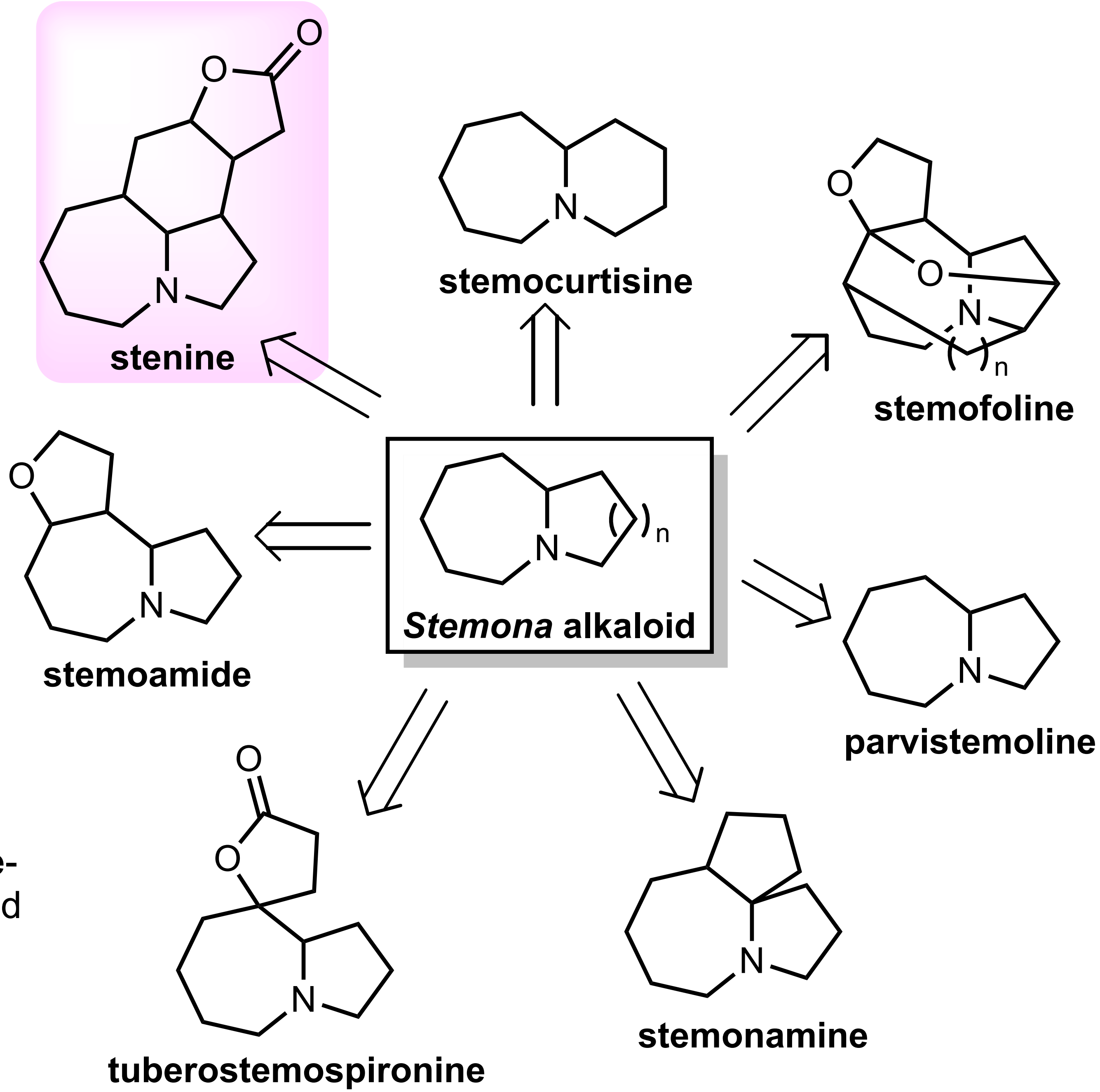
Asymmetric Total Synthesis of the *Stemona Alkaloid* (−)-Stenine

Peter Wipf *et al. J. Am. Chem. Soc.* **1995**, *117*, 11106-11112.

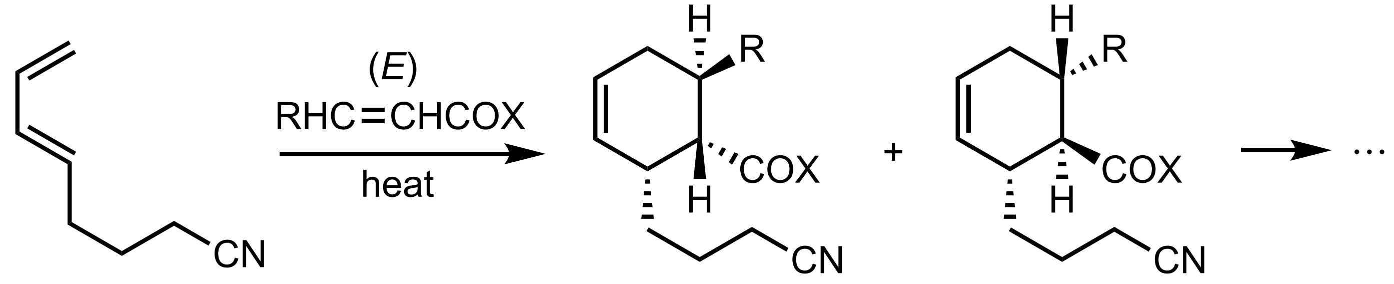
the 7th **TS**
Yumeng Liao

traditional herbal medicine
in east Asia(China, Japan…)
and southeast Asia (Vietnam…)

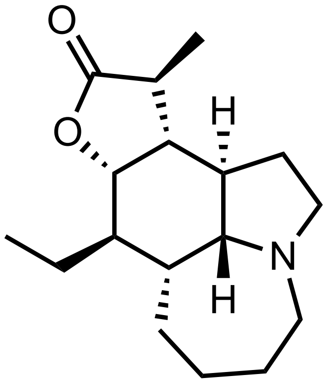
suppress coughing, having antituberculosis, antibacterial, antifungal and antihelmintic properties



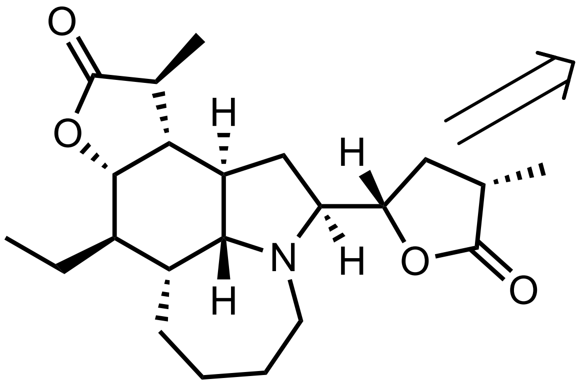
Racemic synthesis of stenine



D. J. Hart *et al. J. Org. Chem.* **1993**, *58*, 3840-3849.

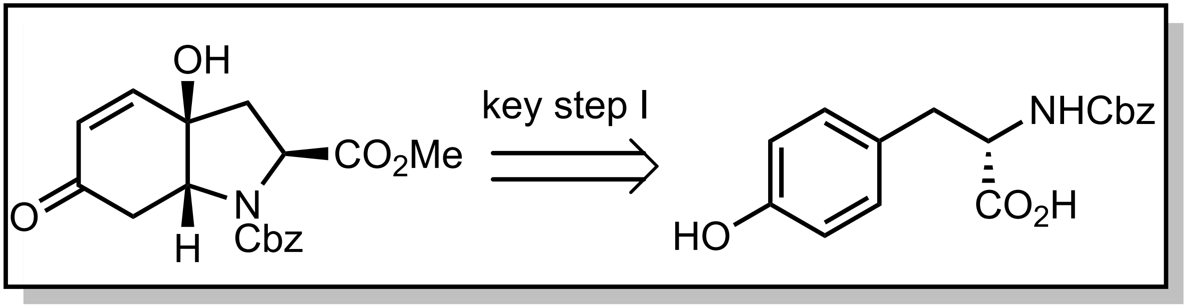


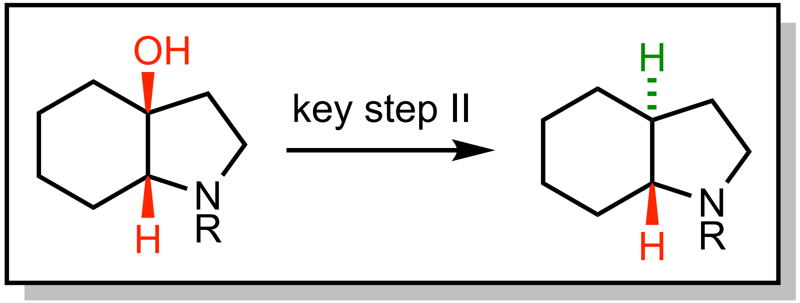
Stenine (1)

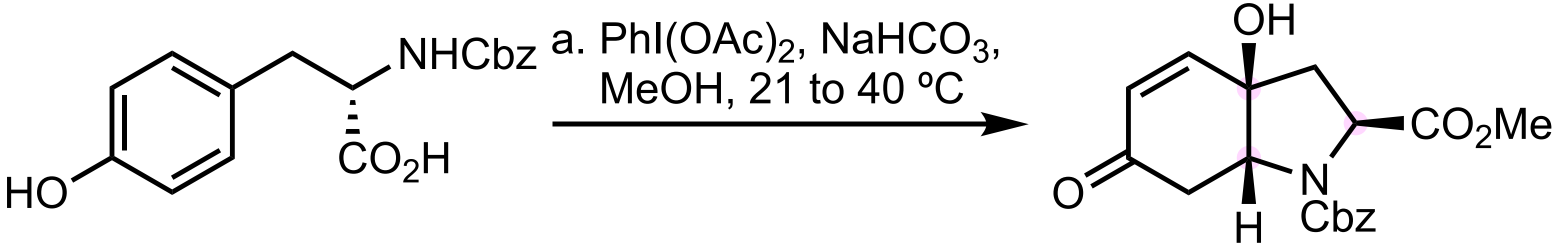


Tuberostemonine (2)

This Work: Asymmetric synthesis of (−)-stenine





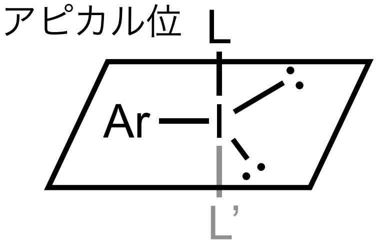


1

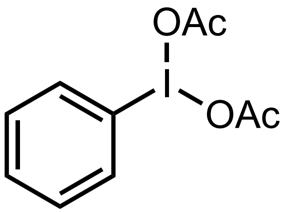
2
three stereocenters

超原子価ヨウ素 (hypervalent iodine)

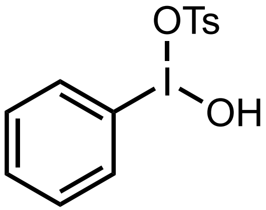
ヨウ素はハロゲン元素の中で、サイズが大きく、分極しやすく、
電気陰性度が小さい。そのため、超原子価を取りやすい。
超原子価ヨウ素化合物の反応性や安定性はアピカル位の原子団
に支配されている。その脱離に伴い、安定なI価のヨウ素へ還元
され、大きな脱離能や酸化能を示す。



