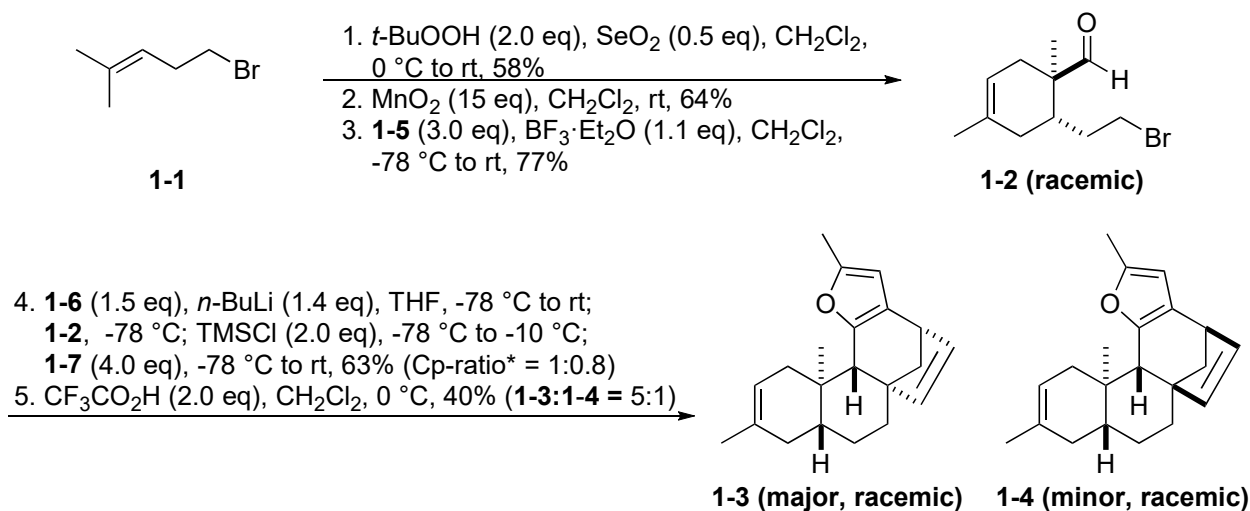


Problem Session (1)

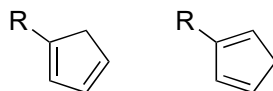
2020/12/19 Yosuke Nakata

Please provide the reaction mechanisms of schemes (1) and (2).

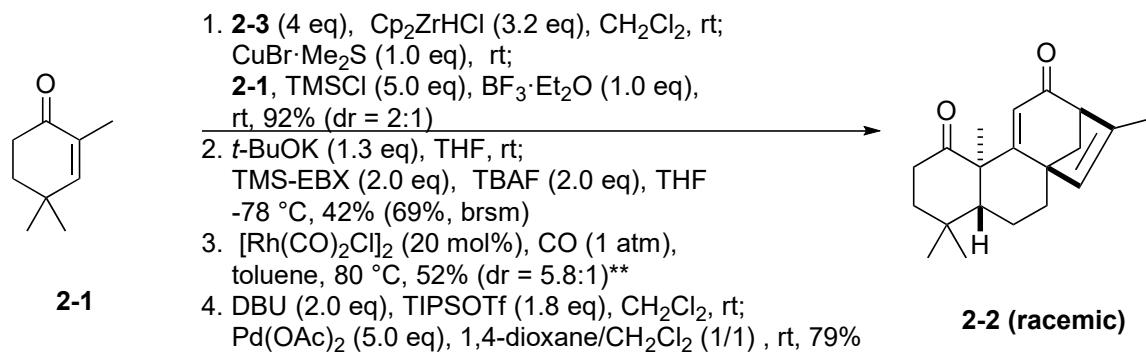
(1)



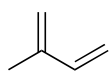
*Cp-ratio means the ratio of the cyclopentadiene regioisomers like the structures shown below.



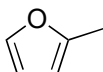
(2)



**Major product was used in the next step.



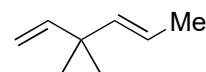
1-5



1-6



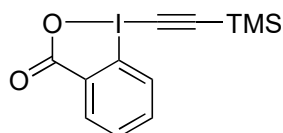
1-7



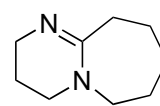
2-3



Cp₂ZrHCl



TMS-EBX



DBU

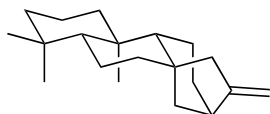
Problem Session (1) -Answer-

2020/12/19 Yosuke Nakata

Topic: Concise construction of ent-kaurene and ent-beyerene type structure

ent-kaurene and ent-beyerene

• 6/6/6/5 ring system containing [3.2.1] bicyclic system



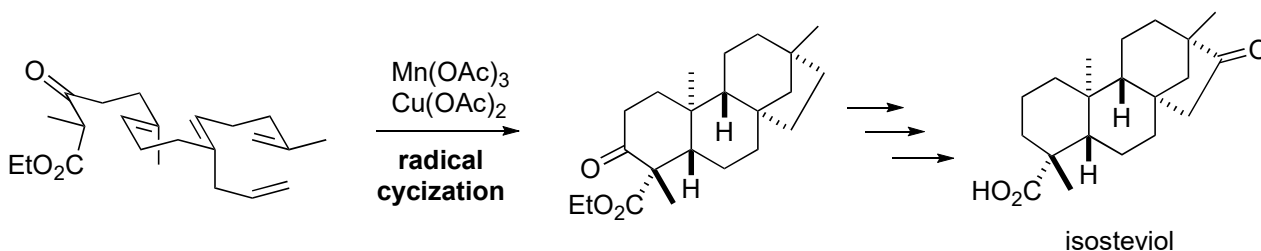
ent-kaurene



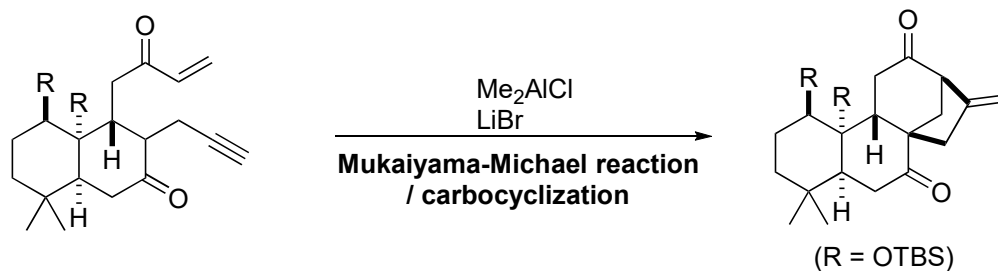
ent-beyerene

• Many natural products possessing these ring systems were isolated and synthesized.

