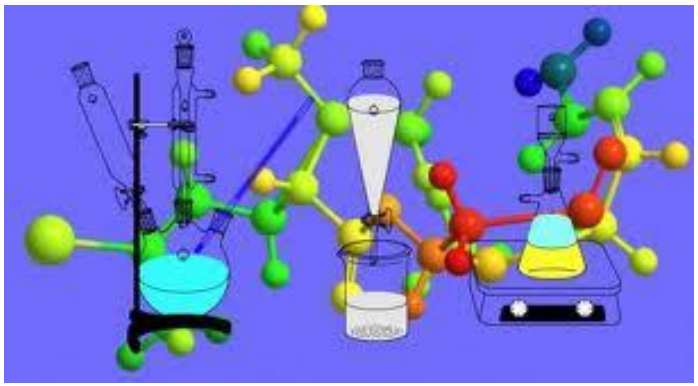
Università degli studi di Trento
Tirocinio Formativo Attivo
aa 2011/12

Chimica Organica Mod. II

Ines Mancini

SINTESI ORGANICA: QUALI LE ULTIME TENDENZE ?



Povo, 28 Febbraio2013

Contenuti

- Cos'è la sintesi organica
- Scopi
- Un po' di storia
- Concetti fondamentali
  - tipi di reazioni
  - strategie di sintesi: approccio retrosintetico
  - sintesi convergenti

- *Biocatalysis*

- *Green chemistry*

- Metodi speciali
  - Solventi
  - Sintesi supportata in fase solida
  - Irraggiamento a microonde

- Chimica Combinatoria
- La sintesi organica nello sviluppo di nuovi farmaci
- *Click chemistry*

What is Organic Synthesis?

If Chemistry is the science of matter and of its transformations

Synthetic chemistry is the science of constructing molecules from atoms and/or simpler molecules.

The discipline may be divided, according to the molecules involved, into

Synthetic Organic Chemistry and Synthetic Inorganic Chemistry.

The term Organic Synthesis is often used –may be incorrectly in strict terms– to mean the same

as Synthetic Organic Chemistry

Nicolaou, K. C. *Classics in Total Synthesis*

... the intentional construction of molecules by means of chemical reactions

Cornforth, J. W. 1994

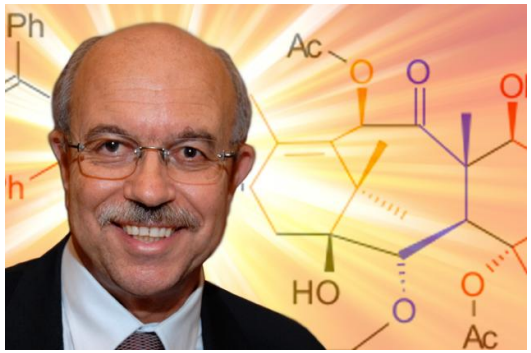
Chemistry creates its subject.

This creative ability, similar to that of art, essentially distinguishes Chemistry among the natural sciences.

Berthelot, J. 1860

Then...

*The ultimate goal of Organic Synthesis is to assemble a given organic compound (**target molecule**)*
from readily available starting materials and reagents in the most efficient way.
*This process usually begins with the **design of a synthetic plan (strategy)***
which calls upon various synthetic reactions to address individual synthetic objectives in a certain sequence.
If a transformation or a strategic maneuver required by the synthetic plan has to be demonstrated before,
*the plan must rely on the development of a suitable **synthetic method** or **tactic***
to solve the particular problem at hand.
Thus, the science of organic synthesis is constantly enriched by new inventions and discoveries
pursued deliberately for their own sake or as subgoals within a program directed
towards the the synthesis of a target molecule.



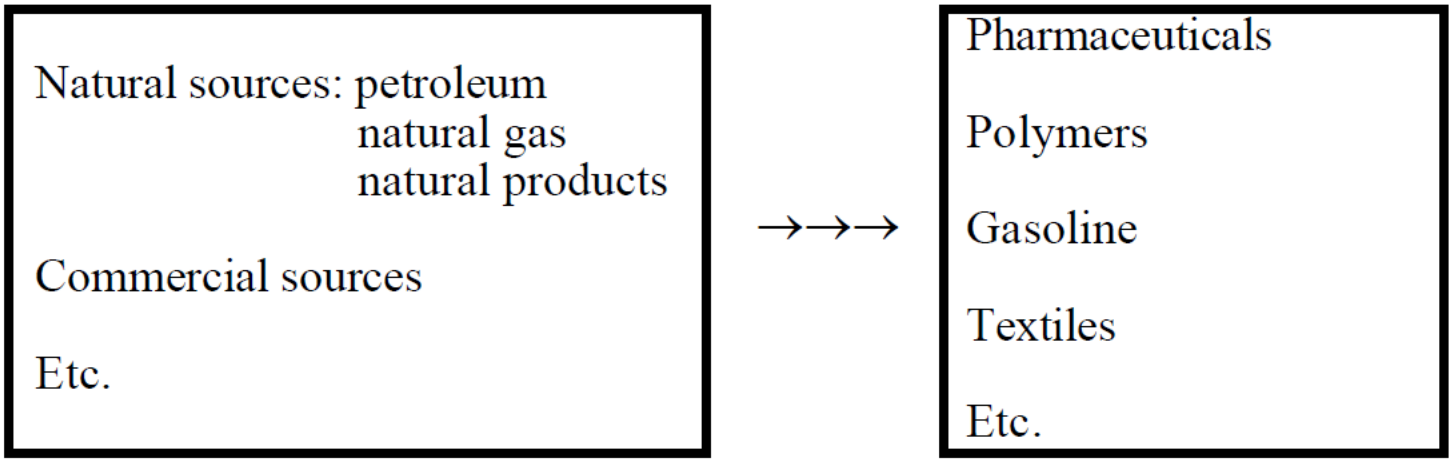
Nicolaou, K. C. *Classics in Total Synthesis*

K. Nicolau, Scripps Res.Inst., San Diego, CA

In summary, Organic synthesis deals with the construction of any organic structure.
Projects only must take into account industrial or lab scale
and time, technical or economical limitations.
In any case, the synthetic process should be simple, high yielding, cheap
and ...preferably in a single step.

Multi-step Organic Synthesis

Conversion of existing molecules into other useful molecules.



- Little molecules ----> big molecules
- Synthesis of unnatural products
- Modification of existing structures
- Synthesis of rare and useful natural products

Natural and Synthetic Organic Compounds

- **Natural**

  All compounds coming from natral sources:

  animal and plant extracts

  secondary metabolites produced by fermentation (biotechnology)

- **Natural-exactly alike**

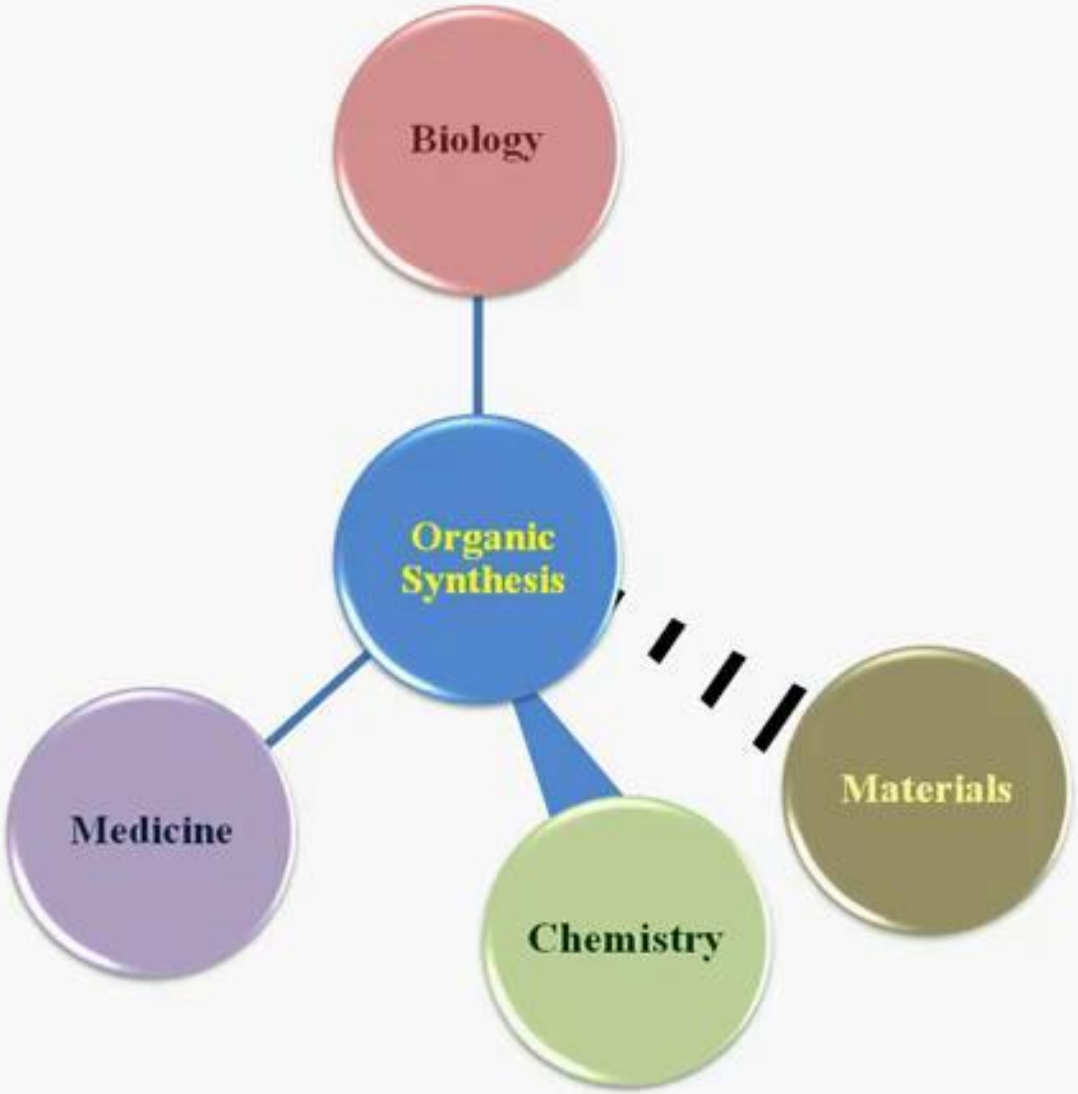
  Compounds equal to natural ones, ut produced by organic synthesis

- **Artificial (unnatural)**

  Synthetic compounds produced by chemical synthesis and not present in Nature

- **Why and When Organic Synthesis?**

Role of Organic Synthesis



THE ESSENCE AND IMPACT OF TOTAL SYNTHESIS

- Rendering Scarce Natural Products Readily Available for Biological Investigations
- Providing Opportunities for Discovery and Invention of New Synthetic Methods and Strategies
- Opening Access to Otherwise Inaccessible Natural Product Analogs for Biological Evaluation
- Structural Elucidation of Natural Products – Assigning Absolute Configurations and Revising Wrongly Assigned Structures
- For Advancing the Art of Total Synthesis for its Own Sake and for the Excitement it Provides

- Synthesis Provides the Foundation for the Pharmaceutical, Biotechnology, Material, and Nanotechnology Industries
- The Condition of the Art of Total Synthesis Reflects the State of Synthesis in General, and Symbolizes its Power at Any Given Time

- Natural products have always played an important role in medicine and they have increasingly become major players in recent drug discovery.

More than 40% of therapeutic agents and 60% of antitumor drugs currently used are based on a natural molecules.

- The extremely scarce availability of biologically active substances represents a great drawback in terms of freely using the natural reservoir for bioassays and therapy.

- To overcome these difficulties chemical synthesis represents still one of the routes by choice .

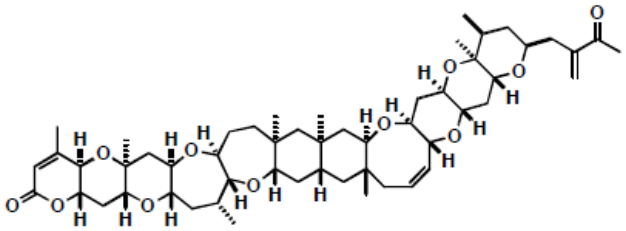
Synthetic organic chemistry

- is able to produce sufficient amounts for a broad biological screening
- and to provide access to synthetic unnatural analogs for structure-activity relationships (SAR) studies
- may be used to clarify natural processes at the molecular level through biomimetic approaches,
- to confirm the structures of natural compounds which are usually established relying only on spectral data,
- to develop new synthetic methods
- To produce compounds relevant for other areas of science and technology

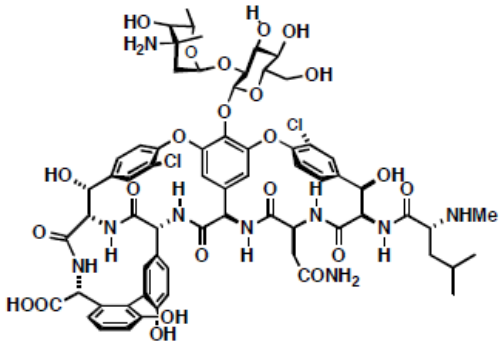
I.Mancini, *Anti-Infective Agents in Medicinal Chemistry,* 2007*, 6,* 17-48

Scopi

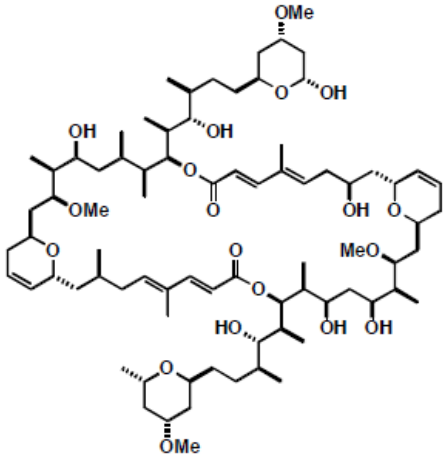
The targets can be Natural Products ...



Brevetoxin B
marine neurotoxin associated with the red tide catastrophes
[Nicolaou 1995]

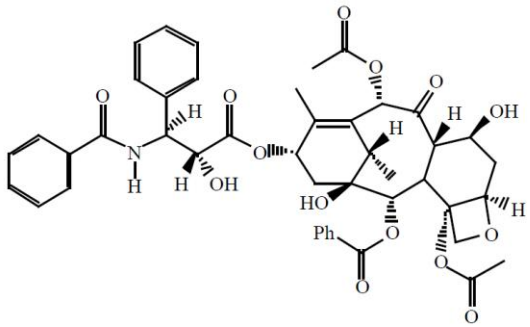


Vancomycin
antibiotic of last resort against anti-drug resistant bacteria
Evans 1995]

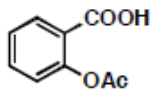


Swinholide A
cytotoxic potent activity against multi-drug-resistant (MDR) carcinoma cell lines
[Paterson 1994]

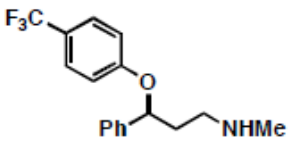
Example: Paclitaxel (taxol): anticancer drug and rare natural product



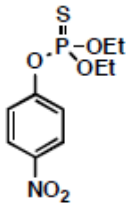
The targets can be compounds with interesting activities ...



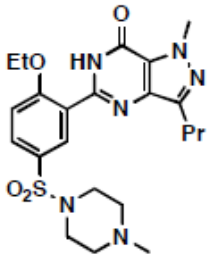
Acetylsalicilic acid (*Aspirin, Bayer*)



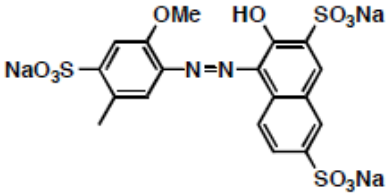
Fluoxetine (*Prozac, Eli Lilly*)
depressions



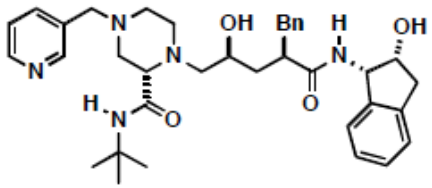
Parathion
insecticide



Sildenafil (*Viagra, Pfizer*)
male erection disfunction



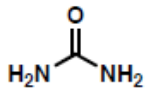
Allura red AC (Allied Chem)
red pigment



Crixivan (*Merck*)
anti AIDS

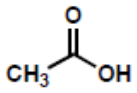
the History of Organic Synthesis

Nineteenth century



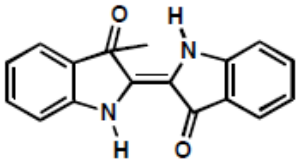
Urea
[Wöhler 1828]

The Organic Chemistry is born ...



Acetic acid
[Kolbe 1845]

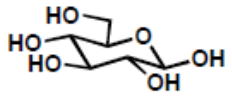
The word synthesis is introduced



Indigo
[Baeyer 1879]

German dye industry

Nobel Prize for Chemistry (1905)

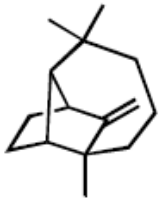


D–Glucose
[Fischer 1890]

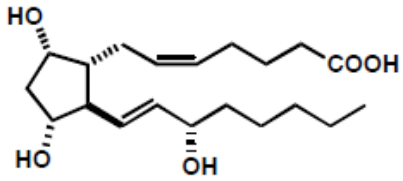
Stereochemical control is possible

Nobel Prize for Chemistry (1902)

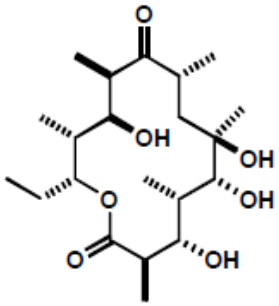
The Corey Era (1960–1990)



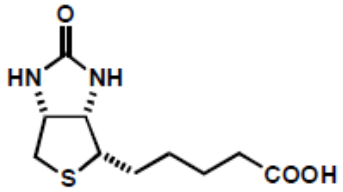
Longifolene
[1961]



Prostaglandin $F_{2\alpha}$
[1969]



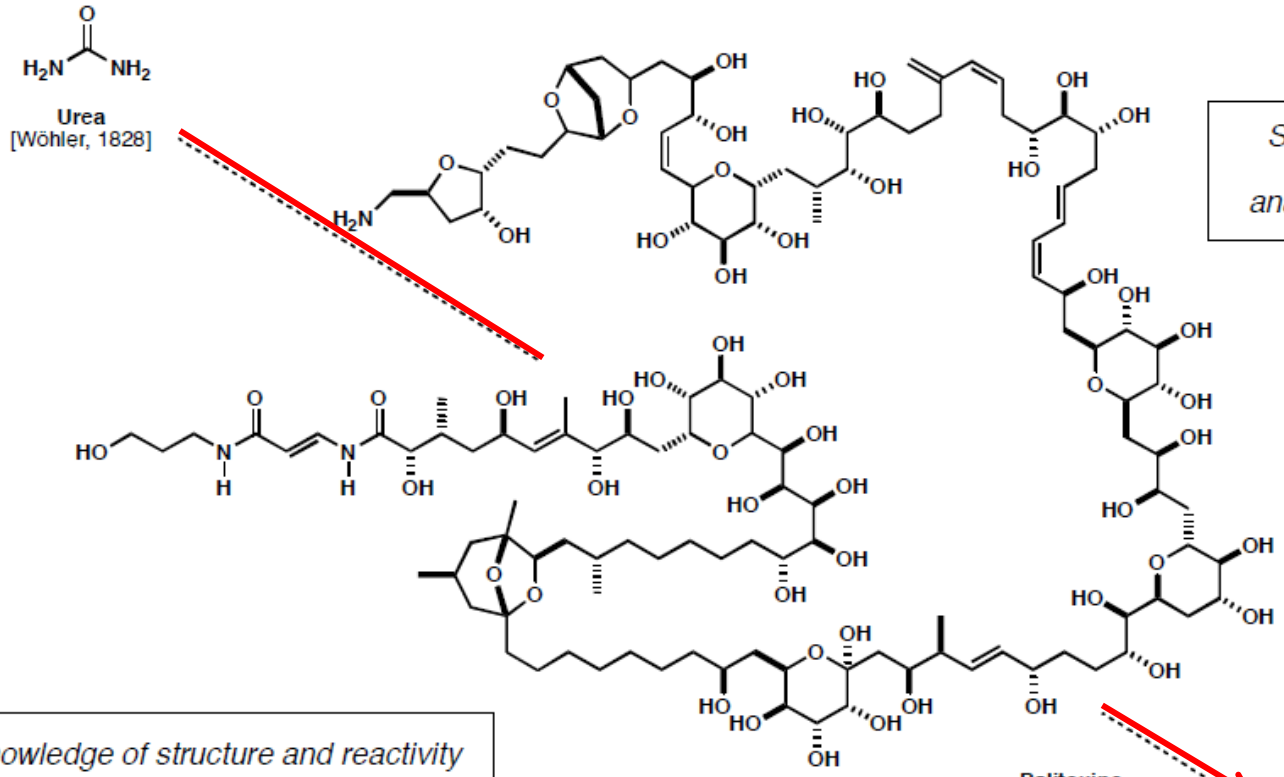
Erythronolide B
[1975]



(+)-Biotin
[1988]

Corey's pursuit of total synthesis was marked by two distinctive elements,

retrosynthetic analysis *and the development of new synthetic methods as an integral part of the endeavor, even though Woodward (conciously or unconsciously) must be engaged in such practices*



Spectroscopic &

analytic techniques

Knowledge of structure and reactivity

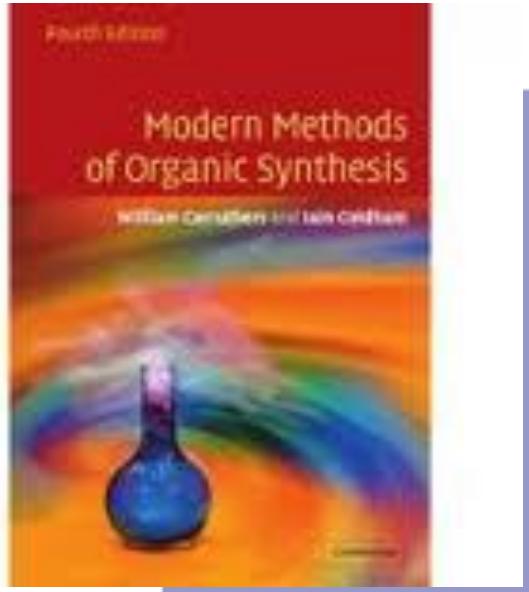
Sophisticated reagents & selective processes

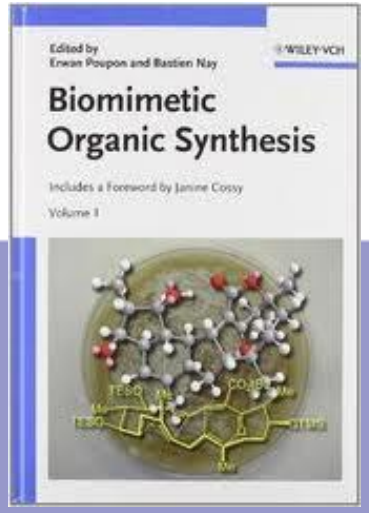
Stereochemical control

XXI Century

Where now?

- Settori della sintesi organica





Synthesis Types

- ***Partial (or semi-synthesis)***

when it is confined to chemical modifications on compounds from natural sources

- ***Total***

It is the complete chemical synthesis of organic molecues, also very complex, starting from simple, commercially available compounds
(which are chemicals deriving from petrochemical , or natural precursors).

Fundamental Synthesis Operations

⇒ *C-C bond formation*

⇒ *functional group interconversions* (FGI):

- oxidation
- reduction
- substitution
- elimination
- addition
- others

⇒ *skeletal rearrangements*

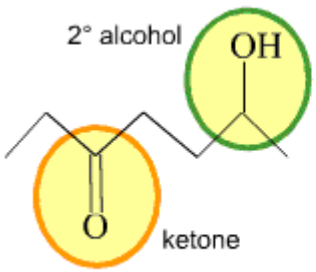
⇒ *protection/deprotection*

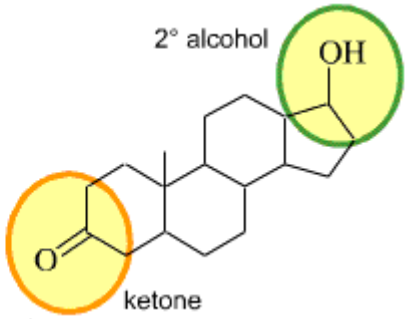
Functional group (FG)

Definition:
part of a molecule that results in characteristic features,responsible of physical chemical properties and giving a peculiar reactivity.

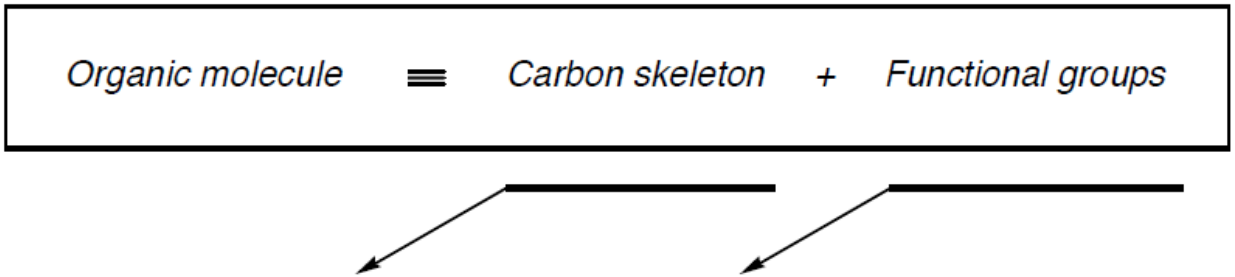
This reactivity marginally depends from the carbon skeleton of the molecule, whereas it is common of the suitable functional group also present in different molecules, on condition that more functional groups are present far each other
(the reactivity of two close FG is affected each other)

FG within a molecule need to be identified when naming.





Functional groups?



The concept of functional group provides a valuable framework for understanding reactivity
and
an useful tool to go deeply into retrosynthetic analysis

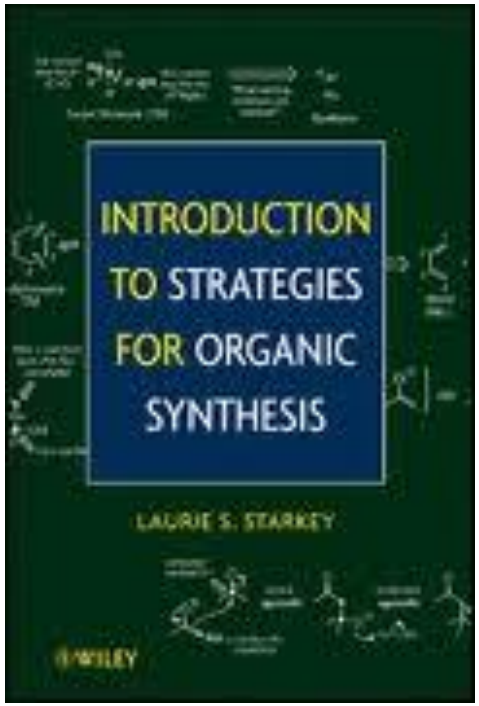
- FG are centers of chemical reactivity

The functional group approach "*works"* because the properties and reaction chemistry of a particular FG can be remarkably independent of environment.

Therefore, it is only necessary to know about the chemistry of a few generic functions in order to predict the chemical behaviour of thousands of real organic chemicals.

- Chemical modifications are mainly related to functional group interconversion (see it below)

Strategy in Organic Synthesis



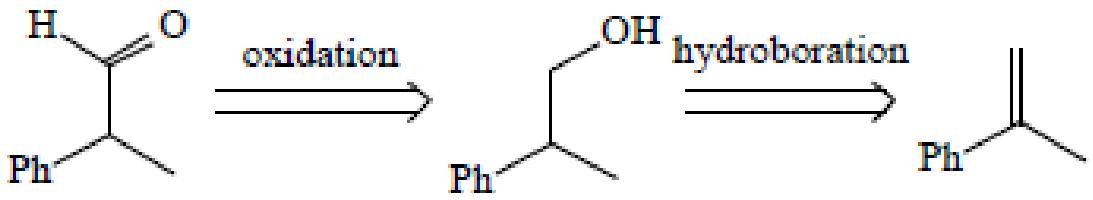
Approccio retrosintetico

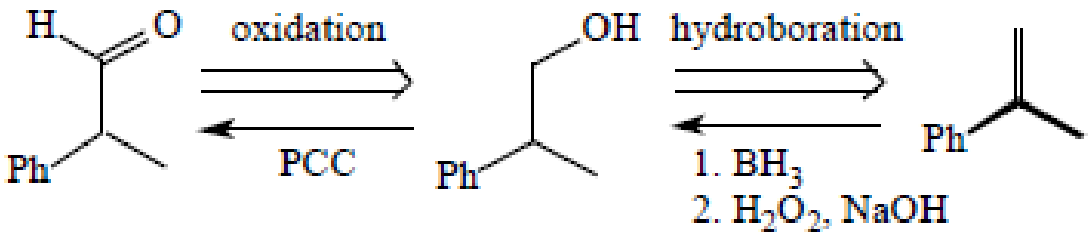
- Think backwards: **retrosynthesis** (E.J. Corey, Harvard, Nobel Prize in Chemistry, 1990)

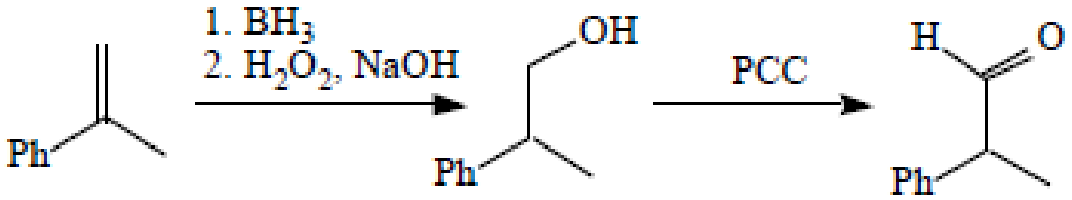
  Retrosynthesis (Corey's definition): "a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis"

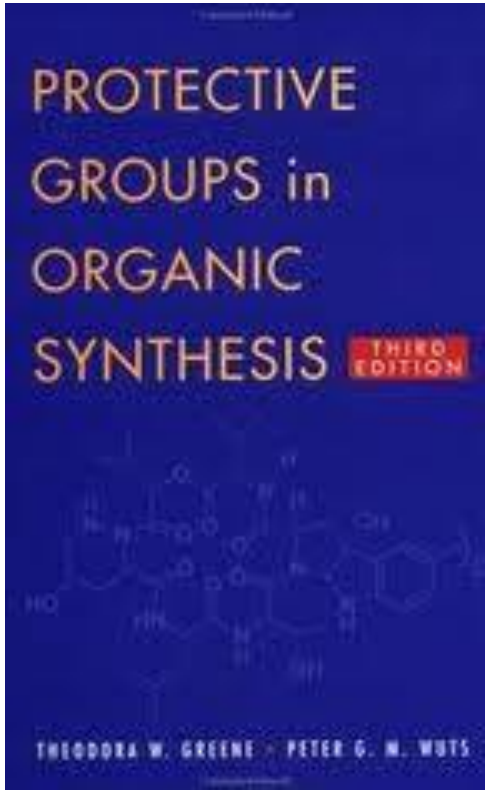
$\Longrightarrow$ means: "thinking backwards"
"the molecule on the left could be made from the molecule on the right by the reaction above the arrow"

Complete Retrosynthesis:





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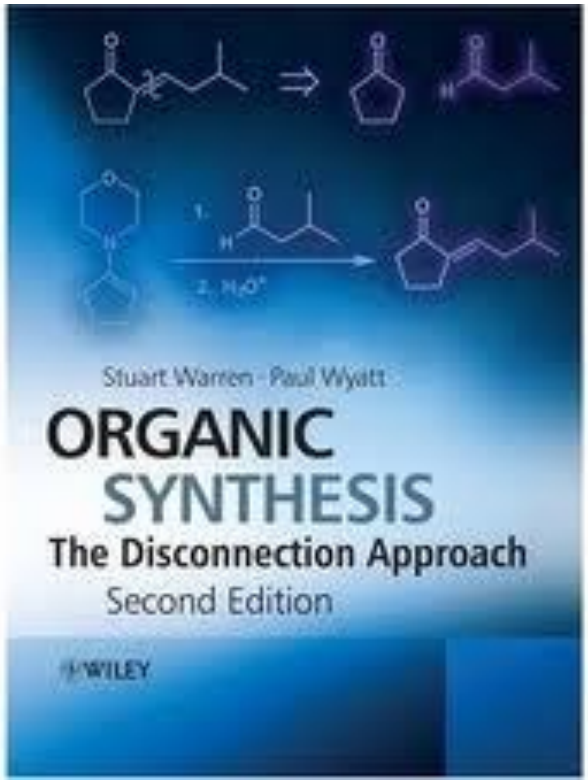
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ORGANIC
SYNTHESIS
The Disconnection Approach
Second Edition
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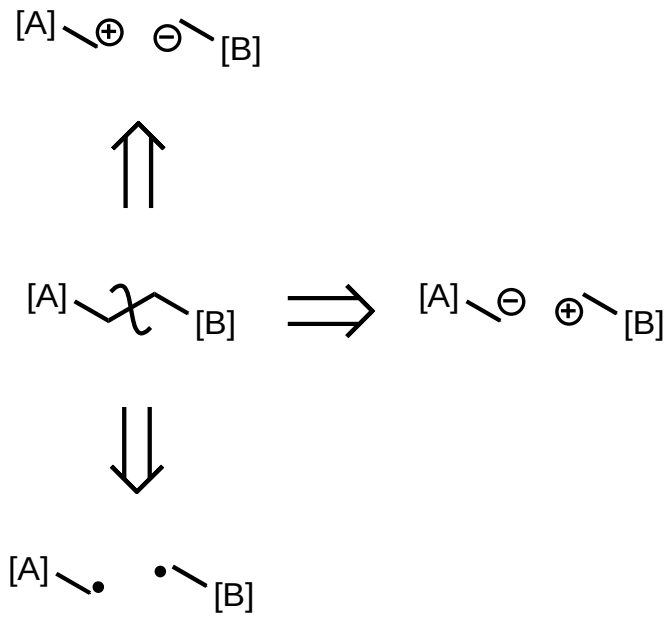
Synthesis design

- E.J. Corey brought a more formal approach to synthesis design, based on retrosynthetic analysis, for which he won the Nobel prize for Chemistry in 1990.
- In this approach, the research is planned backwards from the product, using standard rules.
- The steps are shown using retrosynthetic arrows (drawn as =>), which in effect means "is made from".
- Computer programs have been written for designing a synthesis

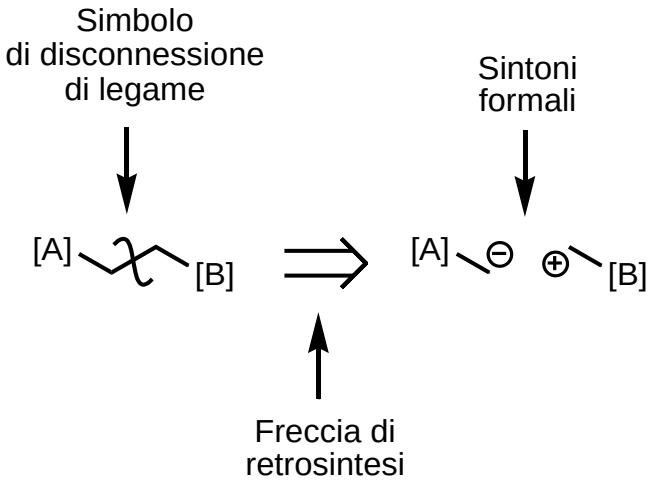
Corey, E. J; Cheng, X-M. (1995). *The Logic of Chemical Synthesis*. New York Wiley

In a synthetic sequence C-C bond must be built
In a retrosynthetic sequence C-C bonds must be <u>disconnected</u>

A generic C-C bond can be disconnected in 3 ways:
2 heterolytic (by formation of ionic species) and 1 homolytic (by formation of radicals).
The most used disconnections are the heterolytic ones



Graphic formalism adopted for a disconnection



Synthons are ideal fragments able to react together to produce a new C-C bond.

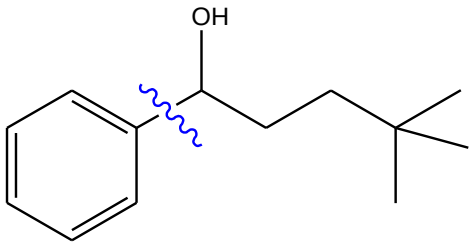
Synthetic equivalents are the real reagents, whose pair corresponds to the synthon pair

DEFINITIONS

TARGET MOLECULE (TM)	**what you need to make**
RETROSYNTHETIC ANALYSIS	**the process of deconstructing the TM by breaking it into simpler molecules until you get to a recognisable SM**
STARTING MATERIAL (SM)	**an available chemical that you can arrive at by retrosynthetic analysis and thus probably convert into the target molecule**
DISCONNECTION	**taking apart a bond in the TM to see if it gives a pair of reagents**
FUNCTIONAL GROUP INTERCONVERSION (FGI)	**changing a group in the TM into a different one to see if it gives an accessible intermediate**
SYNTHON	**conceptual fragments that arise from disconnection**
SYNTHETIC EQUIVALENT	**chemical that reacts as if it was a synthon**

A Simple Example of Retrosynthetic Analysis

Target Molecule



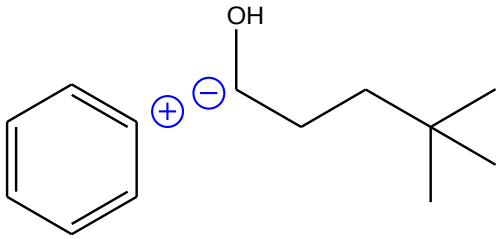
DISCONNECT

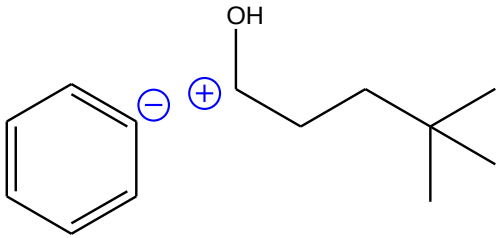
A

B

A and B are two heterolytic disconnections

SYNTHONS



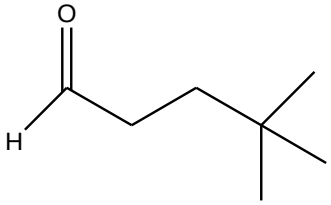


SYNTHONS

REAGENTS

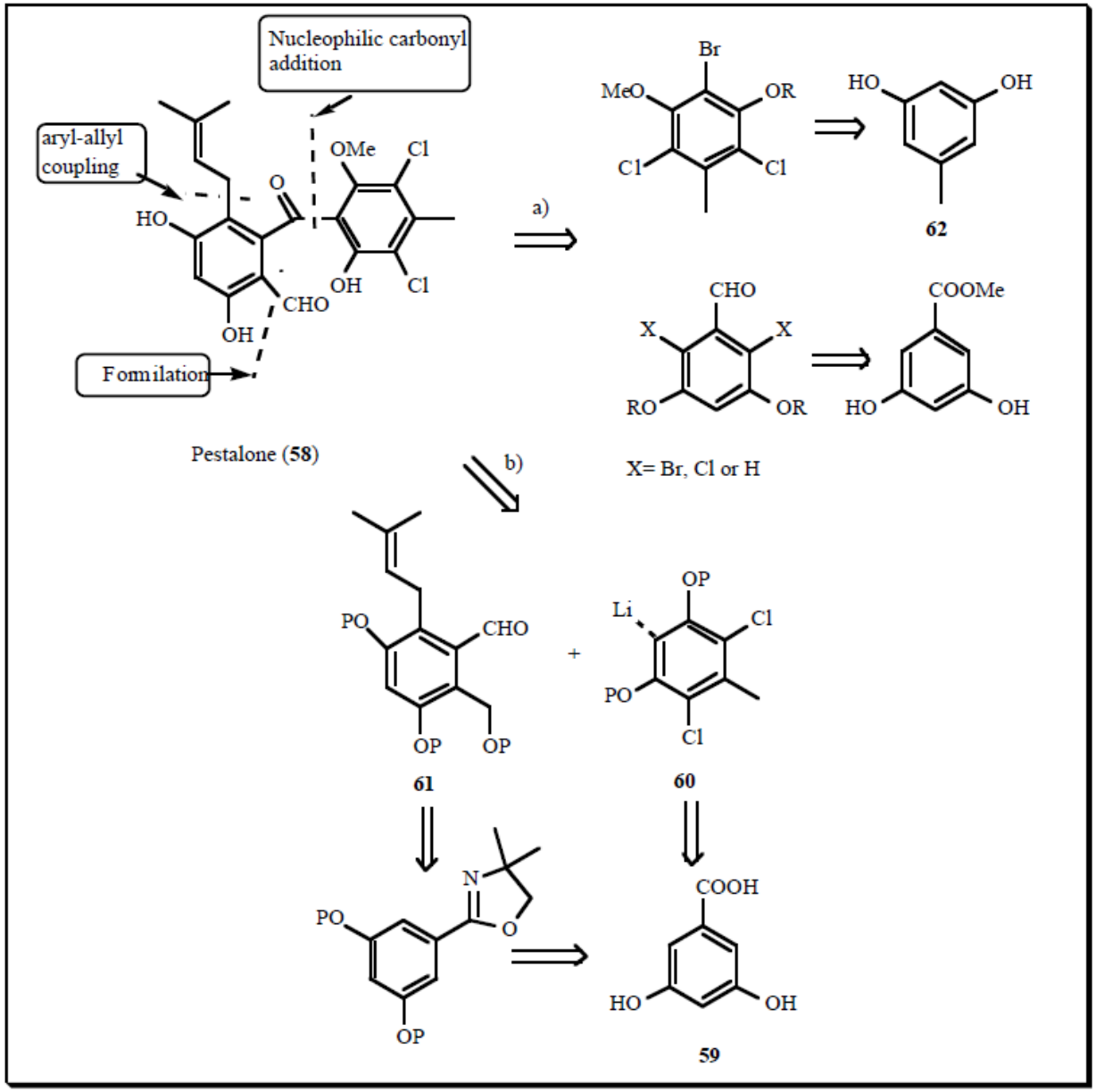
? ?

PhMgBr



REAGENTS

Synthetic equivalents



Scheme 11. Retrosynthetic analysis for pestalone and symplified analogs by Schmalz, 2003 (route a) and for total synthesis by Nishiyama, 2004 (route b).

from I. Mancini, Anti-Infective Agents in Medicinal Chemistry, 2007, 6, 17-48

Classification of Chemical Reactions Involved in a Synthesis

1. **Functional group interconversion (FGI)**

2. **C-C bond building**

3. **Extra-steps (e.g. protective/deprotective reactions)**

2. C-C bond building

•These reactions are able to build the carbon skeleton of a molecule

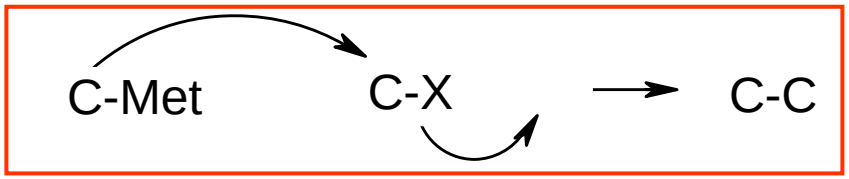
• C-C is an apolar bondand it is usually formed by the reaction between a nucleophile C and an electrophile C

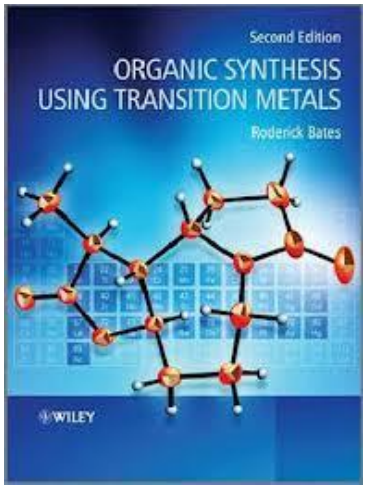
Electrophile; (= affinity for electrons) atom or centre poor of electrons

C with a positive charge (carbocation) or partial charge, because linked to an electronegative atom (e.g. X= halogen)

Nucleophile: (=affinity for nucleus) atom or centre rich of electrons

C with a negative charge (carbaion) or partial negative charge, because linked to an electropositive atom (e.g. metal)

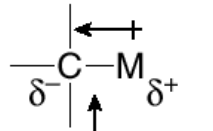




Organometallics

- *Organometallic reagents* contain a carbon atom bonded to a metal.

Organometallic reagents—General structure



polar bond

= R—M

M = metal

Most common metals:
M = Li, Mg, Cu

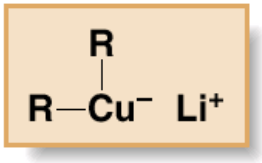
- General structures of the three common organometallic reagents:

R—Li

organolithium reagents

R—Mg—X

organomagnesium reagents or Grignard reagents

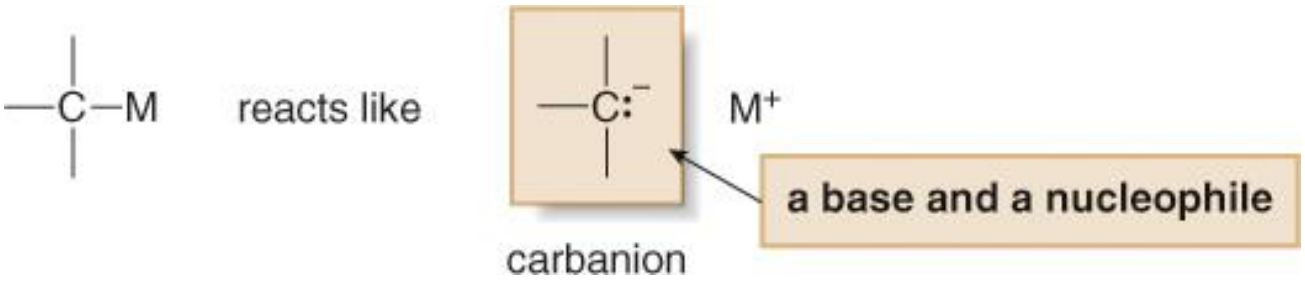


organocopper reagents or organocuprates

- **The more polar the carbon–metal bond, the more reactive the organometallic reagent.**

Experimental conditions: dry solvent, inert atmosphere

- Since both Li and Mg are very electropositive metals, organolithium (RLi) and organomagnesium (RMgX) reagents contain very polar carbon—metal bonds and are therefore very reactive reagents.
- Organomagnesium reagents are called Grignard reagents.
- In organometallic reagents, carbon bears a δ- charge.



The same species can act as a base or as a nucleophile

Definition: A species rich of electrons able to react with an acid proton is a **base,** if reacts with an electrophile C is a **nucleophile**

•Organometallic reagents are strong **nucleophiles** that react with electrophilic carbon atoms to form new carbon—carbon bonds.

•These reactions are very valuable in forming the carbon skeletons of complex organic molecules.

Nucleophile, electrophile and reaction mechanisms

The typycal reactivity can be summarized as:

ADDITION (reagent wth sp^2 C gives a product with sp^3 C)

SUBSTITUTION (the ibridization of C atom is unchanged)

REARRAGEMENT
(or TRANSPOSITION)

Electrophilic addition : alkene

Electrophilic substitution: benzene

Nucleophilic addition : aldehyde and ketone

Nucleophilic substitution: halogenoalkane

3. Extra-steps

They are steps not strictly necessary in the synthesis of the organic target molecule.

Extra-steps include:
•purification and isolation of the synthetic intermediates

•functional groups protections, introduced to improve the selectivity and control of the synthesis

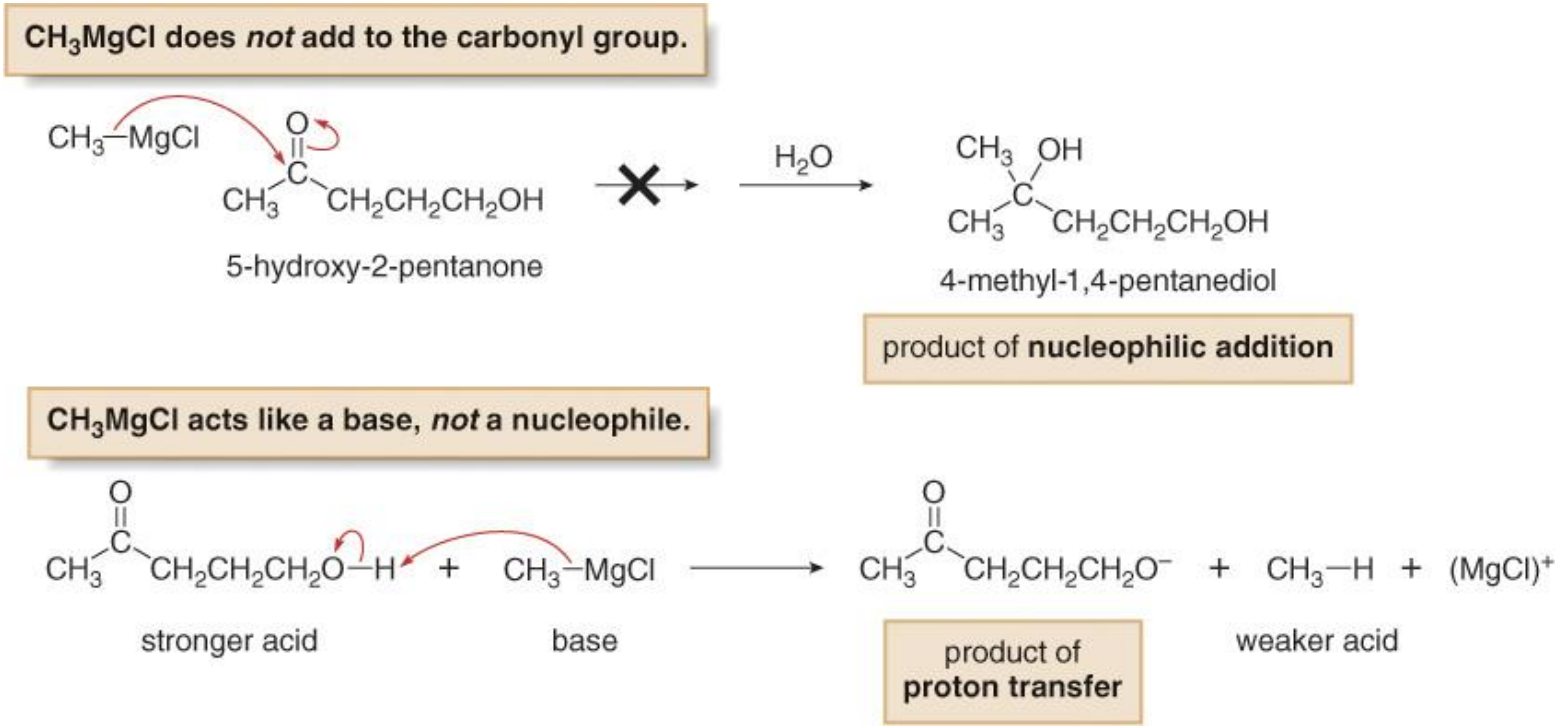
Protecting groups
It is an extra-step useful when a reactive is not chemoselective , that is when it is uncompatible with another FG present in the molecule.

Requirements for a protective group. It must be:
• easily inserted (by simple a reaction and high yield)
• able to protect a FG from a specific class of reactions
• easily removed (by a simple reaction and high yield)

An ideal efficient synthesis must use no protecting groups and it is given only by C-C bond building reactions.
The lowest number of protecting/ deprotecting steps has to be planned .

Examples in Using Protecting Groups

- Addition of organometallic reagents cannot be used with molecules that contain both a carbonyl group (C=O) and N—H or O—H bonds.
- Carbonyl compounds that also contain N—H or O—H bonds undergo an acid-base reaction with organometallic reagents, not nucleophilic addition.



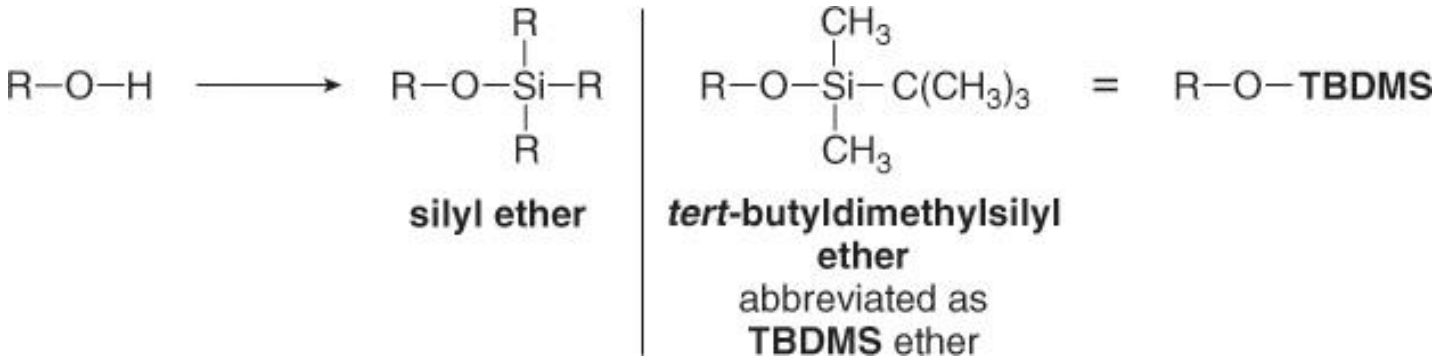
Solving this problem requires a three-step strategy:

[1] Convert the OH group into another functional group that does not interfere with the desired reaction. This new blocking group is called a protecting group, and the reaction that creates it is called “protection.”

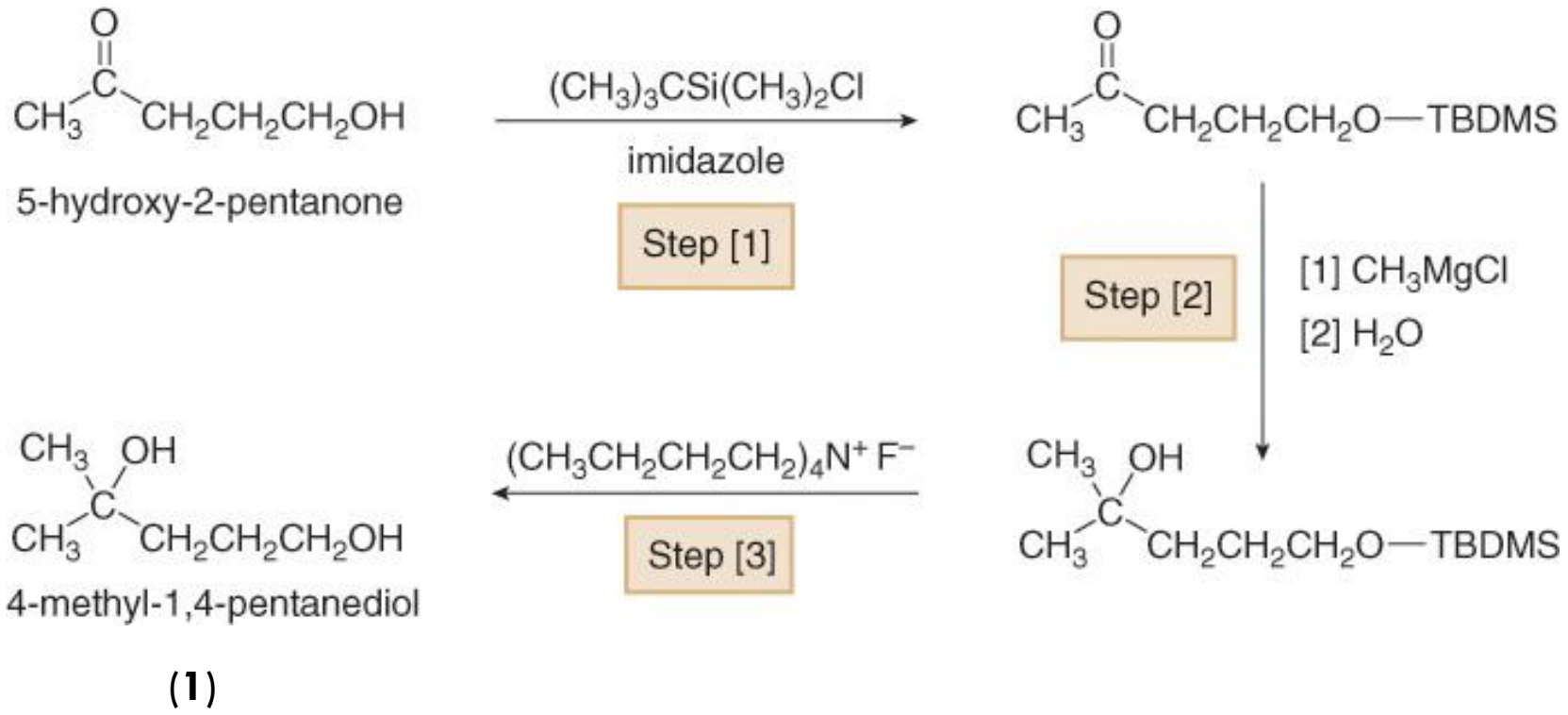
[2] Carry out the desired reaction.

[3] Remove the protecting group. This reaction is called “deprotection.”

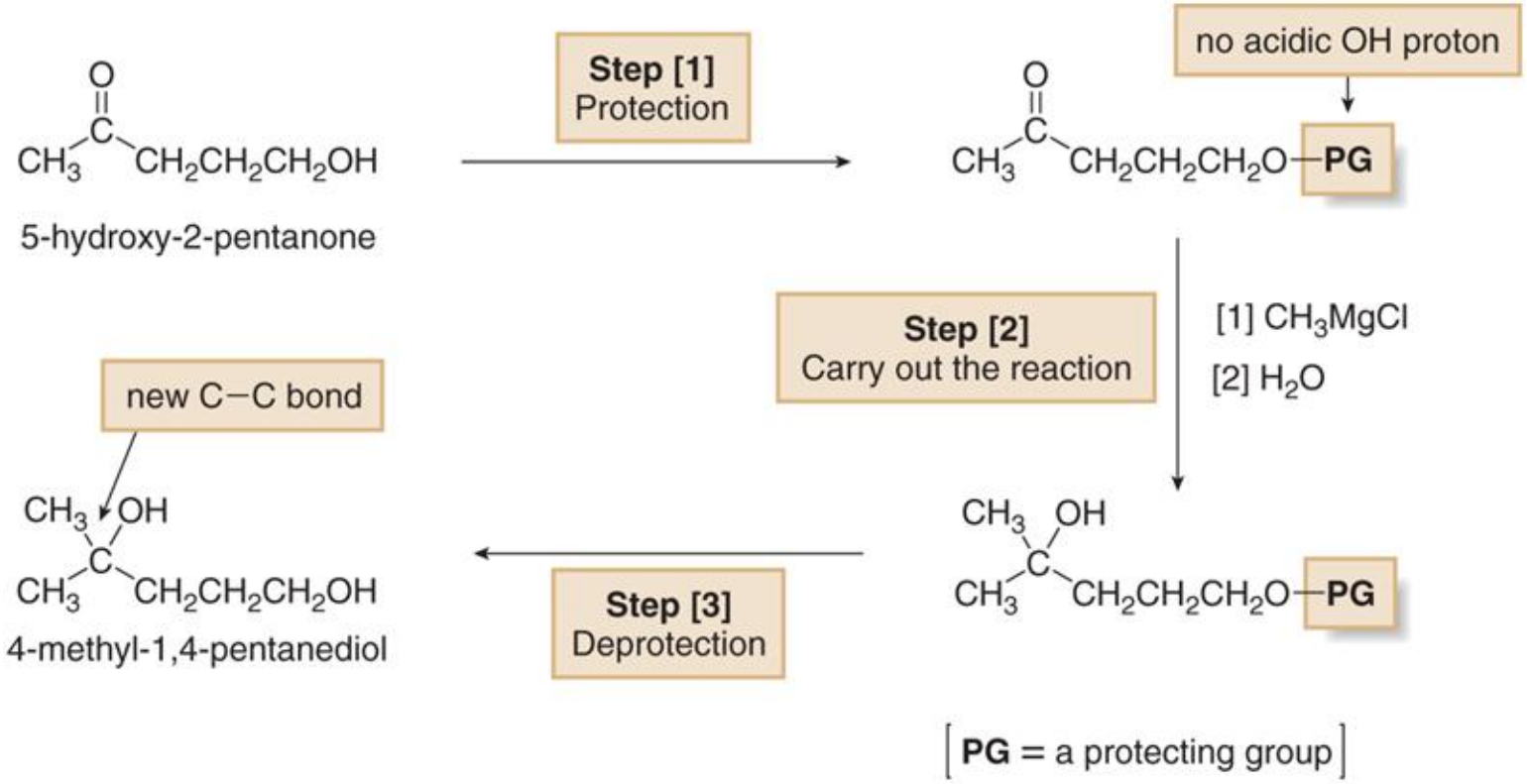
A common OH protecting group is a silyl ether.



The use of *tert*-butyldimethylsilyl (TBDMS) ether as a protecting group makes possible the synthesis of 4-methyl-1,4-pentanediol (**1**) by a three-step sequence.



General strategy for using a protecting group for OH functionality



•Each FG has got its own protective groups

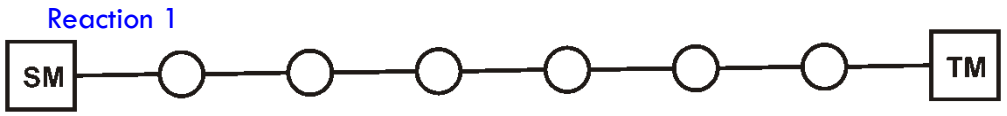
•In order to work as protecting/deprotecting group, a reaction must be reversible

Analysis of a synthetic sequence

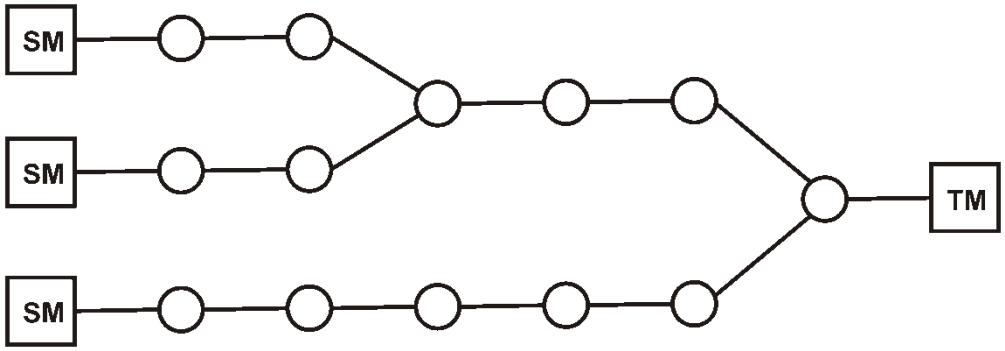
The synthesis of a molecule (**TM**, Target Material) consists of a series of synthetic steps, starting from commercially available compounds (**SMs,** Starting Materials).

A syntehtic sequence is the set of all synthetic steps (reactions). It can be :

- ***linear***



- ***convergent*** (formed by more than one linear sequences)



Yields and conversion

$$y(\%) = \frac{\text{Weight of the product}}{\text{Expected theoric weight}} \times 100$$

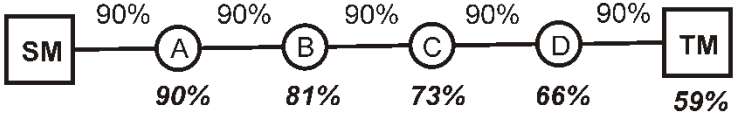
$$conversion\ (\%) = \frac{\text{mols of obtained product}}{\text{mols of used reagent}} \times 100$$

$$yield\ (\%) \leq conversion\ (\%) \leq 100\%$$

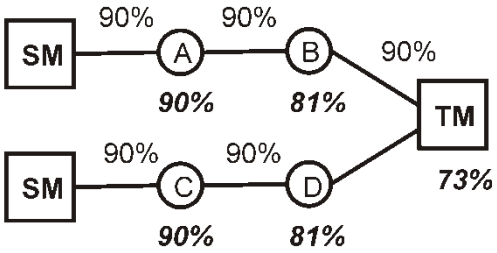
- Global yield of a synthetic sequence

$$Y(\%) = \left(\prod_{i=1}^{n} \frac{y_i}{100} \right) \times 100$$

- Comparison for a 5-step sequence



Linear



convergent

Taxol

It is used in the therapeutic treatment of some tumors (Paclitaxel)

(studied in the inhibition of ovarian tumor in 1989 and approved against breast tumor in 1994)

Until 1995 it was extracted in a low amount from the bark of *Taxus brevifolia .*

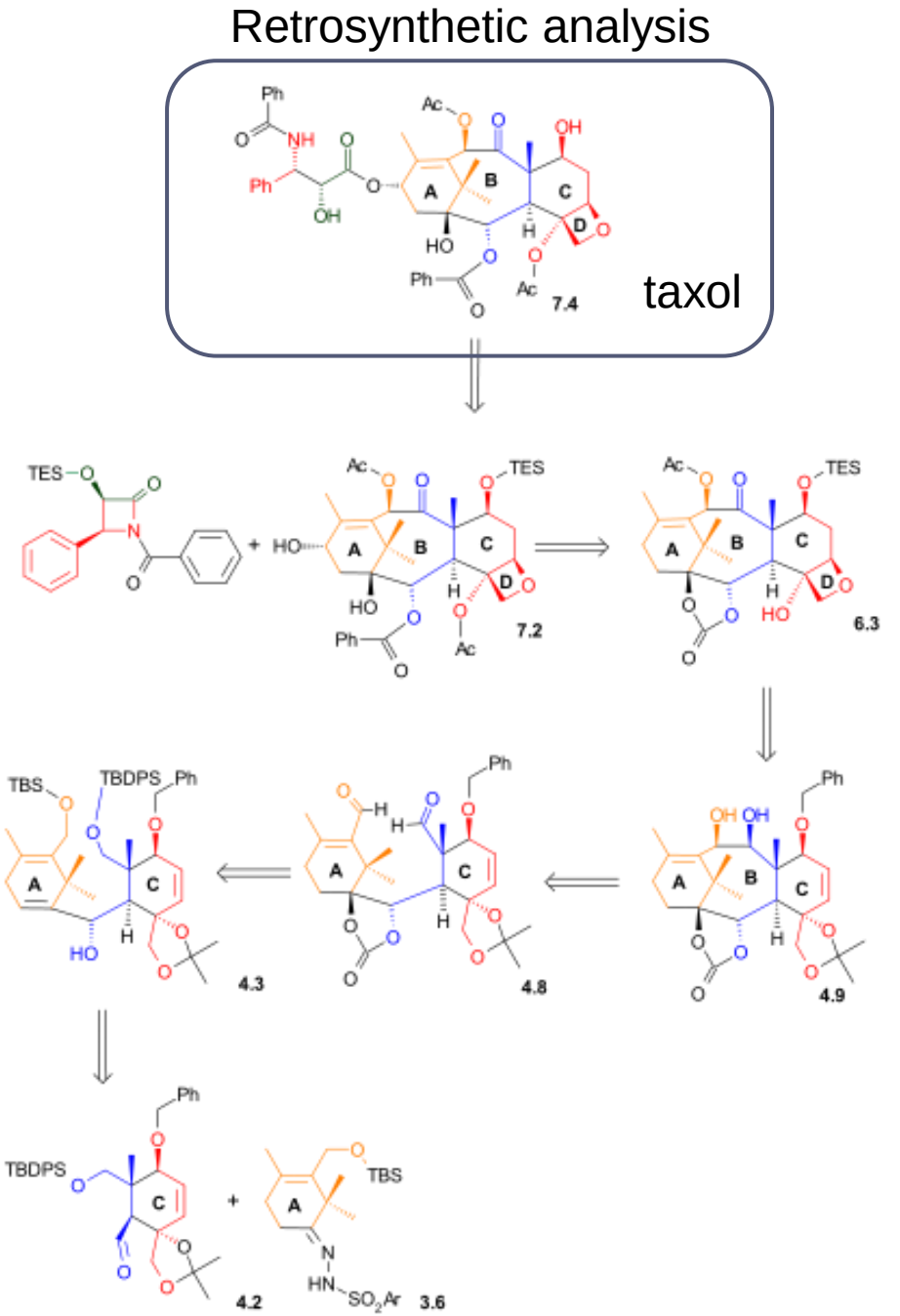
For the treatment of a single patient six 100-year old trees are necessary !

Leaves of the European *Taxus (Taxus baccata)* contain a similar molecule, baccatin III , from where taxol could be obtained by semi-synthesis.

Currently taxol is produced by total synthesis.

The taxol synthesis by Nicolau

It is a good example of **convergent synthesis** because the molecule is assembled from 3 pre-assembled synthons.



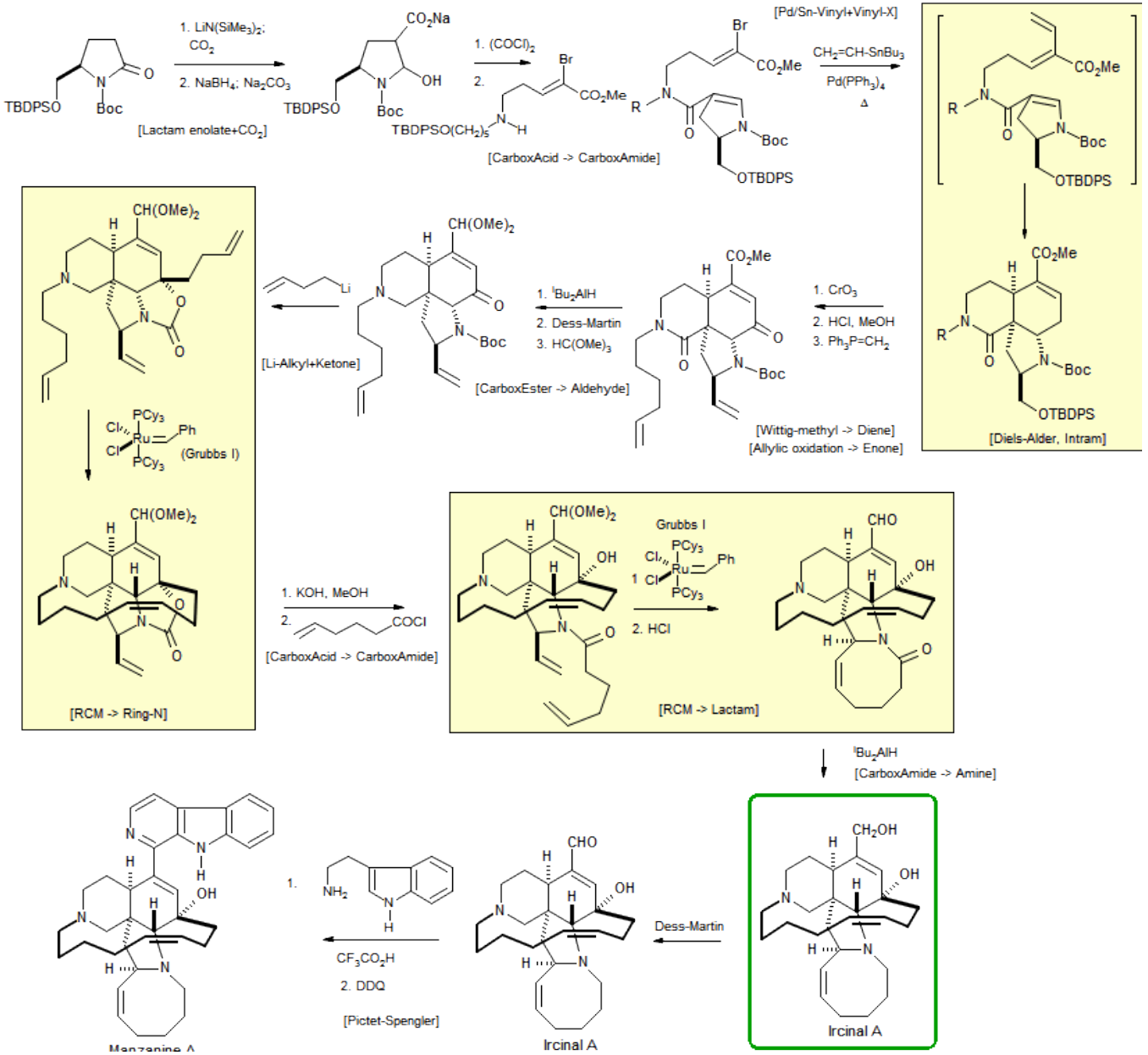
Nicolaou, KC; et al , *Nature* 1994, **367** 630.

Example 2

Manzamine Ircinal A

02-17

Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584-92.



Asymmetric Synthesis

It is an important method by which enantiopure chiral molecules may be obtained

Asymmetric synthesis

It is an organic synthesis which introduces one or more new and desired elements of chirality.

Definitions

SPECIFICITY = HIGHLY SELECTIVITY

CHEMOSELECTIVITY: preferential reaction of a reagent for a specific functional group

e.g. reaction on aldehyde in the presence of an alcohol

REGIOSELECTIVITY A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible direction

e.g. attack on a C of the two C in the epoxide group

STEREOSELECTIVITY The preferential formation in a chemical reaction of one stereoisomer over another.

Enanatioselectivity = When the stereisomers are enantiomers

Approaches

- There are three main approaches to asymmetric synthesis:
- **1. Chiral pool synthesis**
- **2. Asymmetric induction**
- **3. Asymmetric catalysis**

- Chirality must be introduced to the substance first. Then, it must be maintained.

- Example:

A S_N1 substitution reaction converts a molecule that is chiral by merit of non-planarity into a planar molecule, which has no handedness.

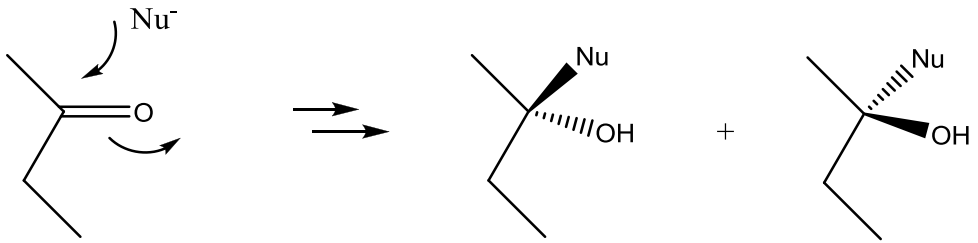
In a S_N2 substituttion reaction on the other hand the chirality inverts.

1. Chiral pool synthesis

- A chiral starting material (SM) is manipulated through successive reactions using achiral reagents which retain its chirality to obtain the desired target molecule.
- SM can be naturally occurring building block (e.g. sugar, amino acids).
- This approach requires a stoichiometric amount of the enantiopure SM, which may be rather expensive, whereas chiral catalysis requires only a catalytic amount of chiral material

2. Asymmetric induction

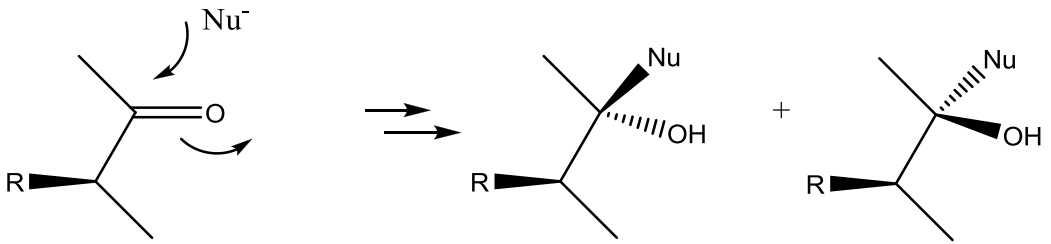
- The aim is to make enantiomers into diasteroisomers , since the latter ones have different reactivity, but enantiomers do not.



achiral

50: 50 enantiomers

Example of asymmetry induced by steric reasons: Nu attacks preferentially from the opposite side of R



R = alkyl chain

enantiomer

minor

major

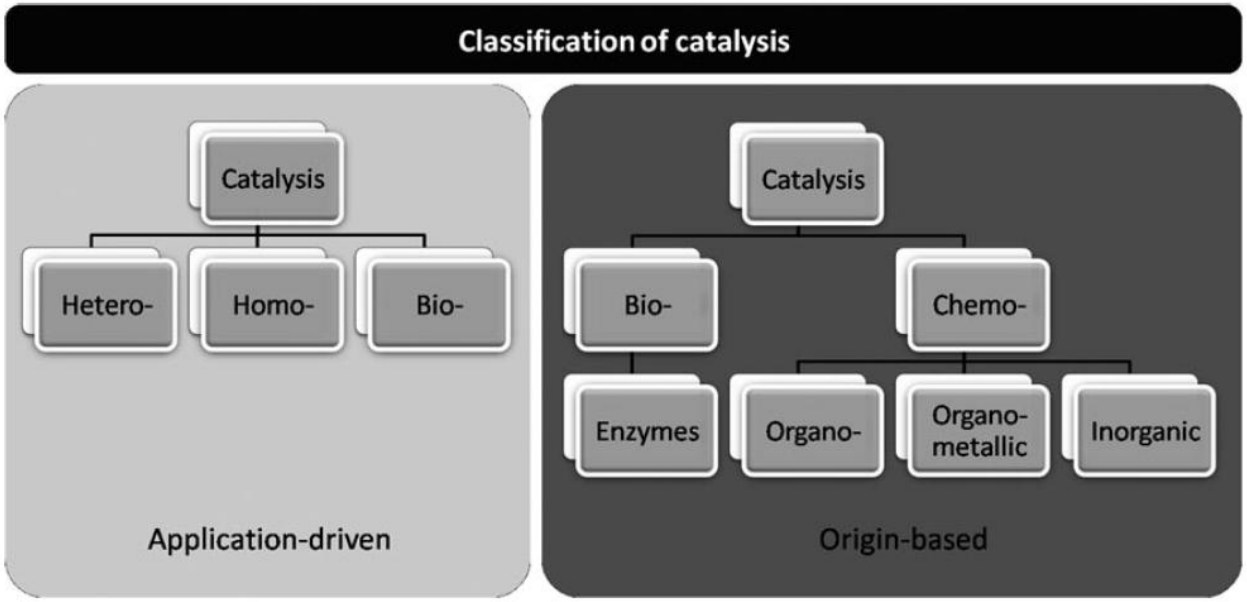
two diasteroisomers

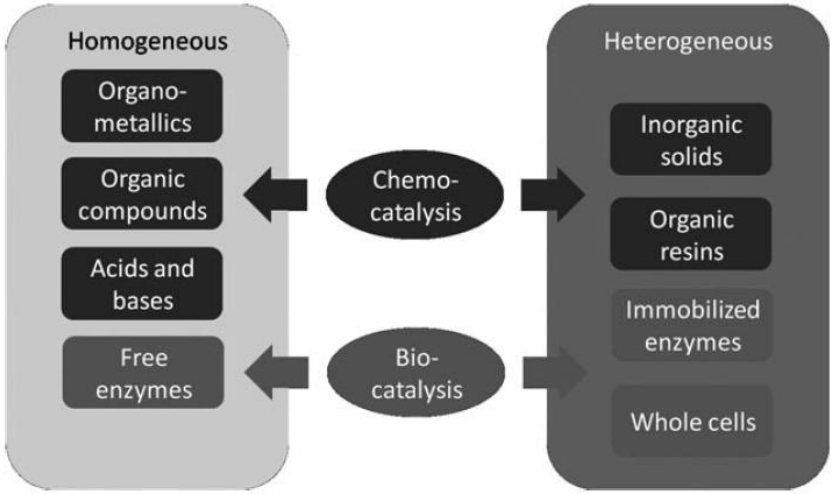
3. Asymmetric catalysis

- Small amounts of chiral, enantiomerically pure catalysts promote reactions and lead to the formation of large amounts of enantiomerically pure

Different kinds of chiral catalysts :

- Metal ligand complexes derived from chiral ligands
- chiral organocatalysts
- biocatalyst
-
- The first methods of asymmetric catalysis were pioneered by R. Noyori.





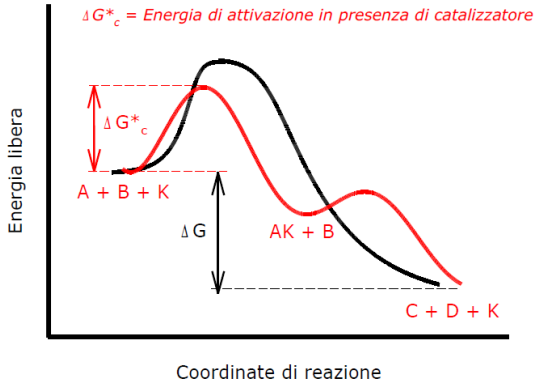


Figure 2. Biocatalysis, like chemocatalysis, can be either homogeneous or heterogeneous.

Biocatalysis

It was employed to do chemical modifications on non-natural organic compounds and the last 30 years have seen a substantial increase in the application of biocatalysis to produce fine chemicals, especially for the pharmaceutical industry.

It makes use of **enzymes** to effect chemical reagents stereoselectively.

Advantages

High selectivity which is necessary to obtain a high yield of a specific product.

Why Biocatalysis?

- Mild conditions: ambient temperature and pressure and physiological pH
- Fewer steps (avoids protection/deprotection steps)
- Largely avoids toxic/hazardous reagents & solvents
- High chemo-,regio- and stereoselectivities

The best synthesis

- Total
- Biomimetic
  - Chiral
  - Efficient

    (high yield and e.e., reduced number of steps)
  - Catalyzed
  - Eco-friendly

Green chemistry

It is a new “technological philosophy”.
The term was coined by P. Anastas in 1991.

The main concepts are:

- ✓ the design of processes to maximize the amount of raw material that ends up in the product
- ✓ the use of safe, environment-benign substances, including solvents
- ✓ the design of energy efficient processes
- ✓ the best form of waste disposal: not to create it in the first place

The 12 Principles of Green Chemistry

- **1. Prevention**
  It is better to prevent waste than to treat or clean up waste after it has been created.
- **2. Atom Economy**
  Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
- **3. Less Hazardous Chemical Syntheses**
  Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- **4. Designing Safer Chemicals**
  Chemical products should be designed to affect their desired function while minimizing their toxicity.
- **5. Safer Solvents and Auxiliaries**
  The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
- **6. Design for Energy Efficiency**
  Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

(*Anastas and Warner, 1998*)

The 12 Principles of Green Chemistry

- **7. Use of Renewable Feedstocks**
  A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
- **8. Reduce Derivatives**
  Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
- **9. Catalysis**
  Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- **10. Design for Degradation**
  Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
- **11. Real-time analysis for Pollution Prevention**
  Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- **12. Inherently Safer Chemistry for Accident Prevention**
  Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

(*Anastas and Warner, 1998*)

In Summary:

1. Waste prevention instead of remediation
2. Atom efficiency
3. Less hazardous/toxic chemicals
4. Safer products by design
5. Innocuous solvents and auxiliaries
6. Energy efficient use by design
7. Renewable raw materials and solvents should be used
8. Shorter synthesis
9. Catalytic rather than thermal process

E-Factor

$$\text{E-Factor} = \frac{\text{Total Waste (Kg)}}{\text{Product (Kg)}}$$

- Depends on one's definition of 'waste'
  - Include:
    - Process use only
    - Or chemicals needed for scrubbing
- Very useful metric for industry
- E-factor can be split into different sub-categories:
  - Organic waste
  - Aqueous waste
- The **smaller** the number, the closer to zero waste being produced
  - (0-∞)

Typical values of E-Factor in pharmaceutical industry are:

- Bulk chemistry : < 0.1 Kg of waste/kg of product
- Fine chemicals: 5.50 Kg of waste / Kg of product
- Pharmaceutical processes: 25-100 Kg of waste/ Kg of product

Low values of E-Factor implies green processes

Biocatalysis and E-Factor

Using biocatalysis is in favour of a green E- factor, because:

- It reduce waste, being a catalyst
- It minimizes the use of protective / deprotective steps, being selective

Atom Economy

$$\% \text{ Atom Economy} = 100 \times \frac{\text{m.w. of Product C}}{\text{m.w. of A} + \text{m.w. of B}}$$

A + B → C + by-products

- Defined: 'a calculation of how much of the reactants remain in the final product' (Constable *et al.*)
- Simple calculation
- Does not account for solvents, reagents, reaction yield, and reactant molar excess
- The **larger** the number, the higher the percent of all reactants appearing in the product
  - (0-100%)

Atom Efficiency

Atom Efficiency = %Yield X Atom Economy

- Importance:
  - Could be used to replace Yield and Atom economy
  - Example: Atom economy could be 100% and yield 5% making this a not very green reaction
- The closer to **100%**, the greener the process
  - (0-100%)

More on Atom Efficiency (AE)

This idea is due to Barry Trost , Stanford University winner of the Presidential Green Chemistry Challange Award in 1998.

How many atoms present in the reagent molecules are incorporated in the final product (and not in by-products) and how many are instead lost?

EXAMPLE of calculation of **AE**

In the reaction of 1-bromobutane from 1-butanol:

$CH_3CH_2CH_2CH_2OH + NaBr + H_2SO_4 = CH_3CH_2CH_2CH_2Br + NaHSO_4 + H_2O$

By the sum of the atoms present in the product:

$4C + 9H + 1Br = 137$ uma

The sum of all the atoms in the reagents:

$4C + 12H + 5O + 1Br + 1Na + 1S = 275$ uma.

% EA = 137 : 275 x 100 = 50%

The value indicates that for this reaction only 50% of the reagent atoms are found in the product.

Biocatalysis and Green Chemistry

Box 2. Green credentials of biocatalysis

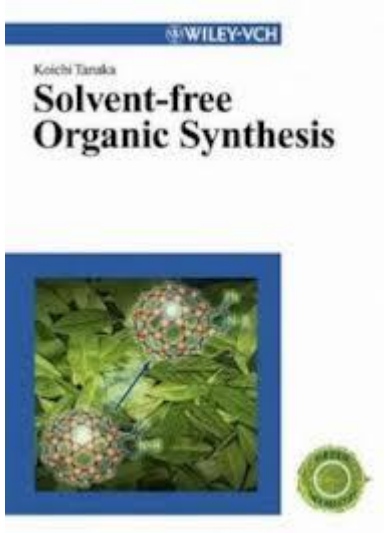
Biocatalysis:

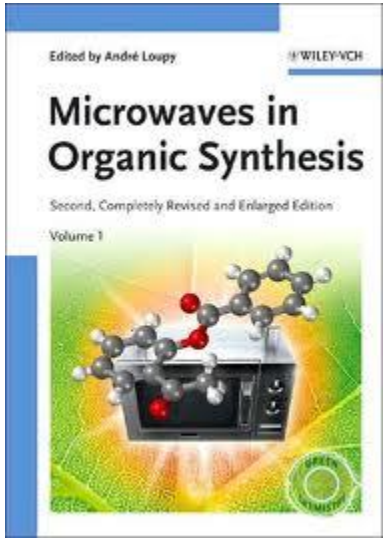
- operates in water (thus replacing organic solvents)
- has highly selective catalysis, including regio- and stereo-selectivity (thus reducing E-factors)
- operates in mild conditions, avoiding the need for protection (thus reducing E-factors)
- overcomes the use of some hazardous materials (resulting in improved LCA)
- uses renewable resources (resulting in improved LCA)
- can be modified, that is, the biocatalyst properties can be altered to suit the process (thus improving the ease of processing)
- is rarely endo- or exo-thermic (thus reducing energy requirements)
- provides a high yield as a result of selectivity and mild conditions (thus improving the efficiency of processing)
- is catalytic rather than stoichiometric (thus improving the ease of processing)

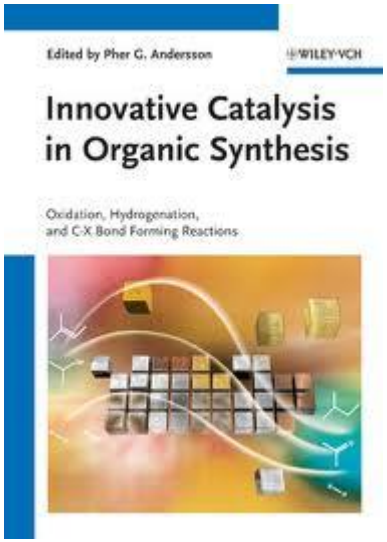
J.M. Woodley, Cell Press, 2008

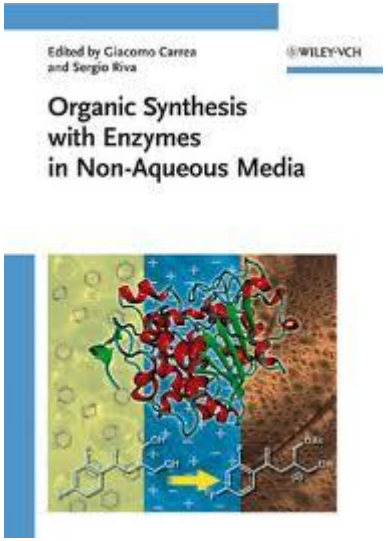
Environmental **E-factor** calculation is defined by the ratio of the mass of waste per unit of product: E-factor = total waste (kg) / product (kg)

Metodi speciali in sintesi organica









Solvents in Organic Synthesis

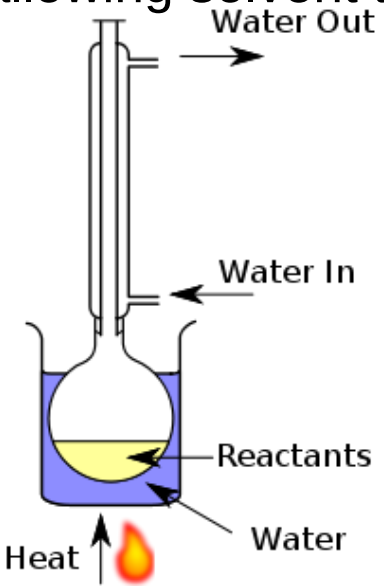
- ✓ Classification
- ✓ The role of solvents
- ✓ Water
- ✓ Ionic liquids
- ✓ SC-CO_2
- ✓ Solvent-free conditions

Classification of solvents

- **NON-POLAR** (hexane, toluene, chloroform , diethyl ether)
- **POLAR**
  - **APROTIC** (THF, ethul acetate, acetone, acetonitrile DMSO, DMF)
  - **PROTIC** (ethanol, methanol, water, acetic acid)

The role of solvents: as a reaction medium

- Used to bring reactants together at suitable concentrations, usually in batch processes
- Energy control
  - Endothermic reactions require energy – heat can be supplied by heating solution (Figure)
  - Exothermic reactions – solvent acts as a heat sink preventing runaway reactions. Heat can be removed by allowing solvent to boil.
- Efficient mixing and stirring
- Addition of solid reagents as a solution



Solvent replacement in synthetic chemistry

- Can be very difficult to replace solvents.

- As reaction media:
  - Solvents have a substantial effect on a reaction, allowing a degree of control not possible in its absence
  - Can affect:
    - Rates of reaction
    - Chemo-, regio- and stereoselectivity

    e.g. different mechanism S_N1/S_N2 by changing solvent

    (S_N1 in polar solvent stabilizing carbocation intermediate species)

    - Outcome of reaction – may not work at all, or may do something totally different!

- If can be exploited then may give extra incentive for adoption of new technology.

Strategies of solvent replacement

- Avoid or minimise solvents in first place
- Use less toxic solvents
- Use renewable solvents (not derived from petrochemicals)
- Avoid VOC's – solvents with low vapour pressure / high boiling points may be preferable as long as this does not lead to other complications.

VOC = Volatile Organic Compounds

Some current approaches to solvent replacement in synthetic chemistry

- Water
- Ionic liquids
- Carbon dioxide
- No solvent

All have advantages and disadvantages which need to be considered when assessing suitability for replacement

What are Green Solvents?

- Low toxicity
- Easy recyclability (no disposal)
- Further desirable characteristics:
  - -Easy removal from the product
  - -Low reactivity

Some current approaches to solvent replacement in synthetic chemistry

- **Water**
- Ionic liquids
- Carbon dioxide
- No solvent

Water as a reaction medium

Economically & Environmentally attractive

- Inexpensive and abundantly available
- Non-inflammable and non-toxic
- Odourless and colourless

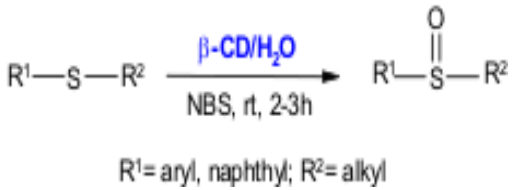
Highly polar reaction medium

- Novel reactivity of organometallic complexes
- Facile product separation/catalyst recycling
- Reduced product contamination

Water as Solvent in Organic Reactions

- **Oxidation in water**

Example 1



CD = cyclodextrin
NBS = N-Bromo succinimide

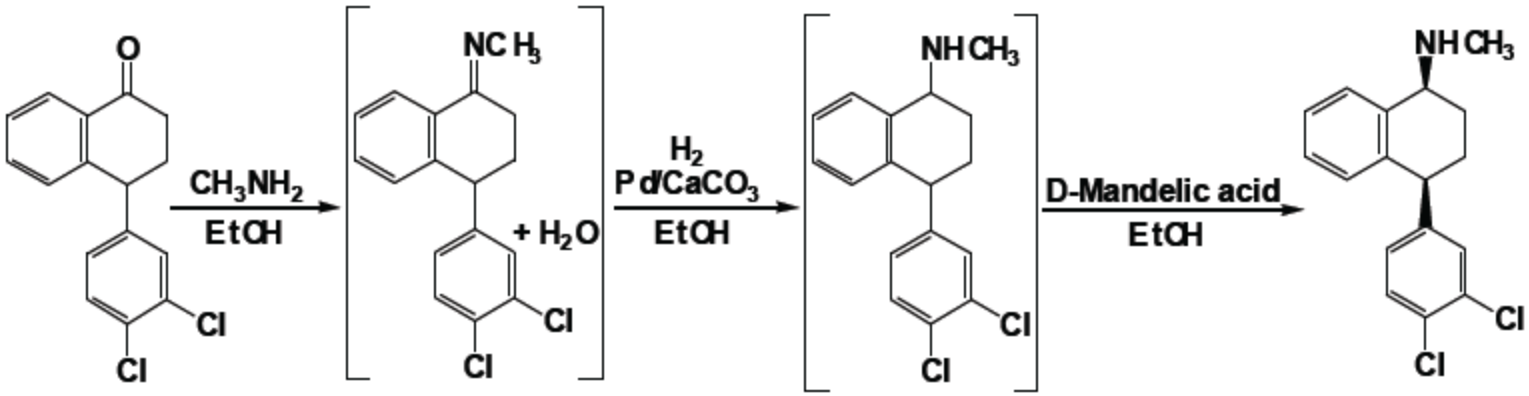
Example 2

Using a chemoenzymic oxidation methodology, water-soluble (81-93% yield) and lipophilic alkenes (60-99% yield) were successfully epoxidised.

Commercial Glucose Oxidase (GOx) is used to produce *in situ* hydrogen peroxide via the enzymic oxidation of glucose. The addition of catalytic amounts of sodium bicarbonate/manganese sulphate increases the rate and the yield of the process. In the case of lipophilic alkenes, sodium dodecyl sulphate (SDS) was used as a surfactant.

a) water-soluble alkenes: Glucose (0.2 M), GOx (175 units/mL), O_2, $NaHCO_3$ (0.5 M), $MnSO_4$ (0.1 mol%), pH 7.0 phosphate sol.; **b)** water-insoluble soluble alkenes: same conditions plus SDS (5 mM).

New Sertraline process (Pfizer's Antidepressant) is Greener



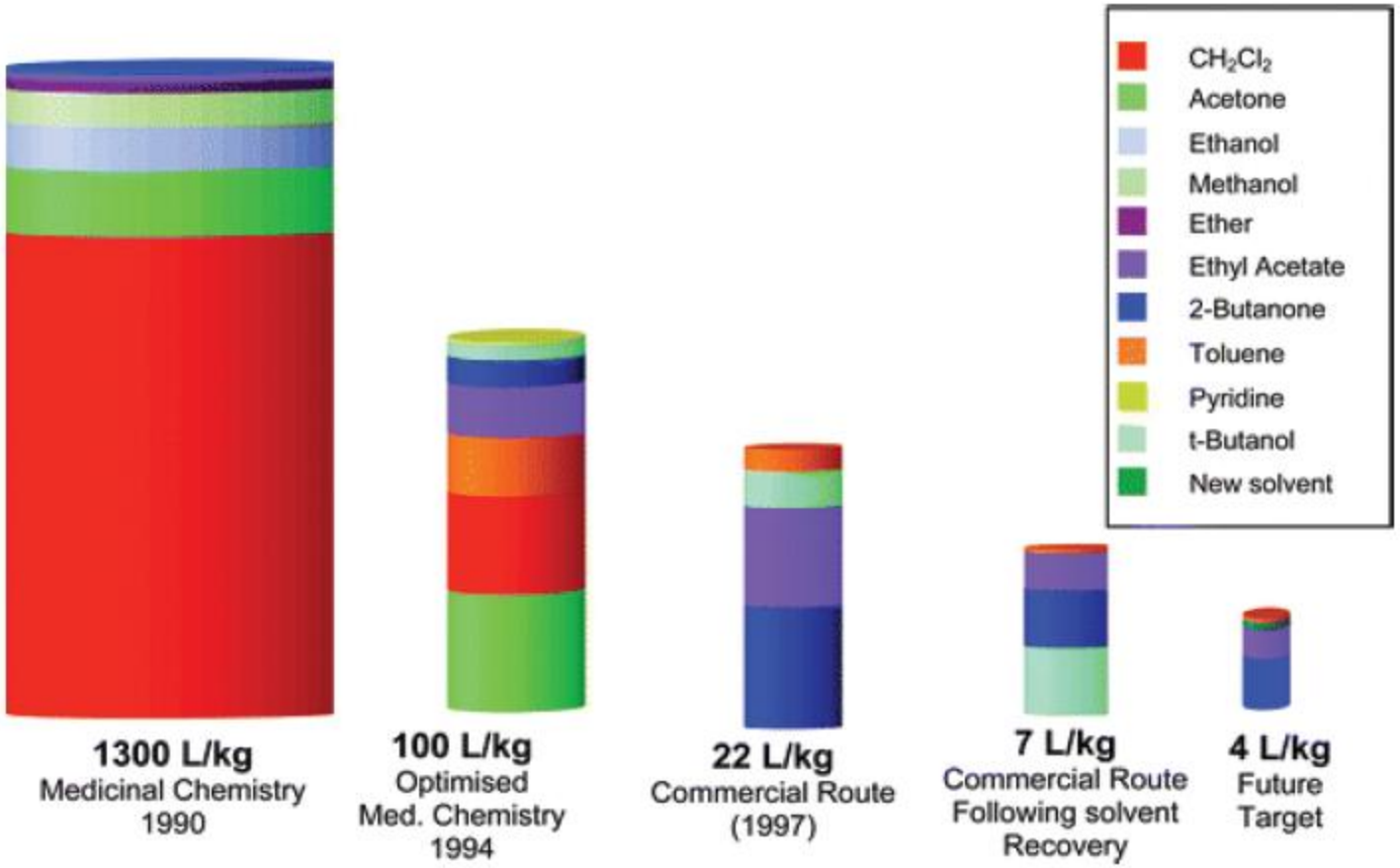
Sertraline •HCl

Three step process
Introduction of EtOH as solvent
Replacement of Pd/C with Pd/$CaCO_3$ - higher yields

Elimination of titanium chloride, toluene, THF, CH_2Cl_2, and hexane

Reduction of solvents from 60,000 to 6,000 gal/ton

Elimination of 440 tons of titanium dioxide, 150 tons of 35% HCl, and 100 tons of 50% NaOH



P.J.Dunn,S.Galvin and K.Hettenbach,Green Chem. 6,43(2004)

Some current approaches to solvent replacement in synthetic chemistry

- Water
- Ionic liquids
- Carbon dioxide
- No solvent

Ionic liquids' properties

The properties of ILs, such as melting point, viscosity, and solubility of reagents and other solvents, are determined by the substituents on the organic component and by the counter-ion. Many ionic liquids have even been developed for specific synthetic problems. For this reason, ionic liquids have been termed "designer solvents".

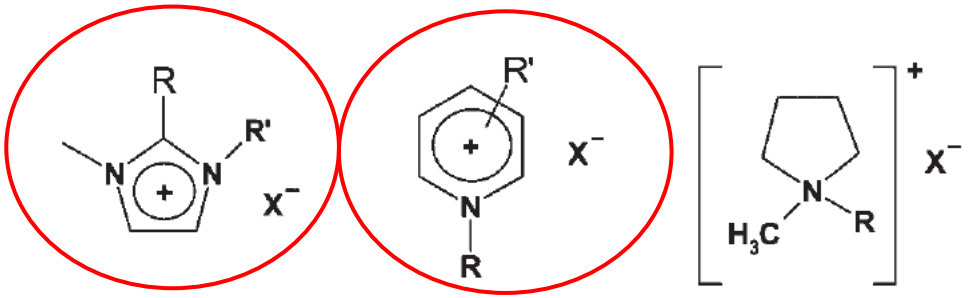
The properties of ILs for their applications in synthesis are

- *Nonvolatility*: ILs present negligible vapor pressure. This property makes them ideal candidates to replace volatile organic solvents as a "green" alternative.
- *High thermal and chemical stability*: It is widely claimed that many ILs (excluding "Lewis acid" ILs) are both air and moisture sensitive, and in many cases, pyrolysis occurs at temperatures higher than 300 °C.
- *Broad solubility range*: ILs can dissolve a wide variety of organic, inorganic, and organometallic compounds, sometimes several orders of magnitude higher than traditional organic solvents can. In addition, ILs present low nucleophilicity providing a week coordinating or non-coordinating environment.
- *Low combustibility*: In general, ILs are non-flammable compounds, and consequently, safe for handling.
- *Catalytic properties*: ILs can act as both solvents and/or catalysts in organic and inorganic reactions [16,17] as well as biocatalytic transformations [18].
- Large electrochemical window and relatively high electrical conductivity.

Structures of Ionic Liquids

Some typical cations:

$[NR_xH_{4-x}]+$ $[SR_xH_{3-x}]+$ $[PR_xH_{4-x}]+$



Some typical anions:

1) $AlCl_4^-$, $AlCl_7^-$

2) PF_6^-, BF_4^-, SbF_6^-

3) $[(CF_3SO_2)_2N]^-$, $CF_3SO_2\text{-}N^-\text{-}COCF_3$

4) $ROSO_3^-$, RSO_3^-

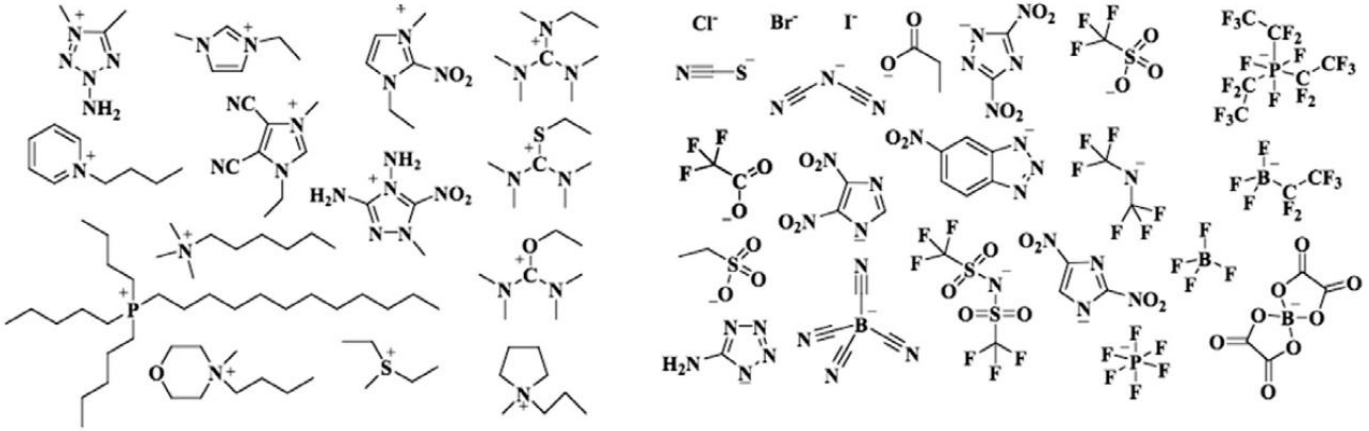


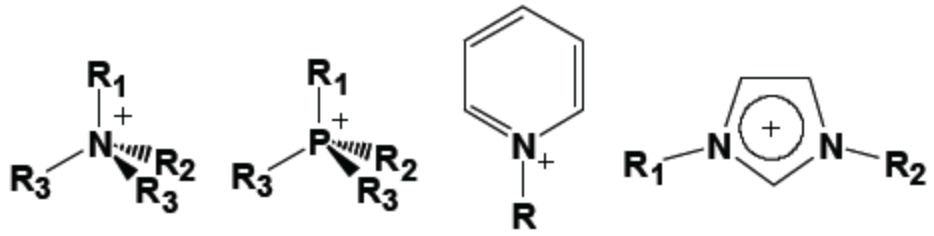
Figure 1. Examples of cations (left) and anions (right) that can be paired to make an ionic liquid.

Table 1 Applications of ILs in different research fields

Research fie	Applications
Energy	Batteries
	Fuel cell
	Heat storage
	Supercaps
Chemistry |	Organic synthesis, including chiral
	Surfactants
	Polymerization
	Catalyst
	Analytical chemistry
New materials |	Liquid crystal
	Nanoparticles
	Advanced fluid
	Artificial muscles
Biotechnology |	Biocatalysis
	Purification of proteins
Chemical engineering | |	Extraction processes
	Separation processes
	Selective membranes
	Extractive distillation

CATALYSIS IN IONIC LIQUIDS

CATIONS



ANIONS

BF_4^-, PF_6^-, SbF_6^-, NO_3^-

$CF_3SO_3^-$, $(CF_3SO_3)_2N^-$,

$ArSO_3^-$, $CF_3CO_2^-$, $CH_3CO_2^-$,

$Al_2Cl_7^-$

- Liquid at room temperature/no vapor pressure
- Liquid range of 300 °C (c.f. H_2O, 100 °C)
- Designer solvents, e.g. bmim BF_4 hydrophilic, bmim PF_6 hydrophobic

Examples of application

Biotechnology and Bioprocess Engineering 2010, 15: 40-53
DOI/10.1007/s12257-009-3079-z

BBE

Toward Advanced Ionic Liquids. Polar, Enzyme-friendly Solvents for Biocatalysis

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Available online at www.sciencedirect.com

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Enzyme and Microbial Technology 37 (2005) 19–28

ENZYME AND MICROBIAL TECHNOLOGY

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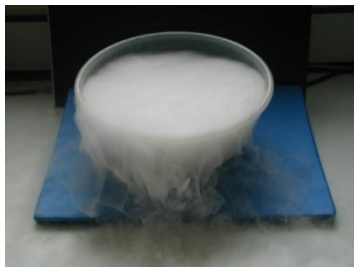
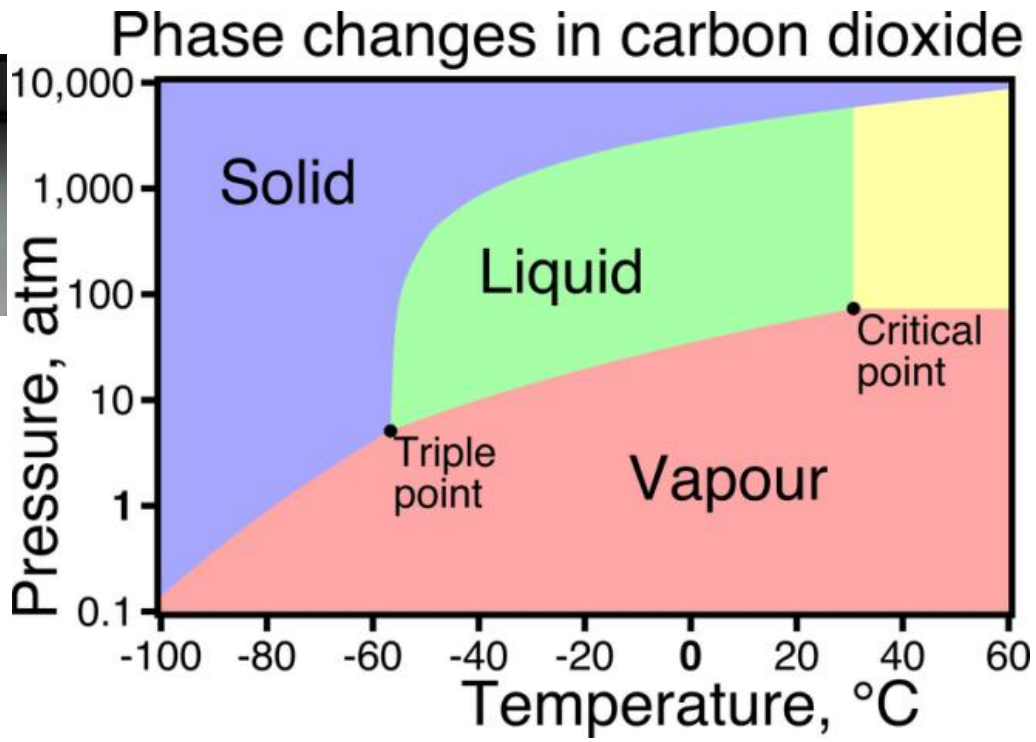
Review

Ionic liquids: Green solvents for nonaqueous biocatalysis

Some current approaches to solvent replacement in synthetic chemistry

- Water
- Ionic liquids
- Carbon dioxide
- No solvent





Tc (31.1 C) ;
Pc (72.9 atm/7.39 MPa)

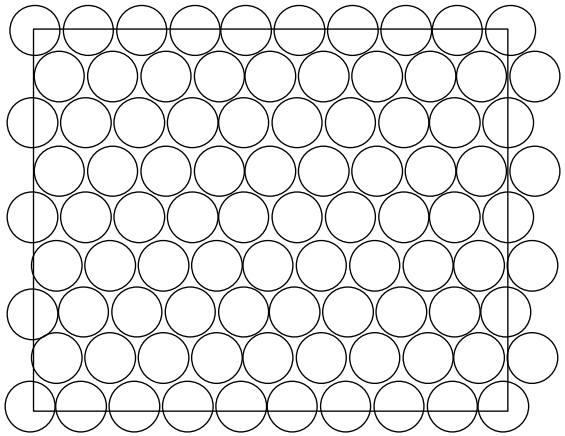
solv.	T_c(°C)	p_c(atm)
H_2O	374	221
MeOH	239	81
CO_2	**31**	**74**
Etere	127	54
Benzene	289	30
Esano	234	30

Supercritical carbon dioxide (SC-CO_2)

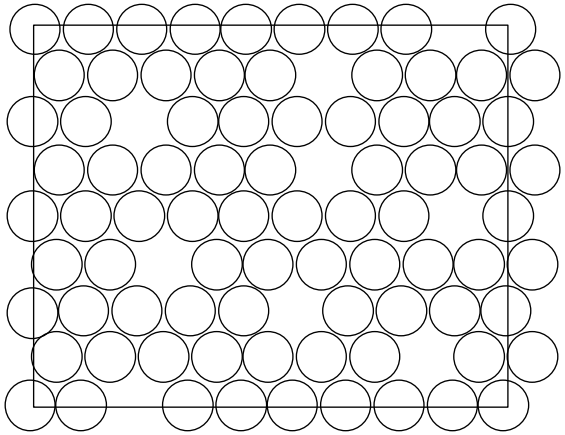
It is a stable fluid; if T is higher than critcal point, the properties are the ones beteween a gas and a liquid

It expands as a gas, but with a density similar to a liquid

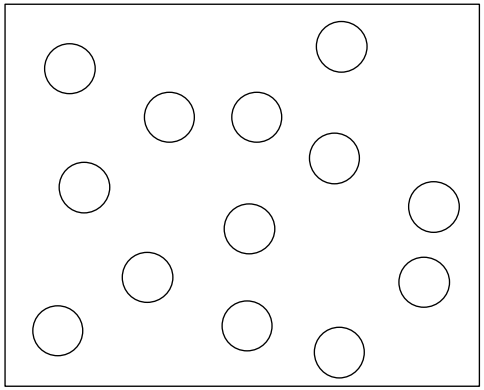
SCFs are intermediate between liquids and gases



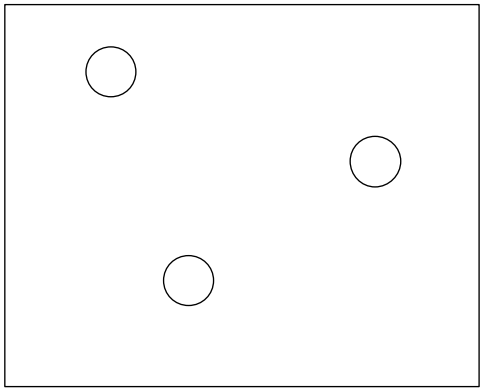
Solid



Liquid



Supercritical Fluid



Gas

Carbon Dioxide-1

- Similar advantages to water
  - Natural, cheap
  - Available in >99.9% pure form
  - By-product of brewing, ammonia synthesis, combustion
- Already being adopted in a variety of commercial processes
- Non-toxic and properties well understood
  - **BUT** asphyxiant at high concentrations
- Easily removed and recycled, and can be disposed of with no net increase in global CO_2
  - Simple product isolation by evaporation, to 100% dryness.
- No solvent effluent
- Potential for product processing (extraction, particle formation, chromatography etc.)

Carbon Dioxide- 2

- ✓ Supercritical CO_2 is becoming an important commercial and industrial solvent due to its role in chemical extraction. Hydrophobic substrates offer good solubility to SC-CO_2

- ✓ Separation of the reaction components from the starting material is much simpler than with traditional organic solvents

- ✓ In addition to its ***low toxicity and environmental impact*.** The relatively low temperature of the process and the stability of CO_2 also allows most compounds to be extracted with little damage or denaturing.

- ✓ It is seen as a promising **green solvent** because it is non-toxic, and a byproduct of other industrial processes.

.

- ✓ ***It is an attractive medium for industrial application*** because it is of natural origin, inexpensive, non-toxic, non-flammable, and environmentally acceptable; also, ***it causes no problem of residual solvents.***

Other advantages of SC-CO_2

- High compressibility
  - Large change in solvent properties for relatively small change in pressure – infinite range of solvent properties available
  - Ability to tune solvent to favour a particular reaction pathway simply by optimising temperature or pressure
- Small amounts of co-solvents can further modify solvent properties
- High diffusion rates offer potential for increased reaction rates.
- Potential for homogeneous catalytic processes.
  - High solubility of light gases, some catalysts and substrates; bring all together in single homogeneous phase
- Inert to oxidation; resistant to reduction
  - Excellent medium for oxidation and reduction reactions.

Solid supported synthesis

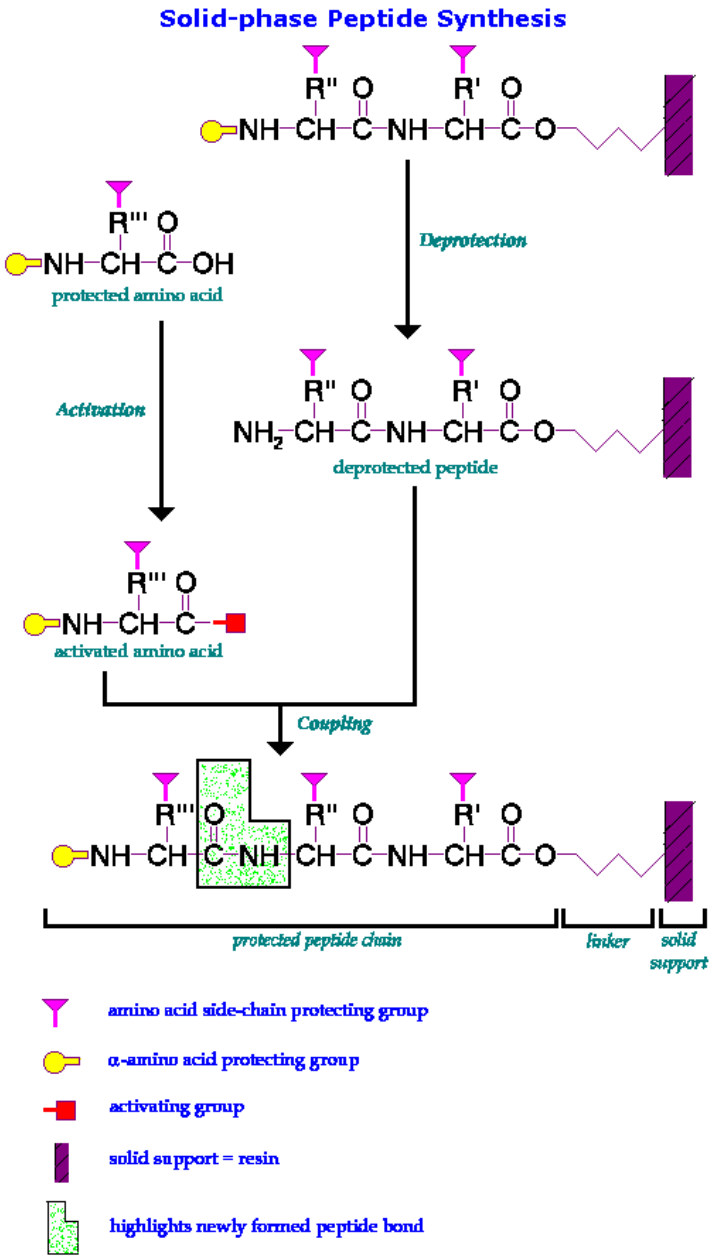
Solid Phase Peptide Synthesis

General principles

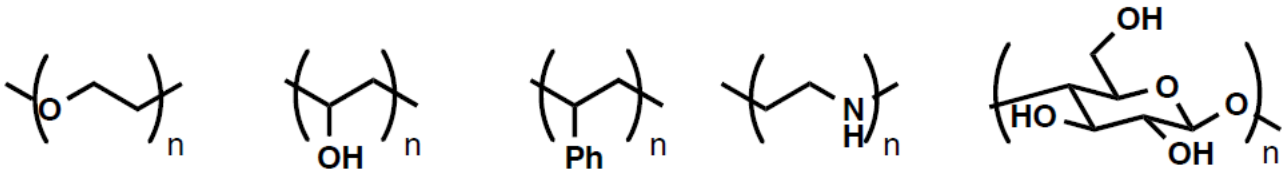
✓ Merrifield in 1959 : the peptide is bound to an insoluble support then any unreacted reagents left at the end of any synthetic step can be removed by a simple wash procedure, greatly decreasing the time required for synthesis.

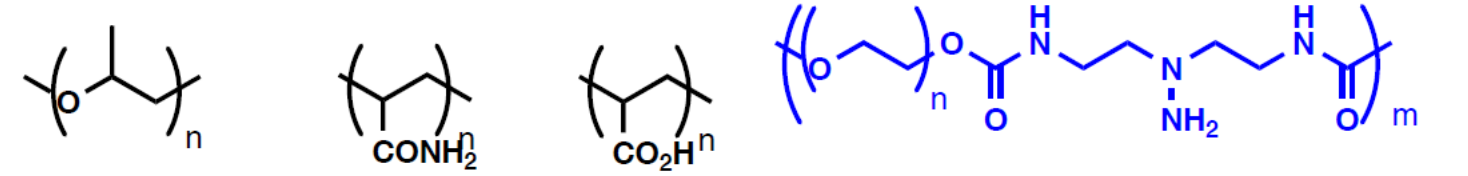
✓ Automation

✓ This is only valid, however, if the individual synthetic steps occur with essentially quantitative yields.



Solid polymeric supports





POLIMERO	applicazioni			
OMOPOLIMERI	**A**	**B**	**C**	**D**
polistirene	x	x	x	
polivinil alcol	x	x	x	x
polietilen immina	x			
acido poliacrilico	x			
PEG	x	x	x	x
polipropilene ossido	x			
cellulosa		x		
poliacrilammide			x	
COPOLIMERI				
PEG+3,5–diisocianato benzilcloruro	x			
PEG+3–ammino–3–azapentano–1,5–diisocianato	x			
polivinilalcol+polivinilpirrolidinone	x	x		
polistirene+polivinil monosaccaridi			x	
poliacrilammide+acido poliacrilico				x

A sintesi peptidica

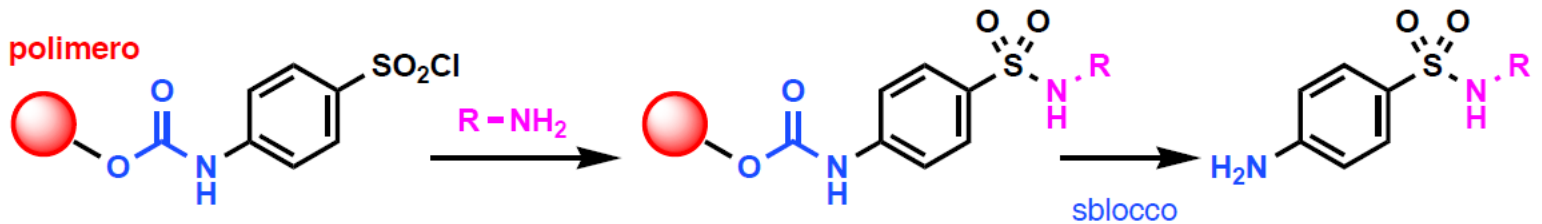
B sint. oligonucleot.

C sint. oligosaccar.

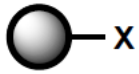
D sint. organica

Polymeric supports

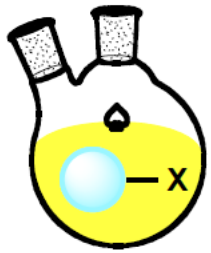
✓ are considered a sort of protective group for the molecule of reagent the final product is obtaind free from solid dupport ata the end



Se il supporto polimerico è solubile nell'ambiente di reazione, il processo avviene in fase omogenea, se il polimero è insolubile in fase eterogenea



molecola X legata a polimero



✓ Unsoluble solid supports allow an easy workup, by simple filtration.

Solid phase synthesis is confirmed as a very well established and popular method for:

i) easy purification steps;
ii) susceptibility to automation;
iii) access to largely diversified combinatorial libraries of oligomers and small organic molecules;
iv) versatility/modulability/compatibility with a wide range of reagents/conditions

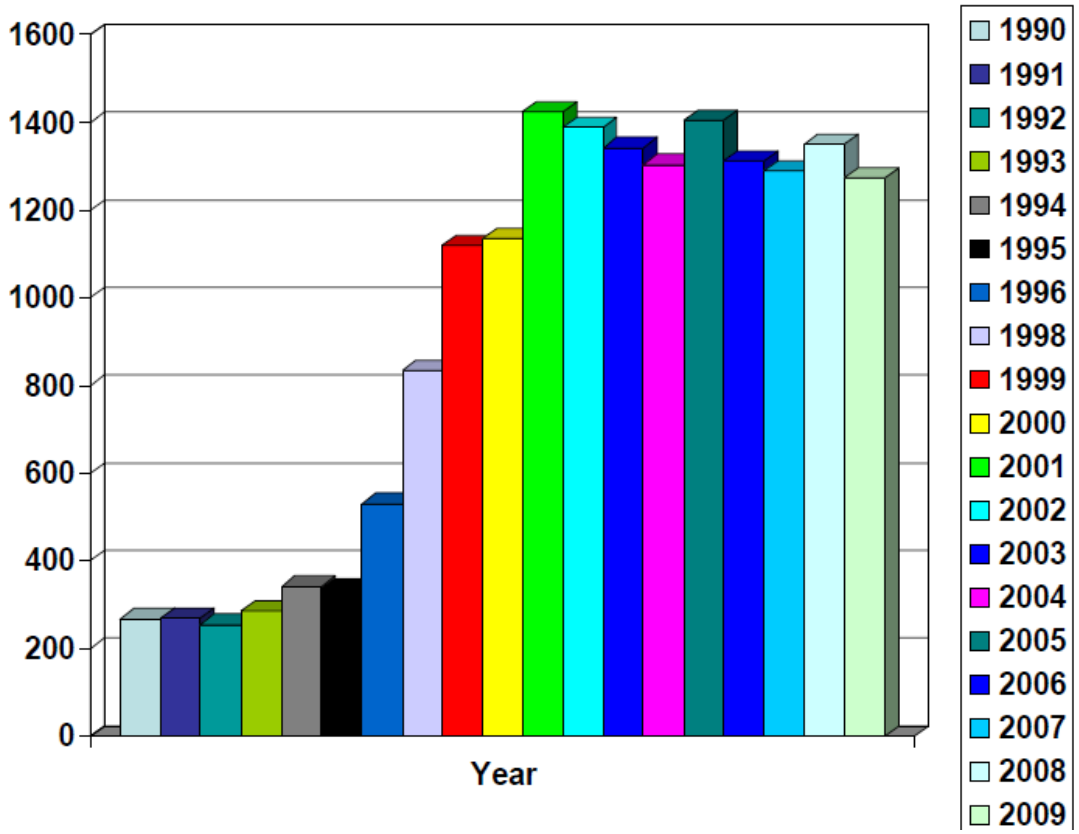
Disadventages of solid phase synthesis

✓ Analytical techniques applied to follow
the conversion during the reaction time

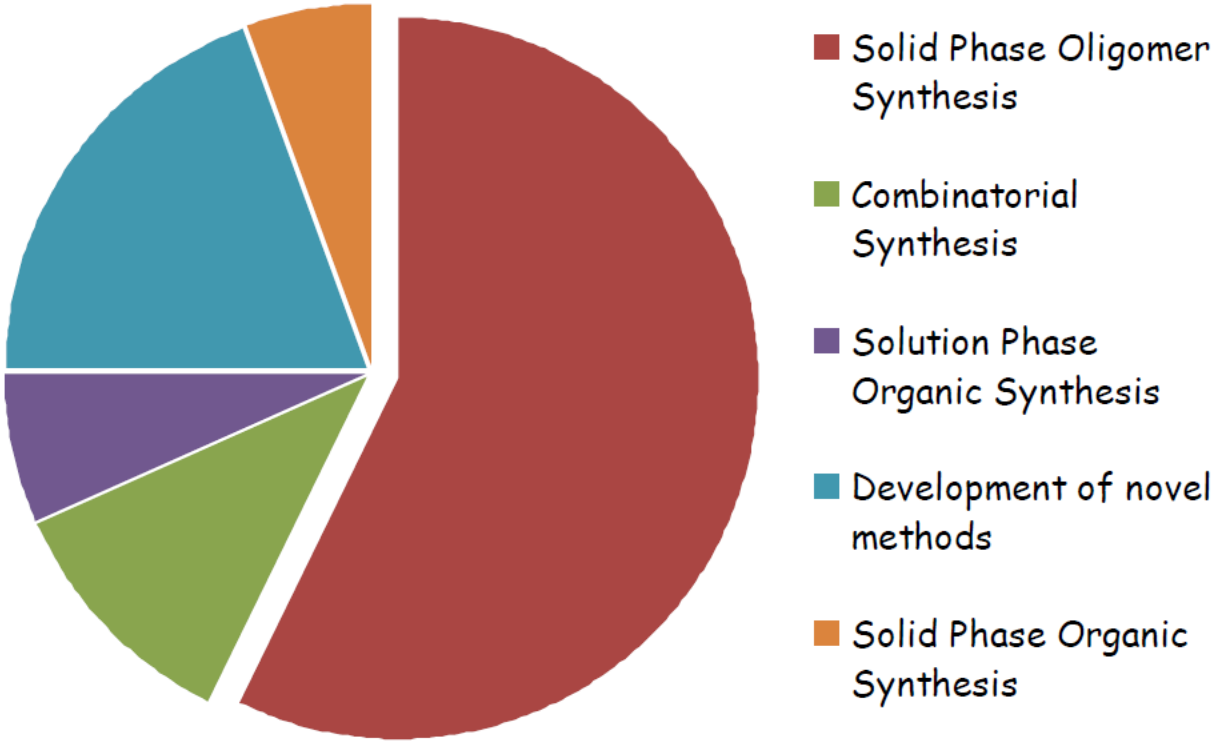
It is not possible to use TLC and
any other techniques for the analysis of solutions

Used techniques: IR spectroscopy, Solid state NMR

Total number of papers (articles, reviews, patents) produced from 1990 to 2009 on the subject "*Solid phase synthesis*"

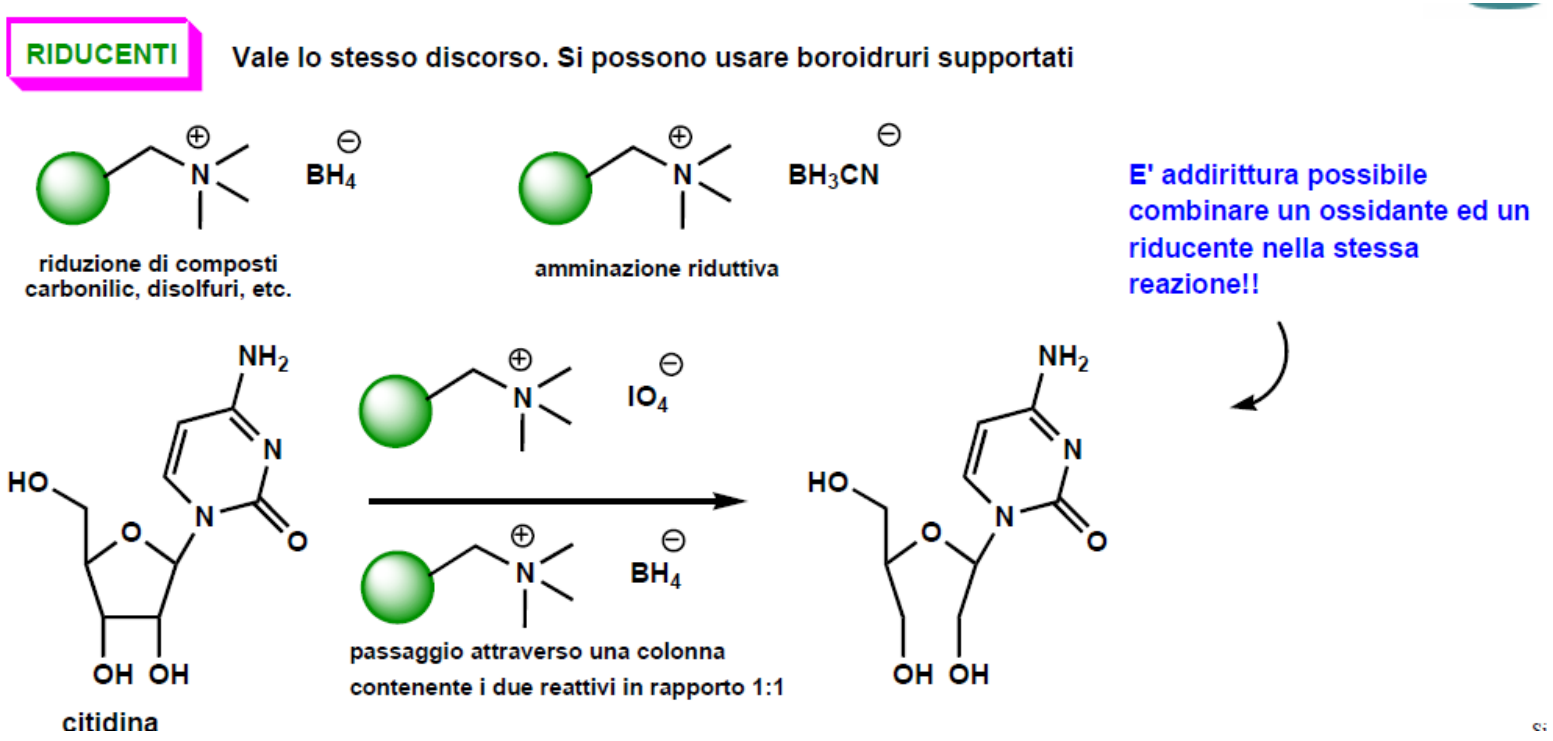


Distributions of the papers published in 2009 on the different research areas of SPS

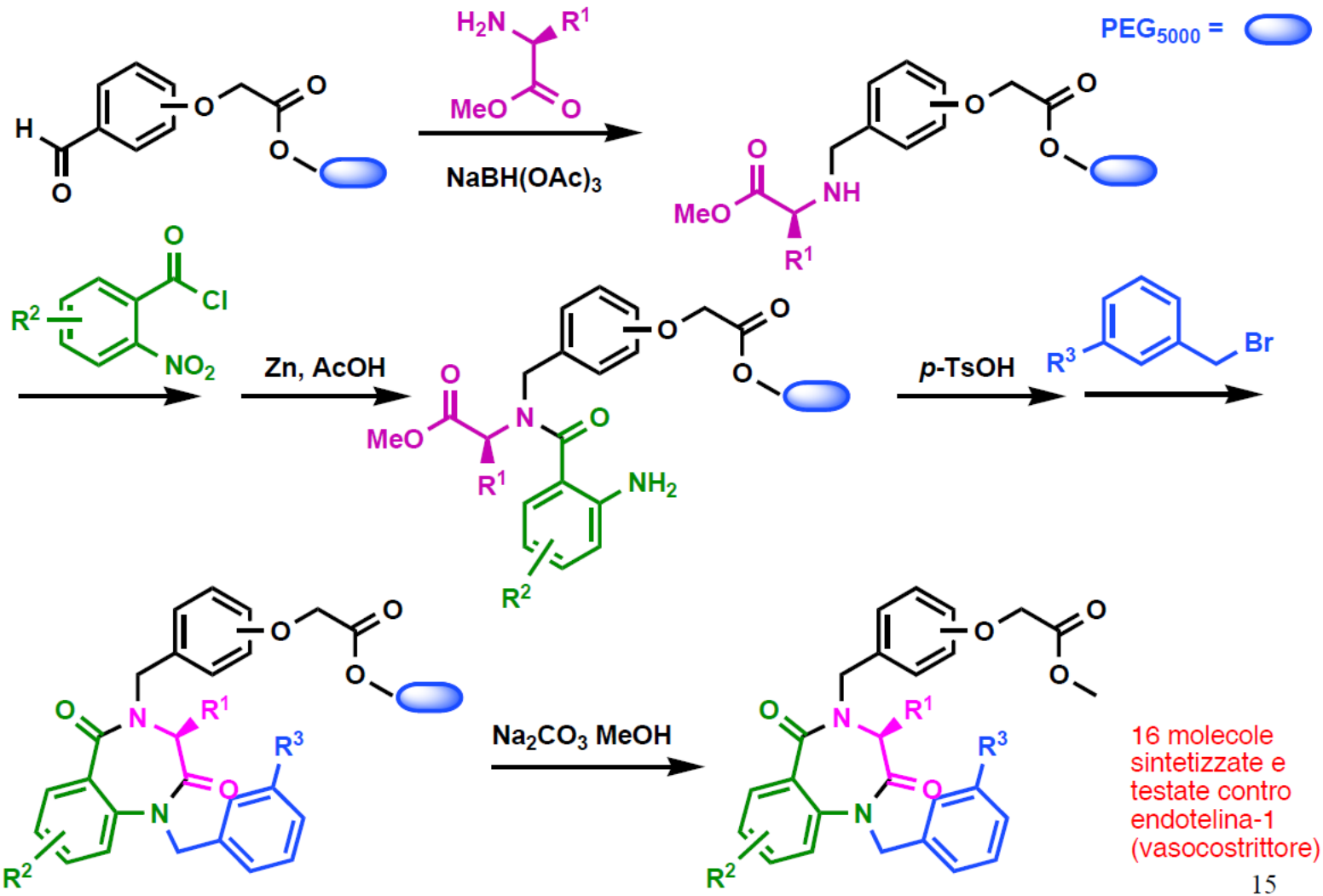


Reagents useful in oxidation and reduction reaction are commercilly available as supported on solid phase

Example: borohydride reductive reagent supported on polymers



Example of Solid Supported Synthesis



✓ More environmentally friendly methods for the solid phase peptide synthesis (SPPS)

ORGANIC LETTERS

2009
Vol. 11, No. 20
4488−4491

Solid-Phase Peptide Synthesis in Water Using Microwave-Assisted Heating

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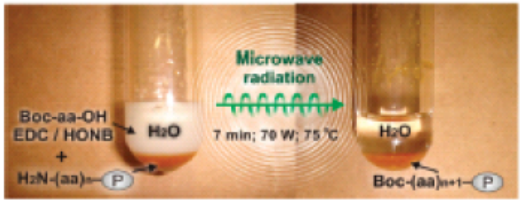
Received June 8, 2009

ABSTRACT



An approach using water as a solvent (coupling and deprotection) was developed for the solid-phase synthesis of peptides using the most common Boc-amino acid derivatives. Key aspects of this methodology are the use of a PEG-based resin, EDC-HONB as a coupling method, and microwave irradiation as an energy source.

Unconventional techniques

- ✓ **Microwave irradiation**
- ✓ Sonochemistry

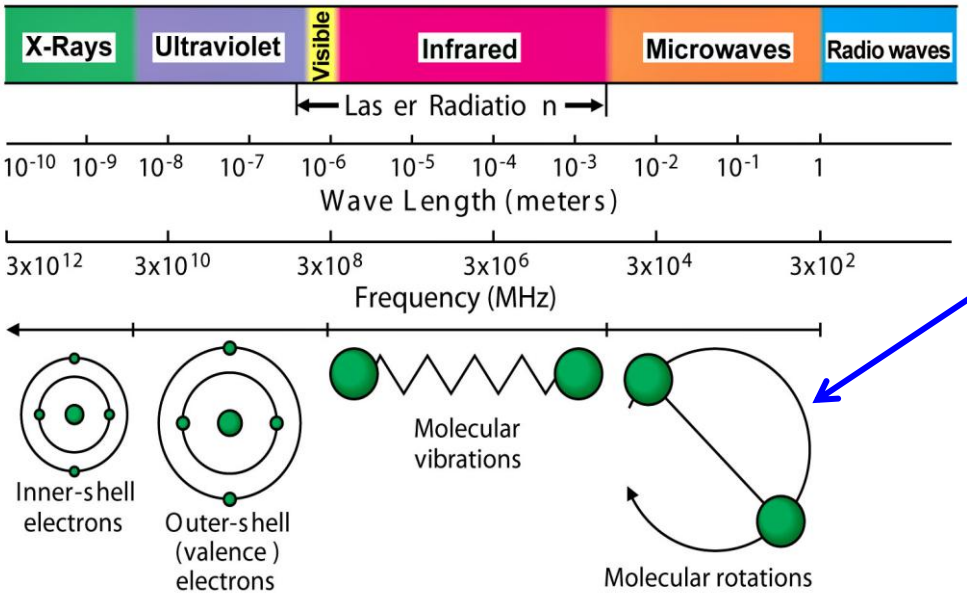
Microwave (MW) irradiation

The most common benefits described are:

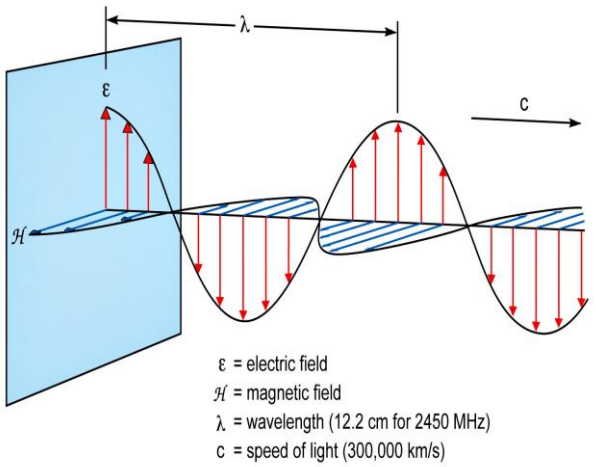
- very rapid reactions, frequently a few minutes, brought about by high and homogeneous temperatures and combined with pressure effects (if conducted in closed vessels);
- higher degree of purity achieved due to short residence time at high temperatures;
- yields often better, obtained within shorter times and with purer products.

→ Solvent-free microwave organic synthesis as an efficient procedure for green chemistry

- ✓ Microwave are electromagnetic radiation with 300-300000MHz frequencies, corresponding to energy able to act on molecular rotational levels.
- ✓ Instruments used in the lab. generally work with a frequency generator (magnetron) at 2450 MHz (λ=12.2 cm).



- ✓ Microwaves are formed by ana electric and a magnetic oscillant fields. Only the electric field isa able to transfer energy to the sample.

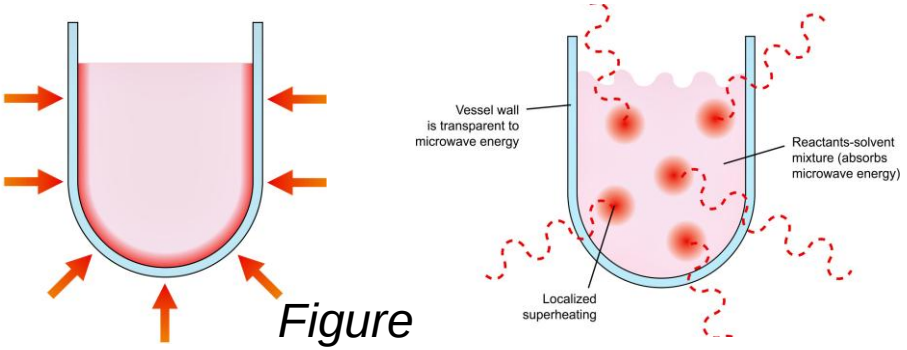


✓ In conventional organic synthesis the trasfer of heat is by conduction, through ana oil bath (slow and of low efficacy) (*Figure, left*).

Mechanism of MW heating

✓ Thermic MW effect is different : there is a fast heating localized on molecules able to absorb MW, by dipole rotation, or by ionic conductivity.

Dipole rotation : Polar molecules have an electrical dipole moment and they can align themselves in an electromagnetic field. If the field is oscillating (as it is in an electromagnetic wave or in a rapidly-oscillating electric field), these molecules rotate to continuously align with it.. As the field alternates, the molecules reverse direction. Rotating molecules collide with other molecules distributing the energy to adjacent molecules and causing heating heat



Figure

✓ Molecules with permament dipoles (as reagents or solvent) are necessary.

Electromagnetic Field

ν = 2450 MHz λ = 12.2 cm

Dipolar Polarization

Orientation of Dipoles in an Electric field

Alternative Field of High Frequency

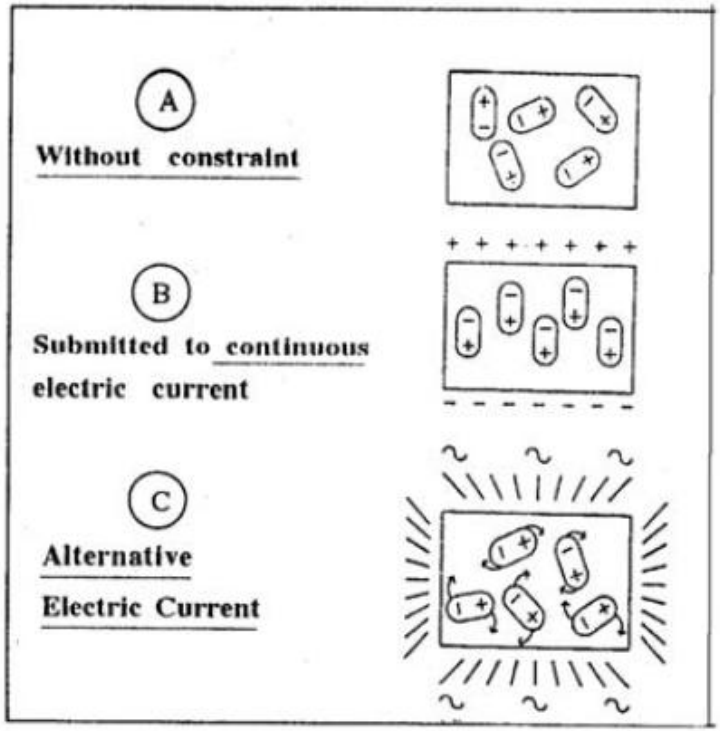
Inversion of orientation at every alternance

⇒ Stirring and Friction of molecules

⇓

Internal Homogeneous Heating

Thermal phenomena (conduction, convexion, radiation) only play a minor part in "a posteriori" equilibration in temperature.



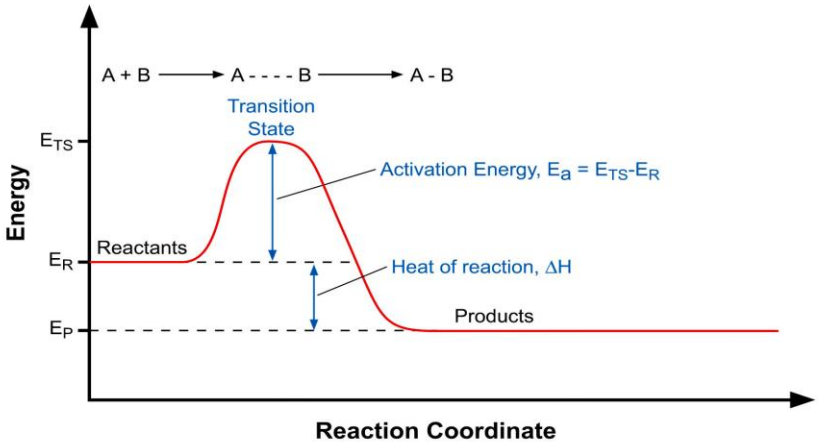
Influence of Electric Field on a Dielectric Compound

Fig. Microwave heating.

- ✓ This mechanism is able to explain the efficient transfer of thermal energy, so that this is the reason why MW induced reactions are faster than conventional heating

Conventional	Microwave
4 hrs	10 min
8-18 hrs	30 min
> 18 hrs	1 hr

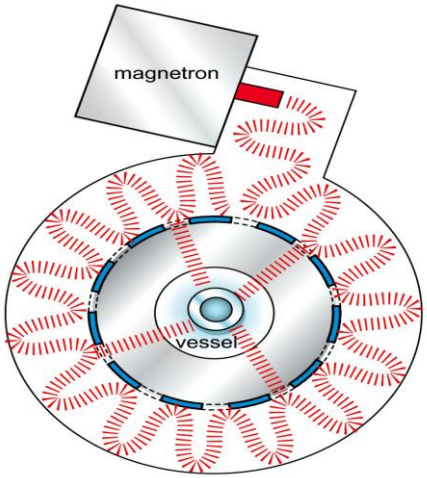
- ✓ MW do not change activation energy (Figure), but are able to tranfer this energy faster than traditional heating.



- ✓Chemical reaction has been carried out in domestic MW oven (multimode system) , but they are not good for safety reason (solvents or reagents can be flammable)

- ✓Specific ***monomode*** MW has been used for scientific application, where the electromagnetic wave produced by *magnetron* is addressed to a toroidal cavity surrounding the sampel to be irradiated. In this way a good focus of the waves on the sample is possible. There are then sensors for T and pressure.

MW reactor

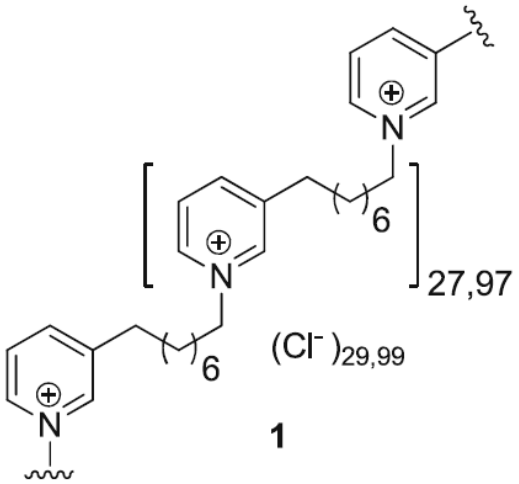


Scheme of a MW monomode system

✓As known, reaction rate depends form the reagent concentration. MW irradiation allows to do reaction under **solvent-free conditions,** if one reagent is liquid or with a low melting point.

Example

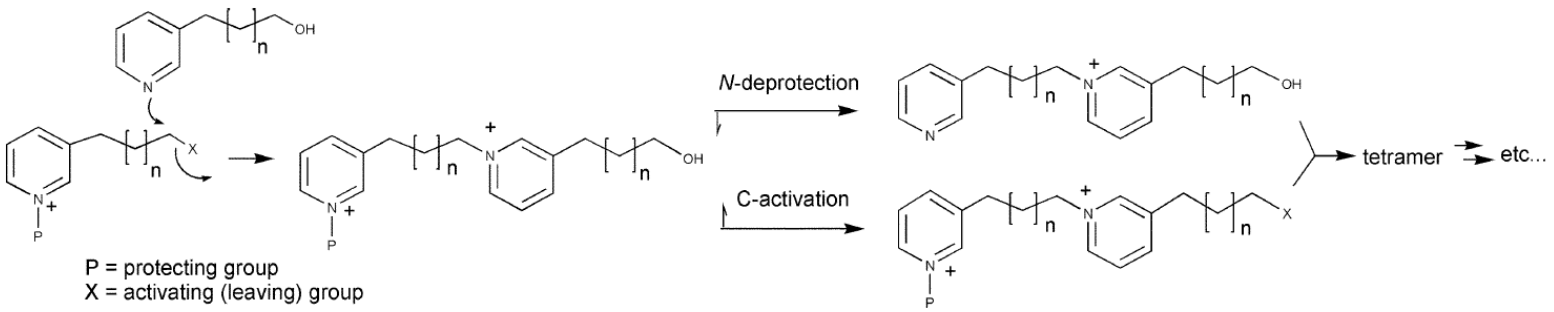
Synthesis of a polymeric natural product with bioactivities
(antibacterial, inhibition of AChE, anti-fouling)



1

Structure of polymeric alkylpyridinium metabolites **1 (Poly-APS)** from the sponge *Reniera sarai*.

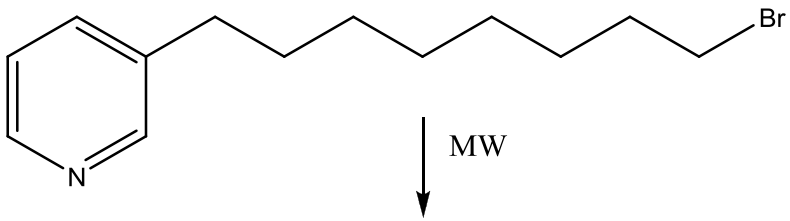
✓ *Conventional iterative synthesis* (by using protective/deprotecive steps)



Scheme 1 Synthetic strategy for the preparation of linear oligomeric analogues of polyAPS **1**.

Mancini et. al, Org. Biomol. Chem. 2004

✓ *Microwave assisted synthesis* (under solvent-free conditions*)*



polymer similar to the natural one
(with the same bioactivities)

Di-substituted pyridinium polymers and synthesis thereof. Jaspars M; HoussenW; Lu Z; Scott R; Edrada-Ebel R; Mancini I. (University Court of the University of Aberdeen, UK). PCT Int. Appl. (2010)

Combinatorial Chemistry

Combinatorial Chemistry

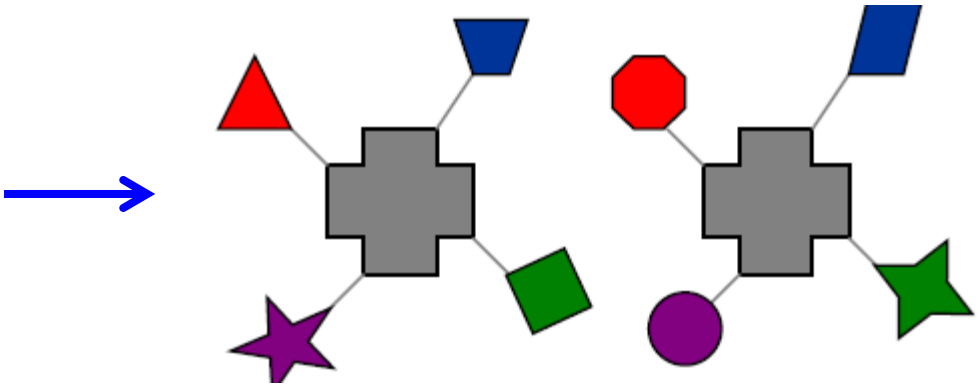
The basic principle of combinatorial chemistry is to prepare and screen a large number of different molecules at the same time

Combinatorial chemistry is a general method for discovering molecules that possess a desired property. The property can be almost anything: electrical conductivity or semiconductivity, an attractive color, a sweet odor, the ability to block pollen from binding to a histamine receptor, the ability to kill cancerous tumor cells, the ability to kill bacterial cells. Obviously in drug discovery, the latter types of properties are of interest. What distinguishes combinatorial chemistry is its ability to screen many (thousands to millions) of new compounds for a desired property.

1 synthetic method

1 scaffold

n sets of substituents



Building of a **library** of compounds

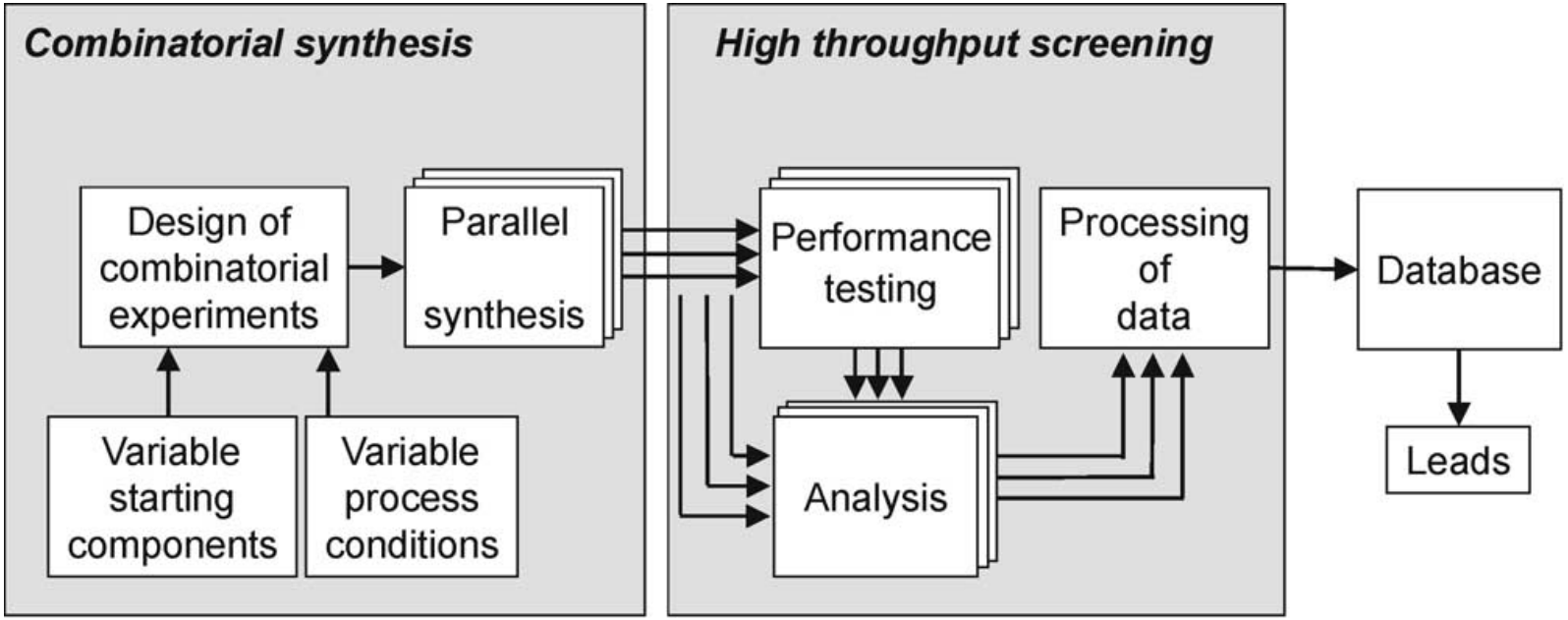


Figure. Combinatorial materials science and HTS discovery cycle.

Combinatorial Synthesis and Discovery of an Antibiotic Compound

Combinatorial Synthesis of Hydrazones

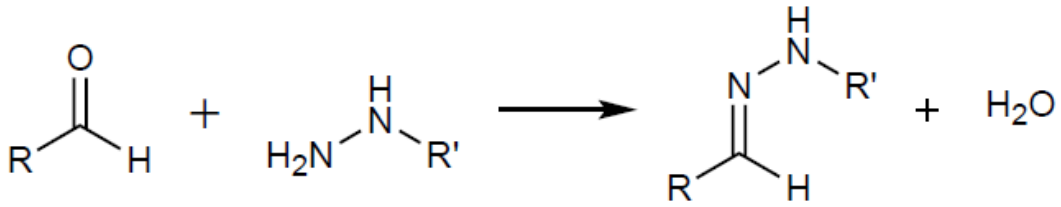
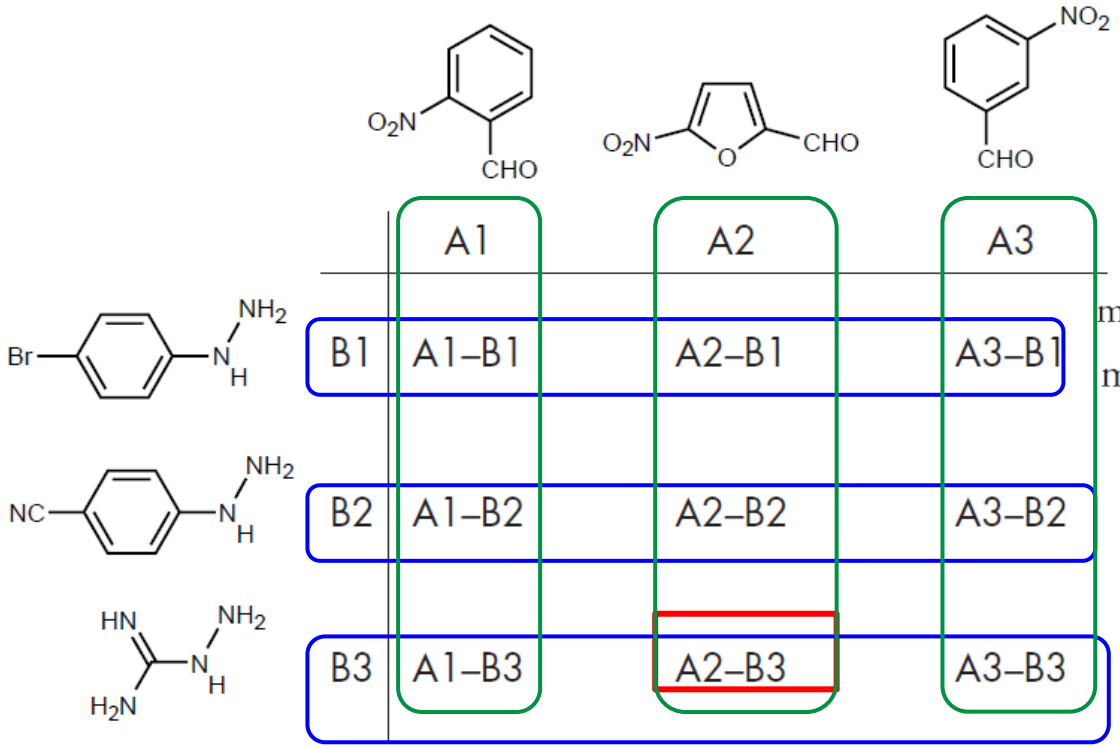


Table 1. Aldehyde and Hydrazine Reactants and All Possible Hydrazone Products



mixtures M1–M3 are represented in the columns

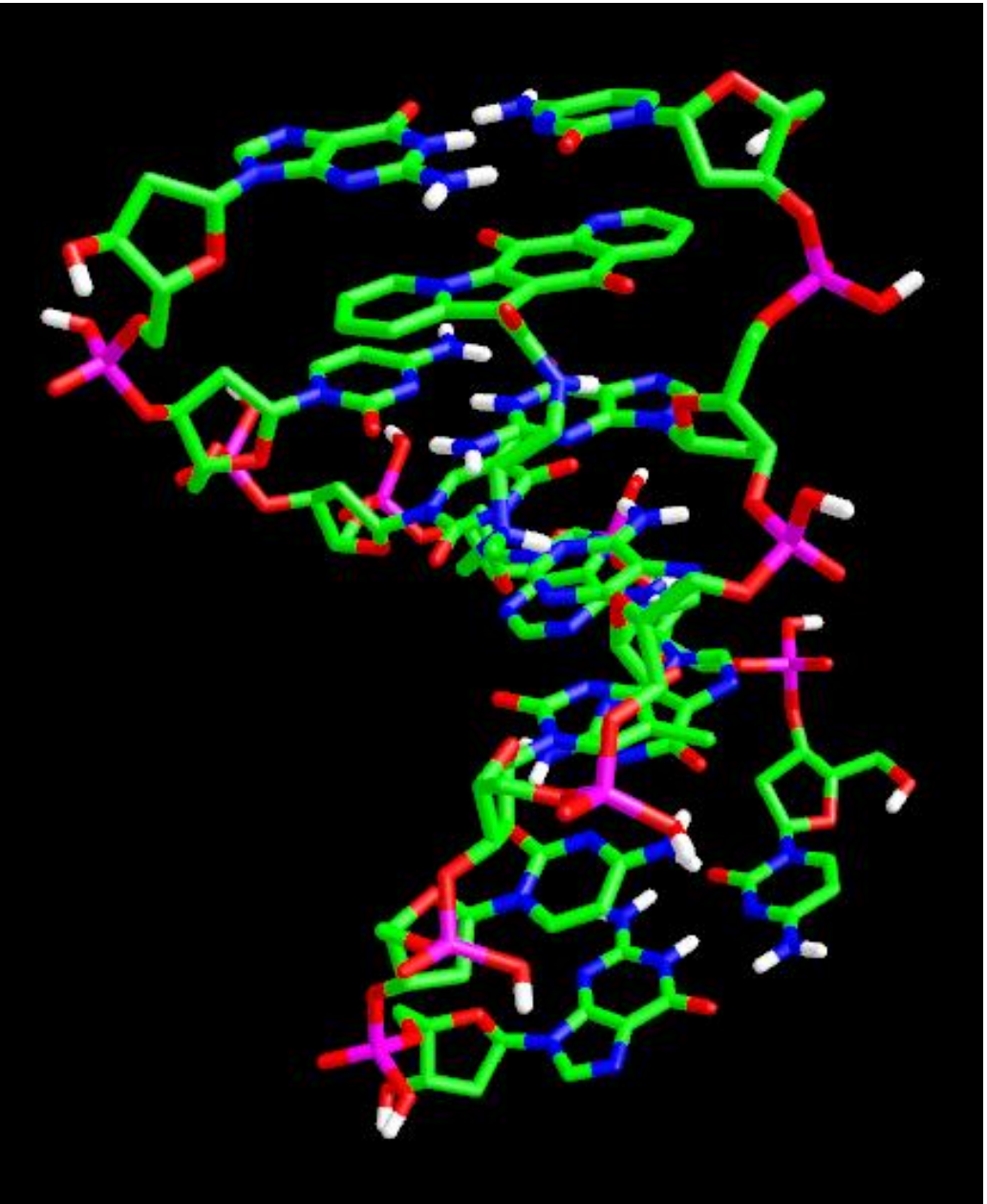
mixtures M4–M6 are represented in the rows.

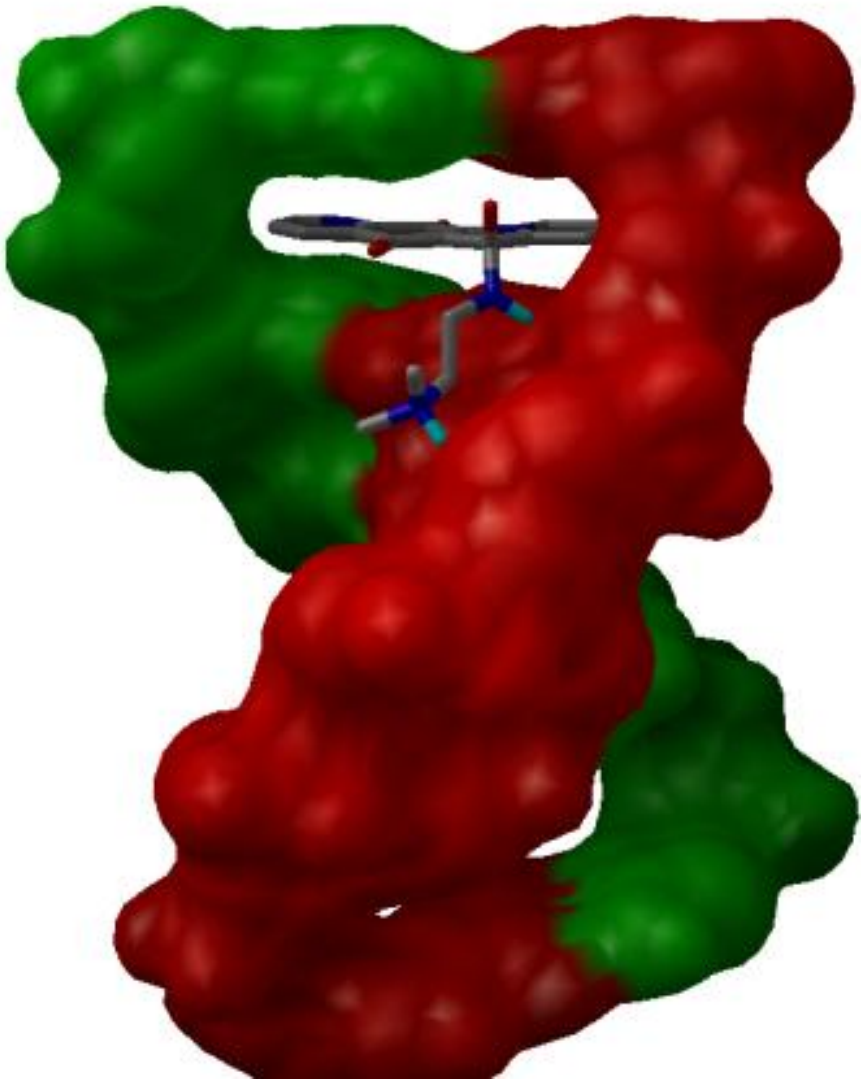
Reduction of 33% of reactions

➢ Organic Synthesis in Modern Drug Delivery

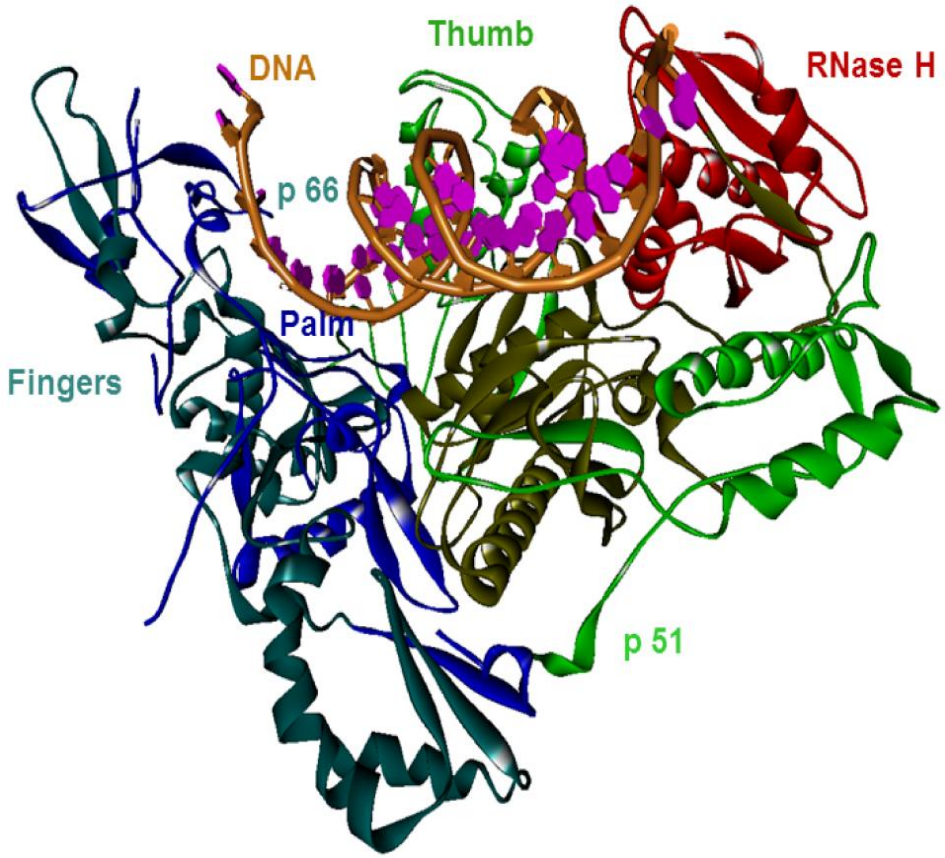
- ✓ Modern drug development: drug design by docking calculations
- ✓ Biomimetic approach based on natural products
- ✓ Combinatorial chemistry

Docking Calculation Results

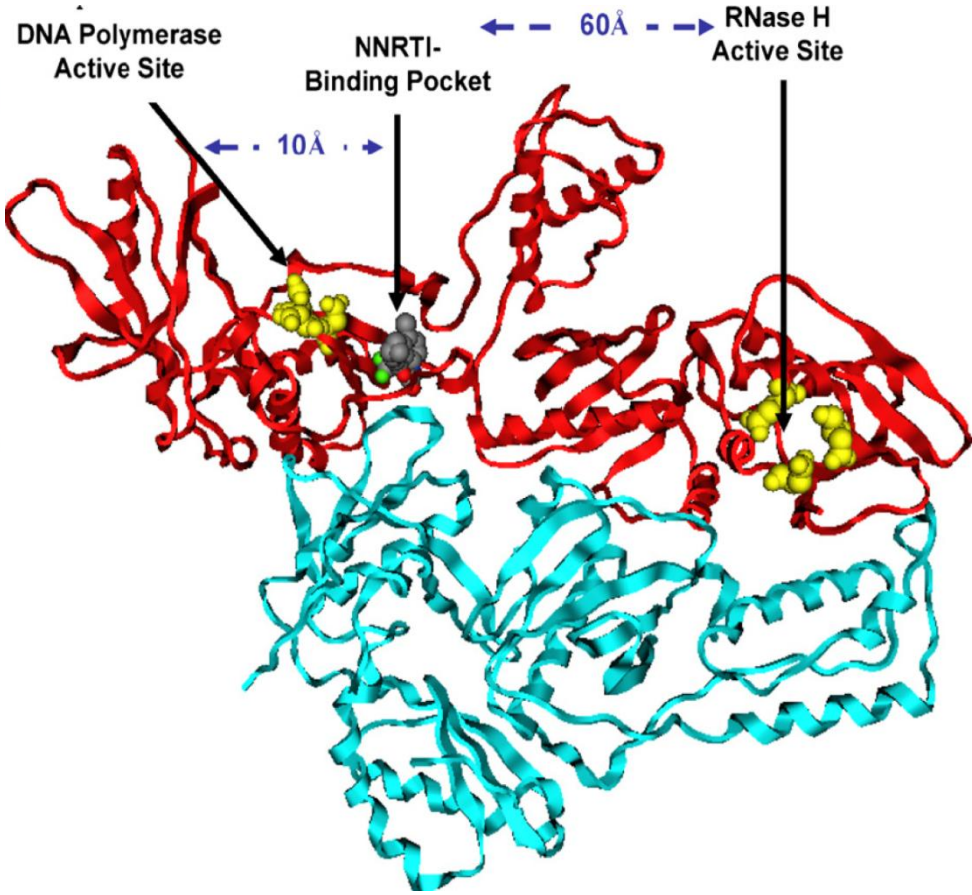




Example



3D-Structure of HIV-1 reverse transcriptase in the complex with DNA (PDB code: 3KJV)



HIV-1 RT with binding site for NRTIs/NtRTIs and the binding site NNRTIs

Considerations

- The use of computational methods gives a rational approach in drug discovery
- It allows to increase the development rate of new bioactive scaffolds
- In particular AutoDock is a free software, which gives good score results

Click Chemistry

History

Click chemistry is a concept introduced by K. Barry Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together as nature does**.**

- ✓ In biochemistry, proteins are made from repeating amino acid units and sugars are made from repeating monosaccharide units. The connecting units are based on carbon - hetero atom bonds C-X-C rather than carbon - carbon bonds. In addition, enzymes ensure that chemical processes can overcome large enthalpy hurdles by division into a series of reactions each with a small energy step.
- ✓ **Mimicking nature** in organic synthesis of new pharmaceuticals is essential given the large number of possible structures.

Definitions

Click Chemistry is a general term that identifies a class of chemical transformations with a number of attaractive features including excellent functional-group tolerance, high yields and good selectivity under mild experimental conditions.

As defined by K. B. Sharpless – "'Click' chemistry…a set of powerful, virtually 100% reliable, selective reactions for the rapid synthesis of new compounds via heteroatom links (C-X-C)…Click chemistry is integral now to all research within the Sharpless Lab.**"**

Borman, S. *C & En*. **2002**, *80(6)*, 29**.**

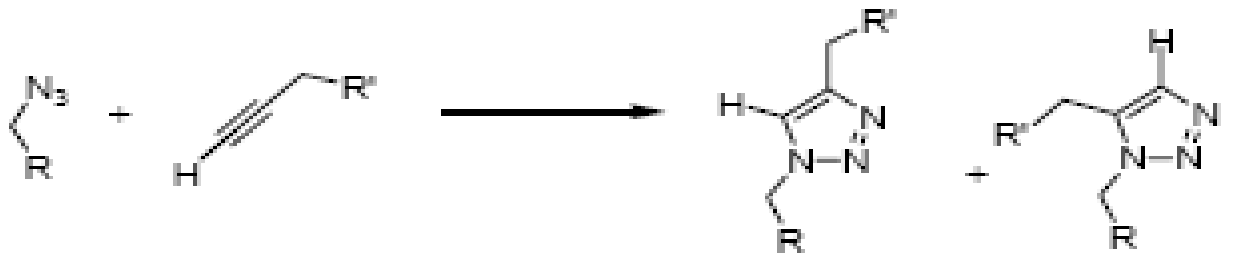
Click Chemistry: Diverse Chemical Function from a Few Good Reactions

Following nature's lead, we endeavor to generate substances by joining small units together with heteroatom links (C–X–C). The goal is to develop an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large-scale applications. We have termed the foundation of this approach "click chemistry," and have defined a set of stringent criteria that a process must meet to be useful in this context. The reaction must be *modular*, *wide in scope*, give *very high yields*, generate only *inoffensive byproducts* that can be removed by nonchromatographic methods, and be *stereospecific* (but not necessarily enantioselective). The required process characteristics include *simple reaction conditions* (ideally, the process should be insensitive to oxygen and water), *readily available starting materials and reagents*, the use of *no solvent or a solvent that is benign* (such as water) *or easily removed*, and *simple product isolation*. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions.

B Sharpless, 2004

Classes of ‘Click’ Reactions

- Nucleophilic opening of highly strained rings
  - SN2 ring opening reactions
  - Epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions
- “Protecting Group” Reactions
  - Reversible carbonyl chemistry
  - Acetals, ketals and their aza-analogs
- Cycloaddition Reactions
  - Hetero Diels-Alder, 1,3 dipolar cycloadditions involving heteroatoms



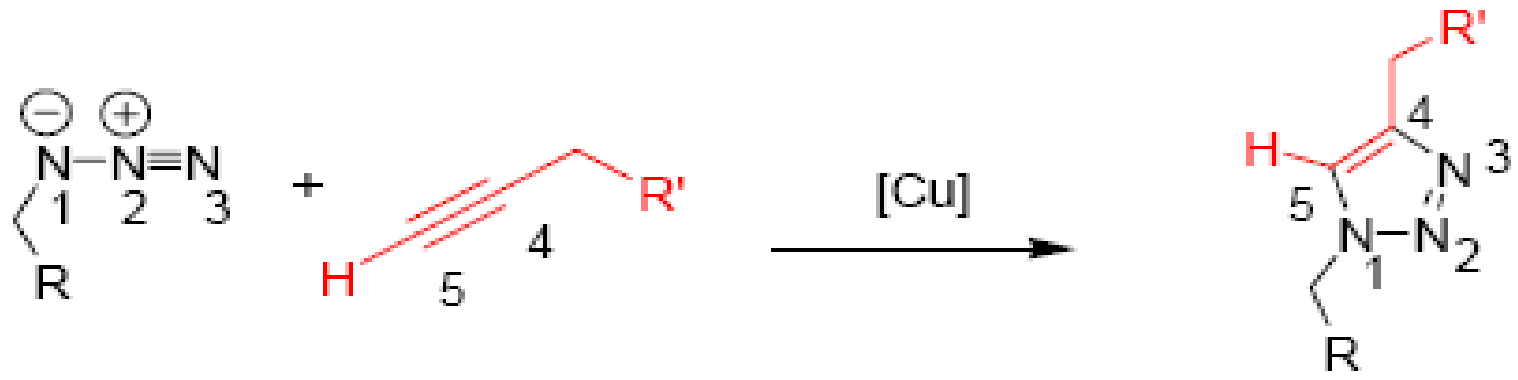
Why “Click” Chemistry?

- Functional group tolerance
- Aqueous conditions
- Shorter reaction time
- High yield
- High purity
- Regiospecificity

Regioselectivity of “Click” Chemistry

- Addition of Cu(I)-catalyst

– “the champion “click” process…”



“Click” Chemistry Using a Solid Support

- Solid Phase Organic Synthesis (SPOS)

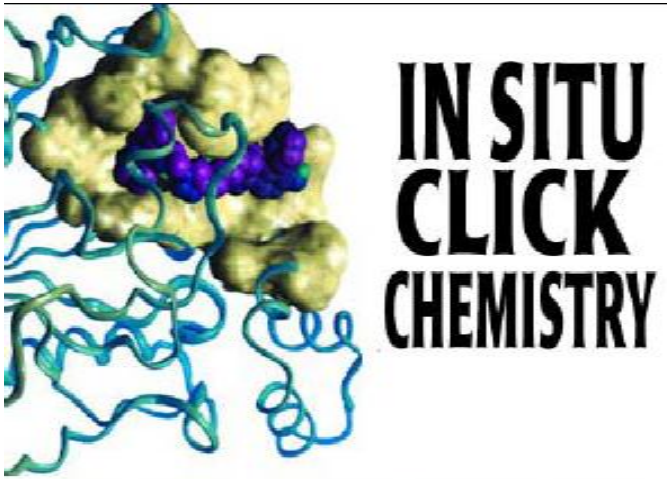
- Solid Phase Peptide Synthesis (SPPS)

Click Chemistry in Biology

- Construction of fluorescent Oligonucleotides for DNA sequencing
- Introducing additional functional groups in DNA

•Biological Inhibitors (e.g. HIV-1 protease, AChE)

•In-situ “Click” approach



Templating strategy offers potential route to new drugs and other functional compounds

Click Chemistry in Life Sciences

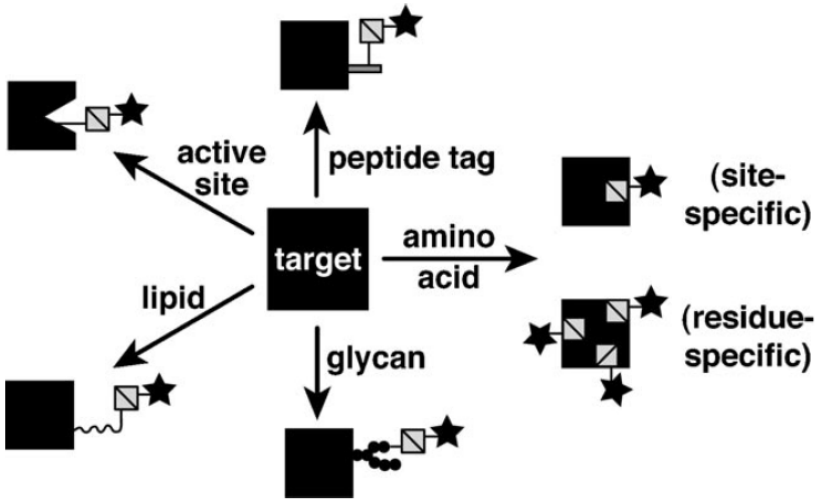


Figure 5. Strategies for labeling biomolecules with chemical reporters *in vitro* and *in vivo*. (Clockwise from top left) Enzymes that are catalytically active can be specifically labeled with activity-based probes bearing chemical reporters. Proteins can be labeled with a chemical reporter by enzymatic modification of a short peptide sequence. Individual amino acids within proteins can be replaced, either in a site-specific or residue-specific manner, with unnatural amino acids bearing chemical reporters. Glycans can be metabolically labeled with chemical reporters using unnatural monosaccharide precursors. Lipids can be metabolically labeled with chemical reporters using unnatural lipids.

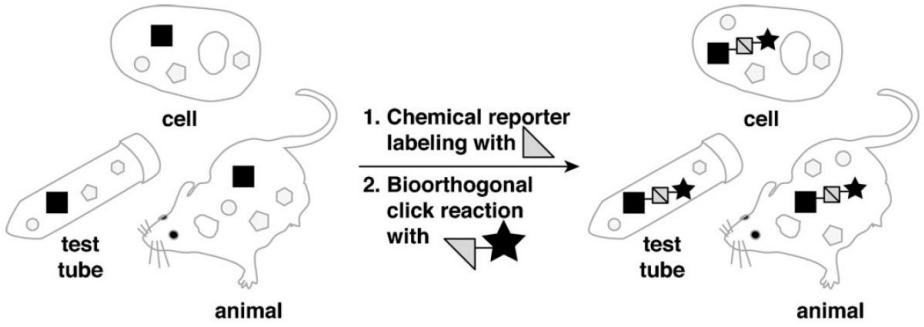


Figure 4. Bioorthogonal chemical reporter strategy. (1) Target biomolecules (black square) are labeled in the presence of non-target biomolecules (gray shapes) *in vitro* or *in vivo* with a chemical reporter (triangle). (2) The chemical reporter is then detected using bioorthogonal click chemistry to append a functional probe of interest (star).