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# Total synthesis of Gelsenicine via a Catalyzed Cycloisomerization Strategy

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Journal club (18.01.16)  
Renaud Group  
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*PhD: California Institute of Technology (2000-2005) Prof. Brian Stoltz*

*Postdoc: Stanford (2005-2008) Prof. Barry Trost*

Reaction mechanism  
Synthetic Methodologies  
Synthesis of natural products

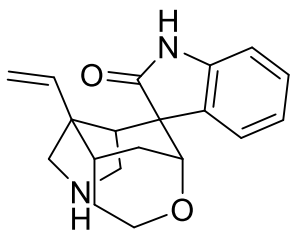
# Gelsemium alkaloids



*Gelsemium elegans*

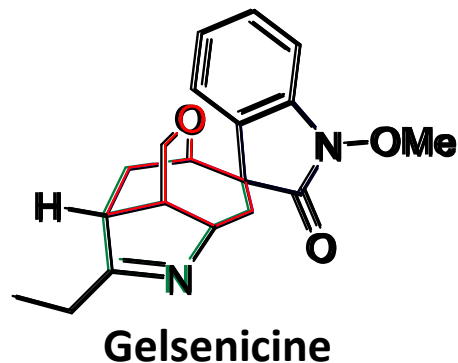
**Gelsedine type**

**Gelsemine type**

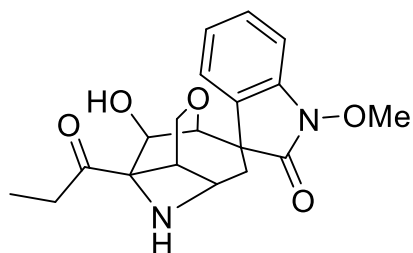


**Gelsemine**

8 Synthetic approaches



