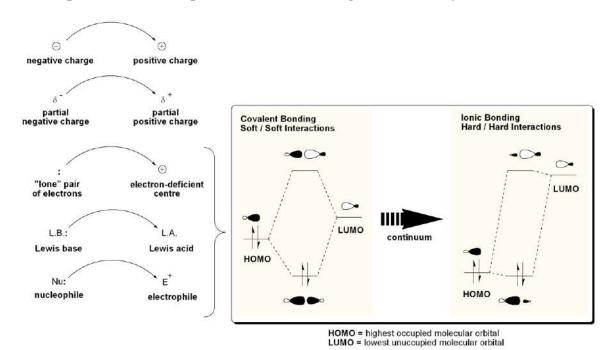
Chemistry 432 – Lecture Notes

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



notes_01

Updated: Spring 2016

Synthesis 1: Strychnine

Woodward, 1954

- Nobel 1965

Classics I, 21

Reactions:

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



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.

- E.J. Corey, Nobel 1990

Retrosynthesis:

Methodology:

1.1 Fischer Indole Synthesis:

- 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:

38 years from 1st to 2nd synthesis! Magnus, 1992 – J.Am. Chem. Soc. 1992, 4403.

Stork, 1992 – lecture (Iscia Porto, Italy).

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

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

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! ...

1st enantioselective synthesis

Synthesis 2: Progesterone

Marker, 1943

Reactions:

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



Concepts:

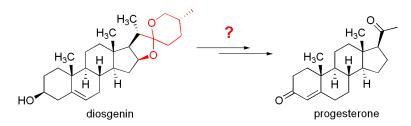
· Semisynthesis

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)

Methodology:

2.1 Oxidative Degradations:

Handout #1: Oxidation

More modern conditions: HIO_4 / MnO_4 (cat.) = Lemieux-Von Rudloff NalO₄ / RuO_4 (cat.)

 $\stackrel{\mathsf{R}}{\longrightarrow} \stackrel{\mathsf{R}^{"}}{\longrightarrow} \stackrel{\mathsf{R}}{\longrightarrow} 0 \quad 0 \stackrel{\mathsf{R}^{"}}{\longrightarrow} 0$

These allow you to stop at the aldehyde:

$$\begin{array}{c}
R \\
R'
\end{array}
\xrightarrow{R}
\xrightarrow{NalO_4/RuO_4 \text{ (cat.)}}
\xrightarrow{R}
\xrightarrow{R}$$

$$0 \quad 0 \stackrel{R}{\rightleftharpoons}$$

Cyclic precursors can be particularly useful:

A plausible mechanism:

$$\begin{array}{c} R \\ O \\ ML_n \\ R' \\ H \end{array} \longrightarrow \begin{array}{c} H \\ R' \\ ML_n \\ R' \\ H \end{array} \longrightarrow \begin{array}{c} H \\ R' \\ ML_n \\ R' \\ ML_n \end{array}$$

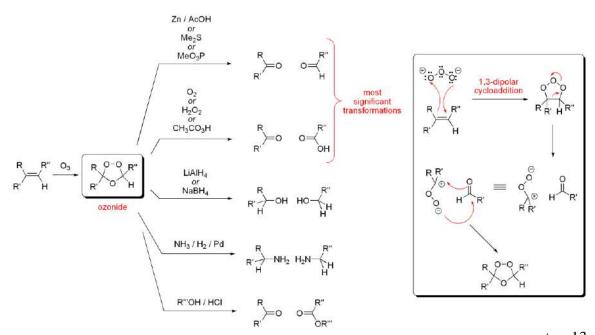
Similarly..

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:



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-Kellog extrusion reaction
- · Asymmetric Diels-Alder reaction
- · Baeyer-Villiger oxidation
- · CBS reduction
- · Iodolactonization

$$HO$$
 H CO_2H HO H HO H $PGF_{2\alpha}$

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

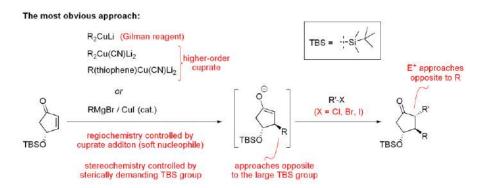
inflammation

sensitivity to pain

constriction / dilation of muscle cells

· PGE₂ and PGF₂ are used to induce childbirth or abortion

Synthetic Strategies:



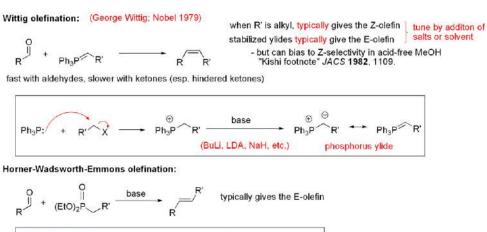
Corey's approach:

notes 15

Retrosynthesis:

Methodology:

3.1 Olefination Reactions:

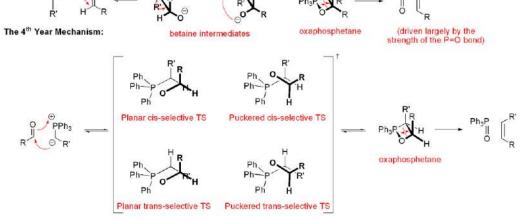


Still-Gennari olefination:

notes_17

Origin of Z-selectivity in Wittig reactions :

The 3rd Year Mechanism:



A concerted - but asynchronous - cycloaddition

Other notable ways to make olefins:



Heteroaryl variants for '1-pot' coupling:

notes_20

Peterson olefination:

separate diastereomers if a mixture



A neat application:

$$\begin{array}{c} R_{2} \\ R_{1} \end{array} \xrightarrow{R_{3}} \begin{array}{c} R_{3} \\ R_{4} \end{array} \xrightarrow{\text{mCPBA}} \begin{array}{c} R_{2} \\ R_{1} \end{array} \xrightarrow{R_{4}} \begin{array}{c} \Theta \\ OH \\ OF \\ H_{3}O \end{array} \xrightarrow{R_{1}} \begin{array}{c} R_{3} \\ R_{1} \end{array} \xrightarrow{R_{4}} \begin{array}{c} HO \\ R_{2} \\ R_{1} \end{array} \xrightarrow{R_{4}} \begin{array}{c} R_{2} \\ R_{3} \end{array} \xrightarrow{R_{4}} \begin{array}{c} R_{4} \\ R_{4} \end{array} \xrightarrow{R_{4}} \begin{array}{c} R_{4} \\ R_{4}$$

notes_21

Barton-Kellog Extrusion Reaction:

(Derek Barton Nobel 1969)

$$R_1$$
 R_2 R_3 R_4 R_5 R_4 R_5 R_5 R_5 R_6 R_7 R_8 Useful for the preparation of extremely hindered olefins.

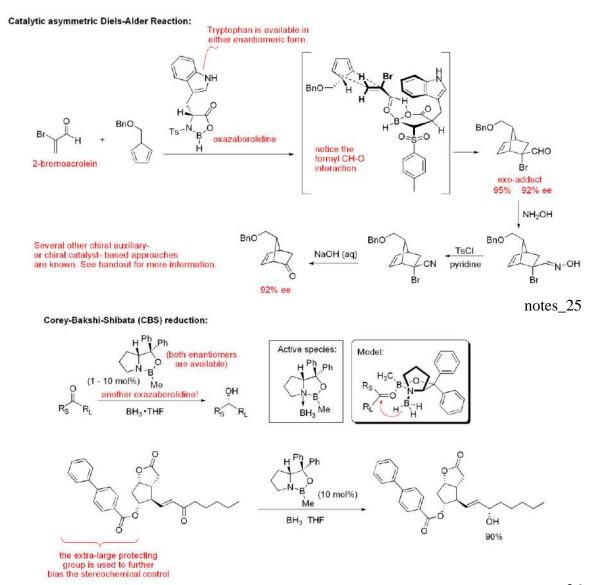
Synthesis:

Problems with the synthesis:

- racemic
- Zn(BH₃)₄ reaction

Methodology 3.2:

- Catalytic, asymmetric Diels-Alder reaction
- 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:

notes 27

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

Retrosynthesis:

$$\begin{array}{c} O \\ O \\ CH_3 \\ \hline \\ Deriplanone B \end{array} \begin{array}{c} O \\ O \\ CH_3 \\ \hline \\ PGO \end{array} \begin{array}{c} O \\ CH_3 \\ \hline \\ PGO \end{array} \begin{array}{c} O \\ CH_3 \\ \hline \\ PGO \end{array} \begin{array}{c} O \\ CH_3 \\ \hline \\ PGO \end{array} \begin{array}{c} O \\ CH_3 \\ \hline \\ PGO \end{array} \begin{array}{c} O \\ CH_3 \\ \hline \\ PGO \end{array}$$

notes_28

Methodology:

4.1 Cope-type reactions:

3,3-Sigmatropic Rearrangments

Stereochemical Consequences:

Synthesis:

notes_30

Section 5: Palladium-Mediated Coupling Strategies

Reactions:

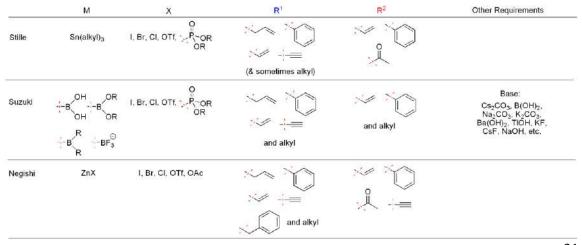
- · General discussion of:
 - · Stille coupling
 - · Heck coupling
 - · Suzuki coupling
 - · Sonogashira coupling
 - · Negishi coupling
 - · Tsuji-Trost coupling
 - · Pd- Pt- & Au-mediated cycloisomerizations

Concepts:

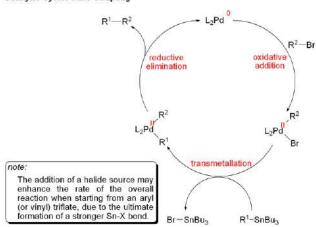
- · Catalytic cycles oxidative addition, reductive elimination, etc.
- · Increased synthetic efficiency using organometallic coupling strategies.

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

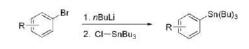
$$R^1-M + R^2-X \xrightarrow{Pd^{(0)} \text{ (catalytic)}} R^1-R^2$$



Catalytic Cycle: Stille Coupling

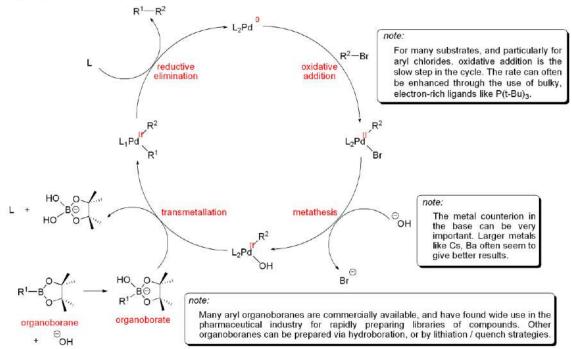


$notes_31$ Formation of alkyl stannanes:



$$R \xrightarrow{l'} \stackrel{\text{Br}}{\longrightarrow} \frac{(Bu)_3 Sn - Sn(Bu)_3}{Pd(PPh_3)_4} \qquad R \xrightarrow{l'} \stackrel{\text{Sn}(Bu)_3}{\longrightarrow}$$

Catalytic Cycle: Suzuki Coupling



notes_32

Some useful methods for the formation of organoboranes:

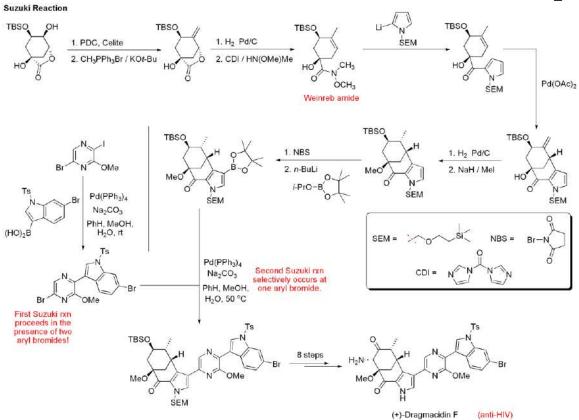
Synthesis 5.1. Some illustrative syntheses:

Stille Reaction

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

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

notes_35



Methodology 5.2. The Heck reaction:

base
$$\cdot$$
 HX

$$L_2Pd$$

$$R^2 - X$$

oxidative addition
$$L_2Pd$$

$$R^2 - X$$

oxidative addition
$$L_2Pd$$

$$R^2 - X$$

oxidative addition
$$R^2 - X$$

coordination
$$R^2 - X$$

$$L_2Pd$$

$$R^2 - X$$

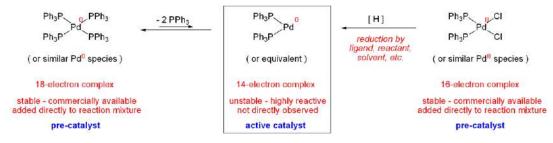
oxidative addition
$$R^2 - X$$

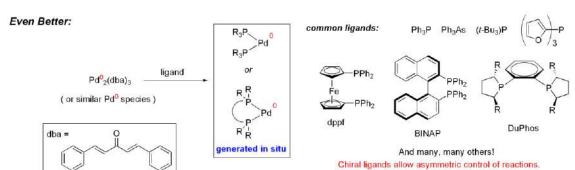
$$R^2 - X$$

o

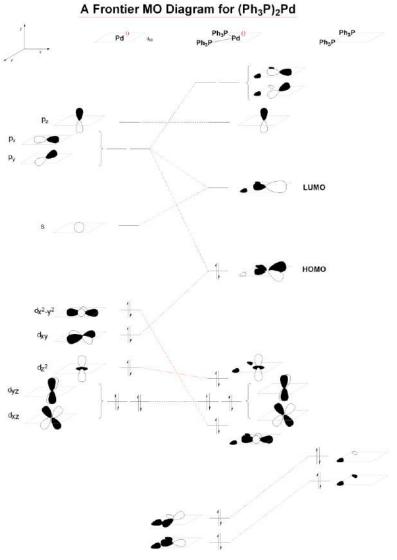
On the nature of " L₂Pd⁰ "

