

# **Total Syntheses of Hetisine-Type Diterpenoid Alkaloids**

**2021.9.18. Literature Seminar  
B4 Hisahiro Morozumi**

# **Contents**

**1. Introduction**

**2. Total synthesis of Cossomidine  
(by Sarpong Group)**

**3. Total synthesis of (+)-Davisinol  
(by Ding Group)**

**4. Summary**

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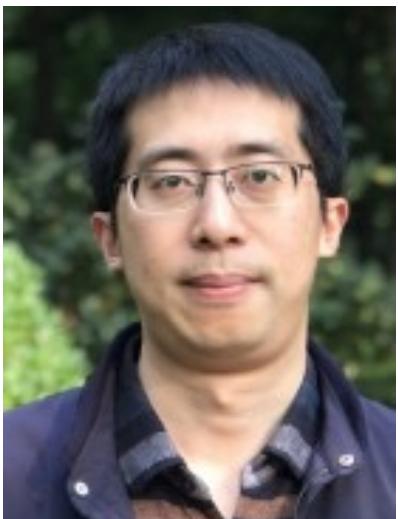
# **Introduction of Prof. Sarpong and Ding**



**Prof. Richmond Sarpong**

**1995 B.S., @ Macalester College (Prof. Rebecca C. Hoye)  
2001 Ph.D., @ Princeton University (Prof. Martin F. Semmelhack)  
2001- Postdoctoral fellow @ Caltech (Prof. Brian M. Stoltz)  
2004- Assistant Professor @ the University of California, Berkeley  
2010- Associate Professor @ the University of California, Berkeley  
2014- Professor @ the University of California, Berkeley**

**Research topic: total synthesis of complex molecules, development of synthetic methods**



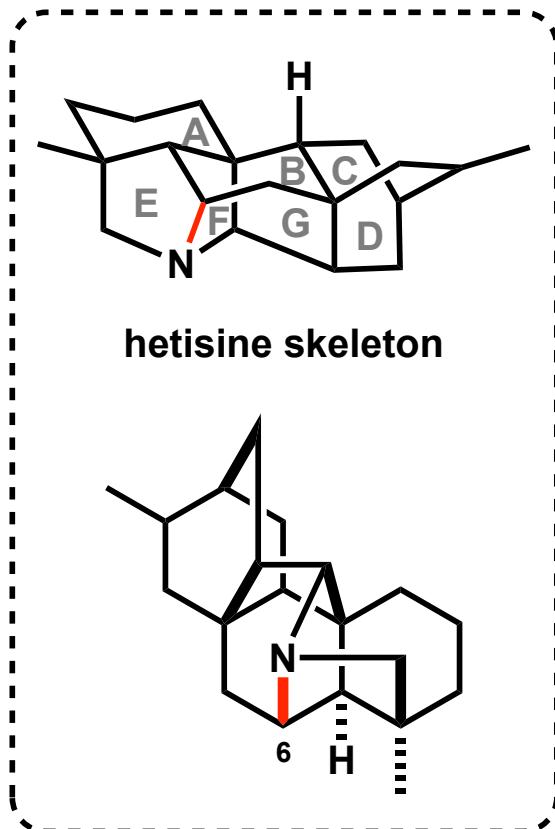
**Prof. Hanfeng Ding**

**2003 B.S., @ Zhejiang University  
2008 Ph.D., @ Zhejiang University (Prof. Cheng Ma)  
2008- Postdoctoral fellow @ Agency for Science Technology and Research (Prof. K. C. Nicolaou)  
2011 Scientist I @ Agency for Science Technology and Research  
2011- Assistant professor @ Zhejiang University  
2017- Professor @ Zhejiang University**

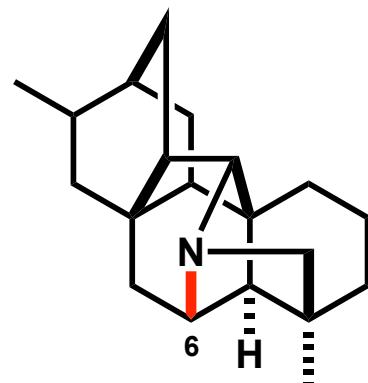
**Research topic: development of novel strategies and methodologies for the total synthesis of structurally complex and biologically active natural products**

1) <https://sarponggroup.com/richmond-sarpong/>  
2) <https://person.zju.edu.cn/en/0011114>

# Hetisine-Type Diterpenoid Alkaloids



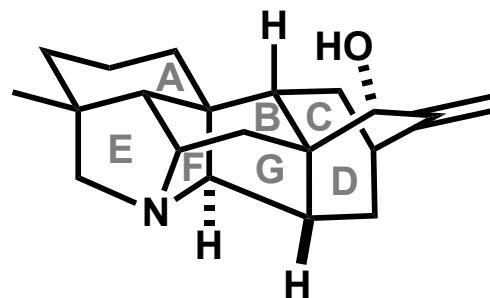
hetisine skeleton



6

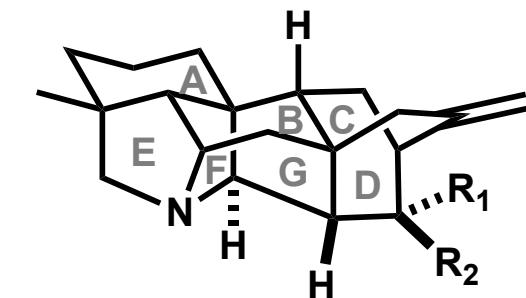
H

Total syntheses:



nominine

Muratake and Natsume group (2004)  
Gin and Peese group (2006)



R<sub>1</sub>, R<sub>2</sub> = O: spirasine IV  
R<sub>1</sub> = OH, R<sub>2</sub> = H: spirasine XI

Zhang group (2018)

## Features

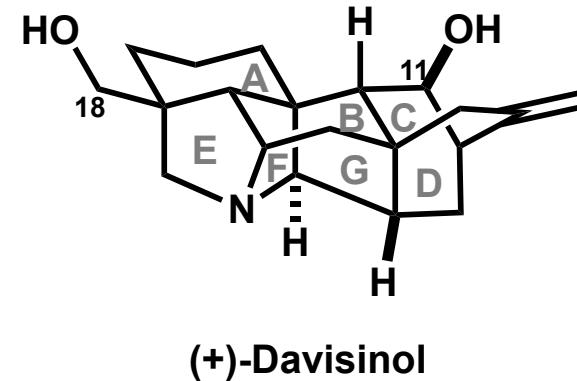
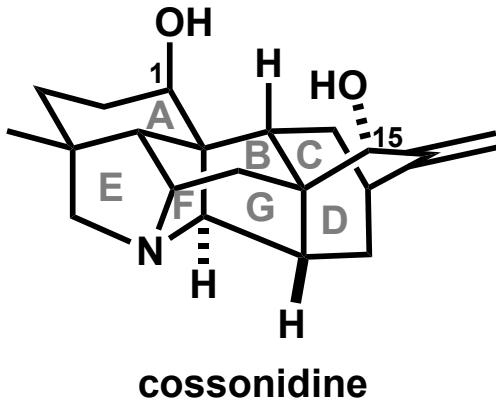
- cage-like heptacyclic skeleton
- tertiary amine embedded within both the E and F rings
- N-C6 bond

1) Muratake, H.; Natsume, M. *Angew. Chem., Int. Ed.* **2004**, 43, 4646-4649

2) Peese, K. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, 128, 8734-8735.

3) Zhang, Q.; Zhang, Z.; Huang, Z.; Zhang, C.; Xi, S.; Zhang, M.; *Angew. Chem., Int. Ed.* **2018**, 57, 937-941.

# cossomidine and (+)-Davisonol



Isolation: *Delphinium cossonianum* (1996)<sup>1)</sup>

*Delphinium davisii* (1996)<sup>2)</sup>

Structural features: hetisine skeleton  
C-1 and C-11 hydroxy group

hetisine skeleton  
C-15 and C-18 hydroxy group

Total synthesis: Sarpong (2018 (23 steps, racemic))<sup>3)</sup>

Ding (2021 (17 steps, enantioselective))<sup>4)</sup>

1) Reina, M.; Gavin, J. A.; Madinaveitia, A.; Acosta, R. D.; de la Fuente, G. *J. Nat. Prod.* **1996**, 59, 145-147.

2) Ulubelen, A.; Desai, H. K.; Srivastava, S. K.; Hart, B. P.; Park, J.-C.; Joshi, B. S.; Pelletier, S. W.; Mericli, A. H.; Mericli, F.; Ilarslan, R. *J. Nat. Prod.* **1996**, 59, 360-366.

3) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, 140, 8105-8109.

4) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, 143, 10576-10581.

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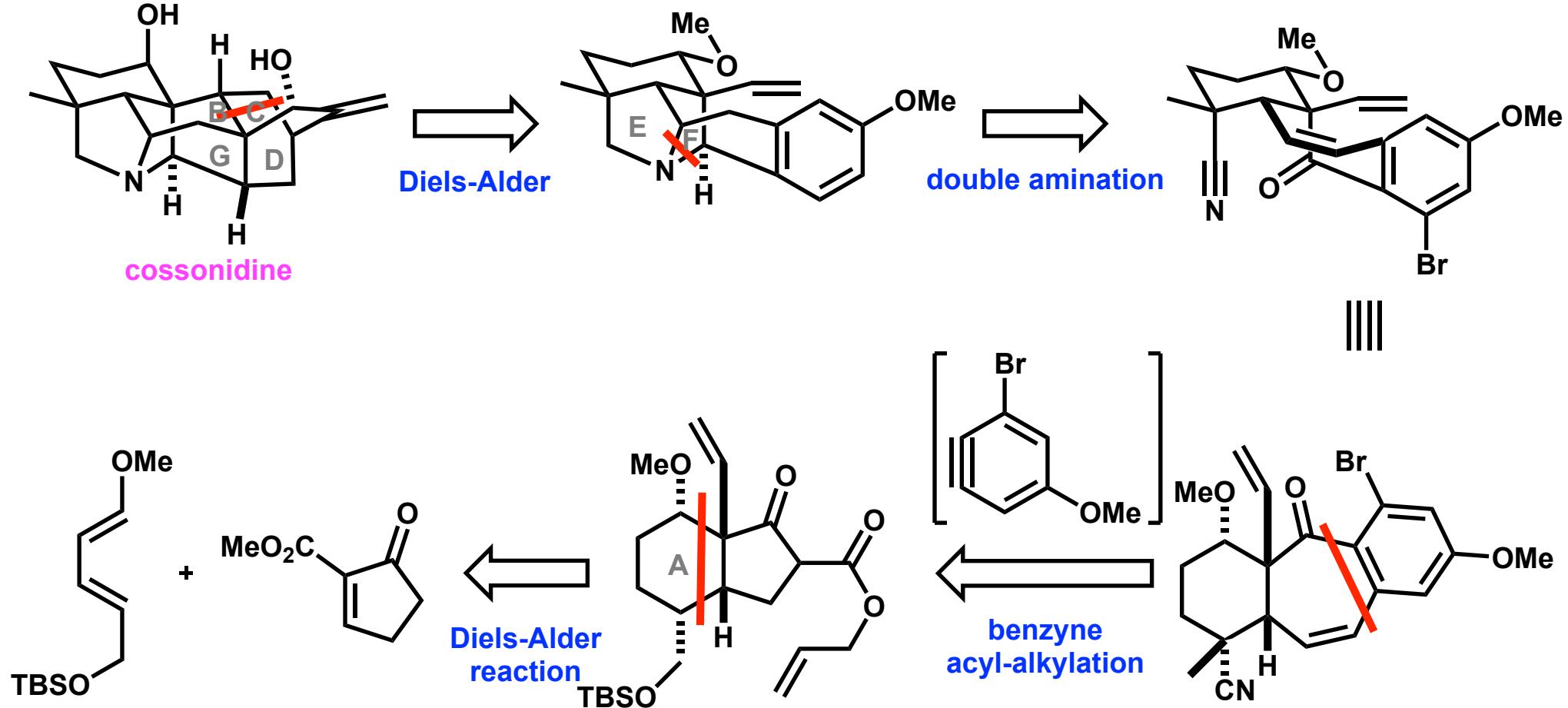
## **1. Introduction**

