ENVIRONMENTAL ASPECTS

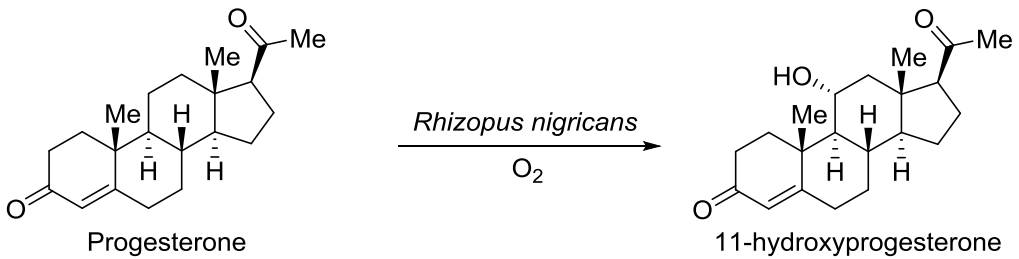
Petr Beňovský

GREEN CHEMISTRY, SUSTAINABLE CHEMISTRY

The design of chemical products and processes that reduce or eliminate the use or generation of hazardous substancese;

Systematically pursued from the 90s of the 20th century;

1952 – Upjohn – the synthesis of cortisone – just 10 step synthesis of cortisone using fermentation for a key hydroxylation reaction at position 11 of progesterone



GREEN CHEMISTRY METRICS

Atom Economy

Characterizes the “greeness“ of a synthetic process by calculating the number of atoms from all of the reactants that make it into the final product;
Does not address the hazard, reaction yield, stoichiometry, the amount of solvent, …

% Atom Economy = Molecular weight of the product / Molecular weight of all products x 100

Trost, B. *Science 254*, 1471 (**1991**)

GREEN CHEMISTRY METRICS

Environmental Factor, *E*-Factor

The ratio of **waste** over **product**

It is usual to calculate *E*-factor without process water

E-Factor = the amount of waste (kg) / the amount of the product (kg)

Industry Segment	Volume (t/y)	*E*-Factor
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 - 10^2	25 - 100

GREEN CHEMISTRY METRICS

Reaction Mass Efficiency (RME)

The idea is to keep the simplicity of the atom economy concept, but avoid the high impact of solvents which are found in the *E*-factor; RME takes into account reaction yield, stoichiometry and the use of catalysts or other reagents;

% Reaction Mass Efficiency = Mass of desired product / Mass of all reactants x 100

GREEN CHEMISTRY METRICS

Process Mass Intensity (PMI)

