Enantioselective Total Synthesis of Lyconadins A-E through A Palladium-Catalyzed Heck-Type Reaction

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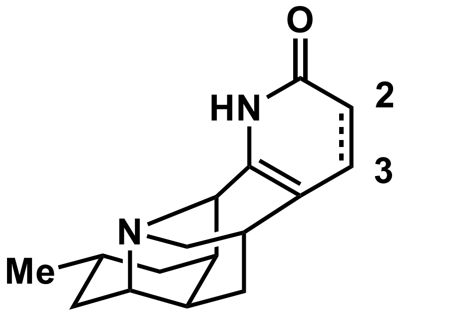
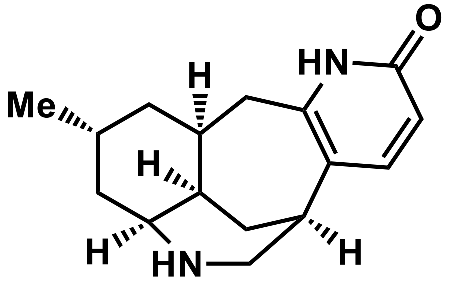
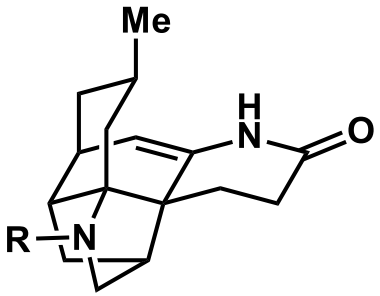


(+)-Lyconadin A ($\Delta^{2,3}$, 1)
(-)-Lyconadin B (2)



(-)-Lyconadin C (3)



(-)-Lyconadin D (R = Me, 4)
(-)-Lyconadin D (R = H, 5)

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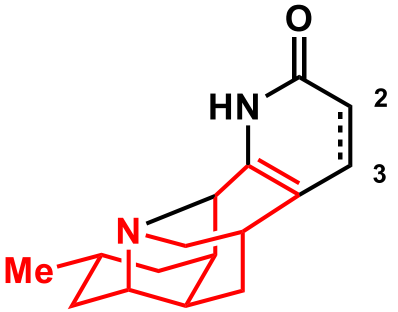
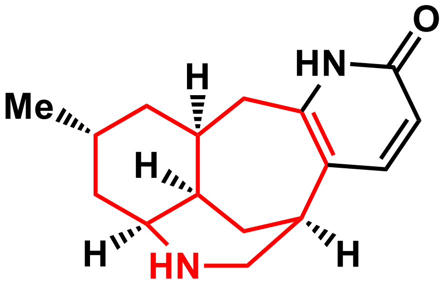
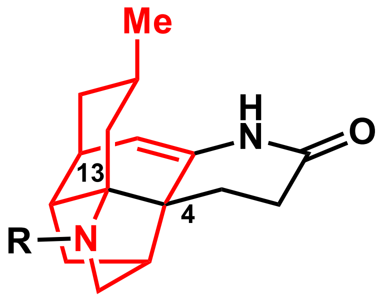


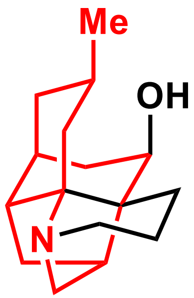
(+)-Lyconadin A ($\Delta^{2,3}$, 1)
(-)-Lyconadin B (2)



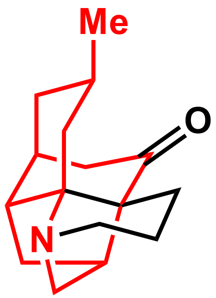
(-)-Lyconadin C
(3)



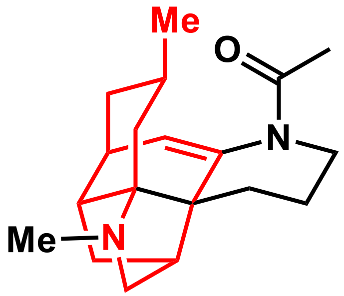
(-)-Lyconadin D (R = Me, 4)
(-)-Lyconadin D (R = H, 5)



(-)-Lycopecurine (6)

