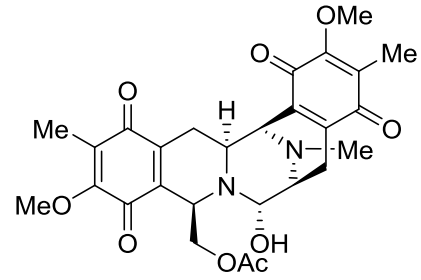
Concise total syntheses of (–)-jorunnamycin A and (–)-jorumycin enabled by asymmetric catalysis

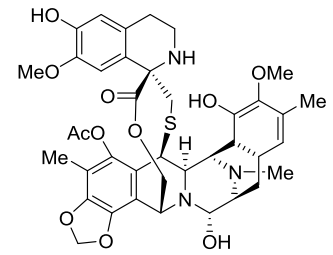
Eric R. Welin, Aurapat Ngamnithiporn, Max Klatte, Guillaume Lapointe, Gerit M. Pototschnig, Martina S. J. McDermott, Dylan Conklin, Christopher D. Gilmore, Pamela M. Tadross, Christopher K. Haley, Kenji Negoro,Emil Glibstrup, Christian U. Grünanger, Kevin M. Allan, Scott C. Virgil,Dennis J. Slamon, Brian M. Stoltz.

Science, **2019***, 363,* 270-275.

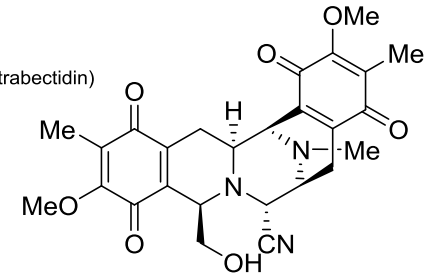
- In Jorumycin and Jorunnamycin A, a central pro-iminium serves as an alkylating agent *in vivo*, resulting in covalent modification of DNA in a process that ultimately leads to cell death.
- The quinone rings are rapidly reduced in cells to their hydroquinone oxidation states. These highly electron rich functional groups are key components in the biosynthetic pathways.
- Congener ecteinascidin 743 is an approved anticancer drug.



Jorumycin



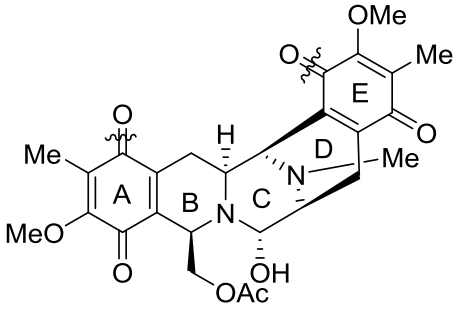
Ecteinascidin 743 (Yondelis, trabectidin)



Jorunnamycin A

Presented by Yuanzhe Zhang, Liu group.

