Evolution of a Strategy for the Enantioselective Synthesis of (−)-Cajanusine

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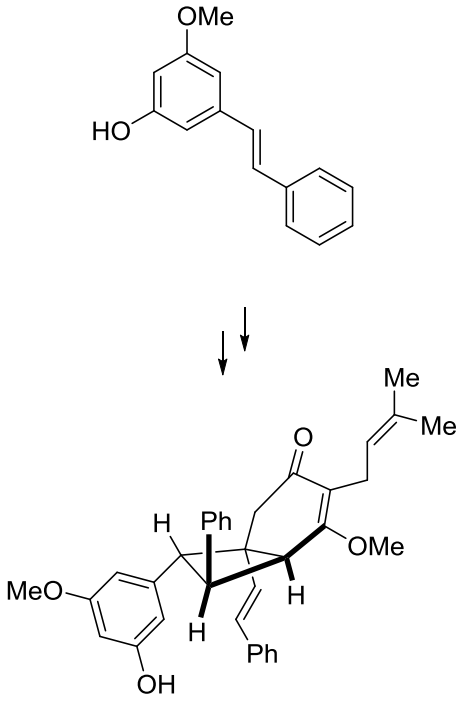
The stilbenoid oligomers constitute a broad family of natural products.

From biosynthetic aspect, most stilbenoid oligomers are synthesized from stilbenoid resveratrol via a radical-mediated cyclization, usually leading to a five member ring or greater. The more strained cyclobutane stilbenoid dimers are also known.

(+/-)-Cajanusine were isolated from leaves of *Cajanus Cajan* in 2014 in China with a cyclobutyl ring, which is presumably biosynthesized via a formal [2+2] cycloaddition.

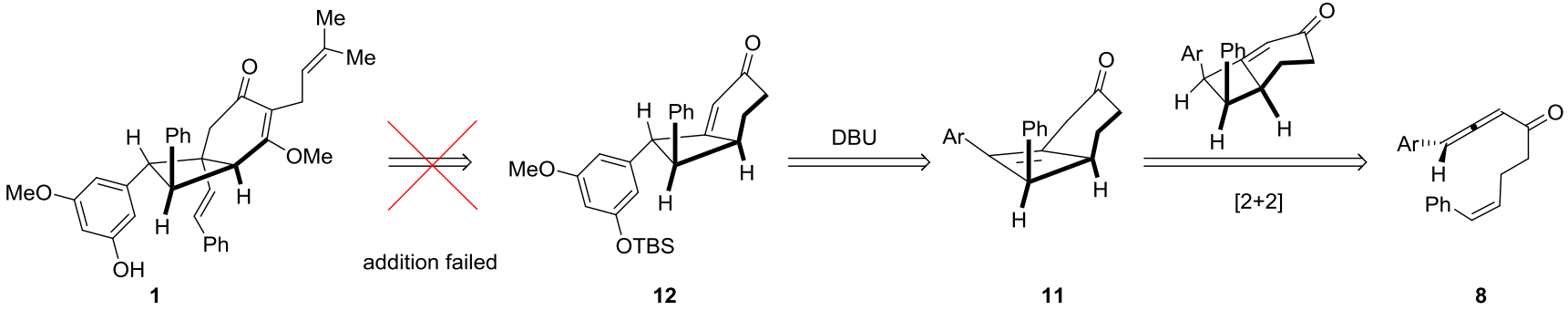


(-)-cajanusine

Presented by Yuanzhe Zhang, Liu group.

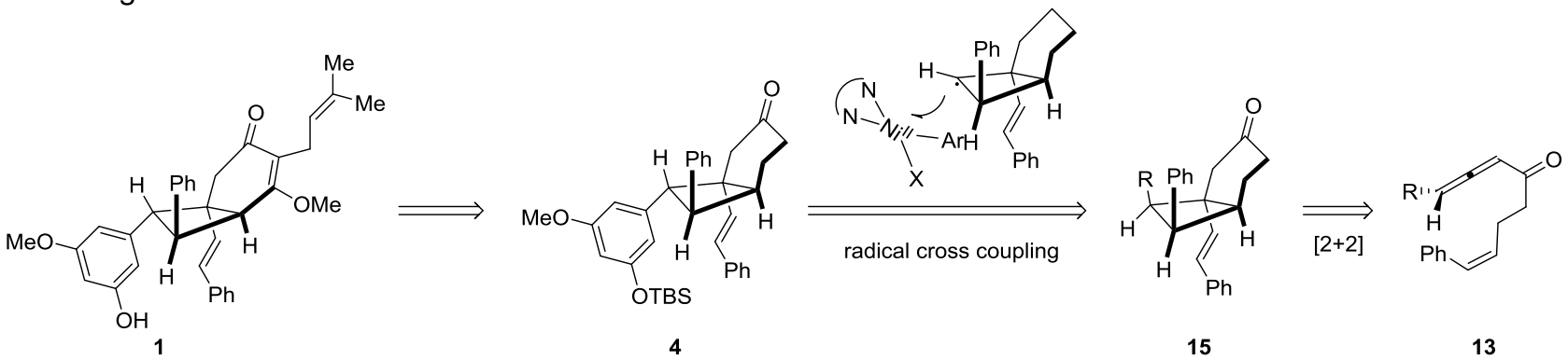
retro-synthetic route

First generation:

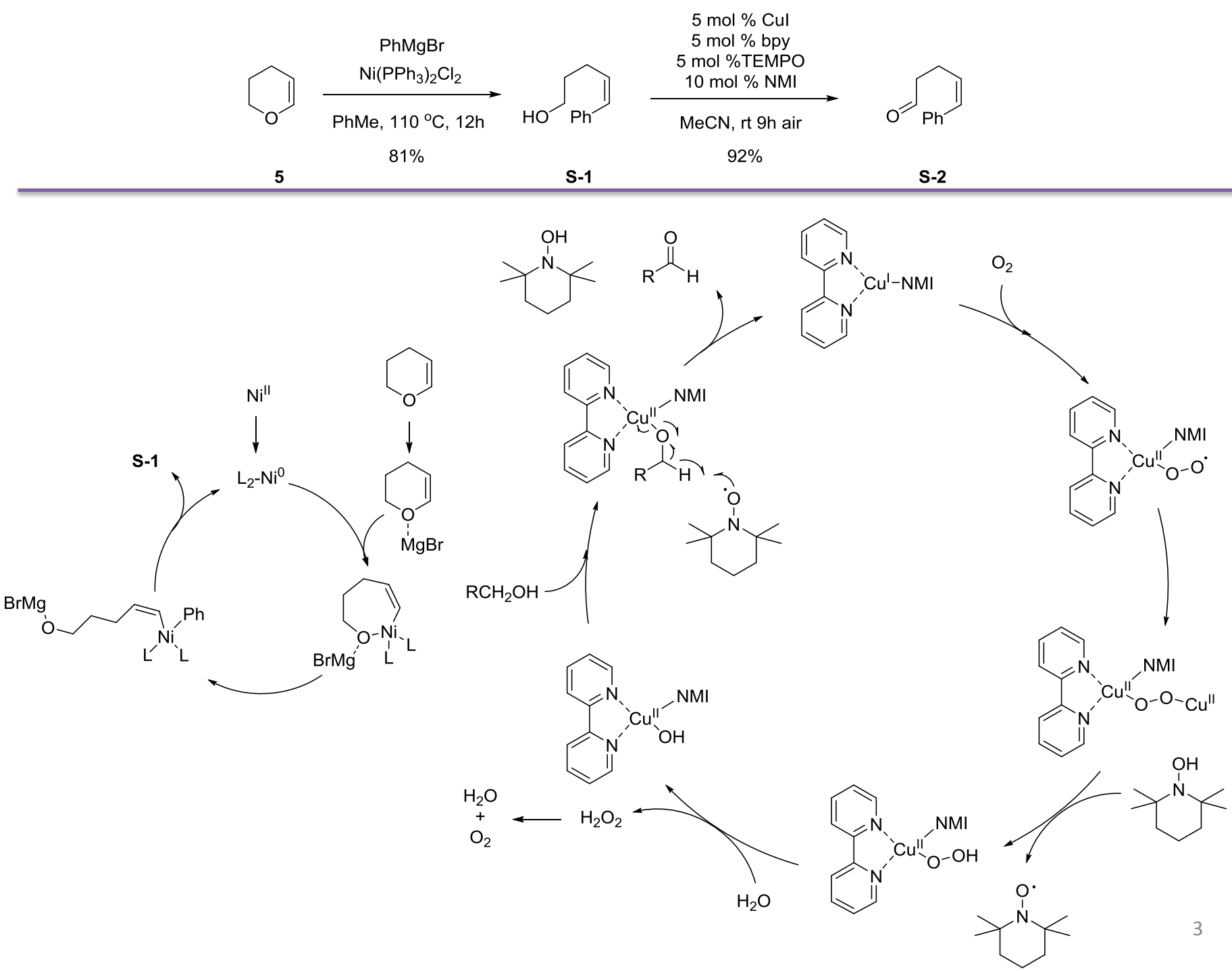


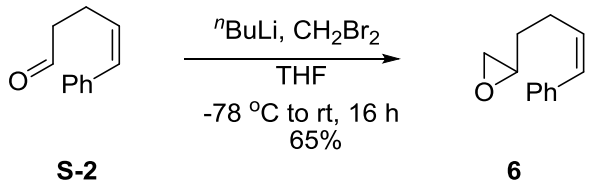
1 **12** **11** **8**

Second generation:

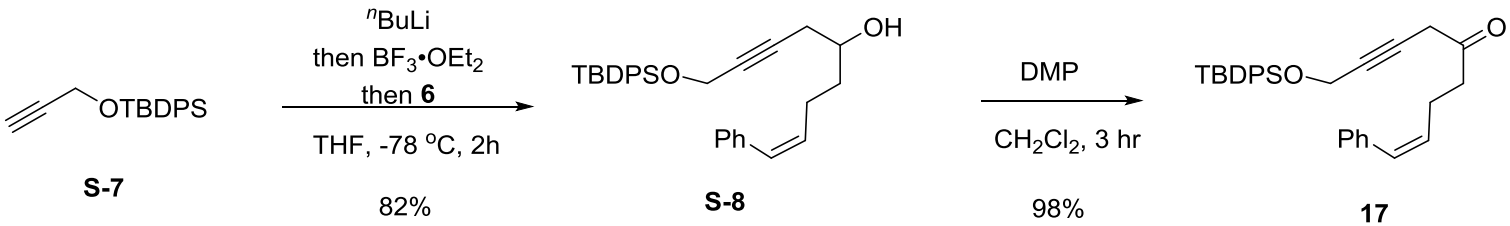


1 **4** **15** **13**

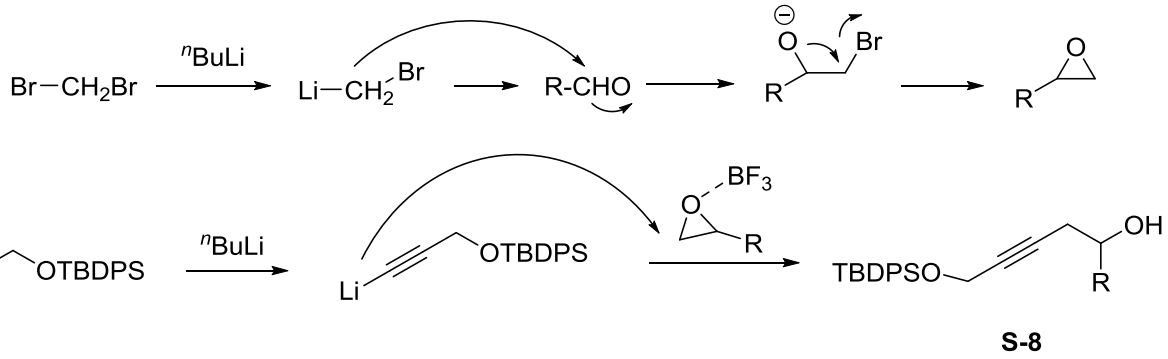

PhMgBr
Ni(PPh3)2Cl2
PhMe, 110 °C, 12h
81%
5
S-1
5 mol % CuI
5 mol % bpy
5 mol %TEMPO
10 mol % NMI
MeCN, rt 9h air
92%
S-2
Ni^II
L2-Ni^0
S-1
MgBr
BrMg
Ph
Ni
L
RCH2OH
H2O2
H2O
+
O2
Cu^I–NMI
Cu^II
NMI
OH
O2
H2O



