Problem Session (1) Answer

2023/02/03 Masahiro Toyoda

Topic: Total synthesis by Ullrich Jahn

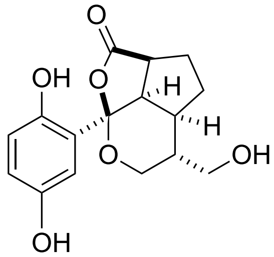
Introduction

Prof. Ullrich Jahn

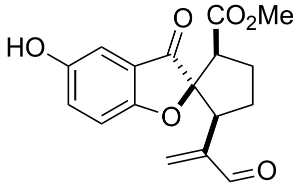
1988 : B.S. Martin-Luther-Universität Halle (Prof. Roland Spitzner)
1992 : Ph. D. Martin-Luther-Universität Halle (Prof. Roland Spitzner)
1993-1995 : Postdoc. University of Pittsburgh (Prof. Dennis P. Curran)
2008- : Professor. IOCB Prague

Research Topic: Total Synthesis of Natural Products and their Biological Investigation

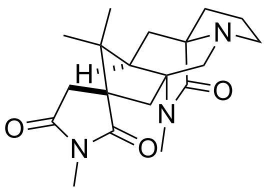
Total Synthesis:



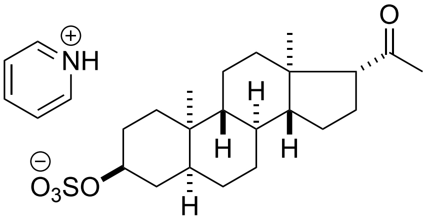
Applanatumols B
(**Problem 1**)
Org. Lett. **2022**, *24*, 4552



2′-*epi*-Spiroapplanatumine O
Org. Lett. **2022**, *24*, 4552



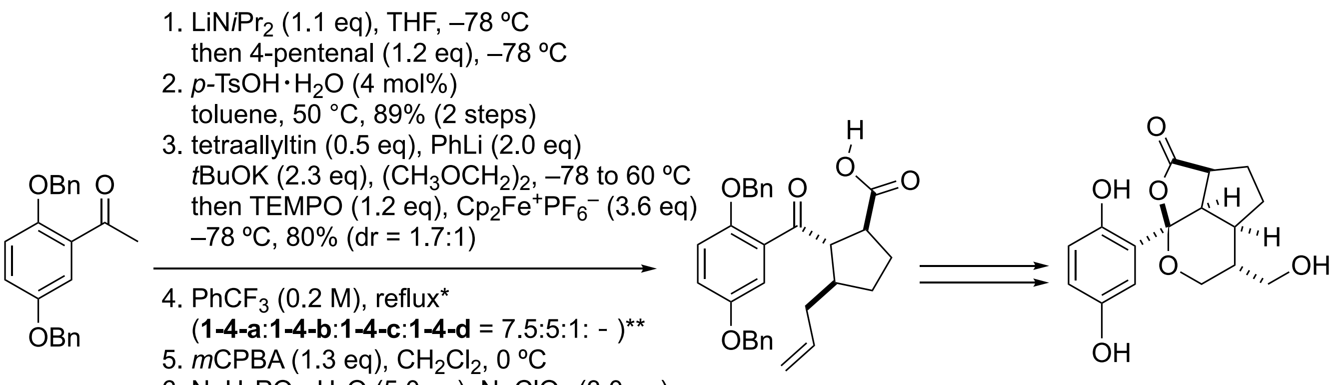
ent-asperparaline C
(**Problem 2**)
Chem. Commun. **2019**, *55*, 3931



ent-Pregnanolone Sulfate
Org. Lett. **2018**, 20, 946

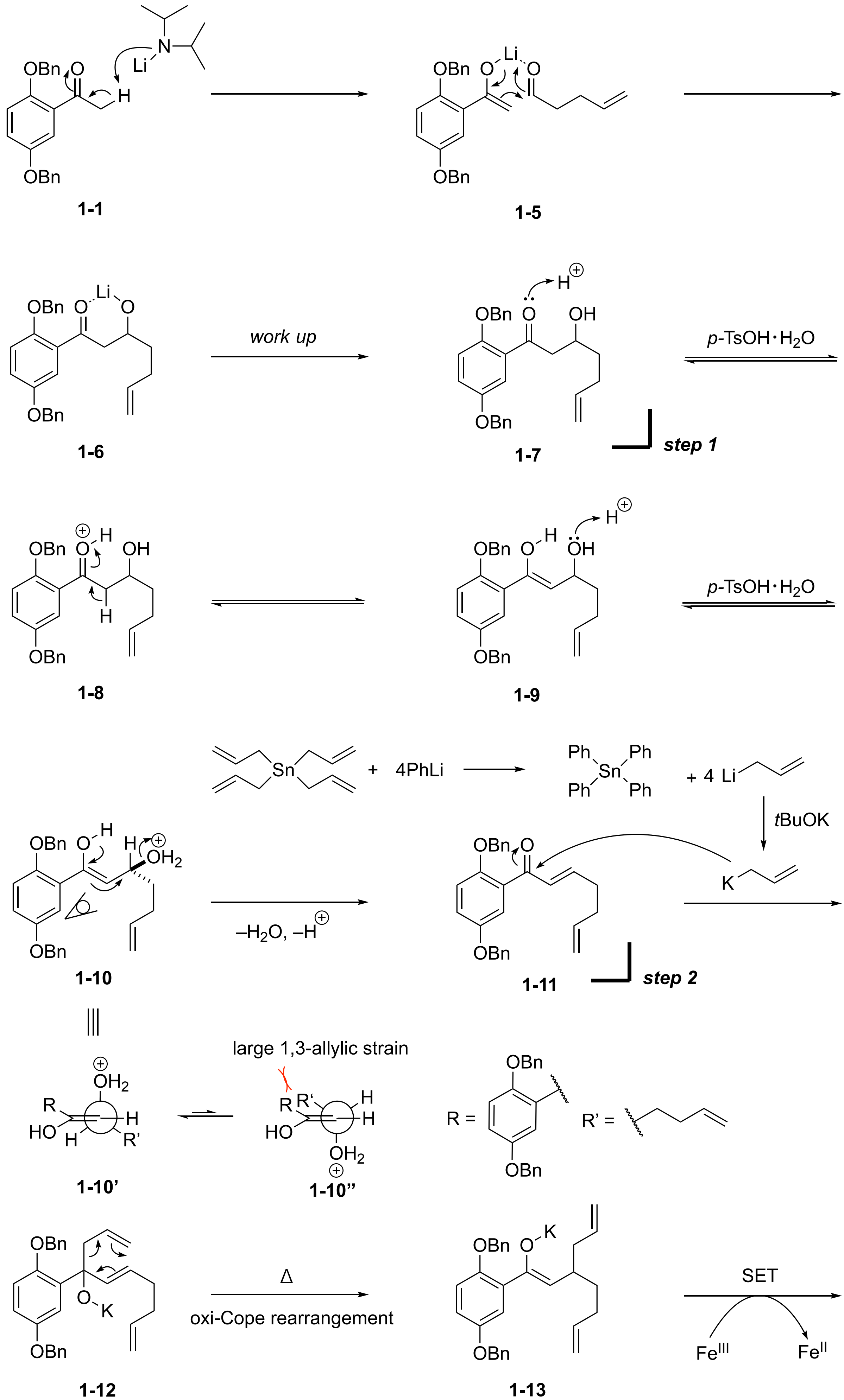
Answer:

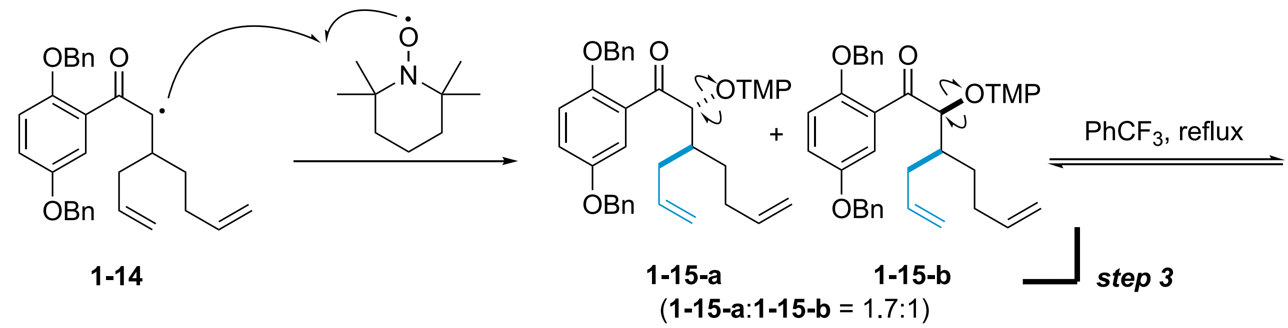
1-1. Reaction mechanism

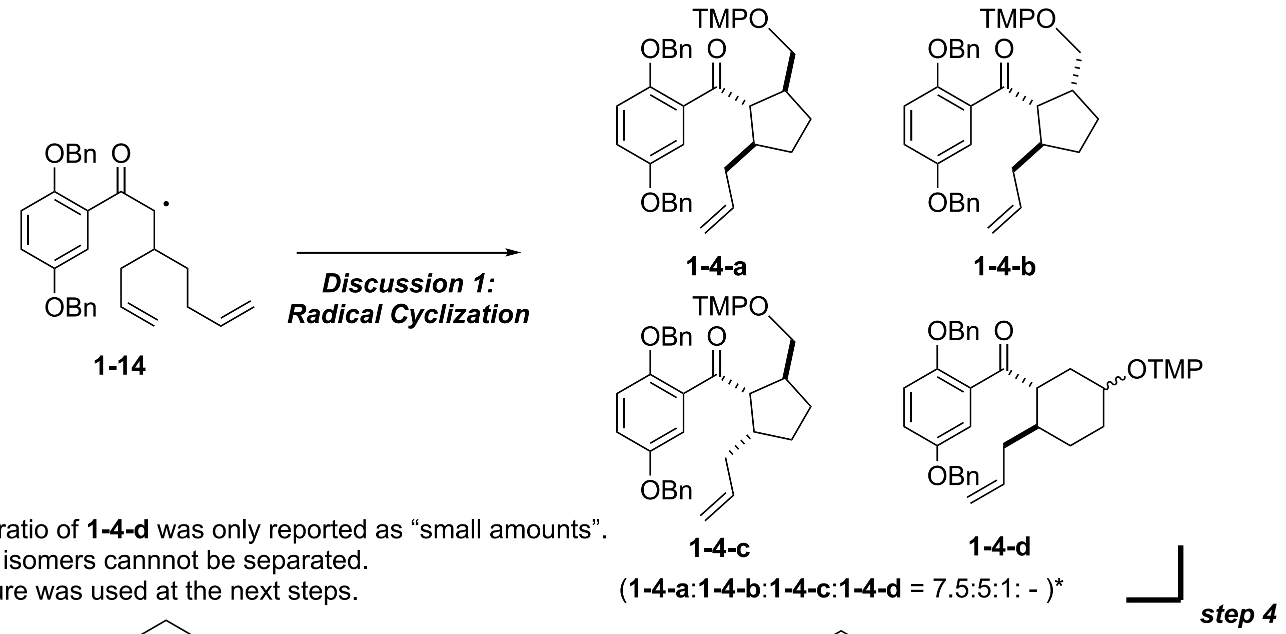


*$PhCF_3$ (b.p. 102 ºC) **The ratio of **1-4-d** was only reported as "small amounts".
Four isomers cannot be separated.
Mixture was used at the next step.

Michal, S.; Katerina, B.; Samy, I.; Miroslav, H.; Ivana, C.; Ullrich, J. *Org. Lett.* **2022**, *24*, 4552


OBn
OBn
Li
N
H
1-1
1-5
1-6
work up
1-7
p-TsOH·H2O
step 1
1-8
1-9
p-TsOH·H2O
Sn
+ 4PhLi
Ph
Sn
+ 4 Li
tBuOK
1-10
–H2O, –H
1-11
K
step 2
large 1,3-allylic strain
1-10'
1-10''
R =
R' =
1-12
Δ
oxi-Cope rearrangement
1-13
SET
FeIII
FeII





