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Communication

Enantioselective Total Synthesis of (+)-Stephadiamine

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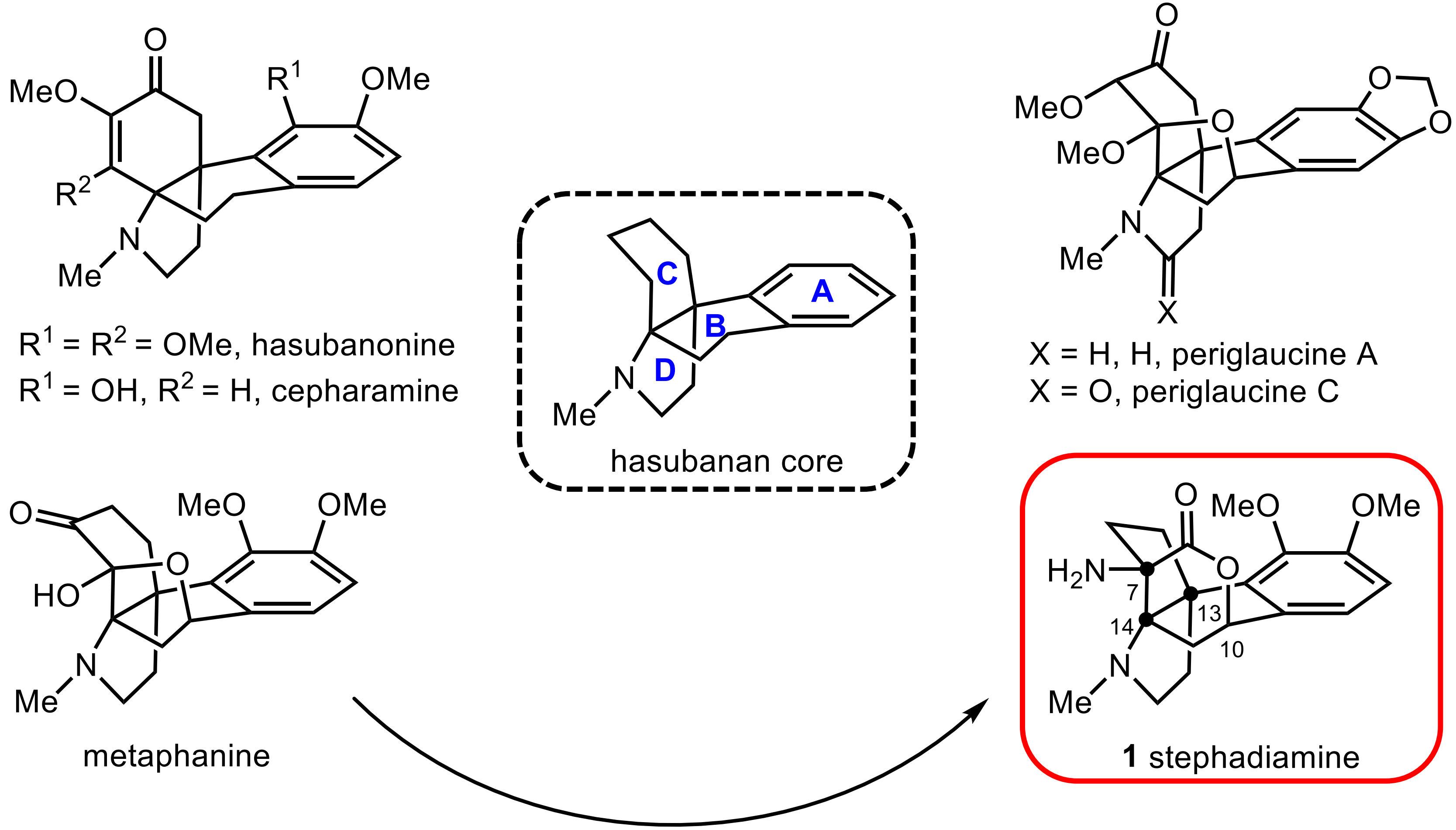
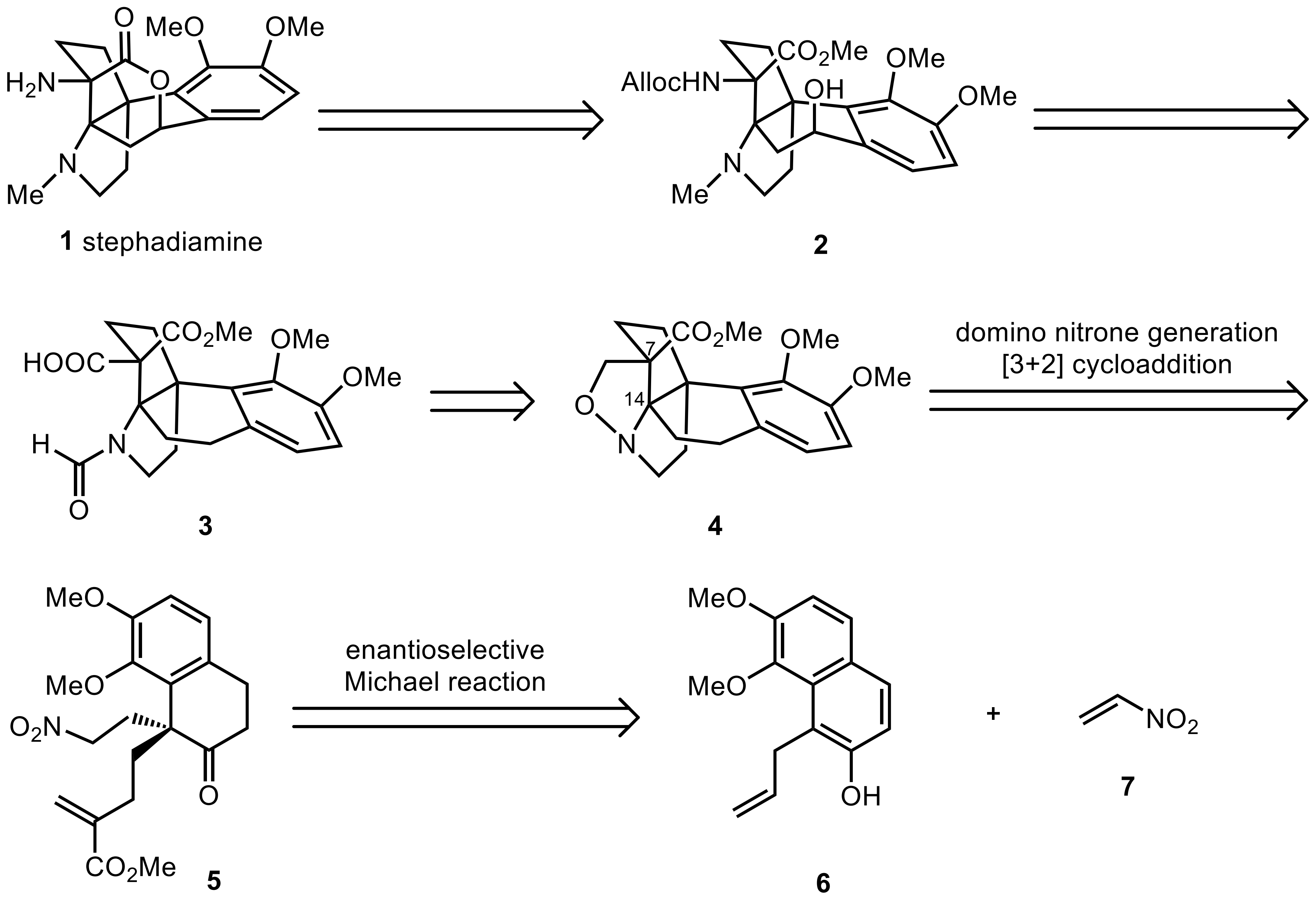
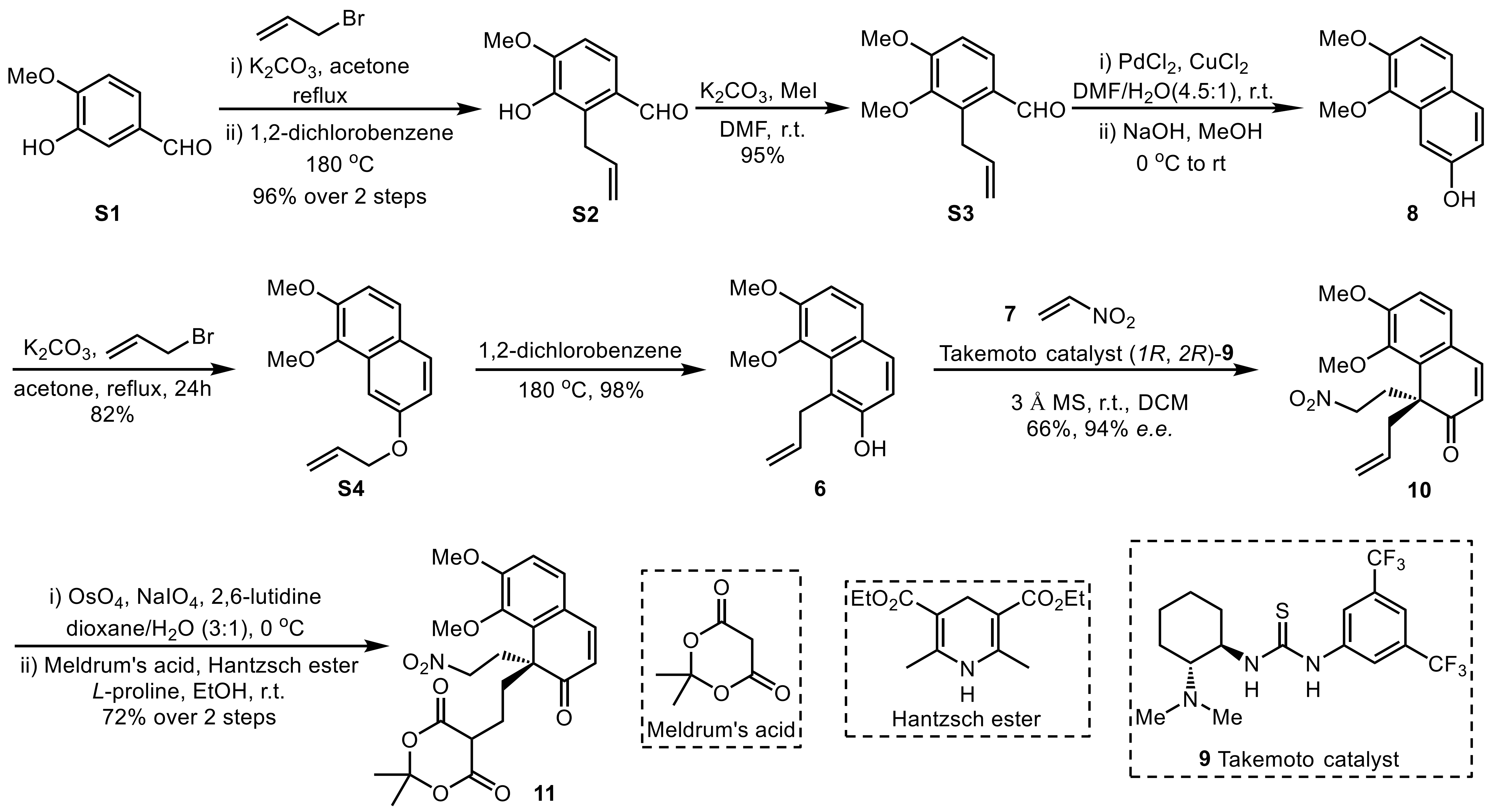
Background