PMI measures the mass of materials used to make 1 kg of the API

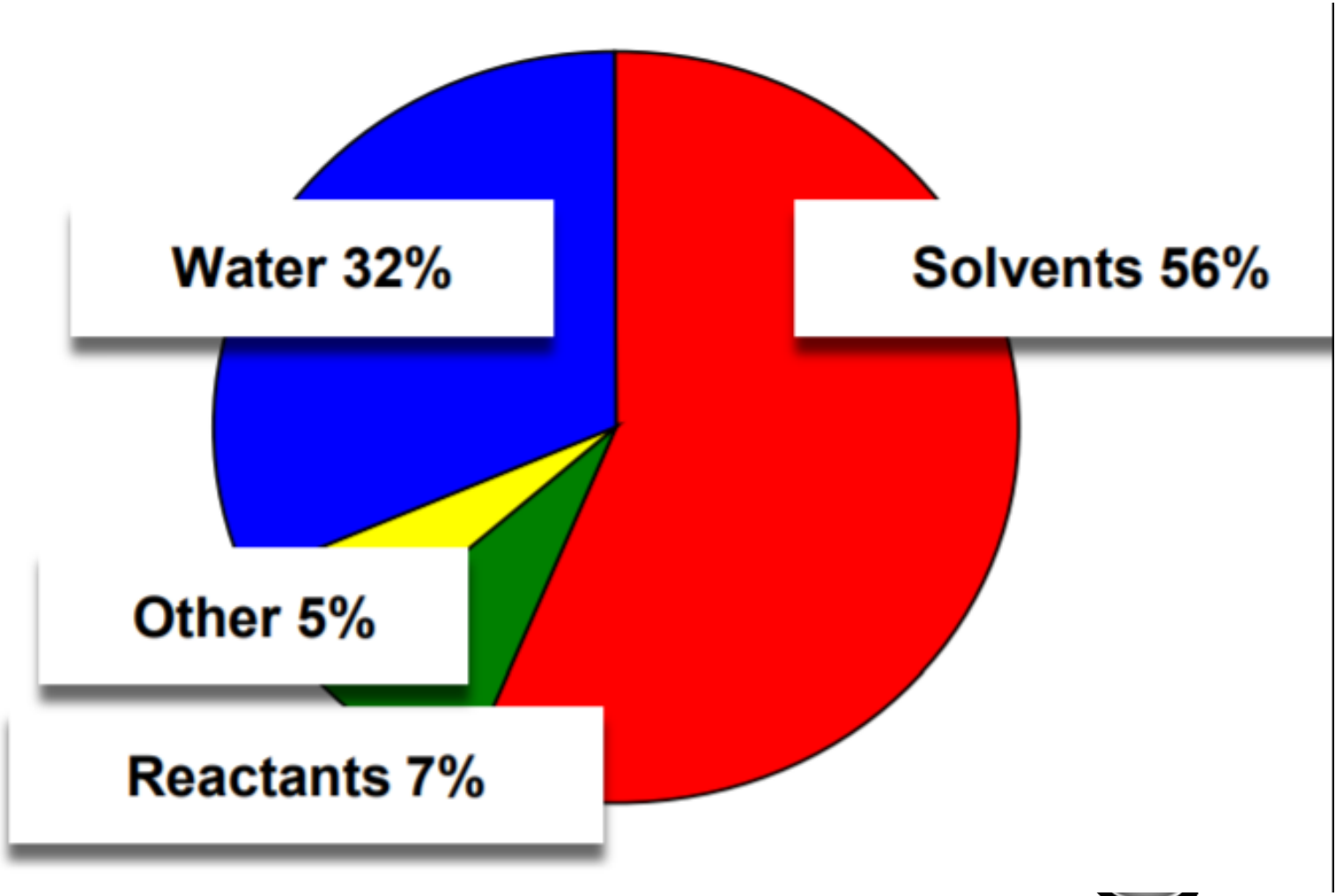
% Process Mass Intensity = Mass of all material used to make the product (kg) / Mass of product (kg) x100

Allows companies to benchmark and quantify improvements to the efficiency and sustainability of their production

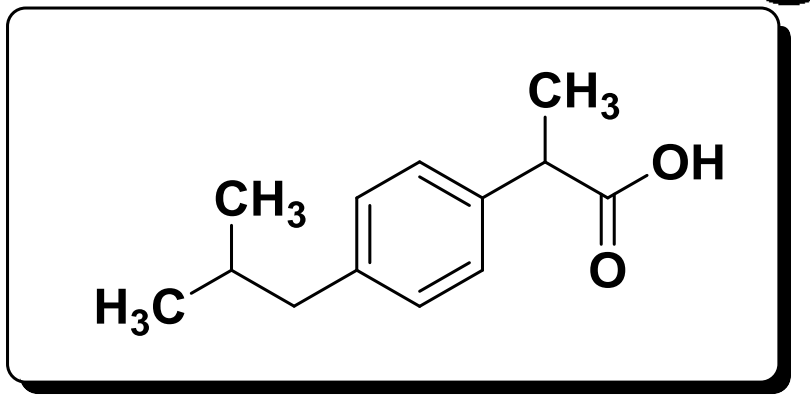
Reasonable target of a single synthetic step is any value between 10 and 40

GREEN CHEMISTRY METRICS

- Process Mass Intensity (PMI)



