# ENVIRONMENTAL ASPECTS

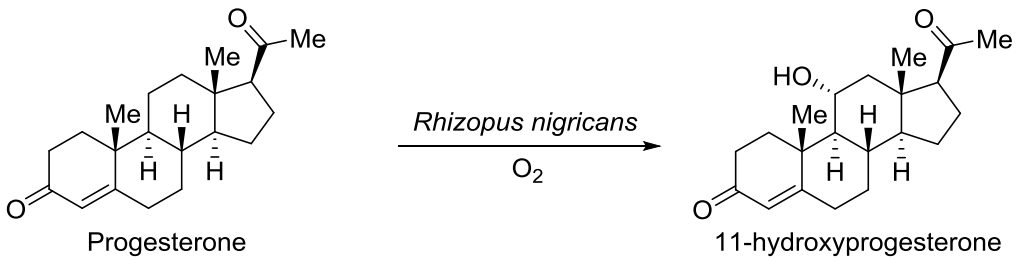
Petr Beňovský

# 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 20$^{th}$ 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

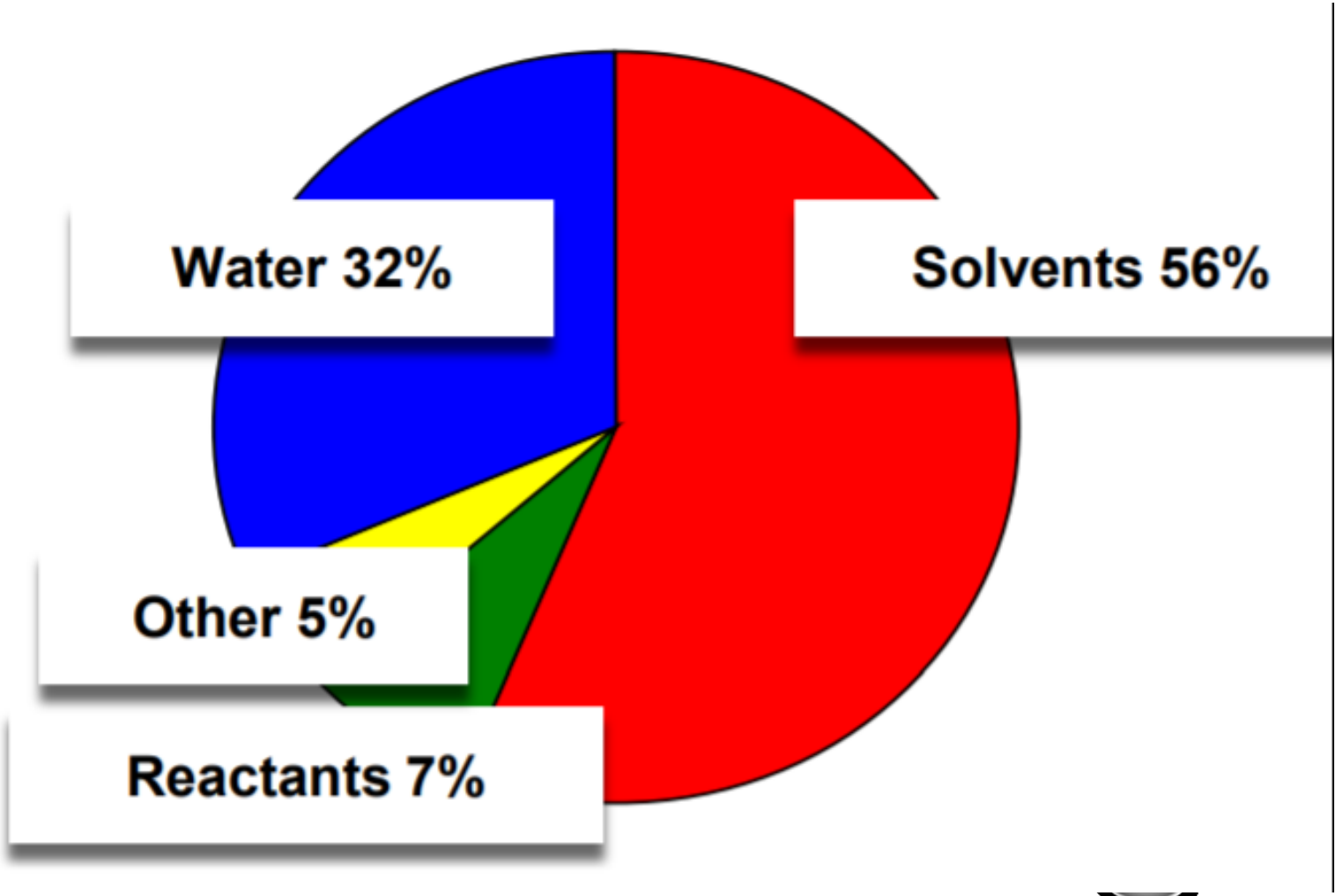
% Process Mass Intensity = Mass of all material used to make the product (kg) / Mass of product (kg) x100

