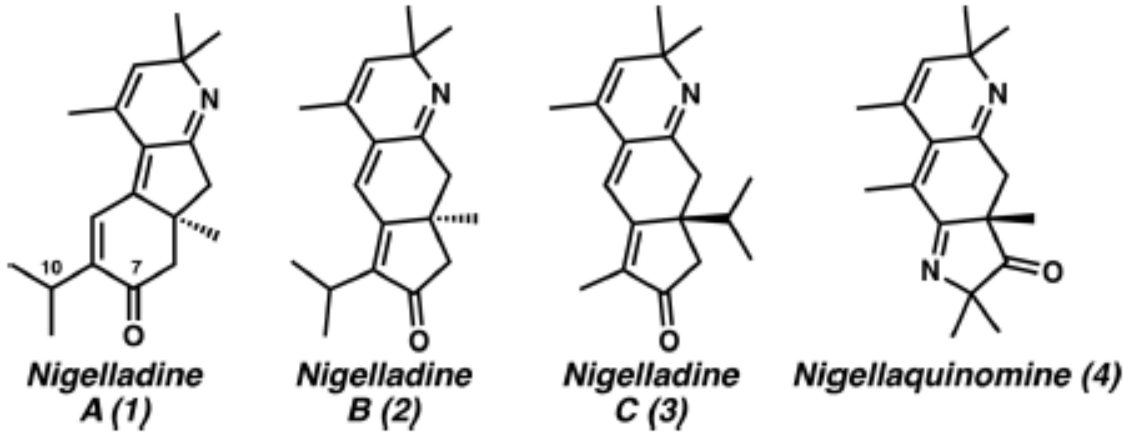
Enantioselective Total Synthesis of Nigelladine A via Late-Stage C–H Oxidation Enabled by an Engineered P450 Enzyme

Loskot S. A., Romney D. K., . Arnold F. H. Arnold, Stoltz B. M. *J. Am. Chem. Soc.* **2017**, 139, 10196-10199

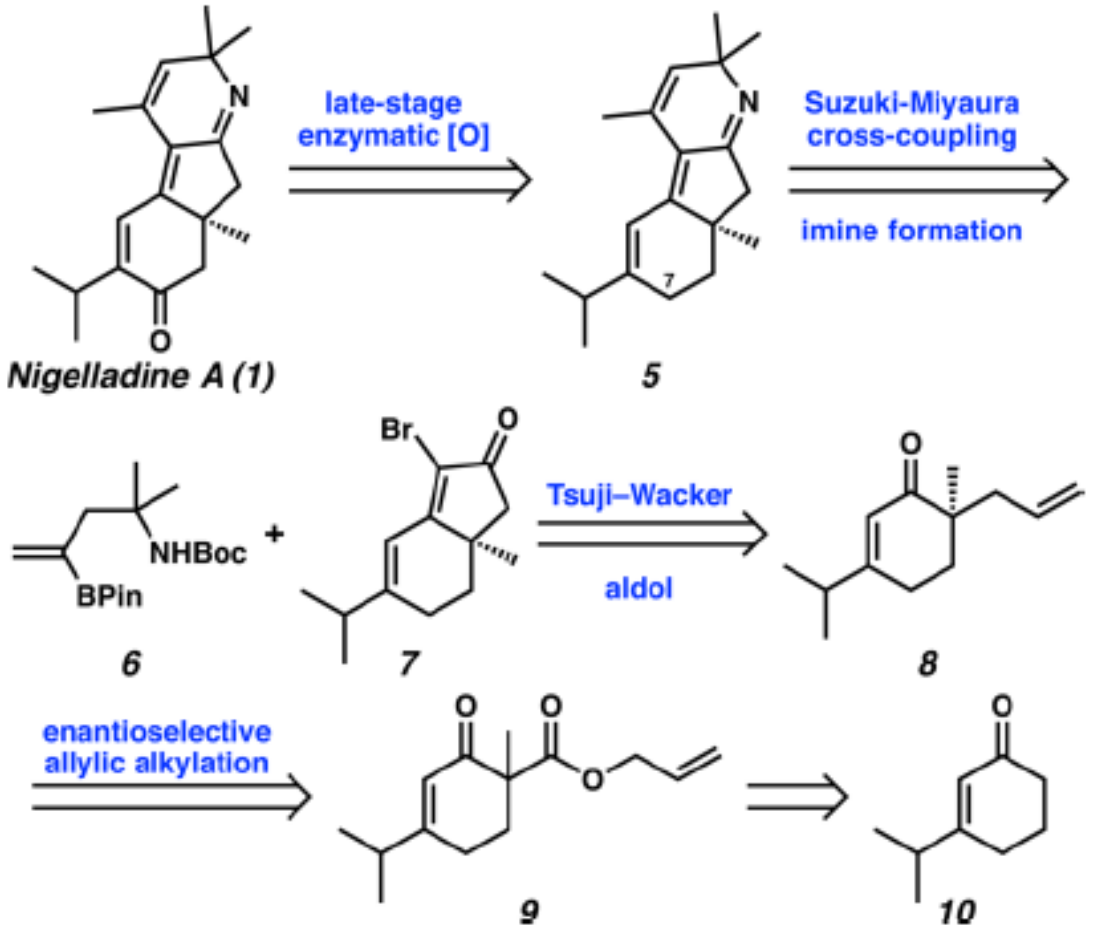


norditerpenoid alkaloids, nigelladines A–C (**1**–**3**), and pyrroloquinoline alkaloid, nigellaquinomine (**4**)

