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Article

Total Synthesis of (−)-Rauvomine B via a Strain-Promoted Intramolecular Cyclopropanation

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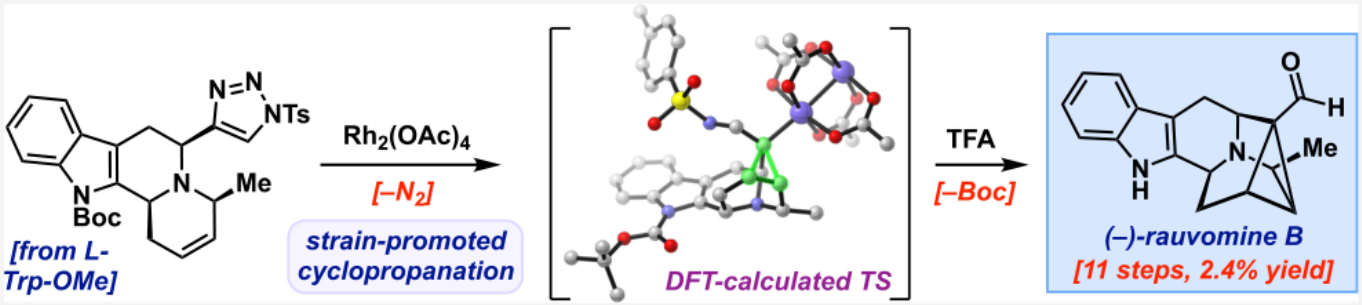
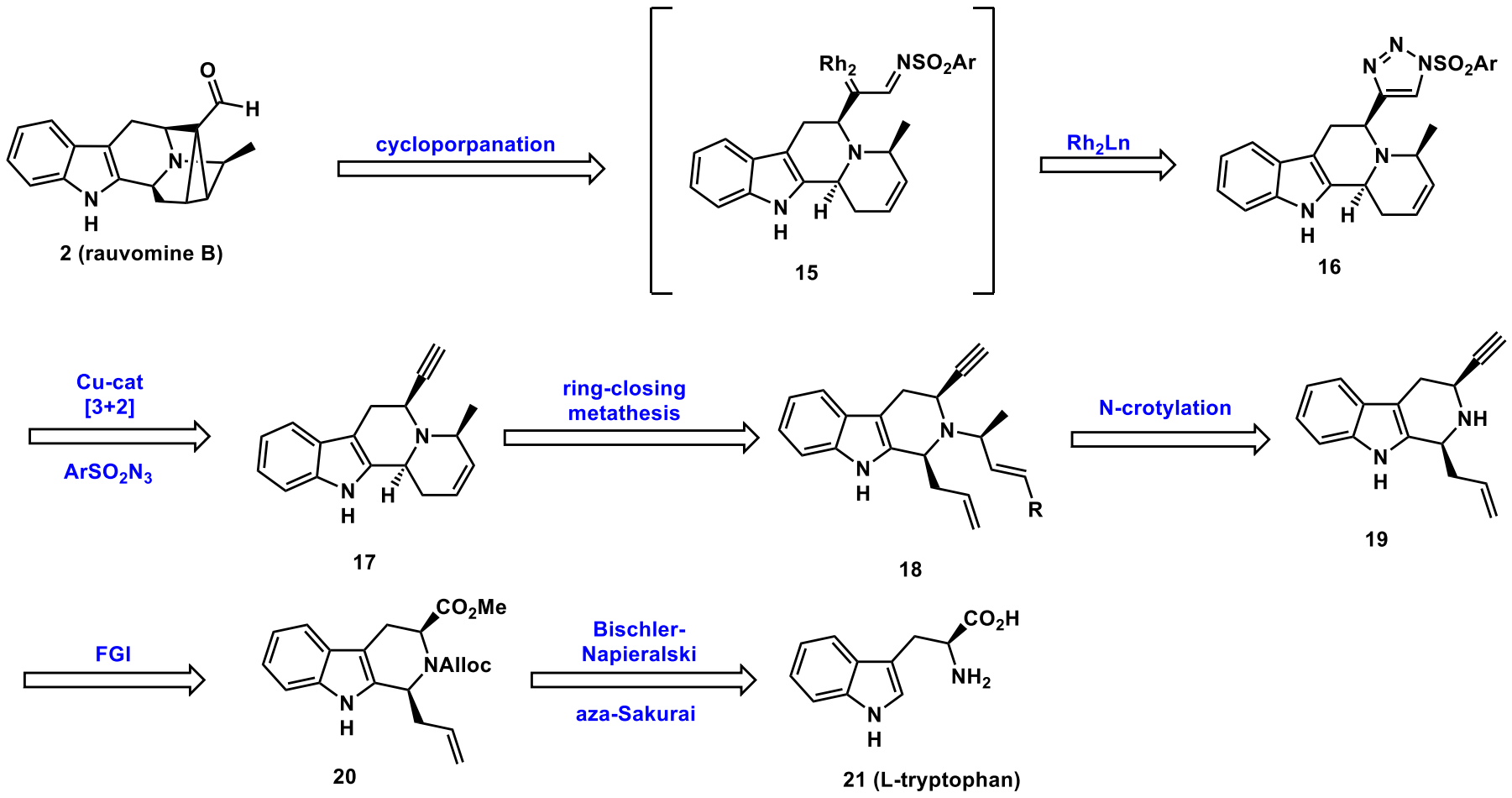
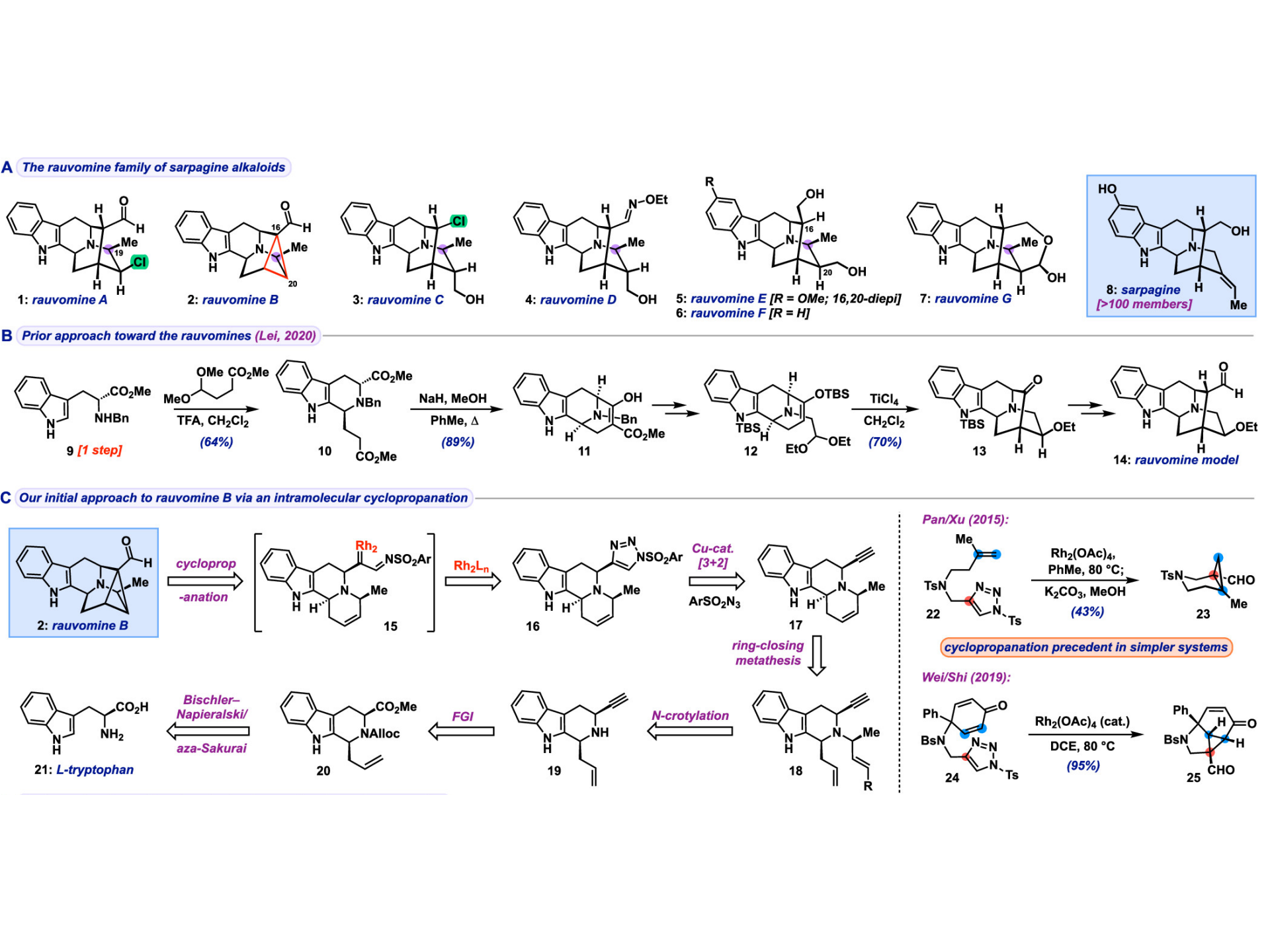
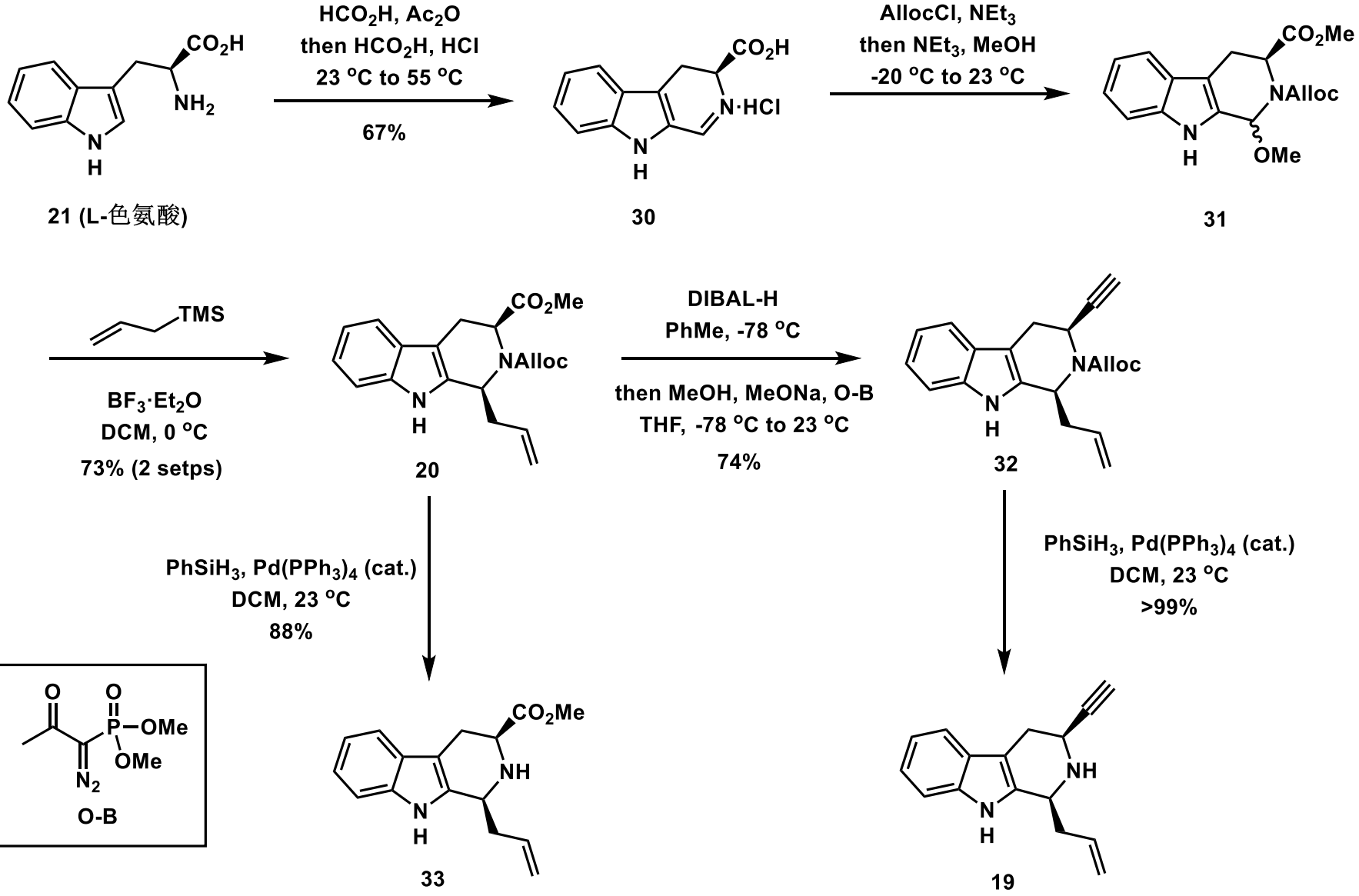



