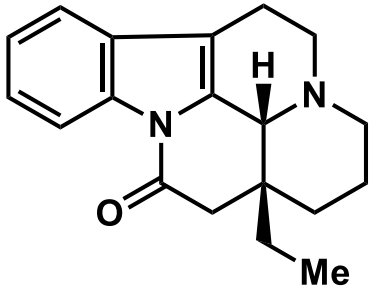
10.1002/anie.202106184

WILEY-VCH

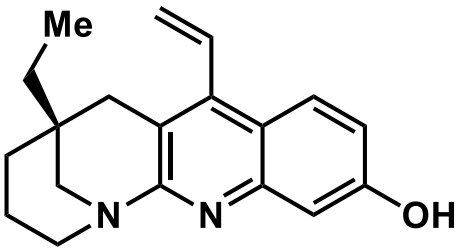
COMMUNICATION

The Enantioselective Synthesis of Eburnamonine, Eucophylline, and 16'-*epi*-Leucophyllidine

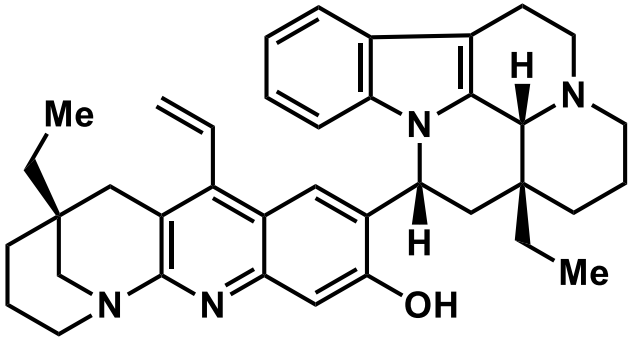
Christopher E. Reimann[†],[a] Aurapat Ngamnithiporn[†],[a],[c] Kohei Hayashida.[a],[b] Daisuke Saito.[a],[b] Katerina M. Korch,[a] Brian M. Stoltz*[a]



(8)
Eburnamonine

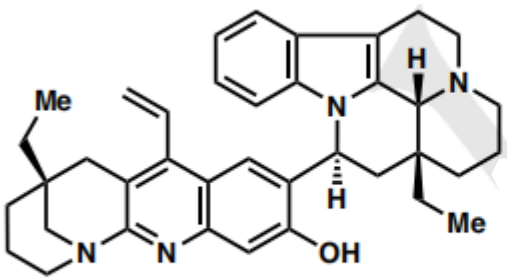


(5)
Eucophylline

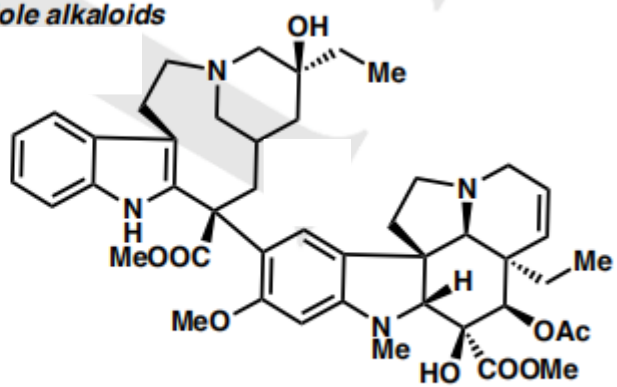


40
16'-epi-leucophyllidine

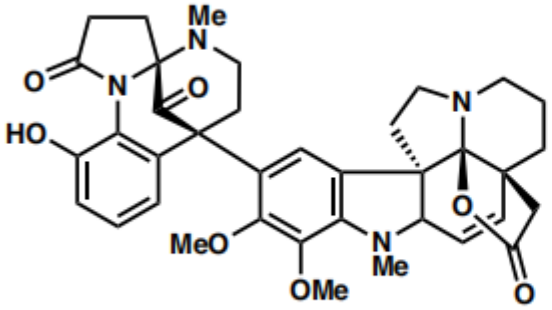
a. Representative heterodimeric bisindole alkaloids



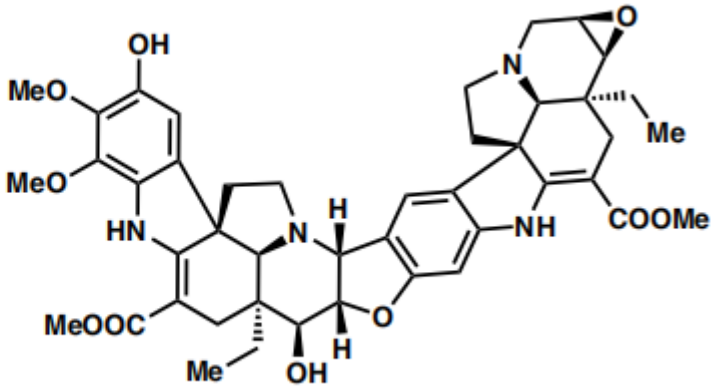
Leucophyllidine (1)



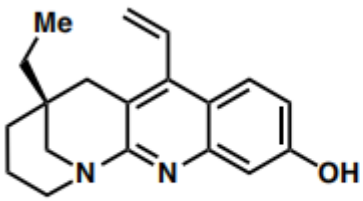
Vinblastine (2)



Haplophytine (3)

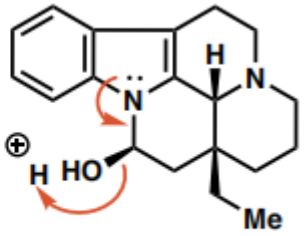


Conophylline (4)



Eucophylline (5)

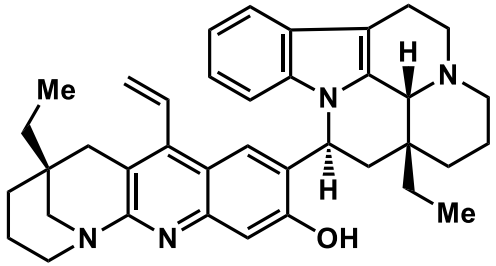
+



Eburnamine (6)

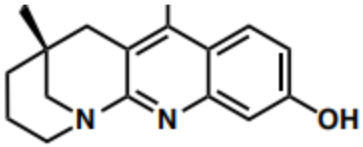
Enzymemediated

Friedel–Crafts Alkylation



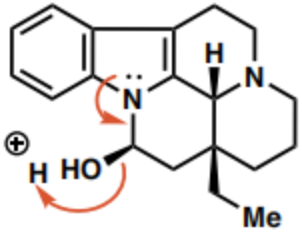
leucophyllidine(**1**)

upling attempt by Pandey (2017)



Eucophylline (5)

+

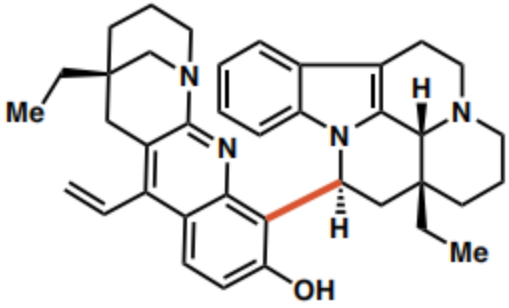


Eburnamine (6)

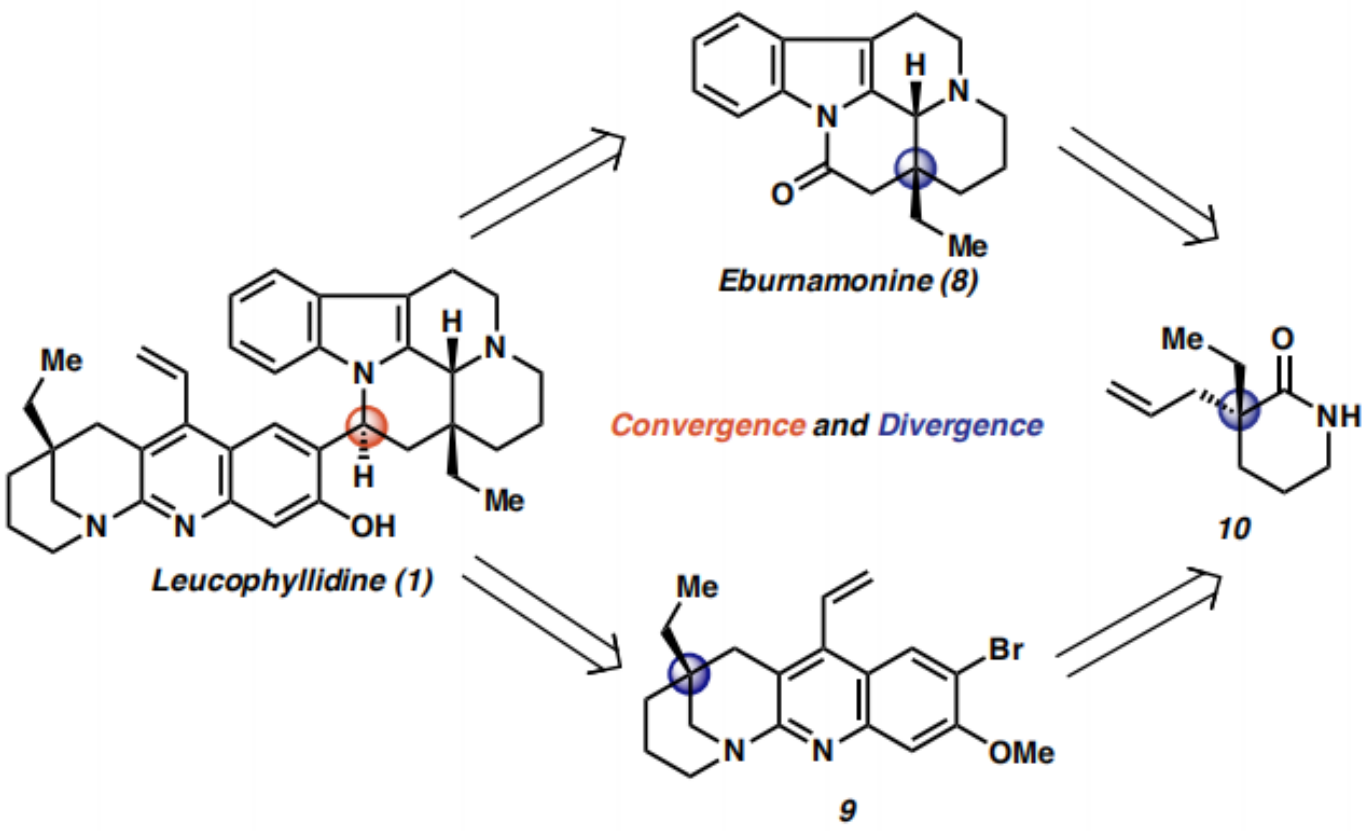
2% HCl (aq)

