Catalytic, Asymmetric Total Synthesis of (+)-α-, (+)-β-, (+)-γ-, and (−)-δ-Lycorane

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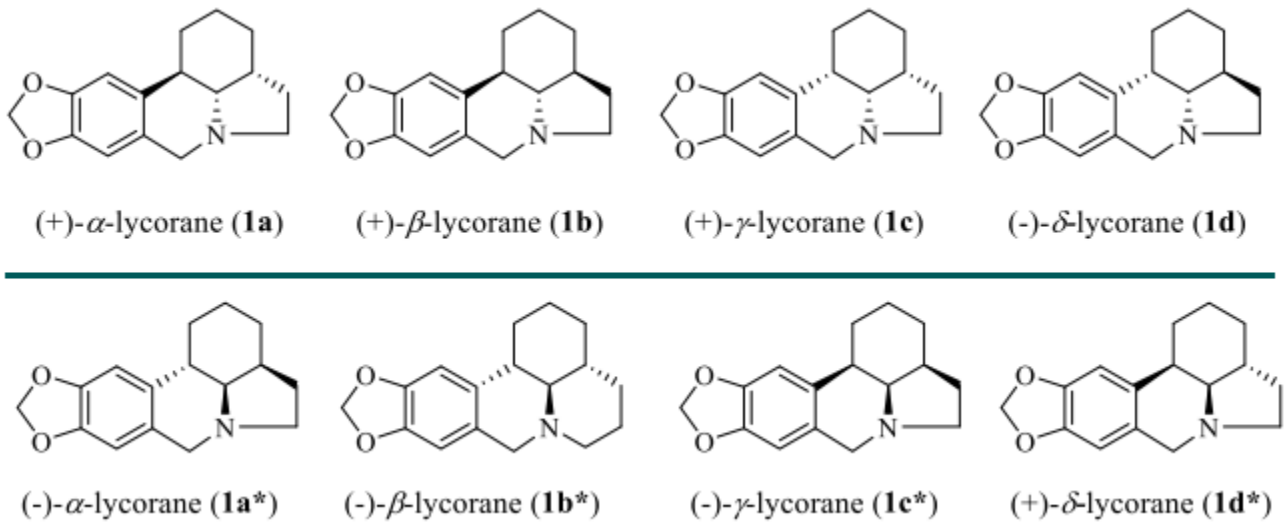

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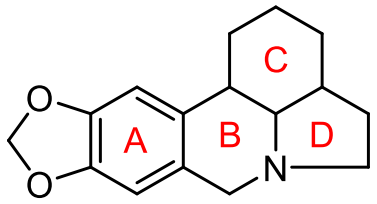
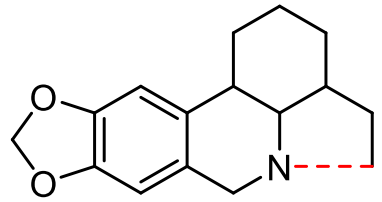
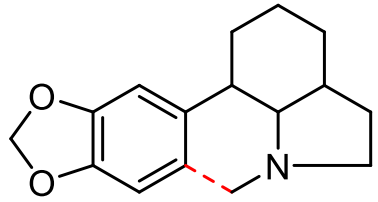


1a-d



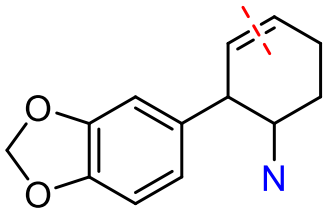
2

or



3

RCM



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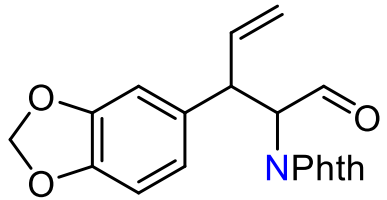
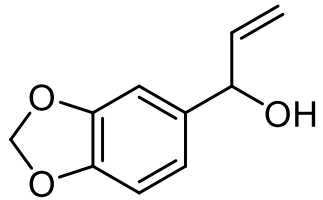