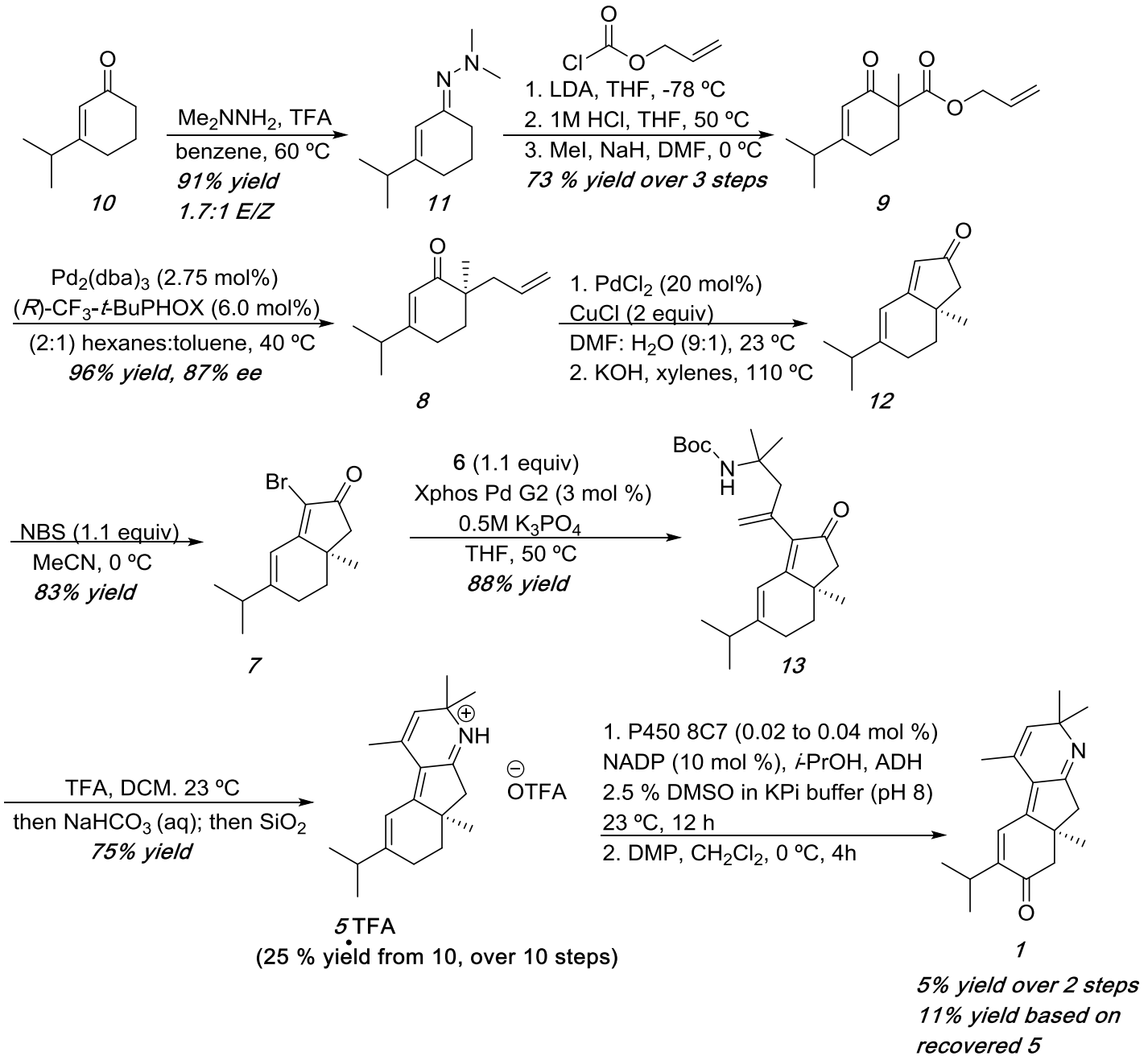
1. Were recently isolated from *Nigella glandulifera*. All possessing new skeletons with highly conjugated
2. These alkaloids exhibited potent protein tyrosine phosphatase 1B (PTP1B) inhibitory activity
3. The first enantioselevtive total synthesis of Nigelladine A

Retrosynthesis：

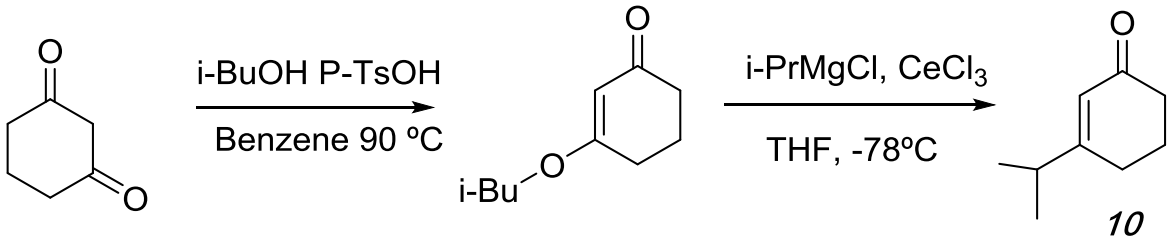
Challenge : intallation of C7 ketone at late-stage

