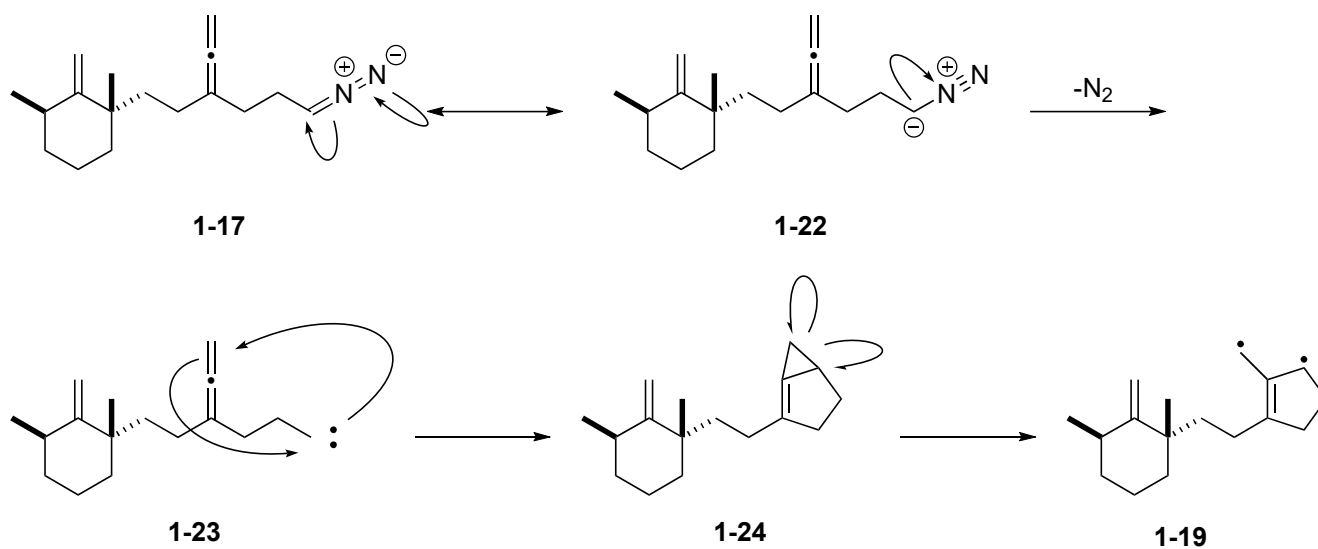




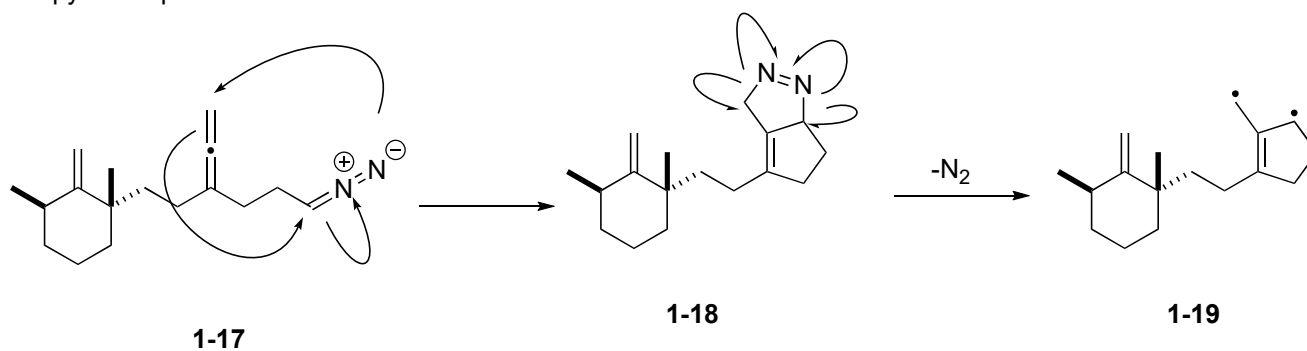
discussion 1: Construction of tetracycle

1.1. carbene vs enediyne

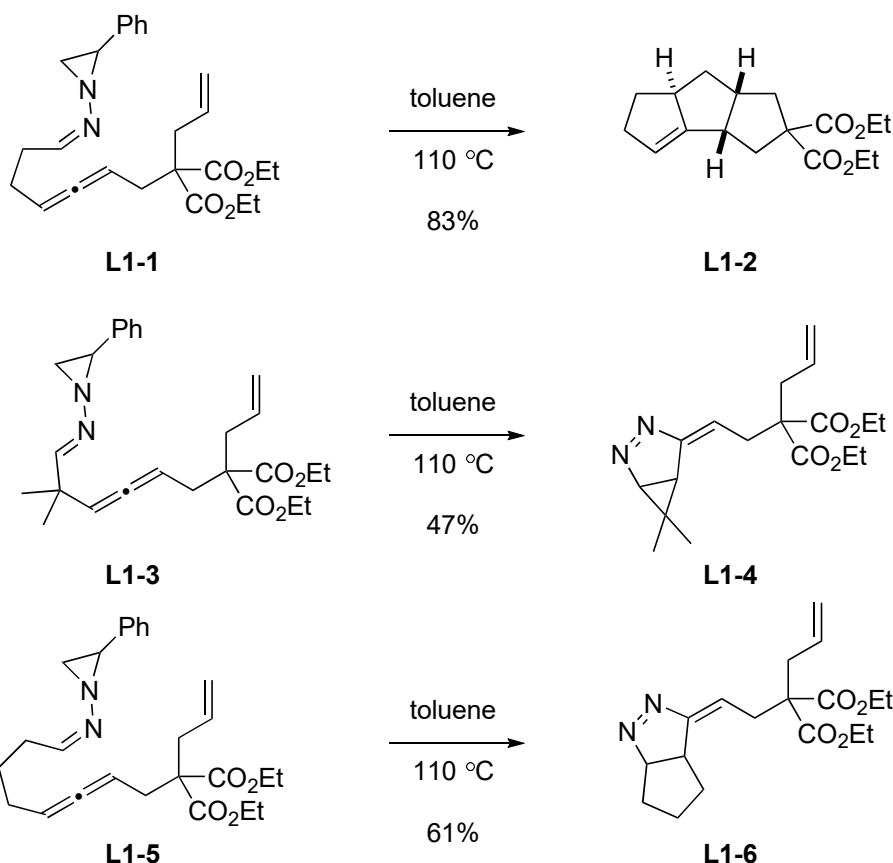
carbene path



enediyne path



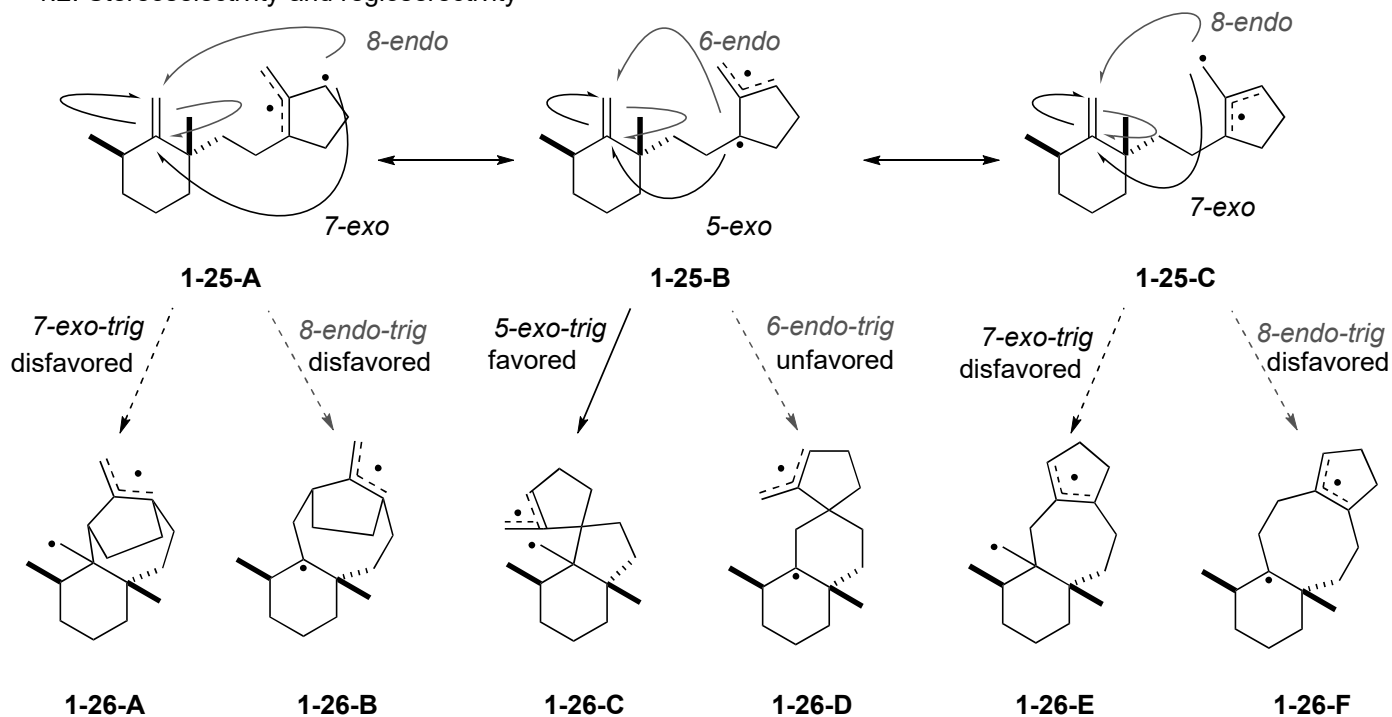
From diazo compound **1-17**, carbene **1-23** and enediyne **1-18** can be considered as an intermediate to generate biradical **1-19**.



