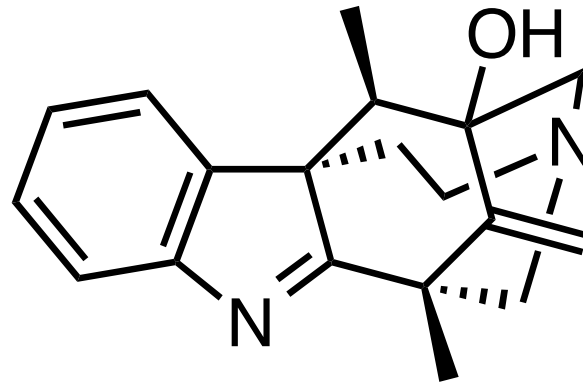


# Total Synthesis Arboridinine

P. Gan, J. Pitzen, P. Qu, S. A. Snyder, *J. Am. Chem. Soc.* **2018**, *140*, 919–925.



Journal Club

Valentin Soulard  
Group Renaud  
08.02.17

*u*<sup>b</sup>

---

b  
UNIVERSITÄT  
BERN

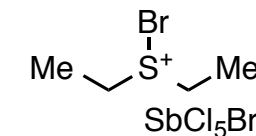
# Scott A. Snyder

- > Undergraduate Studies: Williams College 1999
- > Ph.D.: The Scripps Research Institute with Prof. K. C. Nicolaou (2004)
- > Post-Doc: Harvard University with Prof. E. J. Corey (2006)
- > Assistant and Associate Professor: Columbia University (2006-2013) / The Scripps Research Institute (2013-2015)
- > Full Professor: The University of Chicago (since 2015)



- > Research of interests : Synthesis of complex natural products
- > Developed unique group of halogenating reagents
- > Co-authored : Classics in Total Synthesis II / Organic Chemistry (11 & 12 ed.) /

SOS – Domino Transformations in Organic Synthesis / Teach Better, Save time and Have More fun