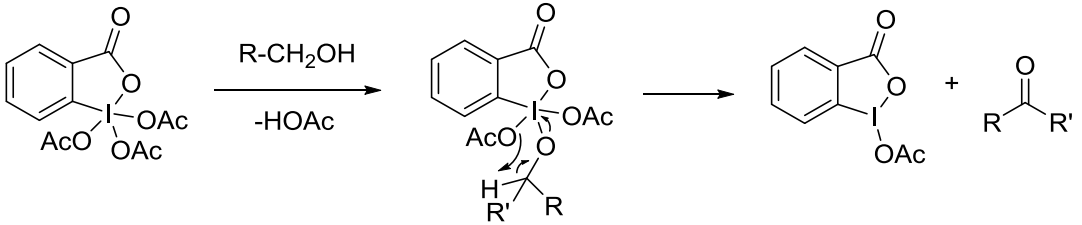
S-2 **6**

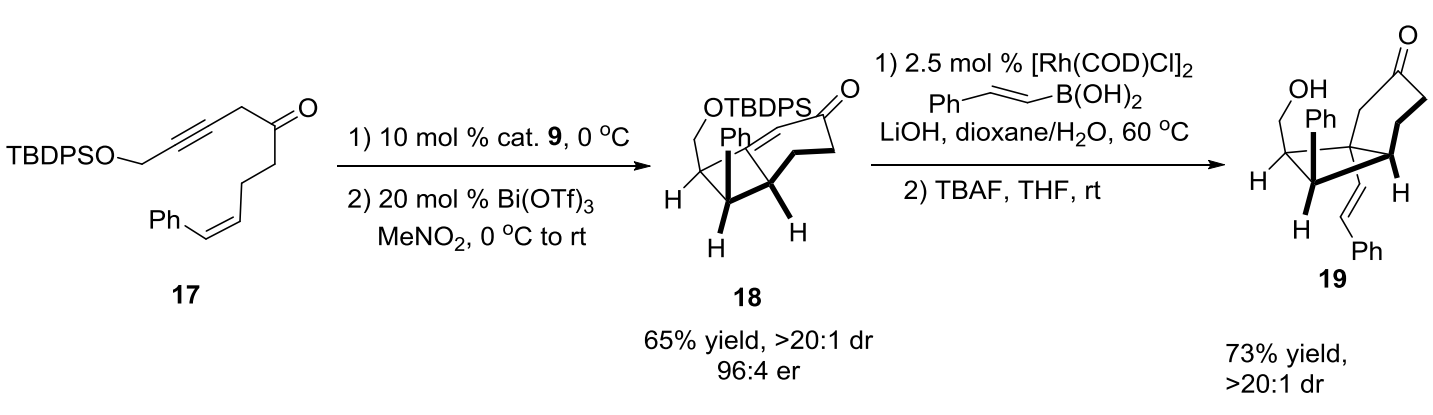


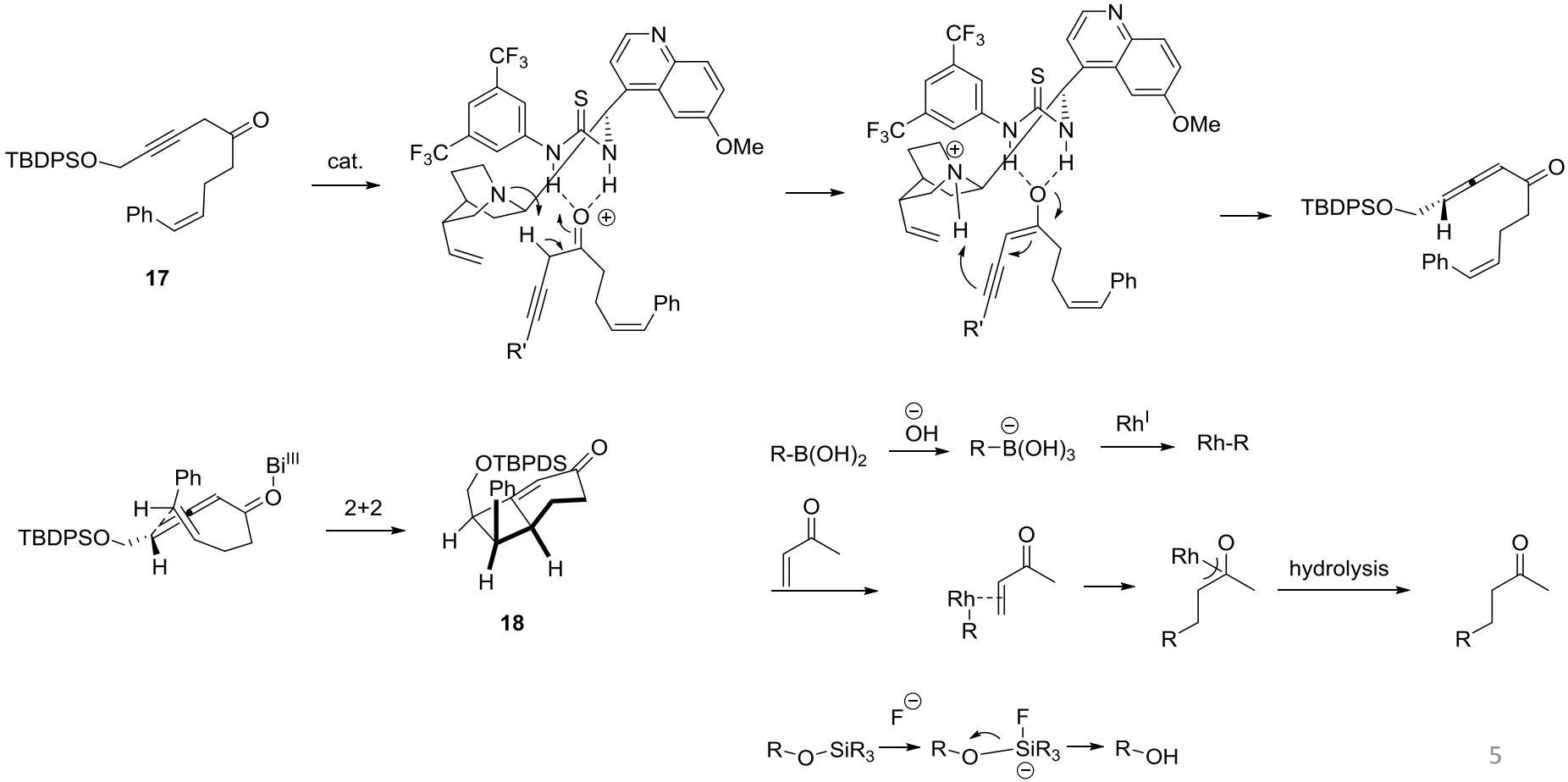
S-7 **S-8** **17**

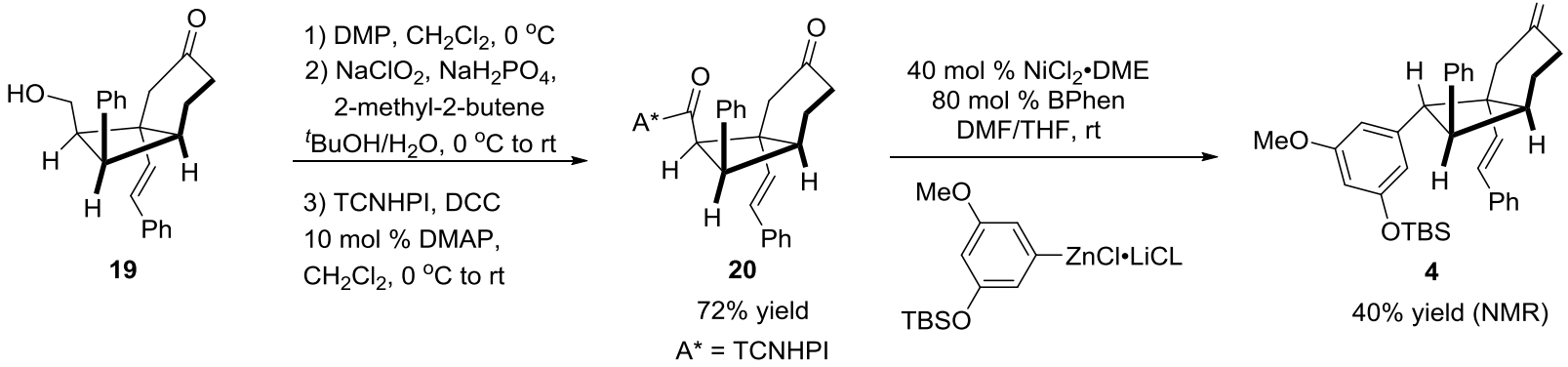


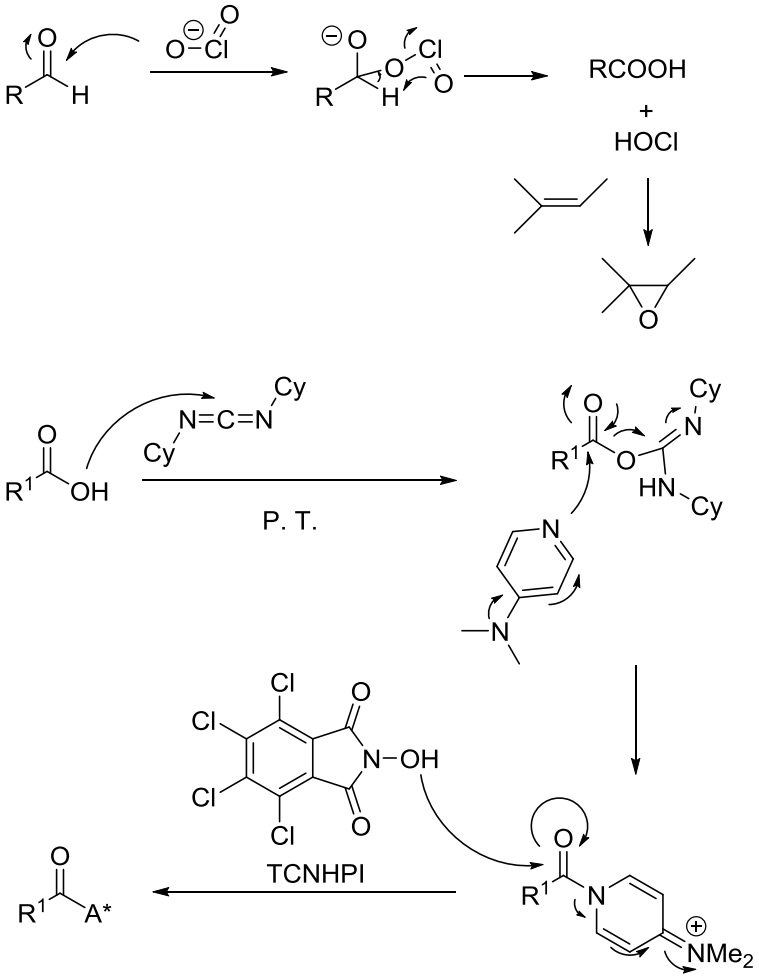
S-8

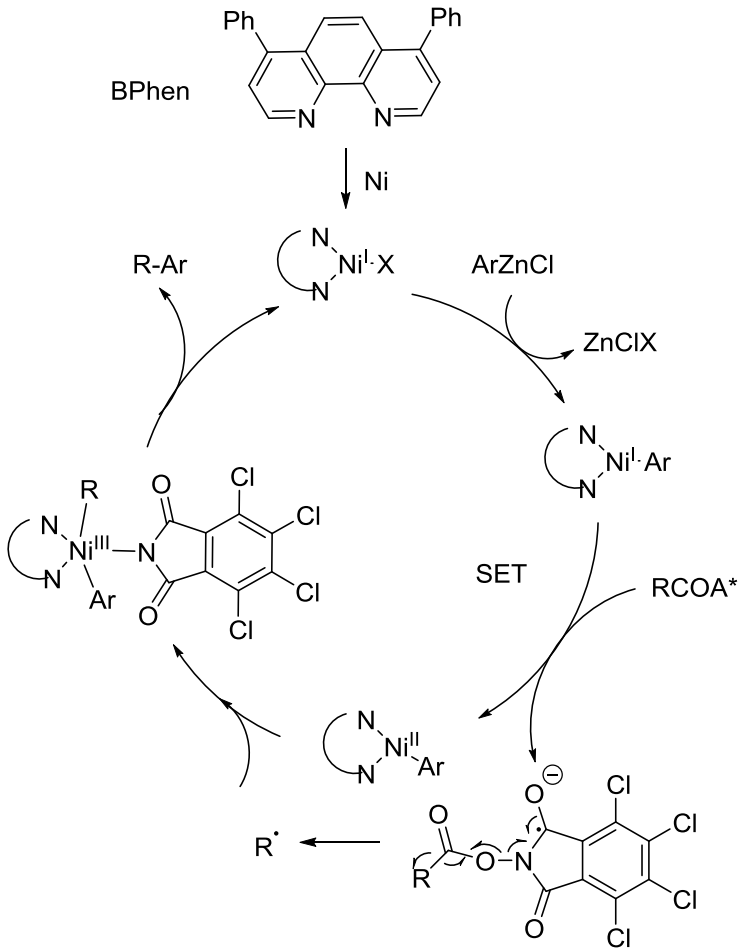


