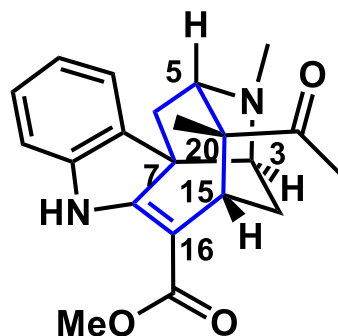


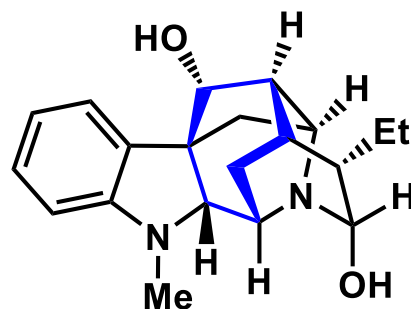
Asymmetric Total Synthesis of (+)-Alstonlarsine A

DOI:10.1021/jacs.2c06518

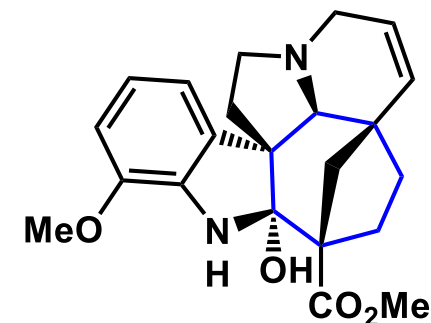
Jun-Jun Yao, Rui Ding, Xiaoming Chen, and Hongbin Zhai*



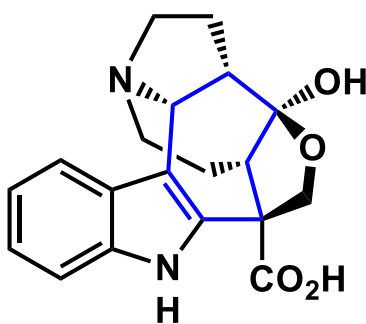
(+)-alstonlarsine A (1)



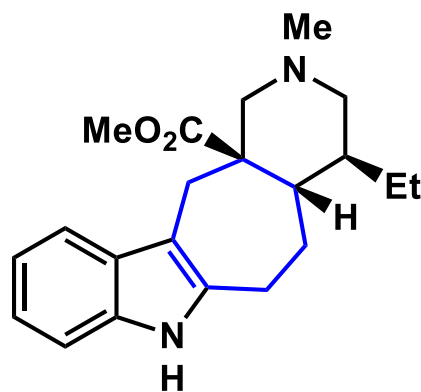
ajmaline (2)



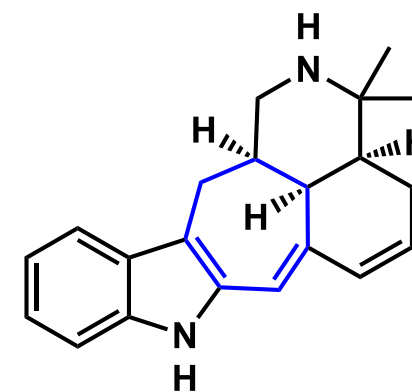
(-)-kopsifoline A (3)



(-)-actinophyllic acid (4)



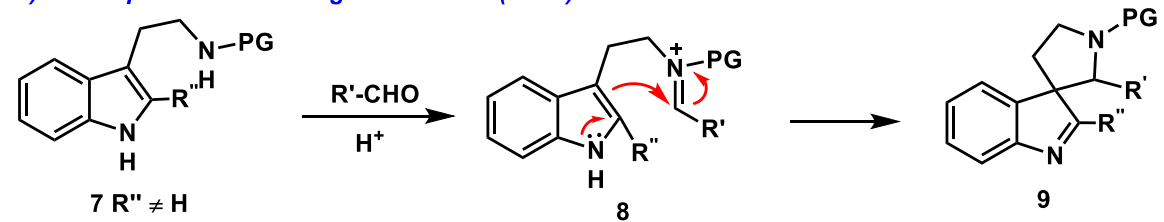
ervatamine (5)



aristolasene (6)

Figure 1. Structures of (+)-alstonlarsine A (1) and other representative monoterpenoid indole alkaloids (MIAs) containing the cyclohepta[*b*]indole motif.

