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Total Synthesis | Hot Paper

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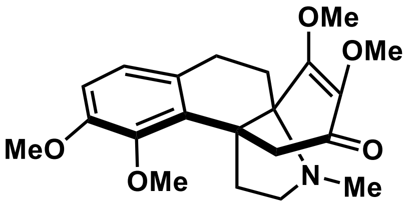
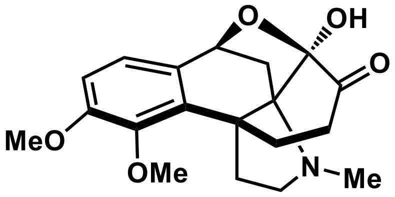
Total Synthesis of Metaphanine and Oxoepistephamiersine

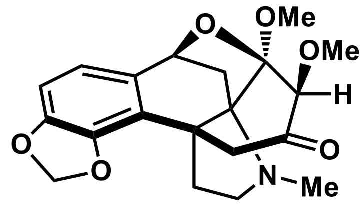
Ya-Kui Sun[+], *Jin-Bao Qiao*[+], *Yu-Meng Xin, Qin Zhou, Zhi-Hua Ma, Hui Shao, and Yu-Ming Zhao**



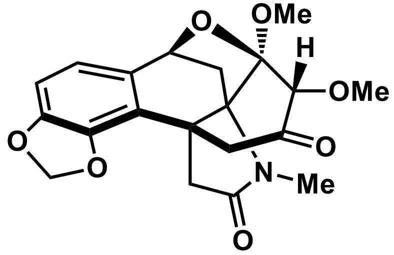
Hasubanonine (1)



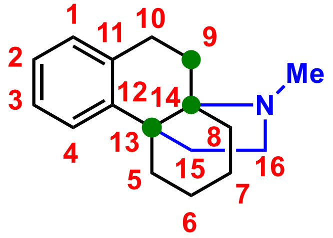
Metaphanine (2)



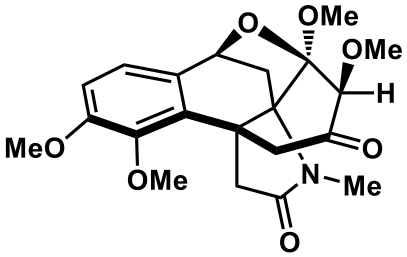
Periglaucine B (3)



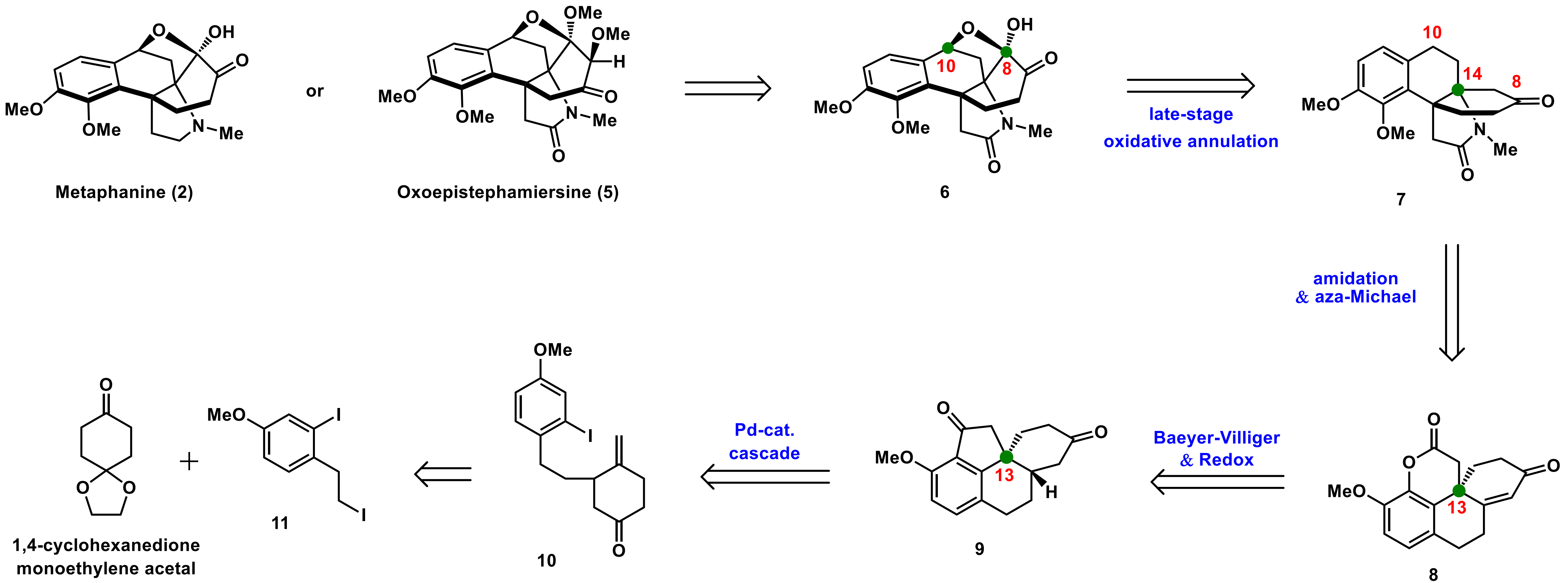
Periglaucine C (4)



