

University of Zagreb
Faculty of Chemical Engineering and Technology
Study programme Chemical and Environmental Technology

MODERN METHODS OF ORGANIC SYNTHESIS

Prof. Marijana Hranjec, PhD

Academic year 2023/2024

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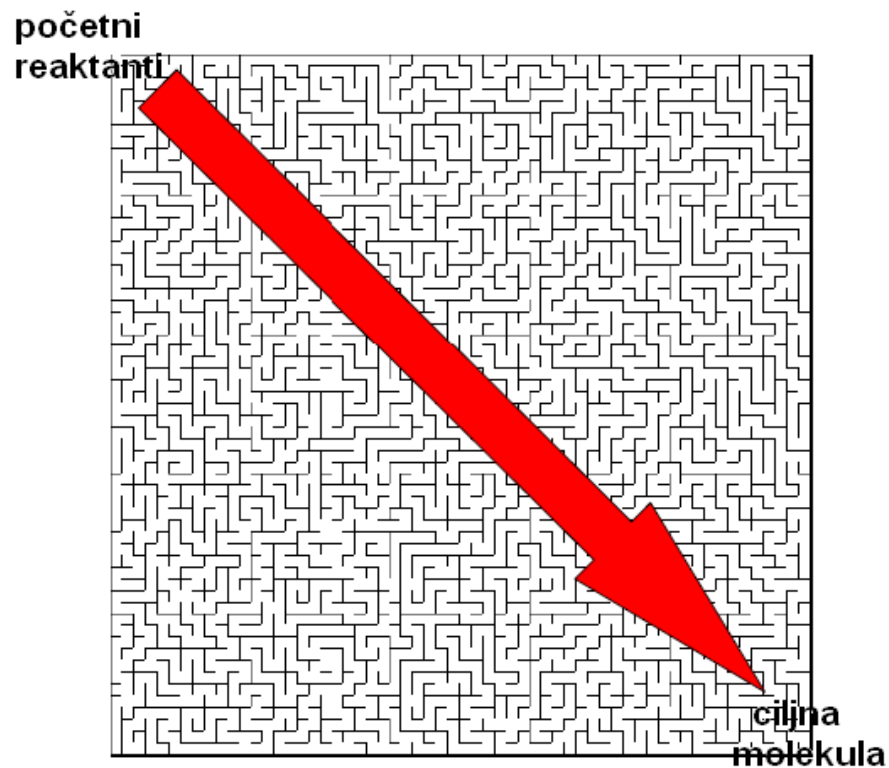
Introduction. Strategies of organic synthesis: Planning and control. Retrosynthesis.

Prof. Marijana Hranjec, PhD

Academic year 2020/2021

INTRODUCTION

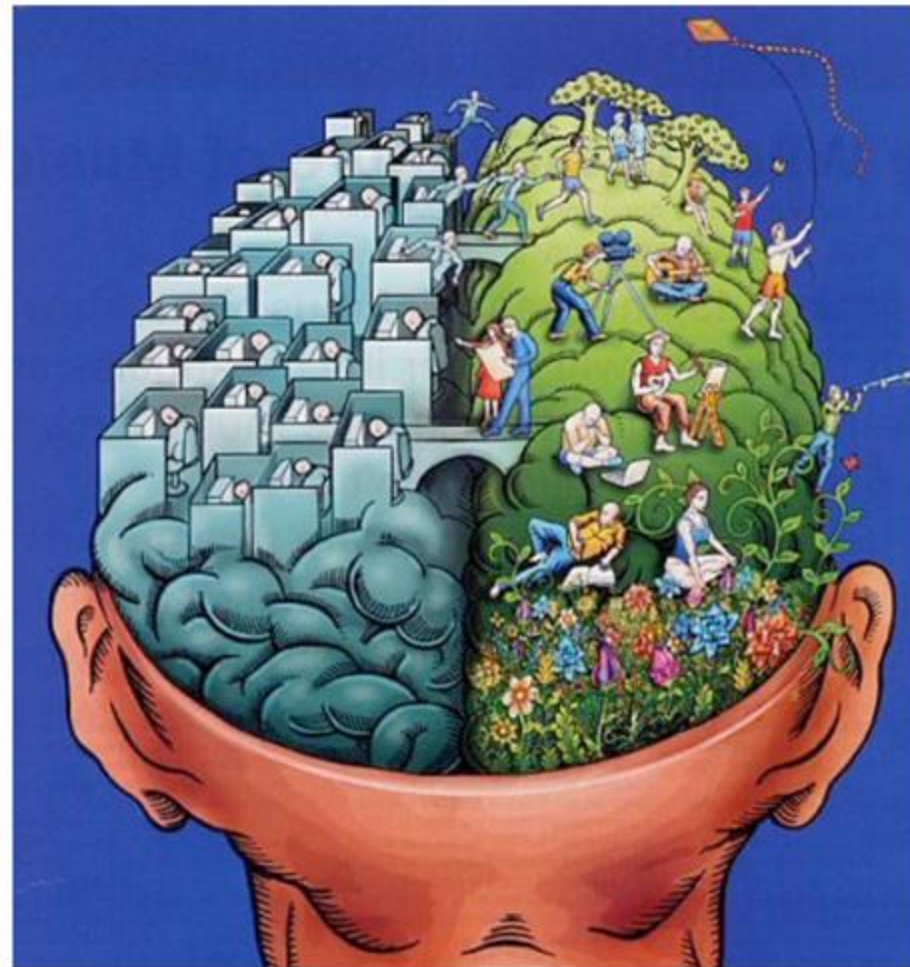
- ❖ **modern organic chemistry** - a large number of new and complex molecules in the last few decades
- ❖ **synthesis** - the process of creating target molecules from the initial reactants using chemical reactions
- ❖ **synthesis of complex molecules**
- ❖ **several synthetic steps and reactions starting from the reactant to the target molecule**
- ❖ **the goal of planning of synthesis** - find the most efficient and shortest synthetic route
- ❖ **each of the synthetic steps can also give numerous side effects products which depends on the choice of the type of the reaction and reaction conditions**
- ❖ **control of synthesis**



INTRODUCTION

RIGHT SIDE OF THE BRAIN

Logic
Analysis
Organization
Knowledge/Facts
Details
Mathematics
Science



LEFT SIDE OF THE BRAIN

Intuition
Feelings
Spirituality
Faith
Art
Music
Images

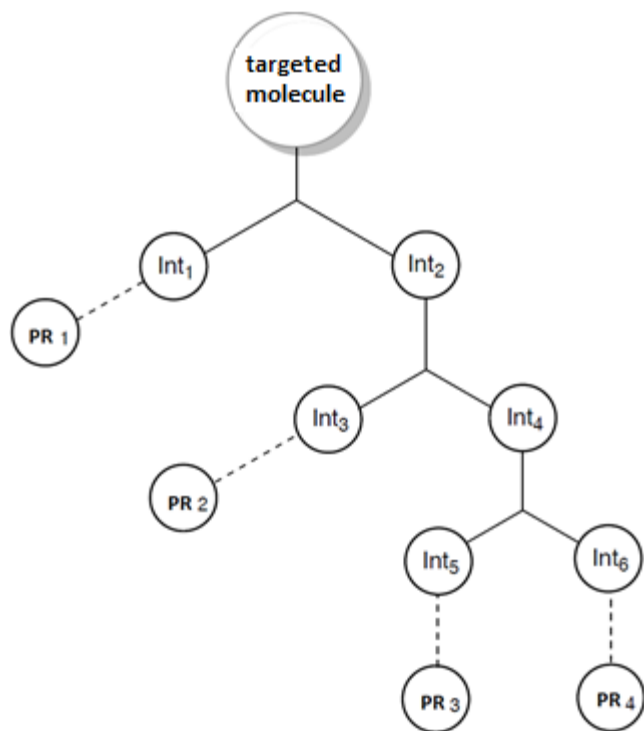
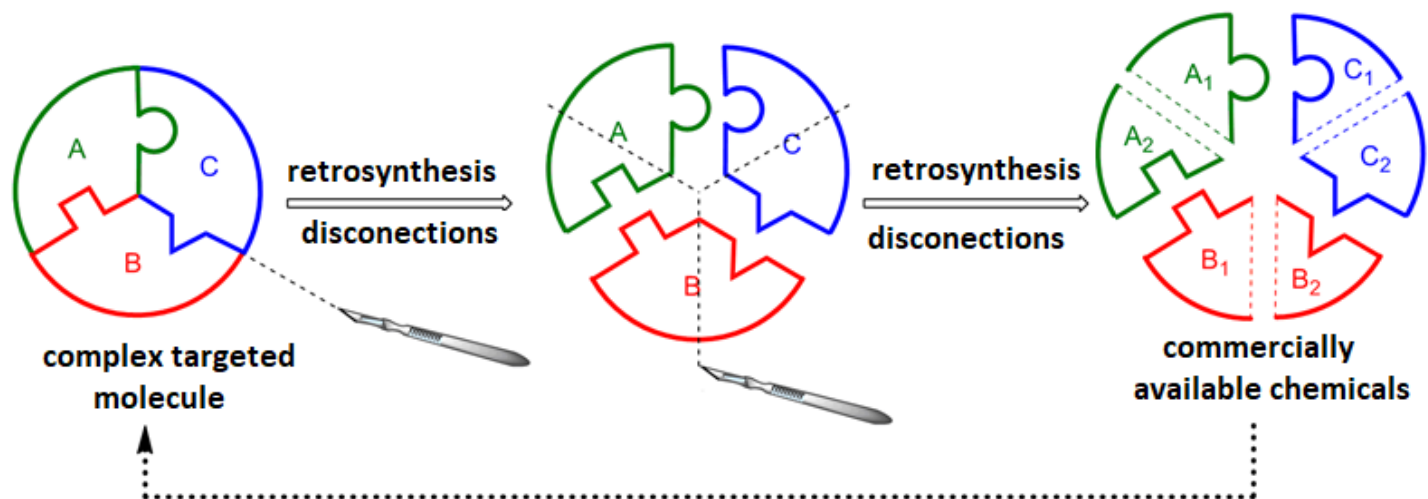
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TACTICS



STRATEGY

INTRODUCTION



ORGANIC CHEMISTRY

PURPOSE:

- **prepare a new target molecule with appropriate chemical, physical or biological characteristic**
- **prepare a target molecule of a certain purity for further testing**
- **plan a new synthetic pathway for existing molecules that will be simplified or more cost-effective**

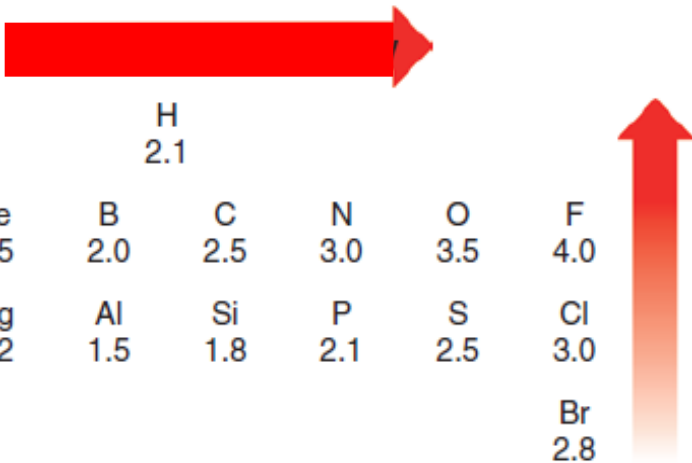
IMPORTANCE:

- **total synthesis of interesting and / or important natural products**
- **target molecules important for application and industry**
- **molecules important for theoretical calculations**
- **molecules important for structure confirmation (natural compounds)**
- **development of new synthetic methodologies**
- **application in other fields of science and technology**
- **for scientific research - new problems provide new solutions and can lead to the development of new chemistry, reagents, etc.**
- **prepare a specific compound for studying the reaction mechanism or biological metabolism (eg labeled compounds)**

ELECTRONEGATIVITY

- ❖ **the ability of an atom of an element to receive (attract) electrons**
(the property of an atom to attract electron density in a molecule from the bond by which it is attached to another atom)
- ❖ electronegativity increases from left to right in the period and upwards in individual group of the periodic table and from the lower left to the upper right corner of the periodic table
- ❖ the most electronegative atom is fluorine (F) which can best stabilize excess of electron density

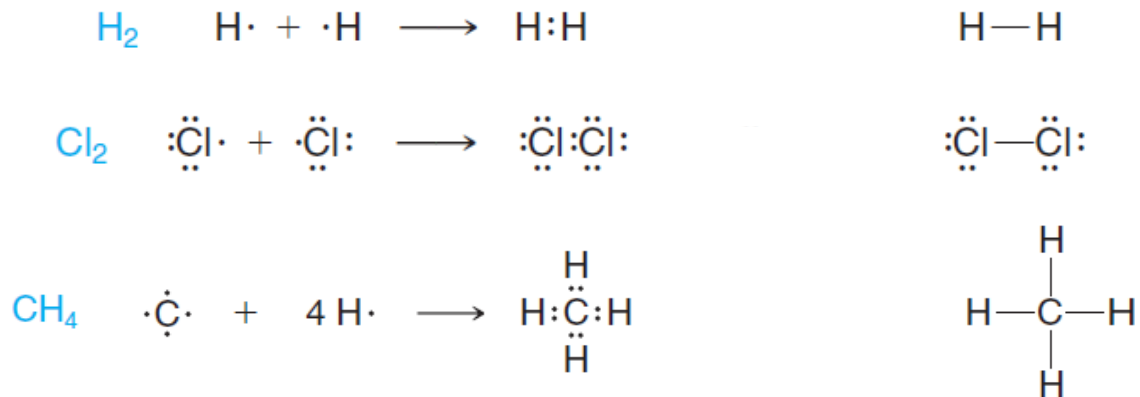
TABLE 1.1 ELECTRONEGATIVITIES OF SOME OF THE ELEMENTS



			H 2.1				
Li 1.0	Be 1.5	B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	
Na 0.9	Mg 1.2	Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	
K 0.8						Br 2.8	

COVALENT BOND

- ❖ occurs between atoms that have the same or similar electronegativity and are close to each other in the periodic table
- ❖ the two atoms that form a covalent bond share a common electron pair (divide valence electrons and thus satisfy the octet rule)
- ❖ valence electrons can be written in dots (Lewis structural formulas) and the usual way of marking electrons is a dash



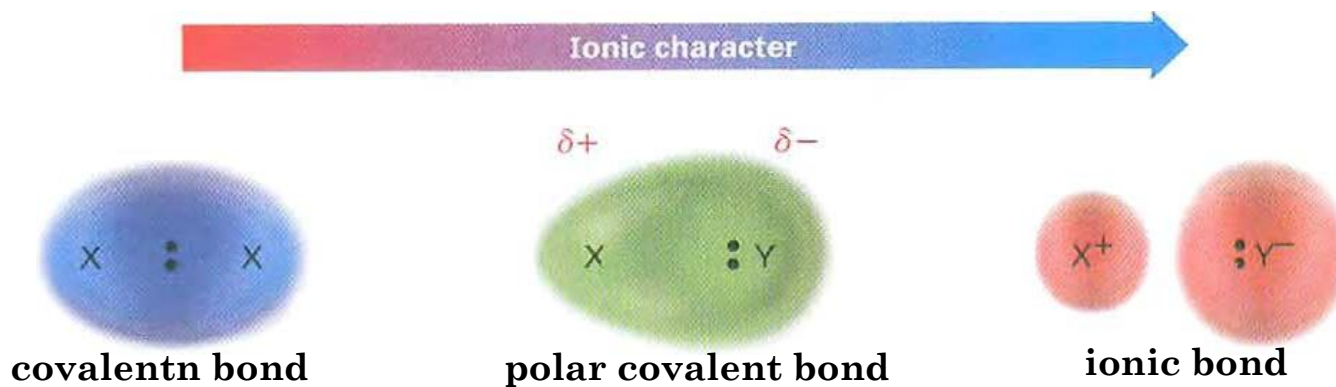
- ❖ atoms can split two or more electron pairs to form multiple bonds



POLAR COVALENT BOND

- ❖ any diatomic molecule in which two atoms of different electronegativities are connected will have a dipole moment
- ❖ in more complex molecules, the dipole moment is obtained by summing the individual dipole moments of the bonds μ
- ❖ the electron distribution is not equal and the bond is polarized

Dipole moments of simple molecules			
Formula	μ (D)	Formula	μ (D)
H ₂	0	CH ₄	0
HF	1.83	CH ₂ Cl ₂	1.55
HCl	1.08	CHCl ₃	1.02
HBr	0.80	CCl ₄	0
HI	0.42	NH ₃	1.47
BF ₃	0	NF ₃	0.24
CO ₂	0	H ₂ O	1.85



TYPES OF ARROWS IN ORGANIC SYNTHESIS

❖ a simple reaction arrow 

❖ resonance arrow 

❖ equilibrium arrow 

❖ bent arrow – shows the moving of two electrons 

❖ hooked arrow – shows the moving of one electron 

❖ retrosynthetic arrow 

CURLY ARROWS

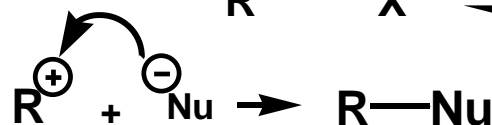
- ❖ to show the moving of electron pairs in a reaction mechanism
- ❖ covalent bonds consist of pairs of electrons - then the arrows show the bursting and / or formation of a covalent bond

❖ **a bent arrow can only start in the high electron density range:**

✓ in the middle of covalent bond



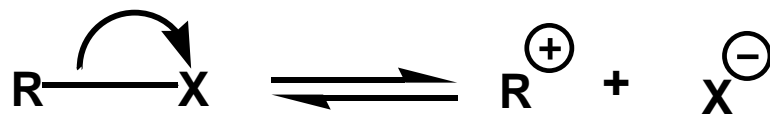
✓ at negative charge



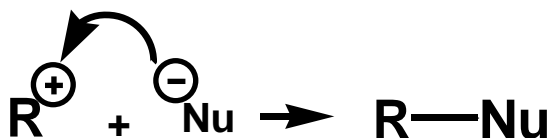
✓ at free electronic pair

❖ **a bent arrow can only end in the low electron density range:**

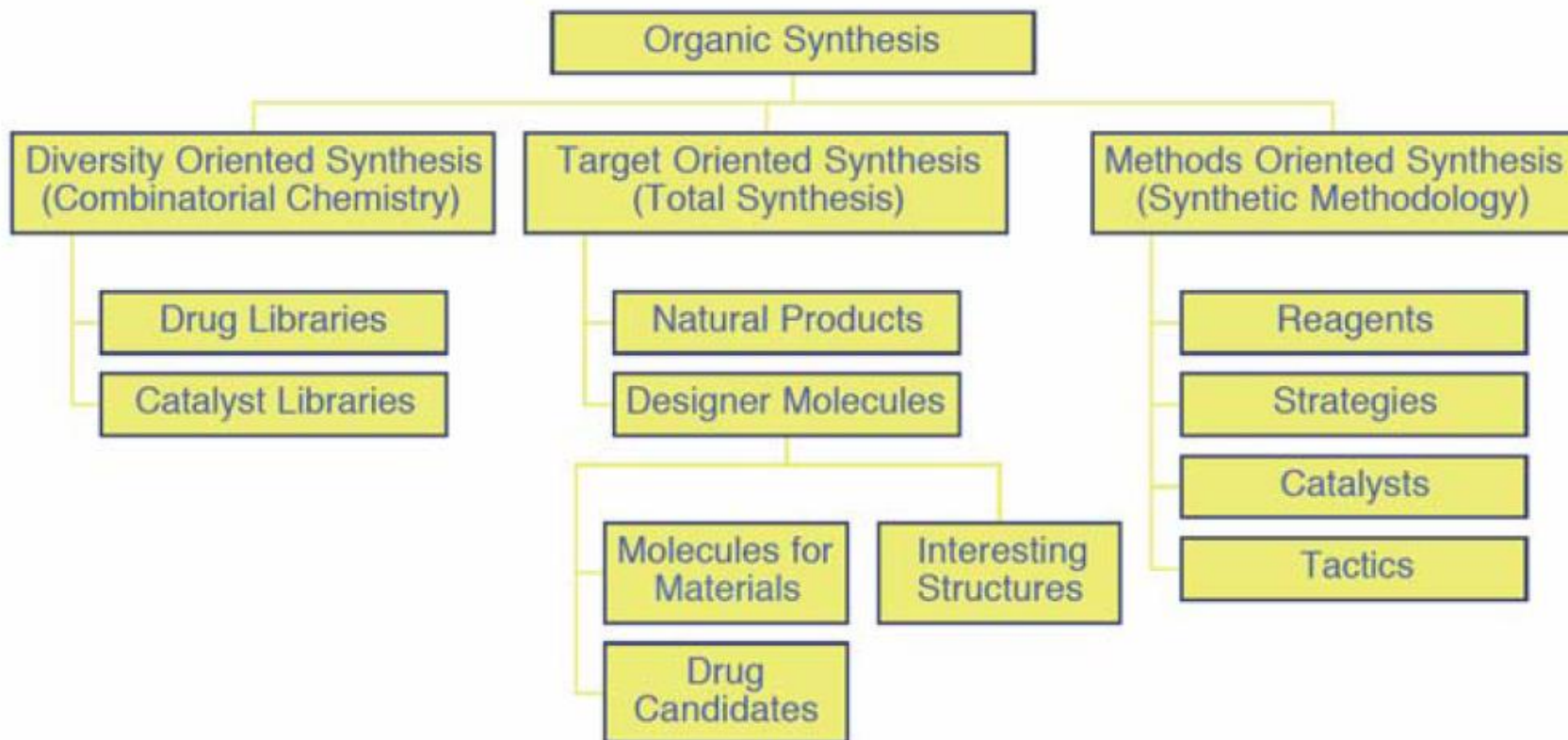
✓ on an uncharged atom or group → results in cracking of the bond and creation of a negative charge on the atom or group



✓ on a positively charged atom or group → results in the formation of a bond and the quenching of the positive charge



CLASSIFICATION OF ORGANIC SYNTHESIS



ORGANIC SYNTHESIS

Synthetic methods

1. *Total synthesis* – complete organic synthesis of a very complex molecule
2. *Partial synthesis* – starts with an available natural product and involves several synthetic steps
3. *Biosynthesis*

Synthesis efficiency

- ❖ try to choose the shortest possible synthetic route use reactions that do not give a mixture of products (chemoselectivity, regioselectivity, stereoselectivity)
- ❖ use a convergent synthetic pathway if possible with respect to a linear synthetic pathway
- ❖ mainly use already existing and optimized reactions, especially for the synthesis of molecules to be commercialized
- ❖ environmentally friendly synthetic routes - green chemistry
- ❖ economically acceptable synthetic routes

ORGANIC SYNTHESIS

Well-planned organic synthesis involves:

- ❖ starting from readily available and commercially acceptable reactants
- ❖ use of efficient and selective reactions avoiding extreme and hazardous reactants
- ❖ reaction conditions flexibility
- ❖ to have plan B if plan A fails
- ❖ very good knowledge of organic reactions and mechanisms
- ❖ adaptability commercially acceptable total synthetic route with respect to environmental criteria
- ❖ "green chemistry" innovation and creativity

Selectivity - the efficiency of the synthetic pathway

1. CHEMOSELECTIVITY - reaction of only one functional group in relation to all existing functional groups in the structure of the molecule
2. REGIOSELECTIVITY - formation of only one regioisomer in relation to all possible regioisomers
3. STEREOSELECTIVITY - formation of one stereoisomer - diastereoselectivity and enantioselectivity

TYPES OF ORGANIC SYNTHESIS

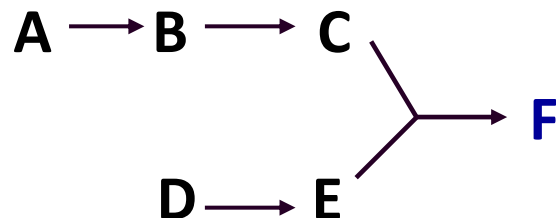
LINEAR SYNTHESIS

- ❖ the target molecule is synthesized by a series of linear transformations



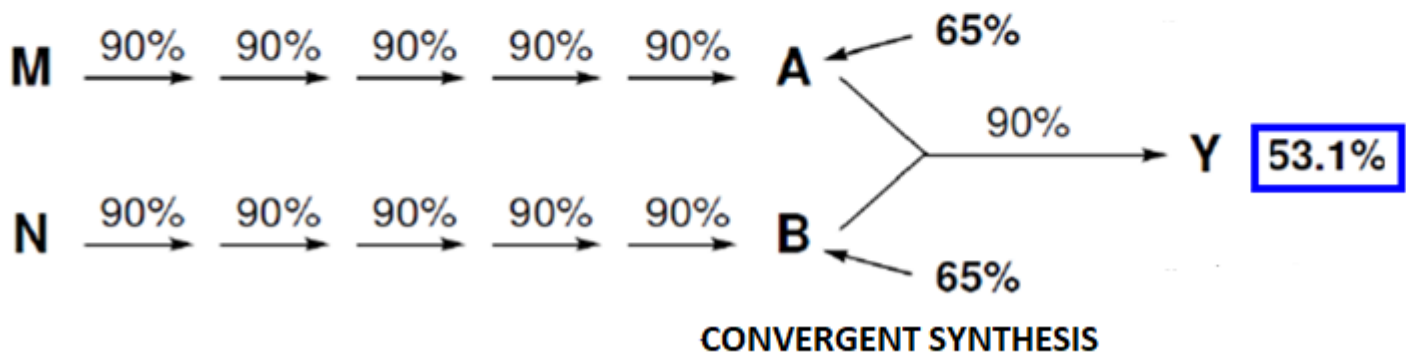
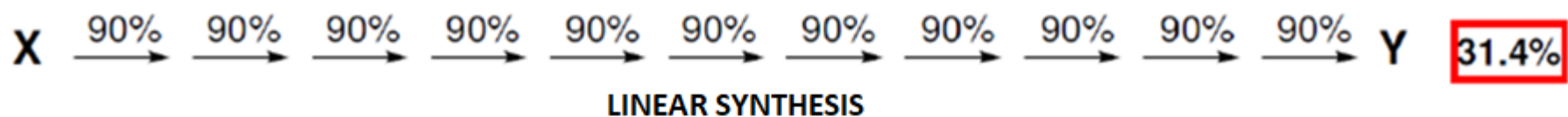
CONVERGENT SYNTHESIS

- ❖ individually prepared molecules react to give the target molecule



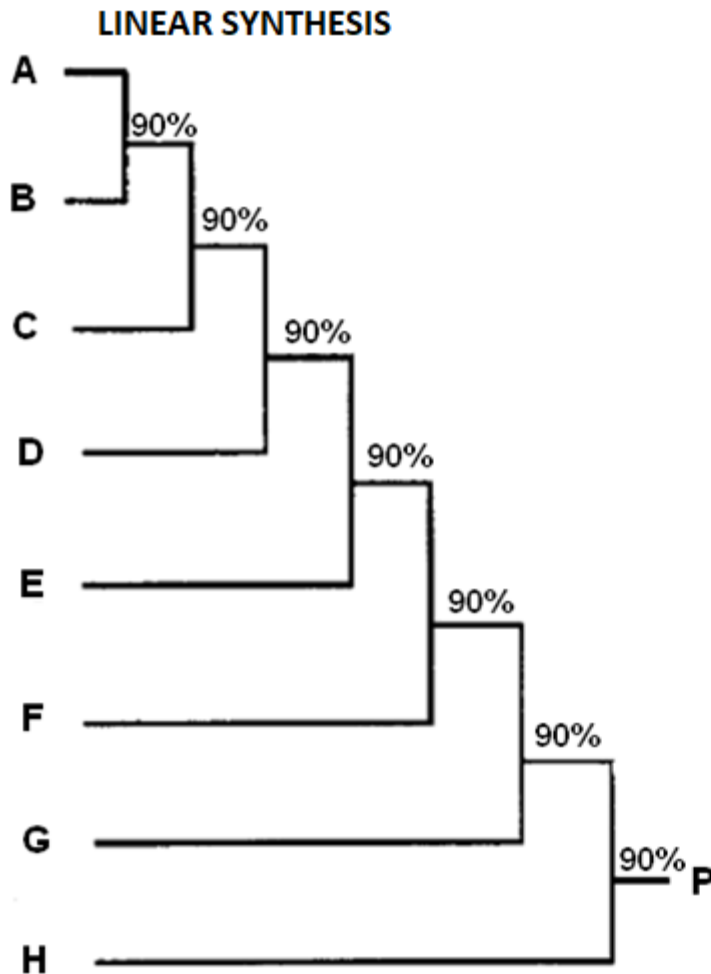
- ❖ it is used in the synthesis of very complex molecules, and involves the independent synthesis of fragments and their fusion

COMPARISON OF CONVERGENT AND LINEAR SYNTHESIS

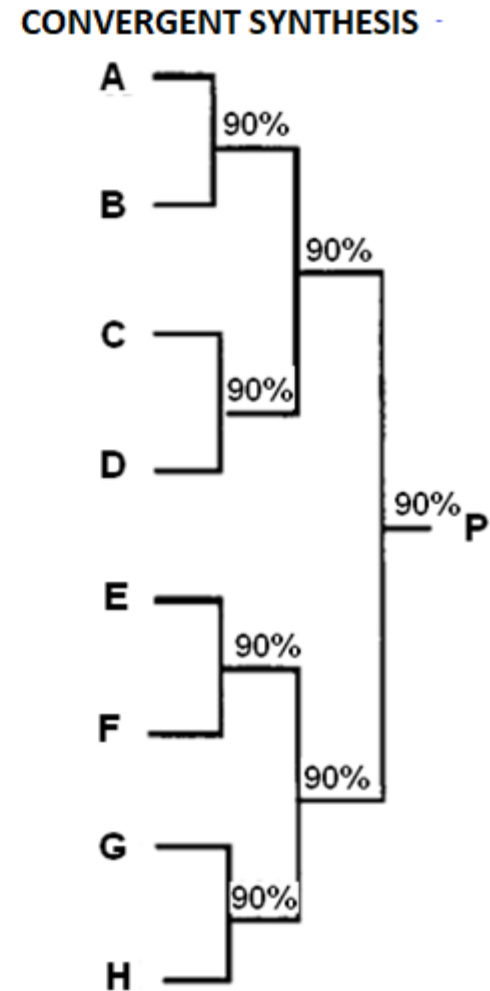


- ❖ linear synthesis involves 11 synthetic steps, while in convergent synthesis the longest linear path involves 6 synthetic steps - the total yield in convergent synthesis is higher

COMPARISON OF CONVERGENT AND LINEAR SYNTHESIS

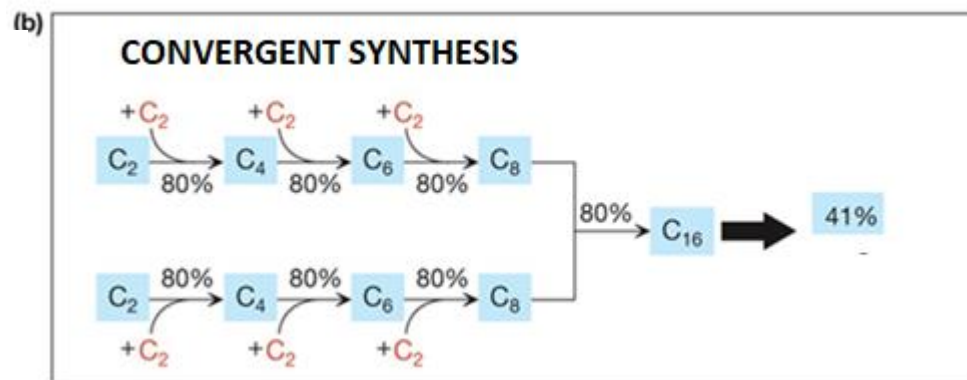
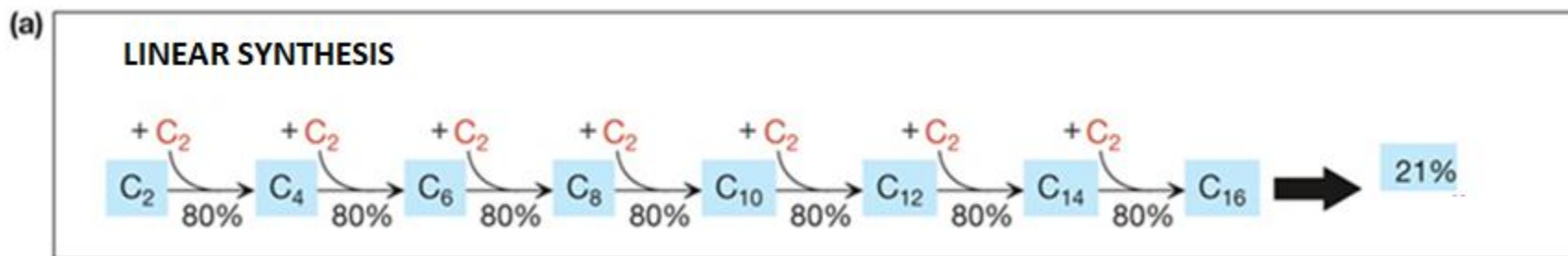


$$0,9^7 \times 100 = 47,8 \%$$



$$0,9^3 \times 100 = 72,9 \%$$

COMPARISON OF CONVERGENT AND LINEAR SYNTHESIS



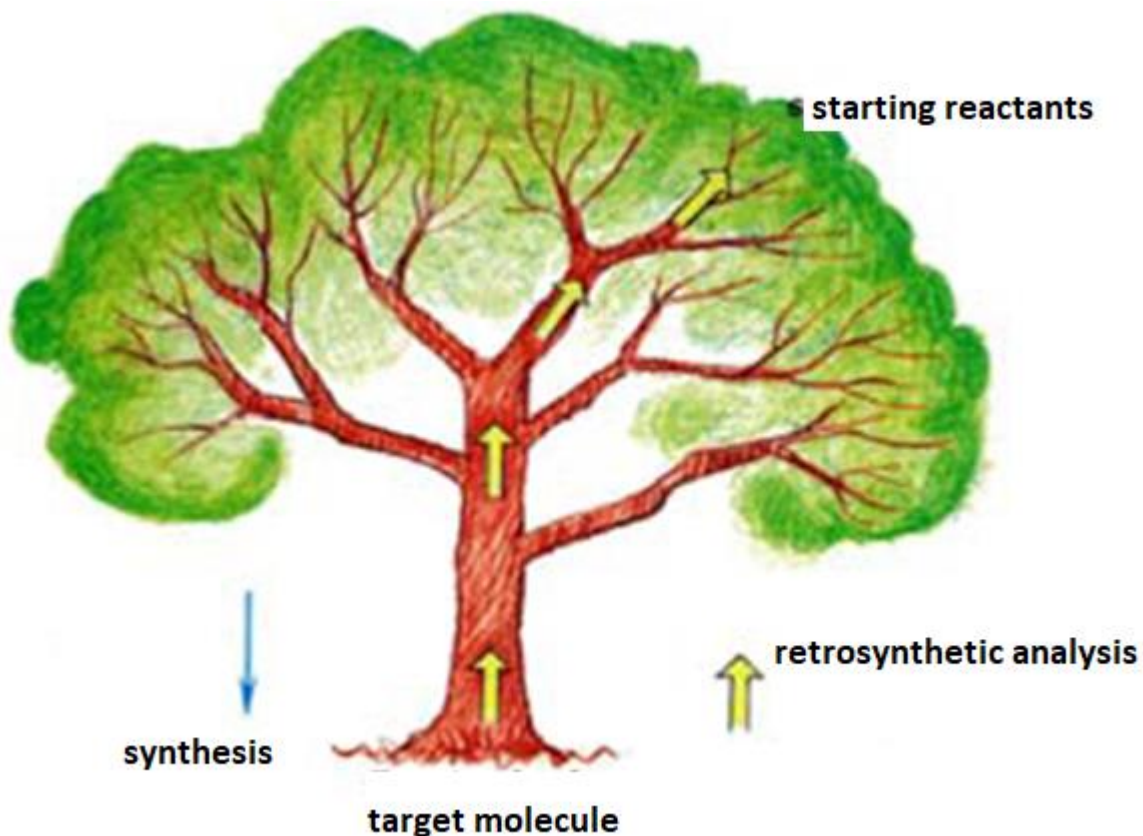
THE NUMBER OF SYNTHETIC STEPS	YIELD	TOTAL YIELD
5	90%	59%
5	80%	33%
5	70%	17%
10	90%	35%
10	80%	11%
10	70%	2.8%
20	90%	12%
20	80%	1.1%
20	70%	0.08%

TERMS IMPORTANT FOR PLANNING ORGANIC SYNTHESIS

- ❖ **retrosynthetic analysis** - meaningful cleavage of the structure of the target molecule to determine possible synthetic pathways
- ❖ **disconnection** - a term opposite to synthesis, meaningful breaking of chemical bonds that leads to the definition of possible initial reactants in the synthesis of the target molecule
- ❖ **IFS** - functional group interconversion (FGI) - the process of converting one function group to another to make disconnection possible
- ❖ **synthon** - an ideal fragment formed by the disconnection of chemical bonds, most often a cation or anion
- ❖ **synthetic equivalent** - a reagent that has the function of a synthon that is most often unstable to use on its own target molecule CM

RETROSYNTHESIS

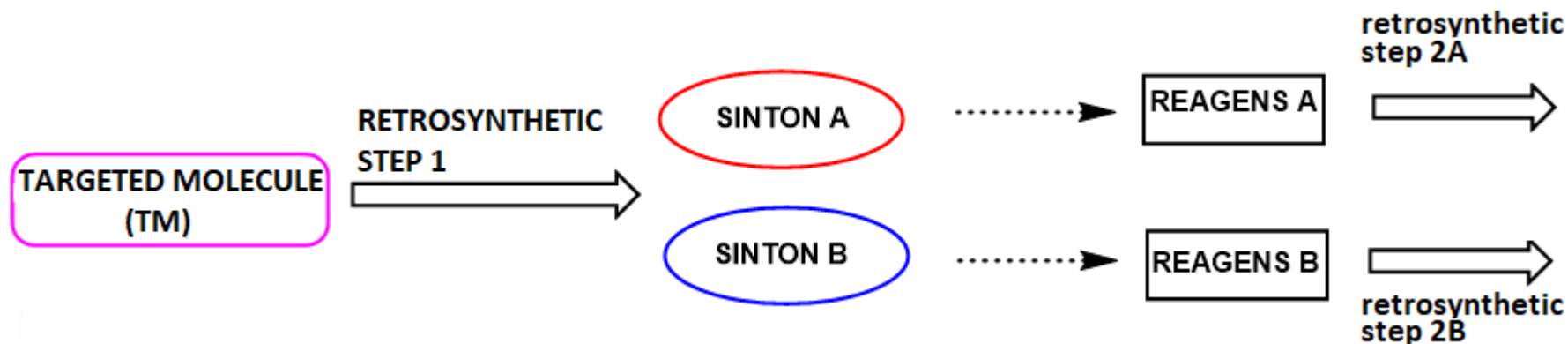
- ❖ cleavage of the structure of the target molecule in order to obtain meaningful possible synthetic pathways
- ❖ disconnection - the result of disconnection should be reactions that are feasible and have high yields



retrosynthetic tree

RETROSYNTHESIS

- **mental cleavage of the structure** (disconnection) of the target molecule (CM) into simpler structures (easily accessible compounds)
- by disconnection obtained simpler structures that can be synthesized by meaningful synthetic pathways
- the result of disconnection should be the reactions that are feasible and have a high yields



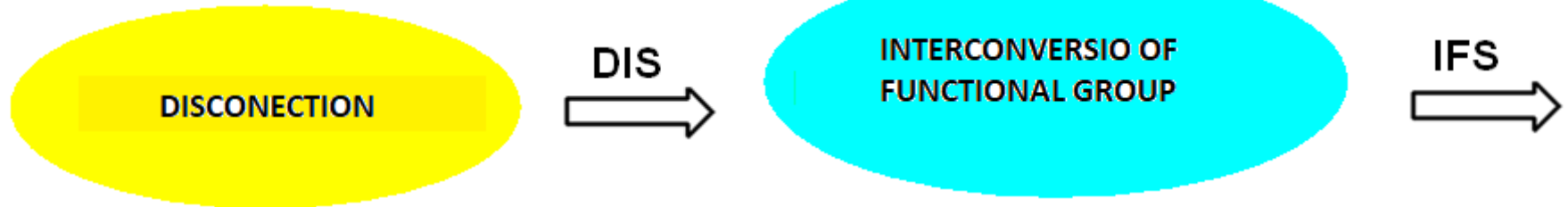
Synthones

- ❖ anionic, cationic or radical fragments
- ❖ shows with + or -
- ❖ could be or do not have to be intermediers in the reactions

Synthetic equivalents

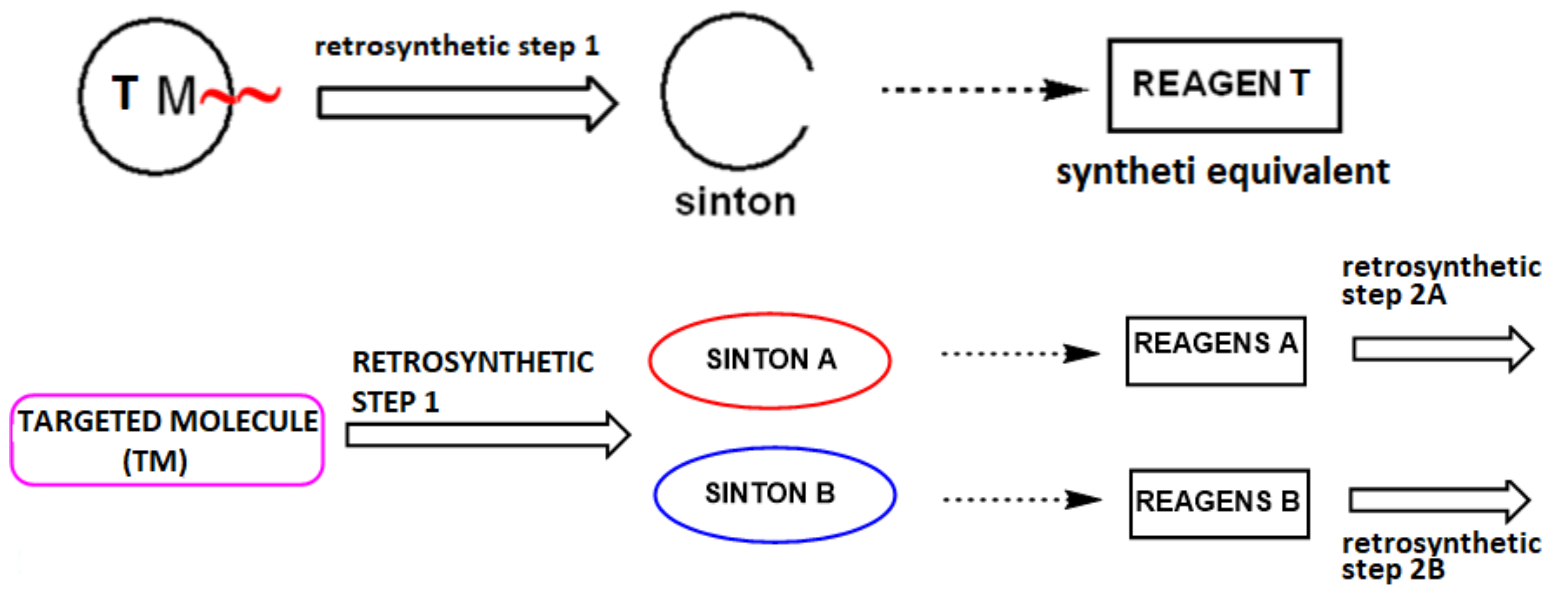
- ❖ reagens, neutral molecules
- ❖ real molecules which stand behind the syntons

RETROSYNTHETIC ANALYSIS



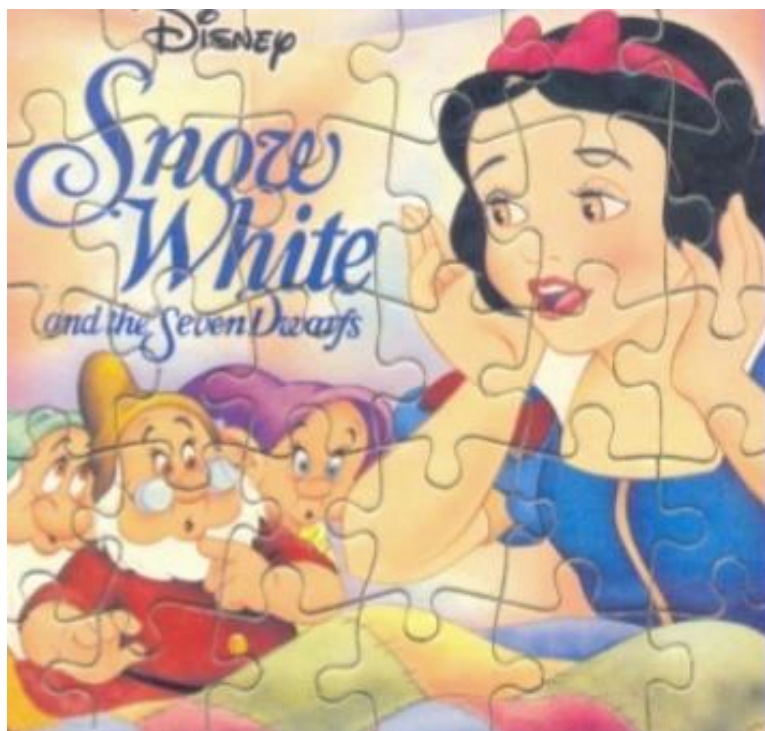
❖ imaginary splitting of ties - on paper disconnection usually produces negative and positive ions - SYNTHONES is usually displayed ~

- ✓ IFS
- ✓ the process of transforming one functional group into another to aid in the planning of a synthetic pathway

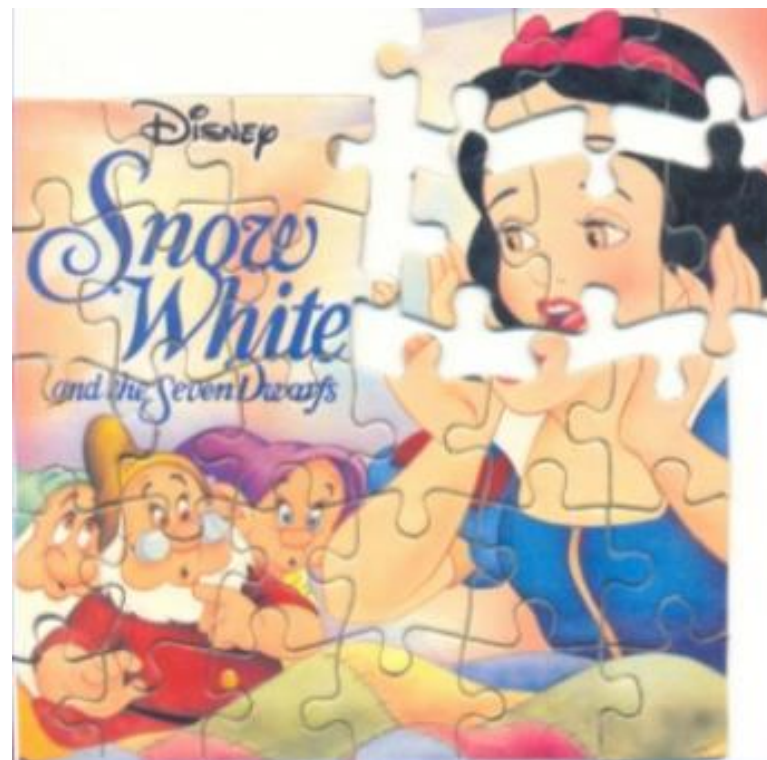


DISCONNECTION

finished puzzle
(targeted molecule)



puzzle
(disconnection)



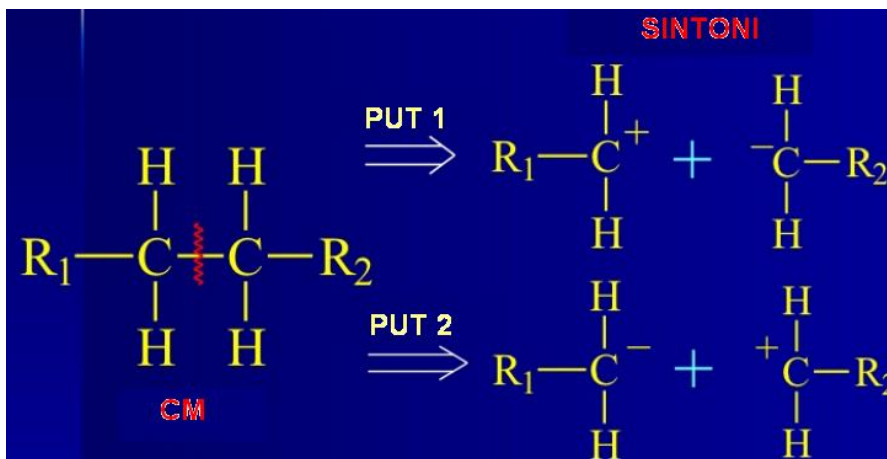
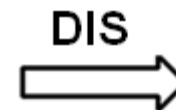
DISCONNECTION OF C-C BOND

LOGIC

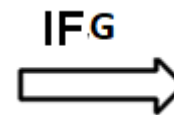
- ❖ when the disconnection of the C-C bond is performed so that the charges on the synthons are stabilized by adjacent groups, disconnection is following the correct mechanism
- ❖ synthons have a stabilized charge (+ or -), an electronic sextet in carbenes or are neutral molecules

UNLOGIC

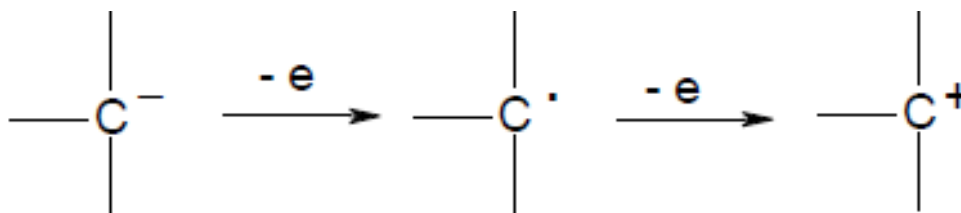
- ❖ by disconnection of the C-C bond the synthons obtained do not have a stabilized charge
- ❖ the disconnection does not follow the correct mechanism



INTERCONVERSION OF FUNCTIONAL GROUP (IFG)

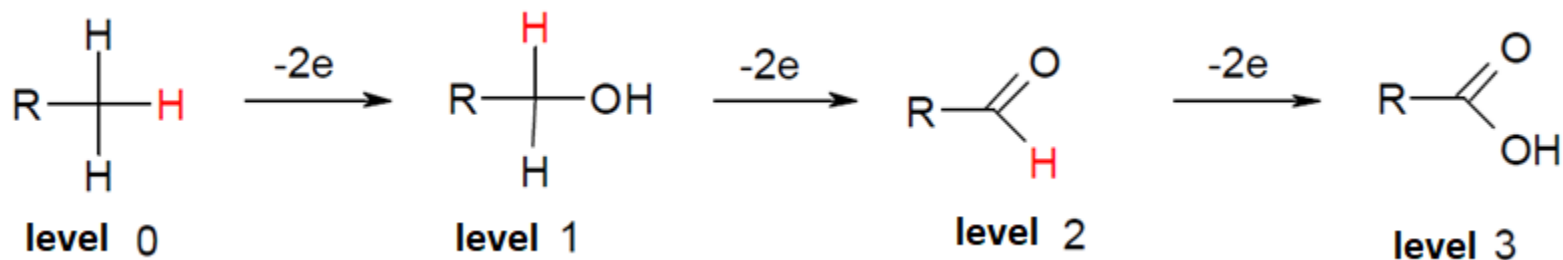


- ❖ one of the ways to transform a functional group, by changing its oxidation state or by changing the heteroatom in the group
 - ❖ change of oxidation state → eg interconversion of an ester group by reduction to an aldehyde or a primary alcohol; oxidation of secondary alcohol to a ketone, change of heteroatoms in a functional group
 - ❖ a disconnection of a C-heteroatom bond within a group is characteristic → eg conversion of ester to amide, ketone to thioketone, haloalkane to alcohol
- ❖ **adition**
 - ✓ **substitution**
 - ✓ **elimination**
 - ✓ **oxidation/reduction**
 - ✓ **reactions of free radicals**



INTERCONVERSION OF FUNCTIONAL GROUP (IFG)

- ❖ **FGC** – combination of functional groups
- ❖ **FGA** – addition of functional group
- ❖ the conversion of one functional group to another can occur without a change in the oxidation state or with a change in the oxidation state



Oxidation level 1:

C-X (X = Hal, OH, OR, OAc, OTs, NR₂, NO₂, SR, *etc*);

Oxidation level 2:

C=X (X = O, NR); CXY (X, Y = Hal, OR, SR);

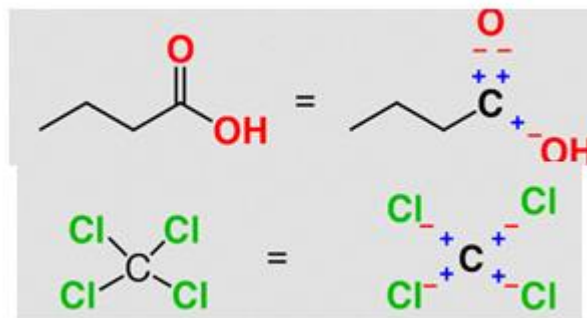
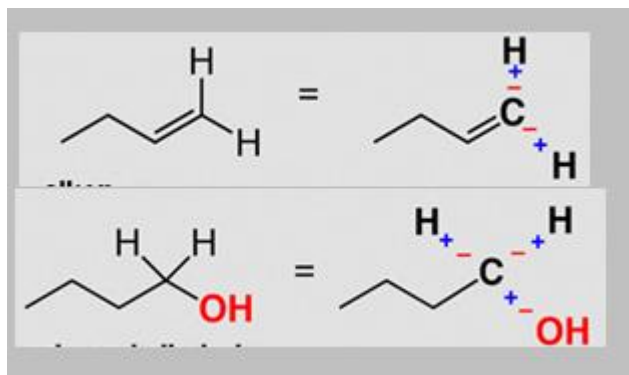
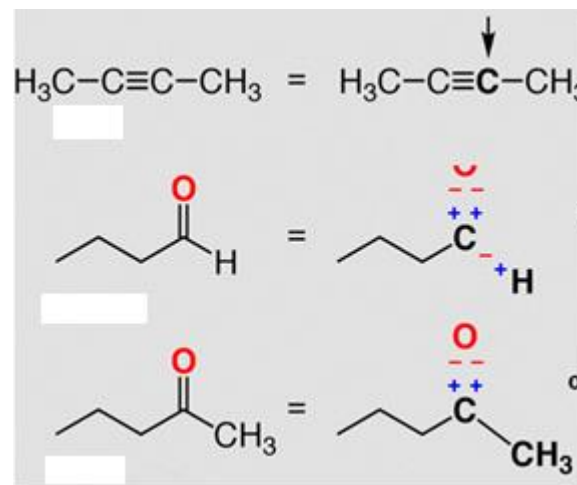
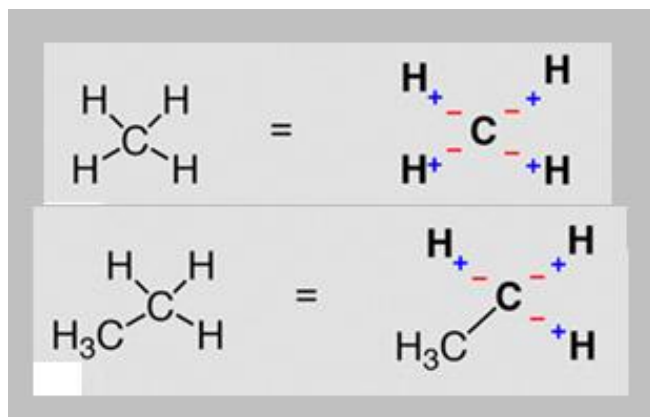
C=C-X (X = Hal, OR, OSiR₃); C≡C; X-C-C-Y

Oxidation level 3:

COOH, COX (X = OR, Hal, OCOR, NR₂); C≡N, C=C-C=O, C=C-C≡C

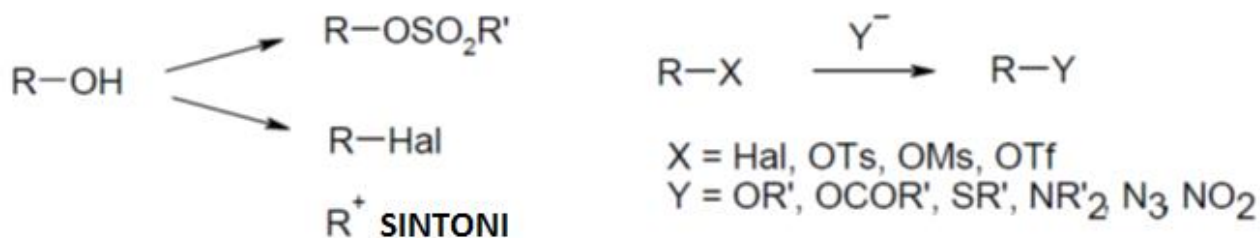
OXIDATION LEVELS OF CARBON

- ❖ any bond between C and C does not change the oxidation state
- ❖ each bond between C and H reduces the oxidation state by 1
- ❖ each bond between a C and a more electronegative atom (O, N, Hal) increases the oxidation state by 1

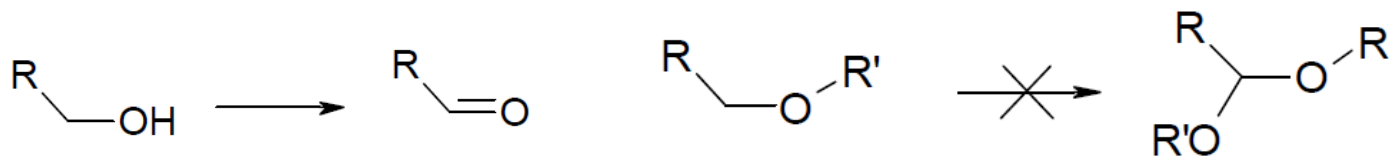


INTERCONVERSION OF FUNCTIONAL GROUP (IFG)

- ❖ **interconversion of functional groups** that are at the same oxidation level usually takes place slowly - these are synthetic equivalents



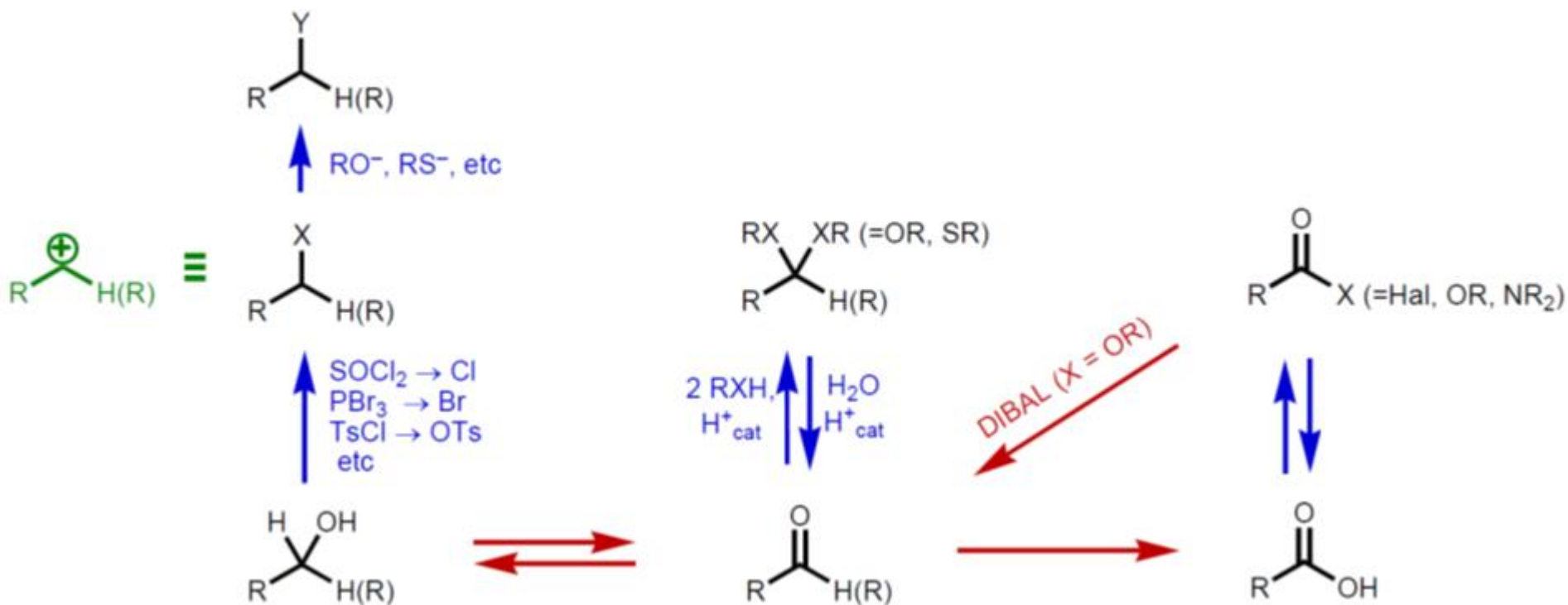
- ❖ interconversion of functional groups that are not at the same oxidation level can take place only in some cases



- ❖ OH (hydroxy group) - oxygen functional group with the lowest oxidation state (-1); COOH (carboxyl group) - oxygen functional group with the highest oxidation state (+3); CO (carbonyl group) - oxidation state +1 for aldehydes and +2 for ketones
- ❖ oxidation of alcohol to carboxylic acid changes the oxidation state of carbon from -1 to +3

INTERCONVERSION OF FUNCTIONAL GROUP (IFG)

IFG WHICH DOES NOT INCLUDE THE CHANGE OF THE OXIDATION LEVEL

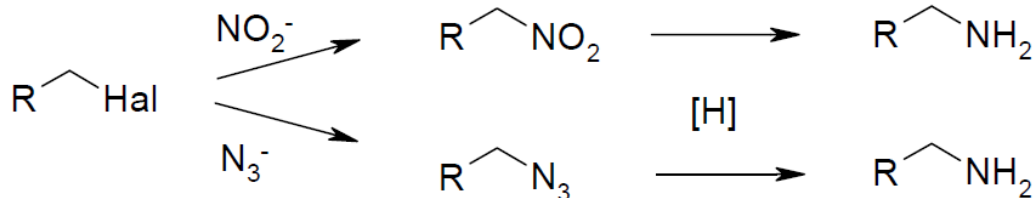
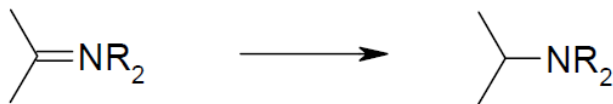
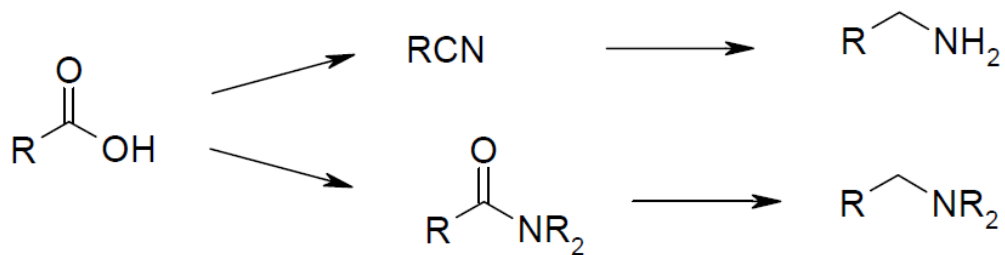
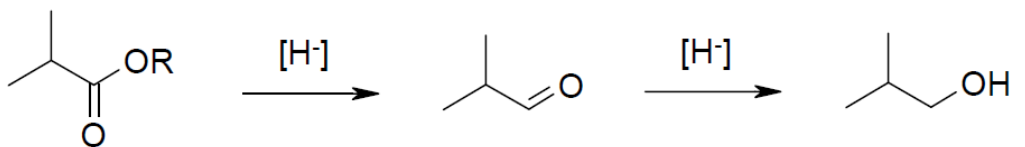
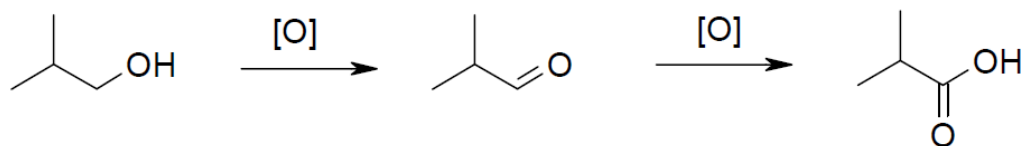


❖ functional groups obtained without changing the oxidation state are prepared from precursors with the same number of C-heteroatom bonds

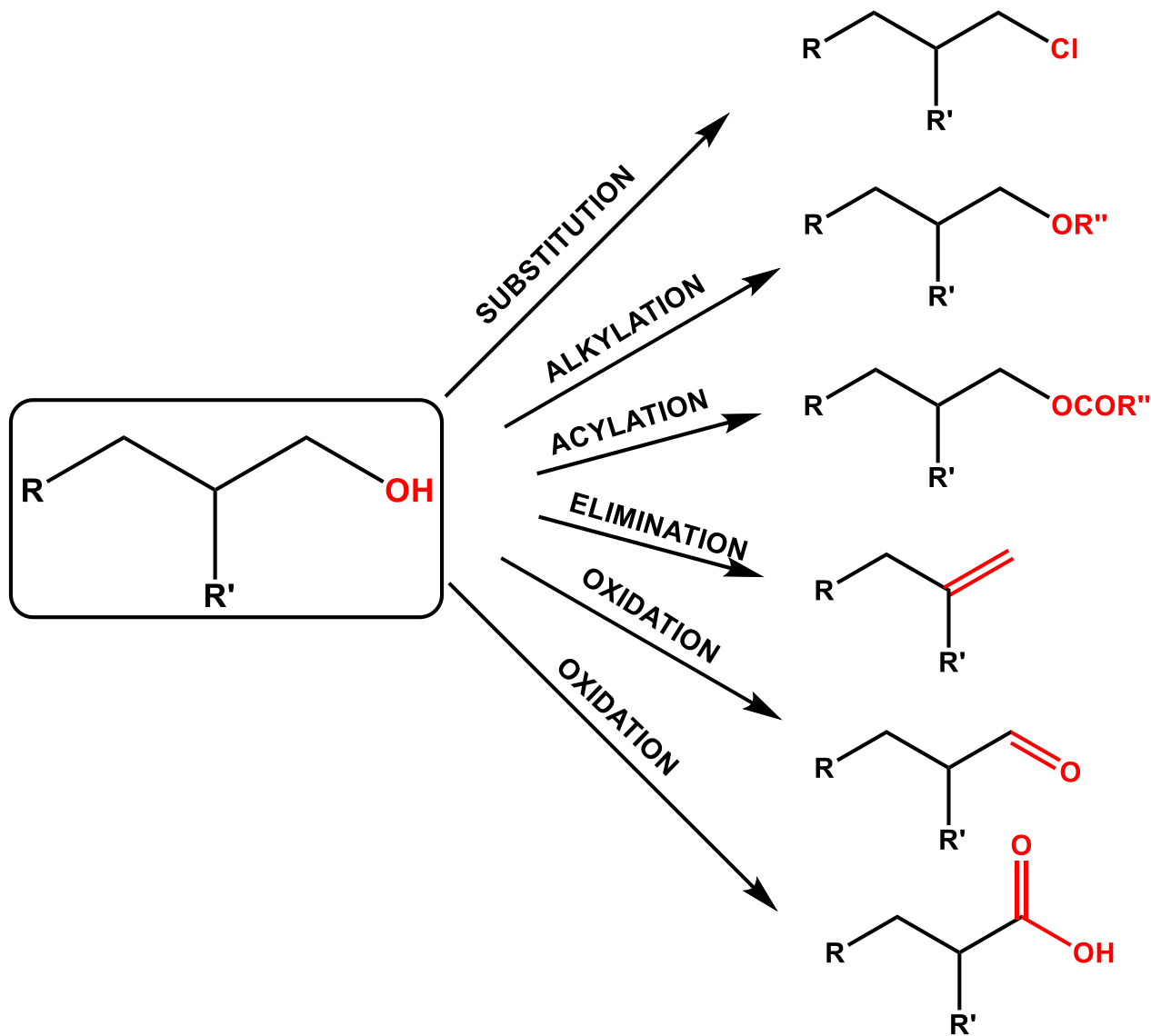
INTERCONVERSION OF FUNCTIONAL GROUP (IFG)

GROUP (IFG)

IFG WHICH DOES INCLUDE THE CHANGE OF THE OXIDATION LEVEL

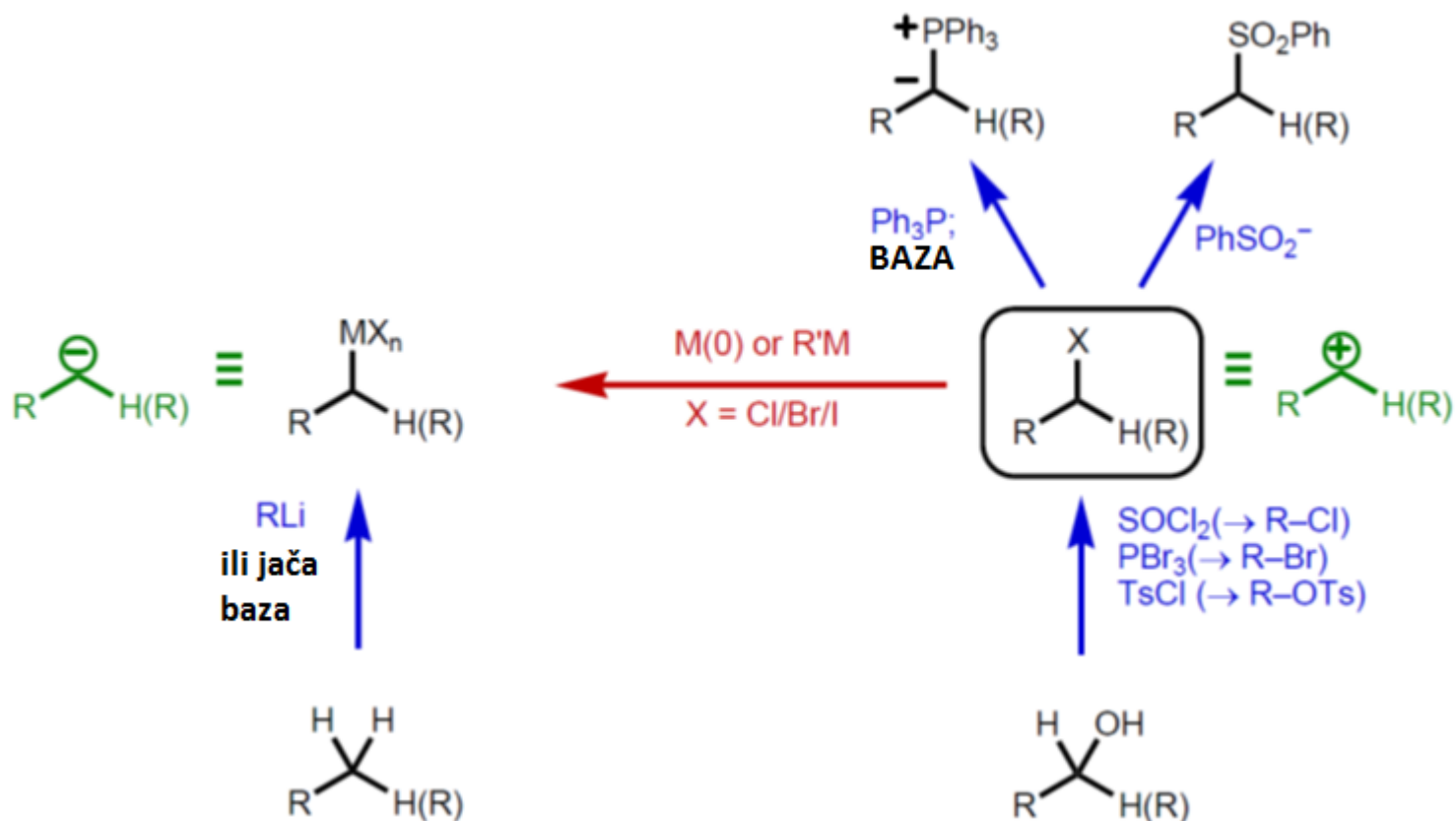


SYNTHETIC TRANSFORMATIONS OF ALCOHOLS IN ONE STEP

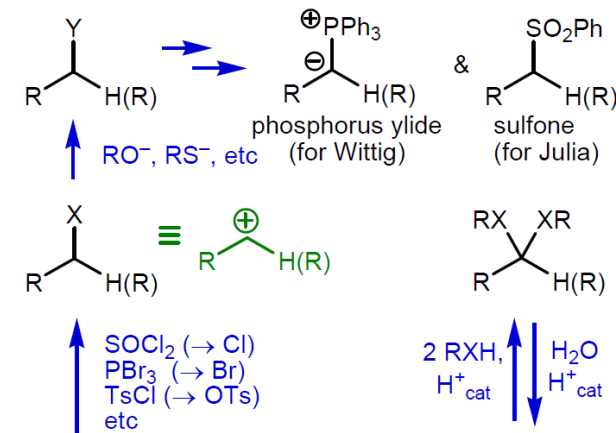
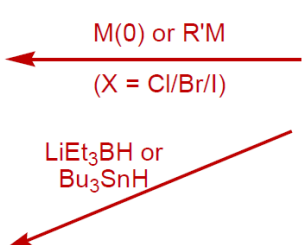
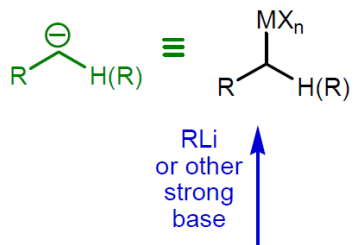


THE IMPORTANCE OF THE ALKYL-HALOGENIDES

- ❖ alkyl halides are very important because R^+ are synthetic equivalents and precursors for obtaining R^- synthons
- ❖ they are also important for the preparation of ylides or sulfones which are the main precursors for the synthesis of $C = C$ bonds

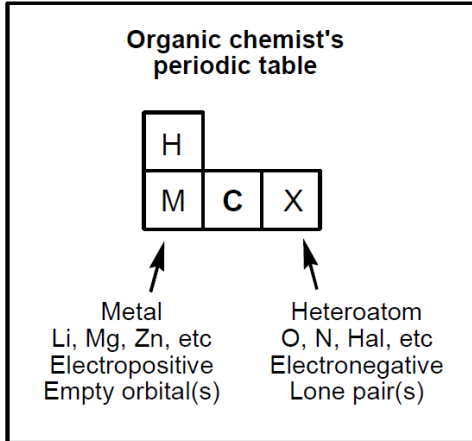
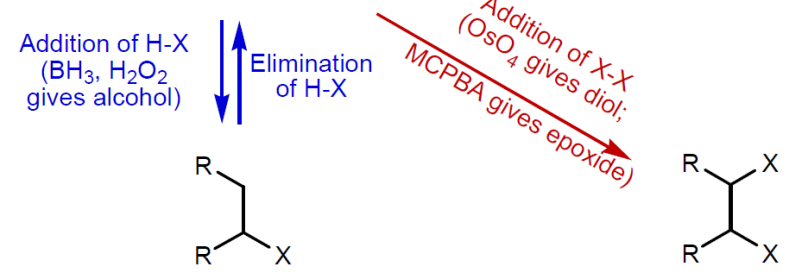


Common Functional Group Interconversions (Methods in Organic Synthesis, MC)



Alcohol Interconversions:
 $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow{\text{H}_2, \text{TM}_{\text{cat}}} \text{R}-\text{CH}_2-\text{CH}_3$
 $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow{\text{H}_2\text{CrO}_4 \text{ or PDC in DMF}} \text{R}-\text{CHO}$
 $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow{\text{Swern or PDC in CH}_2\text{Cl}_2} \text{R}-\text{CHO}$
 $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow{\text{Jones (H}_2\text{CrO}_4, \text{acetone)}} \text{R}-\text{COOH}$
 $\text{R}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow{\text{NaBH}_4, \text{etc}} \text{R}-\text{CHO}$
 $\text{R}-\text{CHO} \xrightarrow{\text{LiAlH}_4 \text{ or BH}_3} \text{R}-\text{CH}_2-\text{CH}_2-\text{OH}$
 $\text{R}-\text{CHO} \xrightarrow{\text{N}_2\text{H}_4, \text{KOH, Heat (Wolff-Kischner) or Zn, HCl (Clemmensen) or Raney Nickel hydrogenolysis of dithioacetals}} \text{R}-\text{CH}_2-\text{CH}_2-\text{OH}$

Alkene Interconversions:
 $\text{R}-\text{CH}=\text{CH}-\text{R} \xrightarrow{\text{H}_2, \text{TM}_{\text{cat}}} \text{R}-\text{CH}_2-\text{CH}_2-\text{R}$
 $\text{R}-\text{CH}=\text{CH}-\text{R} \xrightarrow{\text{H}_2, \text{Pd/BaSO}_4 \text{ (Lindlar's) } \textit{syn}}$
 $\text{R}-\text{CH}=\text{CH}-\text{R} \xrightarrow{\text{Na/NH}_3 \textit{anti}}$
 $\text{R}-\text{CH}=\text{CH}-\text{R} \xrightarrow{\text{C=C Formation: Julia (trans), Wittig (cis)}}$
 $\text{R}-\text{CH}=\text{CH}-\text{R} \xrightarrow{\text{Oxidative C=C cleavage: O}_3 \text{ or OsO}_4, \text{NaIO}_4}$



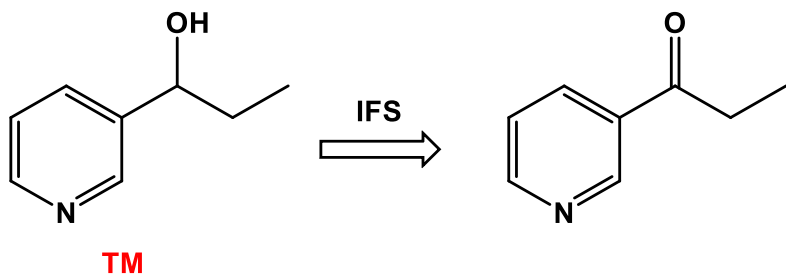
RETROSYNTHETIC ANALYSIS



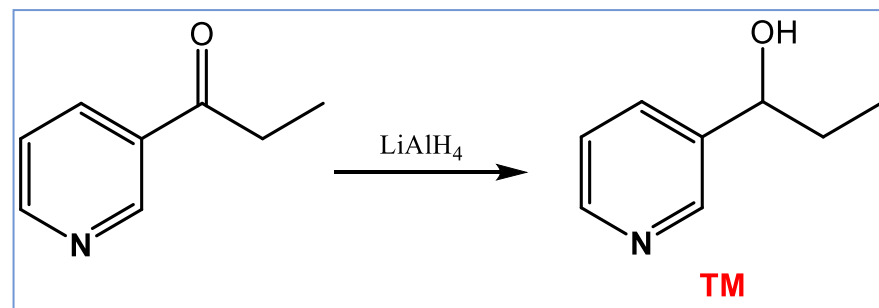
Planning of the organic synthesis

- ❖ determine the functional groups in the target molecule
- ❖ make an appropriate disconnection
- ❖ suggest reagents, conditions and synthetic route

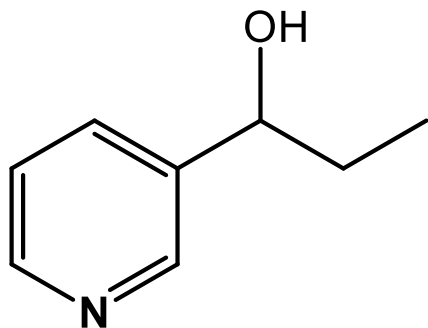
Retrosynthetic
analysis



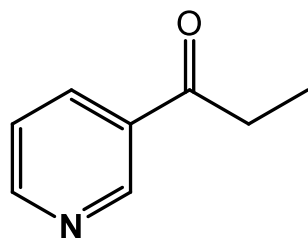
The synthesis



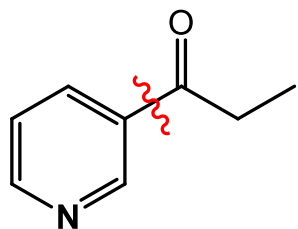
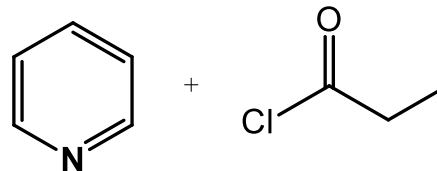
THE EXAMPLE OF THE RETROSYNTHETIC ANALYSIS



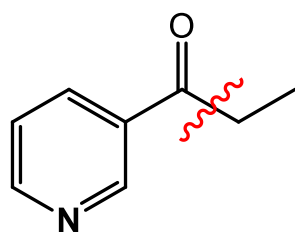
TM



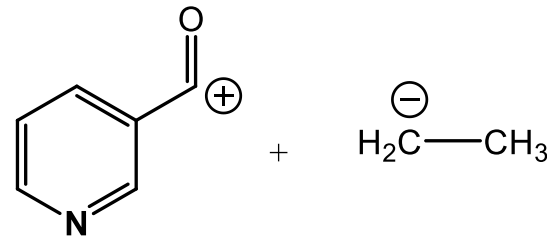
~~DIS~~



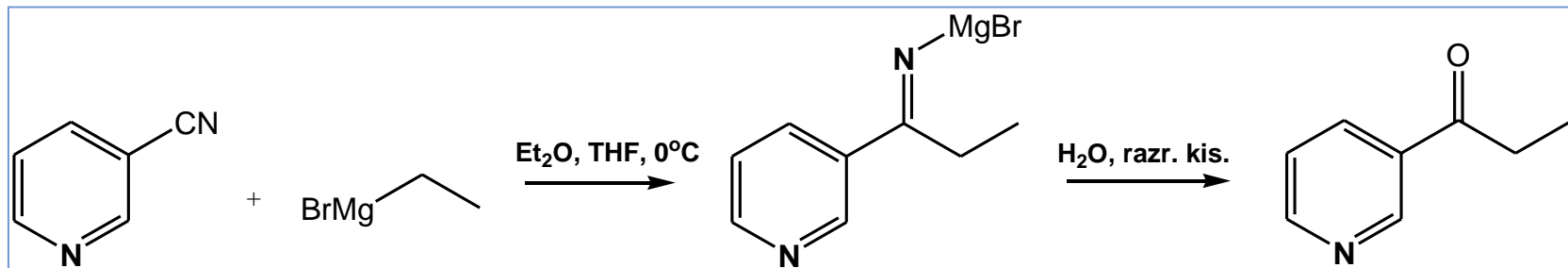
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DIS



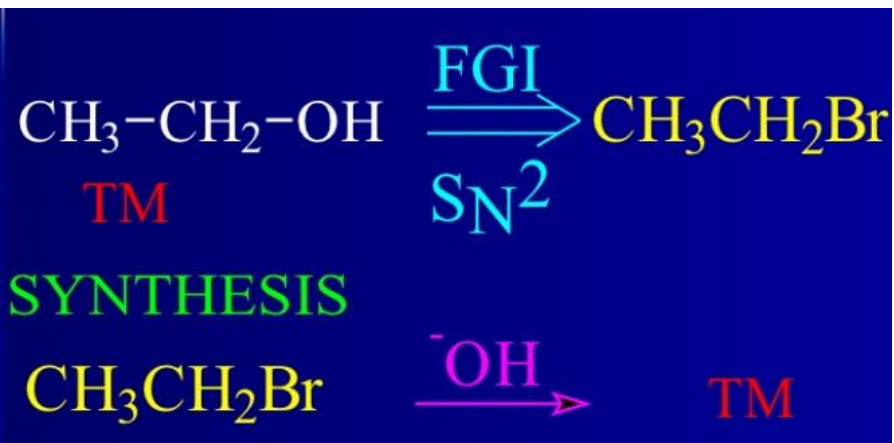
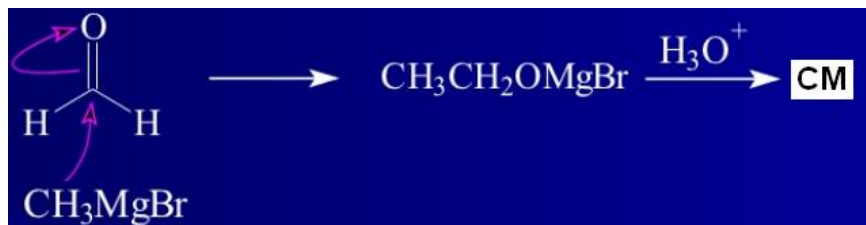
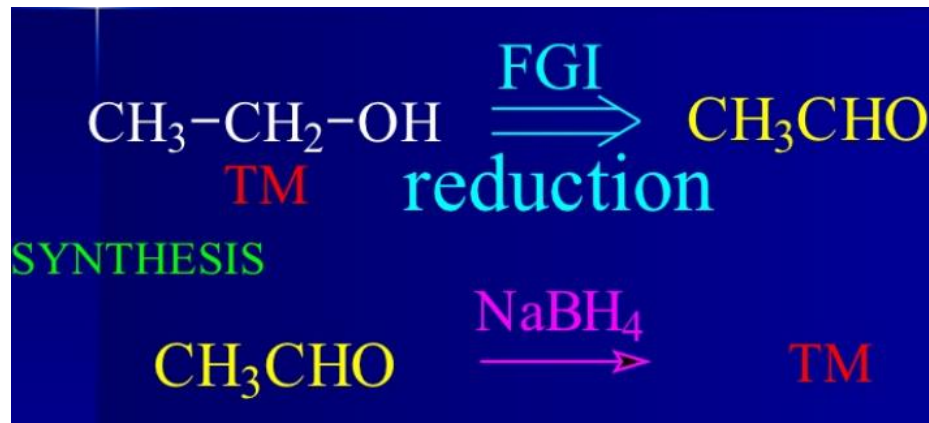
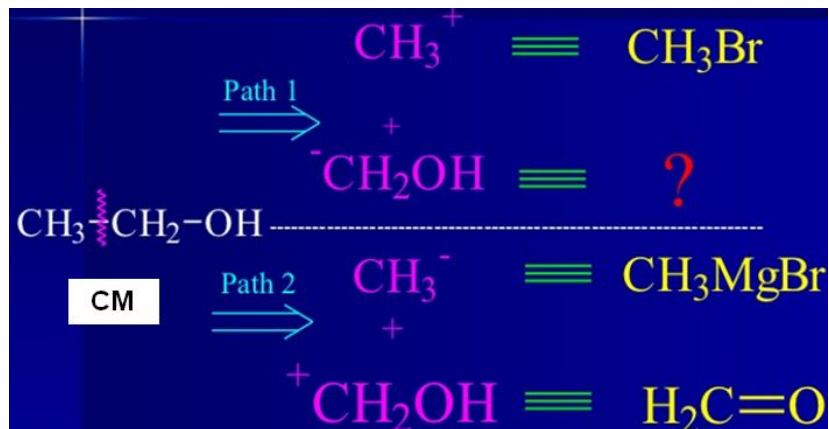
GOOD
DIS



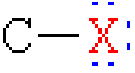

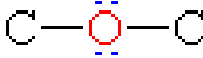
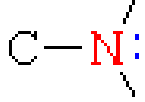
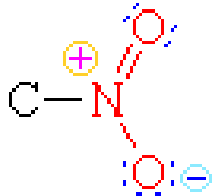
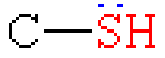

PROPOSAL OF THE SYNTHESIS



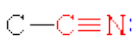
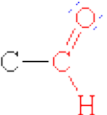
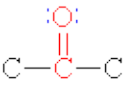
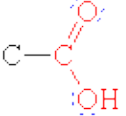
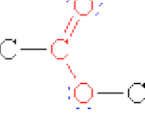
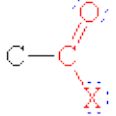
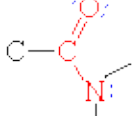
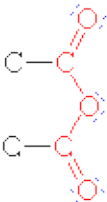
THE EXAMPLE OF THE RETROSYNTHETIC ANALYSIS OF ETHANOL



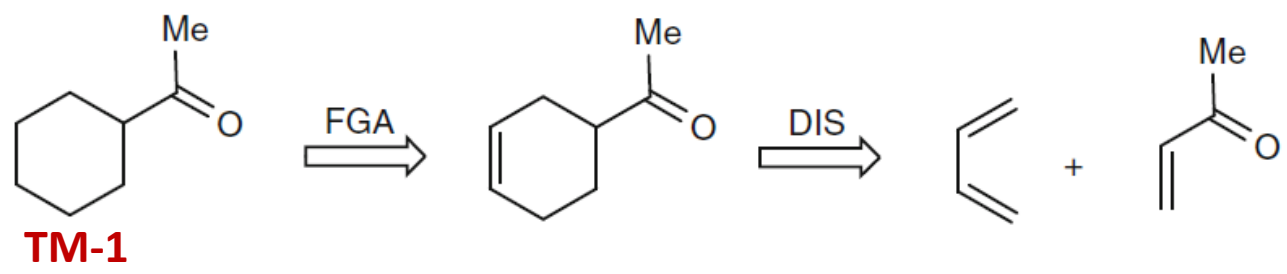
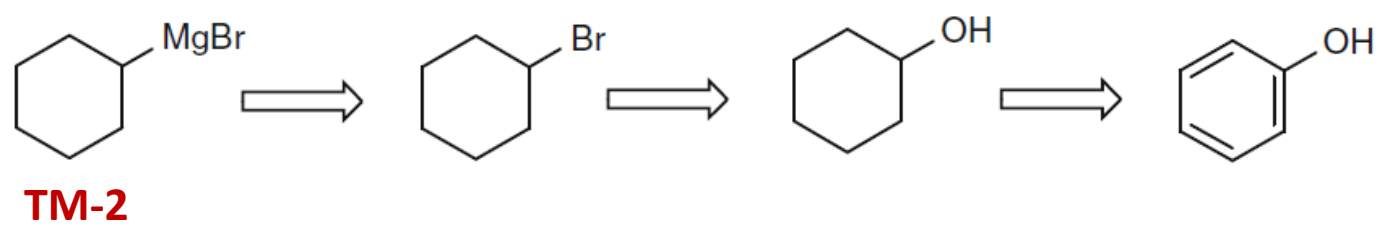
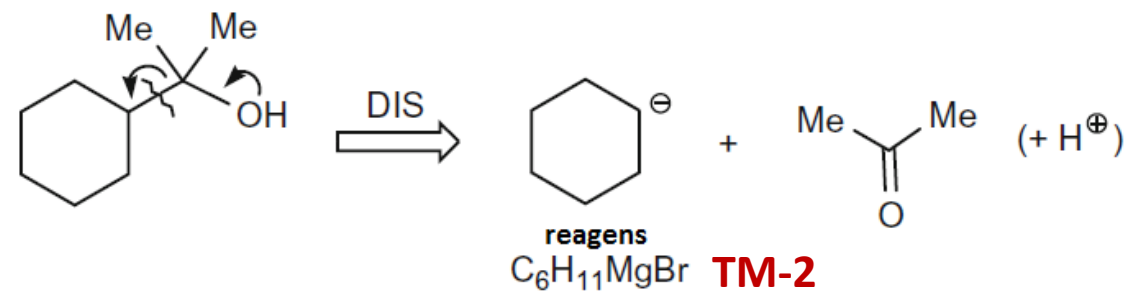
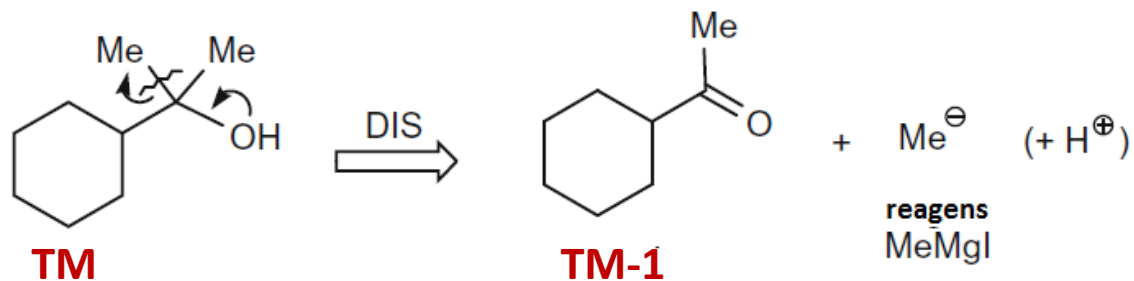
Functional groups bonded with the single bond to the heteroatome

Formula	Classes	Example	IUPAC
	Halides Alkyl-halogenides	$\text{H}_3\text{C-I}$	Iodomethane
	Alchooles	$\text{CH}_3\text{CH}_2\text{OH}$	Ethanol
	Ethers	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	Diethyl-ether
	Amines	$\text{H}_3\text{C-NH}_2$	Aminomethane
	Nitro compounds	$\text{H}_3\text{C-NO}_2$	Nitromethane
	Tioles	$\text{H}_3\text{C-SH}$	Metanthiole
	Sulfides	$\text{H}_3\text{C-S-CH}_3$	Dimethyl-sulfide

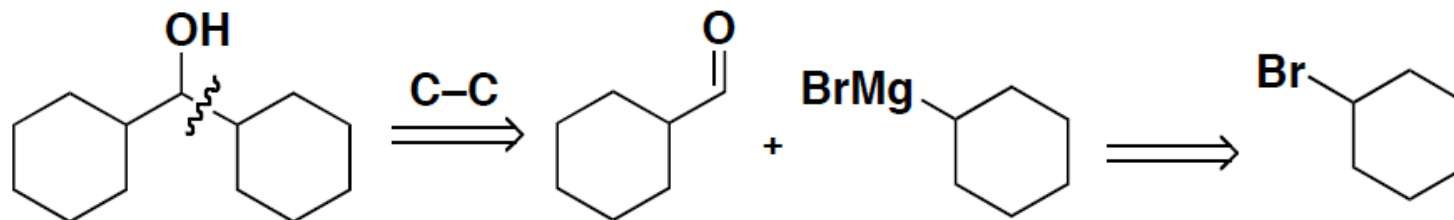
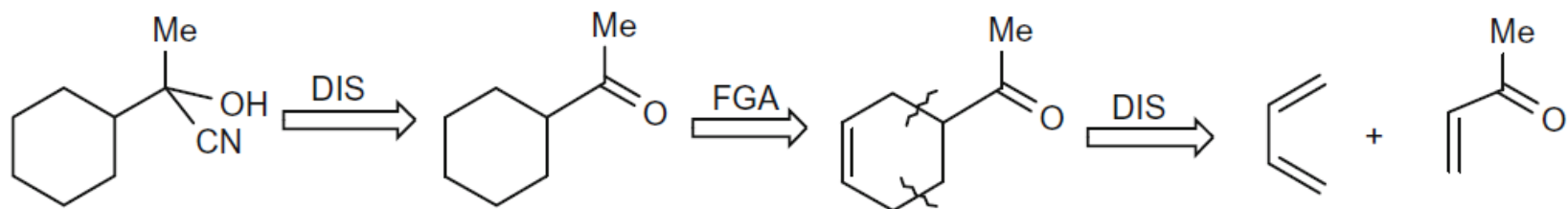
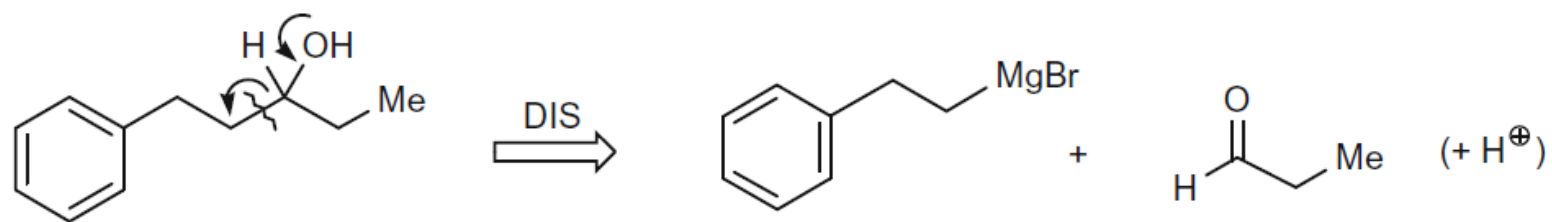
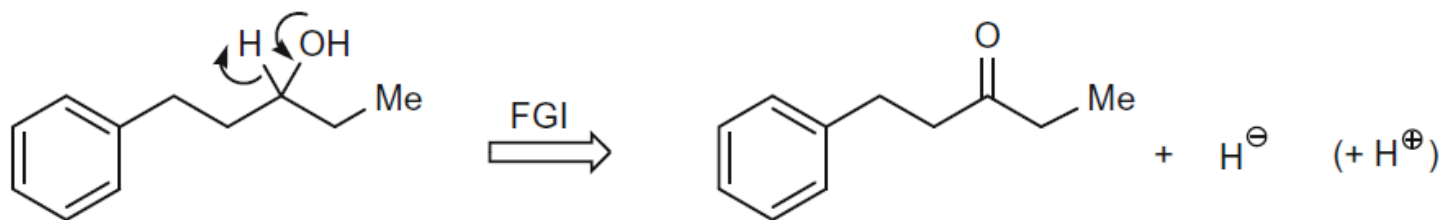
Functional groups bonded with the multiple bond to the heteroatome

Formula	Class	Example	IUPAC	Trivial name
	Nitriles	$\text{H}_3\text{C-CN}$	Ethanenitrile	Acetonitrile
	Aldehydes	H_3CCHO	Ethanal	Acetaldehyde
	Ketones	H_3CCOCH_3	Propanon	Acetone
	Carboxylic acids	$\text{H}_3\text{CCO}_2\text{H}$	Ethan acid	Acidic acid
	Esters	$\text{H}_3\text{CCO}_2\text{CH}_2\text{CH}_3$	Ethyl-etanoate	Ethyl-acetate
	Acyl-halogenides	H_3CCOCl	Ethanoil-chloride	Acethyl-chloride
	Amides	$\text{H}_3\text{CCON}(\text{CH}_3)_2$	<u>N,N</u> -Dimehyilethanamide	<i>N,N</i> -Dimethylacetamide
	Anhydrides	$(\text{H}_3\text{CCO})_2\text{O}$	Acidic acid anhydride	Acetanhydride

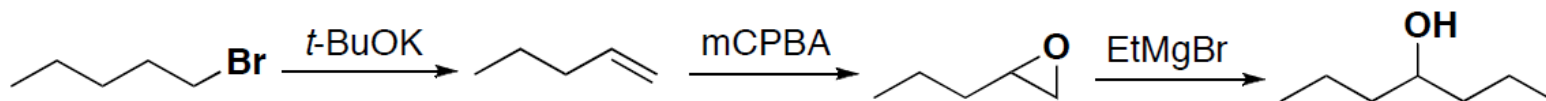
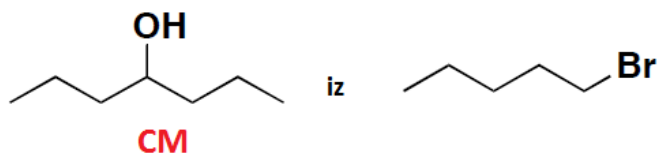
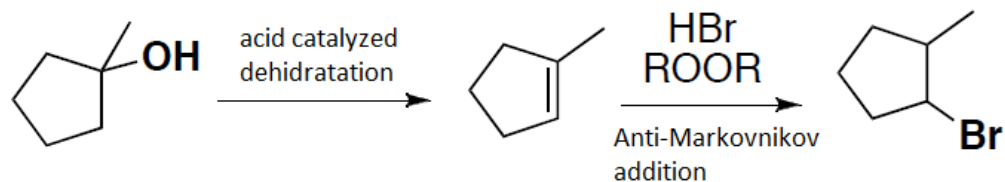
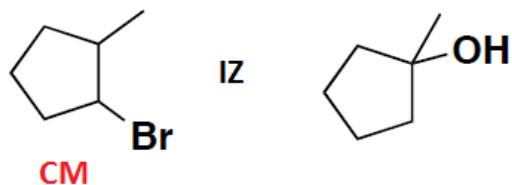
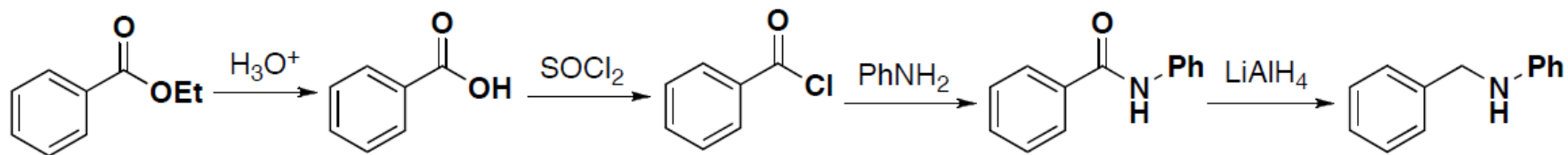
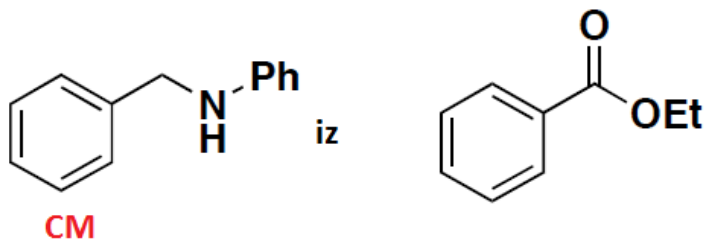
THE EXAMPLES OF RETROSYNTHESIS



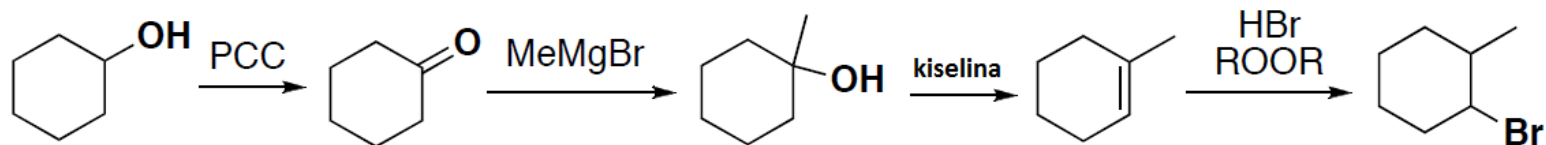
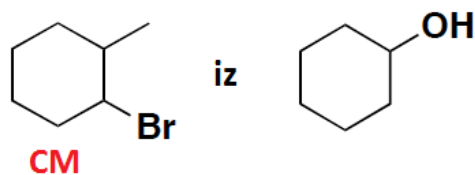
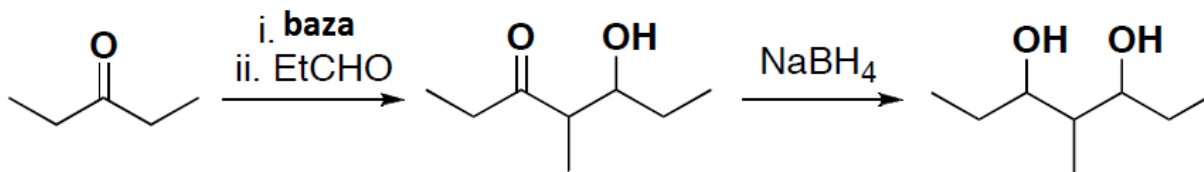
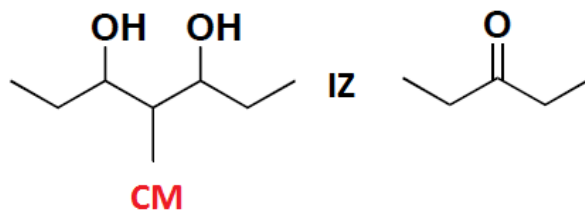
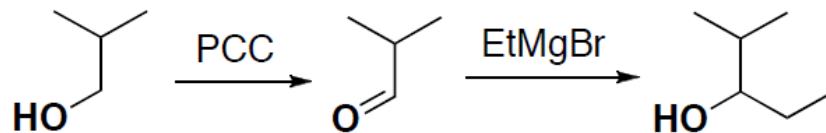
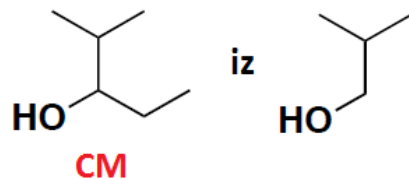
THE EXAMPLES OF RETROSYNTHESIS



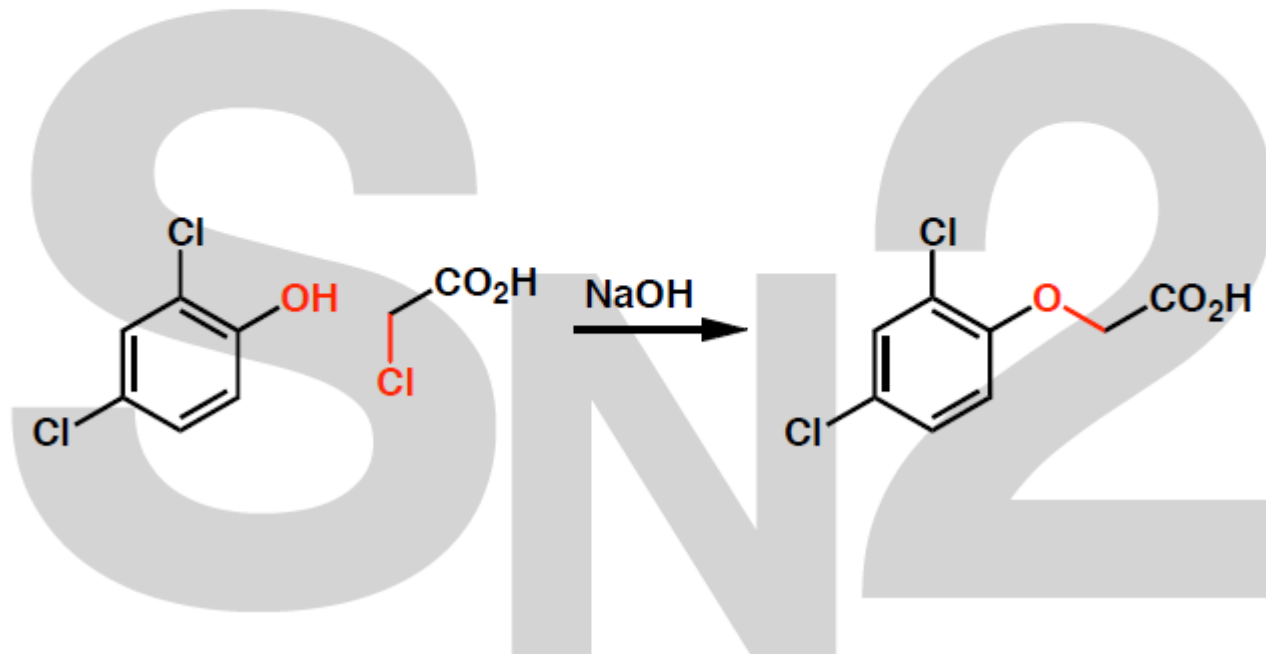
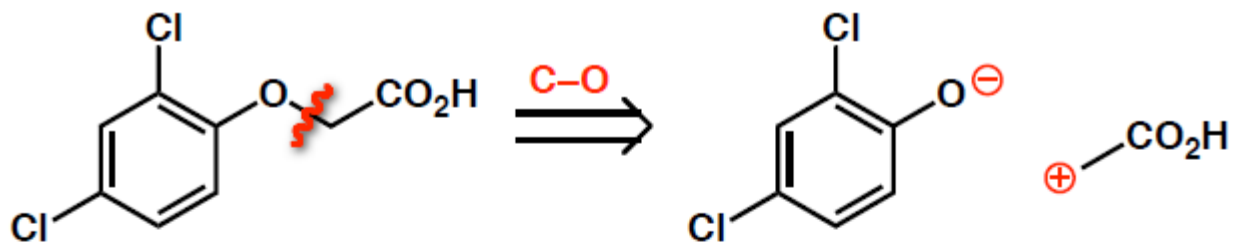
THE EXAMPLES OF RETROSYNTHESIS



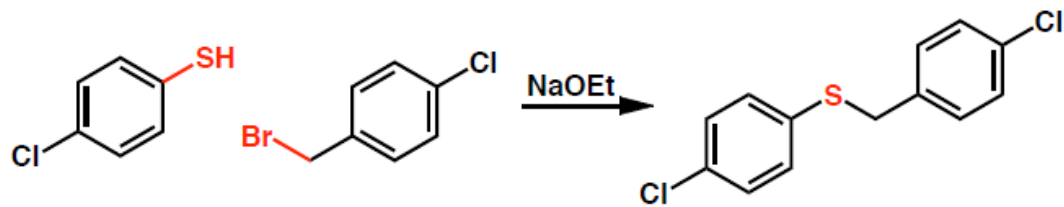
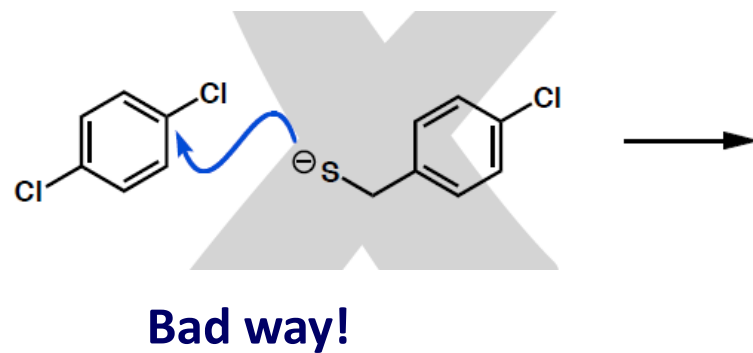
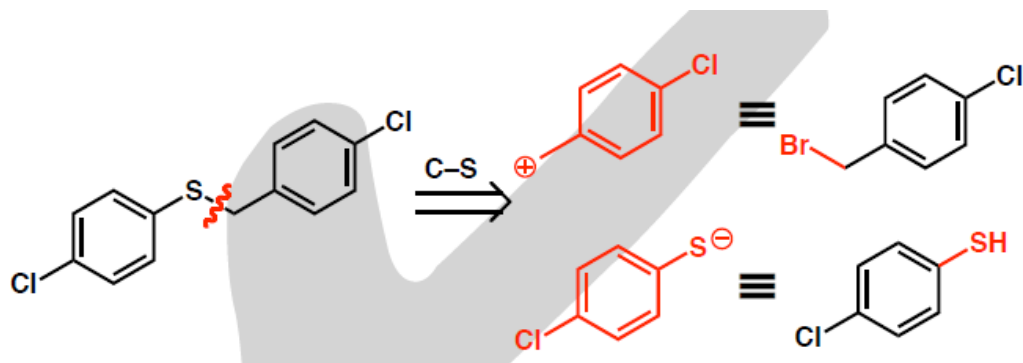
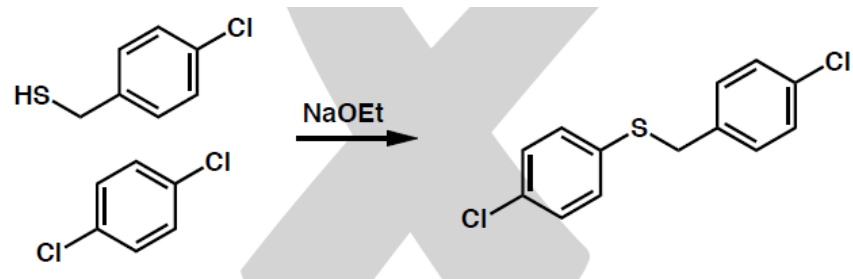
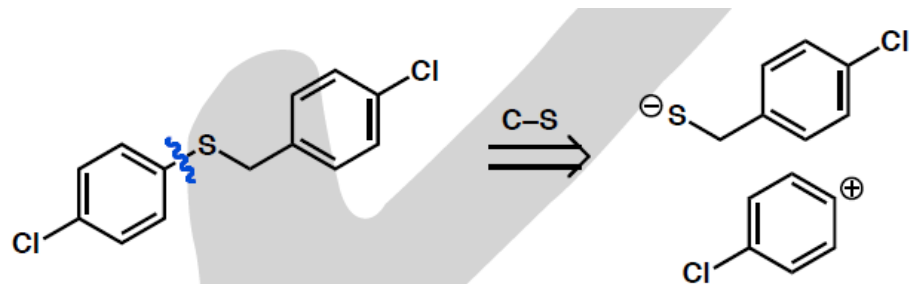
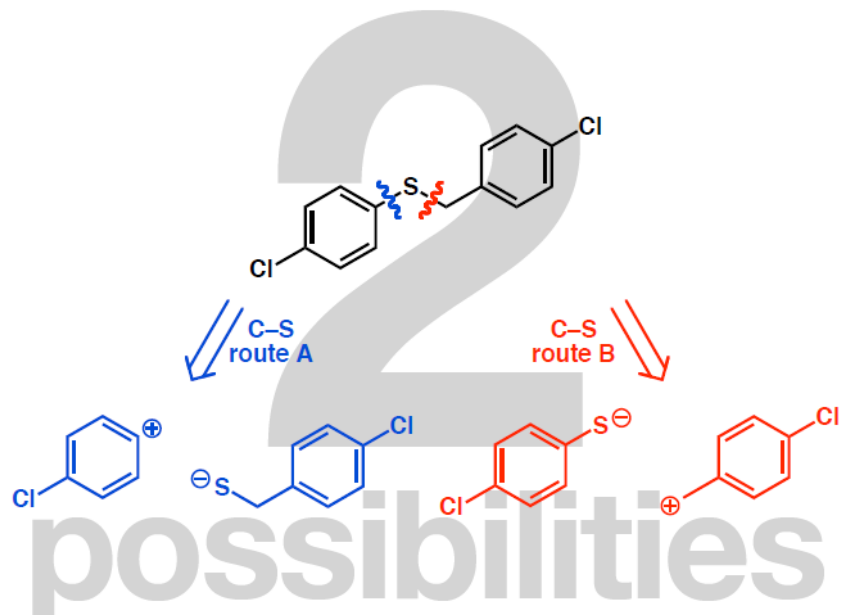
THE EXAMPLES OF RETROSYNTHESIS



THE EXAMPLES OF RETROSYNTHESIS



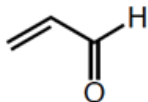
THE EXAMPLES OF RETROSYNTHESIS

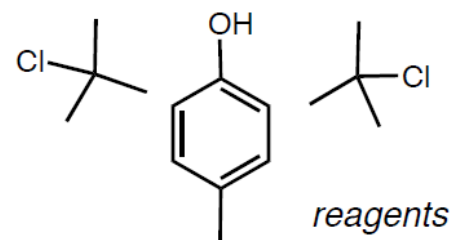
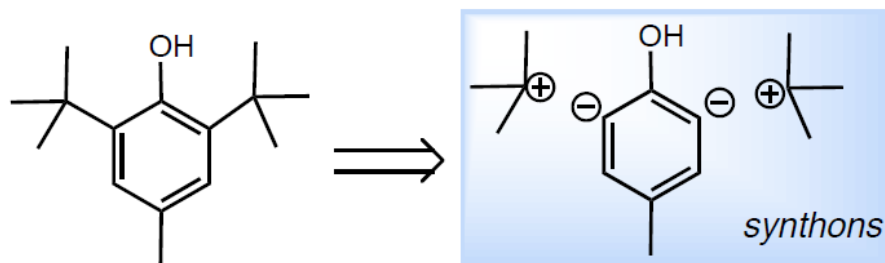
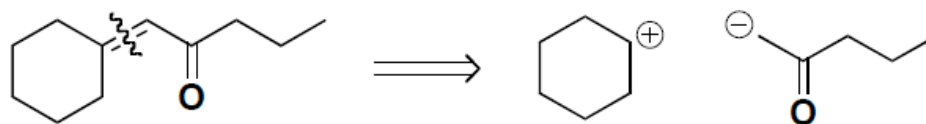
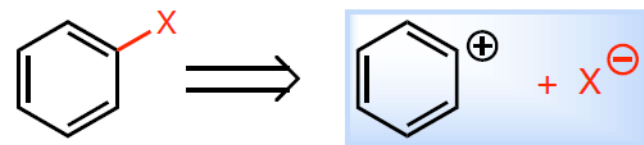
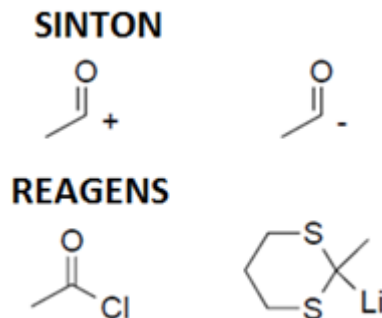


Good way!

SYNTHONS

- **SYNTHON** is an ideal fragment obtained by retrosynthesis that can be incorporated into the structure of the target molecule - usually a cation or anion
- synthon can be cut from the target molecule so as to obtain a meaningful chemical burst of the bond
- reagents are chemical compounds that are actually used instead of synthons

SINTON	REAGENS
$^+\text{CH}_3$	CH_3I or CH_3OTs
$^-\text{CH}_3$	CH_3MgBr
$^+\text{CH}_2\text{CH}_2\text{CHO}$	



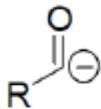
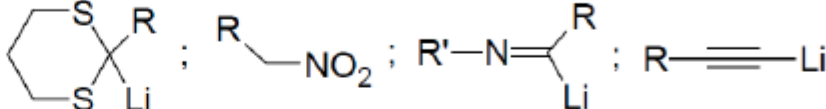
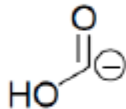
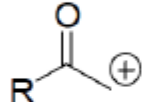
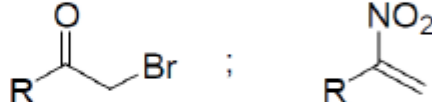
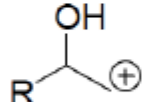
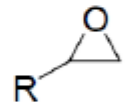
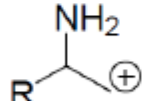
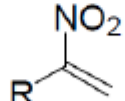
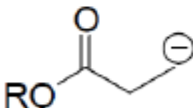
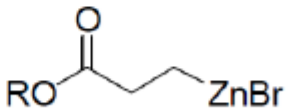
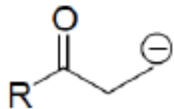
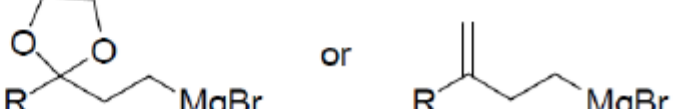
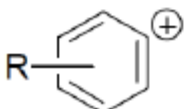
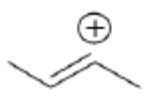
EXAMPLES OF SYNTHONS

synthon	reagents	functional group	synthon	reagents	functional group
MeS^\ominus	MeSH		PMe_2^\oplus	ClPMe_2	
$\text{C}\equiv\text{N}^\ominus$	$\text{KC}\equiv\text{N}$	$\text{—C}\equiv\text{N}$			—CO—
$\text{CH}_2\text{CHO}^\ominus$	CH_3CHO	—CHO			—CO—
$\text{C}=\text{C—COOMe}^\ominus$	$\text{HC}\equiv\text{C—COOMe}$	$\text{—CO}_2\text{Me}$			—COOMe
Me^\ominus	MeLi		Me^\oplus	MeI	

NATURAL SYNTHONS

SINTON	SINTETIC EQUIVALENT
Br^-	NaBr
N_3^-	NaN_3
RO^-	RONa from ROH
RS^-	RSNa from RSH
$\begin{array}{c} \oplus \\ \\ \text{R}-\text{C}-\text{R}' \end{array}$	$\begin{array}{c} \text{Hal} \\ \\ \text{R}-\text{C}-\text{R}' \\ \\ \text{MgHal} \end{array}$
alkyl, allyl or benzyl	alkyl, allyl or benzyl Hal = Br, I
$\begin{array}{c} \ominus \\ \\ \text{R}-\text{C}-\text{I} \end{array}$	$\begin{array}{c} \text{R} \\ \\ \text{MgHal} \\ \\ \text{R}' \end{array}$
alkyl, allyl or benzyl	
$\begin{array}{c} \ominus \\ \\ \text{R}-\text{C}=\text{C}-\text{R}' \\ \\ \text{R}'' \end{array}$	$\begin{array}{c} \text{R} \\ \\ \text{MgHal} \\ \\ \text{R}' \end{array}$
vinyl or aryl	vinyl or aryl
$\text{R}-\text{C}\equiv\text{C}^-$	$\text{R}-\text{C}\equiv\text{C}-\text{M}$ M = Li, MgHal
$\begin{array}{c} \text{OH} \\ \\ \text{R}-\text{C}^+-\text{R}' \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{R}' \end{array}$
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}^+ \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{OR}' \end{array}$ or $\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{Hal} \end{array}$ or $\begin{array}{c} \text{O} \quad \text{O} \\ \quad \\ \text{R}-\text{C}-\text{O}-\text{C}-\text{R} \end{array}$
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}^- \end{array}$	$\begin{array}{c} \text{OLi} \\ \\ \text{R}-\text{C}=\text{C} \end{array}$ or $\begin{array}{c} \text{OSiMe}_3 \\ \\ \text{R}-\text{C}=\text{C} \end{array}$ or $\begin{array}{c} \text{NR}'_2 \\ \\ \text{R}-\text{C}=\text{C} \end{array}$
$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{CH}_2^+ \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{CH}=\text{CH}_2 \end{array}$

UNNATURAL SYNTHONS

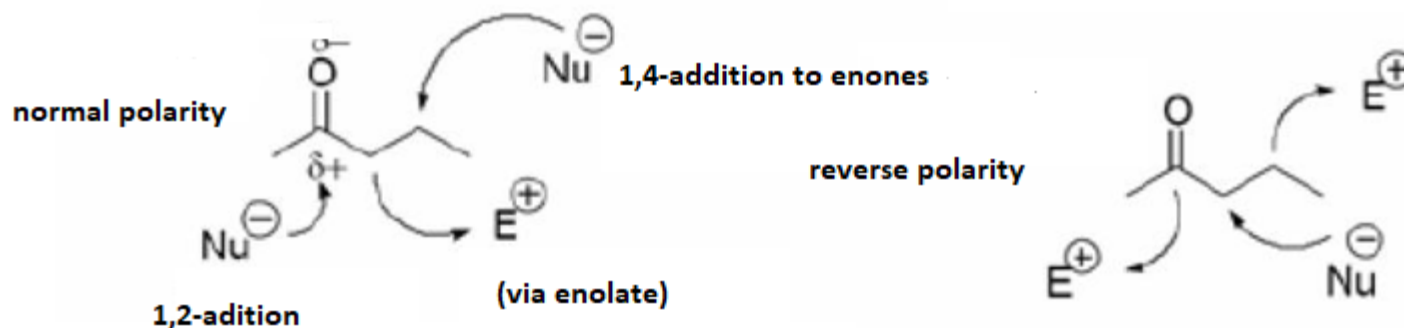
SINTON	SYNTHETIC EQUIVALENTS
Br^+ O^{2+} or HO^+ RS^+	Br_2 SeO_2 $RSCl$ ili $RSSR$
 acyl anion	
	CN^- (KCN)
	
	
	
 homoenolat	
 homoenolat	
 i	

DISCONNECTION OF THE MOLECULE WITH REGARD TO PRESENT FUNCTION GROUP

- ❖ as the reactions are most often polar, the formation of a bond (and corresponding transformations) can be considered as a combination of donor (d) and acceptor (a) synthons
- ❖ the molecule can be viewed as an ionic aggregate of carbon atoms with functional groups present

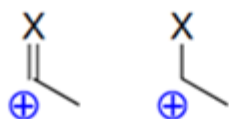


Possibilities of carbonyl group:

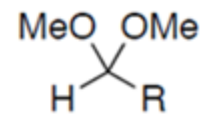
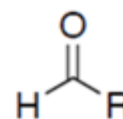
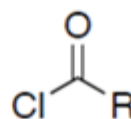


THE TYPES OF SYNTHONS

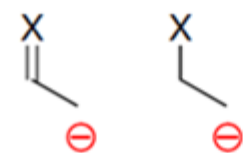
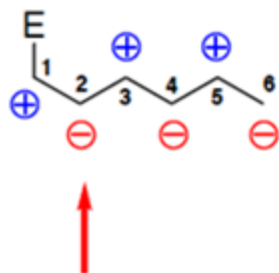
- ❖ SYNTHONS are classified as **electron-donor (d)** or as **electron-acceptor (a)**



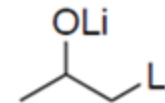
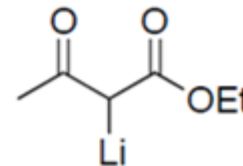
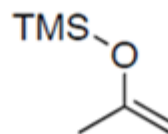
SYNTON d^1



SYNTHETIC EQUIVALENTS



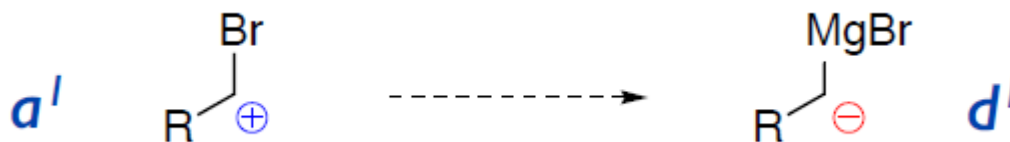
SYNTON d^2



SYNTHETIC EQUIVALENTS

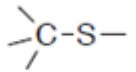
- ❖ to a and d synthons the numbers are given with respect to the relative position relative to the functional group and the reactive carbon atom

$a^0, a^1, a^2, a^3, \dots$ or $d^0, d^1, d^2, d^3, \dots$

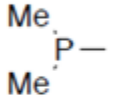



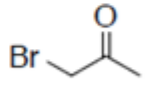
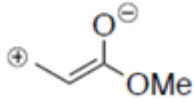
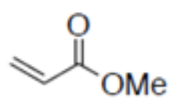


THE TYPES OF SYNTHONS

SINTON d

TYPE	EXAMPLE	REAGENTS	FS
d^0	MeS^\ominus	MeSH	
d^1	$^\ominus\text{C}\equiv\text{N}$	KC≡N	$-\text{C}\equiv\text{N}$
d^2	$^\ominus\text{CH}_2\text{CHO}$	CH ₃ CHO	$-\text{CHO}$
d^3	$^\ominus\text{C}=\text{C}-\text{COOMe}$	HC≡C-COOMe	$-\text{CO}_2\text{Me}$
alkyl- d	Me^\ominus	MeLi	

SINTON a

TYPE	EXAMPLE	REAGENTS	FS
a^0	$^\oplus\text{PMe}_2$	ClPMe ₂	
a^1			$-\text{CO}-$
a^2		Br- 	$-\text{CO}-$
a^3			$-\text{CO}_2\text{Me}$
alkyl- a	Me^\oplus	MeI	

❖ SYNTHONES are classified as electron-donor (d) or as electron-acceptor (a)

THE TYPES OF SYNTHONS

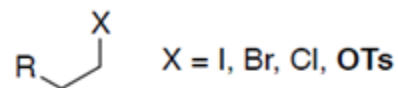
a sinton

most often alkyl-halogenides

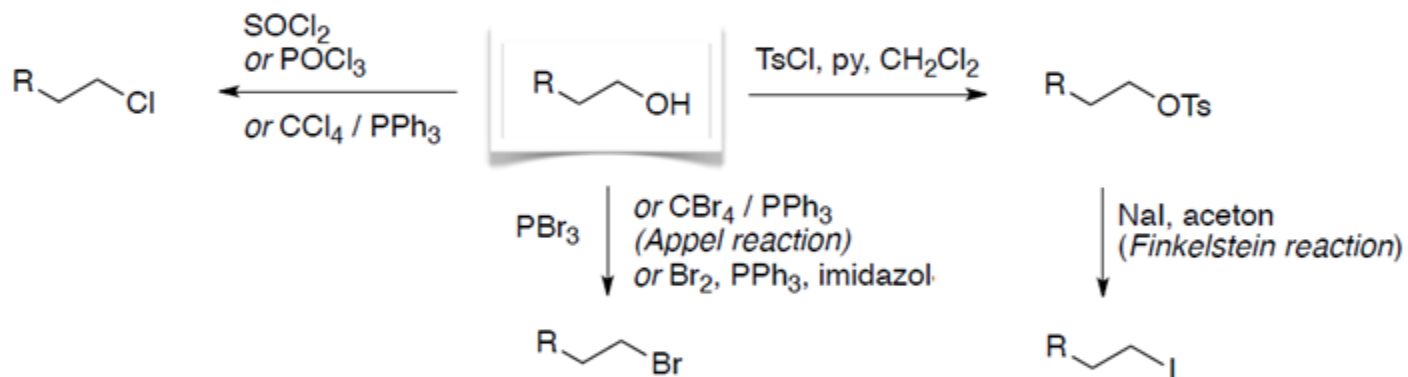
SINTON



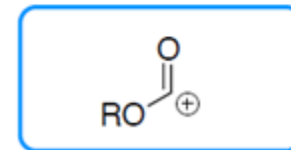
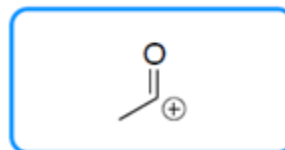
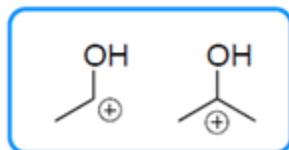
REAGENS



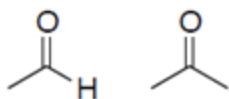
Synthesis mostly from alcohols:



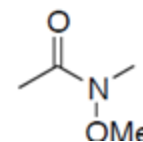
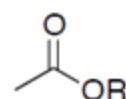
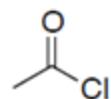
a¹ sinton



Reagens

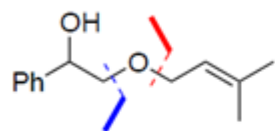


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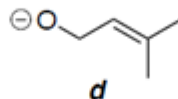
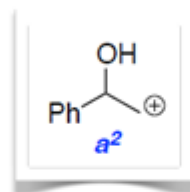
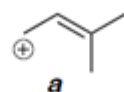
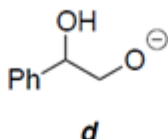


THE TYPES OF SYNTHONS

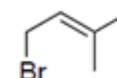
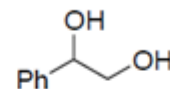
a² SINTON



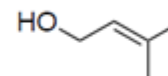
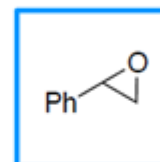
SINTONI



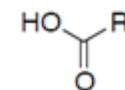
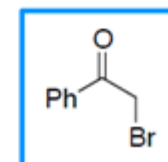
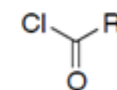
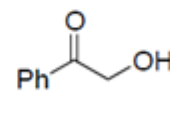
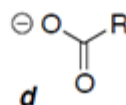
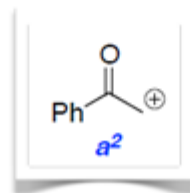
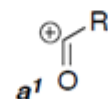
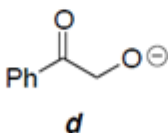
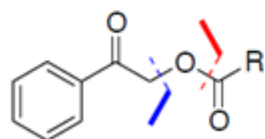
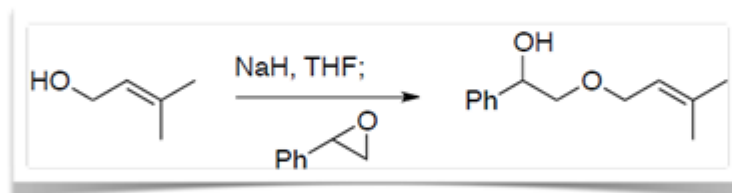
REAGENSI



problem with regioselectivity



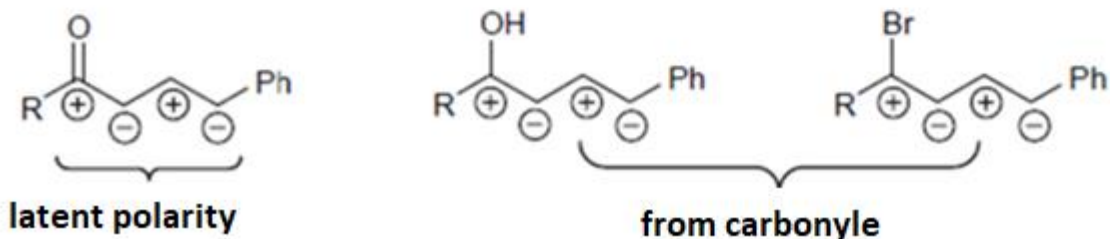
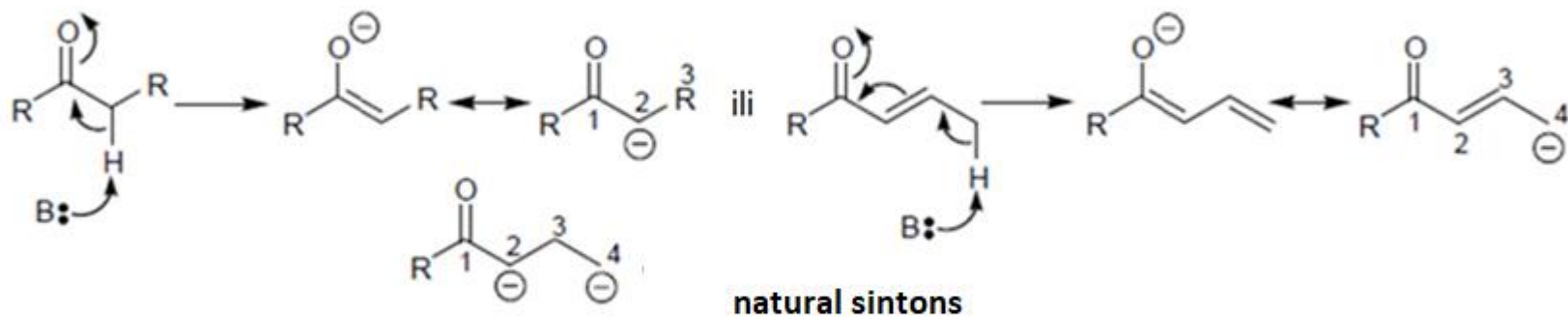
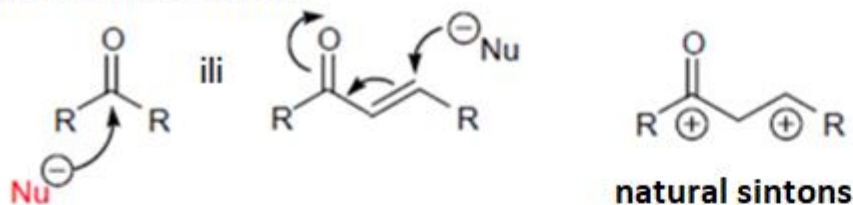
Synthesis:



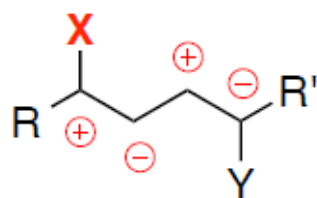
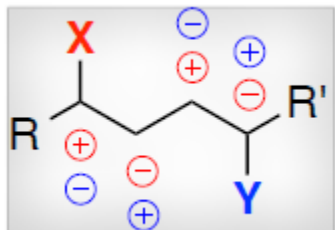
LATENT POLARITY

- ❖ imagined alternating positive and negative charges in the molecule used to facilitate the selection of disconnection and synthons → usually gives the most favorable synthons - not always possible

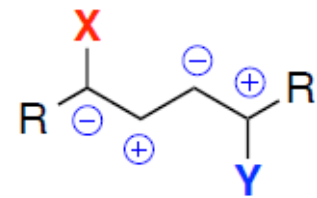
Addition of nucleophile:



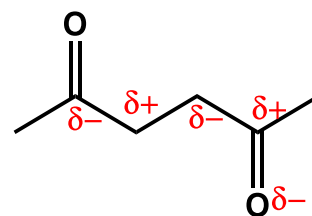
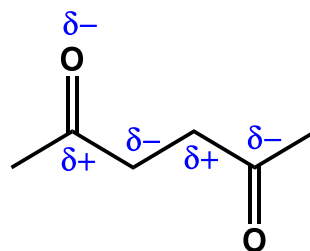
DISONANT POLARITY



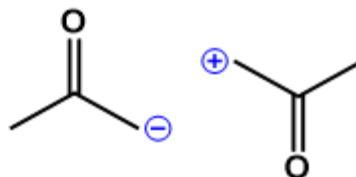
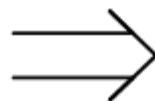
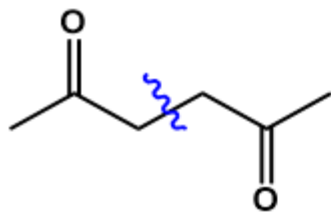
polar distribution with respect to **X**



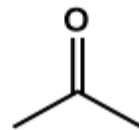
polar distribution with respect to **Y**



disonant polarity



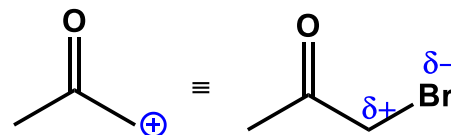
zwitterion



+ base

?

equivalents





Learning outcomes of the teaching unit

- ❖ know the basic concepts related to the retrosynthetic approach
- ❖ understand the principle of retrosynthesis
- ❖ be able to present a retrosynthetic analysis of the target molecule
- ❖ understand interconversions of functional groups
- ❖ understand meaningful disconnections
- ❖ know oxidation levels and degrees of compounds
- ❖ be able to assess whether the retrosynthetic pathway makes sense or not
- ❖ be able to draw the retrosynthesis of simple target molecules
- ❖ be able to draw the synthesis of simple target molecules according to retrosynthetic analysis