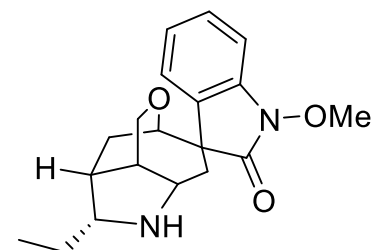
**Gelsenicine**



**Gelsemoxonine**

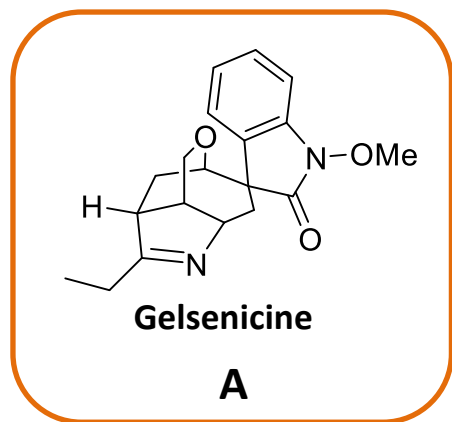
Fukuyama 2011

Carreira 2015

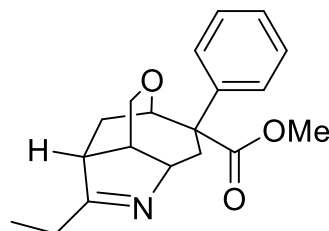


**Gelsedine**

# Retrosynthetic Analysis

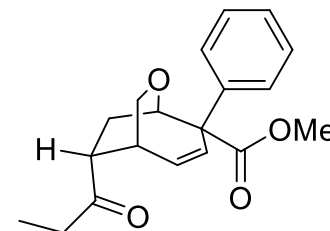


Oxindole  
formation

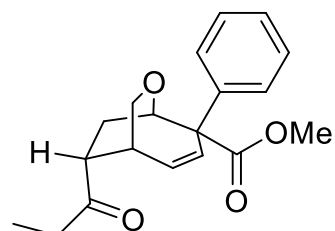


**B**

Pyrrrole  
formation

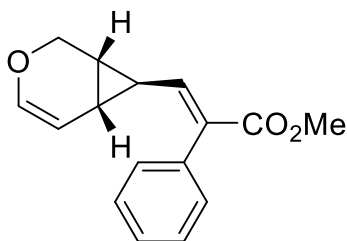


**C**



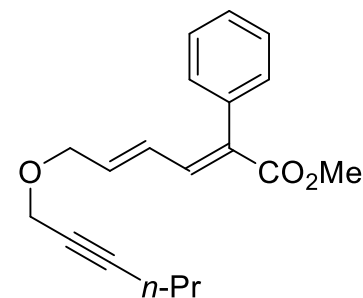
**C**

Trans/Cis  
isomerization  
Cope  
Rearrangement



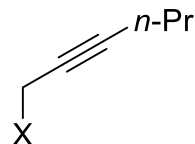
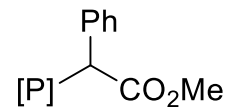
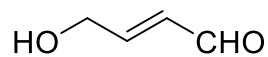
**D**

Cycloisomerization

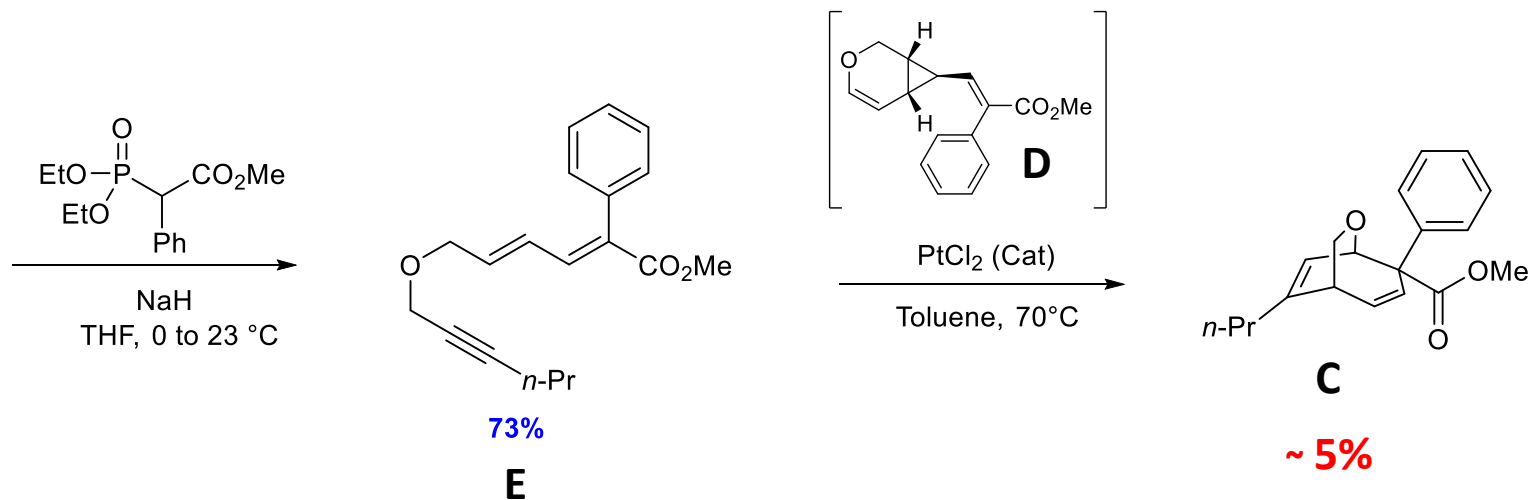
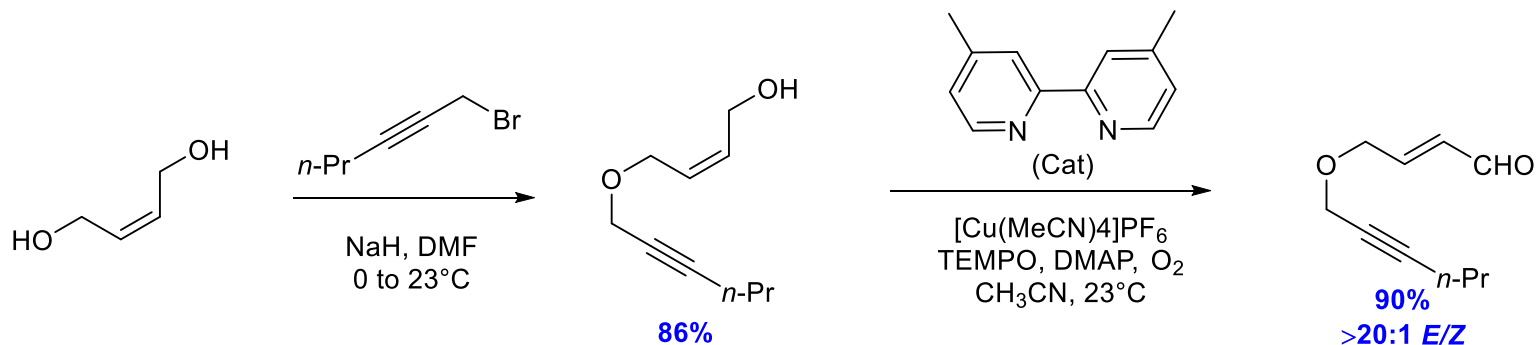