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Four isomers cannnot be separated.
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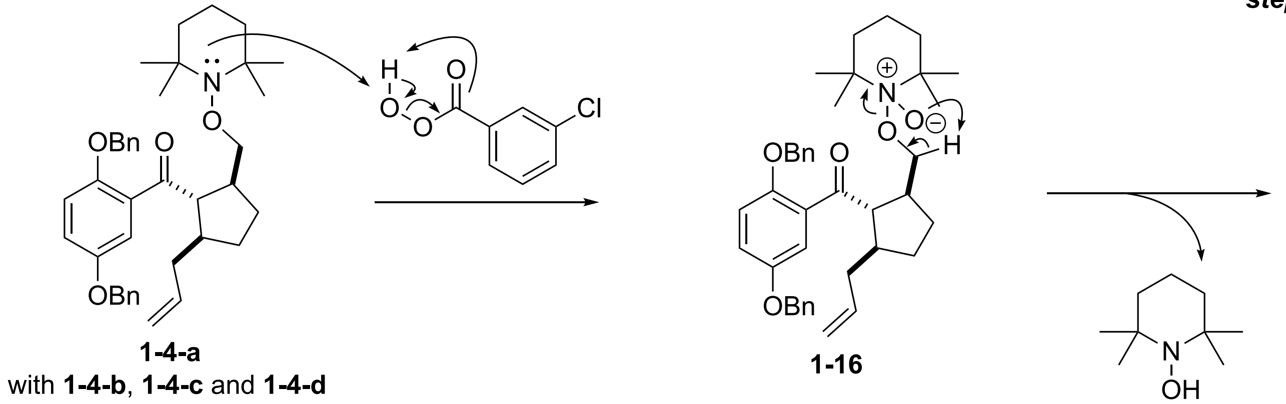
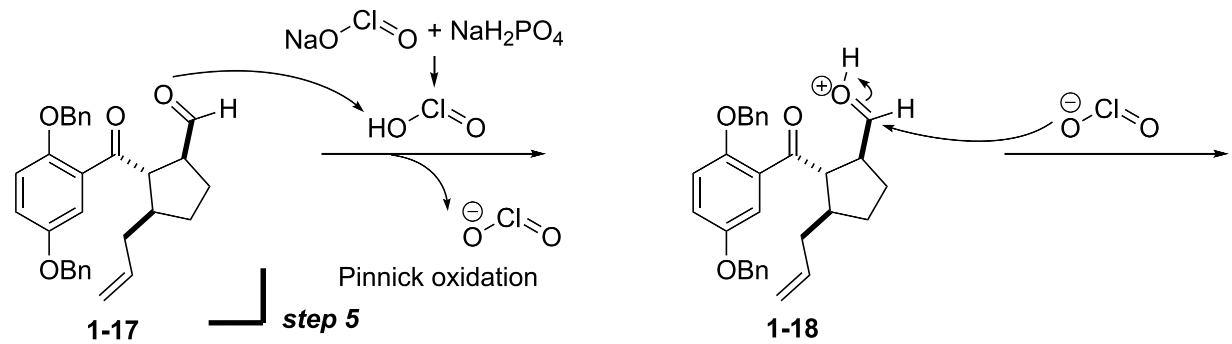
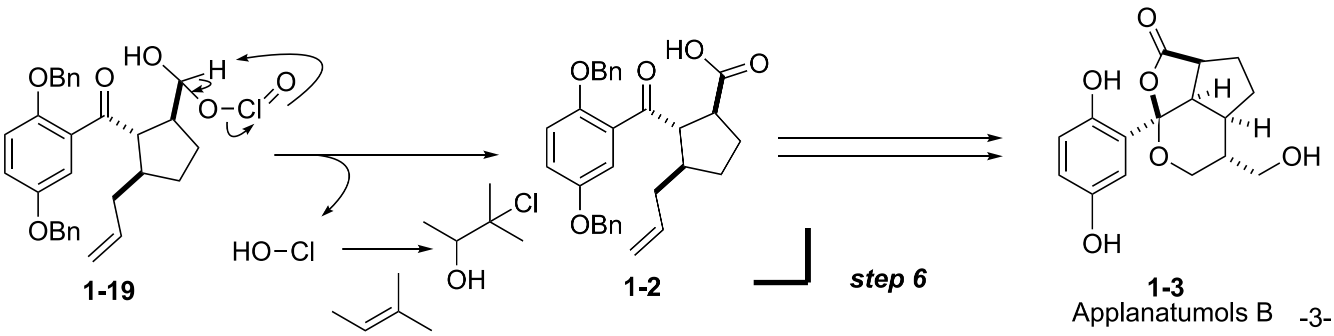
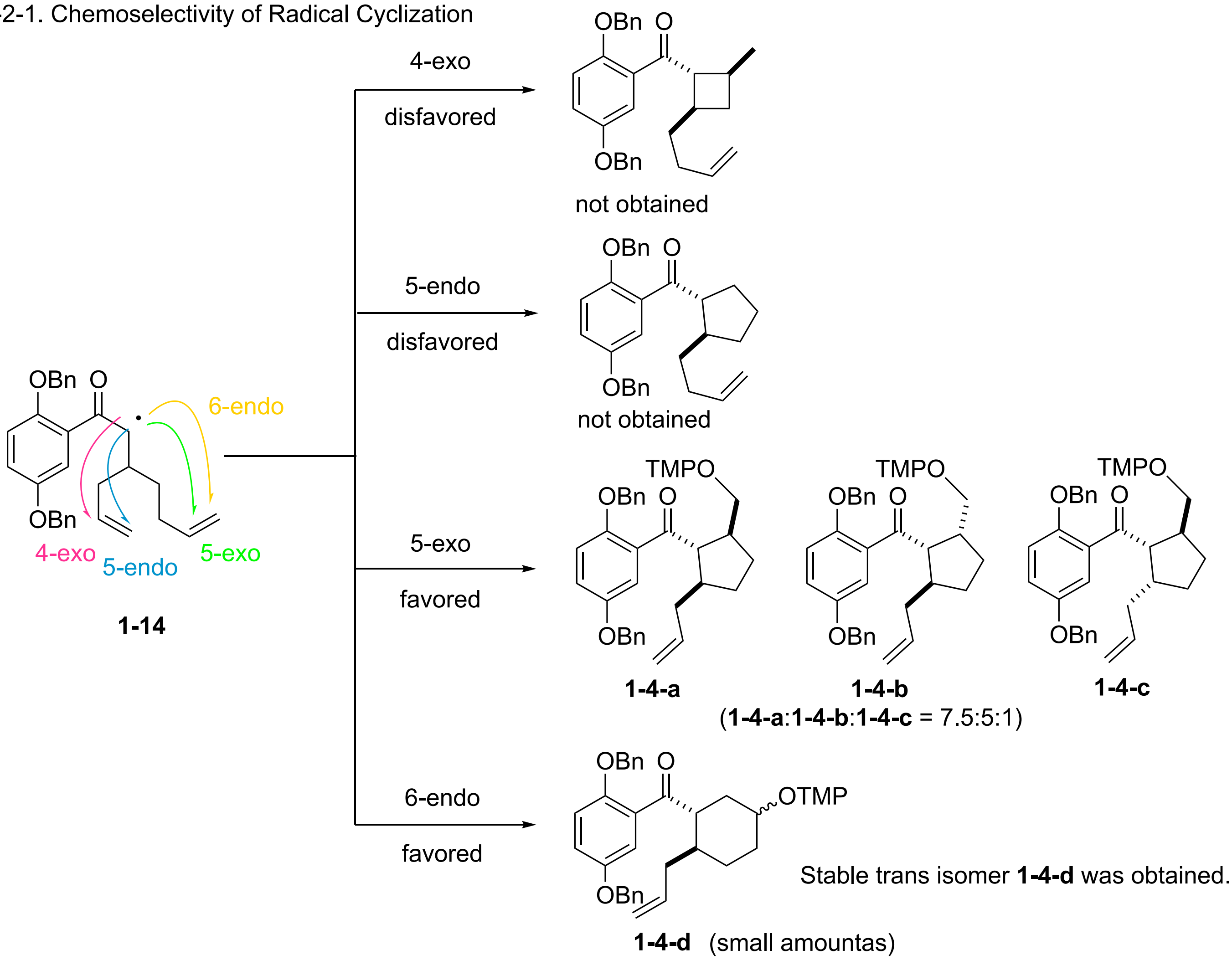




