Total Synthesis Presentation

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Expedient Total Syntheses of Pladienolide-Derived Spliceosome Modulators

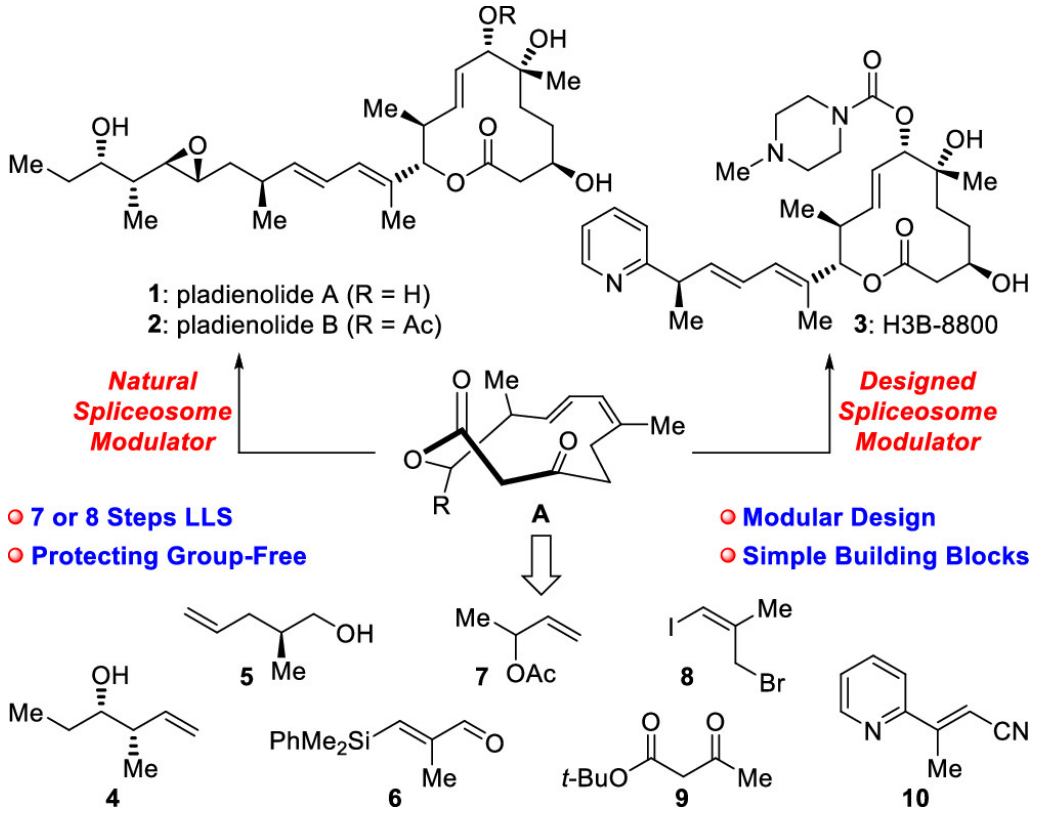
Derek Rhoades,* Arnold L. Rheingold, Bert W. O'Malley,* and Jin Wang*

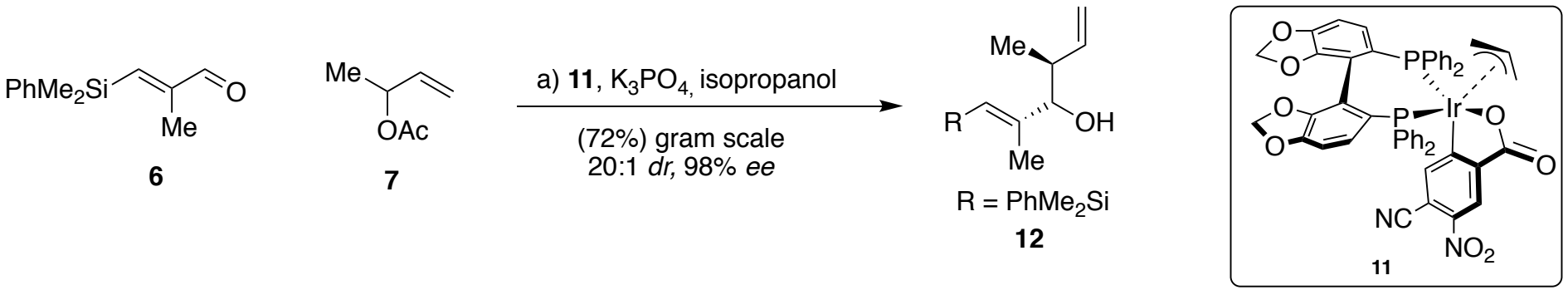
Pladienolides A and B was isolated by Eisai Co. in 2004 from Streptomyces platensis Mer-11107, are among the most potent and structurally complex natural products known to target the spliceosome (catalyzes pre mRNA splicing.

Pladienolides B was recently identified as a potent inhibitor of viral replication for SARS-CoV-2.

