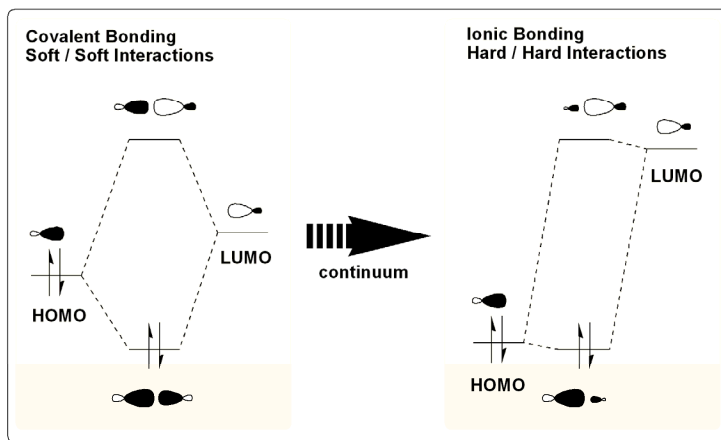
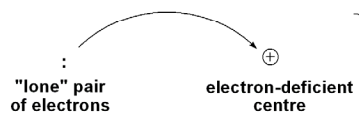
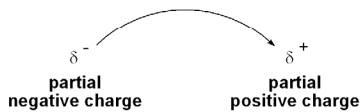
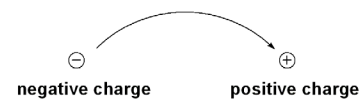


Nucleophiles and Electrophiles: The Basis of Organic Chemistry



HOMO = highest occupied molecular orbital
LUMO = lowest unoccupied molecular orbital

Synthesis 1: Strychnine

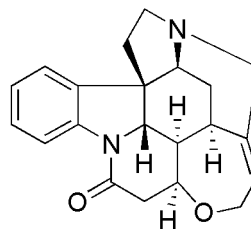
Woodward, 1954

- Nobel 1965

Classics I, 21

Reactions:

- Fischer indole synthesis
- Indole addition
- Dieckmann condensation
- Allylic rearrangement



strychnine

Concepts:

- Retrosynthesis
- Substructure Recognition

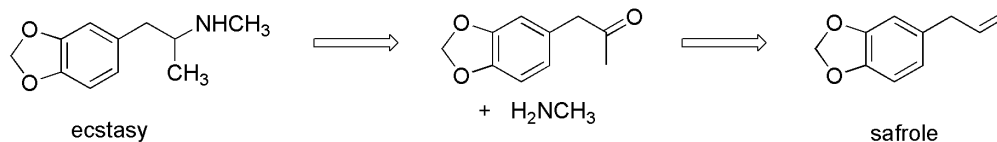
notes_02

Properties:

- A poison from Southeast Asian rainforests
- Known in Europe from the 16th century
- Isolation in 1818 (Pelletier and Caventou)
- Structure determined in 1946; X-ray in 1956
- 6 contiguous stereocentres!

Definition:

Retrosynthesis - A technique for transforming the structure of a synthetic target into a sequence of simpler structures, along a pathway which ultimately leads to known or commercially available starting materials.



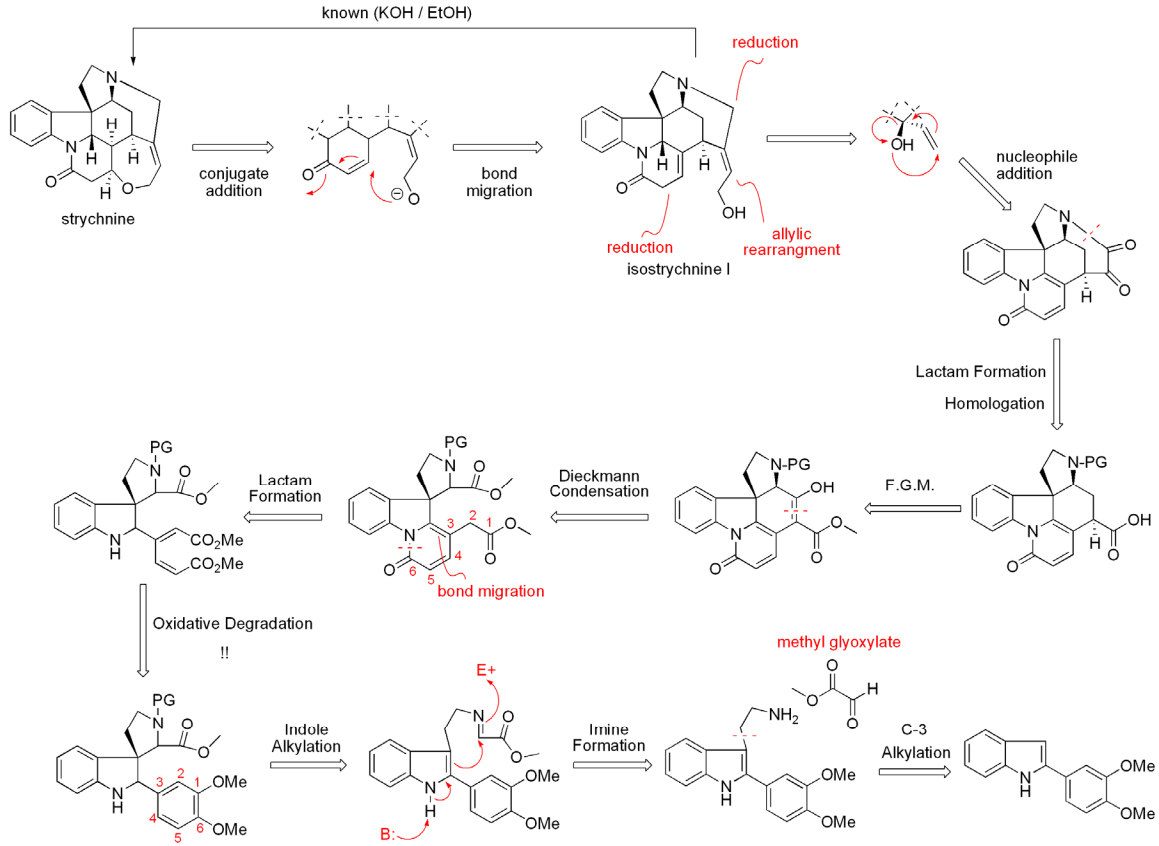
ecstasy

safole

notes_04

- E.J. Corey, Nobel 1990

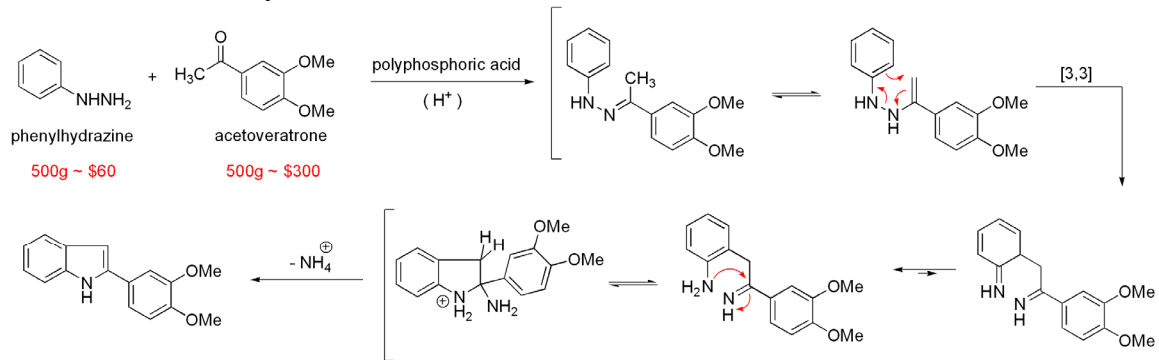
Retrosynthesis:



notes_03

Methodology:

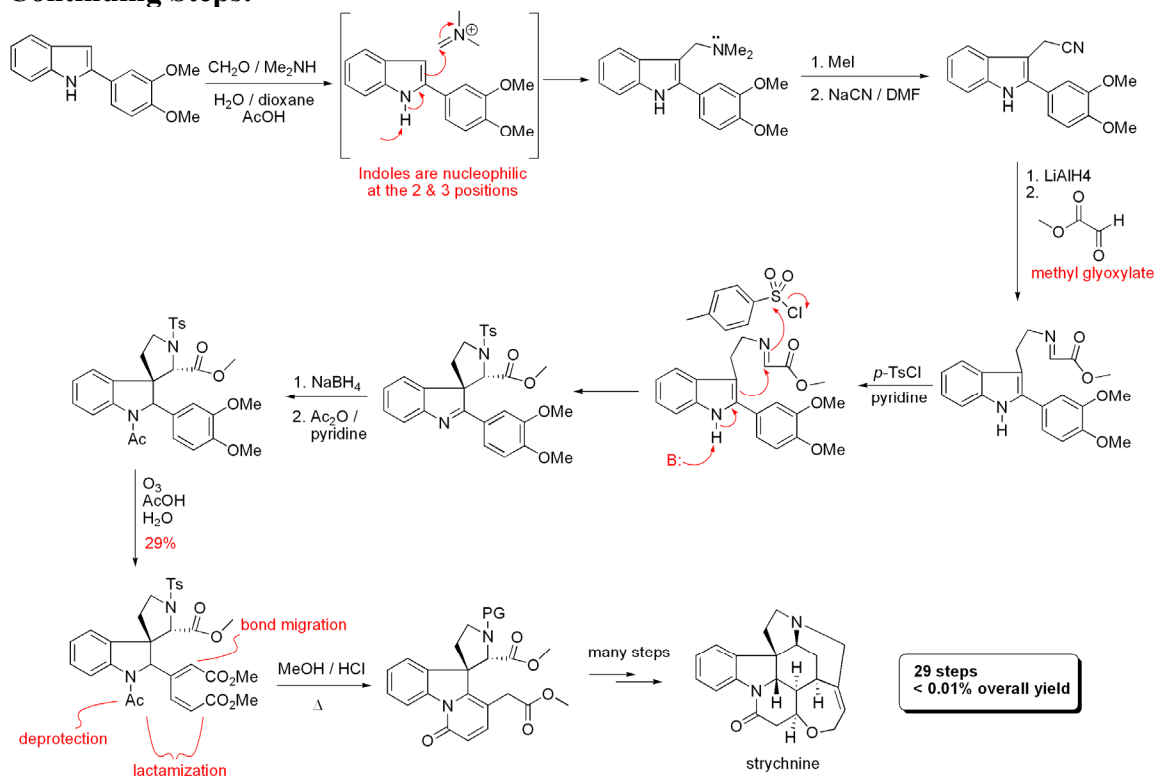
1.1 Fischer Indole Synthesis:



notes_05

- most commonly done with ZnCl₂

Continuing Steps:



notes_06

- How does the ozonolysis work here?
- Let's come back to that after the next section.

Other Syntheses of Strychnine:

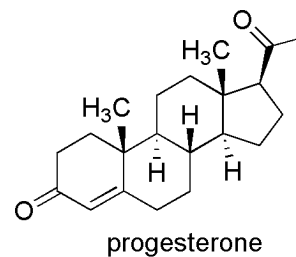
- Magnus, 1992 – *J. Am. Chem. Soc.* **1992**, 4403. - 38 years from 1st to 2nd synthesis!
- Stork, 1992 – lecture (Ischia Porto, Italy).
- Kuehne, 1993 – *J. Org. Chem.* **1993**, 7490.
- Overman, 1993 – *J. Am. Chem. Soc.* **1993**, 9293. - 1st enantioselective synthesis
- Rawal, 1994 – *J. Org. Chem.* **1994**, 2685.
- Martin, 1996 – *J. Am. Chem. Soc.* **1996**, 9804.
- Bonjoch, 1999 – *Angew. Chem. Int. Ed.* **1999**, 395.
- Vollhardt, 2000 – *Org. Lett.* **2000**, 2479.
- Shibasaki, 2002 – *J. Am. Chem. Soc.* **2002**, 14546.
- Mori, 2002 – *Angew. Chem. Int. Ed.* **2002**, 1934.
- Bodwell, 2002 – *Angew. Chem. Int. Ed.* **2002**, 3261.
- Fukuyama, 2004 – *J. Am. Chem. Soc.* **2004**, 10246.
- Padwa, 2007 – *Org. Lett.* **2007**, 279.

Synthesis 2: Progesterone

Marker, 1943

Reactions:

- Oxidative degradations
 - General metal oxide degradations
 - Lemieux-Von Rudloff oxidation
 - Ozonolysis
- Jones oxidation



Concepts:

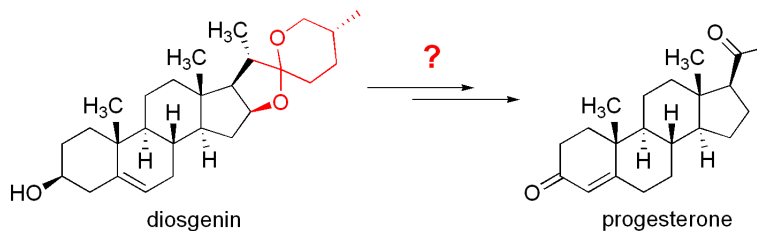
- Semisynthesis

notes_09

Properties:

- Steroid hormone involved in menstruation
- Orally available analogues administered along with estrogen as the birth-control pill.

The problem of access to progesterone for medical studies was solved by Marker's isolation of diosgenin in large quantities from a Mexican yam.



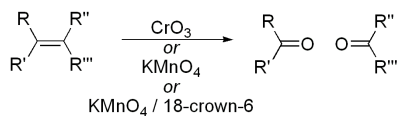
isolated from the roots of cabeza de negro
(a giant mexican yam)

notes_10

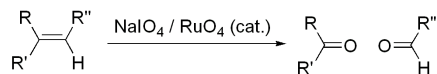
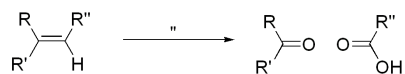
Methodology:

2.1 Oxidative Degradations:

Handout #1: Oxidation

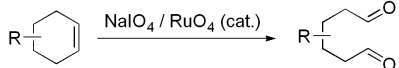


More modern conditions: $\text{HIO}_4 / \text{MnO}_4^-$ (cat.) = Lemieux-Von Rudloff
 $\text{NaIO}_4 / \text{RuO}_4$ (cat.)

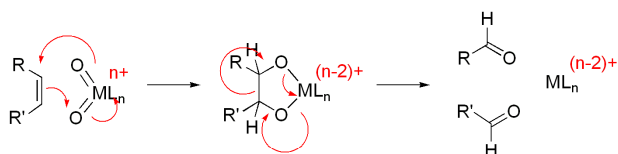


These allow you to stop at the aldehyde:

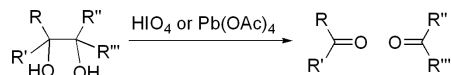
Cyclic precursors can be particularly useful:



A plausible mechanism:



Similarly...

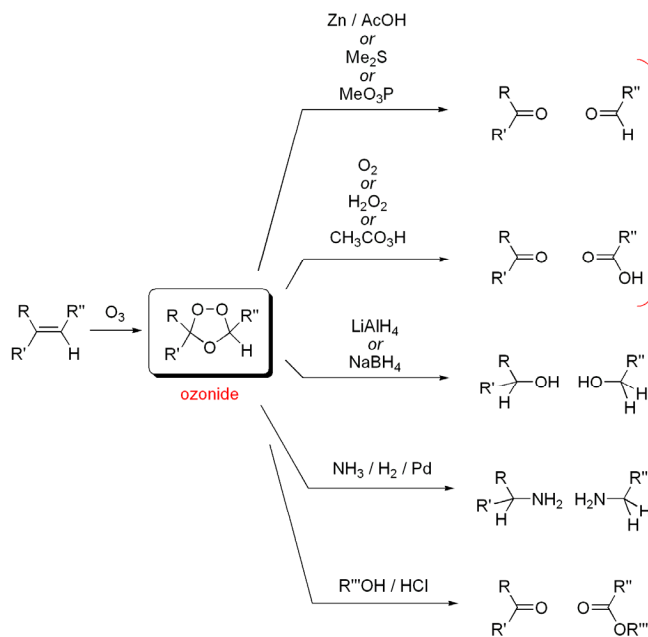


The above reactions are equivalent to a 'one pot' dihydroxylation / cleavage.

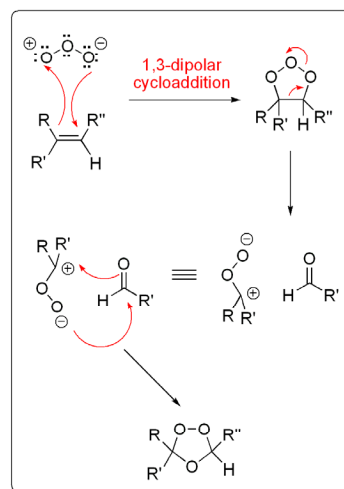
Once at the diol stage, compounds can be very sensitive to oxidizing conditions.

notes_12

2.2 Ozonolysis:

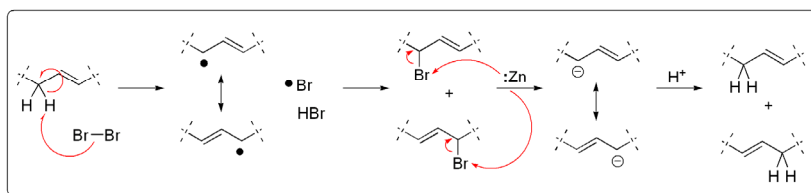
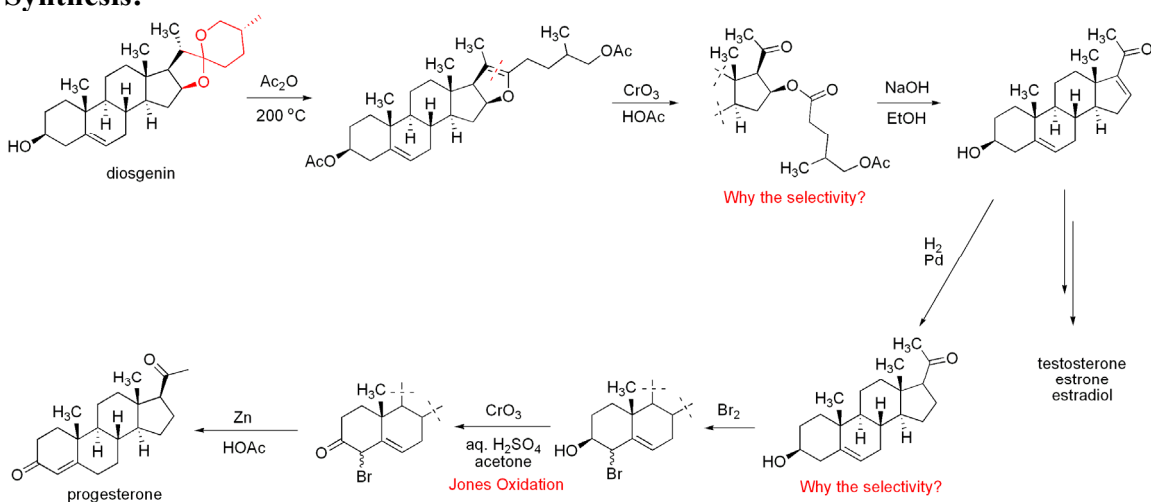


most significant transformations



notes_13

Synthesis:



notes_11

Synthesis 3: Prostaglandin E₂

Corey, 1969 and onward

- Nobel 1990

Classics I, 65

Reactions:

· General discussion of olefin-forming reactions:

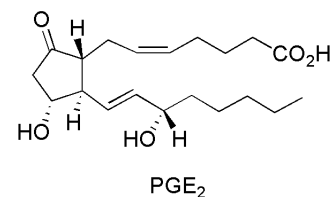
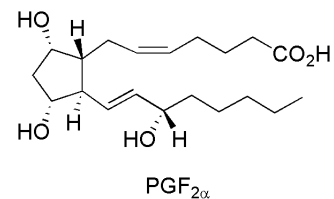
- Wittig reaction
- Horner-Wadsworth Emmons reaction
- Still-Gennari olefination
- Julia olefination
- Corey-Winter olefination
- Peterson olefination
- Barton-Kellogg extrusion reaction