IBUPROFEN EXAMPLE

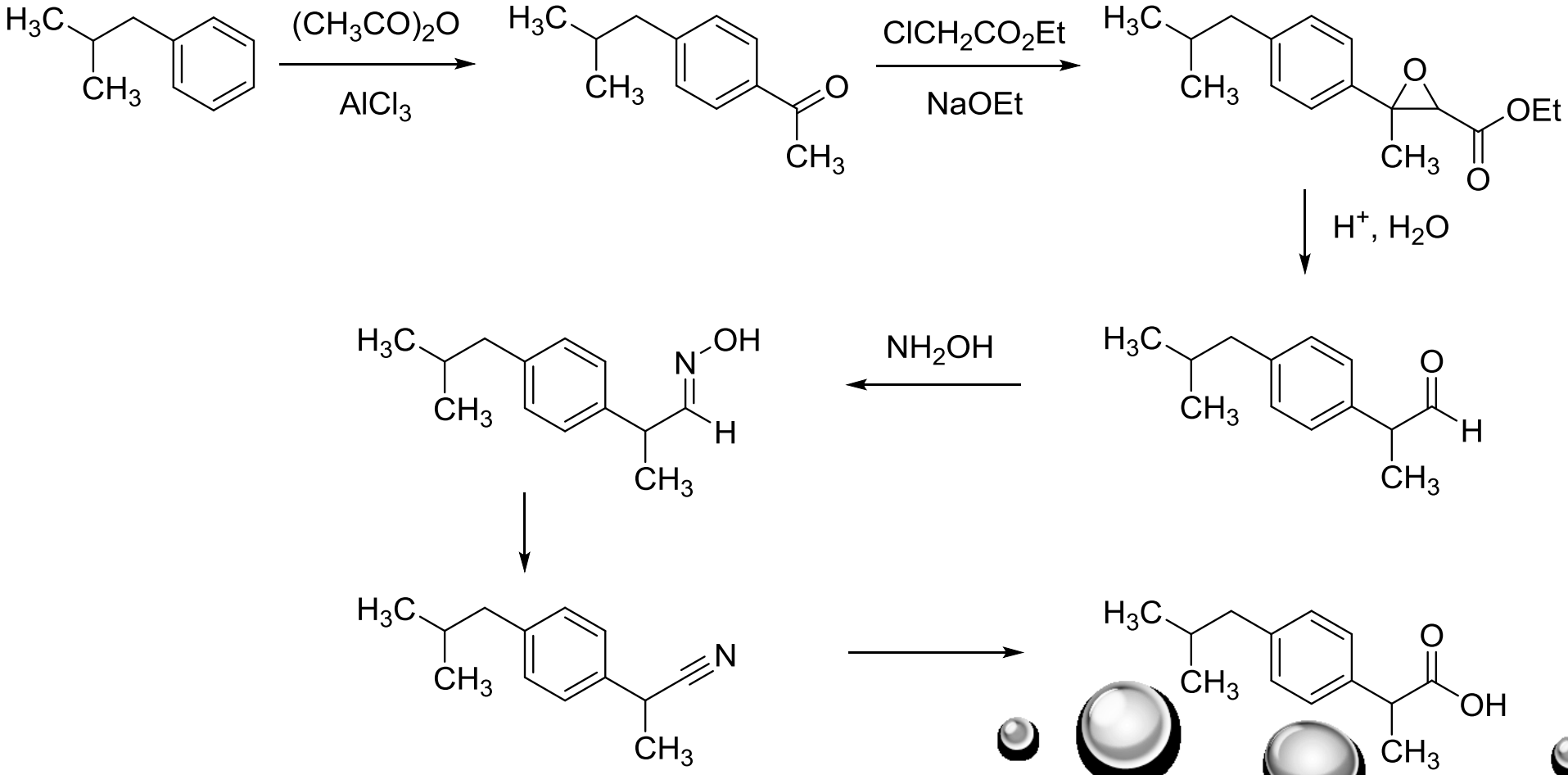


Originator – Boots Group (1960s)
Original name – Brufen (Aspro, Panadol, Nurofen)
Generic names – Motrin, Advil, Nuprin, Ibalgin

