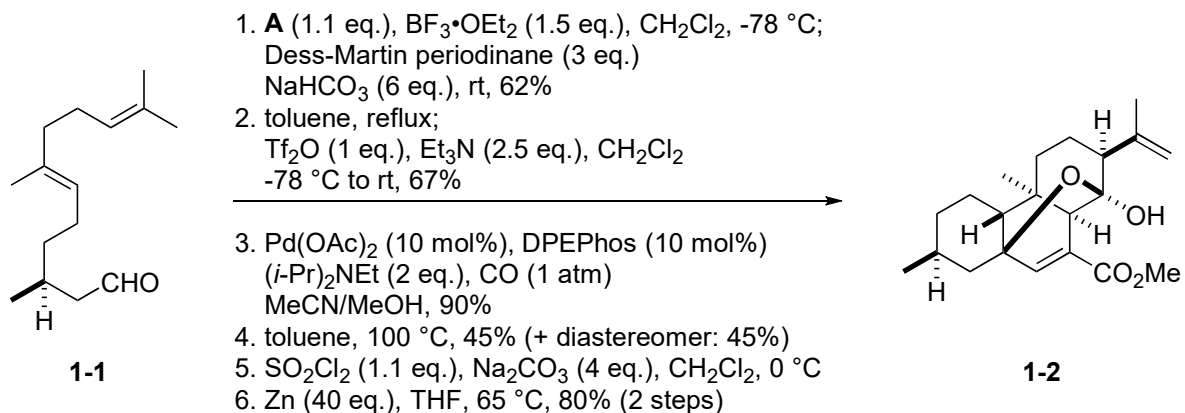


Problem Session (6)

2020.08.01. Yinghua Wang

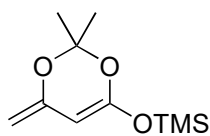
1 Please provide the reaction mechanism and the structure of a diastereomer formed in the 4th step.



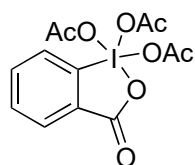
2 Please rearrange the reactions (a-g) to get **2-1** to **2-2** and provide each reaction mechanism.



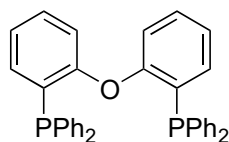
- a. CrO_3 (4 eq.), $\text{H}_2\text{SO}_4/\text{H}_2\text{O}/\text{acetone}$, $0\text{ }^\circ\text{C}$
- b. NaCNBH_3 (7 eq.), $\text{BF}_3 \cdot \text{OEt}_2$ (7 eq.), THF, reflux
- c. MeLi (4 eq.), $\text{LaCl}_3 \cdot 2\text{LiCl}$ (3 eq.), THF, -25 to $0\text{ }^\circ\text{C}$
- d. NaH (1.1 eq.), 4-iodobut-1ene (1.2 eq.), DMF, $0\text{ }^\circ\text{C}$
- e. $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (2.5 mol%), TMSD (2.3 eq.), toluene
- f. $\text{Co}_2(\text{CO})_8$ (1.2 eq.), CH_2Cl_2 ;
 $\text{Me}_3\text{NO} \cdot 2\text{H}_2\text{O}$ (6 eq.), MeCN, -78 to $23\text{ }^\circ\text{C}$
- g. ethynylmagnesium bromide (1.2 eq.), TMSOTf (1.2 eq.)
 CH_2Cl_2 , -78 to $0\text{ }^\circ\text{C}$; 6 M HCl aq. (10 eq.), rt



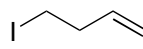
A



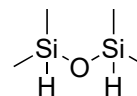
Dess-Martin
periodinane



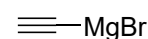
DPEPhos



4-iodobut-1ene



TMSD



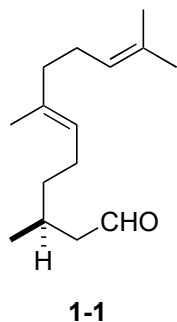
ethynylmagnesium
bromide

Problem Session (6) -Answer-

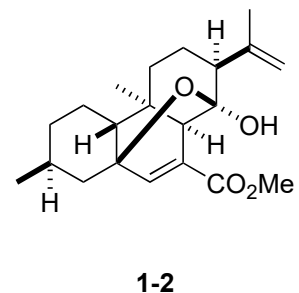
2020.08.01. Yinghua Wang

Topic: Total syntheses achieved at Latimer Hall.

1 Please provide the reaction mechanism and the structure of a diastereomer formed in the 4th step.



- 1.** **A** (1.1 eq.), $\text{BF}_3 \cdot \text{OEt}_2$ (1.5 eq.), CH_2Cl_2 , -78°C ; Dess-Martin periodinane (3 eq.) NaHCO_3 (6 eq.), rt, 62%
- 2.** toluene, reflux; Tf_2O (1 eq.), Et_3N (2.5 eq.), CH_2Cl_2 , -78°C to rt, 67%
- 3.** $\text{Pd}(\text{OAc})_2$ (10 mol%), DPEPhos (10 mol%) ($i\text{-Pr}$) $_2\text{NEt}$ (2 eq.), CO (1 atm), MeCN/MeOH, 90%
- 4.** toluene, 100°C , 45% (+ diastereomer: 45%)
- 5.** SO_2Cl_2 (1.1 eq.), Na_2CO_3 (4 eq.), CH_2Cl_2 , 0°C
- 6.** Zn (40 eq.), THF, 65°C , 80% (2 steps)



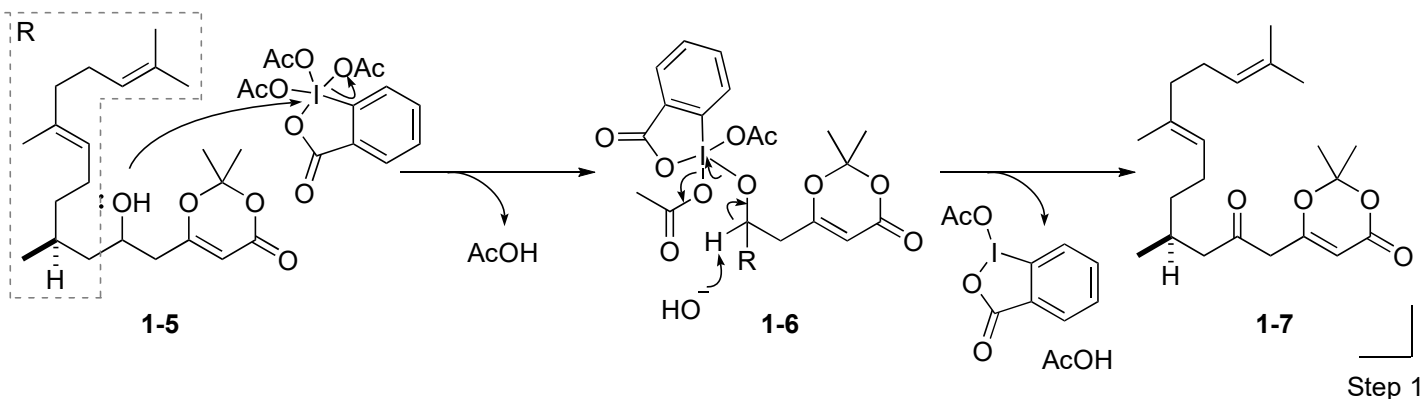
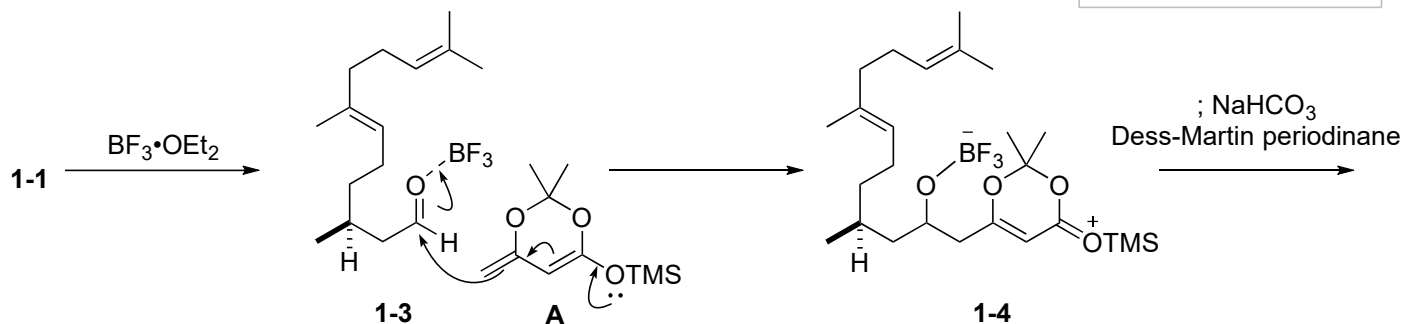
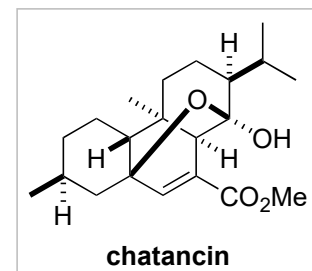
Zhao, Y.-M.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 1223.