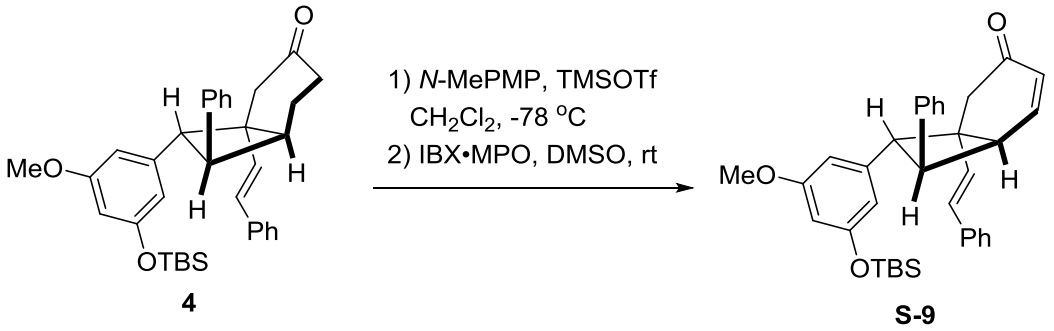

TBDPSO
Ph
17
1) 10 mol % cat. 9, 0 °C
2) 20 mol % Bi(OTf)3
MeNO2, 0 °C to rt
OTBDPS
Ph
18
65% yield, >20:1 dr
96:4 er
1) 2.5 mol % [Rh(COD)Cl]2
Ph
B(OH)2
LiOH, dioxane/H2O, 60 °C
2) TBAF, THF, rt
OH
19
73% yield,
>20:1 dr
CF3
F3C
S
N
H
MeO
9

