

Tapio Nevalainen
Drug Synthesis II
2012

Selected organic reactions



UNIVERSITY OF
EASTERN FINLAND

C-C Bond Forming Reactions

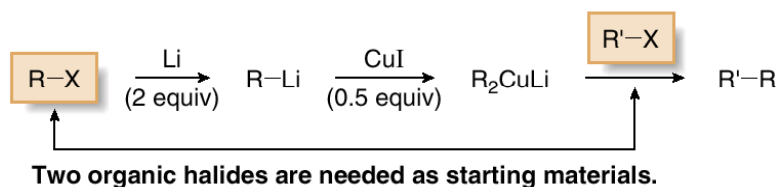
- Coupling Reactions of Organocuprates (also known as Gilman reagents):
 - Organocuprate reagents react a variety of functional compounds including acid chlorides, epoxides and α,β -unsaturated carbonyl compounds.
 - Organocuprate reagents also react with organic halides $R'-X$ to form coupling products $R-R'$ that contain a new C–C bond.
 - Only one R group of the organocuprate is transferred to form the product, while the other becomes part of the RCu , a reaction product.

General reaction



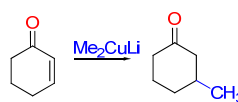
Coupling Reactions of Organocuprates

- Since organocuprate reagents are prepared in two steps from alkyl halides (RX), this method ultimately converts two organic halides (RX and R'X) into a hydrocarbon R–R' with a new carbon–carbon bond.
- Note that this means that using this methodology, a given hydrocarbon can often be made by two different routes.

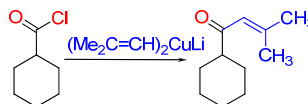


Organocuprate reagents react a variety of functional compounds

- Regiospecific 1,4-addition to α,β -unsaturated carbonyl compounds



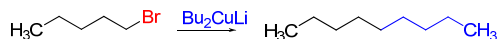
- Li organocuprates form ketones with acid halides



- With epoxides R_2CuLi forms alcohols

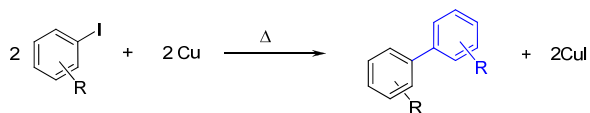


- Organocuprates react with alkyl, alkenyl, and aryl bromides and iodides.



Cross-coupling reactions

- Coupling reaction between aryl halides with copper (Ullmann reaction)



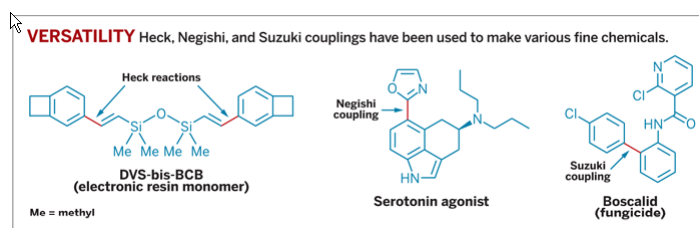
Ullman and Bielecki, Ber., 34, 2174 (1901)

- The Ullmann reaction is limited to electron deficient aryl halides and requires harsh reaction conditions. Reaction is replaced by palladium coupling reactions such as the Suzuki, Heck, Stille, Sonogashira reactions.



Cross-coupling reactions

- Akira Suzuki, Ei-ichi Negishi and Richard Heck share the Nobel Prize in Chemistry 2010 for *palladium-catalyzed cross couplings in organic synthesis*

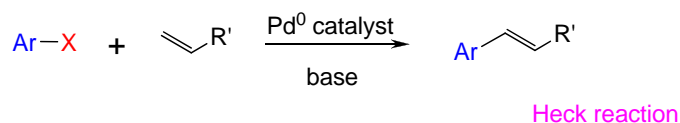
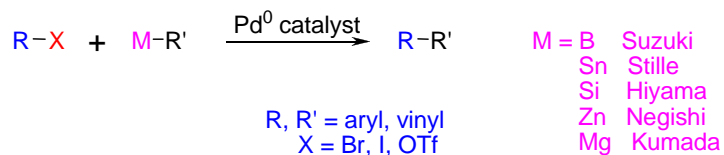


More information:

http://static.nobelprize.org/nobel_prizes/chemistry/laureates/2010/Sciback_2010.pdf

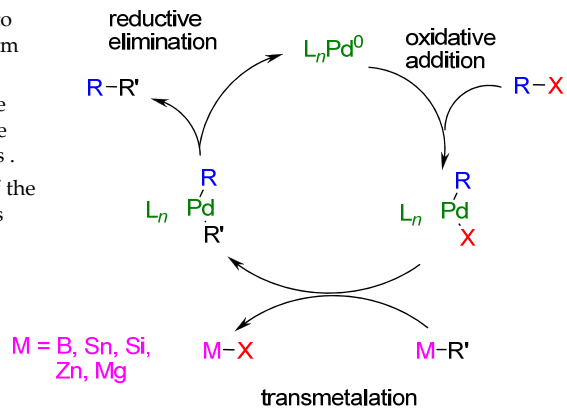


Palladium-Catalyzed Coupling Reactions



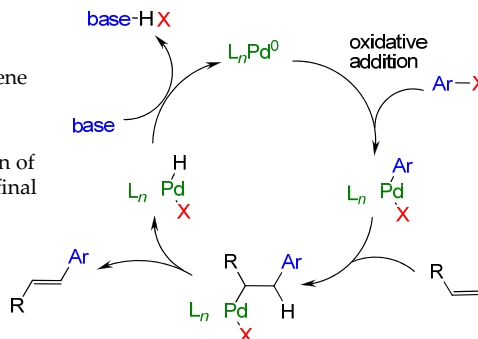
Generalized mechanism for palladium-catalyzed cross coupling reactions

- The first step is the oxidative addition of palladium to the halide to form the organopalladium species.
- Transmetalation with the metal complex forms the organopalladium species.
- Reductive elimination of the desired product restores the original palladium catalyst.



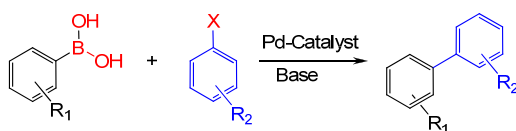
Mechanism of the Heck reaction

- First step is an oxidative addition in which palladium inserts itself in the aryl to halogen bond.
- Palladium then forms a π complex with the alkene and the alkene inserts itself in the palladium - carbon bond in a syn addition step.
- After internal rotation palladium complex liberates the trans-vinyl arene product via β -hydride elimination.
- The palladium(0) compound is regenerated by reductive elimination of the palladium(II) compound in the final step.



