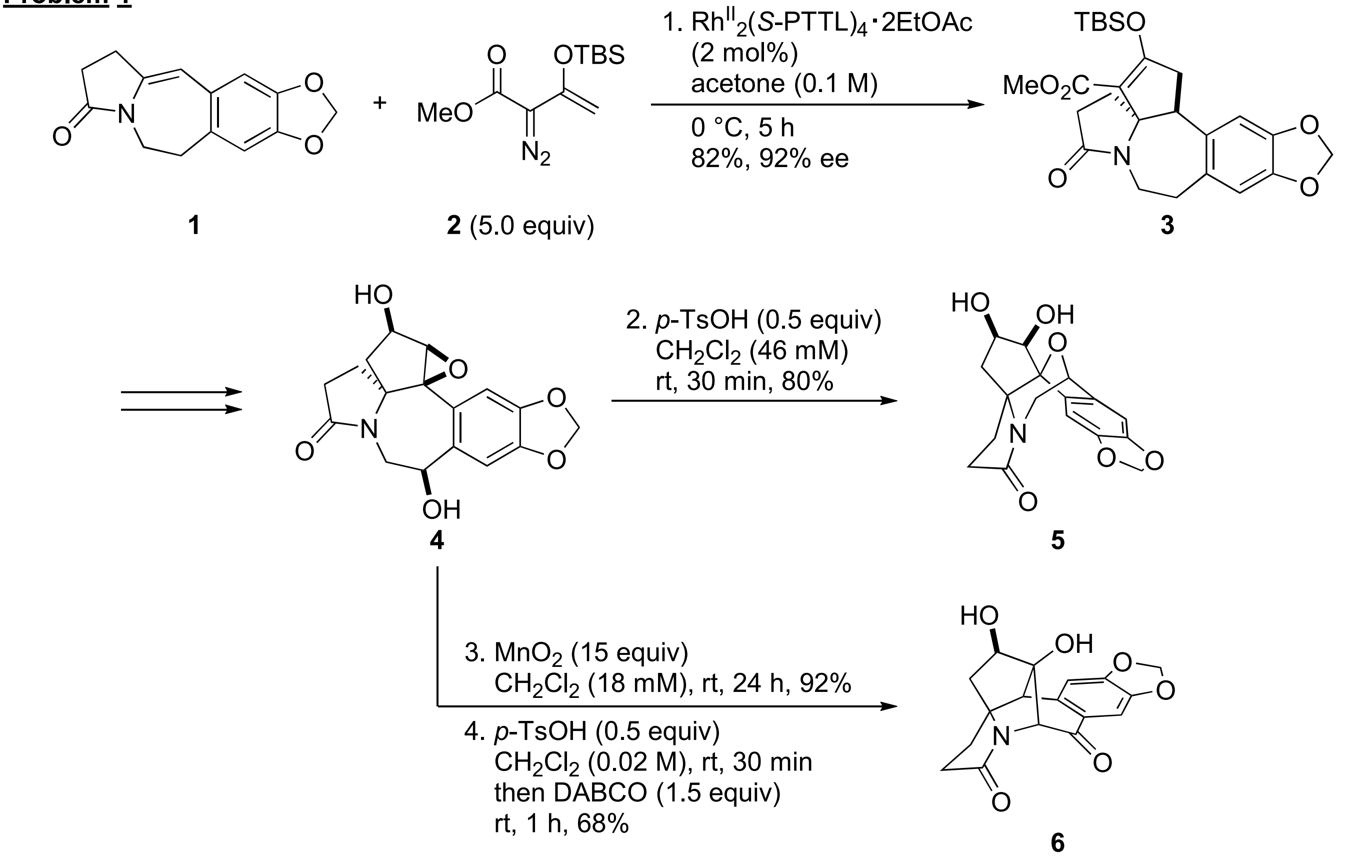
Problem Session (2)

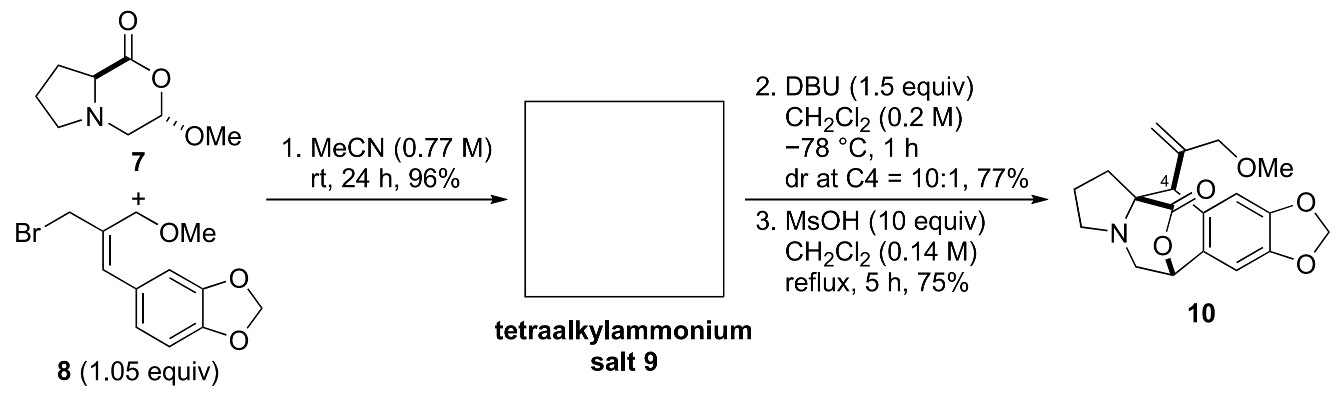
2023/05/06 Wentao Wang

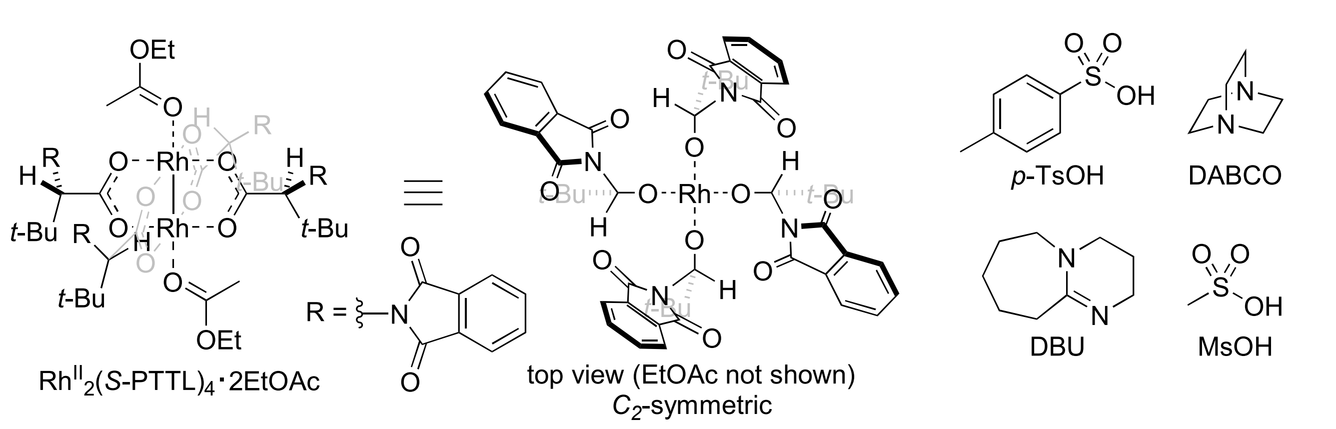
Please provide the mechanisms of the reactions below and explain regio- and stereoselectivities.