### **1. Total synthesis of Cossomidine (by Sarpong Group)**

### **3. Total synthesis of (+)-Davisinol (by Ding Group)**

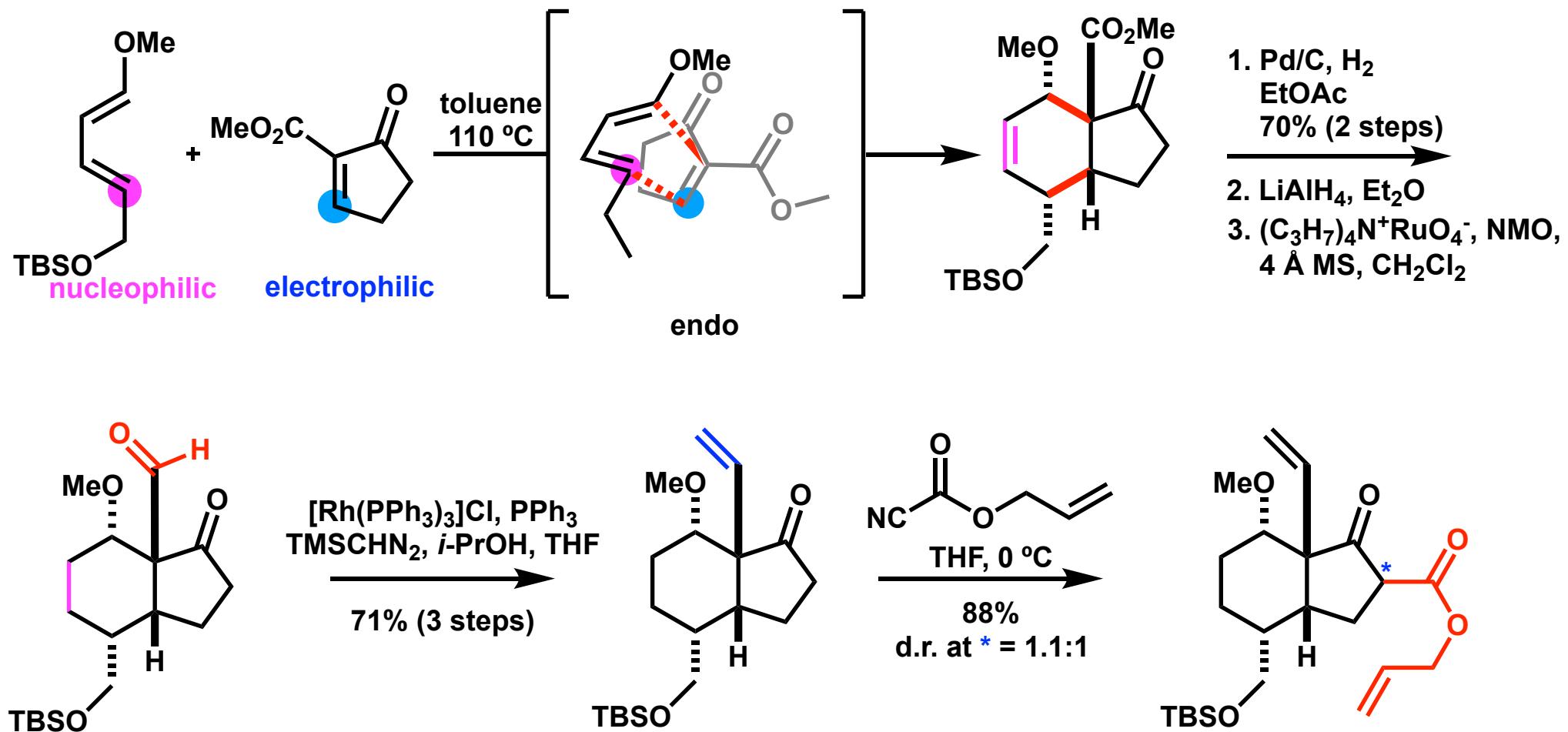
## **4. Summary**

# Retrosynthetic Analysis



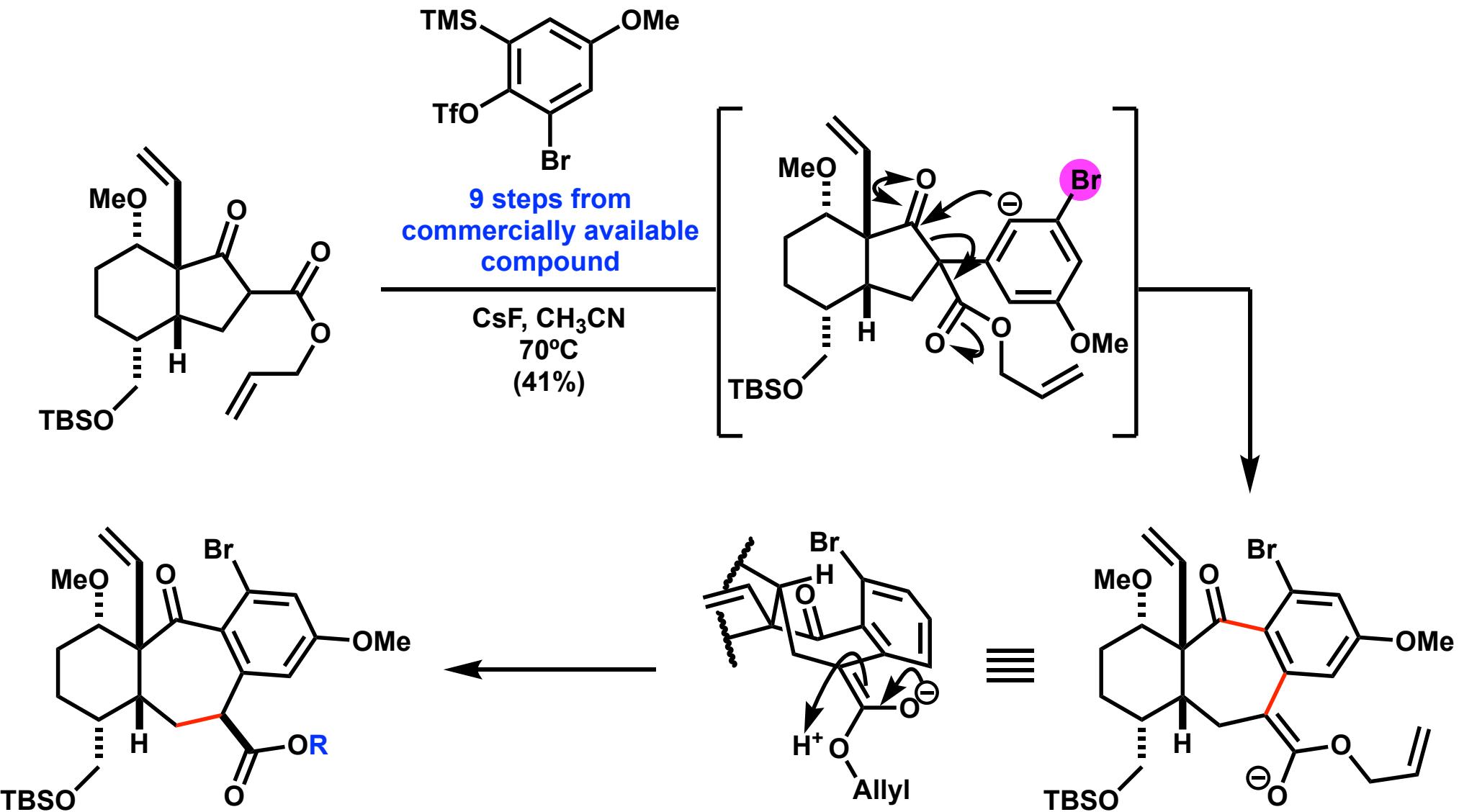
1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, 140, 8105-8109.

# Construction of A-ring



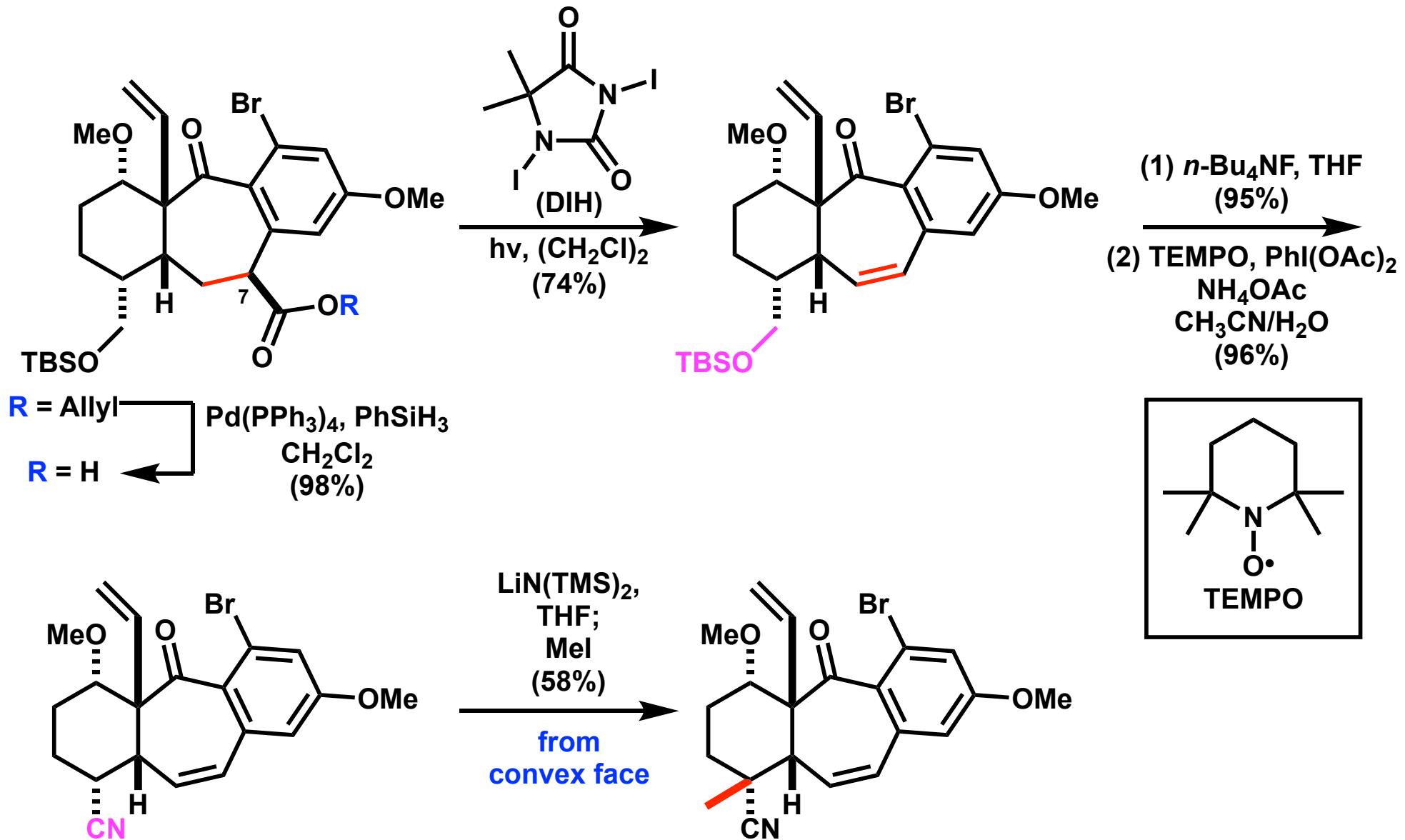
- 1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, 140, 8105-8109.  
 2) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, 126, 320-328.

# Regioselective Benzyne acyl-alkylation



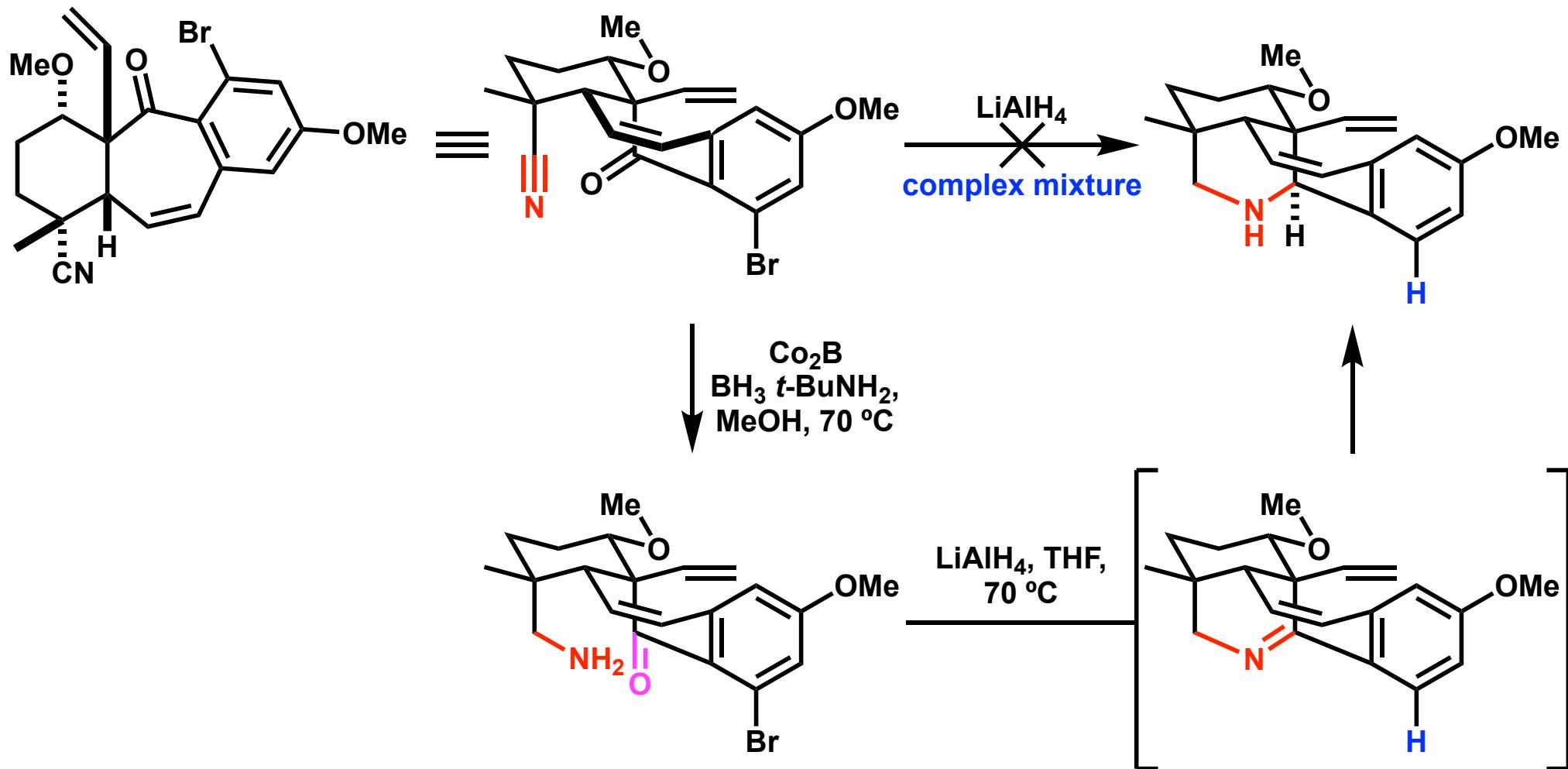
- 1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.  
2) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798-15805.

