Master 1 International

Axe 2: Pharmacy and biotechnology

TU7 Chemistry

C-C bond formation

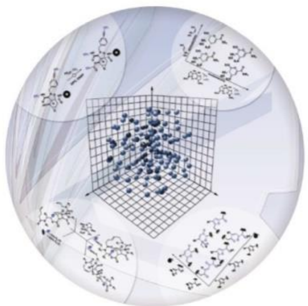
Nicolas GIGANT

nicolas.gigant@universite-paris-saclay.fr

2024-2025

université PARIS-SACLAY

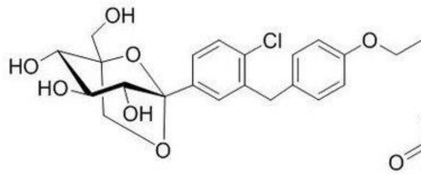
FACULTÉ DE PHARMACIE



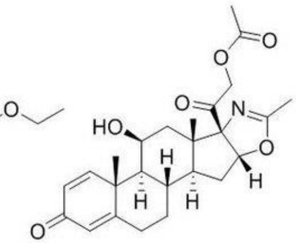
Carbon-carbon bonds...

✓ Carbon-carbon bons are ubiquitous in natural products and drugs

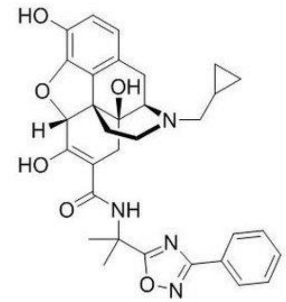
- ➢ C-C : alkane
- ➢ C=C : alkene
- ➢ C≡C : alkyne



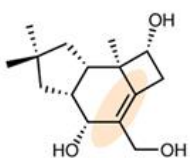
Ertugliflozin



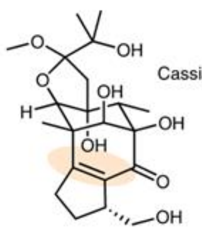
Deflazacort



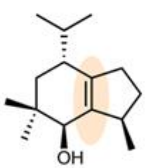
Naldemedine



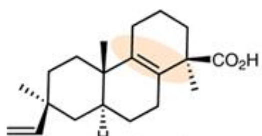
Illudol



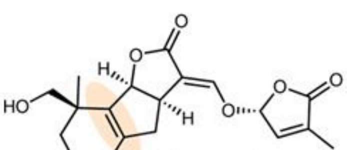
Cassiabudanol A



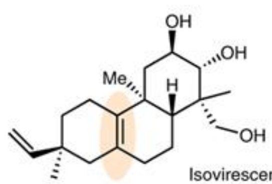
Brasilenol



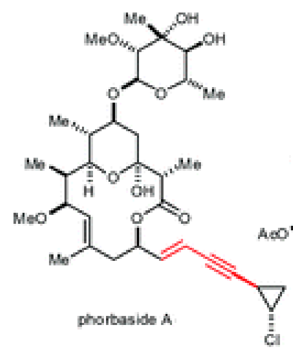
Rosadienonsaeure



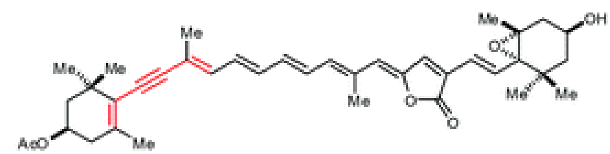
Sorghumol



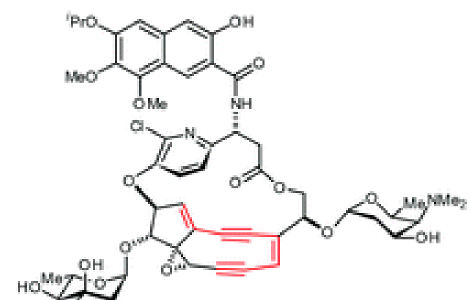
Isovirescenol A



phorbaside A



pyrrhoxanthin

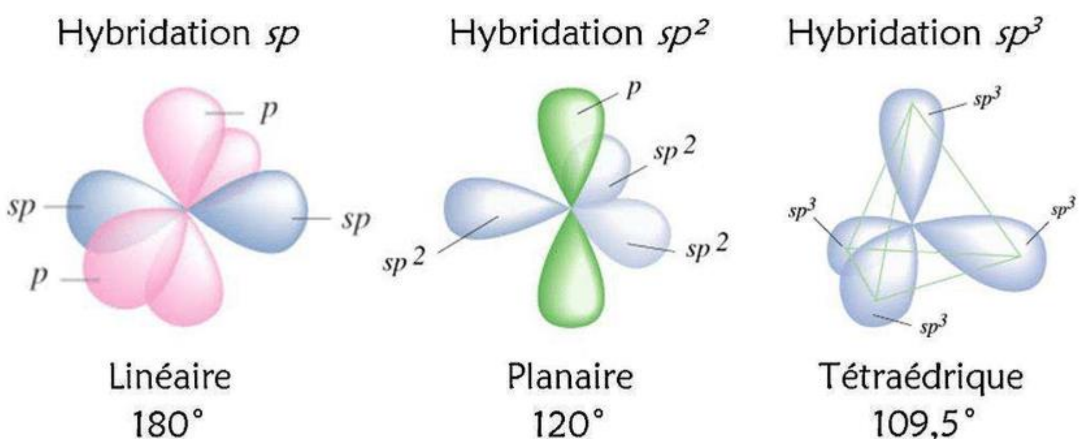


kedarcidin chromophore

Carbon-carbon bonds...

✓ Some general information…

	C-C	**C=C**	**C≡C**
Bond lengths (Å)	1.53	1.32	1.18
Bond energies (kJ.mol^{-1})	345-355	610-630	835
Geometry	tetrahedral	planar trigonal	linear
Hybridization	sp^3	sp^2	sp



Chapter I

C-C bonds formation

I. Carbon-carbon bonds formation

1. Enols, enolates and related compounds
   a. Formation
   b. Alkylation
   c. Reactivity with carbonyl moities

2. Organometallic reagents
   a. Organomagnesium compounds
   b. Organolithium and related compounds

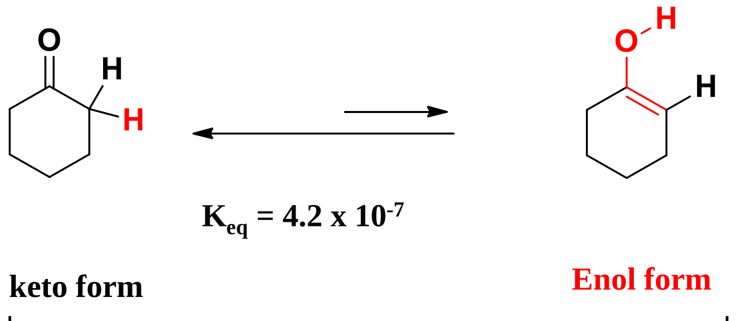
3. Pericyclic reactions
   a. Definition
   b. Diels-Alder reaction
   c. Sigmatropic reaction

4. “One word” about cross-coupling reactions

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

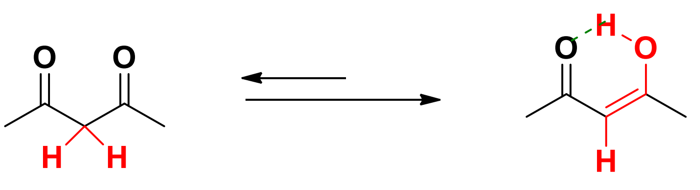
Keto-enol equilibria



Tautomers

✓ The conversion of a carbonyl compound into its enol form : **enolization**

✓ Particular case of 1,3-dicarbonyl compounds (β-dicarbonyl compounds)



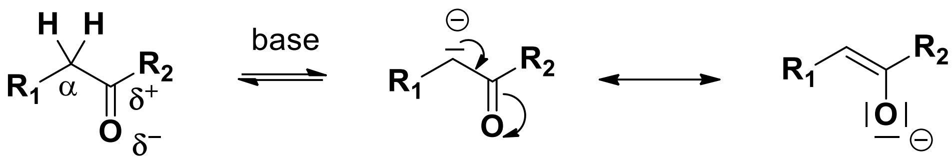
Stabilizing effects of the enol form :

- ➢ Conjugation, resonance
- ➢ Intramolecular hydrogen bond

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

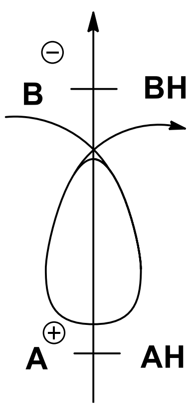
➢ I. 1. a. Formation



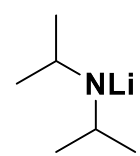
enolate

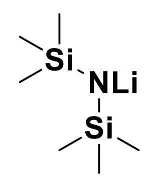
Usually : strong base

The pKa of the base must be stronger then the pKa of the removed H.