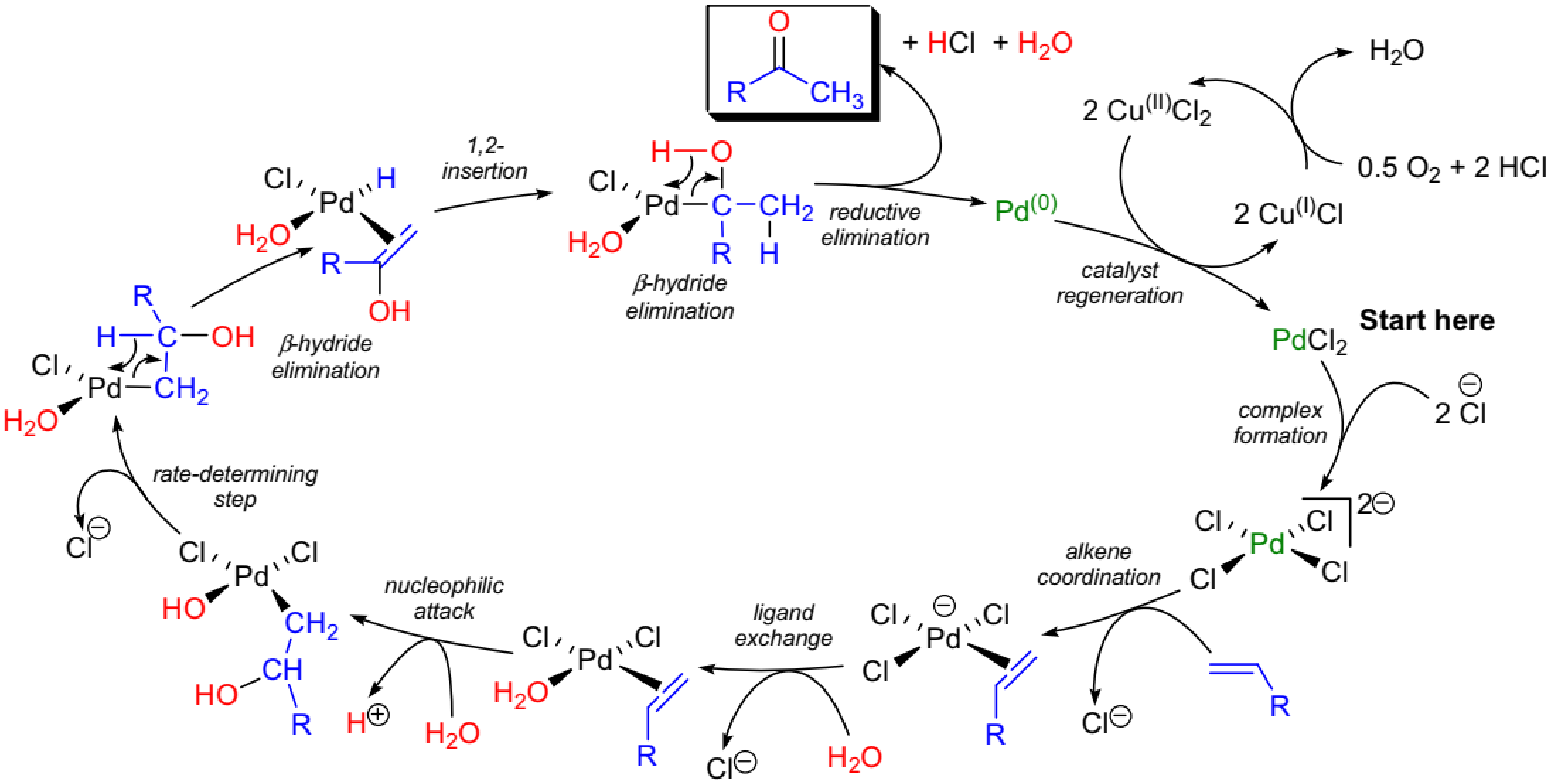
Odagi and Nagasawa et al.

