


Benign Molecular Design

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Today's Outline:



1. Chemistry vs. **Green Chemistry**
2. Definitions
3. How do we measure **greenness**?
4. Examples of **green** and...
5. ... of very **un-green** chemistry
6. Tools: green solvents and catalysis

1. REACH: REGISTRATION, EVALUATION, AUTHORISATION AND RESTRICTION OF CHEMICAL SUBSTANCES





Chemistry?



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Chemistry makes life better!




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Green Chemistry:

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Green Chemistry: definition 1

Sustainable development
Sustainability: "Given reasonable assumption concerning progress in the technology and the activities of a civilization, a sustainable civilization is one in which the net sum of the daily activities of the people who comprise it, individually and collectively, can be carried on into the indefinite future, without undermining the ability of future generations to live with at least a comparably advantageous welfare".


Terrence Collins, *Science*, **2001**, 291, 48.

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Green Chemistry: definition 2

Green chemistry efficiently utilises (preferably renewable) raw materials (and energy), it eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.




Paul Anastas, John Warner *Green Chemistry: Theory and Practice*, Oxford University Press NY 1998




Green Chemistry: 12 principles

- Prevent waste
- Design safer chemicals and products
- Design less hazardous chemical syntheses
- Use renewable feedstocks
- Use catalysts
- Avoid chemical derivatives
- Maximize atom economy
- Use safer solvents and reaction conditions
- Increase energy efficiency
- Design chemicals and products to degrade after use
- Analyze in real time to prevent pollution
- Minimize the potential for accidents

common sense?




Paul Anastas, John Warner *Green Chemistry: Theory and Practice*, Oxford University Press NY 1998



PRODUCTIVELY


Condensed Principles of Green Chemistry

- P - Prevent wastes
- R - Renewable materials
- O - Omit derivatization steps
- D - Degradable chemical products
- U - Use safe synthetic methods
- C - Catalytic reagents
- T - Temperature, Pressure ambient
- I - In-Process Monitoring
- V - Very few auxiliary substances
- E - E-factor, maximise feed in product
- L - Low toxicity of chemical products
- Y - Yes, it is safe



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Samantha L. Y. Tang, Richard L. Smith, Martyn Poliakoff *Green Chem.*,
2005, 7, 761



Green Chemistry: metrics 1

E(nvironmental) Factor

Industry segment	Product tonnage	E Factor (kg waste/kg product)
Oil refining	10^6 – 10^8	<0.1
Bulk chemicals	10^4 – 10^6	<1–5
Fine chemicals	10^2 – 10^4	5–50
Pharmaceuticals	10 – 10^3	25–100



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Roger A. Sheldon, *Chem. Ind.*, 1992, 903
Roger A. Sheldon, *Green Chem.*, 2007, 9, 1273

Green Chemistry: metrics 2

Atom economy

$$\% \text{ AE} = \frac{\text{molecular weight (gmol}^{-1}\text{) product}}{\sum \text{molecular weights of all reagents}}$$

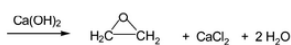


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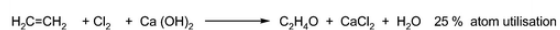
Barry M. Trost, *Science*, 1991, 254, 1471

Atom economy: an example

1. Chlorohydrin process



Overall:



$$E_{\text{th}} = 75/25 = 3$$

2. Direct oxidation

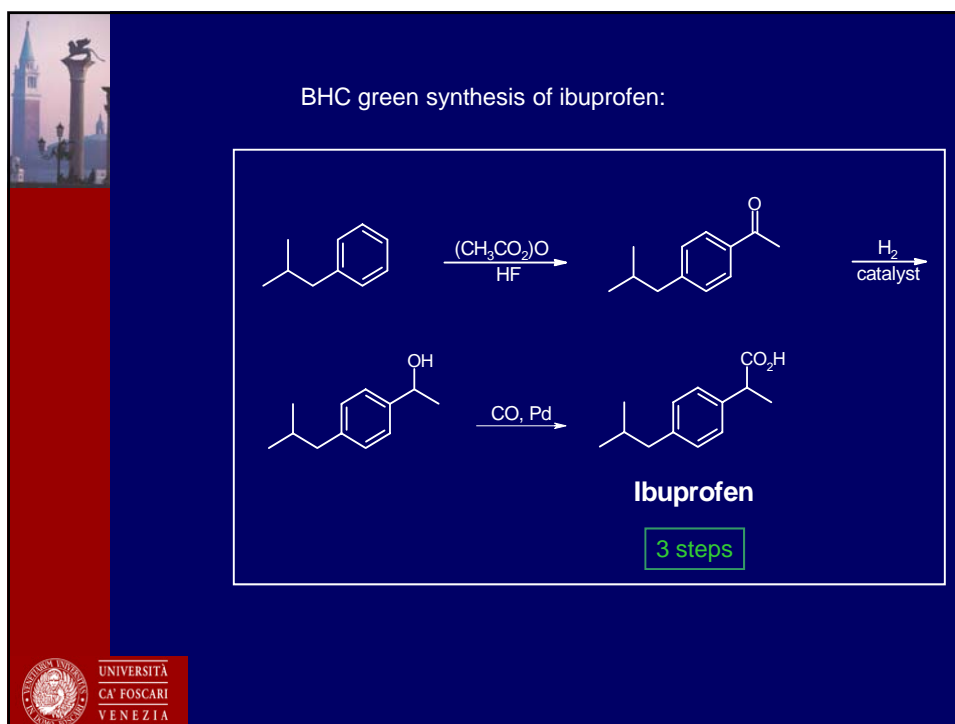
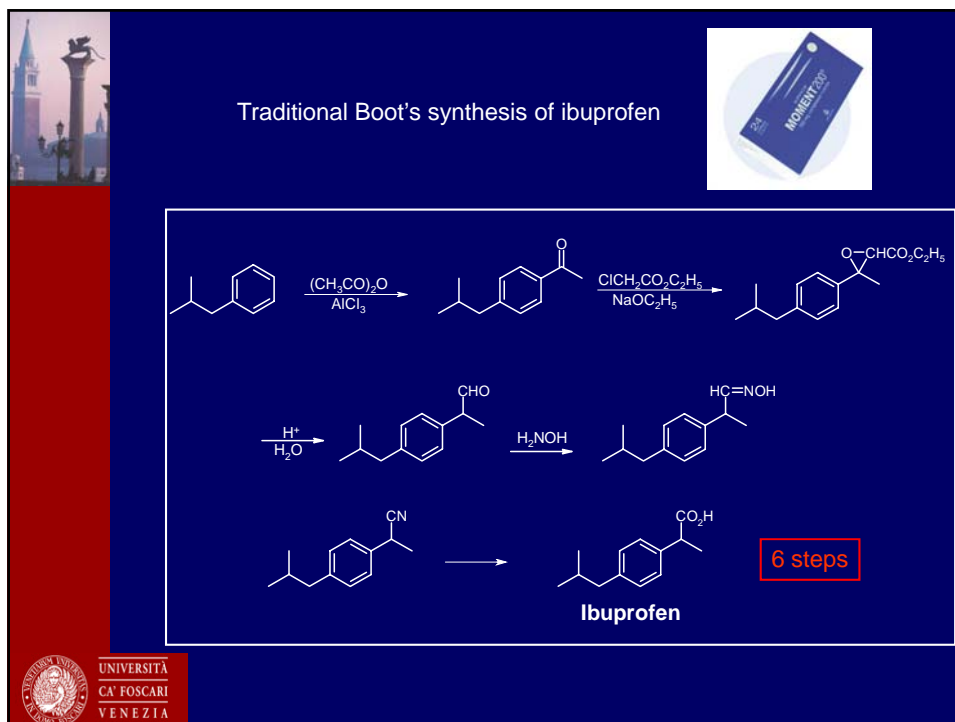


$$E_{\text{th}} = 0/100 = 0$$

Theoretical E factor (E_{th}) is the MW of wasted atoms divided by the MW of product (always much lower than the true E).



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Reagent		Used in ibuprofen		Unused in ibuprofen	
Formula	Mr	Formula	Mr	Formula	Mr
C ₁₀ H ₁₄	134	C ₁₀ H ₁₃	133	H	1
C ₄ H ₈ O ₃	102	C ₂ H ₃	27	C ₂ H ₃ O ₃	75
C ₄ H ₇ ClO ₂	122.5	CH	13	C ₃ H ₅ ClO ₂	109.5
C ₂ H ₅ ONa	68		0	C ₂ H ₅ ONa	68
H ₂ O	19		0	H ₂ O	19
NH ₃ O	33		0	NH ₃ O	33
H ₂ O ₂	36	HO ₂	33	H ₃	3
Total		Ibuprofen		Waste products	
C ₂₀ H ₂₂ NO ₄ CINa	514.5	C ₁₃ H ₁₈ O ₂	206	C ₇ H ₂ NO ₃ CINa	308.5

