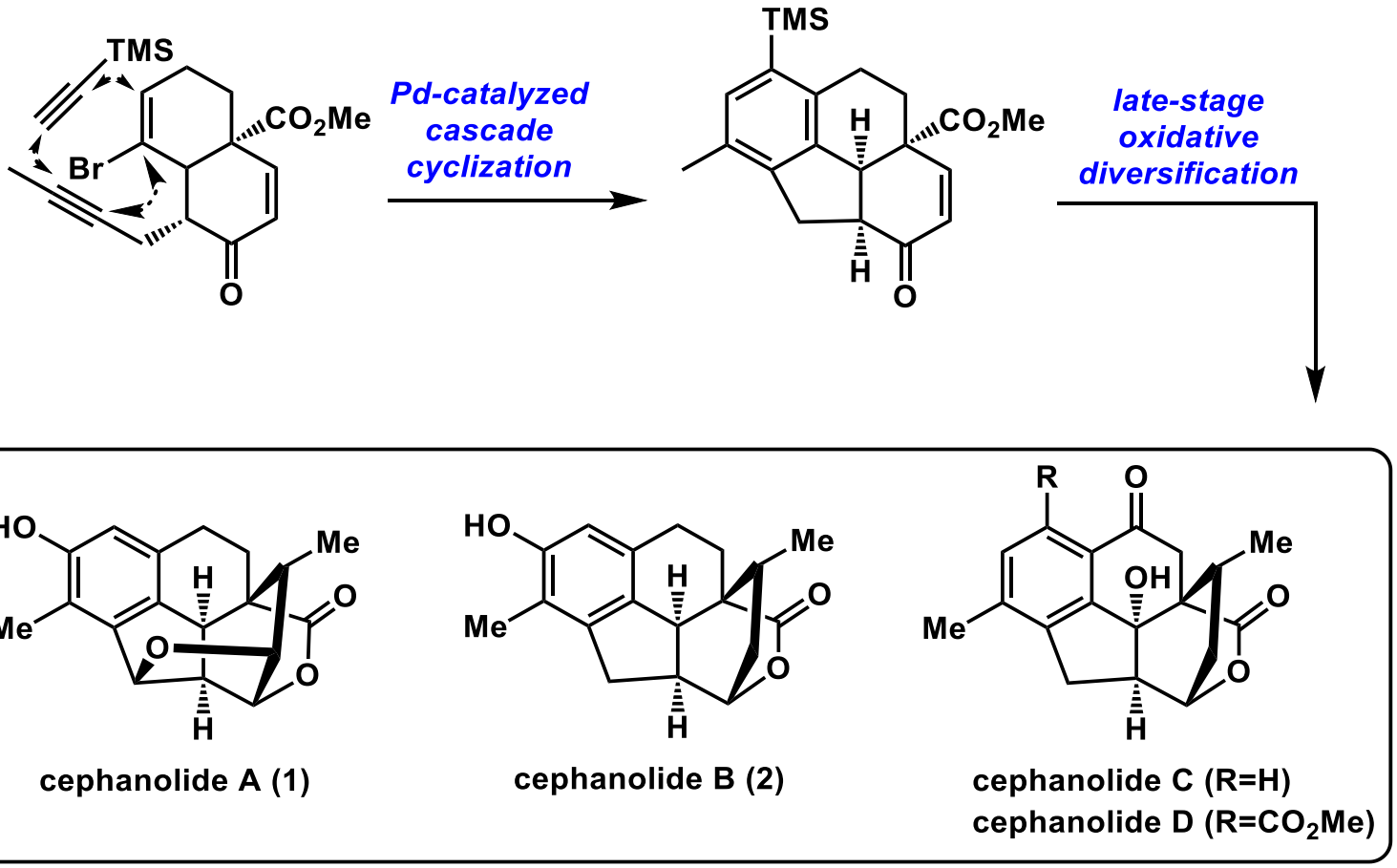
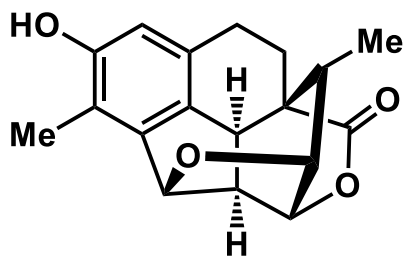
Asymmetric Total Syntheses of Cephalotane-Type Diterpenoids Cephanolides A−D

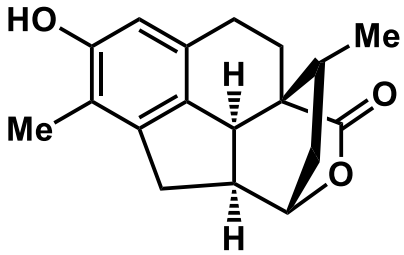
Zhineng Qing, Peng Mao, Tie Wang, and Hongbin Zhai*



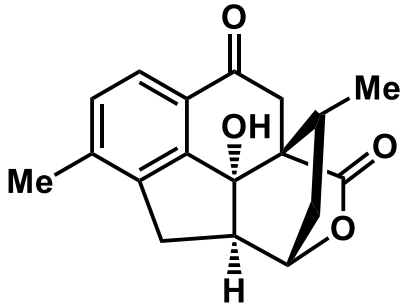
J. Am. Chem. Soc. **2022**, *144*, 10640.



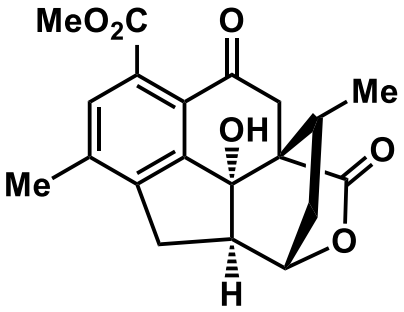
cephanolide A (1)



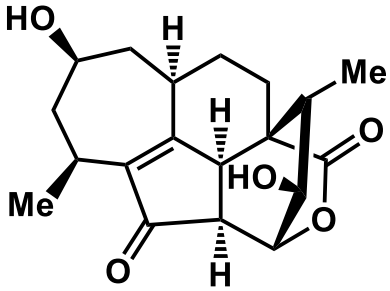
cephanolide B (2)



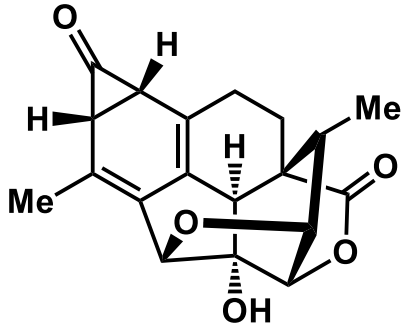
cephanolide C (3)



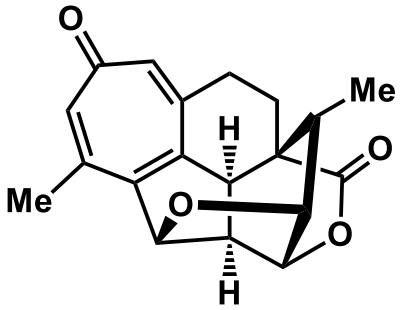
cephanolide D (4)



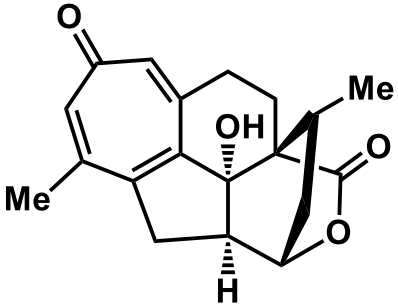
cephafortoid A (5)



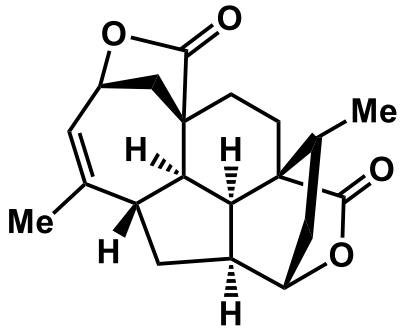
cephalotanin C (6)



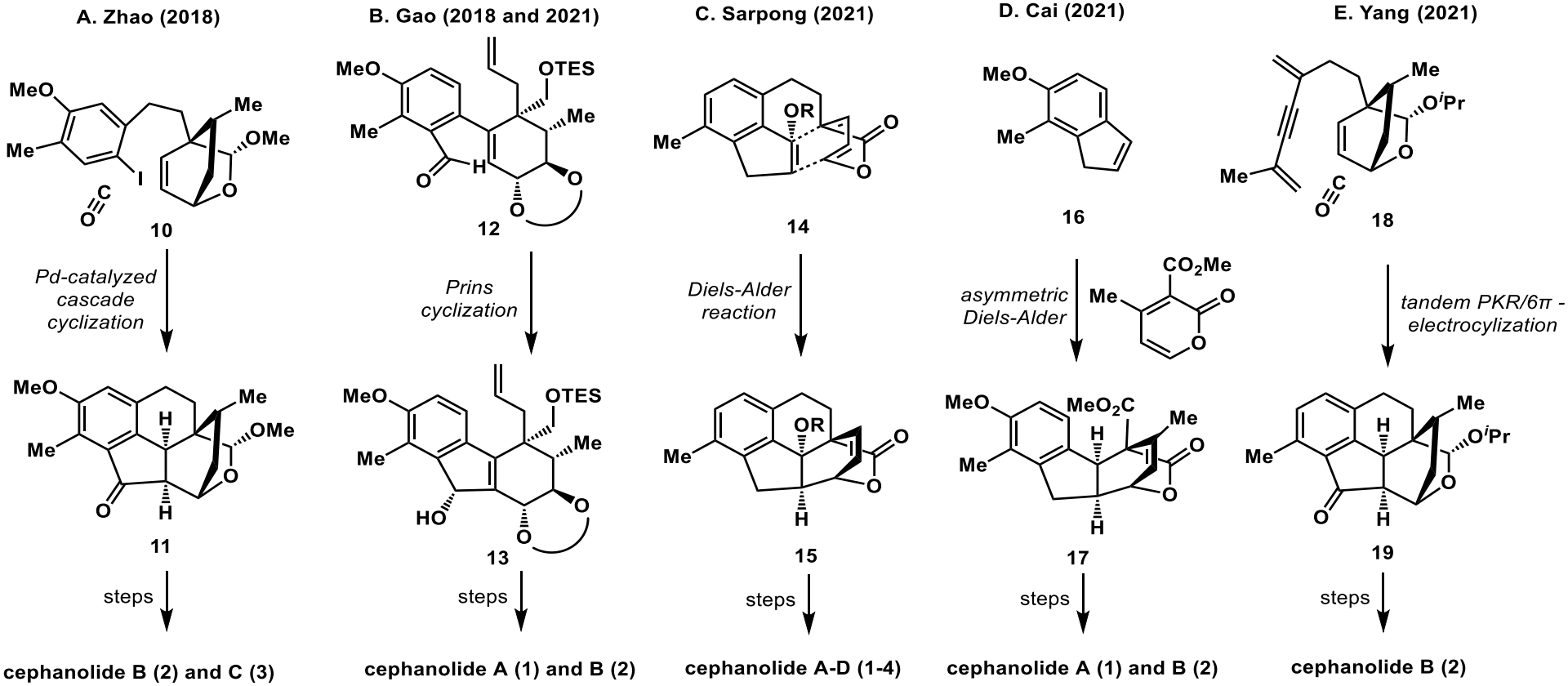
harringtonolide (7)

