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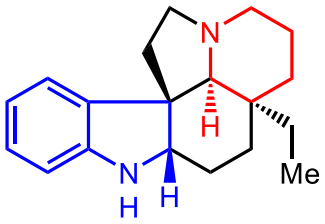
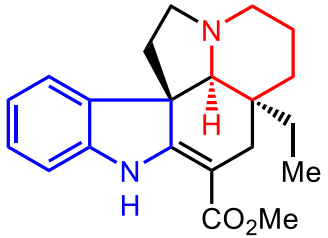
Aza-Achmatowicz rearrangement coupled with intermolecular aza-Friedel–Crafts enables total syntheses of uleine and aspidosperma alkaloids†

Foqing Ma, Yunlong Li, Kornkamon Akkarasereenon, Huiying Qiu, Yuen Tsz Cheung, Zhihong Guo and Rongbiao Tong *

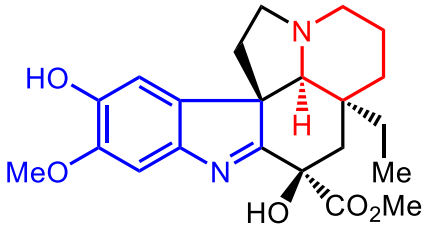
(a) Selected aspidosperma alkaloids



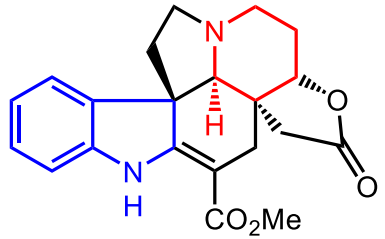
Aspidospermidine



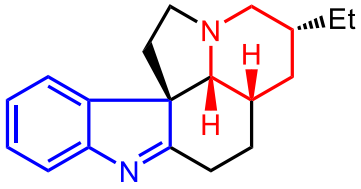
Tabersonine



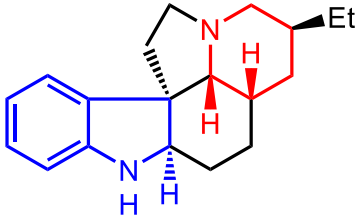
Jerantinine H



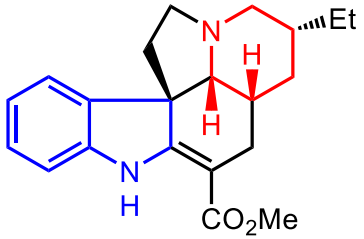
Apodine



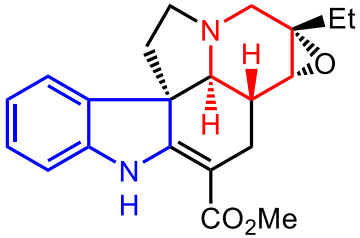
1,2-Didehydropseudo-aspidospermidine



20-*epi*-Pseudo-aspidospermidine

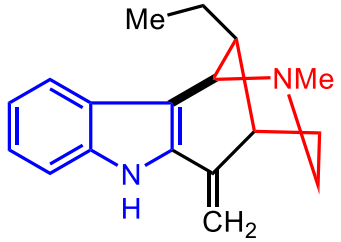


Pseudovincadifformine

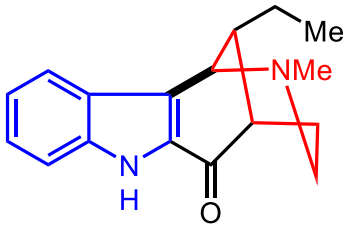


Vidolicine

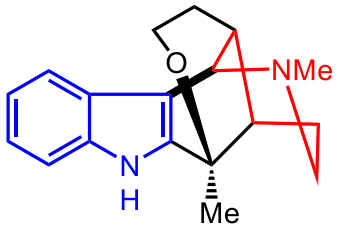
(b) Selected uleine alkaloids



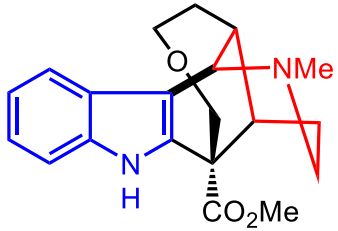
Uleine



3-*epi*-Dasycarpidone

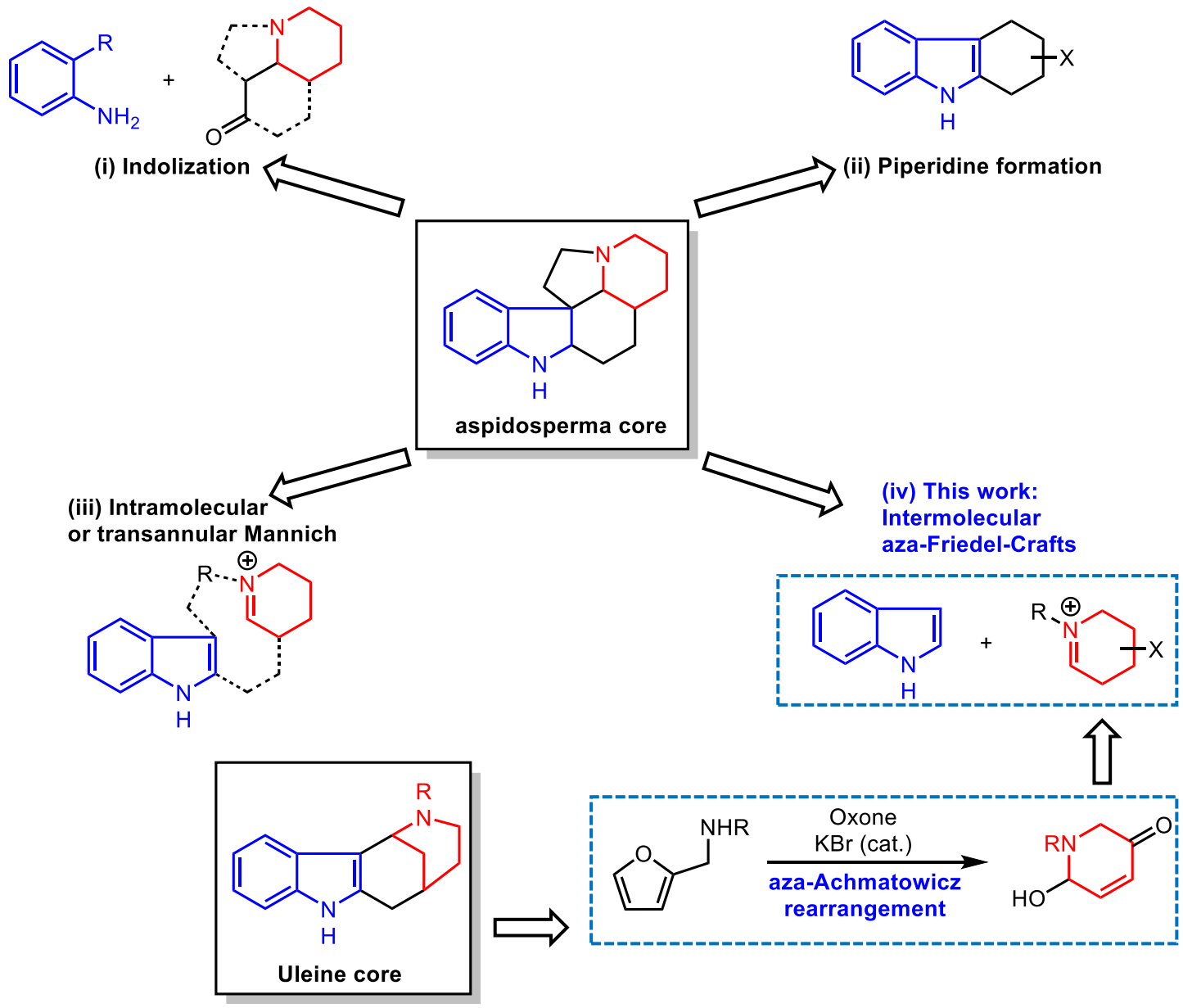


Gilbertine

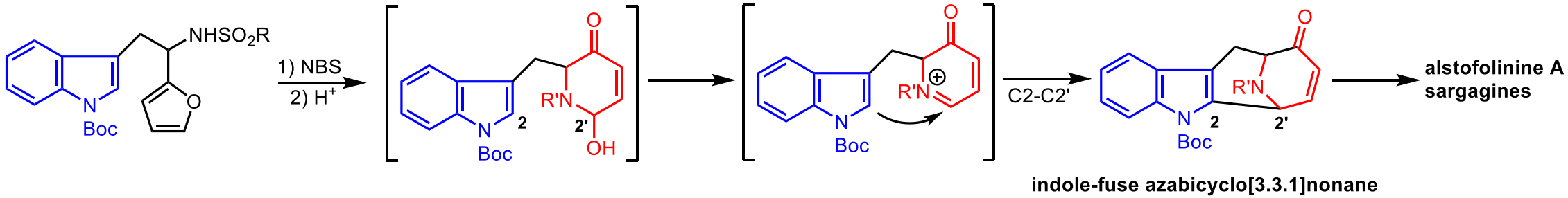


Undolifoline

(c) Representative previous synthetic strategies and our work



(d) Qi's intramolecular reaction of indole with 3-piperidinone hemiaminal (refs. 83-84)



ref 83: *Angew. Chem. Int. Ed.*, **2019**, *58*, 4988.
ref 84: *Angew. Chem. Int. Ed.*, **2023**, *62*, e202304435.