2 (rauvomine B)
cycloporpanation
15
Rh2Ln
16
Cu-cat
[3+2]
ArSO2N3
17
ring-closing
metathesis
18
N-crotylation
19
FGI
20
Bischler-
Napieralski
aza-Sakurai
21 (L-tryptophan)


A The rauvomine family of sarpagine alkaloids
1: rauvomine A
2: rauvomine B
3: rauvomine C
4: rauvomine D
5: rauvomine E [R = OMe; 16,20-diepi]
6: rauvomine F [R = H]
7: rauvomine G
8: sarpagine
[>100 members]
B Prior approach toward the rauvomines (Lei, 2020)
9 [1 step]
TFA, CH2Cl2
(64%)
10
NaH, MeOH
PhMe, Δ
(89%)
11
12
TiCl4
CH2Cl2
(70%)
13
14: rauvomine model
C Our initial approach to rauvomine B via an intramolecular cyclopropanation
2: rauvomine B
cycloprop
-anation
15
Rh2Ln
16
Cu-cat.
[3+2]
ArSO2N3
17
ring-closing
metathesis
18
N-crotylation
19
FGI
20
Bischler–
Napieralski/
aza-Sakurai
21: L-tryptophan
Pan/Xu (2015):
22
Rh2(OAc)4,
PhMe, 80 °C;
K2CO3, MeOH
(43%)
23
cyclopropanation precedent in simpler systems
Wei/Shi (2019):
24
Rh2(OAc)4 (cat.)
DCE, 80 °C
(95%)
25

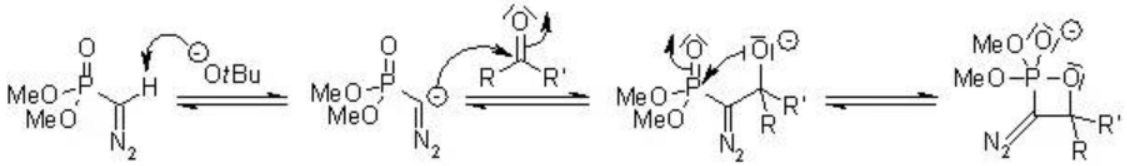

HCO2H, Ac2O
then HCO2H, HCl
23 °C to 55 °C
67%
AllocCl, NEt3
then NEt3, MeOH
-20 °C to 23 °C
21 (L-色氨酸)
30
31
TMS
BF3·Et2O
DCM, 0 °C
73% (2 setps)
20
DIBAL-H
PhMe, -78 °C
then MeOH, MeONa, O-B
THF, -78 °C to 23 °C
74%
32
PhSiH3, Pd(PPh3)4 (cat.)
DCM, 23 °C
88%
PhSiH3, Pd(PPh3)4 (cat.)
DCM, 23 °C
>99%
O-B
33
19

Seyferth-Gilbert 增碳反应

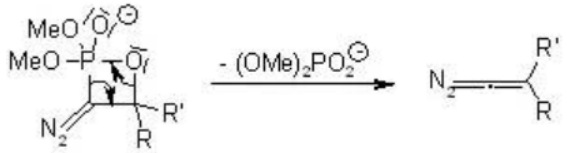
Seyferth-Gilbert 增碳反应的机理:

此机理Gilbert已在文章中详尽描述(*J. Org. Chem.*, **1982**, *47*, 1837-1845. Abstract).