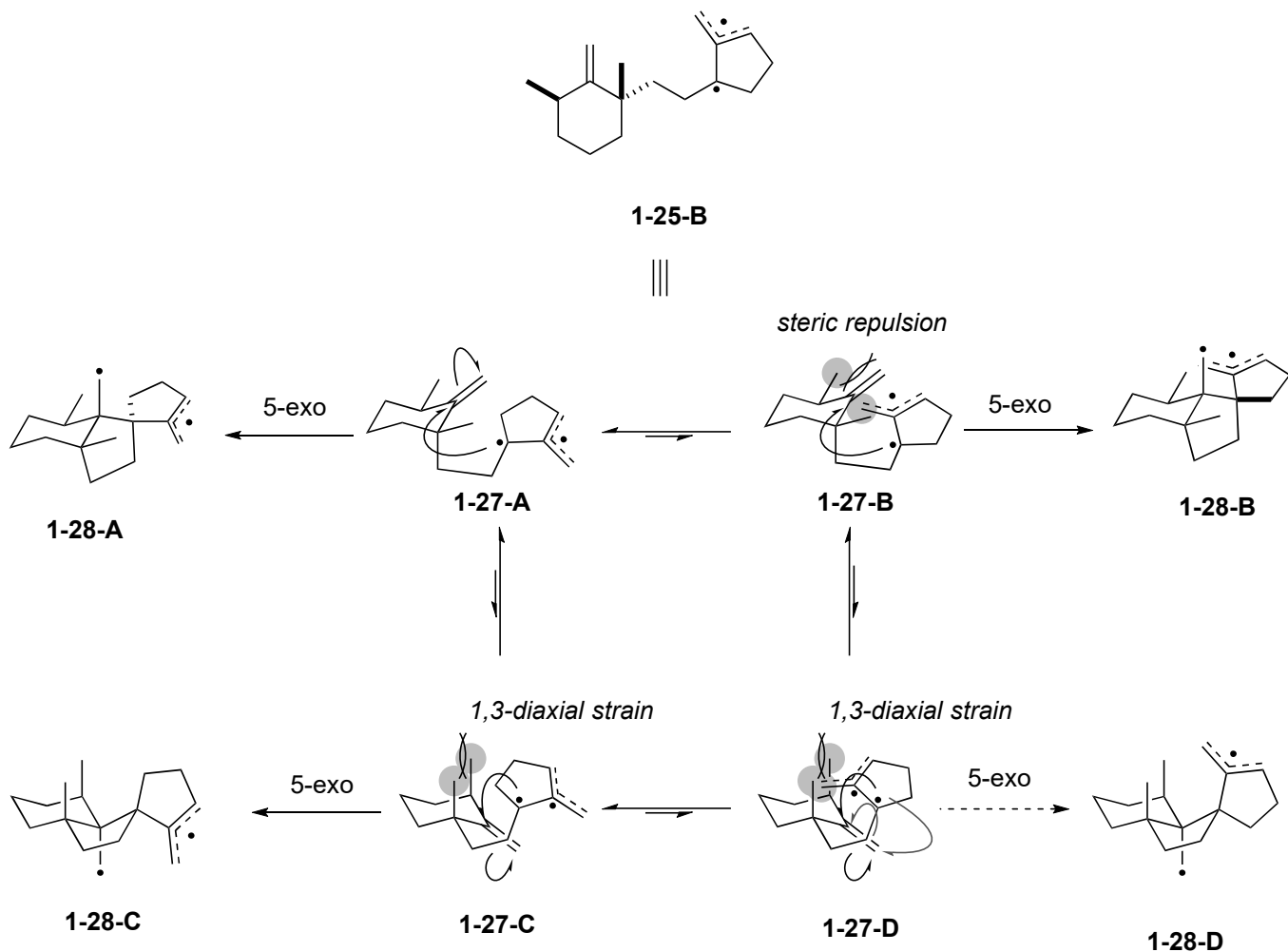
Three-carbon tether compound **L1-1** was subjected to the conditions above, and tricyclic compound **L1-2** was obtained. However, when two-carbon tether and four-carbon tether were employed, pyrazole were isolated. These results suggest that pyrazole intermediate immediately generates before elimination of N_2 to generate carbene.

Also, third entry shows the preference of five-membered ring.

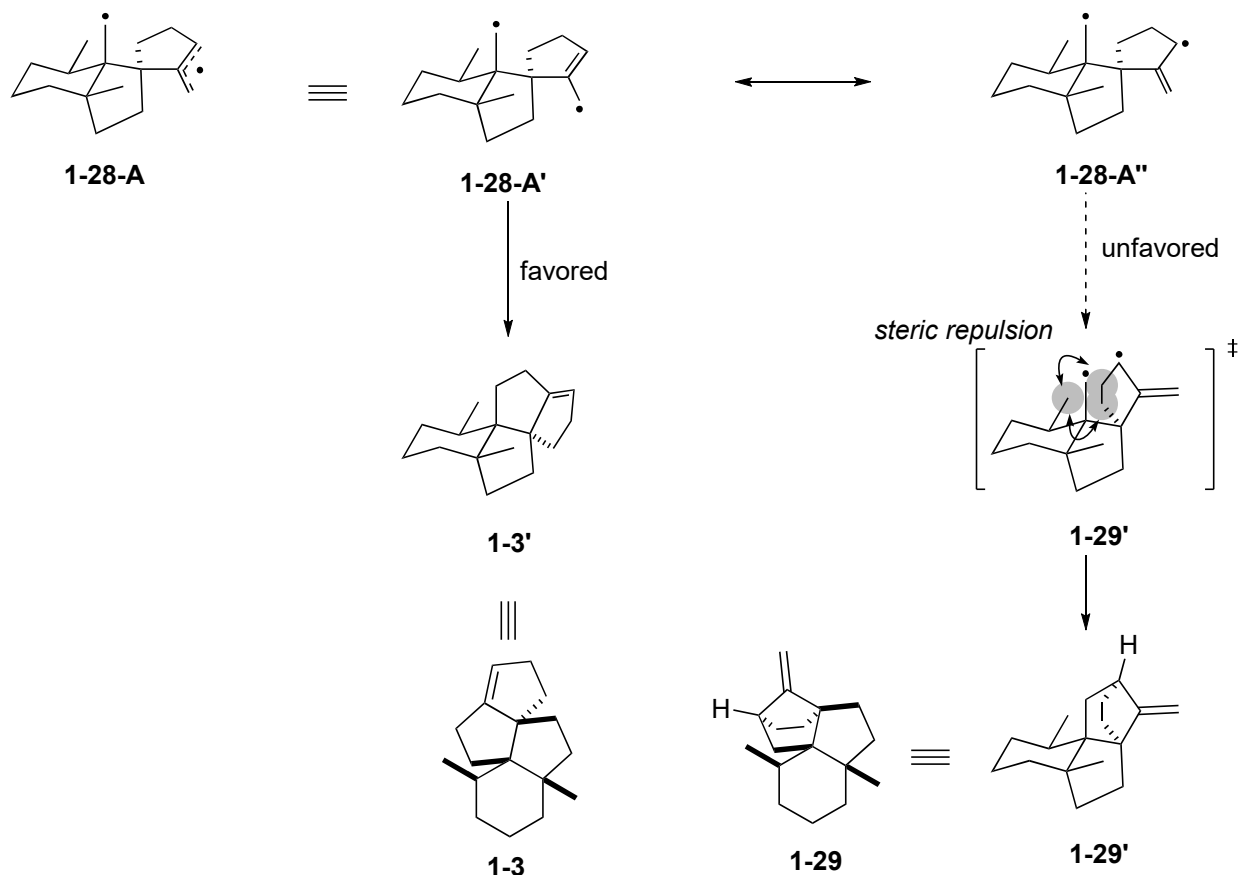
1.2. Stereoselectivity and regioselectivity