40% Atom economy in the Boots' synthesis of ibuprofen

Reagent		Used in ibuprofen		Unused in ibuprofen	
Formula	Mr	Formula	Mr	Formula	Mr
C ₁₀ H ₁₄	134	C ₁₀ H ₁₃	133	H	1
C ₄ H ₈ O ₃	102	C ₂ H ₃ O	43	C ₂ H ₃ O ₂	59
H ₂	2	H ₂	2		0
CO	28	CO	0		0
Total		Ibuprofen		Waste products	
C ₁₅ H ₂₂ O ₄	266	C ₁₃ H ₁₈ O ₂	206	C ₂ H ₄ O ₂	60

77% Atom economy in the green synthesis of ibuprofen

<http://www.rsc.org/education/teachers/learnnet/green/ibuprofen/home.htm>

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Dimethylcarbonate: an alternative green methylating reagent

CH₃Br

H₃CO-S(=O)-OCH₃

Toxic!!

100% NON-TOXIC

Dimethylcarbonate

H₃CO-C(=O)-OCH₃

Ibuprofen

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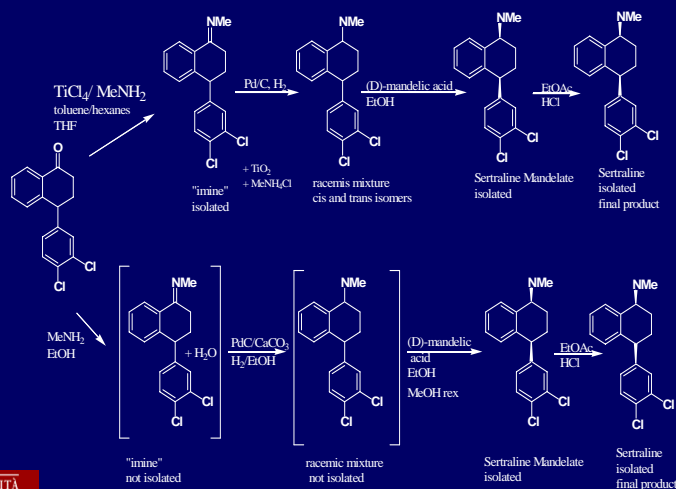
Redesign of the Sertraline Process

- ◆ Sertraline: active ingredient in Zoloft (Pfizer).
- ◆ In 2007, it was the most prescribed antidepressant on the U.S. retail market, with 29,652,000 prescriptions
- ◆ Combined process
 - Doubled yield
 - Ethanol replaced CH_2Cl_2 , THF, toluene, hexane
 - Eliminated use of 140 metric tons/year TiCl_4
 - Eliminated 150 metric tons/year 35% HCl




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Redesign of the Sertraline Process




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Alternative Synthesis of Cytovene

- ◆ antiviral agent used in the treatment of cytomegalovirus (CMV) retinitis infections
- ◆ AIDS and solid-tissue transplant patients
- ◆ Improved synthesis
 - reduced chemical processing steps from 6 to 2
 - reduced number of reagents and intermediates from 22 to 11
 - eliminated 1.12 million kg/year liquid waste
 - eliminated 25,300 kg/year solid waste
 - increased overall yield by 25%




