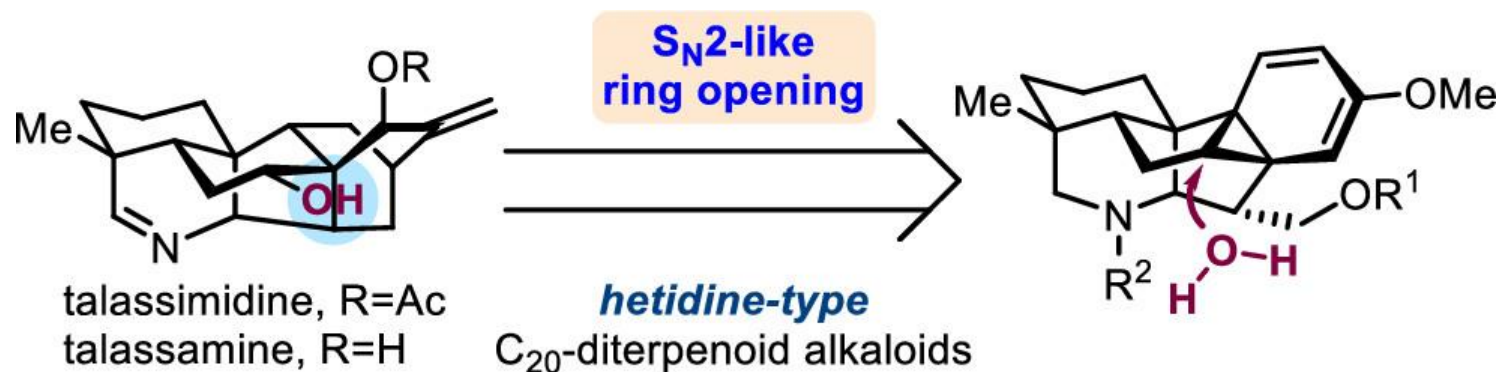
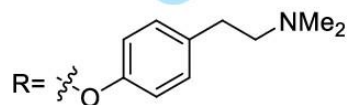
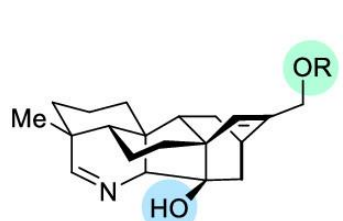
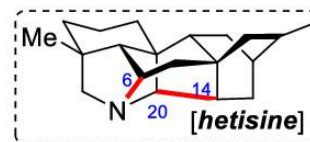
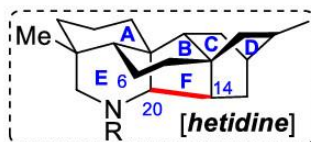
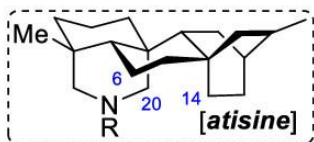


# Asymmetric Total Synthesis of Hetidine-Type C<sub>20</sub>-Diterpenoid Alkaloids: (+)-Talassimidine and (+)-Talassamine

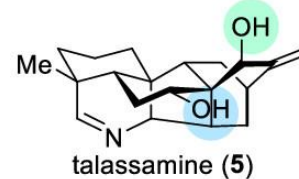
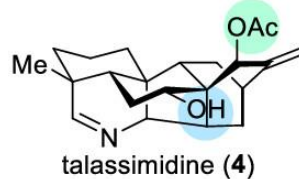
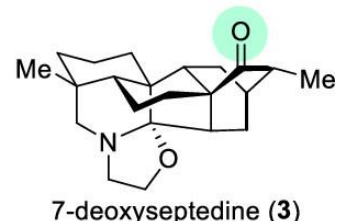
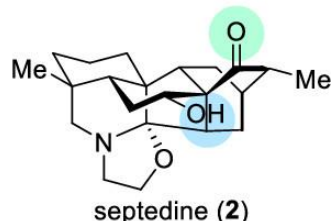
Quanzheng Zhang,<sup>†</sup> Zhao Yang,<sup>†</sup> Qi Wang, Shuangwei Liu, Tao Zhou, Yankun Zhao, and Min Zhang\*



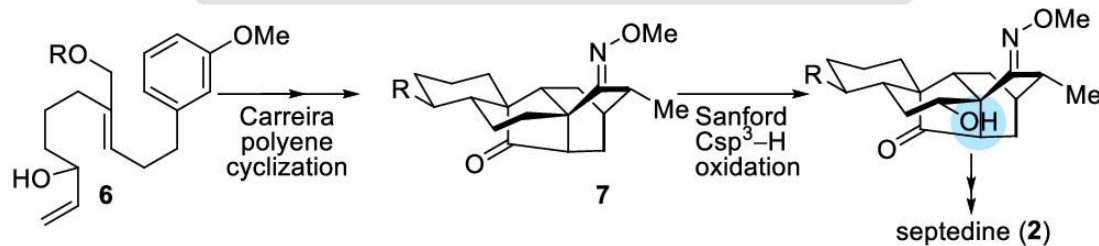
**A) Selected subtypes of C<sub>20</sub>-diterpenoid alkaloids and hetidine-type members**