A) Interrupted Pictet-SPengler Reaction (IPSR)



B) Retrosynthetic Analysis of Alstonlarsine A

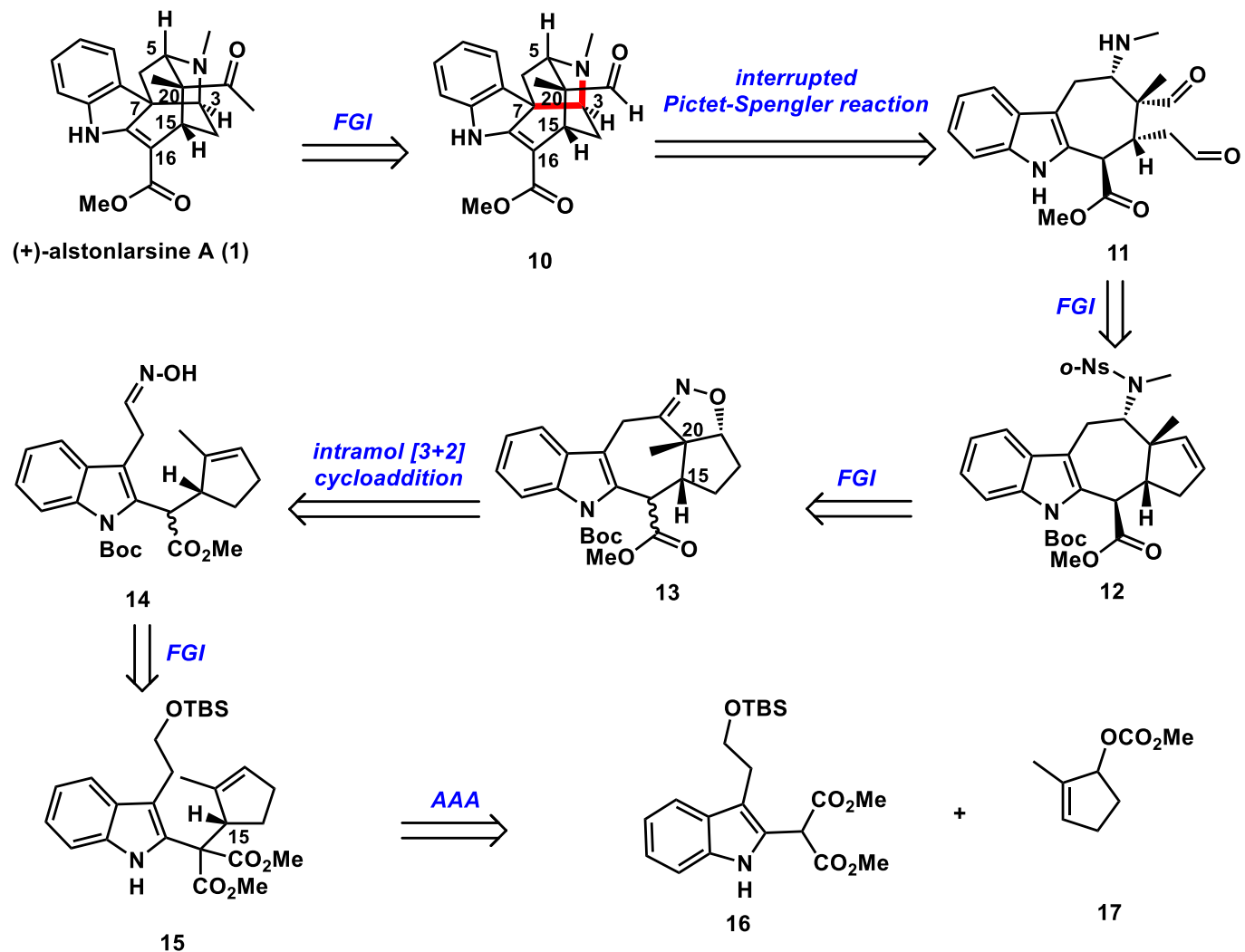
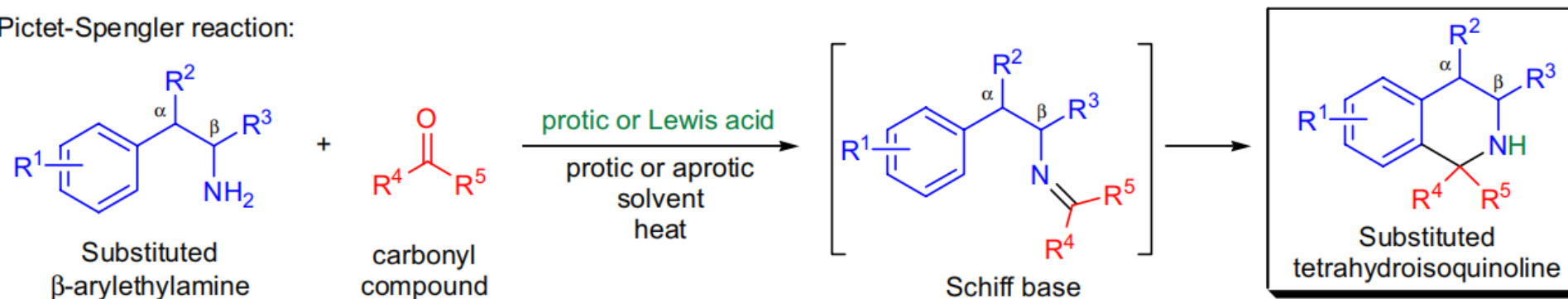


Figure 2. Interrupted Pictet-Spengler reaction (IPSR) and retrosynthetic analysis of (+)-alstonlarsine A.

