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Communication

Enantioselective Total Synthesis of (−)-Hunterine A Enabled by a Desymmetrization/Rearrangement Strategy

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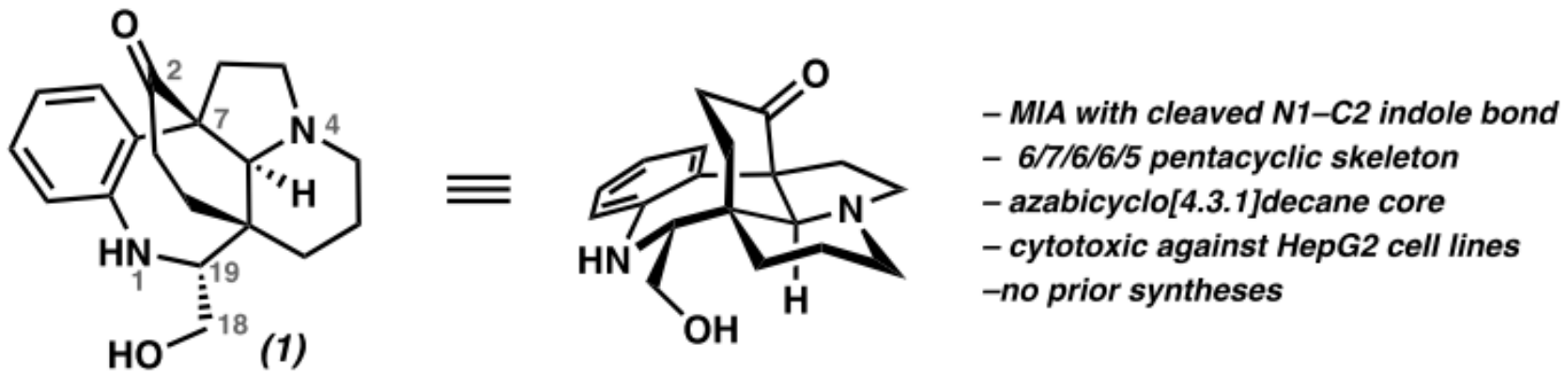
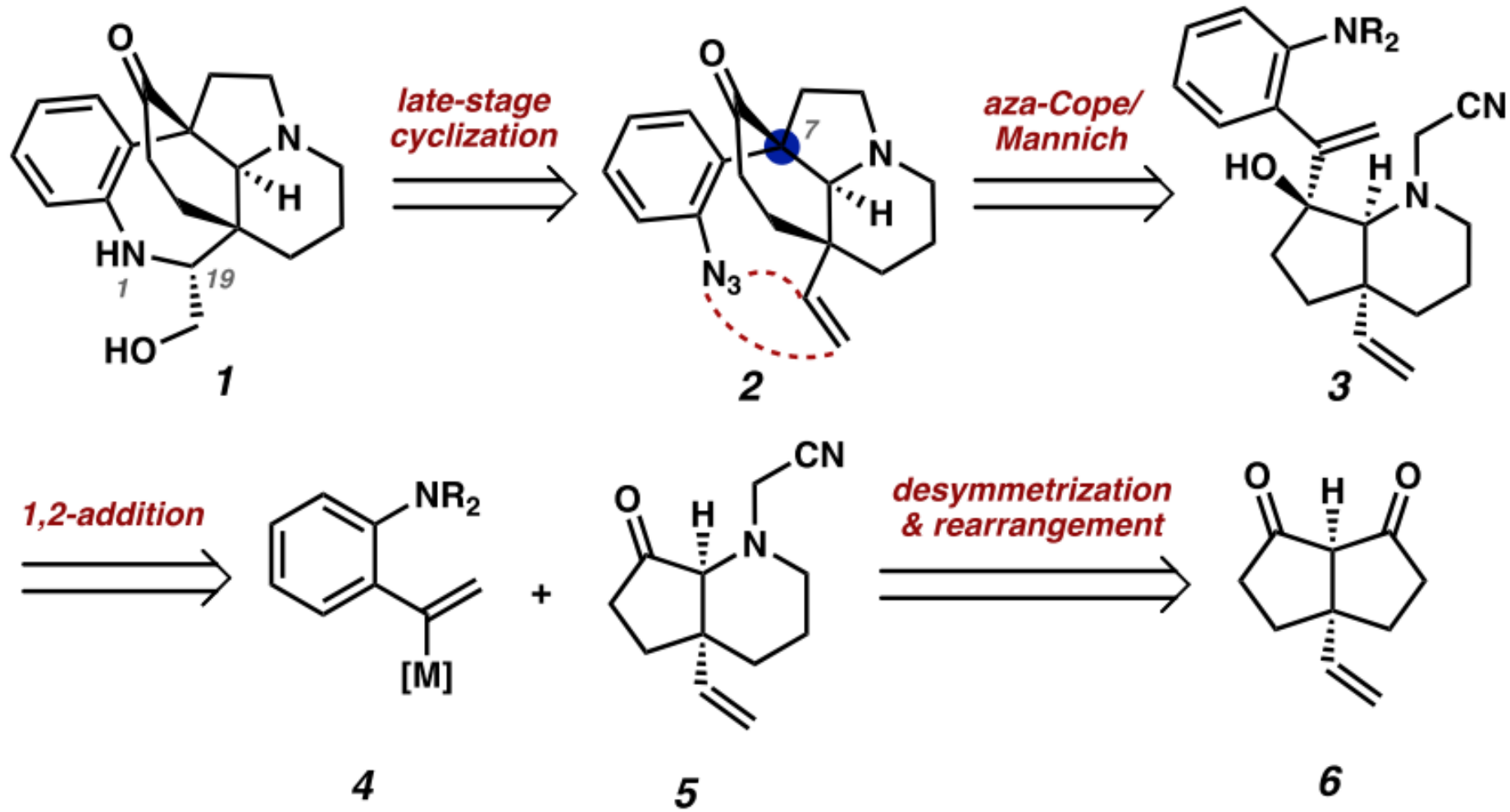
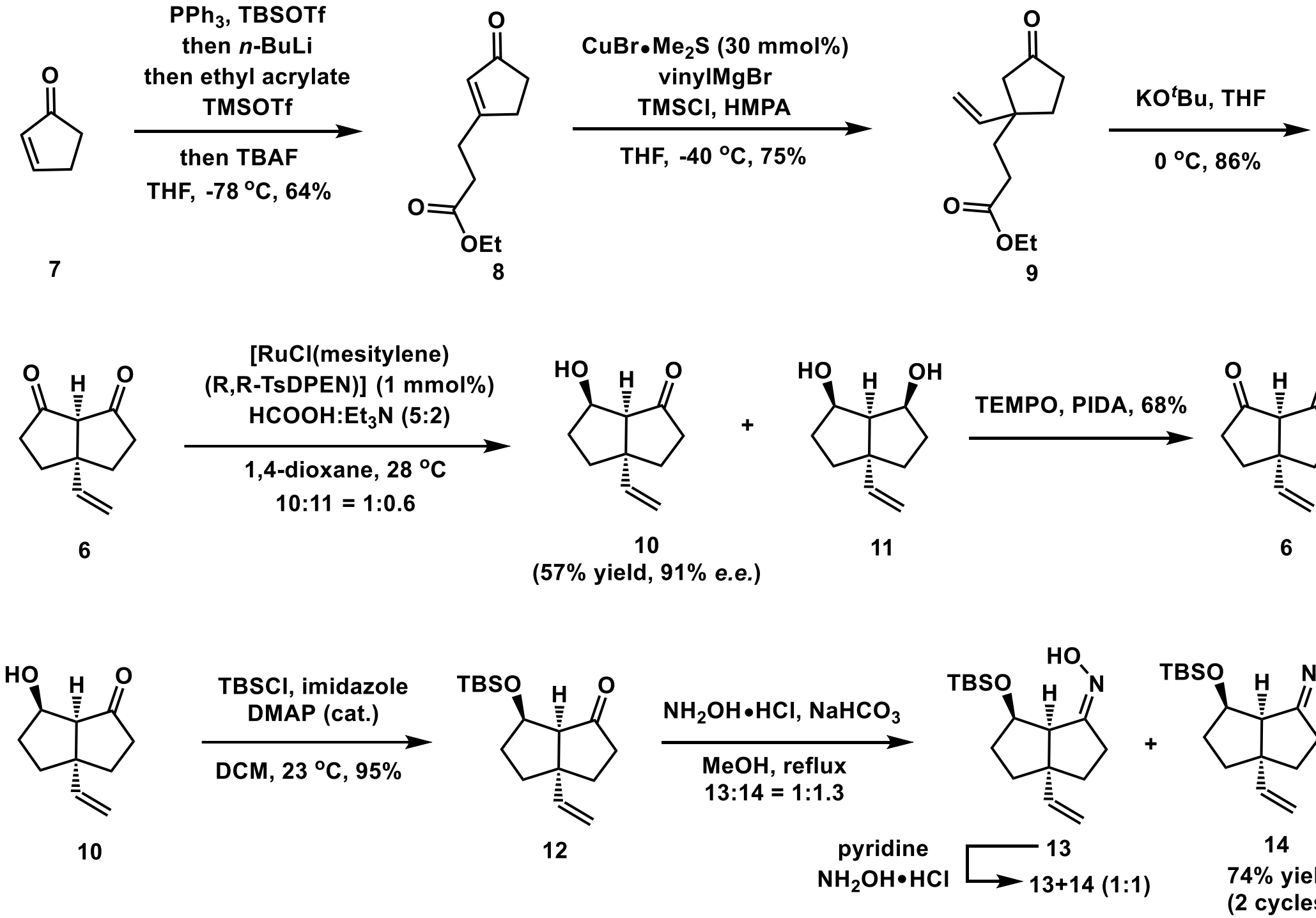
Cite This: J. Am. Chem. Soc. 2024, 146, 4340−4345