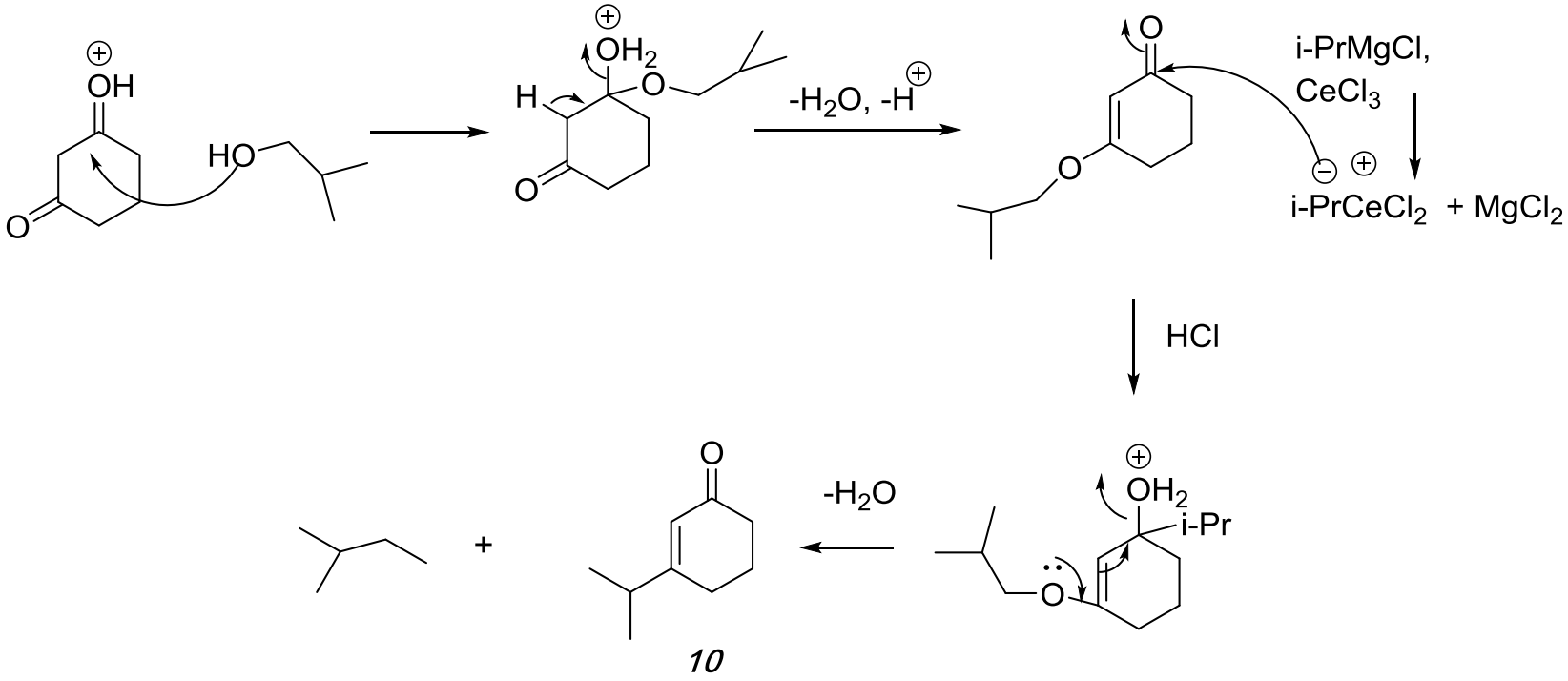


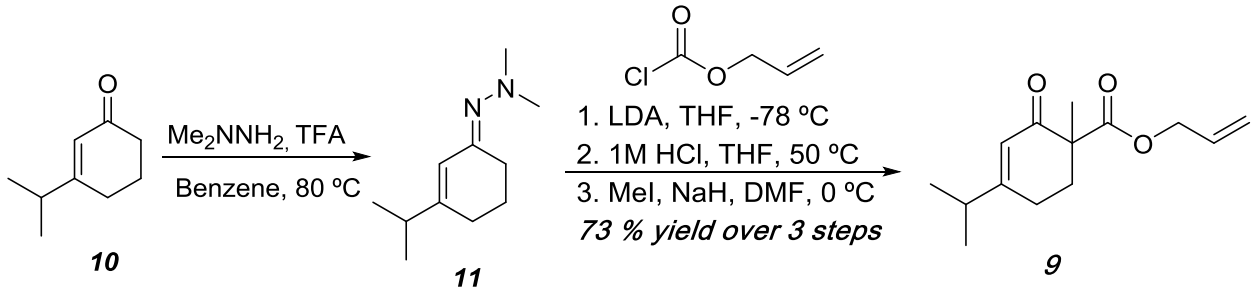
Forward Synthesis

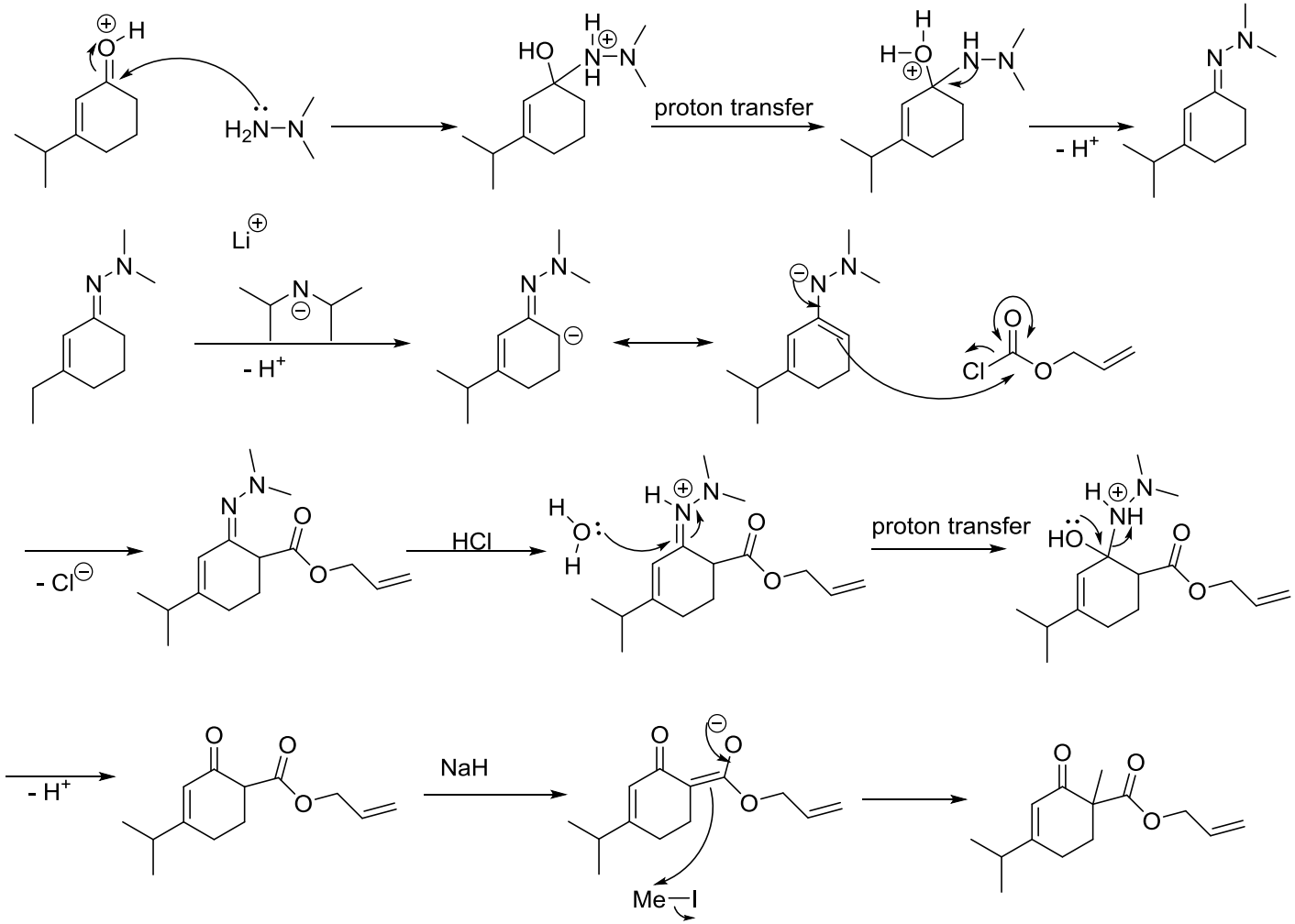


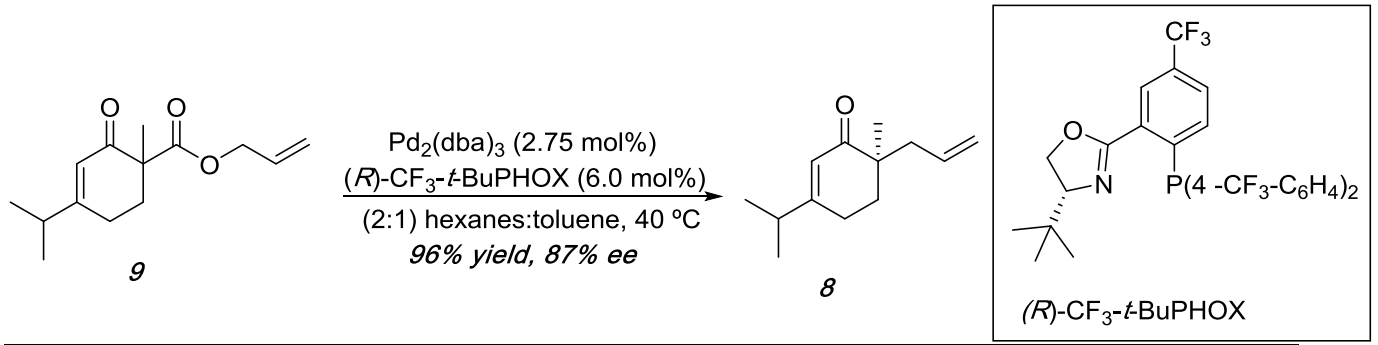
Preparing for Substrate 10