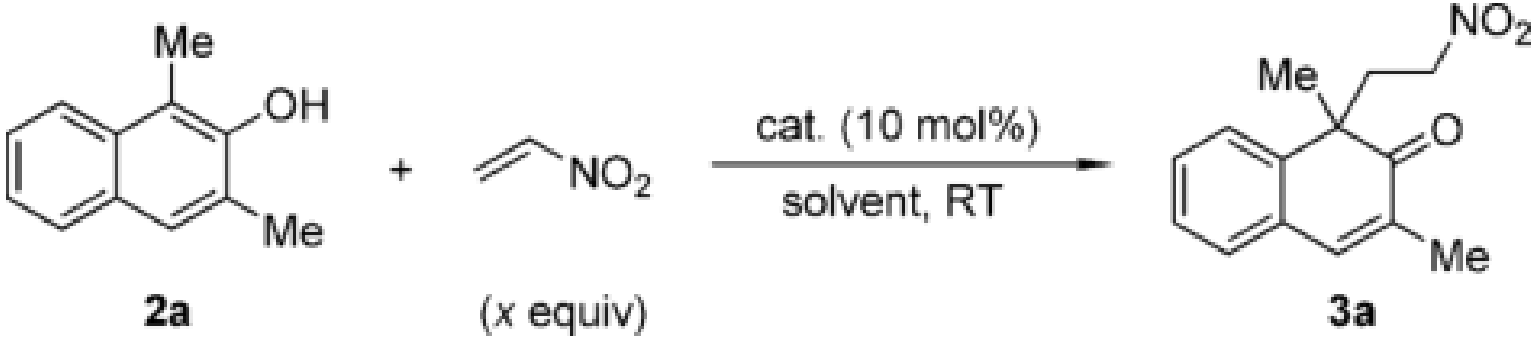
Retrosynthetic Analysis

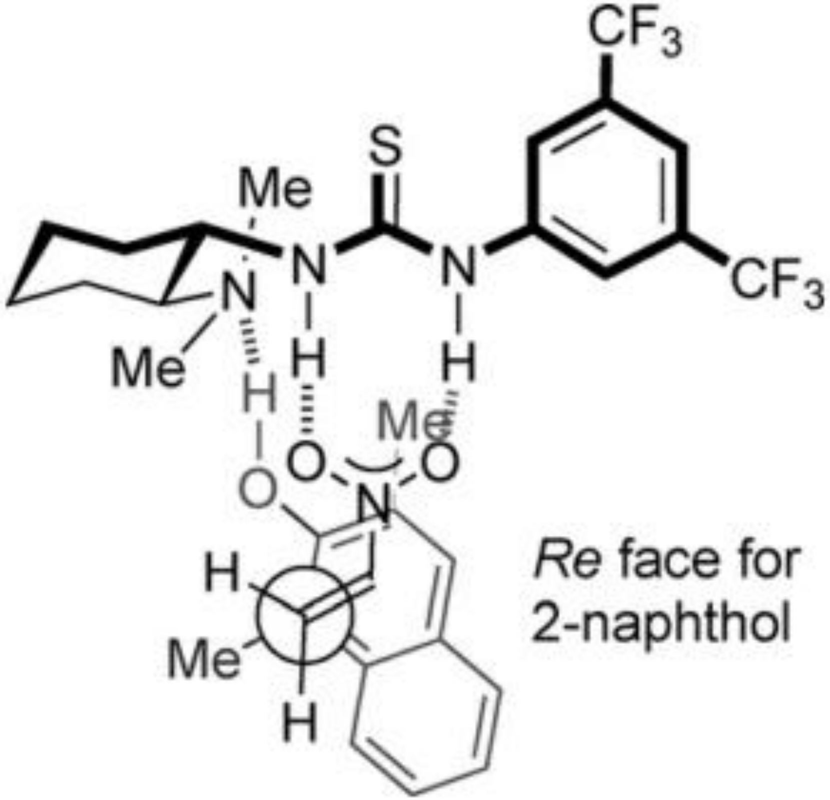


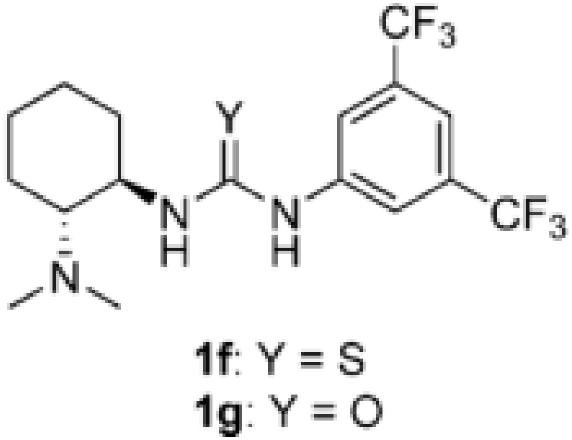

Br
i) K2CO3, acetone
reflux
ii) 1,2-dichlorobenzene
180 oC
96% over 2 steps
S1
S2
K2CO3, MeI
DMF, r.t.
95%
S3
i) PdCl2, CuCl2
DMF/H2O(4.5:1), r.t.
ii) NaOH, MeOH
0 oC to rt
8
K2CO3, Br
acetone, reflux, 24h
82%
S4
1,2-dichlorobenzene
180 oC, 98%
6
7 NO2
Takemoto catalyst (1R, 2R)-9
3 Å MS, r.t., DCM
66%, 94% e.e.
10
i) OsO4, NaIO4, 2,6-lutidine
dioxane/H2O (3:1), 0 oC
ii) Meldrum's acid, Hantzsch ester
L-proline, EtOH, r.t.
72% over 2 steps
11
Meldrum's acid
Hantzsch ester
9 Takemoto catalyst