5

stereodivergent

Carreira's dual
Ir/amine catalysis



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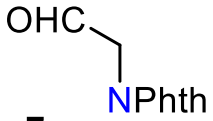
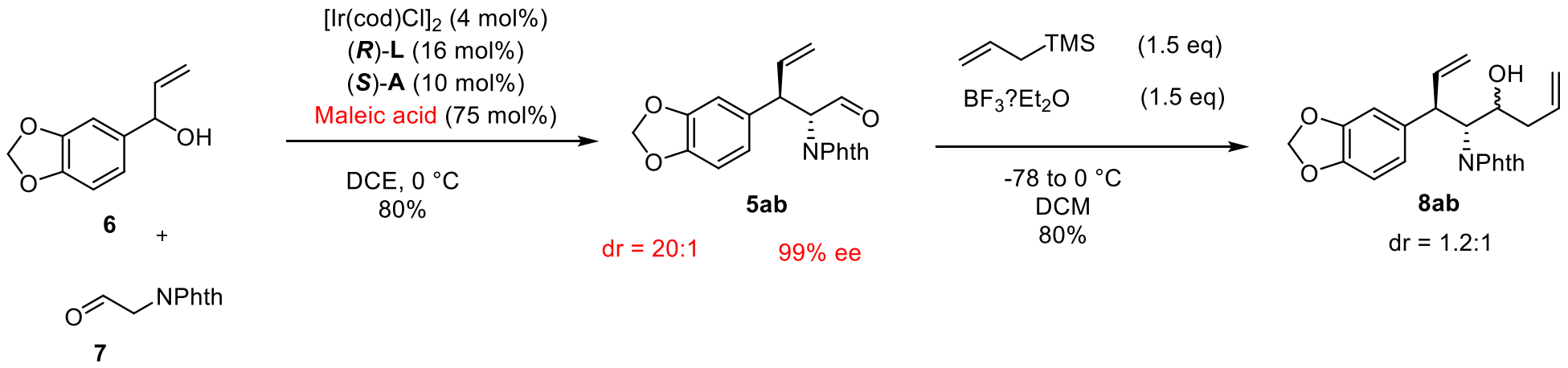
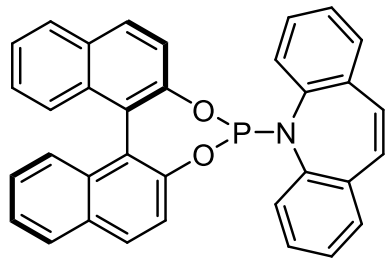
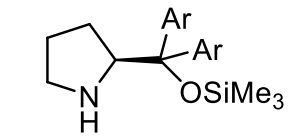


7

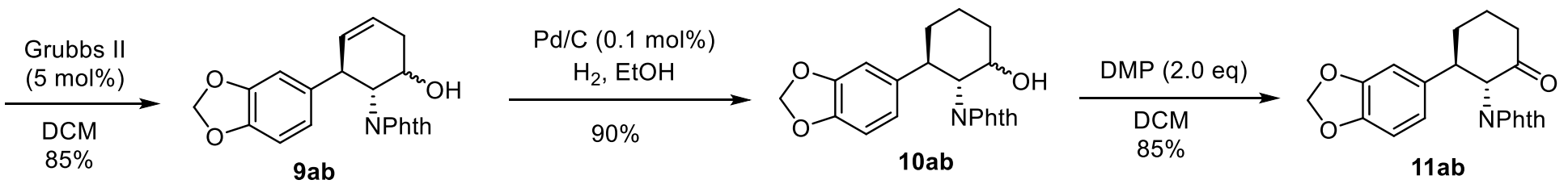

[Ir(cod)Cl]2 (4 mol%)
(R)-L (16 mol%)
(S)-A (10 mol%)
Maleic acid (75 mol%)
DCE, 0 °C
80%
6
+
7
NPhth
5ab
dr = 20:1
99% ee
TMS
(1.5 eq)
BF3?Et2O
(1.5 eq)
-78 to 0 °C
DCM
80%
8ab
dr = 1.2:1

