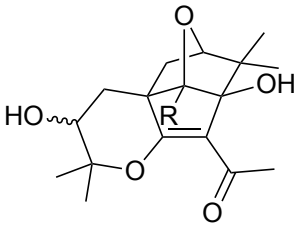
Problem Session (1) -Answer-

2020/11/21 Wataru Shigematsu

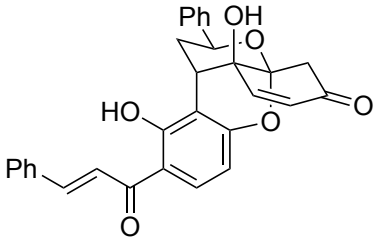
topic: Cycloaddition for formation of ring system in total synthesis

Total synthesis of (±)-Melicolone A and B (Problem 1), Total synthesis of (±)-Caesalpinnone A (Problem 2)

Introduction



1-2: R = CO_2Me
Melicolone A (β-OH)
Melicolone B (α-OH)



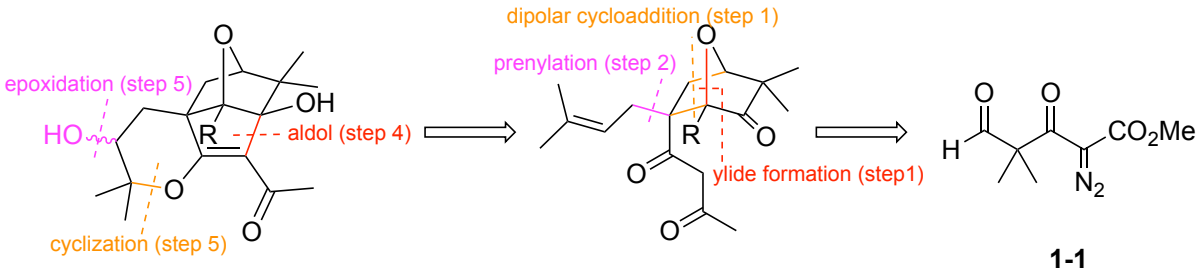
2-3
Caesalpinnone A

Isolation	*Melicope ptelefolia* (2015)[ref.1]	*Caesalpinnea enneaphylla* (2017)[ref.3]
Biological activity	components of folk medicine[ref.2]	cytotoxicity[ref.3]
Total syntheses	Martin, S. F. (racemic, 2020)	Wood, J. L. (enantioselective, 2019)[ref.4] Zheng, H. (racemic, 2019)

1) Xu, J.; Zhao, H.; Wang, X.; Li, Z.; Luo, J.; Yang, M.; Yang, L.; Yu, W.; Yao, H.; Luo, J.; Kong, L. *Org. Lett.* **2015**, *17*, 146
2) Johnson, A. J.; Kumar, R. A.; Rasheed, S. A.; Chandrika, S. P.; Chandrasekhar, A.; Baby, S.; Subramoniam, A. *J. Ethnopharmacol.* **2010**, *130*, 267
3) Zhang, L.-J.; Bi, D.-W.; Hu, J.; Mu, W.-H.; Li, Y.-P.; Xia, G.-H.; Yang, L.; Liang, X.-S.; Wang, L.-Q. *Org. Lett.* **2017**, *19*, 4315
4) Timmerman, J. C.; Sims, N. J.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141*, 10082

Retrosynthetic analysis

Melicolone A and B (problem 1)

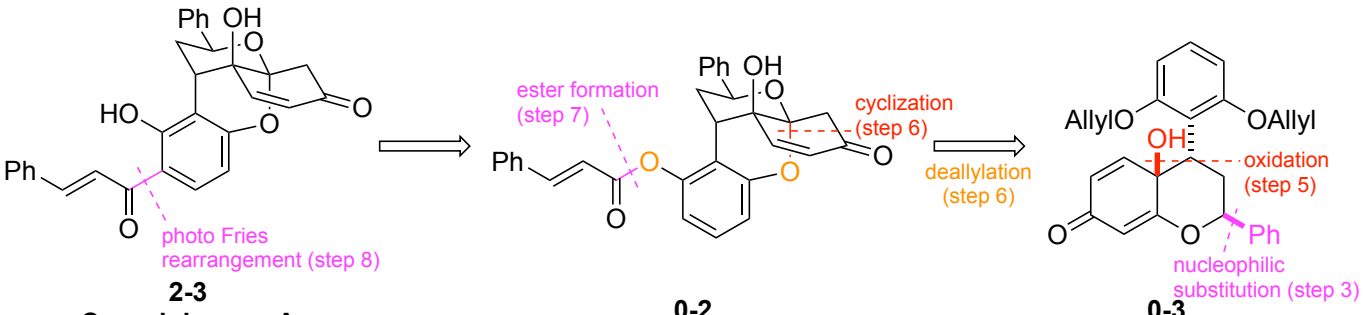


1-2: R = CO_2Me
Melicolone A (β-OH)
Melicolone B (α-OH)

0-1: R = CO_2Me

1-1

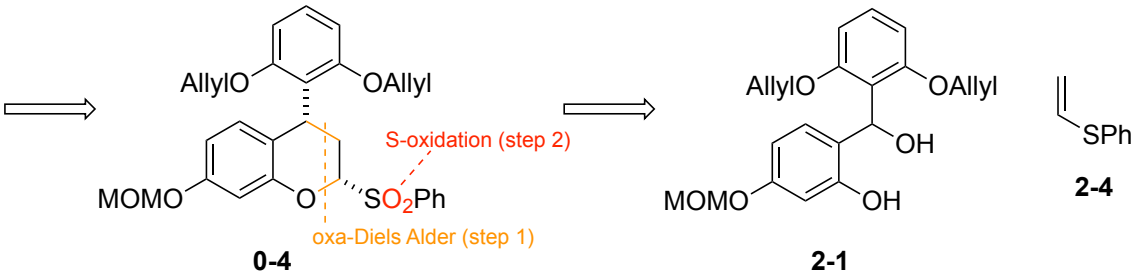
Caesalpinnone A (problem 2)



2-3
Caesalpinnone A

0-2

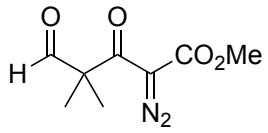
0-3



Answer

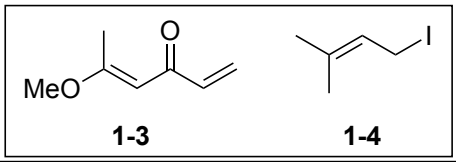
Unless otherwise noted, all compounds are racemic.