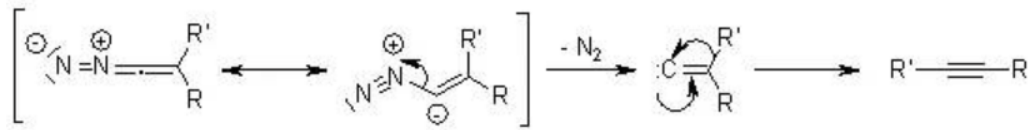
Seyferth-Gilbert试剂脱质子后加成到羰基化合物上得到醇盐，进而转化为一个氧杂四元环磷酸酯:



与 Wittig反应 类似，环消除得到稳定的膦酸二甲酯阴离子和重氮烯烃:



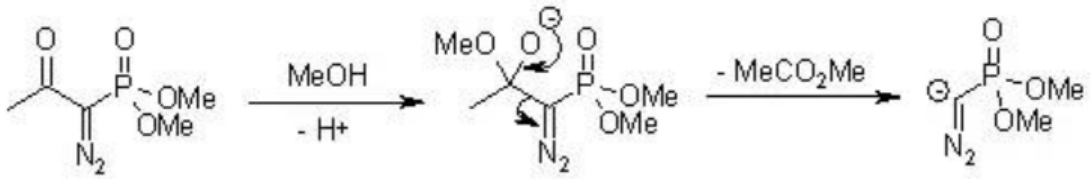
将上述反应体系升至室温后，氮气离去得到一个亚乙烯基卡宾，其中一个取代基发生1,2-迁移得到炔烃:



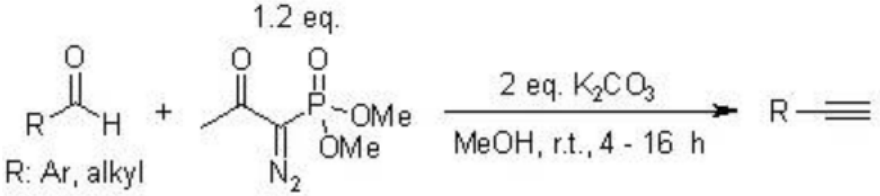
Ohira-Bestmann改进法

Ohira-Bestmann改进法机理：

重氮甲基膦酸二甲酯负离子也可通过1-重氮基-2-氧基丙基膦酸二甲酯温和的酯裂解得到。



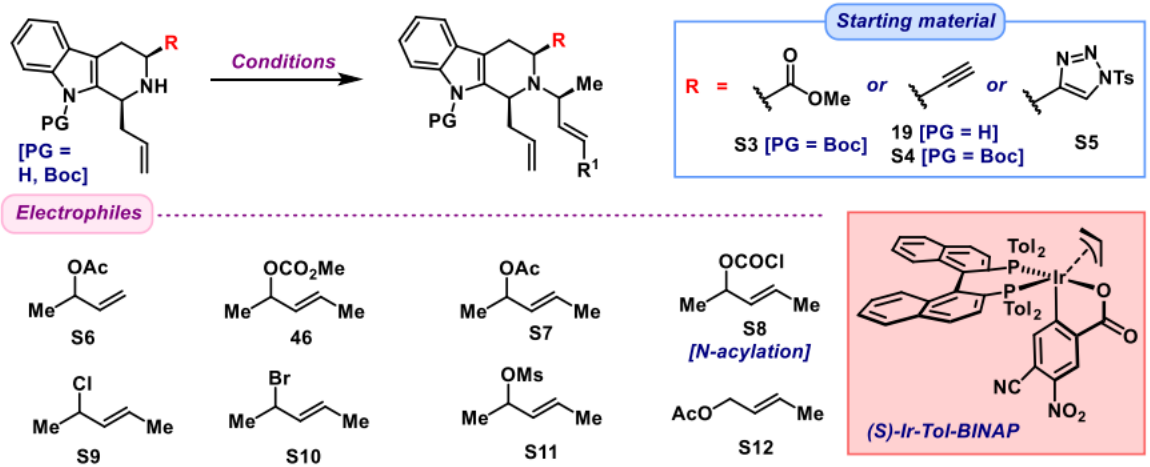
下面就是反应的一般步骤（易发生互变异构的醛也能得到很高产率的产物）：

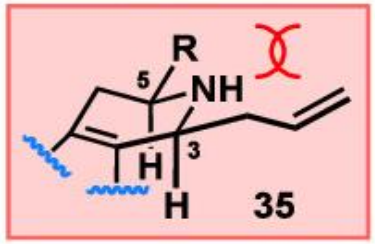


S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett*, **1996**, 521-522.

最开始脂肪醛在碱性的甲醇溶液中反应首先由Ohira 在1986年报导（*Synth. Commun.*,**1986**, *19*, 561. DOI)。Bestmann改进了此反应的一些缺点和限制，可以在简单后处理后得到很高产率的一系列的炔烃。因此1-重氮基-2-氧基丙基膦酸二甲酯被称为Bestmann-Ohiro试剂。

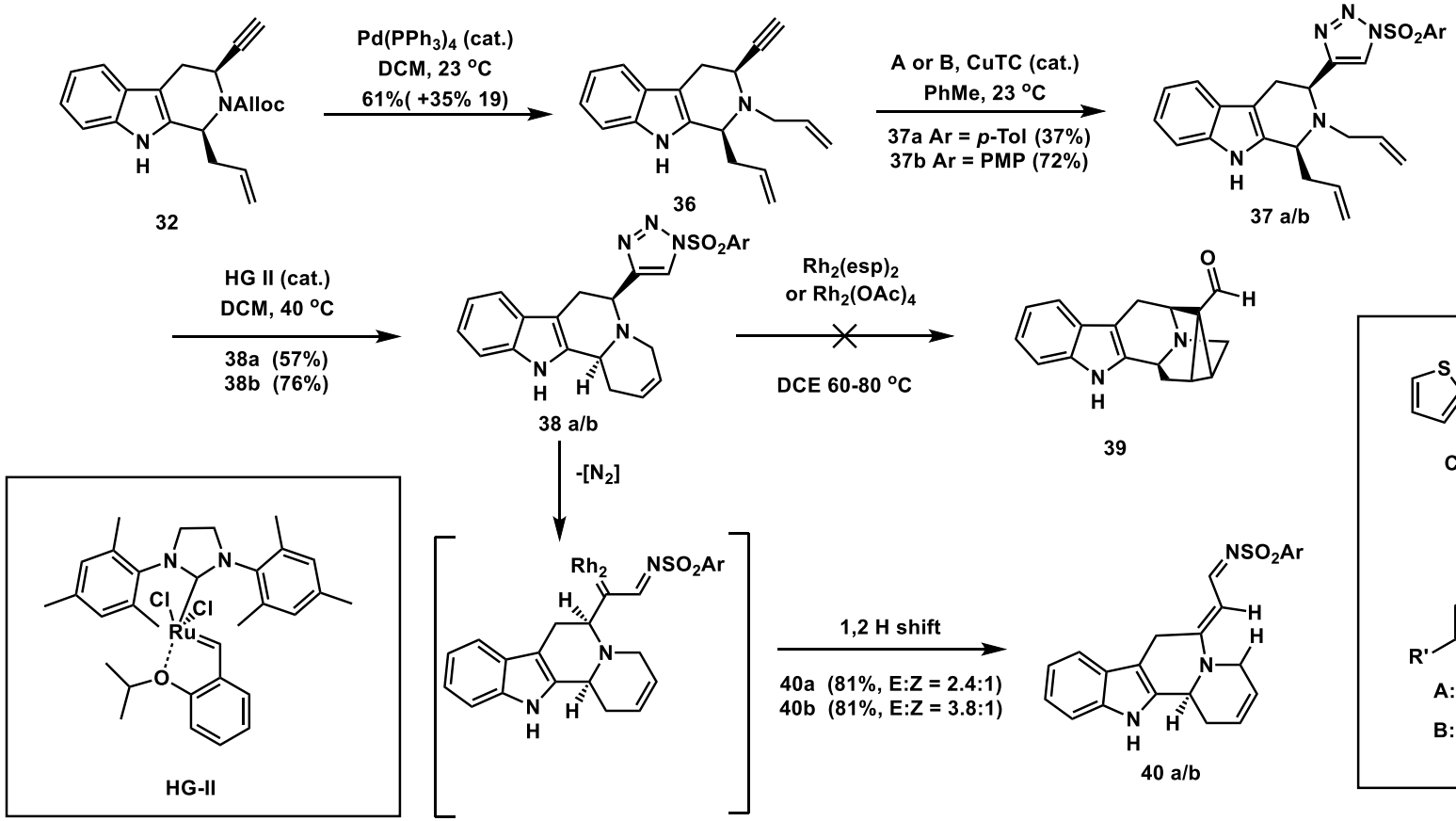
4. *N*-allylation Attempts on Secondary Amine 19, S3–S5 [Table S1]