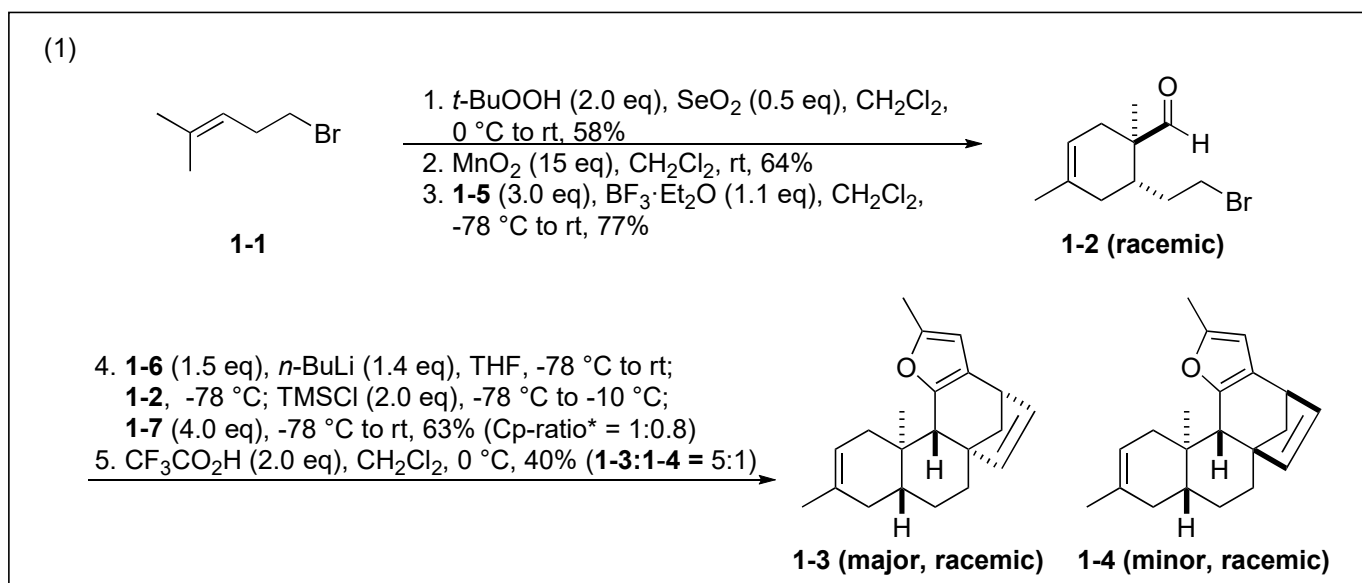
• In total synthesis of these products, multi-step reactions are required to construct the tetracyclic skeleton, especially the [3.2.1] bicyclic octane ring. To scalable synthesis of these compounds, methods for concise construction of the ring system have been investigated.



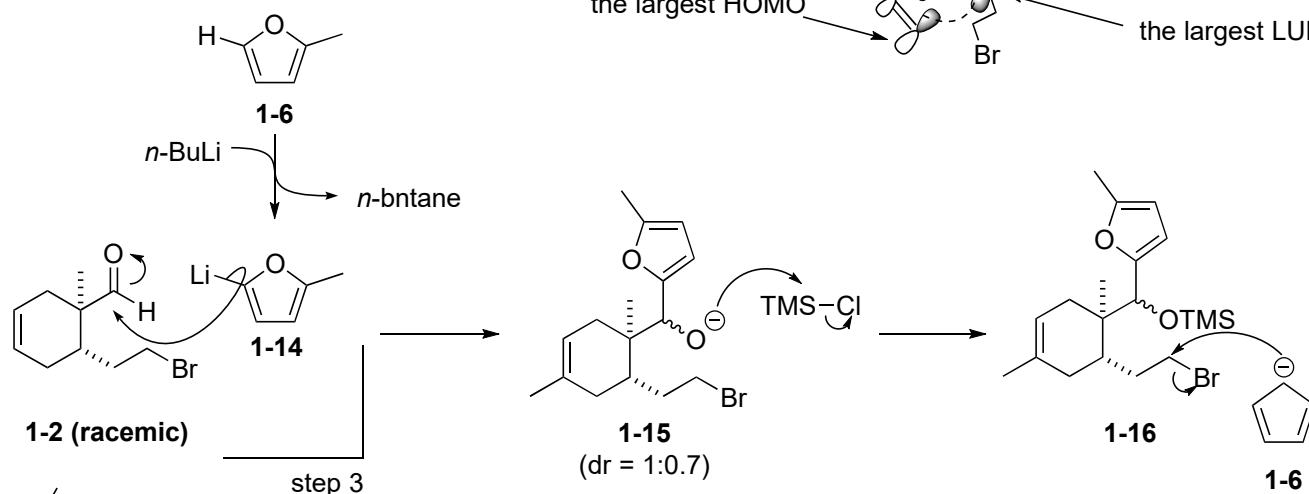
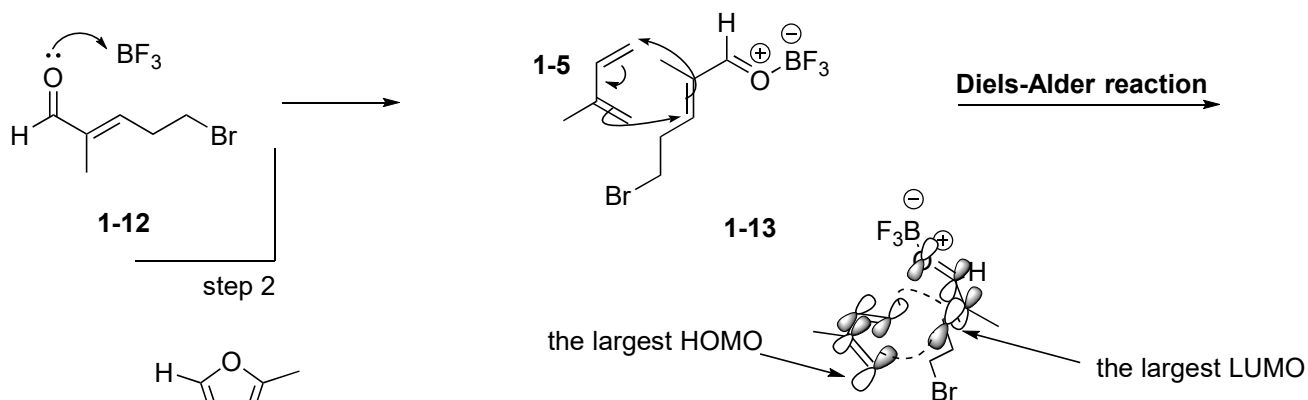
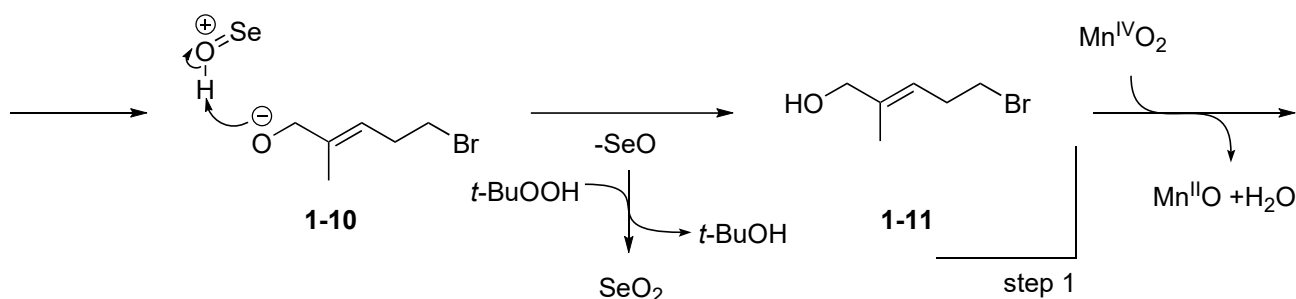
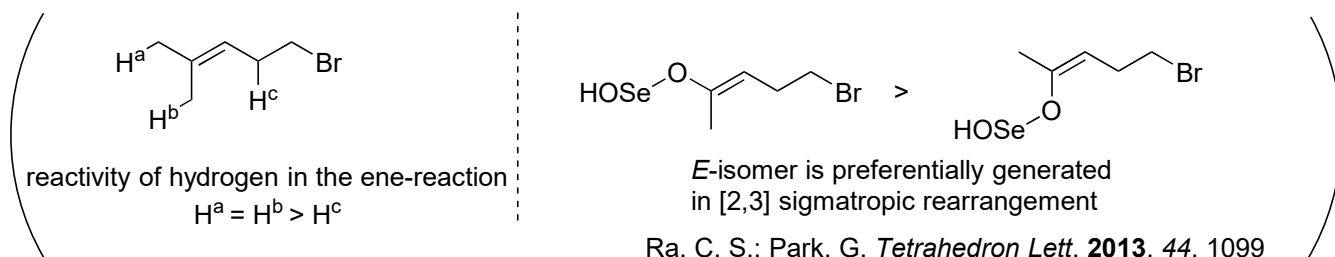
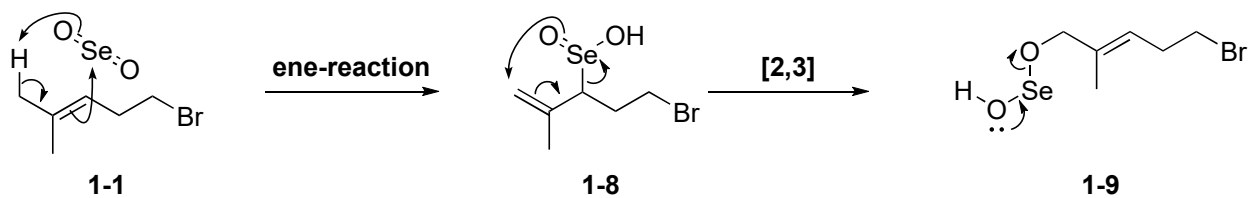
Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945.
(180602_PS_Kotaro_Tokumoto)



