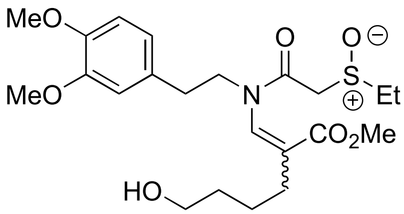
Problem Session (4)

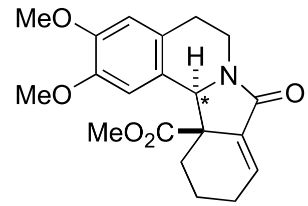
2022.9.24. Shu Nakamura

Topic: oxidation reactions with amine substrate
Please explain the reaction mechanism.

1.



1. CBr_4 (3 eq.), CH_2Cl_2, rt
   ; PPh_3 (3 eq.; devided into several portions), 83%
2. $NaIO_4$ (1.5 eq.), MeOH/H_2O (4/1), rt, 88%
3. CSA (4 eq.), toluene, reflux, 88%[a] (dr = 5:2:1:1)
4. NaH (2.5 eq.), THF, reflux, 67% (+ 25%[b])
5. $NaIO_4$ (3 eq.), MeOH/H_2O (4/1), rt, 90%
6. toluene, reflux, 98%

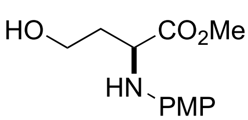


1-1
(*E*/*Z* = 1/4)

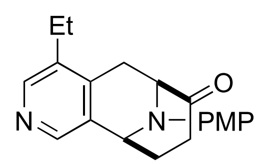
1-2

a) The mixture of 4 diastereomers was used without further purifications in the next reaction.
b) The minor product (diastereomer at *) was seperated.

2.

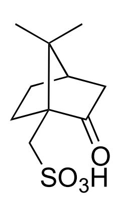


1. **2-2** (2 eq.), K_2CO_3 (2 eq.), MeCN, 60 °C, 84%
2. DMSO (3 eq.), $(COCl)_2$ (2 eq.), CH_2Cl_2, −78 °C
   ; Et_3N (5 eq.), −78 °C to rt
3. *n*-$PrPPh_3$·Br (3 eq.), *n*-BuLi (2.7 eq.)
   THF, −78 °C, 50% (2 steps), (mixture of isomers, *E*/*Z* = 1/3)
4. microwave, DMSO, 200 °C, 65%
5. Ti(O*i*-Pr)$_4$ (1 eq.), EtMgBr (5 eq.), THF, 0 °C, 85%
6. $CuCl_2$ (50 mol%), MS 4A (300 wt%), air, $CHCl_3$, 60 °C, 55%

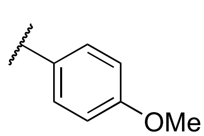


2-1

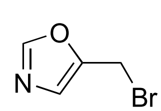
2-3



CSA



PMP



2-2

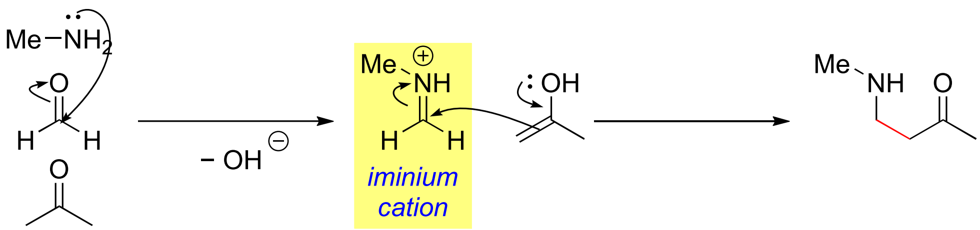
Problem Session (4) -Answer-

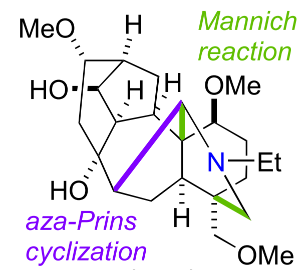
2022.9.24. Shu Nakamura

Topic: Oxidative iminium formation

Introduction: The use of iminium cation

• Mannich reaction (Mannich and Ball *Arch. Pharm.* **1926**, *264*, 65.)

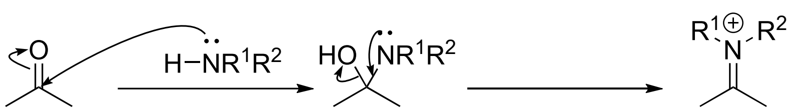




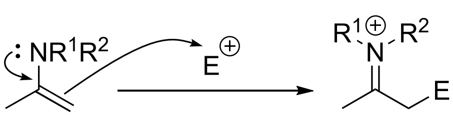
talatisamine
Inoue, M. et al.
ACIE **2020**, *59*, 479.

