

# Total Synthesis of Phalarine

Li, C.; Chan, C.; Heimann, A.C.;  
Danishefsky, S.J.

*Angew. Chem. Int. Ed.* **2007**, 46,  
1448-1450

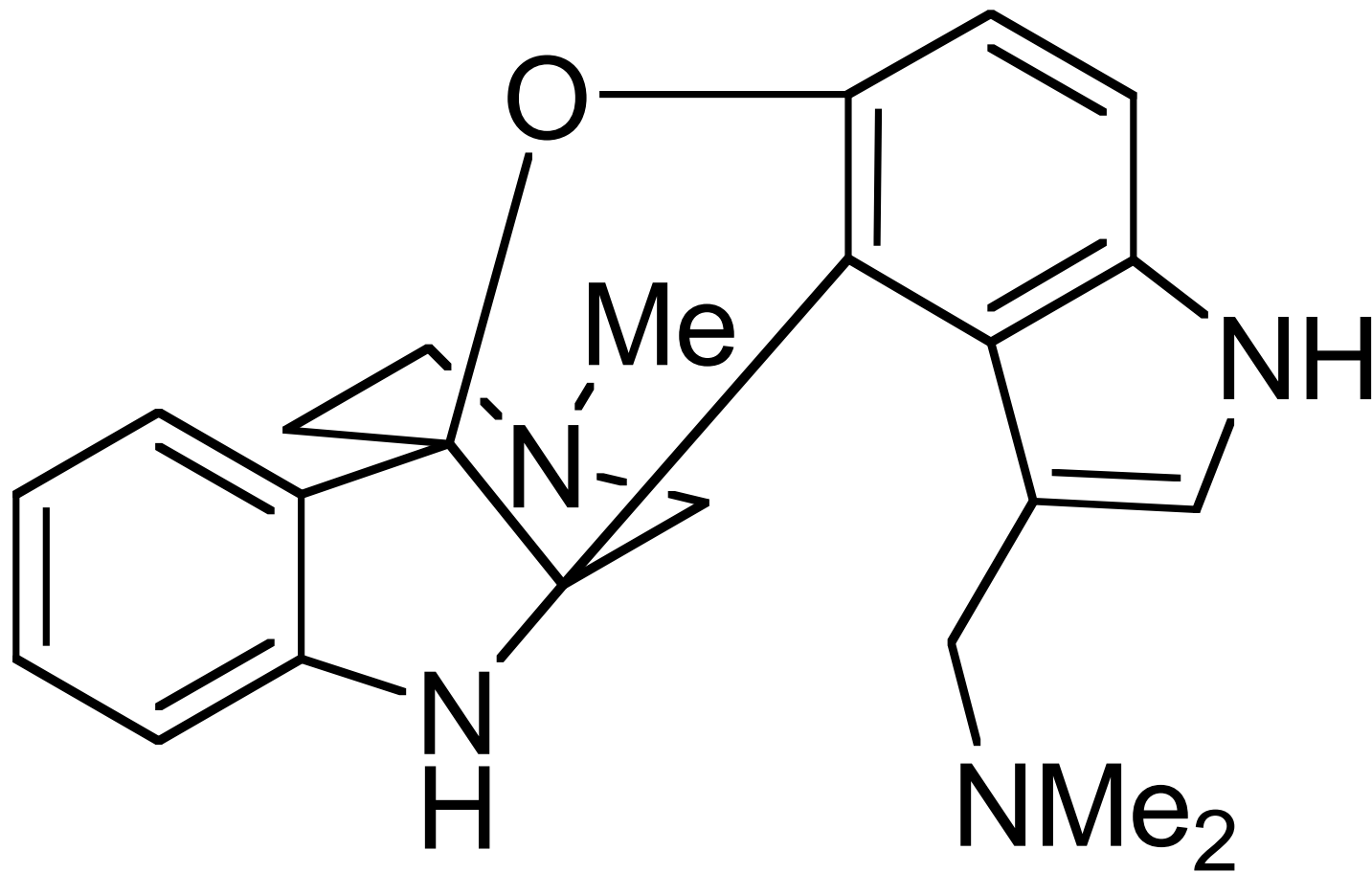
*Presented by Brad Hutnick*

*April 2, 2007*

# Overview

- Background
- Proposed Synthesis
- Rearrangement
- Actual Synthesis
- Summary

# Phalarine



# Blue Canary Grass



*Phalaris coerulescens*

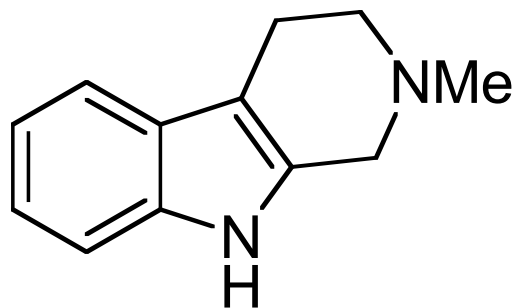
Found naturally in Mediterranean Europe

Short-lived perennial that can grow up to 150cm (6ft)