Palladium coupling reactions: Suzuki Coupling

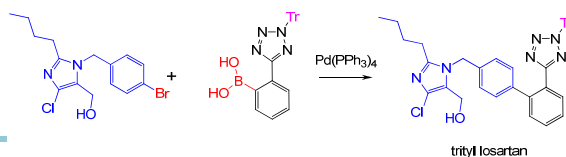
- **Palladium-catalysed cross coupling between organoboronic acid and halides**



N. Miyaura et al., Tetrahedron Letters 1979, 3437;
N. Miyaura, A. Suzuki, Chem. Commun. 1979, 866.

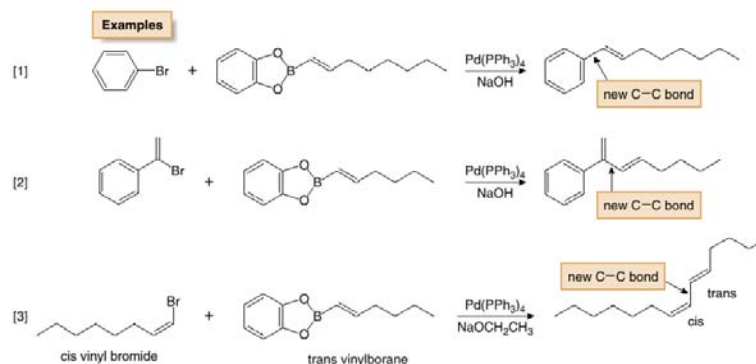
- **Alkyls, alkenyls and alkynyls can also be used as a reaction partners . Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Triflates ($CF_3SO_3^-$) may also be used as coupling partners.**

- **Example: Synthesis of losartan (*J. Org. Chem.* 1994,59, 8151-8156)**



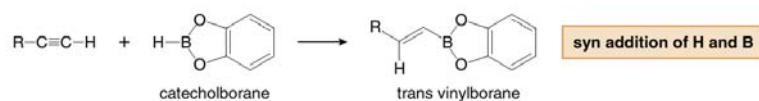
The Suzuki Reaction:

- The Suzuki reaction is completely stereospecific

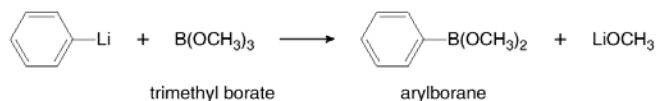


The Suzuki Reaction: The boranes

- Vinylboranes**, which have a boron atom bonded to a carbon-carbon double bond, are prepared by hydroboration using catecholborane, a commercially available reagent.

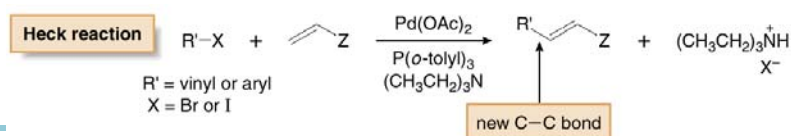


- Arylboranes**, which have a boron atom bonded to a benzene ring, are prepared from organolithium reagents by reaction with trimethyl borate $[\text{B}(\text{OCH}_3)_3]$



The Heck Reaction:

- The Heck reaction is a Pd-catalyzed coupling of a vinyl or aryl halide with an alkene to form a more highly substituted alkene with a new C–C bond.
- Palladium(II) acetate [Pd(OAc)₂] in the presence of a triarylphosphine [P(*o*-tolyl)₃] is the typical catalyst.
- The reaction is carried out in the presence of a base such as triethylamine.
- The Heck reaction is a substitution in which one H atom of the alkene starting material is replaced by the R' group of the vinyl or aryl halide.

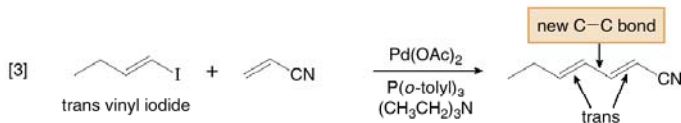
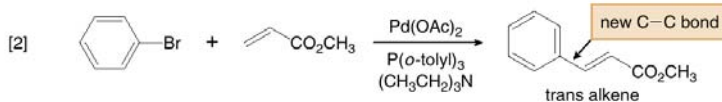
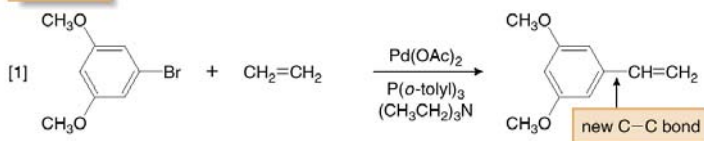


UNIVERSITY OF
EASTERN FINLAND

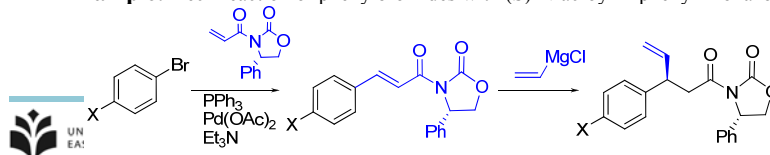
Esityksen nimi / Tekijä 14.2.2012 13

Heck reaction

Examples



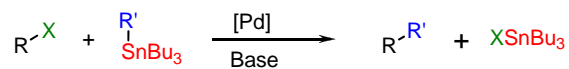
- **Example:** Heck reaction of phenylbromides with (S)-N-acroyl-4-phenyl-2-oxazolidinone



J. Med. Chem., 48 (12), 3945–3948, 2005

Stille Coupling

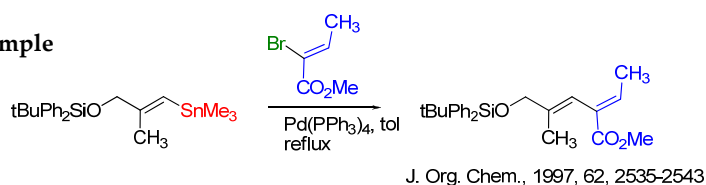
- C-C bond forming reaction between stannanes and halides or pseudohalides, with very few limitations on the R-groups



[Pd] = Pd(PPh₃)₄, PhCH₂(PPh₃)₂Cl
 R1 = alkynyl, alkenyl, aryl, allyl, benzyl, alkyl, acyl
 R2 = alkenyl, allyl, benzyl, aryl, alkynyl
 X = Cl, Br, I, OAc, OSO₂CF₃

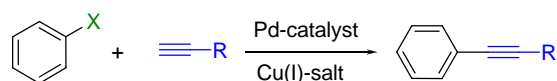
J. Am. Chem. Soc., 1984, 106, 4630.

