# Literature Report 3

## Enantioselective Total Syntheses of Methanoquinolizidine-Containing Akuammiline Alkaloids and Related Studies

**Reporter : Xin-Wei Wang**
**Checker : Chang-Bin Yu**
**Date : 2018-7-2**

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*J. Am. Chem. Soc*. **2018**, *140*, 6483-6492.

# CV of Neil K. Garg

## Education:

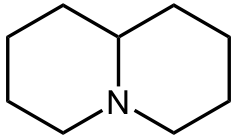
- **1996-2000** B.S., New York University
- **2000-2005** Ph.D., California Institute of Technology
- **2005-2007** Postdoc., University of California, Irvine
- **2007-** Prof., University of California, Los Angeles

## Research:

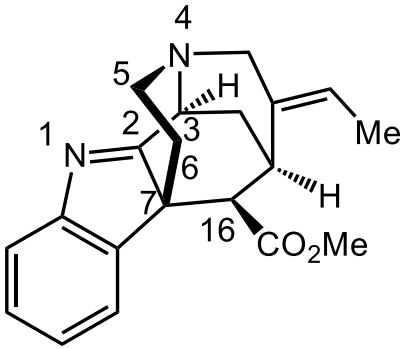
- Cross-coupling reactions
- Green chemistry
- Heterocycle synthesis
- Natural product total synthesis

# Contents

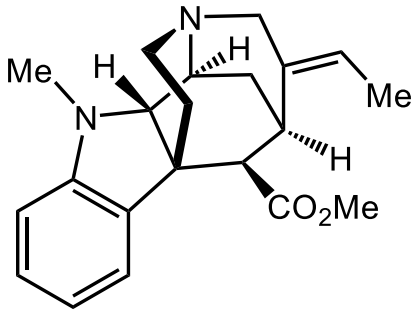
# Introduction



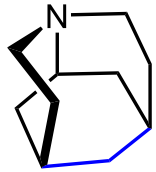

Quinolizidine



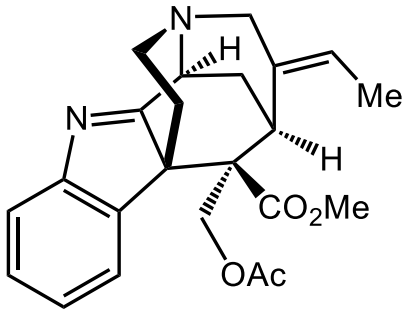

**(+)-Strictamine 1**



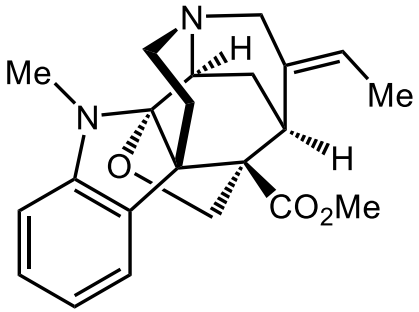

**(-)-2(*S*)-Cathafoline 2**




Methanoquinolizidine

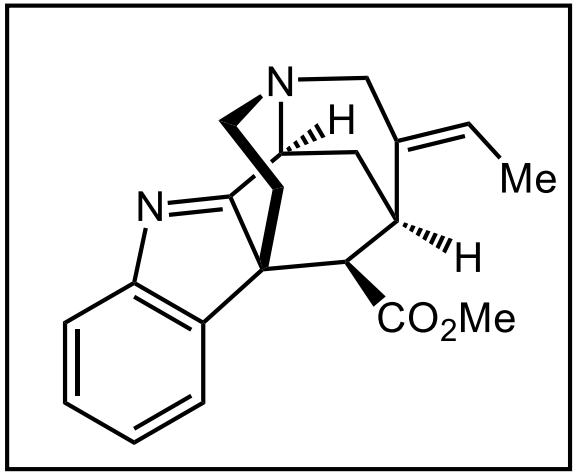



**(+)-Akuammiline 3**

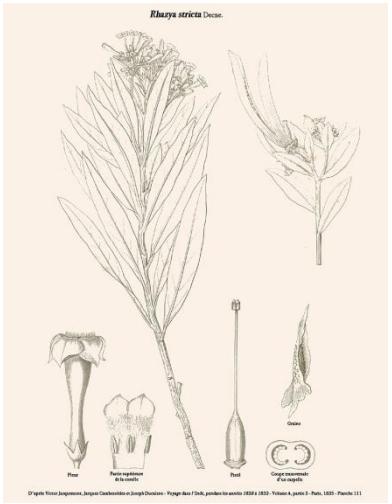



**(-)-Ψ-Akuammigine 4**

# Introduction




**(+)-Strictamine 1**

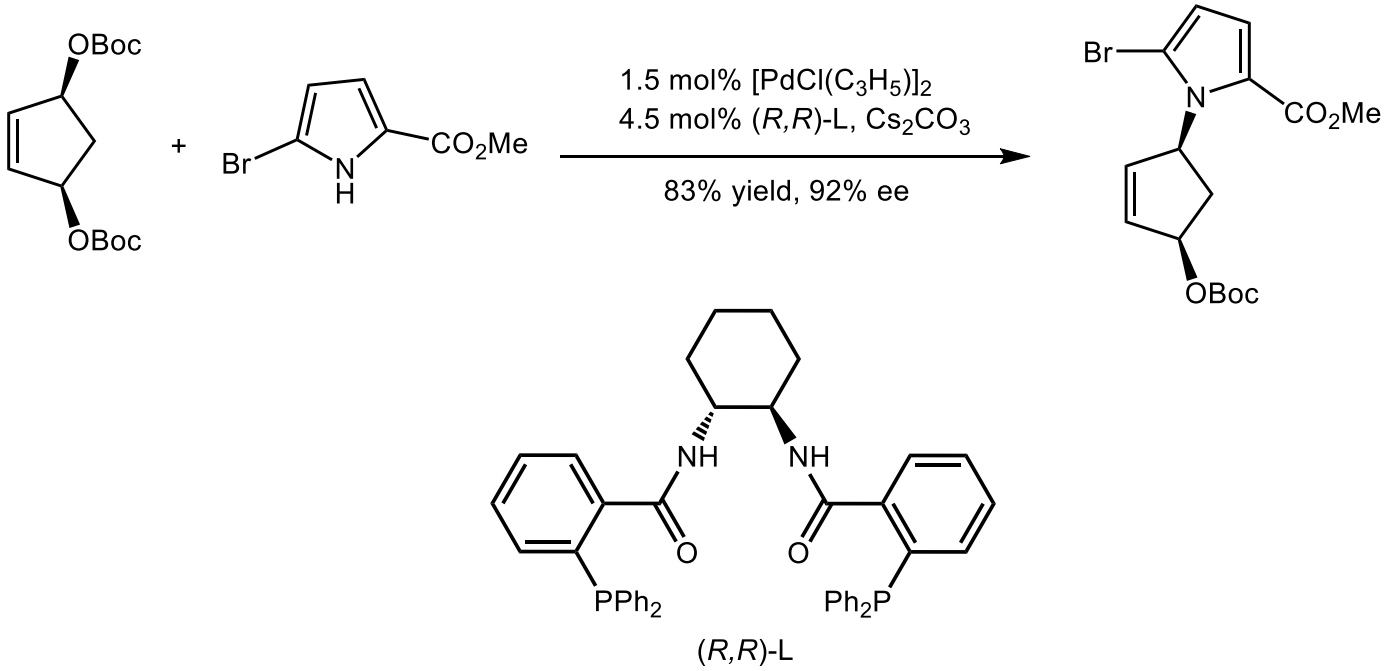



**Rhazya stricta**

- It was isolated from the plant Rhazya stricta in 1966;
- (+)-Strictamine **1** inhibits the transcription factor NF-κB, and may therefore serve as a lead compound for the discovery of new drugs for the treatment of cancer or inflammatory diseases;
- (+)-Strictamine **1** features an indolenine and four stereocenters.