Wacker Oxidation



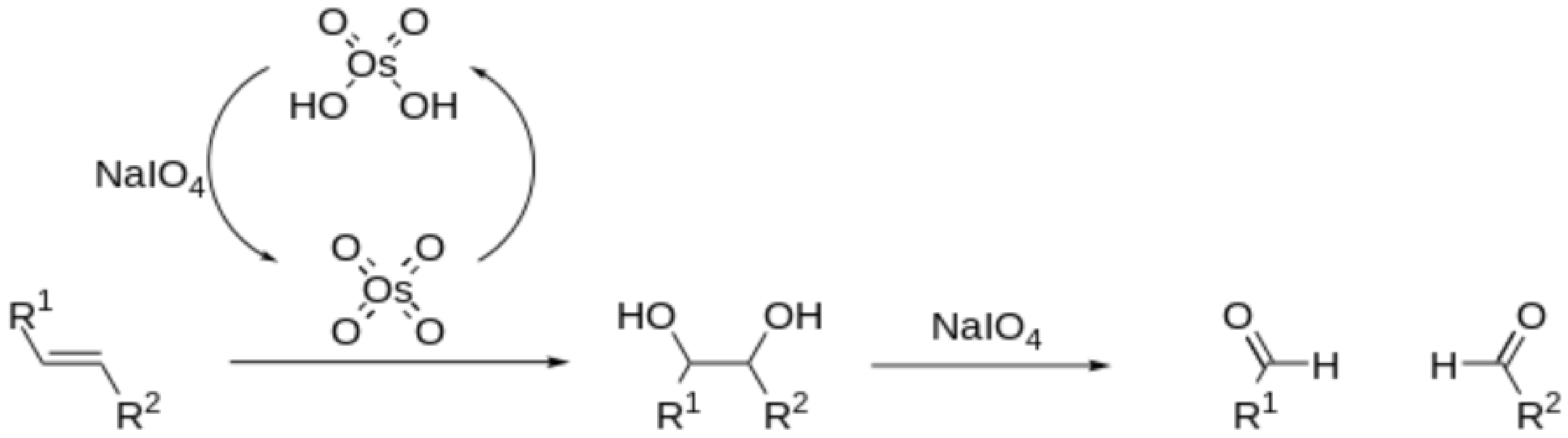






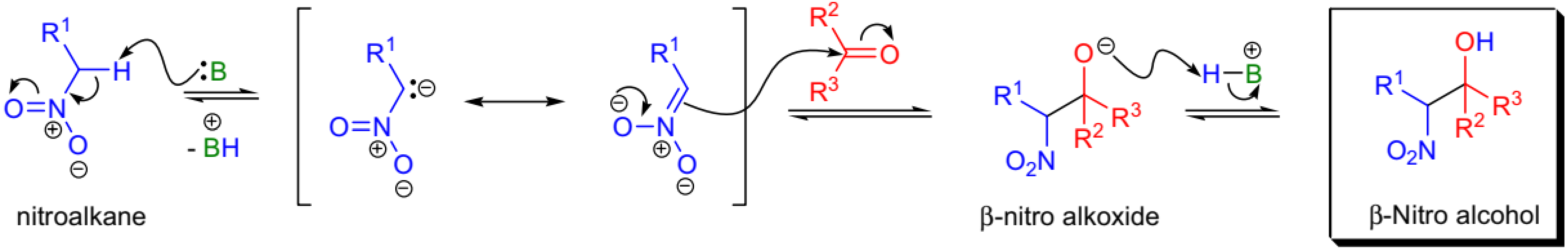
Angew. Chem. Int. Ed., **2015**, *54*, 14929.

Lemieux-Johnson Oxidation Reaction

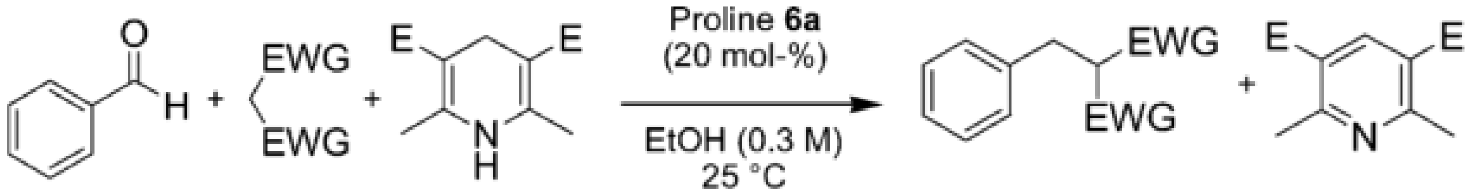


Angew. Chem. Int. Ed., **1997**, *36*, 119.

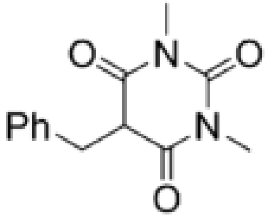
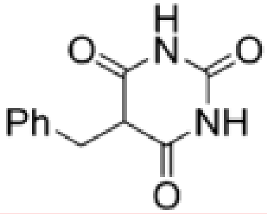
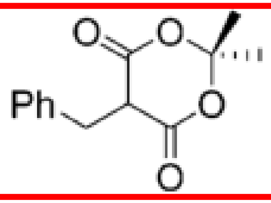
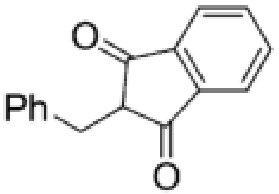
Herry Reaction



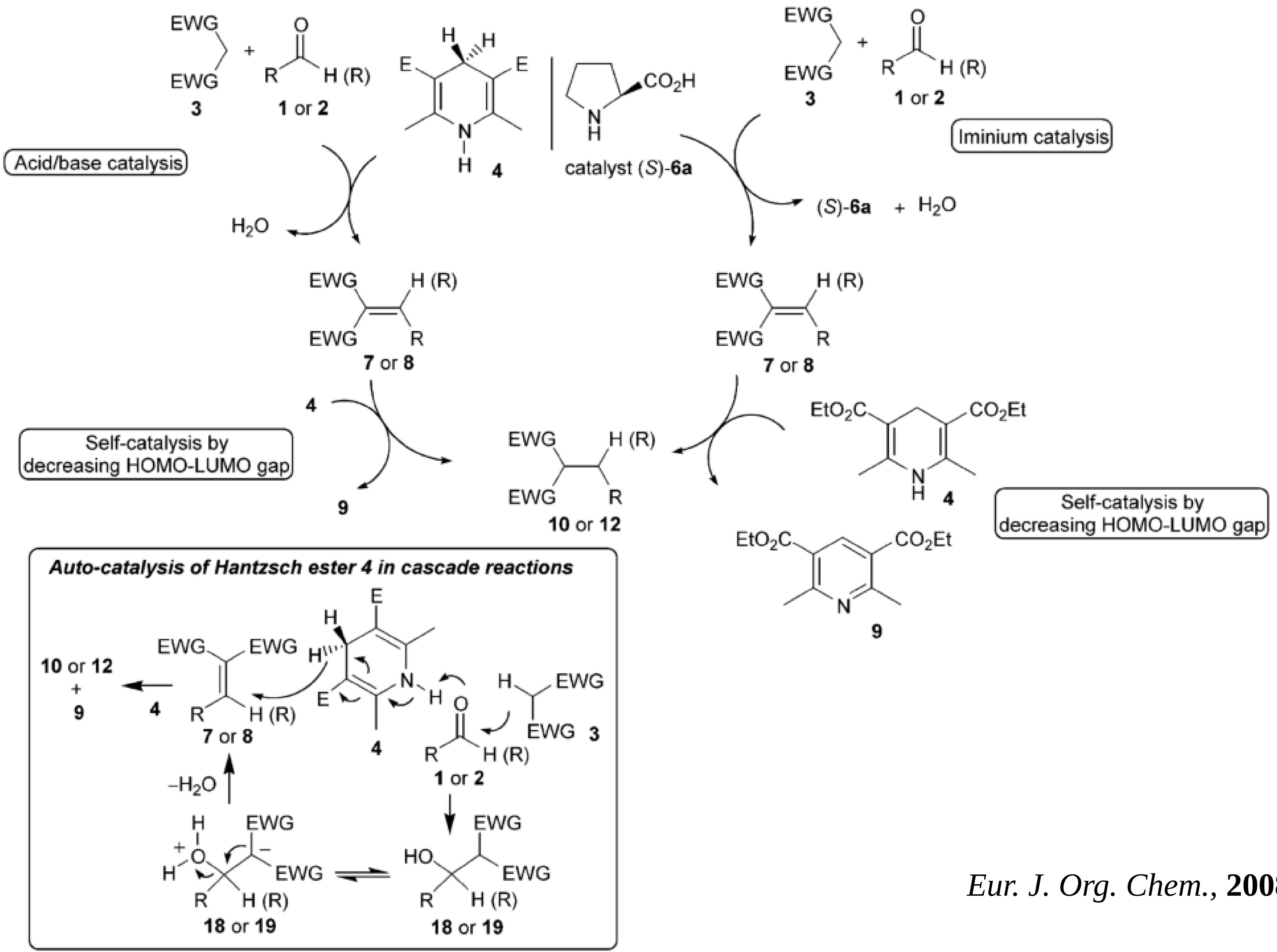
organocatalytic cascade olefination/hydrogenation reaction