Problem 1



Problem 2



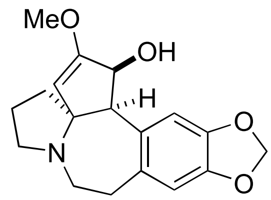


Problem Session (2) - Answer

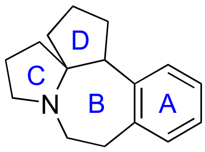
2023/05/06 Wentao Wang

Topic: Total Syntheses of *Cephalotaxus* Alkaloids

0. Introduction



cephalotaxine



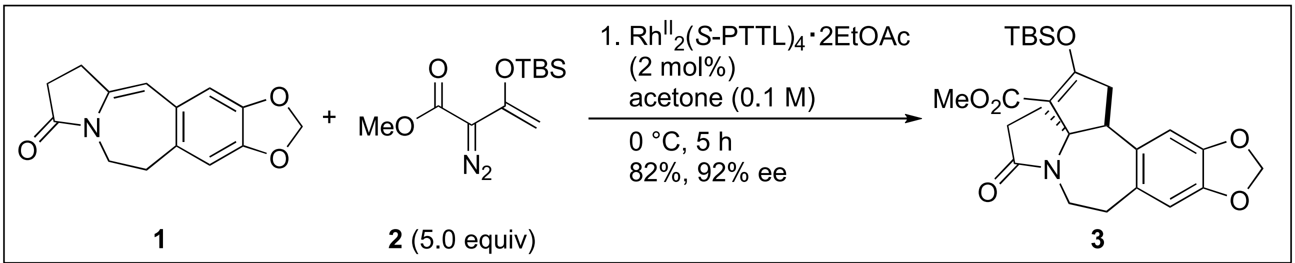
Isolation: *Cephalotaxus* genus
Biological activities: antileukemic, antitumor
Structural features: azaspiranic tetracyclic core
Total syntheses: > 30 examples

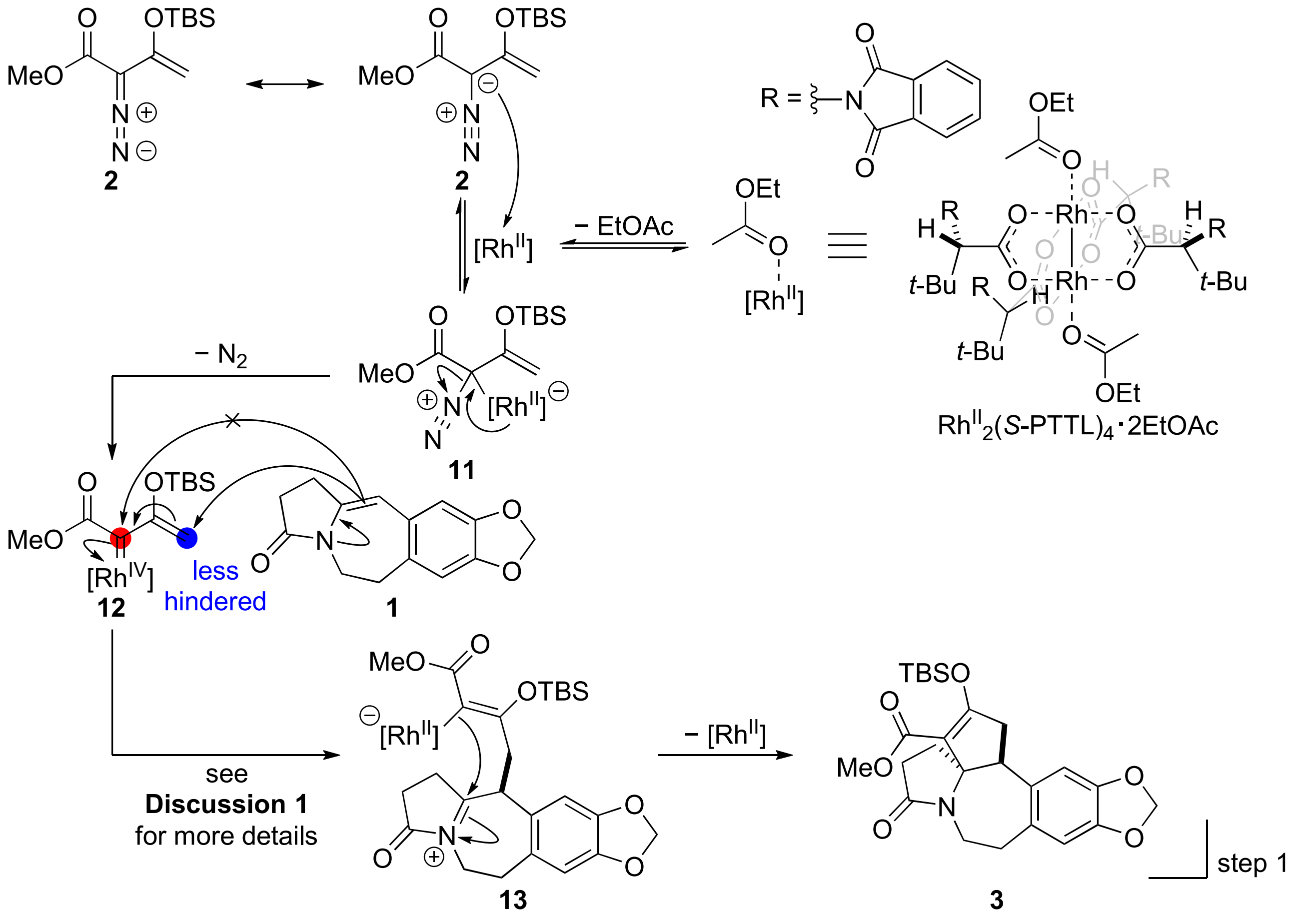
- Weinreb (1972, racemic)[1)]
- Semmelhack (1972, racemic)[2)]
- ...
- Li (2011, racemic)[3)] ⇒ 200125_PS_Shu_Nakamura
- ...
- Kim (2019, asymmetric)[4)]
- Beaudry (2019, asymmetric)[5)] ⇒ 200125_PS_Shu_Nakamura
- **Kim (2021, asymmetric)**[6)] ⇒ Problem 2
- Sakai (2021, asymmetric)[7)]
- **Fan (2023, asymmetric)**[8)] ⇒ Problem 1