**E**

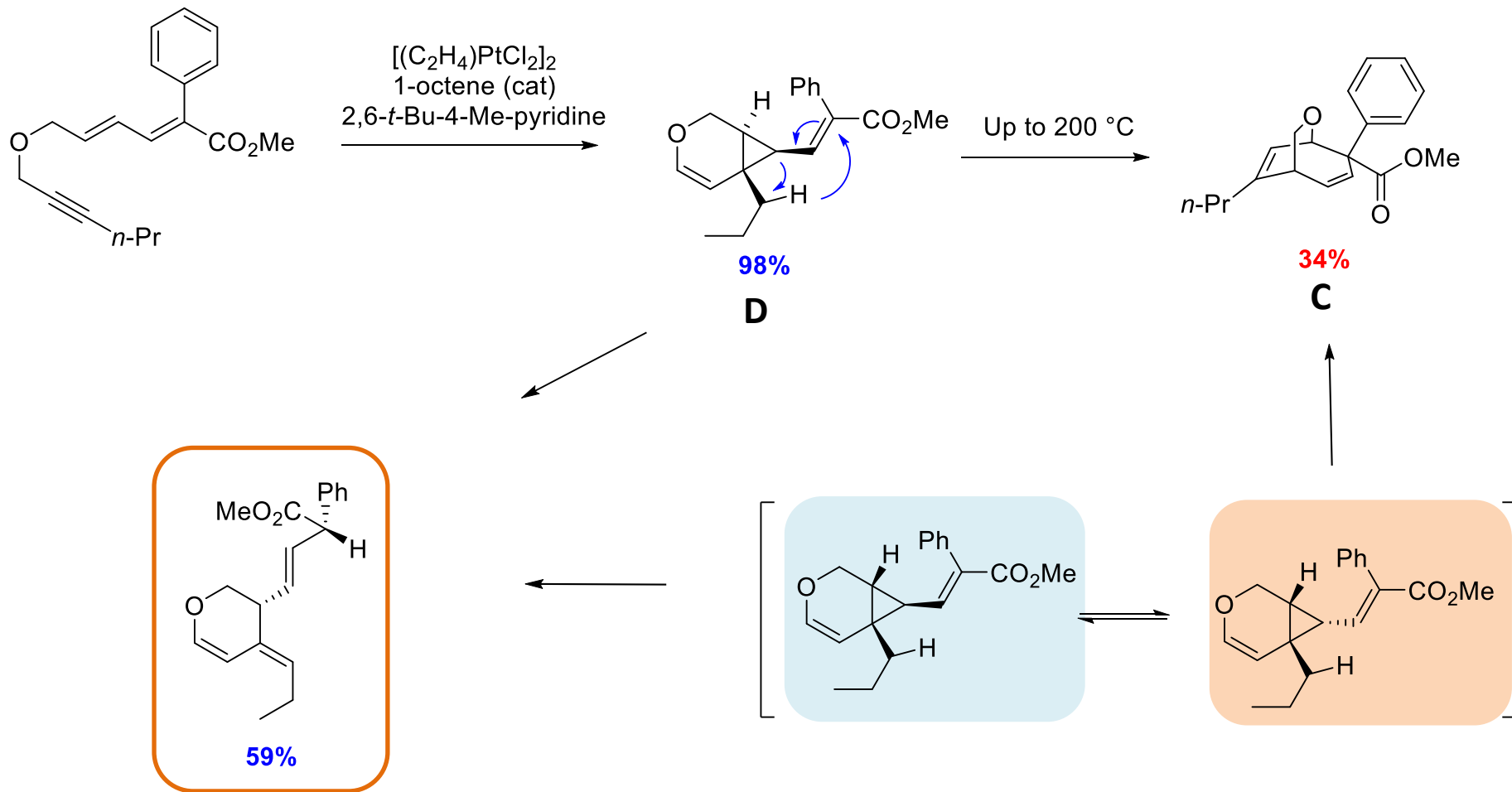
Retrosynthetic arrows pointing to the starting materials.