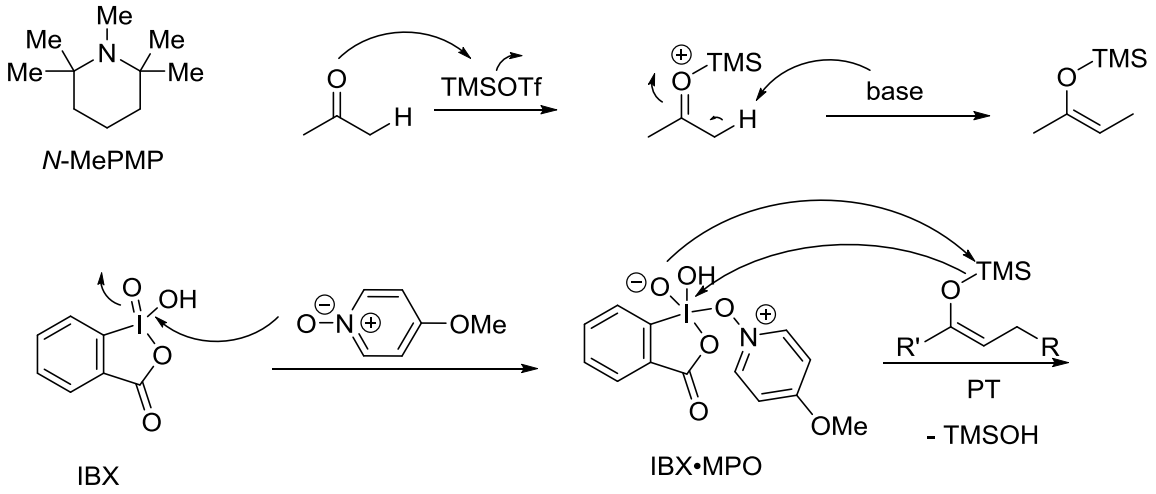

TBDPSO
Ph
17
cat.
CF3
F3C
S
N
H
OMe
R'
TBDPSO
Ph
Bi III
2+2
OTBPDS
18
R-B(OH)2
OH
R−B(OH)3
Rh I
Rh-R
Rh
R
hydrolysis
F
R−O−SiR3
R−OH

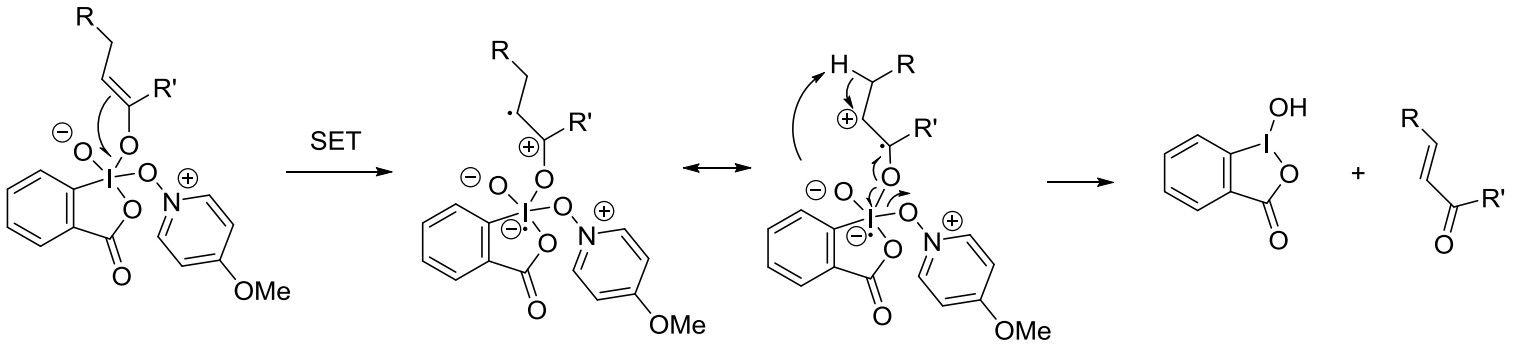

1) DMP, CH_2Cl_2, 0 °C
2) $NaClO_2$, NaH_2PO_4,
2-methyl-2-butene
$^tBuOH/H_2O$, 0 °C to rt
3) TCNHPI, DCC
10 mol % DMAP,
CH_2Cl_2, 0 °C to rt
40 mol % $NiCl_2$•DME
80 mol % BPhen
DMF/THF, rt
ZnCl•LiCL
19
20
72% yield
A* = TCNHPI
4
40% yield (NMR)

