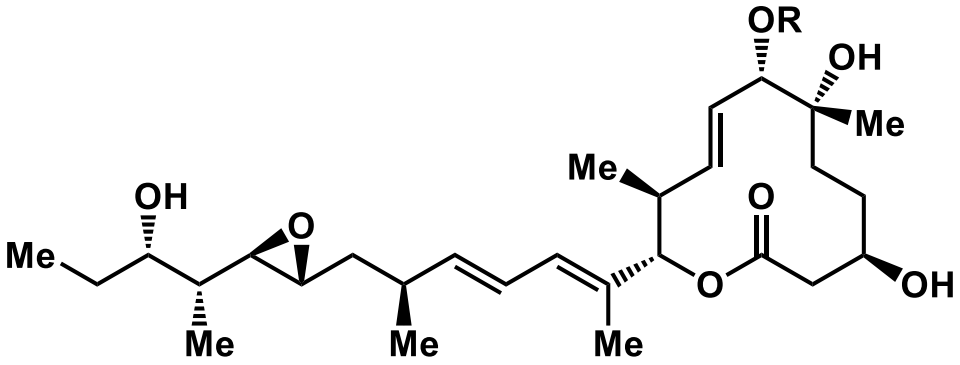
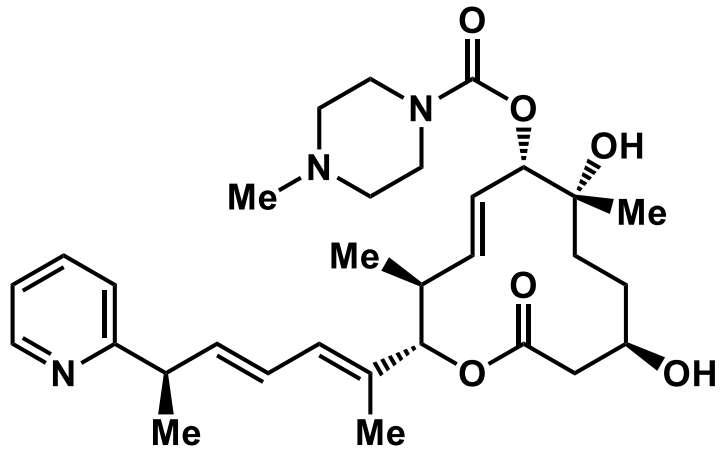
Expedient Total Syntheses of Pladienolide-Derived Spliceosome Modulators

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

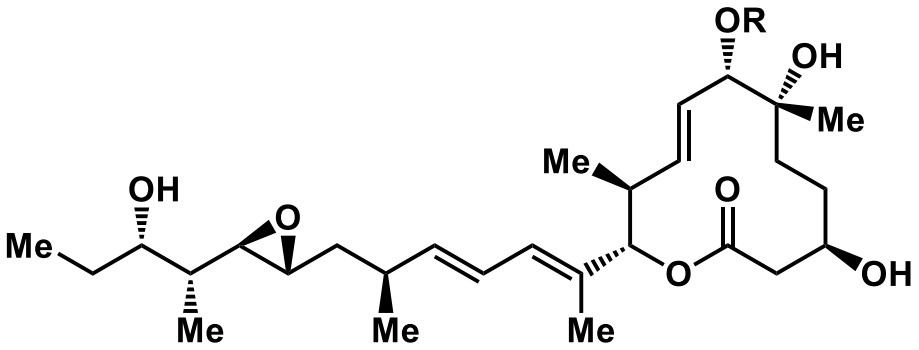


1: Pladienolide A (R = H)
2: Pladienolide B (R = OAc)

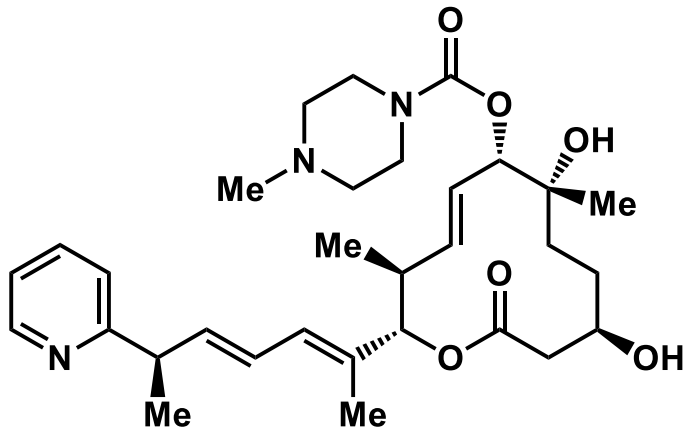


3: H3B-8800

J. Am. Chem. Soc. **2021**, *143*, 4915.



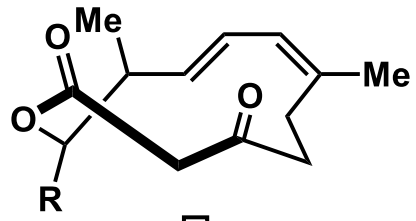
1: Pladienolide A (R = H)
2: Pladienolide B (R = OAc)



3: H3B-8800

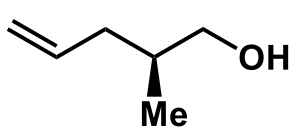
Natural Spliceosome Modulator

- 7 or 8 steps LLS
- No Protecting Groups

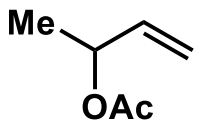


Designed Spliceosome Modulator

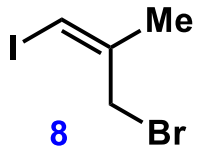
- Modular Design
- Simple Building Blocks