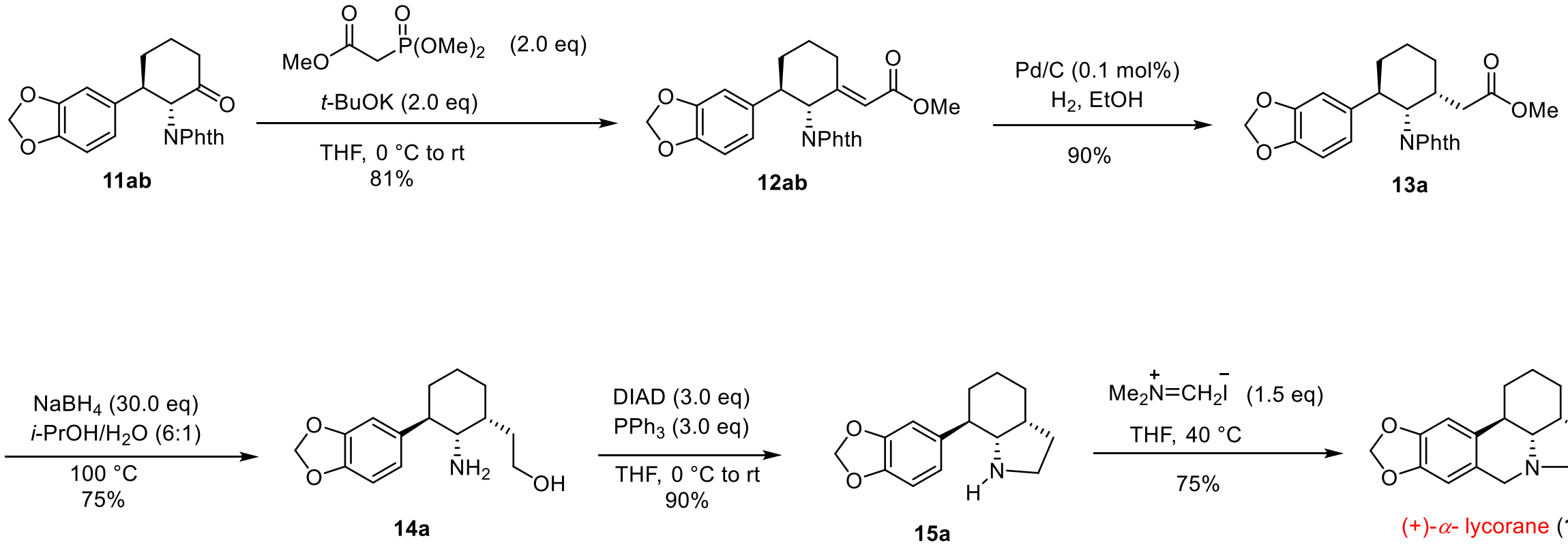


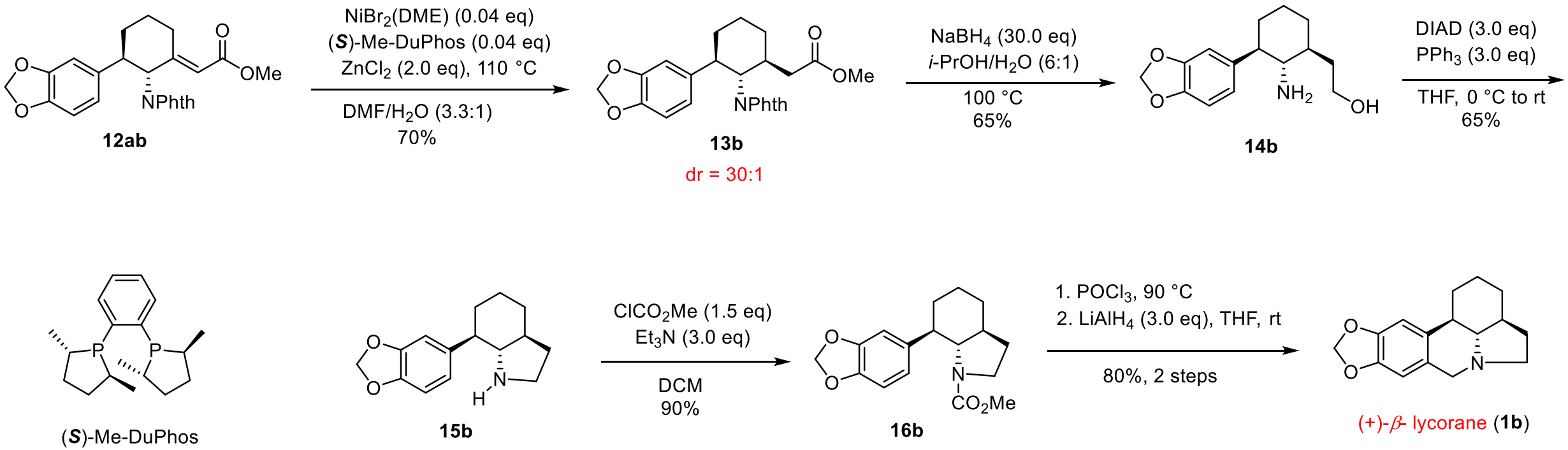
(*R*)-**L**