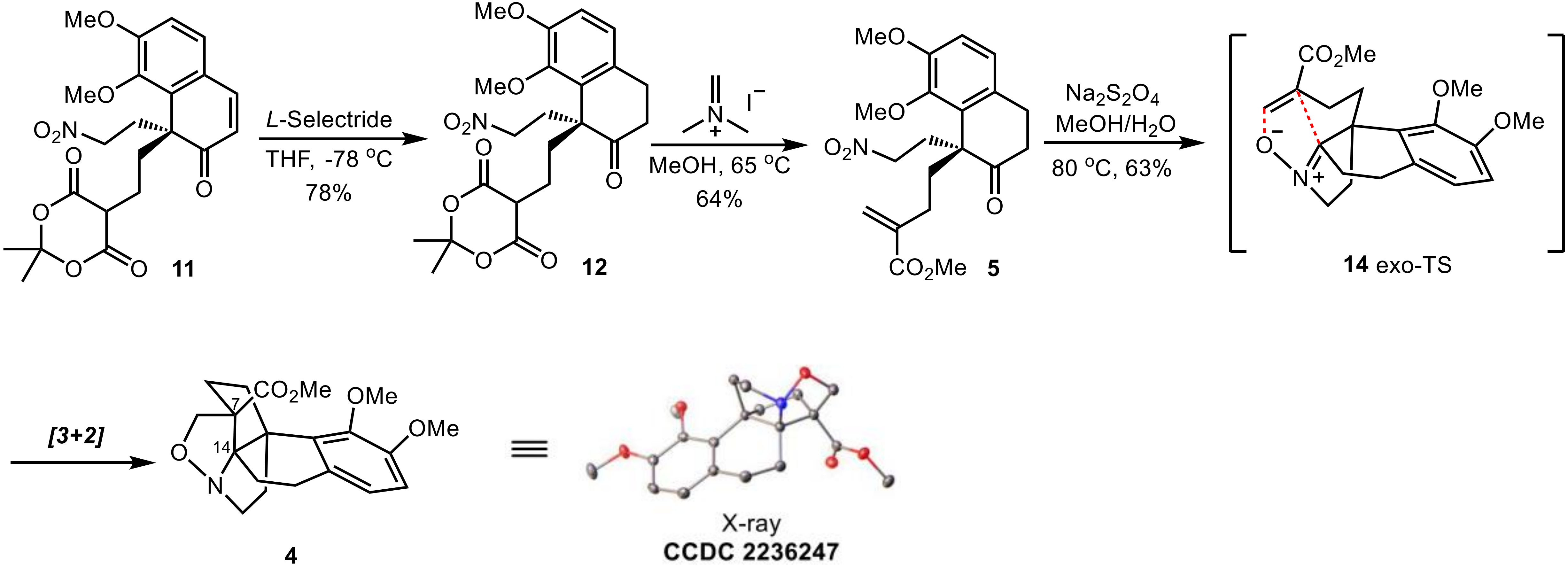
1a + 3a-l + 4, E = CO_2Et → 10aa-al + 9

Entry	CH acid 3	Time [h]	Product		% Yield 10[b]
1	**3a**	2		**10aa**	98
2	**3b**	5		**10ab**	95
3	**3c**	4		**10ac**	90
4	**3d**	26		**10ad**	88

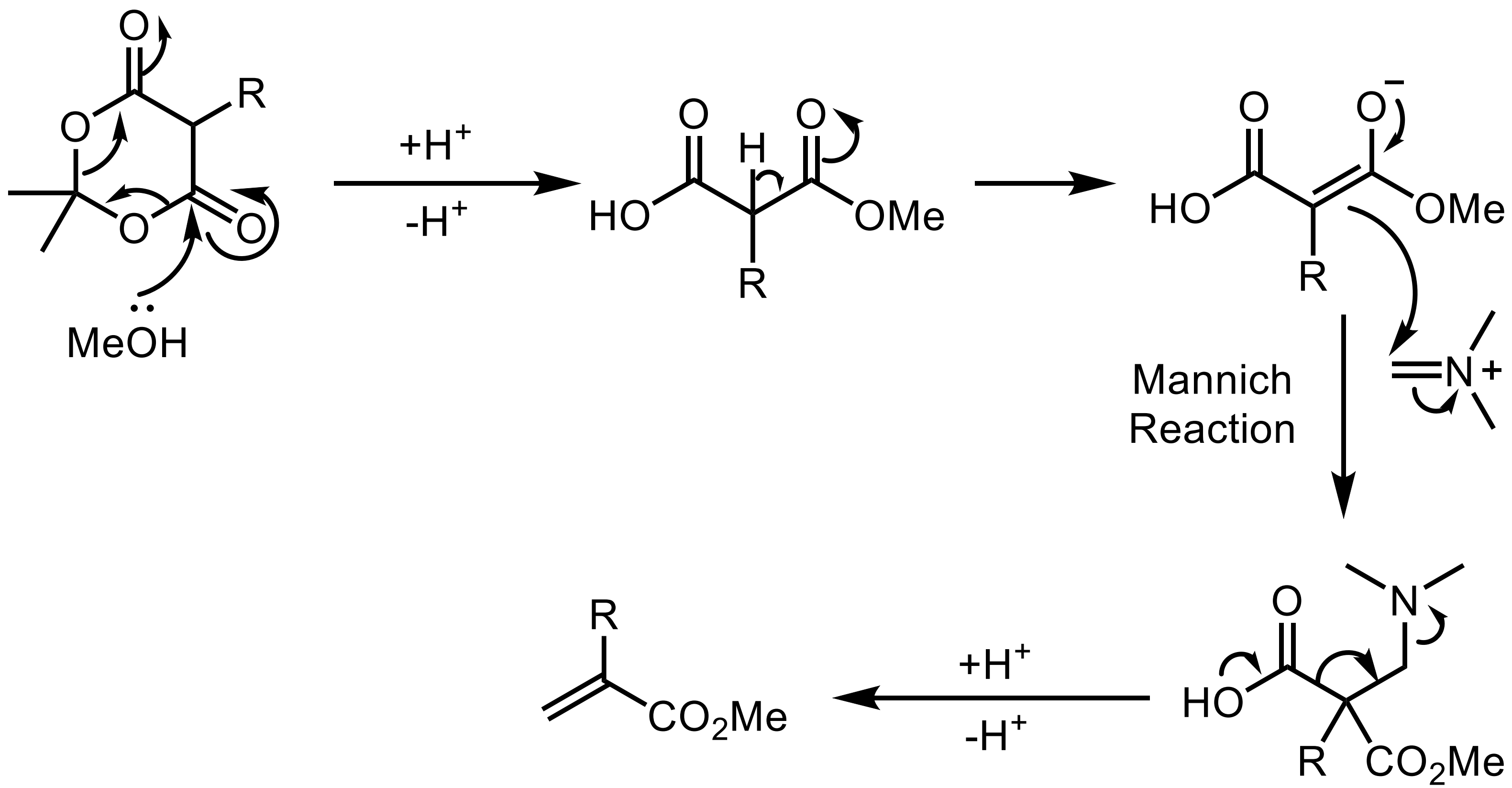
Eur. J. Org. Chem., **2008**, 975.



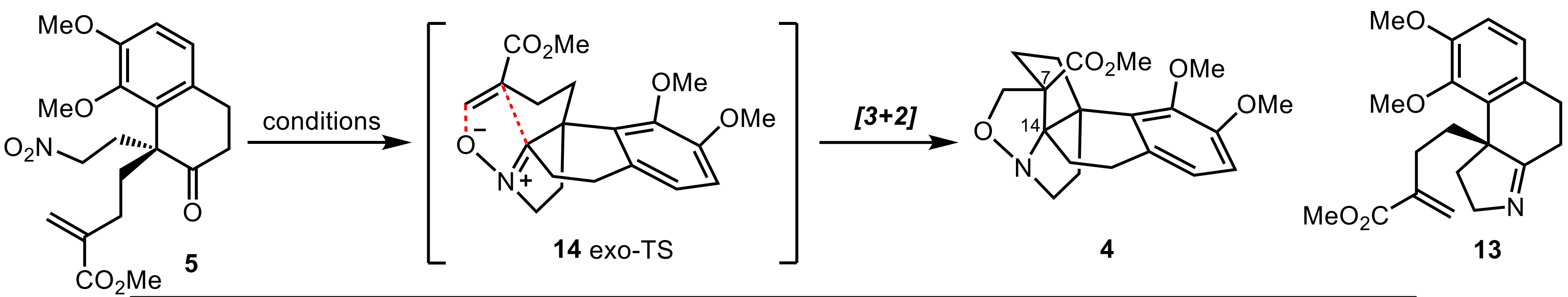
Eur. J. Org. Chem., **2008**, 975.



