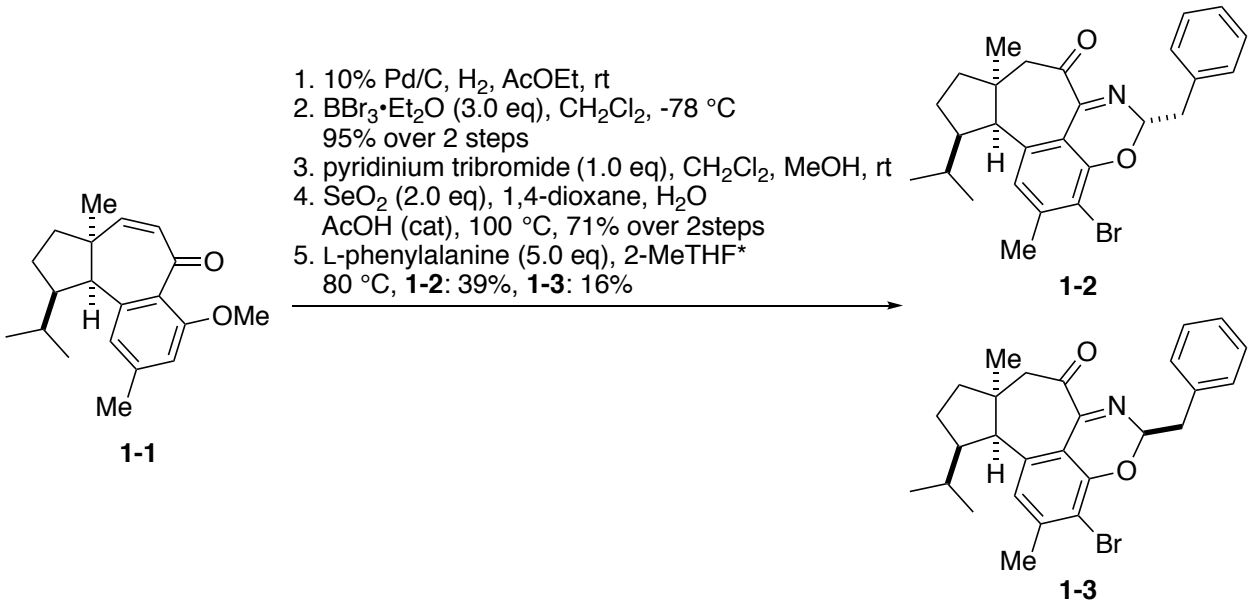
Problem session (4) answer

2020. 8. 29. Kensuke Miura

Please explain reaction mechanism.

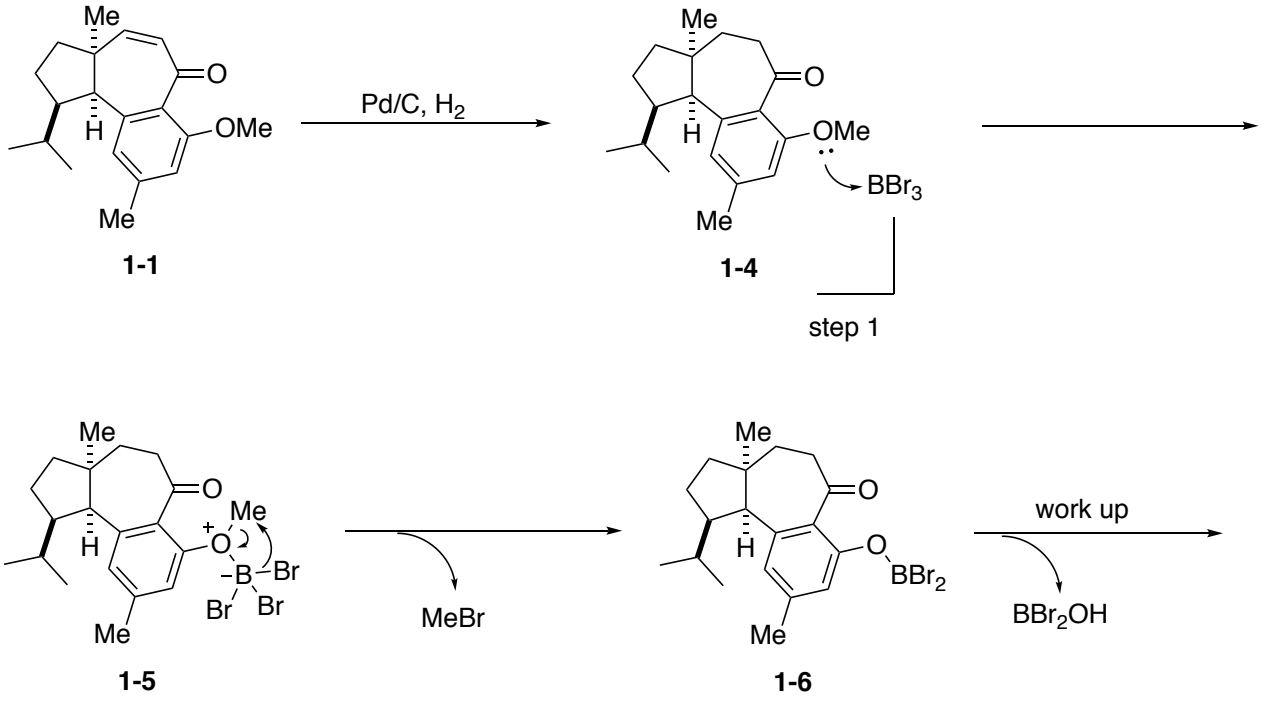
Problem 1.