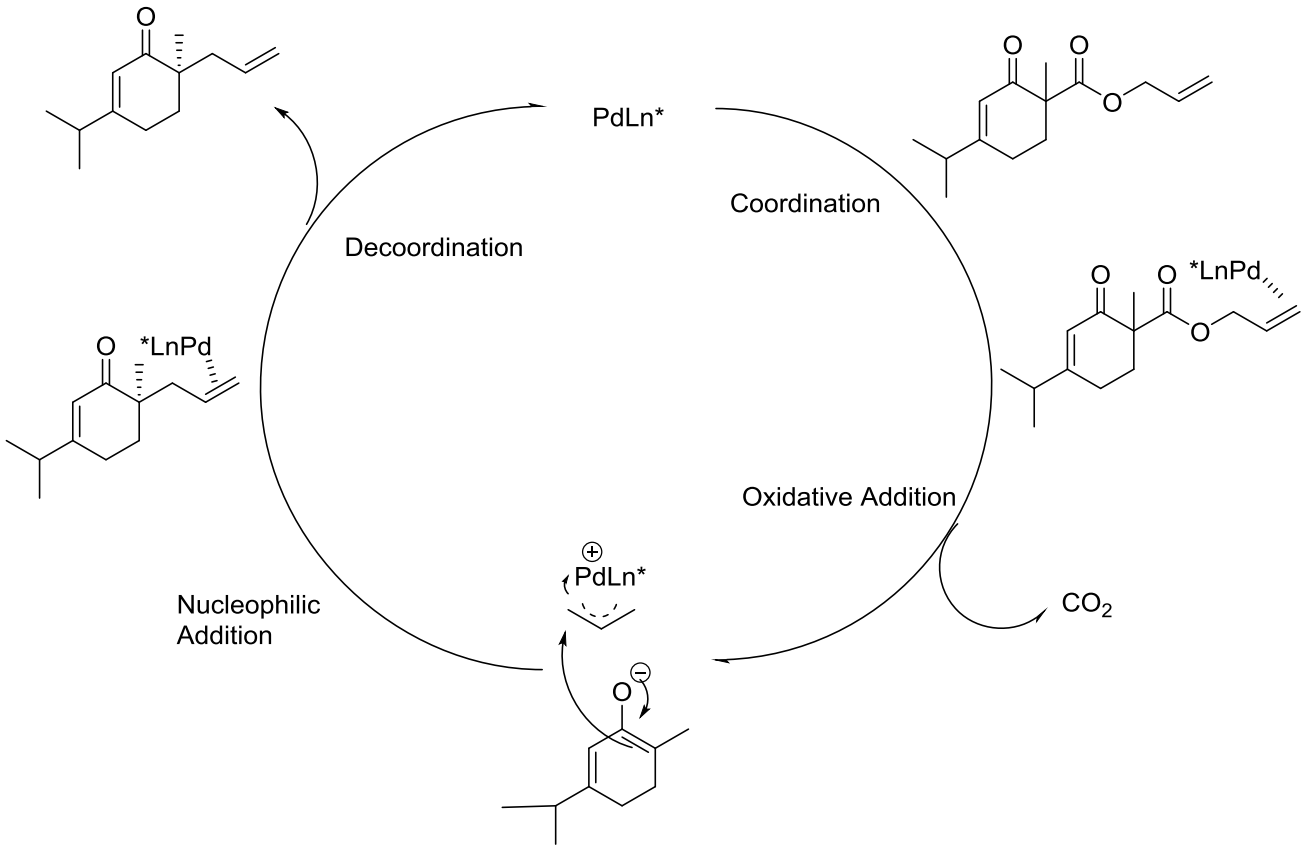


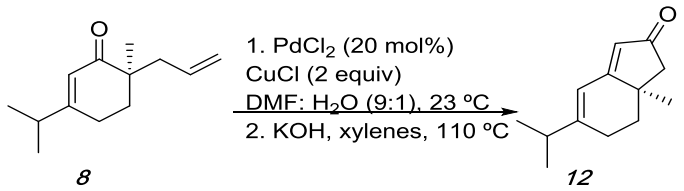



Me2NNH2, TFA
Benzene, 80 ºC
1. LDA, THF, -78 ºC
2. 1M HCl, THF, 50 ºC
3. MeI, NaH, DMF, 0 ºC
73 % yield over 3 steps
10
11
9

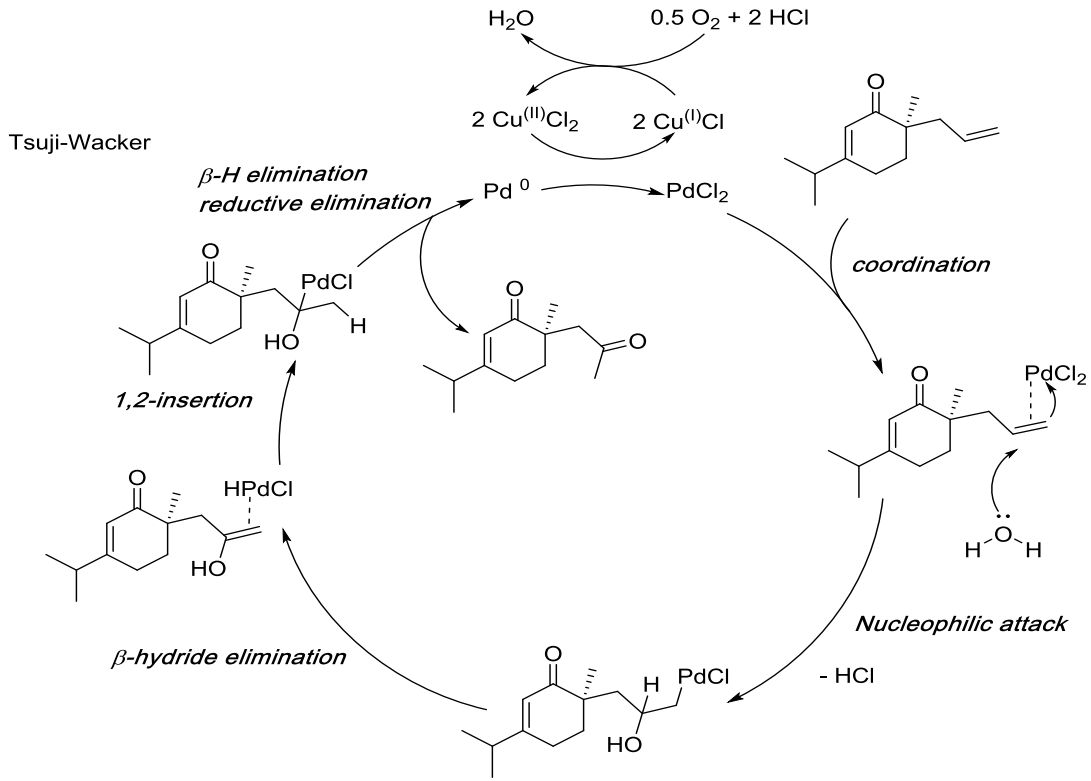

proton transfer
- H+
Li
- H+
- Cl
HCl
proton transfer
- H+
NaH
Me—I


Pd2(dba)3 (2.75 mol%)
(R)-CF3-t-BuPHOX (6.0 mol%)
(2:1) hexanes:toluene, 40 ºC
96% yield, 87% ee
9
8
CF3
P(4 -CF3-C6H4)2
(R)-CF3-t-BuPHOX