MeO
MeO
O2N
11
L-Selectride
THF, -78 °C
78%
12
MeOH, 65 °C
64%
5
CO2Me
Na2S2O4
MeOH/H2O
80 °C, 63%
14 exo-TS
OMe
[3+2]
7
14
4
X-ray
CCDC 2236247



O
R
O
O
O
MeOH
+H+
-H+
O
H
O
HO
OMe
R
O
O-
HO
OMe
R
Mannich
Reaction
N+
N
O
HO
R
CO2Me
+H+
-H+
R
CO2Me

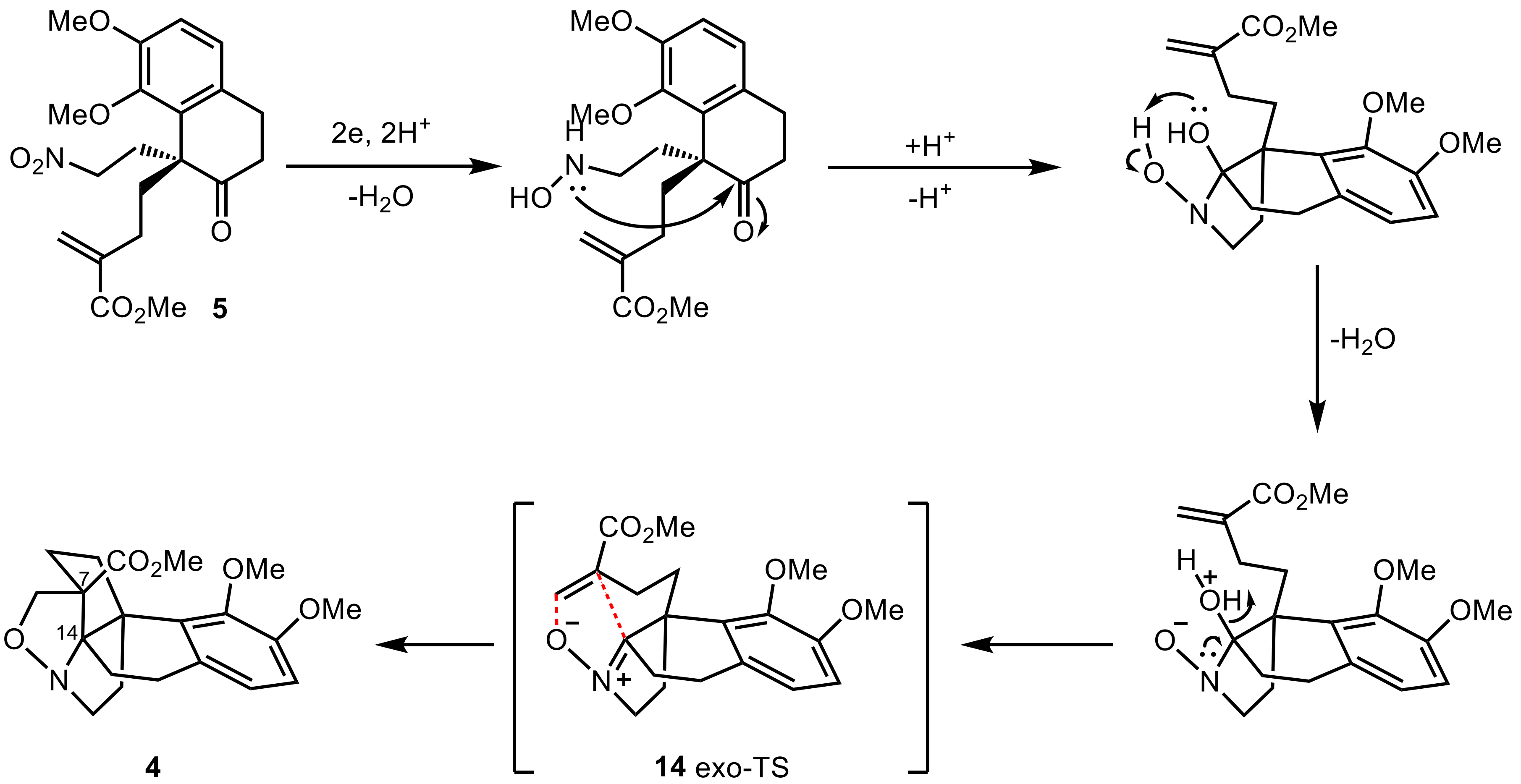


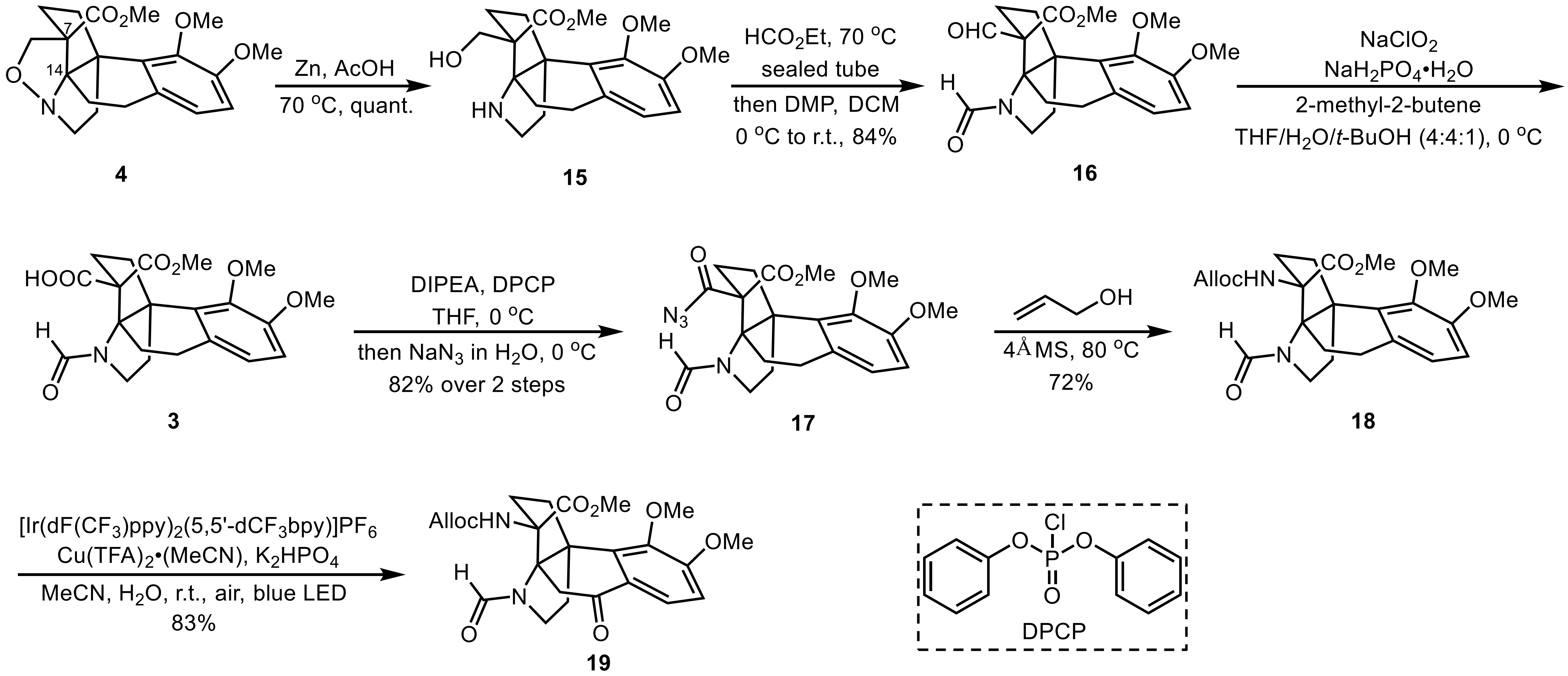
entry	conditions	time	result[a]
1	Zn (10 equiv.), sat. NH_4Cl/EtOH (1:1), 0 °C	1.5 h	**4**, 36%; **13**, 28%
2	Zn (10 equiv.), NH_4Cl (2 equiv.) THF/H_2O (3:1), rt	23 h	~50% conversion **4**, 20%
3	Zn (20 equiv.), AcOH/EtOH(1:1), 0 °C	23 h	**4**, 42%; **13**, 20%
4	$NiCl_2 \cdot 6H_2O$ (2 equiv.), $NaBH_4$ (5 equiv.) MeOH, 0 °C to rt	1.5 h	ND
5	Fe (10 equiv.), AcOH/EtOH(1:1) 0 °C to rt	23 h	NR
6	Fe (10 equiv.), 2*N* HCl (8 equiv.), EtOH, rt	23 h	88% conversion **4**, 38%; **13**, 20%
7	$SnCl_2 \cdot H_2O$ (10 equiv.), EtOAc, reflux	20 h	63% conversion **4**, 25%
8	$Na_2S_2O_4$ (20 equiv.), Na_2CO_3 (10 equiv.) MeOH, reflux	20 h	**4**, 56%
9	$Na_2S_2O_4$ (25 eq), MeOH, reflux	11 h	**4**, 54%[b]
10	$Na_2S_2O_4$ (25 eq), MeOH/H_2O (14:1), 80 °C	8 h	**4**, 63%