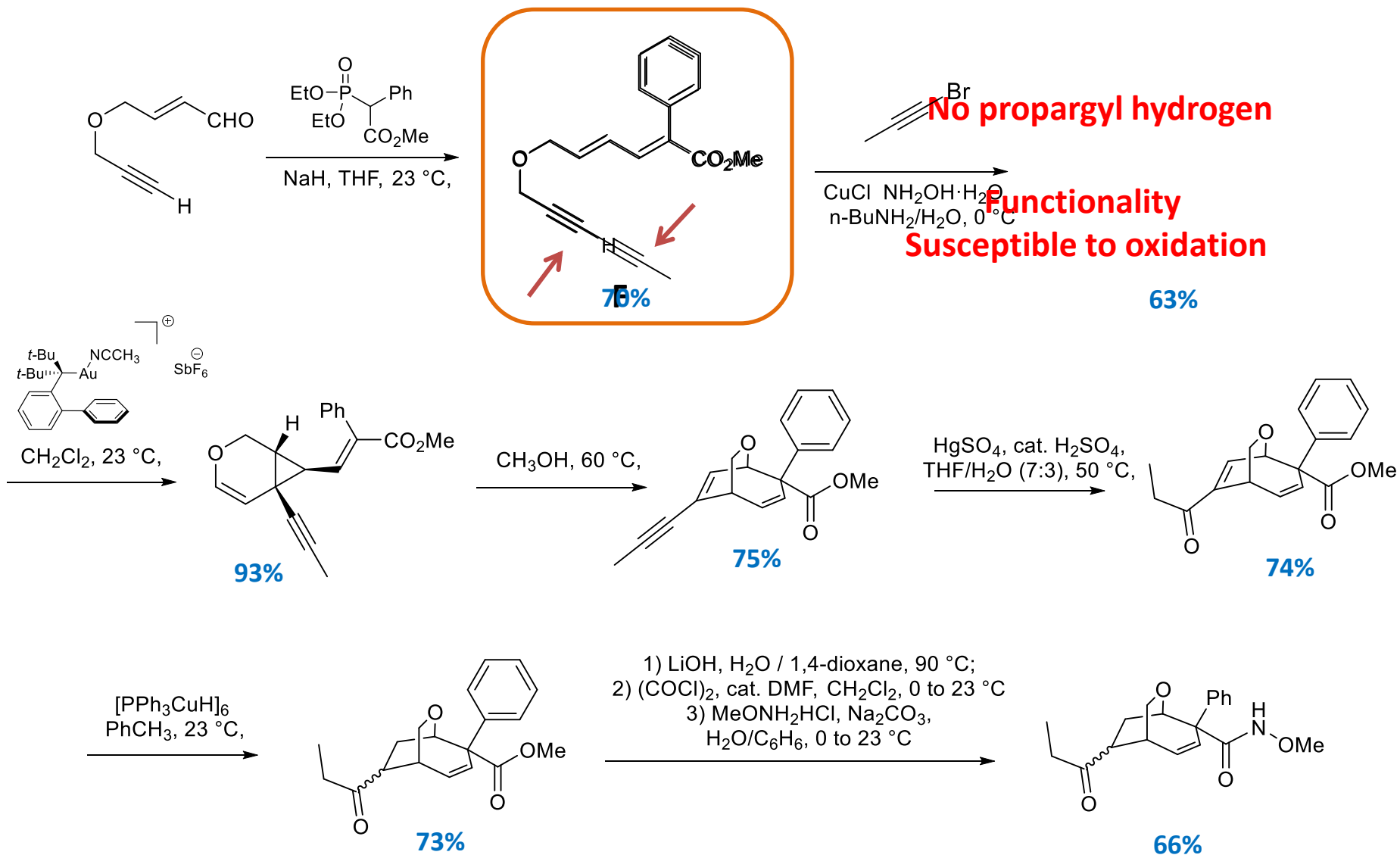
# Synthesis of fragment E



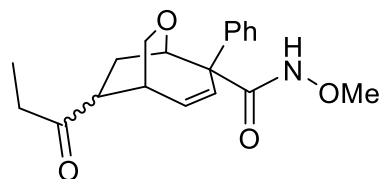
# Synthesis of fragments D and C



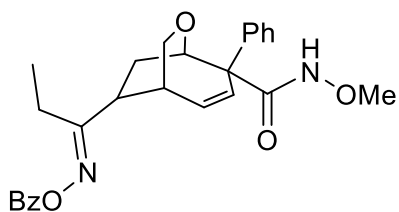
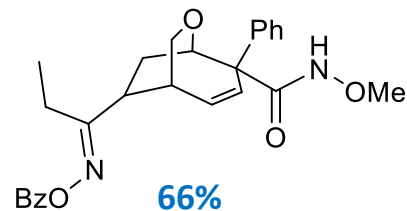
# Avoiding isomerization (Synthesis of an alternative precursor