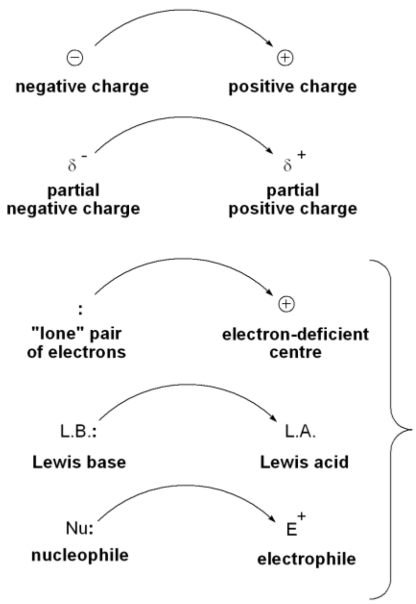
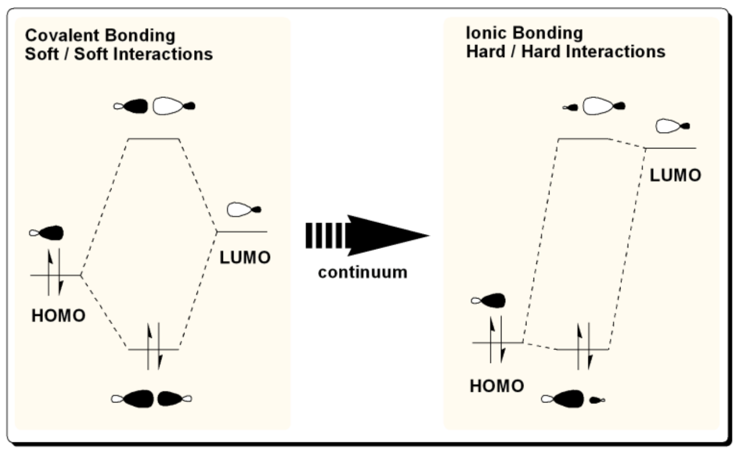
Chemistry 432 – Lecture Notes **Updated: Spring 2016**

Course Organization: Things You Need to Know

1. Named Reactions and Reagents
2. Vocabulary
3. Concepts
4. HOW TO DO SYNTHESIS

Nucleophiles and Electrophiles: The Basis of Organic Chemistry





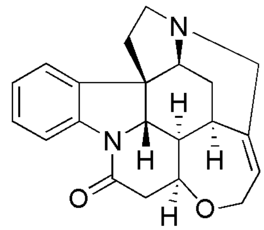
HOMO = highest occupied molecular orbital
LUMO = lowest unuccupied molecular orbital

Synthesis 1: Strychnine

Woodward, 1954
- Nobel 1965

Classics I, 21

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



strychnine

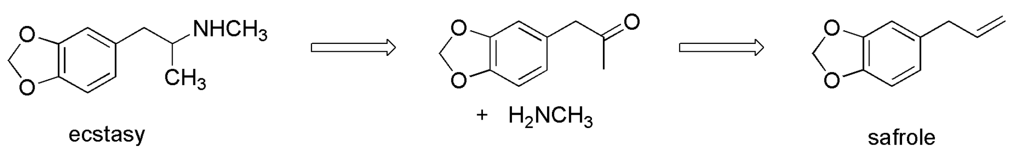
Concepts:
- Retrosynthesis
- Substructure Recognition

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:

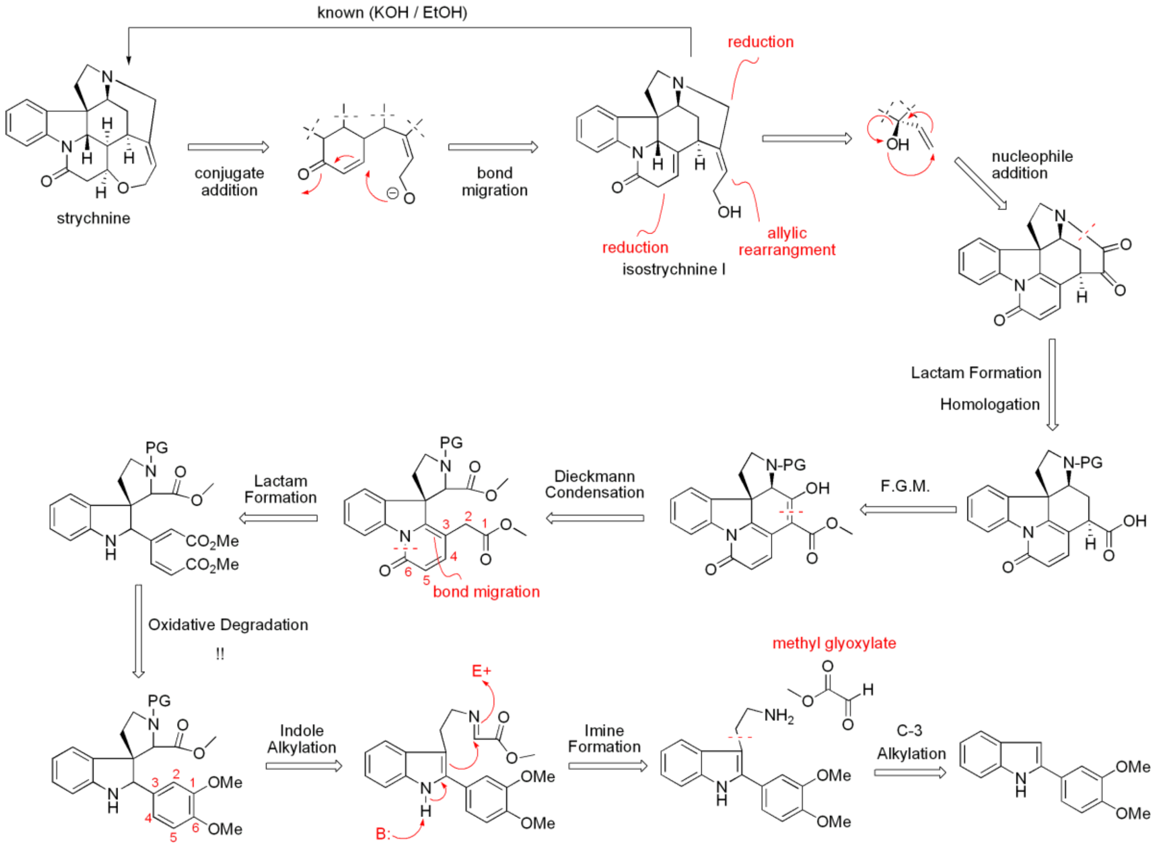
Retrosynthesis - A technique for transforming the structure of a synthetic target into a sequence of simpler structures, along a pathway which ultimately leads to known or commercially available starting materials.



notes_04

- E.J. Corey, Nobel 1990

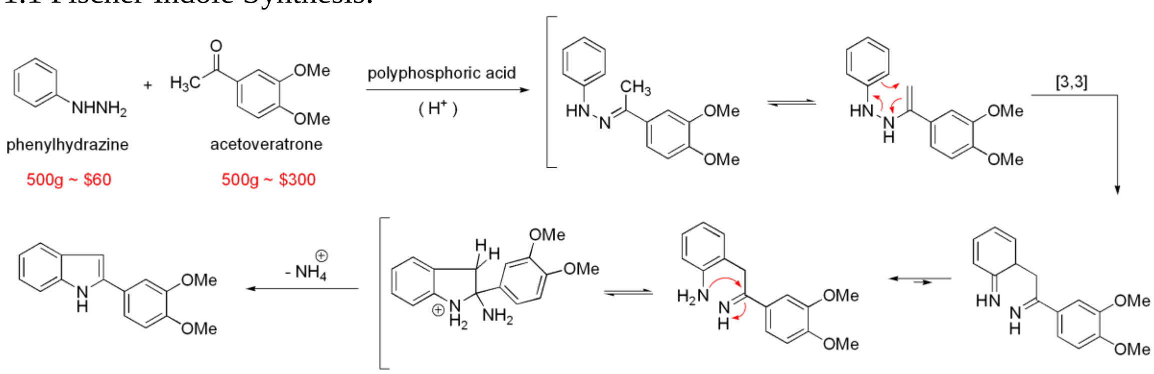
Retrosynthesis:



notes_03

Methodology:

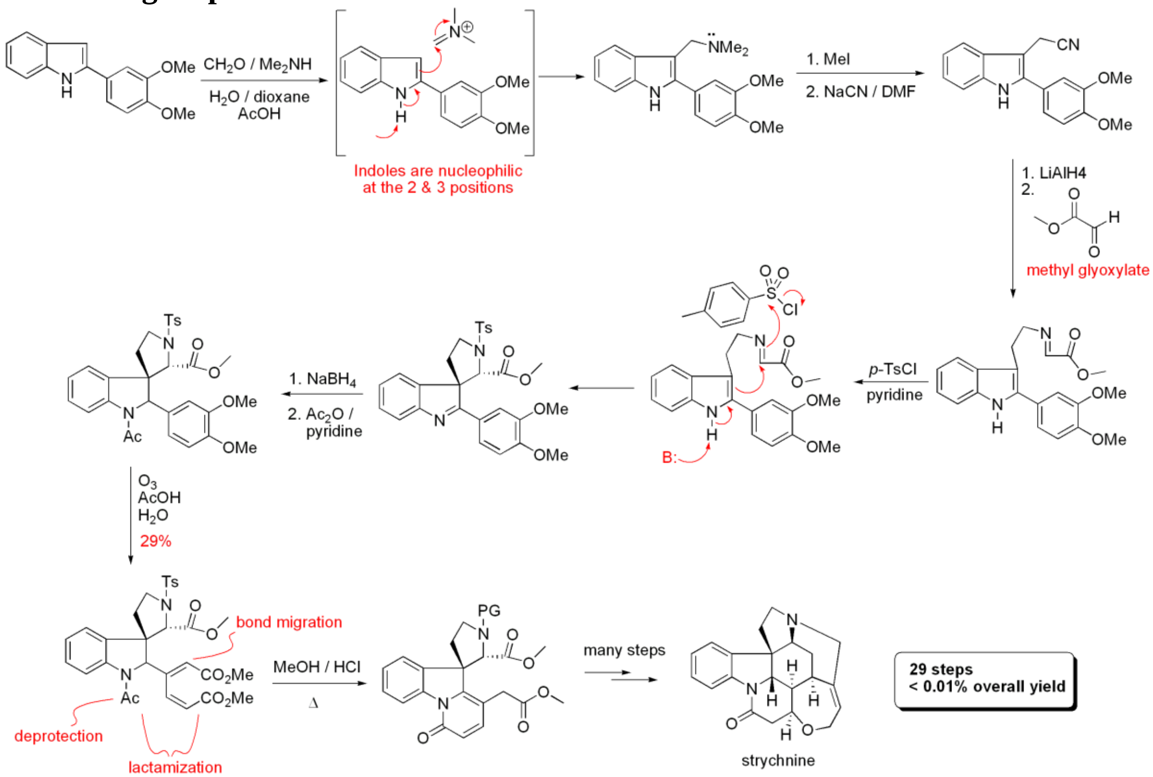
1.1 Fischer Indole Synthesis:



notes_05

- most commonly done with $ZnCl_2$

Continuing Steps:



notes_06

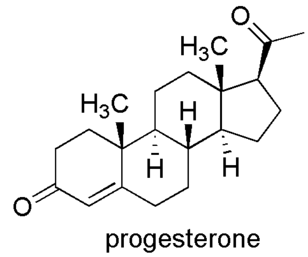
- How does the ozonolysis work here?
- Let’s come back to that after the next section.

Other Syntheses of Strychnine:

Magnus, 1992 – *J.Am.Chem.Soc*. **1992**, 4403. - 38 years from 1st to 2nd synthesis!
Stork, 1992 – lecture (Iscia 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.
Andrade, 2010 – *J.Org.Chem.* **2010**, 3529.
Vanderwal, 2010 – ACS abstratcts
MacMillan, 2010 – ACS abstracts
Reissig, 2010 – *Angew. Chem. Int. Ed.* **2010**, 8021.
… and many others since! …

Synthesis 2: Progesterone

Marker, 1943



Reactions:

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

Concepts:

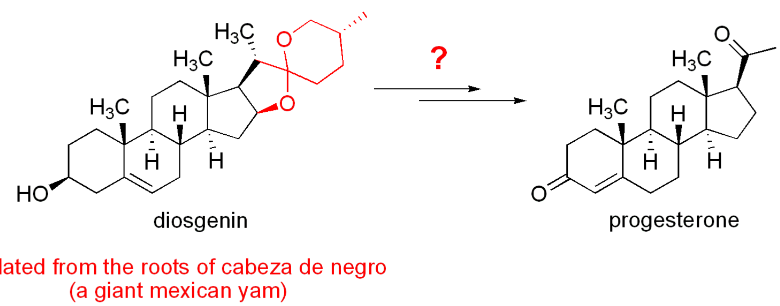
- Semisynthesis

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.

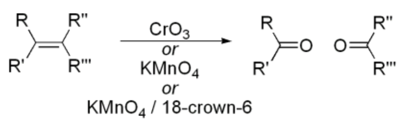


notes_10

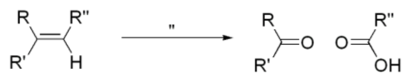
Methodology:

2.1 Oxidative Degradations:

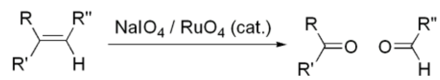
Handout #1: Oxidation



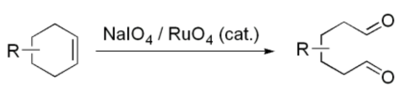
More modern conditions: HIO_4 / MnO_4^- (cat.) = Lemieux-Von Rudloff
$NaIO_4$ / RuO_4 (cat.)



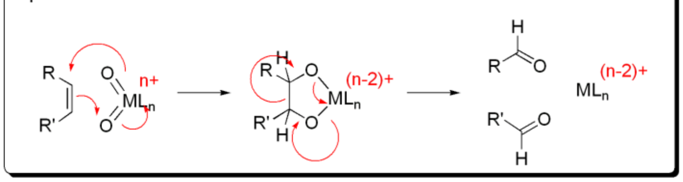
These allow you to stop at the aldehyde:



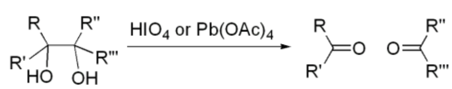
Cyclic precursors can be particularly useful:



A plausible mechanism:



Similarly...

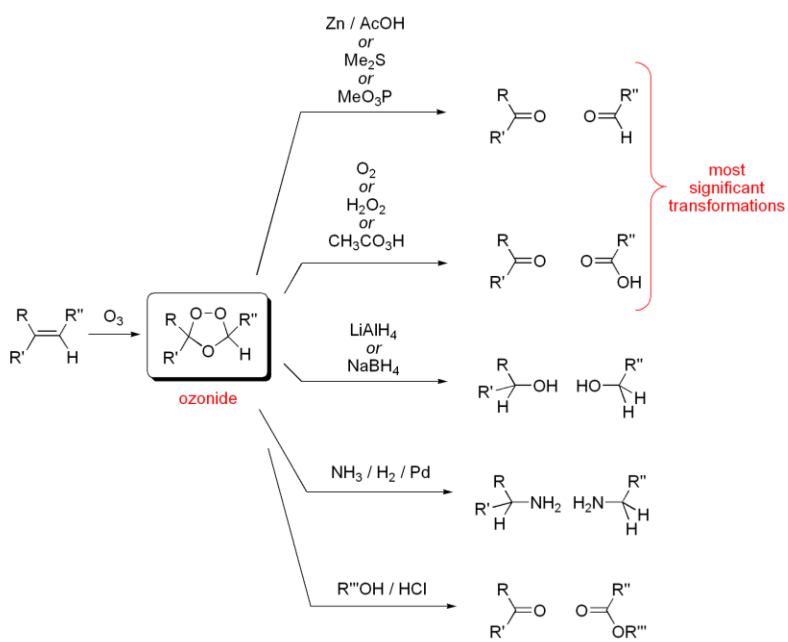


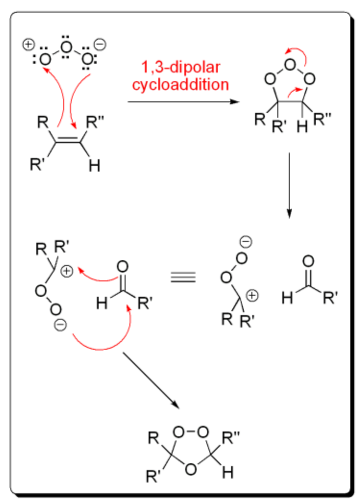
The above reactions are equivalent to a 'one pot' dihydroxylation / cleavage.

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

notes_12

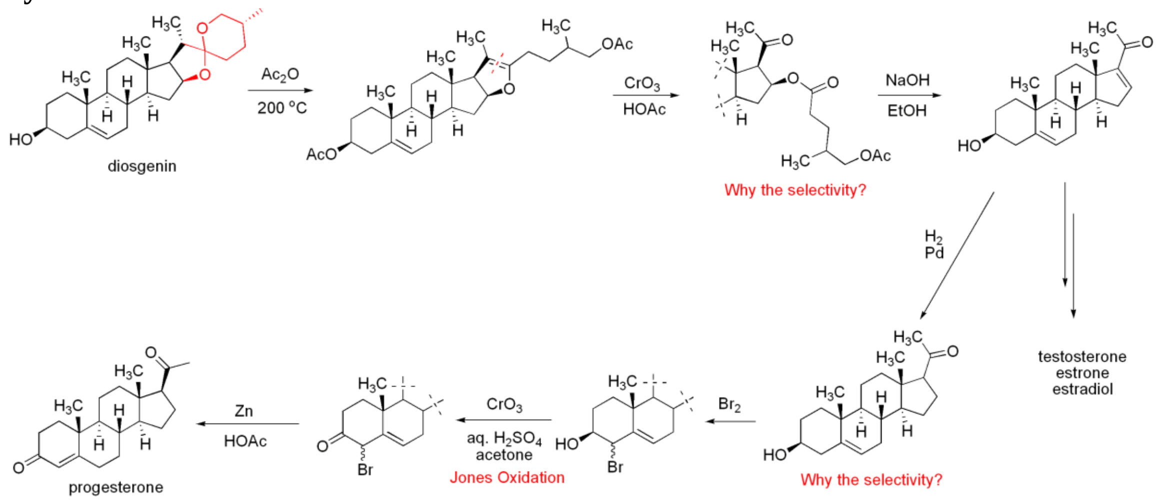
2.2 Ozonolysis:

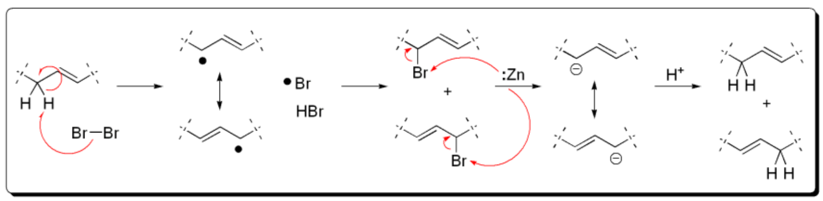




notes_13

Synthesis:





notes_11

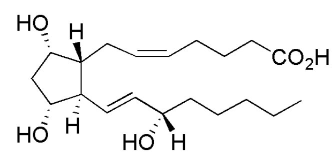
Synthesis 3: Prostaglandin E_2

Corey, 1969 and onward
- Nobel 1990

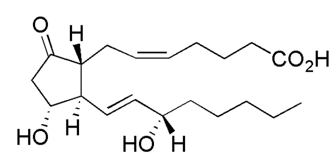
Classics I, 65

Reactions:

- <u>General discussion of olefin-forming reactions:</u>
  - Wittig reaction
  - Horner-Wadsworth Emmons reaction
  - Still-Gennari olefination
  - Julia olefination
  - Corey-Winter olefination
  - Peterson olefination
  - Barton-Kellog extrusion reaction
- <u>Asymmetric Diels-Alder reaction</u>
- Baeyer-Villiger oxidation
- <u>CBS reduction</u>
- Iodolactonization



$PGF_{2\alpha}$



PGE_2

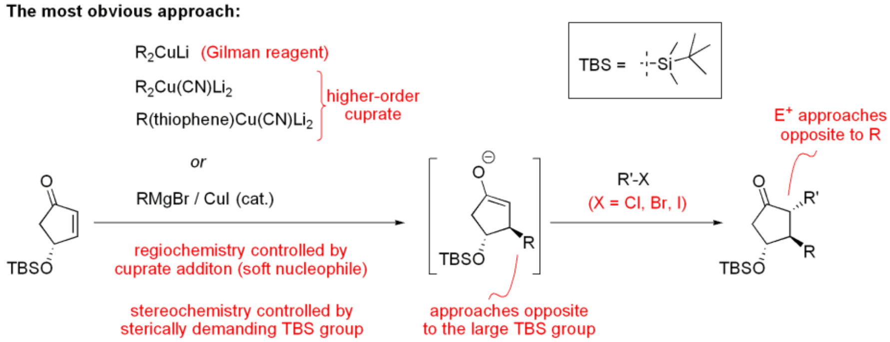
notes_14

Properties:

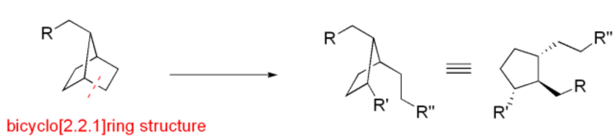
- The prostaglandins are a large family of lipophilic C-20 hormones.
- Isolated in the 1930's, structures in 1960's.
- Originate from action of COX1 and COX2 on arachidonic acid.
  (aspirin targets both enzymes, vioxx selectively targets COX2)
- Various prostaglandins may control:
  cell growth
  hormone regulation
  inflammation
  sensitivity to pain
  constriction / dilation of muscle cells
- PGE_2 and PGF_2 are used to induce childbirth or abortion

Synthetic Strategies:

The most obvious approach:

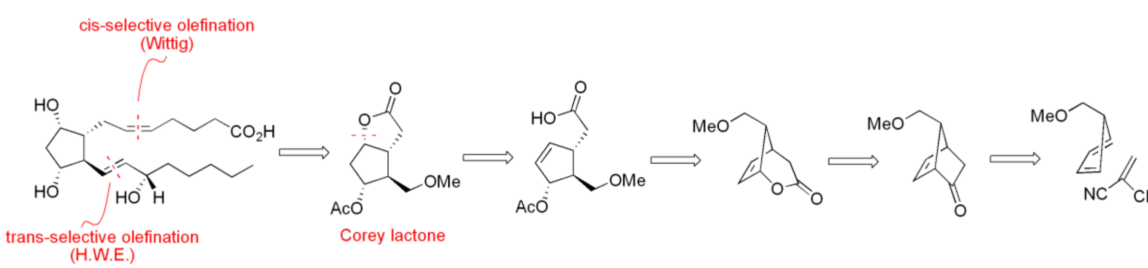


Corey's approach:



notes_15

Retrosynthesis:

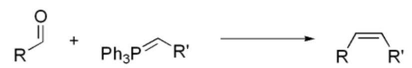


notes_16

Methodology:

3.1 Olefination Reactions:

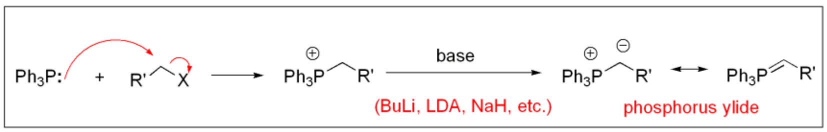
Wittig olefination: (George Wittig; Nobel 1979)



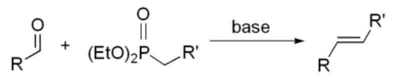
when R' is alkyl, typically gives the Z-olefin
stabilized ylides typically give the E-olefin
} tune by additon of salts or solvent

- but can bias to Z-selectivity in acid-free MeOH "Kishi footnote" *JACS* **1982**, 1109.

