RESEARCH ARTICLE WILEY-VCH

Divergent Total Syntheses of (−)-Daphnezomines A and B and (+)-Dapholdhamine B

Shaobin Su,[a] Chengcheng Lin,[a] and Hongbin Zhai*[a,b,c,d]

[a] S. Su, C. Lin, Prof. Dr. H. Zhai
The State Key Laboratory of Chemical Oncogenomics, Guangdong Provincial Key Laboratory of Nano-Micro Materials Research, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, (China)
E-mail: zhaihb@pkusz.edu.cn

[b] Prof. Dr. H. Zhai
Shenzhen Bay Laboratory, Shenzhen 518055, (China)

[c] Prof. Dr. H. Zhai
Institute of Marine Biomedicine, Shenzhen Polytechnic, Shenzhen 518055, (China)

[d] Prof. Dr. H. Zhai
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, (China)

Supporting information for this article is given via a link at the end of the document.

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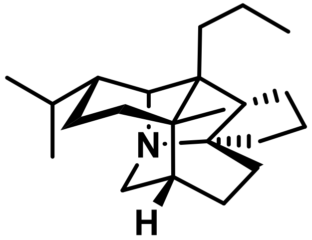
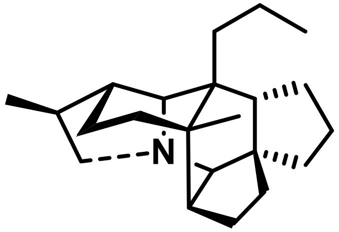
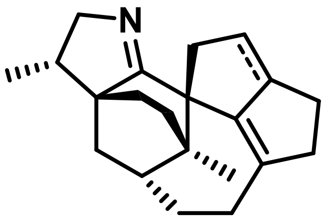


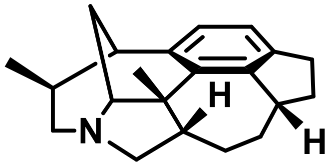
daphniphylline-type
(Heathcock)



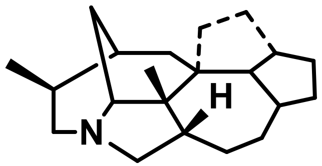
secodaphniphylline-type
& bukittinggine-type
(Heathcock#, Xu#)



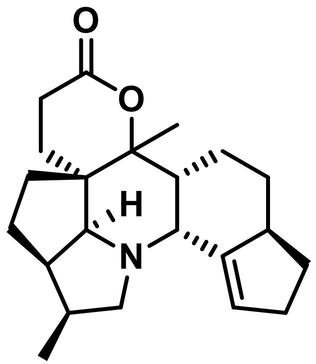
daphmanidin A-type
(Carreira, Smith)



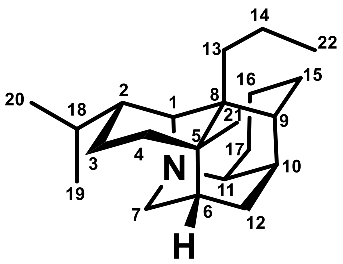
daphenylline
(A. Li, Fukuyama, Zhai, Qiu, Lu)



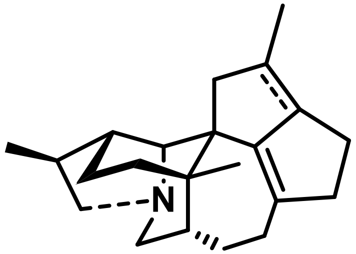
calyciphylline A-type
(A. Li, Dixon, Zhai, Xu#, Gao, Qiu)



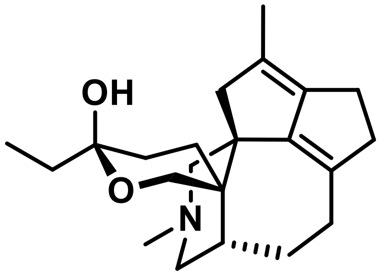
calyciphylline B-type
(Hanessian, Sarpong)



daphnezomine A-type
(Xu, C. Li)

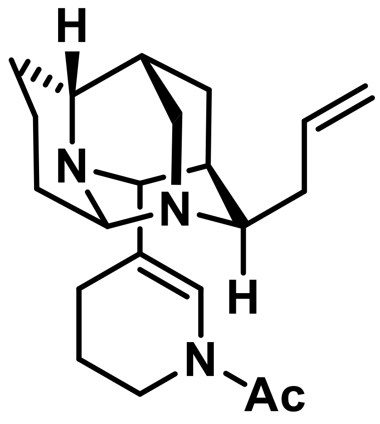


yuzurimine-type
& macrodaphniphyllamine-type
(Xu, A. Li)

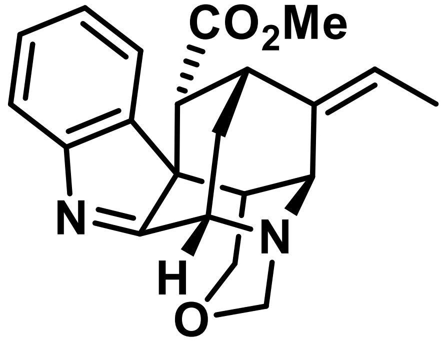


yuzurine-type
(C. -C. Li)