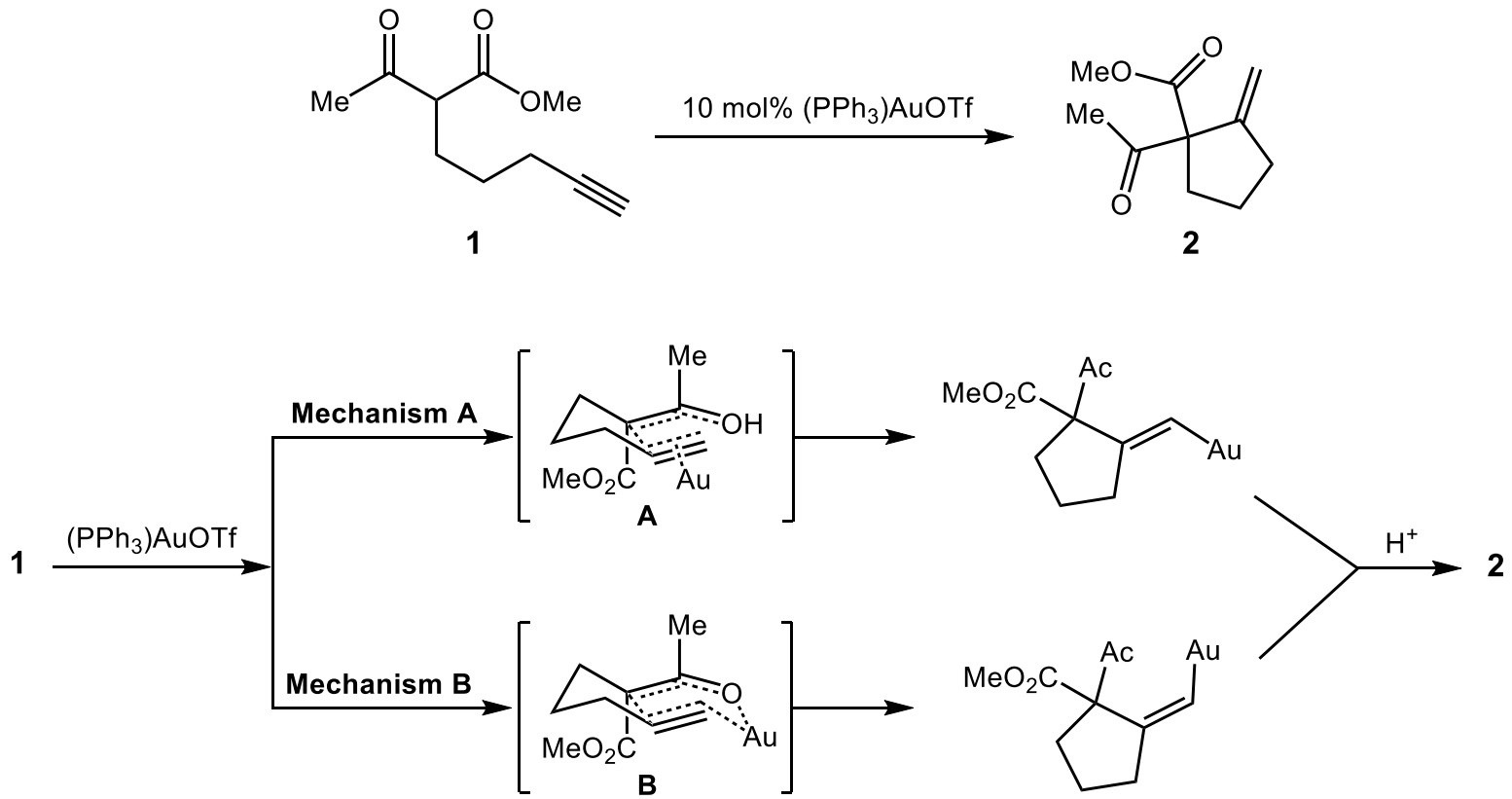

Schnoes,H. K. *et al. J. Org. Chem.* **1966**, *31*, 1641.
Ahmad, Y. *et al. J. Am. Chem. Soc.***1977**, *99*, 1943.

# Pd-Catalyzed Asymmetric Allylic Alkylation



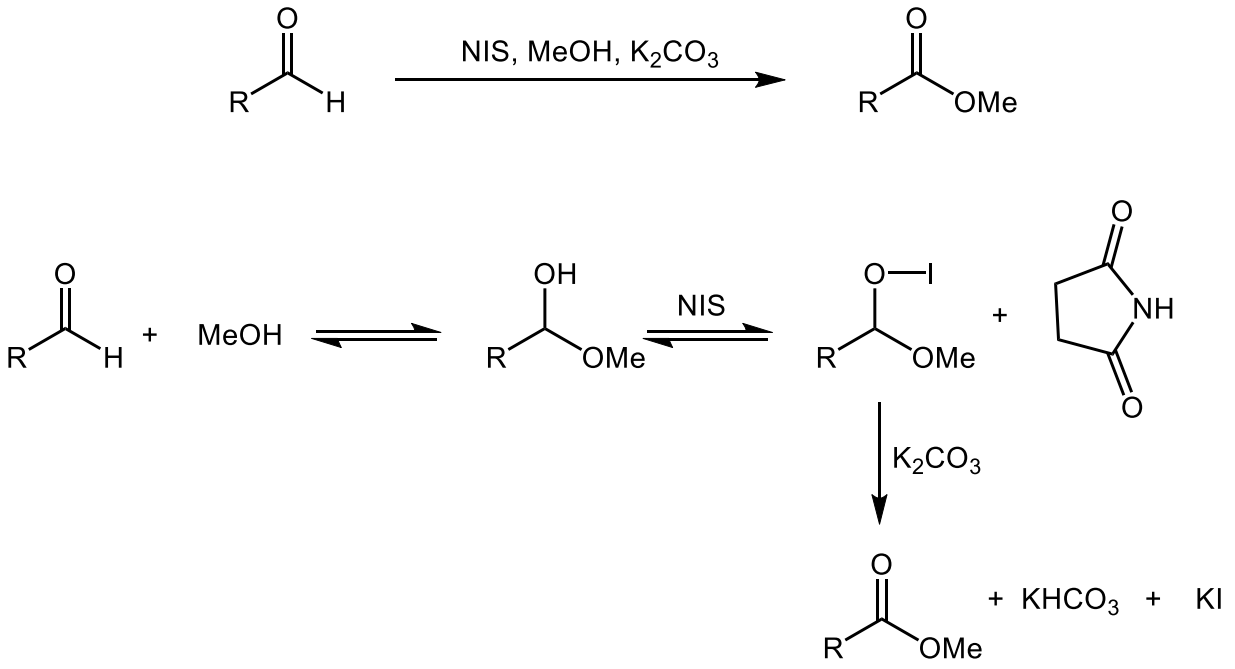

Trost, B. M. *et al. J. Am. Chem. Soc*. **2006**, *128*, 6054.

# Gold Catalyzed Cyclization



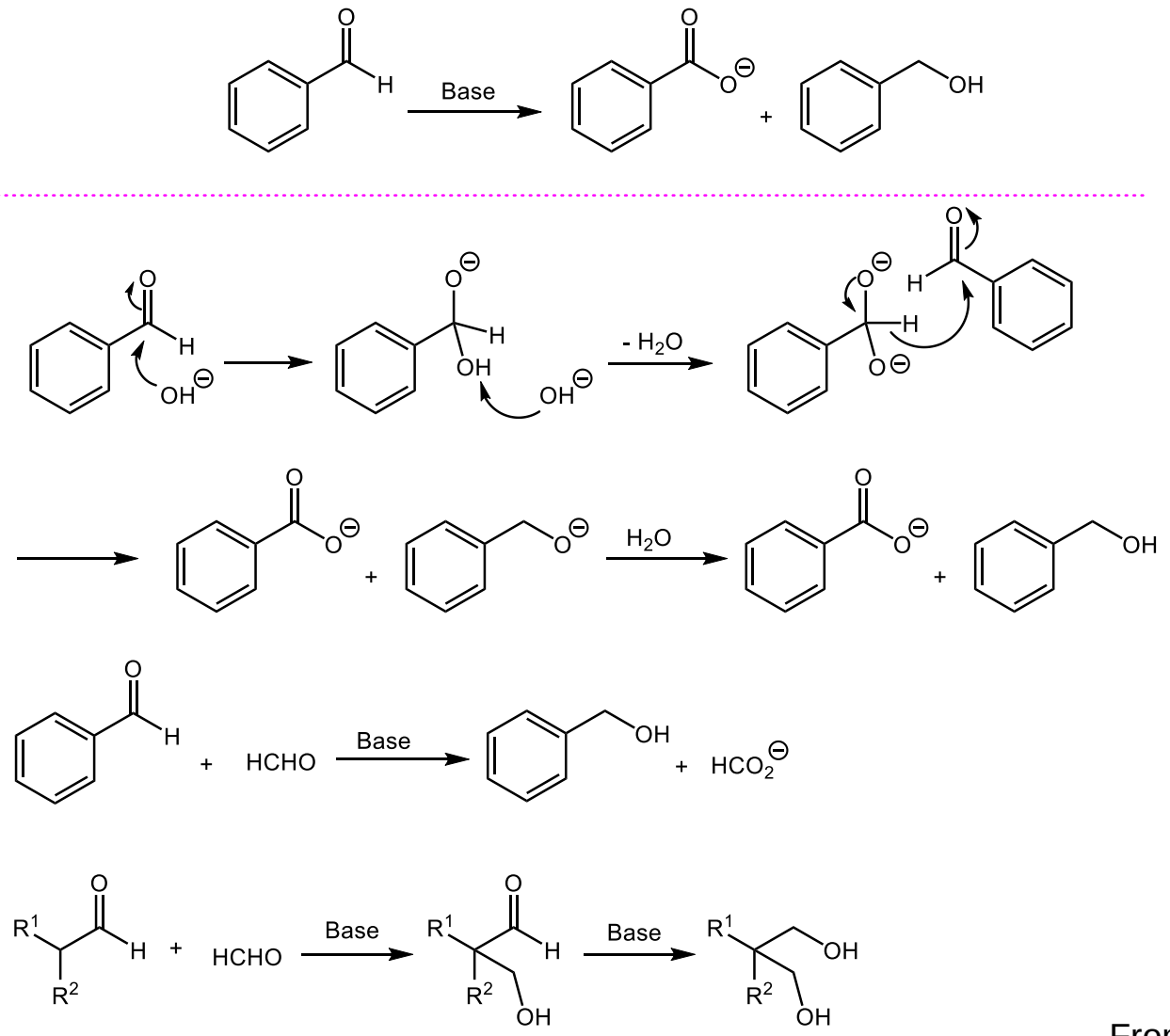

Toste, F. D. *et al*. *J. Am. Chem. Soc*. **2004**, *126*, 4523.