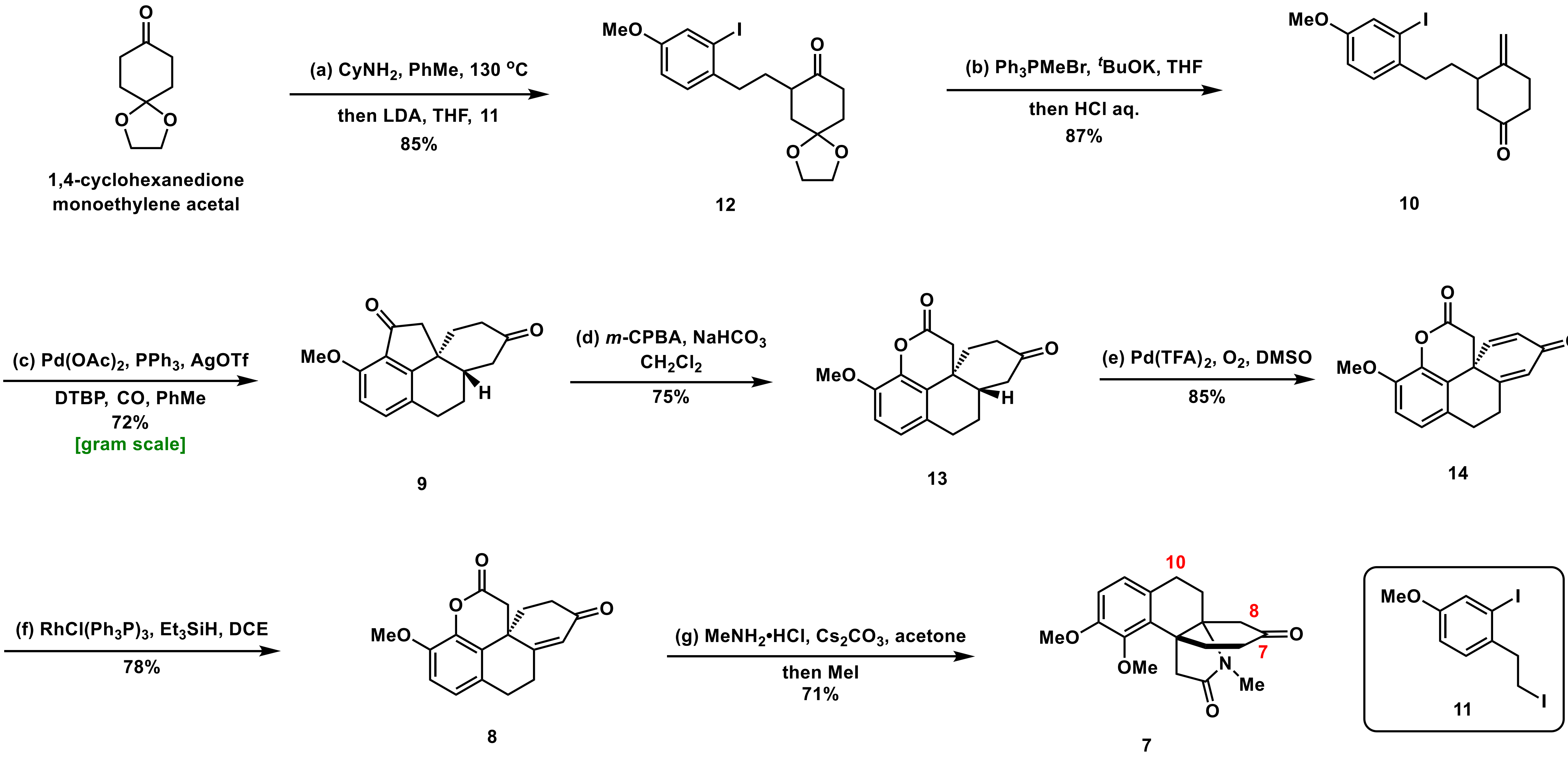
benzannulated
aza[4.4.3]propellane core



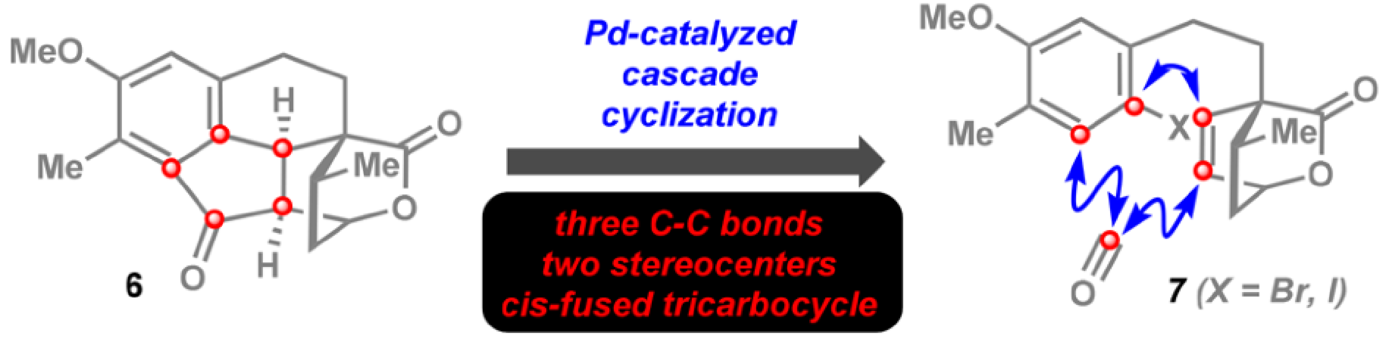
Oxoepistephamiersine (5)