(e) Our hypothesis (Aza-Achmatowicz rearrangement is coupled with intermolecular aza-Friedel-Crafts reaction)

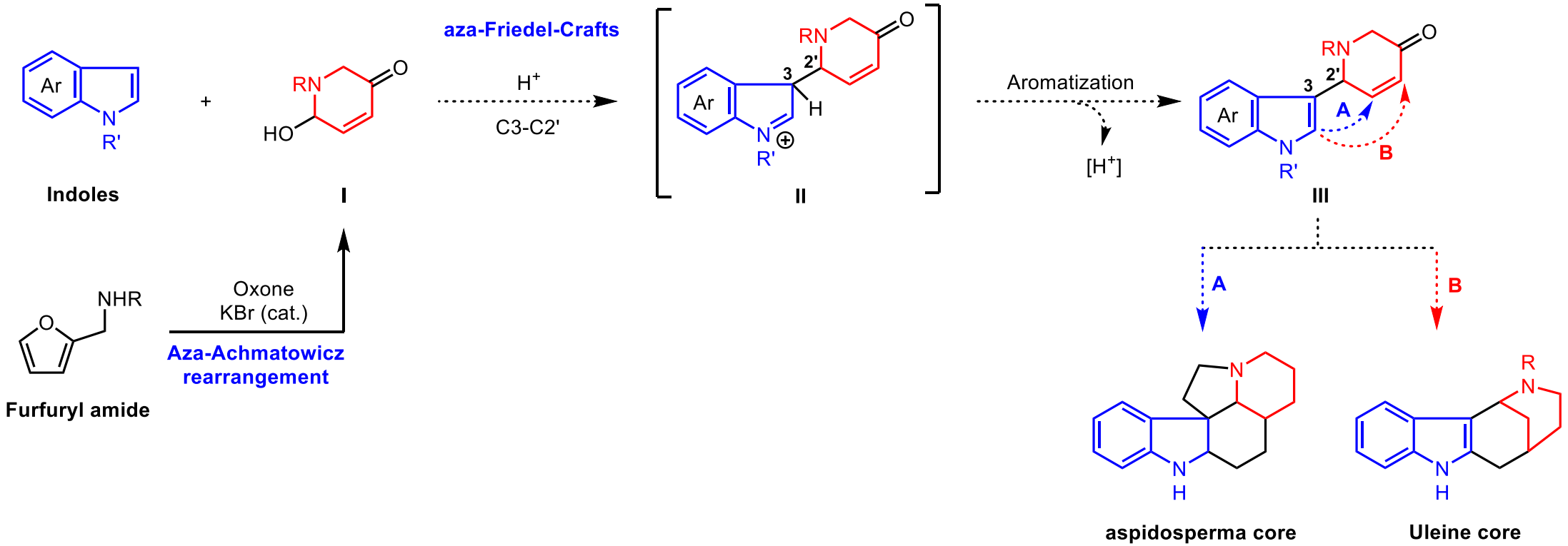
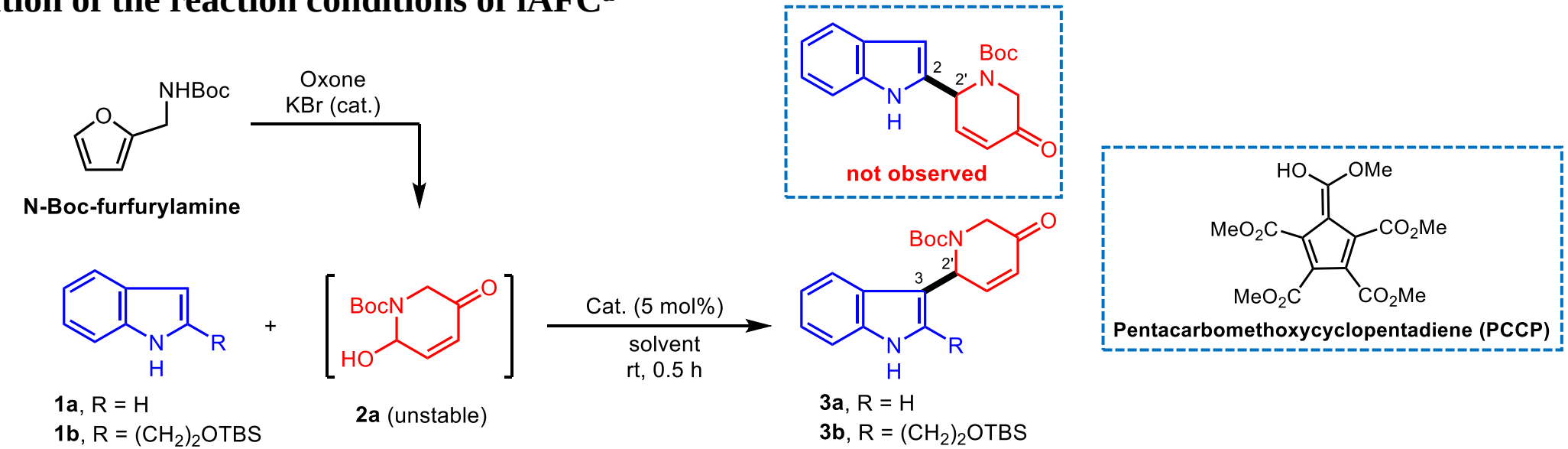


Table 1 Optimization of the reaction conditions of iAFC[a]



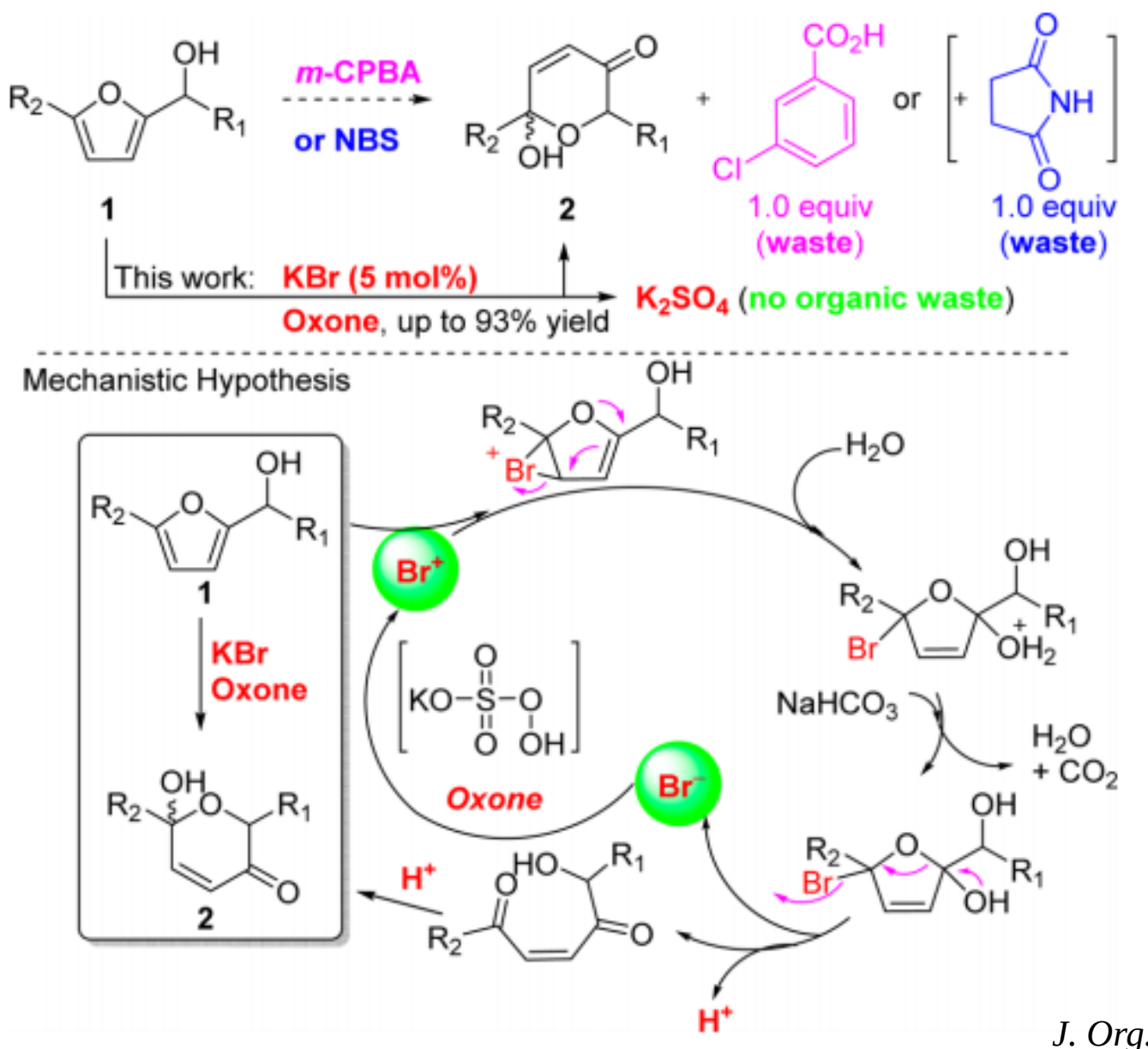
Entry	1a/1b	Catalyst	Solvent	Yield (%)
1	**1a**	TFA	DCM	82
2	**1a**	TFA	PhMe	88
3	**1a**	TFA	MeOH	78
4	**1a**	TFA	DCE	85
5	**1a**	TFA	THF	81
6	**1a**	TFA	EtOAc	86
7	**1a**	TFA	$CHCl_3$	88
8	**1a**	BF_3–Et_2O	DCM	60
9	**1a**	PCCP	PhMe	90