# NIS-based Oxidative Esterification



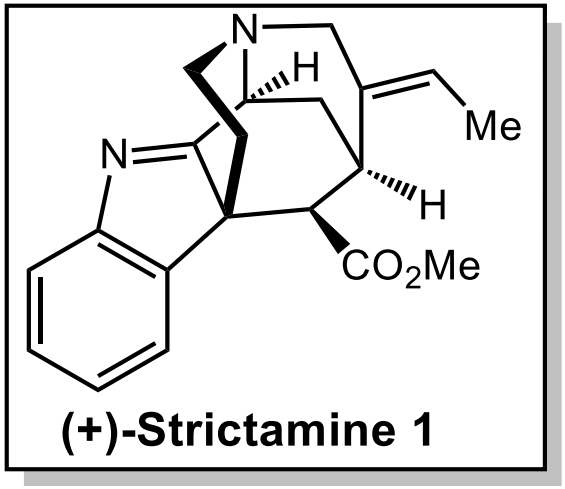

McDonald, C. *et al. J. Org. Chem*. **1989**, *54*, 1213.

# Cannizzaro Reaction

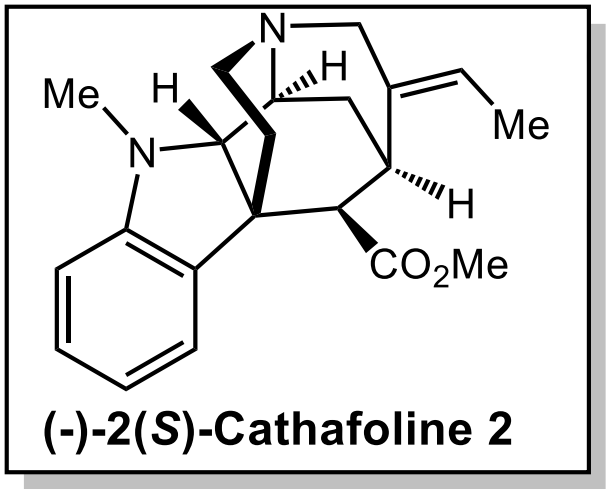



From Wikipedia

# Total Syntheses of (+)-1 and (-)-2

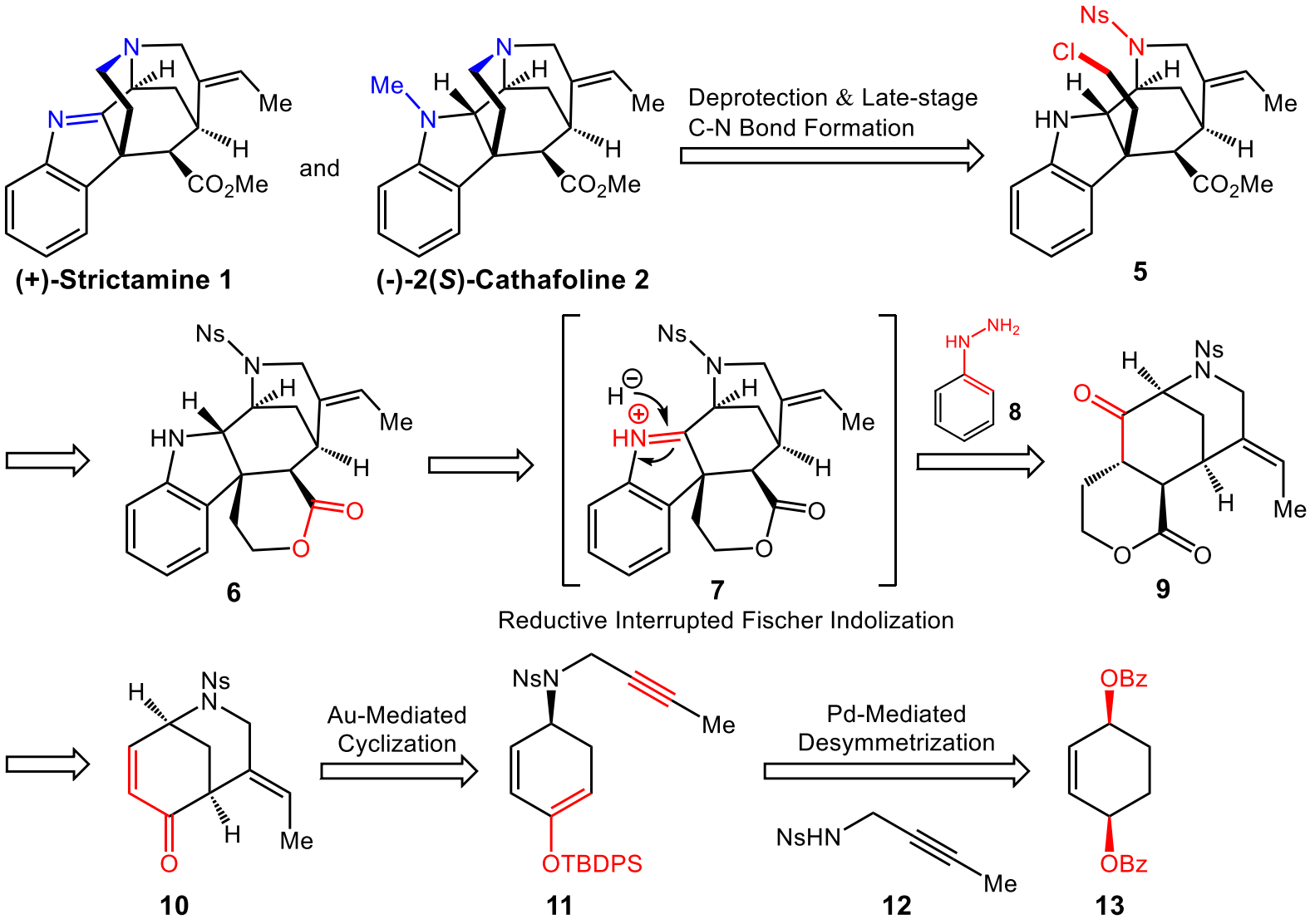



**(+)-Strictamine 1**

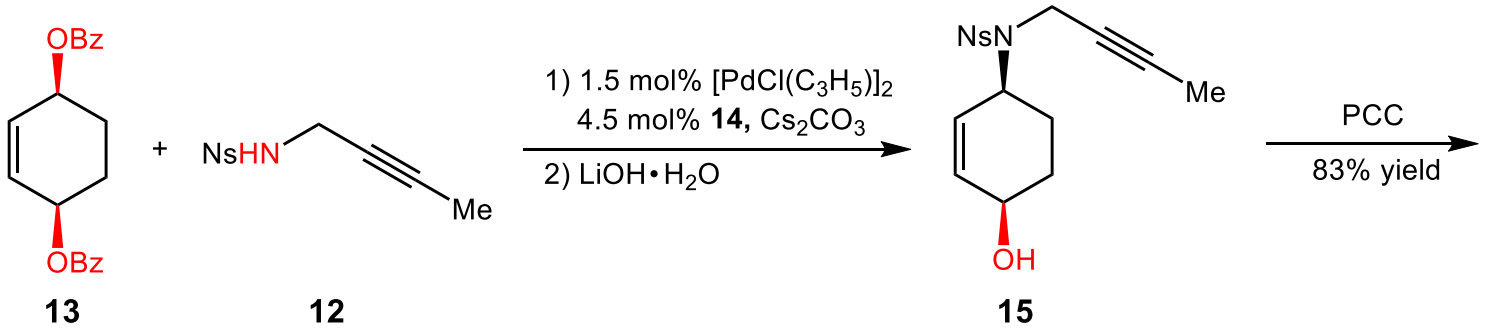


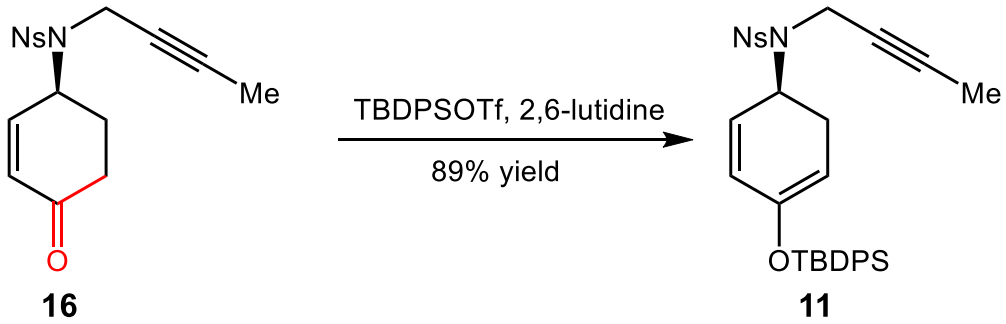

**(-)-2(*S*)-Cathafoline 2**

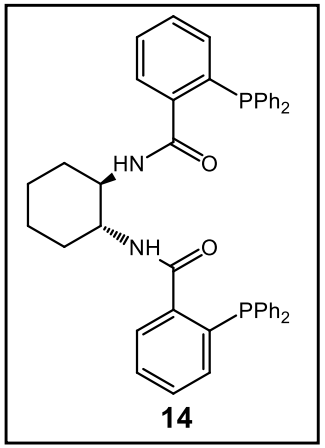
# Retrosynthetic Analysis of (+)-1 and (-)-2