# Installation of N atom



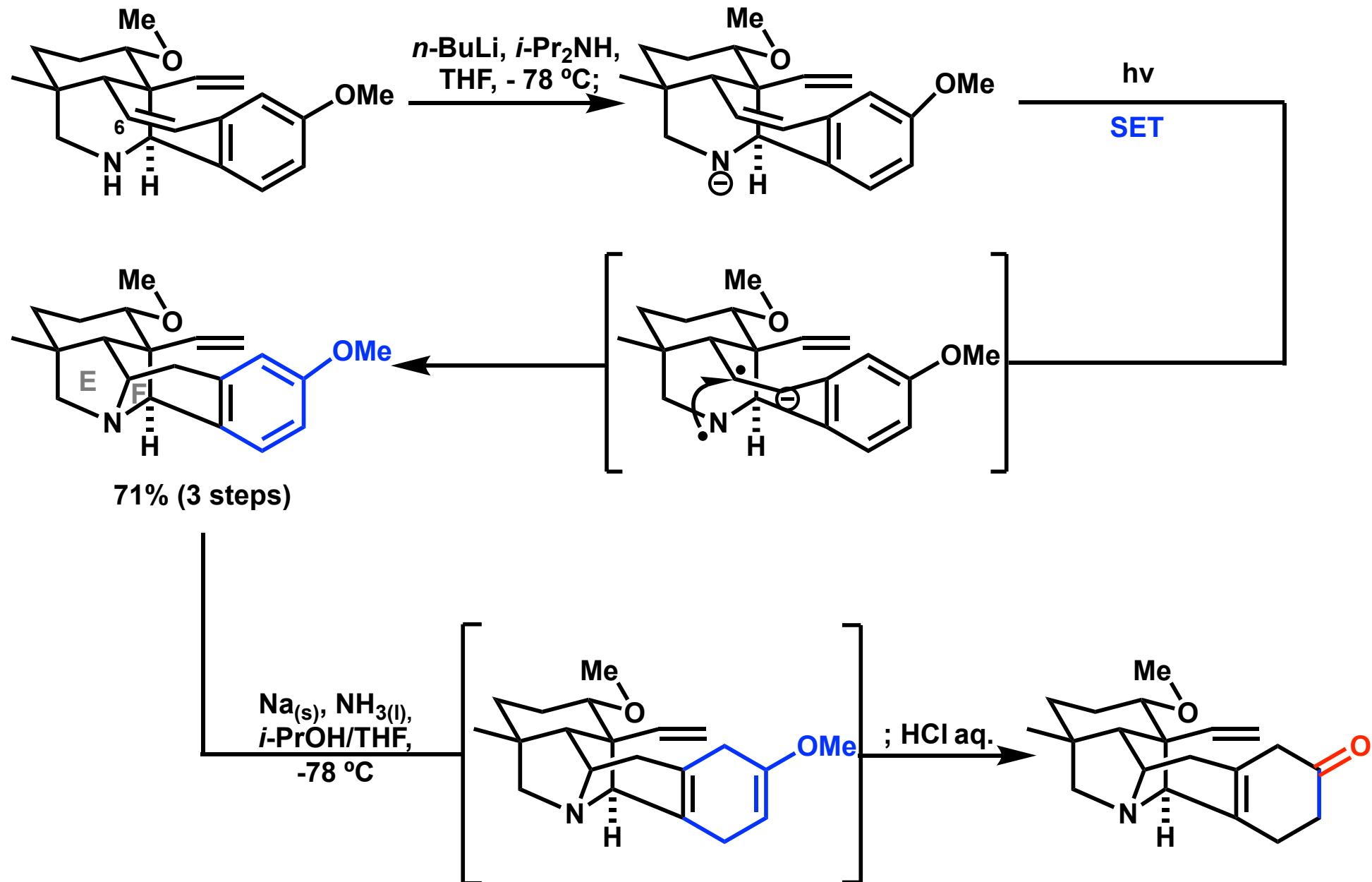
- 1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.  
 2) Kulbitski, K.; Nisnevich, G.; Gandelman, M. *Adv. Synth. Catal.* **2011**, *353*, 1438-1442.

# Formation of Cyclic Amine



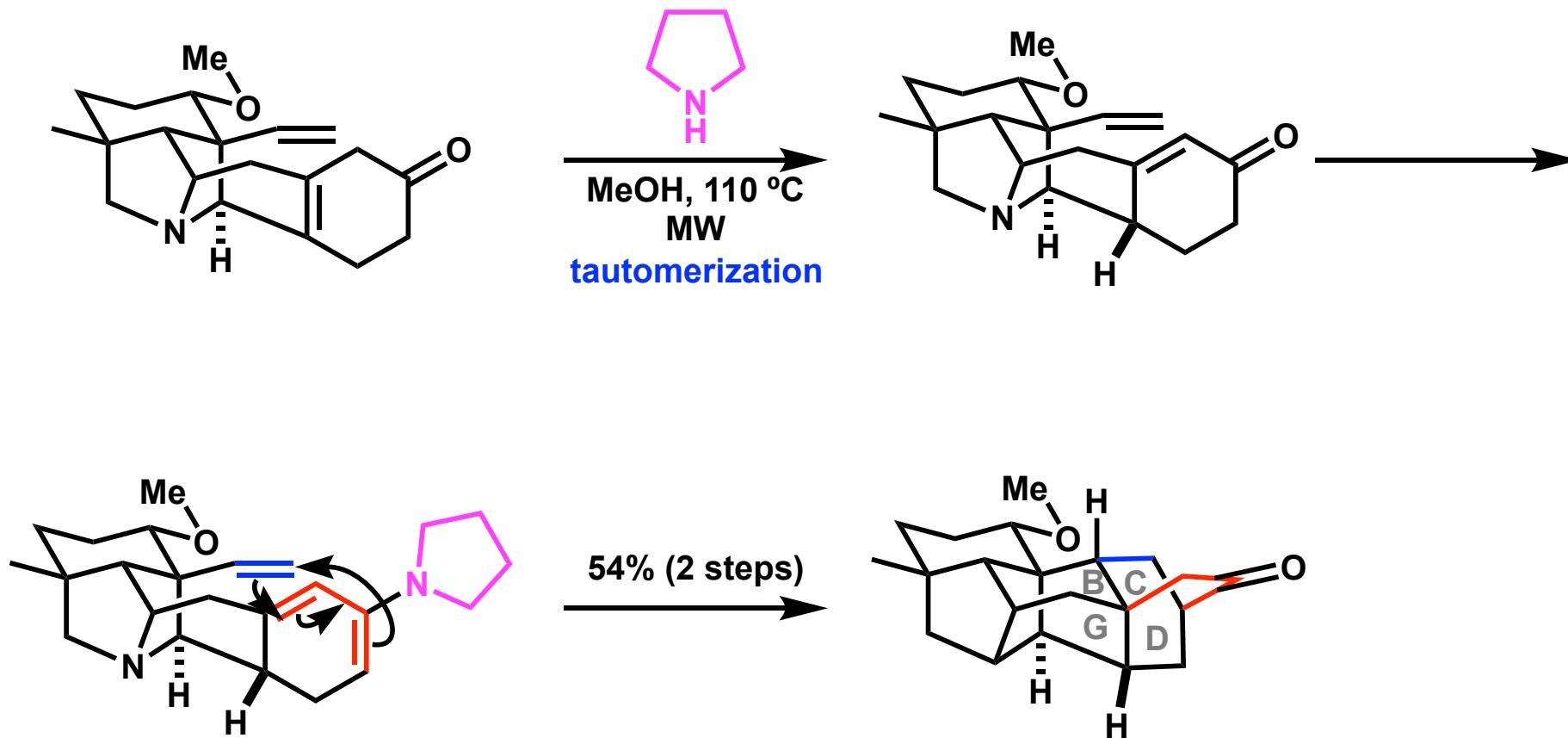
- 1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.
- 2) Heinzman, S. W.; Genem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801-6802.
- 3) Osby, J. O.; Heinzman, S. W.; Genem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67-72.

# Construction of E, F-rings



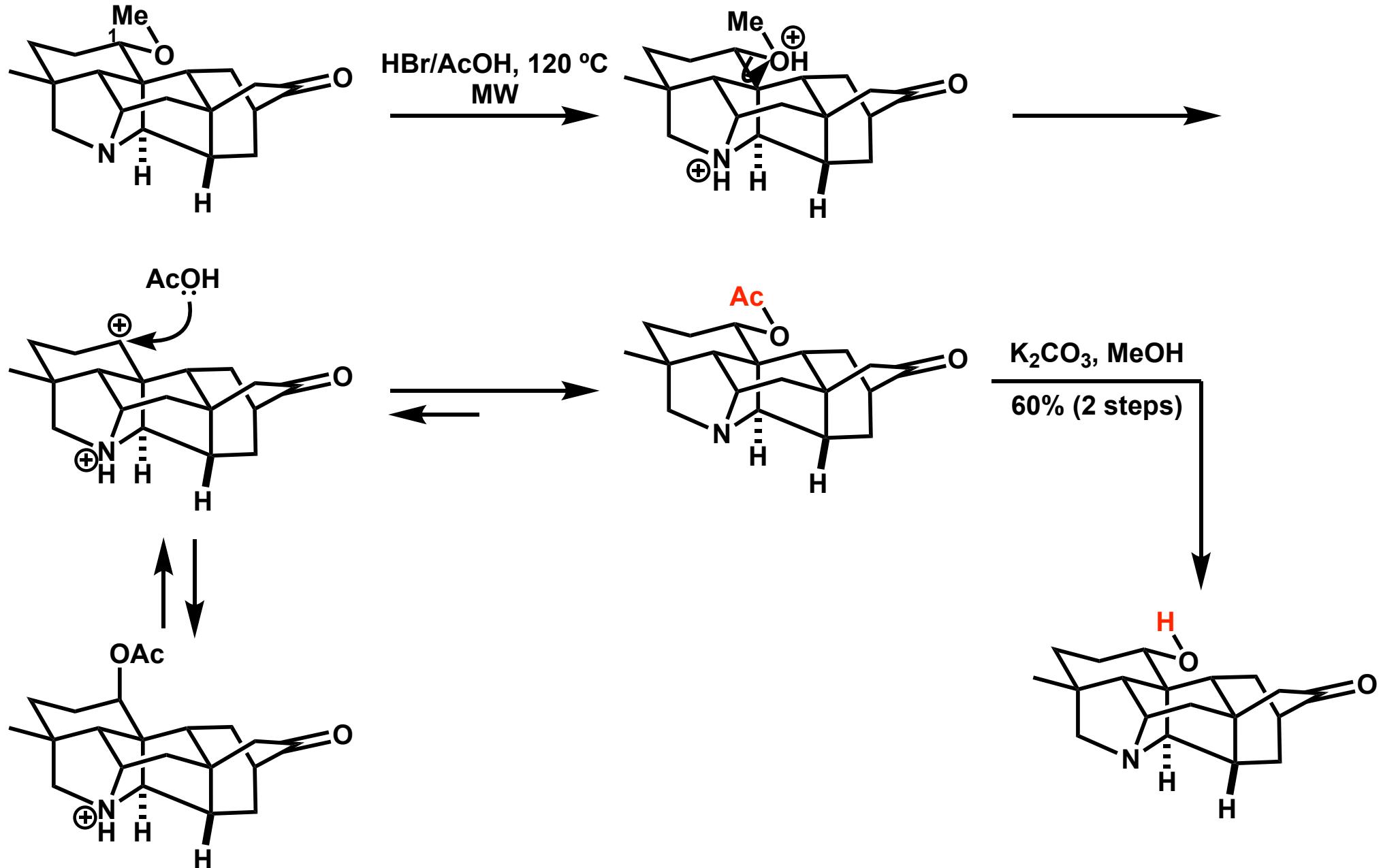
- 1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.  
 2) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528-6535.