Sold as the racemate despite the fact that (*S*)-(+)-Ibuprofen is the active form;
Fast epimerization *in vivo*

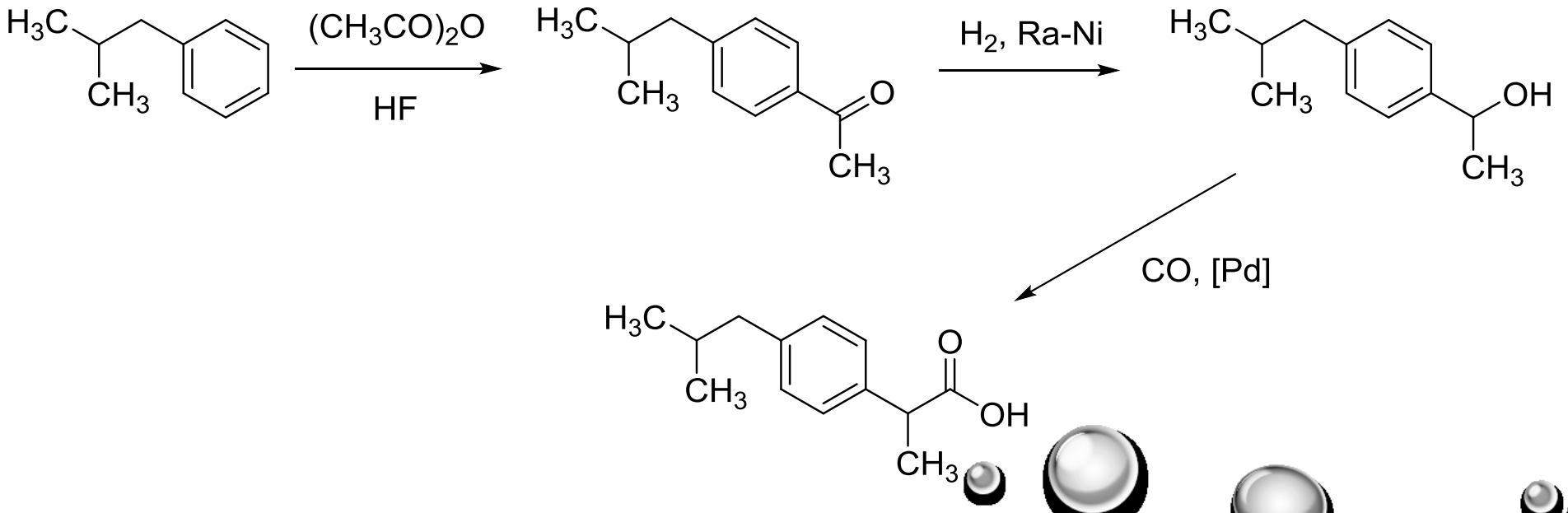
IBUPROFEN EXAMPLE

Original synthesis – overall yield 40%
Annual production in Great Britain 3000 tones



IBUPROFEN EXAMPLE

New synthesis – BHC company (1990)
Overall yield 77%
Presidential Green Chemistry Challenge Greener Synthetic Pathways Award v roce 1997



BIOCATALYSIS

Myths of biocatalysis:

- Expensive
- Unstable
- Not readily available
- Sensitive to reaction conditions
- Not good enough or wrong selectivity
- Give poor volumetric productivity
- Difficult work-up