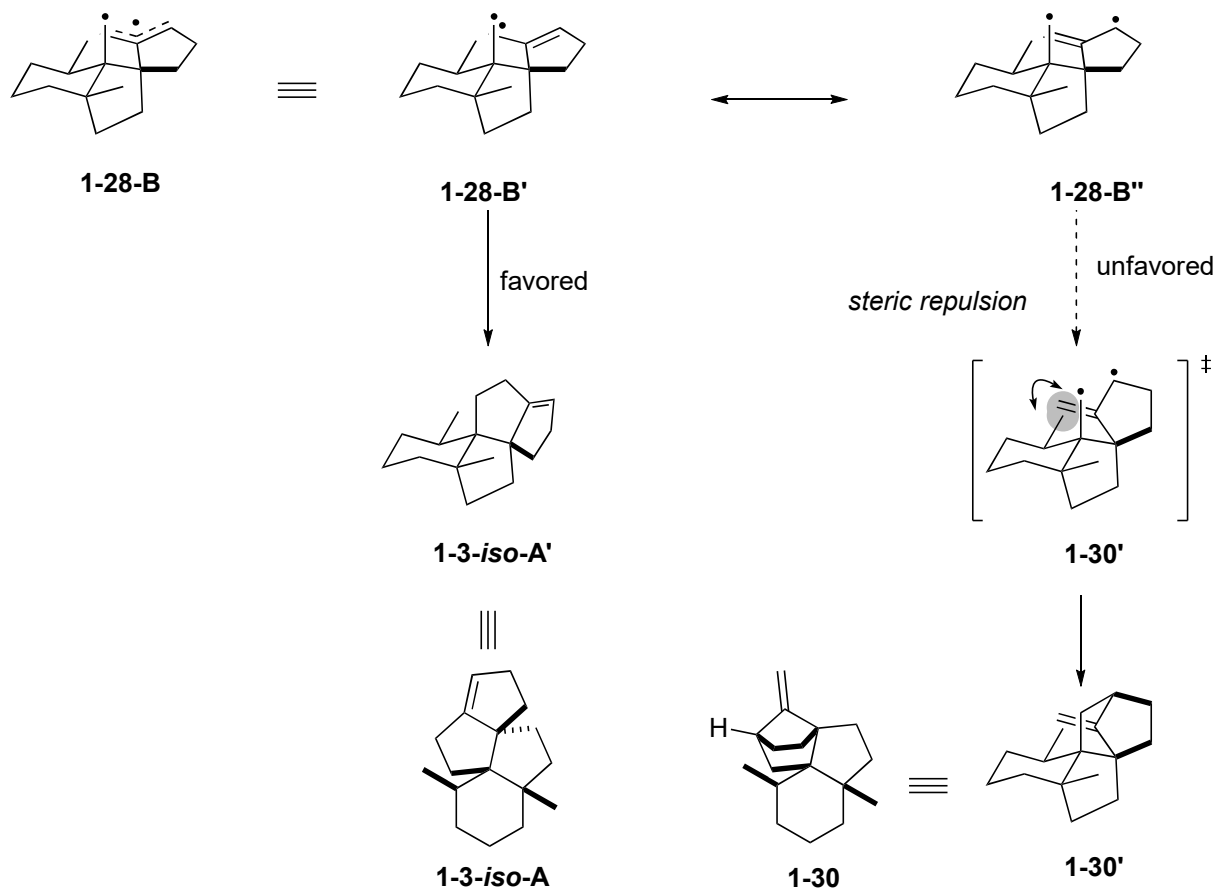
1-25-A, **1-25-B**, **1-25-C** are considerable resonance structure. However, only 7-exo-trig and 8-endo-trig are available from **1-25-A** and **1-25-C**. 7-exo-trig and 8-endo-trig are disfavored, so only **1-25-B** is reactive. From **1-25-B**, kinetically favored 5-exo-trig cyclization proceeds.



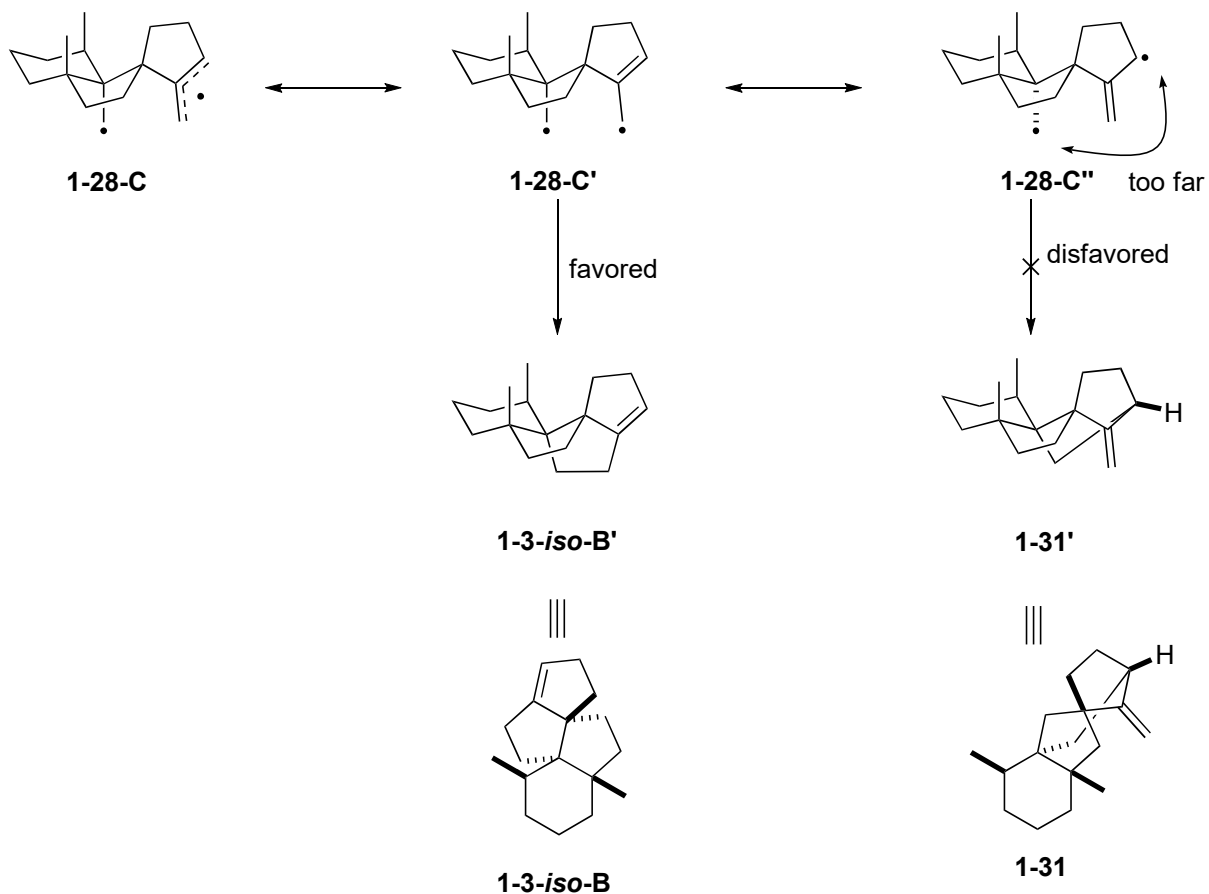
The conformations of **1-25-B** can be described as **1-27-A**, **1-27-B**, **1-27-C** and **1-27-D**. **1-27-C** and **1-27-D** have 1,3-diaxial strain. Moreover, **1-27-D** has steric repulsion between methyl group on five membered ring and axial methyl group. Therefore, **1-27-D** would be least stable conformation. Also, **1-27-B** has steric repulsion between methyl group on six-membered ring and methyl group on five-membered ring. Therefore, **1-27-A** would be most stable conformation and major product is derived from **1-27-A**.



From **1-28-A'**, biradical reacts and tetra cyclic compound **1-3** is produced. When the biradical of **1-28-A''** reacts, methyl group on six-membered ring and methylene groups on five-membered ring have to be close position. It is kinetically unfavored. Therefore, cyclization from **1-28-A'** is favored.

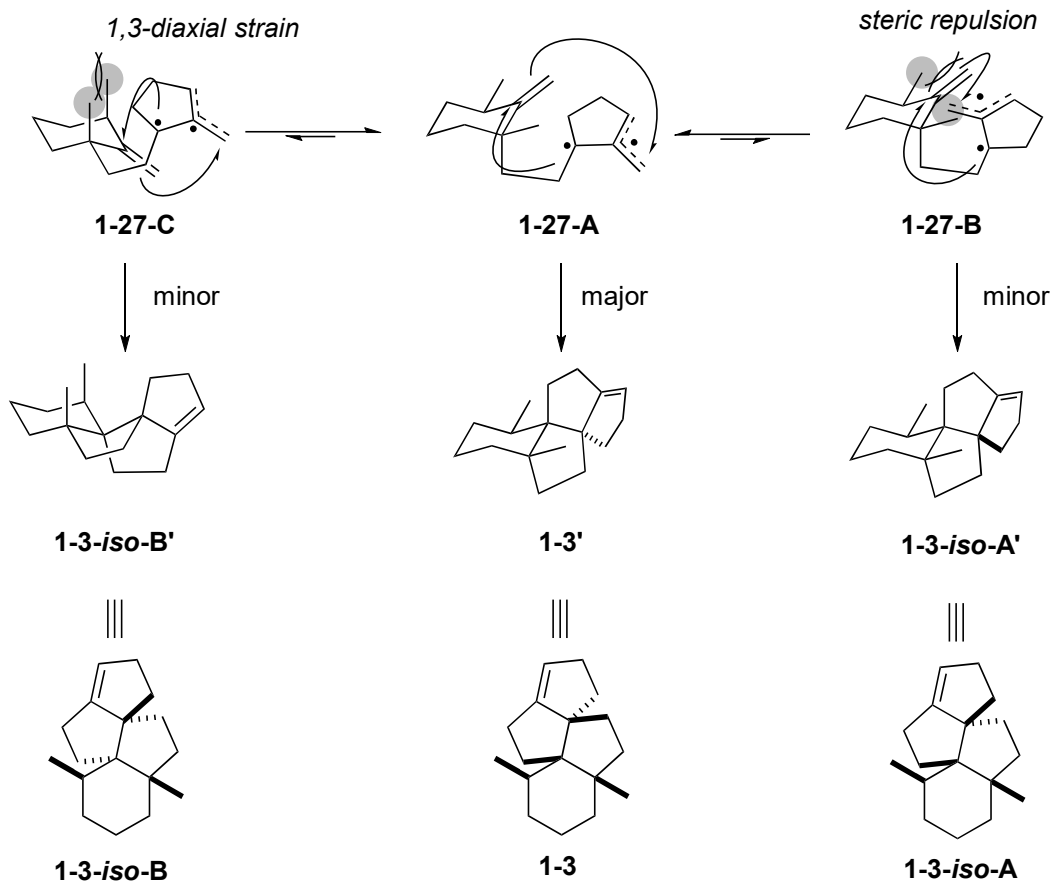


From **1-28-B'**, biradical reacts and tetra cyclic compound **1-3-iso-A** is produced. When the biradical of **1-28-B''** reacts, methyl group on six-membered ring and olefin on five-membered ring have to be close position. It is kinetically unfavored. Therefore, cyclization from **1-28-B'** is favored.