1

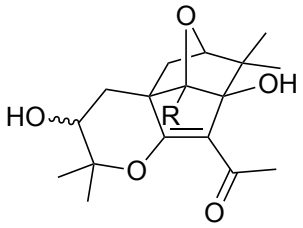


1-1

1. **1-3** (1.1 eq.), $Rh_2(HNAc)_4$ (2 mol%) toluene, 100 °C, 65% (dr = 15:1)
2. $NaN(TMS)_2$ (1.5 eq.), THF, -78 °C; **1-4** (2 eq.), THF, -78 °C, 65%
3. TMS-I (1.3 eq.), $CHCl_3$, rt; MeOH
4. DBU (2 eq.), THF, rt, 75% (2 steps)
5. *m*-CPBA (1.1 eq.), CH_2Cl_2, rt; (+)-CSA (1 eq.), CH_2Cl_2, rt, 85% (dr = 1.1:1)

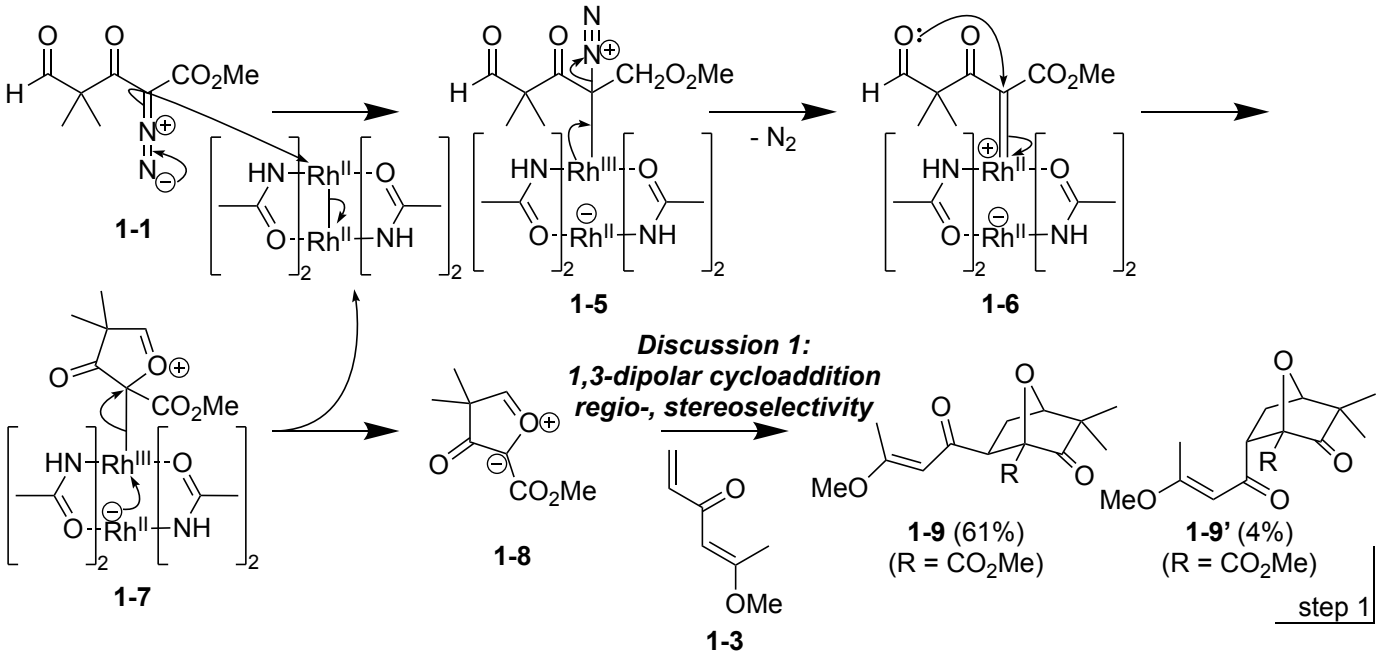


1-3 **1-4**

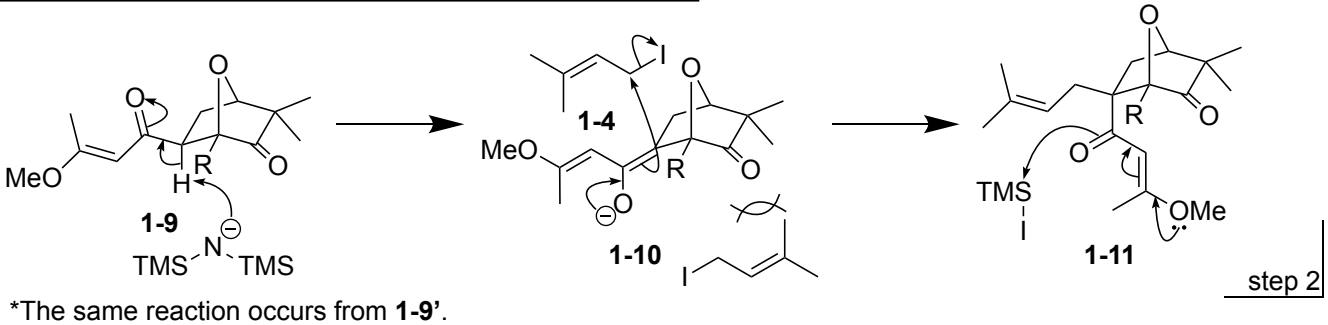


1-2: R = CO_2Me (racemic)