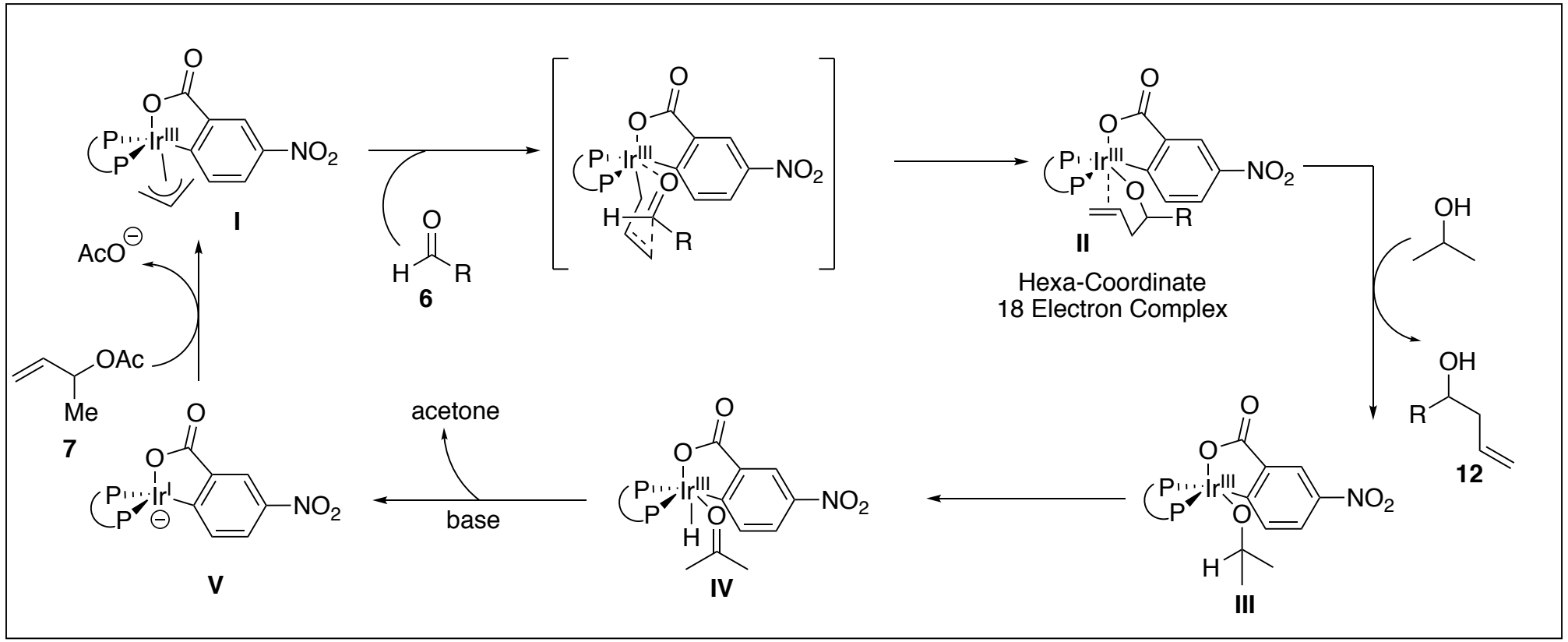
Previous reported syntheses typically have longest linear sequence (LLS) of 18–22 steps (0.63%–2.9% overall yields), 33–51 steps in total.

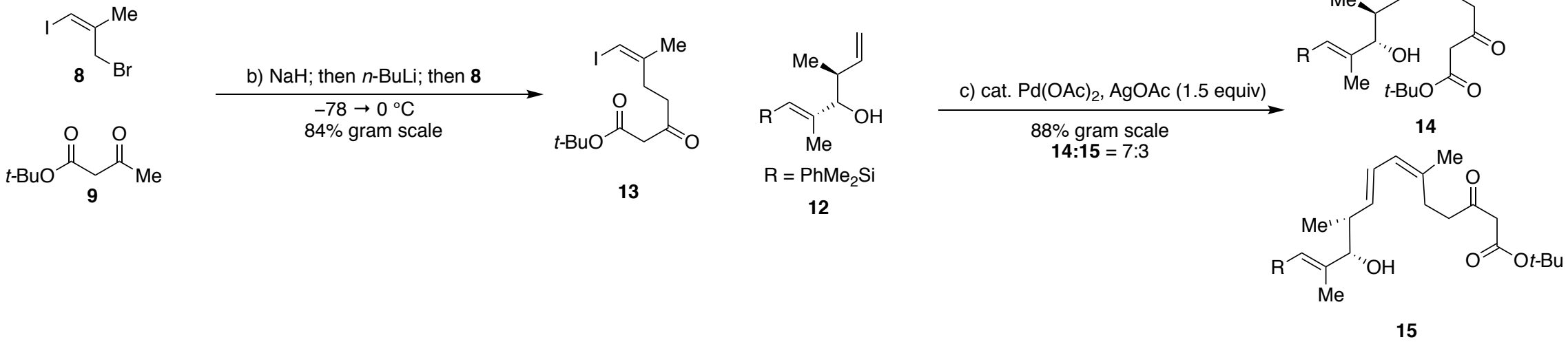
One reported semisynthesis of clinical candidate **3** requires 16 chemical steps