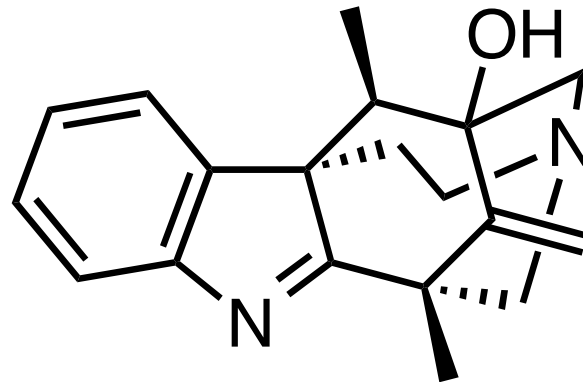


Bromodiethylsulfonium bromopentachloroantimonate  
6.68 CHF/mmol

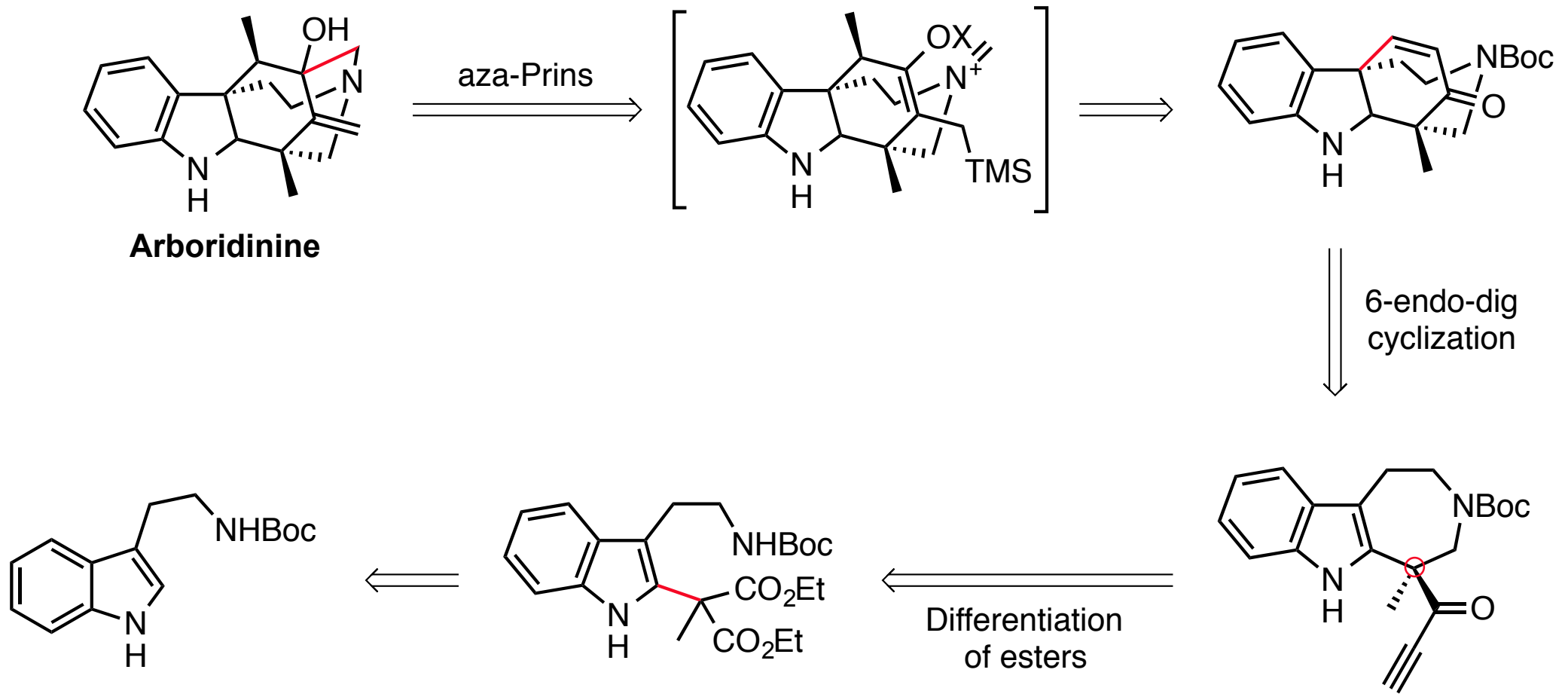
# Arboridine

---

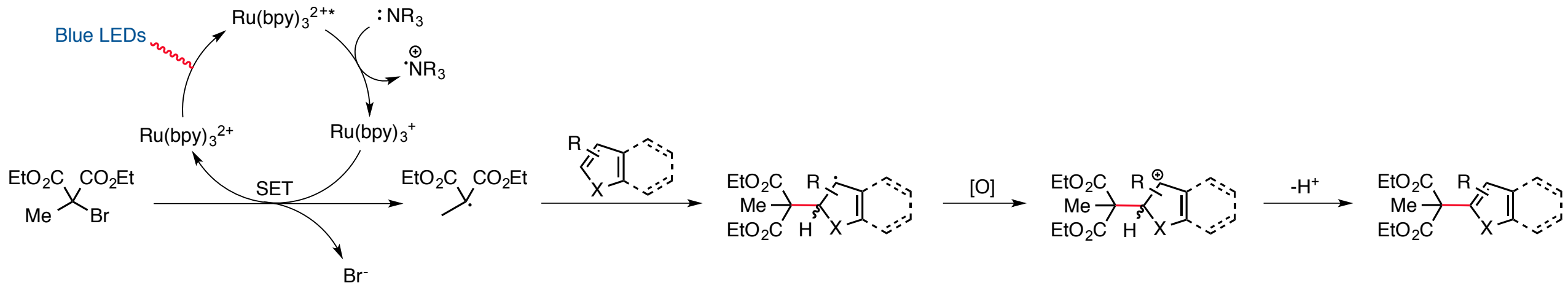