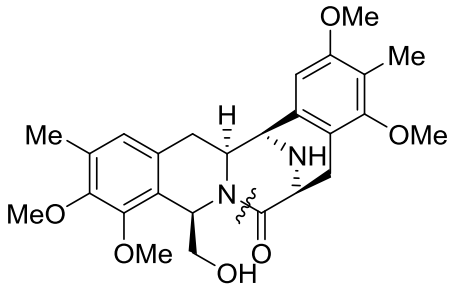
Retro-synthetic Route



1

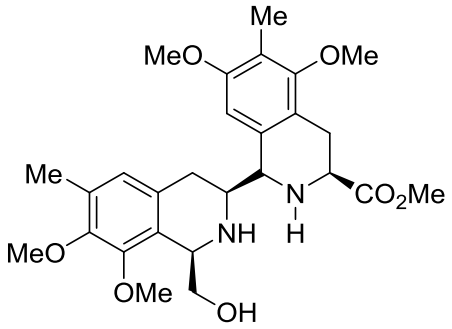
Jorumycin

oxygenation



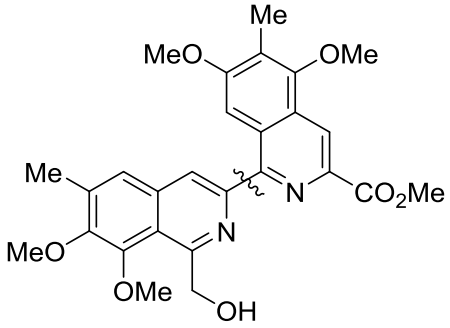
6

lactam formation



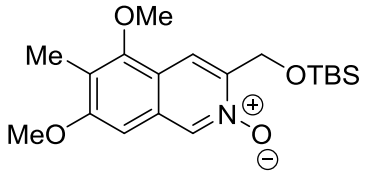
7

dehydrogenation



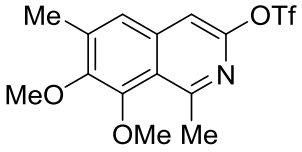
8

Fagnou couplnig

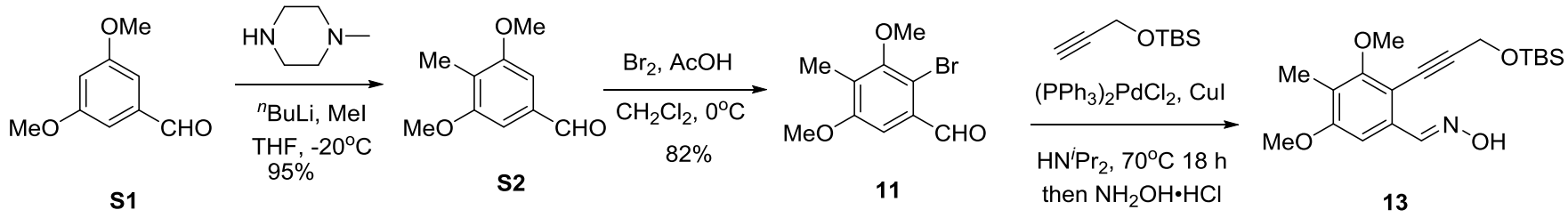


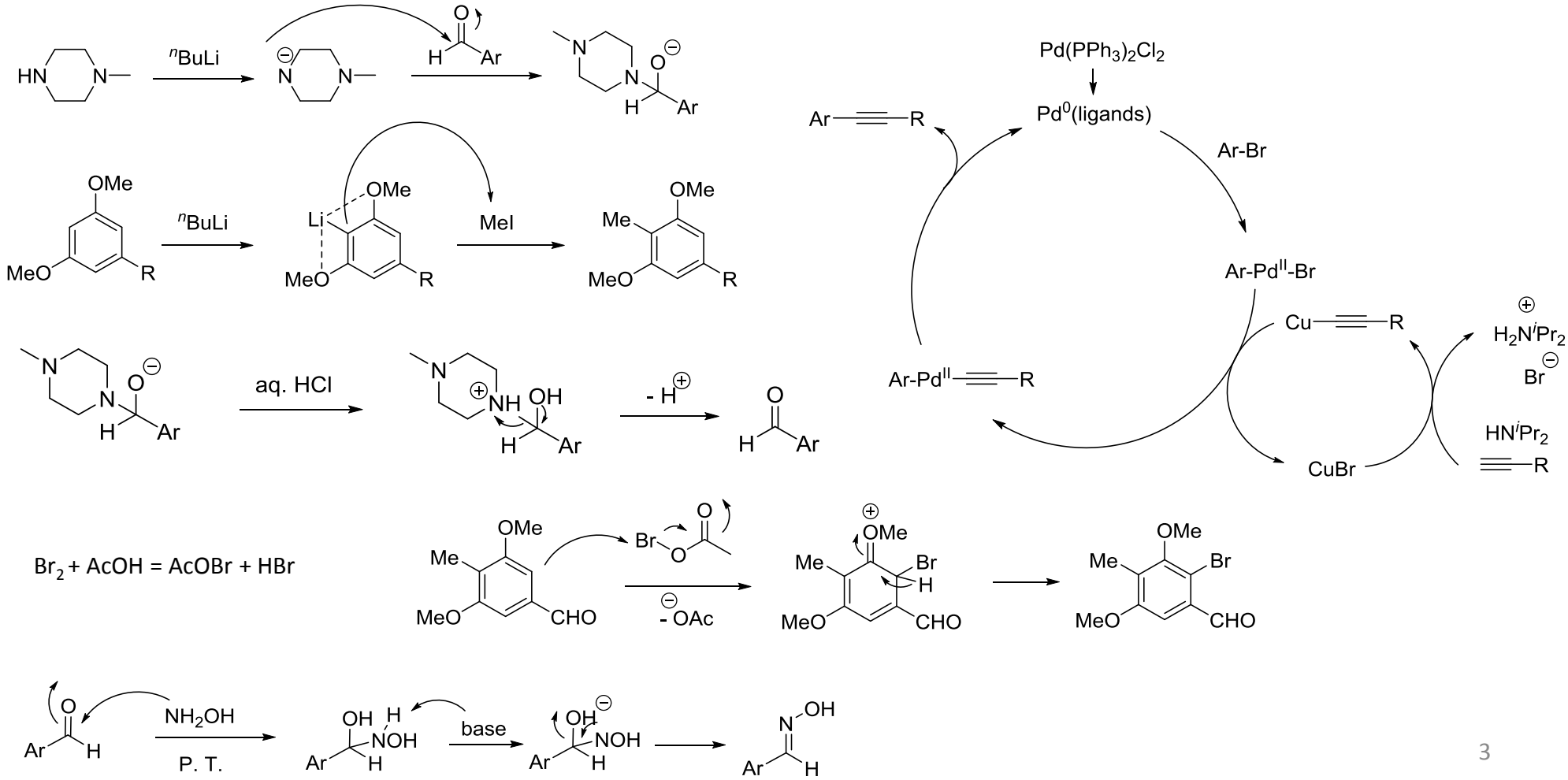
9

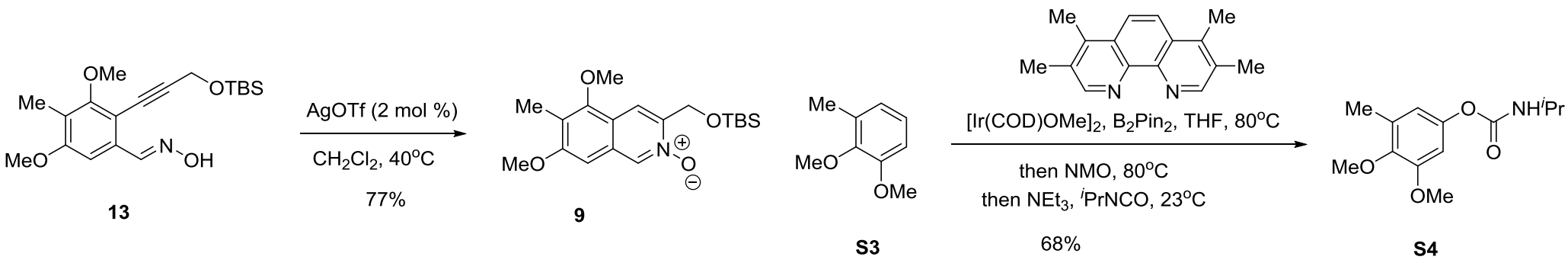
+

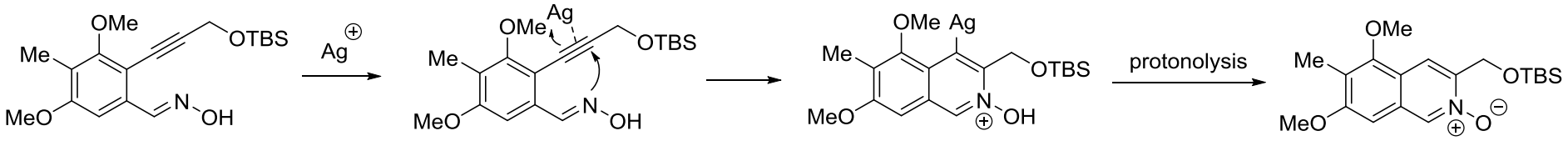


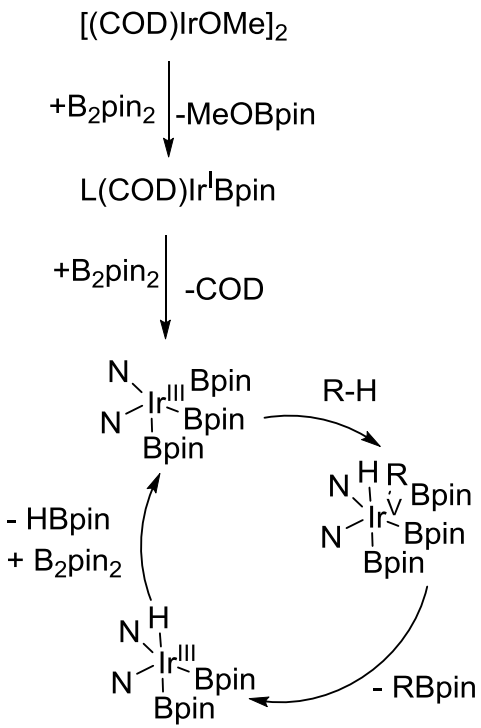
10

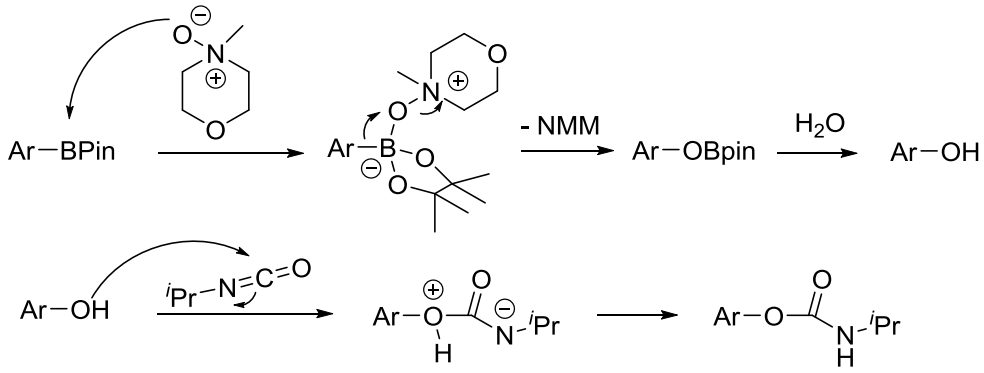

OMe
MeO
CHO
S1
HN
N
nBuLi, MeI
THF, -20°C
95%
Me
S2
Br2, AcOH
CH2Cl2, 0°C
82%
Br
11
OTBS
(PPh3)2PdCl2, CuI
HNiPr2, 70°C 18 h
then NH2OH•HCl
N
OH
13

