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Article

Divergent Total Syntheses of Napelline-Type C20-Diterpenoid Alkaloids: (−)-Napelline, (+)-Dehydronapelline, (−)-Songorine, (−)-Songoramine, (−)-Acoapetaldine D, and (−)-Liangshanone

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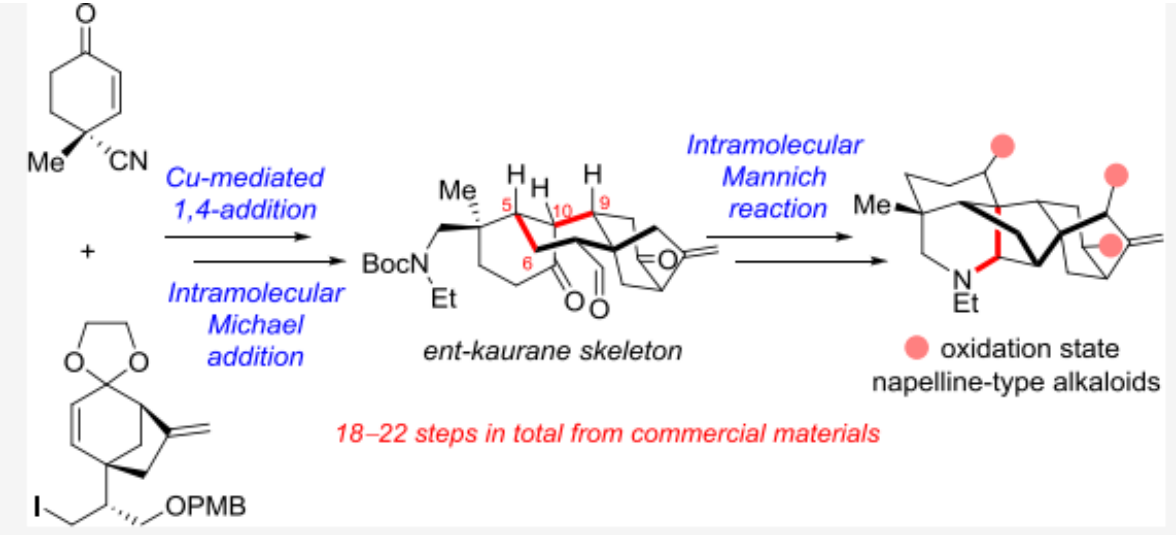
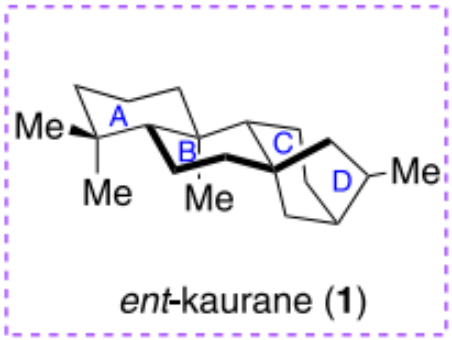
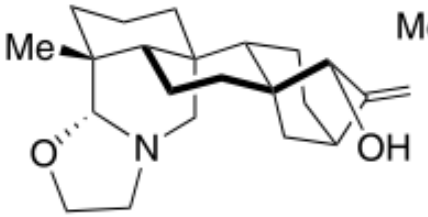




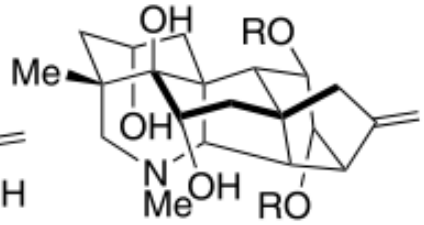
ent-kaurane (**1**)

Veatchine-type



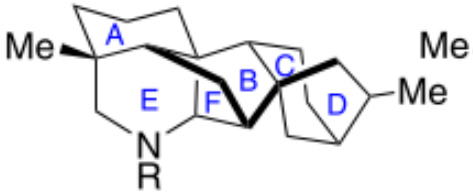
garryine (**2**)

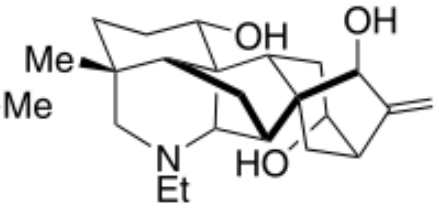
Anopterine-type



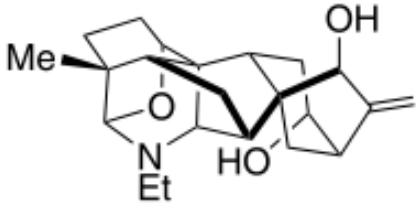
anopterine (**3**)
R = (*E*)-2-methylbut-2-enoyl

Napelline-type

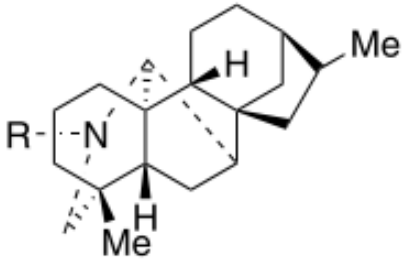




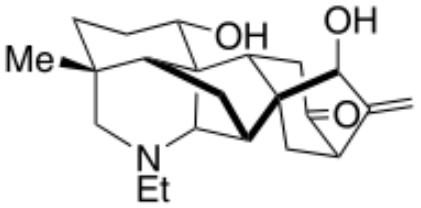
napelline (**4**)



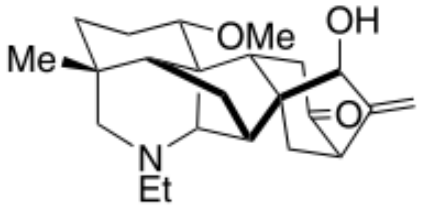
dehydronapelline (**5**)



