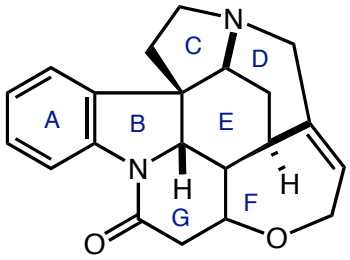
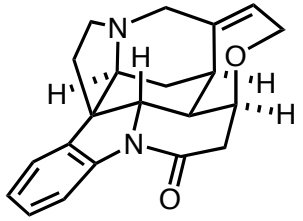
Comparative Total Syntheses of Strychnine



MacMillan Group Meeting

Nathan Jui

July 22, 2009



References: Pre-Volhardt: Bonjoch *Chem. Rev.* **2000**, 3455.

Woodward *Tetrahedron*, **1963**, 247.

Magnus *J. Am. Chem. Soc.* **1993**, 8116.

Overman *J. Am. Chem. Soc.* **1995**, 5776.

Kuehne *J. Org. Chem.* **1993**, 7490.

Kuehne *J. Org. Chem.* **1998**, 9427.

Rawal *J. Org. Chem.* **1994**, 2685.

Bosch, Bonjoch *Chem. Eur. J.* **2000**, 655.

Volhardt *J. Am. Chem. Soc.* **2001**, 9324.

Martin *J. Am. Chem. Soc.* **2001**, 8003.

Bodwell *Angew. Chem. Int. Ed.* **2002**, 3261.

Mori *J. Am. Chem. Soc.* **2003**, 9801.

Shibasaki *Tetrahedron* **2004**, 9569.

Fukuyama *J. Am. Chem. Soc.* **2004**, 10246.

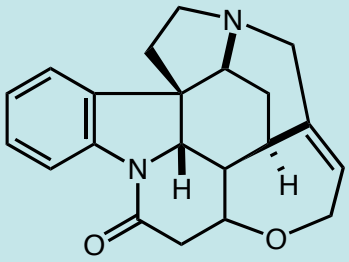
Padwa *Org. Lett.* **2007**, 279.

History and Structure of (–)-Strychnine

Strychnos nux vomica

- Isolated in pure form in 1818 (Pelletier and Caventou)
- Structural Determination in 1947 (Robinson and Leuchs)
- Over 250 publications pertaining to structure
- Notorious poison (lethal dose ~10-50 mg / adult)
- $20.20 / 10 g (Aldrich), ~1.5 wt% (seeds), ~1% (blossoms)

History and Structure of (–)-Strychnine



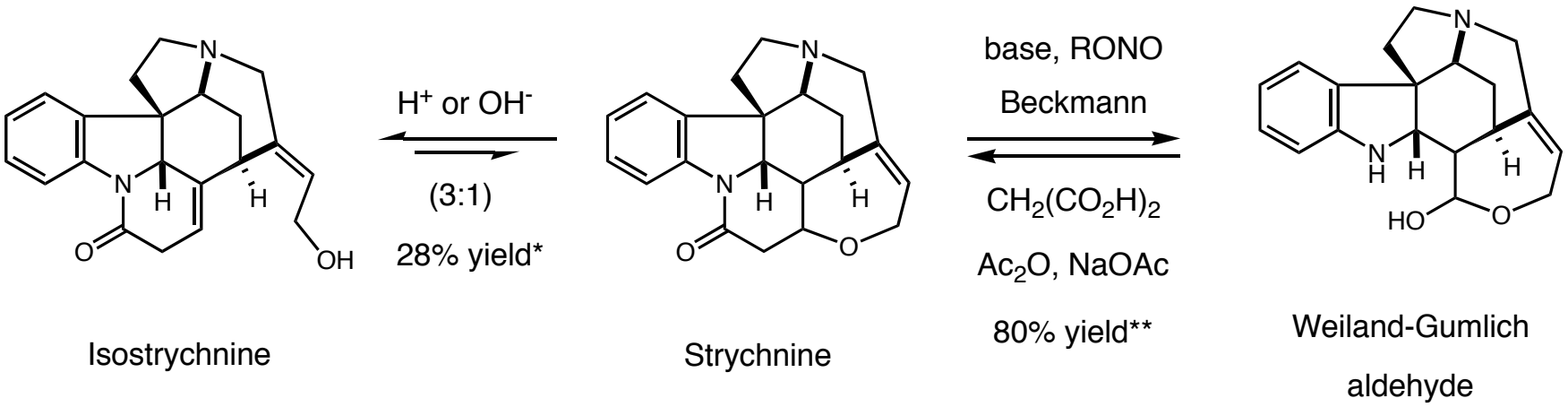
- 24 skeletal atoms ($C_{21}H_{22}N_2O_2$)
- 7-rings, 6-stereocenters
- Spirocenter (C-7)
- CDE ring system
- Hydroxyethylidine

"For it's molecular size it is the most complex substance known." -Robert Robinson

"If we can't make strychnine, we'll take strychnine" -R. B. Woodward

Structural Determination of Strychnine: Degredation Studies

- Degredation studies yielded Isostrychnine and the Wieland-Gumlich Aldehyde

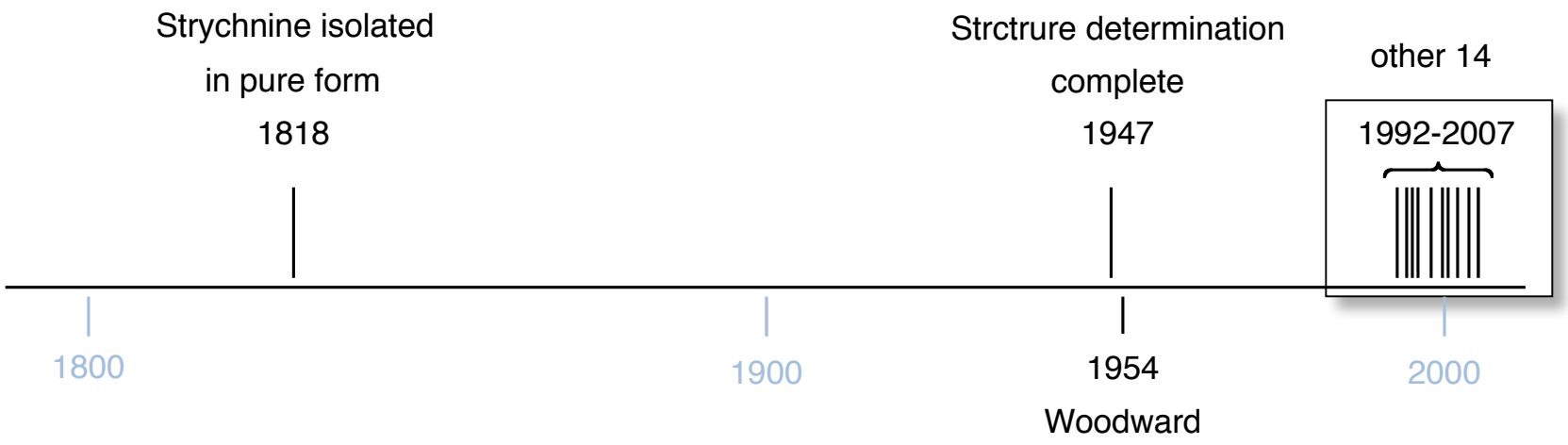


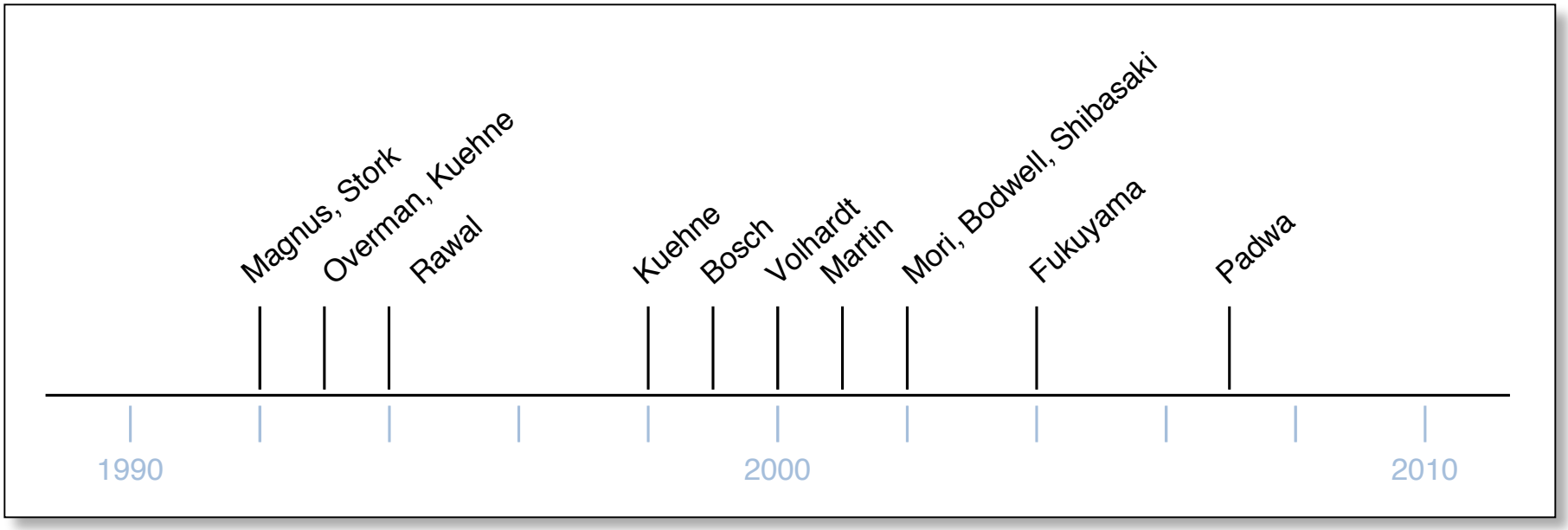
- Both were later discovered to be natural products, serve as ultimate targets for synthesis

Isostrychnine		Wieland-Gummlich aldehyde		
Woodward	Volhardt	Magnus	Stork	Shibasaki
Kuehne	Bodwell	Overman	Bonjoch/Bosch	Fukuyama
Rawal*	Mori	Kuehne	Martin	Padwa**

Total Syntheses of Strychnine Over Time

- Fourteen of the fifteen syntheses were disclosed within the last 17 years (since 1992)





Total Syntheses of Strychnine Over Time

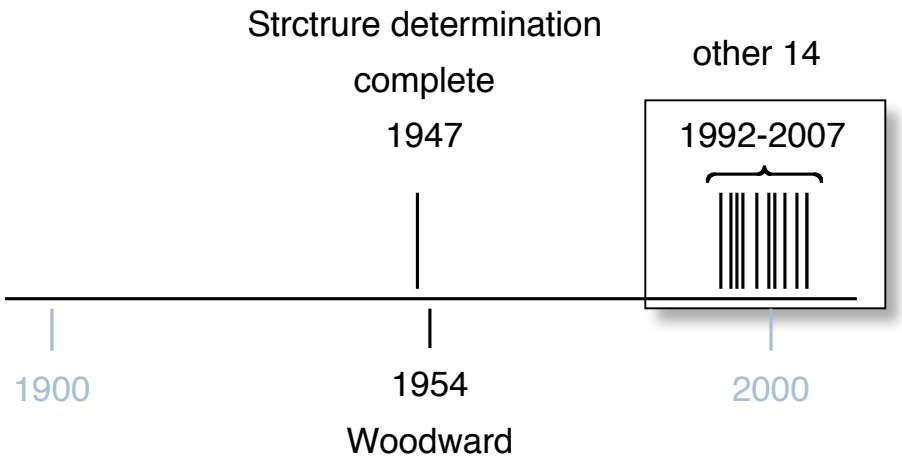
- Fourteen of the fifteen syntheses were disclosed within the last 17 years (since 1992)

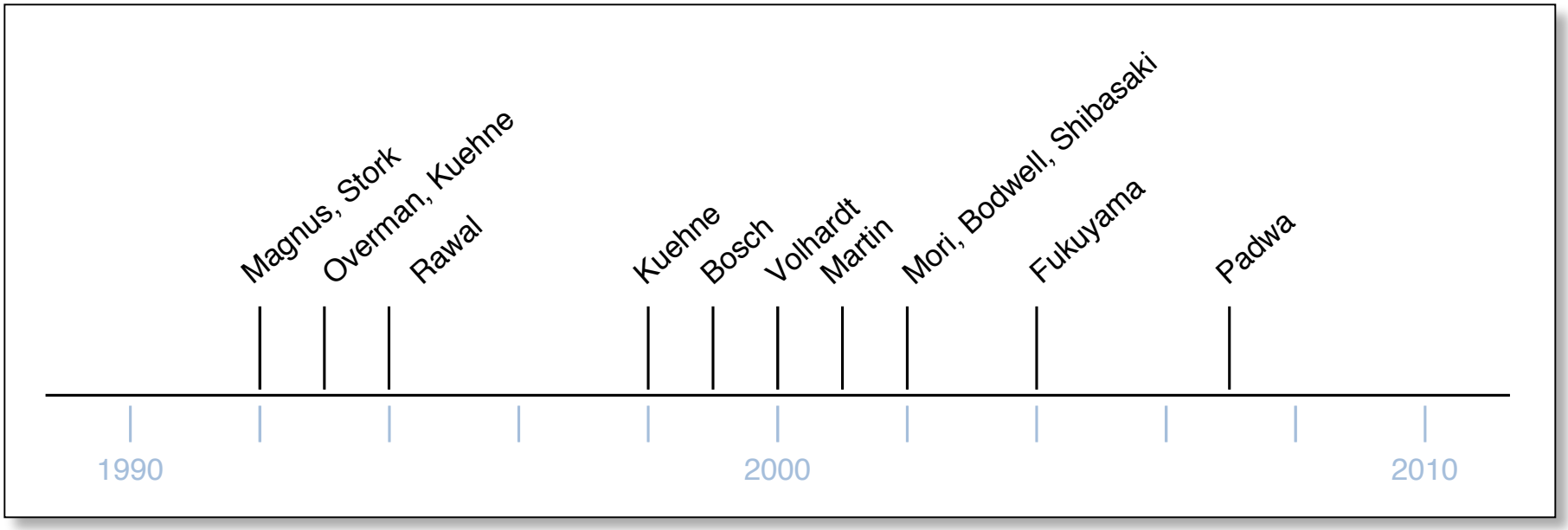
Woodward: 28 steps, 0.00006% yield

Stork: 14 steps, unknown yield (unpublished)

Magnus: 28 steps, 0.03% yield

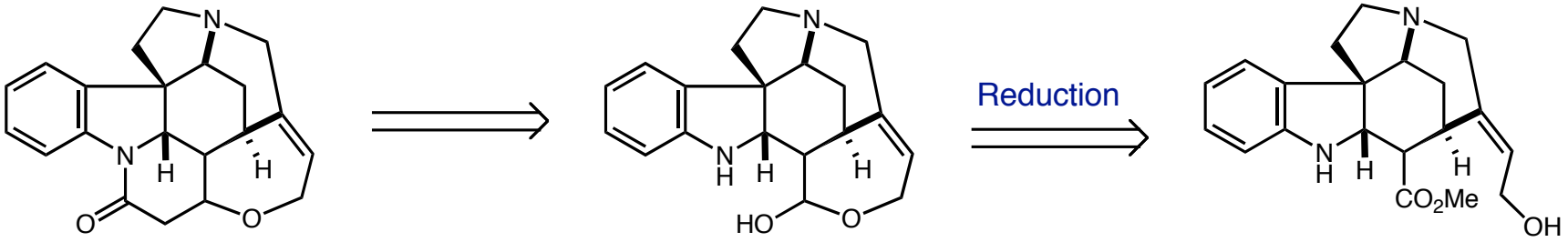
Overman: 24 steps, 3% yield





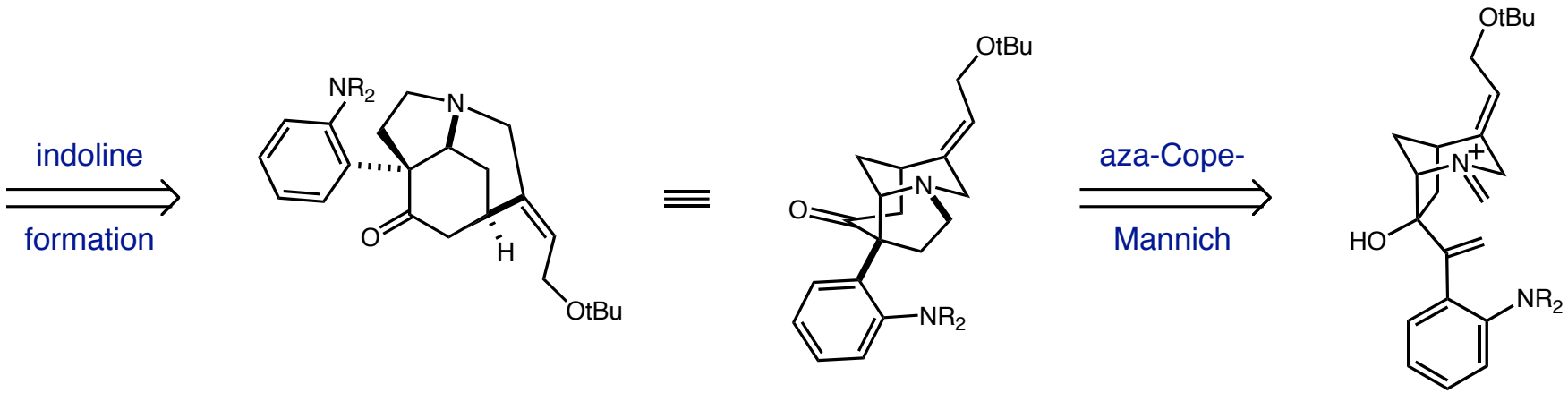
Overman's Retrosynthetic Analysis (1992)

- Overman targets Wieland-Gumlich aldehyde via aza-Cope-Mannich



Strychnine

Weiland-Gumlich aldehyde



Overman *J. Am. Chem. Soc.* **1993**, 9293.