PICTET-SPENGLER TETRAHYDROISOQUINOLINE SYNTHESIS

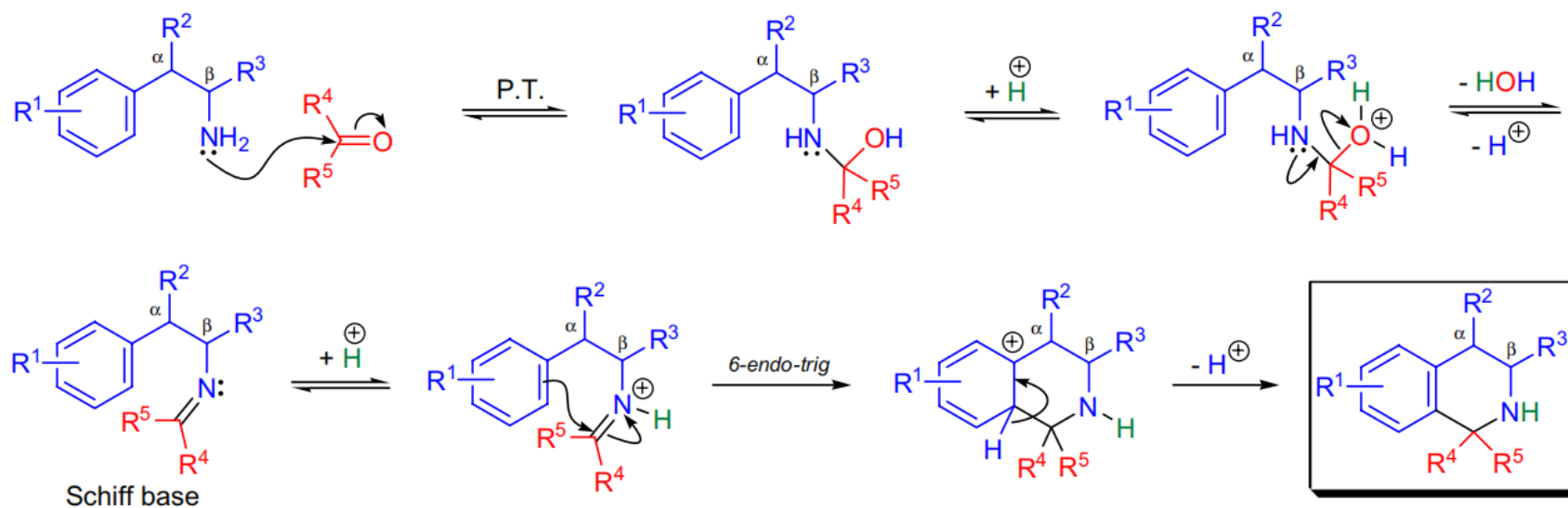
(References are on page 652)

Pictet-Spengler reaction:



R^1 = H, alkyl, aryl, O-alkyl, usually an electron-donating group (EDG); R^{2-3} = H, alkyl, aryl; R^{4-5} = H, alkyl, aryl; protic acid: HCl, H₂SO₄, TFA, silica gel; Lewis acid: BF₃·OEt₂