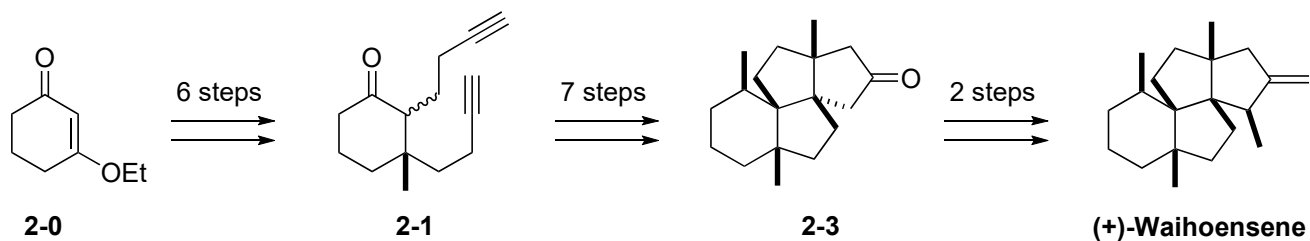


From **1-28-C'**, biradical reacts and tetra cyclic compound **1-3-iso-B** is produced. In contrast, biradical of **1-28-C''** is too far, so cyclization from **1-28-C''** is disfavored.

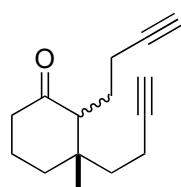
In summary, **1-3** from **1-27-A** is a major product of radical cyclization. **1-3-iso-A** from **1-27-B** and **1-3-iso-B** from **1-27-C** are minor products.



Introduction of problem 2: Yang's synthetic route



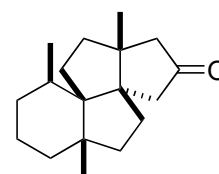
Problem 2



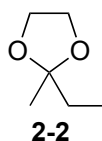
2-1

1. *t*-BuOK (0.5 eq.), DMSO, 83%
2. $\text{Co}_2(\text{CO})_8$ (1.1 eq.), N_2O (1 atm), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 80 °C, 59% (93% ee)
3. $\text{Ni}(\text{acac})_2$ (10 mol%), LiBr (3.0 eq.), Me_2Zn (5.0 eq.), Et_2O , 81%

4. 2-2 (5.0 eq.), PTSA· H_2O (0.05 eq.), Et_2O , 91% (99% brsm)
5. $\text{Ph}_3\text{P}^+\text{MeBr}^-$ (5.0 eq.), *t*-BuOK (4.9 eq.), toluene, reflux, 78% (90% brsm)
6. 1 M HCl (2.6 eq.), THF, 89%
7. $\text{Fe}(\text{acac})_3$ (0.2 eq.), PhSiH_3 (1.0 eq.), EtOH, 60 °C, 75%



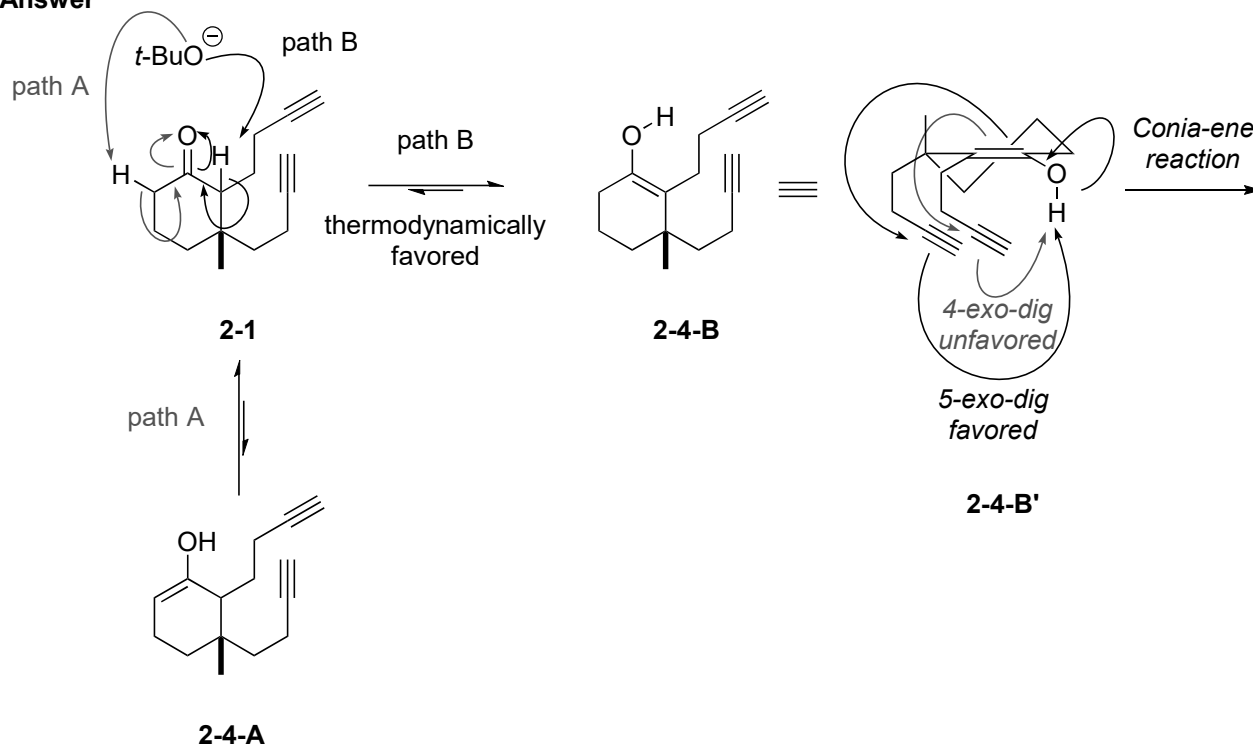
2-3

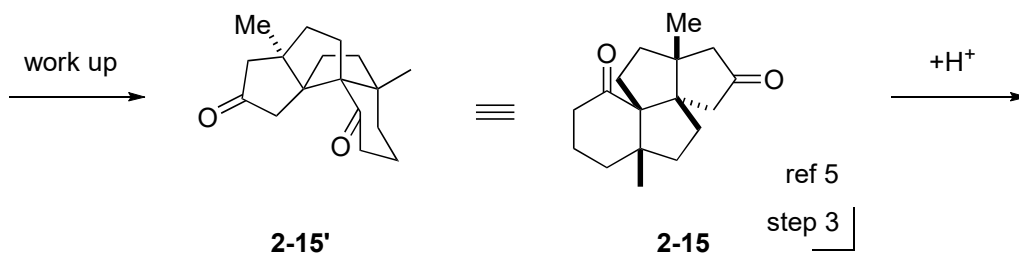
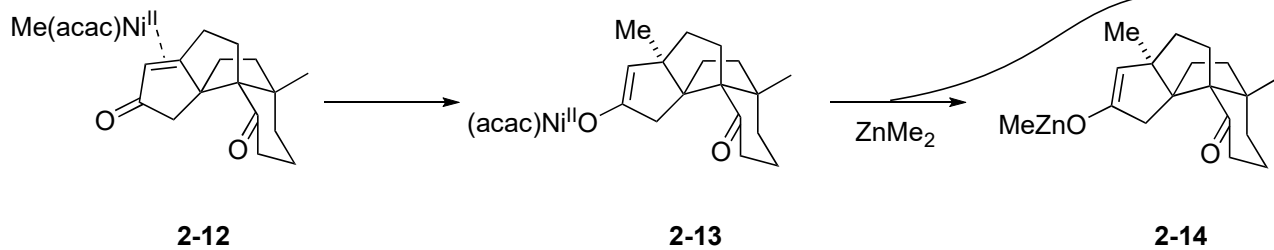
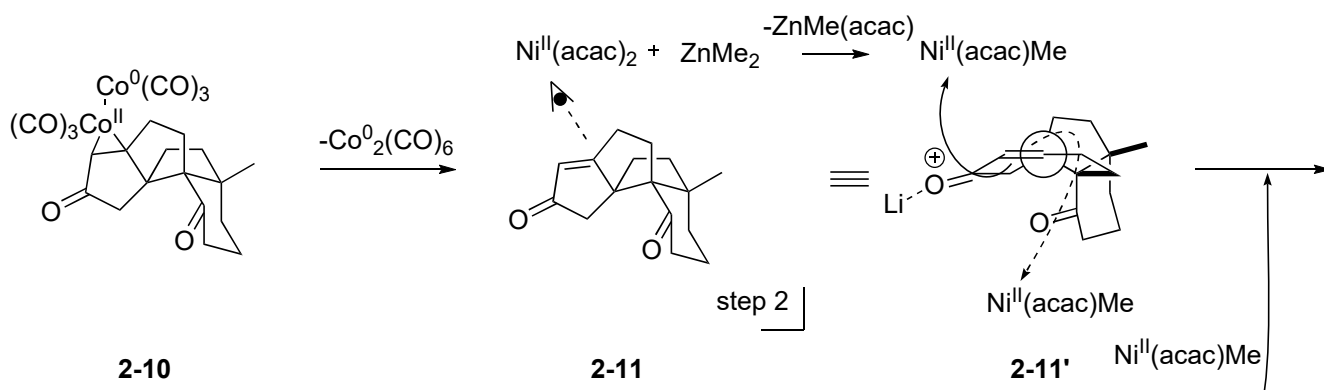
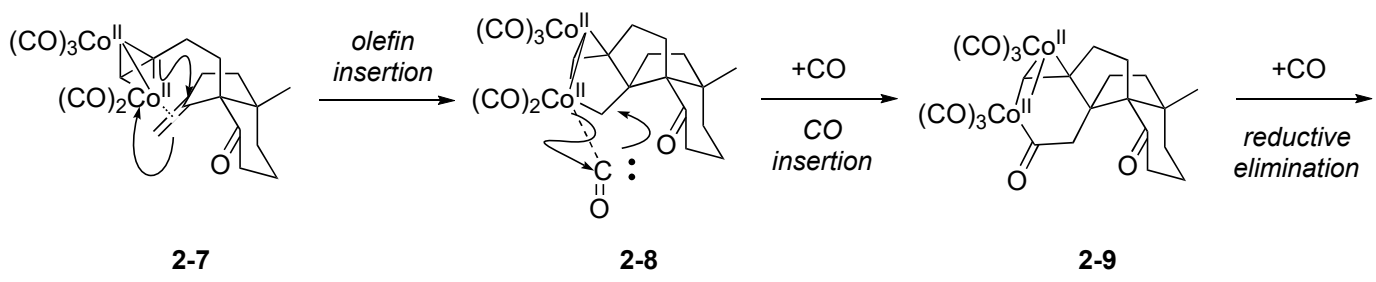
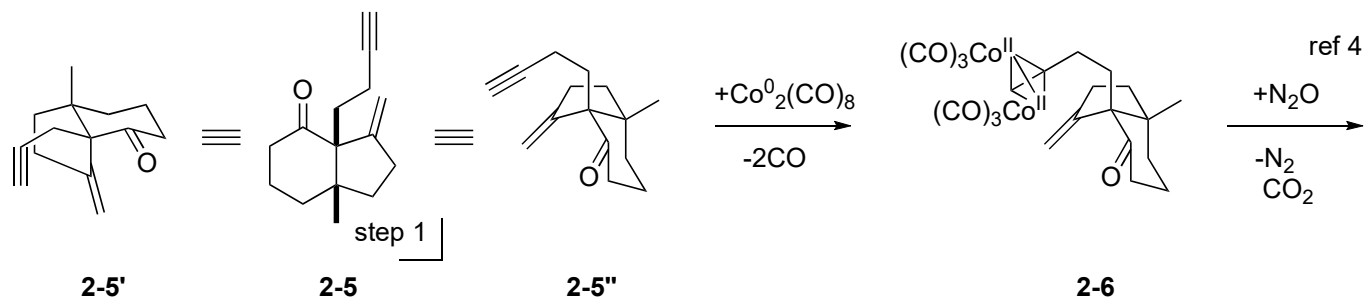


