GDCh Communications Angewa International Edition

Total Synthesis

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Total Synthesis of (−)-Daphenylline

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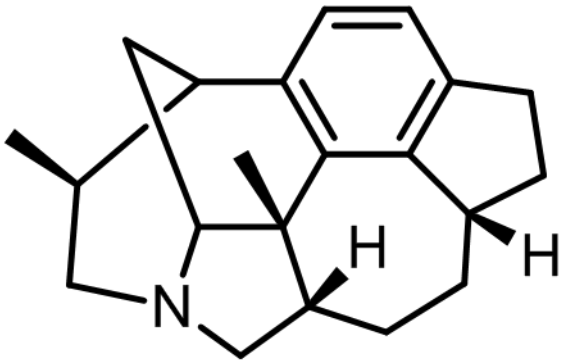
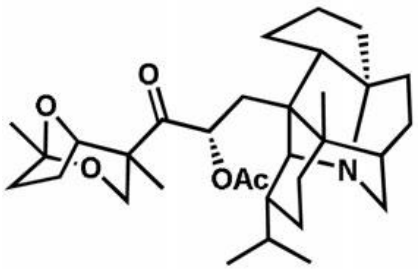
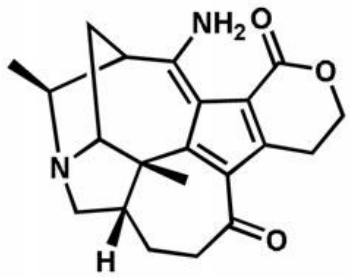
In memory of Leo A. Paquette



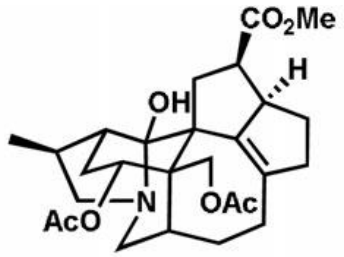
Daphenylline



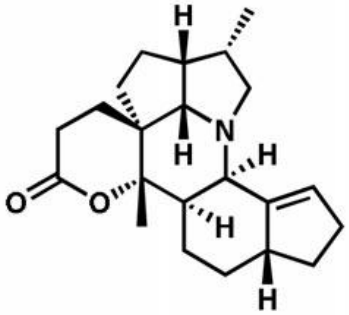
daphniphylline (1)



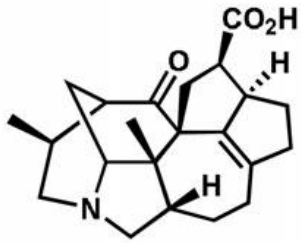
daphnipaxinin (2)



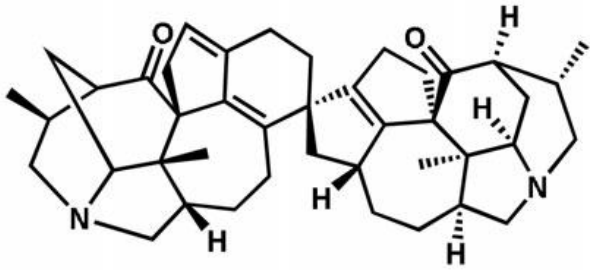
yuzurimine (3)



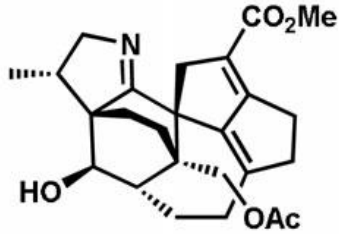
daphlongamine H (4)



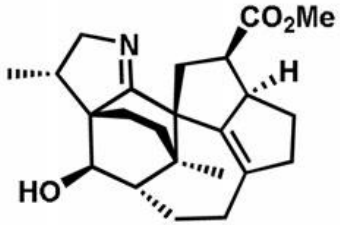
daphnilongeranin C (5)



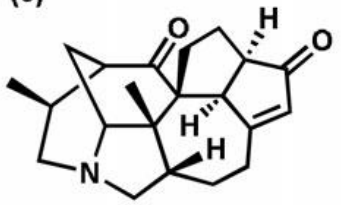
longerac
emin A
(6)

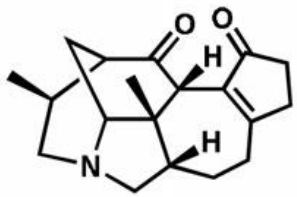


daphmanidin E (7)

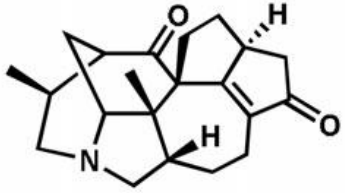


calyciphylline N (8)