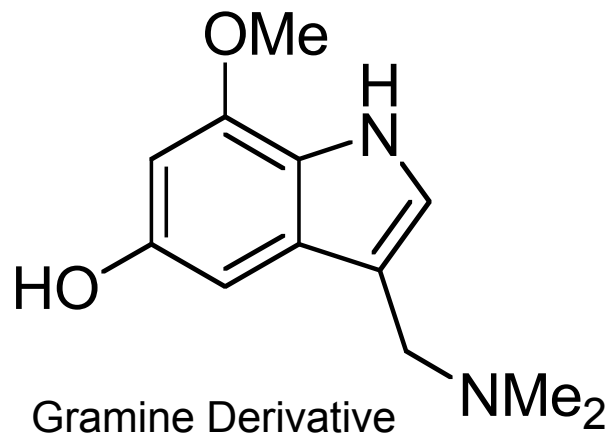
Circumstantial evidence that it causes acute toxicity, probably through heart failure, in horses

*Information from the Department of Primary Industries, Victoria, Australia*

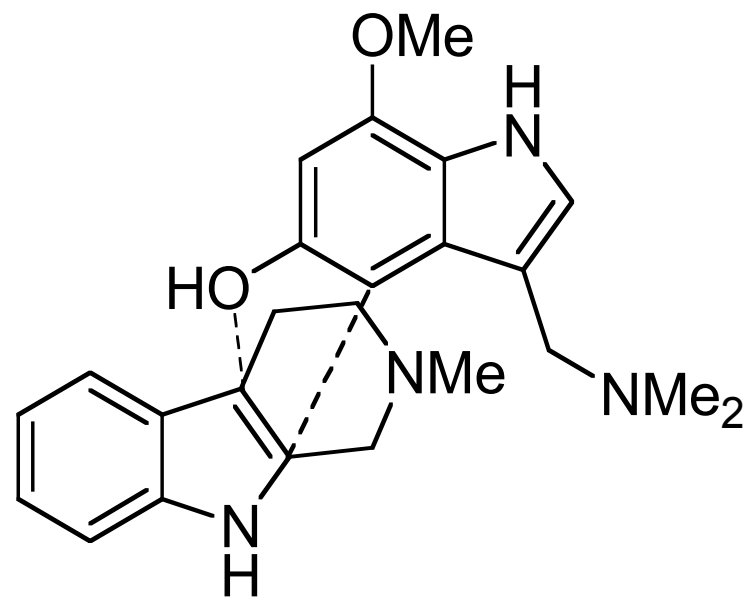
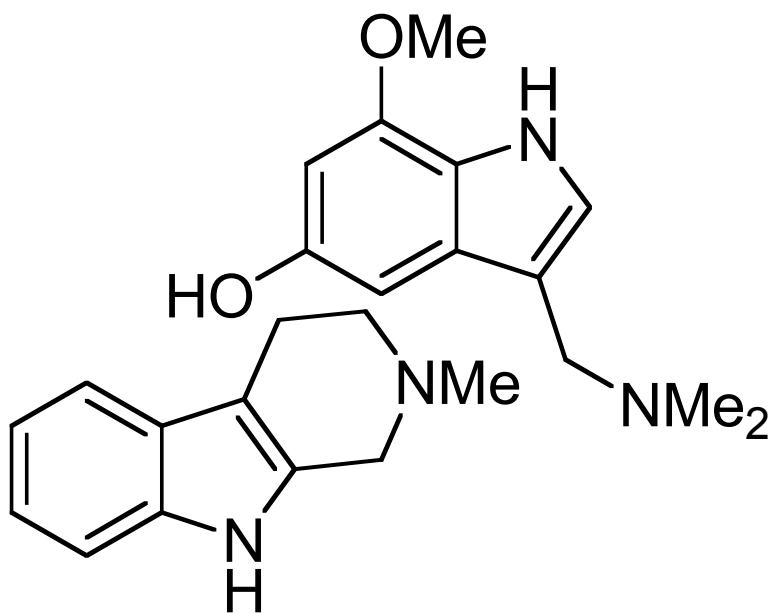
# Biosynthetic Proposal