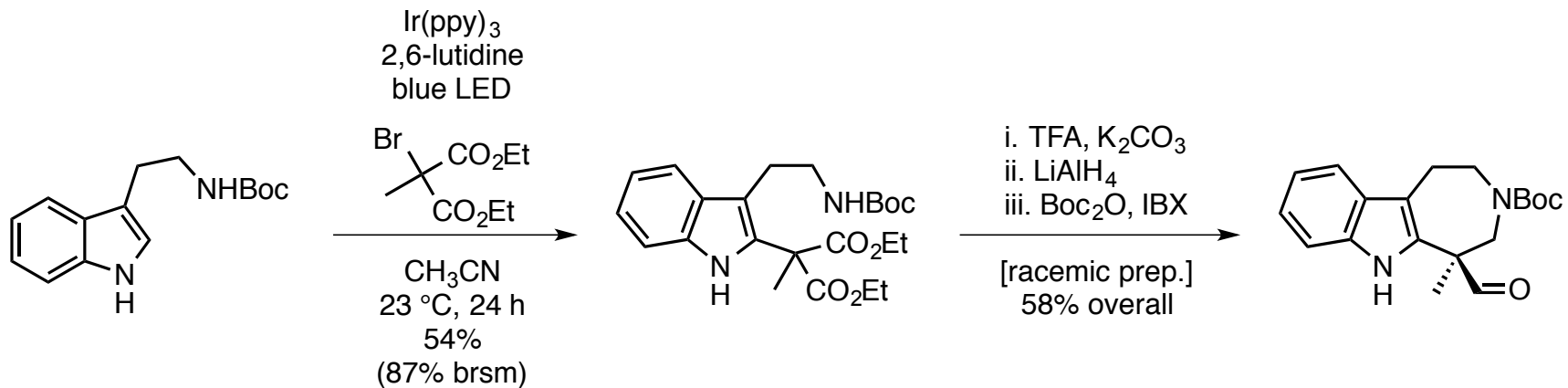
- > Isolated and characterized in 2015 from *Kopsia* in Malaysia
- > Relatively rare natural product (1.5 mg/kg plant material)



