



- Born in 1943 in Chicago, Illinois
- Raised in Hammond, Indiana
- B.A., Earlham College 1965
- Ph.D., University of Wisconsin 1969 with Professor Howard W. Whitlock
- NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University
- He joined University of California, Irvine in 1971 where he is Distinguished Professor of Chemistry

362 publications:

- 128 JACS
- 74 JOC
- 12 Angew. Chem.
- 117 papers with the term "total synthesis"

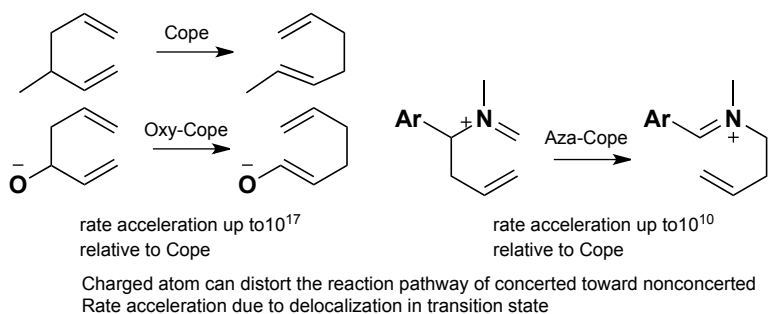
Awards/Honours include:

- ACS Arthur. C. Cope Award (2003)
- ACS Creative work in Synthetic Organic Chemistry (1995)
- 2011 - UCI Medal, University of California, Irvine, American Chemical Society,
- 2010 - Herbert C. Brown Award for Creative Research in Synthetic Methods,
- 2008 - Tetrahedron Prize for Creativity in Organic Chemistry,
- 2007 - The Nagoya Medal of Organic Chemistry,
- 2005 - International Society of Heterocyclic Chemistry Senior Award,
- 2004 - Ta-shue Chou Lectureship Award,
- 2003 - American Chemical Society Arthur C. Cope Award,
- 2002-2003 U.C. Irvine Distinguished Faculty Lectureship Award for Research,
- 2002 - Yamada Prize
- 1999 - Japan Society for the Promotion of Science Fellowship,
  - S. T. Li Prize for Achievements in Science and Technology,
  - Earlham College Distinguished Faculty Award,
- 1997 - Centenary Medal, Chemical Society, U.K.
- 1995 - American Chemical Society Award for Creative Work in Synthetic Organic Chemistry,
- 1993 - 1994 - Guggenheim Fellowship,
- 1993 - C.S. Hamilton Award, University of Nebraska
- 1985 - 1992 - Javits Neuroscience Investigator Award
- 1989 - American Chemical Society Arthur C. Cope Scholar Award
  - Visiting Miller Research Fellow, U.C. Berkeley
- 1985 - 1987 - Alexander von Humboldt U.S. Senior Scientist Award,
- 1976-1981 Camille and Henry Dreyfus Teacher-Scholar Award
- 1981 - U.C. Irvine School of Physical Sciences Distinguished Teaching Award,
- 1979 - U.C. Irvine Alumni Association Distinguished Research Award
- 1975-1977 - Alfred P. Sloan Foundation Fellow

Research Interests: Organic, Inorganic, Organometallic and Chemical Biology

- Professor Overman's research interests center on the invention of new reactions and strategies in organic synthesis and the total synthesis of natural products and their congeners.

### Charge in rearrangement reactions



#### The aza-Cope rearrangement

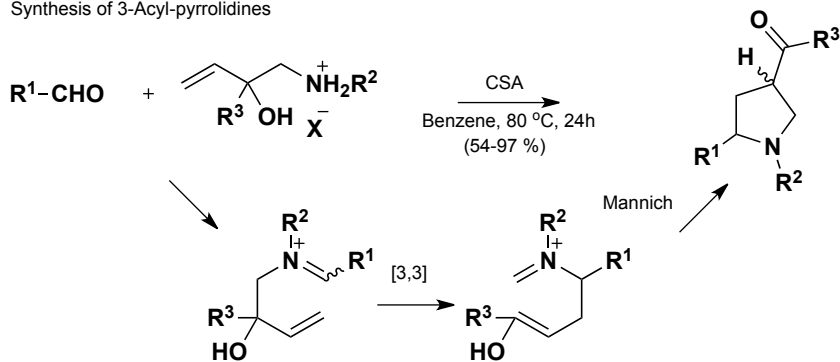
- Mild conditions (100-200 °C below the corresponding Cope rearrangement)
- Usually occurs near rt.
- Reversible (Driven by aryl conjugation of the product iminium ion)
- Charged intermediate lowers free energy of activation

Acc. Chem. Res., **1992**, 25, 352-359

### The aza-Cope-Mannich rearrangement

- Directing the rearrangement by intramolecular trapping
- Double bond incorporated in a suprafacial sense

#### Synthesis of 3-Acyl-pyrrolidines



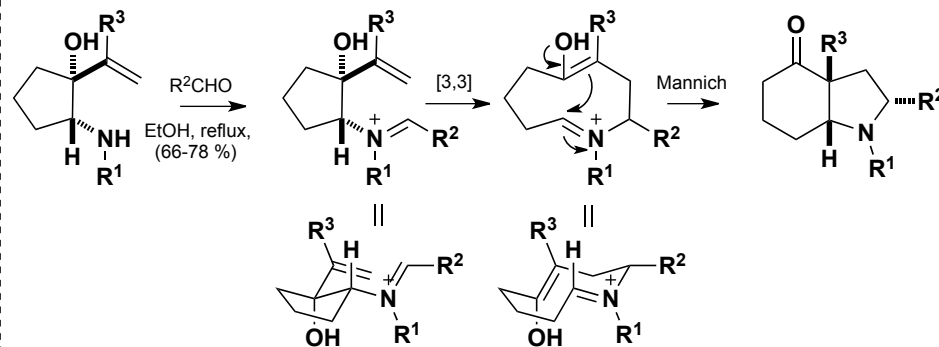
$R^1$  = alkyl, phenyl, thiophene, pyridine;  $R^2$  = alkyl, benzyl;  $R^3$  = H, Me

JACS, **1979**, 101, 1310

JACS, **1983**, 105, 6622

#### Synthesis of cis-fused octahydroindoles and cycloheptapyrrolidines

- One carbon ring expansion
- Present in alkaloids of the Amaryllidaceae, Aspidosperma, and Strychnos families

