

# Literature Report III

## Synthesis of Atisine-type Alkaloids

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**Reporter : Yang Zhao**

**Checker : Zhou-Hao Zhu**

**Date : 2018-7-16**

Ma, D. *et al. Angew. Chem. Int. Ed.* **2018**, 57, 6676  
Baran, P. S. *et al. J. Am. Chem. Soc.* **2014**, 136, 12592

# CV of Prof. Dawei Ma

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## Research:

- Total synthesis of complex natural products
  - New synthetic methodologies: Copper-catalyzed coupling reactions; Asymmetric Michael additions, Henry reaction; Intramolecular Dearomative Oxidative Coupling
  - Biochemistry
- 

## Education:

- **1980–1984** B.S., Shandong University
- **1984–1989** Ph.D., Shanghai Institute of Organic Chemistry (Xiyan Lu)
- **1990–1994** Postdoc., University of Pittsburgh and Mayo Clinic, U.S.A.
- **1995– now** Prof., Shanghai Institute of Organic Chemistry

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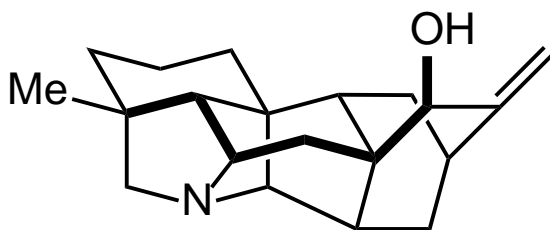
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# Introduction

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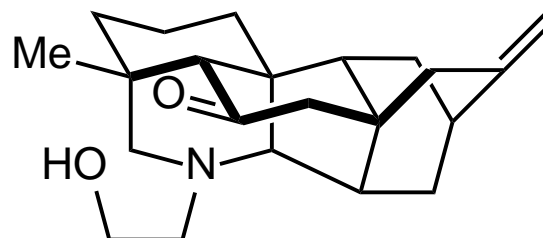
## *C<sub>20</sub> diterpenoid alkaloids*

### *hetisine-type*



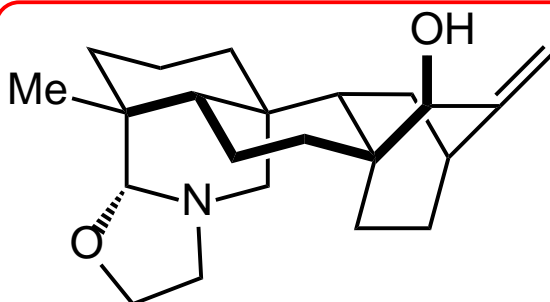
**nominine**

### *hetidine-type*

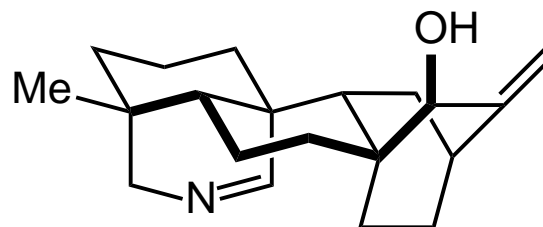


**(-)-spirafine III**

### *atisine-type*



**(-)-isoatisine**

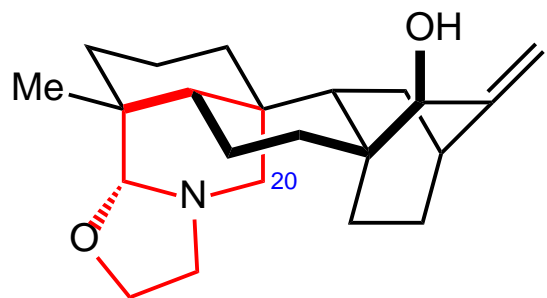


**azitine**

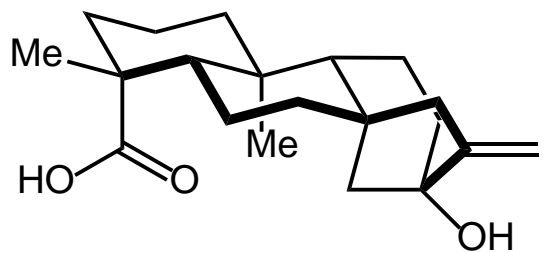
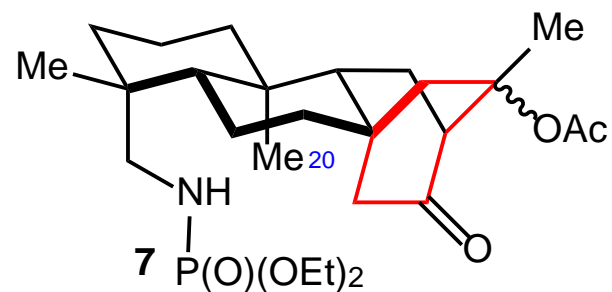
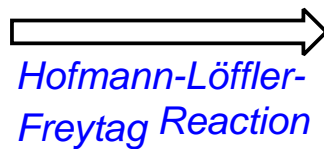
[illegible]

- Yao, B.-H. *et al. J. Pharm. Anal.* **2011**, 1, 57  
Baran, P. S. *et al. J. Am. Chem. Soc.* **2014**, 136, 12592

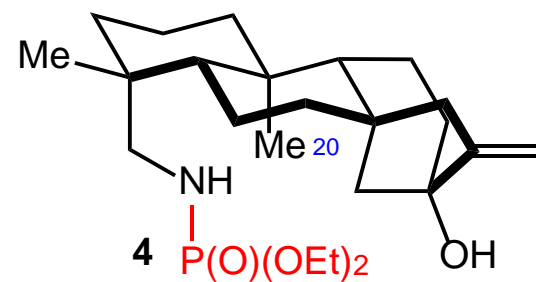
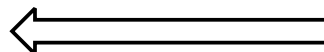
# Retrosynthetic Analysis



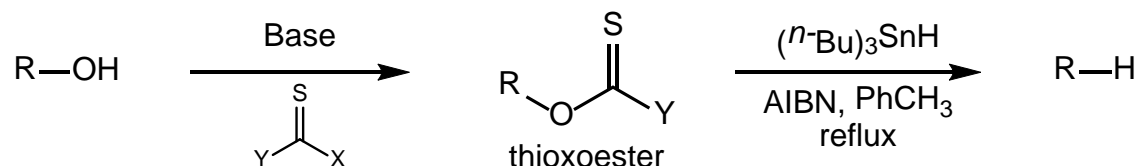
**(-)-Isoatisine**



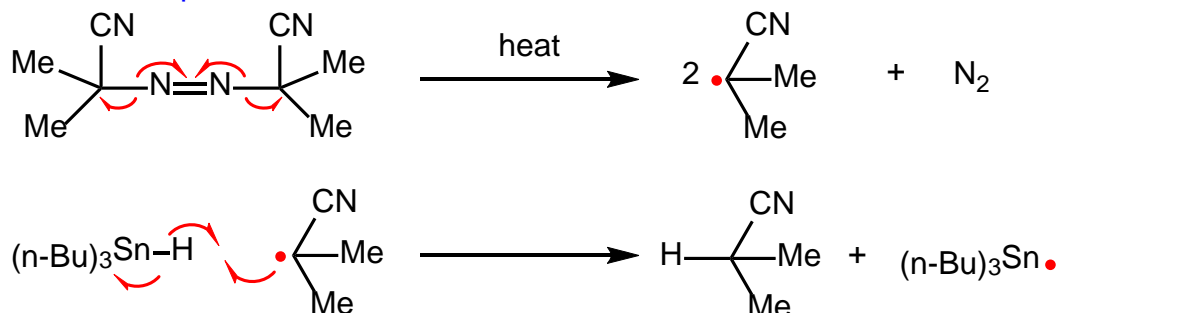
**(-)-Steviol**



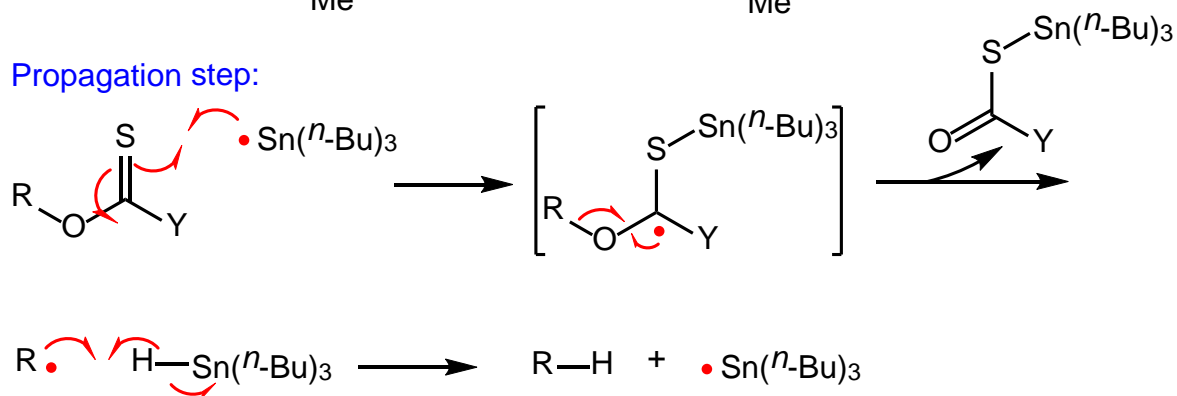
# Barton-McCombie Deoxygenation Reaction