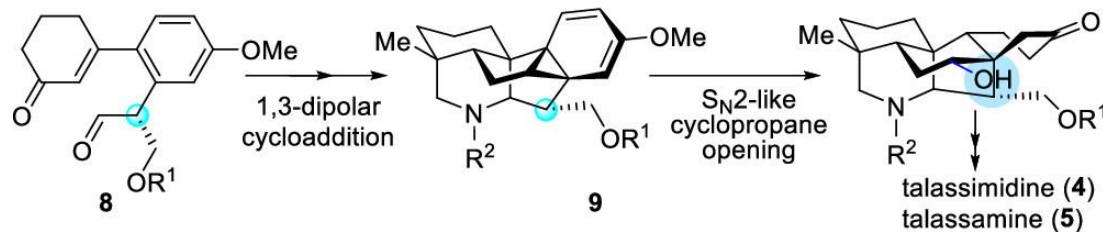
navirine (1)



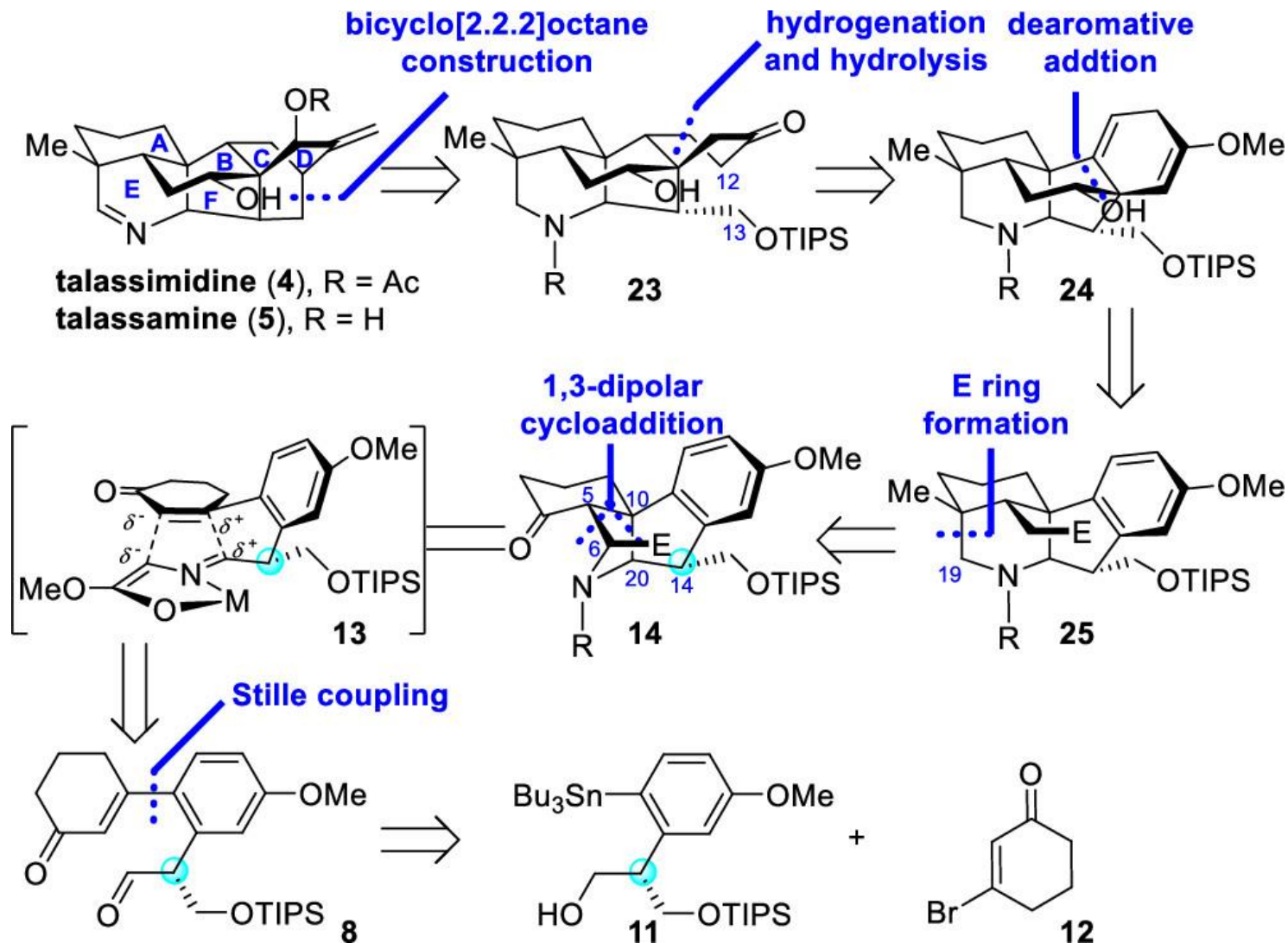
**B) Li's synthetic strategy for the hetidine-type alkaloids**