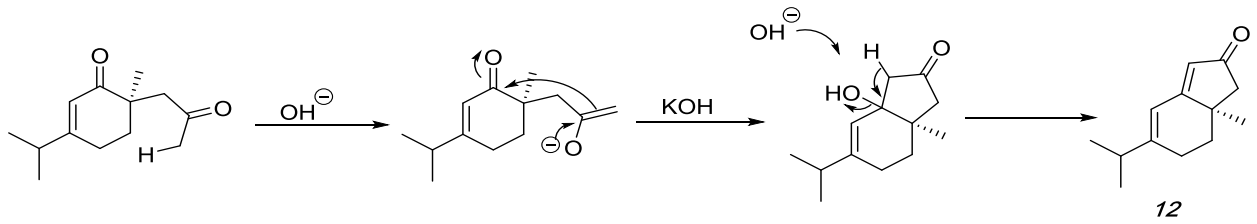

PdLn*
Coordination
Oxidative Addition
CO2
Nucleophilic Addition
Decoordination
*LnPd



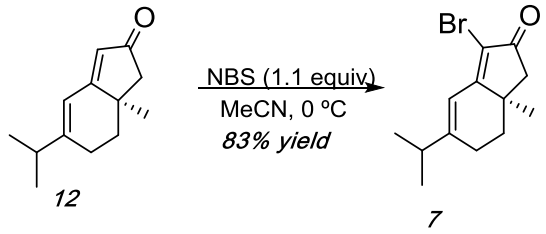
8 *12*

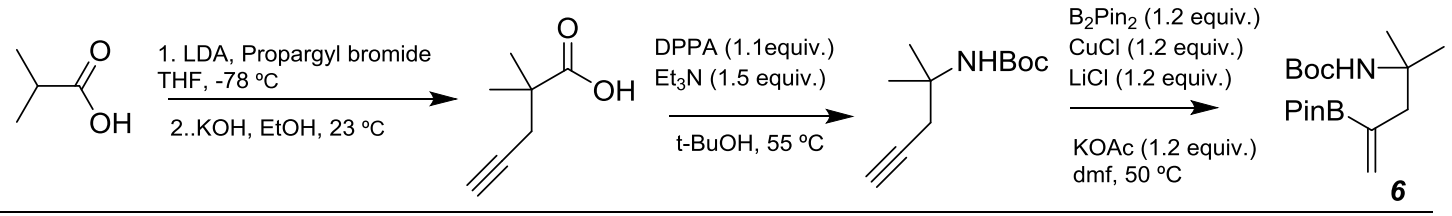


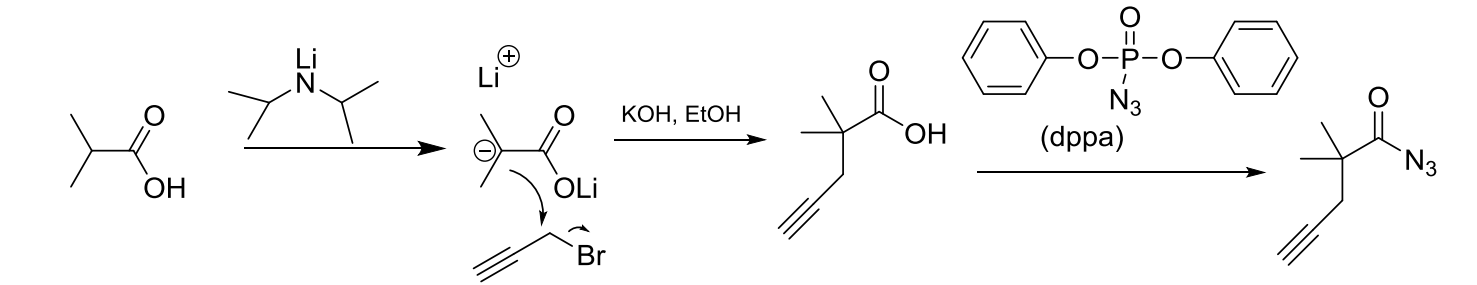
Aldol condensation

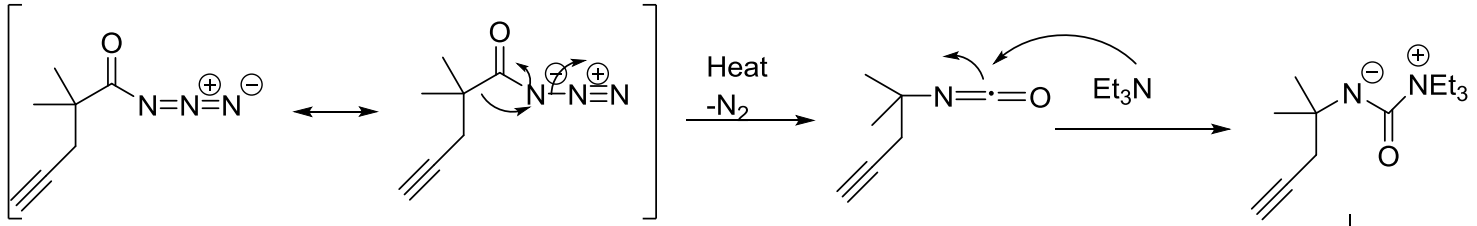


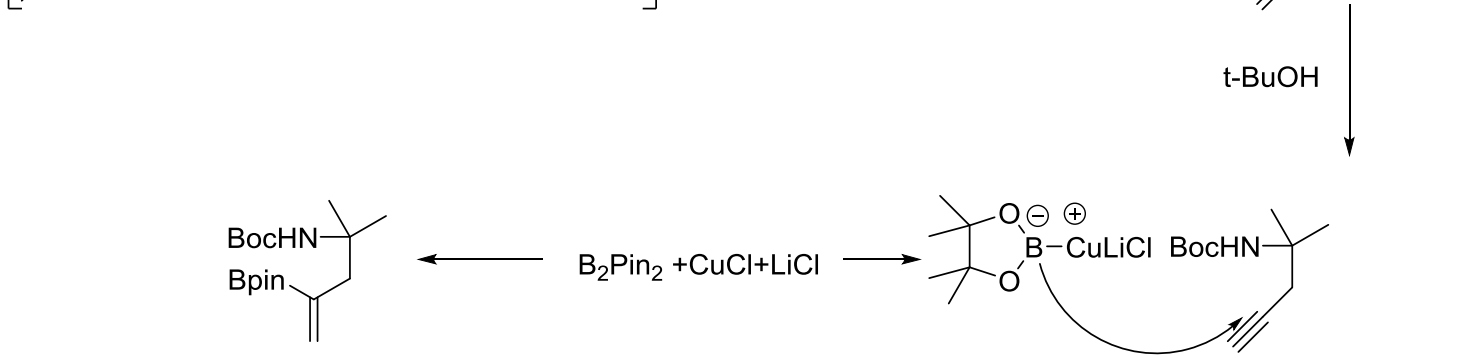