reflux, 7 d

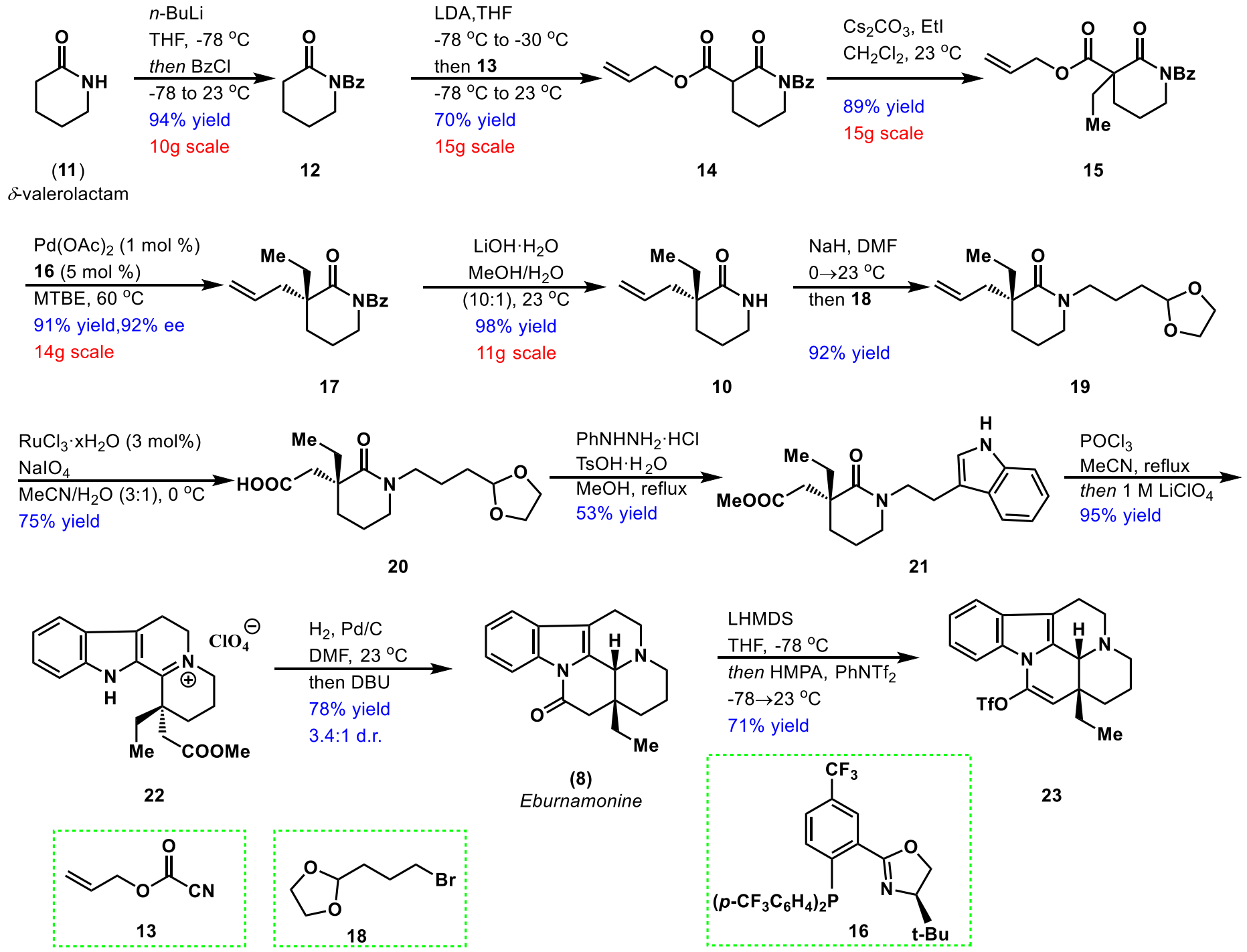
9% yield



iso*-leucophyllidine, *7

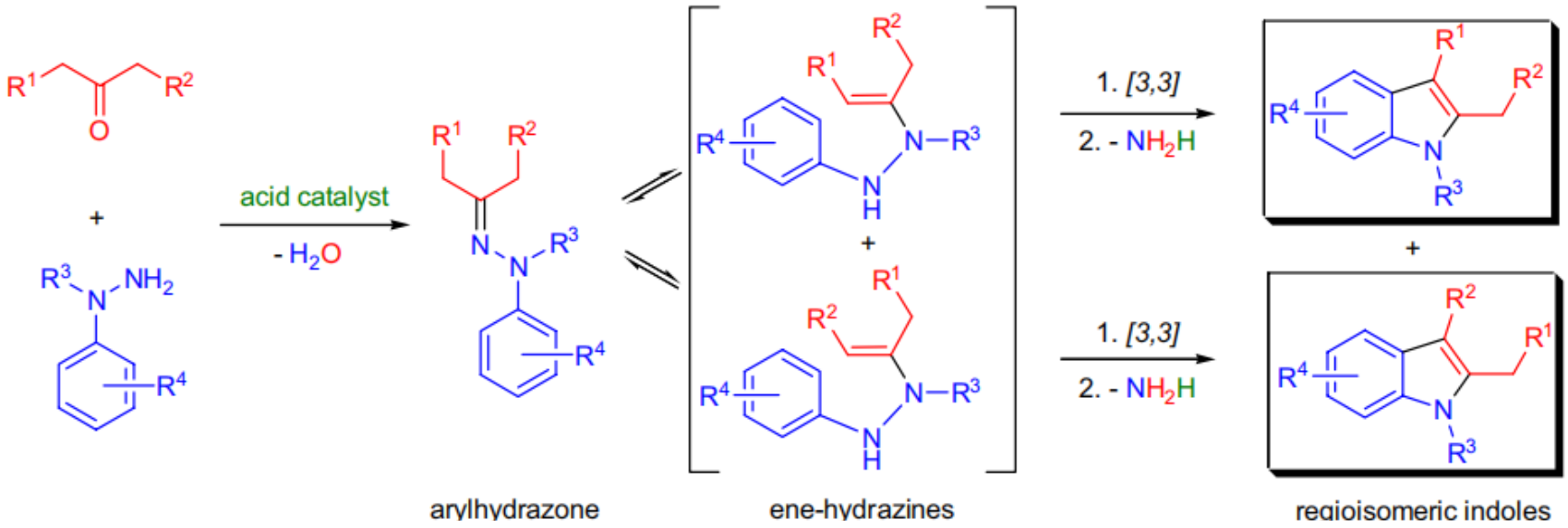


Scheme 2. Retrosynthetic analysis of leucophyllidine. Red circle = α-amino stereogenic center. Blue circle = all-carbon quaternary stereogenic center.


n-BuLi
THF, -78 °C
then BzCl
-78 to 23 °C
94% yield
10g scale
(11)
δ-valerolactam
12
LDA,THF
-78 °C to -30 °C
then 13
-78 °C to 23 °C
70% yield
15g scale
14
Cs2CO3, EtI
CH2Cl2, 23 °C
89% yield
15g scale
15
Pd(OAc)2 (1 mol %)
16 (5 mol %)
MTBE, 60 °C
91% yield,92% ee
14g scale
17
LiOH·H2O
MeOH/H2O
(10:1), 23 °C
98% yield
11g scale
10
NaH, DMF
0→23 °C
then 18
92% yield
19
RuCl3·xH2O (3 mol%)
NaIO4
MeCN/H2O (3:1), 0 °C
75% yield
20
PhNHNH2·HCl
TsOH·H2O
MeOH, reflux
53% yield
21
POCl3
MeCN, reflux
then 1 M LiClO4
95% yield
22
H2, Pd/C
DMF, 23 °C
then DBU
78% yield
3.4:1 d.r.
(8)
Eburnamonine
LHMDS
THF, -78 °C
then HMPA, PhNTf2
-78→23 °C
71% yield
23
13
18
16
t-Bu

