Total Synthesis of (±)- and (−)-Daphnillonin B

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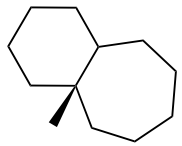
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

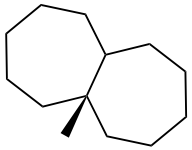
Daphniphyllum alkaloids

- >13 subfamilies, >300 members
- Have complex and diverse structures and interesting biological activities,
- Biologically active natural products
- Several of these alkaloids exhibit interesting cytotoxic activity against murine lymphoma and human epidermoid carcinoma KB cells, with IC50 values in the 0.1−10 μM range

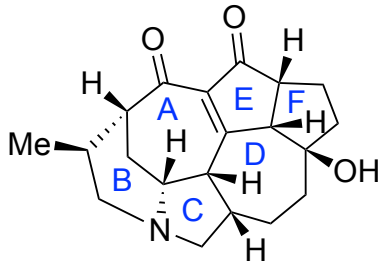
Daphnillonin B was first isolated from *Daphniphyllum longeracemosa* by Yue and co-workers in 2019



Daphniphyllum-type alkaloids
-[6-7] fused core
- previous total syntheses
-Heathcock, Carreria, Smith, A.Li, Fukuyama, Dixon, Zhai, Qui, Xu, Gao, Lu, Xu



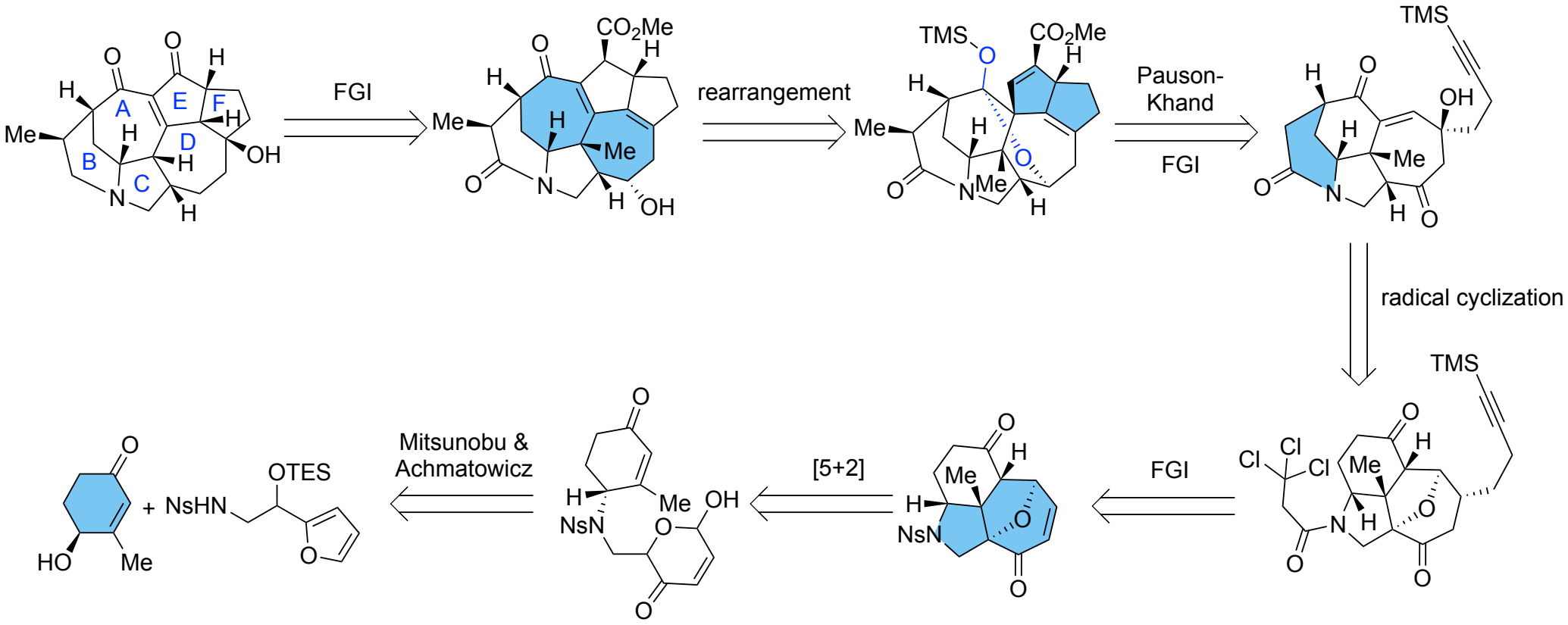
Daphnicyclidin-type alkaloids
-[7-7] fused core
- ~20 members
-previous synthetic studies: Overman, Iwabuchi, Williams,Stockdill, Yang, Harmata
-previous total synthesis: A.Li

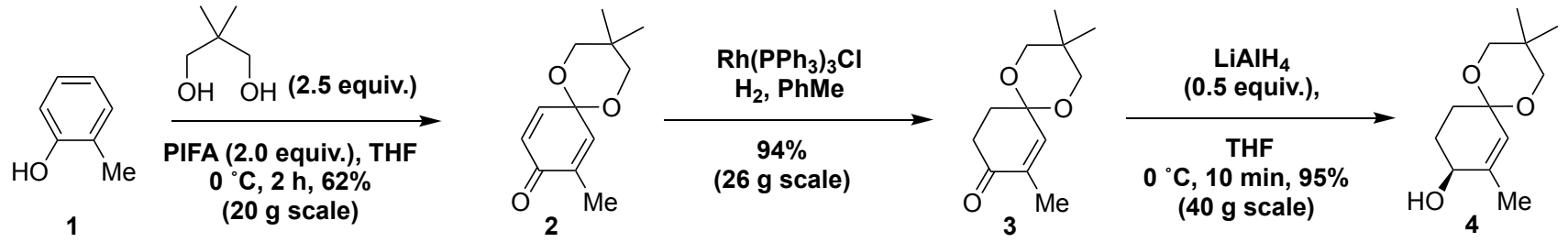


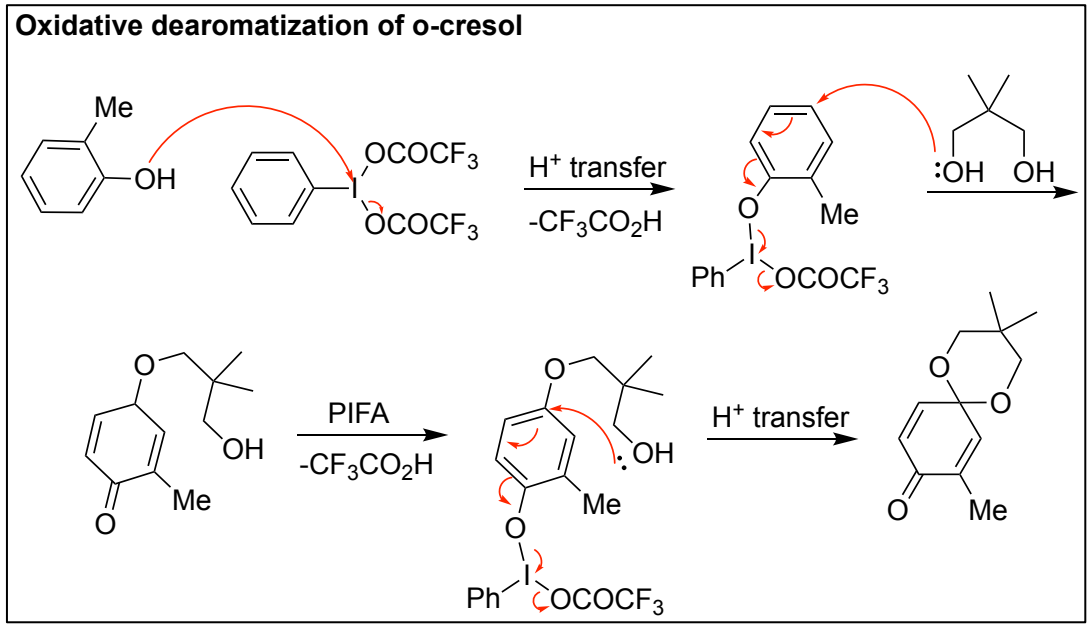
Daphnillonin B
-[7-6-5-7-5-5] hexacyclic core
-azabicyclo[4.2.1] system
-1 tetrasubstituted olefin
-8 stereogenic centers; 2 quaternary
-28 steps, overall yield of 0.045%
first reported total synthesis