• Example

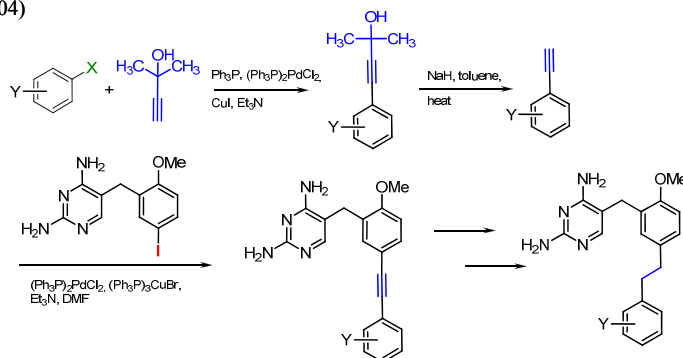


The Sonogashira-reaction

- The Sonogashira-reaction consists of the palladium-catalysed coupling of copper-acetylides and arylhalogenides to yield alkynylarenes (K.Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467-4470)

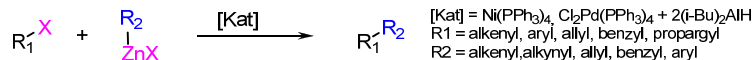


- Example:** 2,4-Diamino-5-(2',5'-substituted benzyl)pyrimidines (*J. Med. Chem.*, 47 (6), 1475-1486, 2004)



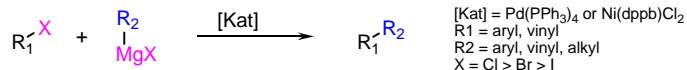
Cross-coupling reactions

- **Negishi Coupling**



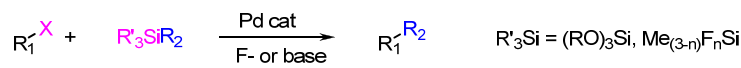
E.-I. Negishi, J. Organometal. Chem. 653 (2002) 34

- **Kumada Coupling**



Kumada. Bull. Chem. Soc. Jpn., 1976, 1958.

- **Hiyama Coupling**



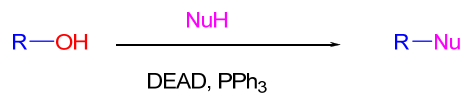
Y. Hatanaka, and T. Hiyama, J. Org. Chem., 1988, 53, 918, Y.

- **Fukuyama Coupling**



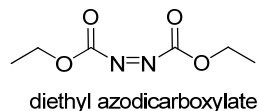
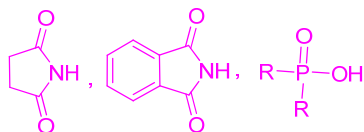
Mitsunobu reaction

- The Mitsunobu reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds. The nucleophile employed should be acidic.



NuH = R'CO₂H, ArOH, RN₃, RSH

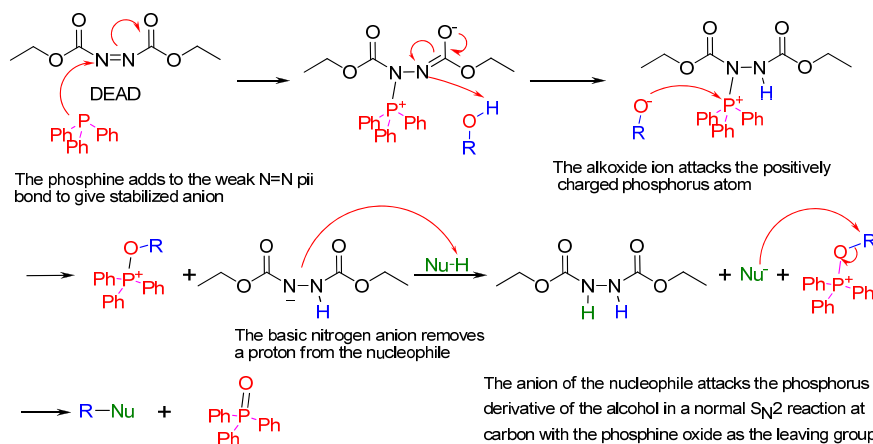
DEAD =



Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679;

Mitsunobu, O. *Synthesis*. **1981**, 1-28. Hughes, D. L. *Org. Reac.* **1992**, *42*, 335-656.

Mitsunobu reaction: Mechanism

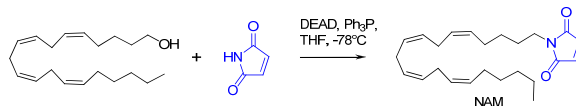


Mitsunobu reaction

- Inversion of configuration in the Mitsunobu reaction

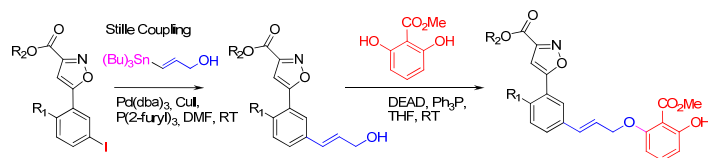


- Example 1: Synthesis of MGL-inhibitor N-Arachidonyl Maleimide



Saario et al. Chemistry & Biology, 12, 649-656, 2005

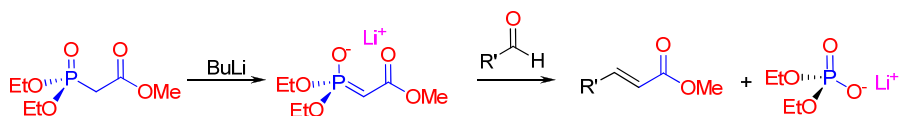
- Example 2: Protein tyrosine phosphatase 1B inhibitors



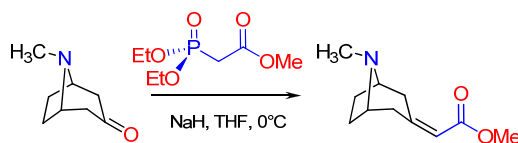
J. Med. Chem., 46 (20), 4232-4235, 2003

The Wittig Reaction: The Wadsworth-Horner-Emmons Reaction

- The reaction of aldehydes or ketones with stabilized phosphorus ylides (phosphonate carbanions) leads to olefins with excellent *E*-selectivity.