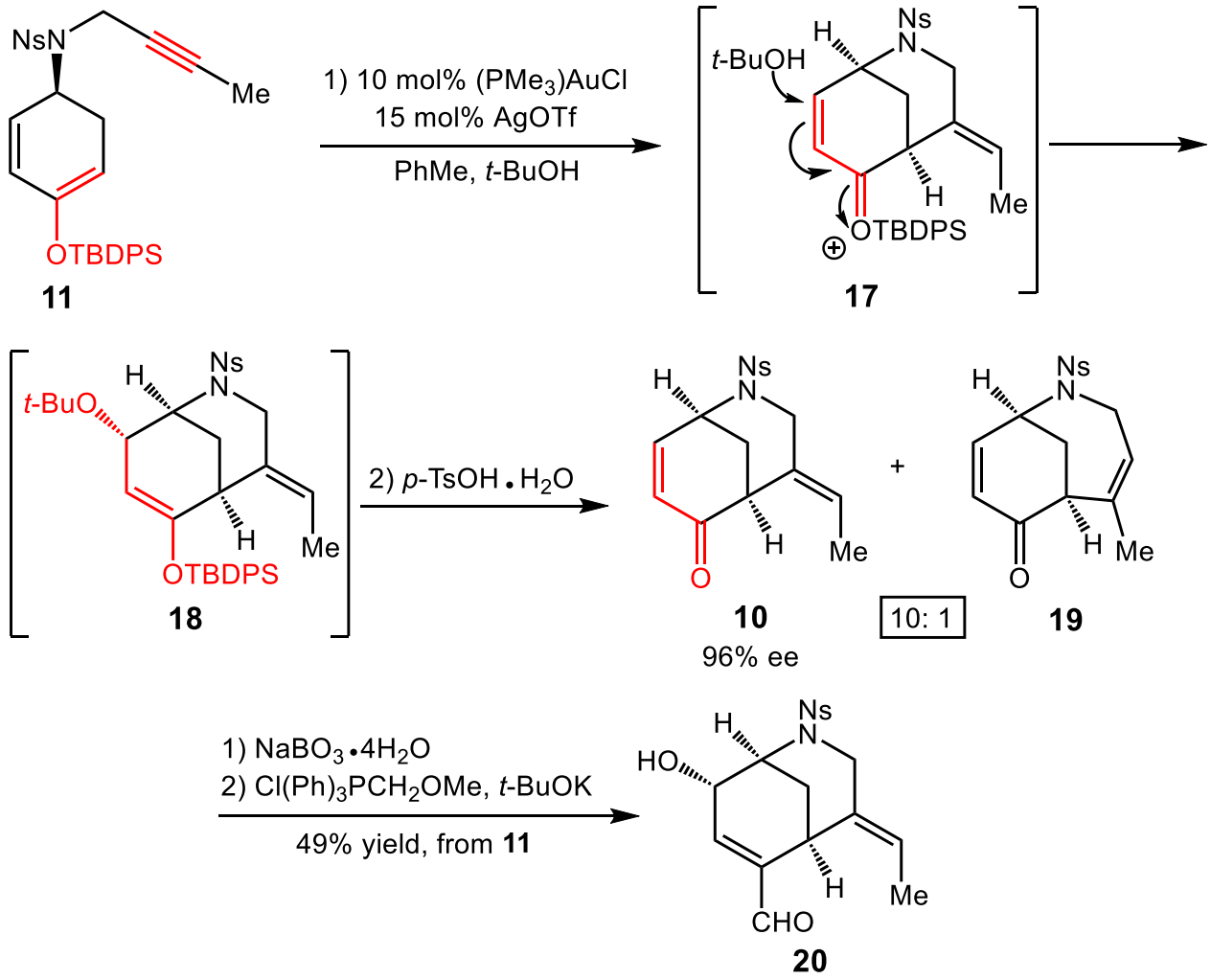
# Trost Desymmetrization and Synthesis of 11