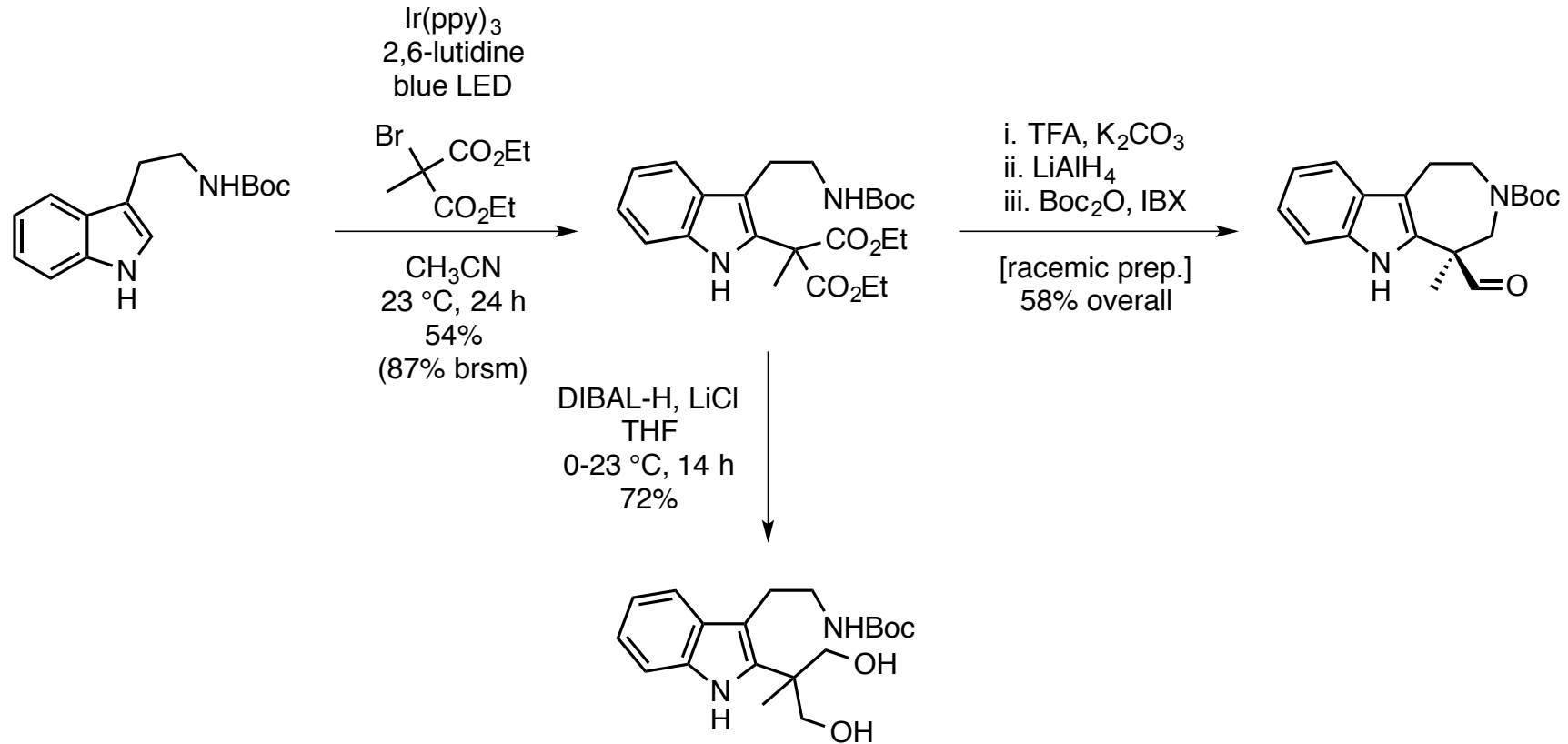
# Retrosynthetic Analysis



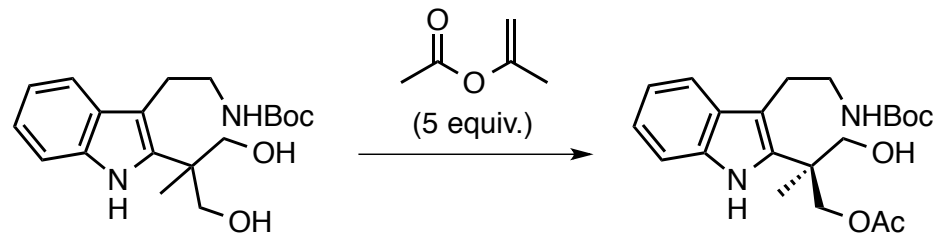
# Total Synthesis of Arboridinine



# Total Synthesis of Arboridinine

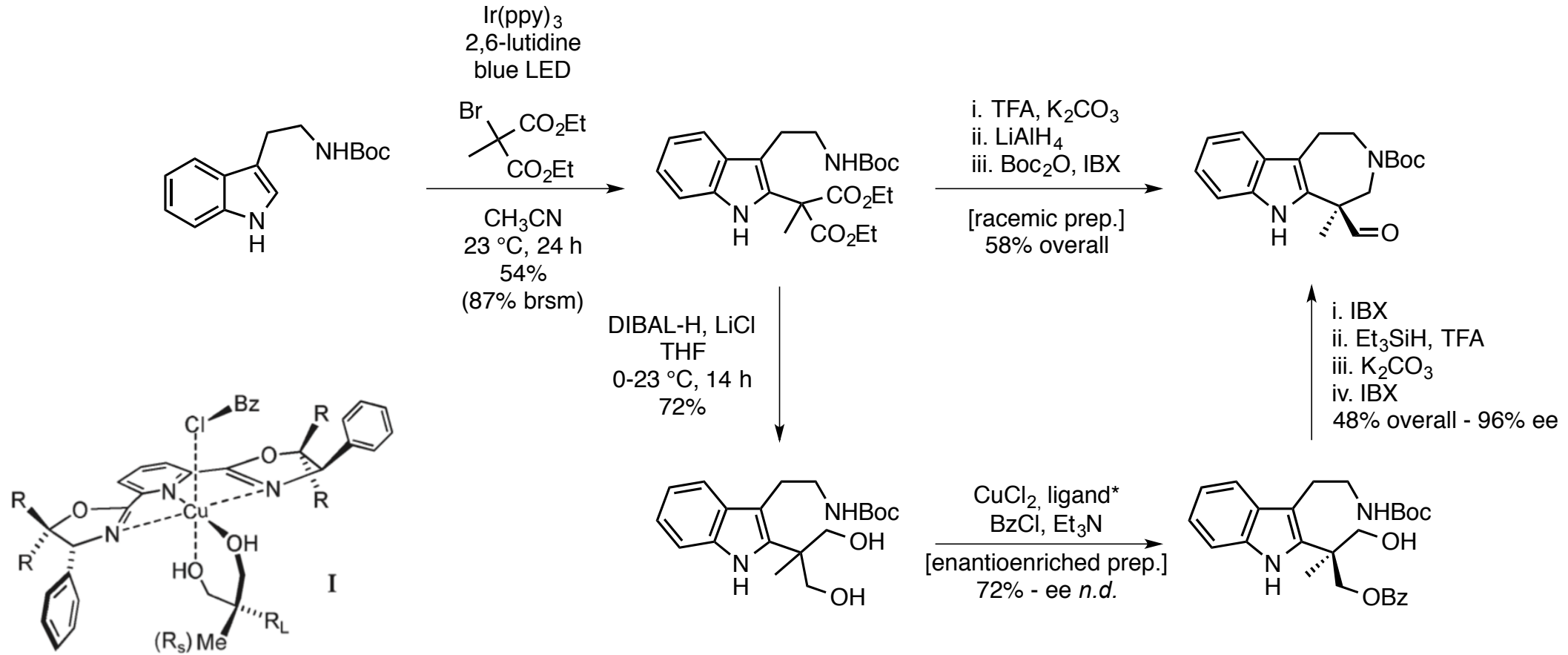


# Total Synthesis of Arboridinine



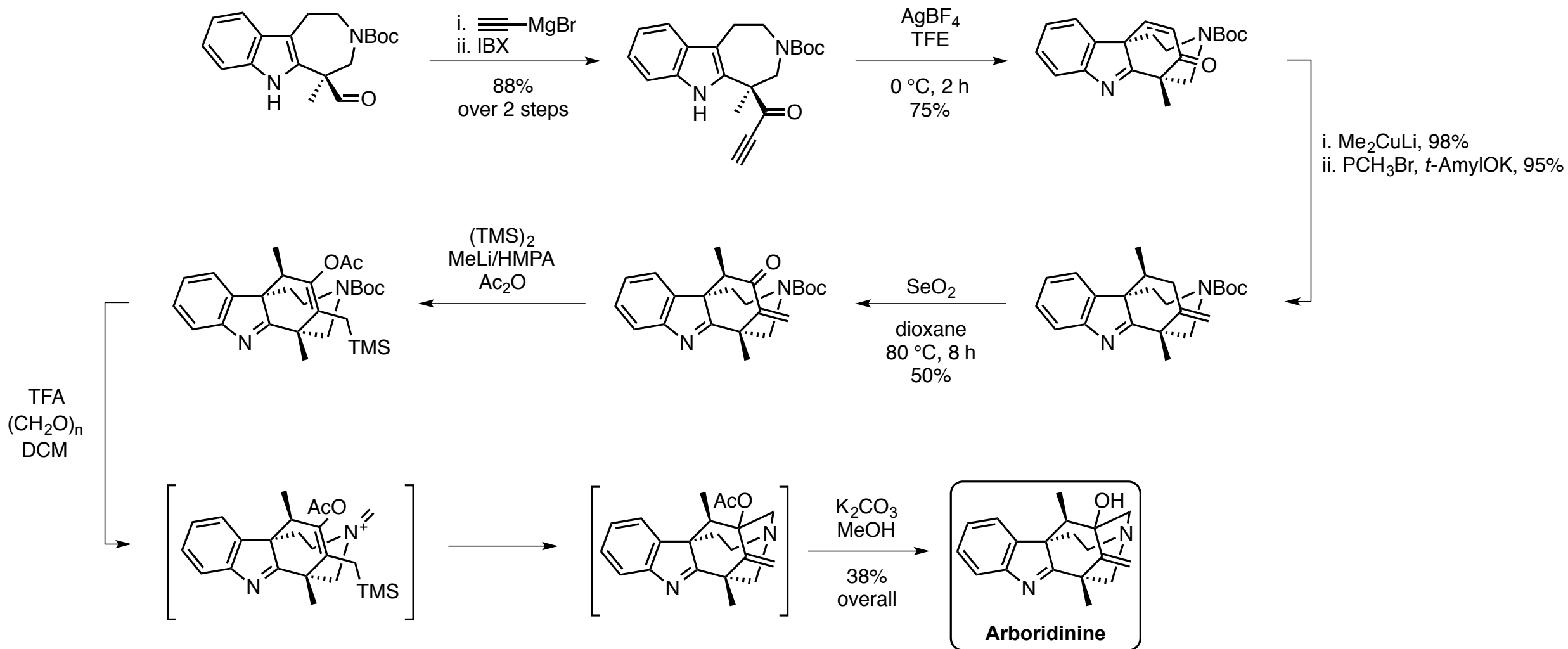
Entry	Conditions	Conversion (%)	ee (%)
1	<i>Candida cylindrica</i> lipase, EtOAc, 40 °C, 48 h	NR	