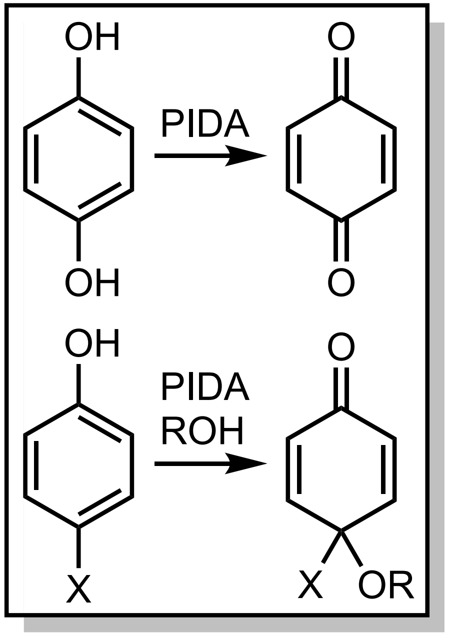
III価



PIDA

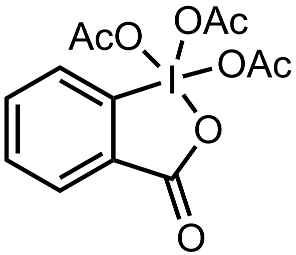


HTIB

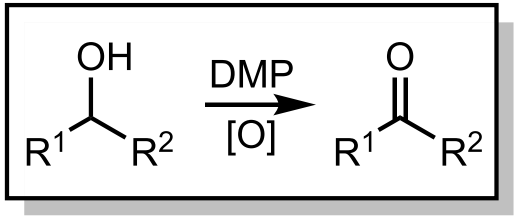


phenol oxidation

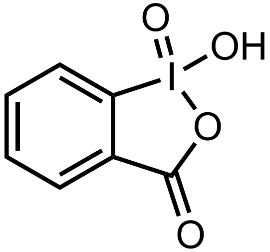
V価



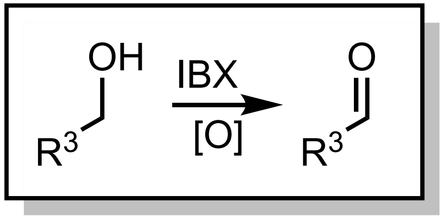
Dess-Martin
Periodinane



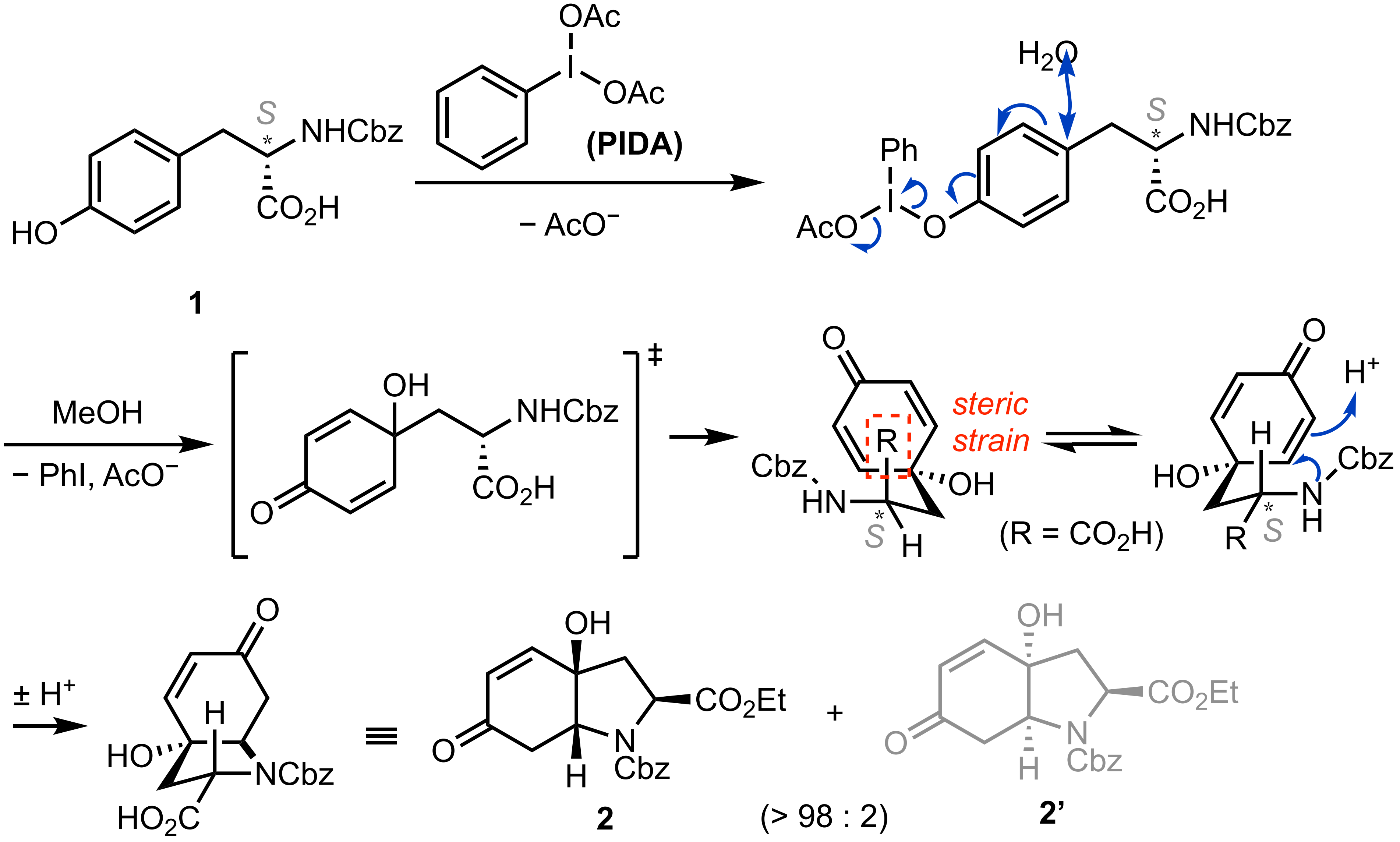
alcohol oxidation



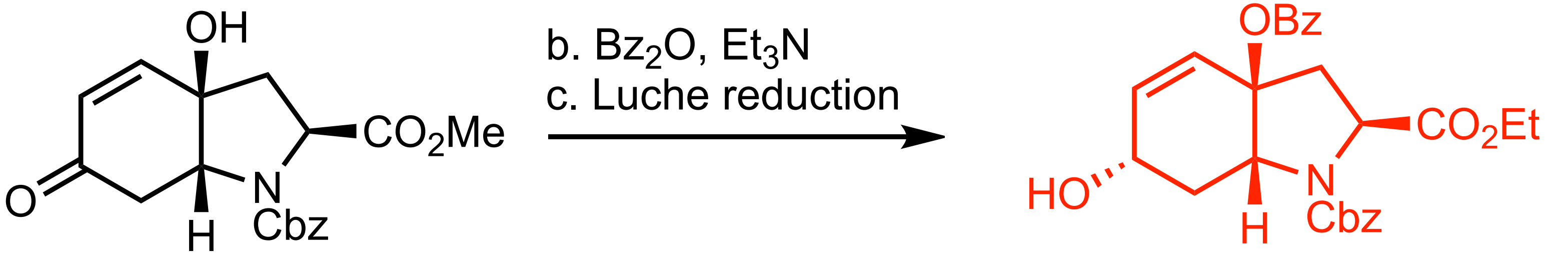
IBX



alcohol oxidation



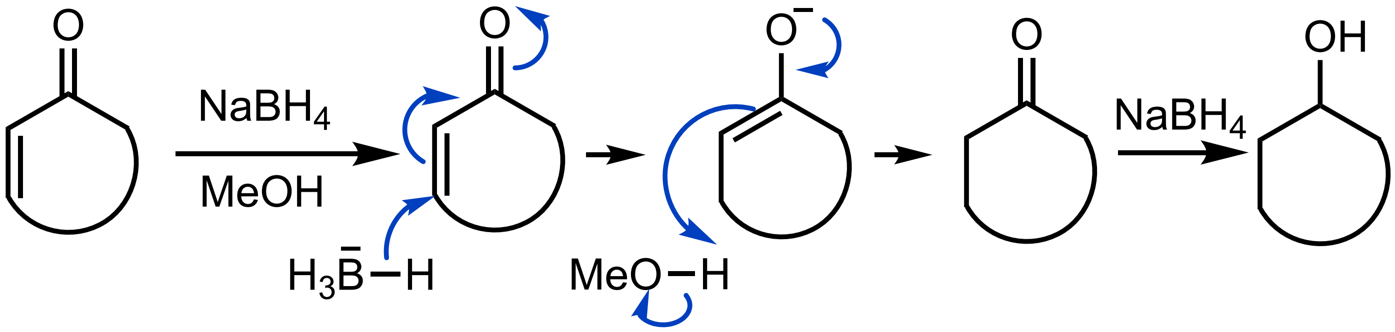
Q1. 反応**a**では、化合物**2**と**-H**と**-OH**が*cis*配置をもつ**2**の立体異性体が、
>98:2の選択性で生成した。このジアステレオ選択性を説明せよ


OH
O
H
N
Cbz
CO$_2$Me
b. Bz$_2$O, Et$_3$N
c. Luche reduction
OBz
HO
H
N
Cbz
CO$_2$Et

2

3

Competitive 1,2-reduction without Ce(III)