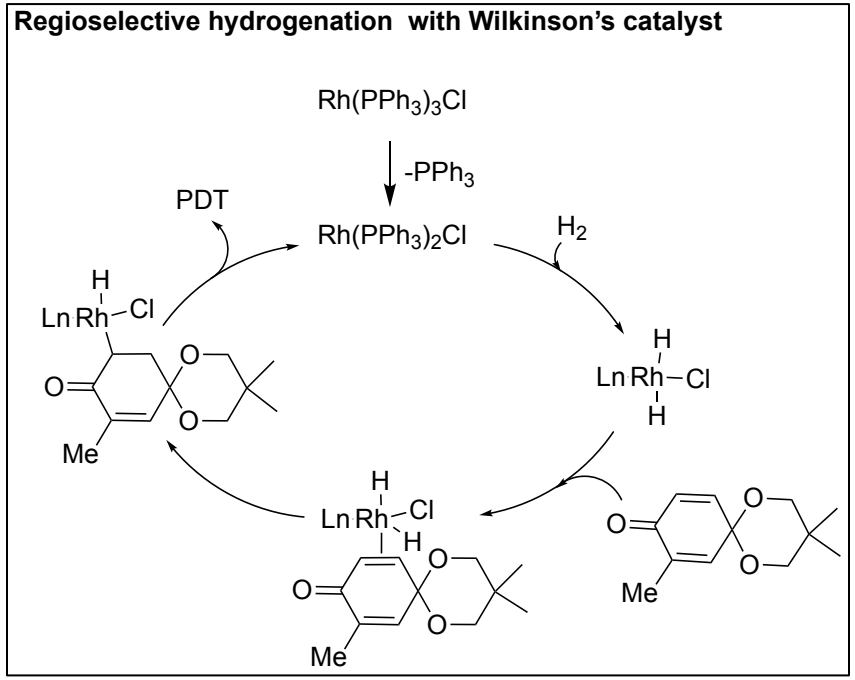
J. Am. Chem. Soc. **2023**, 145, *20*, 10998−11004

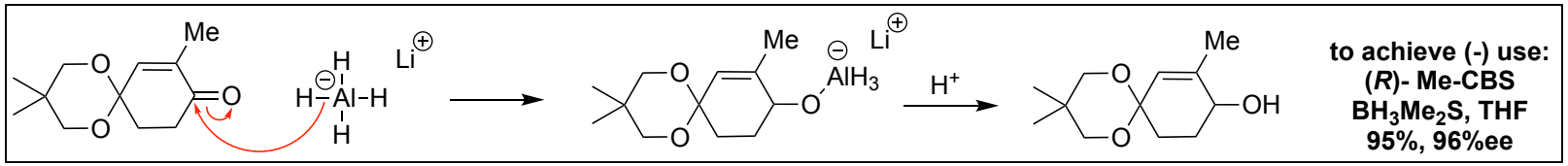
Retrosynthetic Analysis

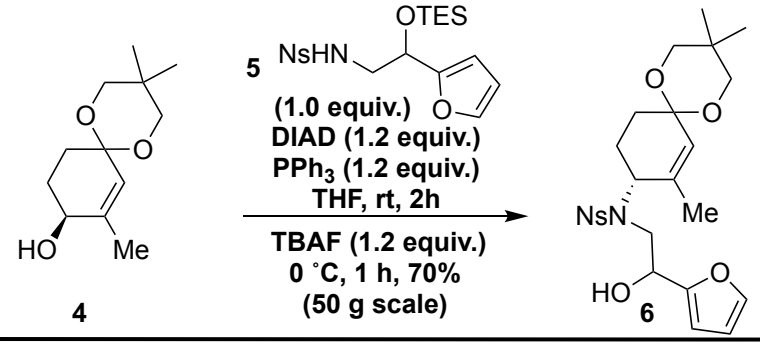



OH OH (2.5 equiv.)
PIFA (2.0 equiv.), THF
0 ˚C, 2 h, 62%
(20 g scale)
Rh(PPh3)3Cl
H2, PhMe
94%
(26 g scale)
LiAlH4
(0.5 equiv.),
THF
0 ˚C, 10 min, 95%
(40 g scale)
1
2
3
4

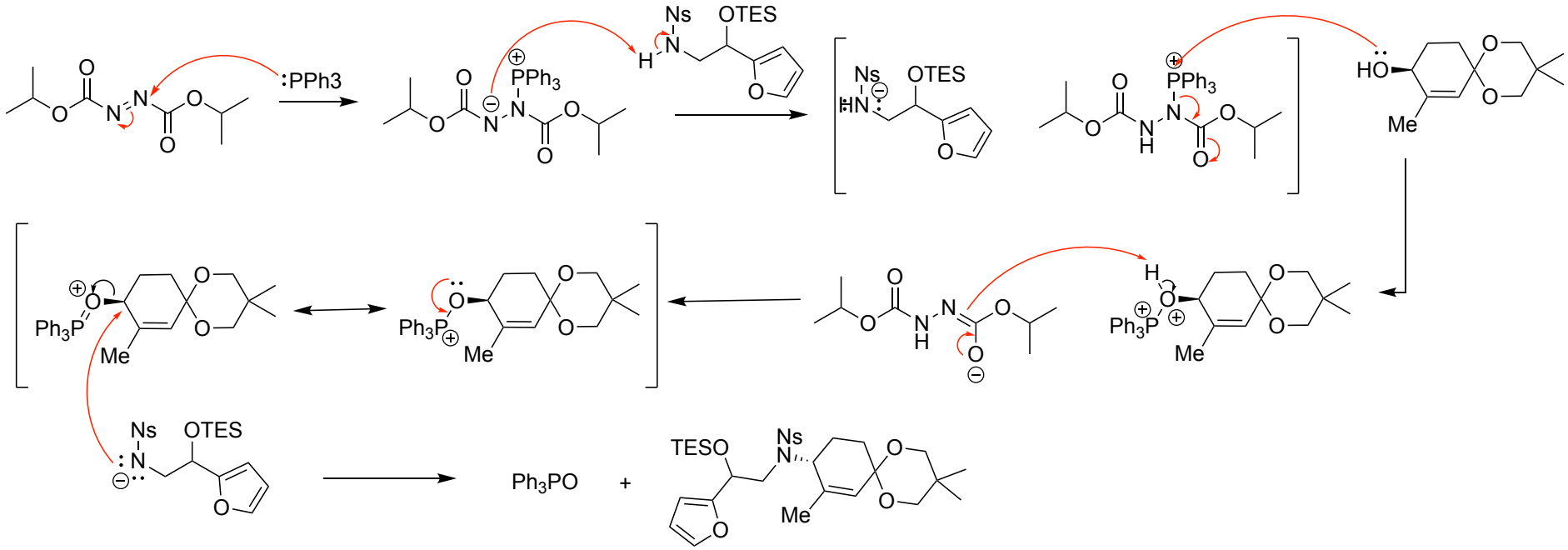

Oxidative dearomatization of o-cresol
H+ transfer
-CF3CO2H
PIFA
-CF3CO2H
H+ transfer


Regioselective hydrogenation with Wilkinson's catalyst
Rh(PPh3)3Cl
-PPh3
Rh(PPh3)2Cl
PDT
H2