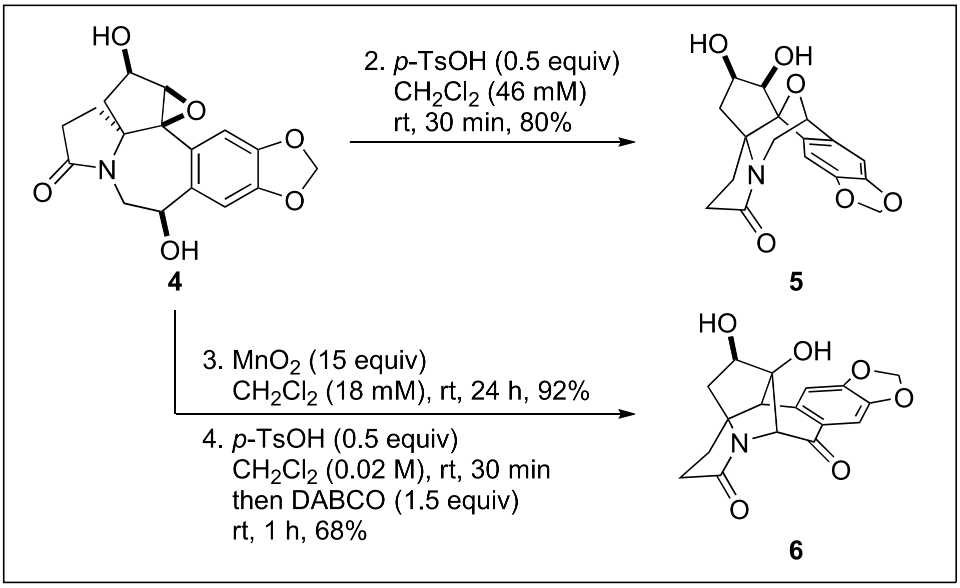
1. Problem 1

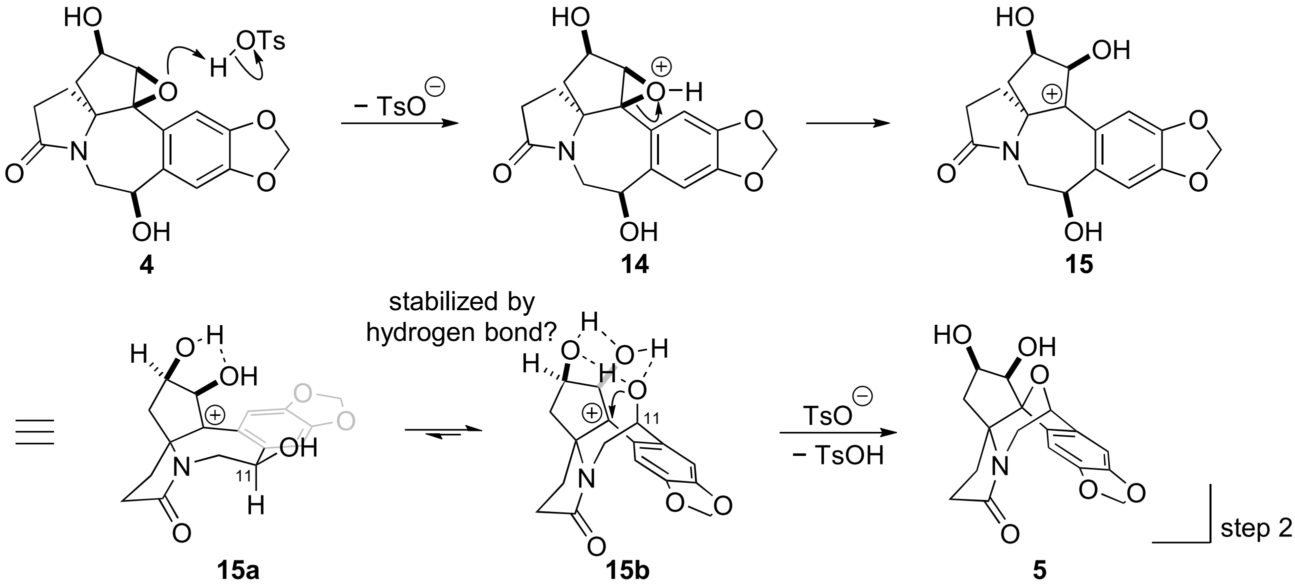
An, X.-T.; Ge, X.-M.; Liu, X.-Y.; Yang, Y.-H.; Zhao, X.-H.; Ma, X.-Y.; Peng, C.; Fan, Y.-J.; Qin, Y.; Fan, C.-A. *J. Am. Chem. Soc.* **2023**, *145*, 9233.

