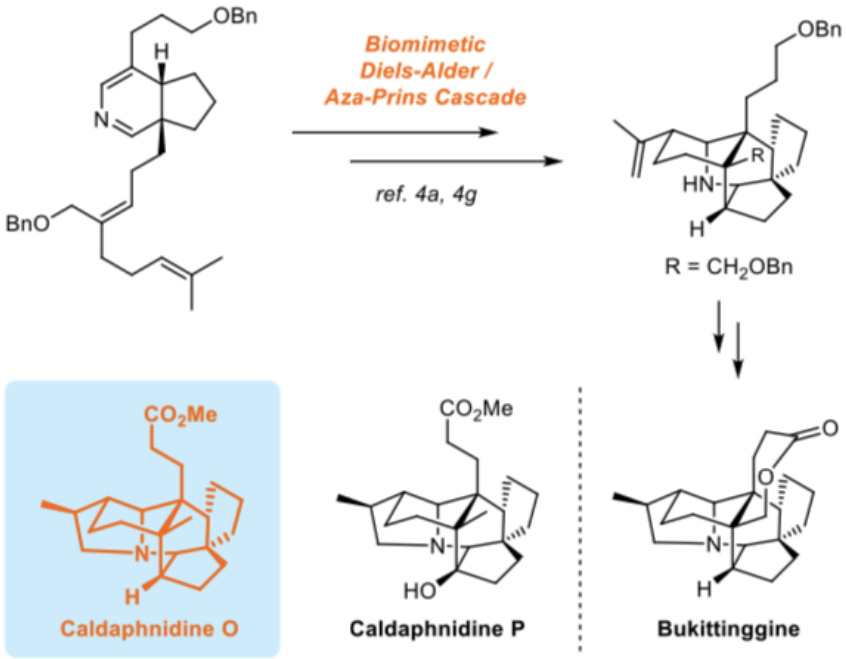
Total synthesis of (-)-Caldaphnidine O

Guo, J .; Hu, J.; Zhang, Y. "Enantioselective Total Synthesis (-)-Caldaphnidine O via a Radical Cyclization Cascade" *J. Am. Chem. Soc.* **2019,** *141,* 13043-13048.

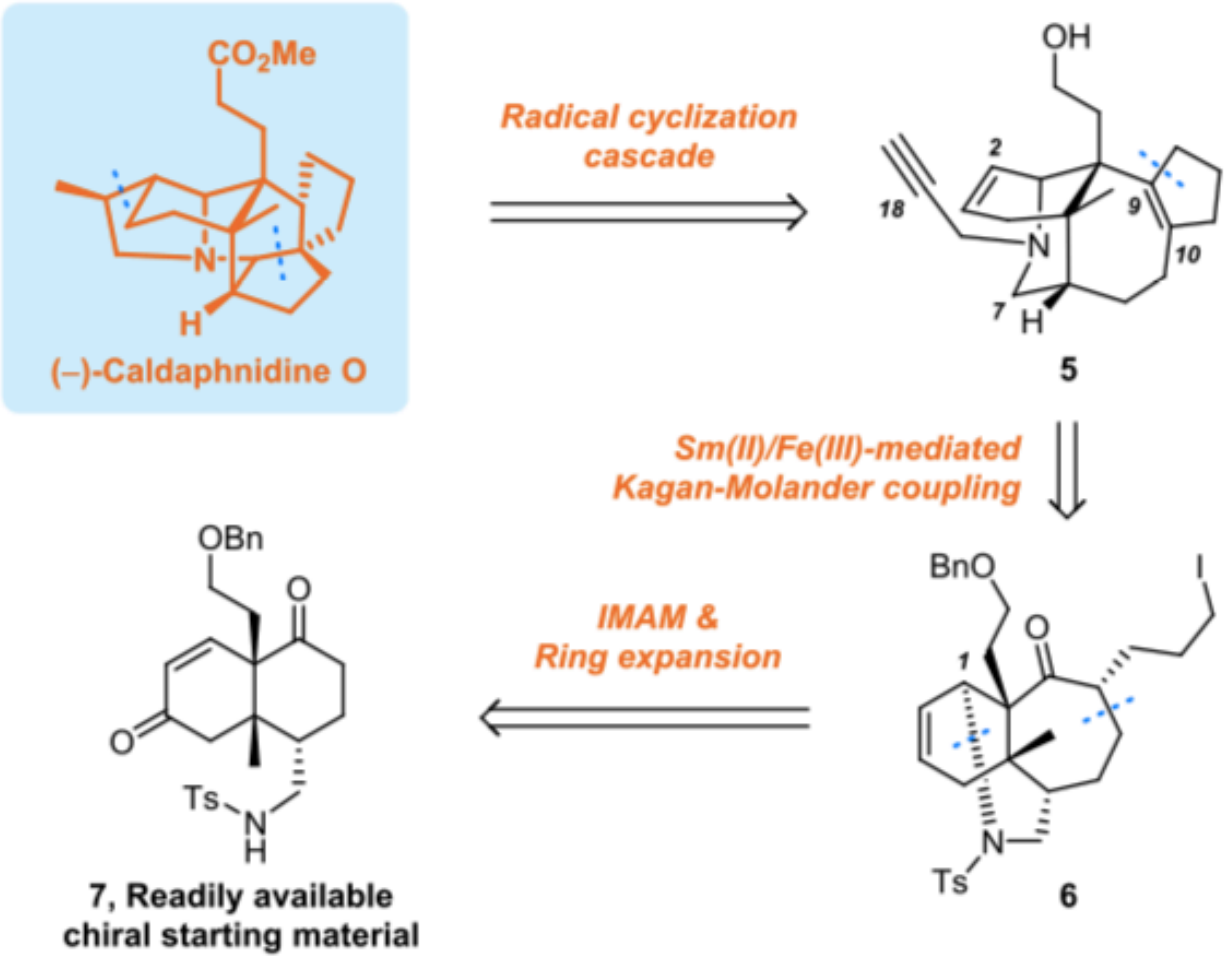
Scheme 1. Heathcock's Landmark Total Synthesis of (±)-Bukittinggine and the Chemical Structures of Representative Bukittinggine-Type Alkaloids