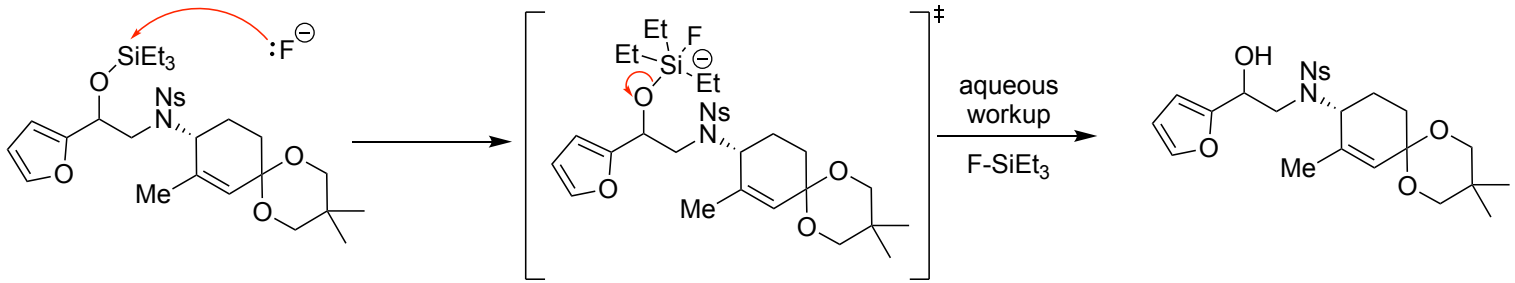

H+
to achieve (-) use:
(R)- Me-CBS
BH3Me2S, THF
95%, 96%ee

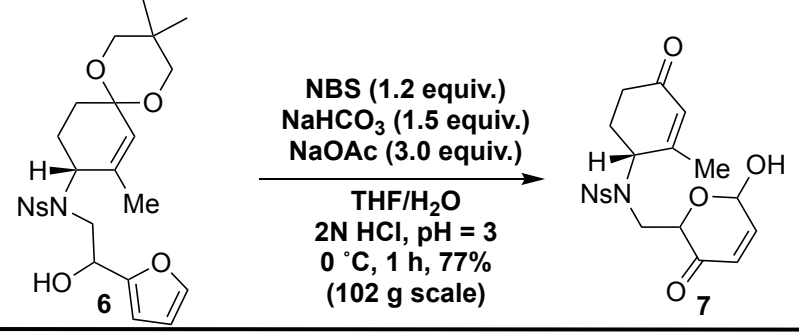


Mitsonobu reaction

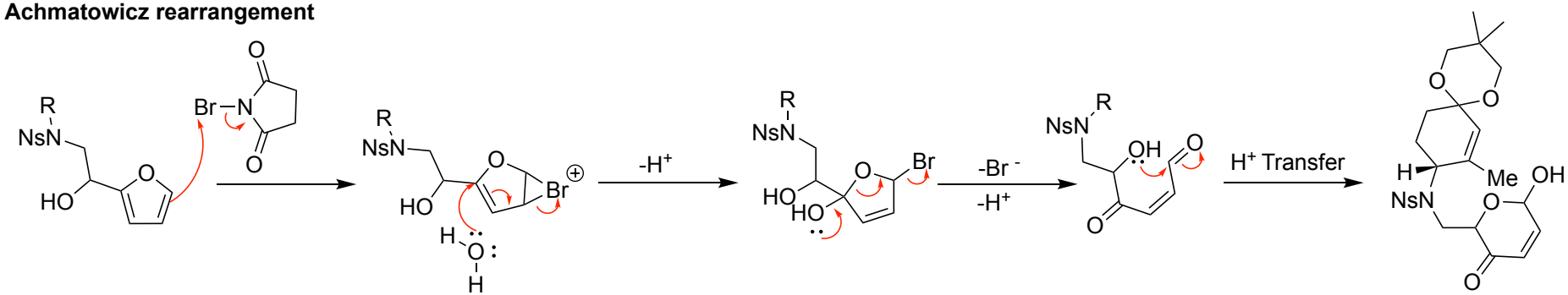


Deprotection with TBAF

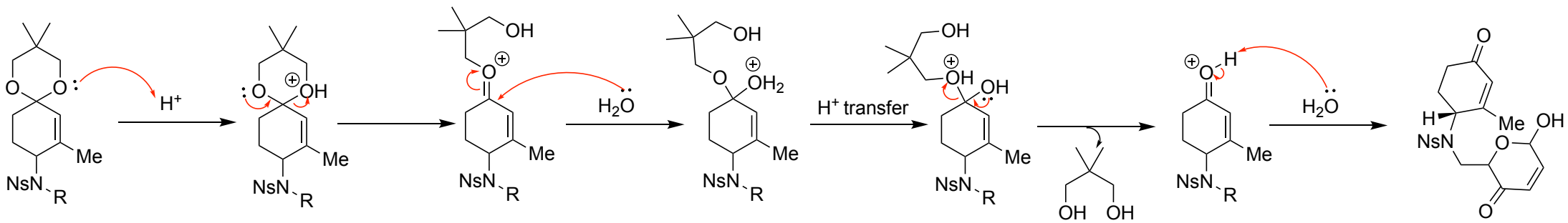


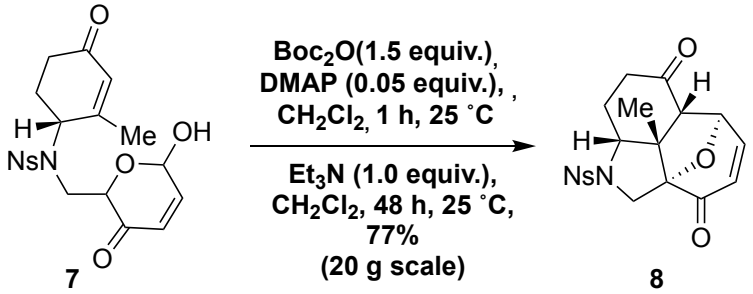


Achmatowicz rearrangement

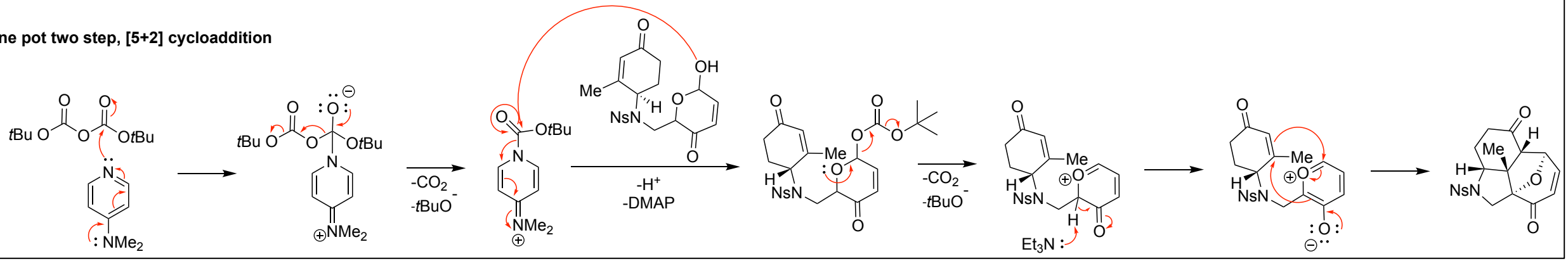


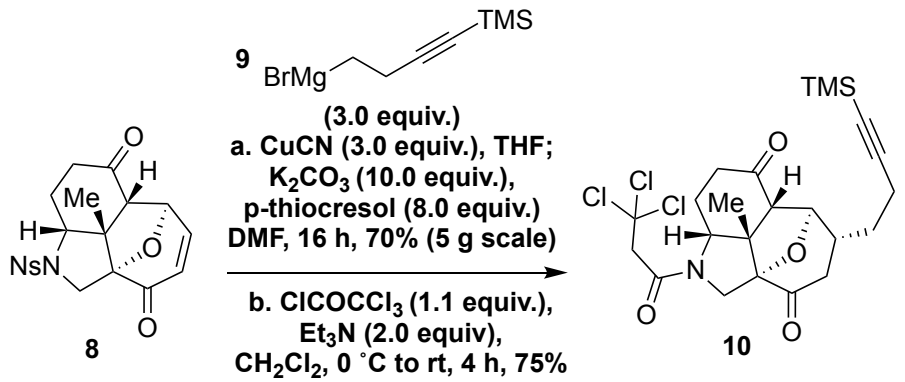
Formation of ketone from dioxaspiro compound with acid