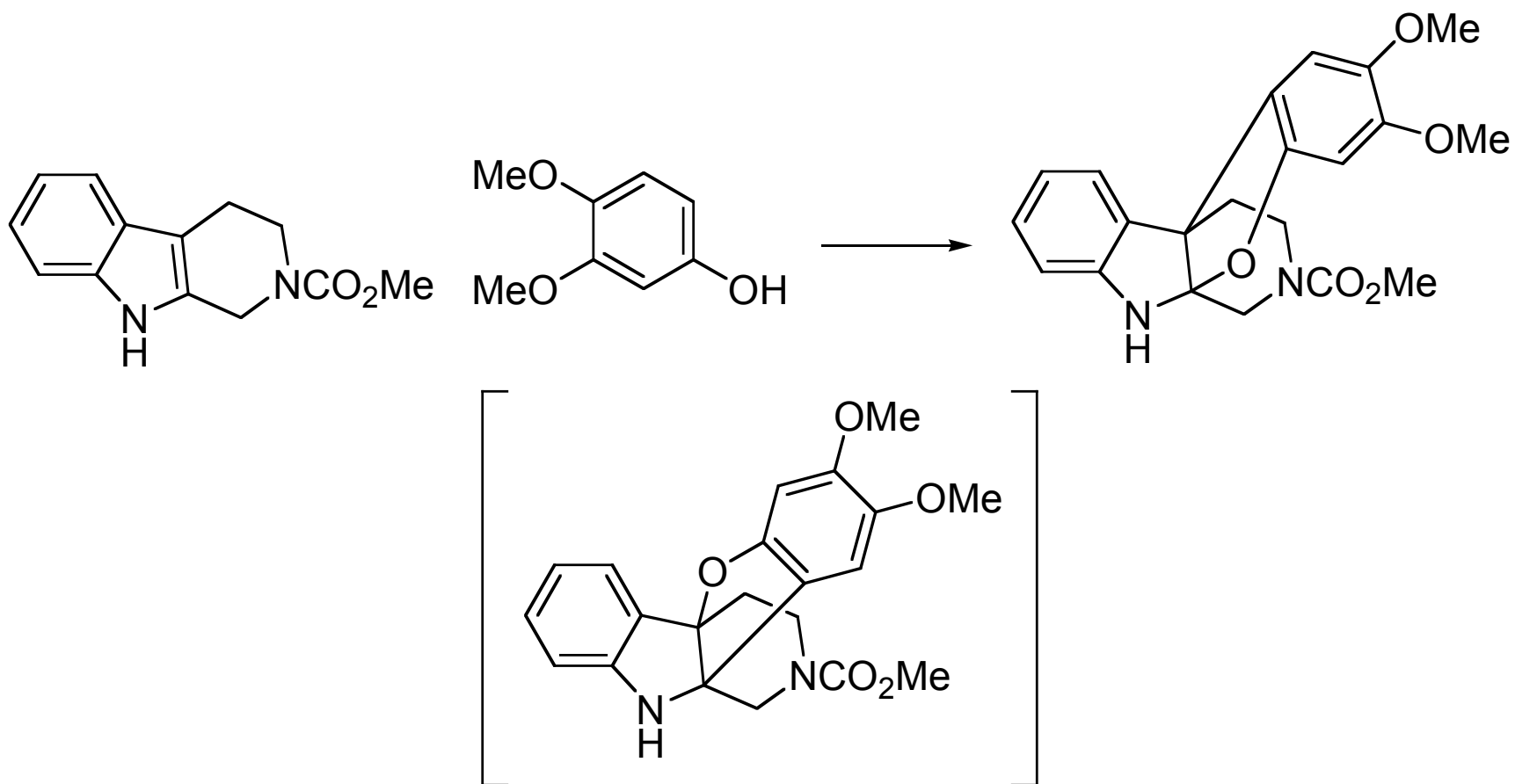
*N*-methyl- $\beta$ -carboline



Gramine Derivative



# Biomimetic Synthesis



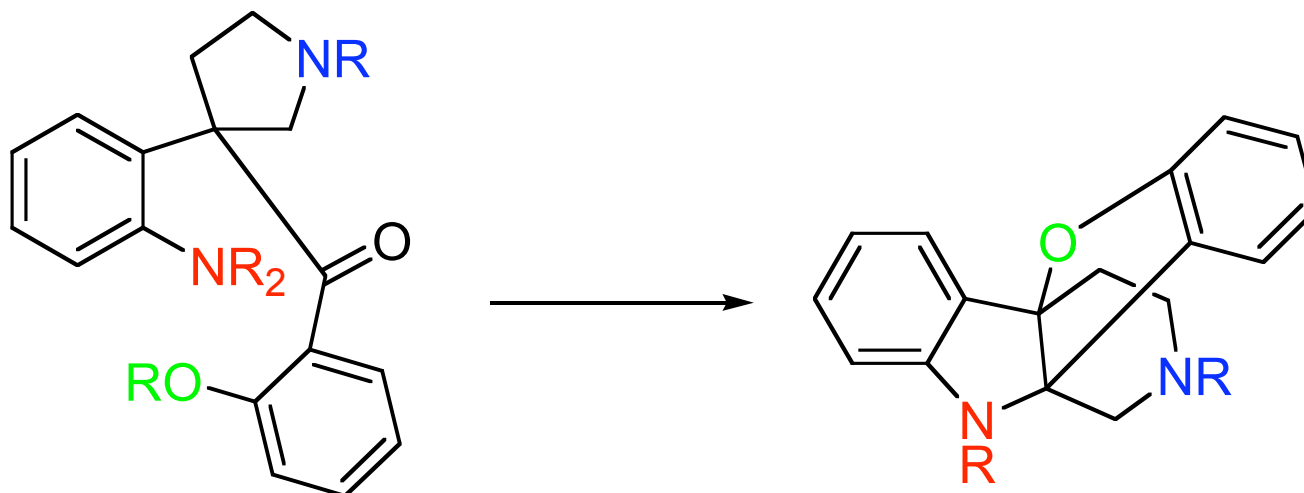
Danishefsky, et al. *Tet. Lett.* **2006**, 47, 4839.