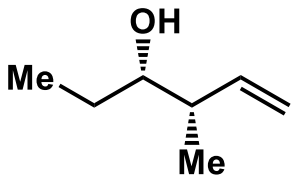
5



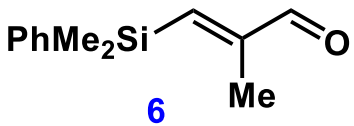
7



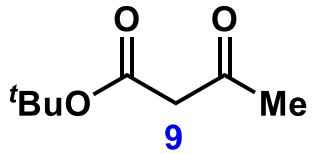
8



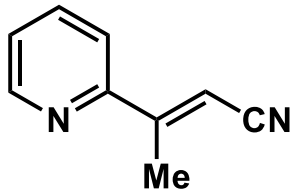
4



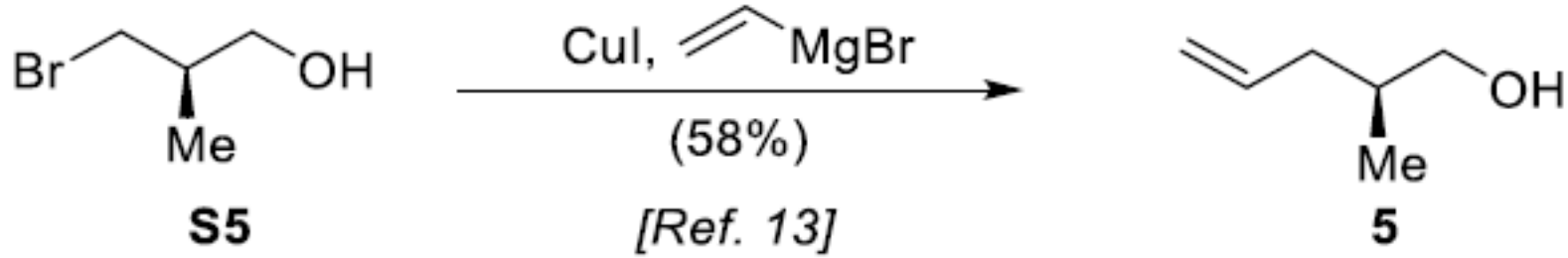
6



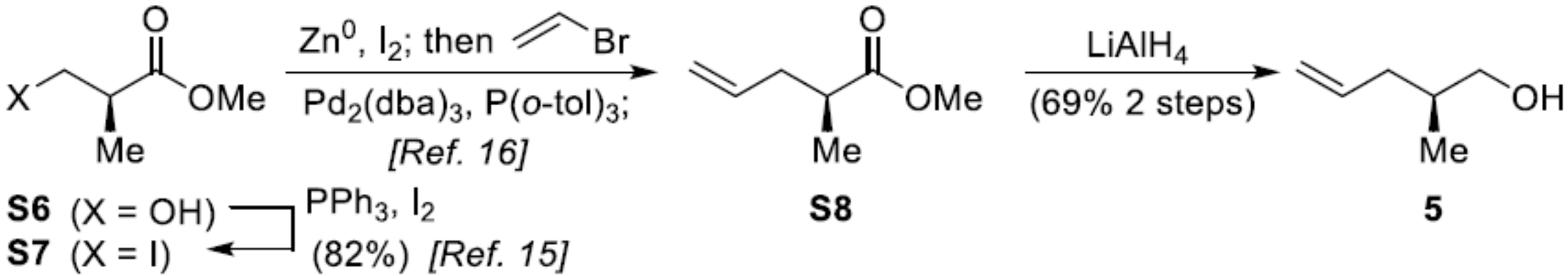
9



10

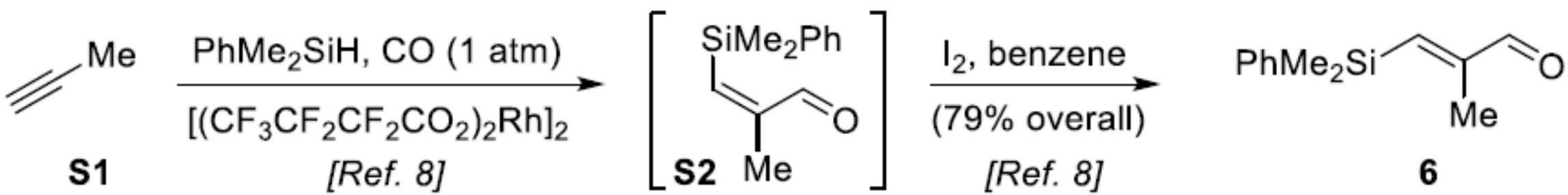


S5 **5**

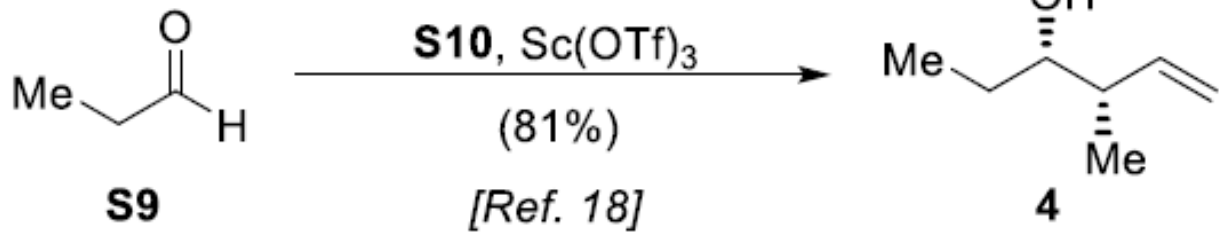


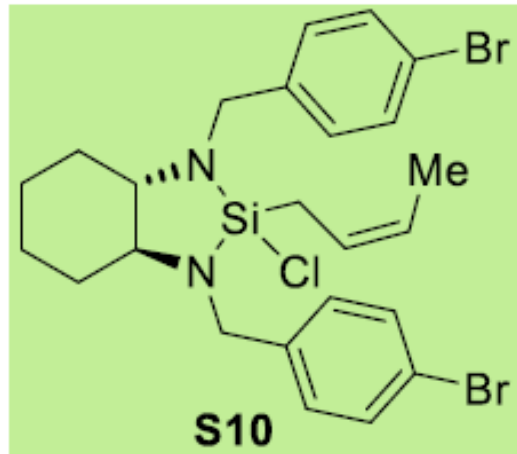
S6 (X = OH)
S7 (X = I)

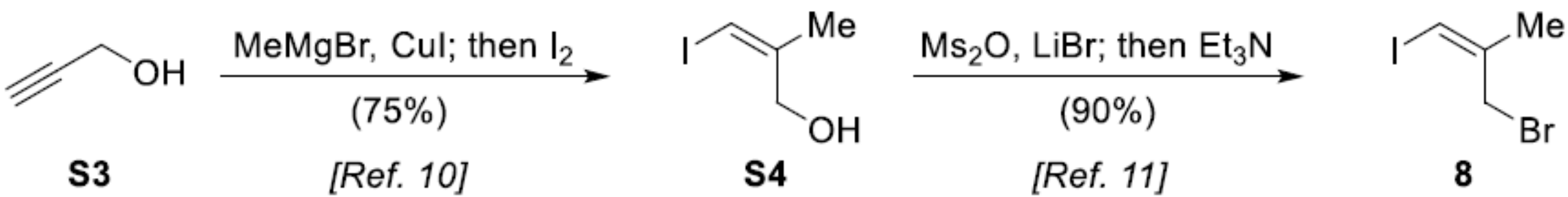
S8 **5**

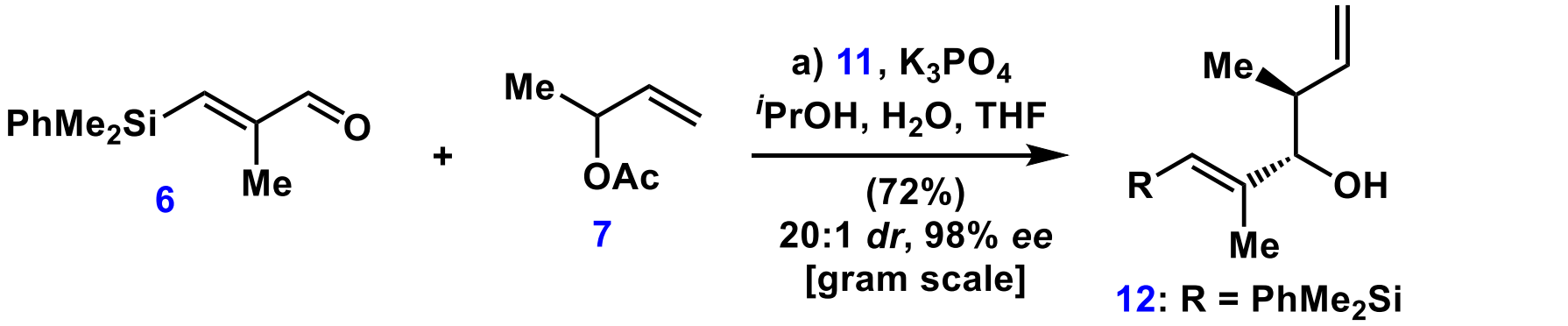


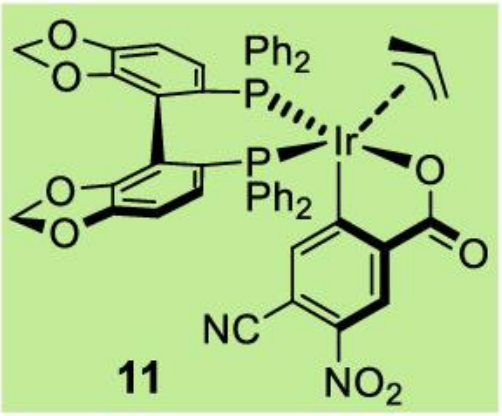
S1 **S2** **6**

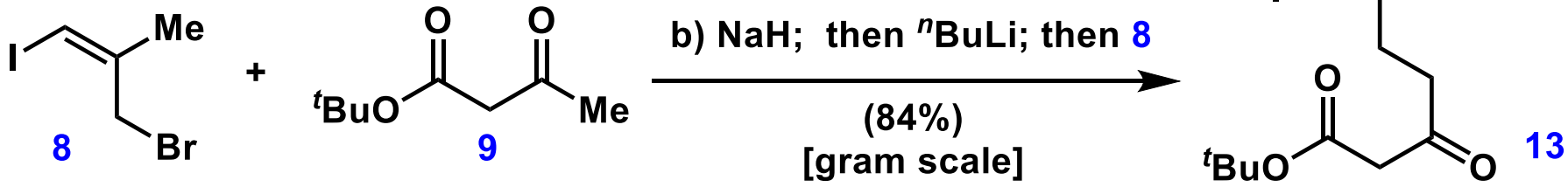

Me
O
H
S9
S10, Sc(OTf)3
(81%)
[Ref. 18]
OH
Me
Me
4


Br
N
Si
Me
N
Cl
Br
S10

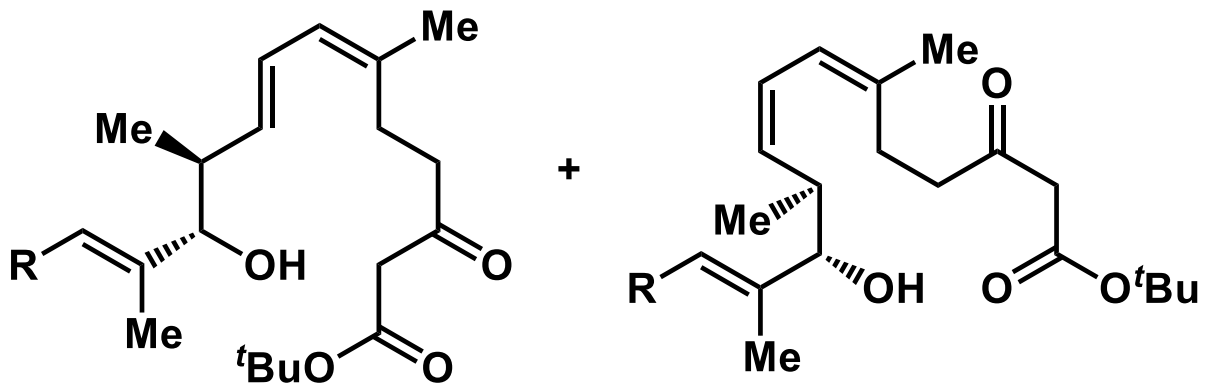

OH
S3
MeMgBr, CuI; then I2
(75%)
[Ref. 10]
I
Me
OH
S4
Ms2O, LiBr; then Et3N
(90%)
[Ref. 11]
I
Me
Br
8







