

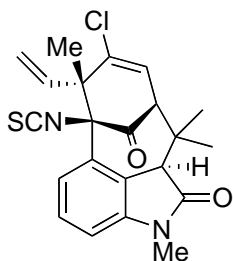
# Synthetic Approachs to the Welwitindolinones

Leighton Group Meeting

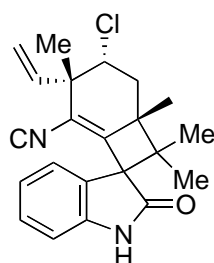
Laura Schacherer

September 22nd, 2006

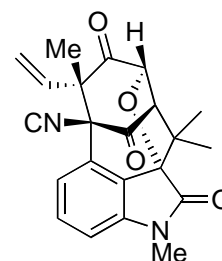
# Welwitindolinones: Isolation



**N-Methyl Welwitindolinone C**



**Welwitindolinone A**

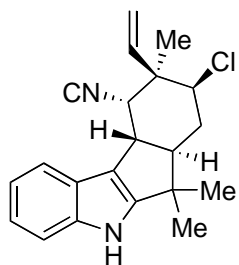


**N-Methyl Welwitindolinone D**

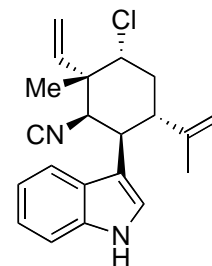
Isolated in 1994 with fischerindoles and hapalindoles, these alkaloids come from blue-green algae

N-Methyl Welwitindolinone may have some multiple drug resistance-reversing properties

Welwitindolinone A is the only spirocyclobutane oxindole isolated

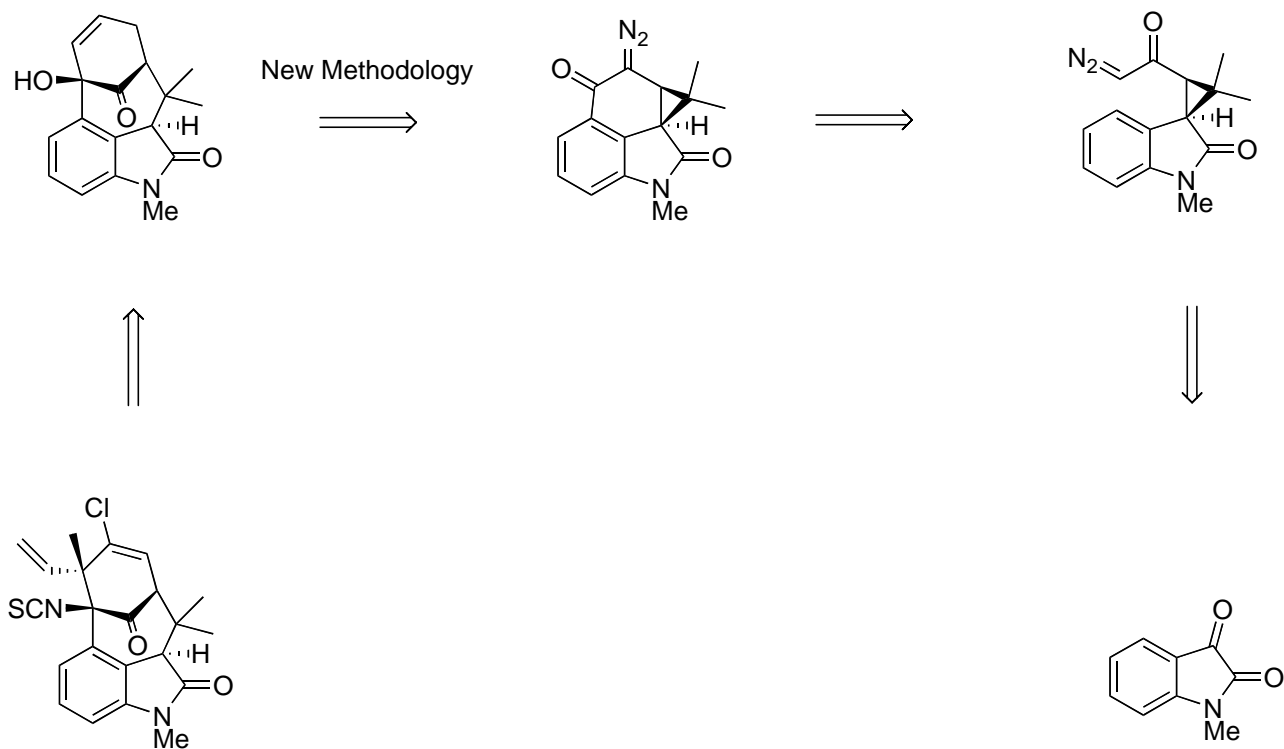


**Fischerindole G**

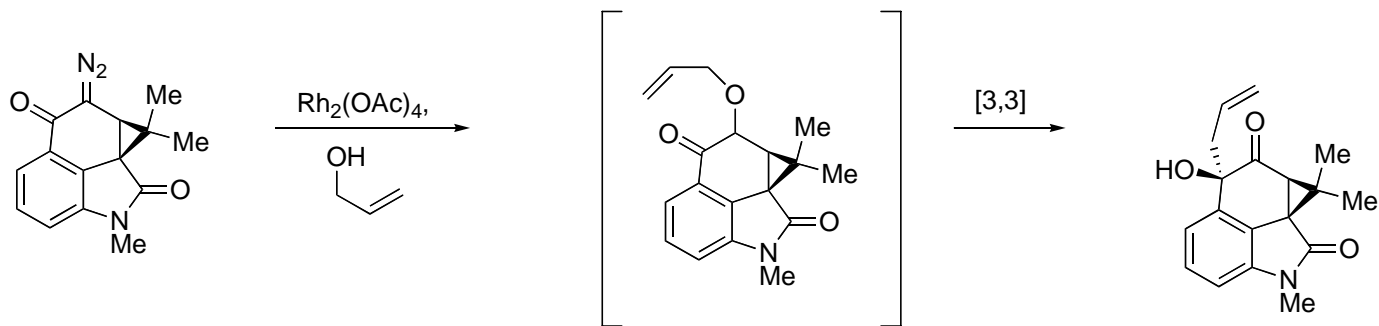
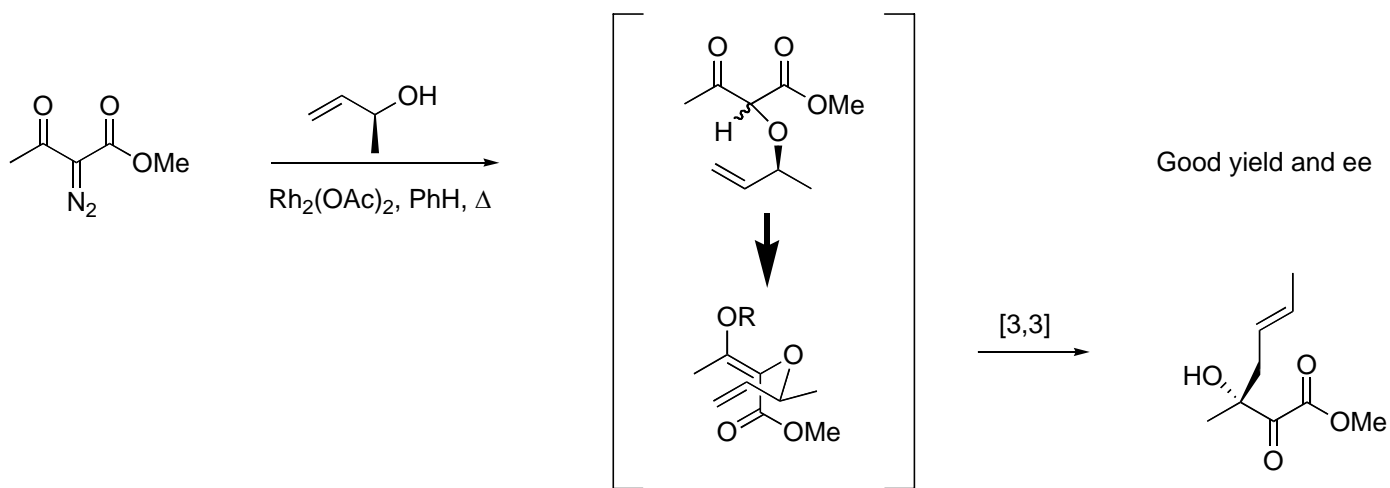


**12-epi-Hapalindole E**

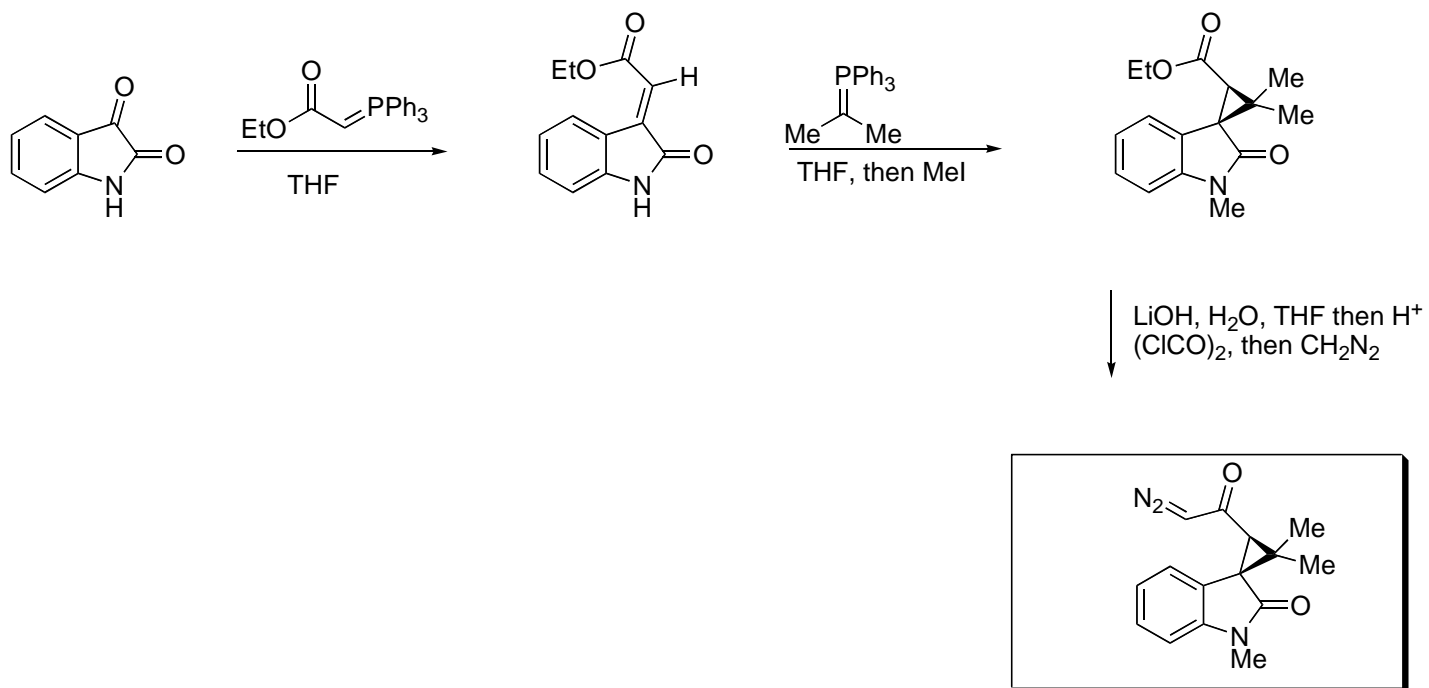
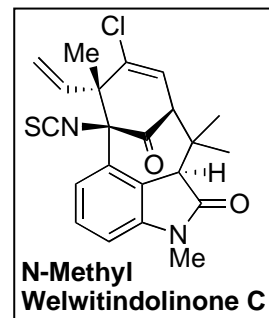
# Wood/Stoltz Retrosynthesis