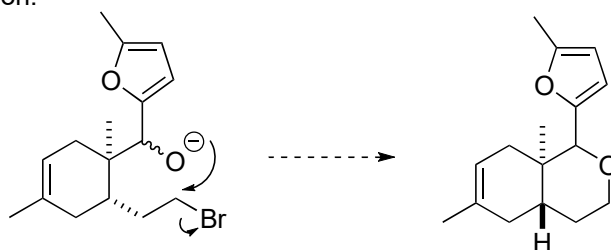
Zhu, L.; Ma, W.; Zhang, M.; Lee, M. M.; Wong, W.; Chan, B. D.; Yang, Q.; Wong, W. T.; Tai, W. C. S.; Lee, C. S. *Nat Commun.* **2018**, *9*, 1283.

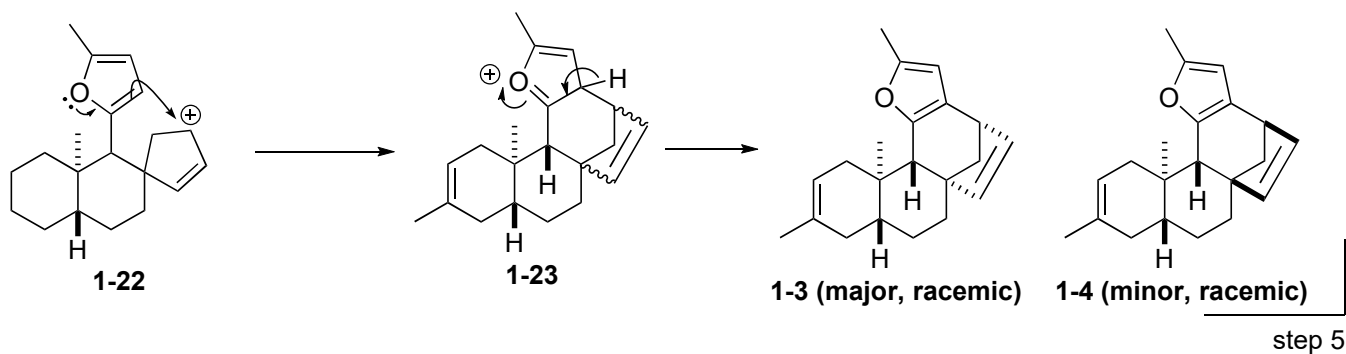
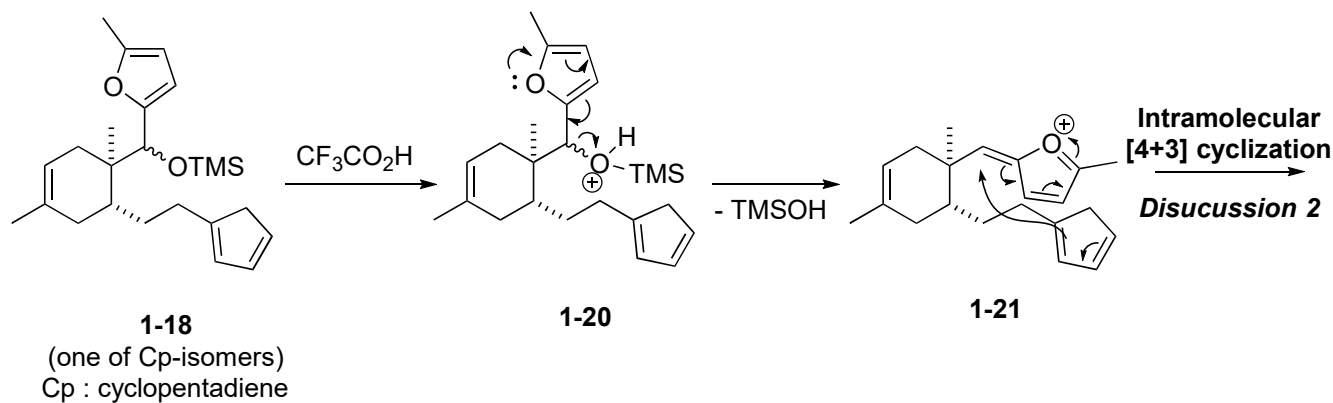
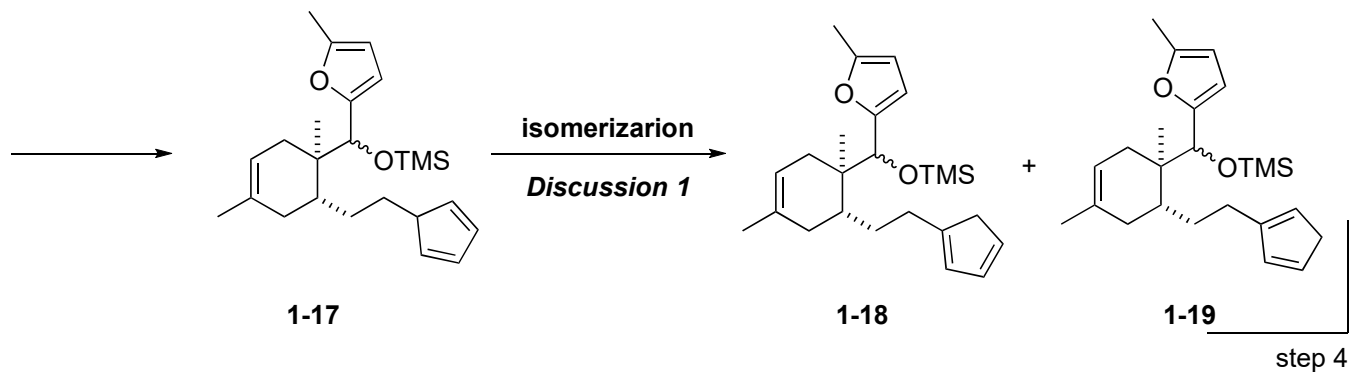


Callebaut, B.; Hullaert, J.; Hecke, V. K.; Winne, M. J.; *Org. Lett.* **2019**, *21*, 310.



TMSCl was used for trapping the alkoxide to avoid intramolecular cyclization by substitution reaction at the other electrophilic position.