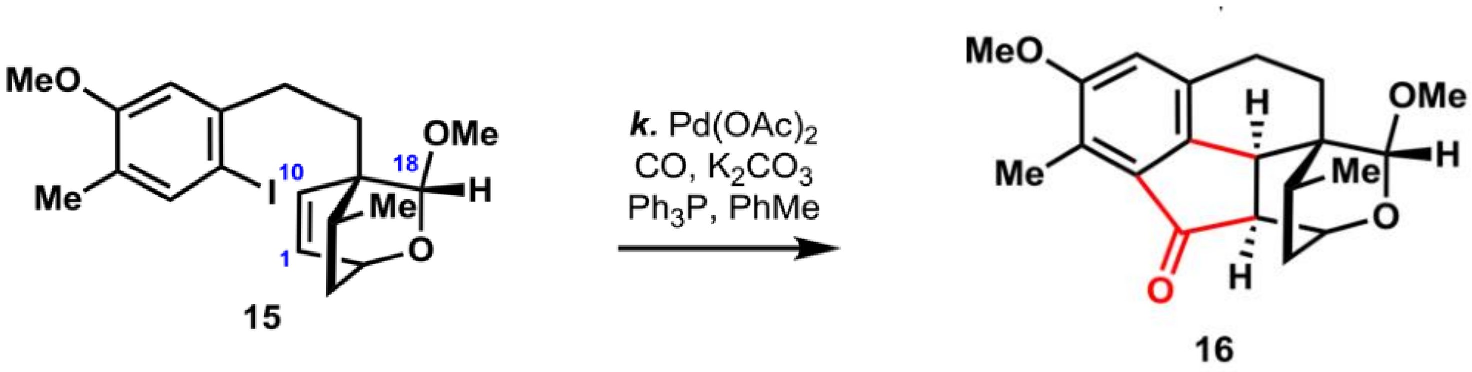


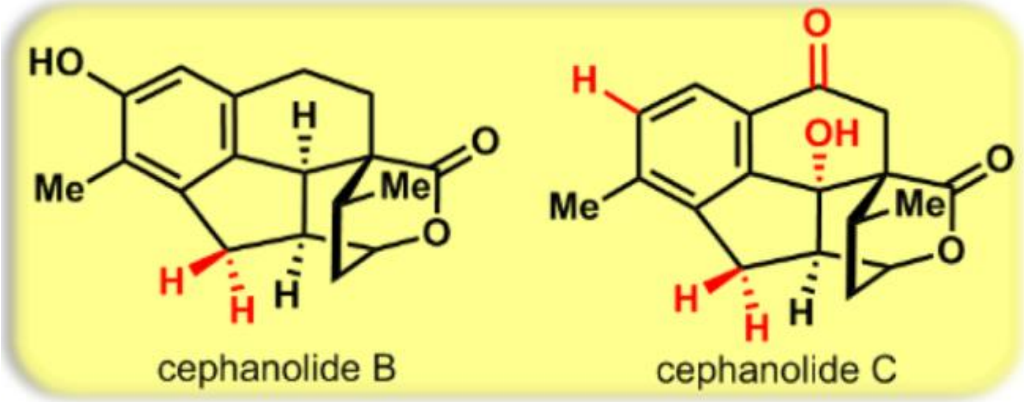
MeO
OMe
OH
O
N
Me
Metaphanine (2)
or
OMe
H
Oxoepistephamiersine (5)
10
8
6
late-stage
oxidative annulation
14
7
amidation
& aza-Michael
Baeyer-Villiger
& Redox
13
8
9
Pd-cat.
cascade
I
10
11
1,4-cyclohexanedione
monoethylene acetal



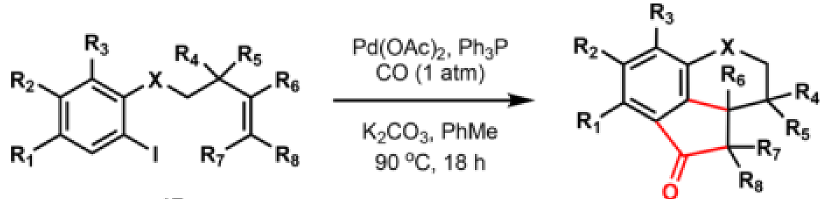
O
O
O
1,4-cyclohexanedione
monoethylene acetal
(a) CyNH2, PhMe, 130 °C
then LDA, THF, 11
85%
MeO
I
12
(b) Ph3PMeBr, tBuOK, THF
then HCl aq.
87%
10
(c) Pd(OAc)2, PPh3, AgOTf
DTBP, CO, PhMe
72%
[gram scale]
H
9
(d) m-CPBA, NaHCO3
CH2Cl2
75%
13
(e) Pd(TFA)2, O2, DMSO
85%
14
(f) RhCl(Ph3P)3, Et3SiH, DCE
78%
8
(g) MeNH2•HCl, Cs2CO3, acetone
then MeI
71%
10
8
7
OMe
N
Me
7
11



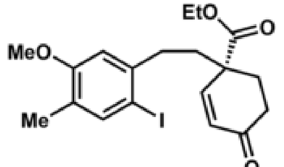
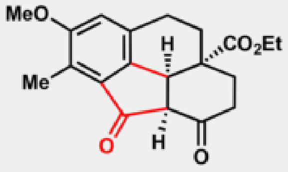
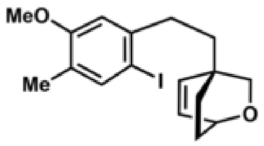
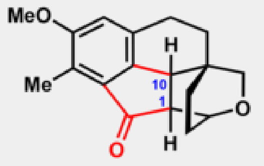
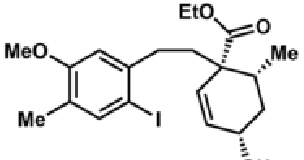
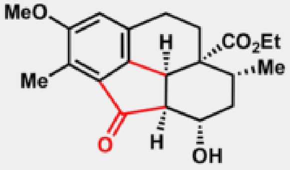
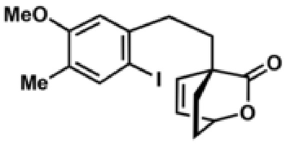
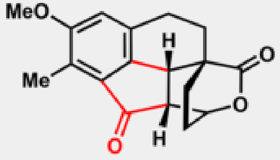
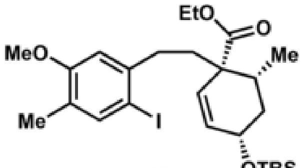
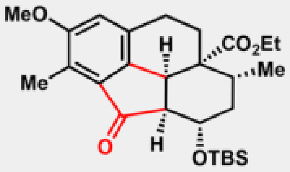
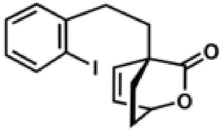
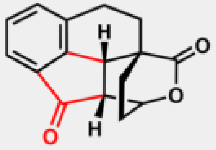
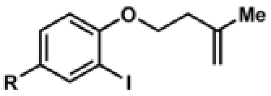
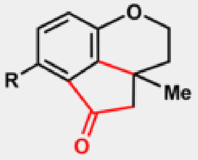
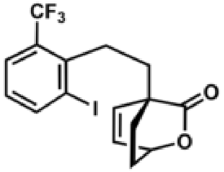
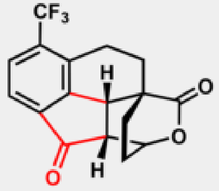