· Asymmetric Diels-Alder reaction

· Baeyer-Villiger oxidation

· CBS reduction

· Iodolactonization



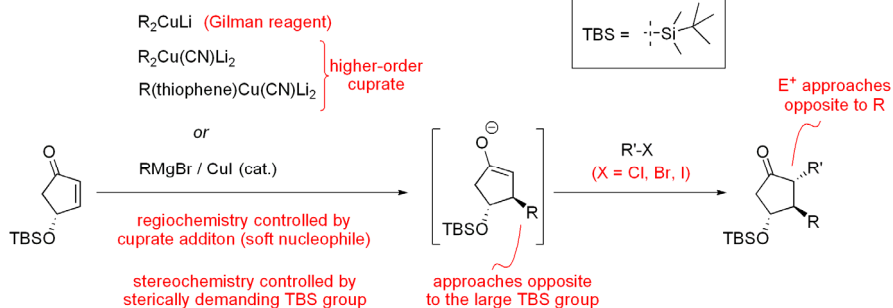
notes_14

Properties:

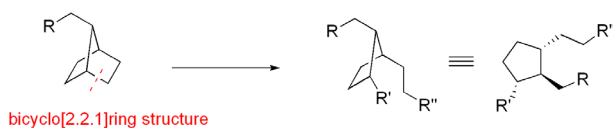
- The prostaglandins are a large family of lipophilic C-20 hormones.
- Isolated in the 1930's, structures in 1960's.
- Originate from action of COX1 and COX2 on arachidonic acid.
(aspirin targets both enzymes, viox selectively targets COX2)
- Various prostaglandins may control:
 - cell growth
 - hormone regulation
 - inflammation
 - sensitivity to pain
 - constriction / dilation of muscle cells
- PGE₂ and PGF₂ are used to induce childbirth or abortion

Synthetic Strategies:

The most obvious approach:

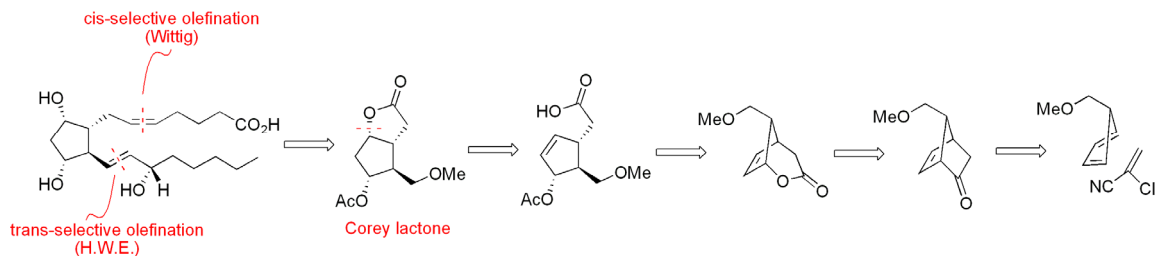


Corey's approach:



notes_15

Retrosynthesis:

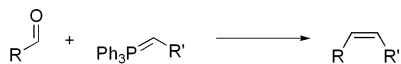


notes_16

Methodology:

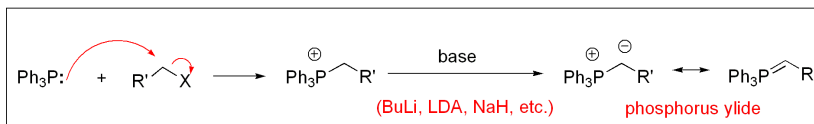
3.1 Olefination Reactions:

Wittig olefination: (George Wittig; Nobel 1979)

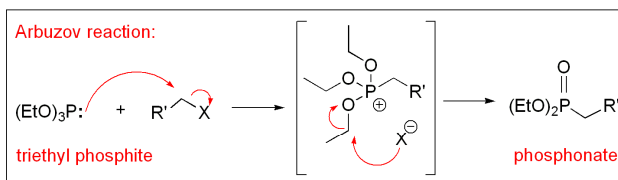
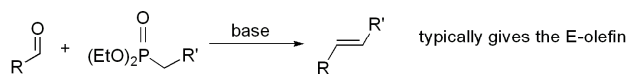


when R' is alkyl, typically gives the Z-olefin } tune by addition of
 stabilized ylides typically give the E-olefin } salts or solvent
 - but can bias to Z-selectivity in acid-free MeOH
 "Kishi footnote" JACS 1982, 1109.

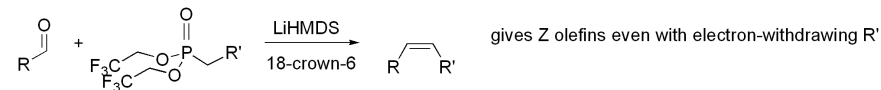
fast with aldehydes, slower with ketones (esp. hindered ketones)



Horner-Wadsworth-Emmons olefination:



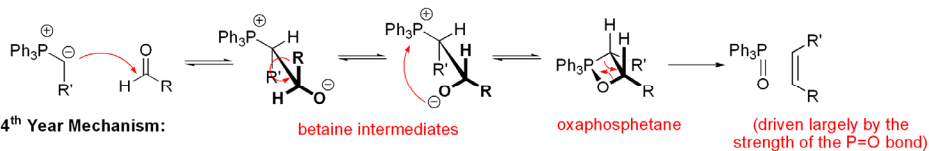
Still-Gennari olefination:



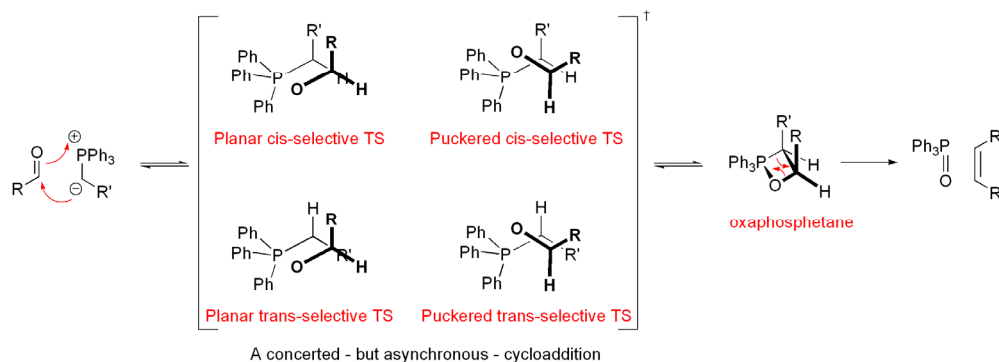
notes_17

Origin of Z-selectivity in Wittig reactions :

The 3rd Year Mechanism:



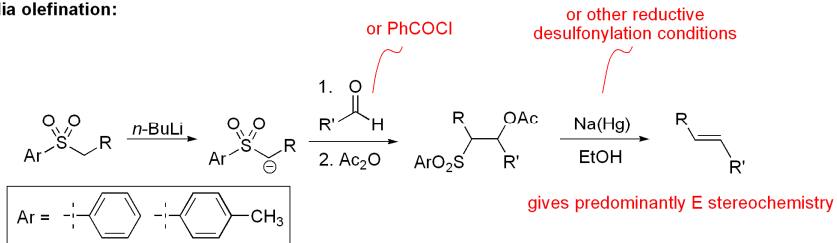
The 4th Year Mechanism:



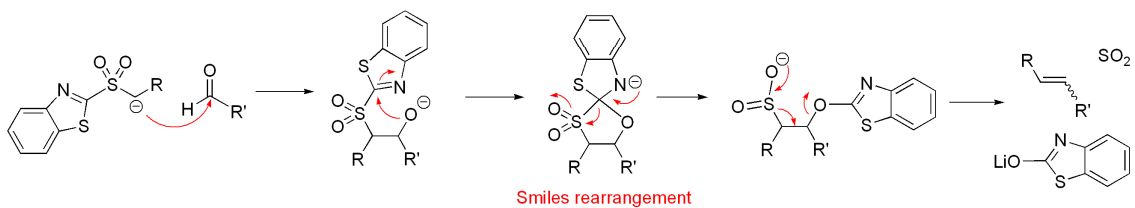
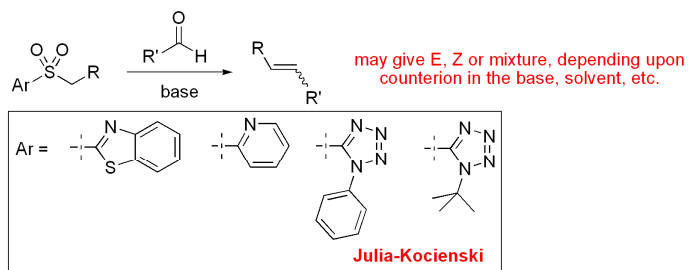
notes_18

Other notable ways to make olefins:

Julia olefination:

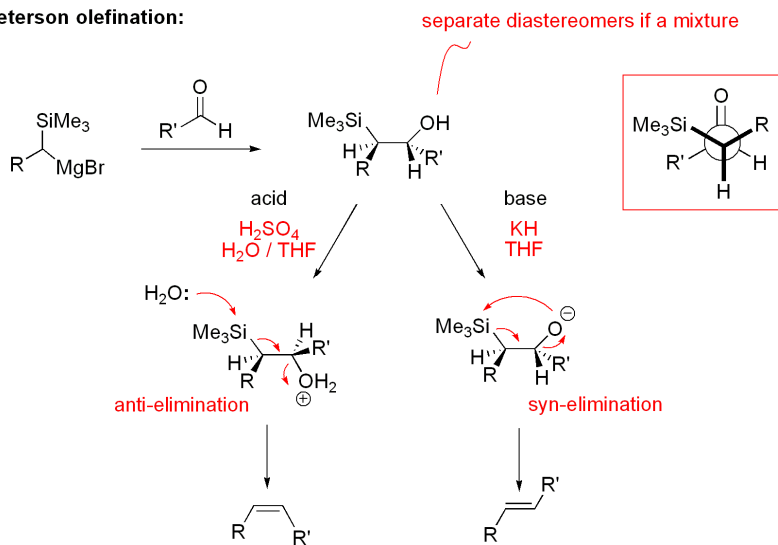


Heteroaryl variants for '1-pot' coupling:



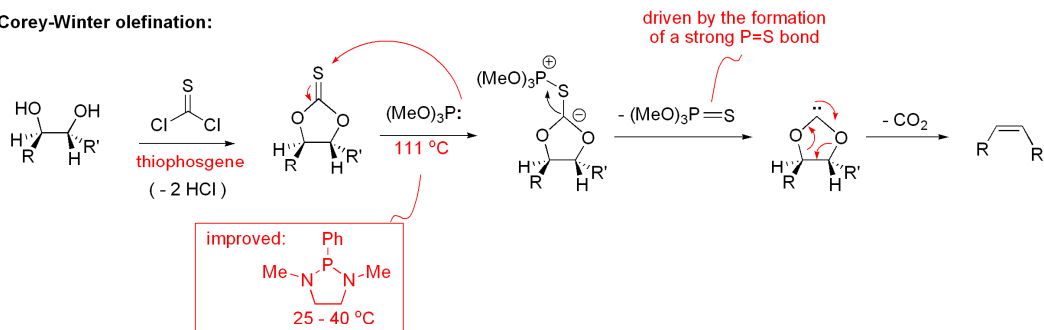
notes_20

Peterson olefination:

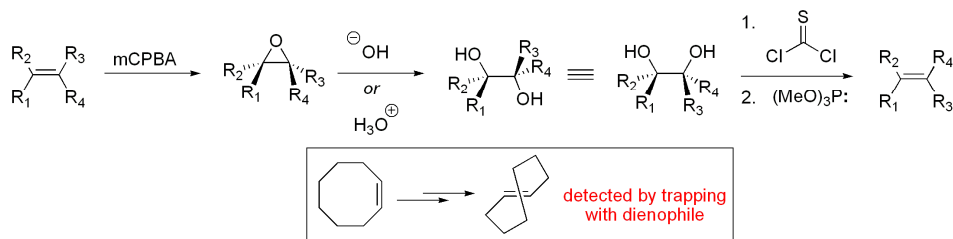


notes_20

Corey-Winter olefination:



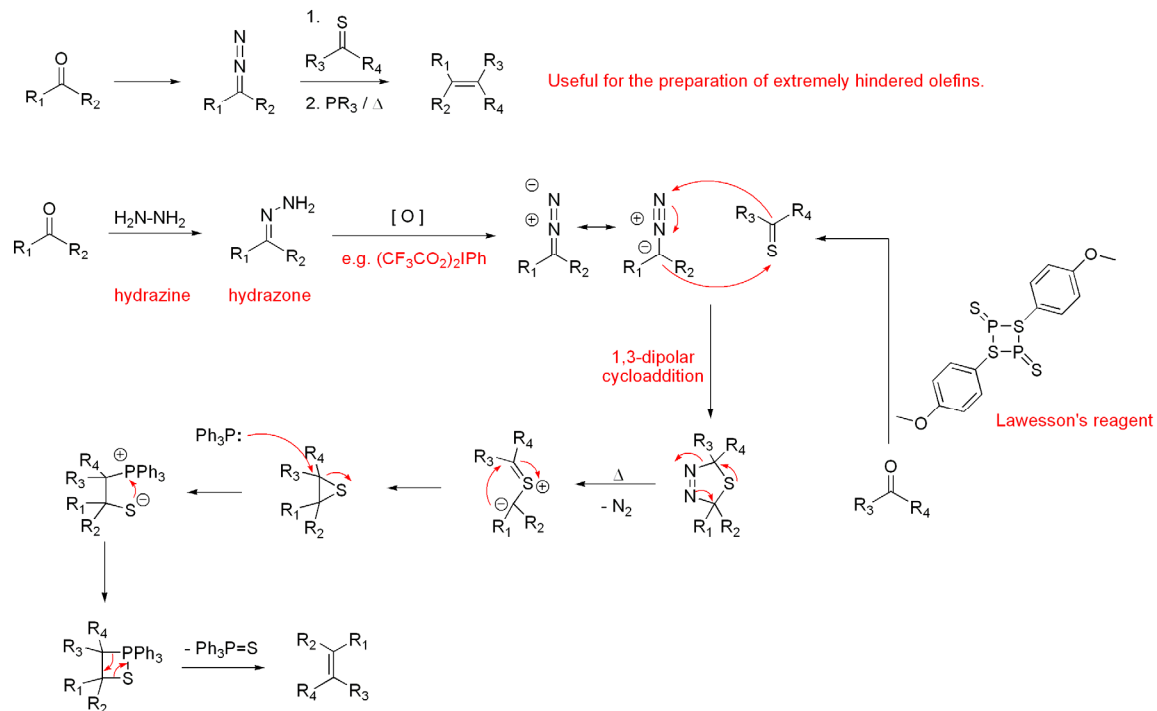
A neat application:



notes_21

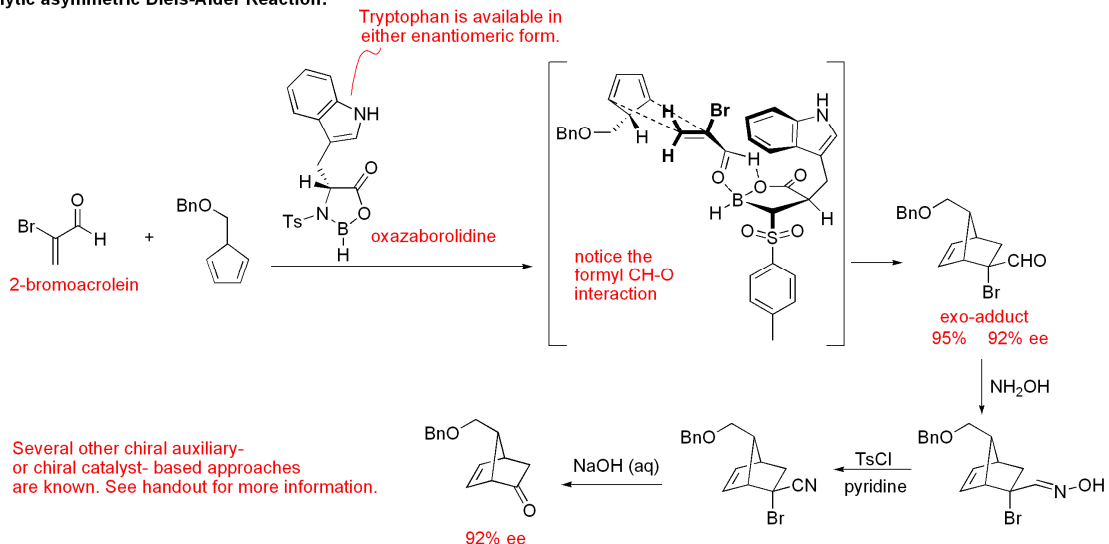
Barton-Kellogg Extrusion Reaction:

(Derek Barton Nobel 1969)



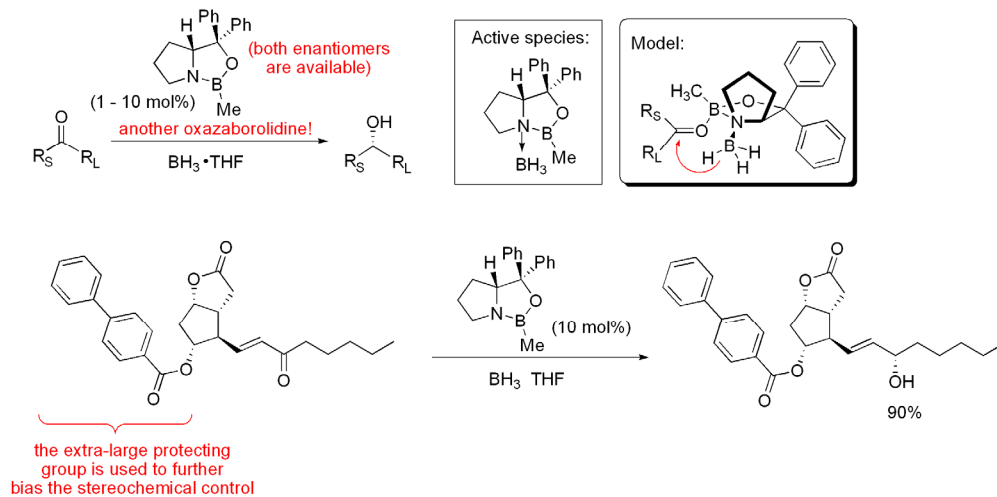
notes_22

Catalytic asymmetric Diels-Alder Reaction:



notes_25

Corey-Bakshi-Shibata (CBS) reduction:



notes_26

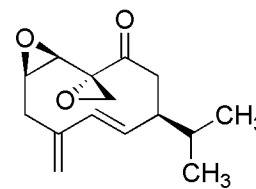
Synthesis 4: Periplanone B

Still, 1979 (largely credited with the invention of flash chromatography)

Classics, I, 211

Reactions:

- Anionic oxy-Cope
- Rubottom oxidation
- Selective epoxidations



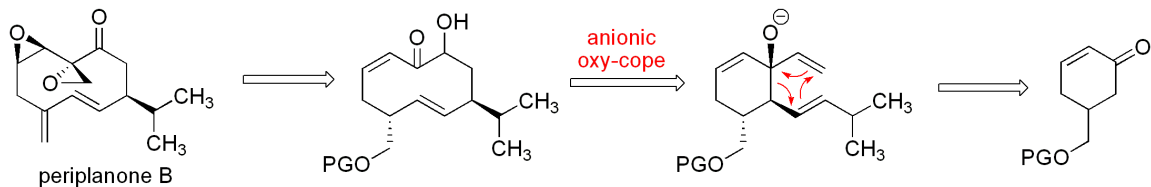
periplanone B

Concepts:

- Use of medium- or large-ring conformation to control stereochemistry

notes_27

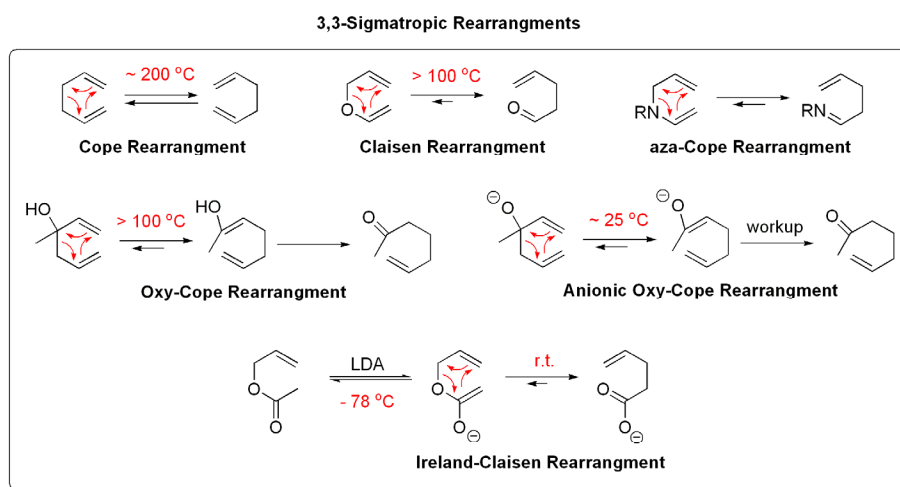
Retrosynthesis:



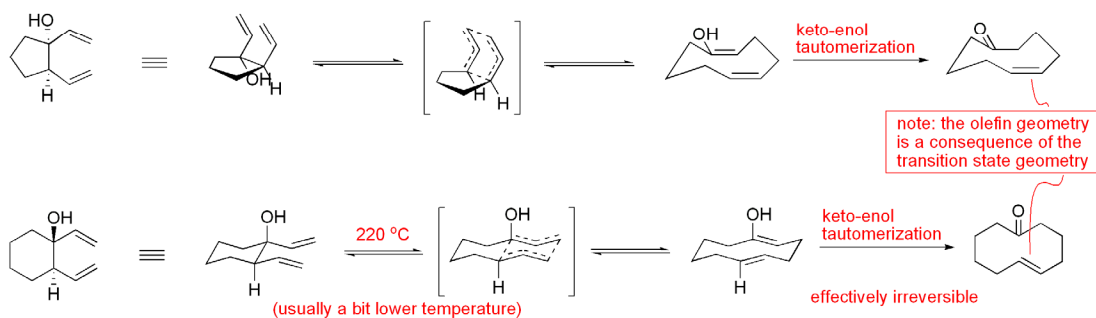
notes_28

Methodology:

4.1 Cope-type reactions:

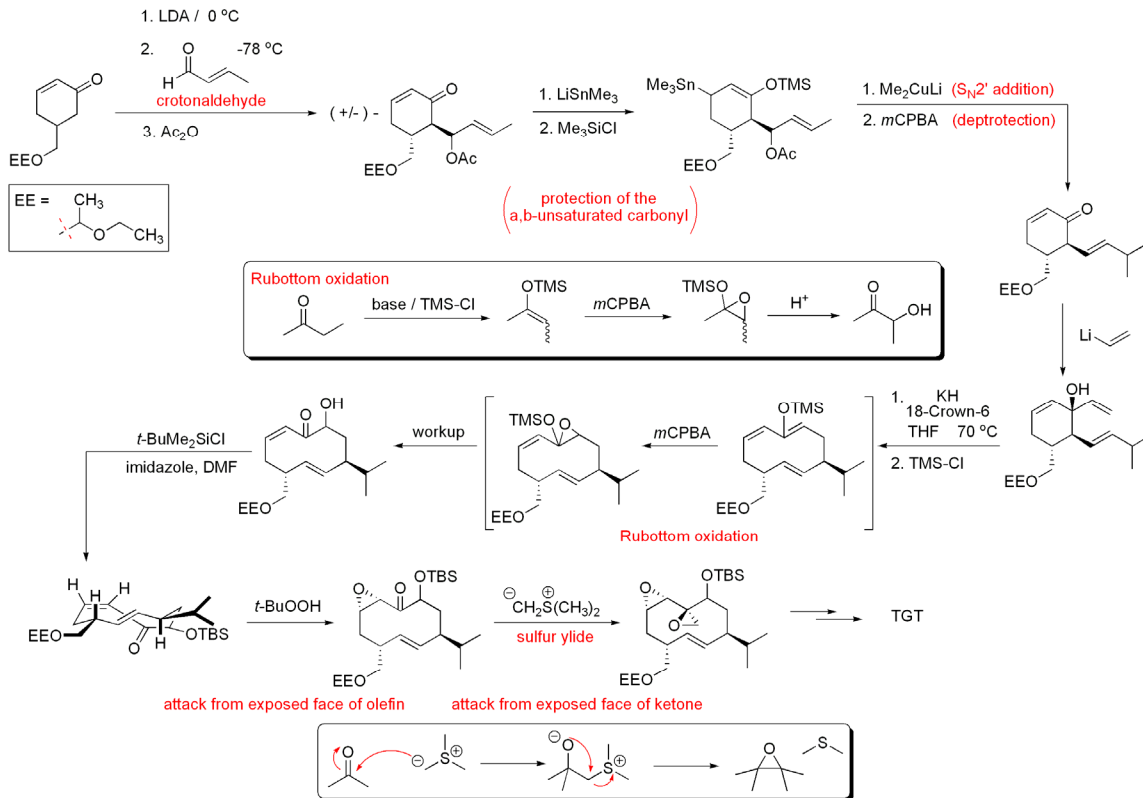


Stereochemical Consequences:



notes_29

Synthesis:



notes_30

Section 5: Palladium-Mediated Coupling Strategies

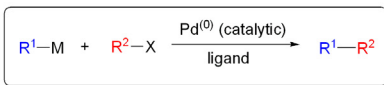
Reactions:

- General discussion of:
 - Stille coupling
 - Heck coupling
 - Suzuki coupling
 - Sonogashira coupling
 - Negishi coupling
 - Tsuji-Trost coupling
 - Pd- Pt- & Au-mediated cycloisomerizations

Concepts:

- Catalytic cycles – oxidative addition, reductive elimination, etc.
- Increased synthetic efficiency using organometallic coupling strategies.

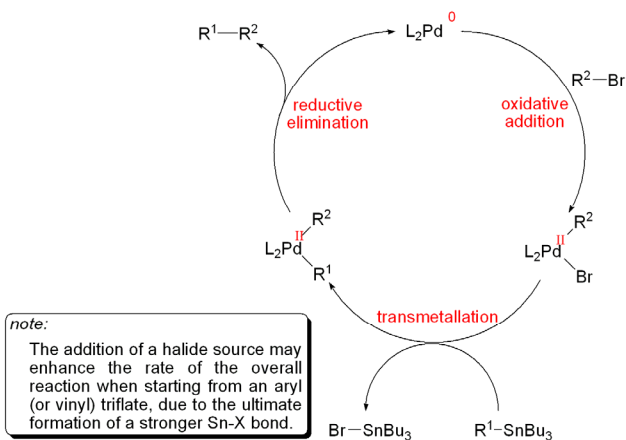
Methodology 5.1. The Stille, Suzuki & Negishi reactions - Related Mechanisms



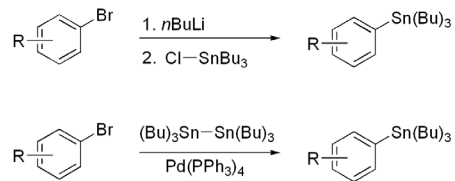
	M	X	R ¹	R ²	Other Requirements
Stille	Sn(alkyl) ₃	I, Br, Cl, OTf,			
			(& sometimes alkyl)		
Suzuki		I, Br, Cl, OTf,			Base: Cs ₂ CO ₃ , B(OH) ₃ , Na ₂ CO ₃ , K ₂ CO ₃ , Ba(OH) ₂ , TIOH, KF, CsF, NaOH, etc.
			and alkyl	and alkyl	
Negishi	ZnX	I, Br, Cl, OTf, OAc			
			and alkyl		

notes_31

Catalytic Cycle: Stille Coupling

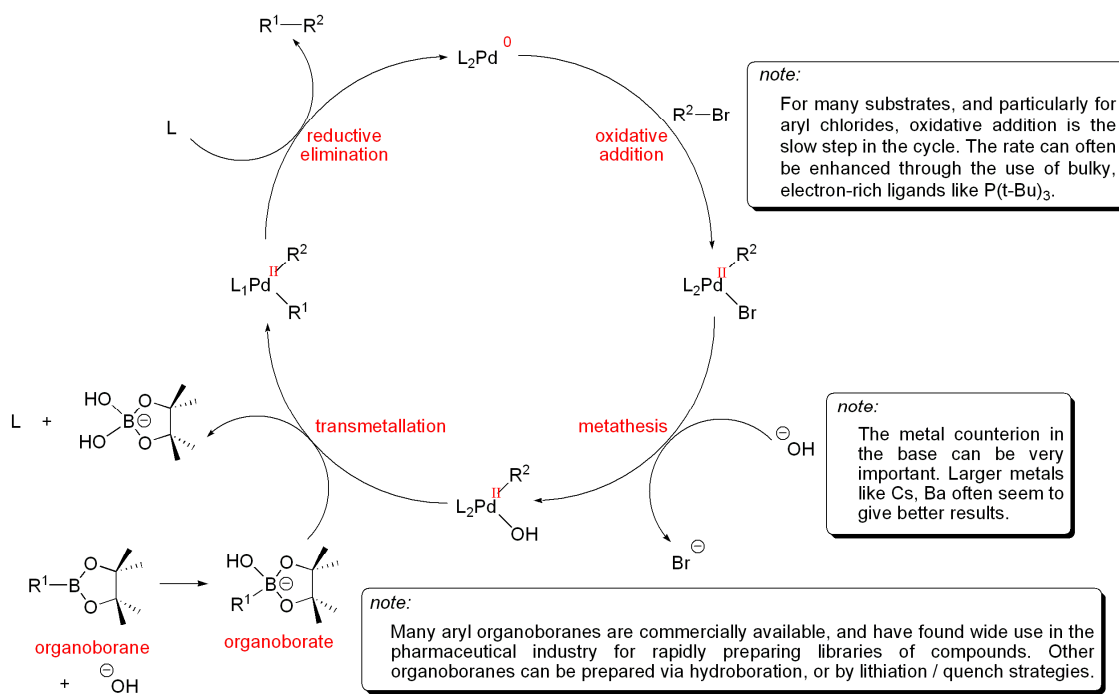


Formation of alkyl stannanes:



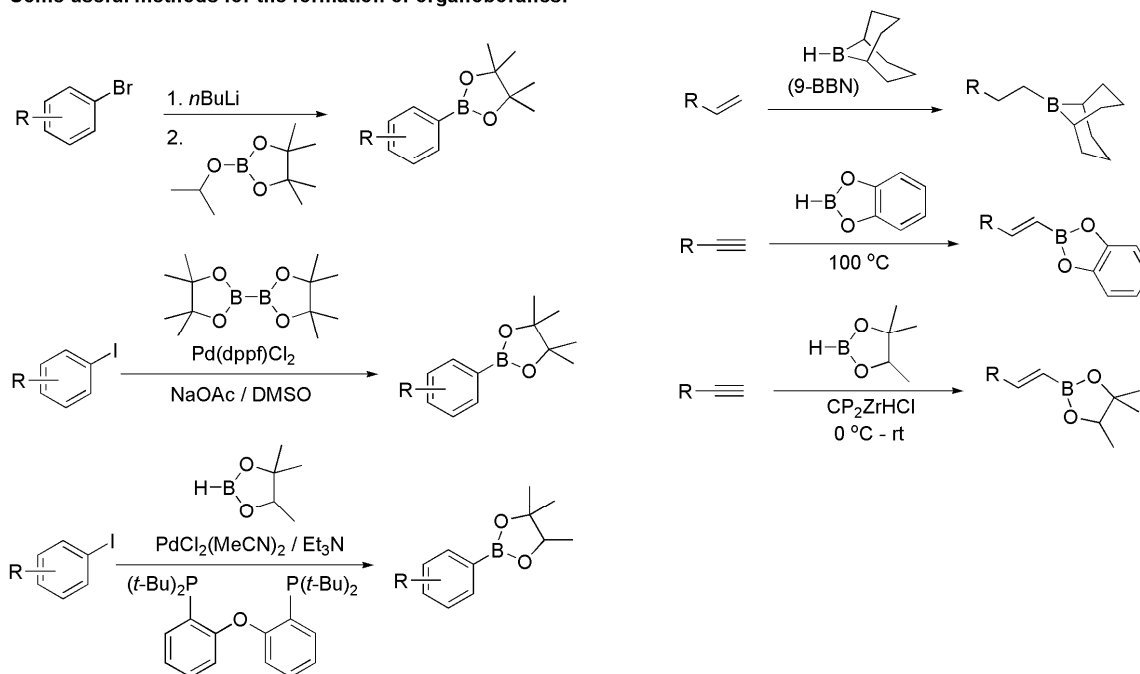
notes_34

Catalytic Cycle: Suzuki Coupling



notes_32

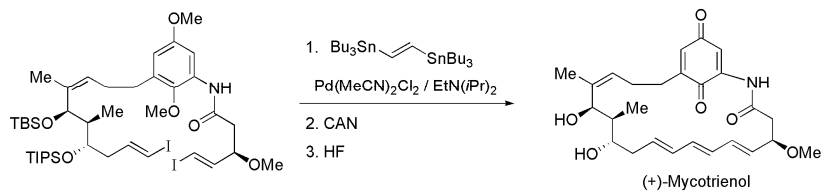
Some useful methods for the formation of organoboranes:



notes_33

Synthesis 5.1. Some illustrative syntheses:

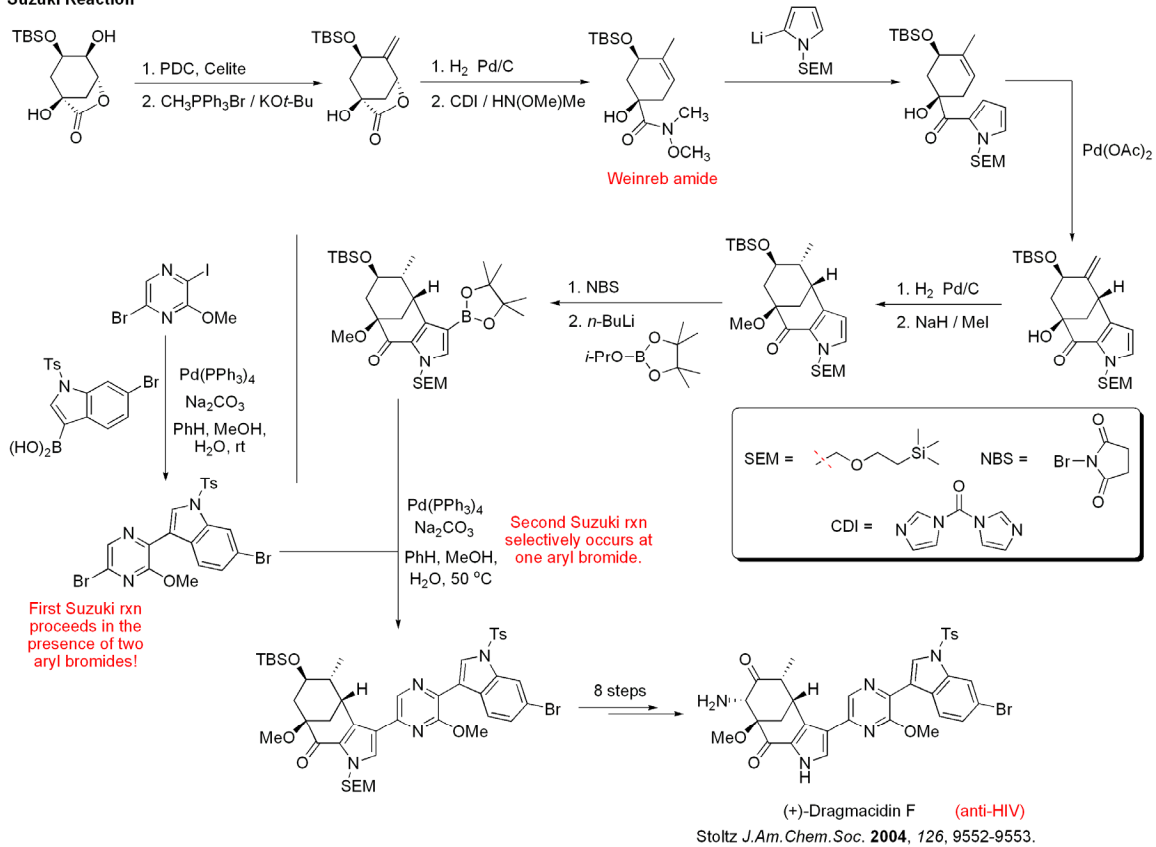
Stille Reaction



Panek *J. Am. Chem. Soc.* **1998**, *120*, 4123-4134

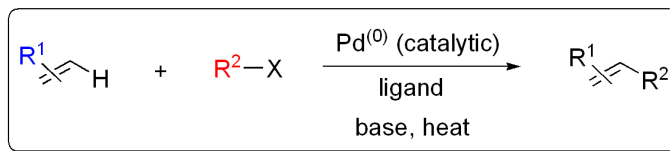
notes_35

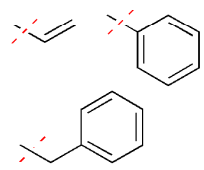
Suzuki Reaction

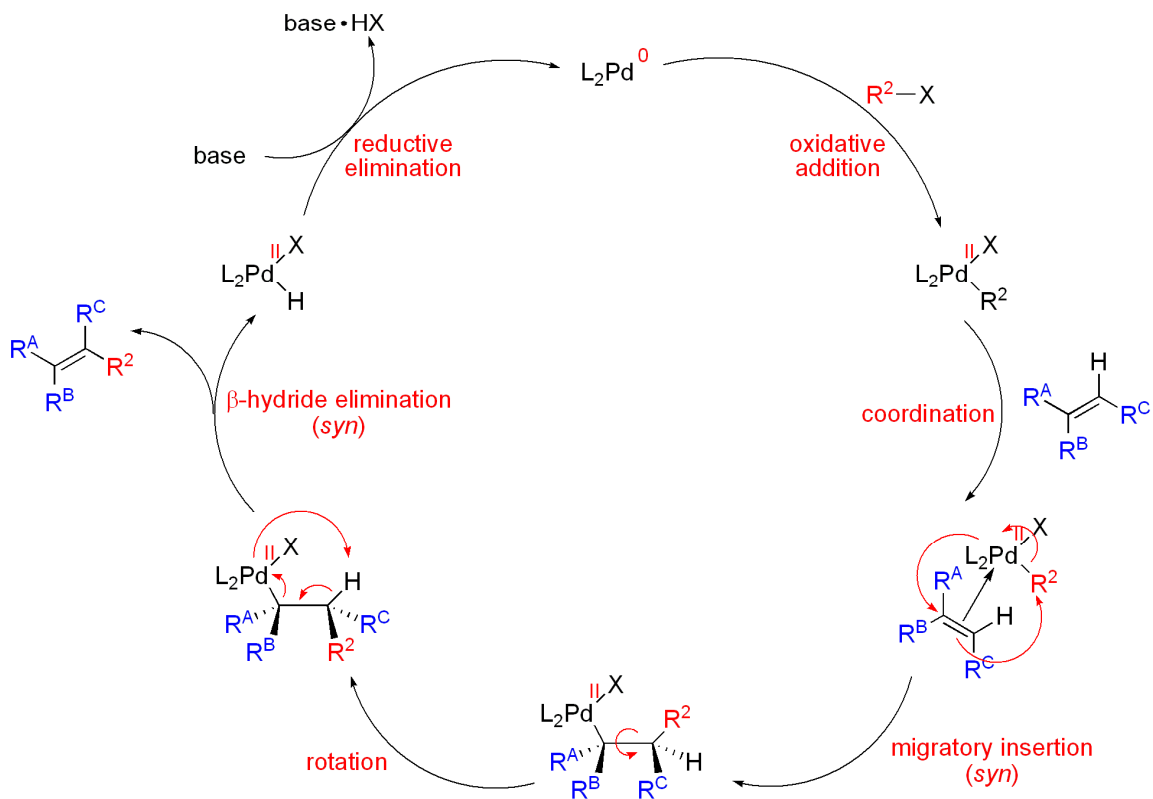


notes_36

Methodology 5.2. The Heck reaction:

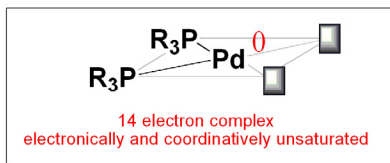


R^2	X	base
	I, Br, Cl, OTf, OTs, N_2^+	2° or 3° amine KOAc, NaOAc, NaHCO_3
or sometimes alkyl (w/ no β -hydrogen)		

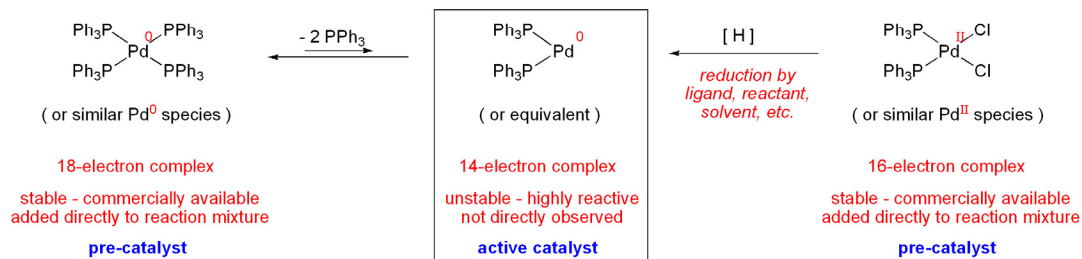


notes_37

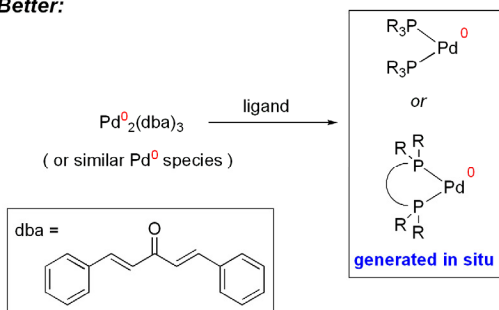
On the nature of " L₂Pd⁰ "