Generation of iminium cation

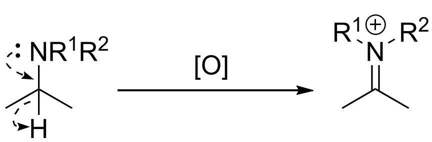
1) Condensation with carbonyl compound



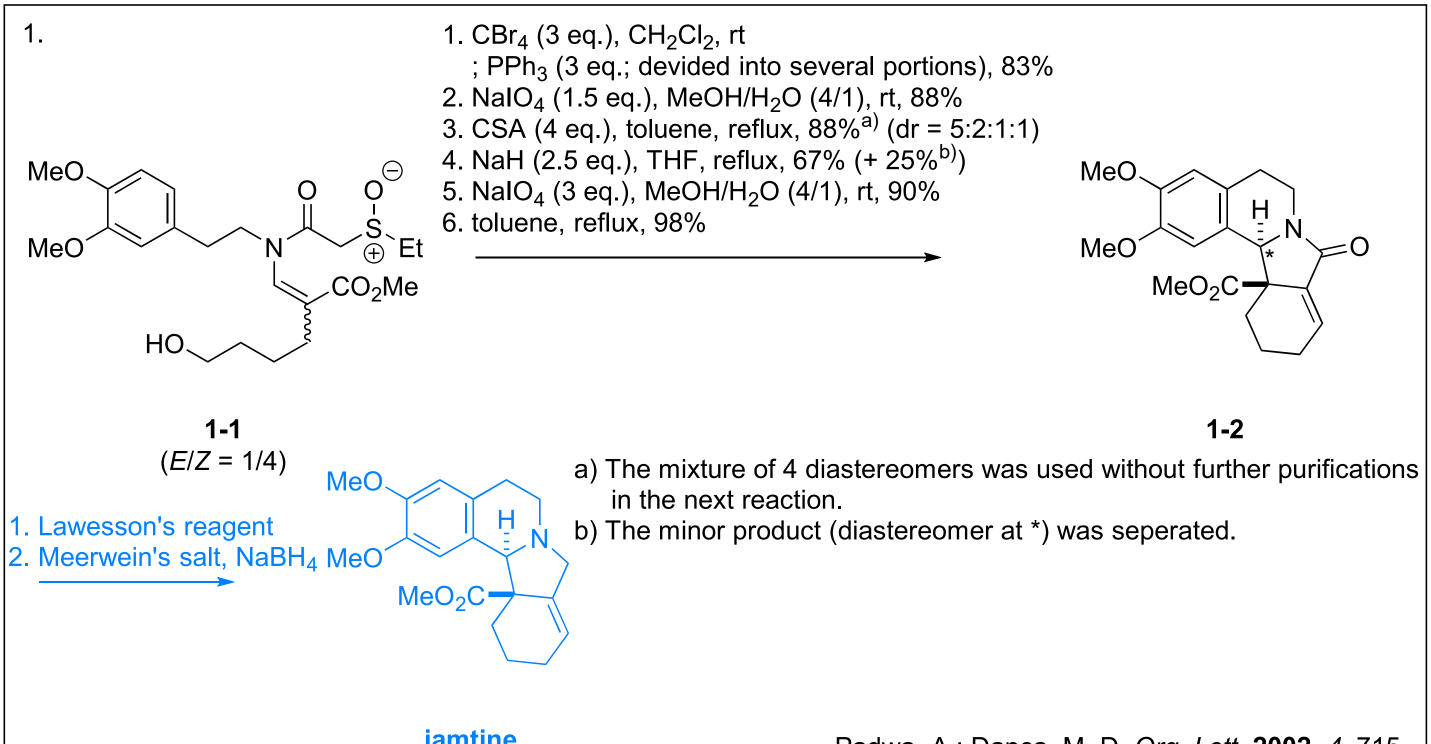
2) Electrophilic addition to enamine



3) Oxidation of amine

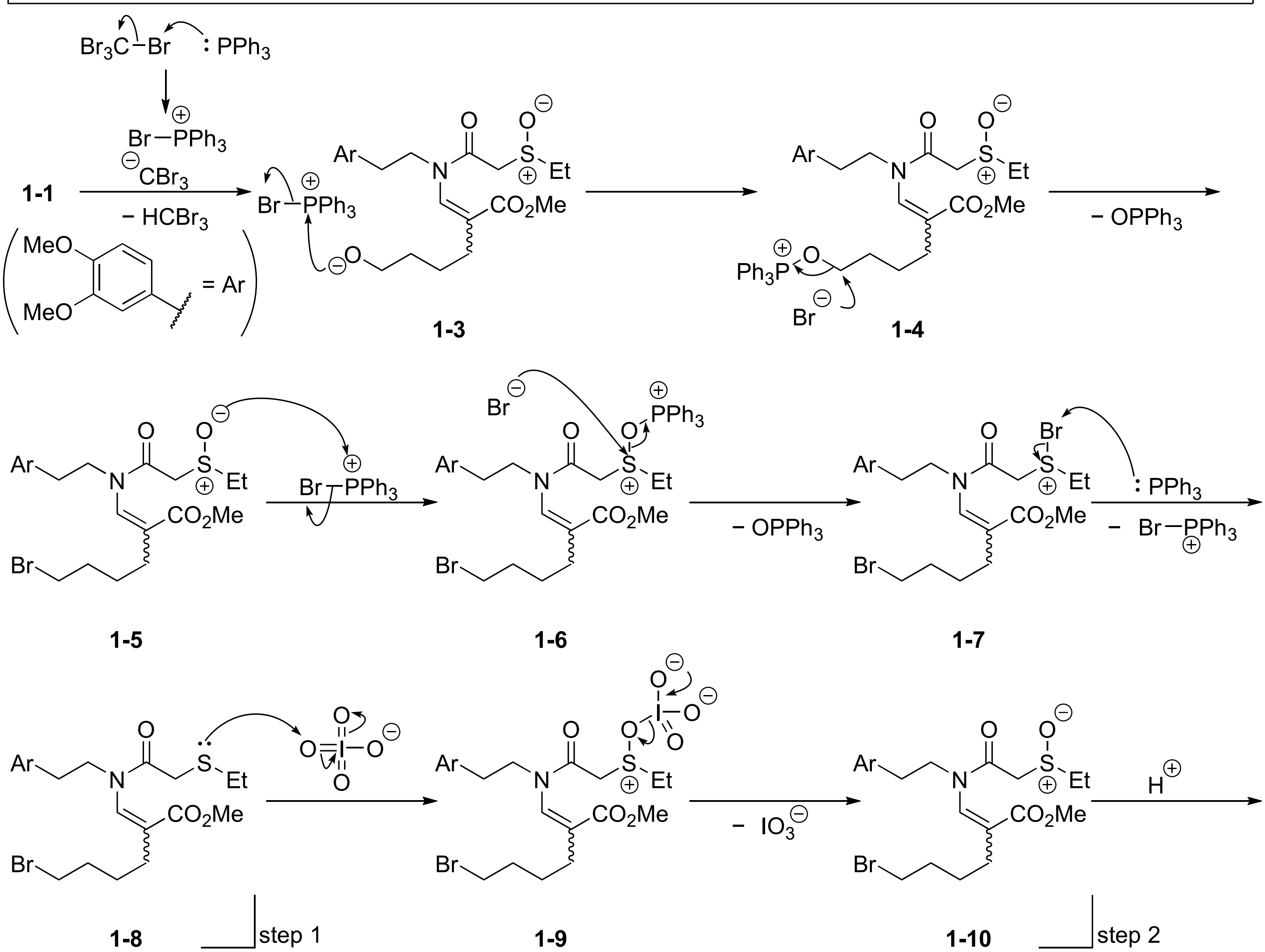


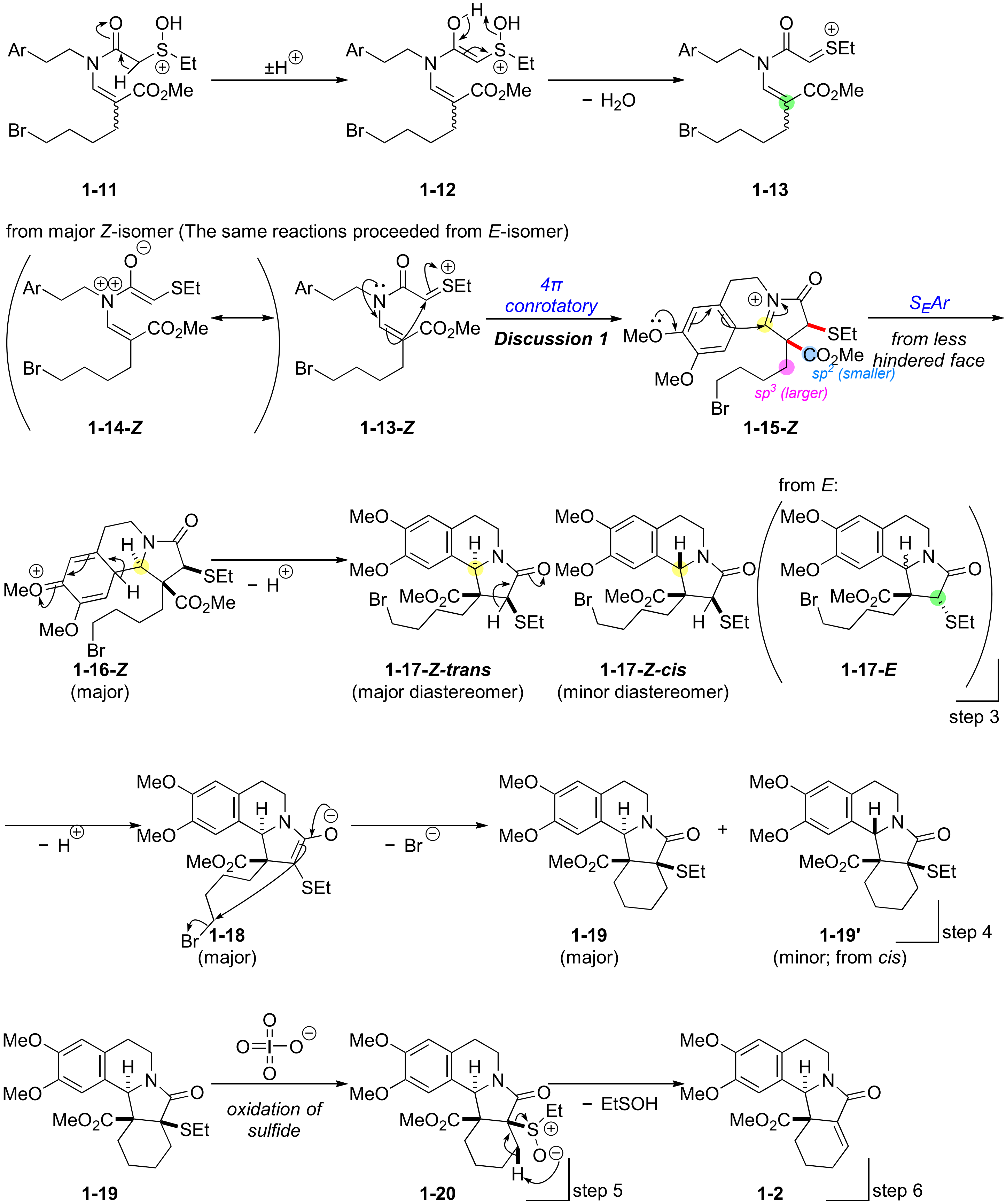
1.



a) The mixture of 4 diastereomers was used without further purifications in the next reaction.
b) The minor product (diastereomer at *) was seperated.

Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, *4*, 715.
Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929.

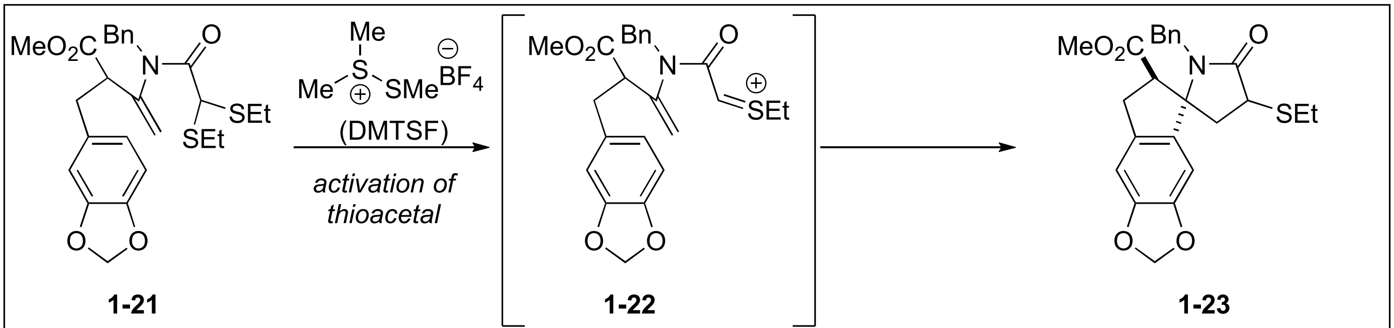