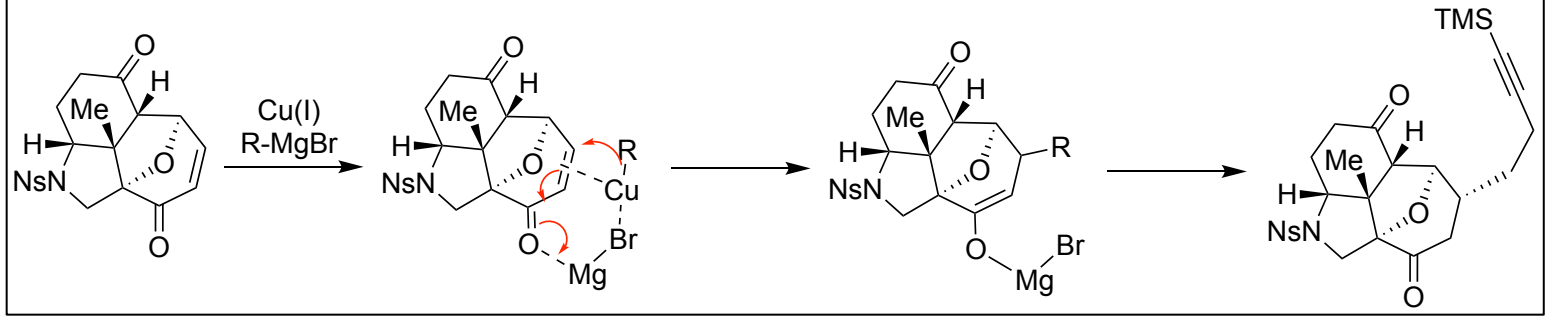


One pot two step, [5+2] cycloaddition



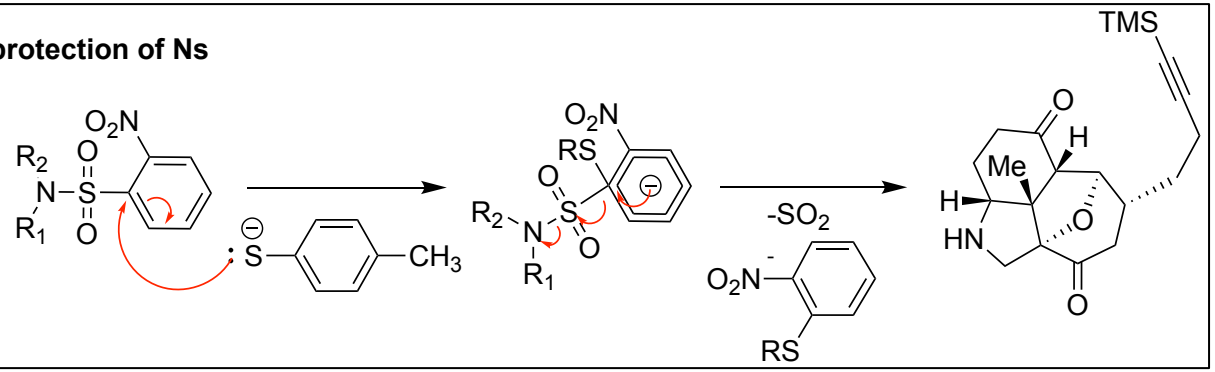


Diasterioselective 1,4 addition of cuprate

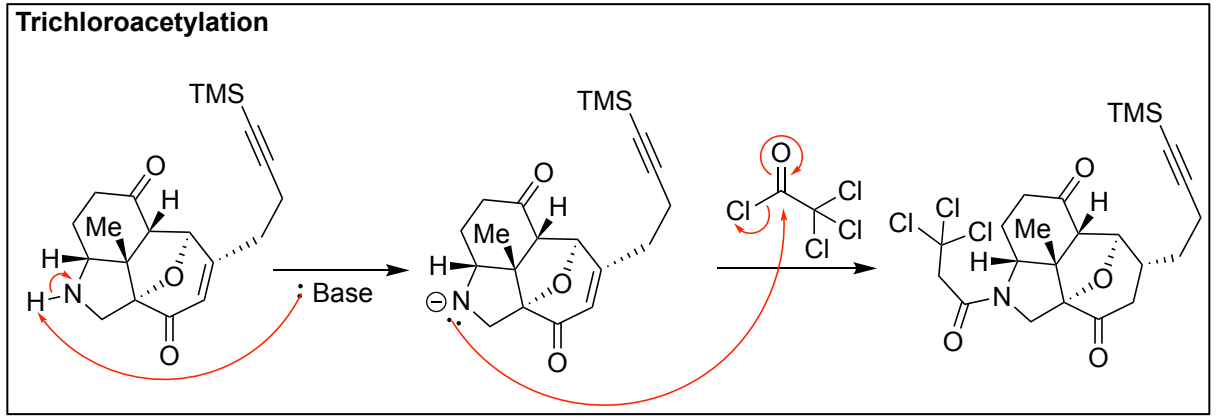


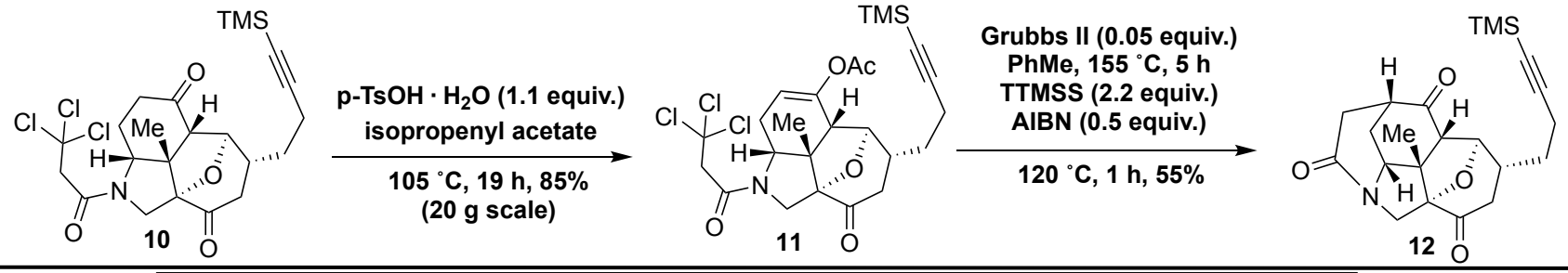
Coordination of Cu to bridging O determines diastereoselectivity

Deprotection of Ns

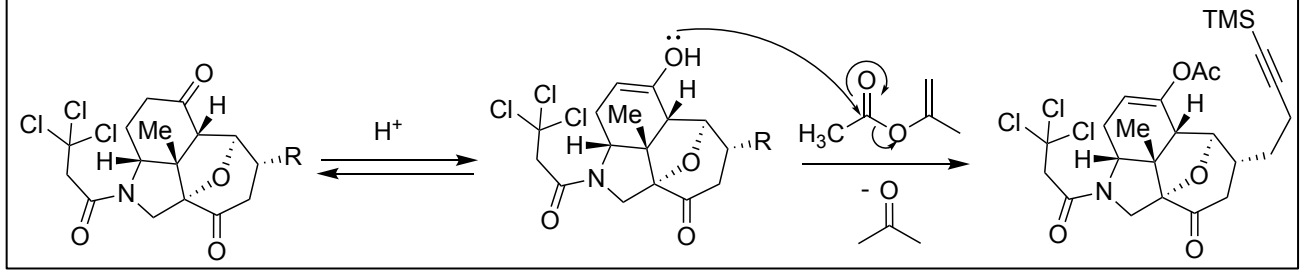


Trichloroacetylation

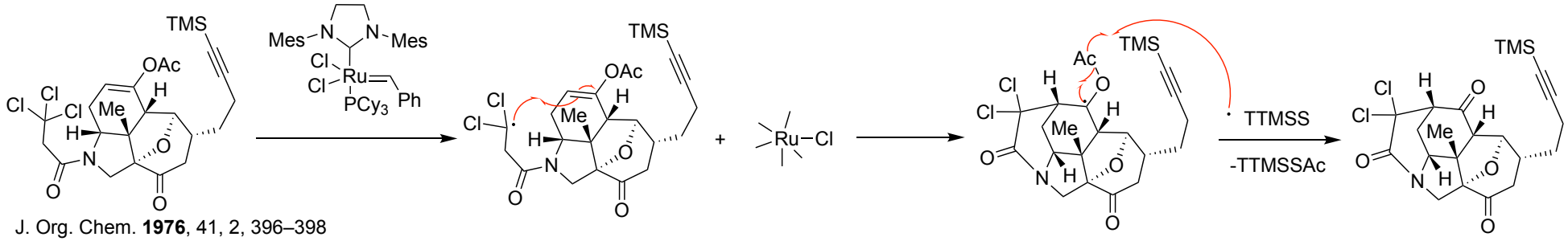




Formation of enol acetate with isopropenyl acetate treatment of ketone

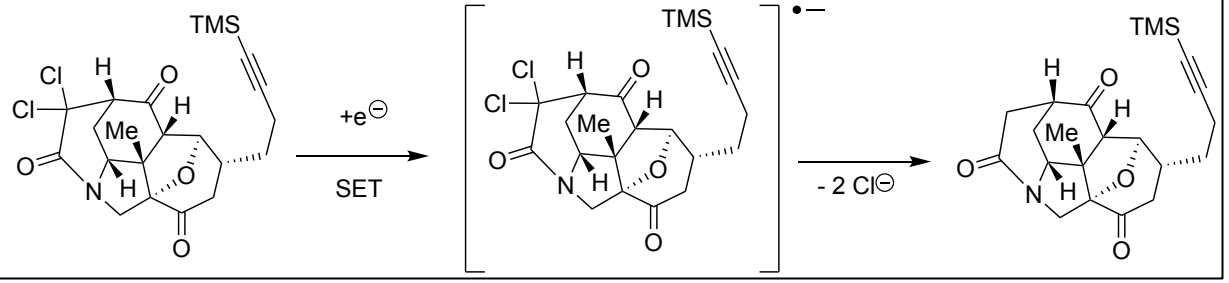


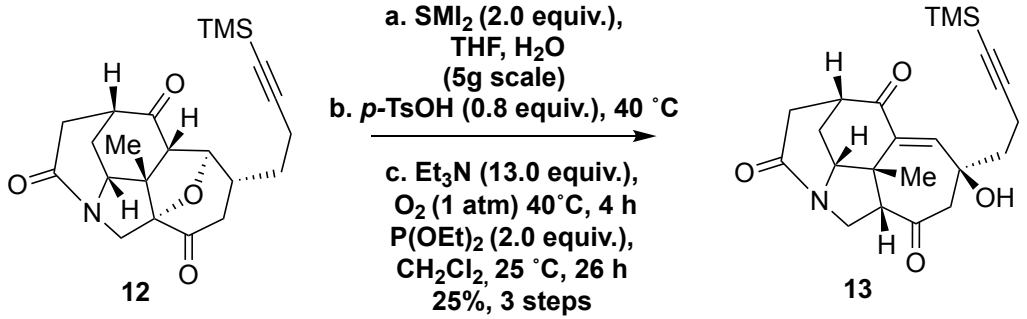
G2 catalyzed radical cyclization (Kharash addition)