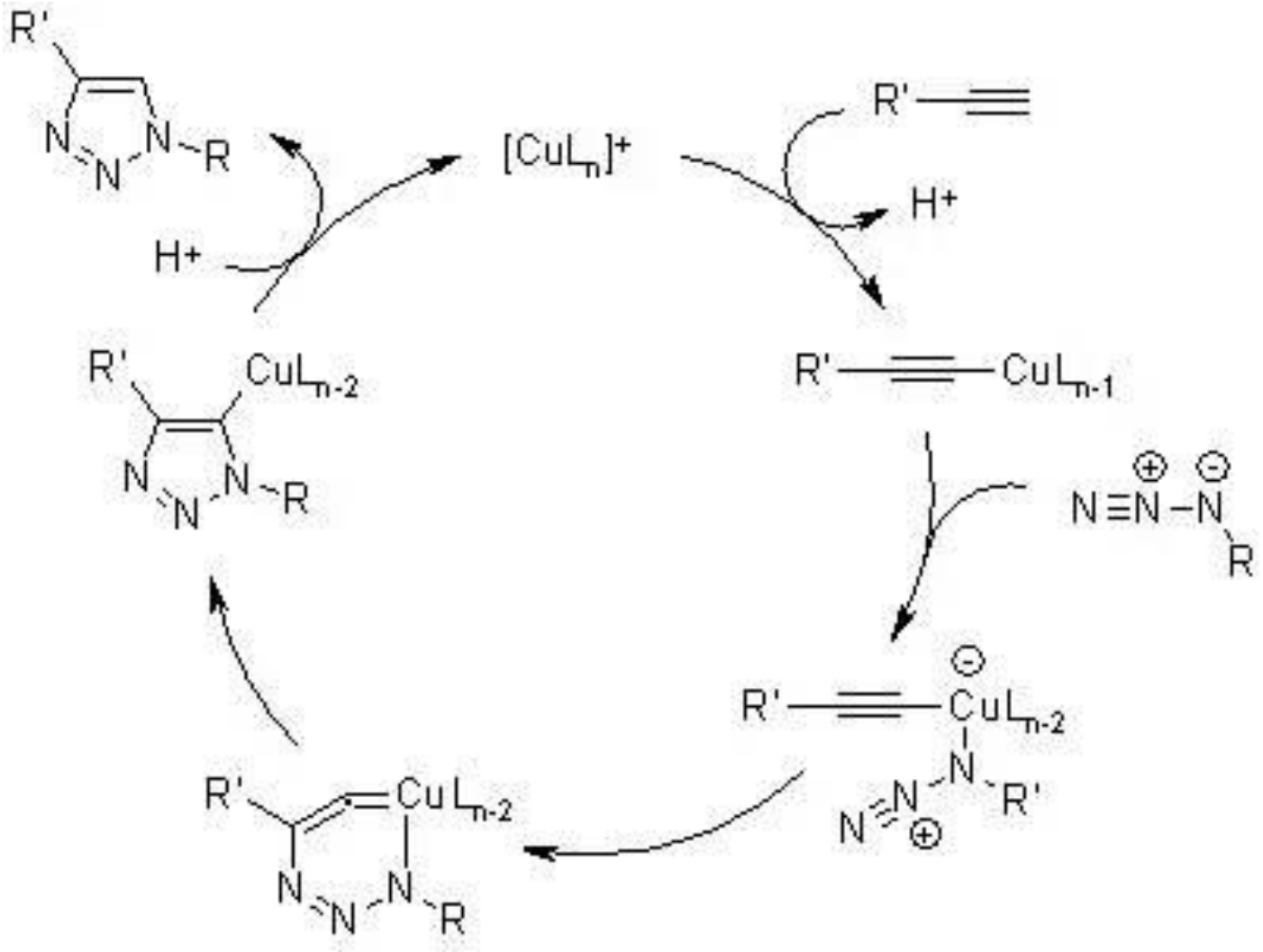


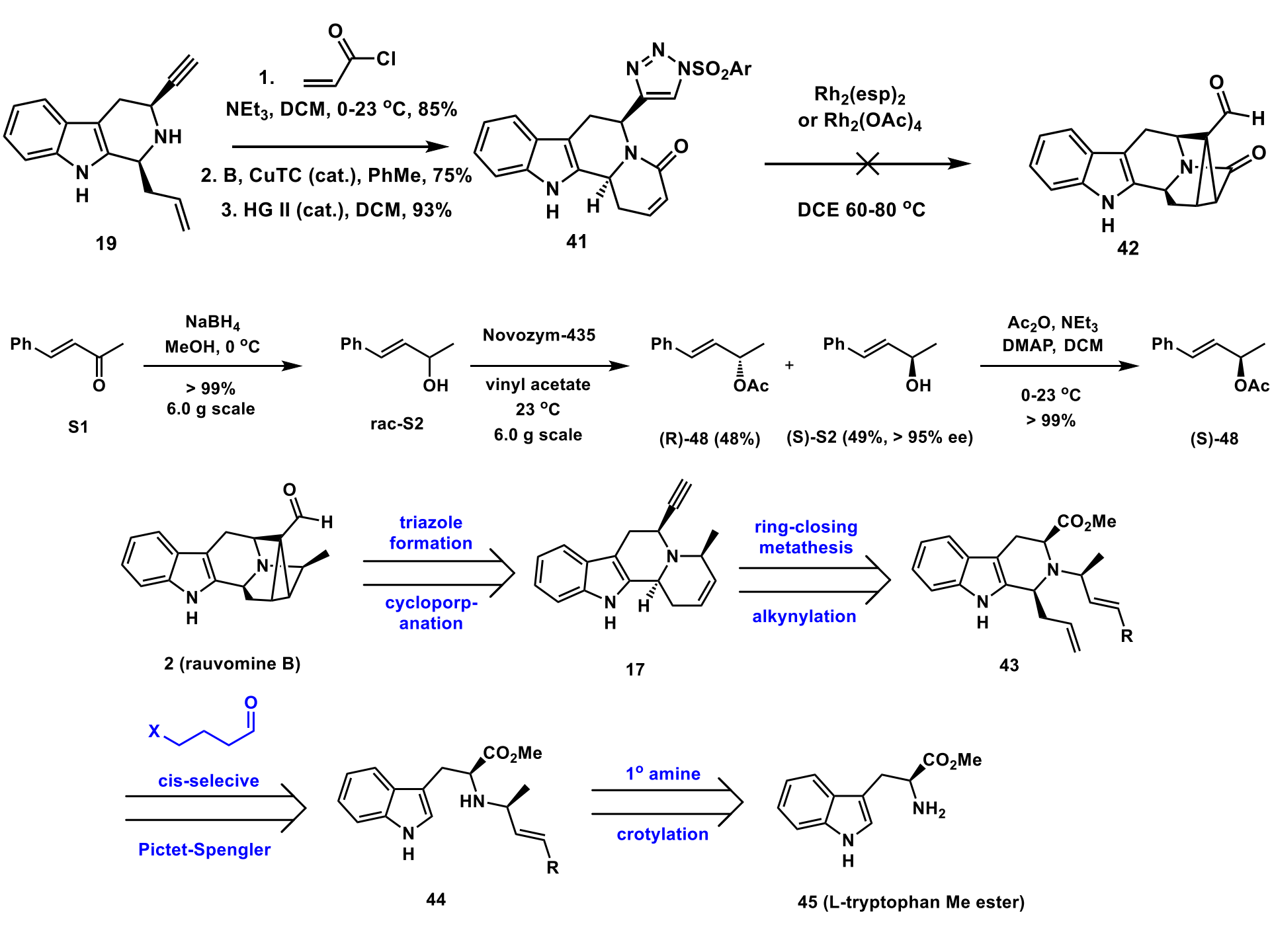
Entry	Starting material	PG	Electrophile	Conditions	Result
1	S3	Boc	S6	(S)-Ir-Tol-BINAP, Cs_2CO_3, DMF, 70 to 90 °C, 16 h	NR
2	S3	Boc	46	$Pd(PPh_3)_4$, PhMe, 23 to 45 °C, 4 h	NR
3	S3	Boc	S9	K_2CO_3, TBAI, DMF, 60 °C, 16 h	NR
4	S3	Boc	S10	K_2CO_3, TBAI, DMF, 60 °C, 16 h	NR
5	S3	Boc	S11	K_2CO_3, DMF, 23 to 80 °C	NR
6	S3	Boc	S11	*i*-Pr_2NEt, DMF, 23 to 80 °C	NR
7	S3	Boc	S12	$[(allyl)PdCl]_2$, CyJohnPhos, DBU, THF, 23 to 45 °C, 20 h	NR
8	19	H	S6	(S)-Ir-Tol-BINAP, Cs_2CO_3, DMF, 50 to 70 °C, 72 h	NR
9	19	H	S7	SPhos Pd G4, DBU, THF, 23 °C, 20 h	NR
10	19	H	S7	$Pd(PPh_3)_4$, Cs_2CO_3, THF, 23 to 40 °C, 18 h	CM
11	19	H	46	$Pd(PPh_3)_4$, THF, 23 to 40 °C, 18 h	CM
12	19	H	S8	NEt_3, DMAP, CH_2Cl_2, 0 to 23 °C, 20 h	NR
13	S4	Boc	S8	*i*-Pr_2NEt, DMAP, CH_2Cl_2, 0 to 23 °C, 20 h	NR