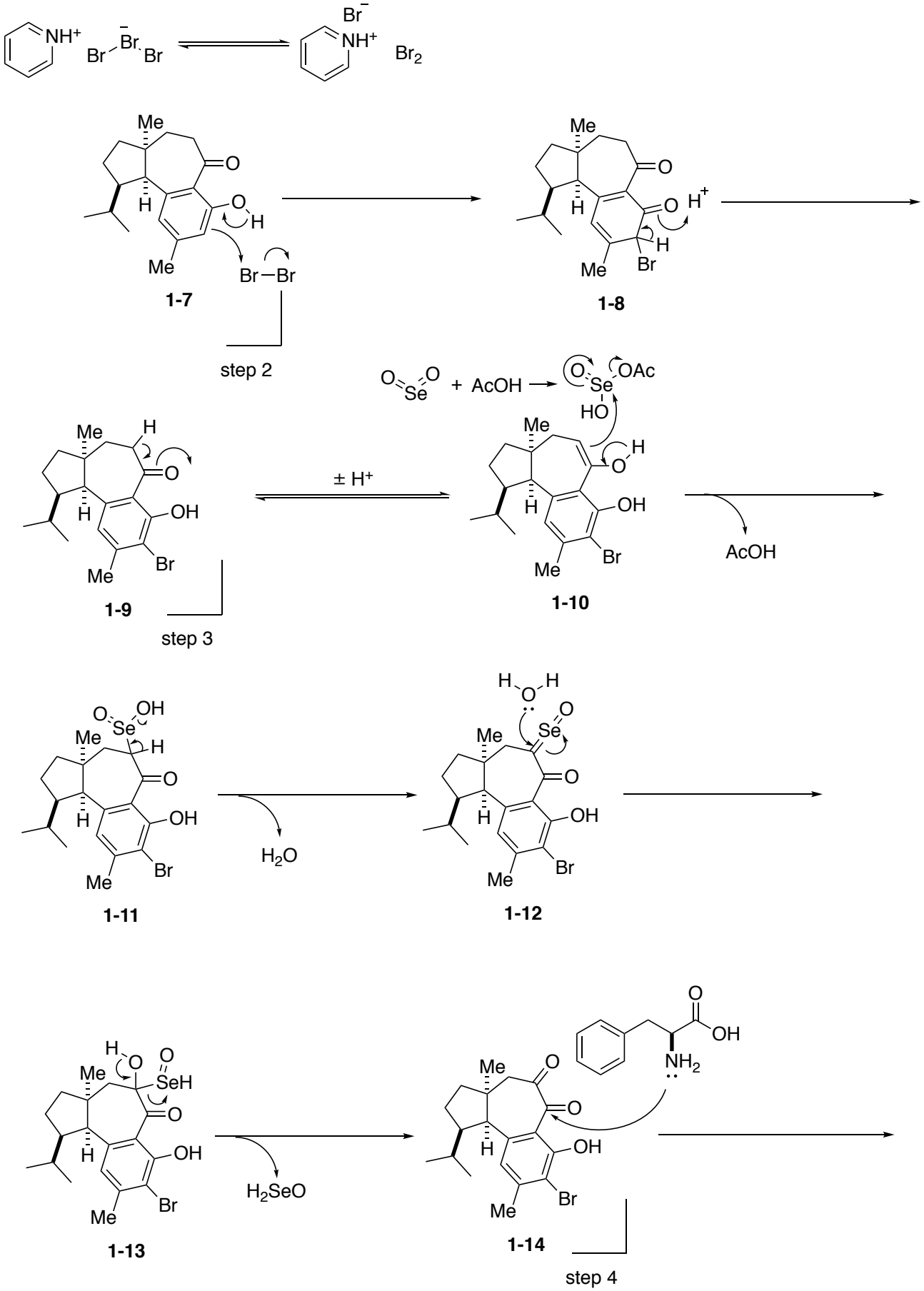


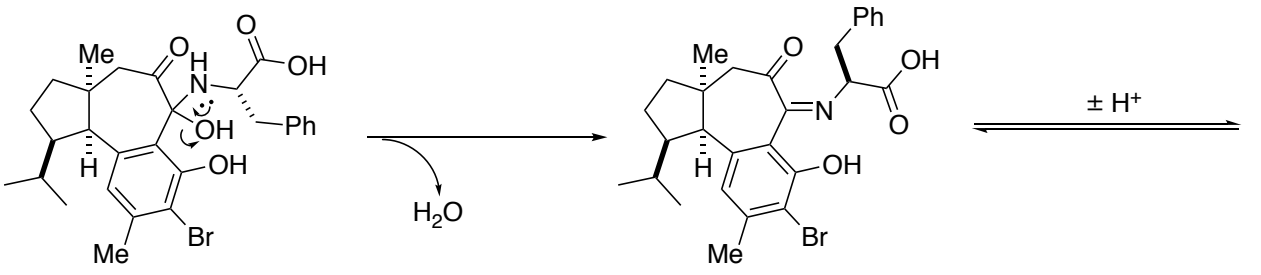
* Although all reaction were carried out under a nitrogen atmosphere, please condidering dissolved oxygen in step 5

Li, X.; Xue, D.; Wang, C.; Gao, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9942