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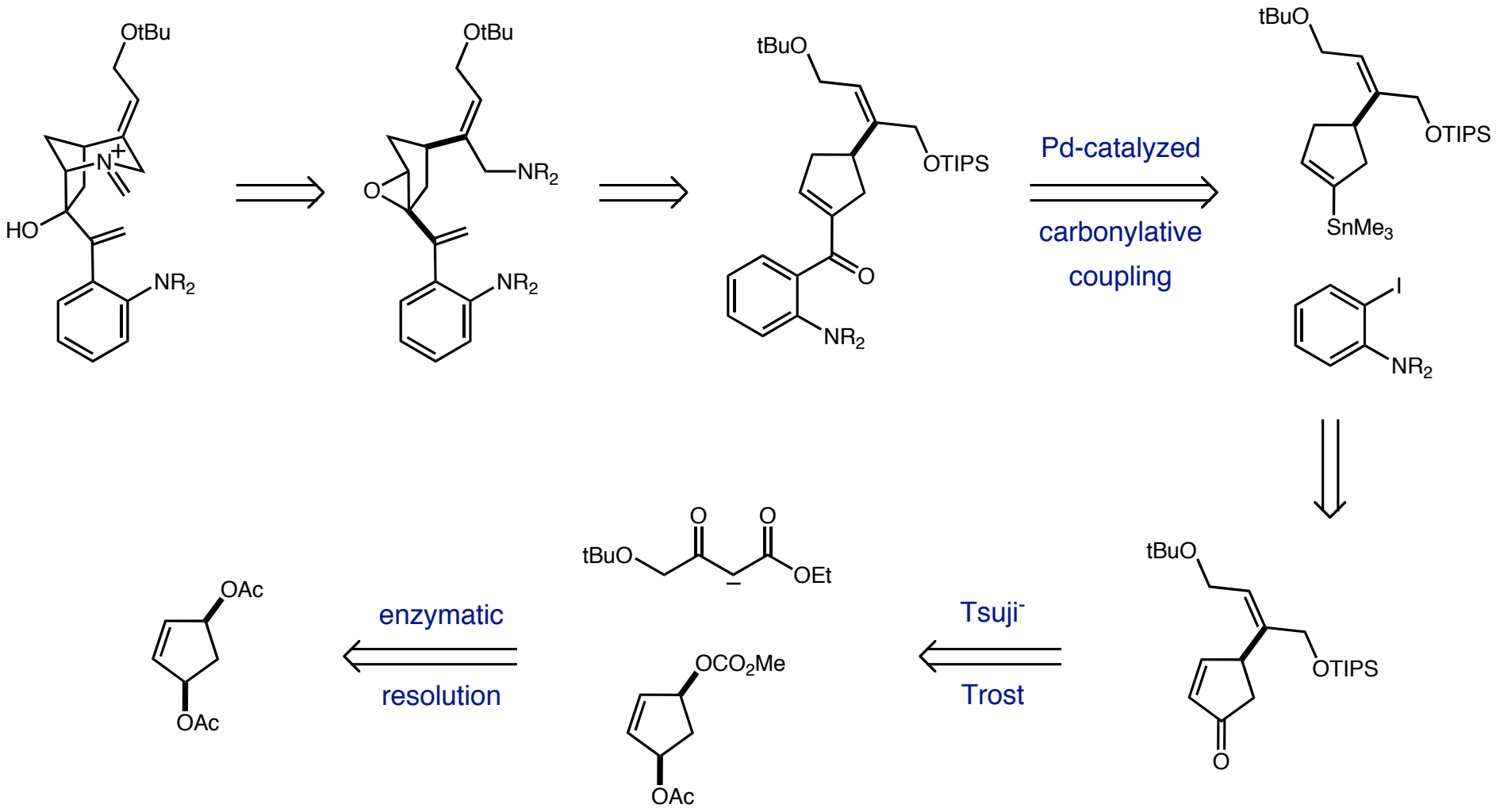
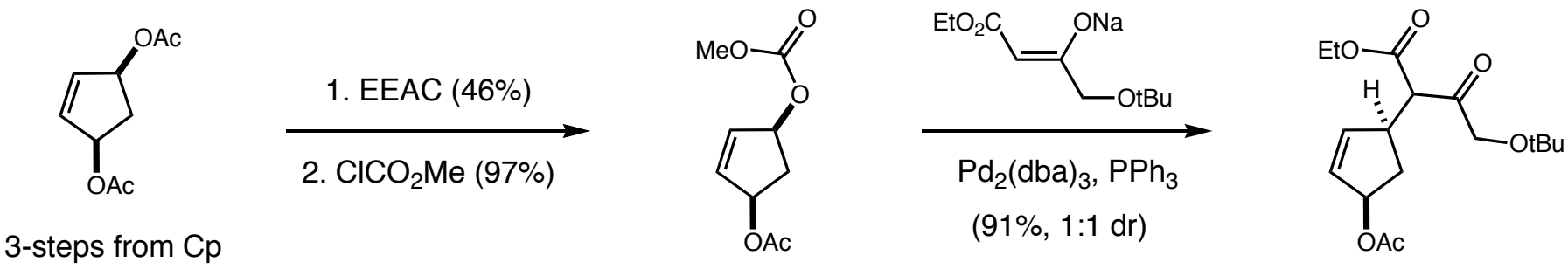
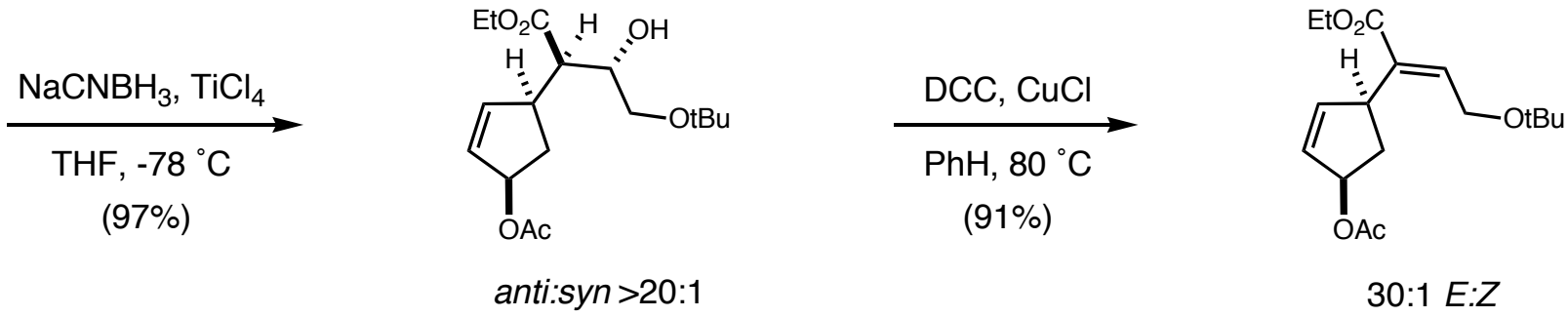


Overman: Early Construction of Trans-Hydroxyethylidine Unit

- Enzymatic resolution grants access to enantiopure starting material (>99% ee)

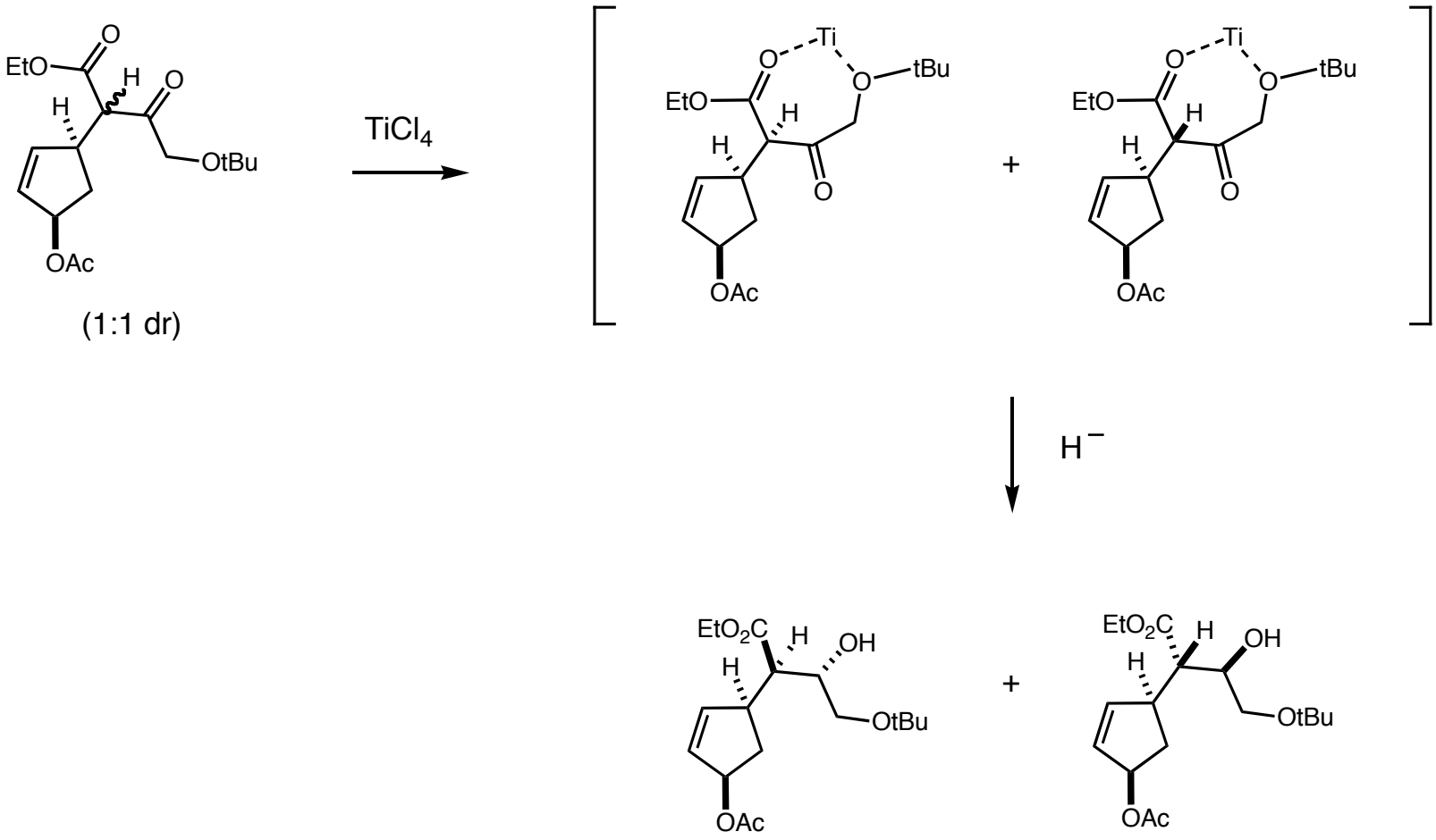


- *Anti*-selective ketone reduction allows for highly selective formation of *E*-olefin



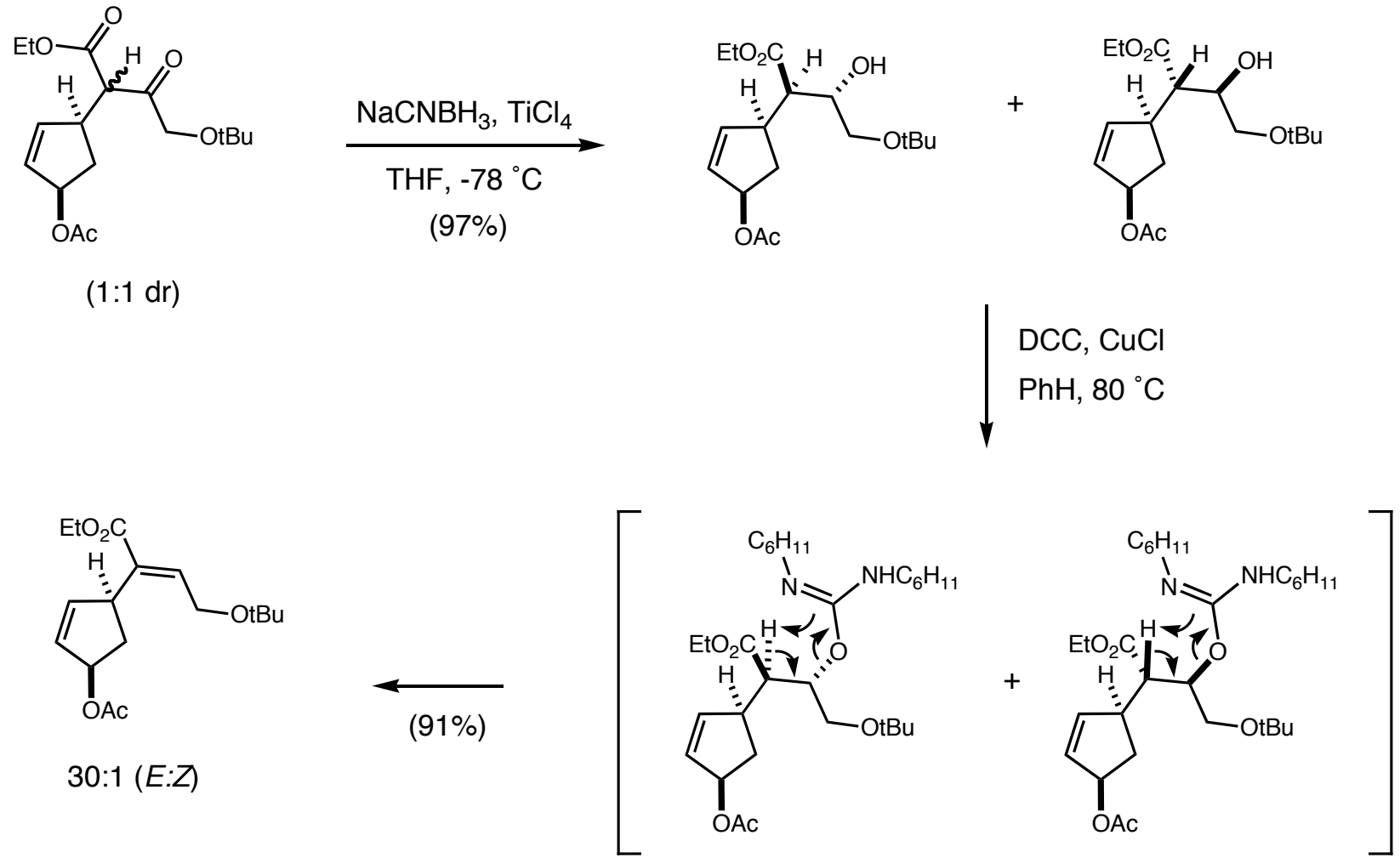
Overman: Stereoselective Ethylidine Construction

- 7-Membered chelate affords needed rigidity for stereoselective hydride delivery



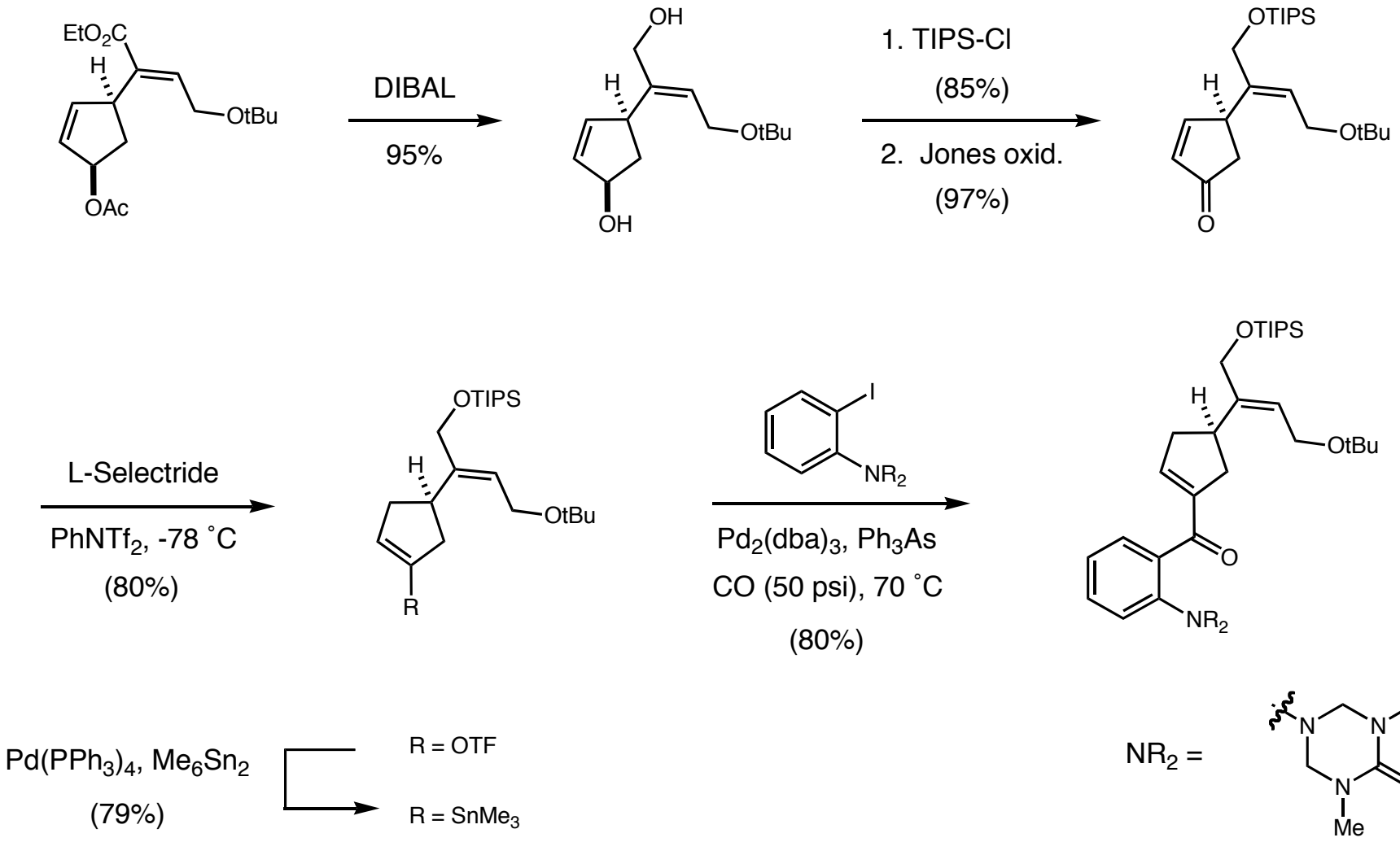
Overman: Stereoselective Ethylidine Construction

- DCC promoted stereospecific dehydration sets olefin geometry



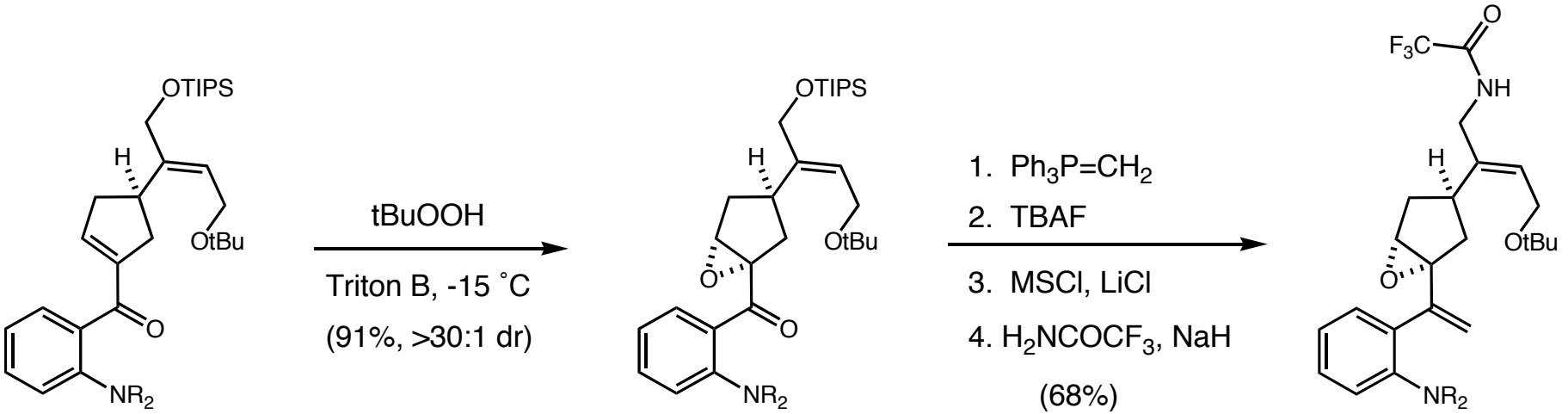
Overman: Building the Key Aza-Cope-Mannich Intermediate

- Palladium catalyzed carbonylative aniline coupling forms requisite enone

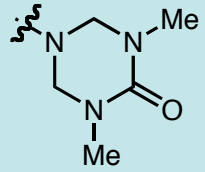


Overman: Finishing the Key Aza-Cope-Mannich Intermediate

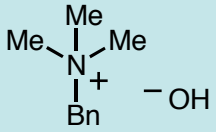
- Palladium catalyzed carbonylative aniline coupling forms requisite enone

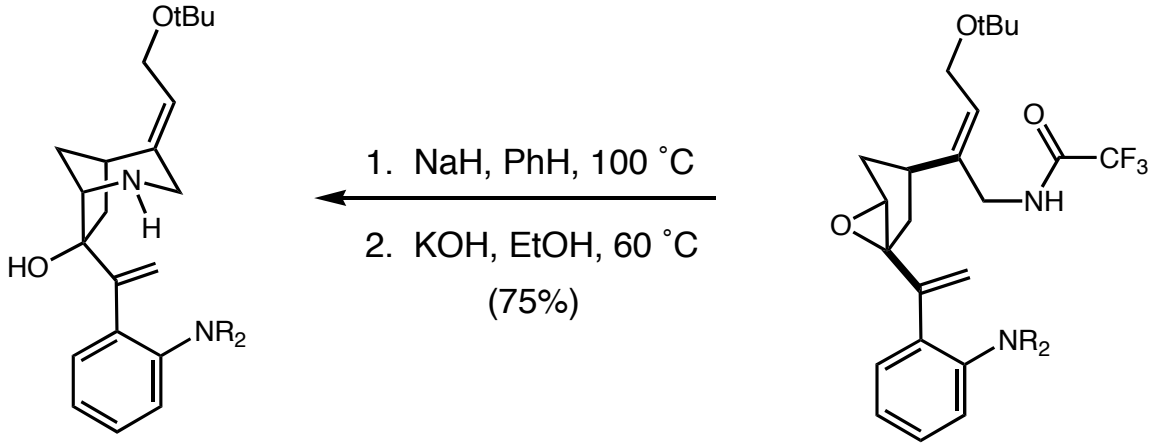


NR_2:



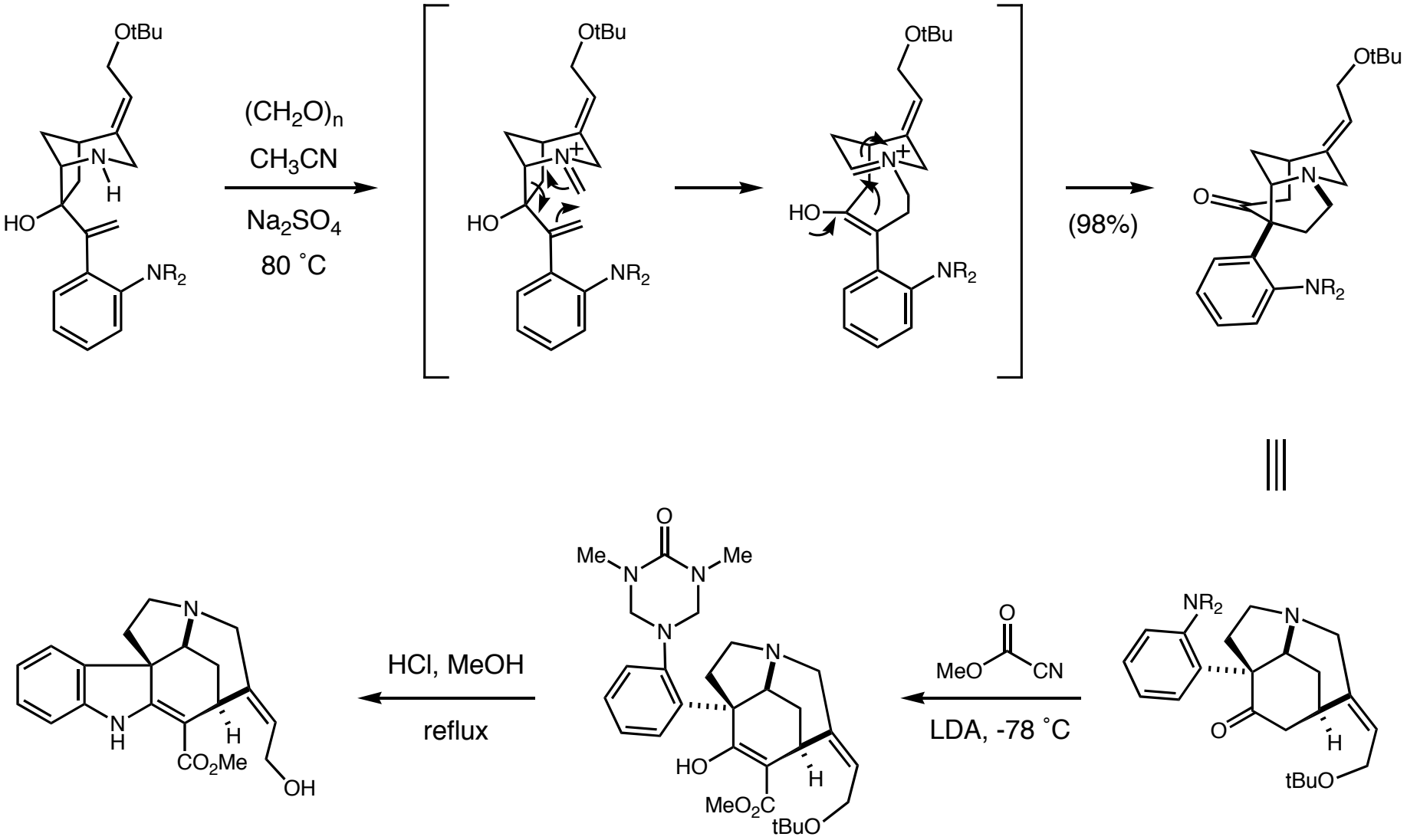
Triton B:





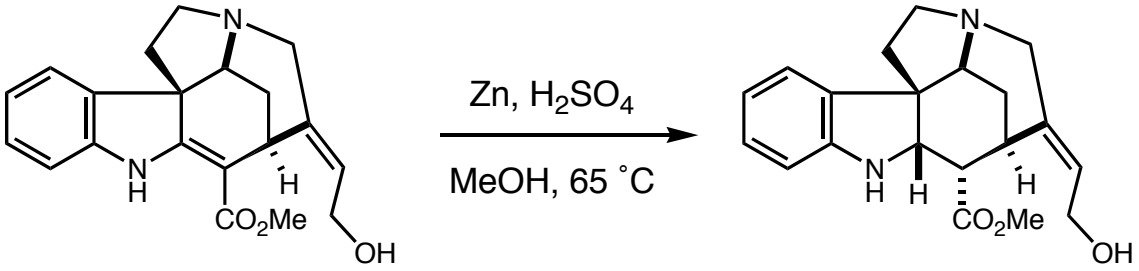
Overman: Key Aza-Cope-Mannich Cascade Forges Strychnine Core

- Single step constructs BCD ring system in nearly quantitative yield



Overman: Completion of the Natural Product

- Iminium reduction / basic epimerization set final stereocenters



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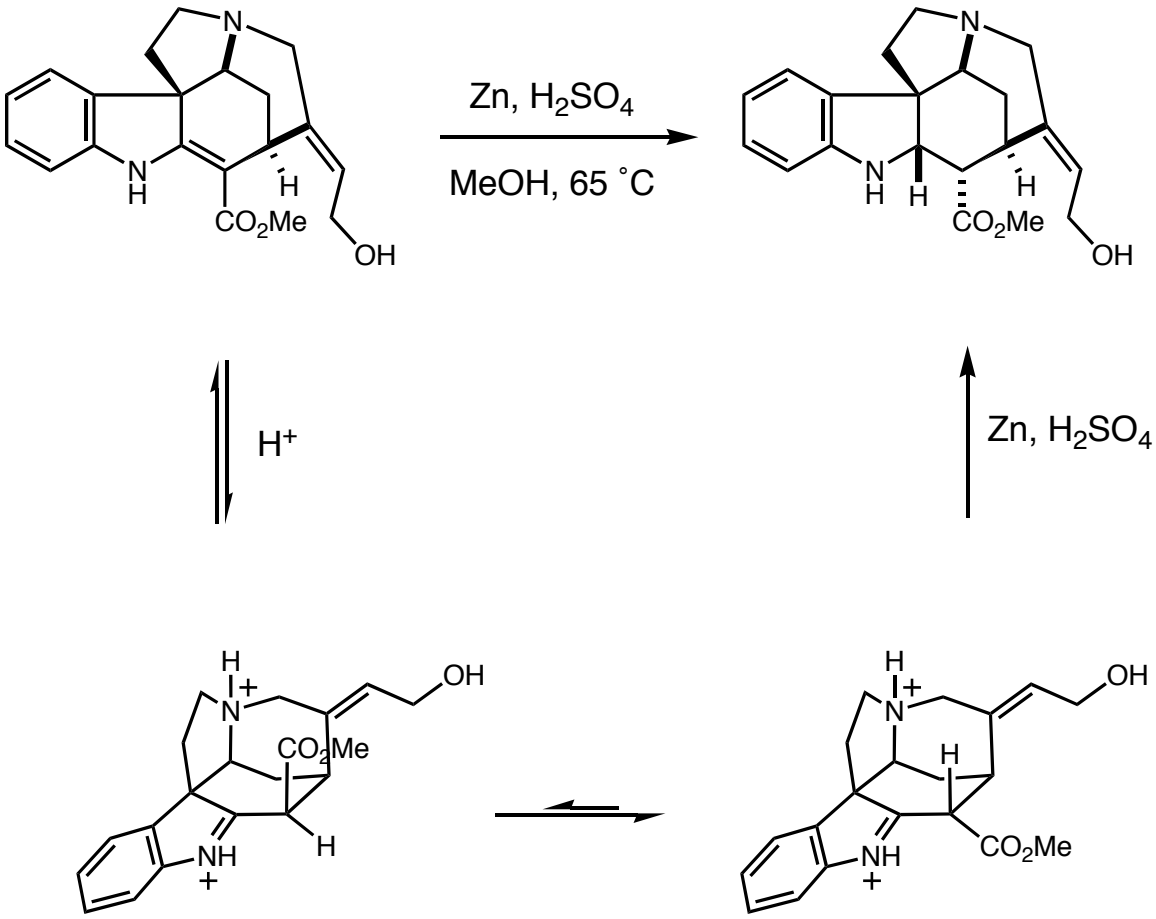

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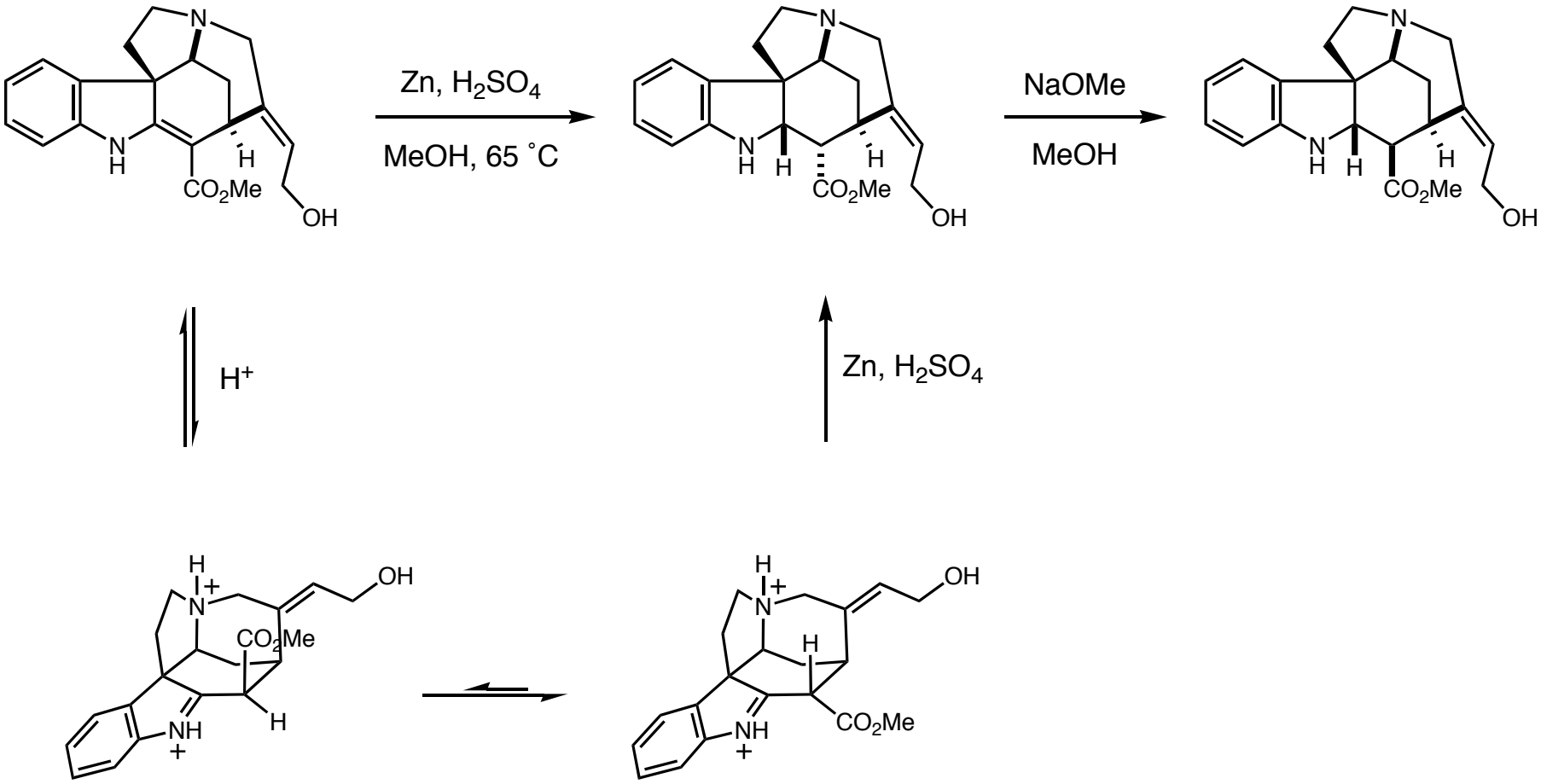

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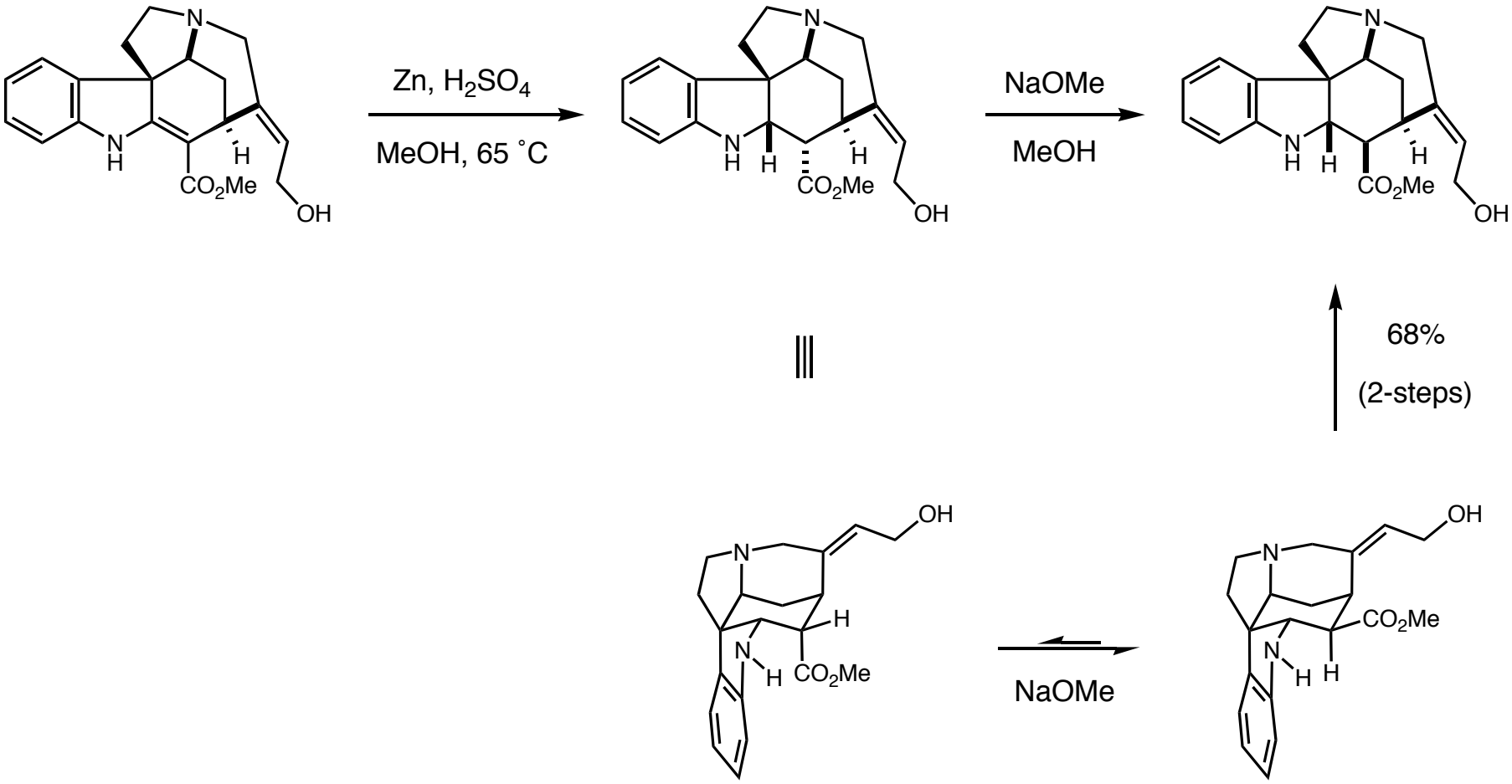

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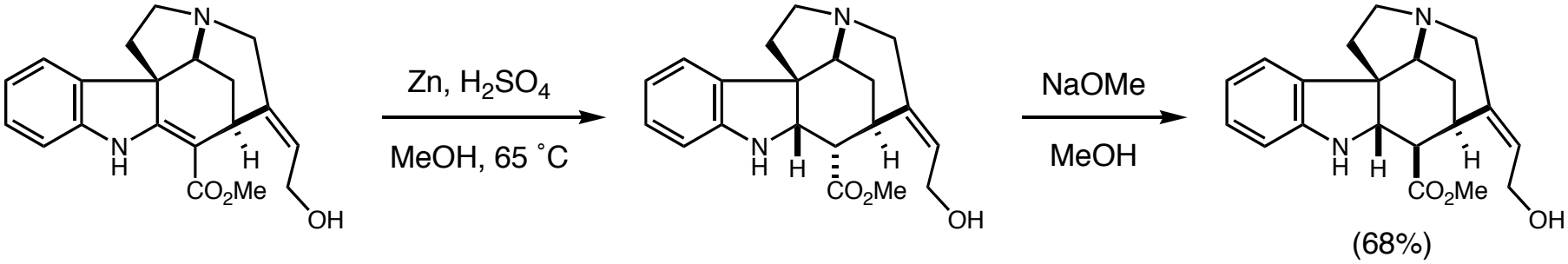
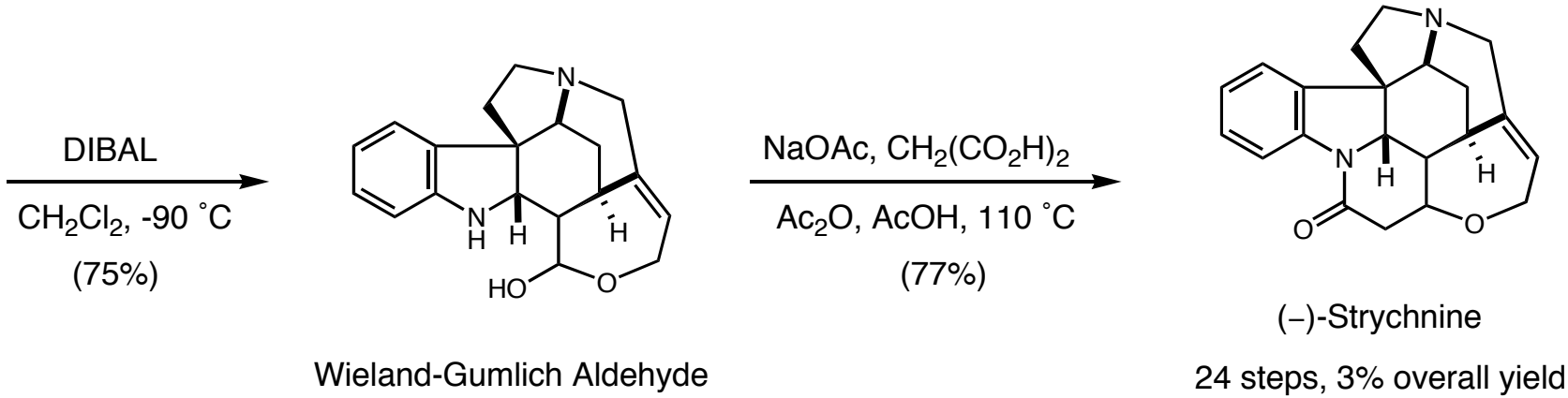




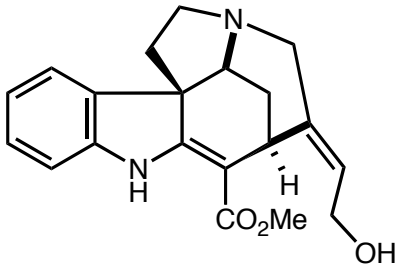
Wieland-Gumlich Aldehyde

(–)-Strychnine

24 steps, 3% overall yield

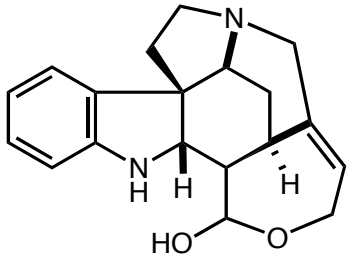
Many Routes Utilize the Same Endgame

- Iminium reduction / basic epimerization correctly set final stereocenters



Common Intermediate

1. Zn, H_2SO_4, or $NaBH(OAc)_3$
2. NaOMe or NaH, MeOH, rt
3. DIBAL, CH_2Cl_2 or toluene



Wieland-Gumlich Aldehyde

- 9 Routes go through the Wieland-Gumlich aldehyde
- 6 Use the same sequence to set sterochemistry:

1992: Magnus (similar): (±), 28 steps, 0.03% yield

1993: Overman: (–), 24 steps, 3% yield

1998: Kuehne: (–), 19 steps, 3% yield

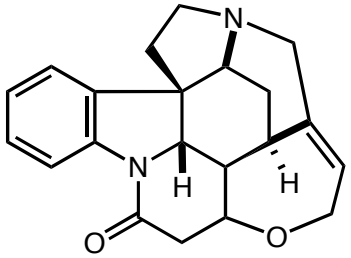
2000: Bonjoch/ Bosch: (–), 16 steps, 0.2% yield

2001: Martin: (±), 16 step formal, ca 1% yield*

2004: Fukuyama: (–), 25 steps, 2% yield

NaOAc, $CH_2(CO_2H)_2$

Ac_2O, AcOH, 110 ˚C

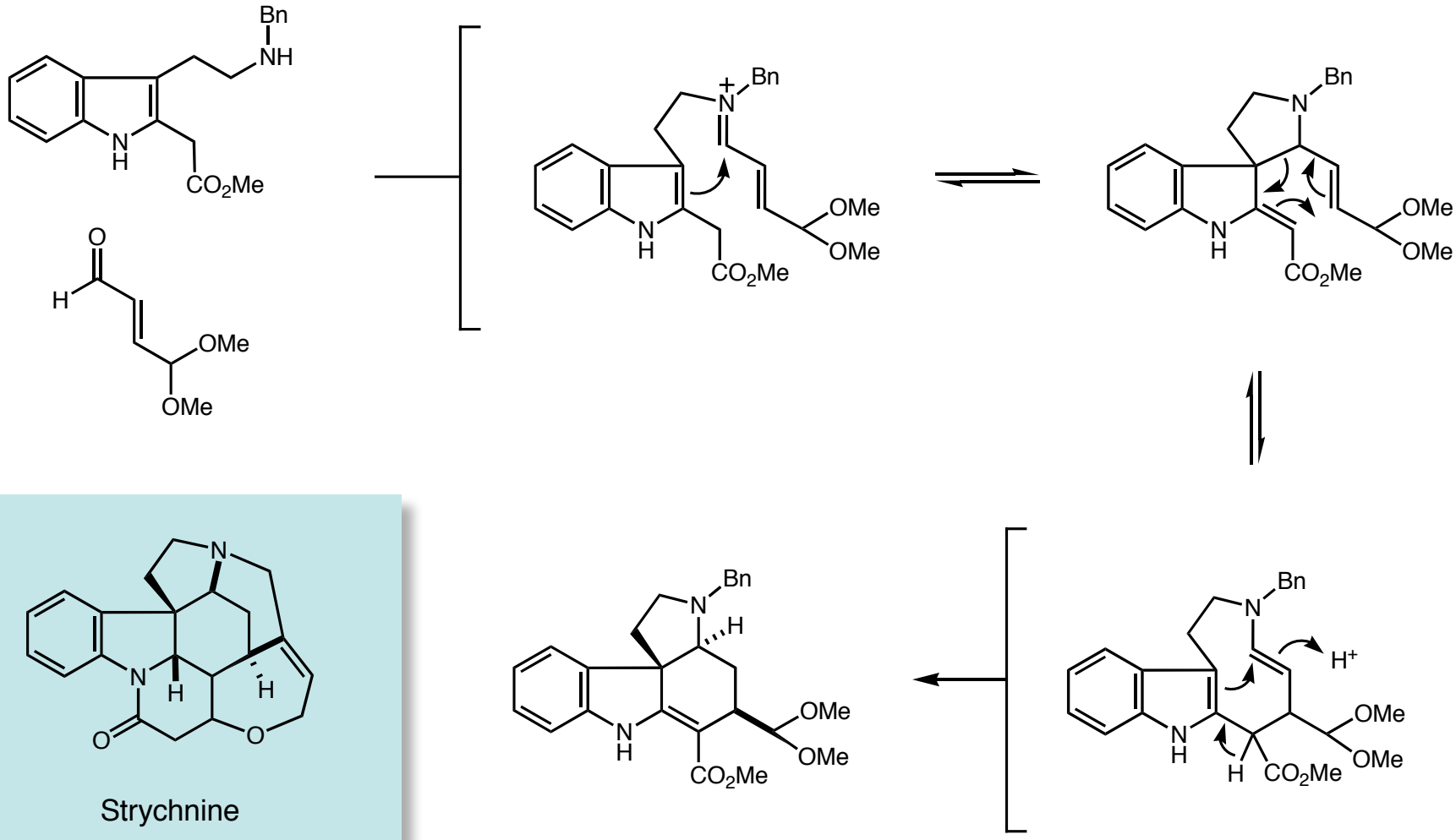


Strychnine

*Calculated using Overman's yields.

Kuehne's Plan for Strychnine

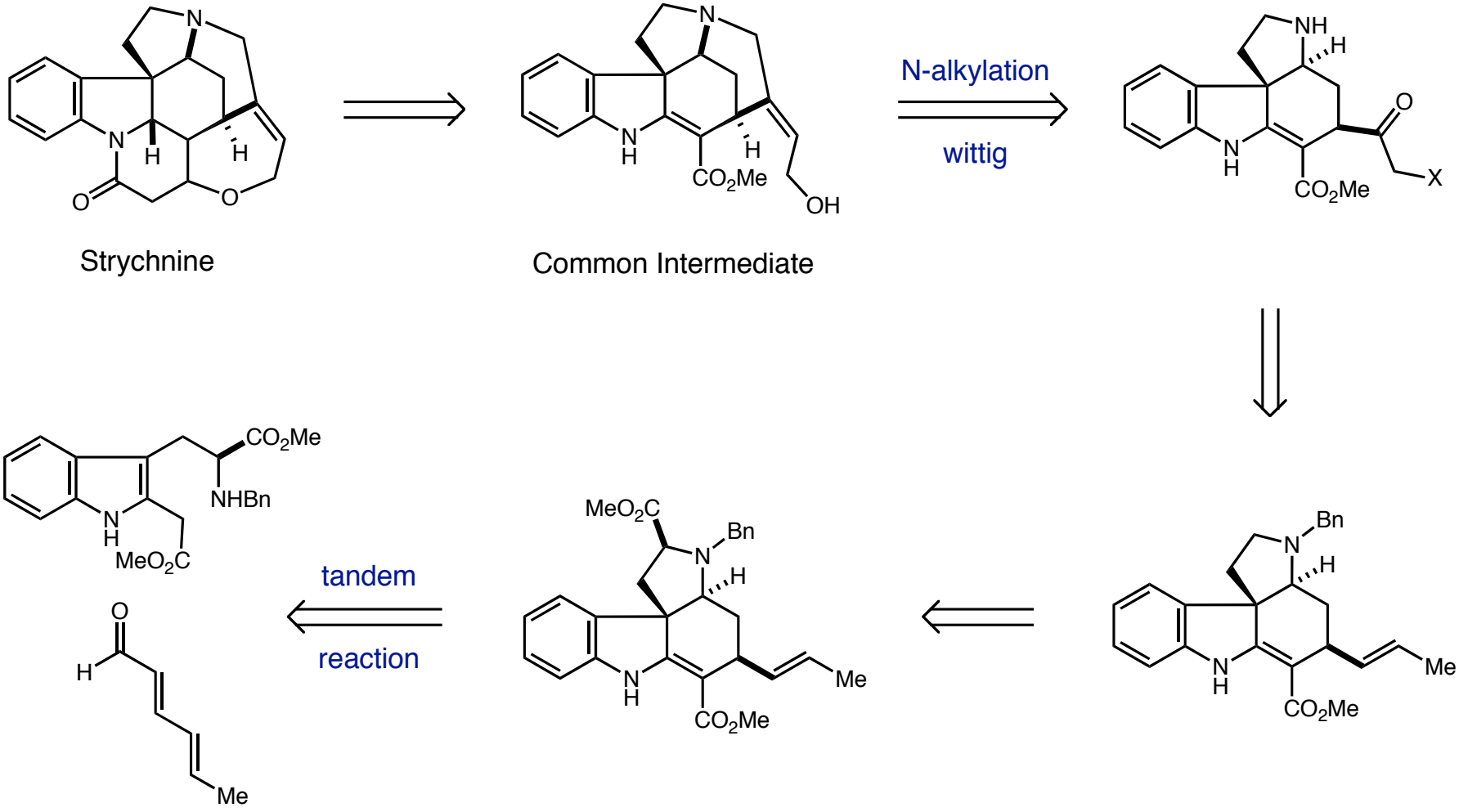
- Tandem Mannich-[3,3]-sigmatropic rearrangement-Mannich reaction



racemic: Kuehne *J. Org. Chem.* **1993**, 7490.

Kuehne's Retrosynthetic Analysis of the Common Intermediate (1998)

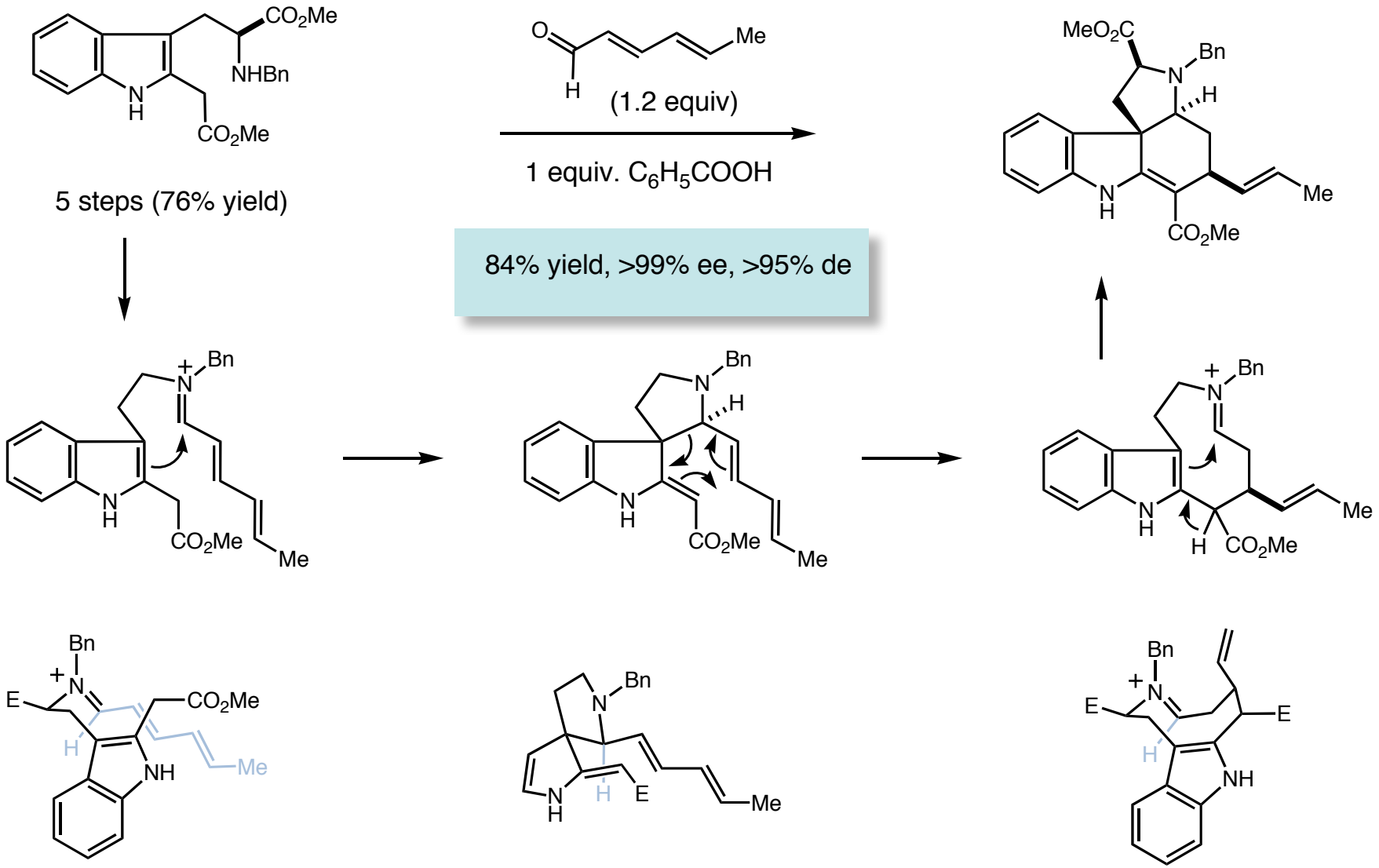
- Tryptophan-derived starting material would allow for enantioselective synthesis



enantioselective: Kuehne *J. Org. Chem.* **1998**, 9427.

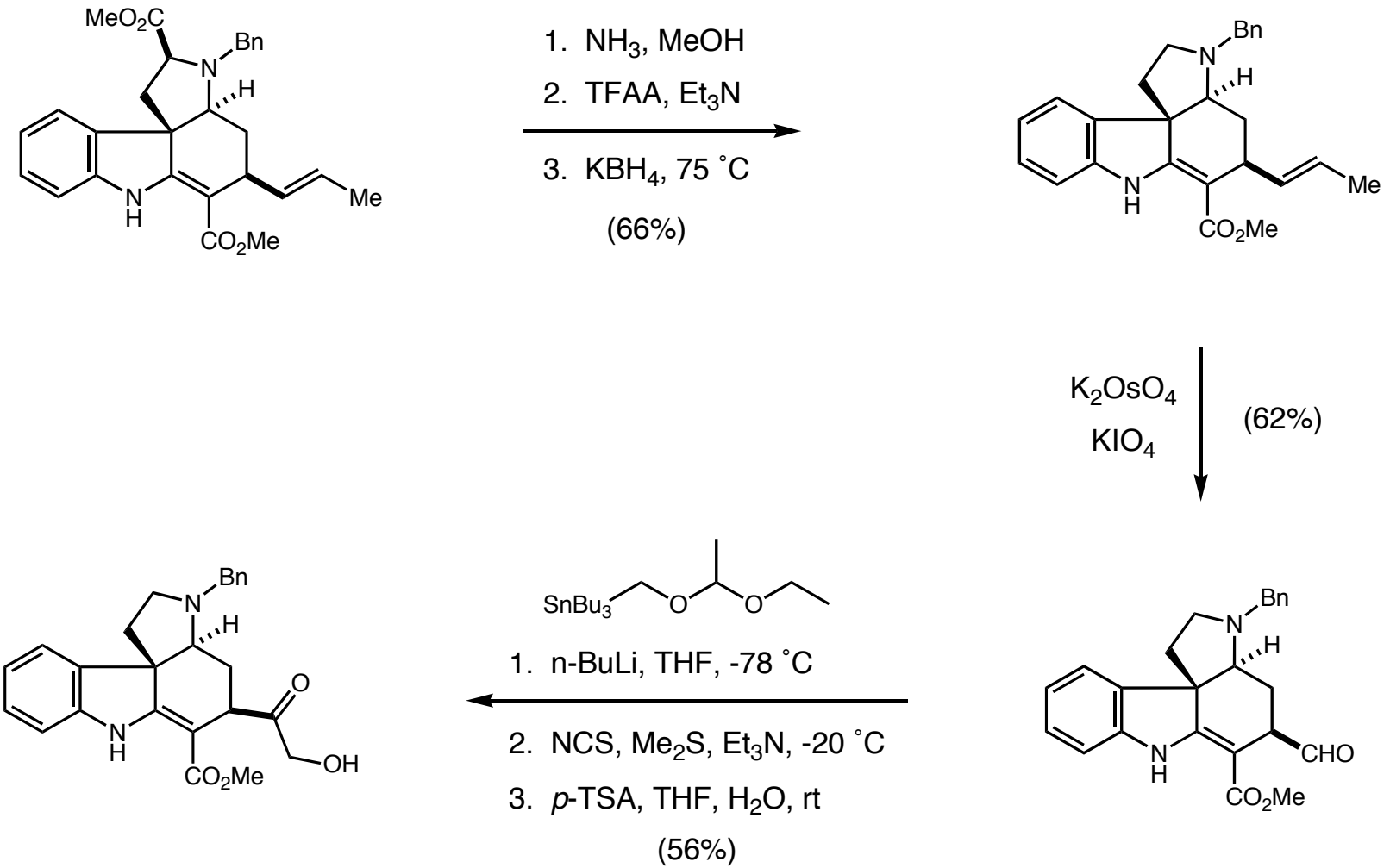
Kuehne: Diastereoselective Mannich-[3,3]-Mannich Cascade

- Ester stereocenter allows for complete stereoselectivity (3 new stereocenters)



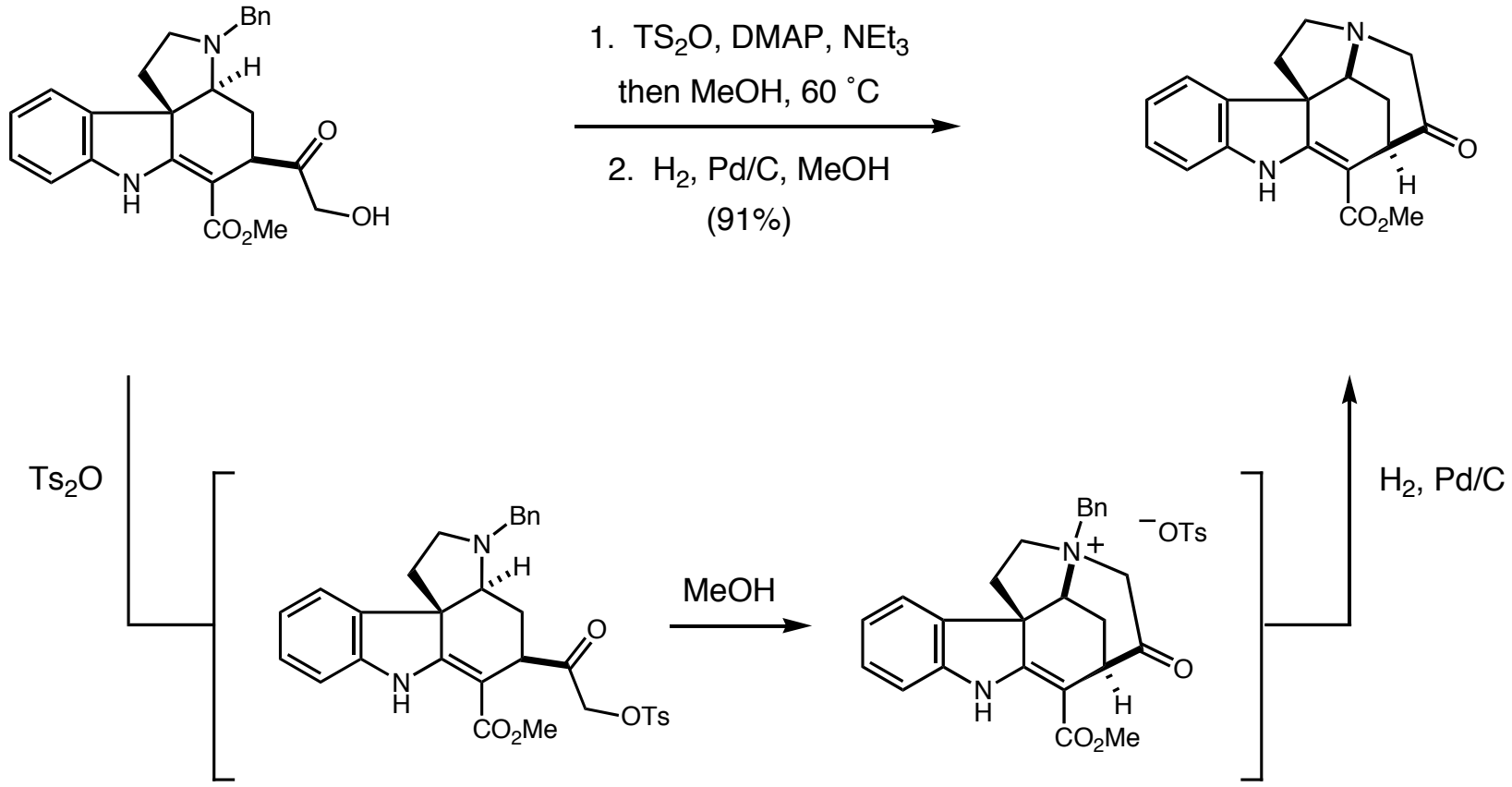
Kuehne: Further Elaboration of the Cascade Product

- α-Aminonitrile reduction with KBH_4 removes the chirality source



Kuehne: Completion of the Common Intermediate

- N-Alkylation reaction forms D-ring via ammonium reduction



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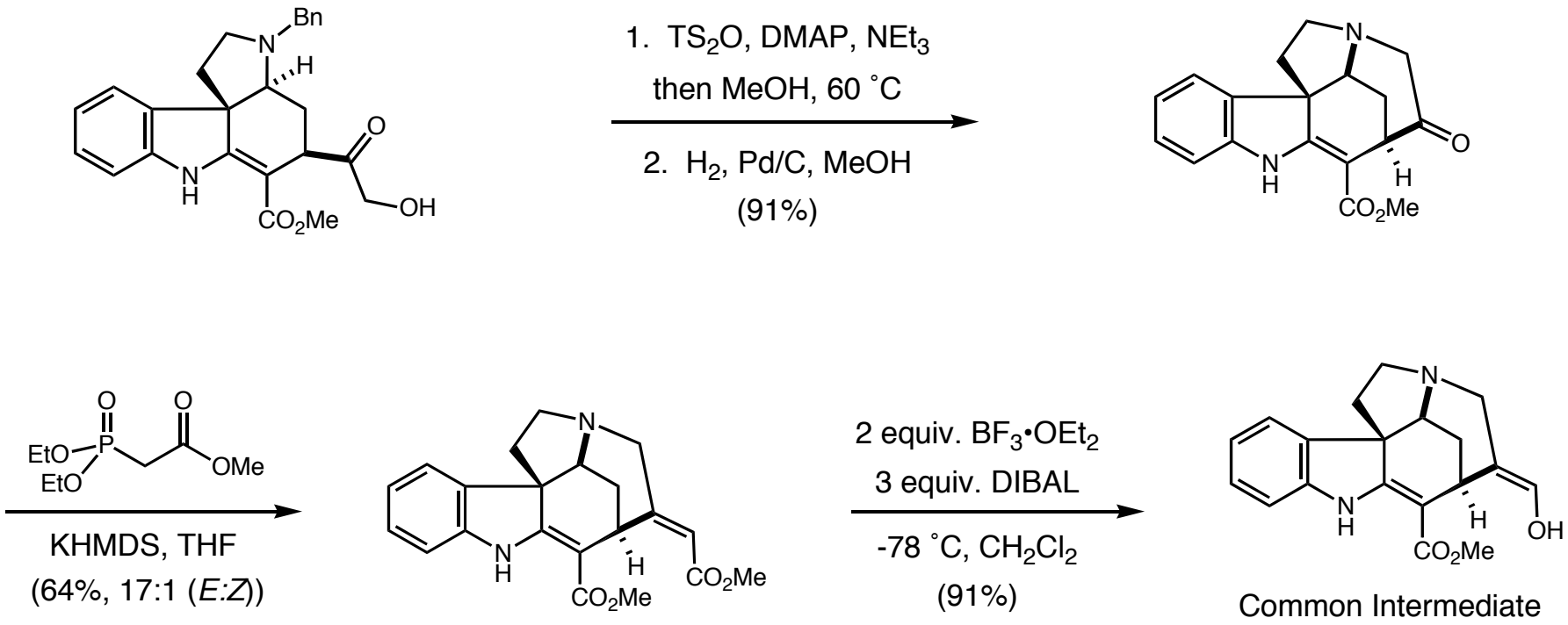

(–)-Strychnine (19 steps, 3% overall yield)

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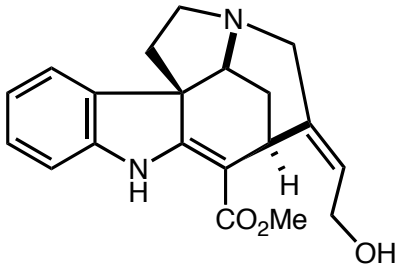

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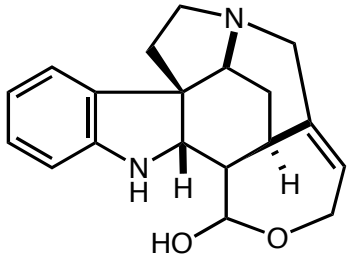

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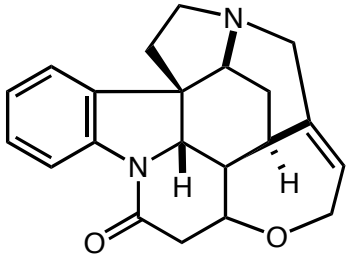
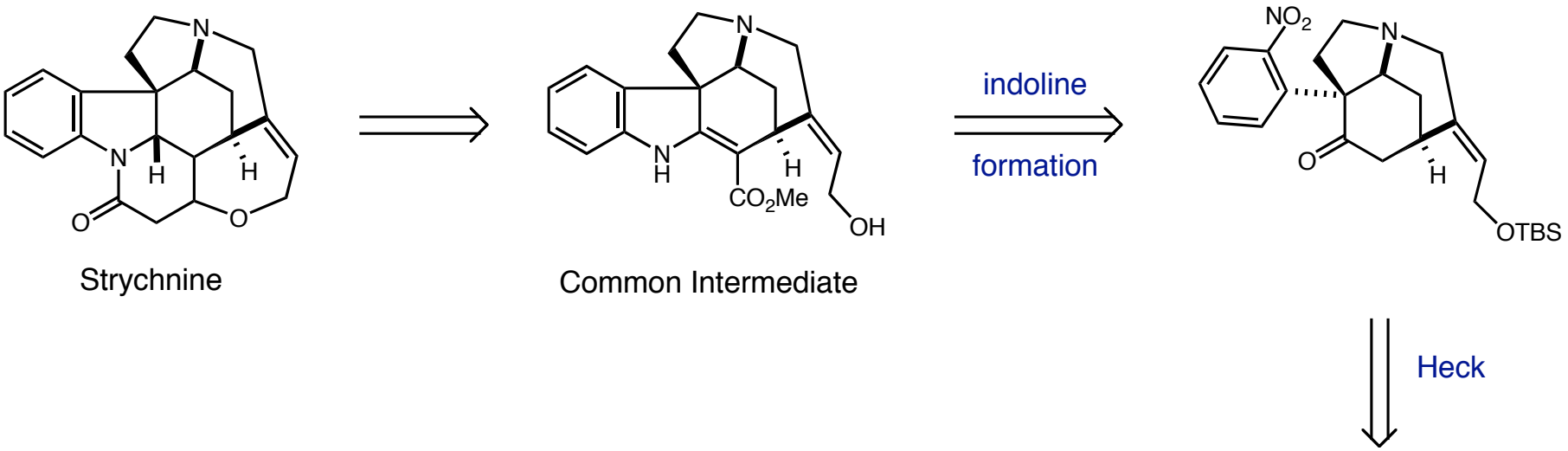


Strychnine

*Calculated using Overman's yields.

Bonjoch and Bosch: Retrosynthetic Analysis

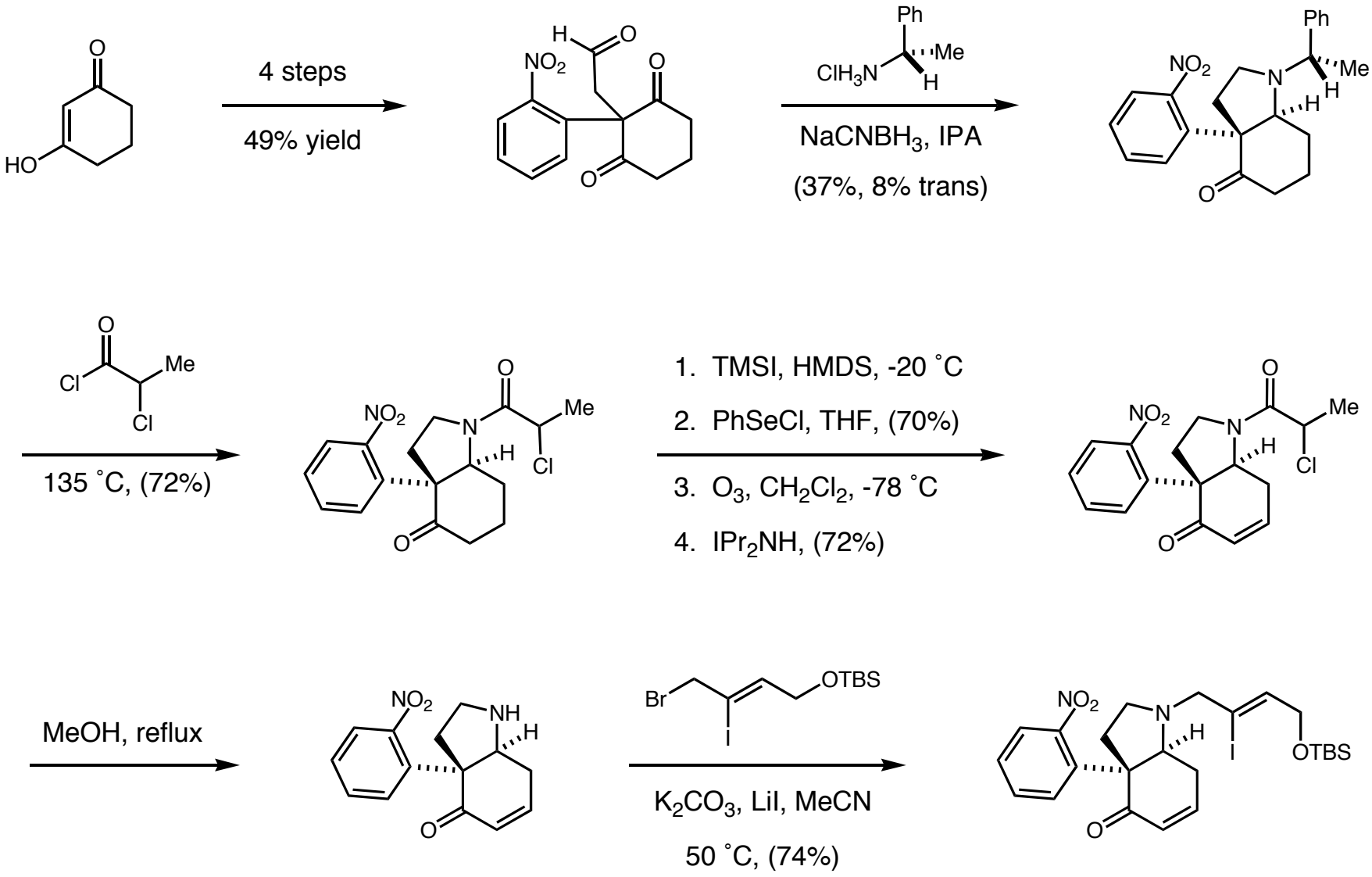
- Diastereoselective reductive amination would induce asymmetry, vinylation to set core



Bonjoch and Bosch *Angew. Chem. Int. Ed.* **1999**, 395.

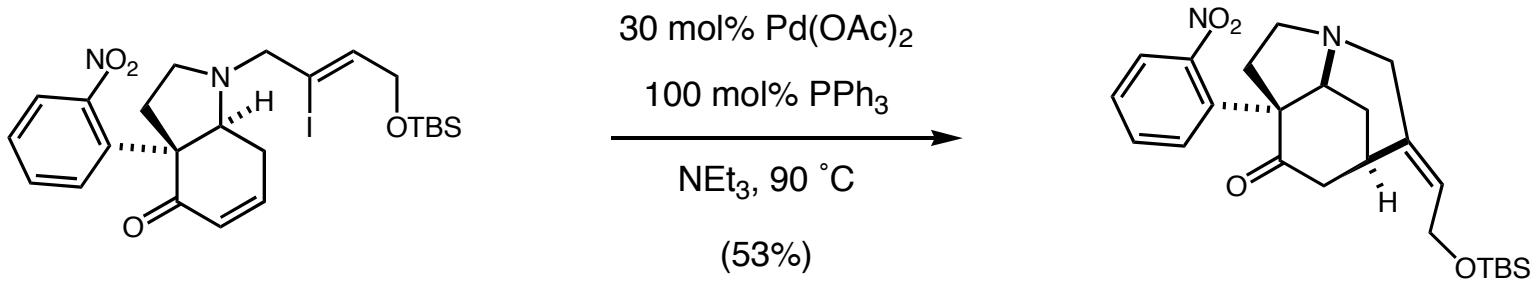
Bonjoch and Bosch: Disapointing Double Reductive Amination

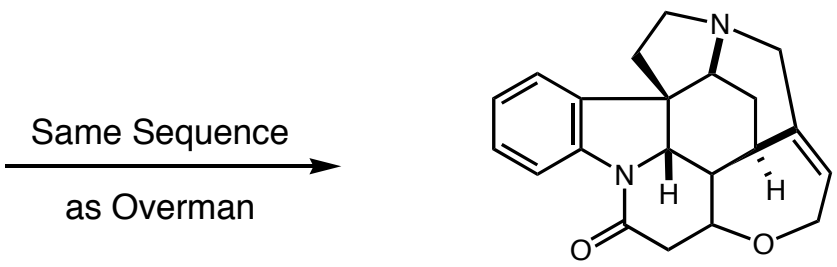
- Preparation of the required vinyl iodide substrate has a rough beginning



Bonjoch and Bosch: D-Ring Formation via Heck Reaction

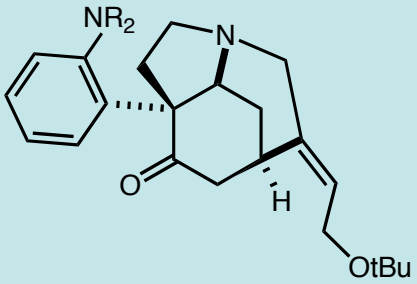
- Intramolecular Heck reaction provides desired tetracyclic product in moderate yield





(–)-Strychnine

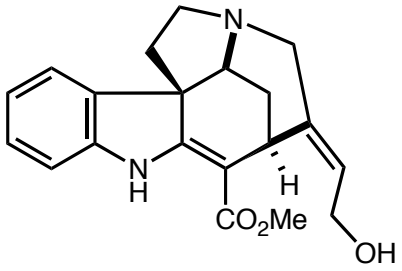
16 steps, 0.2% yield



Overman Intermediate

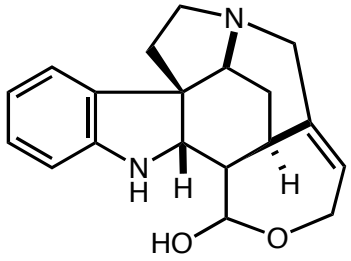
Many Routes Utilize the Same Endgame

- Iminium reduction / basic epimerization correctly set final stereocenters



Common Intermediate

1. Zn, H_2SO_4, or $NaBH(OAc)_3$
2. NaOMe or NaH, MeOH, rt
3. DIBAL, CH_2Cl_2 or toluene



Wieland-Gumlich Aldehyde

- 9 Routes go through the Wieland-Gumlich aldehyde
- 6 Use the same sequence to set sterochemistry:

1992: Magnus (similar): (±), 28 steps, 0.03% yield

1993: Overman: (–), 24 steps, 3% yield

1998: Kuehne: (–), 19 steps, 3% yield

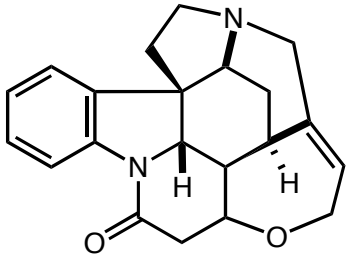
2000: Bonjoch/ Bosch: (–), 16 steps, 0.2% yield

2001: Martin: (±), 16 step formal, ca 1% yield*

2004: Fukuyama: (–), 25 steps, 2% yield

NaOAc, $CH_2(CO_2H)_2$

Ac_2O, AcOH, 110 ˚C

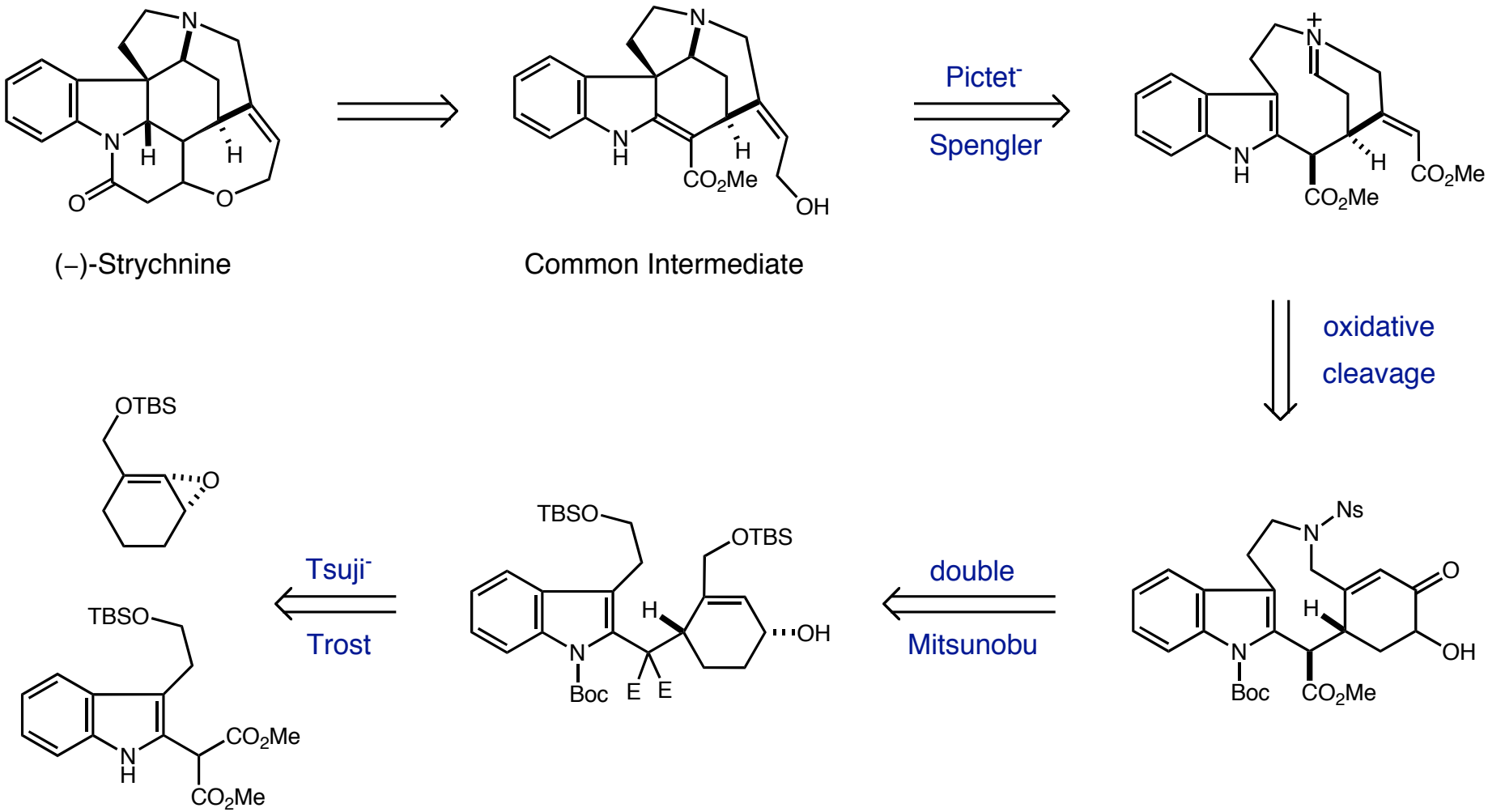


Strychnine

*Calculated using Overman's yields.