F)



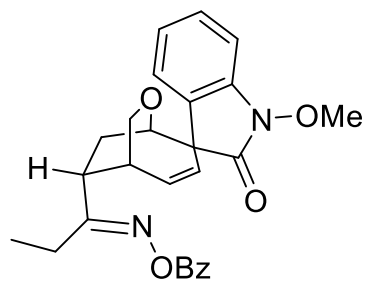
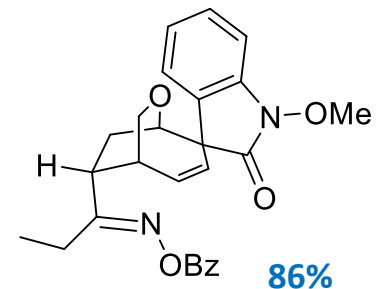
# Completion of the Synthesis



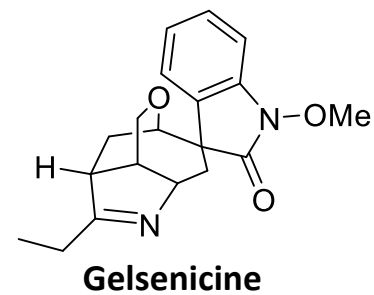
1)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , pyridine, 0 to 23°C  
2)  $\text{BzCl}$ , pyridine, THF, 0 to 23°C



