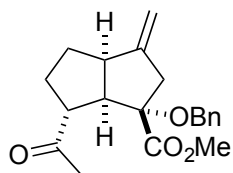


Problem Session (3)

2016. 12. 10. Daiki Kamakura

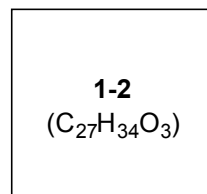
- 1) Please provide the reaction mechanisms.
- 2) Please fill in the blanks **1-2**, **2-2** and **2-4**.

1

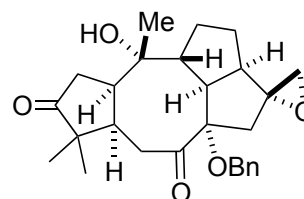


1-1
(C₂₀H₂₄O₄)

1. *t*-BuLi, **A**, THF, -78 °C, 88%
2. Tebbe reagent, pyridine
THF, toluene, -40 °C to rt
3. *p*-cymene, 130 °C, 85% (2 steps)
4. TBAF, THF, 91%

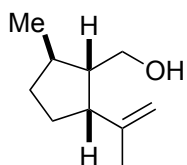


1. *m*-CPBA (3.5 eq.), NaHCO₃, CH₂Cl₂, 86% (dr = 6.5 : 1)
2. TPAP (3 mol%), NMO (1.5 eq), Et₃N, CH₂Cl₂, MS4A, 84%
3. H₂, Pd/C, EtOAc, 92%



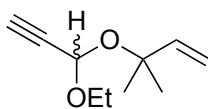
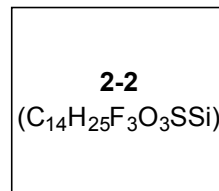
1-3
(C₂₇H₃₄O₅)

2



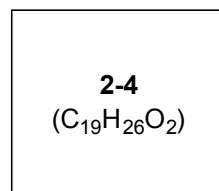
2-1
(C₁₀H₁₈O)

1. *n*-BuLi (3 eq.), *t*-BuOK (3 eq.), -20 °C to 0 °C
; TMSCl (3 eq.), -78 °C
2. K₂CO₃, MeOH, 50% (2 steps, brsm: 78%)
3. Tf₂O, 2,6-di-*t*-butyl-4-methylpyridine
-30 °C to -10 °C



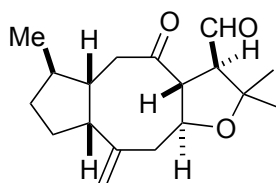
2-3
(C₁₀H₁₆O₂, racemic)

1. *n*-BuLi, HMPA; **2-2**, -35 °C to rt
74% (2 steps, dr = 1 : 1)
2. Co₂(CO)₈, Et₂O
3. TMSOTf, Et₂O, -78 °C
82% (2 steps, dr = >20 : 1)
4. NMO, CH₂Cl₂, 85% (dr = 11 : 1)

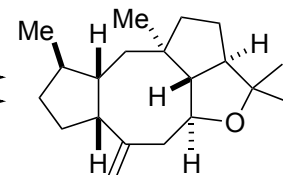


1. Li, NH₃, THF, -78 °C ; isoprene, NH₄Cl
66% (+9% of a minor isomer)
2. KN(TMS)₂ (4 eq.), HMPA, THF
; Davis reagent (5 eq.), -78 °C
3. NaHB(OAc)₃, THF, 74% (2 steps)
4. Pb(OAc)₄, EtOAc
5. DBU, CH₂Cl₂*
61% (2 steps + 6% of a minor isomer)

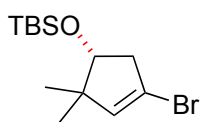
*In this reaction two isomers were formed. After column chromatography, the same reaction was conducted using a minor isomer.



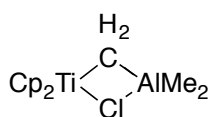
2-5
(C₁₈H₂₆O₃)



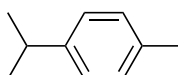
(+)-epoxydictymene (**2-0**)



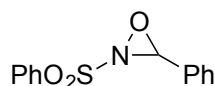
A
(C₁₃H₂₅BrOSi)



Tebbe reagent



p-cymene

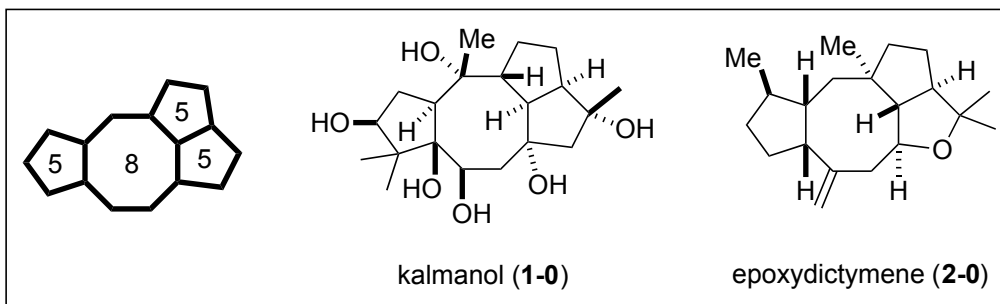


Davis reagent

Problem Session (3)-Answer

2016. 12. 10. Daiki Kamakura

Topic: Diterpene having a 5/8/5/5 ring system



0-1. Introduction to kalmanol (1-0)

Isolation: from *Kalmia angustifolia*

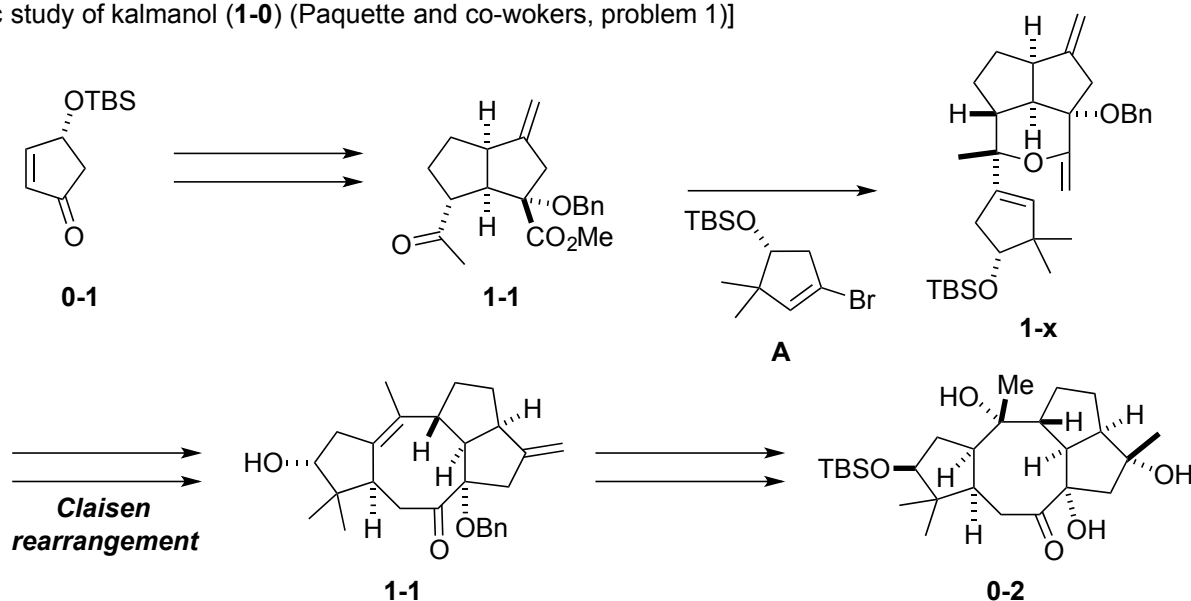
Burke, J. W.; Duskotch, R. W. Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5832

Biological activity: cardiotoxic activity

Structural features: highly oxygenated (having six OH groups) 5/8/5/5 skeleton

Synthetic study: Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727.