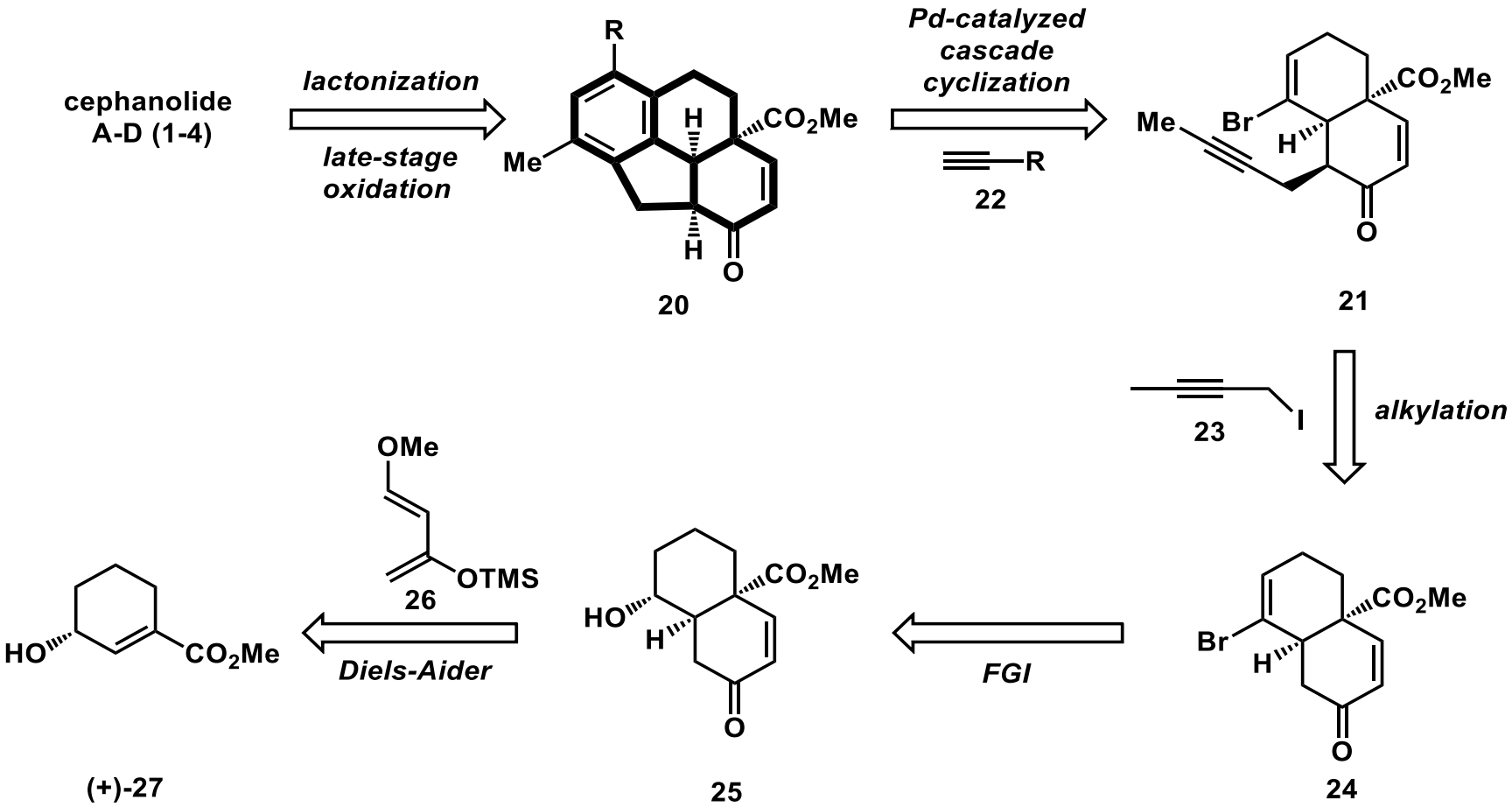


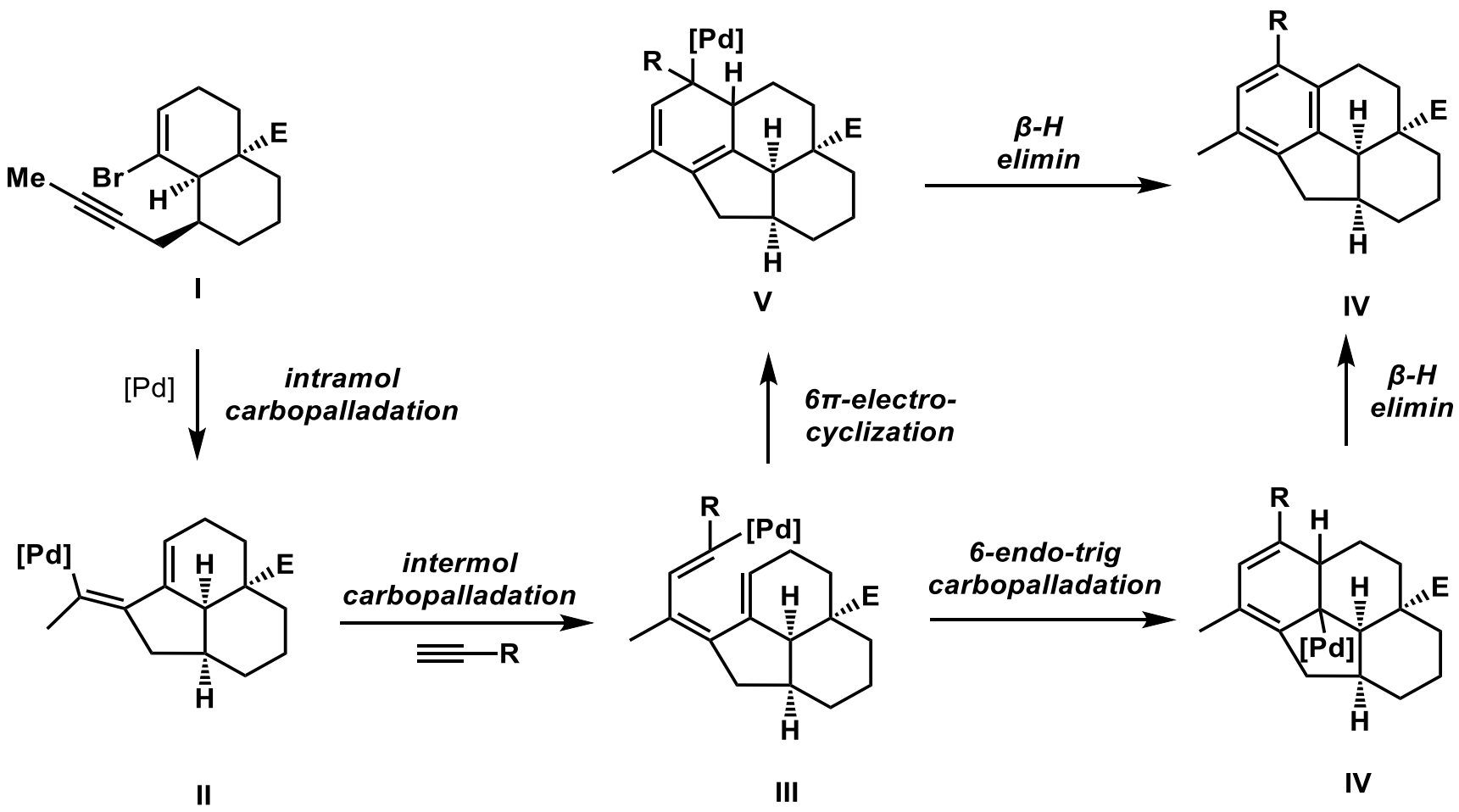
fortunolide A (8)