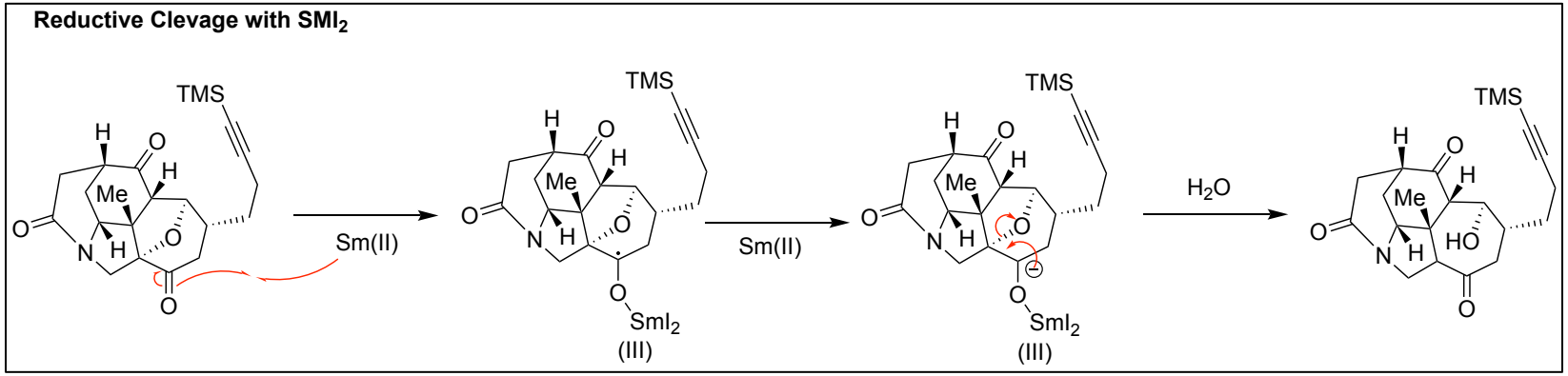


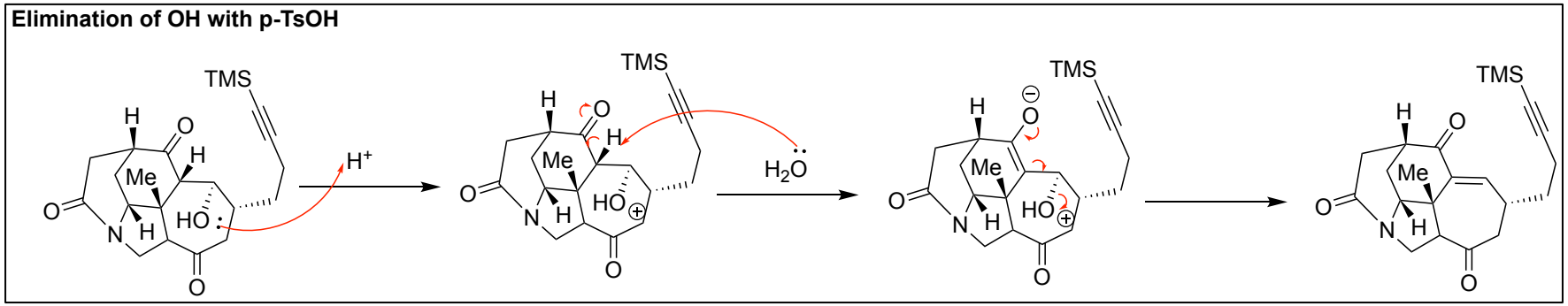
J. Org. Chem. **1976**, 41, 2, 396–398
Matsumoto, J. Organomet. C **1979**, 174, 157
Chatgilialoglu, *J. Org. Chem.* **1988**, *53*, 3641-3642.

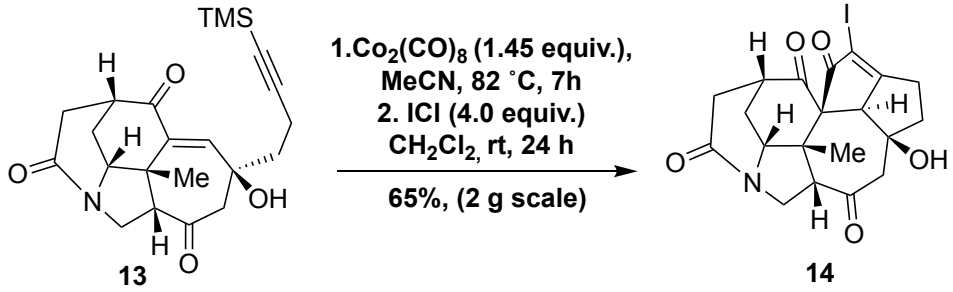
Dechlorination with AIBN




TMS
H
O
H
Me
O
N
H
O
O
12
a. SmI2 (2.0 equiv.),
THF, H2O
(5g scale)
b. p-TsOH (0.8 equiv.), 40 ˚C
c. Et3N (13.0 equiv.),
O2 (1 atm) 40˚C, 4 h
P(OEt)2 (2.0 equiv.),
CH2Cl2, 25 ˚C, 26 h
25%, 3 steps
TMS
H
O
H
Me
O
N
H
OH
O
13