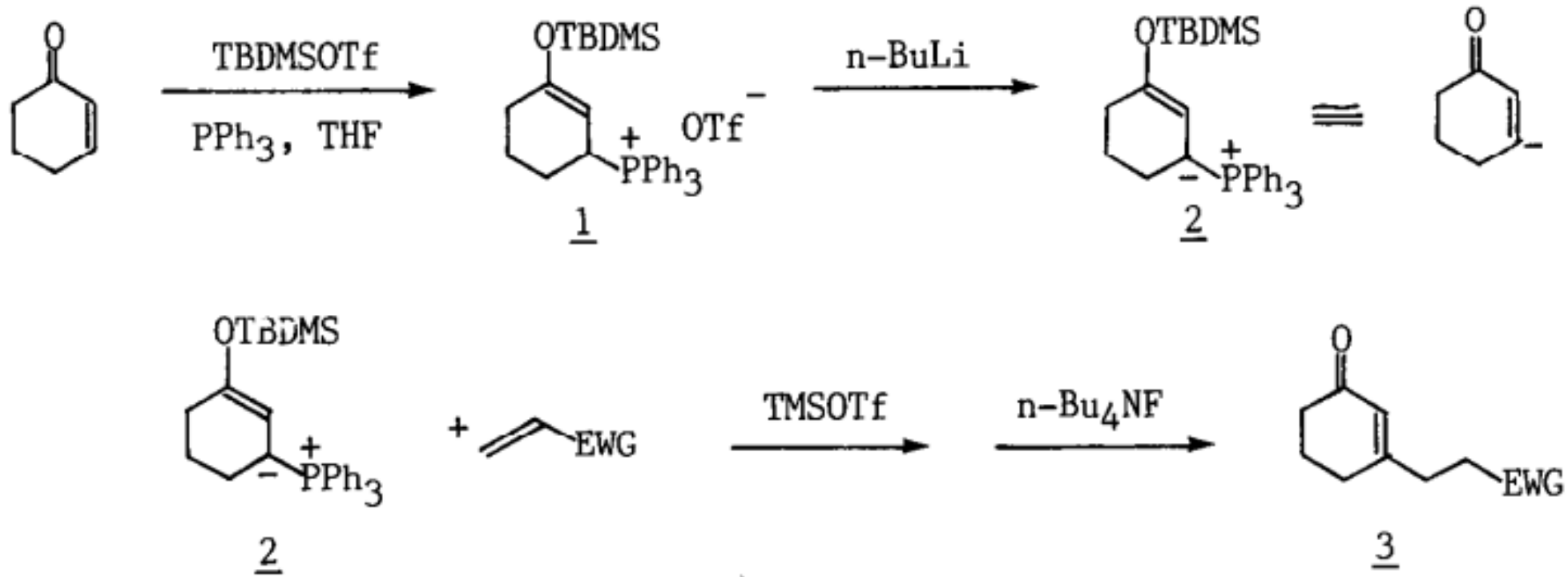
Read Online



- *MIA with cleaved N1–C2 indole bond*
- *6/7/6/6/5 pentacyclic skeleton*
- *azabicyclo[4.3.1]decane core*
- *cytotoxic against HepG2 cell lines*
- *no prior syntheses*


O
N
H
HN
1
19
HO
1
late-stage
cyclization
O
7
N
H
N3
2
aza-Cope/
Mannich
NR2
CN
HO
H
N
3
1,2-addition
NR2
[M]
4
+
CN
O
H
N
5
desymmetrization
& rearrangement
O
H
O
6


PPh3, TBSOTf
then n-BuLi
then ethyl acrylate
TMSOTf
then TBAF
THF, -78 °C, 64%
CuBr•Me2S (30 mmol%)
vinylMgBr
TMSCl, HMPA
THF, -40 °C, 75%
KO^tBu, THF
0 °C, 86%
7
8
9
[RuCl(mesitylene)
(R,R-TsDPEN)] (1 mmol%)
HCOOH:Et3N (5:2)
1,4-dioxane, 28 °C
10:11 = 1:0.6
TEMPO, PIDA, 68%
6
10
(57% yield, 91% e.e.)
11
6
TBSCl, imidazole
DMAP (cat.)
DCM, 23 °C, 95%
NH2OH•HCl, NaHCO3
MeOH, reflux
13:14 = 1:1.3
10
12
pyridine
NH2OH•HCl
13
13+14 (1:1)
14
74% yield
(2 cycles)



Tetrahedron Lett., **1988**, *29*, 5413.