[Synthetic study of kalmanol (1-0) (Paquette and co-workers, problem 1)]



0-2. Introduction to epoxydictymene (2-0)

Isolation: from *Dictyota dichotoma*

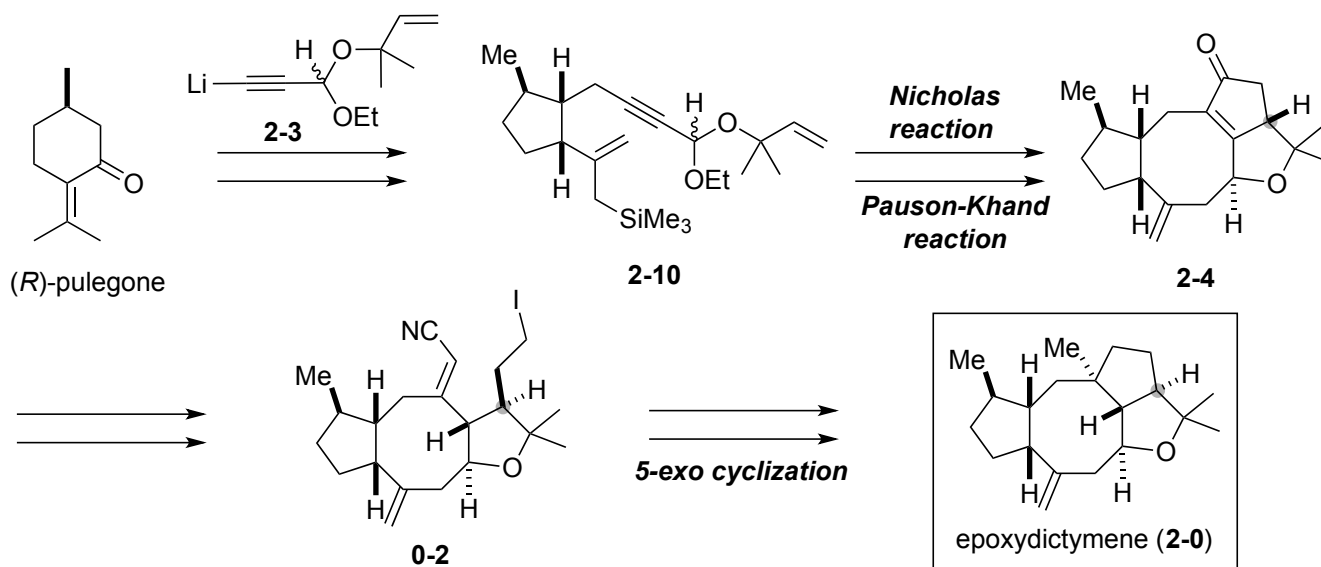
Enoki, N.; Furusaki, A.; Suehiro, K.; Ishida, R.; Takeshi, M. *Tetrahedron Lett.* **1983**, *24*, 4341

Structural features: 5/8/5/5 skeleton include *trans*-fused 5/5 moiety

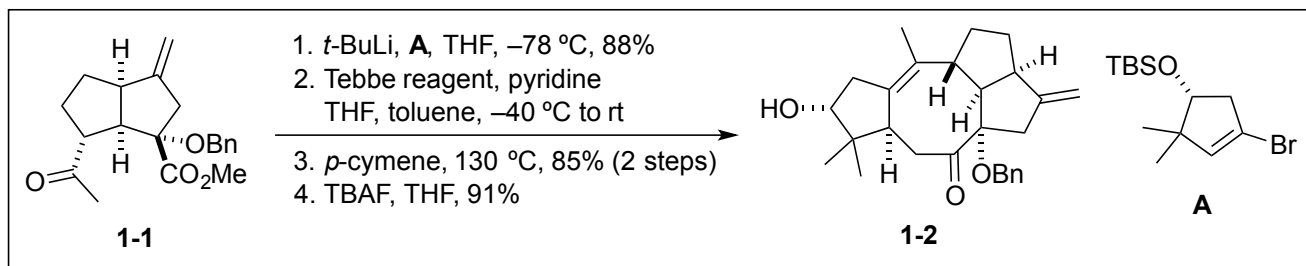
Total synthesis: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.

Paquette, L. A.; Sun, L.-Q.; Friedrich, S. D.; Savage, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 8438.

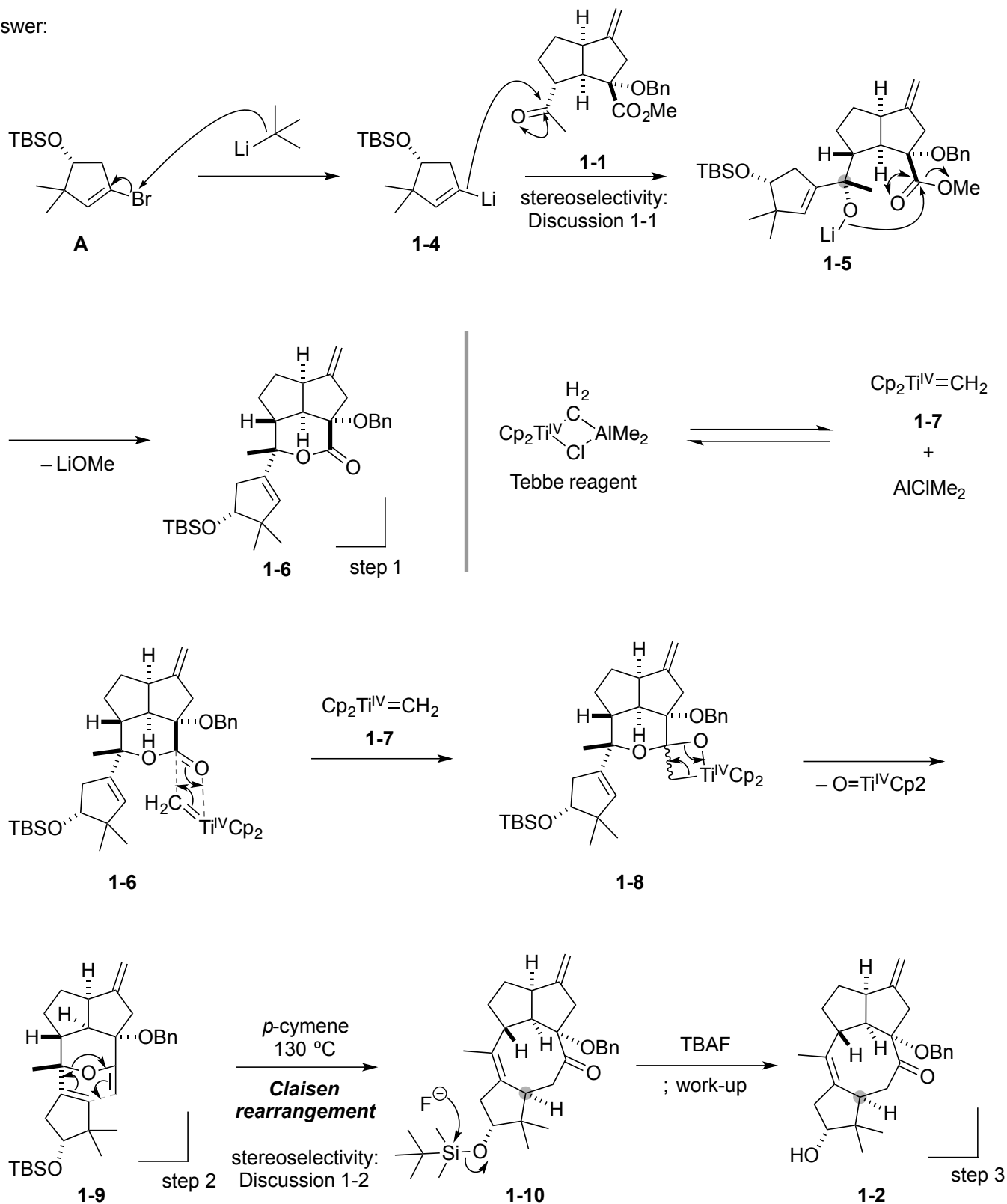
[Asymmetric total synthesis of epoxydictymene (2-0) (Schreiber and co-workers, problem 2)]