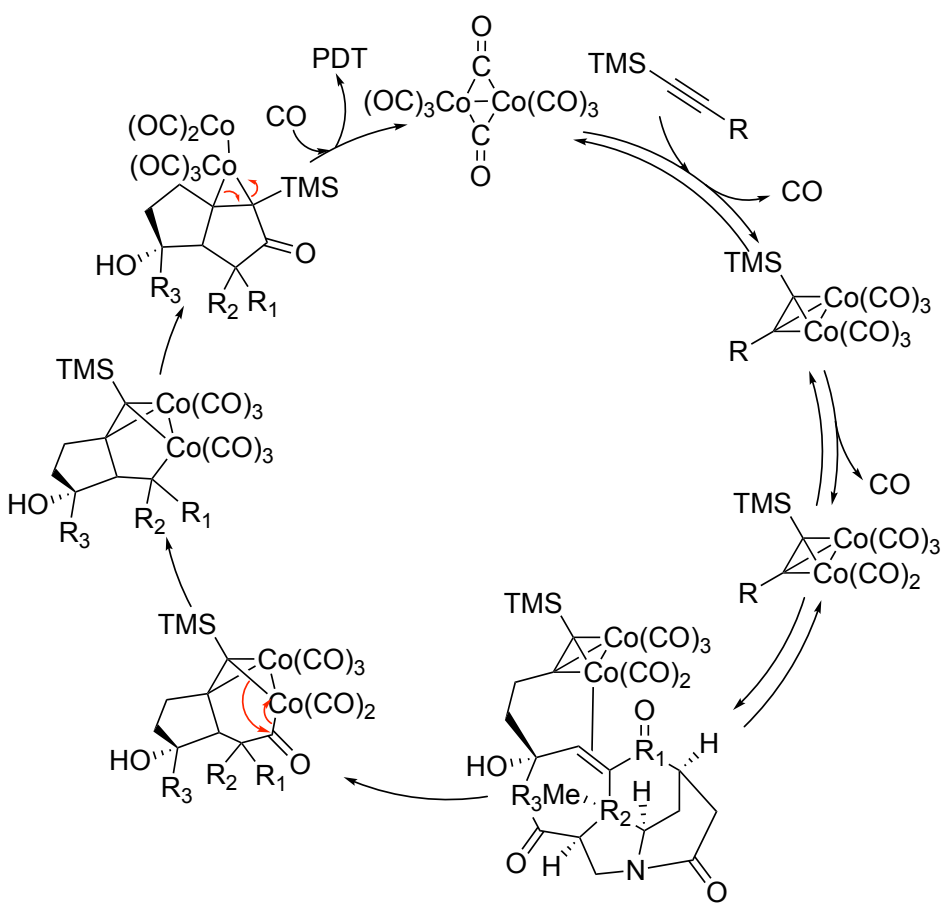

Reductive Clevage with SmI2
TMS
Sm(II)
SmI2
(III)
Sm(II)
SmI2
(III)
H2O
HO


Elimination of OH with p-TsOH
TMS
H+
H2O
HO

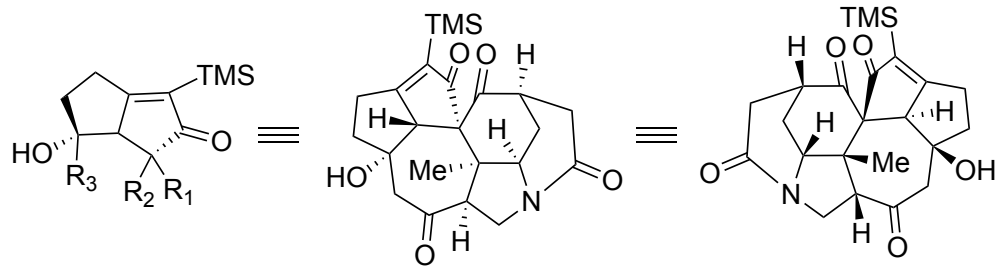


13 14

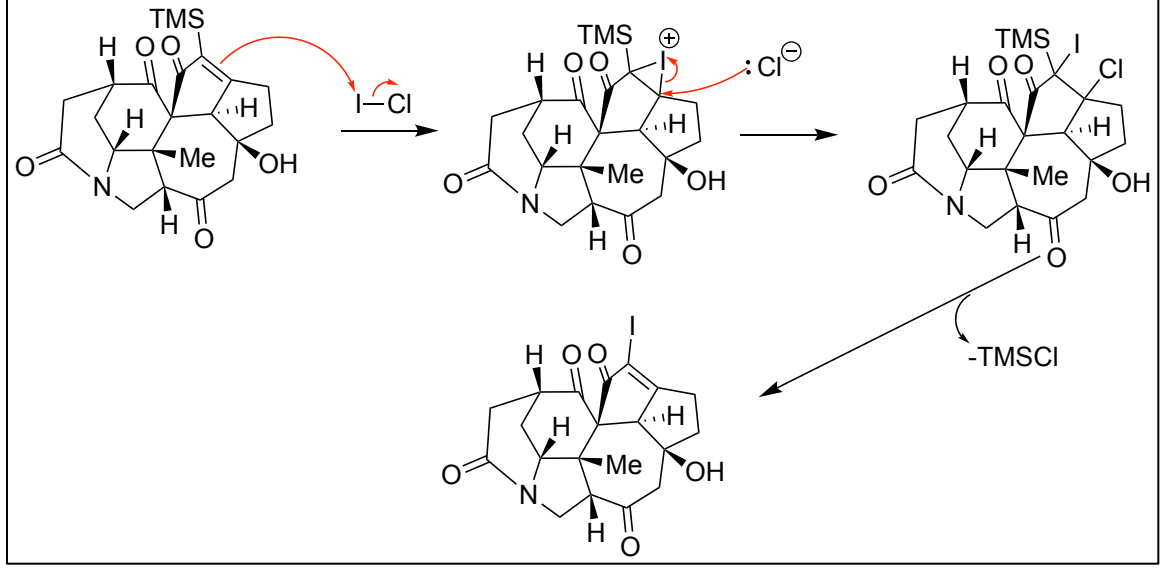
Pauson−Khand reaction

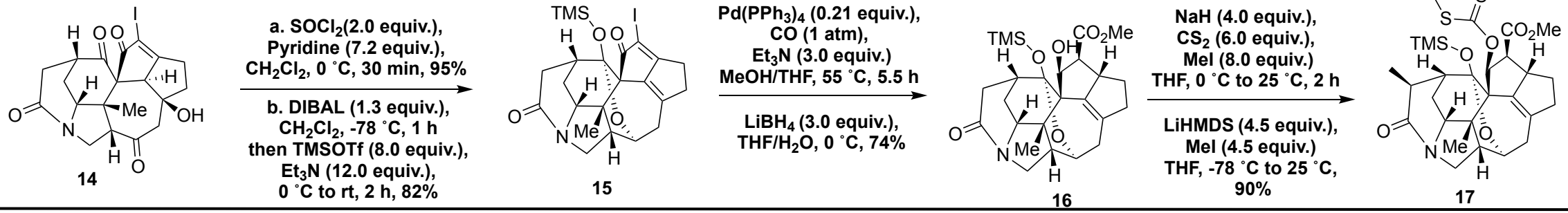


PDT=

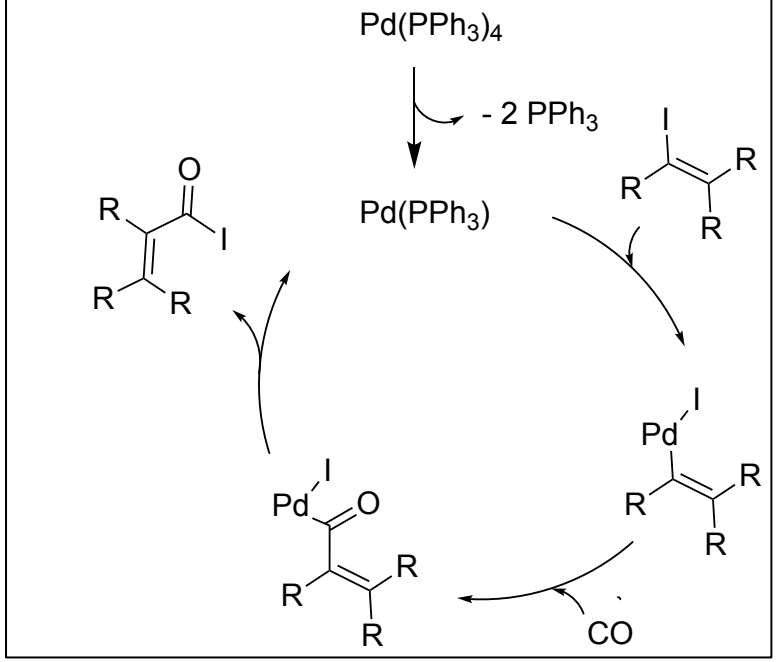


Iodination

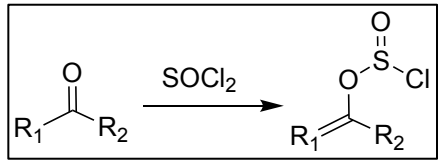




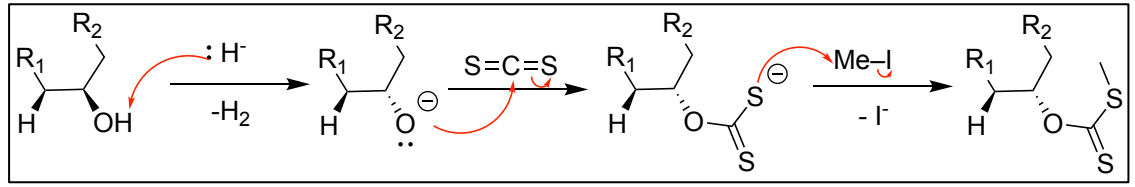