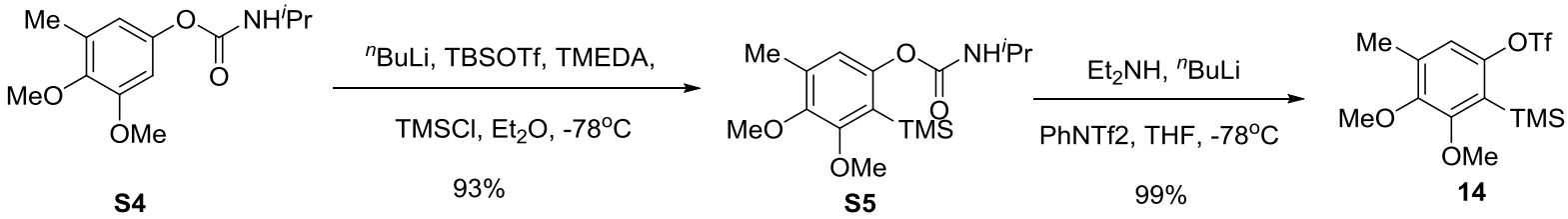

nBuLi
H
Ar
aq. HCl
- H
Li
MeI
R
Pd(PPh3)2Cl2
Pd0(ligands)
Ar-Br
Ar-PdII-Br
Ar-PdII
Cu
CuBr
H2NiPr2
Br
HNiPr2
Br2 + AcOH = AcOBr + HBr
- OAc
NH2OH
P. T.
base
NOH

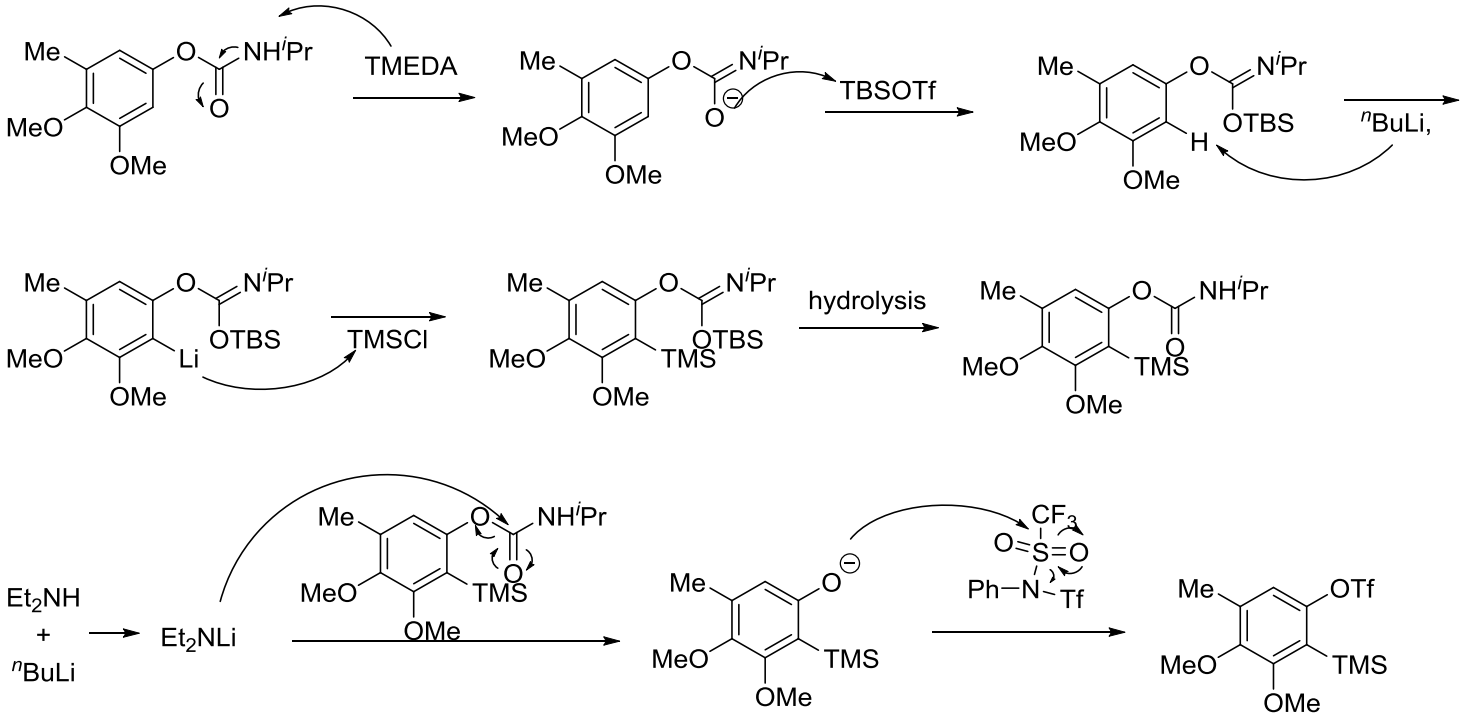

OMe
Me
OTBS
MeO
N
OH
13
AgOTf (2 mol %)
CH2Cl2, 40°C
77%
9
S3
Me
Me
Me
Me
N
N
[Ir(COD)OMe]2, B2Pin2, THF, 80°C
then NMO, 80°C
then NEt3, iPrNCO, 23°C
68%
O
NHiPr
O
S4