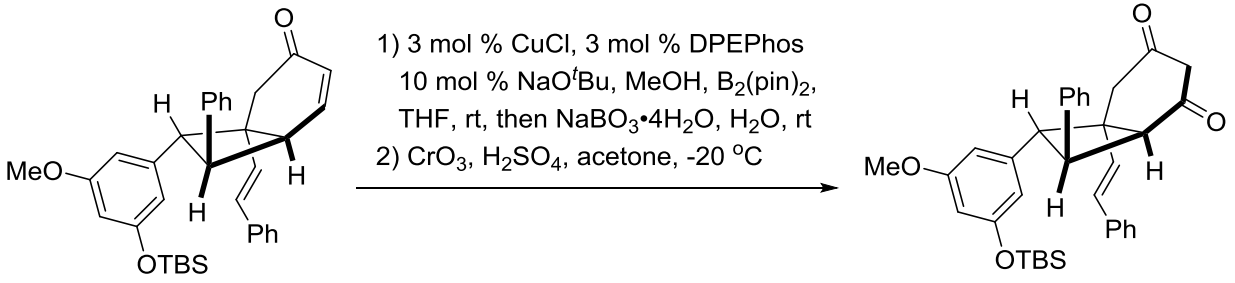

RCOOH
+
HOCl
P. T.
TCNHPI


BPhen
Ni
R-Ar
ArZnCl
ZnClX
SET
RCOA*
R•


1) N-MePMP, TMSOTf
CH2Cl2, -78 °C
2) IBX•MPO, DMSO, rt
MeO
OTBS
H
Ph
O
4
S-9

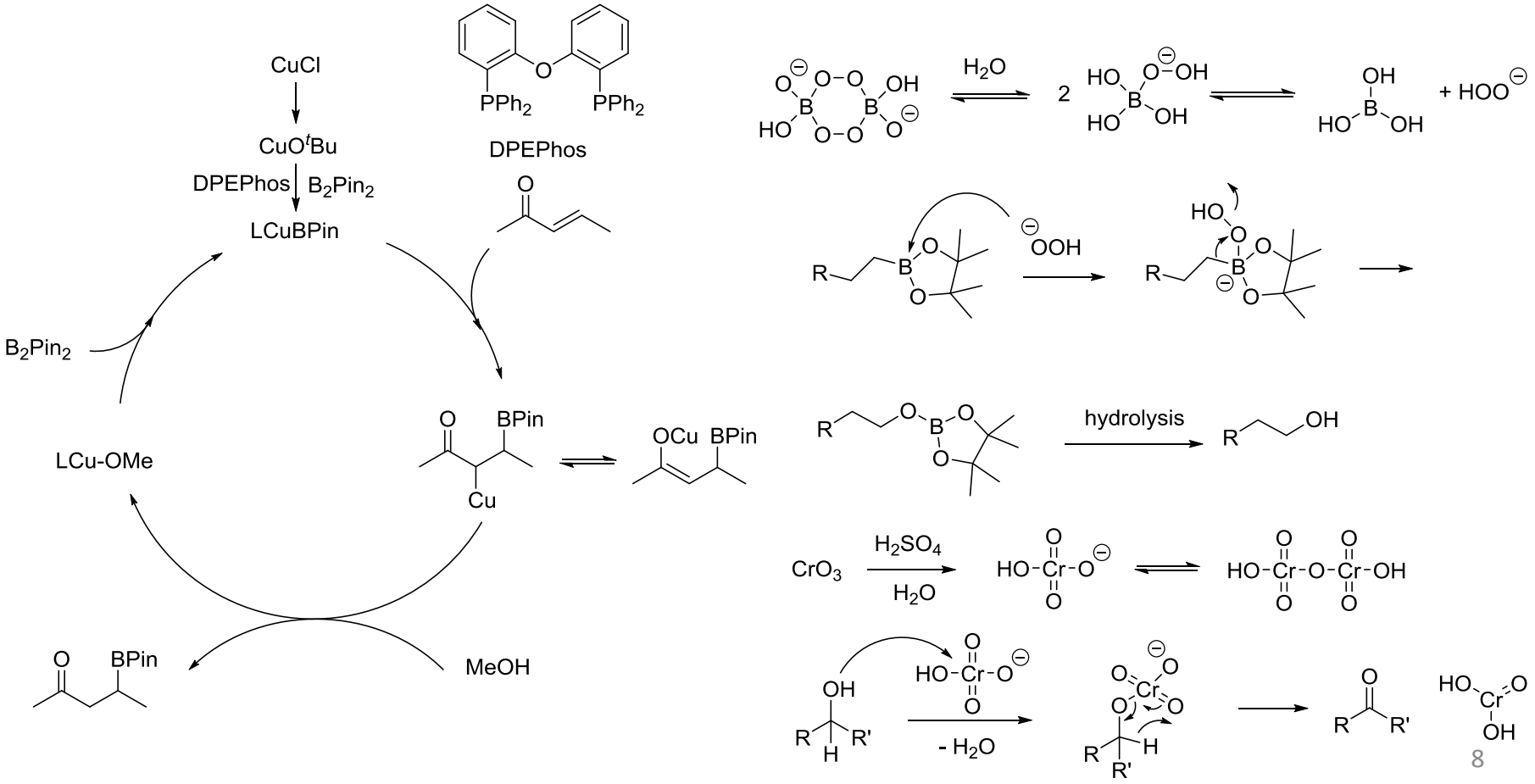

N-MePMP
TMSOTf
base
TMS
IBX
IBX•MPO
OMe
OH
PT
- TMSOH

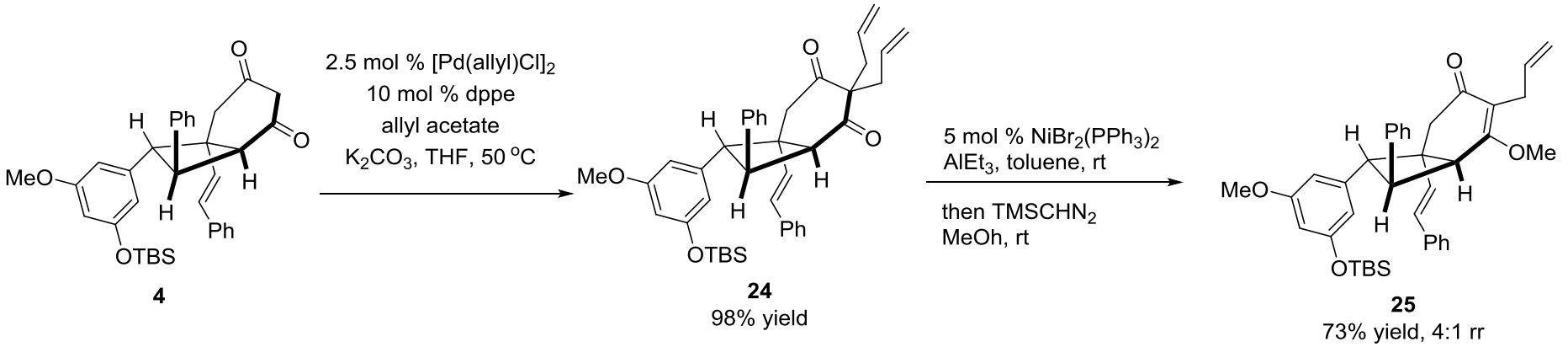

SET
R
R'
OMe

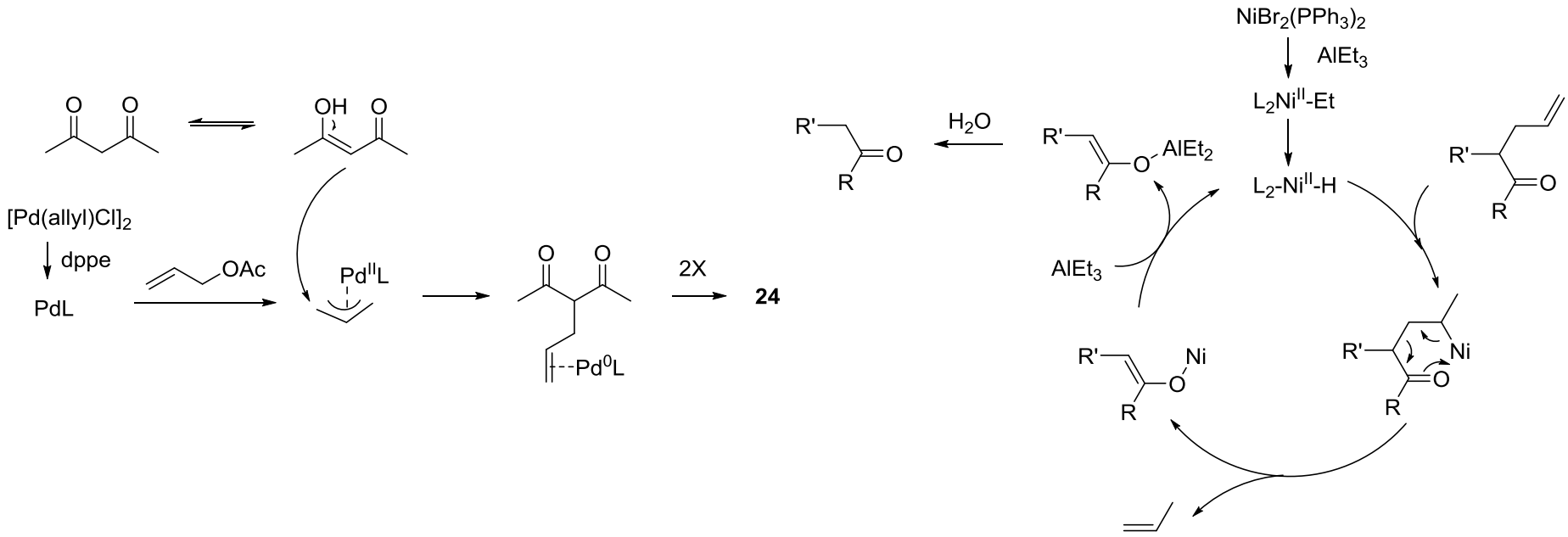


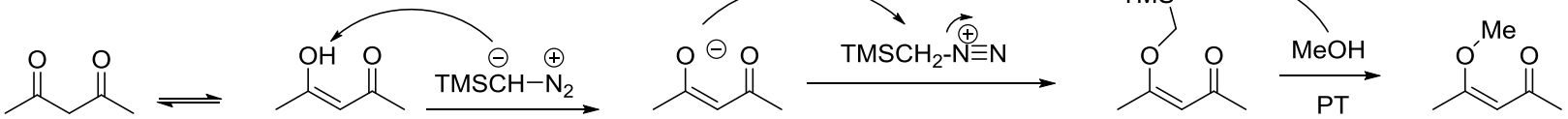
S-9 → **4**

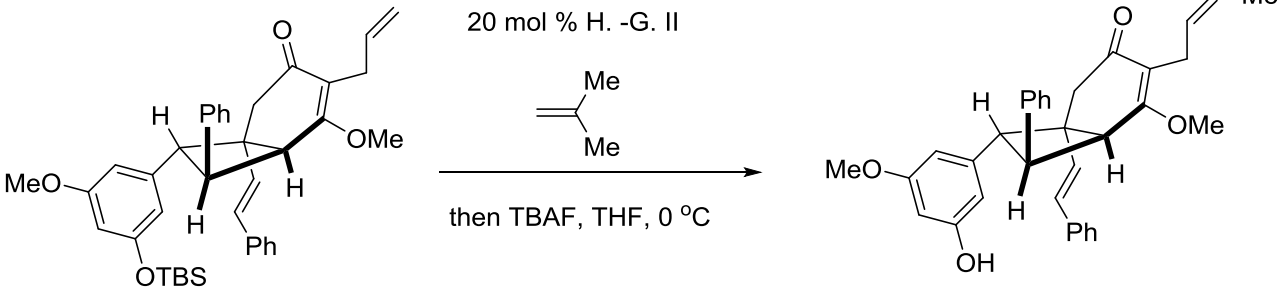
20% yield from **20**