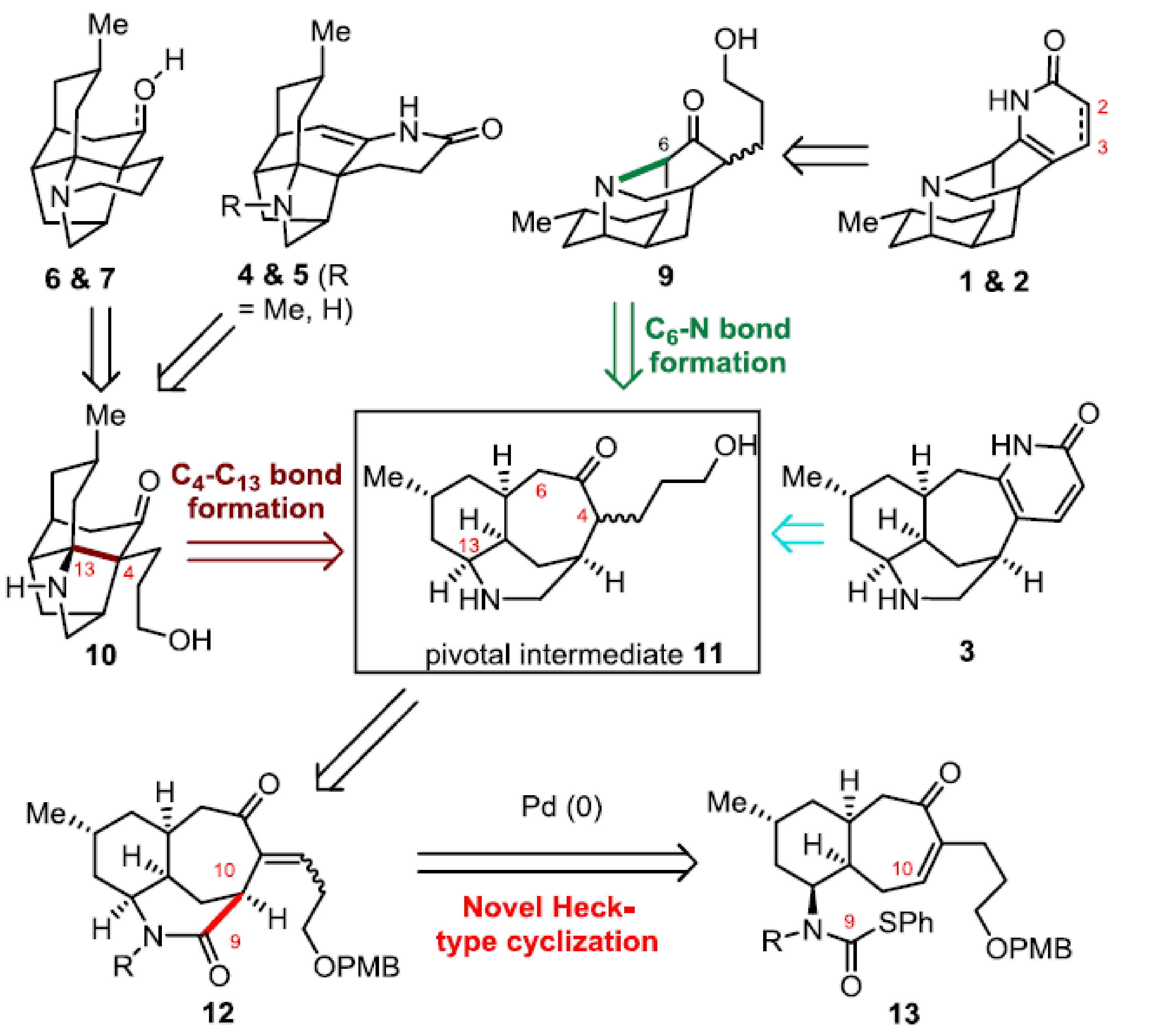


(-)-Dehydro-
Lycopecurine (6)



(+)-Fastigiatine (8)

Figure 1. Lycopodium alkaloids 1-8.



Scheme 1. Retrosynthetic Analysis of alkaloids **1-7**.