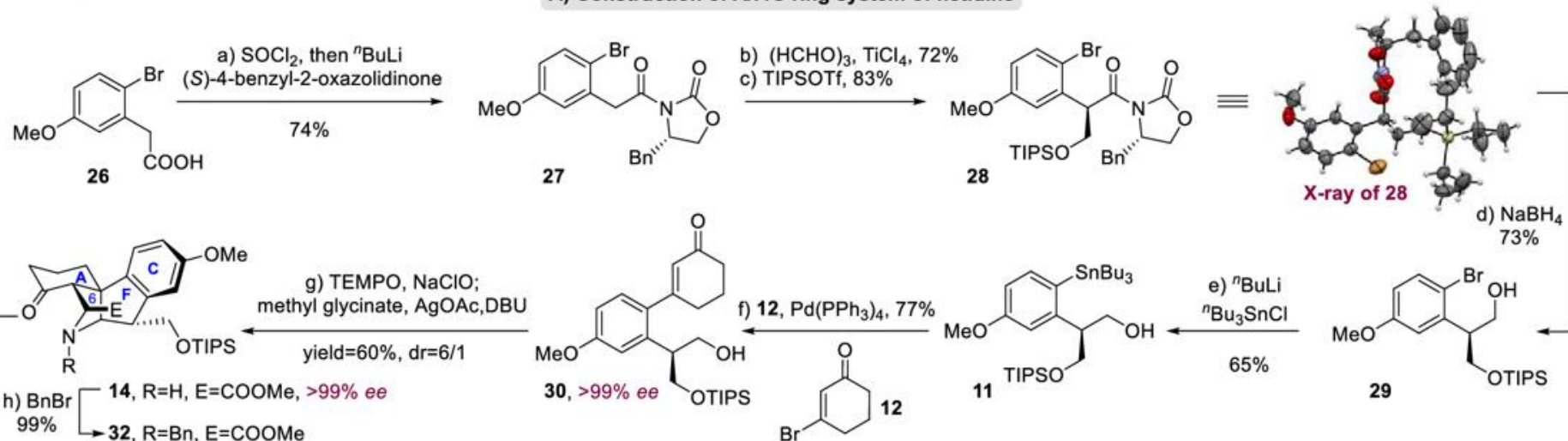
**C) Our strategy for the hetidine-type alkaloids (this work)**



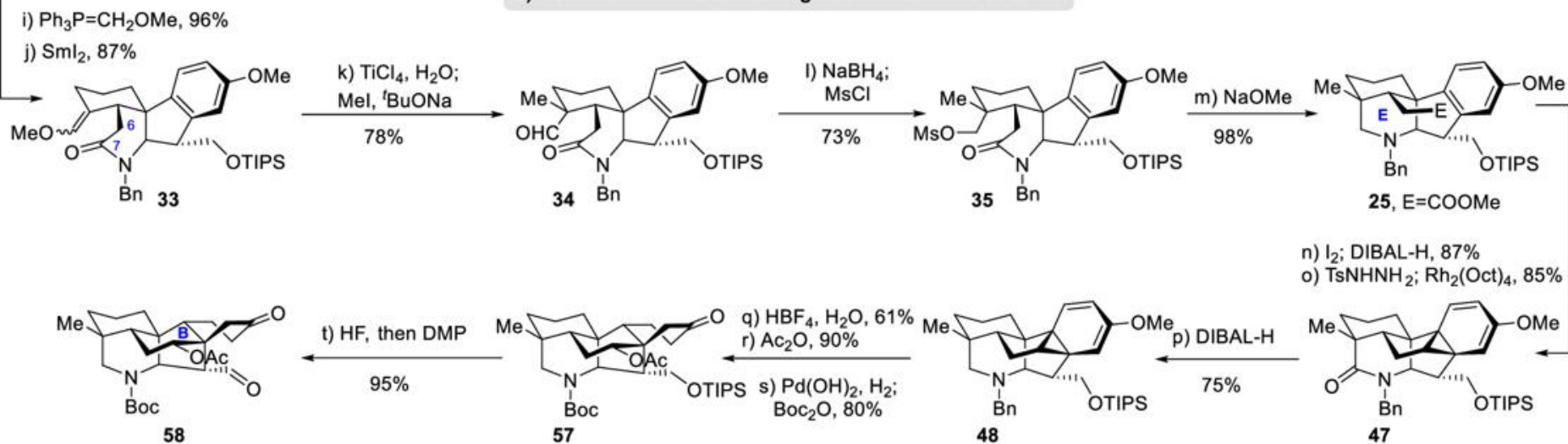
# Retrosynthetic Analysis of (+)-Talassimidine and (+)-Talassamine