12

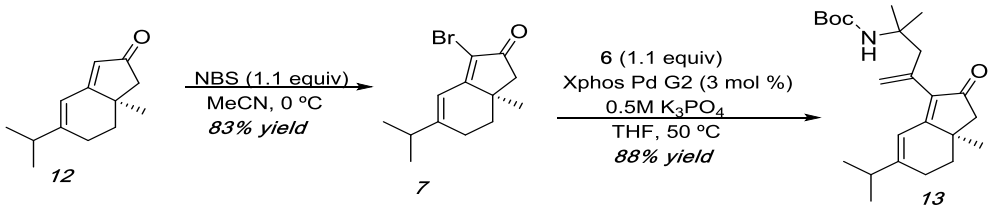

NBS (1.1 equiv)
MeCN, 0 ºC
83% yield
12
7

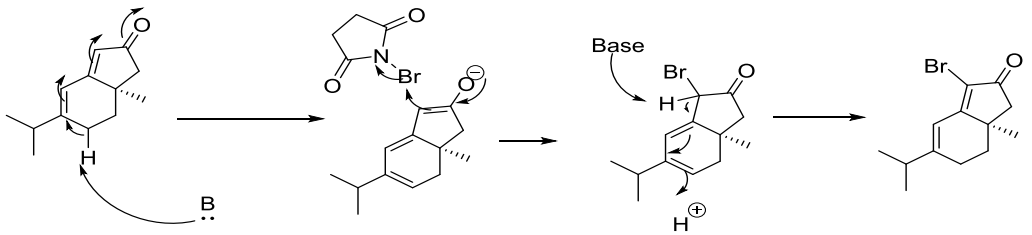

1. LDA, Propargyl bromide
THF, -78 ºC
2..KOH, EtOH, 23 ºC
DPPA (1.1equiv.)
Et3N (1.5 equiv.)
t-BuOH, 55 ºC
B2Pin2 (1.2 equiv.)
CuCl (1.2 equiv.)
LiCl (1.2 equiv.)
KOAc (1.2 equiv.)
dmf, 50 ºC
BocHN
PinB
6