# Intramolecular Diels-Alder reaction



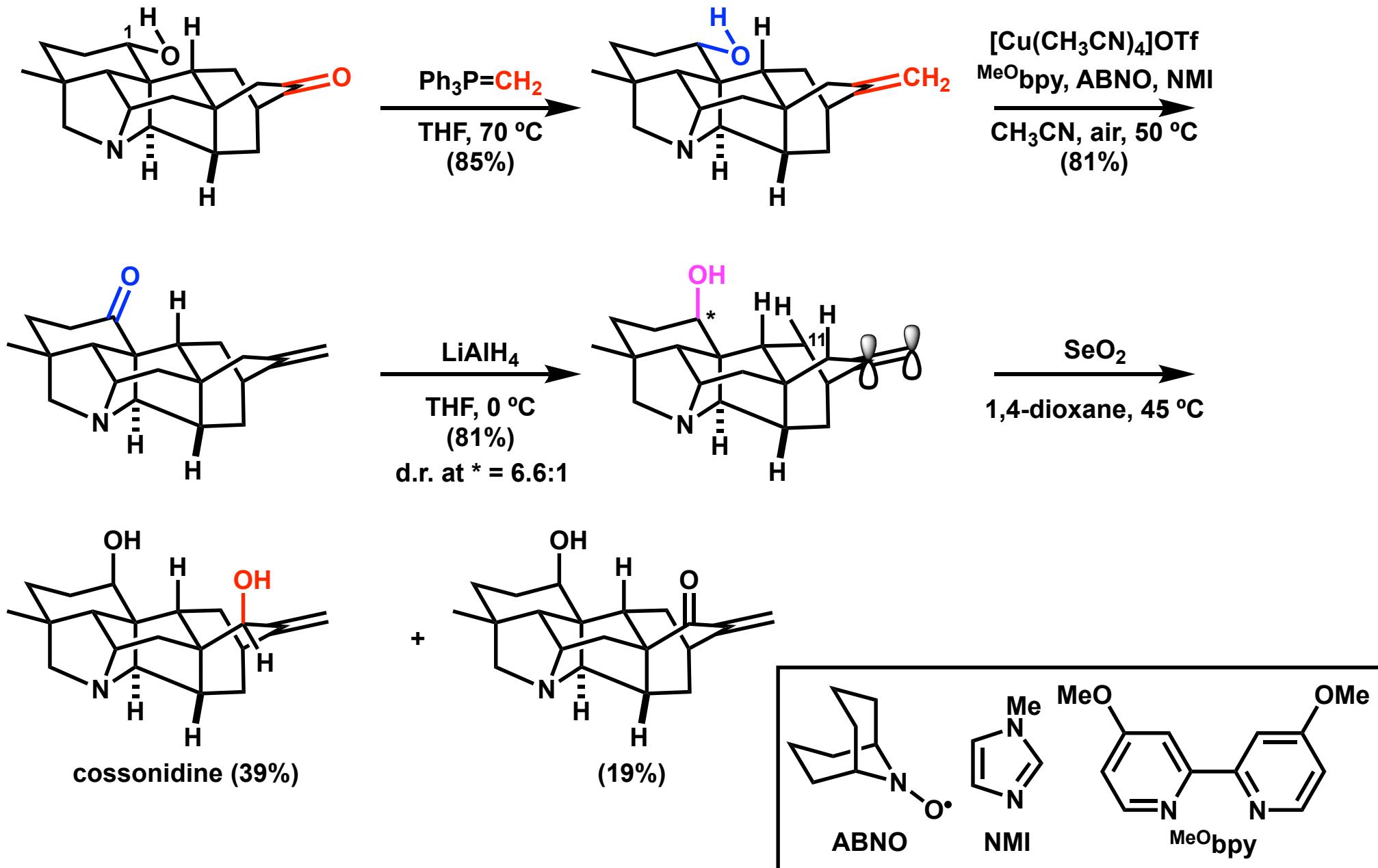
1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.

# Installation of C1-hydroxy group



1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.

# Total Synthesis of cossonidine



1) Kou, K. G. M.; Pflueger, J. J.; Kiho, T.; Morrill, L. C.; Fisher, E. L.; Clagg, K.; Lebold, T. P.; Kisunzu, J. K.; Sarpong, R. *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.

2) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742-15745.

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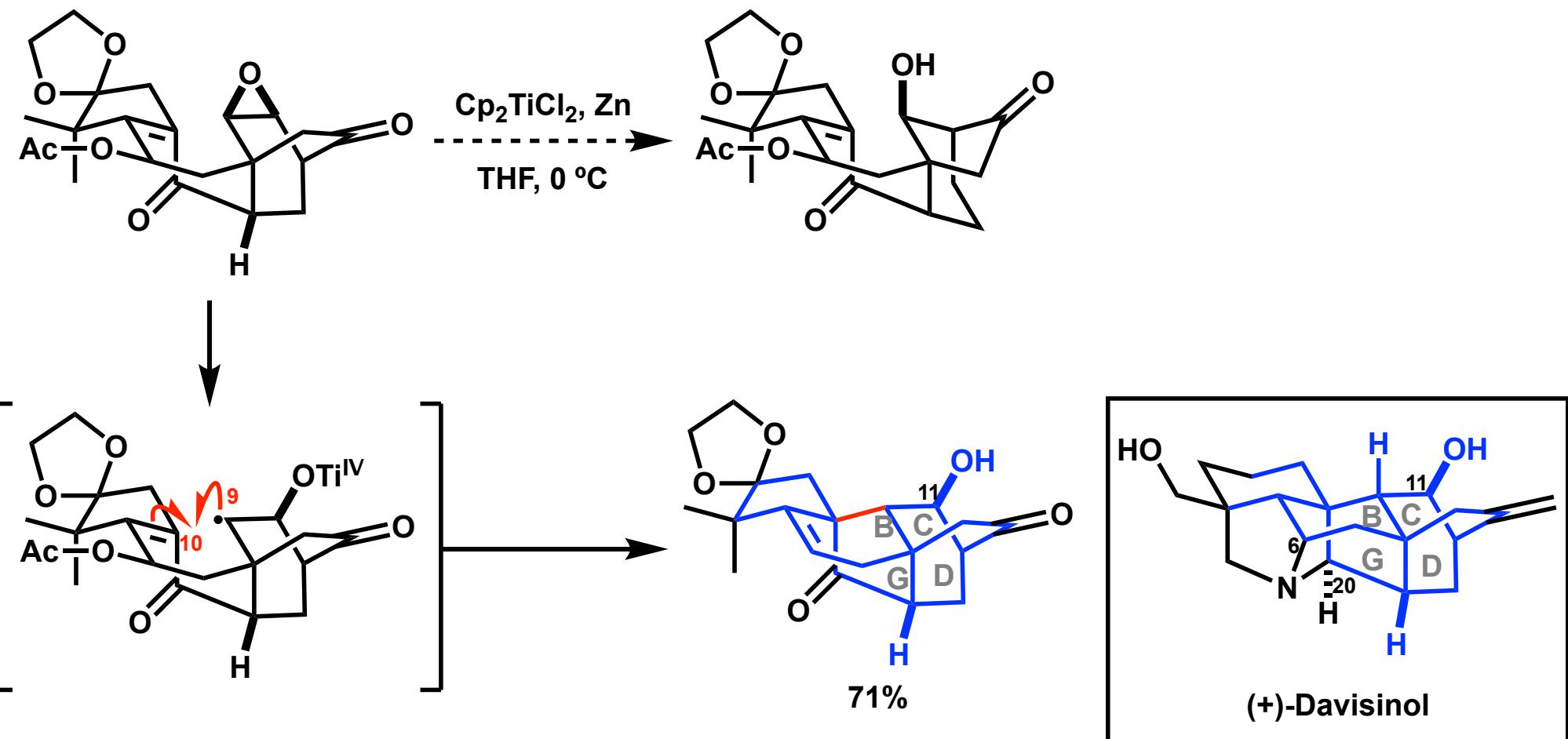
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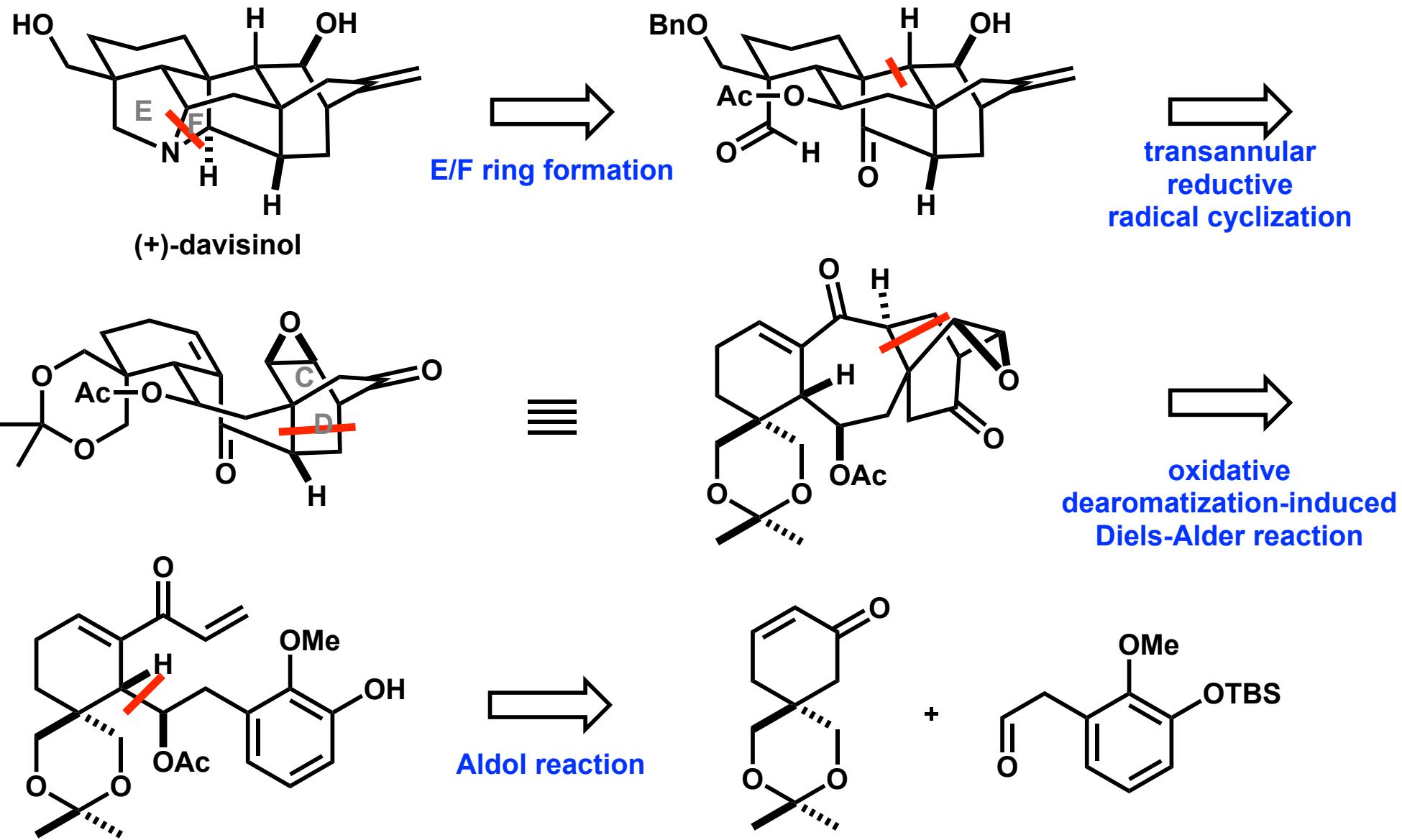
**3. Total synthesis of (+)-Davisinol  
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**4. Summary**