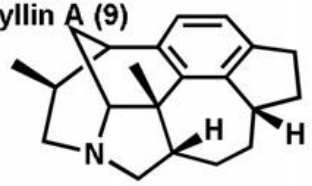


himalensine (10)



daphnilongeranin B (11)

longeracinp
hyllin A (9)



dapheny
lline (12)

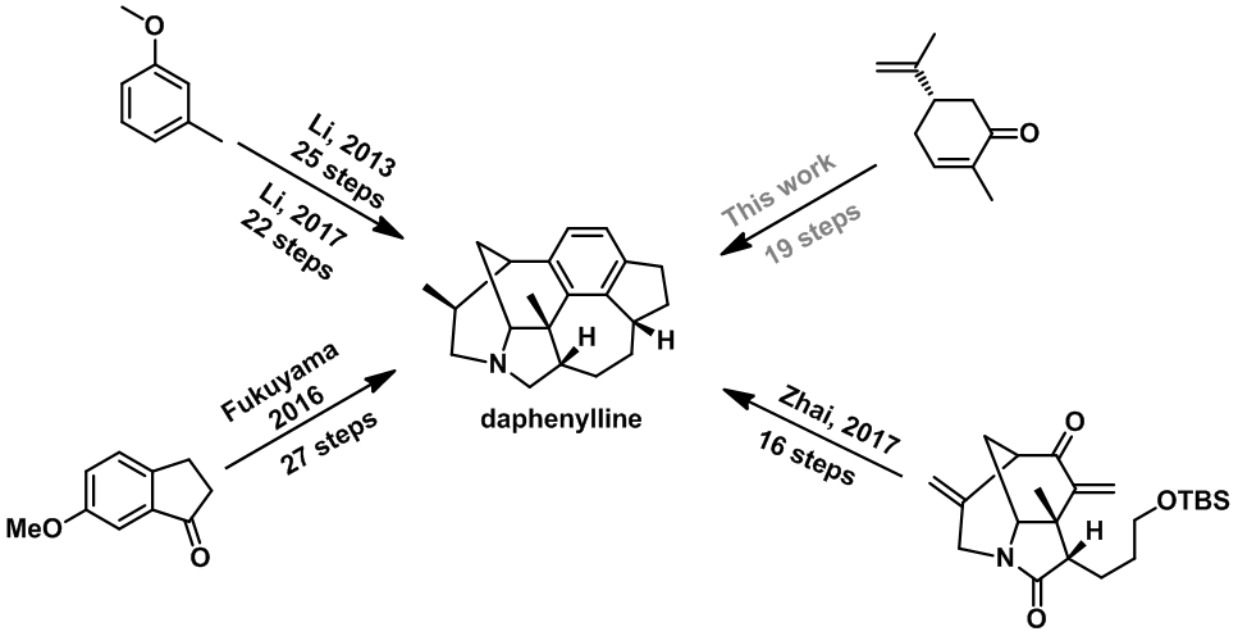


Figure 2. An outline of the previous syntheses of daphenylline.