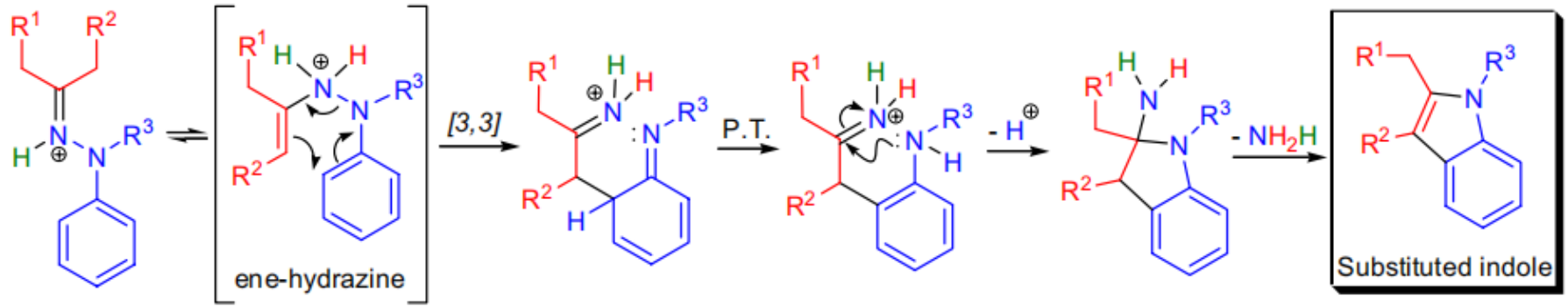
FISCHER INDOLE SYNTHESIS

(References are on page 587)



Mechanism: [22-39]

The currently accepted mechanism of the *Fischer indole synthesis* was originally proposed by R. Robinson in 1924.[22] There are five distinct steps: 1) coordination of the Lewis acid (e.g., proton) to the imine nitrogen; 2) tautomerization of the hydrazone to the corresponding ene-hydrazine; 3) disruption of the aromatic ring by a *[3,3]-sigmatropic rearrangement*; 4) rearomatization *via* a proton shift and formation of the 5-membered ring by a favored *5-exo-trig* cyclization; and 5) the loss of a molecule of ammonia to finally give rise to the indole system.



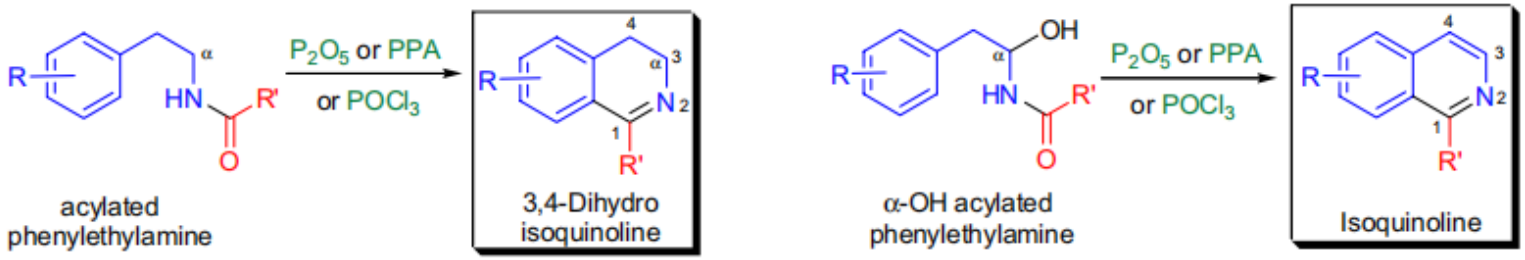
BISCHLER-NAPIERALSKI ISOQUINOLINE SYNTHESIS

(References are on page 553)

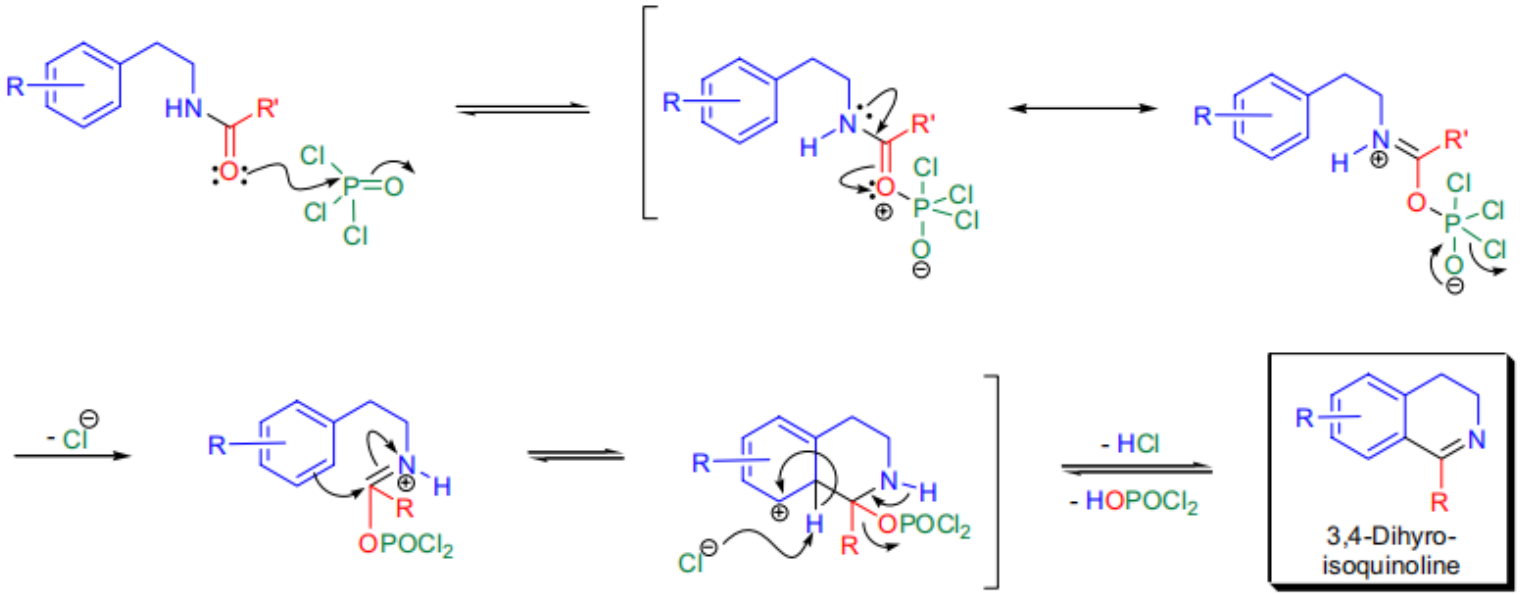
Importance:

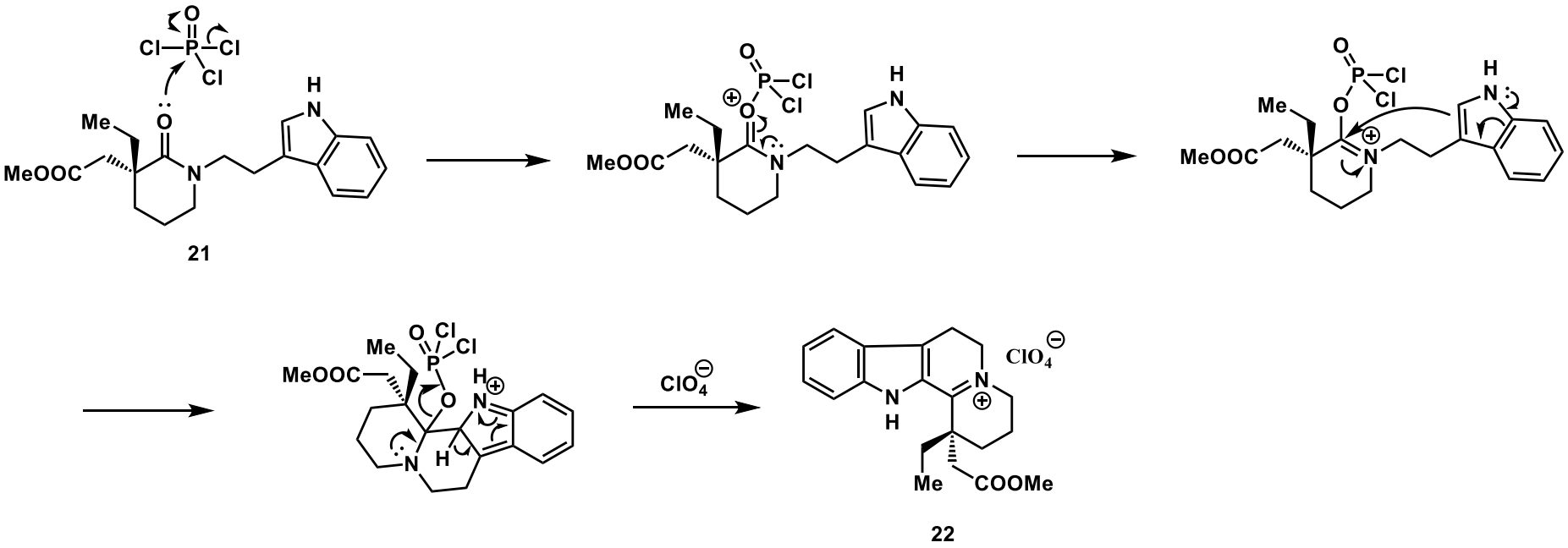
[*Seminal Publication*[1]; *Reviews*[2-4]; *Modifications & Improvements*[5-15]]