• Total synthesis of chatancin

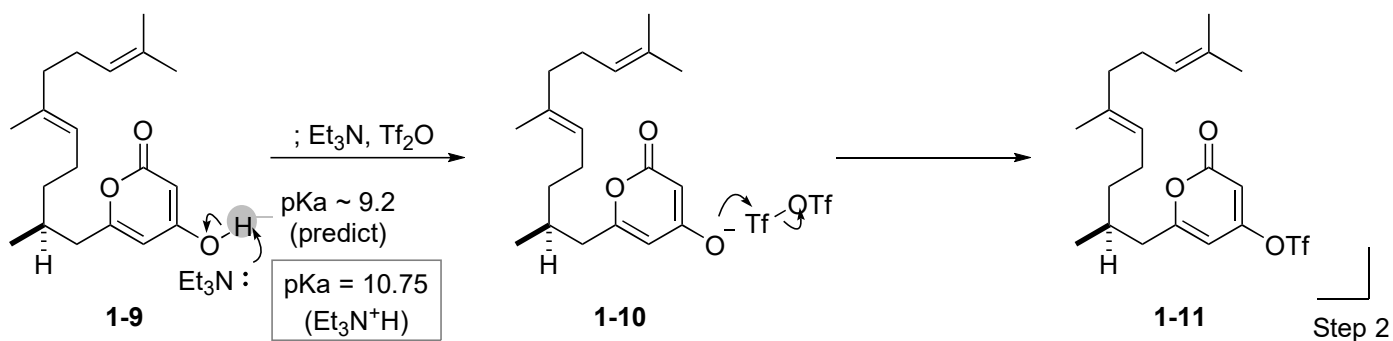
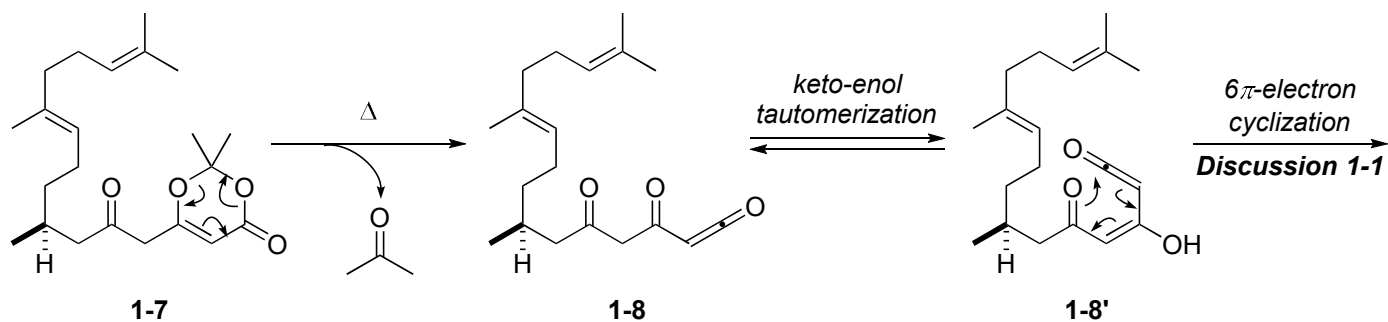
4 total syntheses have been reported; by Gössinger (1998), Deslongchamps (2003), Maimone (2015), and Lin and Ding (2019)

• Key reaction: transannular Diels-Alder reaction using hydroxypyrrone

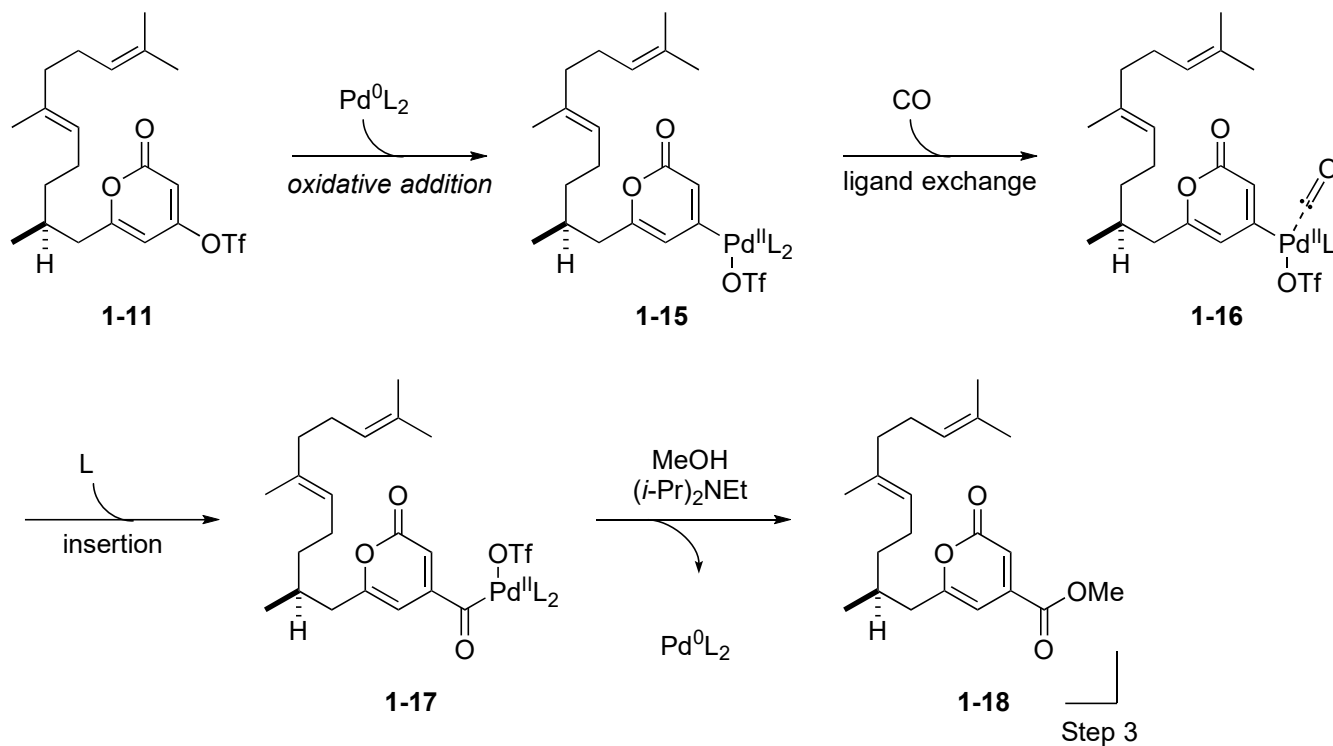
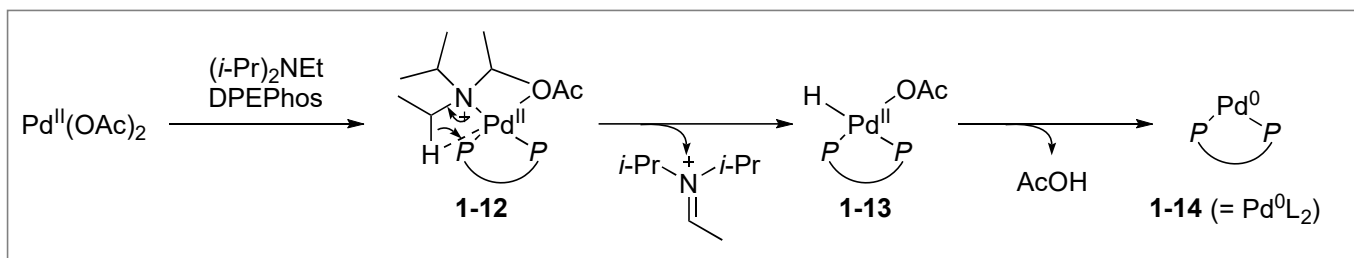
Step 1. Vinyllogous Mukaiyama aldol reaction.