Mechanism: 2,9



Scheme 1. Preparation of Compounds 16 and 17

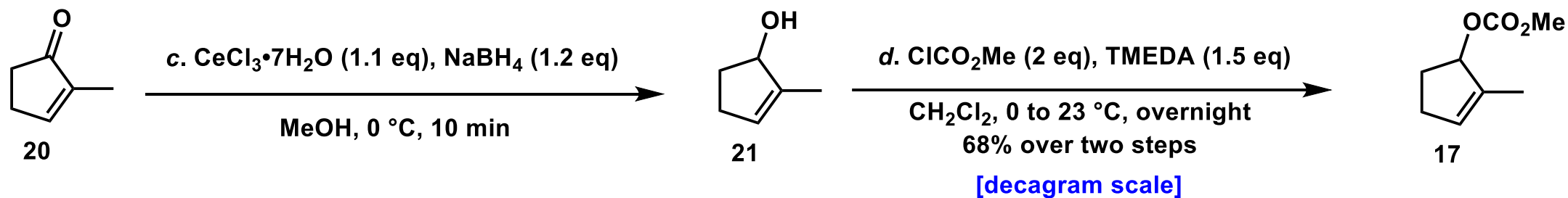
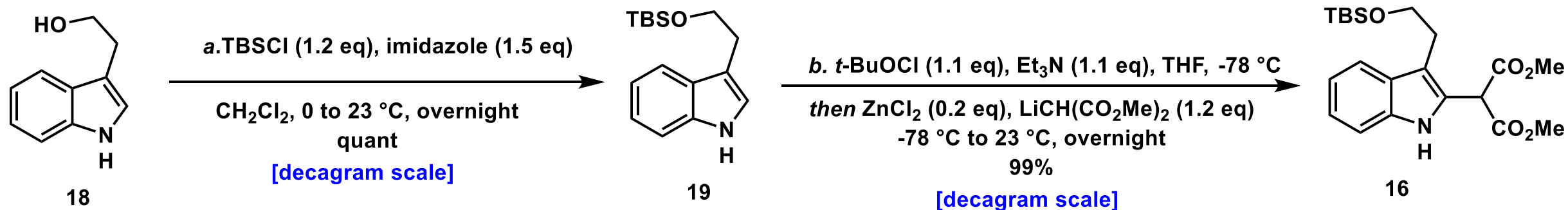
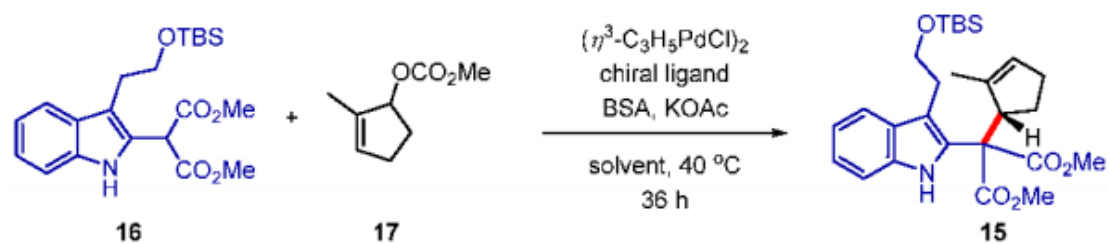
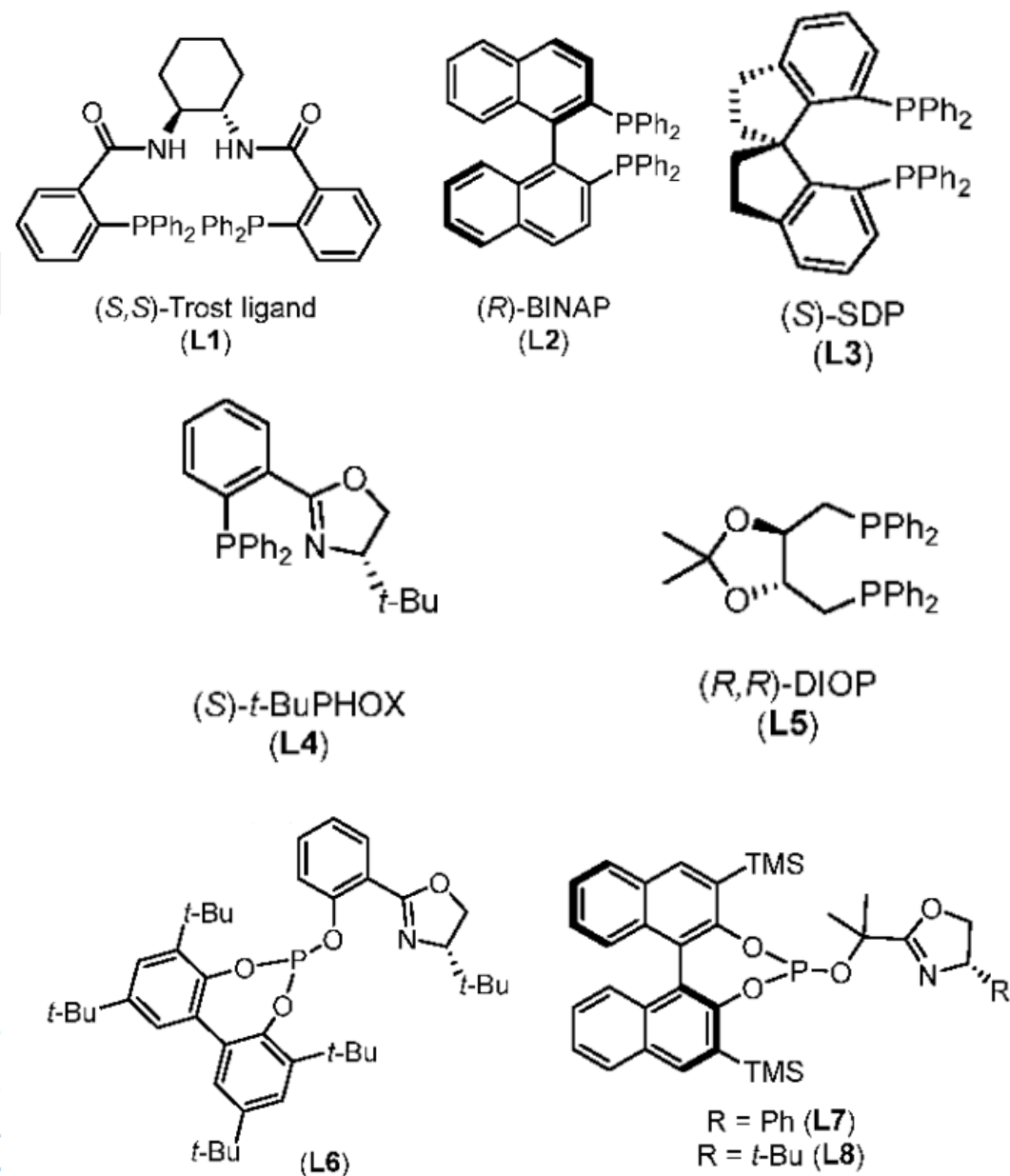