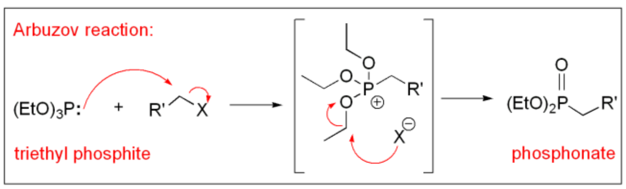
fast with aldehydes, slower with ketones (esp. hindered ketones)



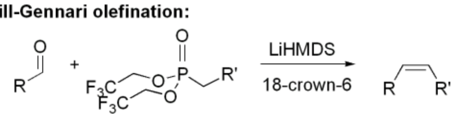
Horner-Wadsworth-Emmons olefination:



typically gives the E-olefin



Still-Gennari olefination:

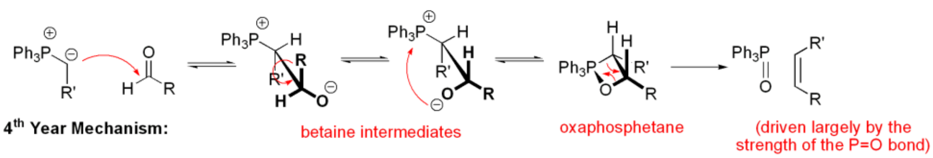


gives Z olefins even with electron-withdrawing R'

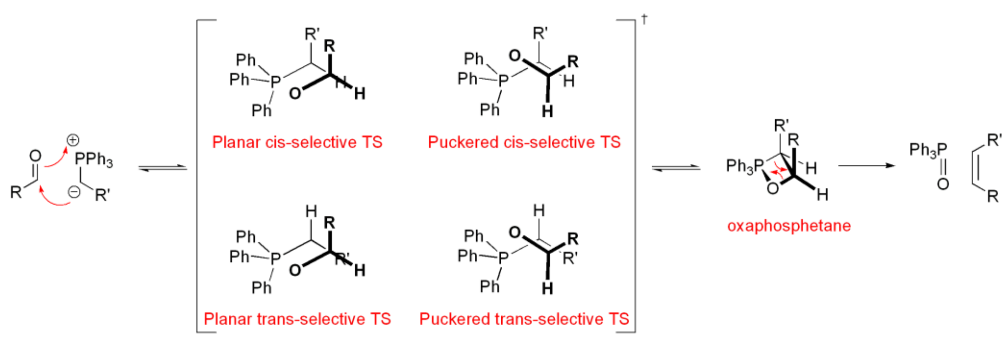
notes_17

Origin of Z-selectivity in Wittig reactions :

The 3rd Year Mechanism:



The 4th Year Mechanism:

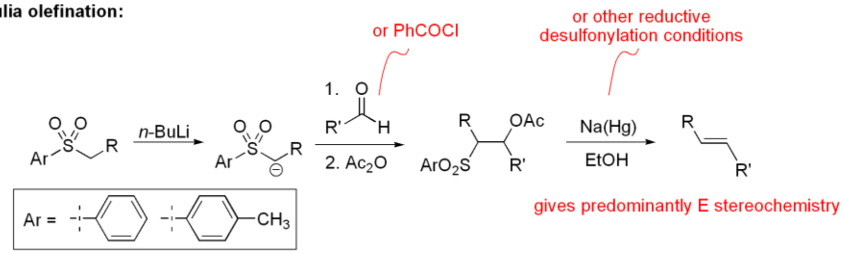


A concerted - but asynchronous - cycloaddition

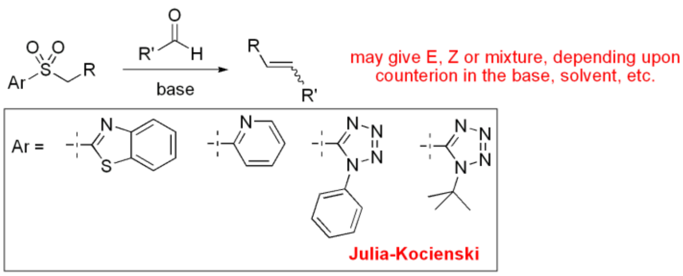
notes_18

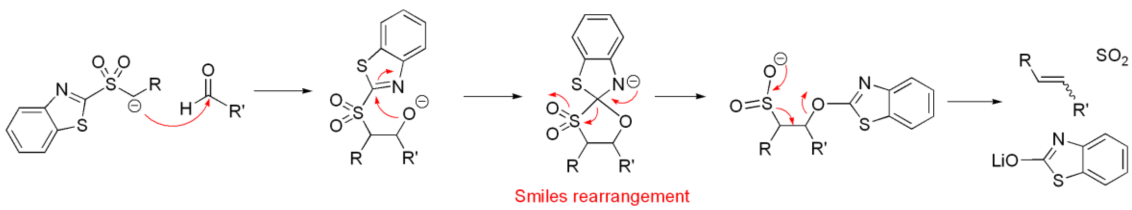
Other notable ways to make olefins:

Julia olefination:



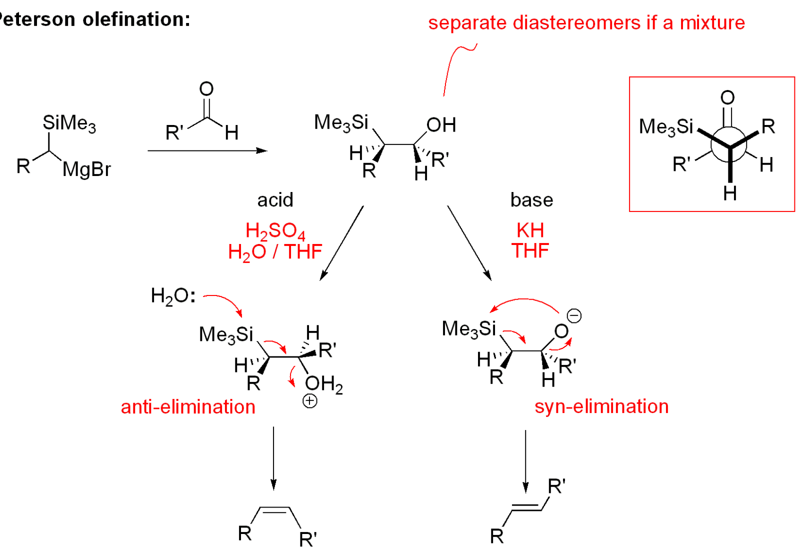
Heteroaryl variants for '1-pot' coupling:





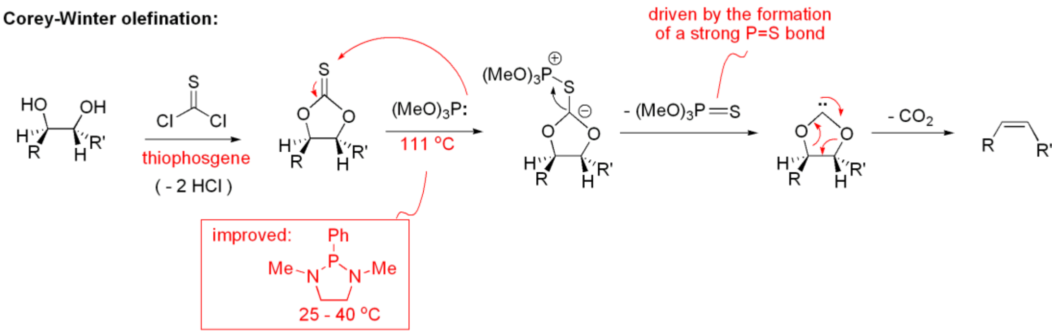
notes_20

Peterson olefination:

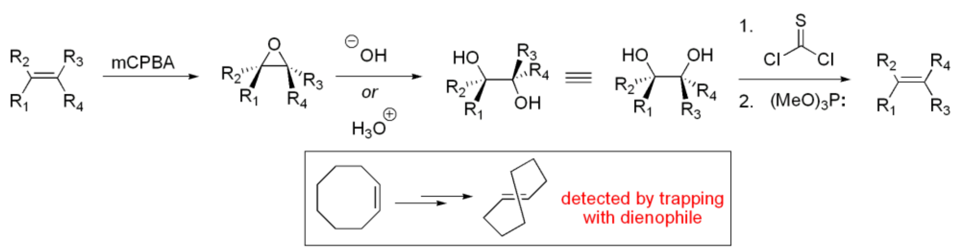


notes_20

Corey-Winter olefination:



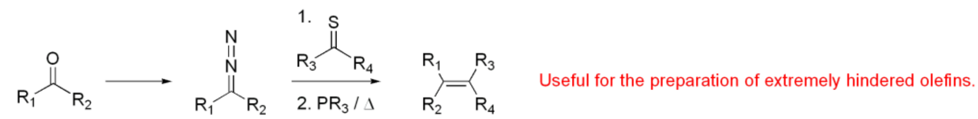
A neat application:

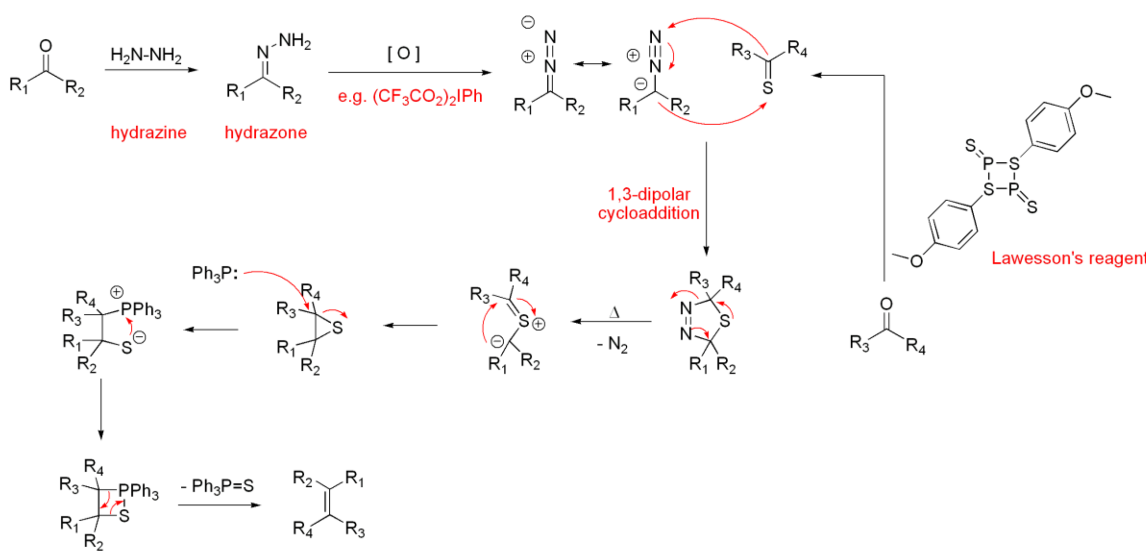


notes_21

Barton-Kellog Extrusion Reaction:

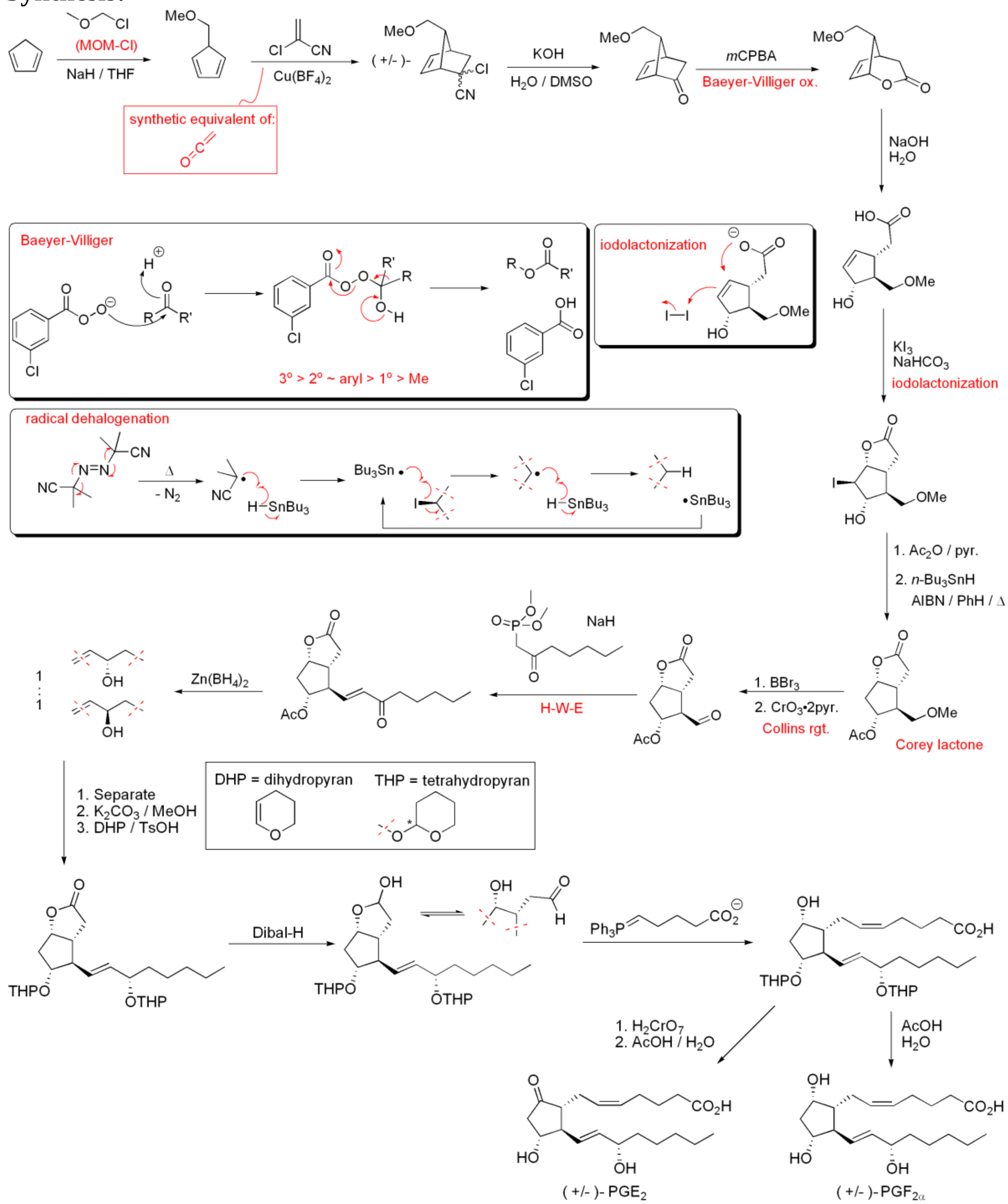
(Derek Barton Nobel 1969)





notes_22

Synthesis:



notes_23 & notes_24

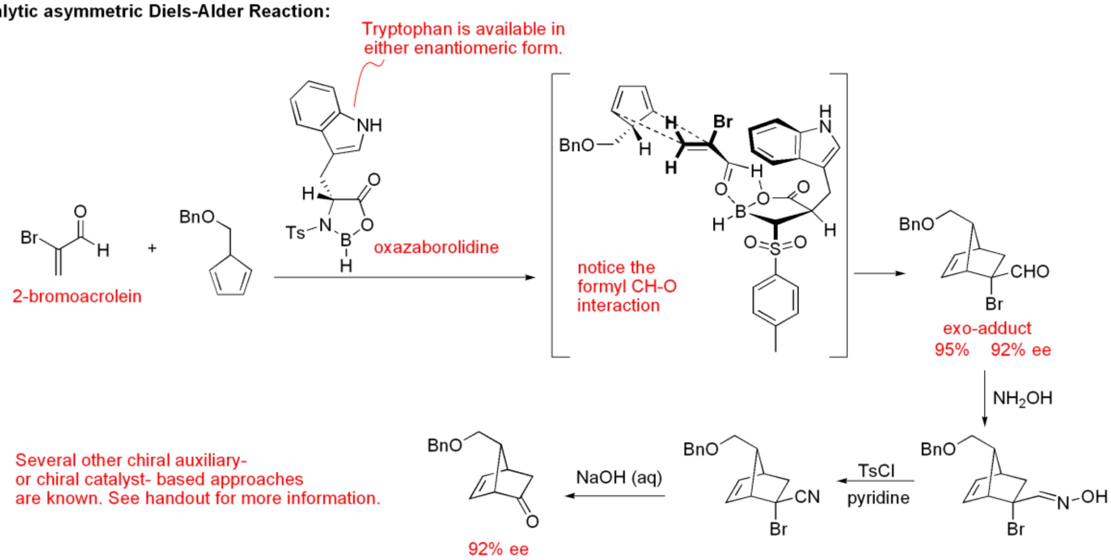
Problems with the synthesis:

- racemic
- $Zn(BH_3)_4$ reaction

Methodology 3.2:

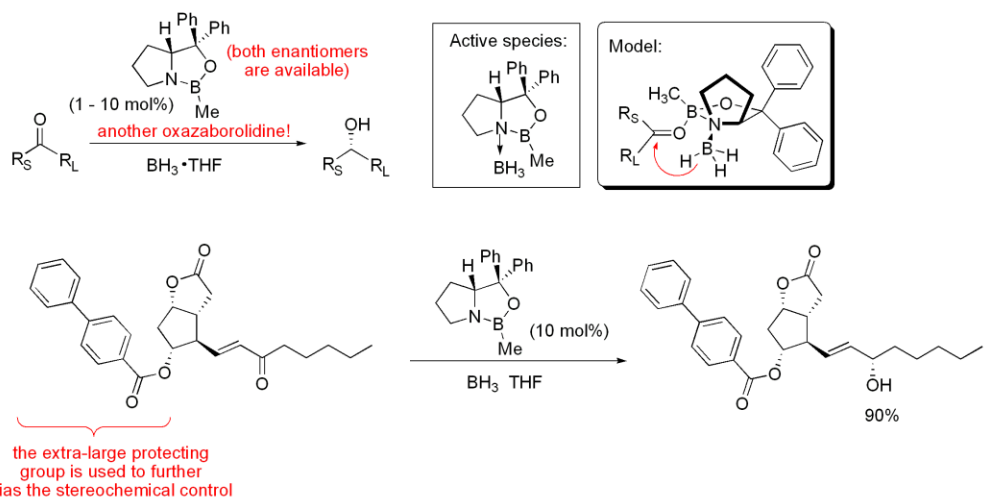
- Catalytic, asymmetric Diels-Alder reaction
- CBS reduction

Catalytic asymmetric Diels-Alder Reaction:



notes_25

Corey-Bakshi-Shibata (CBS) reduction:



notes_26

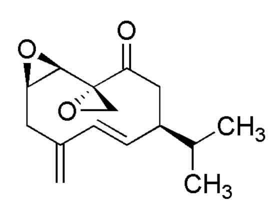
Synthesis 4: Periplanone B

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

Classics, I, 211

Reactions:

- · Anionic oxy-Cope
- · Rubottom oxidation
- · Selective epoxidations



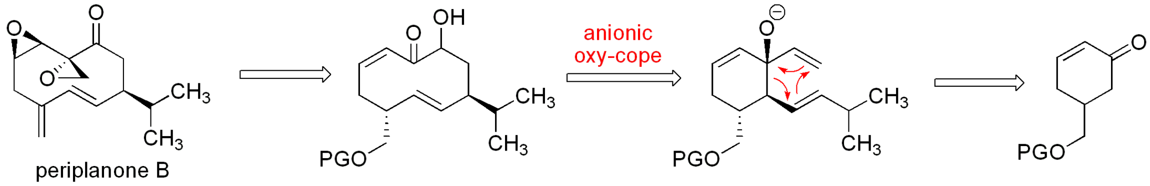
periplanone B

Concepts:

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

notes_27

Retrosynthesis:

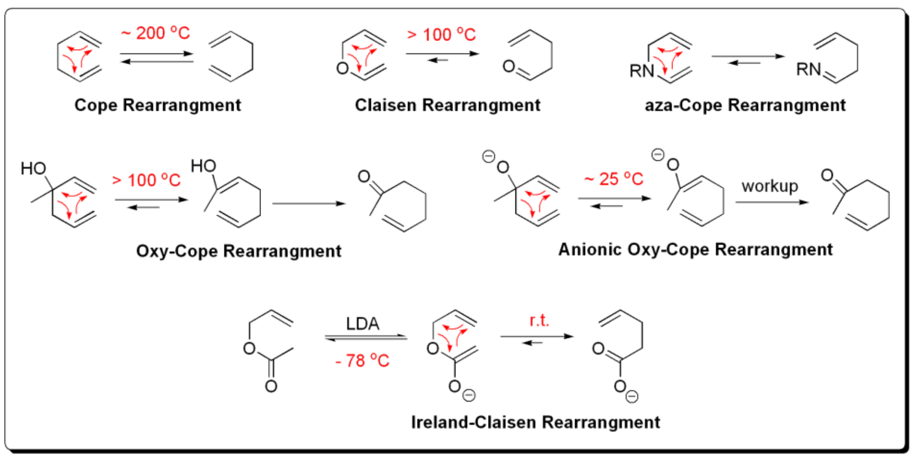


notes_28

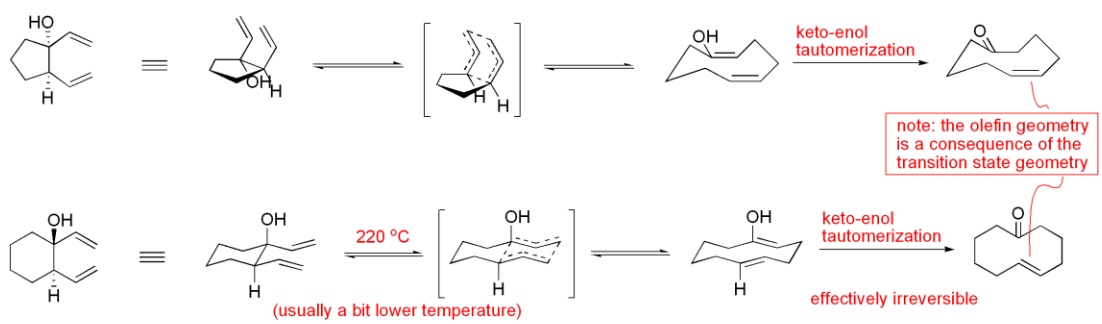
Methodology:

4.1 Cope-type reactions:

3,3-Sigmatropic Rearrangments

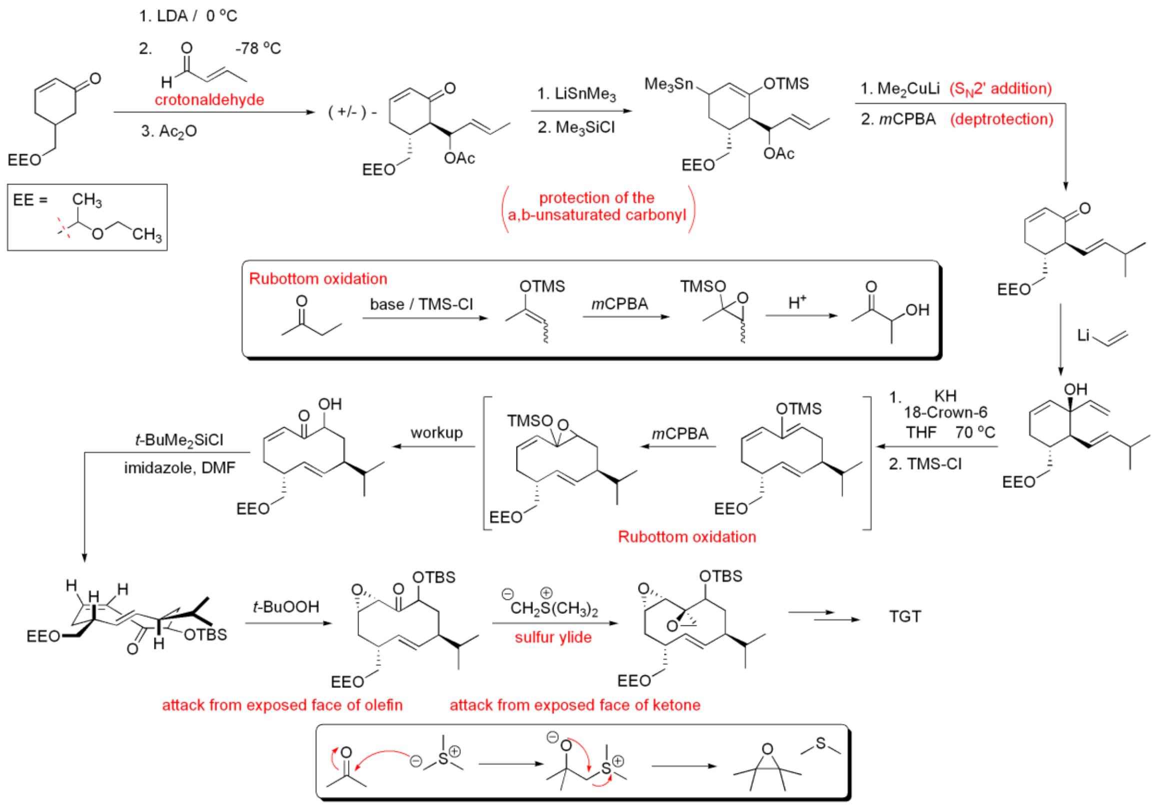


Stereochemical Consequences:



notes_29

Synthesis:



notes_30

Section 5: Palladium-Mediated Coupling Strategies

Reactions:

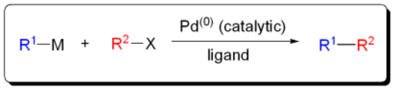
· <u>General discussion of:</u>

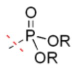
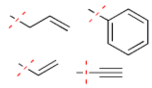
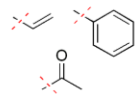
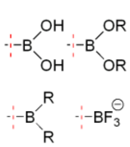
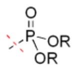
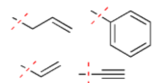
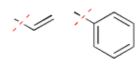
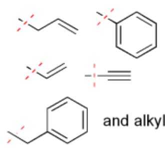
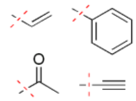
- · Stille coupling
- · Heck coupling
- · Suzuki coupling
- · Sonogashira coupling
- · Negishi coupling
- · Tsuji-Trost coupling
- · Pd- Pt- & Au-mediated cycloisomerizations

