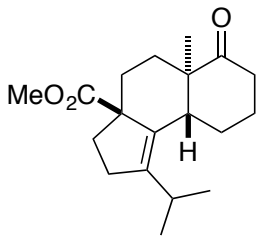
Problem Session (5)

2016. 6. 18. Keisuke Masuda

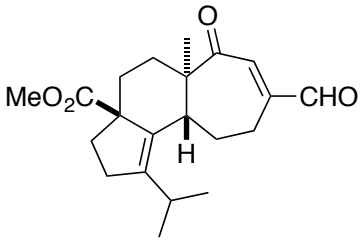
Please propose the reasonable reaction mechanism and fill the blank **2-2**, **3-2**.

1)



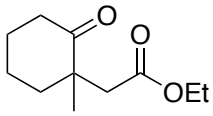
1-1

1. NaH, HCO_2Et, DME, 97%
2. *n*-PrSH, *p*-TSA
   C_6H_6, 50 ˚C, 93%
3. $MeOCH_2SPh$, *n*-BuLi
   THF, -78 ˚C
4. $HgCl_2$, HCl aq. / MeCN
   80 ˚C, 86% (2 steps)



1-2

2)

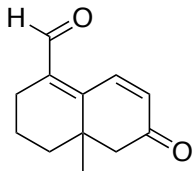


2-1
$C_{11}H_{18}O_3$

1. NaOEt, HCO_2Et
   Et_2O, 53%
2. *n*-BuSH, *p*-TSA
   C_6H_6, reflux, 90%
3. **ylide A**, NaOH aq. / CH_2Cl_2
   48˚C; SiO_2, 94%
4. HCl aq. / THF, 92%

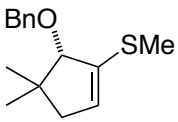
2-2
$C_{13}H_{18}O_3$

1. NaOH aq., 85 ˚C, 73%
2. $(COCl)_2$, CH_2Cl_2
3. CH_2N_2, Et_3N, Et_2O
   0 ˚C, 61% (2 steps)
4. $Rh_2(OAc)_4$ (cat.)
   CH_2Cl_2, 78%



2-3
$C_{12}H_{14}O_2$

3)

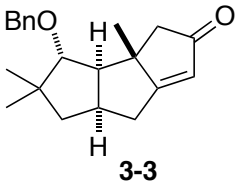


3-1
$C_{15}H_{20}OS$

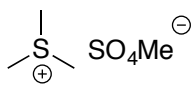
1. **enol A**, $EtAlCl_2$
   CH_2Cl_2, -45 to 0 ˚C
2. *n*-Bu_3SnH, AIBN (cat.)
   C_6H_6, reflux, 40% (2 steps)
3. EtSH, TMSCl, CH_2Cl_2, 90%

3-2
$C_{20}H_{28}OS$

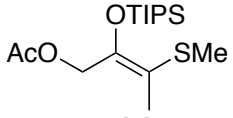
1. **enol B**, $EtAlCl_2$, CH_2Cl_2
   -45 to 0 ˚C; TBAF, 84%
2. PhSH, PhSLi, DME, 90%



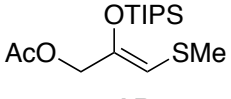
3-3
$C_{21}H_{26}O_2$



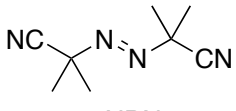
ylide A



enol A



enol B

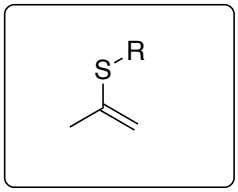


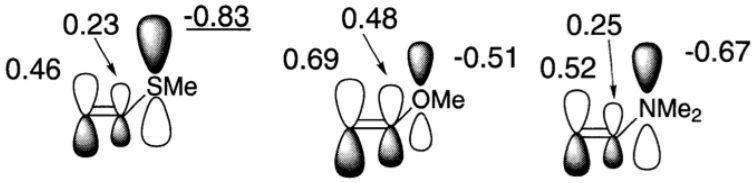
AIBN

Problem Session (5)

2016. 6. 18. Keisuke Masuda

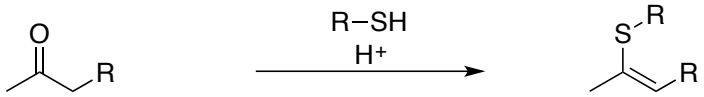
reaction of vinyl sulfide in total synthesis





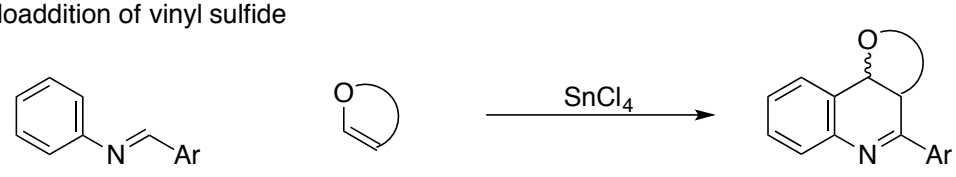
HOMO coefficients of donor olefine calculated by PM3.