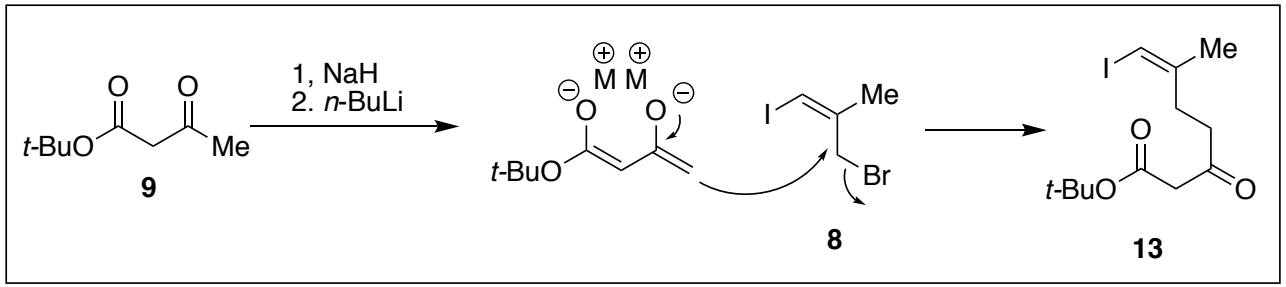


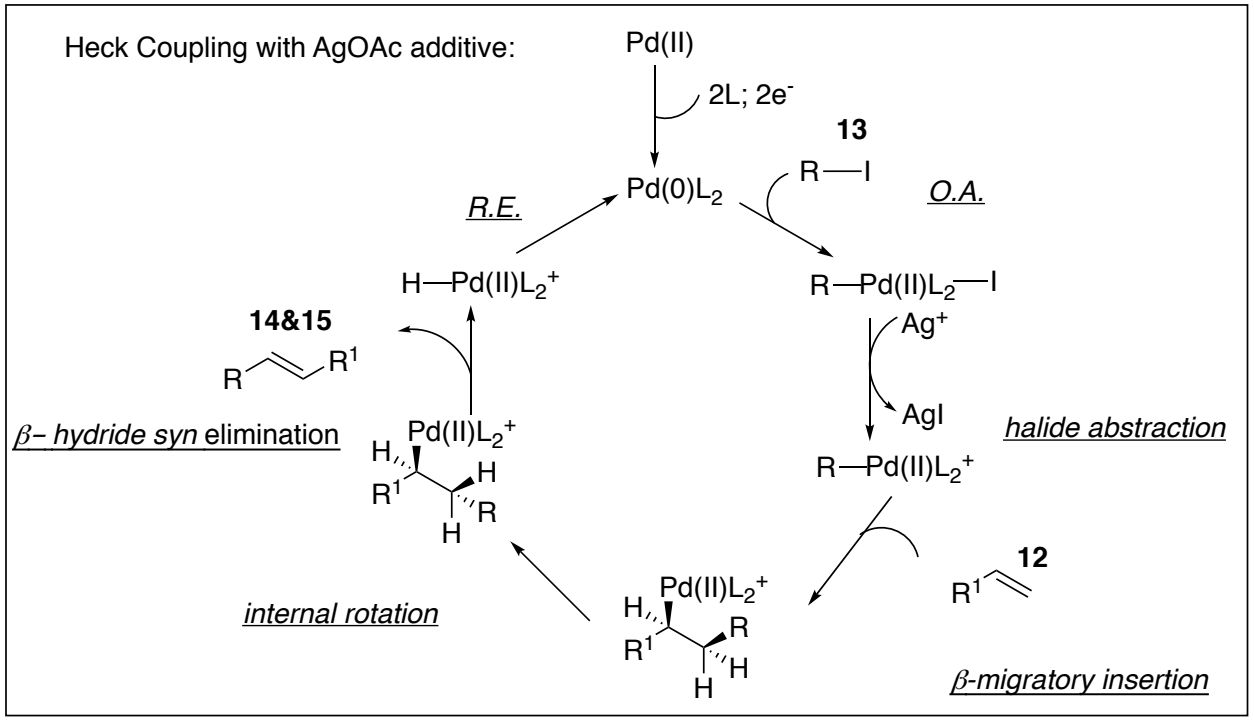


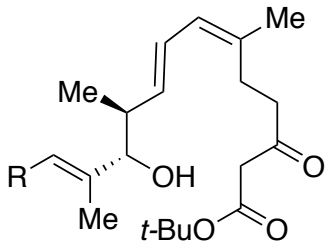
Krische's Crotylation. (Ref. *J. Am. Chem. Soc.* **2009**, *131*, 2514.)




8
9
b) NaH; then n-BuLi; then 8
–78 → 0 °C
84% gram scale
13
R = PhMe2Si
12
c) cat. Pd(OAc)2, AgOAc (1.5 equiv)
88% gram scale
14:15 = 7:3
14
15


9
1, NaH
2. n-BuLi
8
13

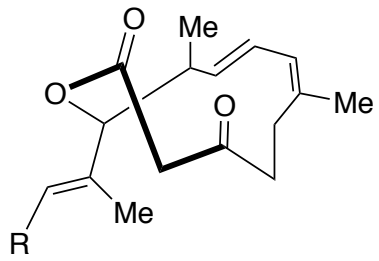

Heck Coupling with AgOAc additive:
Pd(II)
2L; 2e-
13
Pd(0)L2
R.E.
O.A.
H—Pd(II)L2+
R—Pd(II)L2—I
Ag+
AgI
14&15
β– hydride syn elimination
halide abstraction
Pd(II)L2+
R—Pd(II)L2+
12
internal rotation
β-migratory insertion



14

d) 125 ºC, PhMe

70% gram scale

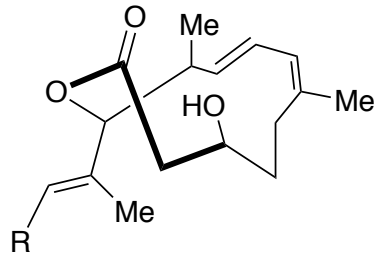


16

transesterification: *t*-BuOH b.p. : 82 °C, drive the equilibrium

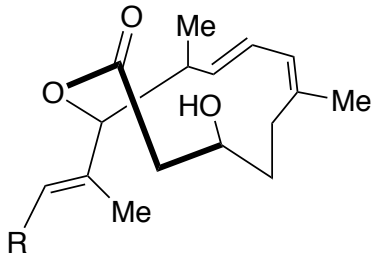
e) KEt_3BH, –78 °C

91% gram scale



18

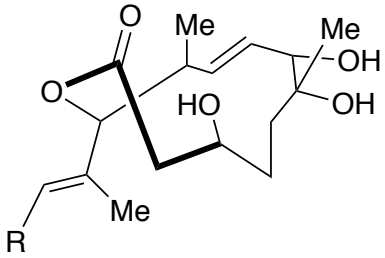
stereoselective and chemoselective ketone reduction: generate a sinlge diastereomer