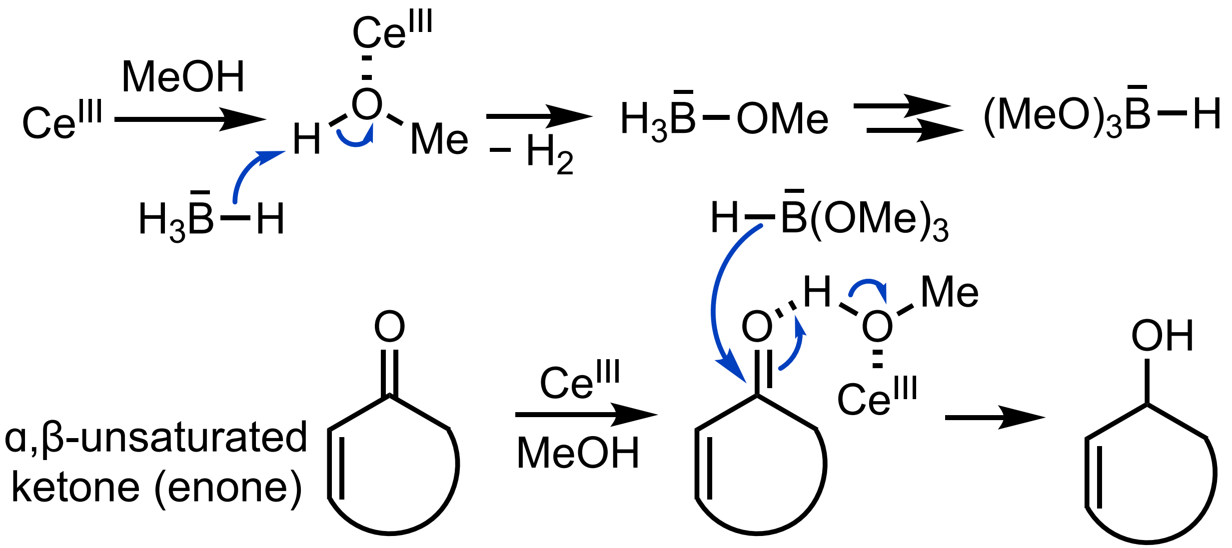


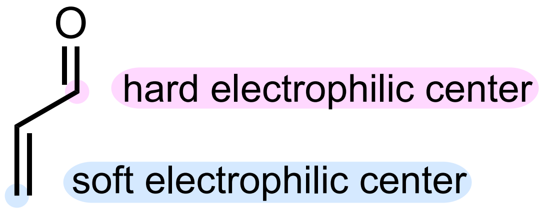
Luche reduction

for 1,2-reduction of enones

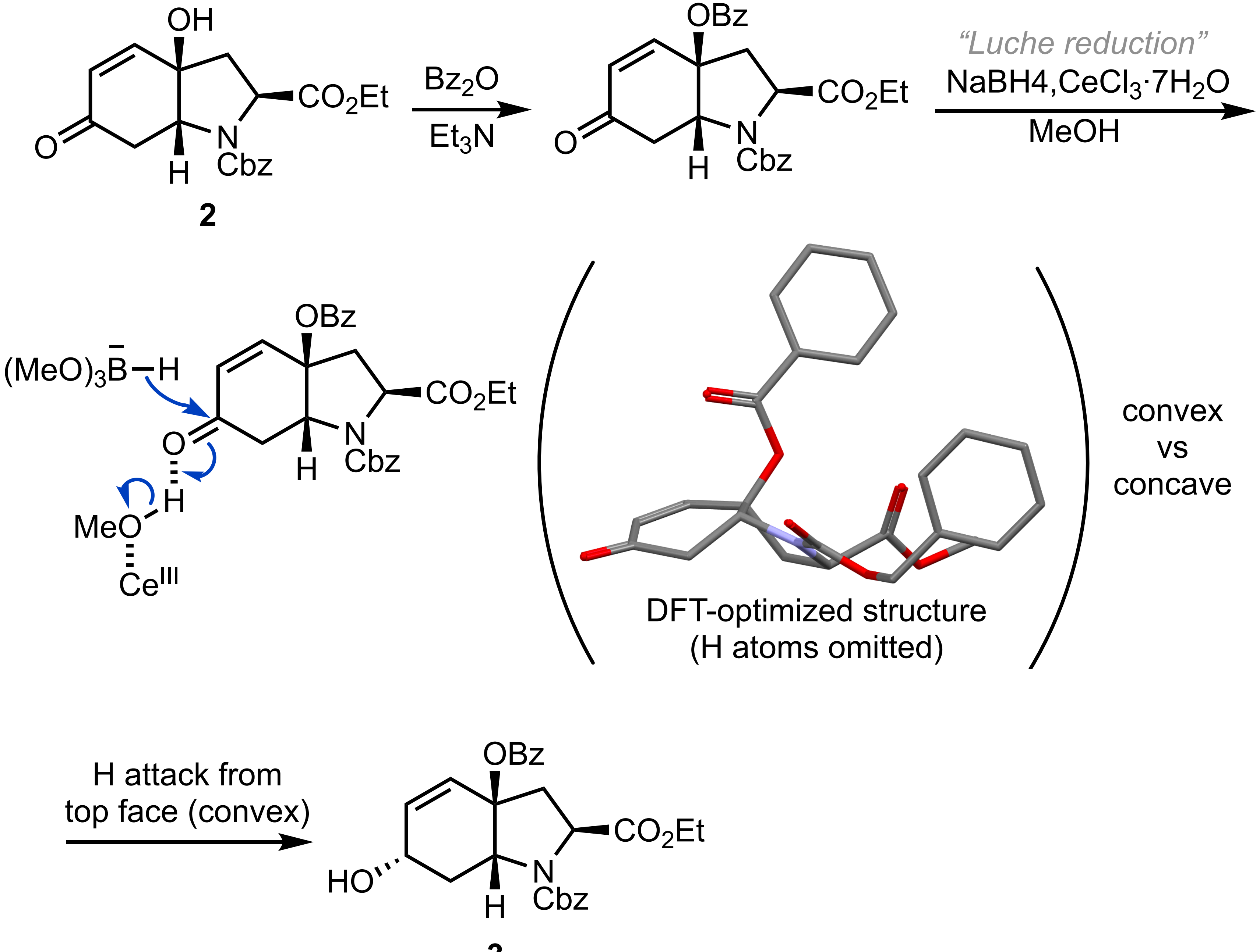
hardness

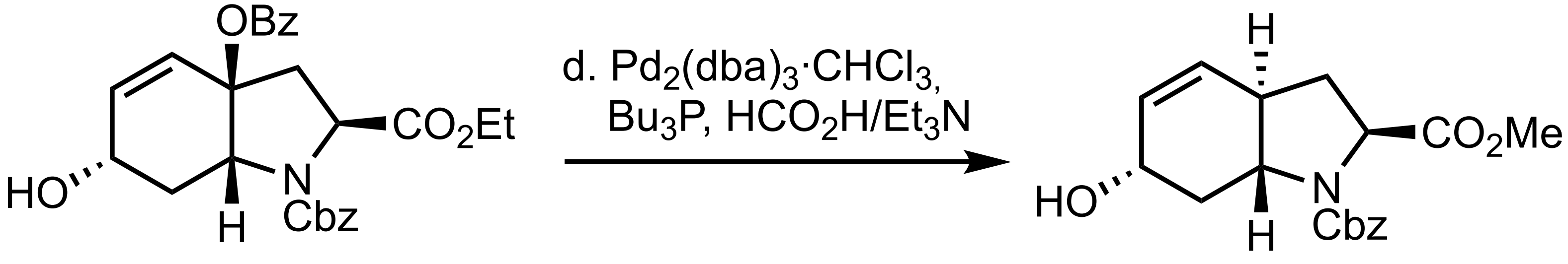
$BH(OMe)_3^- > BH_4^-$





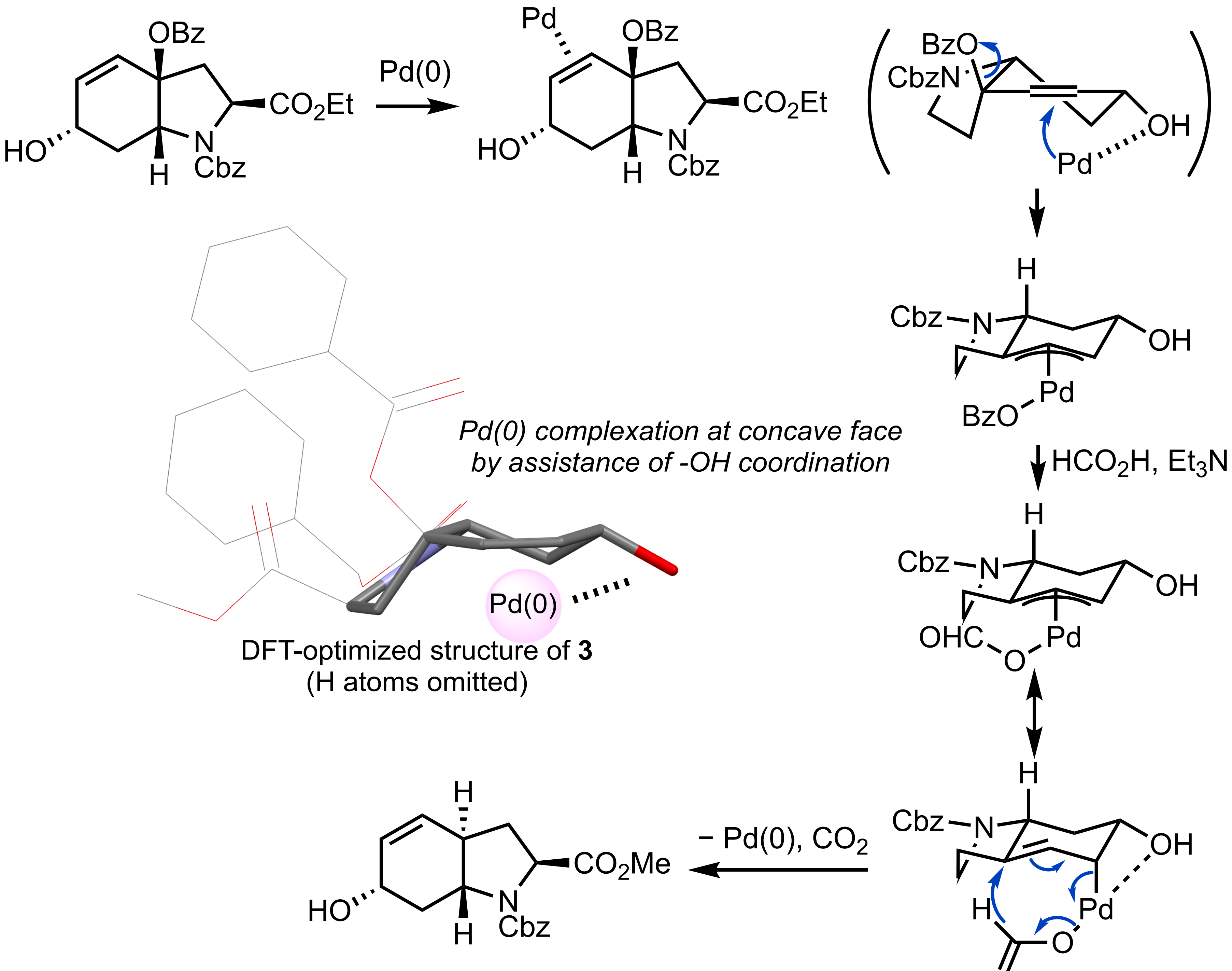
J.-L. Luche *et al. J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.


OH
CO$_2$Et
N
Cbz
H
O
2
Bz$_2$O
Et$_3$N
OBz
"Luche reduction"
NaBH4,CeCl$_3$·7H$_2$O
MeOH
(MeO)$_3\bar{B}$–H
O
H
MeO
Ce^{III}
DFT-optimized structure
(H atoms omitted)
convex
vs
concave
H attack from
top face (convex)
HO
3


OBz
CO_2Et
HO
H
N
Cbz
d. $Pd_2(dba)_3\cdot CHCl_3$,
Bu_3P, HCO_2H/Et_3N
H
CO_2Me
HO
H
N
Cbz

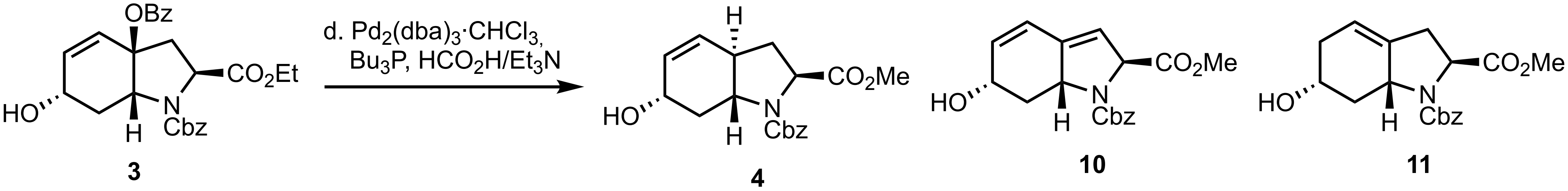
3

4



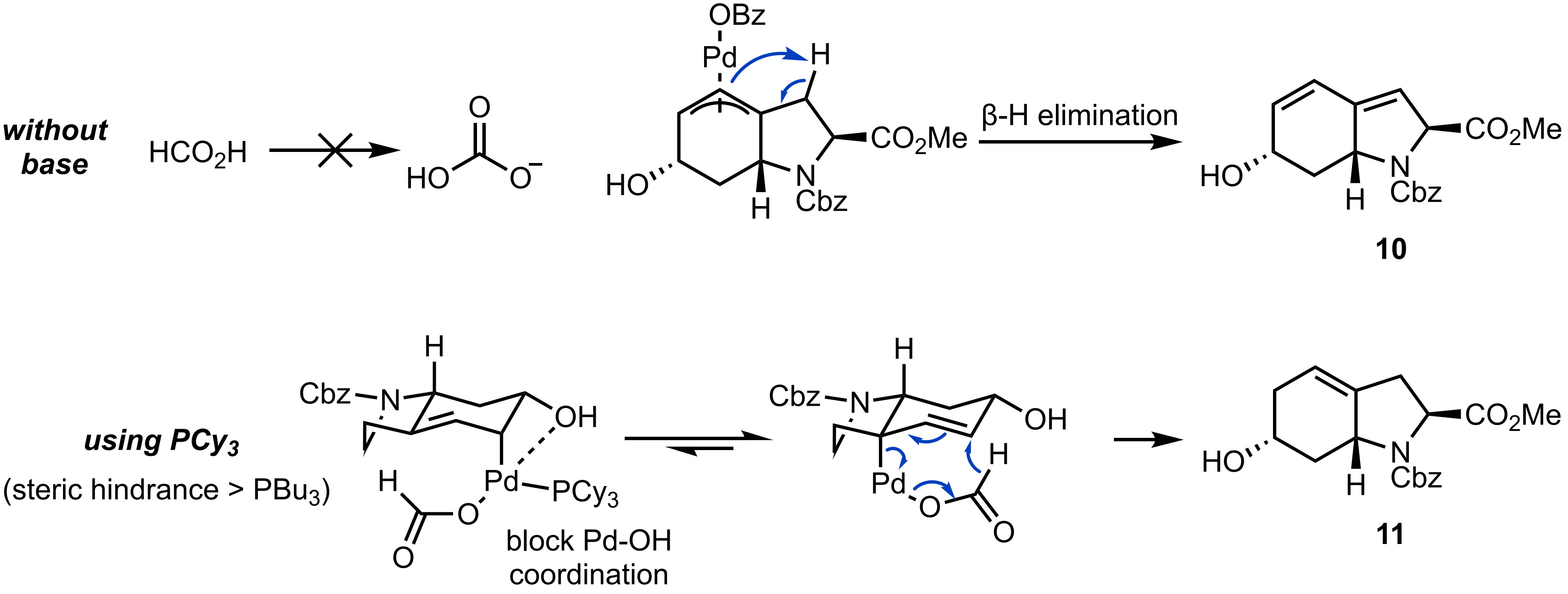
DFT-optimized structure of **3**
(H atoms omitted)

4



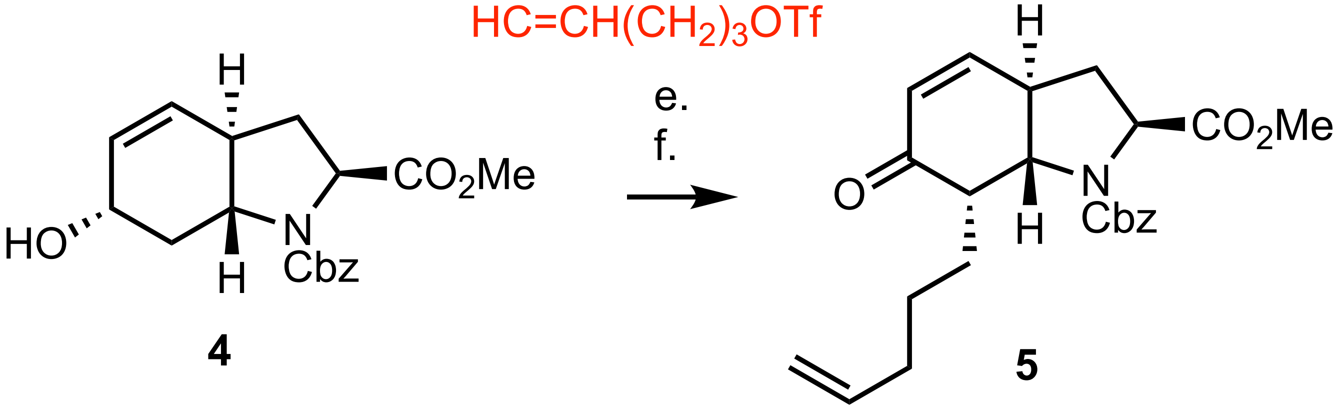
entry	conditions (solvt. = THF)	isolated yields (%)		
		4	**10**	**11**
1	$Pd_2(dba)_3 \cdot CHCl_3$, Bu_3P, HCO_2H/Et_3N, 60 ºC	68	6	11
2	$Pd_2(dba)_3 \cdot CHCl_3$, Bu_3P, HCO_2NH_4, 60 ºC	69	11	12
3	$Pd_2(dba)_3 \cdot CHCl_3$, Cy_3P, HCO_2NH_4, 60 ºC	7	6	65
4	$Pd_2(dba)_3 \cdot CHCl_3$, Bu_3P, HCO_2H, 60 ºC	/	82	/
5	$Pd_2(dba)_3 \cdot CHCl_3$, Bu_3P, $NaBH_4$, 22 ºC	7	/	65
6	$Pd(Ph_3P)_4$, Ph_3P, $NaBH_4$, 22 ºC	37	/	52

Q2. **d**において塩基を用いないと10が単一の生成物として得られ、Bu_3Pの代わりにCy_3Pを用いると**11**が主生成物となる。これらの生成機構及び**4**が立体選択的に生成する理由を説明せよ



without base
HCO$_2$H
HO
O
O$^-$
OBz
Pd
H
HO
H
N
Cbz
CO$_2$Me
β-H elimination
10
using PCy$_3$
(steric hindrance > PBu$_3$)
Cbz
N
OH
Pd
PCy$_3$
block Pd-OH coordination
11