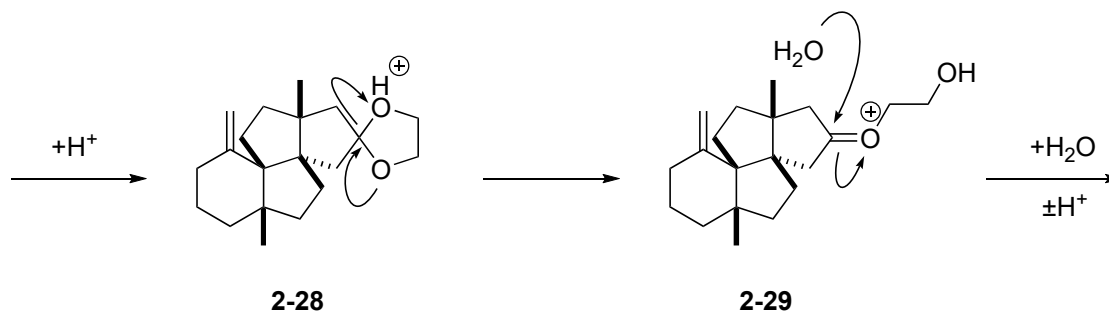
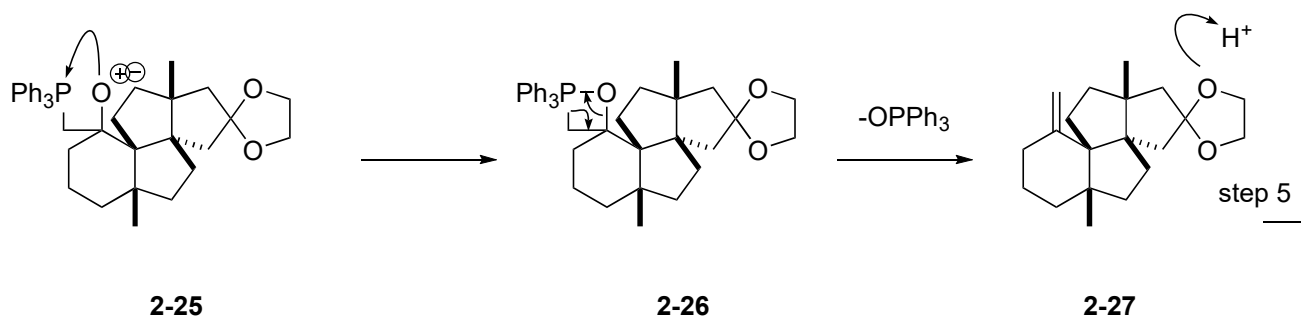
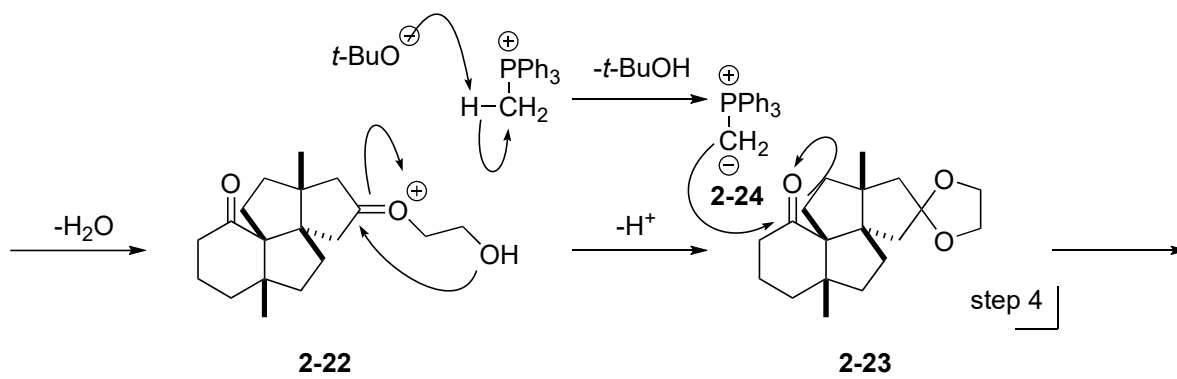
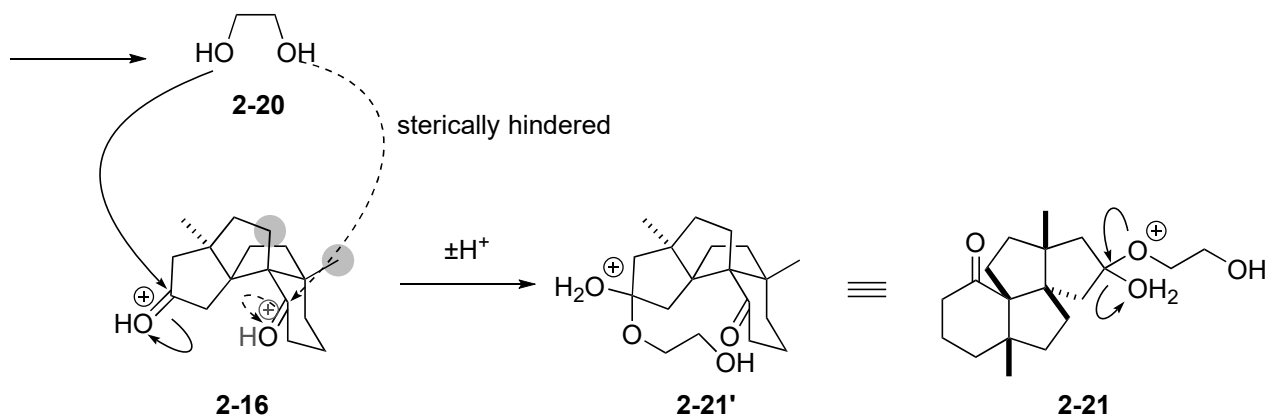
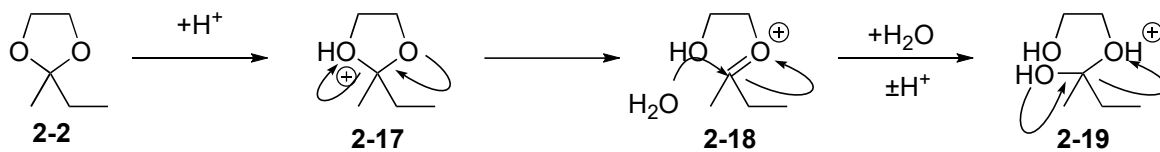
2-2