# Biomimetic Synthesis Summary

- The normal reactivity of the carbonyl needed to be overcome in order to achieve the right regioisomeric product.
- Under the reaction conditions, the “natural bias” could not be overcome.
- Even if nature uses this route, it appears to not be viable for this synthesis, and was abandoned.

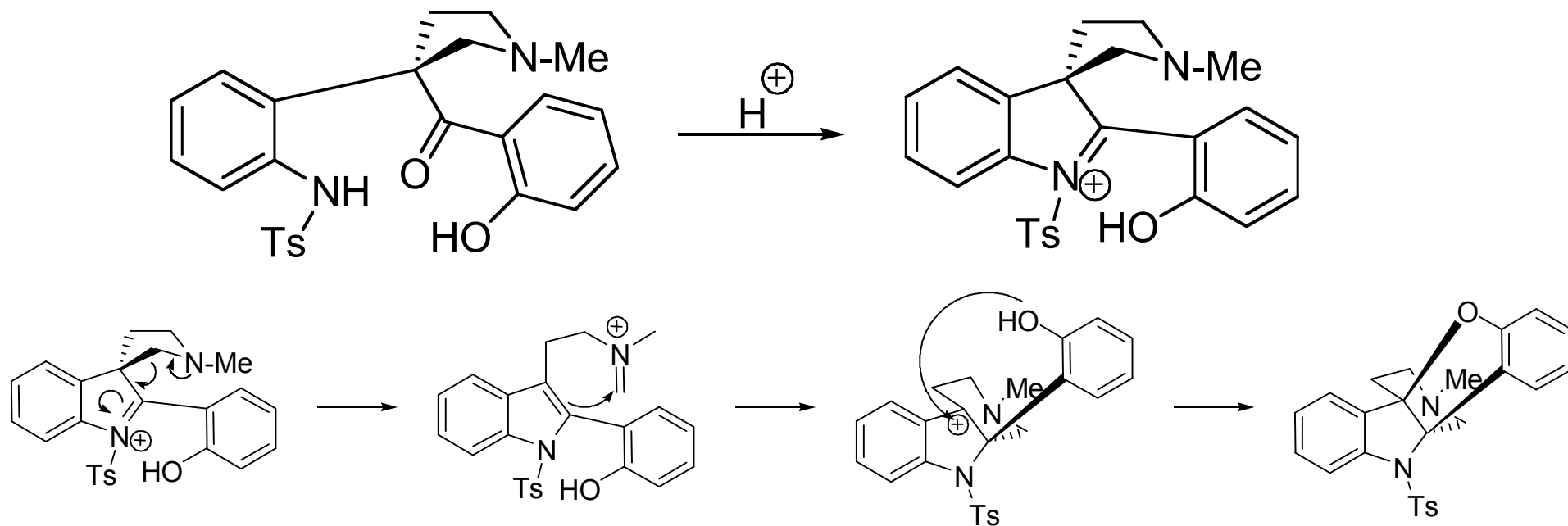
# New Synthetic Approach

- Ring-expansion of an azaspiroindolenine

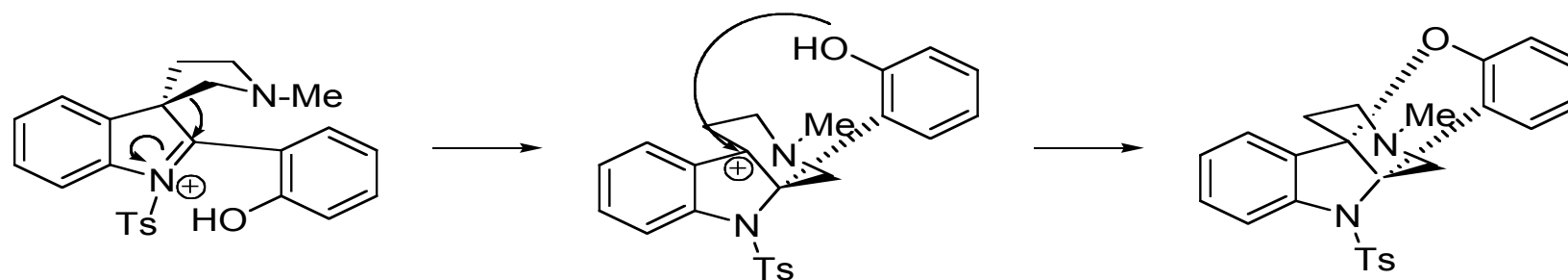




# Rearrangement Mechanism

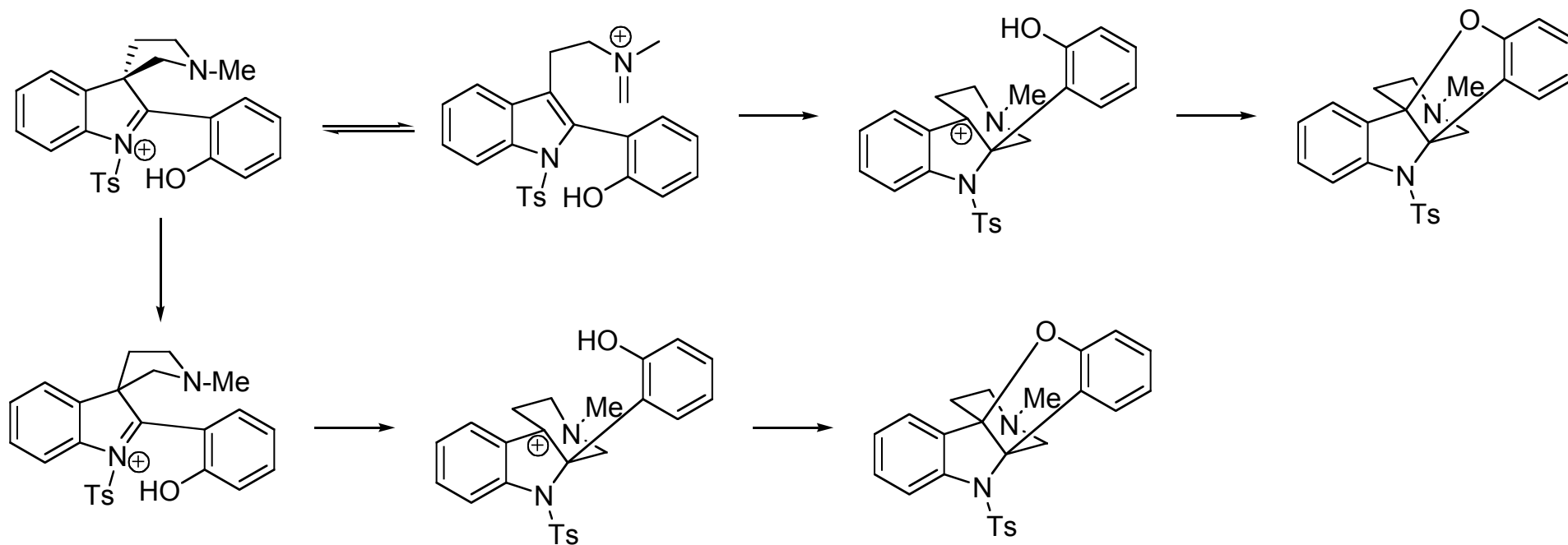
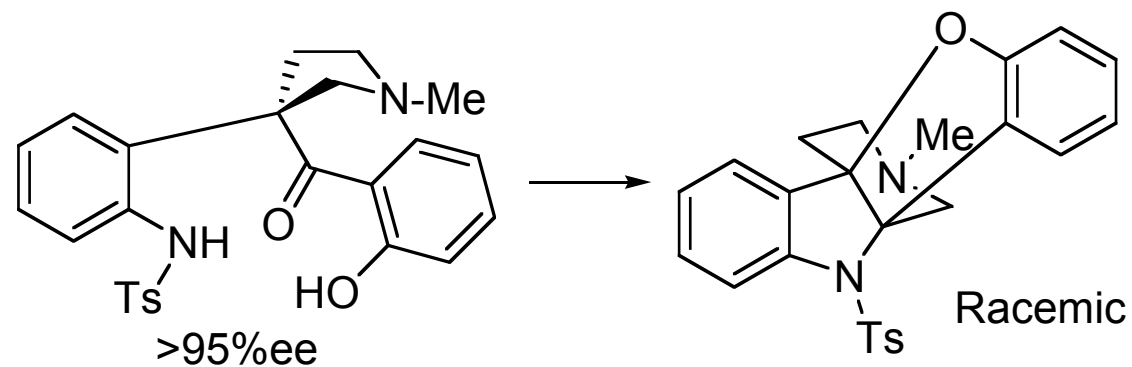