Nowadays, all of them are mostly wrong

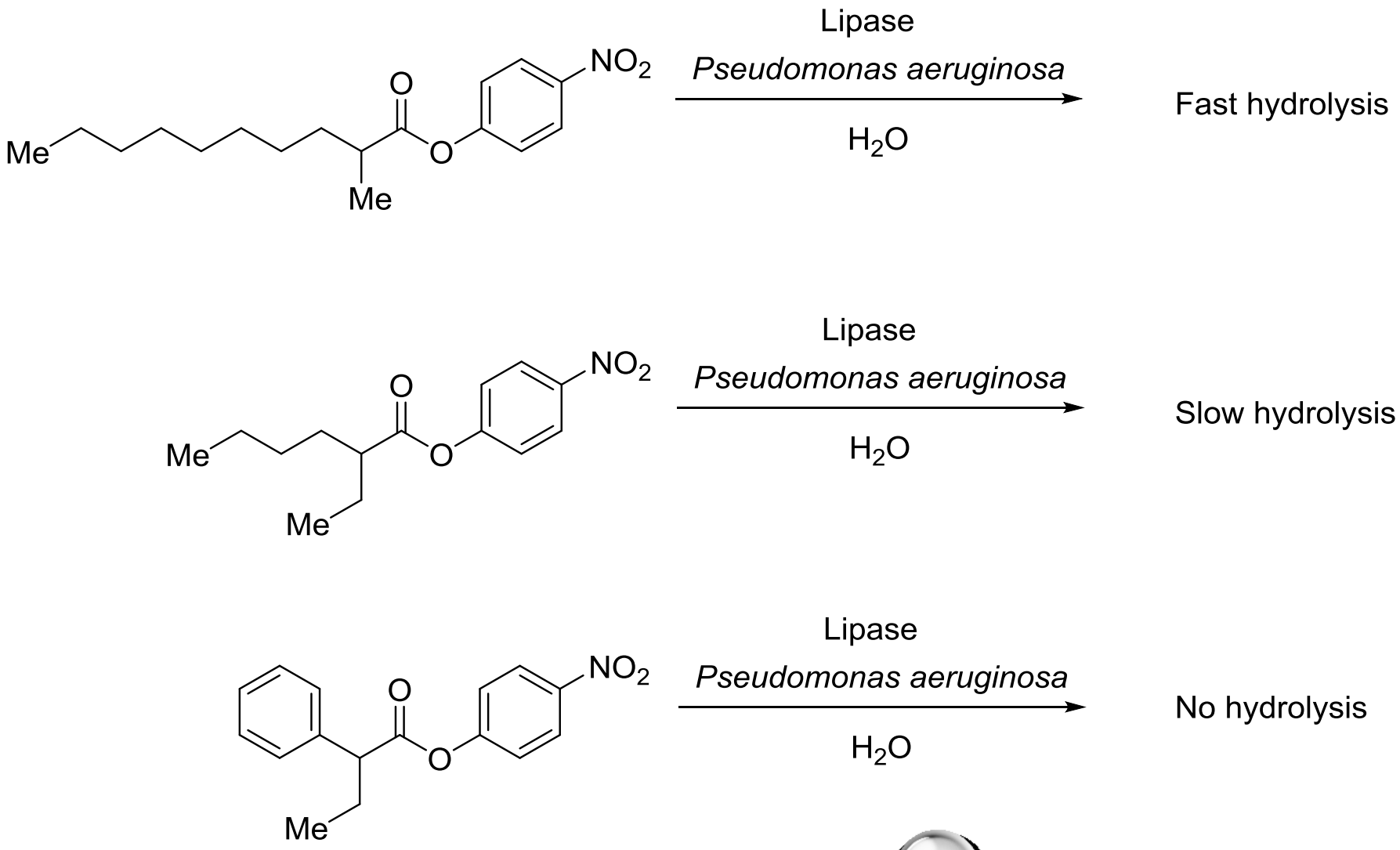
BIOCATALYSIS

2018 – Nobel Prize for directed evolution of enzymes (Frances H. Arnold, George P. Smith)

Iterative change of amino acids in the enzyme until the desired property (acitivity, stability, selectivity) is achieved;

Directed evolution mimics the processes of Darwinian evolution in a test tube

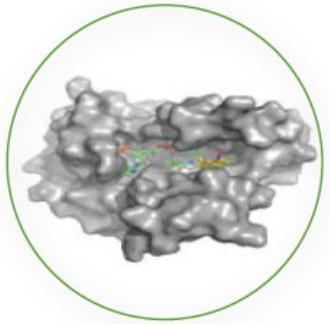
BIOCATALYSIS



Bornscheuer, U.T. *et al Angew.Chem.Int.Ed. 43*, 6032 (**2004**)