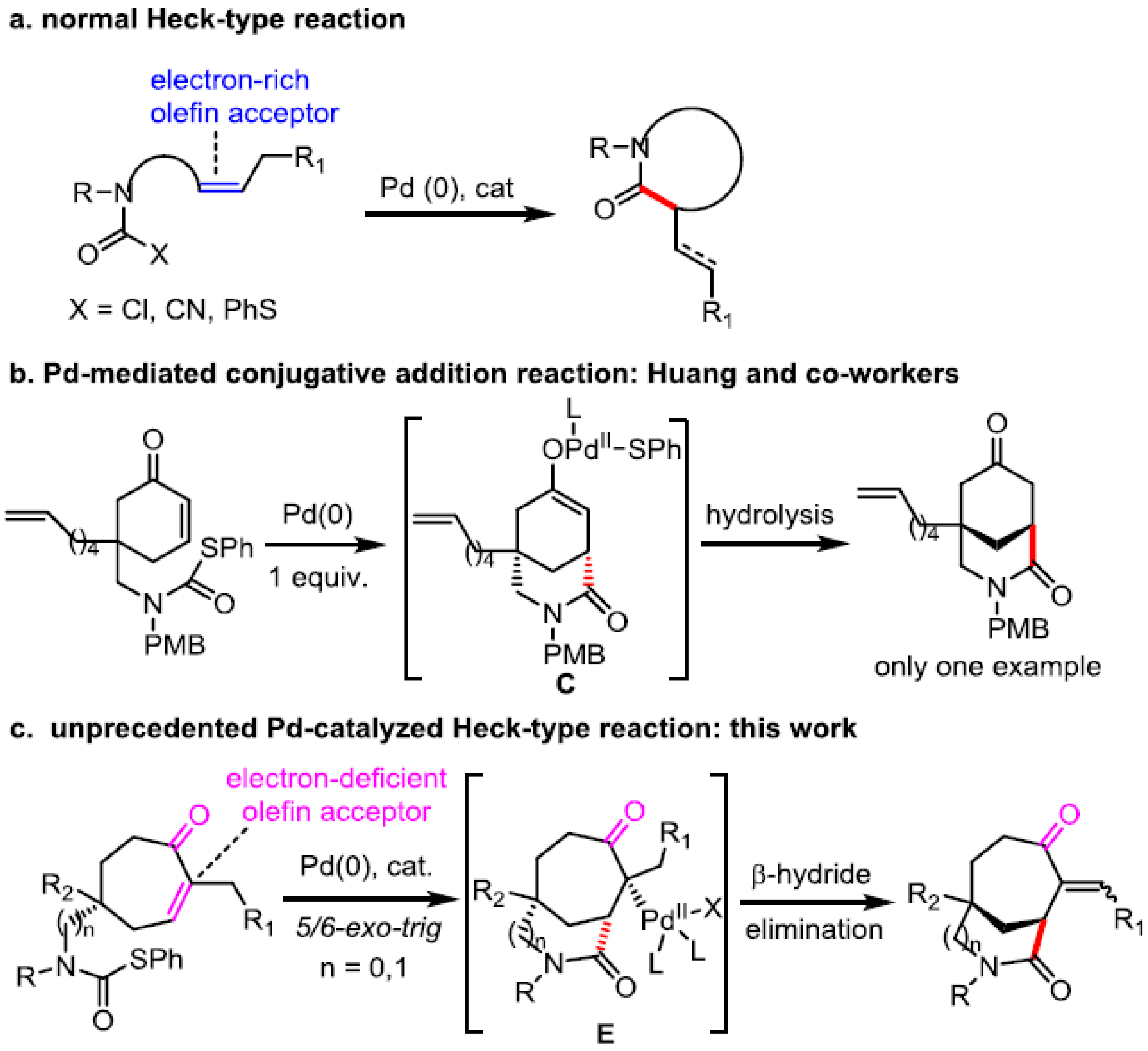
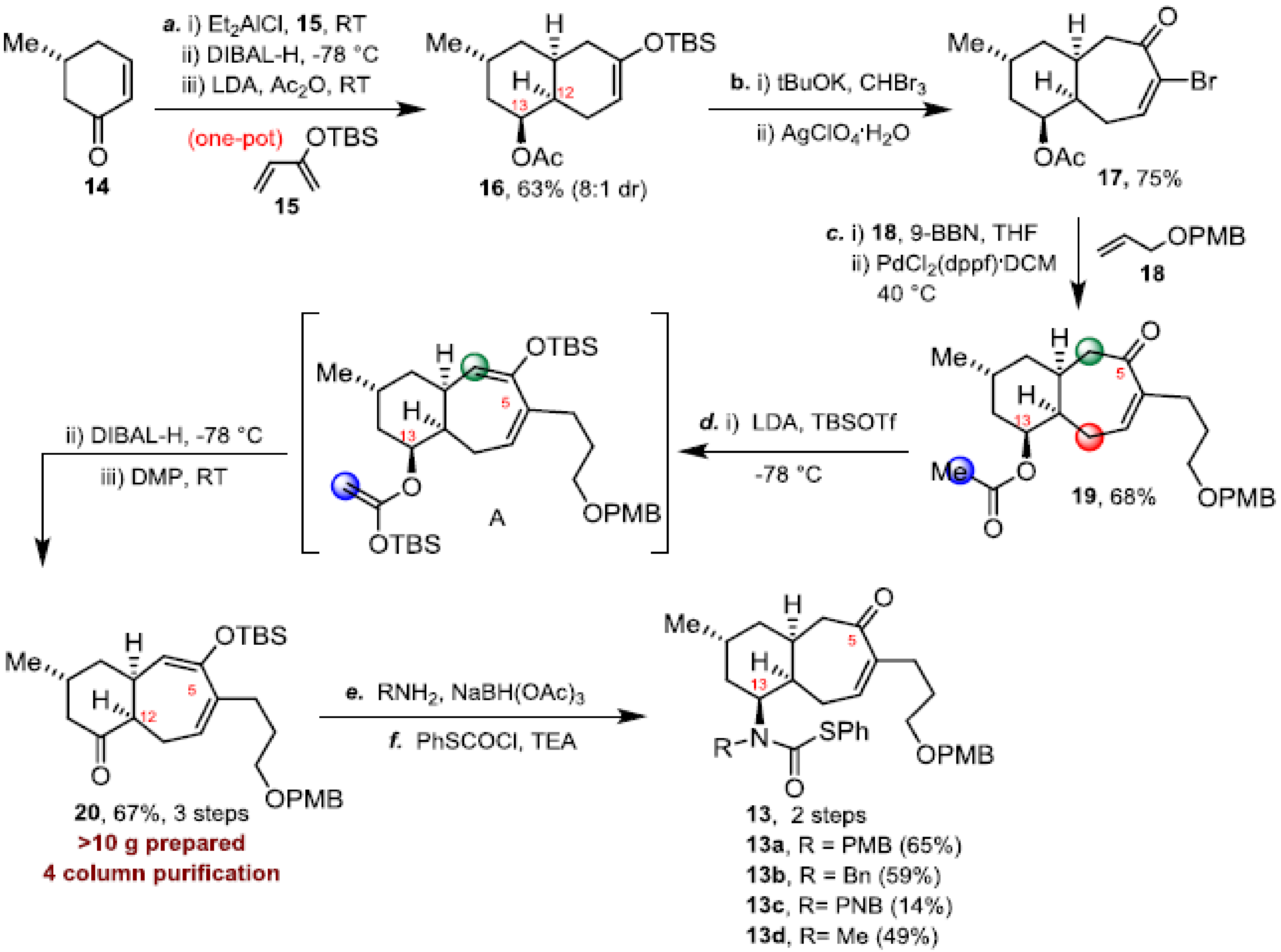