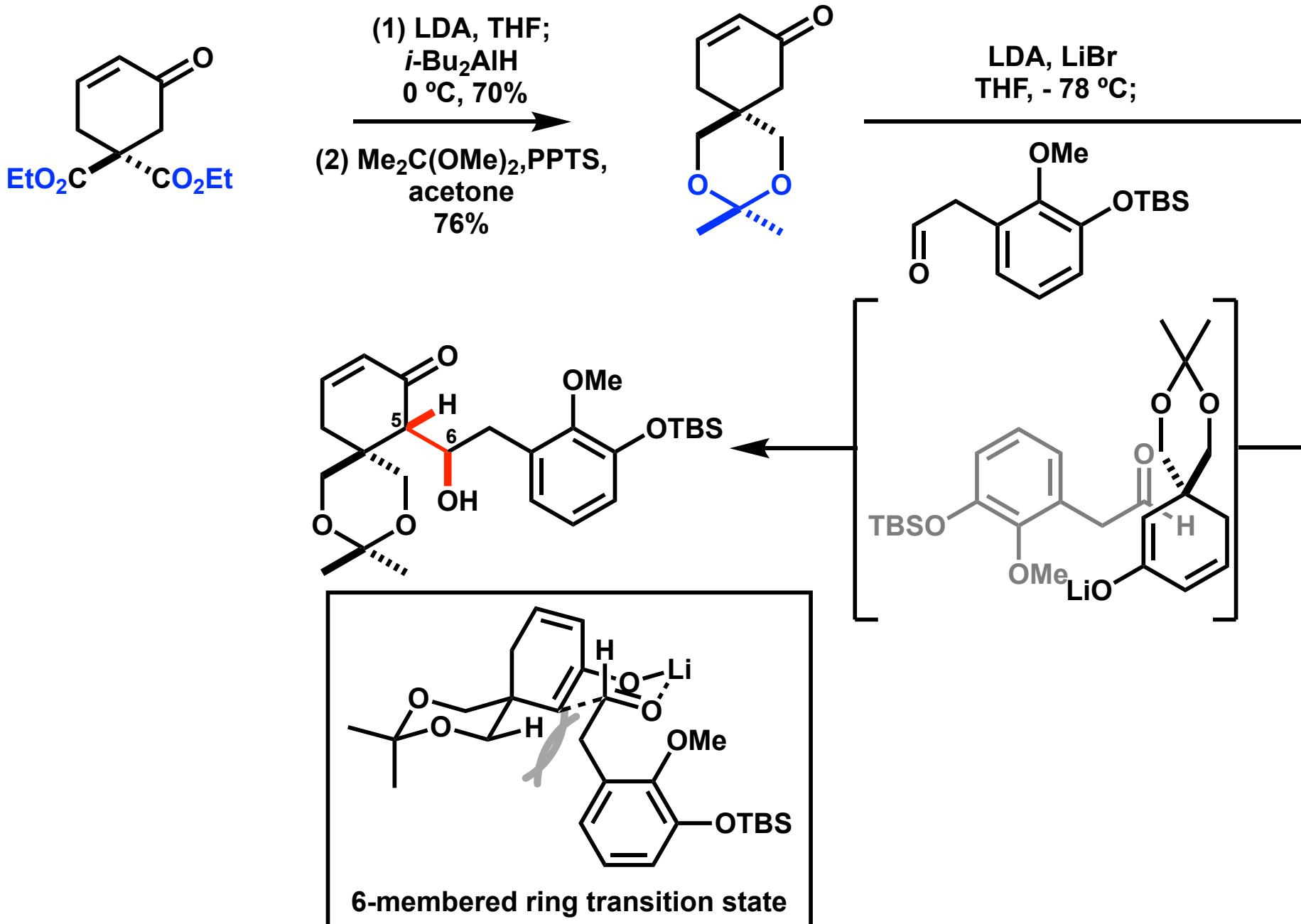
# Previous Observation



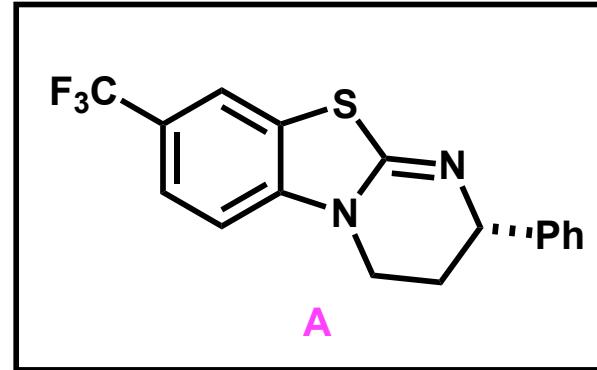
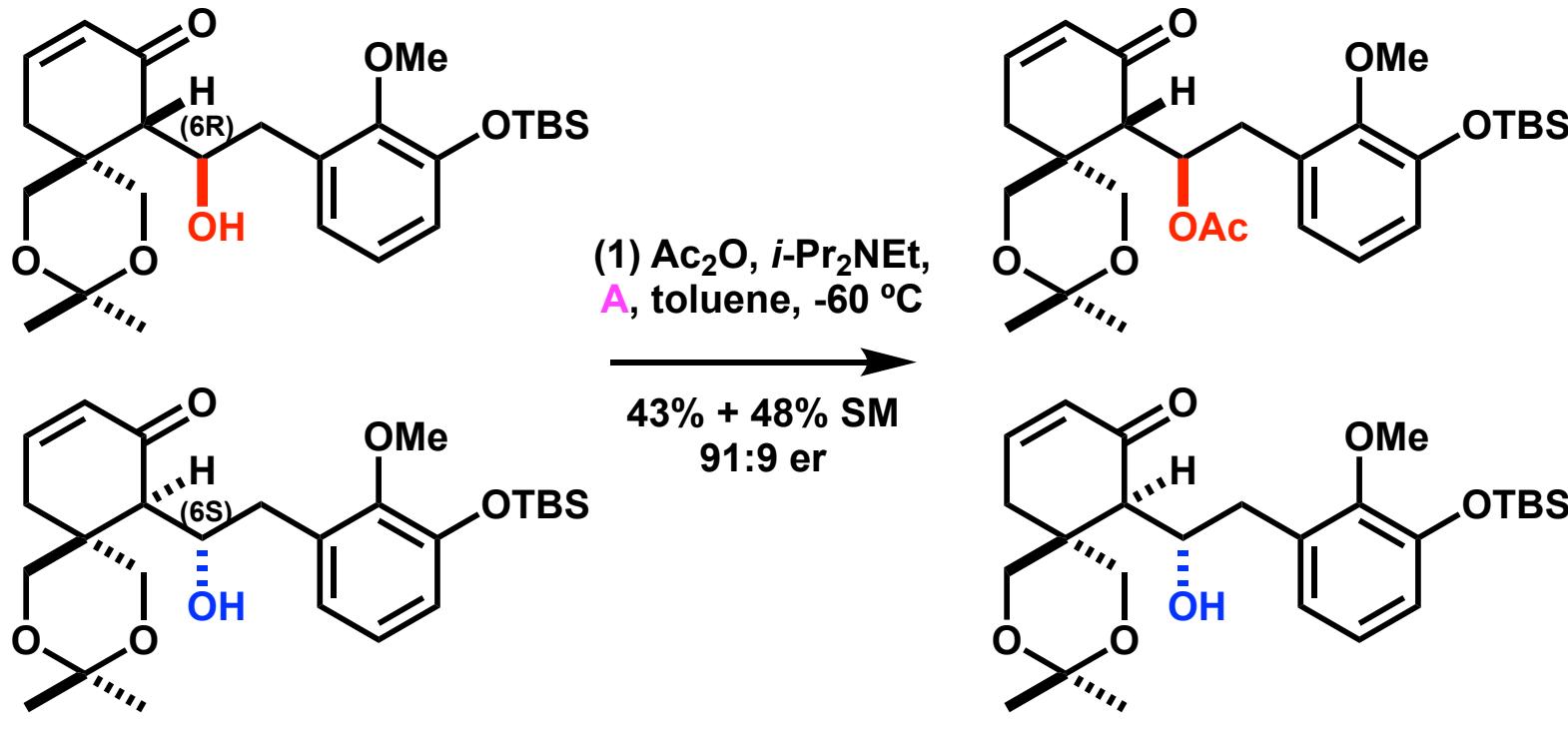
# Retrosynthesis Analysis



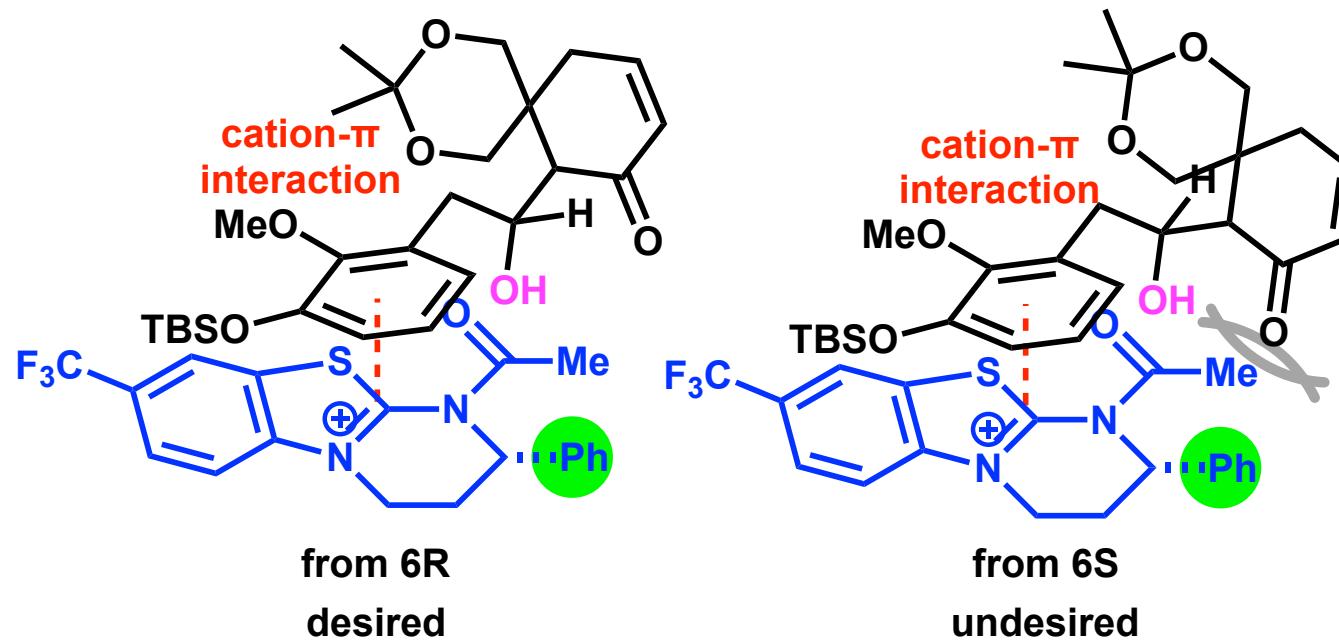
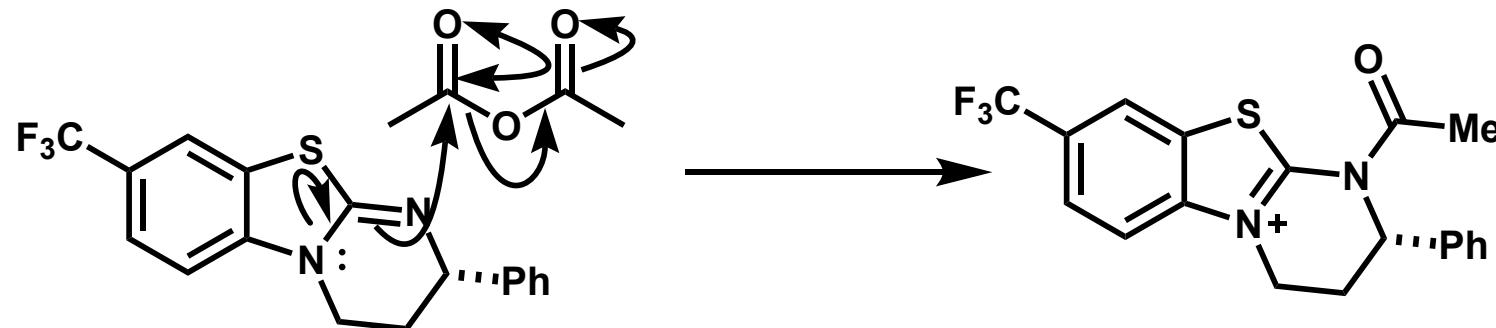
# Aldol reaction