CLAISEN CONDENSATION / CLAISEN REACTION

(References are on page 559)

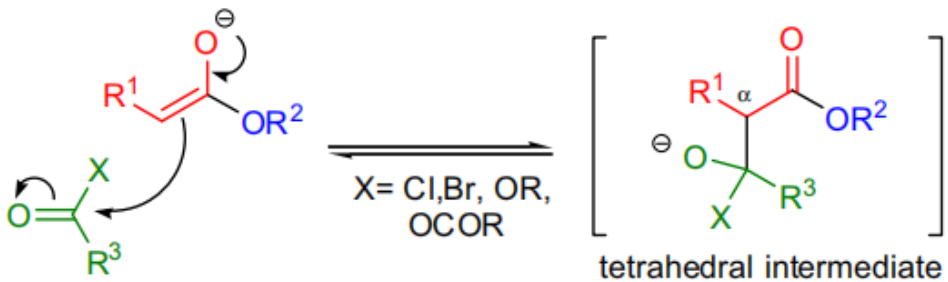
Importance:

[*Seminal Publication*[1]; *Reviews*[2-8]; *Modifications & Improvements*[9-11]; *Theoretical Studies*[12-14]]

First step:

ester enolate

Second step:



tetrahedral intermediate

Third step:

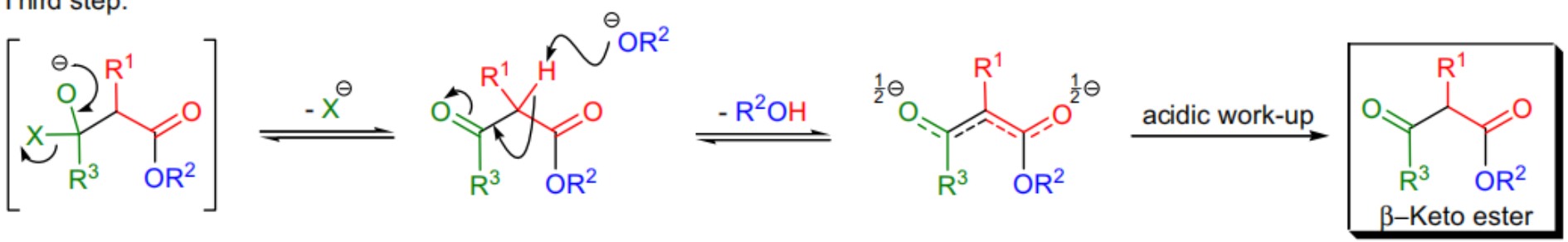
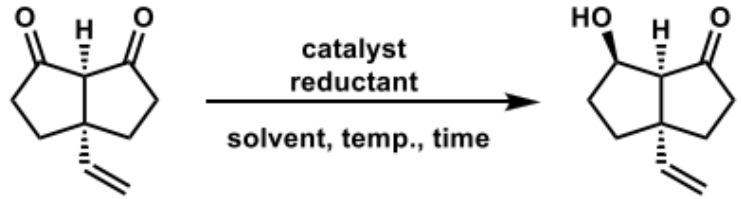
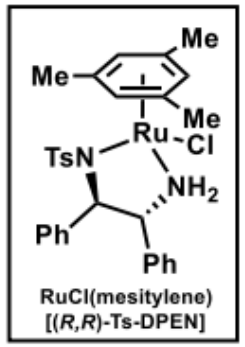


Table 1. Desymmetrization of Diketone 6



6 10

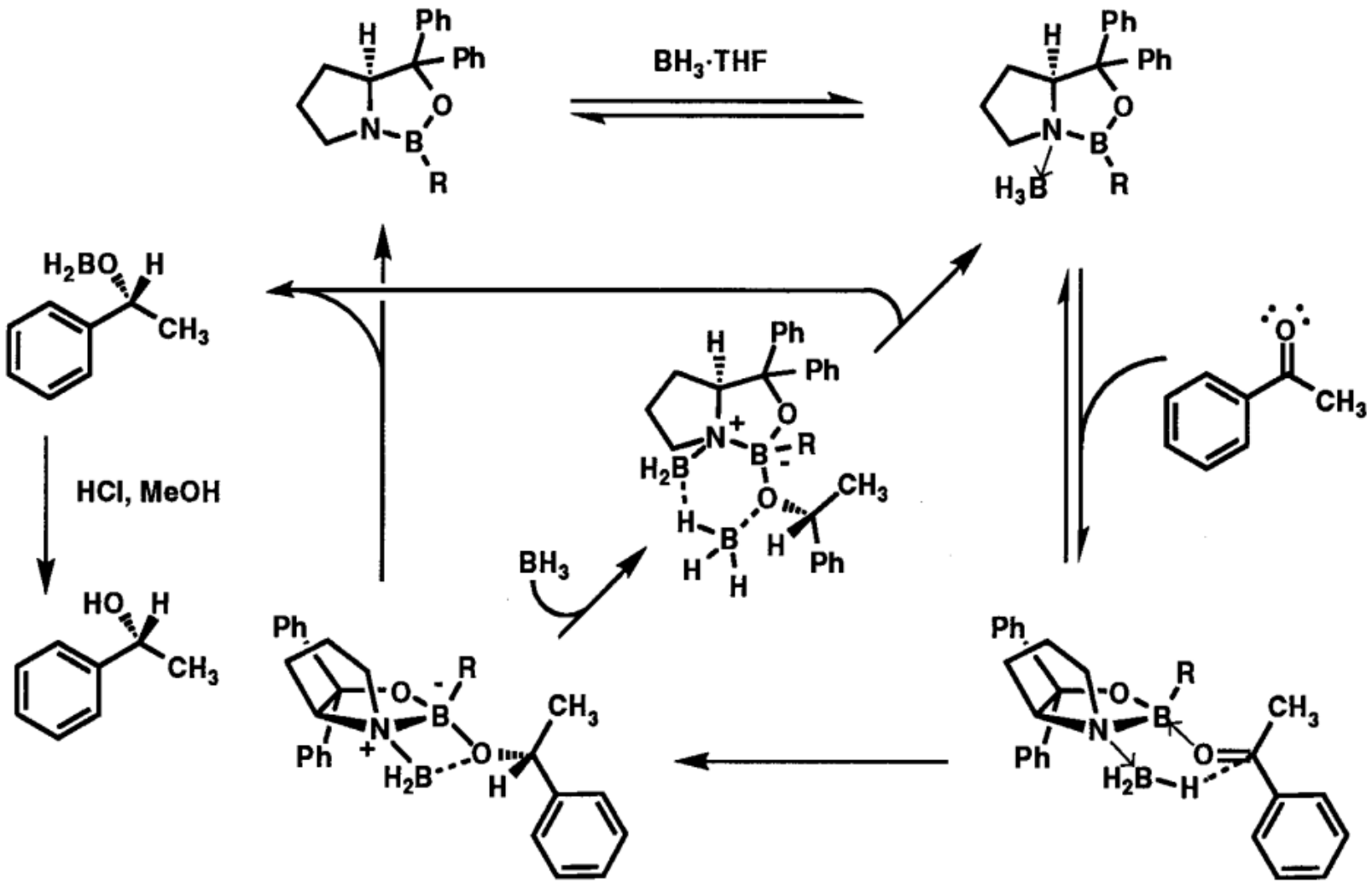


RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]