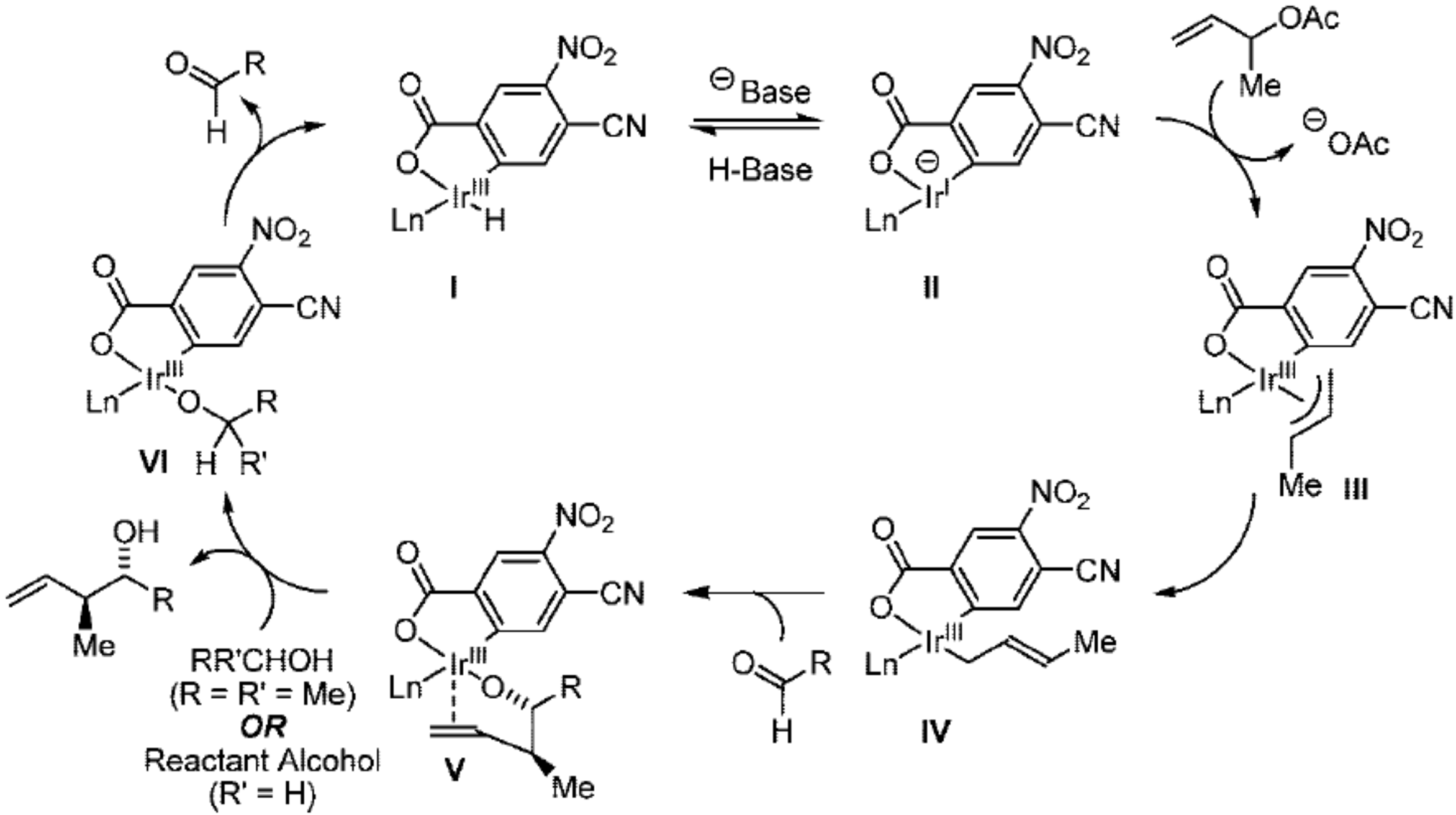
12 + 13 → Pd(OAc)$_2$, AgOAc
(88%, 14:15 = 7 : 3)
[gram scale]
Tabal 1



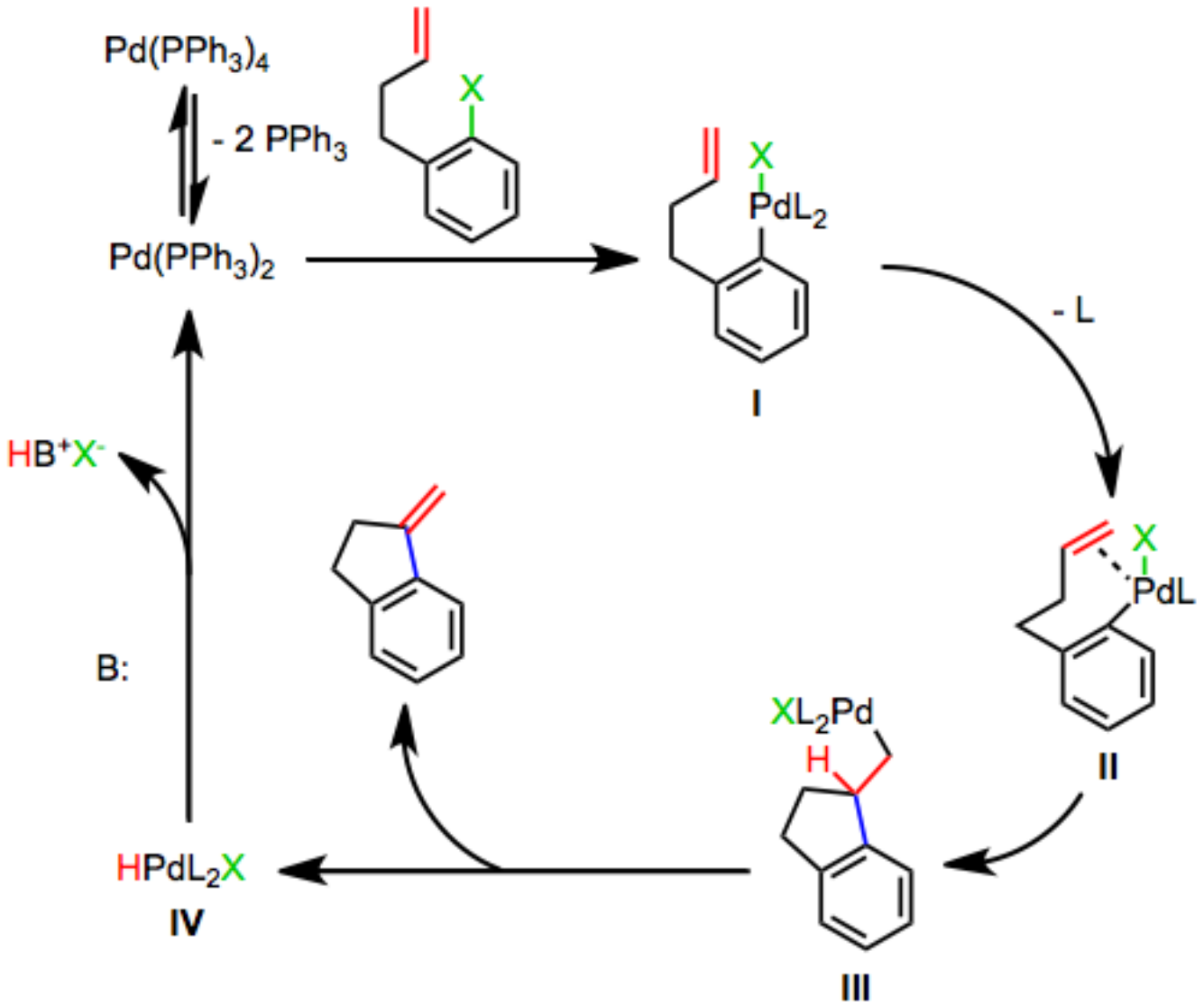
+

Table 1

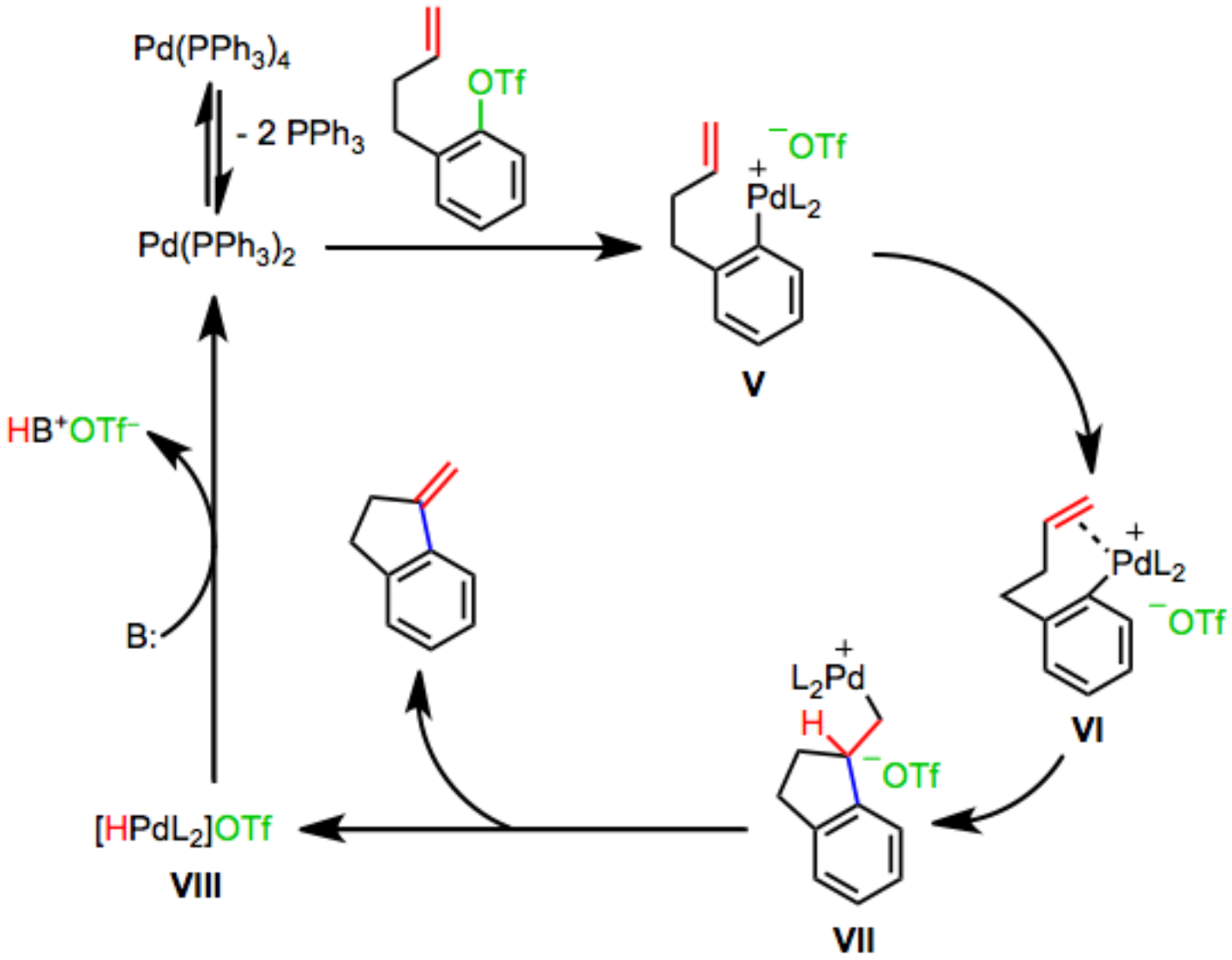
additives	yield
Ag_2CO_3	42%
$NaHCO_3$	–
Ag_3PO_4	32%
PPh_3	–
AgOAc	88%