0-1. synthesis of vinyl sulfide

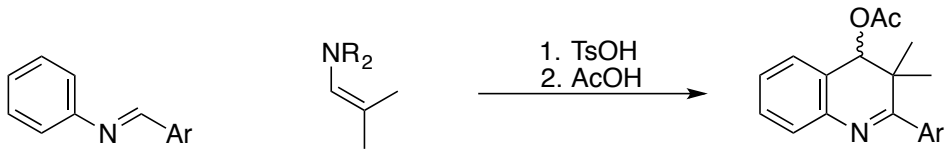


0-1 **0-2**

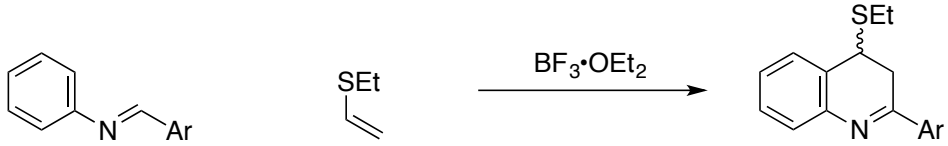
0-2. cycloaddition of vinyl sulfide



0-3 **0-4** **0-5**
10-40%



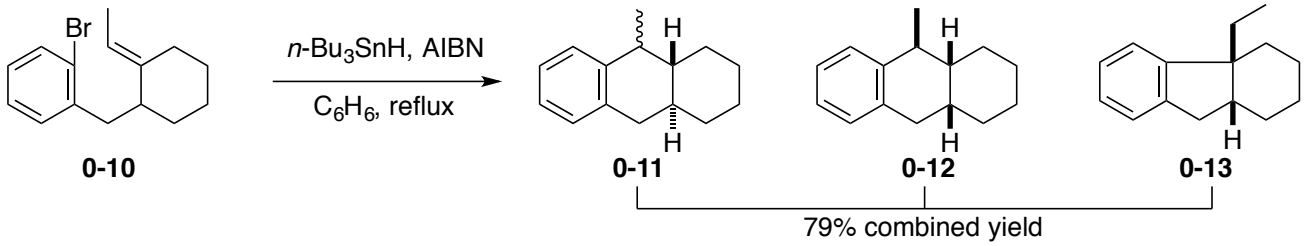
0-3 **0-6** **0-7**
50-60%



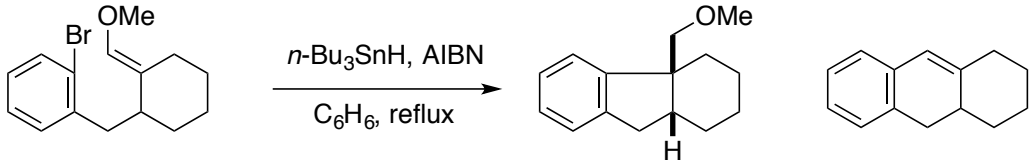
0-3 **0-8** **0-9**
90%

Nomura, Y.; Kimura,M.; Takeuchi, H.; Tomoda, S. *Chem. Lett.* **1978**, 26.

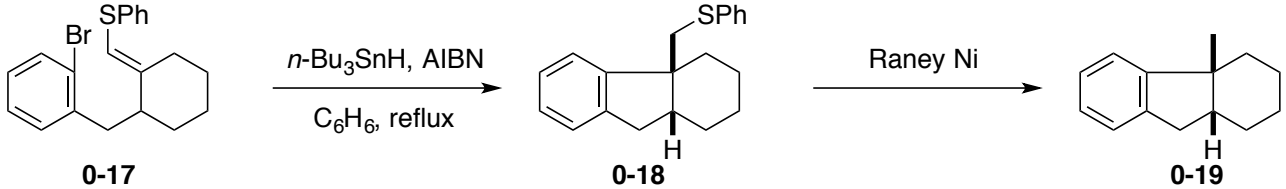
0-3. change of redioselectivity using vinyl sulfide



0-10 **0-11** **0-12** **0-13**
79% combined yield



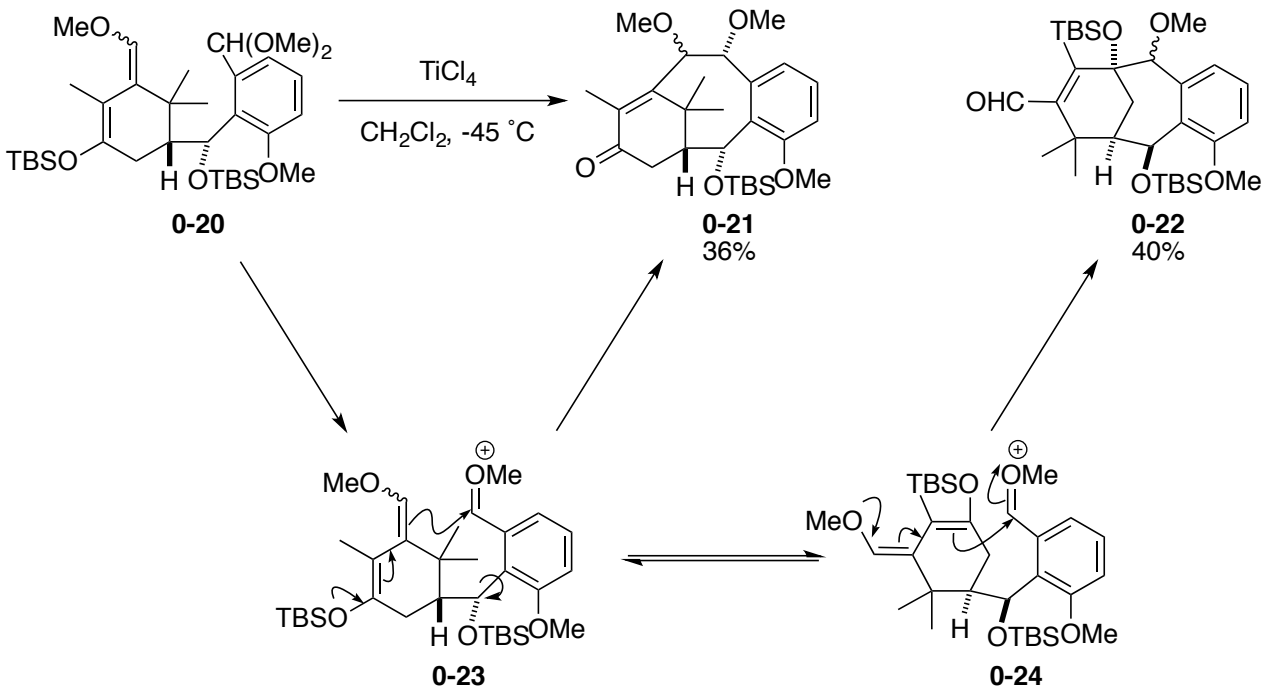
0-14 **0-15** **0-16**
55% 15%



0-17 **0-18** **0-19**
91% quant.

Ishibashi, H.; Kobayashi, T. Nakashima, S.; Tamura, O. *J/ Org. Chem.* **2000**, *65*, 9022.