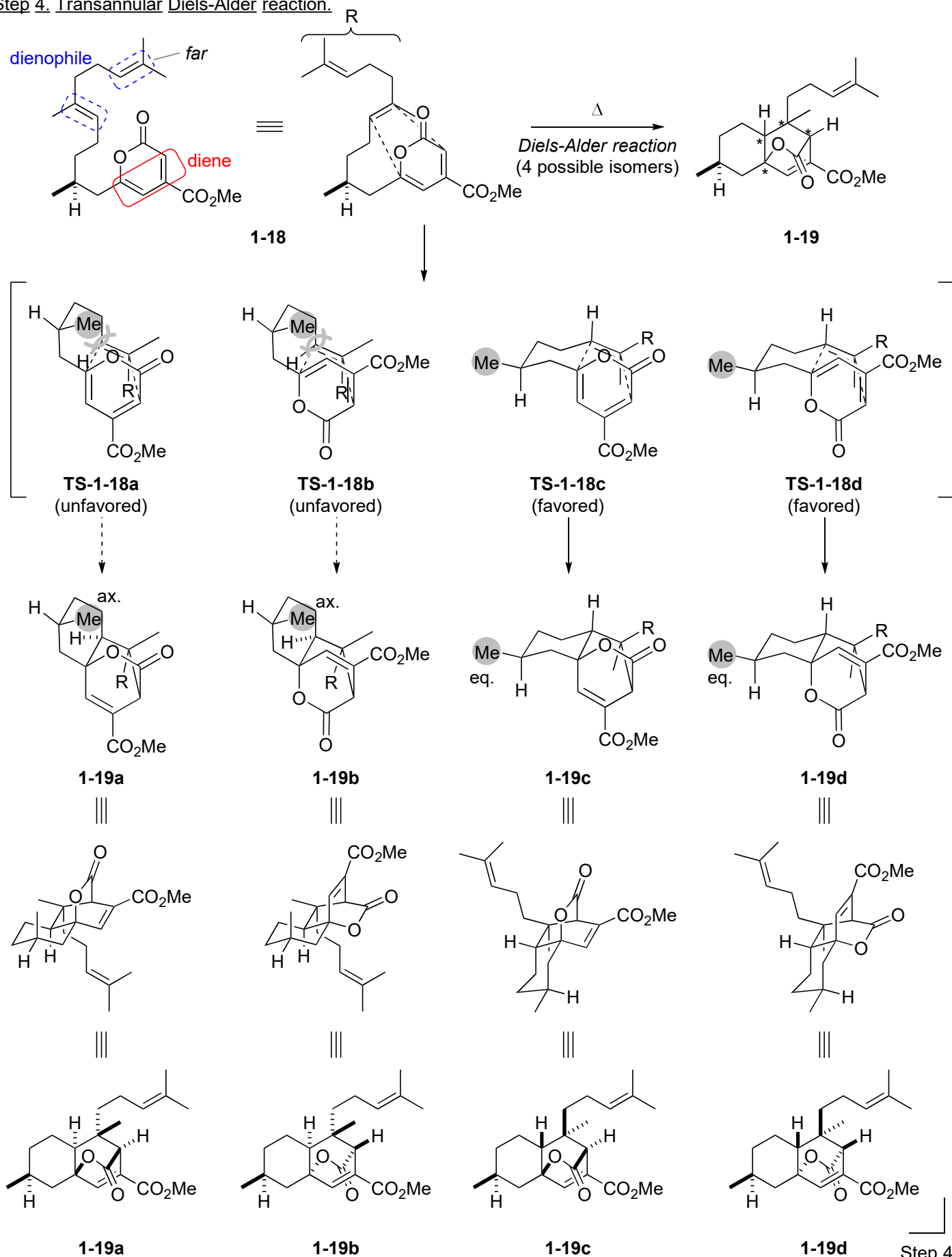
Step 2. Preparation of hydroxy pyrone.



Step 3. Carbonylative cross coupling.

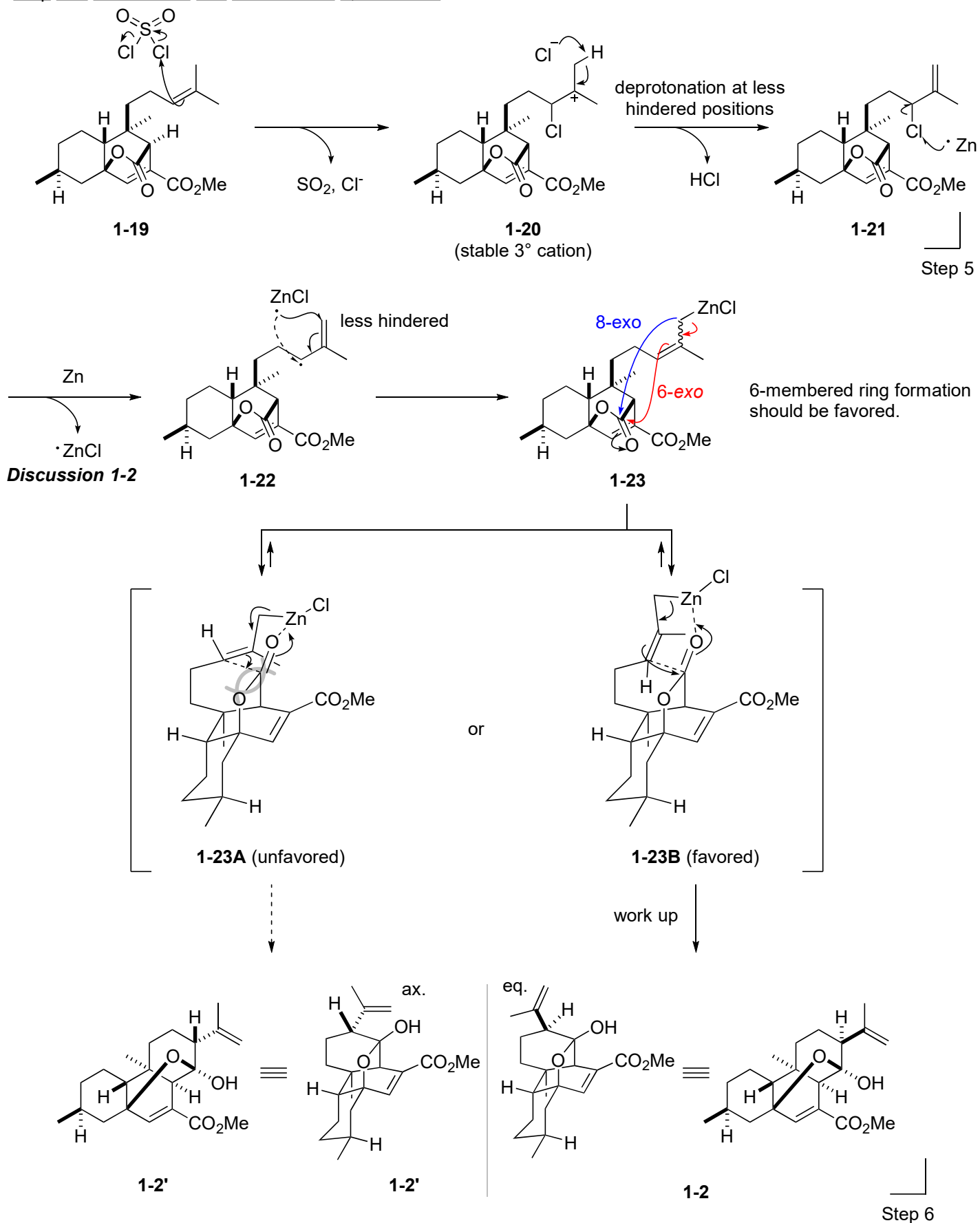


Step 4. Transannular Diels-Alder reaction.