Carbonylation of aryl iodine



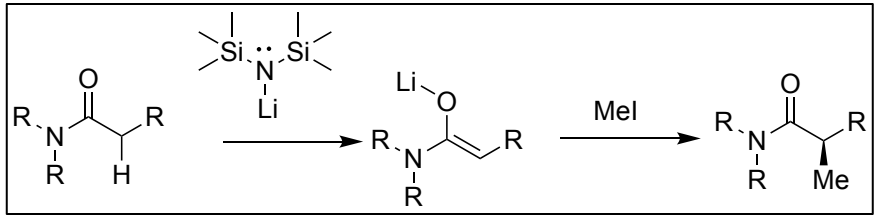
Reaction with SOCl2

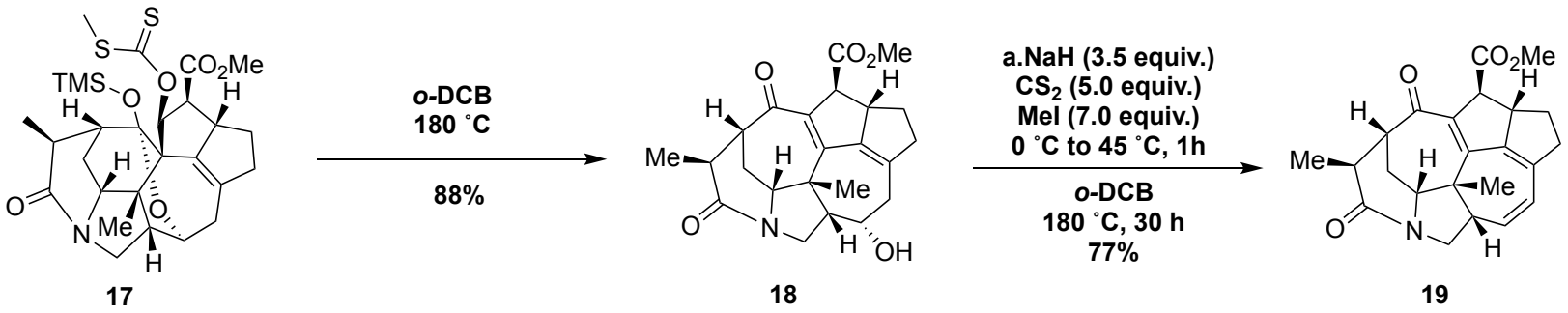


Reaction with CS_2

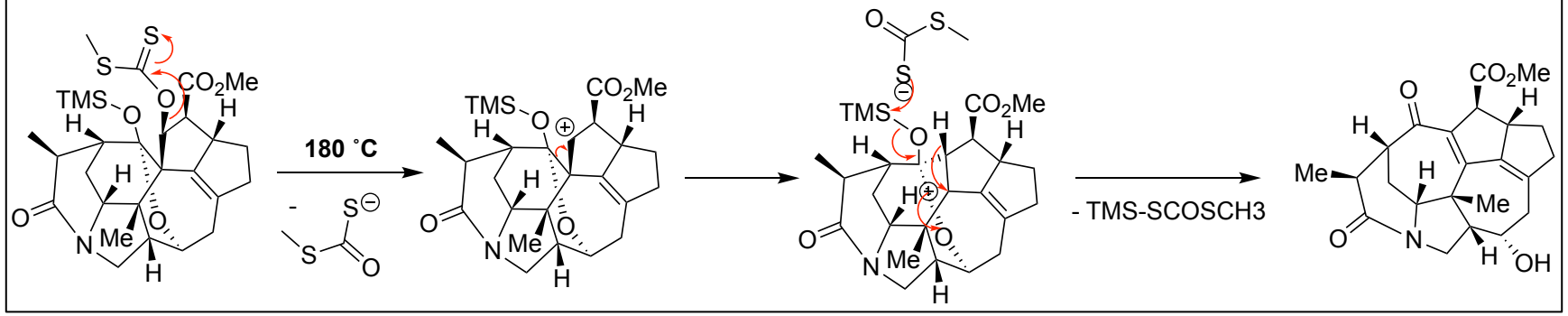


Methylation

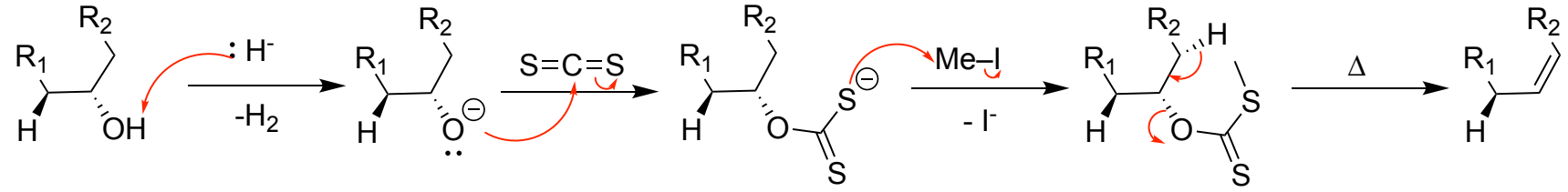


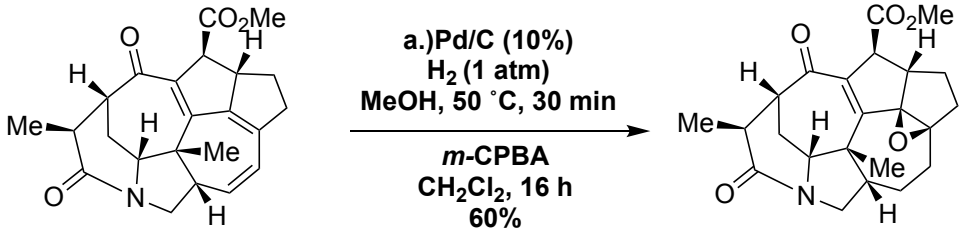


Wagner-Meerwein rearrangement



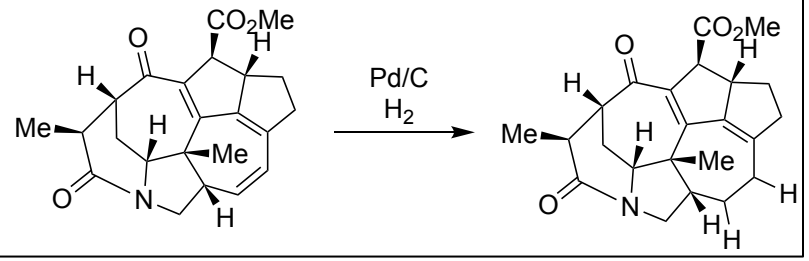
Chugaev elimination



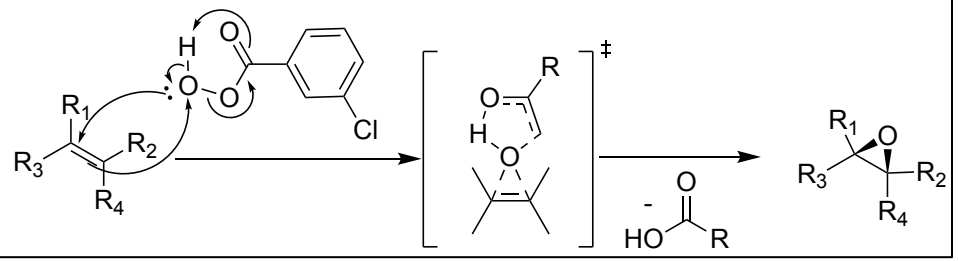


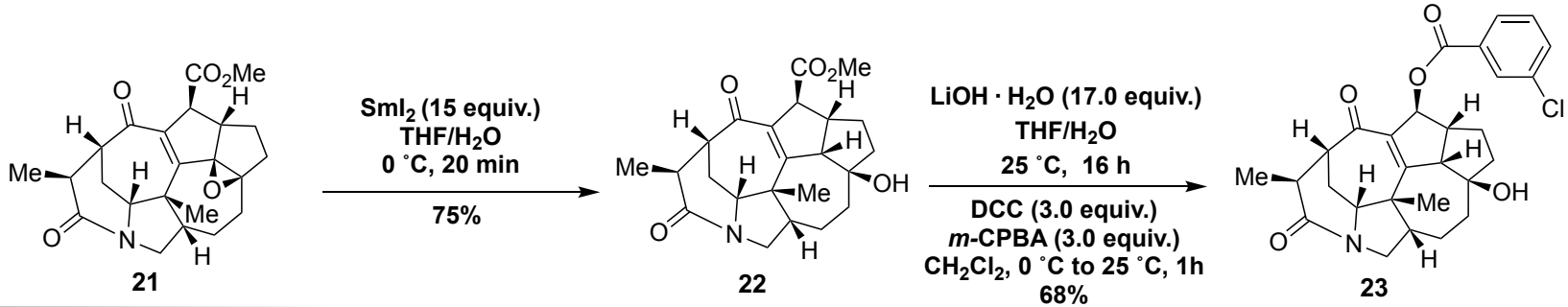
19 **20**