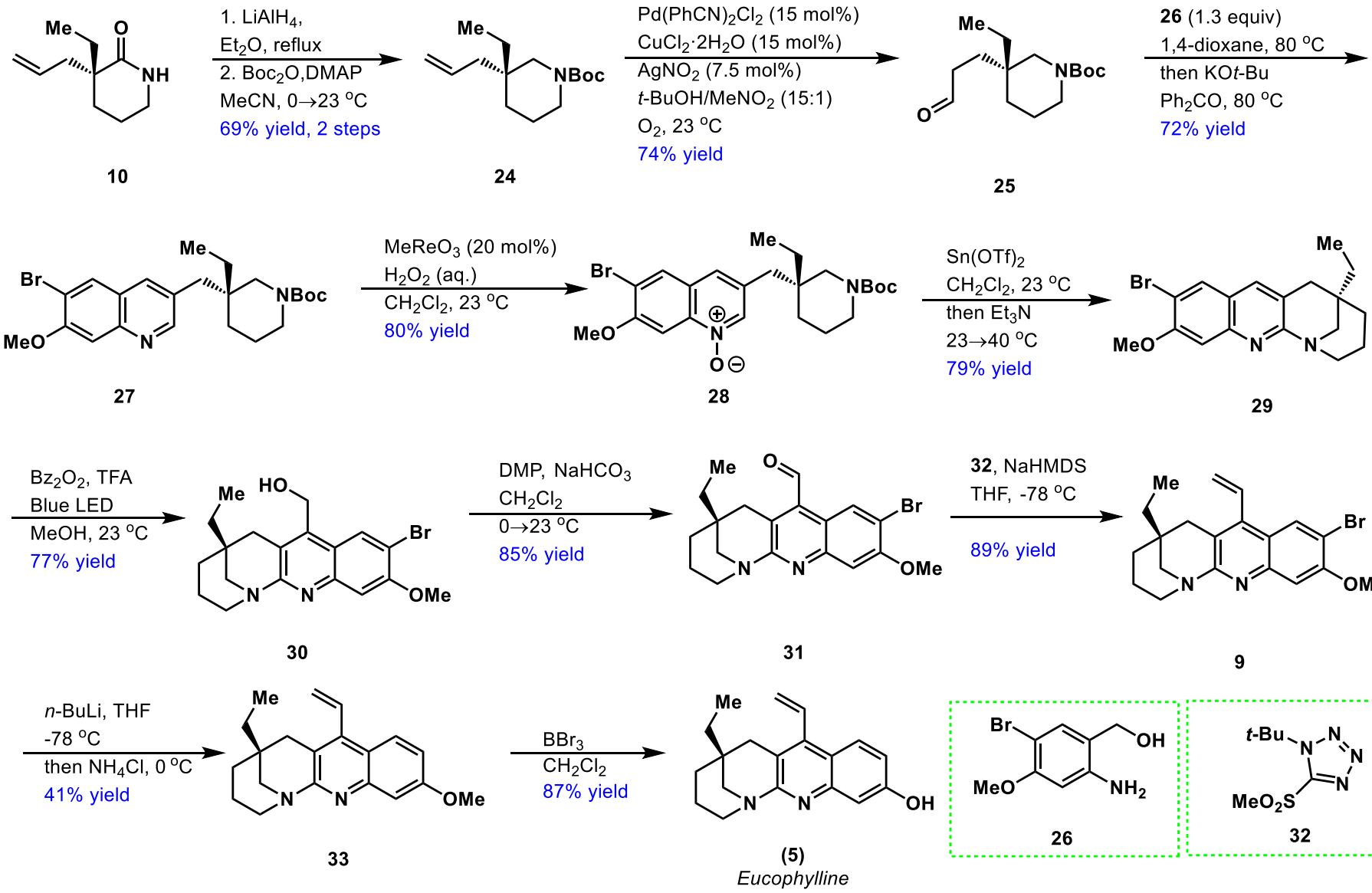
One of the *Friedel-Crafts acylation* routes toward the synthesis of isoquinolines is the *Bischler-Napieralski synthesis*. When an acyl derivative of a phenylethylamine is treated with a dehydrating agent ($POCl_3$, P_2O_5, PPA, TFAA, or Tf_2O)[6] a *cyclodehydration reaction* takes place to form a 3,4-dihydroisoquinoline derivative. If the starting compound contains a hydroxyl group in the α-position, an additional dehydration takes place yielding an isoquinoline.



Mechanism: [16,5]



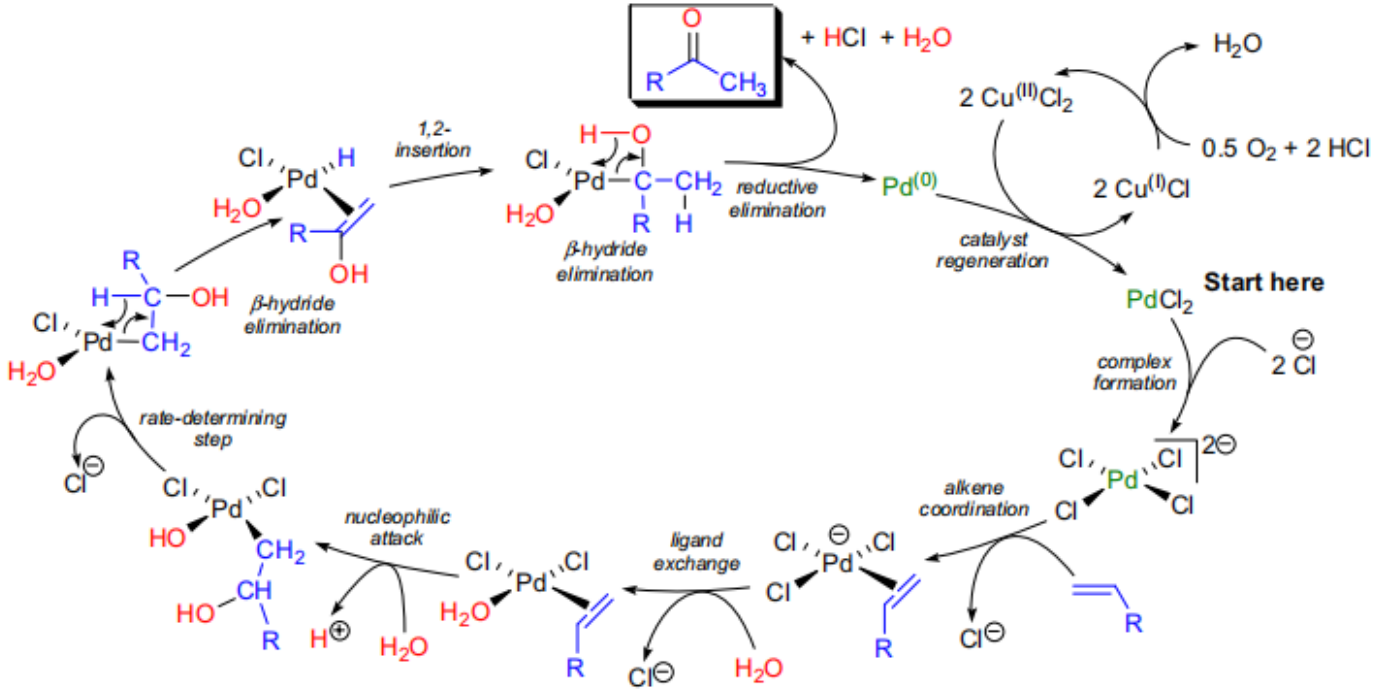

Cl
P
Cl
Cl
O
H
N
Me
MeOOC
N
21
ClO4
22


Me
O
NH
10
1. LiAlH4,
Et2O, reflux
2. Boc2O,DMAP
MeCN, 0→23 °C
69% yield, 2 steps
Me
NBoc
24
Pd(PhCN)2Cl2 (15 mol%)
CuCl2·2H2O (15 mol%)
AgNO2 (7.5 mol%)
t-BuOH/MeNO2 (15:1)
O2, 23 °C
74% yield
Me
NBoc
O
25
26 (1.3 equiv)
1,4-dioxane, 80 °C
then KOt-Bu
Ph2CO, 80 °C
72% yield
Br
MeO
N
Me
NBoc
27
MeReO3 (20 mol%)
H2O2 (aq.)
CH2Cl2, 23 °C
80% yield
Br
MeO
N
O
Me
NBoc
28
Sn(OTf)2
CH2Cl2, 23 °C
then Et3N
23→40 °C
79% yield
Br
MeO
N
N
Me
29
Bz2O2, TFA
Blue LED
MeOH, 23 °C
77% yield
Me
HO
Br
N
N
OMe
30
DMP, NaHCO3
CH2Cl2
0→23 °C
85% yield
Me
O
Br
N
N
OMe
31
32, NaHMDS
THF, -78 °C
89% yield
Me
Br
N
N
OMe
9
n-BuLi, THF
-78 °C
then NH4Cl, 0 °C
41% yield
Me
N
N
OMe
33
BBr3
CH2Cl2
87% yield
Me
N
N
OH
(5)
Eucophylline
Br
MeO
OH
NH2
26
t-Bu
N
N
N
N
MeO2S
32

Mechanism: [58-75,37,19]

Wacker Oxidation (机理书474页)

Certain steps in the mechanism of the *Wacker oxidation* are still unclear despite intensive research. One of these steps, the attack of the coordinated alkene by the nucleophile (OH^- or H_2O), could be both intra- or intermolecular as the observed rate law is consistent with either possibility. One of the plausible catalytic cycles is presented.