Table 1. Study of the Asymmetric Allylic Alkylation^a

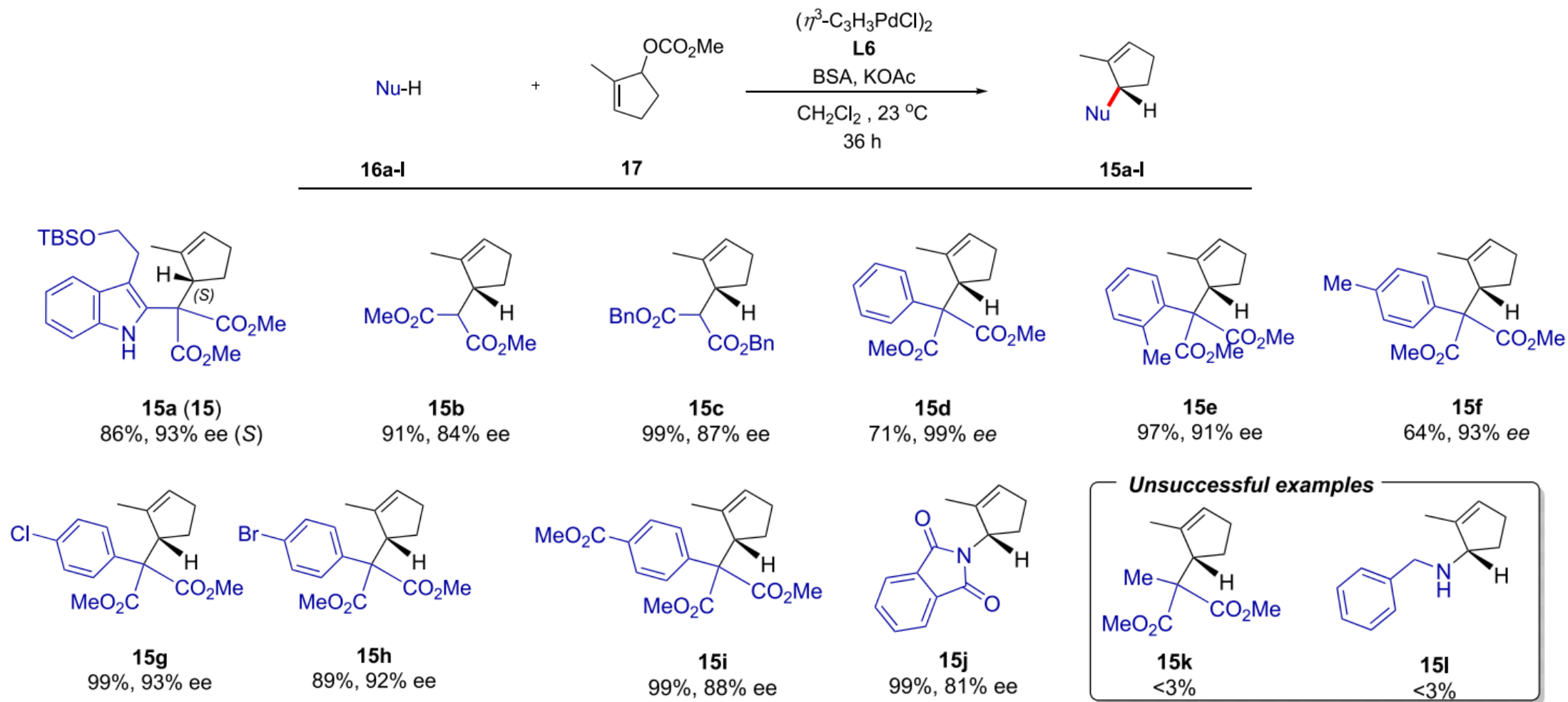


entry	ligand	solvent	yield (%) ^b	ee (%)
1	L1	CH ₂ Cl ₂	0	N/A
2	L2	CH ₂ Cl ₂	63	3
3	L3	CH ₂ Cl ₂	88	21
4	L4	CH ₂ Cl ₂	0	N/A
5	L5	CH ₂ Cl ₂	73	7
6	L6	CH ₂ Cl ₂	86	93
7	L7	CH ₂ Cl ₂	55	77
8	L8	CH ₂ Cl ₂	98	81
9	L6	PhMe	44	85
10	L6	THF	68	92
11	L6	DCE	82	N/A
12 ^c	L6	CH ₂ Cl ₂	86	93
13 ^{c,d}	L6	CH ₂ Cl ₂	95	93