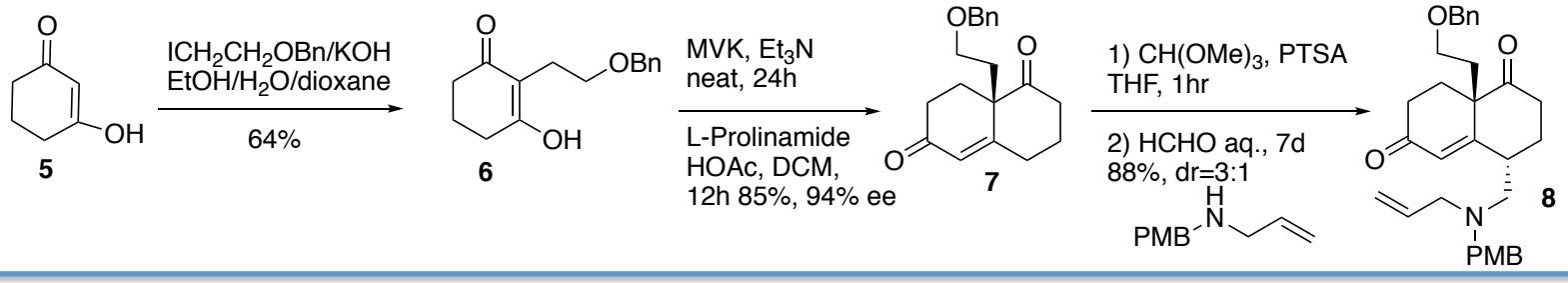


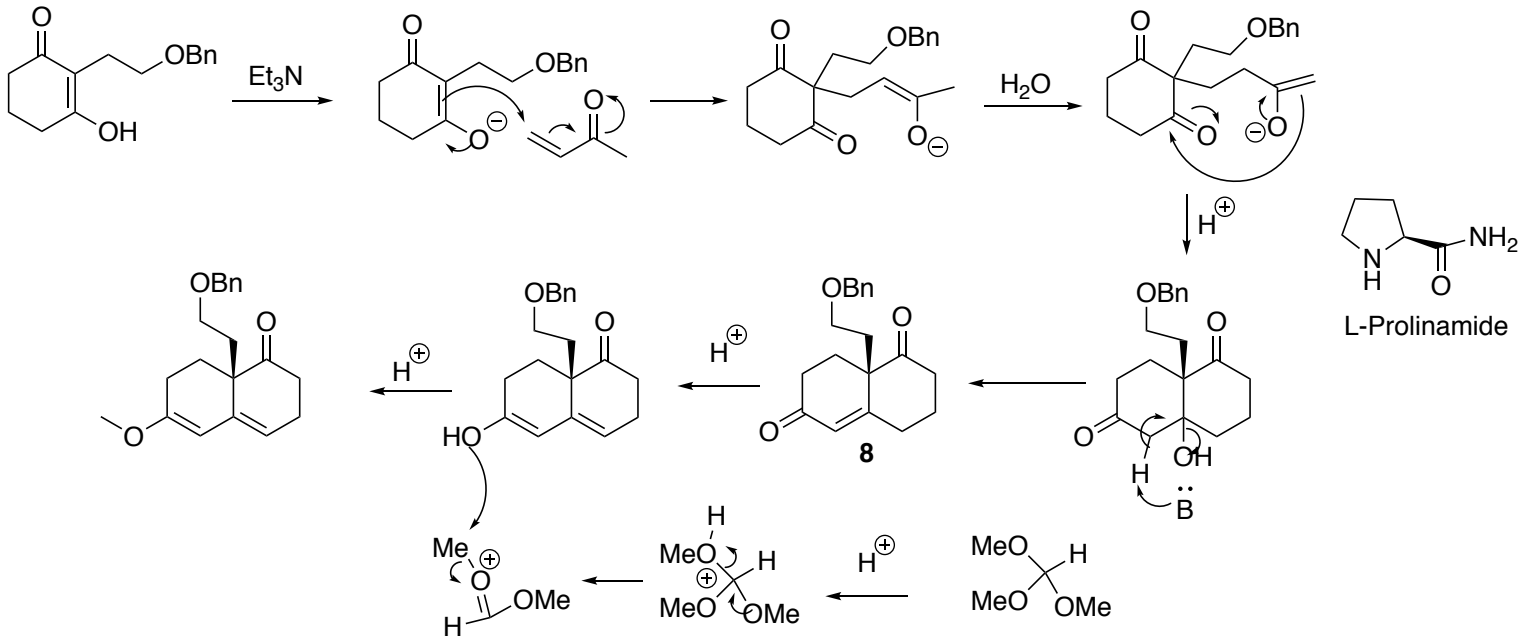
- Daphniphyllum alkaloids are a family of structure complicated natural products that have intriguing polycyclic ring system.
- These alkaloids exhibit promising bioactivities that range from cytotoxic and anticarcinogenic to anti-HIV acitivities.
- To date there is only one reported synthesis of a bukittinggine-type alkaloid, which featured a remarkable biomimetic Diels-Ader/aza-Prins reaction cascade.
- Herein, this is the first and enatioselective nonbiomimetic total synthesis of the bukittinggine-type alkaloid (-)-caldaphnidine O