14	S4	Boc	S8	Na_2CO_3, CH_2Cl_2, H_2O, 23 °C, 20 h	NR
15	S4	Boc	S9	K_2CO_3, TBAI, DMF, 60 °C, 16 h	CM
16	S4	Boc	S6	(S)-Ir-Tol-BINAP, Cs_2CO_3, DMF, 70 to 90 °C, 20 h	NR
17	S4	Boc	S12	$[(allyl)PdCl]_2$, CyJohnPhos, DBU, THF, 23 to 45 °C, 20 h	CM
18	S4	Boc	46	$Pd(PPh_3)_4$, PhMe, 90 °C, 16 h	CM
19	S5	H	S6	(S)-Ir-Tol-BINAP, Cs_2CO_3, DMF, 50 °C, 36 h	NR
20	S5	H	S12	$[(allyl)PdCl]_2$, CyJohnPhos, DBU, THF, 23 to 40 °C, 20 h	NR

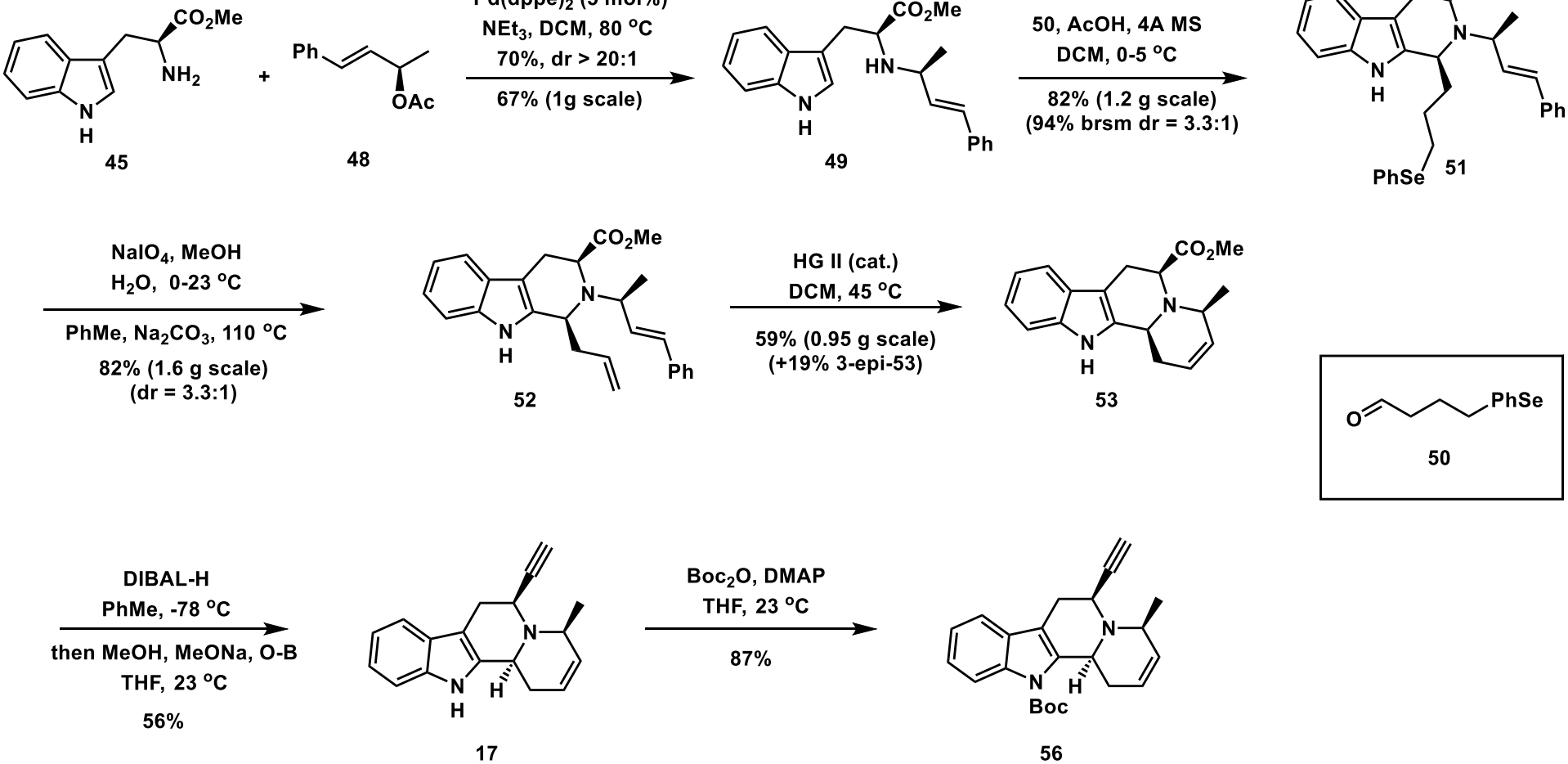
NR = No reaction; CM = Complex mixture


Pd(PPh3)4 (cat.)
DCM, 23 °C
61%(+35% 19)
A or B, CuTC (cat.)
PhMe, 23 °C
37a Ar = p-Tol (37%)
37b Ar = PMP (72%)
HG II (cat.)
DCM, 40 °C
38a (57%)
38b (76%)
Rh2(esp)2
or Rh2(OAc)4
DCE 60-80 °C
-[N2]
1,2 H shift
40a (81%, E:Z = 2.4:1)
40b (81%, E:Z = 3.8:1)
32
36
37 a/b
38 a/b
39
40 a/b
HG-II
CuTC
A: R' = Me
B: R' = OMe