- Example: Synthesis of tropane-like analogues

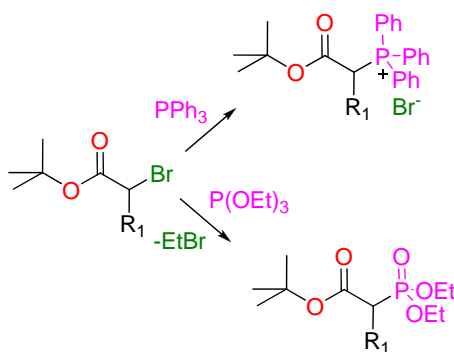


J. Med. Chem., 44 (23), 3937-3945, 2001



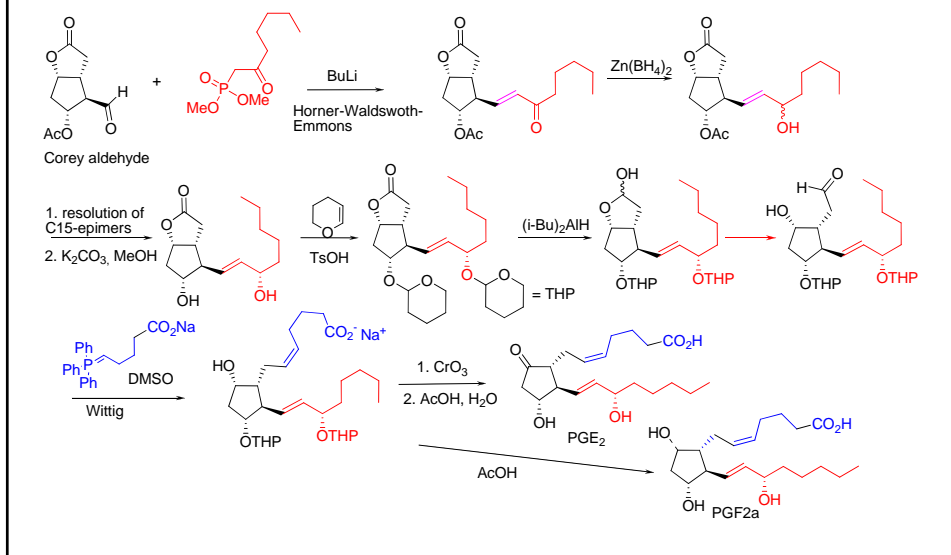
The Wittig Reaction

- Phosphonium salts and phosphonates can be synthesized by reaction of an alkyl halide and a triphenylphosphine (Ph_3P) or a trialkyl phosphite.



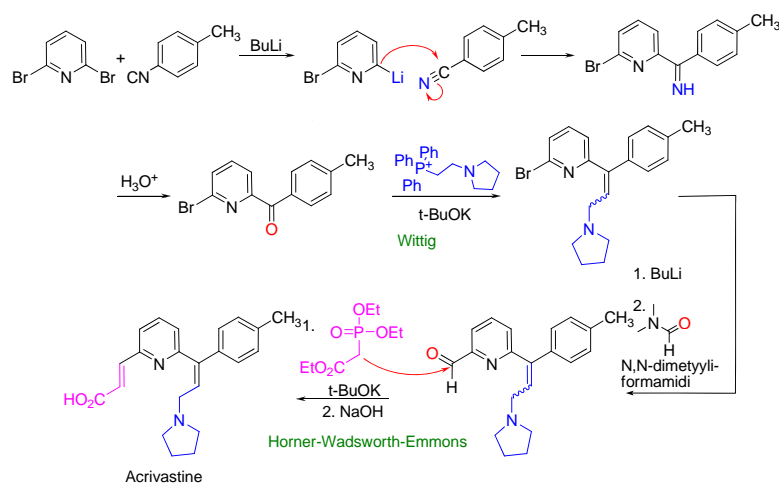
The Wittig Reaction

Synthesis of prostaglandines: PGE₂ ja PGF_{2α}



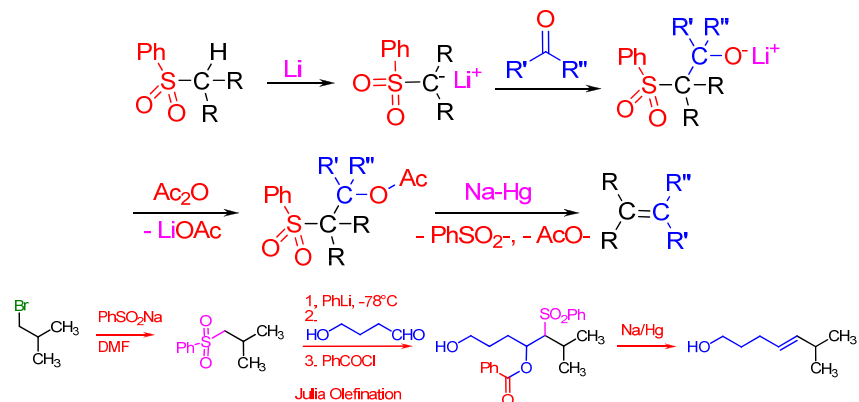
The Wittig Reaction: Synthesis of acrivastine

(antihistamine)



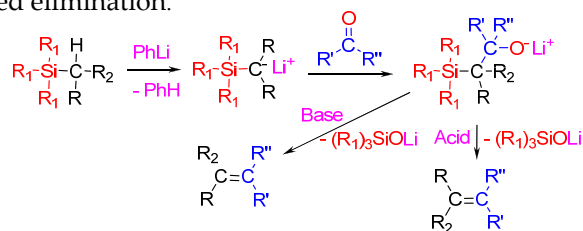
Julia reaction

- The addition of a phenylsulfonyl carbanion to an aldehyde or ketone leads to alcohol, which is esterified in situ. The reductive elimination leads to (*E*)-alkene.

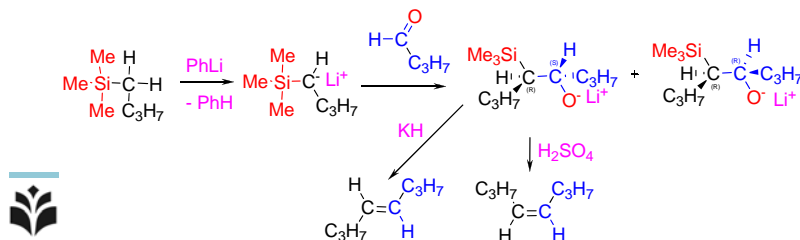


Peterson reaction

- Preparation of alkenes from α -silylcarbanions by acid or base-induced elimination.

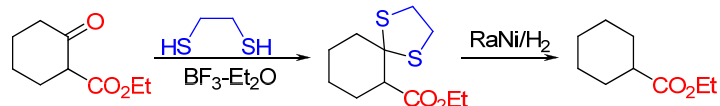


- Stereochemical outcome of the Peterson olefination can be controlled.

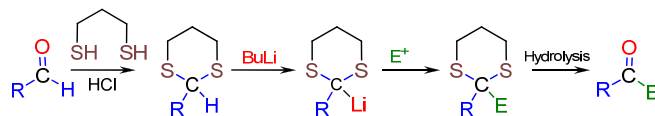


Sulfur containing reagents

- **Thioacetals** can act as effective protecting groups and can be reduced by Raney Nickel to afford the alkane.

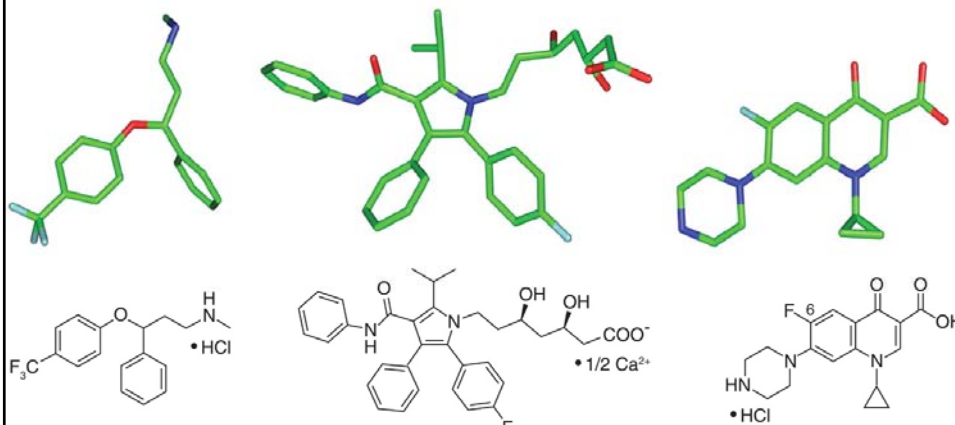


- **Corey-Seebach Reaction-Seebach Umpolung** (reversal of polarity): carbonyl group reacts as an electrophile at carbon which polarity can be reversed when the carbonyl group is converted into a thioacetal (dithiane). Acyl proton can be abstracted by n-butyllithium to generate 2-lithio-1,3-dithiane, which reacts as a nucleophile with electrophiles like alkyl halides and acid chlorides.



UNIVERSITY OF
EASTERN FINLAND

Fluorinated pharmaceuticals

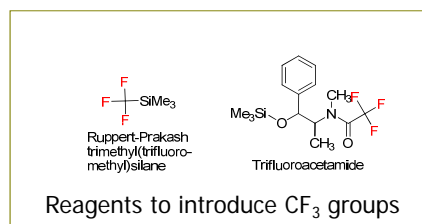
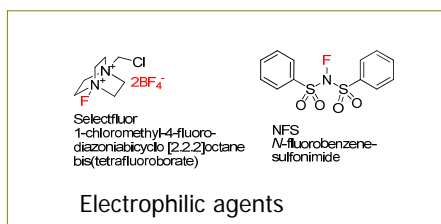
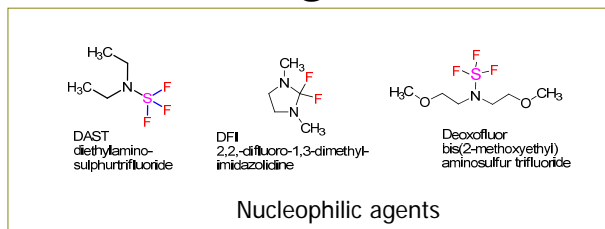


Prozac
UNIVERSITY OF
EASTERN FINLAND

Lipitor

Ciprobay

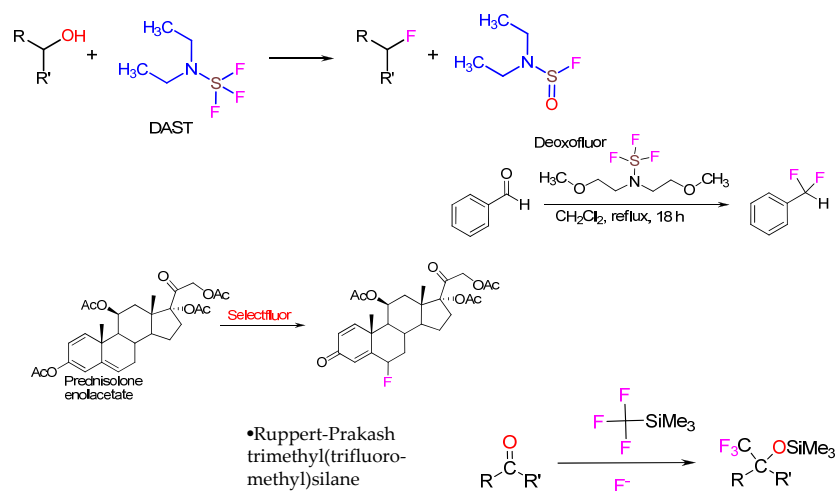
Fluorination agents



More information: http://www.scripps.edu/chem/baran/images/grpmtgpdf/Su_May_08.pdf



Fluorination agents



Oxidizing agents

Chemoselective for C=C doublebonds	Chemoselective for alcohols or carbonyl compounds
peracids, RCO_3H osmium tetroxide, OsO_4 ozone, O_3	Cr(VI) compounds: CrO_3 , $\text{Na}_2\text{Cr}_2\text{O}_7$, PCC (pyridinium chlorochromate), PDC (pyridinium dichromate) Mn(VII) compounds: KMnO_4 some high oxidation state Hal, N, or S compounds: DMSO, DMP

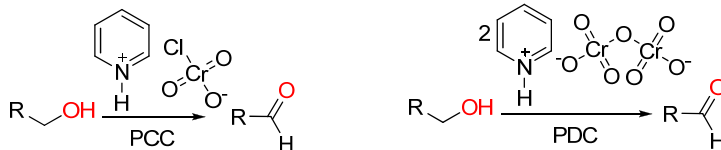
Oxidation Chemistry

• The Jones oxidation

- Chromic acid oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively

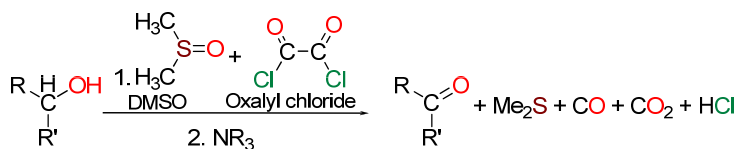


- Pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) are used to selectively oxidize primary alcohols to the aldehyde

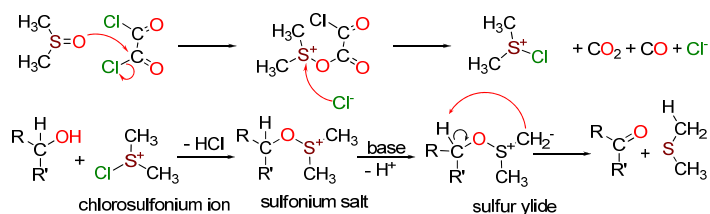


Oxidation Chemistry

• The Swern Oxidation



■ Mechanism

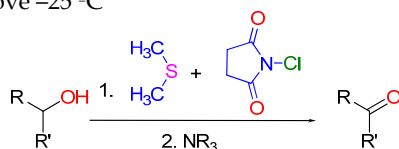


UNIVERSITY OF
EASTERN FINLAND

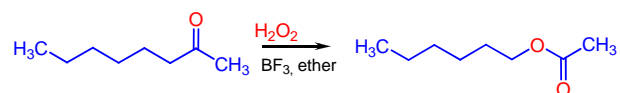
Oxidation Chemistry

• Corey-Kim Oxidation

- Mechanism is comparable to the Swern Oxidation
- allow oxidation above $-25\text{ }^\circ\text{C}$



• The Baeyer-Villiger Oxidation



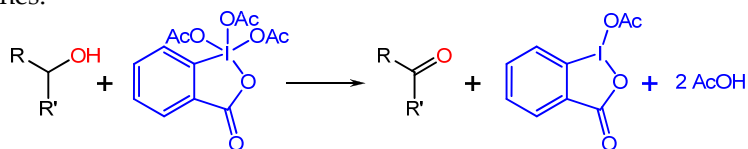
- Ketone is oxidized to an ester by peroxy acids or hydrogen peroxide
- Look also for [Beckmann rearrangement](#)



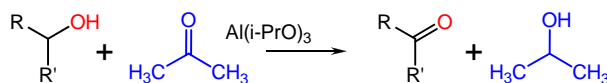
UNIVERSITY OF
EASTERN FINLAND

Oxidation Chemistry

- **Dess-Martin Oxidation:** The Dess-Martin Periodinane (DMP), offers selective and very mild oxidation of alcohols to aldehydes or ketones.

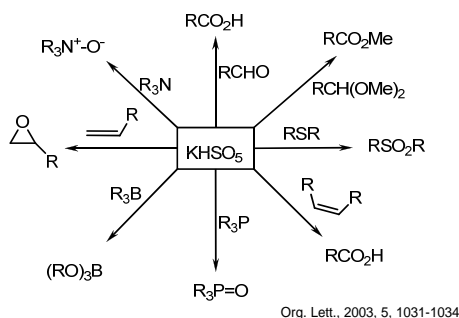


- **Oppenauer Oxidation:** opposite of Meerwein-Ponndorf-Verley reduction. The alcohol is oxidized with aluminium alkoxide in excess acetone

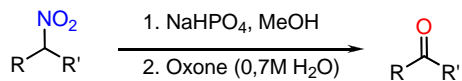


Oxidation Chemistry

- **Oxone®** = potassium monopersulfate (KHSO_5)



- **Nef Reaction:** The conversion of nitro compounds into carbonyls

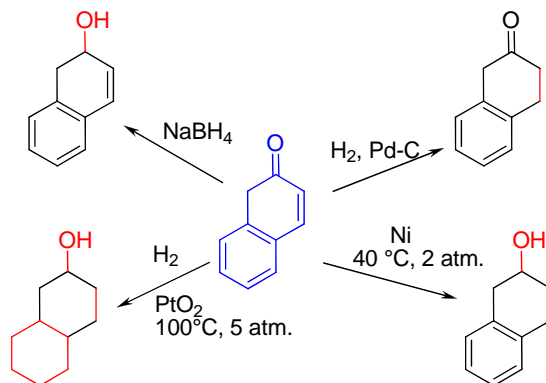


Synth. Commun., 1998, 28, 3057-3064.



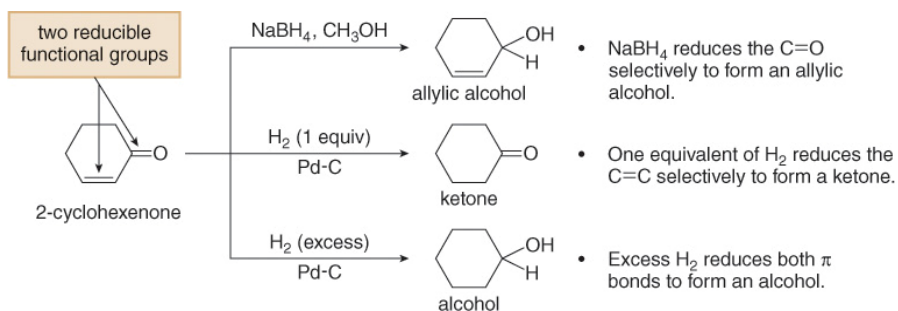
Reducing Agents

■ Selective Hydrogenations



Reduction of Aldehydes and Ketones

- 2-cyclohexenone, which contains both a C=C and a C=O, can be reduced to three different compounds depending upon the reagent used



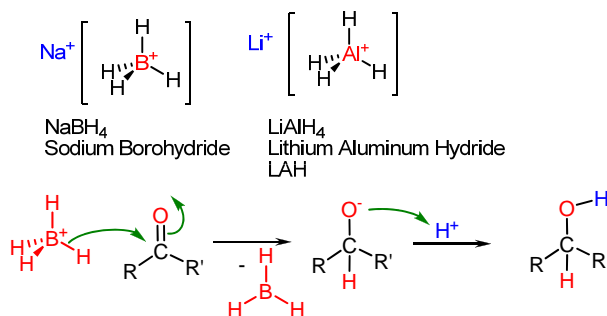
Hydride Reducing Agents

Lithium Aluminium Hydride (LiAlH_4)

- One of the most powerful reductants, Highly flammable

Sodium Borohydride (NaBH_4)

- Reduce aldehydes and ketones in the presence of esters, reactions are carried out in protic solvents including H_2O

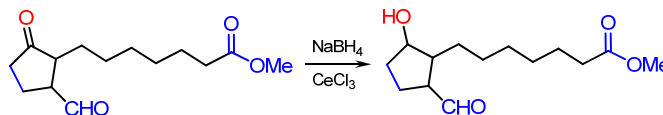
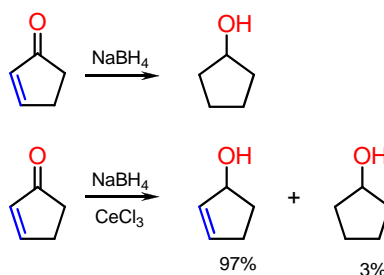


Reducing Agents

• Sodium Borohydride-Cerium (III) Chloride (Luche Reduction)

(*J. Am. Chem. Soc.*, 1981, 103, 5454-5459)

- Chemoselective reduction of a ketone in the presence of a more electrophilic aldehyde



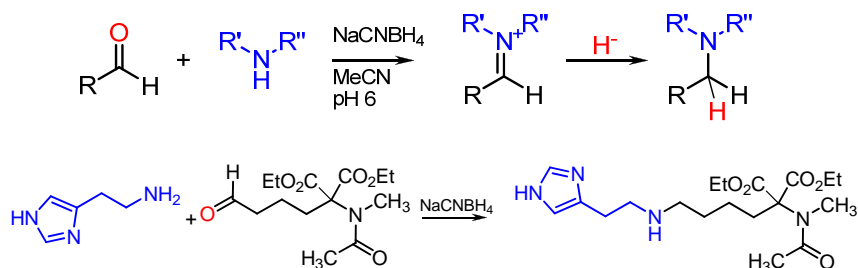
J. Org. Chem., 1979, 44, 4187-4189.



Reducing Agents

• Sodium Cyanoborohydride (NaCNBH₃)

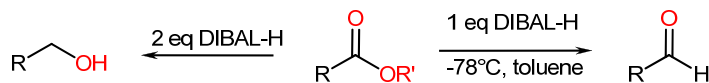
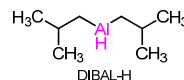
- milder than NaBH₄ at pH 7
- at pH 3-4: NaCNBH₃ readily reduces aldehydes and ketones
- at pH 6-7: NaCNBH₃ readily reduces iminium ions but NOT C=O groups - this property is responsible for its most important use - **reductive amination**:



Reducing Agents

• DIBAL-H, Diisobutylaluminium hydride

- very widely used reducing agent especially for reducing esters
- esters can be reduced to either the aldehyde or the alcohol depending on the stoichiometry and reaction conditions:



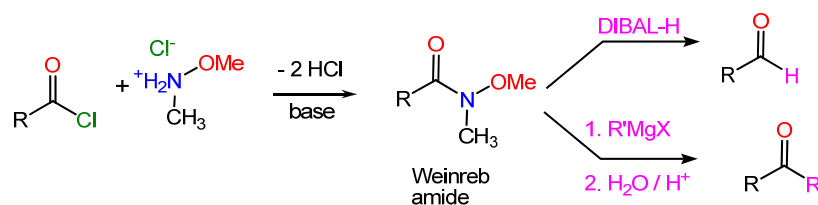
- Nitriles are also reduced to aldehydes



Reducing Agents

• DIBAL-H

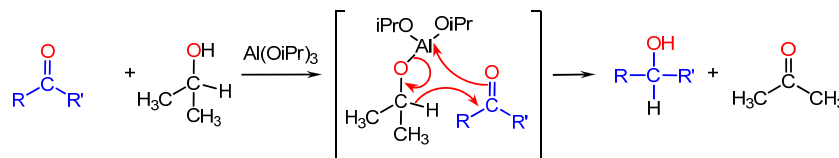
- Reduction of *N*-methoxy-*N*-methyl amides, **Weinreb amides**, is one of the most frequent means of converting a carboxylic acid to an aldehyde.
- The reaction of Weinreb amides with organo-magnesium compounds leads to ketones in high yields,



Reducing Agents

• **Meerwein-Ponndorf-Verley Reduction** with $\text{Al}(\text{O}i\text{Pr})_3$

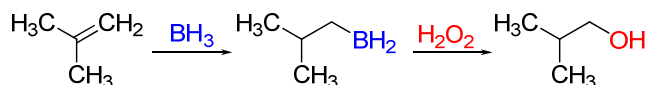
- isopropanol behaves as the hydride donor
- the by-product is acetone
- the reaction is reversible - the reverse oxidation is known as the **Oppenauer Oxidation**.



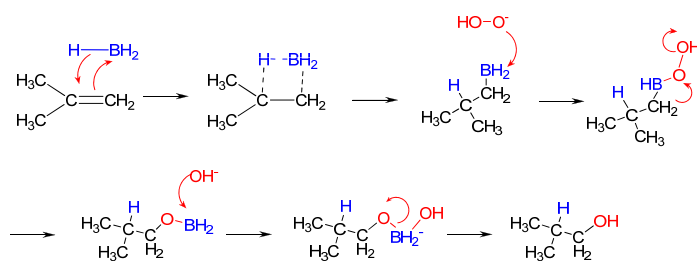
Reducing Agents: Borane

- **Borane** BH_3 is gas and unstable to be isolated, but exists either as the dimer B_2H_6 or a Lewis acid-Lewis base complex *e.g.* $\text{BH}_3 \cdot \text{THF}$ or $\text{BH}_3 \cdot \text{Me}_2\text{S}$

- Hydroboration of Alkenes



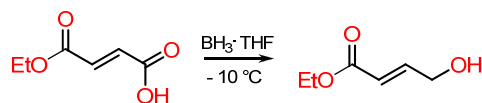
- Mechanism:



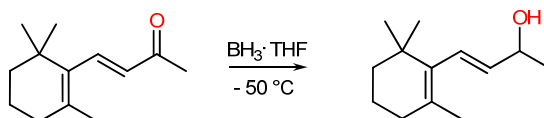
Reducing Agents: Borane

Reduction of Carboxylic Acids

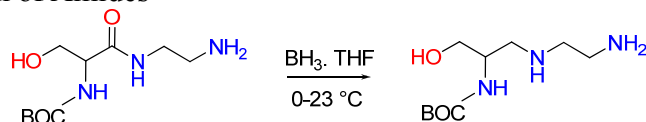
- Borane is best reagent for selectively reducing carboxylic acids to alcohols in the presence of esters



Reduction of Ketones and Enones



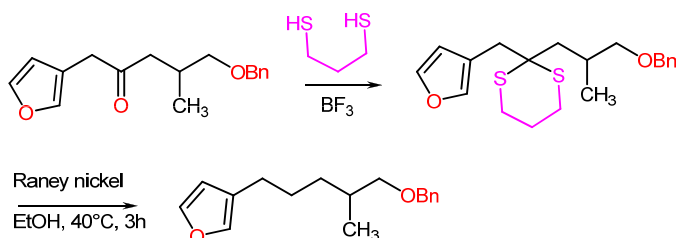
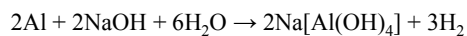
Reduction of Amides



Reducing Agents

• Raney-Nickel

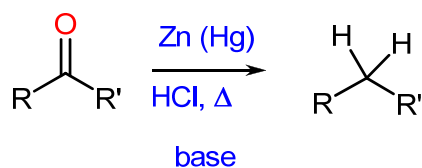
- most widely used in the *hydrogenolysis* of C-S bonds.
- also used in the hydrogenation of alkenes and alkynes.
- Produced by treating nickel-aluminium alloy with concentrated sodium hydroxide



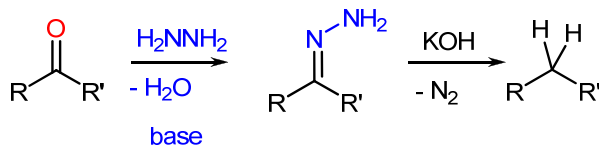
Reducing Agents

■ Clemmensen Reduction

- A classical method for complete reduction of a carbonyl group (in ketones and aldehydes).

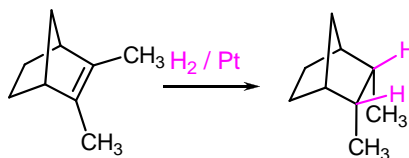


■ Wolff-Kishner Reduction



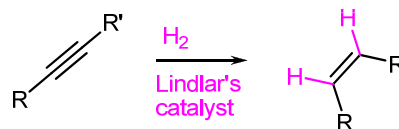
Reducing Agents

- Hydrogenation with Hydrogen and a Transition Metal Catalyst



- Partial Reduction of Alkynes

- Lindlar's catalyst (Pd-CaCO₃-PbO) is the most widely used.
- The reaction is **stereospecific** giving only the **syn** addition product

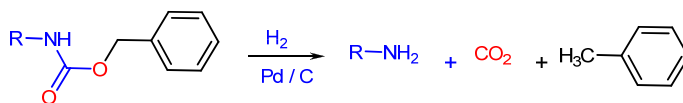
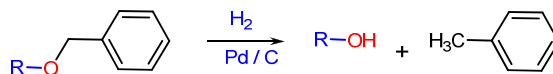


UNIVERSITY OF
EASTERN FINLAND

Reducing Agents

Hydrogenolysis

- Benzyl ether** and **benzyloxycarbonyl** protecting groups are readily cleaved by Pd/C/H₂ under mild and neutral conditions.