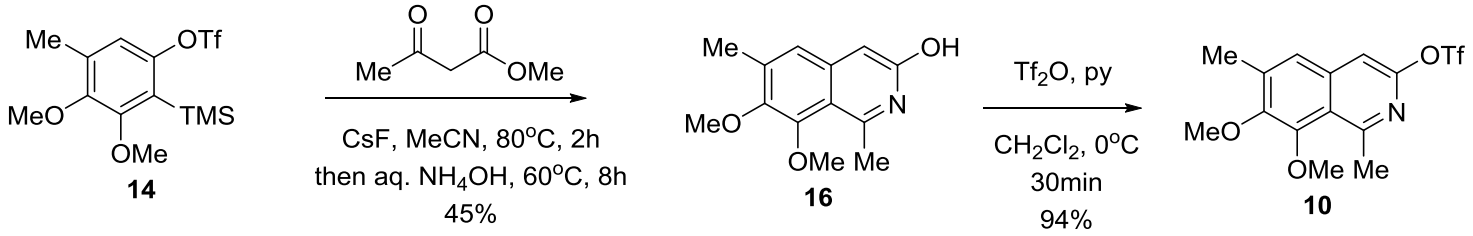

OMe
Me
OTBS
MeO
N
OH
Ag
protonolysis

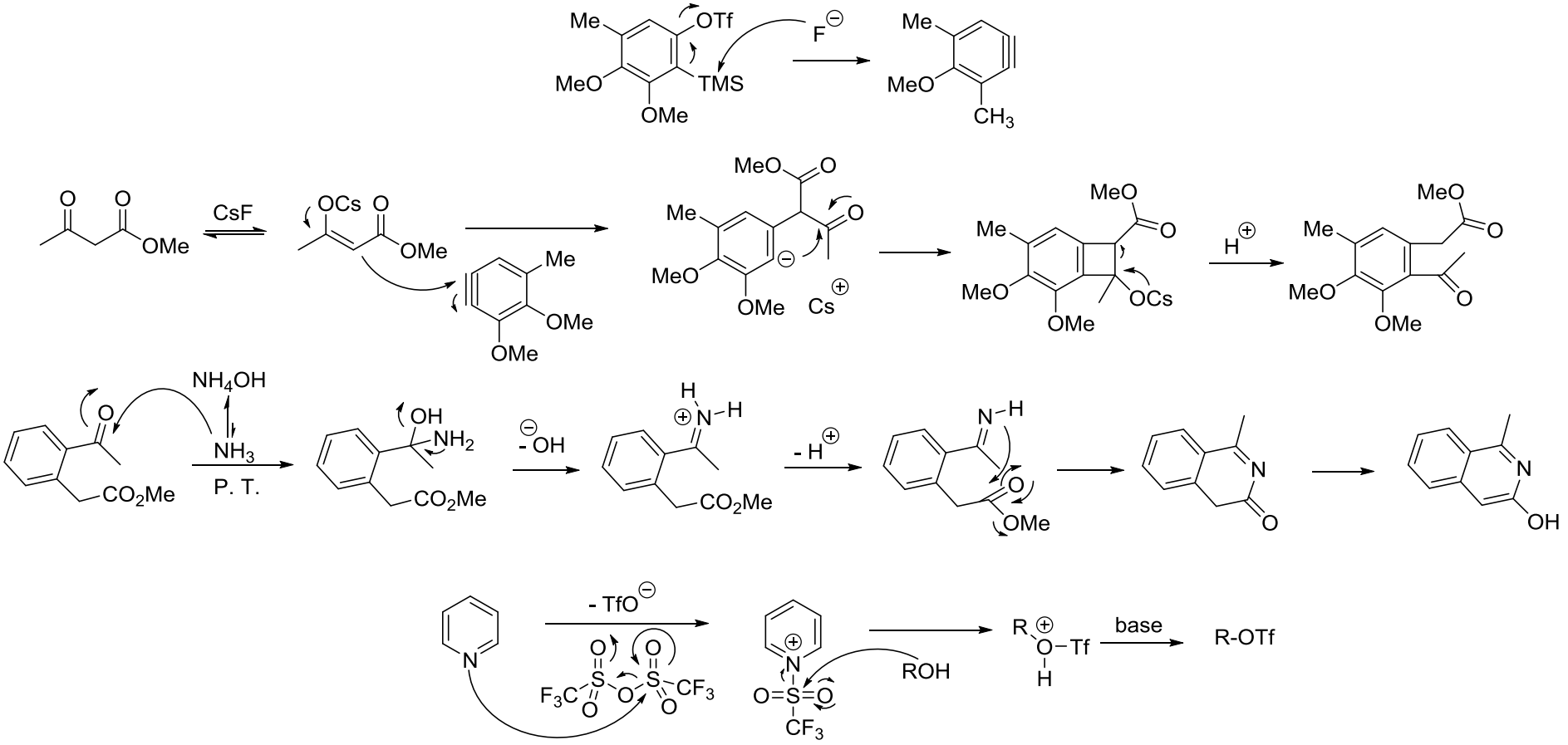

[(COD)IrOMe]2
+B2pin2
-MeOBpin
L(COD)IrIBpin
+B2pin2
-COD
N
IrIII
Bpin
R-H
IrV
H
R
- HBpin
+ B2pin2
- RBpin

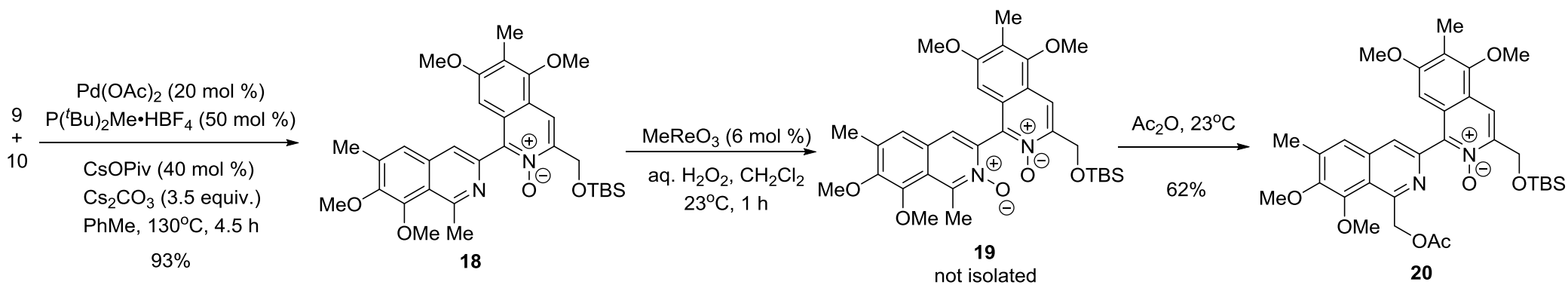

Ar—BPin
Ar—B
O
N
- NMM
Ar—OBpin
H2O
Ar—OH
Ar—OH
iPr—N=C=O
Ar—O
H
N—iPr
Ar—O
N—iPr
H