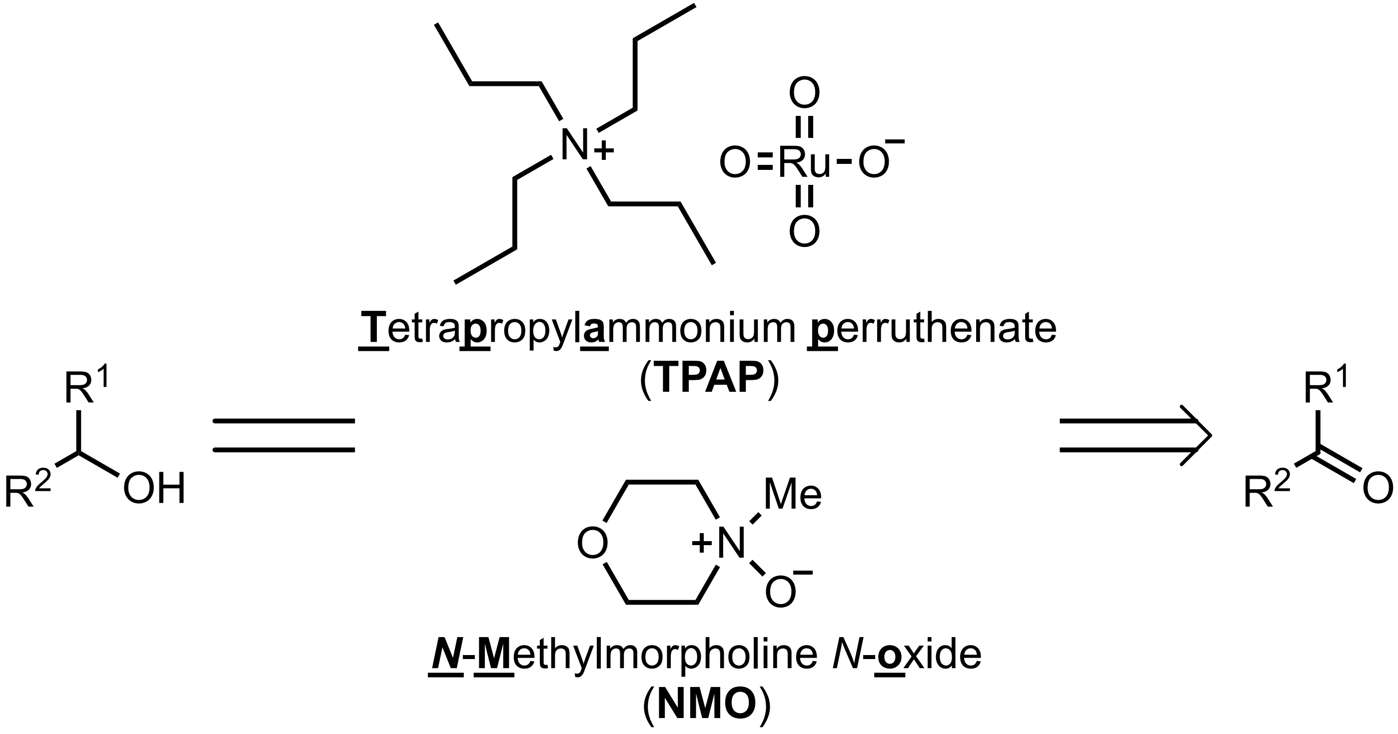
e. TPAP, NMO
f. KHMDSA, -80 ºC
$HC{=}CH(CH_2)_3OTf$



4

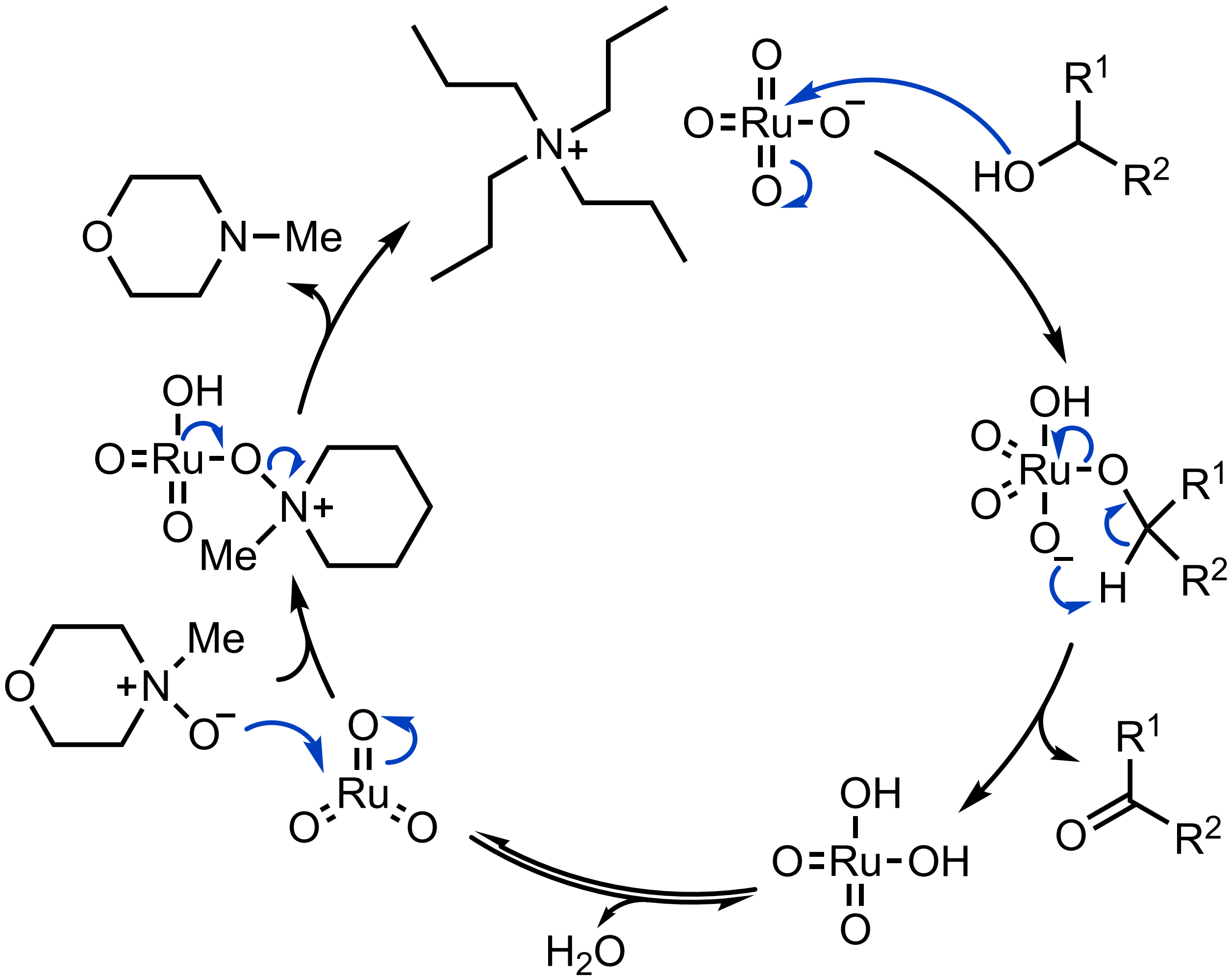
5

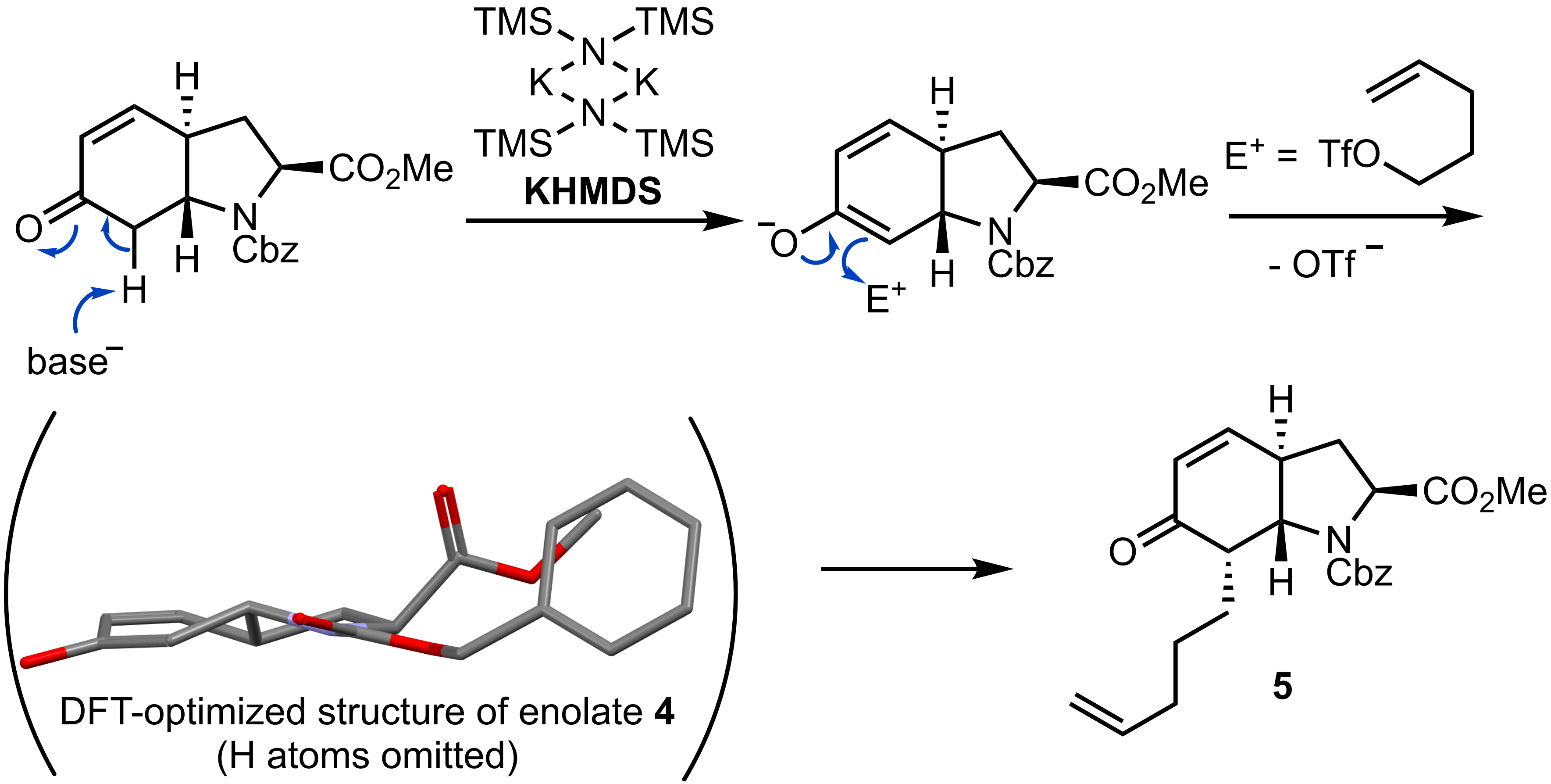
Ley-Griffth Oxidation



Tetra**p**ropyl**a**mmonium **p**erruthenate
(**TPAP**)

N-**M**ethylmorpholine *N*-**o**xide
(**NMO**)