18

f) AD-mix-β

77% 10:1 *dr*



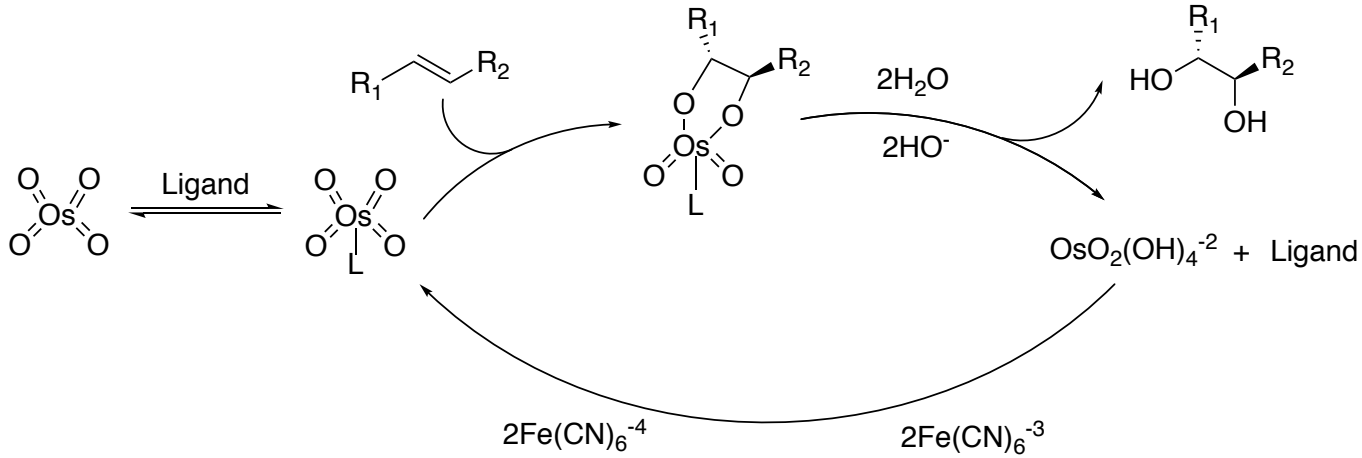
20

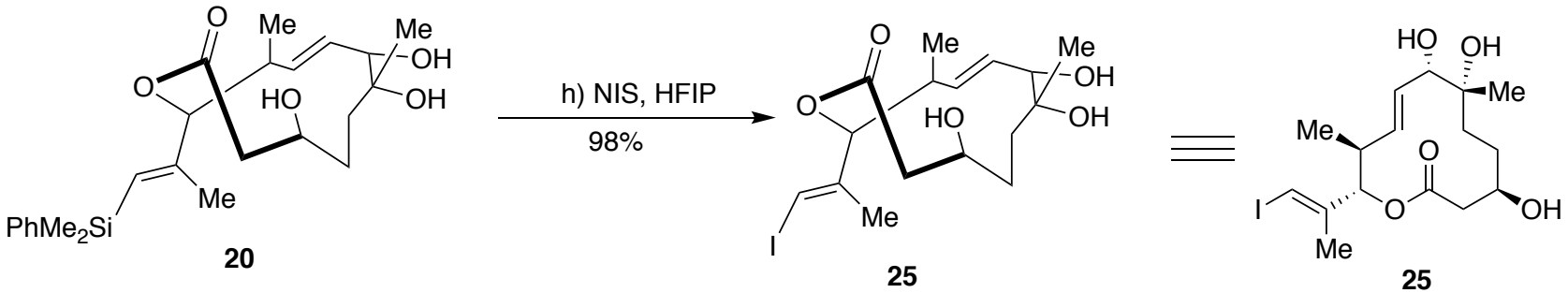
site- and stereoselective dihydroxylations of macrocyclic conjugated dienes

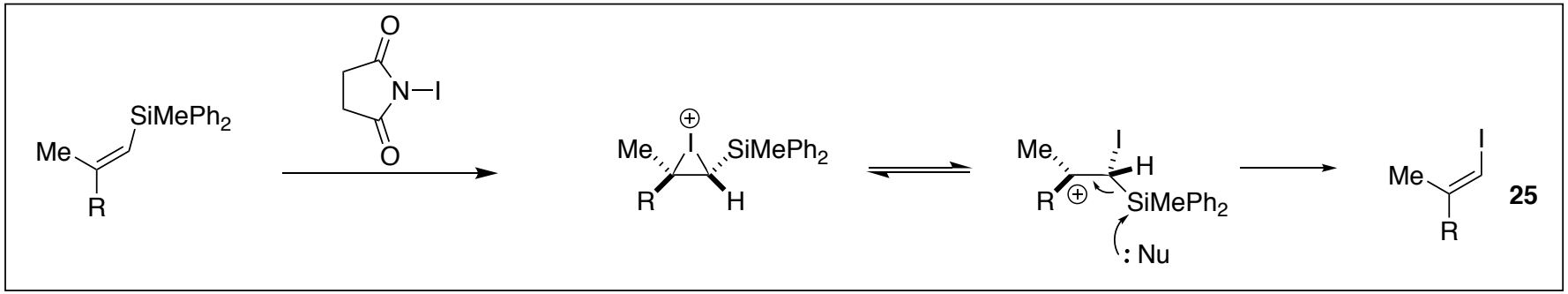
AD-mix-β $K_2OsO_2(OH)_4$ as the source of Osmium tetroxide

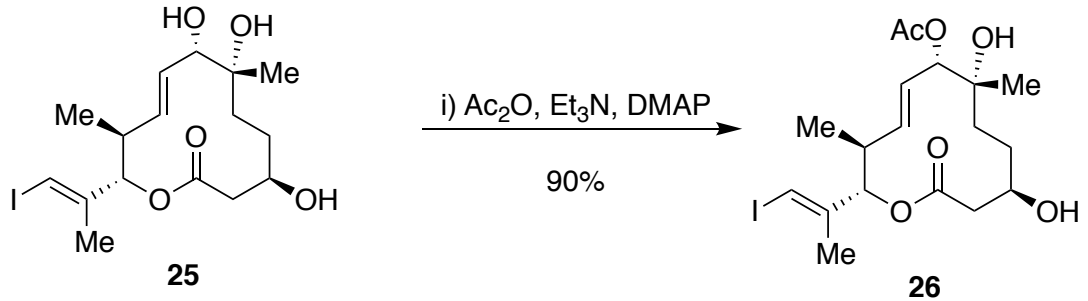
$K_3Fe(CN)_6$, re-oxidant in the catalytic cycle