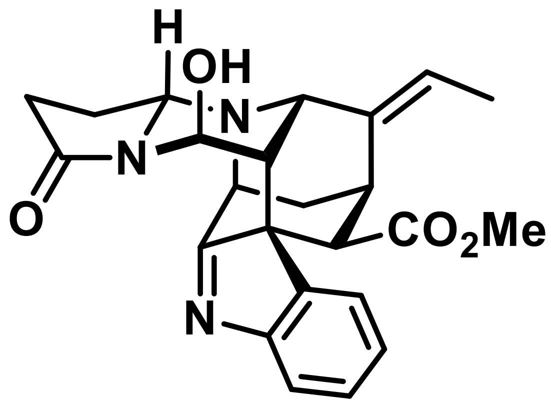
Natural product with aza-adamantane



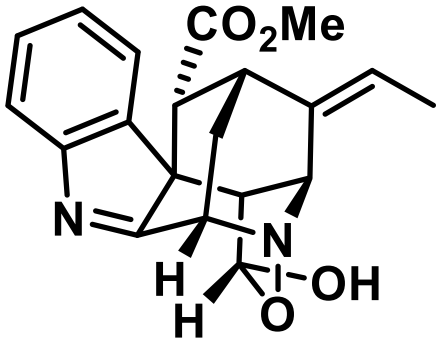
panacosmine



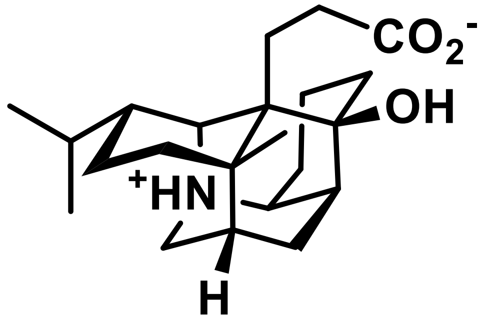
scholarisine H



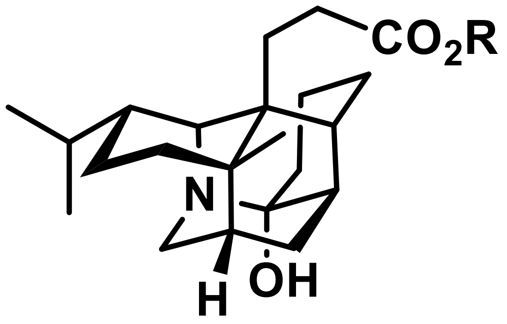
alstoscholarisine K



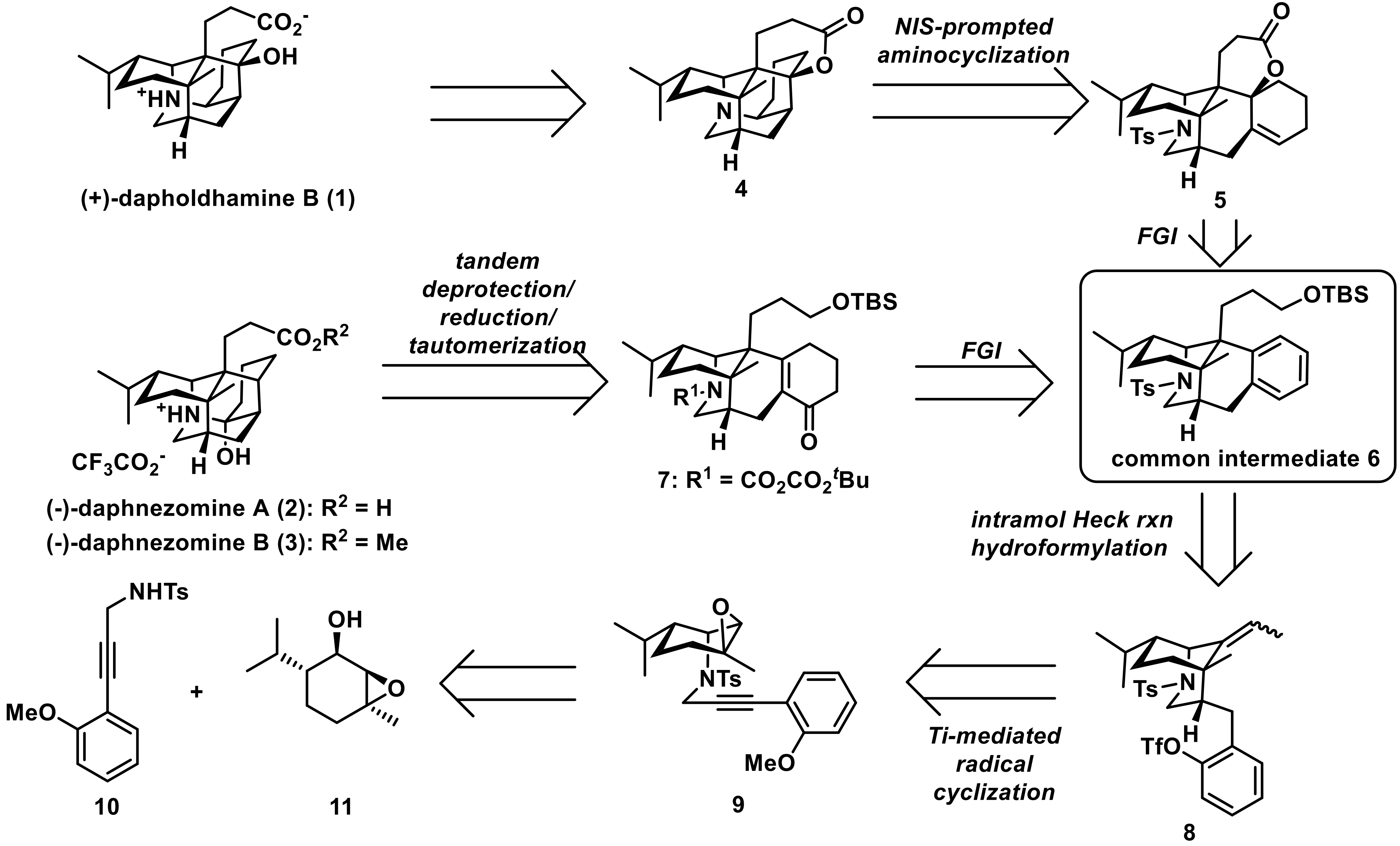
nareline

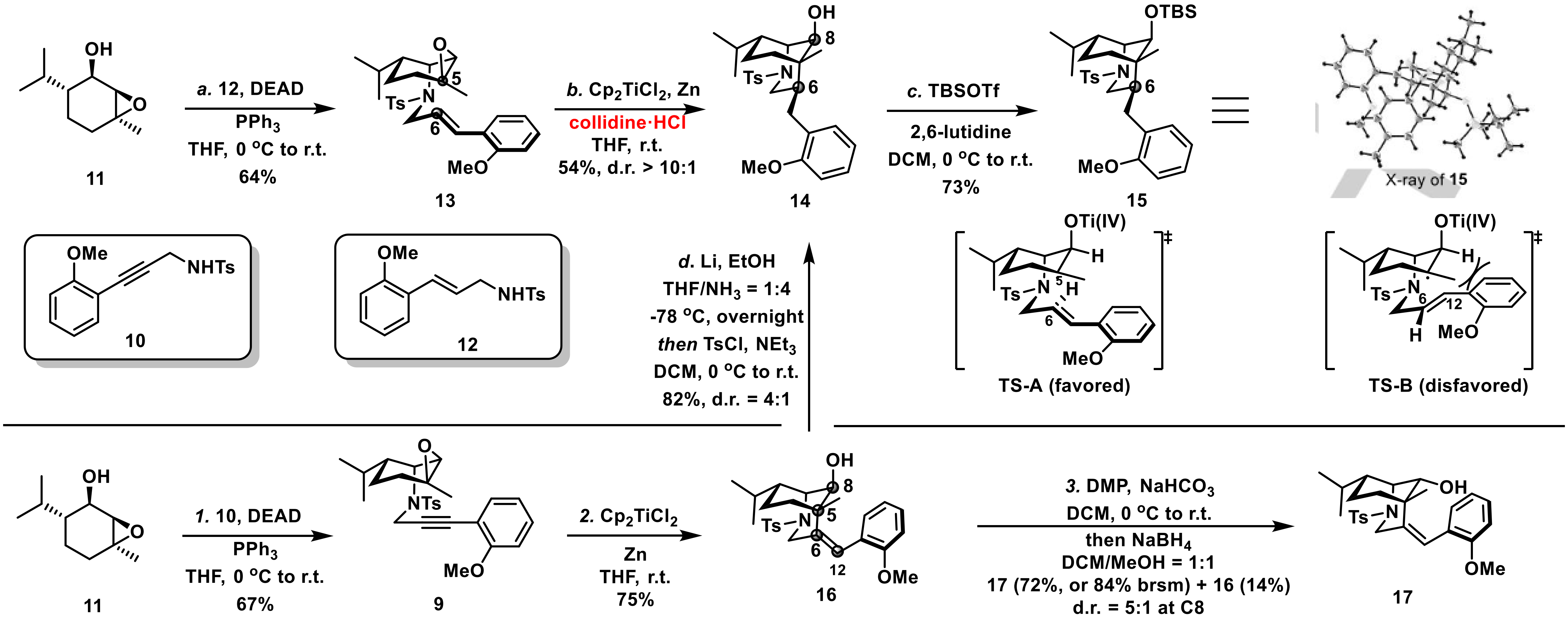


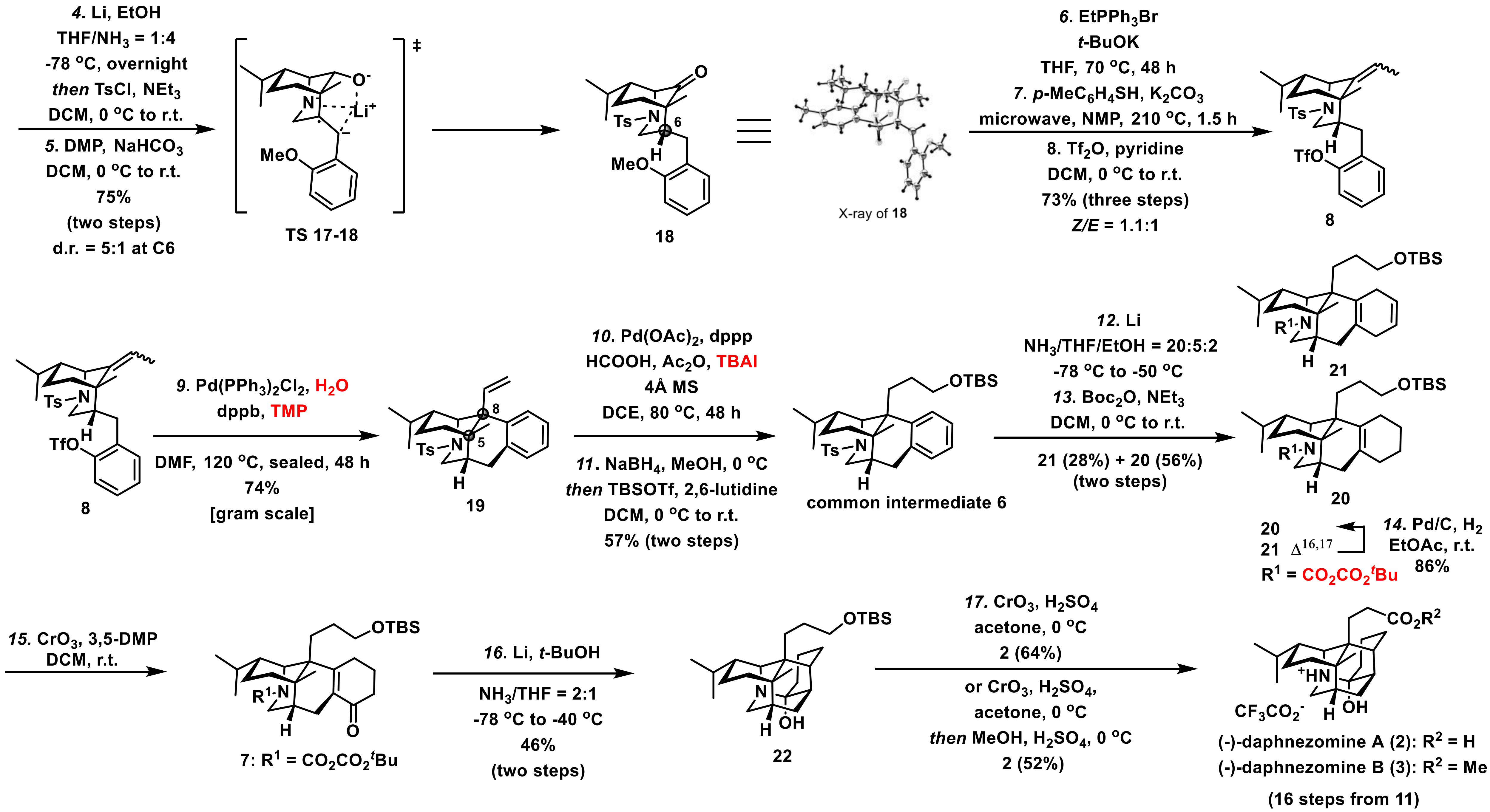
(+)-dapholdhamine B

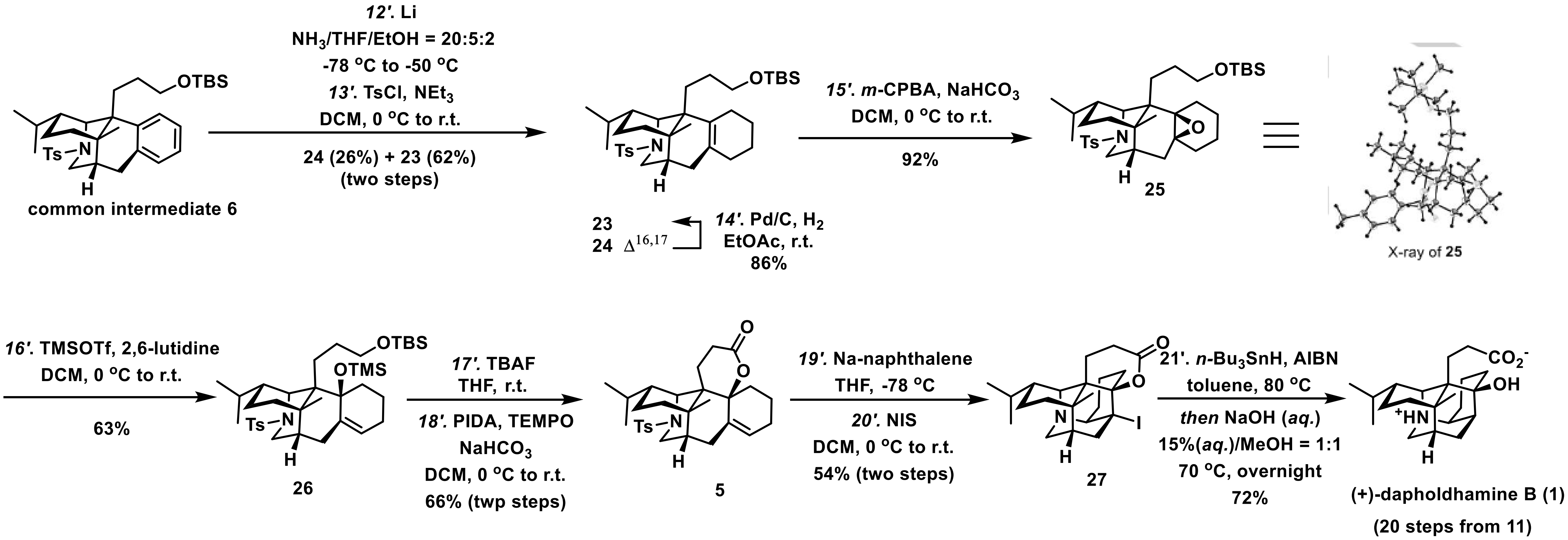


(-)-daphnezomine A:
R = H (inner salt)
(-)-daphnezomine B:
R = Me

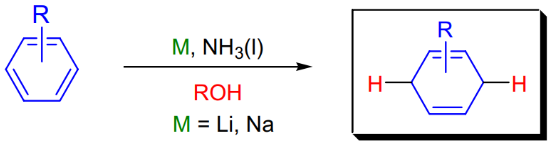

CO2-
OH
+HN
H
(+)-dapholdhamine B (1)
O
O
N
H
4
NIS-prompted
aminocyclization
O
O
Ts
N
H
5
FGI
tandem
deprotection/
reduction/
tautomerization
CO2R2
+HN
CF3CO2-
H
OH
(-)-daphnezomine A (2): R2 = H
(-)-daphnezomine B (3): R2 = Me
OTBS
R1-N
H
O
7: R1 = CO2CO2tBu
FGI
OTBS
Ts
N
H
common intermediate 6
intramol Heck rxn
hydroformylation
NHTs
MeO
10
+
OH
O
11
O
NTs
MeO
9
Ti-mediated
radical
cyclization
Ts
N
H
TfO
8