2	<i>Pseudomonas cepacia</i> lipase, EtOAc, 40 °C, 48 h	NR	
3	<i>Pseudomonas fluorescens</i> lipase, EtOAc, 40 °C, 48 h	NR	
4	pig liver esterase, EtOAc, 40 °C, 48 h	NR	
5	porcine pancreatin, EtOAc, 40 °C, 48 h	NR	
6	<i>Candida antartica</i> lipase, EtOAc, 23 °C, 24 h	NR	
7	<i>Candida antartica</i> lipase, EtOAc, 40 °C, 216 h	39	34
8	<i>Candida antartica</i> lipase, EtOAc, 40 °C, 48 h	10-20	60
9	<i>Candida antartica</i> lipase, EtOAc, 80 °C, 24 h	50	20
10	<i>Candida antartica</i> lipase, THF, 40-60 °C, 48 h	<10	ND
11	<i>Candida antartica</i> lipase, CH <sub>2</sub> Cl <sub>2</sub> , 40-60 °C, 48 h	<10	ND
12	<i>Candida antartica</i> lipase, pH 7.4 phosphate buffer, 40-60 °C, 48 h	NR	

# Total Synthesis of Arboridinine

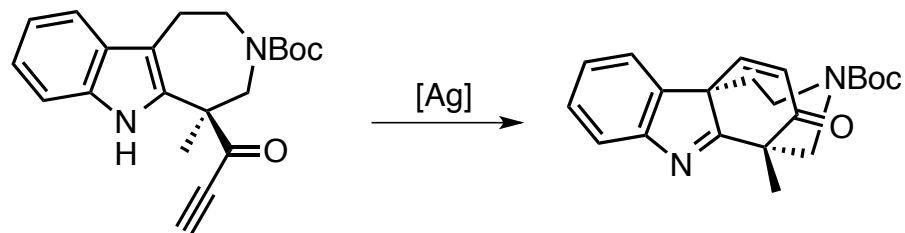




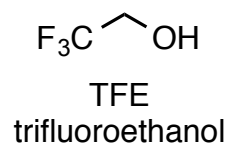
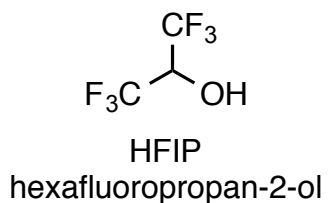
# Total Synthesis of Arboridinine