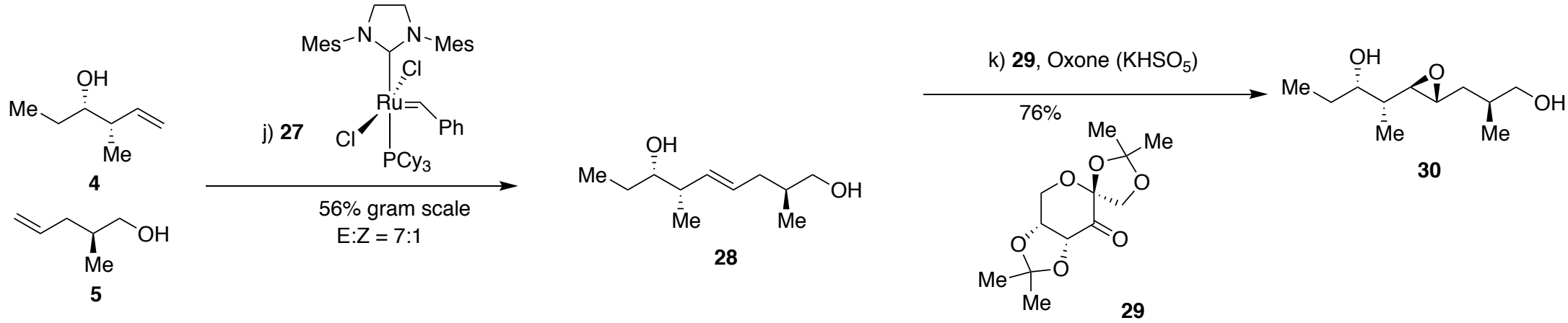
$DHQD)_2PHAL$ as chiral ligand

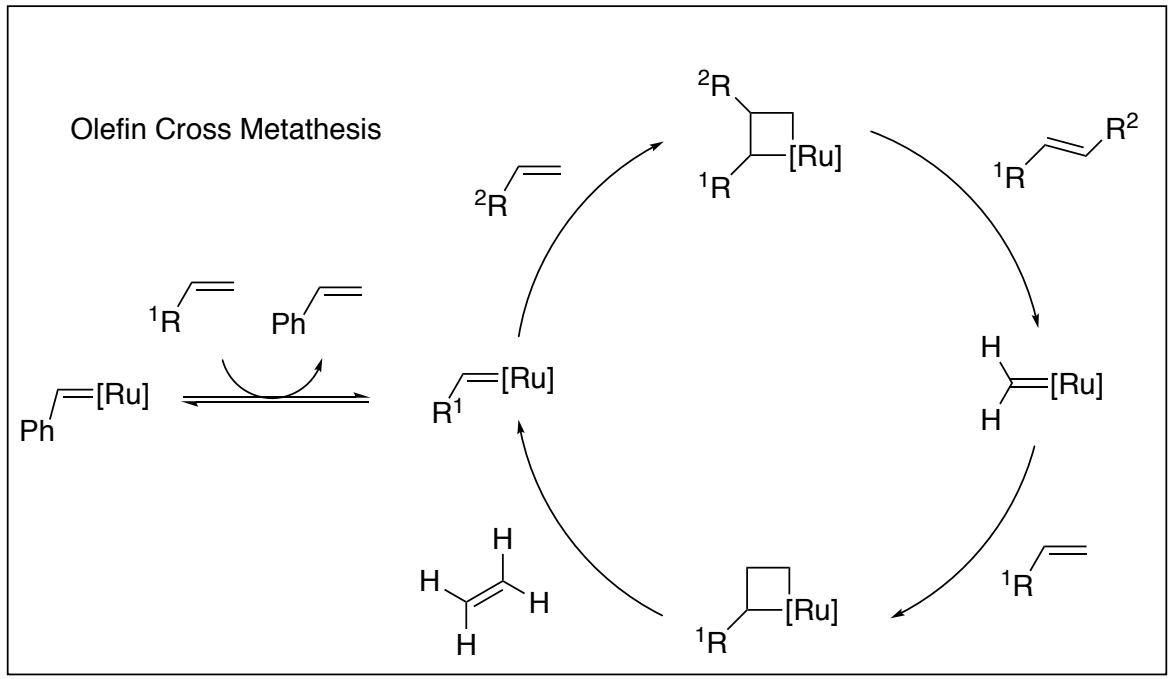


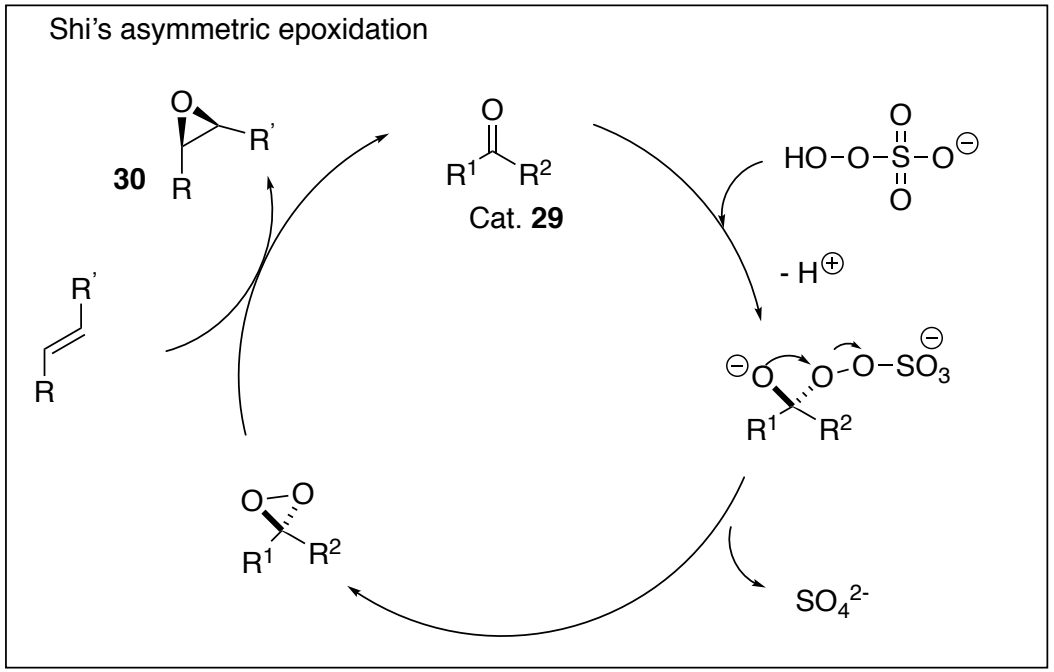

h) NIS, HFIP
98%
20
25
25

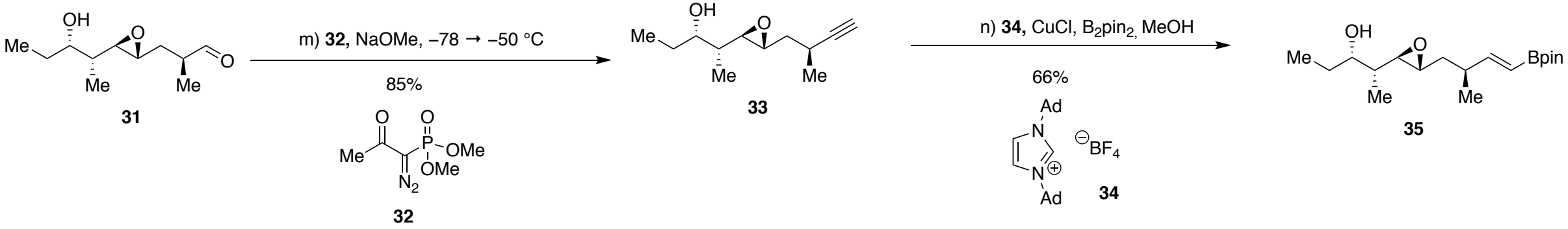

SiMePh2
Me
R
N—I
O
O
Me
I
SiMePh2
R
H
Me
I
H
R
SiMePh2
: Nu
Me
I
R
25

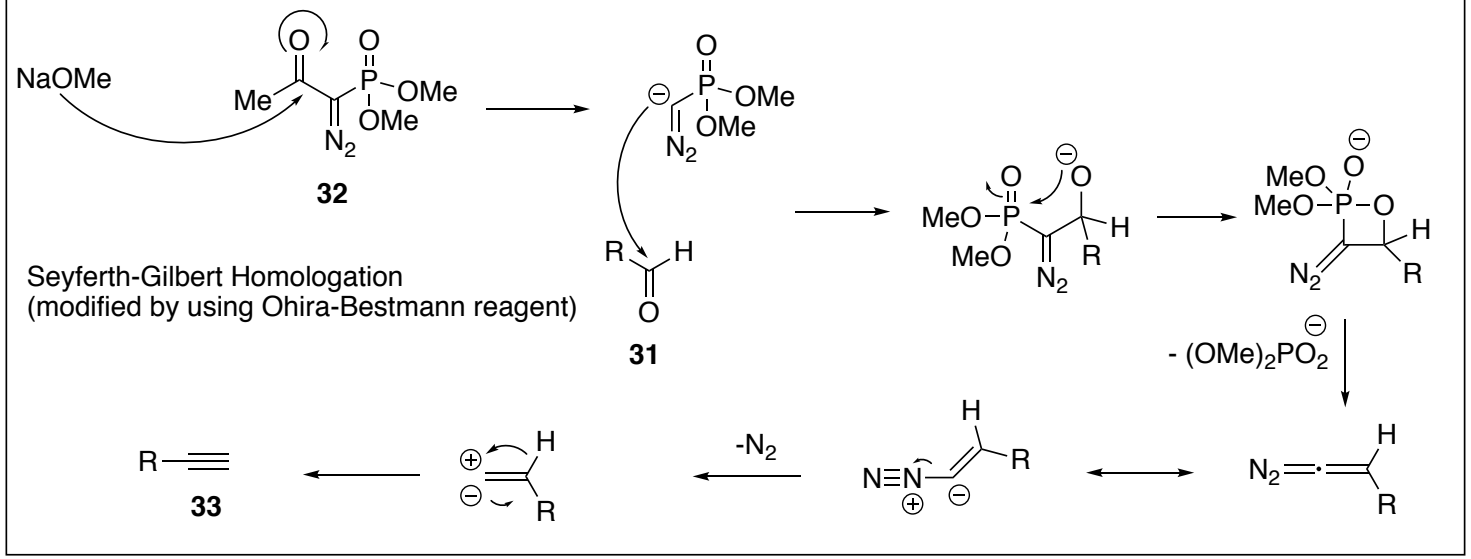

i) Ac2O, Et3N, DMAP
90%
25
26

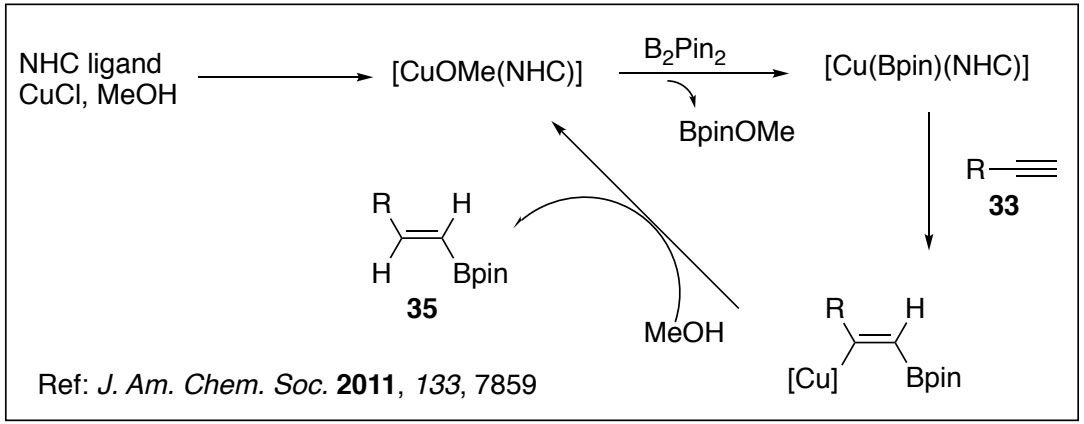

OH
Me
Me
4
OH
Me
5
Mes
N
N
Mes
Cl
Ru
Cl
Ph
PCy3
j) 27
56% gram scale
E:Z = 7:1
OH
Me
Me
OH
28
k) 29, Oxone (KHSO5)
76%
Me
Me
O
O
O
O
O
Me
Me
29
OH
Me
O
OH
Me
Me
30

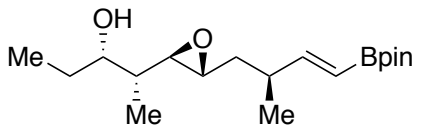

Olefin Cross Metathesis
1R
Ph
Ph
[Ru]
2R
[Ru]
1R
R2
1R
H
H
[Ru]
1R
[Ru]
1R
H
H