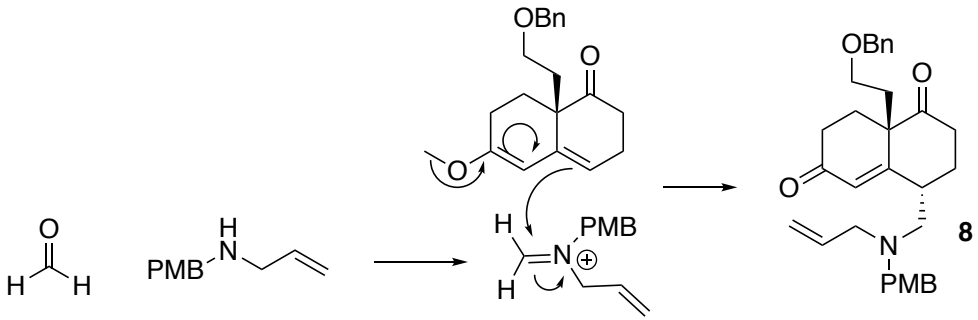
Retrosynthetic analysis

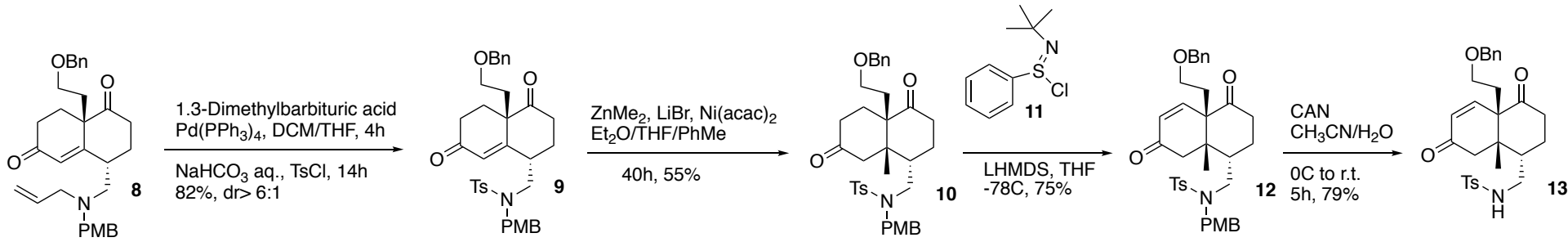
Retrosynthetic analysis of the bukittinggine-type alkaloid (–)-caldaphnidine O

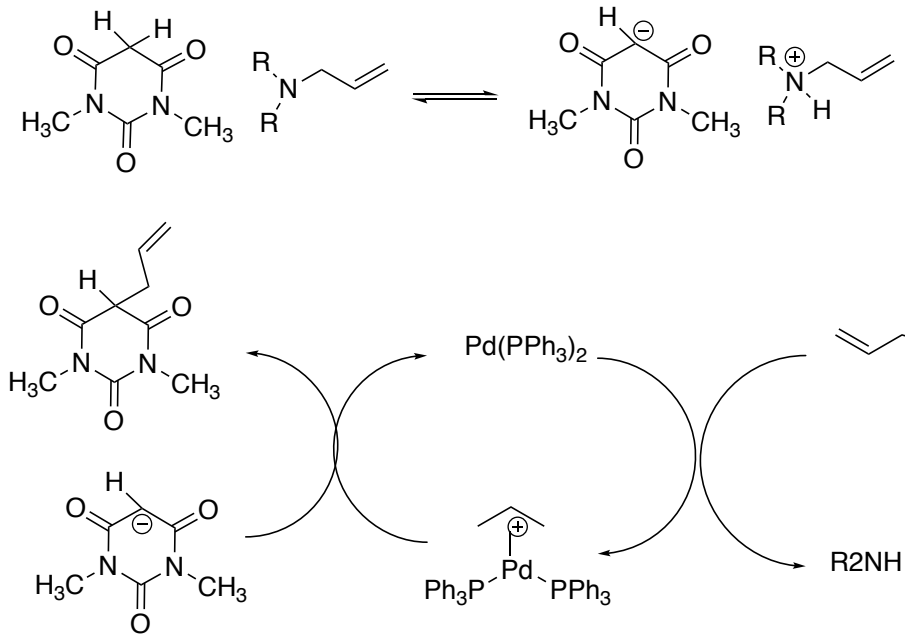


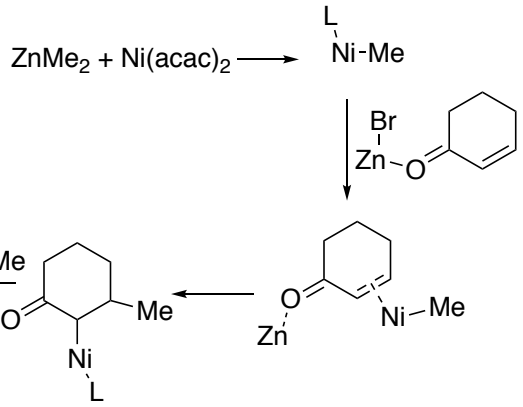

ICH2CH2OBn/KOH
EtOH/H2O/dioxane
64%
MVK, Et3N
neat, 24h
L-Prolinamide
HOAc, DCM,
12h 85%, 94% ee
1) CH(OMe)3, PTSA
THF, 1hr
2) HCHO aq., 7d
88%, dr=3:1
PMB
5
6
7
8