Typical Formation:





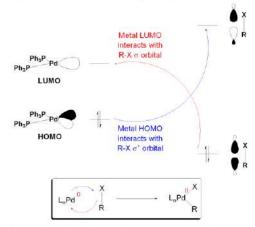
A closer look at what those curved arrows are doing:



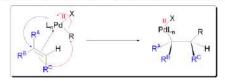
notes_38b

What You Need to Remember

Somewhere in the $(Ph_3P)_2Pd^0$ 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) .



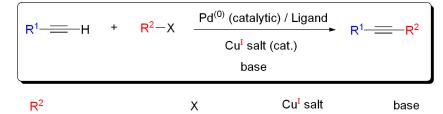
Something similar happens in the case of the subsequent addition of the olefin.

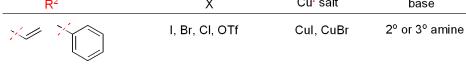


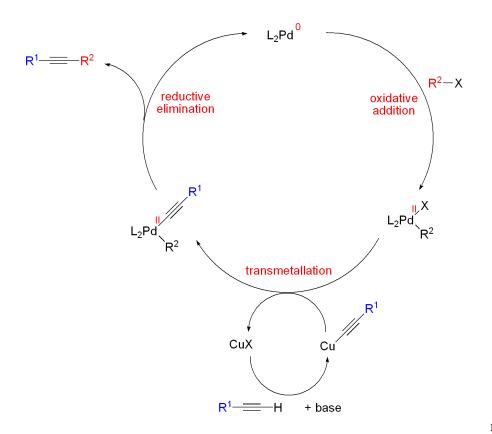
For arrow-pushing purposes, the Pd acts simultaneously as a nucleophile and an electrophile.

An example of an asymmetric "double" Heck reaction

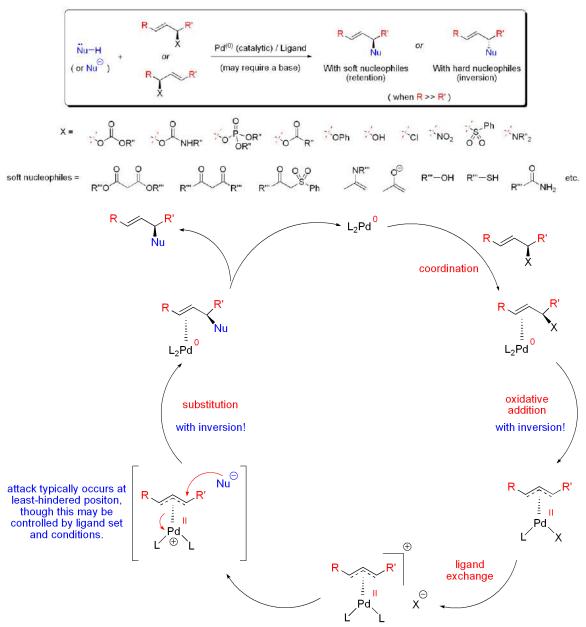
Methodology 5.3. Sonogashira coupling:







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.

Reactions:

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

notes_45

Concepts:

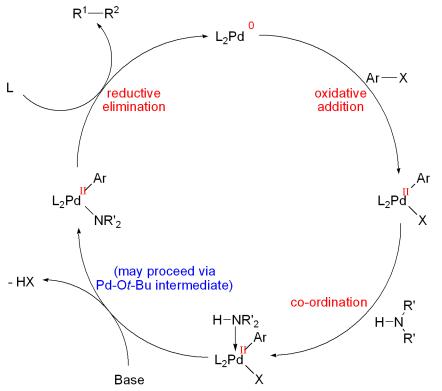
- · Desymmetrization
- · Stereodivergent synthesis

Methodology:

6.1 Buchwald-Hartwig coupling:

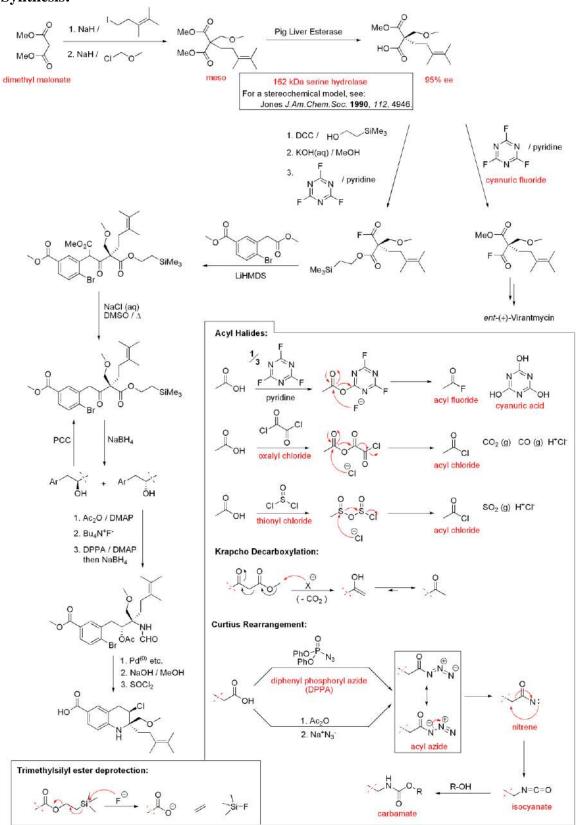
(Ligand = BINAP, DPPF, etc.) Base = NaOt-Bu, LHMDS, K $_2$ CO $_3$, Cs $_2$ CO $_3$

Catalytic Cycle:



 $notes_48$

Synthesis:



notes_46

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

(+)-8-epi-xanthatin

notes_50

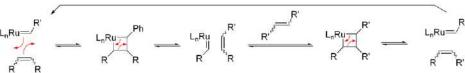
Retrosynthesis:

Methodology:

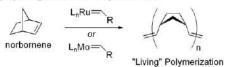
7.1 Olefin Metathesis: (Nobel 2005)



General Mechanism:



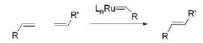
Ring-Opening Metathesis Polymerization:



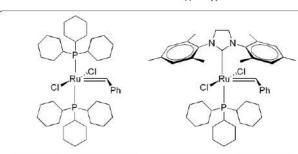
Ring-Closing Metathesis:



Cross Metathesis:



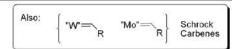
see: Grubbs J.Am.Chem.Soc. 2003, 125, 11360.



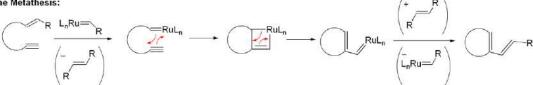
Grubbs' 1st_Generation Catalyst

Grubbs' 2nd-Generation Catalyst

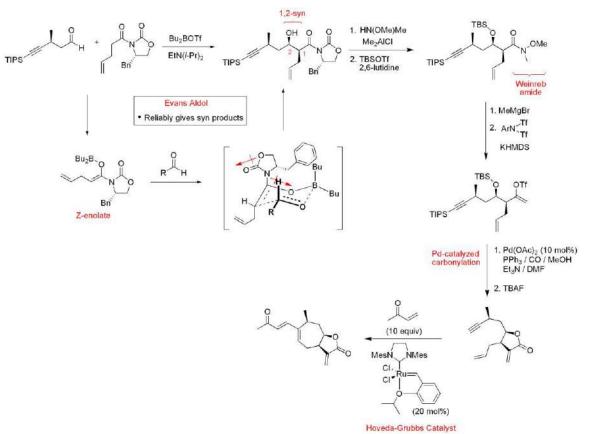
 Grubbs' catalysts are generally tolerant of oxygenand nitrogen-functionality - but not acids.



Enyne Metathesis:



Synthesis:



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

Concepts:

· Synthetic planning

Retrosynthesis:

notes_62

notes_62

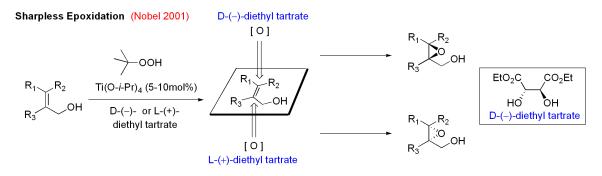
N1999A2

(a 9-membered enediyne)

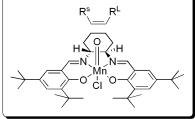
Bergman Rearrangment:

Mechanism of DNA Cleavage:

Methodology 8.1: Asymmetric Epoxidation



Jacobsen-Katsuki Epoxidation

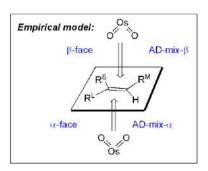


Shi Epoxidation

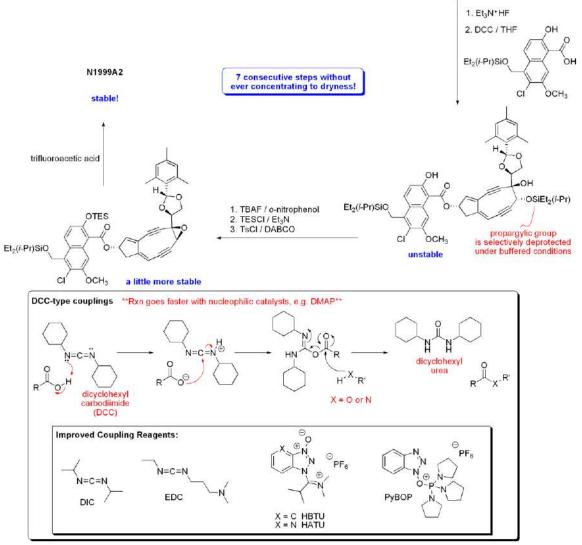
0 R² R³

Methodology 8.2: Asymmetric Dihydroxylation

Sharpless Dihydroxylation (Nobel 2001)



Synthesis:



Synthetic Planning (revisited):

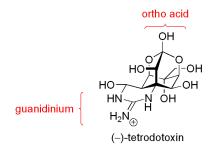
Alternative Retrosynthesis:

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



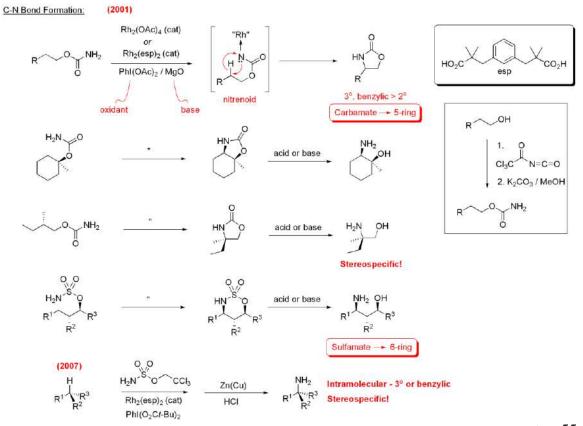
notes_53

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

Retrosynthesis:

Methodology 9.1: C-H insertion reactions

(Justin Du Bois, Stanford)



Synthesis:

Synthesis 10: Hirstutene

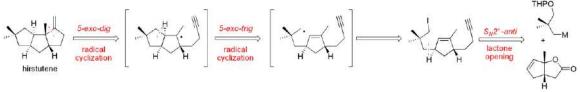
Curran, 1986 Classics I, 382

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

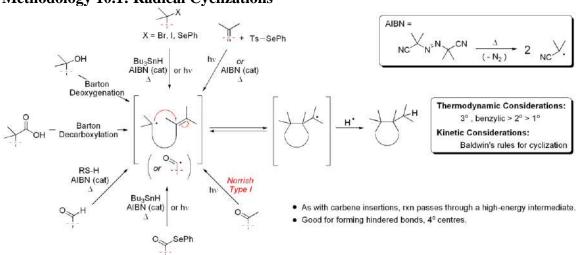


notes_58

hirstutene

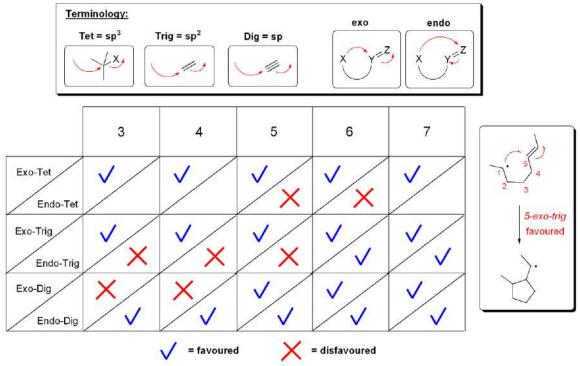
notes_57

Methodology 10.1: Radical Cyclizations



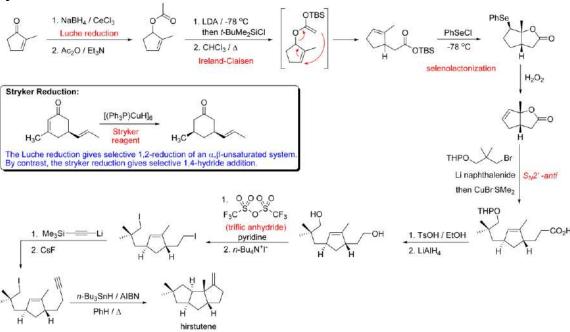
Baldwin's Rules for Cyclization

(applies to 1- and 2-electron processes)



notes_60

Synthesis:



Methodology 10.2: Radical Deoxygenations & Decarboxylations

Barton-McCombie Deoxygenation:

Tin-Free Variant:

Diazene-Mediated Deoxygenation:

Synthesis 11: ent-Sparteine

Aubé, 2002

Org. Lett. 2002, 4, 2577.