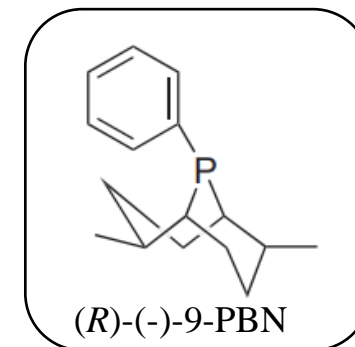
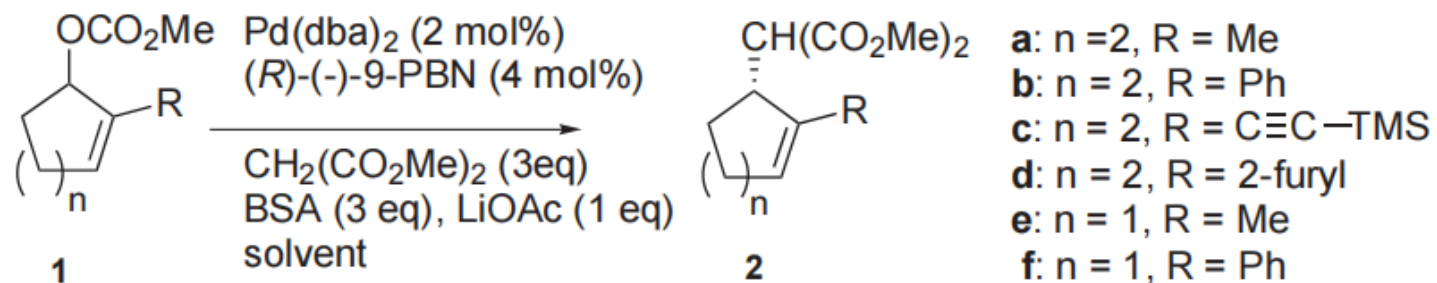


^aAll reactions were performed with **16** (0.2 mmol), **17** (3 equiv), $(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$ (2.5 mol %), chiral ligand (7.5 mol %), BSA (3 equiv), and KOAc (5 mol %) in solvent (2 mL) at 40 °C for 36 h. ^bIsolated yield. ^cReaction was run at 23 °C. ^dReaction was performed at 16.2 g scale of **16**. BSA = N,O-bis(trimethylsilyl)acetamide; DCE = dichloroethane; N/A = not applicable.

Table 2. Scope of the Nucleophiles^{a,b}



^aAll reactions were performed with **16** (0.2 mmol), **17** (3 equiv), (η^3 -C₃H₅PdCl)₂ (2.5 mol %), **L6** (7.5 mol %), BSA (3 equiv), and KOAc (5 mol %) in CH₂Cl₂ (2 mL) at 23 °C. ^bIsolated yield. BSA = N,O-bis(trimethylsilyl)acetamide.

Table 1. Asymmetric allylic substitution reaction using 9-PBN and palladium

Run	n	R	Time	Solvent	Yield	% ee
1	2	Me	12 h	$\text{ClCH}_2\text{CH}_2\text{Cl}$	95%	51 ^a
2	2	Ph	2 h	$\text{ClCH}_2\text{CH}_2\text{Cl}$	97%	95 ^b
3	2	Ph	2 h	THF	96%	91
4	2	Ph	2 h	PhCF_3	96%	90
5	2	$\text{C}\equiv\text{C}-\text{TMS}$	3 h	$\text{ClCH}_2\text{CH}_2\text{Cl}$	97%	90 ^a
6	2	2-furyl	4 h	$\text{ClCH}_2\text{CH}_2\text{Cl}$	96%	54 ^c
7	1	Me	12 h	THF	97%	50 ^{a,d}
8	1	Ph	4 h	$\text{ClCH}_2\text{CH}_2\text{Cl}$	96%	83 ^{b,d}

^a Determined by NMR analysis using $\text{Eu}(\text{hfc})_3$.

^b Determined by HPLC analysis using Daicel Chiralcel OD-H after conversion to the anilide of the corresponding monocarboxylic acid.

^c Determined by HPLC analysis using Daicel Chiralcel OD-H.

^d The absolute configuration was not determined.