±H⊕
− H2O
1-11
1-12
1-13
from major Z-isomer (The same reactions proceeded from E-isomer)
1-14-Z
1-13-Z
4π conrotatory
Discussion 1
1-15-Z
sp3 (larger)
sp2 (smaller)
SEAr
from less hindered face
1-16-Z
(major)
− H⊕
1-17-Z-trans
(major diastereomer)
1-17-Z-cis
(minor diastereomer)
from E:
1-17-E
step 3
− H⊕
1-18
(major)
− Br⊖
1-19
(major)
1-19'
(minor; from cis)
step 4
oxidation of sulfide
1-19
1-20
step 5
− EtSOH
1-2
step 6

Discussion 1: "Tandem Pummerer/Mannich cyclization sequence"

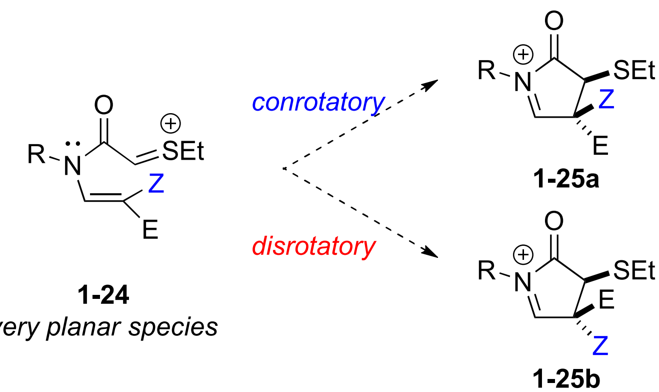
1-1. Evidence for thionium intermediate

Another thionium source can give the cyclized product.