Leads to a racemic product

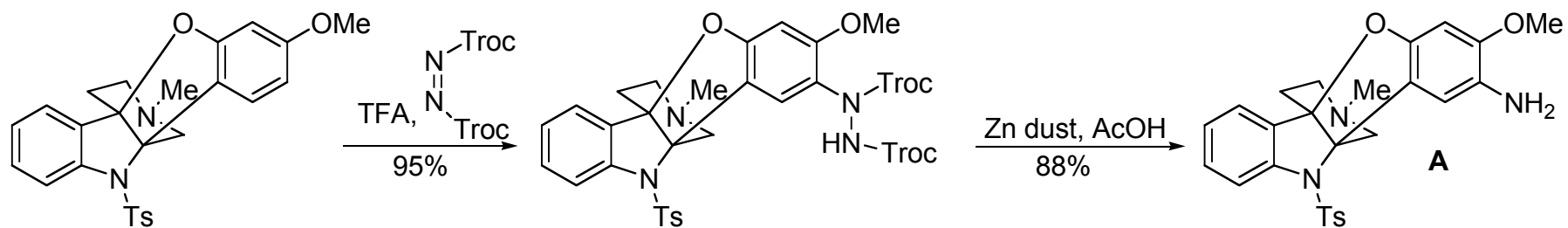
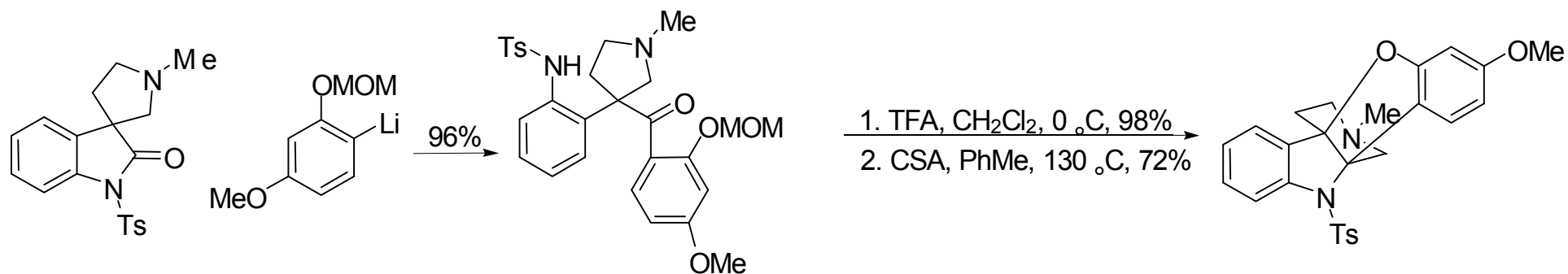
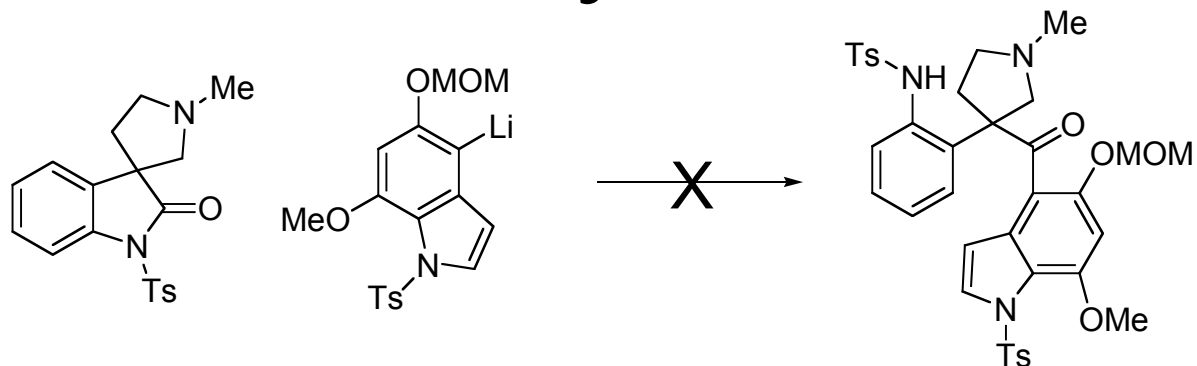