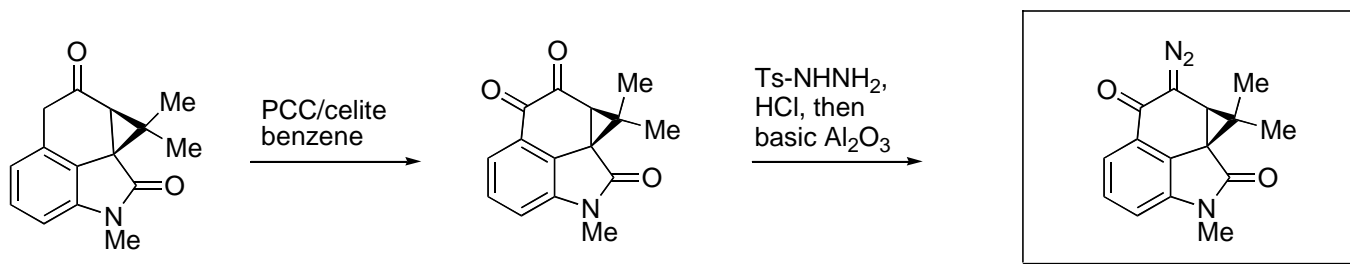
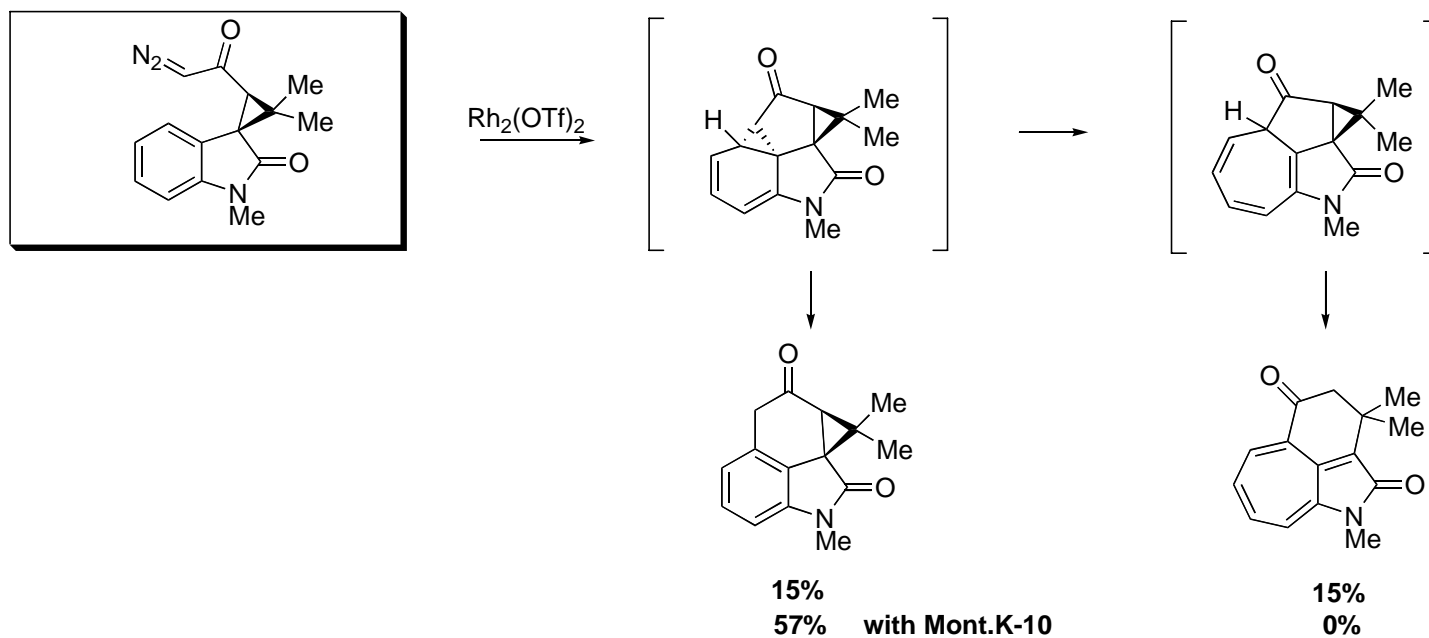
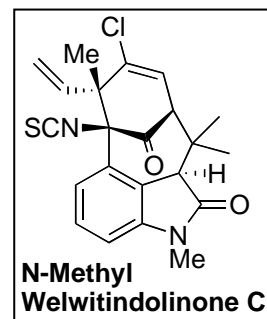
# Tandem O-H Insertion Claisen



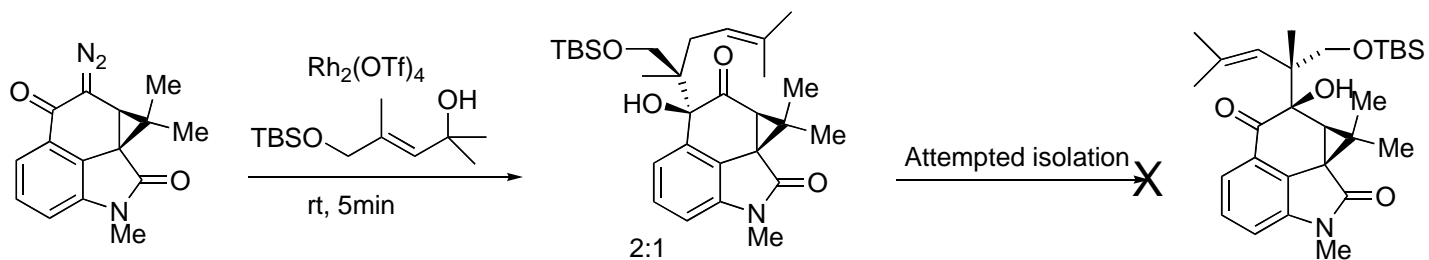
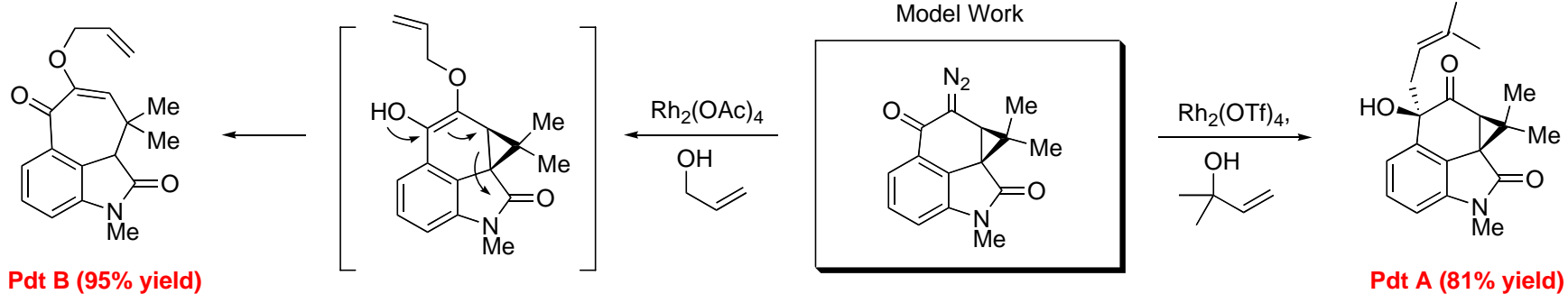
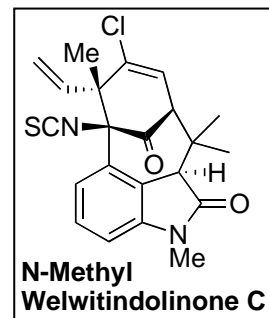
# Wood/Stoltz Approach



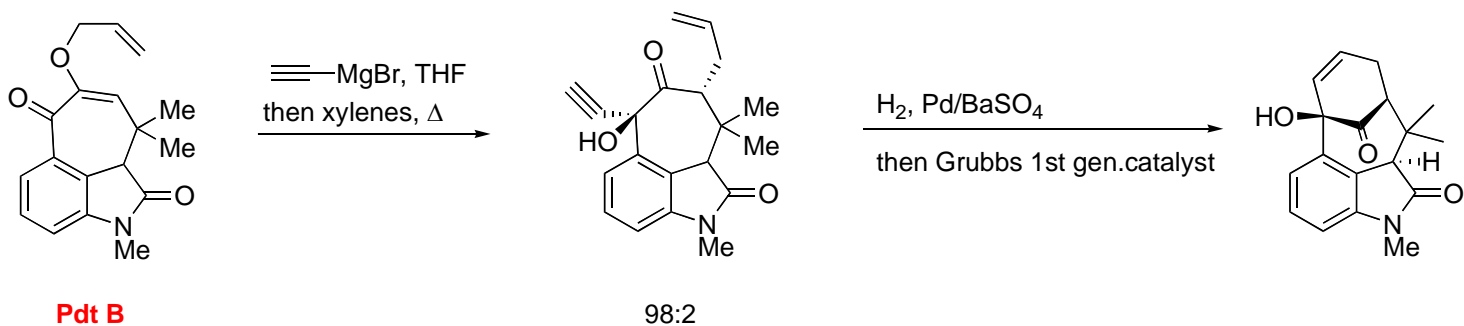
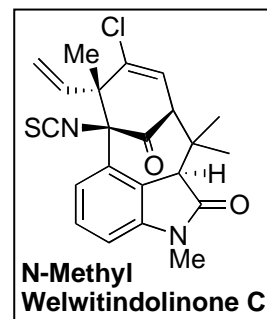
# Wood/Stoltz Approach