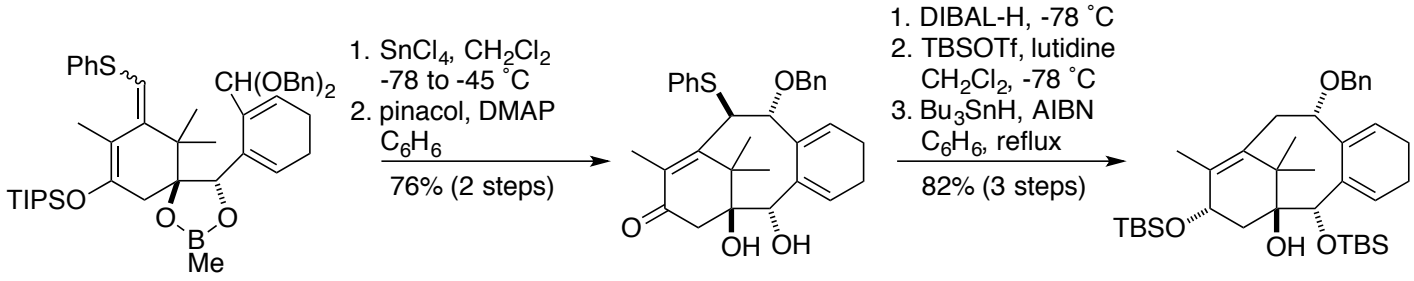
0-3. change of redioselectivity using vinyl sulfide (continued)



0-20 **0-21** 36% **0-22** 40%

0-23 **0-24**

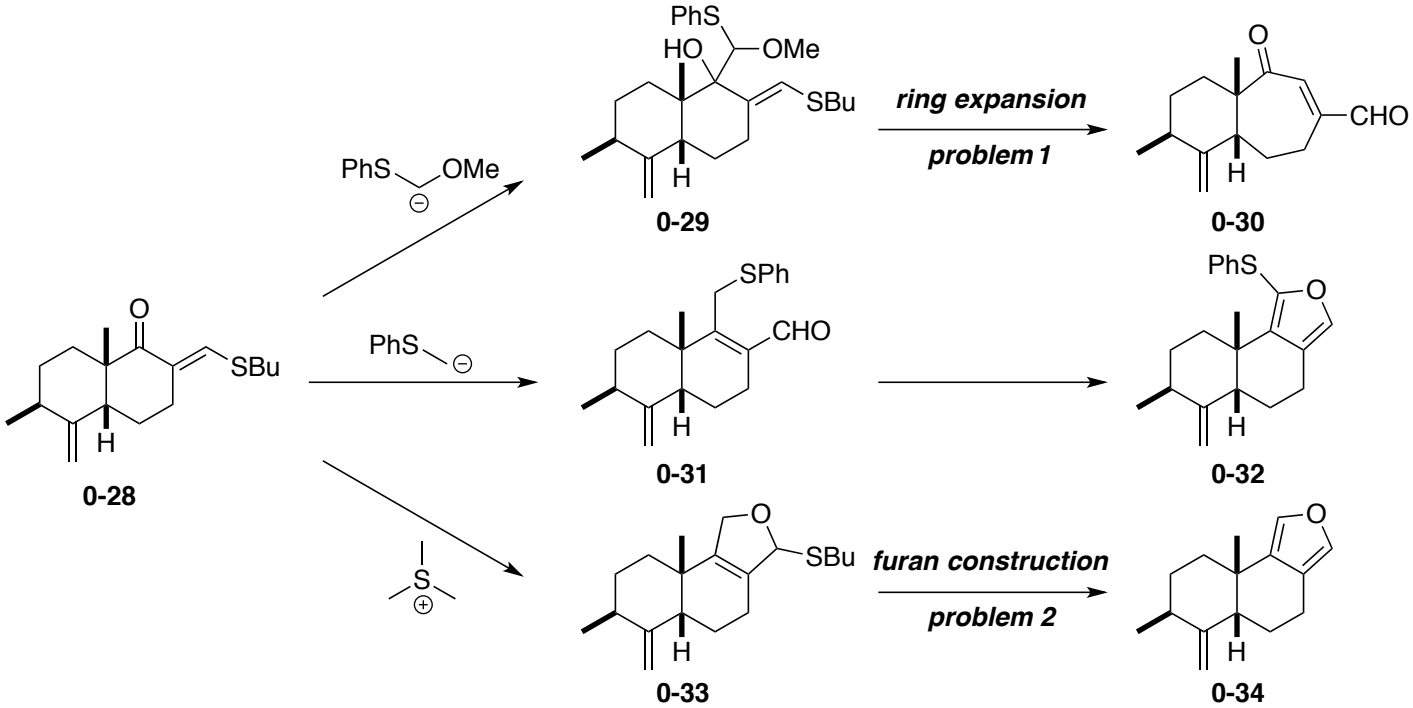
Morihira,K.; Seto, M.; Furukawa T.; Horiguchi Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345.



0-25 **0-26** **0-27**

Kusama,H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H. Nakamura, N.; Morihira,K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

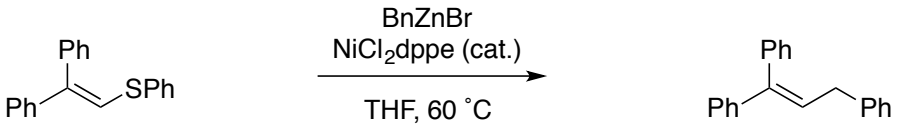
0-4. transformation of vinyl sulfide



0-28 **0-29** **0-30** **0-31** **0-32** **0-33** **0-34**

Carmely, S.; Kashman, Y. *J. Org. Chem.* **1986**, *51*, 784.

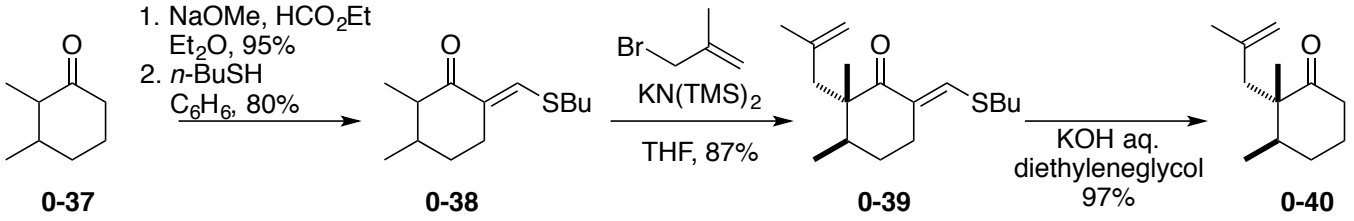
0-5. cross-coupling reaction of vinyl sulfide



0-35 **0-36**

Baba, Y.; Toshimitsu, A.; Matsubara, S. *Synlett.* **2008**, 2061.