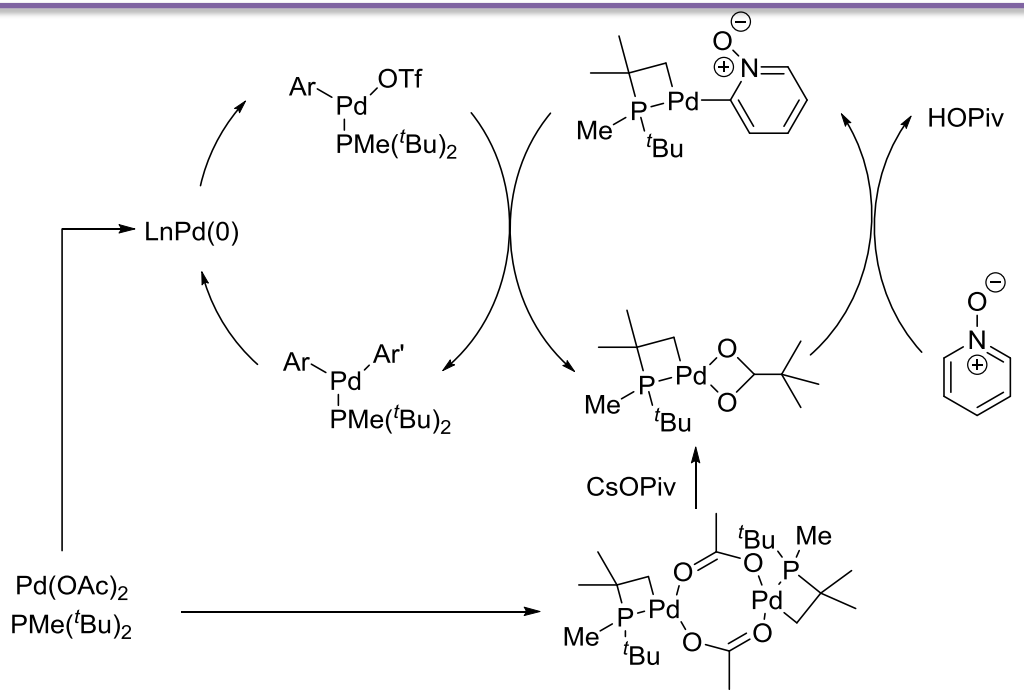

Me
MeO
OMe
O
NH^{i}Pr
O
S4
^{n}BuLi, TBSOTf, TMEDA,
TMSCl, Et$_2$O, -78^{o}C
93%
TMS
S5
Et$_2$NH, ^{n}BuLi
PhNTf2, THF, -78^{o}C
99%
OTf
14

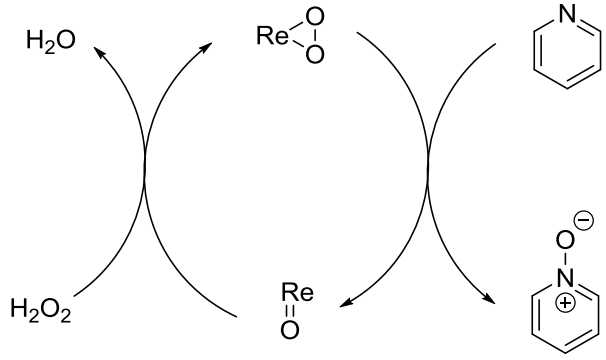

TMEDA
TBSOTf
OTBS
H
^{n}BuLi,
Li
TMSCl
hydrolysis
TMS
Et$_2$NH
+
^{n}BuLi
Et$_2$NLi
CF$_3$
Ph—N—Tf
OTf

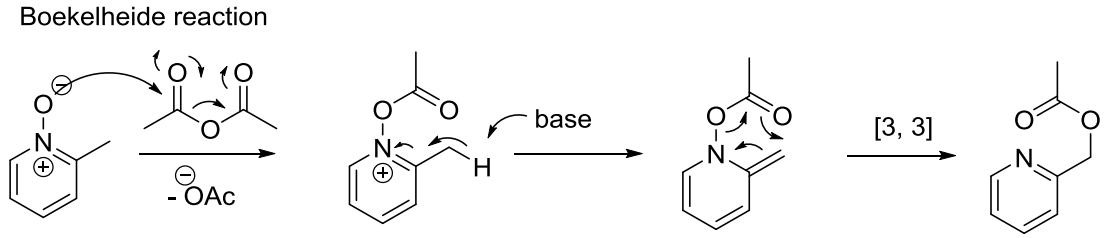

Me
OTf
MeO
TMS
OMe
14
Me
OMe
CsF, MeCN, 80°C, 2h
then aq. NH4OH, 60°C, 8h
45%
Me
OH
MeO
N
OMe Me
16
Tf2O, py
CH2Cl2, 0°C
30min
94%
Me
OTf
MeO
N
OMe Me
10

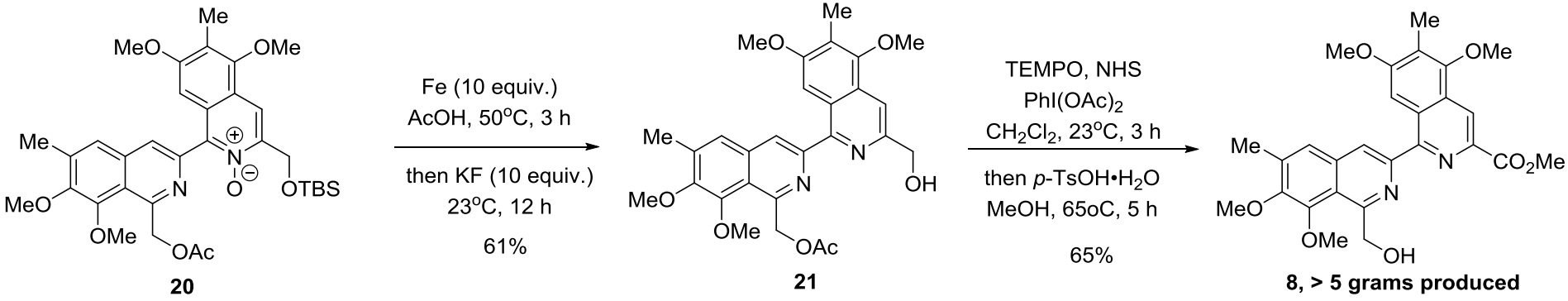

Me
OTf
MeO
TMS
OMe
F⊖
Me
MeO
CH3
CsF
OMe
OCs
O
Me
OMe
OMe
MeO
Me
MeO
OMe
Cs⊕
OCs
H⊕
NH4OH
NH3
P. T.
CO2Me
OH
NH2
⊖OH
H
N
H
⊕
CO2Me
- H⊕
OMe
N
O
OH
- TfO⊖
F3C
S
CF3
ROH
R
O
Tf
H
base
R-OTf


9
+
10
Pd(OAc)2 (20 mol %)
P(tBu)2Me•HBF4 (50 mol %)
CsOPiv (40 mol %)
Cs2CO3 (3.5 equiv.)
PhMe, 130°C, 4.5 h
93%
18
MeReO3 (6 mol %)
aq. H2O2, CH2Cl2
23°C, 1 h
19
not isolated
Ac2O, 23°C
62%
20