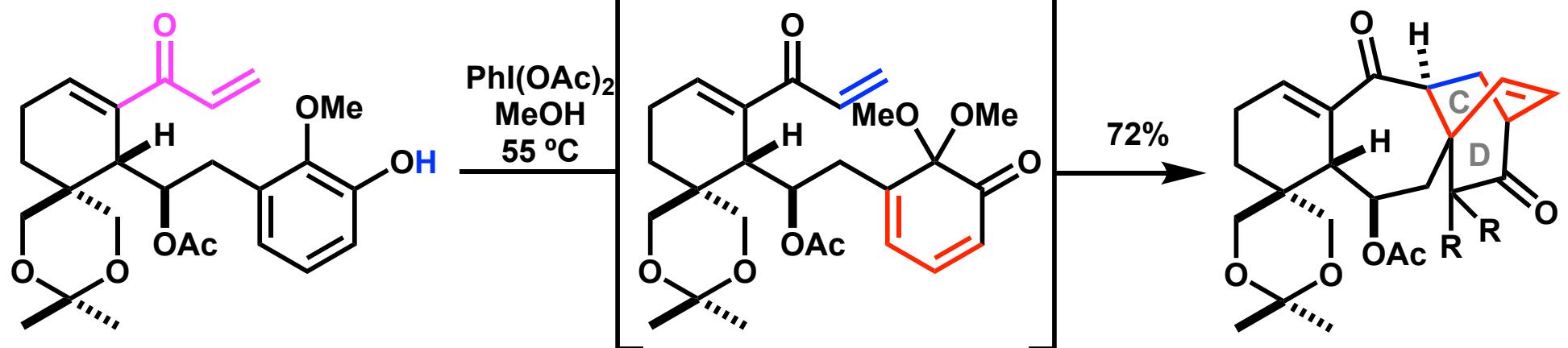
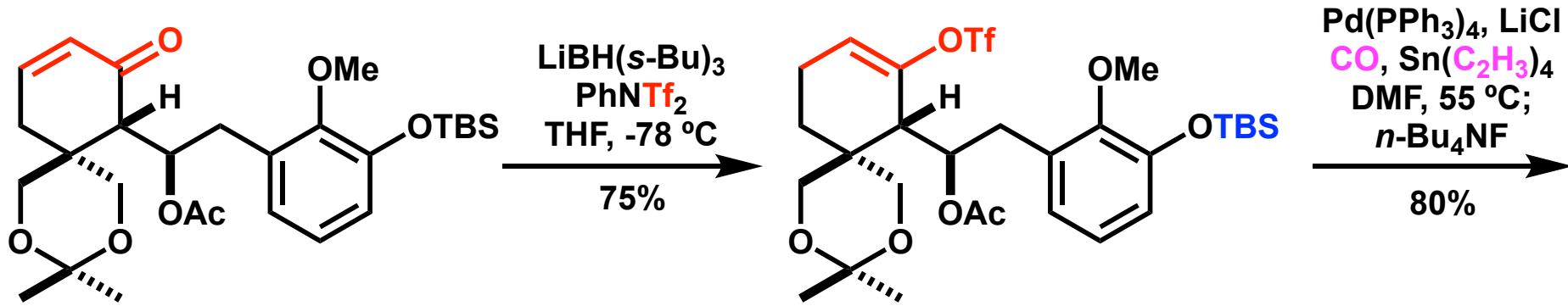
# Enantioselective Acylation



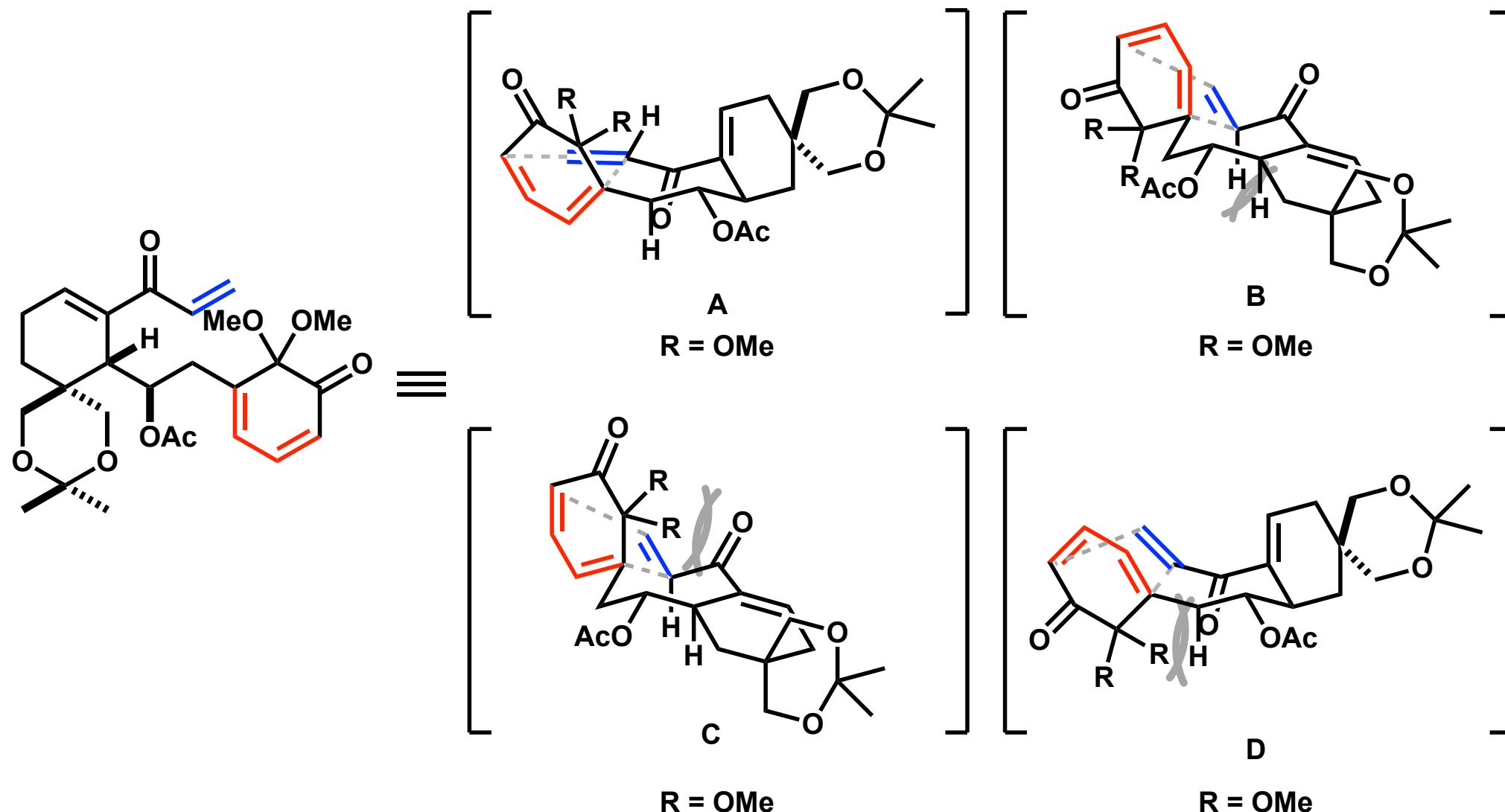
# Proposed Mechanism of Chiral Recognition



# Intramolecular Diels-Alder reaction

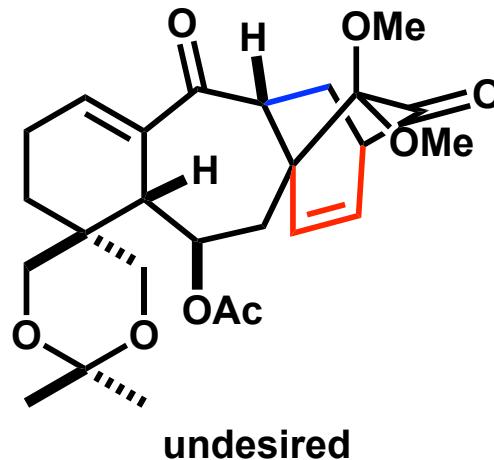
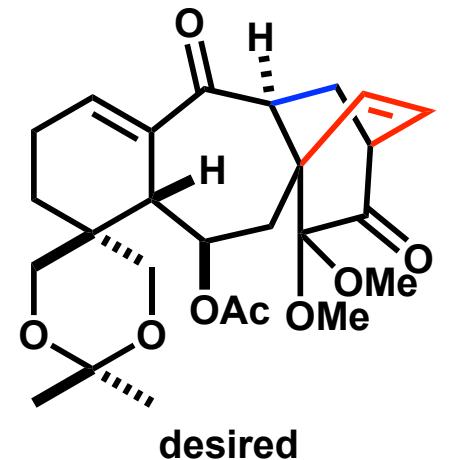
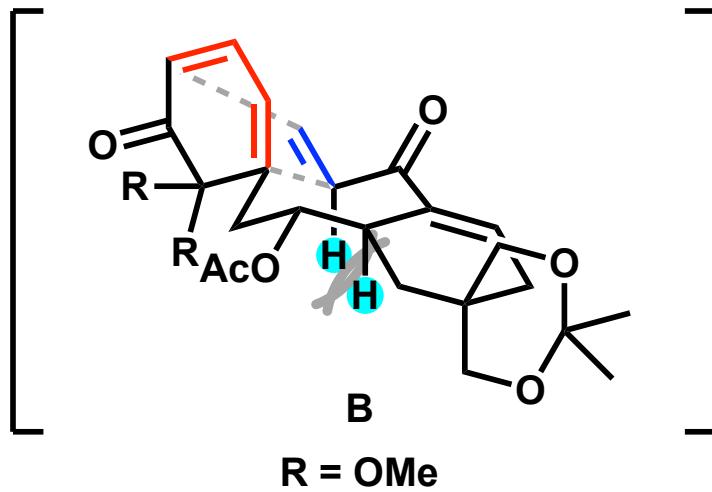
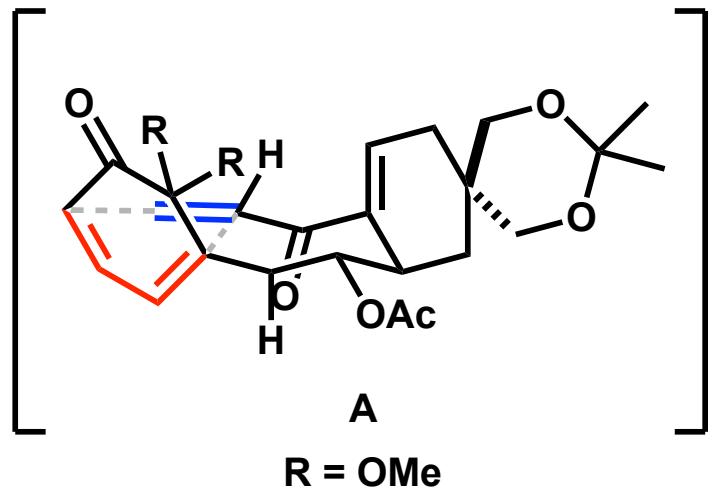


# Diastereoselectivity of Diels-Alder reaction(I)



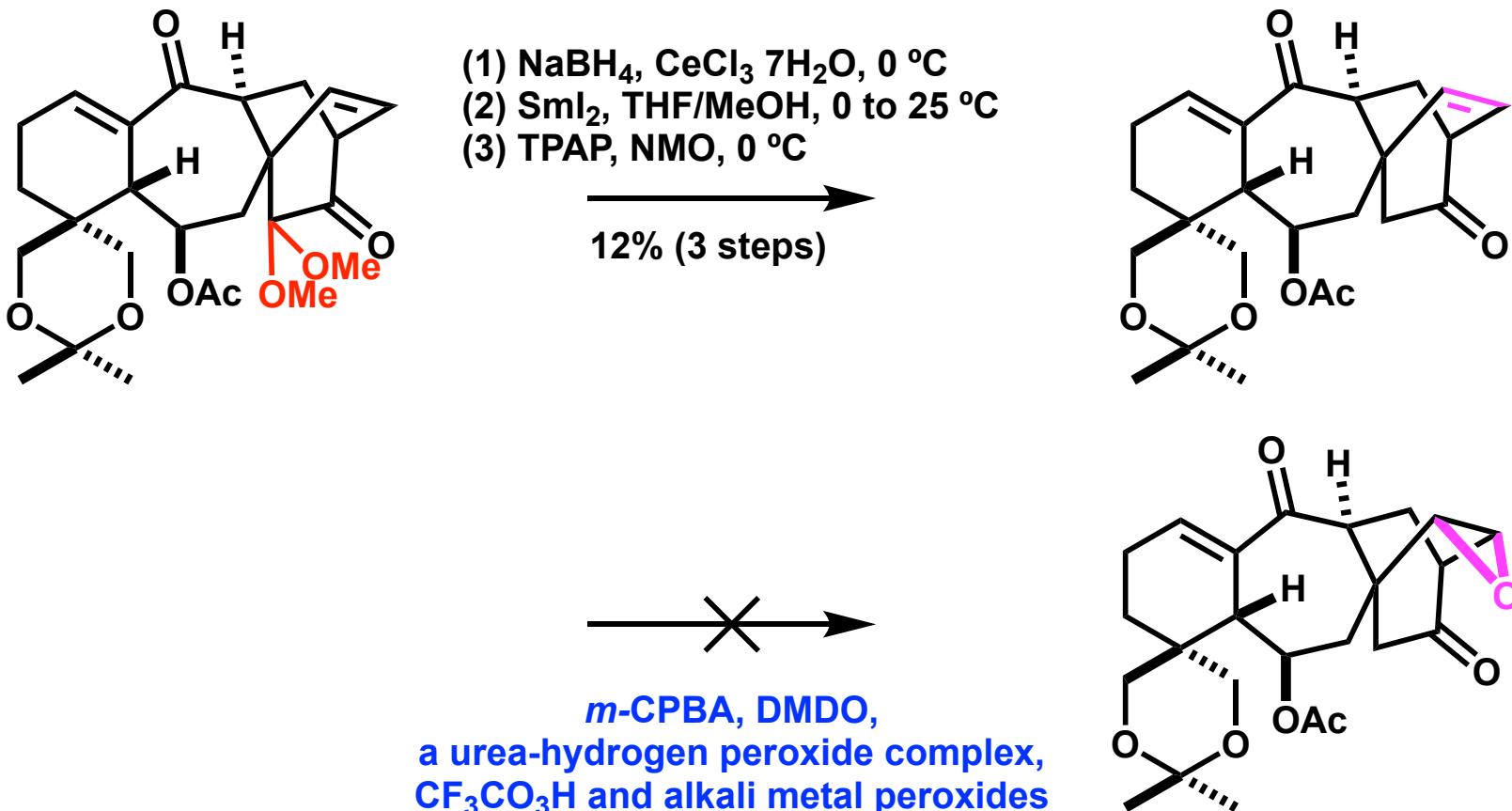
1) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, 143, 10576-10581.