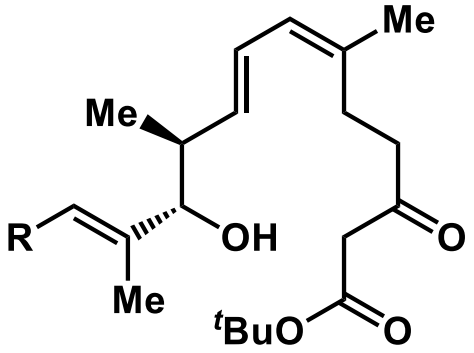

NO2
CN
O
Ln
Ir
H
I
⊖Base
H-Base
II
OAc
Me
⊖OAc
III
IV
V
VI
R
H
R'
OH
RR'CHOH
(R = R' = Me)
OR
Reactant Alcohol
(R' = H)

Heck反应——中性途径


Pd(PPh3)4
- 2 PPh3
Pd(PPh3)2
X
X
PdL2
I
- L
X
PdL
II
XL2Pd
H
III
HPdL2X
IV
B:
HB+X-

Heck反应——阳离子途径





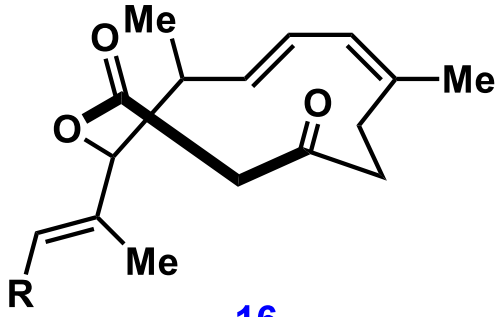
14

d) 4Å MS, 125 °C

(70%)

[gram scale]

Tabal 2



16

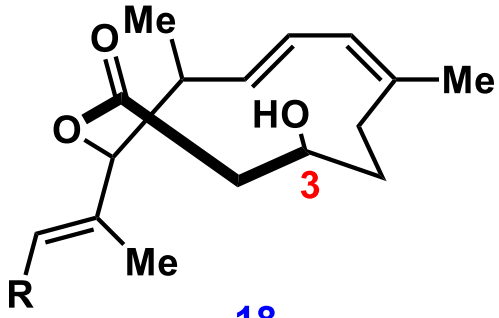
Single isomer

e) KEt_3BH

(91%)

[gram scale]

Tabal 3



18

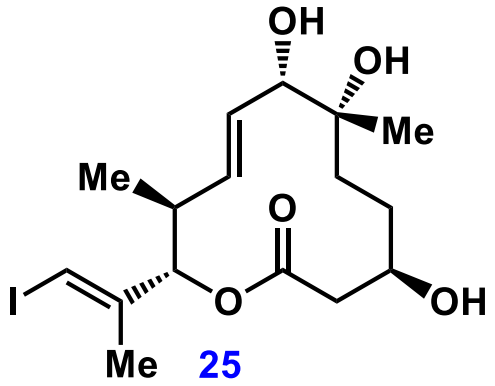
Table 2

solvent	yield
PhH	30%
PhCl	41%
PhMe	43%
PhMe*	70%

*with 4 Å MS

Table 3

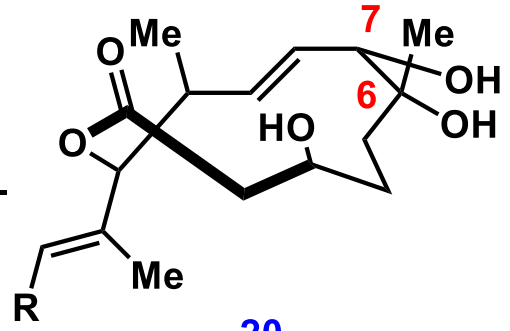
[H]	yield
$NaBH_4$	58%
K-selectride	49%
DIBAL	41%
$LiAlH(Ot\text{-}Bu)_3$	18%
KEt_3BH	91%



25

h) NIS

(98%)



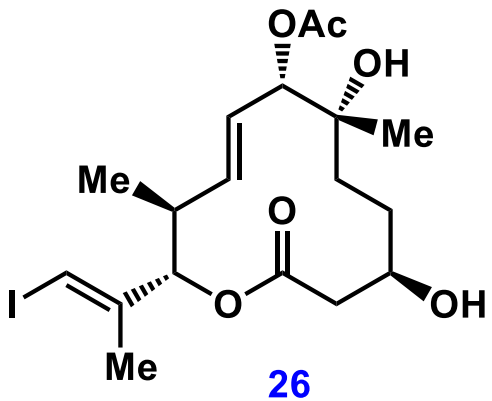
20

f) AD-mix-β

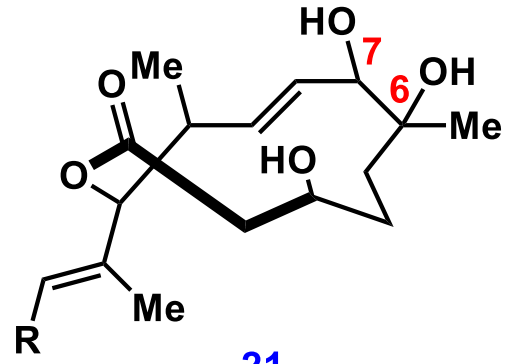
(77%)

10:1 *dr*

i) Ac_2O, TEA, DMAP



26

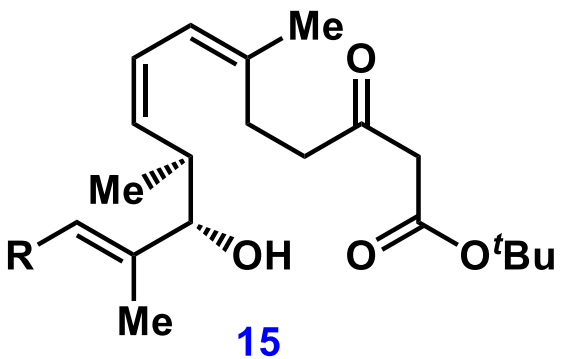


21

f) AD-mix-α

(68%)

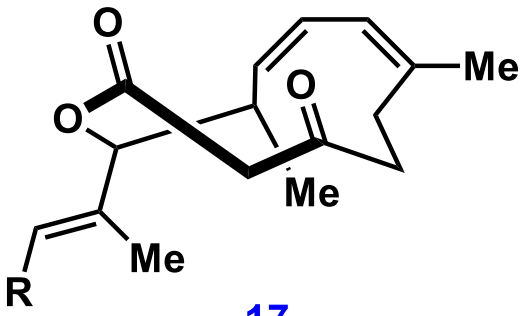
3:1 *dr*



15

d) 4Å MS, 125 °C

(65%)

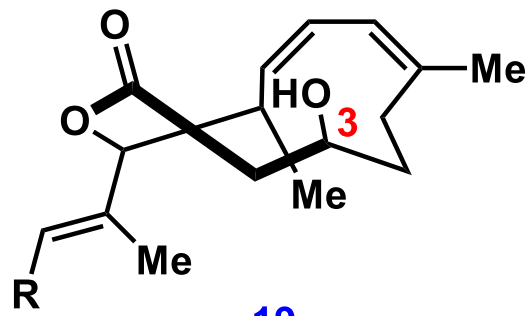


17

Single isomer

e) KEt_3BH

(88%)

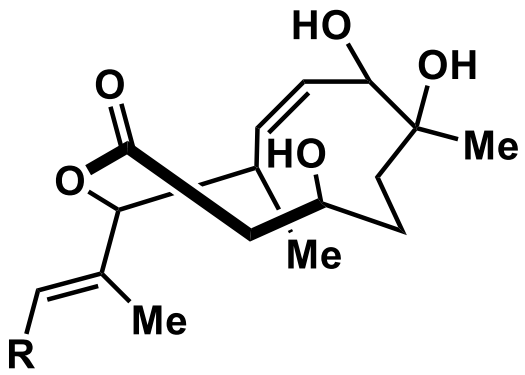


19

f) AD-mix-α
or AD-mix-β

(81%)