# Wood/Stoltz Approach



# Wood/Stoltz Approach



## Highlights:

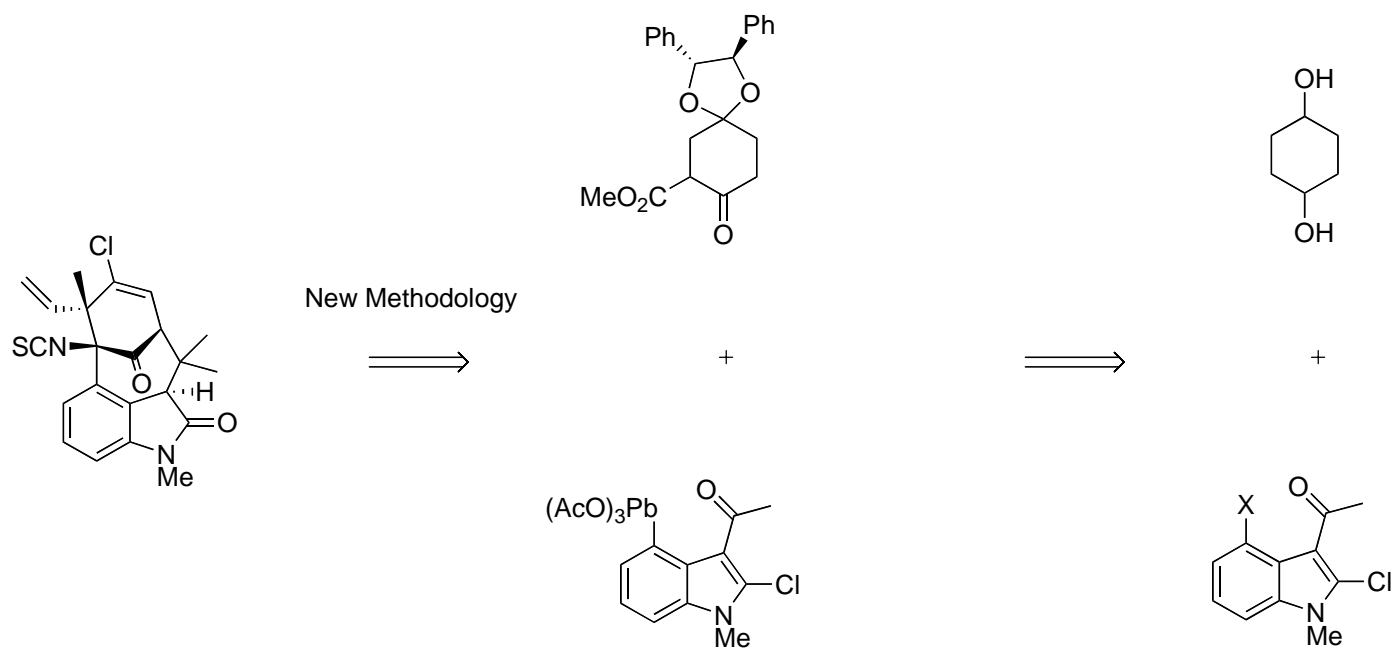
15 Steps, 9.88% yield

1 C-H insertion

1 Tandem O-H insertion/cyclopropane fragmentation

Claisen and RCM

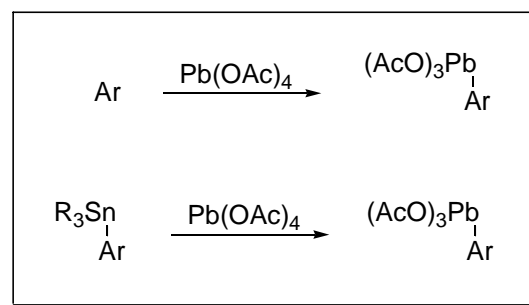
# Konopelski Retrosynthesis



# Aryl Lead Reagents

Can be prepared via two means:

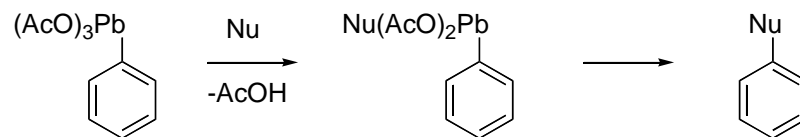
direct plumbation  
or transmetallation



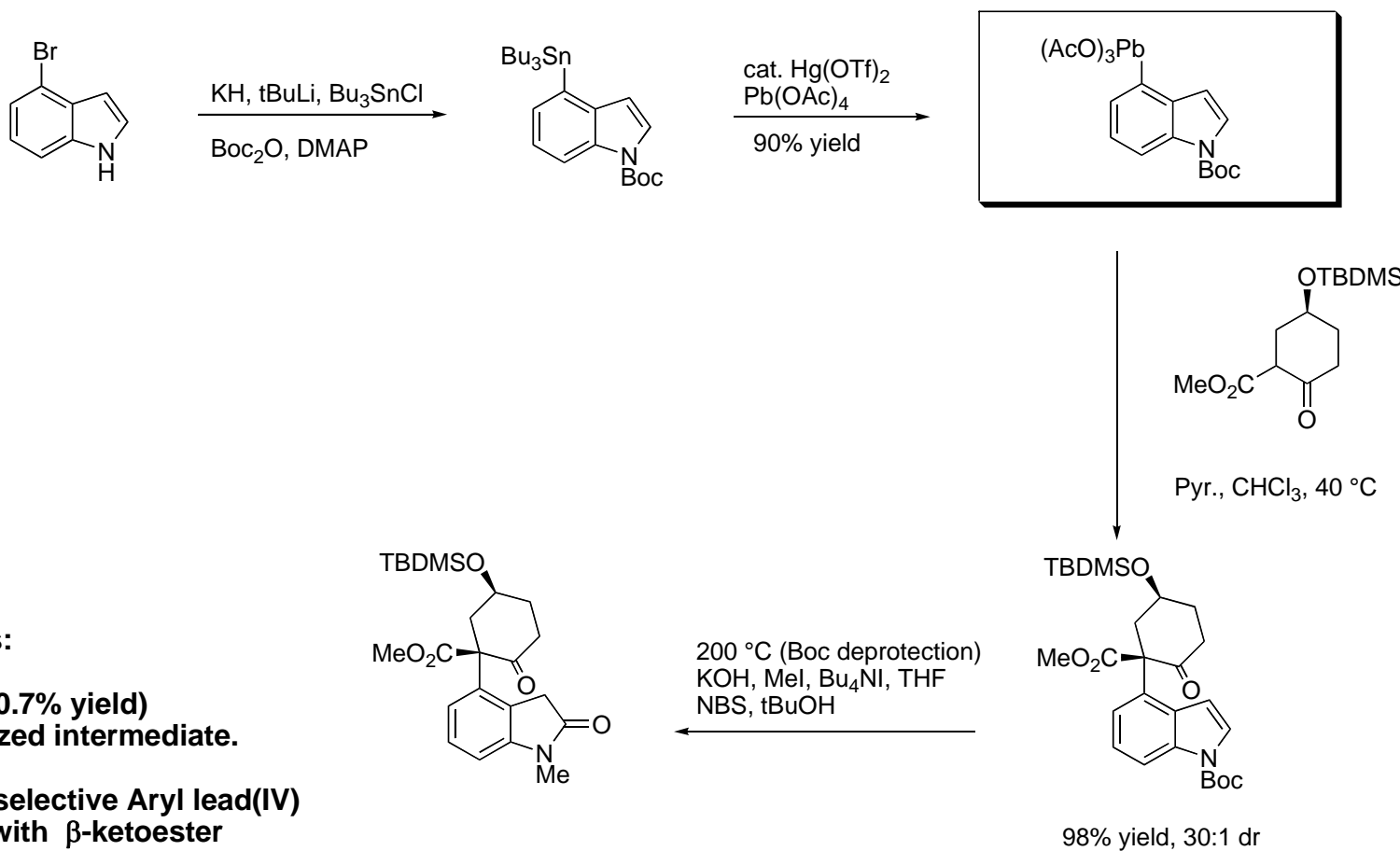
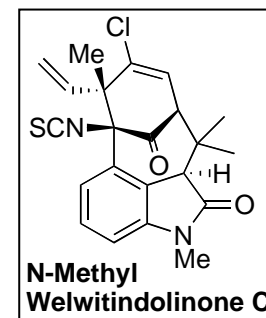
Can be used in four types of reactions:

metal-metal exchange  
acid-catalyzed bond Pb-aryl bond cleavage  
Cu-catalyzed N-arylation  
and reaction with soft nucleophiles.