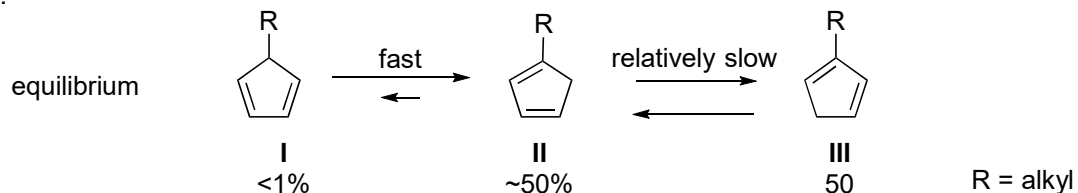


Discussion 1: isomerization

1-1. isomerization of 5-substituted cyclopentadiene

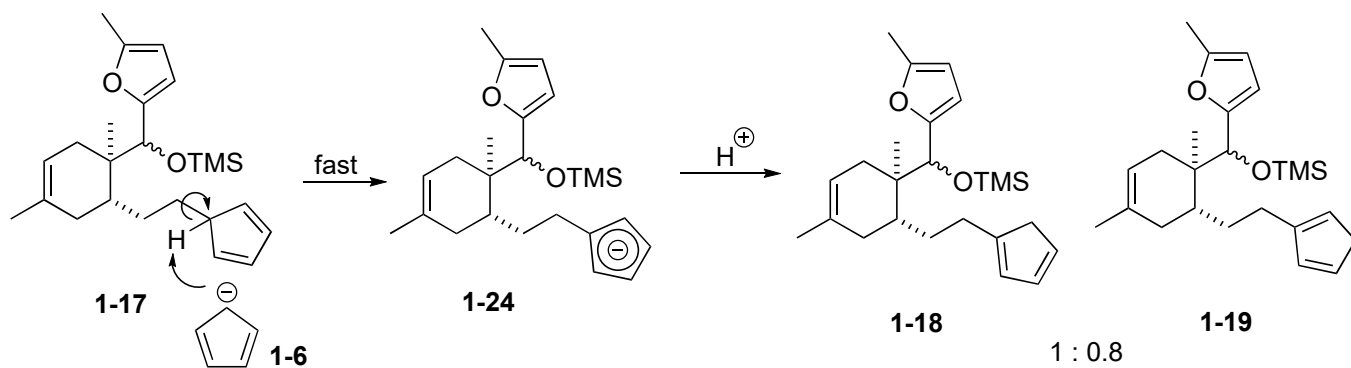
(Mironov. A. V.; Fedorovich. A. D.; Akhrem. A. A. *Russ. Chem. Rev.* **1981**, *50*, 666)

- It is known that 5-substituted cyclopentadiene **I** was unstable and quickly isomerized to 1-substituted isomer **II** via 1,5-hydride shift. **II** is also isomerized to 2-substituted isomer **III** and almost 1:1 mixture of **II** and **III** is obtained.



- This isomerization is accelerated by the presence of strong base and products quickly reach the equilibrium.

1-2. isomerization in this problem



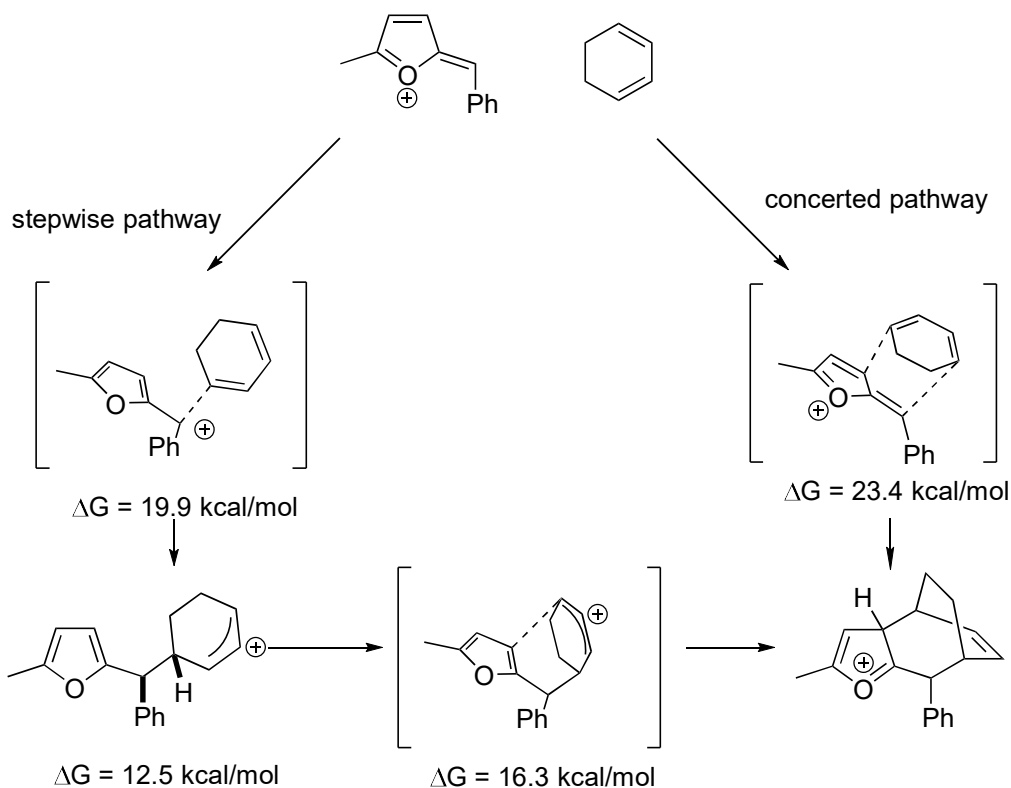
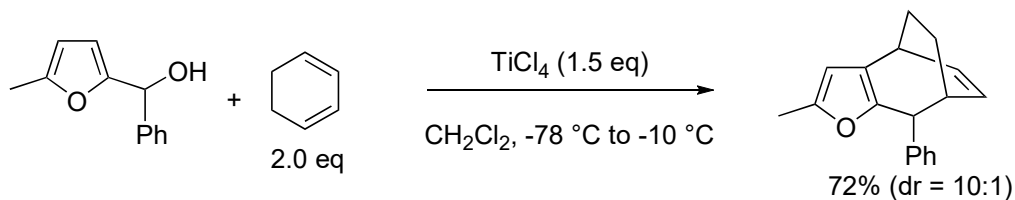
• In this problem, **1-17** is initially generated and quickly converted to **1-18** or **1-19** via **1-24** which is generated by deprotonation with excess **1-6**.

Discussion 2: Intramolecular [4+3] cycloaddition

2-1. stepwise pathway vs concerted pathway

• DFT calculation of similar reaction

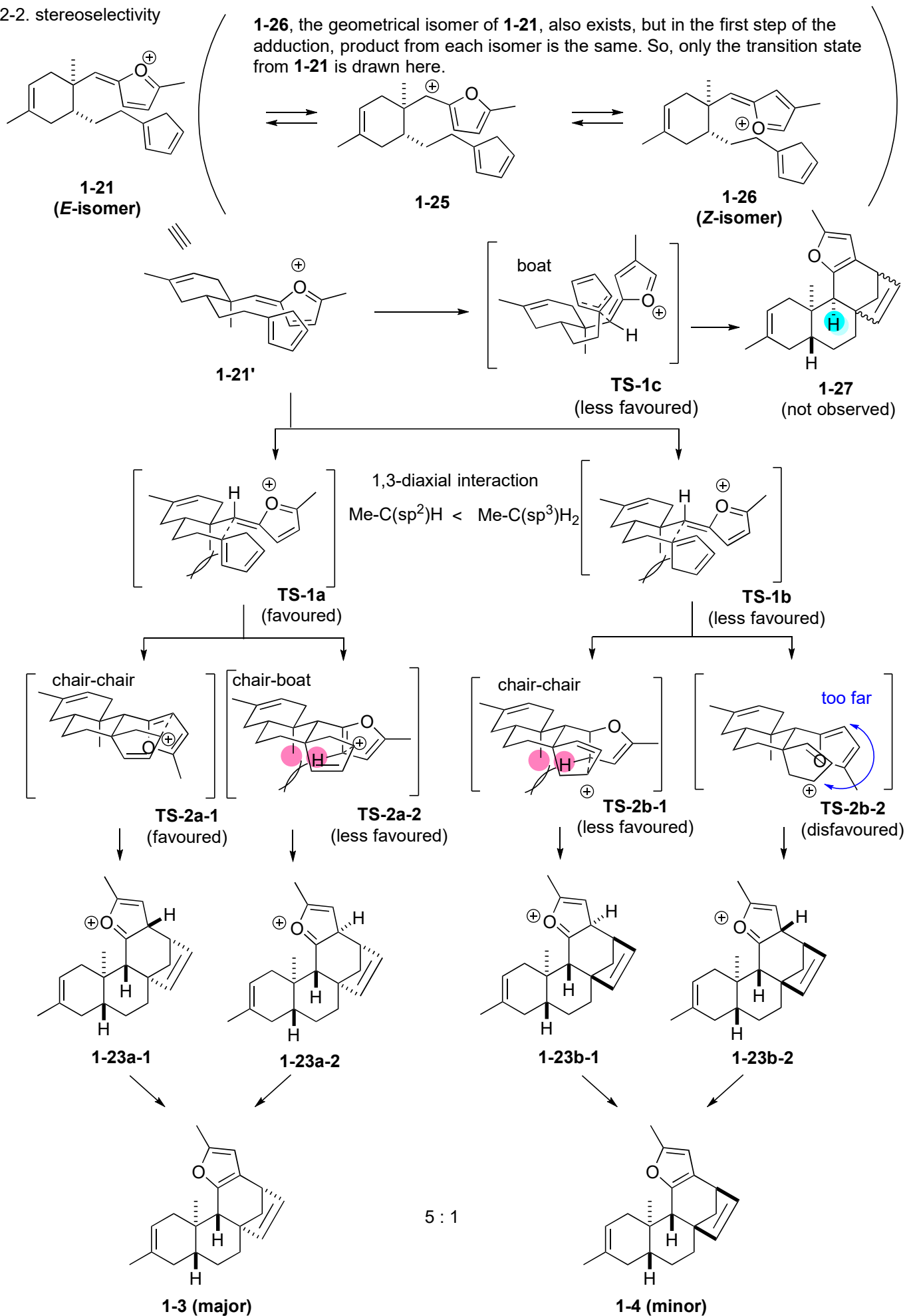
(Winne, J. M.; Catak, S.; Waroquier, M.; Van Speybroeck, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 11990)