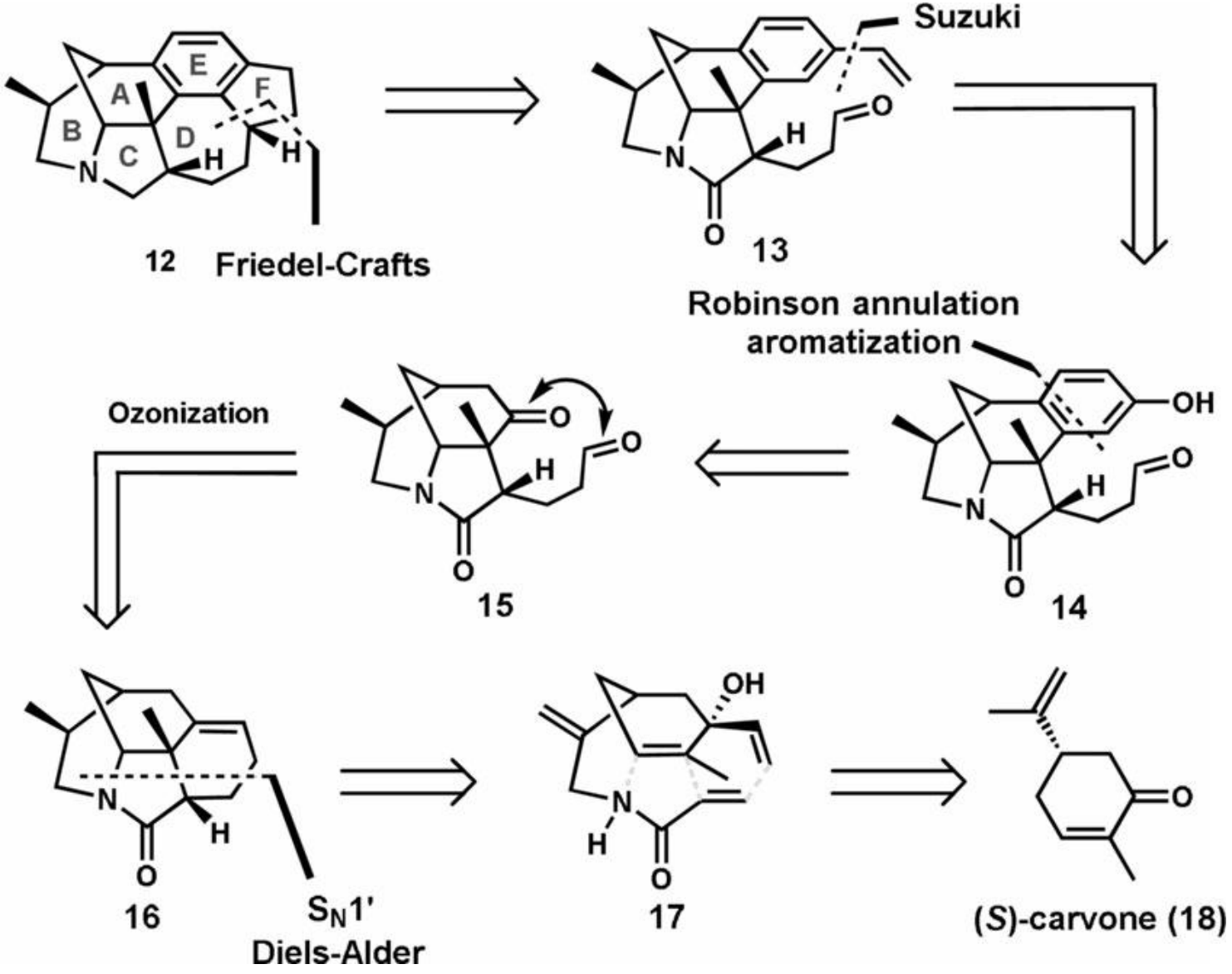
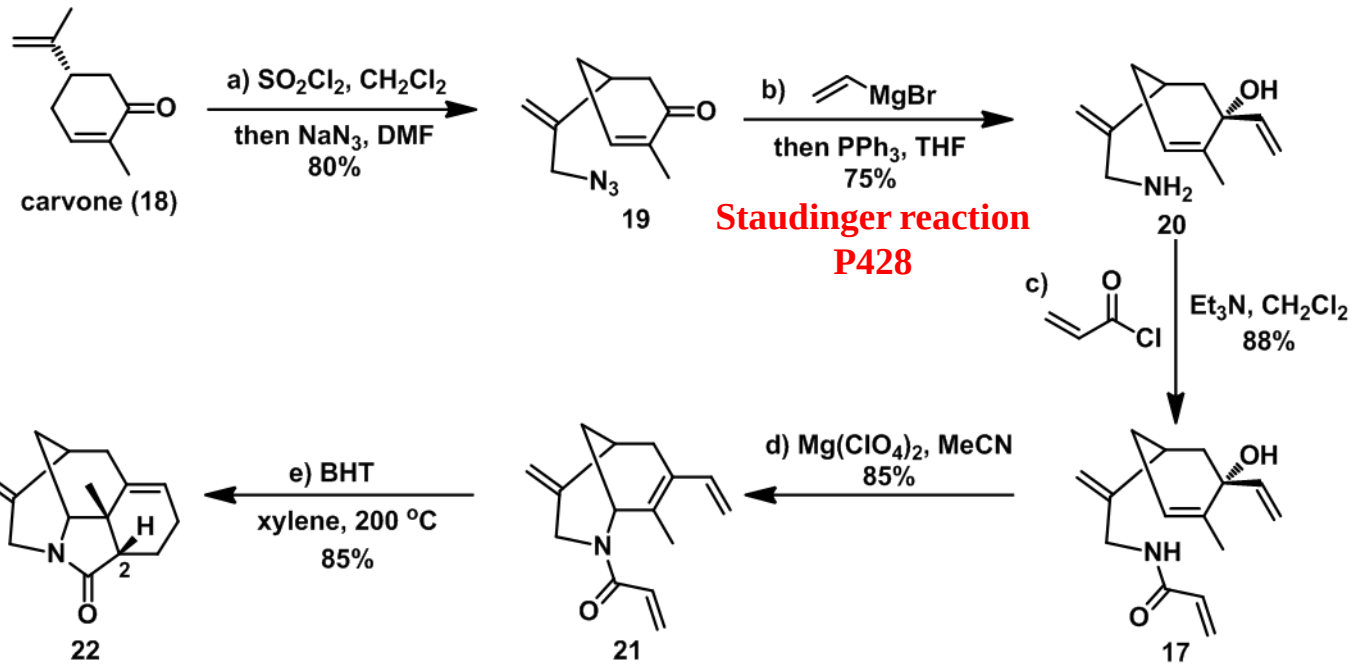
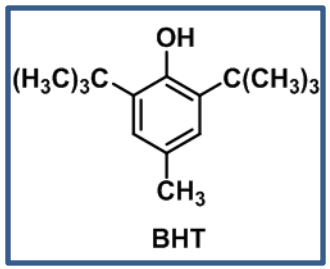
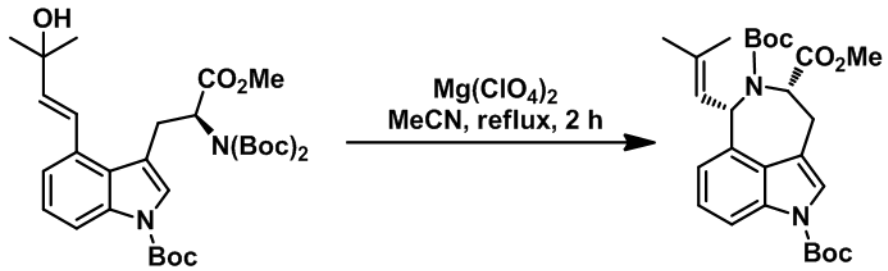