1b was not fully consumed

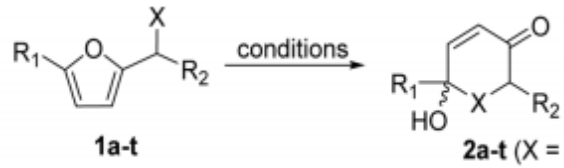
10	**1b**	TFA	DCM	35
11	**1b**	(−)-CSA	DCM	37
12	**1b**	F_2CHCO_2H	DCM	42
13	**1b**	*p*TSA·H_2O	DCM	40
14	**1b**	$ClCH_2CO_2H$	DCM	Trace
15	**1b**	Cl_2CHCO_2H	DCM	40
16	**1b**	Cl_3CCO_2H	DCM	24
17	**1b**	—	HFIP	10
18	**1b**	PCCP	DCM	58

[a] Conditions: **1a**/**1b** (0.1 mmol), **2a** (0.12 mmol), acid (0.005 mmol), solvent (0.05-0.2 M), room temperature, 0.5-12 h. Yield was determined by ^{1}H NMR analysis using dibromomethane as the internal standard. PCCP: pentacarbomethoxycyclopentadiene.

Achmatowicz Rearrangement

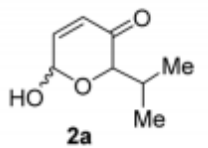


J. Org. Chem., **2016**, *81*, 4847.

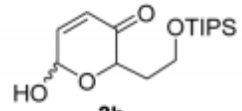


1a-t **2a-t** (X = O or N)

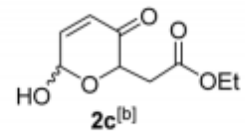
Method A: KBr (5 mol%), Oxone (1.2 eq), $NaHCO_3$ (0.5 eq) in THF/H_2O (4/1) at 0°C
Method B: NBS (1.2 eq), $NaHCO_3$ (2 eq), NaOAc (1 eq) in THF/H_2O (4/1) at 0°C
Method C: *m*-CPBA (1.2 eq) in DCM at 0°C



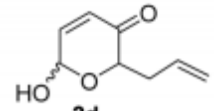
2a
A: 92%/0.5 h
B: 79%/0.5 h
C: 77%/2 h



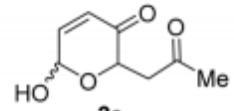
2b
A: 85%/0.5 h
B: 78%/0.5 h
C: 67%/3 h



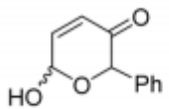
2c[b]
A: 78%/3 h
B: 75%/2 h
C: 82%/1 h



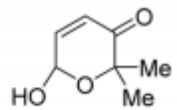
2d
A: 75%/0.5 h
B: 60%/3 h
C: 82%/3 h



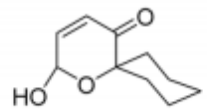
2e
A: 88%/0.5 h
B: 81%/0.5 h
C: 73%/4 h



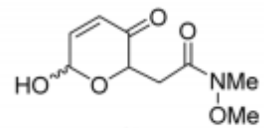
2f
A: 80%/0.5 h
B: 87%/0.5 h
C: 79%/1 h



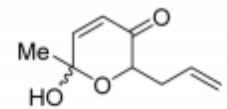
2g
A: 87%/0.5 h
B: 80%/0.5 h
C: 72%/3 h



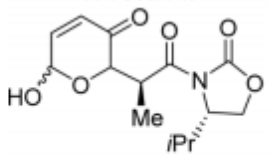
2h
A: 81%/0.5 h
B: 78%/1 h
C: 76%/4 h



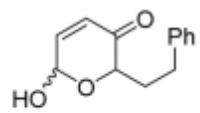
2i
A: 90%/1 h
B: 76%/4 h
C: 85%/3 h



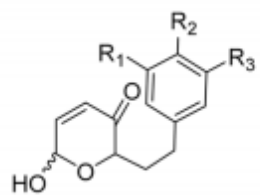
2j
A: 83%/0.5 h
B: 68%/0.5 h
C: 79%/3 h



2k
A: 90%/0.5 h
B: 85%/0.5 h
C: 78%/4 h



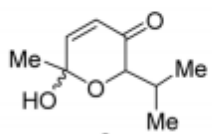
2l
A: 88%/0.5 h
B: 73%/0.5 h
C: 82%/2 h



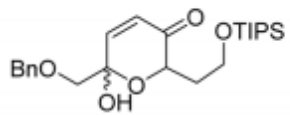
2m: R_1= H
R_2 = OMe
R_3 = OTIPS
A: 91%/1 h
B: 90%/0.5 h
C: 82%/3 h

2n
R_1= R_3 = H
R_2 = OTIPS
A: 89%/1 h
B: 80%/1 h
C: 78%/3 h

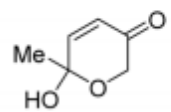
2o
R_1= R_2 = R_3 = OMe
A: 74%/0.5 h
B: 78%/0.5 h
C: 72%/3 h