calculated at the BMK/6-311+G(d,p)//B3LYP/6-31+G(d,p) level

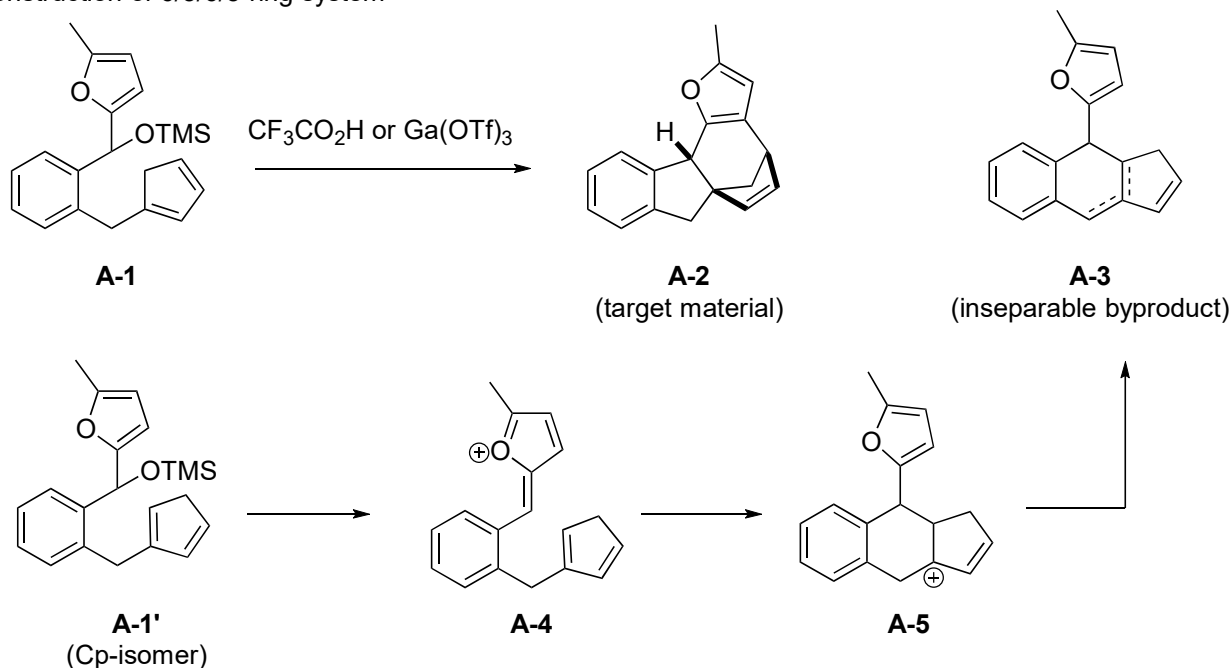
• From DFT calculation, stepwise pathway seems favourable.

2-2. stereoselectivity



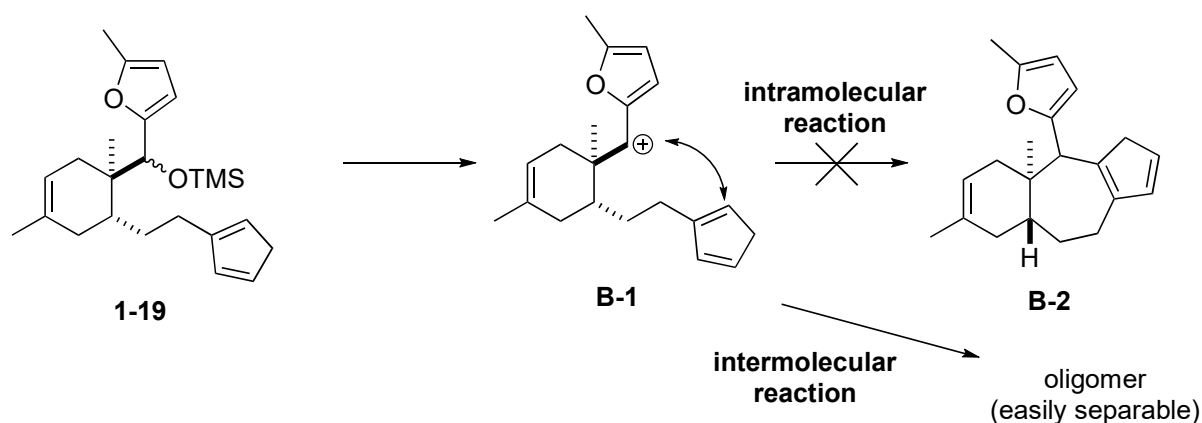
2-3. reaction of another Cp-isomer

A. construction of 6/5/6/5 ring system



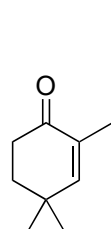
- From Cp-isomer **A-1'**, monocyclized byproduct **A-3** was generated.

B. reaction of 1-19



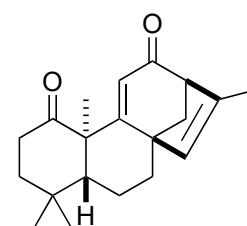
- Compared with the construction of 6/5/6/5 ring system, the distance of the adduct position is farther, leading to the generation of the oligomer via intermolecular reaction instead of monocyclized product via intramolecular reaction.