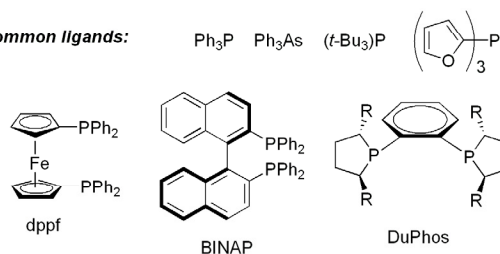
Typical Formation:



Even Better:



common ligands:

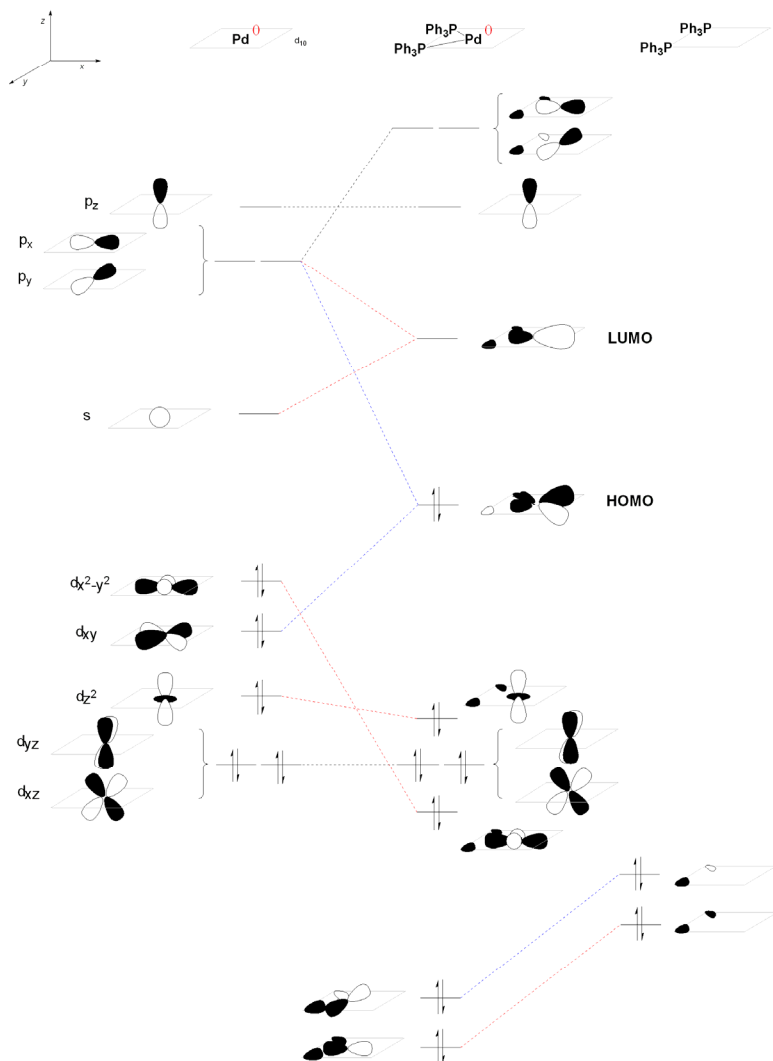


And many, many others!

Chiral ligands allow asymmetric control of reactions.

A closer look at what those curved arrows are doing:

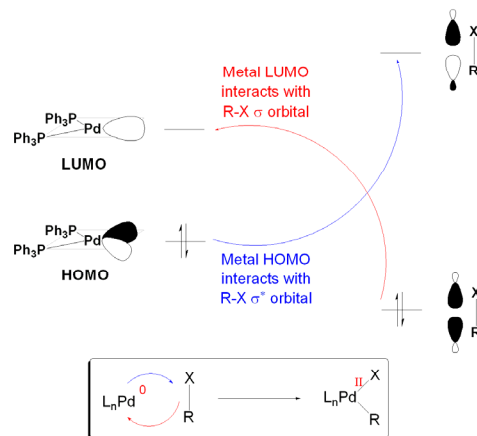
A Frontier MO Diagram for $(\text{Ph}_3\text{P})_2\text{Pd}$



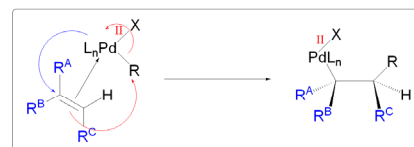
notes_38b

What You Need to Remember

Somewhere in the $(\text{Ph}_3\text{P})_2\text{Pd}^0$ frontier MO's is a filled orbital of the right symmetry for interacting with the R-X antibonding orbital (σ^*) and an empty orbital of the right symmetry for interacting with the R-X bonding orbital (σ).

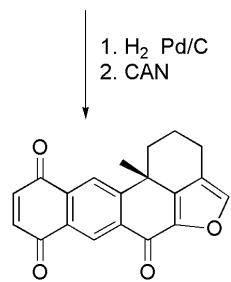
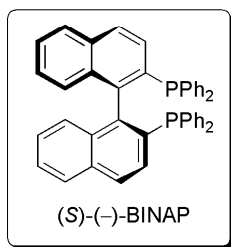
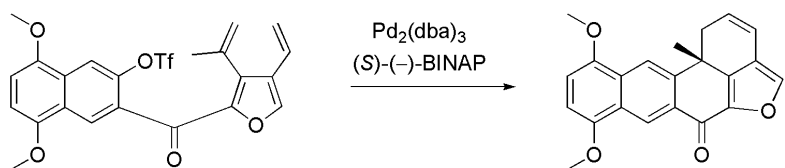


Something similar happens in the case of the subsequent addition of the olefin.



For arrow-pushing purposes, the Pd acts simultaneously as a nucleophile and an electrophile.

An example of an asymmetric “double” Heck reaction

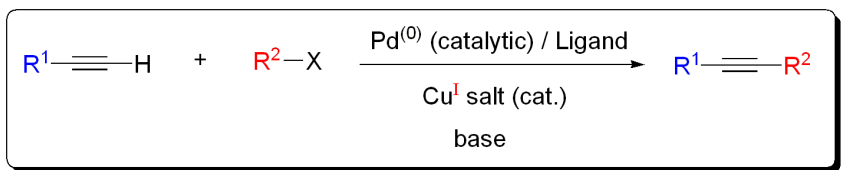



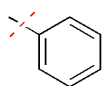
(+)-Xestoquinone
Keay *J. Am. Chem. Soc.* **1996**, *118*, 10766

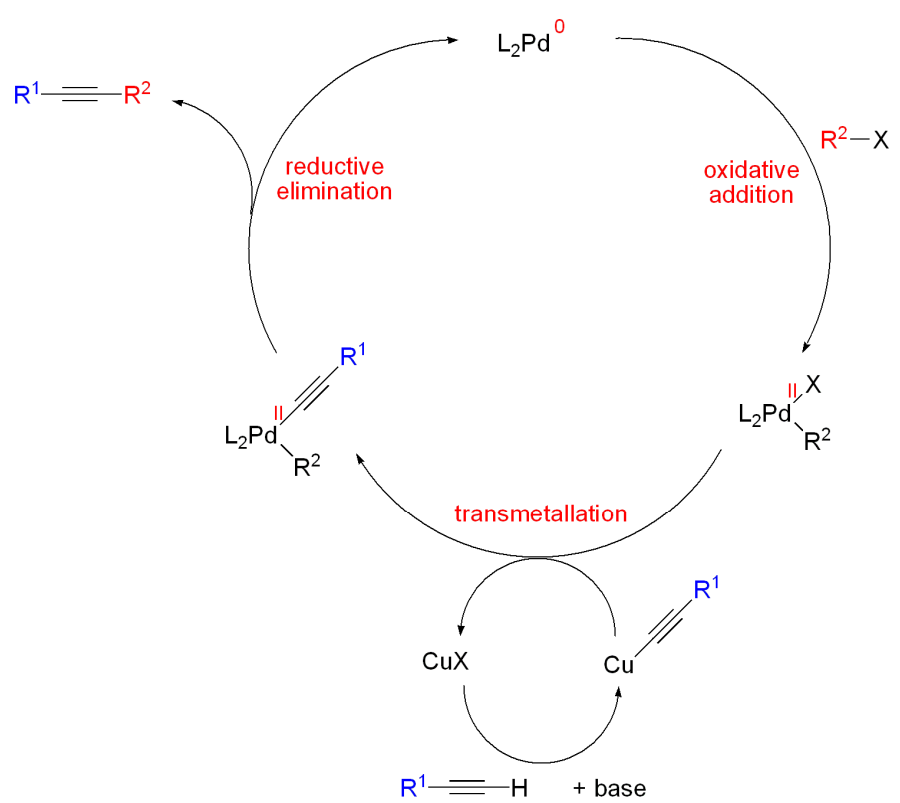
notes_43

Some other noteworthy Pd-coupling strategies:

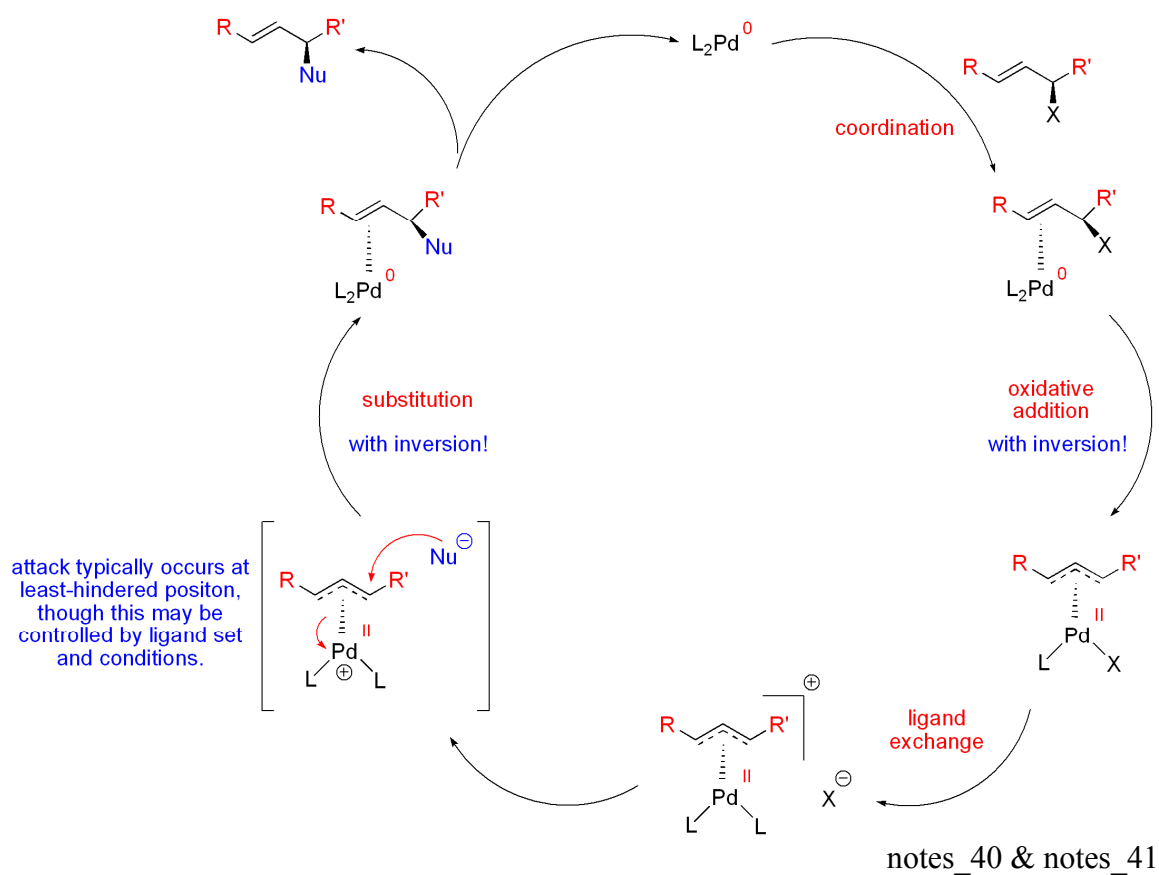
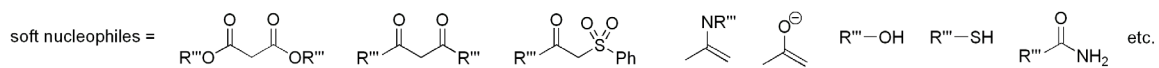
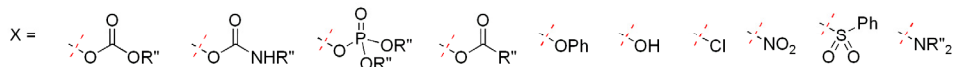
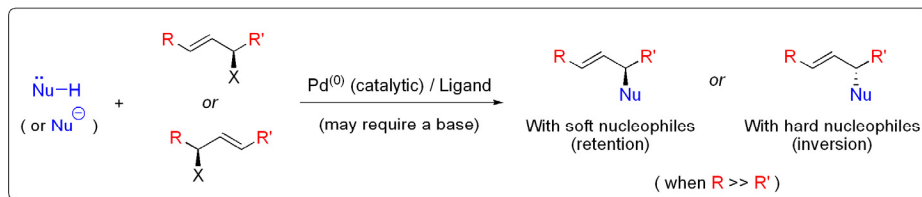
Methodology 5.3. Sonogashira coupling:



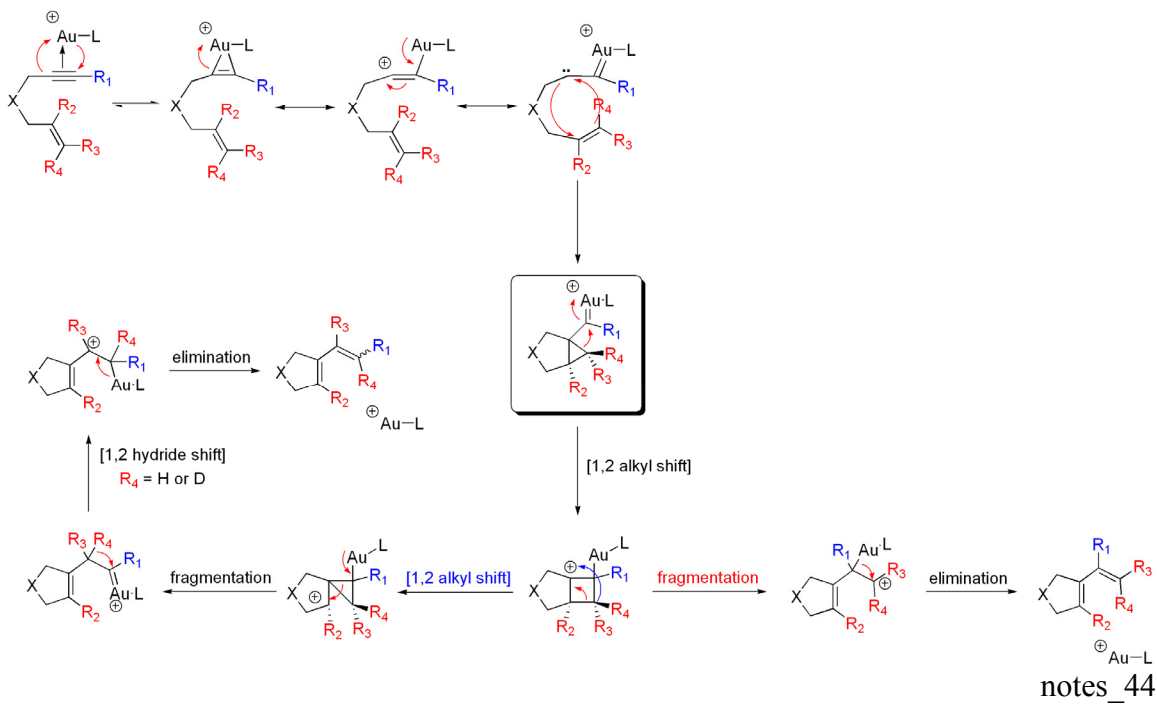
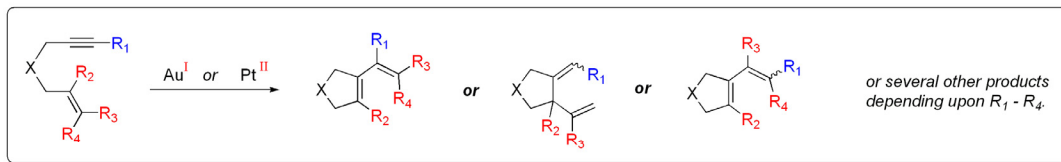
R^2	X	Cu^I salt	base
 	I, Br, Cl, OTf	CuI, CuBr	2° or 3° amine



Methodology 5.4. Tsuji-Trost coupling:



Methodology 5.5. Au- and Pt-Catalyzed Cyclizations of Eneynes:



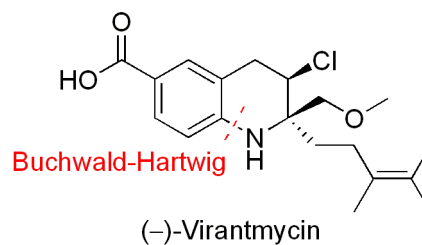
Synthesis 6: Virantmycin

Back, 2004

Angew. Chemie Int. Ed. **2004**, 43, 6493.

Reactions:

- Buchwald-Hartwig coupling
- Acid chloride / fluoride formation
- Curtius rearrangement
- Krapcho decarboxylation
- Enzyme-mediated reactions



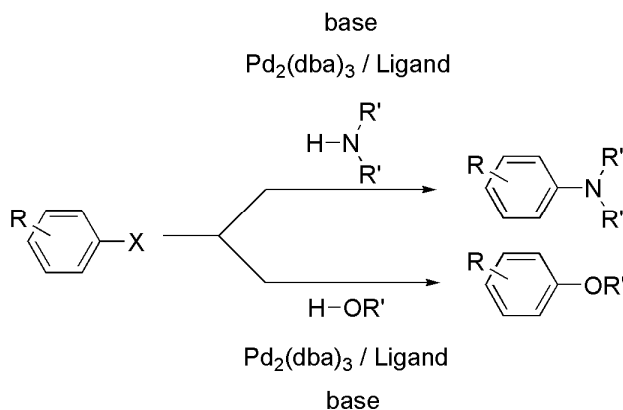
notes_45

Concepts:

- Desymmetrization
- Stereodivergent synthesis

Methodology:

6.1 Buchwald-Hartwig coupling:

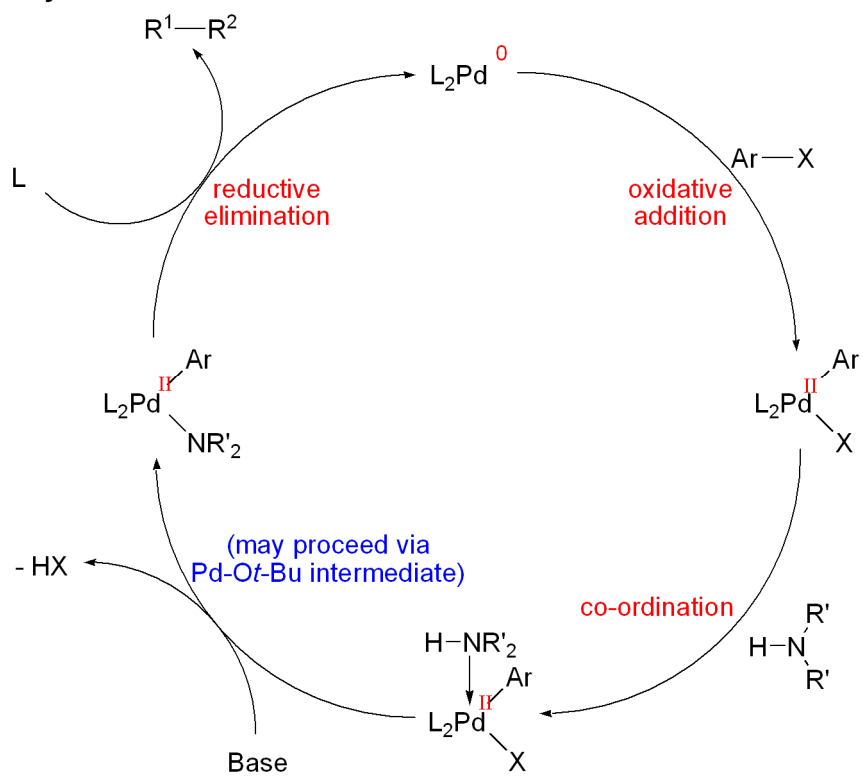


(Ligand = BINAP, DPPF, etc.)

Base = $\text{NaO}t\text{-Bu}$, LHMDS, K_2CO_3 , Cs_2CO_3

notes_47

Catalytic Cycle:



Synthesis 7: Xanthatin

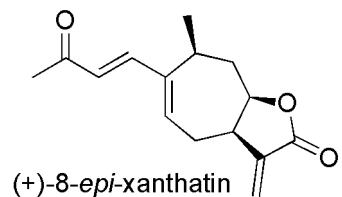
Martin, 2006

Tetrahedron 2006, 62, 11437

Reactions:

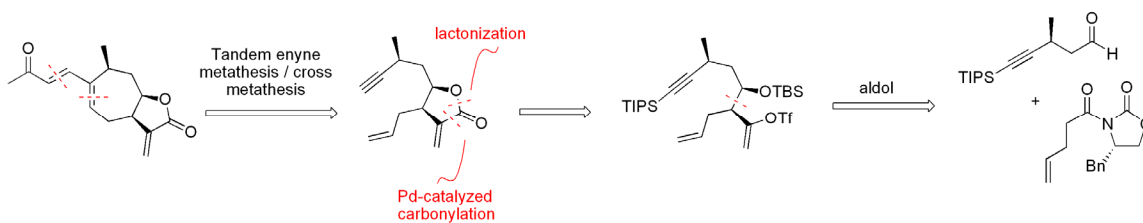
· General discussion of olefin metathesis:

- Ring-opening metathesis polymerization
- Ring-closing metathesis
- Cross metathesis
- Ene-yne metathesis



notes_50

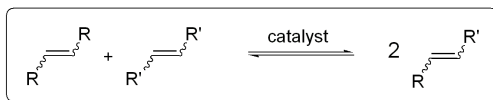
Retrosynthesis:



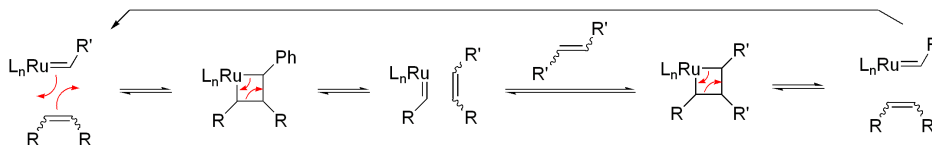
notes_51

Methodology:

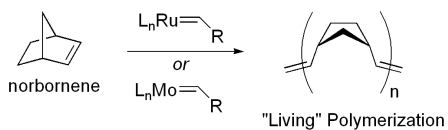
7.1 Olefin Metathesis: (Nobel 2005)



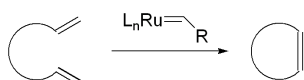
General Mechanism:



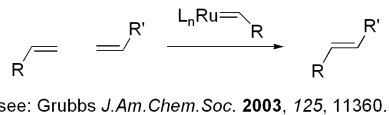
Ring-Opening Metathesis Polymerization:



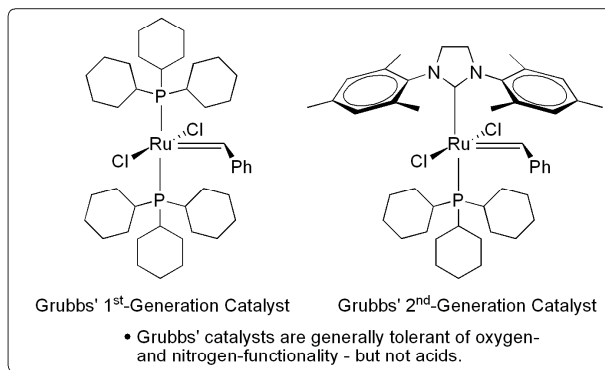
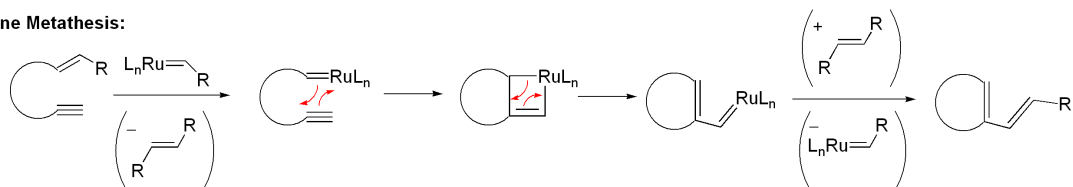
Ring-Closing Metathesis:



Cross Metathesis:

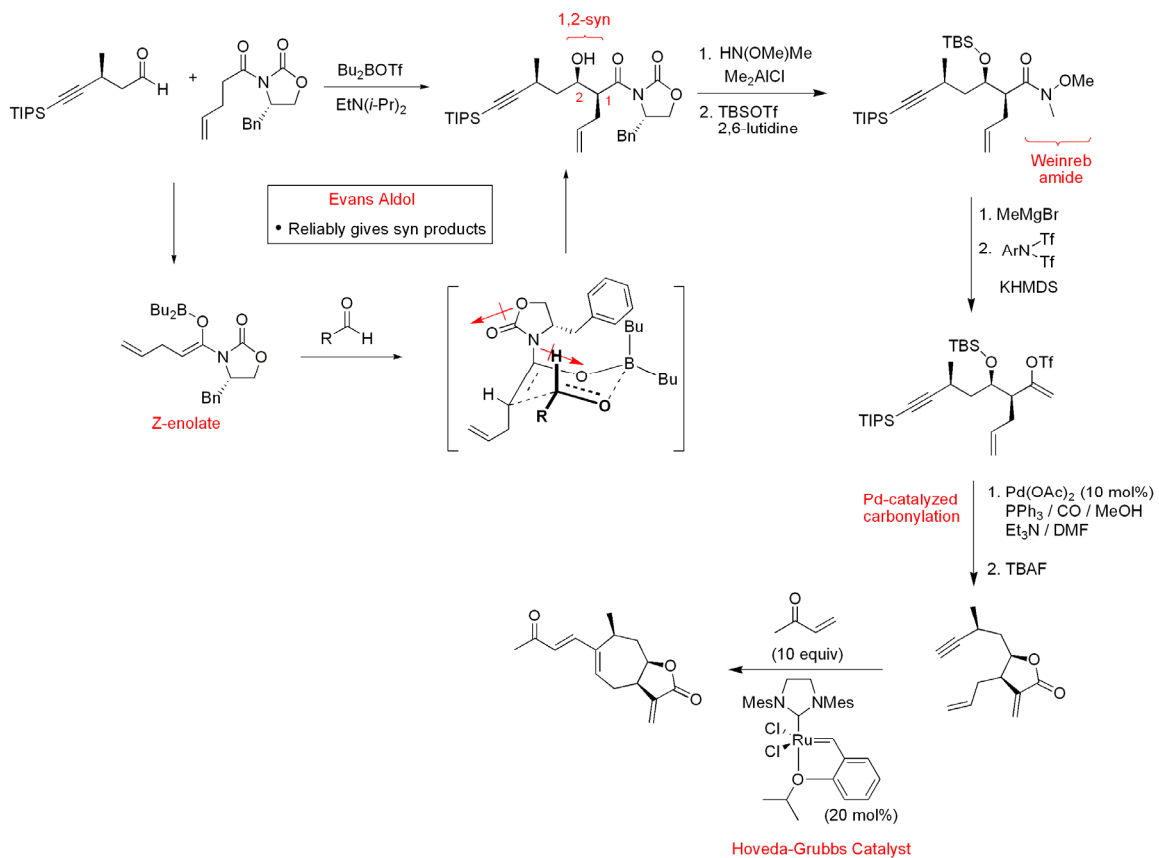


Enyne Metathesis:



Also: $\left\{ \begin{array}{l} \text{"W"}=CH-R \\ \text{"Mo"}=CH-R \end{array} \right\}$ Schrock Carbenes

Synthesis:



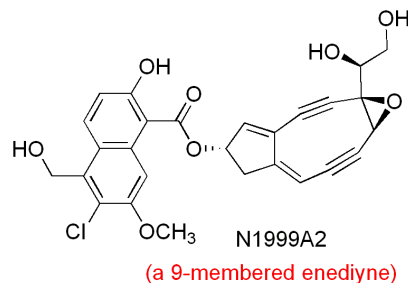
notes_52

Synthesis 8: N1999A2

Myers, 2006 – *J. Am. Chem. Soc.* **2006**, *128*, 14825.

Reactions:

- Bergman cycloaromatization
- Swern-type oxidations
- Asymmetric epoxidations
- Asymmetric dihydroxylations
- Amide couplings with DCC / EDC / HATU etc.
- Corey-Fuchs reaction
- Glaser reaction

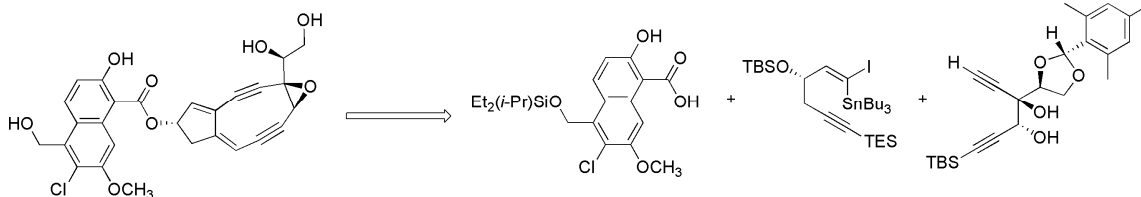


notes_62

Concepts:

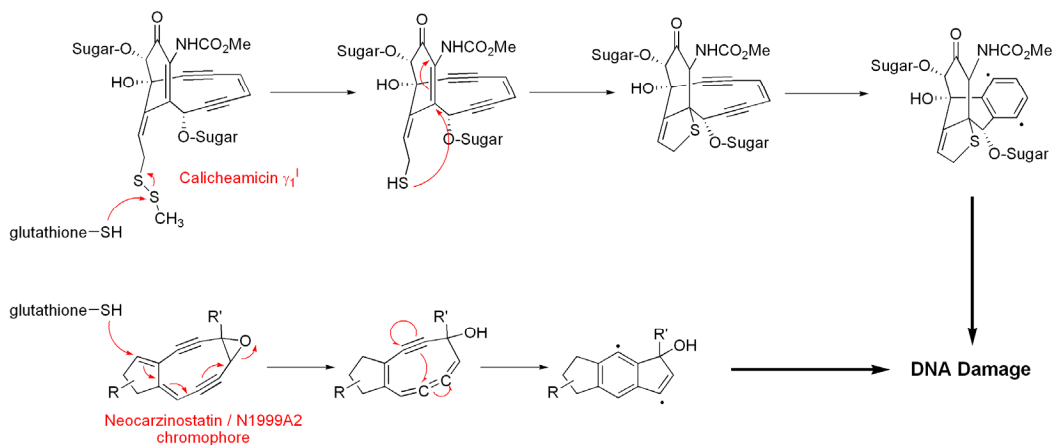
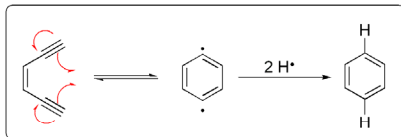
- Synthetic planning

Retrosynthesis:

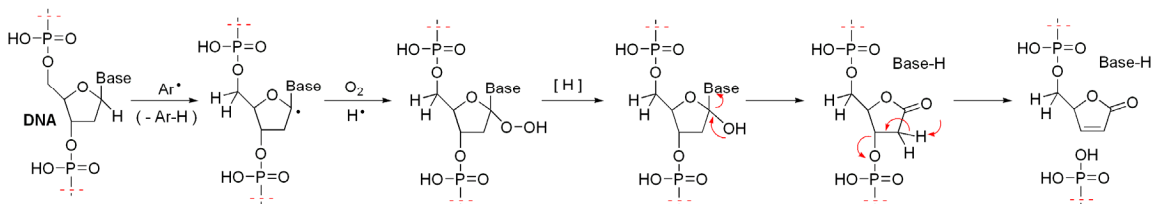


notes_62

Bergman Rearrangement:

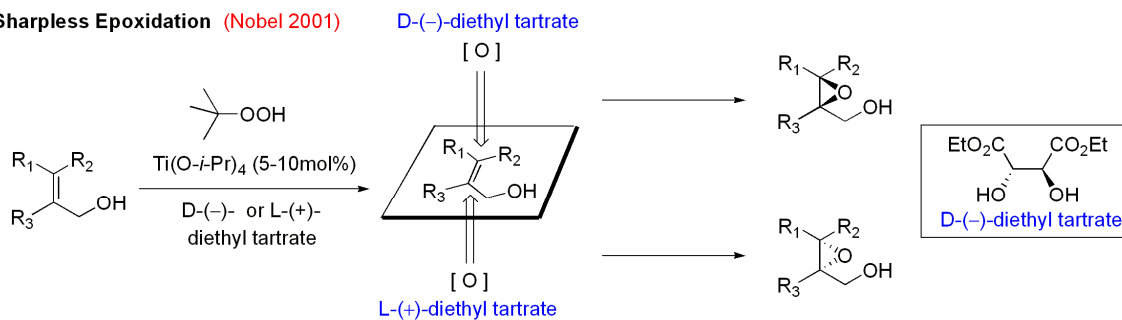


Mechanism of DNA Cleavage:

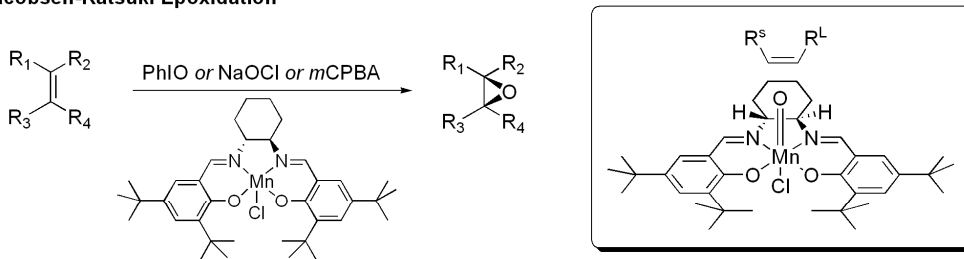


Methodology 8.1: Asymmetric Epoxidation

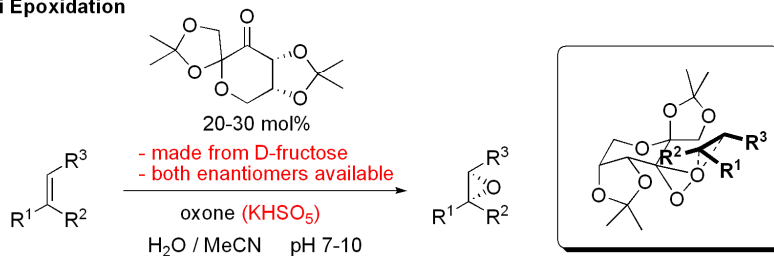
Sharpless Epoxidation (Nobel 2001)



Jacobsen-Katsuki Epoxidation

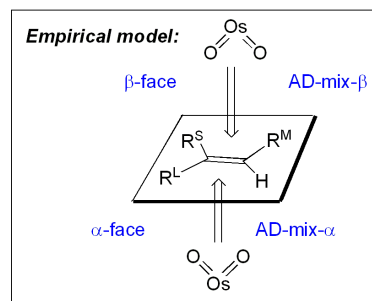
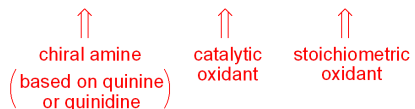
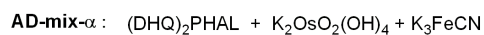
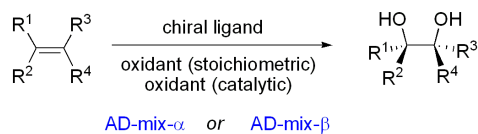


Shi Epoxidation

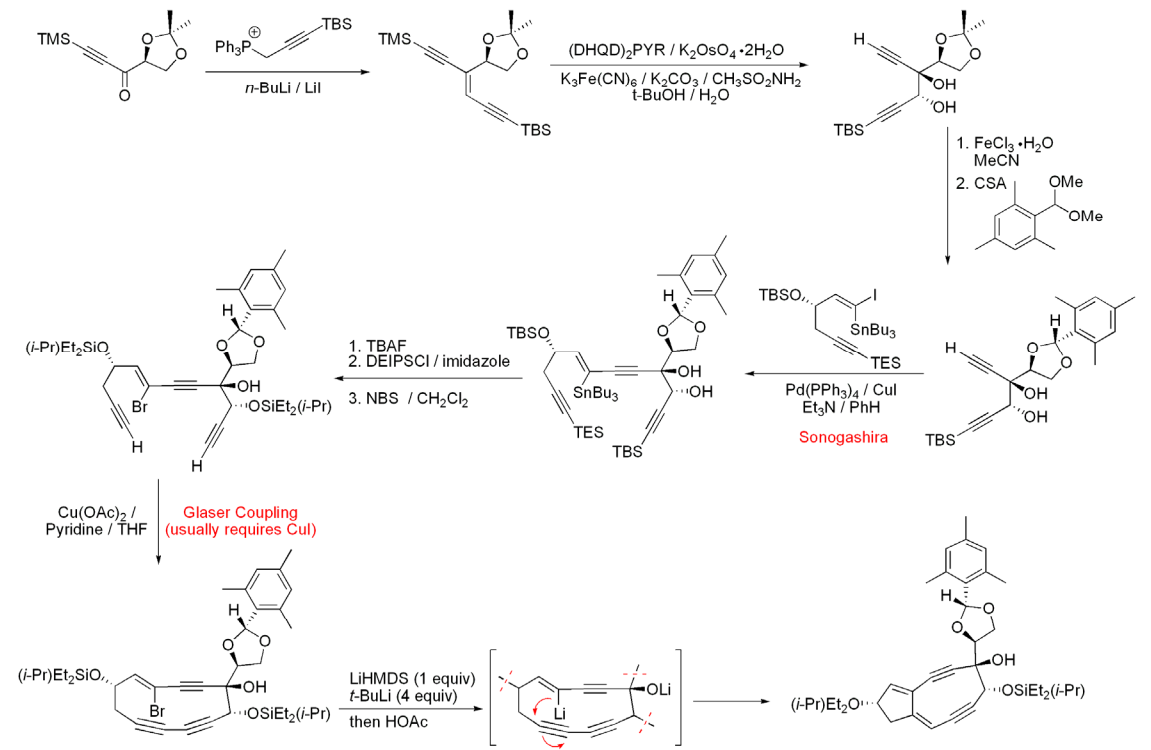
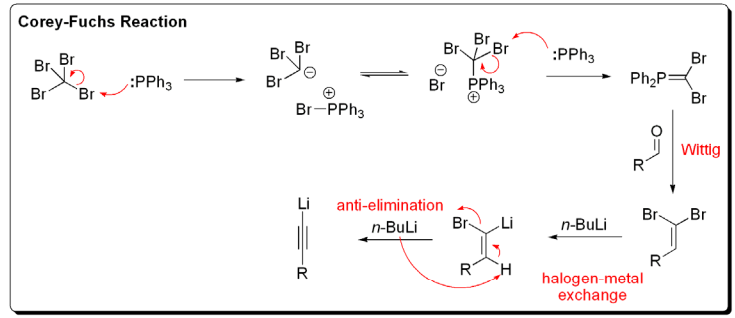
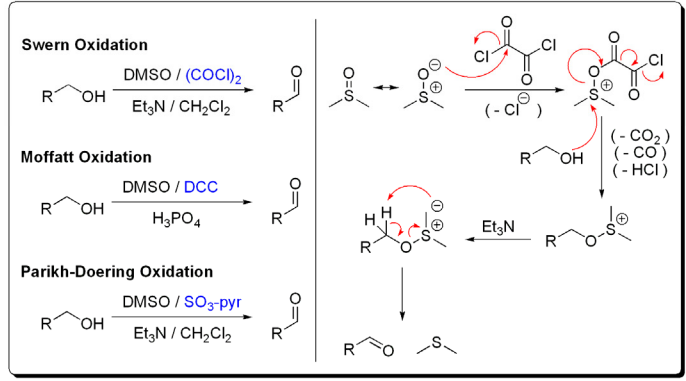
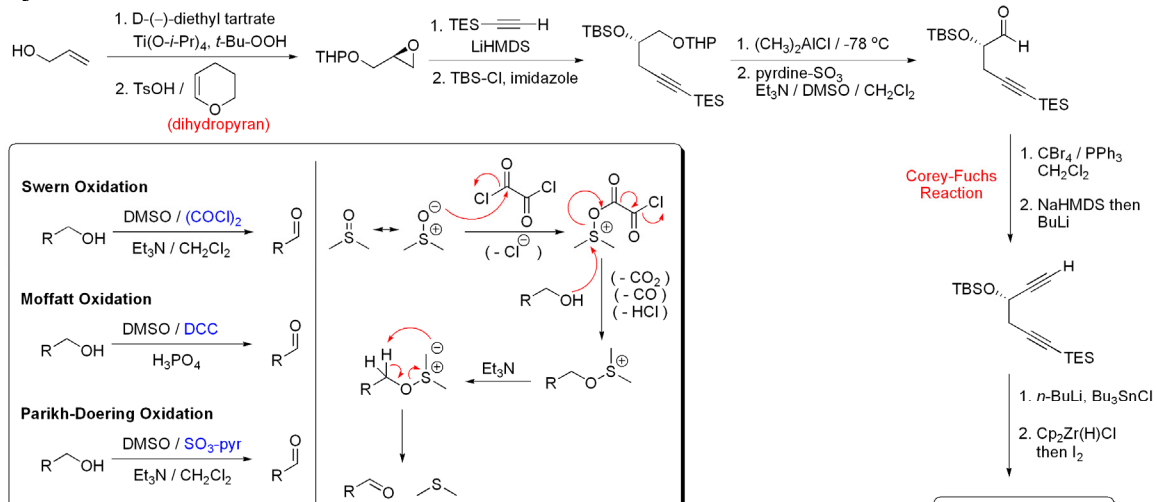


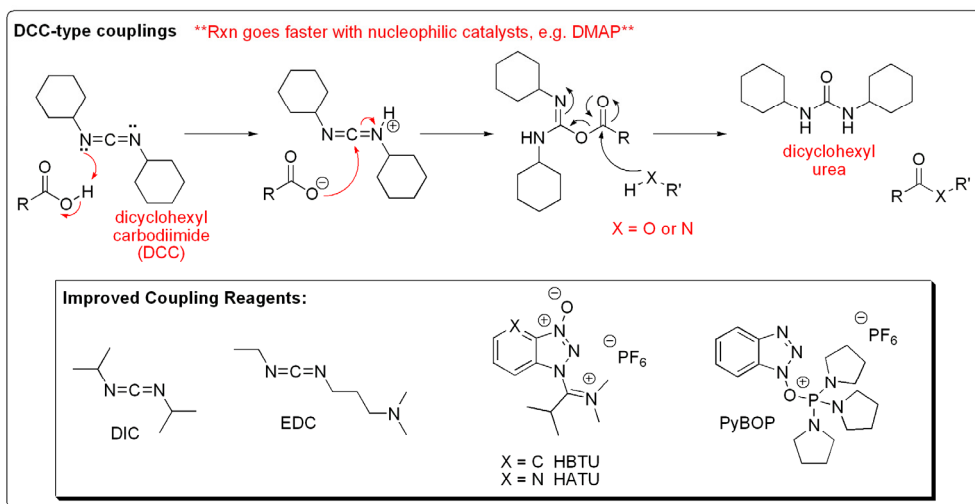
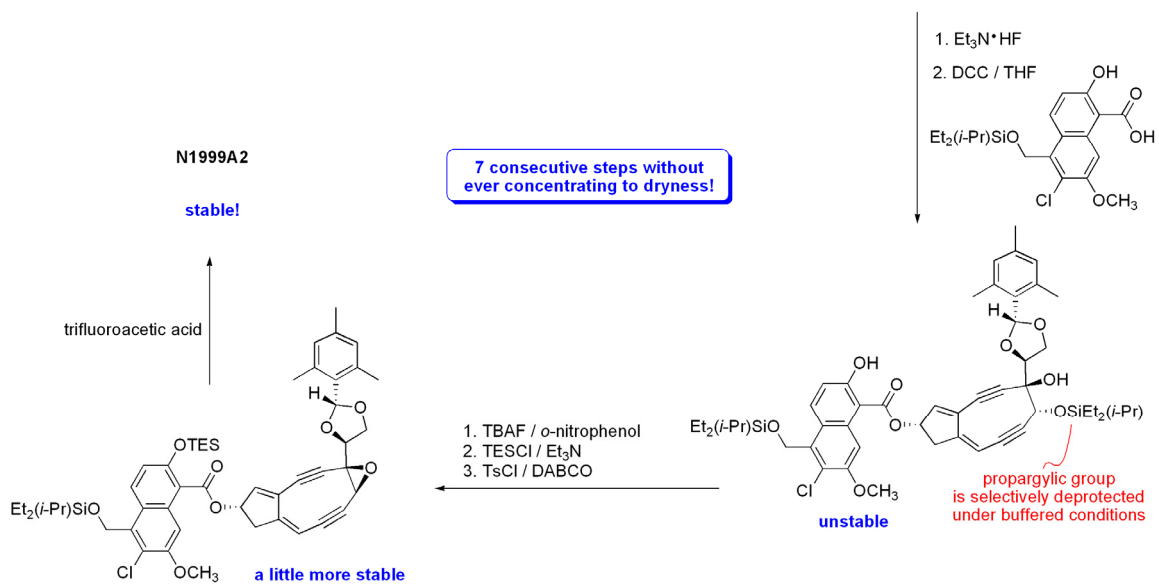
Methodology 8.2: Asymmetric Dihydroxylation

Sharpless Dihydroxylation (Nobel 2001)



Synthesis:





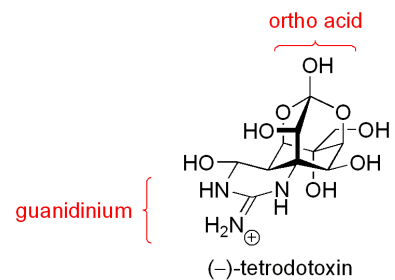
Synthesis 9: Tetrodotoxin

Du Bois, 2003

J. Am. Chem. Soc. **2003**, *125*, 11510

Reactions:

- Carbene insertion reactions
- Oxidative degradations
- Methylene-forming reactions
- Selenoxide elimination
- TPAP/NMO oxidations
- Allylic oxidations

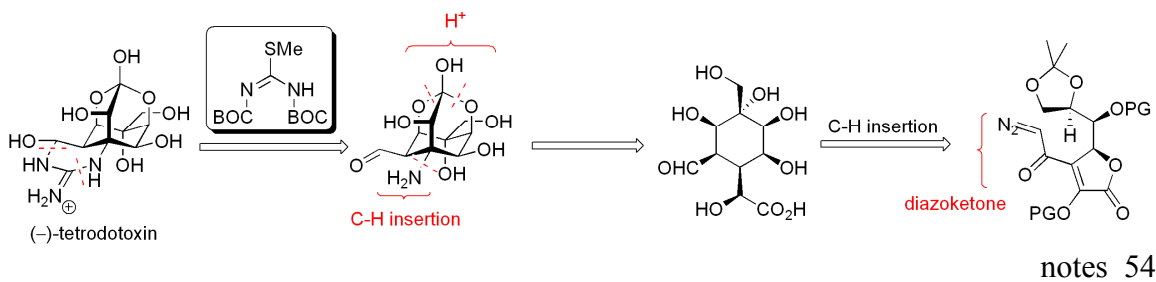


(-)-tetrodotoxin

notes_53

Also see: Kishi *J. Am. Chem. Soc.* **1972**, *94*, 9217, 9219.

Retrosynthesis:



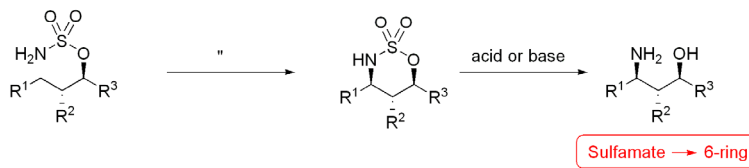
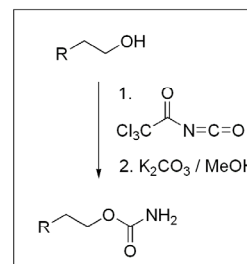
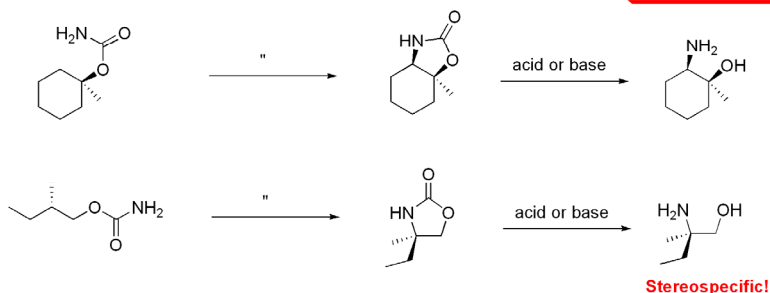
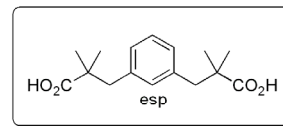
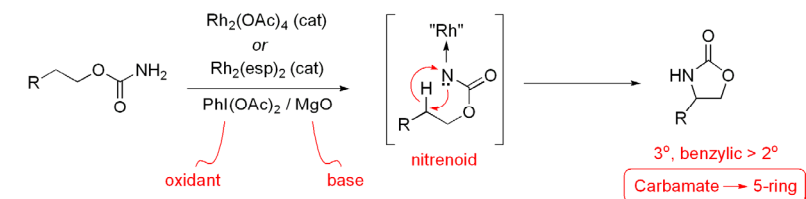
notes_54

Methodology 9.1: C-H insertion reactions

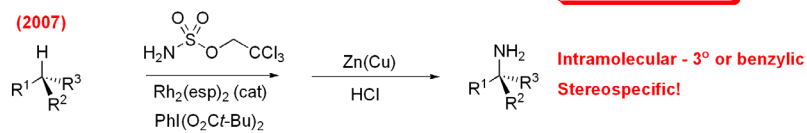
(Justin Du Bois, Stanford)

C-N Bond Formation:

(2001)

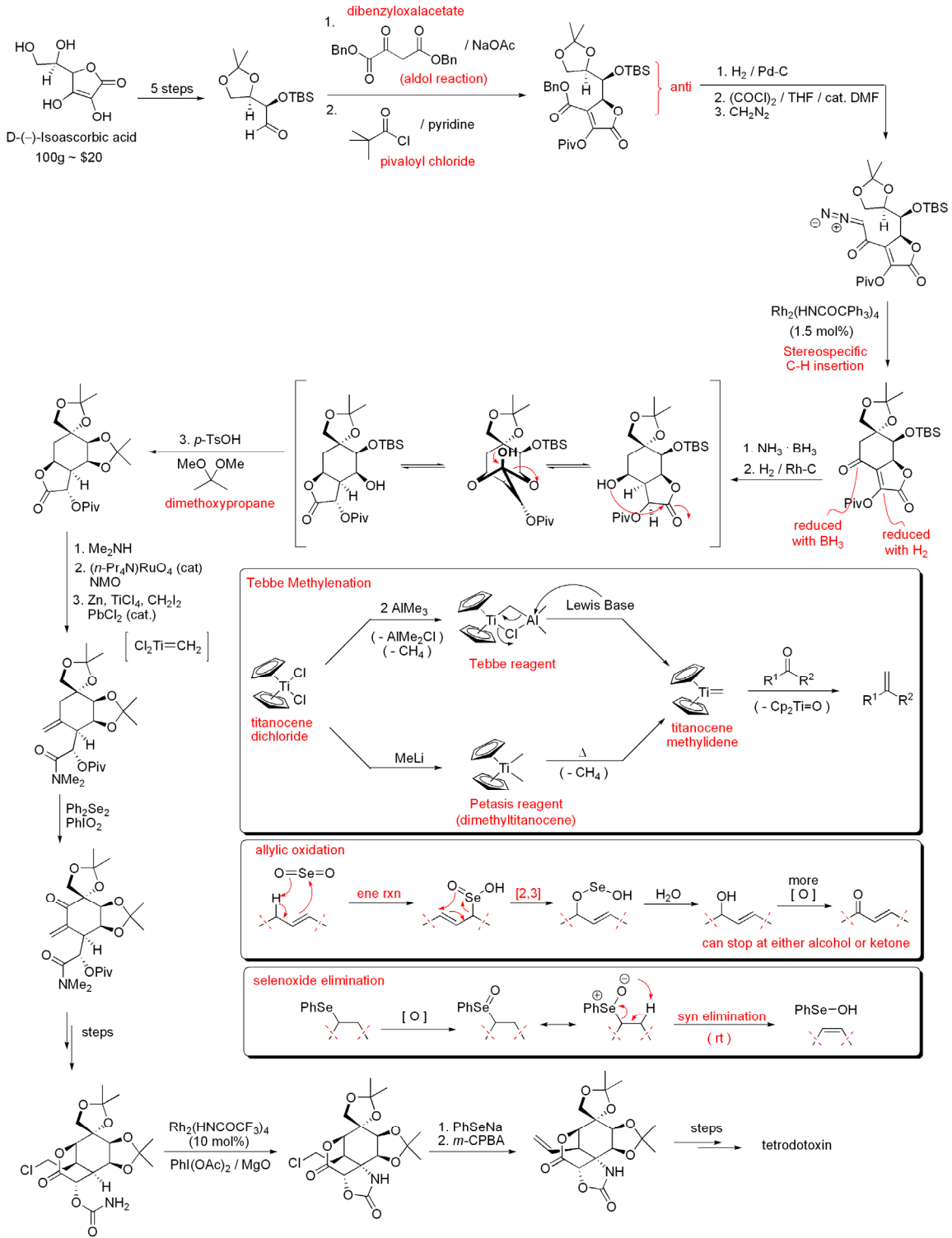


(2007)



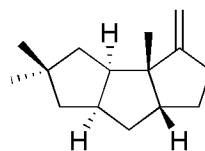
notes_55

Synthesis:



Synthesis 10: Hirstutene

Curran, 1986
Classics I, 382



hirstutene

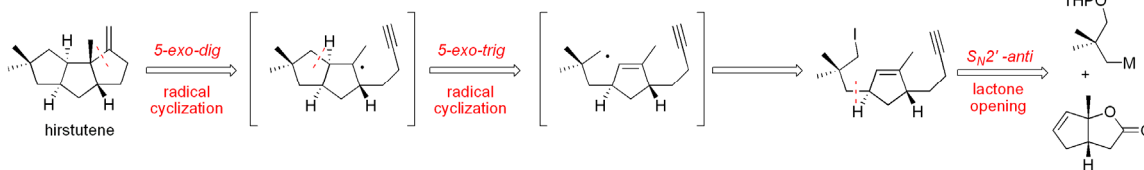
notes_57

Reactions:

- General discussion of Radical Cyclizations
- Luche reduction
- Stryker reduction
- Ireland-Claisen rearrangement
- Selenolactonization
- Radical deoxygenations & decarboxylations
 - Barton-McCombie deoxygenation
 - Tin-free variant of the Barton-McCombie
 - Barton decarboxylation
 - Diazene-mediated deoxygenation

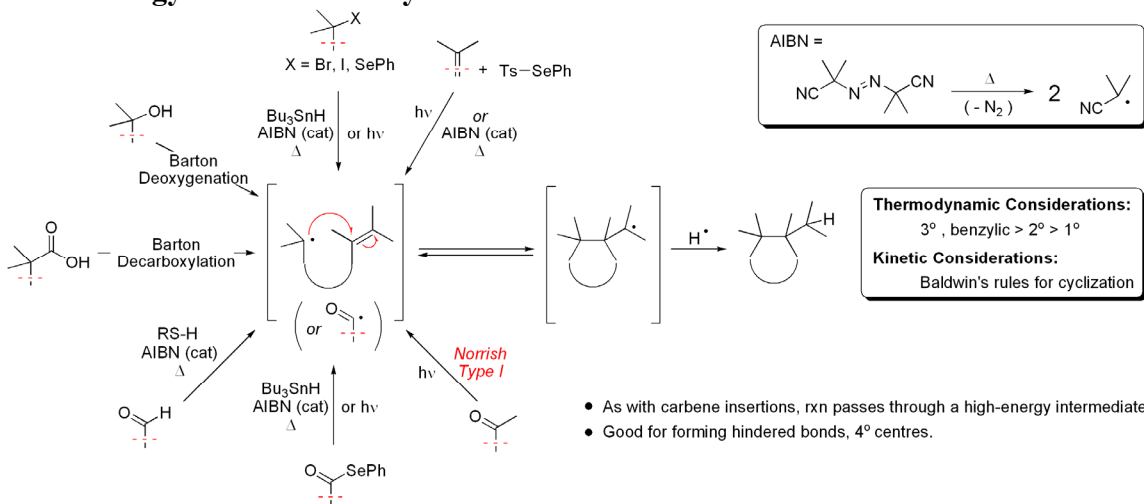
Concepts:

- Baldwin's rules for cyclization



notes_58

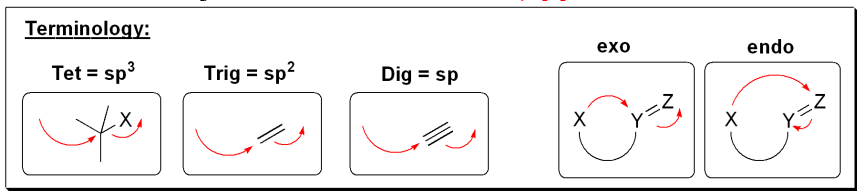
Methodology 10.1: Radical Cyclizations



notes_59

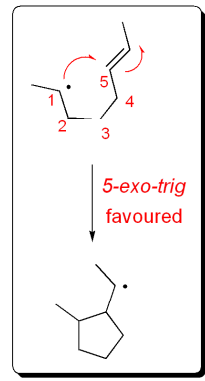
Baldwin's Rules for Cyclization

(applies to 1- and 2-electron processes)



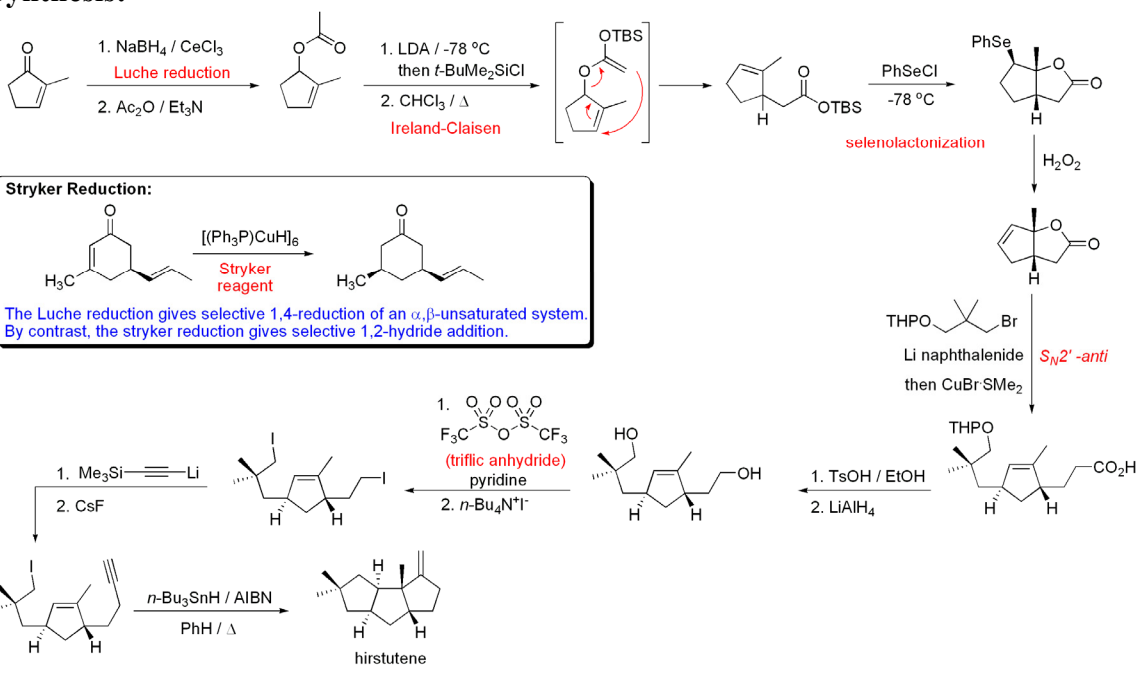
	3	4	5	6	7
Exo-Tet	✓	✓	✓	✓	✓
Endo-Tet			✗	✗	
Exo-Trig	✓	✓	✓	✓	✓
Endo-Trig	✗	✗	✗	✓	✓
Exo-Dig	✗	✗	✓	✓	✓
Endo-Dig	✓	✓	✓	✓	✓

✓ = favoured ✗ = disfavoured



notes_60

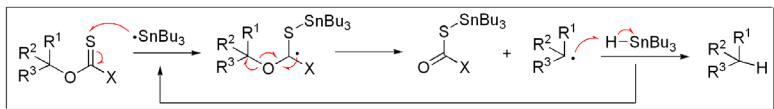
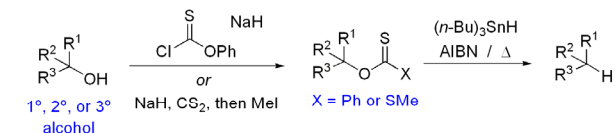
Synthesis:



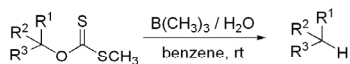
notes_61

Methodology 10.2: Radical Deoxygenations & Decarboxylations

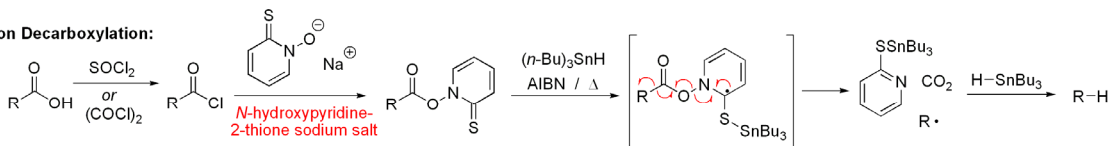
Barton-McCombie Deoxygenation:



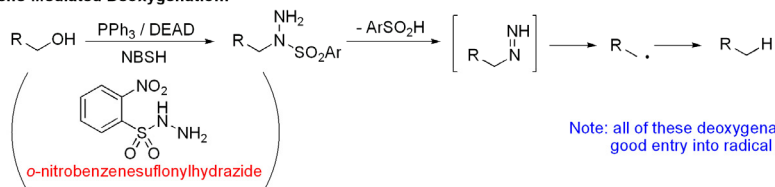
Tin-Free Variant:



Barton Decarboxylation:



Diazeno-Mediated Deoxygenation:

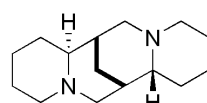


Note: all of these deoxygenation / decarboxylations also provide good entry into radical cyclization / oxygenation reactions.