C)

polar attack (classic Wacker)

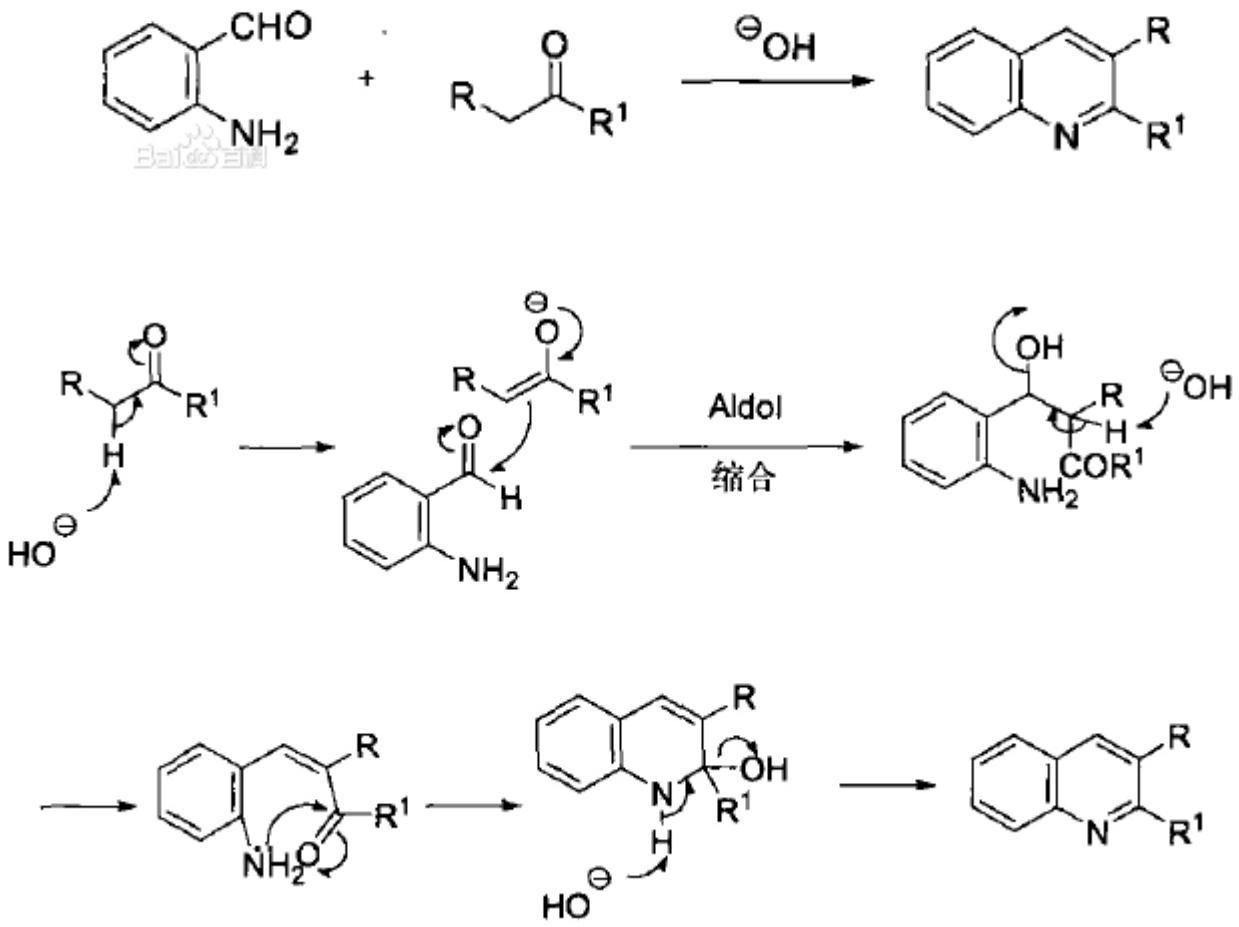
radical attack (this work?)

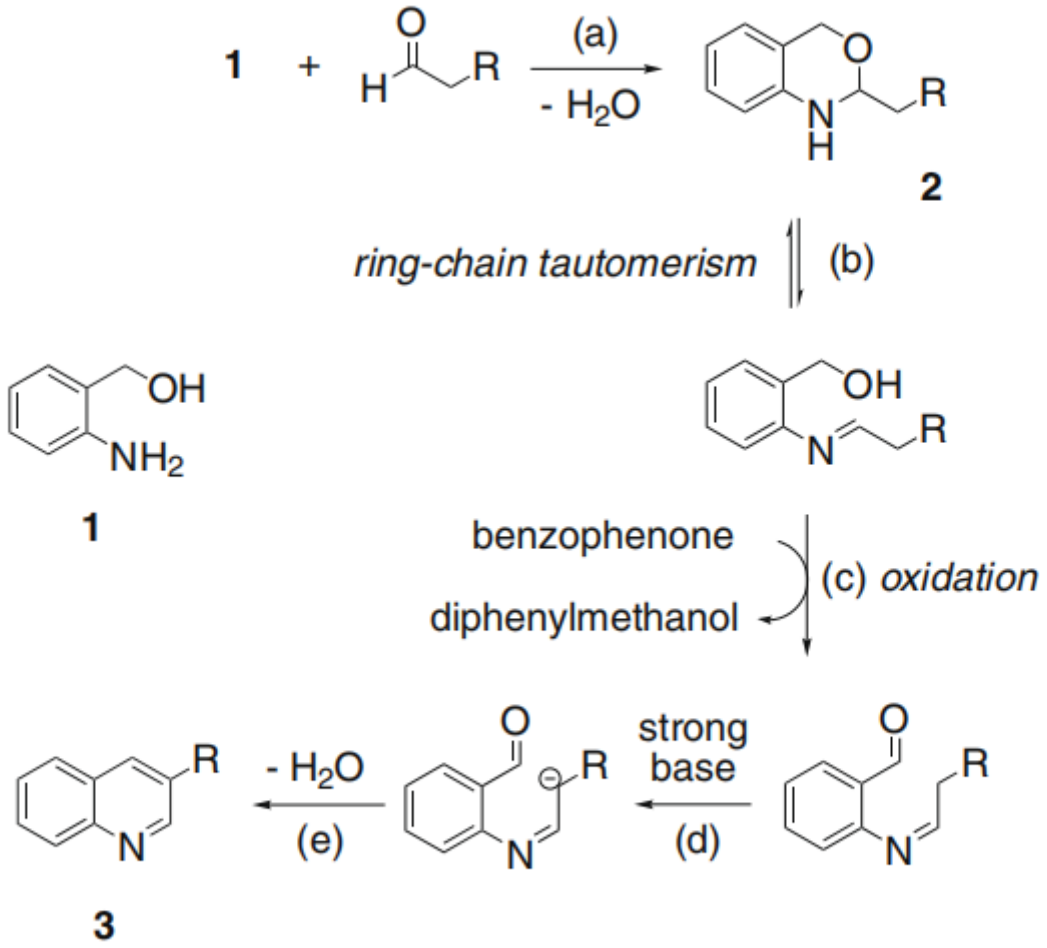
classic Wacker reverse Wacker

stability of radical provides selectivity

Angew. Chem. Int. Ed. **2013**, *52*, 11257.

Friedlander 喹啉合成



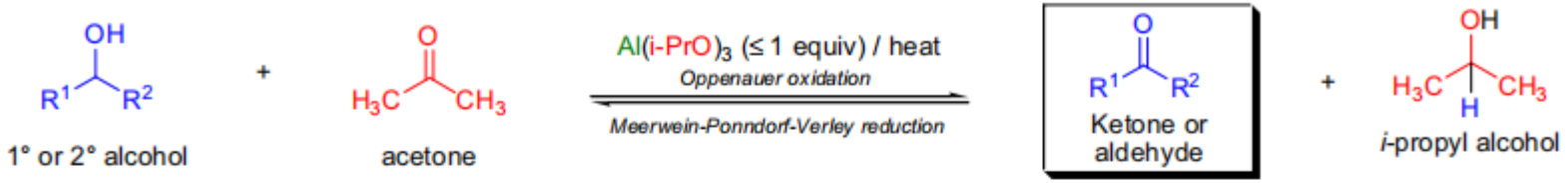


Scheme 2. General reaction mechanism.

Tetrahedron Lett. **2009**, *50*, 201.