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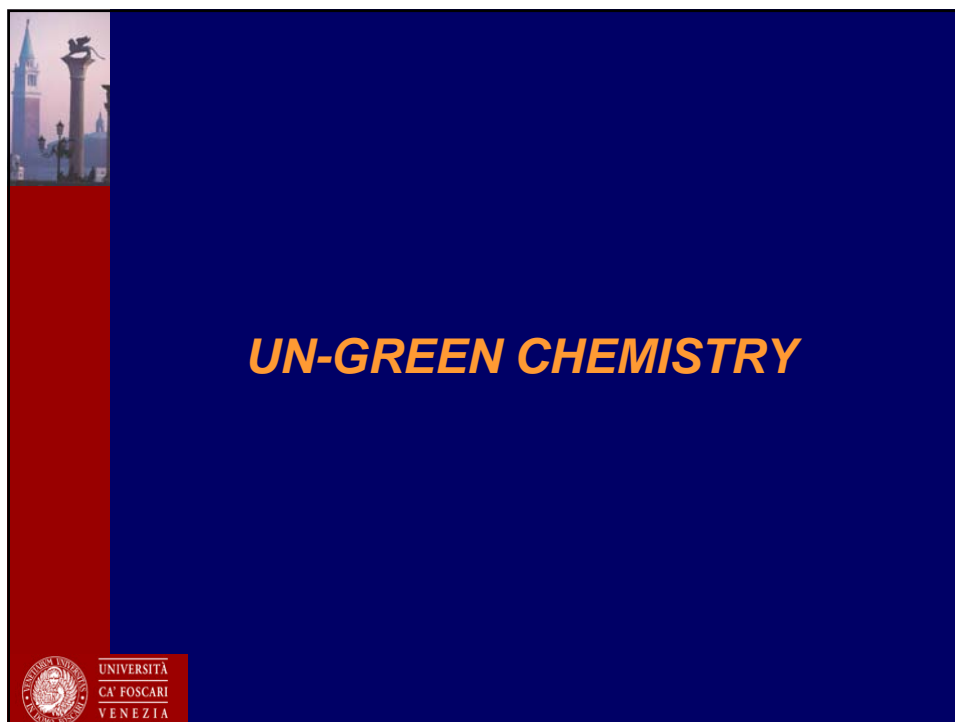
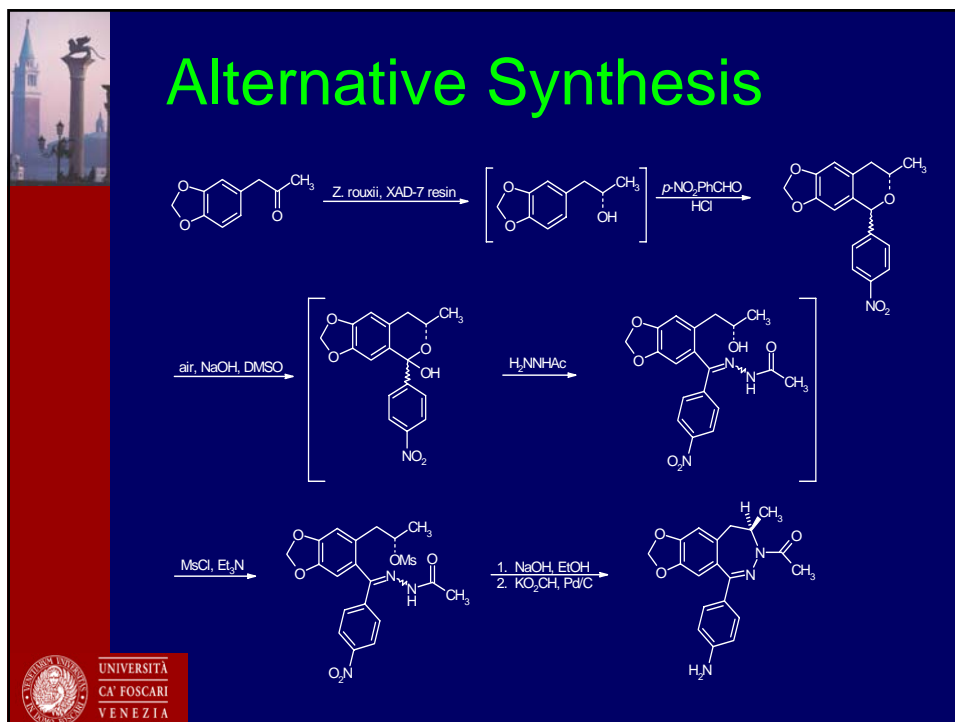


Alternative Synthesis

- ◆ Improved synthesis of a central nervous system compound (Eli Lilly & Co)
 - interdisciplinary approach, combining chemistry, microbiology, and engineering
- ◆ For every 100 kg product,
 - 300 kg chromium waste eliminated
 - 34,000 liters solvent eliminated



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SEVESO: DIOXIN CONTAMINATION

clorofene (a disinfectant)

2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Evacuazione della popolazione di Seveso
Il 27 luglio 1976 presso la ditta ICMESA di Melegnano, in provincia di Milano, si verificò una fuoriuscita di gas tossici contenente dioxina. Fu necessario ordinare la temporanea evacuazione della popolazione di Seveso, un centro situato nei pressi degli stabilimenti.

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Dichloro-Diphenyl-Trichloroethane

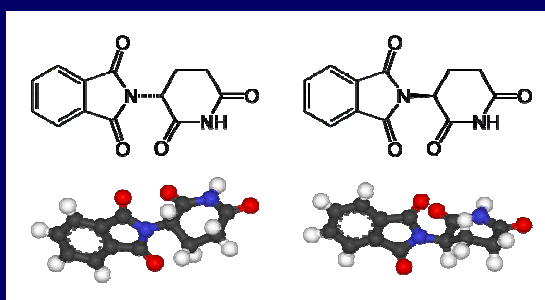
DDT

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Thalidomide

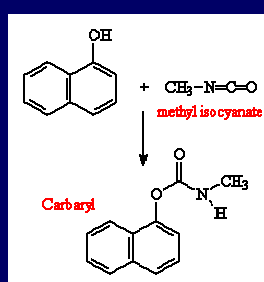
Thalidomide was used by pregnant women in Europe to lessen the effects of morning sickness'. About 10000 children were born with acute birth defects, in many cases in the form of missing or deformed limbs.