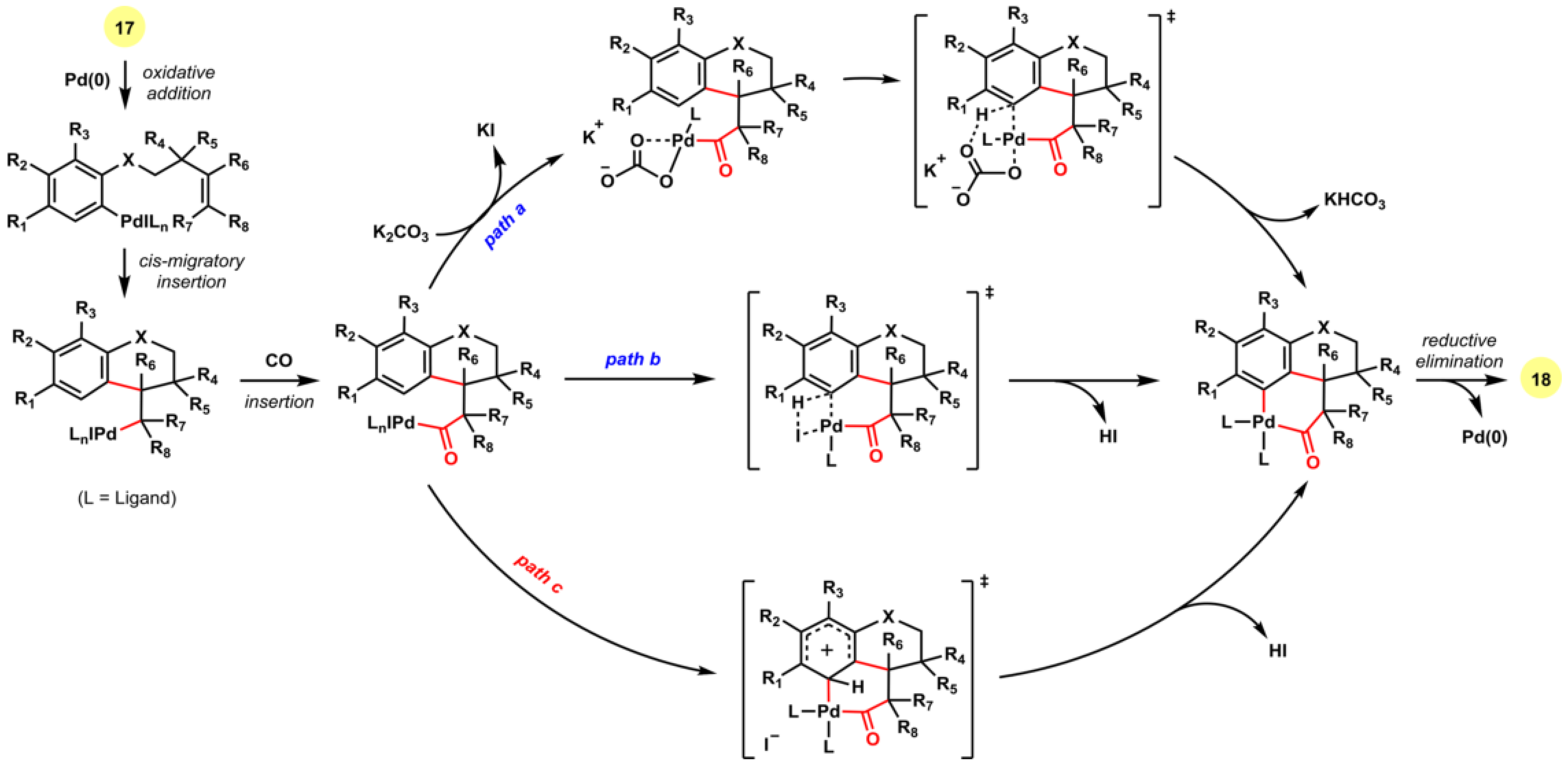


J. Am. Chem. Soc., **2018**, *140*, 5653.

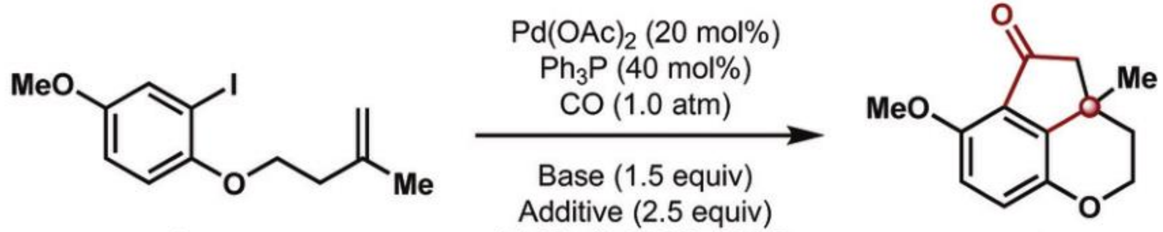


17 → **18**

Substrates	Products	Substrates	Products
 **17a**	 **18a**, n.d.	 **17f**	 **18f**: 1-Hβ,10-Hβ **18f'**:1-Hα,10-Hα 84% (**18f** : **18f'** = 2 : 1[c])
 **17b**	 **18b**, n.d.	 **17g**	 **18g**, 62%
 **17c**	 **18c**, n.d.	 **17h**	 **18h**, 50%
 **17d** (R = OMe) **17e** (R = H)	 **18d** (R = OMe), < 5% **18e** (R = H), n.d.	 **17i**	 **18i**, 31%



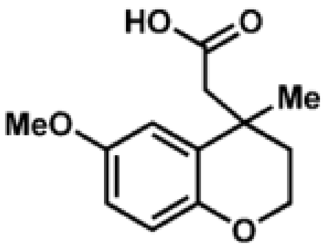
17
Pd(0)
oxidative addition
cis-migratory insertion
(L = Ligand)
CO
insertion
K2CO3
KI
path a
path b
path c
KHCO3
HI
HI
reductive elimination
Pd(0)
18



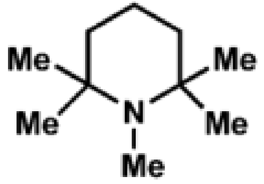
1a **2a**

Entry	Base		Additive	Yield[b]
1	K_2CO_3		—	< 5%
2	K_2CO_3		AgOTf	< 5%
3	CsOPiv		AgOTf	< 5%
4	NaOAc		AgOTf	< 5%
5	K_3PO_4		AgOTf	< 5%
6	DIPEA		AgOTf	< 5%
7	**4**		AgOTf	25%
8	**5**		AgOTf	35%
9	2,6-Lutidine		AgOTf	12%
10	2,4,6-Collidine		AgOTf	< 5%
11	**6**		AgOTf	62%
12	**6**		$AgSbF_6$	35%
13	**6**		AgTFA	< 5%
14	**6**		AgOAc	< 5%
15	**6**		Ag_3PO_4	< 5%
16	**6**		$AgNO_3$	< 5%
17	**6**		$AgNTf_2$	40%
18[c]	**6**	1 h	AgOTf	70%
19[d]	**6**	3 h	AgOTf	94%
20[def]	**6**	10 mol% catalyst 20 mol% PPh_3	AgOTf	83%