OPPENAUER OXIDATION

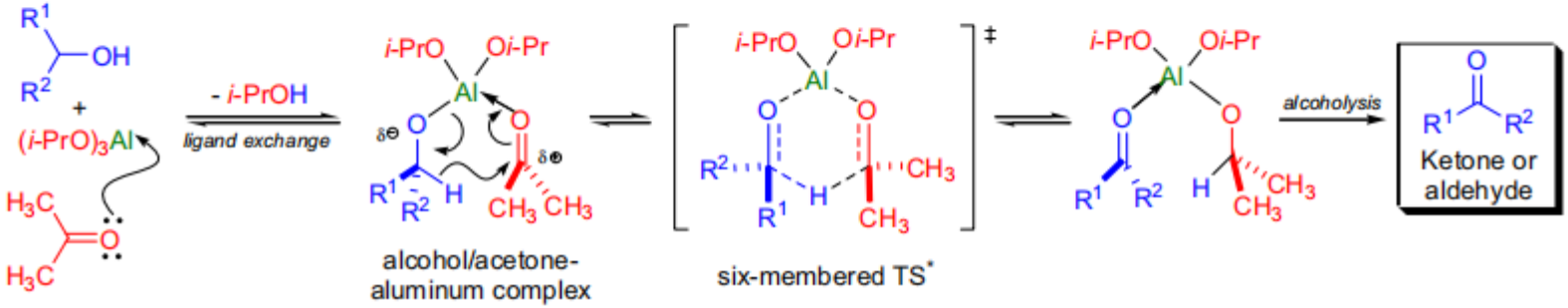
(References are on page 642)



R^1 = alkyl, aryl, alkenyl; R^2 = H, alkyl, aryl, alkenyl

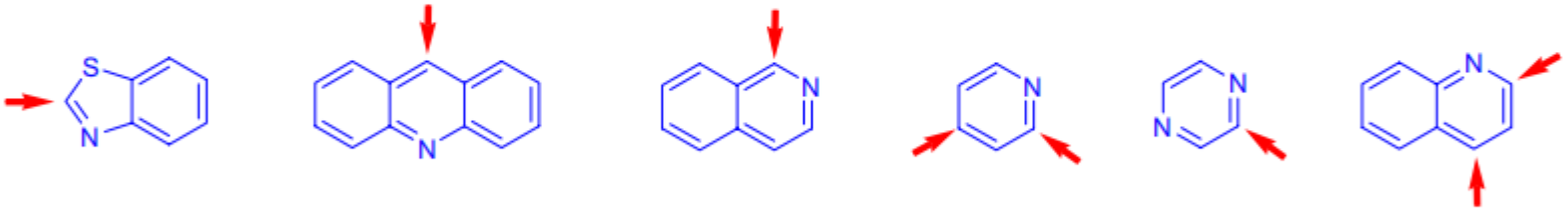
Mechanism: [24-29]

Both the oxidant carbonyl compound (acetone) and the substrate alcohol are bound to the metal ion (aluminum). The alcohol is bound as the alkoxide, whereas the acetone is coordinated to the aluminum which activates it for the hydride transfer from the alkoxide. The hydride transfer occurs *via* a six-membered chairlike transition state. The alkoxide product may leave the coordination sphere of the aluminum *via* alcoholysis, but if the product alkoxide has a strong affinity to the metal, it results in a slow ligand exchange, so a catalytic process is not possible. That is why often stoichiometric amounts of aluminum alkoxide is used in these oxidations.



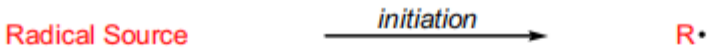
MINISCI REACTION

(References are on page 630)

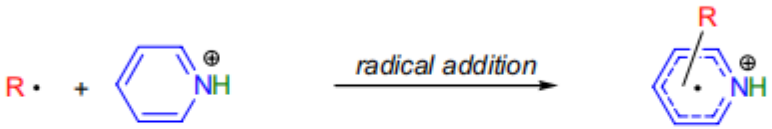


benzothiazole | acridine | isoquinoline | pyridine | pyrazine | quinoline

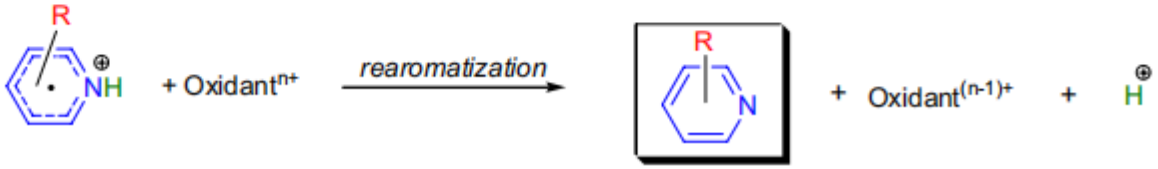
First step:



Second step:

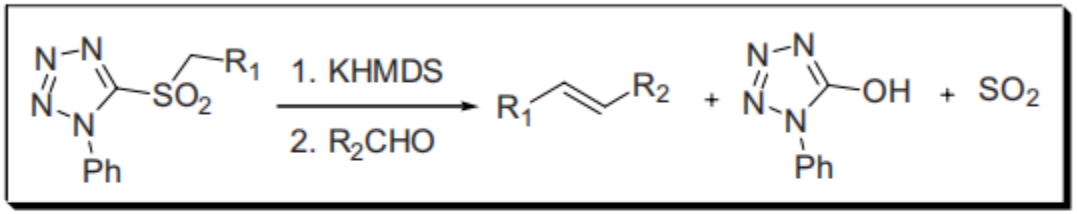


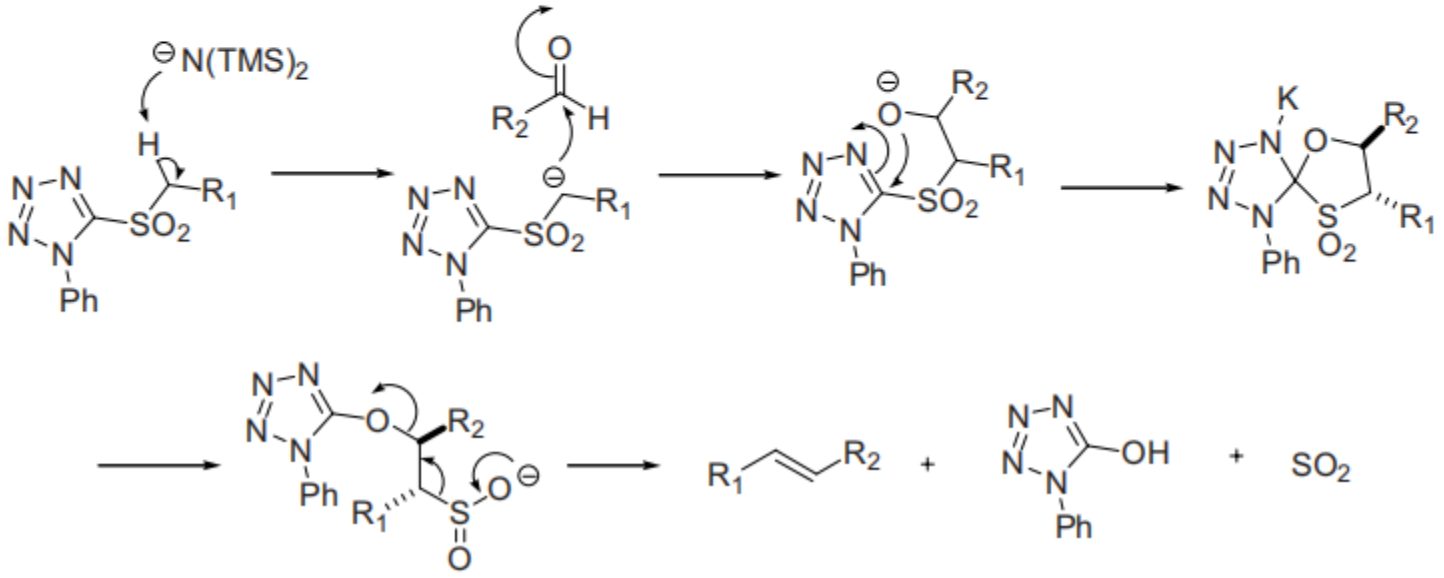
Third step:



Julia–Kocienski olefination

Modified one-pot Julia olefination to give predominantly (*E*)-olefins from heteroarylsulfones and aldehydes. A sulfone reduction step is *not* required.