***n*-BuLi**	**$NaNH_2$**	**LDA**	**LiHMDS**	**KH**
50	38	36	35	35

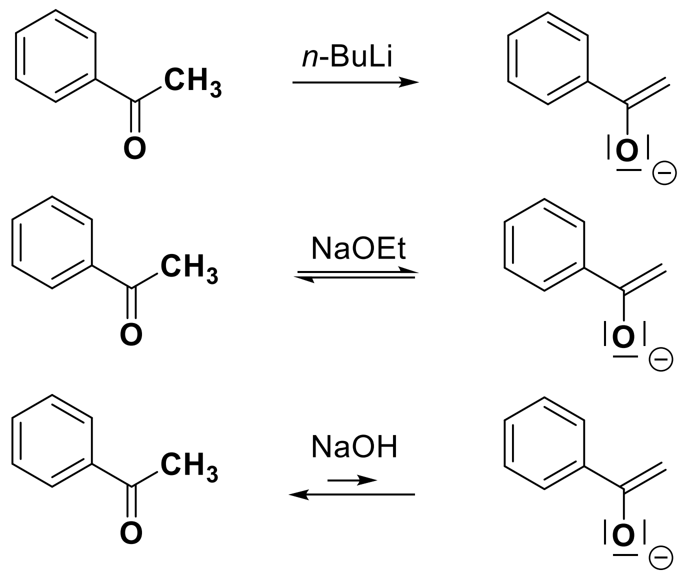




I. Carbon-carbon bonds formation

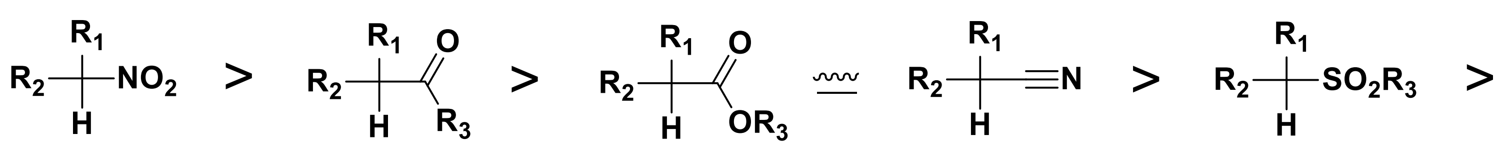
✓ I. 1. Enols, enolates and related compounds

Base effect :

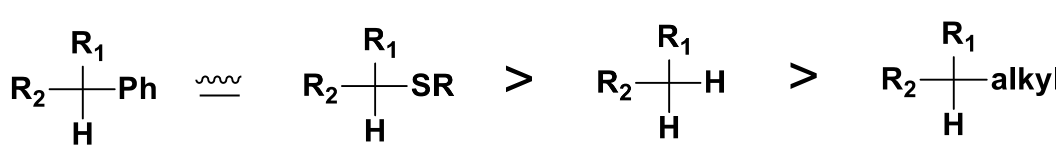


pKa
50
16
14

Acidity scale:



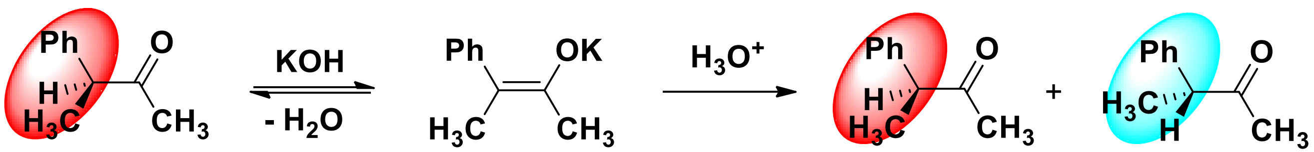
pKa = 10 pKa = 20-25 pKa = 25



I. Carbon-carbon bonds formation

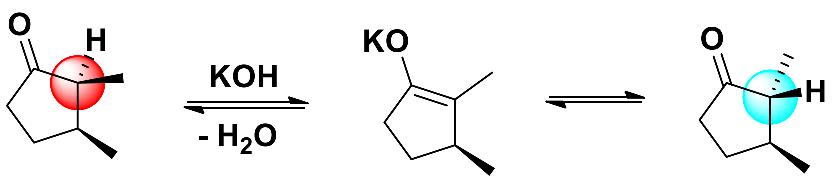
✓ I. 1. Enols, enolates and related compounds

Racemization :



Loss of stereochemical information

Isomerization :

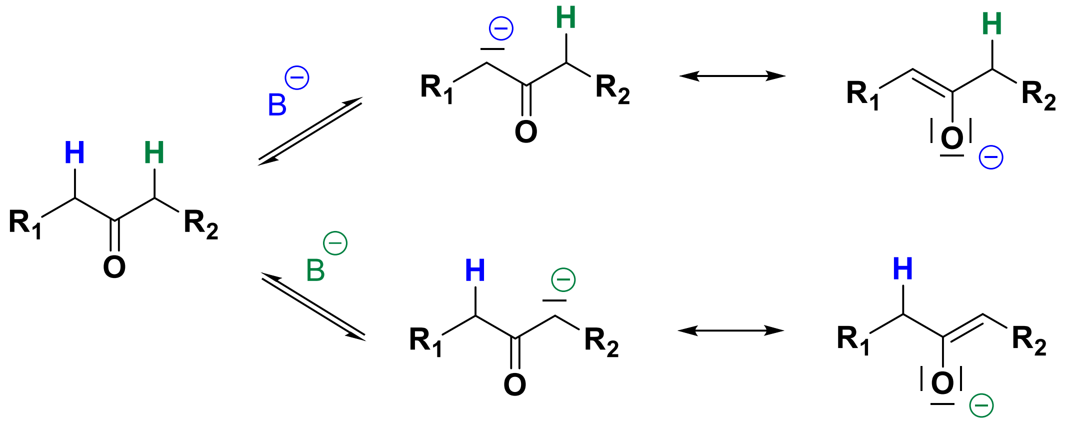


thermodynamic ketone

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

Unsymmetrical substrates, selectivity ?



The selectivity depends on reaction conditions :
kinetic *versus* thermodynamic control

Kinetic control :
the more acidic and accessible H

- Low temperature
- Base excess
- Short reaction time
- Strong base
- Aprotic solvent

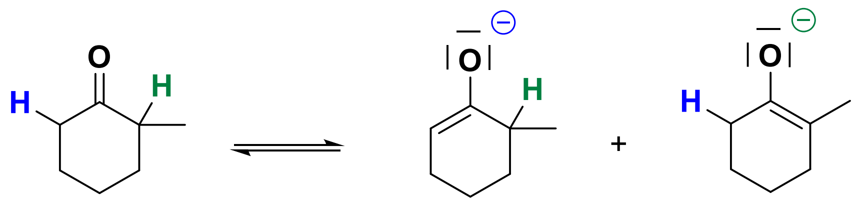
Thermodynamic control :
the less acidic and accessible H

- Higher temperature
- Ketone excess
- Long reaction time
- Mild base
- Protic solvent

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

Unsymmetrical substrates, selectivity ?



LDA, DME, -78 °C	99%	1%
Et_3N, DMF	22%	78%

Kinetic control :
the more acidic and accessible H

- Low temperature
- Base excess
- Short reaction time
- Strong base
- Aprotic solvent

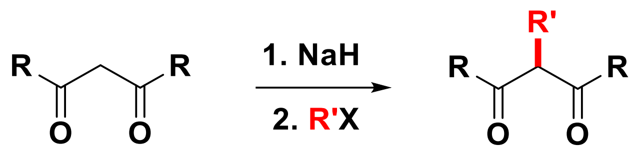
Thermodynamic control :
the less acidic and accessible H

- Higher temperature
- Ketone excess
- Long reaction time
- Mild base
- Protic solvent

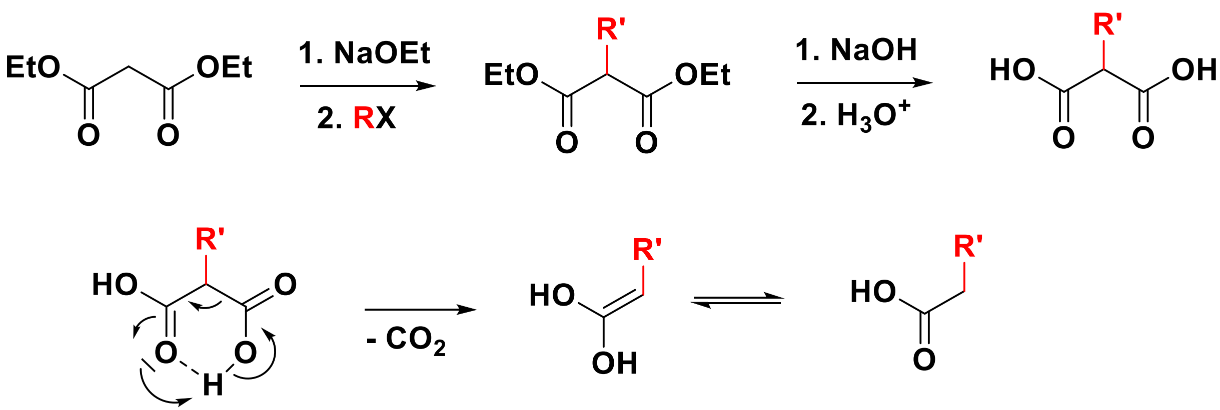
I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds
  - ➢ I. 1. b. Alkylation