The later is a non-radical process that involves ligand exchange and coupling



# Konopelski Approach

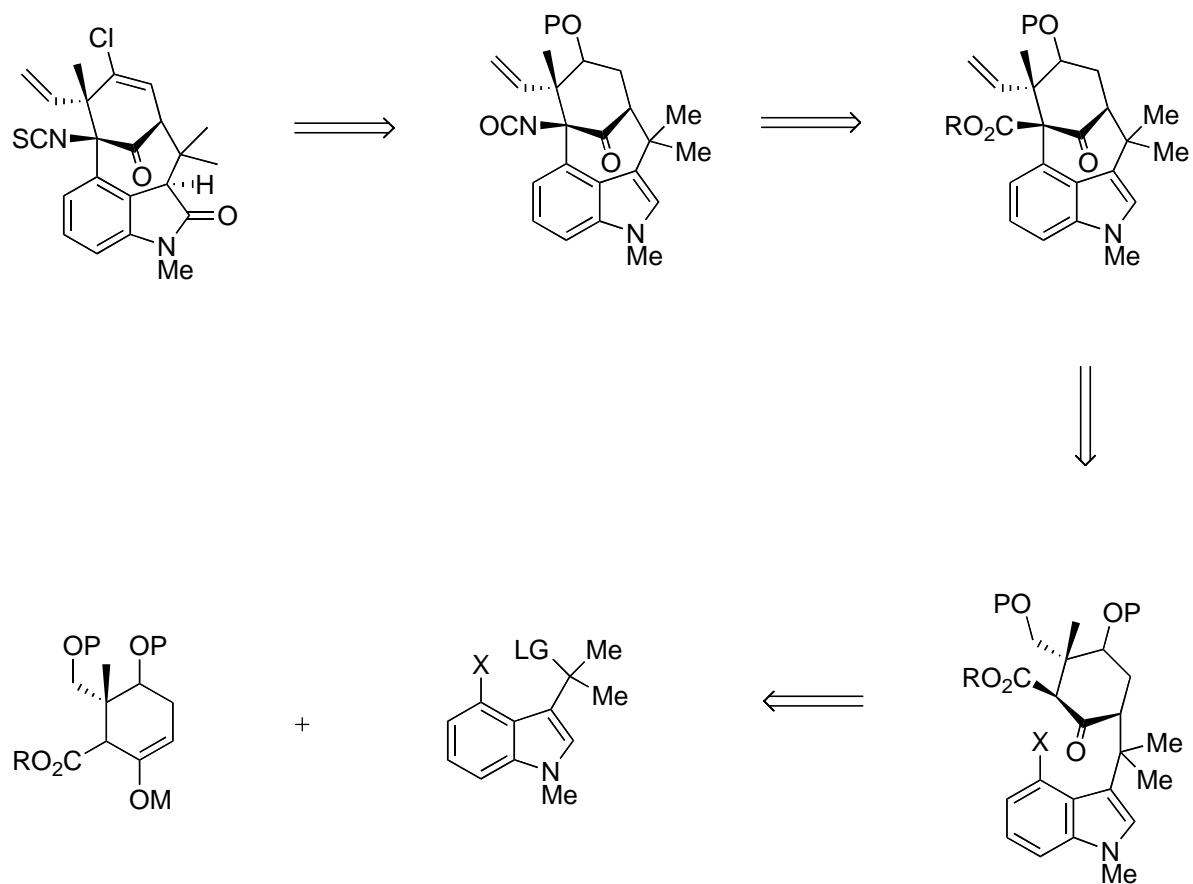


## Highlights:

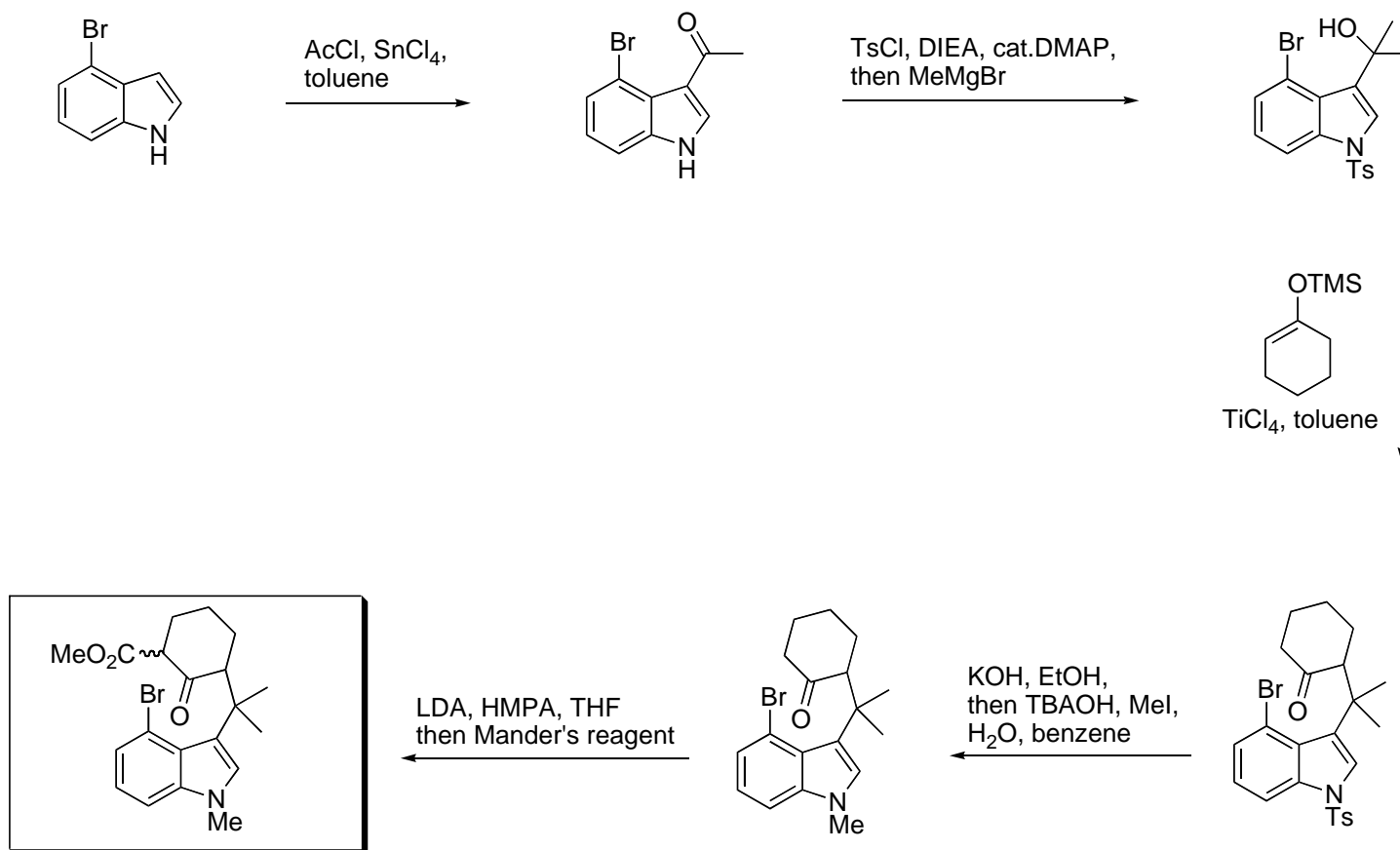
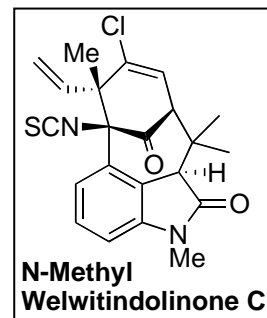
**6 steps (30.7% yield)  
to uncyclized intermediate.**

**Diastereoselective Aryl lead(IV)  
coupling with  $\beta$ -ketoester**

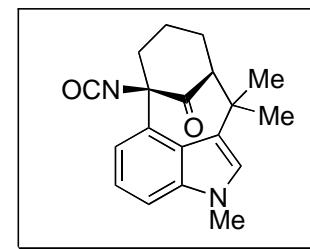
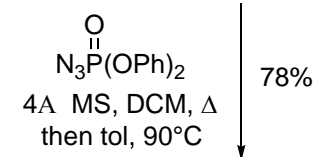
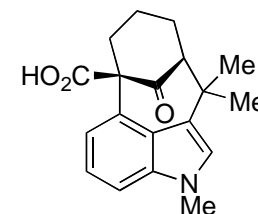
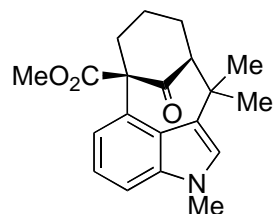
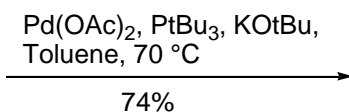
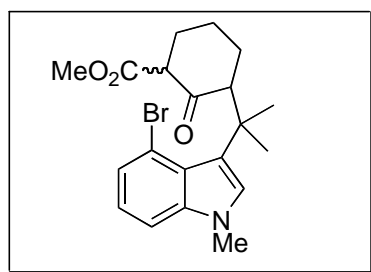
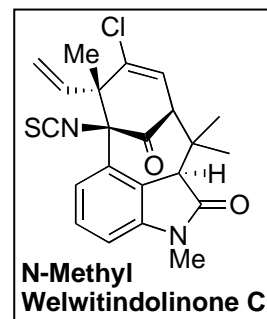
# Rawal Retrosynthesis