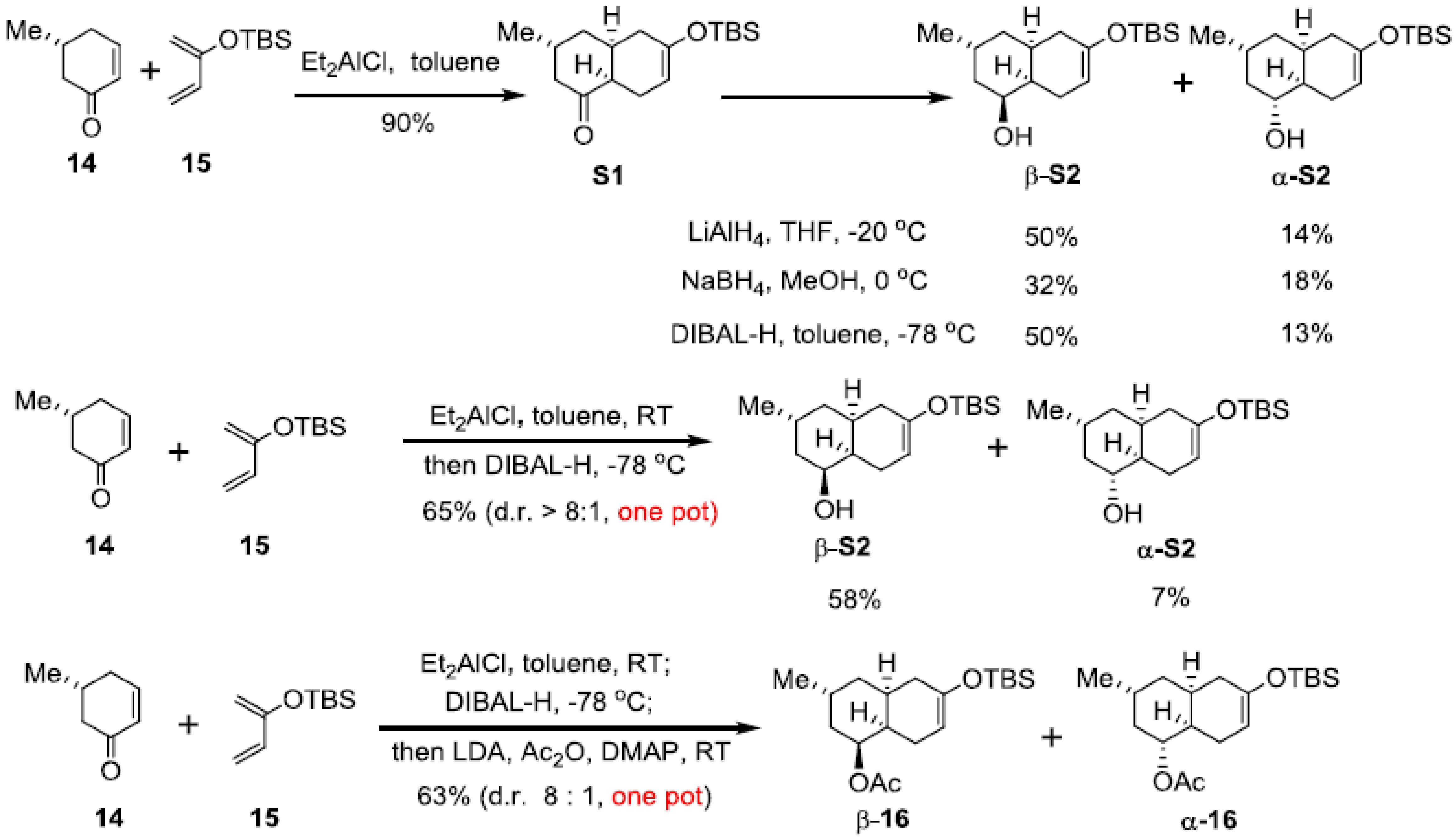
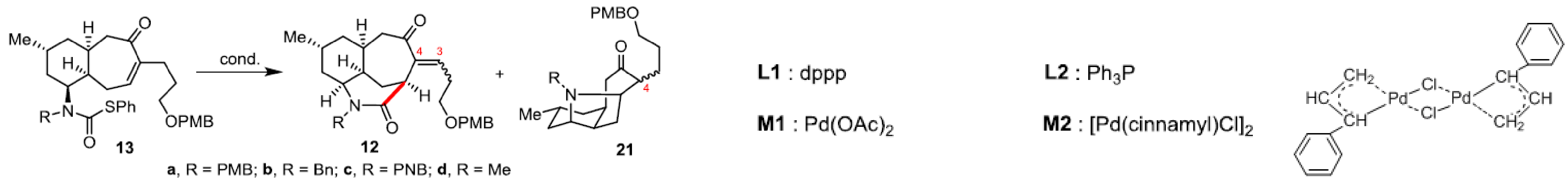