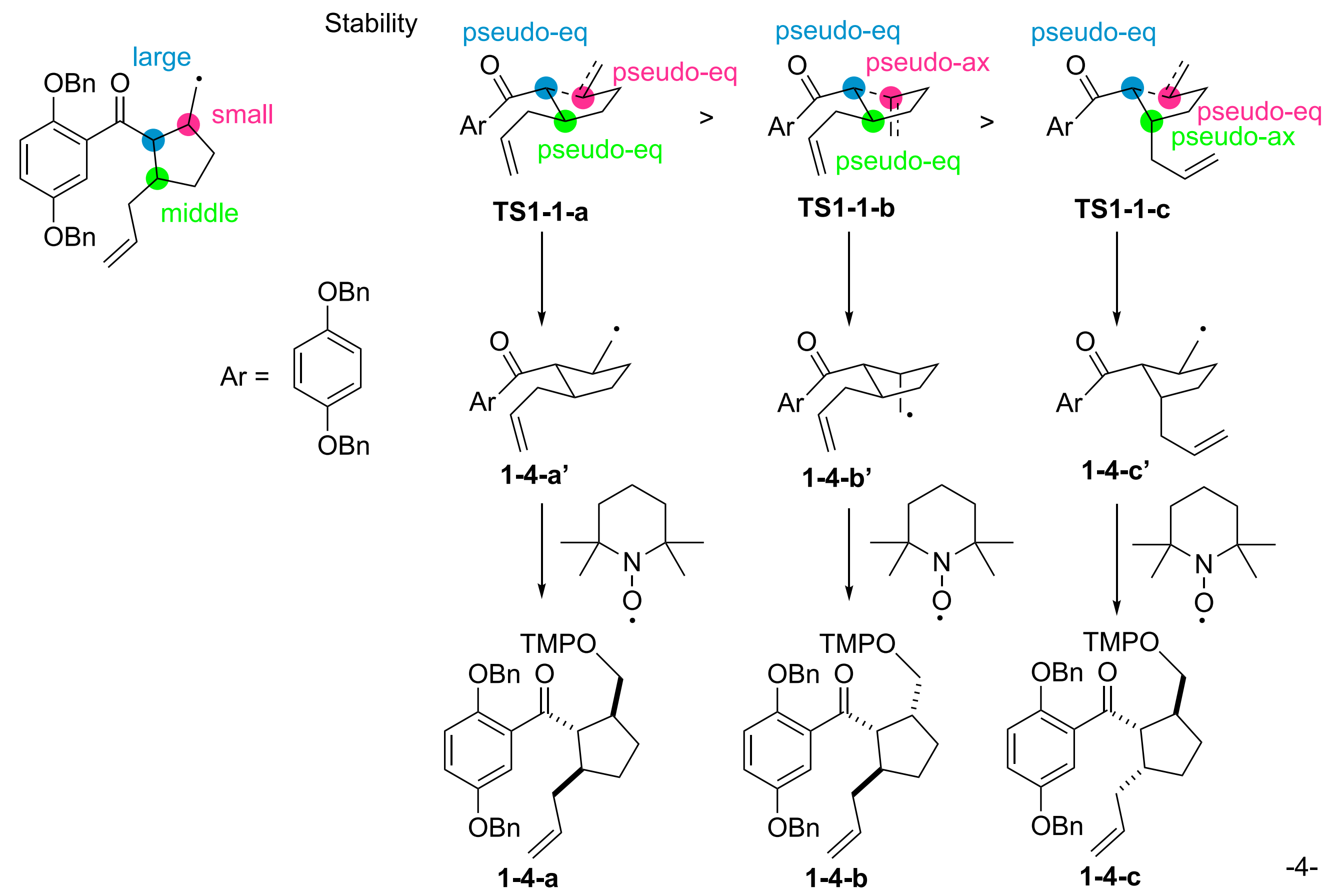


1-2. Discussion 1: Radical Cyclization

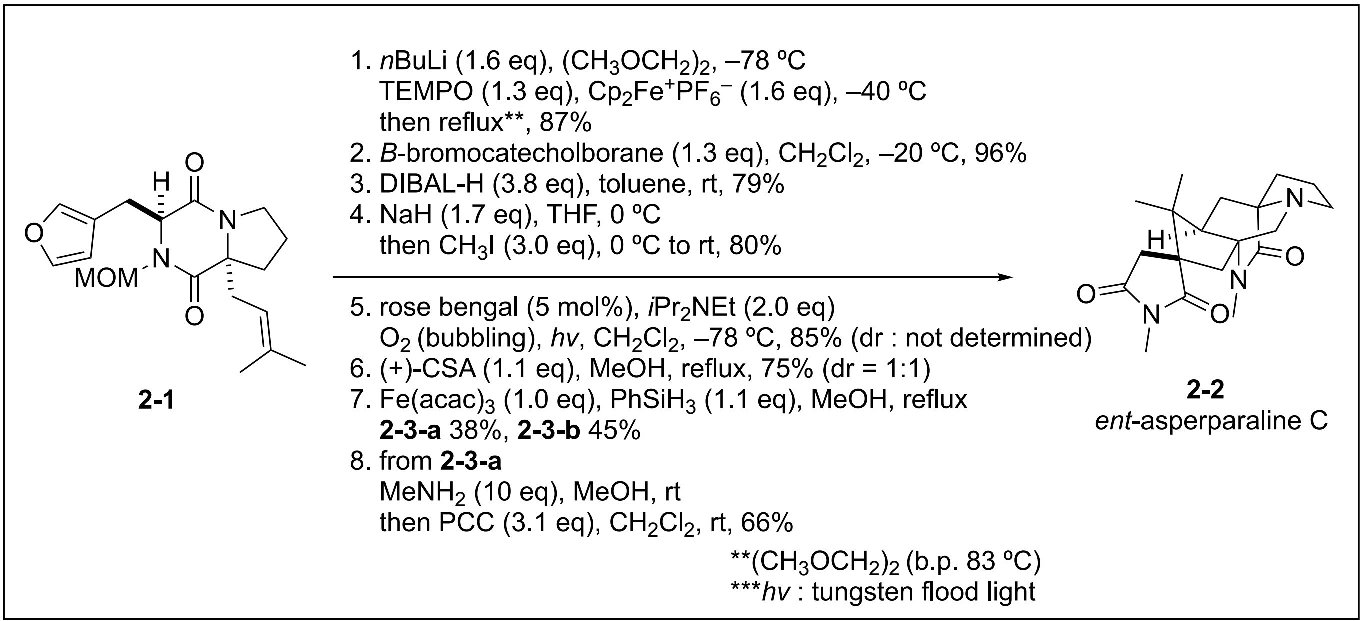
1-2-1. Chemoselectivity of Radical Cyclization