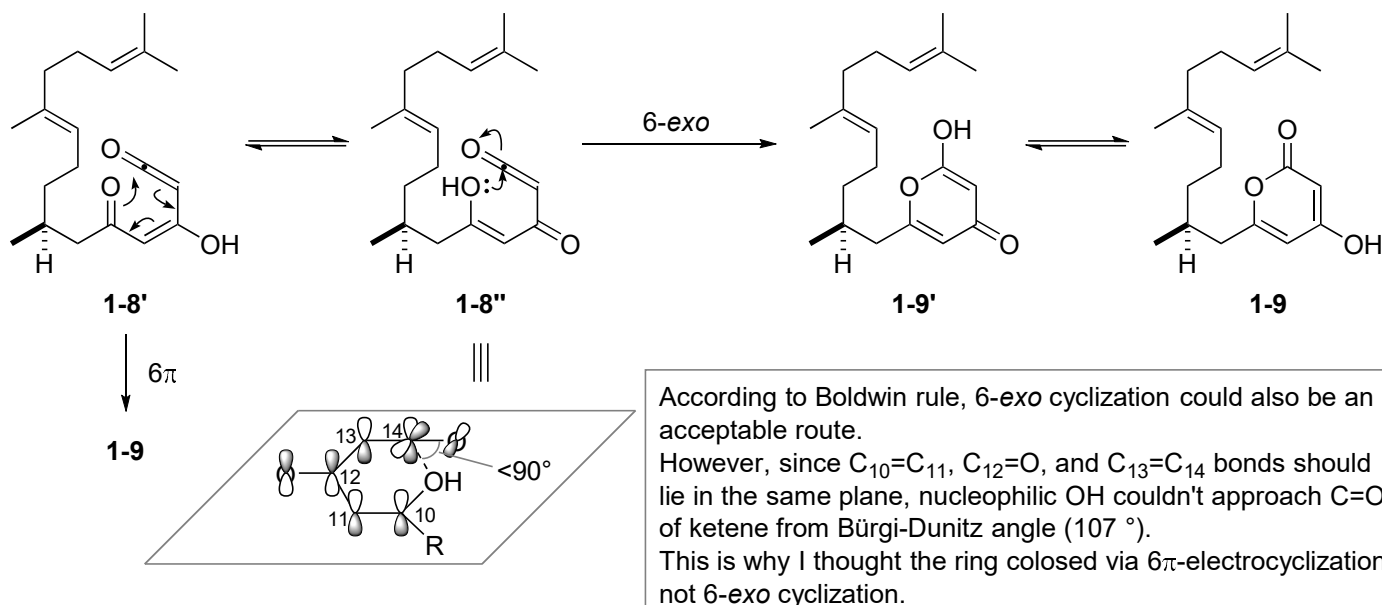


Step 4

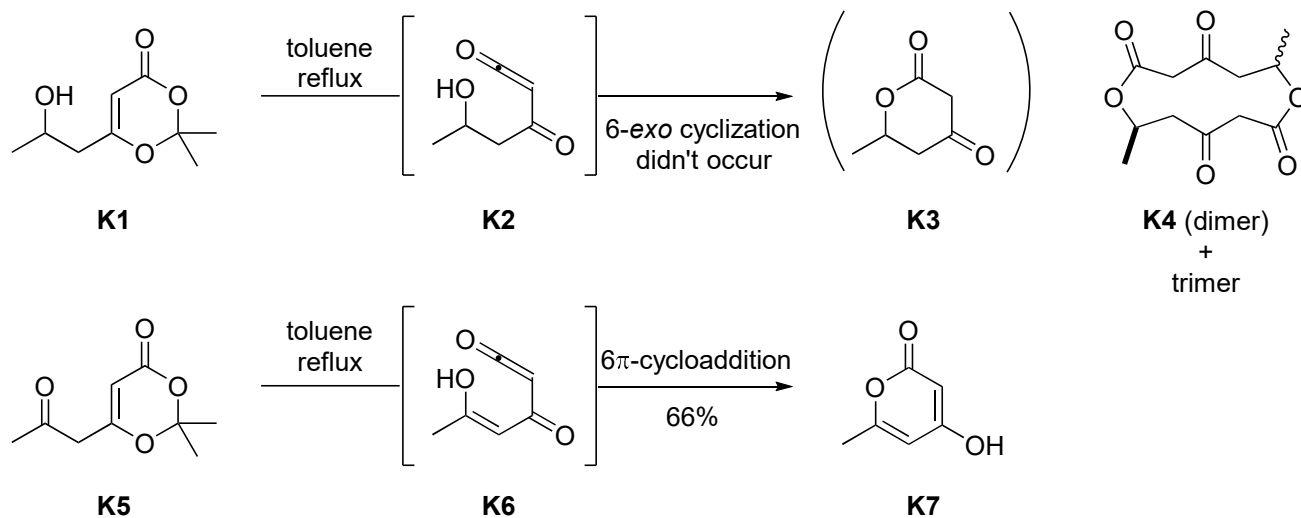
Step 5-6. Chlorination and Zn-mediated 1,2-addition.



Discussion 1-1: How to close a ring to form the pyrone?

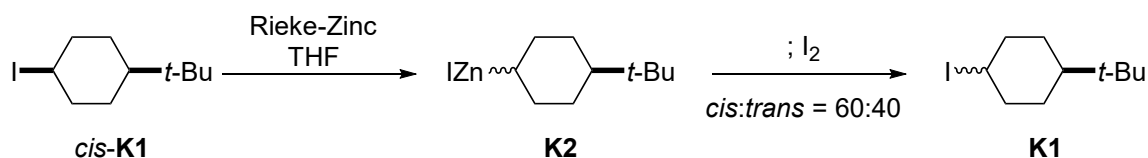


- Differences of reactivity between alcohol and ketone derivatives of 1,3-dioxin-4-one.



Sato, M.; Sasaki, J.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. *Tetrahedron* **1991**, *47*, 5689.

Discussion 1-2: The mechanism of zinc insertion into an alkyl halide.

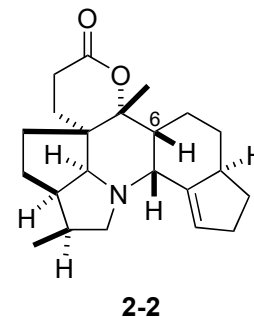
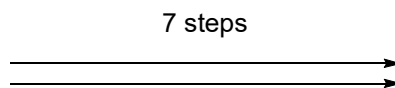
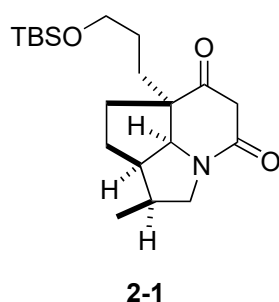


- When *cis*-K1 was converted to K2 and K2 was trapped with I_2 , K1 was obtained as a diastereomeric mixture.
- This result indicated that Zn might not directly insert into C-I bond, which suggested the radical pathway.

For details and more information about C-Zn bonds, see:

Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415.
 Guijarro, A.; Rieke, R. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 1475.

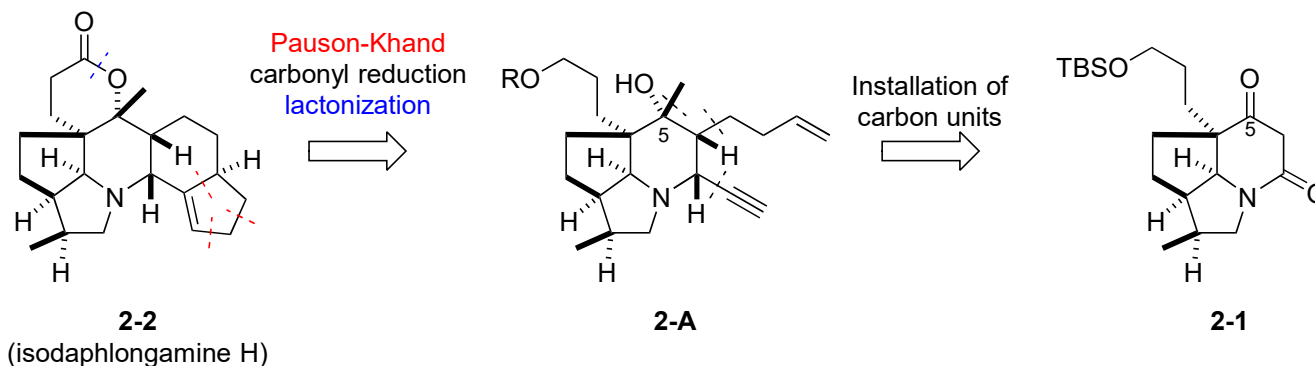
2 Please rearrange the reactions (a-g) to get **2-1** to **2-2** and provide each reaction mechanism.