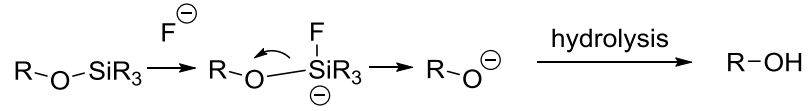

LnPd(0)
Pd(OAc)2
PMe(tBu)2
CsOPiv
HOPiv

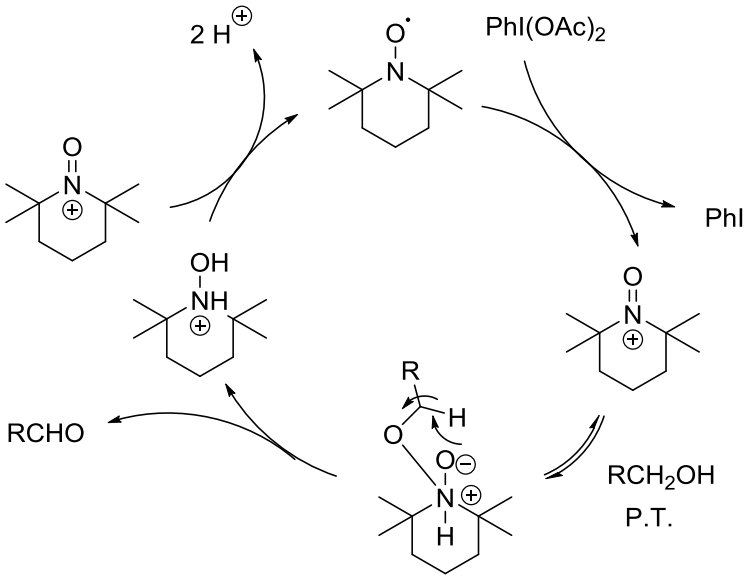

H2O
H2O2
Re
O

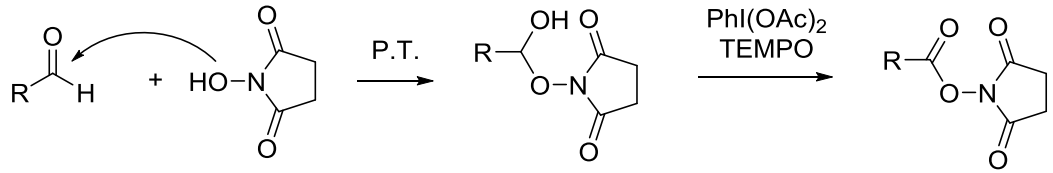

Boekelheide reaction
- OAc
base
[3, 3]

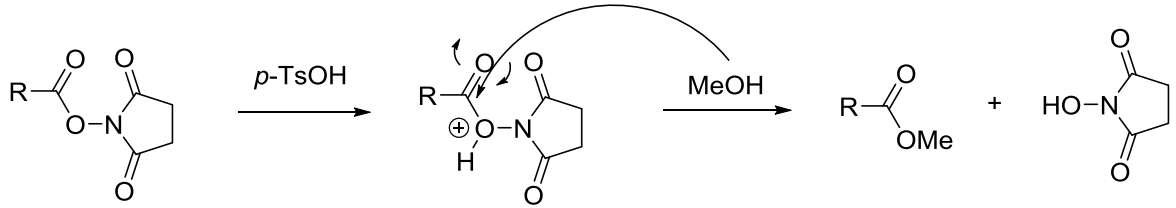


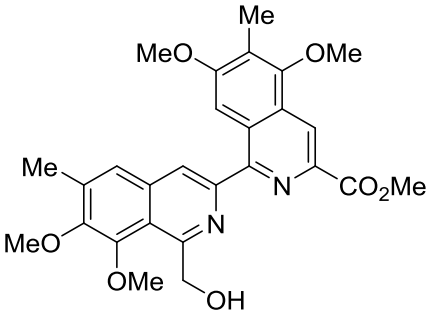
$$Fe + 2AcOH = Fe(OAc)_2 + H_2$$





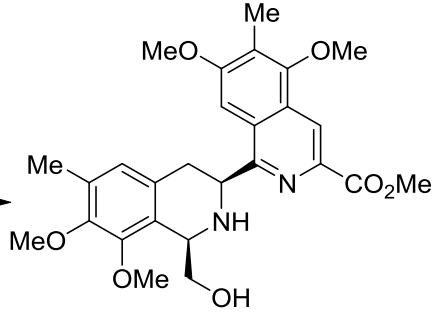




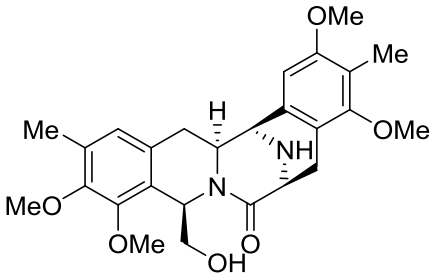


8

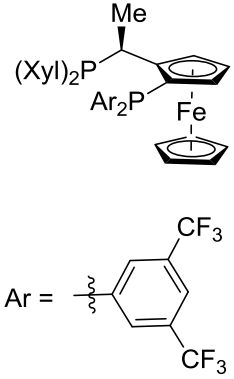
H_2 (60 bar), $[Ir(COD)Cl]_2$
TBAI, L*
temp., 18 h