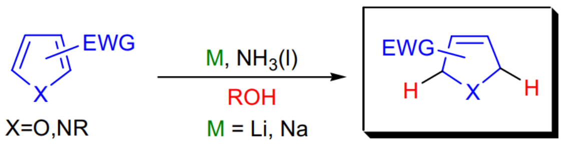

11
a. 12, DEAD
PPh3
THF, 0 °C to r.t.
64%
13
b. Cp2TiCl2, Zn
collidine·HCl
THF, r.t.
54%, d.r. > 10:1
14
c. TBSOTf
2,6-lutidine
DCM, 0 °C to r.t.
73%
15
X-ray of 15
10
12
d. Li, EtOH
THF/NH3 = 1:4
-78 °C, overnight
then TsCl, NEt3
DCM, 0 °C to r.t.
82%, d.r. = 4:1
TS-A (favored)
TS-B (disfavored)
11
1. 10, DEAD
PPh3
THF, 0 °C to r.t.
67%
9
2. Cp2TiCl2
Zn
THF, r.t.
75%
16
3. DMP, NaHCO3
DCM, 0 °C to r.t.
then NaBH4
DCM/MeOH = 1:1
17 (72%, or 84% brsm) + 16 (14%)
d.r. = 5:1 at C8
17


4. Li, EtOH
THF/NH3 = 1:4
-78 °C, overnight
then TsCl, NEt3
DCM, 0 °C to r.t.
5. DMP, NaHCO3
DCM, 0 °C to r.t.
75%
(two steps)
d.r. = 5:1 at C6
O-
N
Li+
MeO
‡
TS 17-18
O
Ts
N
6
H
MeO
18
X-ray of 18
6. EtPPh3Br
t-BuOK
THF, 70 °C, 48 h
7. p-MeC6H4SH, K2CO3
microwave, NMP, 210 °C, 1.5 h
8. Tf2O, pyridine
DCM, 0 °C to r.t.
73% (three steps)
Z/E = 1.1:1
Ts
N
TfO
H
8
Ts
N
TfO
H
8
9. Pd(PPh3)2Cl2, H2O
dppb, TMP
DMF, 120 °C, sealed, 48 h
74%
[gram scale]
8
Ts
N
5
H
19
10. Pd(OAc)2, dppp
HCOOH, Ac2O, TBAI
4Å MS
DCE, 80 °C, 48 h
11. NaBH4, MeOH, 0 °C
then TBSOTf, 2,6-lutidine
DCM, 0 °C to r.t.
57% (two steps)
OTBS
Ts
N
H
common intermediate 6
12. Li
NH3/THF/EtOH = 20:5:2
-78 °C to -50 °C
13. Boc2O, NEt3
DCM, 0 °C to r.t.
21 (28%) + 20 (56%)
(two steps)
OTBS
R1-N
H
21
OTBS
R1-N
H
20
20
21
Δ16,17
14. Pd/C, H2
EtOAc, r.t.
86%
R1 = CO2CO2tBu
15. CrO3, 3,5-DMP
DCM, r.t.
OTBS
R1-N
H
O
7: R1 = CO2CO2tBu
16. Li, t-BuOH
NH3/THF = 2:1
-78 °C to -40 °C
46%
(two steps)
OTBS
N
H
OH
22
17. CrO3, H2SO4
acetone, 0 °C
2 (64%)
or CrO3, H2SO4,
acetone, 0 °C
then MeOH, H2SO4, 0 °C
2 (52%)
CO2R2
+HN
CF3CO2-
H
OH
(-)-daphnezomine A (2): R2 = H
(-)-daphnezomine B (3): R2 = Me
(16 steps from 11)


12'. Li
NH3/THF/EtOH = 20:5:2
-78 °C to -50 °C
13'. TsCl, NEt3
DCM, 0 °C to r.t.
24 (26%) + 23 (62%)
(two steps)
OTBS
Ts
N
H
common intermediate 6
23
24 Δ16,17
14'. Pd/C, H2
EtOAc, r.t.
86%
15'. m-CPBA, NaHCO3
DCM, 0 °C to r.t.
92%
O
25
X-ray of 25
16'. TMSOTf, 2,6-lutidine
DCM, 0 °C to r.t.
63%
OTMS
26
17'. TBAF
THF, r.t.
18'. PIDA, TEMPO
NaHCO3
DCM, 0 °C to r.t.
66% (twp steps)
5
19'. Na-naphthalene
THF, -78 °C
20'. NIS
DCM, 0 °C to r.t.
54% (two steps)
I
27
21'. n-Bu3SnH, AIBN
toluene, 80 °C
then NaOH (aq.)
15%(aq.)/MeOH = 1:1
70 °C, overnight
72%
CO2-
OH
+HN
(+)-dapholdhamine B (1)
(20 steps from 11)

BIRCH REDUCTION

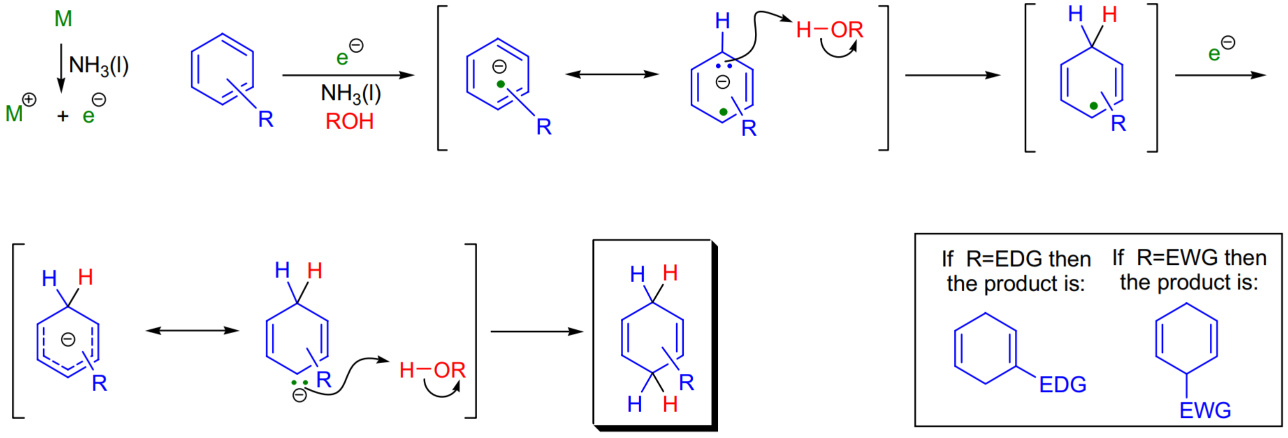




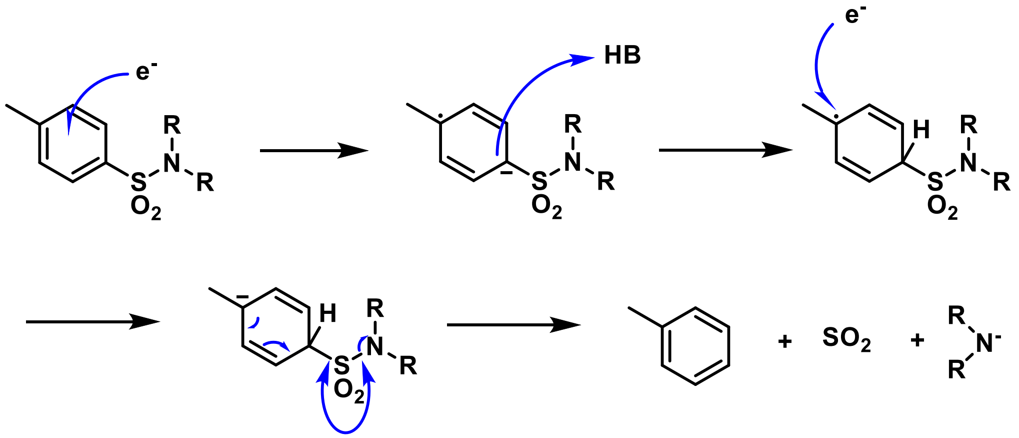
Li/DBB(4,4′-di-*t*-bulylbiphenyl)、Na/naphthalene等更加温和的还原条件相比于使用液氨的Birch反应来说对官能团的耐受性更强。