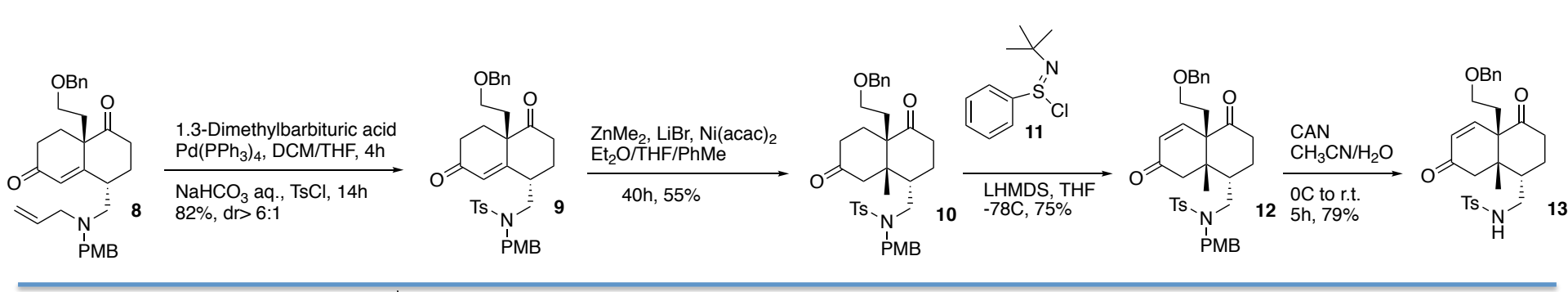

Et3N
H2O
L-Prolinamide
8

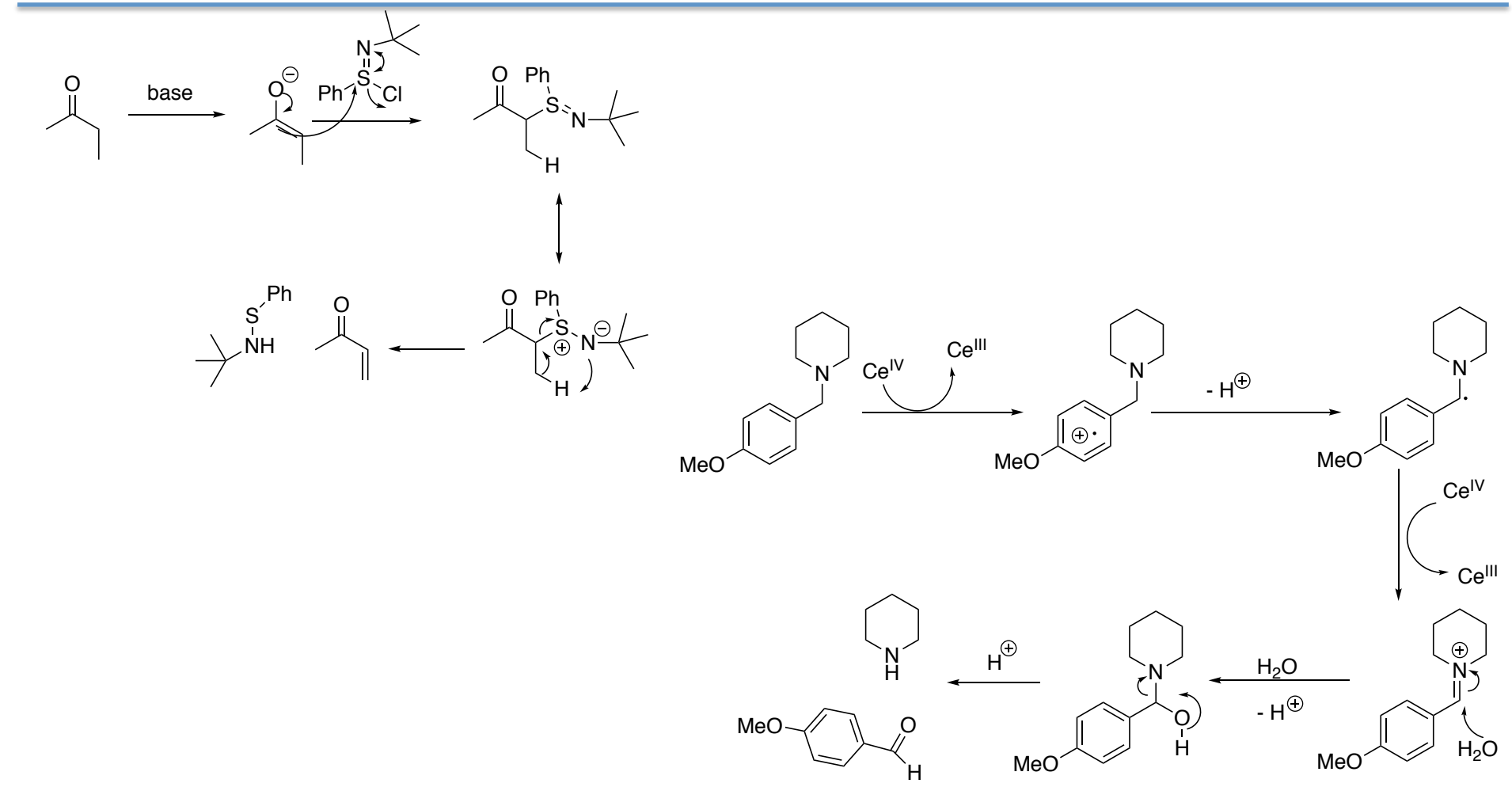

PMB
8

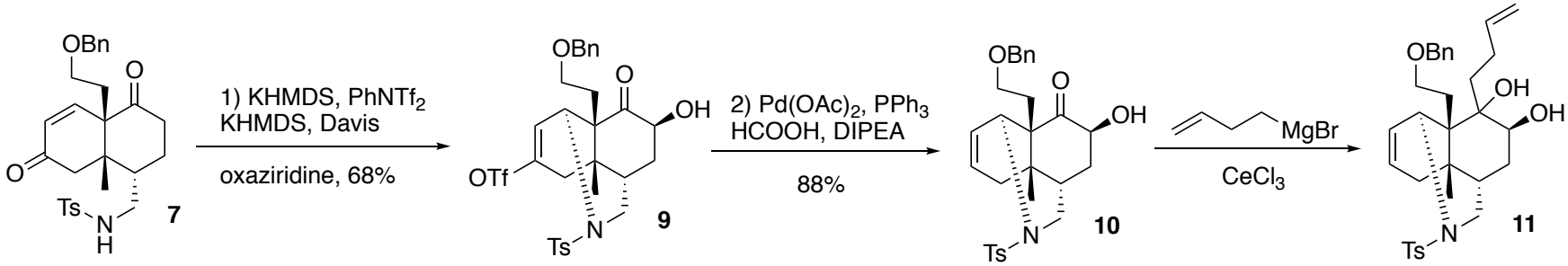

OBn
O
O
N
PMB
8
1.3-Dimethylbarbituric acid
Pd(PPh3)4, DCM/THF, 4h
NaHCO3 aq., TsCl, 14h
82%, dr> 6:1
Ts
9
ZnMe2, LiBr, Ni(acac)2
Et2O/THF/PhMe
40h, 55%
10
11
LHMDS, THF
-78C, 75%
12
CAN
CH3CN/H2O
0C to r.t.
5h, 79%
13