Initiation step:

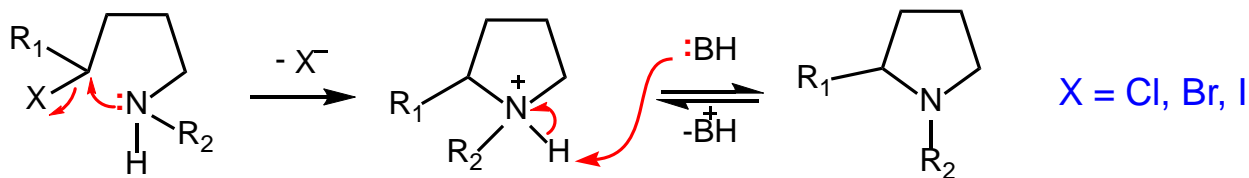
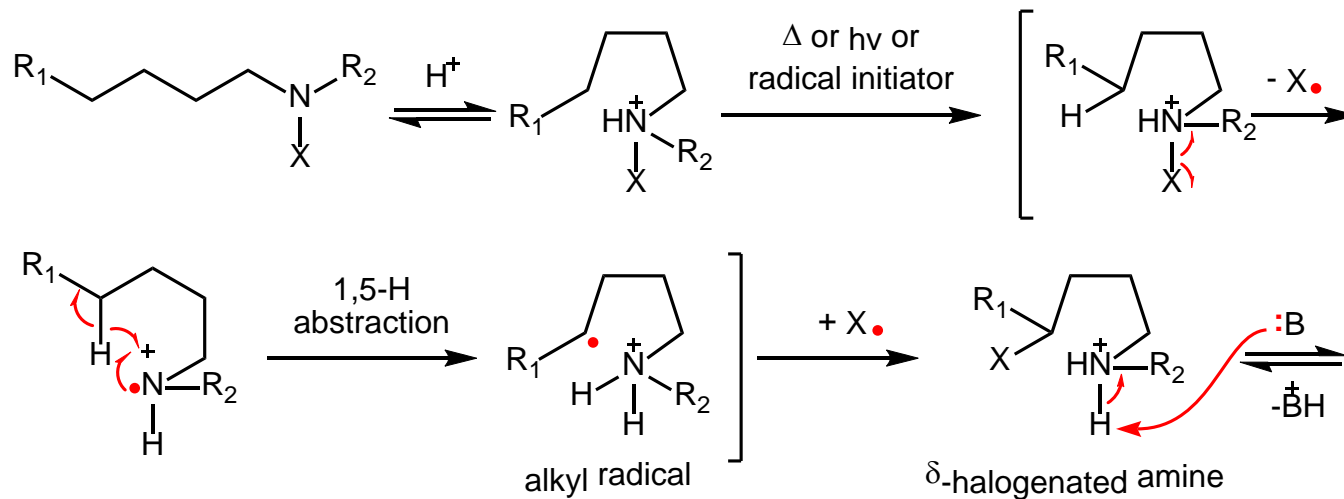
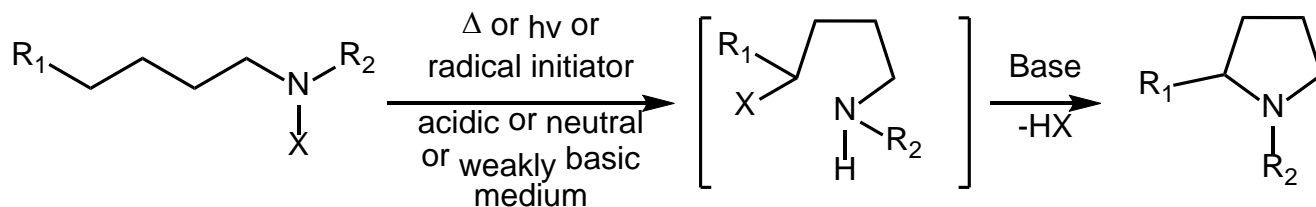


Propagation step:



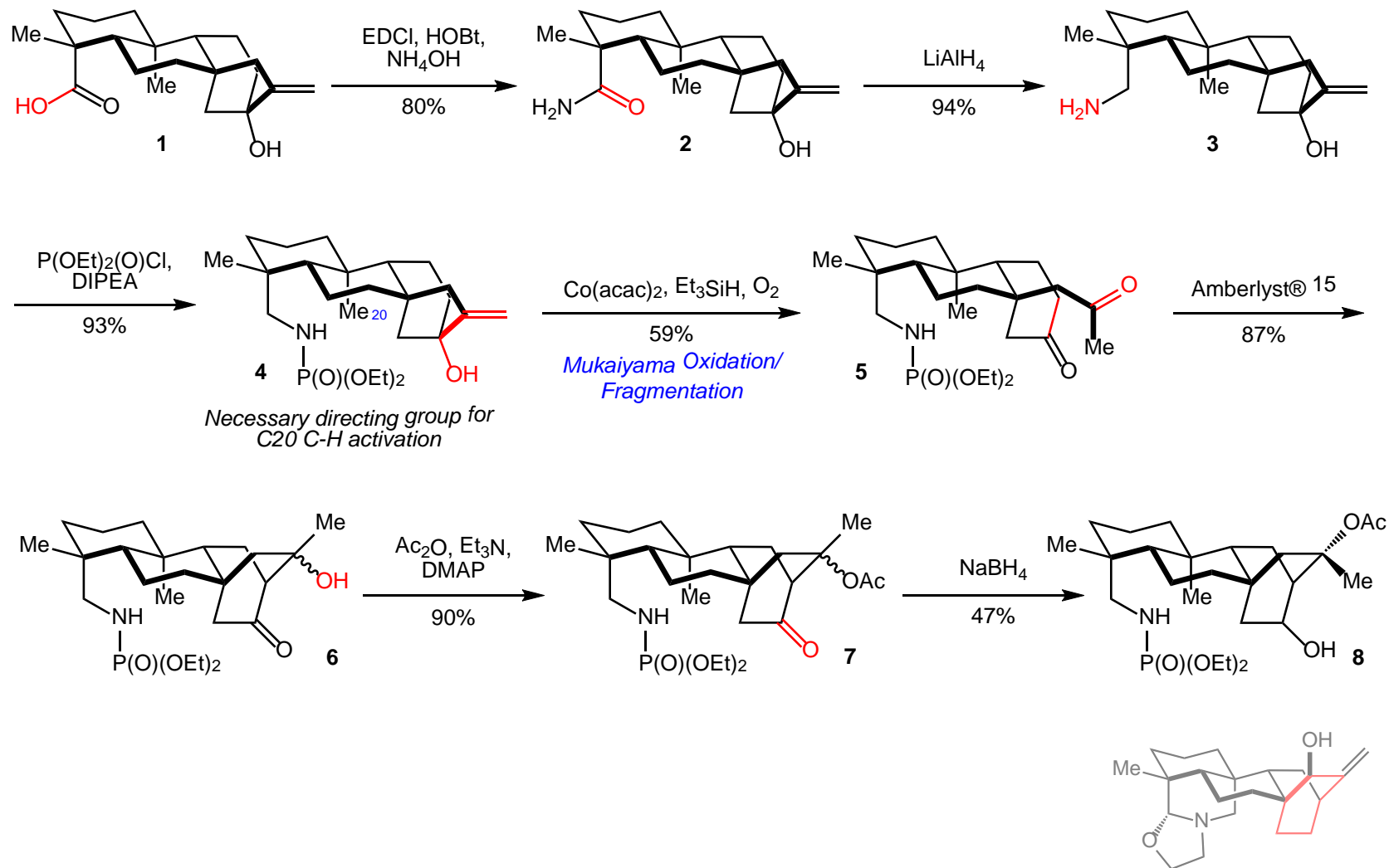
X = Cl, imidazolyl; Y=SMe, imidazolyl, OPh, OMe; R-OH = 1°, 2° or 3° alcohol