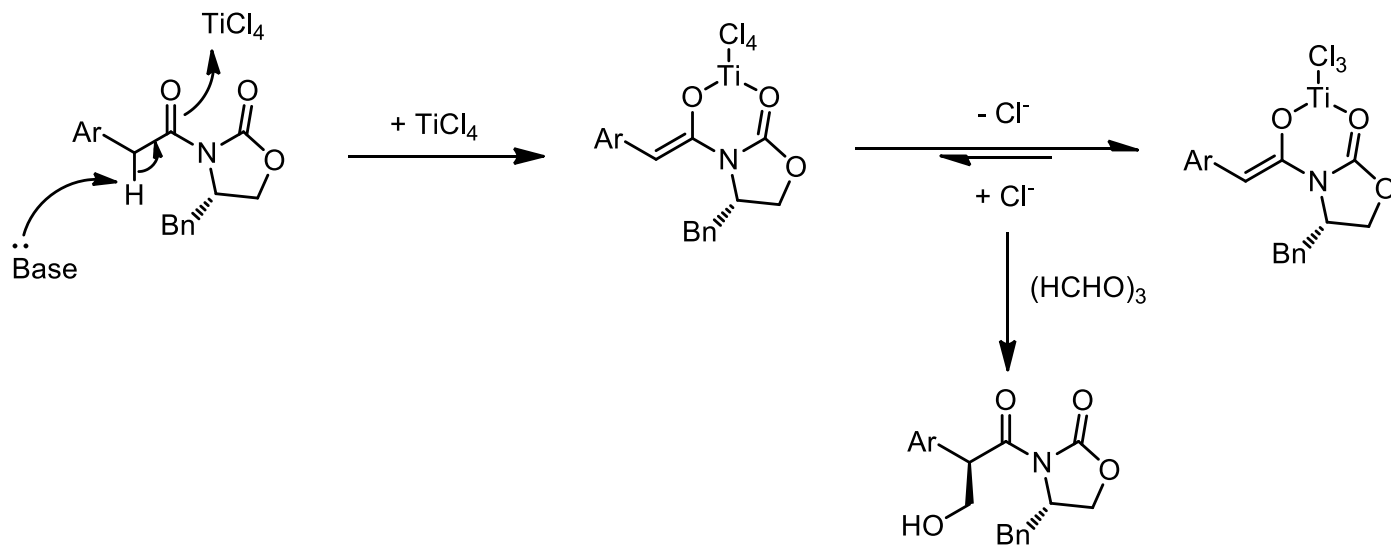
### A) Construction of A/F/C ring system of hetidine



### B) Construction of E and B rings and installment of C7-OH

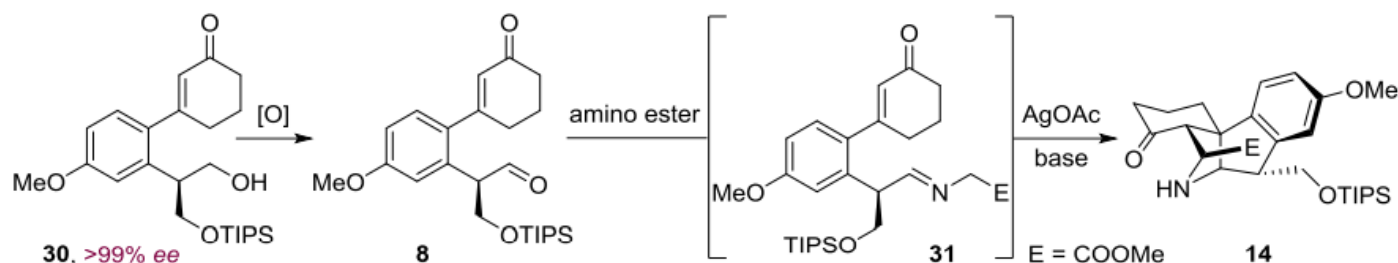


# Evans asymmetric aldol reaction



*J. Am. Chem. Soc.* **1990**, *112*, 8215.

# Optimization of the Asymmetric 1,3-Dipolar Cycloaddition



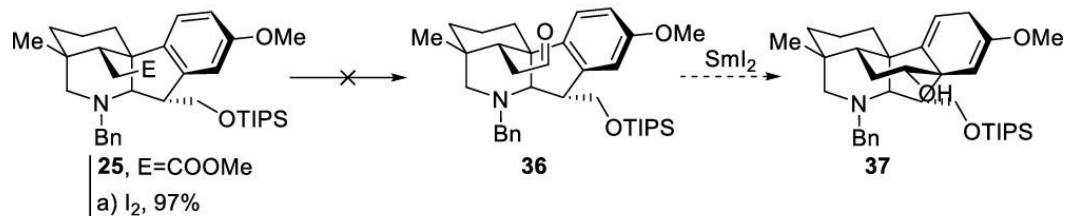
entry	[O] <sup>a,b</sup>	amino ester source <sup>c,d</sup>	base <sup>e</sup>	yield (%) <sup>f</sup>	dr <sup>g</sup>	ee (%) <sup>h</sup>
1	[DMP]	Ph <sub>3</sub> P=NCH <sub>2</sub> CO <sub>2</sub> Me	DBU	54	7:1	45
2	[DMP]	Ph <sub>3</sub> P=NCH <sub>2</sub> CO <sub>2</sub> Me	Et <sub>3</sub> N	45	5:1	54
3	[DMP]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	Et <sub>3</sub> N	40	4:1	50
4 <sup>i</sup>	[DMP]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	Et <sub>3</sub> N	<5		
5 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	Et <sub>3</sub> N	51	4:1	>99
6 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	DIPEA	53	4:1	>99
7 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	TMG	56	4:1	>99
8 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	DBU	65	6:1	>99
9 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	Cs <sub>2</sub> CO <sub>3</sub>	37	4:1	>99
10 <sup>i</sup>	[TEMPO]	NH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Me	K <sub>2</sub> CO <sub>3</sub>	42	4:1	>99
11 <sup>i</sup>	[TEMPO]	Ph <sub>3</sub> P=NCH <sub>2</sub> CO <sub>2</sub> Me	DBU	45	5:1	36