Bis-activated reagent



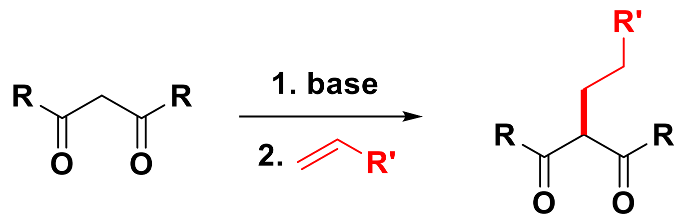
Malonic synthesis



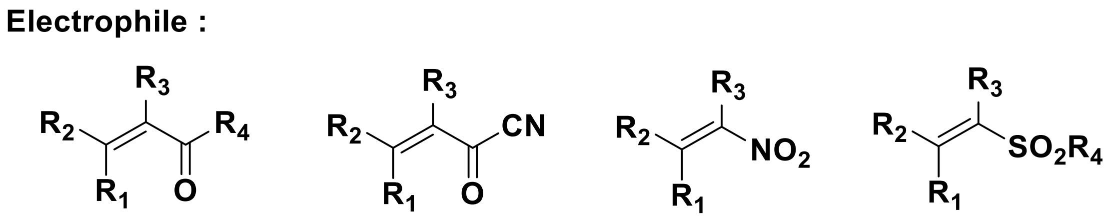
I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

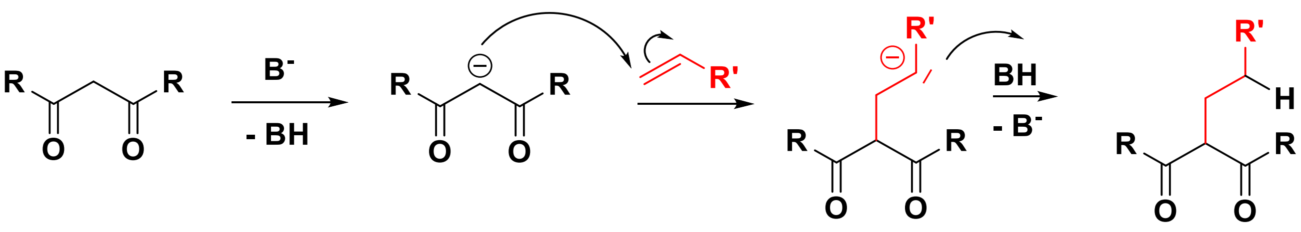
Nucleophilic conjugate addition = Mickael addition



Arthur Michael
(1853-1942)
American chemist



Mechanism :

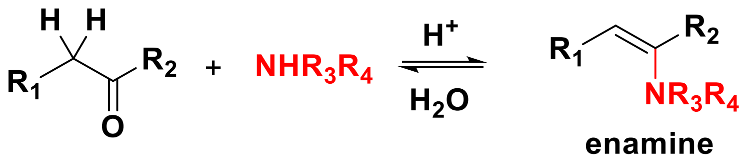


I. Carbon-carbon bonds formation

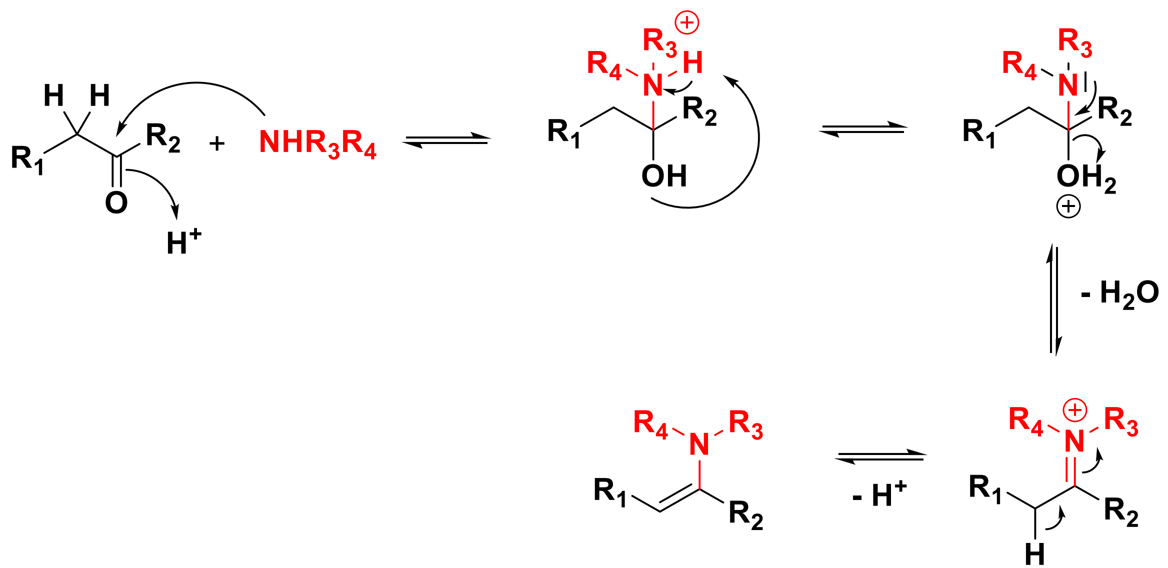
✓ I. 1. Enols, enolates and related compounds

Enamine alkylation

Preparation : secondary amine + carbonyl derivative :



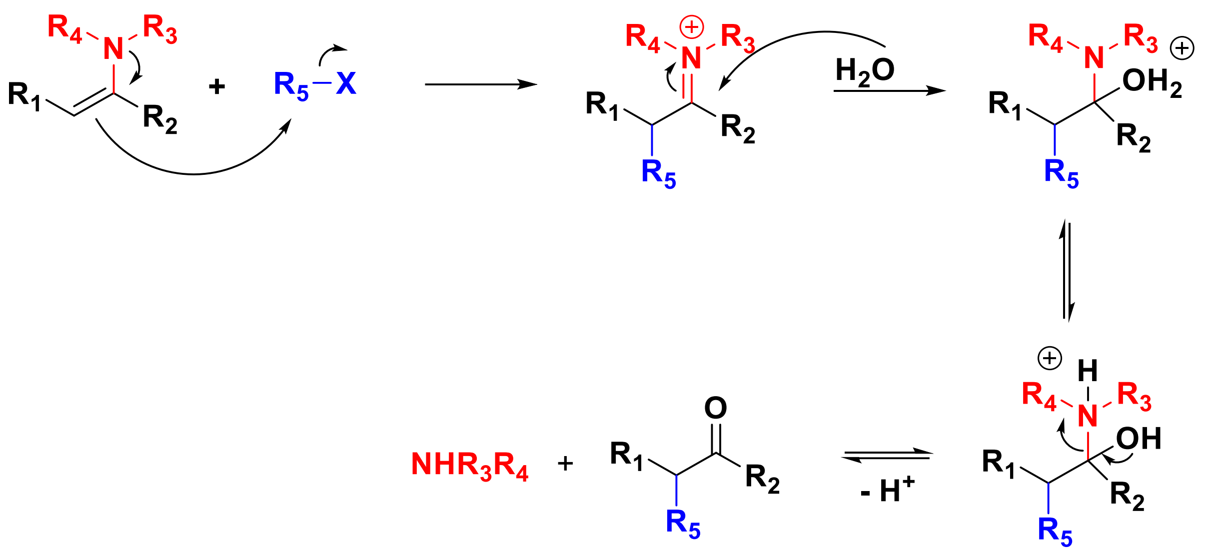
Mechanism :



✓ I. 1. Enols, enolates and related compounds

Enamine alkylation

Alkylation :



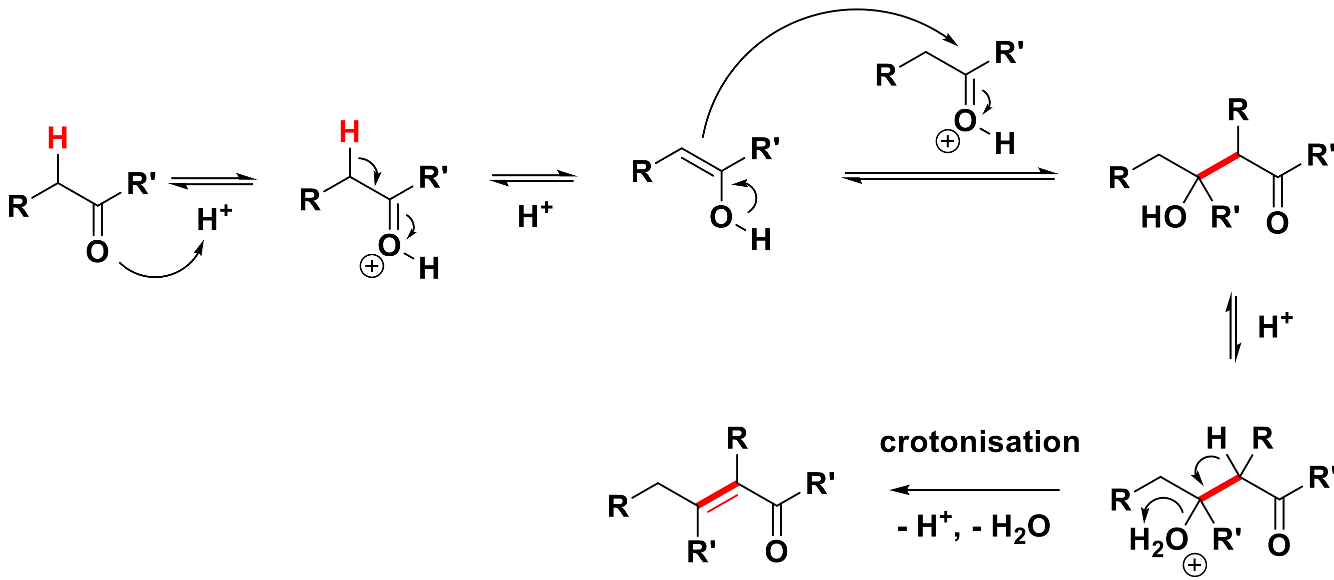
The enamine is more nucleophilic than the enol.