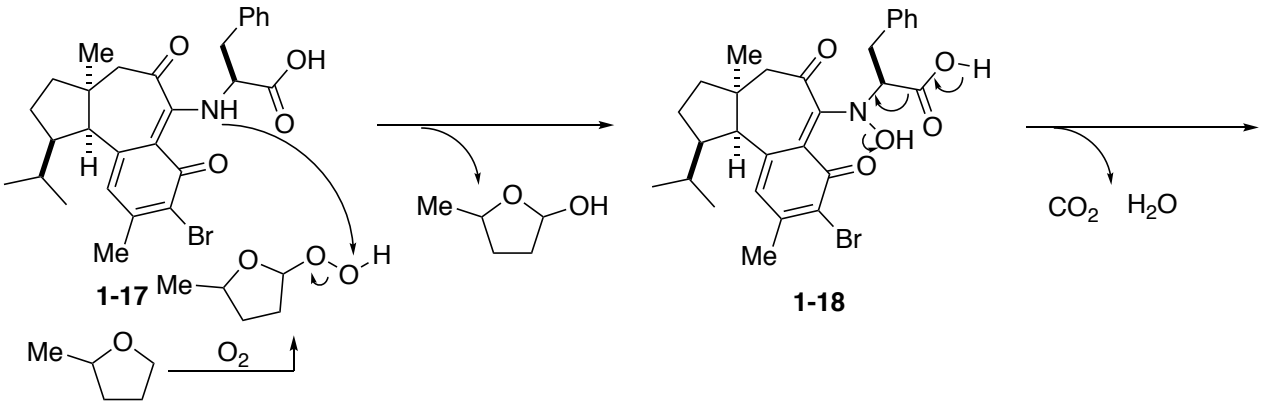
Proposed reaction mechanism



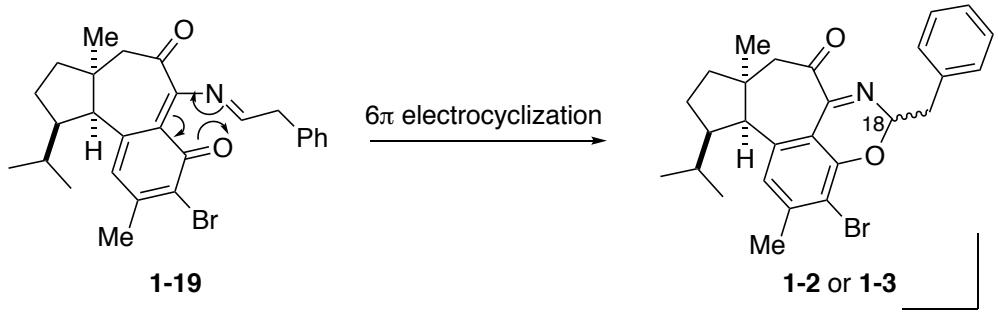

NH+
Br
Br
Br
Br−
NH+
Br2
Me
O
H
O
H
Me
Br—Br
1-7
step 2
Me
O
H
O
H+
H
Me
Br
1-8
O
Se
O
+ AcOH
O
Se
OAc
HO
Me
H
O
H
H
OH
Br
Me
1-9
step 3
± H+
Me
H
O
H
OH
Br
Me
1-10
AcOH
O
Se
OH
Me
H
O
H
OH
Br
Me
1-11
H2O
H
O
H
Se
O
Me
H
O
H
OH
Br
Me
1-12
H
O
O
SeH
Me
H
O
H
OH
Br
Me
1-13
H2SeO
O
OH
NH2
Me
O
O
H
OH
Br
Me
1-14
step 4



1-15 **1-16**



1-17 **1-18**



1-19 **1-2** or **1-3**

step 5

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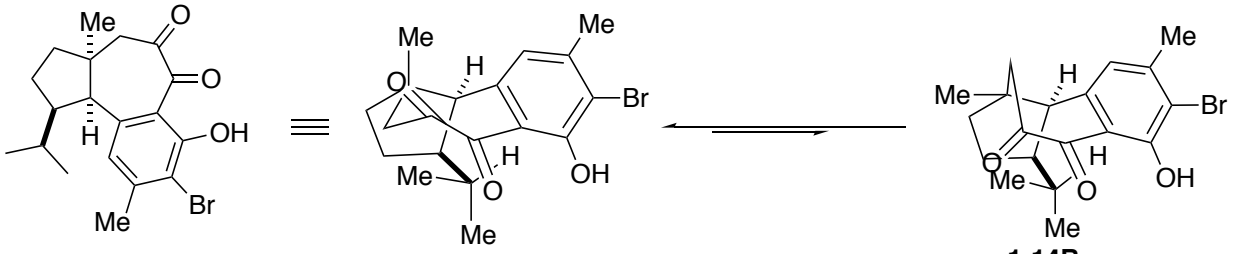
1. Comformation of **1-14**

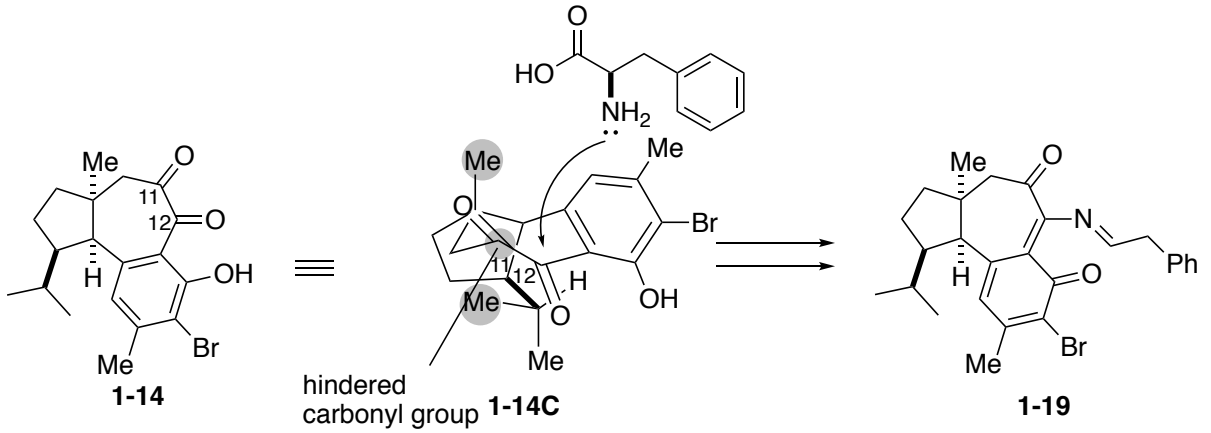


1-14 **1-14C** **1-14B**

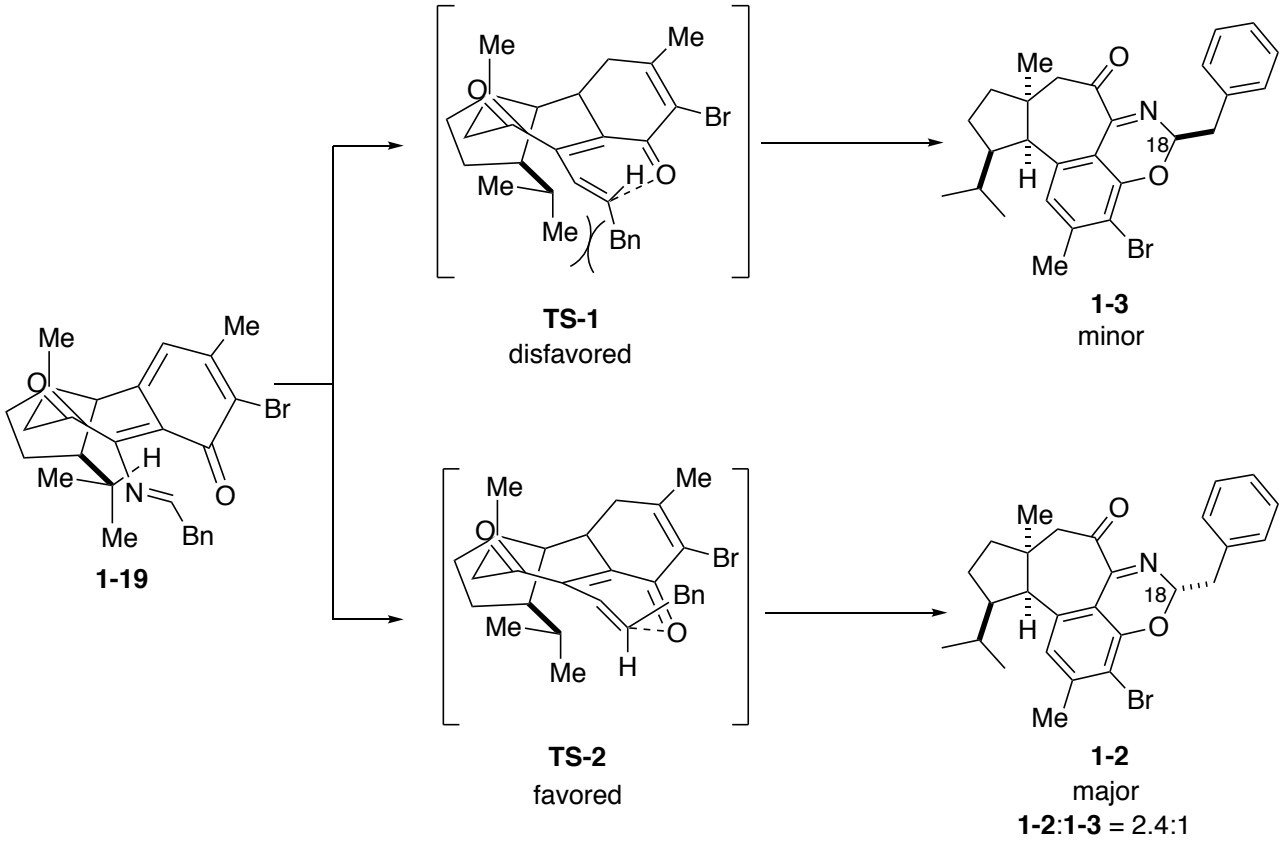
7-membered ring: chair 7-membered ring: boat