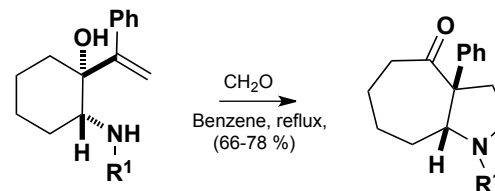


$R^1$  = H, Me;  $R^2$  = H, Me,  $n$ -C<sub>6</sub>H<sub>13</sub>;  $R^3$  = Ph

JACS **1981**, 103, 5579

Tetrahedron Lett. **1982**, 2733

- Cycloheptapyrrolidine moiety present in Gelsemine

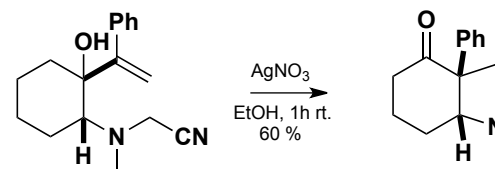


$R^1$  = H, CHPh<sub>2</sub>

Tetrahedron Lett. **1982**, 2737

#### Cyanomethyl as a source for the iminium equivalent

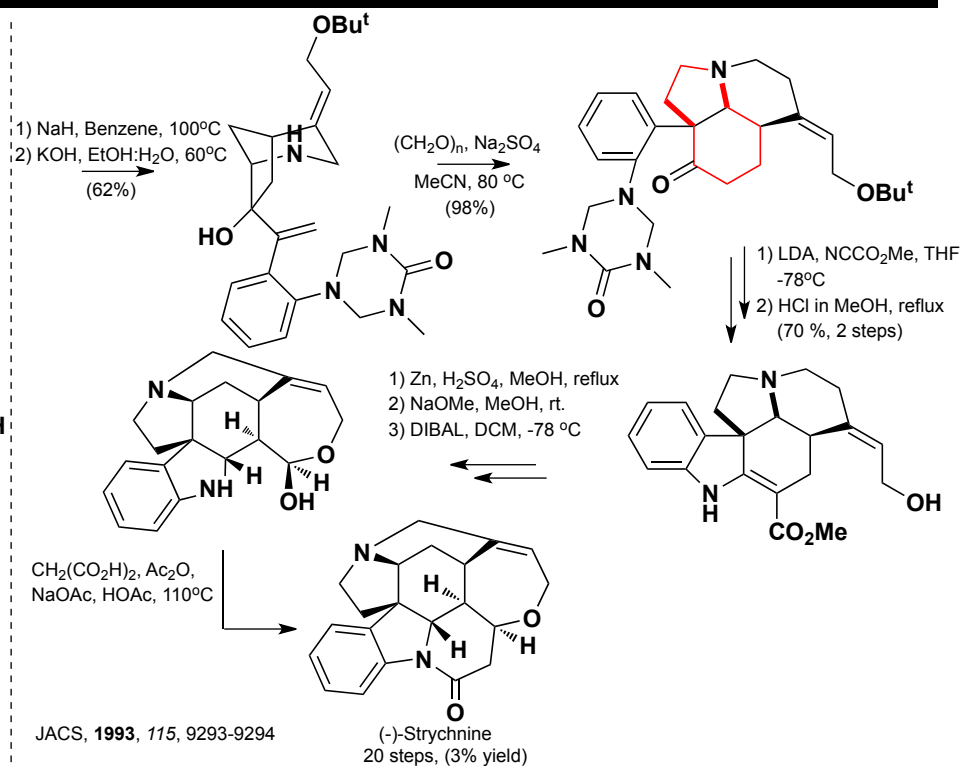
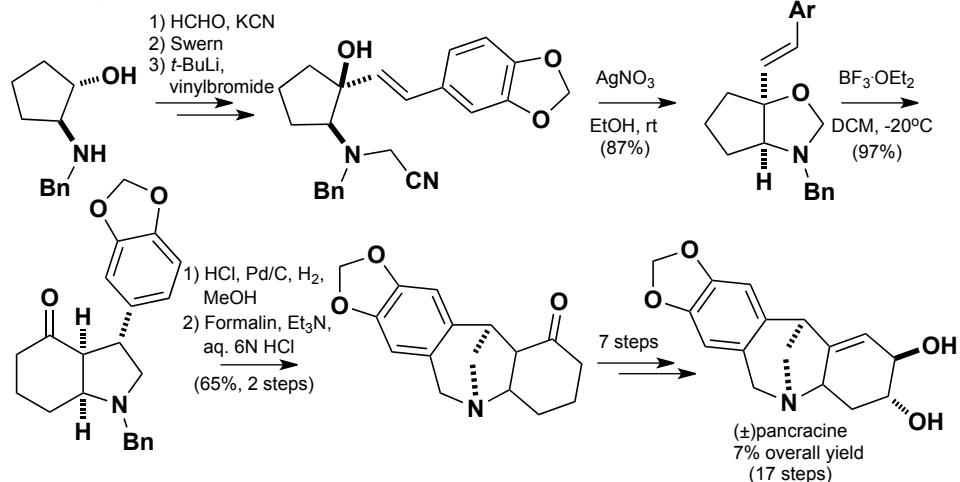
- Also functions as protection group



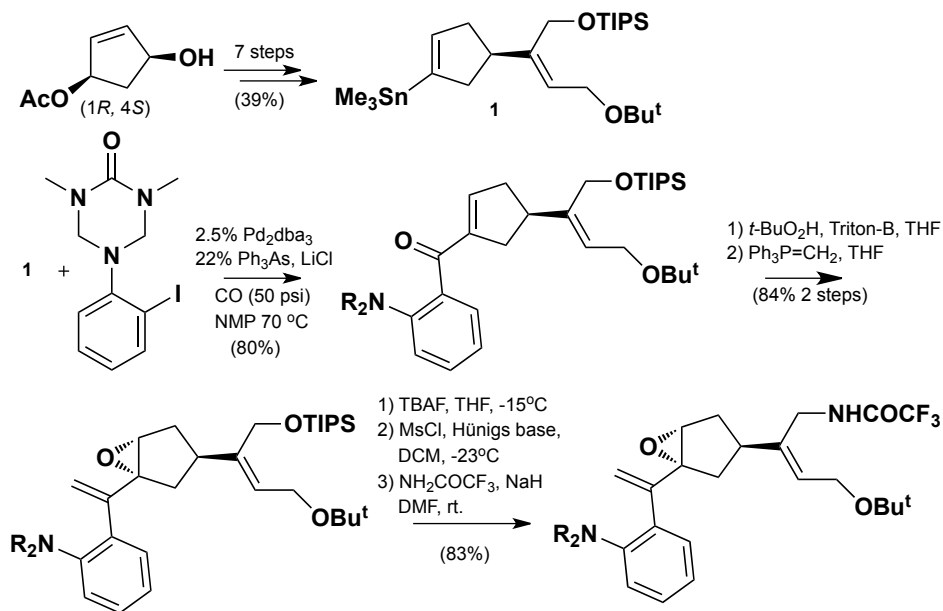
Tetrahedron Lett. **1982**, 2741

### Synthesis of (±)pancracine

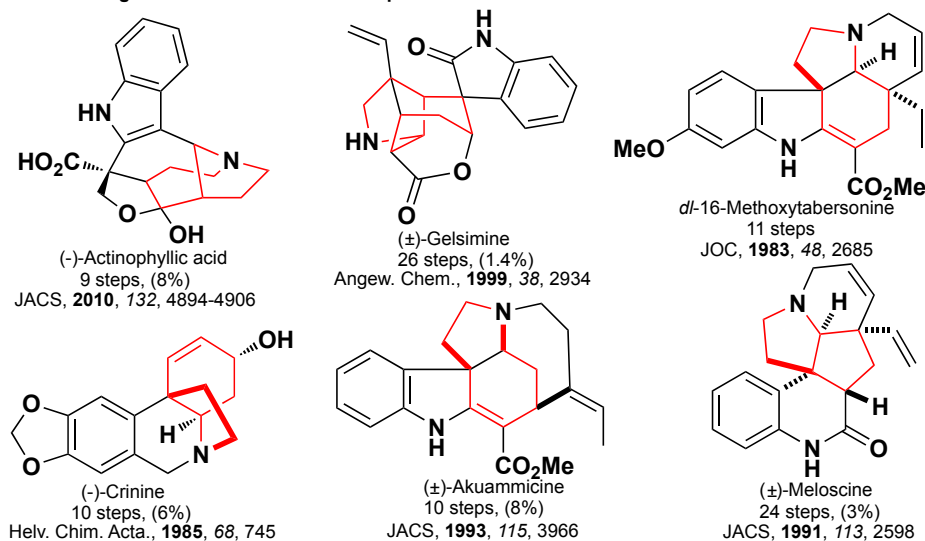
- Amaryllidaceae alkaloid



### Enantioselective total synthesis of (-)-Strychnine

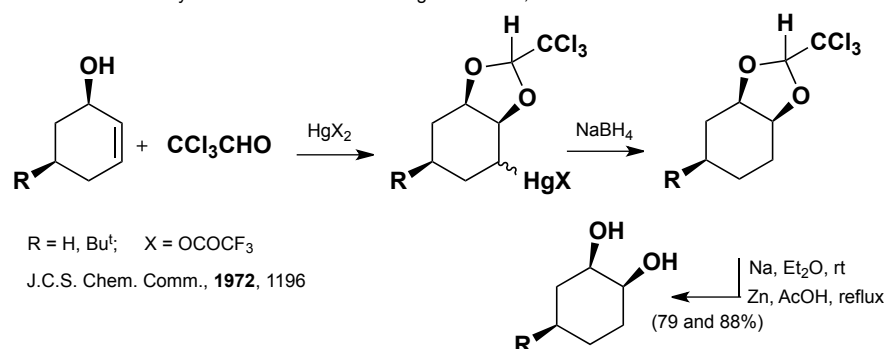


### Selected targets achieved with the Aza-Cope-Mannich reaction



**Conversion of allylic alcohols into a cis-vicinal diol**

- Conventional oxymercuration-demercuration gives trans-1,3-diol

**Synthesis of amines by rearrangement of allylic trichloroacetimidates (Overman rearrangement)**

Allylic imidate rearrangement discovered in 1937

Works for 1°, 2° and 3° allylic alcohols

Large enthalpic driving force (imidate to amide functionality 15 kcal/mol)

Useful for synthesis of hindered amines

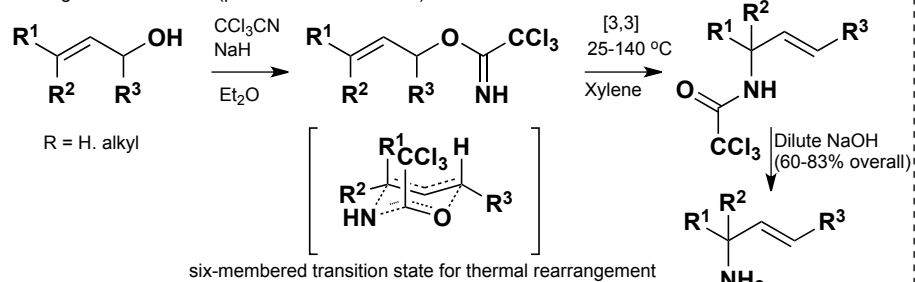
Mild cleavage of the trichloroacetyl group

Trichloroacetimidates often used directly without purification

Preparation typically involve DBU in aprotic solvents or alkali metal hydrides

EWG (CCl<sub>3</sub> or CF<sub>3</sub>) results in more facile rearrangement compared to imidates

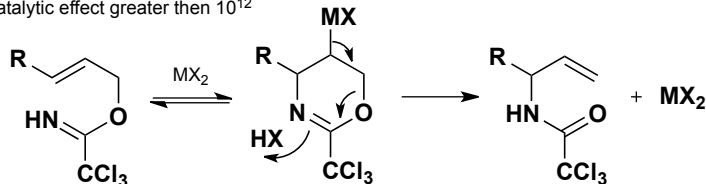
High stereoselection (preference for E isomer)



Hg(II) and Pd(II) salts catalyze rearrangement

Mechanism proceeds through a iminomercuration-deoxymercuration

Catalytic effect greater than 10<sup>12</sup>



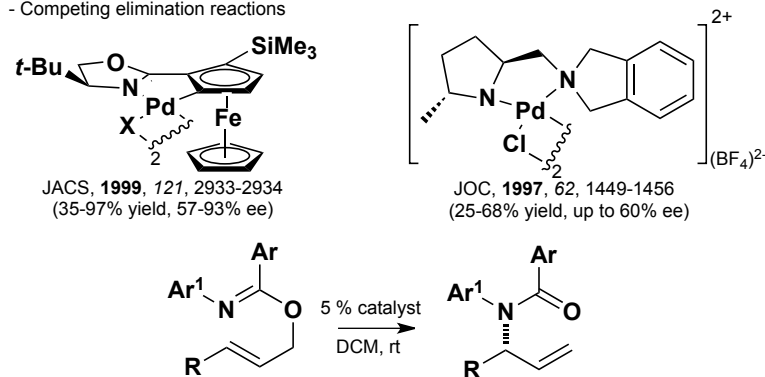
JACS, **1976**, 98, 2901-2910  
 JACS, **1974**, 96, 597

Initial asymmetric Pd(II) catalyst developed

- Only useful for *N*-arylbenzimidates

- Coordination of the basic trichloroacetimidate nitrogen to the palladium center

- Competing elimination reactions



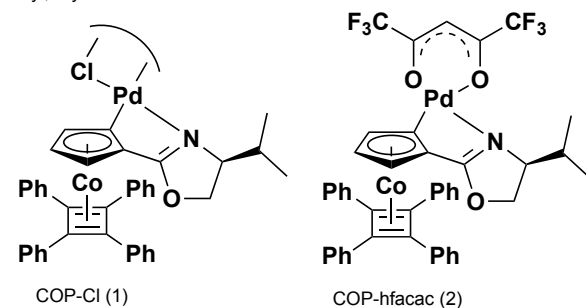
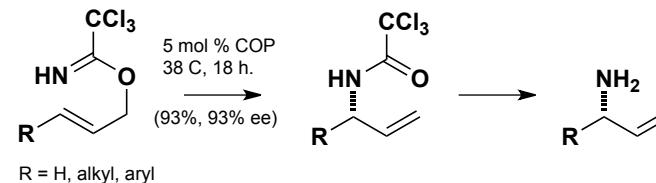
Catalytic asymmetric rearrangement of allylic trichloroacetimidates

- Catalyzed by monomeric cobalt oxazoline palladacycles (COP)

- >90% ee

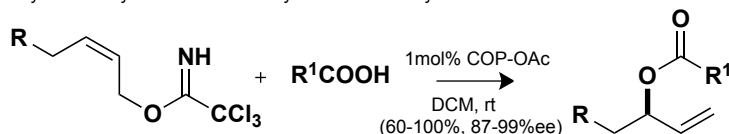
- COP-Cl superior in DCM but low solubility

- COP-hfacac soluble in a wide variety of solvents. Higher solubility

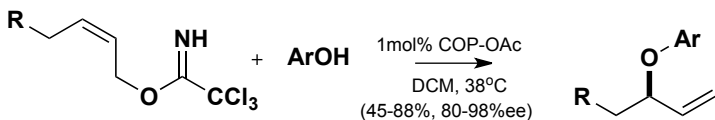


JACS, **2003**, 125, 12412-12413  
 JOC, **2004**, 69, 8101

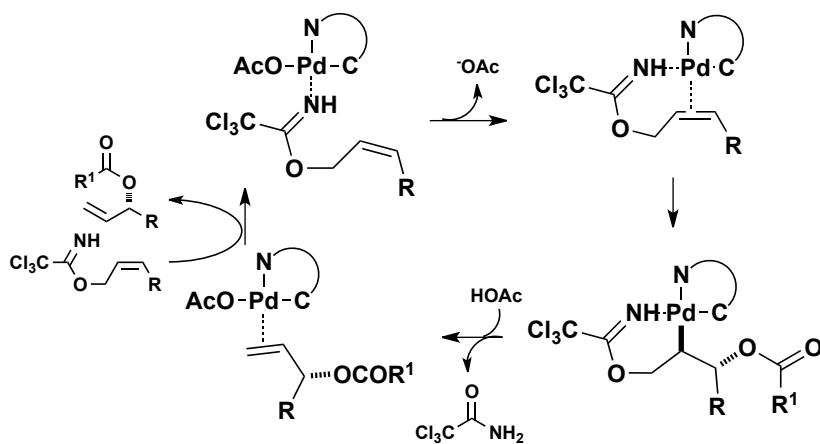
Catalytic asymmetric synthesis of chiral allylic esters and aryl ethers



JACS, 2005, 127, 2866-2867

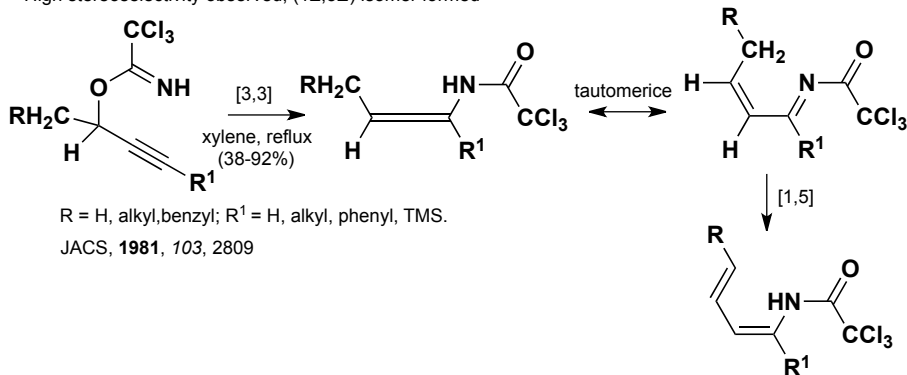


Org Lett., 2007, 9, 911-913



Thermal rearrangement of propargylic trichloroacetimidates

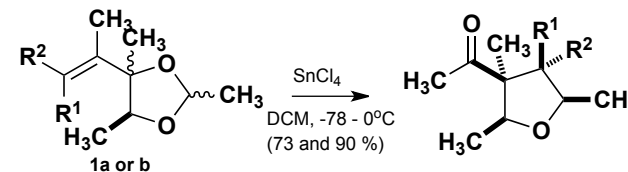
- Synthesis of trichloroacetamido-1,3.dienes
- High stereoselectivity observed, (1Z,3E) isomer formed

R = H, alkyl, benzyl; R<sup>1</sup> = H, alkyl, phenyl, TMS.

JACS, 1981, 103, 2809

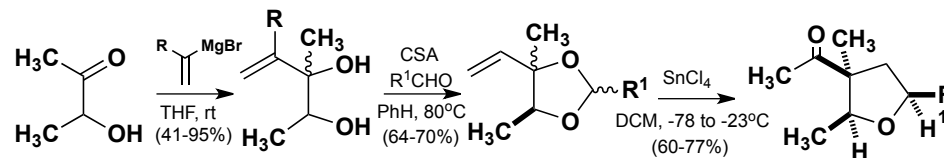
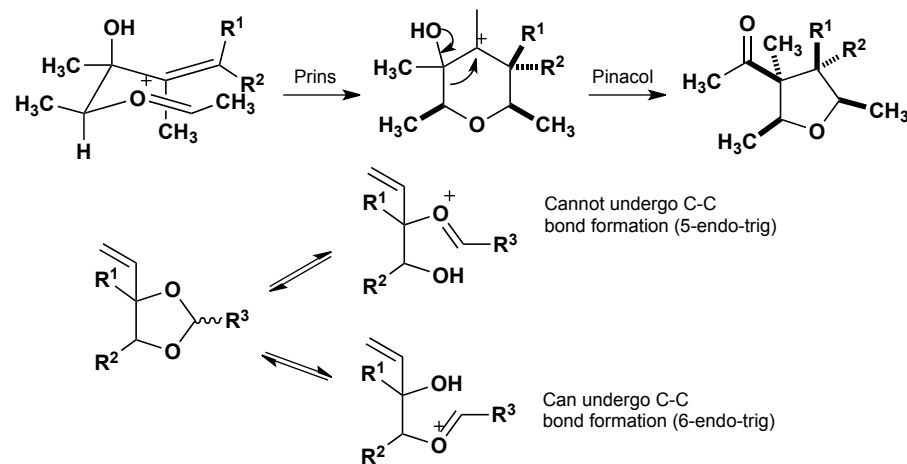
## Prins pinacol rearrangement

- Allylic acetals into highly substituted tetrahydrofurans
- Catalyzed by Lewis (EtAlCl<sub>2</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, SnCl<sub>4</sub>) (SnCl<sub>4</sub> is generally superior)
- Reaction occurs via chair topography with (*E*)-oxonium ion
- Incorporation of double bond in suprafacial sense
- Both diastereoisomers gives the same product

a) R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>3</sub>; b) R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H

JACS, 1987, 109, 4748

Mechanism:



R = H, Me, Ph

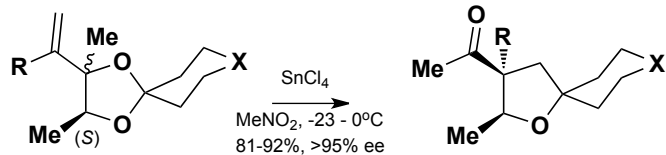
R<sup>1</sup> = Me, Et, *i*-Pr, CH<sub>2</sub>CH<sub>2</sub>Ph, CH=CH<sub>2</sub>, Ph, (*E*)-CH=CHPh

JACS, 1991, 113, 5354-5365

Acc. Chem. Res., 1992, 25, 352-359

### Synthesis of oxacyclic ring systems

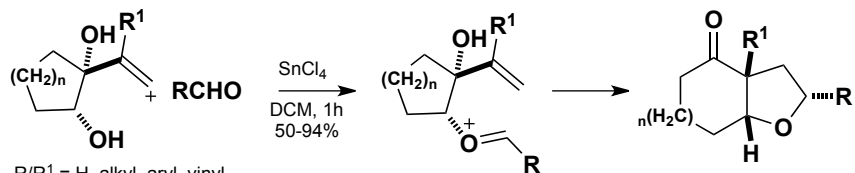
- High enantiomeric purity obtained from nonracemic diols



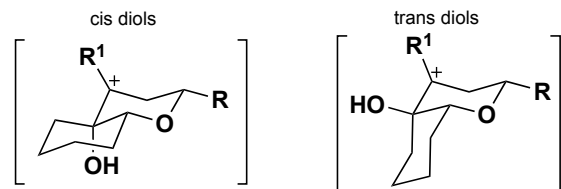
X = NCO<sub>2</sub>Et, O, CH<sub>2</sub>; R = Me, Ph

JOC, **2003**, *68*, 7143-7157

- Ring-enlarging reactions (cis-fused octahydrobenzofurans and cycloheptatetrahydrofurans)  
- In most cases both cis and trans fused diols gives cis-fused rings



R/R<sup>1</sup> = H, alkyl, aryl, vinyl  
n = 0, 1, 2

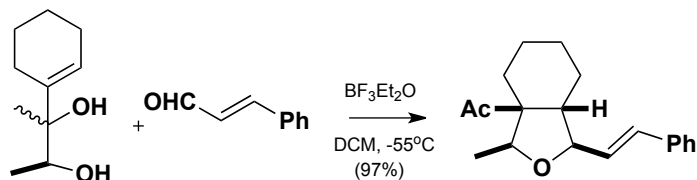


JOC, **1987**, *52*, 3711

JACS, **1991**, *113*, 5365

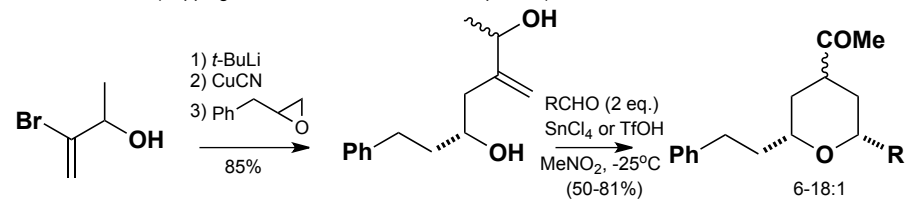
Hexahydroisobenzofuran synthesis

- Alkene contained in ring  
- Synthesis of ladiellin, briarellin and asbestinin diterpenes

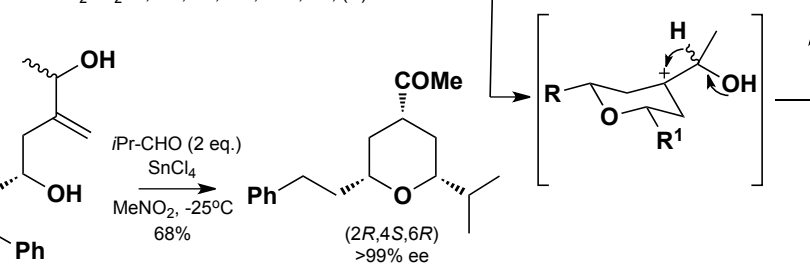


JACS, **2001**, *123*, 9033

- Synthesis of trisubstituted tetrahydropyrans  
- Stereochemistry of sidechains evolves from single stereocenter  
- Found in polyether antibiotics, marine toxins and pheromones  
- DCM not suitable (trapping of carbocation with halide competitive)



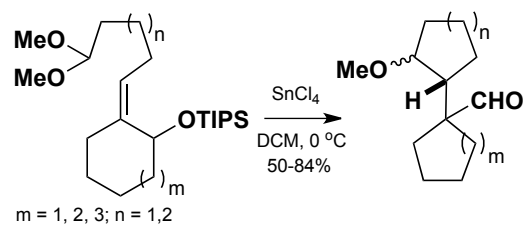
R = CH<sub>2</sub>CH<sub>2</sub>Ph, Me, Bn, *i*-Pr, *t*-Bu, Ph, (*E*)-CH=CHPh



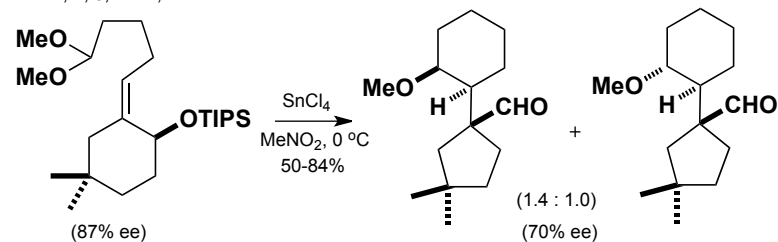
JACS, **1999**, *121*, 1092-1093

### Synthesis of carbocyclic ring systems

- Oxocarbenium external to the ring formed upon Prins  
- Synthesis of attached rings with ring contraction

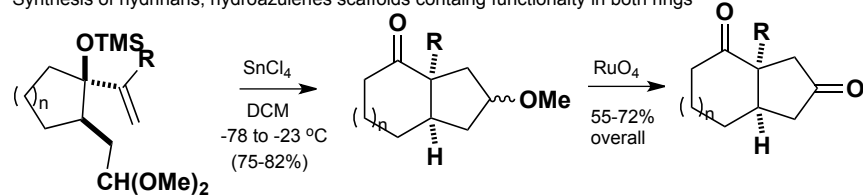


m = 1, 2, 3; n = 1, 2

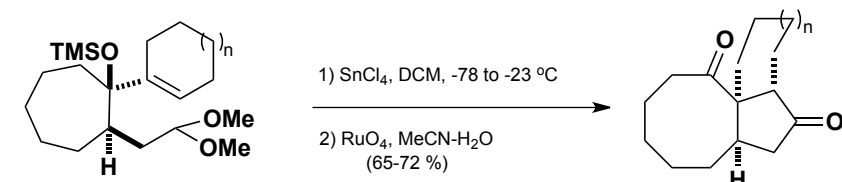


JOC, **2006**, *71*, 1581

Synthesis of hydrinans, hydroazulenes scaffolds containing functionality in both rings

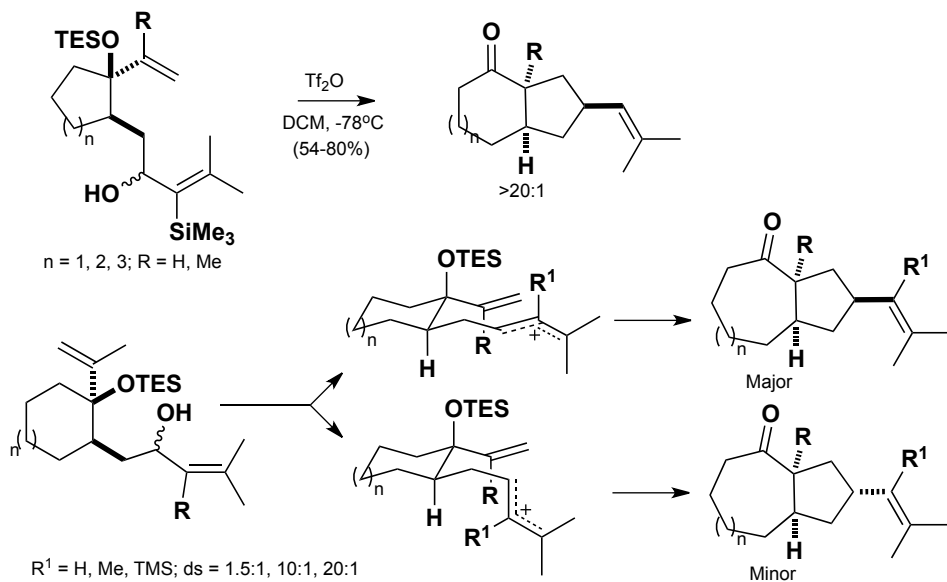


R = H, Me; n = 1, 2, 3  
 JACS, **1989**, *111*, 1514



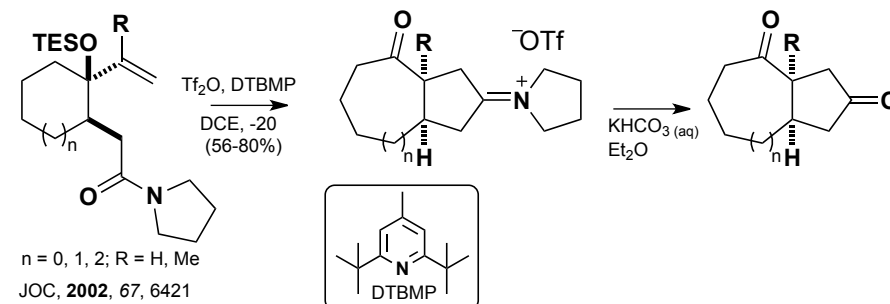
R = H, Me; n = 0, 1  
 Tetrahedron, **2002**, *58*, 6473

- Allyl cation-initiated cyclization rearrangement to install 2-alkenyl substituent.  
 - Protodesilylation occurs under reaction conditions with TMS

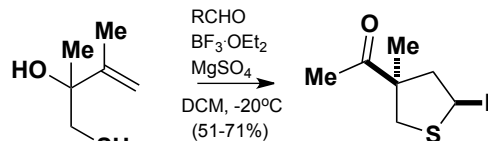


JOC, **2002**, *67*, 6421

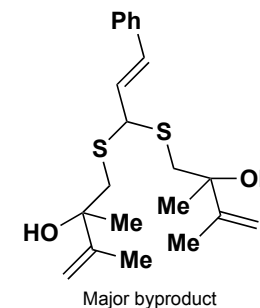
- Keteniminium ion initiated cyclization-pinacol rearrangements



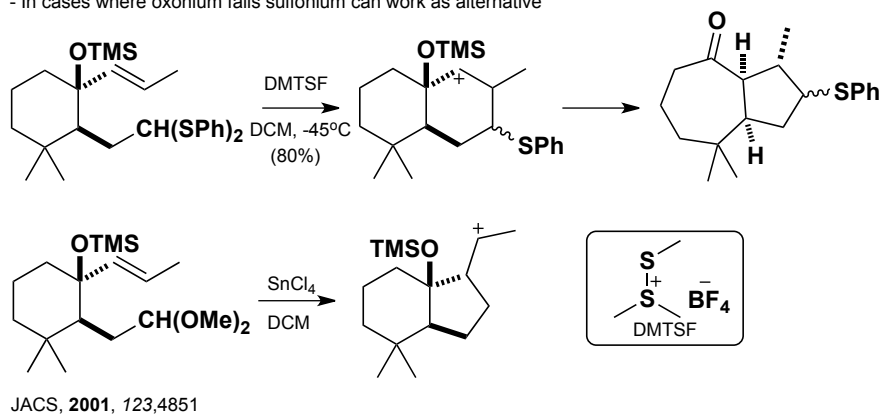
- Synthesis of tetrahydrothiophenes  
 -  $\text{BF}_2\text{OEt}_2$  performs best



R =  $\text{CH}_2\text{CH}_2\text{Ph}$ , Ar, (E)- $\text{CH}=\text{CHPh}$   
 JACS, **2000**, *122*, 8672



- In cases where oxonium fails sulfonium can work as alternative

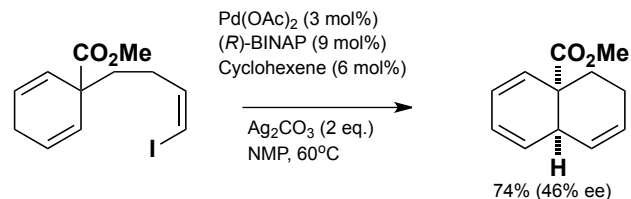




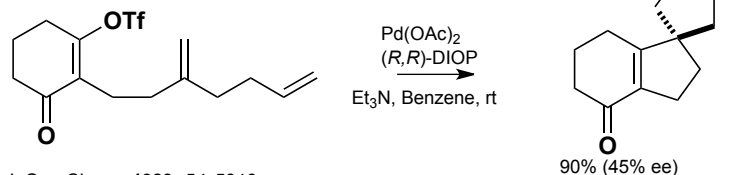


### Intramolecular asymmetric Heck reaction

- Initial findings



- Synthesis of spirocycles with quaternary centers

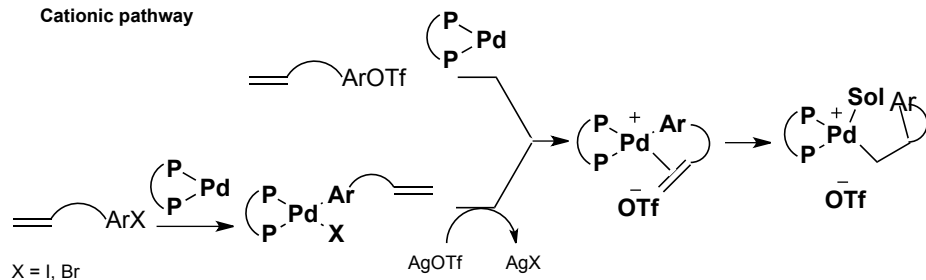


J. Org. Chem., **1989**, 54, 5846

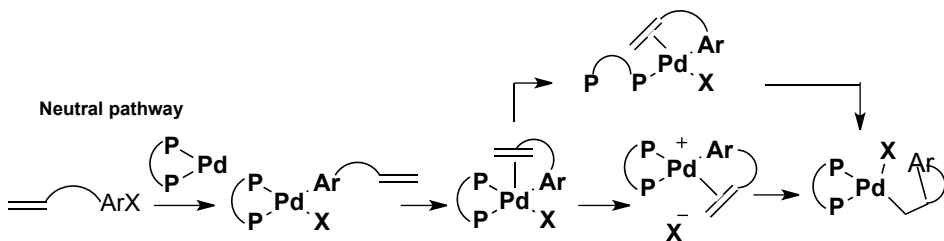
General features

- Two pathways proposed (Cationic and neutral)

**Cationic pathway**



**Neutral pathway**



JACS, **1998**, 120, 6488

Reaction of arylhalides through neutral pathway often gives lower %ee  
 Silver and Thallium salts ( $\text{Ag}_2\text{CO}_3$ ,  $\text{Ag}_2\text{O}$ ,  $\text{Ag}_3\text{PO}_4$ ,  $\text{Tl}_2\text{CO}_3$ ,  $\text{TlOAc}$ ) used to promote the cationic pathway. (JACS, **1998**, 120, 6488)

Common bases used ( $\text{K}_2\text{CO}_3$ ,  $\text{CaCO}_3$ ,  $\text{Et}_3\text{N}$ ,  $i\text{-Pr}_2\text{NEt}$ , PMP)

Polar aprotic solvents are typically used (THF, ACN, DMF, DMA, NMP)

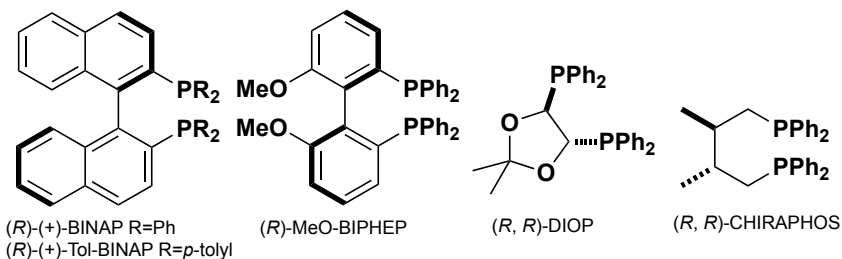
Less basic silver salts ( $\text{AgOAc}$ ,  $\text{AgNO}_3$ ) results in lower reaction rate and little asymmetric induction (JOC, **1992**, 57, 4571)

BINAP is by far the most widely used ligand.

Depending on how HX is scavenged either enantiomer of the product can be formed using a single enantiomer of a chiral diphosphine.