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

➢ I. 1. c. Reactivity with carbonyl moities

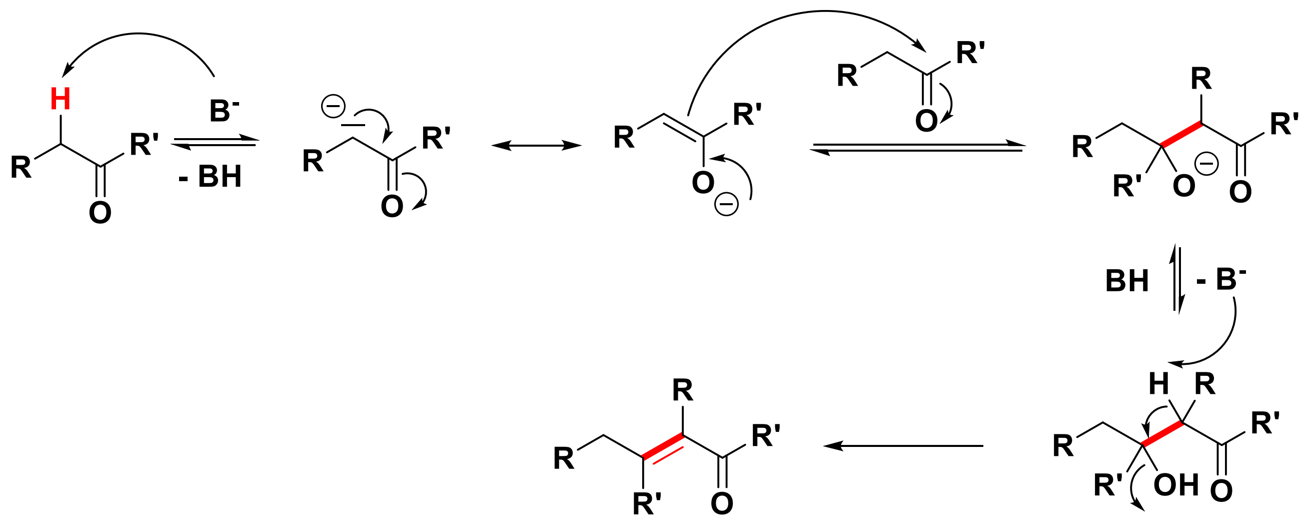
Aldol addition / condensation : acid catalyzed



The formation of the conjugated system is the driving force for this spontaneous dehydration.

✓ I. 1. Enols, enolates and related compounds

Aldol addition / condensation : based catalyzed



I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

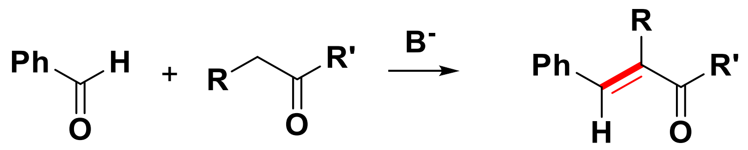
Mixed condensation

2 ketones under basic conditions = 4 products !

The most reactive enolate will react with the most electrophilic carbonyl.

One solution : 1 aldehyde (with no enolization) + 1 ketone = Claisen-Schmidt condensation

- The C=O from the aldehyde is the most electrophilic moiety.
- The enolate from the keton is the most nucleophilic moiety.



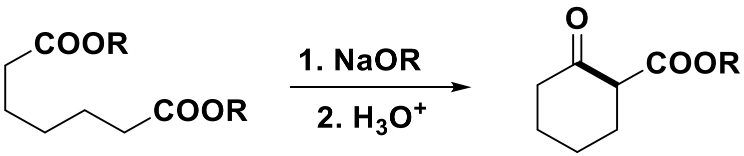
I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

Claisen condensation

Ludwig Claisen
(1851-1930)
German chemist

Dieckmann condensation



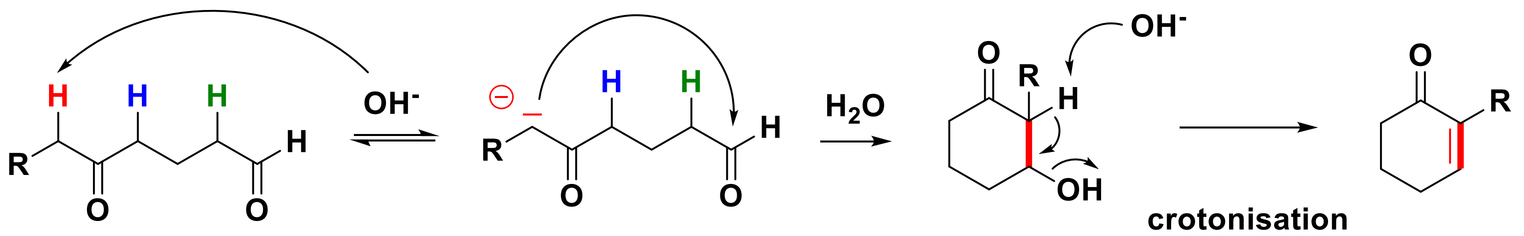
Walter Dieckmann
(1869-1925)
German chemist

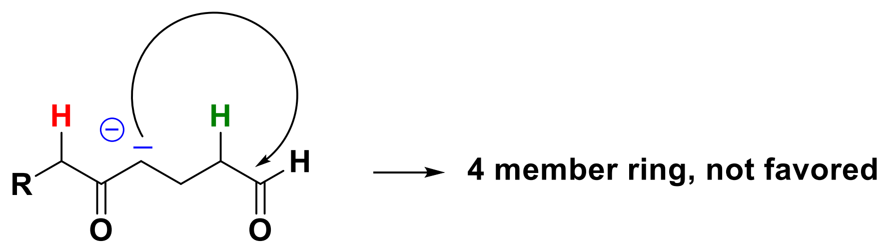
I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

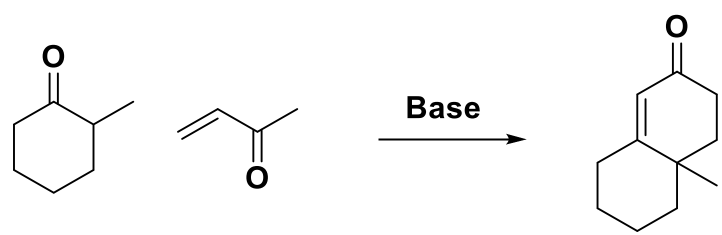
Intramolecular condensation

5 or 6 member rings formation





Robinson annelation

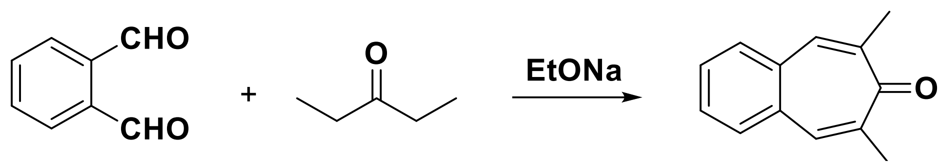


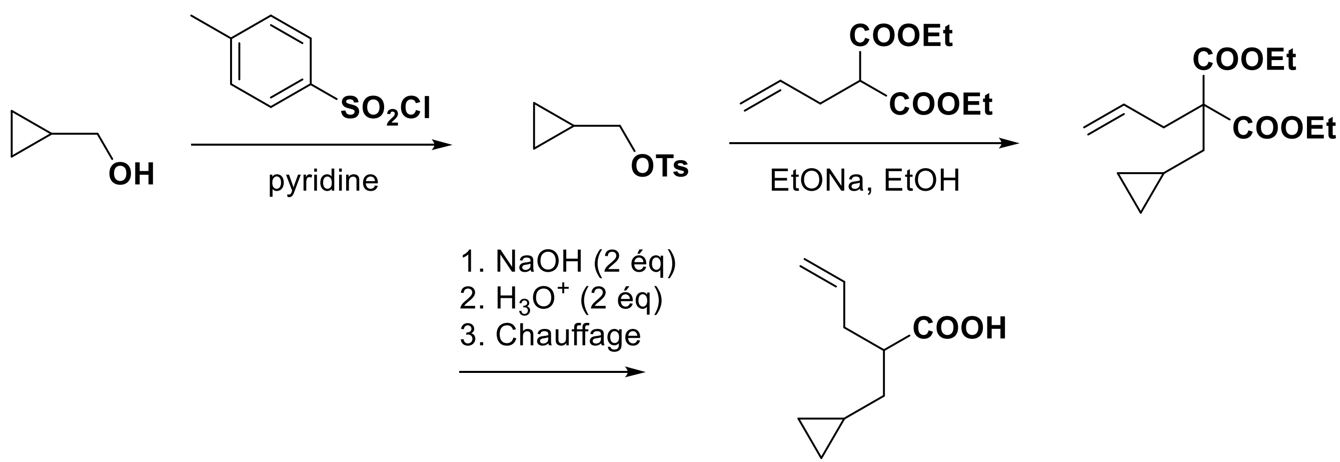
Sir Robert Robinson
(1886-1975)
English chemist