[a] isolated yield; [b] HNMR yield using CH_2Br_2 as internal standard.

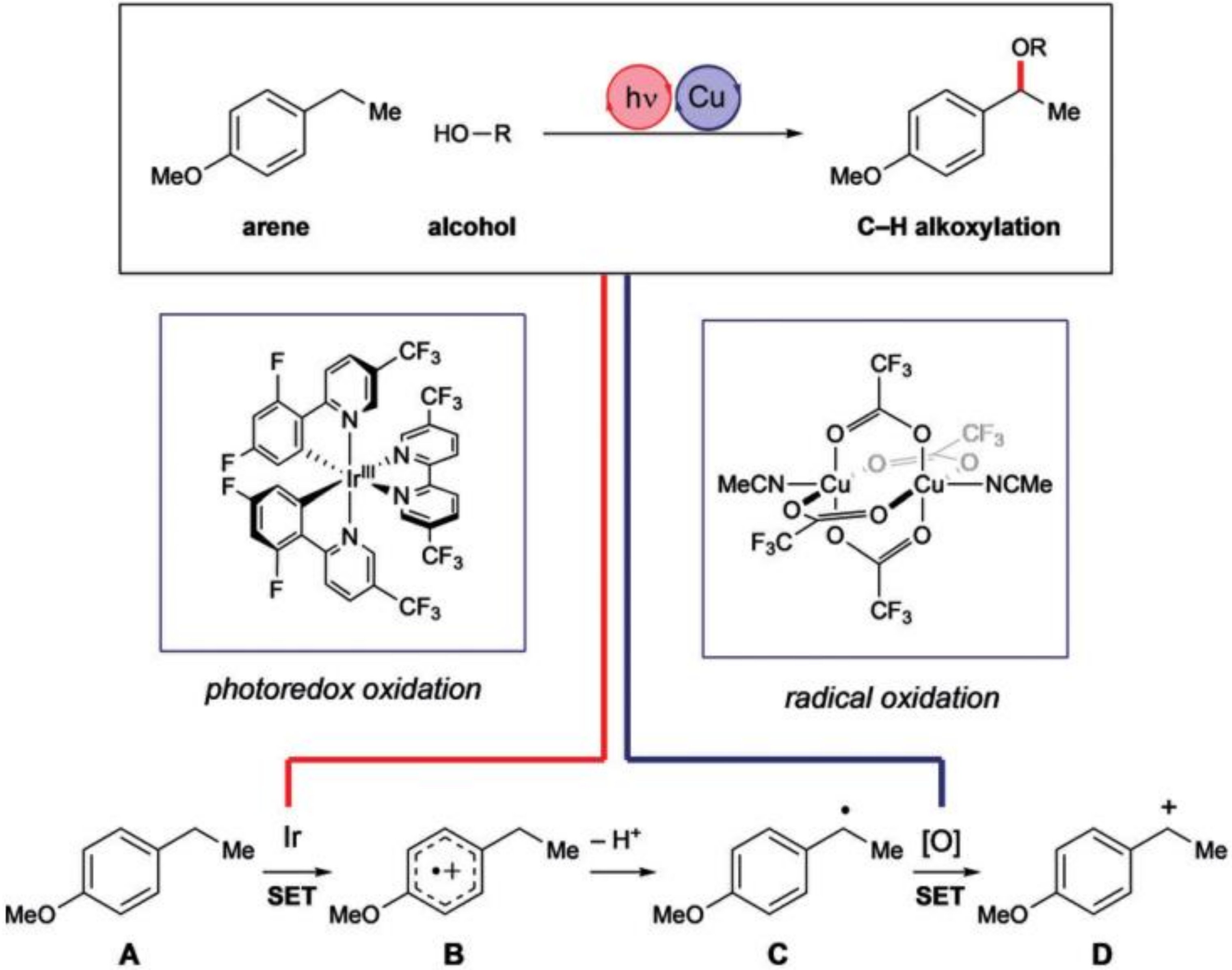
$$RNO_2 \xrightarrow[-\,H_2O]{2e,\ 2H^+} RNO \xrightarrow{2e,\ 2H^+} RNHOH \xrightarrow[-\,H_2O]{2e,\ 2H^+} RNH_2 \quad (1)$$