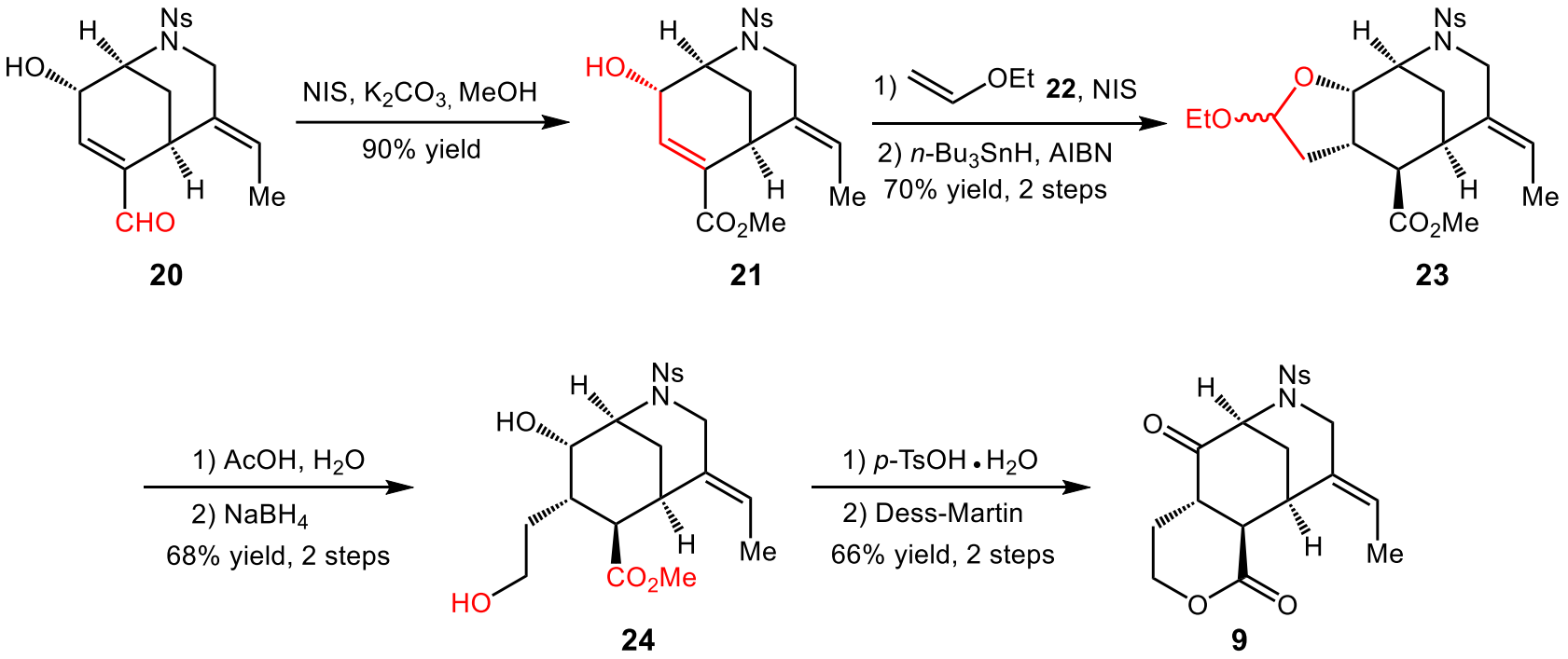



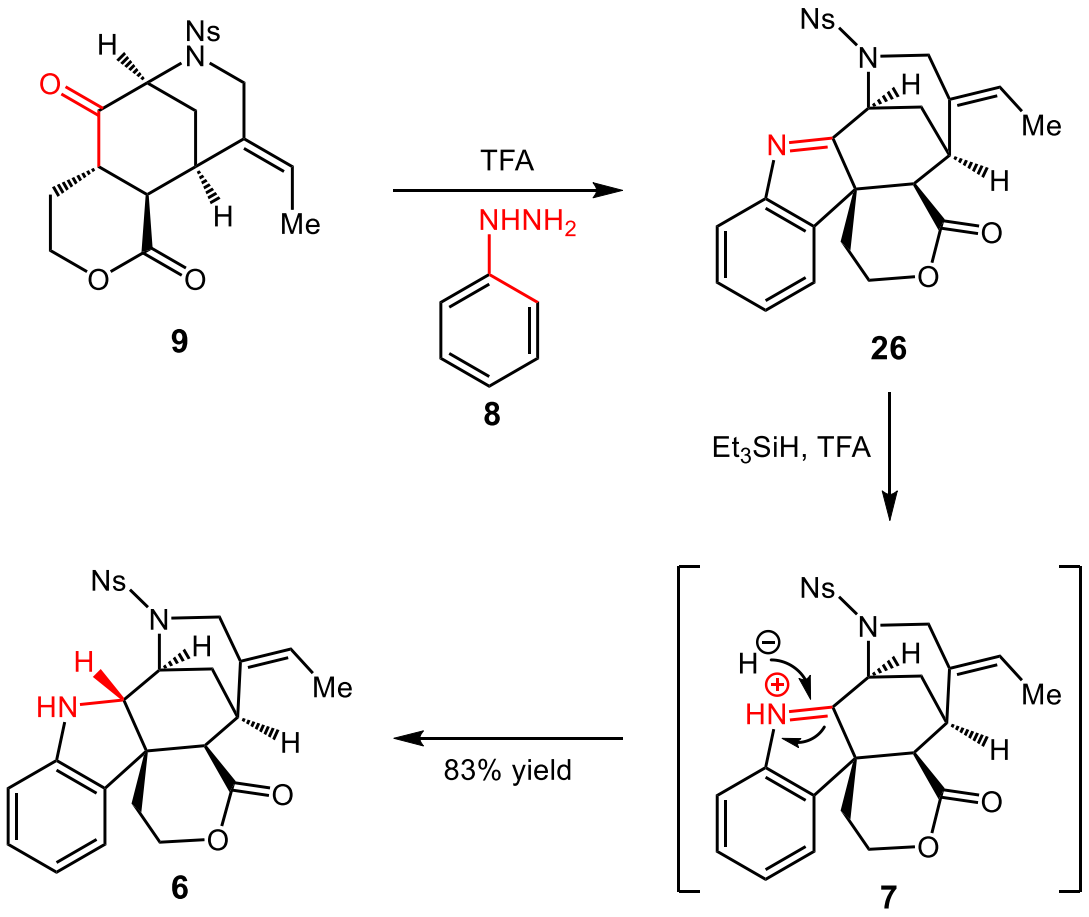
# Gold-Catalyzed Cyclization



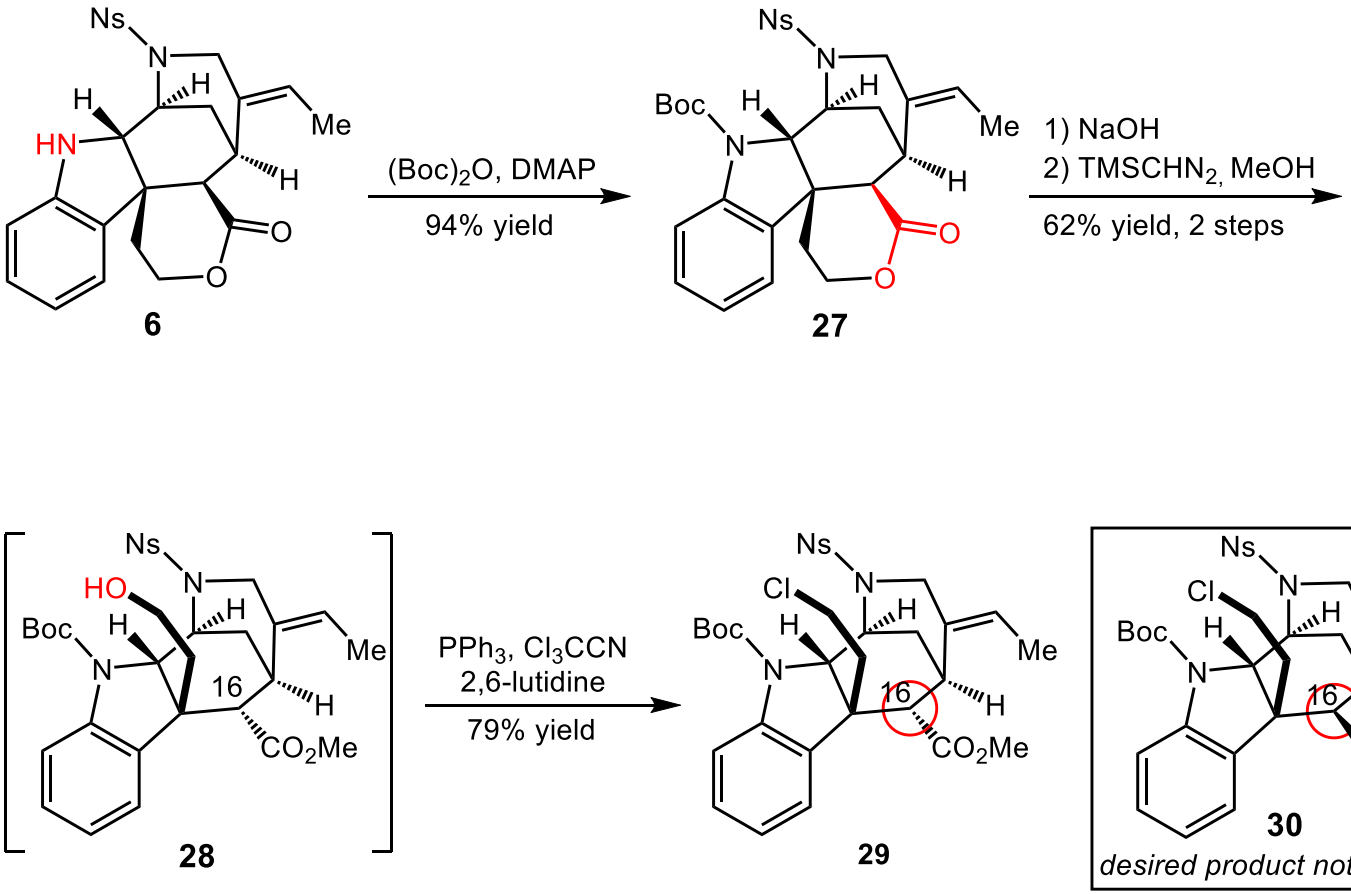
# Synthesis of Ketolactone 9



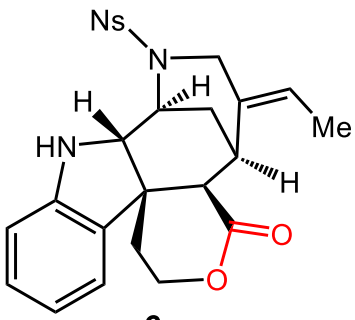
# Reductive Interrupted Fischer Indolization Reaction