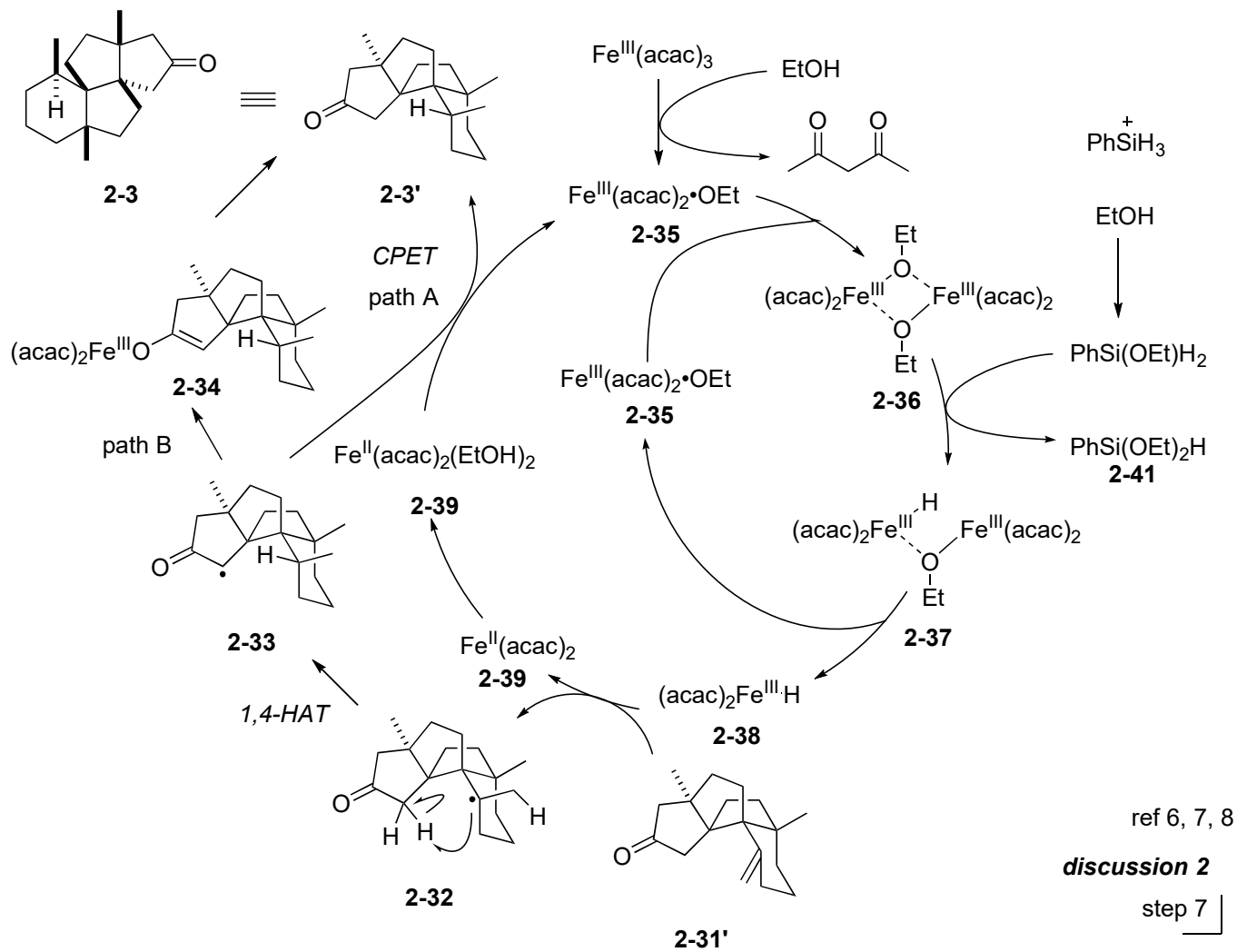
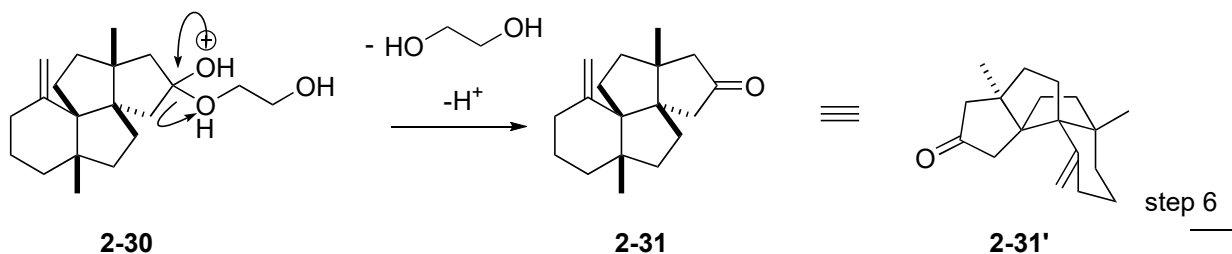
Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 6511.

Answer



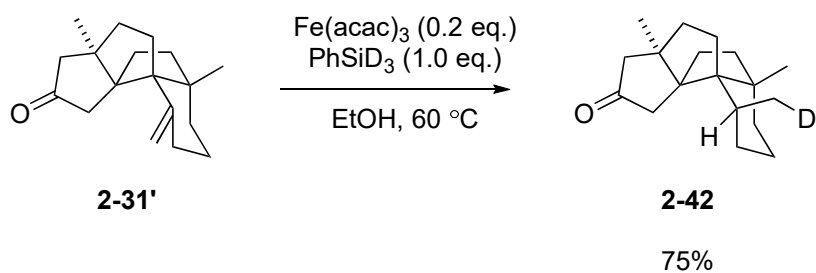






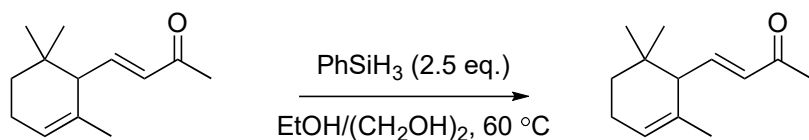
discussion 2: Stereoselective reduction of olefin

2.1. Mechanistic study



This result shows that olefin is reduced by hydride from $PhSiH_3$.

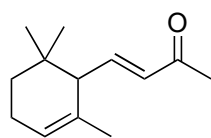
Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304.



L2-1

L2-1

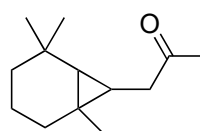
recovery



L2-1

Fe(acac)₃ (0.3 eq.)
PhSiH₃ (2.5 eq.)

degassed
EtOH/(CH₂OH)₂
N₂, 60 °C

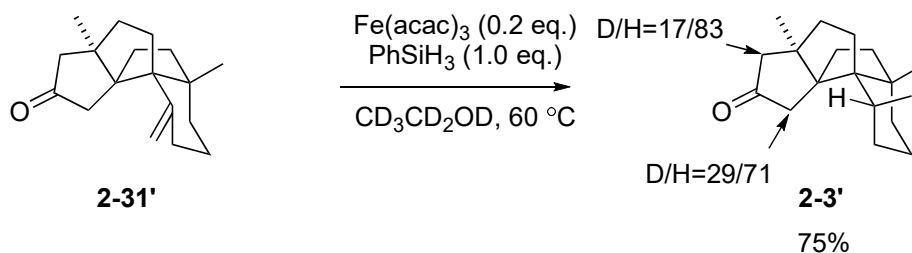


L2-2

full conversion

These results show that Fe(acac)₃ is necessary for olefin reduction. It indicates that hydride of PhSiH₃ moves to Fe(III) first, then moves to olefin.

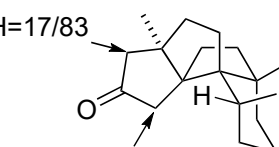
Also, second entry shows that oxygen does not oxidize Fe(II), which generates in olefin reduction.



2-31'

Fe(acac)₃ (0.2 eq.)
PhSiH₃ (1.0 eq.)

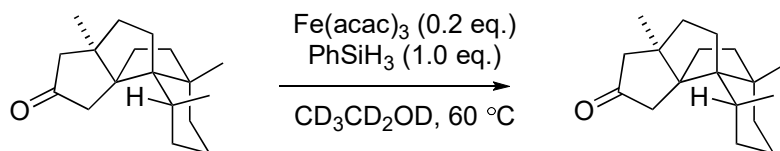
CD₃CD₂OD, 60 °C



D/H=17/83
D/H=29/71

2-3'

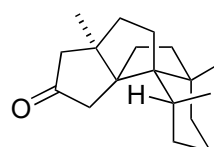
75%



2-3'

Fe(acac)₃ (0.2 eq.)
PhSiH₃ (1.0 eq.)

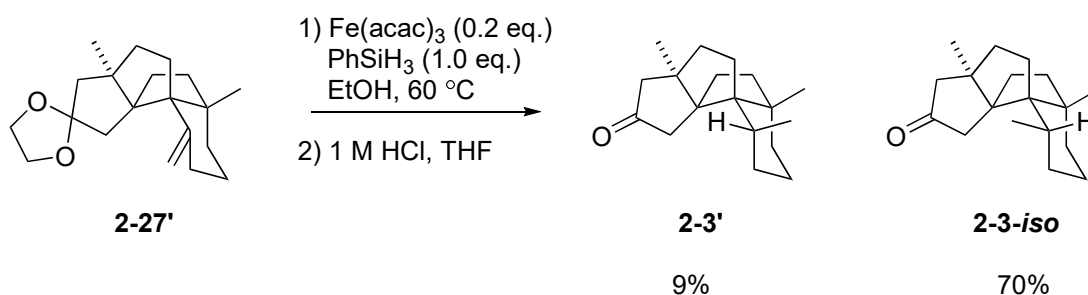
CD₃CD₂OD, 60 °C



2-3'

90% (recovery)

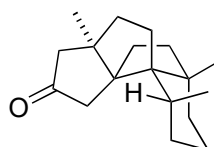
These results show that protonation of α -position of ketone is caused by solvent. Also, proton exchange does not occur.