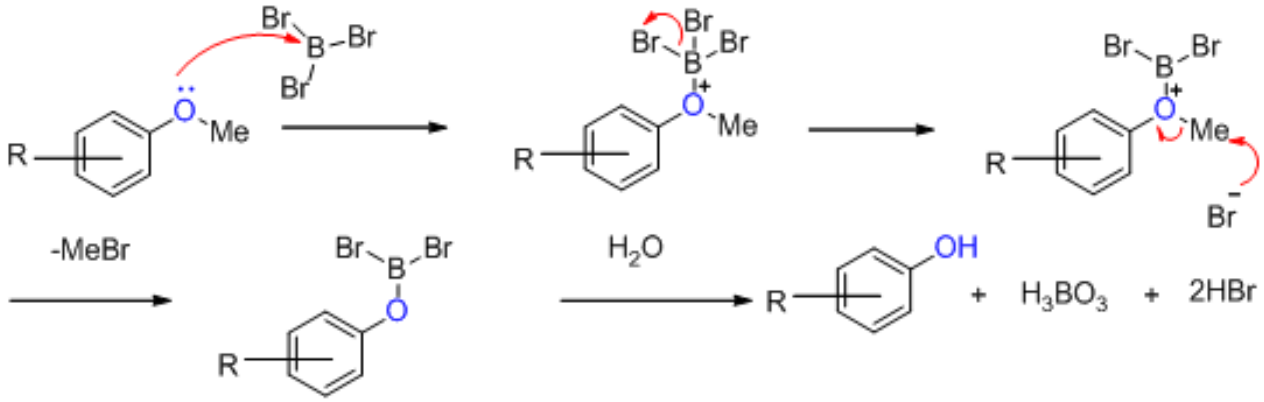




酸性条件下脱甲基

常见的酸性脱甲基试剂有三溴化硼、三氯化铝、氢溴酸、硫酸等。以三溴化硼为例：

反应机理

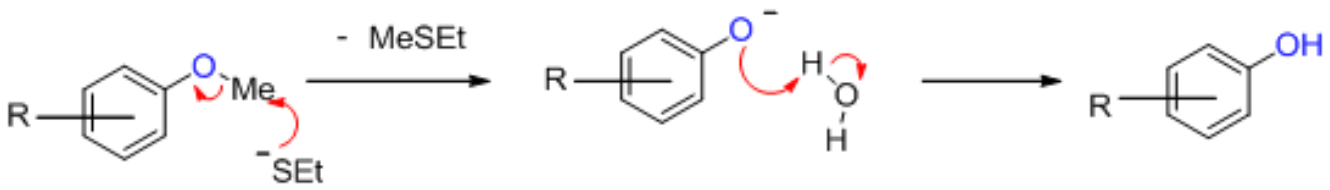


主要利用B的亲电性和Br的亲核性,常用的溶剂为二氯甲烷。

碱性条件下脱甲基

若芳基甲醚除甲氧基外其他结构对碱不敏感，对酸敏感。可以采用碱性脱甲基试剂进行脱除甲基，常见的碱性脱甲基试剂有乙硫醇钠、氨基钠等。以乙硫醇钠为例：

反应机理

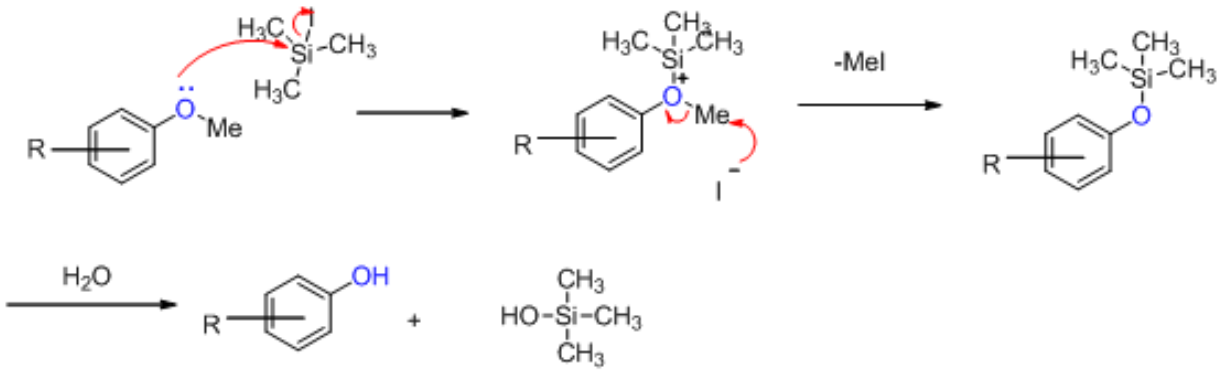


主要利用S的亲核性大于O，常用的溶剂为DMF。

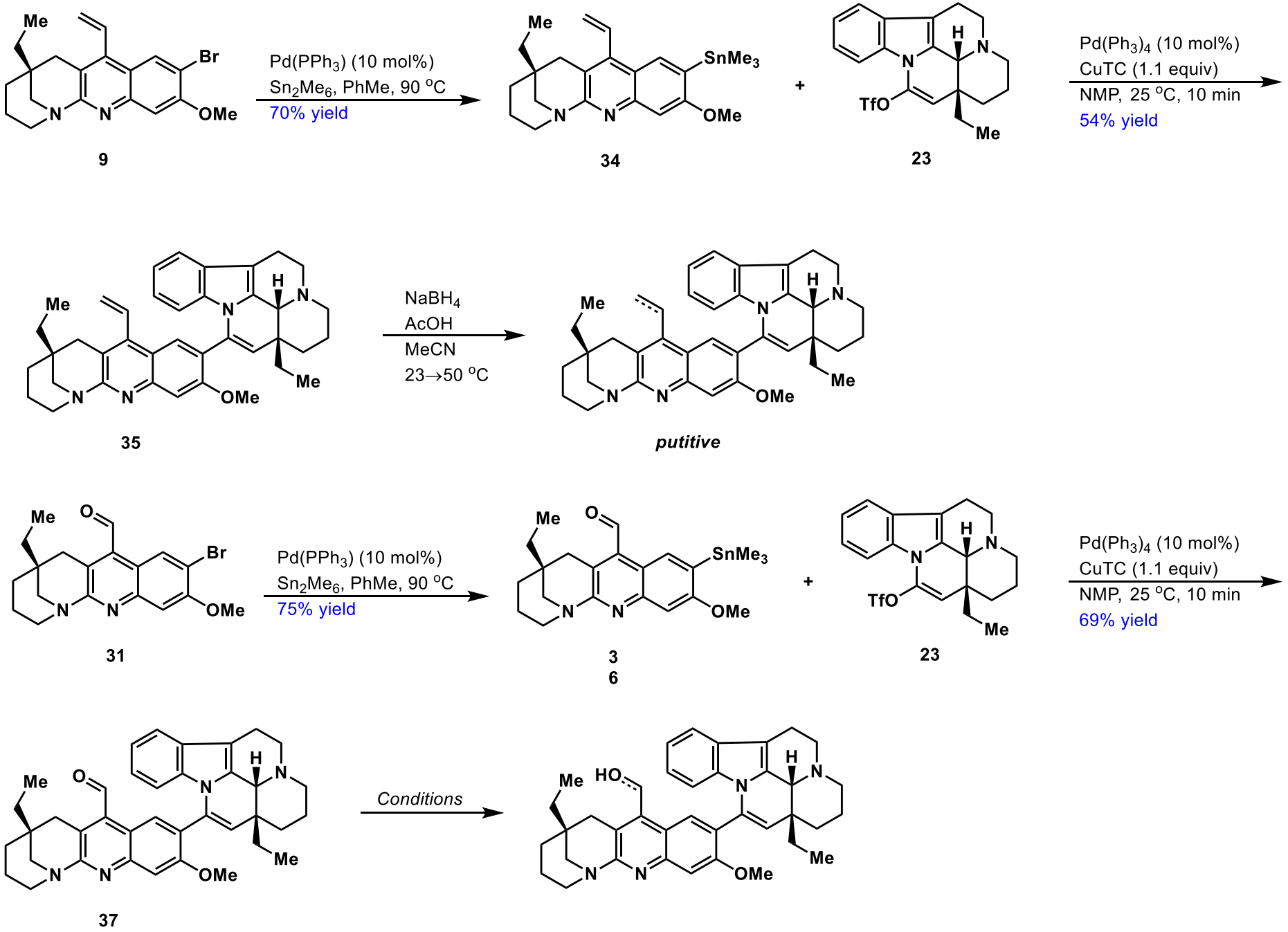
其他条件脱甲基

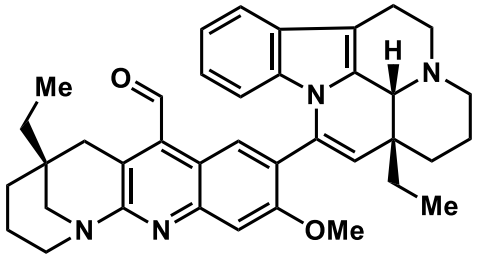
以三甲基碘硅烷为例，通过芳基甲醚与三甲基碘硅烷生成芳基硅醚，在经过水解得到脱甲基产物。

反应机理



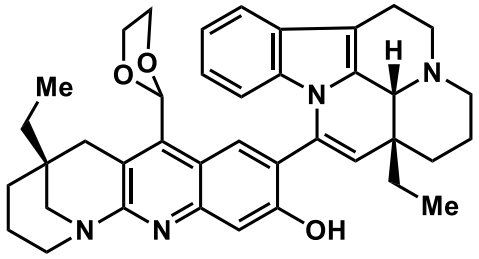
利用氧与硅的较强结合能力，以及碘的亲核性。


Me
Br
N
N
OMe
9
Pd(PPh3) (10 mol%)
Sn2Me6, PhMe, 90 °C
70% yield
Me
SnMe3
N
N
OMe
34
+
H
N
N
TfO
Me
23
Pd(Ph3)4 (10 mol%)
CuTC (1.1 equiv)
NMP, 25 °C, 10 min
54% yield
H
N
N
Me
N
N
OMe
Me
35
NaBH4
AcOH
MeCN
23→50 °C
putitive
O
31
3
6
Conditions
HO
37



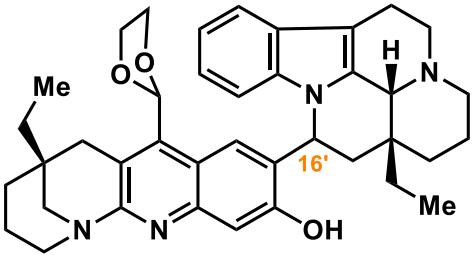
37

1. $HOCH_2CH_2OH$
$BF_3{\cdot}OEt_2$
CH_2Cl_2, 0 °C
2. NaH,EtSH
DMF, 140 °C
60% yield, 2 steps



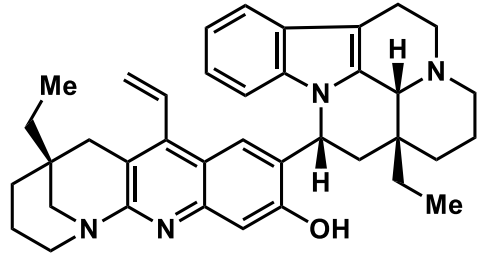
38

$[Rh(COD)(dppb)]BF_4$ (10 mol%)
H_2(20 bar), LiO*t*-Bu
MeOH, 23 °C
99% yield
>20:1 d.r. at C16'