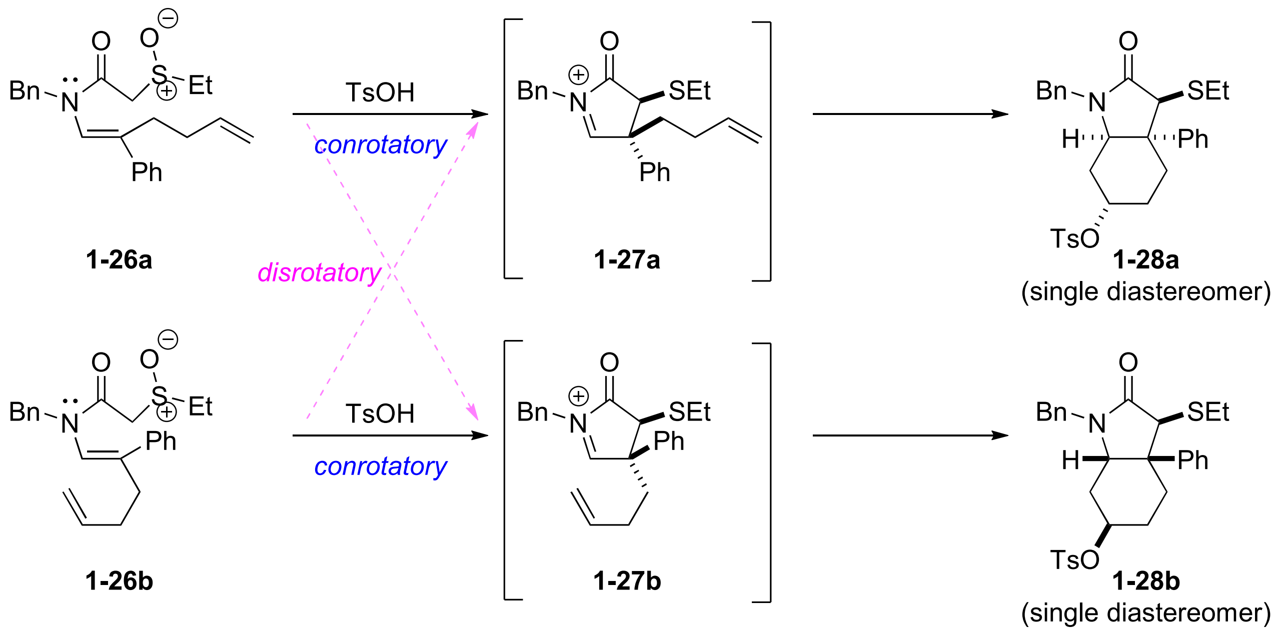


Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. *J. Org. Chem.* **1998**, *63*, 6778.