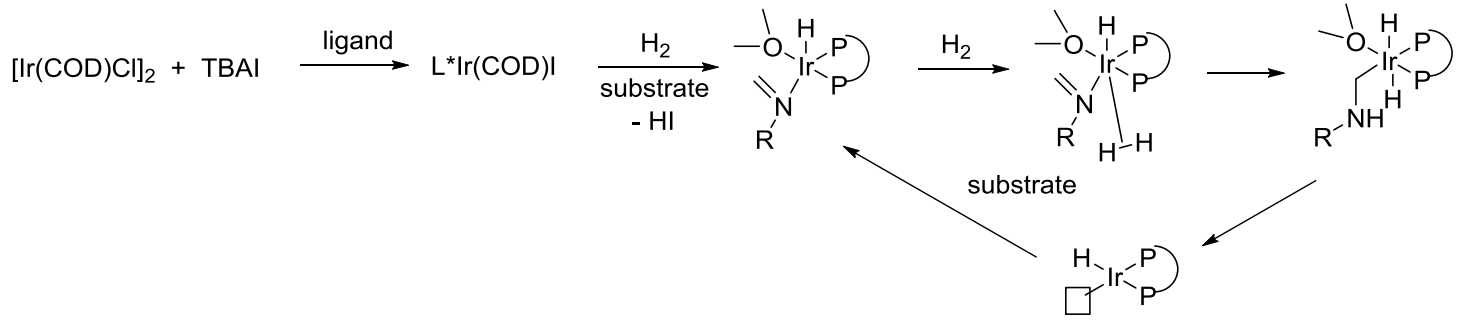


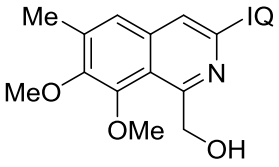
22



6

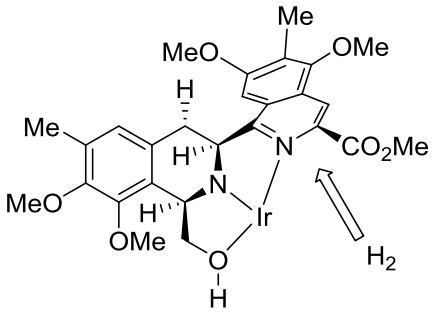


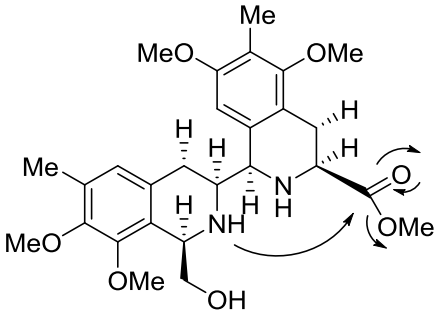




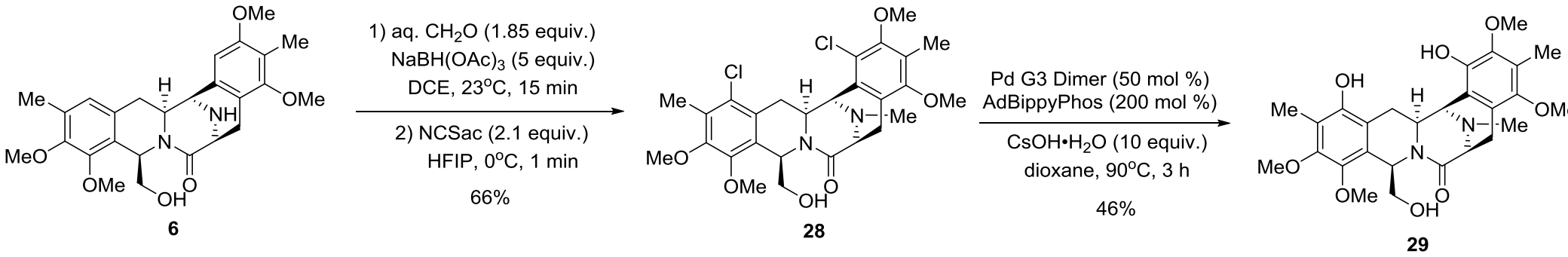
8

Ir/H_2

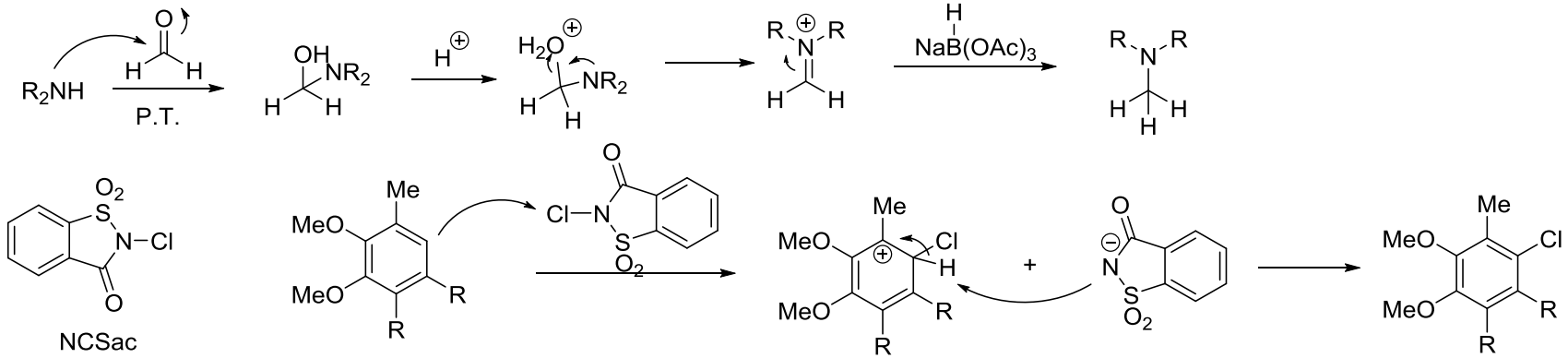


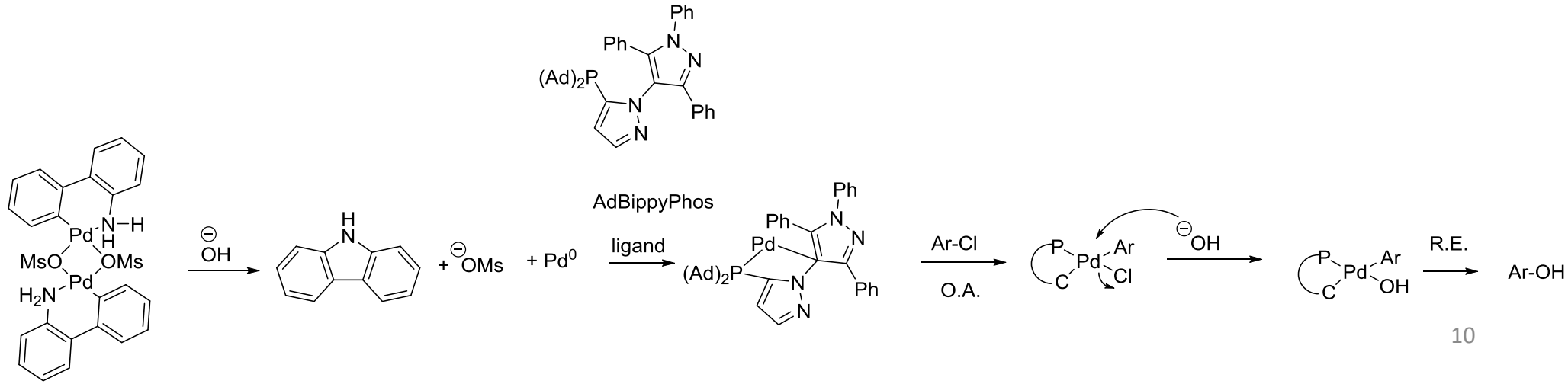


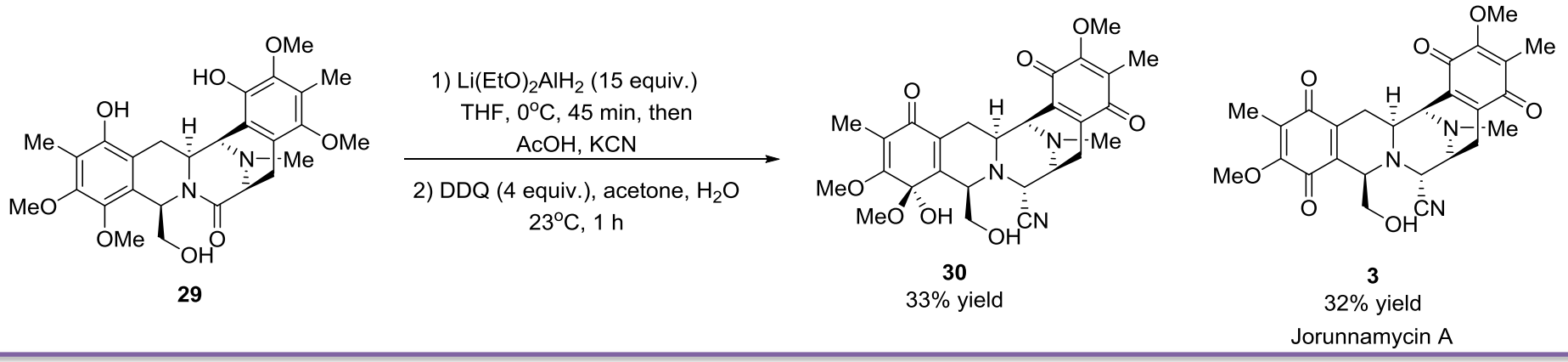
6


1) aq. CH2O (1.85 equiv.)
NaBH(OAc)3 (5 equiv.)
DCE, 23°C, 15 min
2) NCSac (2.1 equiv.)
HFIP, 0°C, 1 min
66%
Pd G3 Dimer (50 mol %)
AdBippyPhos (200 mol %)