# Rawal Approach



# Rawal Approach

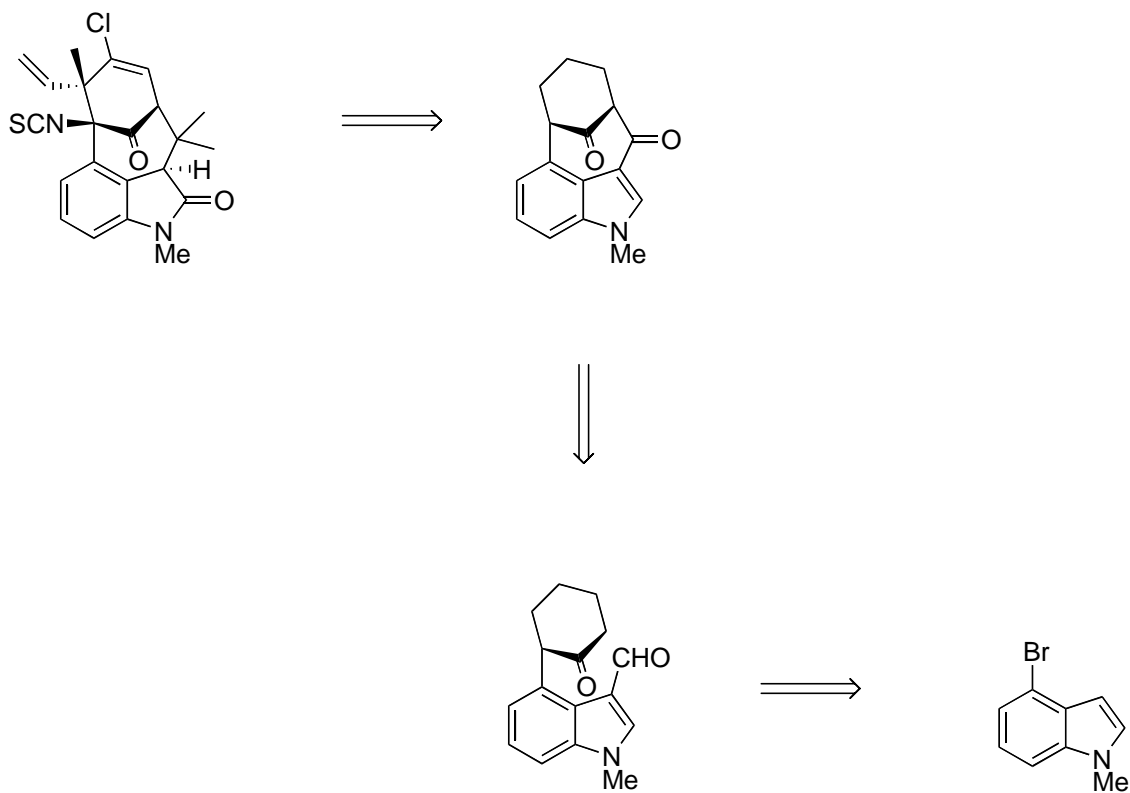


## Highlights:

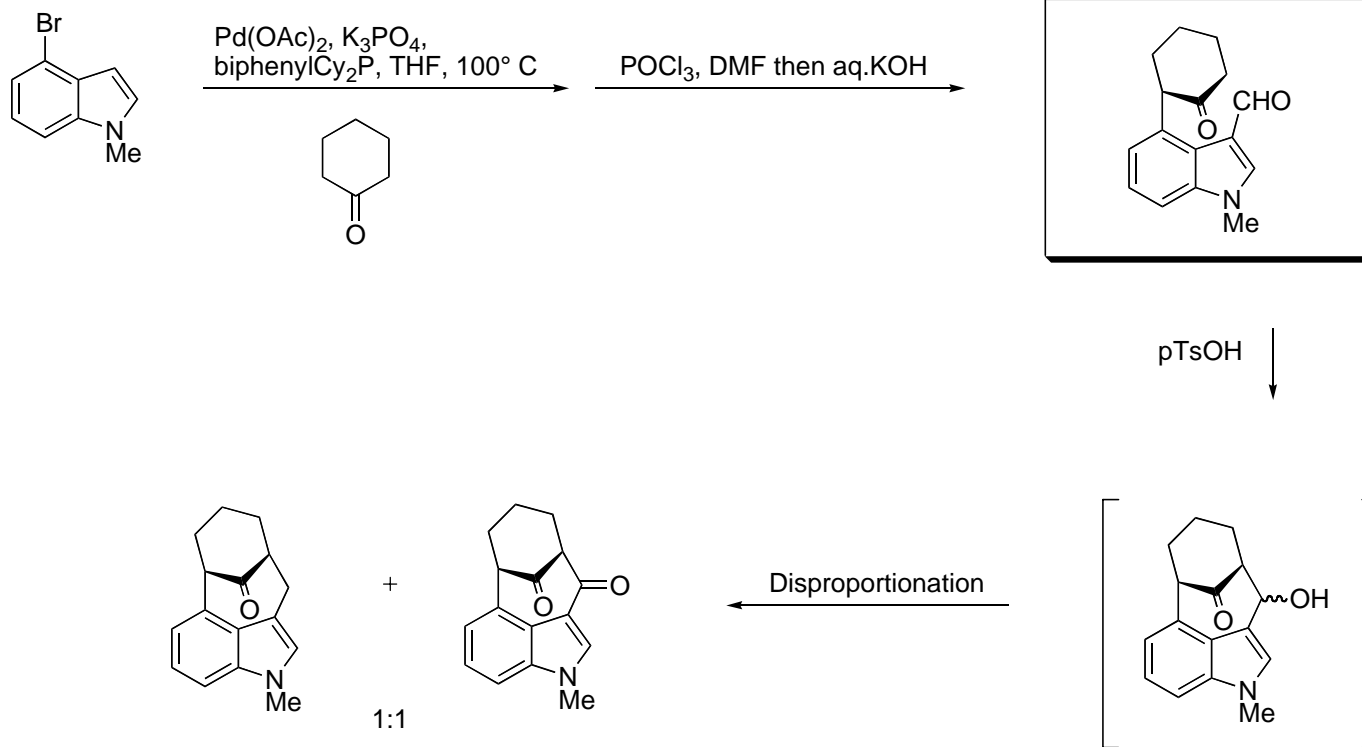
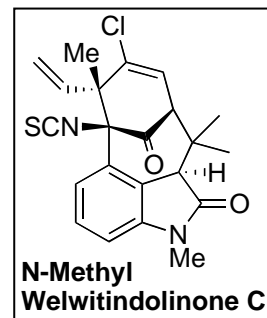
11 Steps, 30.97% yield

Hartwig Enolate Arylation  
Curtius Rearrangement

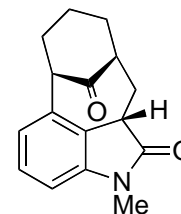
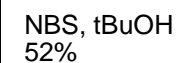
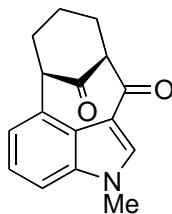
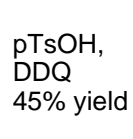
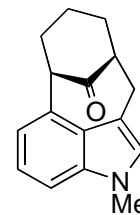
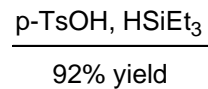
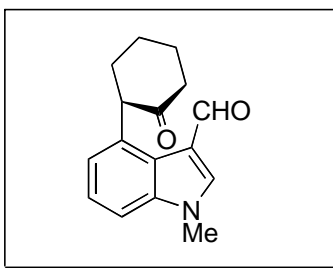
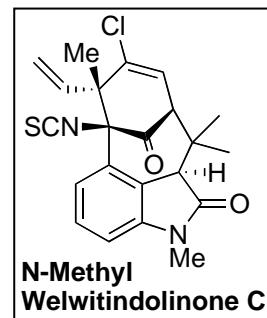
# Simpkins Retrosynthesis



# Simpkins Approach



# Simpkins Approach

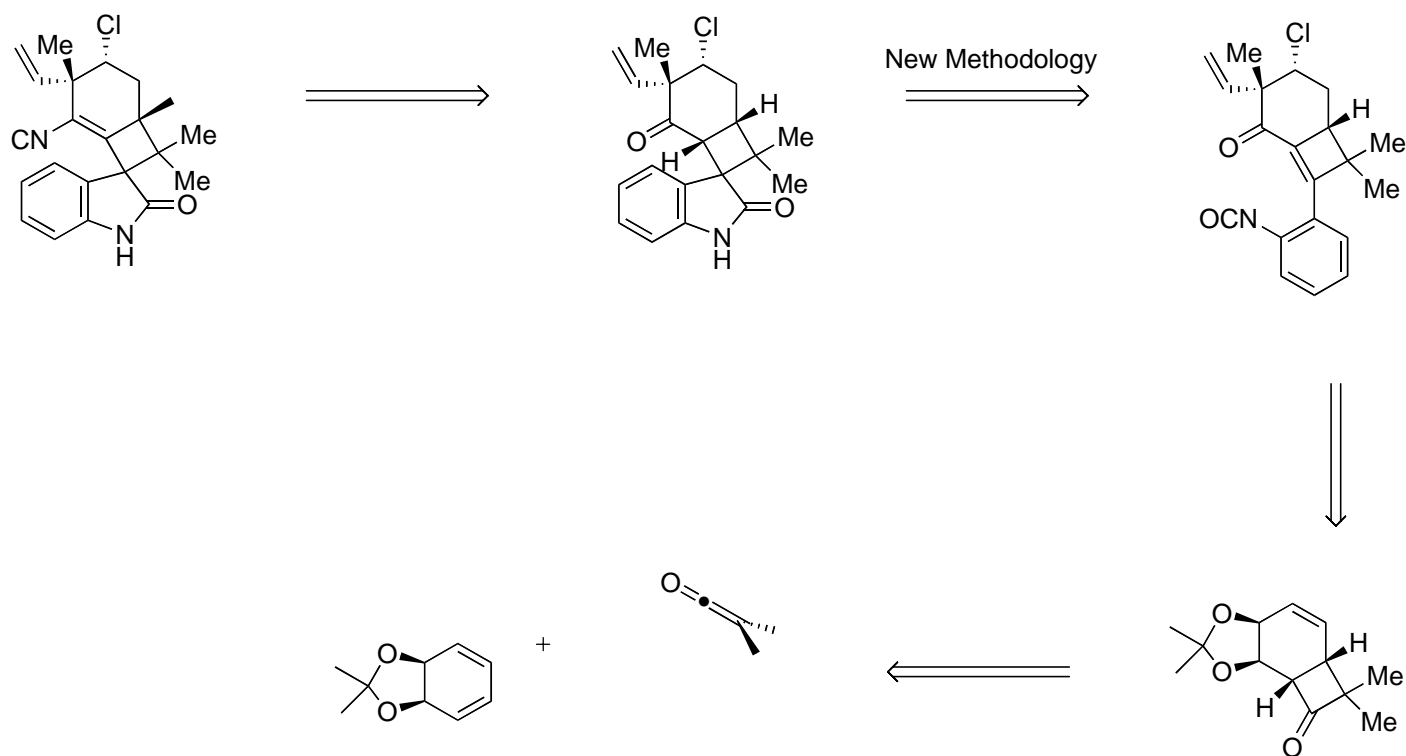


**Highlights:**

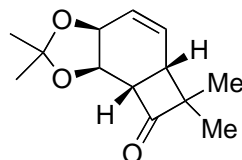
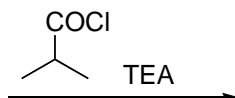
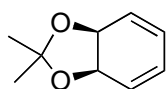
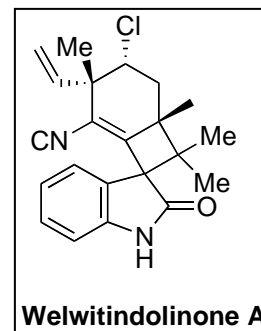
**3 steps, 24.6% yield**

**Unique retrosynthetic disconnection  
Hartwig Enolate Arylation**

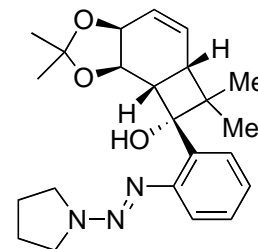
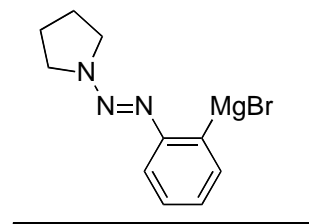
# Wood/Reisman Retrosynthesis



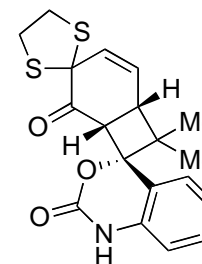
# Wood/Reisman Synthesis



Can be made asymmetric

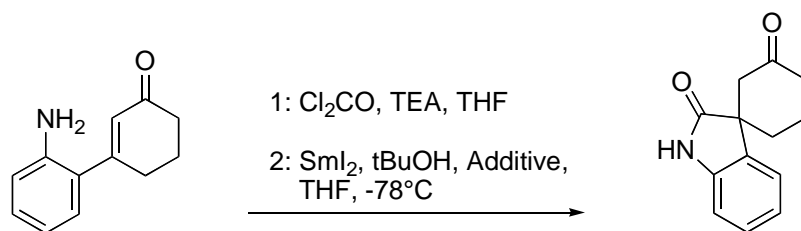
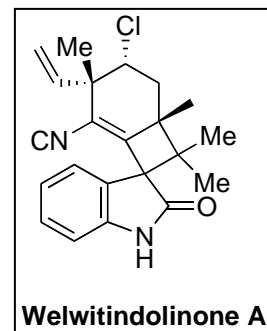


Raney Ni  
p-NO<sub>2</sub> phenylchloroformate  
AcOH/H<sub>2</sub>O  
Bu<sub>2</sub>SnO, MeOH, NBS, Δ  
Ethanedithiol, BF<sub>3</sub>·OEt<sub>2</sub>  
Swern