- a. CrO₃ (4 eq.), H₂SO₄/H₂O/acetone, 0 °C, 68% (2 steps)
 b. NaCNBH₃ (7 eq.), BF₃·OEt₂ (7 eq.), THF, reflux
 c. MeLi (4 eq.), LaCl₃·2LiCl (3 eq.), THF, -25 to 0 °C
 d. NaH (1.1 eq.), 4-iodobut-1ene (1.2 eq.), DMF, 0 °C, 62%
 e. IrCl(CO)(PPh₃)₂ (2.5 mol%), TMSD (2.3 eq.), toluene, 73%
 f. Co₂(CO)₈ (1.2 eq.), CH₂Cl₂;
 Me₃NO·2H₂O (6 eq.), MeCN, -78 to 23 °C, 55% (2 steps)
 g. ethynylmagnesium bromide (1.2 eq.), TMSOTf (1.2 eq.)
 CH₂Cl₂, -78 to 0 °C; 6 M HCl aq. (10 eq.), rt, 79% (dr at C6 = 3.6:1)

Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 8431.

• Retrosynthesis (answer for the sorting problem)



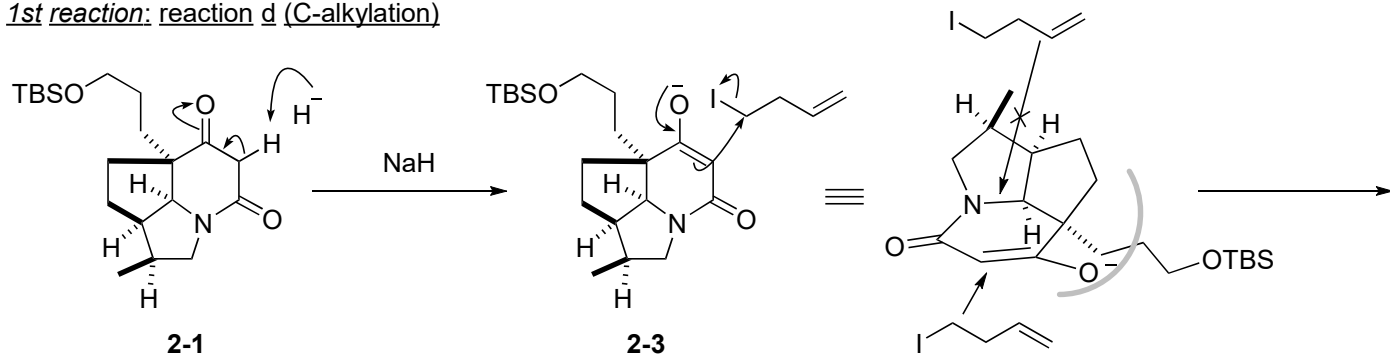
- Pauson-Khand reaction (reaction f)
enone formation = C5-Me should be installed before.
 - Decarbonylation of enone (reaction b)
no other carbonyl groups would be preferable
 - Lactone construction (reaction a)
this reaction might be the last step?
(Considering reaction conditions shown above,
"a" → "b" would be also acceptable because
lactone might not react under the condition "b".)
- f → b → a (or f → a → b)**

- Installation of carbon chains (reaction d and g):
reaction d: C-alkylation
reaction g: 1,4-addition? (1,2-addition on amide is tough)
reaction g would included cleavage of TBS group
= "d" should carry out before "g" (only 1.1 eq. of NaH)
 - Reduction of amide (reaction e)
enone was needed for "g" = enaminone formation?
 - Installation of Me group (reaction c)
C5-ketone was necessary for installation of carbon chains
= C5-Me was the last carbon unit
- d → e → g → c**

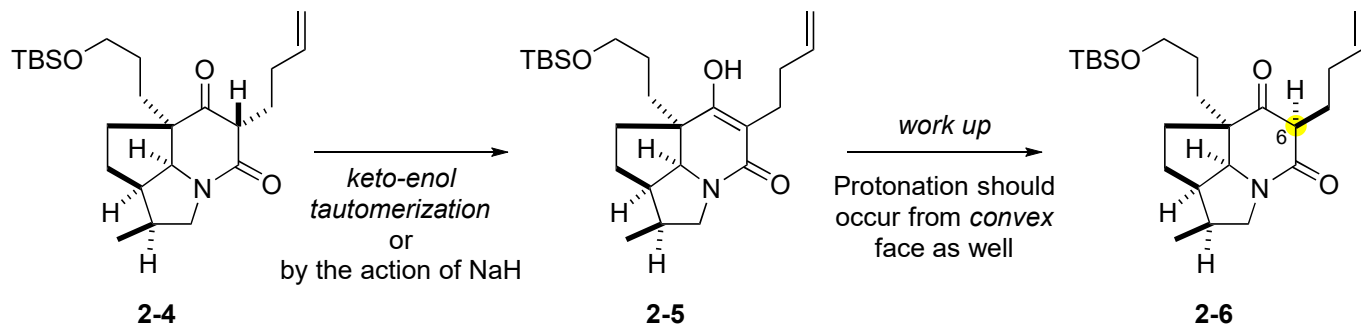
The order is:

d → e → g → c → f → b → a
(or **d → e → g → c → f → a → b**)

1st reaction: reaction d (C-alkylation)

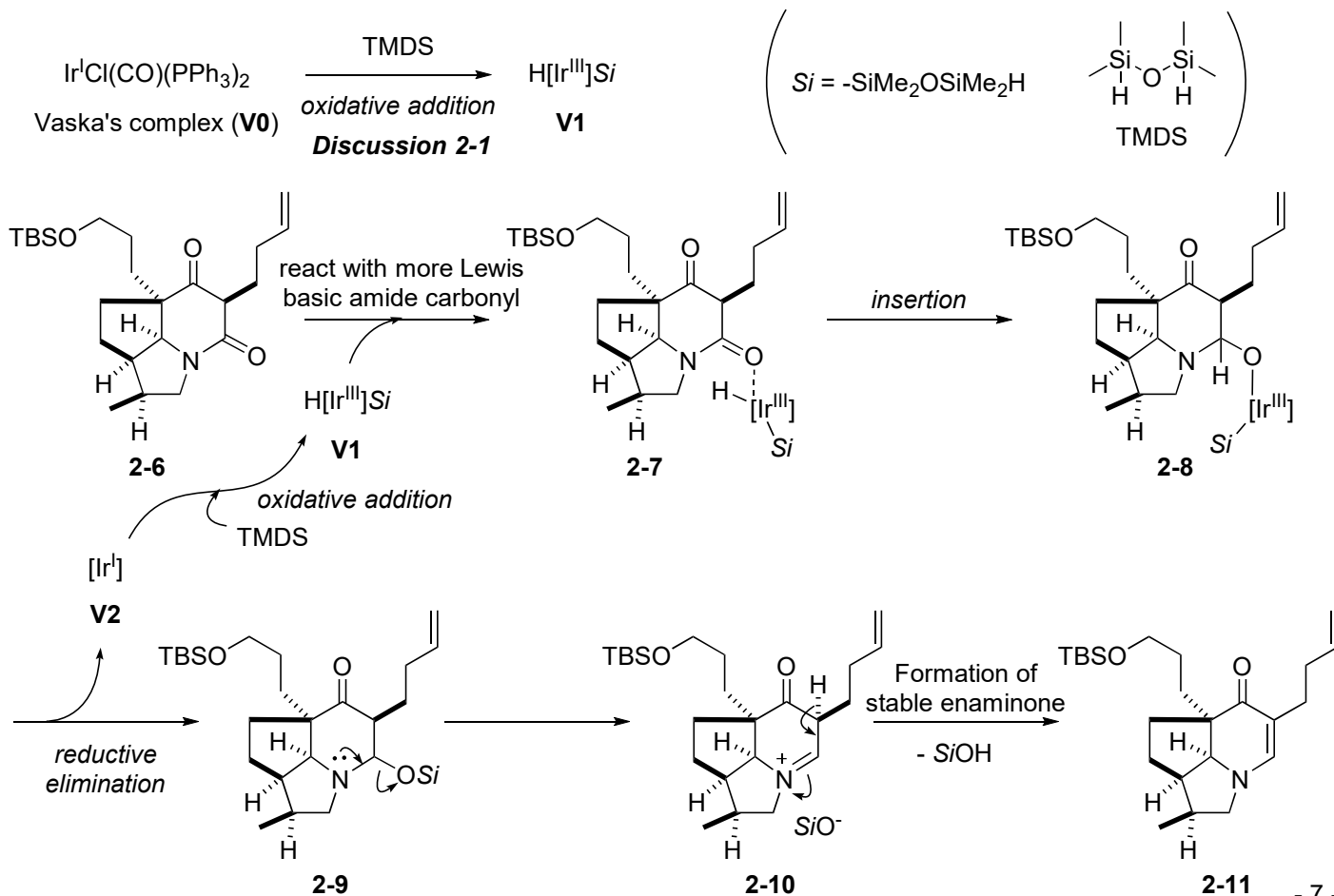


An electrophile might approach from *convex* face of the fused 5-5-6 ring system.