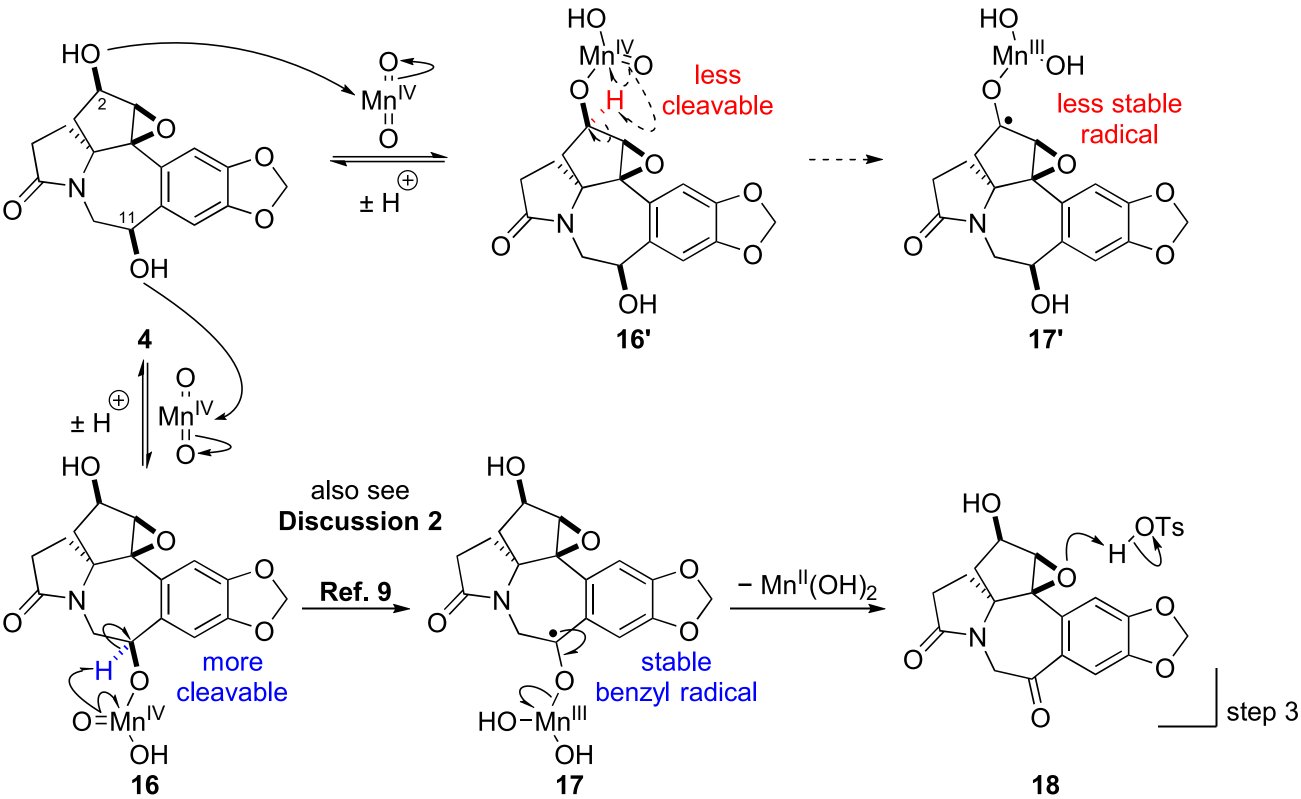
1-1. Answer

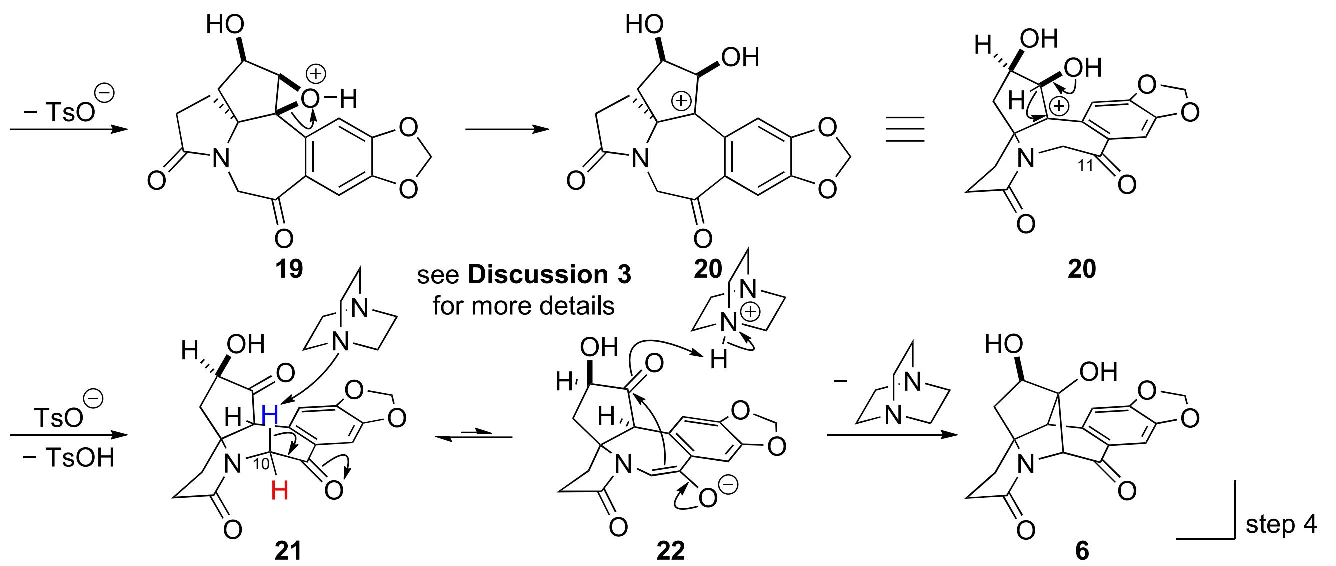




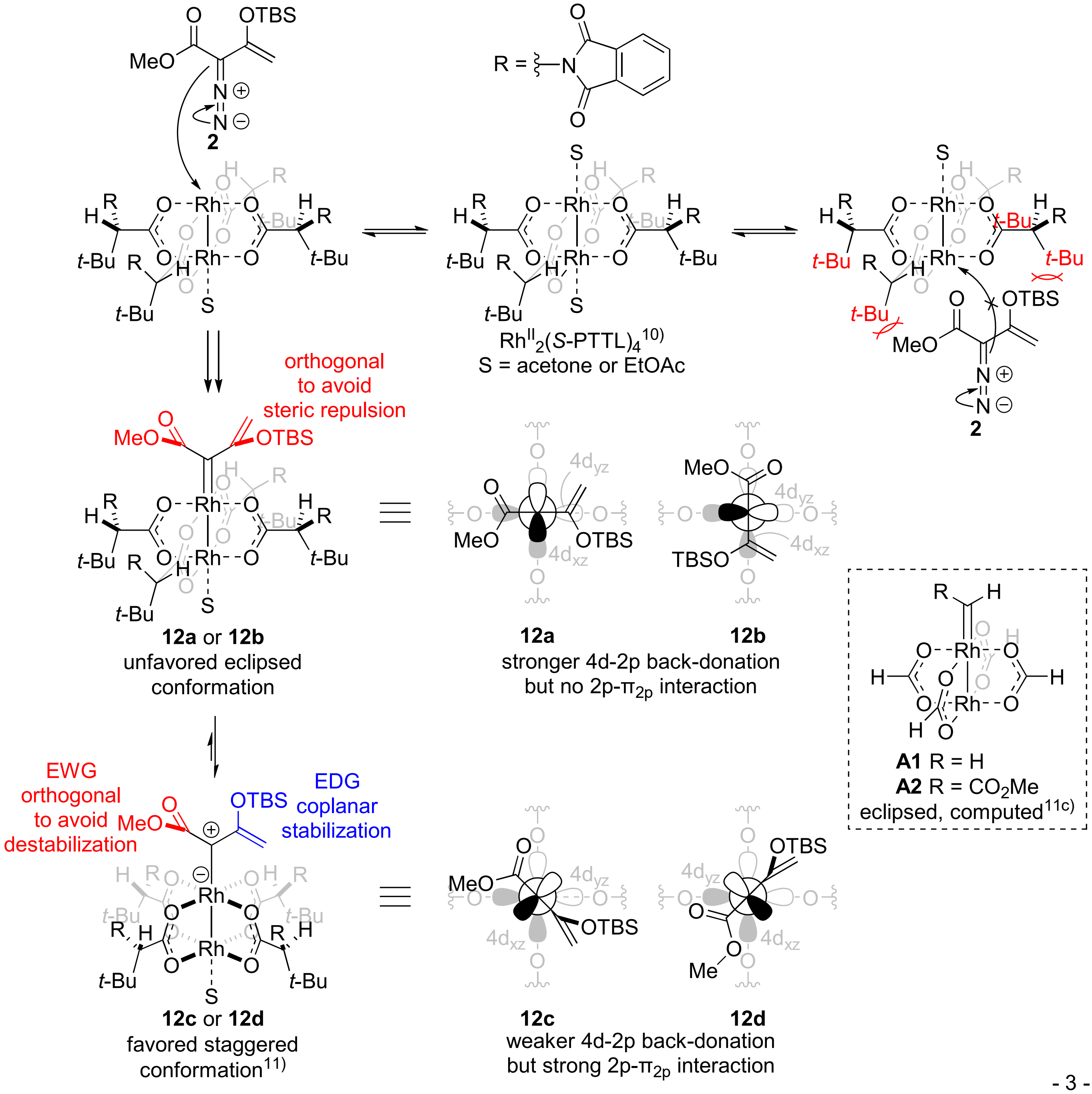

2. p-TsOH (0.5 equiv)
CH2Cl2 (46 mM)
rt, 30 min, 80%
3. MnO2 (15 equiv)
CH2Cl2 (18 mM), rt, 24 h, 92%
4. p-TsOH (0.5 equiv)
CH2Cl2 (0.02 M), rt, 30 min
then DABCO (1.5 equiv)
rt, 1 h, 68%
4
5
6