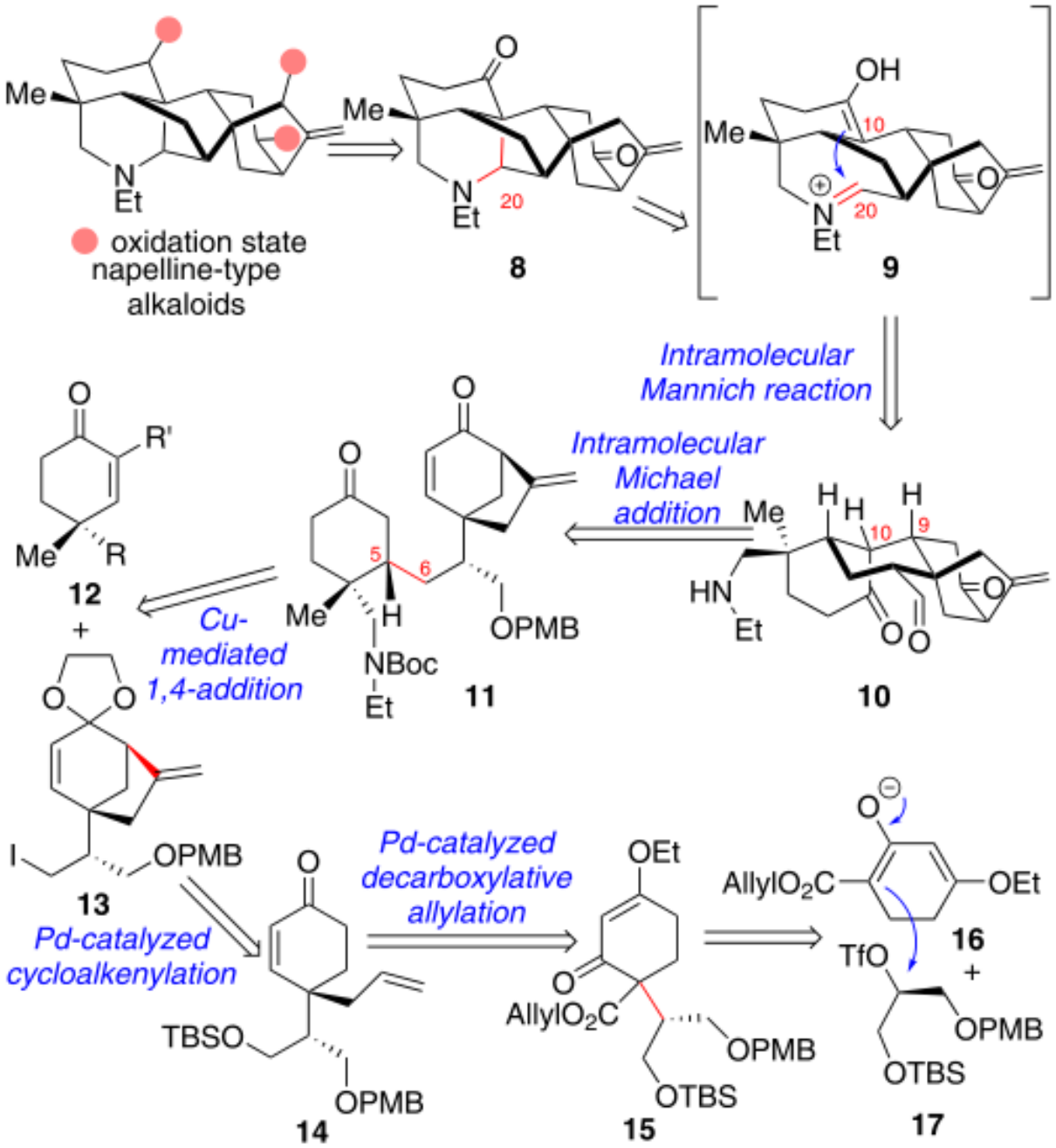
napelline skeleton

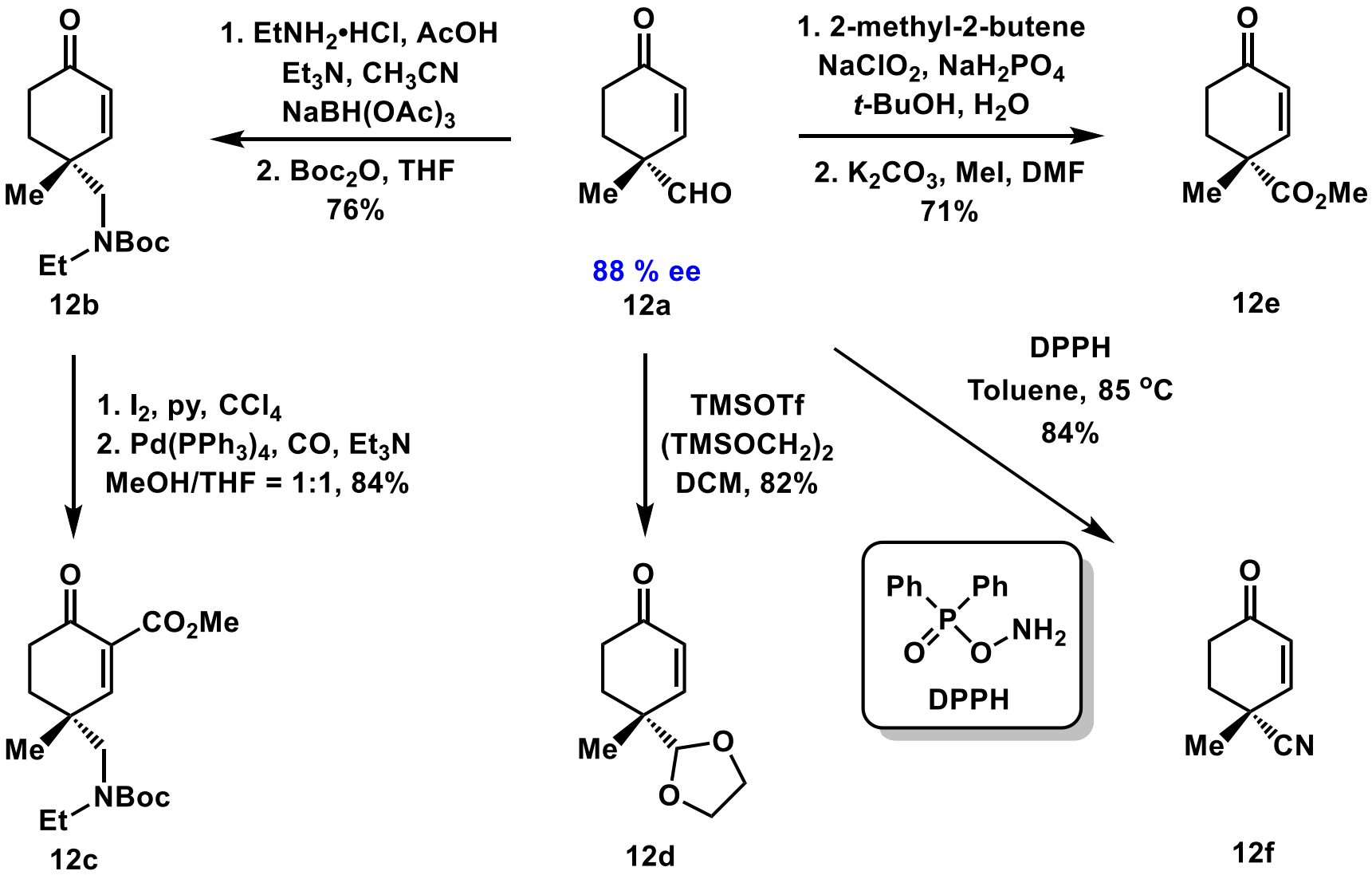


songorine (**6**)



liangshanone (**7**)


oxidation state
napelline-type
alkaloids
8
9
Intramolecular
Mannich reaction
Intramolecular
Michael
addition
10
11
12
+
Cu-
mediated
1,4-addition
13
Pd-catalyzed
cycloalkenylation
14
Pd-catalyzed
decarboxylative
allylation
15
16
+
17


1. EtNH2•HCl, AcOH
Et3N, CH3CN
NaBH(OAc)3
2. Boc2O, THF
76%
1. 2-methyl-2-butene
NaClO2, NaH2PO4
t-BuOH, H2O
2. K2CO3, MeI, DMF
71%
88 % ee
12a
12b
12e
1. I2, py, CCl4
2. Pd(PPh3)4, CO, Et3N
MeOH/THF = 1:1, 84%
TMSOTf
(TMSOCH2)2
DCM, 82%
DPPH
Toluene, 85 °C
84%
DPPH
12c
12d
12f