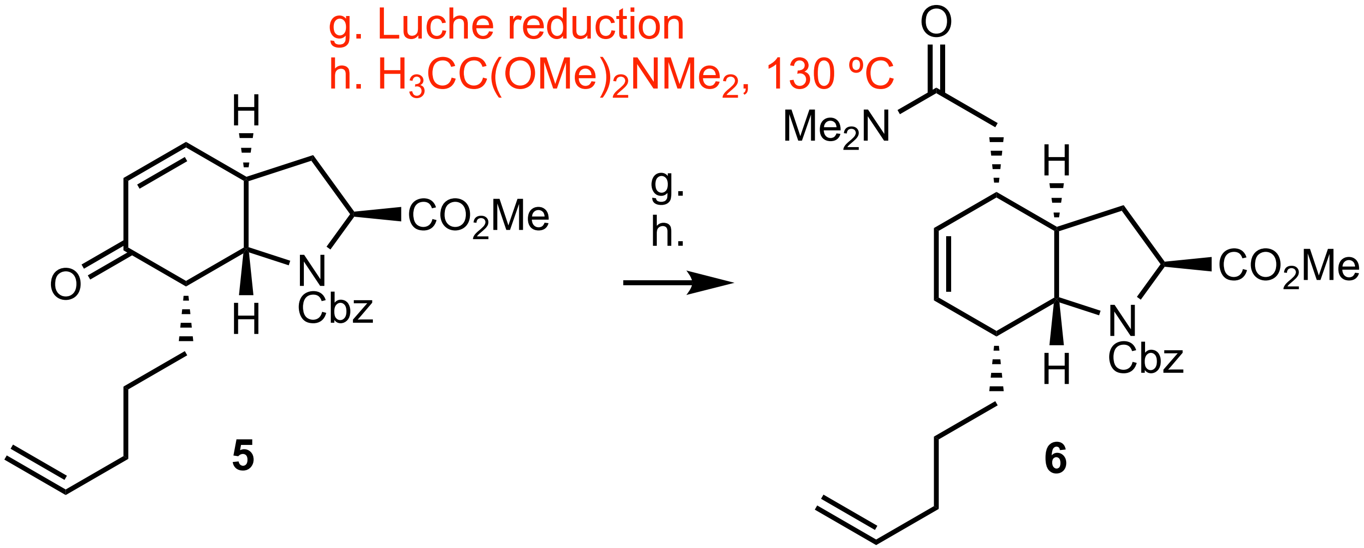

N+
O=Ru-O−
O
O
R1
R2
HO
OH
O
O
Ru
O
R1
R2
O−
H
R1
O
R2
OH
O=Ru-OH
O
H2O
O
Ru
O
O
O
+N
Me
O−
OH
O=Ru-O
O
N+
Me
O
N-Me

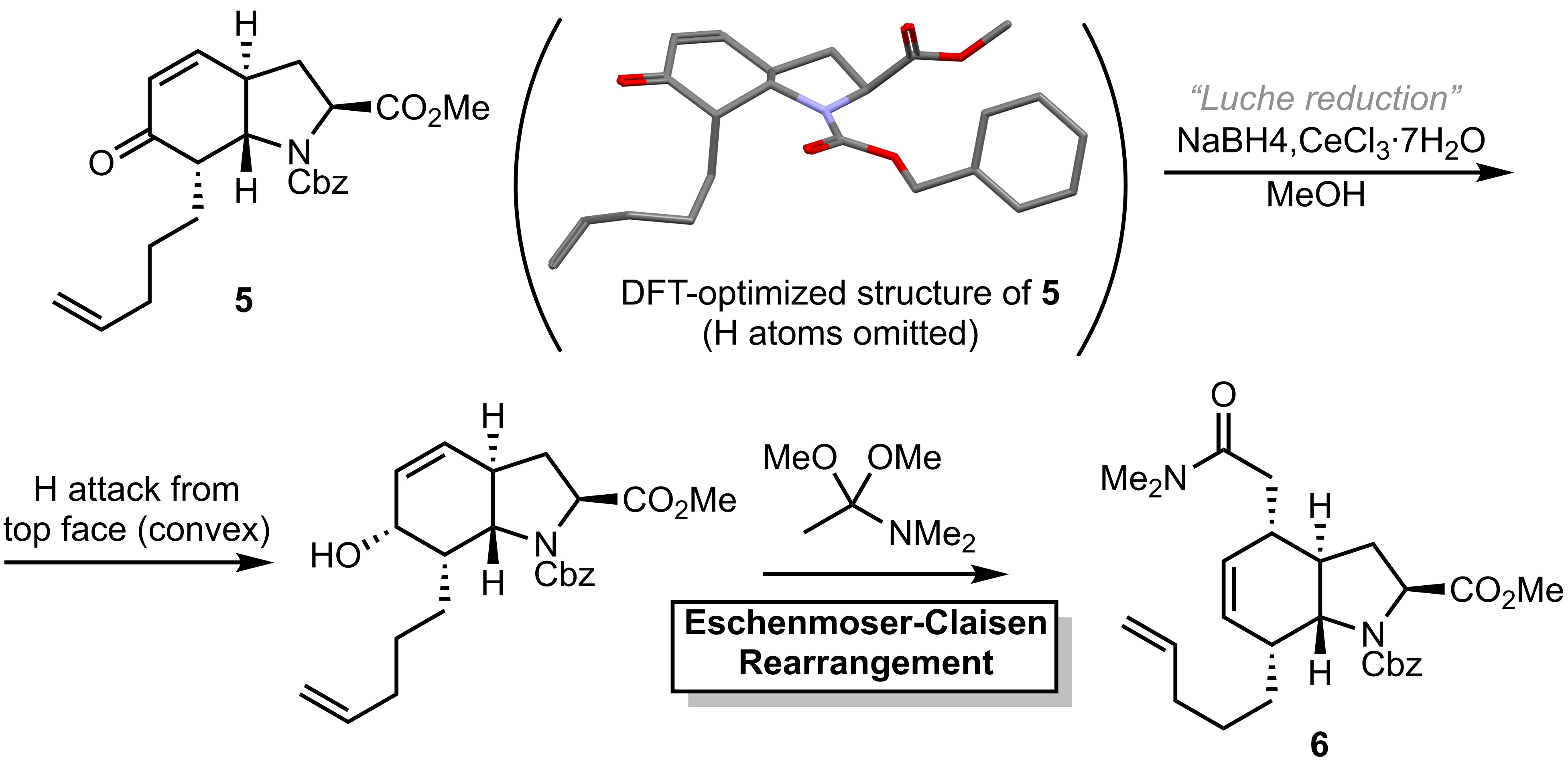


DFT-optimized structure of enolate **4**
(H atoms omitted)

g. Luche reduction

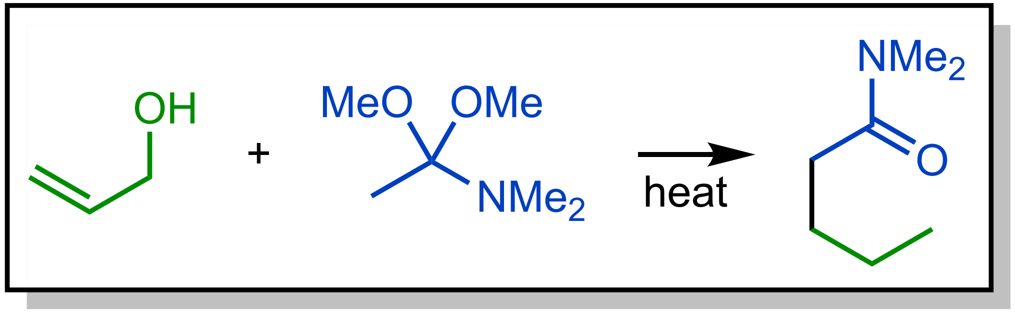
h. $H_3CC(OMe)_2NMe_2$, 130 ºC

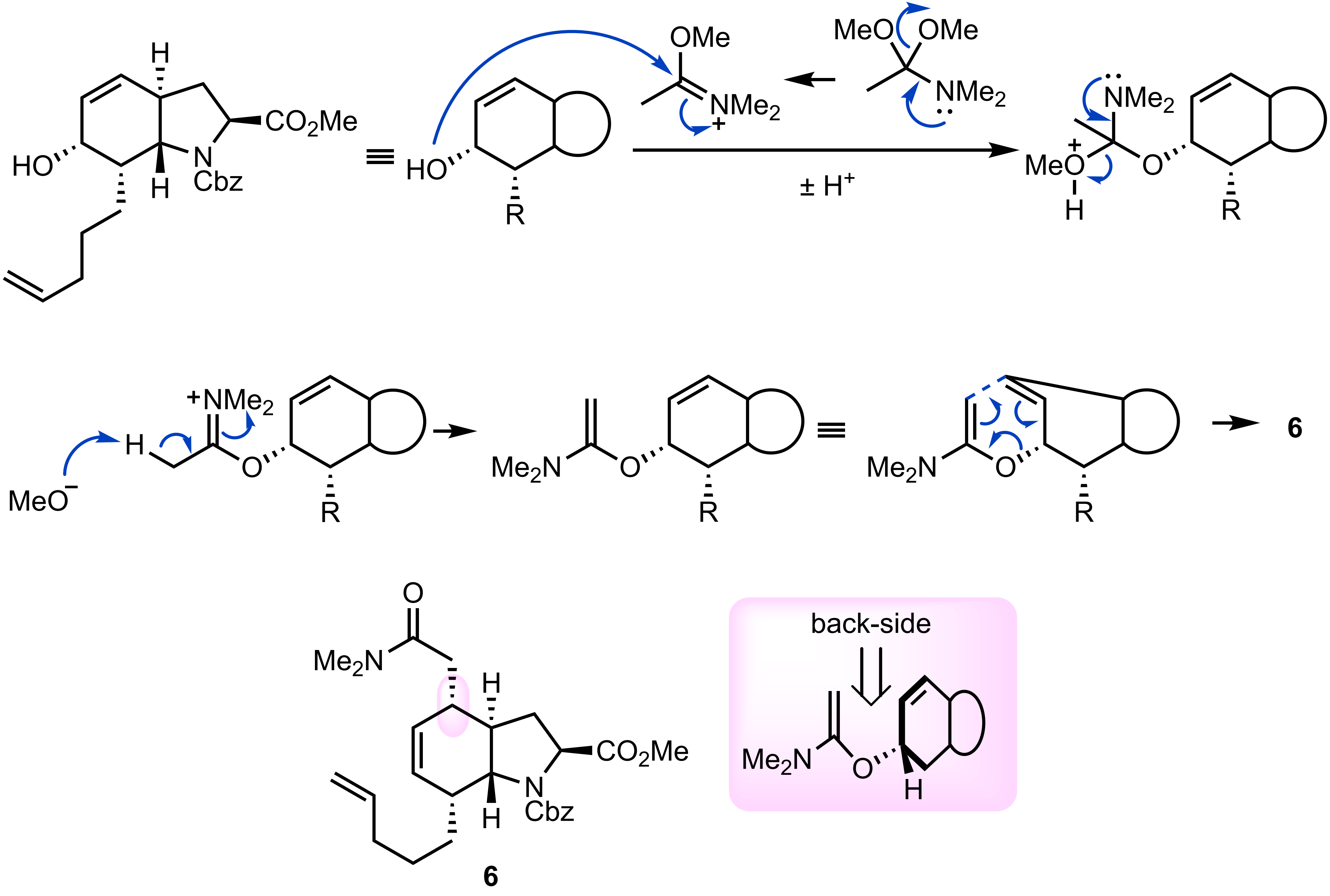


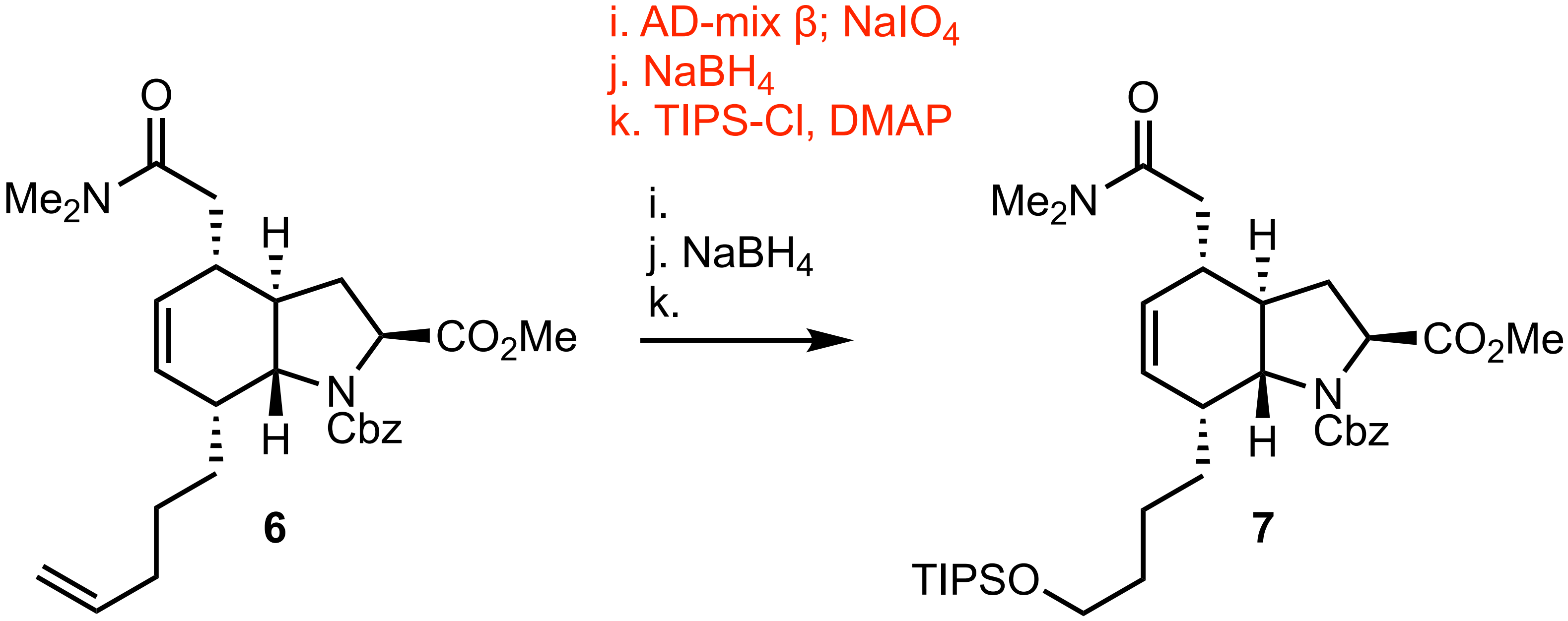

H
CO2Me
O
N
Cbz
H
DFT-optimized structure of 5
(H atoms omitted)
"Luche reduction"
NaBH4,CeCl3·7H2O
MeOH
H attack from
top face (convex)
HO
MeO OMe
NMe2
Eschenmoser-Claisen
Rearrangement
Me2N
O