2-27'

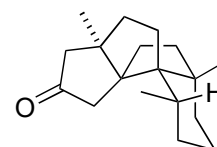
1) Fe(acac)₃ (0.2 eq.)
PhSiH₃ (1.0 eq.)
EtOH, 60 °C

2) 1 M HCl, THF



2-3'

9%

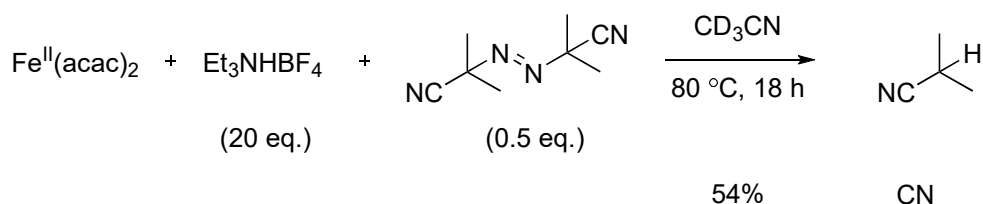
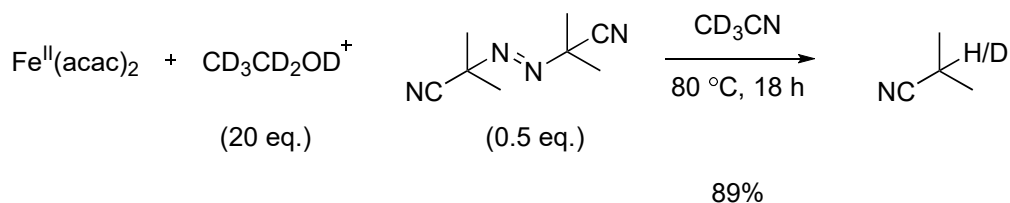
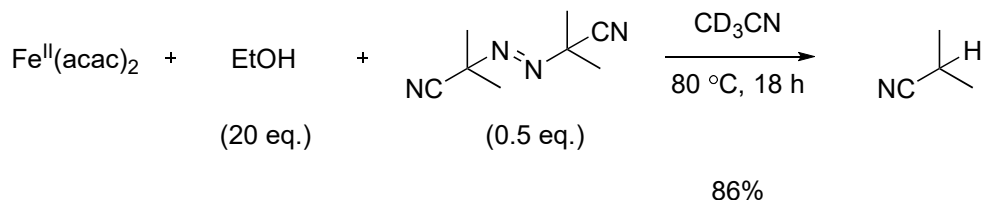
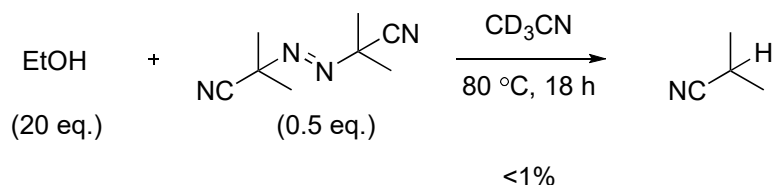


2-3-iso

70%

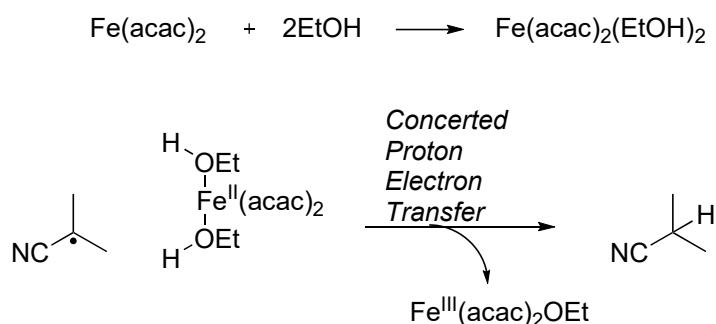
This result shows that proton has to be activated by carbonyl group. Also, this result indicates intramolecular HAT occurred.

Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. *J. Am. Chem. Soc.* **2019**, *141*, 7473.



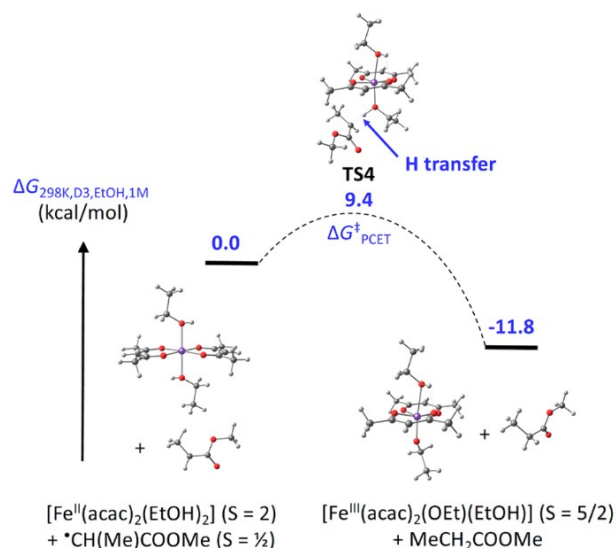
Radical experiment using AIBN was conducted.

Without $\text{Fe}(\text{acac})_2$, hydrogenation did not occur. Though hydrogen source is solvent (shown by deuterium experiment), $\text{Fe}(\text{acac})_2$ is necessary. Also, when Et_3NHBF_4 was used as an hydrogen source, yield was low. It indicates that coordination of EtOH to $\text{Fe}(\text{acac})_2$ is necessary. These experiments indicate following reaction mechanism.



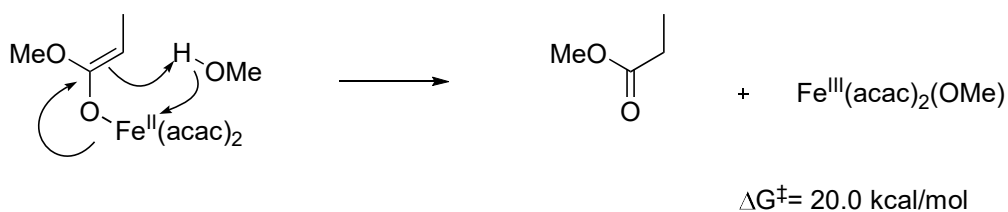
This mechanism is path A on page11.

DFT calculation shows that $\Delta G^{\ddagger}_{\text{PCET}}$ is 9.4 kcal/mol.

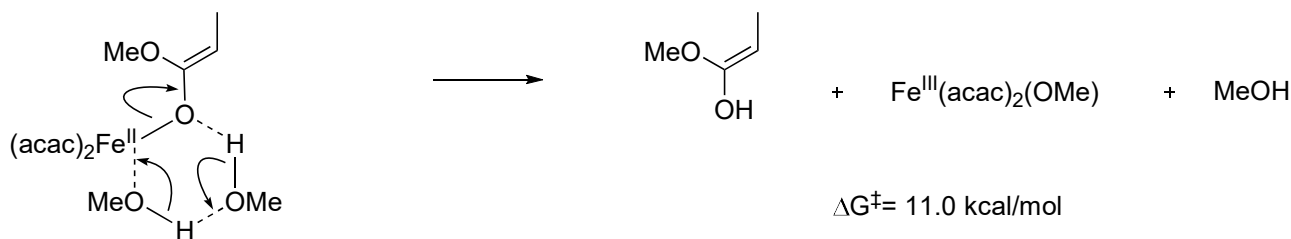


Also, DFT calculation of other paths was conducted.

a) One MeOH molecule is involved.



b) One MeOH molecules are involved.