CsOH•H2O (10 equiv.)
dioxane, 90°C, 3 h
46%

6 **28** **29**


R2NH
P.T.
H2O
NaB(OAc)3
NCSac

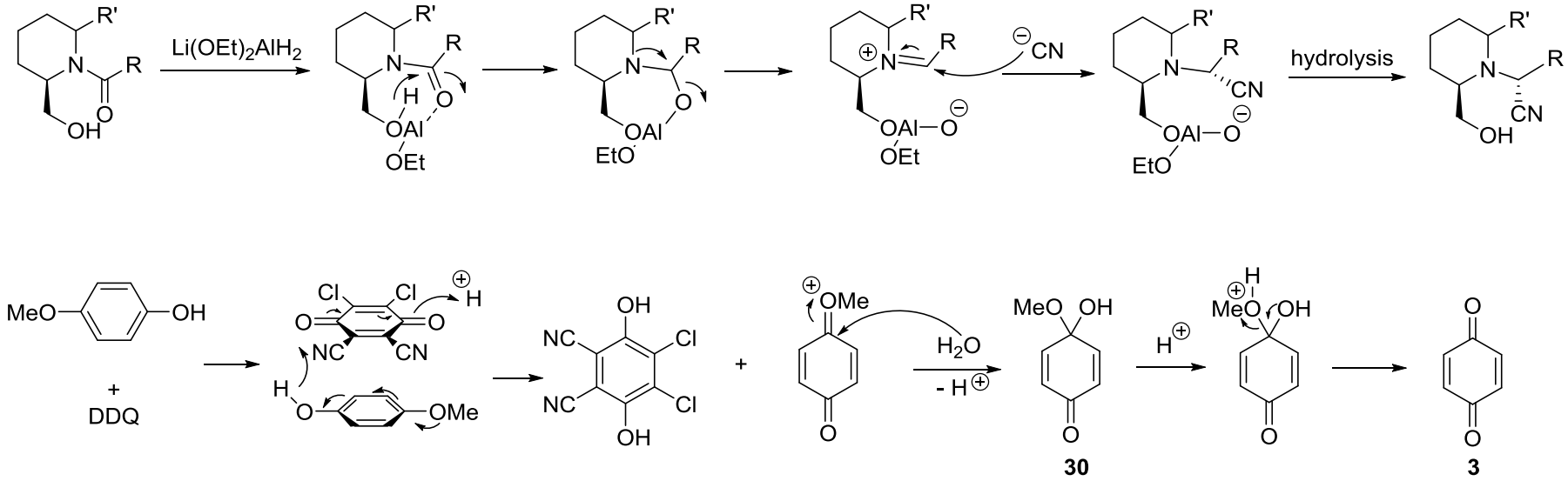

AdBippyPhos
ligand
+ OMs
+ Pd0
Ar-Cl
O.A.
R.E.
Ar-OH

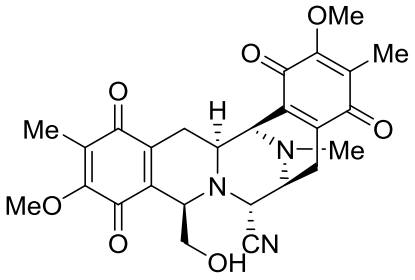


29

30
33% yield

3
32% yield
Jorunnamycin A



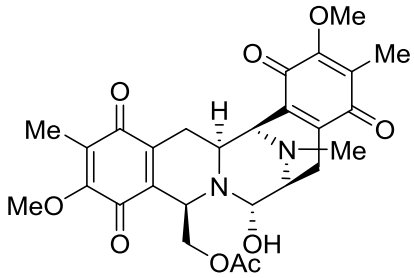


3

Jorunnamycin A

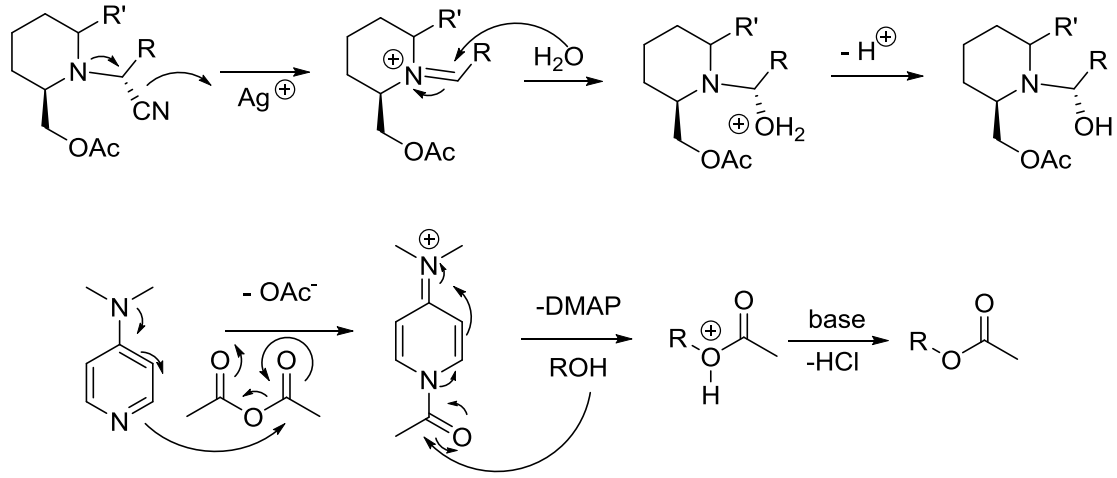
Ac_2O (3 equiv.)
DMAP (3 equiv.), MeCN
then aq. $AgNO_3$ (25 equiv.)
45°C, 30 min

68%



1

Jorumycin



Jorunnamycin A 15 steps and Jorumycin 16 steps