Figure 2. Heck-type reaction of carbamoyl derivatives.

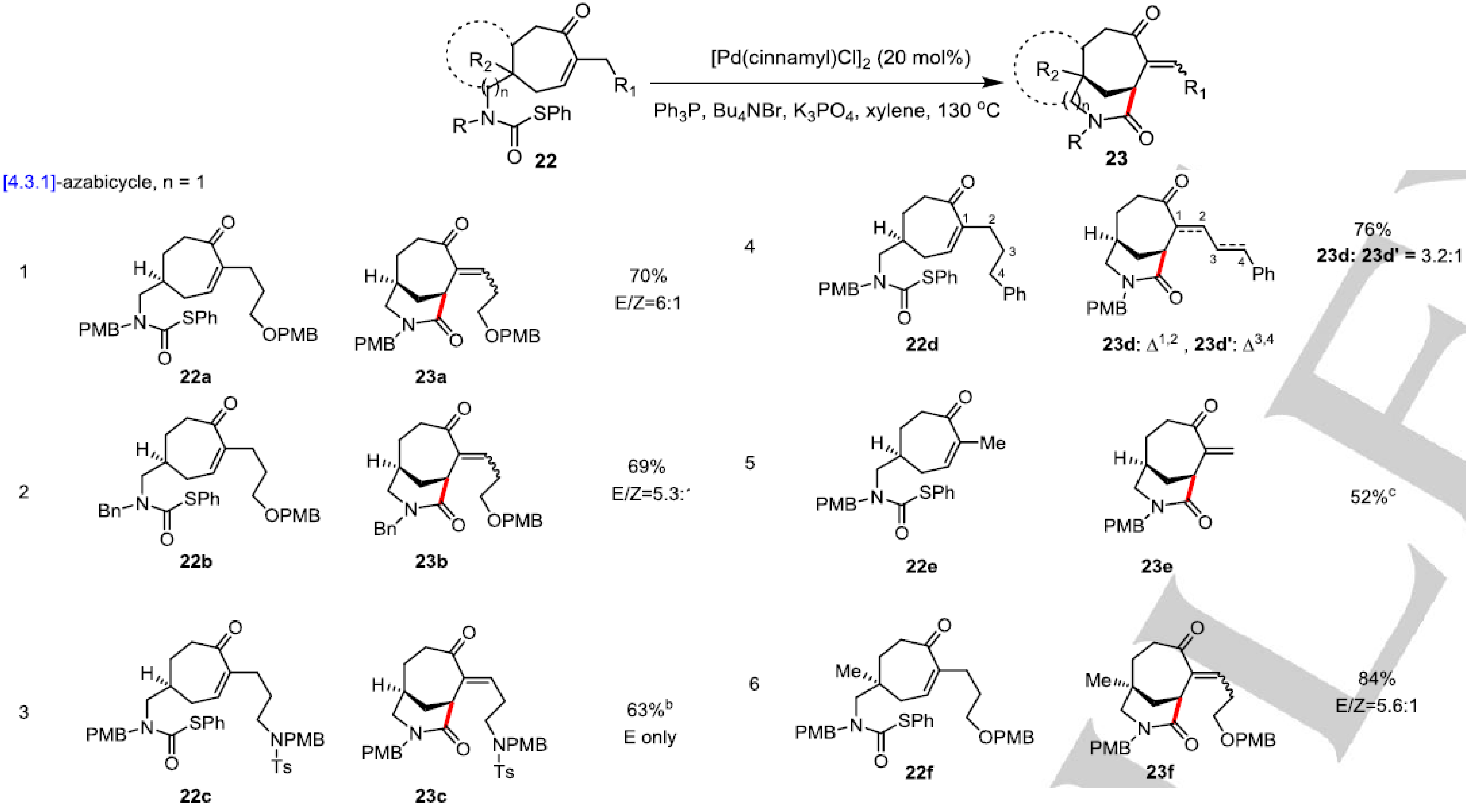


Scheme 2. Preparation of Heck reaction precursor **13.**

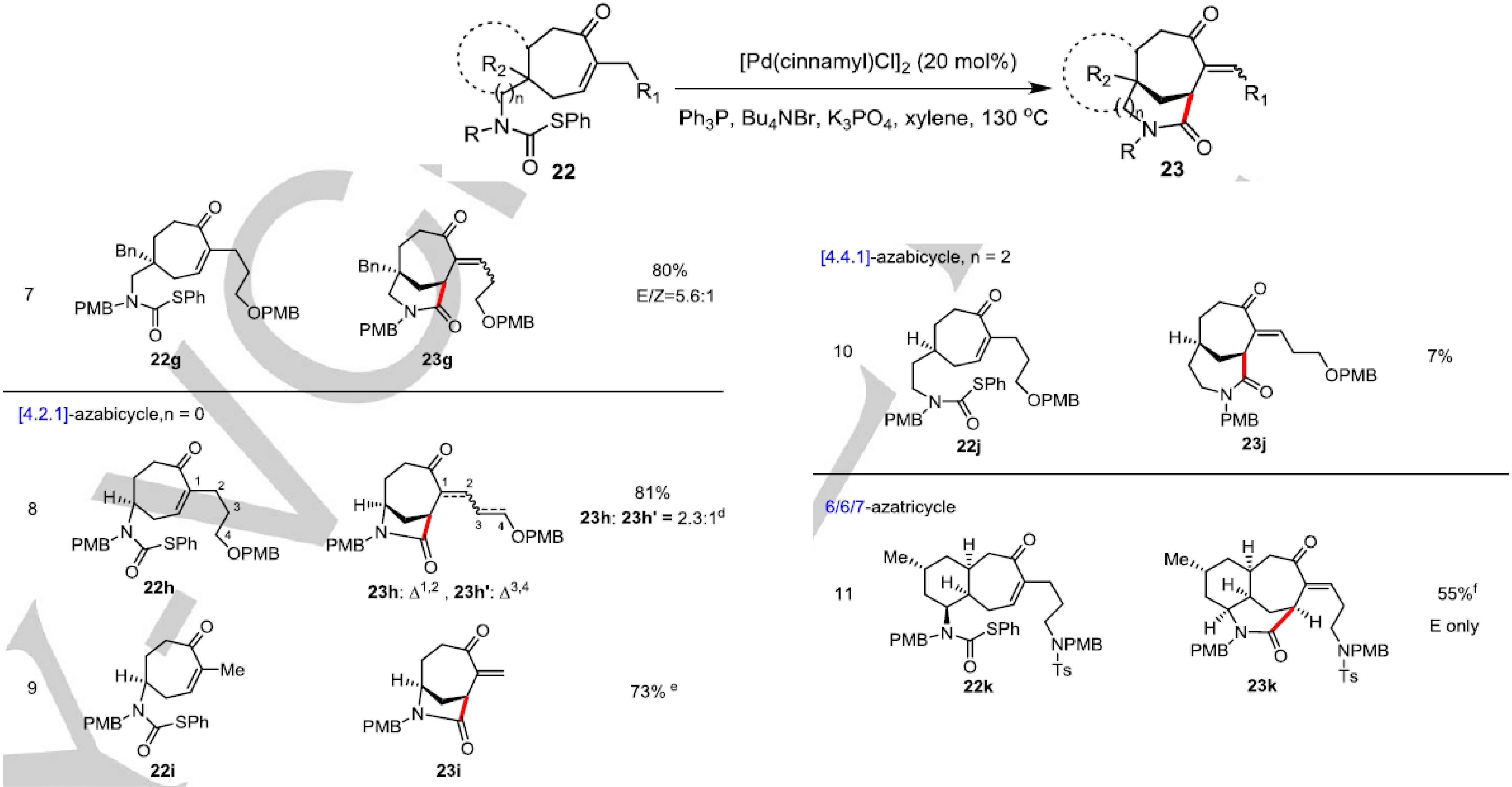

Me
OTBS
Et2AlCl, toluene
90%
14
15
H
H
S1
OH
β-S2
α-S2
LiAlH4, THF, -20 °C 50% 14%
NaBH4, MeOH, 0 °C 32% 18%
DIBAL-H, toluene, -78 °C 50% 13%
Et2AlCl, toluene, RT
then DIBAL-H, -78 °C
65% (d.r. > 8:1, one pot)
58%
7%
Et2AlCl, toluene, RT;
DIBAL-H, -78 °C;
then LDA, Ac2O, DMAP, RT
63% (d.r. 8 : 1, one pot)
OAc
β-16
α-16



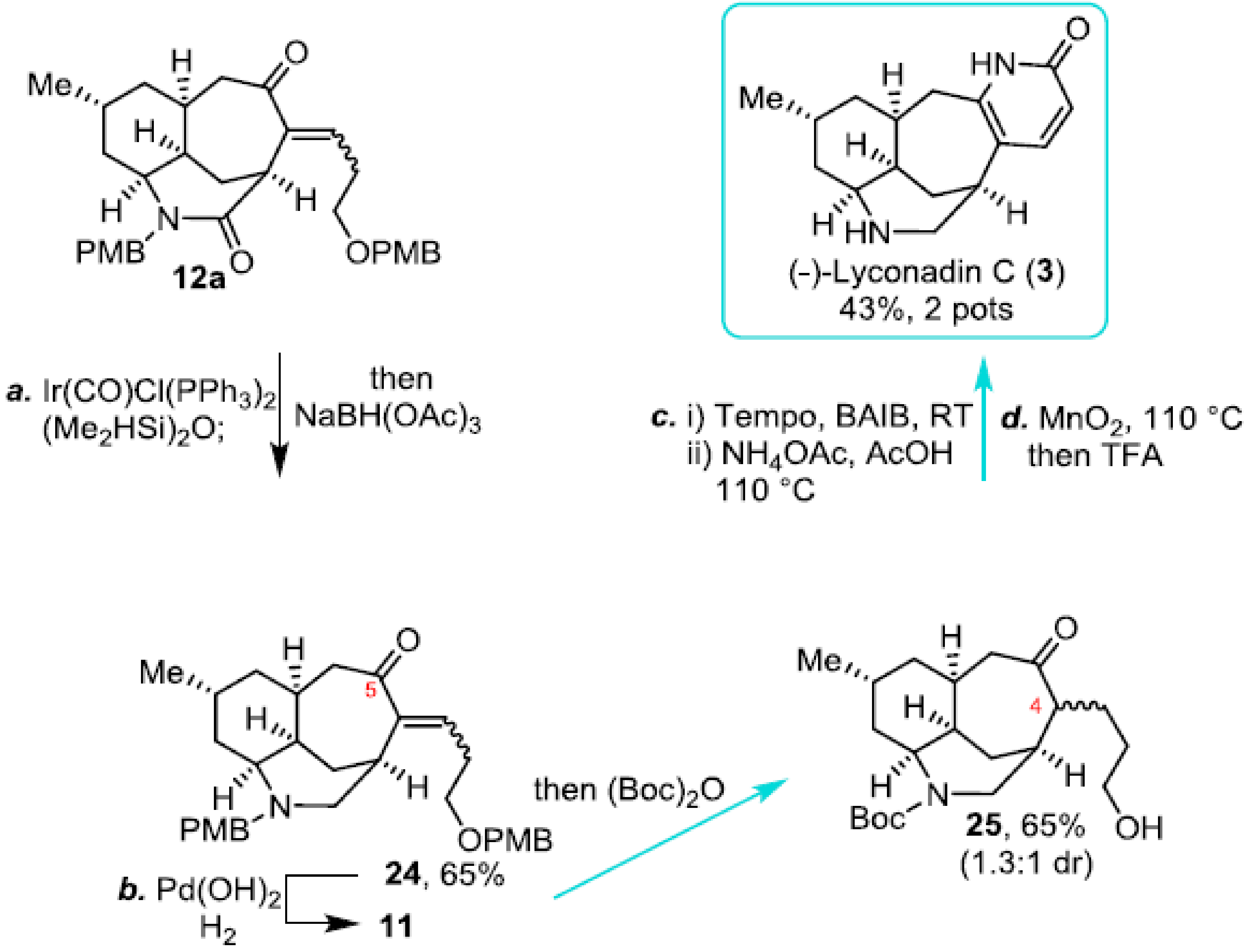
Entry	R	Metal (equiv)	Ligand (equiv)	Additive (equiv)	Yield(%)[b] 12, 21, 13
1	PMB	M1 (1.0)	L1 (2.0)	-	0, 94, 0
2	PMB	M1 (1.0)	L1 (2.0)	-	0, 75, 0
3	PMB	M2 (0.5)	L2 (1.0)	-	17, 27,13
4	PMB	M2 (0.5)	L2 (1.0)	Bu_4NCl (3.0)	40, 24, 0
5	PMB	M2 (0.5)	L2 (1.0)	Bu_4NI (3.0)	41,16, 0
6	PMB	M2 (0.5)	L2 (1.0)	Bu_4NBr (3.0)	50,14, 0
7	PMB	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4)	66, 5, 0[e]
8	PMB	M2 (0.3)	L2 (0.6)	Bu_4NBr (2.4)	50, T, 23
9	PMB	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4), K_3PO_4 (1.0)	61, T, 0
10	PMB	M2 (0.4)	L2 (0.8)	Ag_3PO_4 (0.5), K_3PO_4 (1.5)	15, 30, 27
11	PMB	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4), Ag_3PO_4 (0.5)	16, 29, 34
12	PMB	M2 (0.4)	L2 (0.8)	KBr (2.4)	T, 0, 86
13	PMB	M2 (0.4)	L2 (0.8)	LiBr (2.4)	13, 0, 72
14	Bn	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4)	55, T, 0
15	PNB	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4)	32, 30, 0
16	Me	M2 (0.4)	L2 (0.8)	Bu_4NBr (2.4)	13, 55, 0