如果用短脂肪链的胺替代液氨的话，胺作为质子源，可以相对升高温度反应，其还原能力也随之变强(**Benkeser还原**)。

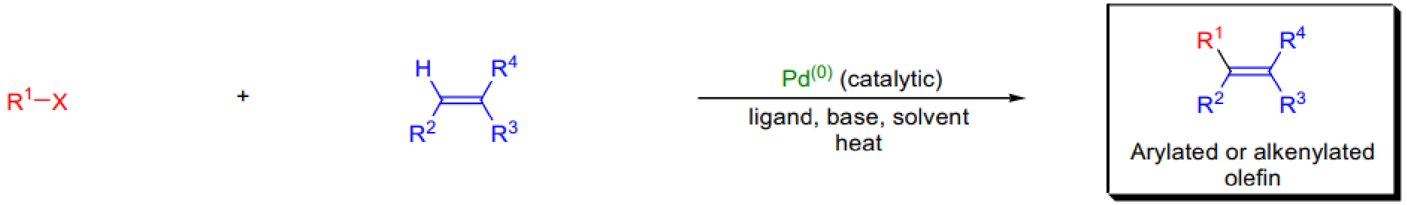
Mechanism: [34-38]



脱Ts



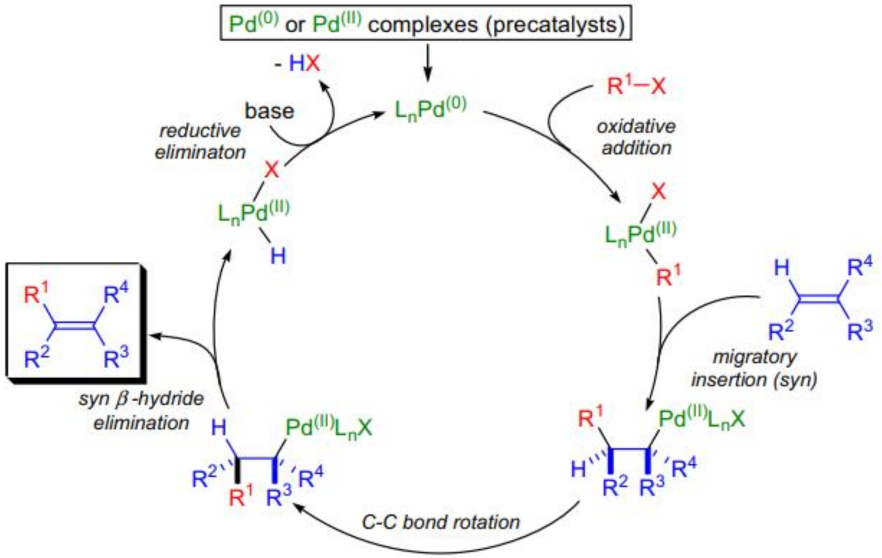
Heck Reation



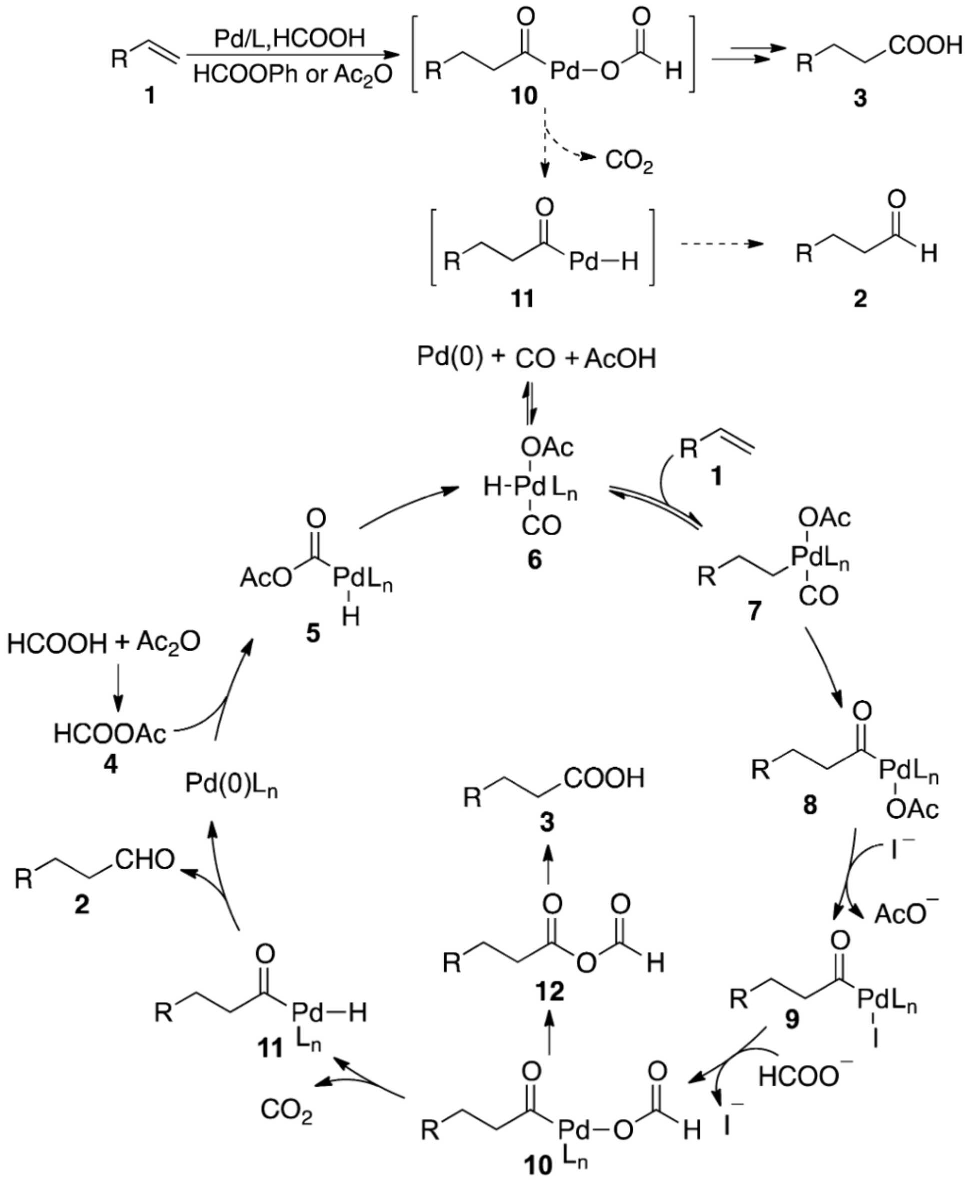
R^1 = aryl, benzyl, vinyl (alkenyl), alkyl (no β hydrogen); R^2, R^3, R^4 = alkyl, aryl, alkenyl; X = Cl, Br, I, OTf, OTs, N_2^+;
ligand = trialkylphosphines, triarylphosphines, chiral phosphines; base = 2° or 3° amine, KOAc, NaOAc, $NaHCO_3$

Mechanism: [58,59,21,22,51,53]