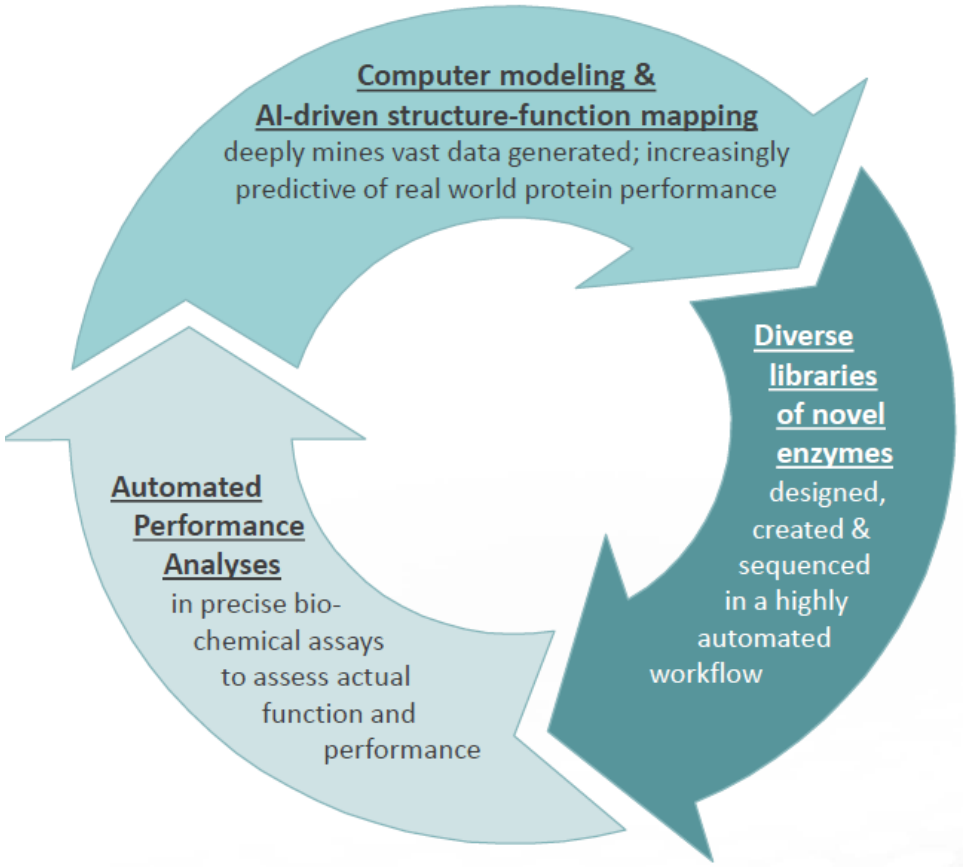
BIOCATALYSIS

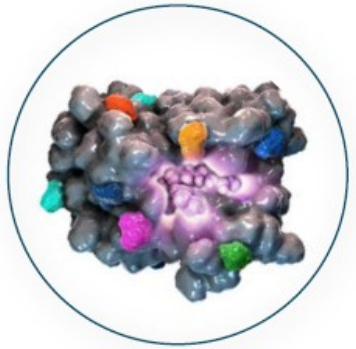
CODEXIS



Starting Protein

from nature, Codexis libraries, or *in silico* inspired





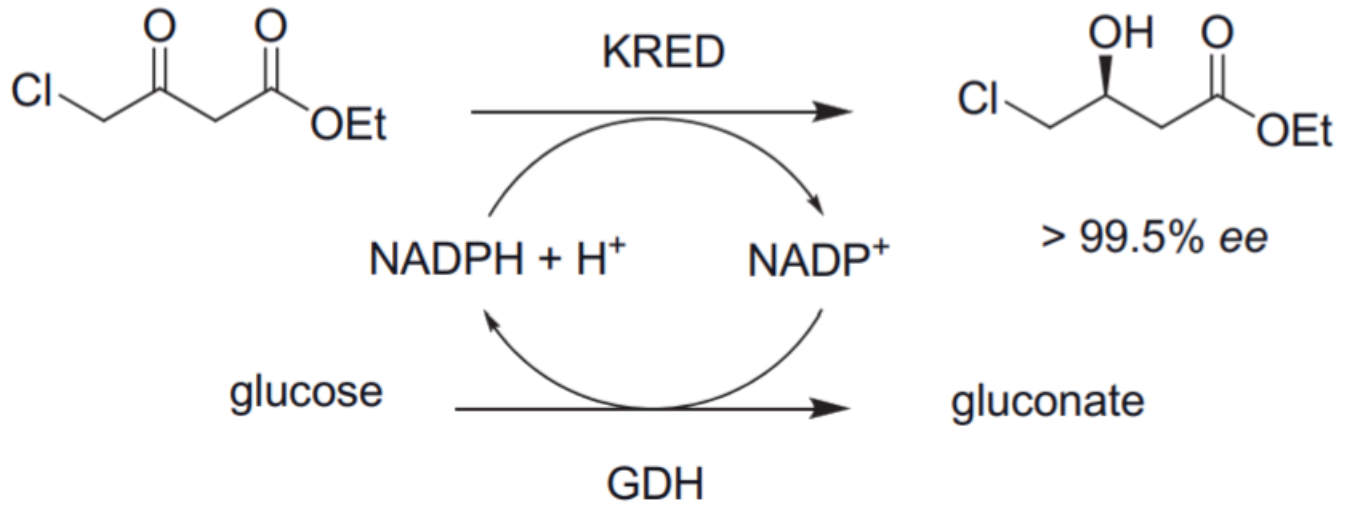
CodeEvolver® Engineered Protein

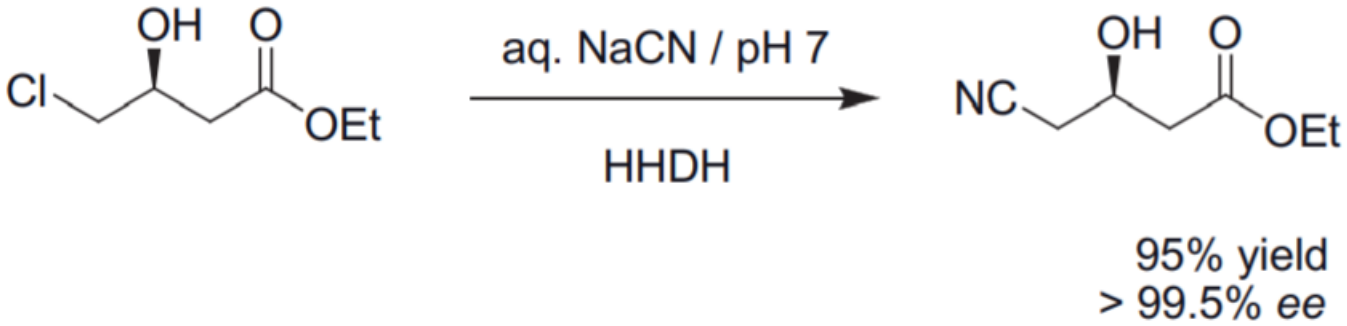
tailored for specific end use application

https://www.youtube.com/watch?v=up5QUdTLsBU&feature=youtu.be

BIOCATALYSIS

CODEXIS





KRED = ketoreductase
GDH = glucose dehydrogenase
HHDH = halohydrin dehalogenase

BIOCATALYSIS

CODEXIS

Atorvastatin (Lipitor®)
2006 – Presidential Green Chemistry Challenge Award
Substantial waste reduction
Overall yield > 90%
Purity > 98%
ee > 99.9%
Low loading of enzymes
Solvent recycling
E-Factor is 5.8 (without used water)
E-Factor is 18 (with used water)

GREEN CHEMISTRY, SUSTAINABLE CHEMISTRY

Ryoji Noyori

**“Green chemistry is not just a mere catch phrase;
it is the key to the survival of mankind“**