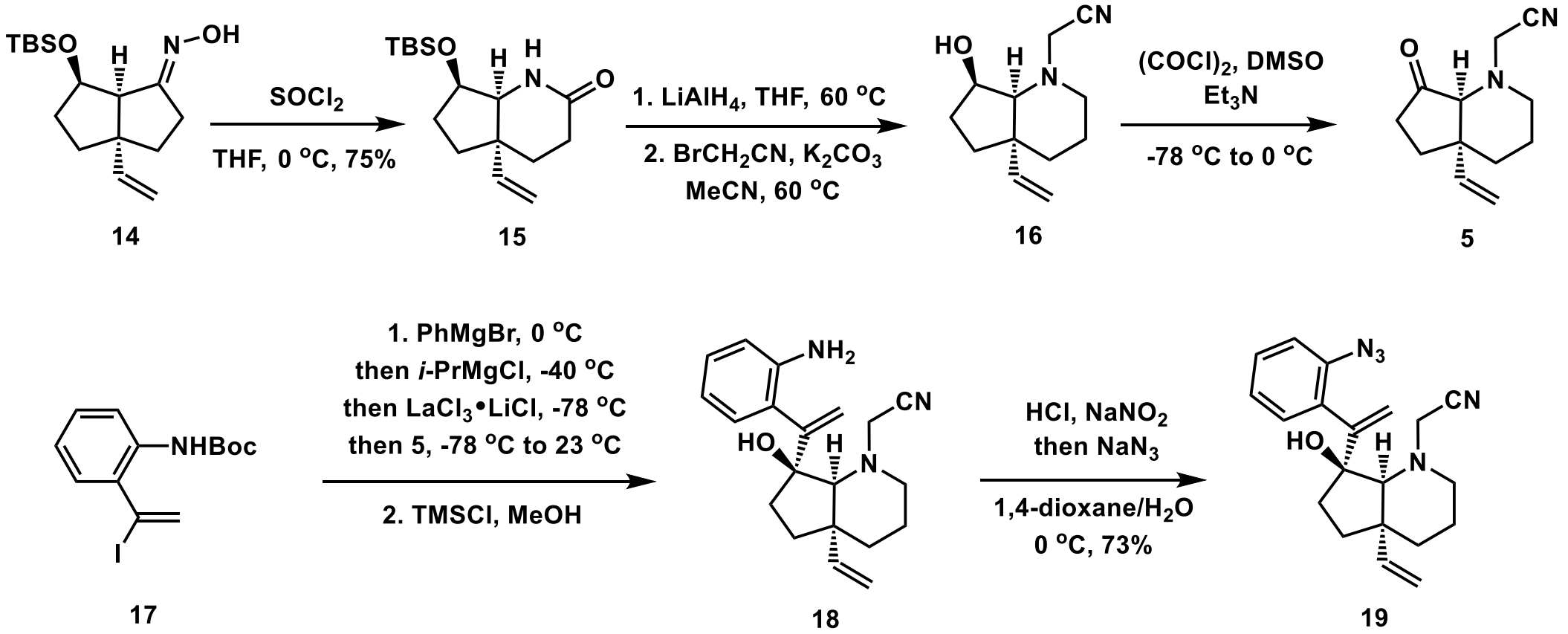
Entry	*Catalyst*[a]	*Reductant*	*Solv./Temp./Time*	*Conversion*[c]	*10:11*	*ee*
1	Baker's yeast, yeast extract	—	H_2O:DMSO (70:1) 25 °C, 48 h	30%	1 : 0	–95%
2	*(S)-n*-Bu-CBS	catecholborane	toluene –78 °C, 3 h	40%	—	—
3	RuCl(*p*-cymene) [(*R*,*R*)-Ts-DPEN][b]	*i*-PrOH	*i*-PrOH, 28 °C 24 h	<5%	n.d.	n.d.
4	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN][b]	*i*-PrOH	*i*-PrOH, 28 °C 24 h	20%	1 : 0	15%
5	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	CH_2Cl_2 28 °C, 14 h	88%	1 : 1.2	79%
6	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	THF 28 °C, 14 h	99%	1 : 1	82%
7	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	1,4-dioxane 28 °C, 14 h	99%	1 : 0.6	91%
8	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]	HCOOH:Et_3N (5:2) (1.5 equiv)	1,4-dioxane 28 °C, 14 h	95%	1 : 0.3	85%
9	RuCl(mesitylene) [(*R*,*R*)-Ts-DPEN]	HCOOH:Et_3N (5:2) (1 equiv)	1,4-dioxane 28 °C, 14 h	90%	1 : 0.12	81%

[a]Reactions were conducted with 1 mol % [Ru] catalyst. [b]Five mol % KOH added. [c]Conversion determined by the ^{1}H NMR ratio of the remaining diketone **6** relative to the CH_2Br_2 internal standard.

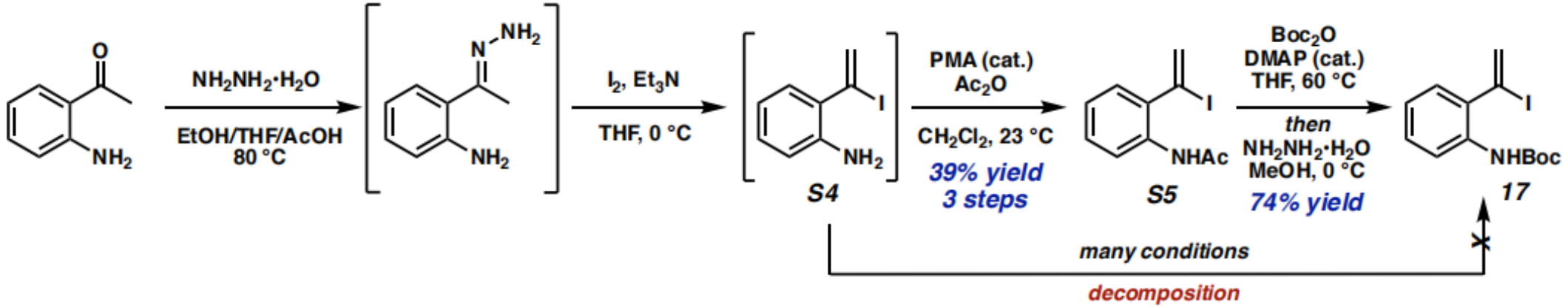
CBS还原：



Angew. Chem. Int. Ed., **1998**, *37*, 1986.



Scheme S2. Synthesis of vinyl iodide **17**.

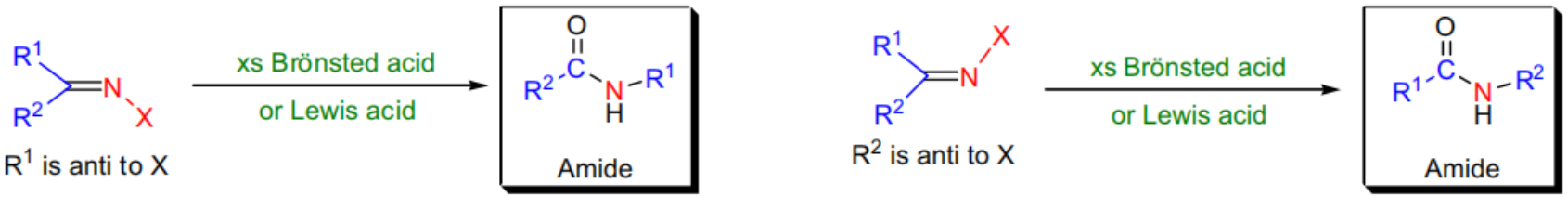


BECKMANN REARRANGEMENT

(References are on page 548)

Importance:

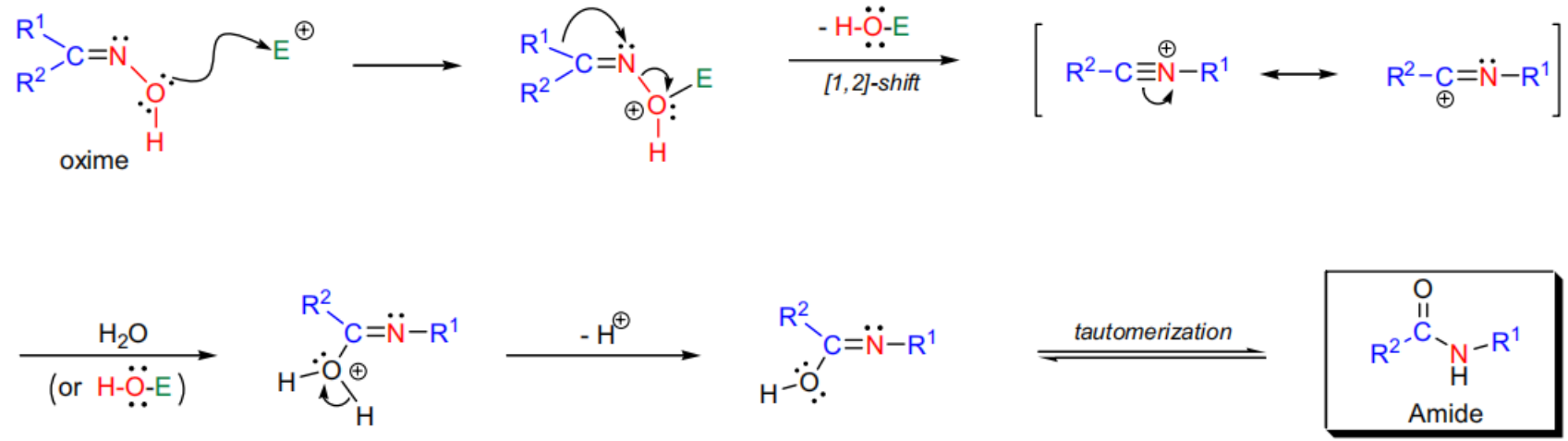
[*Seminal Publication*[1]; *Reviews*[2-5]; *Modifications & Improvements*[6-17]; *Theoretical Studies*[18-27]]