<sup>a</sup>[DMP] oxidation: **30** (0.1 mmol), Dess–Martin periodinane (0.15 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), rt, 0.5 h, chromatography on silica gel. <sup>b</sup>[TEMPO] oxidation: **30** (0.10 mmol), TEMPO (0.01 mmol), KBr (0.20 mmol), NaClO (10% in H<sub>2</sub>O, 0.20 mmol), NaHCO<sub>3</sub> (saturated aqueous solution, 2 mL), CH<sub>2</sub>Cl<sub>2</sub> (3 mL), 0 °C to rt, 3 min, aqueous workup. <sup>c</sup>**8**, N<sub>3</sub>CH<sub>2</sub>COOMe/PPh<sub>3</sub> (0.11 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), 0 °C, 1 h. <sup>d</sup>**8**, NH<sub>2</sub>CH<sub>2</sub>COOMe·HCl (0.20 mmol), Et<sub>3</sub>N (0.22 mmol), MgSO<sub>4</sub> (0.60 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), 0 °C, 1 h. <sup>e</sup>Crude **31**, AgOAc (0.01 mmol), base (0.11 mmol), toluene (2 mL), rt, 1 h. <sup>f</sup>Isolated yield of the major diastereoisomer from **30**. <sup>g</sup>Ratio of yields of the two isolated diastereoisomers. <sup>h</sup>Of the major diastereoisomer; determined by chiral HPLC analysis. <sup>i</sup>Crude **8** was used for the next step without chromatography purification.