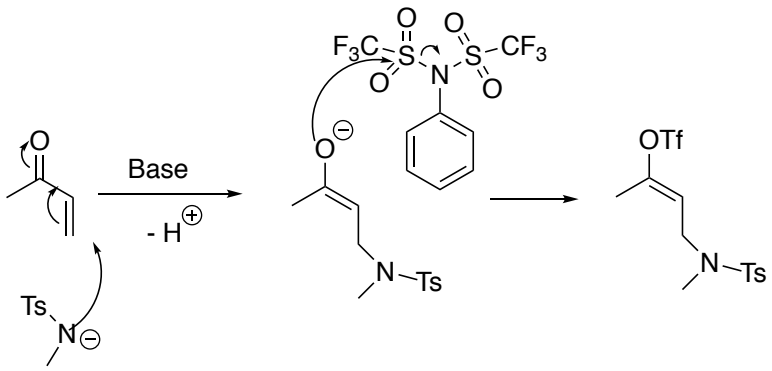

Pd(PPh3)2
NHR2
R2NH
Ph3P
Pd
PPh3

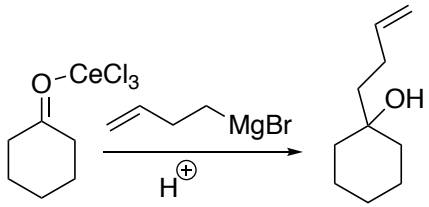

ZnMe2 + Ni(acac)2
L
Ni-Me
Br
Zn
O
Me
ZnMe
Ni
L
H
Zn
Me

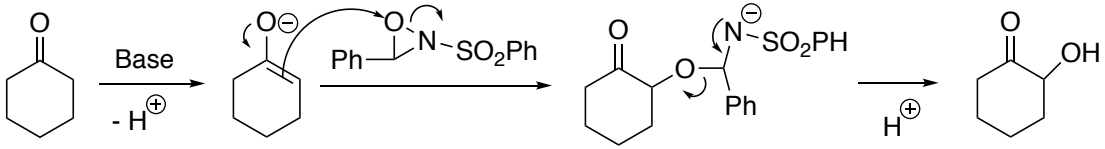

OBn
O
O
N
PMB
8
1.3-Dimethylbarbituric acid
Pd(PPh3)4, DCM/THF, 4h
NaHCO3 aq., TsCl, 14h
82%, dr> 6:1
Ts
9
ZnMe2, LiBr, Ni(acac)2
Et2O/THF/PhMe
40h, 55%
10
11
LHMDS, THF
-78C, 75%
12
CAN
CH3CN/H2O
0C to r.t.
5h, 79%
13

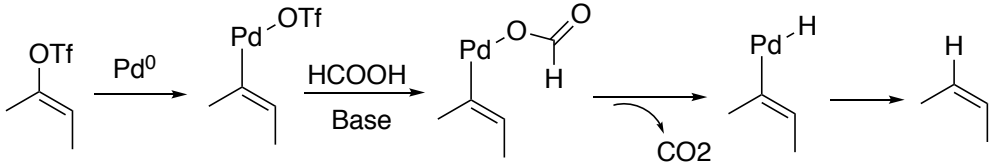

base
Ph
Cl
H
MeO
CeIV
CeIII
- H⊕
H2O
- H⊕
H⊕

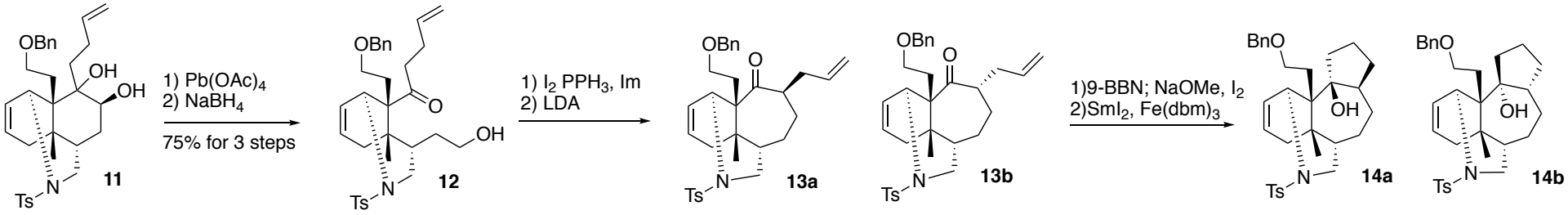

OBn
O
O
Ts
N
H
7
1) KHMDS, PhNTf2
KHMDS, Davis
oxaziridine, 68%
OBn
O
OH
OTf
Ts
N
9
2) Pd(OAc)2, PPh3
HCOOH, DIPEA
88%
OBn
O
OH
Ts
N
10
MgBr
CeCl3
OBn
OH
OH
Ts
N
11