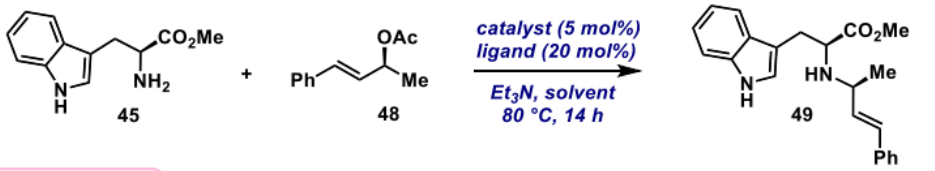
点击化学


R'
N
N
N
R
H+
[CuLn]+
R'
H+
R'
CuLn-2
N
N
N
R
R'
CuLn-1
N≡N−N
R
R'
CuLn-2
N
N
R'
R'
CuLn-2
N
N
N
R

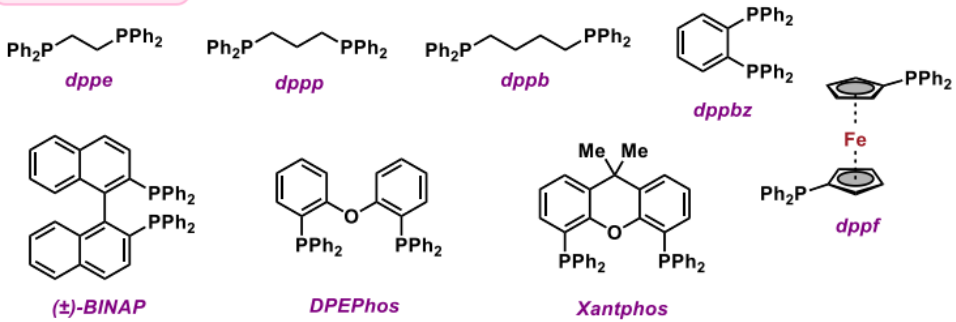

1.
NEt3, DCM, 0-23 °C, 85%
2. B, CuTC (cat.), PhMe, 75%
3. HG II (cat.), DCM, 93%
Rh2(esp)2
or Rh2(OAc)4
DCE 60-80 °C
19
41
42
NaBH4
MeOH, 0 °C
> 99%
6.0 g scale
S1
rac-S2
Novozym-435
vinyl acetate
23 °C
6.0 g scale
(R)-48 (48%)
(S)-S2 (49%, > 95% ee)
Ac2O, NEt3
DMAP, DCM
0-23 °C
> 99%
(S)-48
triazole formation
cycloporp-anation
ring-closing metathesis
alkynylation
2 (rauvomine B)
17
43
cis-selecive
Pictet-Spengler
1° amine
crotylation
44
45 (L-tryptophan Me ester)


CO2Me
NH2
N
H
45
+
Ph
OAc
48
Pd(dppe)2 (5 mol%)
NEt3, DCM, 80 °C
70%, dr > 20:1
67% (1g scale)
CO2Me
HN
N
H
Ph
49
50, AcOH, 4A MS
DCM, 0-5 °C
82% (1.2 g scale)
(94% brsm dr = 3.3:1)
CO2Me
N
N
H
Ph
PhSe
51
NaIO4, MeOH
H2O, 0-23 °C
PhMe, Na2CO3, 110 °C
82% (1.6 g scale)
(dr = 3.3:1)
CO2Me
N
N
H
Ph
52
HG II (cat.)
DCM, 45 °C
59% (0.95 g scale)
(+19% 3-epi-53)
CO2Me
N
N
H
53
O
PhSe
50
DIBAL-H
PhMe, -78 °C
then MeOH, MeONa, O-B
THF, 23 °C
56%
N
N
H
H
17
Boc2O, DMAP
THF, 23 °C
87%
N
N
H
H
Boc
56