1-2. Stereoselectivity

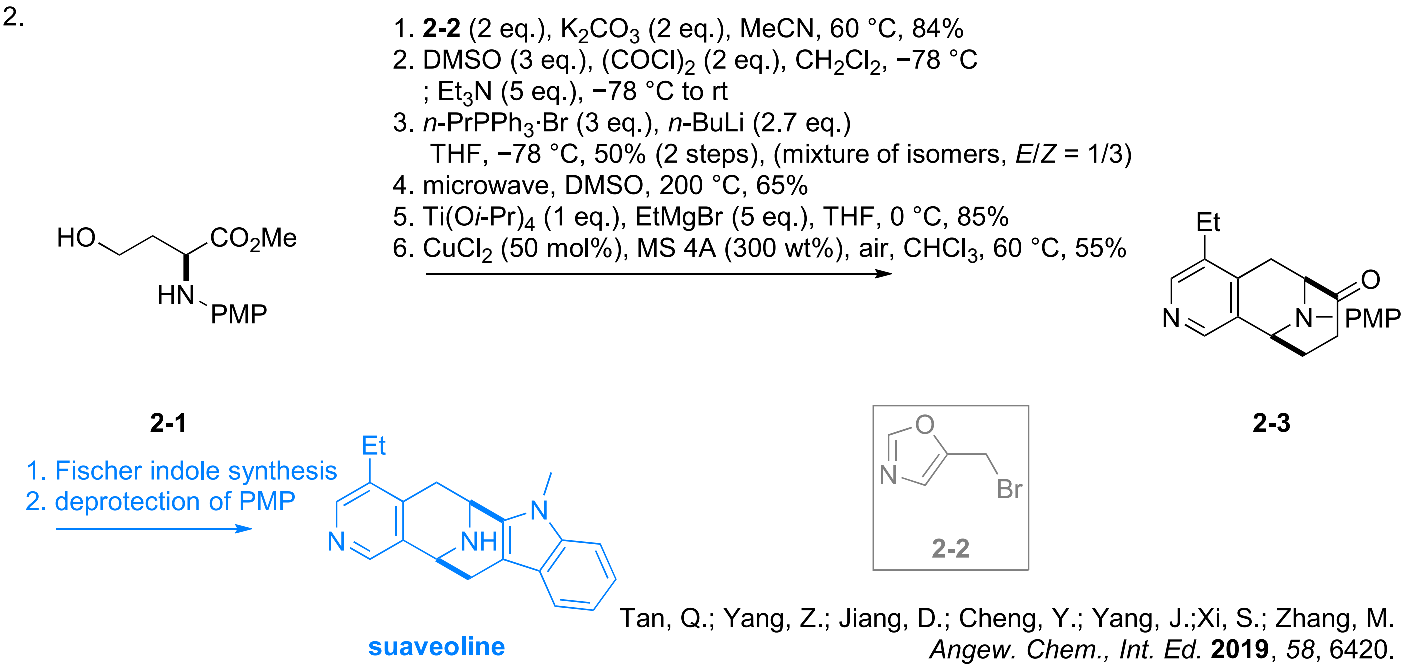


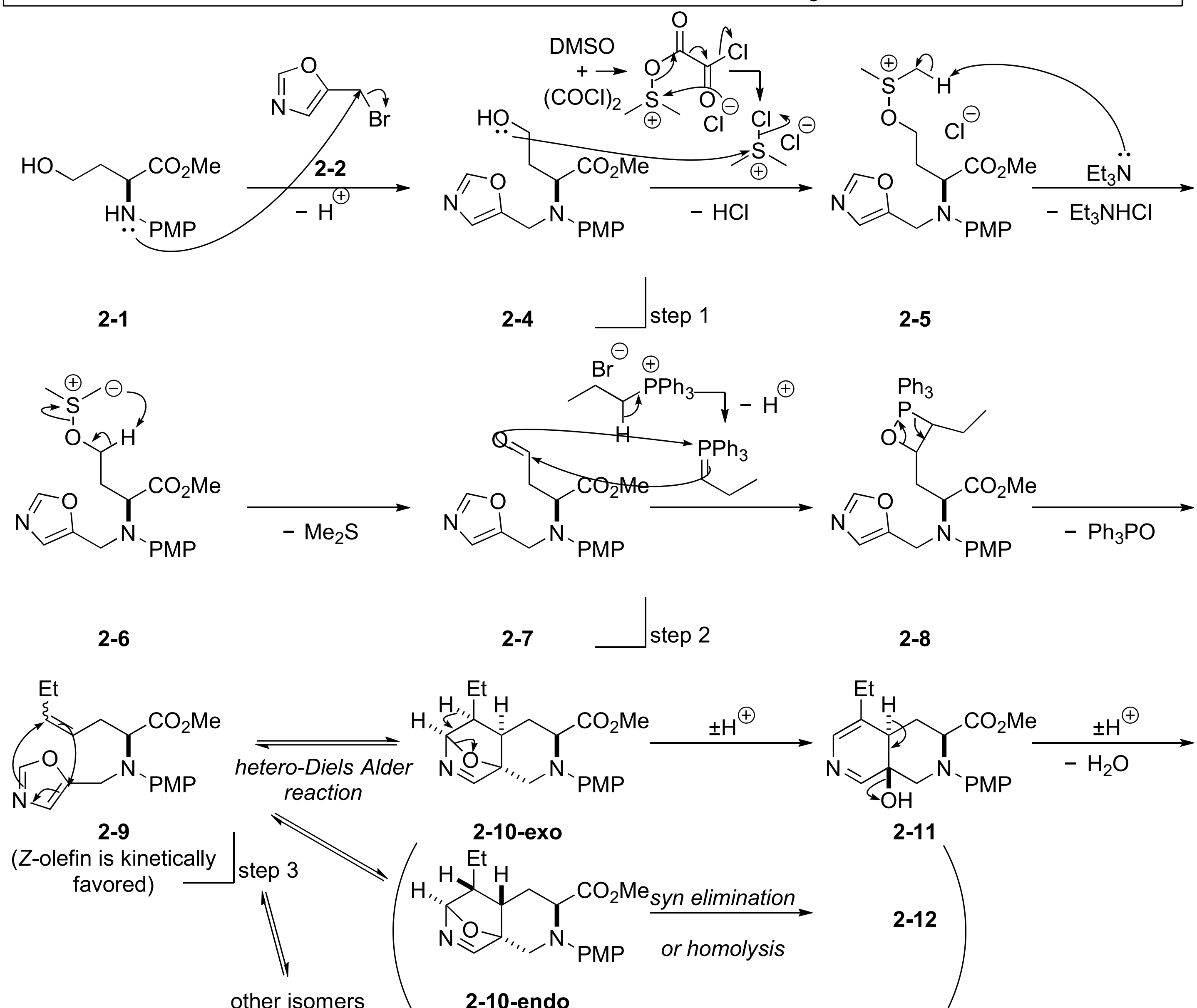
Model compounds **1-26** were treated with the similar acidic conditions.
As a result, each **1-26** gave only a single diastereomer.

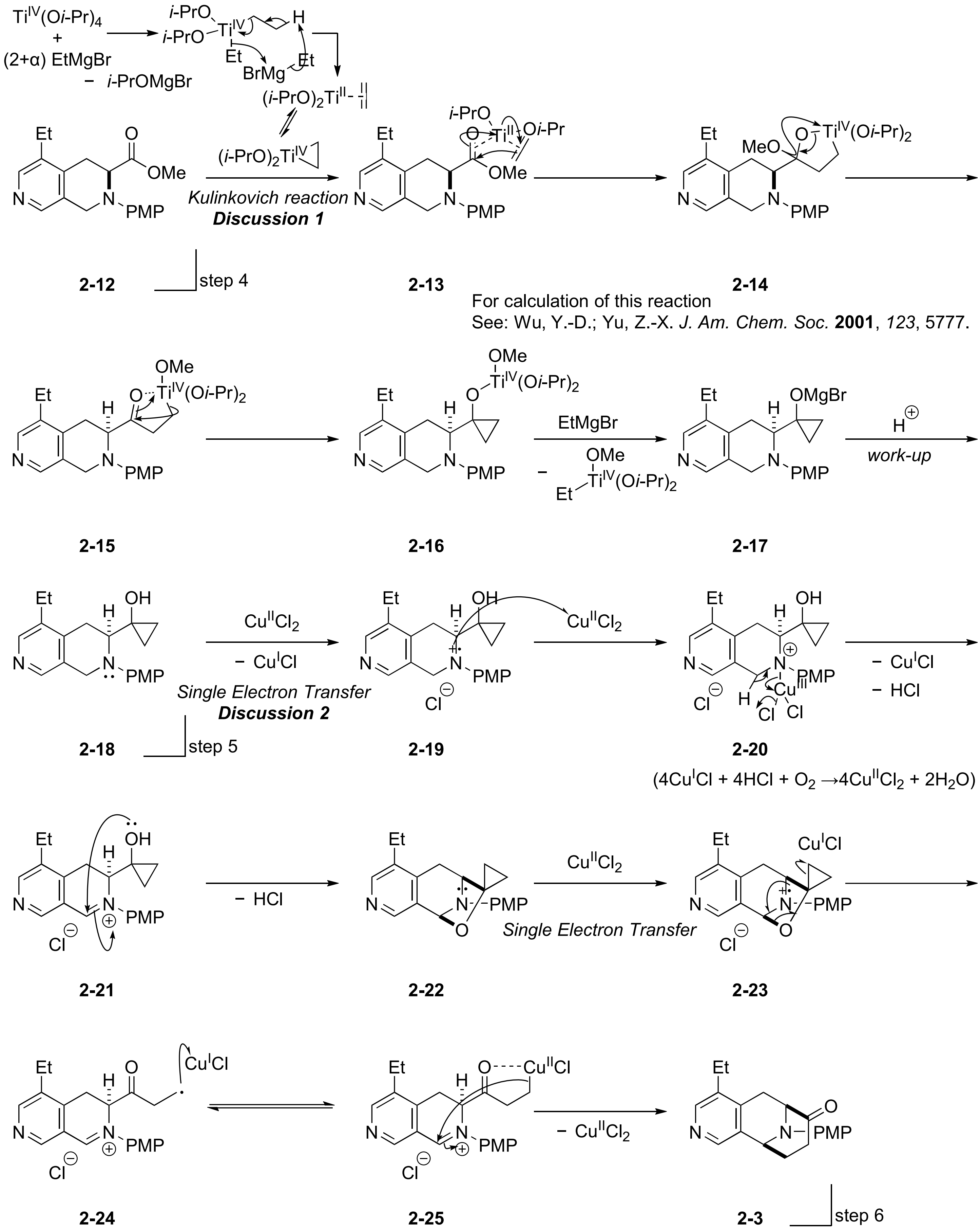


This stereospecific ring construction proceeded in a conrotatory manner, following 4π-electrocyclic reaction system.