# Undesired C16 Epimerization



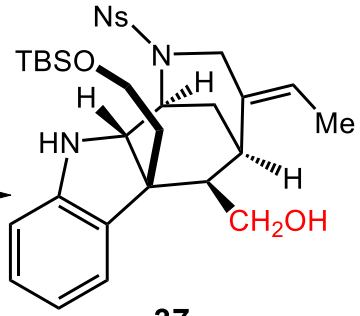
# Total Syntheses of (+)-1 and (-)-2




**6**

1) $LiBH_4$
2) TBSCl, Imid., DMAP

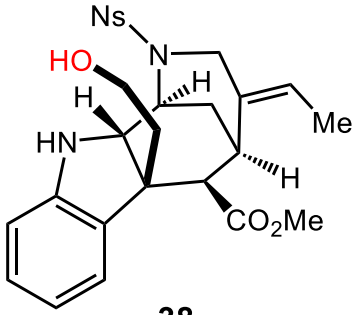
63% yield, 2 steps




**37**

1) Dess-Martin
2) $NaClO_2$, $NaH_2PO_4$
3) $Me_3SiCHN_2$, MeOH, AcOH

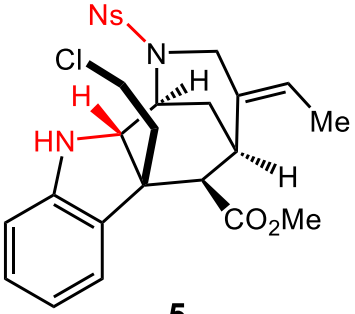
67% yield, 2 steps




**38**

1) MsCl, $Et_3N$
2) LiCl

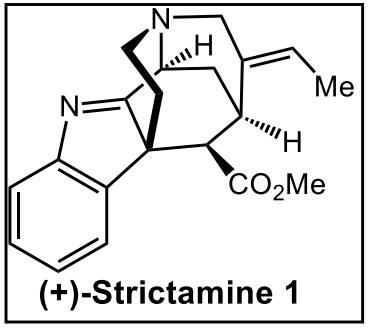
77% yield, 2 steps




**5**

1) PCC
2) HS–Si **32**, $Cs_2CO_3$

quantitative yield




**(+)-Strictamine 1**

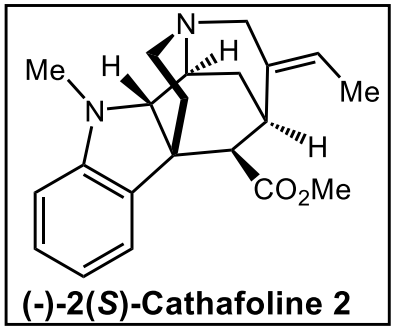
1) HCHO, $NaBH_3CN$, AcOH

71% yield

2) HS–Si **32**

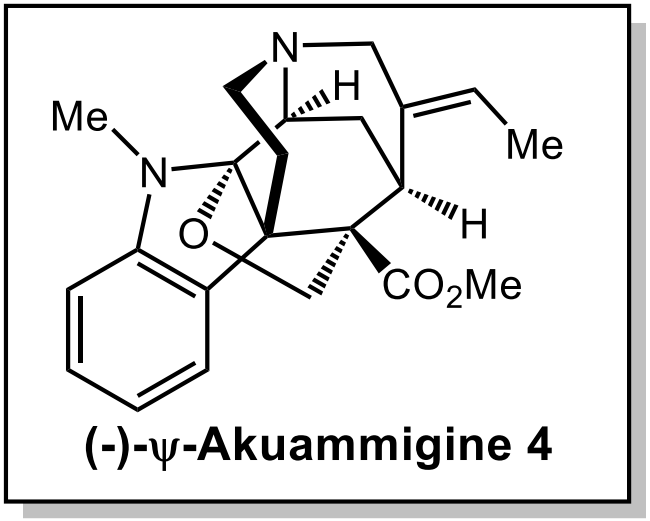
$Cs_2CO_3$

85% yield



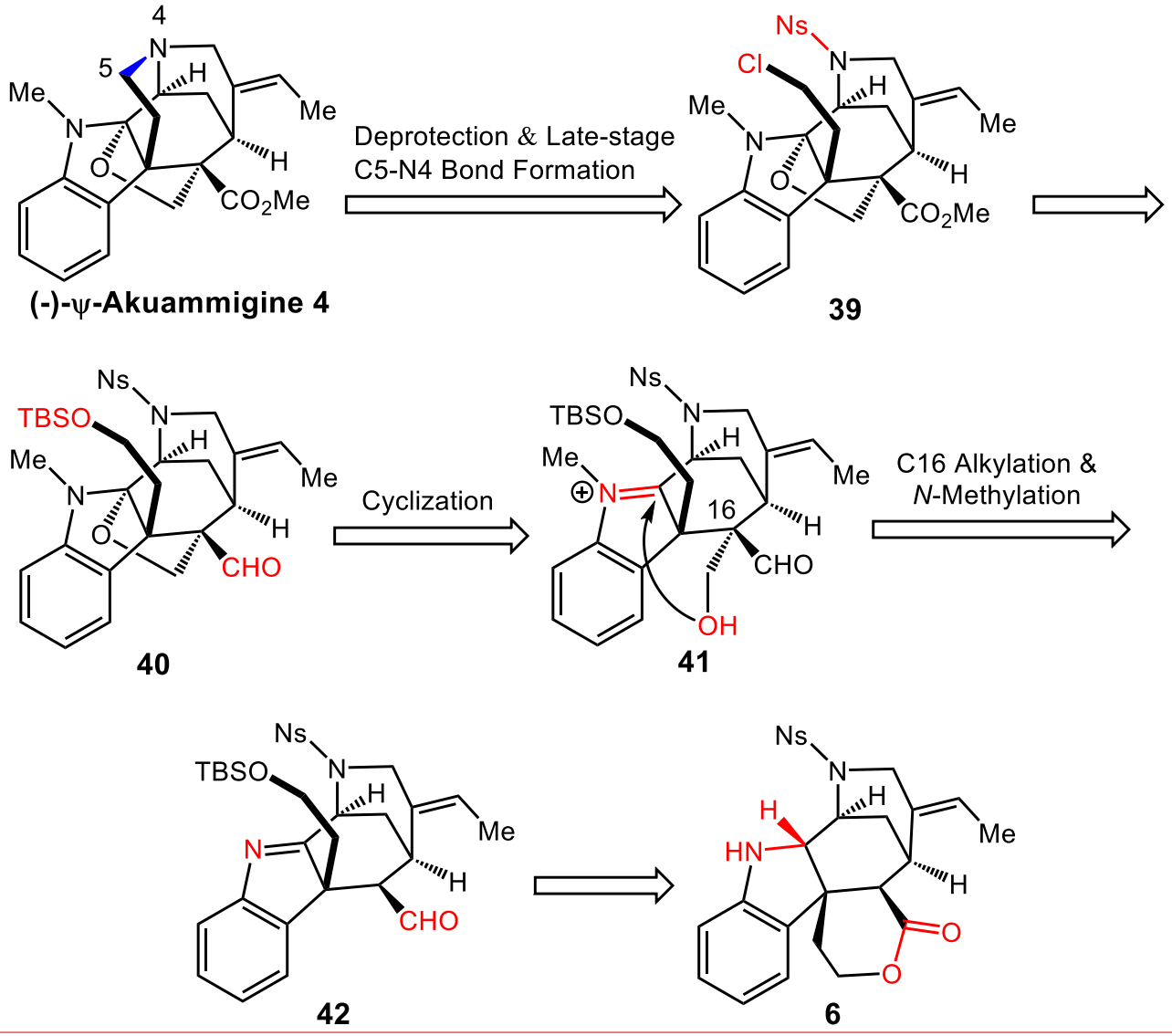

**(-)-2(*S*)-Cathafoline 2**

# Total Synthesis of (-)-4

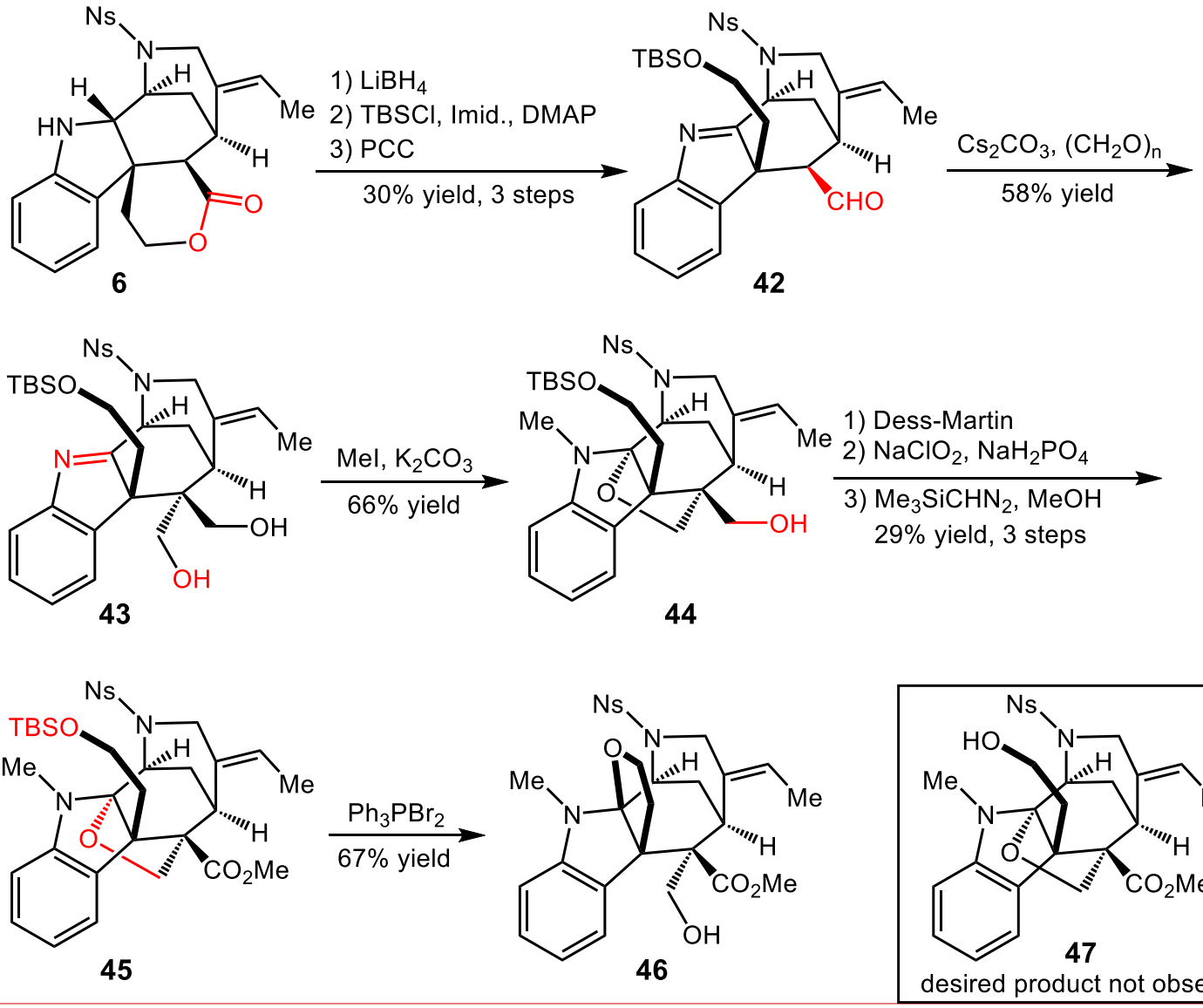



**(-)-ψ-Akuammigine 4**

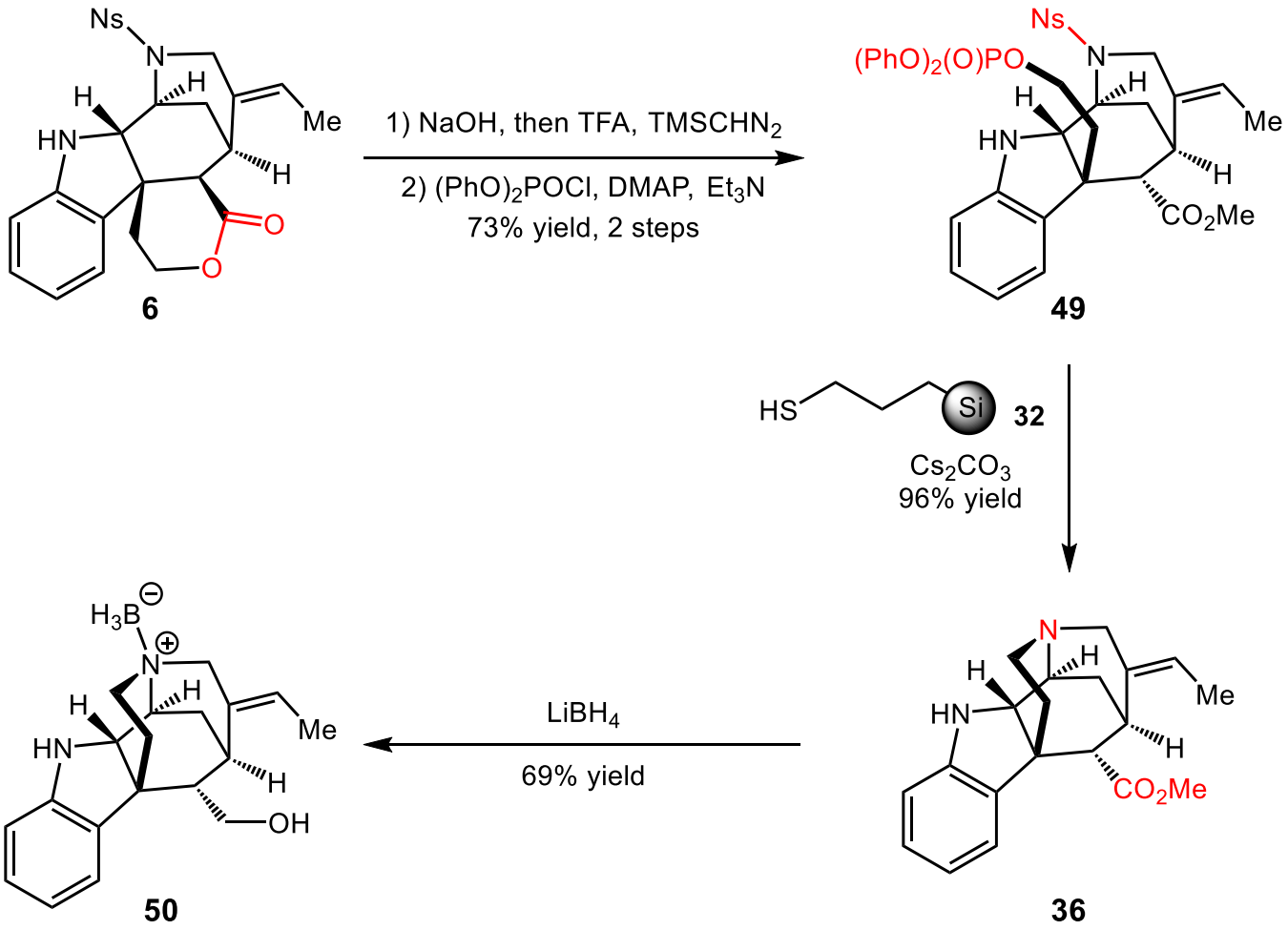
# Retrosynthetic Analysis of (-)-4



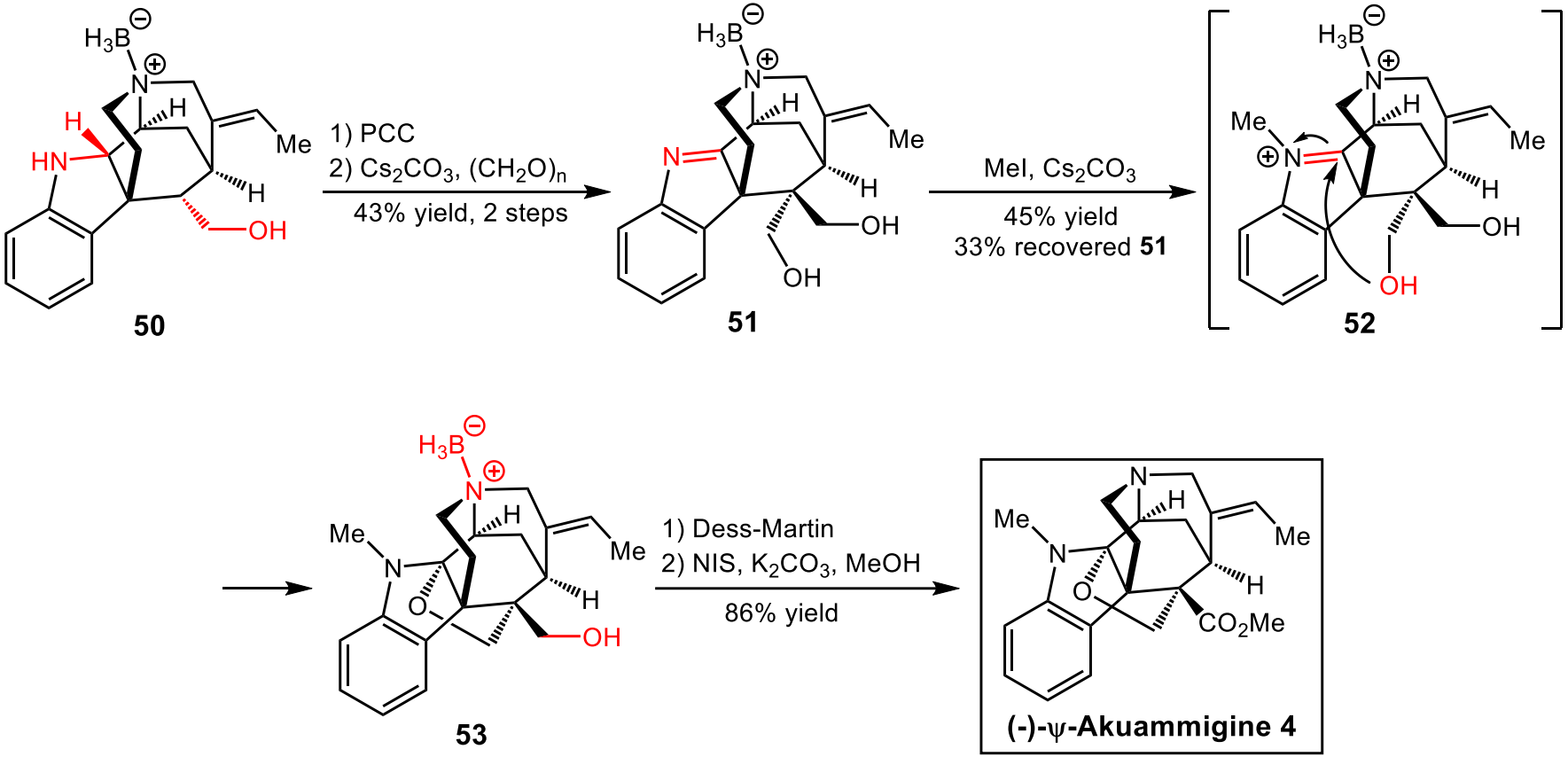
# Undesired Isomerization to Afford 46



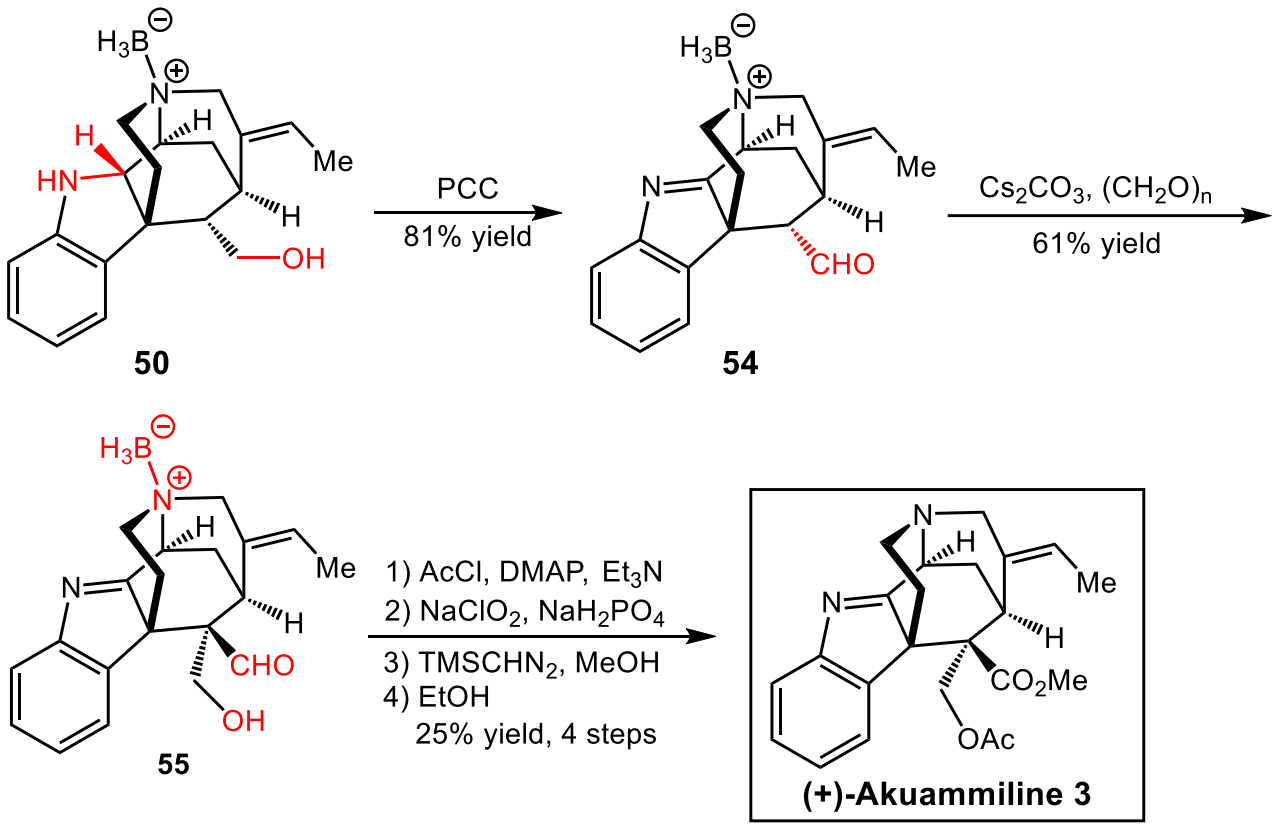
# Introduction of the Methanoquinolizidine Framework



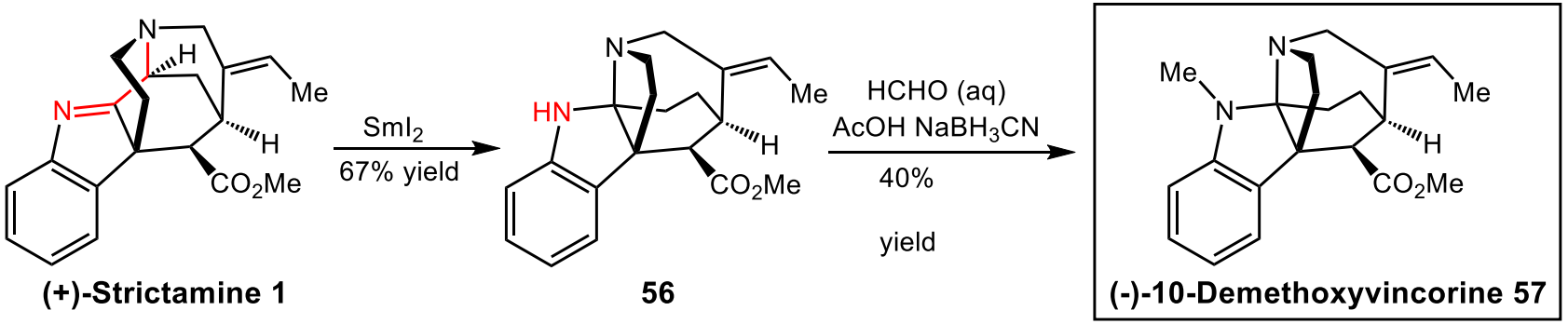
# Total Synthesis of (-)-Ψ-Akuammigine (4)



# Total Synthesis of (+)-Akuammiline (3)



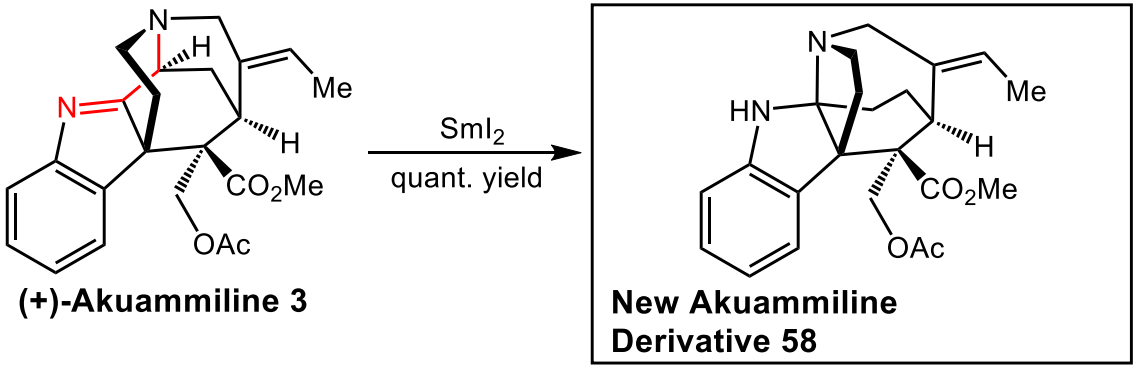
# Structural Rearrangement to Access 57 and 58




**(+)-Strictamine 1**

**56**

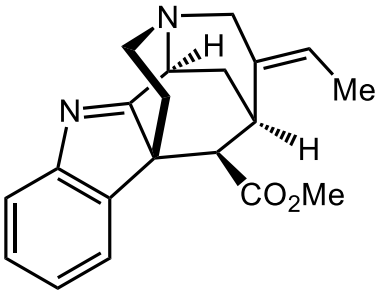