Addition of amino acid would proceed from **1-14C**

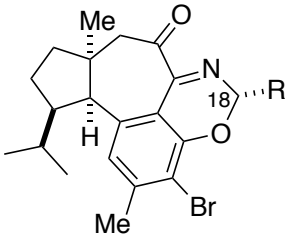
2. Regioselectivity: addtion of amino acid



3. Stereoselectivity of C18 position



Synthesis of other Hamigerans family from **1-15**



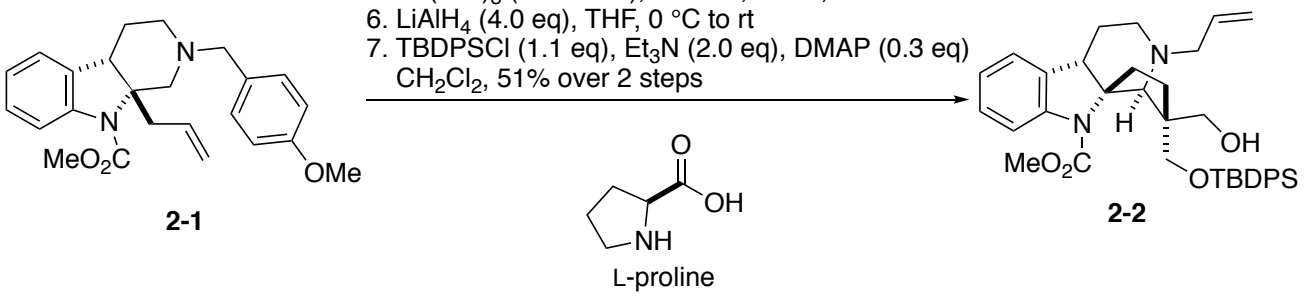
Hamigerans family

Hamigeran O: R = *i*Pr, 43% from **1-15** (dr = 3.9:1 at C18)
Hamigeran D: R = Me, 50% from **1-15** (dr = 1.6:1 at C18)

-> bulkiness of residue reflected the selectivity at C18 position

Problem 2.

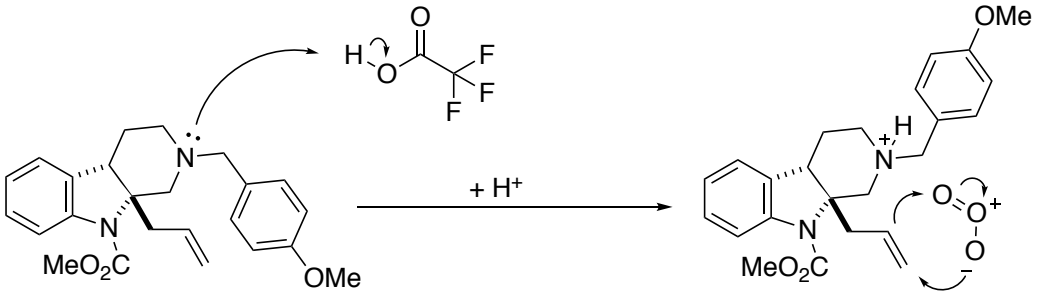
1. TFA (3.0 eq), CH_2Cl_2, 0 °C;
   then O_3, CH_2Cl_2, -78 °C;
   then Me_2S (10 eq), CH_2Cl_2, -78 °C to rt, 90%
2. allyl chloroformate (10 eq), 1,2-dichloroethane
   reflux, 56%
3. $Pd(PPh_3)_4$ (2.5 mol %), CH_2Cl_2, rt, 92%
4. dimethylmalonate (3.0 eq), L-proline (1.5 eq)
   DMSO, rt, 96%
5. $Yb(OTf)_3$ (10 mol %), toluene, reflux, 80%
6. $LiAlH_4$ (4.0 eq), THF, 0 °C to rt
7. TBDPSCl (1.1 eq), Et_3N (2.0 eq), DMAP (0.3 eq)
   CH_2Cl_2, 51% over 2 steps