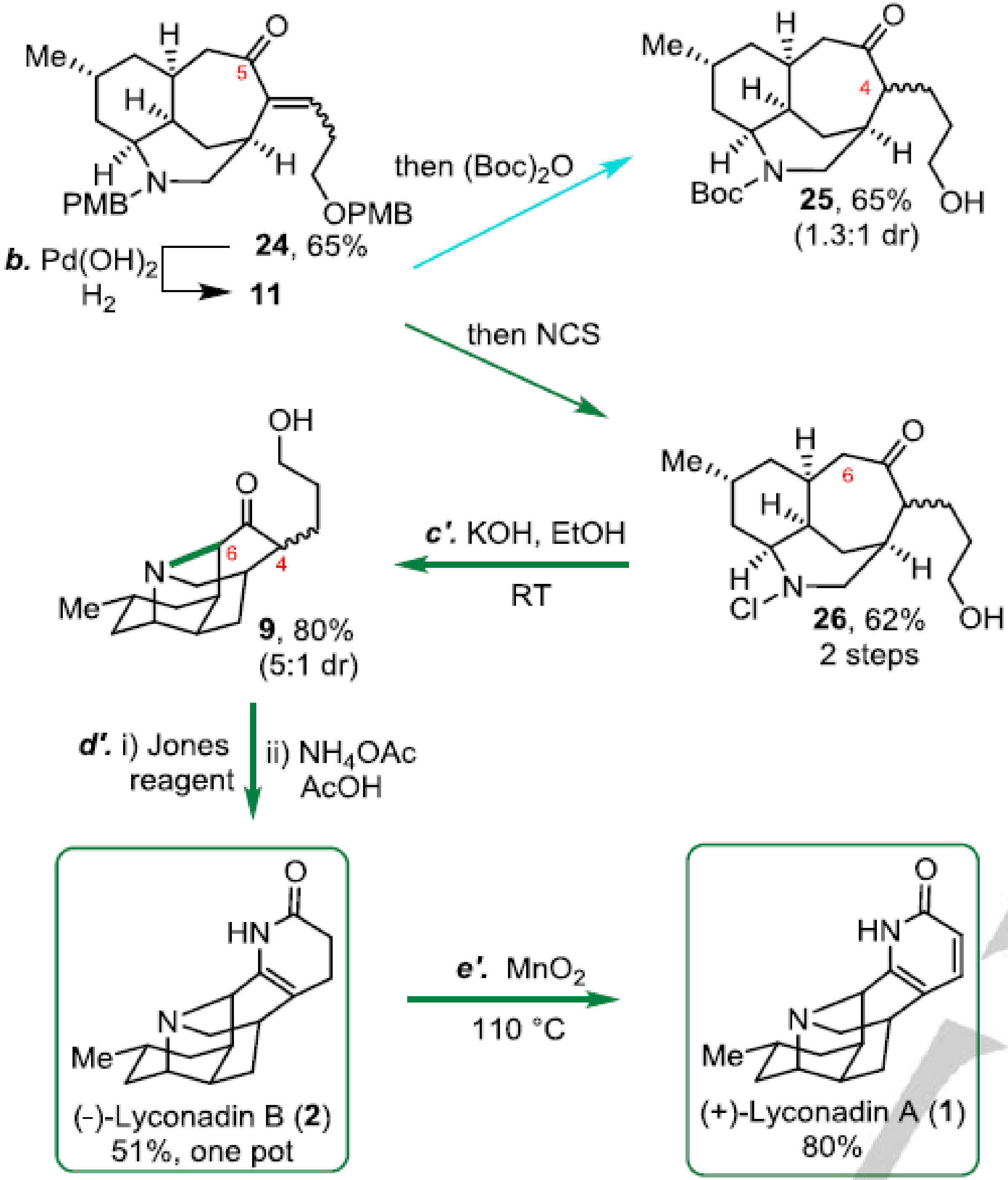
[Pd(cinnamyl)Cl]2 (20 mol%)
Ph3P, Bu4NBr, K3PO4, xylene, 130 °C
22
23
[4.3.1]-azabicycle, n = 1
1
22a
23a
70%
E/Z=6:1
2
22b
23b
69%
E/Z=5.3:1
3
22c
23c
63%b
E only
4
22d
23d: Δ1,2 , 23d': Δ3,4
76%
23d: 23d' = 3.2:1
5
22e
23e
52%c
6
22f
23f
84%
E/Z=5.6:1



