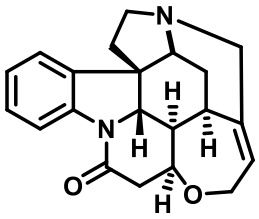
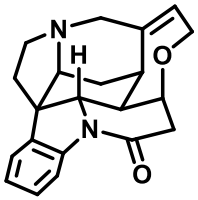
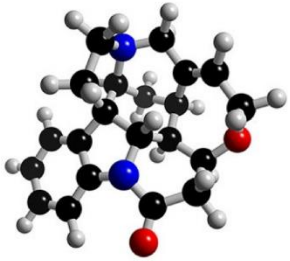
Total Syntheses of Strychnine







Dong Group Meeting

Jianchun Wang

May 27, 2015

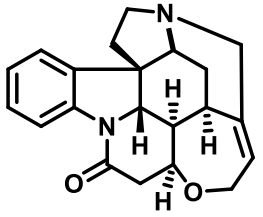
Facts about strychnine

- A legendary poison

  - ✓ Isolated from *Strychnos nux-vomica* in 1818
  - ✓ A famous poison: 50 mg/adult
  - ✓ Related to many dramatic deaths in novels or poetry

- Determination of its structure

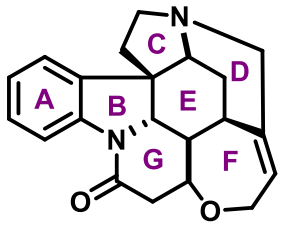
  - ✓ 400+ papers about its structure by degradative methods
  - ✓ Woodward proved its structure by UV in 1948
  - ✓ Structure confirmed by X-ray

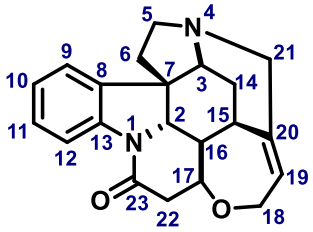


"For its molecular size it is the most complex substance known." - Robert Robinson (1952)

Molecular complexity and synthetic challenges

- Numbering system throughout today's talk





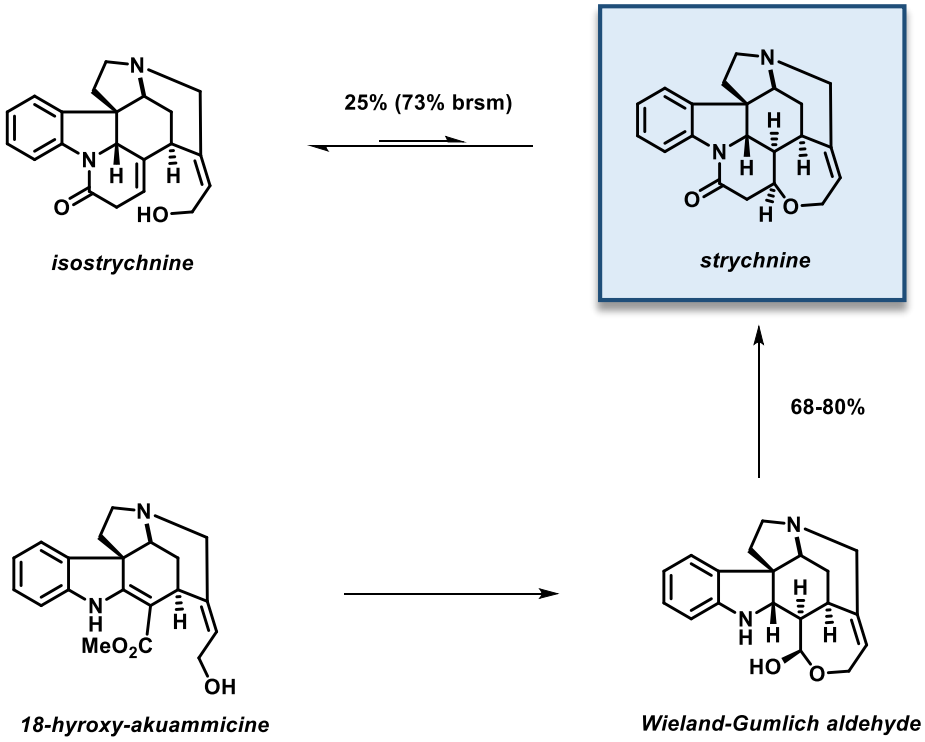
- Structural analysis
  - ✓ 7 fused ring
  - ✓ 6 stereocenter

- Synthetic challenges
  - ✓ C7 spirocenter
  - ✓ E ring

Reliable endgames for strychnine synthesis

The real targets!

- Degradation studies

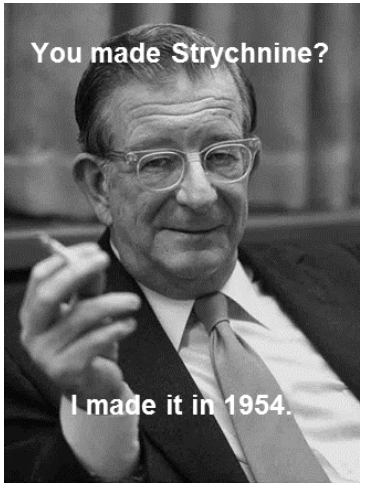


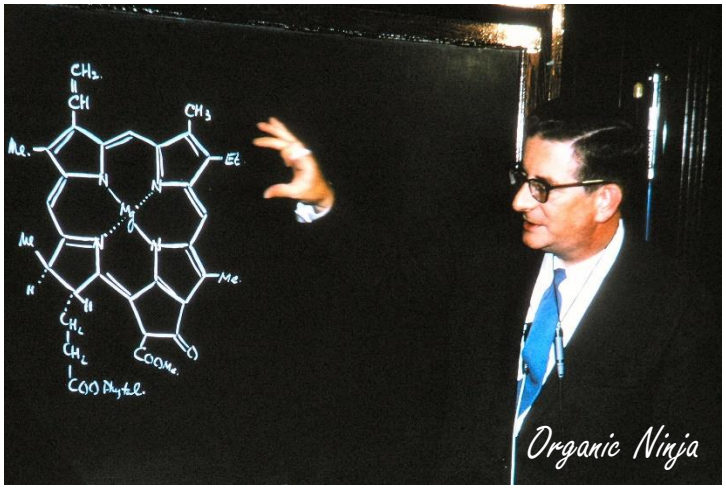
Woodward's synthesis (1954)

About Robert B. Woodward

- About Woodward

1937	Ph.D. Massachusetts Institute of Technology
1965	Nobel prize for his synthesis of complex organic molecules
1973	Vitamin B12 (Woodward-Hoffman rule)



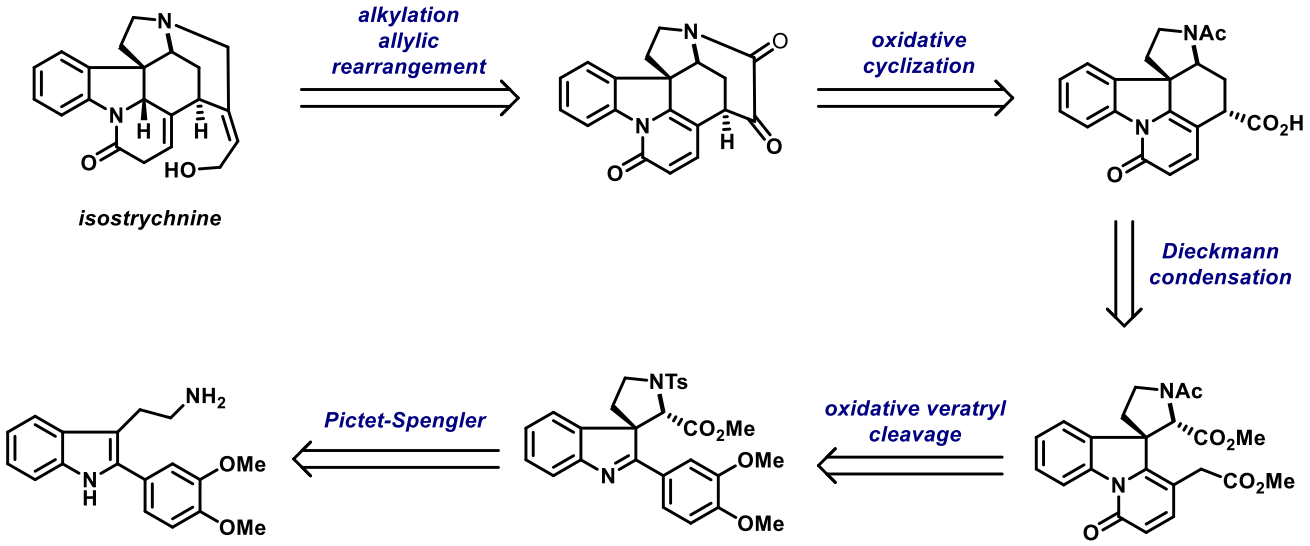


"If we cannot make Strychnine, we will take Strychnine." - R. B. Woodward

Woodward's synthesis (1993)

Synthesis planning

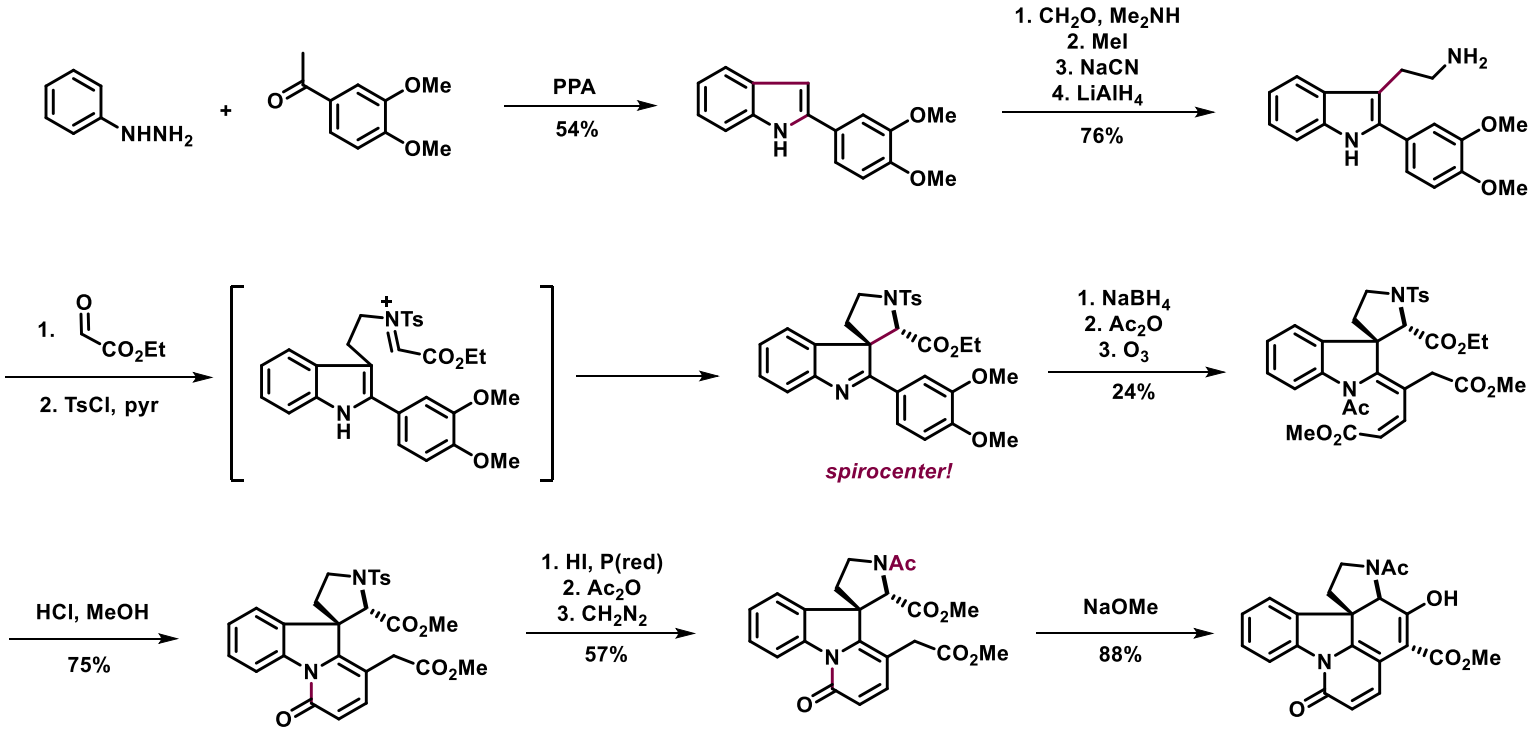
- Pictet-Spengler reaction to build spirocenter



Woodward's synthesis (1993)

Synthetic route

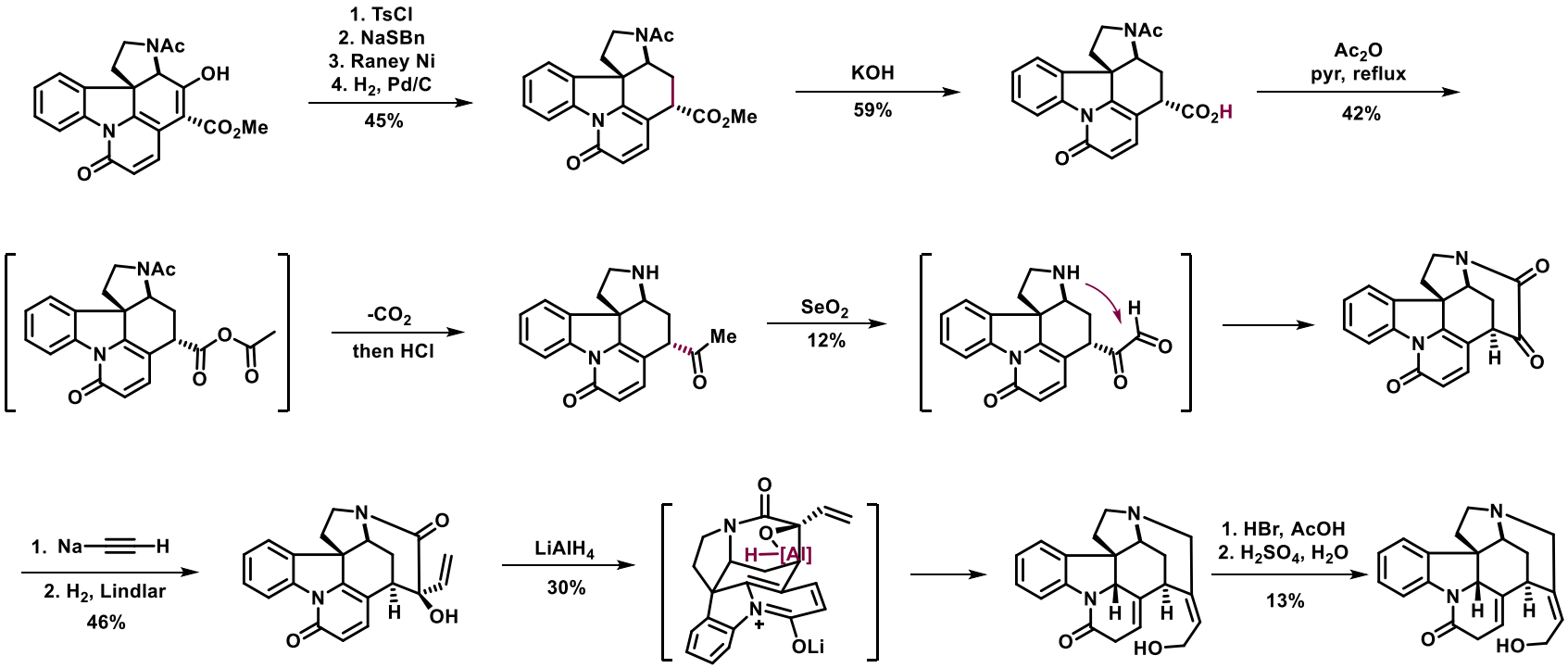
- Step by step synthesis



Woodward's synthesis (1993)

Synthetic route

- Step by step synthesis



Overman's synthesis (1993)

About Larry Overman

- About Overman

1969	Ph.D. University of Wisconsin- Madison
	(Prof. Howard W. Whitlock, Jr.)
1971	Postdoc. Columbia University
	(Prof. Ronald Breslow)
1971-now	Professor of Chemistry University of California, Irvine

- About his group: a small workshop

✓ 5 graduate students

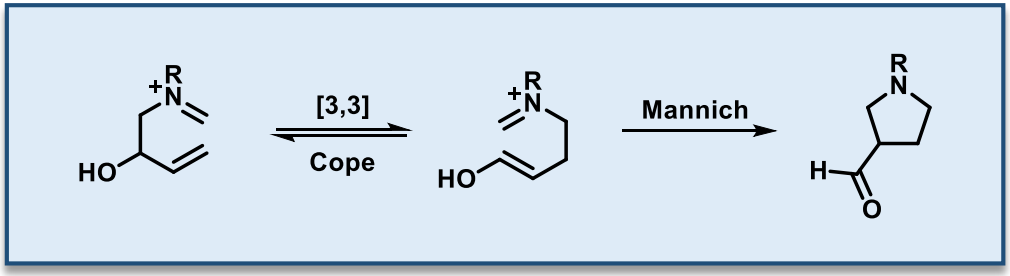
✓ 3 post-docs

✓ 366 publications

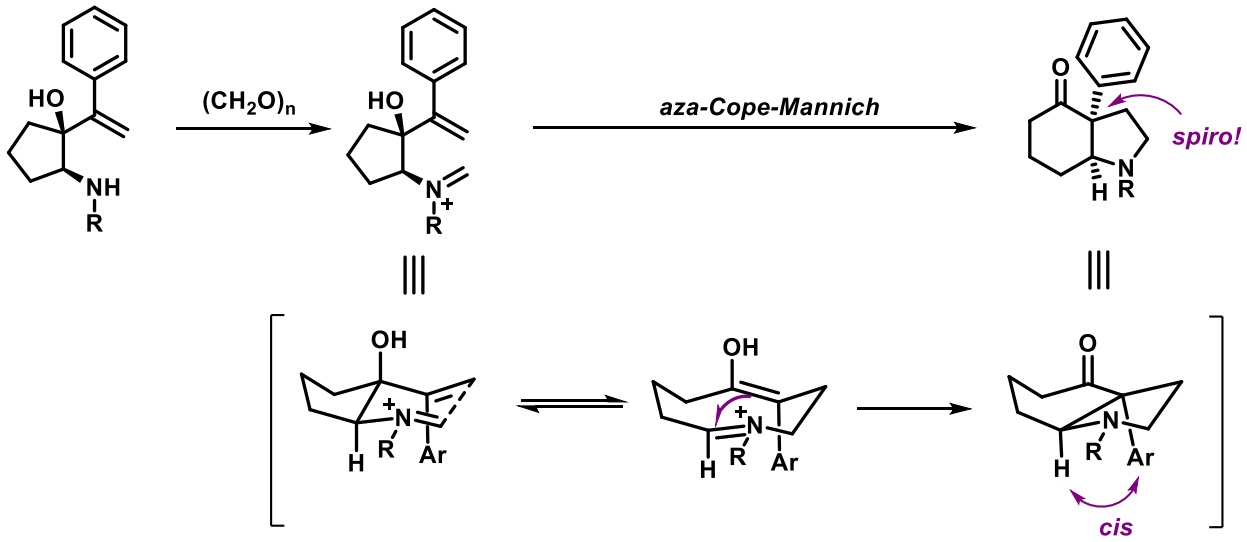
Overman's synthesis (1993)

Aza-Cope-Mannich reaction

- A general reaction scheme



- cis-3a-Aryloctahydroindole unit

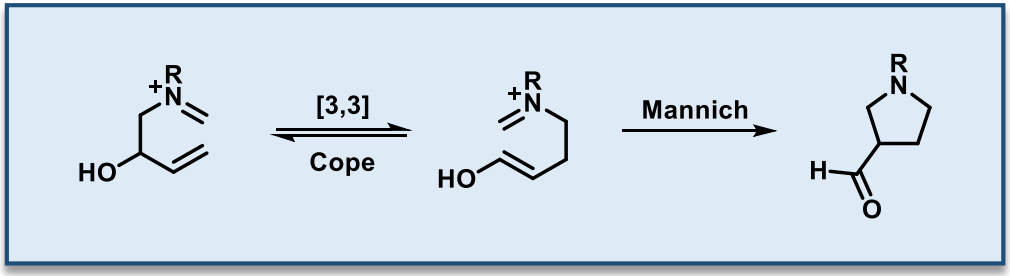


For a review on stories about developing rearrangement reactions, see: *Tetrahedron,* **2009**, *65*, 6432.

Overman's synthesis (1993)

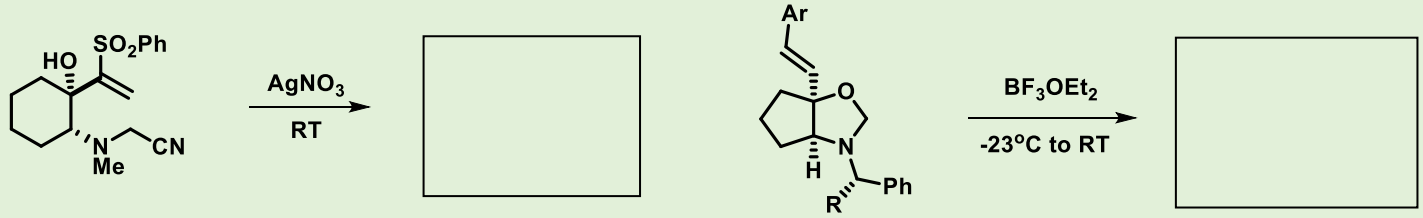
Aza-Cope-Mannich reaction

- A general reaction scheme



- Some examples

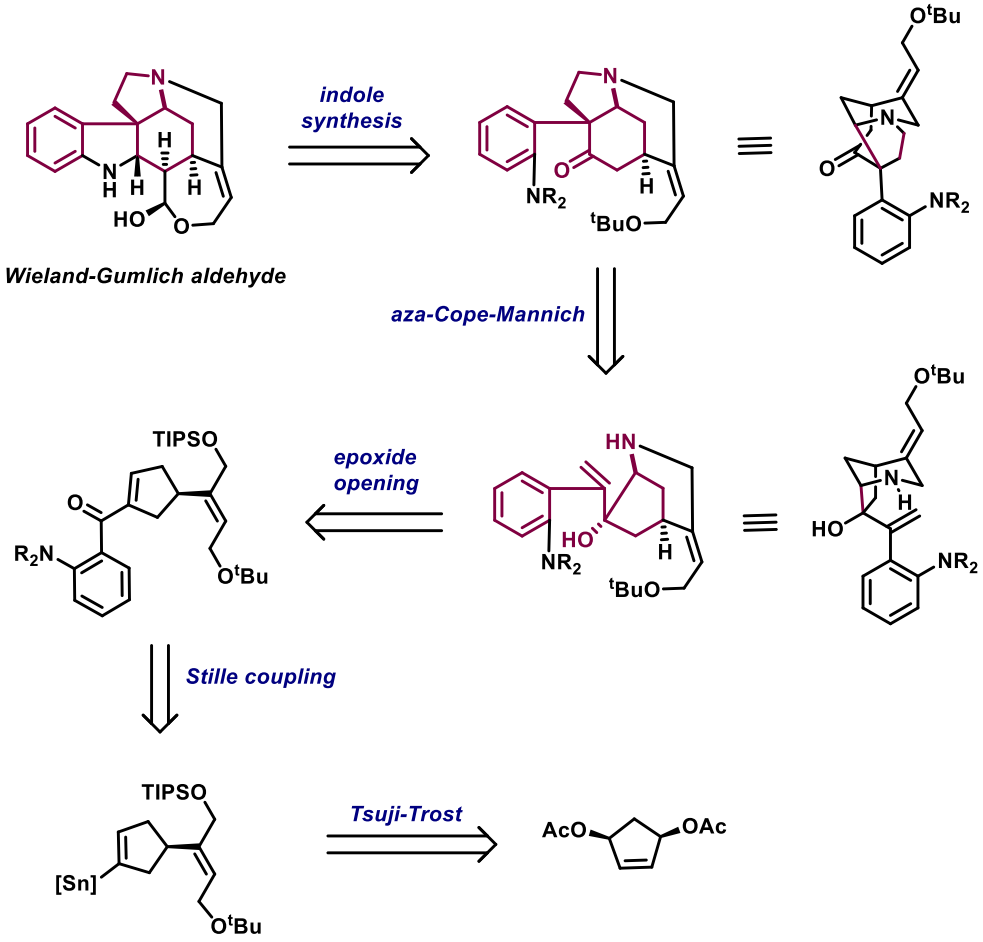
Aza-Cope-Mannich cascade proved to be very powerful in total synthesis. Please complete the following reactions



Overman's synthesis (1993)

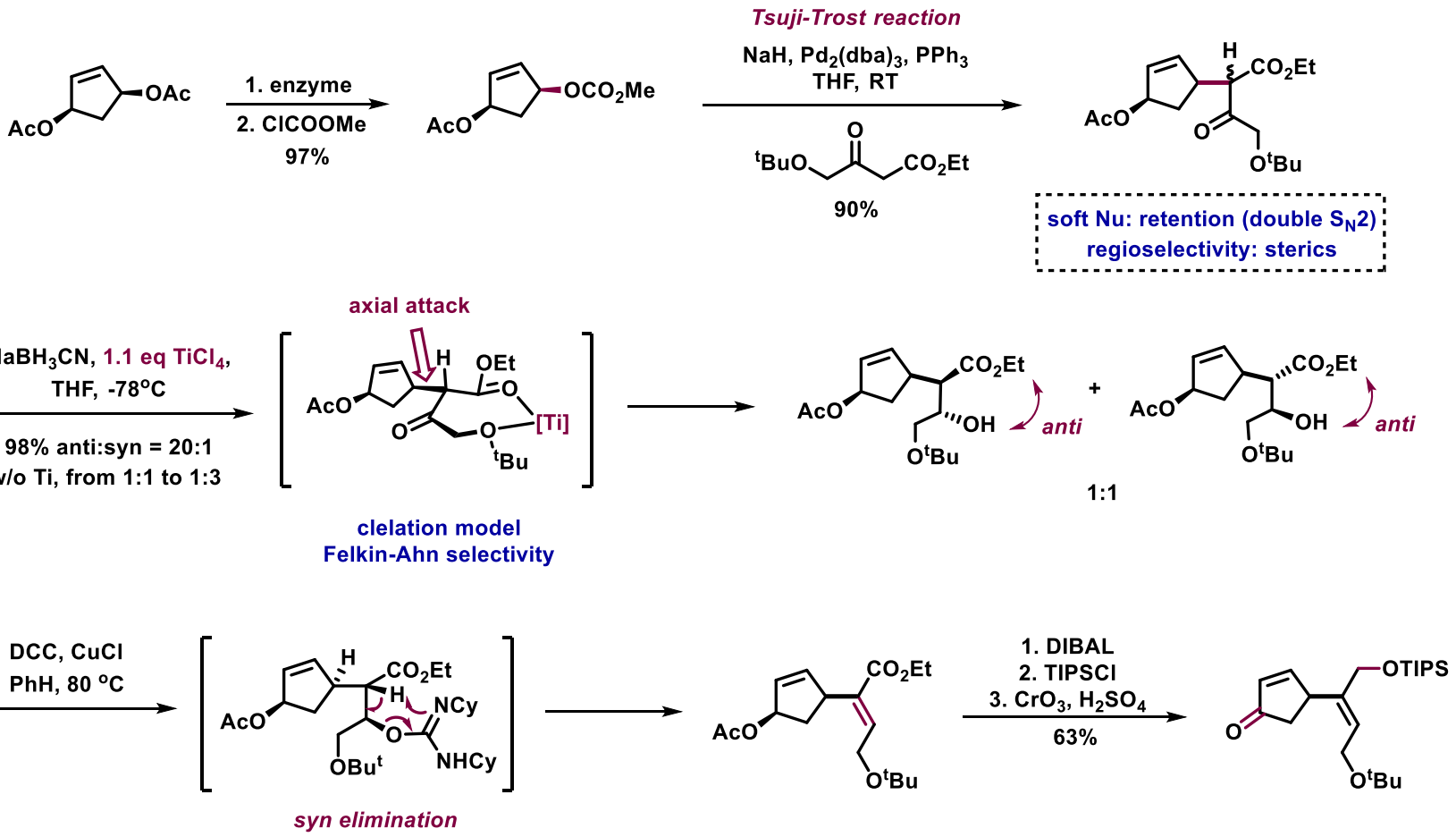
Synthesis planning

- Aza-Cope-Mannich cascade to build the spirocenter



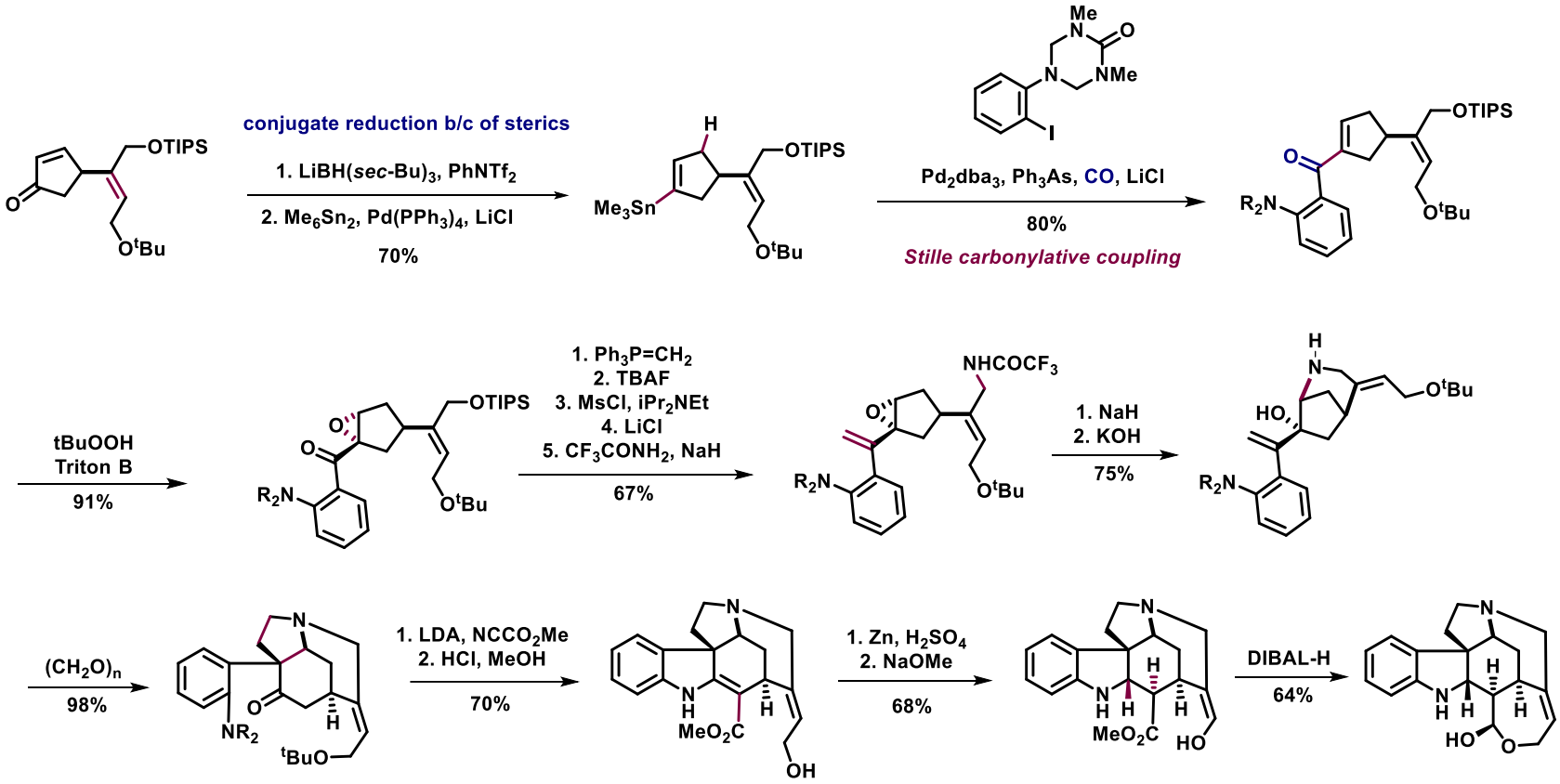
Overman's synthesis (1993)

Synthetic route



Overman's synthesis (1993)

Synthetic route



Rawal's synthesis (1994)

About Viresh Rawal

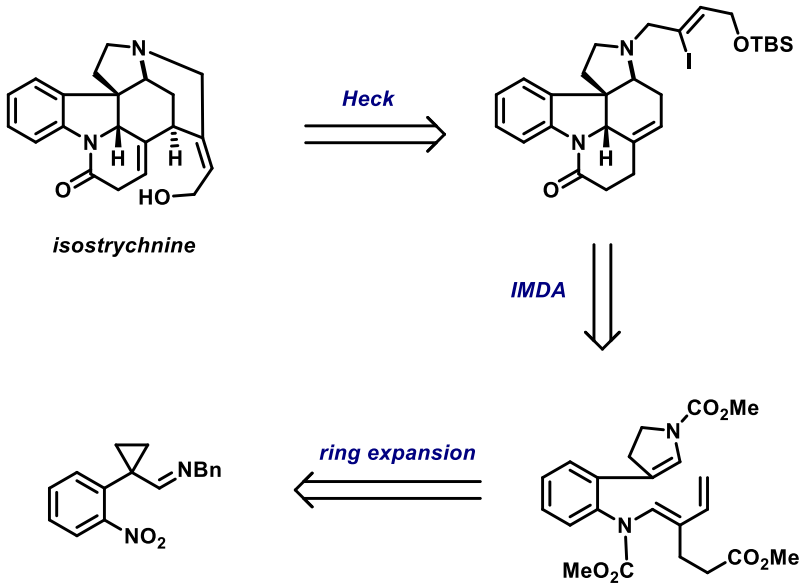
- About Rawal

1986	Ph.D. University of Pennsylvania, Philadelphia
	(Prof. Michael P. Cava)
1988	Postdoc. Columbia University
	(Prof. Gilbert Stork)
1988	The Ohio State University
1995	University of Chicago

Rawal's synthesis (1993)

Synthesis planning

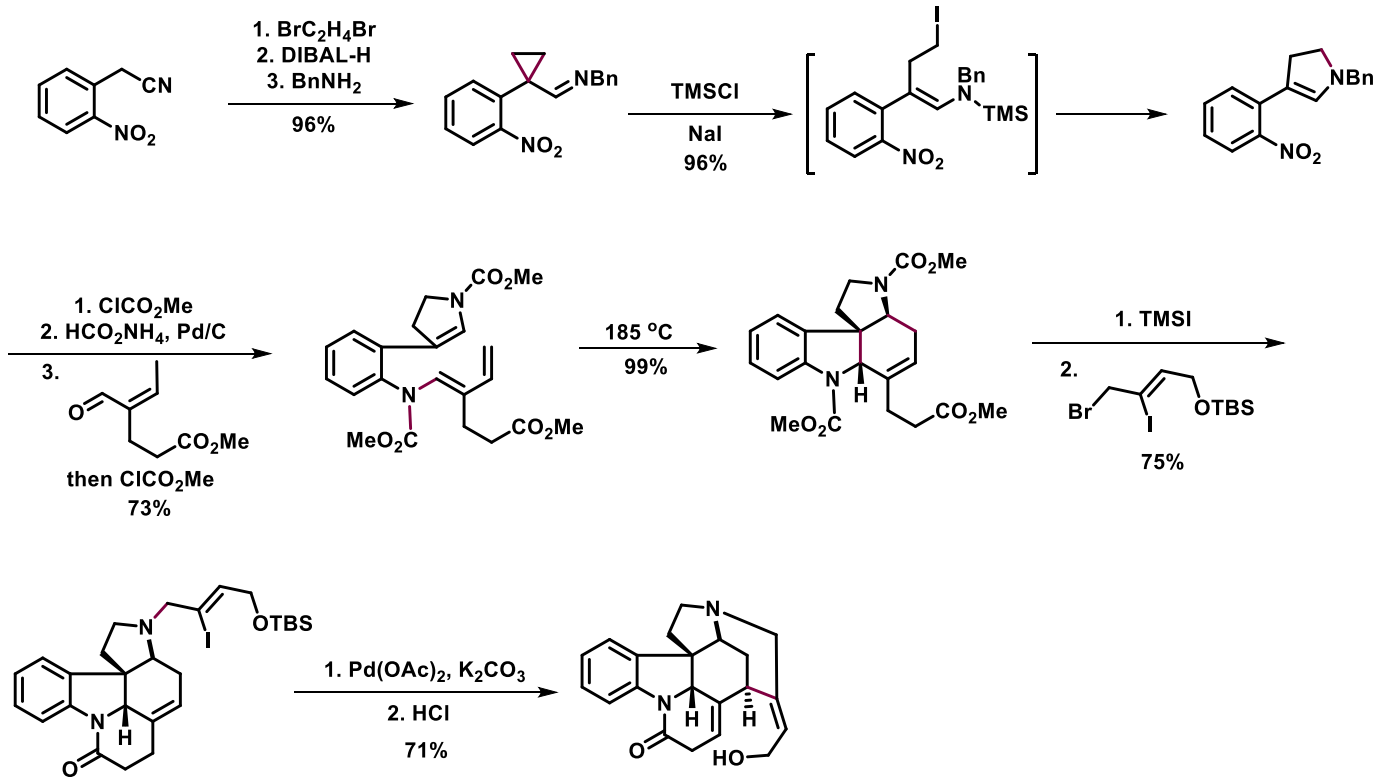
- IMDAto build the spirocenter



Rawal's synthesis (1993)

Synthetic route

- IMDA to build the spirocenter

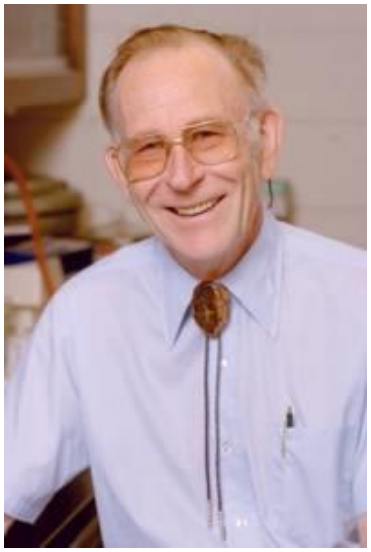


Kuehne's synthesis (1998)

About Martin Kuehne

- About Kuehne

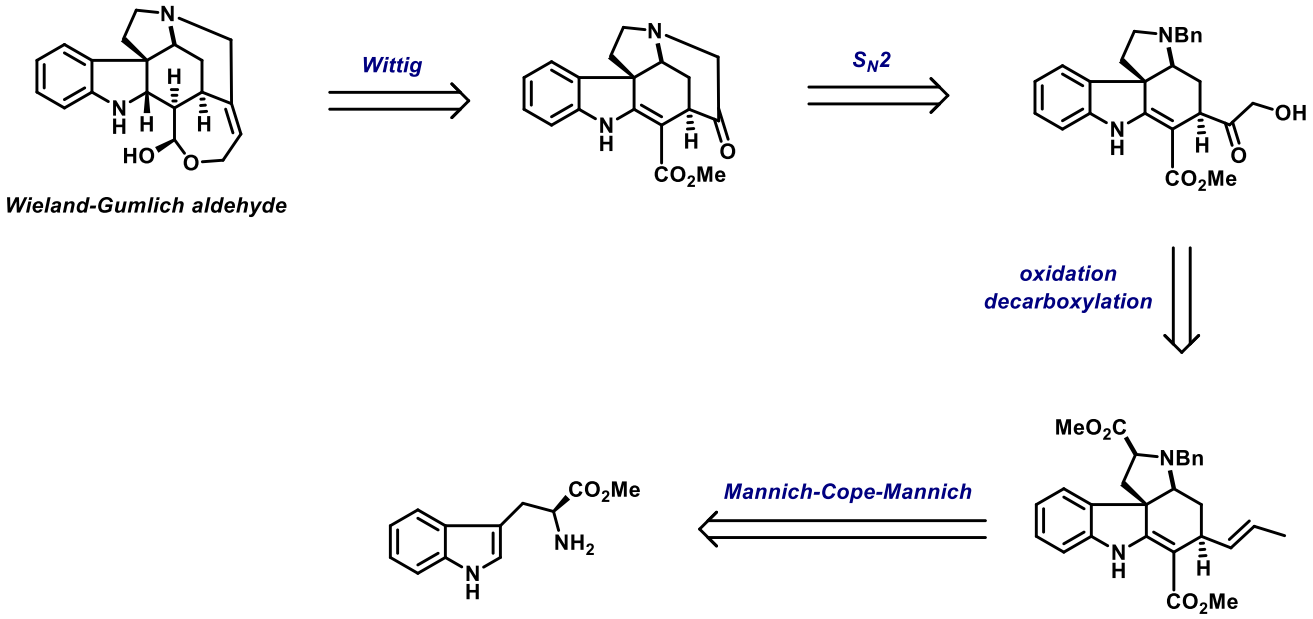
1955	Ph.D. Columbia University
	(Prof. Gilbert Stork)
1961	University of Vermont



Kuehne's synthesis (1993)

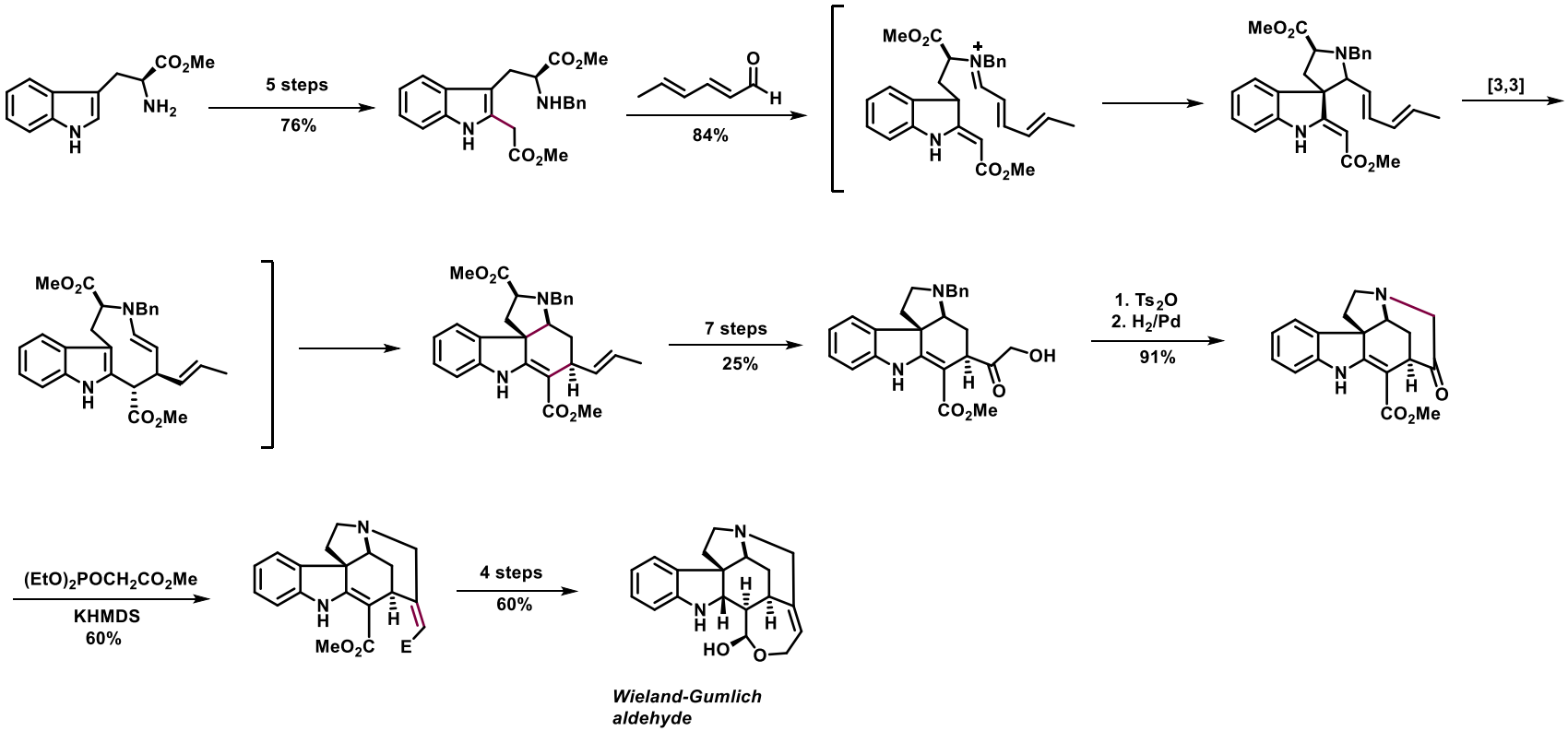
Synthesis planning

- Cationic rearrangement to build the spirocenter



Kuehne's synthesis (1993)

Synthetic route



Wieland-Gumlich aldehyde

Fukuyama's synthesis (2004)

About Tohru Fukuyama

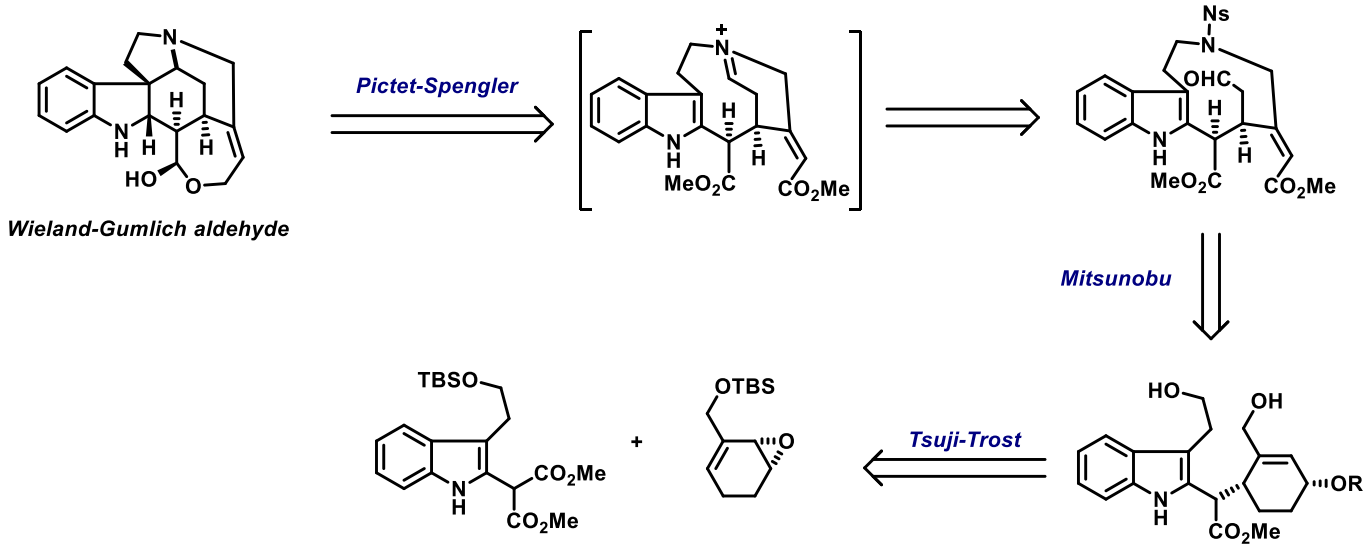
- About Fukuyama

1977	Ph.D. Harvard University
	(Prof. Y. Kishi)
1978	Rice University
1995	University of Tokyo

Fukuyama's synthesis (2004)

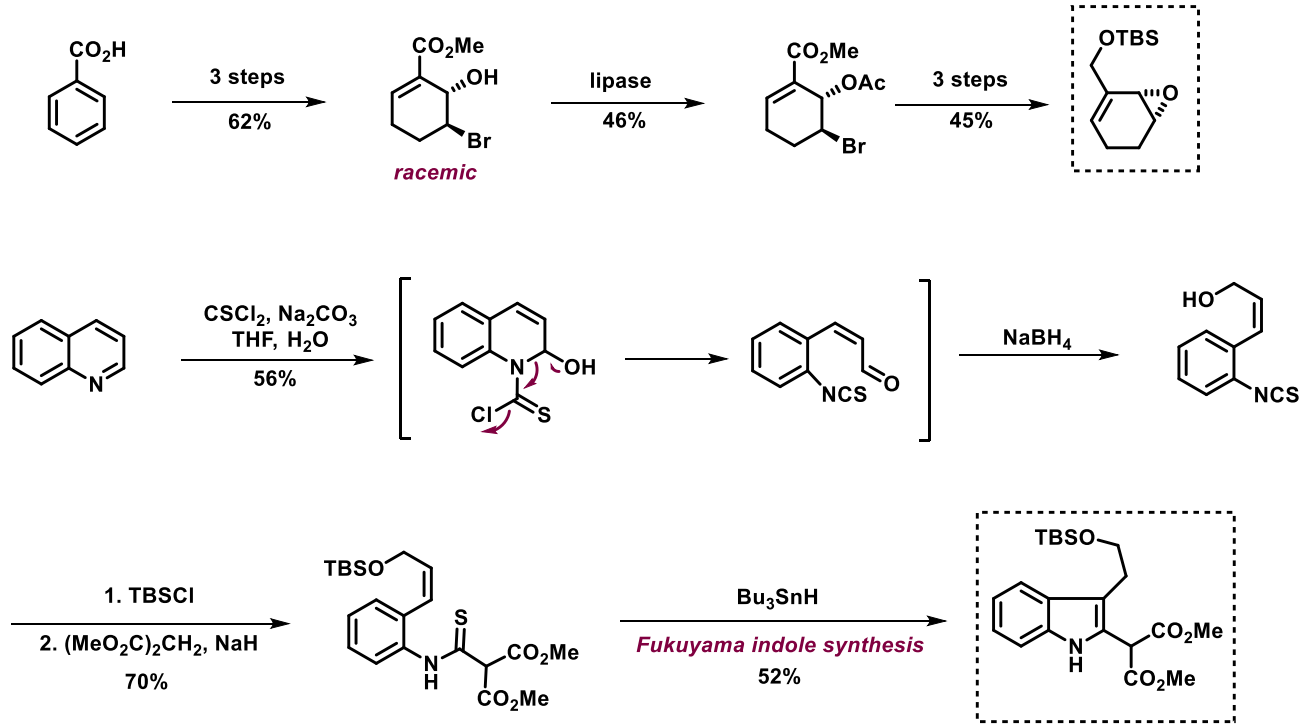
Synthesis planning

- Transannular Pictet-Spengler



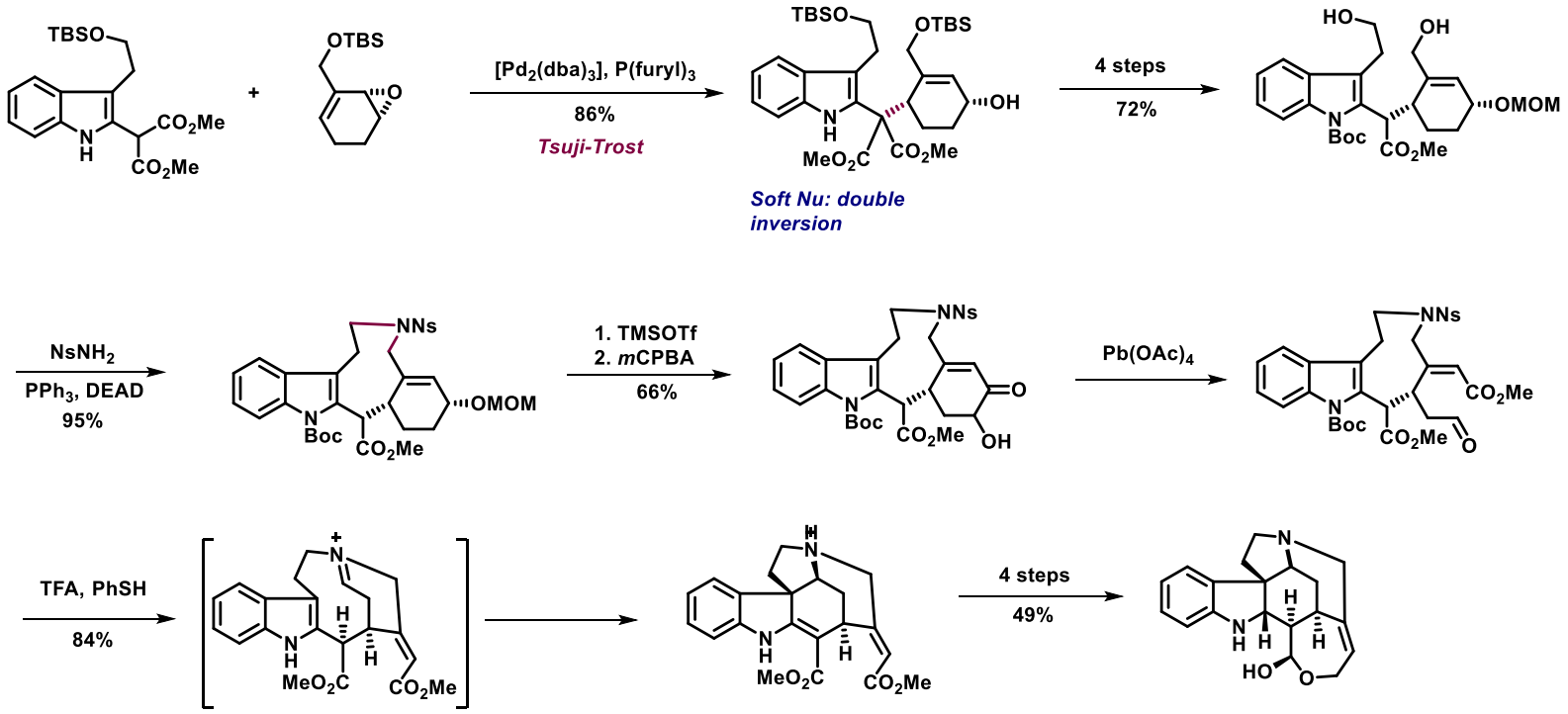
Fukuyama's synthesis (2004)

Synthesis of coupling partners



Fukuyama's synthesis (2004)

Synthetic route



Reissig's synthesis (2010)

About Hans-Ulrich Reißig

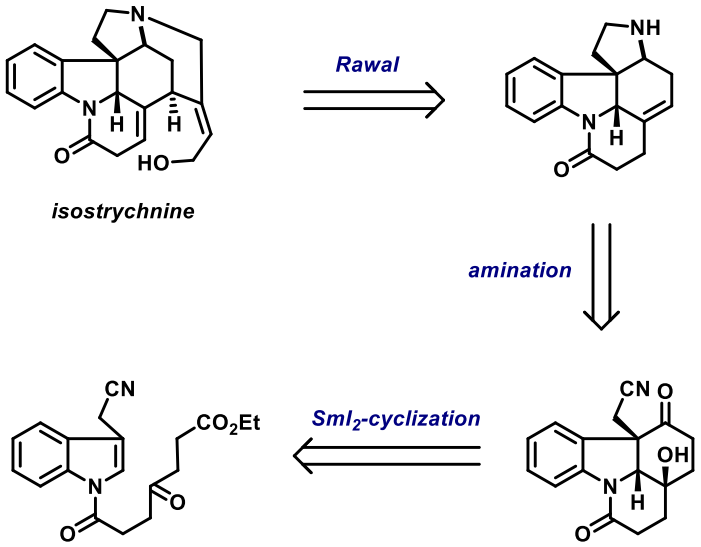
- About Reissig

1986	Ph.D. Ludwig-Maximilians-Universität München
	(Prof. R. Huisgen)
1988	Postdoc. University of British Columbia
	(Prof. E. Piers)
1999	Freie Universität Berlin

Reissig's synthesis (1993)

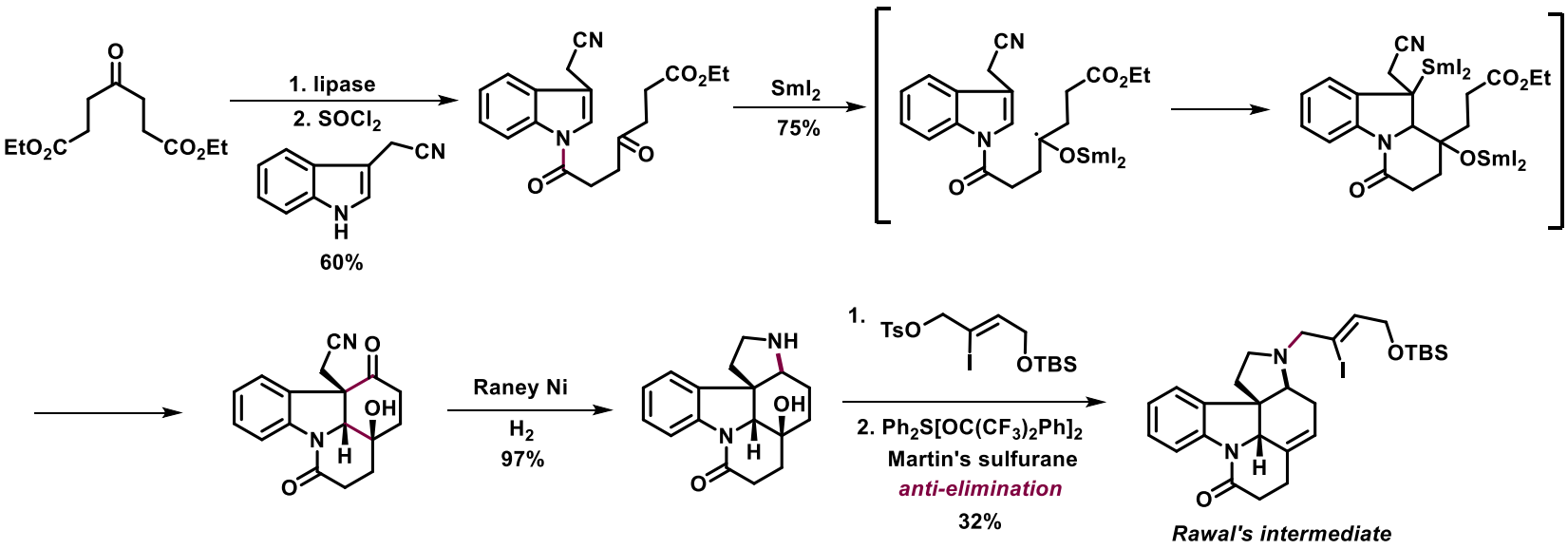
Synthesis planning

- Radical cyclization to build the spirocenter



Reissig's synthesis (1993)

Synthetic route



MacMillan's synthesis (2011)

About David MacMillan

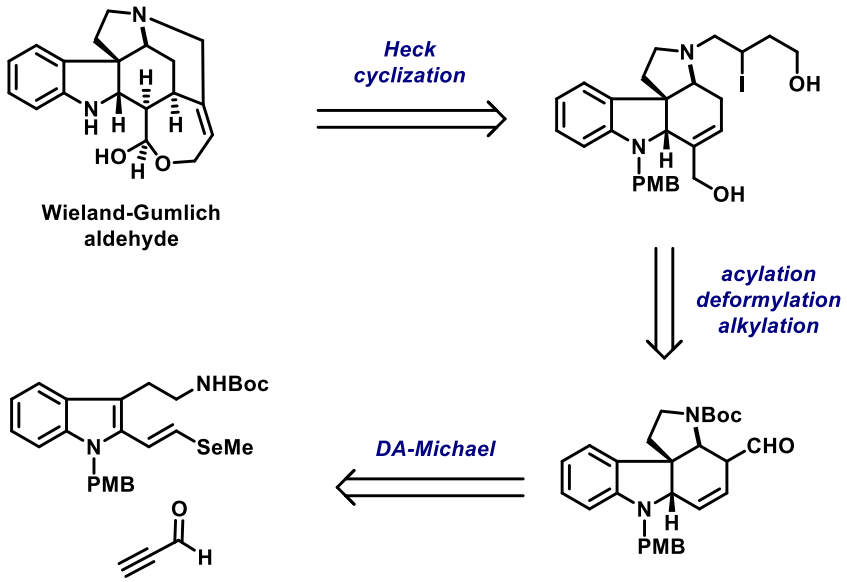
- About MacMillan

1996	Ph.D. University of California, Irvine
	(Prof. Larry Overman)
1998	Postdoc. Harvard University
	(Prof. David Evans)
1998	University of California, Berkeley
2000	California Institute of Technology
2006	Princeton University

MacMillan's synthesis (2011)

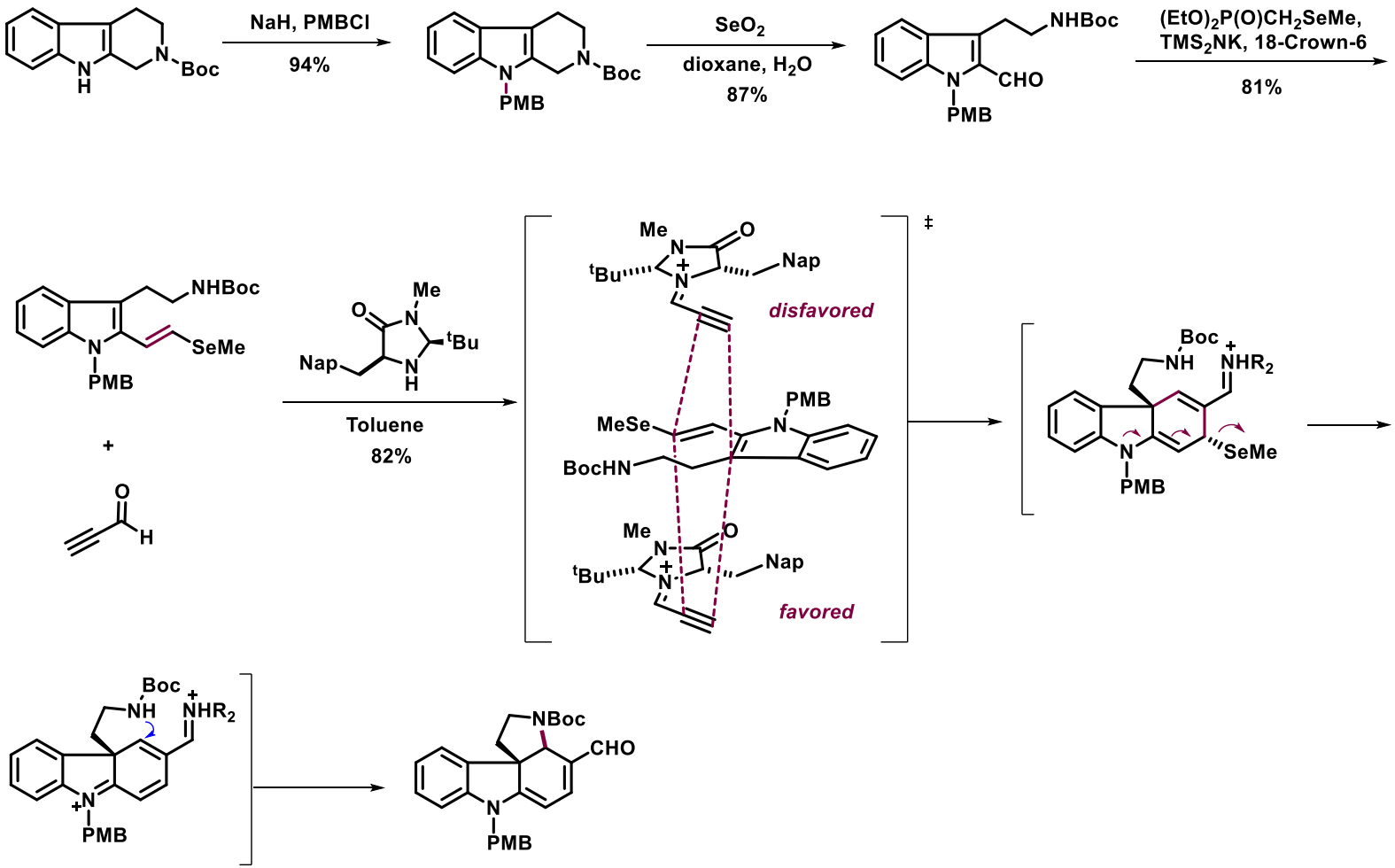
Synthesis planning

- Diels-Alder-Michael cascade reaction to build the spirocenter



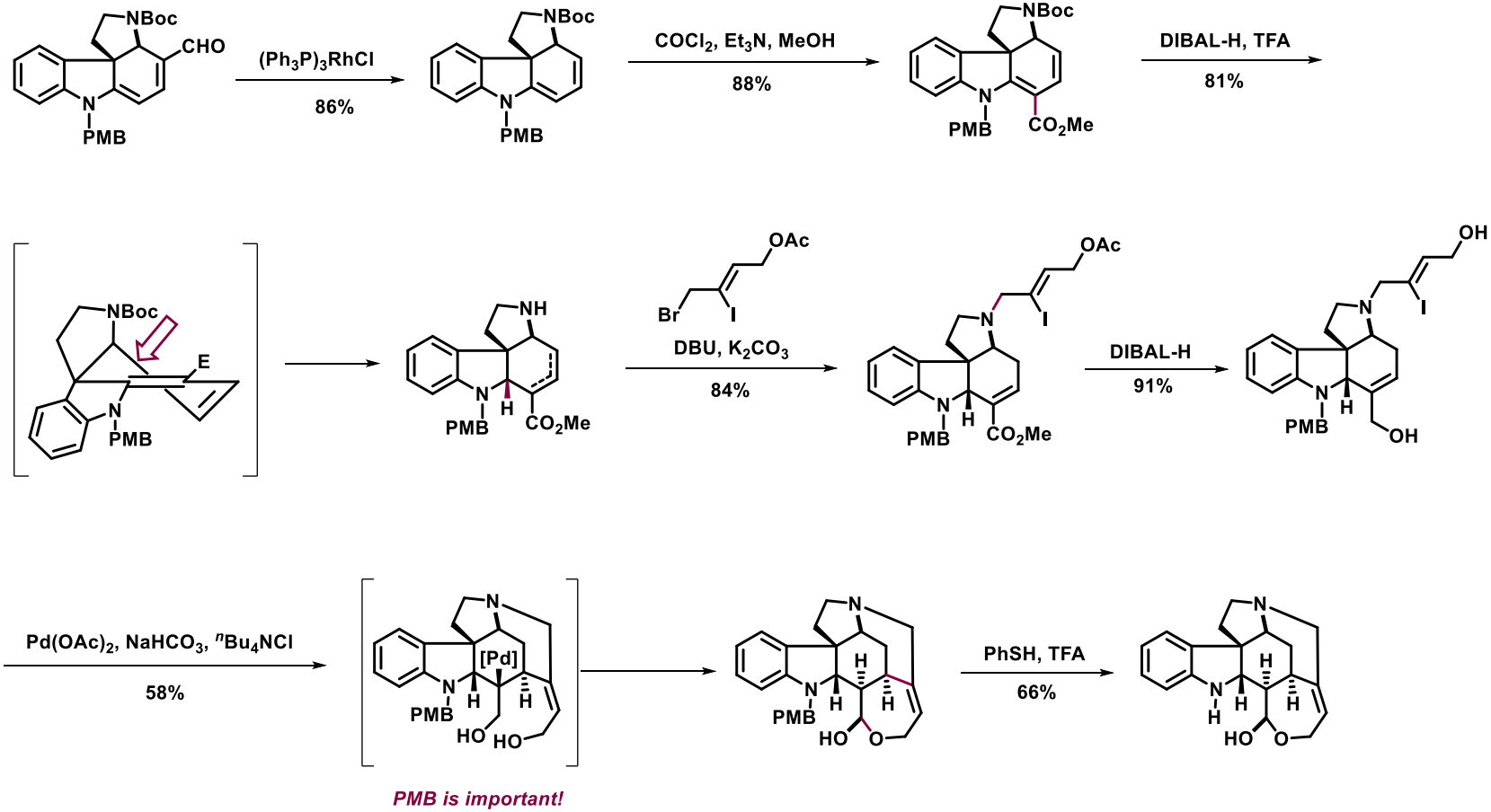
MacMillan's synthesis (2011)

Synthetic route



MacMillan's synthesis (2011)

Synthetic route



PMB is important!

Vanderwal's synthesis (2011)

About Chris Vanderwal

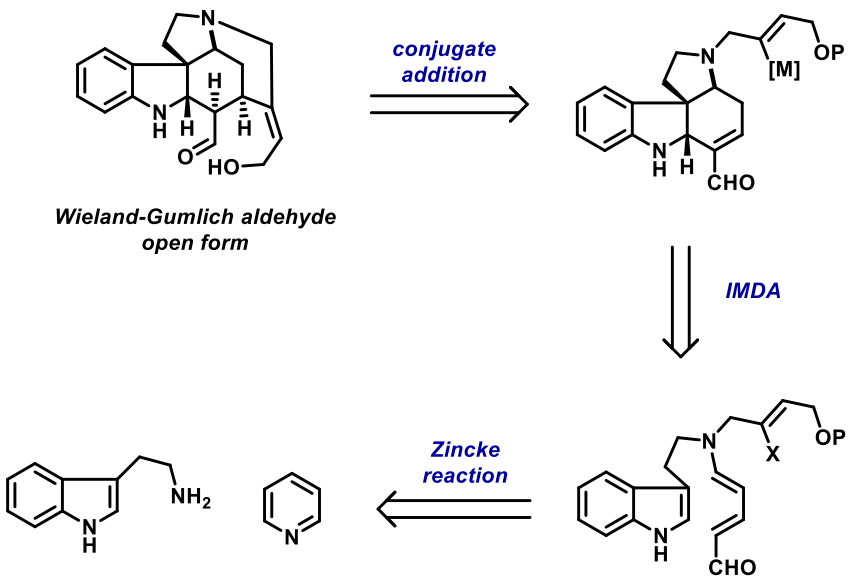
- About Vanderwal

2003	Ph.D. The Scripps Research Institute
	(Prof. Erik Sorensen)
2003	Met his wife Danielle Soenen
	(Prof. Dale Boger)
2005	Postdoc. Harvard University
	(Prof. Eric Jacobsen)
2005-now	Professor of Chemistry University of California, Irvine

Vanderwal's synthesis (2011)

Synthesis planning

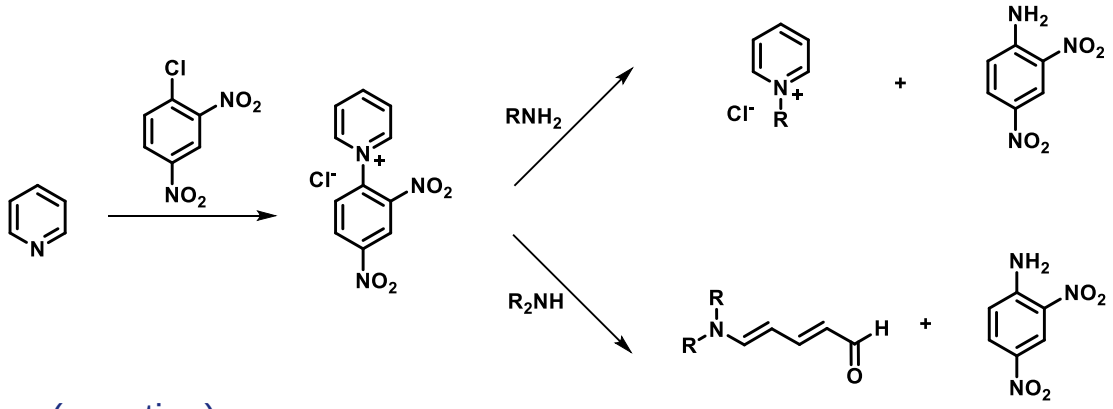
- Diels-Alder reaction to build the spirocenter



Vanderwal's synthesis (2011)

Background: Zinckle reaction

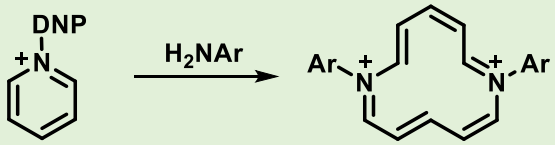
- Zinckle reaction



- Mechanism: (question)

In 2006, a Japanese group claimed novel synthesis of diazaannulene (see below), which was thought to have special diamagnetic properties because of anti-aromaticity. Unfortunately, they did not possessed the knowledge of Zinckle reaction when they published the paper.

What is the correct structure? (They share similar NMR) And what is the mechanism of forming the correct product?

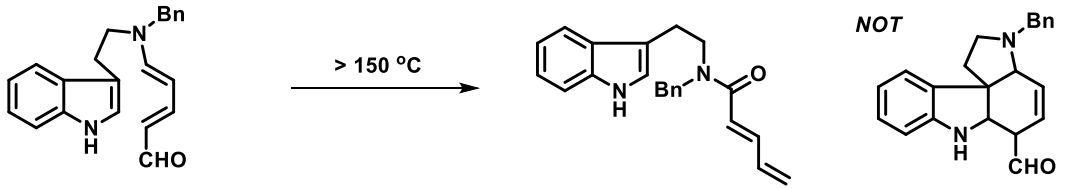


Org. Lett. **2006,** *8,* 4279. (retracted)

Vanderwal's synthesis (2011)

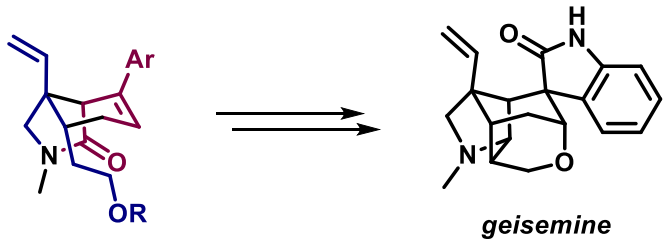
Development of IMDA

- Indole is a poor dienophile, Zincke aldehyde is a poor diene



J. Am. Chem. Soc. **2008,** *130,* 7560.

- Application



geisemine

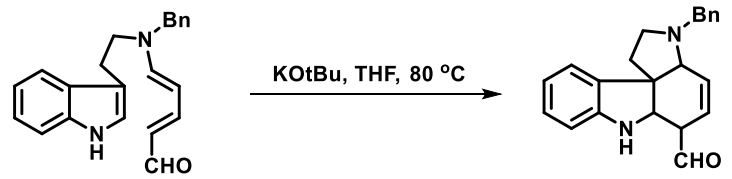
- Mechanism: (question)

In 2011, Houk used DFT calculation to find that the reaction goes through *ketene* intermediate. Notice the regiochemistry as indicated below. Please draw the mechanism.

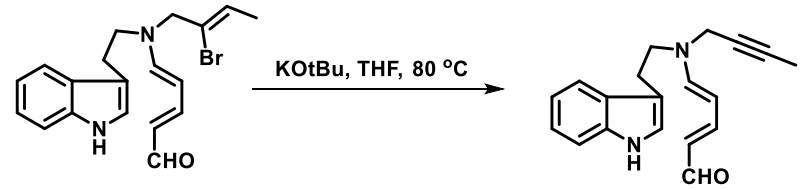
Vanderwal's synthesis (2011)

Development of IMDA

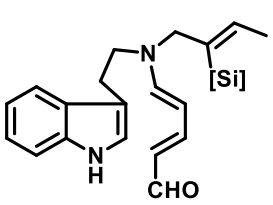
- Lewis acid failed; metallation of indole gave promising result



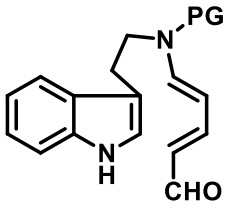
However:



- Solution 1



- Solution 2



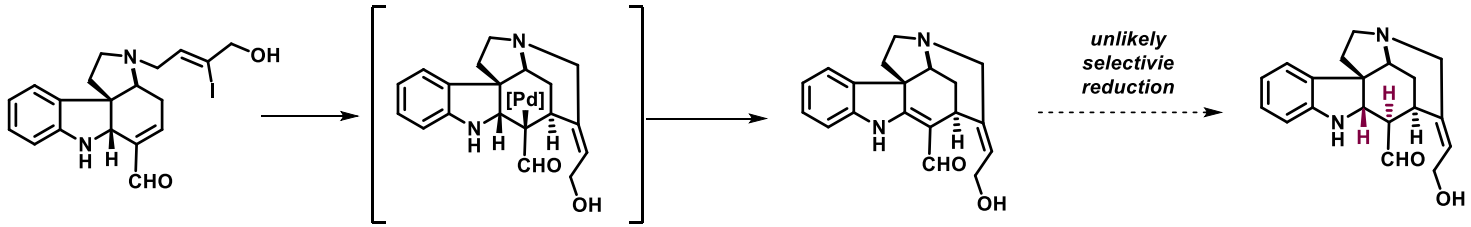
Boc, Ts, Ac: **EWG, not suitable for Zinckle reaction**
Bn: **reductive condition, unsuitable for aldehyde**
PMB: **oxidative condition, unsuitable for indole**
acidic condition, leading to dimerization

Allyl: **good**

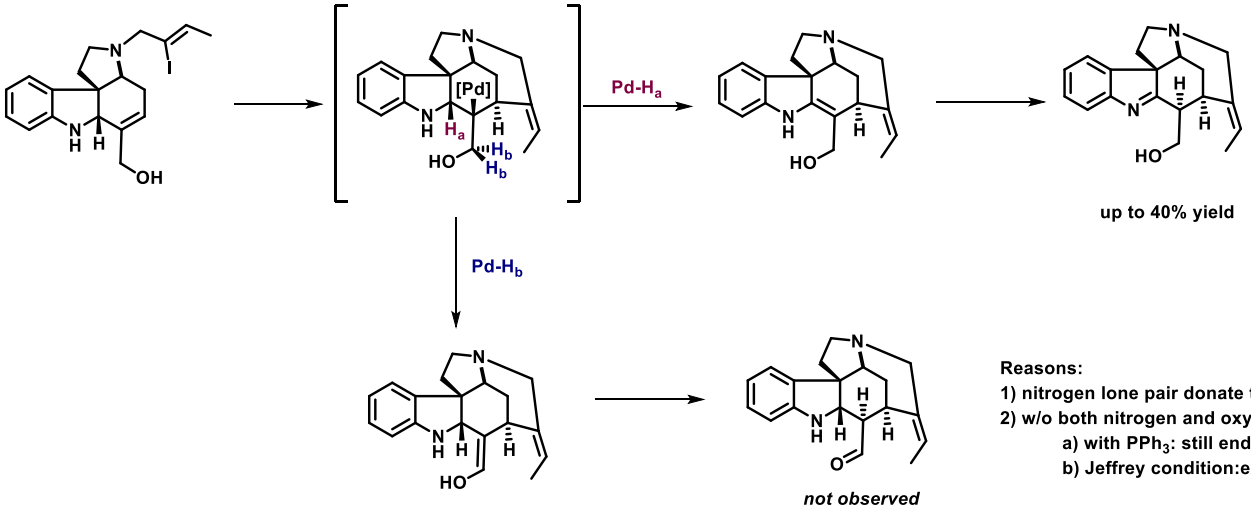
Vanderwal's synthesis (2011)

Development of conjugate addition

- Direct Heck reaction? Seem unlikely…



- Solution: reduction of aldehyde? Undesired regioselectivity!



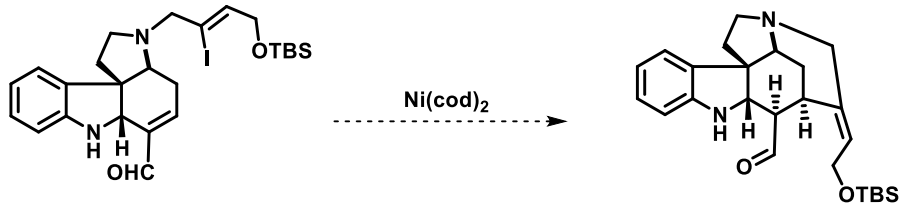
Reasons:
1) nitrogen lone pair donate to C-H anti-bonding
2) w/o both nitrogen and oxygen
   a) with PPh_3: still endocyclic
   b) Jeffrey condition:exocyclic

Vanderwal's synthesis (2011)