Figure 3. Retrosynthetic analysis of daphenylline.







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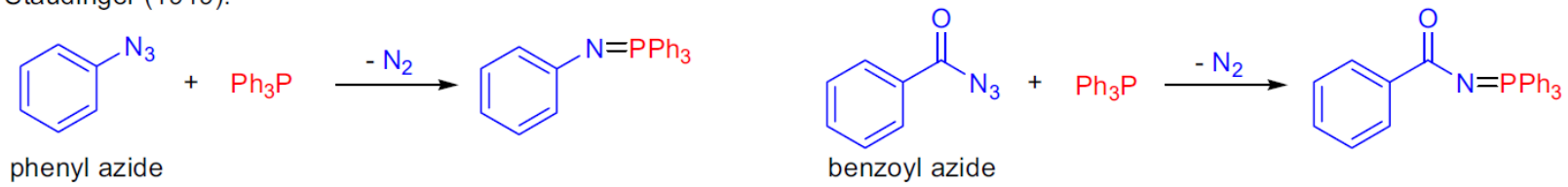
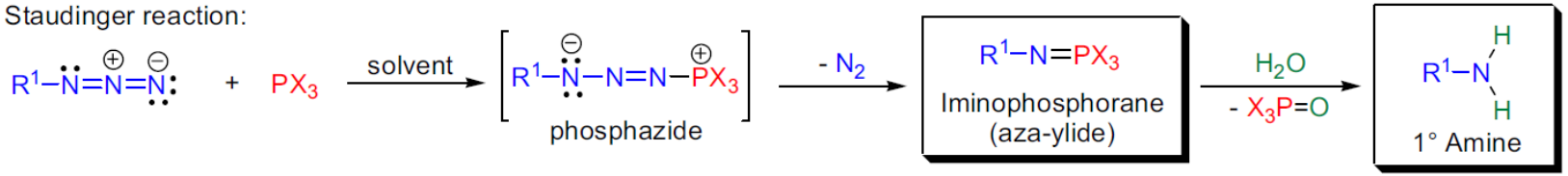
Staudinger reaction

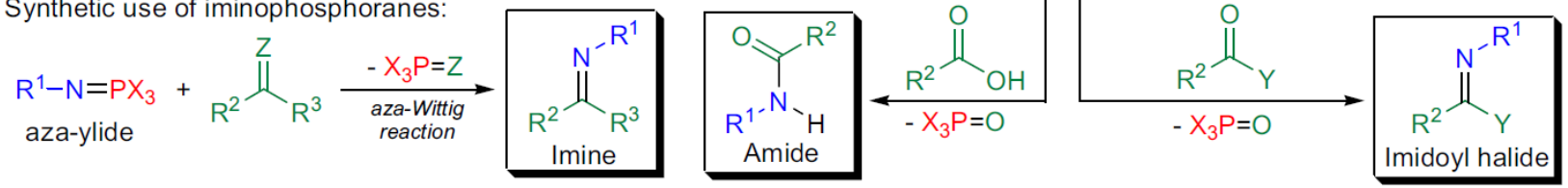
Staudinger (1919):