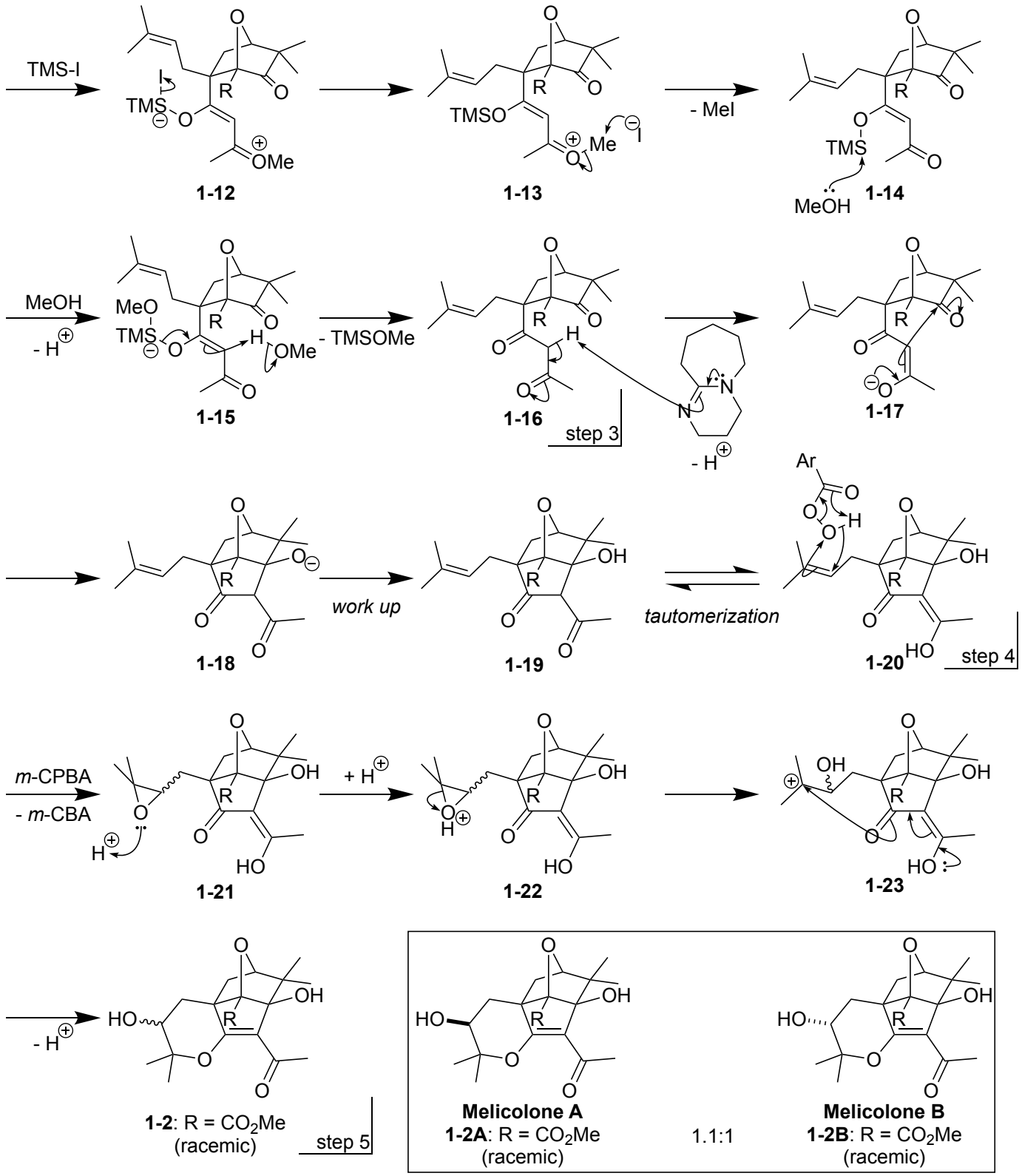
Wang, Z.; Martin, S. F. *Org. Lett.* **2020**, accepted



From **1-9** to **1-23**, substituent R is methyl ester (CO_2Me).



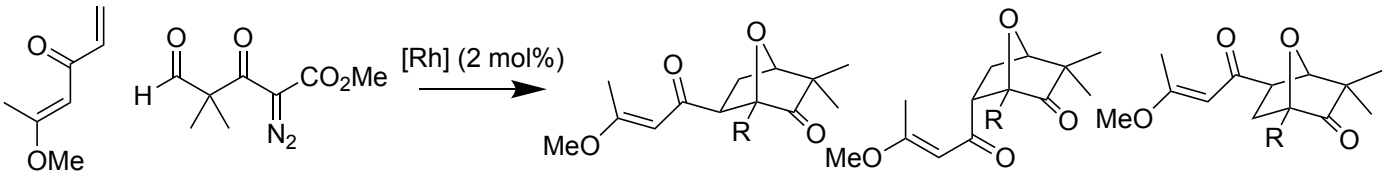
*The same reaction occurs from **1-9'**.


TMS-I
TMS
I
R
O
OMe
1-12
TMSO
Me
I
1-13
- MeI
TMS
MeOH
1-14
MeOH
- H⊕
MeO
TMS
H
OMe
1-15
- TMSOMe
1-16
step 3
- H⊕
1-17
work up
1-18
1-19
tautomerization
Ar
1-20
step 4
m-CPBA
- m-CBA
+ H⊕
HO
1-21
1-22
1-23
- H⊕
1-2: R = CO2Me
(racemic)
step 5
Melicolone A
1-2A: R = CO2Me
(racemic)
1.1:1
Melicolone B
1-2B: R = CO2Me
(racemic)

***Discussion 1*: Regio-, stereoselectivity of 1,3-dipolar cycloaddition**

1-1. Experimental result

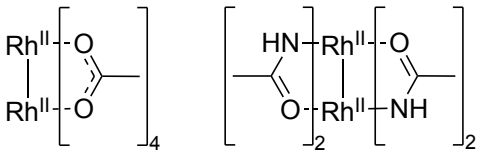
In an initial experiment, the author used $Rh_2(OAc)_4$ as a catalyst, but it didn't give a good result.
This result should help explain why this reaction occured regioselectively and stereoselectively.



1-3 (1.1 eq.) **1-1** (1 eq.) **1-9** ($R = CO_2Me$) **1-9'** ($R = CO_2Me$) **1-24** ($R = CO_2Me$)

Table 1

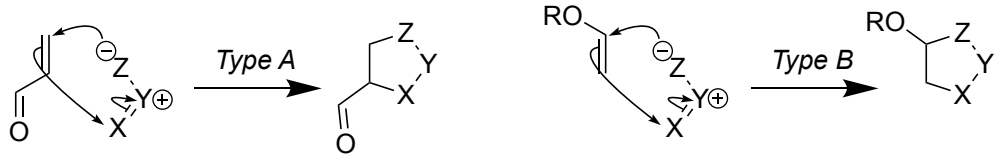
[Rh]	**1-9**	**1-9'**	**1-24**
$Rh_2(OAc)_4$	37%	10%	7%
$Rh_2(HNAc)_4$	61%	4%	4%



$Rh_2(OAc)_4$ $Rh_2(HNAc)_4$

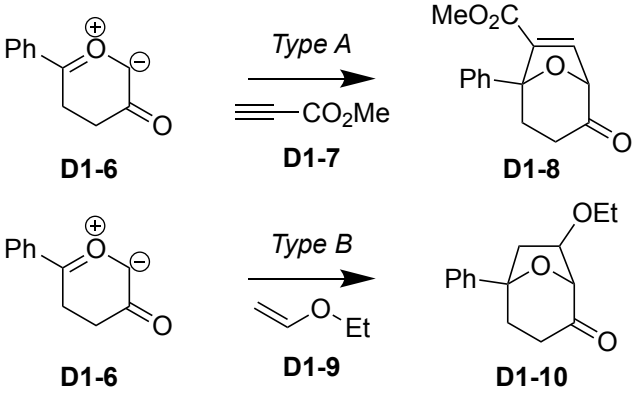
1-2. Regioselectivity

In general, cycloaddition of 1,3-dipole (**D1-2**) and enone (**D1-1**) occurs in *Type A* (as below). The interaction of HOMO of 1,3-dipole ($HOMO^d$) and LUMO of olefin ($LUMO^o$) explains the reaction mechanism.
On the other hand, cycloaddition of 1,3-dipole (**D1-2**) and vinyl ether (**D1-4**) occurs in *Type B* (as below). The interaction of LUMO of 1,3-dipole ($LUMO^d$) and HOMO of olefin ($HOMO^o$) explains the reaction mechanism.