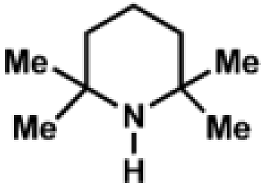
Pre-stirring without CO



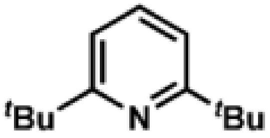
3



4

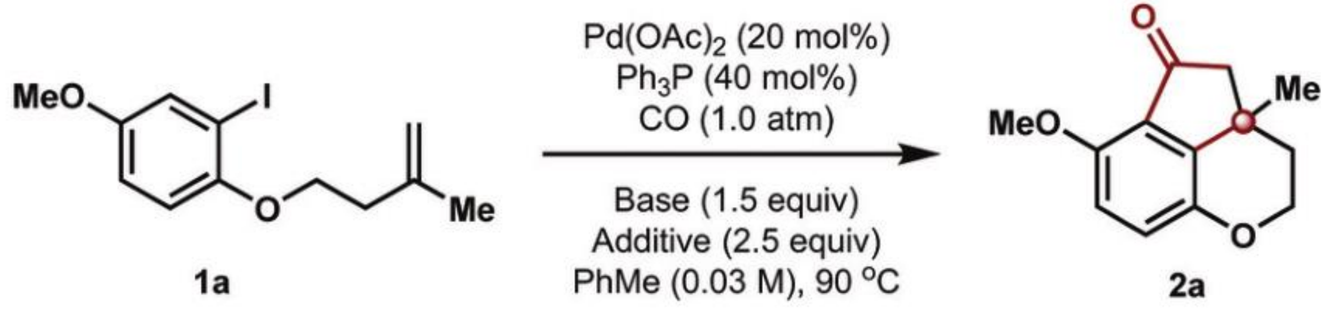


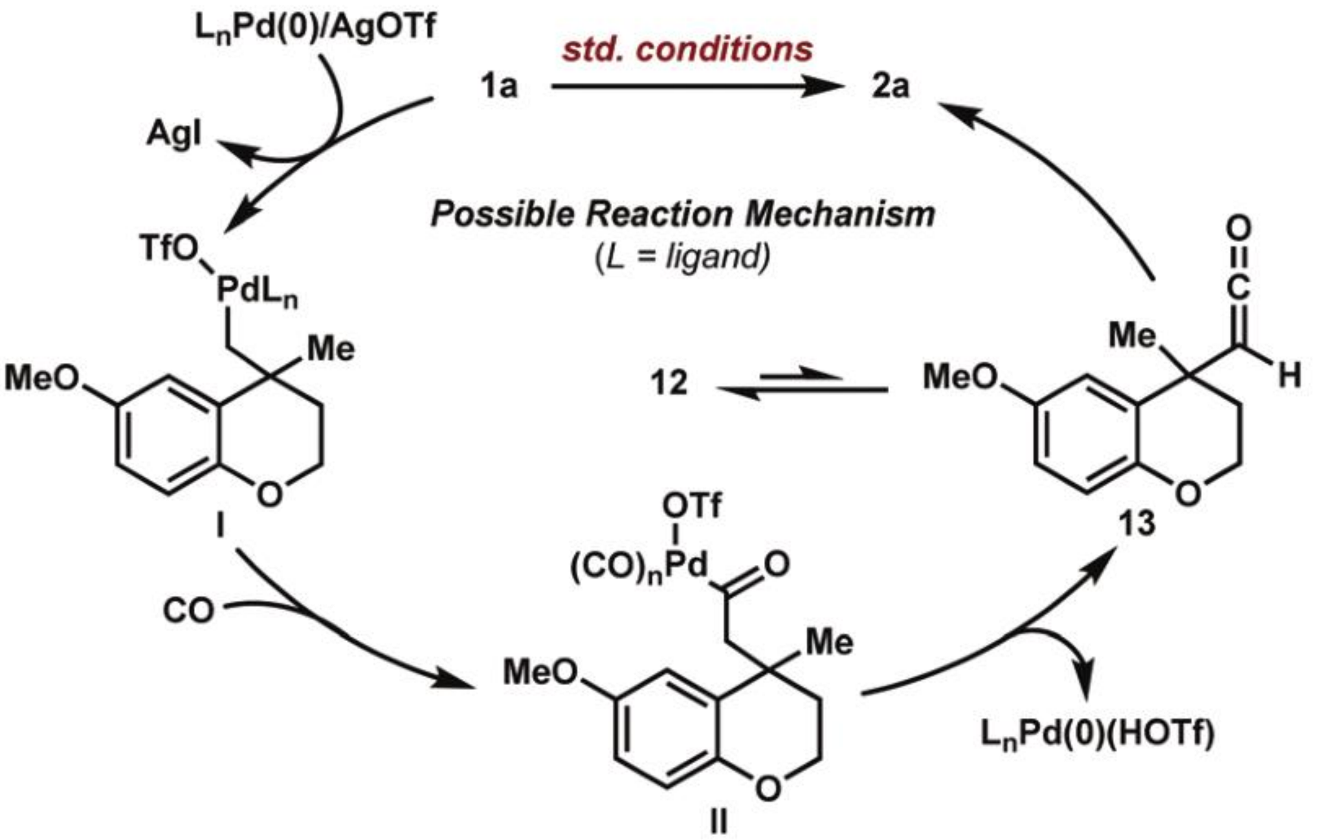
5

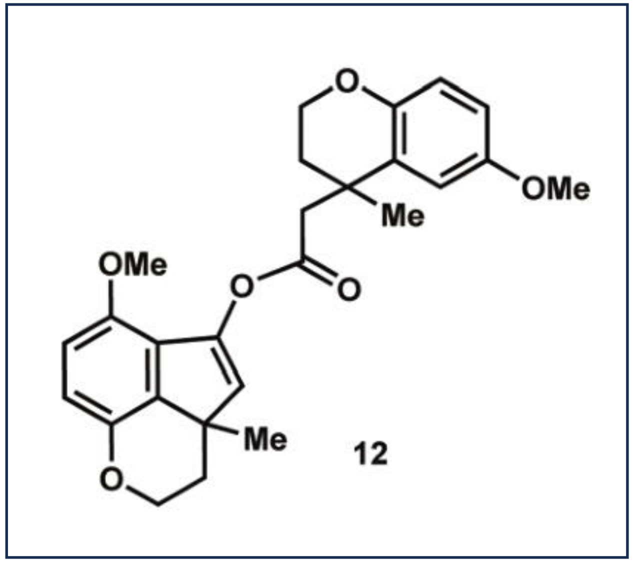


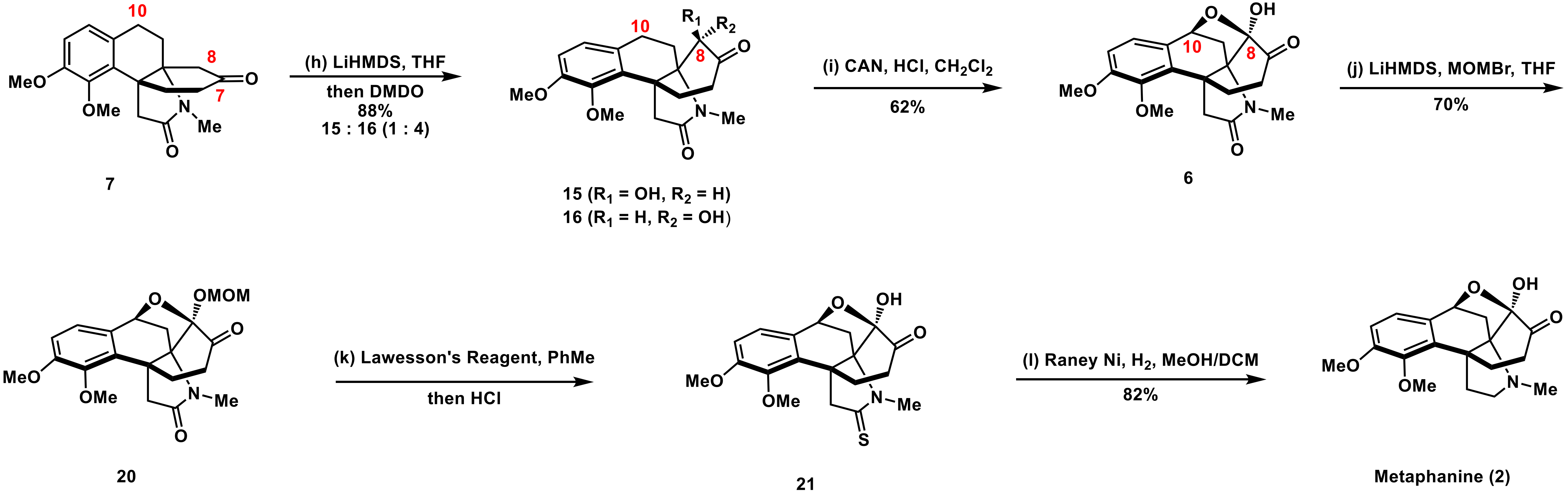
6

Chem. Commun., **2021**, *57*, 7023.

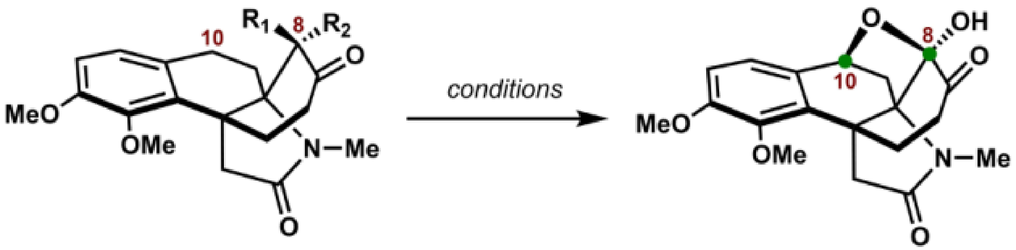

MeO
I
Me
O
1a
Pd(OAc)2 (20 mol%)
Ph3P (40 mol%)
CO (1.0 atm)
Base (1.5 equiv)
Additive (2.5 equiv)
PhMe (0.03 M), 90 °C
O
Me
MeO
O
2a


LnPd(0)/AgOTf
AgI
1a
std. conditions
2a
Possible Reaction Mechanism
(L = ligand)
TfO
PdLn
Me
MeO
O
I
12
Me
MeO
O
C
H
O
13
CO
OTf
(CO)nPd
O
Me
MeO
O
II
LnPd(0)(HOTf)


O
OMe
Me
OMe
O
O
Me
O
12



10
8
7
MeO
OMe
N
Me
O
7
(h) LiHMDS, THF
then DMDO
88%
15 : 16 (1 : 4)
R1
R2
15 (R1 = OH, R2 = H)
16 (R1 = H, R2 = OH)
(i) CAN, HCl, CH2Cl2
62%
OH
6
(j) LiHMDS, MOMBr, THF
70%
OMOM
20
(k) Lawesson's Reagent, PhMe
then HCl
S
21
(l) Raney Ni, H2, MeOH/DCM
82%
Metaphanine (2)



15 (R_1 = OH, R_2 = H)
16 (R_1 = H, R_2 = OH)

6