J. Org. Chem., **1995**, *60*, 6202.

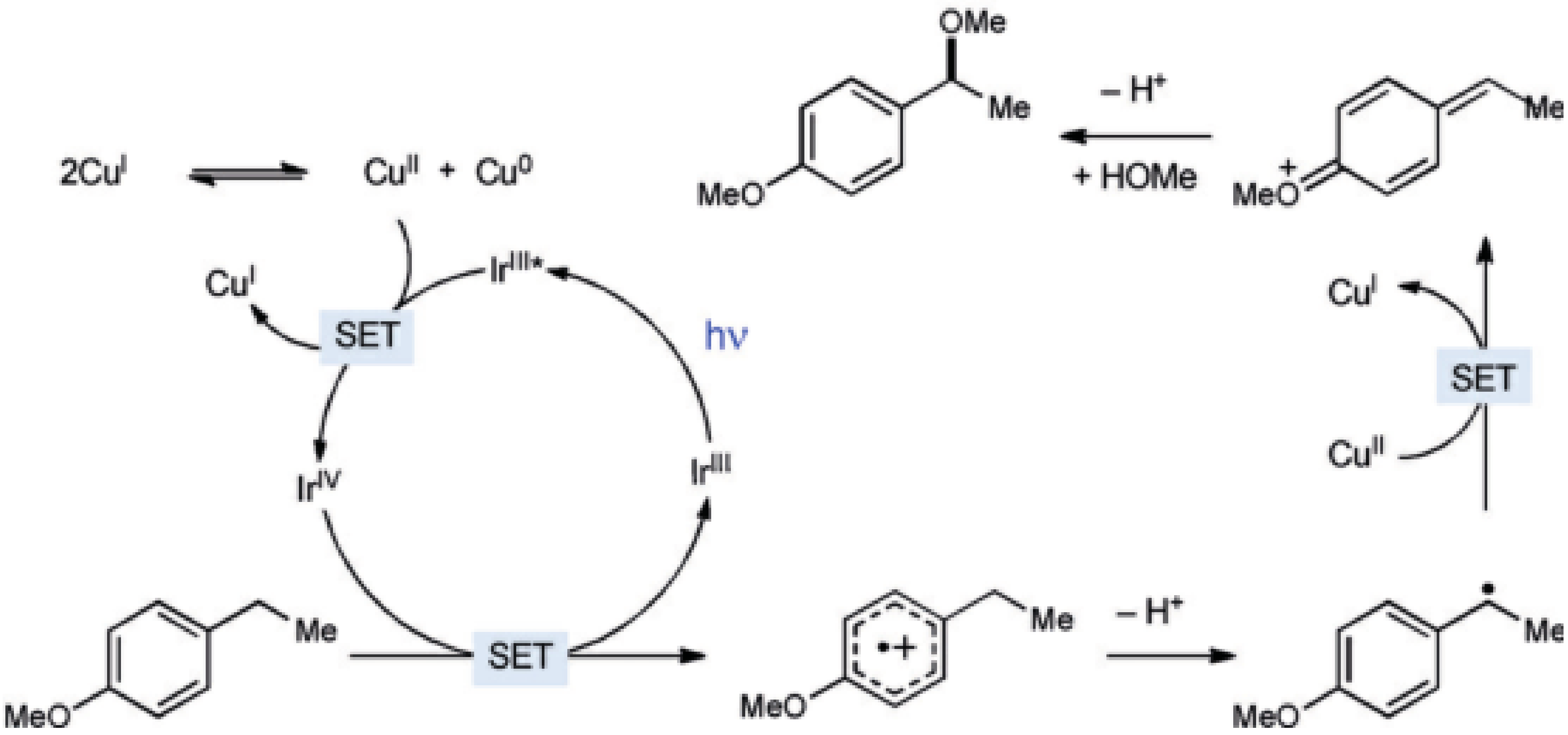




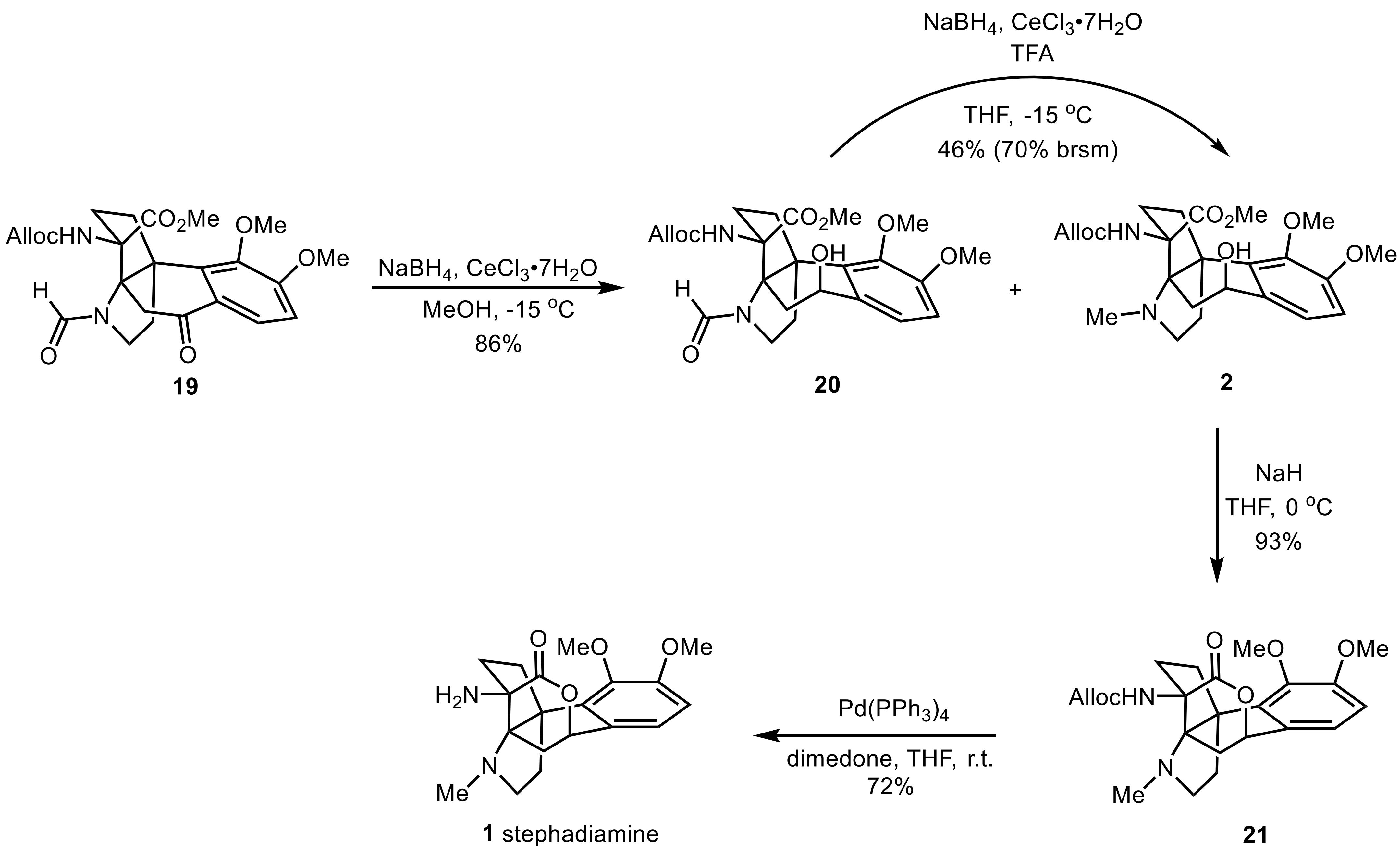
CO2Me
OMe
OMe
7
14
O
N
4
Zn, AcOH
70 °C, quant.
HO
HN
15
HCO2Et, 70 °C
sealed tube
then DMP, DCM
0 °C to r.t., 84%
OHC
H
O
16
NaClO2
NaH2PO4•H2O
2-methyl-2-butene
THF/H2O/t-BuOH (4:4:1), 0 °C
HOOC
3
DIPEA, DPCP
THF, 0 °C
then NaN3 in H2O, 0 °C
82% over 2 steps
N3
17
OH
4Å MS, 80 °C
72%
AllocHN
18
[Ir(dF(CF3)ppy)2(5,5'-dCF3bpy)]PF6
Cu(TFA)2•(MeCN), K2HPO4
MeCN, H2O, r.t., air, blue LED
83%
19
Cl
P
DPCP



Angew. Chem., **2020**, *132*, 203.



Angew. Chem., **2020**, *132*, 203.


AllocHN
CO2Me
OMe
OMe
H
N
O
O
19
NaBH4, CeCl3•7H2O
MeOH, -15 oC
86%
OH
20
+
Me
2
NaBH4, CeCl3•7H2O
TFA
THF, -15 oC
46% (70% brsm)
NaH
THF, 0 oC
93%
MeO
21
Pd(PPh3)4
dimedone, THF, r.t.
72%
H2N
1 stephadiamine