2.


1. 2-2 (2 eq.), K2CO3 (2 eq.), MeCN, 60 °C, 84%
2. DMSO (3 eq.), (COCl)2 (2 eq.), CH2Cl2, −78 °C ; Et3N (5 eq.), −78 °C to rt
3. n-PrPPh3·Br (3 eq.), n-BuLi (2.7 eq.) THF, −78 °C, 50% (2 steps), (mixture of isomers, E/Z = 1/3)
4. microwave, DMSO, 200 °C, 65%
5. Ti(Oi-Pr)4 (1 eq.), EtMgBr (5 eq.), THF, 0 °C, 85%
6. CuCl2 (50 mol%), MS 4A (300 wt%), air, CHCl3, 60 °C, 55%
HO
CO2Me
HN
PMP
2-1
Et
N
O
N
PMP
2-3
1. Fischer indole synthesis
2. deprotection of PMP
Et
N
NH
N
suaveoline
O
N
Br
2-2
Tan, Q.; Yang, Z.; Jiang, D.; Cheng, Y.; Yang, J.;Xi, S.; Zhang, M. Angew. Chem., Int. Ed. 2019, 58, 6420.

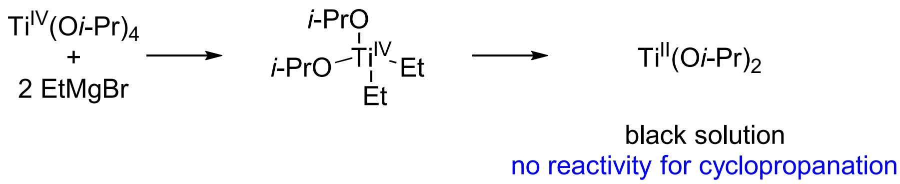

2-1
2-2
− H⊕
2-4
DMSO + (COCl)2
− HCl
2-5
Et3N
− Et3NHCl
step 1
2-6
− Me2S
2-7
Br⊖ PPh3⊕
− H⊕
PPh3
2-8
Ph3
− Ph3PO
step 2
2-9
(Z-olefin is kinetically favored)
hetero-Diels Alder reaction
2-10-exo
±H⊕
2-11
±H⊕
− H2O
step 3
other isomers
2-10-endo
syn elimination
or homolysis
2-12


Ti^IV(Oi-Pr)4 + (2+α) EtMgBr − i-PrOMgBr
i-PrO
i-PrO
Ti^IV
Et
BrMg
Et
H
(i-PrO)2Ti^II
(i-PrO)2Ti^IV
Kulinkovich reaction
Discussion 1
step 4
2-12
2-13
2-14
For calculation of this reaction
See: Wu, Y.-D.; Yu, Z.-X. J. Am. Chem. Soc. 2001, 123, 5777.
2-15
2-16
EtMgBr
OMe
Et–Ti^IV(Oi-Pr)2
2-17
H⊕
work-up
Cu^IICl2
− Cu^ICl
Single Electron Transfer
Discussion 2
2-18
step 5
2-19
2-20
− Cu^ICl
− HCl
(4Cu^ICl + 4HCl + O2 →4Cu^IICl2 + 2H2O)
− HCl
2-21
2-22
Single Electron Transfer
2-23
Cu^ICl
2-24
2-25
Cu^IICl
− Cu^IICl2
2-3
step 6
Et
PMP
OMe
OH
Cl⊖

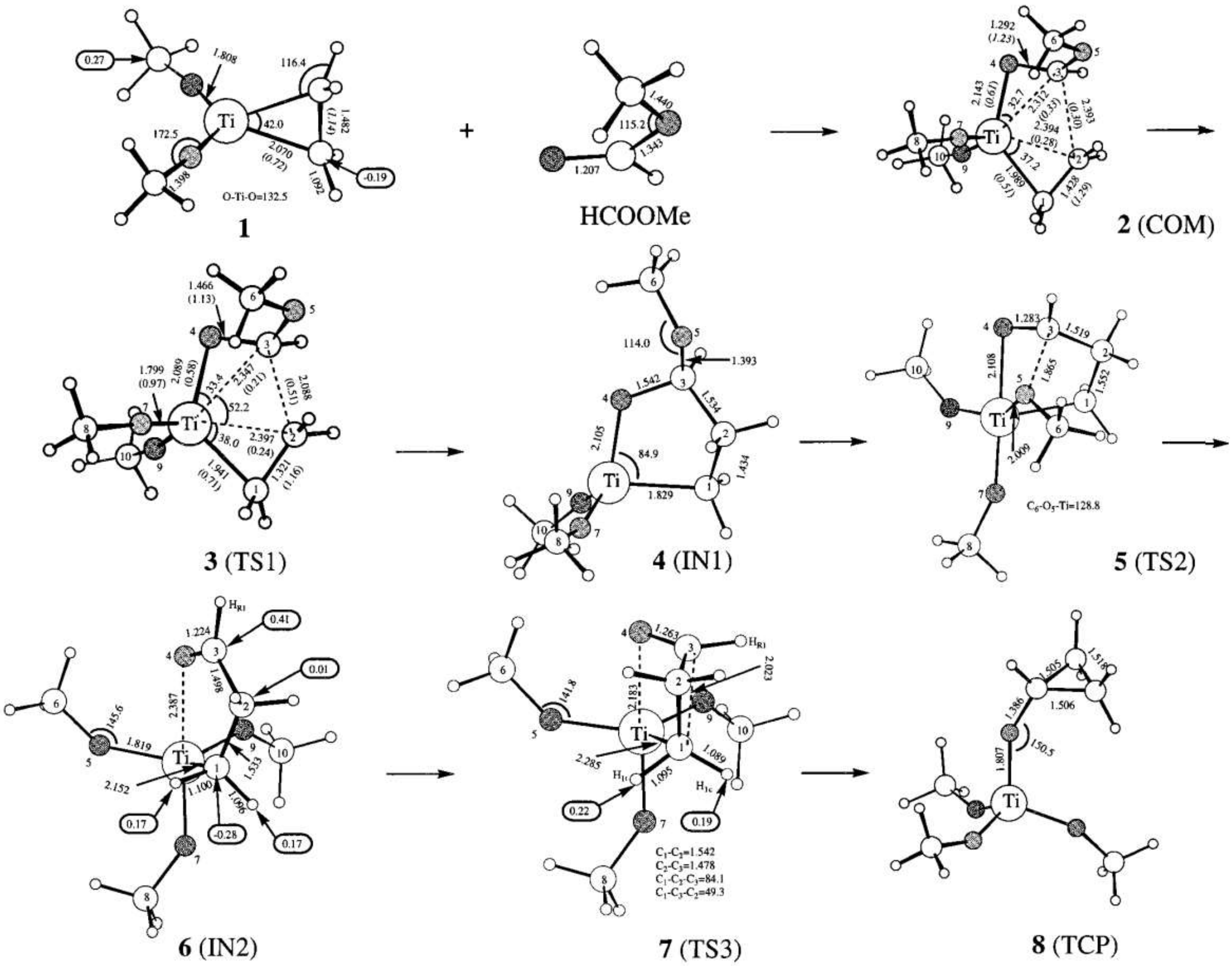
Discussion 1: Kulinkovich reaction

1-1. Preparation of titanacyclopropane

For this cyclopropanation, more than 2 eq. of Grignard reagent are necessary.
(Eisch, J. J.; Adeosun, A. A.; Gitua, J. N. *Eur. J. Org. Chem.* **2003**, 4721.)