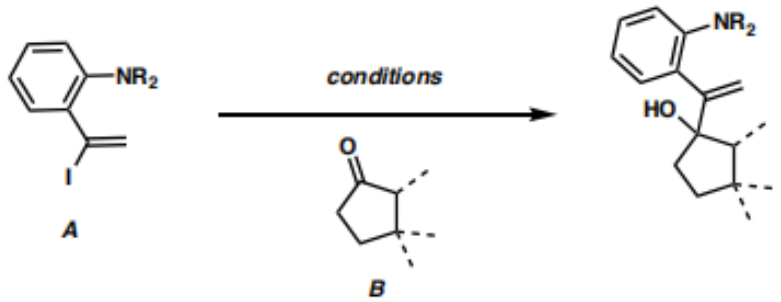


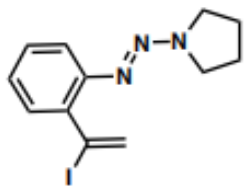
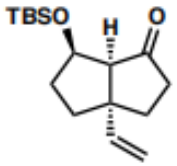
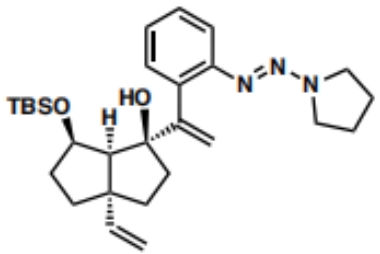
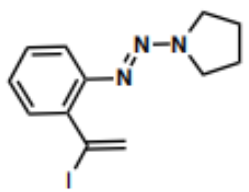
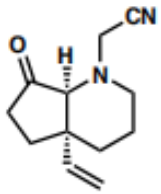
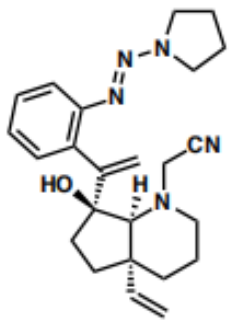
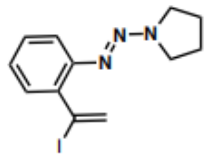
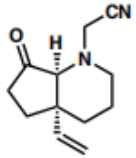
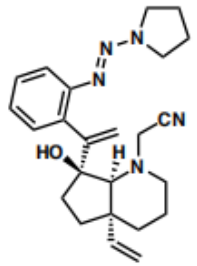
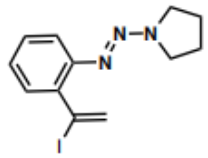
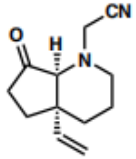
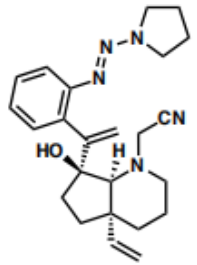
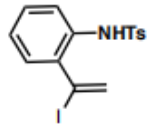
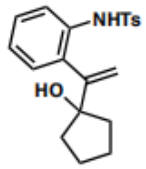
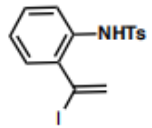
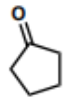
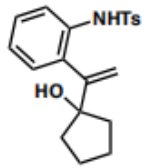
R^1, R^2 = alkyl, aryl, heteroaryl; X = OH, OTs, OMs, Cl

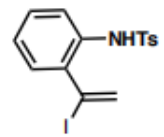
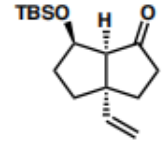
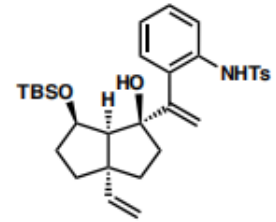
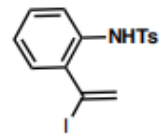
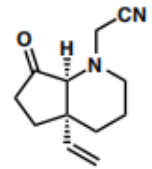
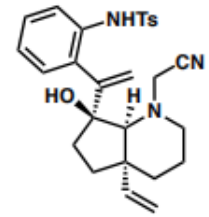
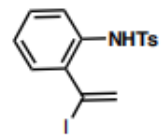
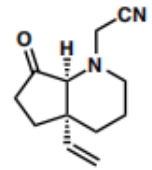
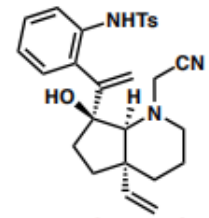
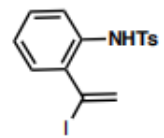
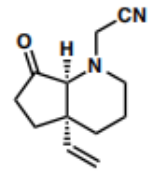
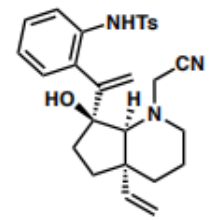
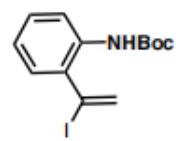
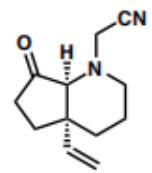
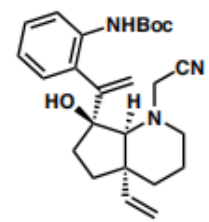
Mechanism: [28,19,22-24,29-31]

In the first step of the mechanism the X group is converted to a leaving group by reaction with an electrophile. The departure of the leaving group is accompanied by the *[1,2]*-shift of the R group, which is *anti* to the leaving group. The resulting carbocation reacts with a nucleophile (a water molecule or the leaving group) to afford the amide after tautomerization.