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

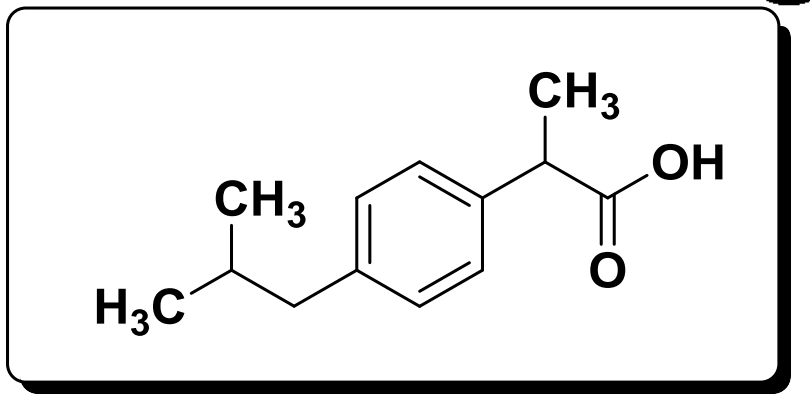
Reasonable target of a single synthetic step is any value between 10 and 40

# GREEN CHEMISTRY METRICS

- Process Mass Intensity (PMI)



# IBUPROFEN EXAMPLE

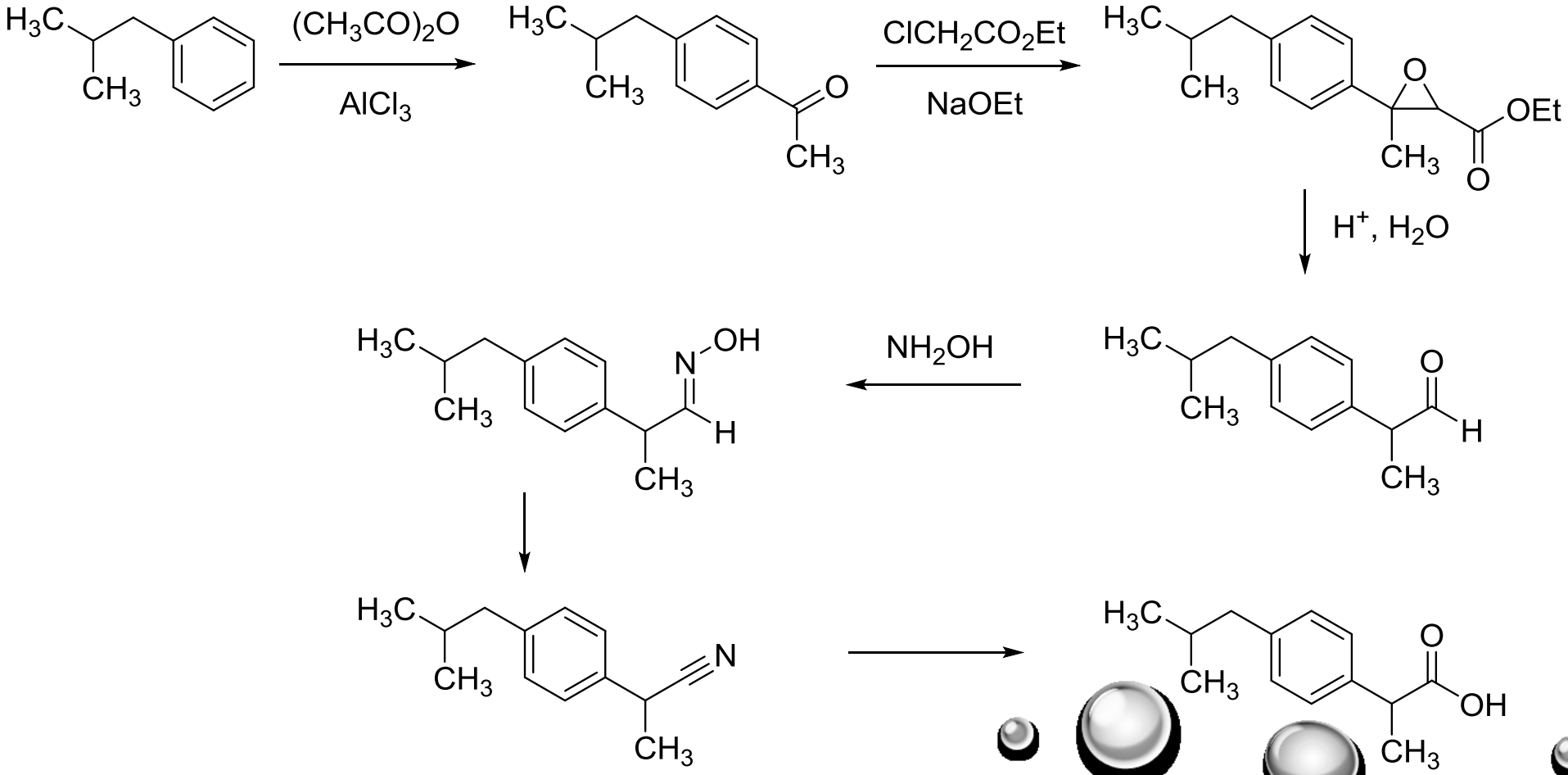



Originator – Boots Group (1960s)
Original name – Brufen (Aspro, Panadol, Nurofen)
Generic names – Motrin, Advil, Nuprin, Ibalgin

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

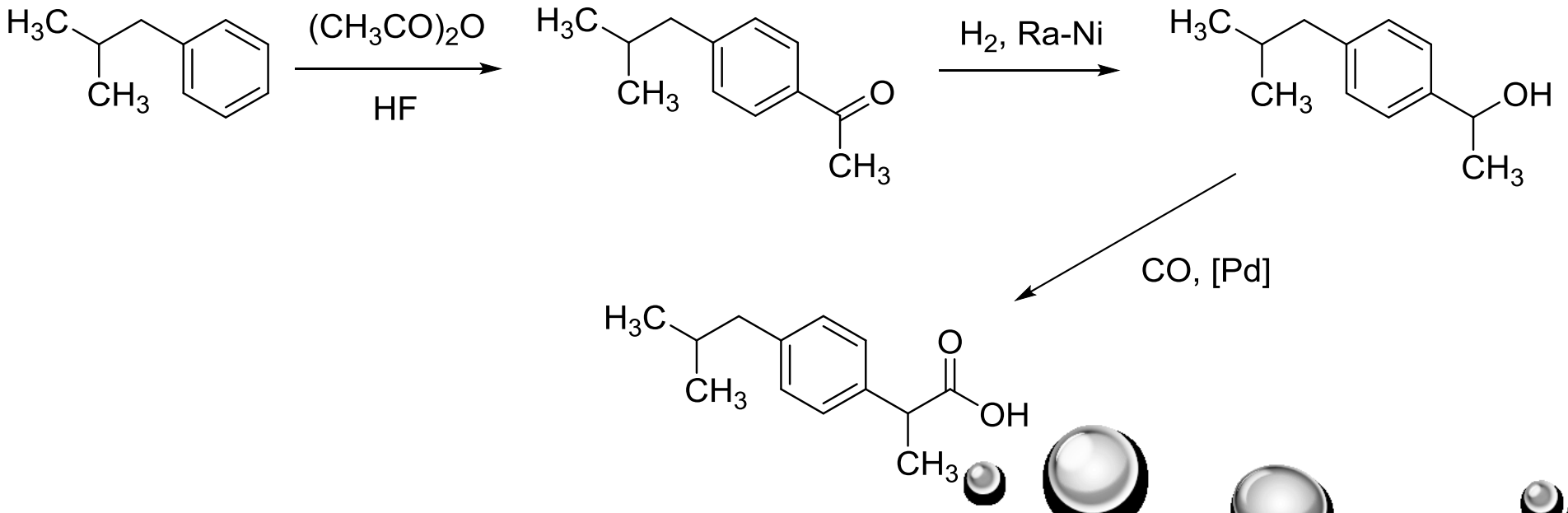
# IBUPROFEN EXAMPLE

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



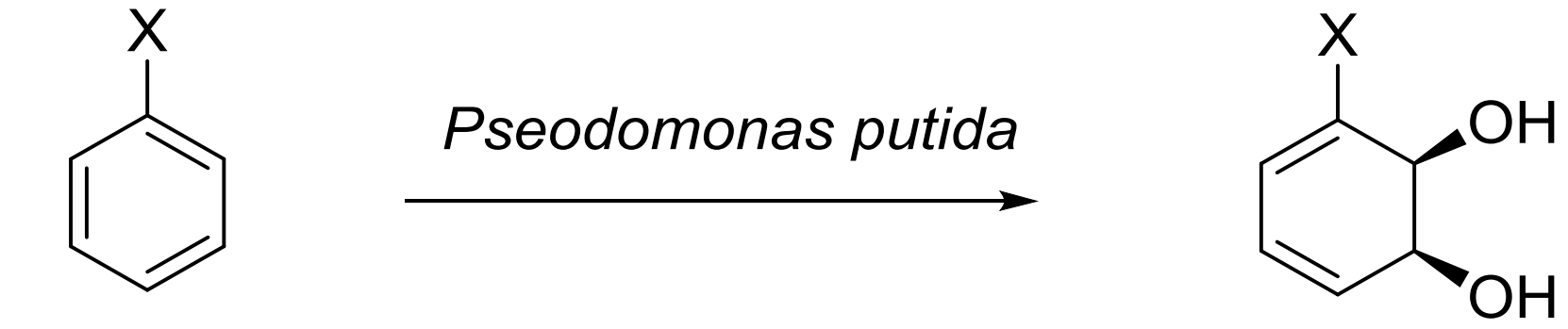
# BIOCATALYSIS

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




X = Cl, Br

Microbial oxidation using bacterial dioxygenase

Hudlicky, T. *et al J.Am.Chem.Soc. 116*, 5108 (**1994**)