One enantiomer is active as a drug, the opposite one is teratogenic.



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BHOPAL disaster



December 3rd 1984, the Union Carbide plant in Bhopal (India) discharged 42 tons of methyl isocyanate into the atmosphere exposing over 500,000 people.



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13 November 2005
China National Petroleum Co. in Jilin.





An explosion dumped in the Songhua river 100 tons of benzene, along with 2 ton. of nitrobenzene, aniline, and xylene.


13 November: accident
24 November: in Harbin drinking water supplies are closed



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Paracelsus



Paracelsus who was born Philippus Aureolus (1493-1541) took the pseudonym of Theophrastus Bombastus Von Hohenheim. He became a renown physician, alchemist and occultist.

“Everything is toxic.
It is simply depends
on the dose.”

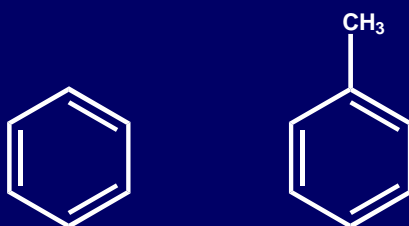


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Solvents

Green chemistry principle no. 8: Use safer solvents and reaction conditions.

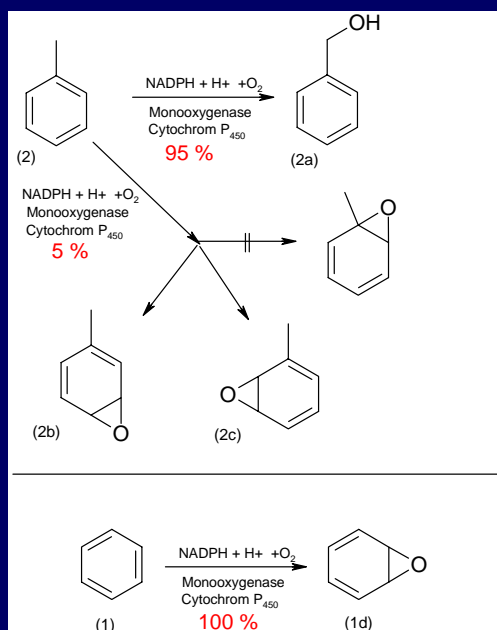
An old example: benzene vs. toluene:



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toluene

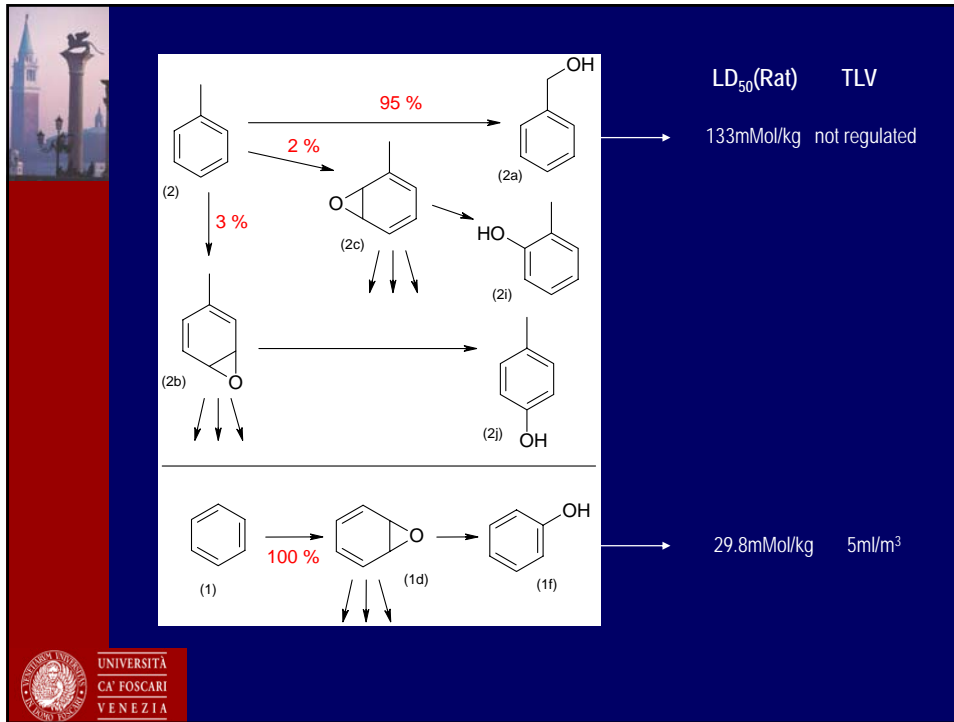
Phase I of
biotransformation
of toluene
and benzene
within
mooxidase
system
in Cytochrom
P450



benzene



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Green solvents in place of toxic and VOC-generating ones