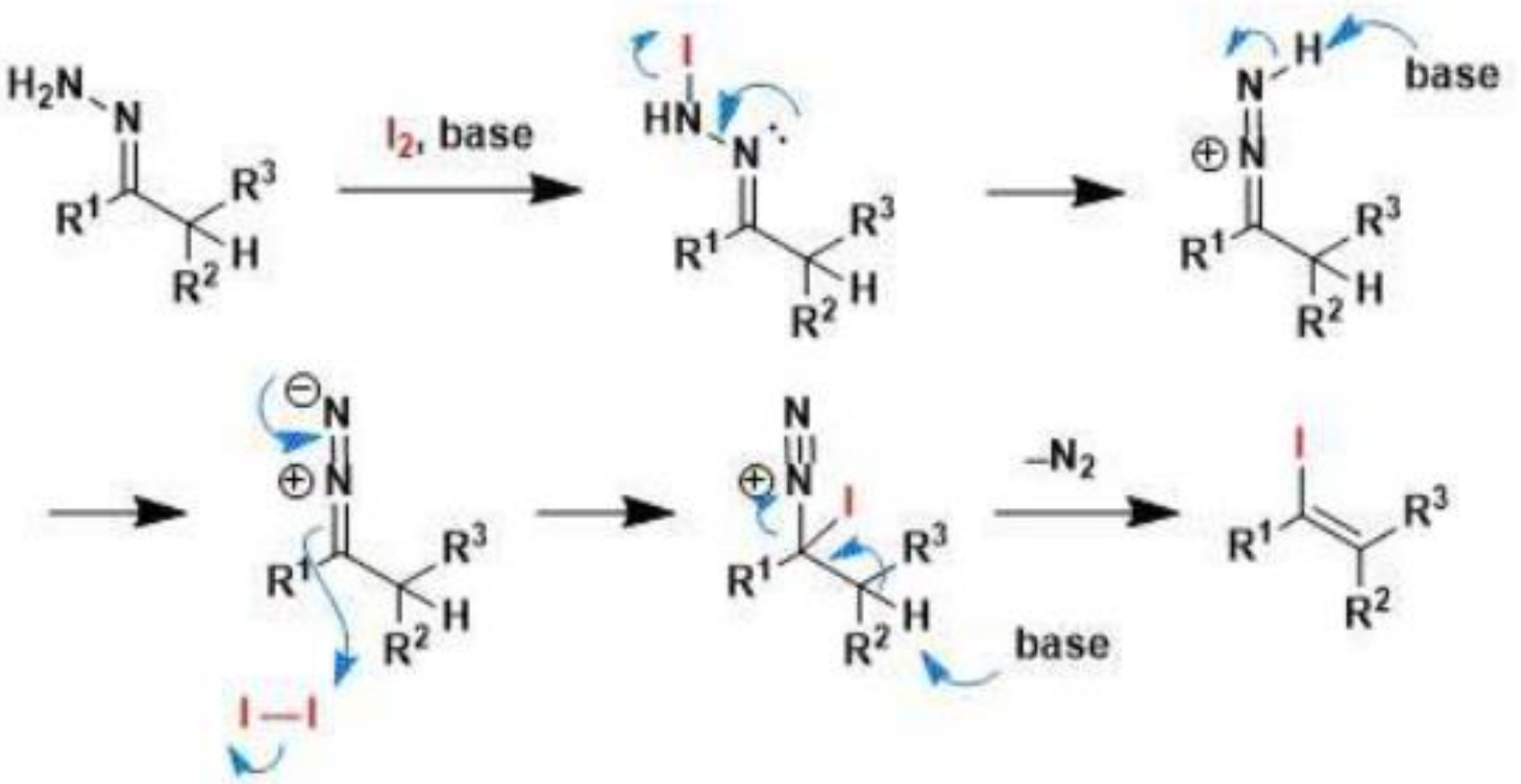


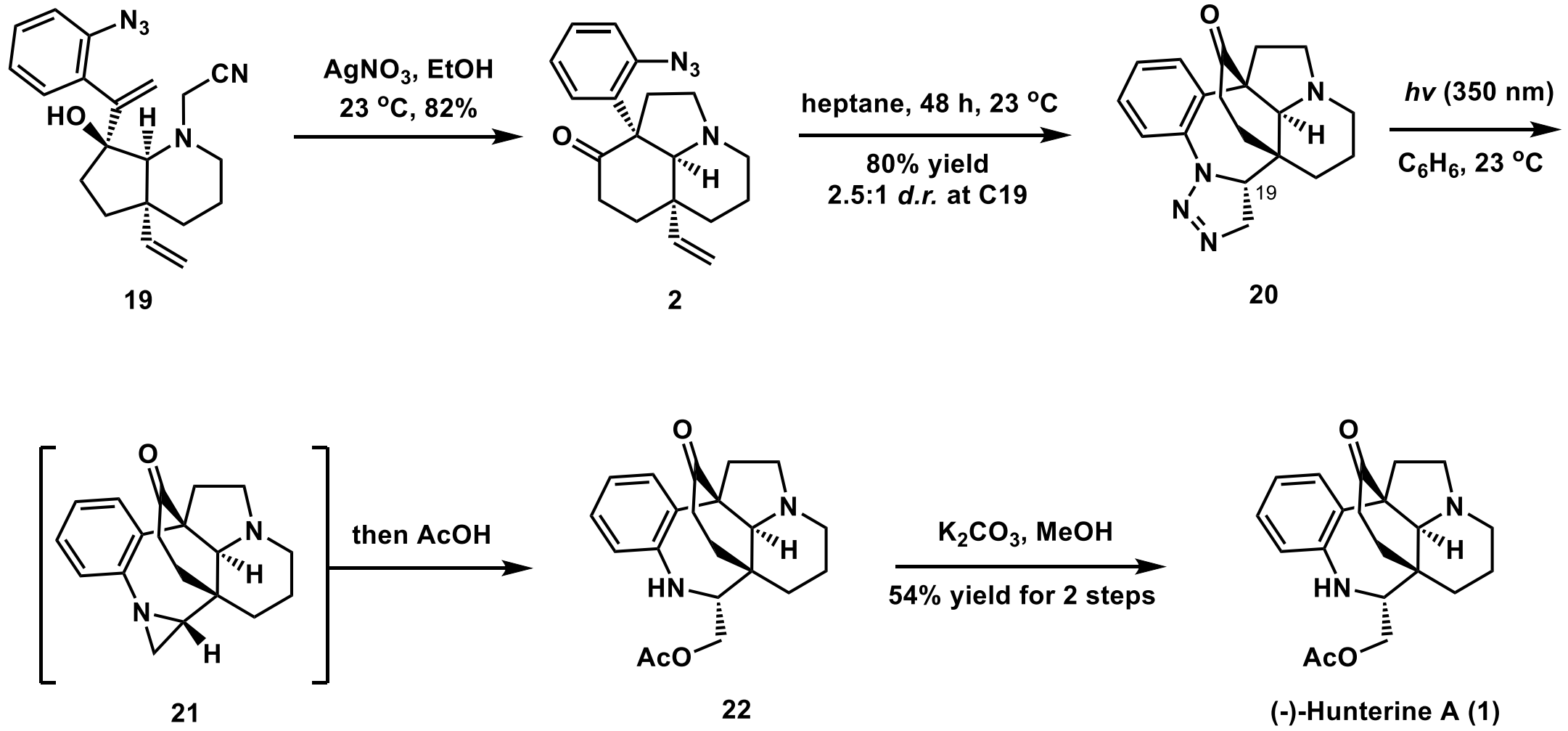


Entry	A (vinyl iodide)	B (ketone)	conditions	product & yield
1			*i*-PrMgCl·LiCl THF, –78 → 23 °C	 30% yield
2			*i*-PrMgCl·LiCl THF, –78 → 23 °C	 not observed
3			*i*-PrMgCl·LiCl $LaCl_3$·2LiCl THF, –78 → 23 °C	 not observed
4			*t*-BuLi $CeCl_3$ THF/Et_2O, –78 → 23 °C	 not observed
5			*i*-PrMgCl·LiCl THF, –78 → 0 °C	 57% yield
6			PhMgBr *then* *i*-PrMgCl·LiCl THF, –78 → 0 °C	 82% yield

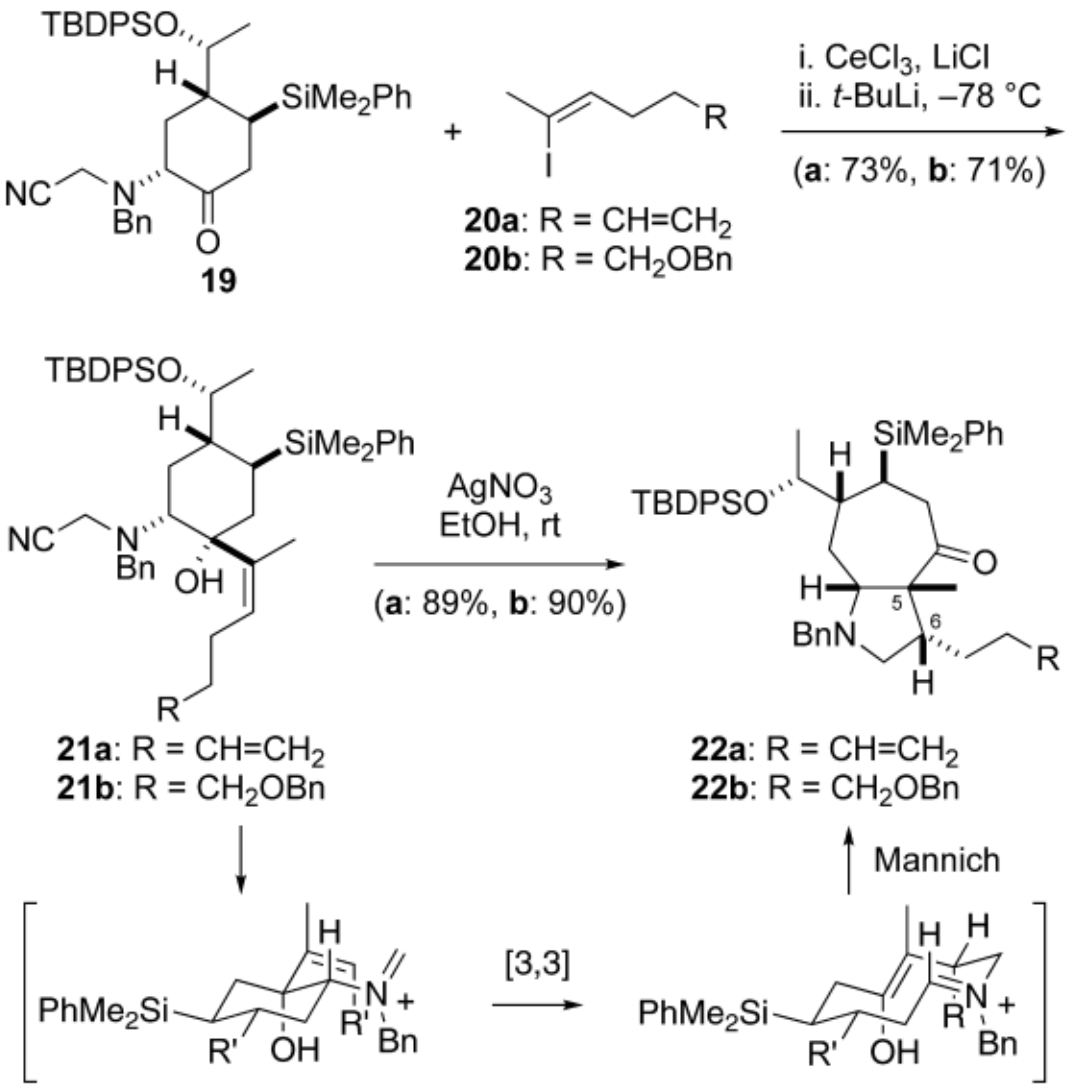
Entry	A (vinyl iodide)	B (ketone)	conditions	product & yield
7			PhMgBr *then* *i*-PrMgCl·LiCl THF, –78 → 0 °C	 47% yield
8			PhMgBr *then* *i*-PrMgCl·LiCl THF, –78 → 0 °C	 11% NMR yield
9			PhMgBr *then* *i*-PrMgCl·LiCl *then* $CeCl_3$ THF, –78 → 0 °C	 not observed
10			PhMgBr *then* *i*-PrMgCl·LiCl *then* $LaCl_3$·2LiCl THF, –78 → 0 °C	 40% yield
11			PhMgBr *then* *i*-PrMgCl·LiCl *then* $LaCl_3$·2LiCl THF, –78 → 0 °C	 68% yield

Barton Vinyl Iodide Synthesis

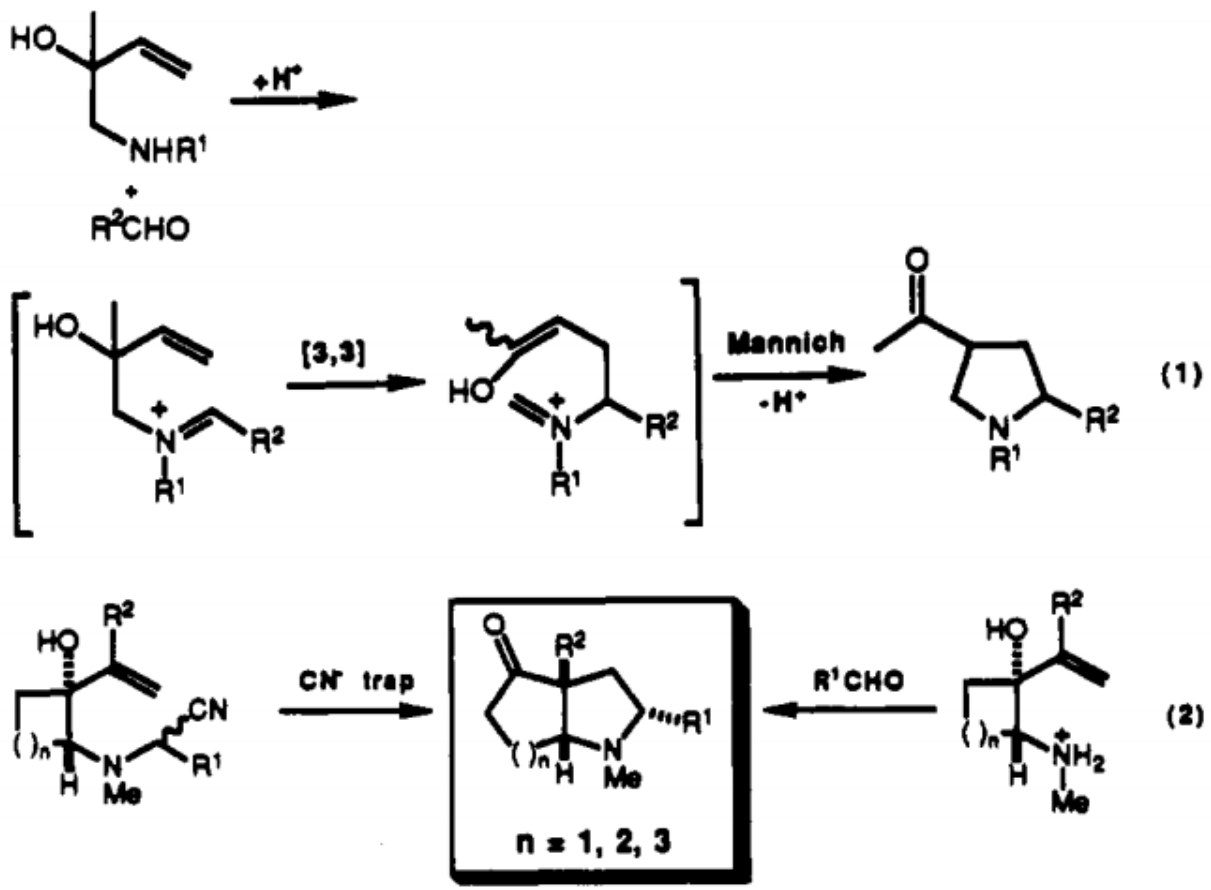



N3
CN
HO
H
N
19
AgNO3, EtOH
23 °C, 82%
N3
O
N
H
2
heptane, 48 h, 23 °C
80% yield
2.5:1 d.r. at C19
O
N
H
N
N
N
19
20
hv (350 nm)
C6H6, 23 °C
O
N
H
N
H
21
then AcOH
O
N
H
HN
AcO
22
K2CO3, MeOH
54% yield for 2 steps
O
N
H
HN
AcO
(-)-Hunterine A (1)