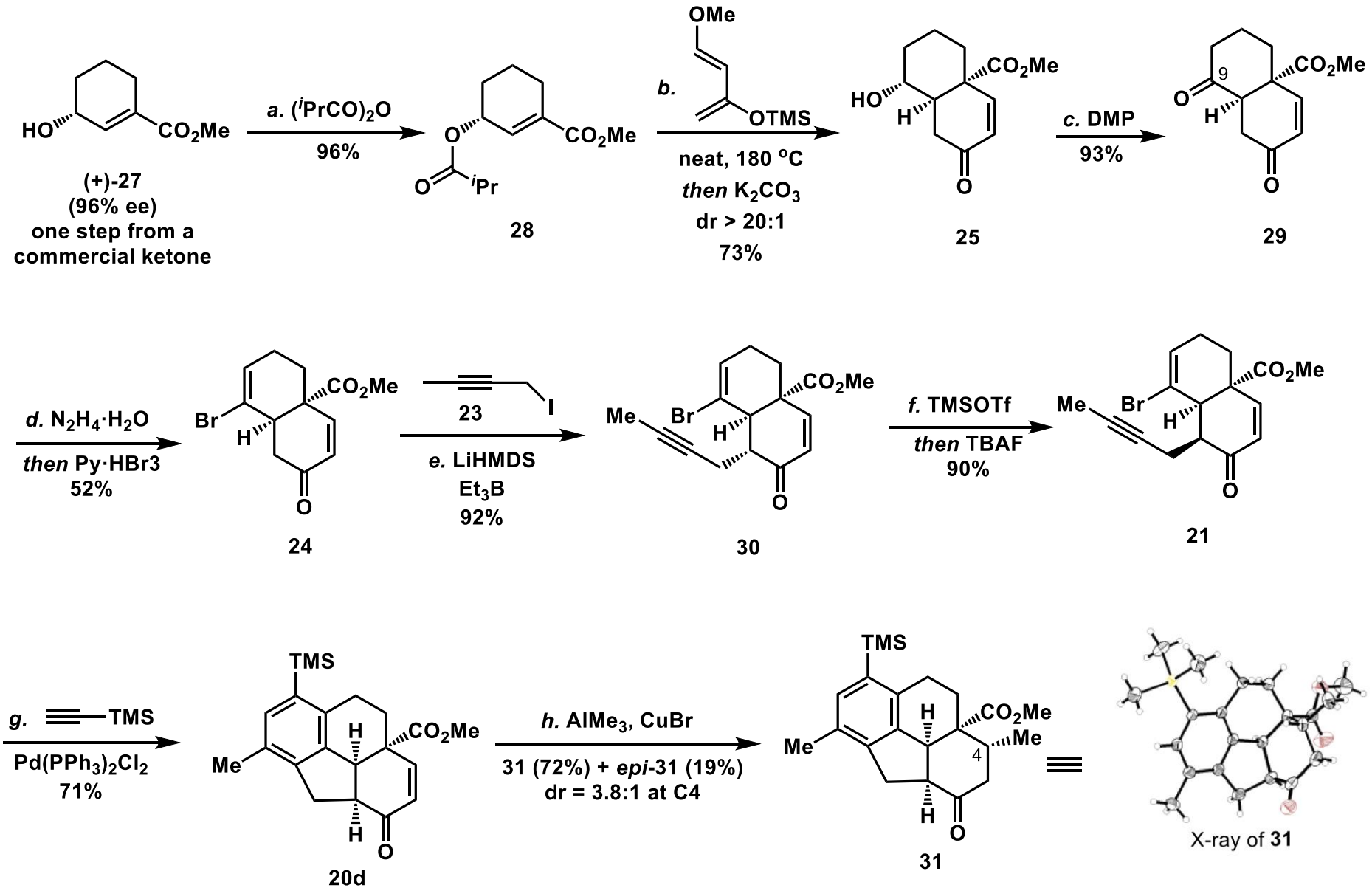


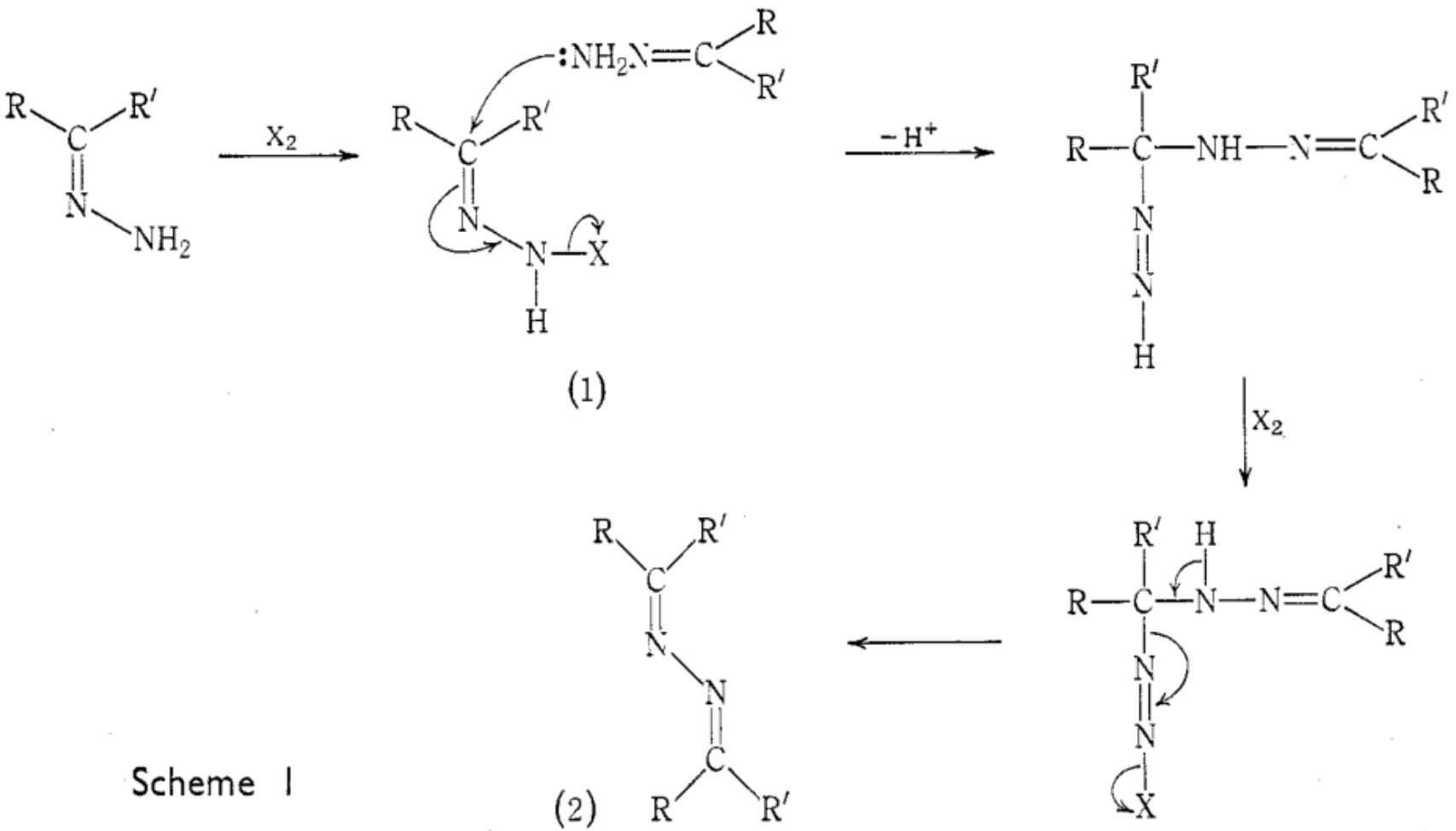
mannolide C (9)


A. Zhao (2018)
B. Gao (2018 and 2021)
C. Sarpong (2021)
D. Cai (2021)
E. Yang (2021)
10
12
14
16
18
Pd-catalyzed cascade cyclization
Prins cyclization
Diels-Alder reaction
asymmetric Diels-Alder
tandem PKR/6π - electrocylization
11
13
15
17
19
steps
cephanolide B (2) and C (3)
cephanolide A (1) and B (2)
cephanolide A-D (1-4)
cephanolide A (1) and B (2)
cephanolide B (2)


cephanolide
A-D (1-4)
lactonization
late-stage
oxidation
R
H
CO2Me
Me
H
O
20
Pd-catalyzed
cascade
cyclization
R
22
Me
Br
H
CO2Me
O
21
23
I
alkylation
OMe
OTMS
26
Diels-Aider
HO
CO2Me
(+)-27
HO
H
CO2Me
O
25
FGI
Br
H
CO2Me
O
24

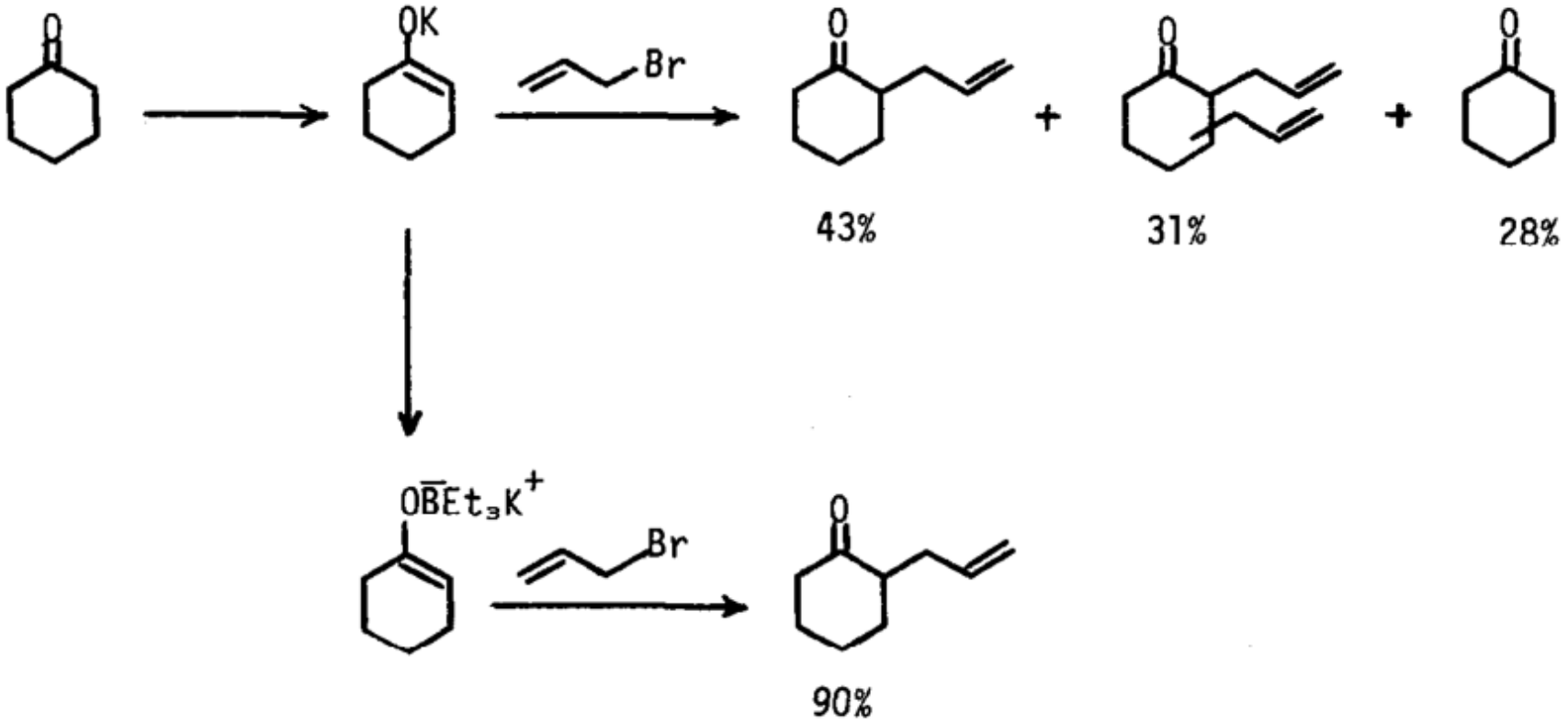

Me
Br
H
E
I
[Pd]
intramol
carbopalladation
[Pd]
H
E
II
intermol
carbopalladation
R
R
[Pd]
H
E
III
6π-electro-
cyclization
R
[Pd]
H
E
V
β-H
elimin
R
H
E
IV
6-endo-trig
carbopalladation
R
H
H
E
[Pd]
IV
β-H
elimin


HO
CO2Me
(+)-27
(96% ee)
one step from a
commercial ketone
a. (iPrCO)2O
96%
O
CO2Me
O
iPr
28
b.
OMe
OTMS
neat, 180 °C
then K2CO3
dr > 20:1
73%
HO
CO2Me
H
O
25
c. DMP
93%
9
O
CO2Me
H
O
29
d. N2H4·H2O
then Py·HBr3
52%
Br
CO2Me
H
O
24
23
I
e. LiHMDS
Et3B
92%
Me
Br
CO2Me
H
O
30
f. TMSOTf
then TBAF
90%
Me
Br
CO2Me
H
O
21
g.
TMS
Pd(PPh3)2Cl2
71%
TMS
Me
H
CO2Me
H
O
20d
h. AlMe3, CuBr
31 (72%) + epi-31 (19%)
dr = 3.8:1 at C4
TMS
Me
H
CO2Me
4
Me
H
O
31
X-ray of 31