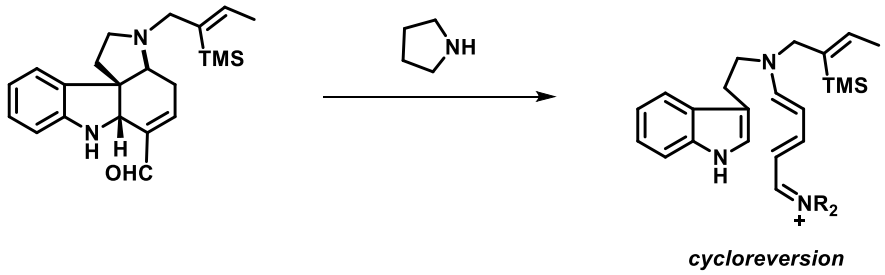
Development of conjugate addition

- Other failed trials…

Reductive Heck



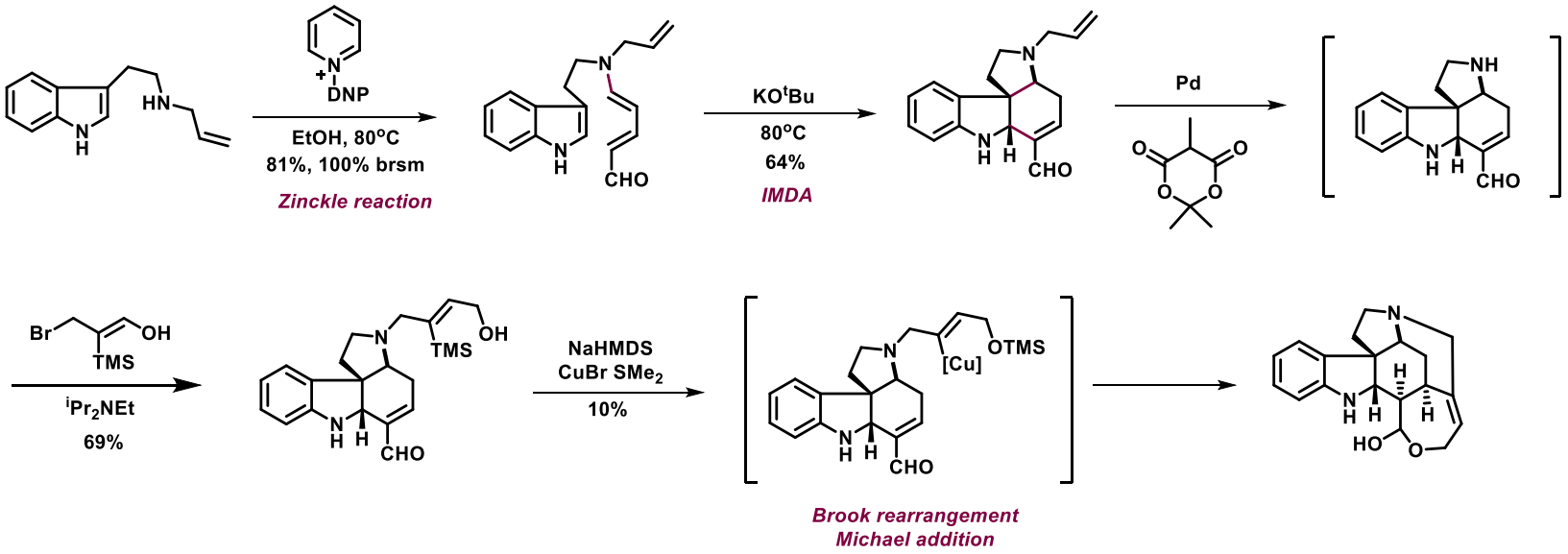
Direct conjugate addition



cycloreversion

Vanderwal's synthesis (2011)

The final route



Summary

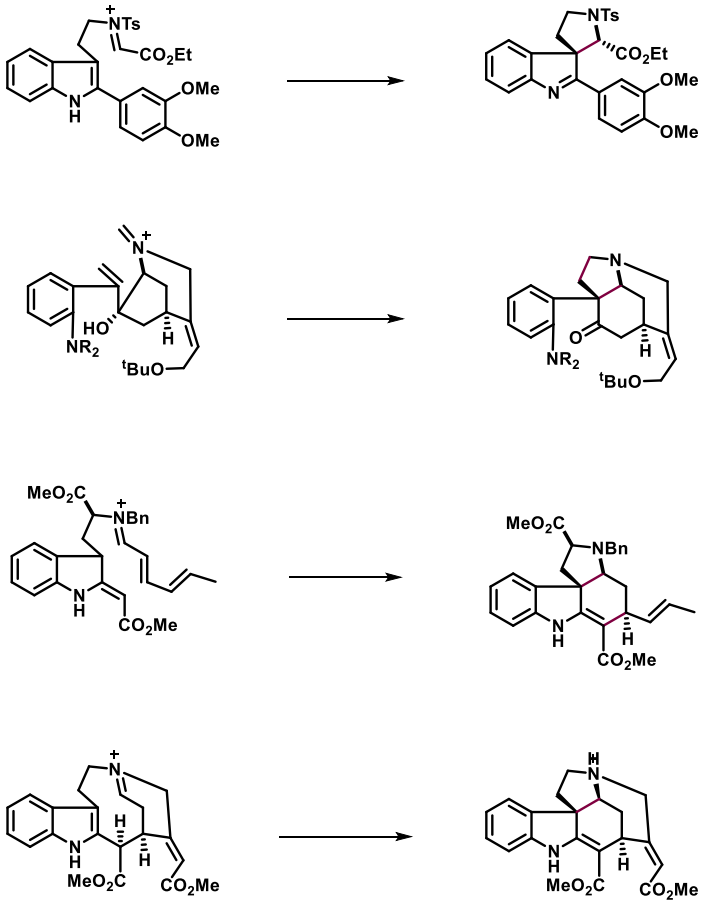
The yield and steps

Year	Chemist	Chiral source	Step	Yield
1954	Woodward	N/A	29	0.0002%
1993	Overman	enzyme	25	3%
1994	Rawal	N/A	12	10%
1998	Kuehne	Amino acid	21	4%
2004	Fukuyama	Enzyme	25	1%
2010	Reissig	N/A	9	4%
2011	MacMillan	Organocatalyst	12	7%
2011	Vanderwal	N/A	6	2-3%

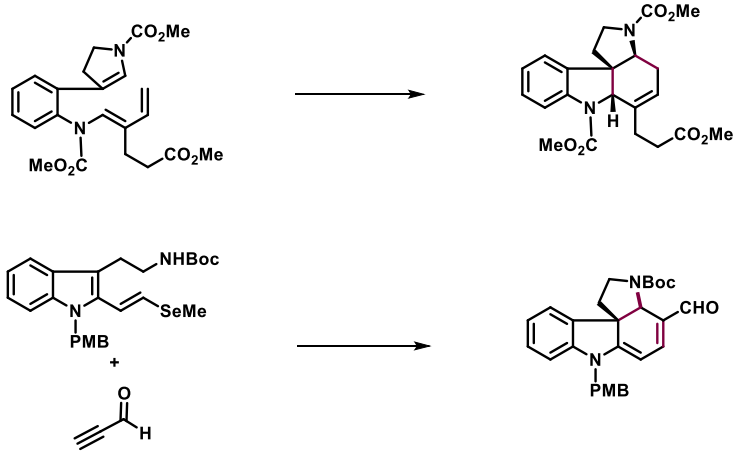
Summary

Formation of spirocenter

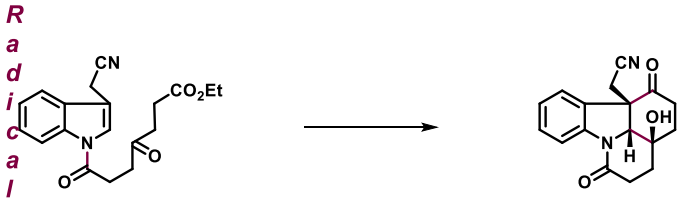
Iminium



DA

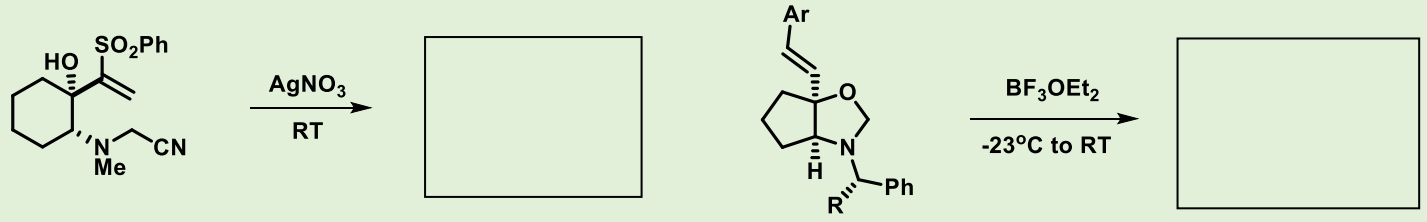


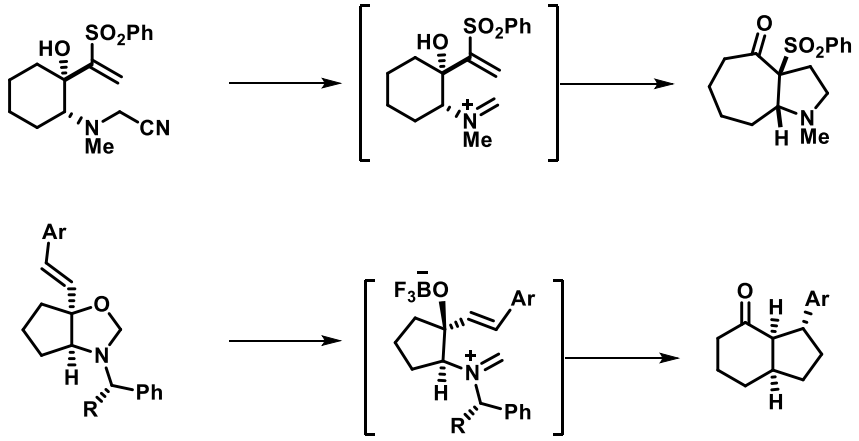
Radical



Thanks for your kind attention!

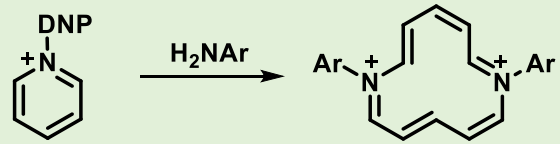
Aza-Cope-Mannich cascade proved to be very powerful in total synthesis. Please complete the following reactions.



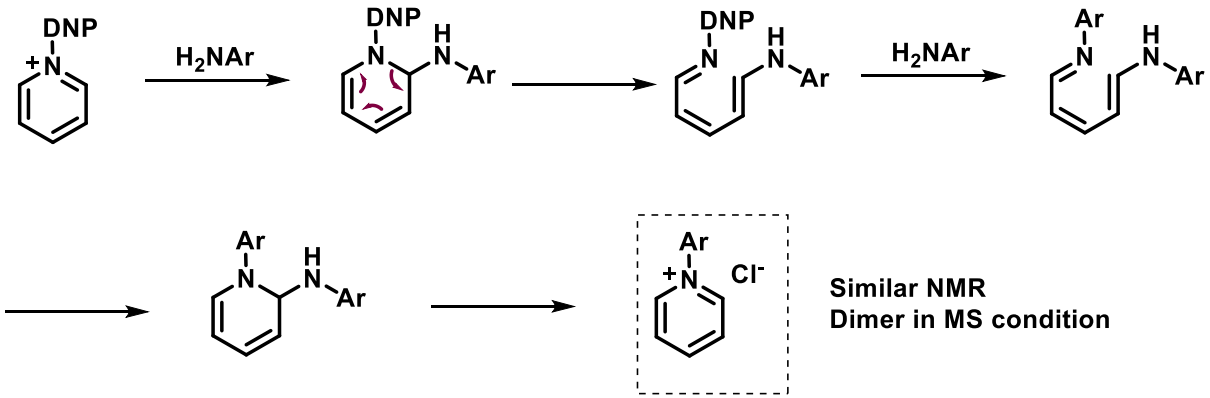


In 2006, a Japanese group claimed novel synthesis of diazaannulene (see below), which was thought to have special diamagnetic properties because of anti-aromaticity. Unfortunately, they did not possessed the knowledge of Zinckle reaction when they published the paper.

What is the correct structure? (They share similar NMR) And what is the mechanism of forming the correct product?



Org. Lett. **2006,** *8,* 4279. (retracted)



In 2011, Houk used DFT calculation to find that the reaction goes through *ketene* intermediate. Notice the regiochemistry as indicated below. Please draw the mechanism.