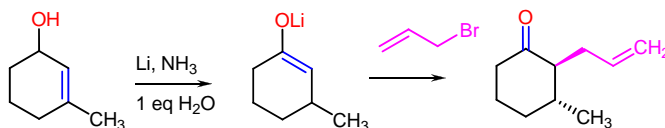


UNIVERSITY OF
EASTERN FINLAND

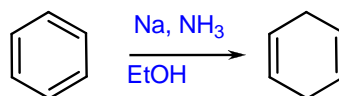
Reducing Agents

- Dissolving Metal Reductions (Sodium/Ammonia or Lithium/Ammonia)

- Regiospecific Enolate Formation



- Birch Reduction: Partial reduction of aromatic rings



- Reduction of Alkynes to (*E*)-alkenes

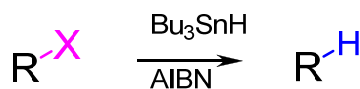


Reducing Agents: Bu_3SnH

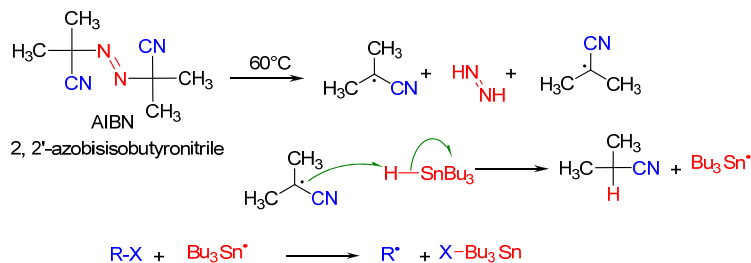
- Free Radical Reductions

with [tributyltin hydride](#)

(Bu_3SnH)

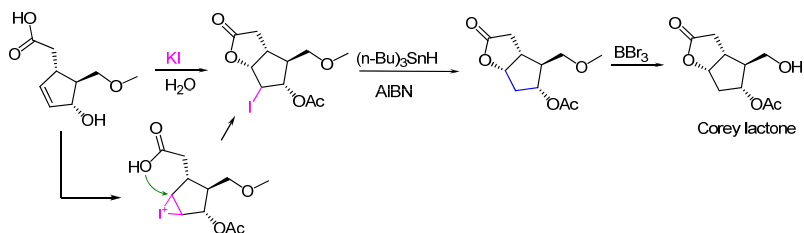


- AIBN undergoes thermal homolysis at 60 °C to give nitrile-stabilized radicals that abstract the hydrogen atom from Bu_3SnH .

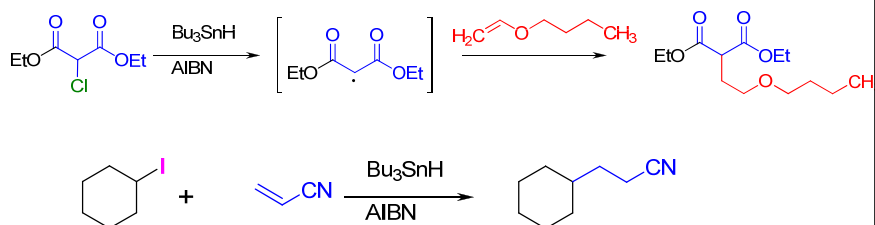


Reducing Agents: Bu₃SnH

■ Synthesis of Corey lactone



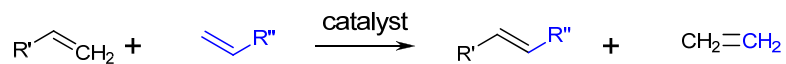
■ Carbon-carbon bond formation using radicals



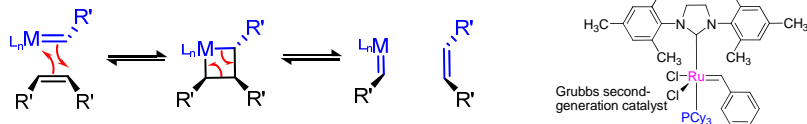
Metathesis

The 2005 Nobel Prize in Chemistry

Yves Chauvin, Robert H. Grubbs, Richard R. Schrock



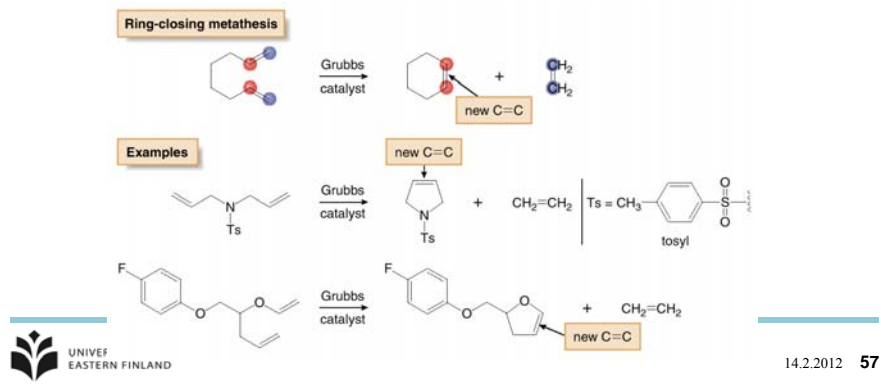
■ Mechanism



■ Example: Ring-Closing Metathesis Reaction for Synthesis of Cyclopentenedicarboxylic Acid

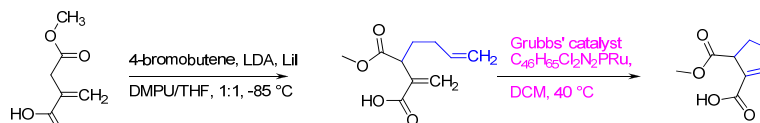
Ring Closing Metathesis (RCM)

- When a diene is used as a starting material, ring closure occurs. These reactions are typically run in very dilute solution so that the reactive ends of the same molecule have a higher probability of finding each other. **High dilution favors intermolecular rather than intramolecular metathesis.** Virtually any ring size can be prepared



Ring Closing Metathesis (RCM)

- Example:** Ring-Closing Metathesis Reaction for Synthesis of Cyclopentenedicarboxylic Acid



J. Med. Chem., 46 (7), 1165 - 1179, 2003