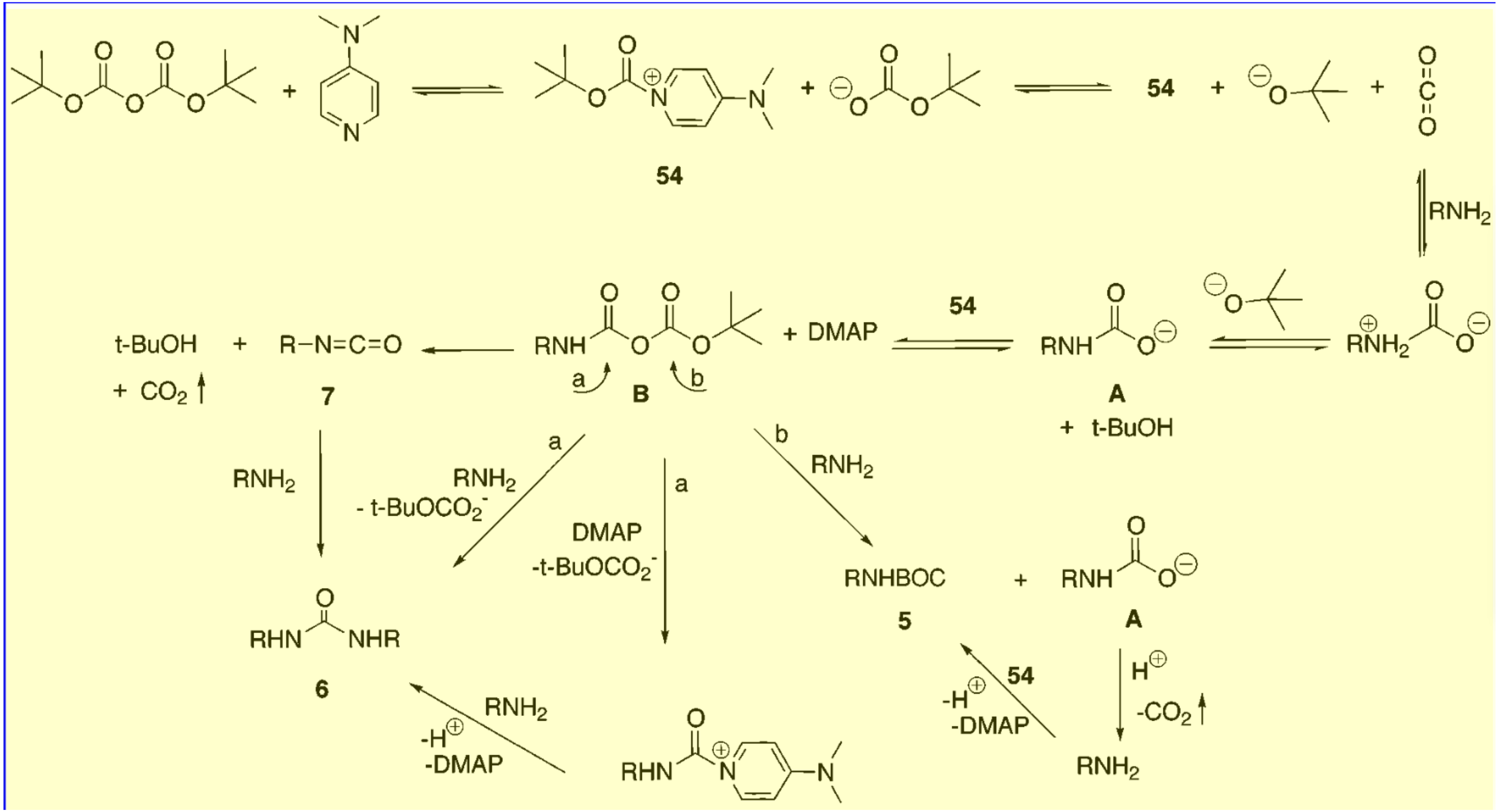
The mechanism of the *Heck reaction* is not fully understood and the exact mechanistic pathway appears to vary subtly with changing reaction conditions. The scheme shows a simplified sequence of events beginning with the generation of the active $Pd^{(0)}$ catalyst. The rate-determining step is the *oxidative addition* of $Pd^{(0)}$ into the C-X bond. To account for various experimental observations, refined and more detailed catalytic cycles passing through anionic, cationic or neutral active species have been proposed.[21,36]



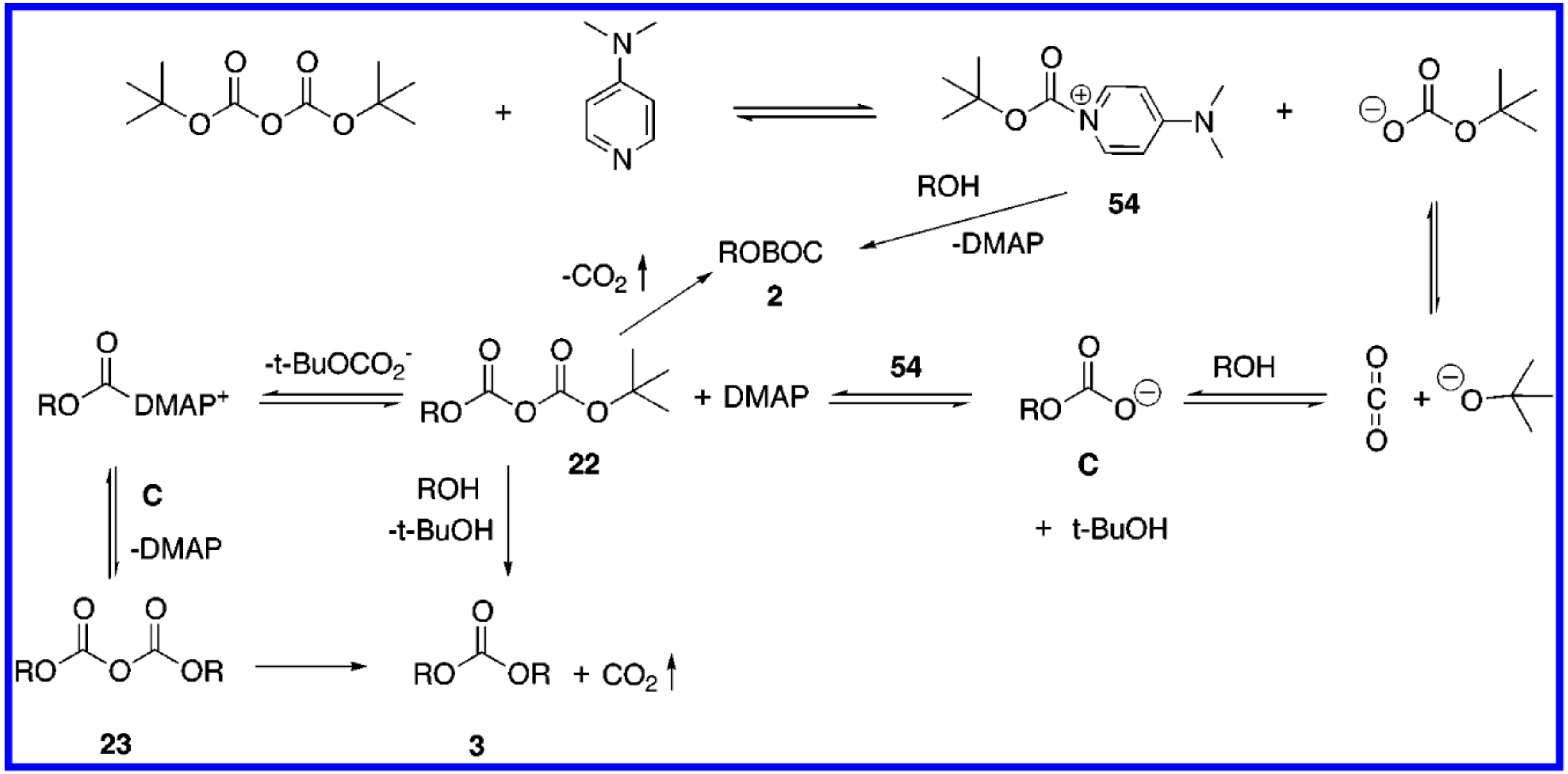
Pd-Catalyzed Regioselective Hydroformylation of Olefins with Formic Acid