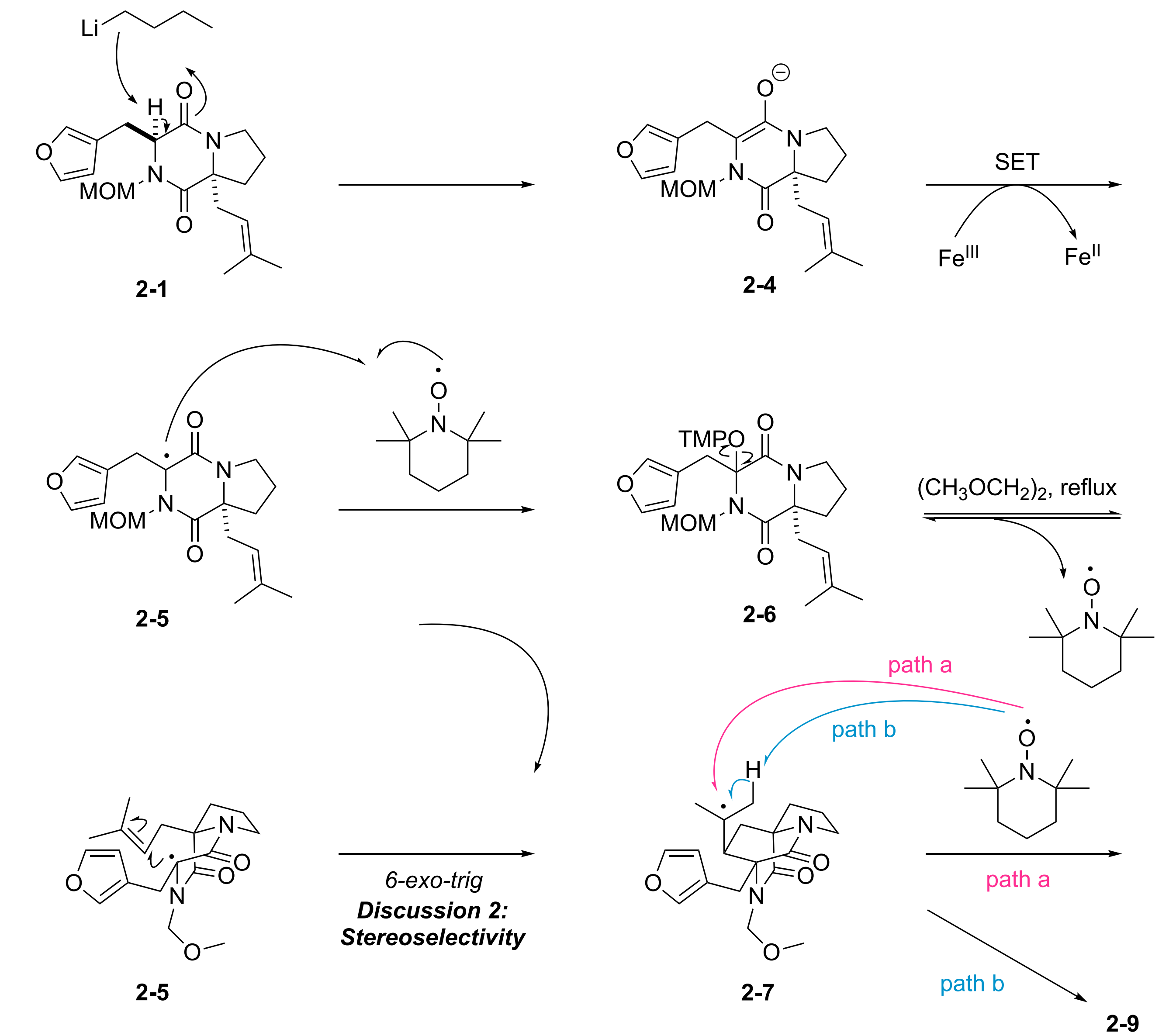
1-2-2. Stereochemistry of 5-exo Radical Cyclization