# Hofmann-Löffler-Freytag Reaction

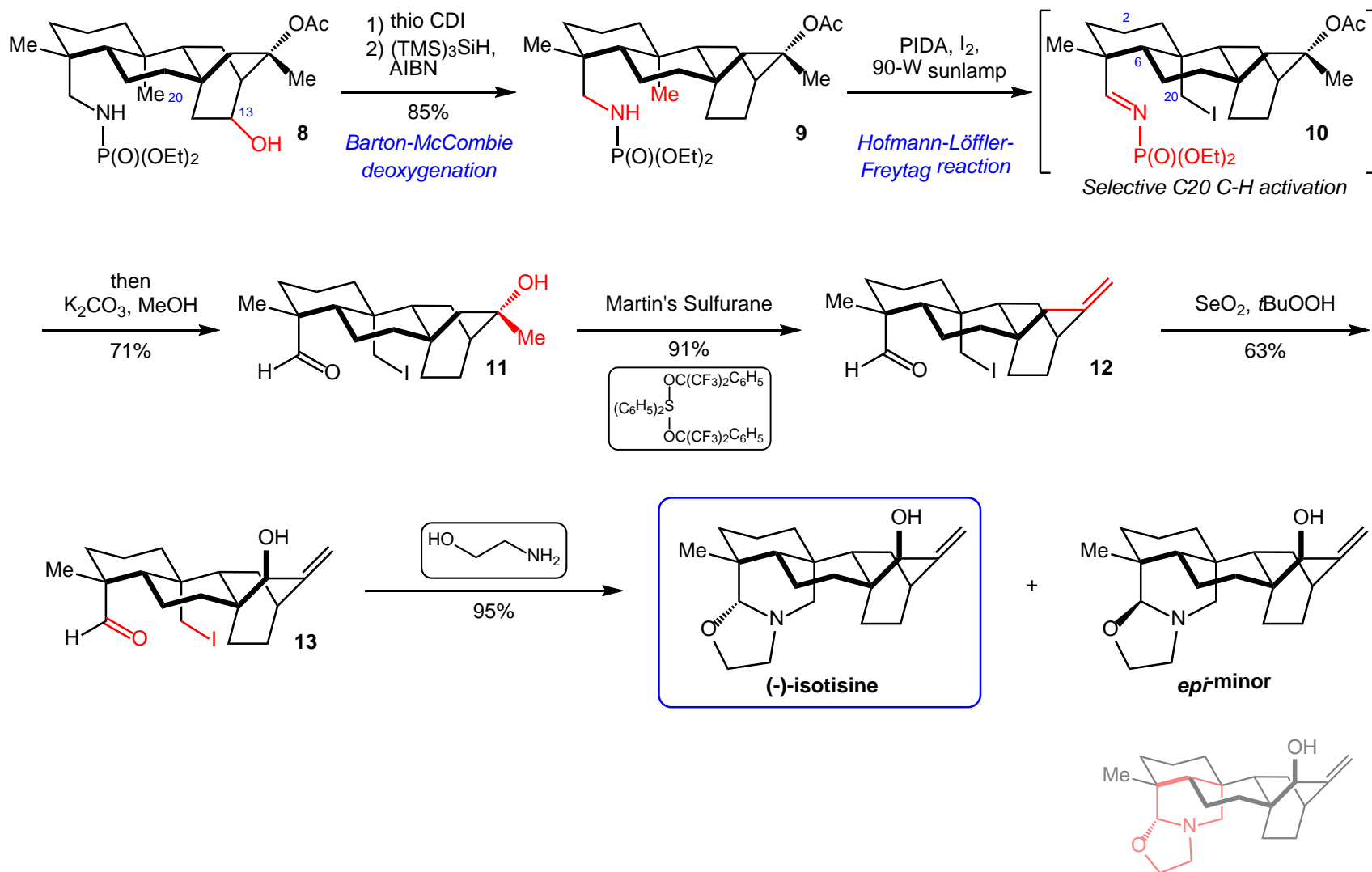




# Semisynthesis of (-)-Isoatisine

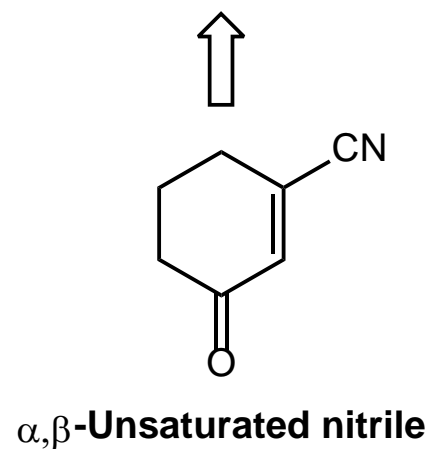
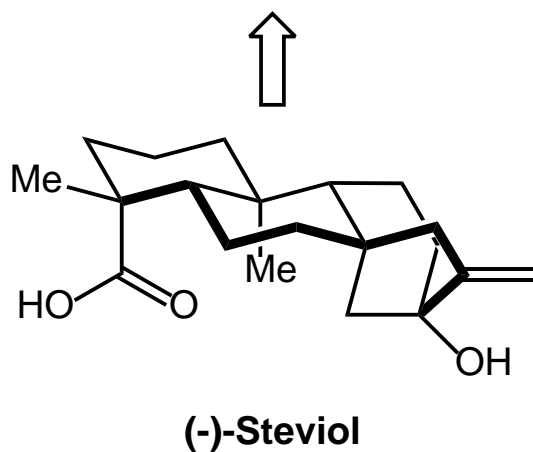
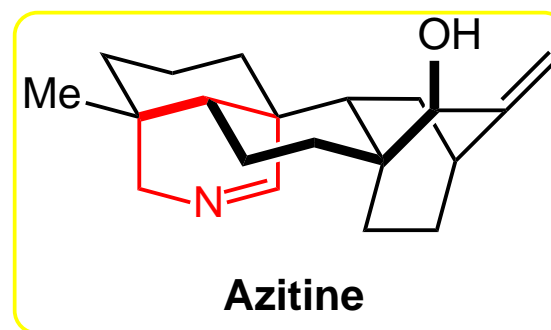
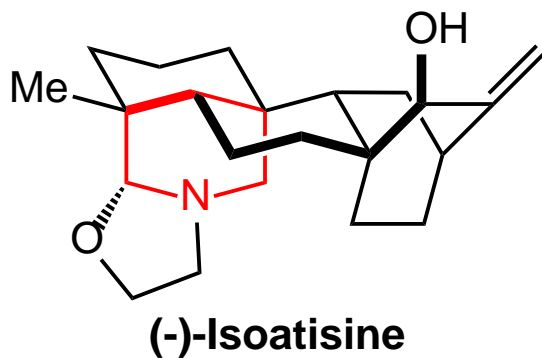