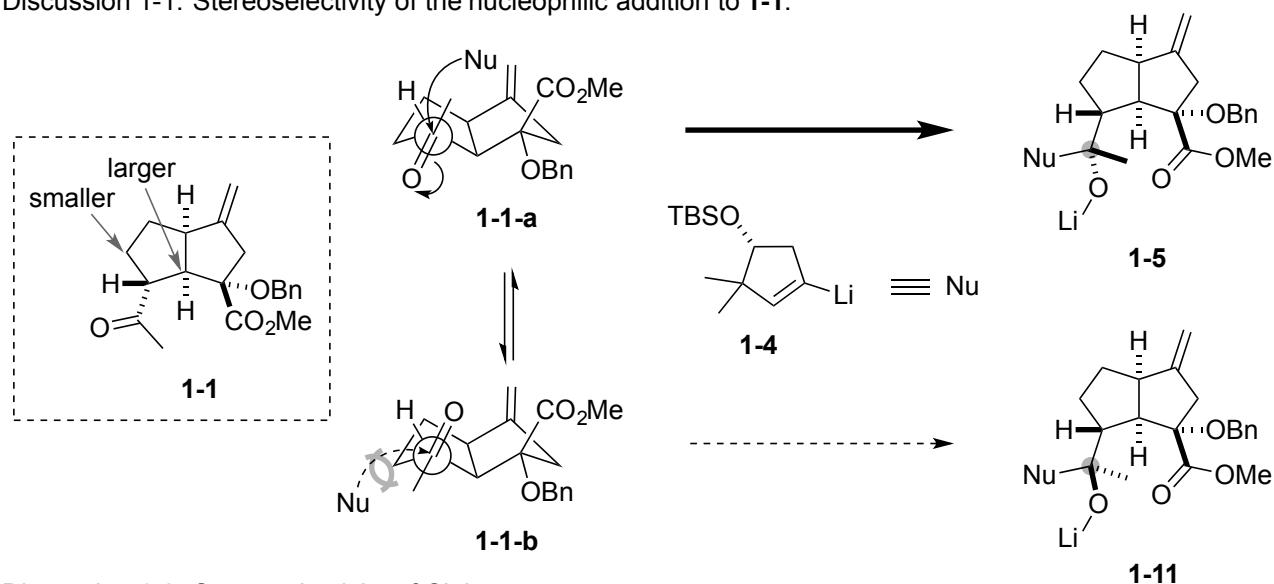
1-1) transformation from **1-1** to **1-2**.



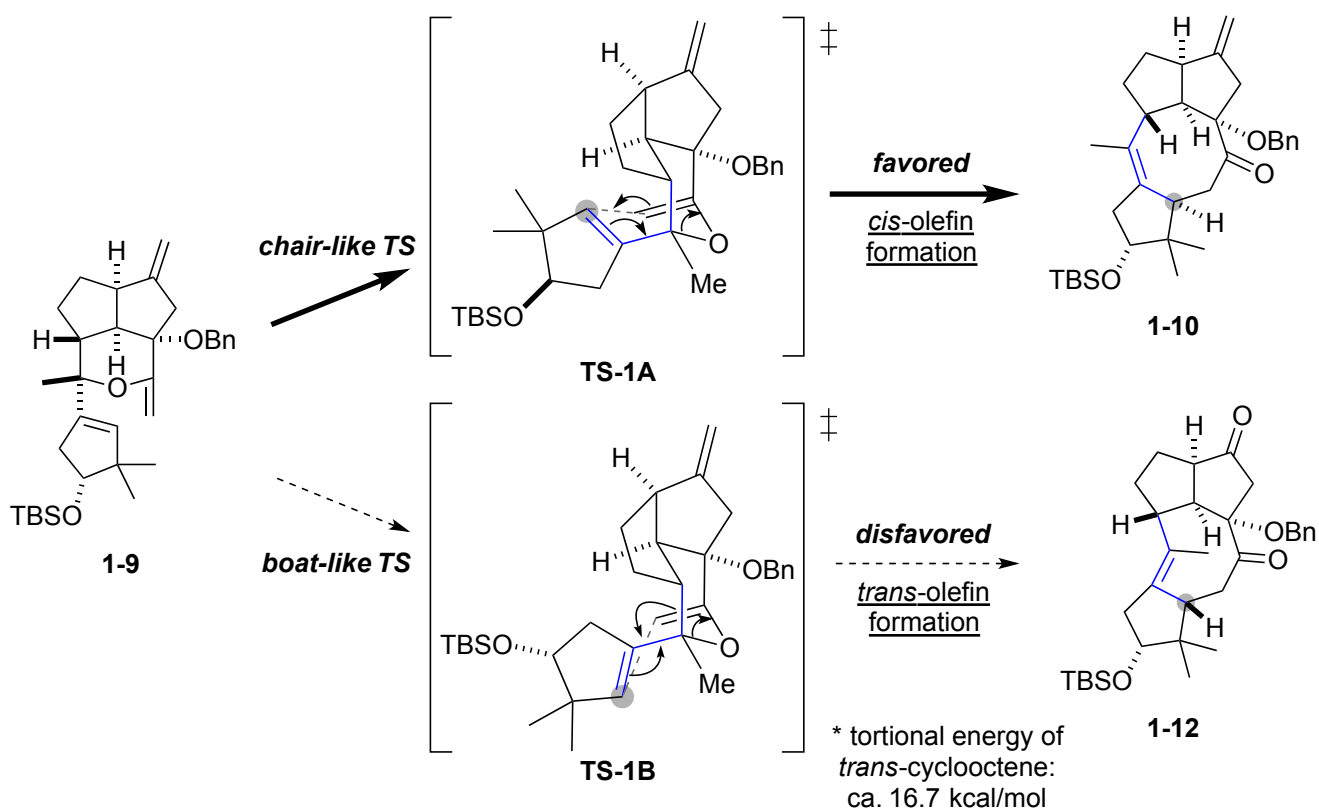
Answer:



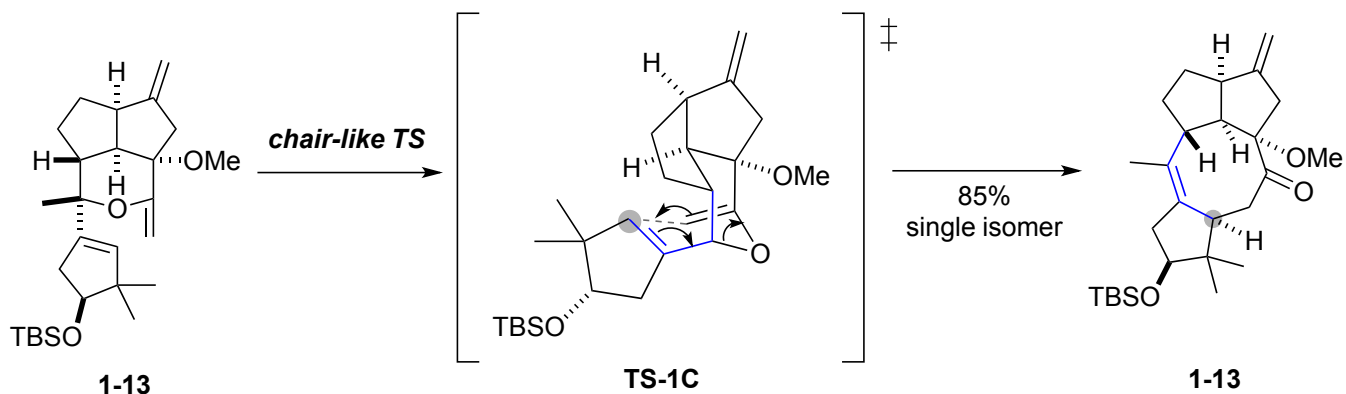
Discussion 1-1: Stereoselectivity of the nucleophilic addition to **1-1**.