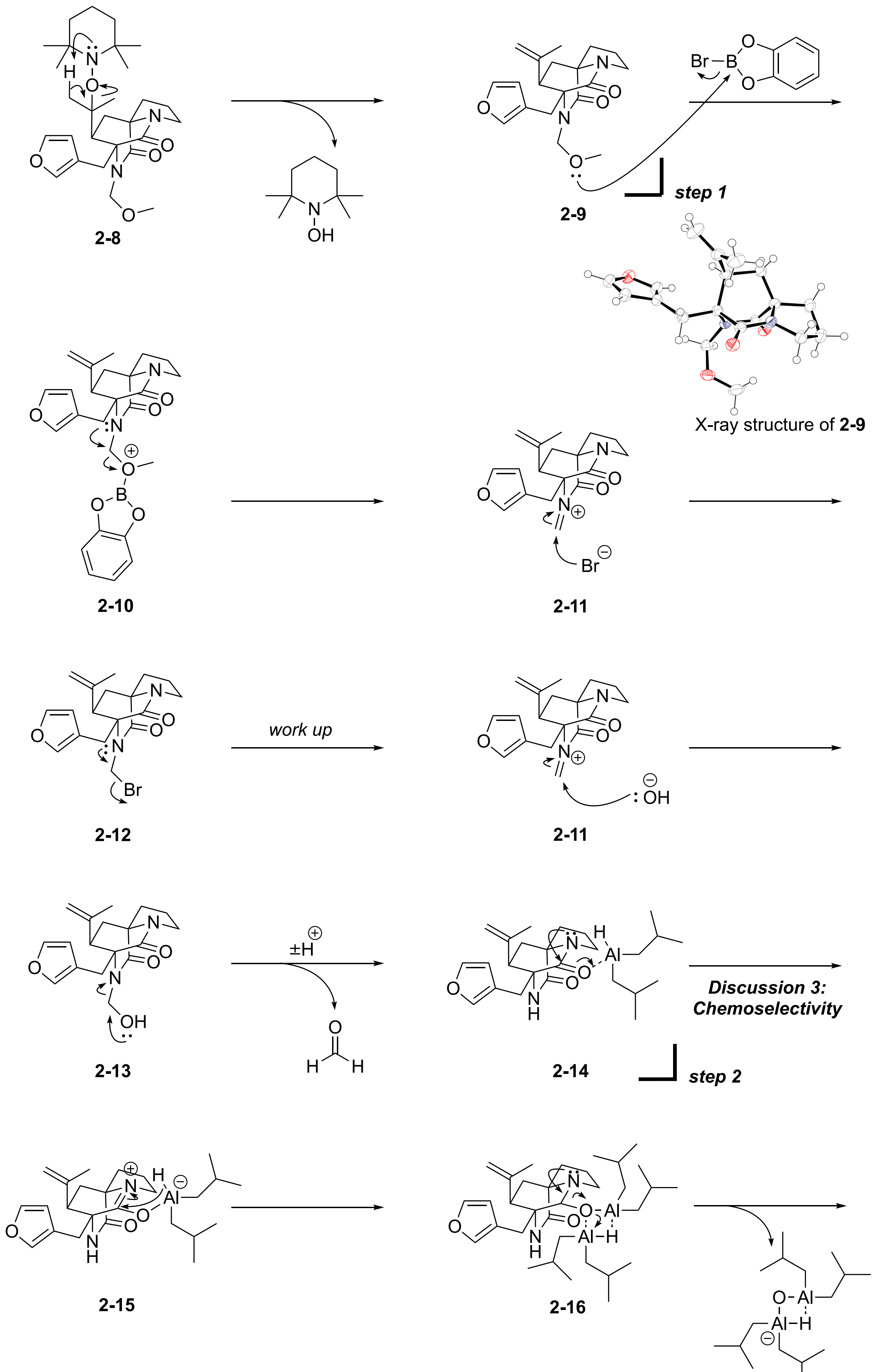


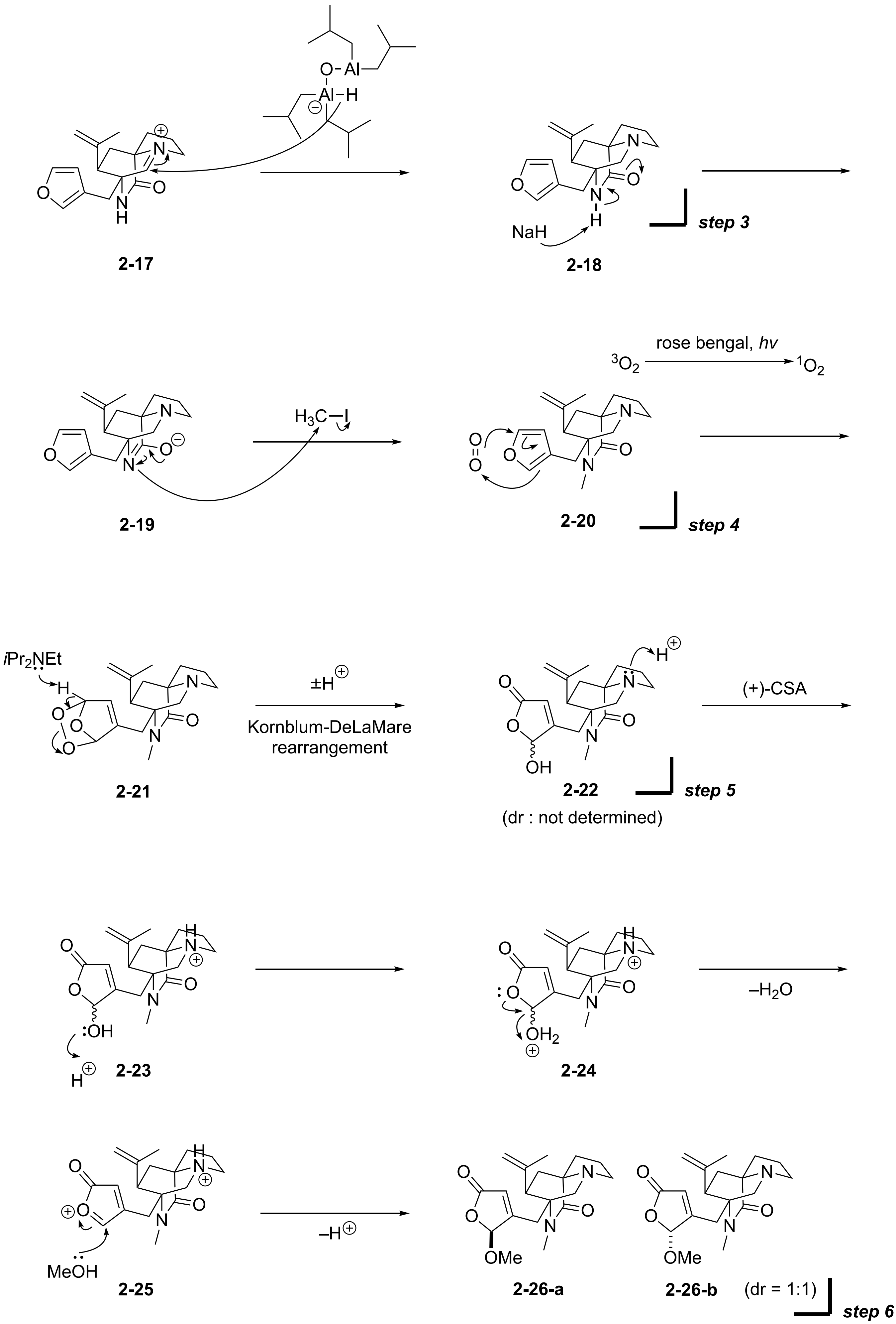
2-1. Reaction mechanism



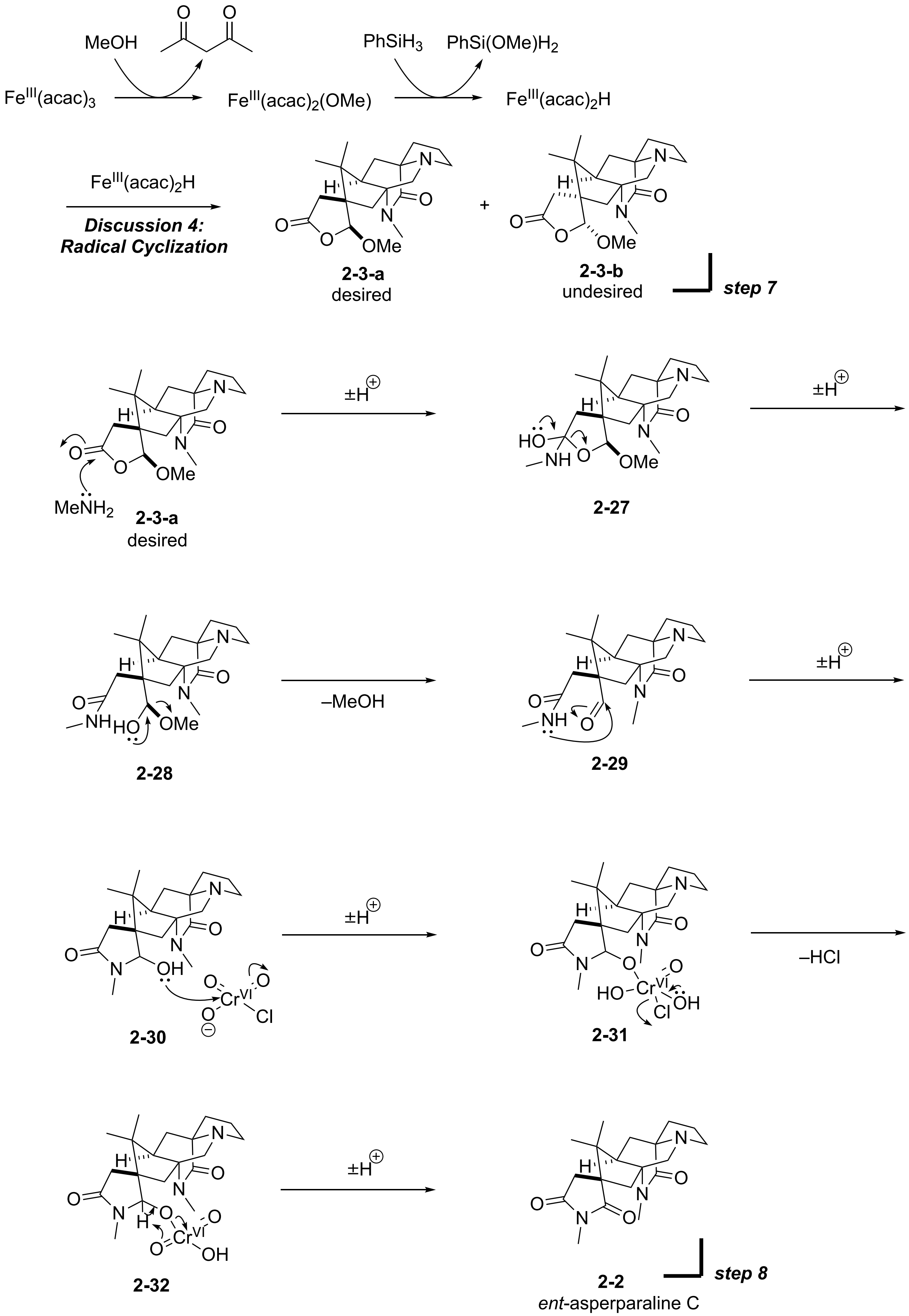
Irena,D.; Radek, P.; Blanka, K.; Ullrich, J. *Chem. Commun.* **2019**, *55*, 3931



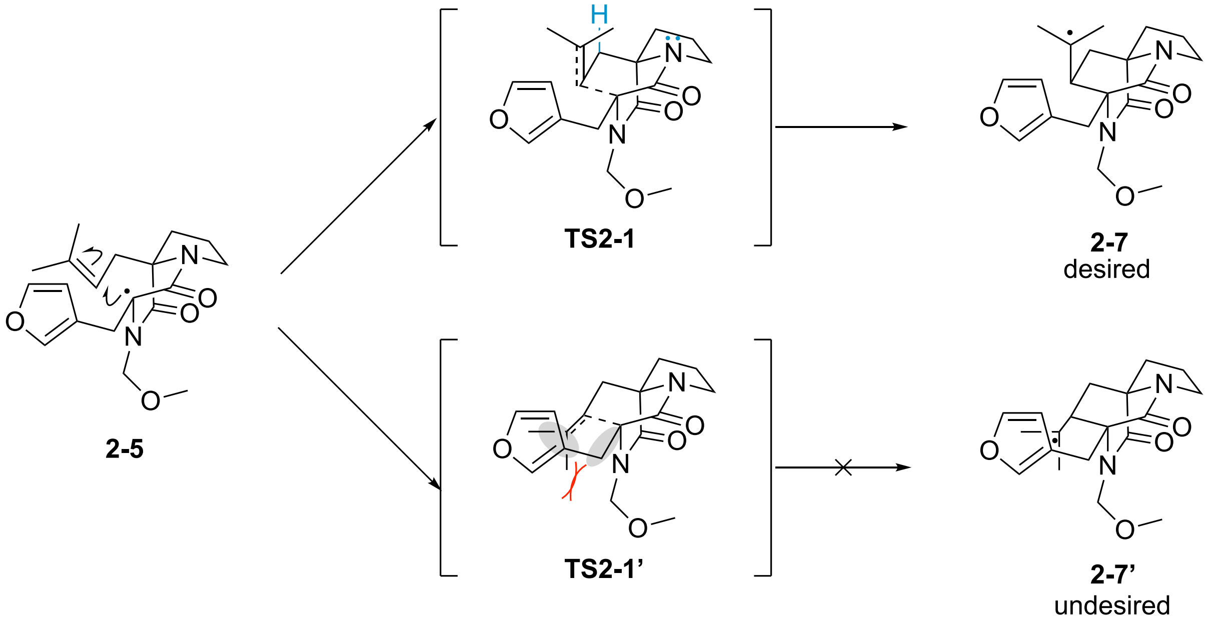

2-8
2-9
step 1
X-ray structure of 2-9
2-10
2-11
work up
2-12
2-11