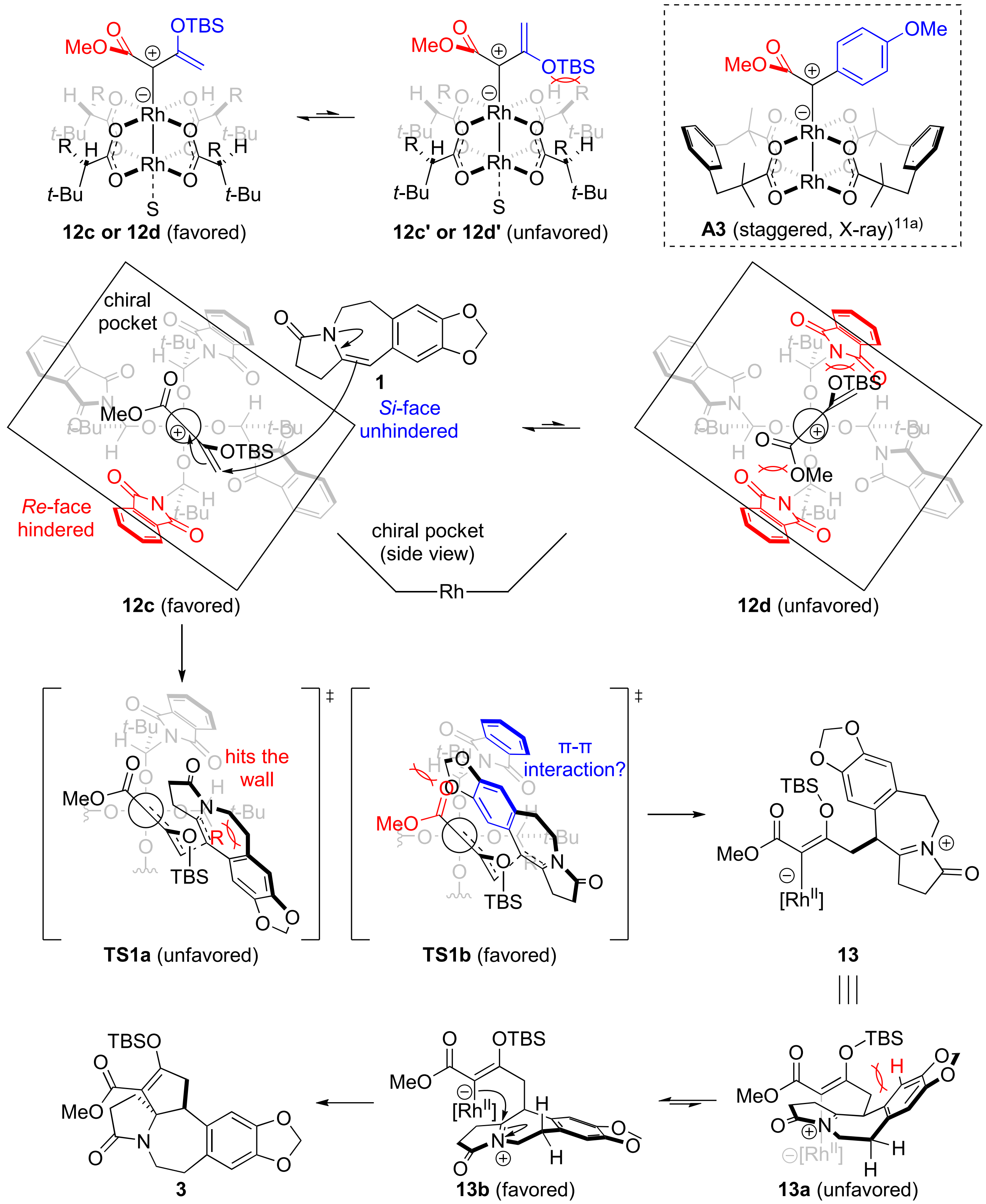

– TsO⊖
4
14
15
stabilized by
hydrogen bond?
15a
15b
TsO⊖
– TsOH
5
step 2


less
cleavable
less stable
radical
4
16'
17'
± H⊕
also see
Discussion 2
Ref. 9
more
cleavable
stable
benzyl radical
– MnII(OH)2
16
17
18
step 3



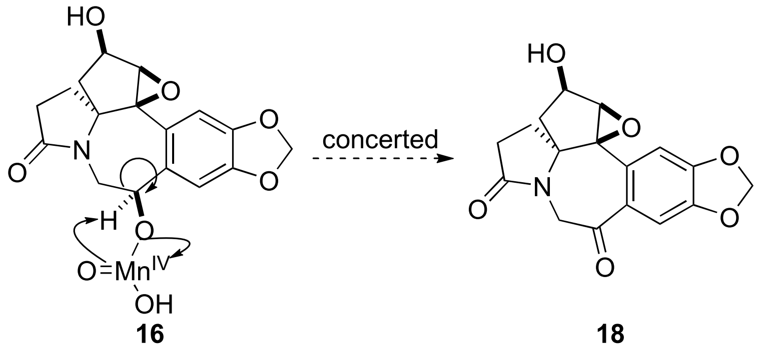
1-2. Disscusion 1: Rh-catalyzed asymmetric formal [3+2]-cycloaddition