Should be stereospecific

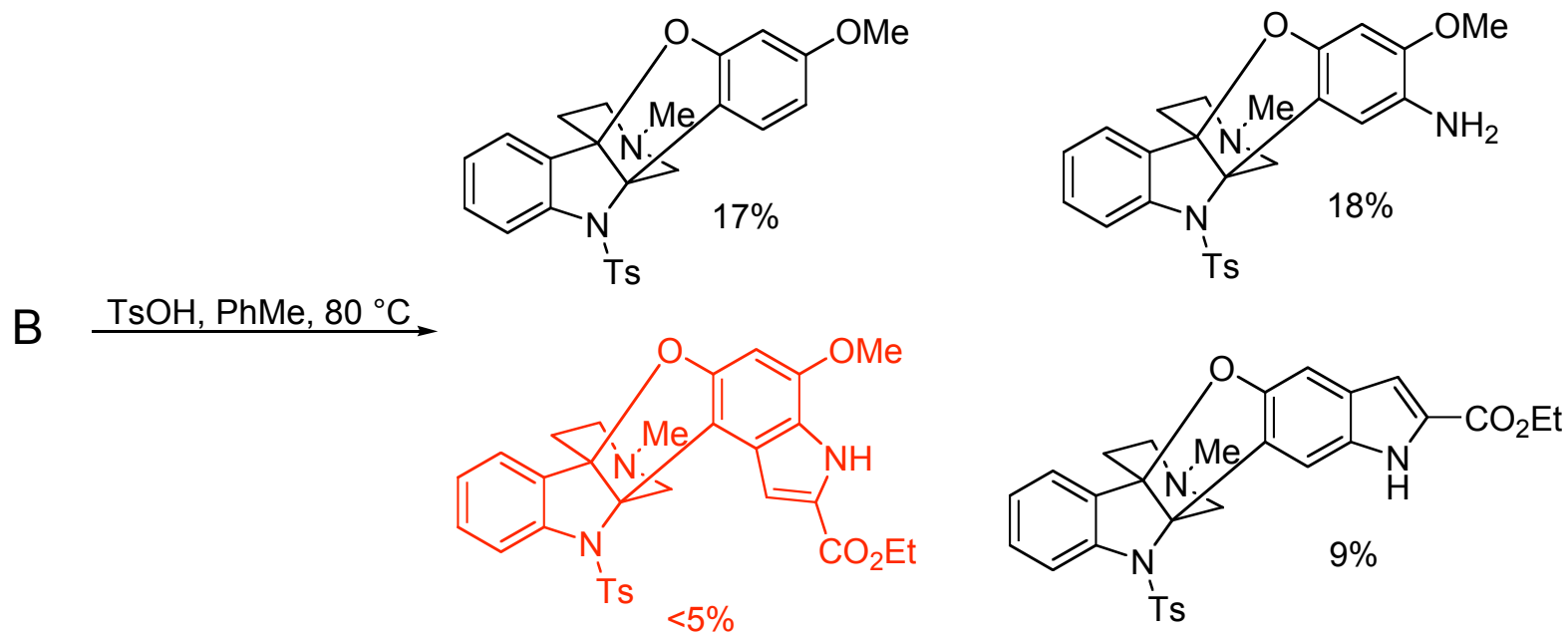
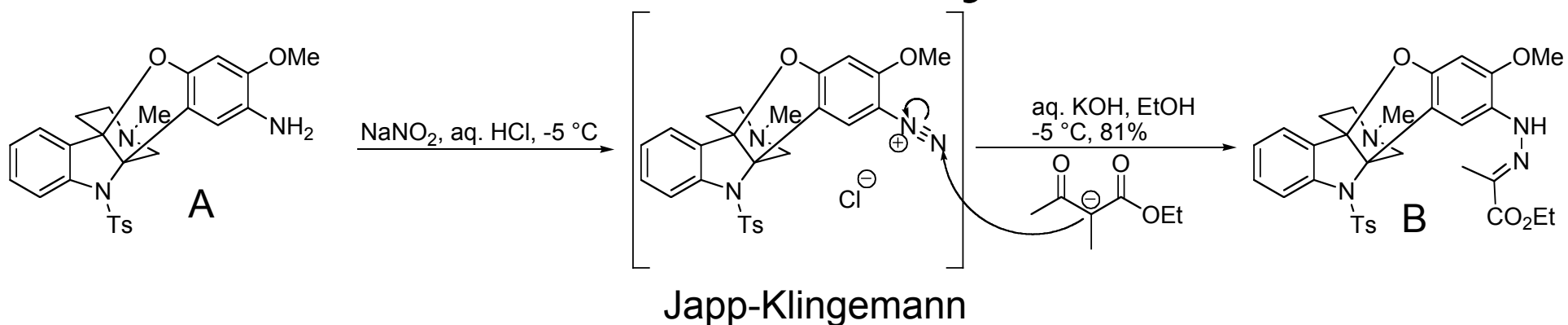
# Rearrangement Mechanism