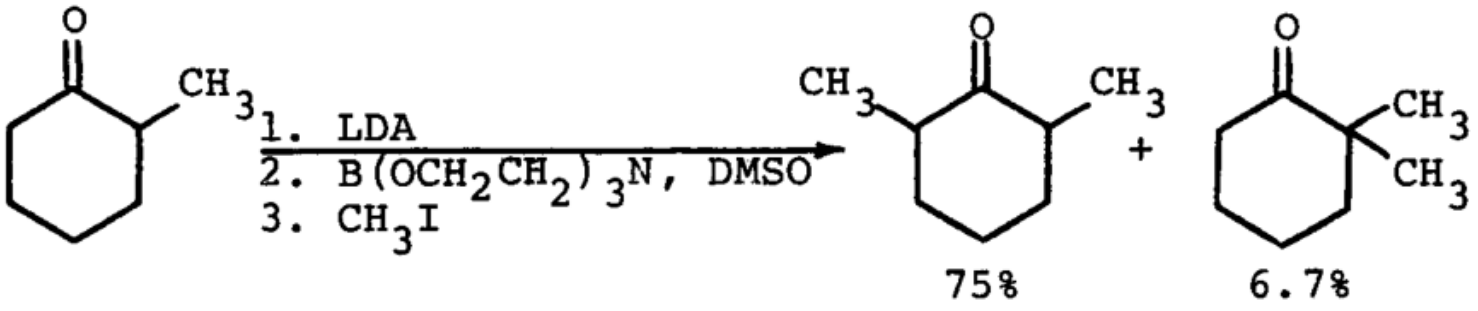
Scheme 1

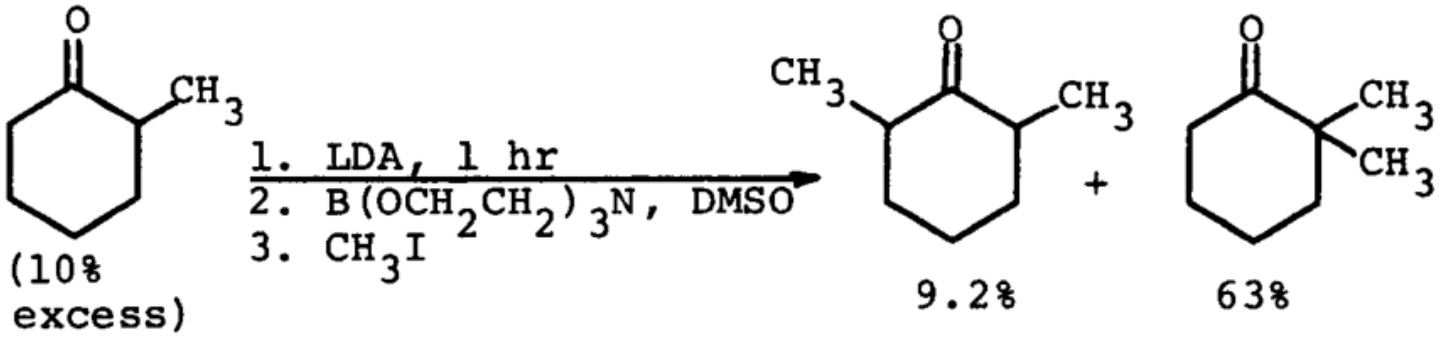
Aust. J. Chem. **1971**, *24*, 1437.



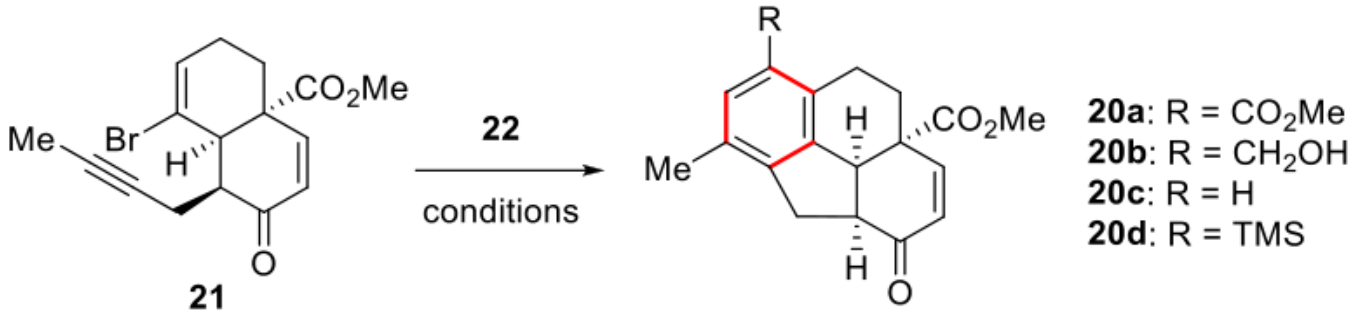
(2)

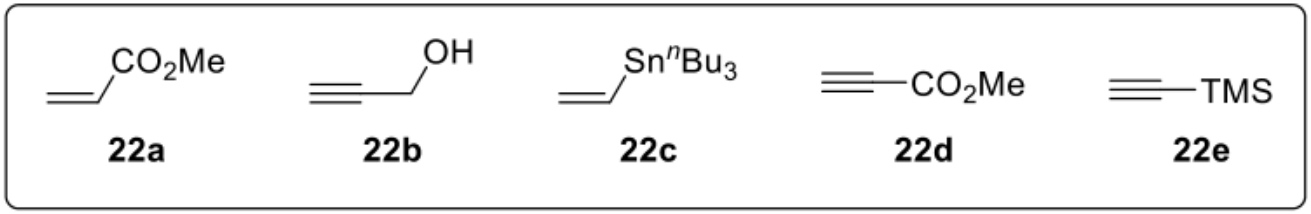
Tetrahedron Lett. **1979**, *20*, 845.





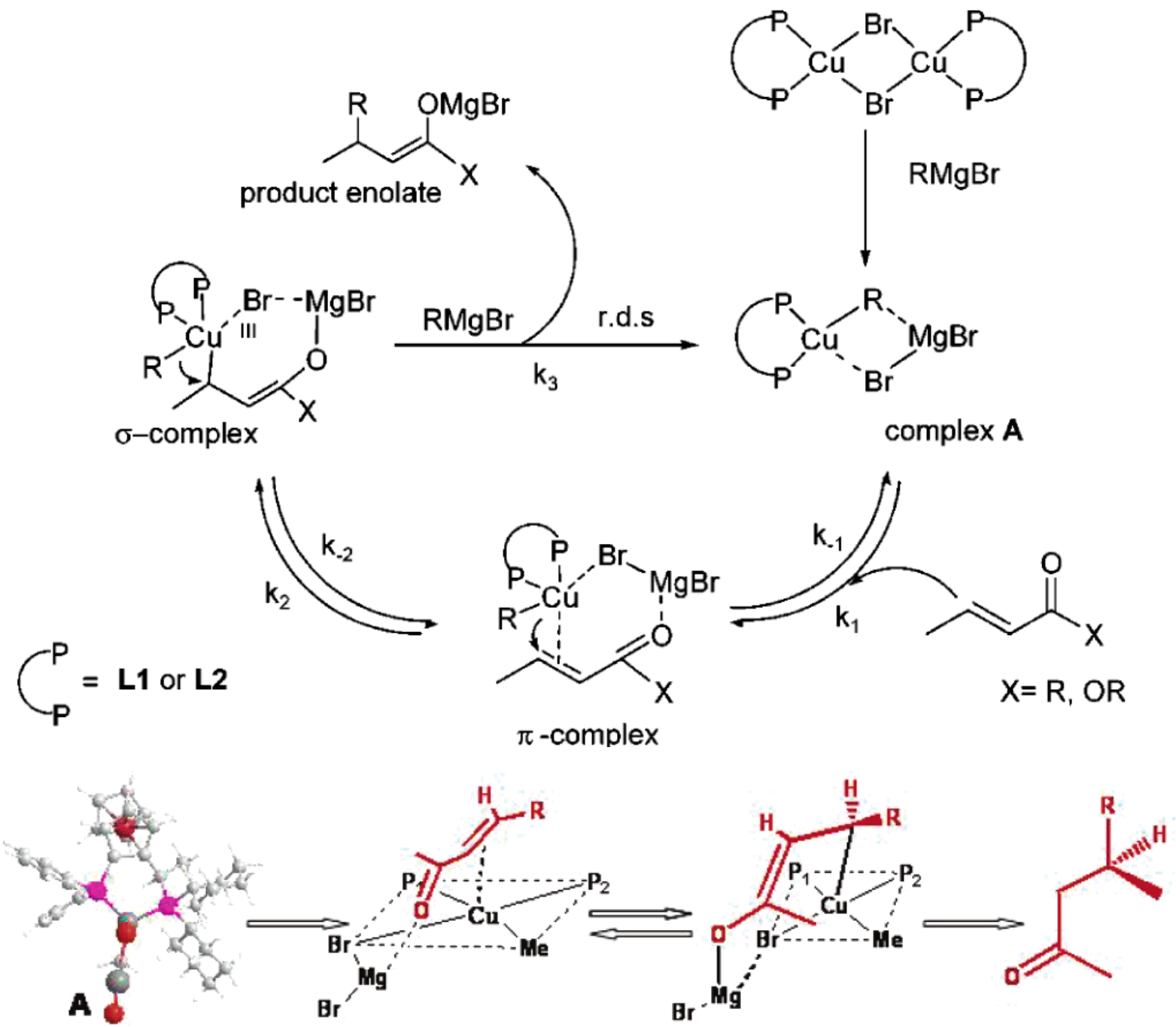
Synth. Commun. **1978**, *8*, 9.