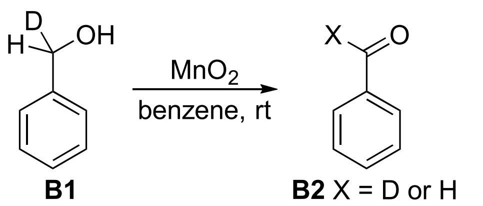


1-3. Disscusion 2: alternative mechanisms of MnO_2 oxidation

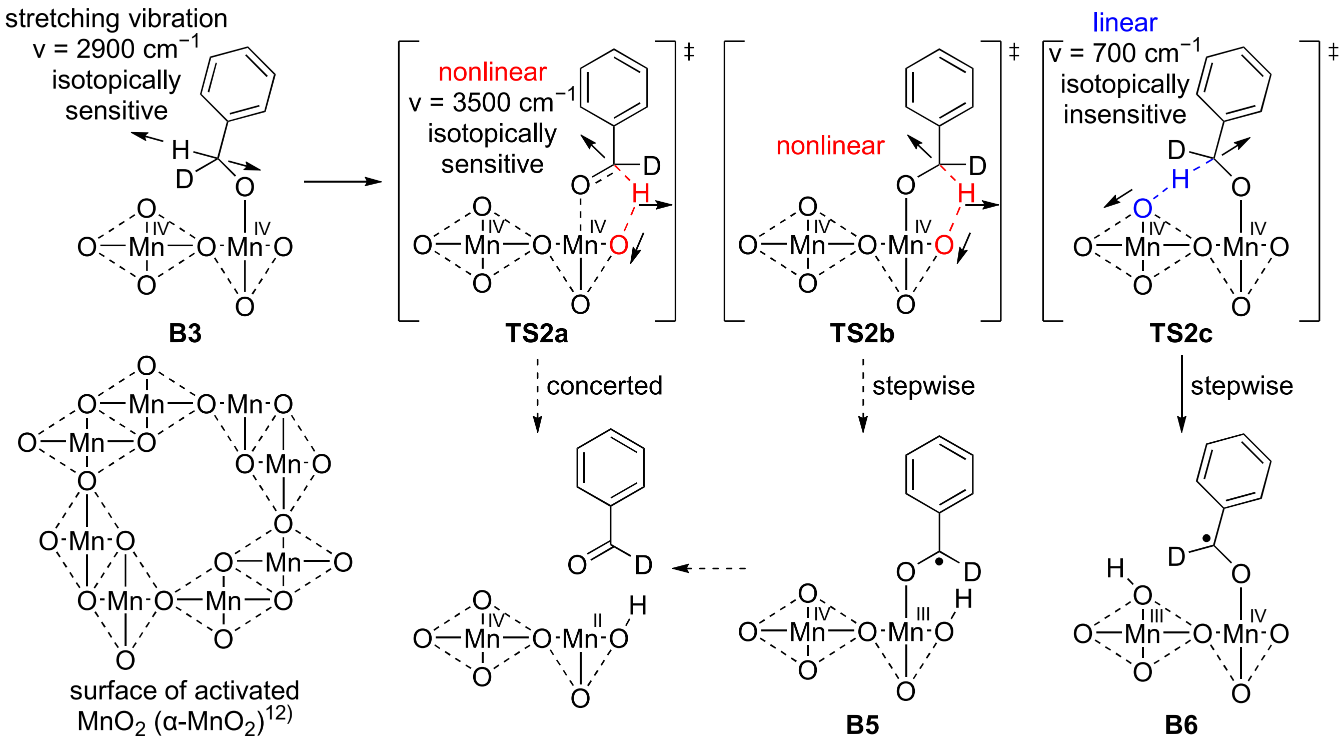
1-3-1. Concerted mechanism



Evidence for stepwise mechanism: a large kinetic isotope effect (KIE) was observed in the oxidation of benzyl alcohol[9]



$k_H/k_D = 14.2 \pm 0.9$



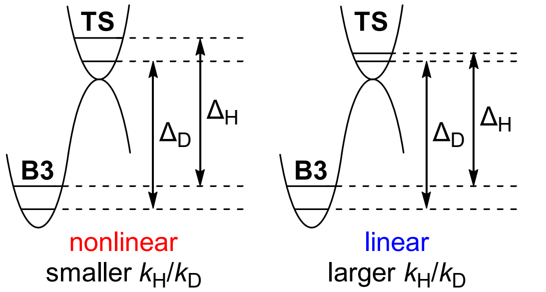
TS2c is the most plausible because:

under neutral (pH = 7) condition[13]:

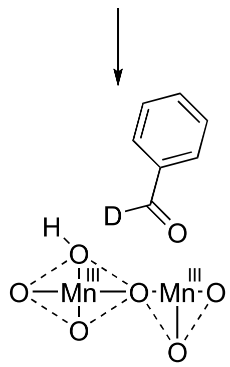
E($Mn^{IV}O_2$/$Mn^{III}OOH$) = ca. 0.56 V

E($Mn^{IV}O_2$/$Mn^{II}(OH)_2$) = ca. 0.37 V

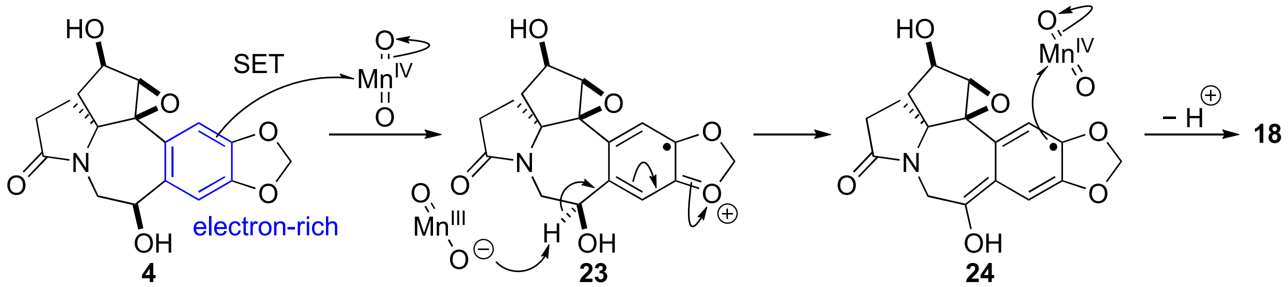
E($Mn^{III}OOH$/$Mn^{II}(OH)_2$) = ca. 0.17 V



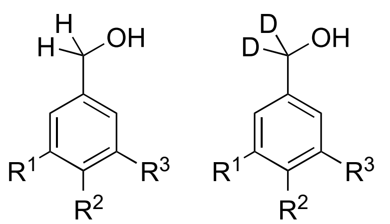
If the transition state is nonlinear, a small k_H/k_D (1~2) should be observed due to the similar energy change of stretching vibration[14].

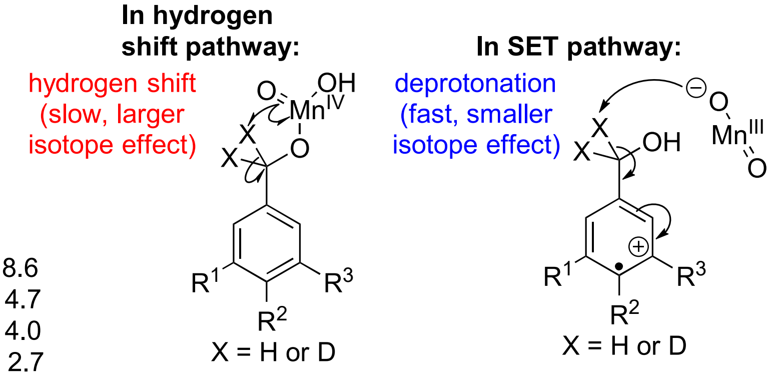


1-3-2. SET oxidation of aromatic ring



Evidence for direct oxidation of aromatic ring[15]: KIE decreases when the electron density increases (conditions: MnO_2, pH = 1.5 buffer (Na_2SO_4 aq. + H_2SO_4 aq.), rt)





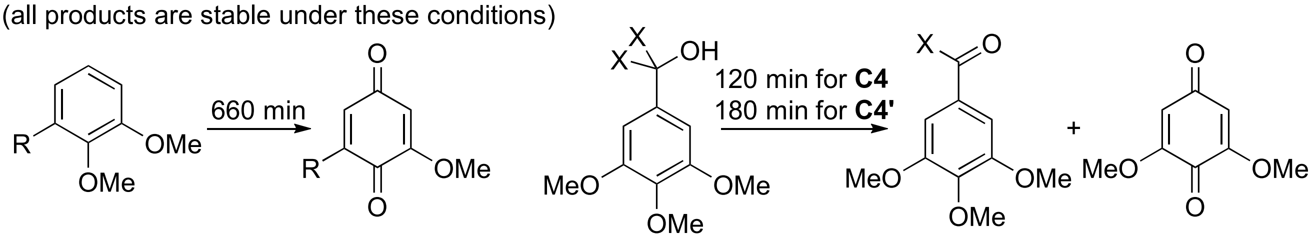
C1&C1' $R^1 = R^3 = H$, $R^2 = Et$ $k_H/k_D = 8.6$