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

Application:



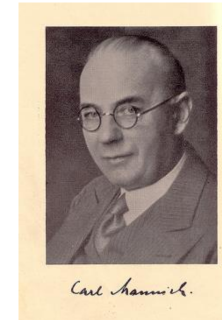


I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

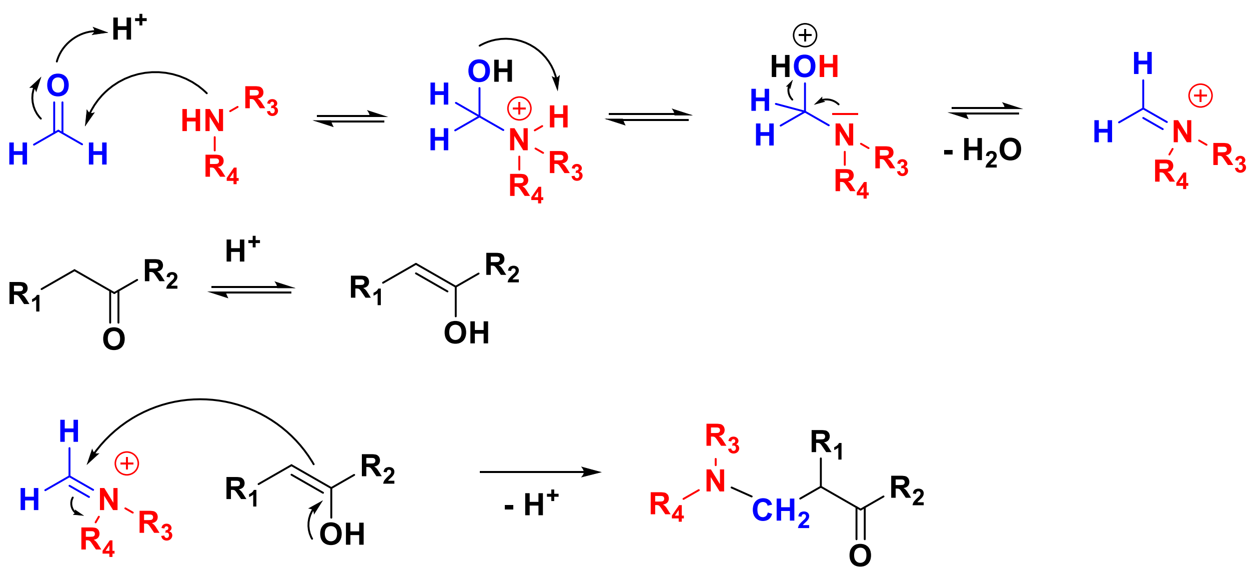
Mannich reaction

Aminomethylation: “$-CH_2-NR_2$”



Carl Mannich
(1877-1947)
German chemist

Mechanism :



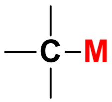
✓ I. 2. Organometallic reagents

➢ I. 2. 1. Organomagnesium compounds

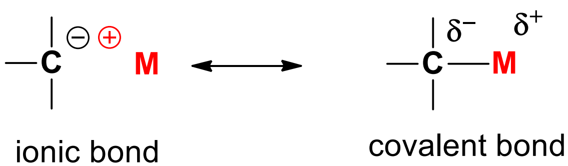
organometallic compound

=

compound with a metal-carbon bond



M = metal = K, Na, Li, Mg, Zn, Cd, Cu, Ce...



✓ The carbon bears a negative charge

✓ Basic and nucleophilic reagent

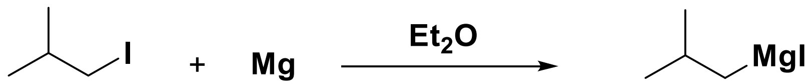
There is a huge among of organometallic compounds

Metal	K	Na	Li	Mg	Zn	Cd	Cu
Electronegativity	0,82	0,93	0,98	1,31	1,65	1,69	2,5
% ionic caracter	51	47	43	35	18	15	0

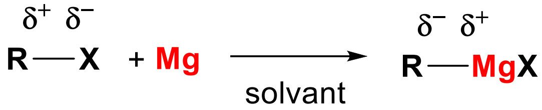
I. Carbon-carbon bonds formation

- 1er example in 1901 from Victor Grignard, Nobel Prize in chemistry 1912 :

Victor Grignard
1871-1935
Nobel Prize 1912
French chemist



- General reaction :

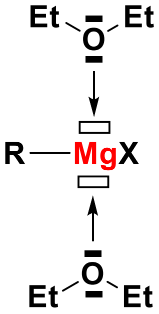


- The carbon polarization is reverse : « umpolung » phenomenon in German

- Solvent : no trace of water, anhydrous conditions

- Solvent : ether to stabilize the species : Et_2O, THF

- Leaving group reacticity : RI > RBr > RCl >> R



I. Carbon-carbon bonds formation

✓ Hydrolysis :

$$R{-}Mg{-}X \xrightarrow{H_2O} R{-}H + {}^{1}/_{2}\, MgX_2 + {}^{1}/_{2}\, Mg(OH)_2$$

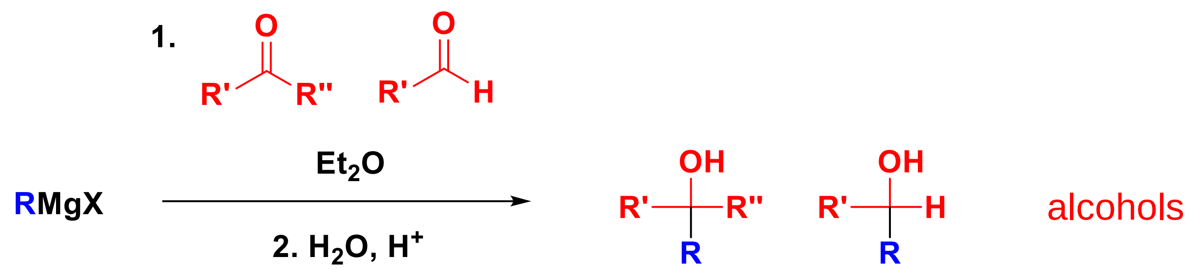
X = Br, I, Cl

✓ Basic reagents : deprotonation of carboxylic acids, phenols, amines … and alkynes

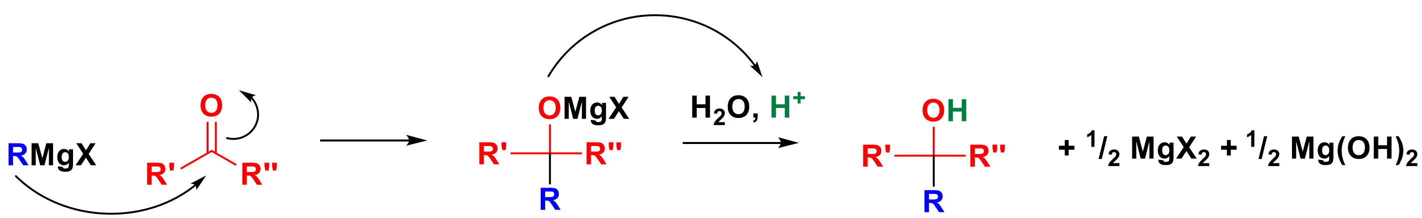
✓ Important case with alkynes :

$$R{-}Mg{-}X \quad H{-}C{\equiv}C{-}R' \xrightarrow{Et_2O} XMg{-}C{\equiv}C{-}R' \; + RH$$

- ✓ Reactivity with ketones et aldehydes

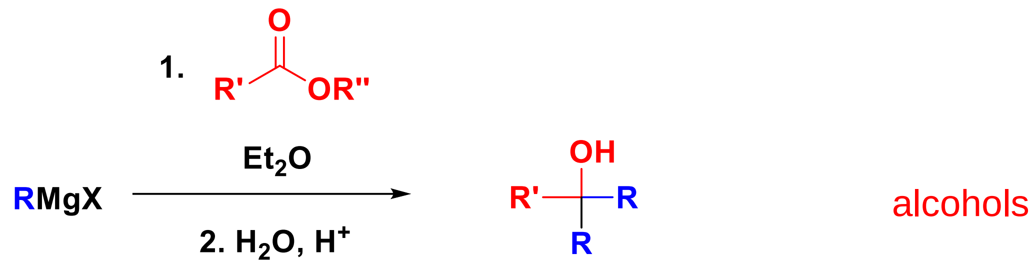


- ✓ Mechanism :

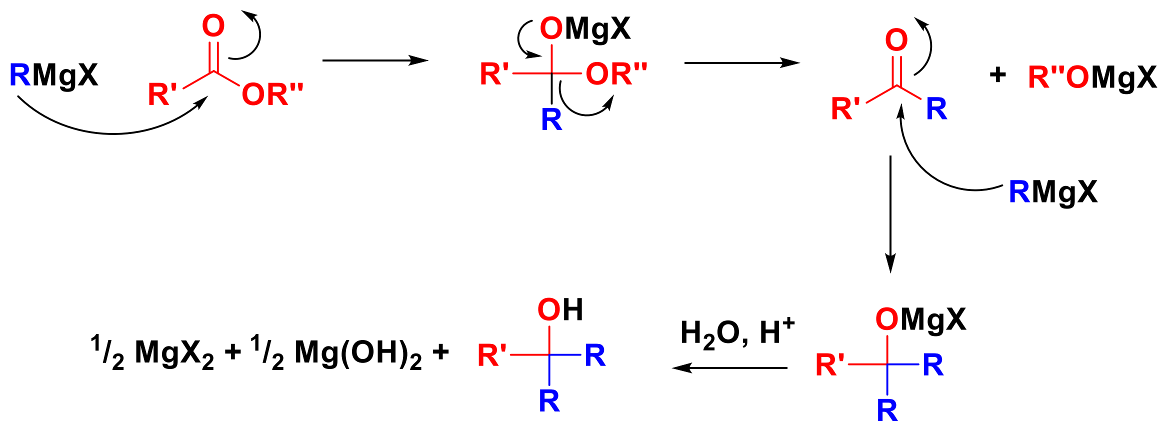


I. Carbon-carbon bonds formation

✓ Reactivity with esters



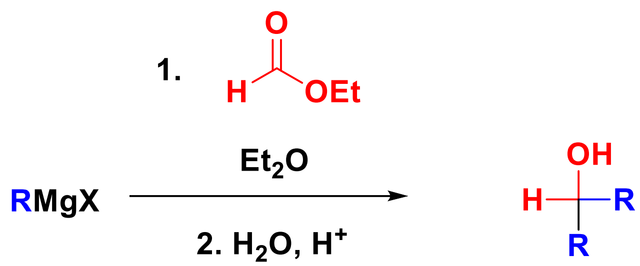
✓ Mechanism :



No mono-addition

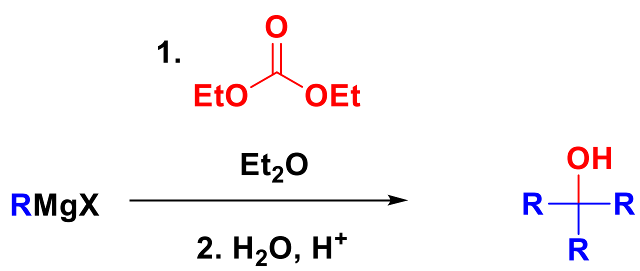
I. Carbon-carbon bonds formation

✓ Reactivity with ethyl formiate



alcohols

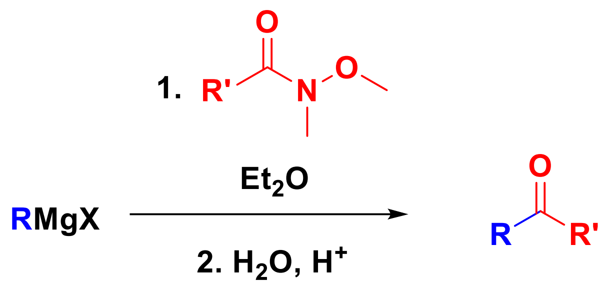
✓ Reactivity with carbonate esters :



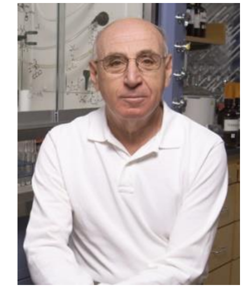
No possibility to create a carbonyl moiety…

I. Carbon-carbon bonds formation

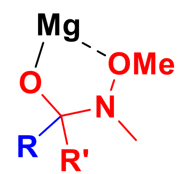
✓ The solution : Weinreb amides



ketones



Steven M. Weinreb
(1941)
American chemist

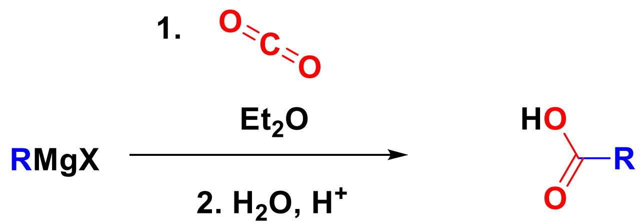


Key intermediate

One limitation : demethoxylation

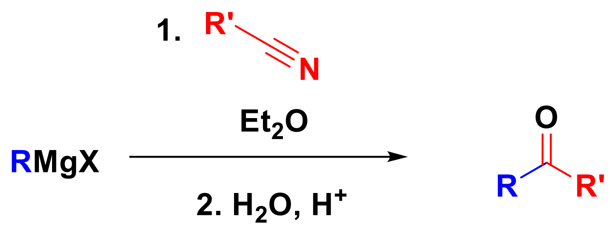
I. Carbon-carbon bonds formation

✓ Reactivity with carbon dioxide



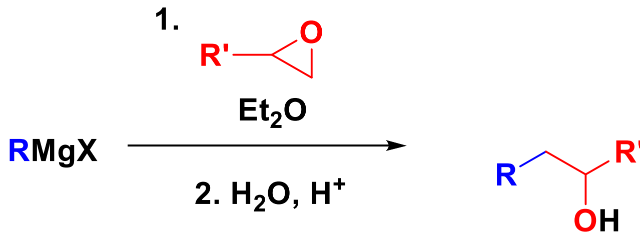
carboxylic acids

✓ Reactivity with nitriles :



ketones

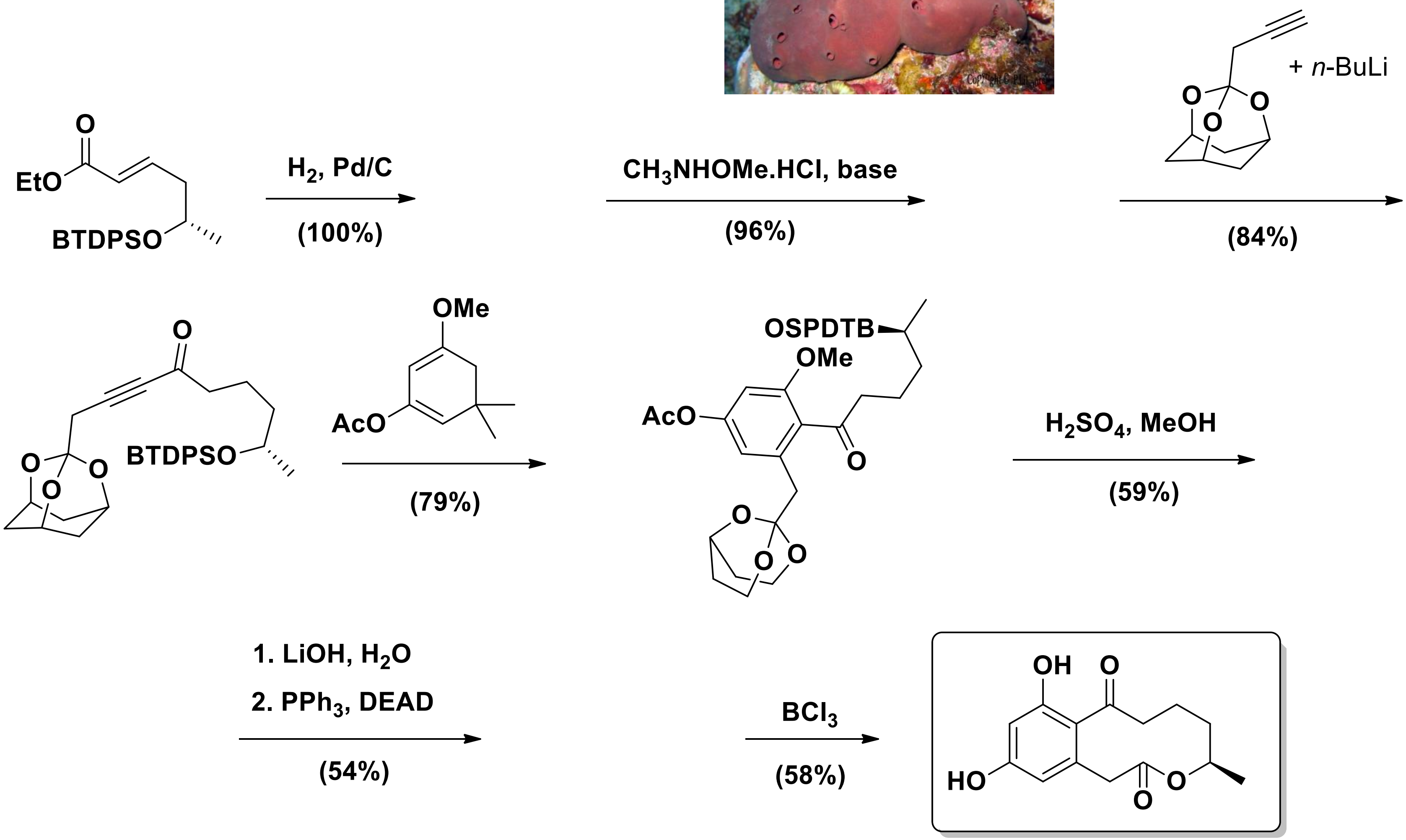
✓ Reactivity with epoxydes :



alcohols

I. Carbon-carbon bonds formation

✓ Synthesis of Xestodecalactone A:

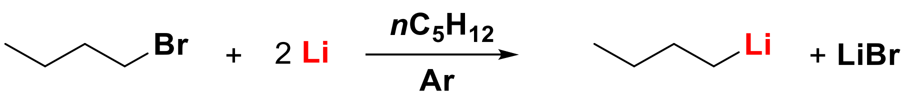


T. Yoshino, F. Ng, S. J. Danishefsky *J. Am. Chem. Soc.* **2006**, *128*, 14185-14191.

✓ I. 2. Organometallic reagents

➢ I. 2. 2. Organolithium and related compounds

✓ The most simple : metal + halogenated derivatives

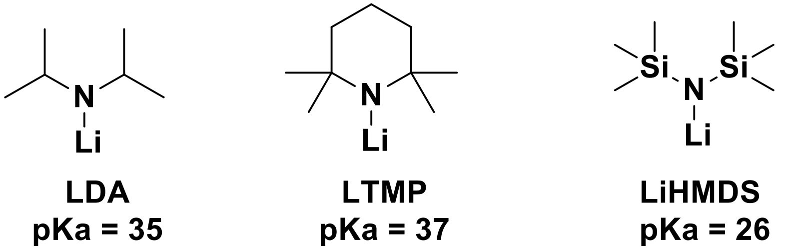


✓ Very reactive reagent : anhydrous conditions, no oxygen

✓ Nucleophile and base

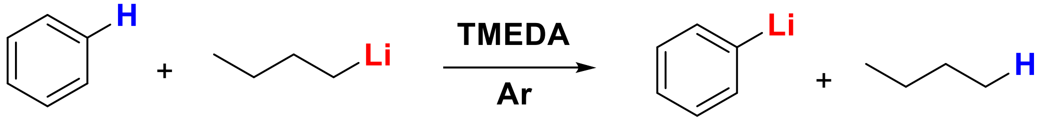
✓ The most used reagent : the *n*-butyllithium, pKa = 50

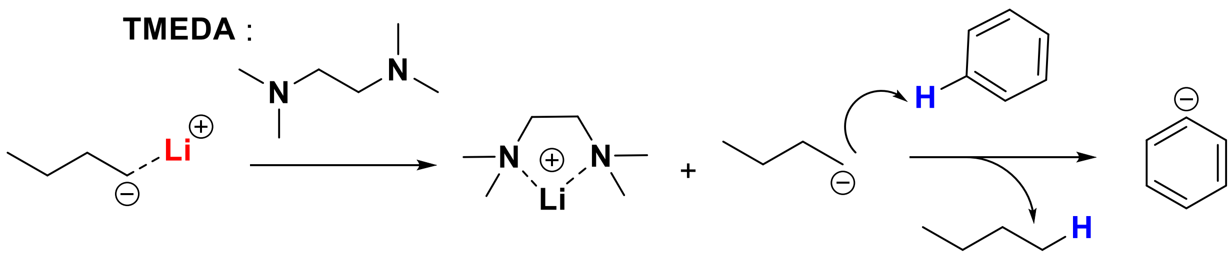
✓ Bulky and non-nucleophilic bases



I. Carbon-carbon bonds formation

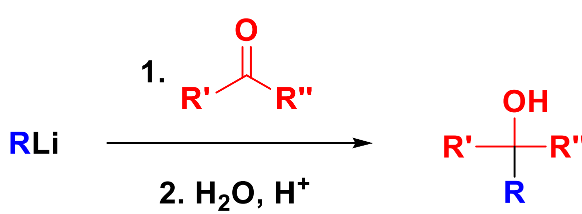
✓ Strong base : metallation :





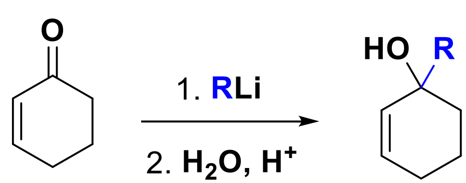
TMEDA = increase the reaction rate

✓ Reactivity :



alcohols

✓ « 1,2 » conjugate addition :



Chapter II

C=C bonds formation

II. C=C bonds formation

1. β-H elimination

2. Phosphorus ylides and related compounds
   a. Wittig reaction
   b. Horner-Wadsworth-Emmons reaction
   c. Peterson Olefination
   d. Julia Olefination

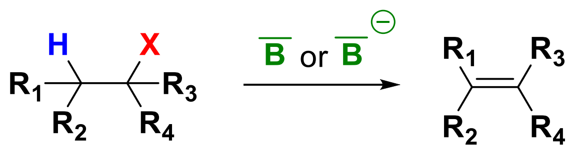
3. Shapiro reaction

4. “One word” about the Heck reaction

II. C=C bonds formation

✓ II. 1. β-H elimination

➢ II. 1. a. Generality



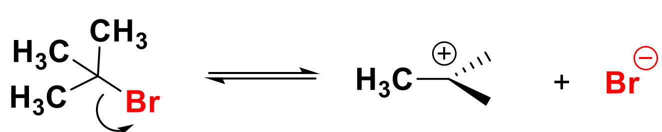
B : Lewis base and/or nucleophile

competition between E and S_N

➢ II. 1. b. Elimination E1, first order, 2 steps

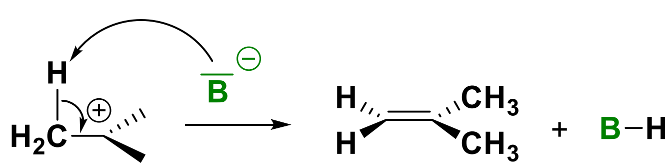
The formed carbocation must be stable

1. Slow step : halogen ionization



planar geometry

2. Fast step : nucleophilic reaction

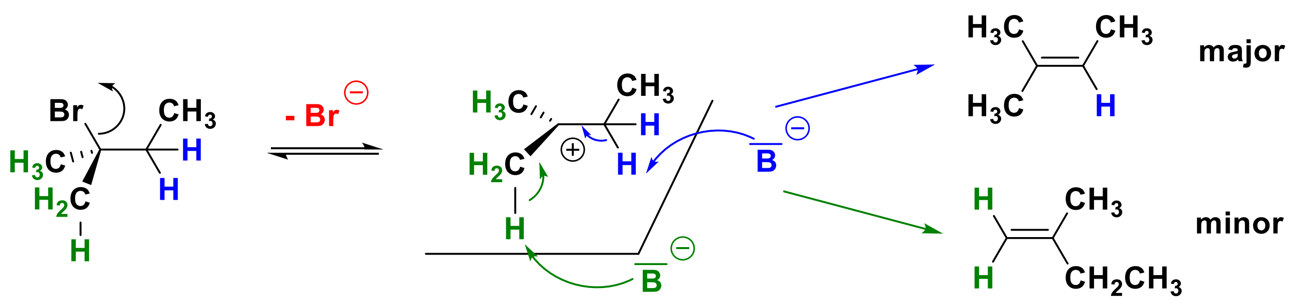


II. C=C bonds formation

✓ II. 1. β-H elimination

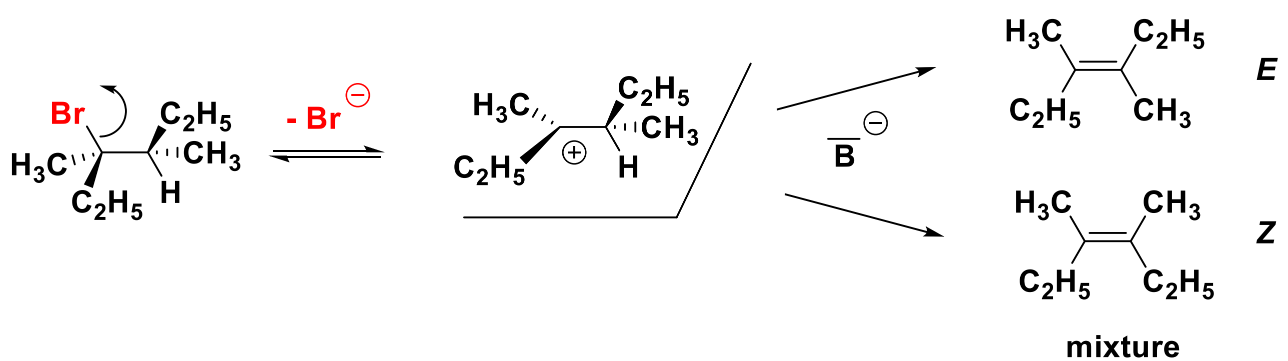
➢ Zaitsev Rule

The most substituted product will be the most stable



➢ No stereospecifitity

Carbocation : planar geometry

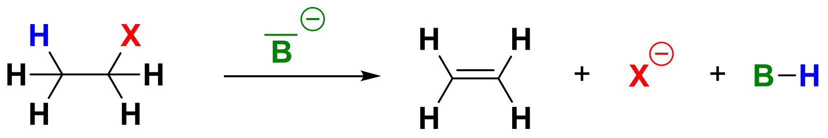


II. C=C bonds formation

✓ II. 1. β-H elimination

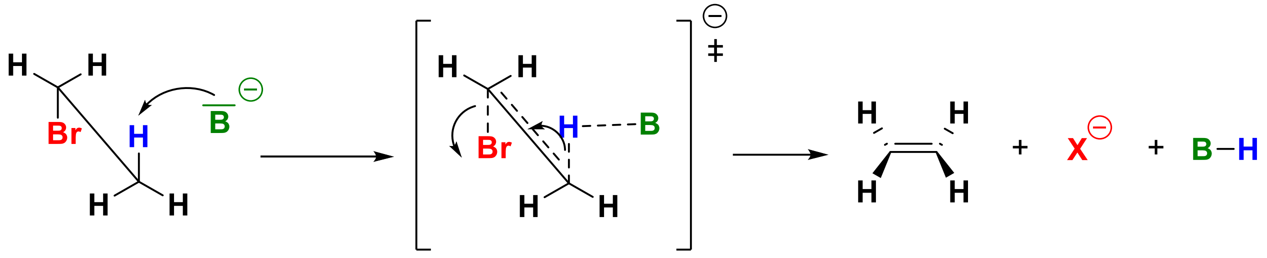
➢ II. 1. c. Elimination E2, second order, 1 step