Discussion 1-2: Stereoselectivity of Claisen rearrangement

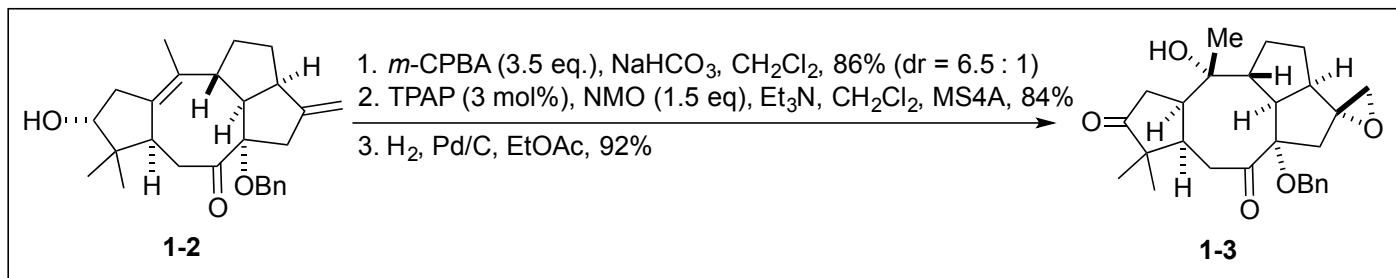


<Claisen rearrangement using **1-13**>

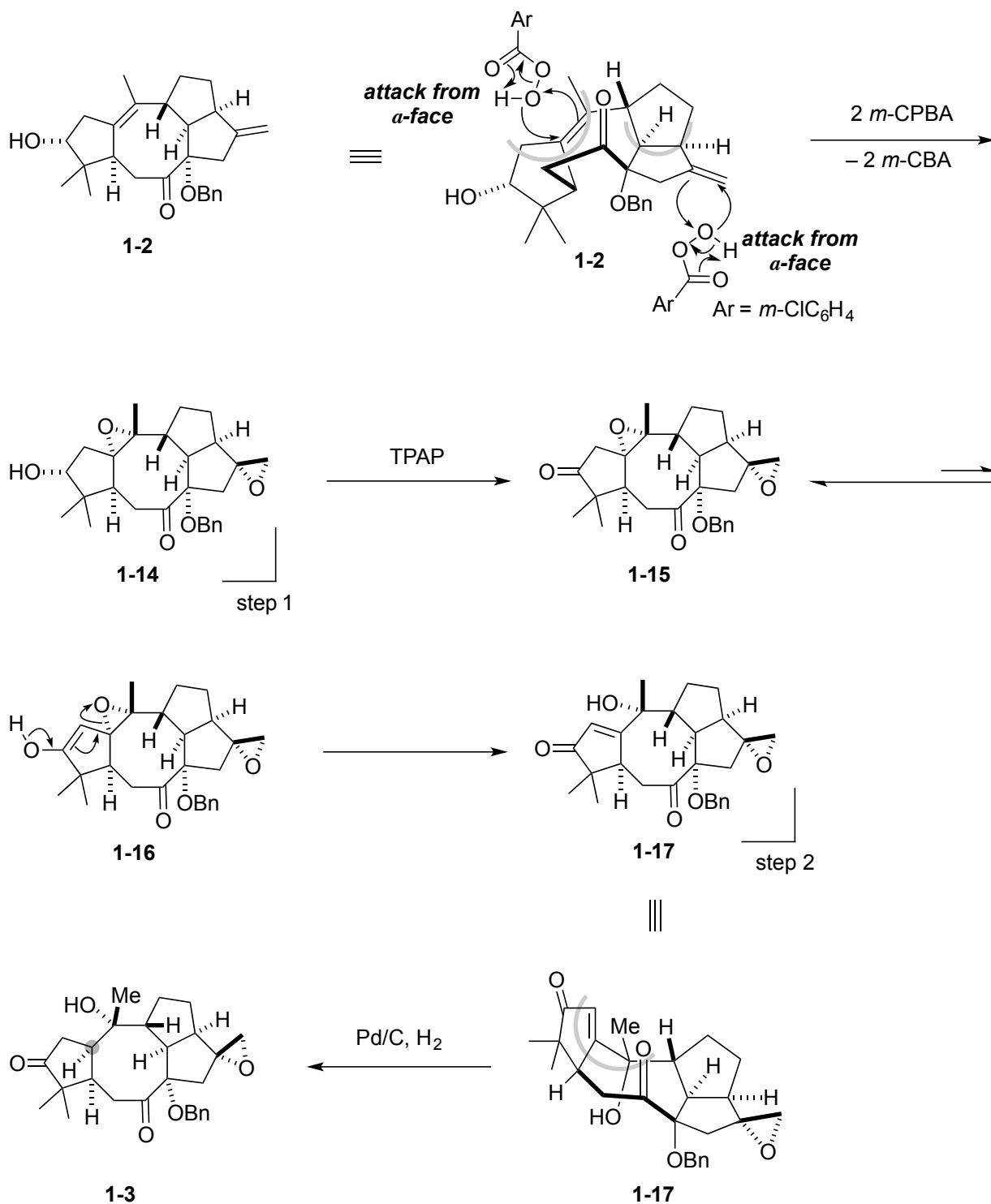


⇒ Stereochemistry of siloxy group was not affected the stereoselectivity at the highlighted position

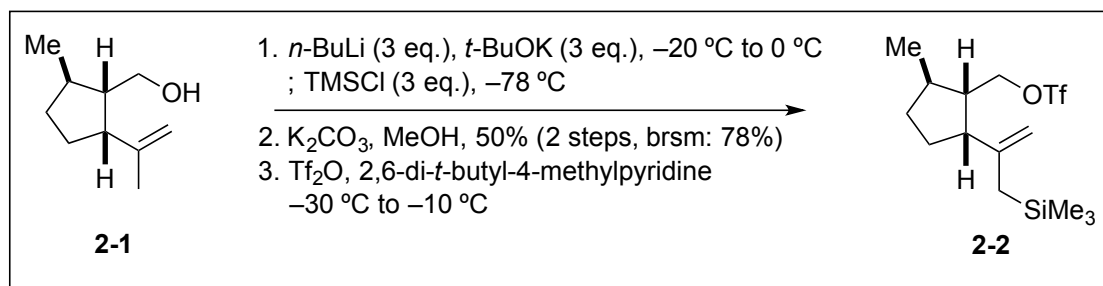
1-2) transformation from 1-2 to 1-3.



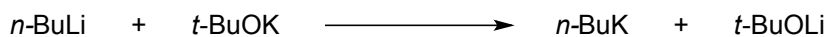
Answer:



2-1) transformation from **2-1** to **2-2**.