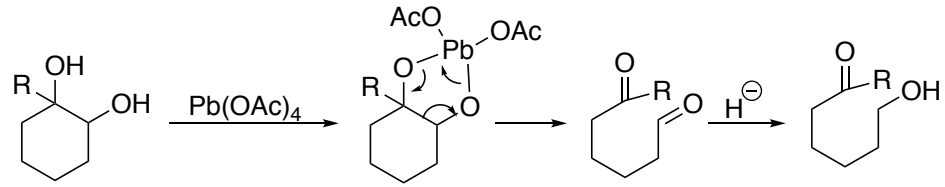

O
Base
- H
Ts
N
F3C
S
O
O
N
S
CF3
O
O
N
Ts
OTf
N
Ts

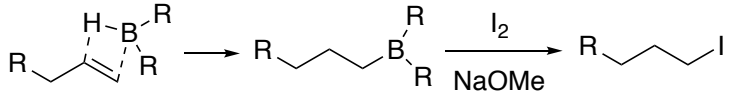

O
CeCl3
MgBr
H
OH


O
Base
- H
O
Ph
N
SO2Ph
O
O
N
SO2PH
Ph
H
O
OH

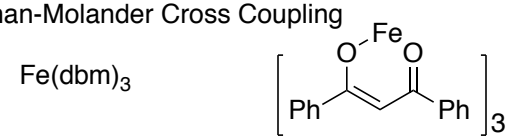

OTf
Pd0
Pd
OTf
HCOOH
Base
Pd
O
O
H
CO2
Pd
H
H

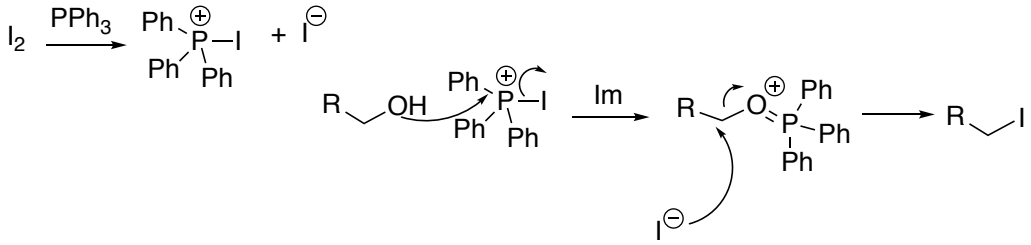




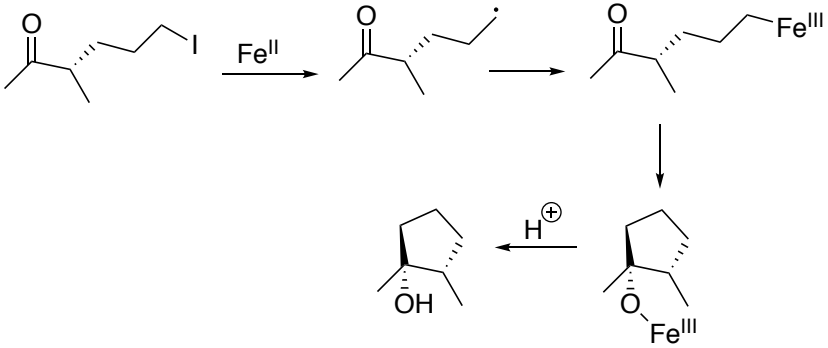


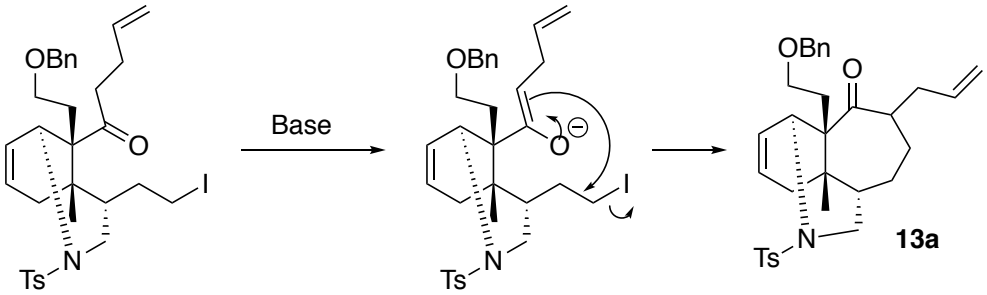
Khan-Molander Cross Coupling

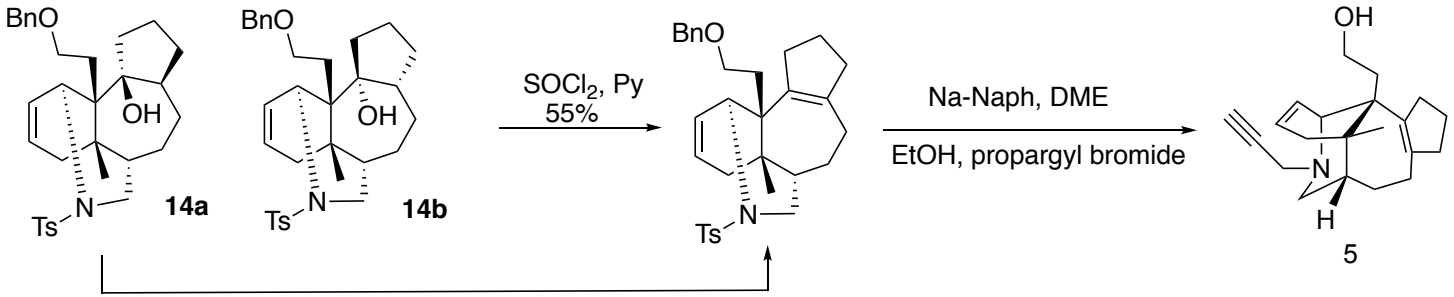


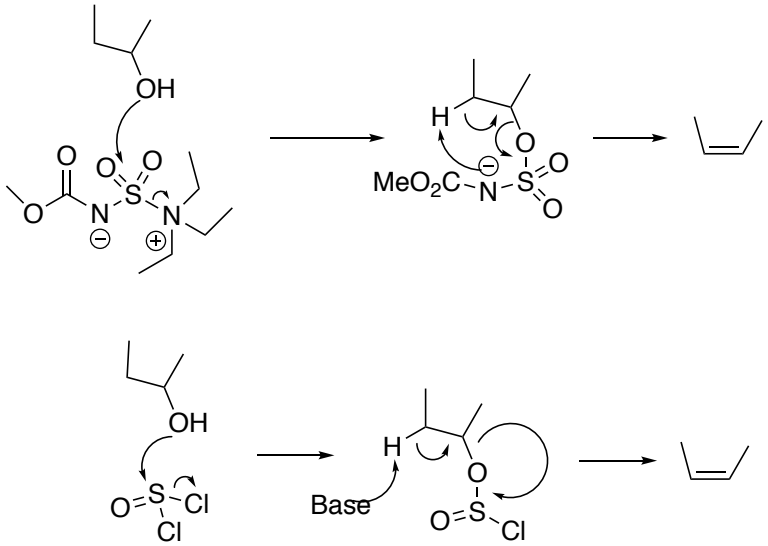


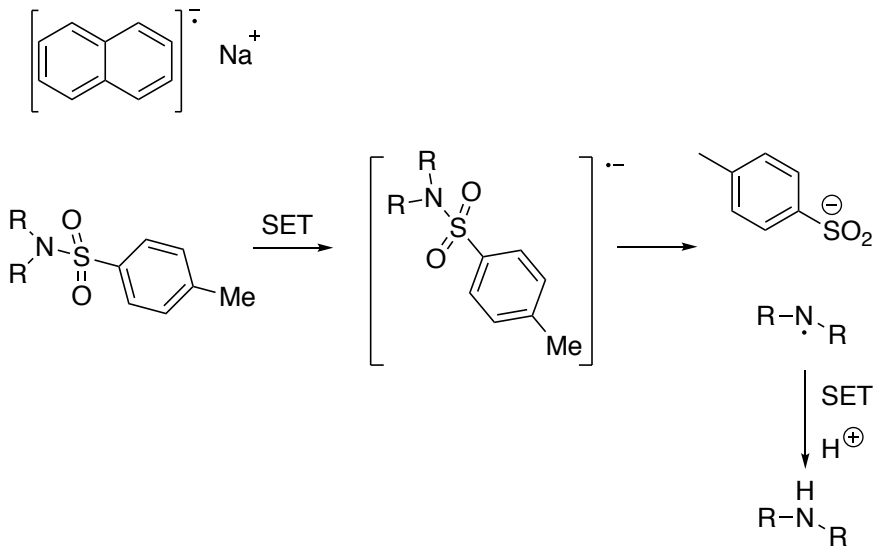
$Fe^{III} + Sm^{II} \longrightarrow Fe^{II} + Sm^{III}$