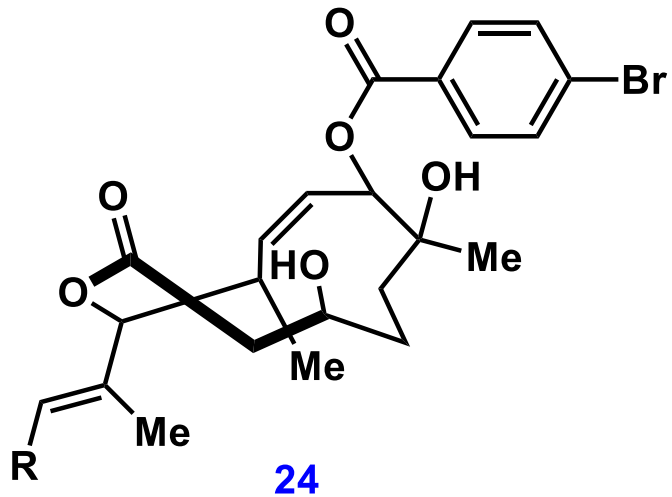
Single isomer



22

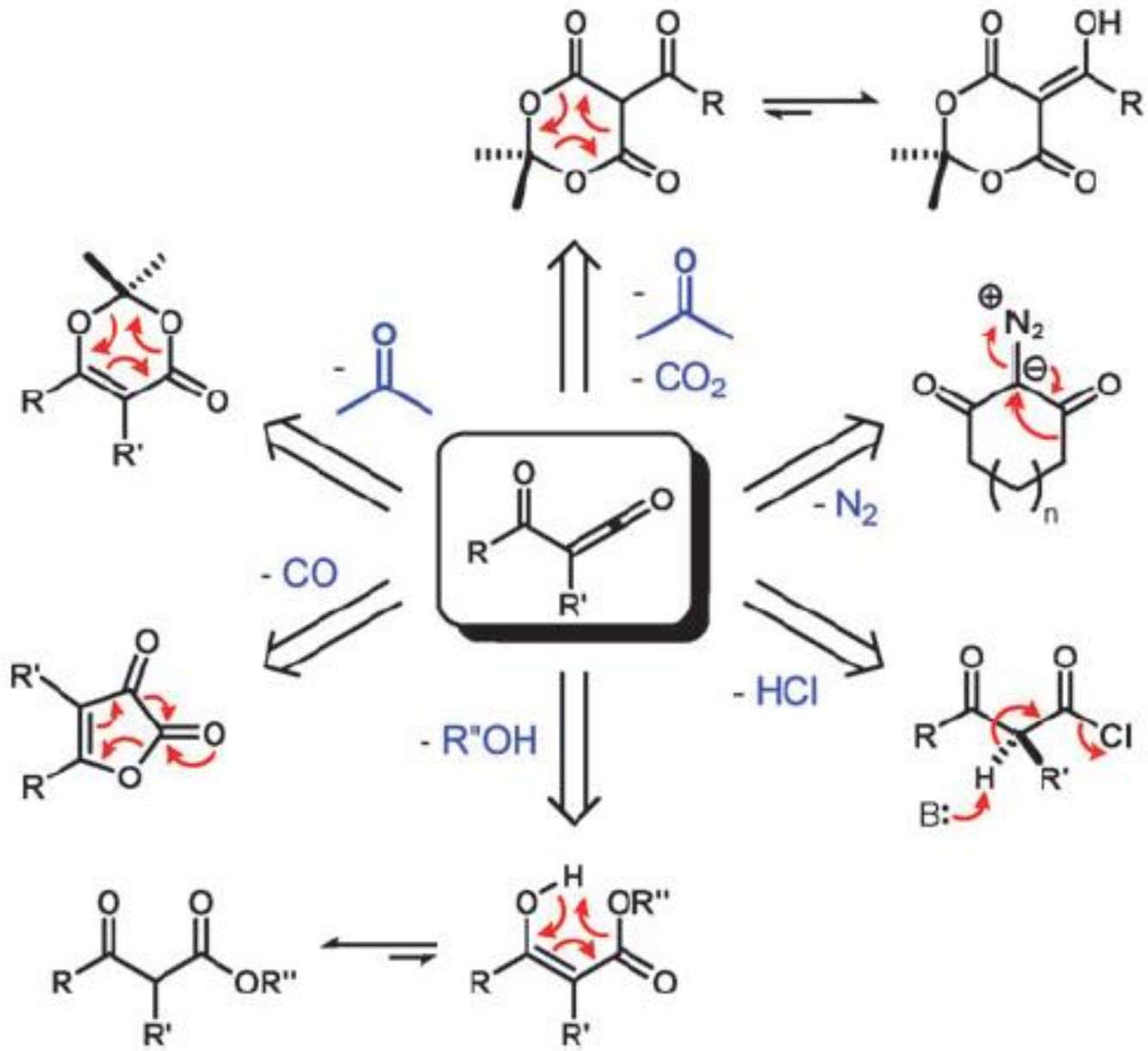
g) 23, TEA, DMAP

(73%)



24

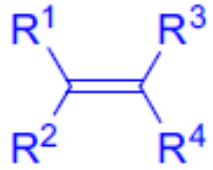
酰基烯酮（acylketene）



Common precursors for generating acylketene intermediates.

Chem. Soc. Rev., **2009**, *38*, 3022–3034

Sharples不对称双羟基化

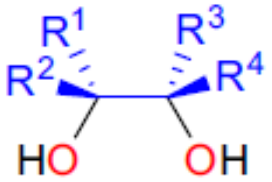


R^{1-4} = H, alkyl ,aryl

Chiral ligand (catalytic)
oxidant (stoichiometric)

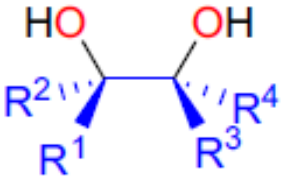
OsO_4 (catalytic)
organic solvent / water

(AD-mix α or AD-mix β)



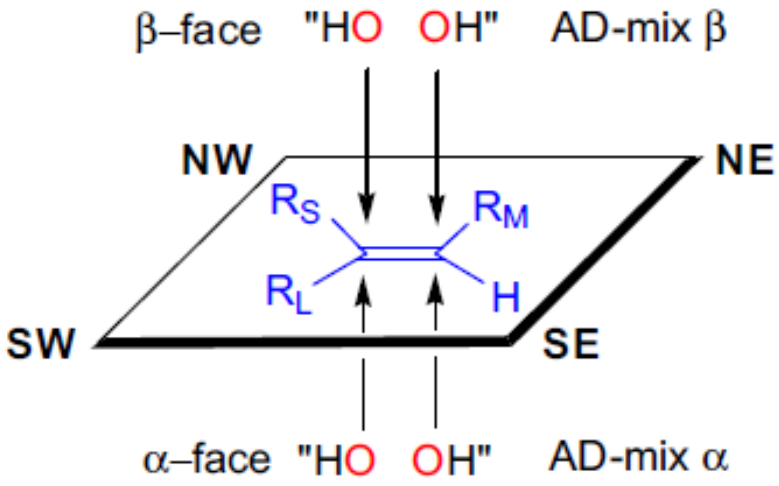
Enantiopure *cis* vicinal diol

or



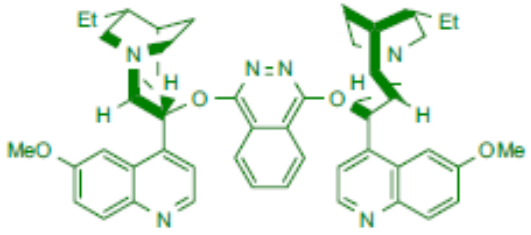
Enantiopure *cis* vicinal diol

Empirical model (mnemonic device):

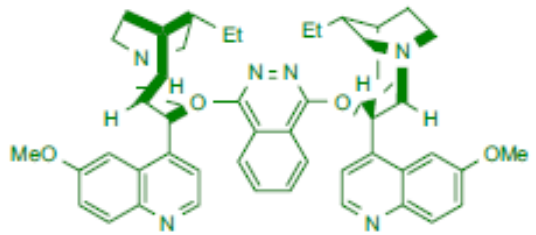


AD-mix α: $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

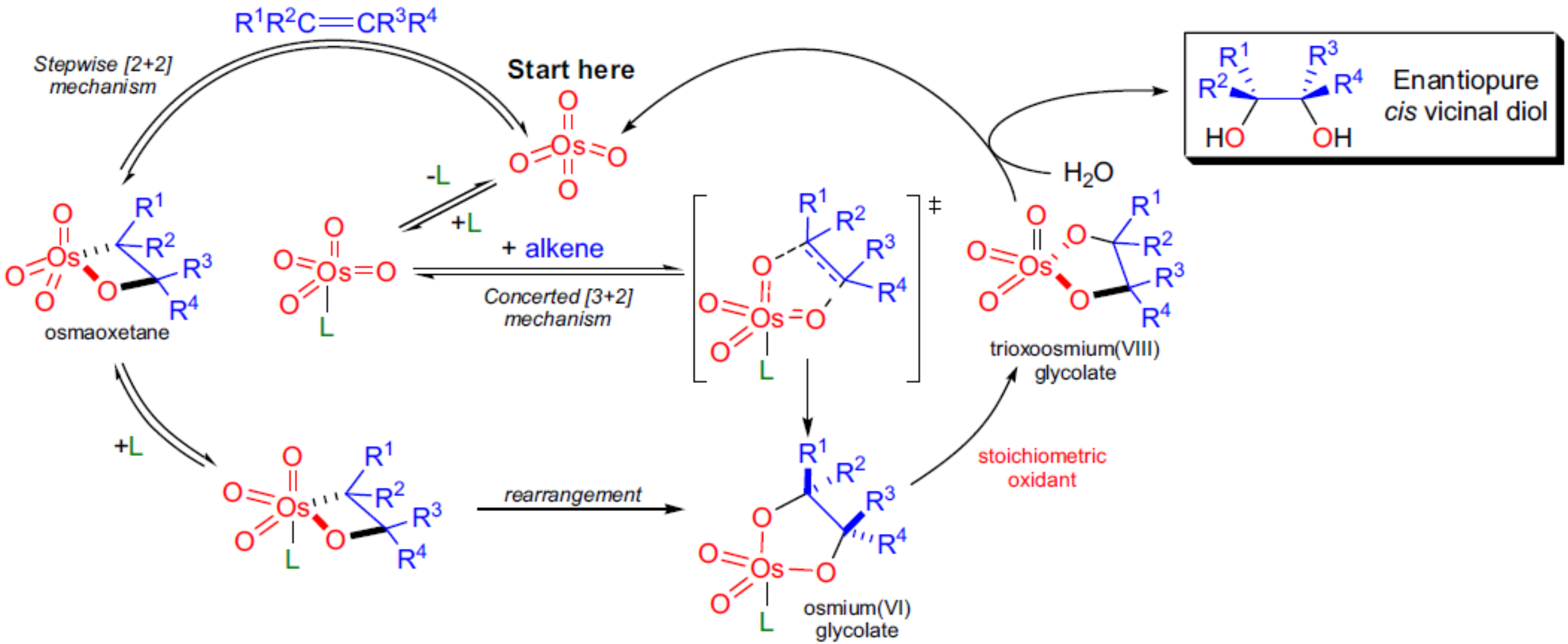
AD-mix β: $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