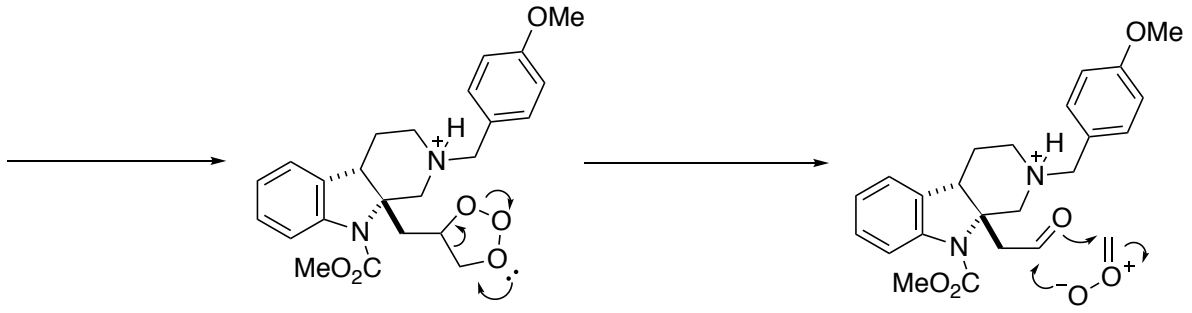
2-1 **2-2**

Zhang, X.; Anderson, C. J. *Angew. Chem.* **2019**, *131*, 2

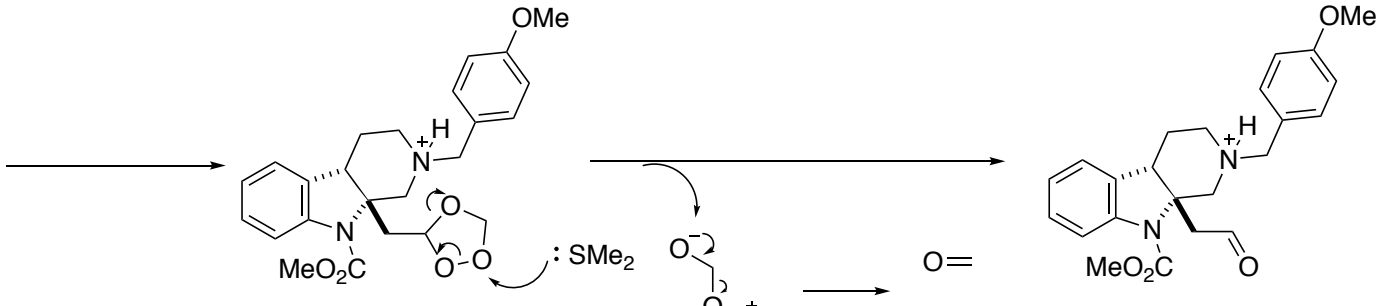
Reaction mechanism



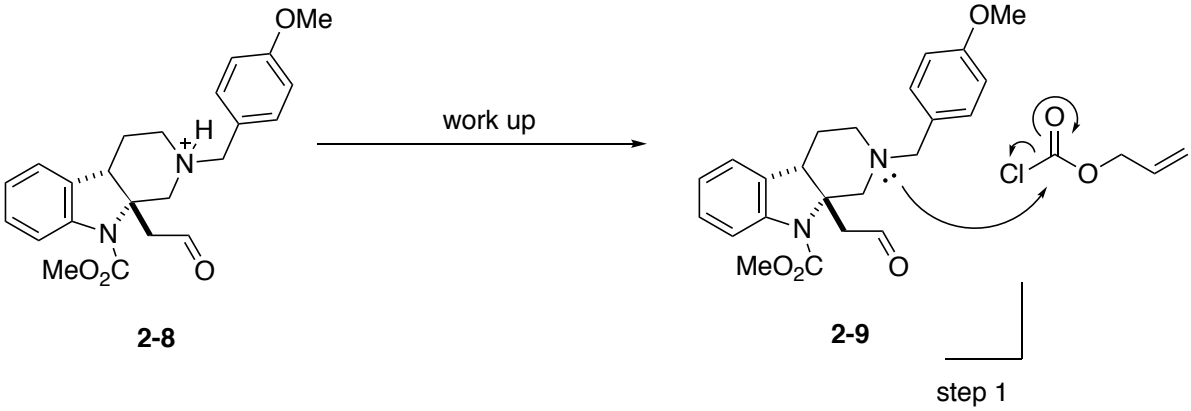
2-1 **2-3**



2-4 **2-5**

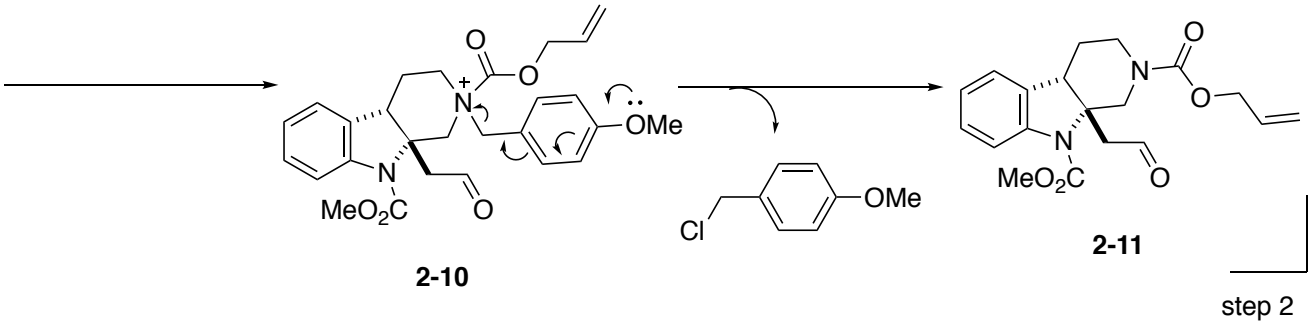


2-6 **2-7**



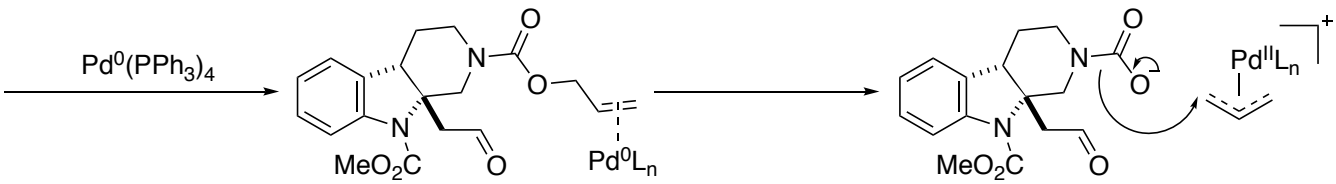
2-8 **2-9**

step 1