# Diastereoselectivity of Diels-Alder reaction(II)



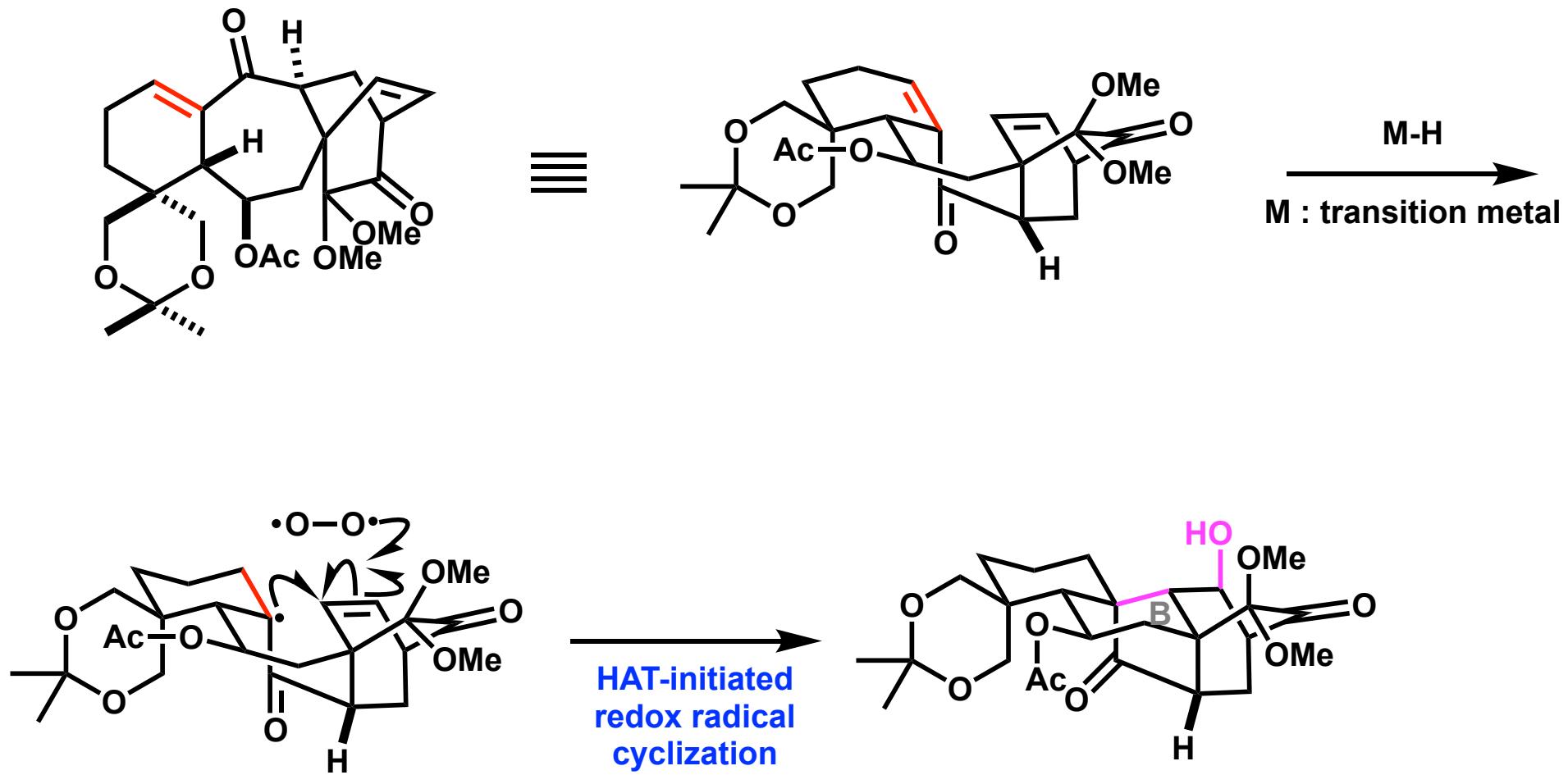
1) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, 143, 10576-10581.

# Attempted Epoxidation

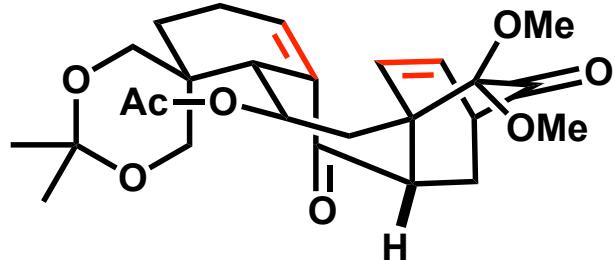


1) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, *143*, 10576-10581.

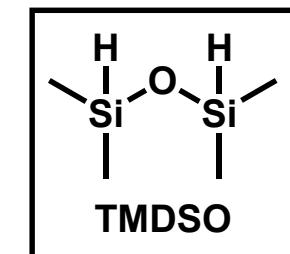
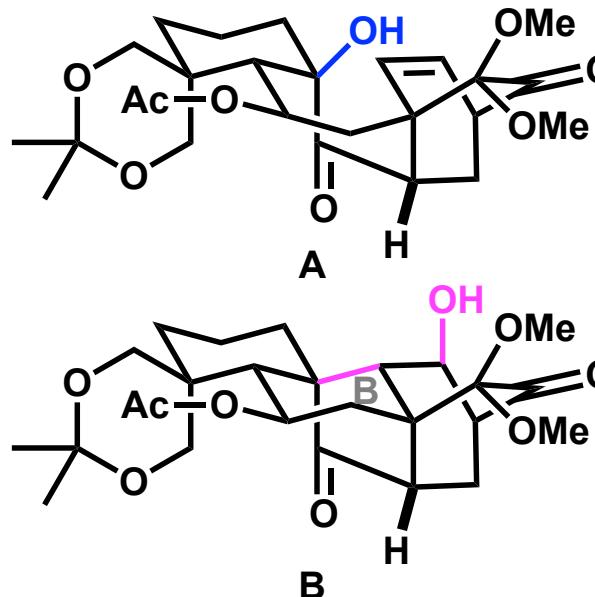
# New synthetic plan of cyclization



# Optimization of the Radical Cyclization

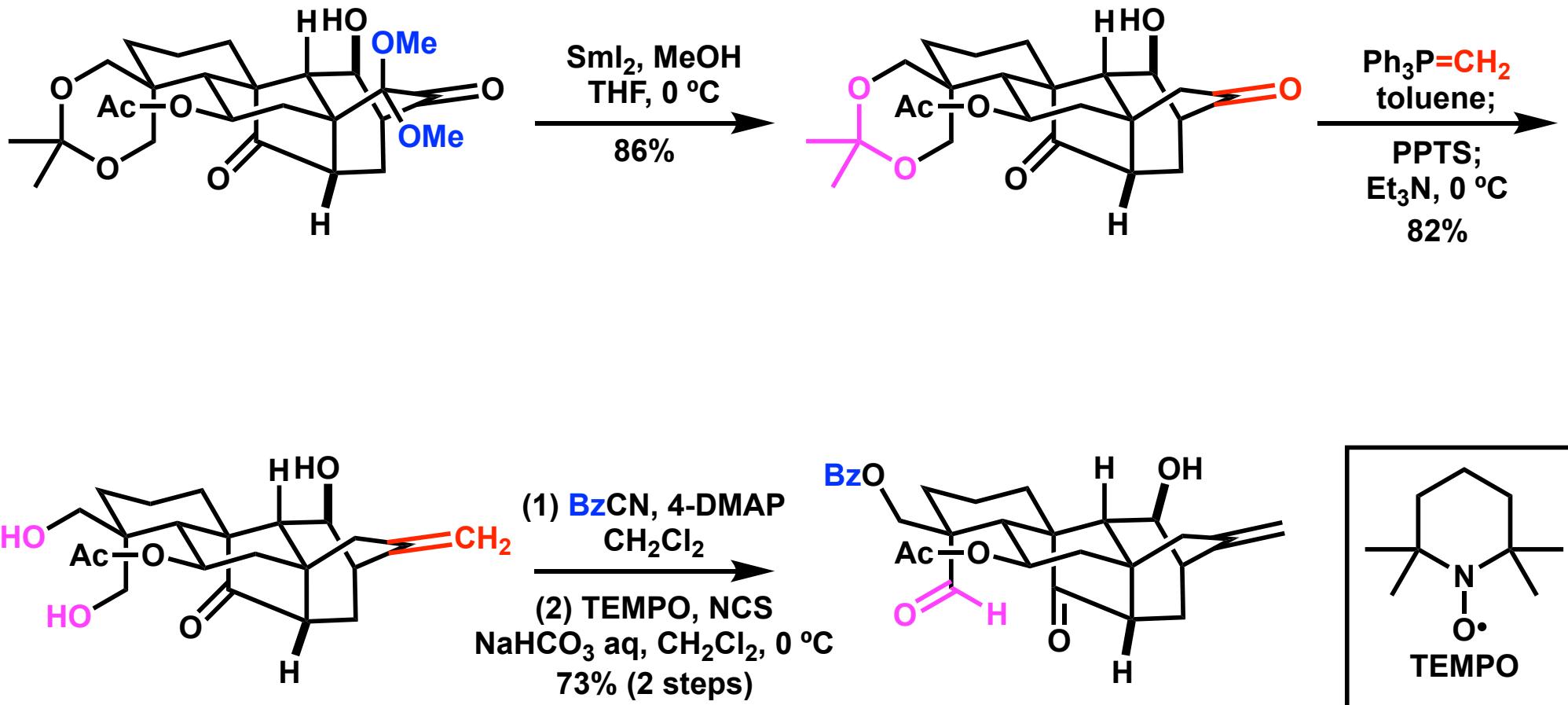


*conditions*



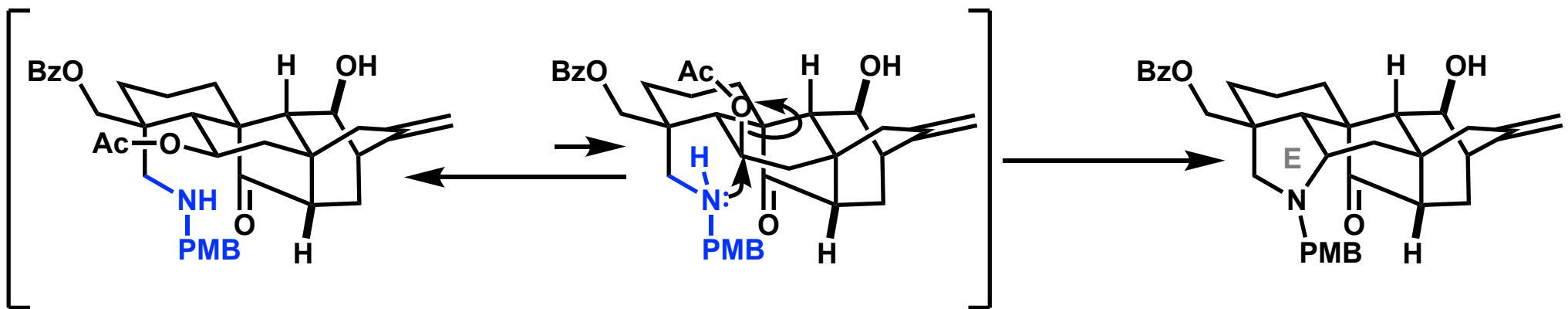
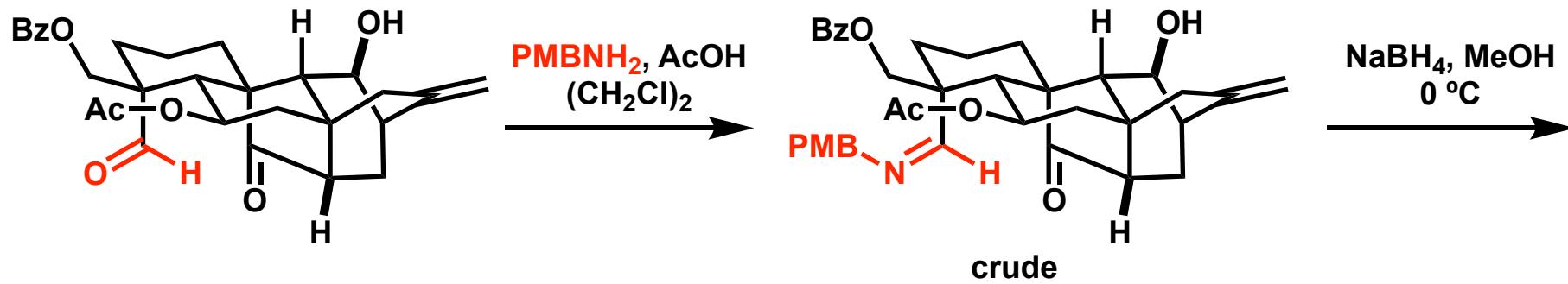
entry	conditions	A	yield B (desired)
1	$\text{Fe}(\text{acac})_3$ , $\text{PhSiH}_3$ or $\text{Ph}(i\text{-PrO})\text{SiH}_2$ , $\text{O}_2$ (2.2 eq.) $\text{EtOH}/(\text{CH}_2\text{OH})_2$ (5:1)	0	0
2	$\text{Mn}(\text{acac})_2$ , $\text{PhSiH}_3$ , $\text{Ph}_3\text{P}$ , $\text{O}_2$ (2.2 eq.), $\text{EtOH}$	89	0
3	$\text{Co}(\text{acac})_2$ , $\text{PhSiH}_3$ , $\text{O}_2$ (2.2 eq.), $i\text{-PrOH}$	<5	75
4	$\text{Co}(\text{acac})_2$ , TMDSO, 4 Å MS, $\text{O}_2$ (2.2 eq.), $i\text{-PrOH}$	<5	83
5	$\text{Co}(\text{acac})_2$ , TMDSO, $\text{O}_2$ (1 atm), $\text{EtOH}$	63	6