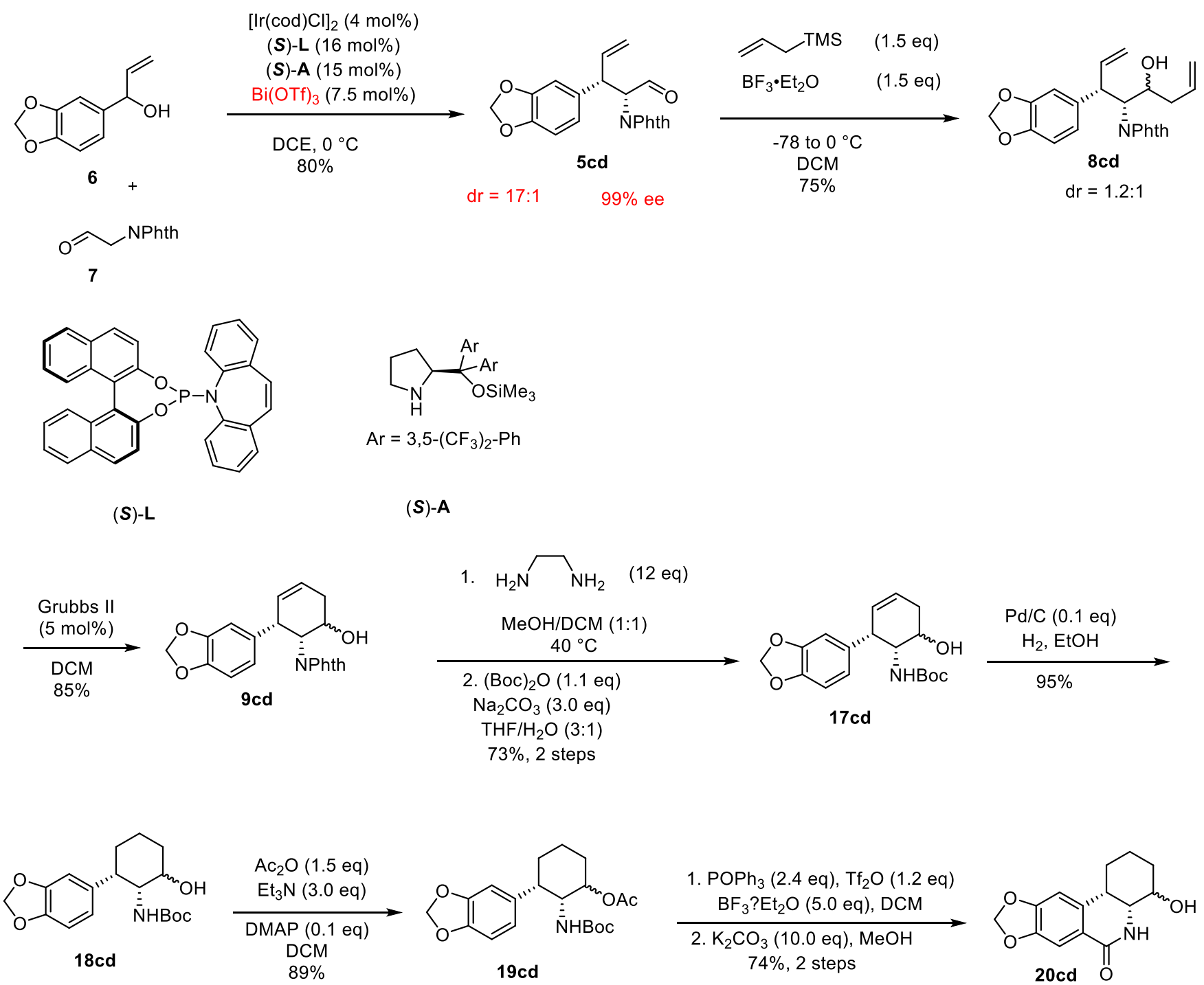

Ar = 3,5-(CF3)2-Ph

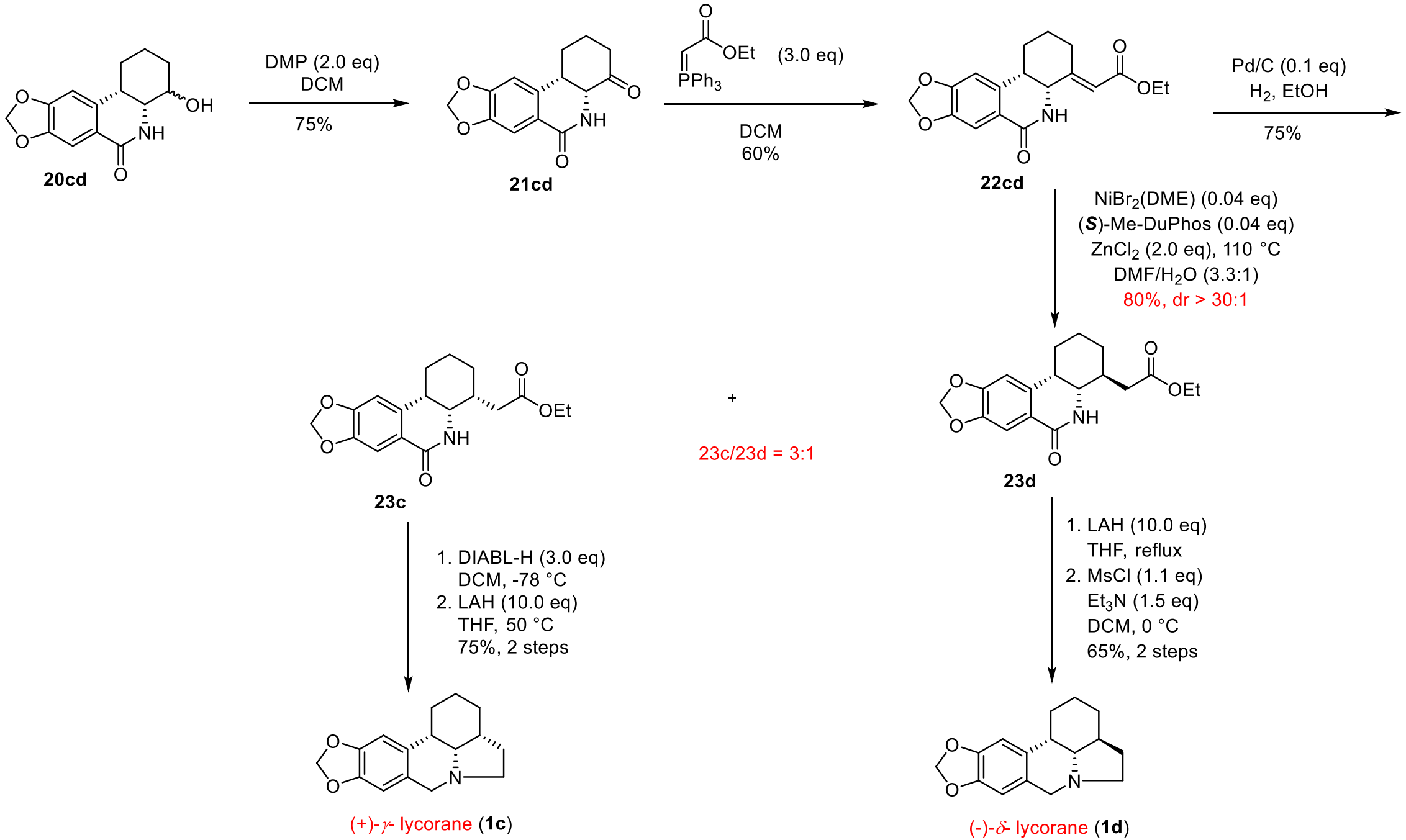
(*S*)-**A**


Grubbs II
(5 mol%)
DCM
85%
9ab
Pd/C (0.1 mol%)
H2, EtOH
90%
10ab
DMP (2.0 eq)
DCM
85%
11ab