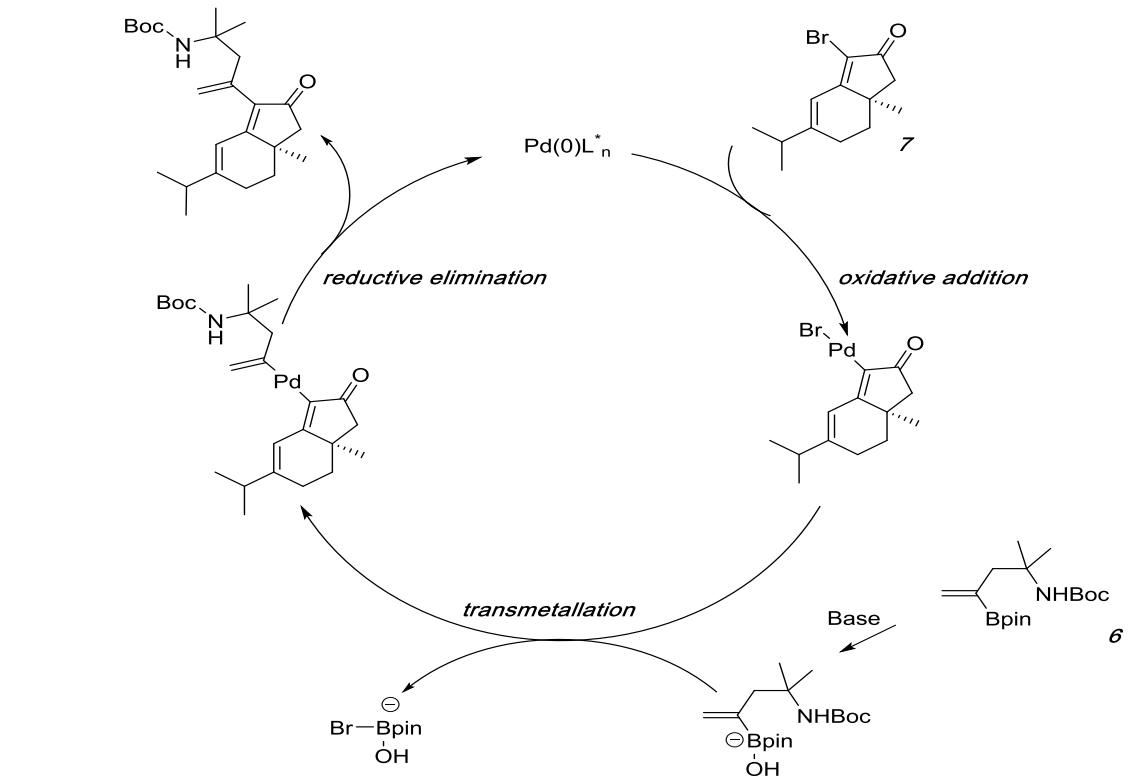

KOH, EtOH
(dppa)

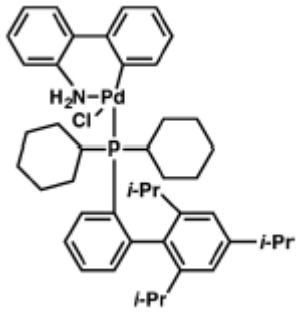

Heat
-N2
Et3N


t-BuOH
BocHN
Bpin
B2Pin2 +CuCl+LiCl
CuLiCl
BocHN

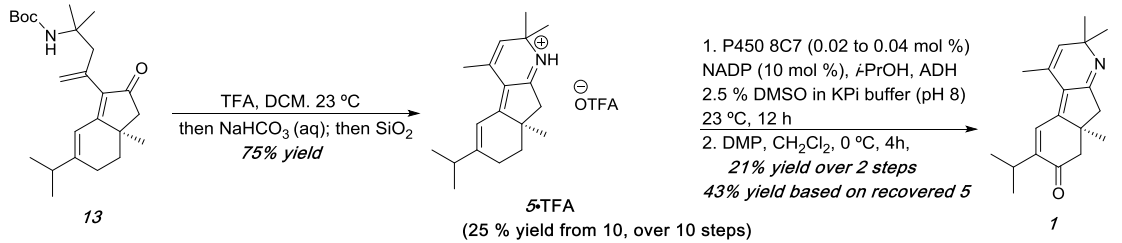


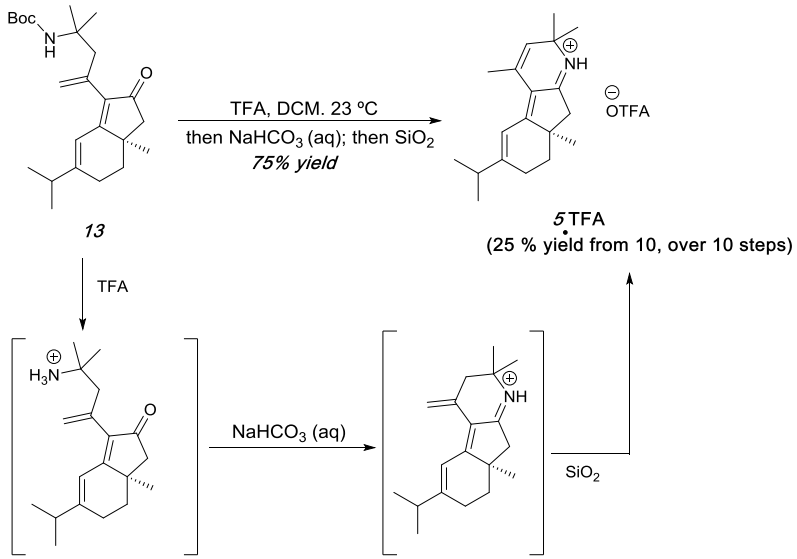


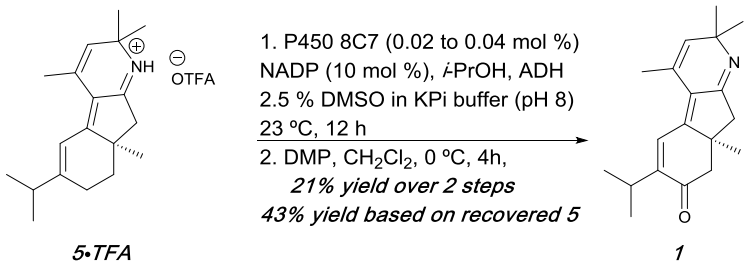




Buchwald's Second-generation Ligand


Boc
N
H
O
13
TFA, DCM. 23 ºC
then NaHCO3 (aq); then SiO2
75% yield
NH
OTFA
5•TFA
(25 % yield from 10, over 10 steps)
1. P450 8C7 (0.02 to 0.04 mol %)
NADP (10 mol %), i-PrOH, ADH
2.5 % DMSO in KPi buffer (pH 8)
23 ºC, 12 h
2. DMP, CH2Cl2, 0 ºC, 4h,
21% yield over 2 steps
43% yield based on recovered 5
N
O
1


Boc
N
H
O
13
TFA, DCM. 23 ºC
then NaHCO3 (aq); then SiO2
75% yield
NH
OTFA
5•TFA
(25 % yield from 10, over 10 steps)
TFA
H3N
NaHCO3 (aq)
NH
SiO2


NH
OTFA
5•TFA
1. P450 8C7 (0.02 to 0.04 mol %)
NADP (10 mol %), i-PrOH, ADH
2.5 % DMSO in KPi buffer (pH 8)
23 ºC, 12 h
2. DMP, CH2Cl2, 0 ºC, 4h,
21% yield over 2 steps
43% yield based on recovered 5
N
O
1