±H
2-13
2-14
Discussion 3: Chemoselectivity
step 2
2-15
2-16



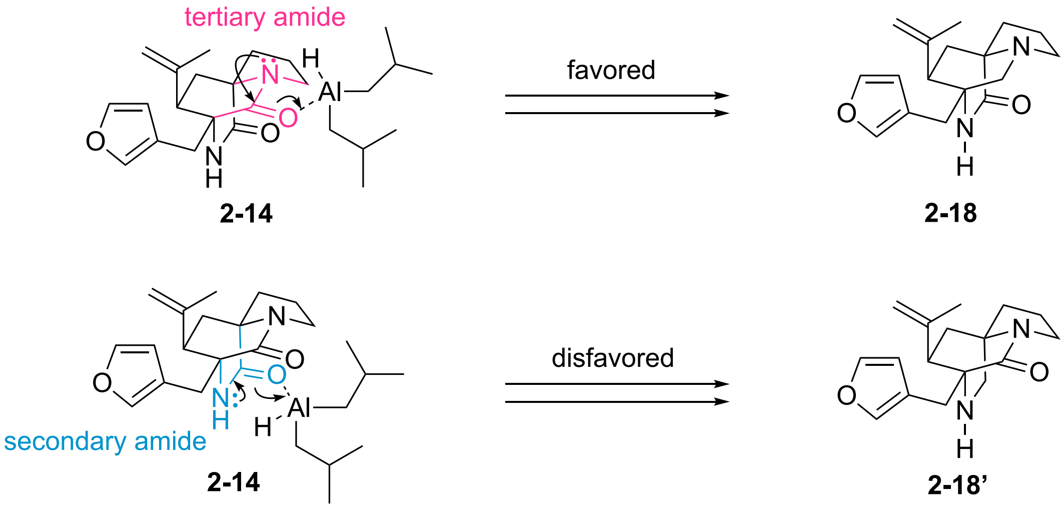
2-17
2-18
NaH
step 3
2-19
H_3C-I
rose bengal, hv
$^3O_2$ → $^1O_2$
2-20
step 4
iPr_2NEt
2-21
±H⊕
Kornblum-DeLaMare rearrangement
2-22
(dr : not determined)
(+)-CSA
step 5
2-23
2-24
$-H_2O$
MeOH
2-25
–H⊕
OMe
2-26-a
2-26-b
(dr = 1:1)
step 6