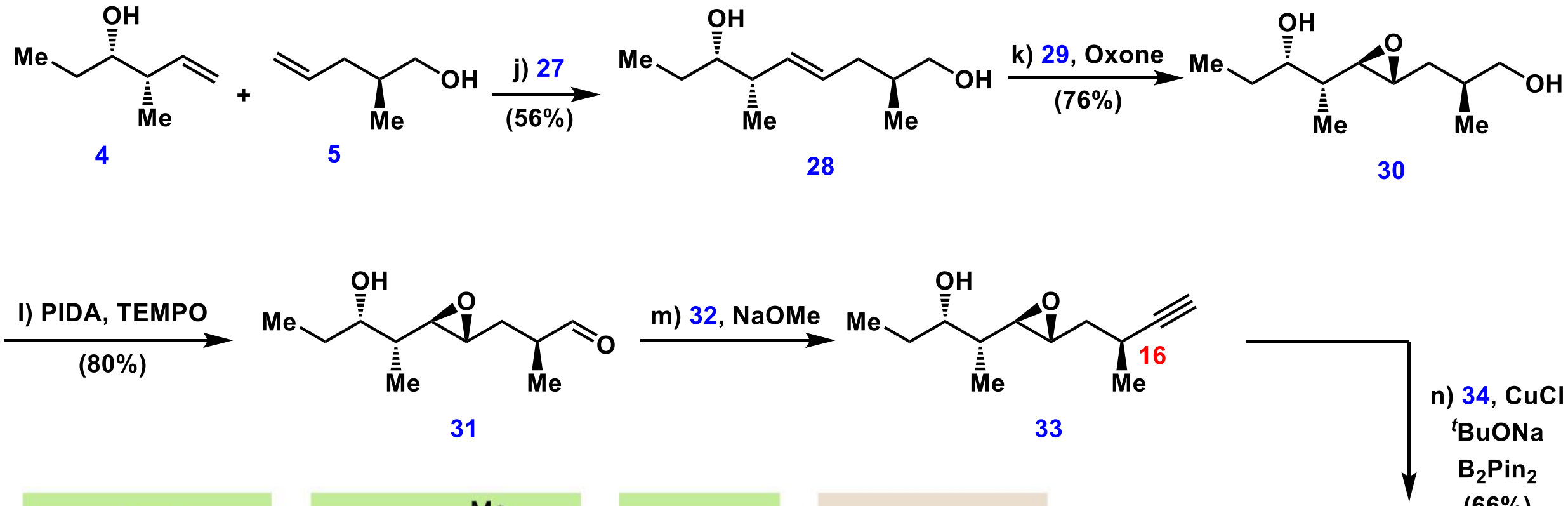


$(DHQ)_2PHAL$

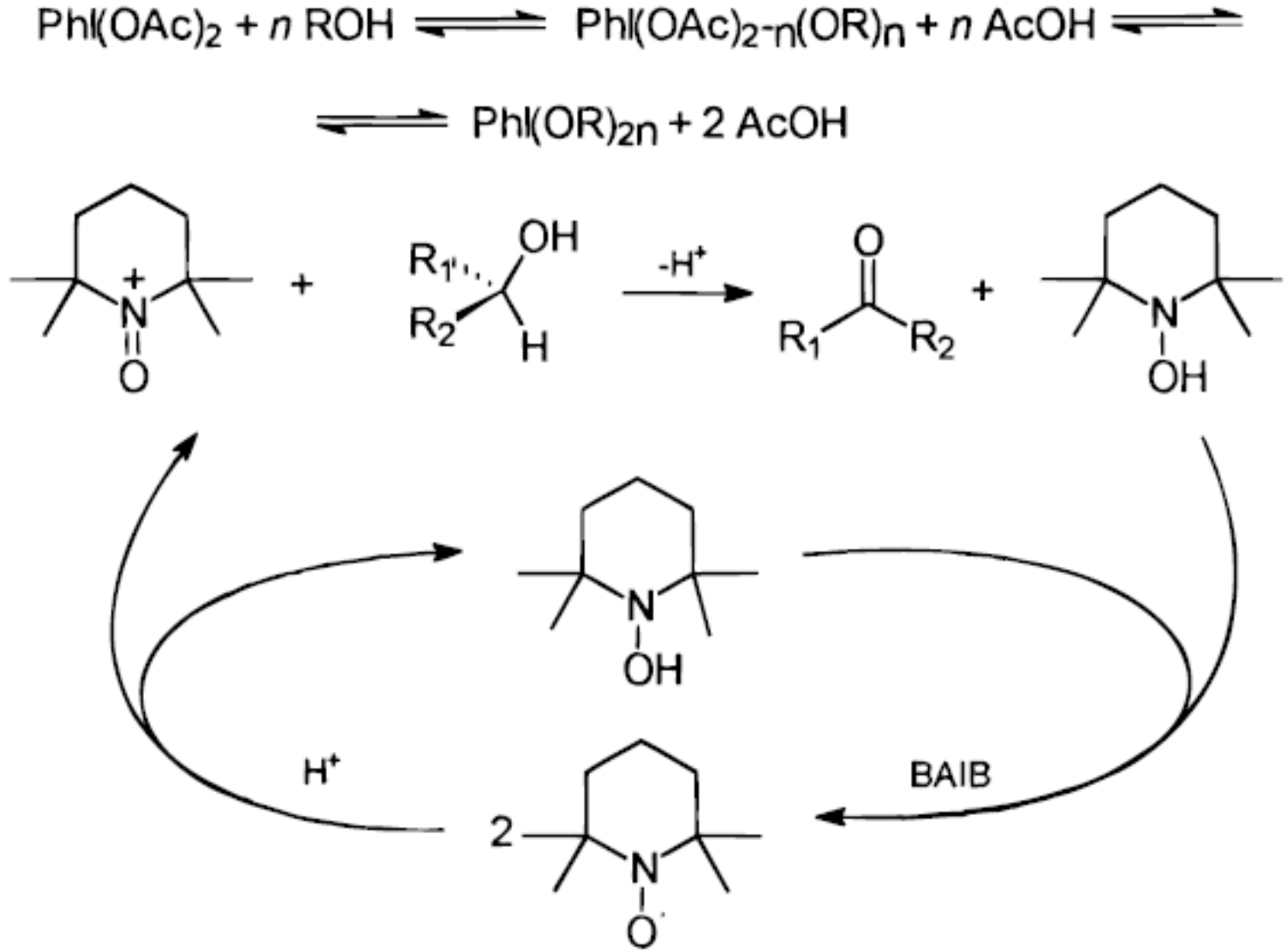


$(DHQD)_2PHAL$


R1R2C=CR3R4
Stepwise [2+2] mechanism
Start here
-L
+L
+ alkene
Concerted [3+2] mechanism
osmaoxetane
+L
rearrangement
osmium(VI) glycolate
stoichiometric oxidant
H2O
trioxoosmium(VIII) glycolate
Enantiopure cis vicinal diol


OH
Me
Me
4
+
OH
Me
5
j) 27
(56%)
OH
Me
Me
OH
28
k) 29, Oxone
(76%)
OH
O
Me
Me
OH
30
l) PIDA, TEMPO
(80%)
OH
O
Me
Me
O
31
m) 32, NaOMe
OH
O
Me
Me
16
33
n) 34, CuCl
tBuONa
B2Pin2
(66%)
OH
O
Me
Me
Bpin
35
Mes
N
N
Mes
Cl
Ru
Ph
Cl
PCy3
27
Me
Me
O
O
O
O
O
O
Me
Me
29
Ad
N
BF4
N
Ad
34
O
O
Me
P
OMe
OMe
N2
32

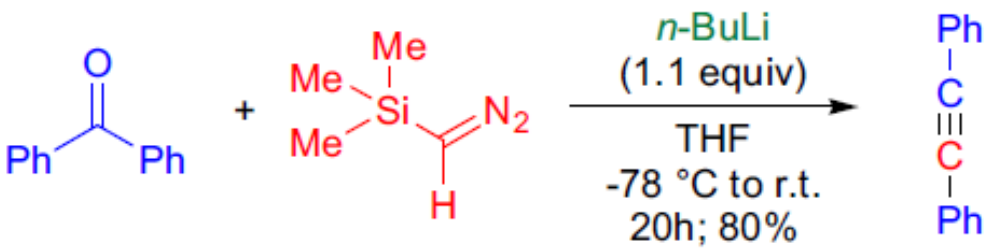
Scheme 2. Proposed Reaction Pathway for the Oxidation of Alcohols with BAIB/TEMPO



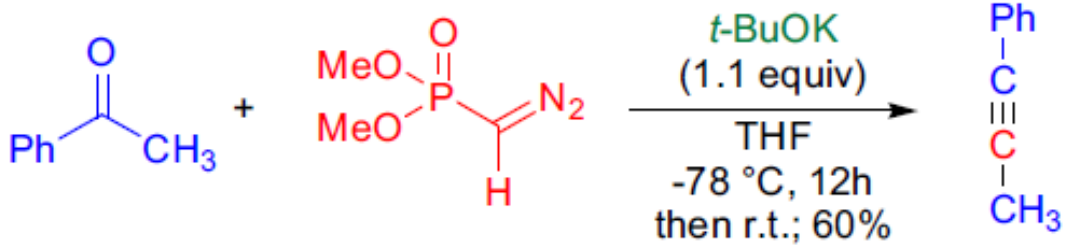
Seyferth-Gilbert 增碳反应

在碱催化下重氮甲基膦酸二烷基酯与醛或芳基酮在低温下反应得到炔的反应。 Ohira-Bestmann改进法转而使用(1-重氮基-2-氧代丙基)膦酸二烷基酯可以使碱不稳定的易互变异构化的醛发生反应。