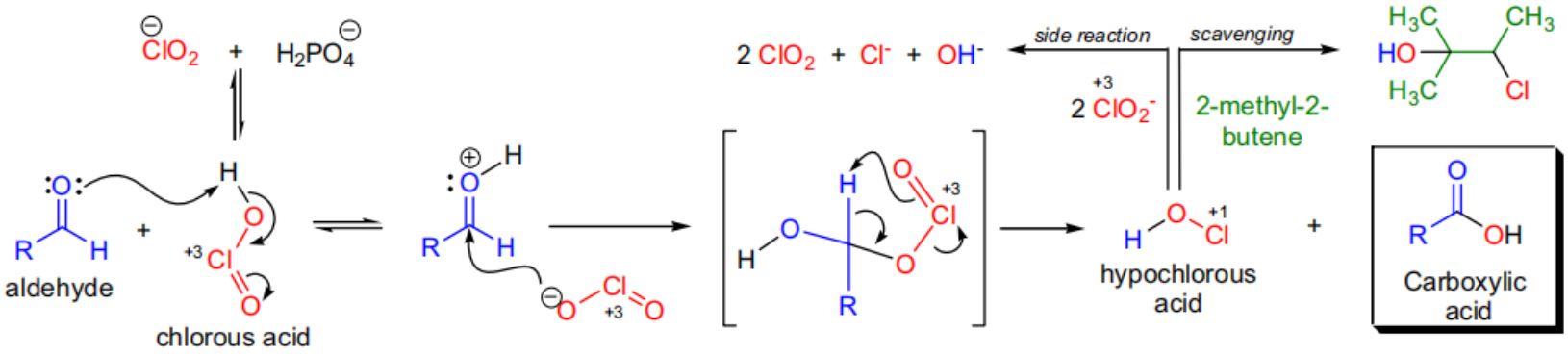
PINNICK OXIDATION

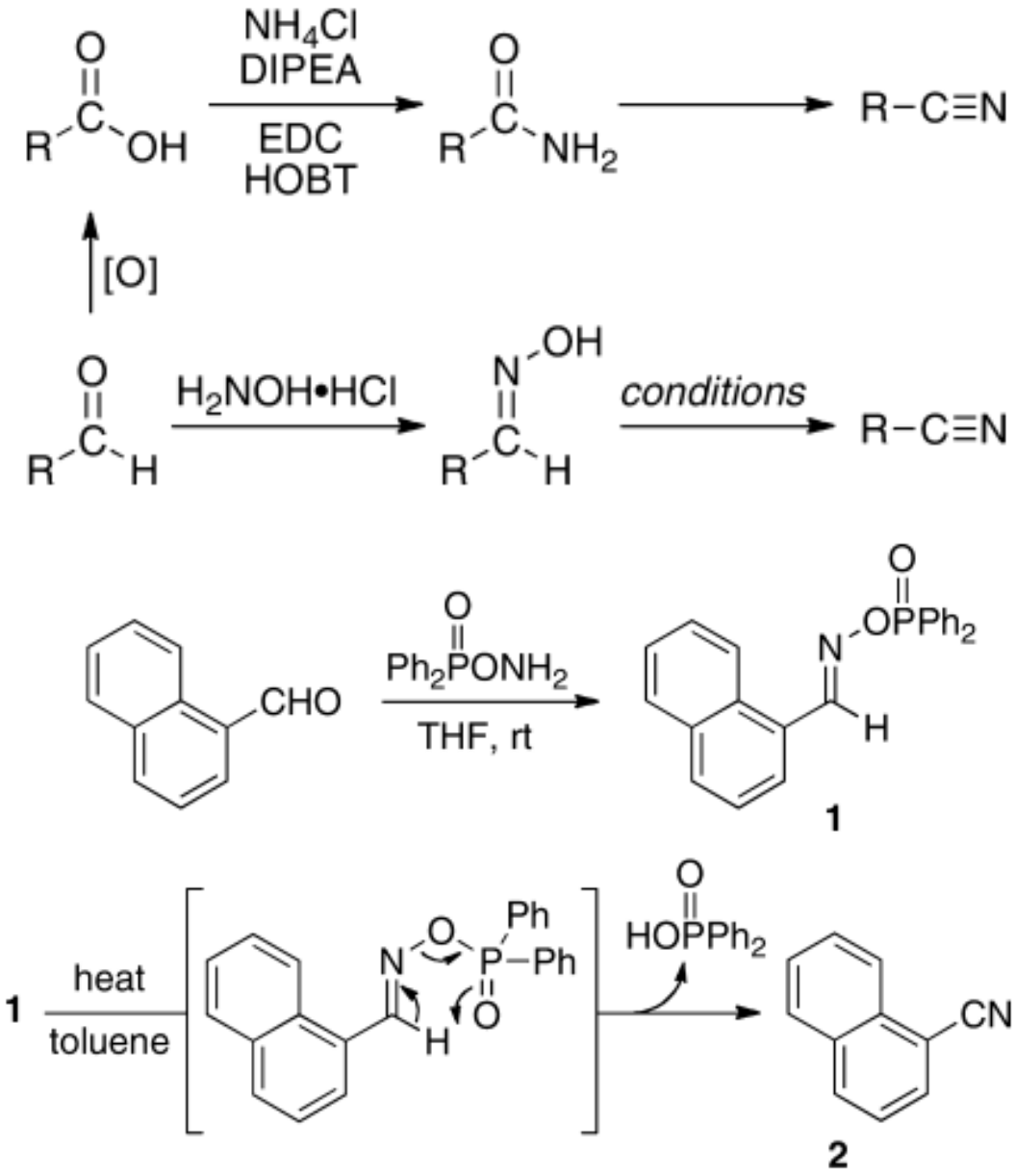
(References are on page 655)

Importance:

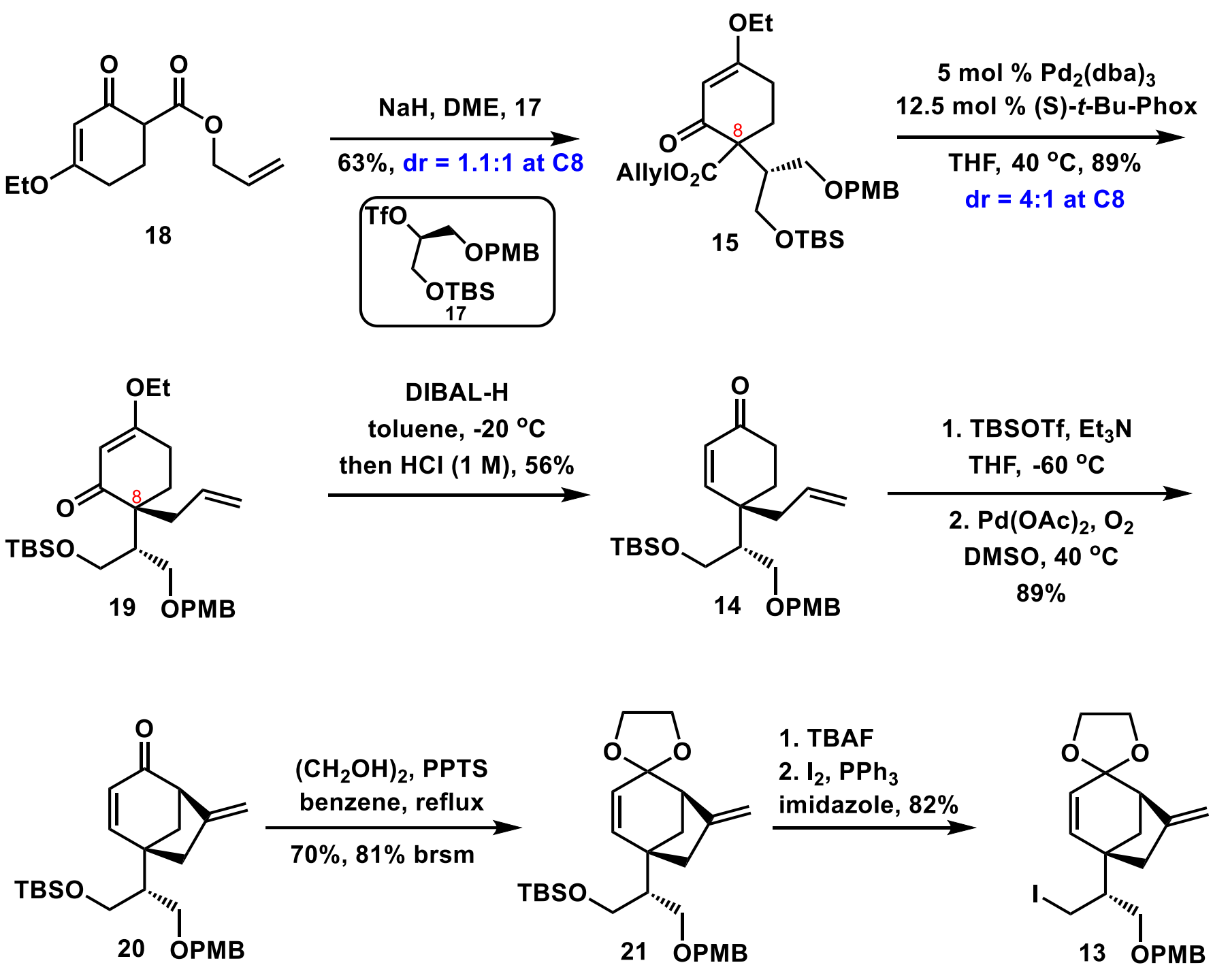
[*Seminal Publications*[1-4]; *Reviews*[5]; *Modifications & Improvements*[6,5,7]]