D1-1 **D1-2** **D1-3** **D1-4** **D1-2** **D1-5**

If ($HOMO^d$ - $LUMO^o$) is smaller than ($HOMO^o$ - $LUMO^d$), the cycloaddition mainly occurs in *Type A*.
If ($HOMO^d$ - $LUMO^o$) is larger than ($HOMO^o$ - $LUMO^d$), the cycloaddition mainly occurs in *Type B*.



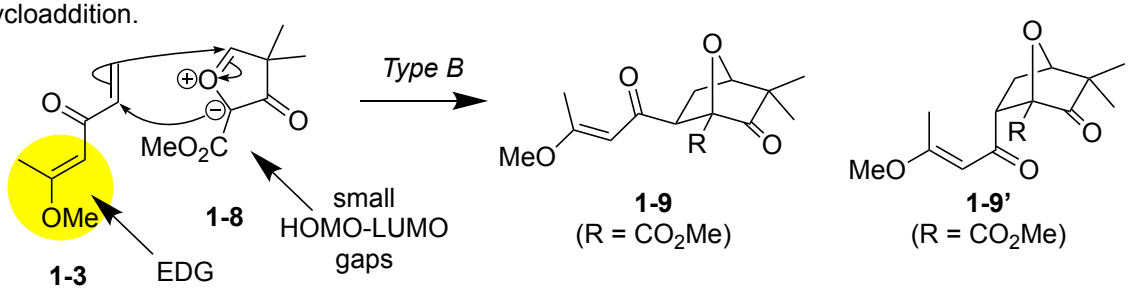
D1-6 **D1-7** **D1-8**

D1-6 **D1-9** **D1-10**

***Table 2*: energy separation (ΔE (eV))** *ref.5*

	D1-6 D1-7	**D1-6 D1-9**
$HOMO^d$ - $LUMO^o$	8.03	9.21
$HOMO^o$ - $LUMO^d$	10.09	8.02

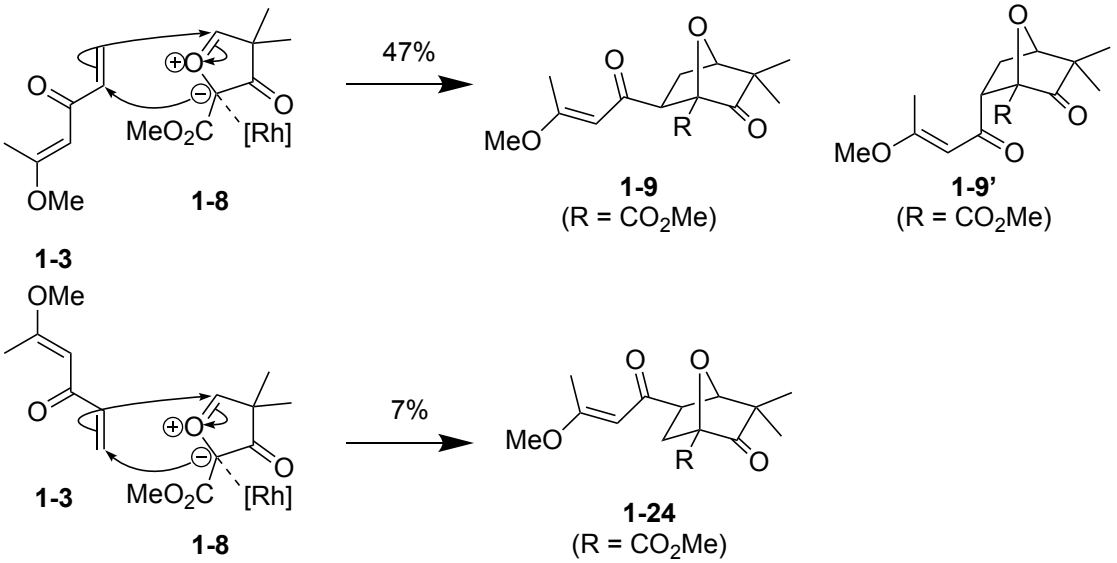
It is said that carbonyl ylides (such as **1-8**) possess small HOMO-LUMO gaps of the common 1,3-dipoles. *ref.5*
In addition, enone **1-3** has electron donating group (vinyl ether).
Vinyl ether also has C=C bond, but this is *tri*-substituted olefin. Therefore, this C=C bond doesn't get involved in the cycloaddition.



1-3 **1-8** **1-9** ($R = CO_2Me$) **1-9'** ($R = CO_2Me$)

5) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100

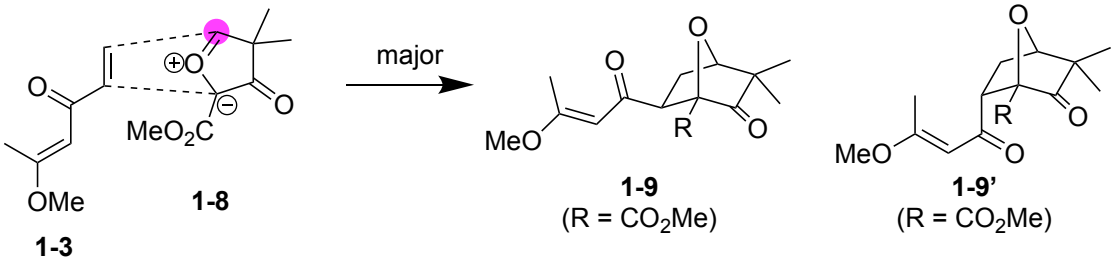
When $Rh_2(OAc)_4$ was used as a catalyst, regioselectivity got worse. This should be because acetoxy group strongly donated electon to **1-8** and HOMO of **1-8** got higher and easily attack enone β posession of **1-3**.



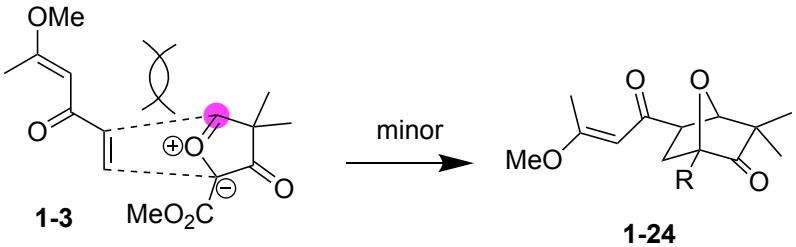
1-3 **1-8** **1-9** (R = CO_2Me) **1-9'** (R = CO_2Me)

1-3 **1-8** **1-24** (R = CO_2Me)

The author said that steric hindrance of the neopentyl center in the carbonyl ylide **1-8** caused this regioselectivity.