Fukuyama's Approach to (–)-Strychnine

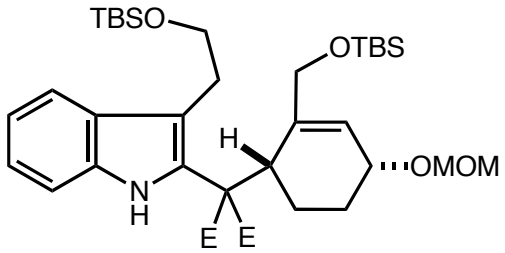
- Double Mitsunobu reaction sets up key Diasteroselective Pictet-Spengler reaction



Fukuyama, *J. Am. Chem. Soc.*, **2004**, 10246.

Fukuyama: Intramolecular Pictet-Spengler Sets Strychnine Core

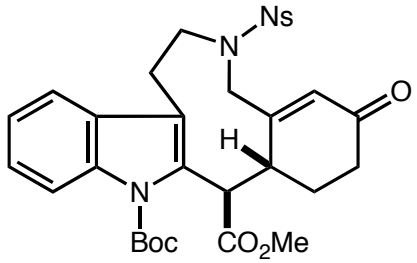
- Key ring contraction forms CDE ring system as a single diastereomer



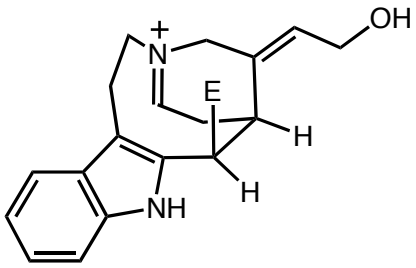
9 steps from benzoic acid (10%)

7 steps

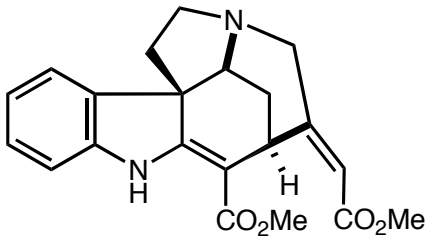
47% yield



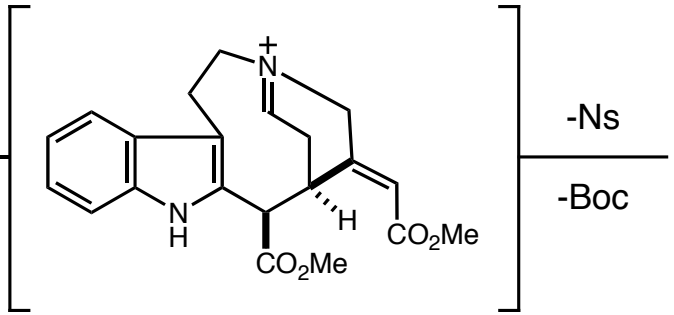
-Ns:	$PhSH, Cs_2CO_3, MeCN$
-Boc:	TFA, Me_2S, CH_2Cl_2
	all at 50 ˚C



3 steps

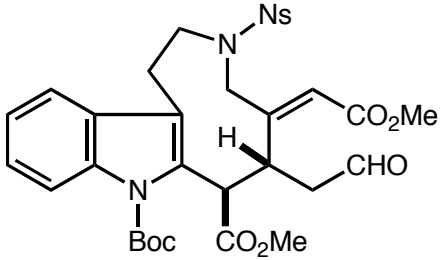


55% (4 steps)



-Ns

-Boc



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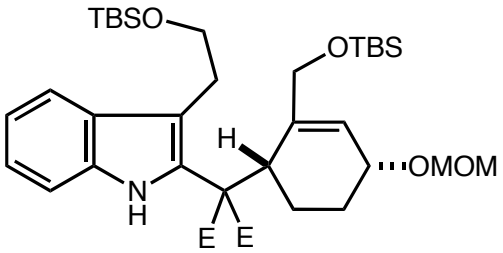

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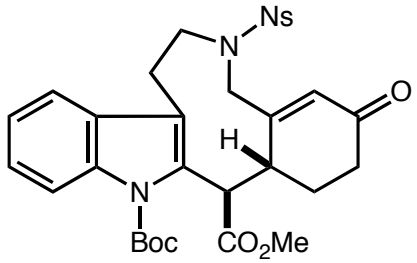

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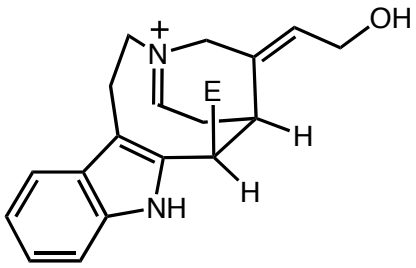
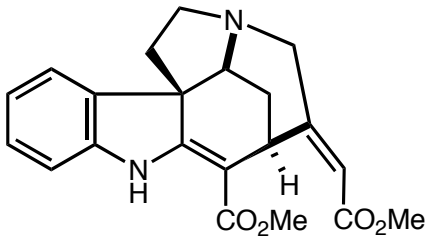
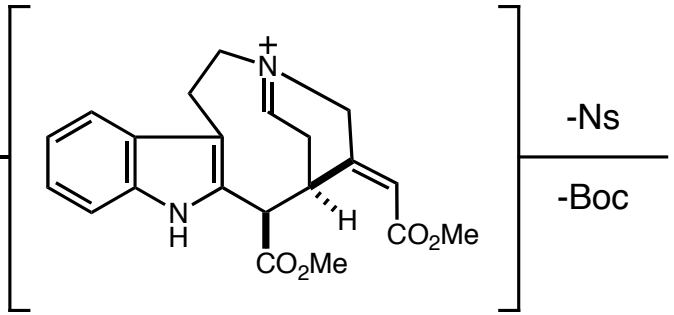


3 steps

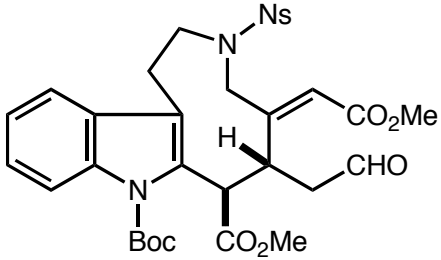


55% (4 steps)



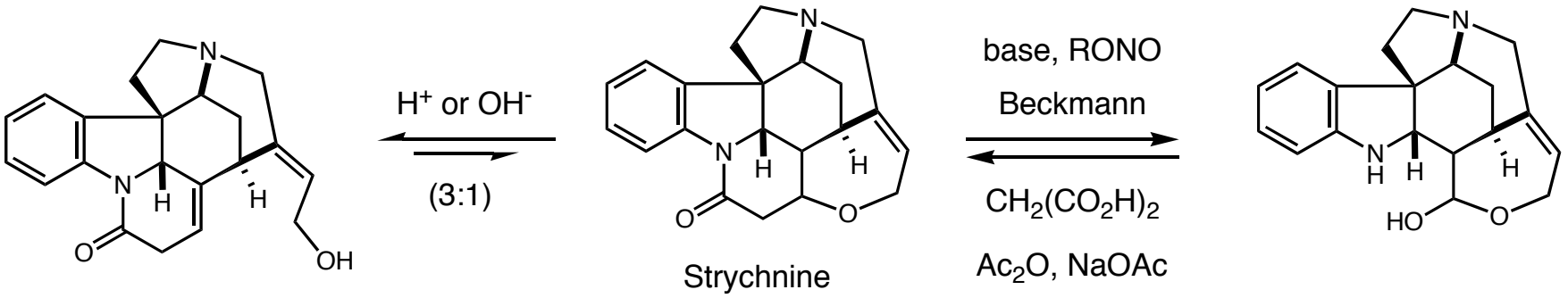
-Ns

-Boc



(–)-Strychnine (25 steps, 2% yield)

Comparing the Syntheses of Strychnine



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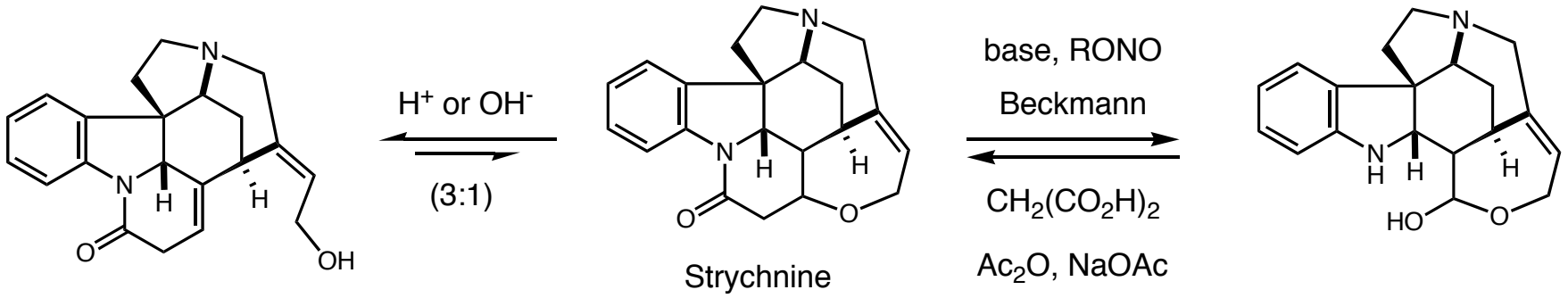

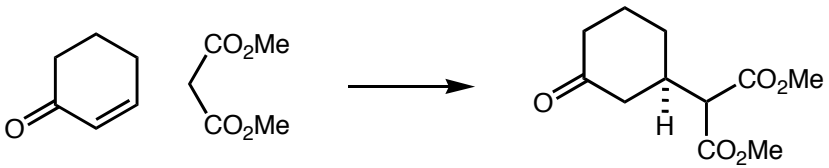

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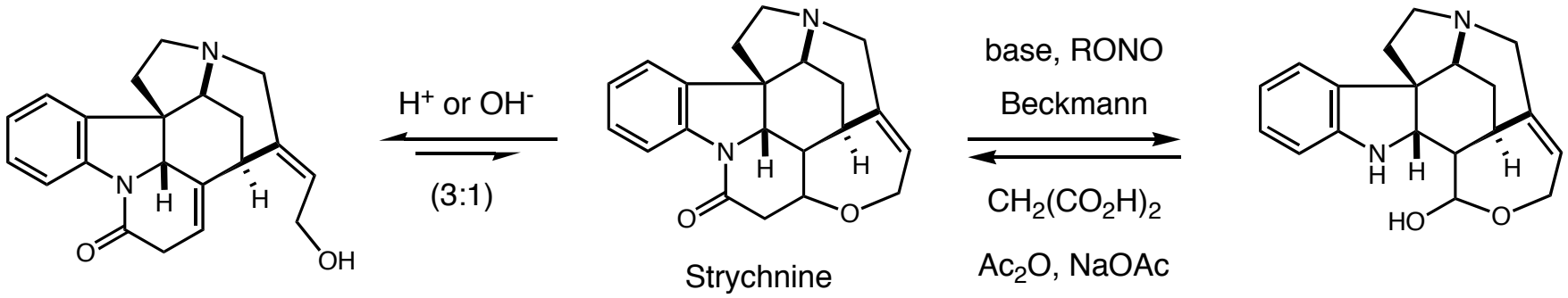

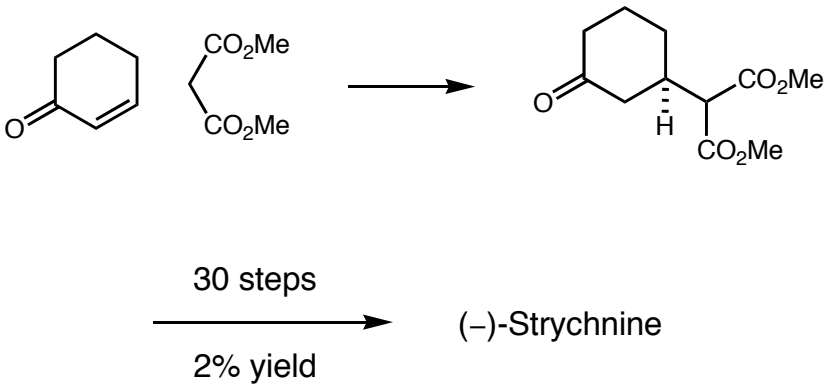

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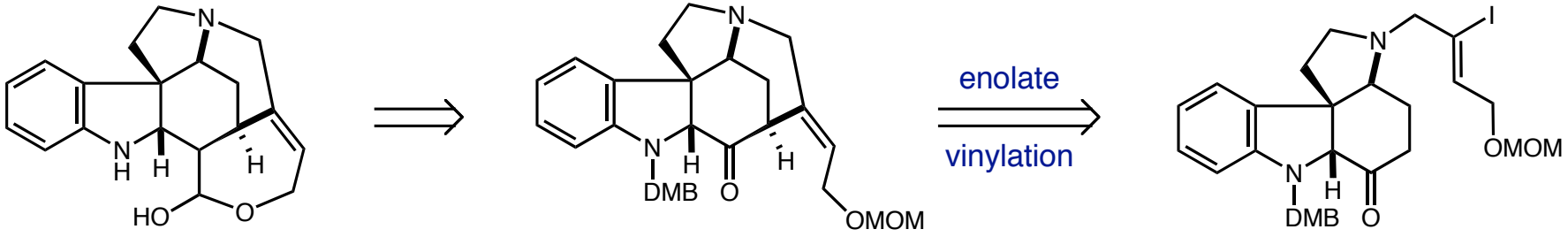
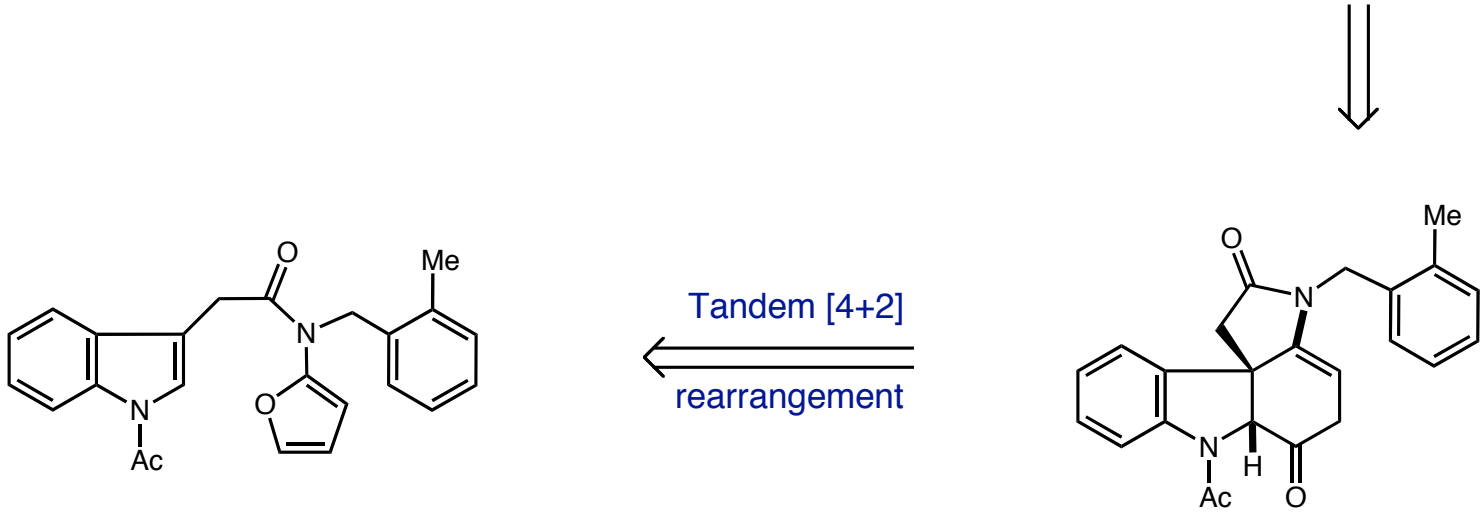
2007: Padwa: (±), 16 steps, 2% yield

Padwa's Retrosynthetic Analysis

- Key Intramolecular Diels-Alder Fragmentation reaction rapidly sets the ABCE core



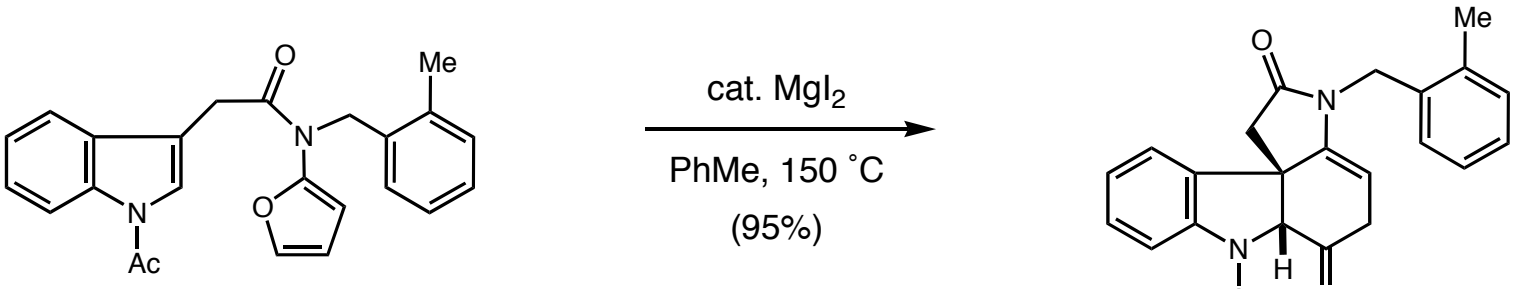
Wieland-Gumlich Aldehyde



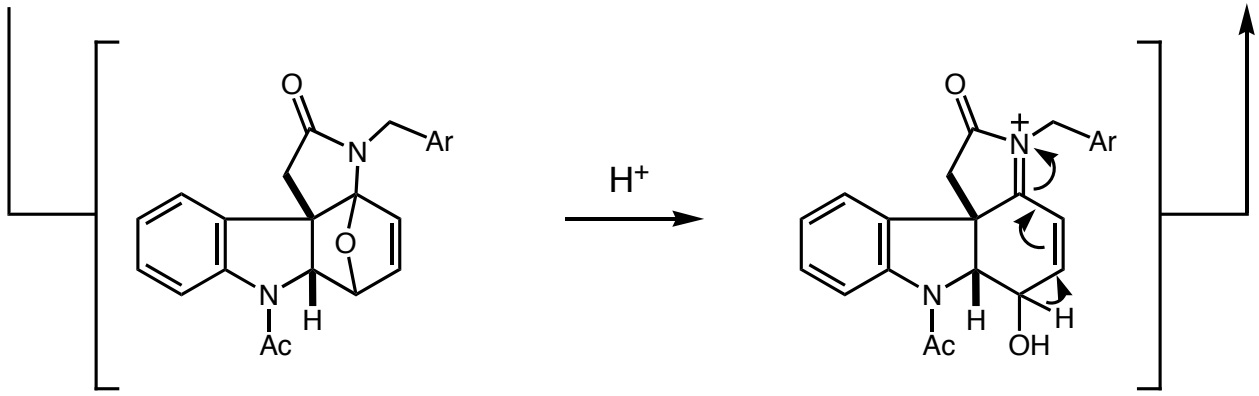
Padwa *Org. Lett.* **2007**, 279.