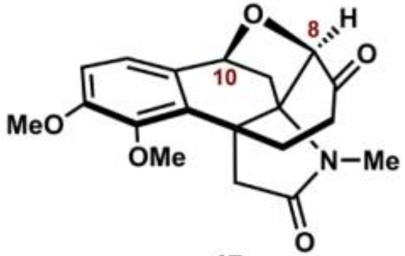
Entry	Conditions	Yield[b]
1	**15**, DDQ, AcOH, CH_2Cl_2, rt	N.R.
2	**15**, DDQ, AcOH, DCE, 75 ℃	N.D.
3[c]	**15/16**, DDQ, HCl, CH_2Cl_2, rt	20%
4[c]	**15/16**, DDQ, H_2O, HCl, CH_2Cl_2, rt	<5%
5[d]	**15/16**, DDQ, HCl, CH_2Cl_2, rt	N.R.
6[e]	**15/16**, DDQ, HCl, CH_2Cl_2, rt	N.R.
7[f]	**15/16**, DDQ, HCl, CH_2Cl_2, rt	N.D.
8[g]	**15/16**, DDQ, HCl, CH_2Cl_2, rt	<5%
9[c]	**15/16**, CAN, HCl, CH_2Cl_2, rt	40%
10[c]	**15/16**, CAN, HCl, 1,4-dioxane, rt	<5%
11[h]	**15/16**, CAN, HCl, CH_2Cl_2, rt	62%

17 (35%) + 15 (45%)

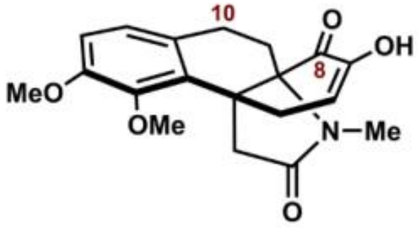
18 (30%) + 19 (20%)

HCl (10 equiv → 50 equiv)

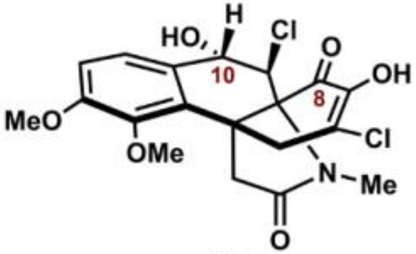
[a] Reactions were performed on a 0.01 mmol scale. [b] Isolated yield. [c] HCl (4.0 M in 1,4-dioxane). [d] HCl (3.5 M in EtOAc). [e] HCl (3.0 M in CyOMe). [f] HCl (4.0 M in MeOH). [g] HCl (1.0 M in AcOH). [h] 50 equiv. HCl (4.0 M in 1,4-dioxane) was added; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, N.R. = no reaction, N.D. = not detected.