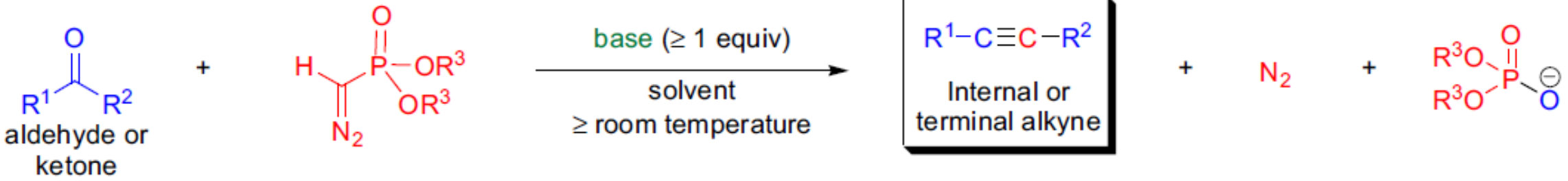
Colvin & Hamill (1973):



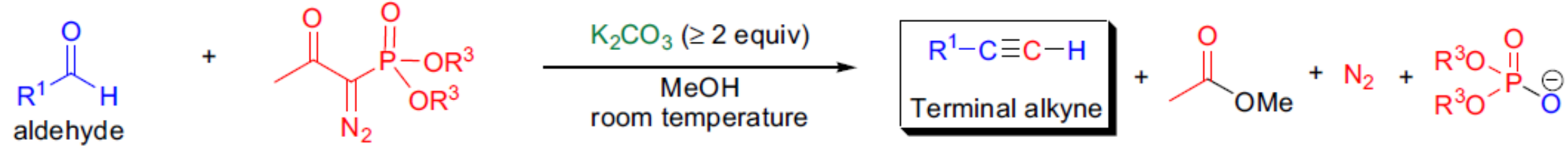
Gilbert & Weerasooriya (1979):



Seyferth-Gilbert homologation:

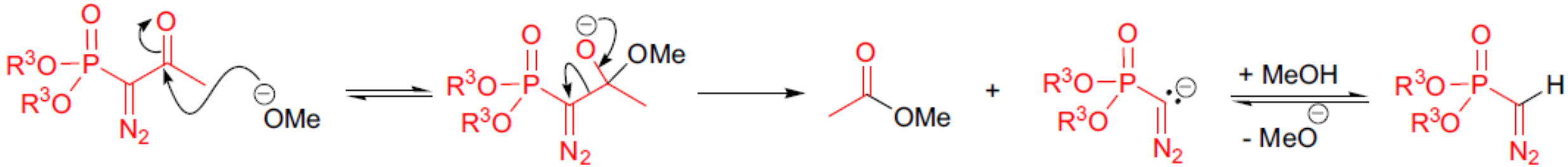


Modification for the synthesis of terminal alkynes (Ohira & Bestmann):

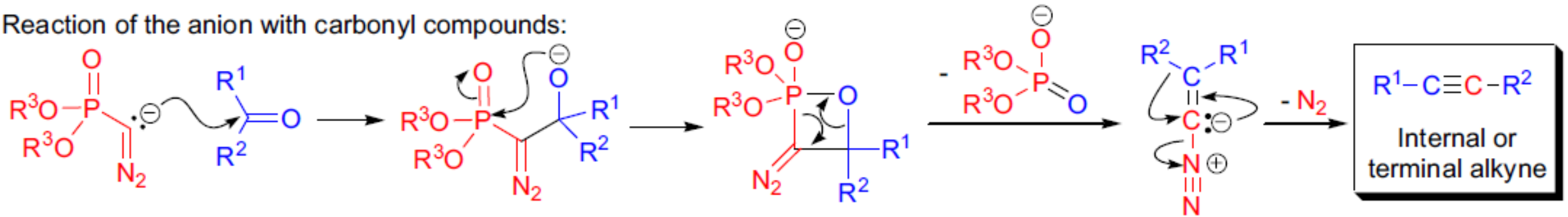


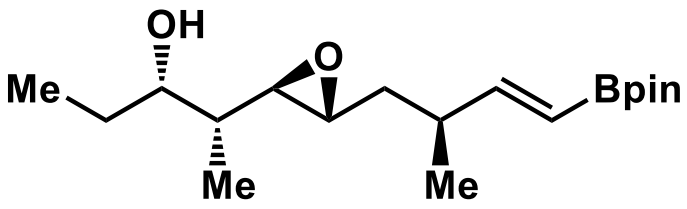
R^1 = alkyl, aryl, heteroaryl; R^2 = H, aryl, heteroaryl; R^3 = Me, Et; base: *n*-BuLi, KO-*t*Bu

Formation of the dialkylphosphonodiazomethane from dialkyl-1-diazo-2-oxopropylphosphonate:



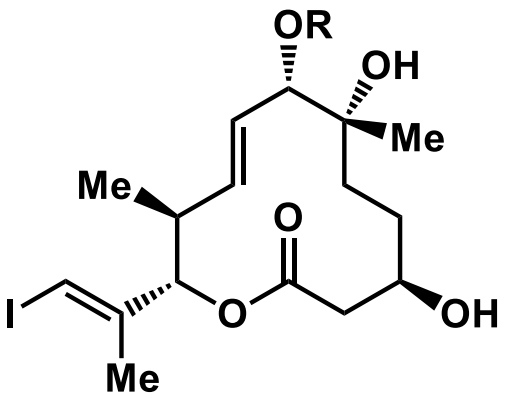
Reaction of the anion with carbonyl compounds:



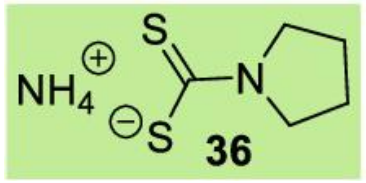


35

+



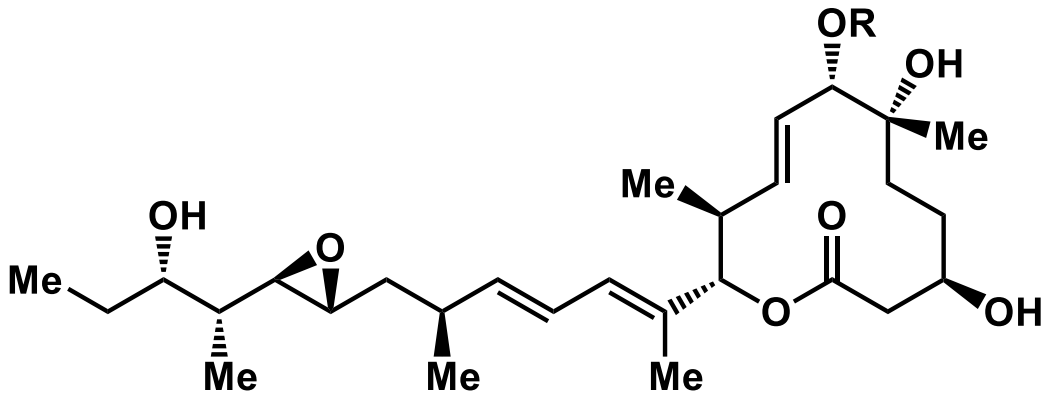
25 (R = H) or 26 (R = OAc)



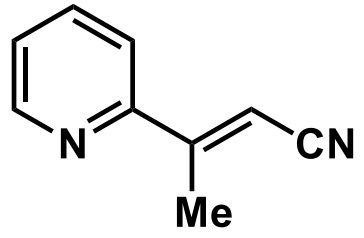
o) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_3PO_4
then 36

(76% for 1, 87% for 2)

- 7 or 8 steps LLS
- No Protecting Groups



1: Pladienolide A (R = H)
2: Pladienolide B (R = OAc)

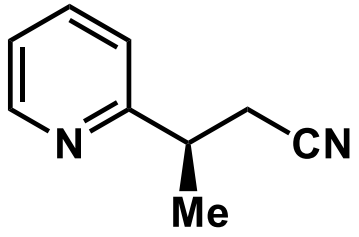


10

a) $Cu(OAc)_2$, 37, PMHS, ^tBuOH

(95%, 94% *ee*)

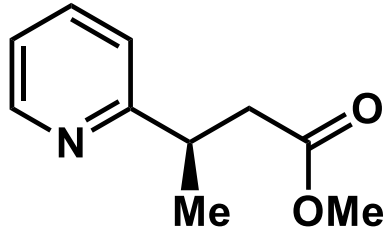
PMHS: polymethylhydrosiloxane



38

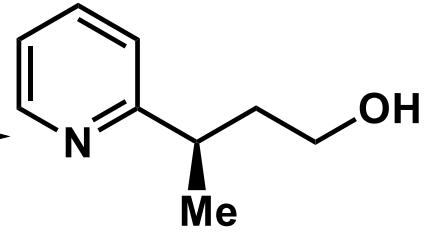
b) HCl in MeOH

(92%)



39

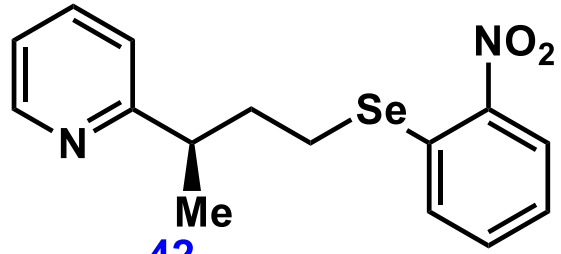
c) LAH



40

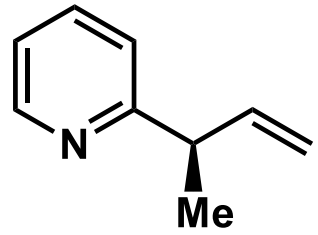
d) 41, $^nBu_3P$

(51%)