# Semisynthesis of (-)-Isoatisine



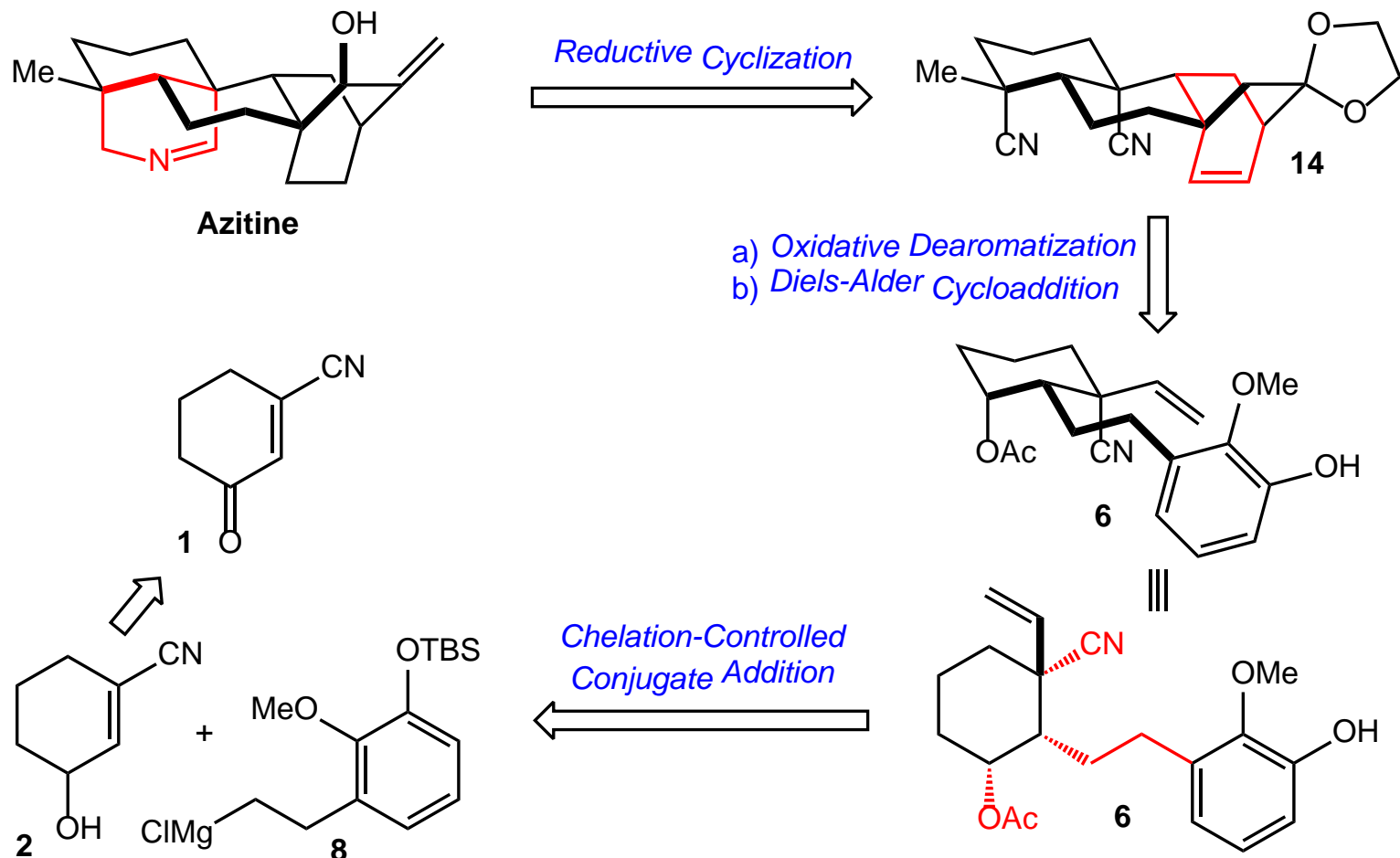
# Introduction

*Atisine-type*

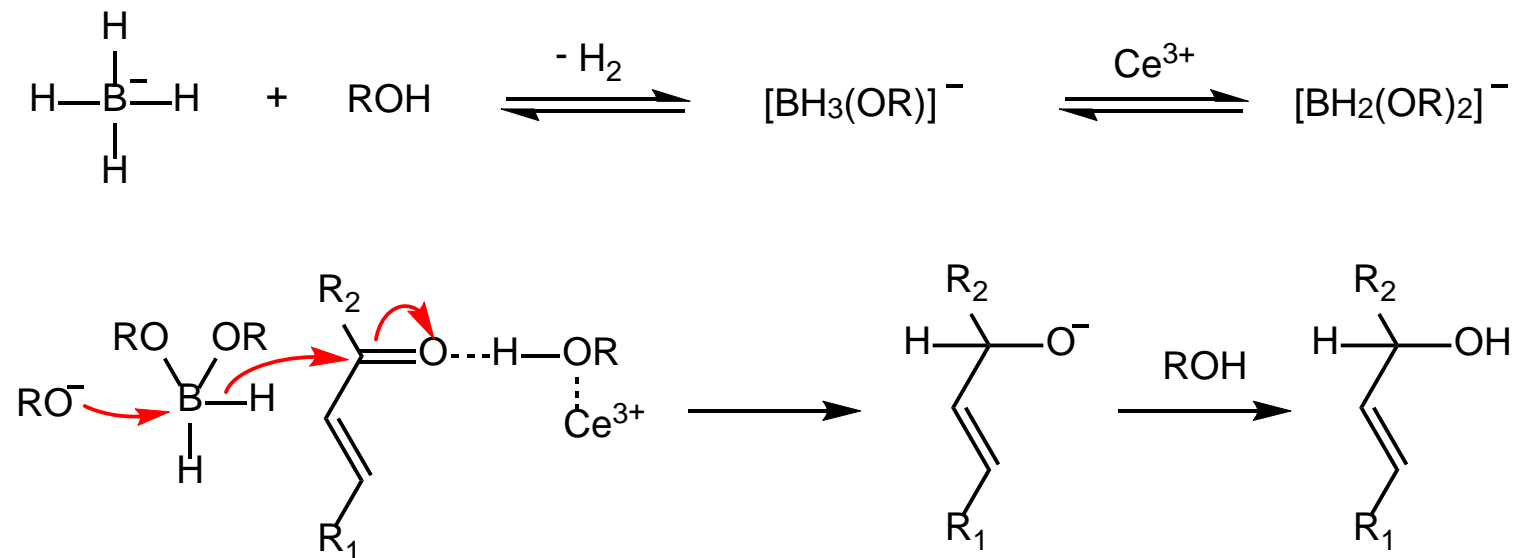
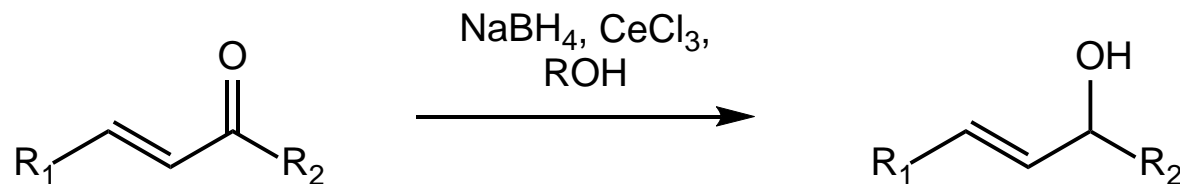


Ma, D. *et al. Angew. Chem. Int. Ed.* **2018**, 57, 6676

# Retrosynthetic Analysis

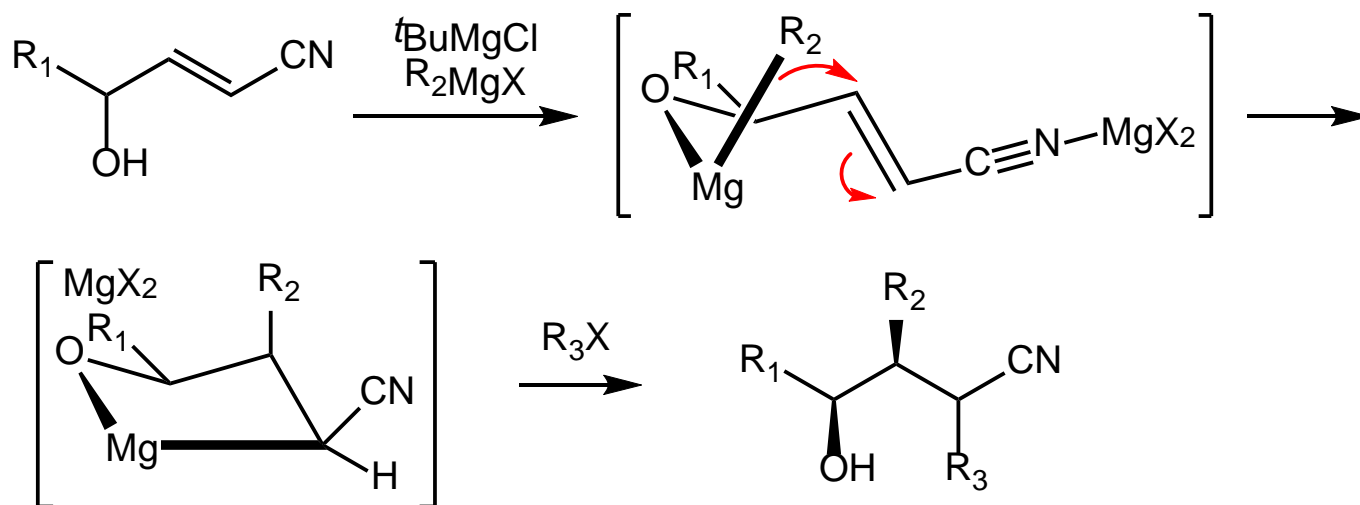
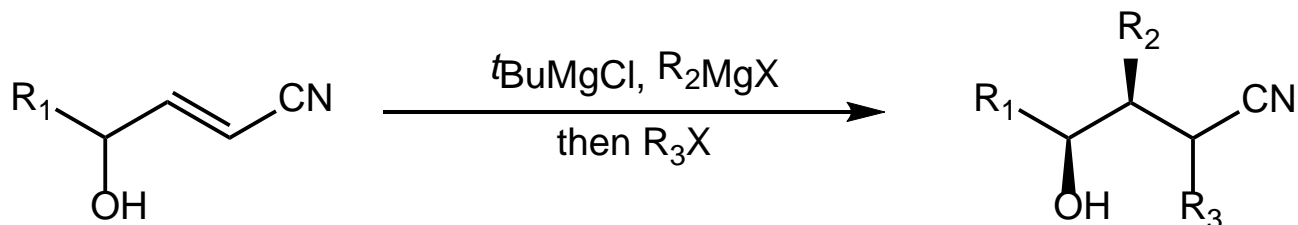