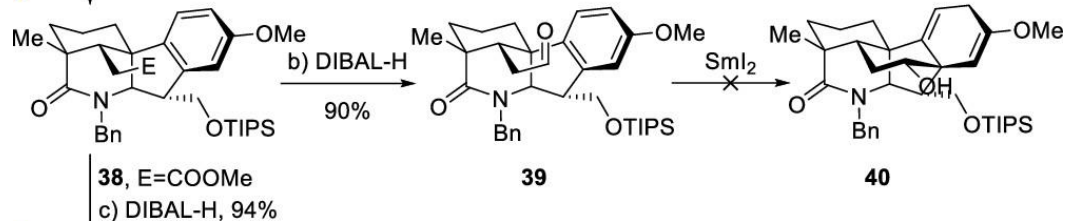


# Failed Attempts to Construct the B Ring

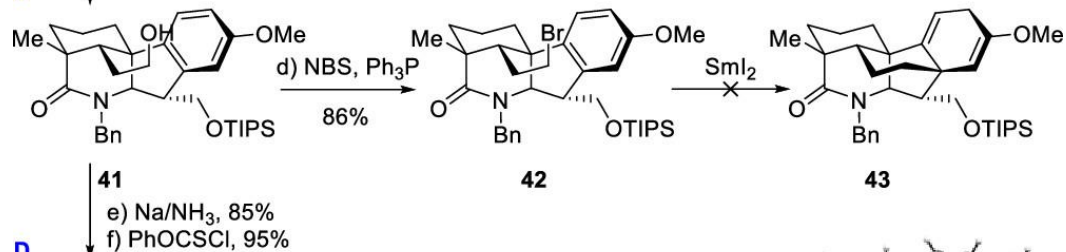
**A**



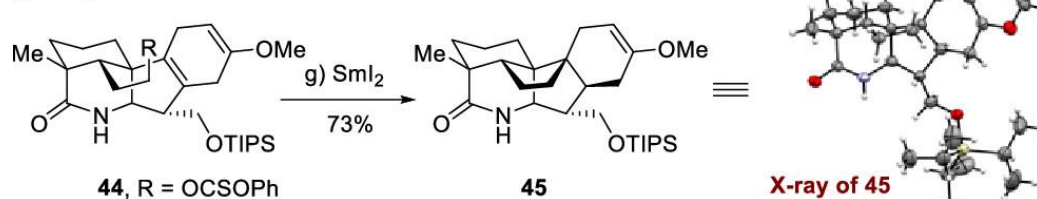
**B**



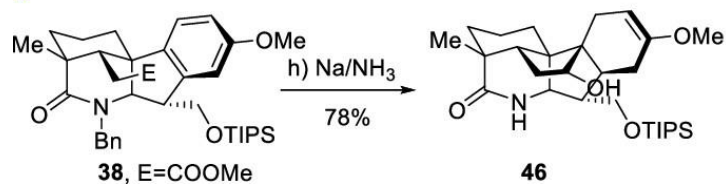
**C**



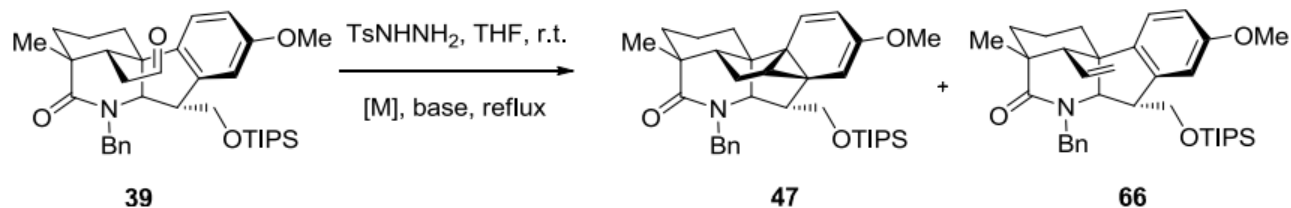
**D**



**E**



## Preparation of 47

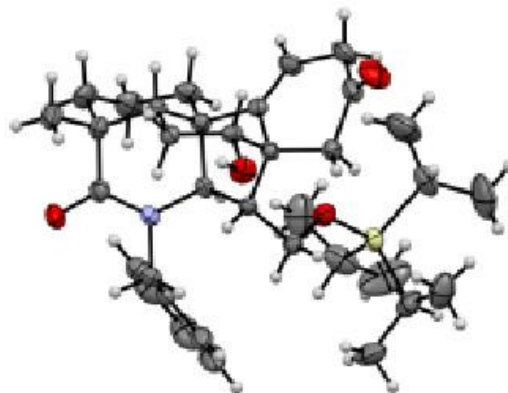
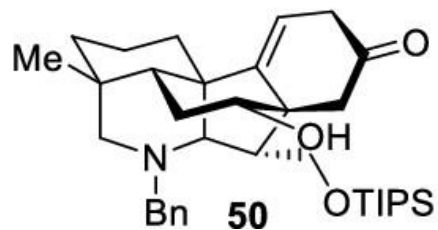
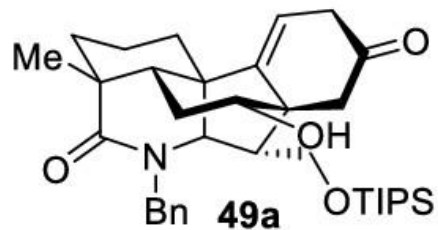
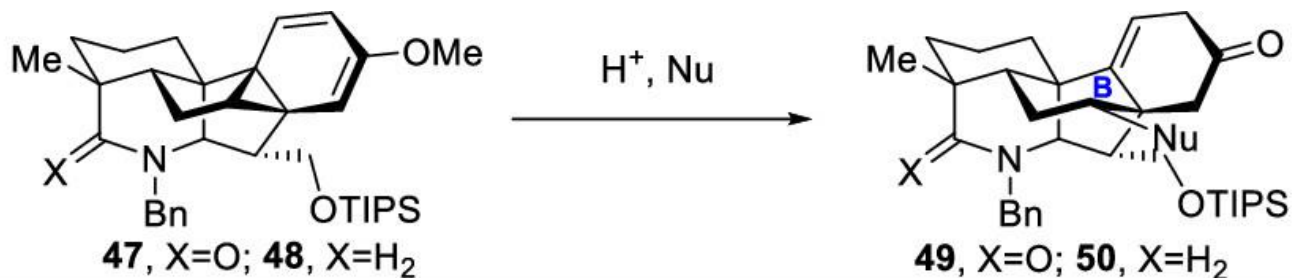