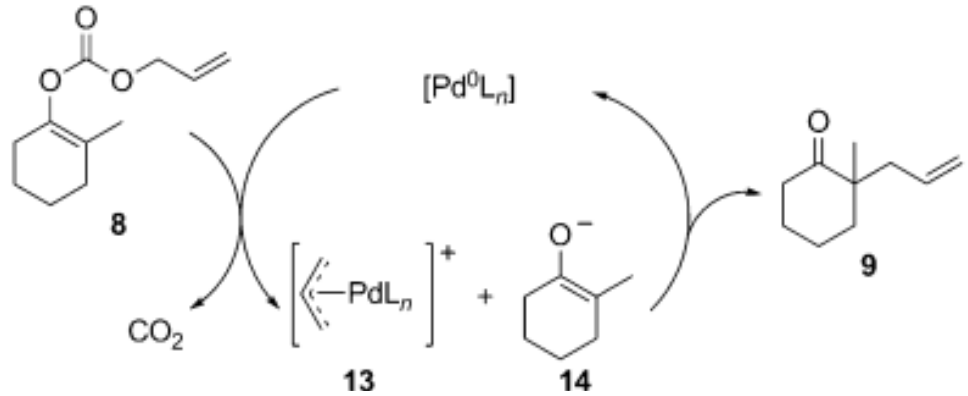
Mechanism: [10,6]

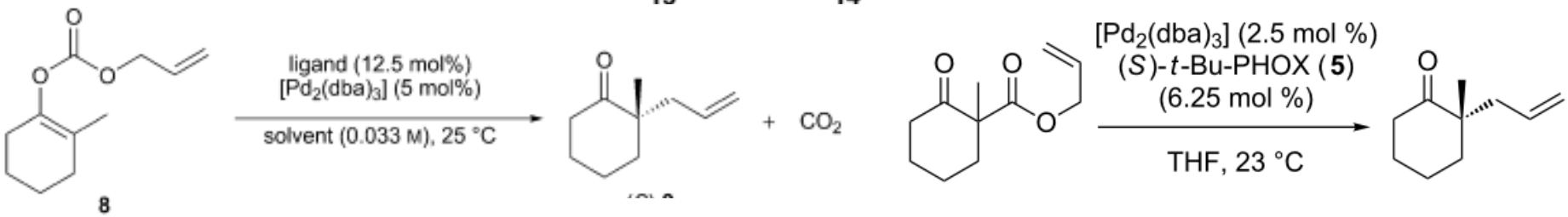


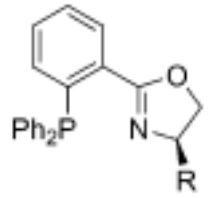
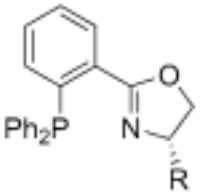


J. Org. Chem., **2012**, *77*, 9334.


O
O
O
EtO
18
NaH, DME, 17
63%, dr = 1.1:1 at C8
TfO
OPMB
OTBS
17
OEt
8
O
AllylO2C
OPMB
15
OTBS
5 mol % Pd2(dba)3
12.5 mol % (S)-t-Bu-Phox
THF, 40 °C, 89%
dr = 4:1 at C8
OEt
8
O
TBSO
19
OPMB
DIBAL-H
toluene, -20 °C
then HCl (1 M), 56%
O
TBSO
14
OPMB
1. TBSOTf, Et3N
THF, -60 °C
2. Pd(OAc)2, O2
DMSO, 40 °C
89%
O
TBSO
20
OPMB
(CH2OH)2, PPTS
benzene, reflux
70%, 81% brsm
O
O
TBSO
21
OPMB
1. TBAF
2. I2, PPh3
imidazole, 82%
O
O
I
13
OPMB

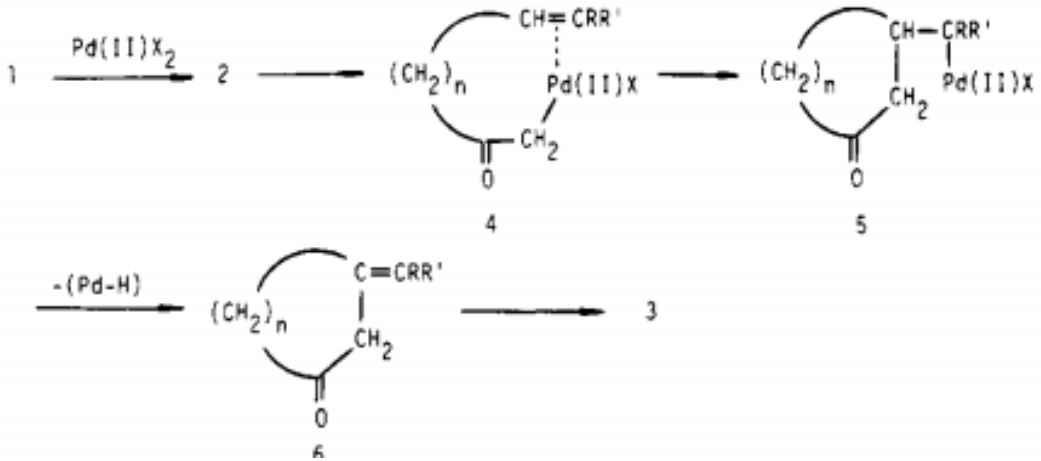


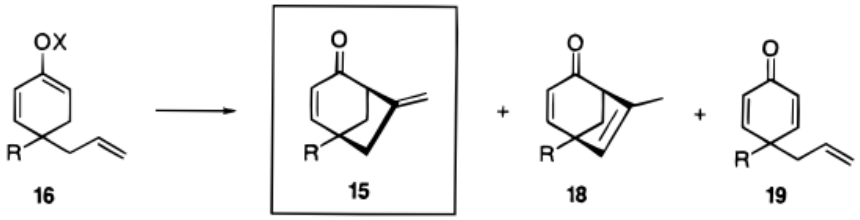


	Ligand		1,4-Dioxane			Tetrahydrofuran		
			t [h]	Yield [%][a]	*ee* [%][b]	*t* [h]	Yield [%][a]	*ee*[b] [%]
7		(*R*)-Ph-PHOX (**16**; R=Ph)	2	95	62[c]	2	95	65[c]
8		(*S*)-*i*Pr-PHOX (**17**; R=*i*Pr)	3	96	82[c]	2	95	83[c]
9		(*R*)-Bn-PHOX (**18**; R=Bn)	3	96	65	5	94	63
10		(*S*)-*t*Bu-PHOX (**19**; R=*t*Bu)	2	95	86	2	96	88

Chem. Eur. J., **2011**, *17*, 14199.