# Total Synthesis

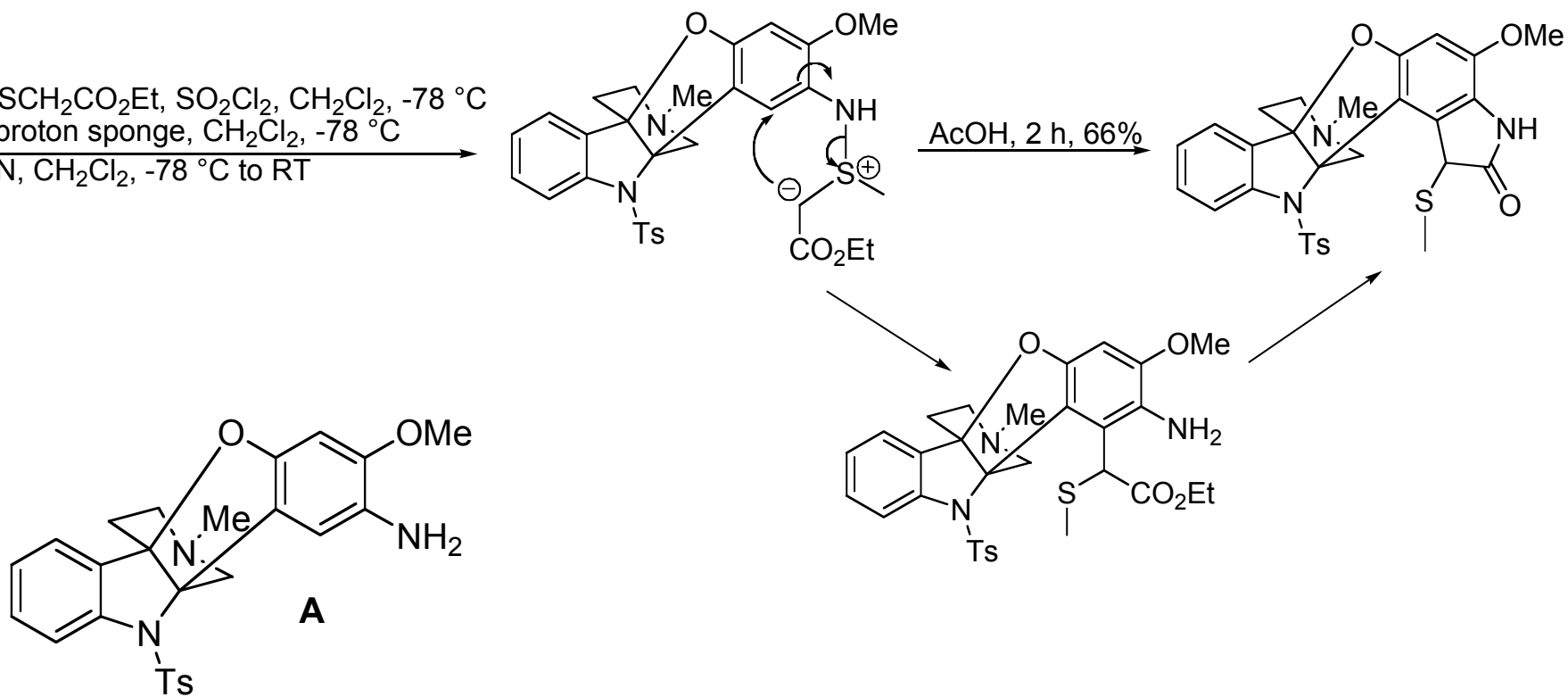


# Fischer Indole Synthesis

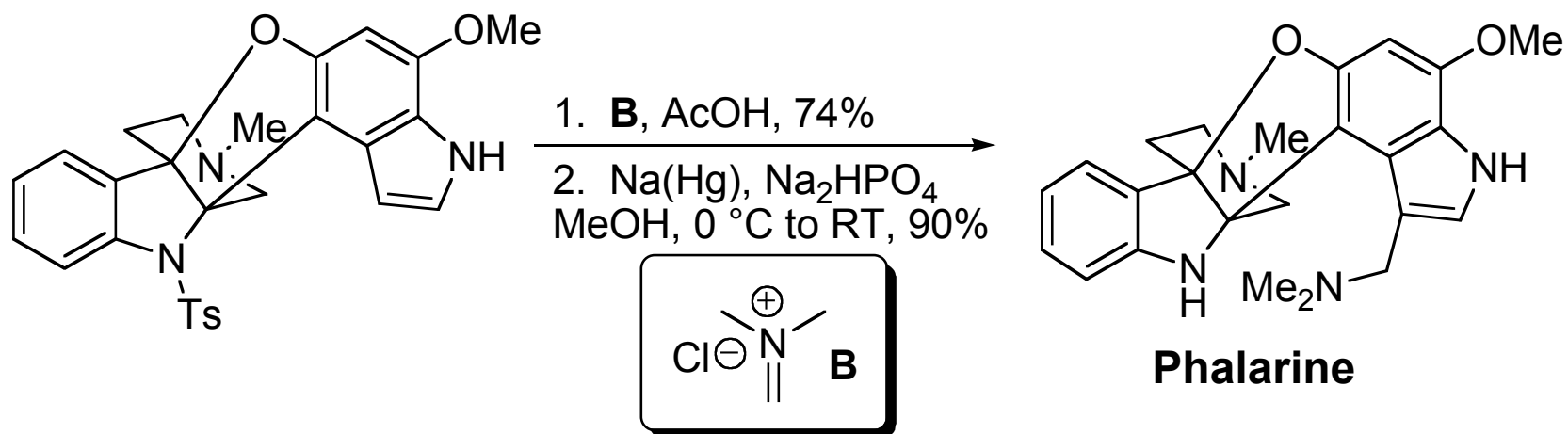
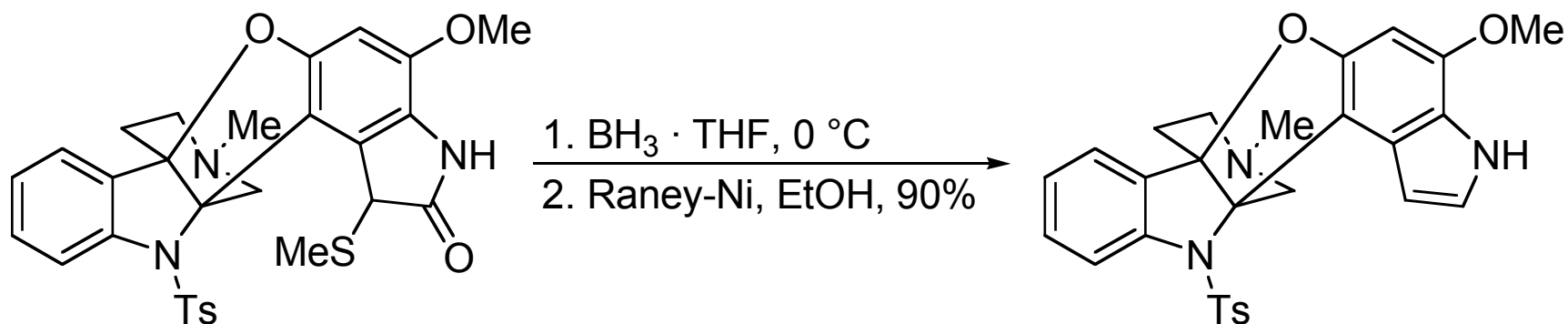


# Gassman Indole Synthesis

1. MeSCH<sub>2</sub>CO<sub>2</sub>Et, SO<sub>2</sub>Cl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C
2. **A**, proton sponge, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C
3. Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to RT



# Completion of Synthesis



# Summary

- Racemic phalarine was synthesized in 10 steps.
- The key step was the rearrangement of the azaspiroindolenine to the phalarine precursor.
- Additional work is needed to make the rearrangement and synthesis enantioselective.