**Table S2 Optimization of Metal-Catalyzed Carbene Dearomatization**

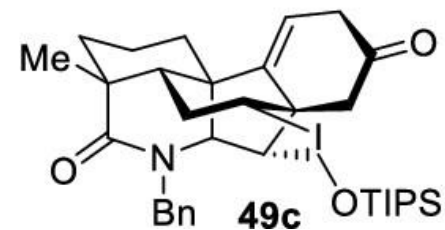
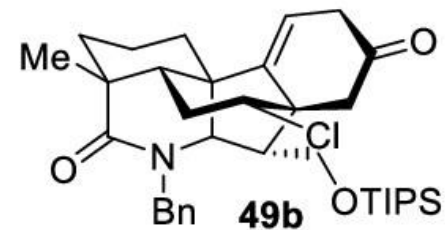
Entry	Conditions	Yield ( <b>47</b> : <b>66</b> )
1	$\text{Cu}(\text{OAc})_2$ , NaH, toluene, 110 °C	30% ( <b>66</b> )
2	$\text{Cu}(\text{OAc})_2$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	93% ( <b>66</b> )
3	$\text{Cu}(\text{acac})_2$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	80% ( <b>66</b> )
4	$\text{AgOAc}$ , toluene, 90 °C	<5% ( <b>66</b> )
5	$\text{Rh}_2(\text{OAc})_4$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	63% ( <b>47</b> : <b>66</b> = 2 : 1)
6	$\text{Rh}_2(\text{Oct})_4$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	88% ( <b>47</b> : <b>66</b> = 5 : 1)
7	$\text{Rh}(\text{PPh}_3)_3\text{Cl}$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	60% ( <b>47</b> : <b>66</b> = 1 : 3)
8	$\text{Rh}_2(\text{acac})_2\text{CO}_2$ , $\text{K}_2\text{CO}_3$ , toluene, 110 °C	78% ( <b>47</b> : <b>66</b> = 1 : 1)
9	$\text{Rh}_2(\text{Oct})_4$ , $\text{K}_2\text{CO}_3$ , 1,4-dioxane, 90 °C	86% ( <b>47</b> : <b>66</b> = 3 : 1)
10	$\text{Rh}_2(\text{Oct})_4$ , $\text{K}_2\text{CO}_3$ , 1,4-dioxane, 130 °C	85% ( <b>47</b> : <b>66</b> = 9 : 1)