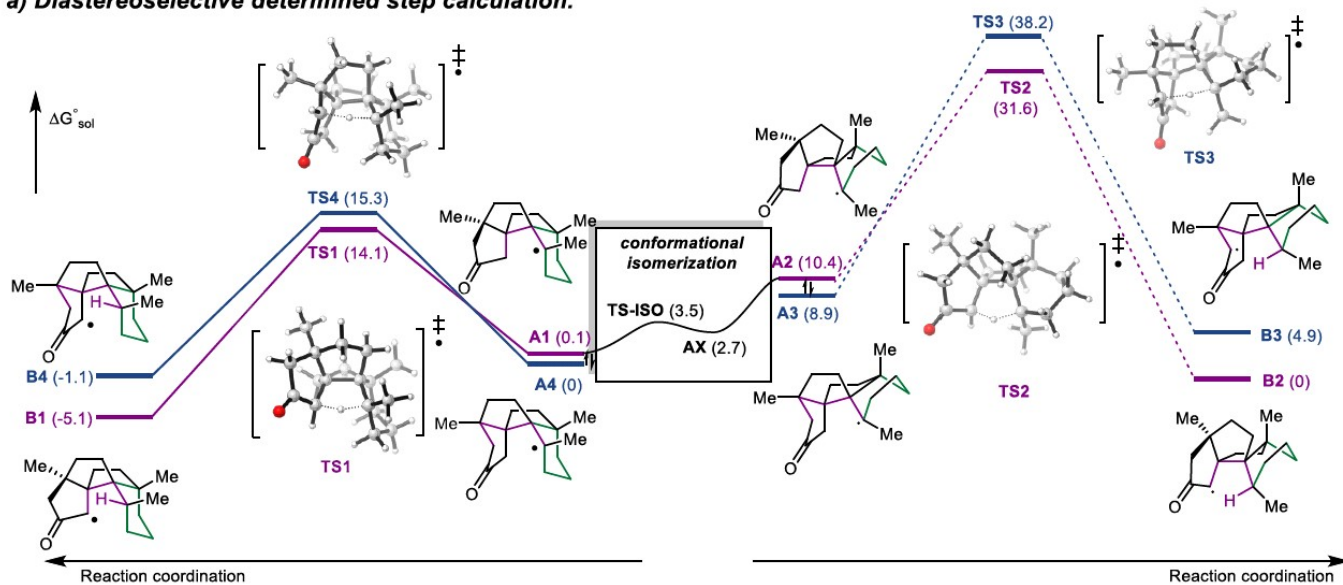


These paths are reduction via Fe enol ether. Path a which involves one MeOH molecule is unfavorable. However, activation barrier of path b which involves two MeOH molecules is relatively low (11.0 kcal/mol, $\Delta G^{\ddagger}_{\text{PCET}} = 9.4$ kcal/mol). Though there is no experimental evidence, path b cannot be rejected.

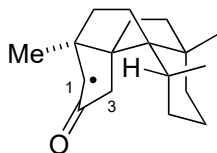
This mechanism is path B on page 11.

2.2. DFT calculation

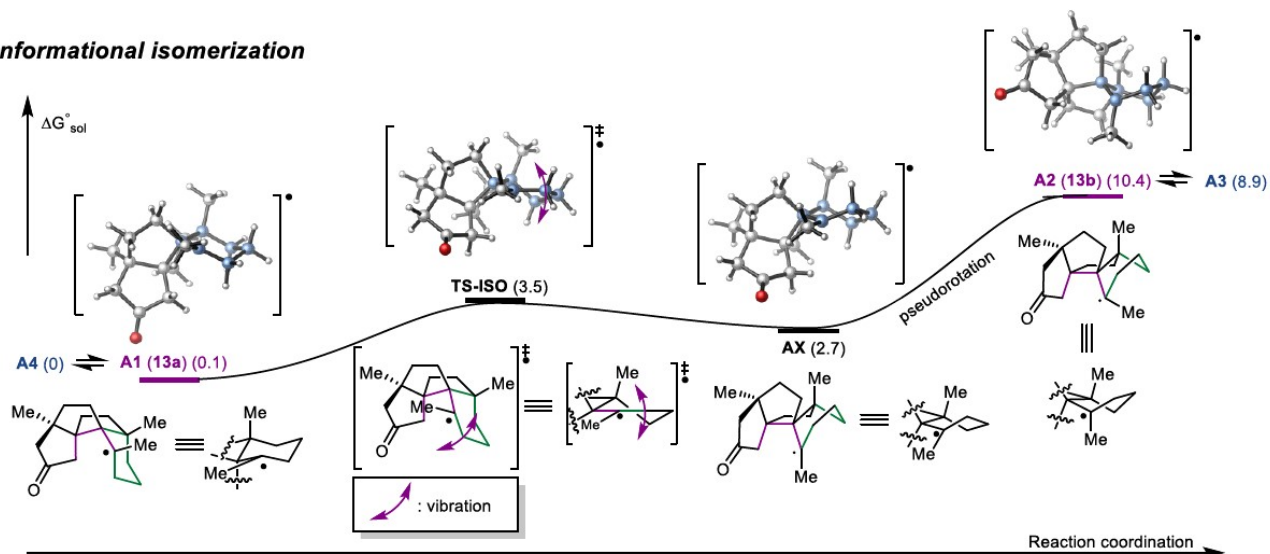
a) Diastereoselective determined step calculation.



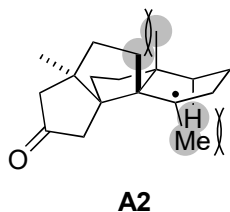
*Correct structure of B4 might be this (radical at C1 position).



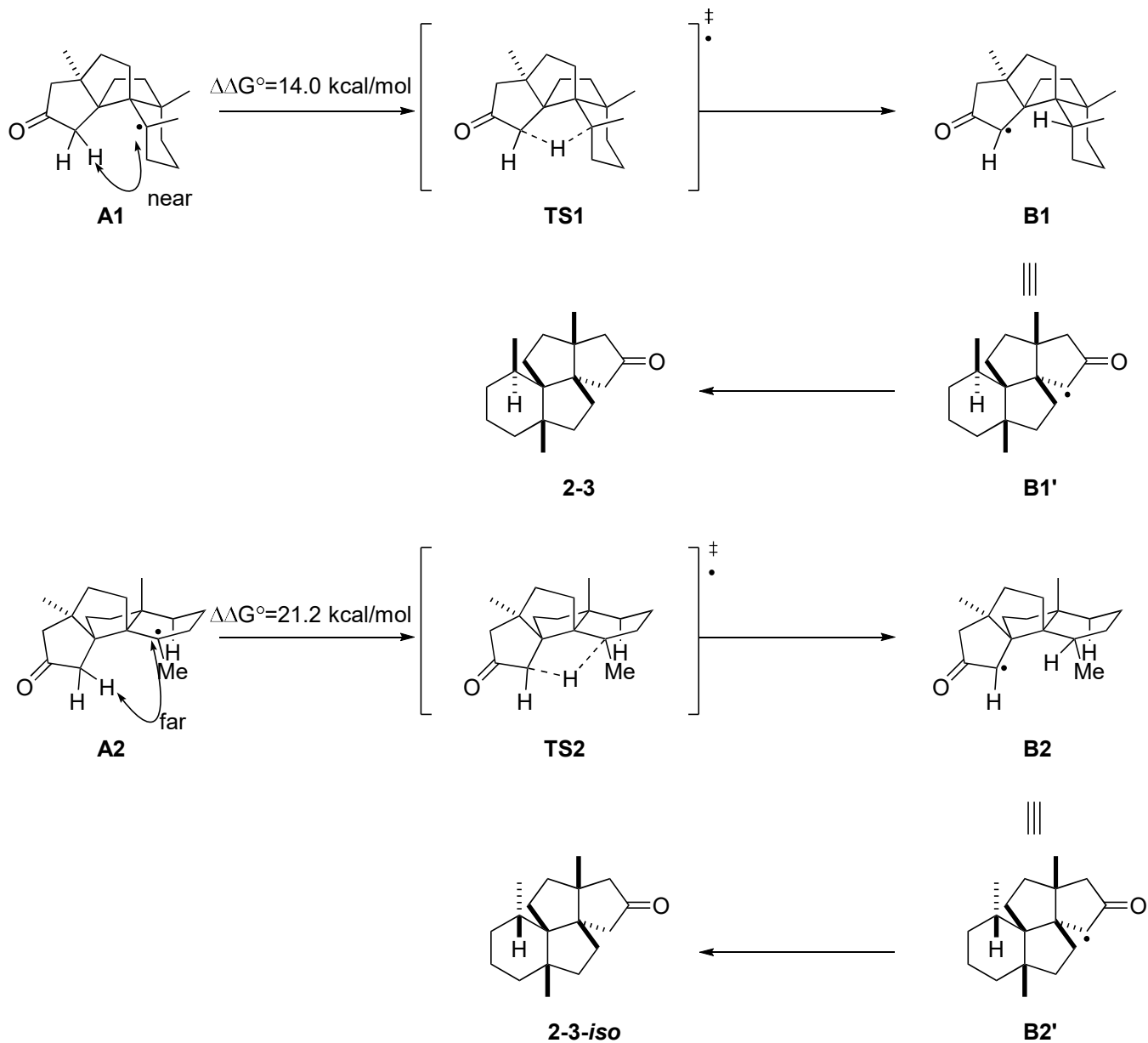
b) conformational isomerization



When the conformation of six-membered ring is chair, HAT occurs in desired way. In contrast, when the conformation is boat, undesired HAT occurs. However, boat conformation is unstable ($\Delta\Delta G^{\circ}$ between chair conformation **A1** and boat conformation **A2** is 10.3 kcal/mol). It would be because there is steric repulsion shown below, so desired HAT from chair conformation occurs.



Also, $\Delta\Delta G^{\circ}$ between **A2** and **TS2** (21.2 kcal/mol) is higher than $\Delta\Delta G^{\circ}$ between **A1** and **TS1** (14.0 kcal/mol). It would be because H atom on α -position of ketone is too far from carbon radical when the conformation is boat.



This DFT calculation supports the selectivity of olefin reduction.

References

- 1) Lai, Y.-H. *Synthesis*, **1981**, 8, 585.
- 2) Gomberg, M.; Backmann, W. E. *J. Am. Chem. Soc.* **1927**, 49, 236.
- 3) Kang, T.; Kim, W.-Y.; Yoon, Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2011**, 133, 18050.
- 4) Ricker, J. D.; Mohmmadrezaei, V.; Crippen, T. J.; Zell, A. M.; Geary, L. M. *Organometallics*. **2018**, 37, 4556.
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- 6) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, 136, 1304.
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- 8) Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. *J. Am. Chem. Soc.* **2019**, 141, 7473.