(-)-sparteine
useful ligand for asymmetric catalysis

H
(+)-sparteine
hard to get

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

Reactions:

- · General discussion of ring expansions and contractions:
- notes_70

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

Retrosynthesis:

Methodology 11.1: Ring Expansions and Contractions

Beckmann Rearrangement

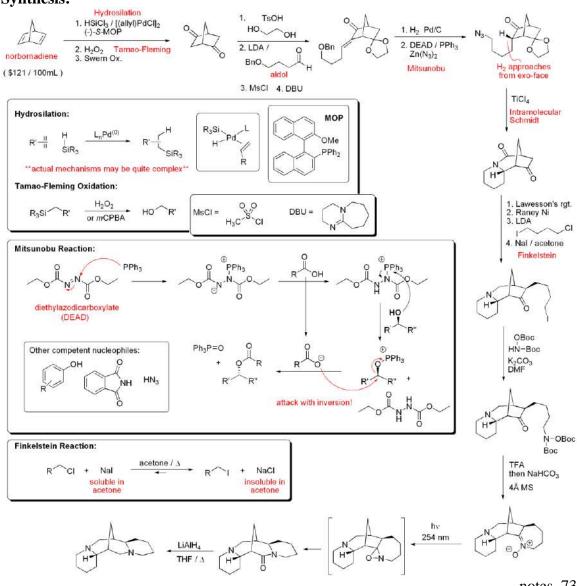
Photo-Beckmann

Favorskii Rearrangement

Tiffeneau-Demjanov Rearrangement

$$(\text{from a ketone} + \overset{\bigcirc}{\text{CN}}) \\ \begin{pmatrix} \text{N} \\ \text{N} \\ \text{N} \\ \text{O} \end{pmatrix} & \begin{pmatrix} \text{N} \\ \text{O} \\ \text{N} \end{pmatrix} & \begin{pmatrix} \text{N} \\ \text{O} \\ \text{O} \end{pmatrix} & \begin{pmatrix} \text{N} \\ \text{O} \end{pmatrix} & \begin{pmatrix} \text{N} \\ \text{O} \\ \text{O} \end{pmatrix} & \begin{pmatrix} \text{N} \\ \text{O} \end{pmatrix} & \begin{pmatrix} \text{$$

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
- · Allylations and Crotylations

Retrosynthesis:

Methodology 12.1: Diastereoselective Aldol Reactions

$$\begin{array}{c} O \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ R \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ C \\ \end{array}$$

$$\begin{array}{c} O \\ C \\ C \\ C \\ C \\ C \\ C \\ \end{array}$$

Boron Enolates: control of enolate geometry

$$\begin{array}{c|c} & Cy_2BCI & OBCy_2 \\ \hline Et_3N / Et_2O & E \\ \hline \\ O & Bu_2BOTf & OBBu_2 \\ \hline \\ B & & & & \\ \end{array}$$

B-OTf bond is more dissociated than B-CI

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

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

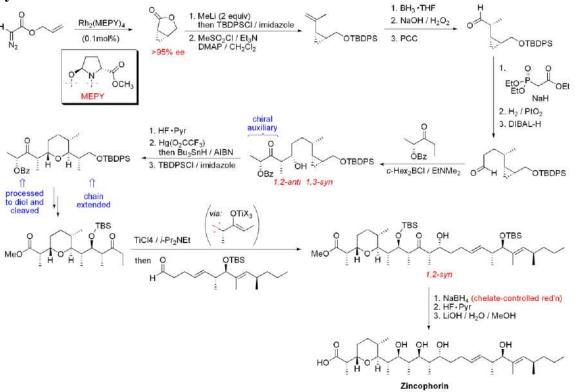
Simmons-Smith Reaction

Cyclopropanation with Diazo Compounds

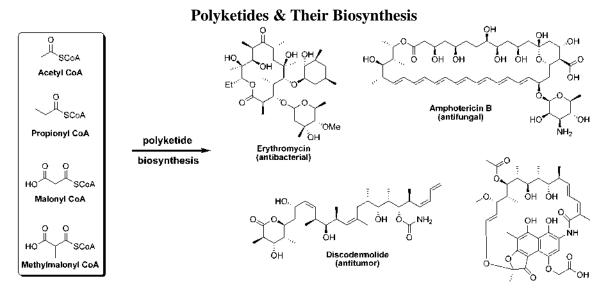
Charette Cyclopropanation

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

Synthesis:



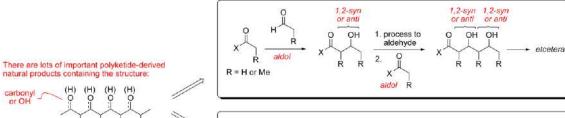
Methodology 12.4 Allylations and Crotylations