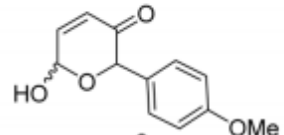
2p
A: 86%/0.5 h
B: 92%/0.5 h
C: 84%/1 h



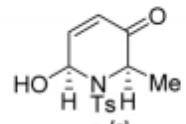
2q
A: 83%/0.5 h
B: 79%/0.5 h
C: 91%/1 h



2r
A: 85%/0.5 h
B: 78%/0.5 h
C: 80%/2 h



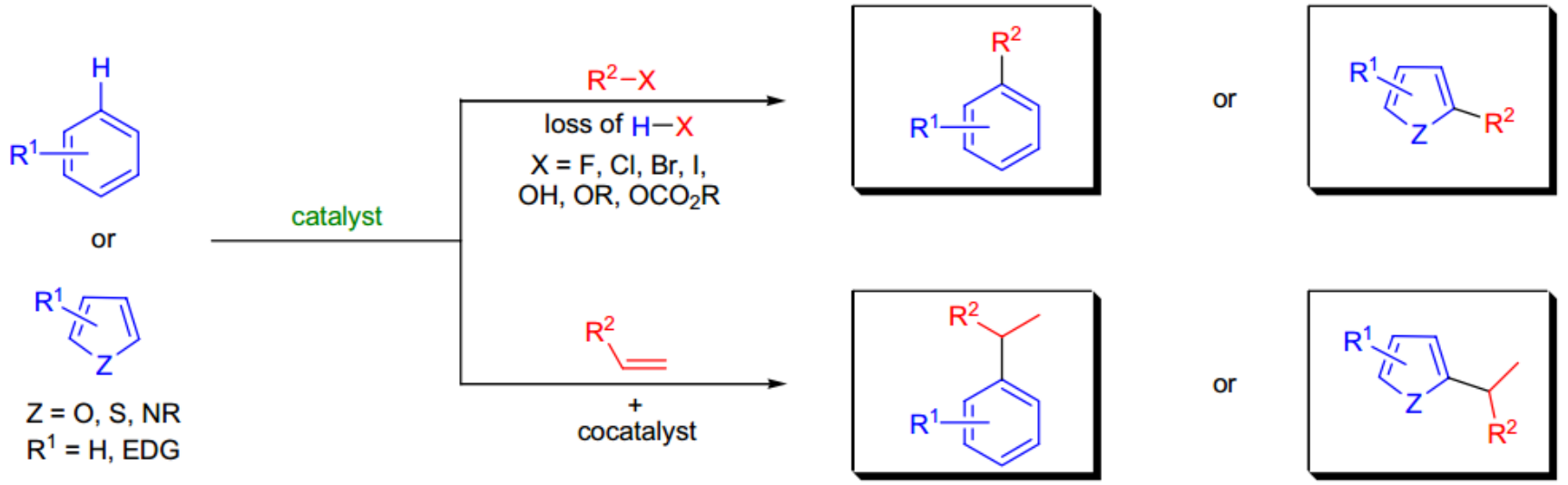
2s
A: 93%/0.5 h
B: 82%/0.5 h
C: 85%/4 h



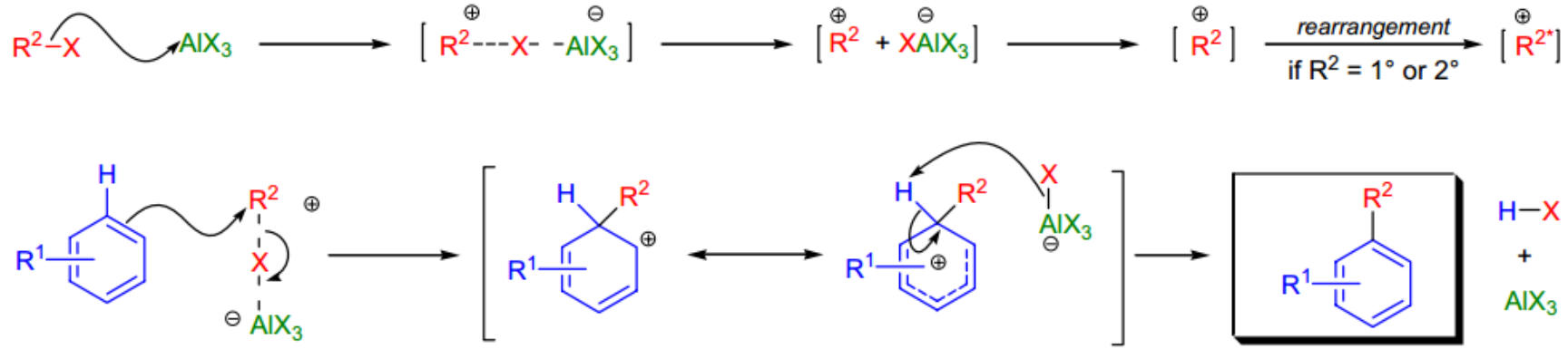
2t[c]
A: 86%/1 h
B: 69%/0.5 h
C: 74%/3 h

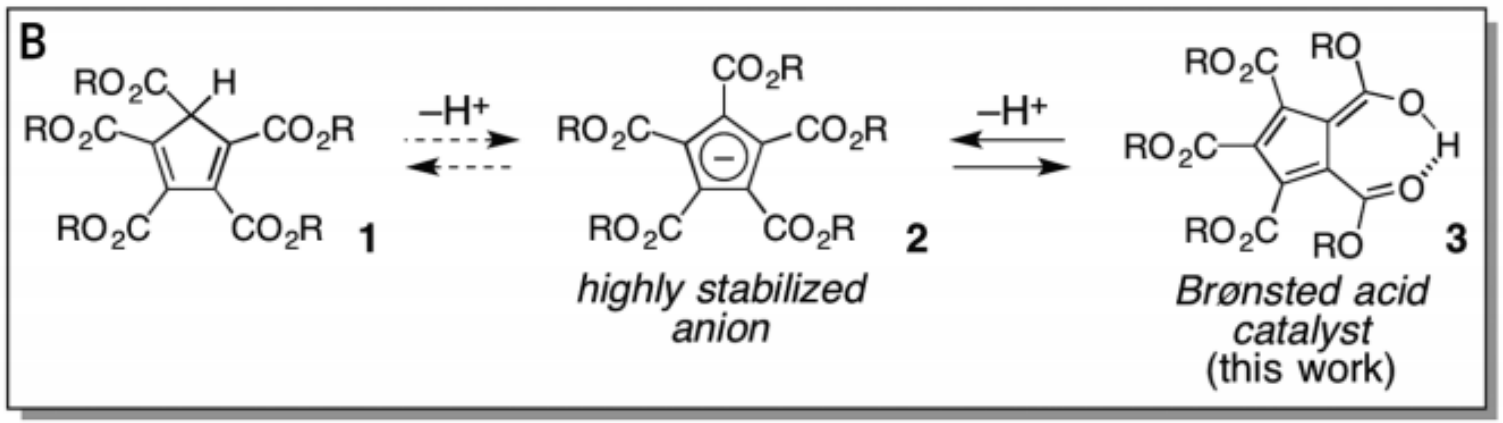
[a]Isolated yield. [b]Reaction was carried out with KBr (20 mol %), Oxone (1.2 equiv), and $NaHCO_3$ (0.5 equiv) in a mixture of THF and H_2O (4/1) at 0 °C. [c]Reaction was carried out with KBr (5 mol %), Oxone (1.2 equiv), and $NaHCO_3$ (2 equiv) in a mixture of THF and H_2O (4/1) at 0 °C.

FRIEDEL-CRAFTS ALKYLATION



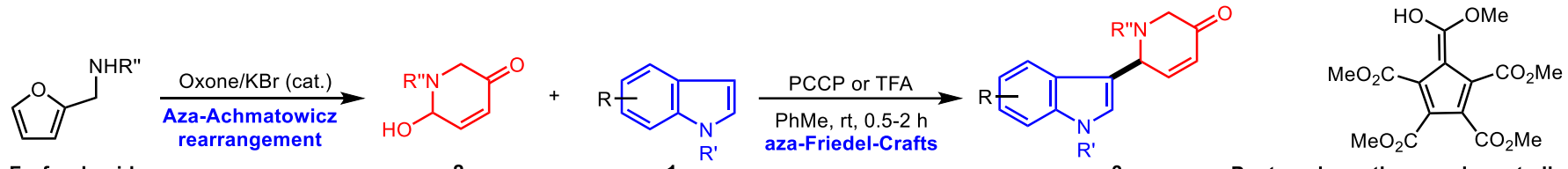
Mechanism: [46-54]





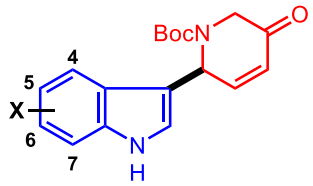
Science, **2016**, *351*, 961.

Table 2 Aza-Friedel-Crafts reaction of indoles (1) with AAR products (2)[a]

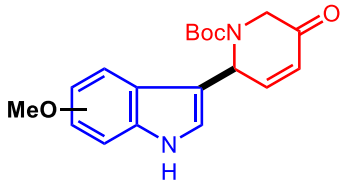


Furfurylamide

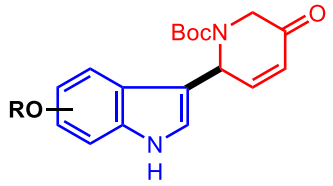
Pentacarbomethoxycyclopentadiene (PCCP)



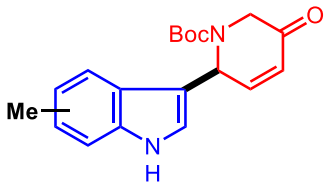
3c (6-F), 85% (79%)
3d (5-Cl), 92% (87%)
3e (4-Br), 92% (79%)
3f (6-Br), 88% (84%)



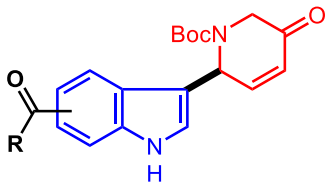
3g (4-OMe), 78% (66%)
3h (5-OMe), 79% (57%)
3i (6-OMe), 85% (50%)
3j (7-OMe), 83% (85%)



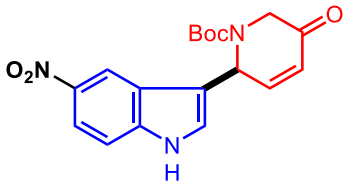
3k (4-OAc), 89%
3l (5-OAc), 84%
3m (4-OH), 38% (73%)
3n (5-OH), 0% 0%)



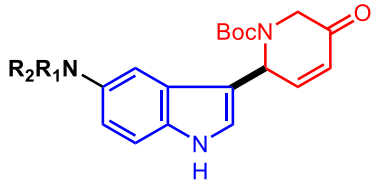
3o (4-OAc), 83%
3p (5-OAc), 80%



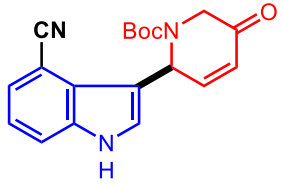
3q (4-CHO), 87% (62%)
3p (7-CHO), 64% (<10%)
3m (5-CO_2Me), 58%



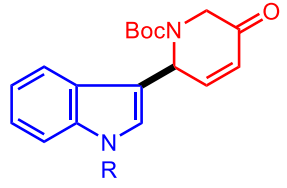
3t, 64%



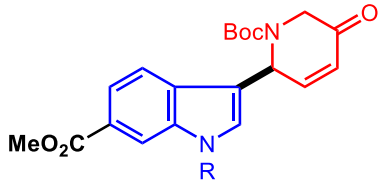
3u (NHTs), 43%
3v (NMe_2), 0%



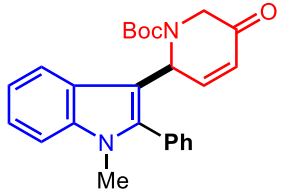
3w, 95% (64%)