(2)



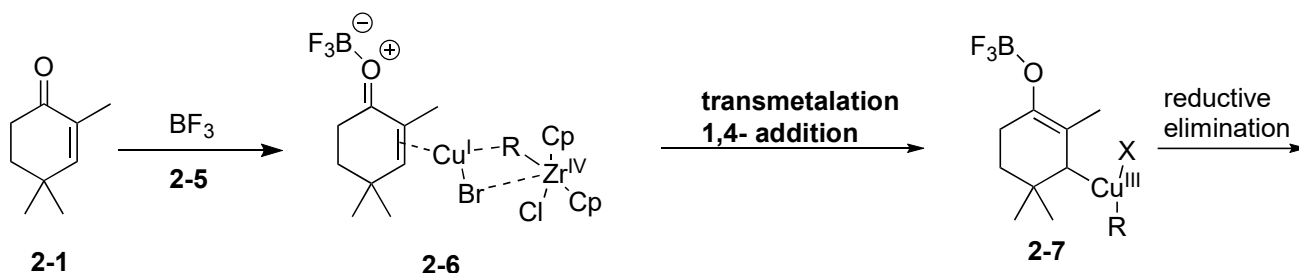
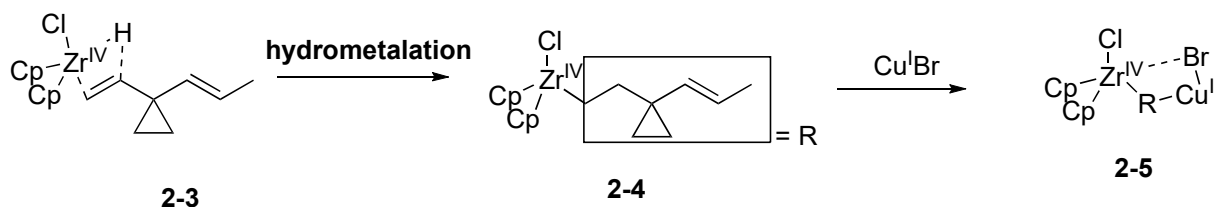
2-1

1. **2-3** (4 eq), Cp_2ZrHCl (3.2 eq), CH_2Cl_2 , rt; $\text{CuBr}\cdot\text{Me}_2\text{S}$ (1.0 eq), rt; **2-1**, TMSCl (5.0 eq), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.0 eq), rt, 92% (dr = 2:1)
2. *t*-BuOK (1.3 eq), THF, rt; TMS-EBX (2.0 eq), TBAF (2.0 eq), THF -78°C , 42% (69%, brsm)
3. $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (20 mol%), CO (1 atm), toluene, 80°C , 52% (dr = 5.8:1)**
4. DBU (2.0 eq), TIPSOTf (1.8 eq), CH_2Cl_2 , rt; $\text{Pd}(\text{OAc})_2$ (5.0 eq), 1,4-dioxane/ CH_2Cl_2 (1/1), rt, 79%

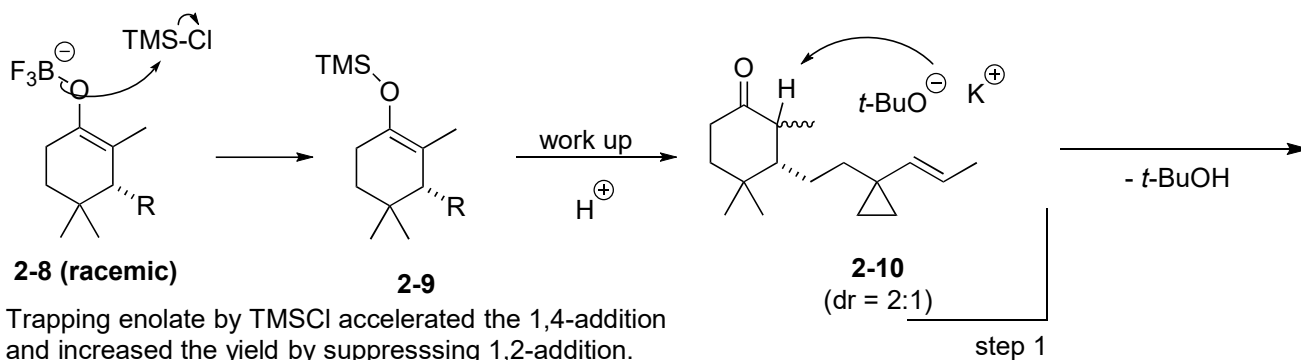


2-2 (racemic)

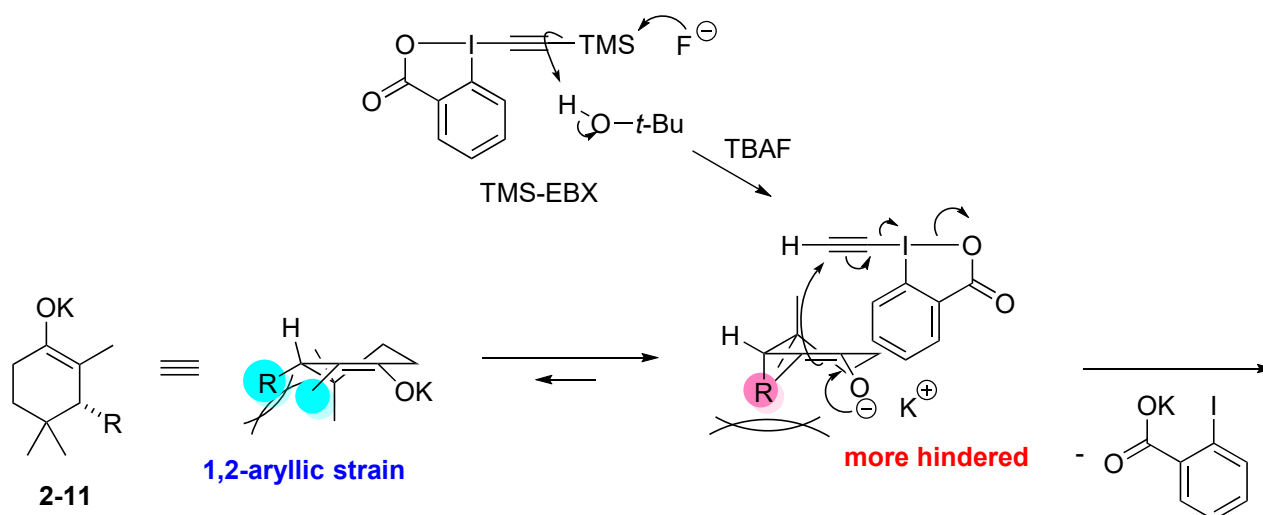
**Major product was used in the next step.



- In the reaction of alkylzirconocenes and Cu(I), ate complex via transmetalation is not generated because alkyl groups are worse bridging ligand than alkenyl groups.
 - The generation of Cu(III) intermediate is hypothesized, but the order and detail mechanism of transmetalation and 1,4-addition have not been known.
- (Wipf, P.; Xu, W.; Smitrovich, H. J.; Lehmann, R.; Venanzi, M. L. *Tetrahedron*. **1994**, *50*, 1935)



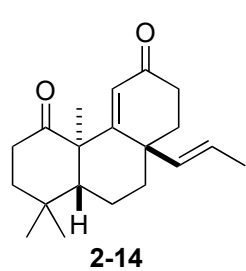
Trapping enolate by TMS-Cl accelerated the 1,4-addition and increased the yield by suppressing 1,2-addition. (Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.)