# Nucleophilic Ring Opening of the Cyclopropane

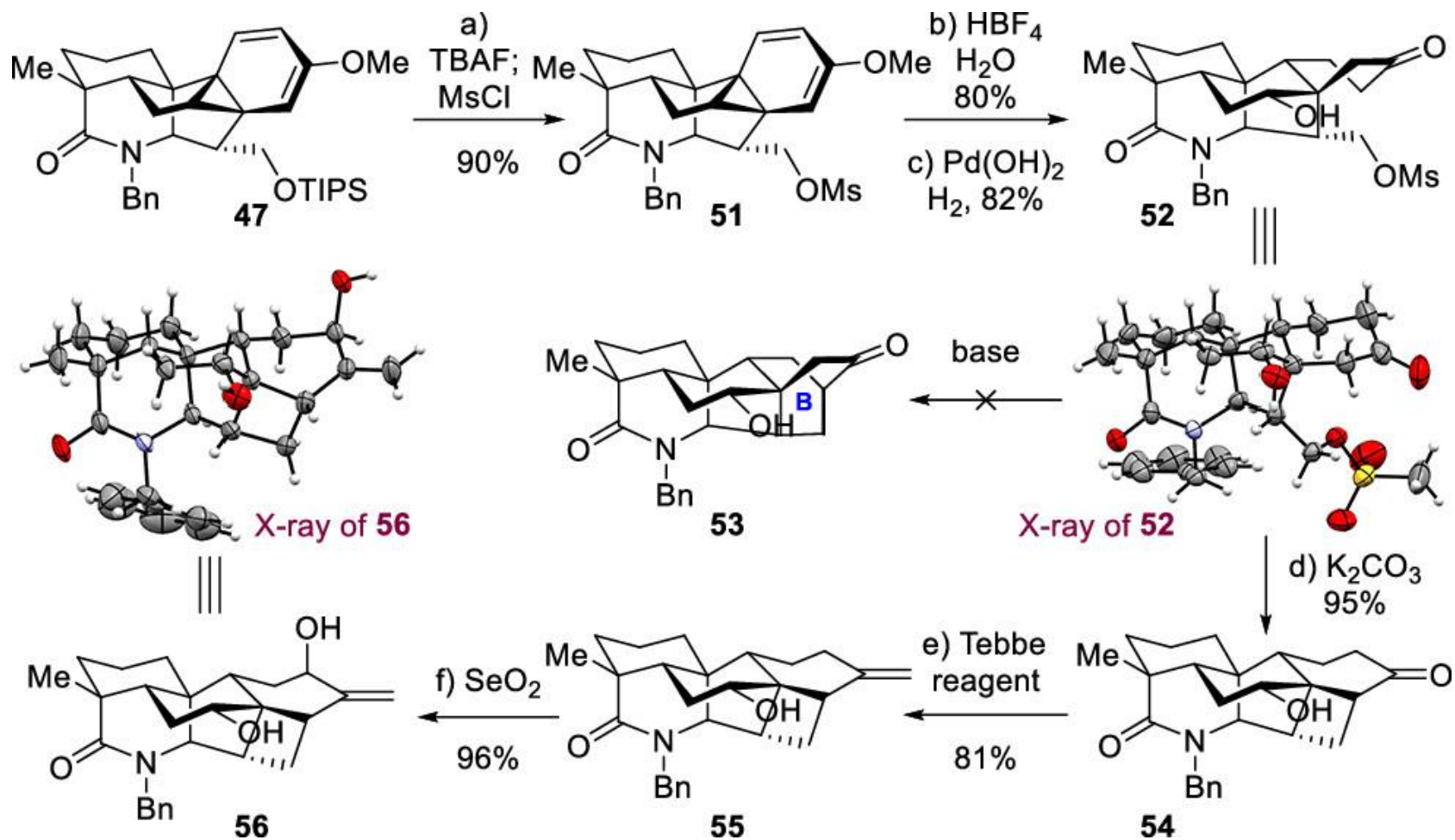


X-ray of **49a**





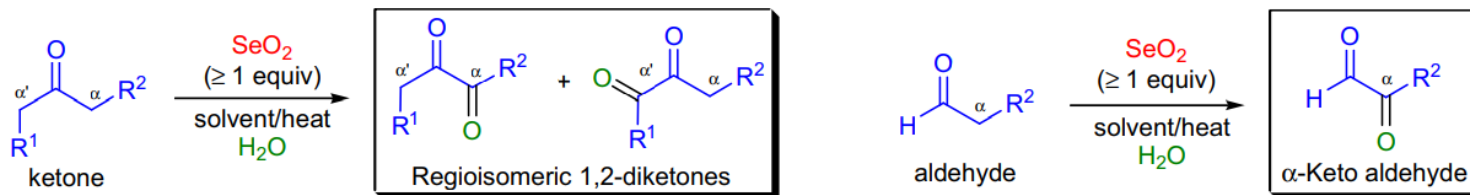
# Failed Attempts to Construct the D Ring by Alkylation



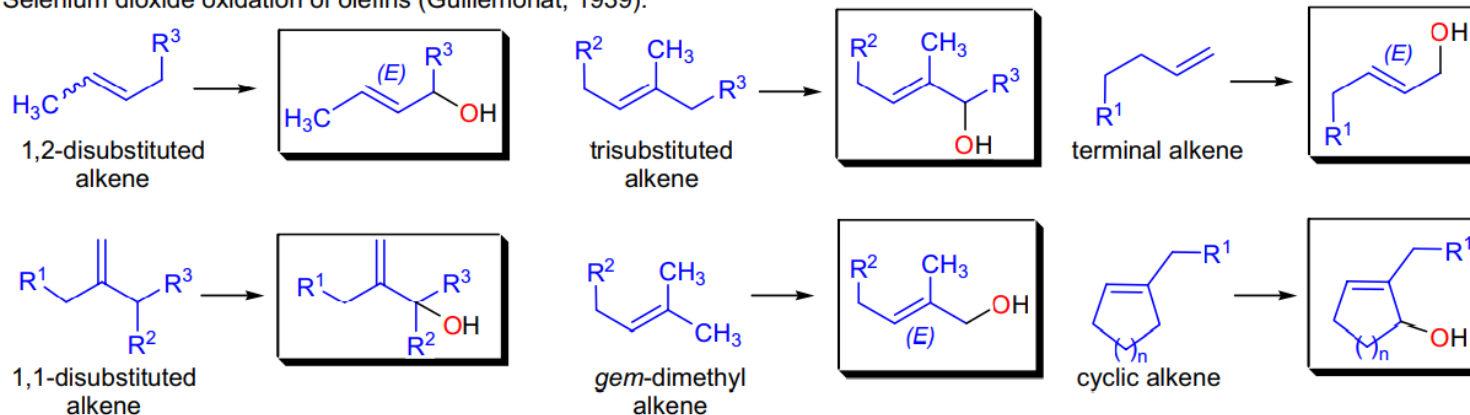
# RILEY Selenium Dioxide Oxidation

(References are on page 663)

Selenium dioxide oxidation of ketones and aldehydes (Riley, 1932):



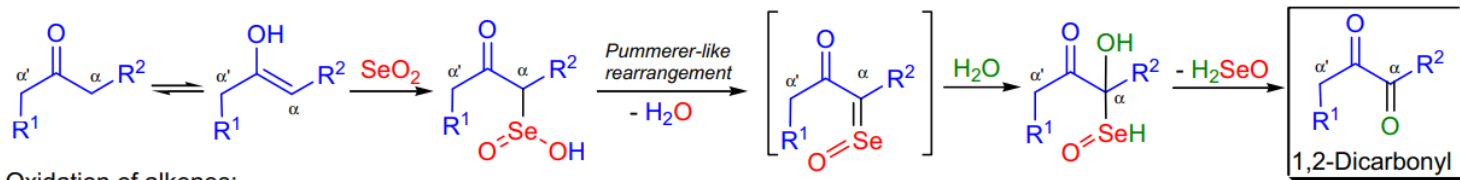
Selenium dioxide oxidation of olefins (Guillemonat, 1939):



$R^{1-2}$  = H, aryl, alkyl, substituted alkyl and aryl;  $R^3$  = alkyl, aryl;  $n$  = 1-3

## Mechanism: <sup>24-41</sup>

Oxidation of carbonyl compounds:



Oxidation of alkenes:

