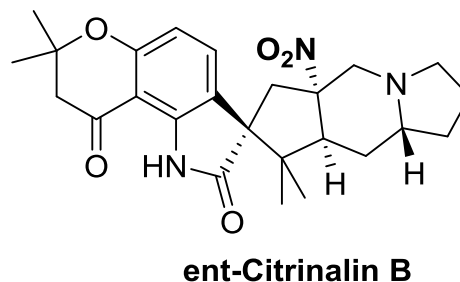
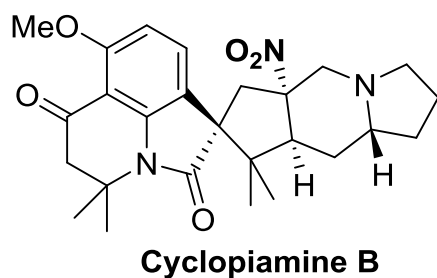


Total synthesis and isolation of citrinalin and cyclopiamine congeners

R. J. Andersen, S. J. Miller, D. J. Tantillo,
R. G. S. Berlinck, R. Sarpong

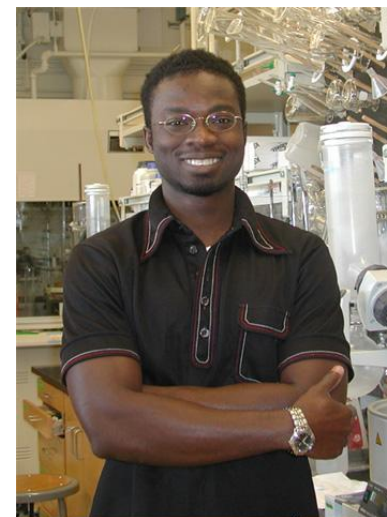
Nature, **2014**, 509, 318–324



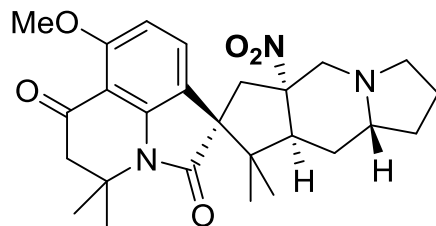
Introduction

- > Richmond Sarpong, Born in 1974 in Ghana
 - Ph.D. in Princeton University under the supervision of Prof. Martin F. Semmelhack (2001)
 - Postdoctoral Fellow in Caltech with Prof. Brian M. Stoltz (2001-2004)
 - Full Professor of Chemistry at University of California, Berkeley since 2014

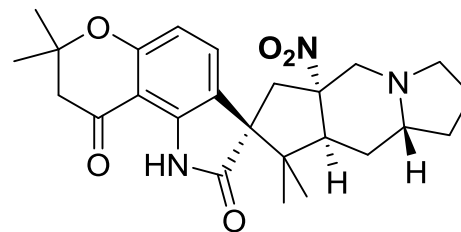
- > Research Interests :
 - Organic and Organometallic Chemistry
 - Total synthesis of natural products



Introduction

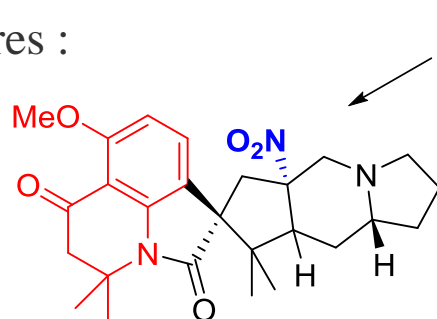


Cyclopiamine B



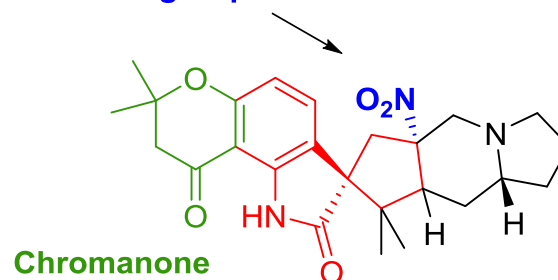
ent-Citrinalin B

- > Belong to prenylated alkaloids family
- > Diverse range of bioactivities (*e.g.* anti-tumor, antibacterial...)
- > Cyclopiamines A and B discovered in 1979 in a toxinogenic strain of *Penicillium cyclopium*
- > Citrinalins A and B discovered in 2010 in a strain of *Penicillium citrinum*
- > Structural features :



Tetrahydroquinolone

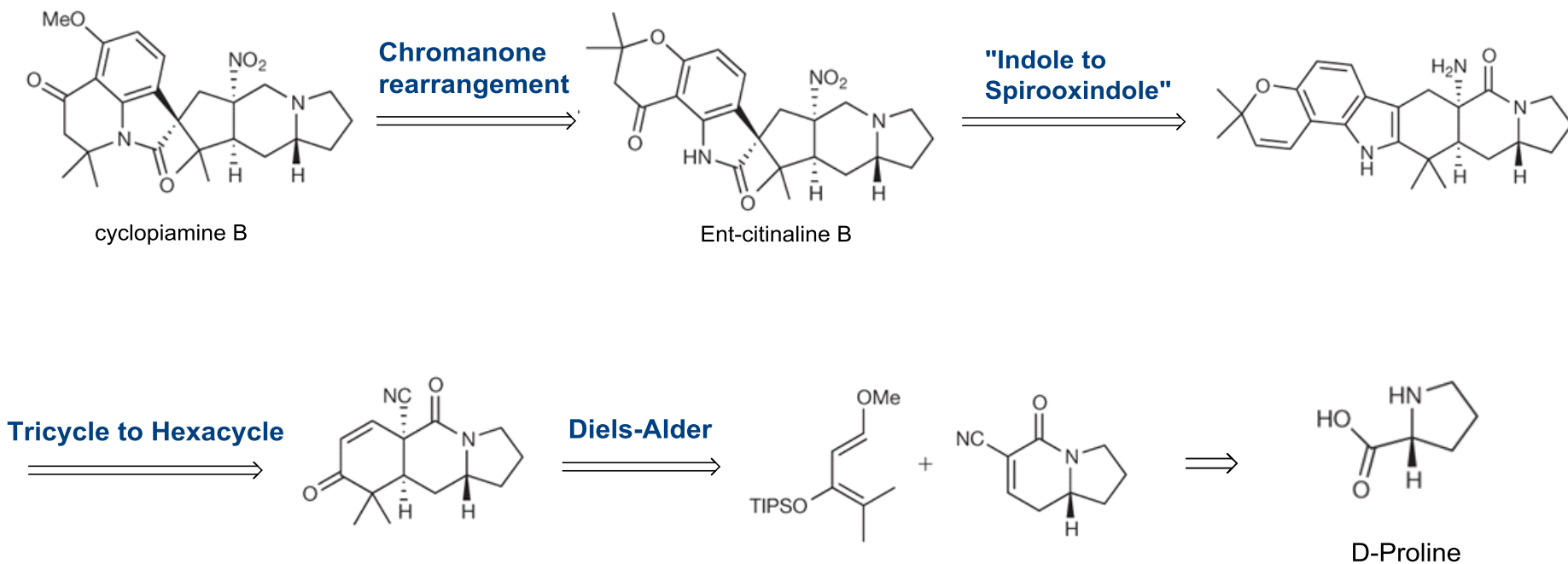
Aliphatic Nitro group



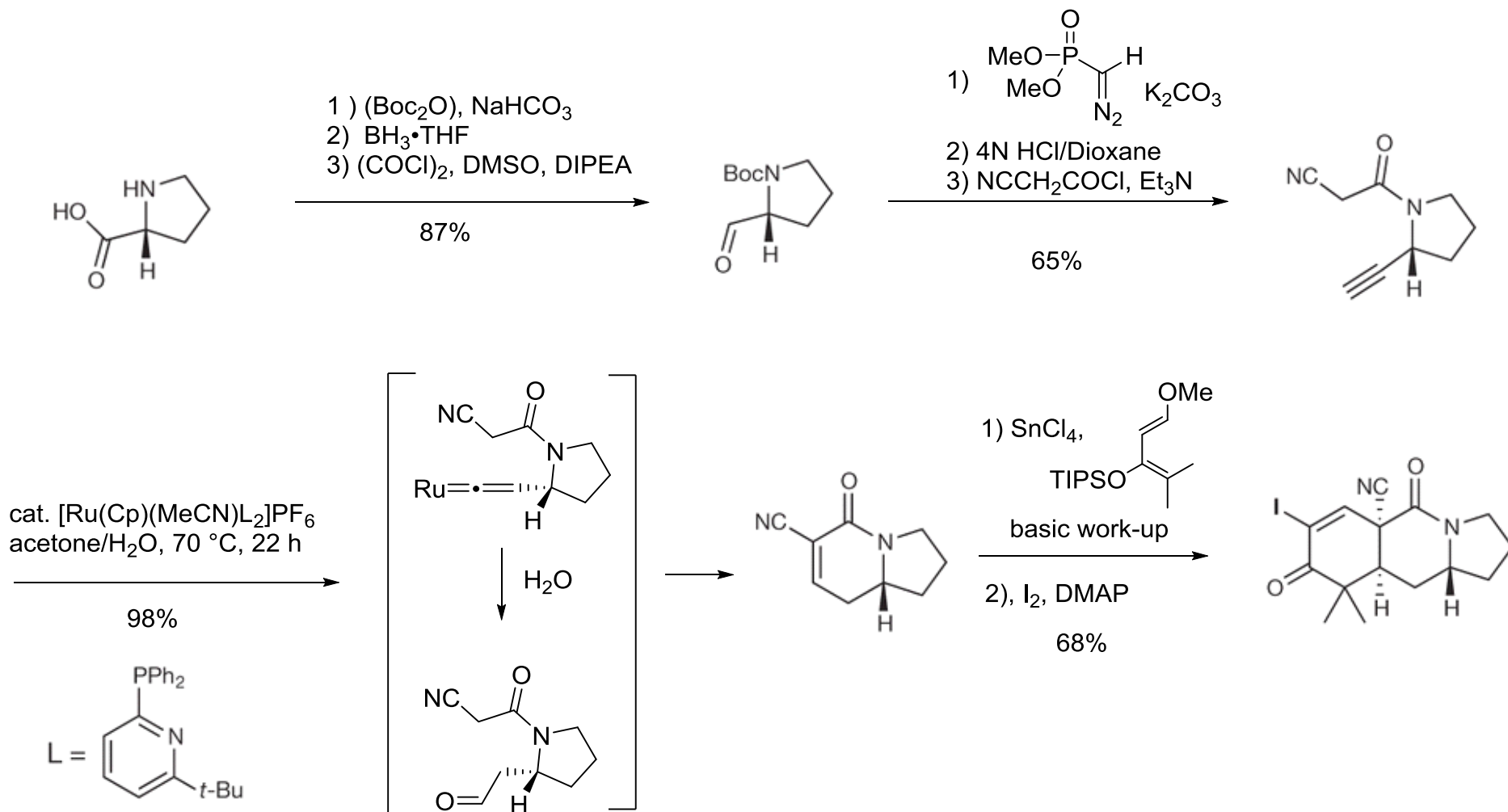
Spirooxindole

Retrosynthetic Analysis

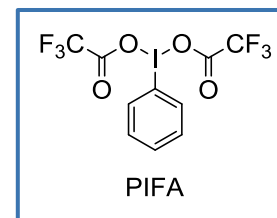
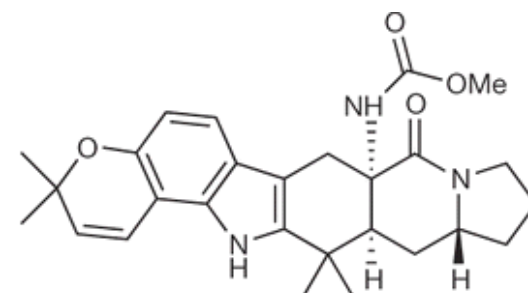
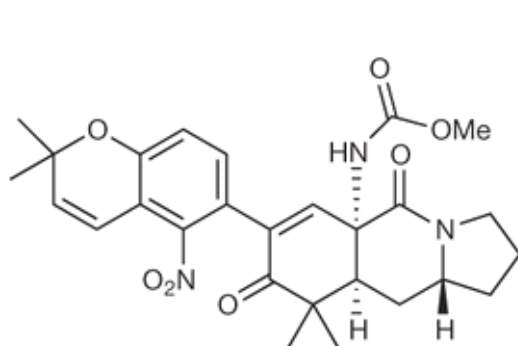
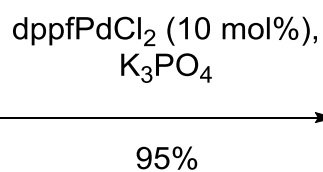
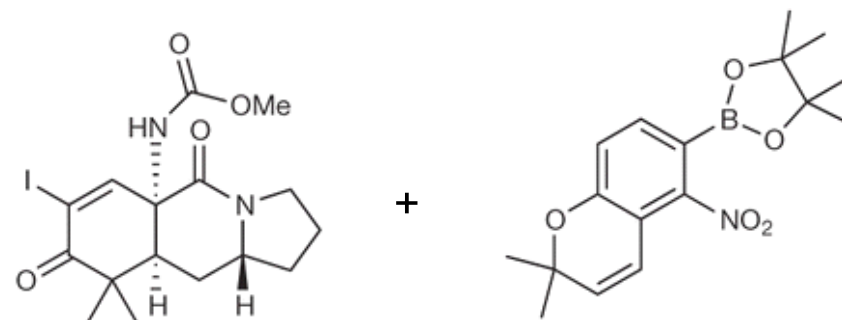
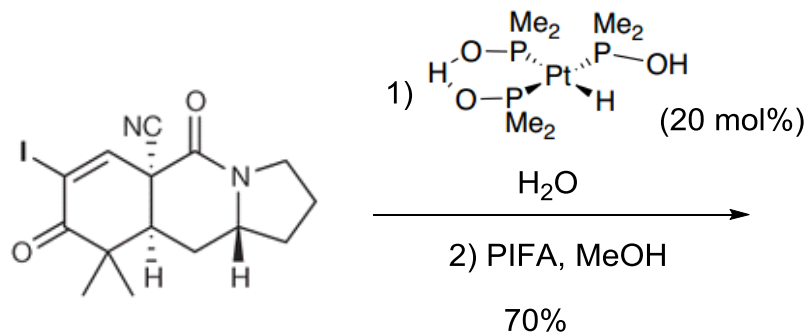
> Two Products obtained from D-Proline



Synthesis of tricycle

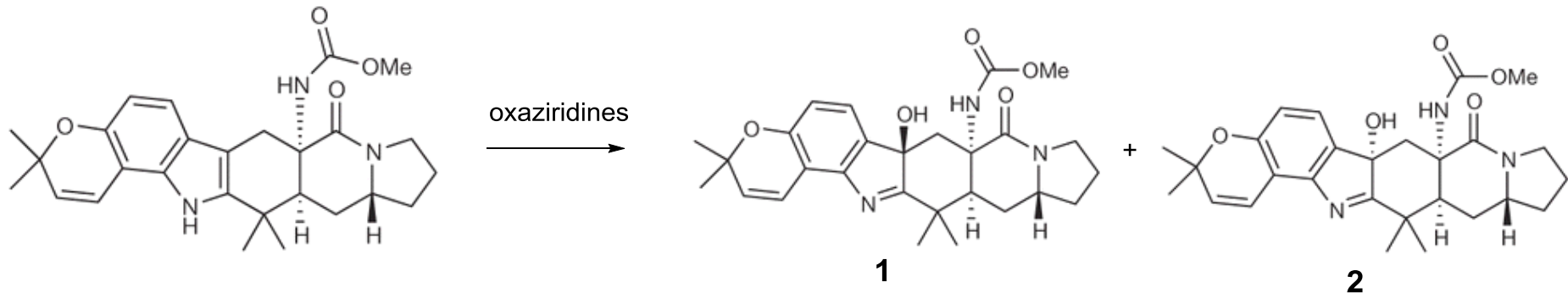


Synthesis of hexacycle

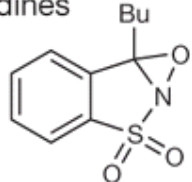


Oxygenation of Indole

> 1st strategy : oxygenation of indole to hydroxyindolenine with Davis' oxaziridines

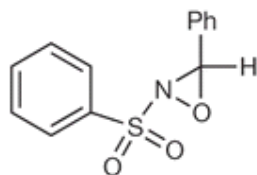


Oxaziridines



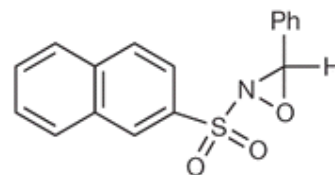
(3.0 equiv.)

61% : traces



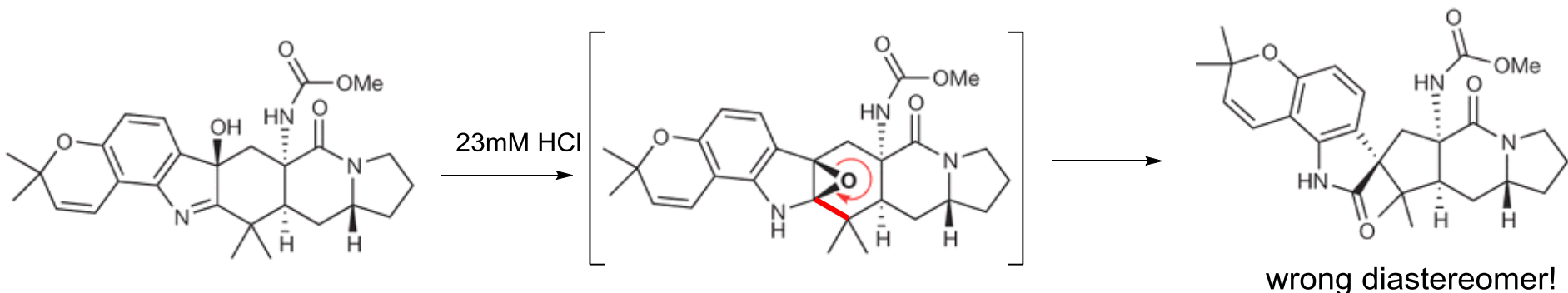
(3.0 equiv.)

4:1



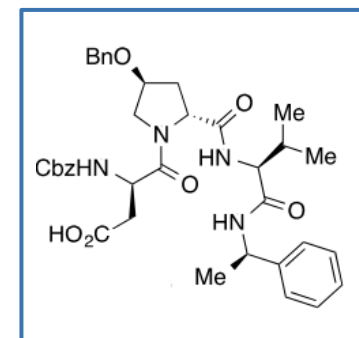
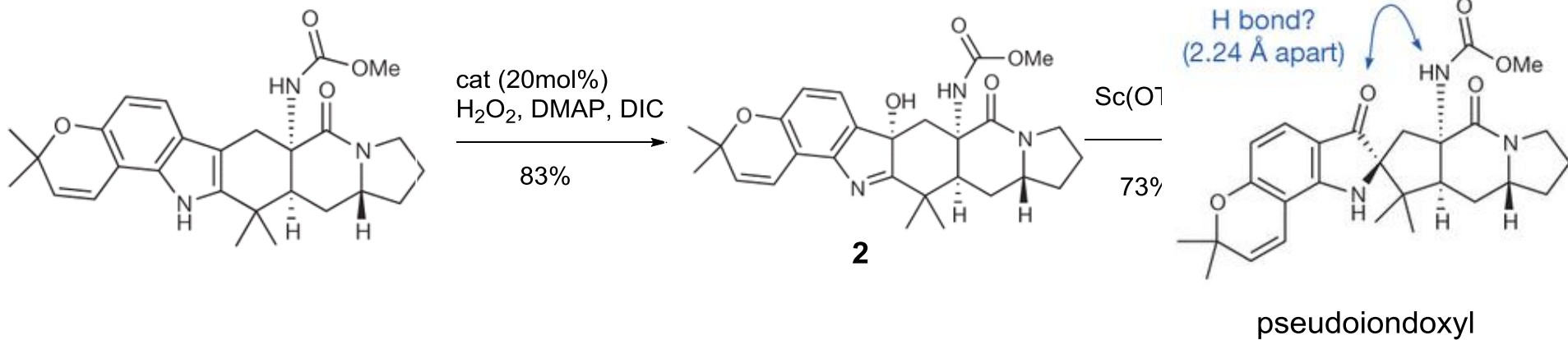
(3.0 equiv.)

1:1



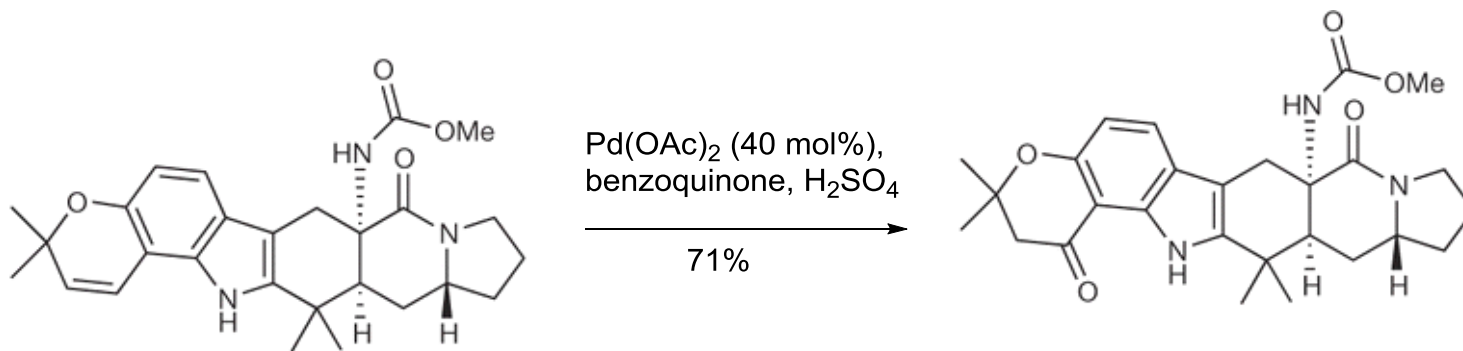
Oxygenation of Indole

- > 2nd strategy : oxygenation of indole to hydroxyindolenine with a peptide catalyst

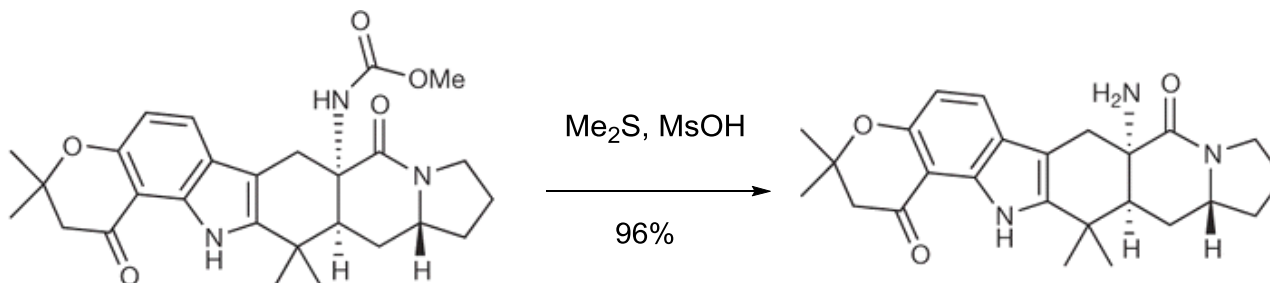


Oxygenation of Indole

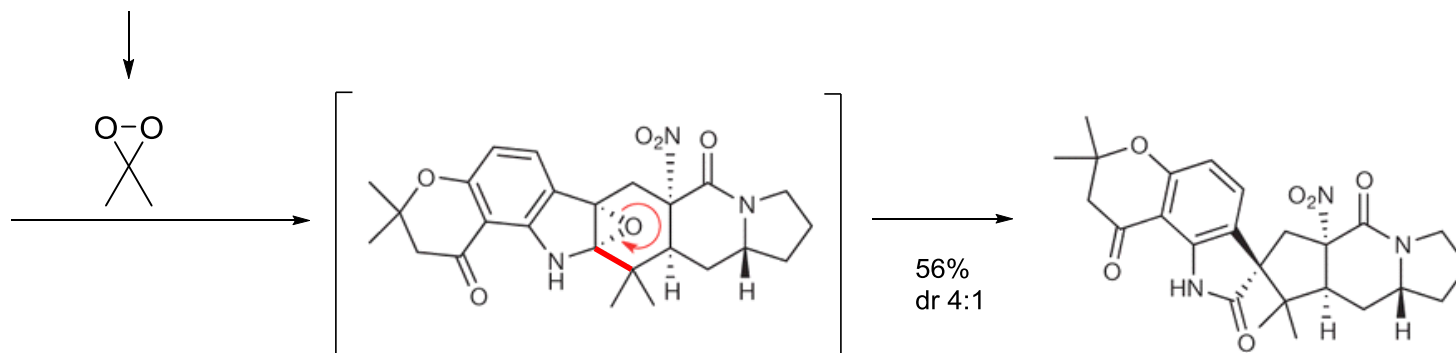
- > 3d strategy : Wacker oxidation



Synthesis of Spirooxindole



Oxone (10 eq), NaHCO_3 ,
acetone and H_2O

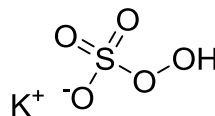


X-ray structure of the major one

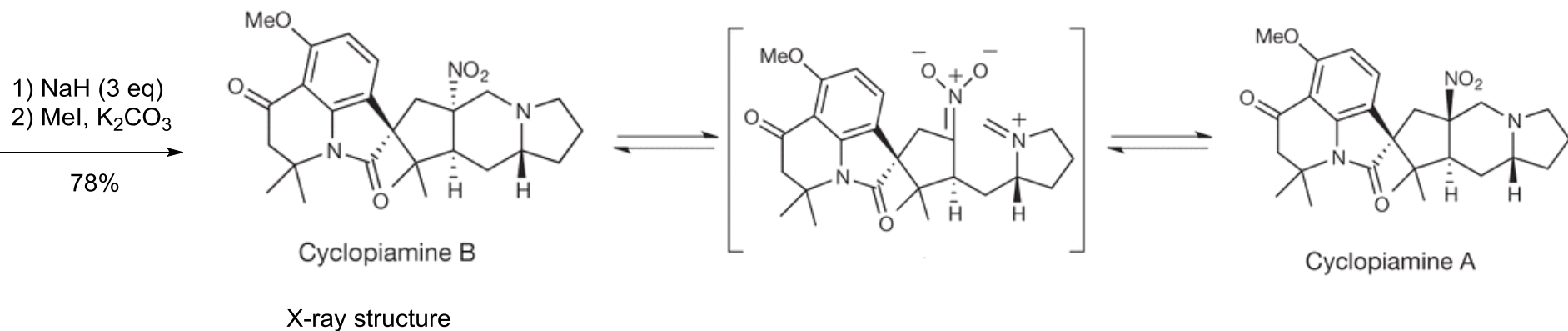
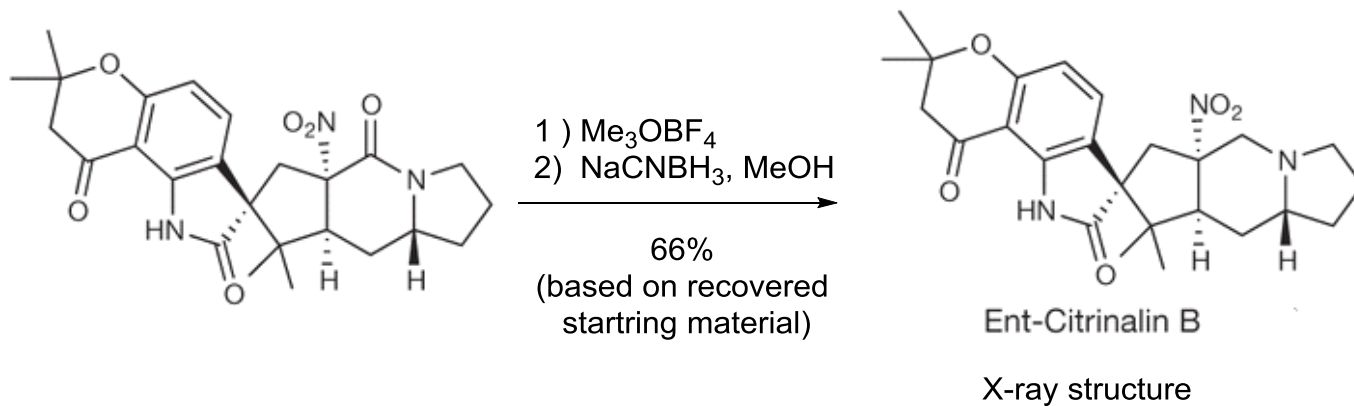
Oxone



Active specie

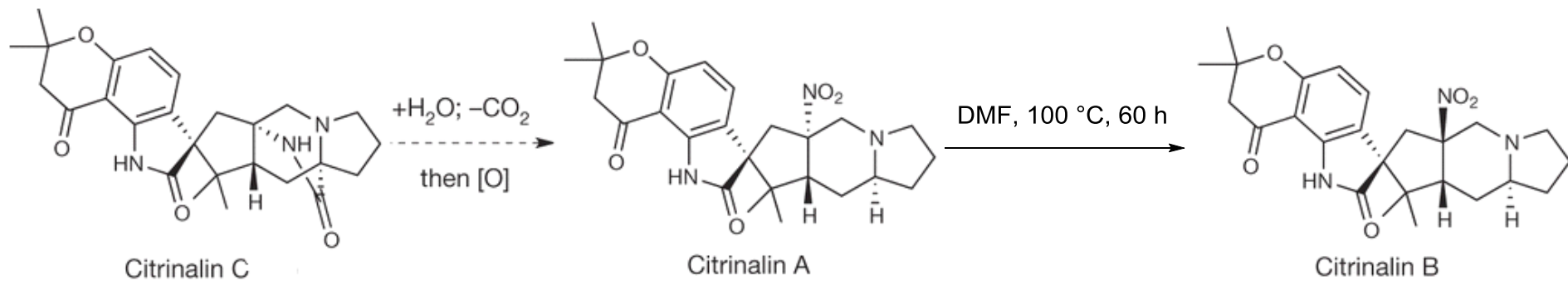


Final Products



Outlook

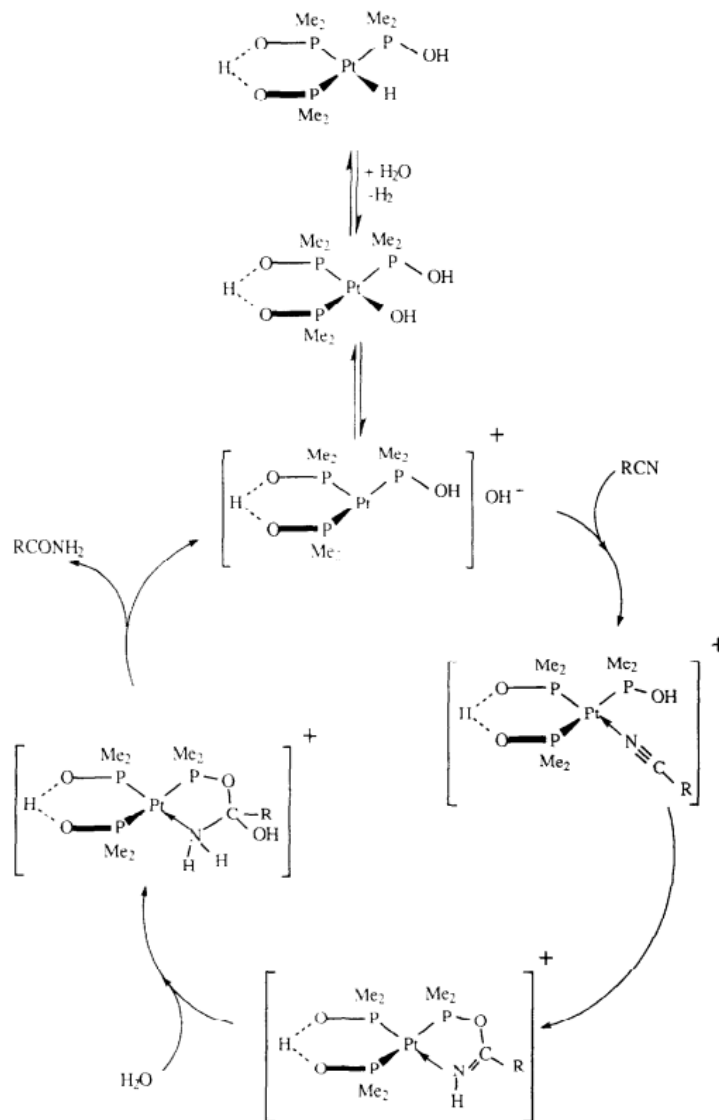
> Connections between Citrinalins



- > Ent-citrinalin B : 19 steps from D-proline, 5.5% overall yield
- > Cyclopiamine B : 21 steps from D-proline, 4.3% overall yield
- > Strategy for conversion of indole to spirooxindole was well explored
- > Chemoselective methods properly used
- > Structures established the structures unambiguously
- > Insight into the biogenesis of these natural products : possible formation of the cyclopiamines from the citrinalins

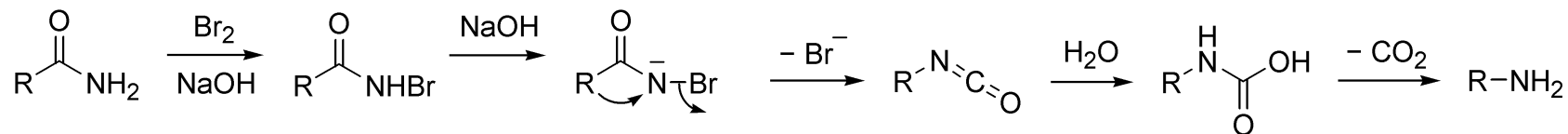
Thank you for your kind attention!

Hydrolysis of Nitrile to Carboxamide

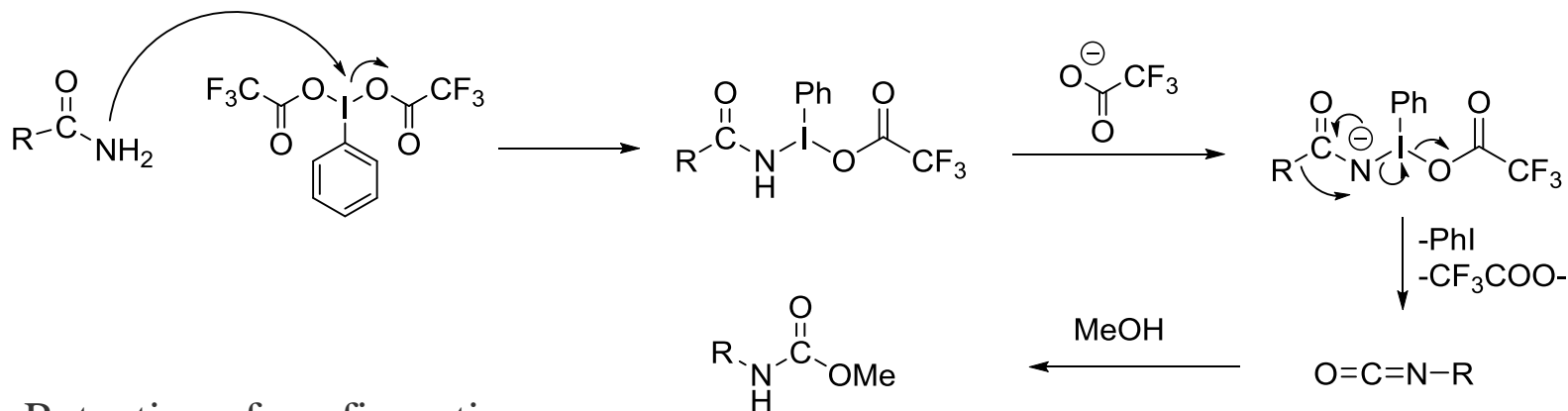


Formation of carbamate

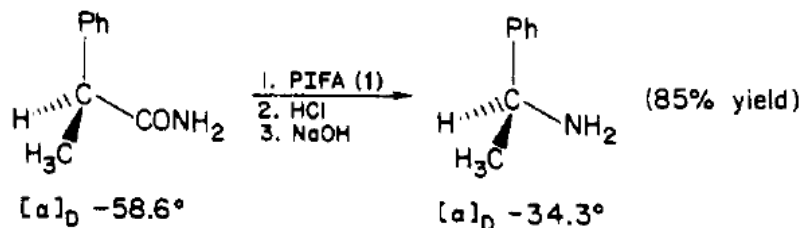
> Reminder Hofmann rearrangement



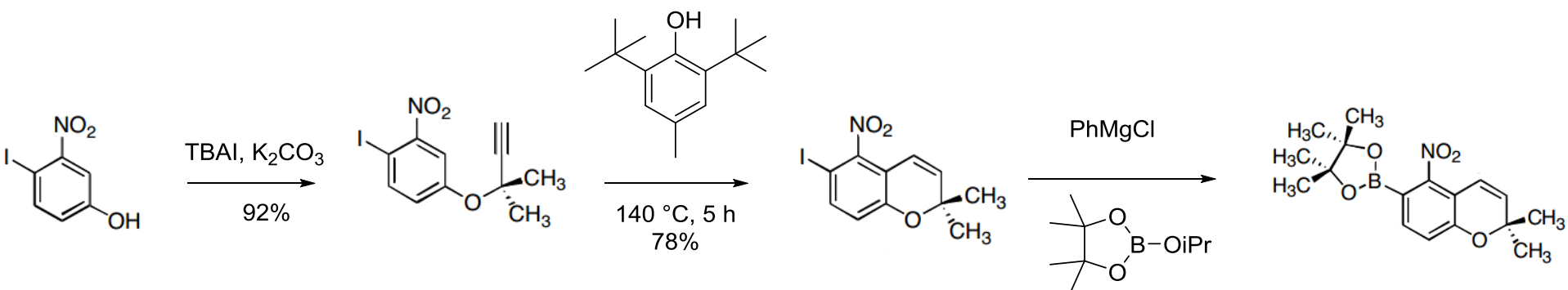
> Mechanism with PIFA



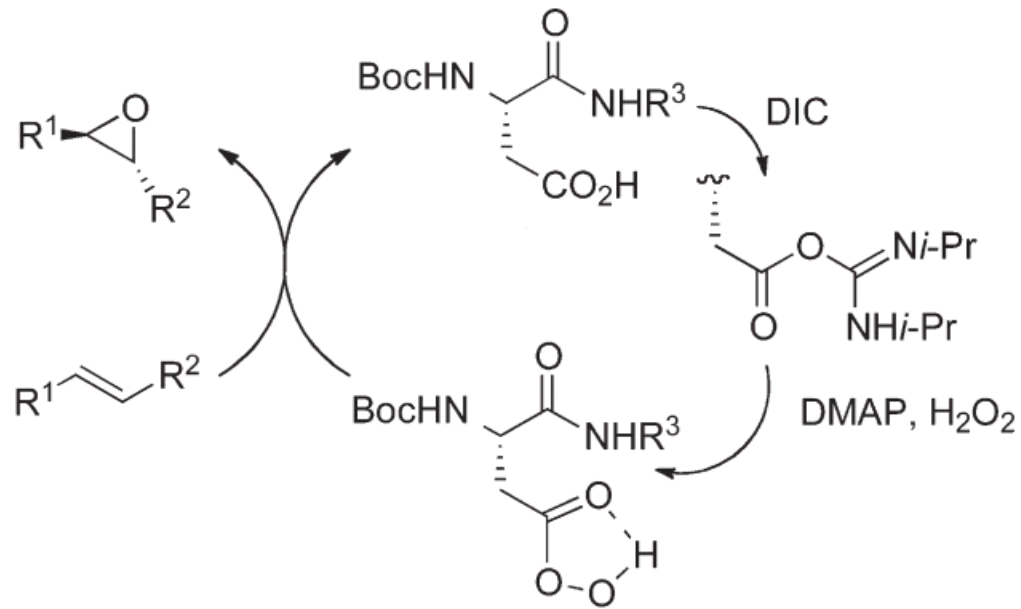
> Retention of configuration



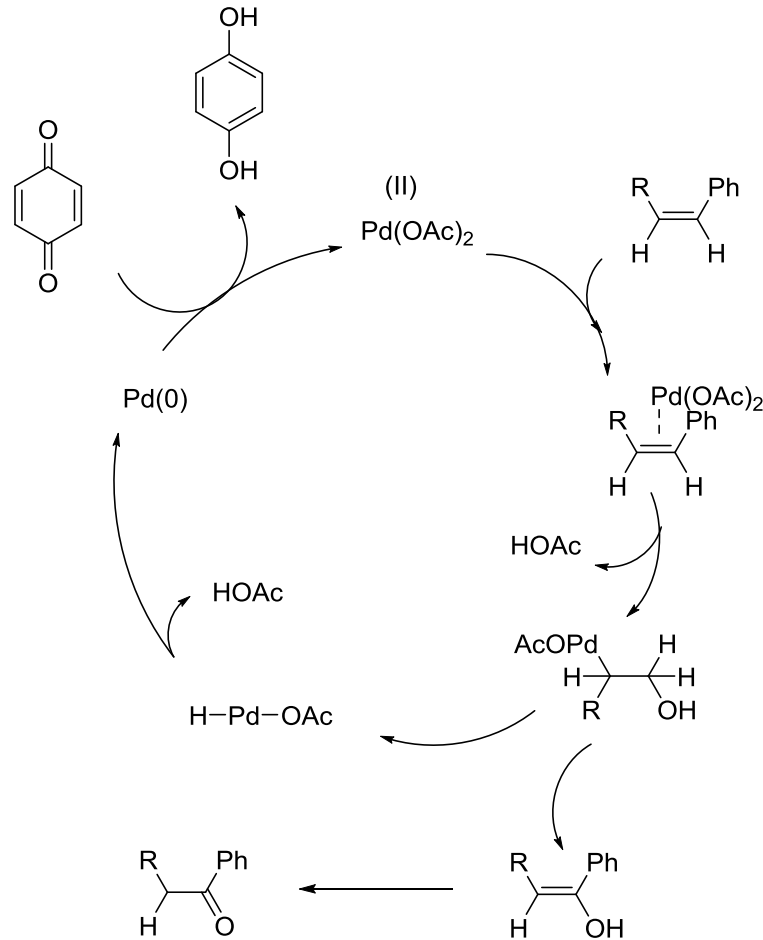
Synthesis of Boronic ester



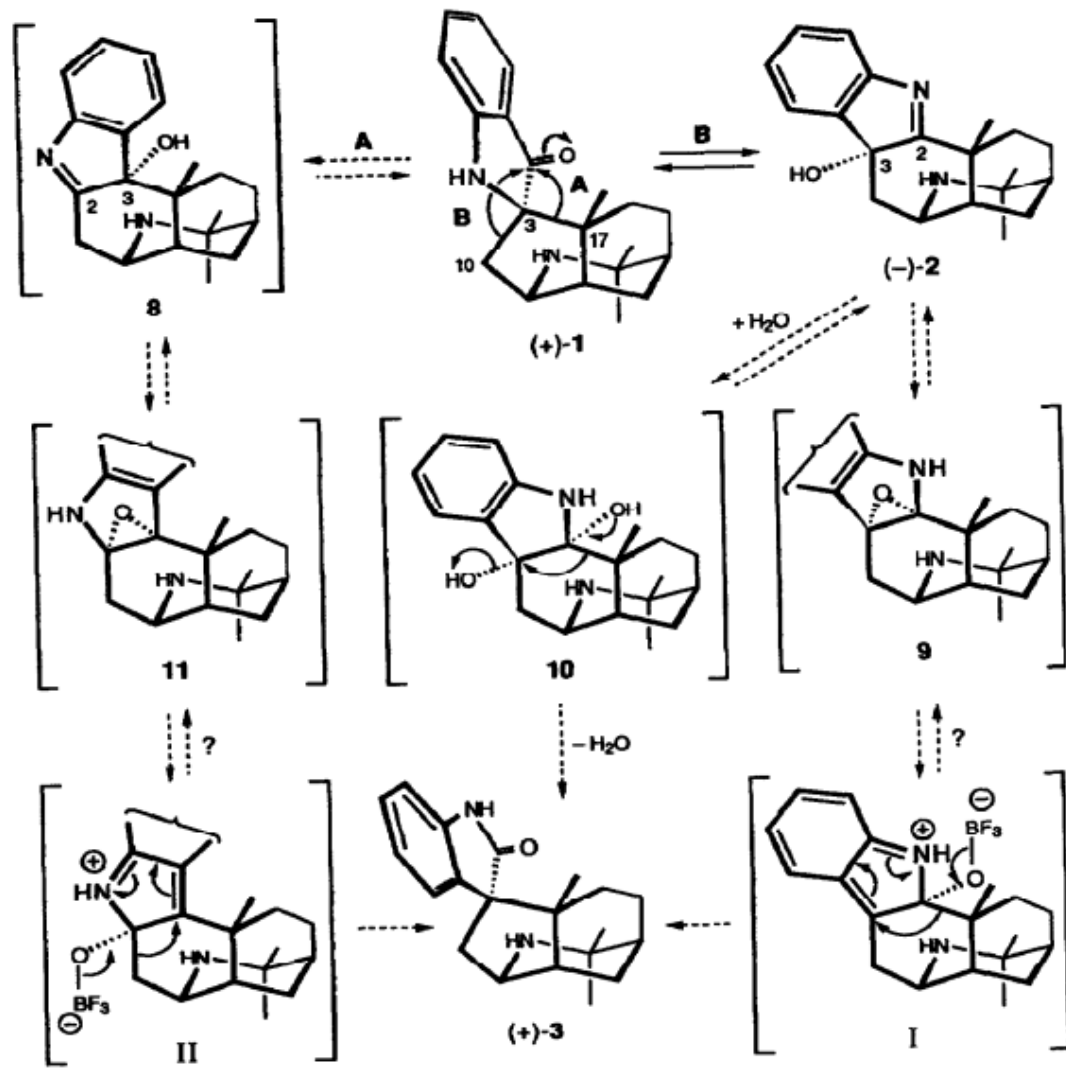
Peptide catalyst



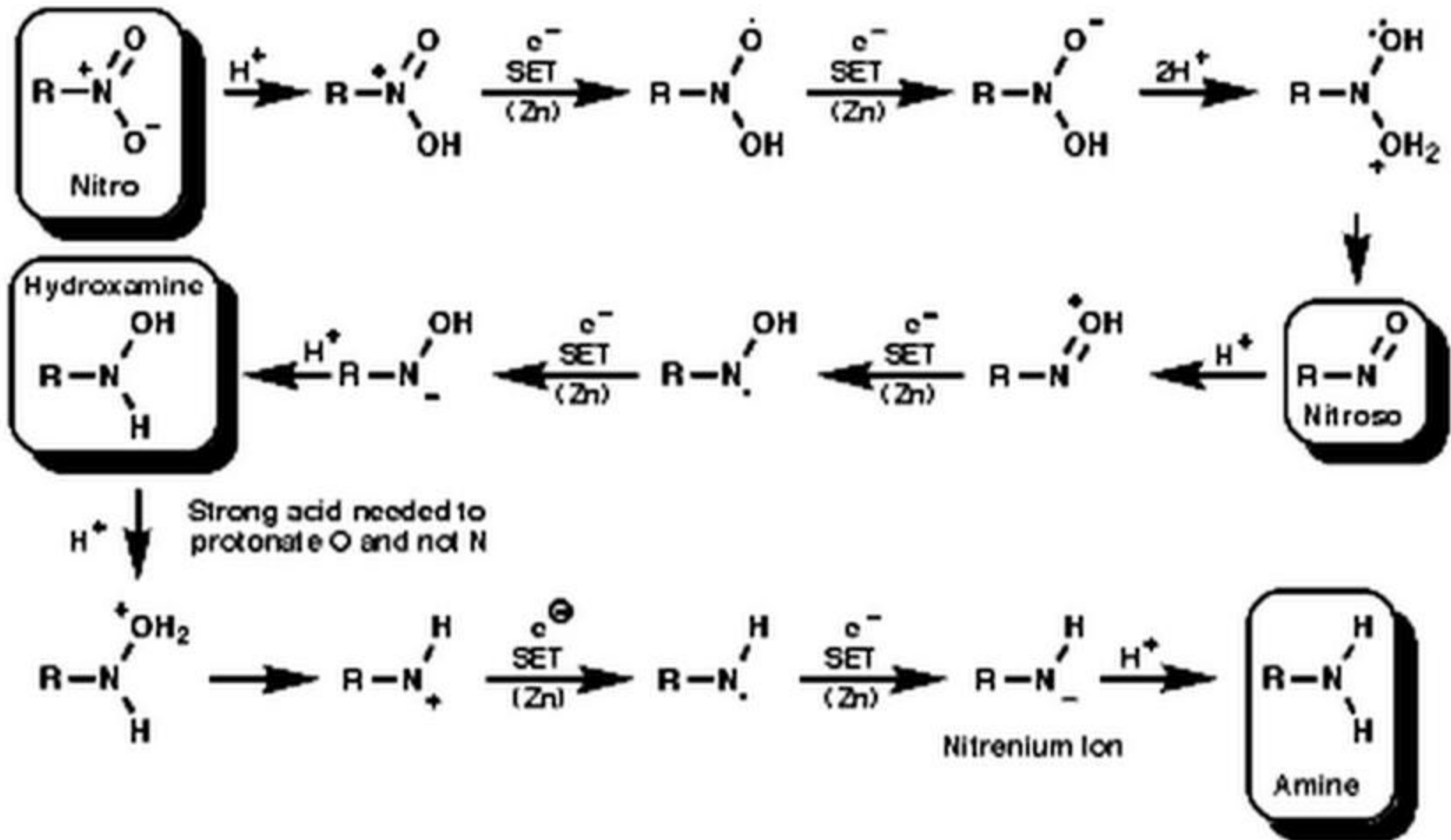
Wacker Process