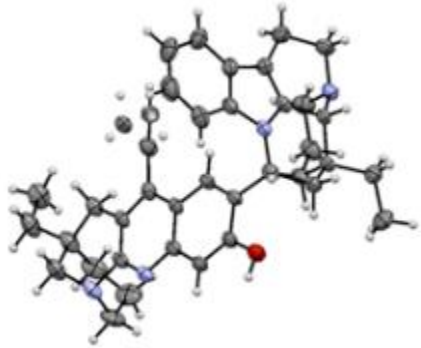
39

1. HCl (aq)
THF/H_2O (1:1), 70 °C
2. $TMSCH_2MgCl$
THF, 23 °C
3. KH, THF, 23 °C
39% yield, 3 steps



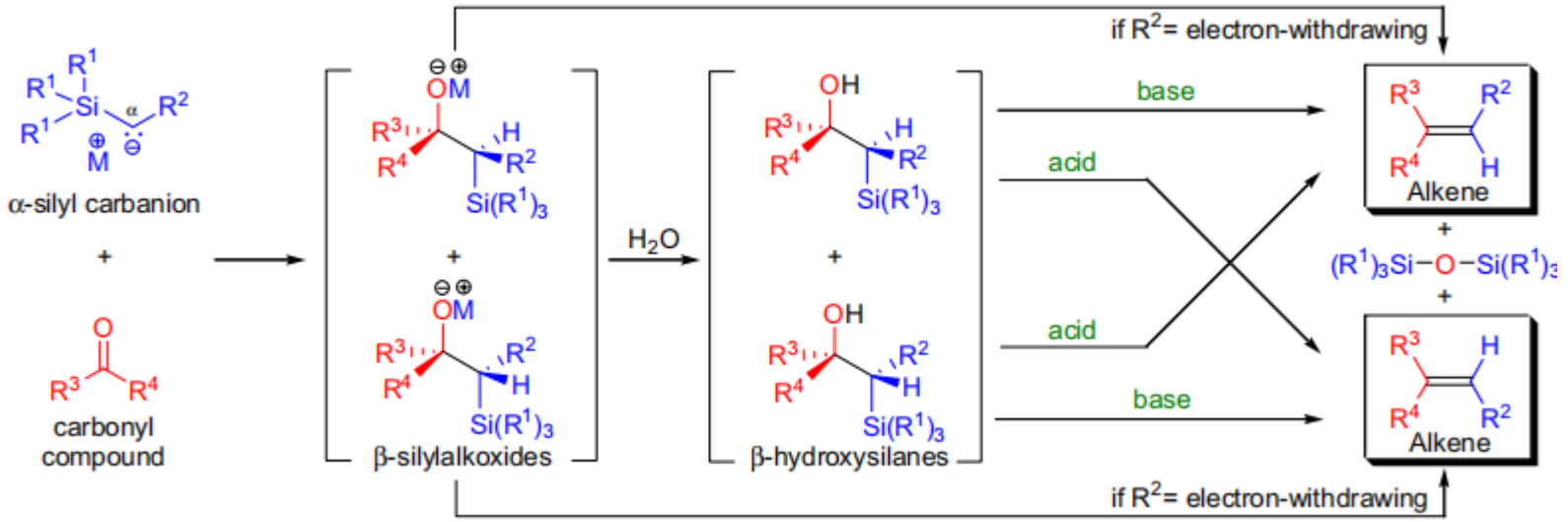
40
16'-epi-leucophyllidine

=

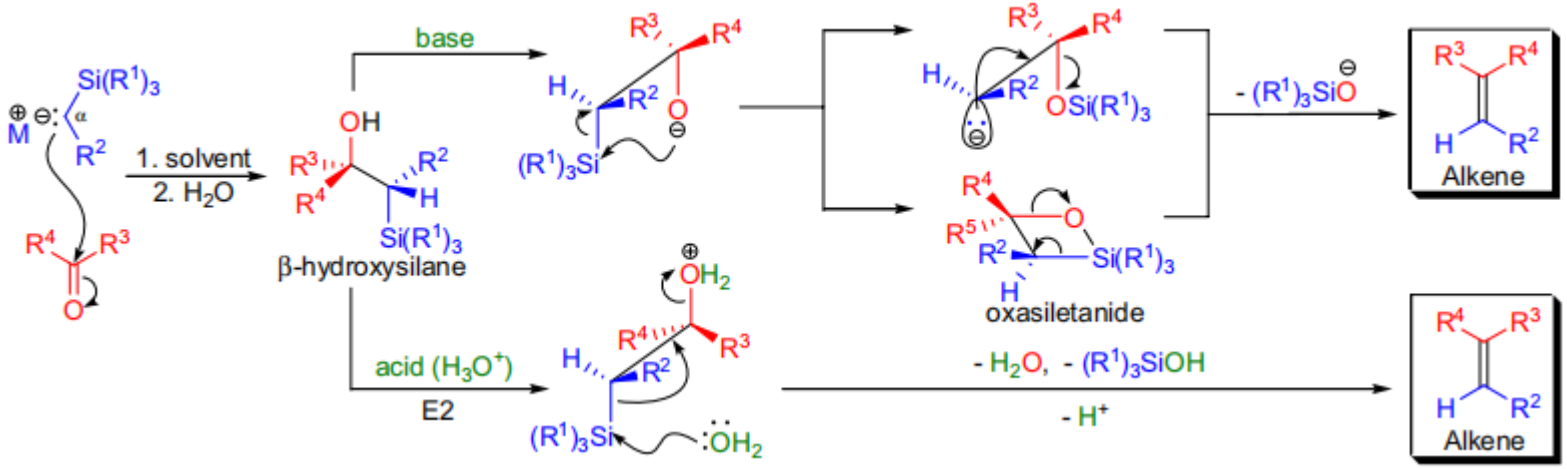


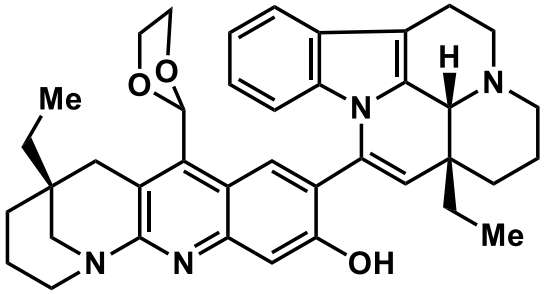
PETERSON OLEFINATION

(References are on page 650)



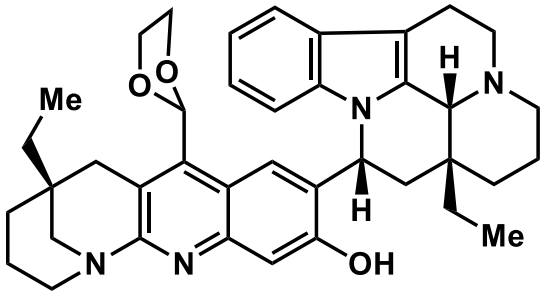
R^1=alkyl, aryl; R^2 = alkyl, aryl, CO_2R, CN, $CONR_2$, CH=NR, SR, SOR, SO_2R, SeR, SiR_3, OR, BO_2R_2; R^3,R^4=alkyl, aryl, H



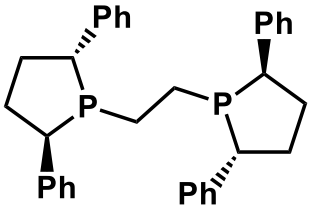


38

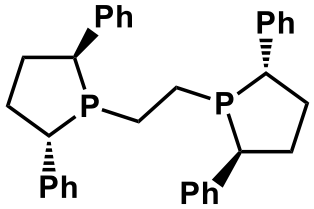
[Rh(cod)L1)]BF_4 or [Rh(cod)L2)]BF_4
H_2(20 bar), LiO*t*-Bu
MeOH, 23 ^oC



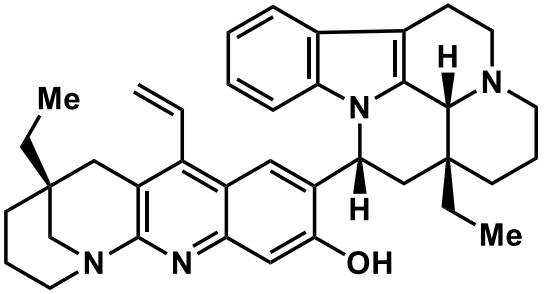
39



L1



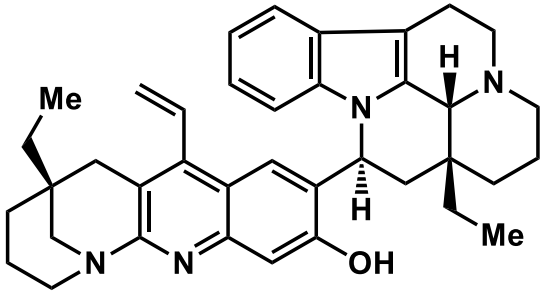
L2



40
16'-epi-leucophyllidine

Conditions

acidic,
basic,
oxidative,
photochemical



leucophyllidine(**1**)