Padwa: Efficient Route to Strychnine Core

- Cascade Diels-Alder-fragmentation-elimination reaction sets CE ring system

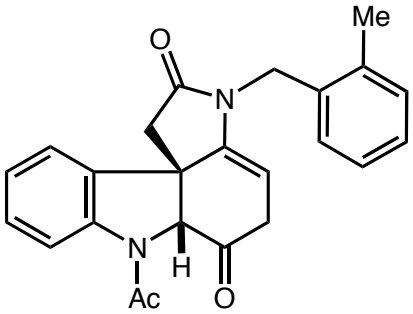


3-steps from acid (55% yield)



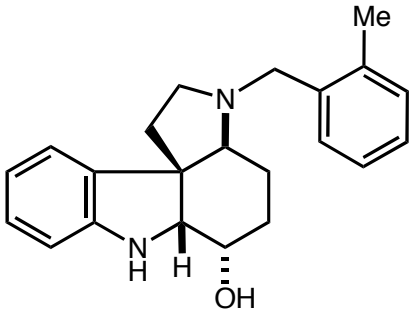
Padwa: Elaboration of Cascade Product

- 4-Step sequence to take down aminde, deprotect amine, set E-ring stereochemistry

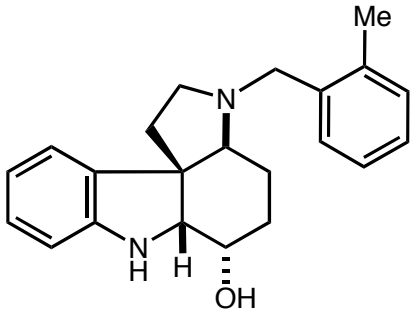


1. $NaBH_4$, MeOH, THF, 0˚C
2. NaOMe, MeOH, rt
3. $LiAlH_4$, THF, reflux
4. $NaBH(OAc)_3$, DCE, -20 ˚C

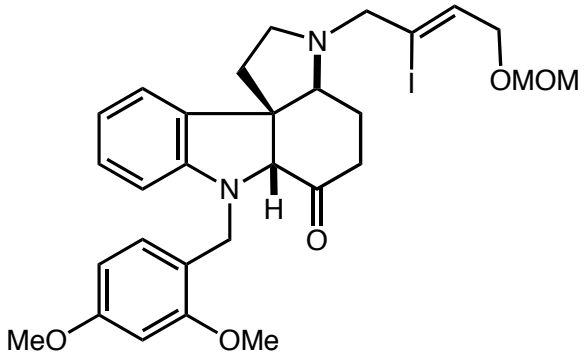
('65% yield of the major diastereomer')



- Deprotection/ N-alkylation sets the stage for D-ring formation via vinylation reaction

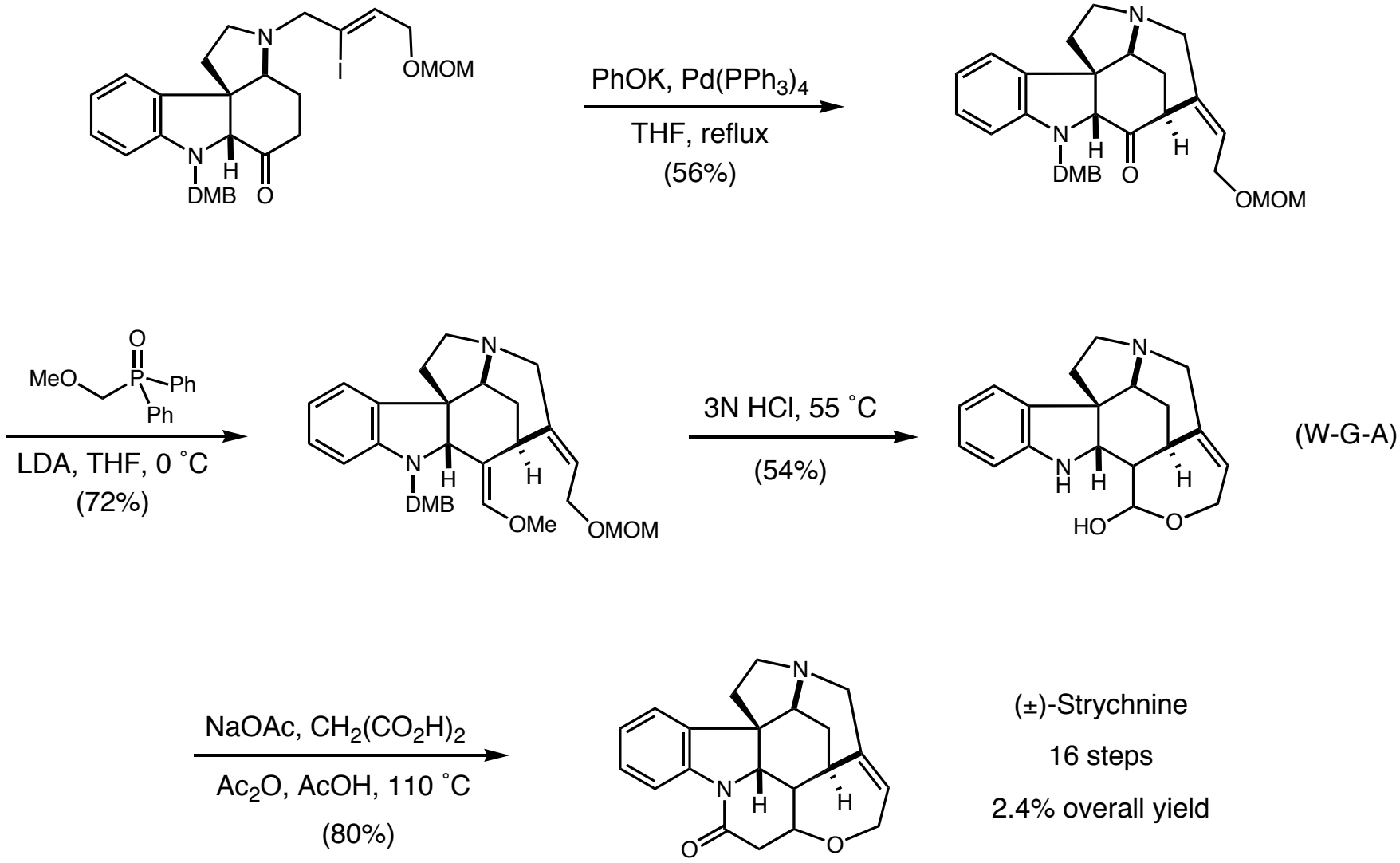


1. $Pd(OH)_2/C$, H_2 (70%)
2. RBr, K_2CO_3, DMF (80%)
3. ArCHO, $NaBH(OAc)_3$ (86%)
4. TPAP, NMO (80%)

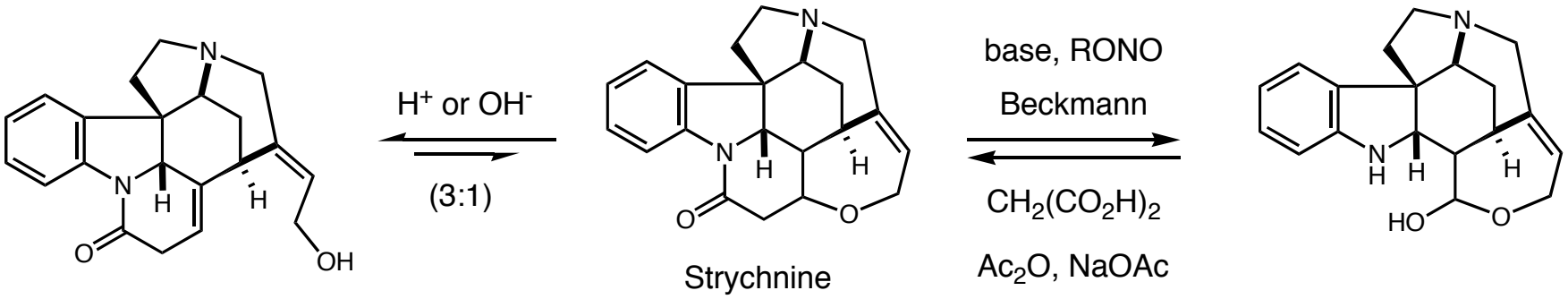


Padwa: The Finishing of Strychnine

- Palladium-catalyzed enolate vinylation reaction finishes skeleton



Comparing the Syntheses of Strychnine



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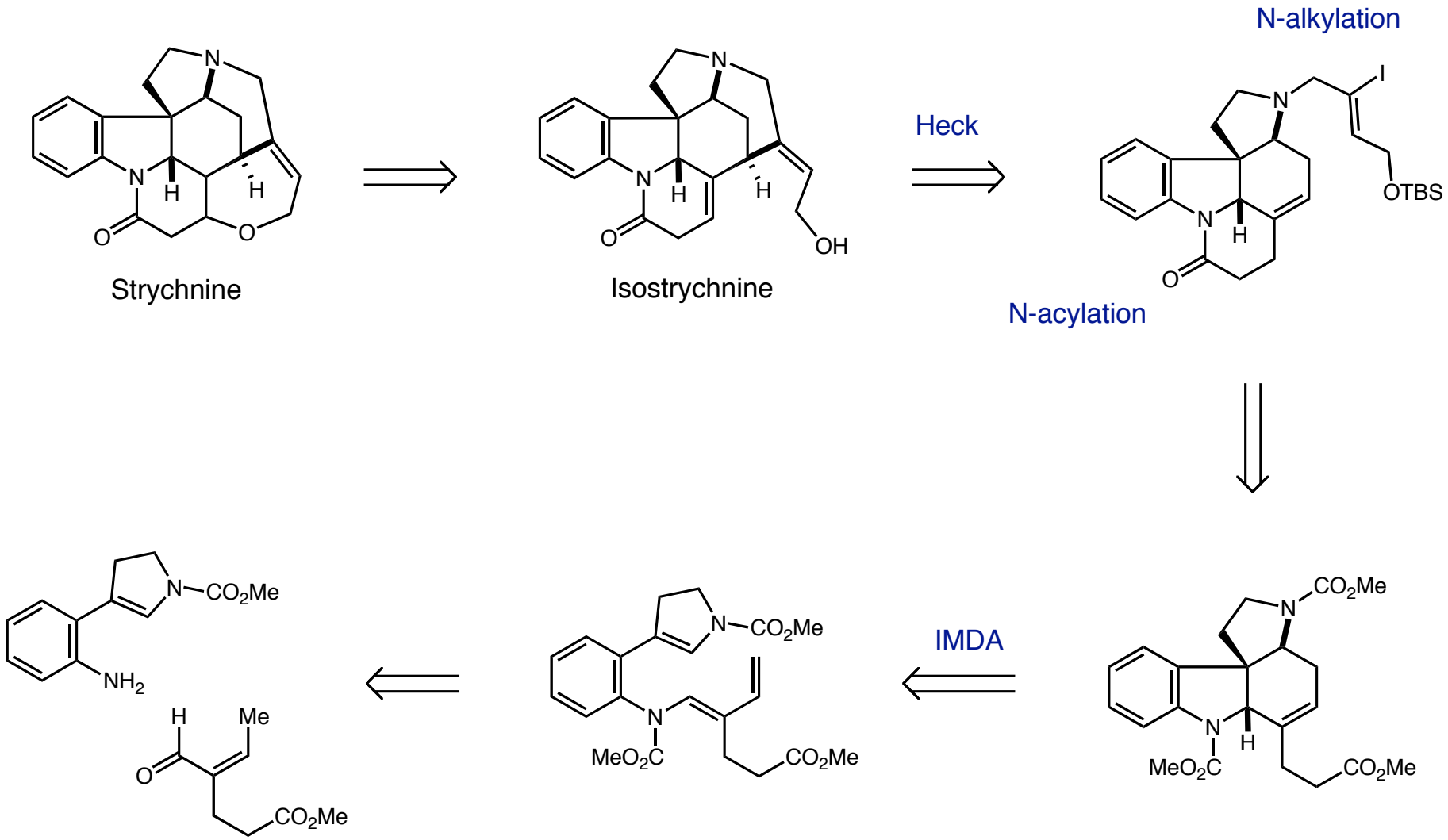
Rawal's Retrosynthetic Analysis of Isostrychnine

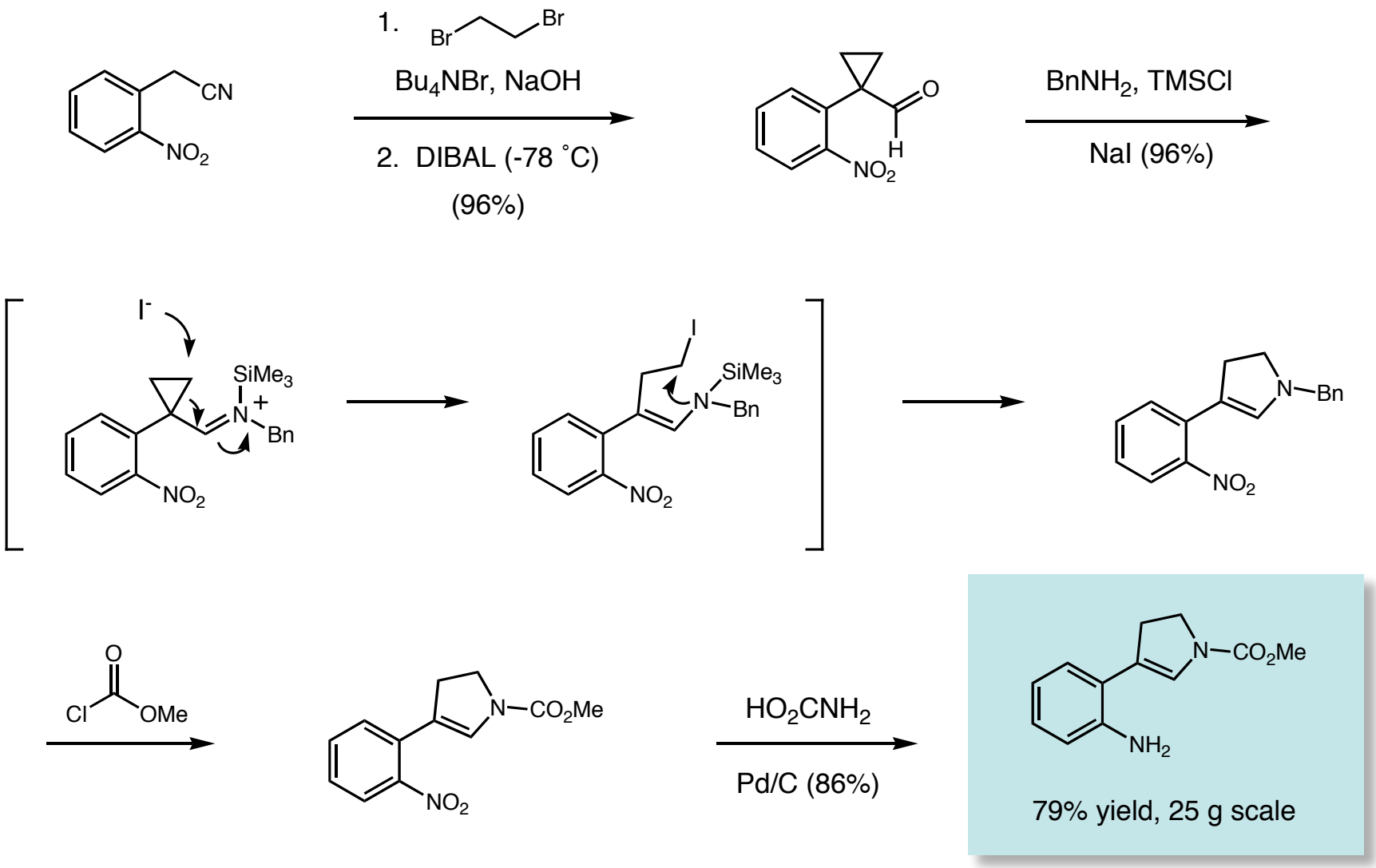
- Rawal uses an exo-selective intramolecular Diels-Alder reaction to forge BCE portion early



Rawal *J. Org. Chem.* **1994**, 2685.