Rifamycin B (antituberculosis)

notes_89

notes_90_ed



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

H or Me ¬

$$\begin{array}{c} H_3C \stackrel{E}{\longleftarrow} B(OR')_2 \\ R \stackrel{H}{\longrightarrow} H \\ \\ \hline \\ CH_3 \stackrel{B}{\longrightarrow} DR' \\ \hline \\ CH_3 \stackrel{B}{\longrightarrow} DR' \\ \hline \\ CH_3 \stackrel{OB(OR')_2}{\longrightarrow} NaOH \\ \hline$$

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:

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

Pictet-Spengler Reaction

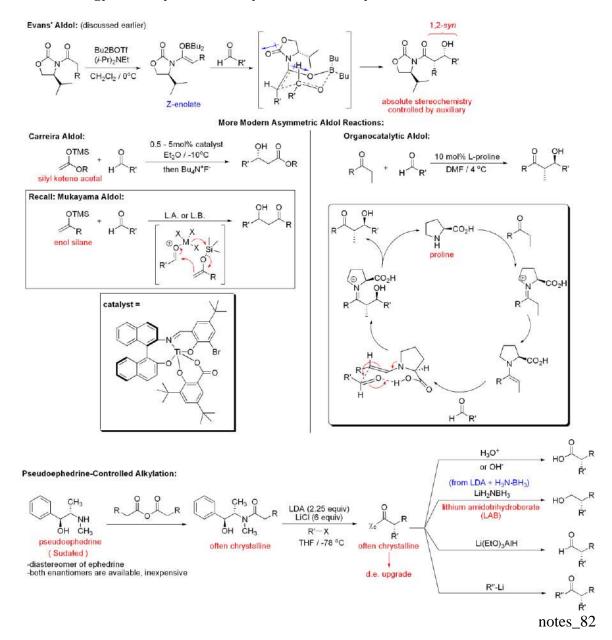
Strecker Reaction

Oxidation to Quinones

The electrochemist's perspective:

The organic chemist's perspective:

Methodology 13.2 Asymmetric Acylations and Alkylations



Synthesis:

Synthesis 14: Endriandric Acids

Nicolaou, 1982 Classics I, 264.

Endriandric Acid C

Endriandric Acid A

Endriandric Acid B · isolated as racemates

notes_74

Reactions:

· Electrocyclic Ring-Closing reaction

Concepts:

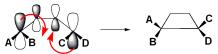
· Woodward-Hoffmann rules

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."



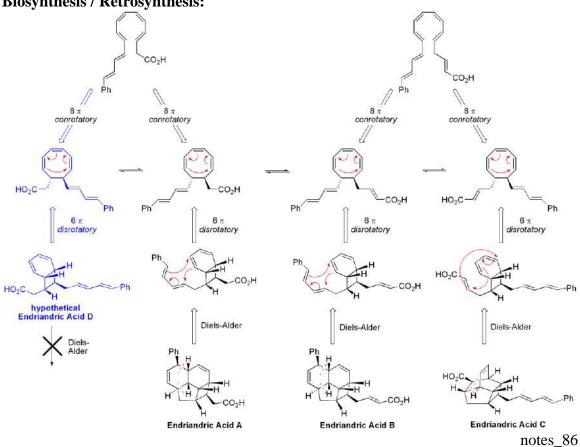


4n electrons : conrotatory rotation

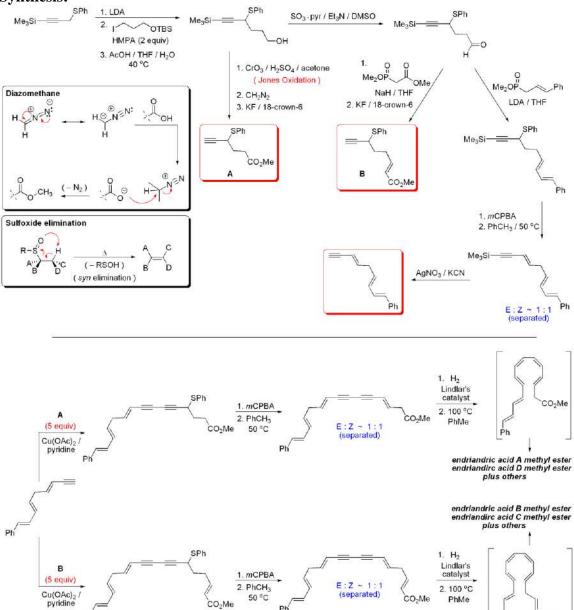
4n+2 electrons : disrotatory rotation

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

Biosynthesis / Retrosynthesis:







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.

CO₂Me

CO₂Me