C2&C2' $R^1 = R^3 = H$, $R^2 = OMe$ $k_H/k_D = 4.7$

C3&C3' $R^1 = H$, $R^2 = R^3 = OMe$ $k_H/k_D = 4.0$

C4&C4' $R^1 = R^2 = R^3 = OMe$ $k_H/k_D = 2.7$

(Continued) Corresponding benzoquinone products were obtained
(all products are stable under these conditions)



C5 R = H (61% rcv.)	**C7** 21%	**C4** X = H (3.5% rcv.)	**C9** 66%	**C8** 7.8%
C6 R = OMe (60% rcv.)	**C8** 13%	**C4'** X = D (12% rcv.)	**C9'** 31%	**C8** 18%

1-4. Disscusion 3: 1,2-hydride shift and intramolecular aldol reaction

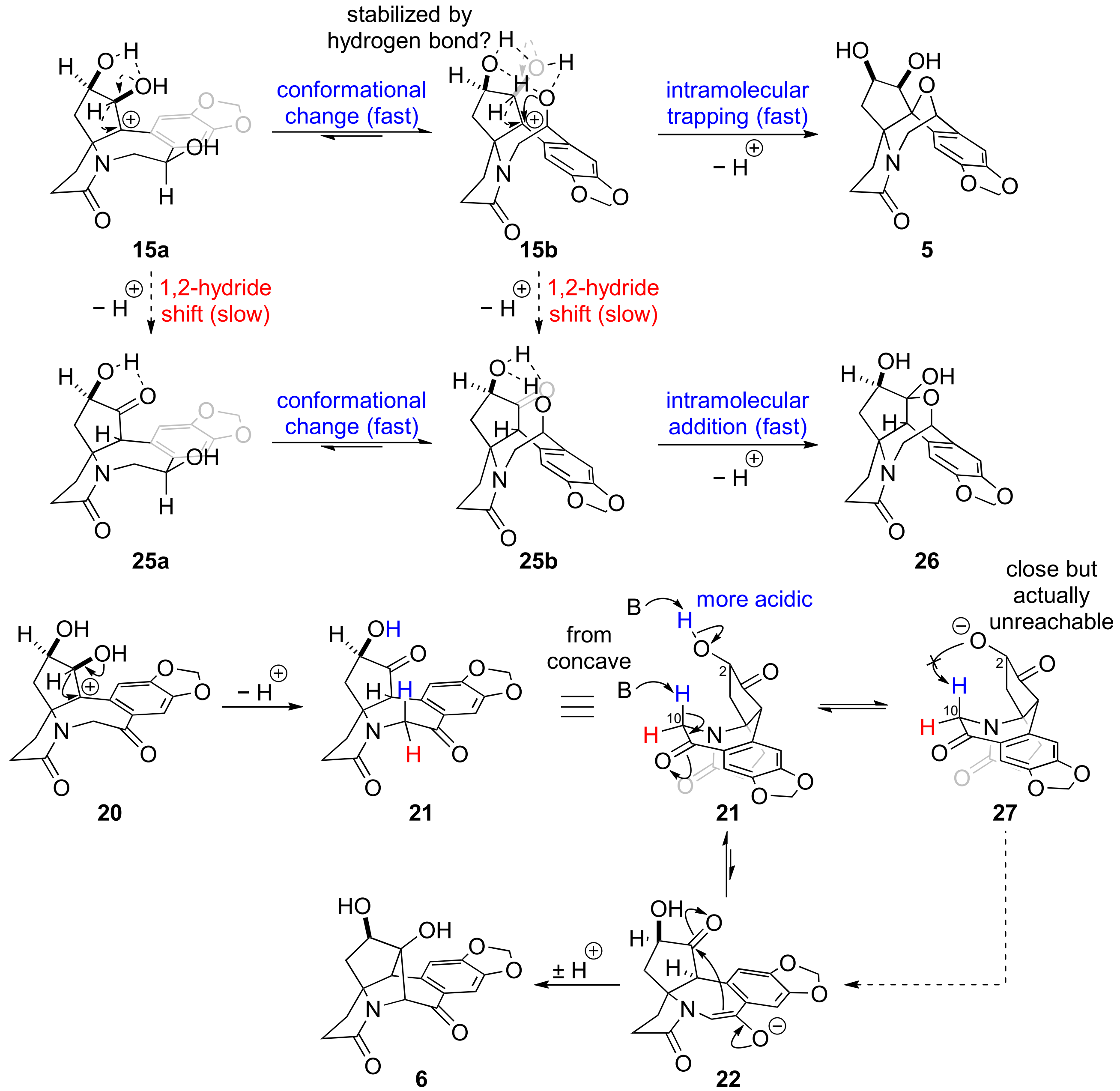


Table 1 Conditions for Aldol Reaction[a]

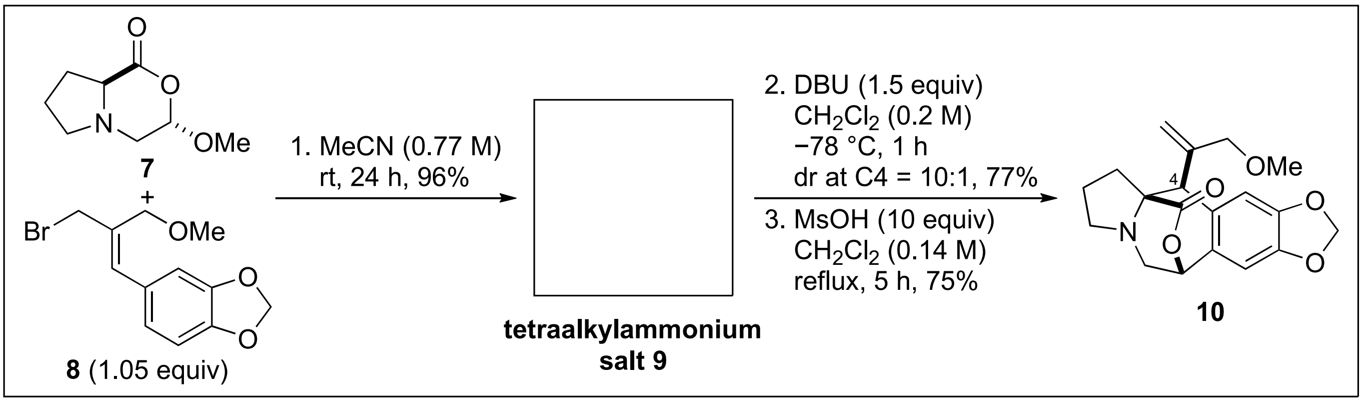
B[b]	bulkiness	time	yield of 6
DABCO	less bulky	1 h	68%
Et_3N	bulkier	1 h	58%
K_2CO_3	/	2 h	no reaction