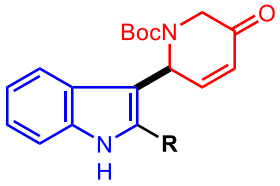
3x (R = Me), 85%
3y (R = Bn), 82%
3z (R = Boc), 0%
3aa (R = Ts), 0%



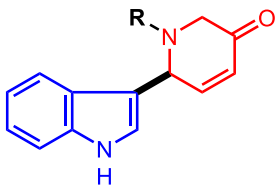
3ab, 87% (49%)



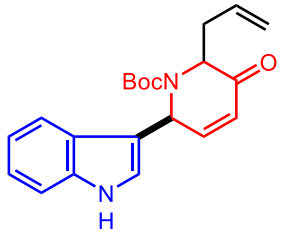
3ac, 50%



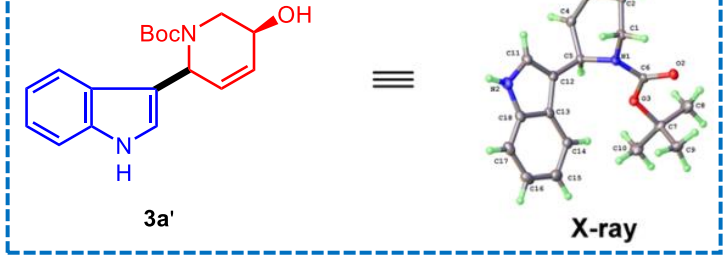
3ad (R = CH_2OAc),83%
3ae [R = $(CH_2)_2I$], 68%
3af (R = Me), 91%
3ag (R = vinyl), 95%