MeO
P(OMe)2
(2.0 eq)
t-BuOK (2.0 eq)
THF, 0 °C to rt
81%
NPhth
OMe
Pd/C (0.1 mol%)
H2, EtOH
90%
11ab
12ab
13a
NaBH4 (30.0 eq)
i-PrOH/H2O (6:1)
100 °C
75%
NH2
OH
DIAD (3.0 eq)
PPh3 (3.0 eq)
THF, 0 °C to rt
90%
Me2N=CH2I (1.5 eq)
THF, 40 °C
75%
14a
15a
(+)-α- lycorane (1a)


12ab
NiBr2(DME) (0.04 eq)
(S)-Me-DuPhos (0.04 eq)
ZnCl2 (2.0 eq), 110 °C
DMF/H2O (3.3:1)
70%
13b
dr = 30:1
NaBH4 (30.0 eq)
i-PrOH/H2O (6:1)
100 °C
65%
14b
DIAD (3.0 eq)
PPh3 (3.0 eq)
THF, 0 °C to rt
65%
(S)-Me-DuPhos
15b
ClCO2Me (1.5 eq)
Et3N (3.0 eq)
DCM
90%
16b
1. POCl3, 90 °C
2. LiAlH4 (3.0 eq), THF, rt
80%, 2 steps
(+)-β- lycorane (1b)


[Ir(cod)Cl]2 (4 mol%)
(S)-L (16 mol%)
(S)-A (15 mol%)
Bi(OTf)3 (7.5 mol%)
DCE, 0 °C
80%
6
+
7
NPhth
5cd
dr = 17:1
99% ee
TMS
(1.5 eq)
BF3•Et2O
(1.5 eq)
-78 to 0 °C
DCM
75%
8cd
dr = 1.2:1
(S)-L
Ar = 3,5-(CF3)2-Ph
(S)-A
Grubbs II
(5 mol%)
DCM
85%
9cd
1. H2N NH2 (12 eq)
MeOH/DCM (1:1)
40 °C
2. (Boc)2O (1.1 eq)
Na2CO3 (3.0 eq)
THF/H2O (3:1)
73%, 2 steps
17cd
Pd/C (0.1 eq)
H2, EtOH
95%
18cd
Ac2O (1.5 eq)
Et3N (3.0 eq)
DMAP (0.1 eq)
DCM
89%
19cd
1. POPh3 (2.4 eq), Tf2O (1.2 eq)
BF3?Et2O (5.0 eq), DCM
2. K2CO3 (10.0 eq), MeOH
74%, 2 steps
20cd


20cd
DMP (2.0 eq)
DCM
75%
21cd
OEt
PPh3
(3.0 eq)
DCM
60%
22cd
Pd/C (0.1 eq)
H2, EtOH
75%
NiBr2(DME) (0.04 eq)
(S)-Me-DuPhos (0.04 eq)
ZnCl2 (2.0 eq), 110 °C
DMF/H2O (3.3:1)
80%, dr > 30:1
23d
23c
+
23c/23d = 3:1
1. DIABL-H (3.0 eq)
DCM, -78 °C
2. LAH (10.0 eq)
THF, 50 °C
75%, 2 steps
1. LAH (10.0 eq)
THF, reflux
2. MsCl (1.1 eq)
Et3N (1.5 eq)
DCM, 0 °C
65%, 2 steps
(+)-γ- lycorane (1c)
(-)-δ- lycorane (1d)