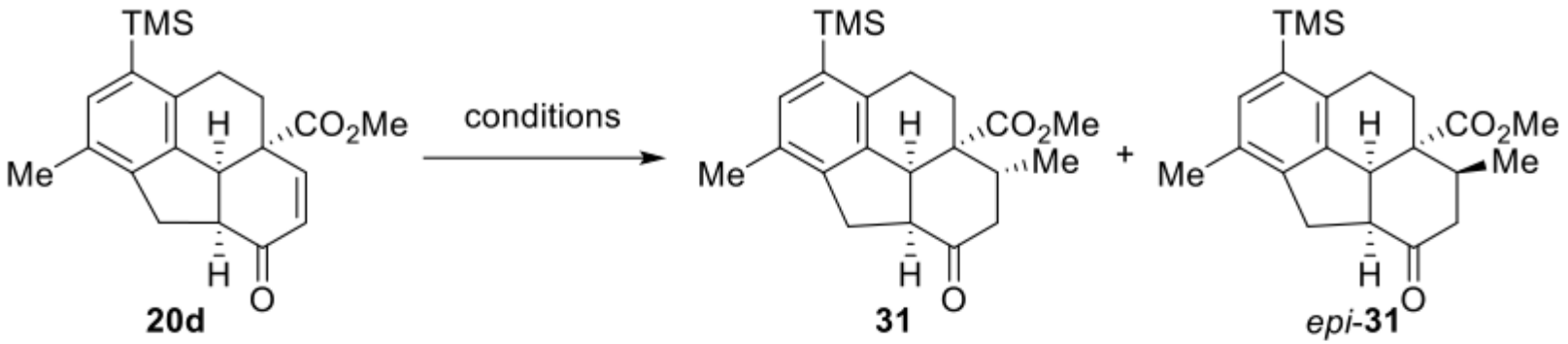


entry	reactant **22**	reaction conditions	yield[b]
1	**22a**	$Pd(OAc)_2$, PPh_3, Ag_2CO_3, MeCN, 120 °C	trace
2	**22b**	$Pd(OAc)_2$, PPh_3, CuI, Et_3N, MeCN, reflux	ND
3	**22c**	$Pd(PPh_3)_4$, PhMe, reflux; DDQ, DCM, rt	trace
4	**22d**	$Pd(PPh_3)_2Cl_2$, Et_3N, CH_3CN, 100 °C	ND
5	**22e**	$Pd(PPh_3)_2Cl_2$, Et_3N, CH_3CN, 100 °C	60%
6	**22e**	$Pd(PPh_3)_4$, Et_3N, CH_3CN, 100 °C	52%
7	**22e**	$Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 100 °C	71%
8	**22e**	$Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 120 °C	68%
9	**22e**	$Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 80 °C	59%

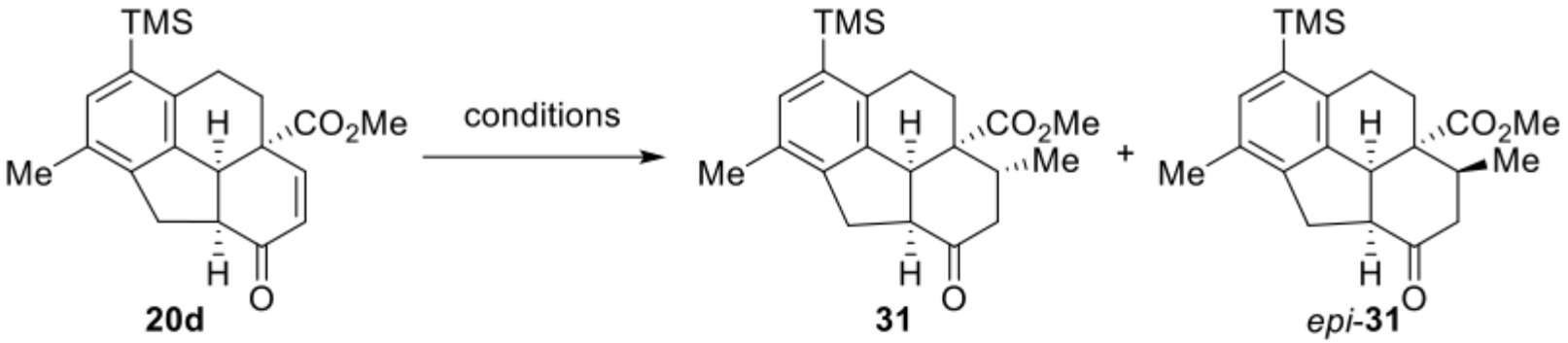
[a]Reactions were performed on 20 mg of **21** scale. ND = not detected, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide. [b]Isolated yield.



J. Am. Chem. Soc. **2006**, *128*, 9103.

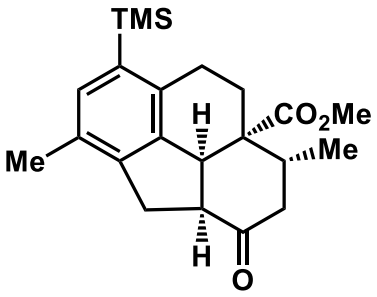


Entry	Conditions	Yield[a]	
		31	*epi*-**31**
1	MeLi (4 equiv), CuI (2 equiv), THF, 0 °C	trace	30%
2	$AlMe_3$ (5.0 equiv), $Ni(acac)_2$ (0.1 equiv), LiBr (3.0 equiv), THF, 0 °C	20%	ND
3	$AlMe_3$ (5.0 equiv), $Ni(acac)_2$ (0.1 equiv), THF, 0 °C	42%	ND
4	$AlMe_3$ (5.0 equiv), $Ni(acac)_2$ (0.5 equiv), THF, 0 °C	35%	ND
5	$AlMe_3$ (5.0 equiv), $Ni(acac)_2$ (0.1 equiv), EtOAc, 0 °C	36%	ND
6	$ZnMe_2$ (5.0 equiv), $Ni(acac)_2$ (0.1 equiv), LiBr (3.0 equiv), THF, 0 °C	No reaction	



Entry	Conditions	Yield[a]	
		31	*epi*-**31**
7	MeMgCl (2 equiv), $MnCl_2$ (0.3 equiv), CuCl (0.05 equiv), THF, 0 °C	13%	70%
8	$AlMe_3$ (4.0 equiv), CuBr (0.1 equiv), THF, 0 °C	52%	18%
9	$AlMe_3$ (4.0 equiv), CuBr (0.1 equiv), TMSCl (3.0 equiv), THF, 0 °C	68%	25%
10	$AlMe_3$ (4.0 equiv), CuBr (0.1 equiv), TMSCl (3.0 equiv), THF, rt	70%	24%
11	$AlMe_3$ (4.0 equiv), CuBr (0.1 equiv), TMSCl (3.0 equiv), THF, -30 °C	53%	39%
12	$AlMe_3$ (4.0 equiv), CuBr (0.3 equiv), TMSCl (3.0 equiv), THF, rt	72%	19%

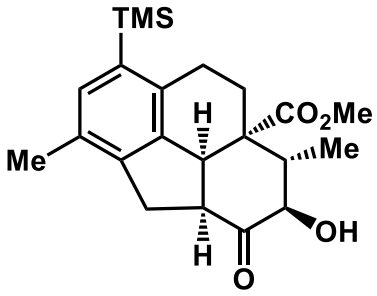
[a]Isolated yield, ND = not detected.



31

i. LiTMP
(+)-camphorsulfonyl
oxazidiridine

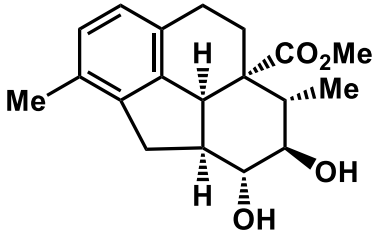
80%
(99% brsm)



32

j. $NaBH_4$

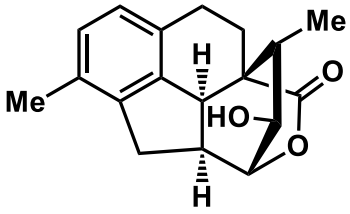
then 2 *N* KOH
81%



33

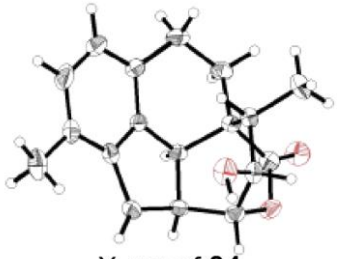
k. TCBC, DMAP

66%



34

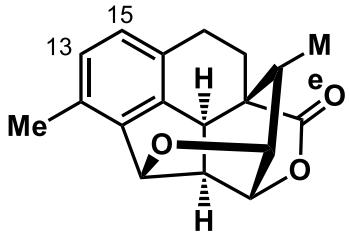
≡



X-ray of **34**

l. I_2, PIDA, *hv*

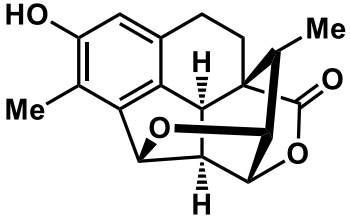
98%



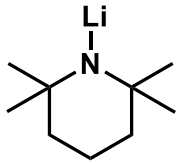
35

m. $MeOCHCl_2$
$FeCl_3$

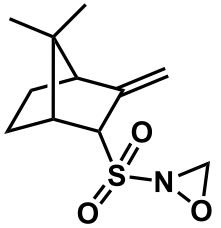
n. mCPBA
62% (two steps)
C13/C15 > 20:1



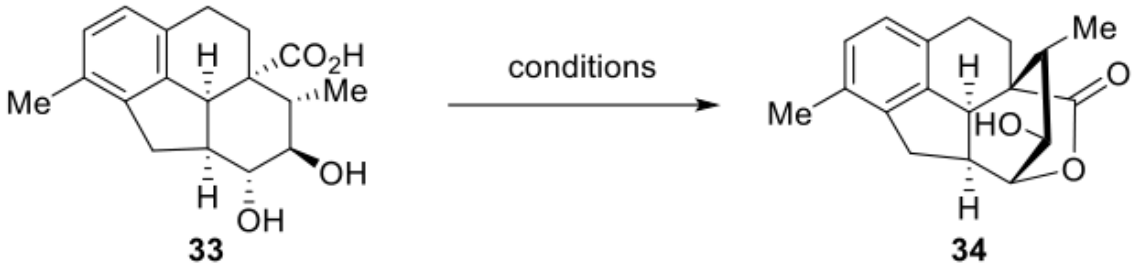
cephanolide A (1)
(14 steps from 27)



i. LiTMP



(+)-camphorsulfonyl
oxazidiridine

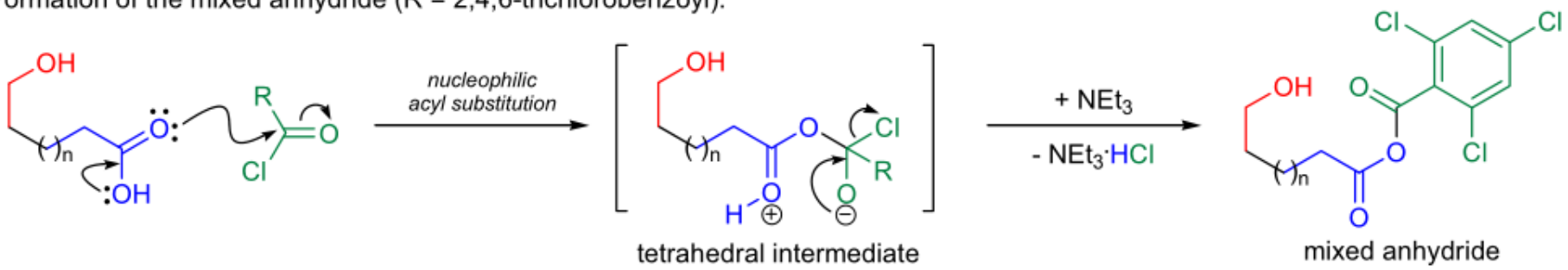


Entry	Conditions	Yield[a]
1	EDCI (3 equiv), DMAP (0.1 equiv), DMF, rt to 100 °C	10%
2	EDCI (3 equiv), DMAP (0.1 equiv), DCM, rt	22%
3	DCC (3 equiv), DMAP (0.1 equiv), DCM, rt	25%
4	Mukaiyama's reagent (2 equiv), Et_3N (3 equiv), DCM, rt	40%
5	TsCl (1 equiv), 1-methylimidazole (2 equiv), CH_3CN, rt	15%
6	BOP-Cl (1.3 equiv), Et_3N (3.0 equiv), DCM, rt	54%
7	TCBC (2 equiv), Et_3N (3 equiv), THF, 0 °C; DMAP (2 equiv), PhMe, 75 °C	66%