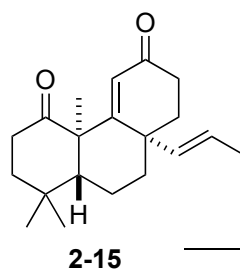
2-12

2-13

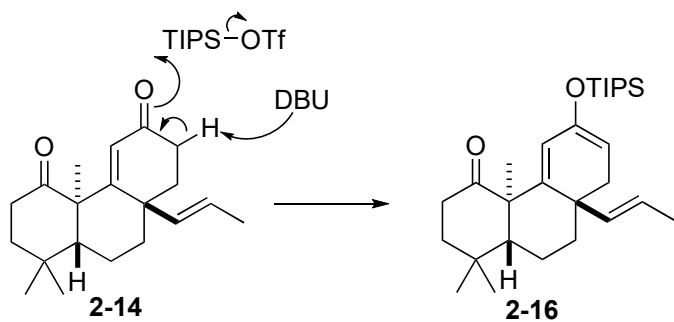
step 2



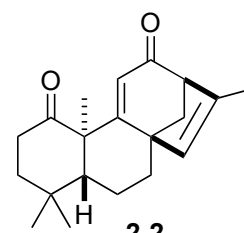
5.8 : 1



step 3



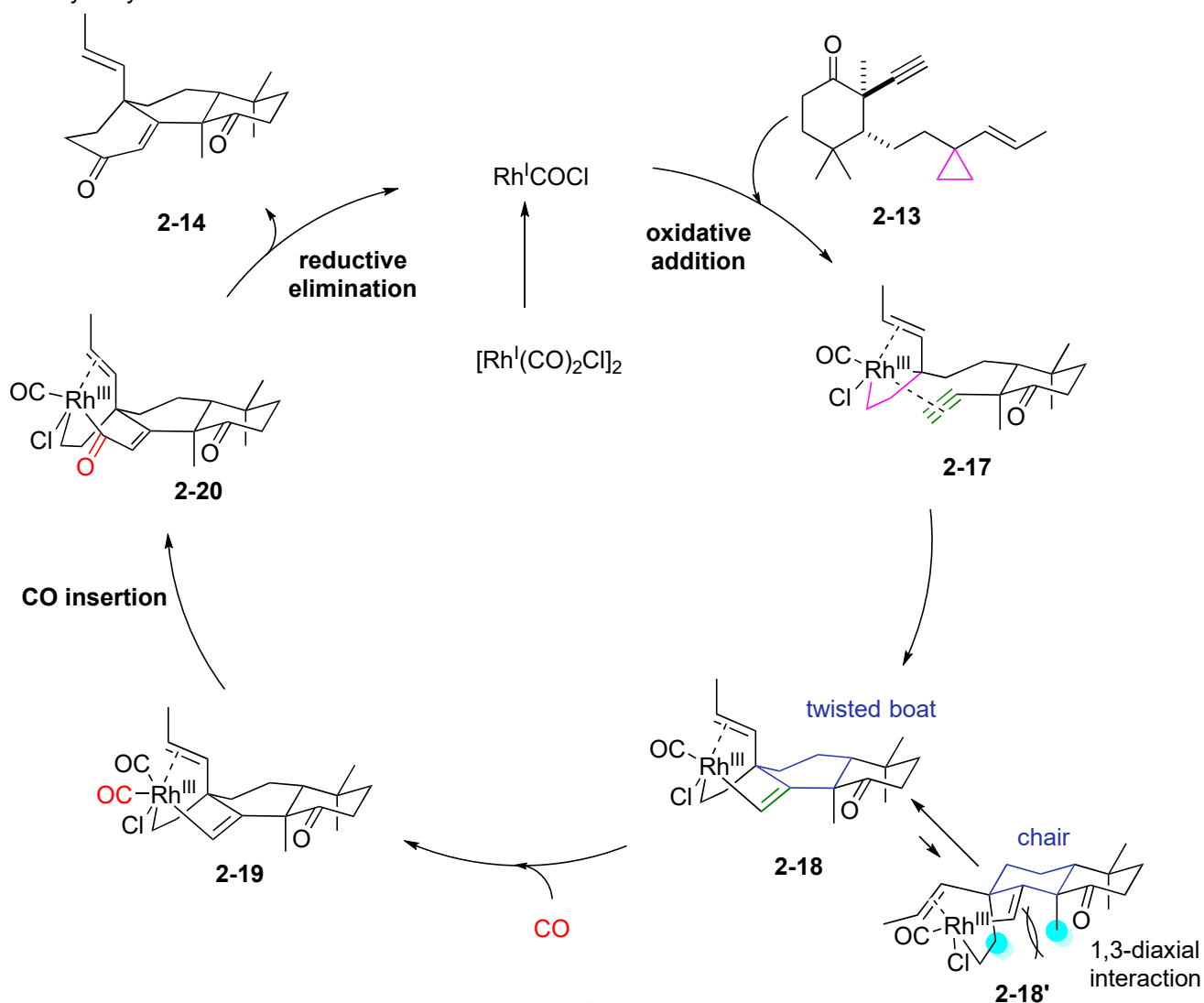
$\xrightarrow{\text{Pd}^{\text{II}}(\text{OAc})_2}$
cycloalkenylation
Discussion 2



step 4

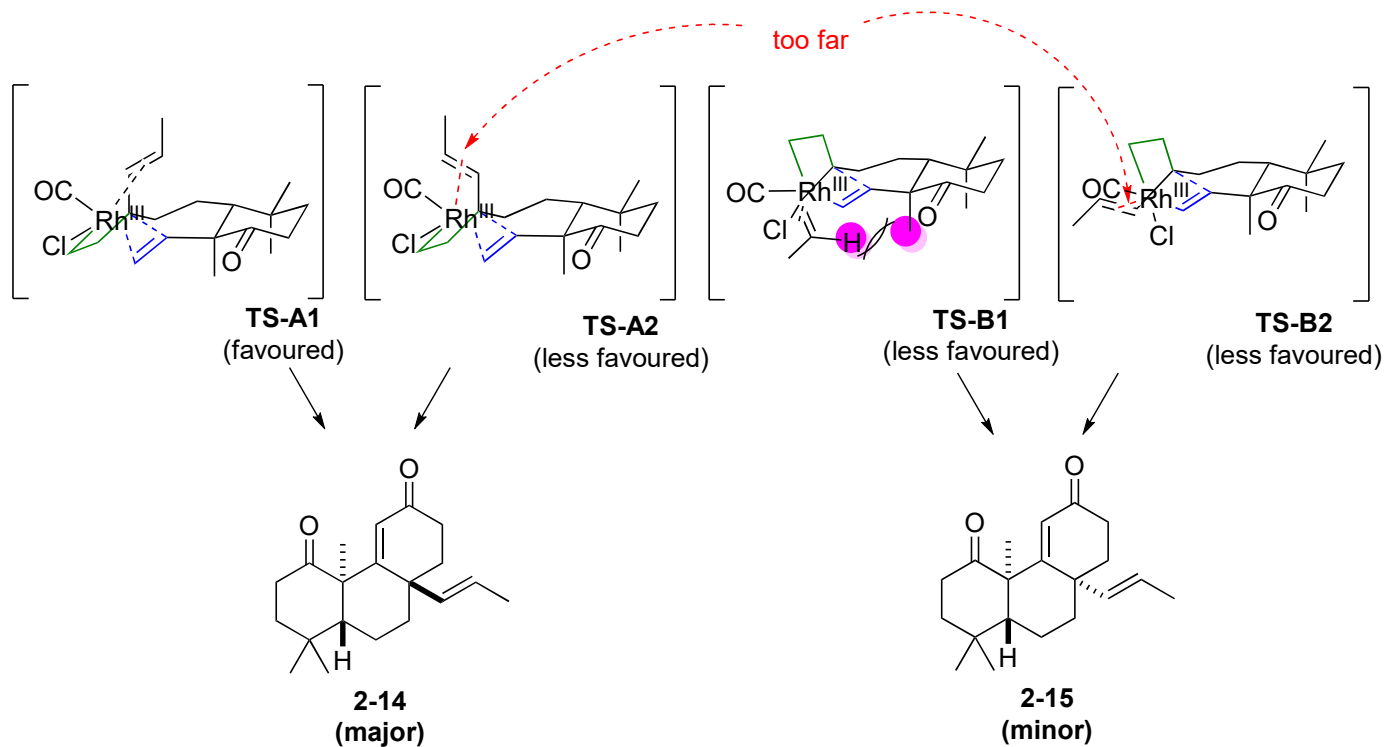
Discussion 1: [3+2+1] cycloaddition

1-1. catalytic cycle



1-2. stereoselectivity

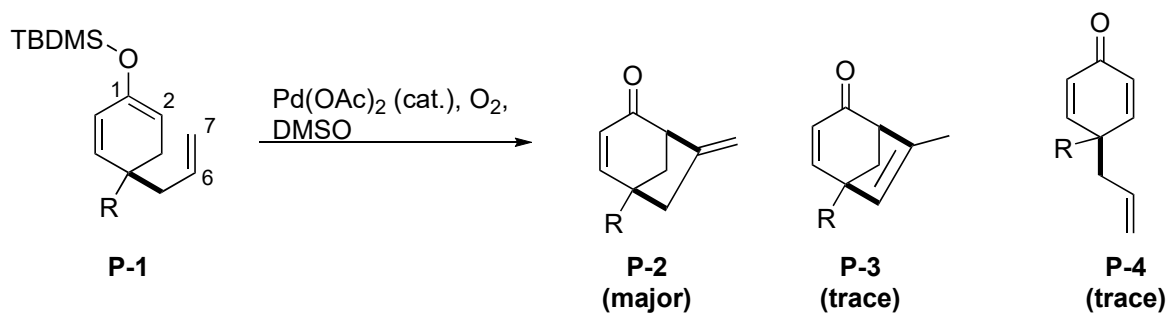
In transition state, Rh is nearer to C=C bond derived from alkyne than to C-C bond derived from cyclopropane because the former is shorter than the latter. So C=C bond of alkene favourably directs to the former in coordinating with Rh.