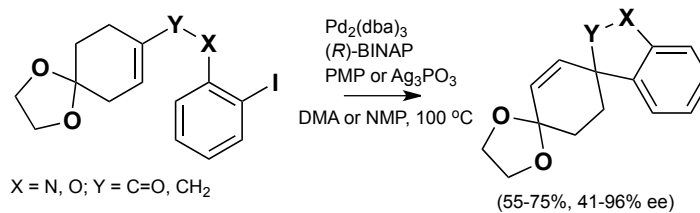
The order of reactivity  $\text{X} = \text{I} > \text{OTf} > \text{Br} > \text{Cl}$

Catalyst loading 5-10%. Most common used precatalysts  $\text{Pd(OAc)}_2$ ,  $\text{Pd}_2(\text{dba})_3$



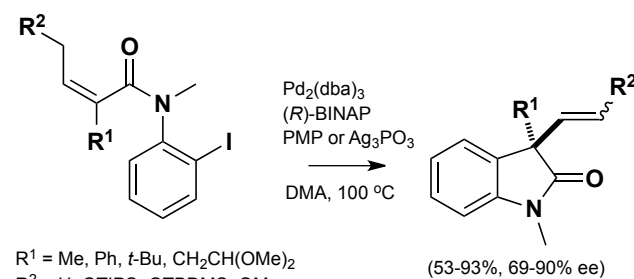
Synthesis of oxindoles, indolines, dihydrobenzofurans

- Depending on how HI is scavenged each enantiomer can be obtained (cationic vs neutral pathway)  
 - Which HI acceptor is optimal for achieving highest %ee is substrate dependent



Intramolecular Heck reactions of (Z)- $\alpha,\beta$ -unsaturated 2-iodoanilides

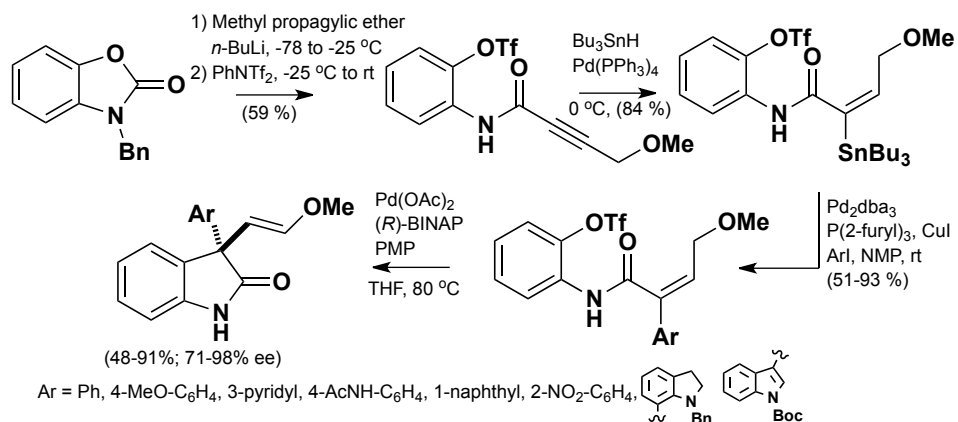
- Synthesis of oxindoles



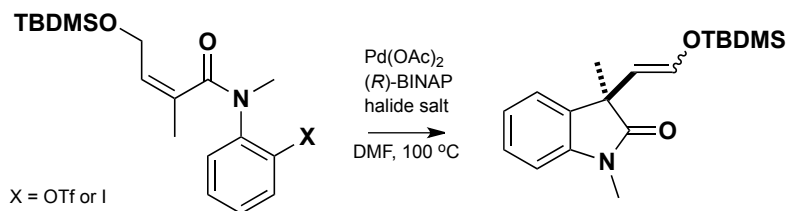
(JACS, **1998**, 120, 6488)

## Synthesis of 3-alkyl-3-aryl oxindoles

- A broad range of indole alkaloids contain a diarylsubstituted quaternary center



JACS, 2003, 125, 6261



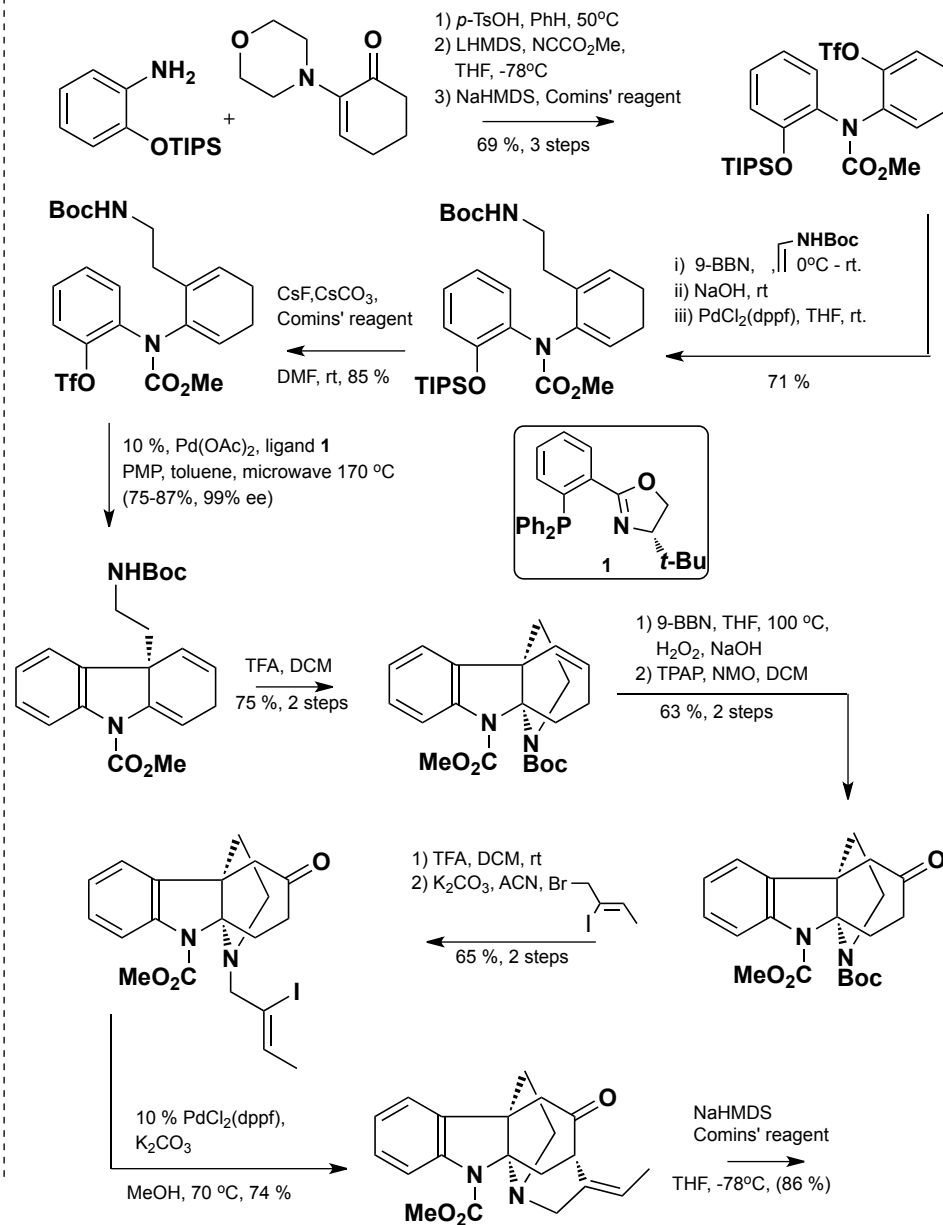
Compound	Additive	Oxindole yield	%ee
OTf	-	72	43
OTf	$n\text{Bu}_2\text{NI}$	62	90
OTf	$n\text{Bu}_4\text{NBr}$	59	93
OTf	$n\text{Bu}_4\text{NCl}$	52	93
OTf	$n\text{Bu}_4\text{NOTf}$	70	42
OTf	PMP•HI	40	91
OTf	PMP•HBr	62	92
OTf	PMP•HCl	60	88
I	-	76	91
I	PMP•HI	62	91
I	PMP•HBr	45	95
I	PMP•HCl	75	94
I	AgOTf	-	43