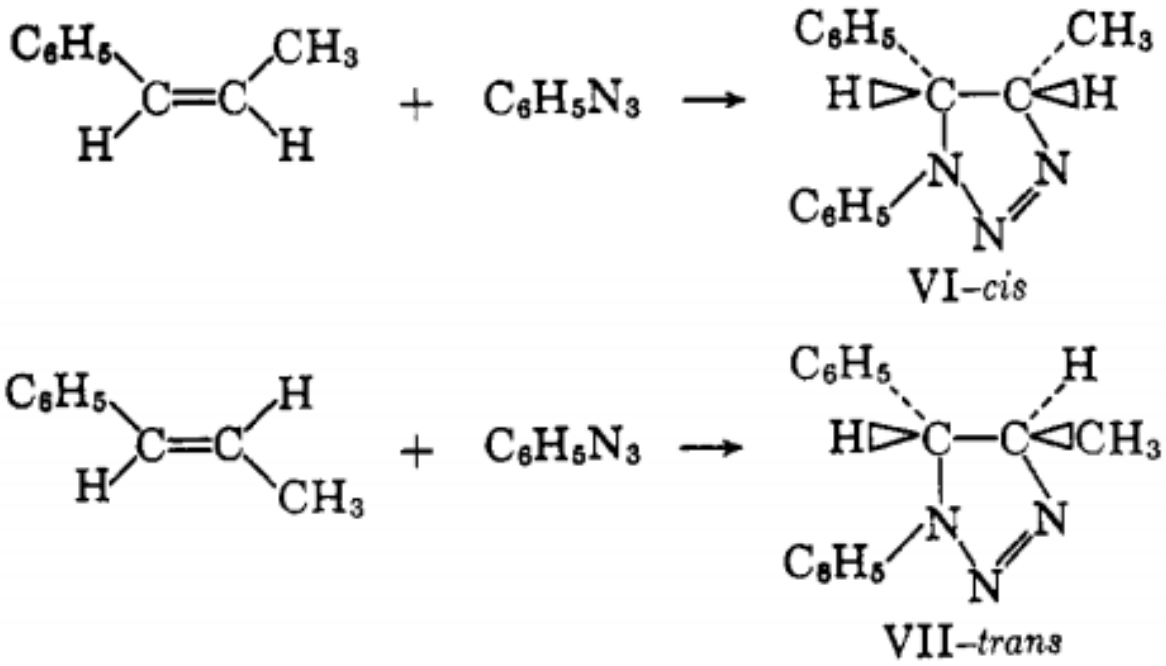
Scheme 3

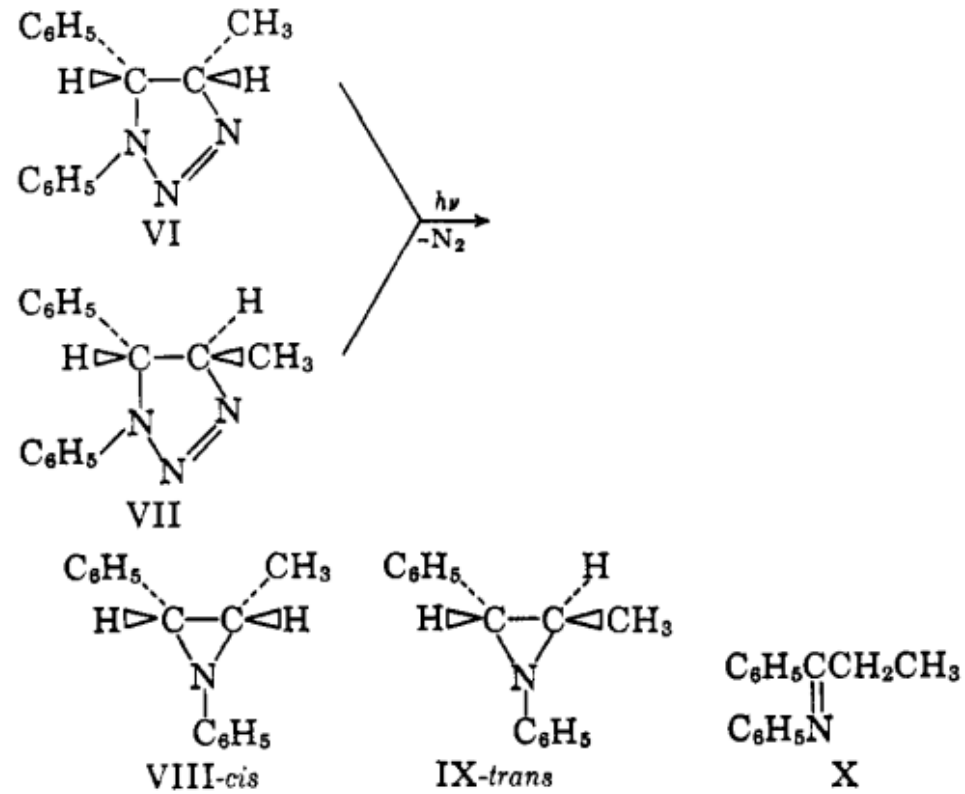


Org. Lett., **2009**, *11*, 24.



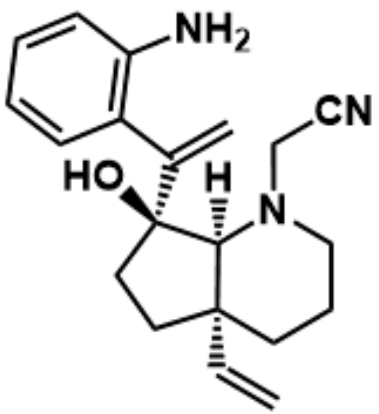
J. Am. Chem. Soc., **1991**, *113*, 7.



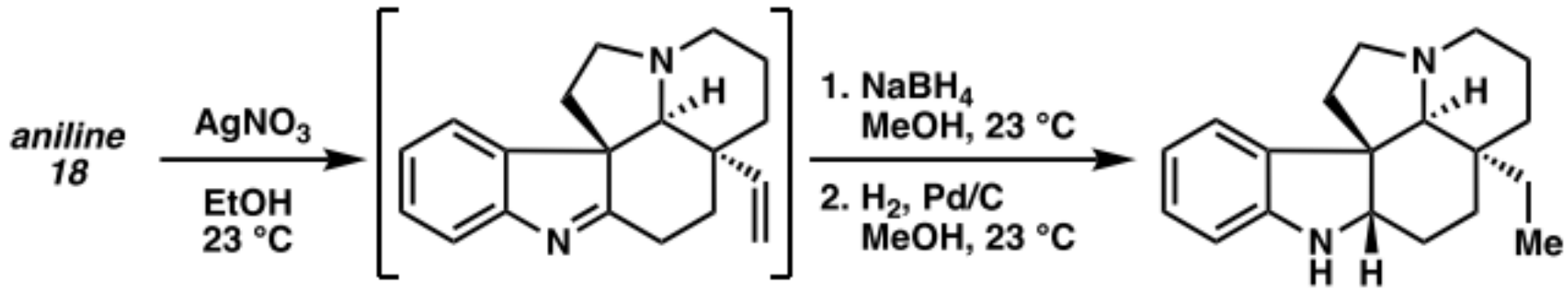


J. Am. Chem. Soc., **1968**, *90*, 988.

Scheme 3. Divergent Access to (−)-Aspidospermidine via Aniline 18



18



23

24

(−)-aspidospermidine

71% yield, 3 steps

Scheme 4. Reactivity Differences between Triazoline 20 and C19-epi-20 and Nitrogen Pyramidality