Scheme I





a: X = TMS, b: X = TES, c: X = TBDMS
R = $-CH_2CH_2OMOM$

run	X	$Pd(OAc)_2$ (mol %)	solvent (mol/L)	time (h)	yield (%) 15	18	19	16
1	TMS	10	DMSO (0.05)	17	62	trace	21	
2	TES	10	DMSO (0.05)	11	76	trace	14	
3	TBDMS	10	DMSO (0.05)	19	81	4	5	
4	TBDMS	5	DMSO (0.05)	4	82	3	3	
5	TBDMS	3	DMSO (0.05)	22	81	5	trace	
6	TBDMS	1	DMSO (0.05)	26	18	trace	trace	64
7	TBDMS	10	DMSO (0.1)	5	89	2	3	
8	TBDMS	10	DMSO (0.3)	15	78	3	5	
9	TBDMS	10	DMSO−H_2O^b (0.05)	4.5	63	trace	trace	
10	TBDMS	10	MeCN (0.05)	13	37	trace	trace	57

J. Am. Chem. Soc., **1998**, *120*, 4916.

SAEGUSA OXIDATION

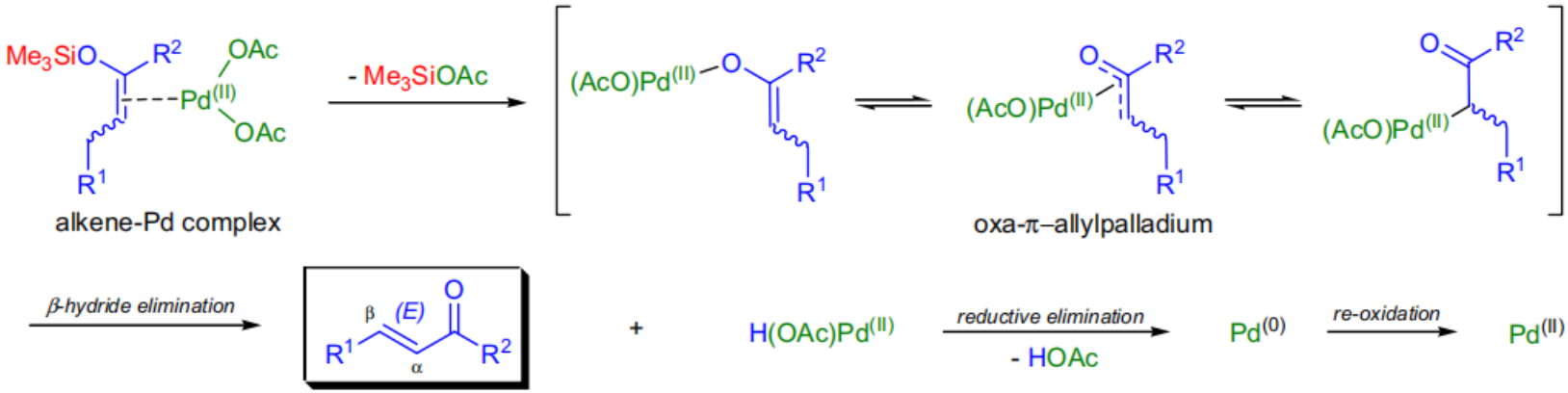
(References are on page 667)

Importance:

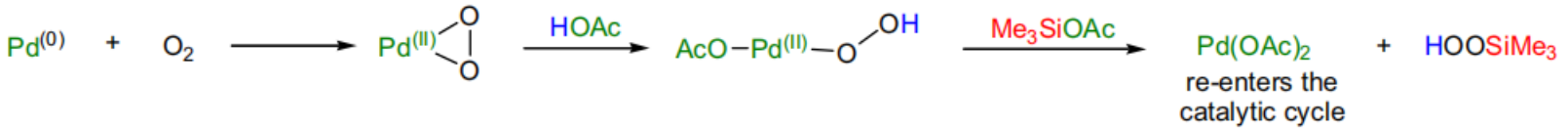
[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-11]]

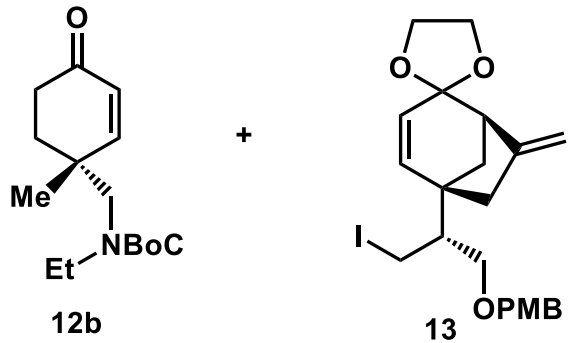
Mechanism:[15,7]

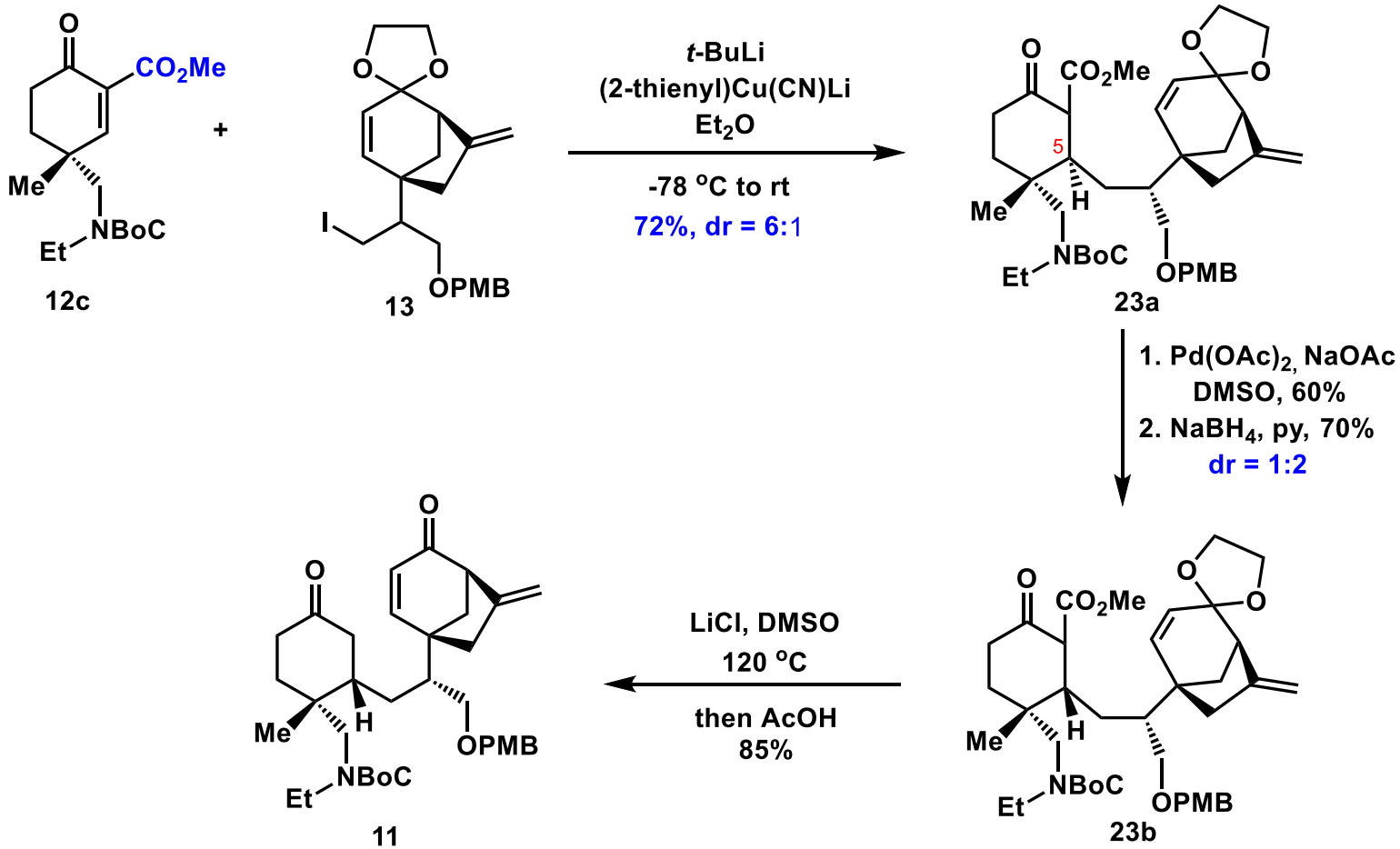
When substoichiometric/stoichiometric amounts of $Pd(OAc)_2$ is used:

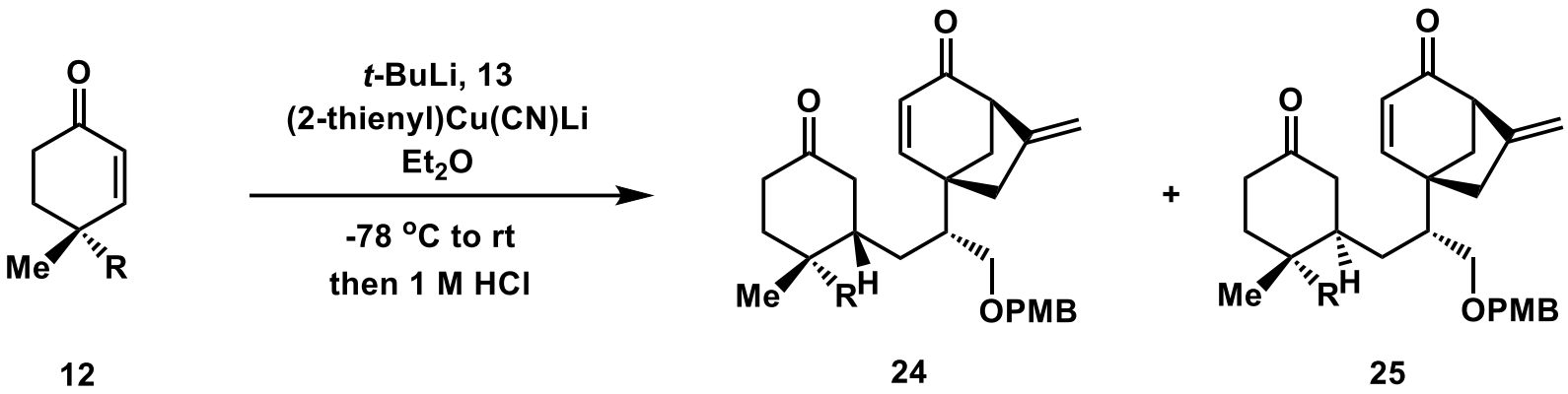


When the oxidation takes place under an oxygen atmosphere with catalytic amounts of $Pd(OAc)_2$:




O
Me
NBoC
Et
12b
+
O
O
I
OPMB
13
copper-mediated or
radical-type 1,4-addition
various conditions
O
O
O
Me
H
OPMB
NBoC
Et
22


O
CO2Me
Me
NBoC
Et
12c
+
O
O
I
OPMB
13
t-BuLi
(2-thienyl)Cu(CN)Li
Et2O
-78 °C to rt
72%, dr = 6:1
O
CO2Me
O
O
5
Me
H
NBoC
Et
OPMB
23a
1. Pd(OAc)2, NaOAc
DMSO, 60%
2. NaBH4, py, 70%
dr = 1:2
O
CO2Me
O
O
Me
H
NBoC
Et
OPMB
23b
LiCl, DMSO
120 °C
then AcOH
85%
O
O
Me
H
OPMB
NBoC
Et
11



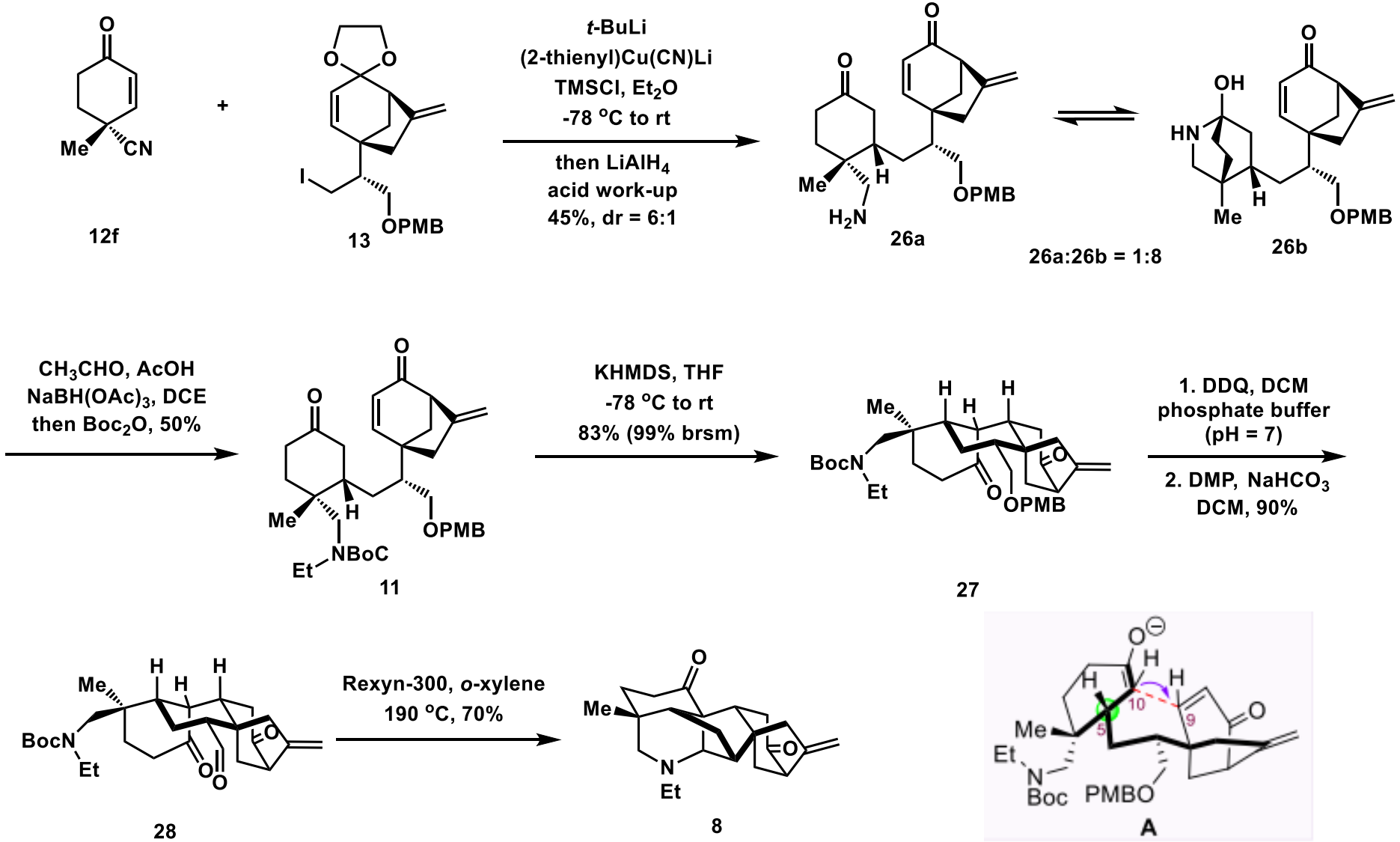
12 24 25

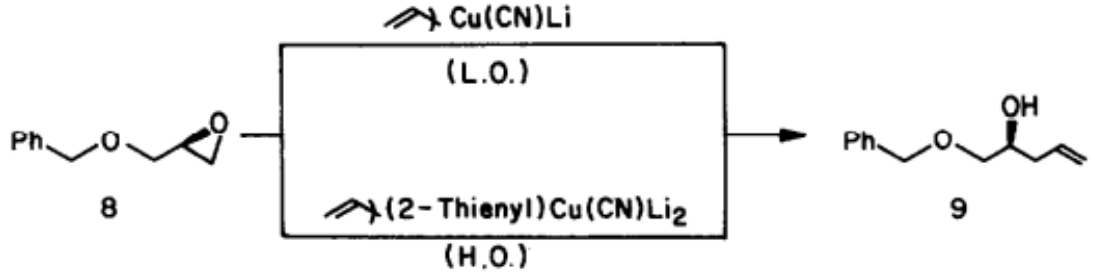
a: R = CHO; d: R = $CH(OCH_2)_2$; e: R = CO_2Me; f: R = CN