Concepts:

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

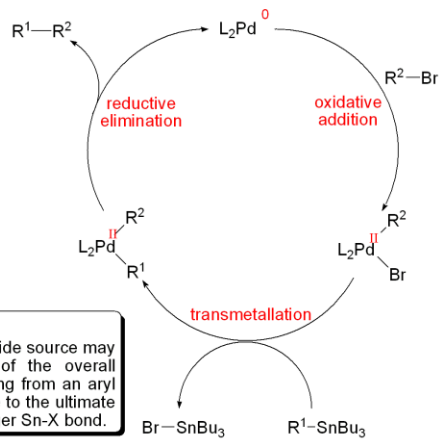
Methodology 5.1. The Stille, Suzuki & Negishi reactions - Related Mechanisms



	M	X	R1	R2	Other Requirements
Stille	$Sn(alkyl)_3$	I, Br, Cl, OTf, 	 (& sometimes alkyl)		
Suzuki		I, Br, Cl, OTf, 	 and alkyl	 and alkyl	Base: Cs_2CO_3, $B(OH)_2$, Na_2CO_3, K_2CO_3, $Ba(OH)_2$, TlOH, KF, CsF, NaOH, etc.
Negishi	ZnX	I, Br, Cl, OTf, OAc	 and alkyl		

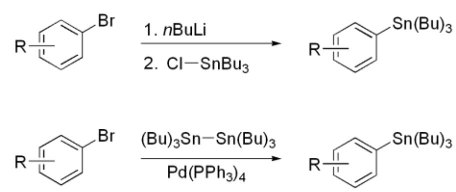
notes_31

Catalytic Cycle: Stille Coupling



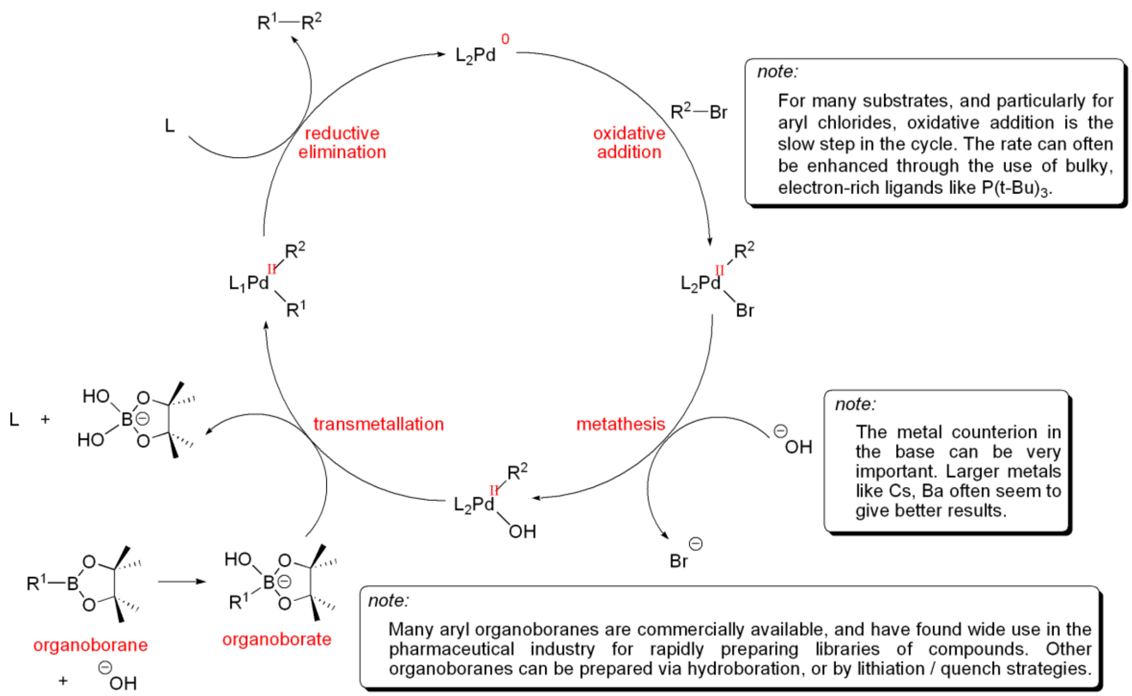
note:
The addition of a halide source may enhance the rate of the overall reaction when starting from an aryl (or vinyl) triflate, due to the ultimate formation of a stronger Sn-X bond.

Formation of alkyl stannanes:



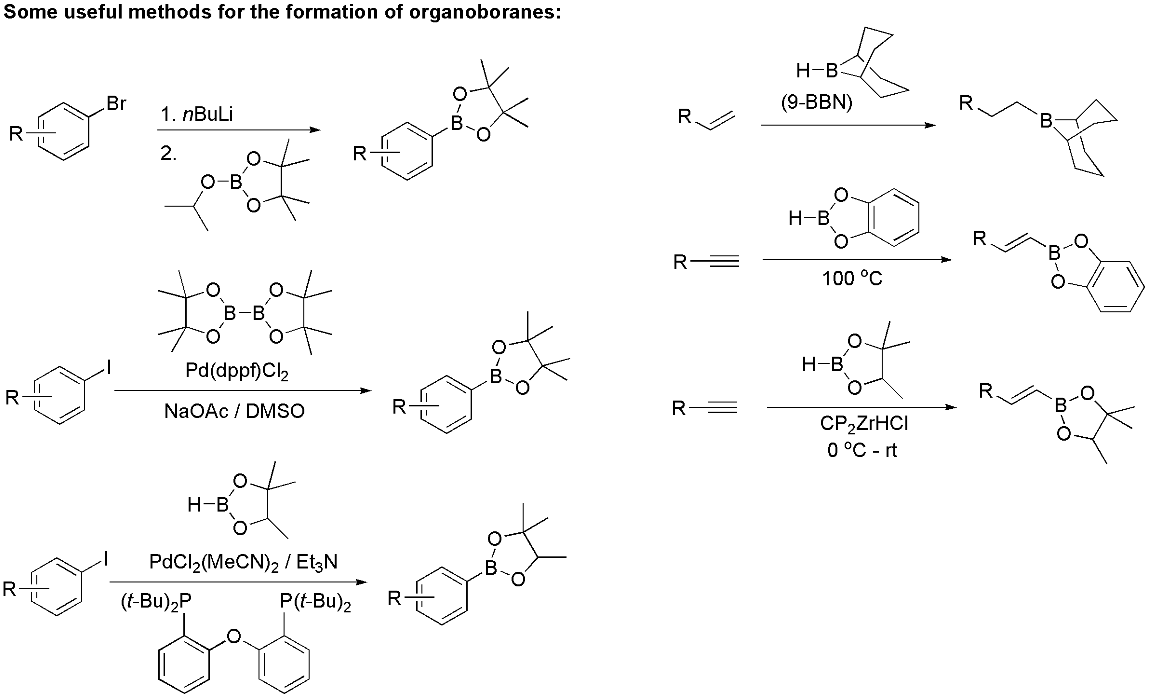
notes_34

Catalytic Cycle: Suzuki Coupling



notes_32

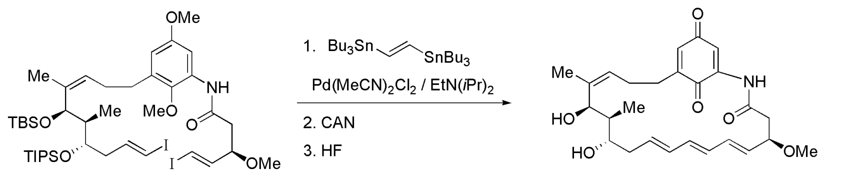
Some useful methods for the formation of organoboranes:



notes_33

Synthesis 5.1. Some illustrative syntheses:

Stille Reaction

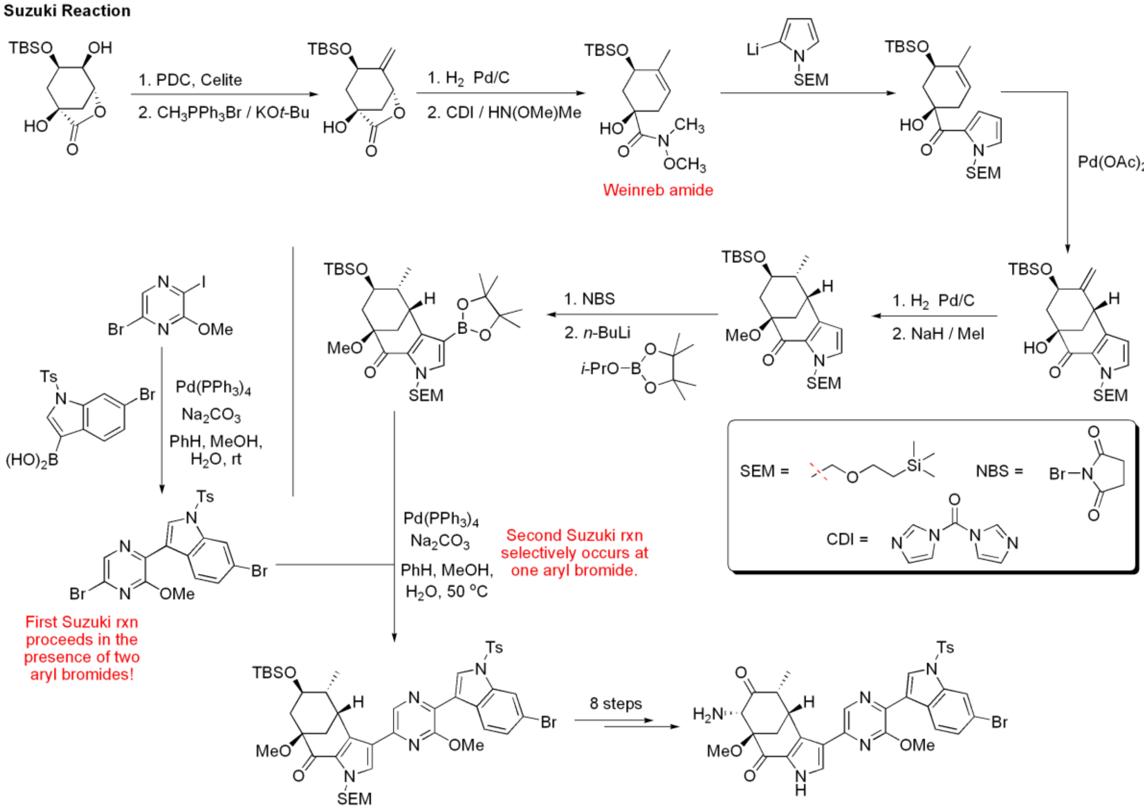


(+)-Mycotrienol

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

notes_35

Suzuki Reaction

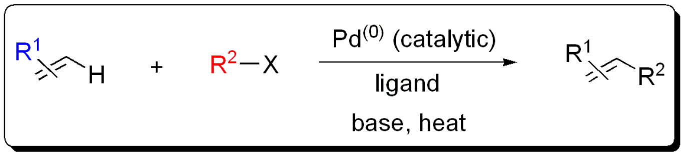


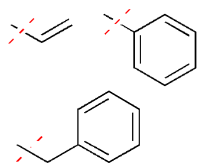
(+)-Dragmacidin F (anti-HIV)

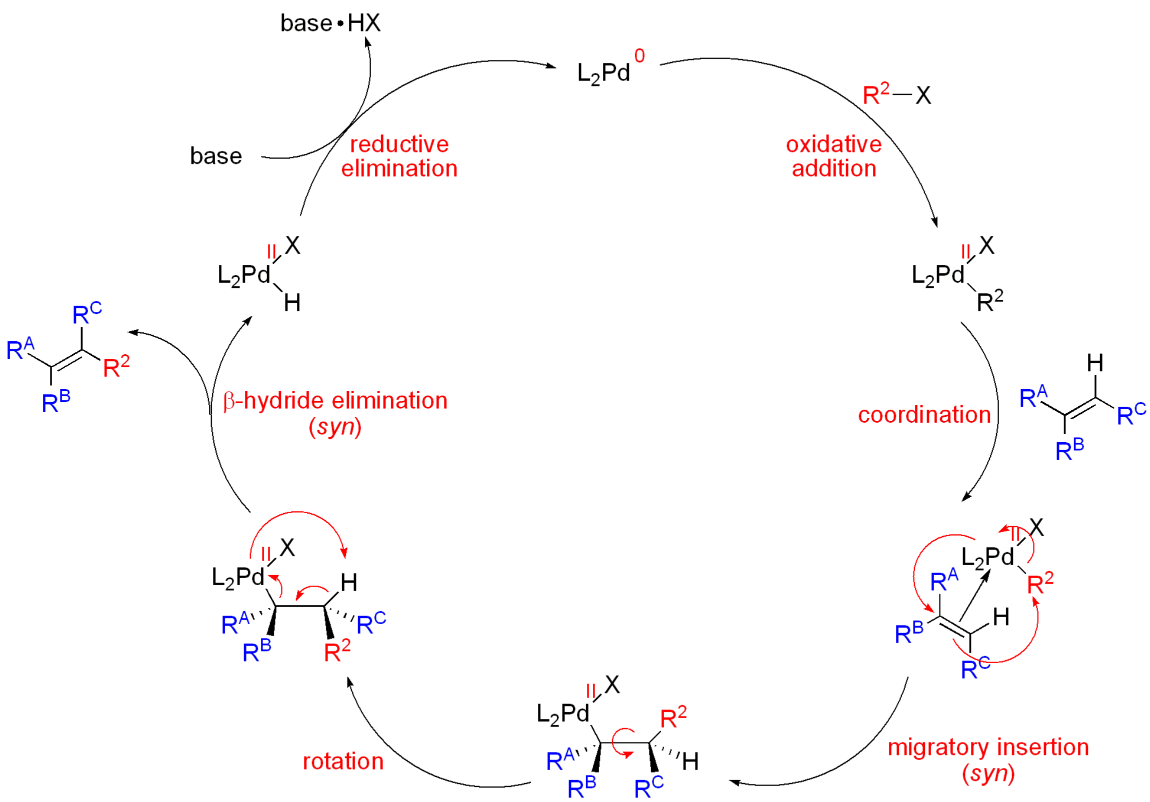
Stoltz *J.Am.Chem.Soc.* **2004**, *126*, 9552-9553.

notes_36

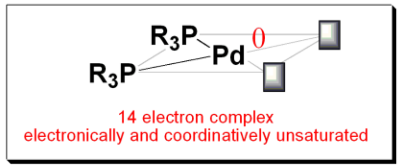
Methodology 5.2. The Heck reaction:



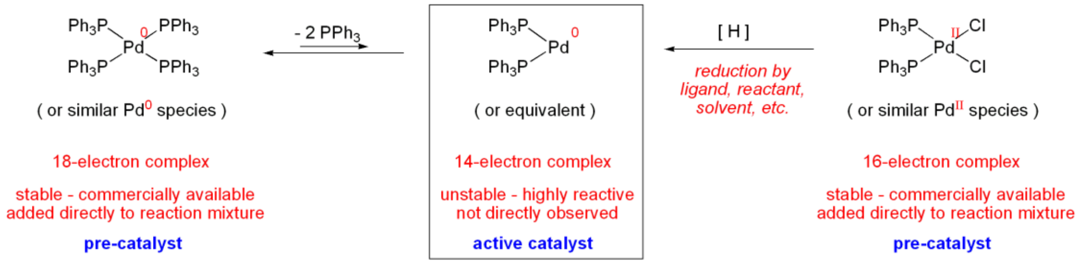
R^2	X	base
 or sometimes alkyl (w/ no β-hydrogen)	I, Br, Cl, OTf, OTs, N_2^+	2° or 3° amine KOAc, NaOAc, $NaHCO_3$



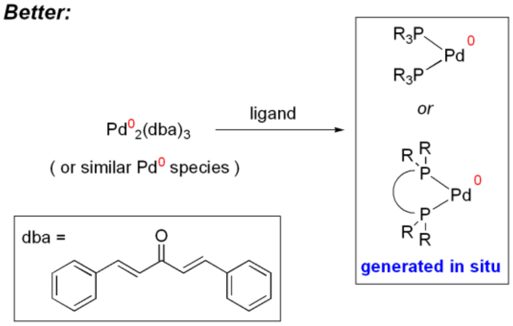
On the nature of " L_2Pd^0 "

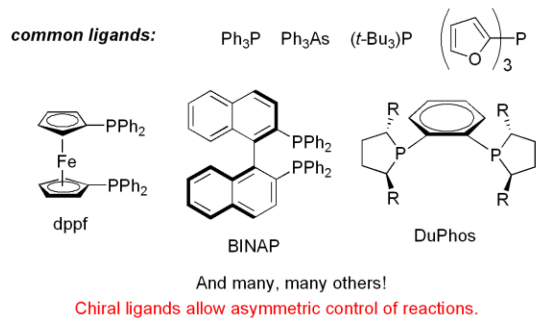


Typical Formation:

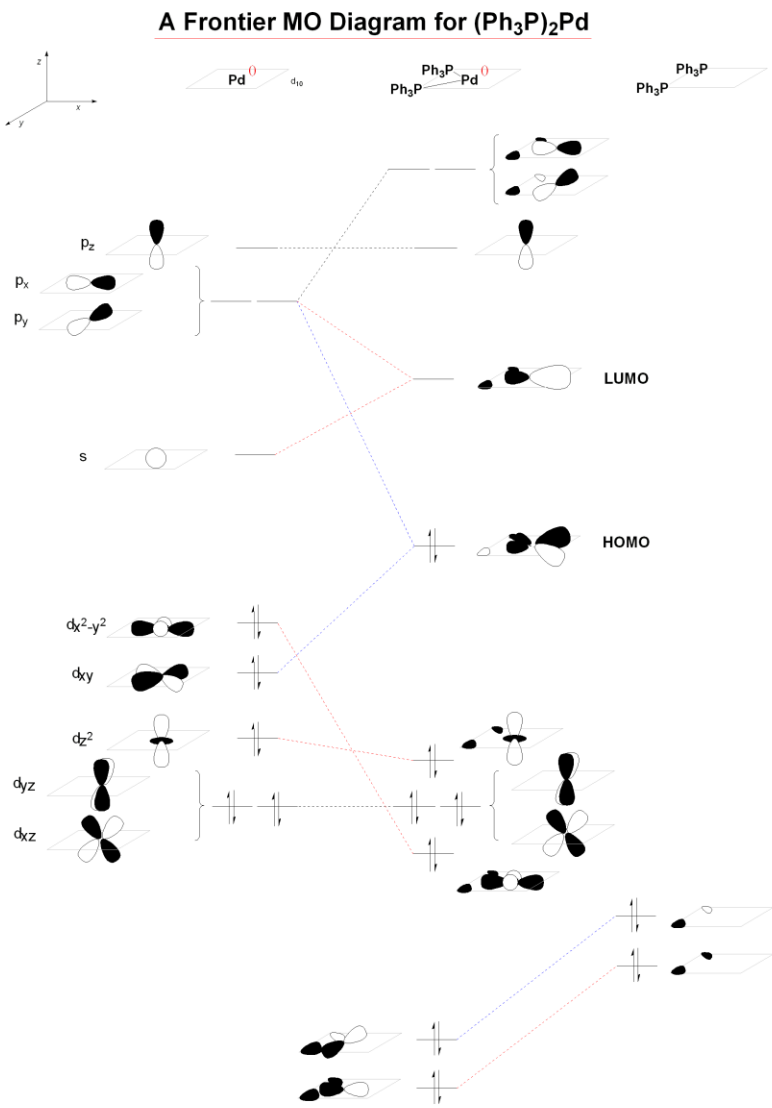


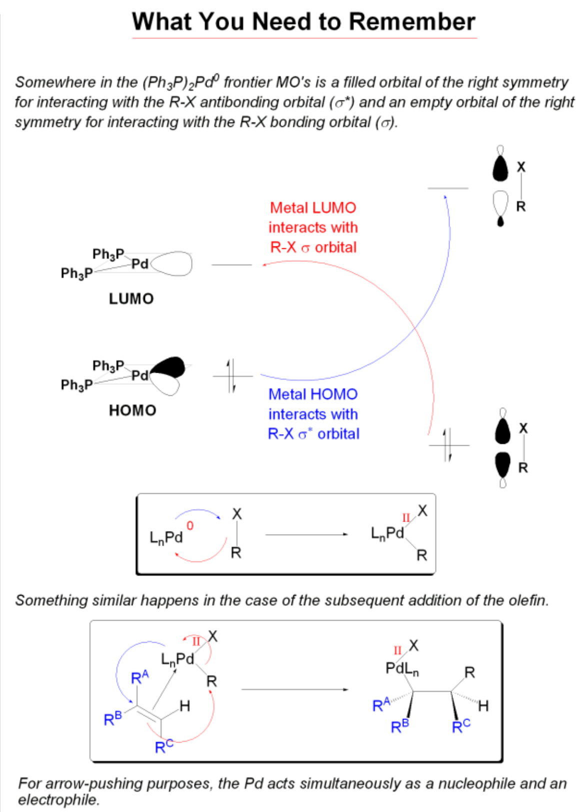
Even Better:





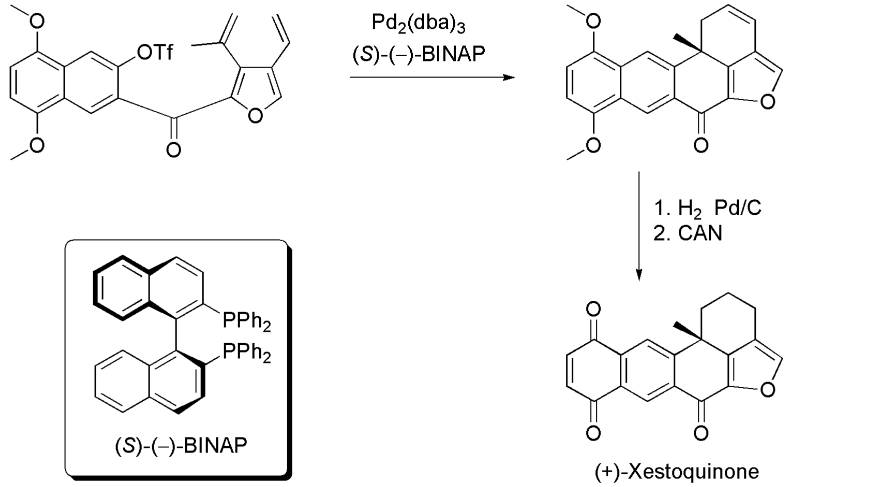
A closer look at what those curved arrows are doing:





notes_38b

An example of an asymmetric “double” Heck reaction

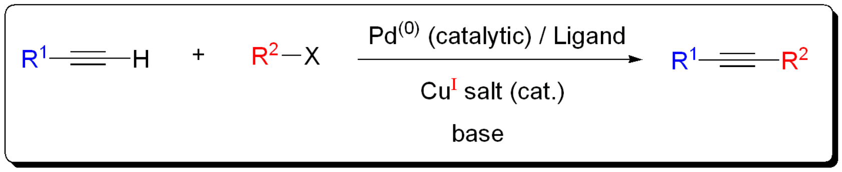


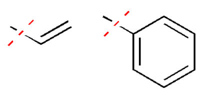
(+)-Xestoquinone

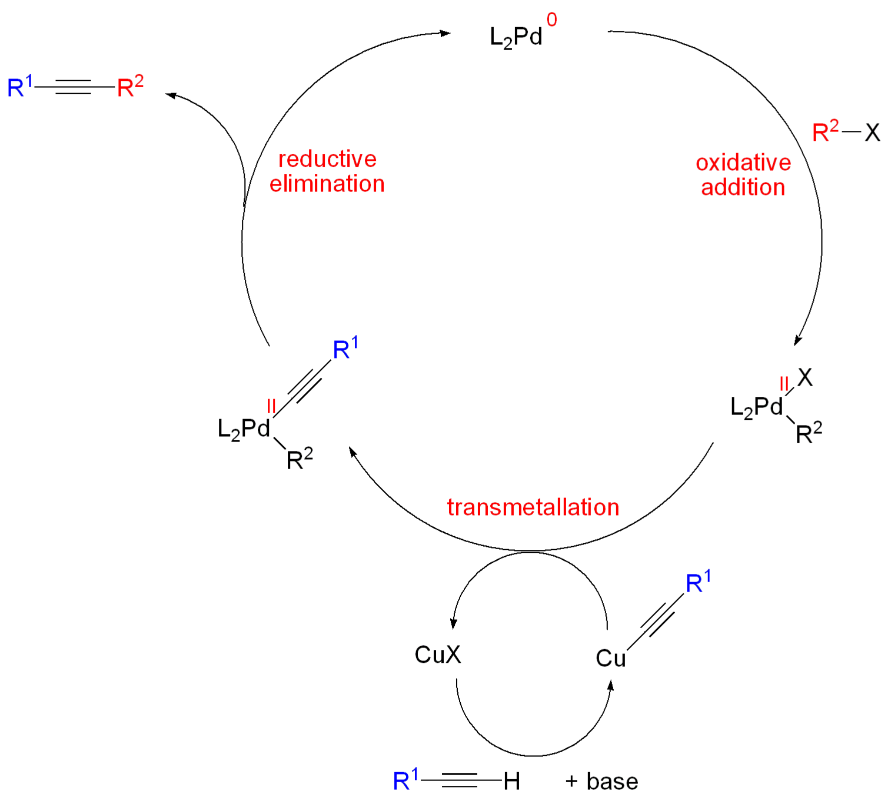
Keay *J.Am.Chem.Soc.* **1996**, *118*, 10766