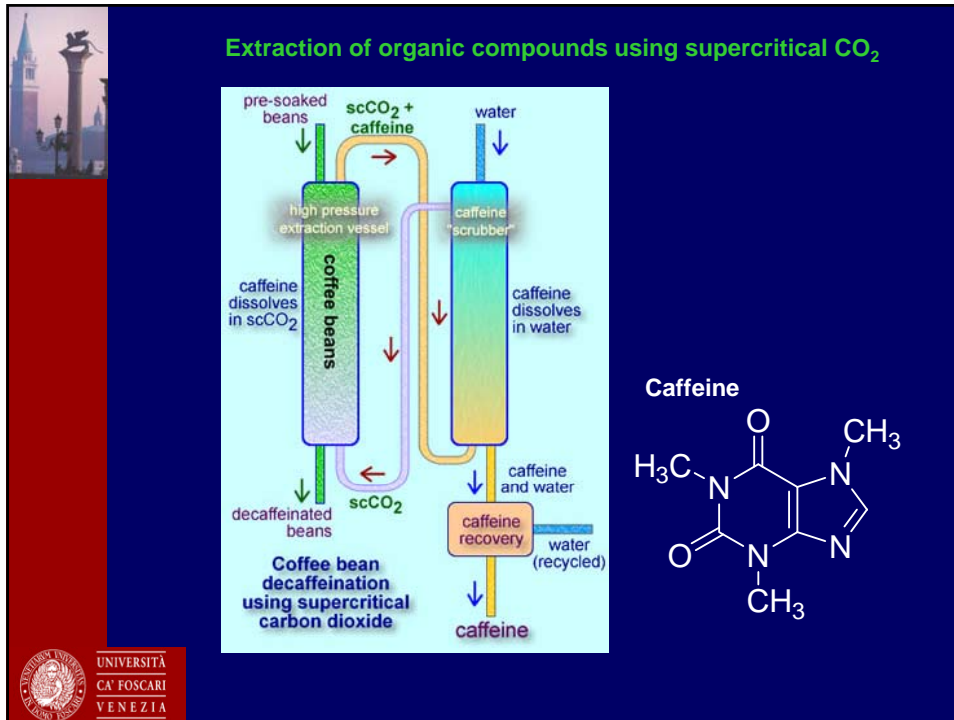
An example: supercritical CO₂

gas

liquid

supercritical

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Green solvents in place of toxic and VOC-generating ones

Another example: ionic liquids

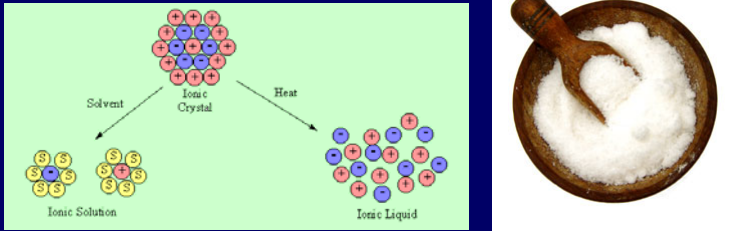



Table salt NaCl
mp = 801 °C

- Made entirely of ions
- Molten at or around room temperature (mp < 100 °C)
- No vapour pressure

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Ionic liquids can be designed to be soluble “as needed”.



A triphasic organic - ionic liquid – aqueous system

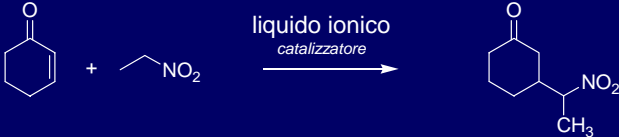
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The best solvent is no solvent

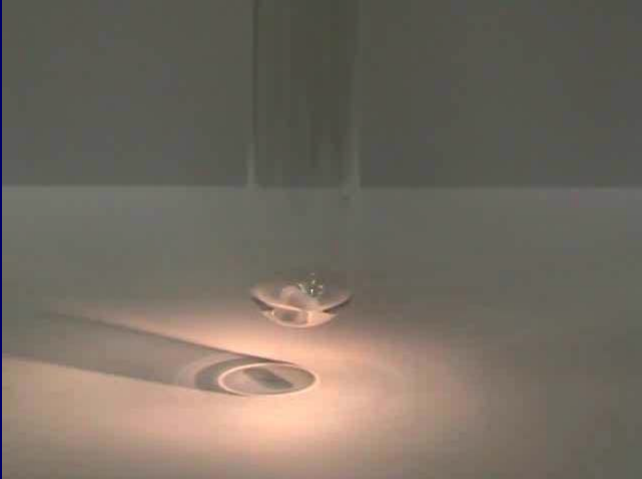


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An example of solventless synthesis with an ionic liquid catalyst