5

6


OH
+
MeO OMe
NMe2
heat
NMe2
O

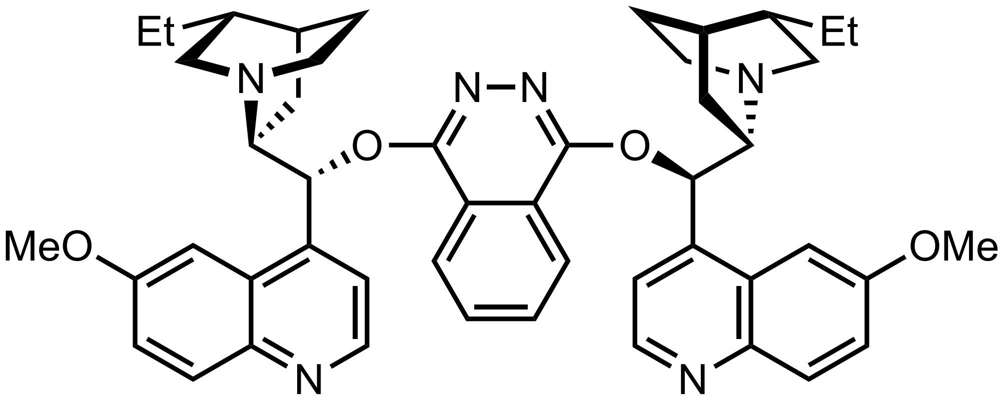

H
HO
H
N
Cbz
CO_2Me
≡
HO
R
OMe
NMe_2
+
MeO
OMe
NMe_2
± H+
NMe_2
MeO
+
H
O
R
MeO−
H
$^+NMe_2$
O
R
Me_2N
O
R
≡
Me_2N
O
R
6
O
Me_2N
H
CO_2Me
N
Cbz
H
6
back-side
Me_2N
O
H



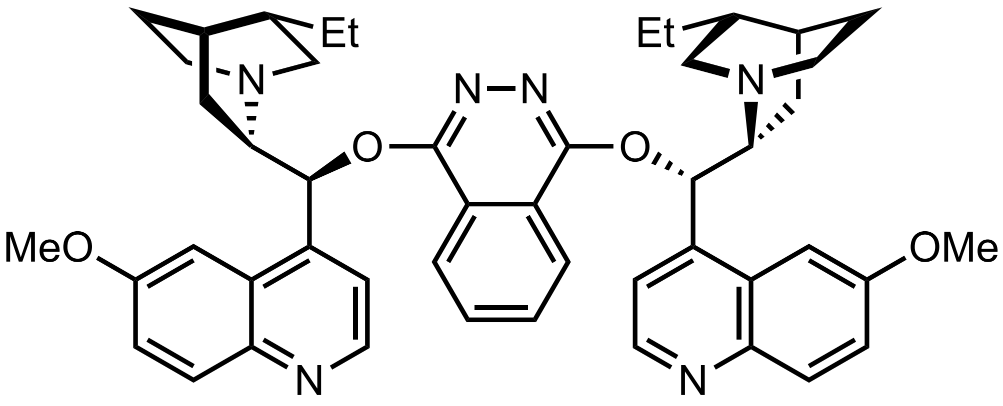
i. AD-mix β; NaIO$_4$
j. NaBH$_4$
k. TIPS-Cl, DMAP

AD-mix

AD: abbreviation of **a**symmetric **d**ihydroxylation
mixture contains: $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, and a chiral ligand

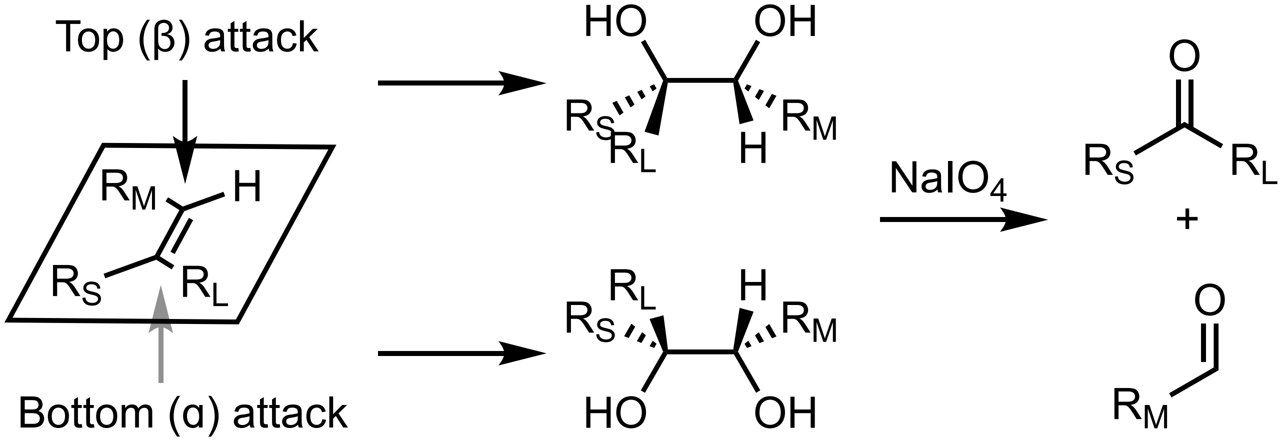


AD-mix α



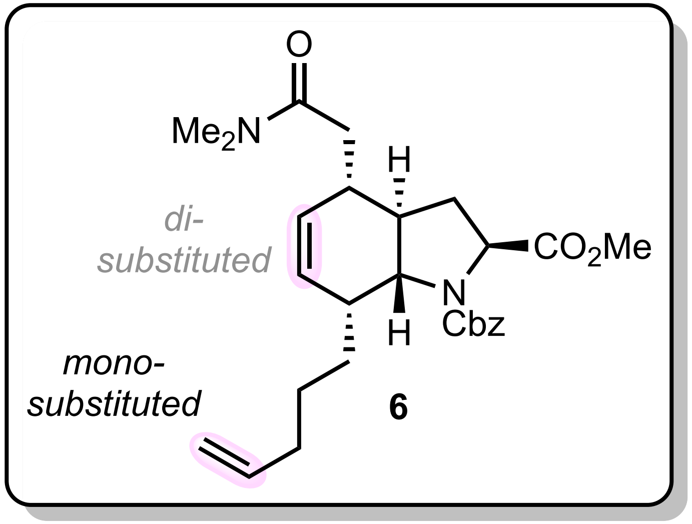
AD-mix β

Offen used in Sharpless dihydroxylation
for enantioselective perparation of 1,2-diols

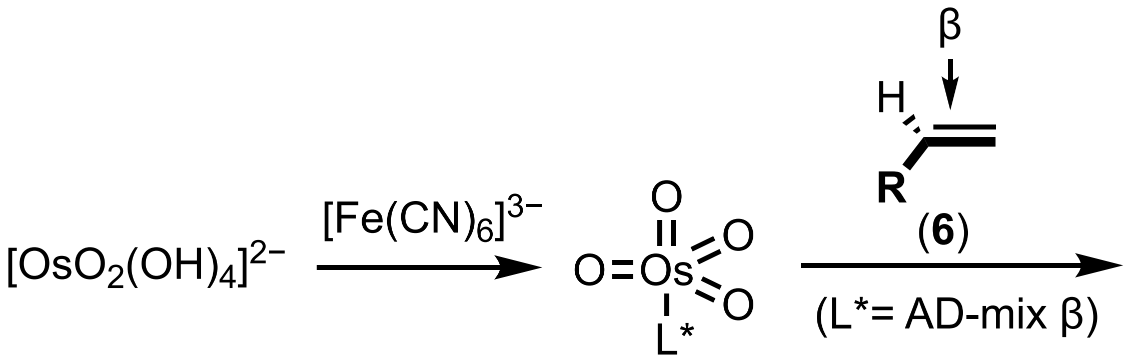


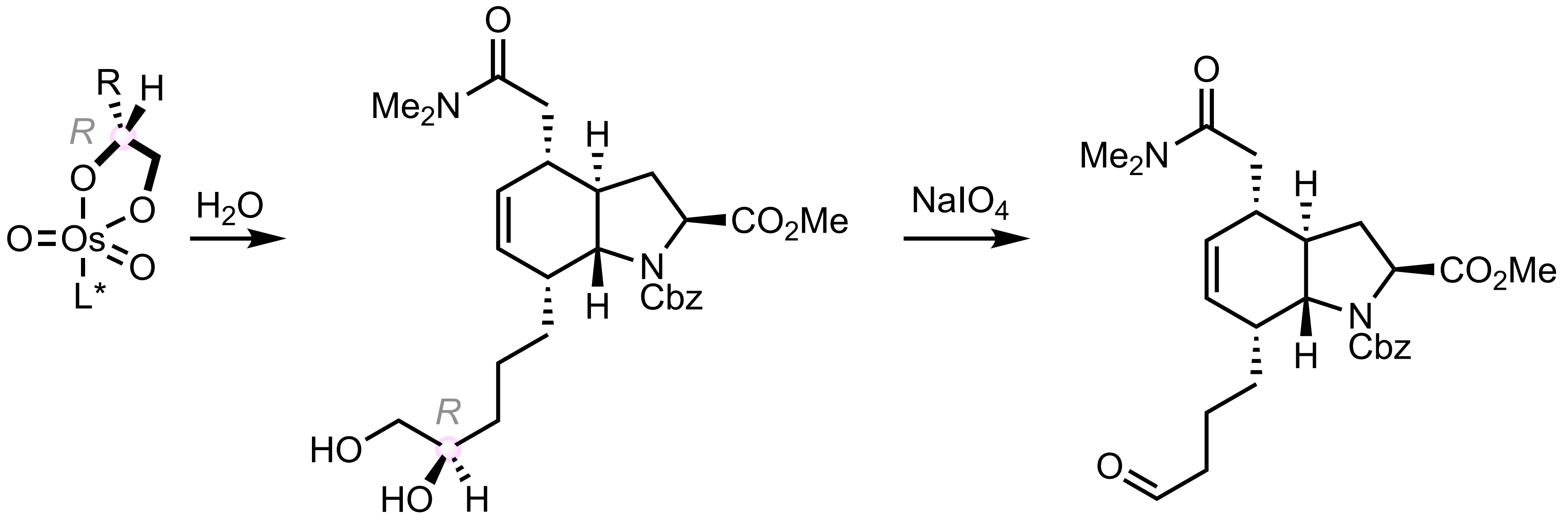
The reason of using AD-mix

Superior regioselectivity (cyclohexene vs **terminal alkene**) comparing with Johnson-Lemieux conditions (OsO_4/$NaIO_4$)

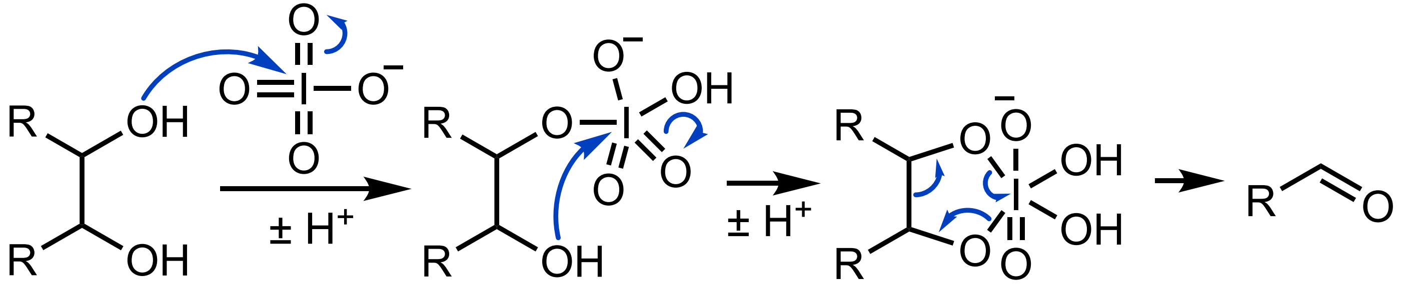


6

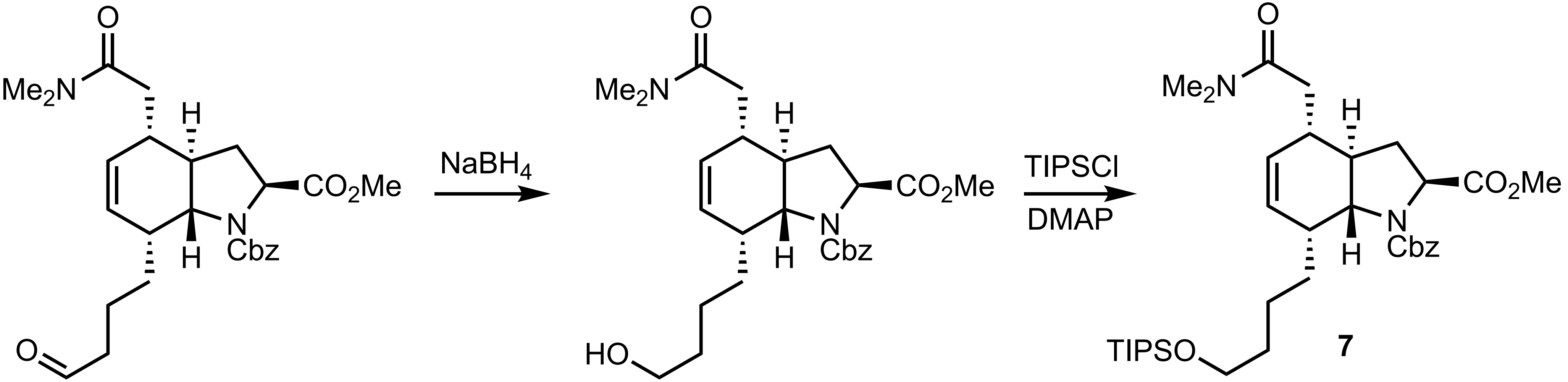




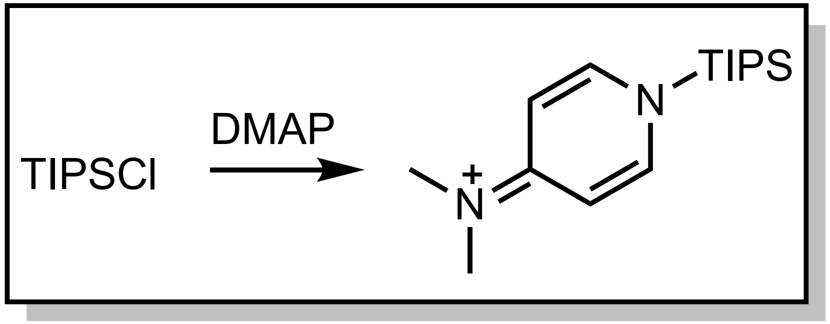
Oxidative cleavage of 1,2-diol by $NaIO_4$