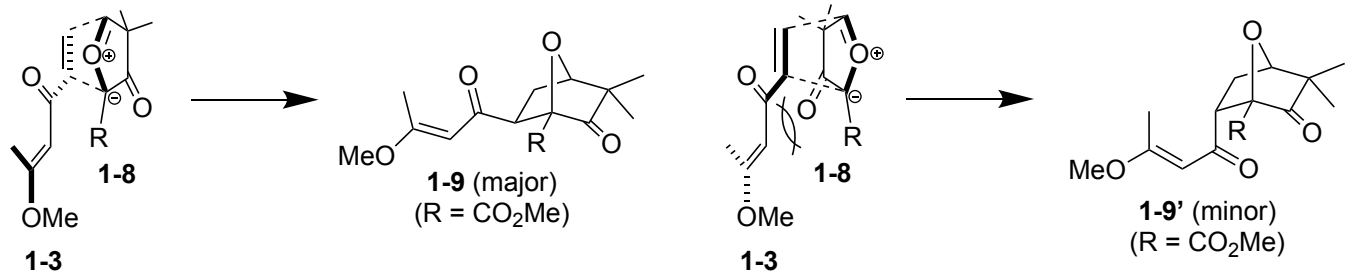
1-3 **1-8** **1-9** (R = CO_2Me) **1-9'** (R = CO_2Me)



1-3 **1-8** **1-24** (R = CO_2Me)

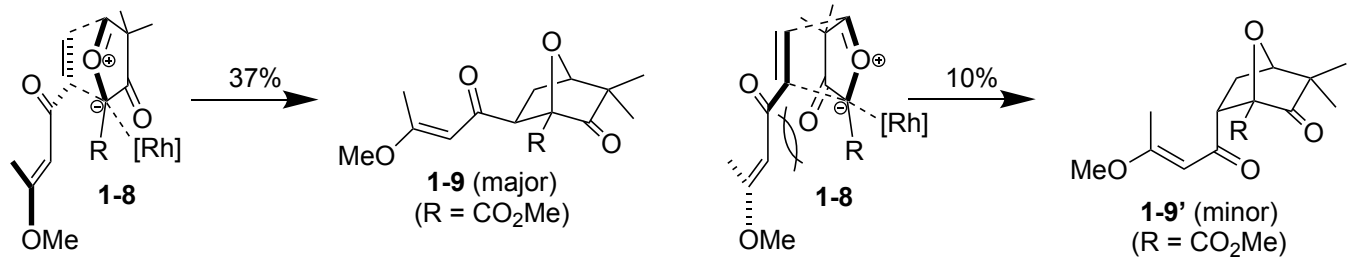
1-3. Stereoselectivity

Stereoselectivity of this reaction is explained by steric hindrance.



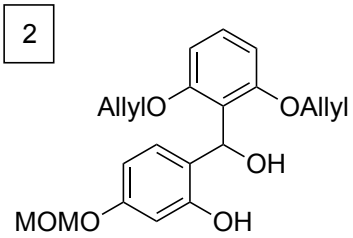
1-3 **1-8** **1-9** (major) (R = CO_2Me) **1-3** **1-8** **1-9'** (minor) (R = CO_2Me)

When $Rh_2(OAc)_4$ was used as a catalyst, stereoselectivity got worse. This might be because acetoxy group strongly donated electon to **1-8** and secondary orbital interaction affected diastereo ratio of this reaction.



1-3 **1-8** **1-9** (major) (R = CO_2Me) **1-3** **1-8** **1-9'** (minor) (R = CO_2Me)

2



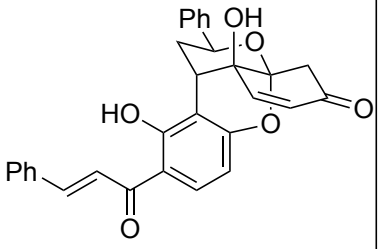
2-1 (racemic)
$C_{21}H_{24}O_6$

1. **2-4** (1.1 eq.), (±)-BPA (0.33 eq.)
   CH_2Cl_2, -15 ºC, 80% (*cis* : *trans* = 3:1)
2. H_2O_2 (10 eq.), $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.3 eq.)
   EtOH, rt, 82% (*cis* : *trans* = 3:1)
3. $ZnBr_2$ (10 eq.), PhMgBr (10 eq.)
   THF, 50 ºC, 81%
4. *p*-TsOH·H_2O (5 eq.), MeOH, rt, 95%
5. $PhI(OAc)_2$ (1.2 eq.), MeCN/H_2O (20/1)
   0 ºC, 21%

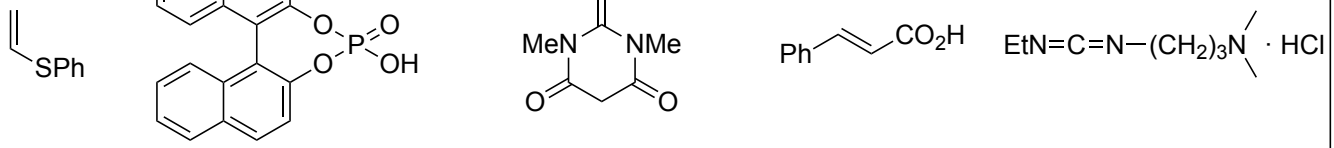
2-2 (racemic)
$C_{27}H_{26}O_5$

2-2 (racemic)

6. 1,3-dimethyl barbituric acid (4 eq.)
   $Pd(PPh_3)_4$ (20 mol%), THF, rt, 57%
7. **2-5** (1.2 eq.), EDCI (1.1 eq.)
   DMAP (0.25 eq.), CH_2Cl_2, rt, 85%
8. hv, benzene, rt, 33%