Answer:



bond dissociation energy

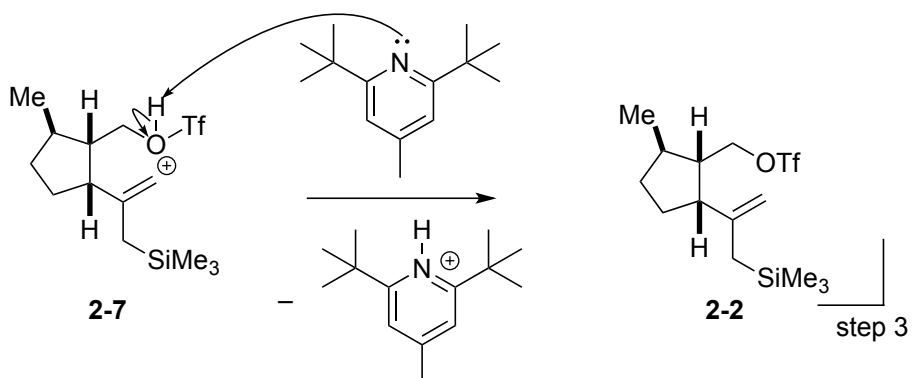
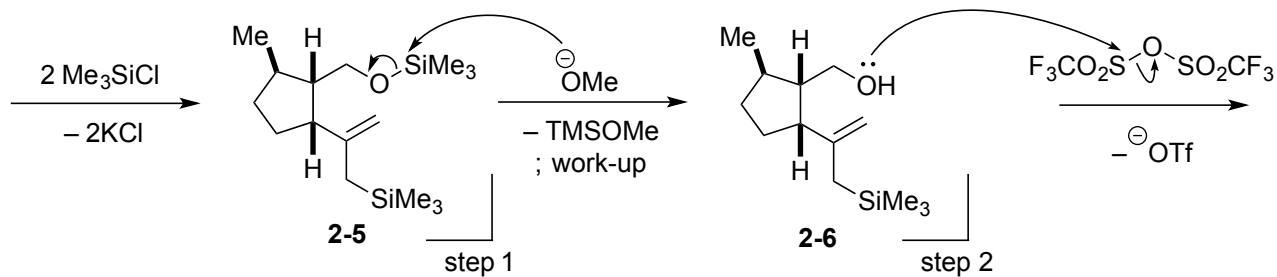
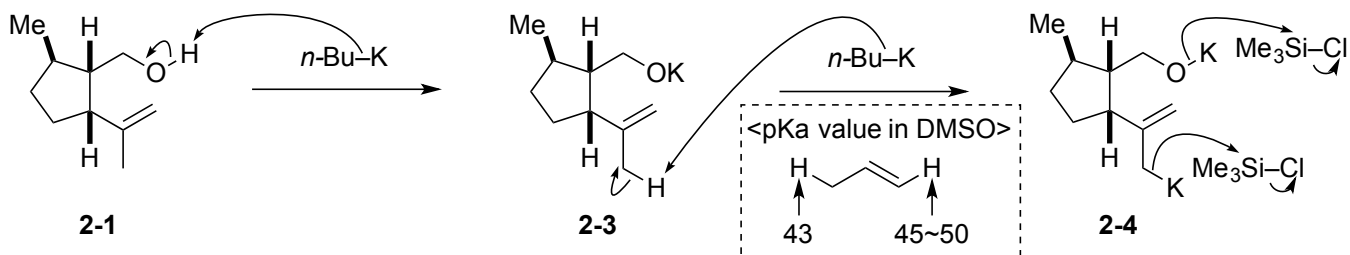
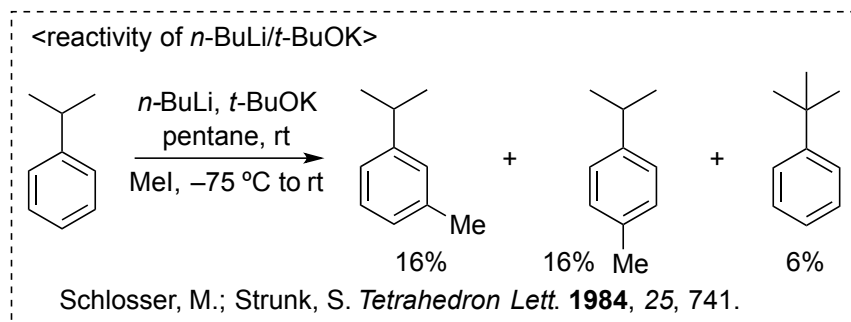
O-Li: 81.6 kcal/mol

O-K: 56.0 kcal/mol

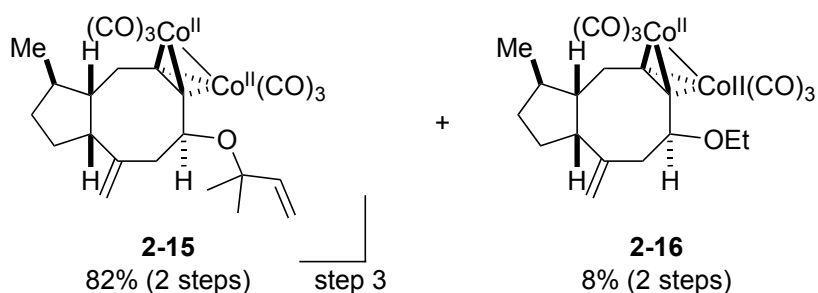
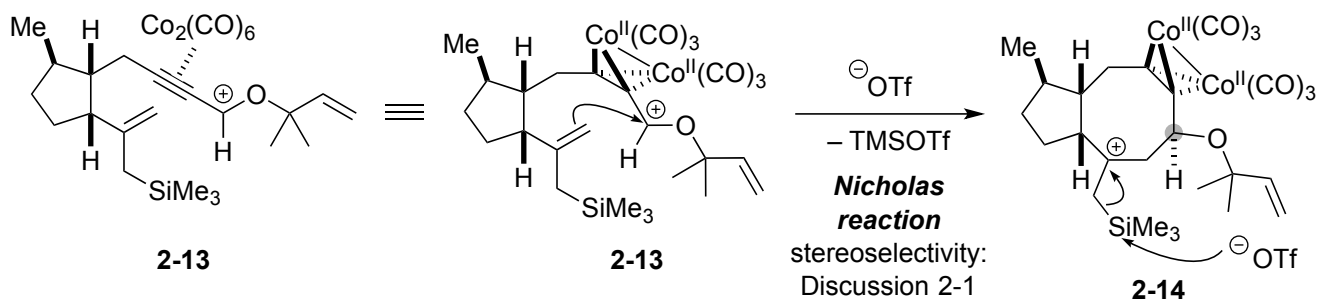
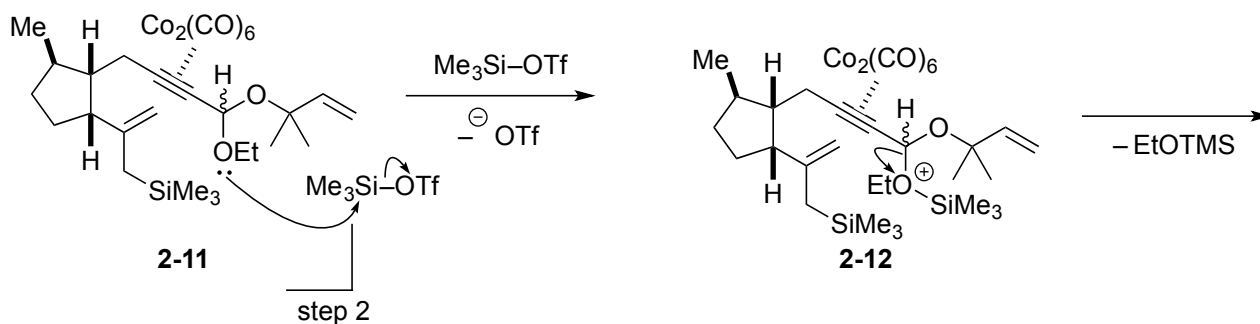
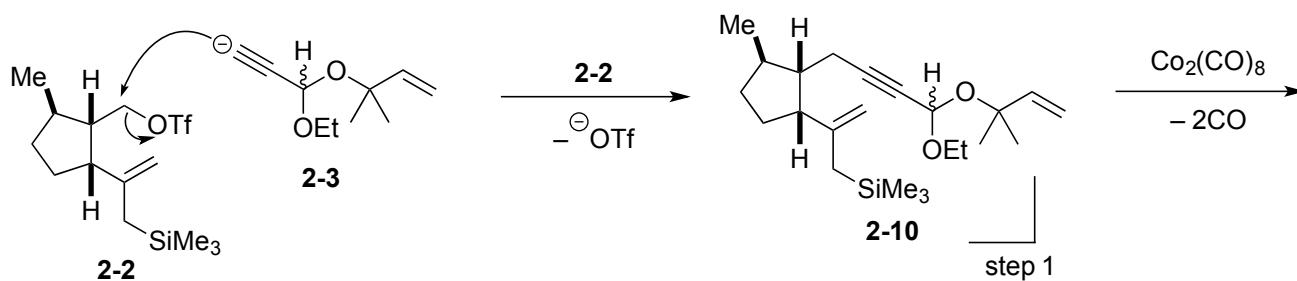
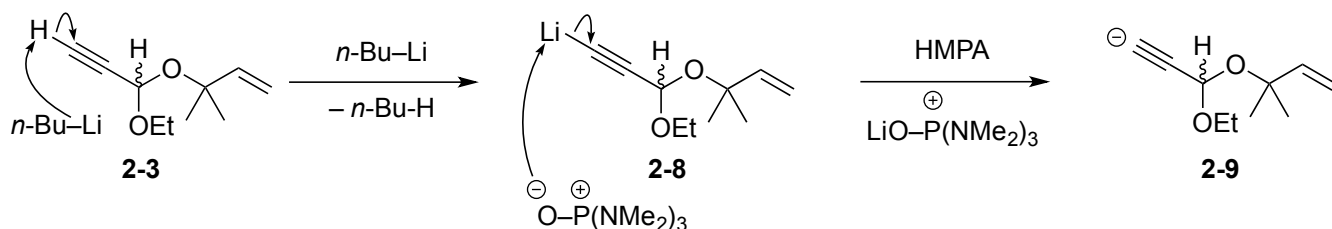
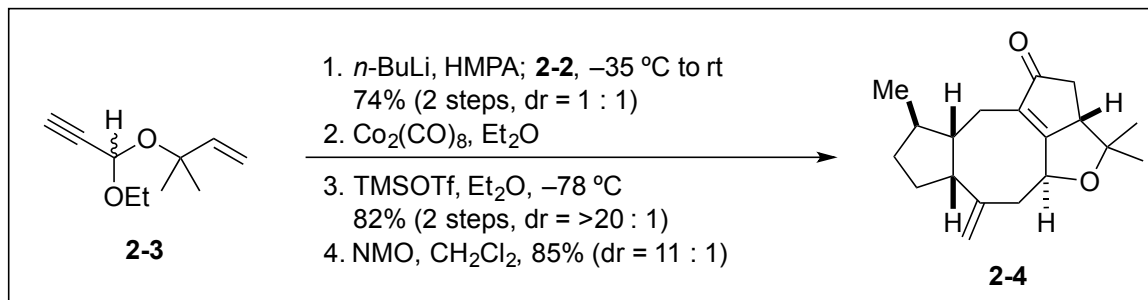
electron negativity