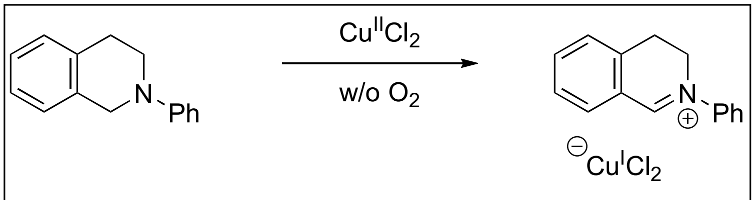
Appendix: Calculated mechanism
(Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777.)



Discussion 2: Oxidative cyclization cascade

2-1. Oxidative iminium formation

Stoichiometric amount of Cu(II) can oxidize the amine without O_2.

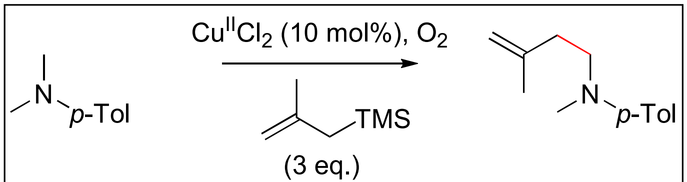


2-26 **2-27**

Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317.

-> O_2 only acts as re-oxidant of Cu.

Benzylamine moiety is not necessary for this oxidation.

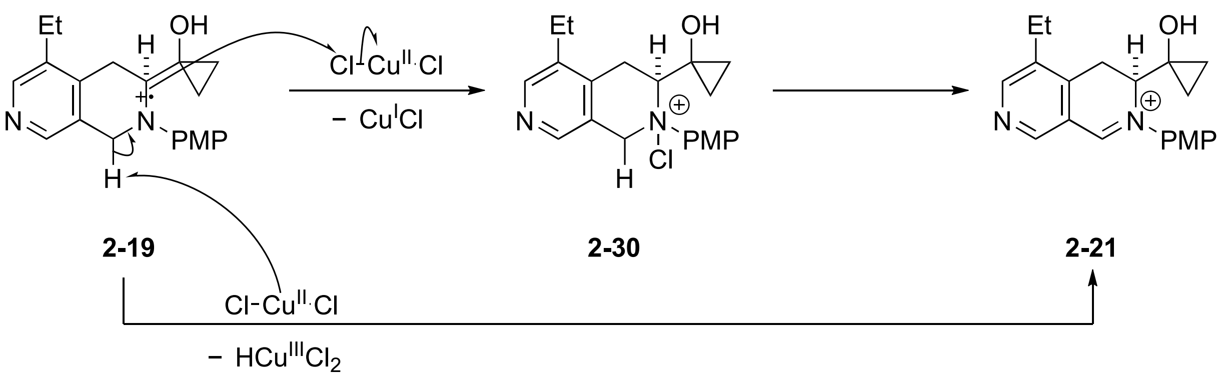


2-28 **2-29**

Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106.

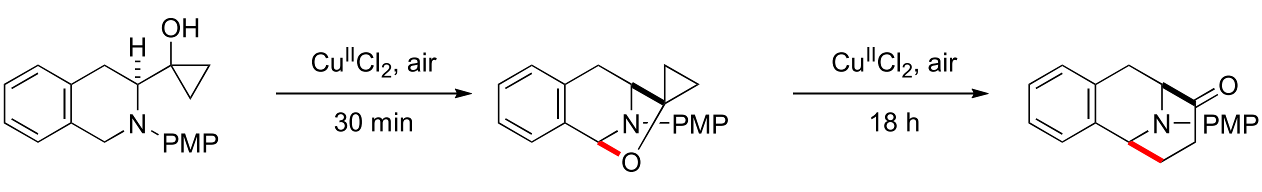
Therefore, oxidation of benzene ring is not included in the mechanism.

Other possible mechanisms



2-19 **2-30** **2-21**

2-2. The order of the reactions

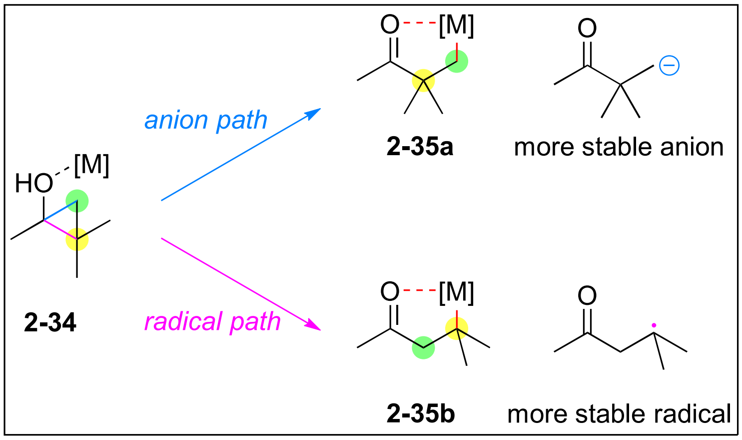


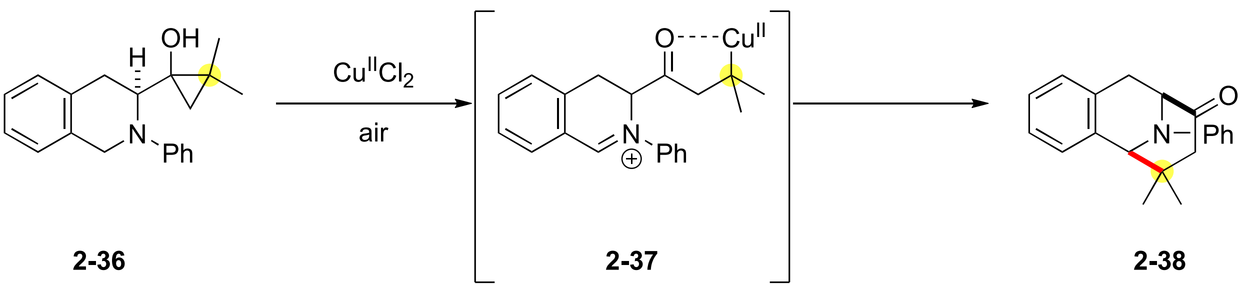
2-31 **2-32** isolated **2-33**

Homoenolate was generated after iminium formation.