# Lucas Reduction



Both acyclic and cyclic enones are reduced to corresponding allylic alcohols

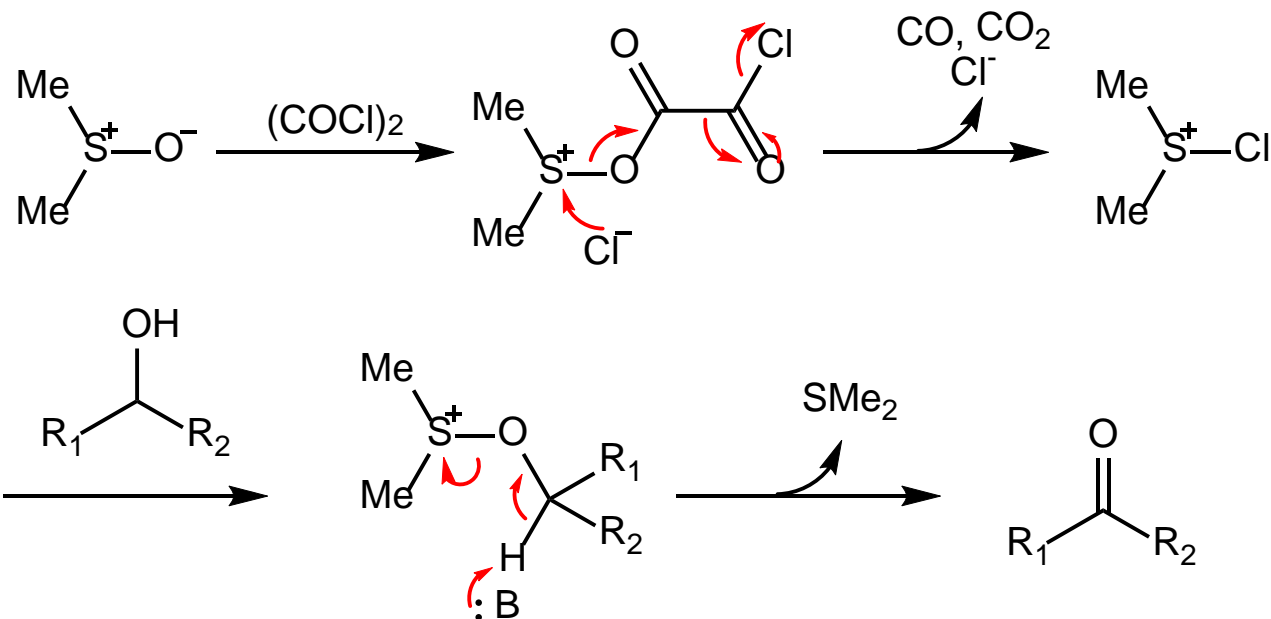
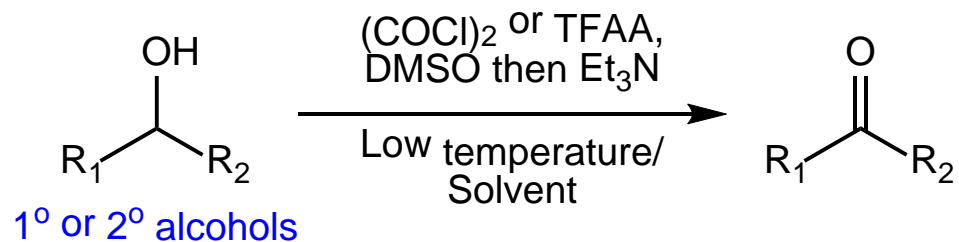
# Chelation-Controlled Conjugate Addition



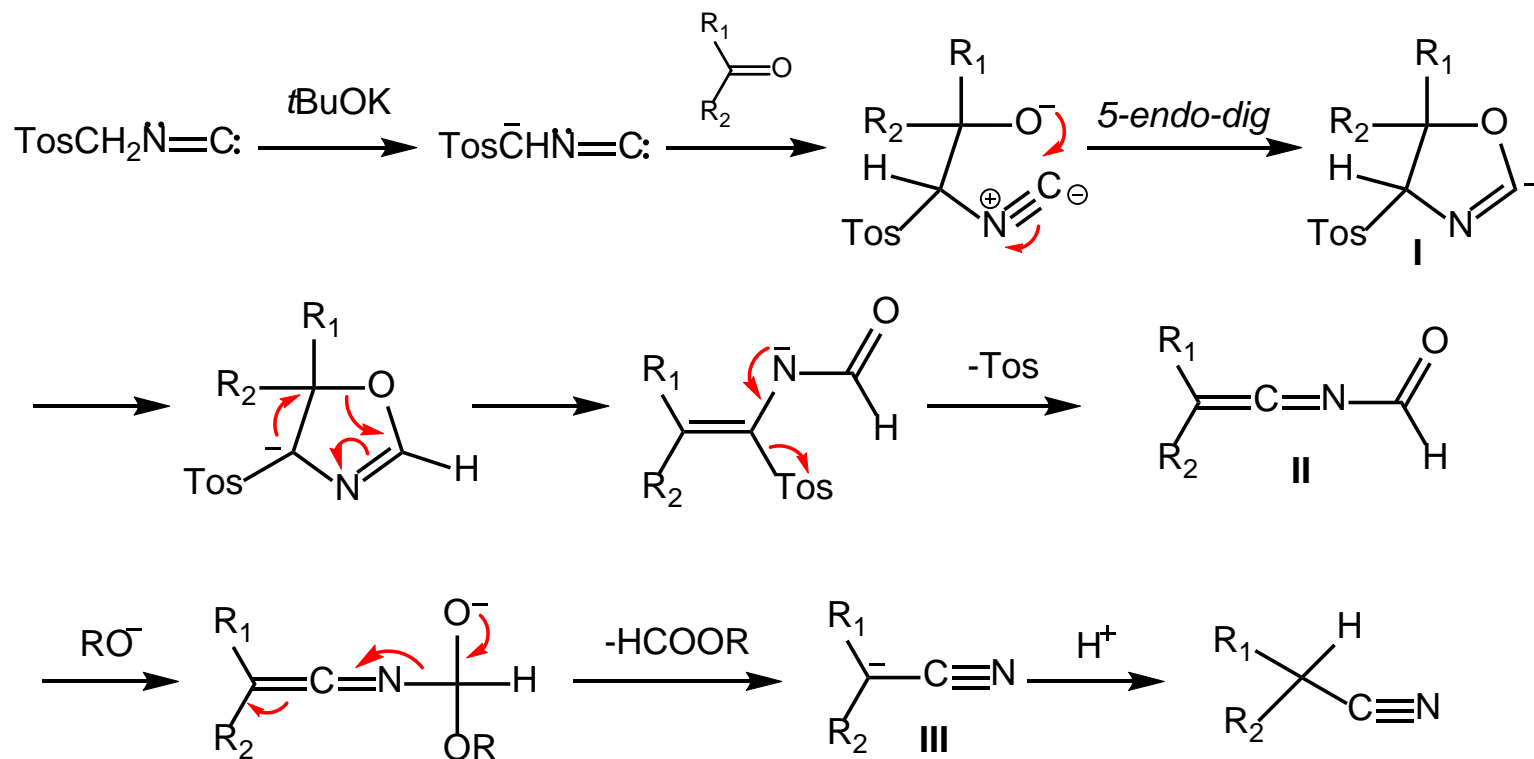
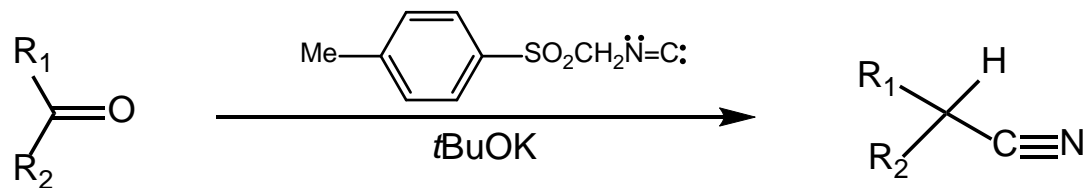
$\gamma$ -hydroxy group in an  $\alpha,\beta$ -unsaturated nitrile could promote the conjugate addition by chelation to the Grignard reagent