J. Am. Chem. Soc., **2016**, *138*, 14864.

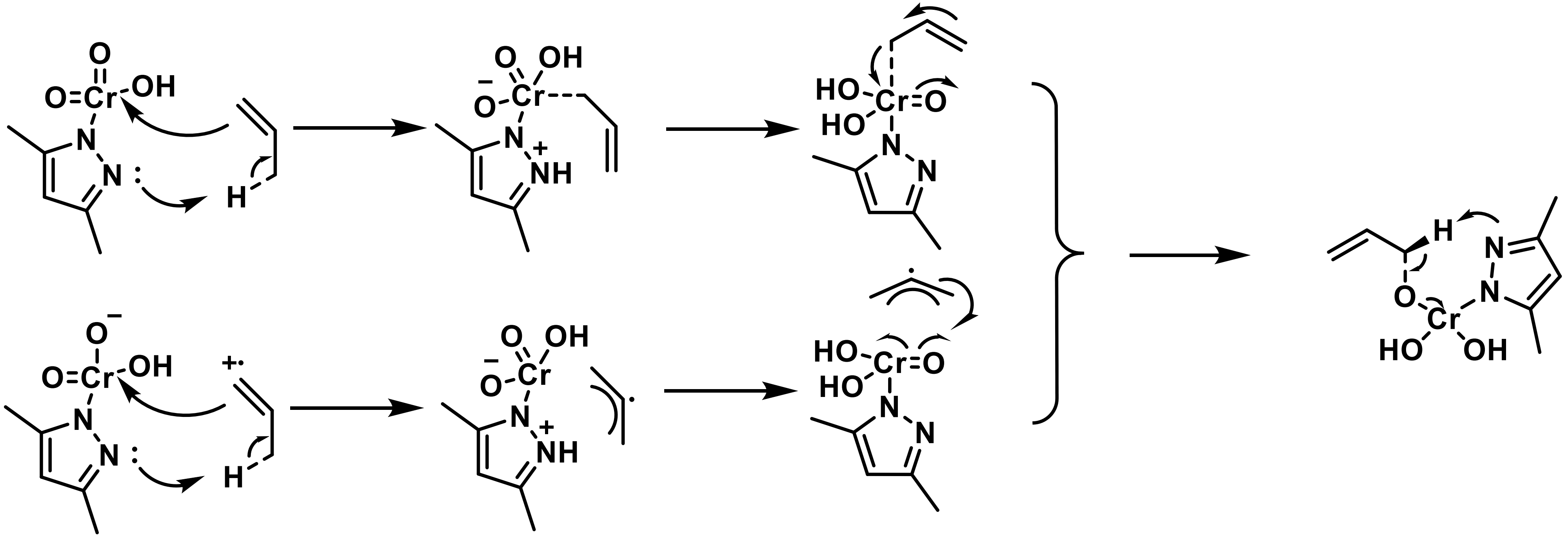


J. Org. Chem., **2000**, *65*, 6368.



J. Org. Chem., **2000**, *65*, 6368.

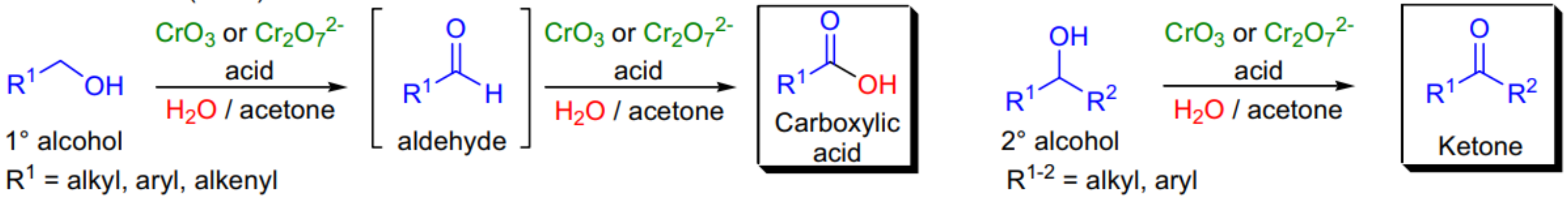
烯丙位氧化



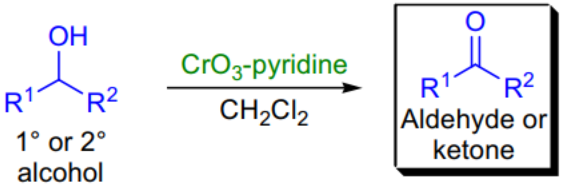
J. Org. Chem., **1978**, *43*, 2057.

JONES OXIDATION / OXIDATION OF ALCOHOLS BY CHROMIUM REAGENTS

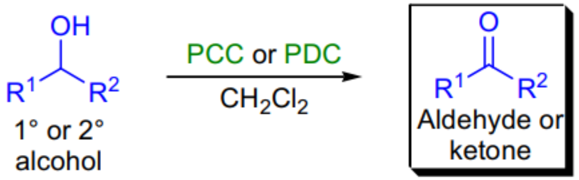
Jones oxidation (1946):



Sarett and Collins oxidations (1953 & 1968):



PCC and PDC oxidations (Corey, 1975 & 1979):



Mechanism: [21,9,22-24]

The concentration and the pH determines the form of $Cr^{(VI)}$ in aqueous solutions: in dilute solution the monomoeric form ($HCrO_4^-$) dominates while in concentrated solution the dimeric form ($HCr_2O_7^-$) is prevalent. The alcohol substrate is first converted to the corresponding chromate ester, which suffers a rate-determining deprotonation by a base to release the $Cr^{(IV)}$ species. This mechanism is supported by a large kinetic isotope effect observed during the oxidation of an α-deuterated alcohol substrate.[21]

Complete mechanism which accounts for the observed stoichiometry:

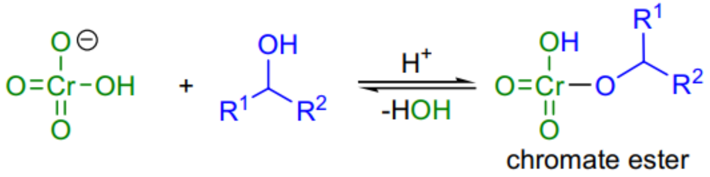
$R^1R^2CHOH + Cr^{(VI)} \longrightarrow R^1R^2C{=}O + Cr^{(IV)} + 2\,H^+$

$R^1R^2CHOH + Cr^{(IV)} \longrightarrow R^1R^2C{=}O + Cr^{(II)} + 2\,H^+$

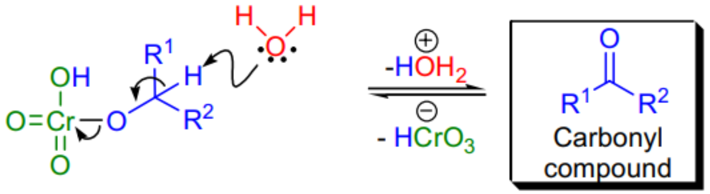
$Cr^{(II)} + Cr^{(VI)} \longrightarrow Cr^{(III)} + Cr^{(V)}$

$R^1R^2CHOH + Cr^{(V)} \longrightarrow R^1R^2C{=}O + Cr^{(III)} + 2\,H^+$

Step #1:

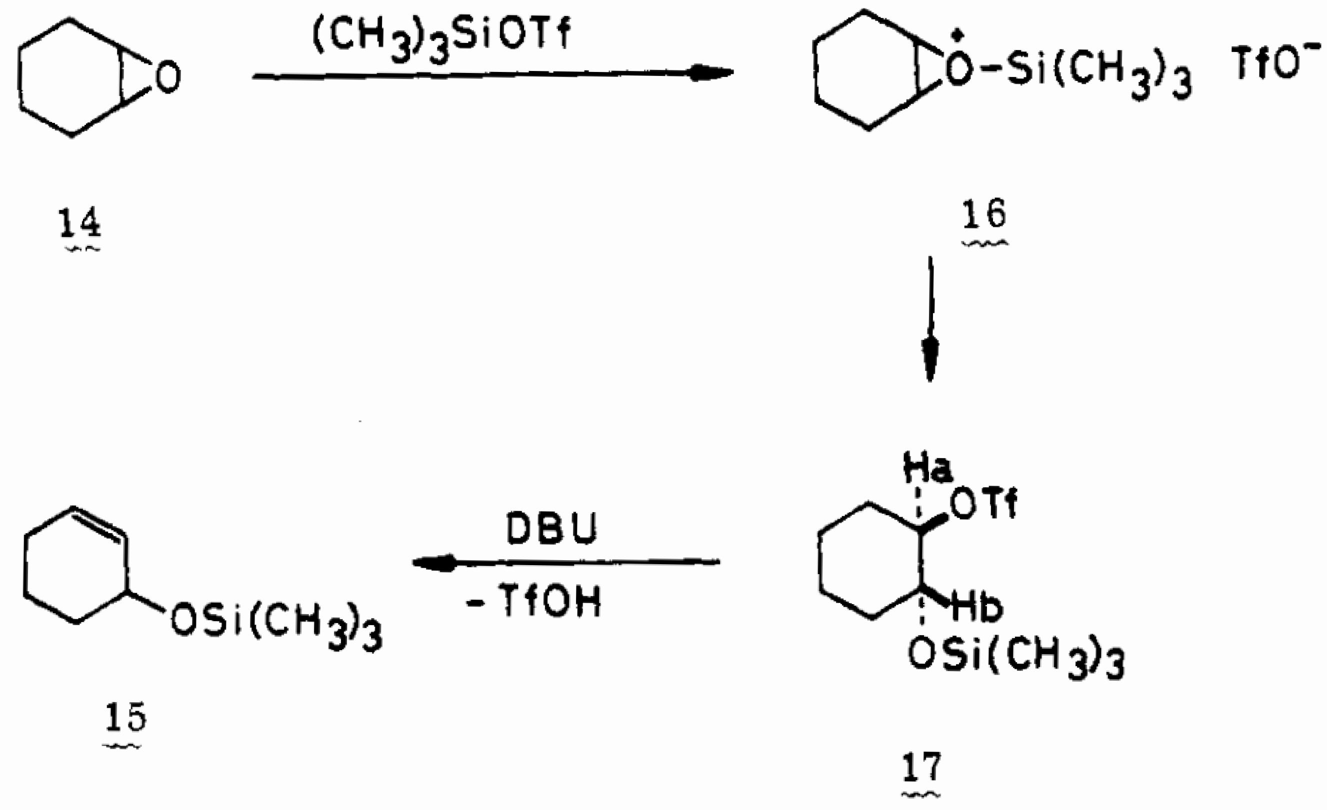


Step #2:

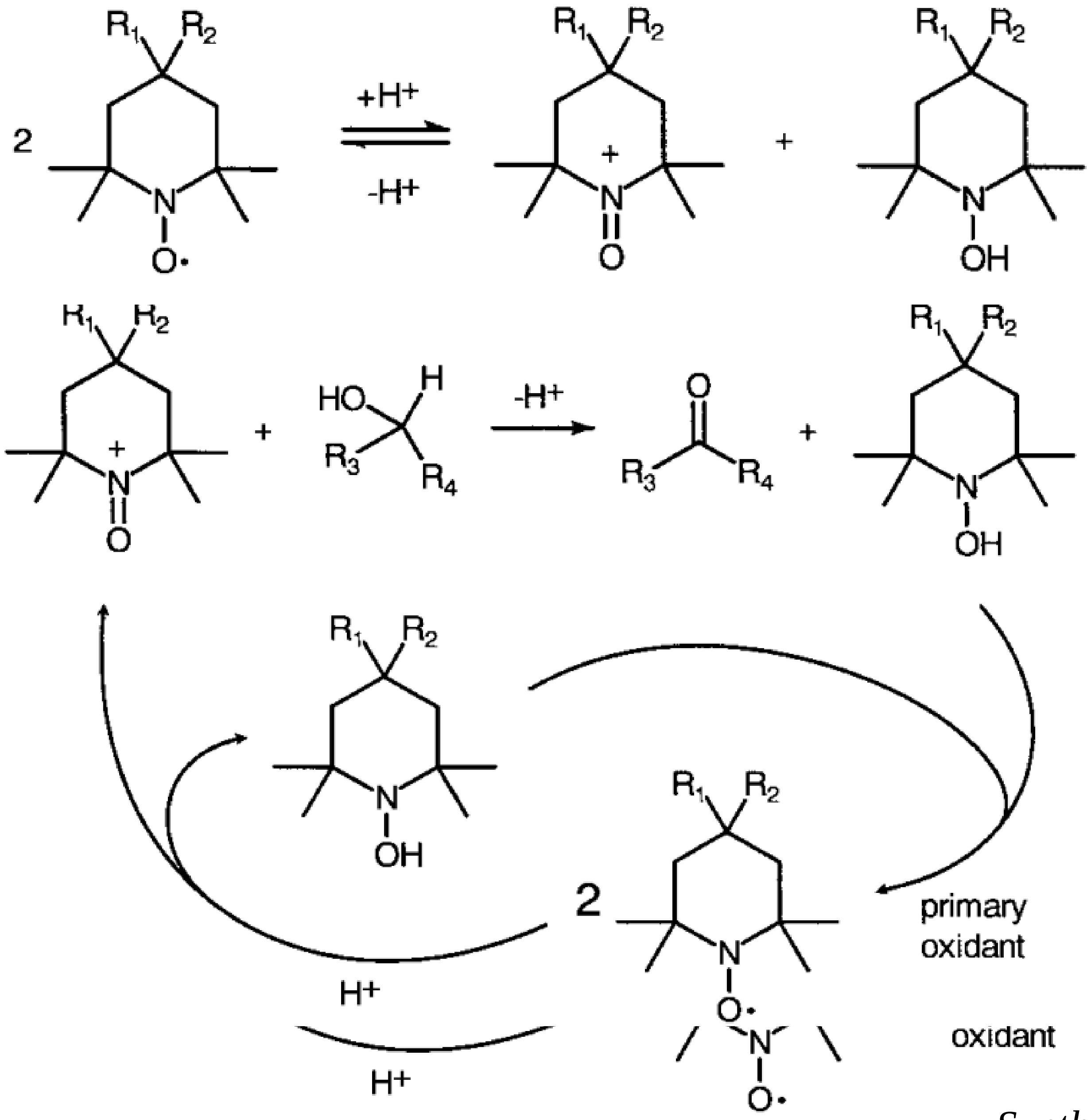


A New Method for Converting Oxiranes to Allylic Alcohols by an Organosilicon Reagent

Scheme I



J. Am. Chem. Soc., **1979**, *101*, 2038.



Synthesis, **1996**, *10*, 1153.