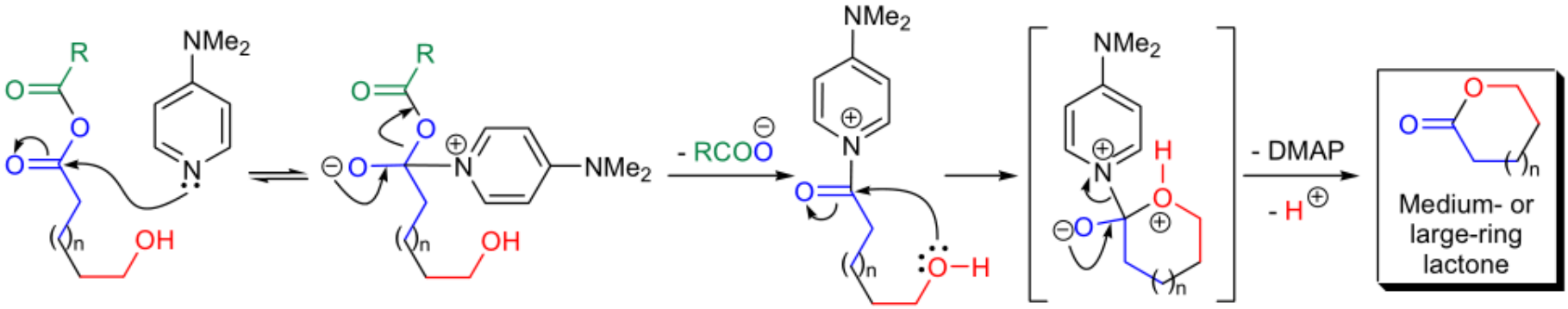
[a]Isolated yield. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine, DMF = N,N-dimethylformamide,

YAMAGUCHI MACROLACTONIZATION

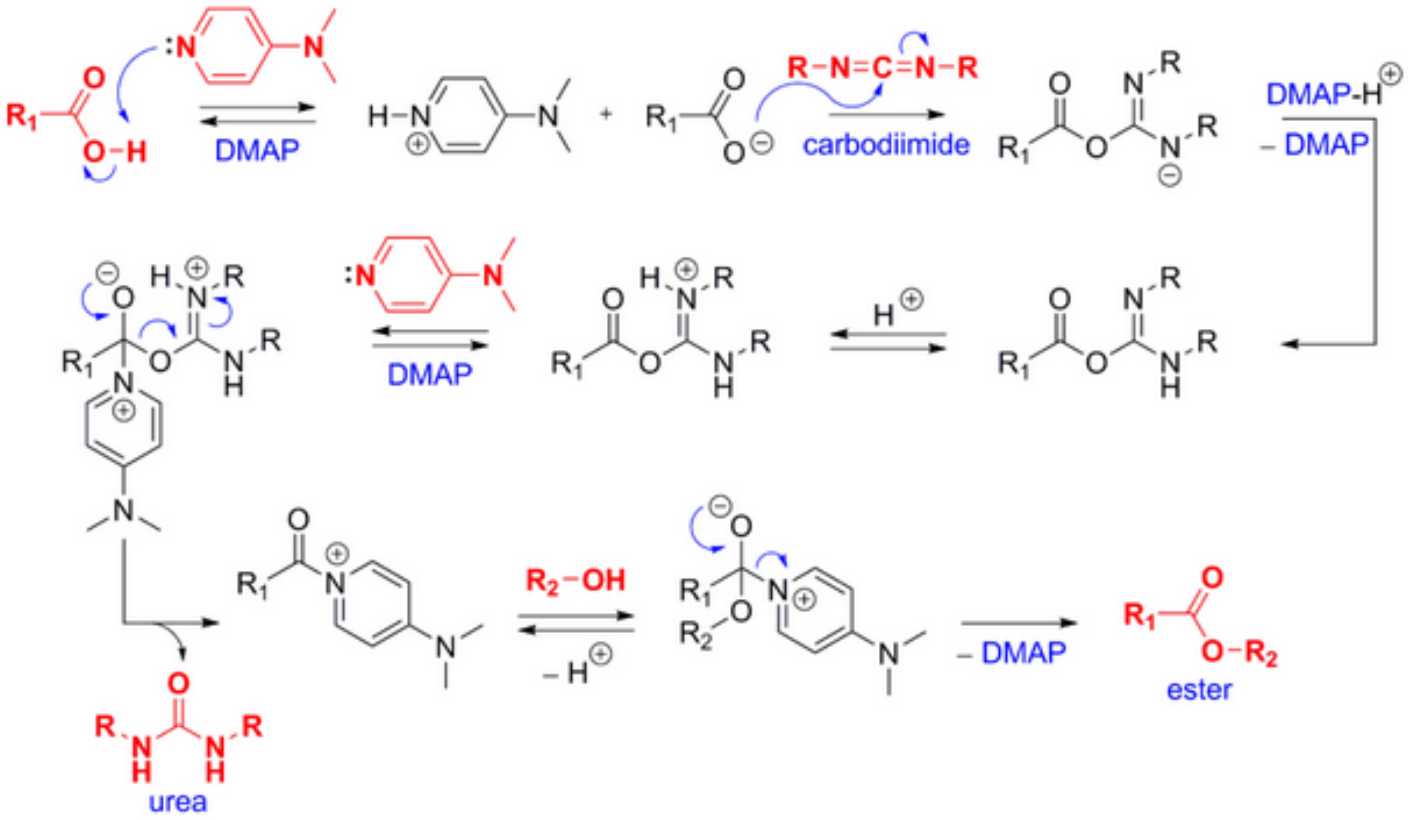
Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):



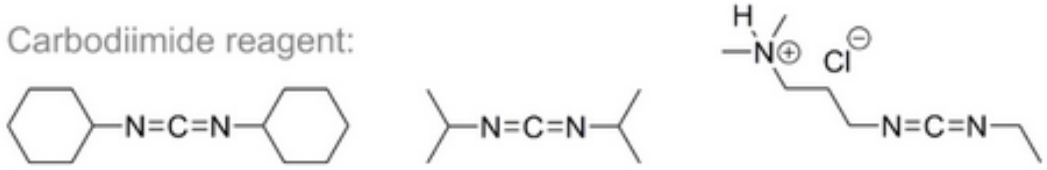
Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