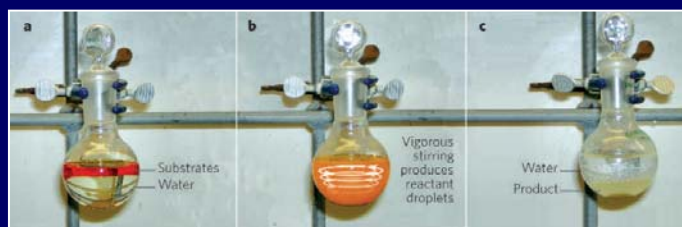


C1=CCCCC1=O + CCO[N+](=O)[O-] $\xrightarrow{\text{liquido ionico catalizzatore}}$ CC1(C)CCCC1=O



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What about water?



“On water” reactions by B. Sharpless (Nobel Prize 2001)

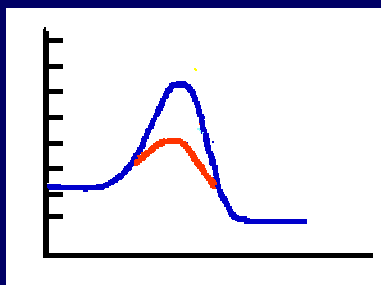


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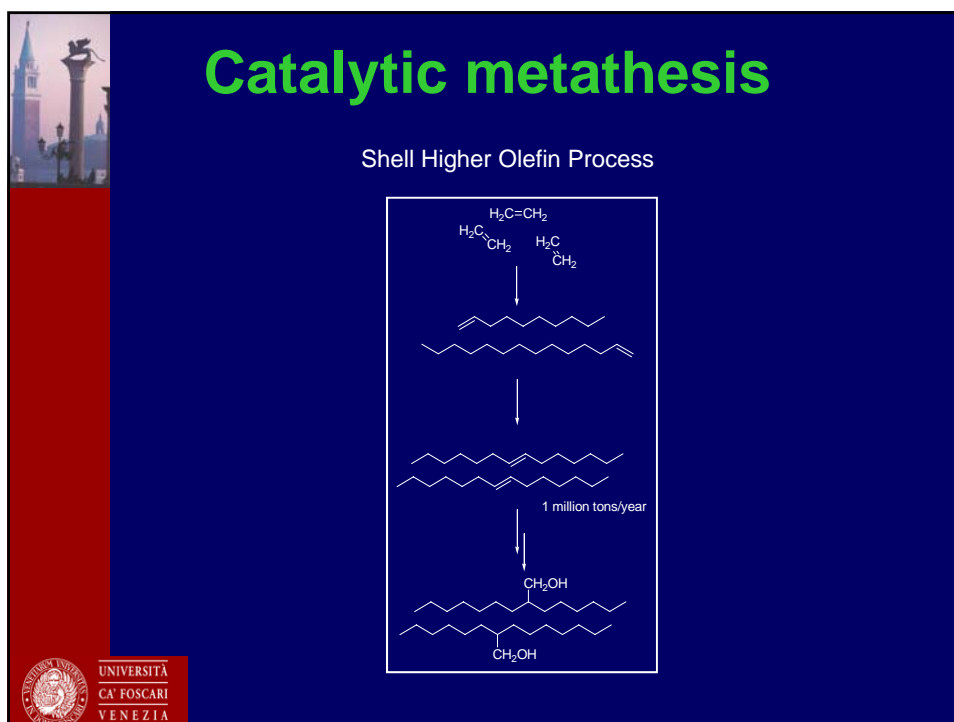
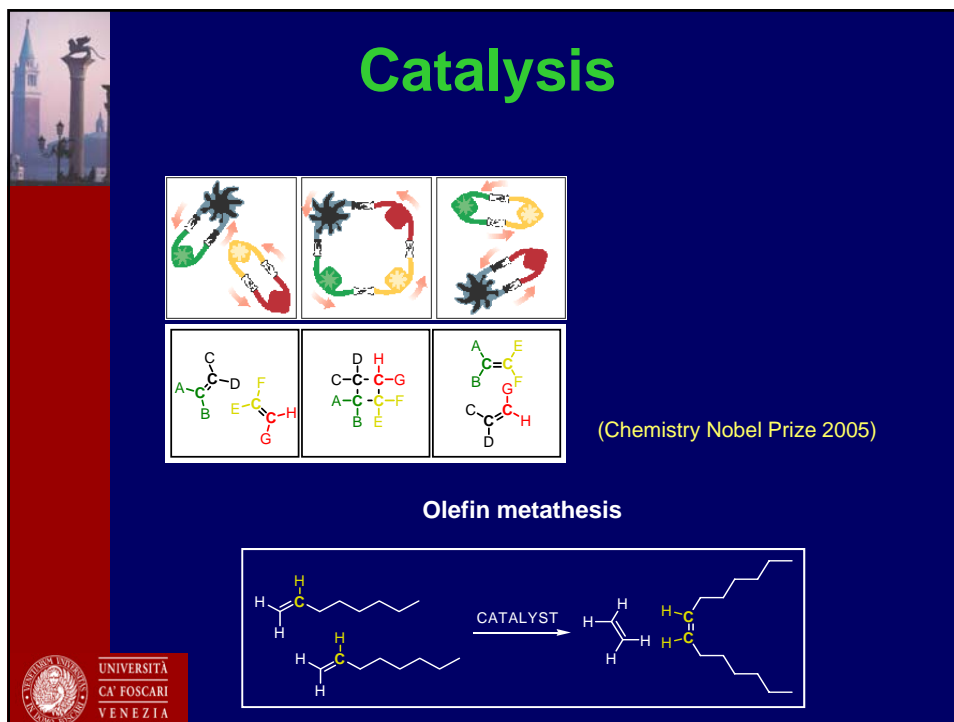
Catalysis

Green chemistry principle no. 5: Use catalysis.

A **CATALYST** IS SOMETHING THAT MAKES A CHEMICAL REACTION GO FASTER, WITHOUT BEING CONSUMED IN THE PROCESS



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Enantioselective catalysis

Particularly in pharmaceutical chemistry, drugs are often chiral, and only one of the enantiomers is active.

In the best case the other enantiomer is useless (50% waste).
In the worst case its toxic (remember thalidomide).

Why get **one** for the price of **two**?

Of the active enantiomer only 50% is used in the body on average.

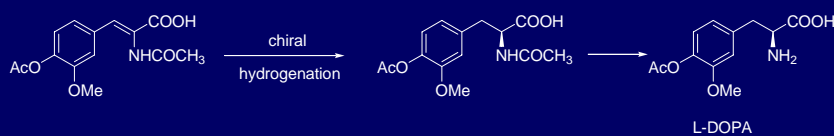
So we might be producing **four** times more active ingredient than needed!



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Step 1: Enantioselective catalysis


Example: Monsanto's L-DOPA process



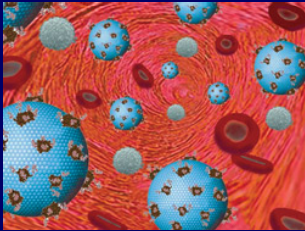
95 % ee
20000 tons




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Step 2: Targeted delivery

By coupling enantioselective catalysis with targeted drug delivery 100% of the drug is used.



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So: why do we need Green Chemistry?

Answer: to allow future generations to live at least as well as us, and to live better and save money in the process.

We would need approximately 3.5 earths if all the 6.6 billion people lived with our standards.



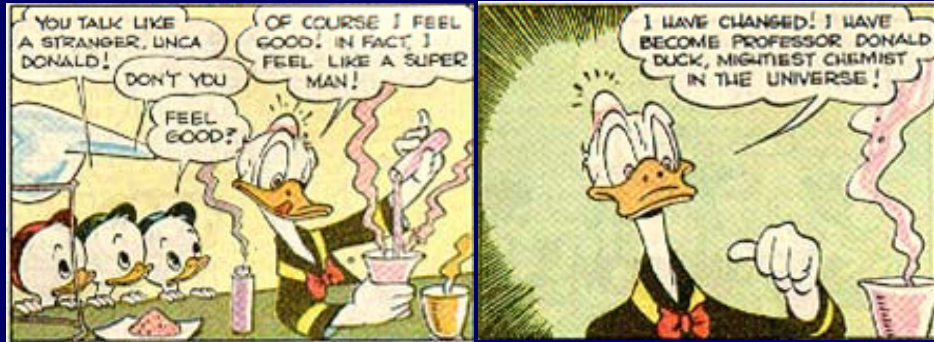





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<http://sustainability.publicradio.org/consumerconsequences/>

Thank you!



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