H
H
2R
R1
[Ru]


Shi's asymmetric epoxidation
30
O
R'
R
Cat. 29
O
R1
R2
HO–O–S(=O)(=O)–O⊖
- H⊕
R'
R
⊖O
O
O–SO3⊖
R1
R2
O
O
R1
R2
SO4 2-

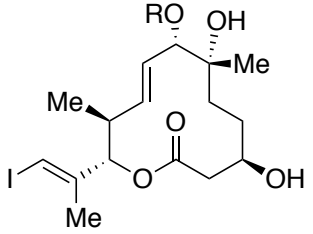

OH
Me
Me
Me
O
O
31
m) 32, NaOMe, –78 → –50 °C
85%
O
O
Me
P
OMe
OMe
N2
32
OH
Me
Me
Me
O
33
n) 34, CuCl, B2pin2, MeOH
66%
Ad
N
N
Ad
BF4
34
OH
Me
Me
Me
O
Bpin
35


NaOMe
O
O
Me
P
OMe
OMe
N2
32
Seyferth-Gilbert Homologation
(modified by using Ohira-Bestmann reagent)
O
O
P
OMe
OMe
N2
R
H
O
31
MeO
O
O
MeO
P
H
MeO
R
N2
MeO
O
MeO
P
O
H
N2
R
- (OMe)2PO2
H
N≡N
R
N2
H
R
-N2
H
R
R
33


NHC ligand
CuCl, MeOH
[CuOMe(NHC)]
B2Pin2
BpinOMe
[Cu(Bpin)(NHC)]
R
33
R
H
H
Bpin
35
MeOH
R
H
[Cu]
Bpin
Ref: J. Am. Chem. Soc. 2011, 133, 7859