2-3. Generation of homoenolate

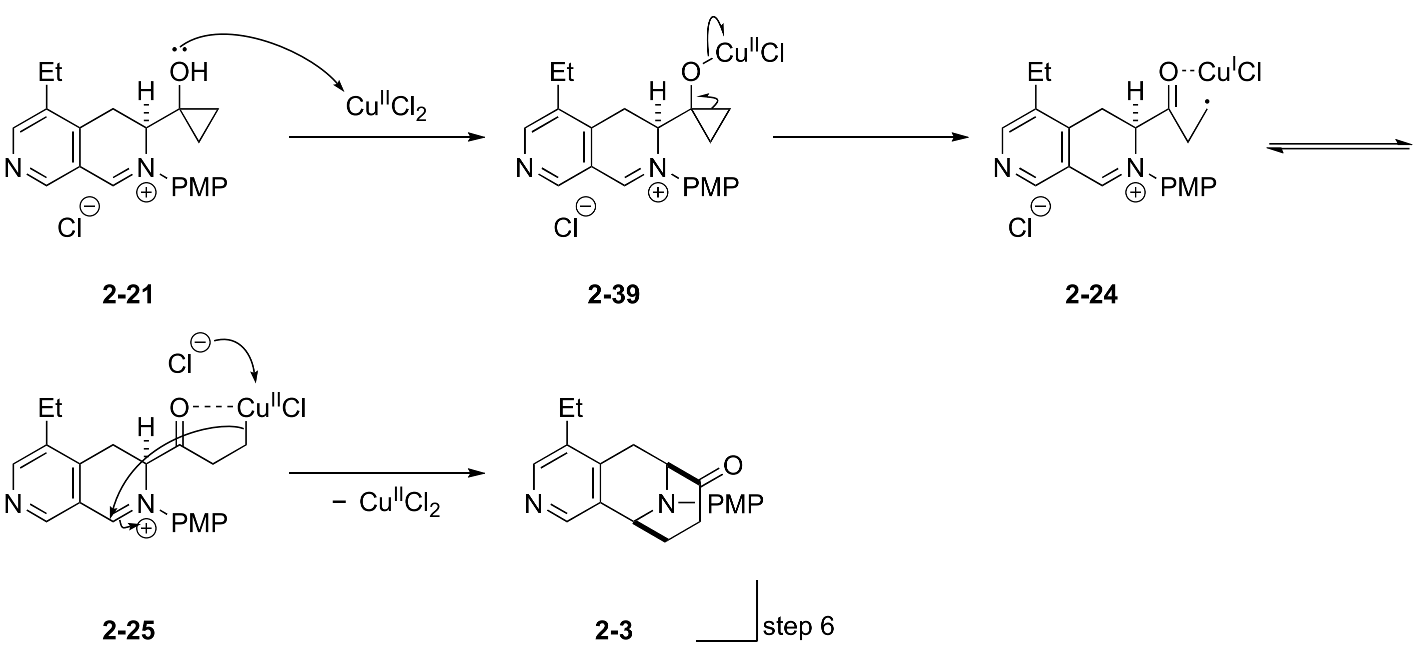
2-3-1. Generation path



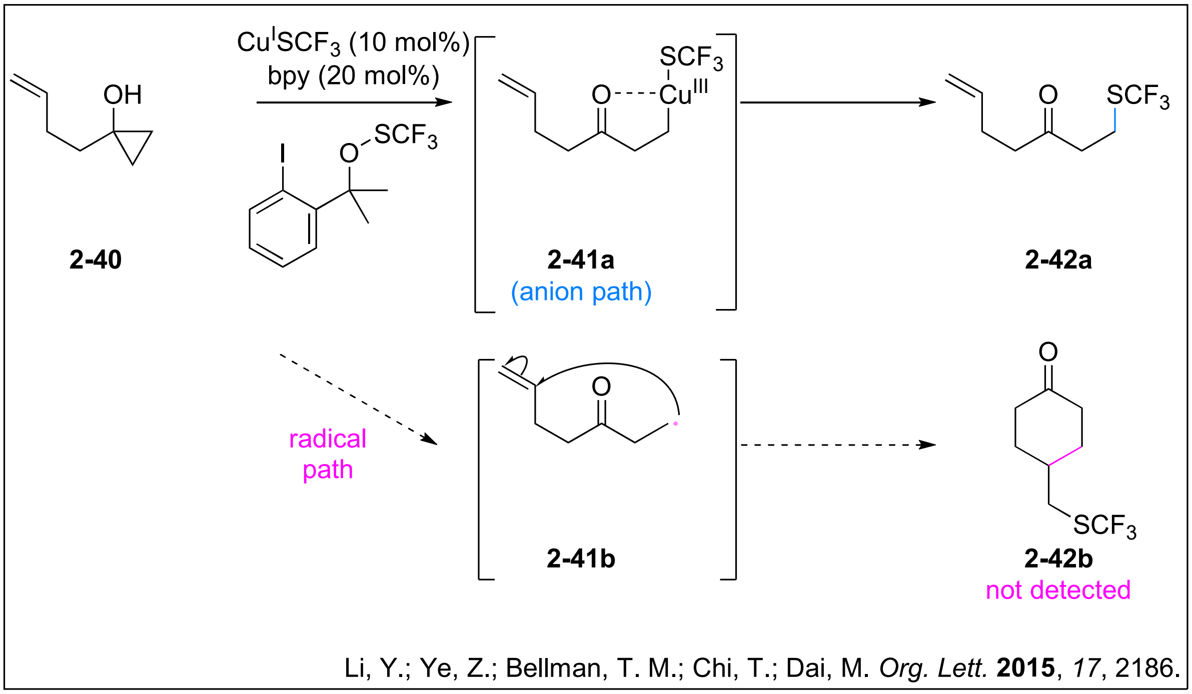


The homoenolate was generated through radical path in this reaction.

2-3-2. Another possible path (by author)



However, Cu-triggered homoenolate generation from cyclopropanol sometimes shows anionic character.



Therefore, SET from amine triggered radical homoenolate generation was proposed in this answer.