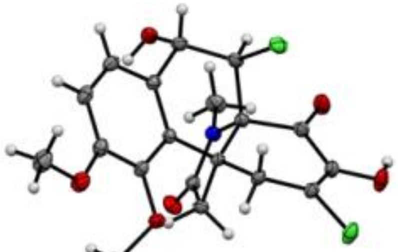
17



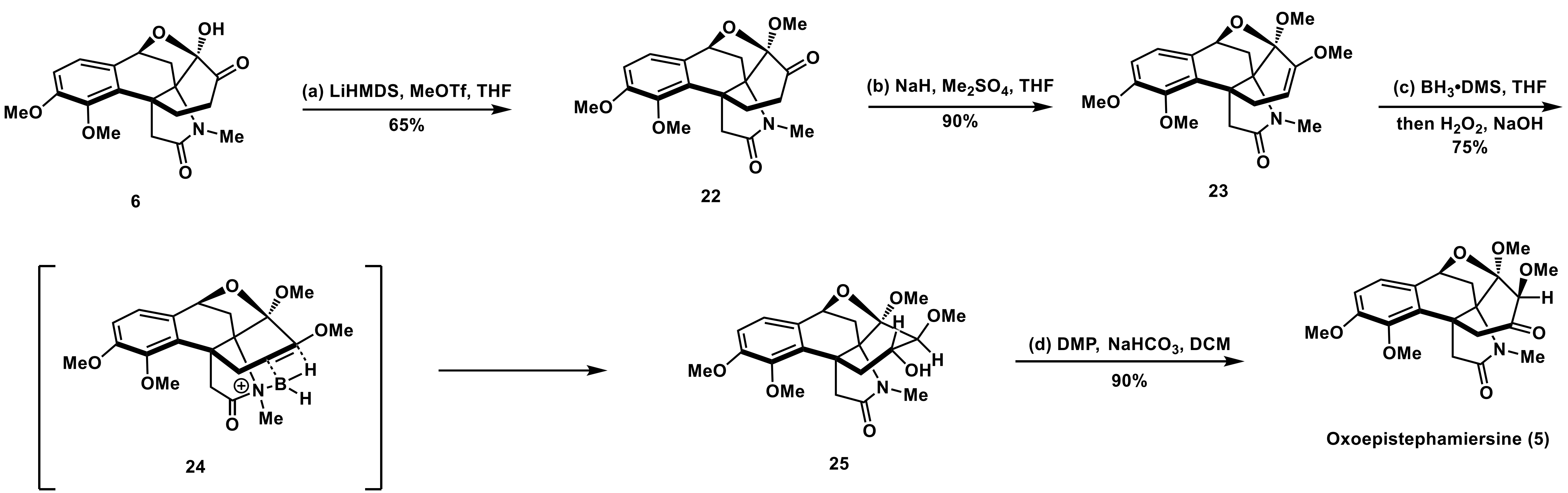
18



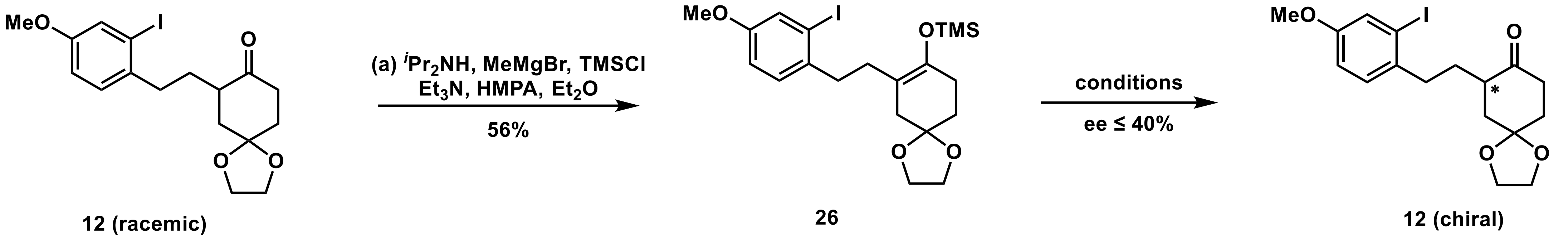
19

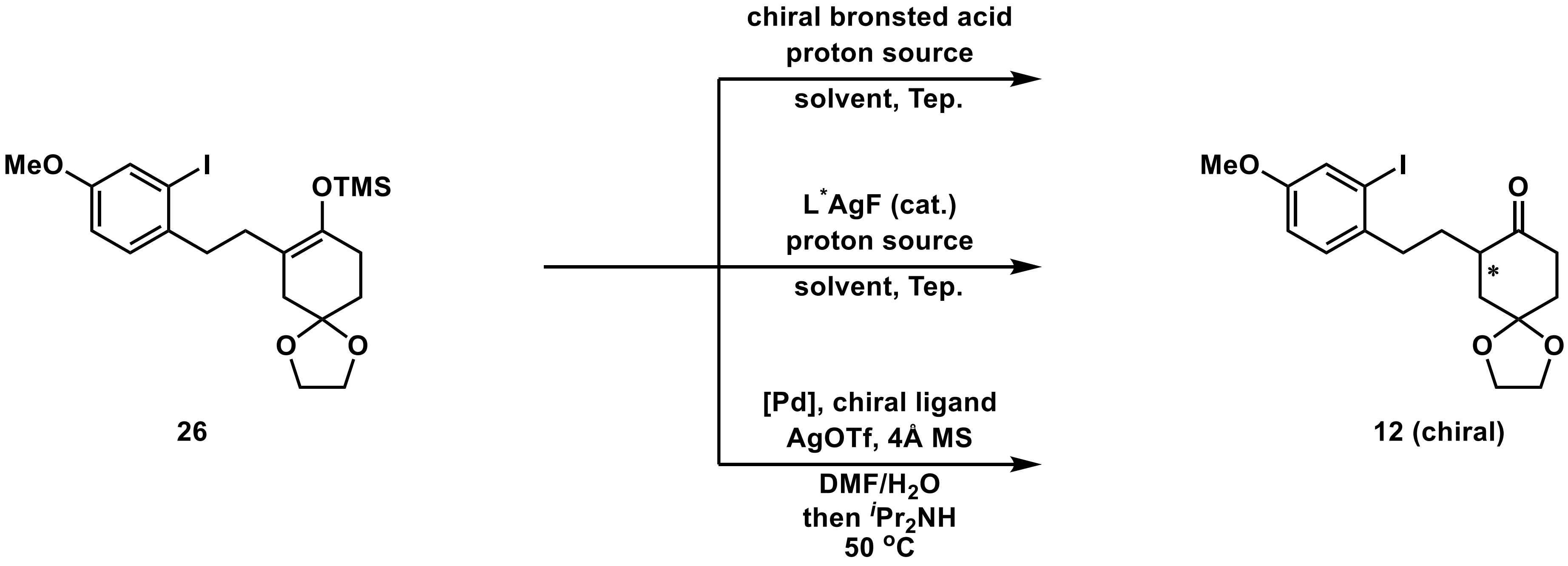


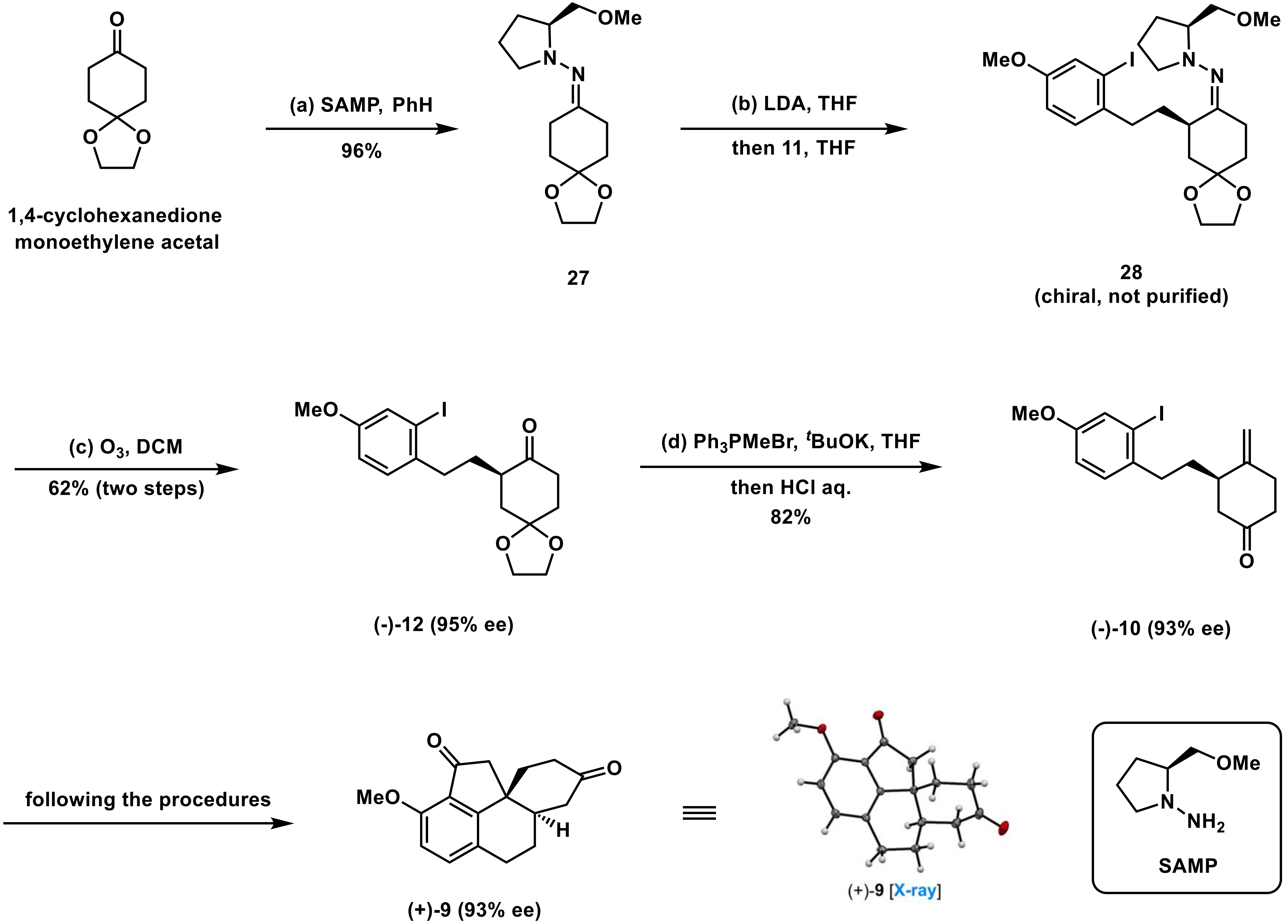
19 [X-ray]



(a) LiHMDS, MeOTf, THF
65%
(b) NaH, Me2SO4, THF
90%
(c) BH3•DMS, THF
then H2O2, NaOH
75%
(d) DMP, NaHCO3, DCM
90%
6
22
23
24
25
Oxoepistephamiersine (5)

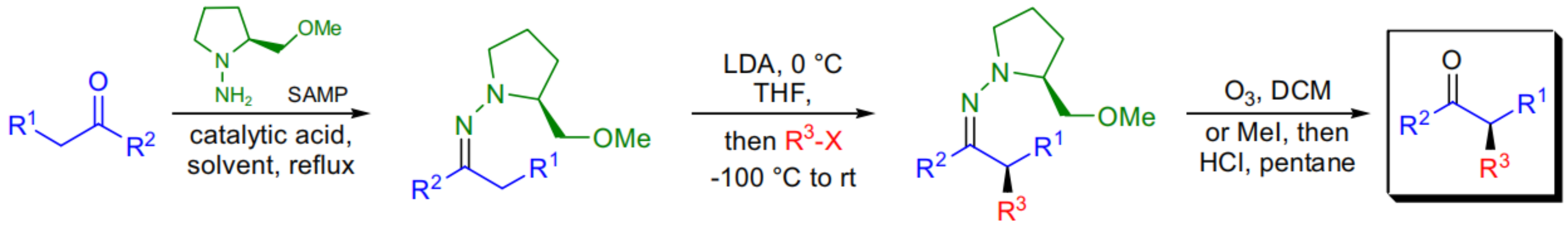

MeO
I
O
O
O
12 (racemic)
(a) $^{i}Pr_2NH$, MeMgBr, TMSCl
Et_3N, HMPA, Et_2O
56%
OTMS
26
conditions
ee ≤ 40%
*
12 (chiral)


MeO
I
OTMS
O
O
26
chiral bronsted acid
proton source
solvent, Tep.
$L^{*}AgF$ (cat.)
proton source
solvent, Tep.
[Pd], chiral ligand
AgOTf, 4Å MS
DMF/H_2O
then $^{i}Pr_2NH$
50 ^{o}C
*
12 (chiral)


1,4-cyclohexanedione monoethylene acetal
(a) SAMP, PhH
96%
27
(b) LDA, THF
then 11, THF
28
(chiral, not purified)
(c) O_3, DCM
62% (two steps)
(-)-12 (95% ee)
(d) Ph_3PMeBr, ^tBuOK, THF
then HCl aq.
82%
(-)-10 (93% ee)
following the procedures
(+)-9 (93% ee)
(+)-9 [X-ray]
SAMP

ENDERS SAMP/RAMP HYDRAZONE ALKYLATION

(References are on page 579)



R^1 = alkyl, aryl; R^2 = H, alkyl, R^1 = R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -CH=CH$(CH_2)_2$-; R^3 = alkyl, benzyl, allyl; X = I, Br;
<u>solvent:</u> benzene, cyclohexane