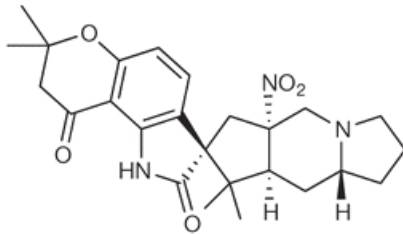
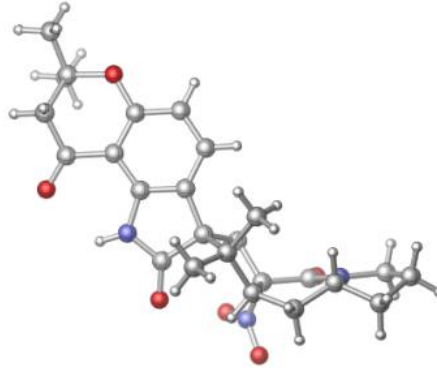
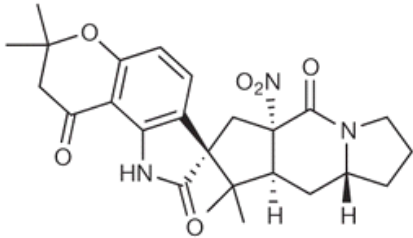
Rearrangement spirooxindole



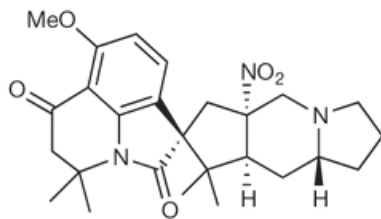
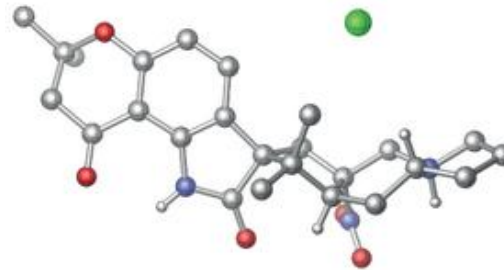
Reduction Nitro to amine



X-ray structures



Ent-Citrinalin B



Cyclopiamine B