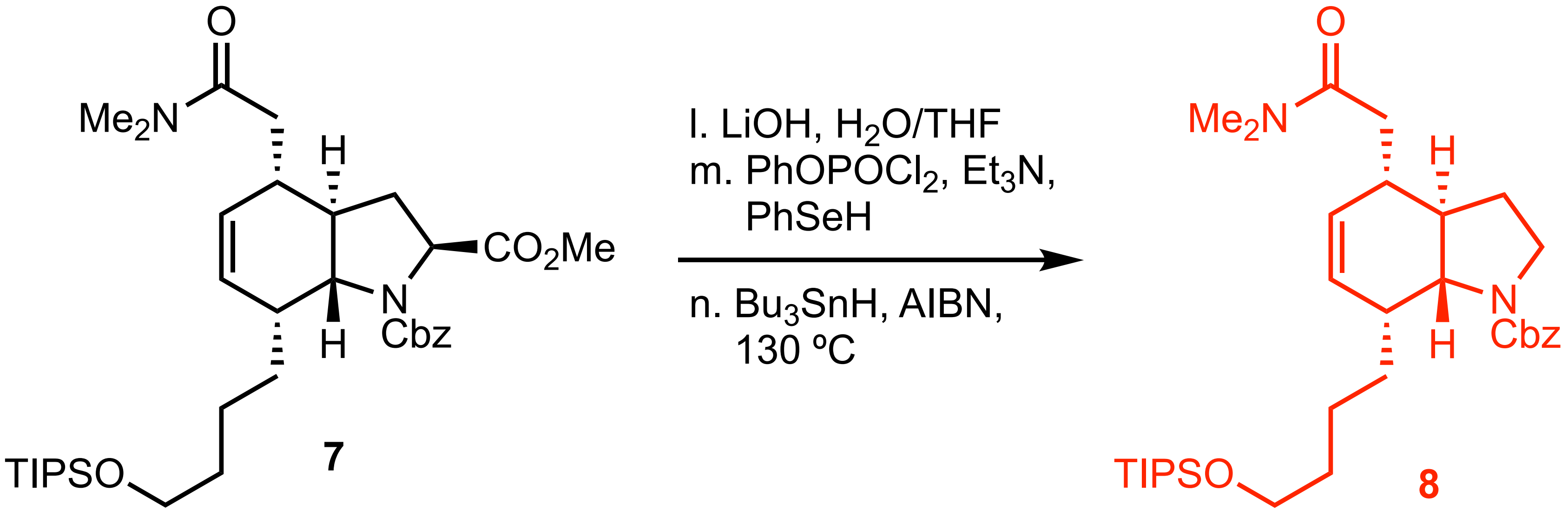


Reduction followed by TIPS protection



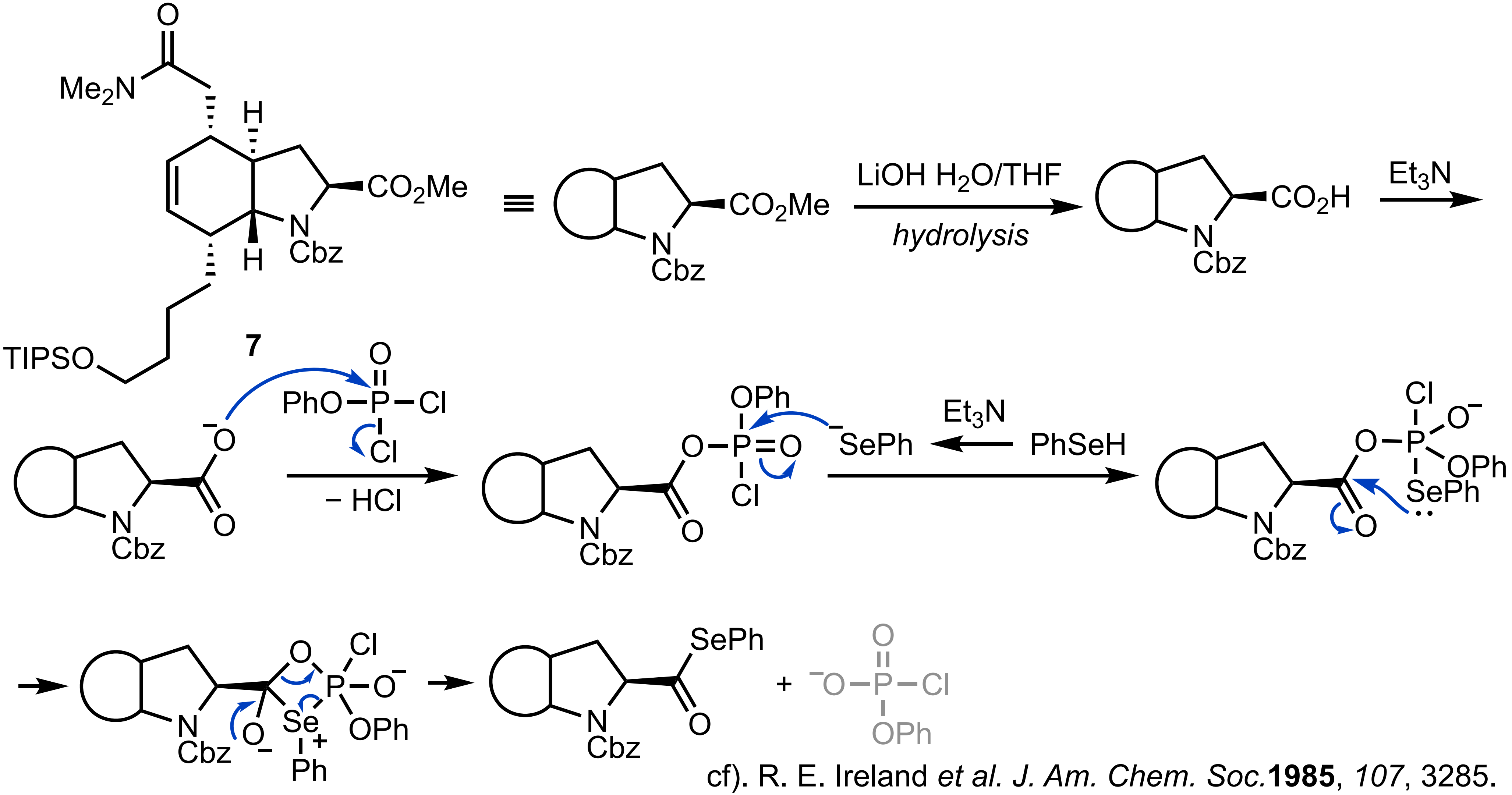
7




O
Me2N
H
CO2Me
N
Cbz
H
TIPSO
l. LiOH, H2O/THF
m. PhOPOCl2, Et3N,
PhSeH
n. Bu3SnH, AIBN,
130 ºC
O
Me2N
H
N
Cbz
H
TIPSO

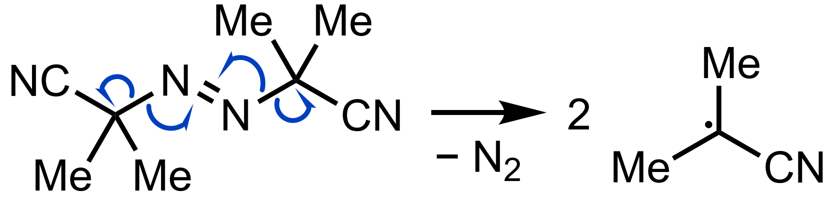
7

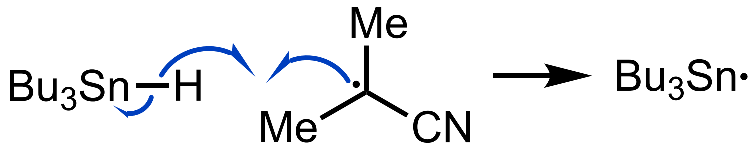
8

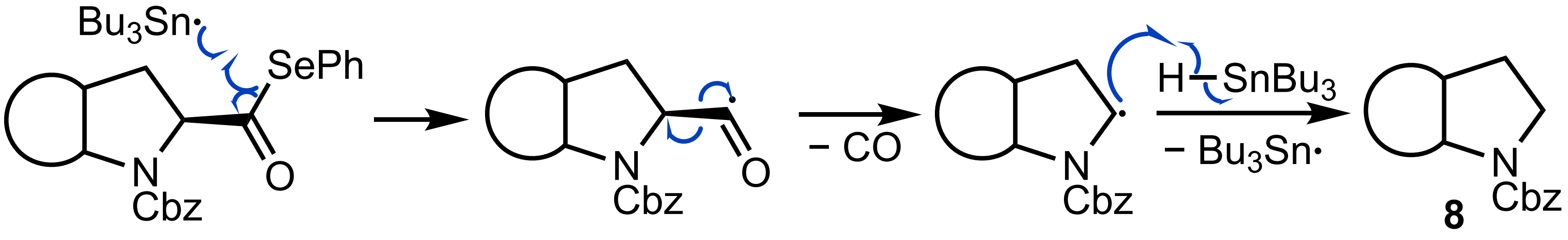


cf). R. E. Ireland *et al. J. Am. Chem. Soc.* **1985**, *107*, 3285.