# Transformation toward E,F-rings construction

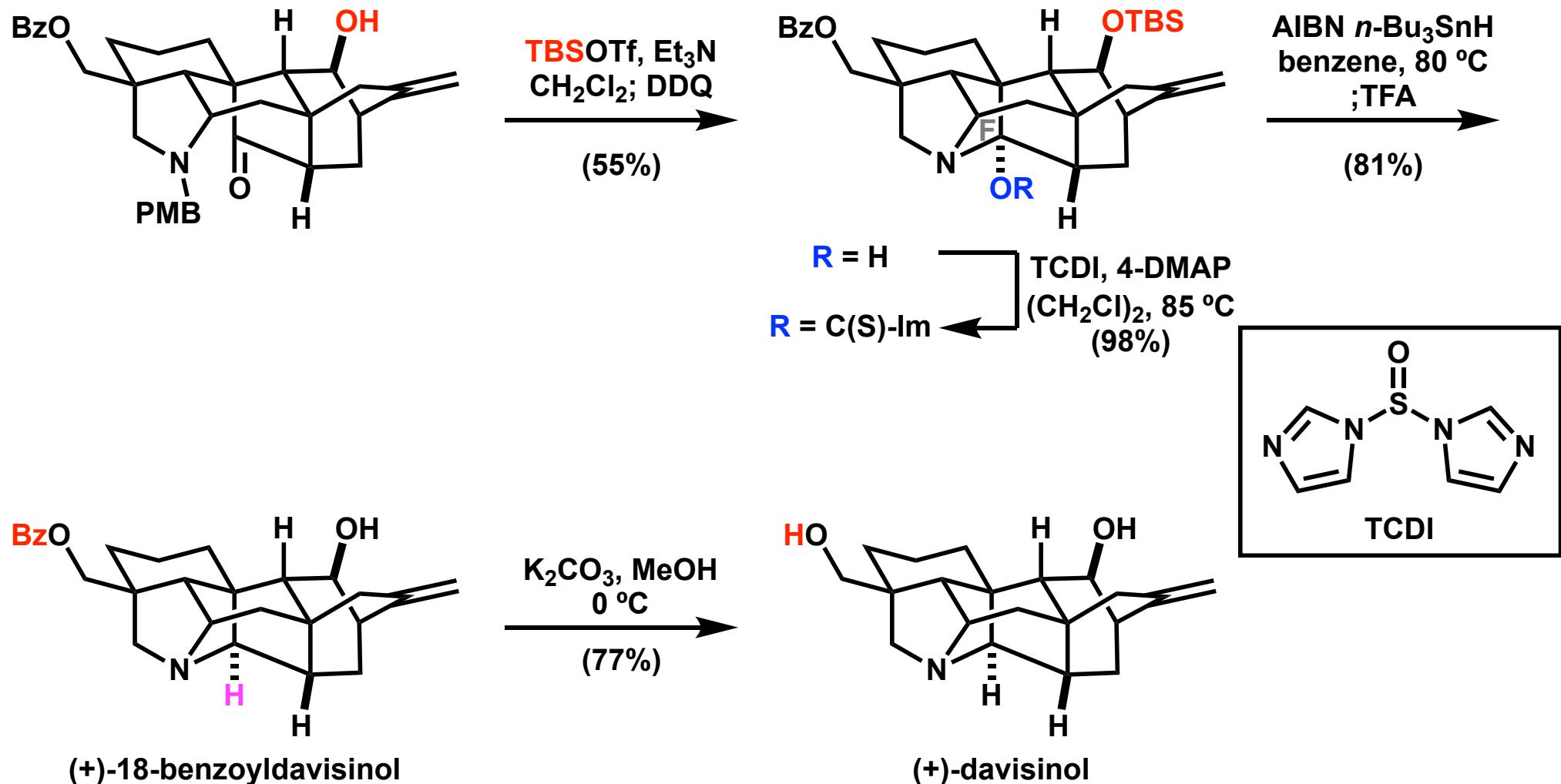


- 1) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, *143*, 10576-10581.
- 2) Holy, A.; Soucek, M. *Tetrahedron Lett.* **1971**, *12*, 185-188.
- 3) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452-7454.

# Construction of E-ring

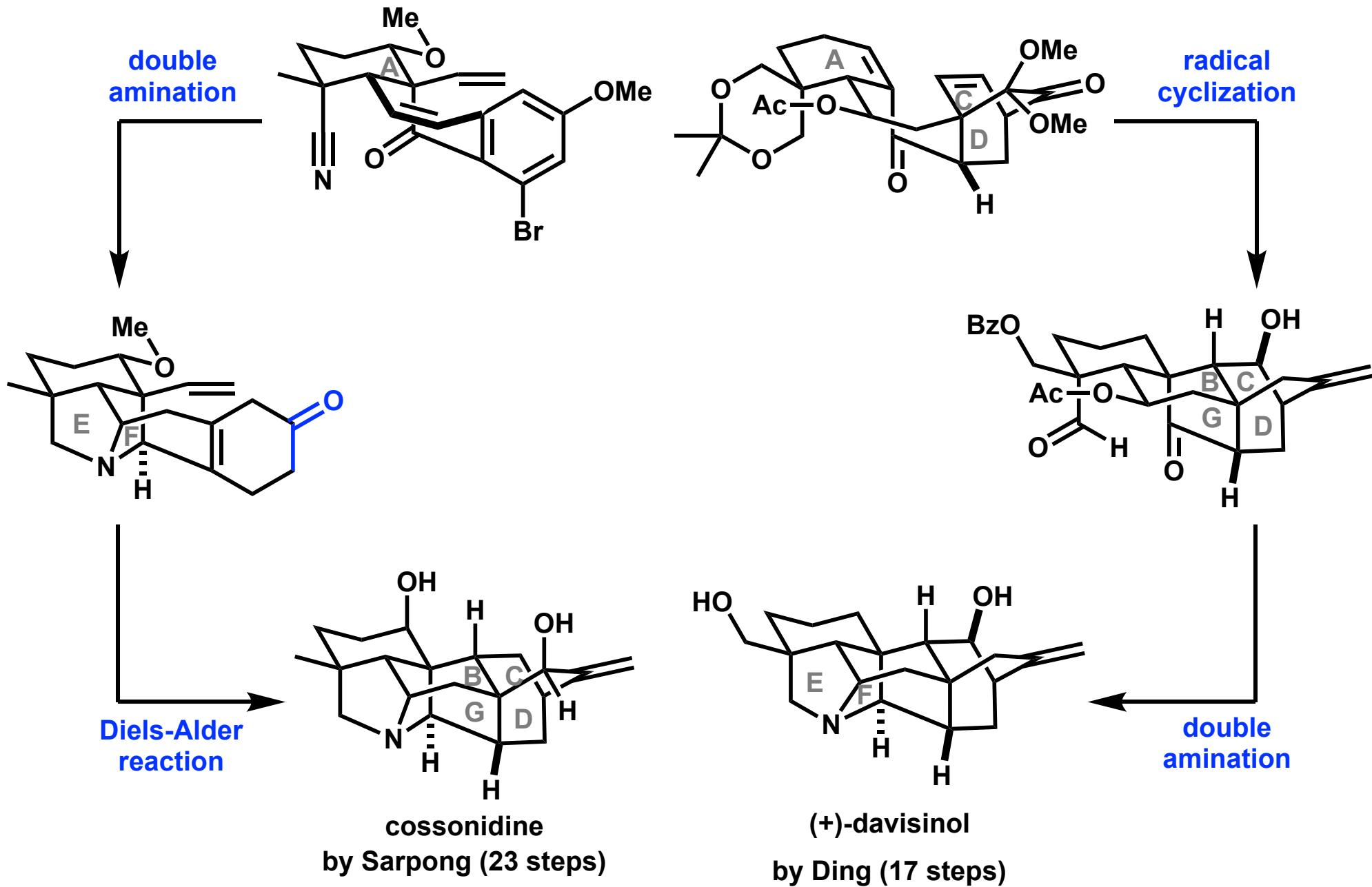


# Total Synthesis of (+)-davisinol



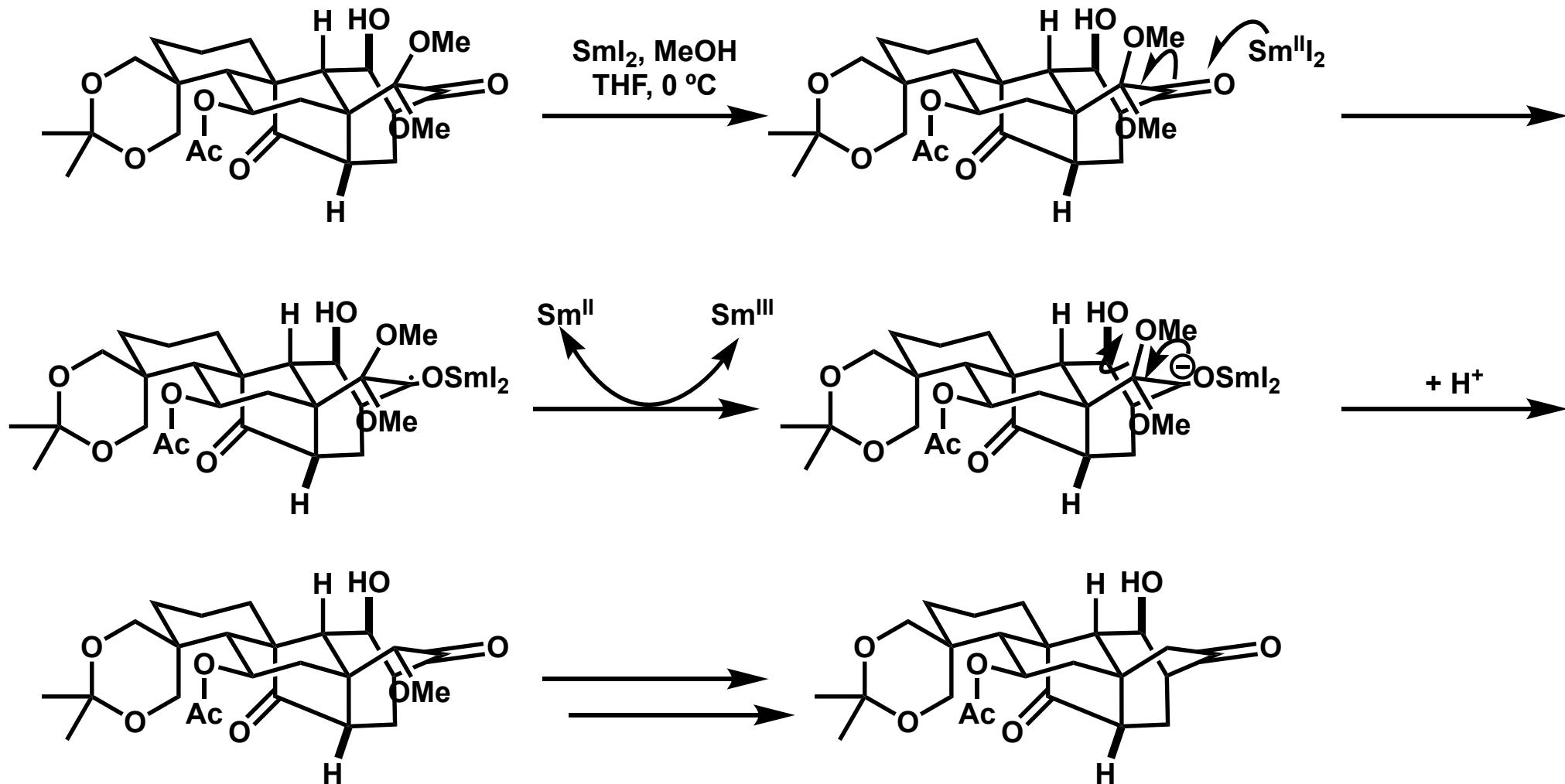
1) Yu, K.; Yao, F.; Zeng, Q.; Xie, H.; Ding, H. *J. Am. Chem. Soc.* **2021**, *143*, 10576-10581.

# Summary



# **Appendix**

# Mechanism of Sm reduction



# Mechanism of B-ring construction