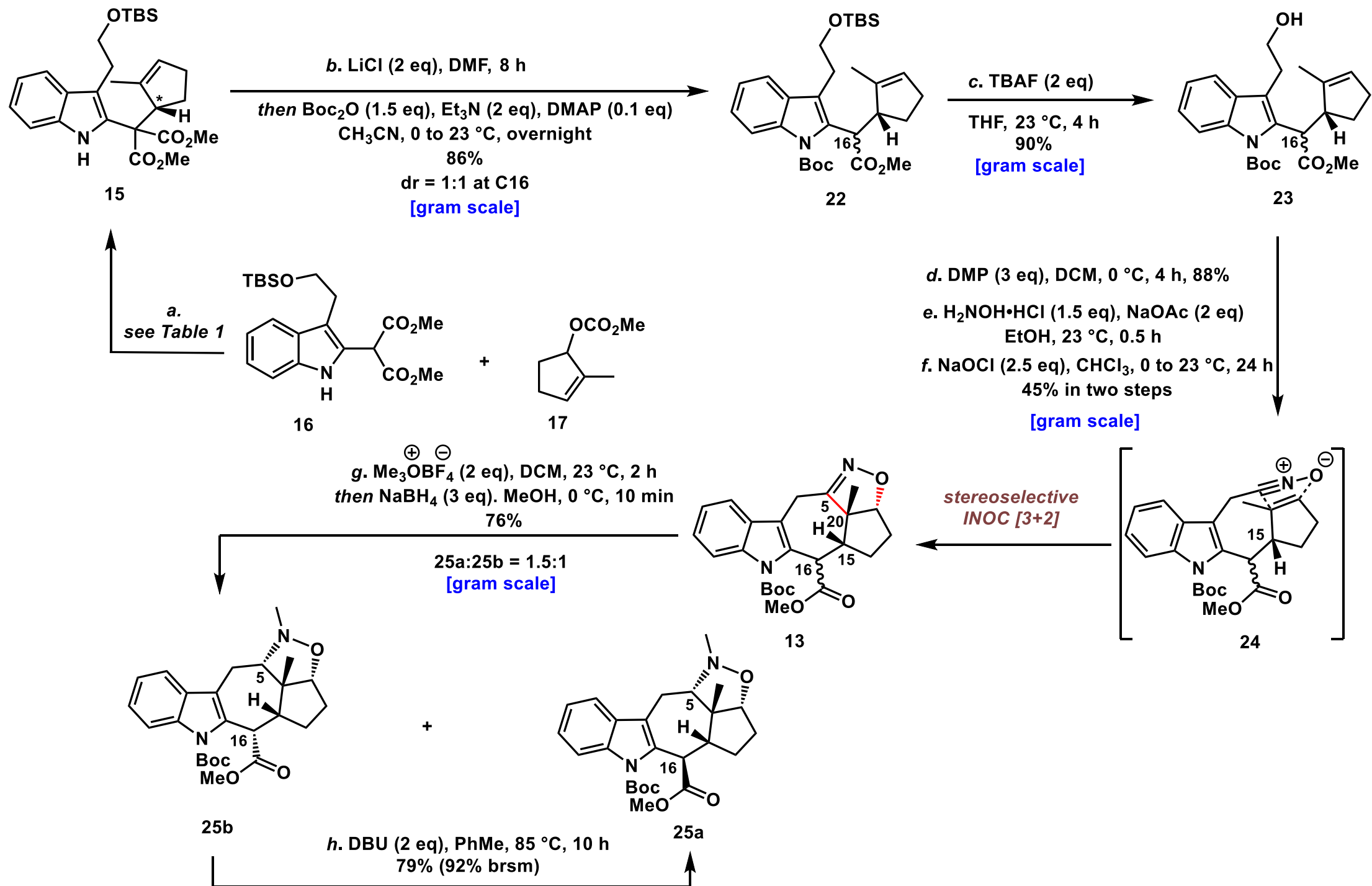
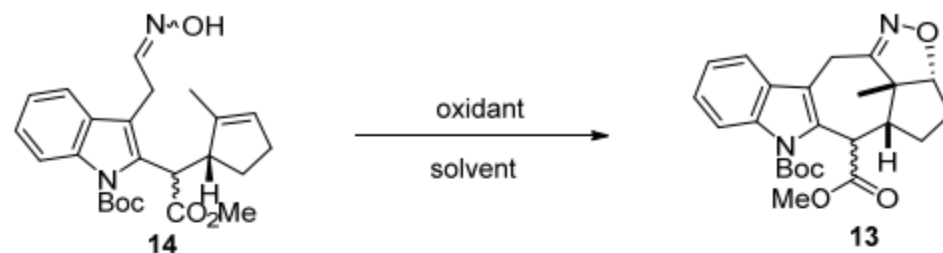
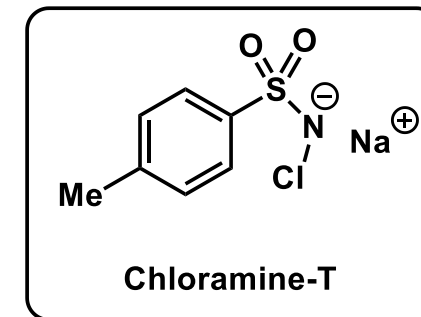
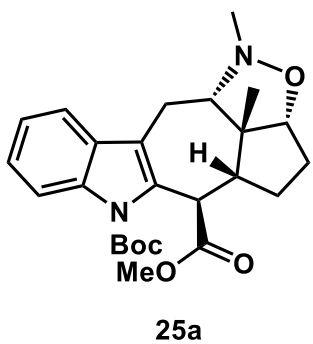