AIBN: radical initiator

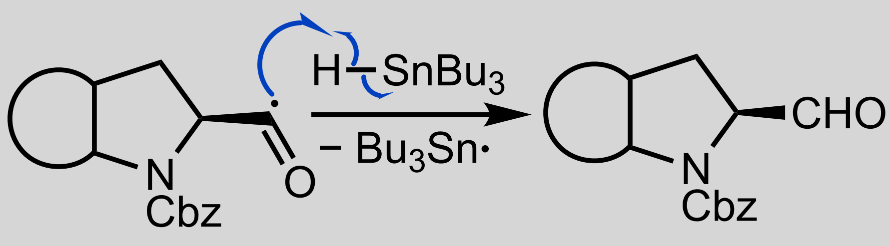






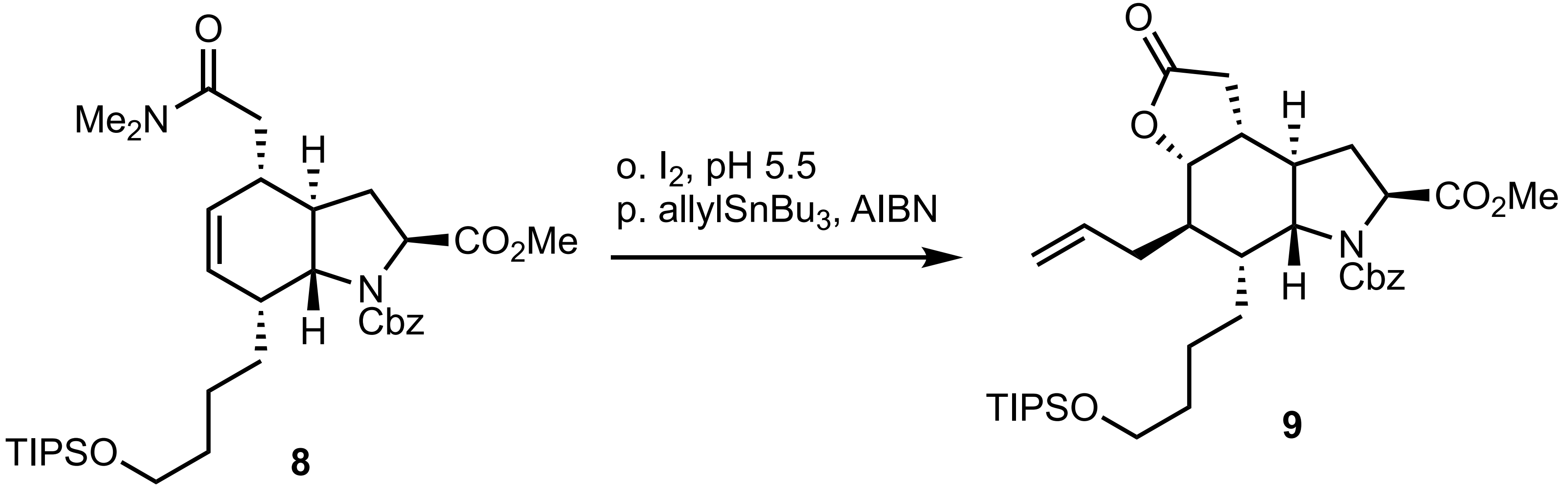
8

aldehyde formation



easily occurs at low temperature

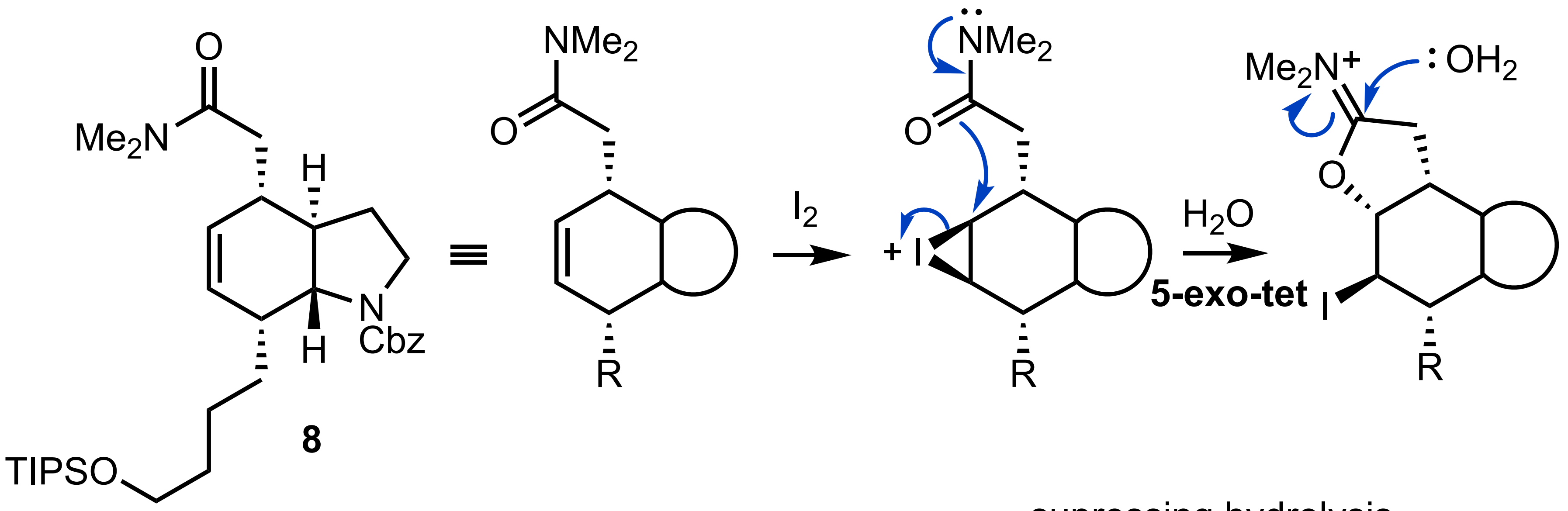
cf). W. Graf *et al. Helv. Chim. Acta* **1980**, *63*, 2328.

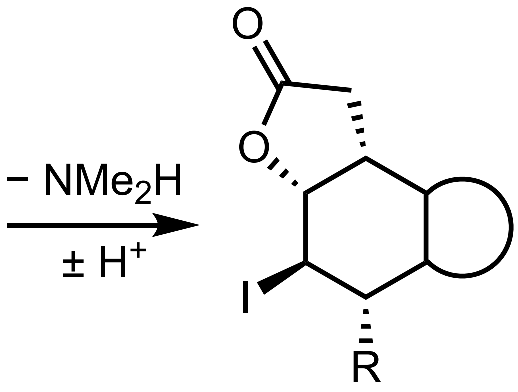

Me$_2$N
O
H
H
CO$_2$Me
N
Cbz
TIPSO
o. I$_2$, pH 5.5
p. allylSnBu$_3$, AIBN
O
O
H
H
CO$_2$Me
N
Cbz
TIPSO

8

9

Iodolactonization

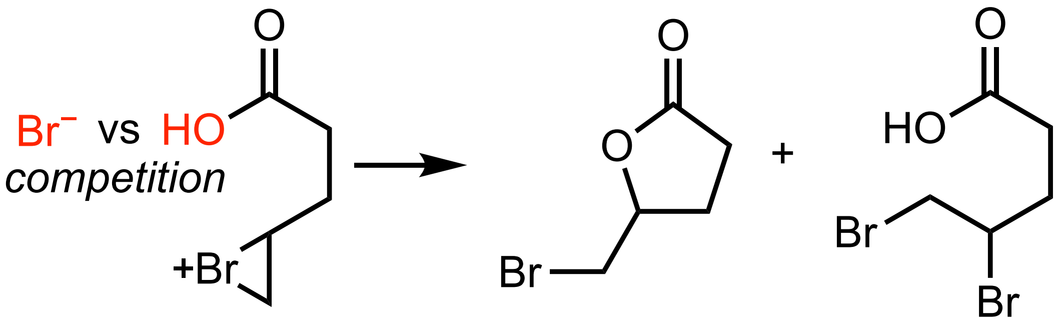




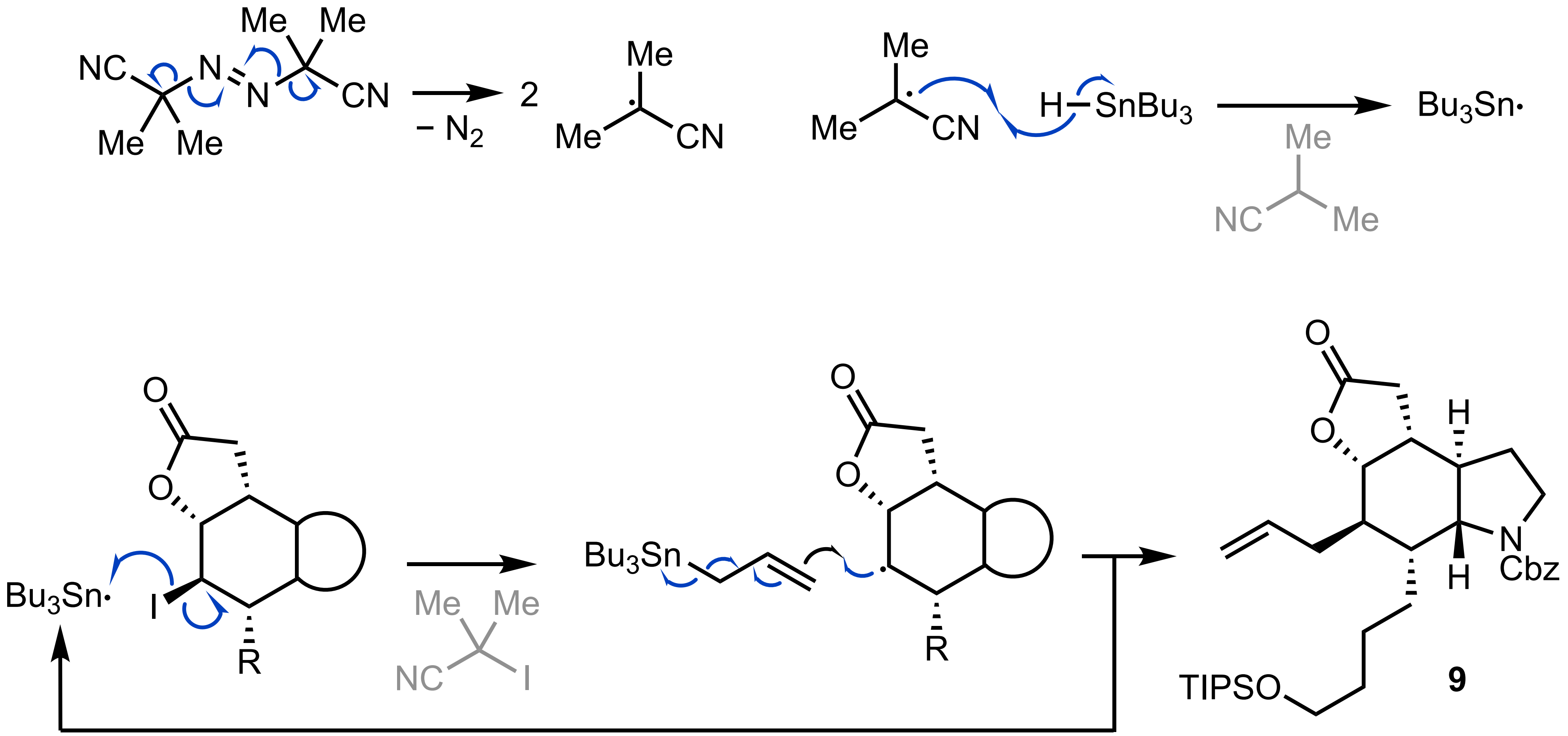
Why pH = 5.5 ?

supressing hydrolysis
of silyl-protective group

Bromolactonization (*not commonly used nowdays*)



AIBN: radical initiator



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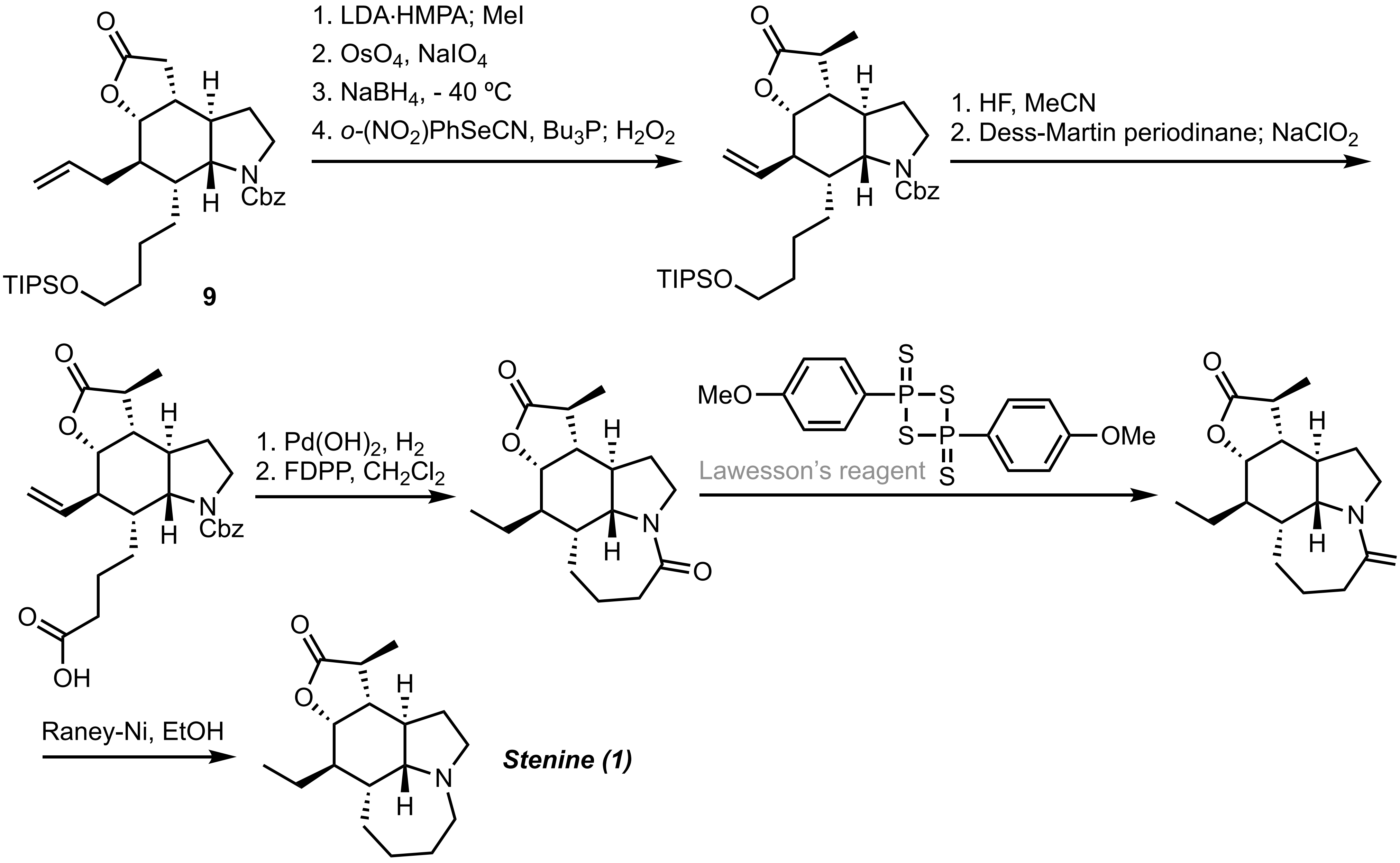
Accomplishment of synthesis



1. LDA·HMPA; MeI
2. OsO_4, $NaIO_4$
3. $NaBH_4$, - 40 ºC
4. *o*-$(NO_2)PhSeCN$, Bu_3P; H_2O_2

1. HF, MeCN
2. Dess-Martin periodinane; $NaClO_2$

1. $Pd(OH)_2$, H_2
2. FDPP, CH_2Cl_2

Lawesson's reagent

Raney-Ni, EtOH

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Stenine (1)