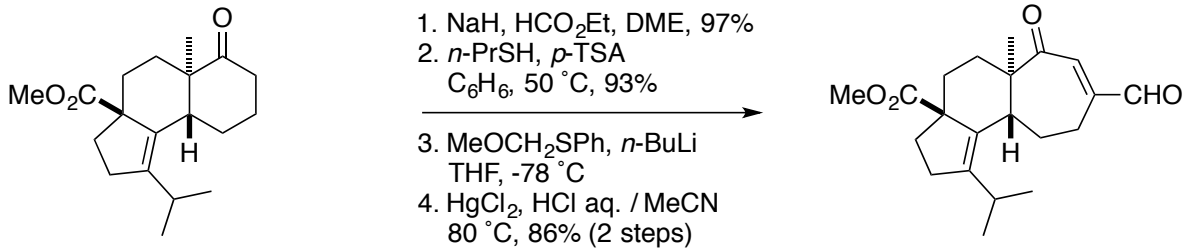
0-6. protection of α position of ketone



0-37 **0-38** **0-39** **0-40**

Mace, L.; Shanmugham, M. S.; White, J.; Drew, M. *Org. Biomol. Chem.* **2006**, *4*, 1020.

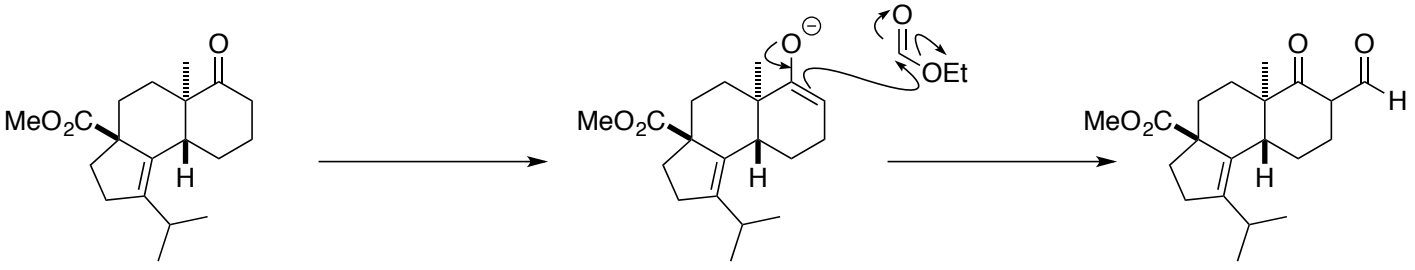
Problem 1:



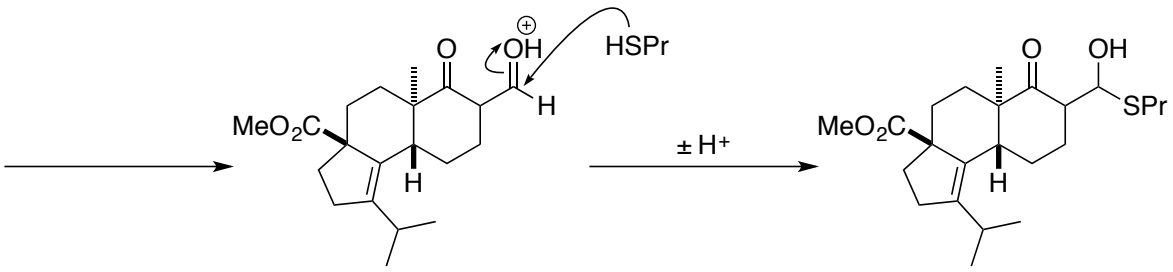
1-1 **1-2**

Waters, S. P.; Tian, Y.; Li, Y-M.; Danishefsky, S. *J. Am. Chem. Soc.* **2005**, *127*, 13514.

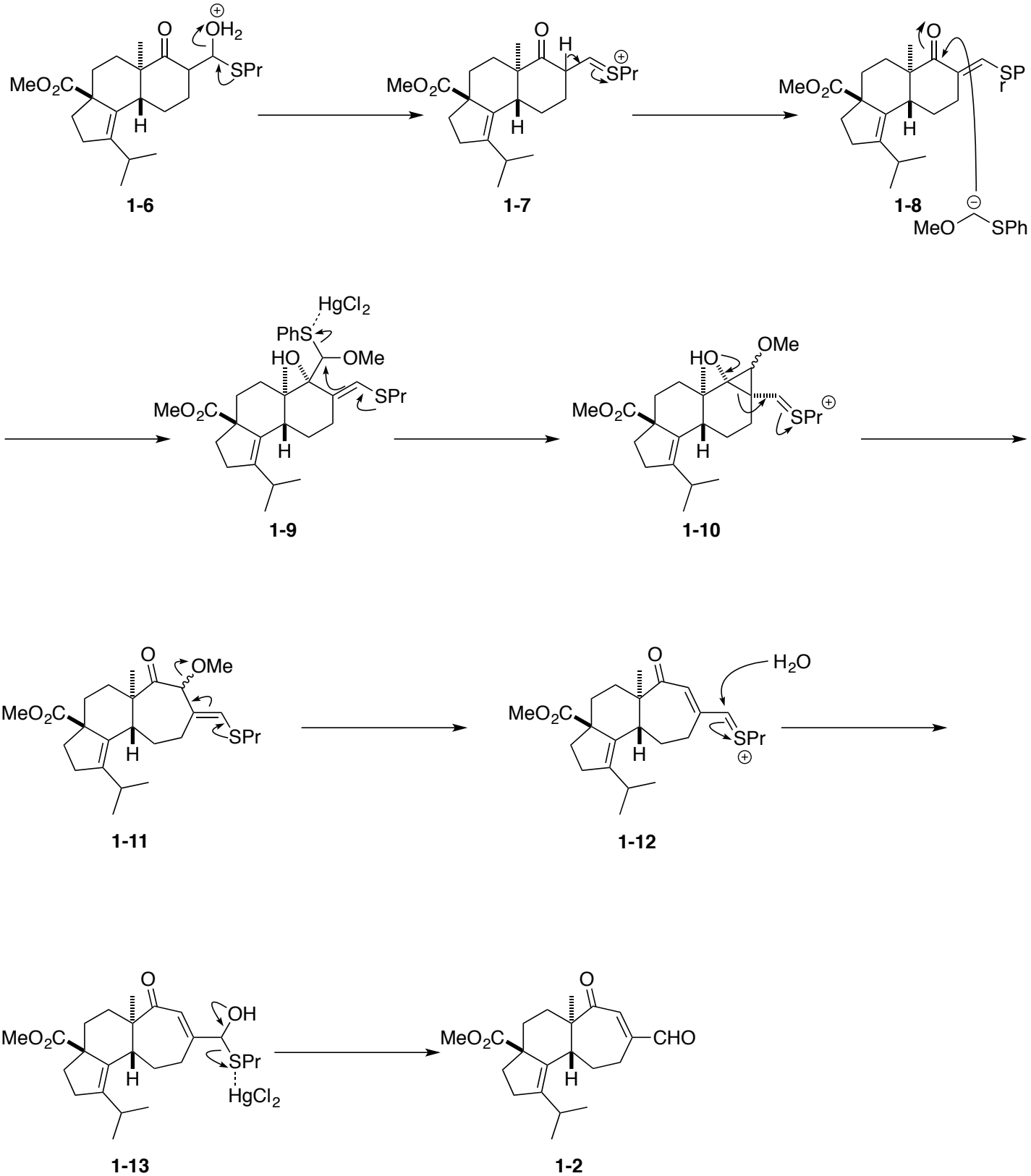
Proposed Mechanism:



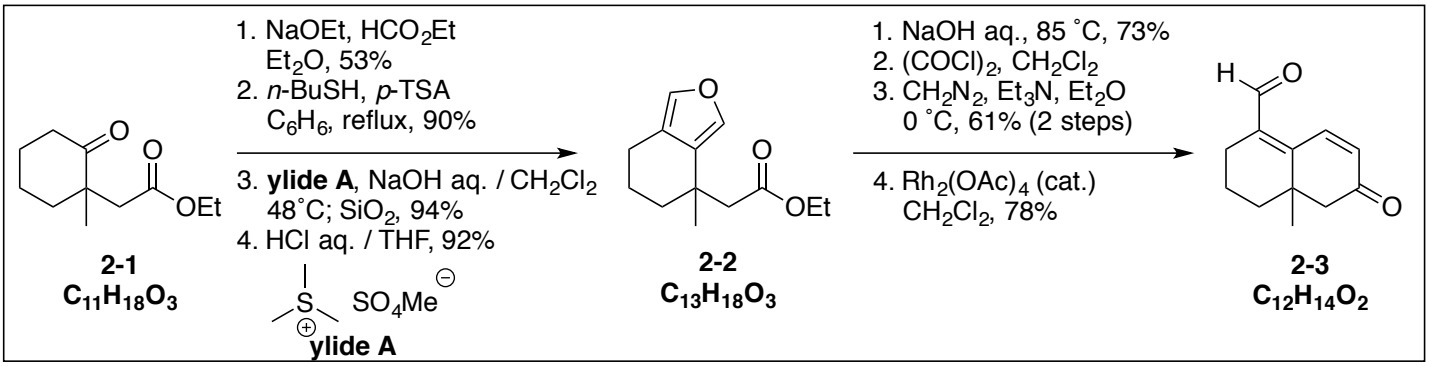
1-1 **1-3** **1-4**



1-5 **1-6**

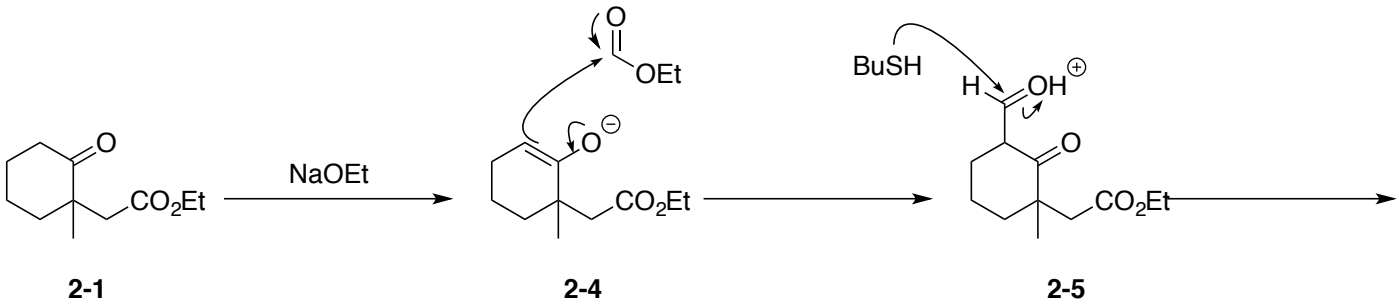

MeO2C
O
OH2
SPr
H
1-6
1-7
1-8
MeO
SPh
HgCl2
PhS
HO
OMe
1-9
1-10
1-11
H2O
1-12
OH
1-13
CHO
1-2

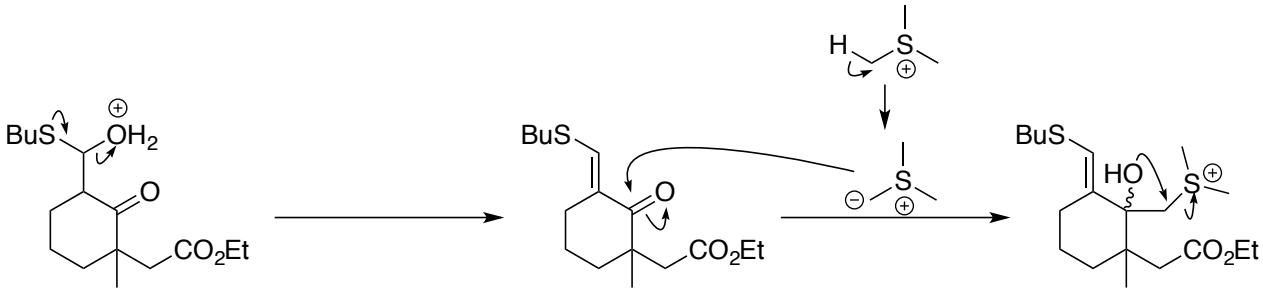
Problem 2:

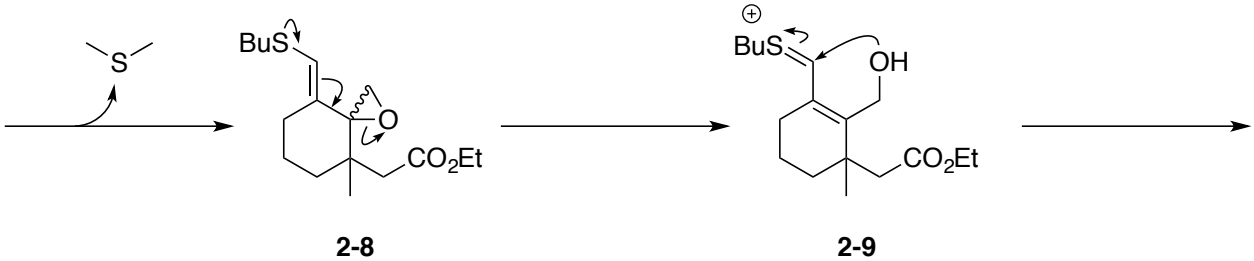


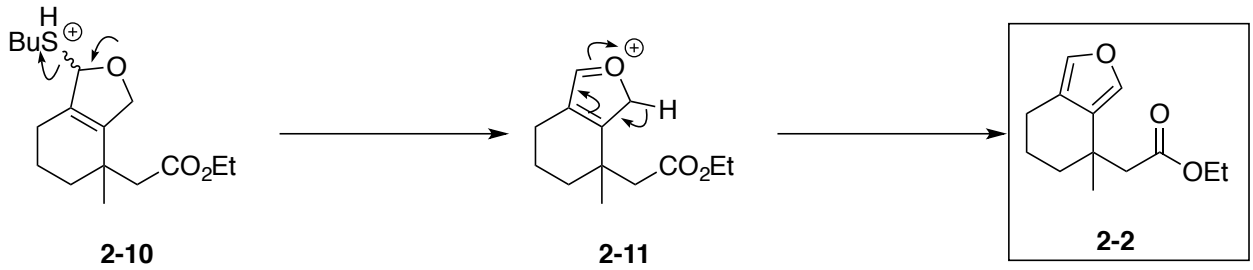
Curini, M.; Epifano, F.; Marcotullio, M.; Rosati, O.; Guo, M.; Guan, Y.; Wenkert, E. *Helv. Chim. Acta.* **2005**, *88*, 330

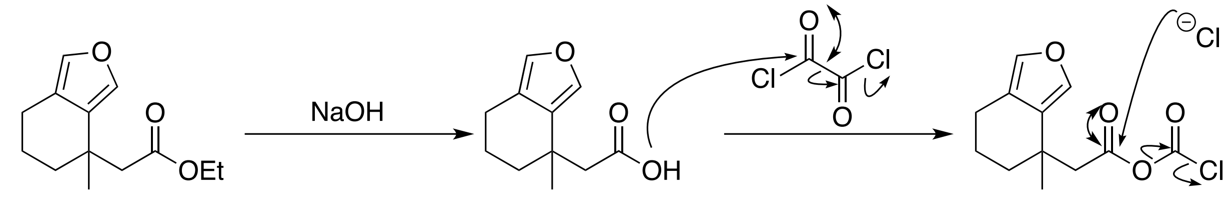
Proposed Mechanism:



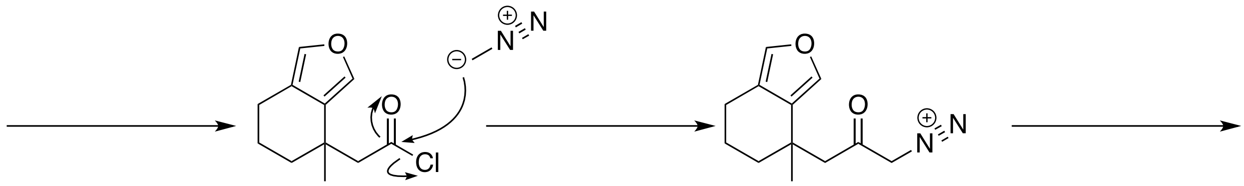






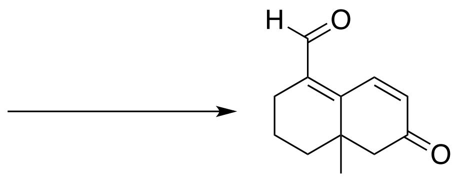


2-2 **2-12** **2-13**



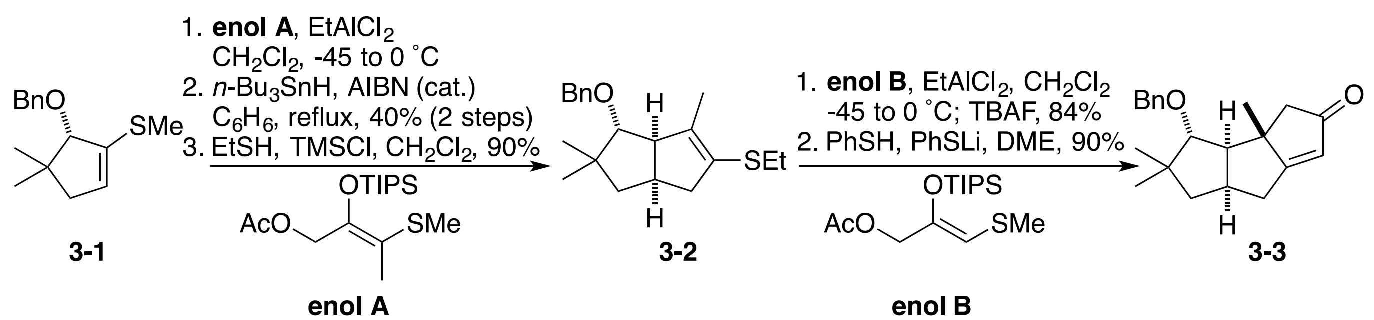
2-14 **2-15**

2-16 **2-16'** **2-17**



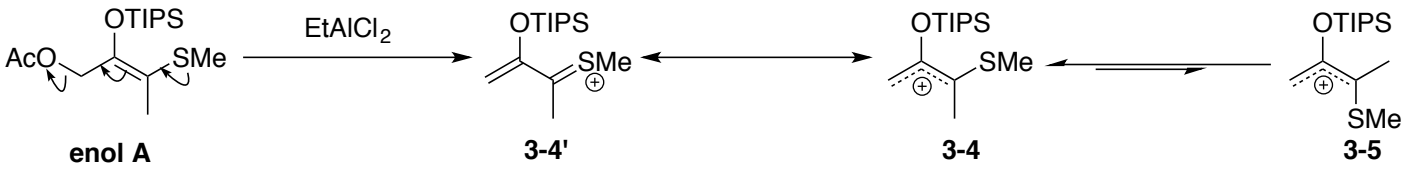
2-3

Problem 3:

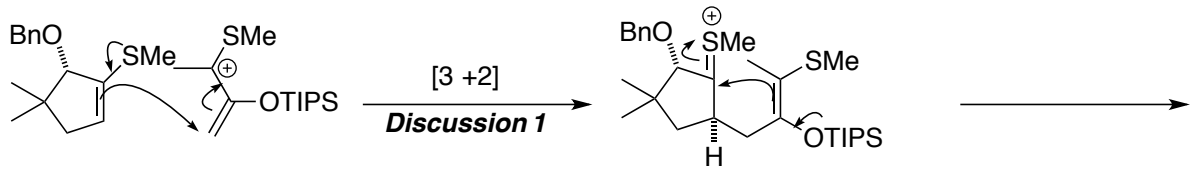


Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1997**, *38*, 465.

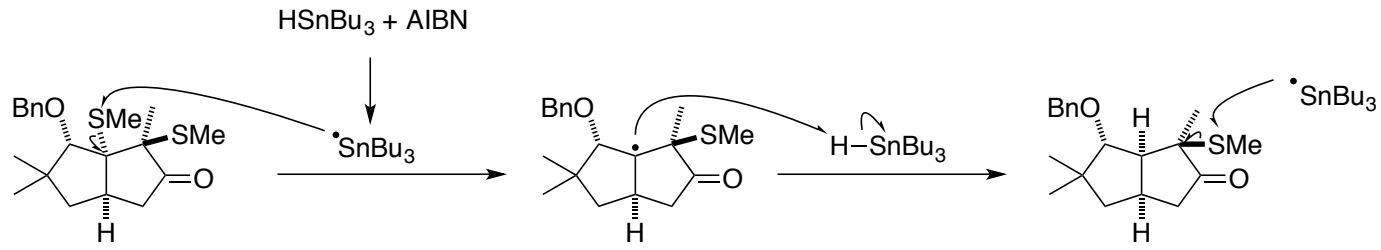
Proposed Mechanism:



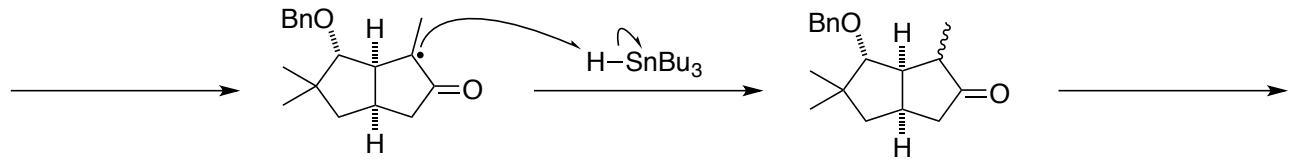
enol A **3-4'** **3-4** **3-5**



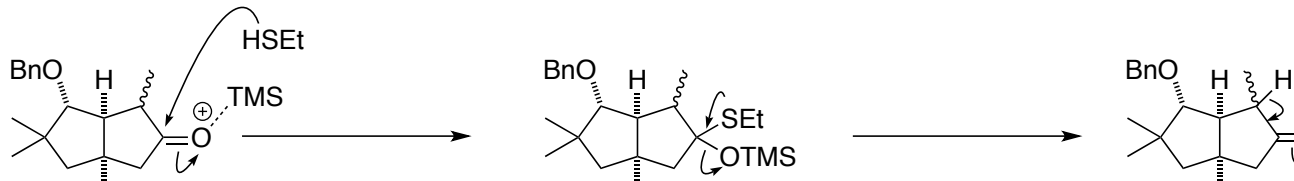
3-1 **3-4** **3-6**



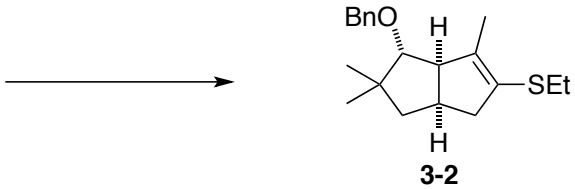
3-7 **3-8** **3-9**



3-10 **3-11**

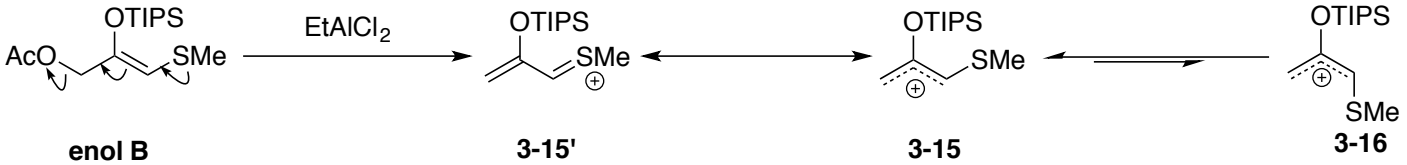


3-12 **3-13** **3-14**

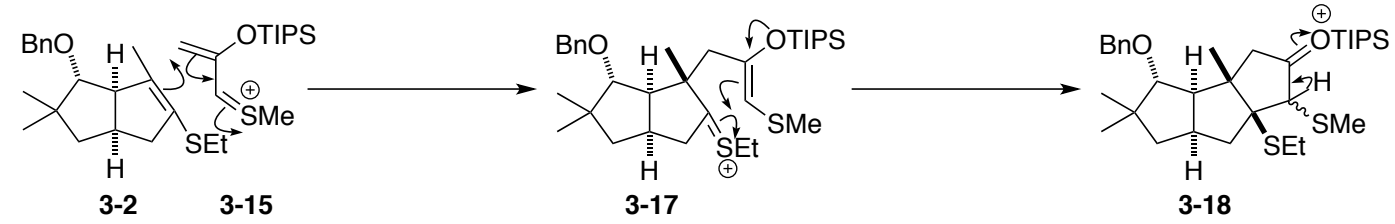


3-2

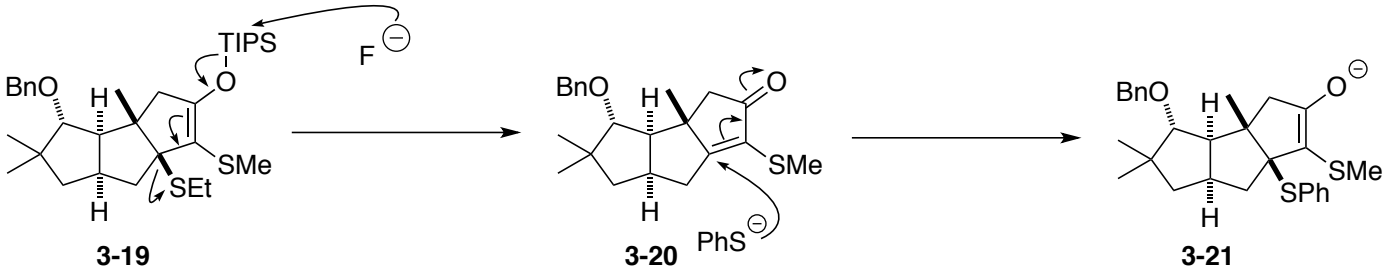
Proposed Mechanism (continued)



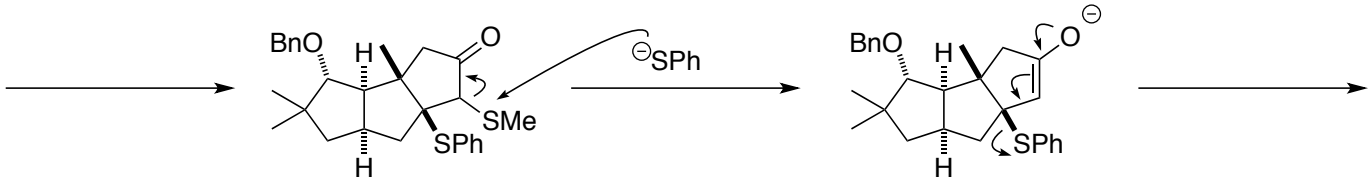
enol B **3-15'** **3-15** **3-16**



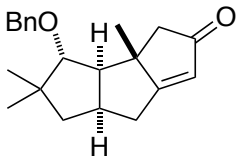
3-2 **3-15** **3-17** **3-18**



3-19 **3-20** **3-21**

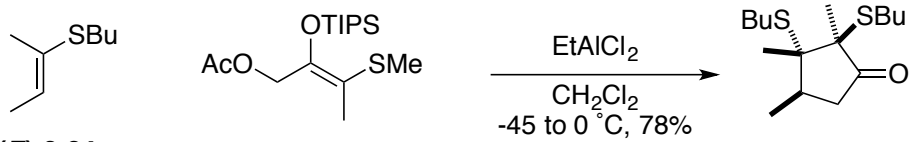


3-22 **3-23**

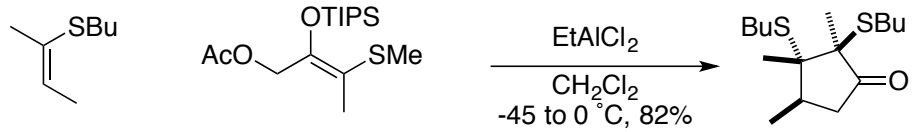


3-3

Discussion 1:
3-1. concerted path or stepwise path



(*E*)-3-24 **enol A** **3-25**

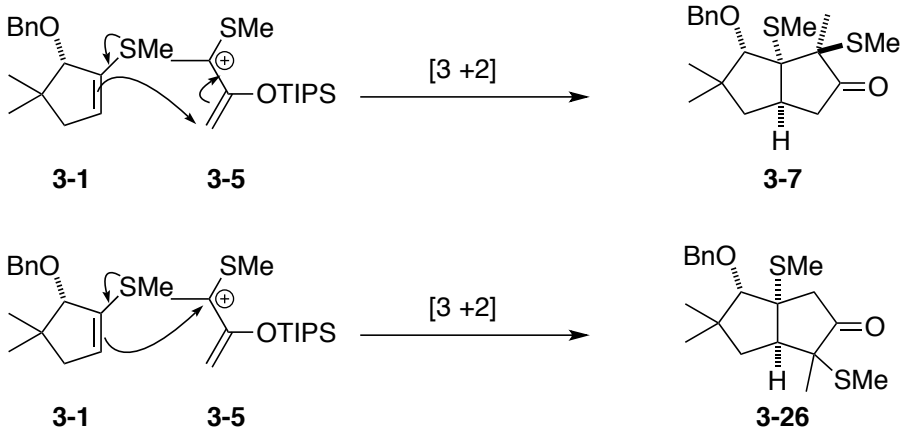


(*Z*)-3-24 **enol A** **3-25**

⇨ [3 + 2] cycloaddition reation proceeds through an ionic stepwise mechanism.

Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 1724.

3-2. regioselectivity of [3 + 2] cycloaddition reaction



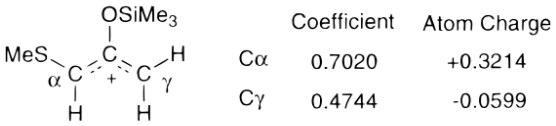


Figure 1. Coefficients and atom charges of the molecular orbital of a model compound calculated by the PM3 Method.

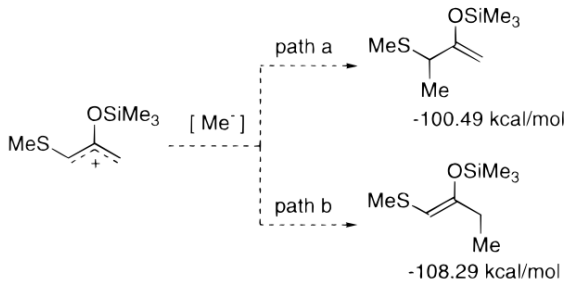


Figure 2. Heat of formation of model compounds for path a and path b calculated by the PM3 method.

3-3. stereoselectivity of first [3 + 2] cycloaddition reaction