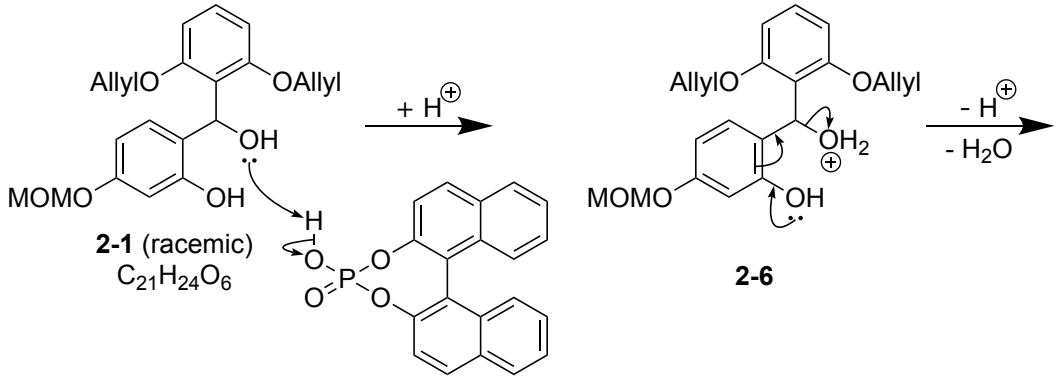


2-3 (racemic)
$C_{30}H_{24}O_6$



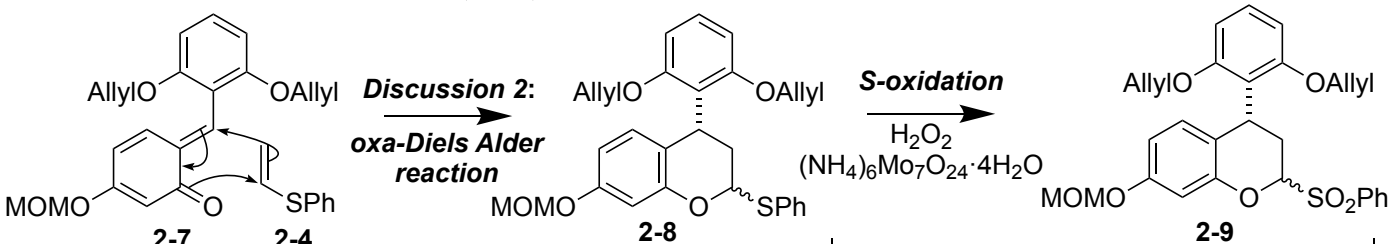
2-4 (±)-BPA 1,3-dimethyl barbituric acid **2-5** EDCI

Liu, Z.; Meng, Y.; Yuan, P.; Wang, Z.; Gao, J.-M.; Zheng, H. *Org. Lett.* **2020**, *22*, 520



2-1 (racemic)
$C_{21}H_{24}O_6$

2-6



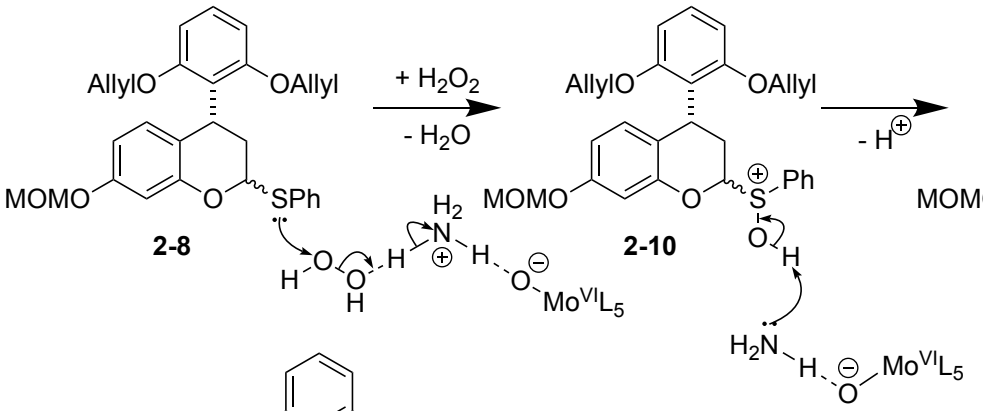
2-7 **2-4**

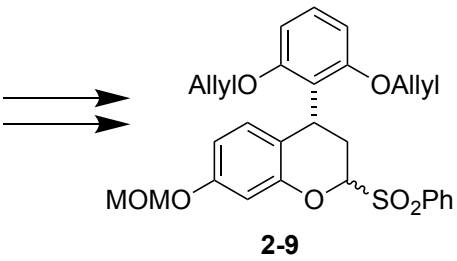
2-8
(*cis* : *trans* = 3:1)
step 1

2-9
(*cis* : *trans* = 3:1)
step 2

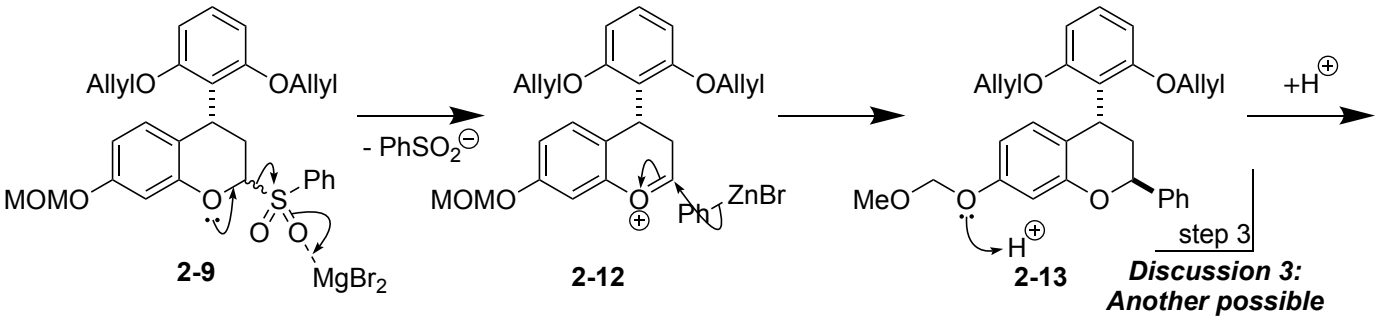
Reaction mechanism of S-oxidation (my proposal)