$\text{PhI}(\text{OTFA})_2$   
 $\text{CHCl}_3$ , 0°C



$\text{Bu}_3\text{SnH}$ , AIBN,  
 $\text{PhCH}_3/\text{cyclohexane}$ , 120 °C



**66%**

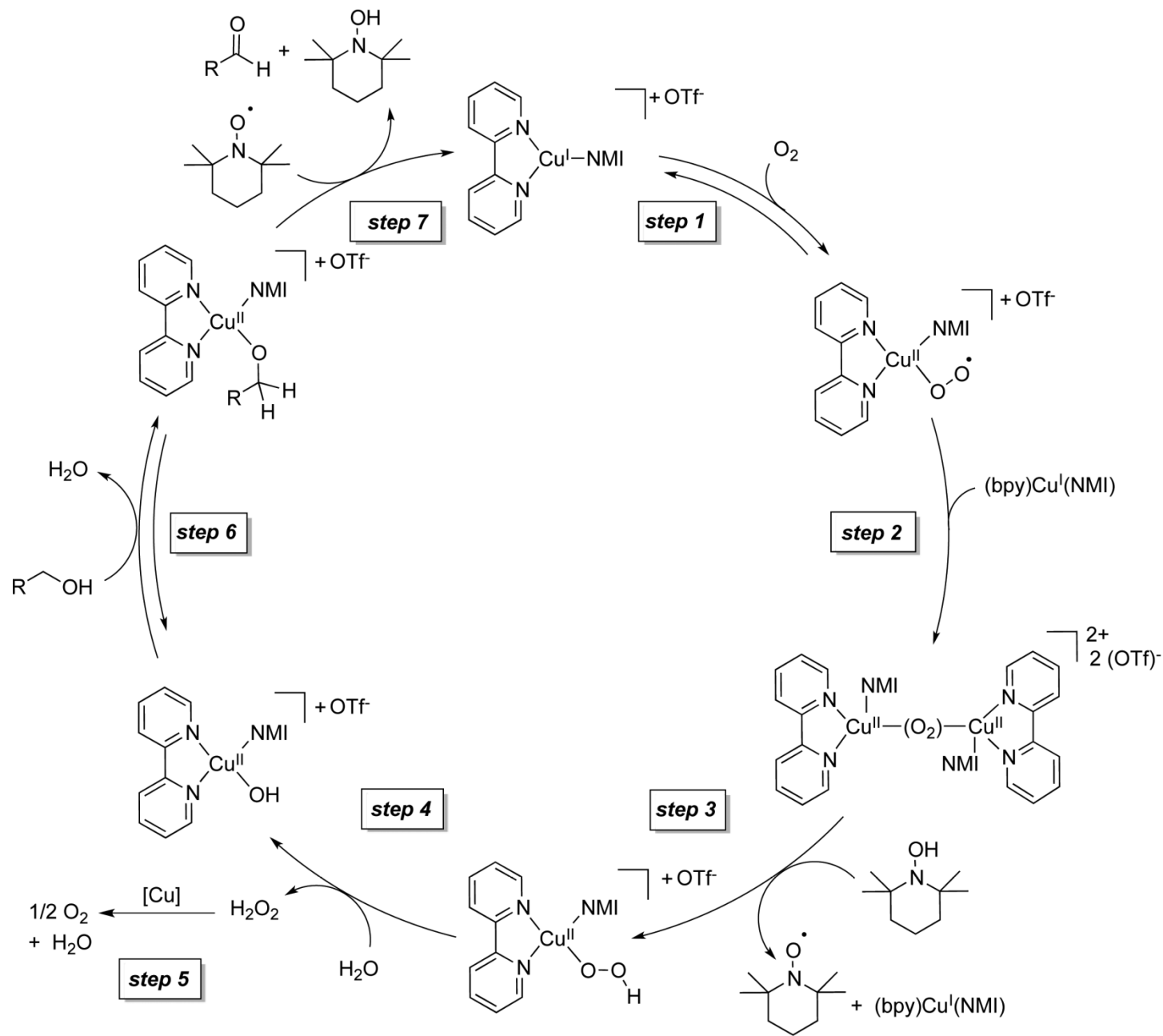


# Conclusion

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- 13 steps in a linear approach
- Lowest yield for a single step: **63%**
- Protecting group-free synthesis
- Shortest total syntheses of a gelsemium alkaloid to date







Proposed mechanism:

