Master 1 International

Axe 2: Pharmacy and biotechnology

TU7 Chemistry

C-C bond formation

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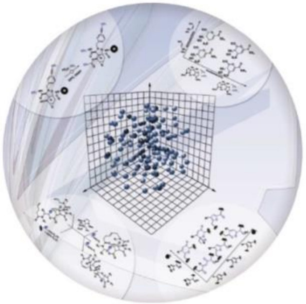
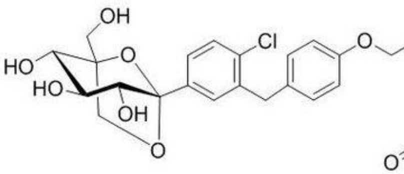
2024-2025



Carbon-carbon bonds...

- ✓ Carbon-carbon bons are ubiquitous in natural products and drugs
  - ➢ C-C : alkane
  - ➢ C=C : alkene
  - ➢ C≡C : alkyne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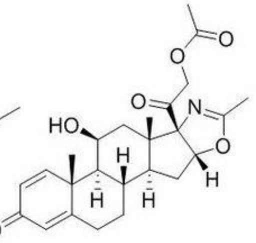
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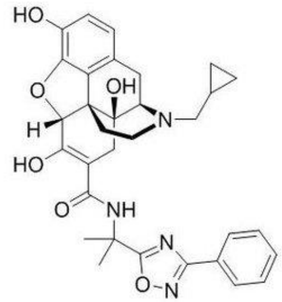
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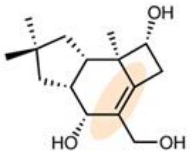
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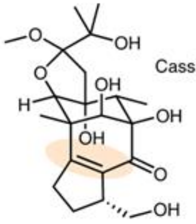
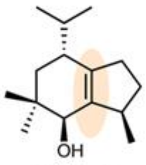

Cassiabudanol A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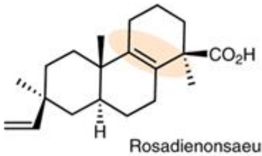
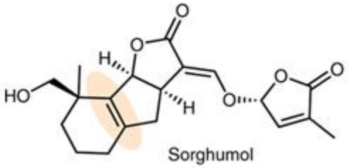
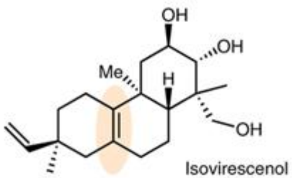

Rosadienonsaeure


Sorghumol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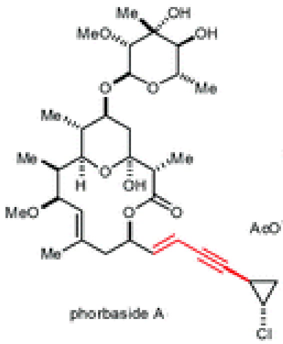
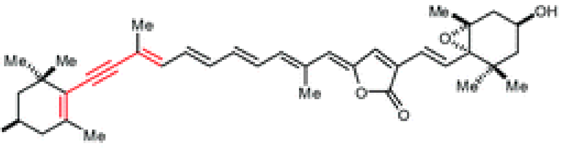
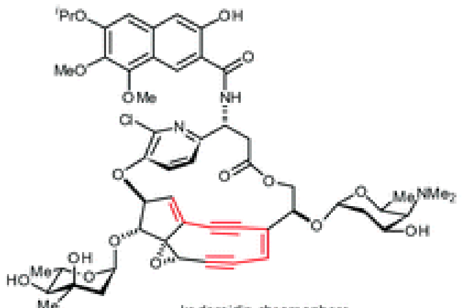

phorbaside A

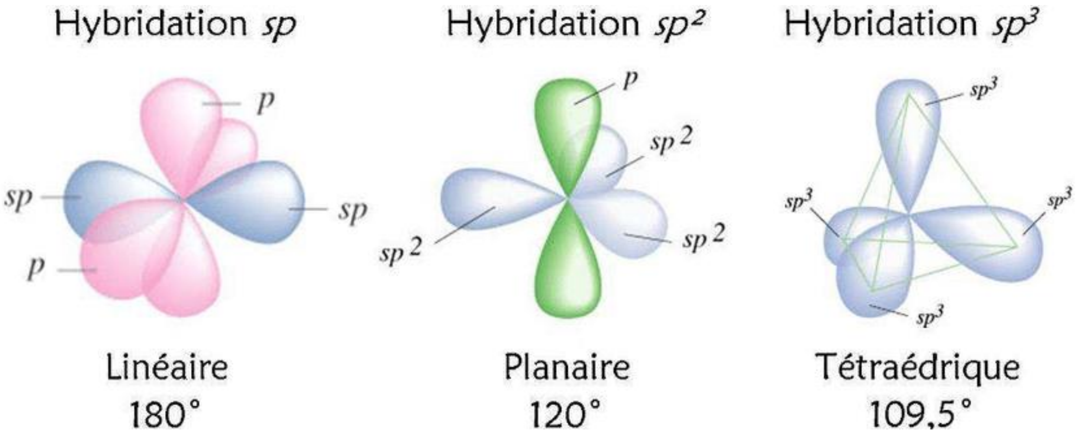

pyrrhoxanthin


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

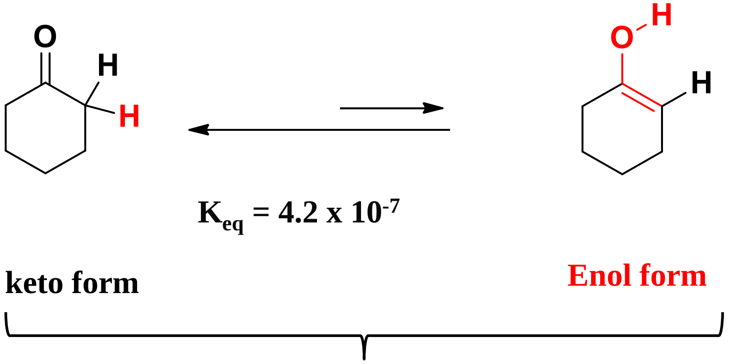
3. Pericyclic reactions
    a. Definition
    b. Diels-Alder reaction
    c. Sigmatropic reaction

4. “One word” about cross-coupling reactions

I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Keto-enol equilibria



$K_{eq} = 4.2 \times 10^{-7}$

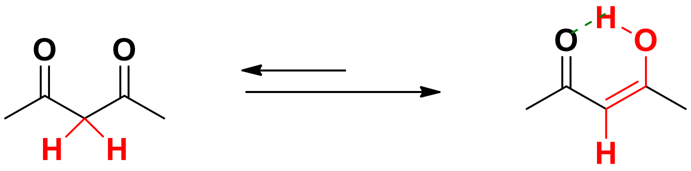
keto form

Enol form

Tautomers

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

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



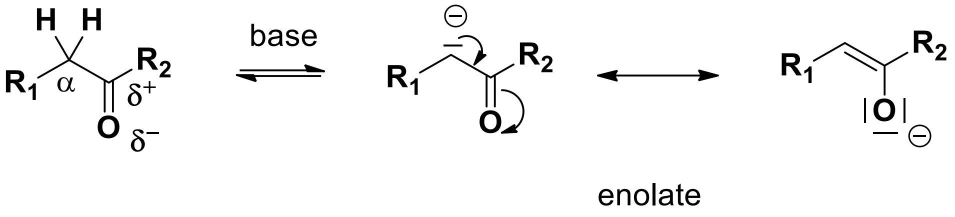
Stabilizing effects of the enol form :

- ➢ Conjugation, resonance
- ➢ Intramolecular hydrogen bond

I. Carbon-carbon bonds formation

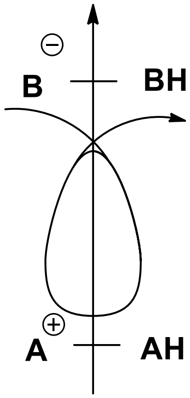
✓ I. 1. Enols, enolates and related compounds

➢ I. 1. a. Formation

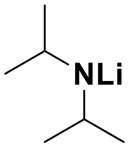


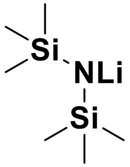
Usually : strong base

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



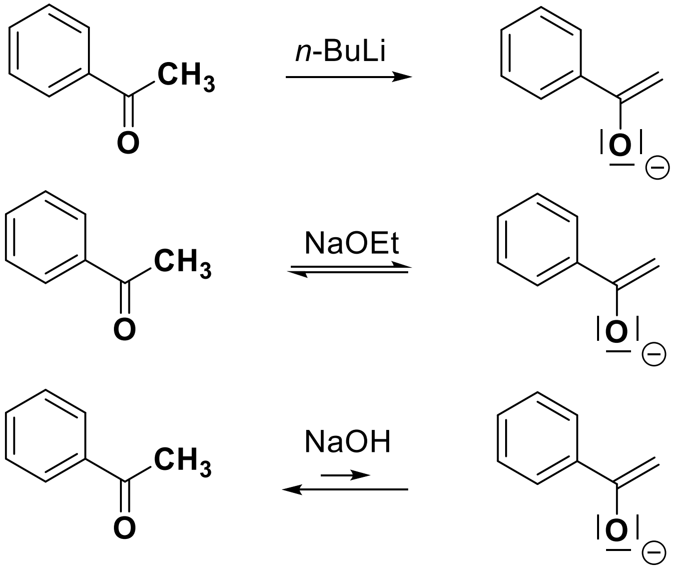


I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

pKa

Base effect :

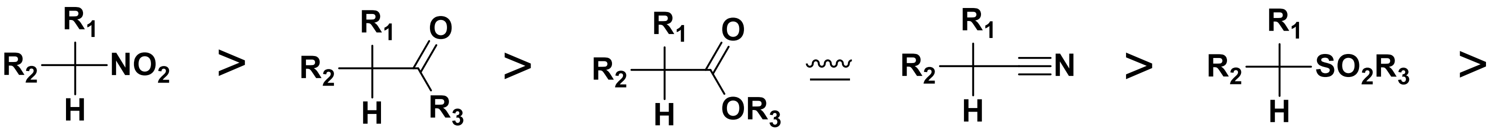


50

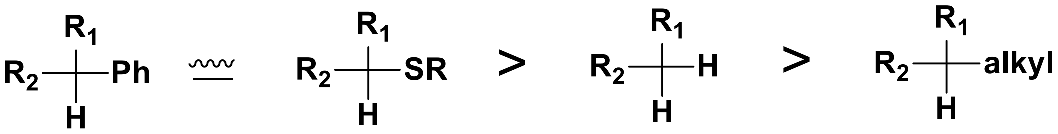
16

14

Acidity scale:



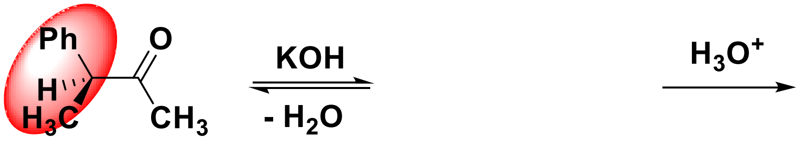
pKa = 10 pKa = 20-25 pKa = 25



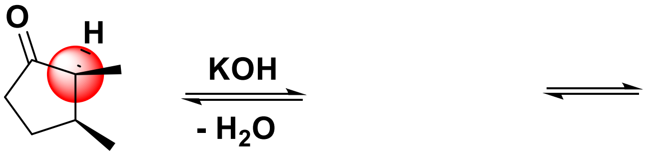
I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Racemization :



Isomerization :

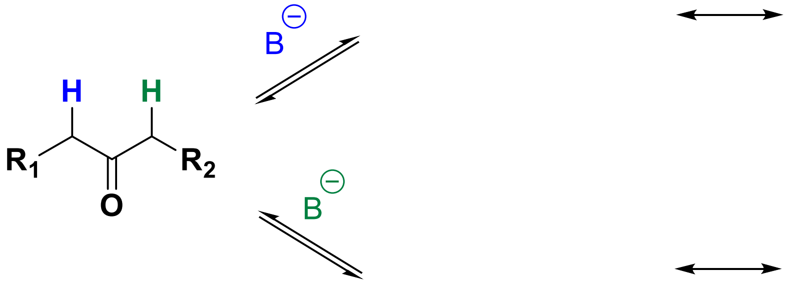


thermodynamic ketone

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

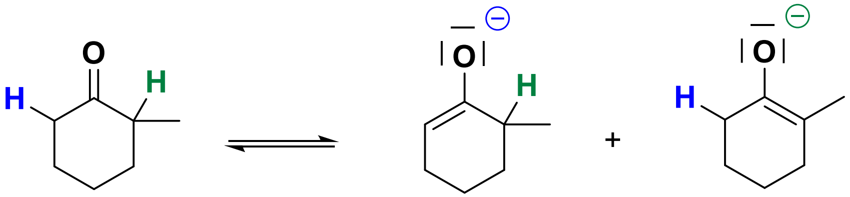
Thermodynamic control :
the less acidic and accessible H

- ➢ 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 ?



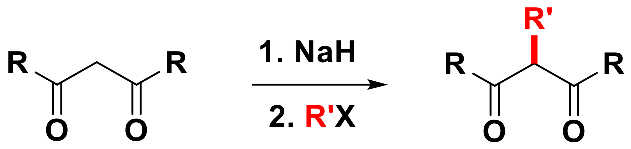
LDA, DME, -78 °C	99%	1%
Et_3N, DMF	22%	78%

Kinetic control : the more acidic and accessible H	Thermodynamic control : the less acidic and accessible H
➢ Low temperature	➢ Higher temperature
➢ Base excess	➢ Ketone excess
➢ Short reaction time	➢ Long reaction time
➢ Strong base	➢ Mild base
➢ Aprotic solvent	➢ Protic solvent

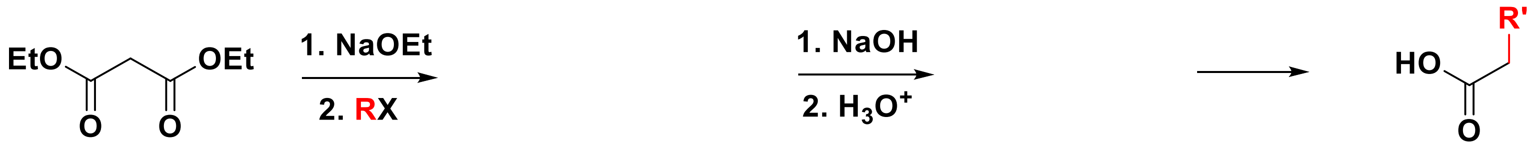
I. Carbon-carbon bonds formation

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

Bis-activated reagent



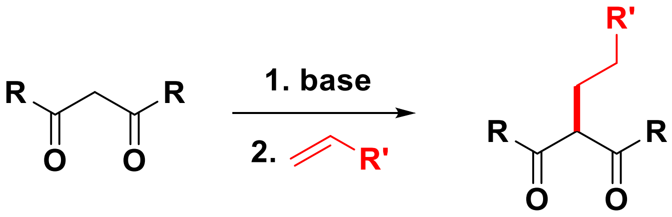
Malonic synthesis



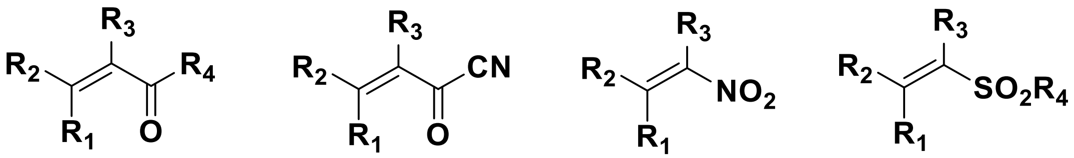
I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Nucleophilic conjugate addition = Mickael addition



Electrophile :



Arthur Michael
(1853-1942)
American chemist

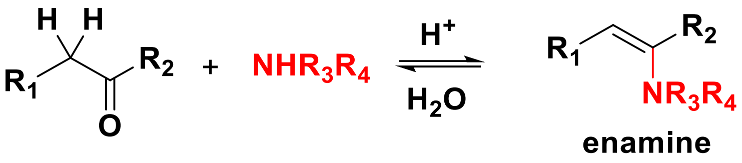
Mechanism :

I. Carbon-carbon bonds formation

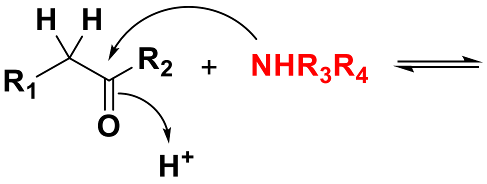
- ✓ I. 1. Enols, enolates and related compounds

Enamine alkylation

Preparation : secondary amine + carbonyl derivative :



Mechanism :

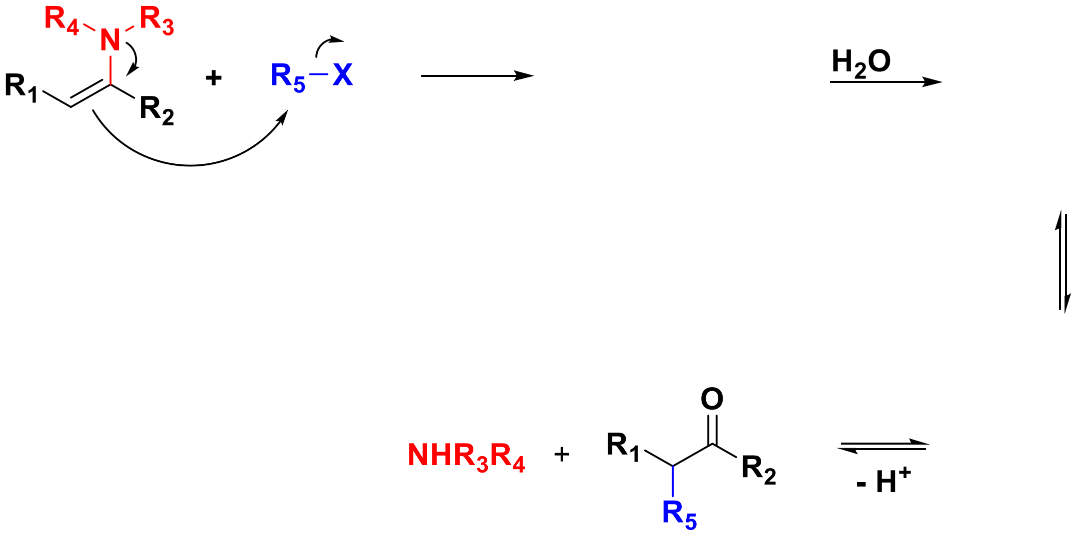


I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Enamine alkylation

Alkylation :

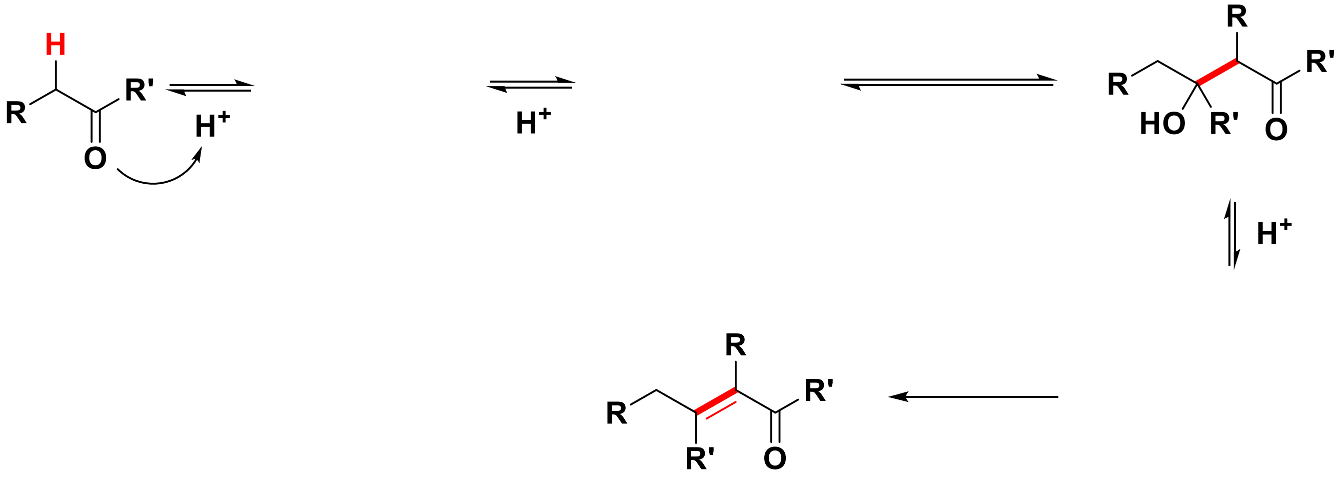


The enamine is more nucleophilic than the enol.

I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds
  - ➢ I. 1. c. Reactivity with carbonyl moities

Aldol addition / condensation : acid catalyzed

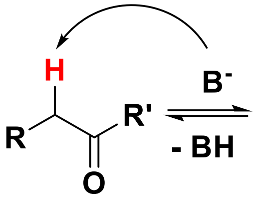


The formation of the conjugated system is the driving force for this spontaneous dehydration.

I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Aldol addition / condensation : based catalyzed



I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

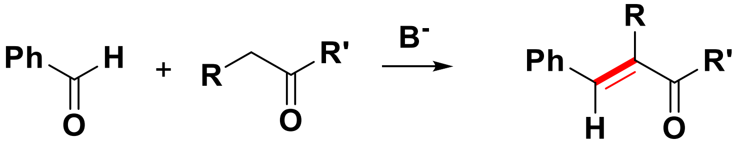
Mixed condensation

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

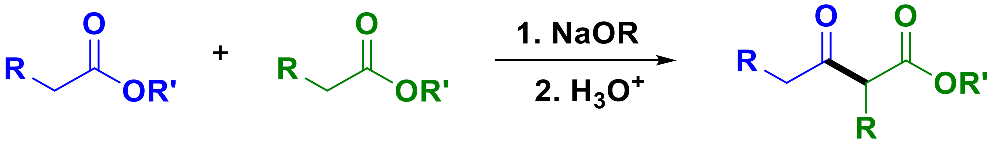
- The C=O from the aldehyde is the most electrophilic moiety.
- The enolate from the keton is the most nucleophilic moiety.



I. Carbon-carbon bonds formation

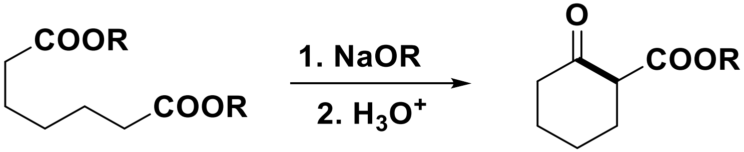
- ✓ I. 1. Enols, enolates and related compounds

Claisen condensation



Ludwig Claisen
(1851-1930)
German chemist

Dieckmann condensation



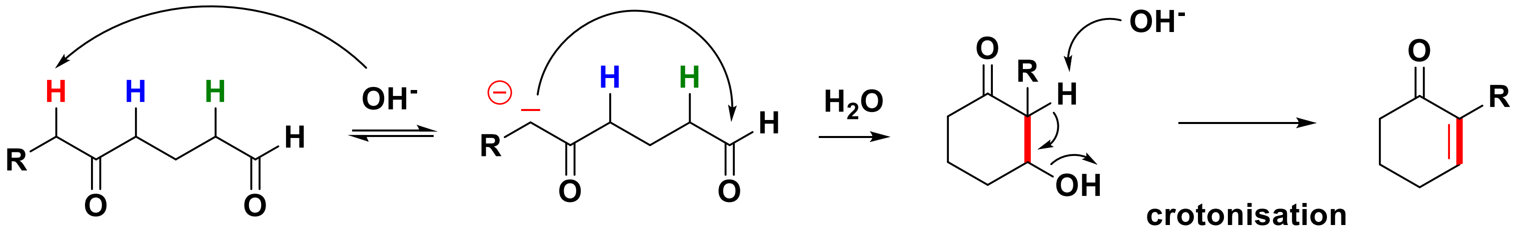
Walter Dieckmann
(1869-1925)
German chemist

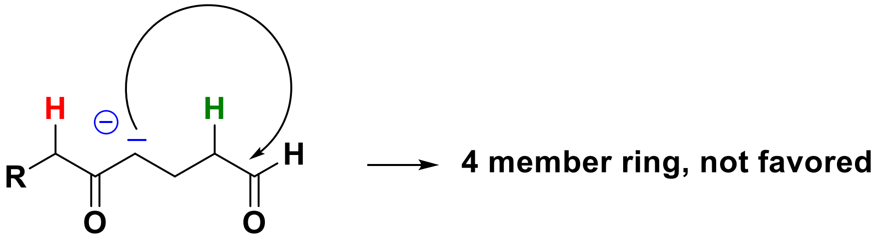
I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

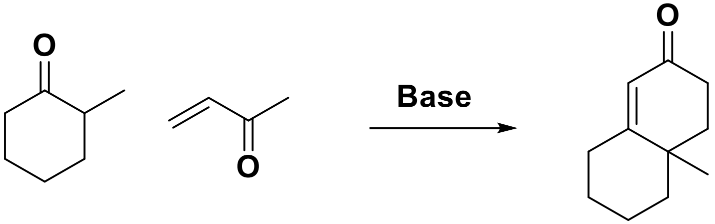
Intramolecular condensation

5 or 6 member rings formation





Robinson annelation

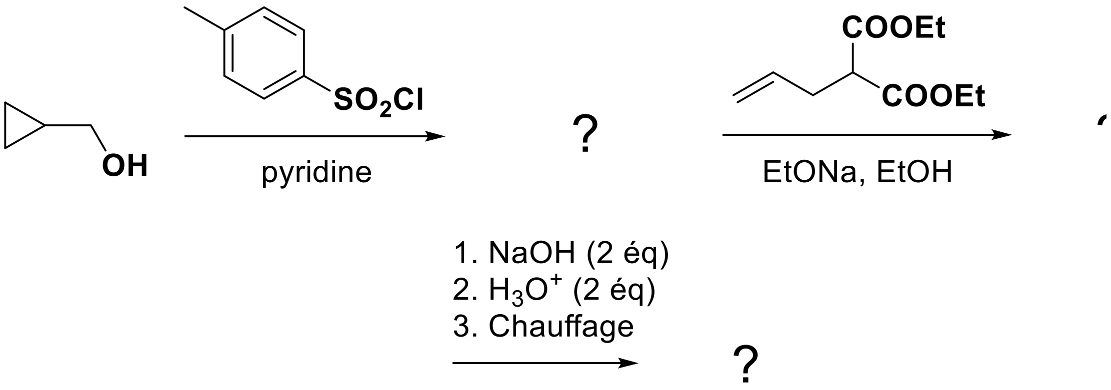


Sir Robert Robinson
(1886-1975)
English chemist

I. Carbon-carbon bonds formation

✓ I. 1. Enols, enolates and related compounds

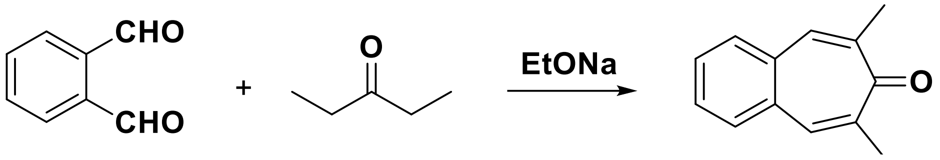
Application:

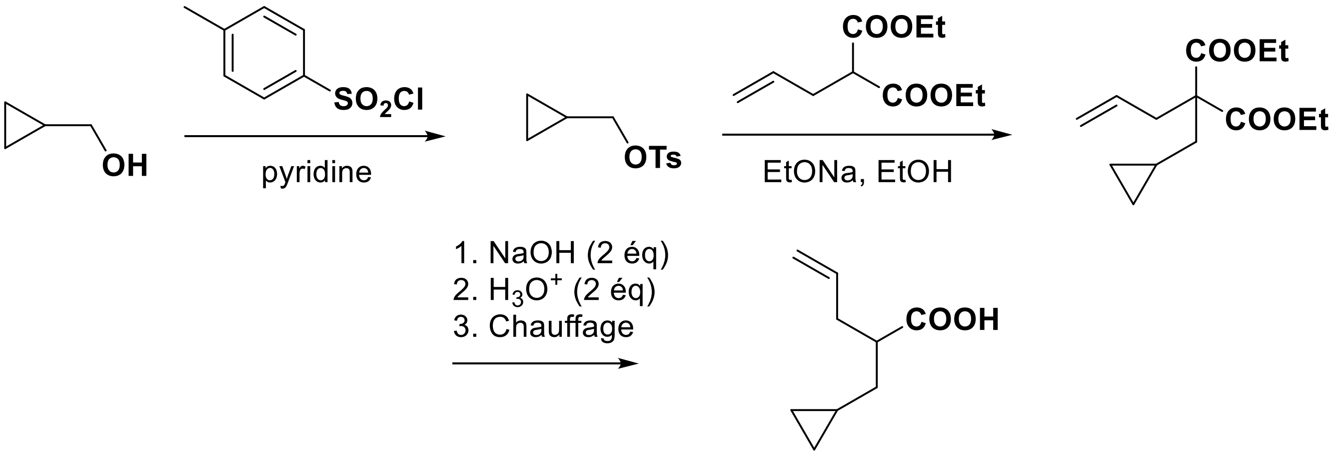


I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Application:



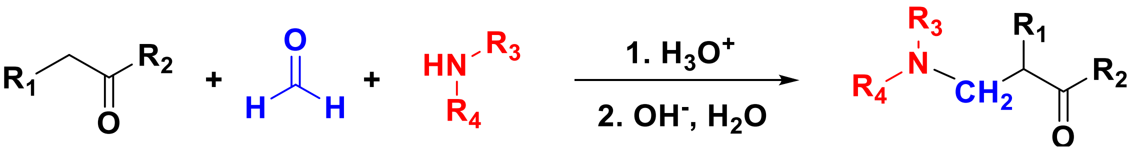


I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Mannich reaction

Aminomethylation: “-CH_2-NR_2”



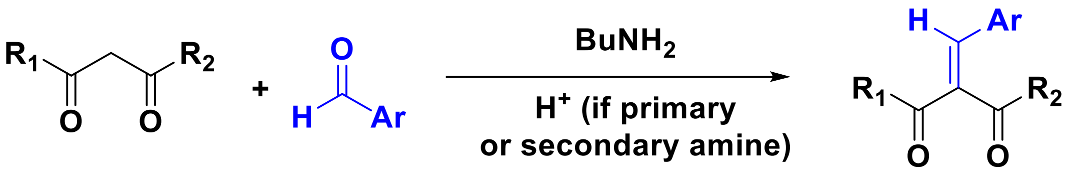
Carl Mannich
(1877-1947)
German chemist

Mechanism :

I. Carbon-carbon bonds formation

- ✓ I. 1. Enols, enolates and related compounds

Knoevenagel Condensation



Emil Knoevenagel
(1865-1921)
German chemist

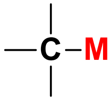
Only with bis-activated substrate

Mechanism :

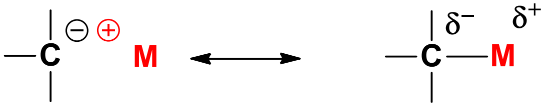
I. Carbon-carbon bonds formation

- ✓ 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...



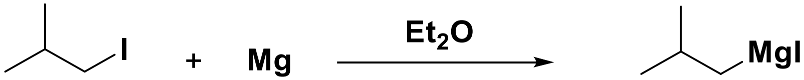
- ✓ The carbon bears a negative charge
- ✓ Basic and nucleophilic reagent

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

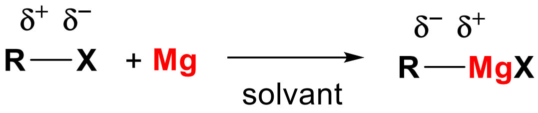
I. Carbon-carbon bonds formation

✓ 1^{er} example in 1901 from Victor Grignard, Nobel Prize in chemistry 1912 :



Victor Grignard
1871-1935
Nobel Prize 1912
French chemist

✓ General reaction :



$$\overset{\delta^+}{R}—\overset{\delta^-}{X} + \mathrm{Mg} \xrightarrow[\text{solvant}]{} \overset{\delta^-}{R}—\overset{\delta^+}{\mathrm{Mg}}X$$

✓ 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

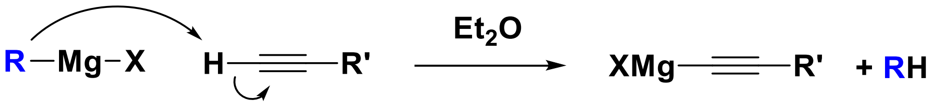
- ✓ Hydrolysis :

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

X = Br, I, Cl

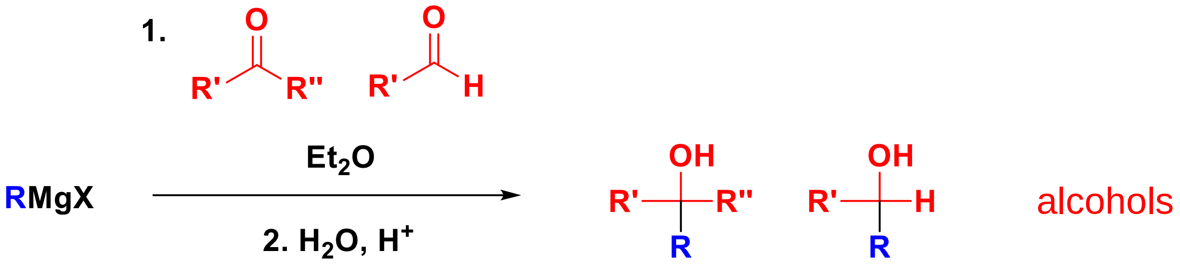
- ✓ Basic reagents : deprotonation of carboxylic acids, phenols, amines … and alkynes

- ✓ Important case with alkynes :



I. Carbon-carbon bonds formation

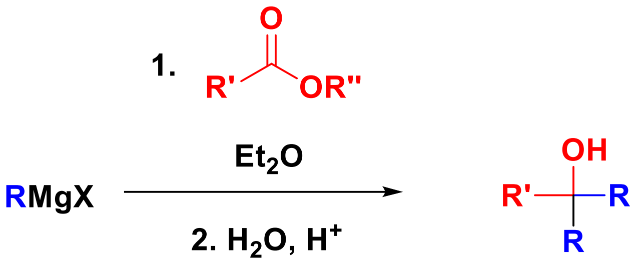
- ✓ Reactivity with ketones et aldehydes



- ✓ Mechanism :

I. Carbon-carbon bonds formation

- ✓ Reactivity with esters



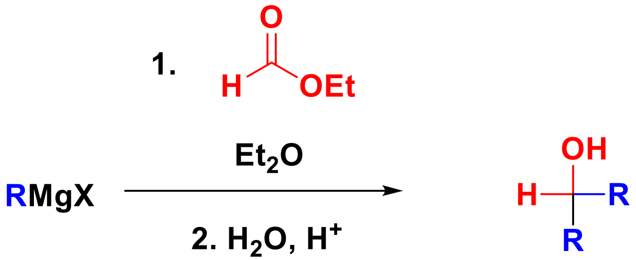
alcohols

- ✓ Mechanism :

No mono-addition

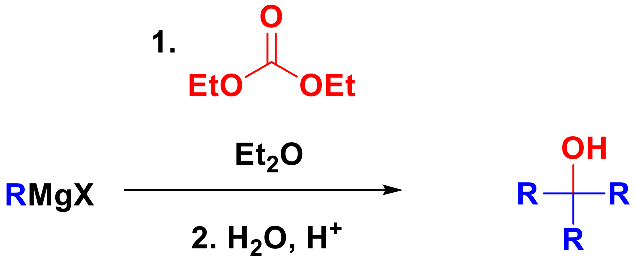
I. Carbon-carbon bonds formation

✓ Reactivity with ethyl formiate



alcohols

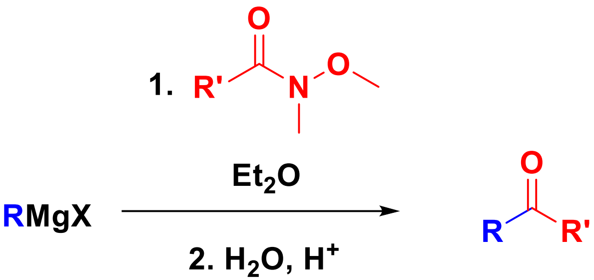
✓ Reactivity with carbonate esters :



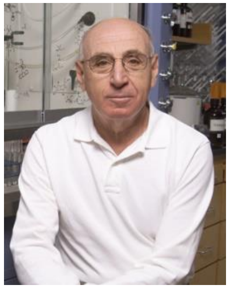
No possibility to create a carbonyl moiety…

I. Carbon-carbon bonds formation

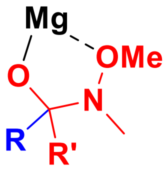
- ✓ The solution : Weinreb amides



ketones



Steven M. Weinreb
(1941)
American chemist

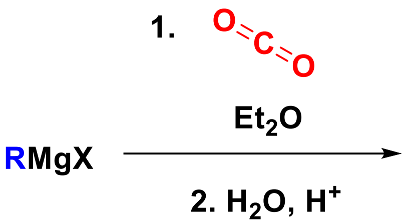


Key intermediate

One limitation : demethoxylation

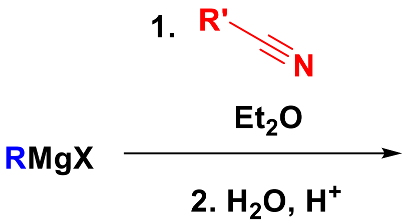
I. Carbon-carbon bonds formation

✓ Reactivity with carbon dioxide



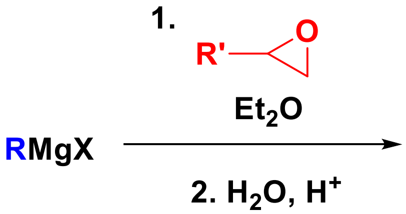
carboxylic acids

✓ Reactivity with nitriles :



ketones

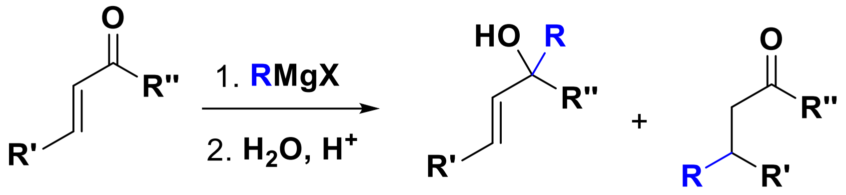
✓ Reactivity with epoxydes :



alcohols

I. Carbon-carbon bonds formation

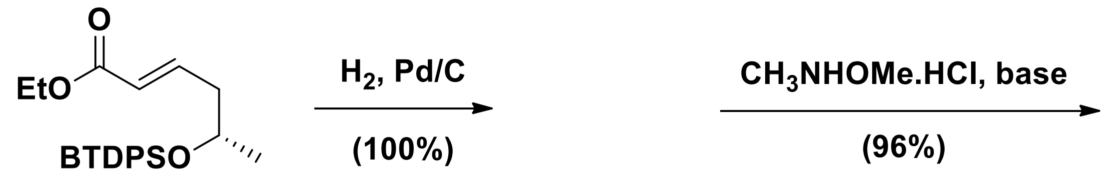
- ✓ Conjugate additions :

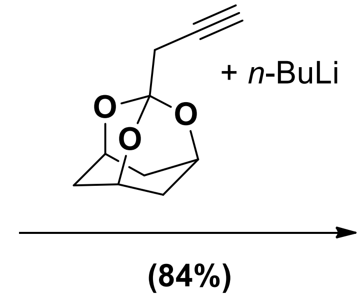


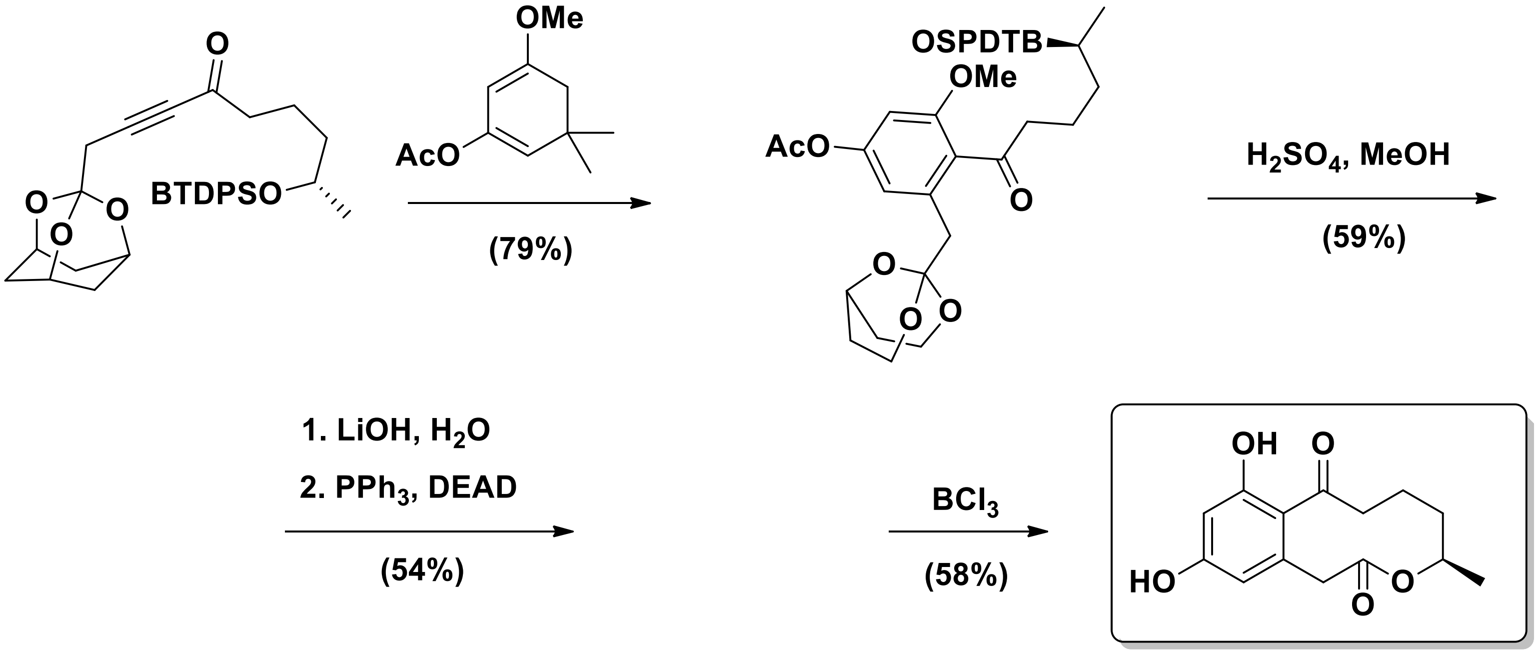
Very often : mixture of « 1,2 » vs « 1,4 » additions

I. Carbon-carbon bonds formation

- ✓ Synthesis of Xestodecalactone A:





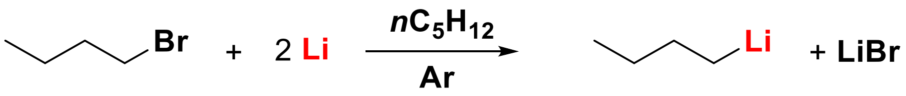


T. Yoshino,F. Ng, S. J. Danishefsky *J. Am. Chem. Soc.* **2006**, *128*, 14185-14191.

I. Carbon-carbon bonds formation

- I. 2. Organometallic reagents
    - I. 2. 2. Organolithium and related compounds

- The most simple : metal + halogenated derivatives

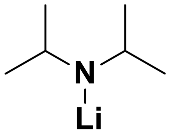


- Very reactive reagent : anhydrous conditions, no oxygen

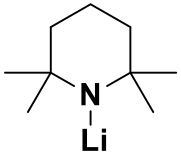
- Nucleophile and base

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

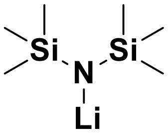
- Bulky and non-nucleophilic bases



LDA
pKa = 35



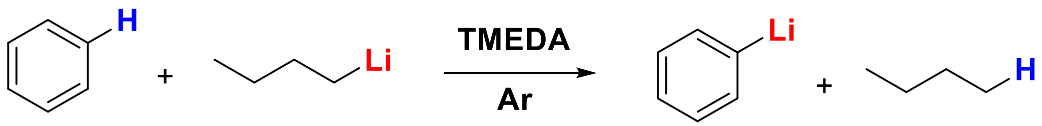
LTMP
pKa = 37

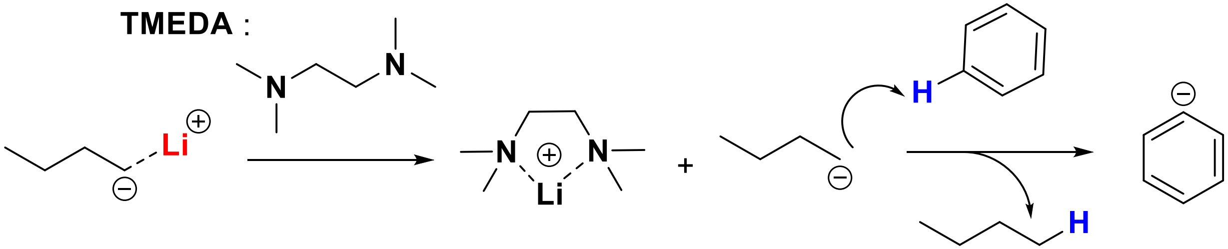


LiHMDS
pKa = 26

I. Carbon-carbon bonds formation

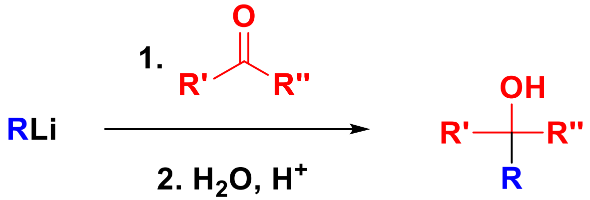
- ✓ Strong base : metallation :





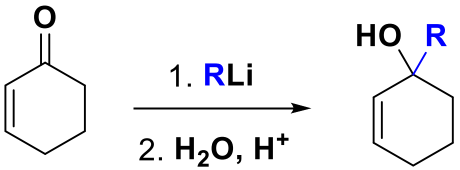
TMEDA = increase the reaction rate

- ✓ Reactivity :



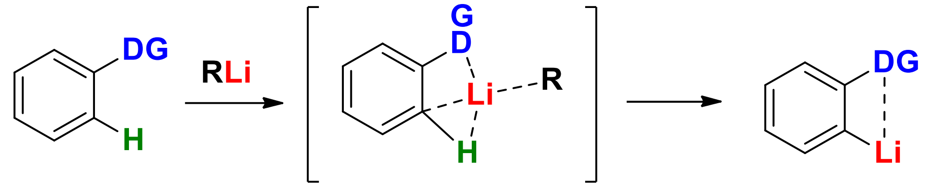
alcohols

- ✓ « 1,2 » conjugate addition :



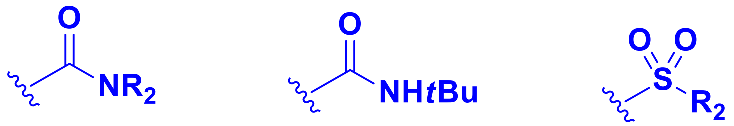
I. Carbon-carbon bonds formation

- ✓ *ortho*-metallation :

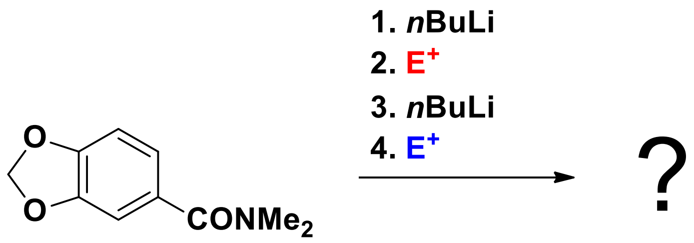


GD = Directing Group

ortho-directed reaction



- ✓ One application :



I. Carbon-carbon bonds formation

- ✓ Organocuprate compounds :

$$2\ RLi + CuI \xrightarrow[Et_2O]{} R_2CuLi + LiI$$

Gilman reagent

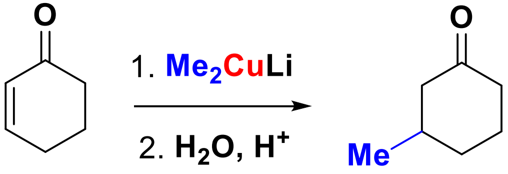
- ✓ Oligomers formation : $(R_2CuLi)_n$

- ✓ S_N2 type addition

$$\text{Alkyl-X} + R_2CuLi \longrightarrow \text{Alkyl-R}$$

X = halogens

- ✓ « 1,4 » conjugate addition:



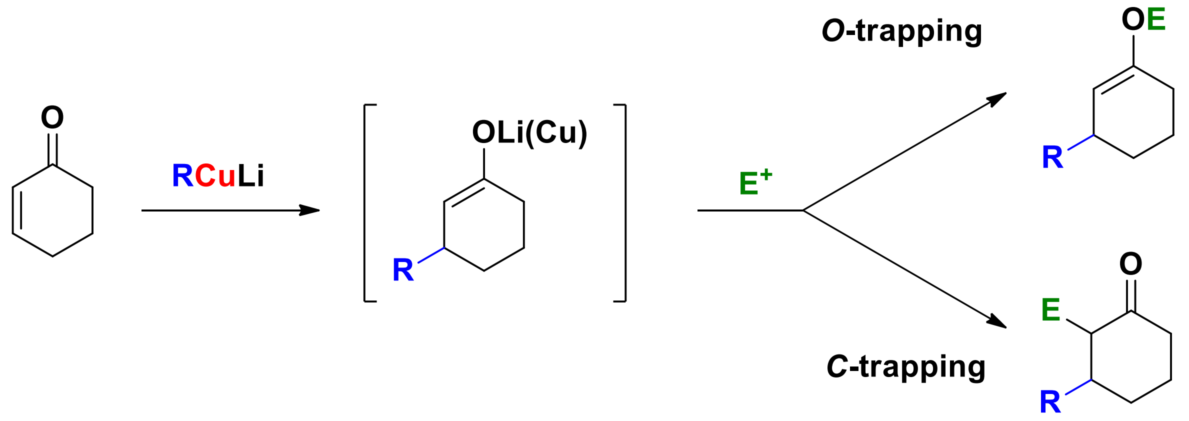
I. Carbon-carbon bonds formation

- ✓ Reactivity :

Compatible with RCOCl with competition with other carbonyl groups

Reactivity order : RCOCl > RCHO > I, OTs > epoxides > Br >> ketones > esters > nitriles

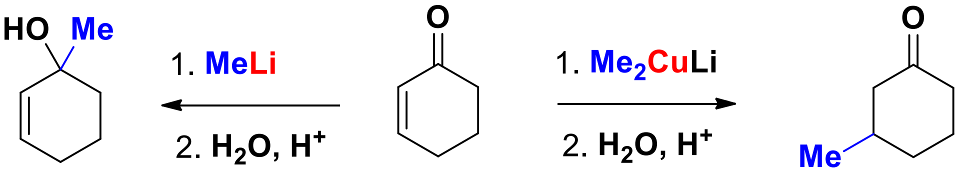
- ✓ Tandem reaction :



***O*-trapping, E = R_3SiCl, $((RO)_2P(O)Cl$**
***C*-trapping, E = RX, Br, I, Cl, aldehyds**

I. Carbon-carbon bonds formation

✓ Come-back : « 1,2 » versus « 1,4 » conjugate additions :

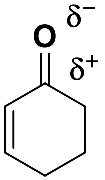


$MeLi \equiv \overset{\ominus}{Me}\ \overset{\oplus}{Li}$

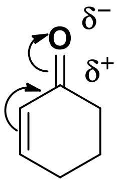
"strong" nucleophile

$Me_2CuLi \equiv \overset{\delta^-}{Me_2}\overset{\delta^+}{Cu}Li$

"weak" nucleophile



"strong" electrophile



"weak" electrophile

Finally : « strong » reacts with « strong » and
« weak » reacts with « weak »

I. Carbon-carbon bonds formation

- ✓ Organocinzic compounds :

- ✓ 1st method :

$$R{-}X + Zn \xrightarrow[\text{solvent}]{} R{-}ZnX$$

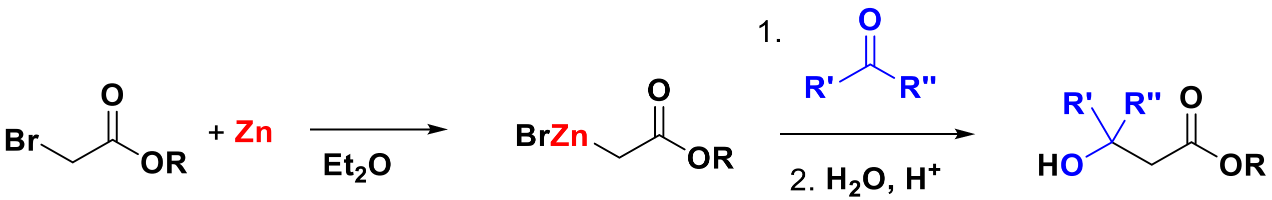
in situ prepared

- ✓ 2nd method :

$$RM + ZnX_2 \longrightarrow RZnX + MX$$

M = Li, Mg

- ✓ Reformatsky reaction (1887)

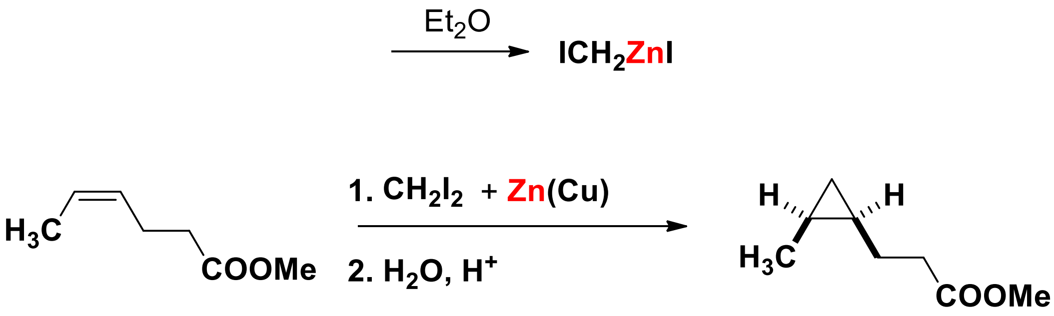


+ aldehyds or ketones
- No reactivity with esters

Crotonisation possible

I. Carbon-carbon bonds formation

- ✓ Simmons and Smith cyclopropanation (1958)



syn addition

- ✓ Today, Furukawa reagent : $Et_2Zn + CH_2I_2$

I. Carbon-carbon bonds formation

- ✓ I. 3. Pericyclic reactions
  - ➢ I. 3. a. Definition

Pericyclic reaction:

- ○ The transition state of the molecule has a cyclic geometry
- ○ Reaction progresses in a concerted fashion
- ○ The bond orbitals involved in the reaction overlap in a continuous cycle at the transition state

Cycloaddition: if p and q are conjugated polyenes, p + q cycloaddition is :

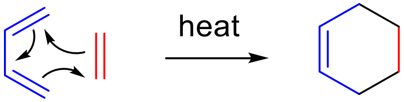
- ○ A pericyclic reaction giving a cyclic adduct
- ○ 2 simple bonds are created
- ○ 2 double bonds are broken

I. Carbon-carbon bonds formation

✓ I. 3. Pericyclic reactions

➢ I. 3. b. Diels-Alder reaction

The Diels-Alder reaction is a conjugate addition reaction of a conjugated diene to an alkene or alkyne (the dienophile) to produce a cyclohexene



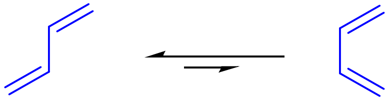
Otto Diels
(1876-1954)
German Chemist

Kurt Alder
(1902-1958)
German Chemist

1950

Cycloaddition: if p and q are conjugated polyenes, p + q cycloaddition is :

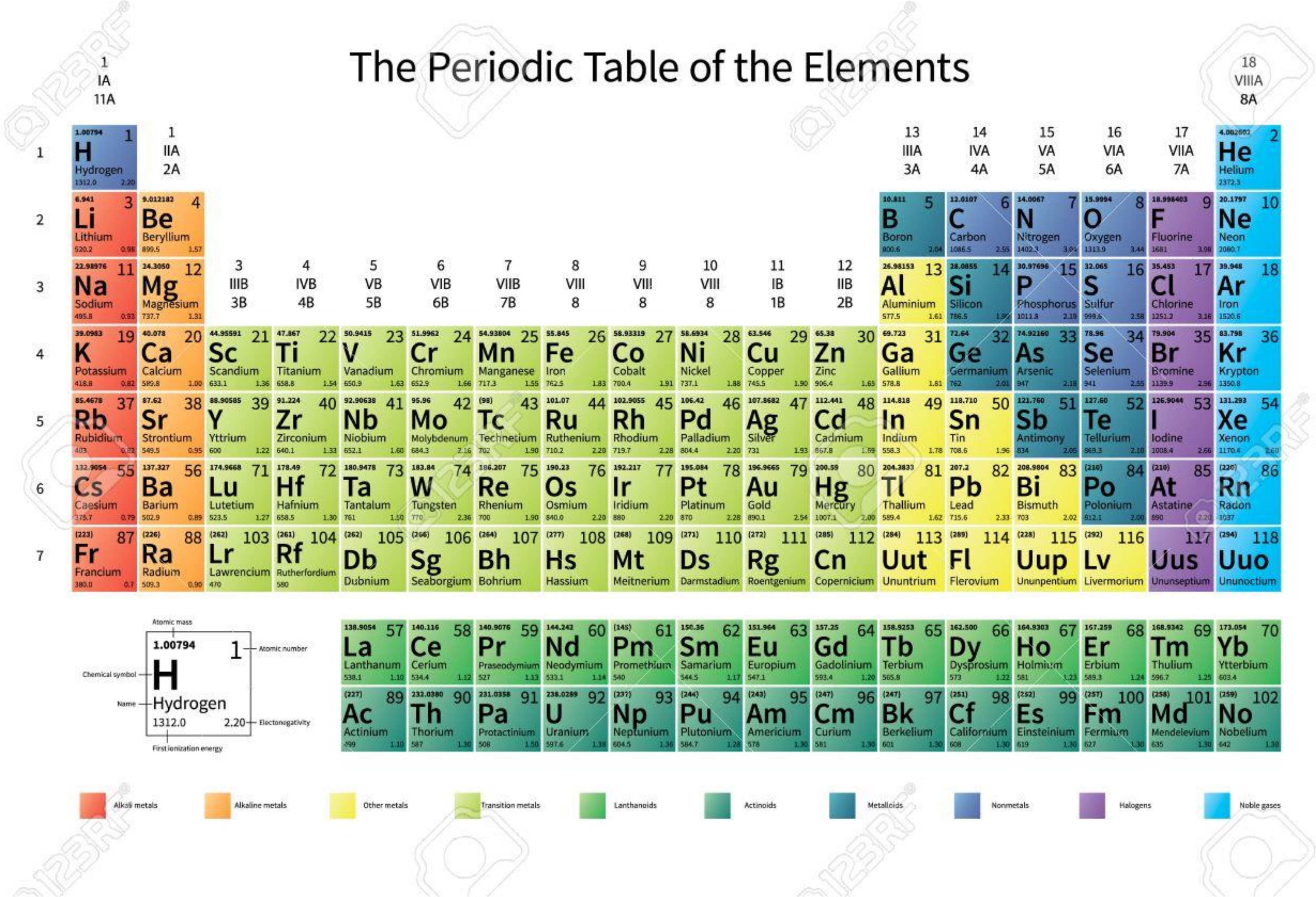
- ○ The reaction is usually thermodynamically favorable
- ○ High degree of both regio- and stereoselectivity



I. Carbon-carbon bonds formation

- ✓ I. 4. “One word” about cross-coupling reactions

A cross-coupling reaction = creation of a C-C bond thanks to a metal catalysts



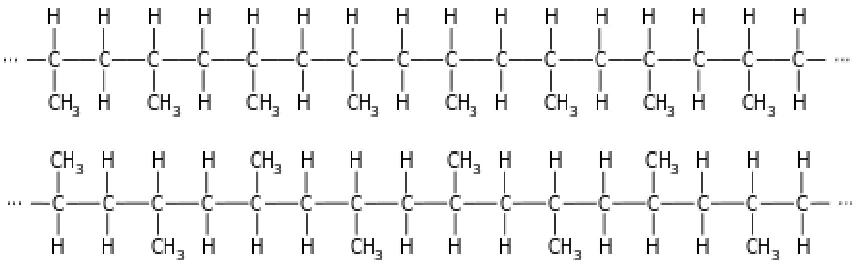
The Periodic Table of the Elements

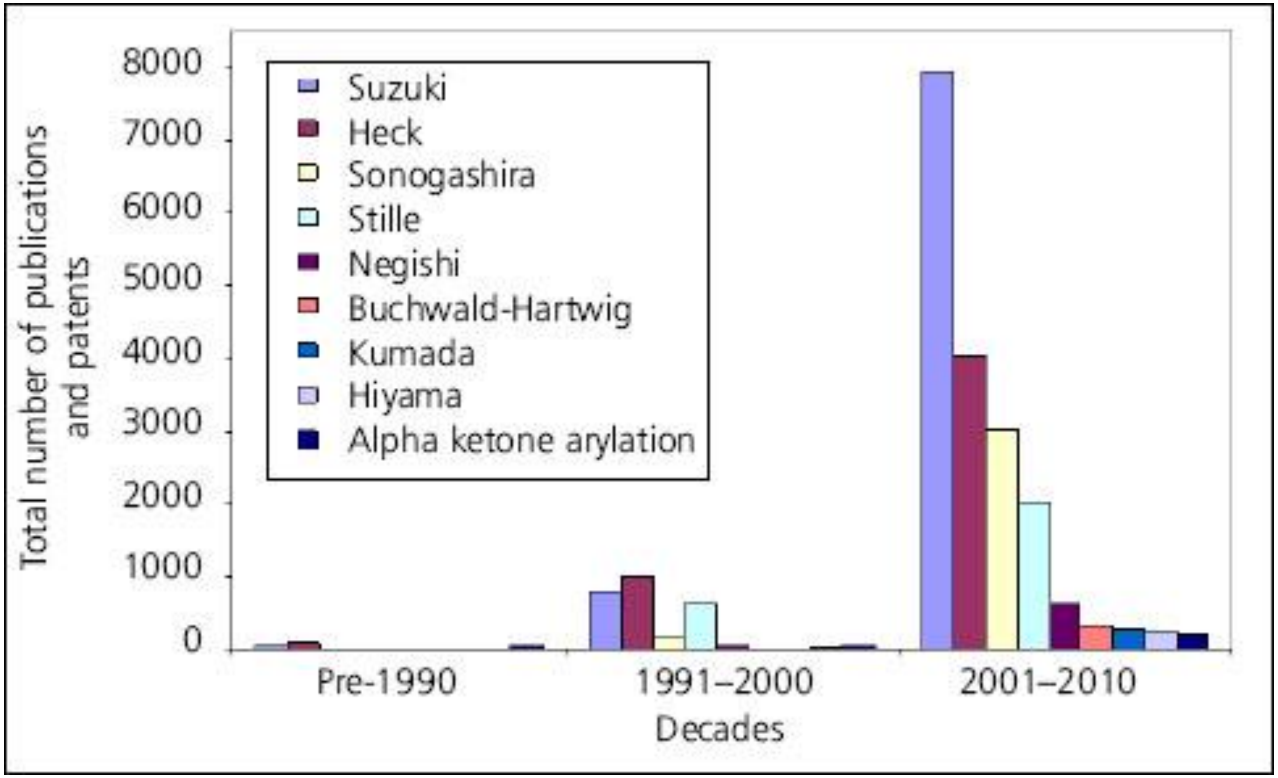
	1 IA 11A	2 IIA 2A	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8 VIII 8	9 VIII 8	10 VIII 8	11 IB 1B	12 IIB 2B	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1	1 H Hydrogen																	2 He Helium
2	3 Li Lithium	4 Be Beryllium											5 B Boron	6 C Carbon	7 N Nitrogen	8 O Oxygen	9 F Fluorine	10 Ne Neon
3	11 Na Sodium	12 Mg Magnesium											13 Al Aluminium	14 Si Silicon	15 P Phosphorus	16 S Sulfur	17 Cl Chlorine	18 Ar Iron
4	19 K Potassium	20 Ca Calcium	21 Sc Scandium	22 Ti Titanium	23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton
5	37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon
6	55 Cs Caesium	56 Ba Barium	71 Lu Lutetium	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon
7	87 Fr Francium	88 Ra Radium	103 Lr Lawrencium	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadium	111 Rg Roentgenium	112 Cn Copernicium	113 Uut Ununtrium	114 Fl Flerovium	115 Uup Ununpentium	116 Lv Livermorium	117 Uus Ununseptium	118 Uuo Ununoctium
					57 La Lanthanum	58 Ce Cerium	59 Pr Praseodymium	60 Nd Neodymium	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium
					89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium

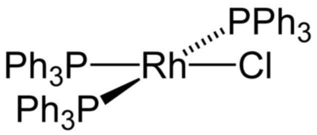
I. Carbon-carbon bonds formation

✓ So many Nobel Prize in Chemistry !

- 1963 : Ziegler and Natta, olefins polymerization
- 1973 : Wilkinson, Wilkinson catalyst
- 2001 : Knowles, Sharpless and Noyori, asymmetric catalyst
- 2005 : Grubbs, Schrock et Chauvin, metathesis
- 2010 : Negishi, Heck, Suzuki, cross-coupling reaction

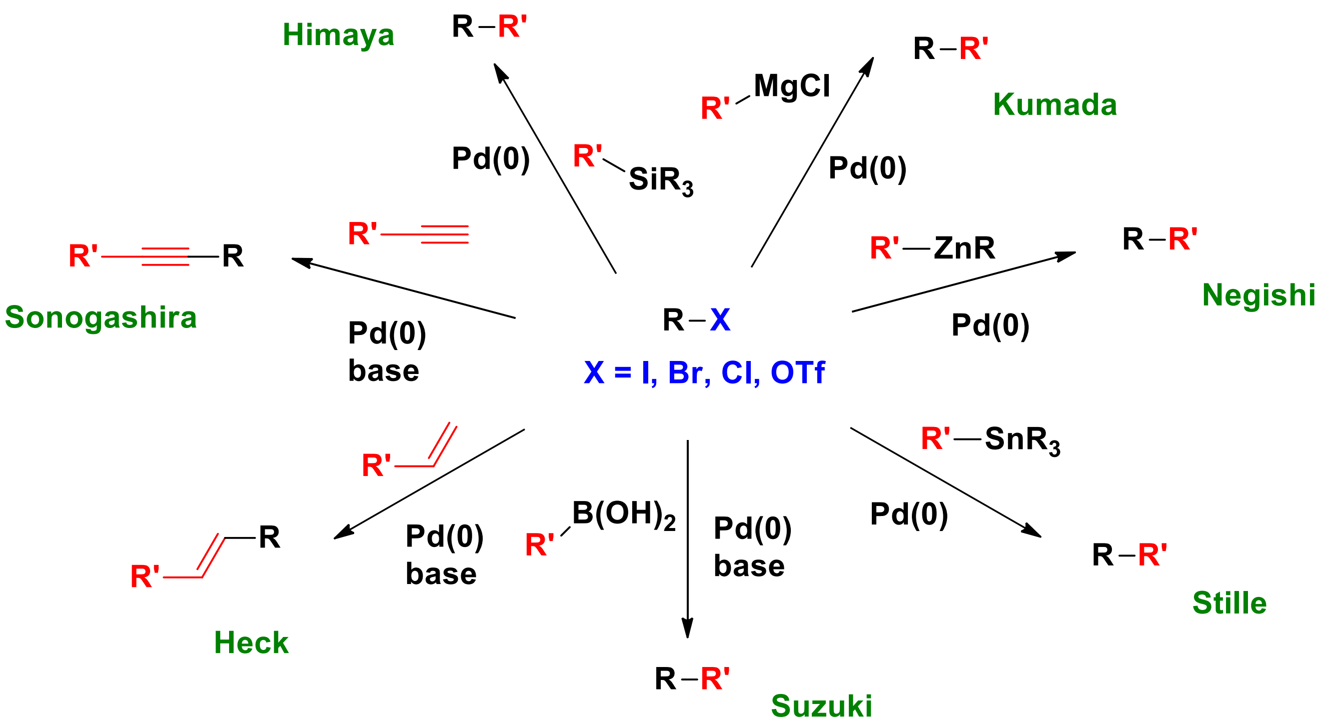






I. Carbon-carbon bonds formation

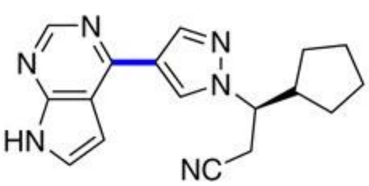
- ✓ These reaction are catalyzed !
- ✓ *sp* or *sp*^{2} carbon are often involved
- ✓ Applied everywhere : natural products, industry, materials, electronic,…



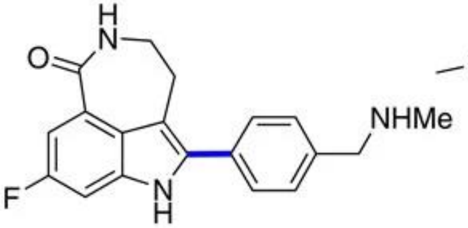
You will see mechanism in the future…

I. Carbon-carbon bonds formation

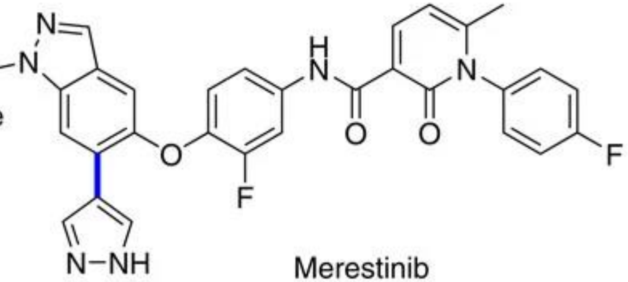
- ✓ Some examples using a Suzuki cross-coupling…



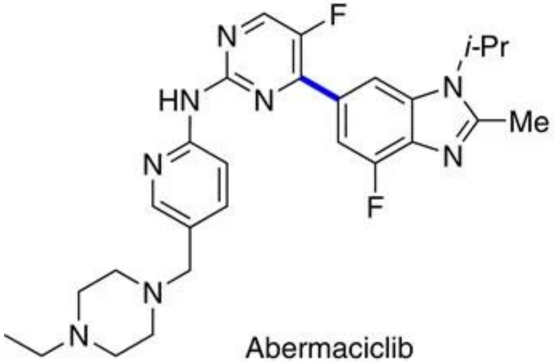
Ruxolitinib
(myelofibrosis)



Rucaparib
(anticancer, in Phase III)

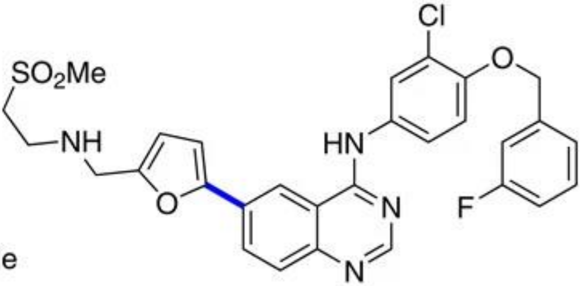


Merestinib
(anticancer, in Phase II)



Abermaciclib
(anticancer, in Phase III)

Etoricoxib
(antiinflammatory)



Lapatinib
(anticancer)

P. Schäfer, T. Palacin, M. Sidera, S. P. Fletcher *Nat. Comm.* **2017**, *8*, 15762.

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

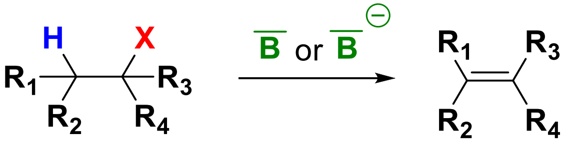
3. Shapiro reaction

4. “One word” about the Heck reaction

II. C=C bonds formation

✓ II. 1. β-H elimination

➢ II. 1. a. Generality



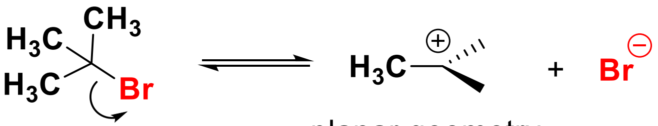
B : Lewis base and/or nucleophile

competition between E and S_N

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

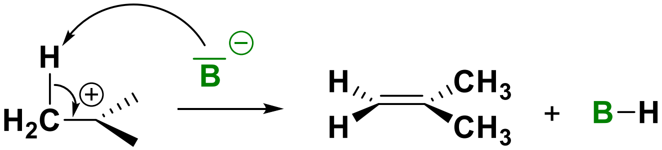
The formed carbocation must be stable

1. Slow step : halogen ionization



planar geometry

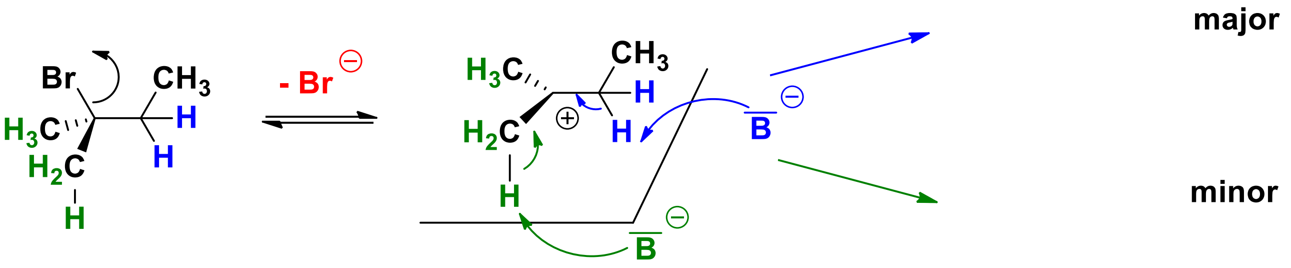
2. Fast step : nucleophilic reaction



II. C=C bonds formation

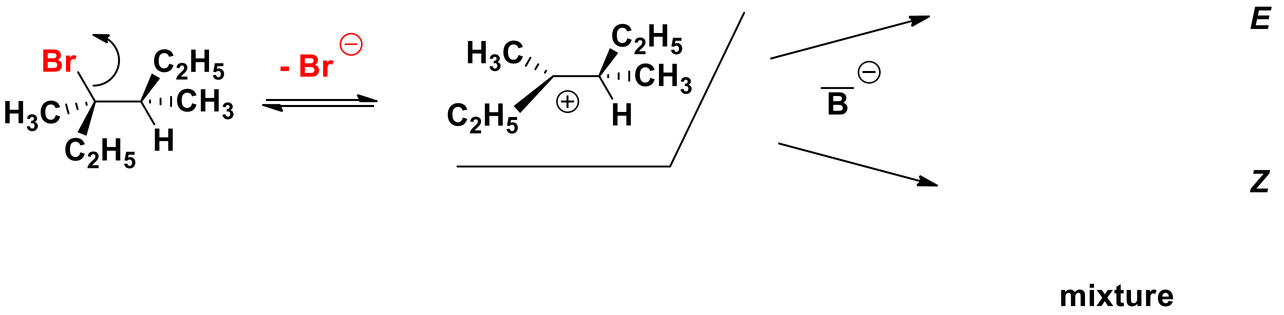
- ✓ II. 1. β-H elimination
  - ➢ Zaitsev Rule

The most substituted product will be the most stable



- ➢ No stereospecifitity

Carbocation : planar geometry

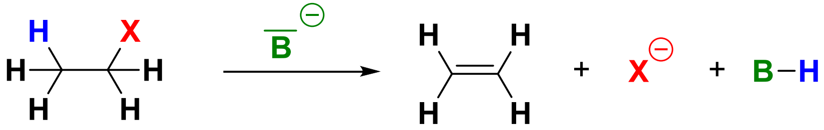


II. C=C bonds formation

✓ II. 1. β-H elimination

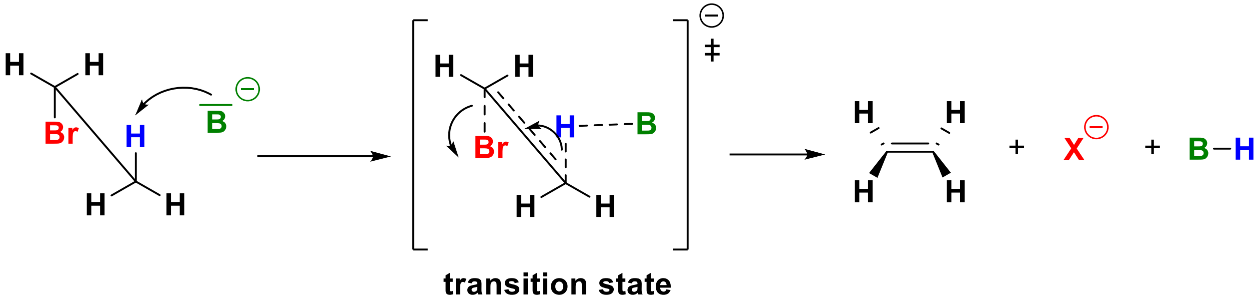
➢ II. 1. c. Elimination E2, second order, 1 step

No carbocation



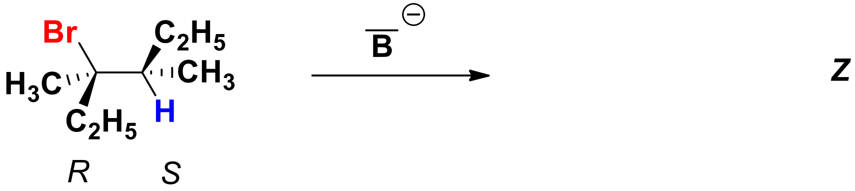
competition between E and S_N

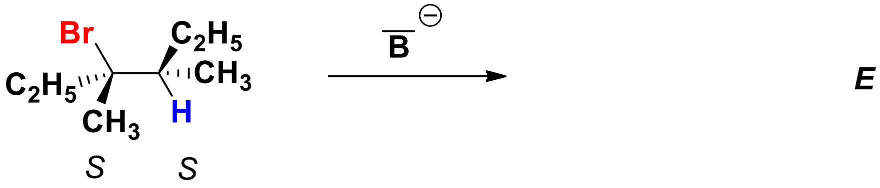
Mechanism : H and Br antiperiplanar



II. C=C bonds formation

- ✓ II. 1. β-H elimination
  - ➢ Stereospecifitity





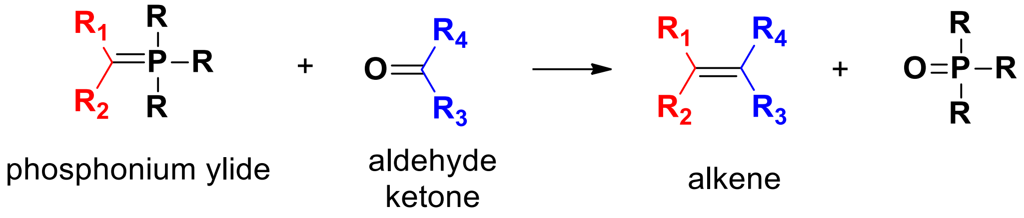
II. C=C bonds formation

- ✓ 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

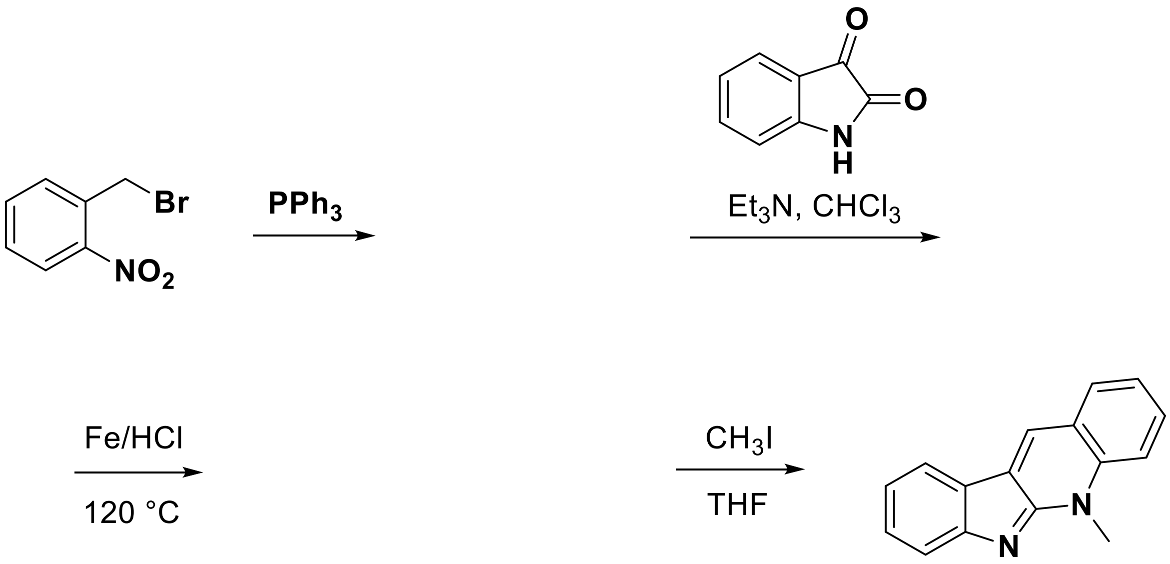


Nobel Prize in Chemistry
in 1979

Mechanism :

II. C=C bonds formation

Exercise : total synthesis of (+)-neocryptolepine

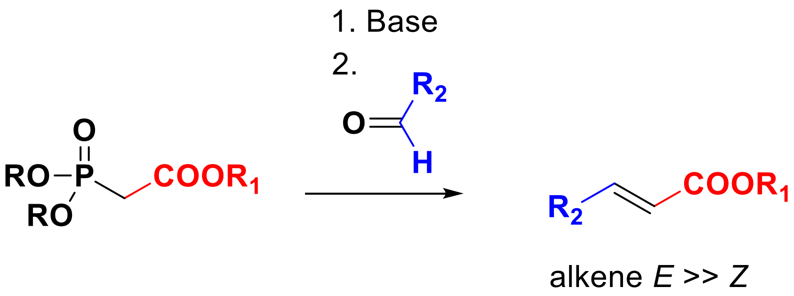


antimicrobial and cytotoxic activity

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

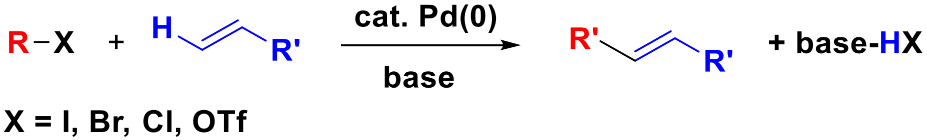
II. C=C bonds formation

- ✓ II. 2. Phosphorus ylides and related compounds
  - ➢ II. 2. b. Horner-Wadsworth-Emmons reaction



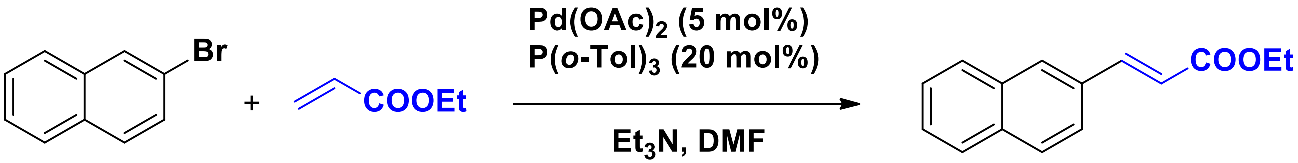
II. C=C bonds formation

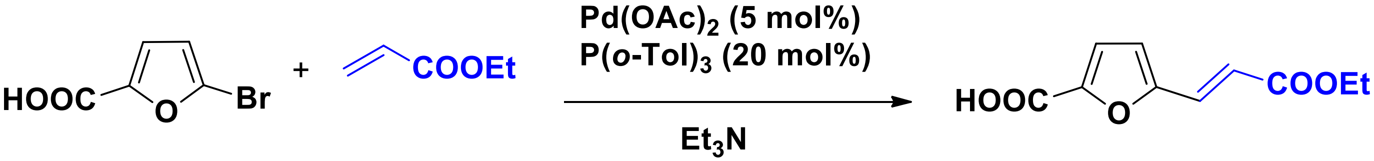
- ✓ I. 4. “One word” about the Heck reaction

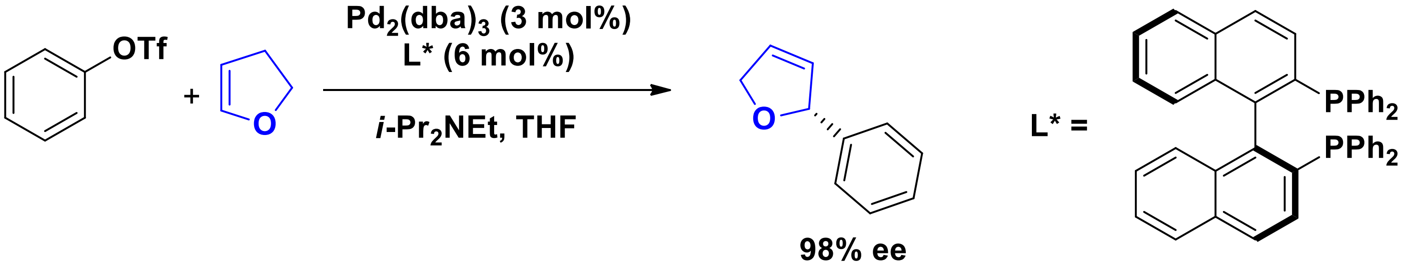


- ✓ Mizoroki-Heck coupling (1971-1972) – historical examples

Nobel Prize in Chemistry
in 2010

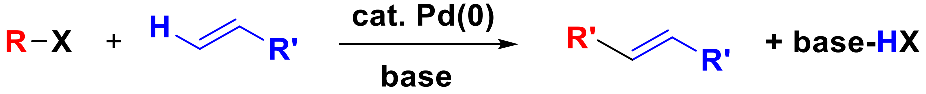




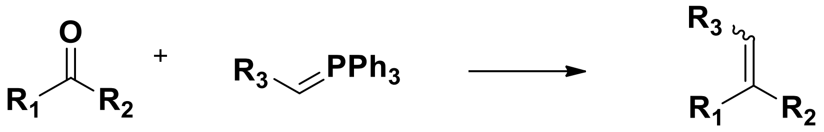


II. C=C bonds formation

- ✓ Heck reaction



- ✓ Wittig reaction



A short comparison… The Heck reaction :

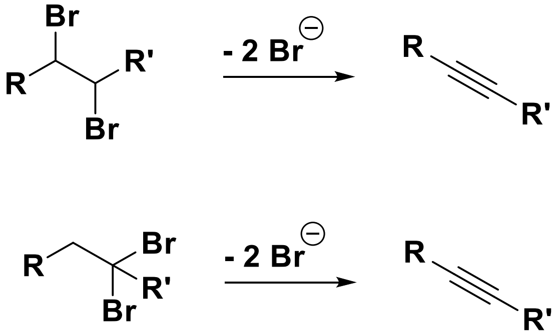
- is often more stereoselective
- requiers only one step
- involves simple reagents
- generates less by-products

Chapter III

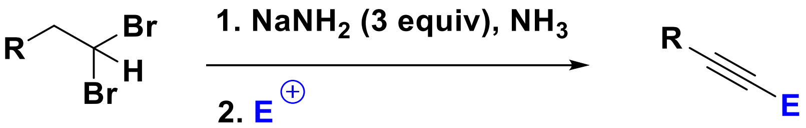
C≡C bonds formation

III. C≡C bonds formation

- ✓ III. 1. Dihaloalkane elimination

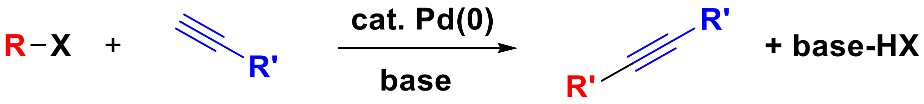


E2 elimination, usually in the presence of a strong base such as $NaNH_2$.



III. C≡C bonds formation

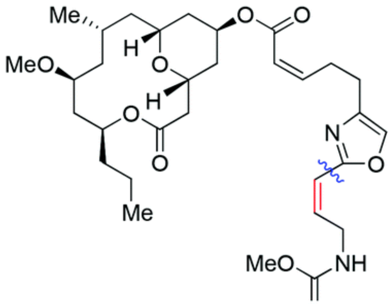
- ✓ III. 3. “One word” about the Sonogashira reaction



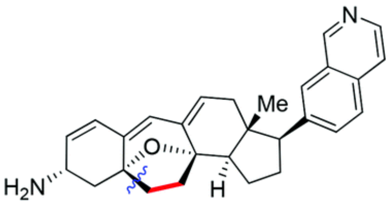
X = I, Br, Cl, OTf

- ✓ Extremely versatile reaction, broad scope and potential synthetic transformations…

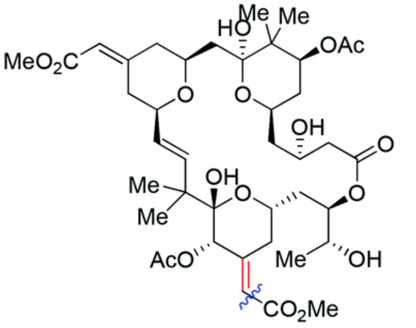
Total synthesis of natural products involving Sonogashira coupling



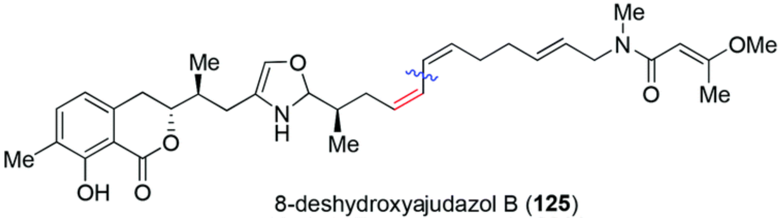
neopeltolide (**122**)
(Martin E. Maier, et al., **2008**)



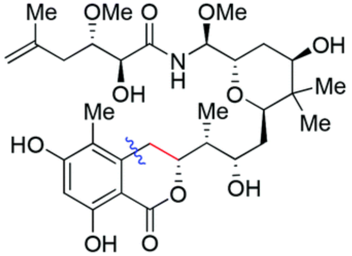
cortistatin J (**123**)
(K. C. Nicolaou, David Y.K. Chen, et al., **2009**)



bryostatin 7 (**124**)
(Michael J. Krische, et al., **2011**)



8-deshydroxyajudazol B (**125**)
(Mark A. Rizzacasa, et al., **2011**)



psymberin = irciniastatin A (**126**)
(Jef K. De Brabander, et al., **2012**)

D. Wang, S. Gao *Org. Chem. Front.* **2014**, *1*, 556-566.