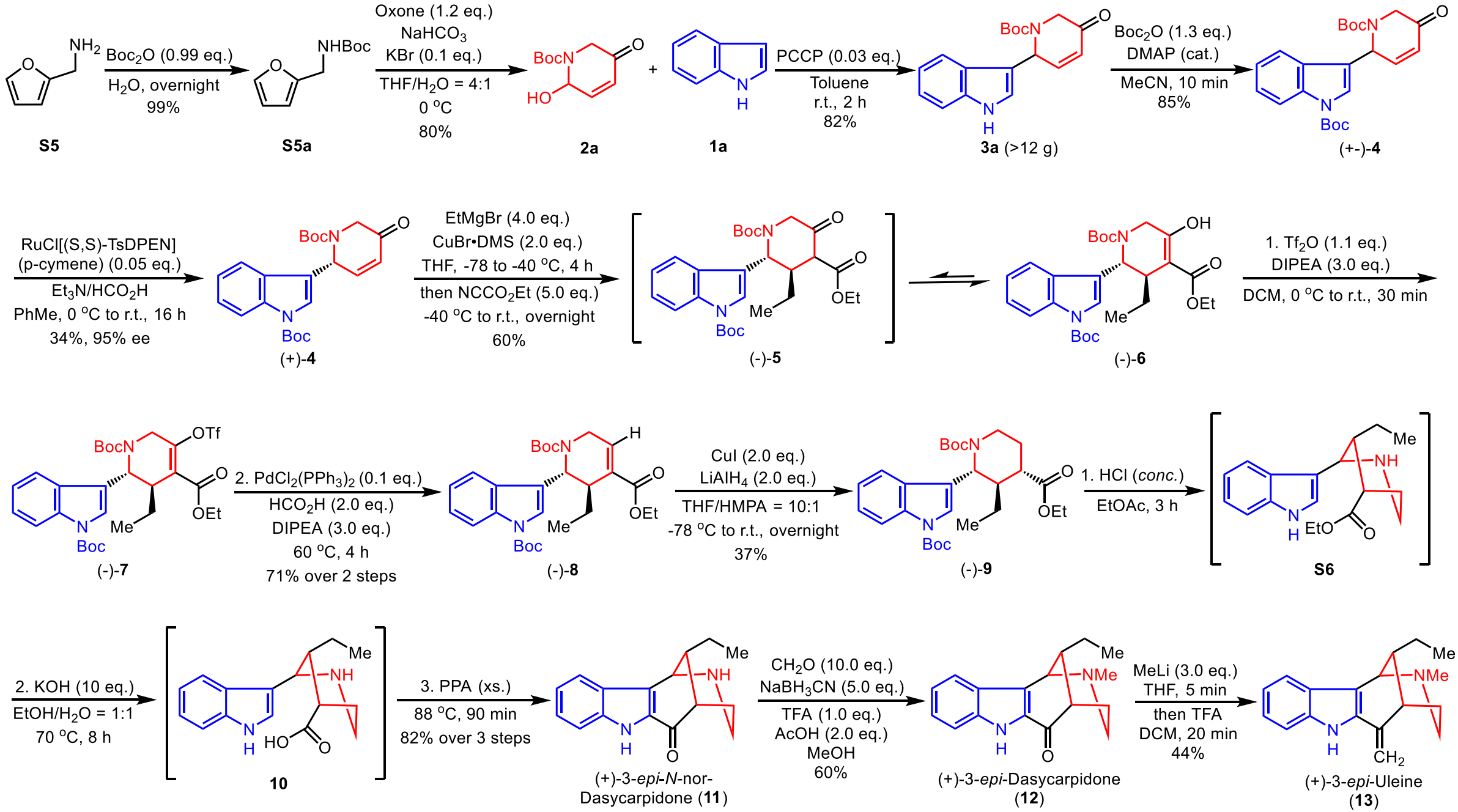
3ah (R = Ts),90%
3ai (R = o-Ns), 98%



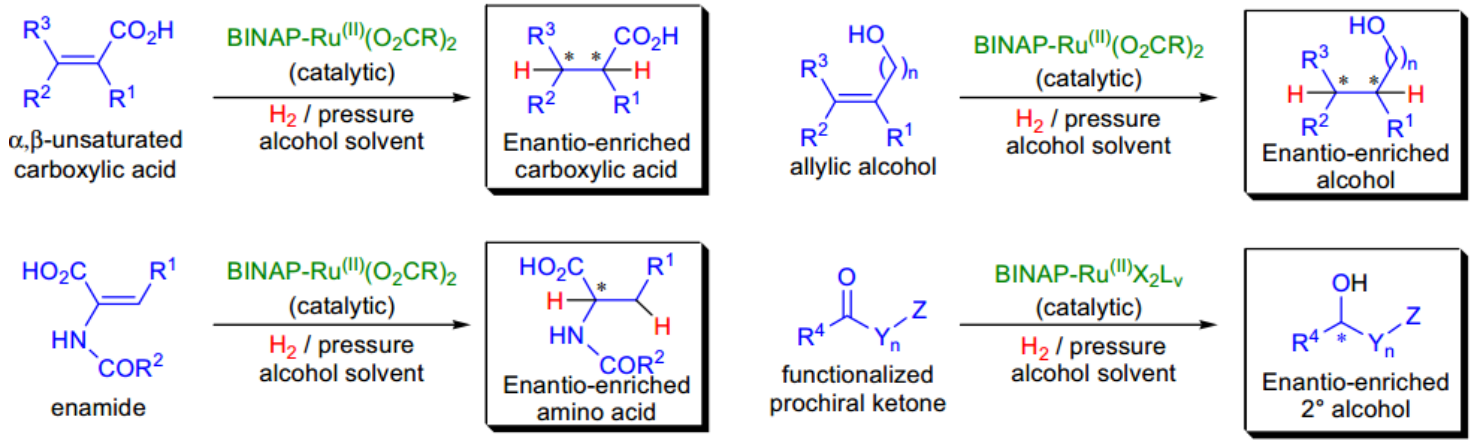
3aj, 72%



Total synthesis of uleine-type alkaloids

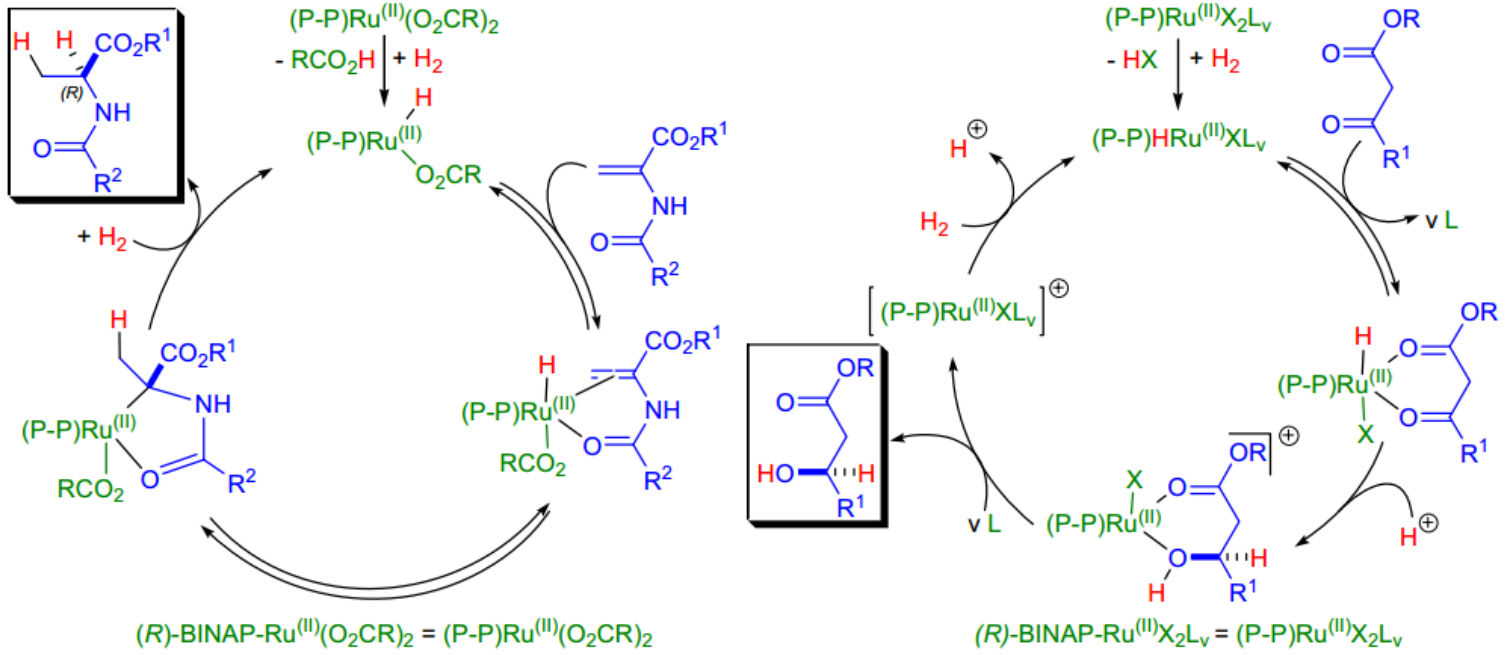


NOYORI ASYMMETRIC HYDROGENATION

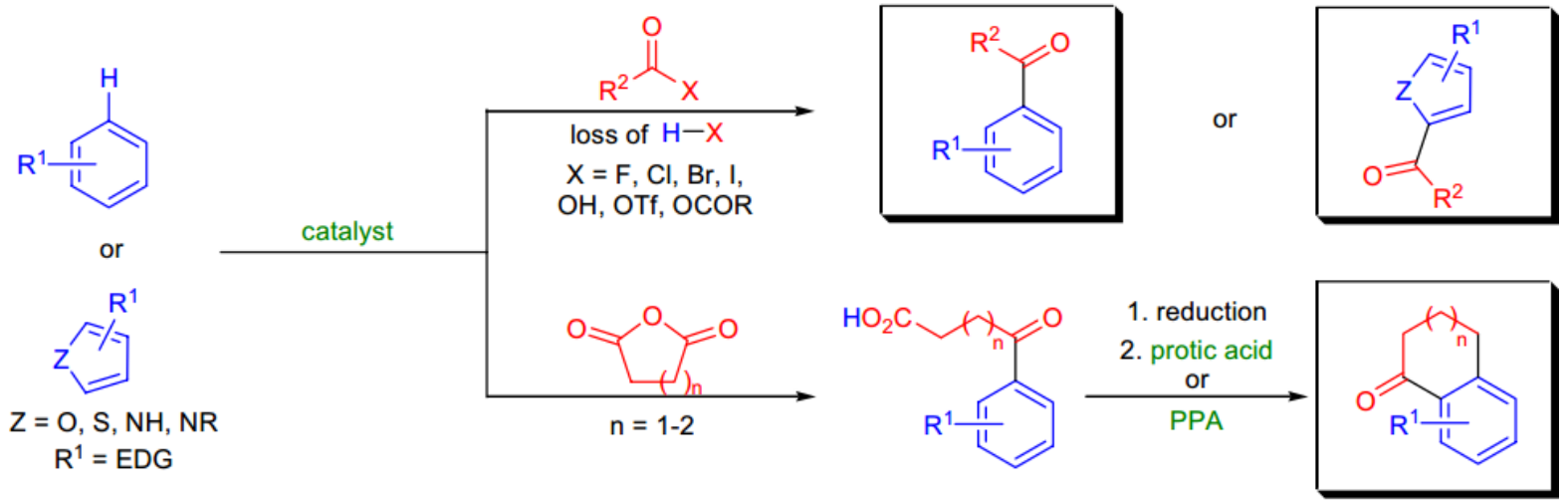


$R^{1\text{-}3}$ = H, alkyl, aryl; R^4 = alkyl, aryl; Z = nitrogen, oxygen, halogen; Y = sp^2 or sp^3 hybridized carbon; n =1-3; X = halogen; L = neutral ligand or solvent; R = alkyl, aryl

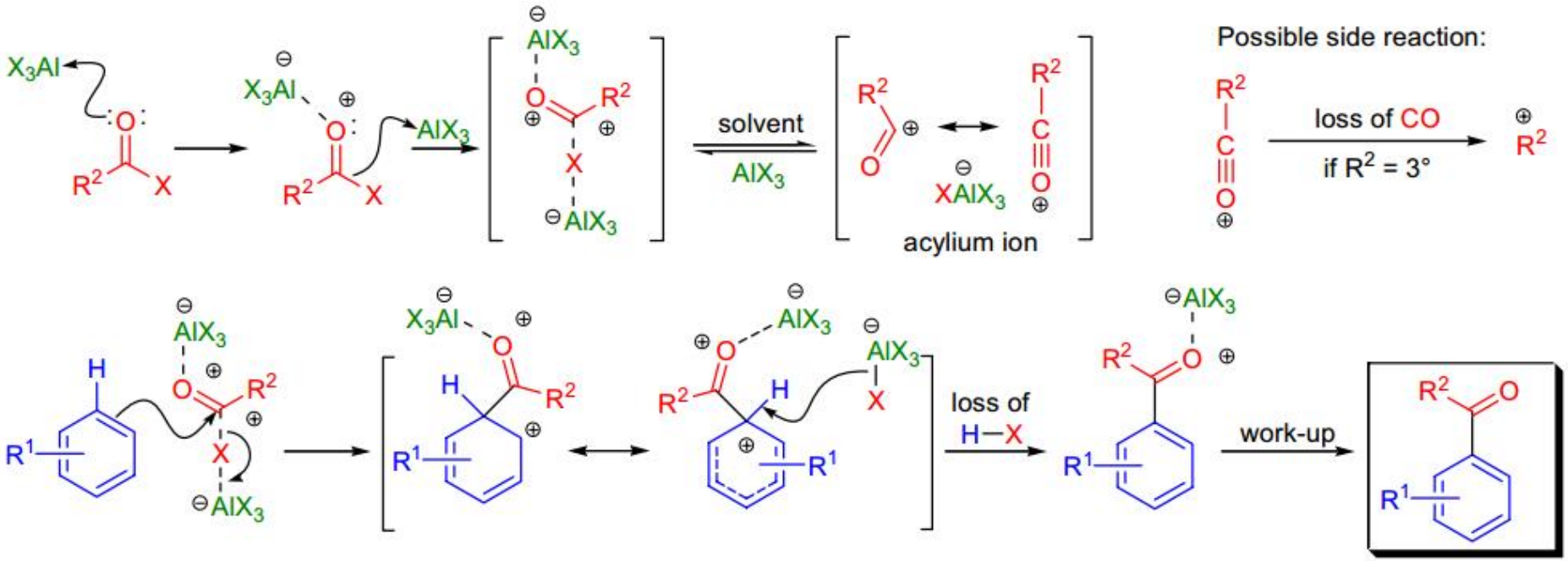
Mechanism: [1,49-64]



FRIEDEL-CRAFTS ACYLATION

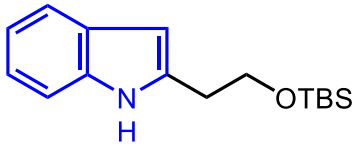


Mechanism: [4,42-47]