Steward, O. W. *et al. Angew. Chem. Int. Ed.* **2004**, 43, 1126

# Swern Oxidation



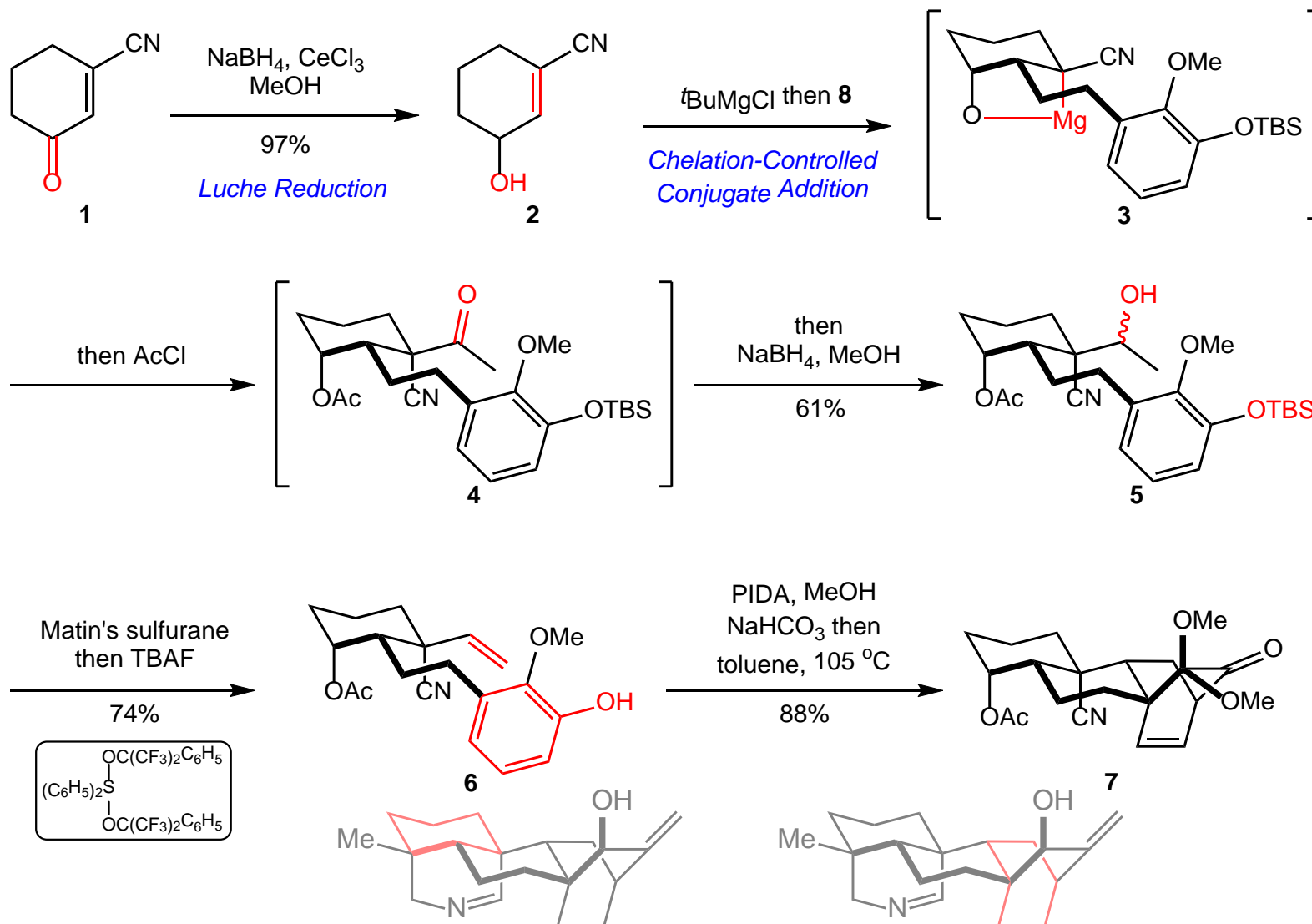
# Van Leusen Reaction



Van Leusen, A. M. *et al. J. Org. Chem.* **1977**, 42, 3115

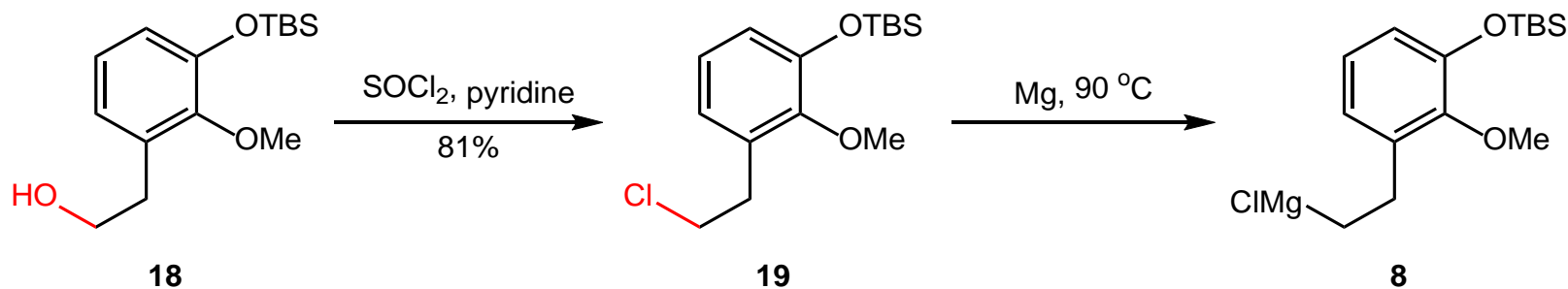


# Total Syntheses of Azitine

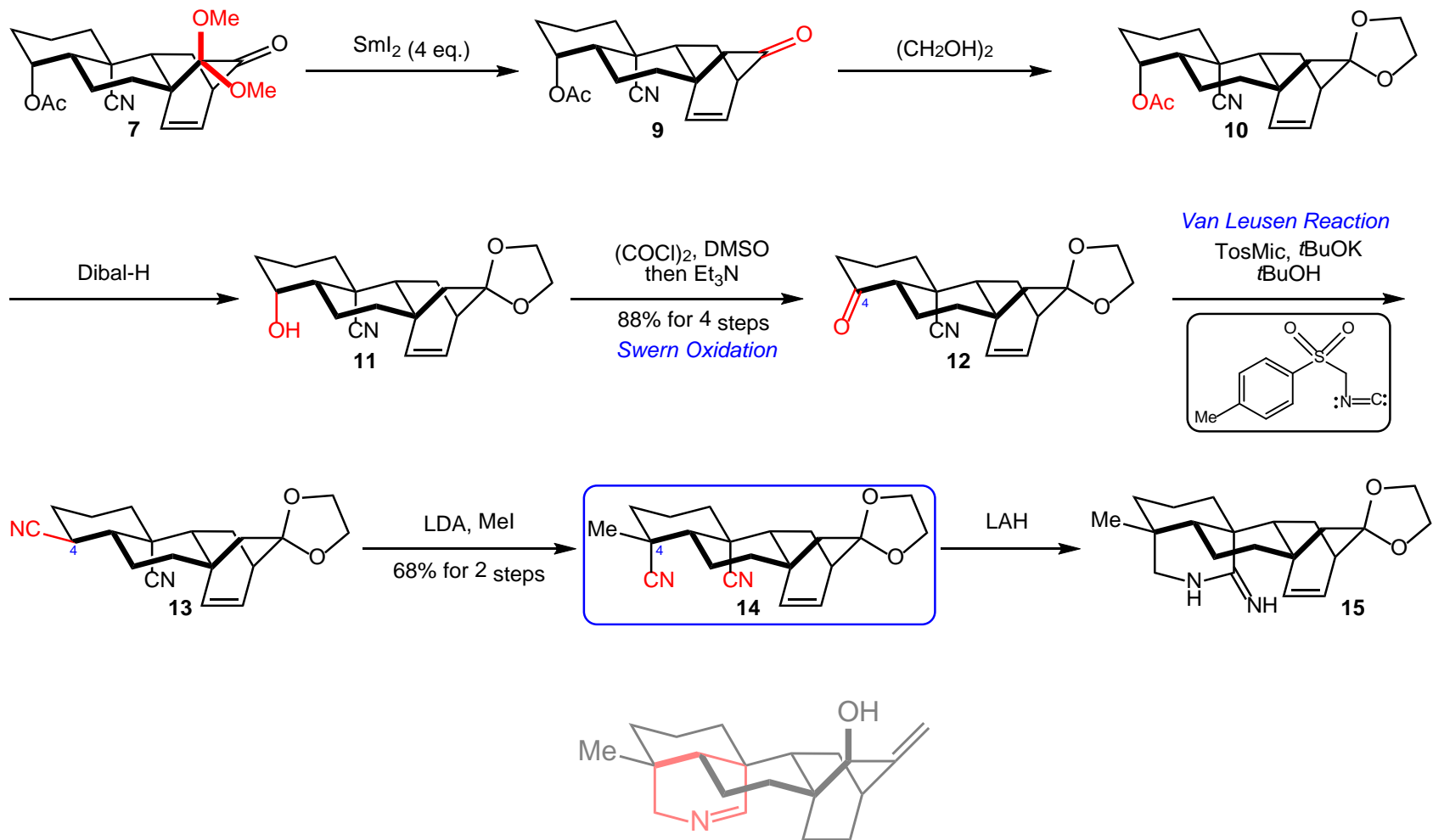


# Preparation of Grignard Reagent 8

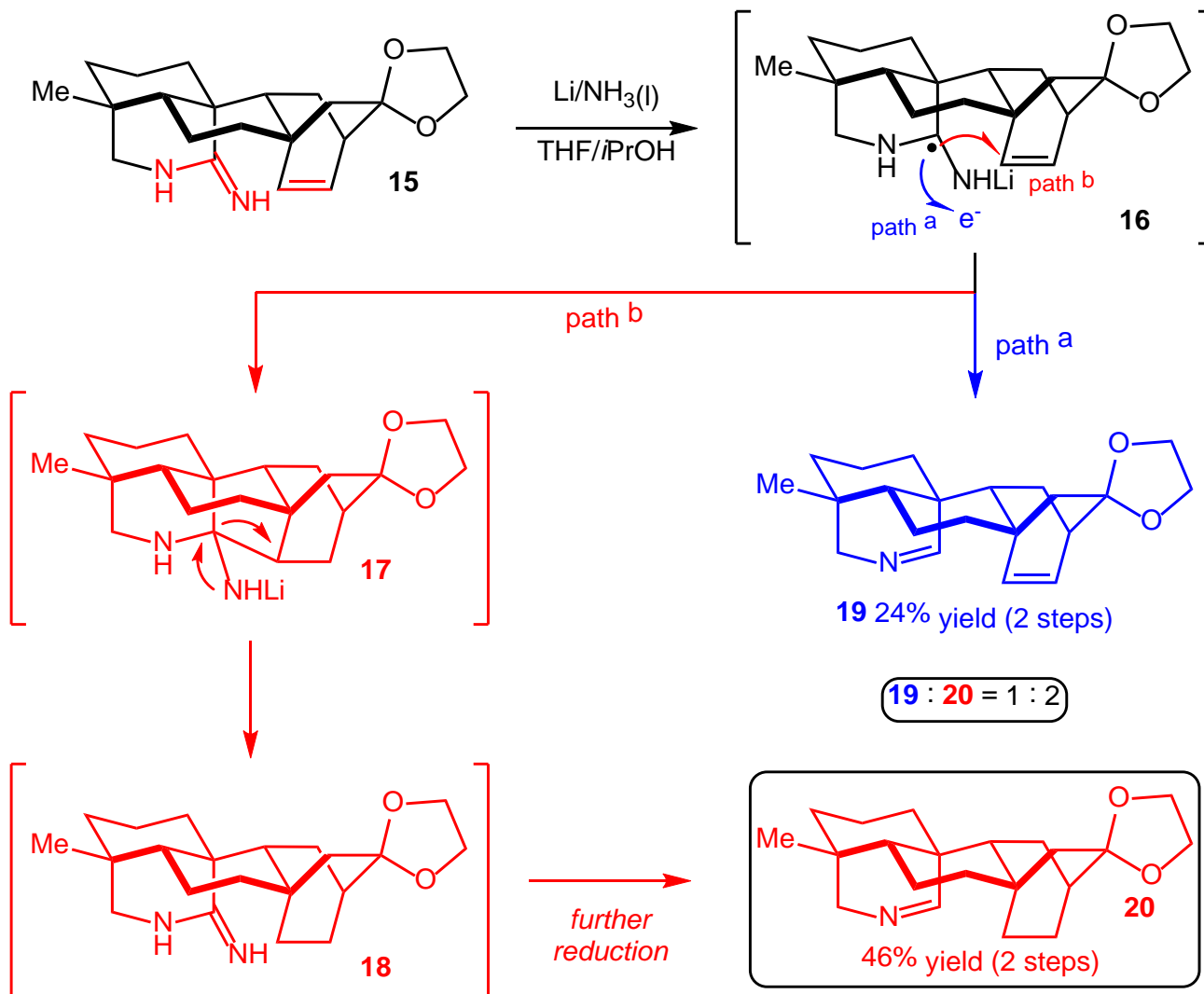
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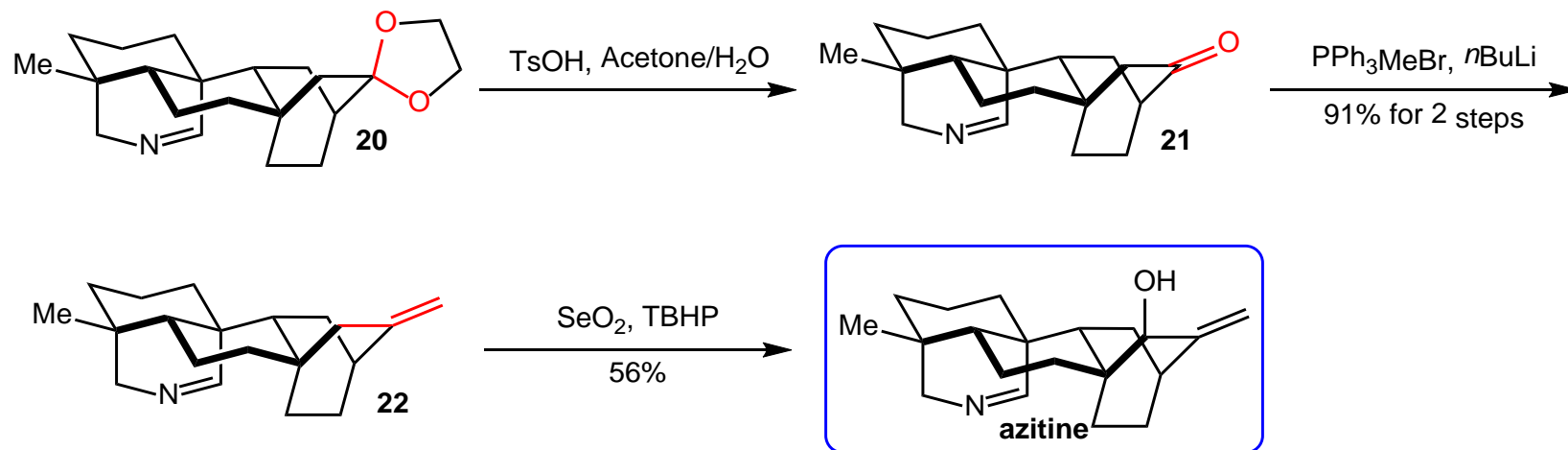
# Total Syntheses of Azitine



# Total Syntheses of Azitine

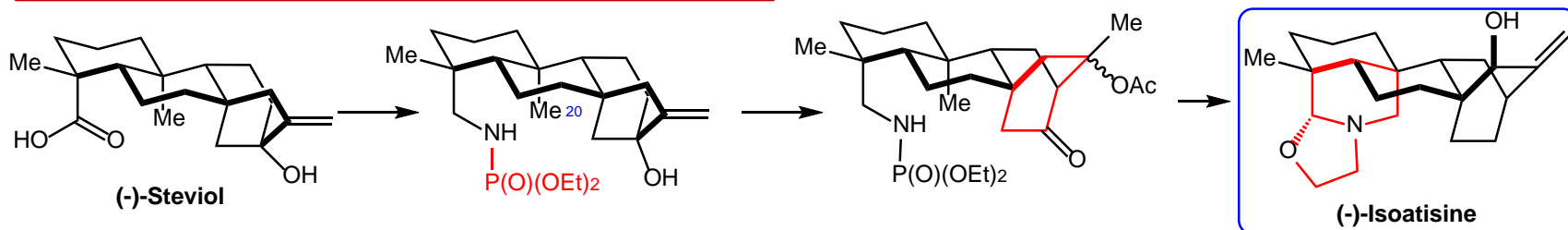


# Total Syntheses of Azitine



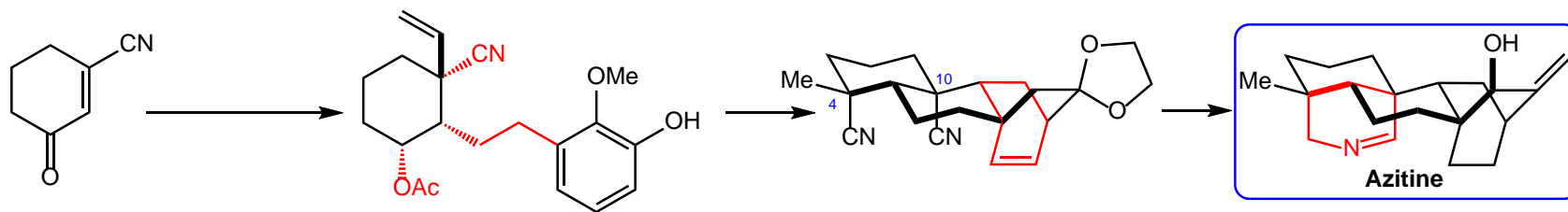
# Summary

## Semisynthesis of (-)-Isoatisine



Baran, P. S. *et al.* *J. Am. Chem. Soc.* **2014**, 136, 12592

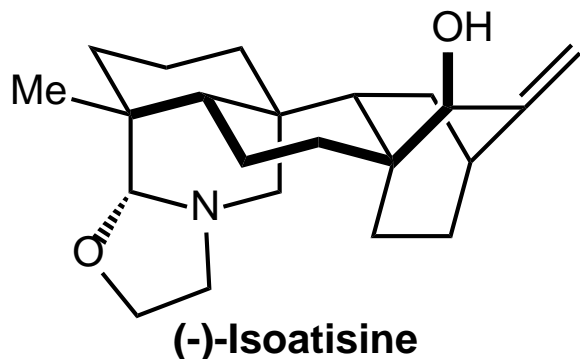
## Total Syntheses of Azitine



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# Summary

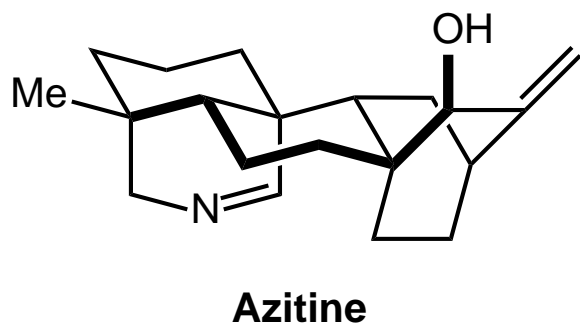
## Semisynthesis of (-)-Isoatisine



- ◆ 13 steps, 4.6% overall yield
- ◆ Mukaiyama oxidation/fragmentation
- ◆ Hofmann-Löffler-Freytag reaction (Suárez modification)

Baran, P. S. *et al. J. Am. Chem. Soc.* **2014**, 136, 12592

## Total Syntheses of Azitine



- ◆ 17 steps, 5.4% overall yield
- ◆ Chelation-triggered conjugate addition
- ◆ Oxidative dearomatization/  
Diels-Alder cycloaddition
- ◆ Reduction of a dinitrile intermediate

Ma, D. *et al. Angew. Chem. Int. Ed.* **2018**, 57, 6676

# The First Paragraph

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Owing to their caged and polycyclic ring systems, the C<sub>20</sub> diterpenoid alkaloids are recognized among the most architecturally complex natural products, and have elicited considerable interest from the synthetic community over the past several decades. These synthetic campaigns culminated in the completion of formal and total syntheses of a subset of C<sub>20</sub> diterpenoid alkaloids, namely nominine, atisine, isoatisine and so on. However, most of these synthetic routes require a large number of steps and are restricted to a very particular structure. There is plenty of room for developing more concise total syntheses towards atisine- and hetidine-type alkaloids. Herein, we report a short and efficient approach for the assembly of a tetracyclic dinitrile compound. By making use of this common intermediate, we achieved the first total synthesis of azitine, an anti-leishmanial atisine-type diterpenoid alkaloid that was first isolated from *Consolida hellespontica*.