6. Optimization of Pd-Catalyzed Stereospecific Allylation [Table S2]

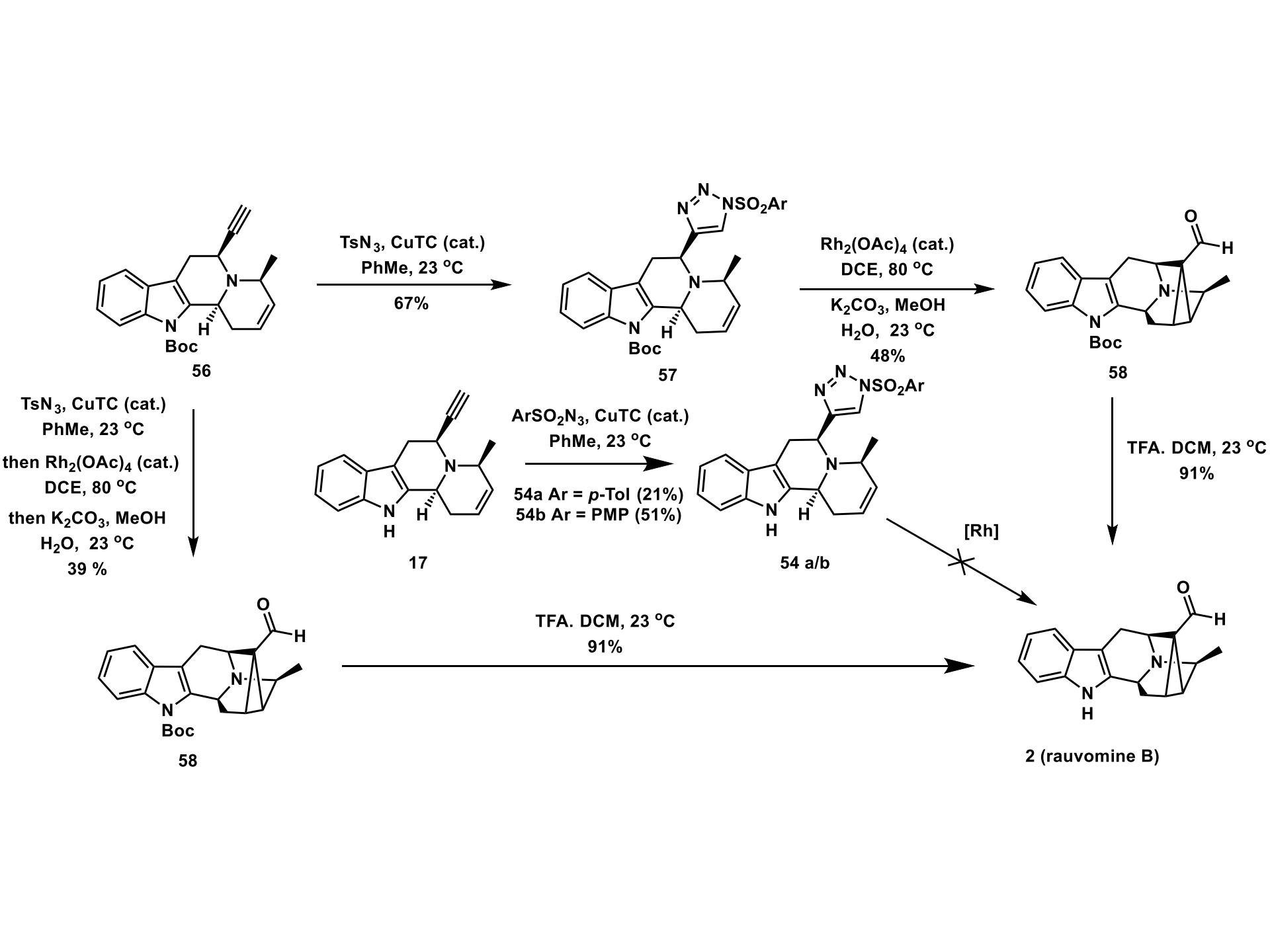


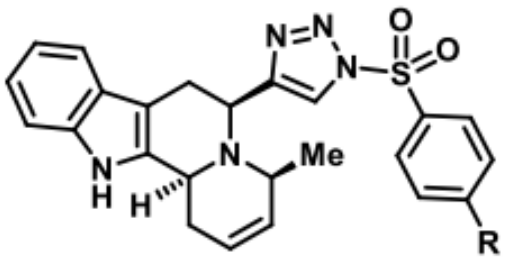
Ligands Screened



Entry	Catalyst	Ligand	Solvent	NMR Yield of major isomer (%)[a]	dr
1	$Pd_2(dba)_3{\cdot}CHCl_3$	dppe	DCE	25	>20:1
2	$Pd_2(dba)_3{\cdot}CHCl_3$	dppp	DCE	37	>20:1
3	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	DCE	55	7.7:1
4	$Pd_2(dba)_3$	dppb	DCE	21	1:0.82
5	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	DCM	31	2.8:1
6	$Pd_2(dba)_3{\cdot}CHCl_3$	dppf	DCE	36	3.1:1
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppbz	DCE	15	>20:1
8	$Pd_2(dba)_3{\cdot}CHCl_3$	(±)-BINAP	DCE	39	5:1
9	$Pd_2(dba)_3{\cdot}CHCl_3$	DPEPhos	DCE	44	6:1
10	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	DCE	57	10:1
11	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	DCM	70	17:1
12	$Pd(dppe)_2$	-	DCE	15	>20:1
13	$Pd(dppe)_2$	-	$PhCF_3$/DCE	7	>20:1
14	*$Pd(dppe)_2$*	-	*DCM*	*82*	*>20:1*

[a]All reactions were carried out in 0.2 mmol scale; 1,3,5-TMB was used as internal standard.

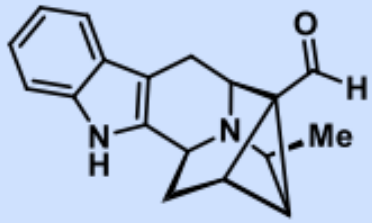

TsN3, CuTC (cat.)
PhMe, 23 °C
67%
Rh2(OAc)4 (cat.)
DCE, 80 °C
K2CO3, MeOH
H2O, 23 °C
48%
TsN3, CuTC (cat.)
PhMe, 23 °C
then Rh2(OAc)4 (cat.)
DCE, 80 °C
then K2CO3, MeOH
H2O, 23 °C
39 %
ArSO2N3, CuTC (cat.)
PhMe, 23 °C
54a Ar = p-Tol (21%)
54b Ar = PMP (51%)
TFA. DCM, 23 °C
91%
[Rh]
TFA. DCM, 23 °C
91%
56
57
58
17
54 a/b
58
2 (rauvomine B)



54a [R = Me]
54b [R = OMe]

Cyclopropanation

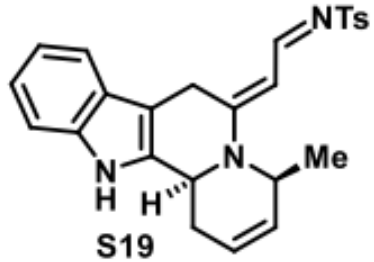
Conditions



2: *rauvomine B*

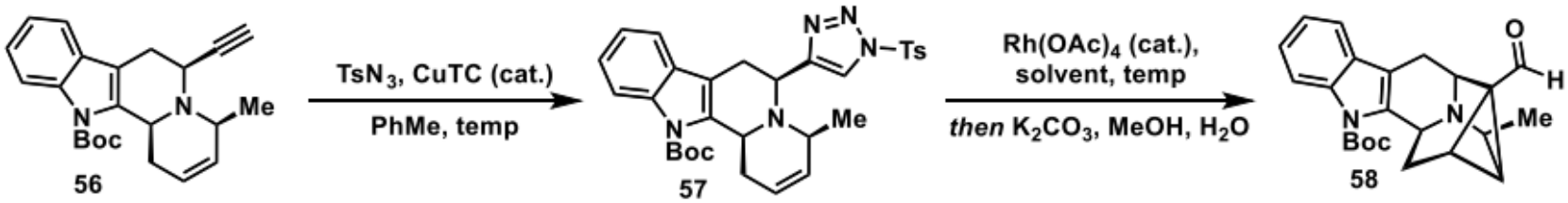
Entry	Substrate	Conditions	Result
1	54b	$Rh_2(esp)_2$, DCE, 65 °C *then* K_2CO_3, MeOH	CM[a]
2	54b	$Rh_2(esp)_2$, Cs_2CO_3 THF, 23 °C	NR[b]
3	54b	TFA, CH_2Cl_2; $Rh_2(esp)_2$, DCE, 65 °C	CM[a]
4	54a	$Rh_2(esp)_2$, DCE, 65 °C	CM[a,c]
5	54a	BH_3THF, CH_2Cl_2; $Rh_2(esp)_2$, DCE, 80 °C	CM[a]