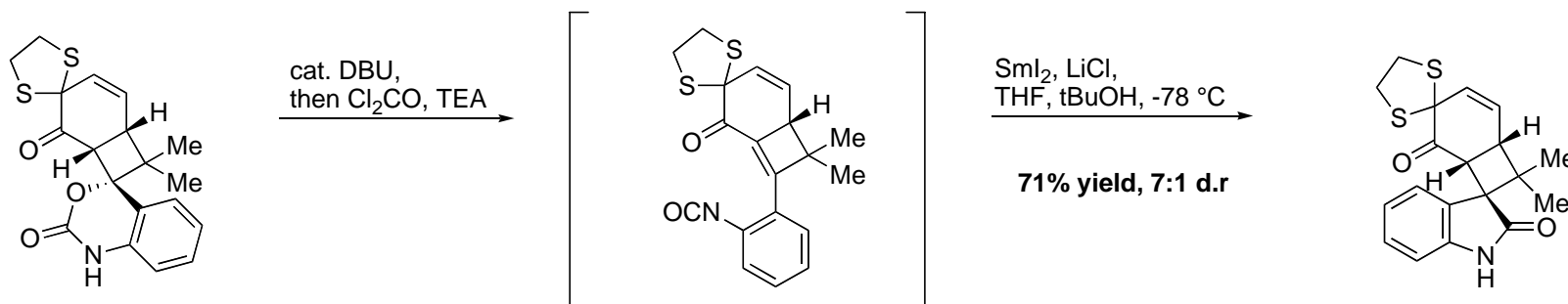
Now Poised for Oxindole Formation

# Wood/Reisman Synthesis

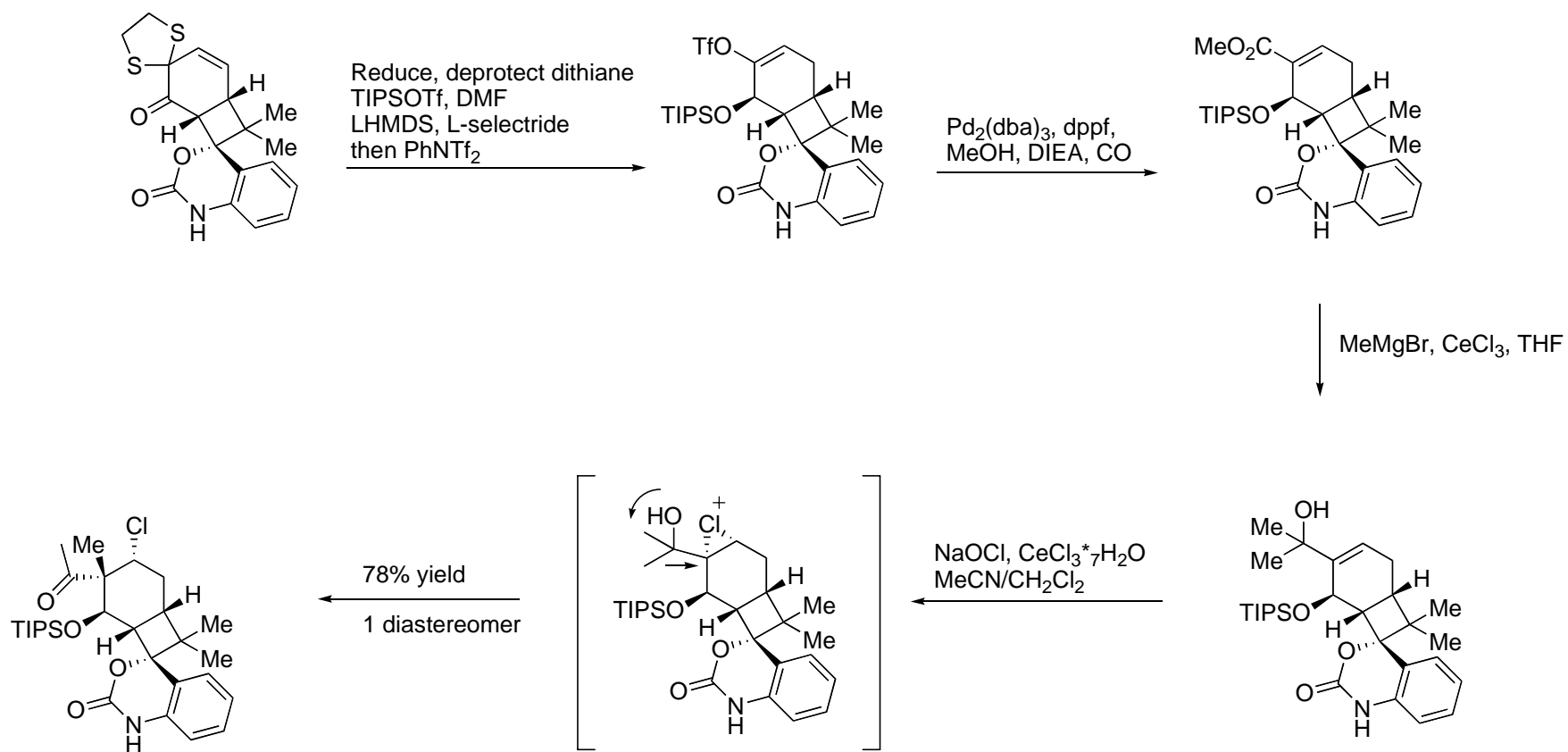
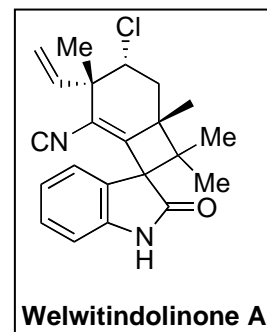


Additive:  
None  
HMPA  
LiCl

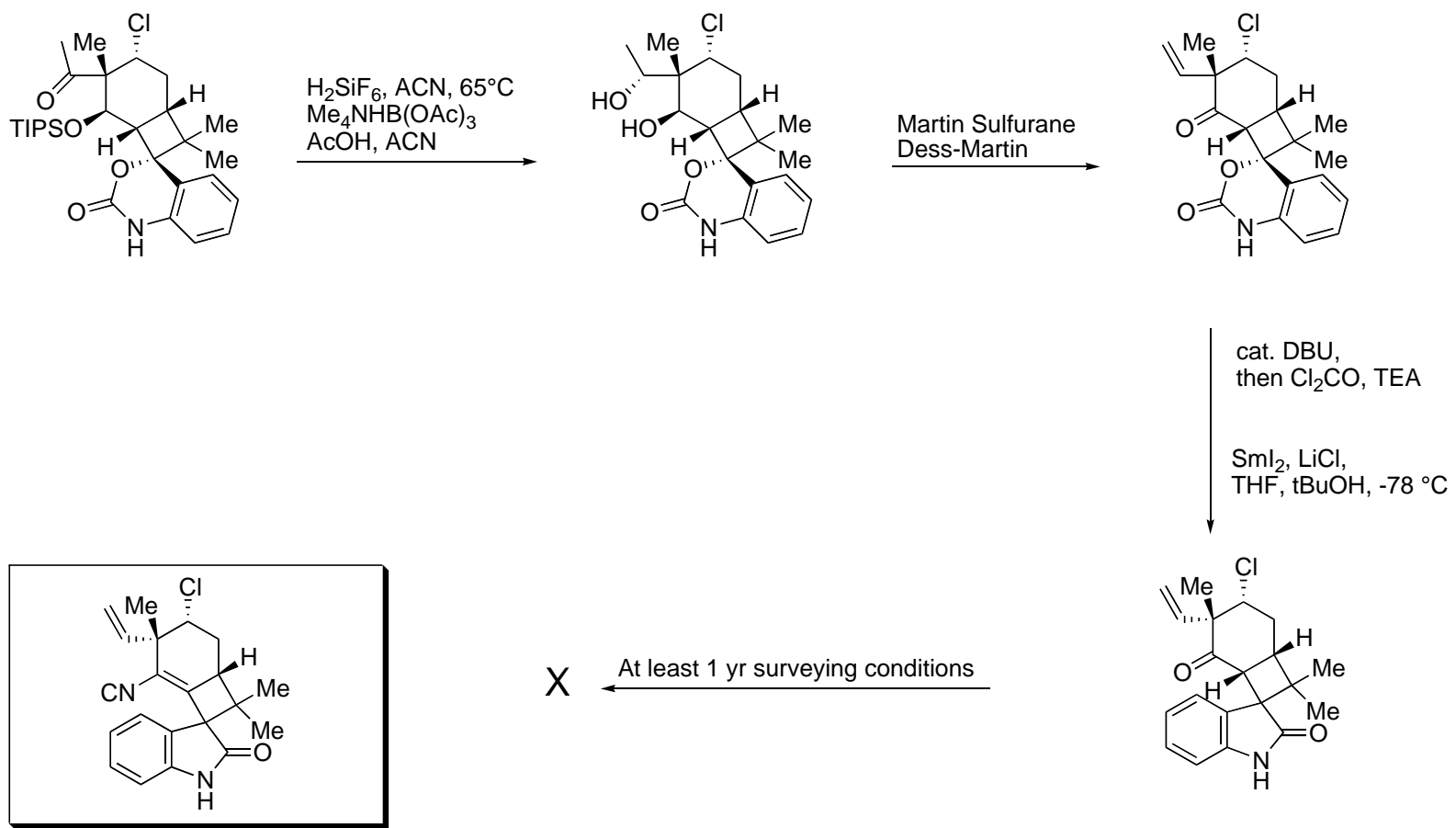
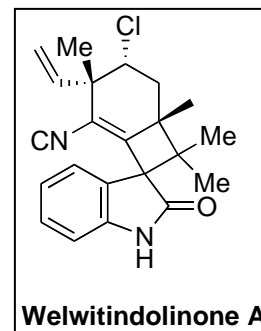
Yield:  
5  
32  
88



# Wood/Reisman Synthesis

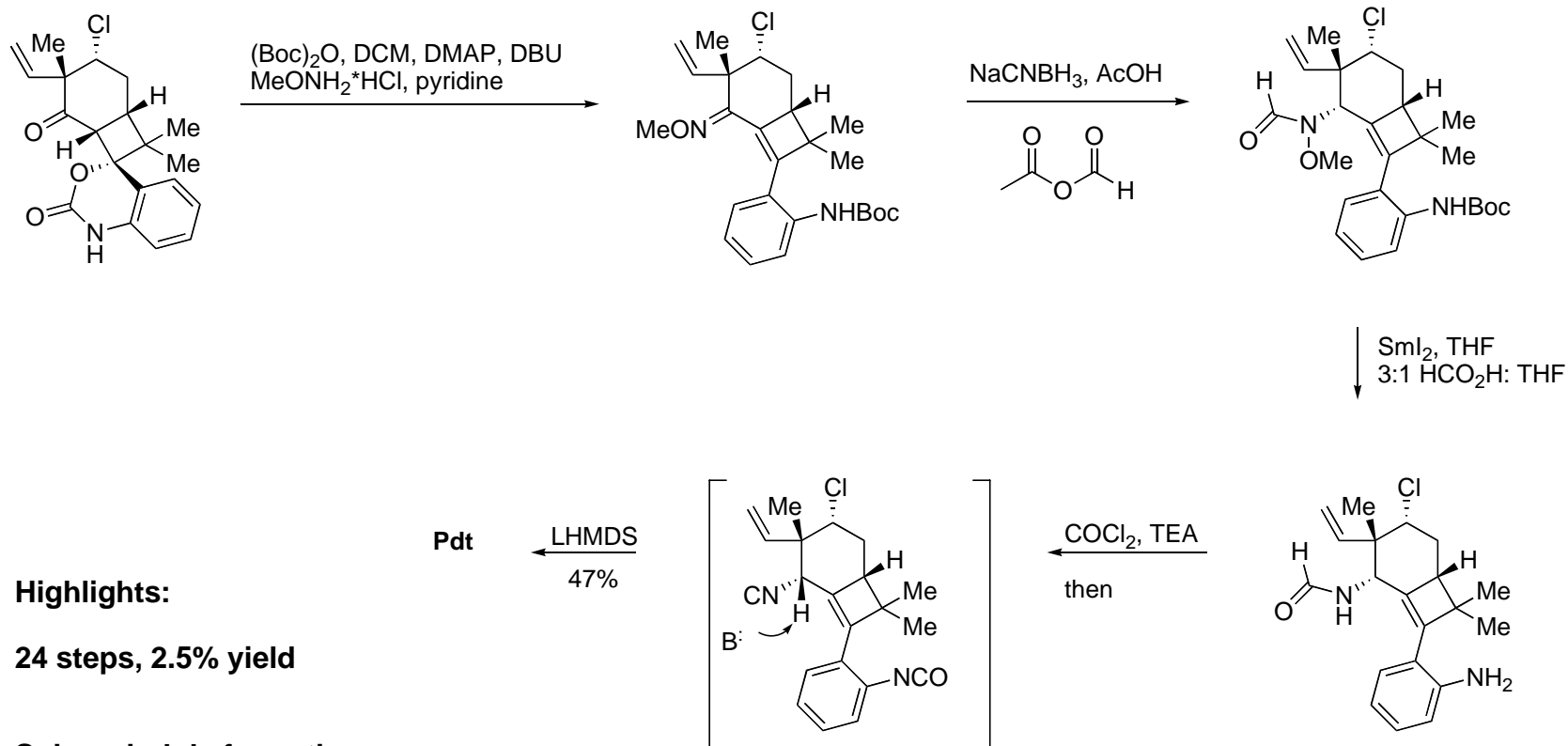
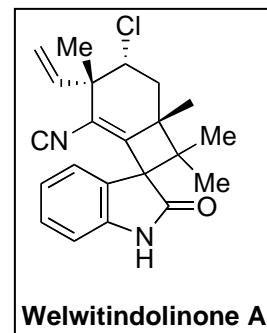