**(-)-10-Demethoxyvincorine 57**




**(+)-Akuammiline 3**

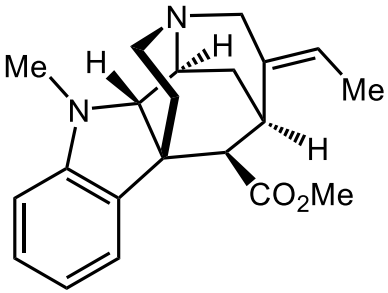
**New Akuammiline Derivative 58**

# Summary



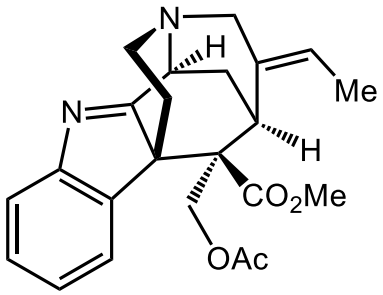

**(+)-Strictamine 1**

1.81% yield
25 steps



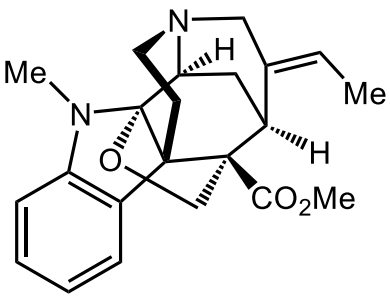

**(-)-2(*S*)-Cathafoline 2**

0.91% yield
25 steps




**(+)-Akuammiline 3**

0.61% yield
26 steps




**(-)-Ψ-Akuammigine 4**

0.73% yield
25 steps

- The first total synthesis;
- Pd-catalyzed desymmetrization;
- Gold-mediated cyclization;
- Reductive interrupted Fischer indolization;
- Late-stage formation of the methanoquinolizidine using a deprotection-cyclization cascade.

# The First Paragraph

The akuammiline alkaloids are an important class of natural products isolated from plants found in India, Africa, and Southeast Asia. These alkaloids, thought to be the active ingredients in traditional medicines used to treat a multitude of ailments in humans and livestock, have been the subject of intense investigations spanning structural elucidation, biosynthesis, biological evaluation, and chemical synthesis. More than 75 akuammilines have now been unambiguously characterized, many of which display exciting biological profiles, and all of which possess provocative chemical structures. It was not until recently that the synthetic community launched efforts toward the akuammiline alkaloids, which have now culminated in total syntheses of several subclasses. This is particularly noteworthy, as even the simplest akuammilines contain at least five interconnected rings, a multitude of stereocenters, and one or more basic nitrogen atoms.

# The Last Paragraph

We have completed the first enantioselective total syntheses of five akuammiline alkaloids, in addition to several unnatural compounds. Our synthetic approach to the methanoquinolizidine-containing natural products **1−4** features a number of key steps, including: (a) a Trost desymmetrization to govern absolute stereochemistry, (b) a gold-mediated cyclization to construct the [3.3.1]-azabicycle, (c) a reductive interrupted Fischer indolization to arrive at pentacycle **6**, and (d) late-stage formation of the methanoquinolizidine using a deprotection−cyclization cascade.

# The Last Paragraph

These efforts mark the first total syntheses of some of the most complex akuammilines known, including those that possess both a methanoquinolizidine core and vicinal quaternary stereocenters. It is expected that our studies will enable biological investigations of akuammilines and unnatural analogs. Moreover, the lessons learned from our synthetic endeavors, including the delicate late-stage manipulations and various undesired setbacks, should inform synthetic forays toward akuammilines and other challenging natural products.

# Acknowledgement

***Thanks***
***for your attention***