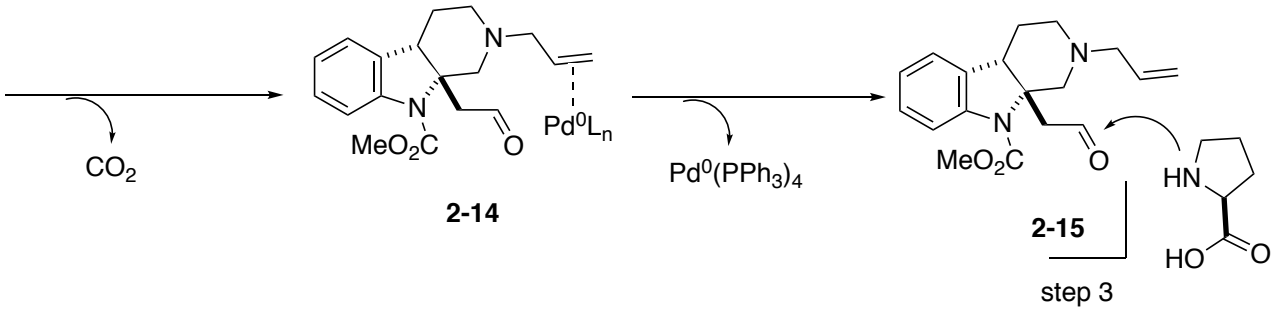


2-10 **2-11**

step 2

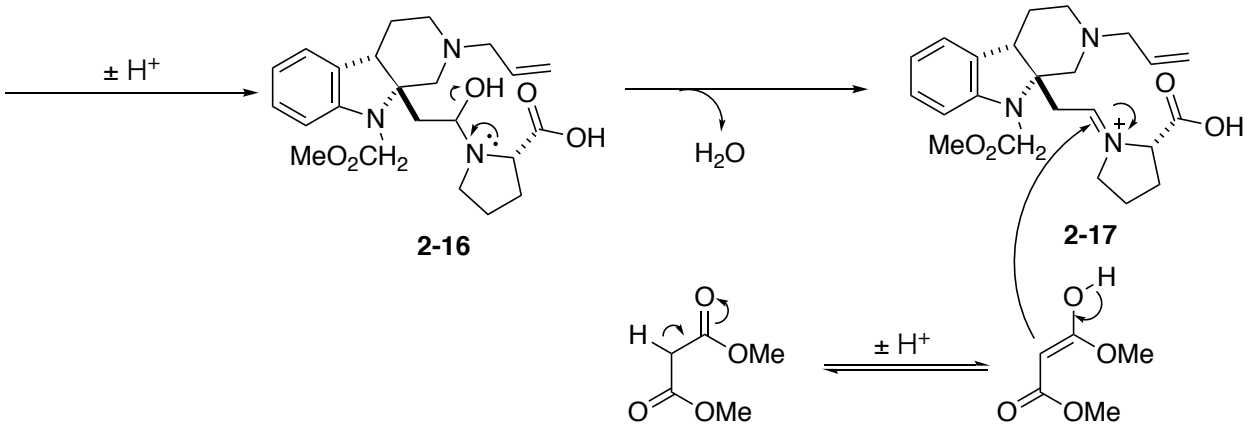


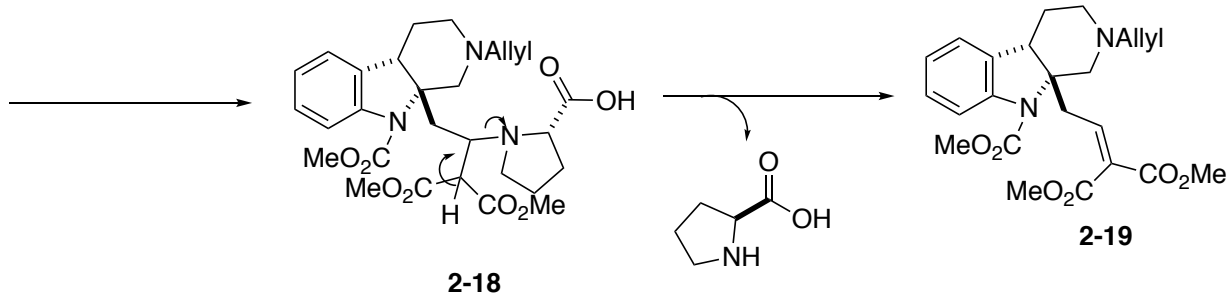
2-12 **2-13**

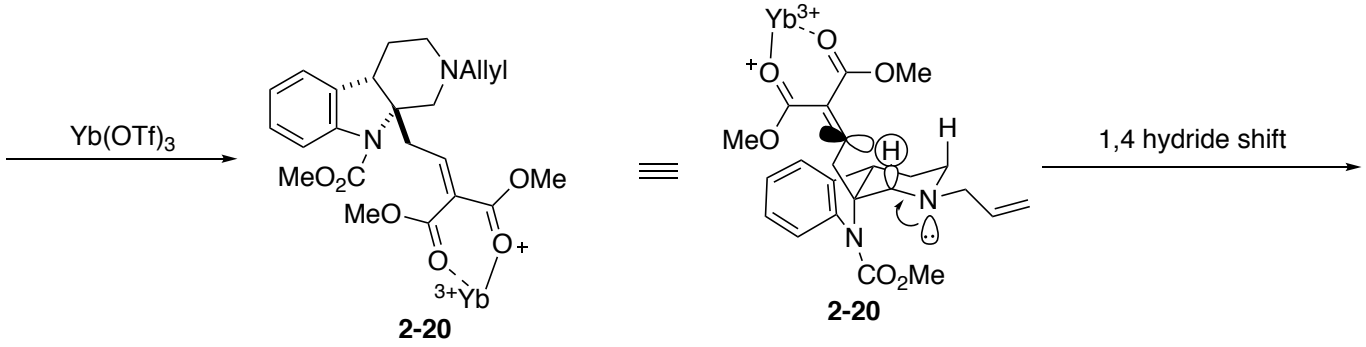


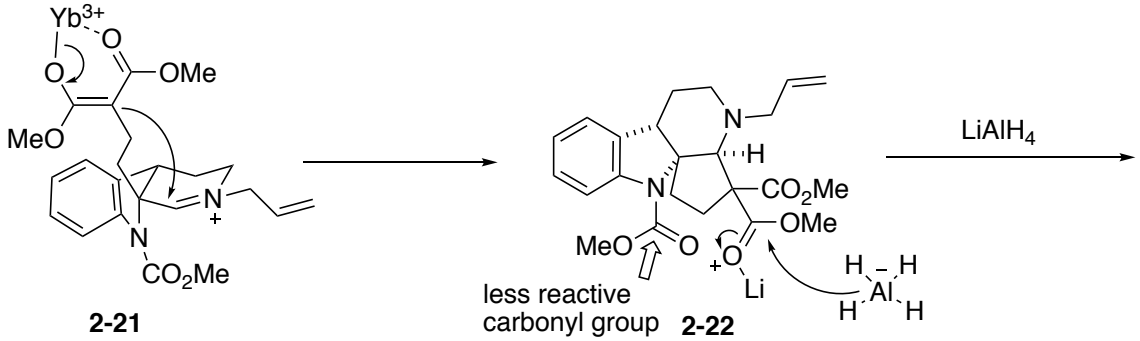
2-14 **2-15**

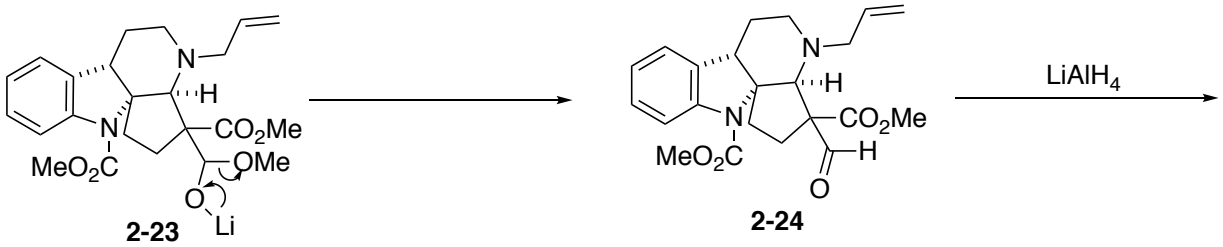
step 3

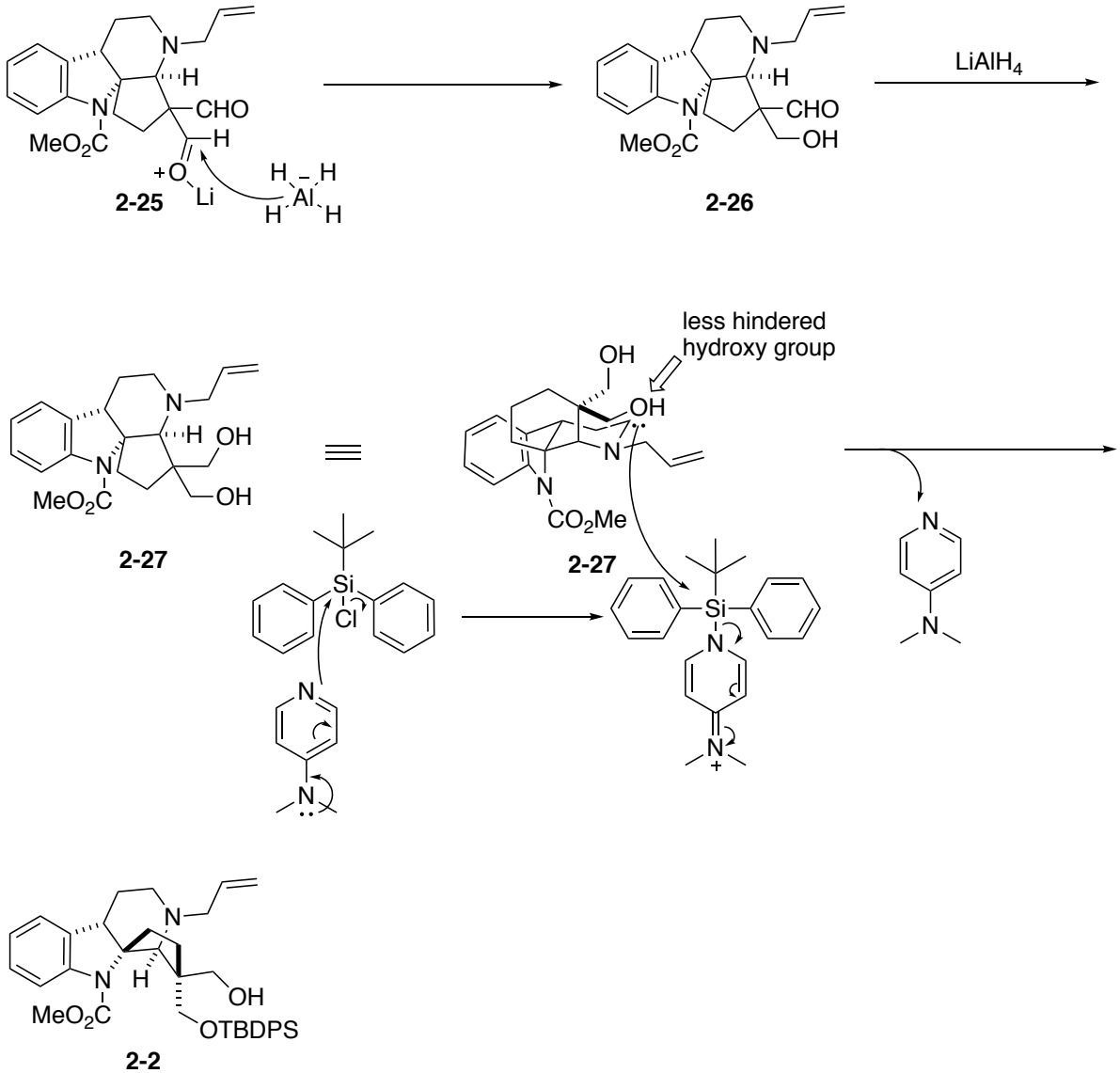

± H+
N
OH
O
OH
N
MeO2CH2
N
2-16
H2O
N
O
OH
N
MeO2CH2
N+
2-17
O
H
OMe
O
OMe
± H+
O
H
OMe
O
OMe


NAllyl
O
OH
N
MeO2C
N
MeO2C
H
CO2Me
2-18
O
OH
NH
NAllyl
N
MeO2C
CO2Me
MeO2C
2-19


Yb(OTf)3
NAllyl
N
MeO2C
OMe
MeO
O
O+
O
3+Yb
2-20
Yb3+
O
+O
OMe
MeO
H
H
N
N
CO2Me
2-20
1,4 hydride shift


Yb3+
O
O
OMe
MeO
N+
N
CO2Me
2-21
N
H
CO2Me
OMe
MeO
O
+O
Li
less reactive
carbonyl group
2-22
LiAlH4
H
H
Al
H
H