# Wood/Reisman Synthesis



75% yield, 1 diastereomer

# Wood/Reisman Synthesis

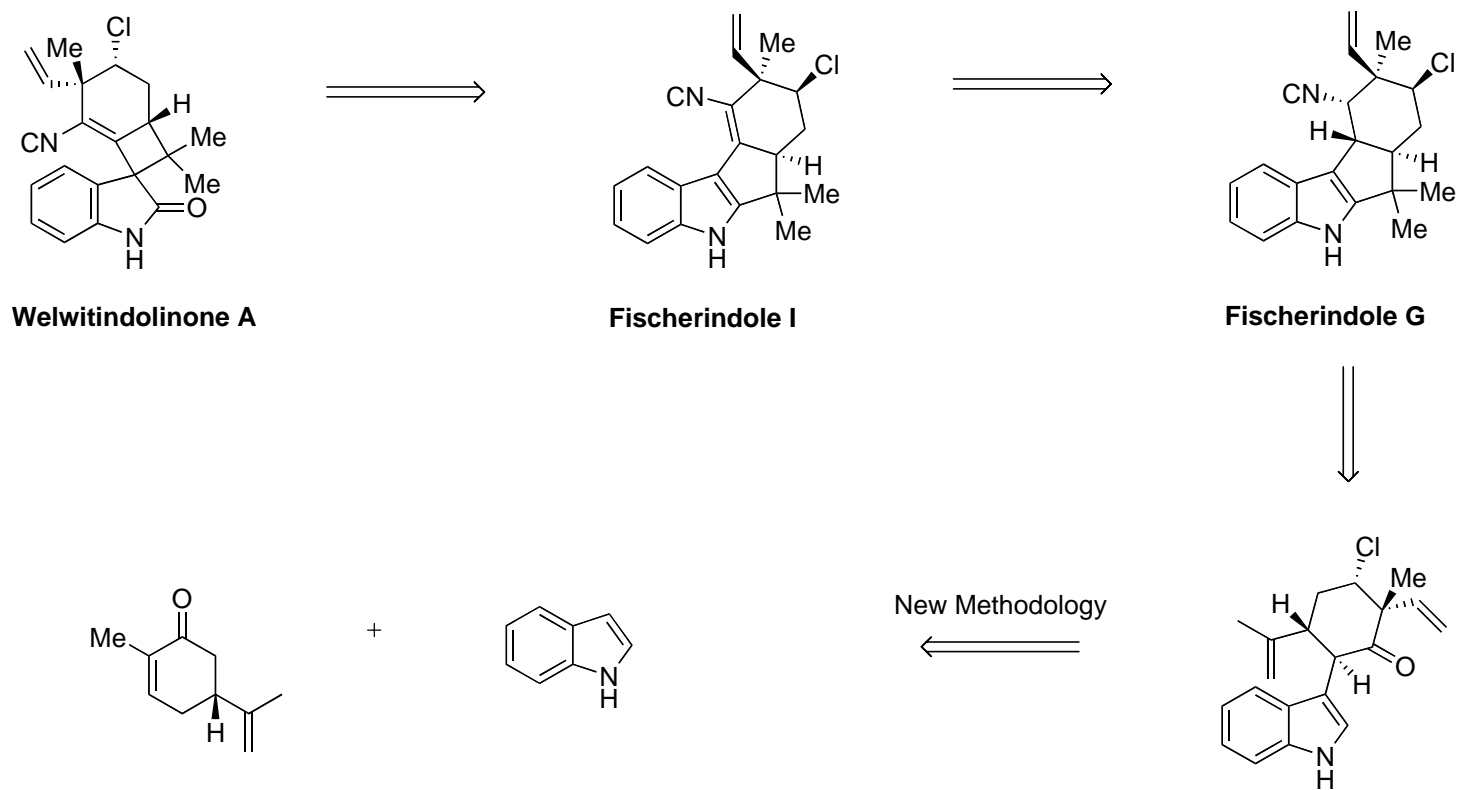


**Highlights:**

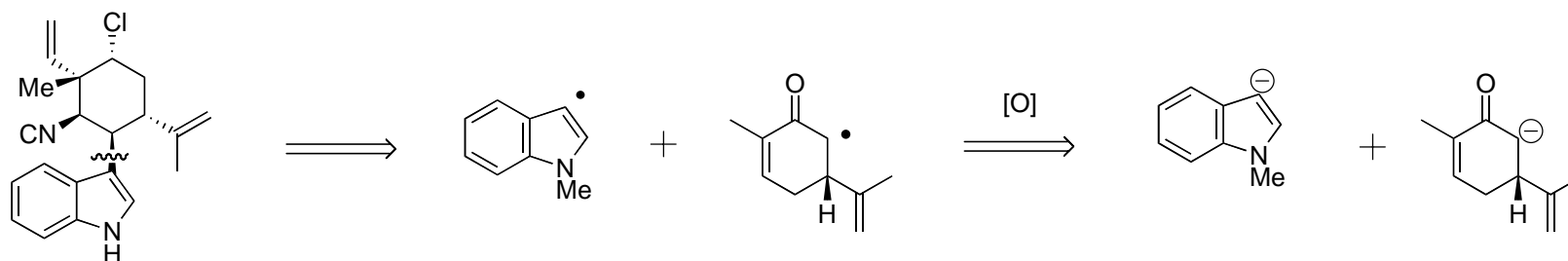
**24 steps, 2.5% yield**

**Spirooxindole formation  
Semi-pinacol to introduce Cl**

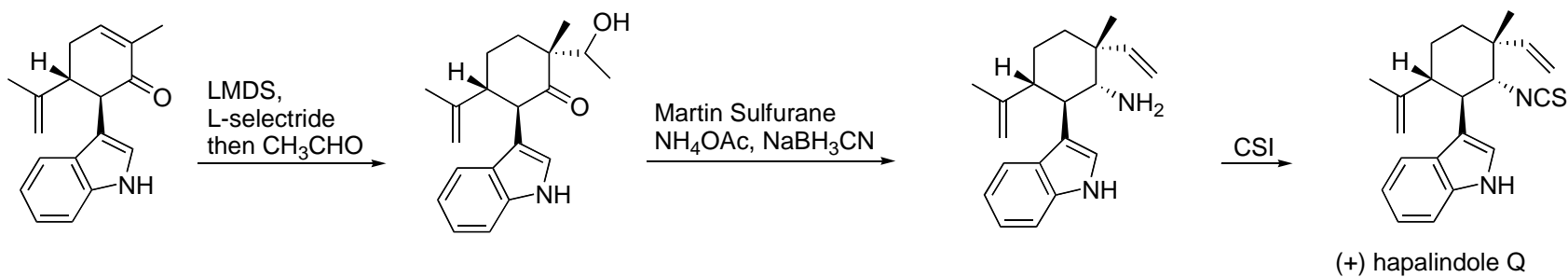
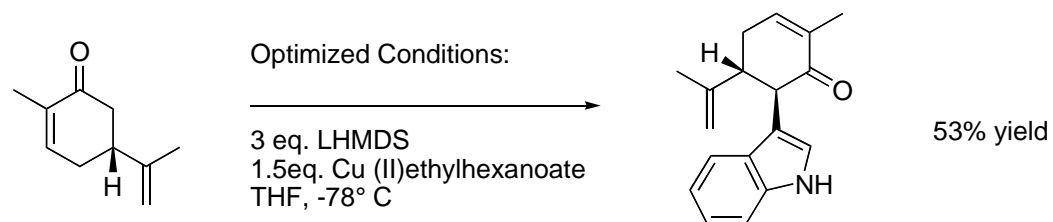
# Baran Retrosynthesis

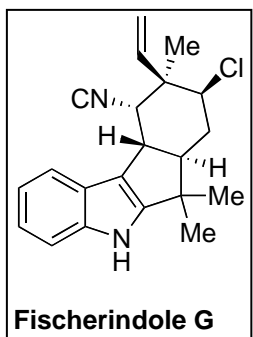


# Indole and Carvone Coupling

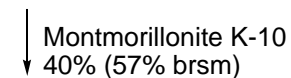
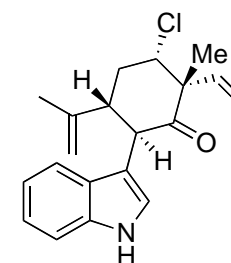
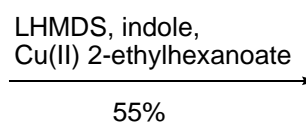
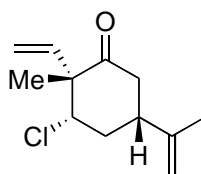
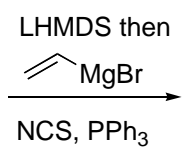
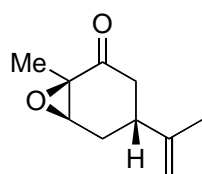
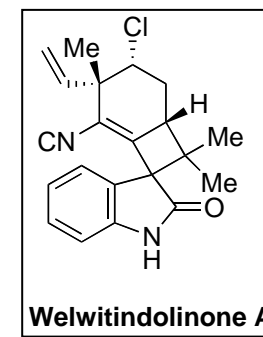


12-epi-Hapalindole E

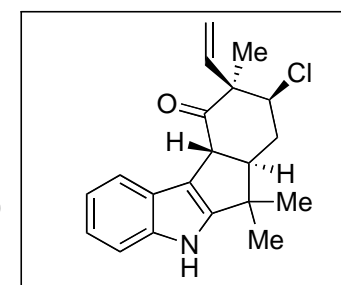
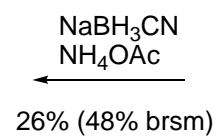
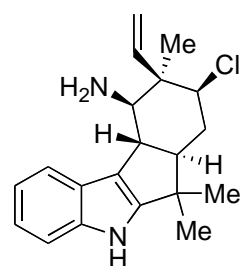