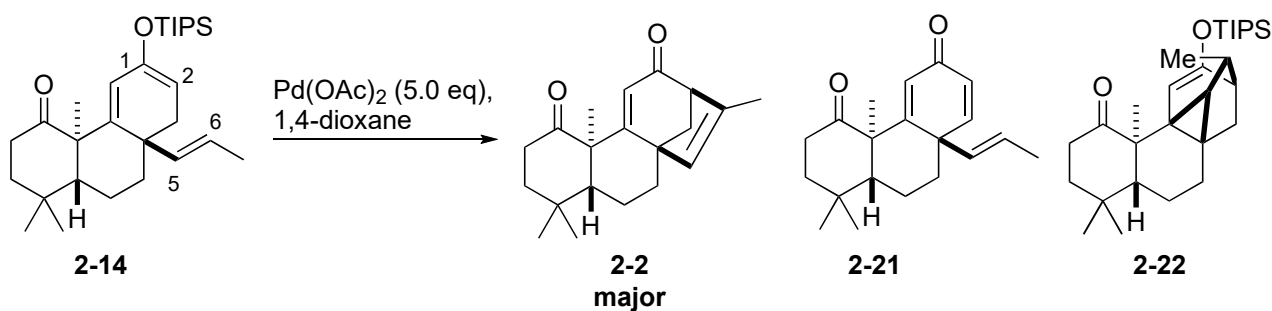
discussion 2: cycloalkenylation

2-1. comparison with previous scheme to construct bicyclo[3,2,1] octane ring

(1) previous scheme (Toyota, M.; Rudyanto, M.; Ihara, M. *J. Org. Chem.* **2002**, 67, 3374)

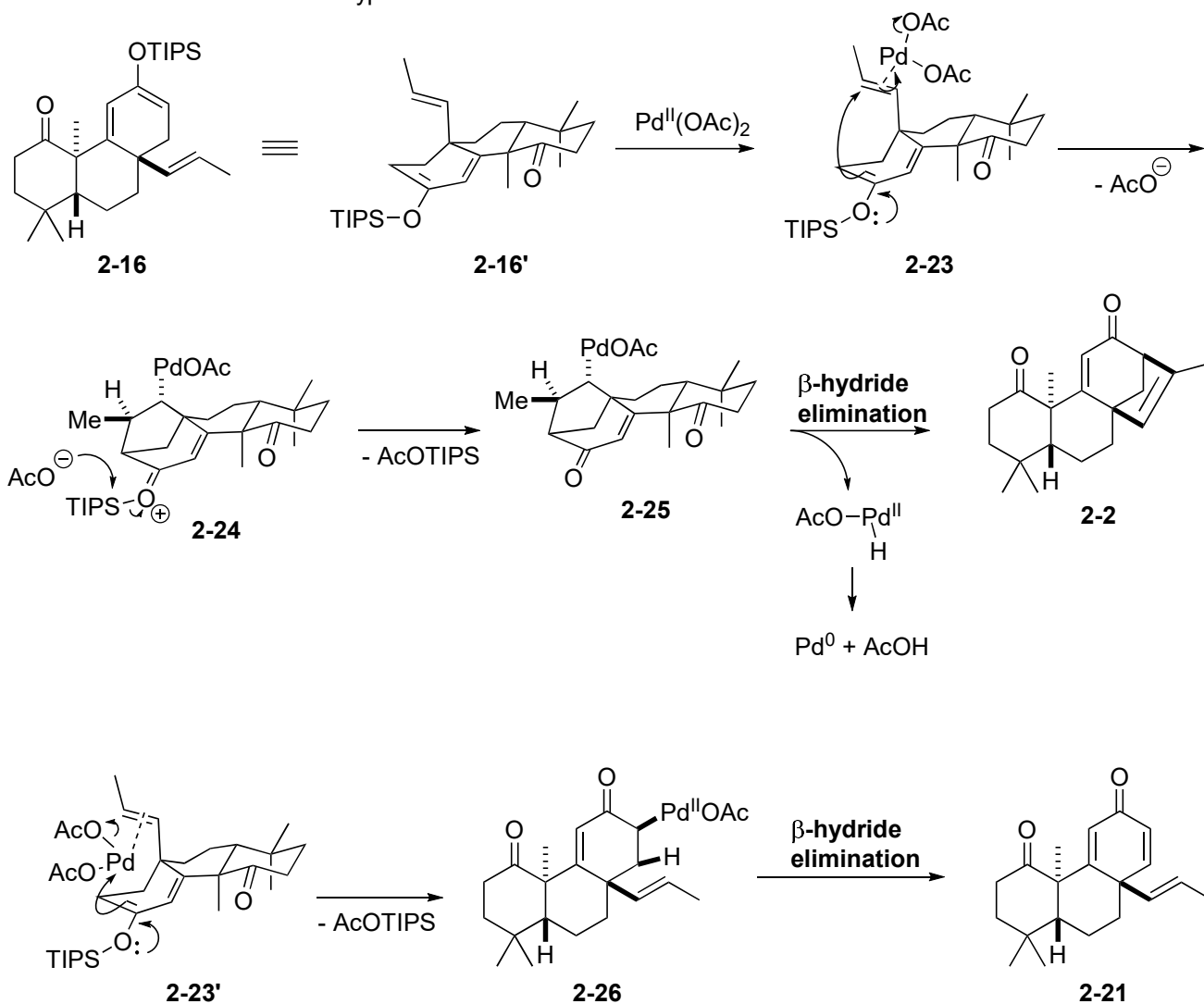


(2) this problem

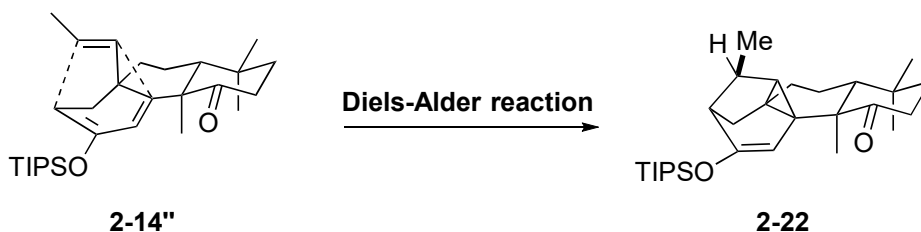


• In the previous scheme, Saegusa oxidation product **P-4** was generated as a byproduct. In this problem, intramolecular Diels-Alder product **2-22** was also produced other than Saegusa oxidation product **2-21**.

2-2. schemes to obtain **2-2** and byproducts



- The generation of **2-21** was suppressed by using 1,4-dioxane as solvent instead of DMSO. Less polarity of 1,4-dioxane inhibited this Saegusa-Ito oxidation.



- The generation of **2-22** was suppressed decreasing the reaction temperature.