# The Last Paragraph

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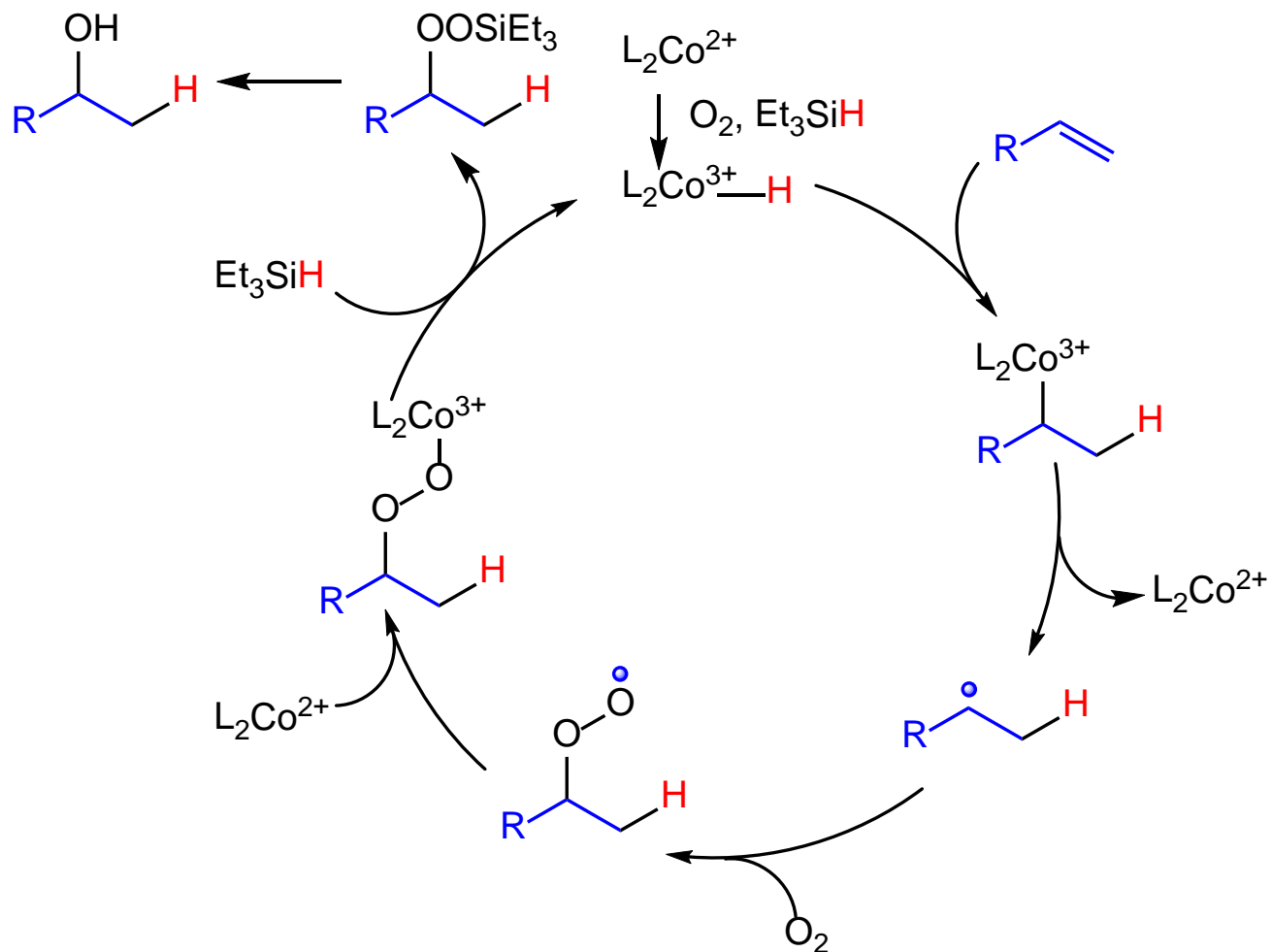
In conclusion, we have described a unified approach towards the atisane-type C<sub>20</sub> diterpenoid alkaloids, as exemplified by the first total syntheses of azitine. The syntheses feature a number of key transformations, including a) chelation-triggered conjugate addition to control the contiguous three stereogenic centers in the cyclohexane unit, b) oxidative dearomatization/Diels–Alder cycloaddition to forge the crucial bicyclo[2.2.2]octane moiety with a free cyano group at the C<sub>20</sub> position, c) reduction of a dinitrile intermediate to form an N-heterocycle with the correct oxidation state at the C<sub>20</sub> position. If other Grignard reagents with functional groups at C<sub>6</sub>/C<sub>7</sub> and functionalized  $\alpha,\beta$ -unsaturated nitriles were employed in the chelation-controlled conjugate addition, it should be facile to assemble other functionalized diterpenoid alkaloids. Thus the present synthetic strategy provides a reliable and efficient approach for diverse syntheses of diterpenoid alkaloids and their analogues.

# Acknowledgement

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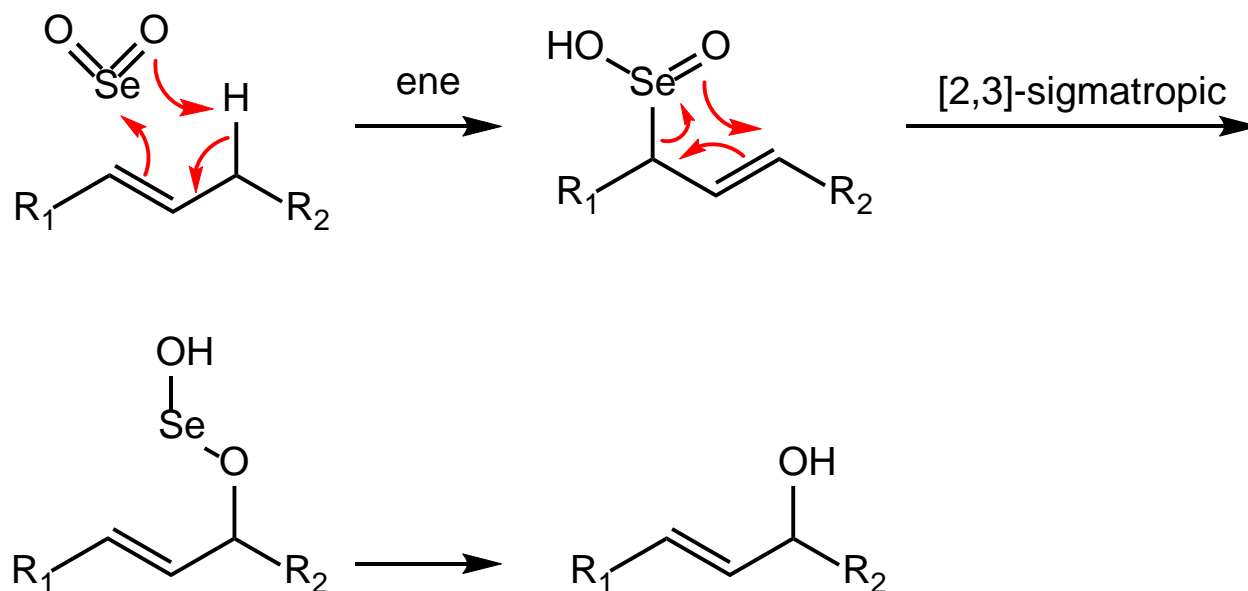
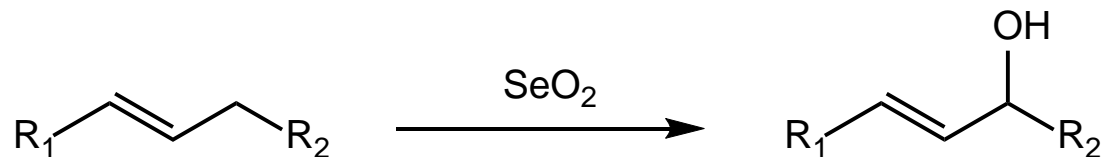
***Thanks  
for your kind attention !***

# Mukaiyama Hydration



From Fan-Jie Meng

# Allylic Hydroxylation of Alkenes with $\text{SeO}_2$



[illegible]