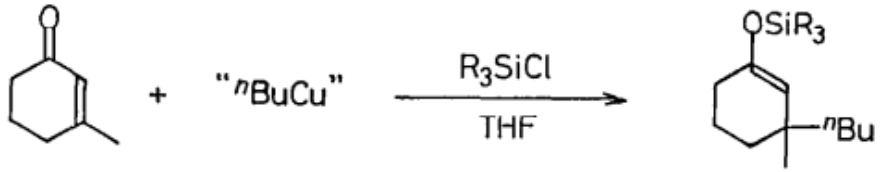
Table 1. Conjugate Addition with Less Bulky Enones[a]

entry	enone	conditions	yield	24:25
1	**12d**	standard conditions	12%	1.2:1
2	**12d**	$CuBr{\cdot}Me_2S$ as the copper source	0%	-
3	**12d**	$BF_3{\cdot}OEt_2$ as the additive	0%	-
4	**12d**	TMSCl as the additive	56%	1:1.2
5	**12e**	TMSCl as the additive	50%	2:1
6	**12f**	TMSCl as the additive	67%	6:1
7	**12a**	standard conditions	0%	-

[a]Standard conditions: *t*-BuLi, **13**, (2-thienyl)Cu(CN)Li, Et_2O, −78 °C to rt, then HCl (1 M).


12f
13
t-BuLi
(2-thienyl)Cu(CN)Li
TMSCl, Et2O
-78 °C to rt
then LiAlH4
acid work-up
45%, dr = 6:1
26a
26a:26b = 1:8
26b
CH3CHO, AcOH
NaBH(OAc)3, DCE
then Boc2O, 50%
11
KHMDS, THF
-78 °C to rt
83% (99% brsm)
27
1. DDQ, DCM
phosphate buffer
(pH = 7)
2. DMP, NaHCO3
DCM, 90%
28
Rexyn-300, o-xylene
190 °C, 70%
8
A





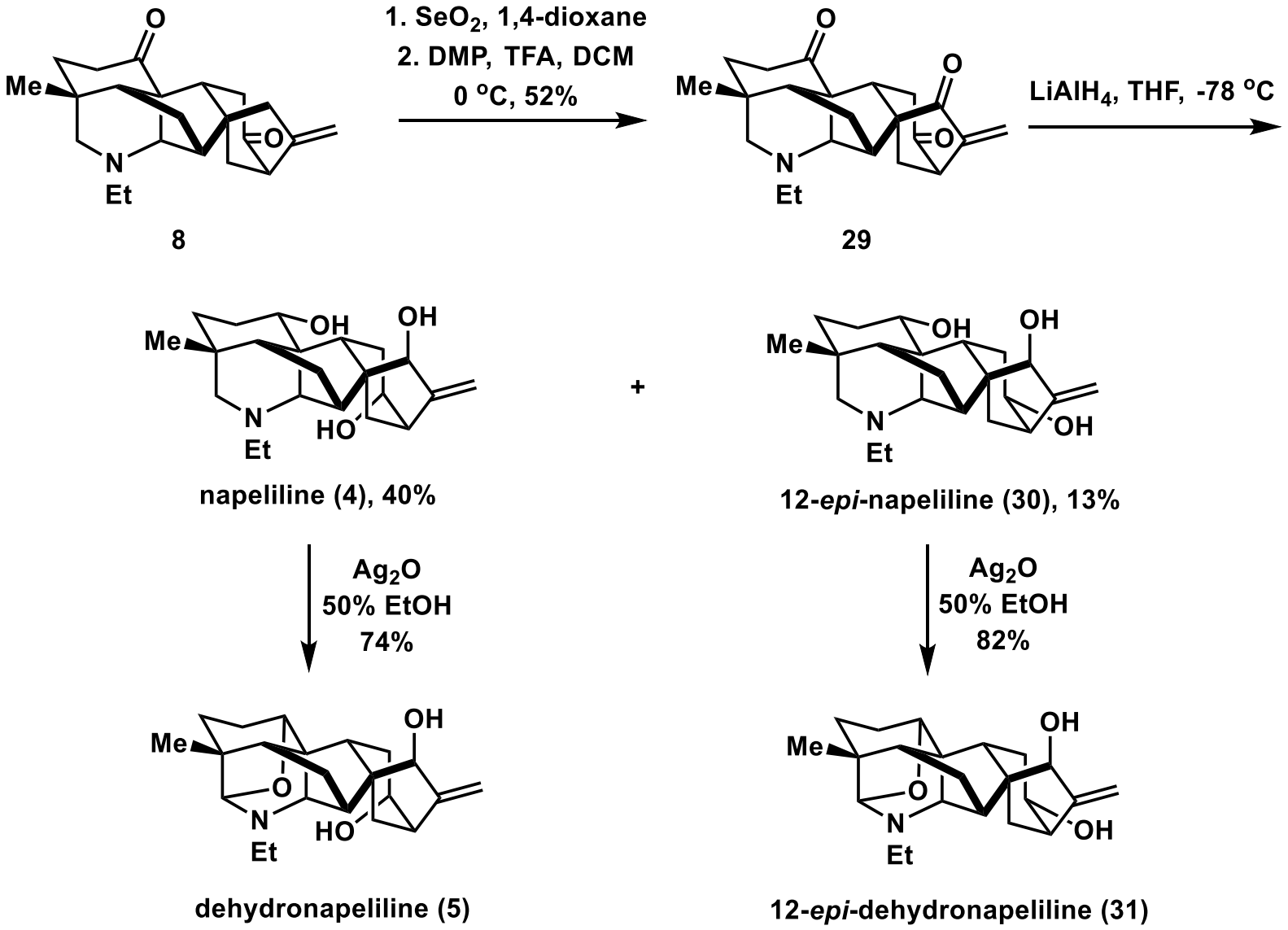
(1)

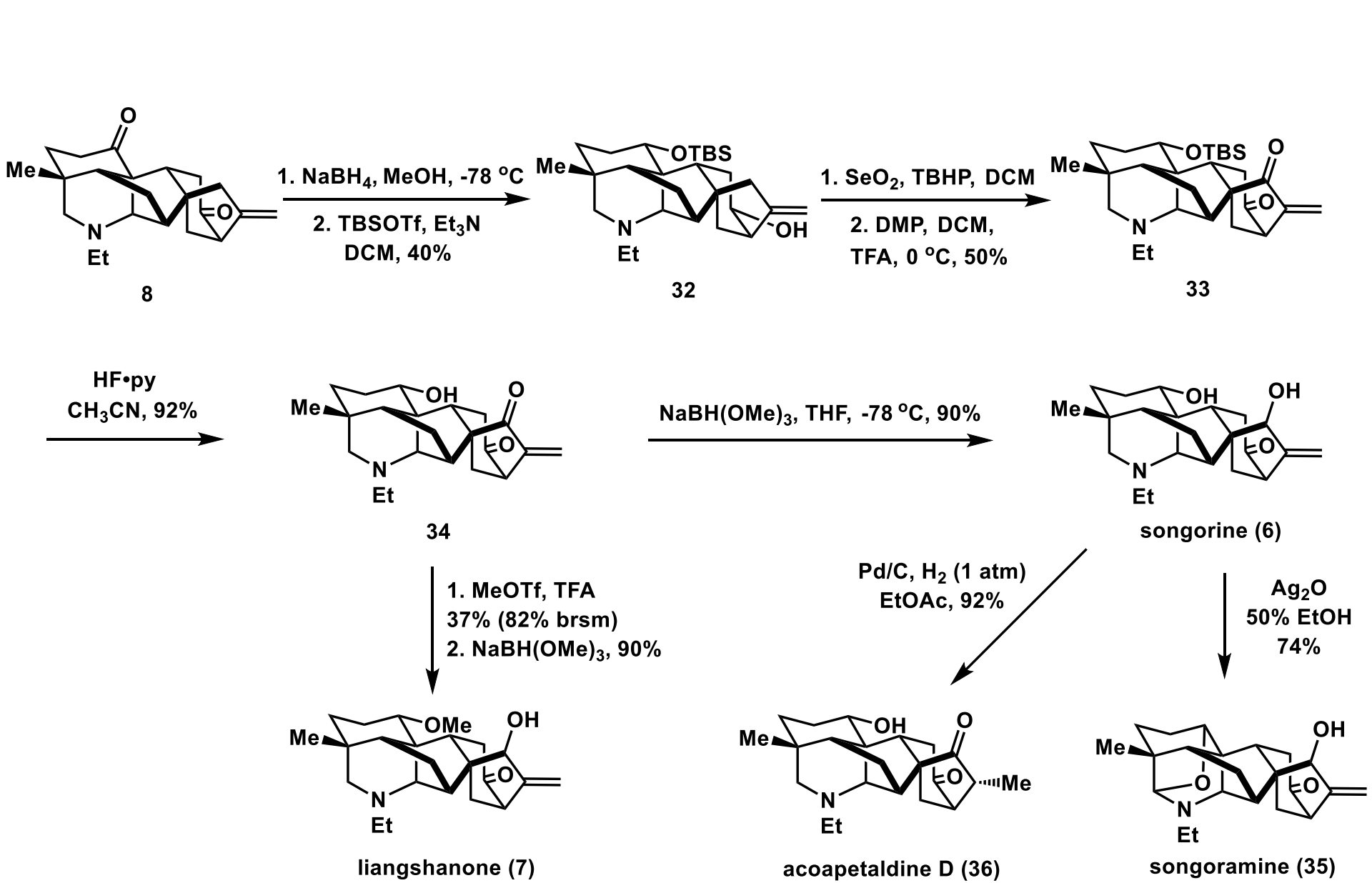
Table I. Me_3SiCl-Assisted Addition onto 3-Methylcyclohexenone at -78 °C in THF