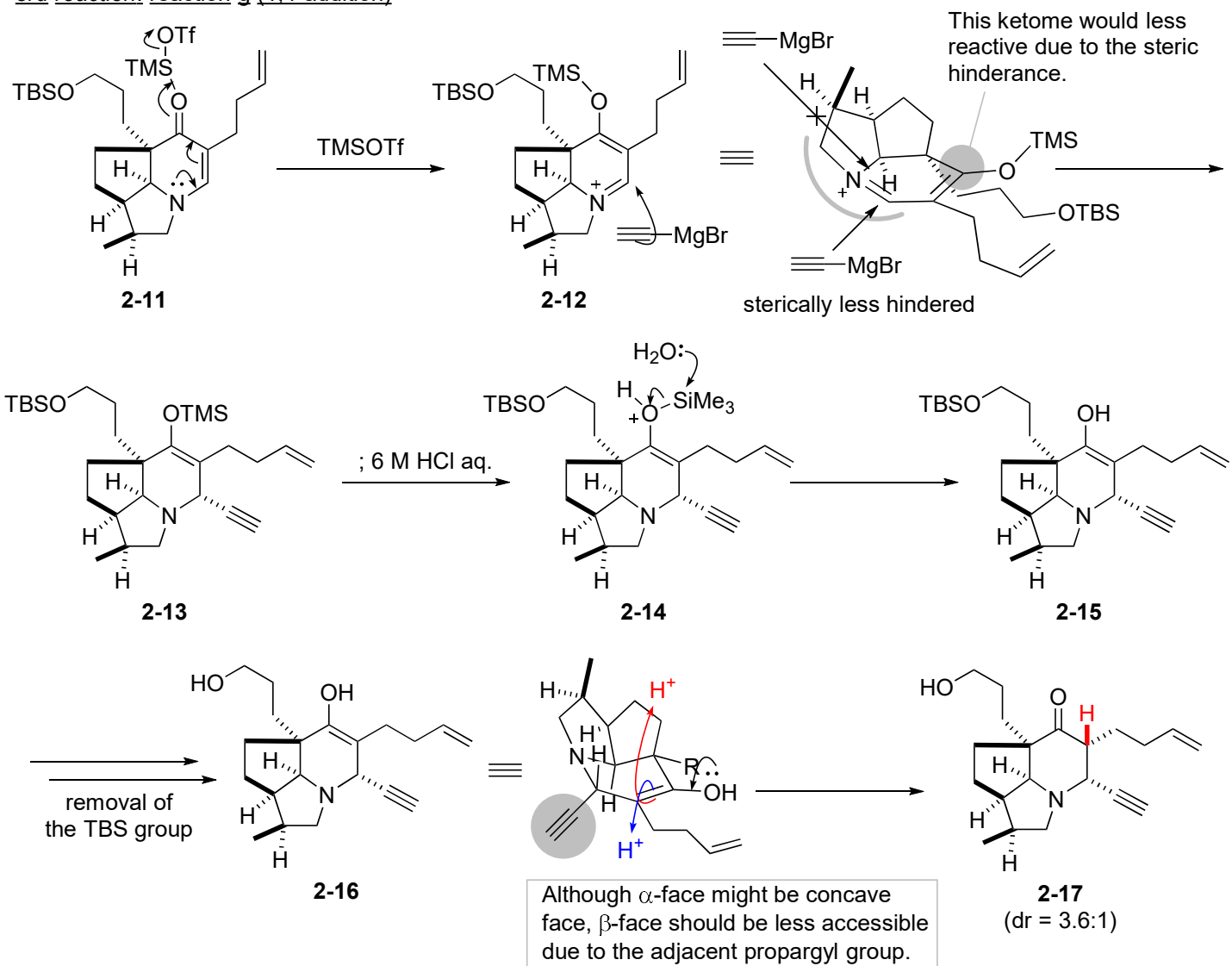


The C6-stereocenter installed in this reaction will disappear in the next reaction anyway.

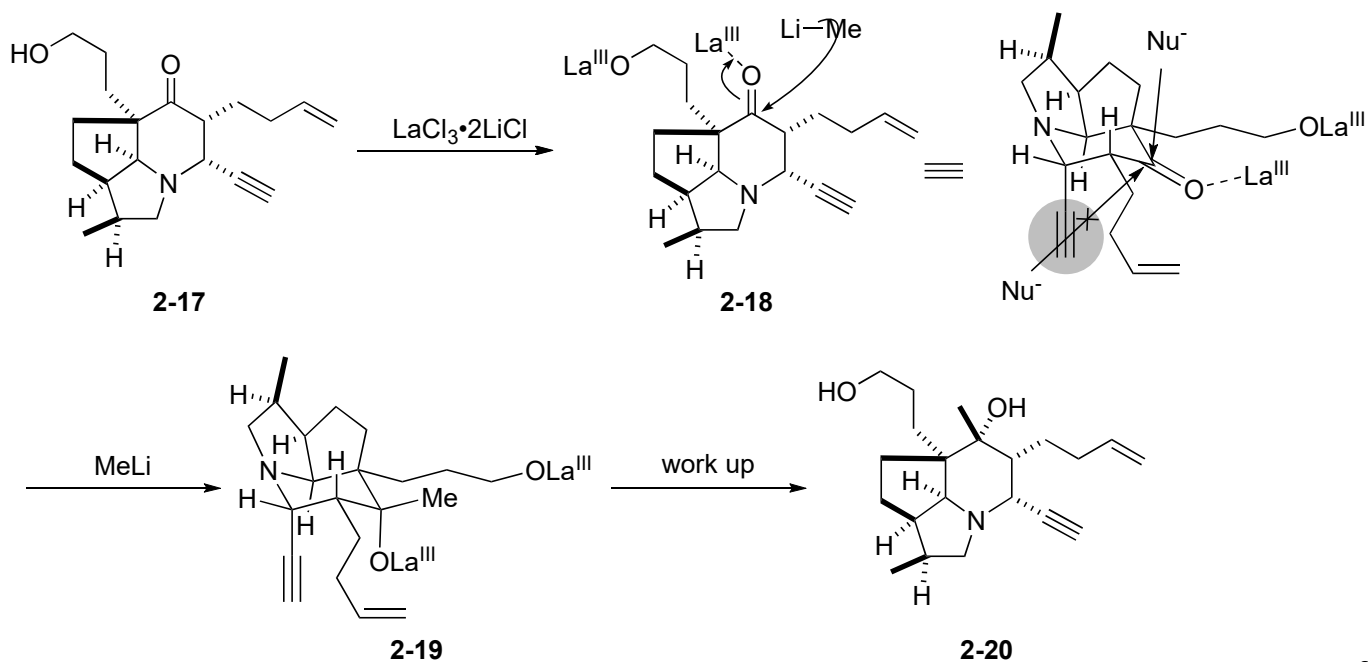
2nd reaction: reaction e (Amide-selective reduction)



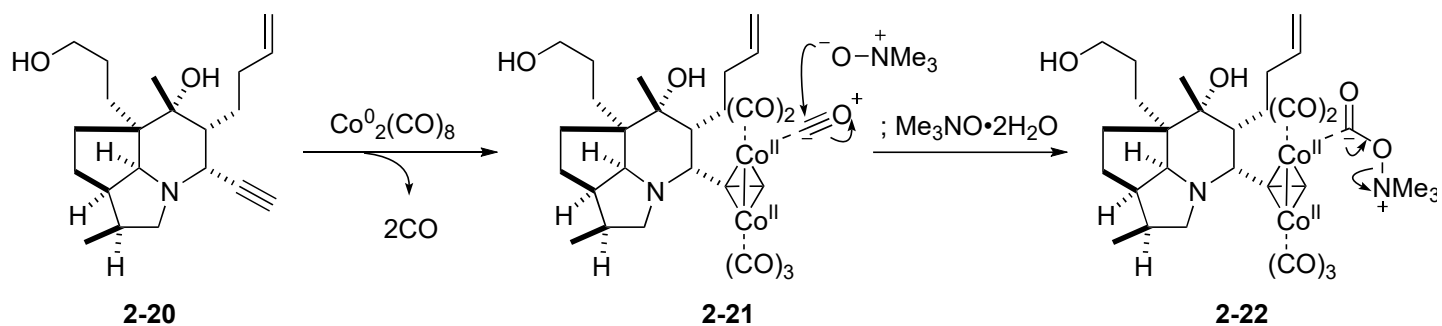
3rd reaction: reaction g (1,4-addition)