MeOH
Fe^III(acac)3
Fe^III(acac)2(OMe)
PhSiH3
PhSi(OMe)H2
Fe^III(acac)2H
Fe^III(acac)2H
Discussion 4:
Radical Cyclization
2-3-a
desired
2-3-b
undesired
step 7
MeNH2
2-3-a
desired
±H+
2-27
±H+
2-28
–MeOH
2-29
±H+
2-30
±H+
2-31
–HCl
2-32
±H+
2-2
ent-asperparaline C
step 8

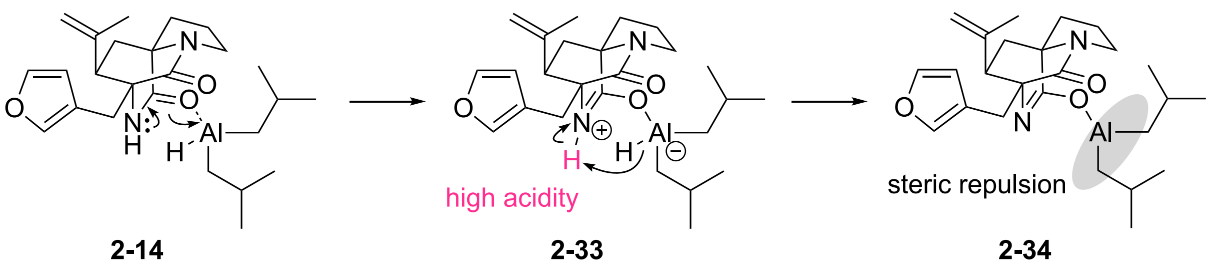
2-1. Discussion 2: Stereoselectivity of Radical Cyclization



2-2. Discussion 3: Chemoselectivity of Reduction of Amide Groups



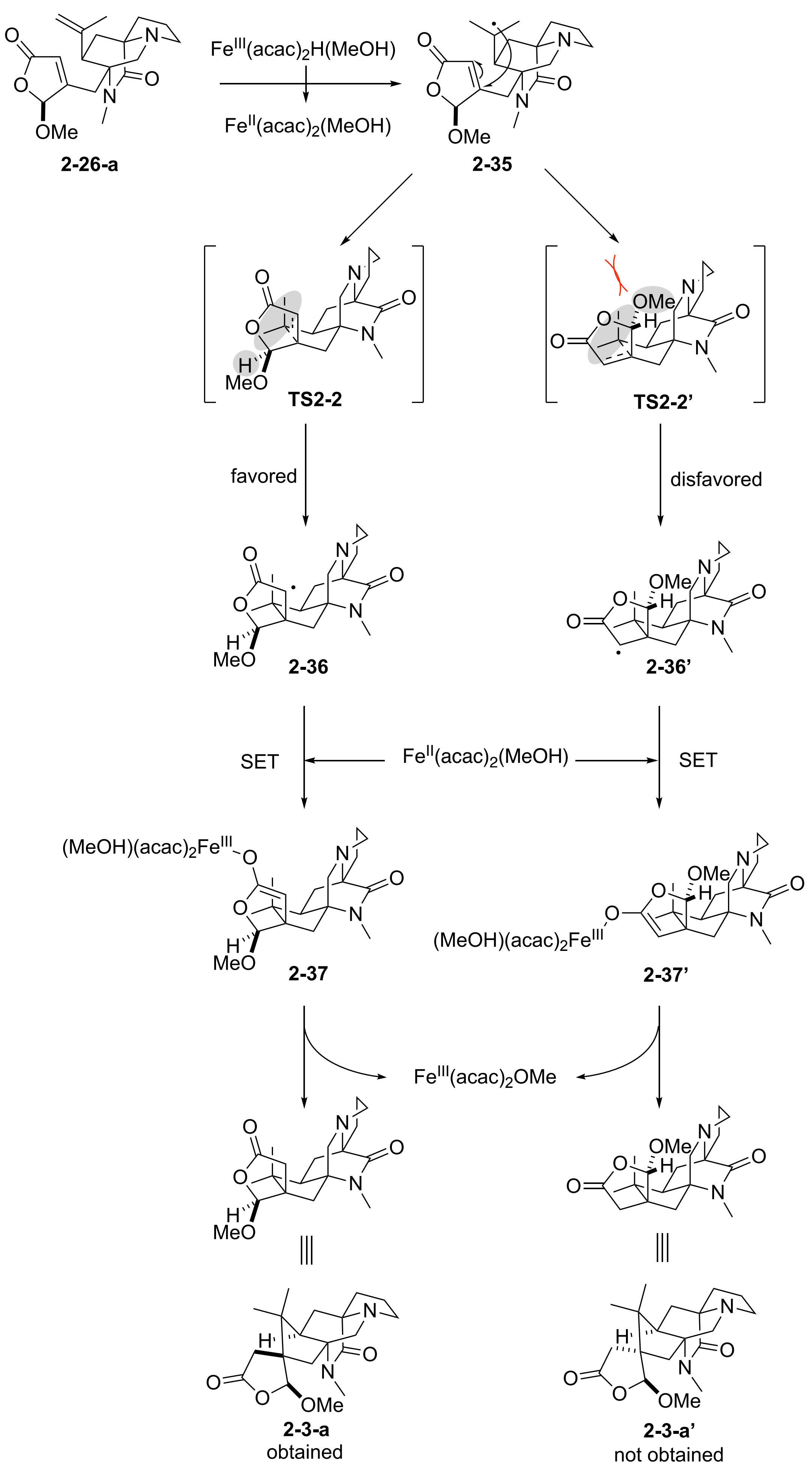
The electron density of the tertiary amide is higher than that of the secondary amide.
The nucleophilicity of the tertiary amide is also higher.



Reduction by DIBAL-H does not proceed from **2-34**.

2-3. Discussion 4: Stereoselectivity of Radical Cyclization

2-3-1. Stereoselectivity of Radical Cyclization using **2-26-a**



2-3-2. Stereoselectivity of Radical Cyclization using **2-26-b**