$Mo_7O_{24}^{6-}{\cdot}4H_2O \rightleftarrows 7MoO_4^{2-} + 8H^+$

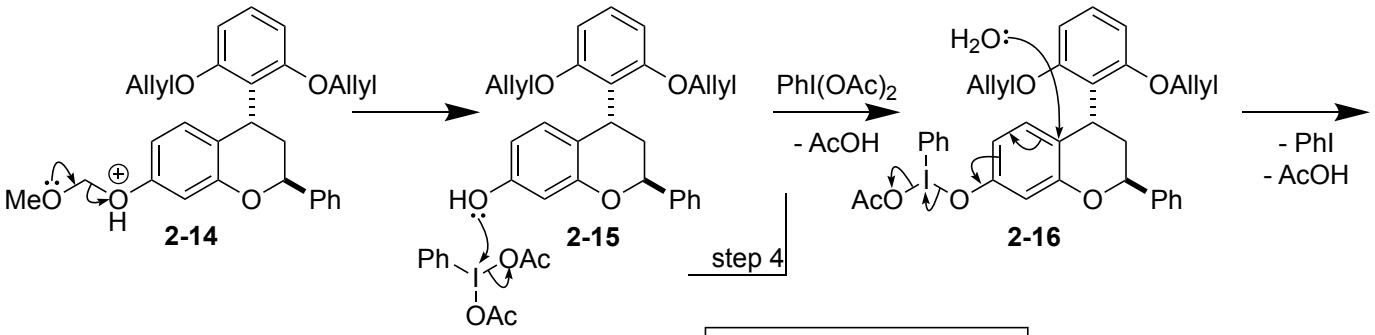


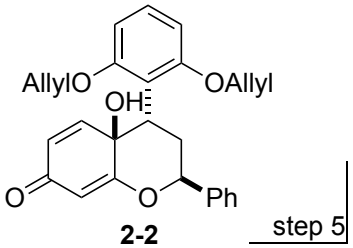


$PhMgBr \xrightarrow[ZnBr_2]{} PhZnBr + MgBr_2$

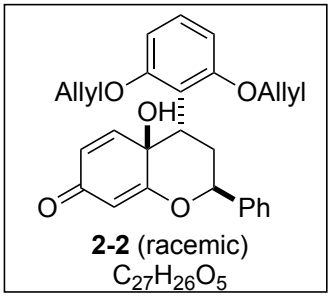


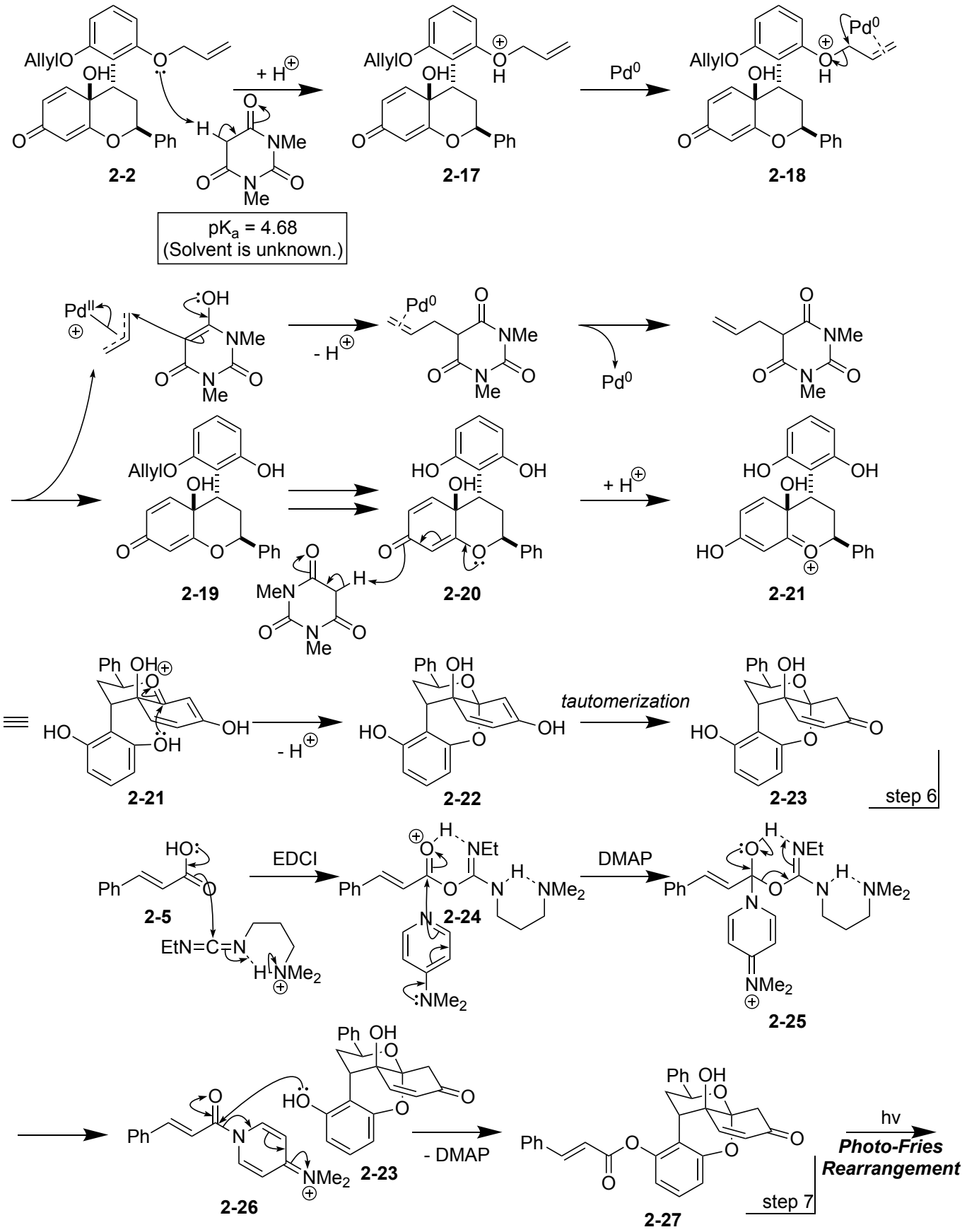
Discussion 3: Another possible mechanism

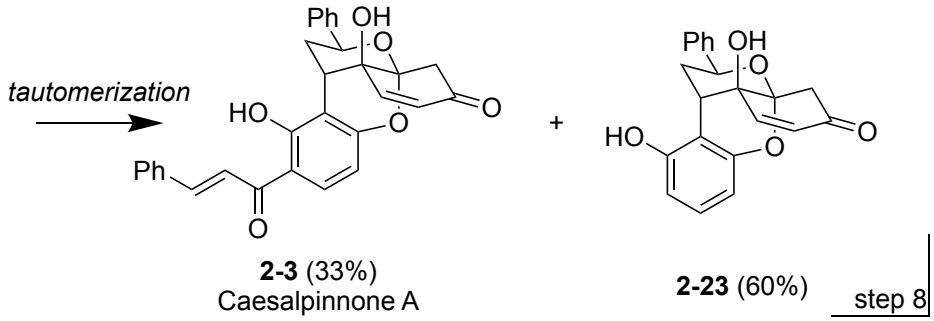




step 5




AllylO
OH
O
Ph
NMe
N
Me
+ H⊕
2-2
2-17
2-18
Pd0
pKa = 4.68
(Solvent is unknown.)
PdII
- H⊕
2-19
2-20
2-21
HO
MeN
tautomerization
2-22
2-23
step 6
EDCI
DMAP
2-5
EtN=C=N
H⊕NMe2
2-24
NEt
NMe2
2-25
2-26
- DMAP
step 7
hv
Photo-Fries
Rearrangement
2-27
2-28
2-29
2-30
2-31