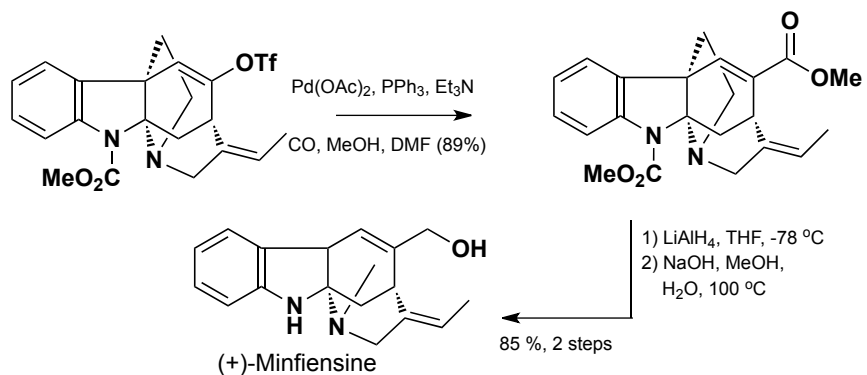
Angew. Chem. 1997, 36, 518

Triflates can be diverted to neutral pathway  
 - Higher enantioselection without presence of silver salt  
 - Identical low ee in presence of AgOTf  
 - Addition of halide salts to the triflate enhanced ee

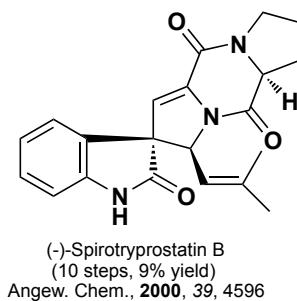
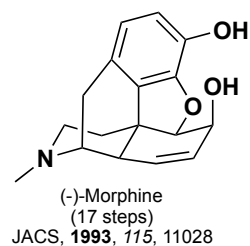
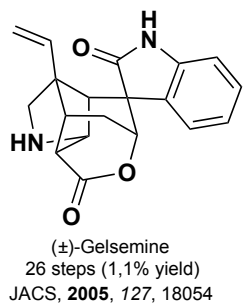
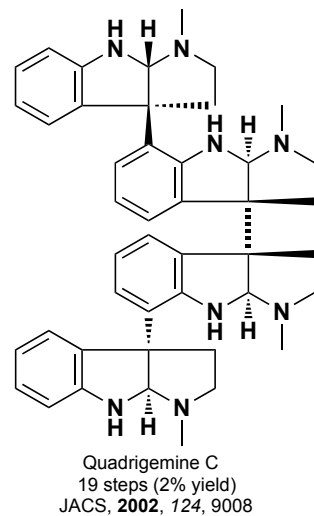
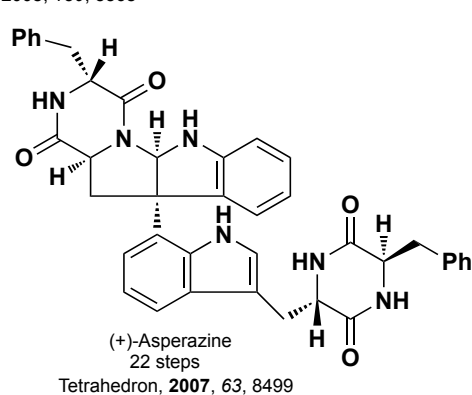
## Synthesis of (+)-Minfiensine

- Strychnos alkaloid

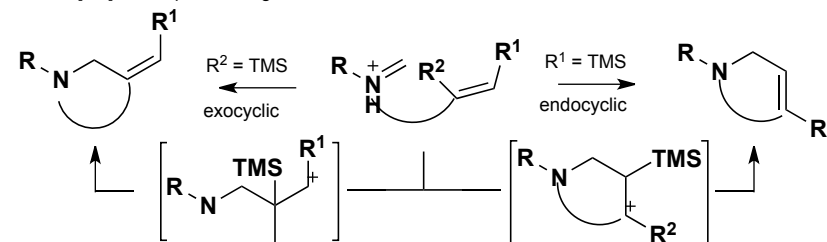




JACS, 2008, 130, 5368

**Vinylsilane terminated cyclization reactions**

- Hyperconjugation stabilizes beta carbonium ion
- Carbon-silicon bond is strongly polarized (Electronegativity 2.35 vs. 1.64)
- Electrophile directed to silicon bearing carbon
- Complete regiocontrol of the double bond
- Two mechanisms can be considered: Direct cyclization through beta silyl cation or via [3,3] aza-cope rearrangement.

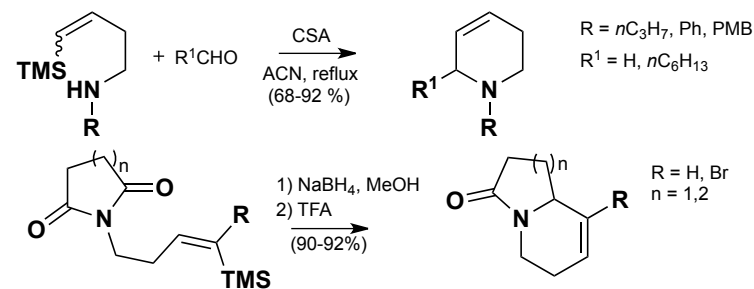


Vinylsilane-terminated cyclizations occur with preference for carbocation in sequence: tertiary trialkyl > secondary beta-silyl > tertiary alpha-silyl > secondary dialkyl > primary beta-silyl cations

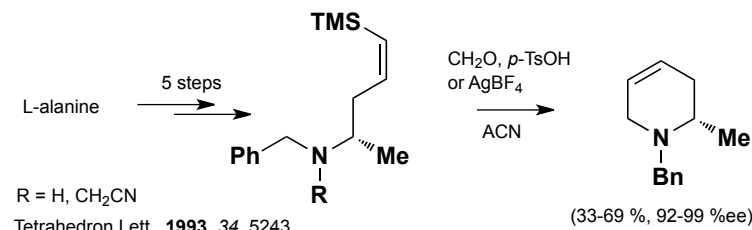
Chemical Reviews, 1986, 86, 857

**Synthesis of unsaturated azacycles (1,2,5,6-tetrahydropyridine)**

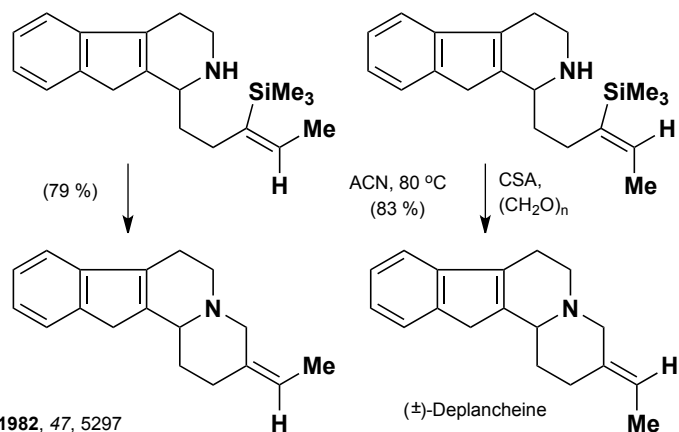
- Found in several alkaloids
- A cyanomethyl amine can be used as formaldehyde equivalent.



JACS, 1983, 105, 6994

**Preparation of enantioenriched tetrahydropyridines from silylpentenylamine**

Synthesis of indoloquinolizidine ring system found in a variety of indole alkaloids  
Both (*E*) and (*Z*)-trisubstituted vinylsilanes can be cyclized with >98% retention



JOC, 1982, 47, 5297

#### Enantioselective totalsynthesis of Pumiliotoxin B and 251D

- Pumiliotoxin B isolated from Panamanian poison frog *Dendrobates pumilio* in 1967 and pumiliotoxin 251 D from skin extracts of the Ecuadorian poison frog
- Dendrobatid alkaloids
- Poison used in blowdarts
- Cardiotonic agent