No carbocation



competition between E and S_N

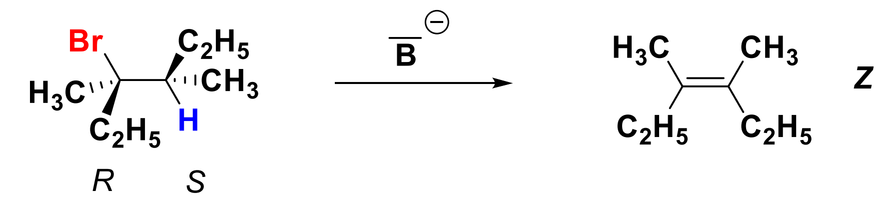
Mechanism : H and Br antiperiplanar

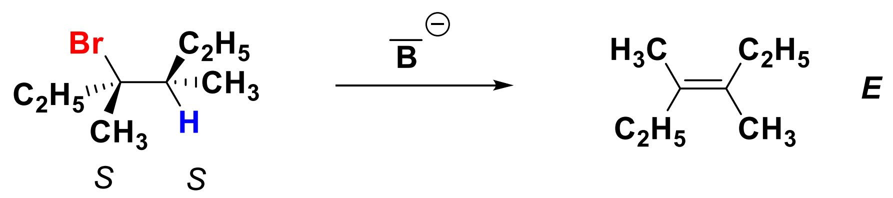


transition state

✓ II. 1. β-H elimination

➢ Stereospecifitity





II. C=C bonds formation

✓ II. 1. β-H elimination

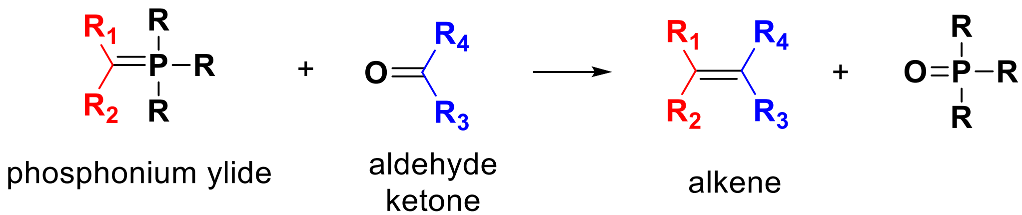
➢ Summary

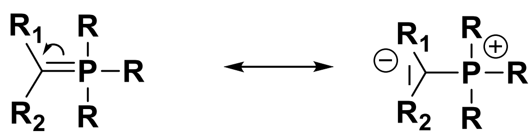
E1	E2
First order	Second Order
2 steps, 1 intermediate	1 step
Stable carbocation	No carbocation
Protic polar solvent	Aprotic polar solvent
Neutral bases	Strong and charged bases
No stereospecific reaction	Stereospecific reaction (H and Br antiperiplanar)
The most substituted alkene (Zaitsev Rule)	It depends

II. C=C bonds formation

✓ II. 2. Phosphorus ylides and related compounds

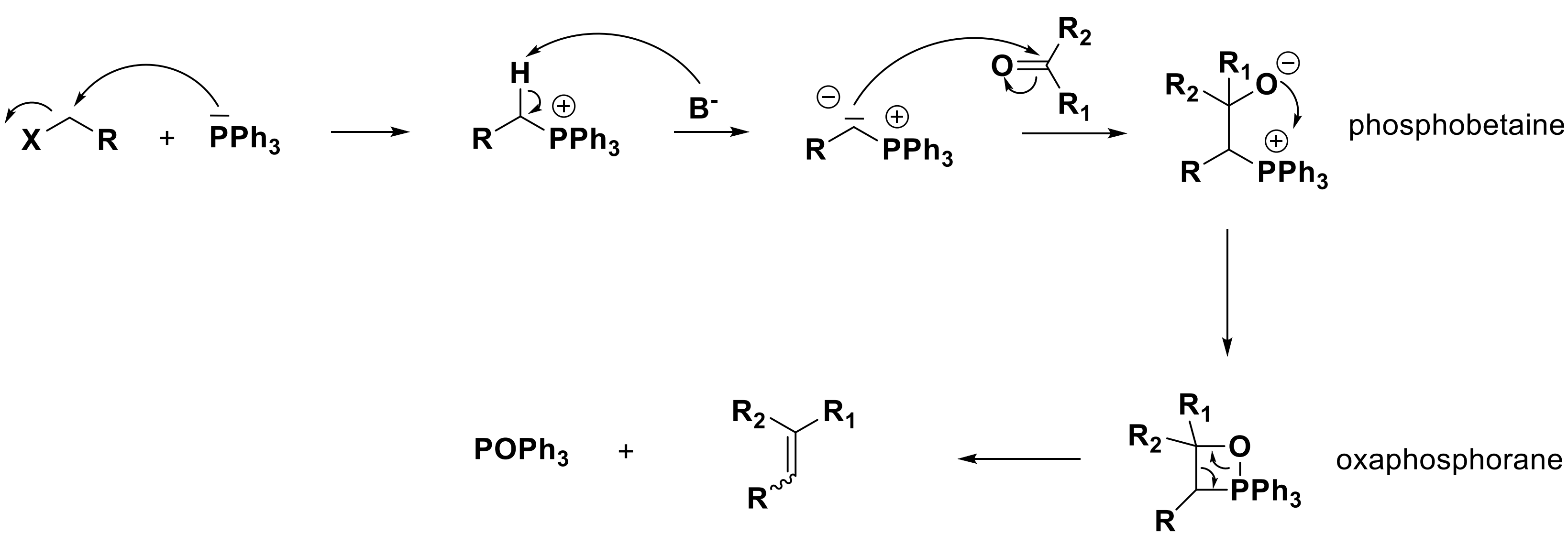
➢ II. 2. a. Wittig reaction





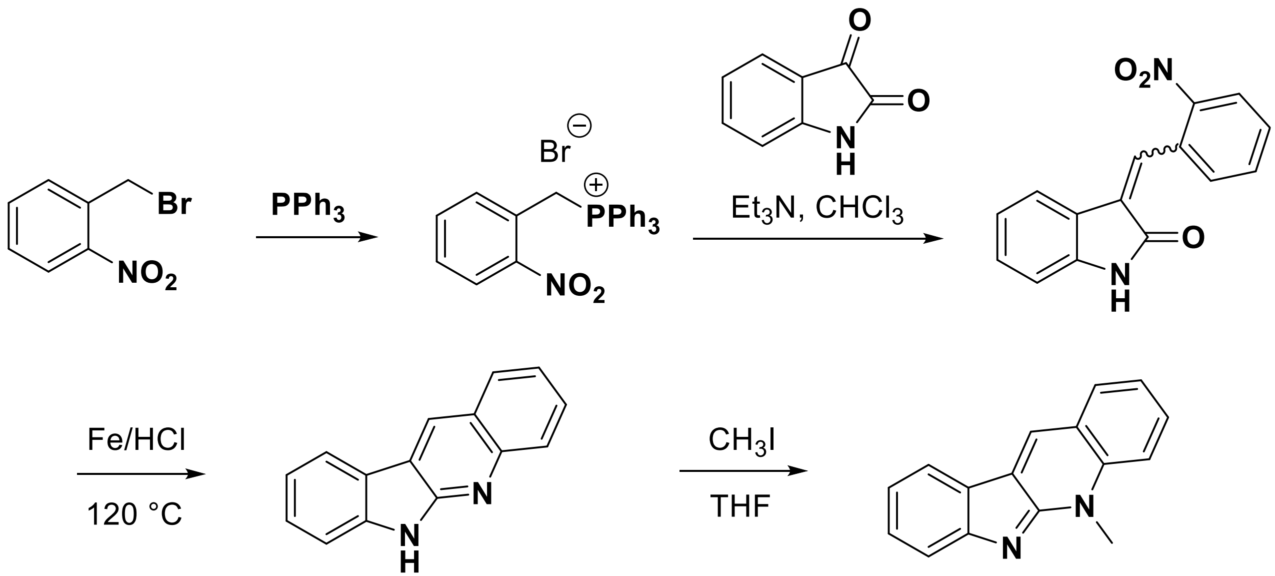
Nobel Prize in Chemistry in 1979

Mechanism :



II. C=C bonds formation

Exercise : total synthesis of (+)-neocryptolepine



antimicrobial and cytotoxic activity

P. T. Parvatkar, S. G. Tilve *Tetrahedron Lett.* **2011**, *52*, 6594-6596.