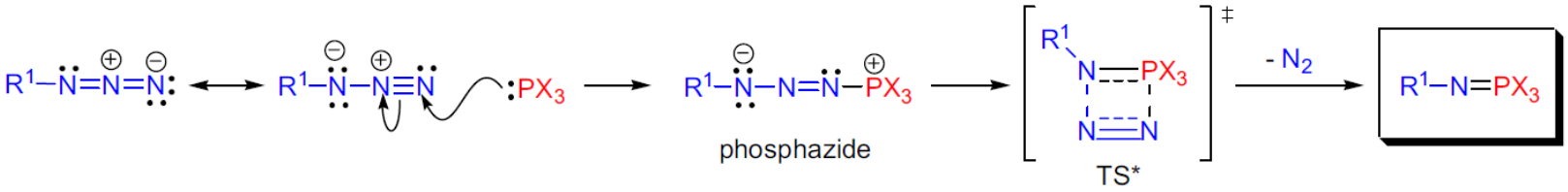
Staudinger reaction:



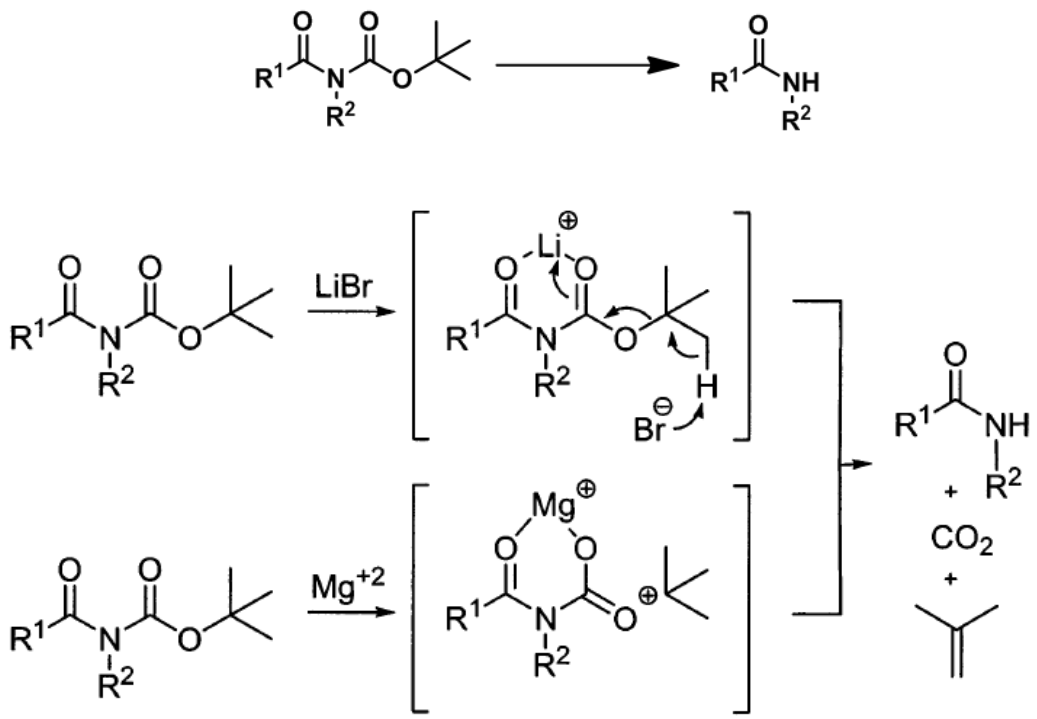
Synthetic use of iminophosphoranes:

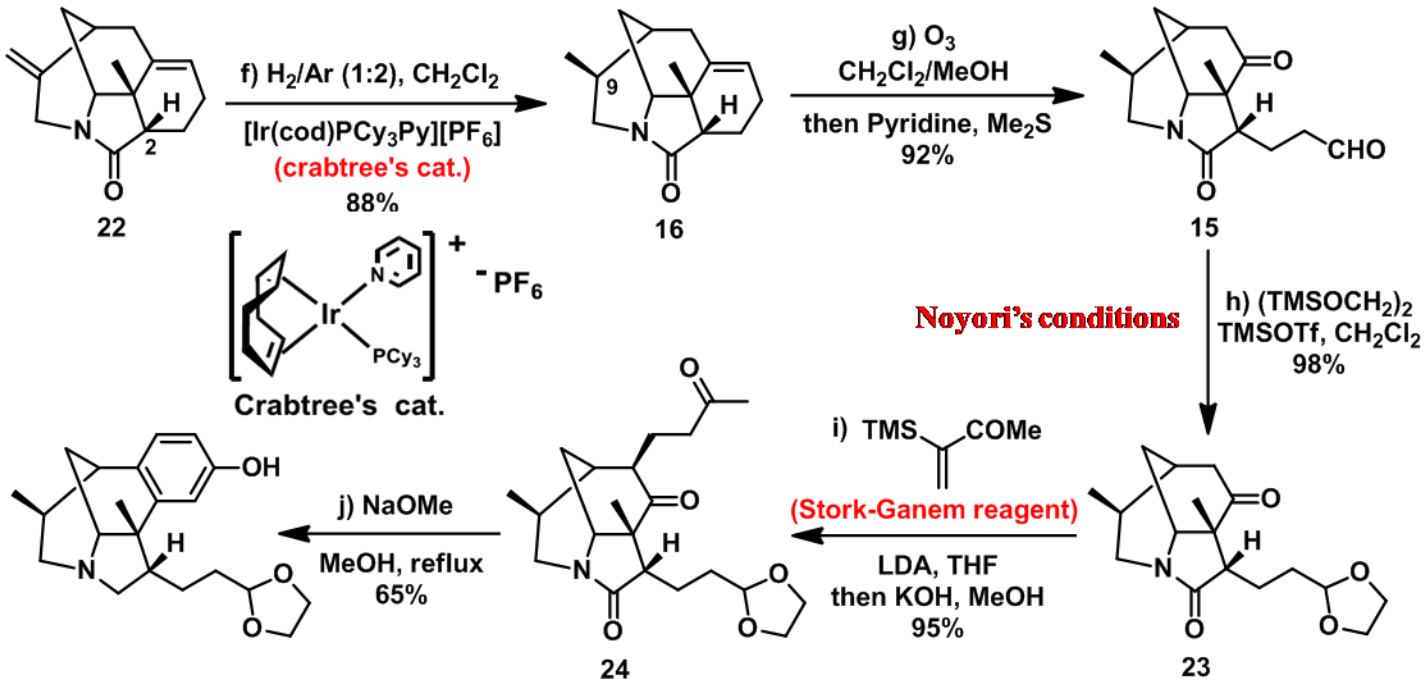


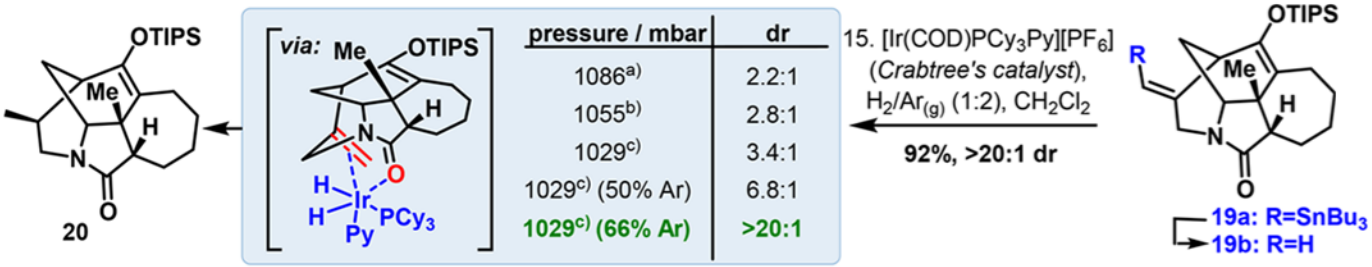
R^1 = alkyl, aryl, heteroaryl, RC(O), RSO_2, RP(O), R_2P, R_3Si, R_3Sn, R_3Ge; R^{2-3} = H, alkyl, aryl, heteroaryl; X = alkyl, aryl, O-alkyl, O-aryl, NH_2, NR_2, Cl, F, NCO, (also the combination of these ligands); Y = Cl, Br; Z = O, S; solvent: THF, Et_2O



Possible modes of attack:


LiBr
Mg+2
CO2





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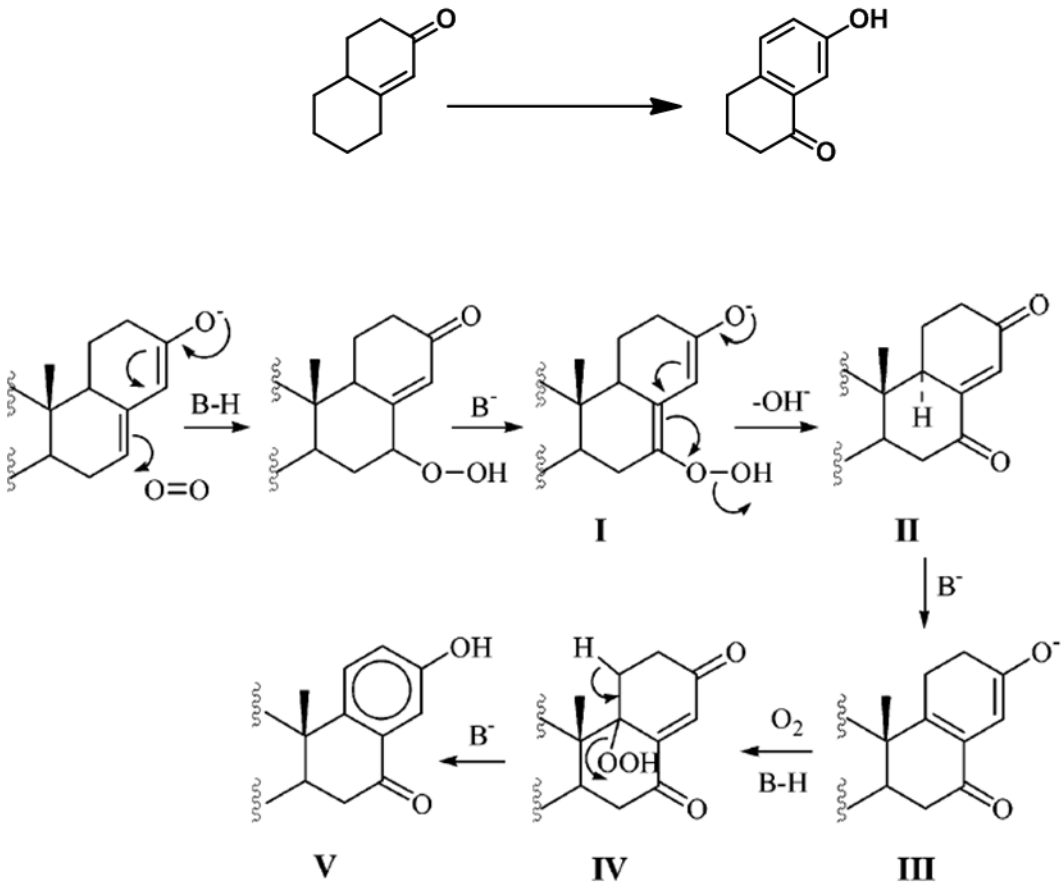
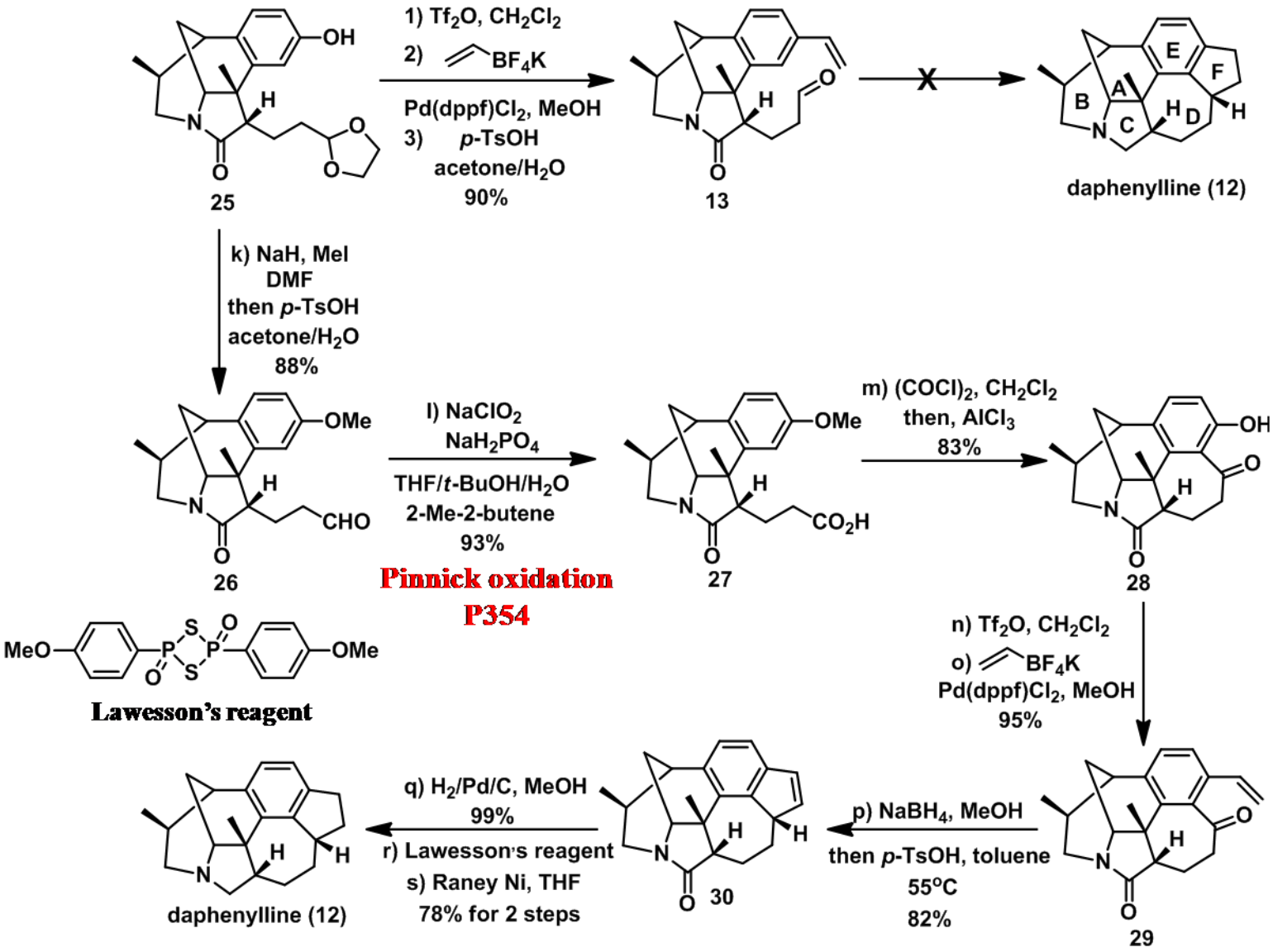
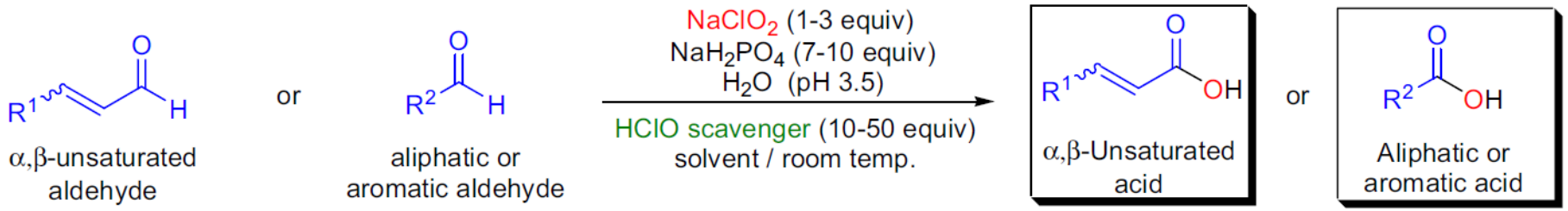

O
OH
O
B-H
O=O
B⁻
O–OH
I
-OH⁻
H
II
B⁻
III
O₂
B-H
OOH
IV
B⁻
V


1) Tf2O, CH2Cl2
2) BF4K
Pd(dppf)Cl2, MeOH
3) p-TsOH
acetone/H2O
90%
25
13
daphenylline (12)
k) NaH, MeI
DMF
then p-TsOH
acetone/H2O
88%
l) NaClO2
NaH2PO4
THF/t-BuOH/H2O
2-Me-2-butene
93%
Pinnick oxidation
P354
26
27
m) (COCl)2, CH2Cl2
then, AlCl3
83%
28
Lawesson's reagent
n) Tf2O, CH2Cl2
o) BF4K
Pd(dppf)Cl2, MeOH
95%
29
p) NaBH4, MeOH
then p-TsOH, toluene
55°C
82%
30
q) H2/Pd/C, MeOH
99%
r) Lawesson's reagent
s) Raney Ni, THF
78% for 2 steps
daphenylline (12)

Pinnick oxidation



R^1 = H, alkyl, aryl, alkenyl, allyl; R^2 = alkyl, aryl, allyl, homoallyl; scavenger = 2-methyl-2-butene, H_2O_2, H_2NSO_3H, *m*-$C_6H_4(OH)_2$, DMSO; solvent = *t*-BuOH, *t*-BuOH/THF

Mechanism: [10,6]