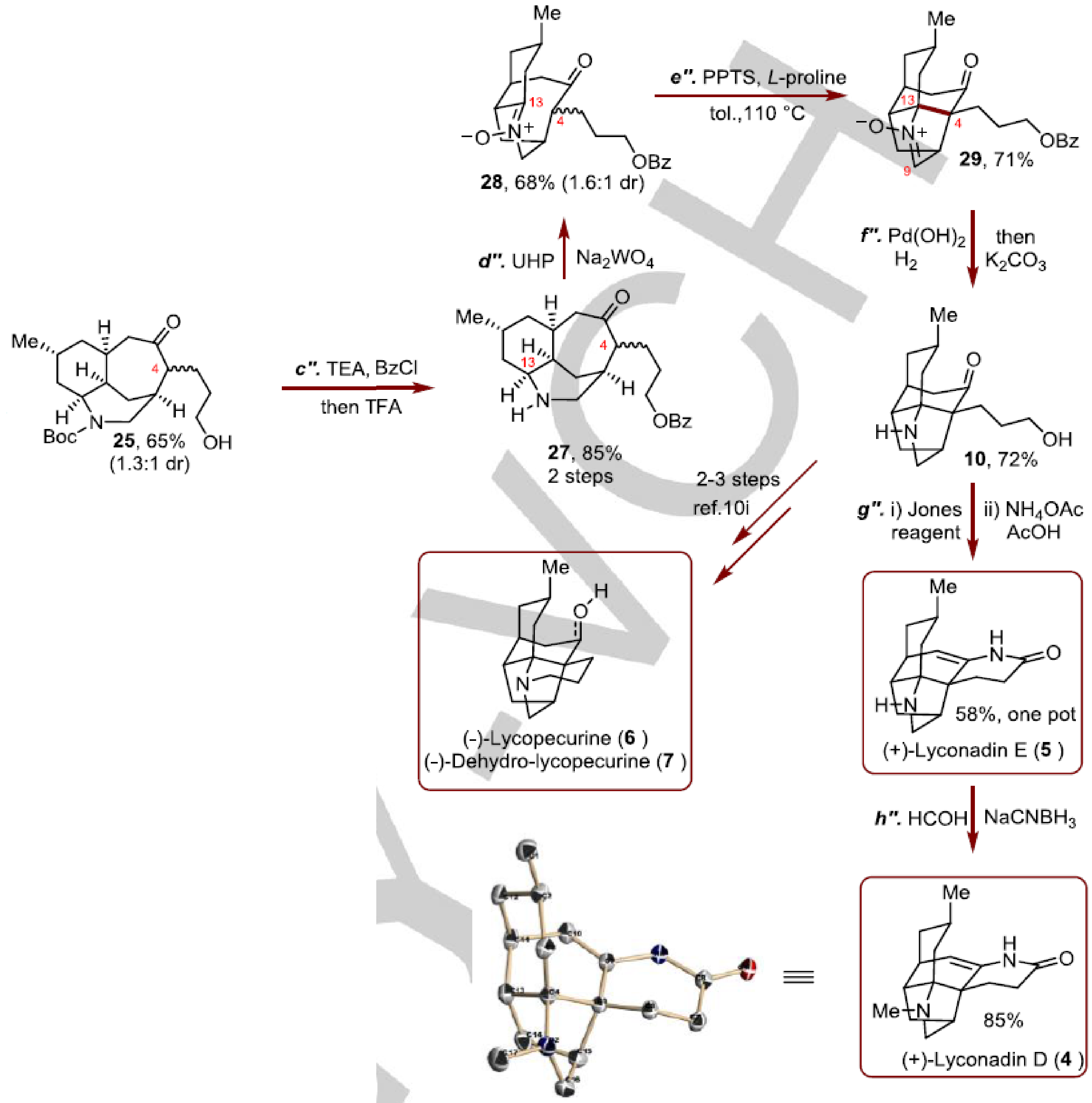
a) Standard condition: [Pd(cinnamyl)Cl]$_2$ (0.2 equiv), Ph$_3$P (0.4 equiv), Bu$_4$NBr (2.4 equiv), K$_3$PO$_4$ (1.0 equiv), xylene (0.025 M), 130 °C, 18 h. b) K$_3$PO$_4$ (0.4 equiv) c) K$_3$PO$_4$ (2.0 equiv), 0.01 M. d) without K$_3$PO$_4$. e) K$_3$PO$_4$ (1.5 equiv), 0.015 M. f [Pd(cinnamyl)Cl]$_2$ (0.4 equiv), Ph$_3$P (0.8 equiv), Bu$_4$NBr (2.4 equiv).



Me
H
O
H
H
H
N
PMB
O
12a
OPMB
a. Ir(CO)Cl(PPh3)2
(Me2HSi)2O;
then
NaBH(OAc)3
Me
H
O
5
H
H
H
PMB
N
OPMB
24, 65%
b. Pd(OH)2
H2
11
then (Boc)2O
Me
H
O
4
H
H
H
N
Boc
25, 65%
(1.3:1 dr)
OH
c. i) Tempo, BAIB, RT
ii) NH4OAc, AcOH
110 °C
d. MnO2, 110 °C
then TFA
HN
O
Me
H
H
H
HN
H
(-)-Lyconadin C (3)
43%, 2 pots



Me
H
O
5
H
H
H
PMB
N
OPMB
24, 65%
b. Pd(OH)2
H2
11
then (Boc)2O
Me
H
O
H
4
H
Boc
N
H
25, 65%
(1.3:1 dr)
OH
then NCS
OH
O
6
4
N
Me
9, 80%
(5:1 dr)
c'. KOH, EtOH
RT
Me
H
O
6
H
H
Cl
N
H
26, 62%
2 steps
OH
d'. i) Jones reagent
ii) NH4OAc AcOH
O
HN
N
Me
(–)-Lyconadin B (2)
51%, one pot
e'. MnO2
110 °C
O
HN
N
Me
(+)-Lyconadin A (1)
80%



Urea hydrogen peroxide