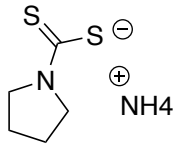
35



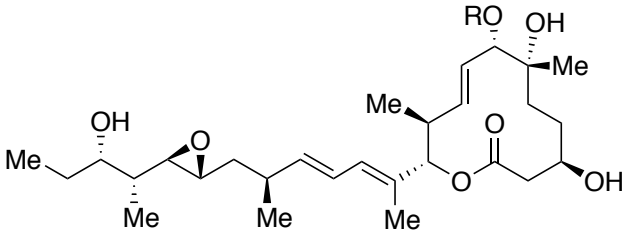
25 R = H **or 26** R = Ac

o) $Pd(dppf)Cl_2$, K_3PO_4; then **36**

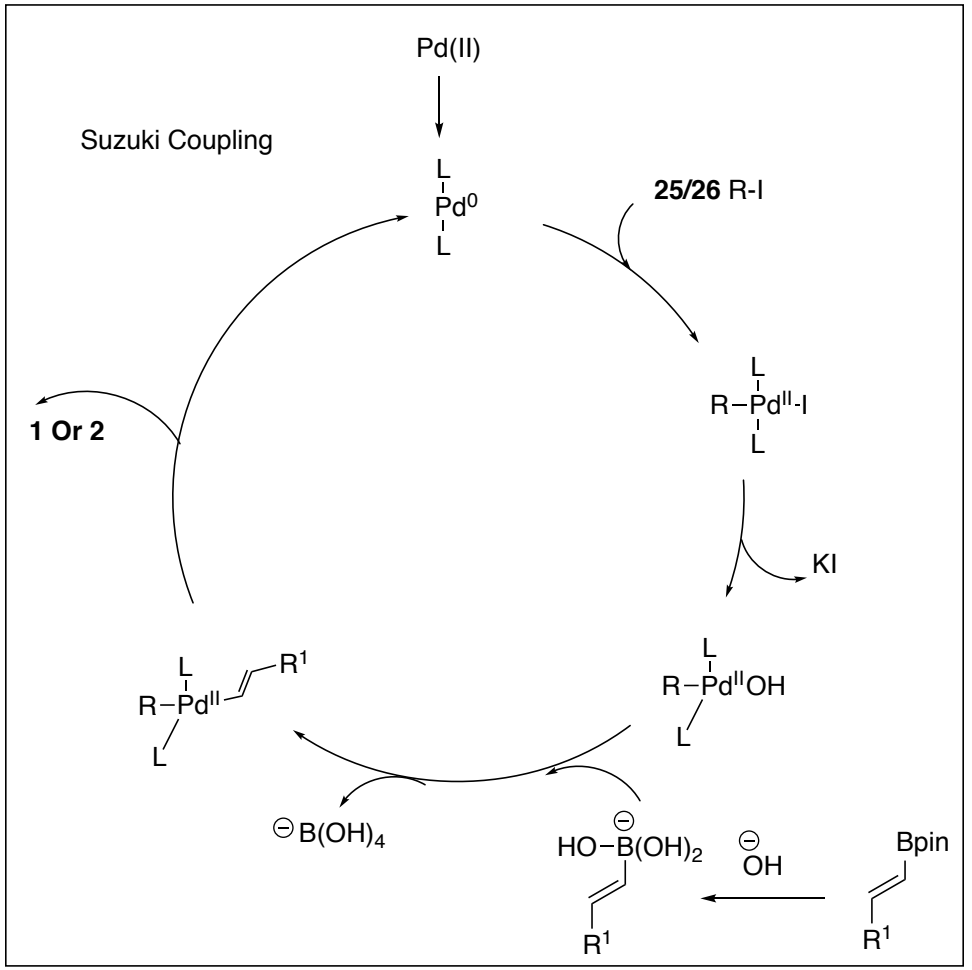
76% for **1**; 87% for **2**

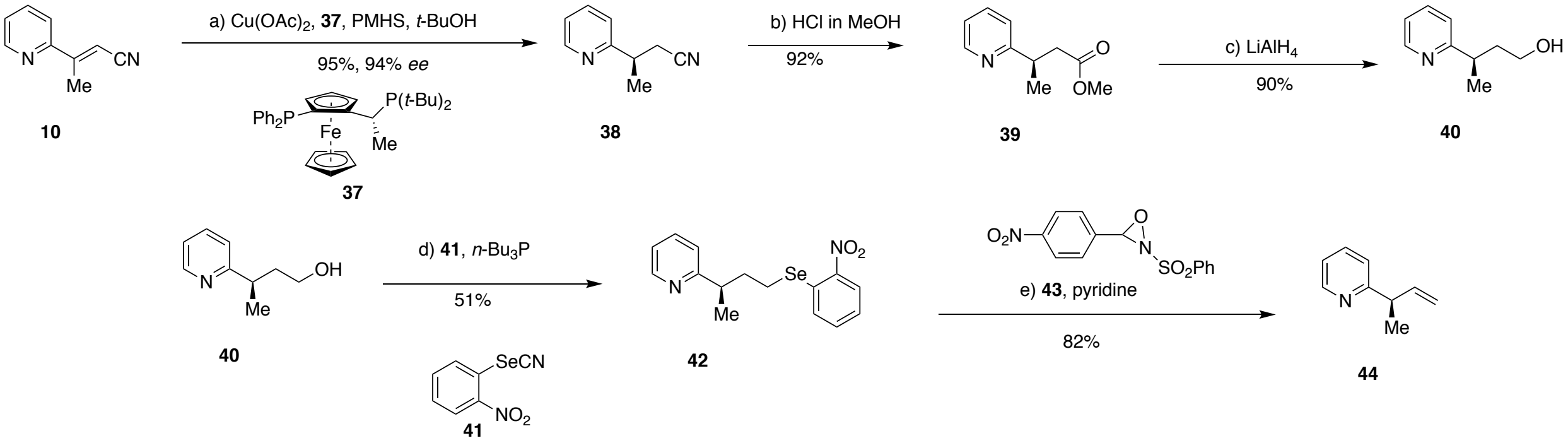


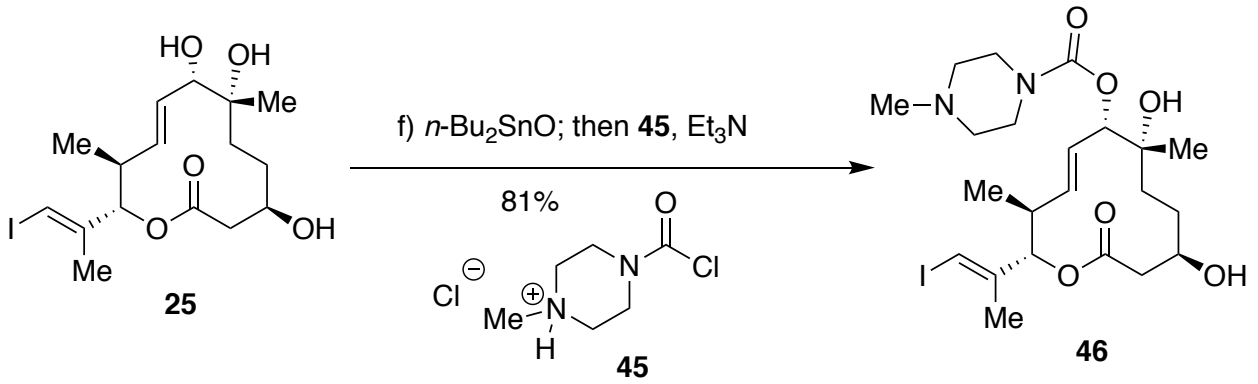
36

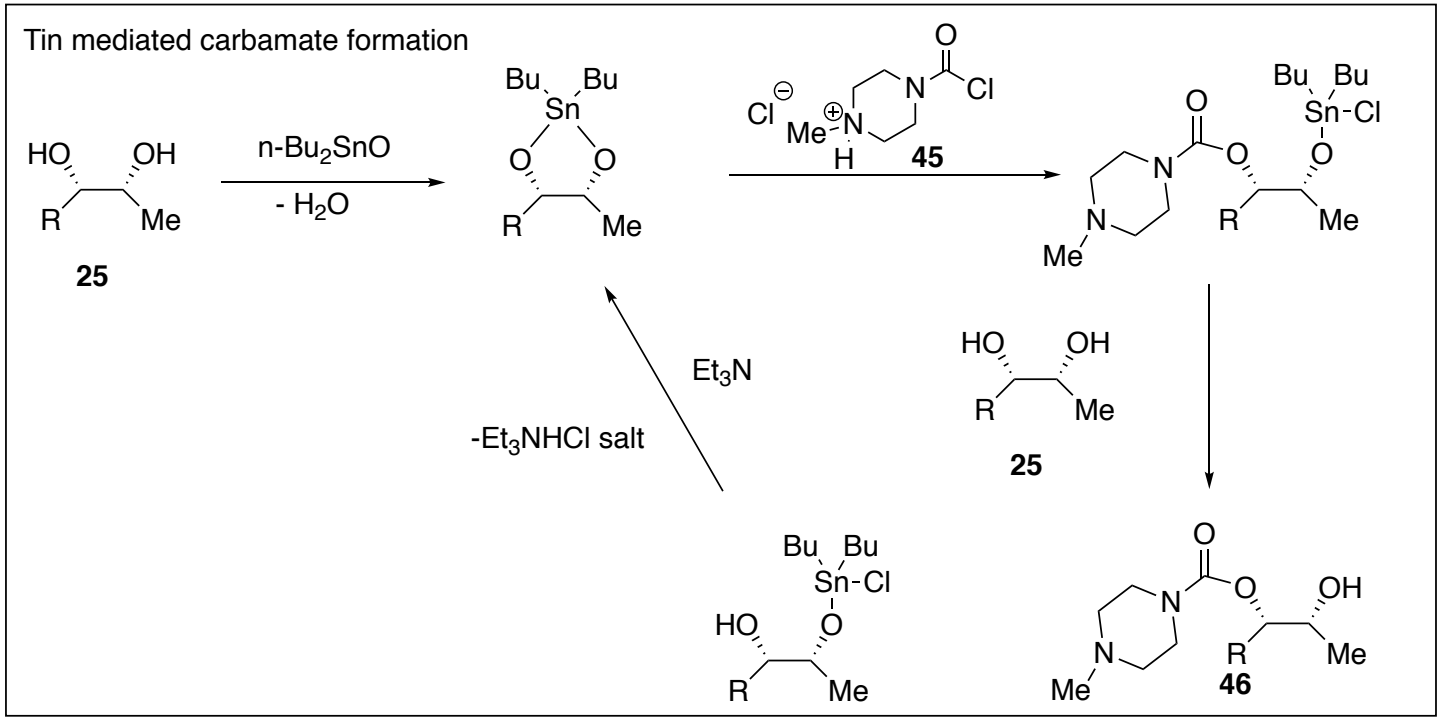


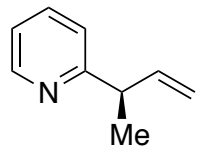
1 R = H; **2** R = Ac



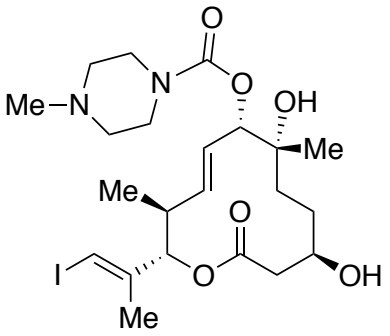