N
H
N
CO2Me
MeO2C
OMe
O
Li
2-23
N
H
N
CO2Me
MeO2C
H
O
2-24
LiAlH4



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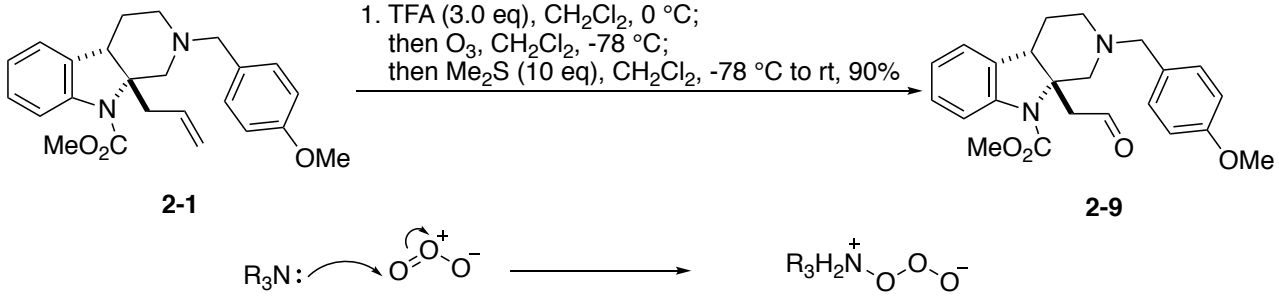
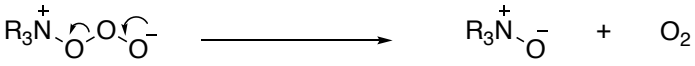
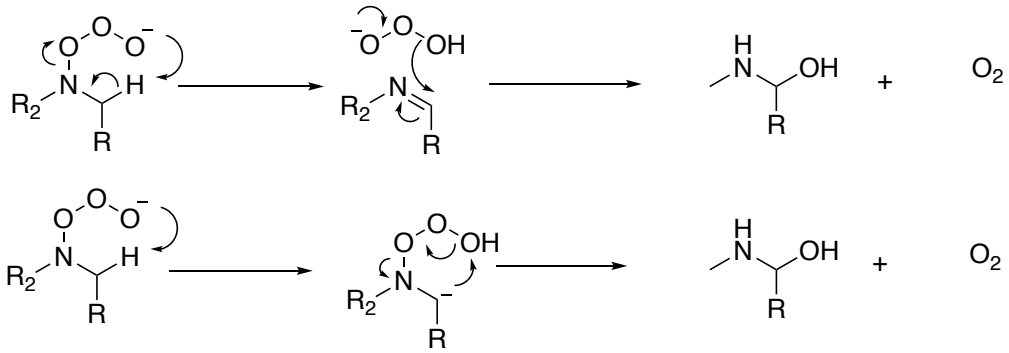
1. Requirement of proronation during ozonolysis (in step 1)



1) amine oxide formation



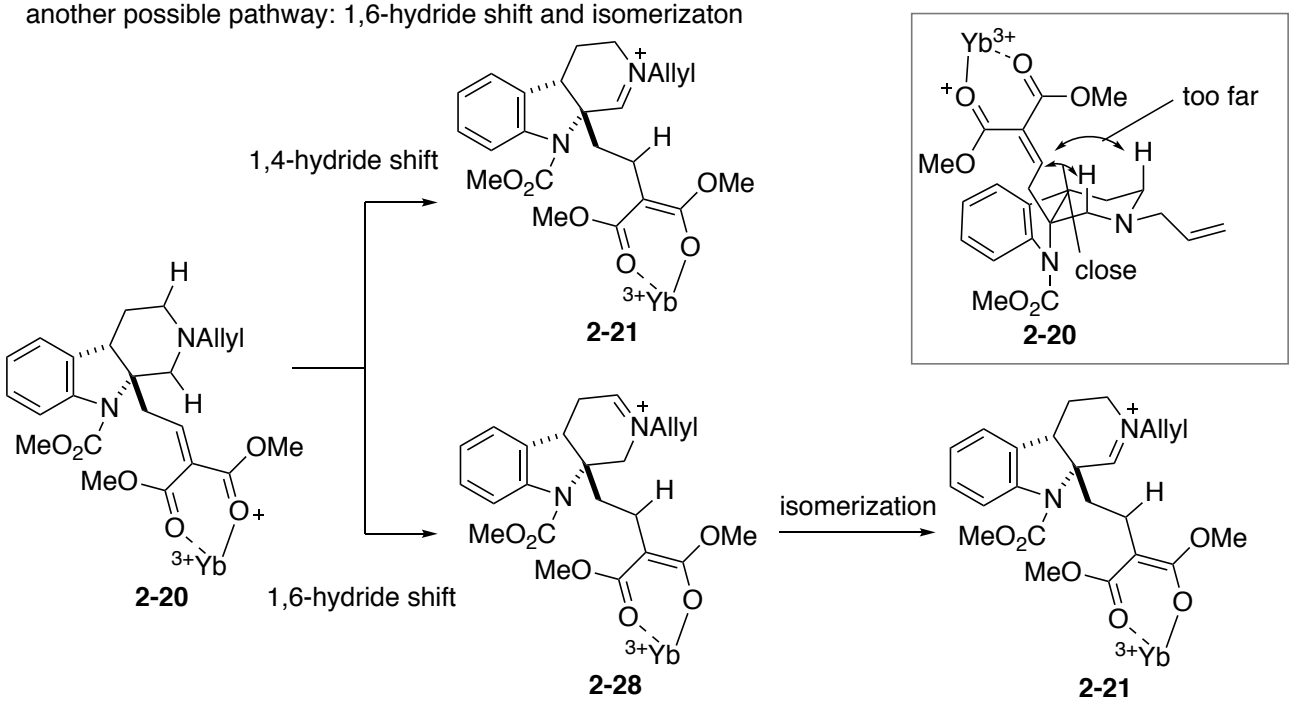
2) side-chain oxidation



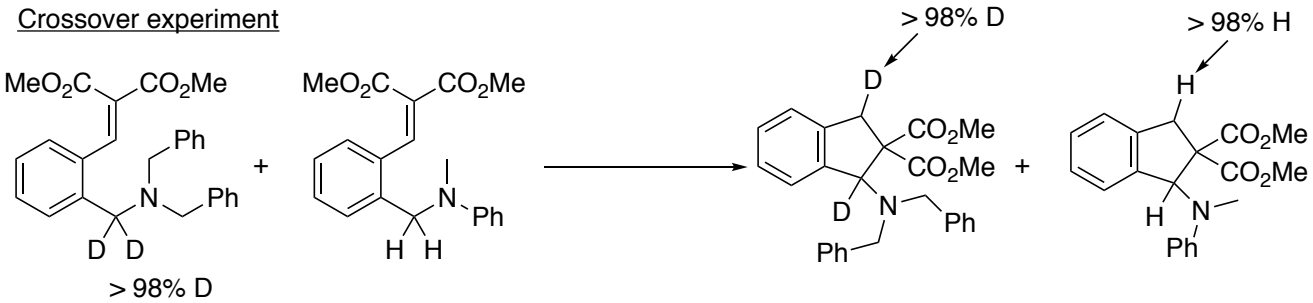
Bailey, S. P.; Mitchard, A. D.; Khashab, A-I. Y. *J. Org. Chem.* **1968**, 33, 2675

2. 1,4-hydride shift and cyclization

another possible pathway: 1,6-hydride shift and isomerizaton



Crossover experiment



Mori, K.; Kurihara, K.; Akiyama, T. *Chem. Commun.* **2014**, *50*, 3729

When the hydride shift proceeded in an intermolecular manner, 1,6-hydride shift pathway could be assumed. In this answer, an intramolecular pathway was adopted because another case shown above suggested that the reaction poceeded via the intramolecular hydride shift process.