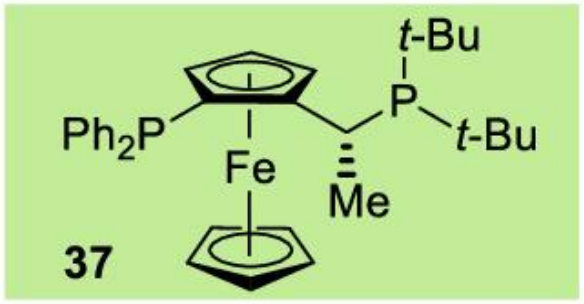


42

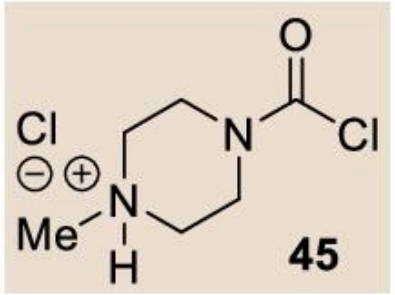
e) 43, Py



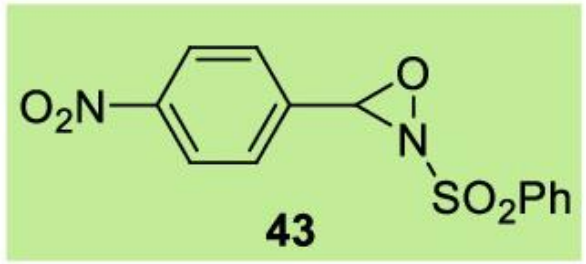
44



37

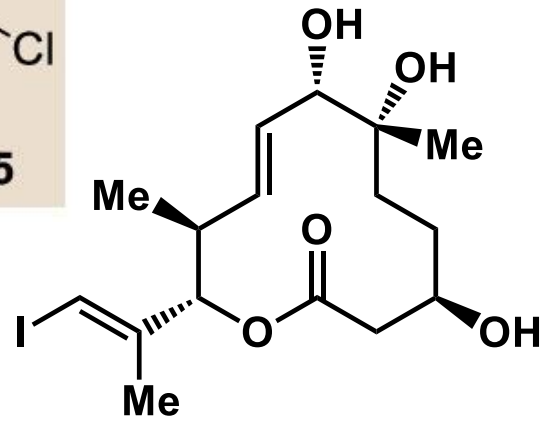


45



43

41

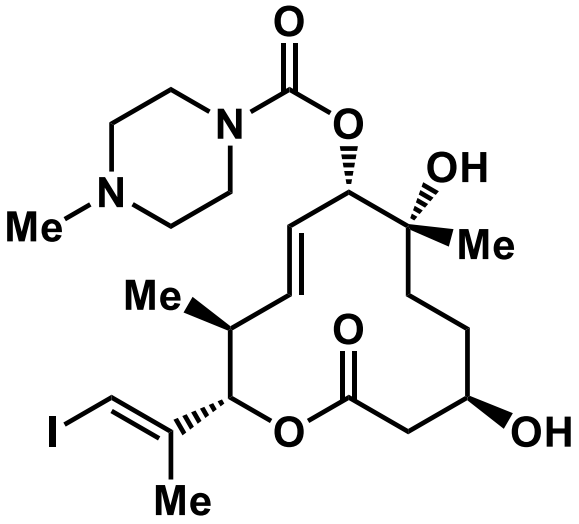


25

f) $^nBu_2SnO$;

then 45, TEA

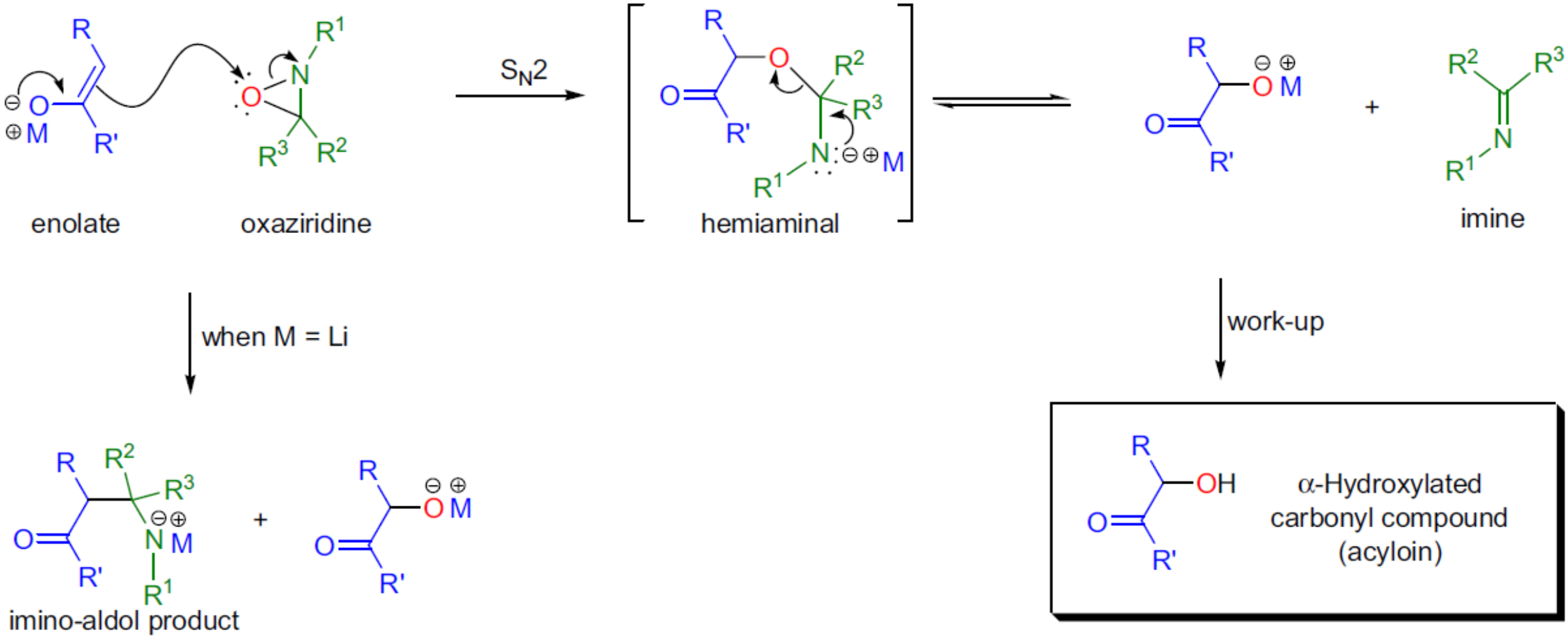
(81%)

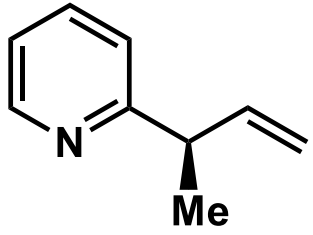


46

Davis氧化反应

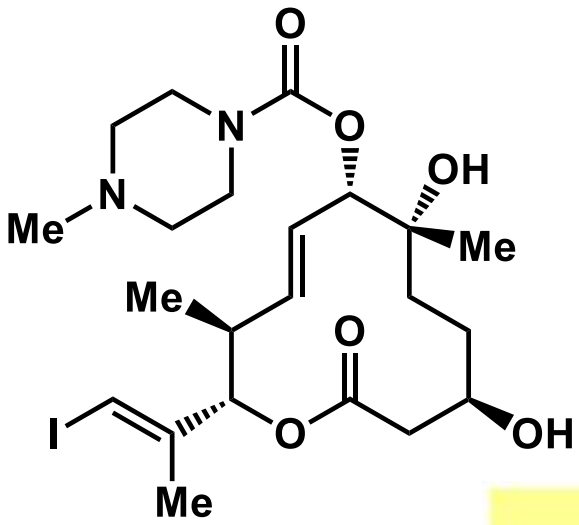
用2-sulfonyloxaziridine （N-磺酰基氧杂吖丙啶，戴维斯试剂）处理烯基氧负离子，羰基和酯基的α位能在温和条件下被氧化。用樟脑磺酸衍生物之类的具有光学活性的oxaziridine能实现不对称氧化。



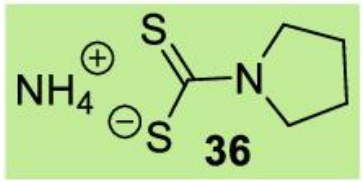


44

+



46

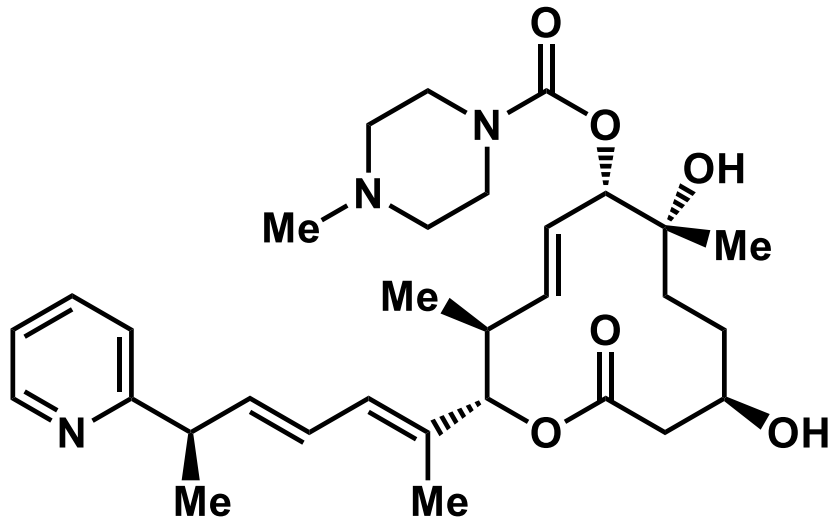


36

$Pd(PPh_3)_4$, TEA;
then 36

(80%)

Tabal 4



3: H3B-8800

Table 4

conditions	(*E*,*E*):(*Z*,*E*)
$Pd(OAc)_2$, P(*o*-tol)$_3$, DMF	3:4
$Pd(OAc)_2$, P(*o*-tol)$_3$, MeCN	1:2
$Pd(PPh_3)_4$, DMF	2:1
$Pd(PPh_3)_4$, MeCN	3:1
$Pd(PPh_3)_4$, PhH	5:1