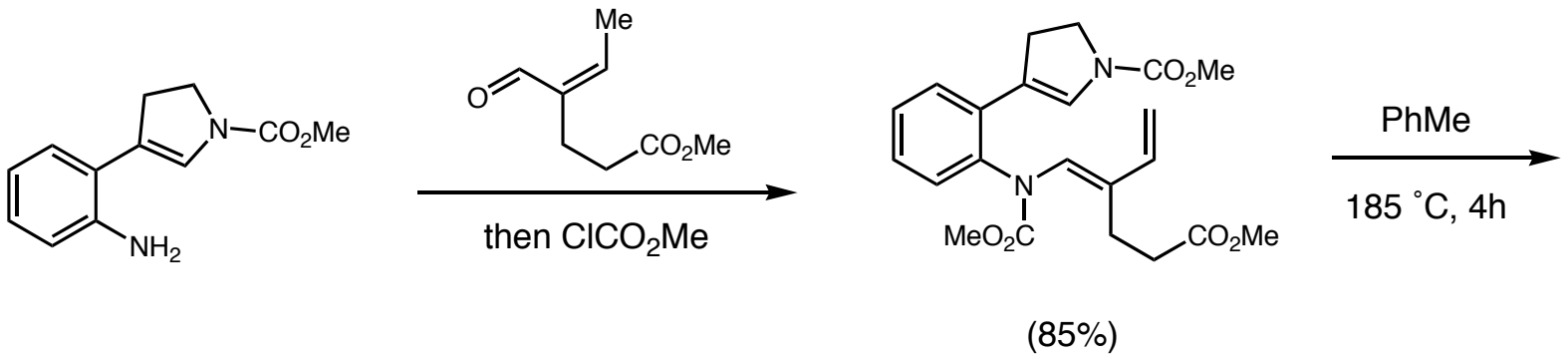
Rawal: Construction of Early Intermediates

- 5-step, scaleable synthesis of pyrrolidine starting material

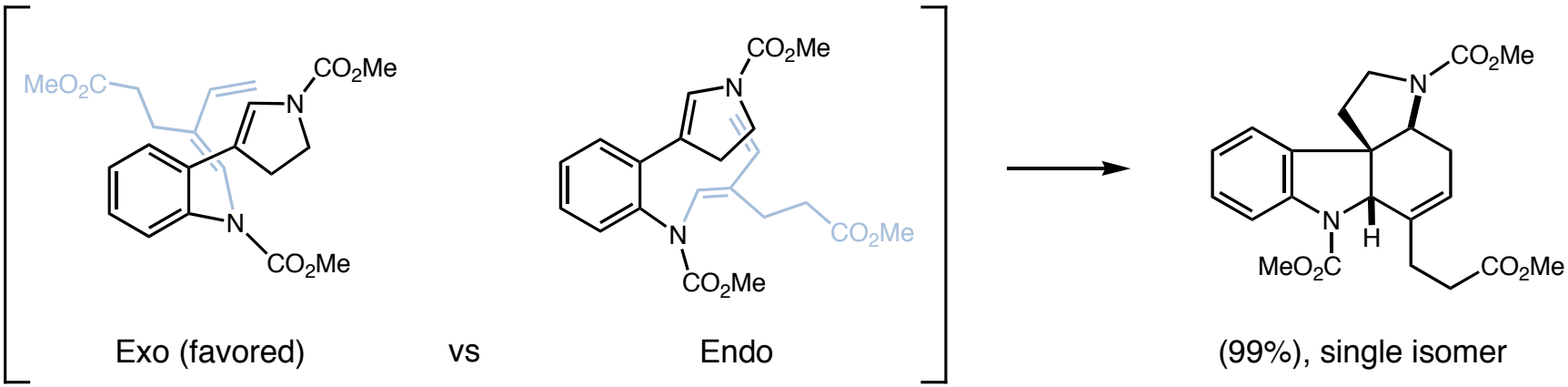


Rawal: Quantitative Key Intramolecular Diels-Alder Cycloaddition

- Thermal acyl dienamine [4+2] forges BCE ring system, C-7 spirocenter simultaneously



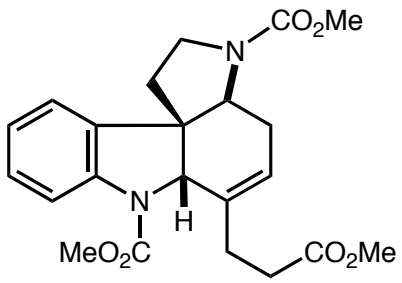
(85%)



(99%), single isomer

Rawal: Completion of the Natural Product via Heck Reaction

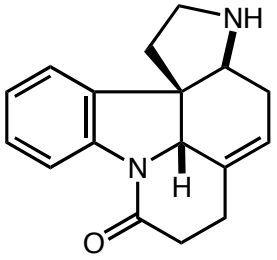
- One-pot deprotection/ acylation sequence forges G-ring, Heck reaction for D-ring



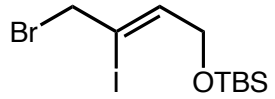
TMSI (10 equiv)

$CHCl_3$ reflux

then MeOH, reflux

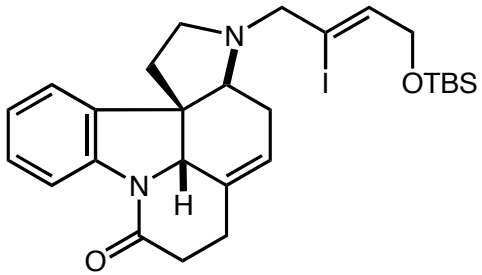


(90%)



K_2CO_3, Acetone

DMF



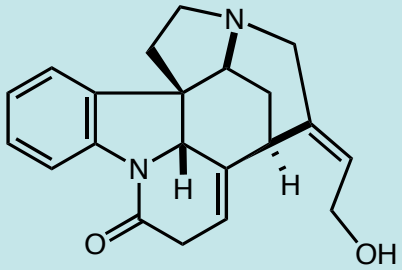
(83%)

1. 30 mol% $Pd(OAc)_2$

Bu_4NCl, DMF, K_2CO_3

70 ˚C, 3h

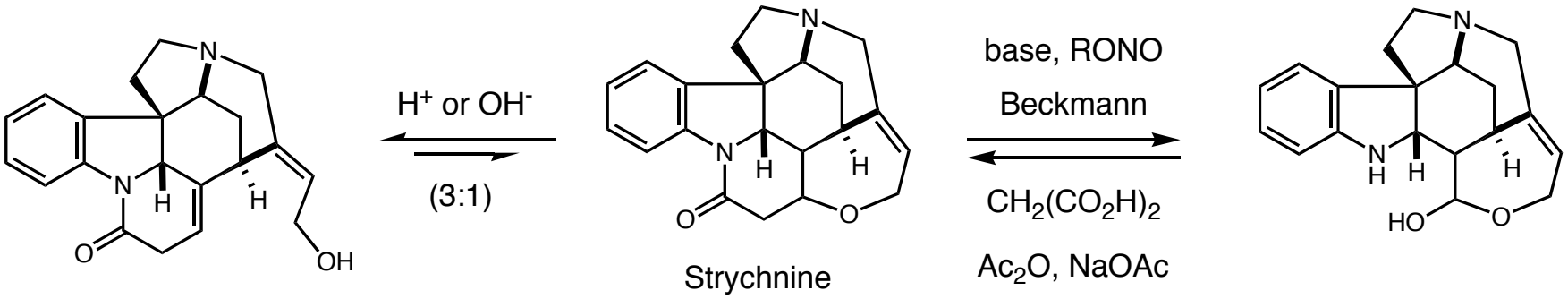
2. HCl, THF



Isostrychnine (71%)

13-steps, 10% overall yield

Comparing the Syntheses of Strychnine



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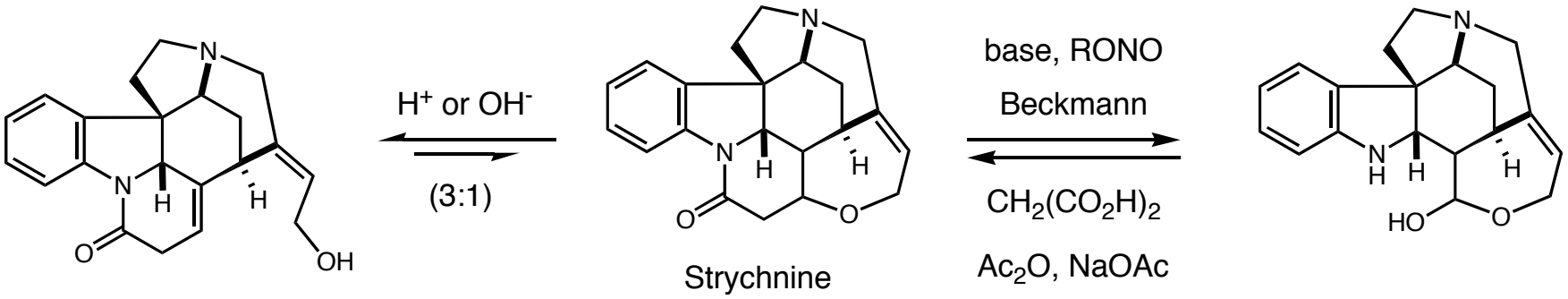

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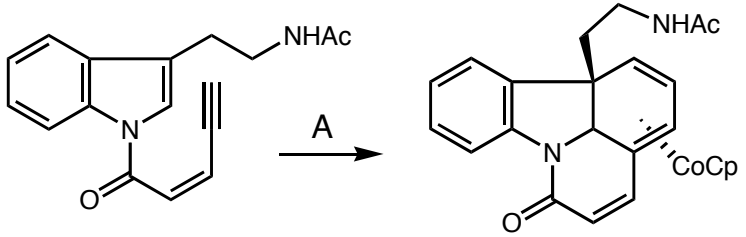


A: $CpCo(C_2H_2)_2$, C_2H_2, THF, 46% yield

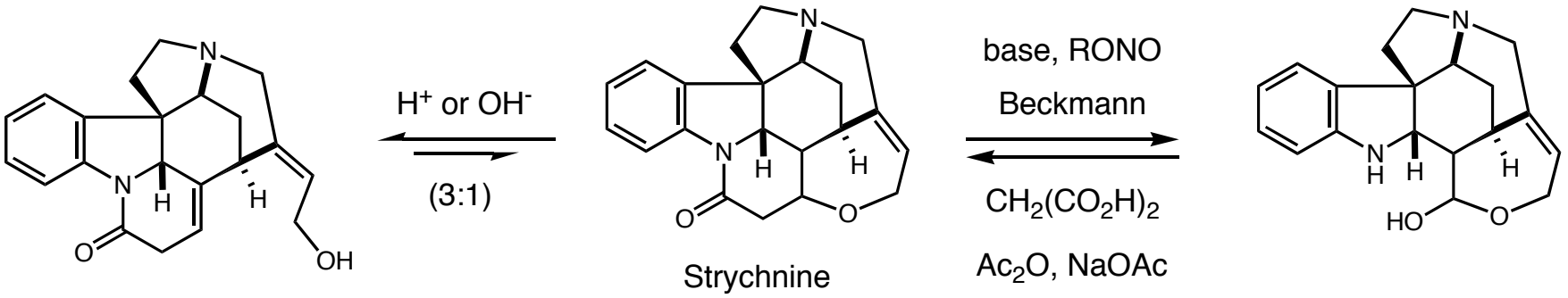
Volhardt *Org. Lett.* **2000**, 2479.

1993: Stork: (±), 14 steps, yield unknown

2002: Shibasaki: (–), 31 steps, 2% yield

2007: Padwa: (±), 16 steps, 2% yield

Comparing the Syntheses of Strychnine



■ Isostrychnine routes (6)

1954: Woodward: (±), 28 steps, 6E-5% yield

1993: Kuehne: (±), 20 steps, 0.6% yield (2%)

1994: Rawal: (±), 14 steps, 3% yield (10%)

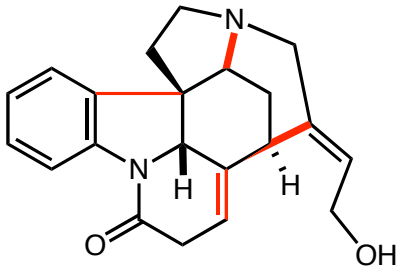
2000: Volhardt: (±), 15 steps, 0.3% yield (1%)

2002: Mori: (–), 23 steps, 0.1% yield (0.5%)

2002: Bodwell: (±), 12 step formal, ca 3% yield

■ Wieland-Gumlich aldehyde routes (9)

1992: Magnus (similar): (±), 28 steps, 0.03% yield



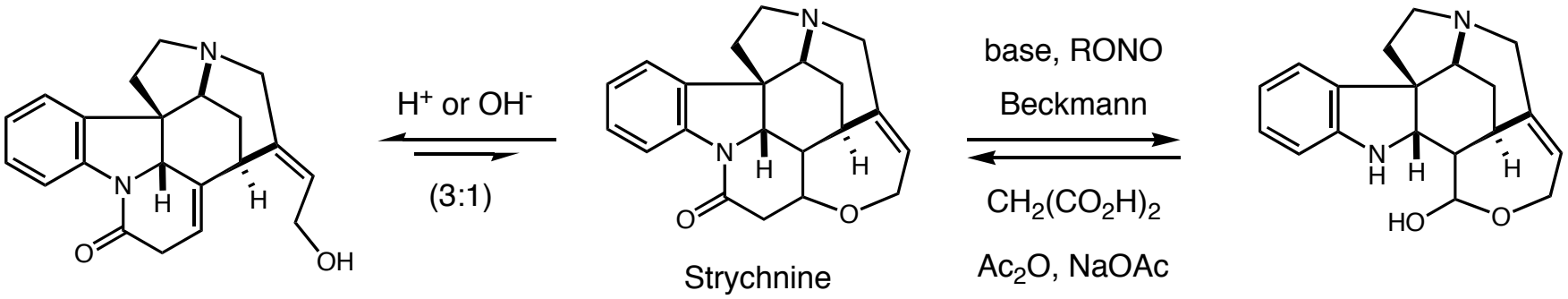
Pd-was here

Mori *Angew. Chem. Int. Ed.* **2002**, 1934.

2002: Shibasaki: (–), 31 steps, 2% yield

2007: Padwa: (±), 16 steps, 2% yield

Comparing the Syntheses of Strychnine



■ Isostrychnine routes (6)

1954: Woodward: (±), 28 steps, 6E-5% yield

1993: Kuehne: (±), 20 steps, 0.6% yield (2%)

1994: Rawal: (±), 14 steps, 3% yield (10%)

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2002: Bodwell: (±), 12 step formal, ca 3% yield

■ Wieland-Gumlich aldehyde routes (9)

1992: Magnus (similar): (±), 28 steps, 0.03% yield

1993: Overman: (–), 24 steps, 3% yield

1998: Kuehne: (–), 19 steps, 3% yield

2000: Bonjoch/ Bosch: (–), 16 steps, 0.2% yield

2001: Martin: (±), 16 step formal, ca 1% yield*

2004: Fukuyama: (–), 25 steps, 2% yield

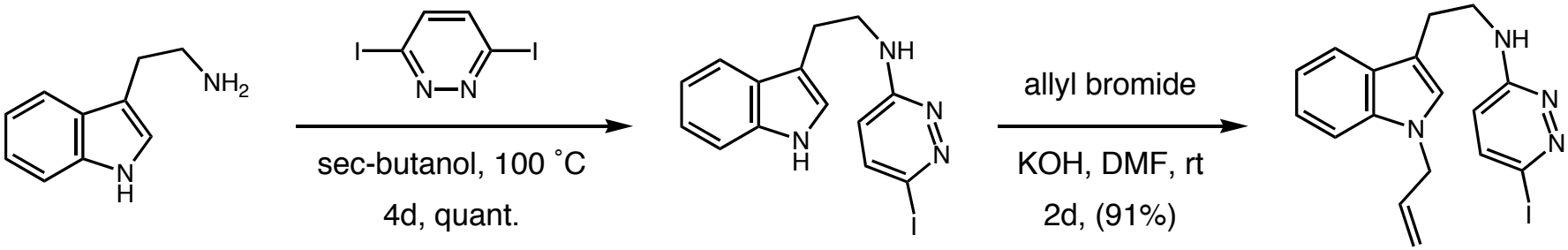
1993: Stork: (±), 14 steps, yield unknown

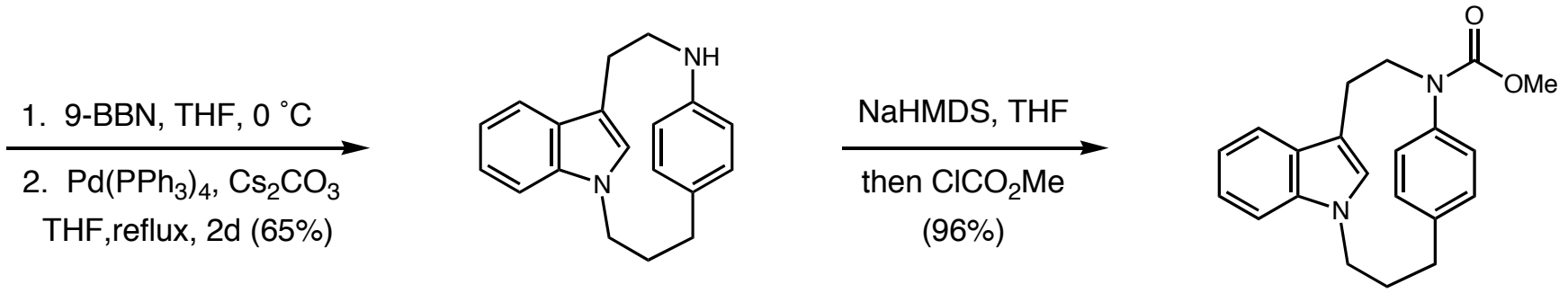
2002: Shibasaki: (–), 31 steps, 2% yield

2007: Padwa: (±), 16 steps, 2% yield

Bodwell: Very Concise Formal Synthesis

- Very simple chemistry sets up the key step

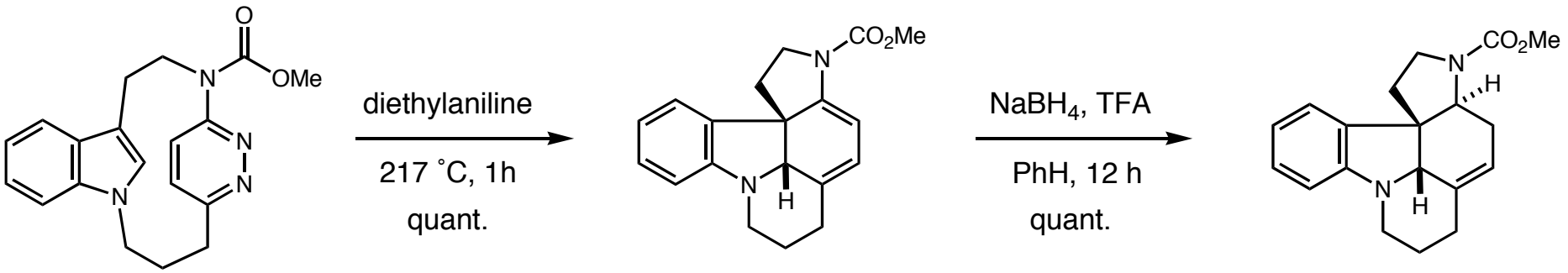


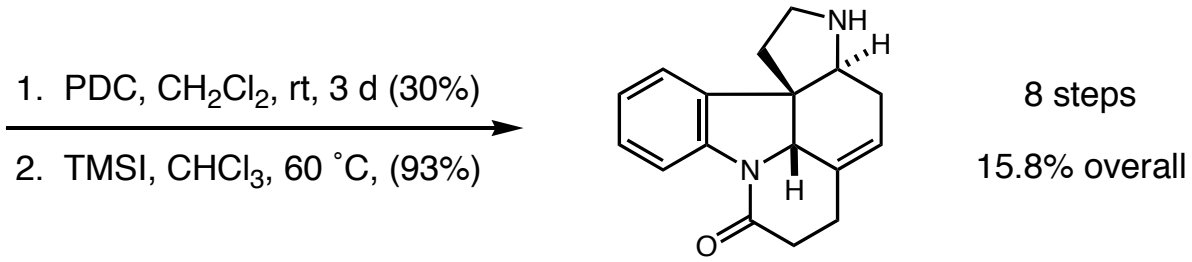


Bodwell *Angew. Chem. Int. Ed.* **2002**, 3261.

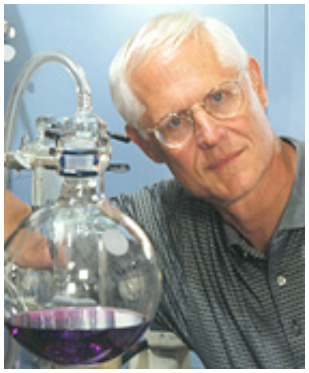
Bodwell: Very Concise Formal Synthesis

- Quantitative key intramolecular inverse-demand Diels-Alder reaction





Selected Total Syntheses of Strychnine



Overman (1993)

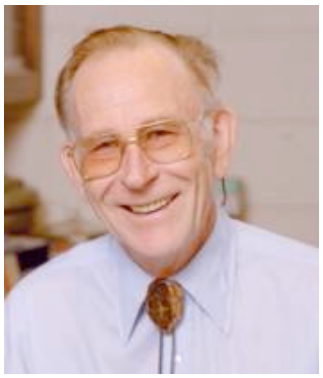
(–)-Strychnine

24-steps, 3% overall yield

Rawal (1994)

(±)-Isostrychnine

13-steps, 10% overall yield



Kuehne (1998)

(–)-Strychnine

19-steps, 3% overall yield

Padwa (2007)

(±)-Strychnine

16-steps, 2% overall yield