Total synthesis of aspidosperma alkaloids

V-40

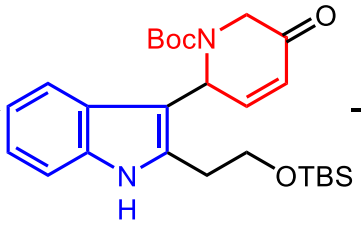


1b

+

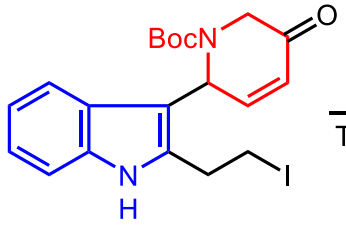
2a

PCCP (0.05 eq.)
Toluene
r.t., 2 h
56%



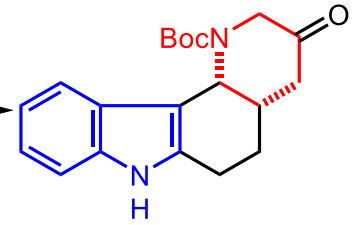
3b

1. TBAF (1.2 eq.)
AcOH (3.0 eq.)
THF, 1 h
2. PPh_3 (1.5 eq.)
I_2 (1.1 eq.)
imidazole (1.5 eq.)
THF, overnight
82% over 2 steps



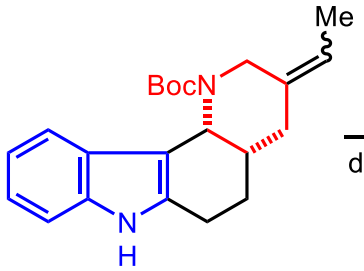
3ae (>26 g)

V-40 (0.4 eq.)
Bu_3SnH (1.7 eq.)
Toluene, 110 °C, 6 h
78%



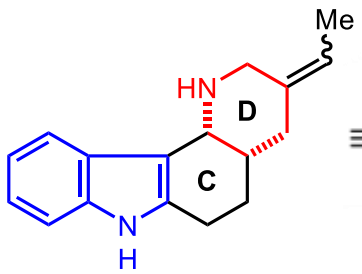
14

Ph_3PEtBr (5.0 eq.)
KHMDS (4.5 eq.)
THF, -78 °C to r.t., overnight
90%, Z/E = 85:15

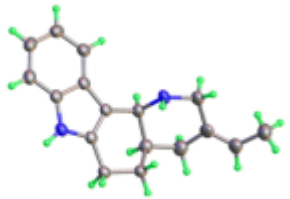


15 (Z/E = 85:15)

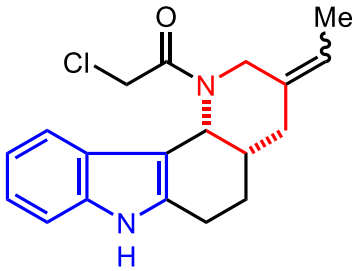
4 M HCl
dioxane, 10 min
85%



16 (Z/E = 85:15)

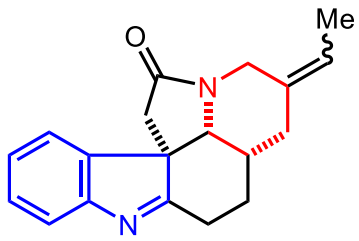

Z-16 (X-ray)

$ClCH_2COCl$ (1.5 eq.)
$NaHCO_3$ (aq.)
DCM, 4 h
85%



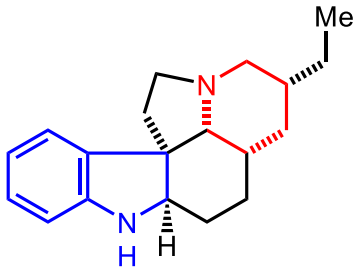
17 (Z/E = 85:15)

1. NaI (10.0 eq.)
acetone, 60 °C, 2 h
2. AgOTf (2.0 eq.)
THF, 16 h
90% over 2 steps



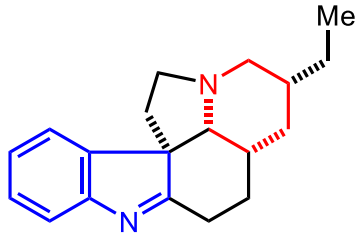
18 (Z/E = 85:15)

1. $LiAlH_4$ (4.5 eq.)
THF, 70 °C, 4 h
2. H_2 (1atm)
$Pd(OH)_2/C$ (100% w/w)
MeOH/EtOH = 5:2, 4 h
80% over 2 steps