Synthesis 11: *ent*-Sparteine

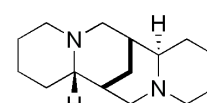
Aubé, 2002

Org. Lett. **2002**, *4*, 2577.



(-)-sparteine

useful ligand for
asymmetric catalysis



(+)-sparteine

hard to get

(\$158 / 100g
as the sulfate pentahydrate)

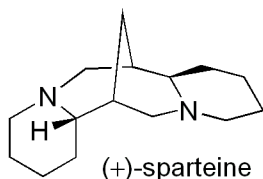
Reactions:

· General discussion of ring expansions and contractions:

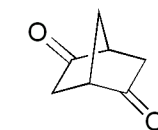
- Beckmann rearrangement
- Favorskii rearrangement
- Tiffeneau-Demjanov rearrangement
- Schmidt reaction
- Finkelstein reaction
- Mitsunobu reaction

notes_70

Retrosynthesis:



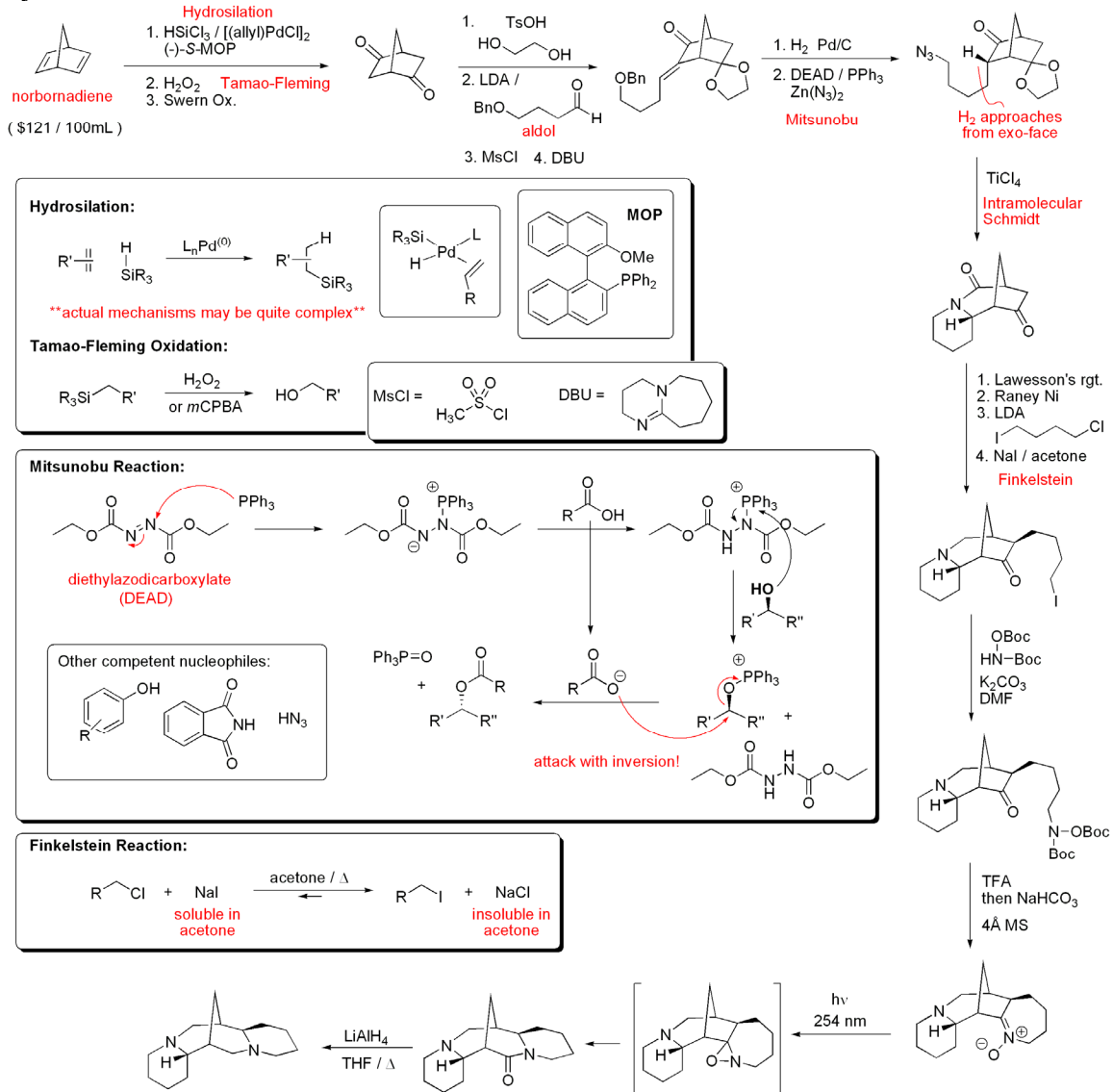
(+)-sparteine



(C2-symmetric)

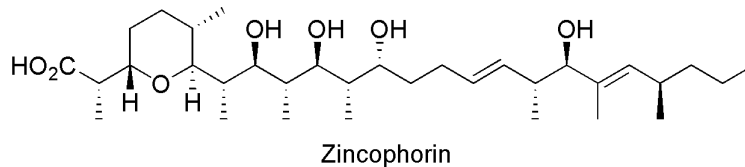
notes_71

Synthesis:



Synthesis 12: Zincophorin

Meyer and Cossy, 2004
J. Org. Chem. **2004**, *69*, 4626.

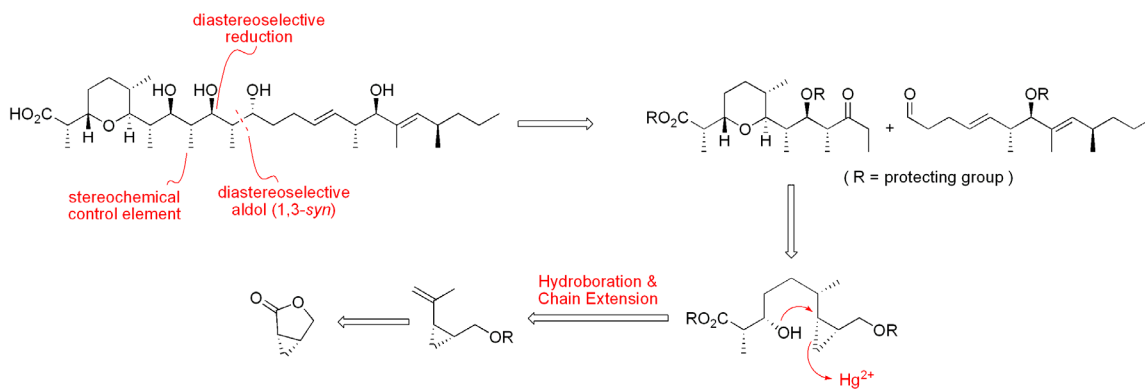


Reactions:

notes_74

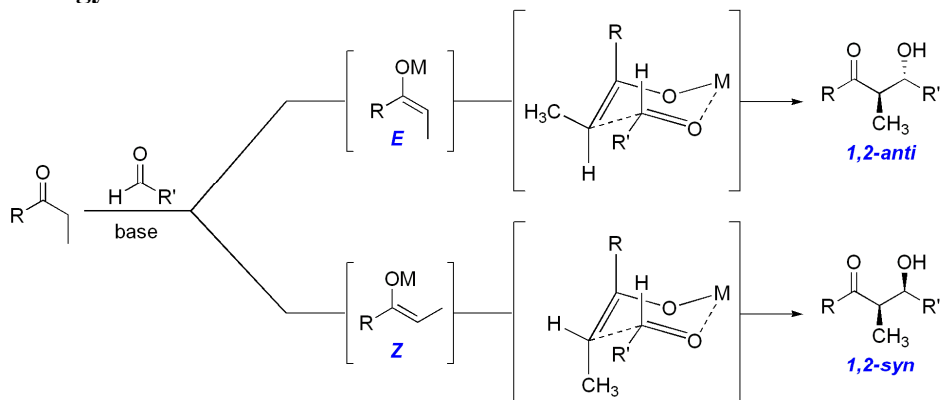
- Diastereoselective aldol reactions (Review)
- General discussion of hydroborations
- General discussion of cyclopropanation strategies

Retrosynthesis:

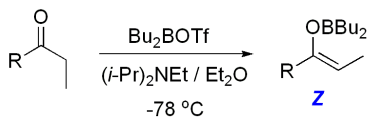
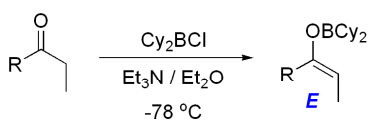


notes_75

Methodology 12.1: Diastereoselective Aldol Reactions

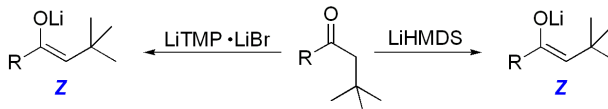
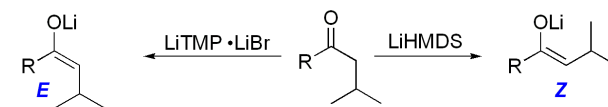


Boron Enolates: control of enolate geometry



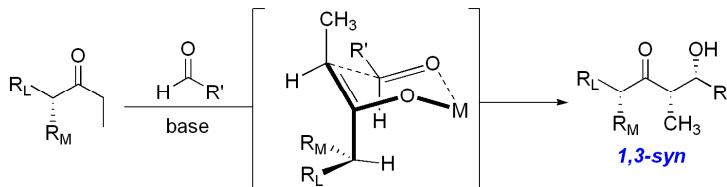
B-OTf bond is more dissociated than B-Cl

Lithium Enolates: also controllable, but harder to predict



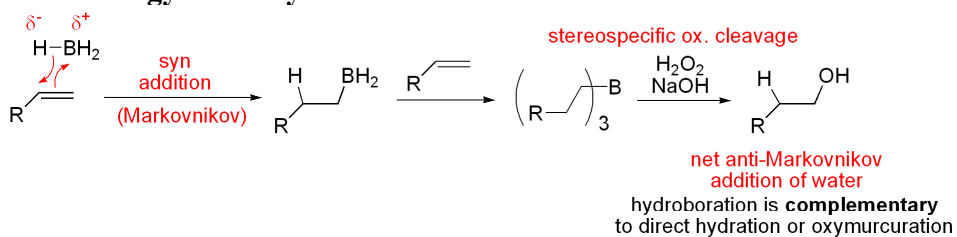
Boron enolates give "tighter" transition states anyway

With an α -Stereocentre:

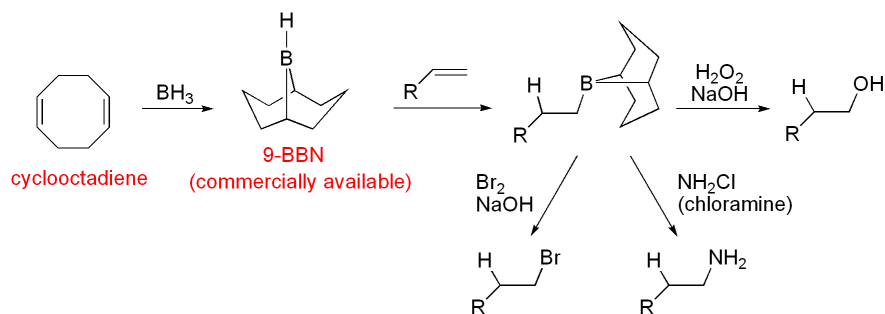


Same outcome for *E*-enolates (for a slightly different reason)
Though 1,3-syn addition is the "typical" result, tuning of conditions can afford 1,3-anti

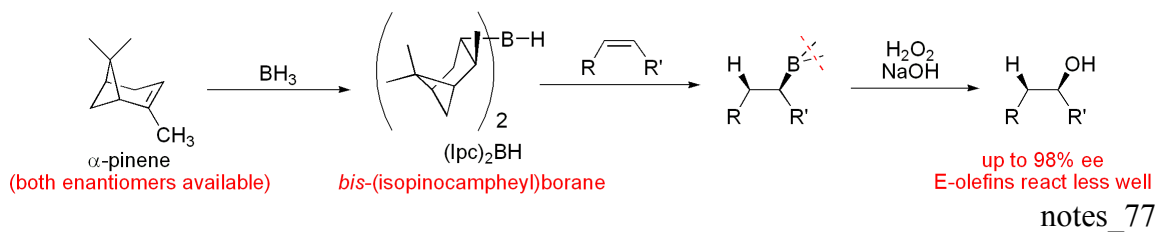
Methodology 12.2: Hydroborations



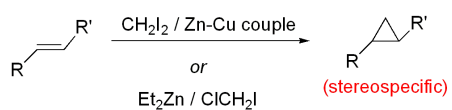
More hindered boranes are more selective



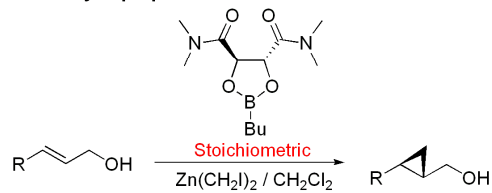
Chiral boranes allow control of enantioselectivity as well as diastereoselectivity and regioselectivity!



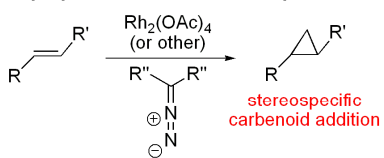
Simmons-Smith Reaction



Charett Cyclopropanation

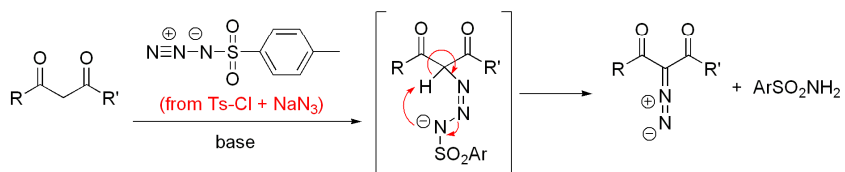


Cyclopropanation with Diazo Compounds

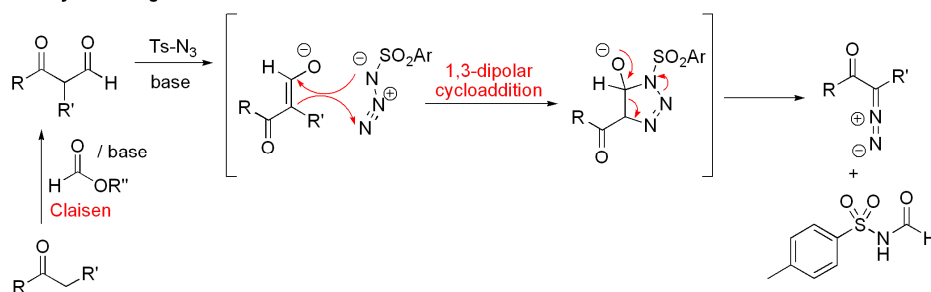


Diazo ketones are available by hydrazone oxidation, diazomethane addition, or Regitz reaction.

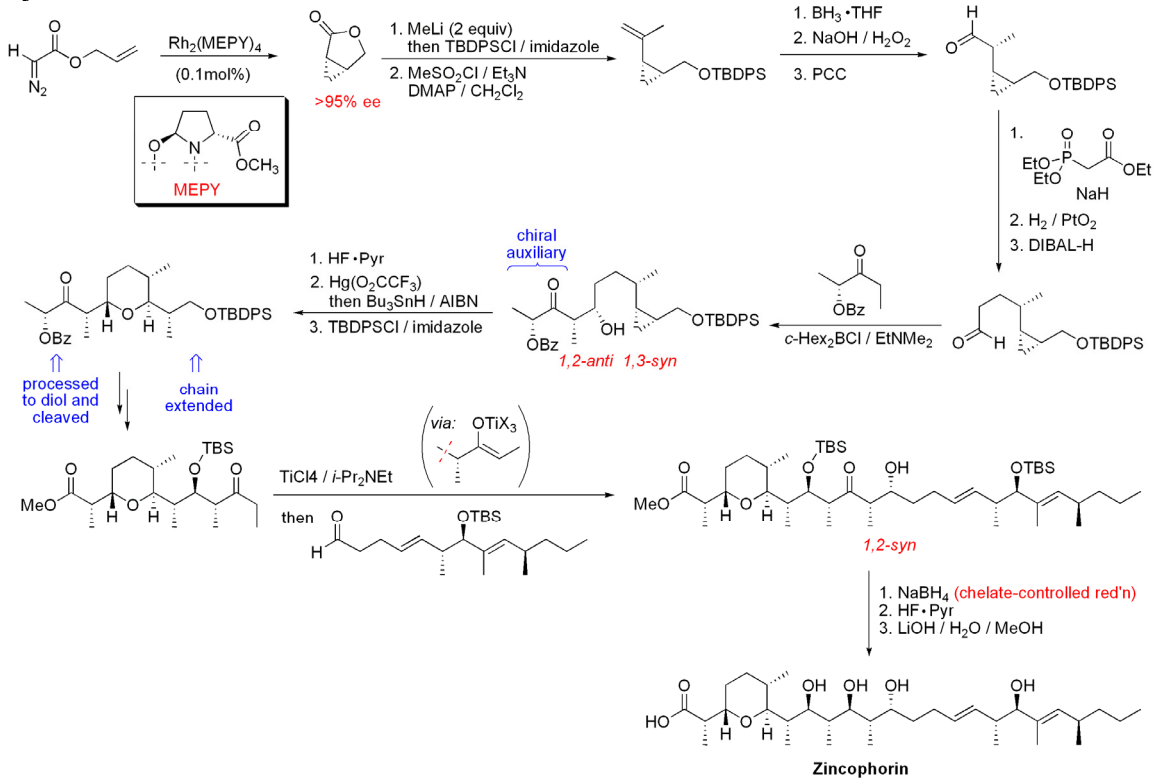
Regitz Diazo Transfer



Deformylative Regitz Diazo Transfer



Synthesis:



Synthesis 13: Saframycin A

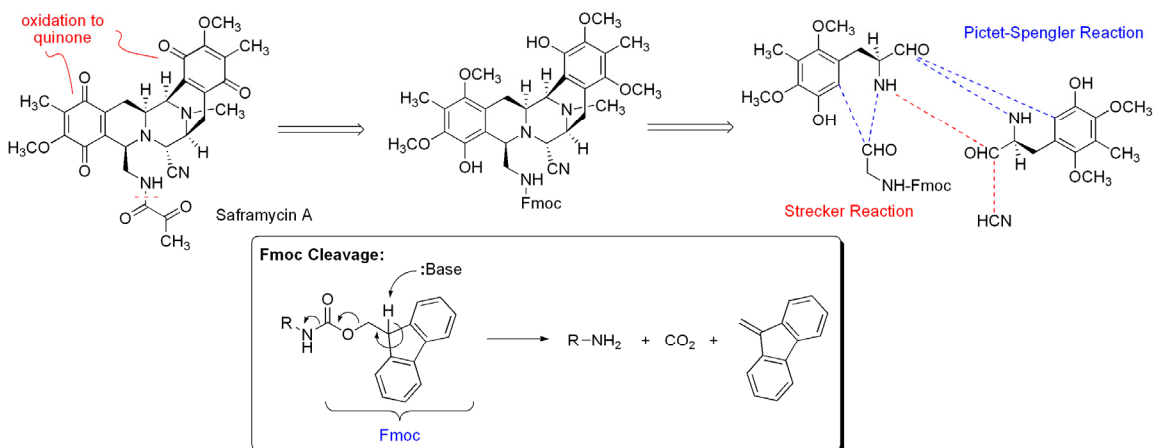
Myers, 1999

J. Am. Chem. Soc. **1999**, *121*, 10828.

Reactions:

- General discussion of auxiliary-controlled additions:
 - Evans' aldol
 - Carreira aldol
 - Pseudoephedrine glycinamide alkylation
- Pictet-Spengler reaction
- Strecker reaction
- Reductive amination

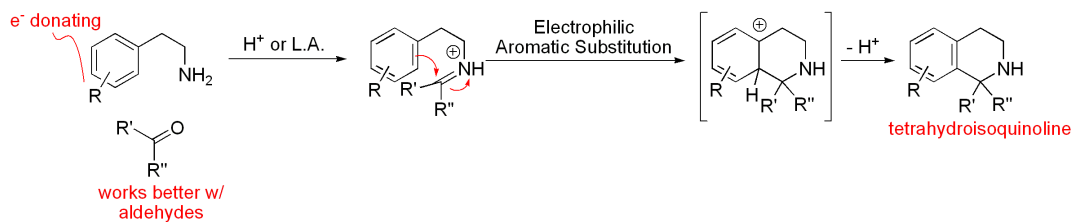
Retrosynthesis:



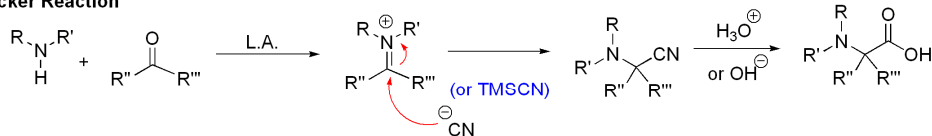
notes_80

Methodology 13.1: Pictet-Spengler and Strecker Aminations Oxidation to Quinones

Pictet-Spengler Reaction

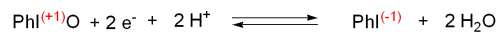
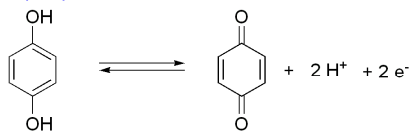


Strecker Reaction

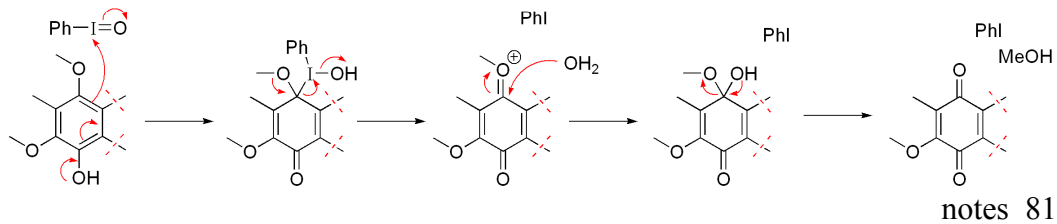


Oxidation to Quinones

The electrochemist's perspective:

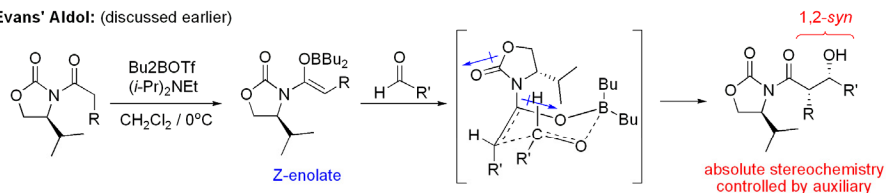


The organic chemist's perspective:



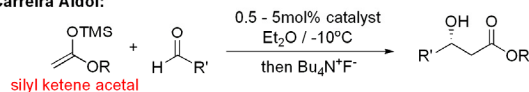
Methodology 13.2 Asymmetric Acylations and Alkylations

Evans' Aldol: (discussed earlier)

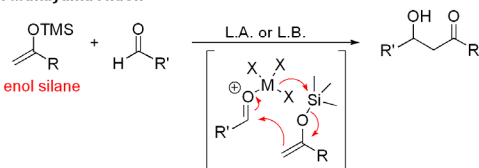


More Modern Asymmetric Aldol Reactions:

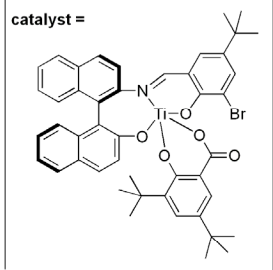
Carreira Aldol:



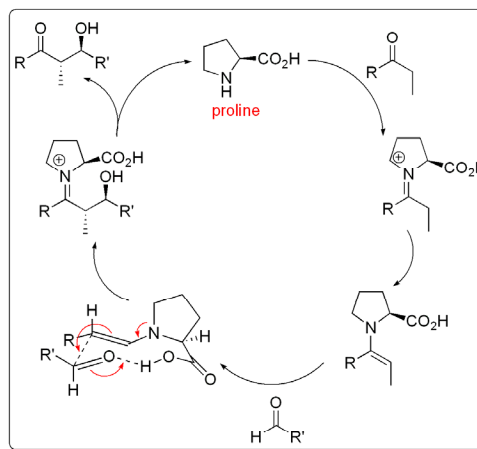
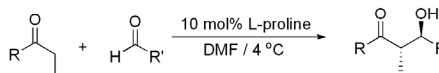
Recall: Mukayama Aldol:



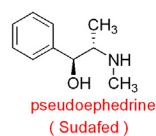
catalyst =



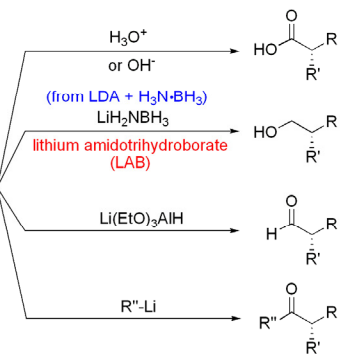
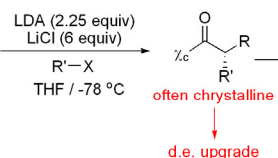
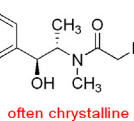
Organocatalytic Aldol:



Pseudoephedrine-Controlled Alkylation:

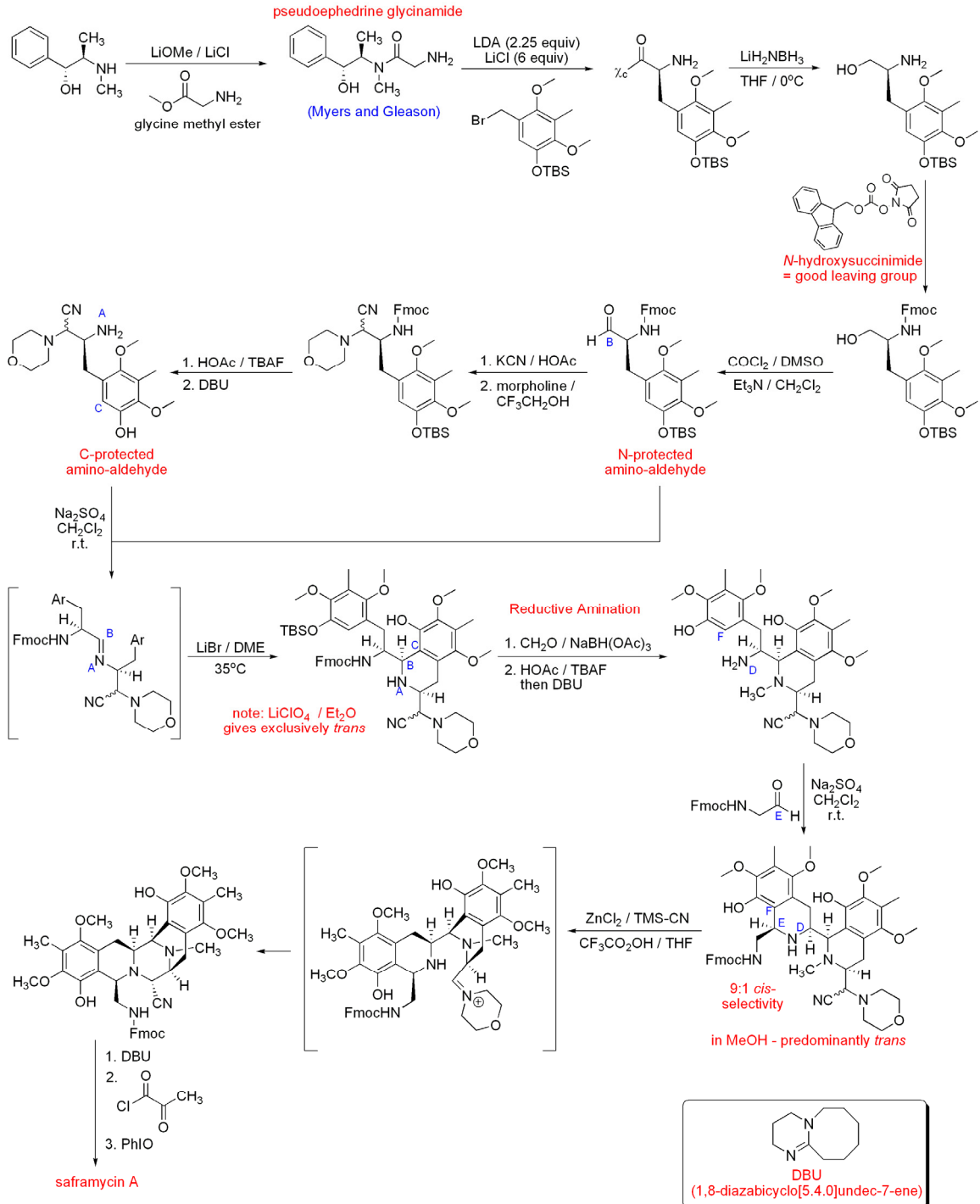


-diastereomer of ephedrine
-both enantiomers are available, inexpensive



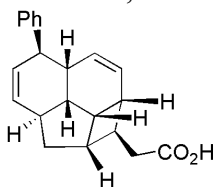
notes_82

Synthesis:



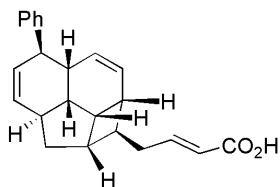
Synthesis 14: Endriandric Acids

Nicolaou, 1982
Classics I, 264.

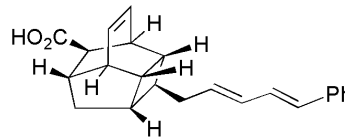


Endriandric Acid A

· isolated as racemates



Endriandric Acid B



Endriandric Acid C

notes_74

Reactions:

- Electrocyclic Ring-Closing reaction

Concepts:

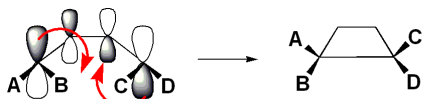
- Woodward-Hoffmann rules

The Rules:

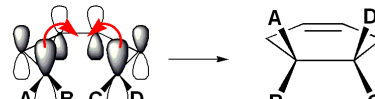
(Nobel 1981: Hoffmann & Fukui)

“In an open chain system with $4n$ electrons, orbital symmetry requires *conrotatory* rotation during ring closure / opening.”

“In an open chain system with $4n+2$ electrons, orbital symmetry requires *disrotatory* rotation during ring closure / opening.”



4n electrons : *conrotatory* rotation

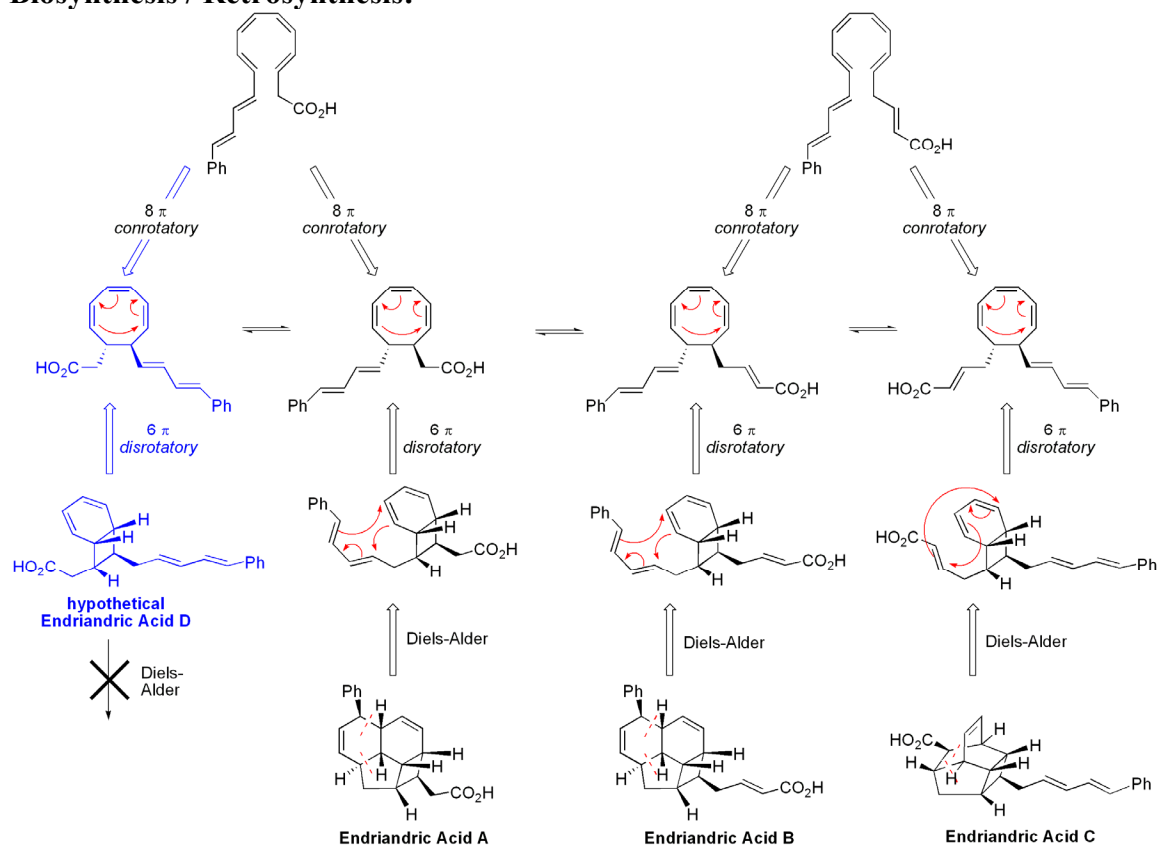


4n+2 electrons : *disrotatory* rotation

“In an photochemical reaction, the effects are reversed.”

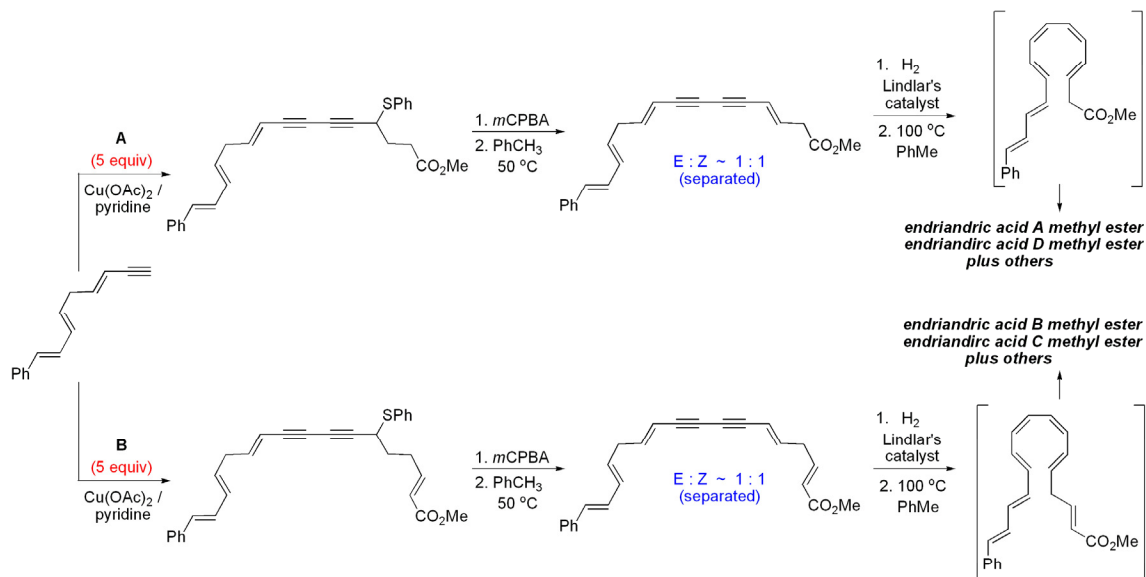
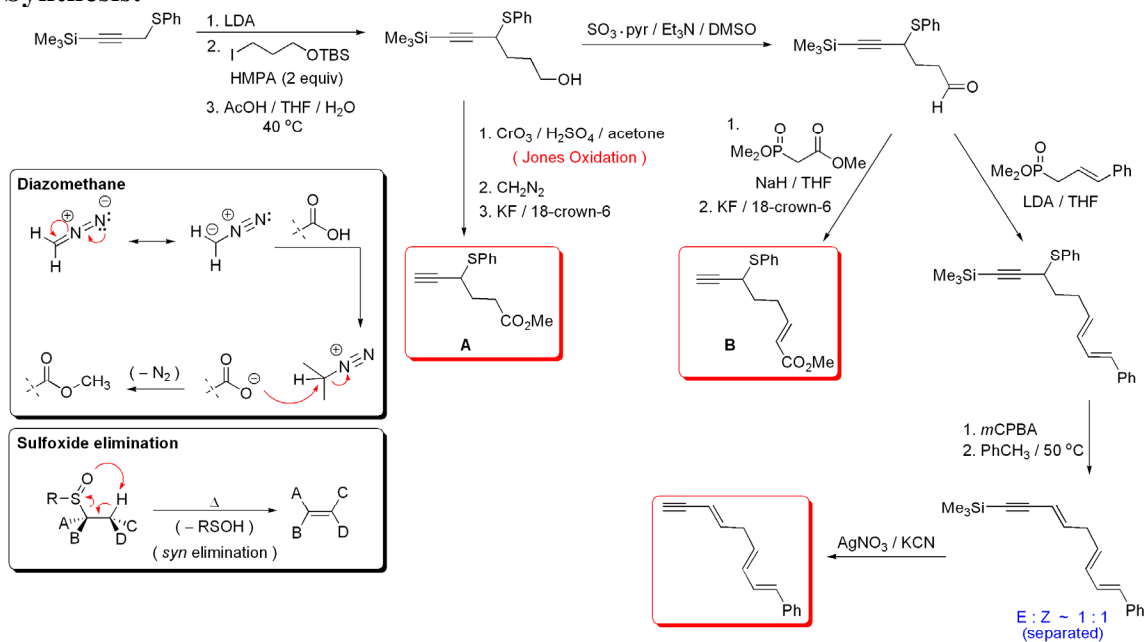
notes_87

Biosynthesis / Retrosynthesis:



notes_86

Synthesis:



The natural product endriandric acid D was eventually isolated in 1982, shortly after it was prepared through synthesis.

see: Aust. J. Chem. 1982, 35, 2247,
Aust. J. Chem. 1983, 36, 627.