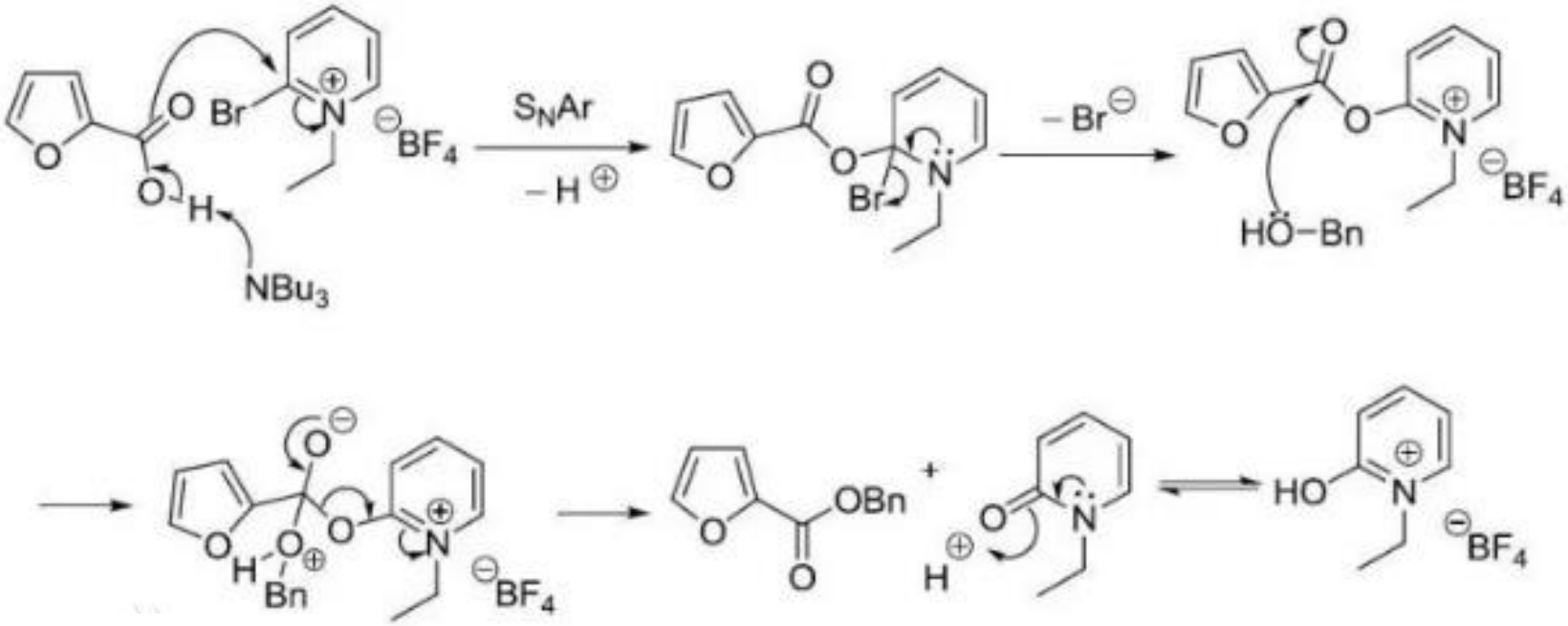
Steglich lactonization

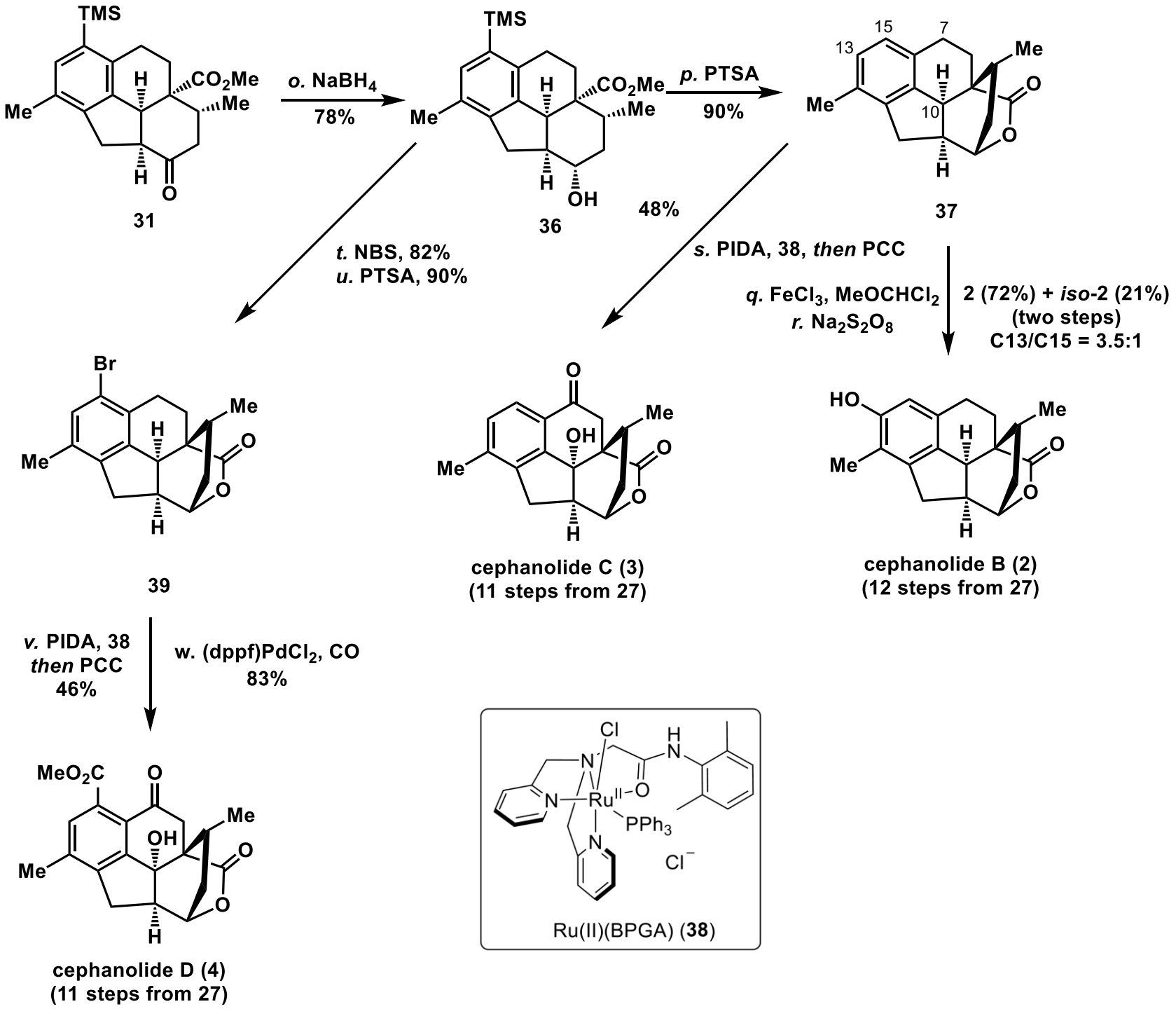


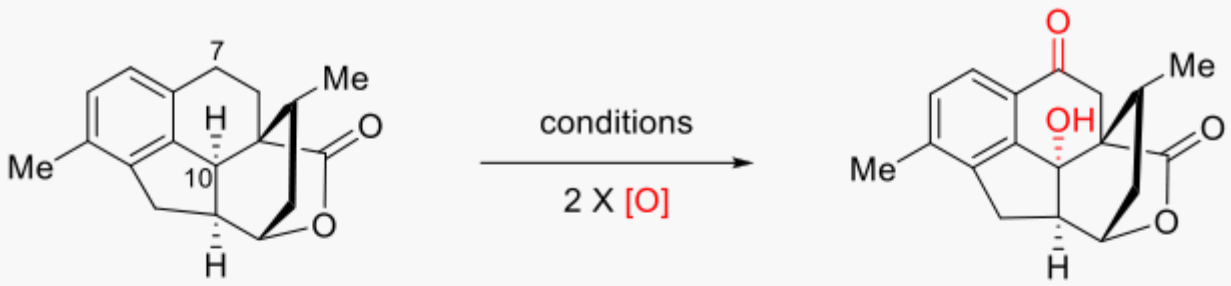
Carbodiimide reagent:



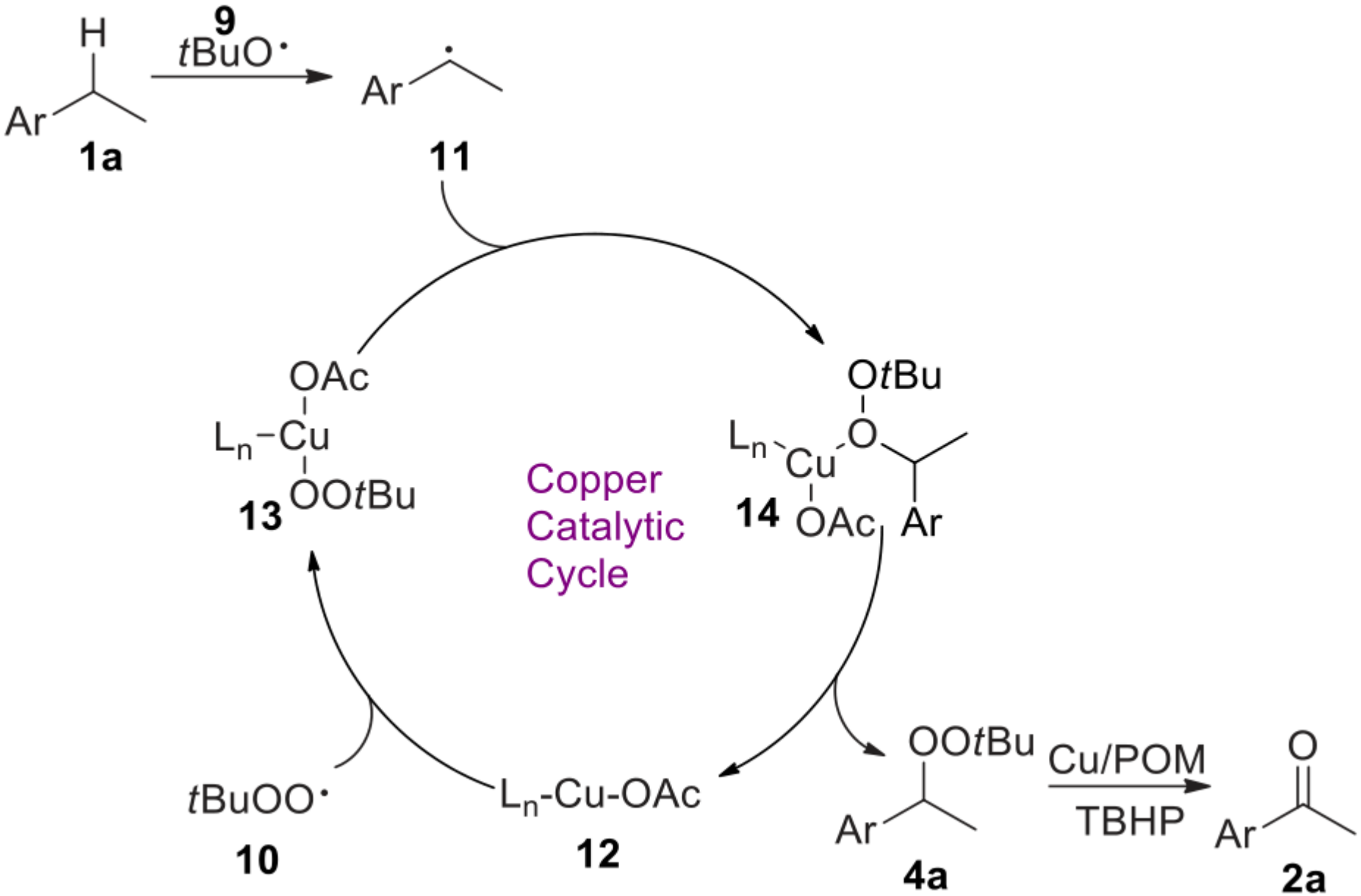
Mukaiyama reagent



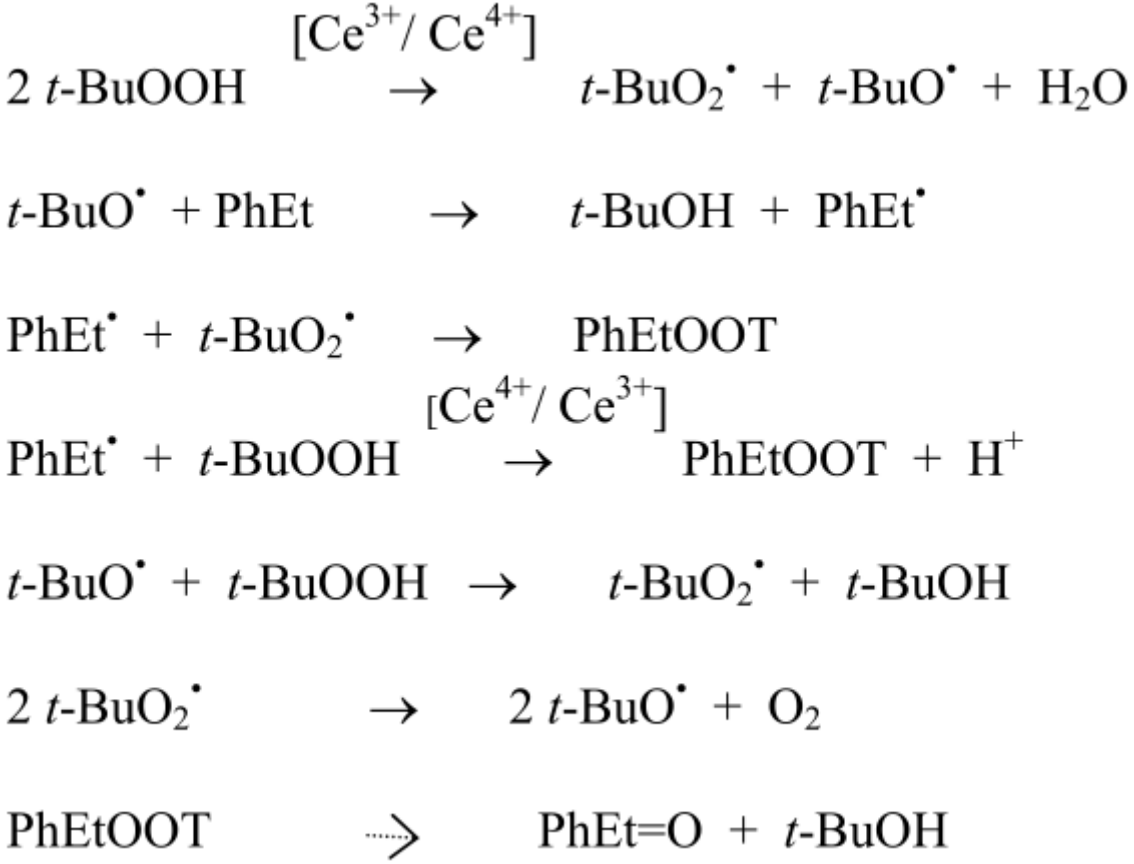

TMS
H
CO2Me
Me
Me
H
O
31
o. NaBH4
78%
TMS
H
CO2Me
Me
Me
H
OH
36
p. PTSA
90%
15
7
13
Me
H
Me
O
10
O
H
37
48%
t. NBS, 82%
u. PTSA, 90%
s. PIDA, 38, then PCC
q. FeCl3, MeOCHCl2
r. Na2S2O8
2 (72%) + iso-2 (21%)
(two steps)
C13/C15 = 3.5:1
Br
H
Me
Me
O
O
H
39
O
OH
Me
Me
O
O
H
cephanolide C (3)
(11 steps from 27)
HO
H
Me
Me
O
O
H
cephanolide B (2)
(12 steps from 27)
v. PIDA, 38
then PCC
46%
w. (dppf)PdCl2, CO
83%
MeO2C
O
OH
Me
Me
O
O
H
cephanolide D (4)
(11 steps from 27)
Cl
H
N
N
N
Ru
II
O
PPh3
N
Cl−
Ru(II)(BPGA) (38)



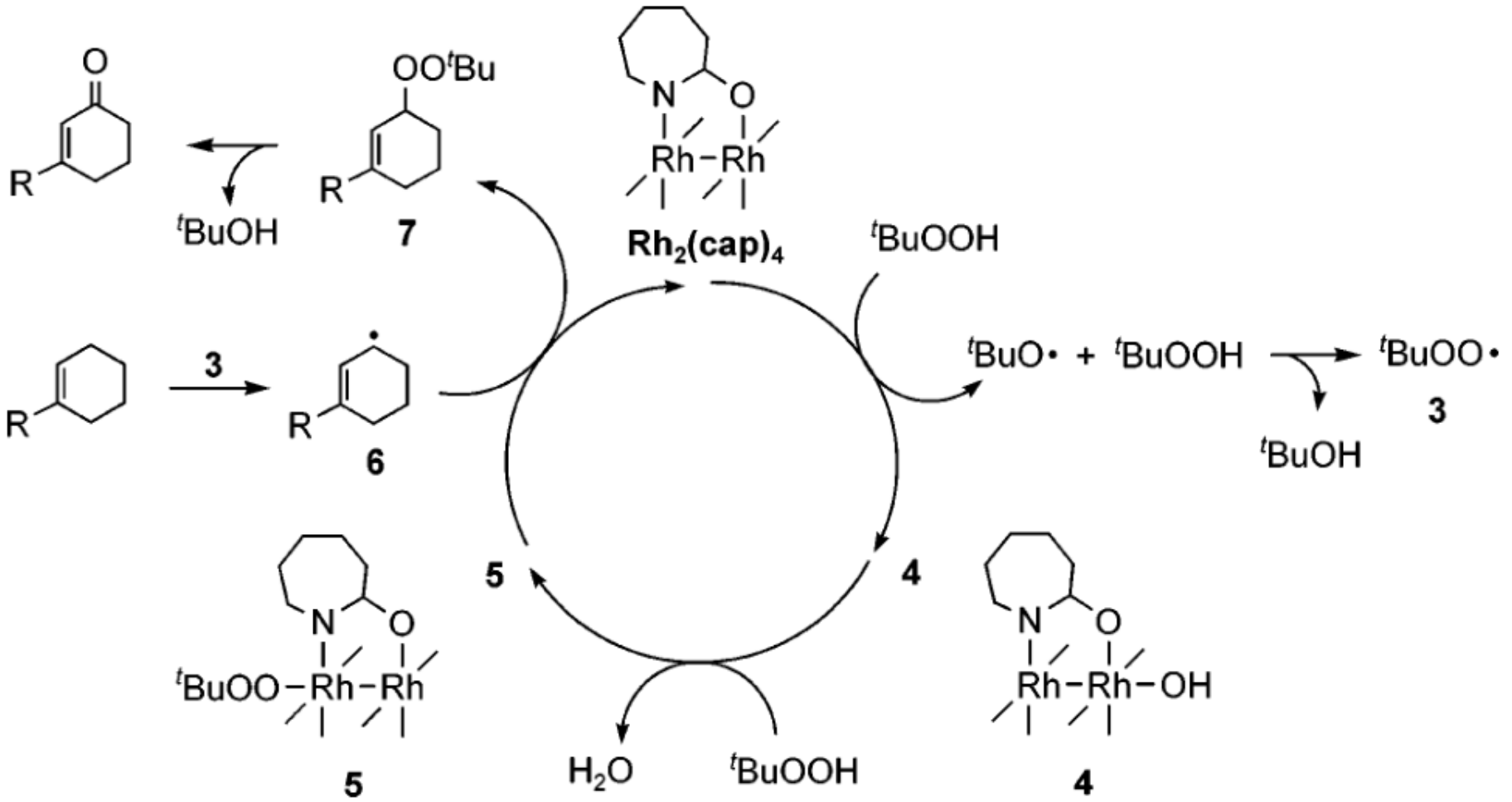
entry	conditions	result
1	DDQ, DCM/H_2O (1:1), rt, 10 h	no reaction
2	$Co(OAc)_2$, TBHP, CH_3CN, 50 °C, 12 h	**3** (12%)
3	CrO_3, 3,5-dimethylpyrazole, DCM, rt, 2 d	**3** (28%)
4	CrO_3, 3,5-dimethylpyrazole, DCM, 50 °C, sealed tube, 2 d	**3** (38%)
5	CrO_3, 3,5-dimethylpyrazole, DCM, 70 °C, sealed tube, 2 d	**3** (30%)
6	CrO_3, AcOH, DCM, rt, 1 h	ND
7	PCC, Celite, PhH, 70 °C, 24 h	ND
8	$Rh_2(cap)_4$, TBHP, $NaHCO_3$, DCE, 40 °C, 7 h	**3** (36%)
9	Ru(II)(BPGA), PIDA, F_5BzOH, H_2O, $(CHCl_2)_2$, 50 °C, 24 h	**3** (37%)
10	Ru(II)(BPGA), PIDA, F_5BzOH, $(CHCl_2)_2$, H_2O 50 °C, 24 h; PCC, 0 °C, 30 min	**3** (48%)



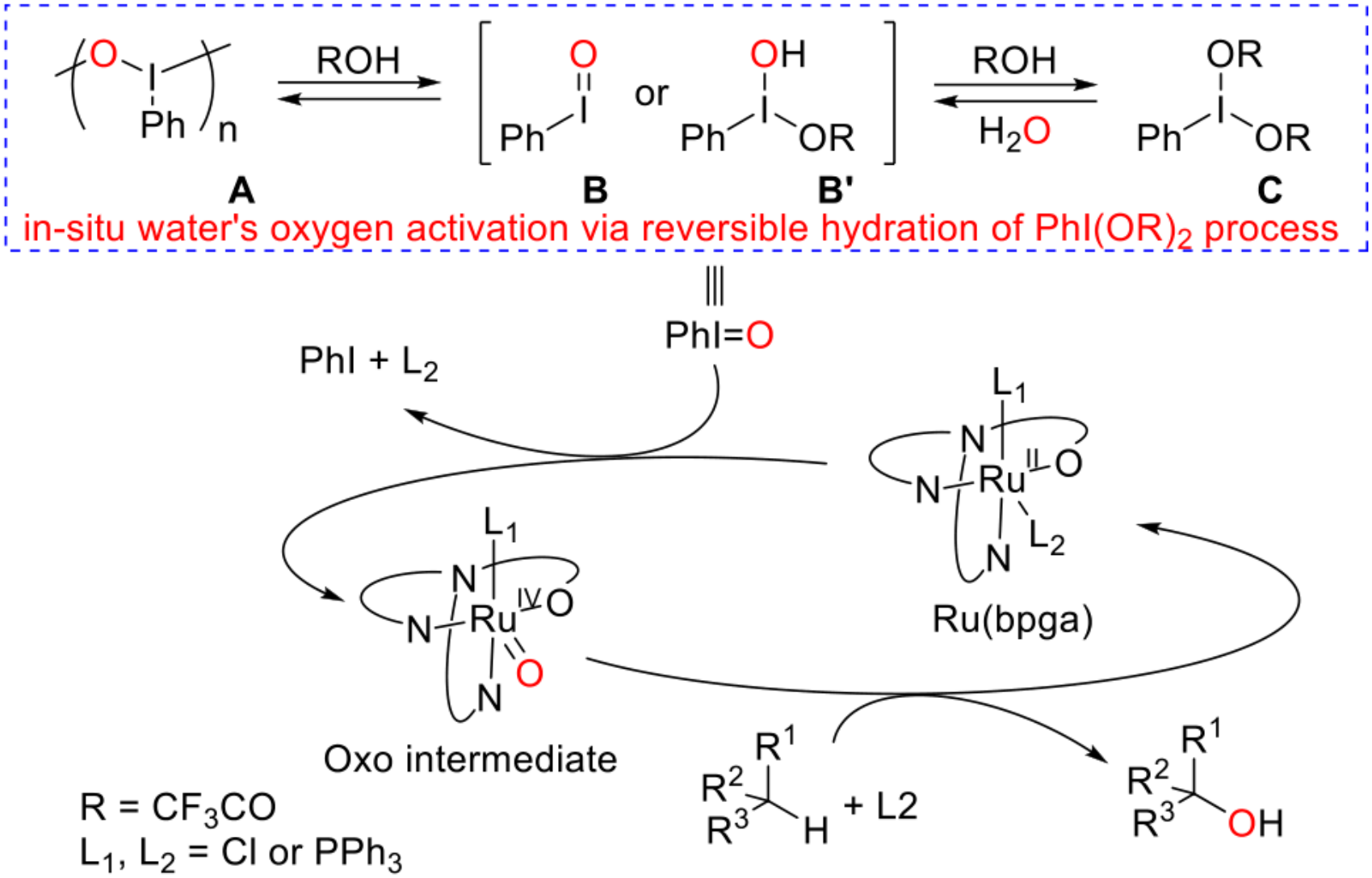
J. Org. Chem. **2020**, *85*, 3101−3109



Molecules **2010**, *15*, 747.



J. Am. Chem. Soc. **2004**, *126*, 13622.



Org. Lett. **2021**, *23*, 7301.