Some other noteworthy Pd-coupling strategies:

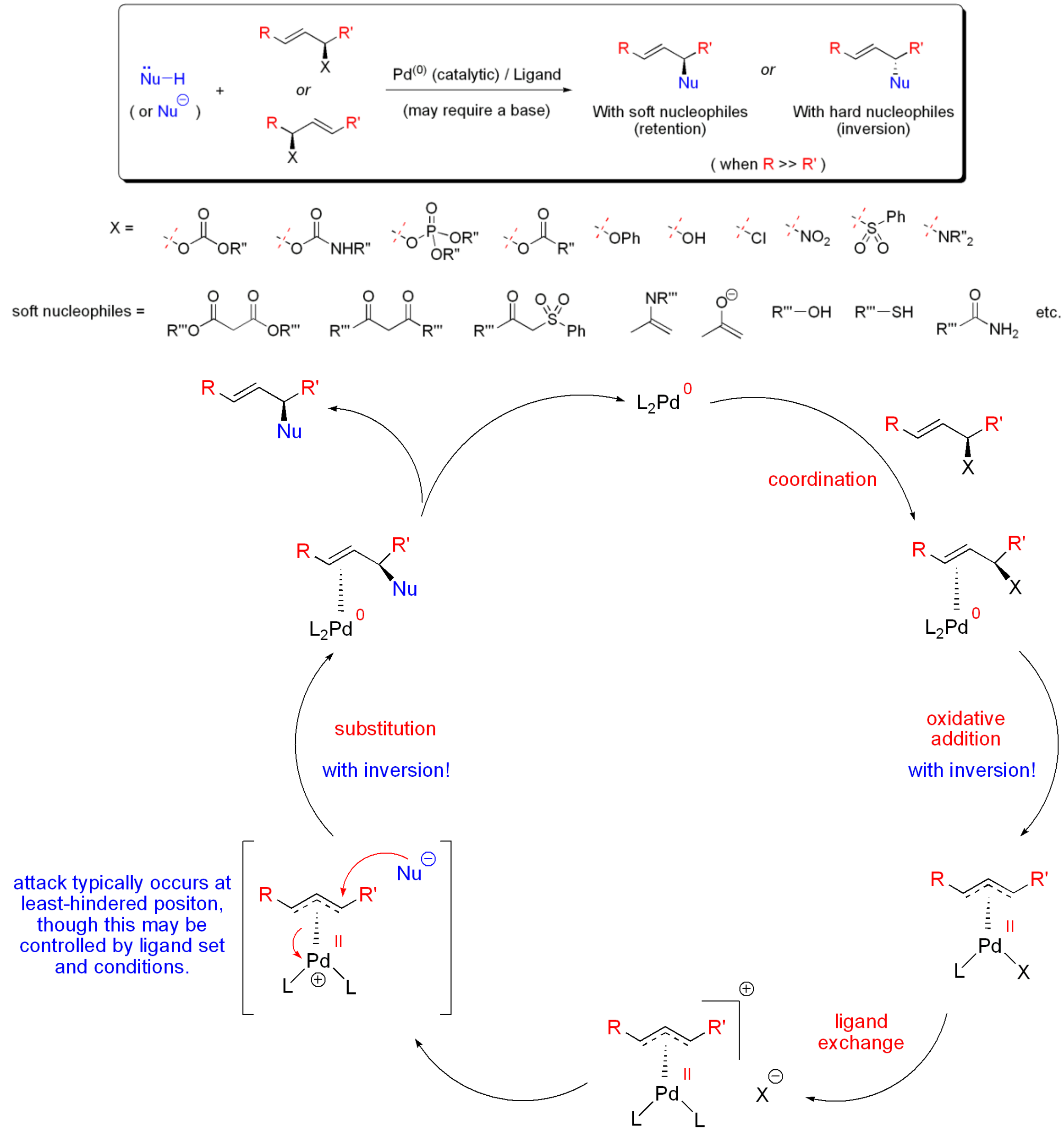
Methodology 5.3. Sonogashira coupling:



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

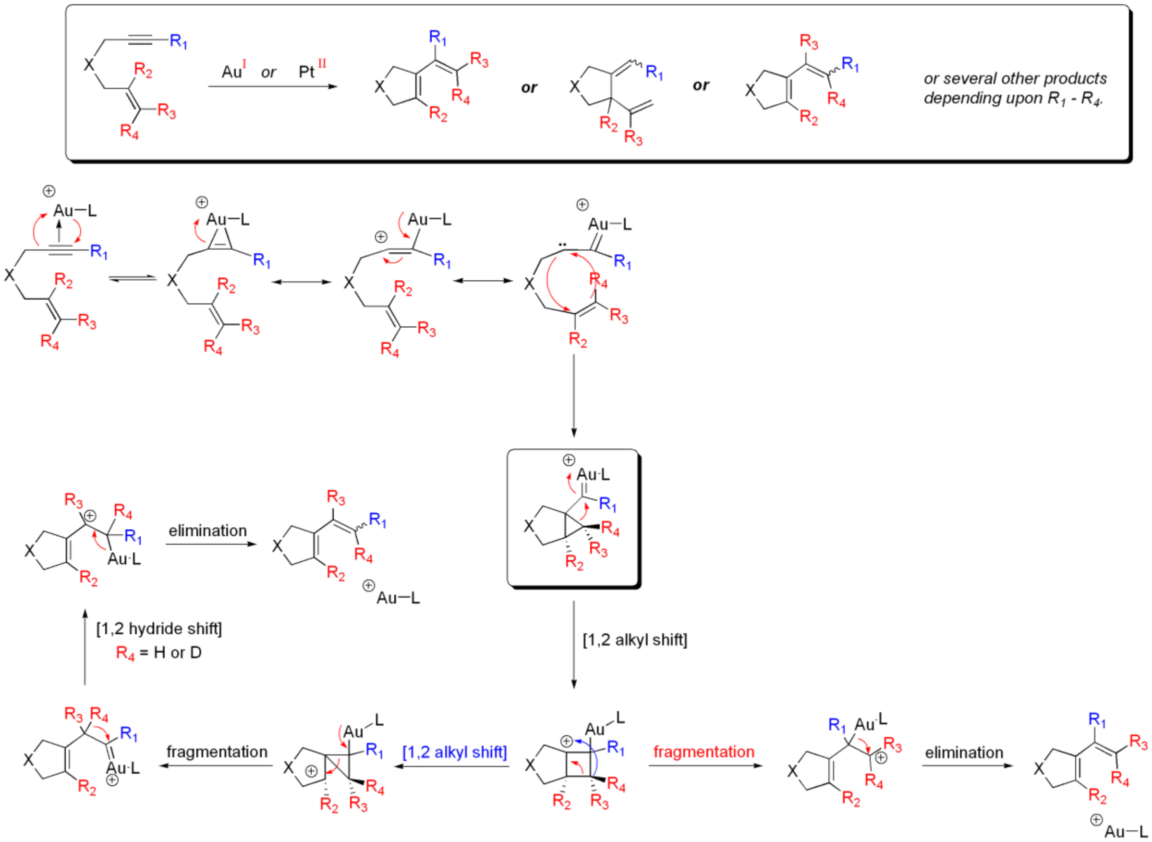


Methodology 5.4. Tsuji-Trost coupling:



notes_40 & notes_41

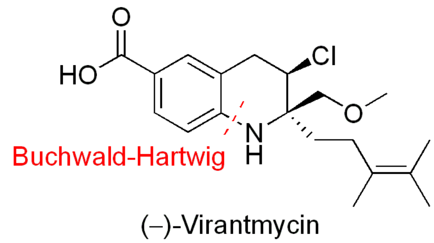
Methodology 5.5. Au- and Pt-Catalyzed Cyclizations of Eneynes:



Synthesis 6: Virantmycin

Back, 2004

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



notes_45

Reactions:

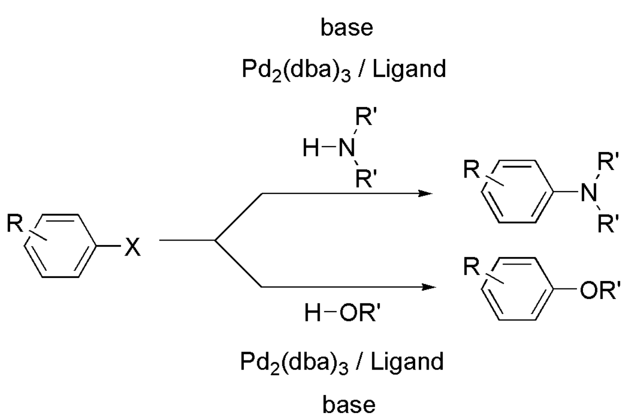
- Buchwald-Hartwig coupling
- Acid chloride / fluoride formation
- Curtius rearrangement
- Krapcho decarboxylation
- Enzyme-mediated reactions

Concepts:

- Desymmetrization
- Stereodivergent synthesis

Methodology:

6.1 Buchwald-Hartwig coupling:

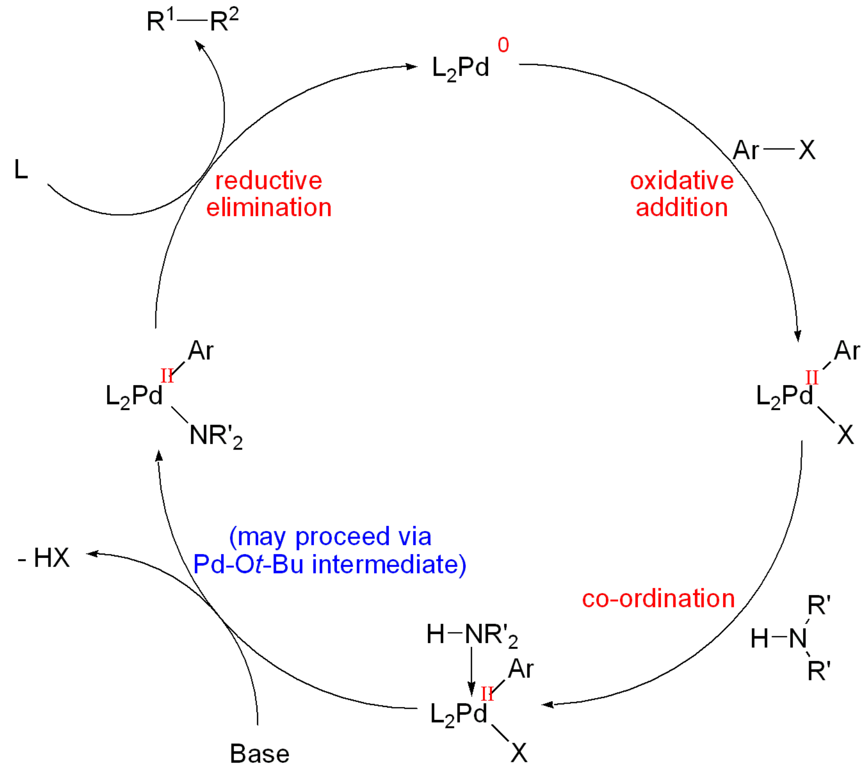


(Ligand = BINAP, DPPF, etc.)

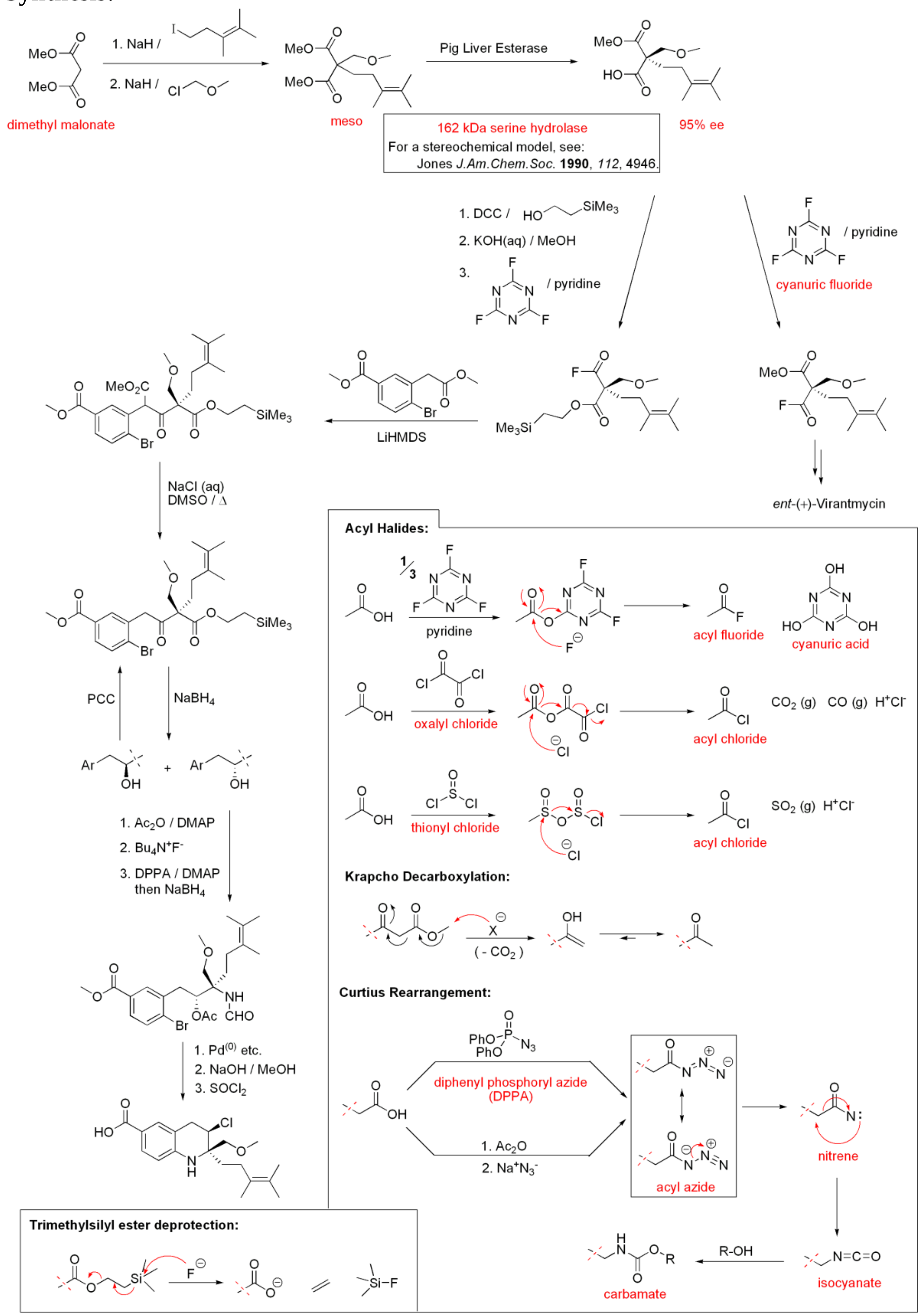
Base = NaO*t*-Bu, LHMDS, K_2CO_3, Cs_2CO_3

notes_47

Catalytic Cycle:



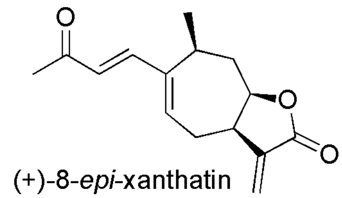
Synthesis:



MeO
1. NaH /
2. NaH /
dimethyl malonate
meso
Pig Liver Esterase
162 kDa serine hydrolase
For a stereochemical model, see:
Jones J.Am.Chem.Soc. 1990, 112, 4946.
95% ee
1. DCC /
2. KOH(aq) / MeOH
3.
/ pyridine
cyanuric fluoride
LiHMDS
ent-(+)-Virantmycin
NaCl (aq)
DMSO / Δ
PCC
NaBH4
1. Ac2O / DMAP
2. Bu4N+F-
3. DPPA / DMAP
then NaBH4
1. Pd(0) etc.
2. NaOH / MeOH
3. SOCl2
Acyl Halides:
pyridine
acyl fluoride
cyanuric acid
oxalyl chloride
acyl chloride
CO2 (g) CO (g) H+Cl-
thionyl chloride
SO2 (g) H+Cl-
Krapcho Decarboxylation:
(- CO2)
Curtius Rearrangement:
diphenyl phosphoryl azide
(DPPA)
1. Ac2O
2. Na+N3-
acyl azide
nitrene
isocyanate
R-OH
carbamate
Trimethylsilyl ester deprotection:

Synthesis 7: Xanthatin

Martin, 2006
Tetrahedron 2006, 62, 11437

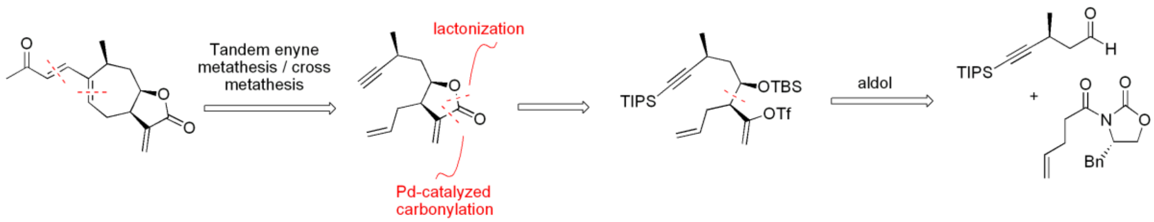


notes_50

Reactions:

- General discussion of olefin metathesis:
    - Ring-opening metathesis polymerization
    - Ring-closing metathesis
    - Cross metathesis
    - Ene-yne metathesis

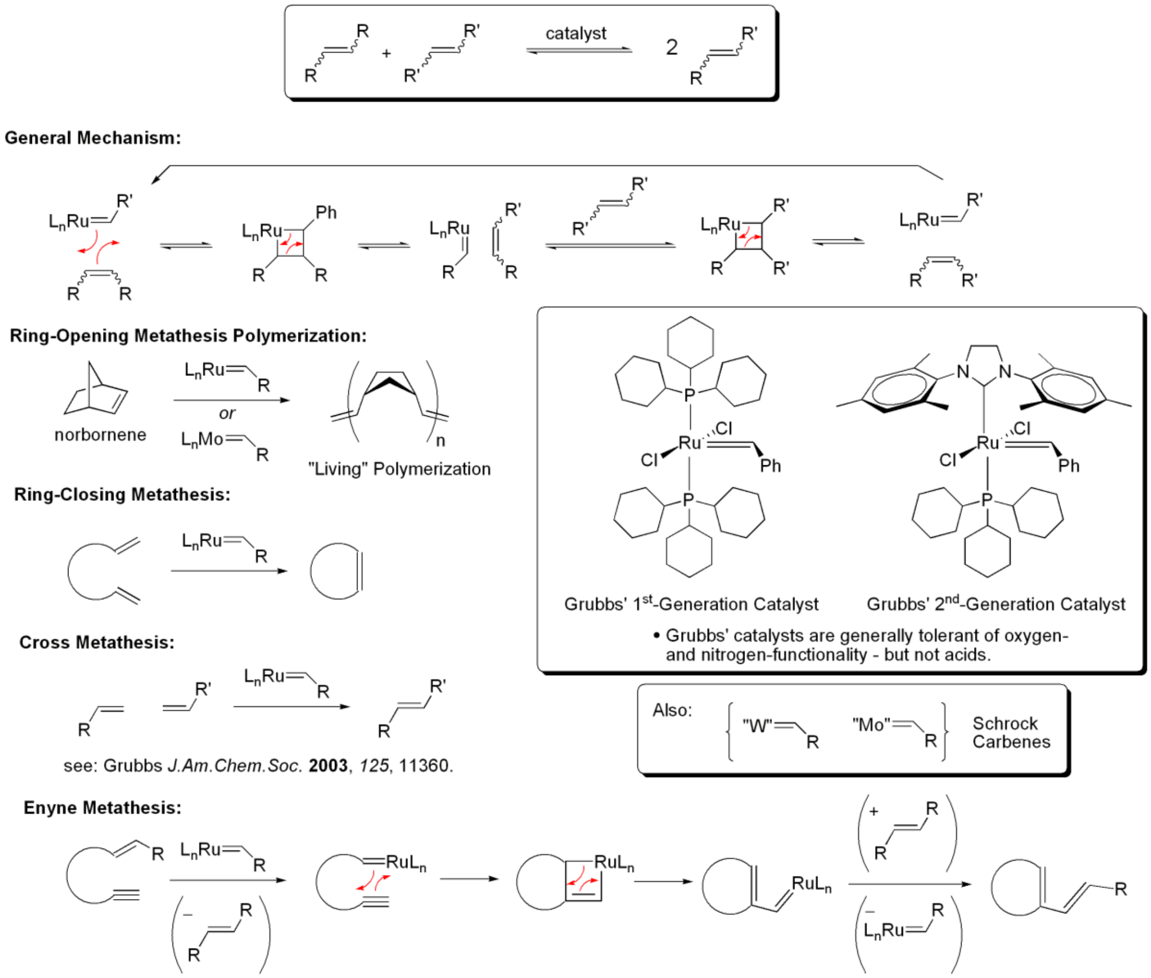
Retrosynthesis:



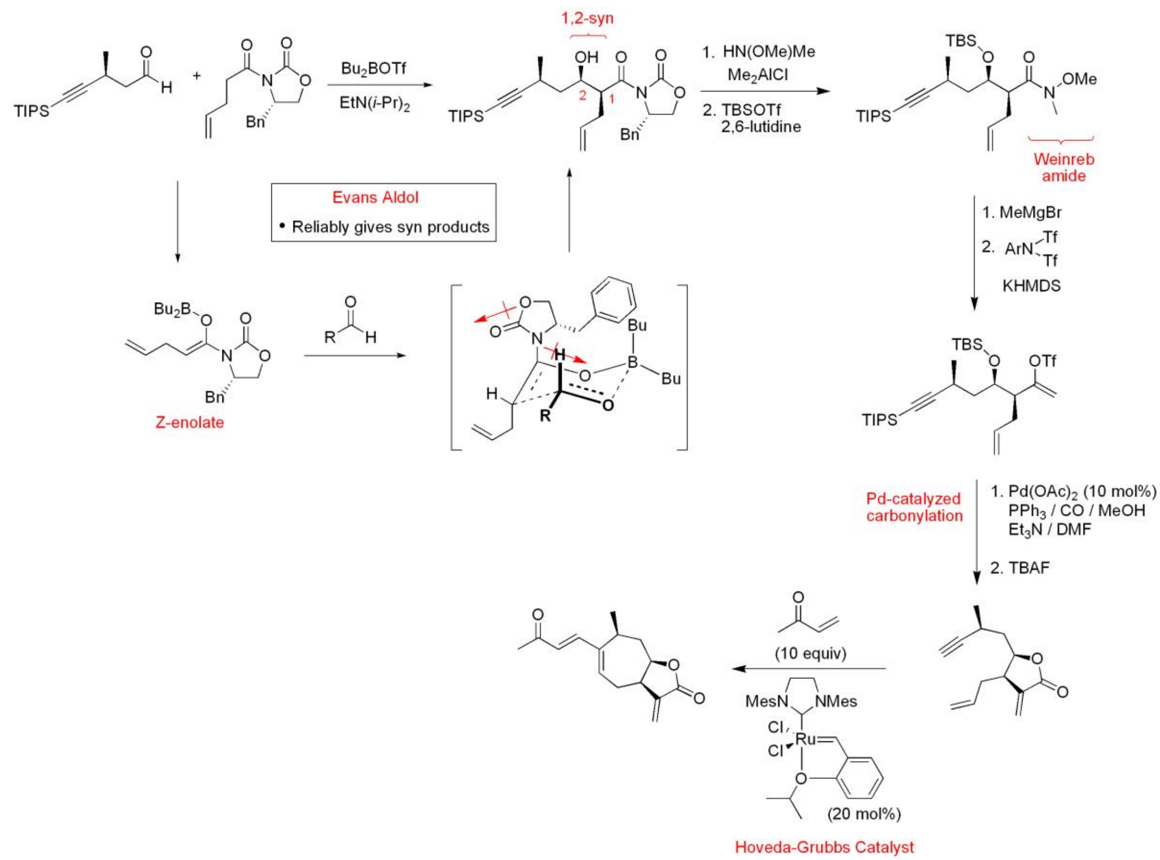
notes_51

Methodology:

7.1 Olefin Metathesis: (Nobel 2005)

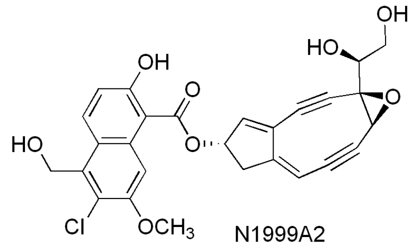


Synthesis:


1,2-syn
TIPS
Bu2BOTf
EtN(i-Pr)2
Bn
1. HN(OMe)Me
Me2AlCl
2. TBSOTf
2,6-lutidine
TBS
OMe
Weinreb amide
Evans Aldol
• Reliably gives syn products
1. MeMgBr
2. ArN Tf Tf
KHMDS
Z-enolate
OTf
Pd-catalyzed carbonylation
1. Pd(OAc)2 (10 mol%)
PPh3 / CO / MeOH
Et3N / DMF
2. TBAF
(10 equiv)
MesN NMes
Cl Ru
(20 mol%)
Hoveda-Grubbs Catalyst

Synthesis 8: N1999A2

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



N1999A2
(a 9-membered enediyne)

Reactions:

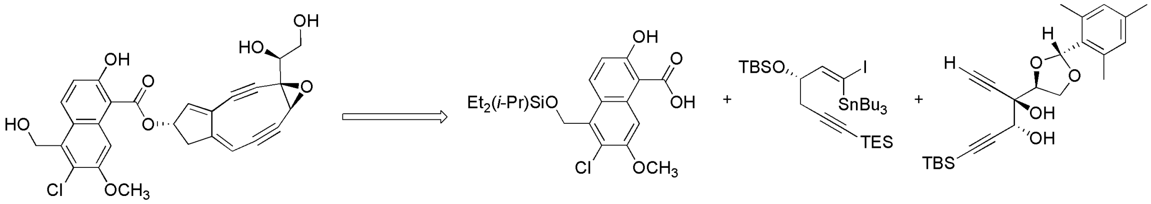
- · <u>Bergman cycloaromatization</u>
- · Swern-type oxidations
- · <u>Asymmetric epoxidations</u>
- · <u>Asymmetric dihydroxylations</u>
- · Amide couplings with DCC / EDC / HATU etc.
- · Corey-Fuchs reaction
- · Glaser reaction

notes_62

Concepts:

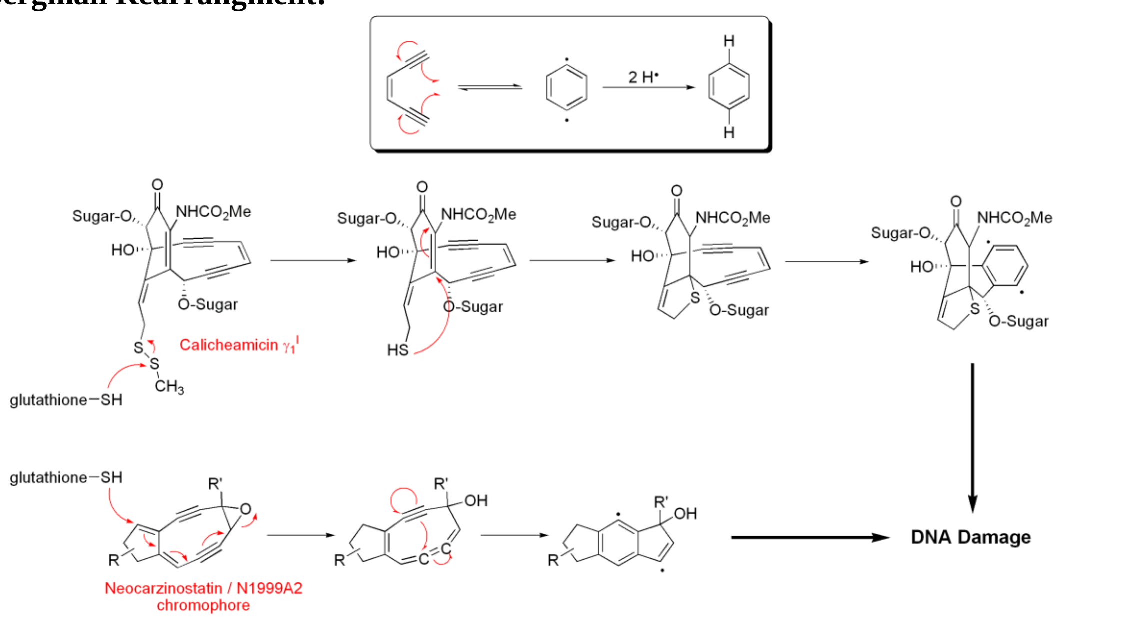
- · Synthetic planning

Retrosynthesis:

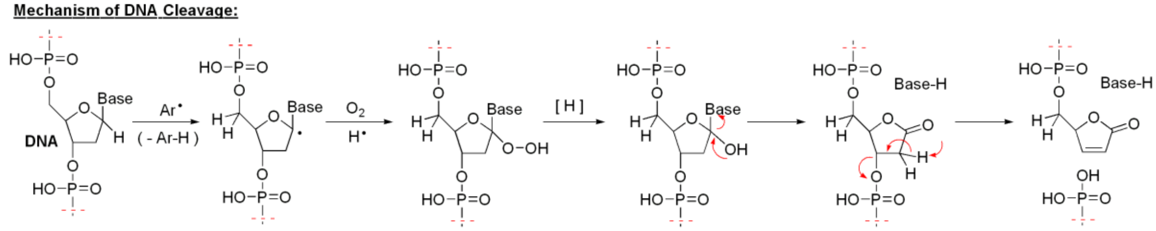


notes_62

Bergman Rearrangment:

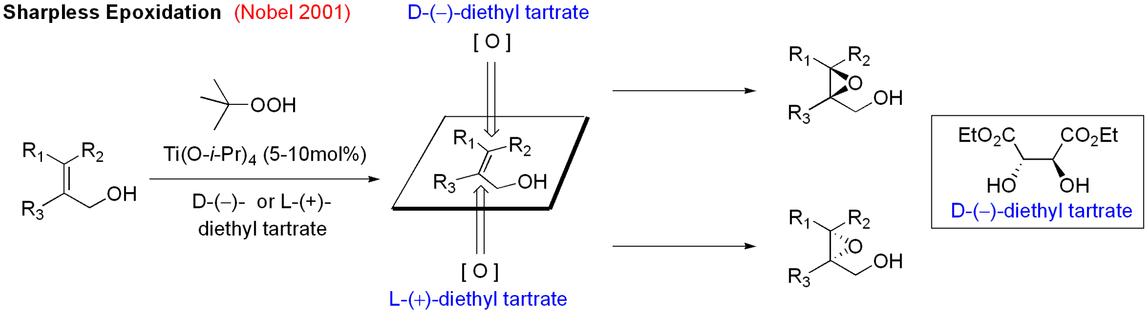


Mechanism of DNA Cleavage:

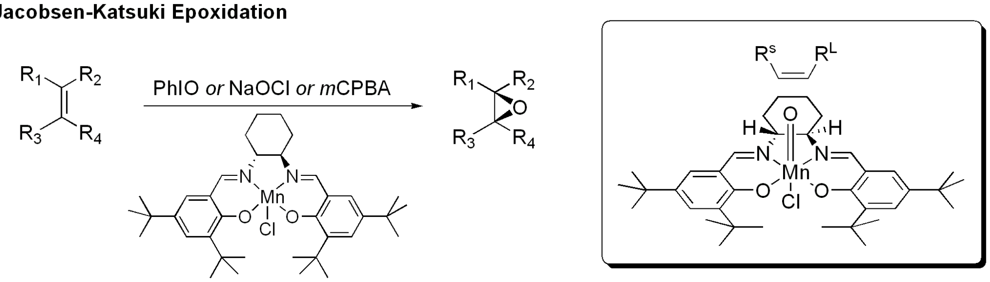


Methodology 8.1: Asymmetric Epoxidation

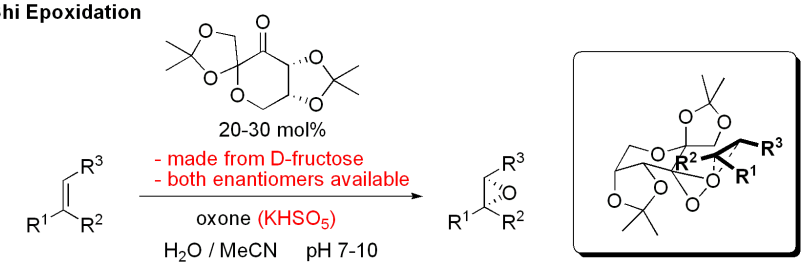
Sharpless Epoxidation (Nobel 2001)



Jacobsen-Katsuki Epoxidation

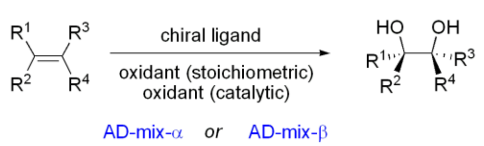


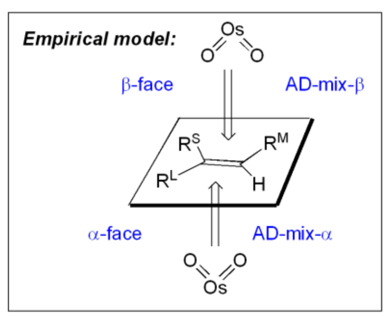
Shi Epoxidation



Methodology 8.2: Asymmetric Dihydroxylation

Sharpless Dihydroxylation (Nobel 2001)



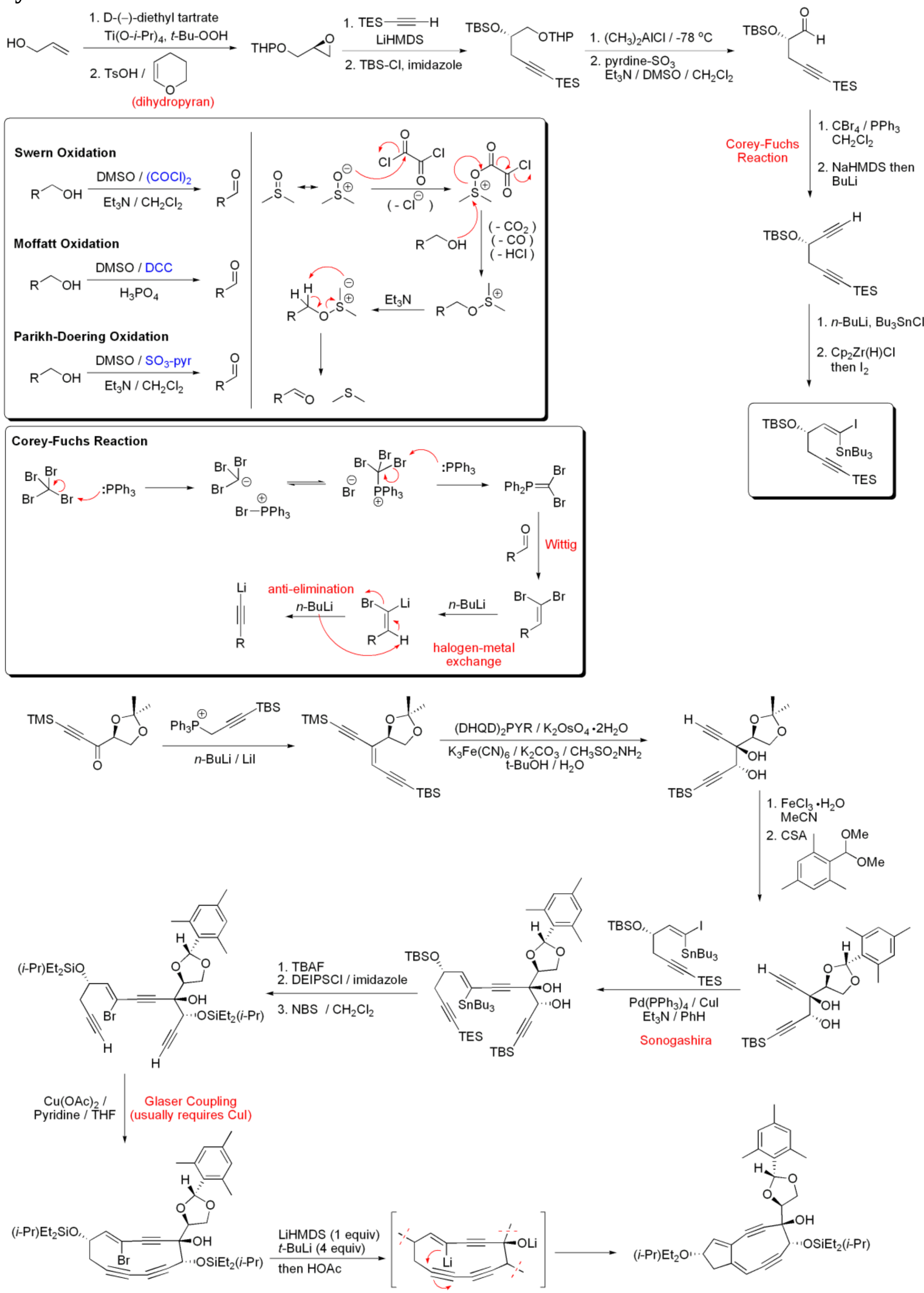


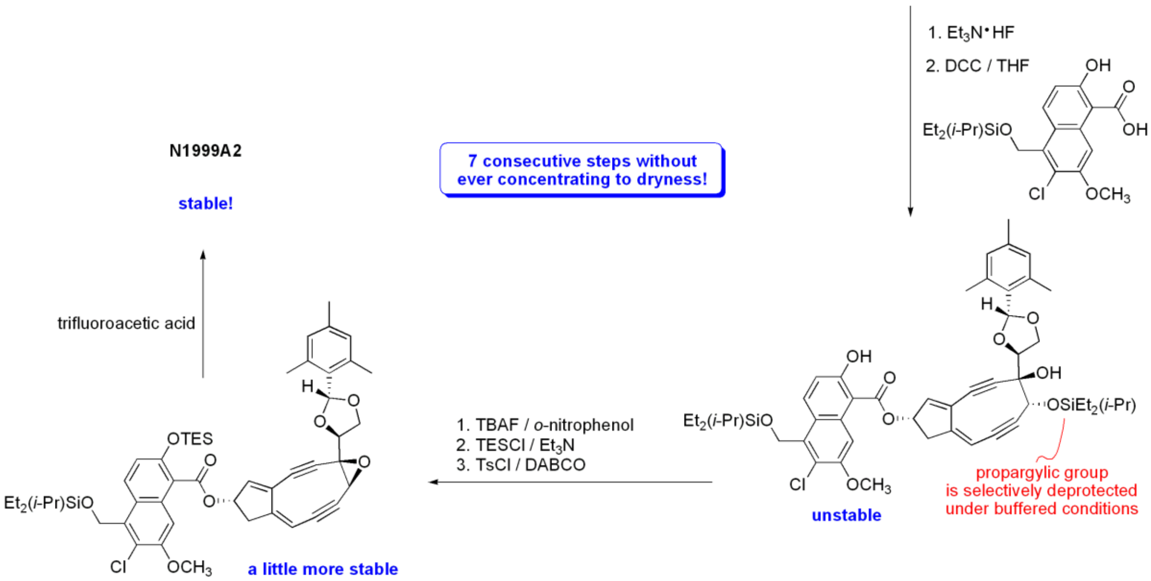
AD-mix-α : $(DHQ)_2PHAL$ + $K_2OsO_2(OH)_4$ + K_3FeCN

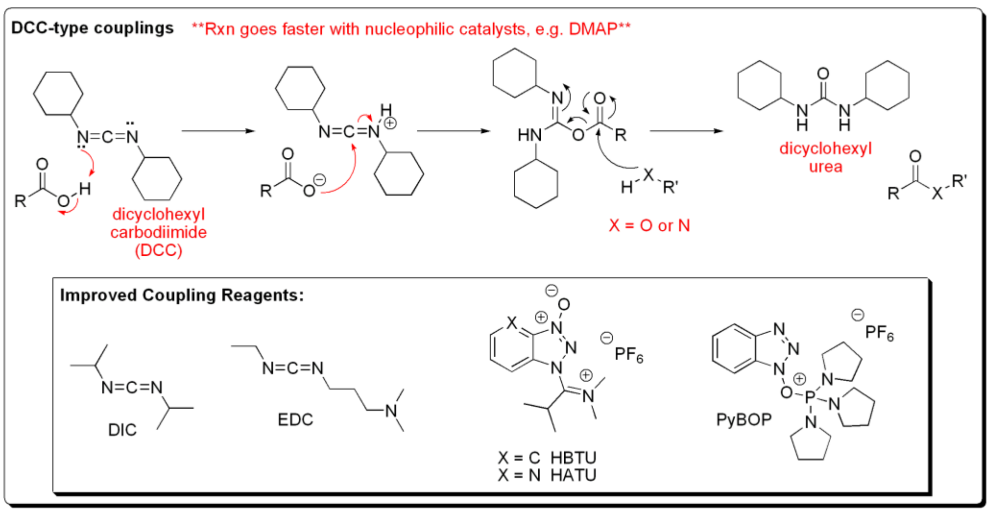
AD-mix-β : $(DHQD)_2PHAL$ + $K_2OsO_2(OH)_4$ + K_3FeCN

⇑ chiral amine (based on quinine or quinidine) — ⇑ catalytic oxidant — ⇑ stoichiometric oxidant

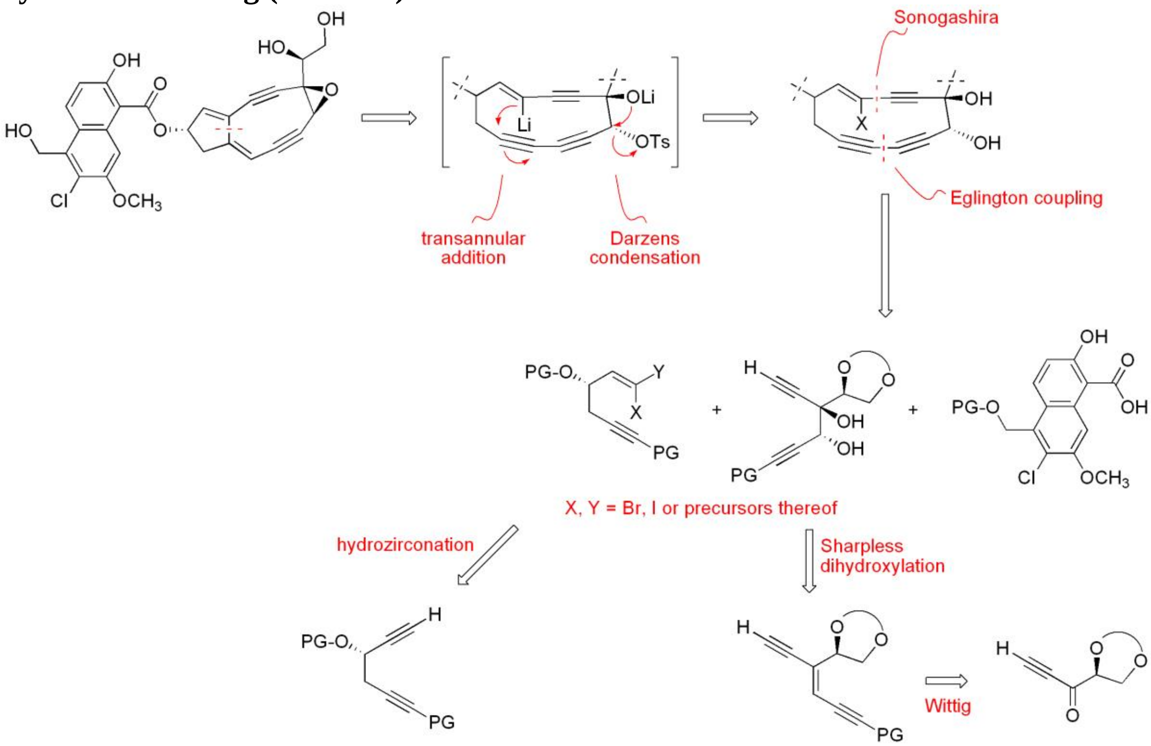
Synthesis:


1. D-(–)-diethyl tartrate
Ti(O-i-Pr)4, t-Bu-OOH
2. TsOH /
(dihydropyran)
1. TES—≡—H
LiHMDS
2. TBS-Cl, imidazole
1. (CH3)2AlCl / -78 °C
2. pyrdine-SO3
Et3N / DMSO / CH2Cl2
Swern Oxidation
DMSO / (COCl)2
Et3N / CH2Cl2
Moffatt Oxidation
DMSO / DCC
H3PO4
Parikh-Doering Oxidation
DMSO / SO3-pyr
Et3N / CH2Cl2
(- Cl⊖)
(- CO2)
(- CO)
(- HCl)
Et3N
Corey-Fuchs Reaction
1. CBr4 / PPh3
CH2Cl2
2. NaHMDS then
BuLi
1. n-BuLi, Bu3SnCl
2. Cp2Zr(H)Cl
then I2
Corey-Fuchs Reaction
Wittig
anti-elimination
n-BuLi
n-BuLi
halogen-metal
exchange
n-BuLi / LiI
(DHQD)2PYR / K2OsO4•2H2O
K3Fe(CN)6 / K2CO3 / CH3SO2NH2
t-BuOH / H2O
1. FeCl3 •H2O
MeCN
2. CSA
Pd(PPh3)4 / CuI
Et3N / PhH
Sonogashira
1. TBAF
2. DEIPSCl / imidazole
3. NBS / CH2Cl2
Cu(OAc)2 /
Pyridine / THF
Glaser Coupling
(usually requires CuI)
LiHMDS (1 equiv)
t-BuLi (4 equiv)
then HOAc


1. Et3N•HF
2. DCC / THF
OH
O
OH
Et2(i-Pr)SiO
Cl
OCH3
N1999A2
stable!
7 consecutive steps without ever concentrating to dryness!
trifluoroacetic acid
H
O
O
OH
OSiEt2(i-Pr)
Et2(i-Pr)SiO
unstable
propargylic group is selectively deprotected under buffered conditions
1. TBAF / o-nitrophenol
2. TESCl / Et3N
3. TsCl / DABCO
OTES
Et2(i-Pr)SiO
a little more stable

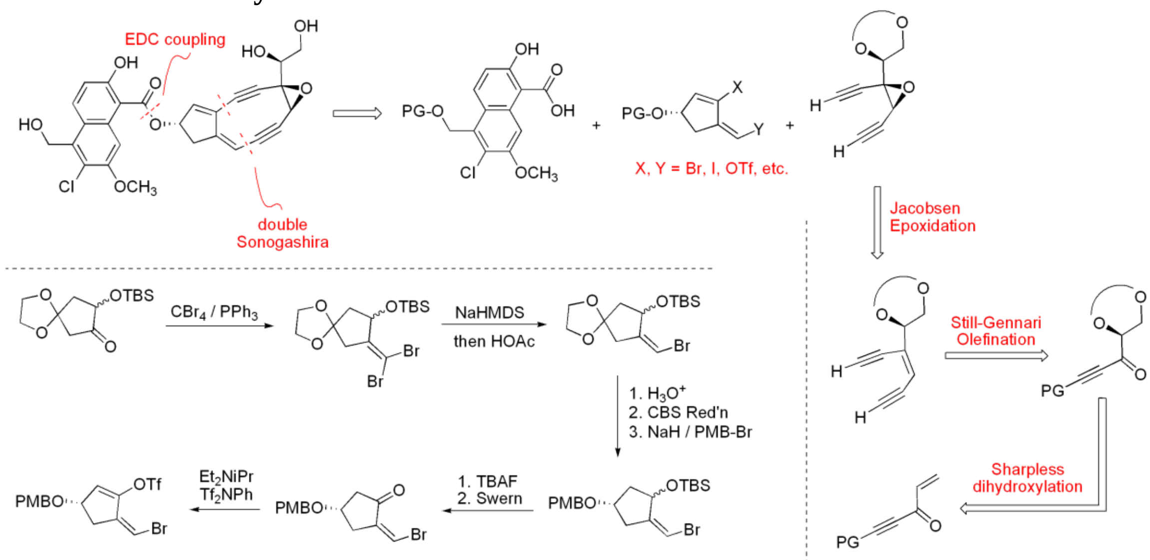

DCC-type couplings
Rxn goes faster with nucleophilic catalysts, e.g. DMAP
N=C=N
R
O
H
dicyclohexyl carbodiimide (DCC)
HN
H X R'
X = O or N
dicyclohexyl urea
Improved Coupling Reagents:
DIC
EDC
PF6
X = C HBTU
X = N HATU
PyBOP

Synthetic Planning (revisited):



notes_68

Alternative Retrosynthesis:



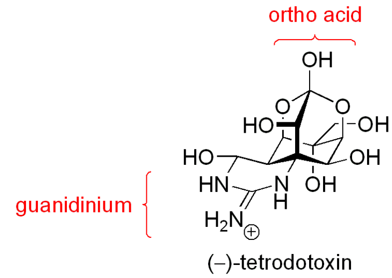
notes_69

Synthesis 9: Tetrodotoxin

Du Bois, 2003

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

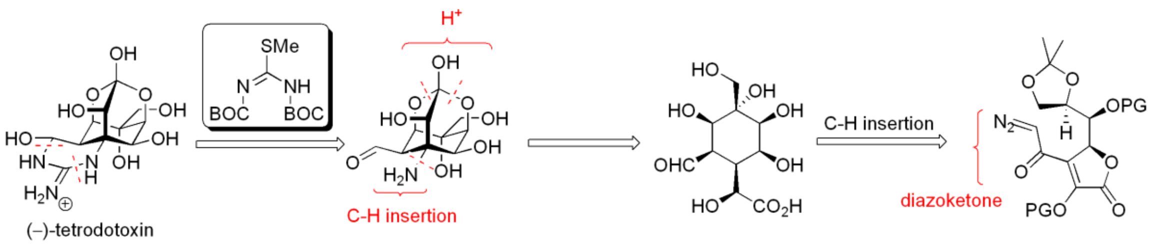
- · Carbene insertion reactions
- · Oxidative degradations
- · Methylene-forming reactions
- · Selenoxide elimination
- · TPAP/NMO oxidations
- · Allylic oxidations



notes_53

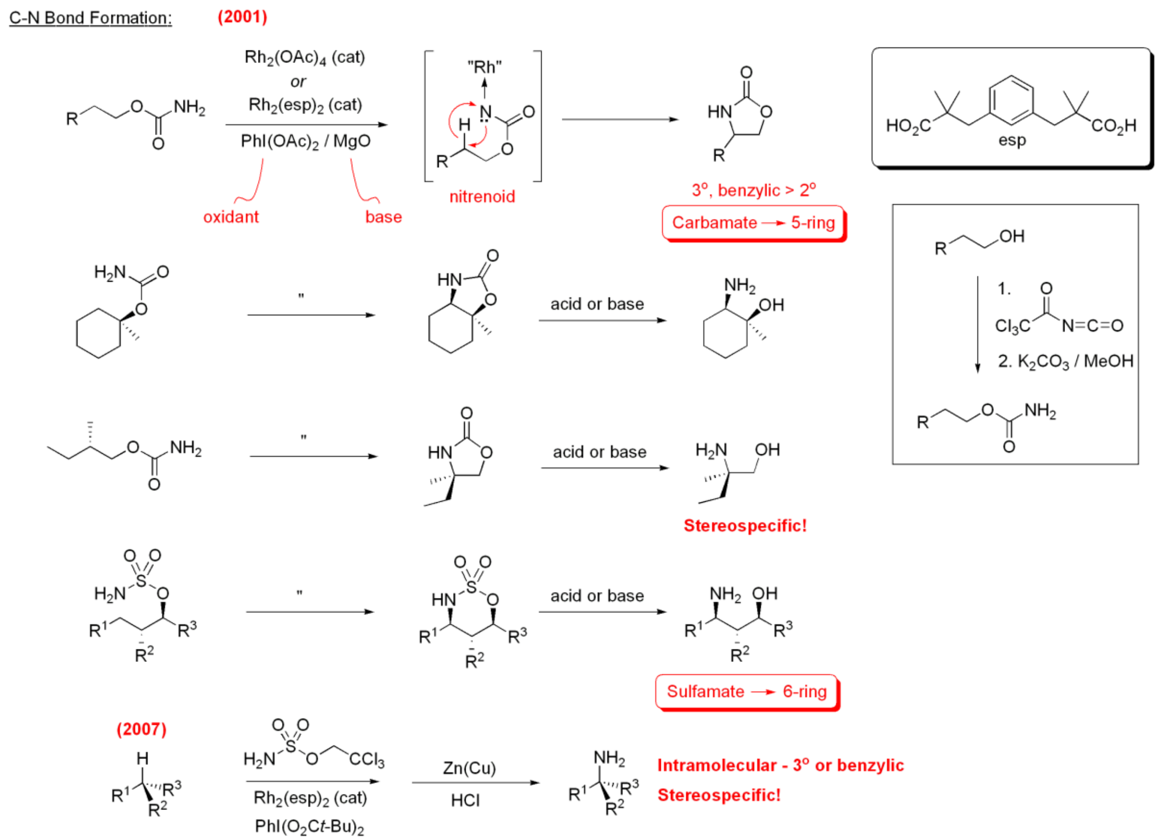
Also see: Kishi *J. Am. Chem. Soc.* **1972**, *94*, 9217, 9219.

Retrosynthesis:

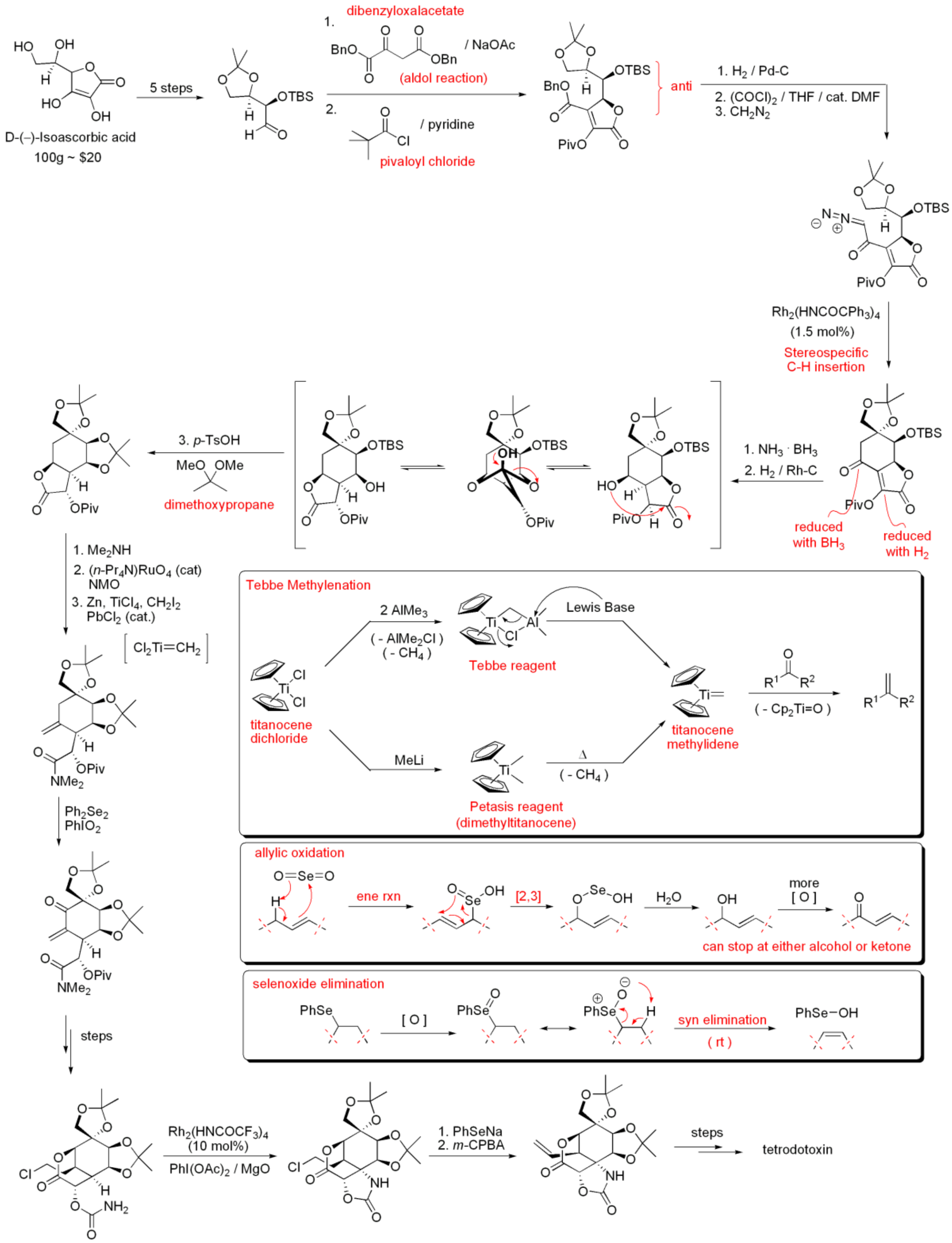


notes_54

Methodology 9.1: C-H insertion reactions (Justin Du Bois, Stanford)



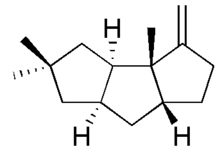
Synthesis:



D-(-)-Isoascorbic acid
100g ~ $20
5 steps
1. dibenzyloxalacetate
BnO
OBn
/ NaOAc
(aldol reaction)
2. / pyridine
pivaloyl chloride
OTBS
anti
PivO
1. H2 / Pd-C
2. (COCl)2 / THF / cat. DMF
3. CH2N2
Rh2(HNCOCPh3)4
(1.5 mol%)
Stereospecific
C-H insertion
1. NH3 · BH3
2. H2 / Rh-C
reduced with BH3
reduced with H2
3. p-TsOH
MeO OMe
dimethoxypropane
OPiv
1. Me2NH
2. (n-Pr4N)RuO4 (cat)
NMO
3. Zn, TiCl4, CH2I2
PbCl2 (cat.)
[Cl2Ti=CH2]
NMe2
Ph2Se2
PhIO2
steps
Tebbe Methylenation
2 AlMe3
(- AlMe2Cl)
(- CH4)
Lewis Base
Tebbe reagent
titanocene dichloride
MeLi
Petasis reagent
(dimethyltitanocene)
Δ
(- CH4)
titanocene methylidene
(- Cp2Ti=O)
allylic oxidation
ene rxn
[2,3]
H2O
more
[O]
can stop at either alcohol or ketone
selenoxide elimination
PhSe
[O]
syn elimination
(rt)
PhSe−OH
Rh2(HNCOCF3)4
(10 mol%)
PhI(OAc)2 / MgO
NH2
NH
1. PhSeNa
2. m-CPBA
steps
tetrodotoxin

Synthesis 10: Hirstutene

Curran, 1986
Classics I, 382



hirstutene

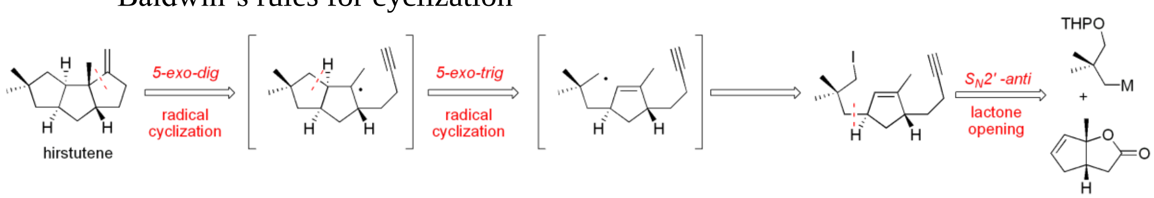
notes_57

Reactions:

- <u>General discussion of Radical Cyclizations</u>
- 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

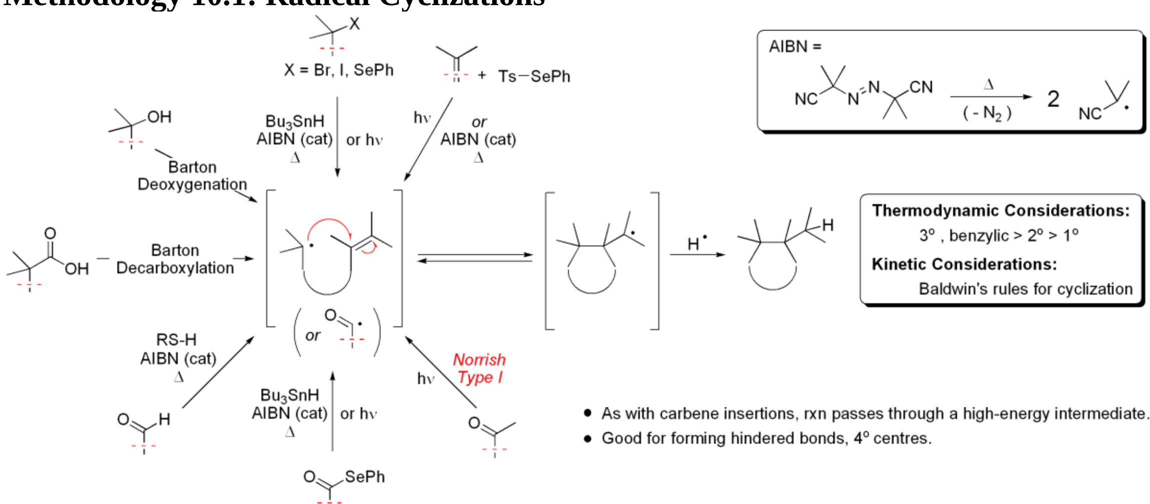
Concepts:

- Baldwin's rules for cyclization



notes_58

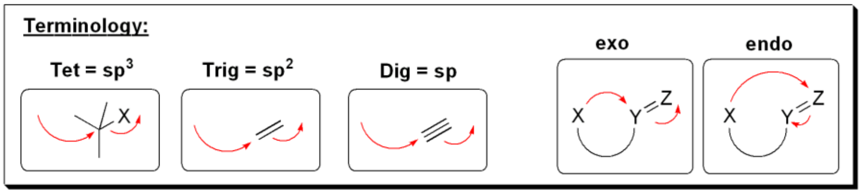
Methodology 10.1: Radical Cyclizations



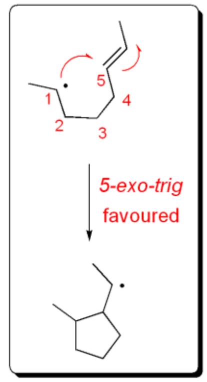
- As with carbene insertions, rxn passes through a high-energy intermediate.
- Good for forming hindered bonds, 4° centres.

notes_59

Baldwin's Rules for Cyclization (applies to 1- and 2-electron processes)



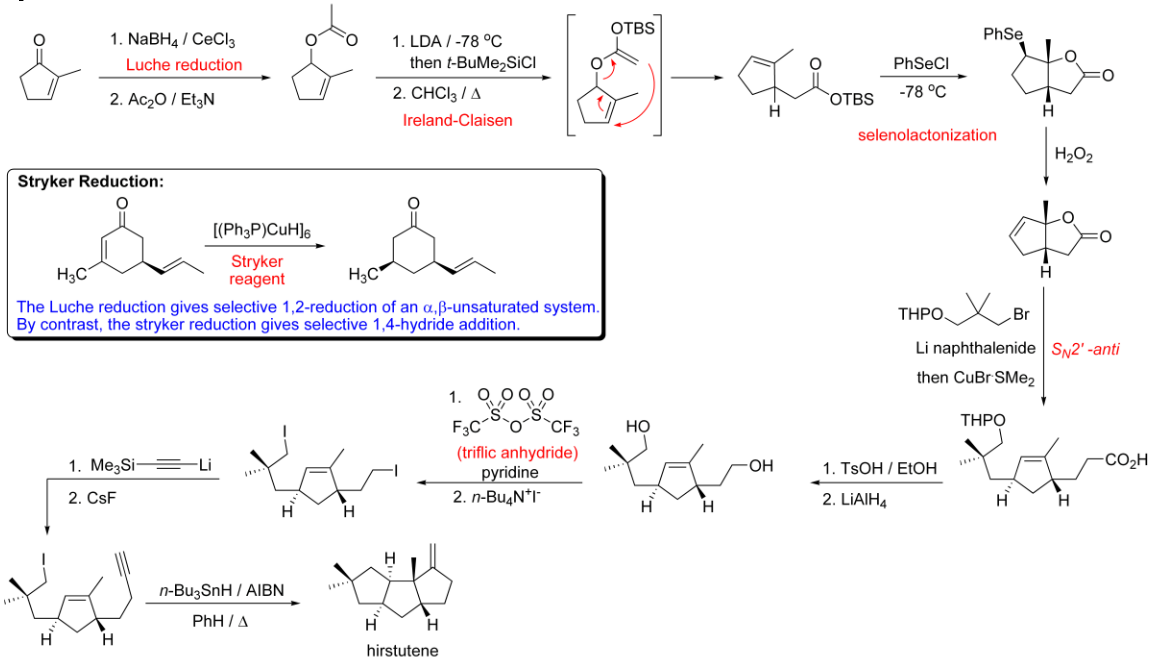
	3	4	5	6	7
Exo-Tet	✓	✓	✓	✓	✓
Endo-Tet			✗	✗	
Exo-Trig	✓	✓	✓	✓	✓
Endo-Trig	✗	✗	✗	✓	✓
Exo-Dig	✗	✗	✓	✓	✓
Endo-Dig	✓	✓	✓	✓	✓



✓ = favoured ✗ = disfavoured

notes_60

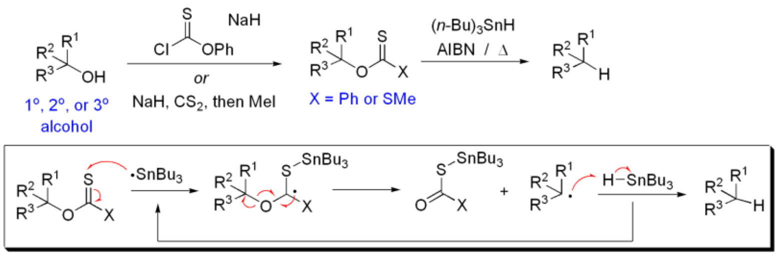
Synthesis:



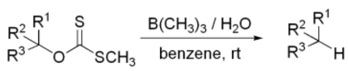
notes_61

Methodology 10.2: Radical Deoxygenations & Decarboxylations

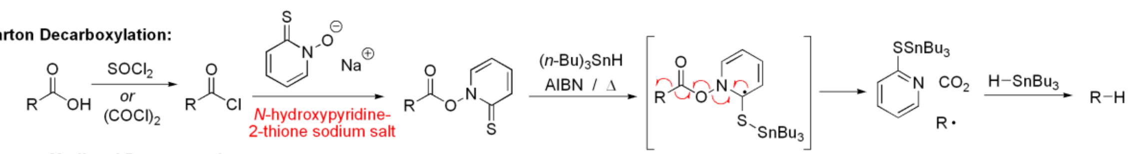
Barton-McCombie Deoxygenation:



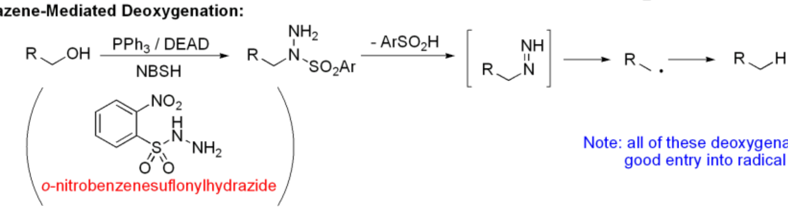
Tin-Free Variant:



Barton Decarboxylation:

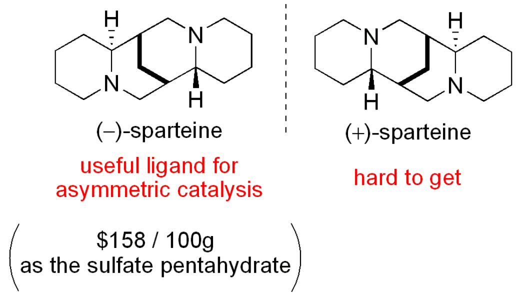


Diazene-Mediated Deoxygenation:



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

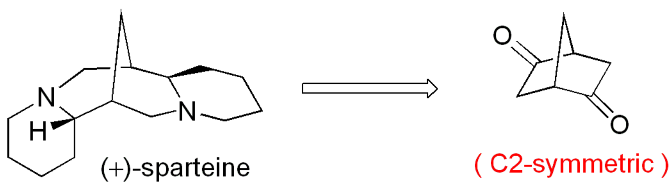
Synthesis 11: *ent*-Sparteine
Aubé, 2002
Org. Lett. **2002**, *4*, 2577.



Reactions:

- <u>General discussion of ring expansions and contractions:</u> notes_70
    - Beckmann rearrangement
    - Favorskii rearrangement
    - Tiffeneau-Demjanov rearrangement
    - Schmidt reaction
- Finkelstein reaction
- Mitsunobu reaction

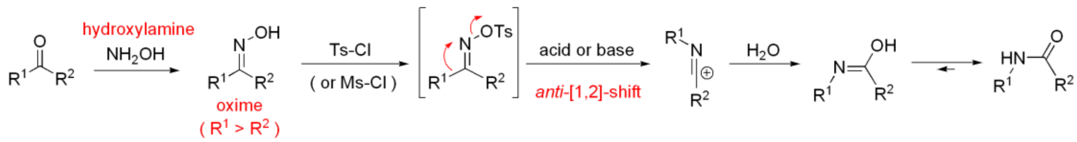
Retrosynthesis:



notes_71

Methodology 11.1: Ring Expansions and Contractions

Beckmann Rearrangement



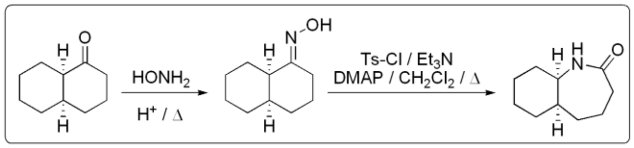
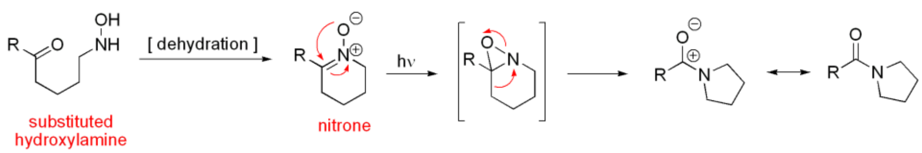
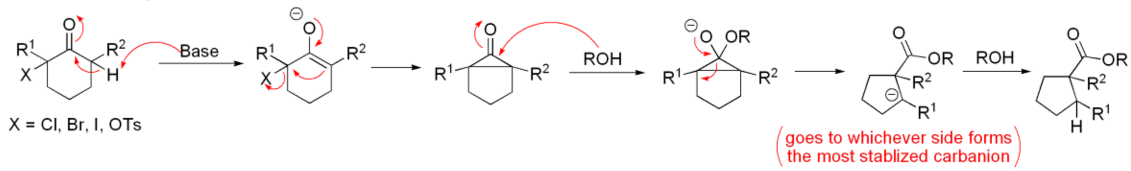


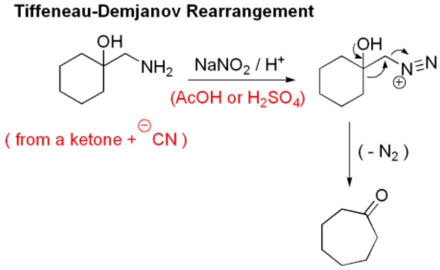
Photo-Beckmann

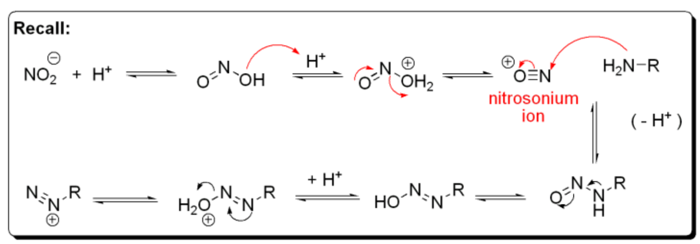


Favorskii Rearrangement

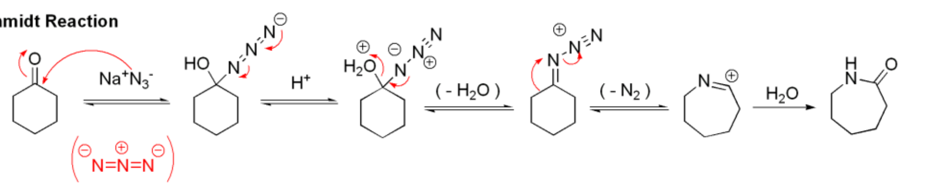


Tiffeneau-Demjanov Rearrangement

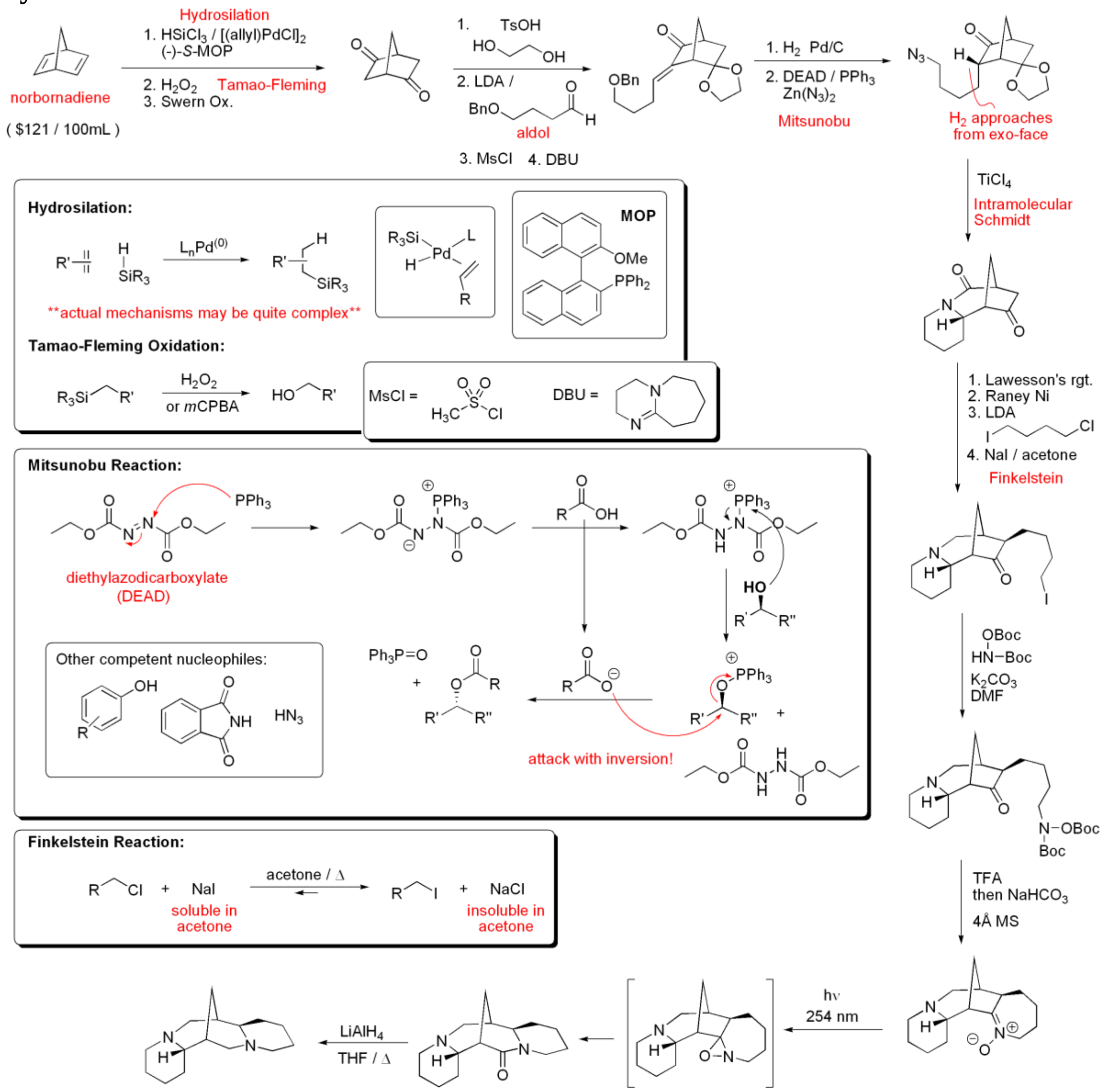




Schmidt Reaction

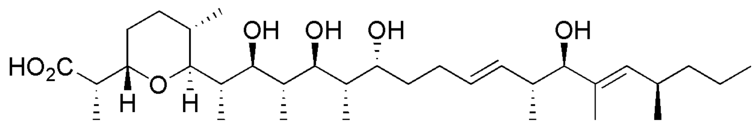


Synthesis:



Hydrosilation
1. HSiCl3 / [(allyl)PdCl]2
(-)-S-MOP
2. H2O2 Tamao-Fleming
3. Swern Ox.
norbornadiene
($121 / 100mL)
1. TsOH
HO OH
2. LDA /
BnO H
aldol
3. MsCl 4. DBU
OBn
1. H2 Pd/C
2. DEAD / PPh3
Zn(N3)2
Mitsunobu
N3
H2 approaches
from exo-face
TiCl4
Intramolecular
Schmidt
Hydrosilation:
LnPd(0)
SiR3
actual mechanisms may be quite complex
MOP
OMe
PPh2
Tamao-Fleming Oxidation:
H2O2
or mCPBA
MsCl =
DBU =
1. Lawesson's rgt.
2. Raney Ni
3. LDA
4. NaI / acetone
Finkelstein
Mitsunobu Reaction:
PPh3
diethylazodicarboxylate
(DEAD)
Other competent nucleophiles:
HN3
Ph3P=O
attack with inversion!
OBoc
HN−Boc
K2CO3
DMF
N−OBoc
Boc
Finkelstein Reaction:
acetone / Δ
NaI
soluble in
acetone
NaCl
insoluble in
acetone
TFA
then NaHCO3
4Å MS
hν
254 nm
LiAlH4
THF / Δ

Synthesis 12: Zincophorin



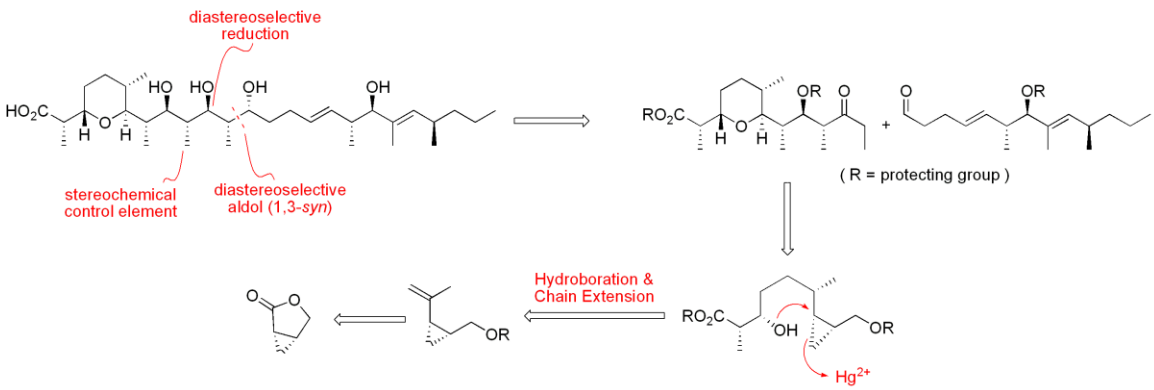
Zincophorin

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

Reactions: notes_74

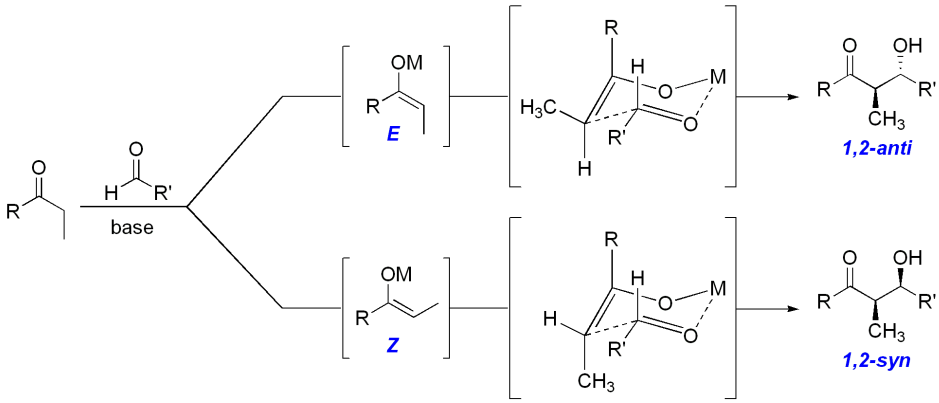
- · Diastereoselective aldol reactions (Review)
- · General discussion of hydroborations
- · General discussion of cyclopropanation strategies
- · Allylations and Crotylations

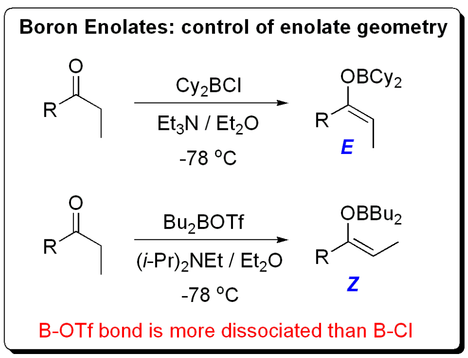
Retrosynthesis:

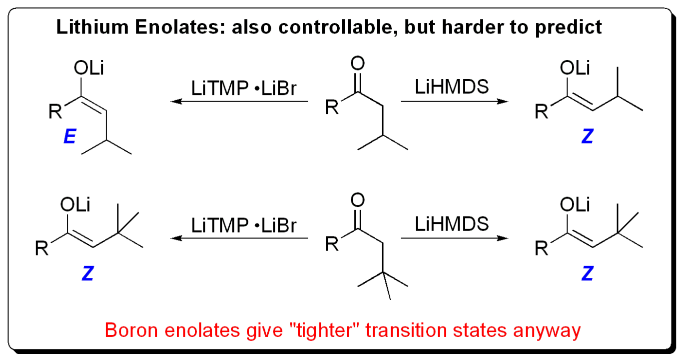


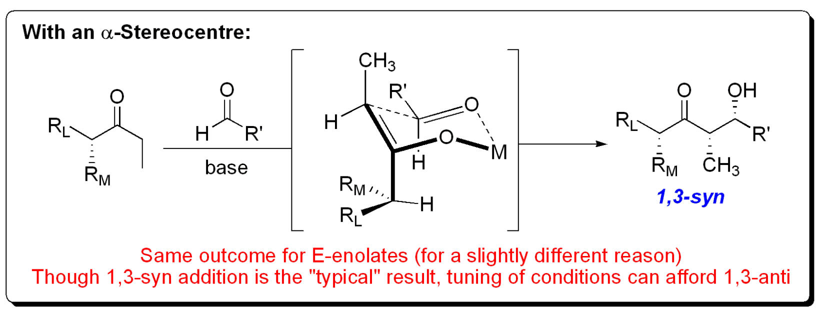
notes_75

Methodology 12.1: Diastereoselective Aldol Reactions

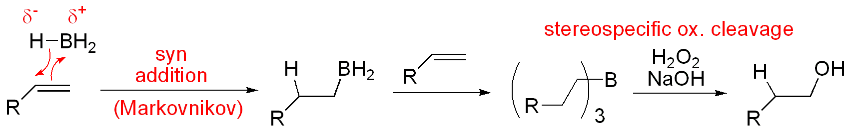








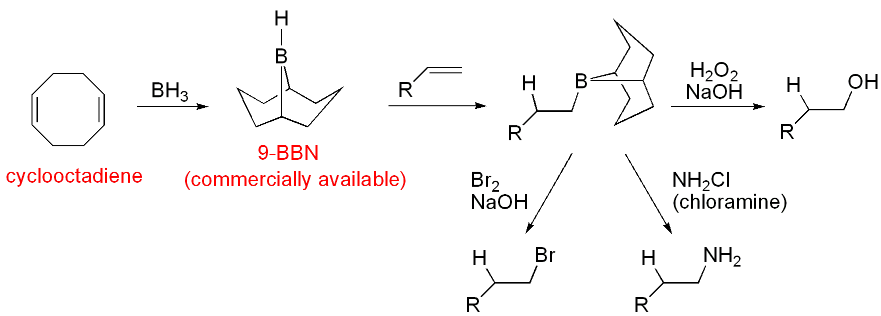
Methodology 12.2: Hydroborations



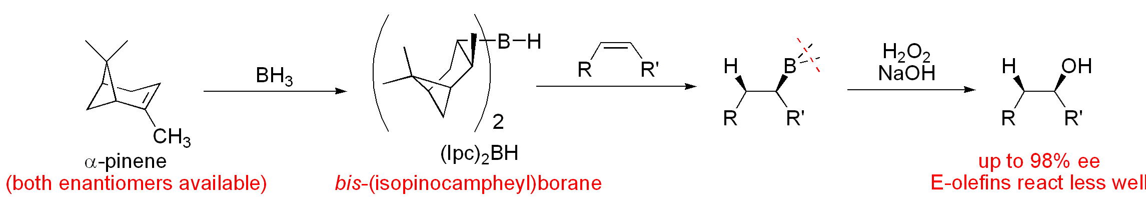
net anti-Markovnikov
addition of water

hydroboration is **complementary**
to direct hydration or oxymurcuration

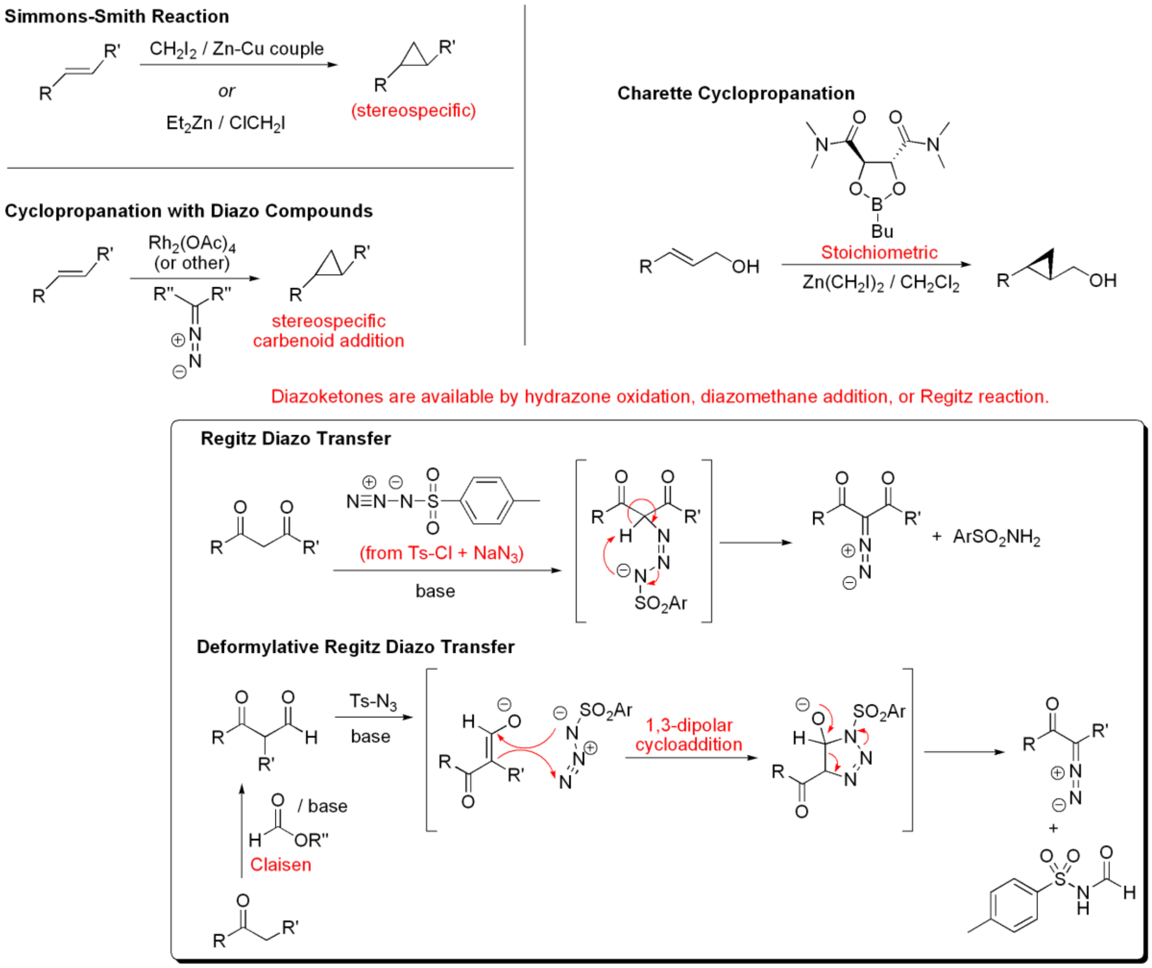
More hindered boranes are more selective



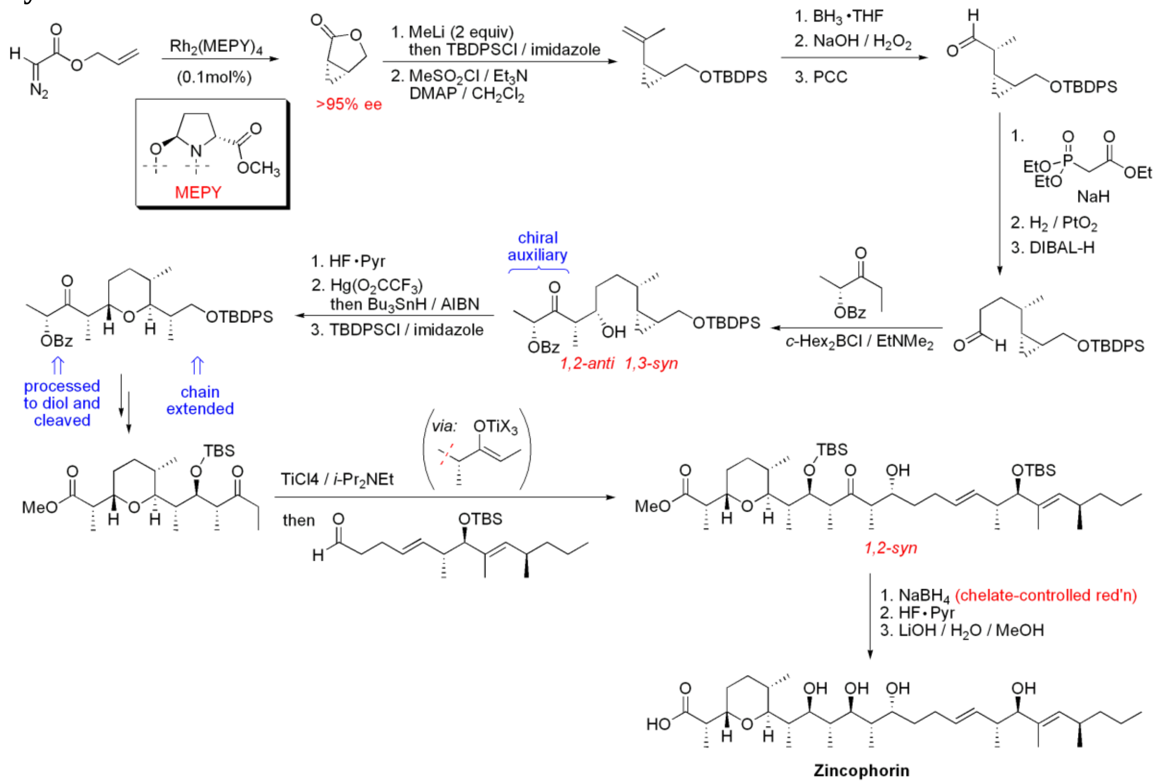
Chiral boranes allow control of enantioselectivity as well as diastereoselectivity and regioselectivity!



Methodology 12.3 Cyclopropanations



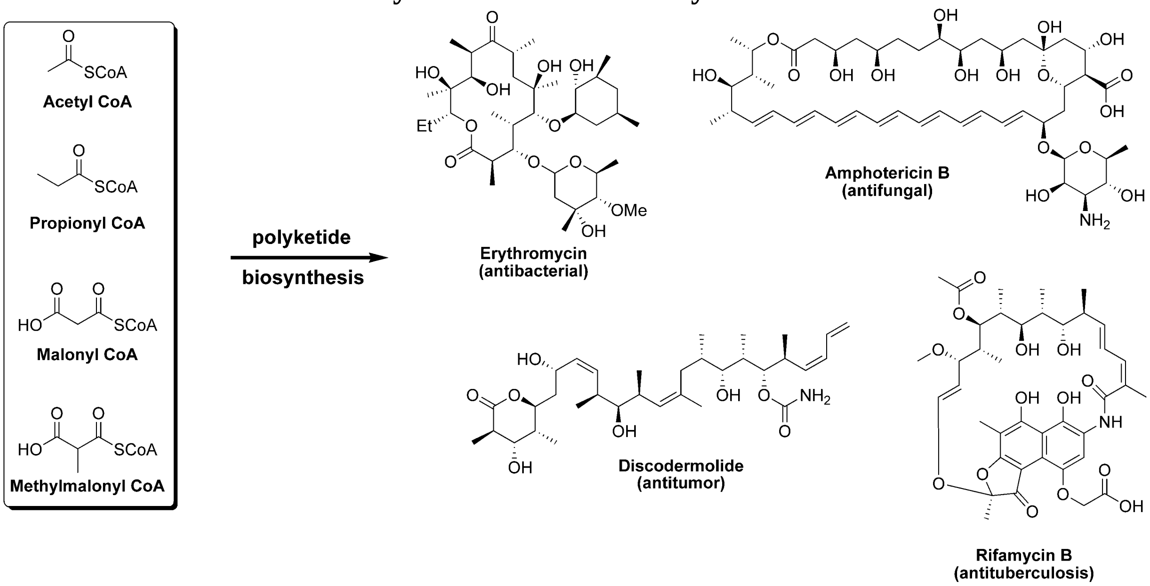
Synthesis:



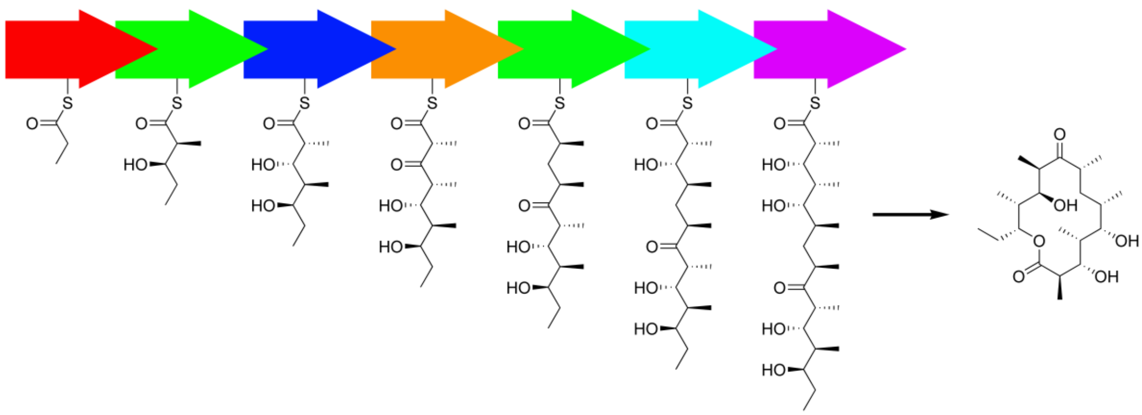
Rh2(MEPY)4
(0.1mol%)
MEPY
>95% ee
1. MeLi (2 equiv)
then TBDPSCl / imidazole
2. MeSO2Cl / Et3N
DMAP / CH2Cl2
OTBDPS
1. BH3•THF
2. NaOH / H2O2
3. PCC
NaH
2. H2 / PtO2
3. DIBAL-H
c-Hex2BCl / EtNMe2
chiral
auxiliary
1,2-anti 1,3-syn
1. HF•Pyr
2. Hg(O2CCF3)
then Bu3SnH / AIBN
3. TBDPSCl / imidazole
processed
to diol and
cleaved
chain
extended
TiCl4 / i-Pr2NEt
via:
then
1,2-syn
1. NaBH4 (chelate-controlled red'n)
2. HF•Pyr
3. LiOH / H2O / MeOH
Zincophorin

Methodology 12.4 Allylations and Crotylations

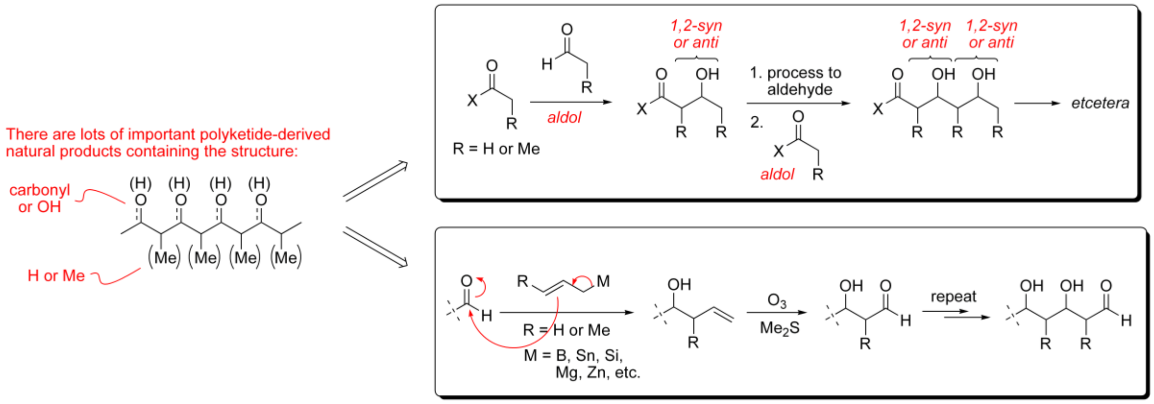
Polyketides & Their Biosynthesis



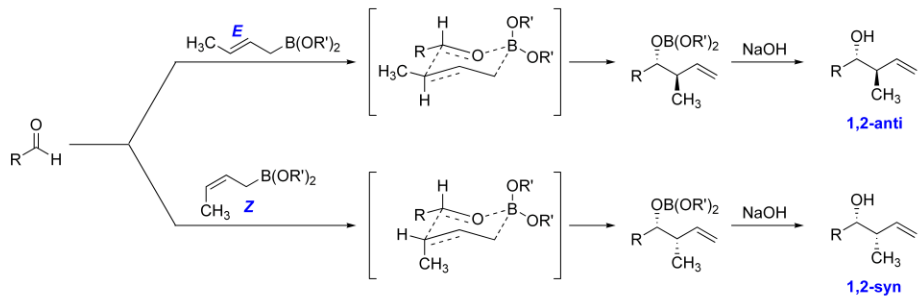
notes_89



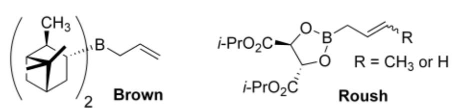
notes_90_ed

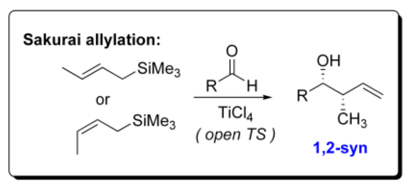


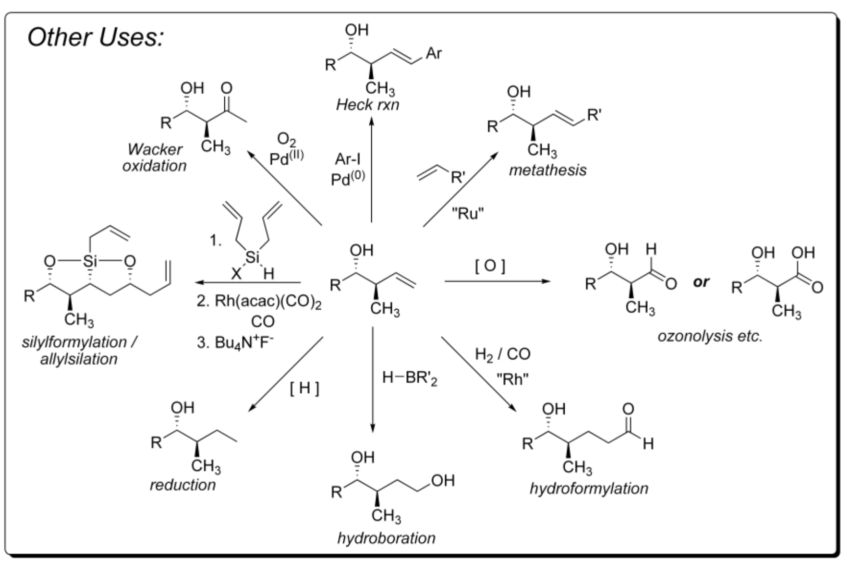
Can control 1,2-relationship (syn, anti)...