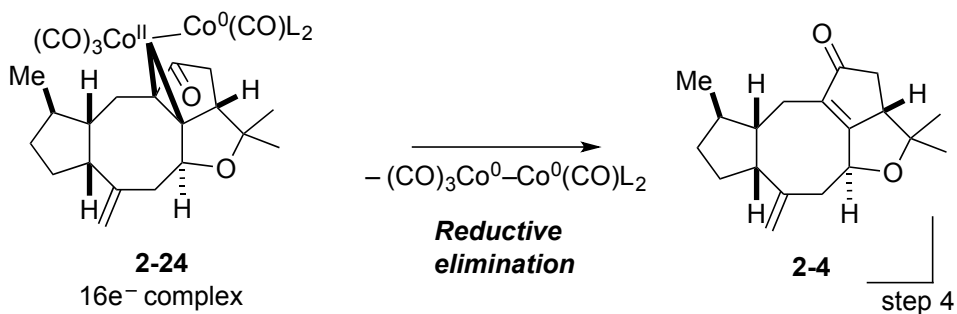
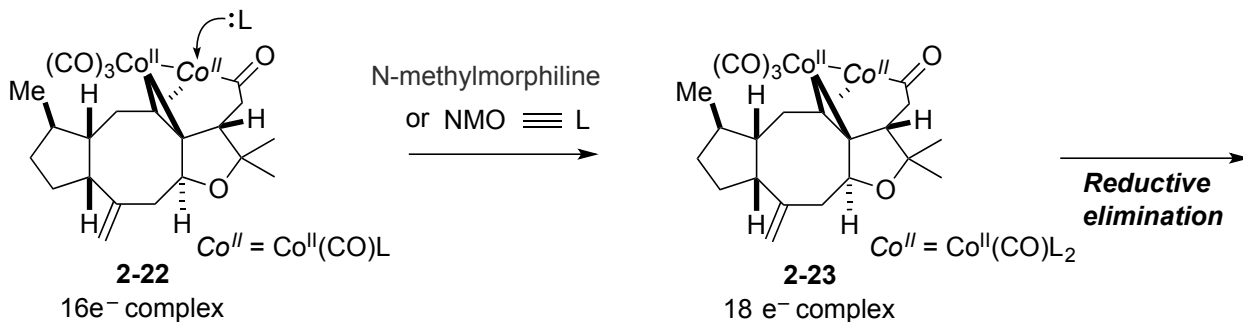
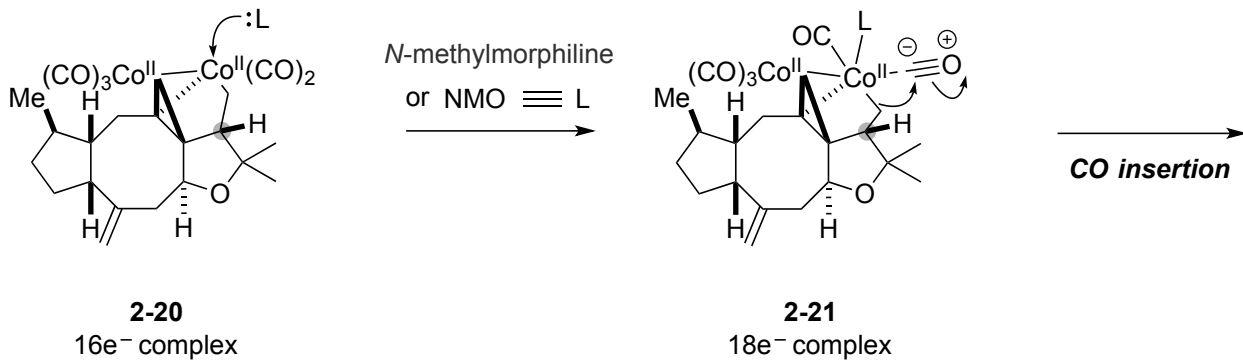
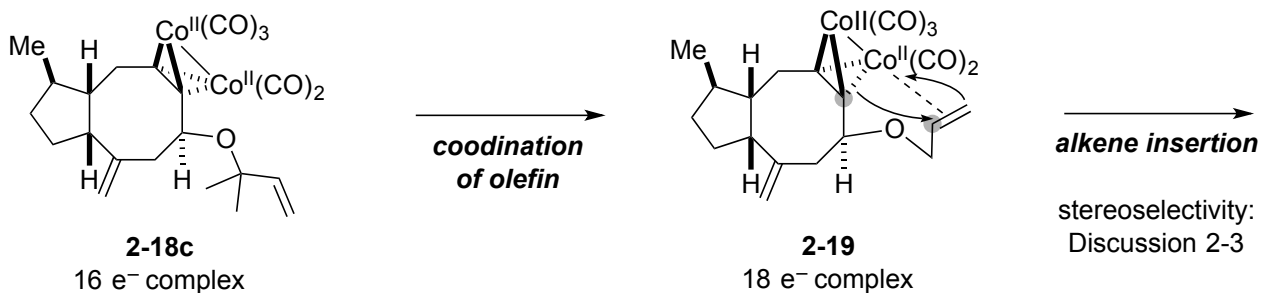
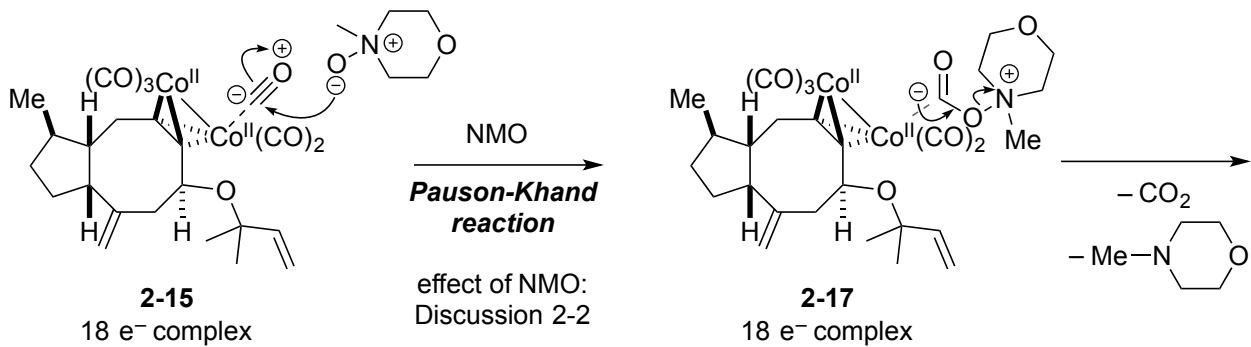
Li: 0.98