a) Cu(OAc)2, 37, PMHS, t-BuOH
95%, 94% ee
b) HCl in MeOH
92%
c) LiAlH4
90%
d) 41, n-Bu3P
51%
e) 43, pyridine
82%
10
38
39
40
37
41
42
44
Grieco Elimination:
: PBu3
Bu3PO
43. oxaziridine


f) n-Bu2SnO; then 45, Et3N
81%
25
45
46


Tin mediated carbamate formation
n-Bu2SnO
- H2O
45
Et3N
-Et3NHCl salt
25
46



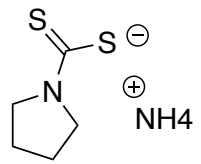
44



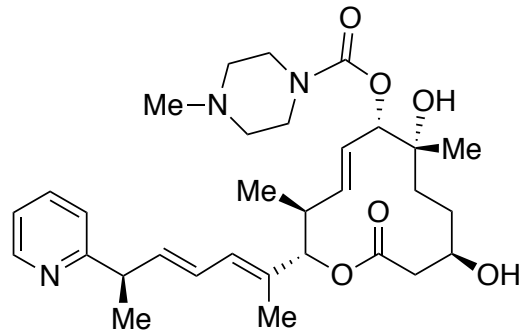
46

g) $Pd(PPh_3)_4$, Et_3N, PhH; then **36**

80% *(E,E):(Z,E)* = 5 : 1



36



3 H3B-8800