Chemoselective hydrogenation

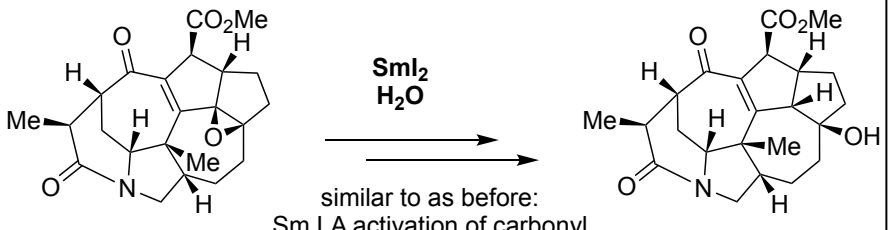


Diasteroselective epoxidation

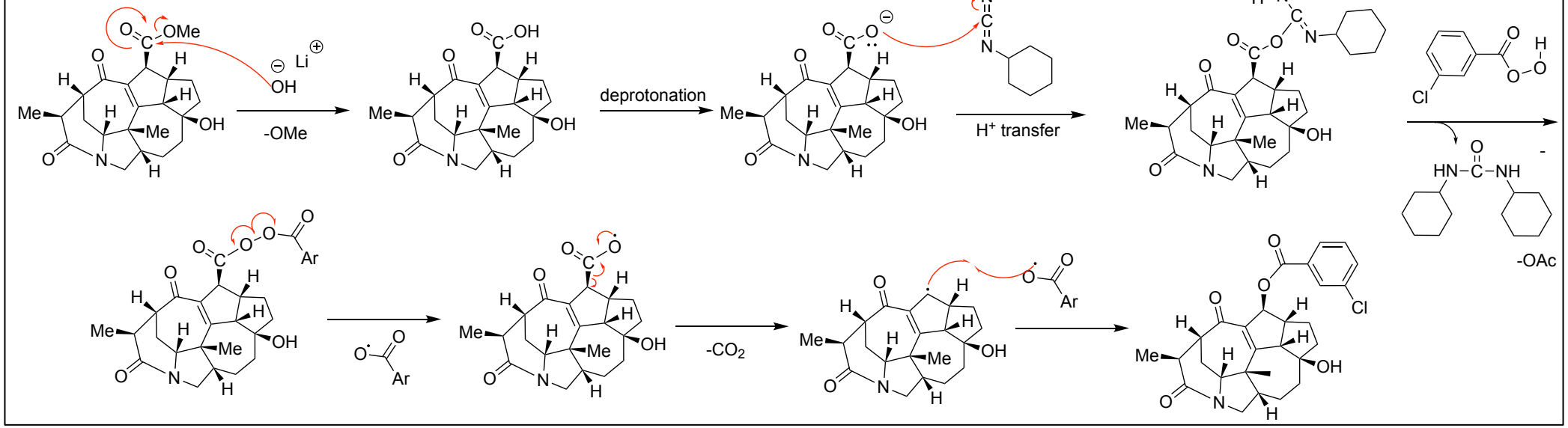


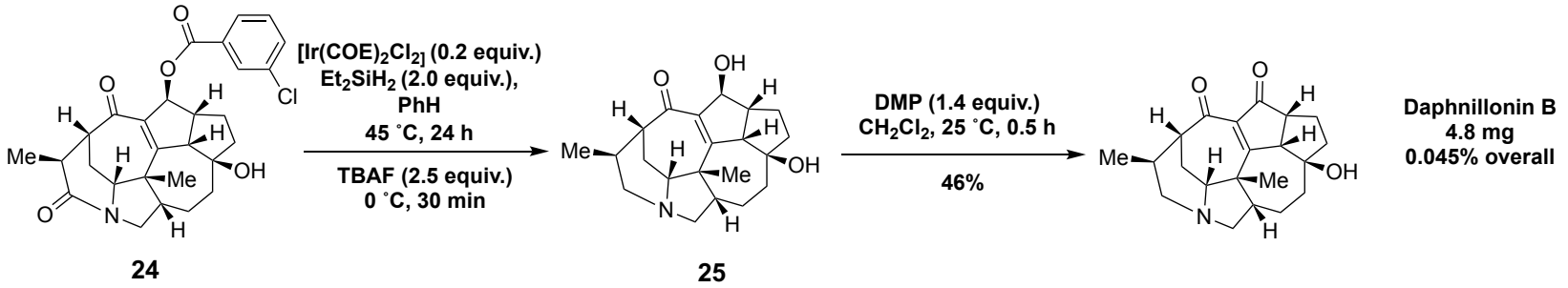


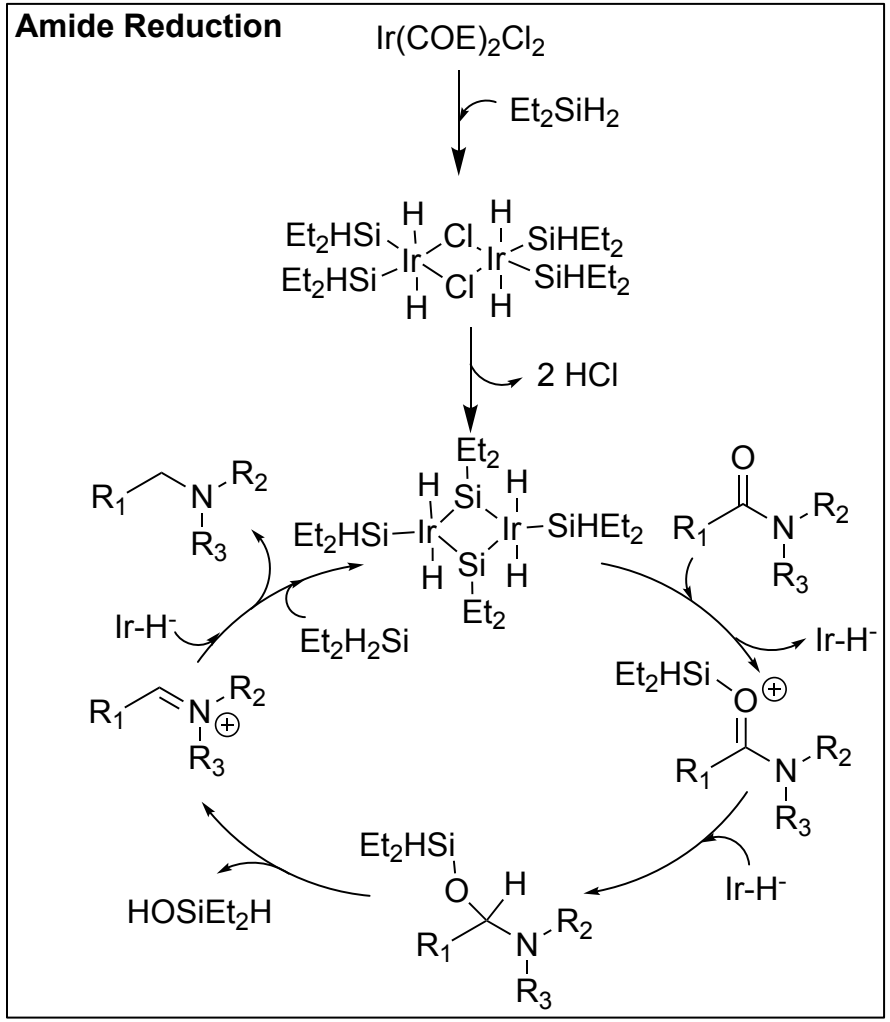
Reductive Clevage with SmI_2

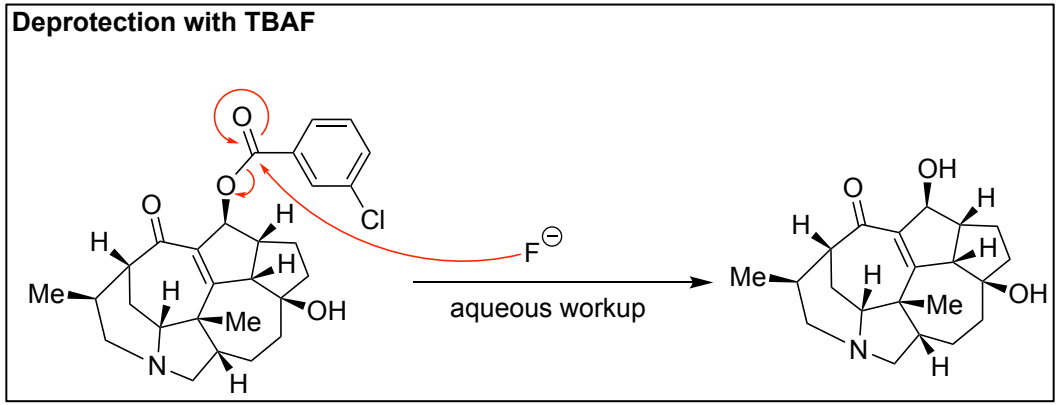


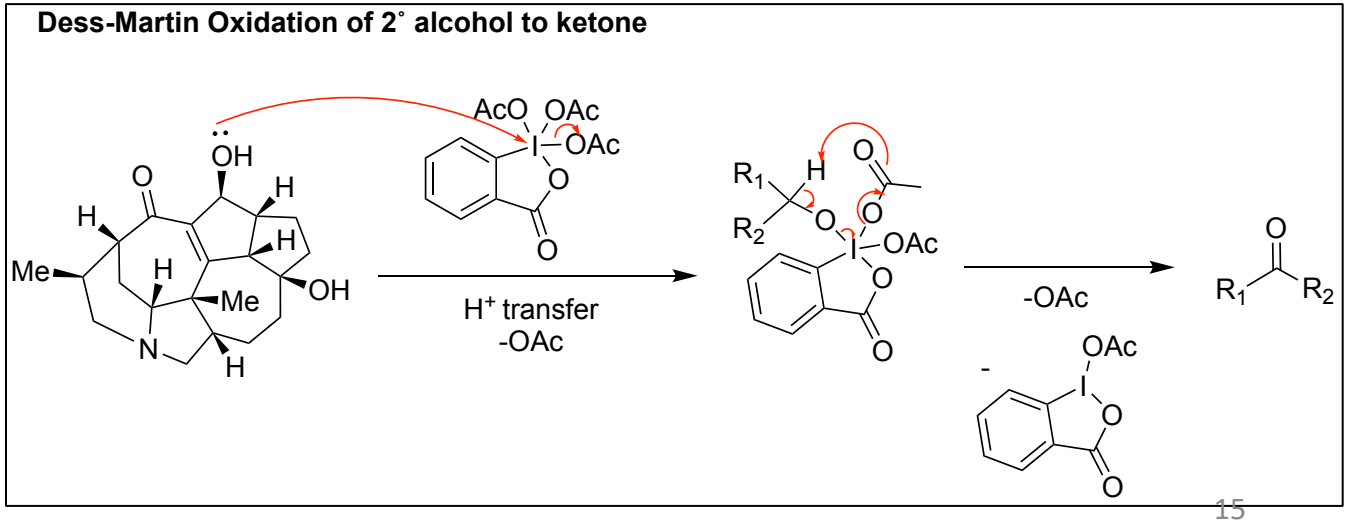
Reaction with LiOH, DCC, and mCPBA











Brookhart M., *et al; J. Am. Chem. Soc.* **2012**, 134, 28, 11304–11307

Thanks!
Questions?