K: 0.82

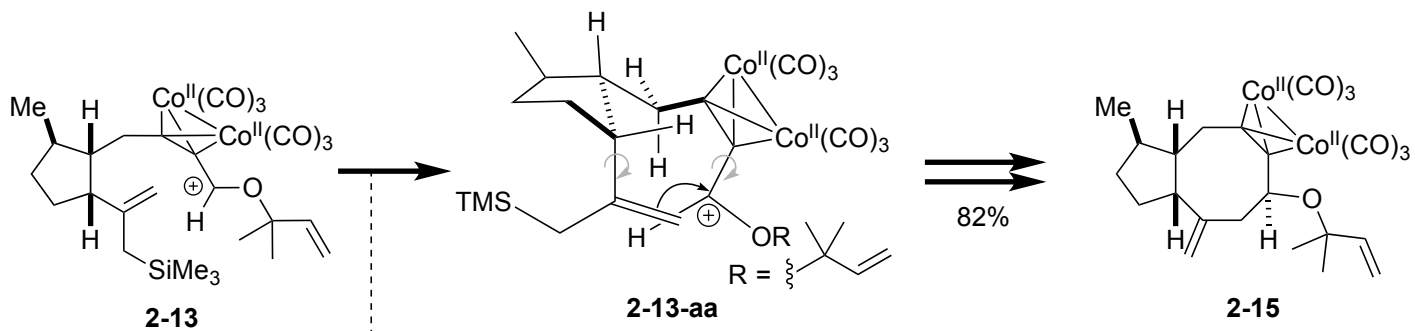


2-1) transformation from 2-1 to 2-2.

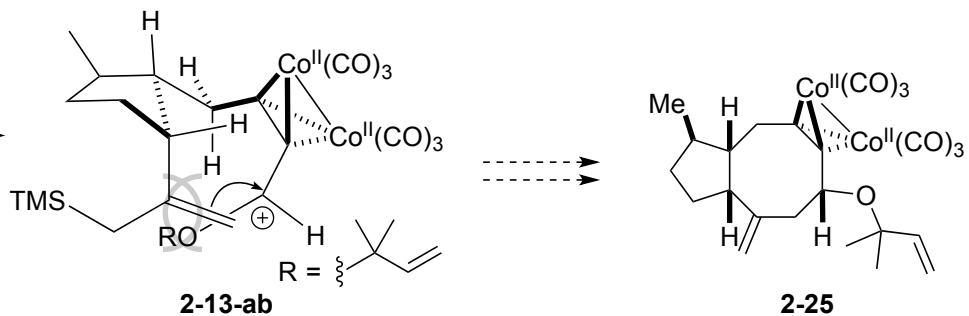




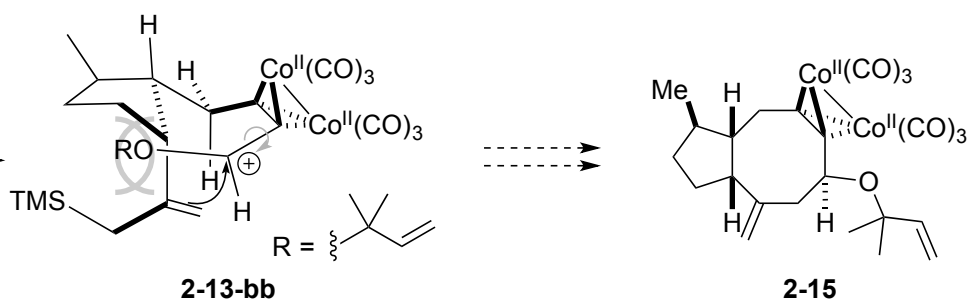
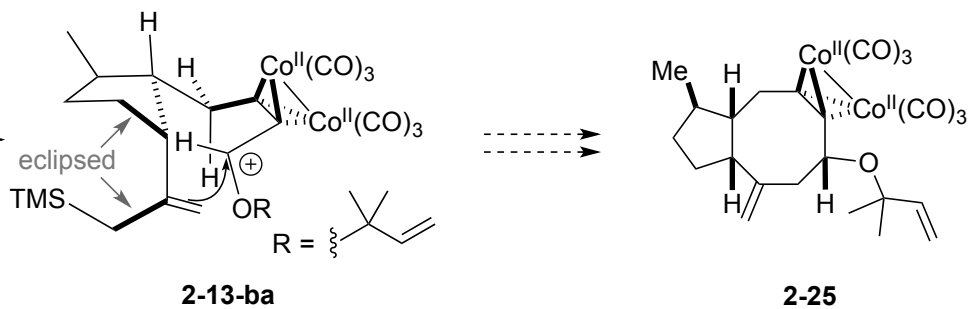
Discussion 2-1: Stereoselectivity of the Nicholas reaction.