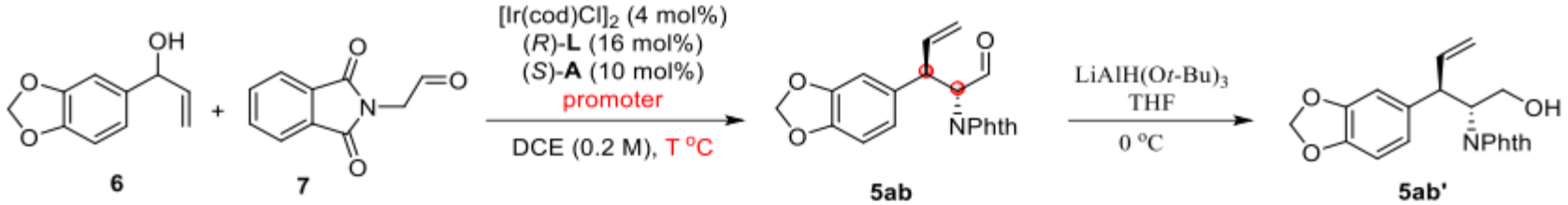


Table 1: Optimization of Dual Catalytic Allylation

entry	promoter (mol%)	temperature	time (h)	d.r[b]	yield (%)[a]	ee (%) [c,d]
1[e]	Cl_2CHCO_2H (75)	rt	2	1.5:1	66	n.d.
2[e]	Cl_3CCO_2H (50)	rt	6	5:1	74	n.d.
3[e]	Citric acid (75)	rt	11	4:1	61	n.d.
4[e]	$CH(CO_2H)_2$ (100)	rt	3	2.6:1	69	n.d.
5[f]	$CH(CO_2H)_2$ (100)	0 °C	7	4:1	75	n.d.
6[e]	Maleic acid (75)	rt	5	5:1	80	n.d.
7[f]	Maleic acid (75)	0 °C	10	20:1	68	99

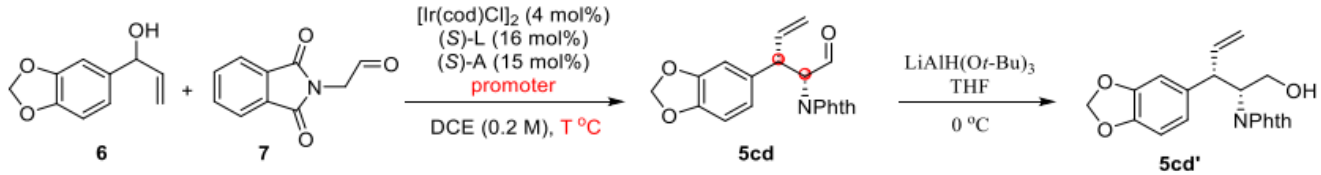
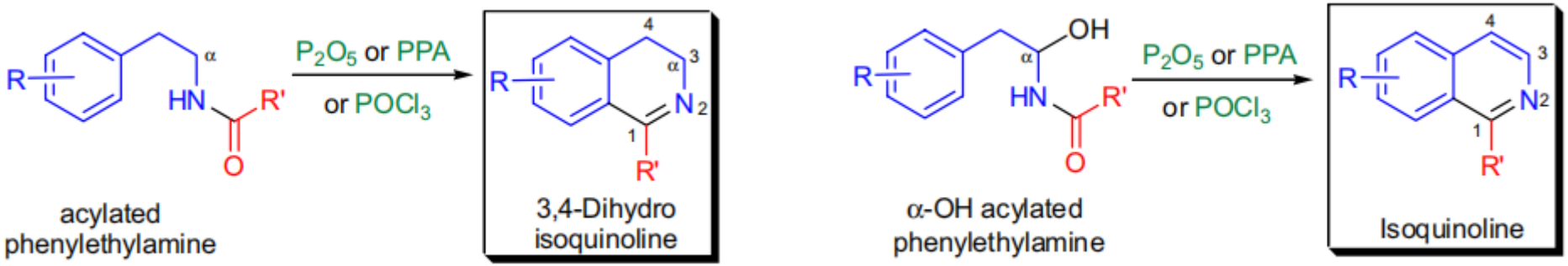


Table 2: Optimization of Dual Catalytic Allylation

entry	promoter (mol%)	temperature	time (h)	d.r[b]	yield(%)[a]	ee(%)[c,d]
1[e]	Maleic acid (75)	rt	4	3:1	54	n.d.
2[e]	$Zn(OTf)_2$ (10)	rt	10	5:1	57	n.d.
3[e]	$Sc(OTf)_3$ (10)	rt	4	3.7:1	54	n.d.
4[e]	$Yb(OTf)_3$ (10)	rt	6	1.5:1	61	n.d.
5[e]	Malonic acid (100)	rt	4	1.4:1	58	n.d.
6[e]	$Bi(OTf)_3$ (10)	rt	6	10:1	30	n.d.
7[e]	$Bi(OTf)_3$ (5)	rt	6	4.7:1	60	n.d.
8[f]	$Bi(OTf)_3$ (5)	0 °C	12	8:1	40	n.d.
9[e]	$Bi(OTf)_3$ (7.5)	rt	6	10:1	30	n.d.
10[g]	$Bi(OTf)_3$ (7.5)	0 °C -rt	10	17:1	60	99

BISCHLER-NAPIERALSKI ISOQUINOLINE SYNTHESIS



acylated phenylethylamine

α-OH acylated phenylethylamine

Mechanism: [16,5]