... and abolute configuration!







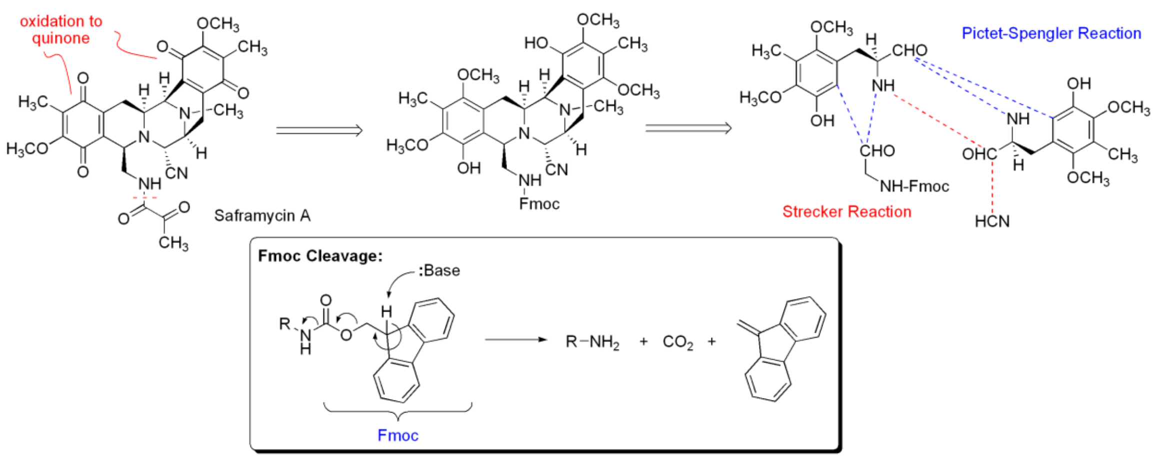
Synthesis 13: Saframycin A

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

Reactions:

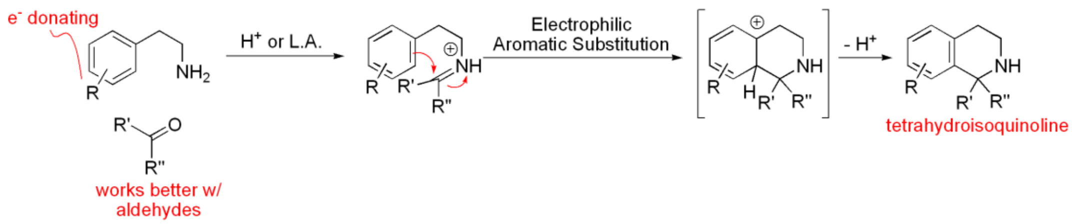
- <u>General discussion of auxiliary-controlled additions:</u>
  - Evans' aldol
  - Carreira aldol
  - Pseudoephedrine glycinamide alkylation
- Pictet-Spengler reaction
- Strecker reaction
- Reductive amination

Retrosynthesis:

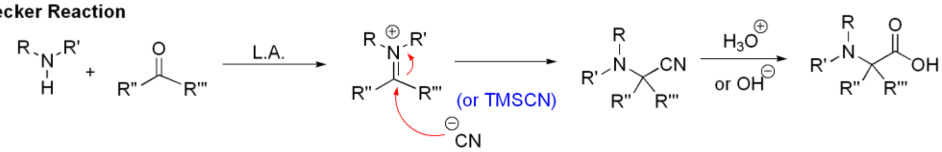


Methodology 13.1: Pictet-Spengler and Strecker Aminations Oxidation to Quinones

Pictet-Spengler Reaction

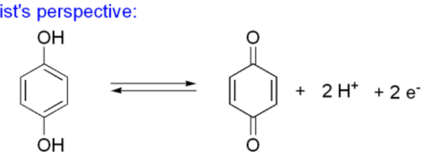


Strecker Reaction



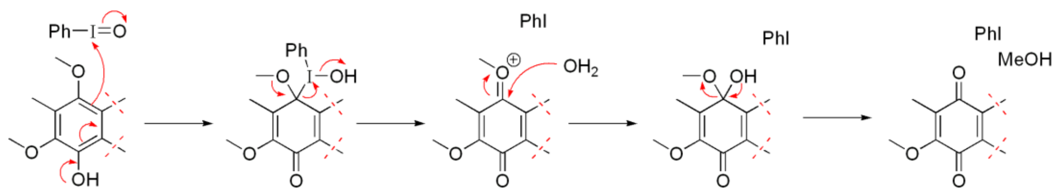
Oxidation to Quinones

The electrochemist's perspective:



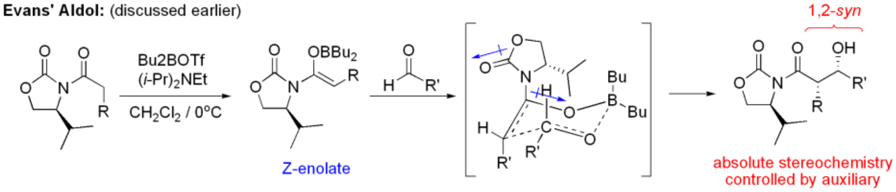
$$PhI^{(+1)}O + 2\,e^- + 2\,H^+ \rightleftharpoons PhI^{(-1)} + 2\,H_2O$$

The organic chemist's perspective:



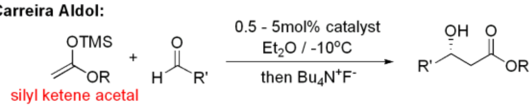
Methodology 13.2 Asymmetric Acylations and Alkylations

Evans' Aldol: (discussed earlier)

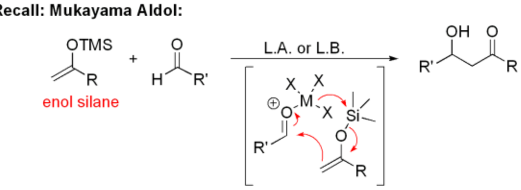


More Modern Asymmetric Aldol Reactions:

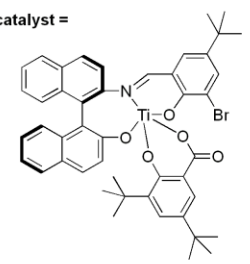
Carreira Aldol:



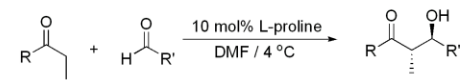
Recall: Mukayama Aldol:

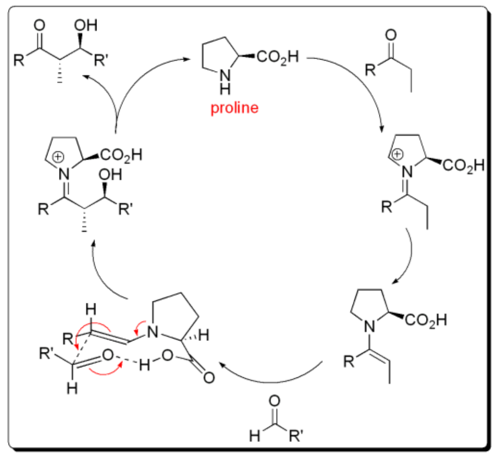


catalyst =

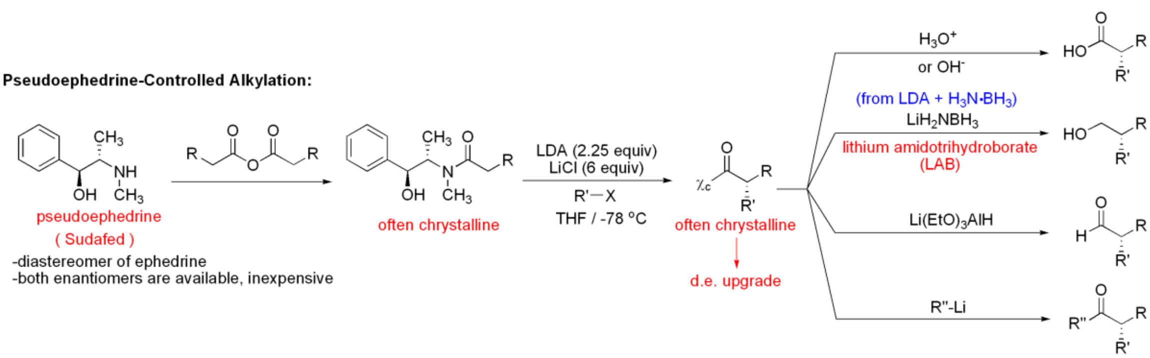


Organocatalytic Aldol:



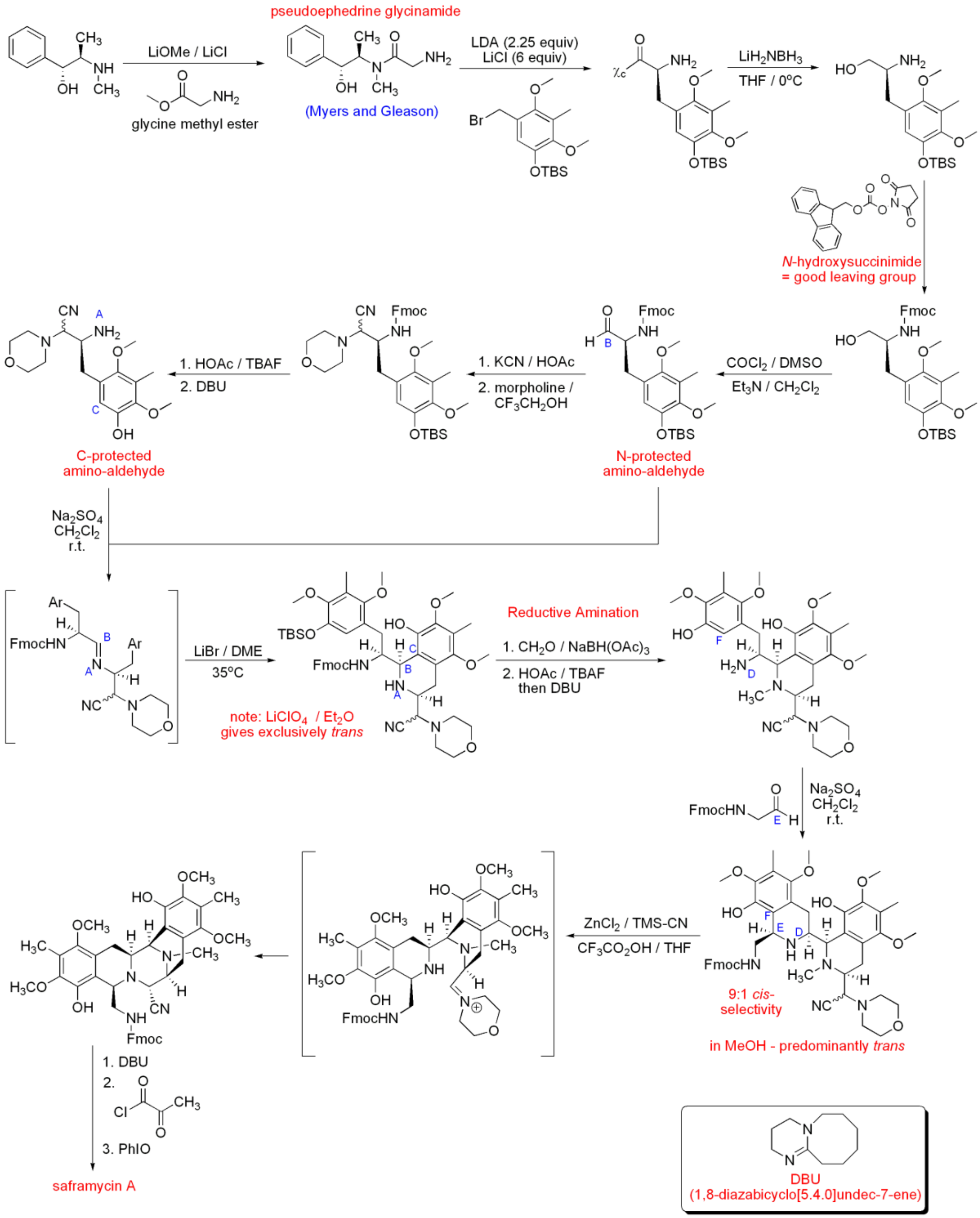


Pseudoephedrine-Controlled Alkylation:



-diastereomer of ephedrine
-both enantiomers are available, inexpensive

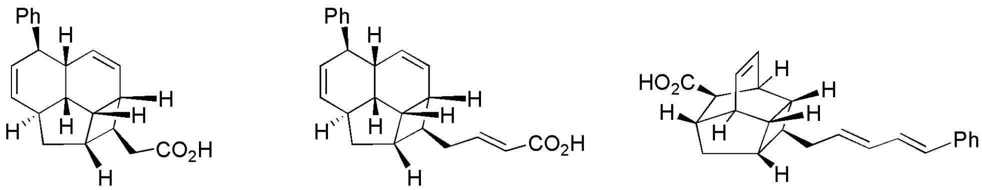
Synthesis:



pseudoephedrine glycinamide
LiOMe / LiCl
glycine methyl ester
(Myers and Gleason)
LDA (2.25 equiv)
LiCl (6 equiv)
OTBS
LiH2NBH3
THF / 0°C
N-hydroxysuccinimide
= good leaving group
COCl2 / DMSO
Et3N / CH2Cl2
N-protected
amino-aldehyde
1. KCN / HOAc
2. morpholine /
CF3CH2OH
1. HOAc / TBAF
2. DBU
C-protected
amino-aldehyde
Na2SO4
CH2Cl2
r.t.
LiBr / DME
35°C
note: LiClO4 / Et2O
gives exclusively trans
Reductive Amination
1. CH2O / NaBH(OAc)3
2. HOAc / TBAF
then DBU
9:1 cis-
selectivity
in MeOH - predominantly trans
ZnCl2 / TMS-CN
CF3CO2OH / THF
1. DBU
2.
3. PhIO
saframycin A
DBU
(1,8-diazabicyclo[5.4.0]undec-7-ene)

Synthesis 14: Endriandric Acids

Nicolaou, 1982
Classics I, 264.



Endriandric Acid A **Endriandric Acid B** **Endriandric Acid C**

· isolated as racemates notes_74

Reactions:

· <u>Electrocyclic Ring-Closing reaction</u>

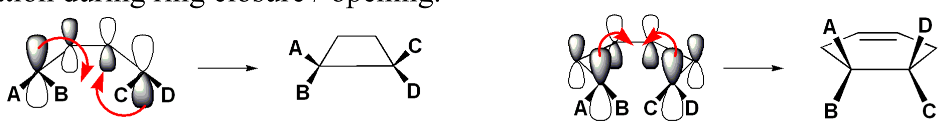
Concepts:

· 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."

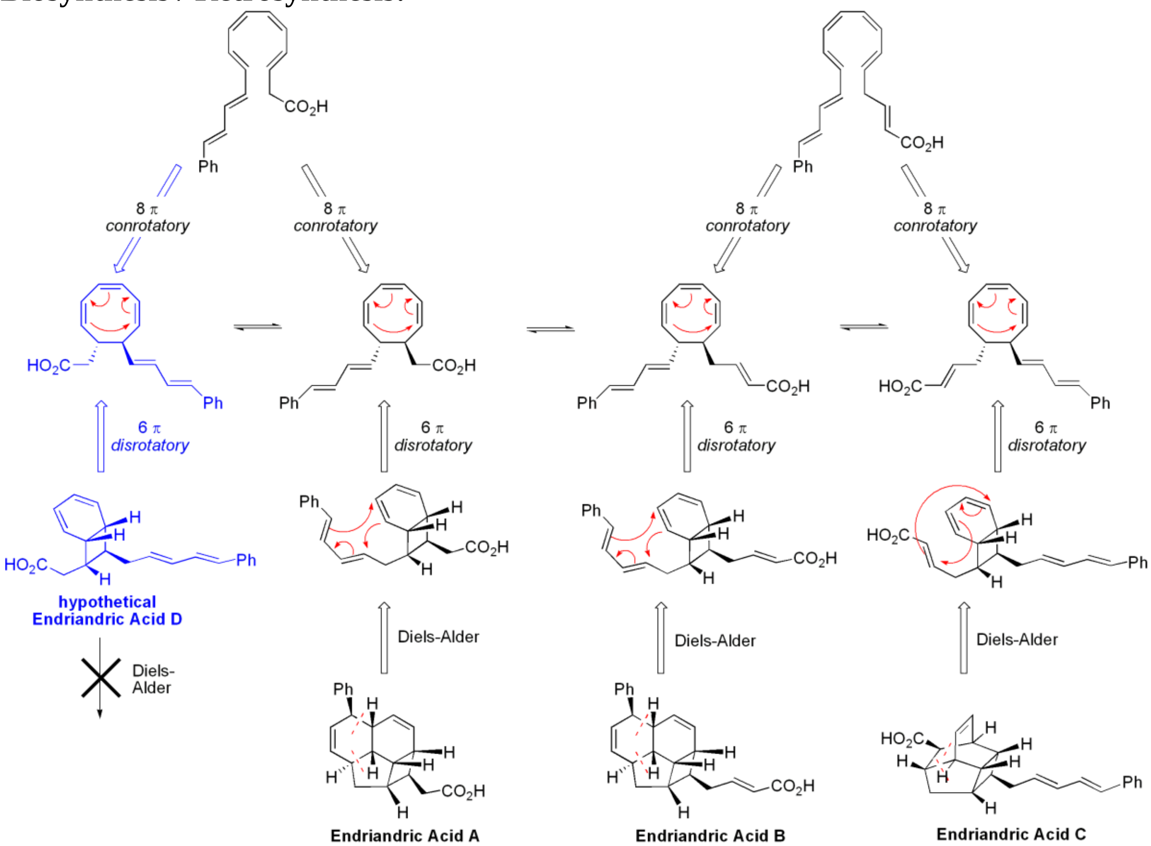
"In an open chain system with 4n+2 electrons, orbital symmetry requires *disrotatory* rotation during ring closure / opening."



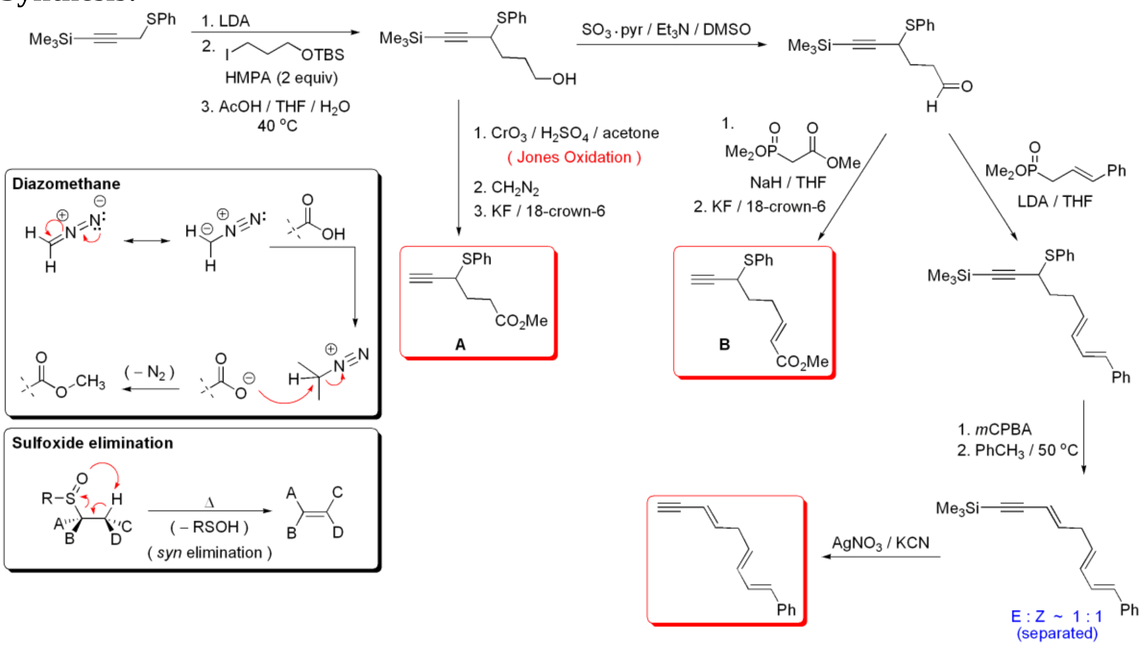
4n electrons : *conrotatory* rotation **4n+2 electrons : *disrotatory* rotation**

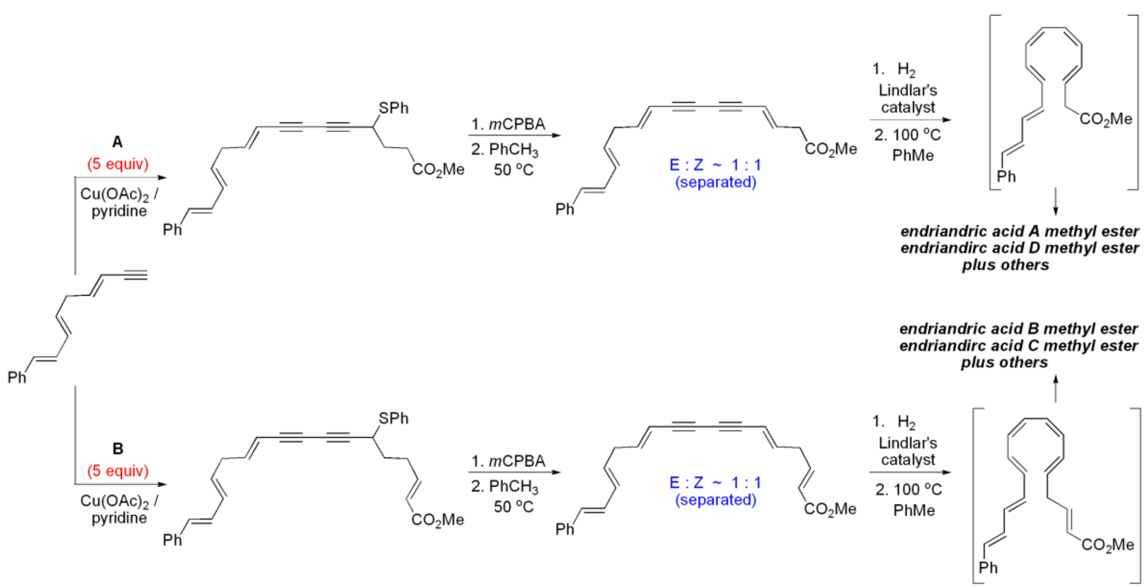
"In an photochemical reaction, the effects are reversed." notes_87

Biosynthesis / Retrosynthesis:



Synthesis:





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

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