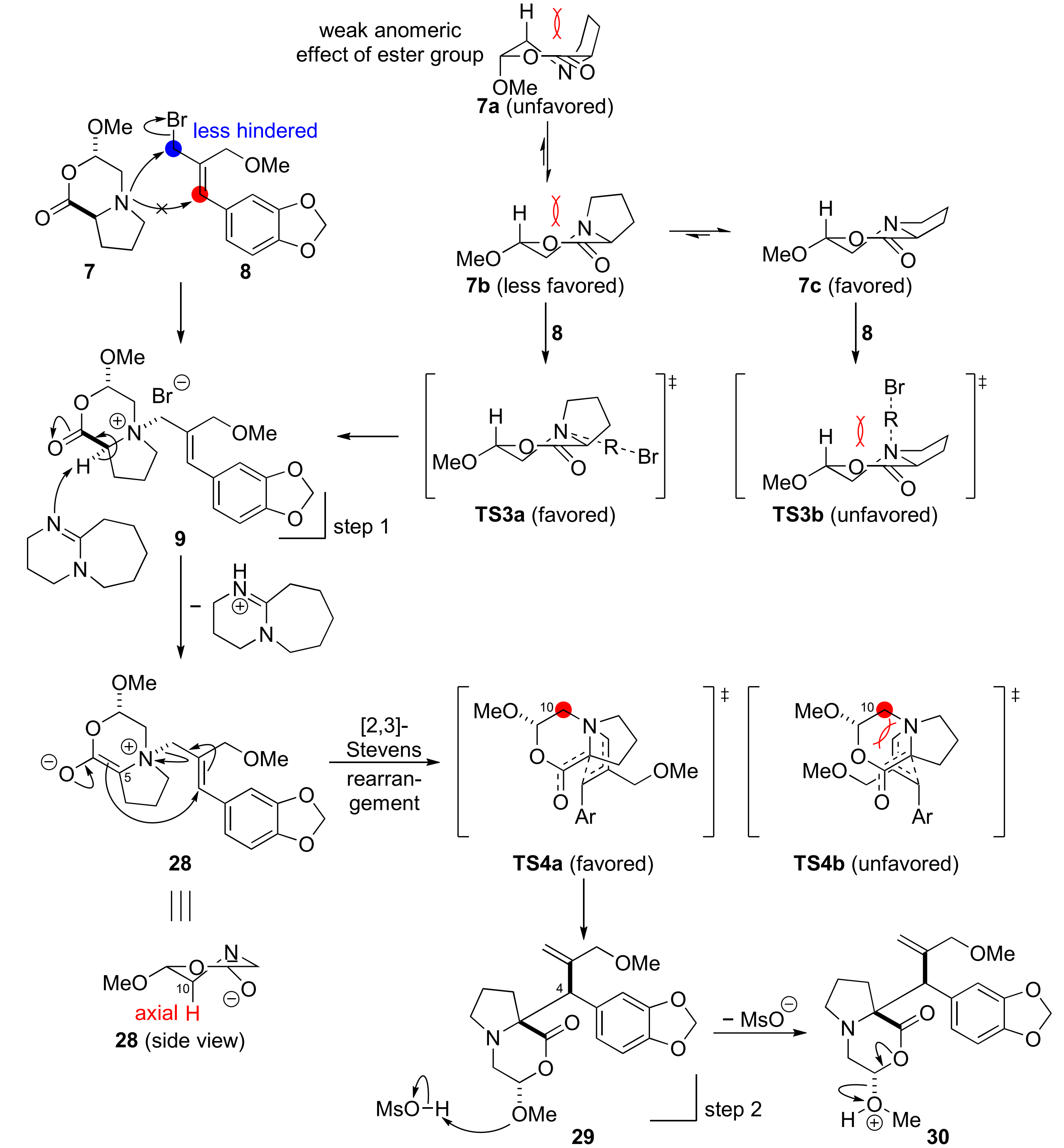
a) in CH_2Cl_2, at rt; b) 1.5 equiv

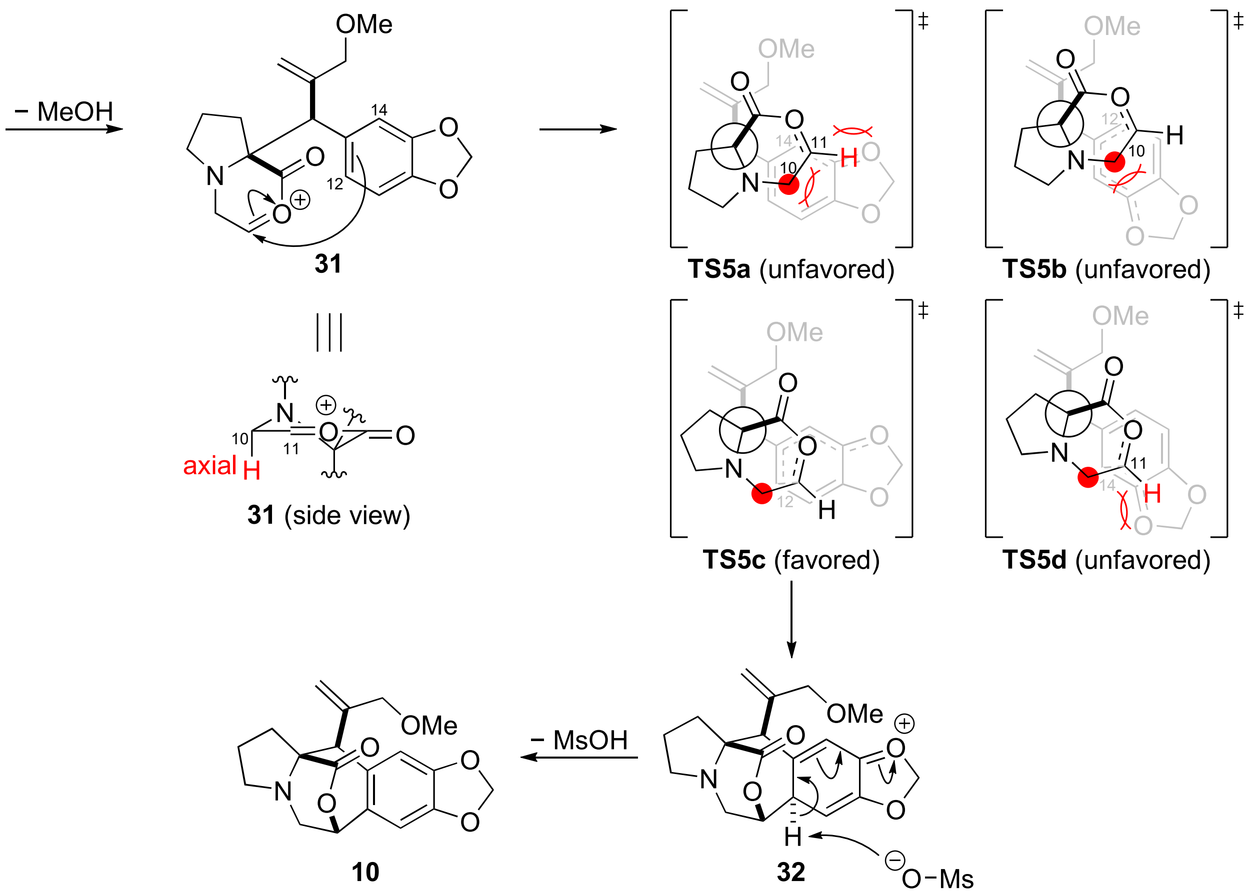
2. Problem 2

Kim, J. H.; Jeon, H.; Park, C.; Park, S.; Kim, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 12060.

2-1. Answer







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