Table S1. Optimization of the INOC [3+2]^a

entry	oxidant	additive	temperature	solvent	yield ^b
1	PIDA	—	0 to 23 °C	CH ₂ Cl ₂	trace
2	PhIO	—	0 to 23 °C	CH ₃ CN	trace
3	MnO ₂	—	0 to 23 °C	CH ₂ Cl ₂	ND
4	Chloramine-T	—	reflux	CH ₃ OH	ND
5	Chloramine-T	—	0 to 23 °C	CH ₃ CN/H ₂ O	trace
6	t-BuOCl	Et ₃ N	0 to 23 °C	CH ₂ Cl ₂	trace
7	oxone	NaCl, Na ₂ CO ₃	23 °C	CH ₃ CN/H ₂ O	ND
8	NaClO	—	0 to 23 °C	CH ₂ Cl ₂	<46%
9	NaClO	—	0 to 23 °C	CHCl ₃	46-53%
10	NaClO	Et ₃ N	0 to 23 °C	CH ₂ Cl ₂	trace
11	NaClO	Et ₃ N	0 to 23 °C	CHCl ₃	trace

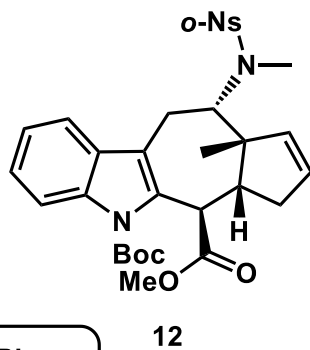


^aAll reactions were performed with 0.1 mmol of **14**, 0.2 mmol of oxidant in 5 mL of solvent; ^bIsolated yield; ND = not detected.



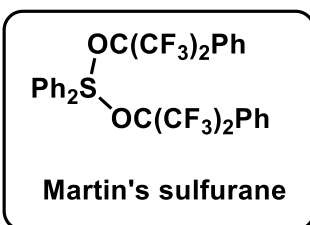
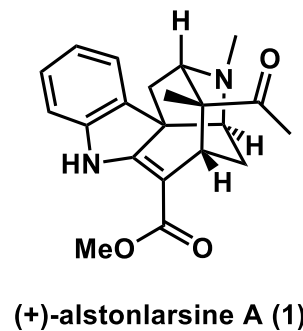
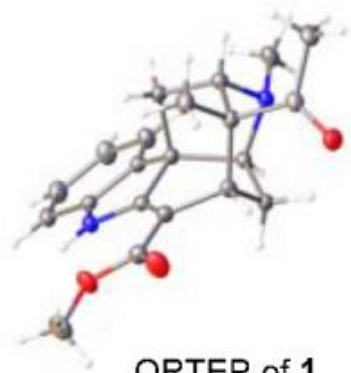
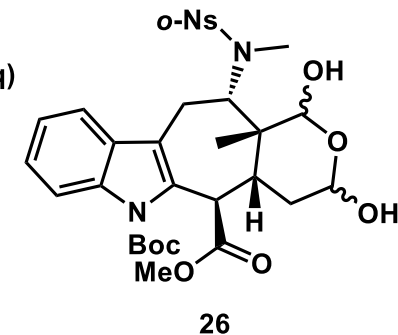
i. Raney Ni, H₂, MeOH, 23 °C

j. Martin's sulfurane (3 eq), DCM, 23 °C, 1 h
 then *o*-NsCl (5 eq), Et₃N (10 eq), DMAP (0.1 eq)
 DCM, 0 to 23 °C, 8 h
 60% over two steps



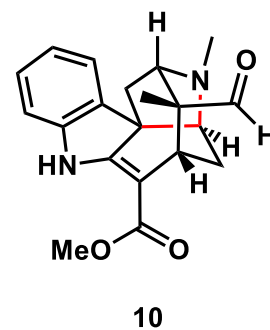
k. K₂OsO₄·2H₂O (5 mol%), NMO (2 eq), citric acid (2 eq)
 acetone/H₂O = 2:1, 23 °C, 16 h

then NaIO₄ (3 eq), THF/H₂O = 2:1, 23 °C, 8 h
 75%



m. MeMgBr (30 eq), THF, 0 °C, 2 h

n. DMP (3 eq), DCM, 0 °C, 2 h
 42% in two steps



l. PhSH (2 eq), Cs₂CO₃ (3 eq)
 CH₃CN, 23 to 50 °C, 2 h

then Me₂S, TFA, DCM, 50 °C, 10 h
 77%