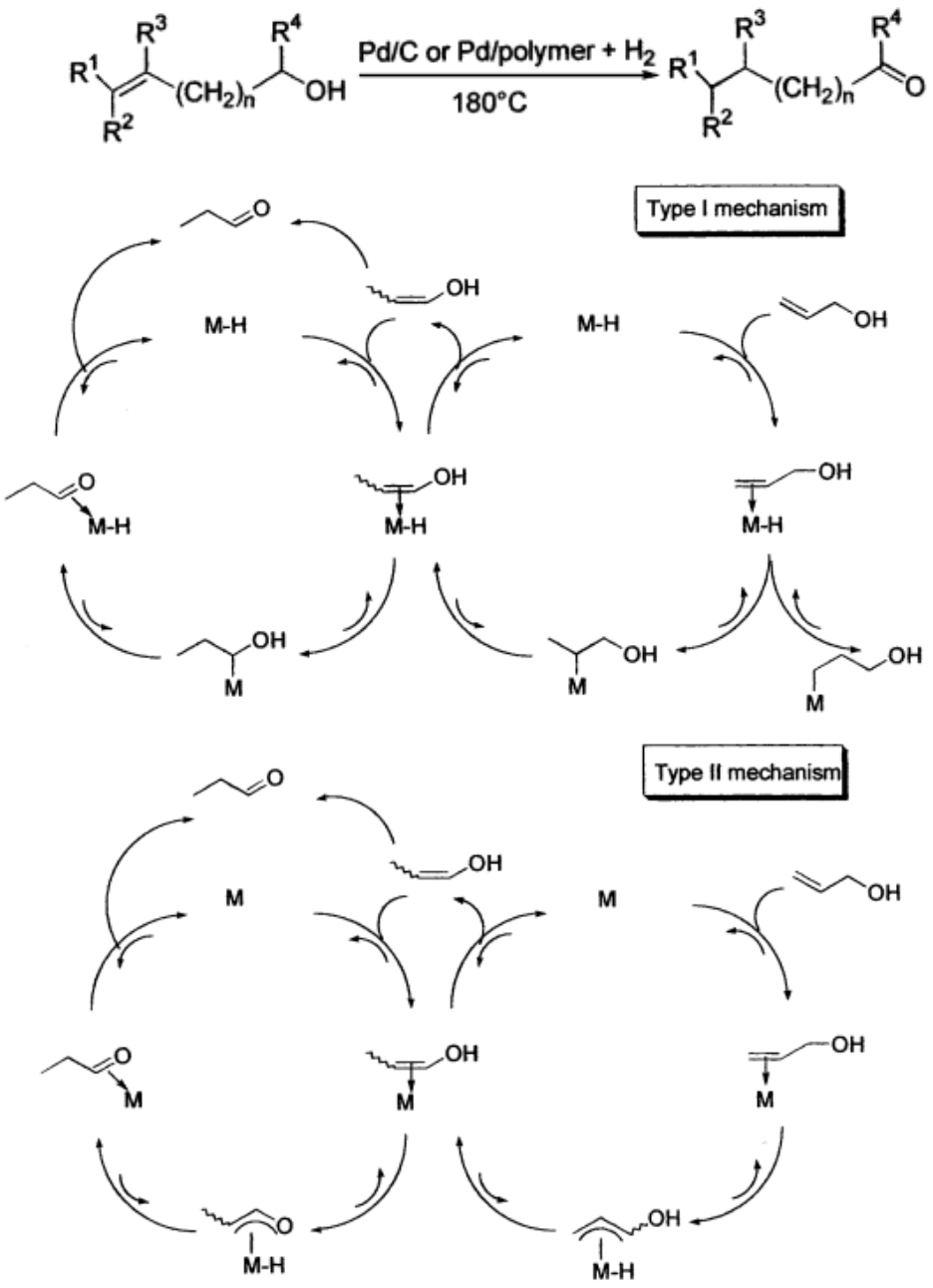
entry	Bu_2CuLi or BuCu (equiv)	R_3SiCl (2 equiv)	additive (2 equiv)	time	GLC yield (%) 1,4-adduct	recovery
1	Bu_2CuLi (2.0)	-	-	1 h	28[a]	70
2	(2.0)	Me_3SiCl	-	5 min	99	0
3	Bu_2CuLi (0.6)	Me_3SiCl	HMPA	3 h	87	13
4	(2.0)	$^tBuMe_2SiCl$	-	1 h	31	63
5	(2.0)	$^tBuMe_2SiCl$	HMPA	1 h	95	5
6	(2.0)	$^tBuMe_2SiCl$	DMAP	1 h	90	10
7	BuCu (1.2)	Me_3SiCl	-	20 min	24[a]	65
8	(1.2)	Me_3SiCl	HMPA	20 min	53[a]	33
9	(1.2)	Me_3SiCl	DMAP	20 min	57[a]	34
10	(1.2)	Me_3SiCl	HMPA	1 h	89[a]	8

[a]Isolated as a ketone after acidic quench.

J. Org. Chem., **1985**, *285*, 431.


1. SeO2, 1,4-dioxane
2. DMP, TFA, DCM
0 °C, 52%
LiAlH4, THF, -78 °C
8
29
napeliline (4), 40%
12-epi-napeliline (30), 13%
Ag2O
50% EtOH
74%
Ag2O
50% EtOH
82%
dehydronapeliline (5)
12-epi-dehydronapeliline (31)


1. $NaBH_4$, MeOH, -78 °C
2. TBSOTf, Et_3N
DCM, 40%
1. SeO_2, TBHP, DCM
2. DMP, DCM,
TFA, 0 °C, 50%
HF•py
CH_3CN, 92%
$NaBH(OMe)_3$, THF, -78 °C, 90%
1. MeOTf, TFA
37% (82% brsm)
2. $NaBH(OMe)_3$, 90%
Pd/C, H_2 (1 atm)
EtOAc, 92%
Ag_2O
50% EtOH
74%
8
32
33
34
songorine (6)
liangshanone (7)
acoapetaldine D (36)
songoramine (35)



Chemical Reviews, **2003**, *103*, 1.