2.5 mol % [Pd(allyl)Cl]2
10 mol % dppe
allyl acetate
K2CO3, THF, 50 °C
5 mol % NiBr2(PPh3)2
AlEt3, toluene, rt
then TMSCHN2
MeOh, rt
4
24
98% yield
25
73% yield, 4:1 rr

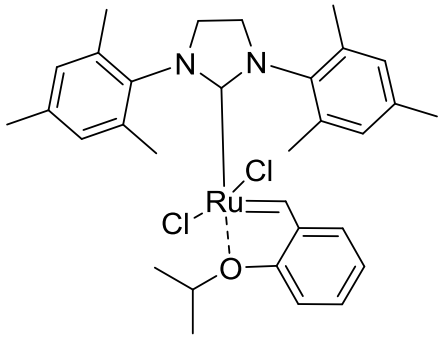

[Pd(allyl)Cl]2
dppe
PdL
OAc
Pd^II L
Pd^0 L
2X
24
NiBr2(PPh3)2
AlEt3
L2Ni^II-Et
L2-Ni^II-H
H2O
AlEt2
AlEt3


TMSCH–N2
TMSCH2-N≡N
TMS
MeOH
PT
Me

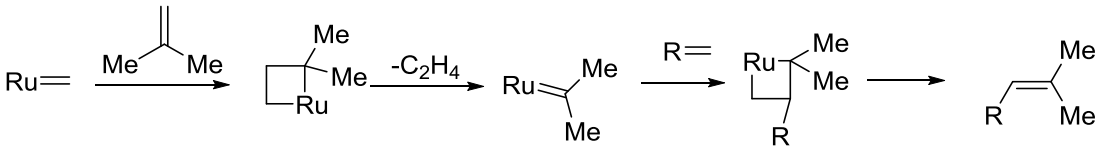


25

(-)-cajanusine **(1)**
82% yield, >100 mg prepared



H -G II



98 mg was prepared in one reaction