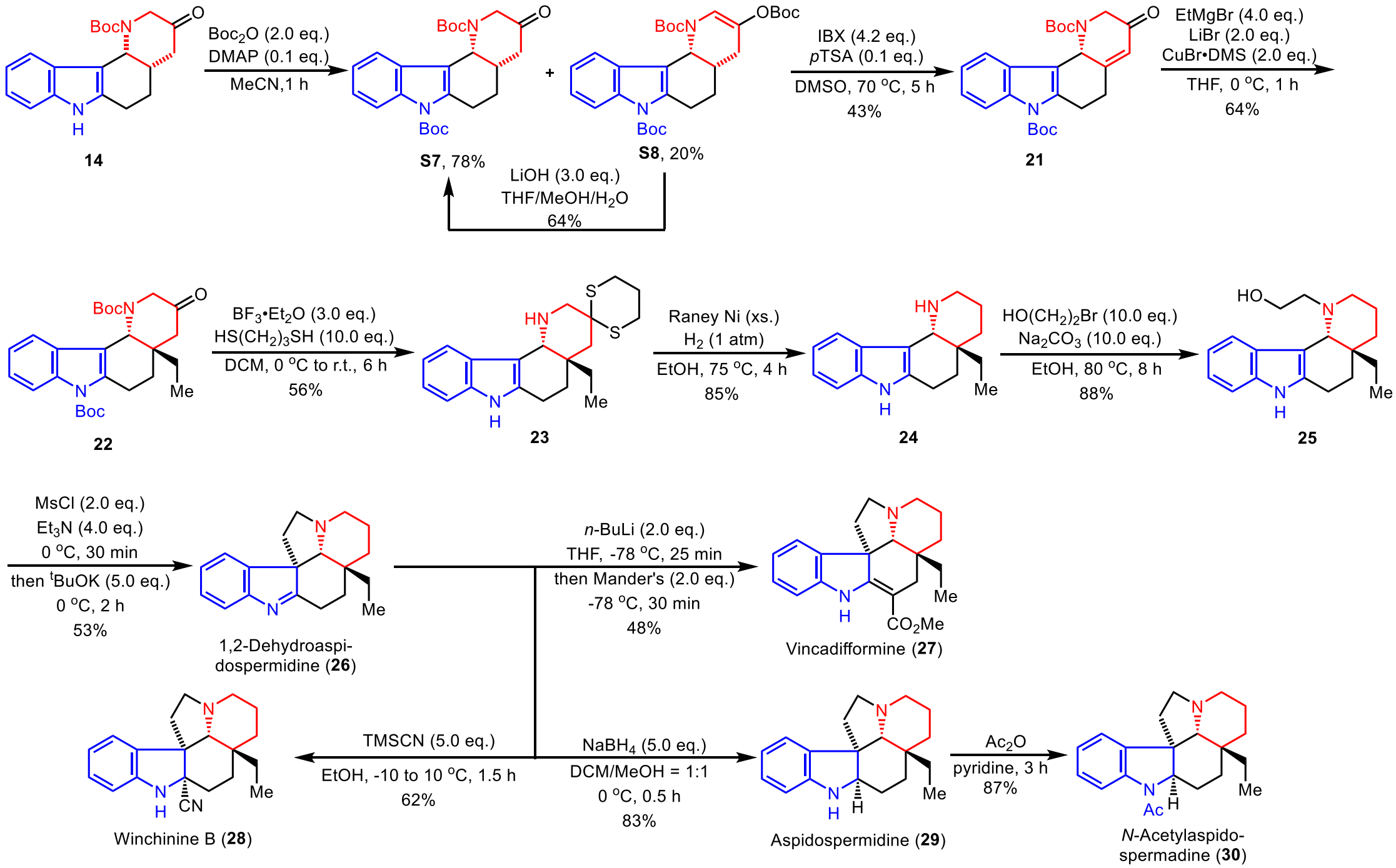


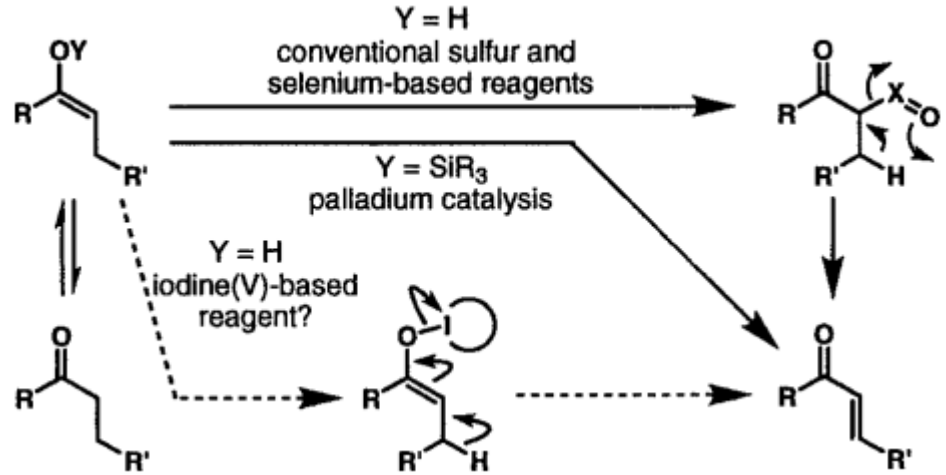
19

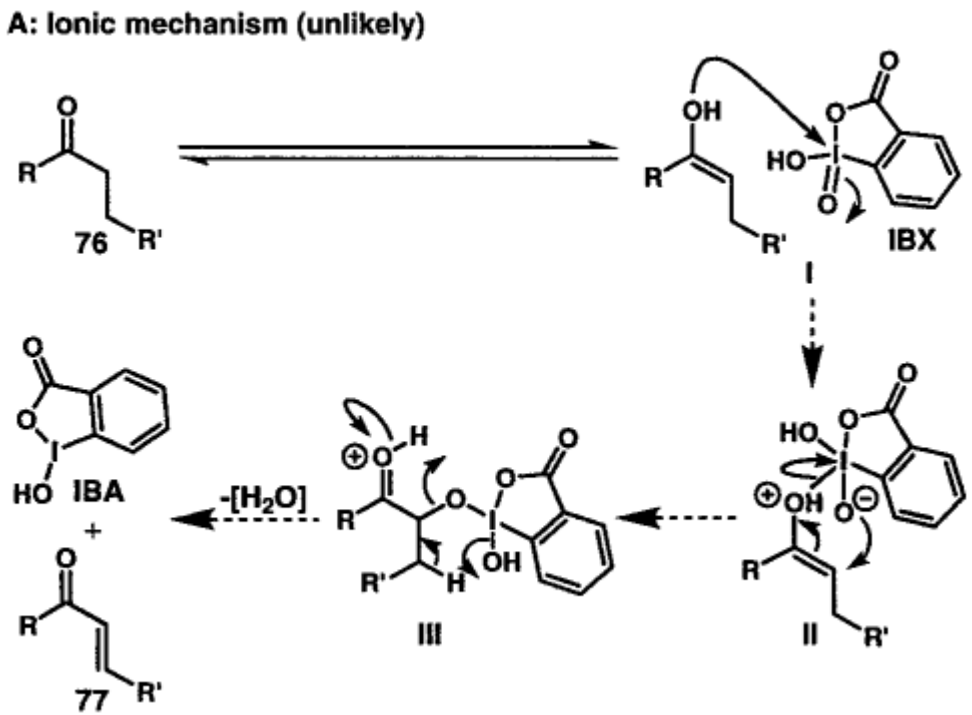
$KMnO_4$ (1.8 eq.)
18-crown-6 (1.8 eq.)
PhMe, 2 h
38%

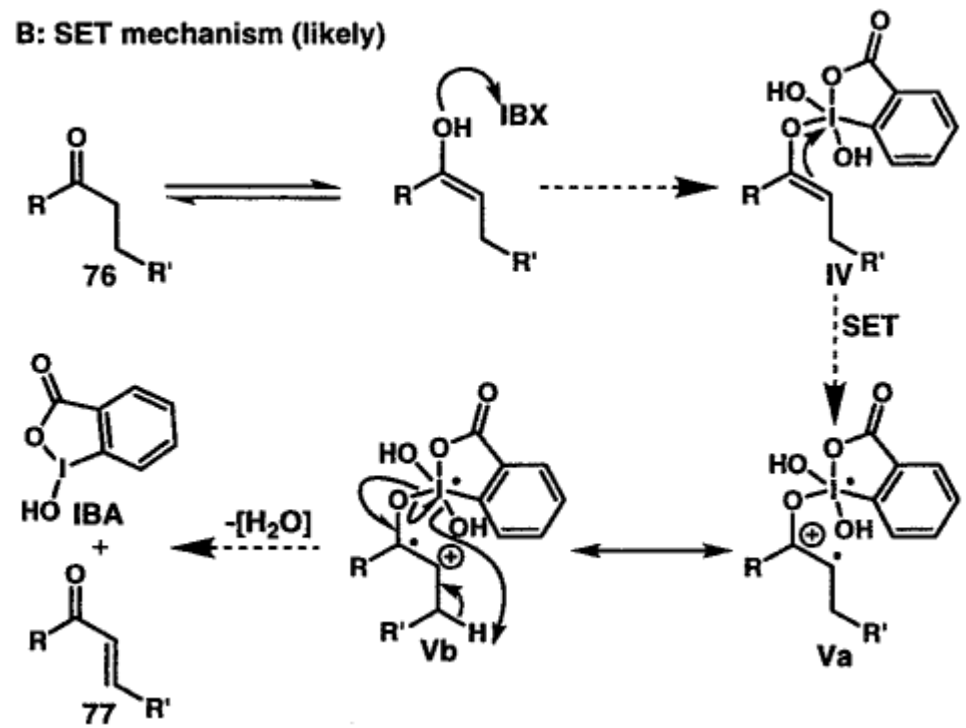


1,2-Didehydropseudo-aspidospermidine (**20**)


14
Boc2O (2.0 eq.)
DMAP (0.1 eq.)
MeCN,1 h
S7, 78%
S8, 20%
LiOH (3.0 eq.)
THF/MeOH/H2O
64%
IBX (4.2 eq.)
pTSA (0.1 eq.)
DMSO, 70 °C, 5 h
43%
21
EtMgBr (4.0 eq.)
LiBr (2.0 eq.)
CuBr•DMS (2.0 eq.)
THF, 0 °C, 1 h
64%
22
BF3•Et2O (3.0 eq.)
HS(CH2)3SH (10.0 eq.)
DCM, 0 °C to r.t., 6 h
56%
23
Raney Ni (xs.)
H2 (1 atm)
EtOH, 75 °C, 4 h
85%
24
HO(CH2)2Br (10.0 eq.)
Na2CO3 (10.0 eq.)
EtOH, 80 °C, 8 h
88%
25
MsCl (2.0 eq.)
Et3N (4.0 eq.)
0 °C, 30 min
then tBuOK (5.0 eq.)
0 °C, 2 h
53%
1,2-Dehydroaspi-
dospermidine (26)
n-BuLi (2.0 eq.)
THF, -78 °C, 25 min
then Mander's (2.0 eq.)
-78 °C, 30 min
48%
Vincadifformine (27)
TMSCN (5.0 eq.)
EtOH, -10 to 10 °C, 1.5 h
62%
Winchinine B (28)
NaBH4 (5.0 eq.)
DCM/MeOH = 1:1
0 °C, 0.5 h
83%
Aspidospermidine (29)
Ac2O
pyridine, 3 h
87%
N-Acetylaspido-
spermadine (30)







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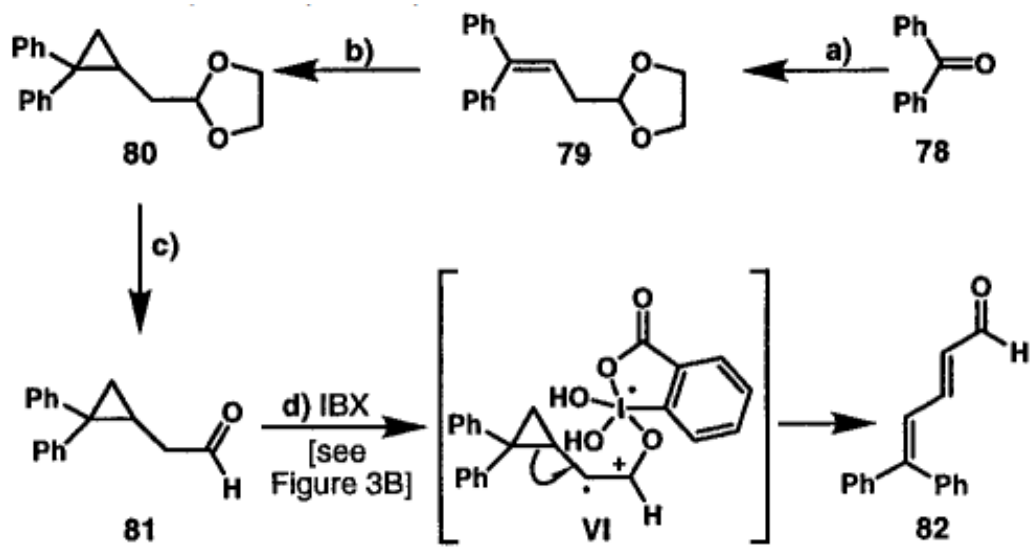

[a] Reagents and conditions: (a) [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide[43] (2.0 equiv), *t*-BuOH (2.0 equiv), THF, 25 °C, 72 h, 43%; (b) Zn−Ag couple,[44] CH_2I_2 (1.3 equiv), Et_2O, reflux, 22 h, 78%; (c) AcOH:H_2O 1:1, 25 °C, 12 h, 81%; (d) IBX (2.0 equiv), DMSO, 70 °C, 7 h, 98%.

J. Am. Chem. Soc., **2002**, *124*, 2245.