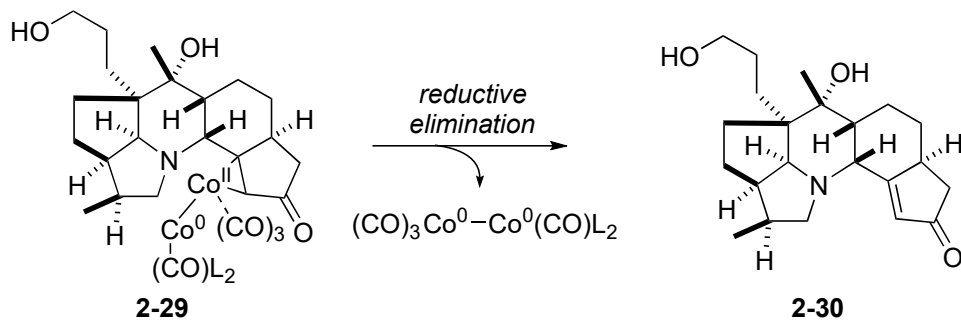
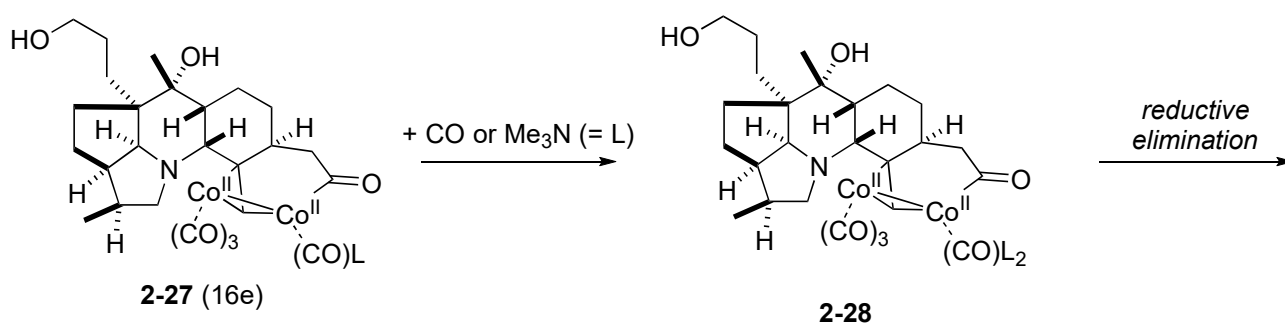
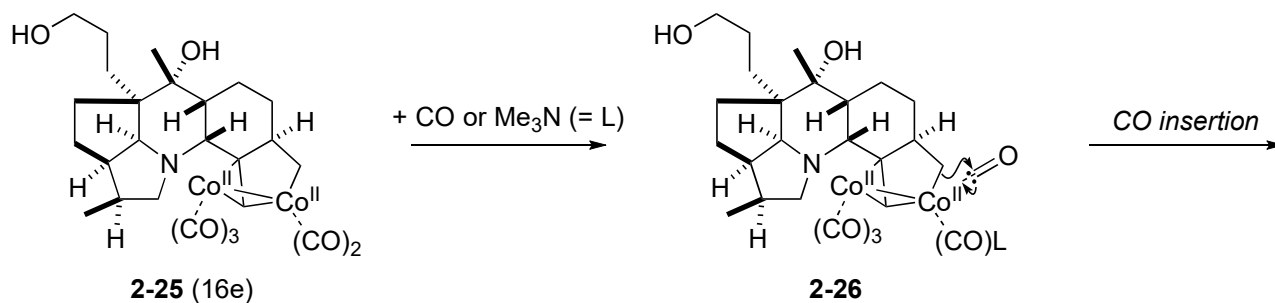
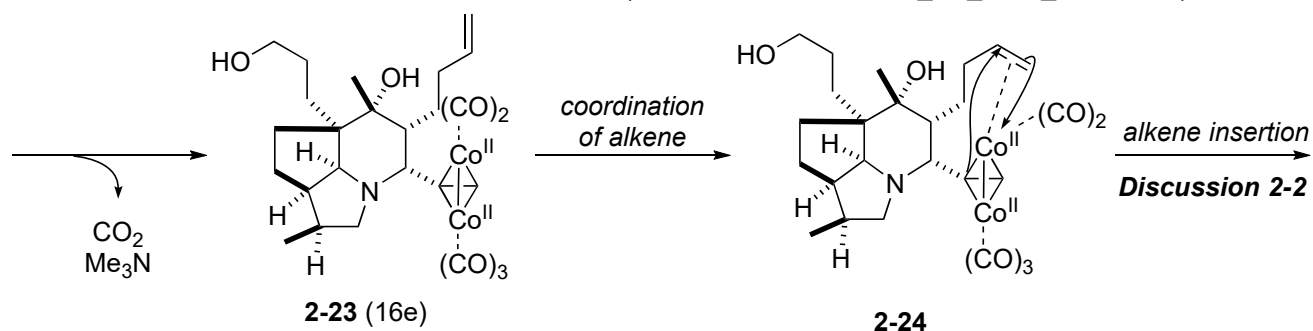
4th reaction: reaction c (1,2-addition)



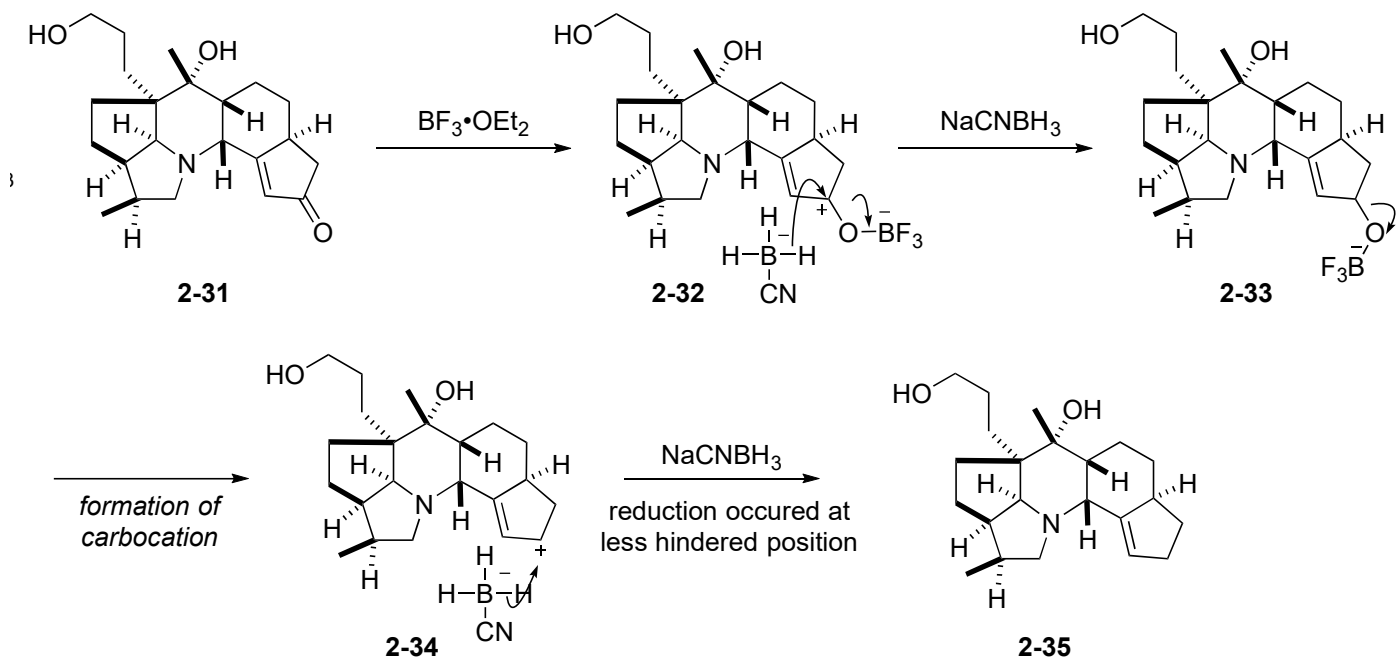
5th reaction: reaction f (Pauson-Khand reaction)



* Me_3NO would accelerate dissociation of one of the CO ligands.
(For details, see: 161210_PS_Daiki_Kamakura)