Discussion 2*: *Stereoselectivity of oxa-Diels Alder reaction

2-1. Experimental result

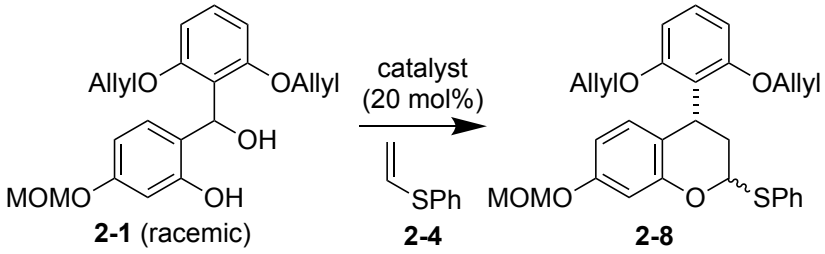
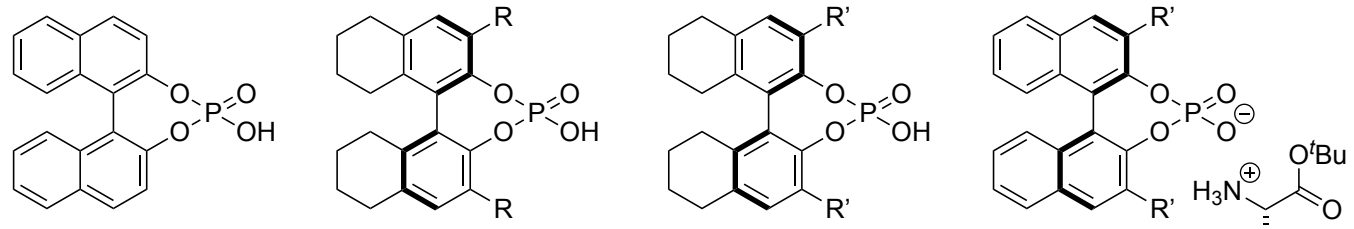


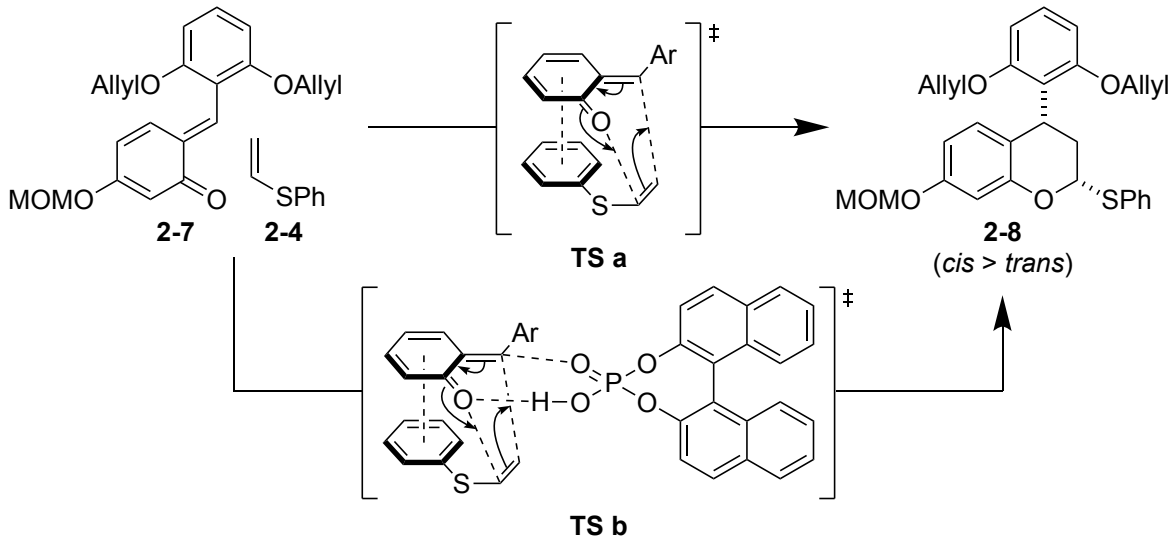
Table 3

catalyst	yield (%)	*cis* : *trans*	ee (%)
(±)-BPA	80	3:1	0
Cat-1	50	2.2:1	3
Cat-2	75	4.6:1	31
Cat-3	77	2.6:1	38



As various catalysts can't give high ee, the author gave up enantioselective synthesis of **2-8**.
The fact that chiral catalysts gave low ee indicated that these catalysts were partially concerned with this cyclization.

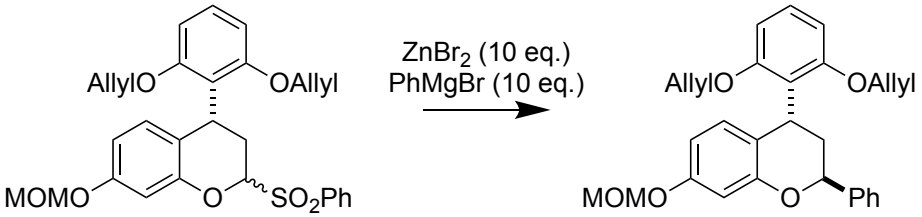
2-2. Transition state of oxa-Diels Alder reaction



At least, two types of reaction mechanism should be considered because various chiral catalysts gave low ee. The main transition state should be **TS a** and the π-π stacking in transition state should give the diastereoselectivity. Also, **TS b** should be assumed.[ref.6] When chiral catalysts were used, enantioselective reaction might occured from this transition state.

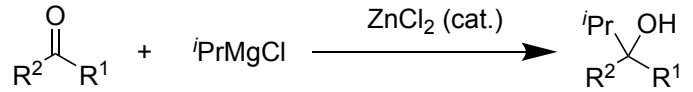
6) Wang, Z.; Sun, J. *Org. Lett.* **2017**, *19*, 2334

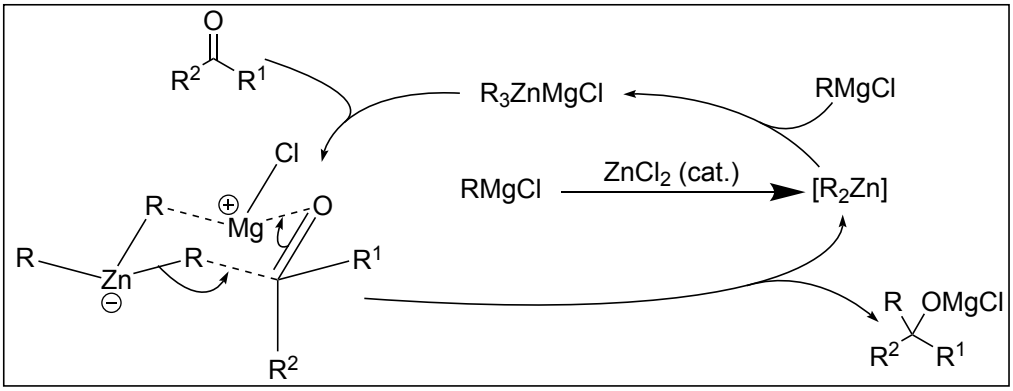
Discussion 3*: *Another possible reaction mechanism of step 3



2-9 **2-13**

It is known that $ZnCl_2$ catalyzes the reaction of ketone and Grignard reagent. Proposed catalytic cycle is shown below.





Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998

In step 3, solution of **2-9** was added to the mixture of $ZnBr_2$ and PhMgBr in THF. If they react as above, the reaction mechanism seems to be the following.