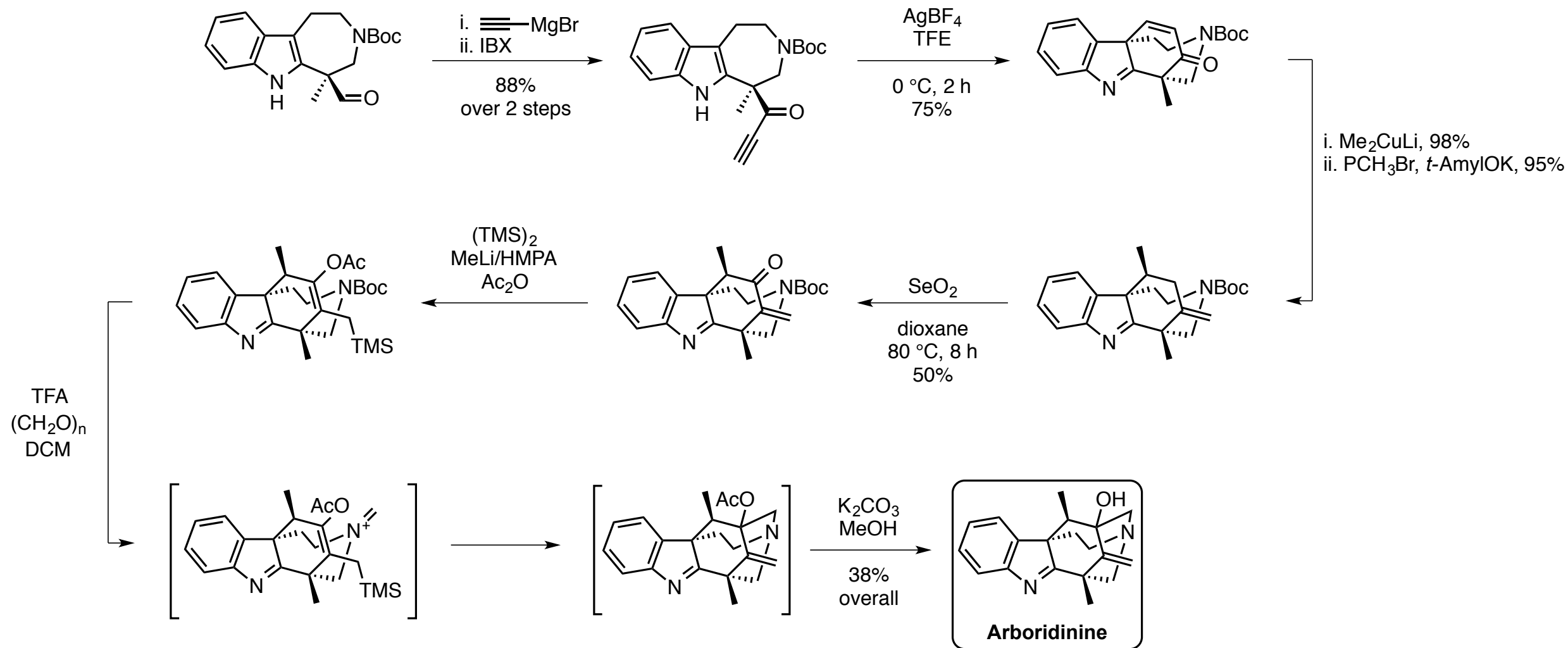
# Ag-Based 6-endo-Dig Cyclization



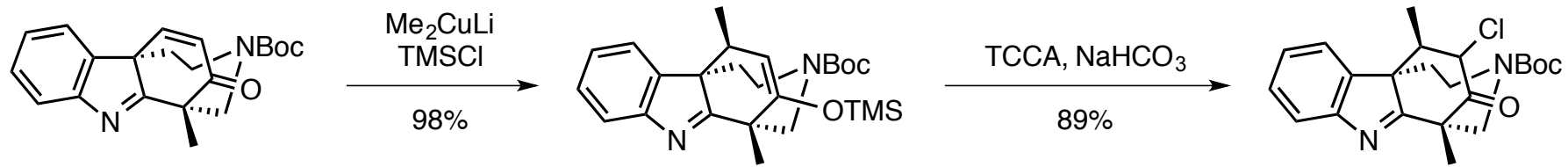
Entry	Conditions	Yield (%)
1	AgBF <sub>4</sub> (1 equiv), CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 20 min	63
2	AgBF <sub>4</sub> (0.1 equiv), THF, 0 °C, 20 min	57
3	AgBF <sub>4</sub> (0.1 equiv), EtOH, 0 °C, 20 min	41
4	AgBF <sub>4</sub> (0.1 equiv), <i>i</i> PrOH, 0 °C, 20 min	74
5	AgBF <sub>4</sub> (0.1 equiv), TFE, 0 °C, 20 min	75
6	AgBF <sub>4</sub> (0.1 equiv), HFIP, 0 °C, 20 min	40
7	AgBF <sub>4</sub> (0.1 equiv), TFE, 0 °C, 1 h	66
8	AgBF <sub>4</sub> (0.1 equiv), TFE, 0 °C, 1 h	59
9	AgBF <sub>4</sub> (0.1 equiv), TFE, 0 °C, 1 h	56



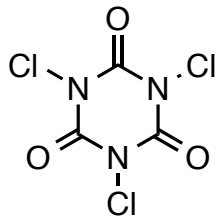
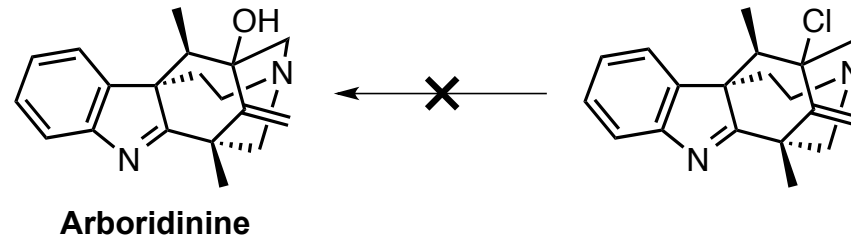
# Total Synthesis of Arboridinine