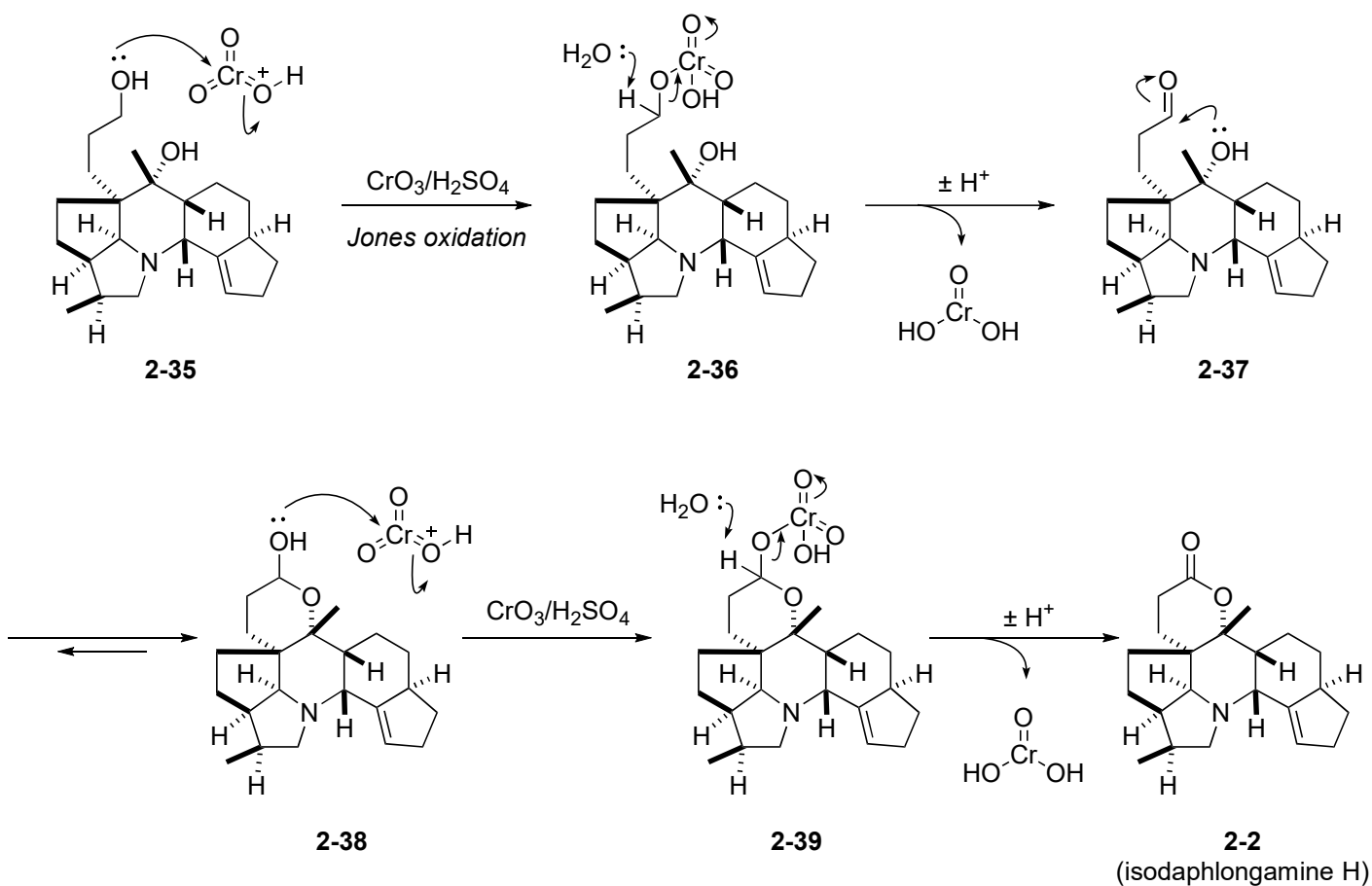


6th reaction: reaction b (Decarbonylation of enone)



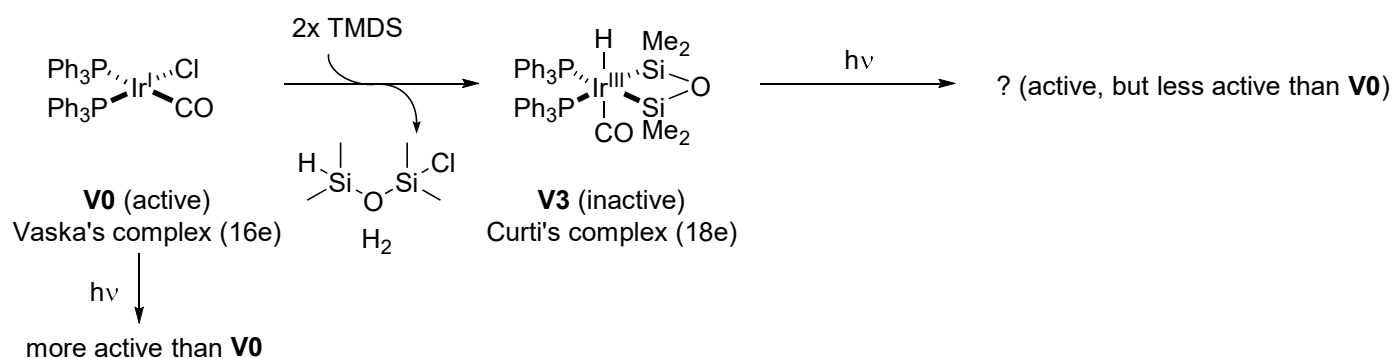
Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Yelamaggad, C. V. *Tetrahedron Lett.* **1995**, *36*, 2347.

7th reaction: reaction a (Lactone construction)

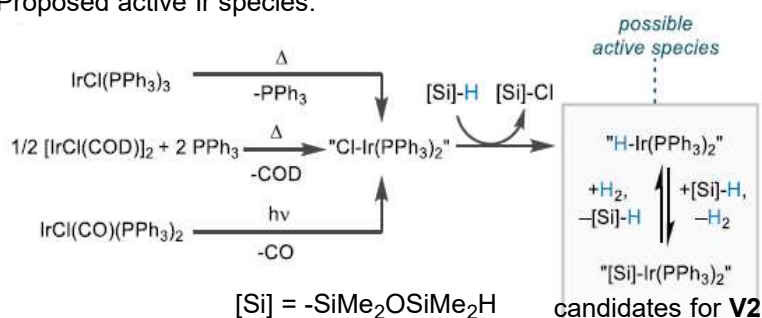


Discussion 2-1: Proposed reaction mechanism for Vaska's complex-mediated reduction.

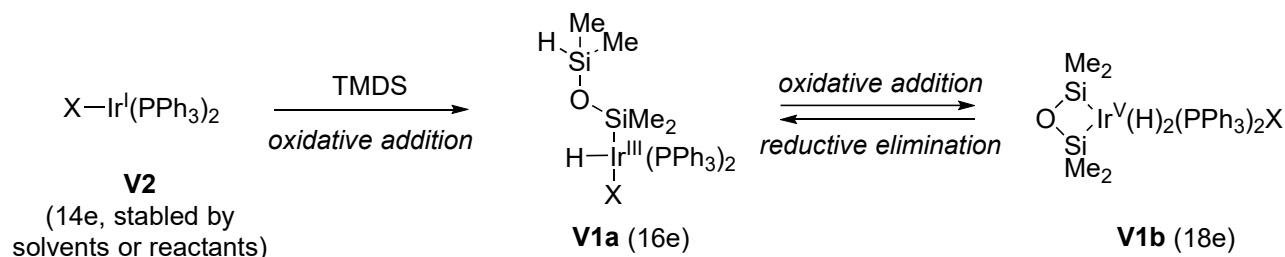
- Deactivation of Vaska's complex (**V0**) and reactivation.



- Proposed active Ir species.



Some experiments indicated that TMDS wouldn't directly insert into Vaska's complex (**V0**), but 14e species $\text{X-Ir}^I(\text{PPh}_3)_2$ ($\text{X} = \text{H}$ or Si) could be generated as initial active species.



Although the exact active species are still unknown, it is said that **V1a** or **V1b** might be the active species (or its dormant species)

For more detailed information:

Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. *Chem. Commun.* **2009**, 1574, 1574.

Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. *Organometallics* **2019**, 38, 852.

Matheau-Raven, D.; Gabriel, P.; Leitch, J. A.; Almeahmedi, Y. A.; Yamazaki, K.; Dixon, D. J. *ACS Catal.* **2020**, 10, 8880.

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