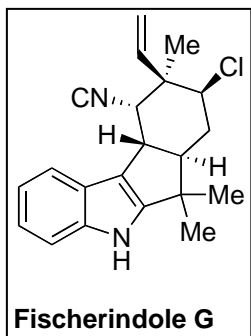


# Baran Synthesis

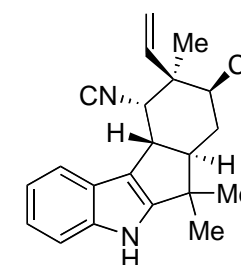
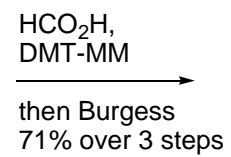
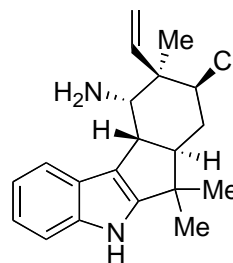
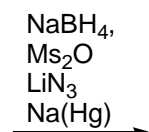
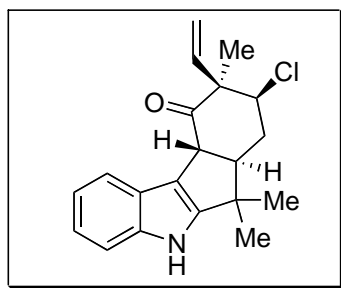
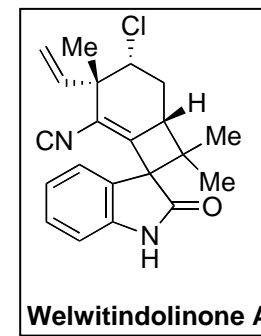


Need Epimer

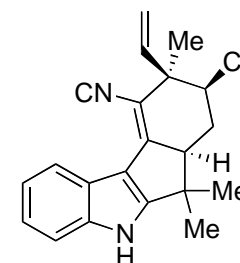
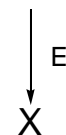




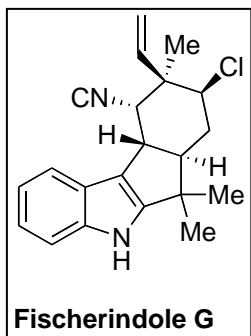
# Baran Synthesis



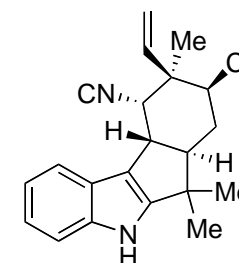
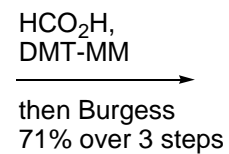
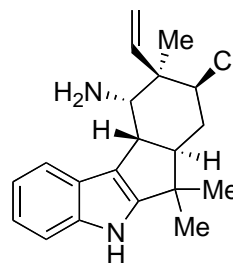
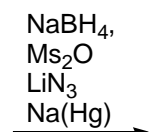
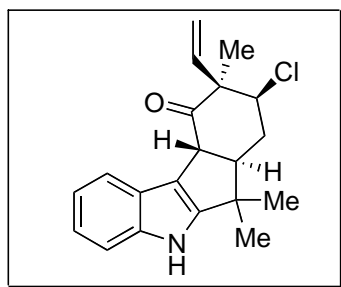
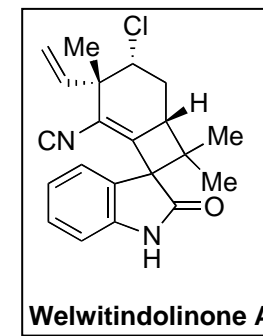
**Fischerindole I**



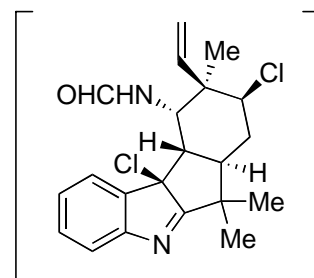
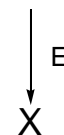
**Fischerindole G**



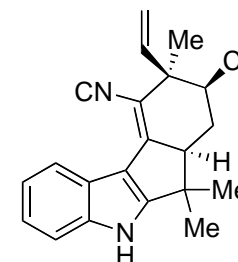
# Baran Synthesis



**Fischerindole I**

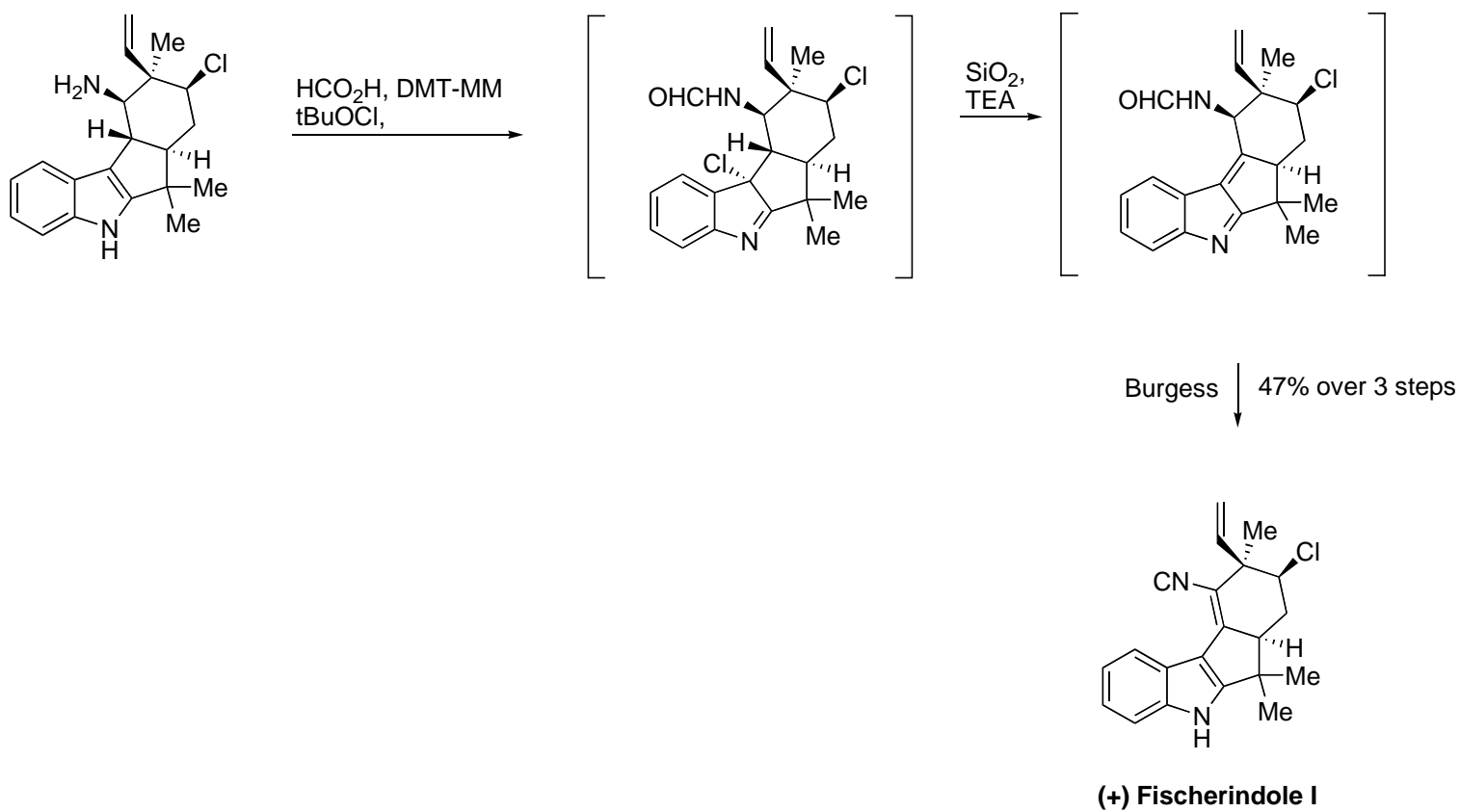
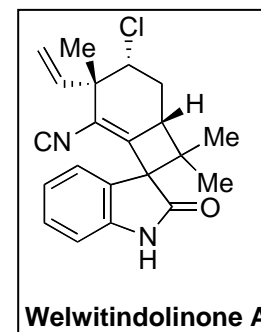


Can't do syn elimination

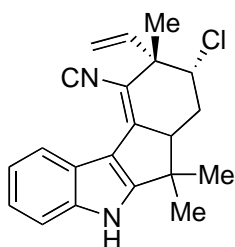
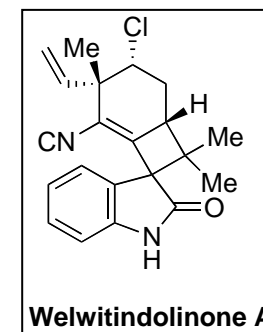


**Fischerindole G**

# Baran Synthesis



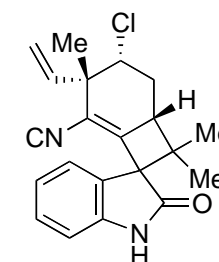
# Baran Synthesis



**(-) Fischerindole I**

1.5 eq of freshly prepared t-BuOCl  
in THF, -30° C for 1 min then solvent removal  
dissolution in THF/H<sub>2</sub>O/TFA  
(95:4:1) at 0° C for 5 min to rt

28%

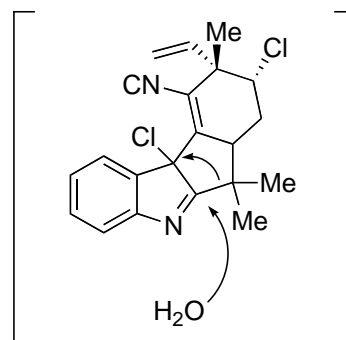


**(+) Welwitindolinone A**

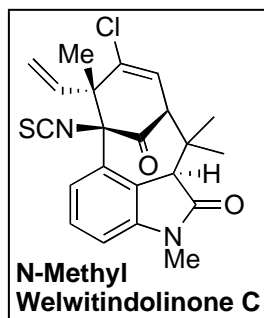
**Highlights:**

**8 steps, 0.12%**

**Enantioselective synthesis**  
**Oxidative coupling of indole, carvone**  
**Biomimetic oxidative contraction**

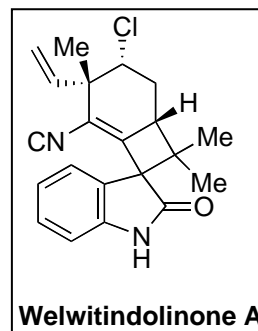


# Summary:



**4 approaches**

**No total synthesis**



**1 racemic synthesis**

**1 enantioselective synthesis  
from (-) fischerindole I**