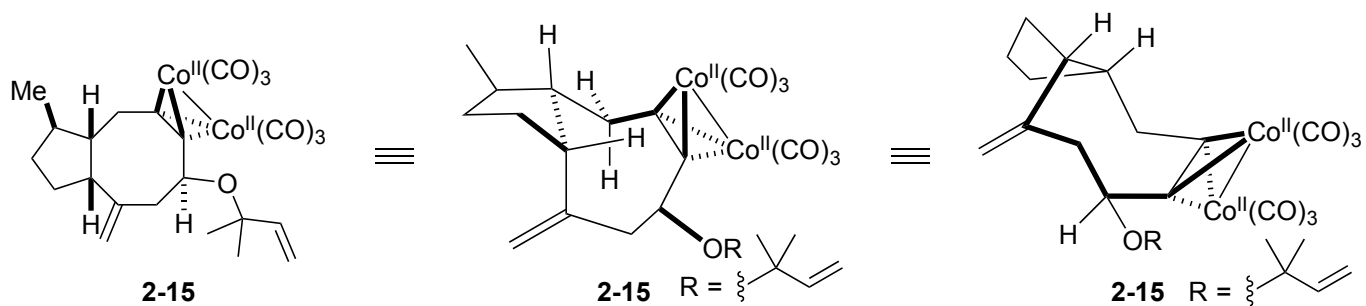
2-13aa and 2-13-ab:
 carbocation is attacked from upper side
 minimum allylic strain



2-13ba and 2-13-bb:
 carbocation is attacked from lower side
 larger allylic strain



<conformation of **2-15**>



Discussion 2-2: Effect of NMO



Table 1

| entry | conditions | results |
|-------|--|--------------------------|
| 1 | CH ₃ CN, reflux, 15 min | 85% (dr at C11 = 5 : 1) |
| 2 | NMO (0.5 mol%), CH ₂ Cl ₂ , rt, 12 h | 70% (dr at C11 = 11 : 1) |
| 3 | ultrasound, CH ₃ CN, 40 °C | 45% (dr at C11 = 3 : 1) |

Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.

⇒ Author mentioned that NMO employs oxidative initiation of cyclization, probably by oxidative dissociation of one of the CO ligands of the cobalt complex to CO₂.

<DFT calculation on Pauson-Khand reaction>

Scheme 1

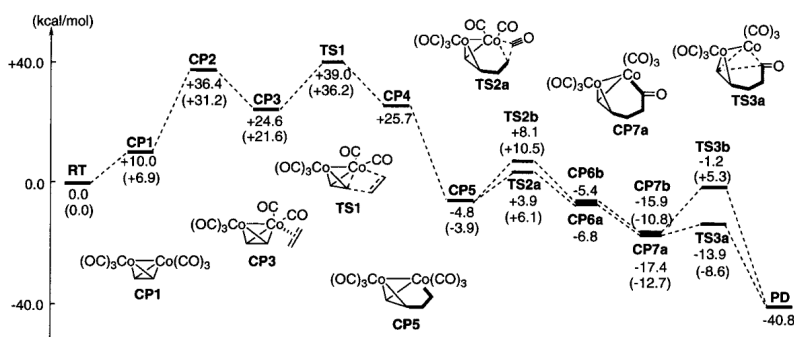
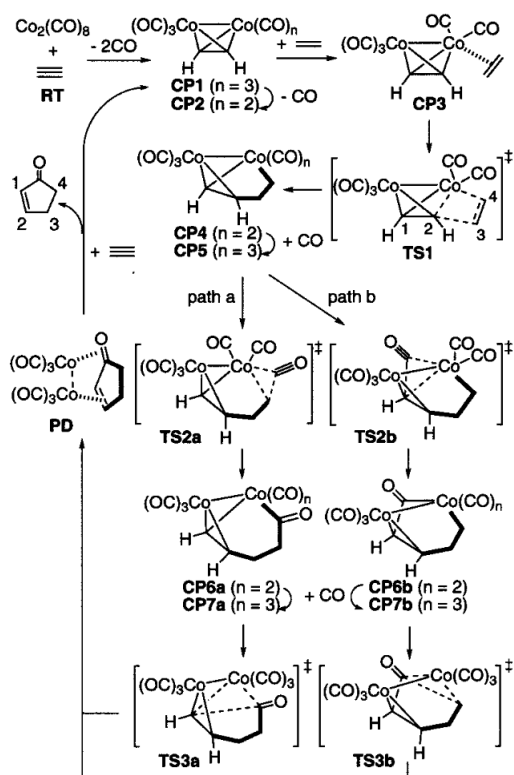


Figure 1

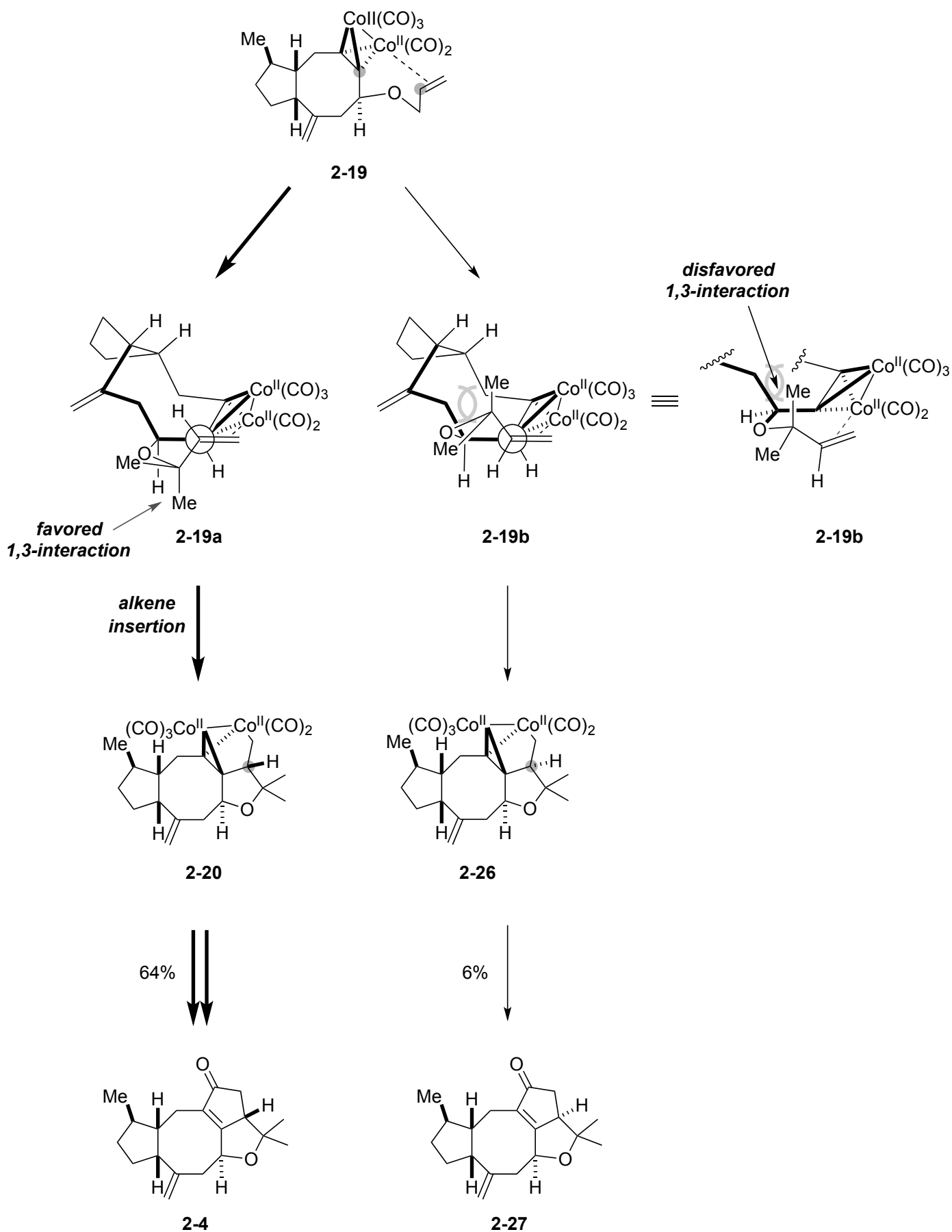
* energetics of pauson-khand reaction at the B3LYP/631LAN level. The values in parentheses are for B3LYP/6311SDD//B3LYP/631LAN

The larger energy barrier: go to CP3 by the loss of a CO from CP1

⇓
NMO would accelarate dissociation of one of the CO ligands.

Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703.

Discussion 2-3: Stereoselectivity of the Pauson-Khand reaction.



2-3) transformation from 2-4 to 2-5.