[a]Complex Mixture; [b]No reaction; [c]Hydride shift byproduct



S19

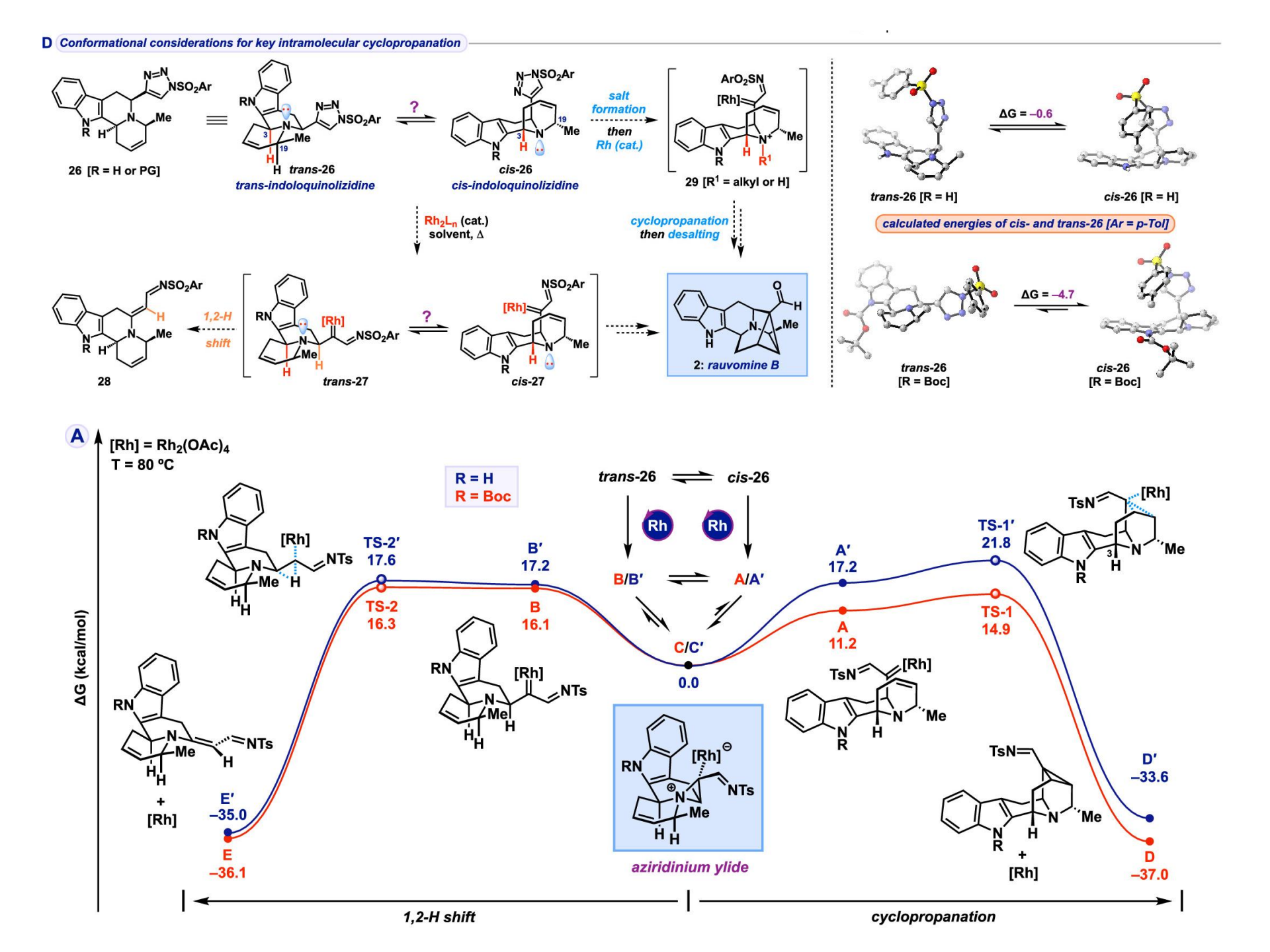
H-shift byproduct

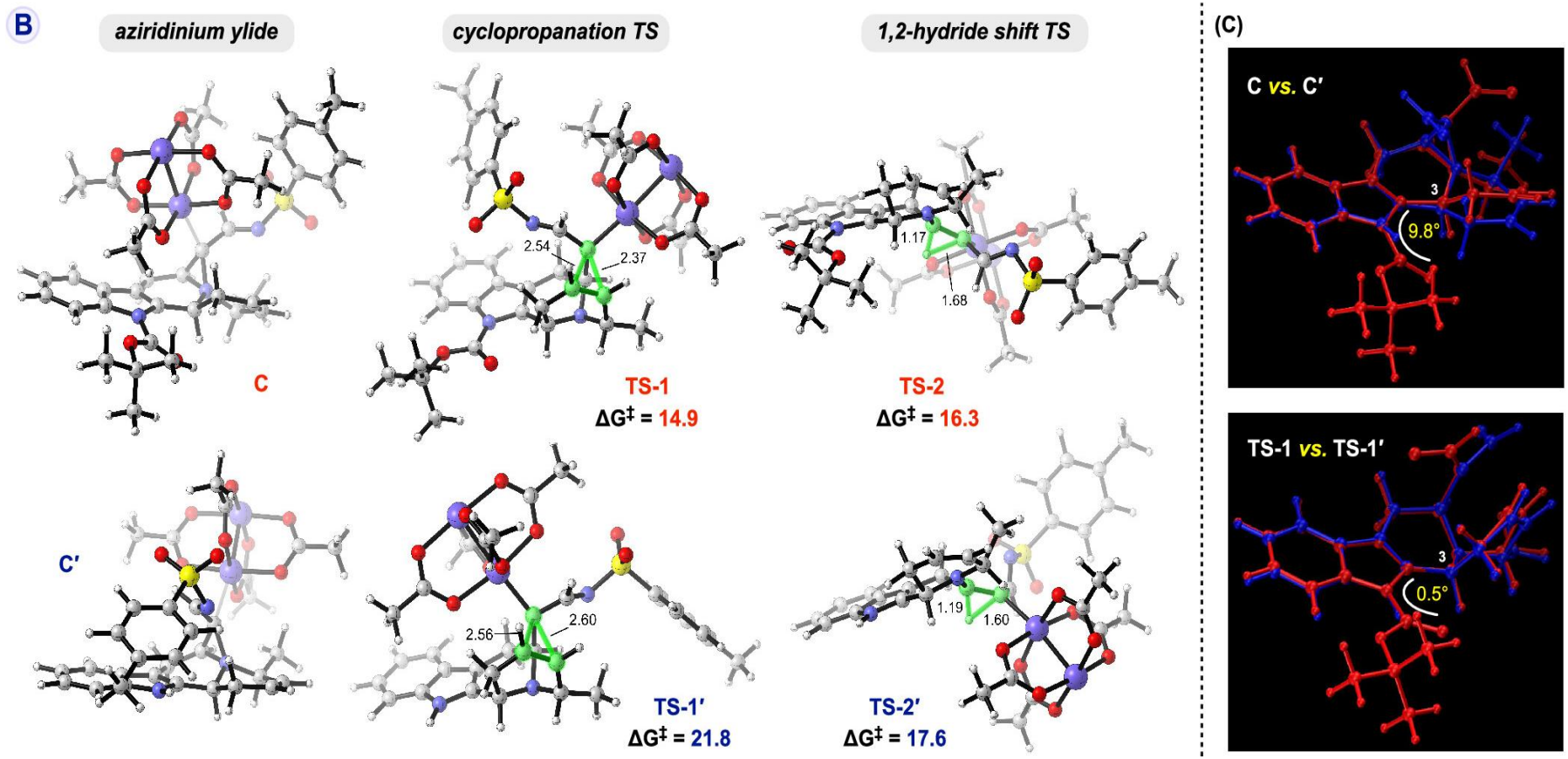


Two-step process

Triazole Formation Step				*Cyclopropanation Step*				
Entry	TsN_3 (equiv)	Temp. (°C)	Yield (%)[a]	Entry	Cat. (equiv)	Temp. (°C)	Solvent	Yield (%)[a]
1	1.5	23	65	1	0.1	80	toluene	41
2	1.5	35	45	2	0.1	80	toluene	39[c]
3	*1.8*	*23*	*67*	*3*	*0.1*	*80*	*DCE*	*48*
4	2.0	23	67	4	0.05	80	DCE	38
5	1.8	23	24[b]	5	0.05	65	DCE	27
				6	0.15	80	DCE	41
				7	0.1	100	DCE	46[d]
				8	0.1	80	CH_2Cl_2	44

[a]Isolated yield; [b]DCE was used as solvent; [c]silica gel was added in the reaction mixture after cyclopropanation step instead of K_2CO_3; [d]reaction completed within 3 h.


D Conformational considerations for key intramolecular cyclopropanation
26 [R = H or PG]
trans-indoloquinolizidine
trans-26
cis-indoloquinolizidine
cis-26
salt formation
then Rh (cat.)
29 [R1 = alkyl or H]
Rh2Ln (cat.)
solvent, Δ
cyclopropanation
then desalting
1,2-H shift
28
trans-27
cis-27
2: rauvomine B
ΔG = –0.6
trans-26 [R = H]
cis-26 [R = H]
calculated energies of cis- and trans-26 [Ar = p-Tol]
ΔG = –4.7
trans-26 [R = Boc]
cis-26 [R = Boc]
A
[Rh] = Rh2(OAc)4
T = 80 °C
R = H
R = Boc
trans-26
cis-26
Rh
B/B′
A/A′
C/C′
0.0
TS-2′ 17.6
TS-2 16.3
B′ 17.2
B 16.1
A′ 17.2
A 11.2
TS-1′ 21.8
TS-1 14.9
E′ –35.0
E –36.1
D′ –33.6
D –37.0
aziridinium ylide
ΔG (kcal/mol)
1,2-H shift
cyclopropanation


B
aziridinium ylide
cyclopropanation TS
1,2-hydride shift TS
C
TS-1
ΔG‡ = 14.9
TS-2
ΔG‡ = 16.3
C′
TS-1′
ΔG‡ = 21.8
TS-2′
ΔG‡ = 17.6
2.54
2.37
1.17
1.68
2.56
2.60
1.19
1.60
(C)
C vs. C′
3
9.8°
TS-1 vs. TS-1′
3
0.5°