# Other Approaches

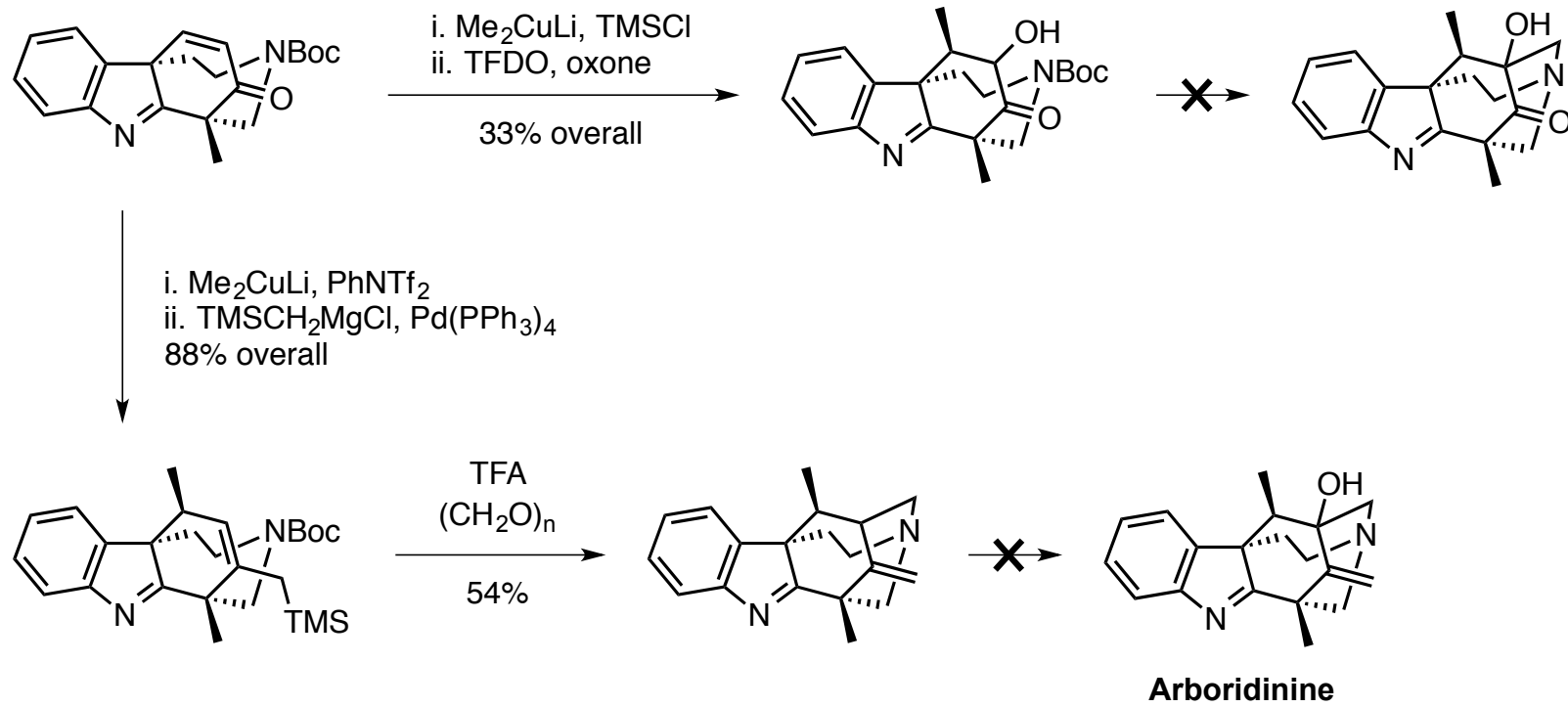


TFA  
 $(\text{CH}_2\text{O})_n$   
53%

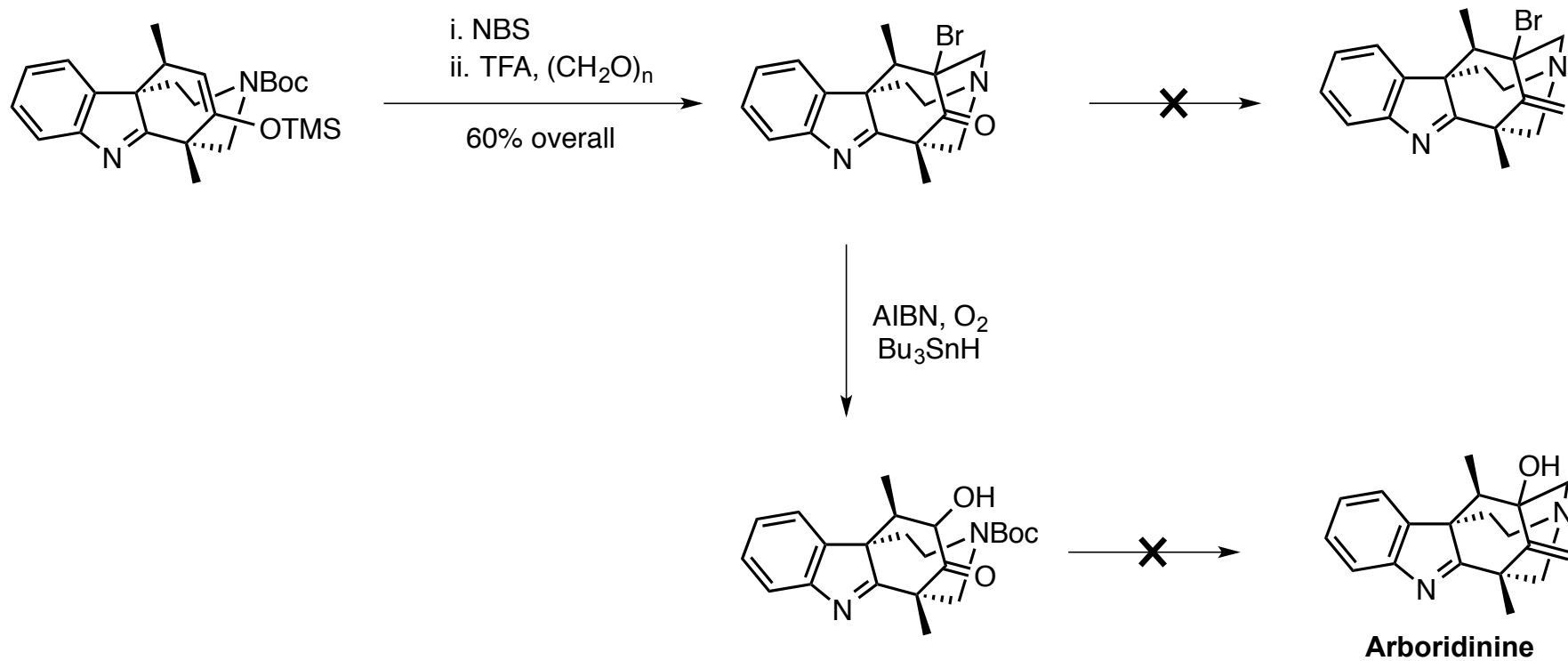


TCCA  
trichloroisocyanuric acid

# Other Approaches



# Other Approaches



# Conclusion

---

- > 13-step racemic of arboridinine.
- > 16-step formal asymmetric synthesis.
- > Terminating *aza*-Prins cyclization to establish the full array of functionality of the target.
- > New scope in terms of metal-mediated 6-endo-dig cyclizations was uncovered.