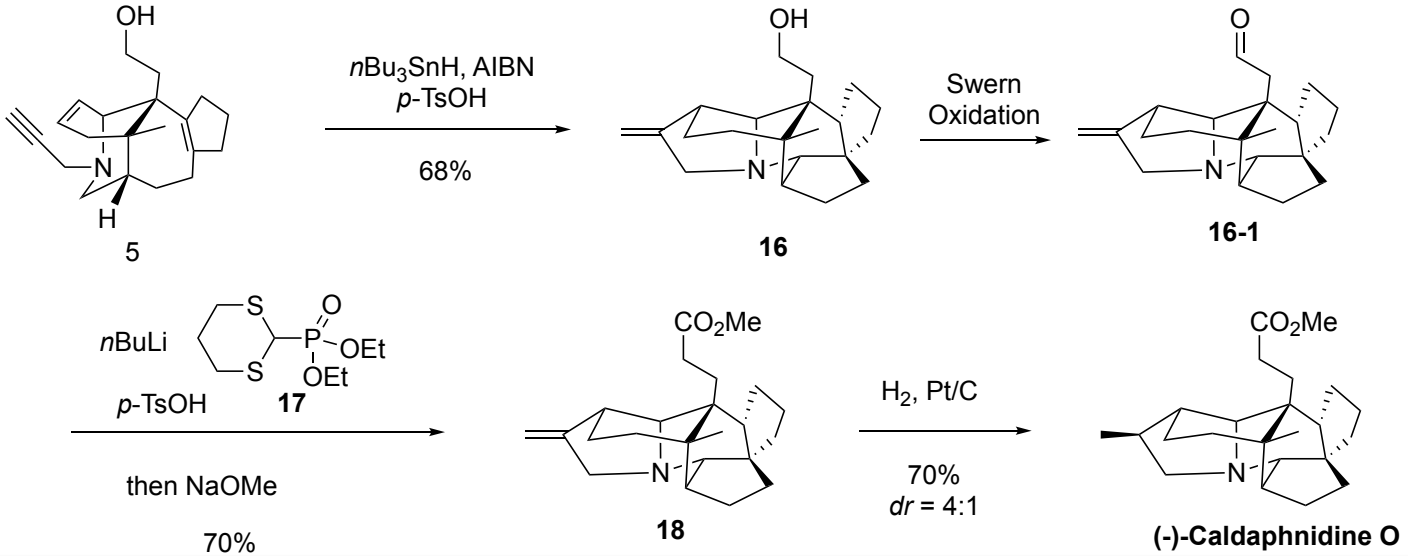


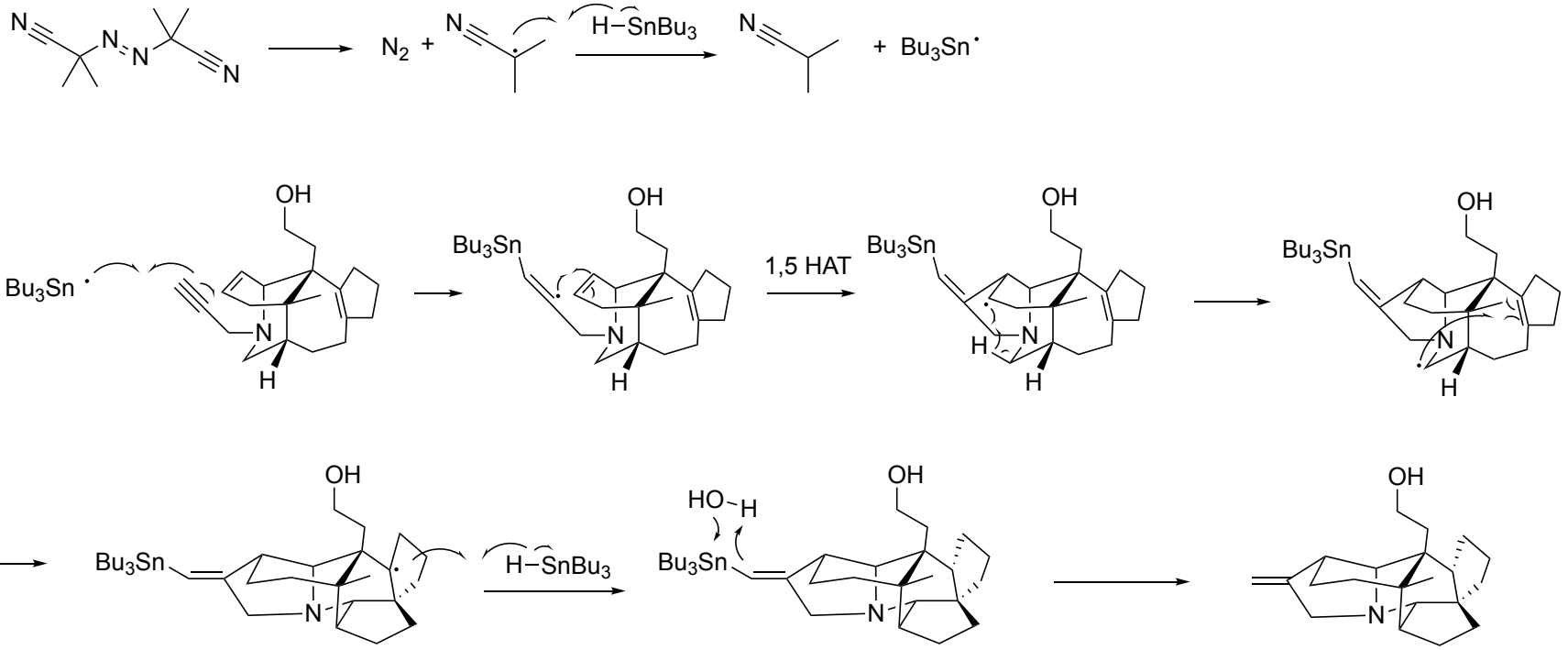


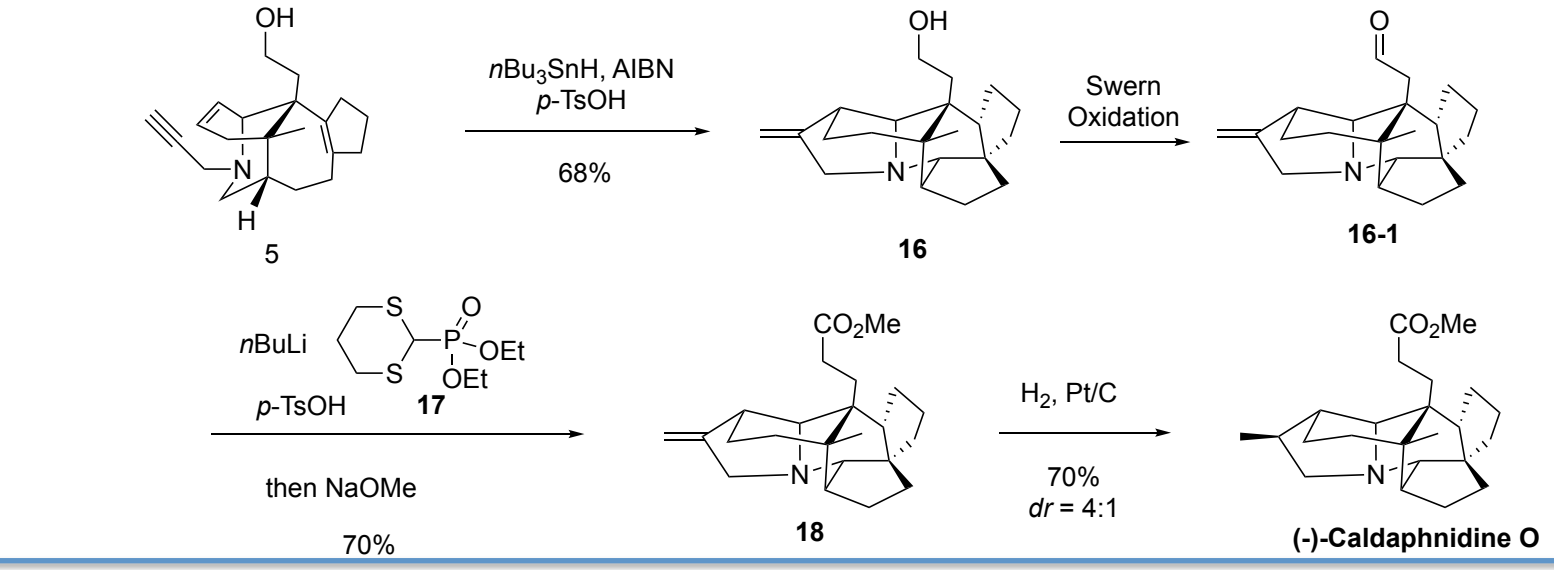

BnO
OH
Ts
N
14a
14b
SOCl2, Py
55%
Na-Naph, DME
EtOH, propargyl bromide
H
5

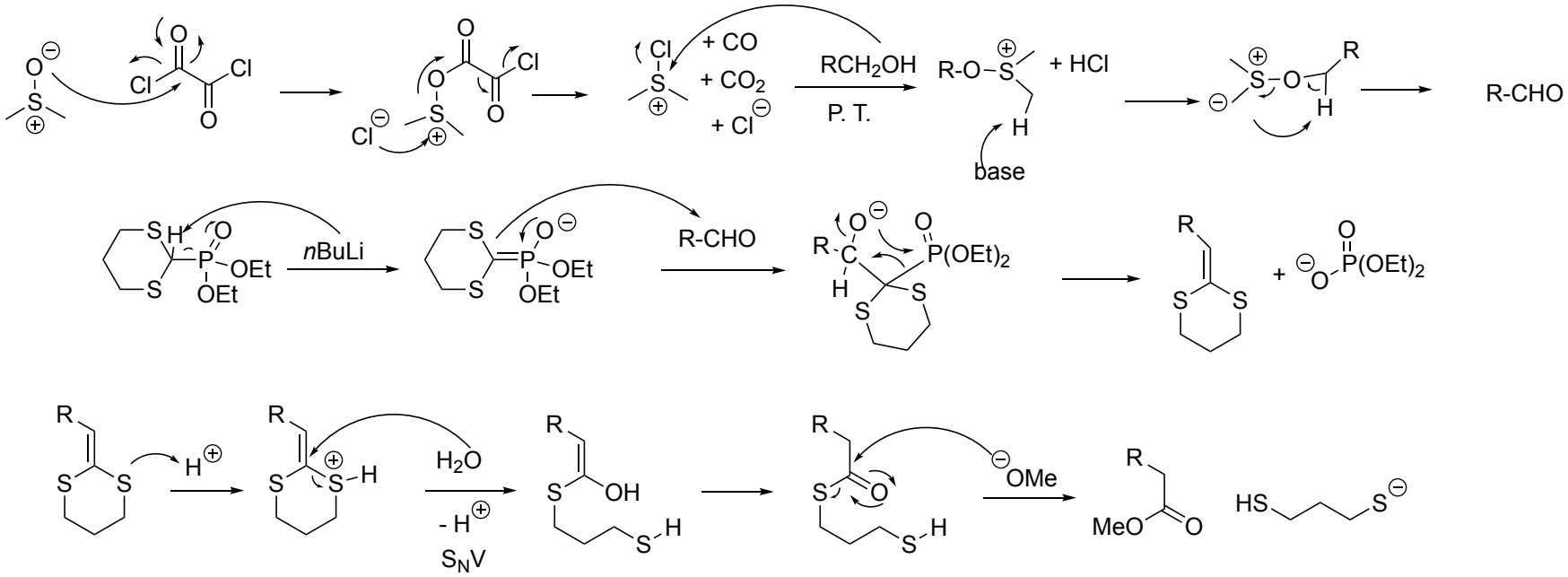

OH
MeO2C
Base
Cl


Na+
SET
Me
SO2
H


OH
nBu3SnH, AIBN
p-TsOH
68%
Swern
Oxidation
O
5
16
16-1
nBuLi
p-TsOH
17
then NaOMe
70%
CO2Me
18
H2, Pt/C
70%
dr = 4:1
(-)-Caldaphnidine O


N2 +
H–SnBu3
+ Bu3Sn•
Bu3Sn
1,5 HAT
HO–H


OH
N
H
5
nBu3SnH, AIBN
p-TsOH
68%
OH
N
16
Swern
Oxidation
O
N
16-1
nBuLi
S
S
P
O
OEt
OEt
17
p-TsOH
then NaOMe
70%
CO2Me
N
18
H2, Pt/C
70%
dr = 4:1
CO2Me
N
(-)-Caldaphnidine O


O
Cl
Cl
O
O
S
Cl
O
O
Cl
S
Cl
+ CO
+ CO2
+ Cl
RCH2OH
P. T.
R-O-S
H
+ HCl
base
S
O
R
H
R-CHO
S
H
O
P
OEt
OEt
S
nBuLi
S
O
P
OEt
OEt
S
R-CHO
R
C
O
O
P(OEt)2
H
S
S
R
S
S
+
O
P(OEt)2
R
S
S
H
H2O
- H
SNV
R
S
OH
S
H
R
S
O
S
H
OMe
R
MeO
O
HS
S