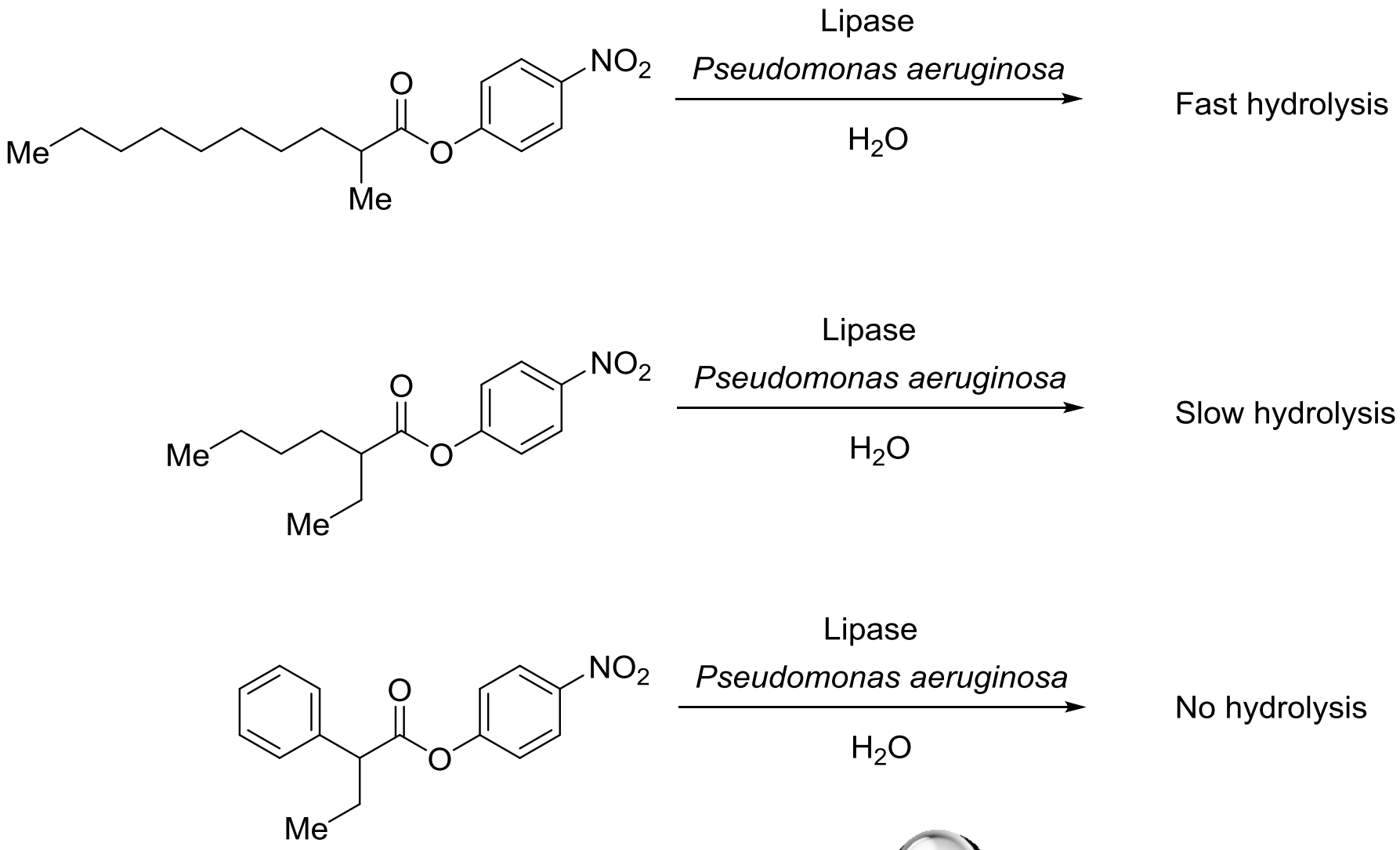
# BIOCATALYSIS

2018 – Nobel Prize for directed evolution of enzymes (Frances H. Arnold)

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

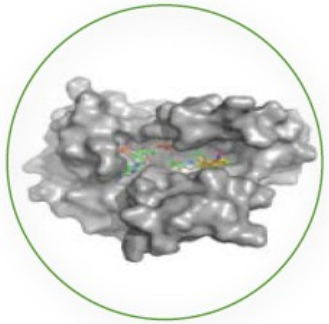
# BIOCATALYSIS




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

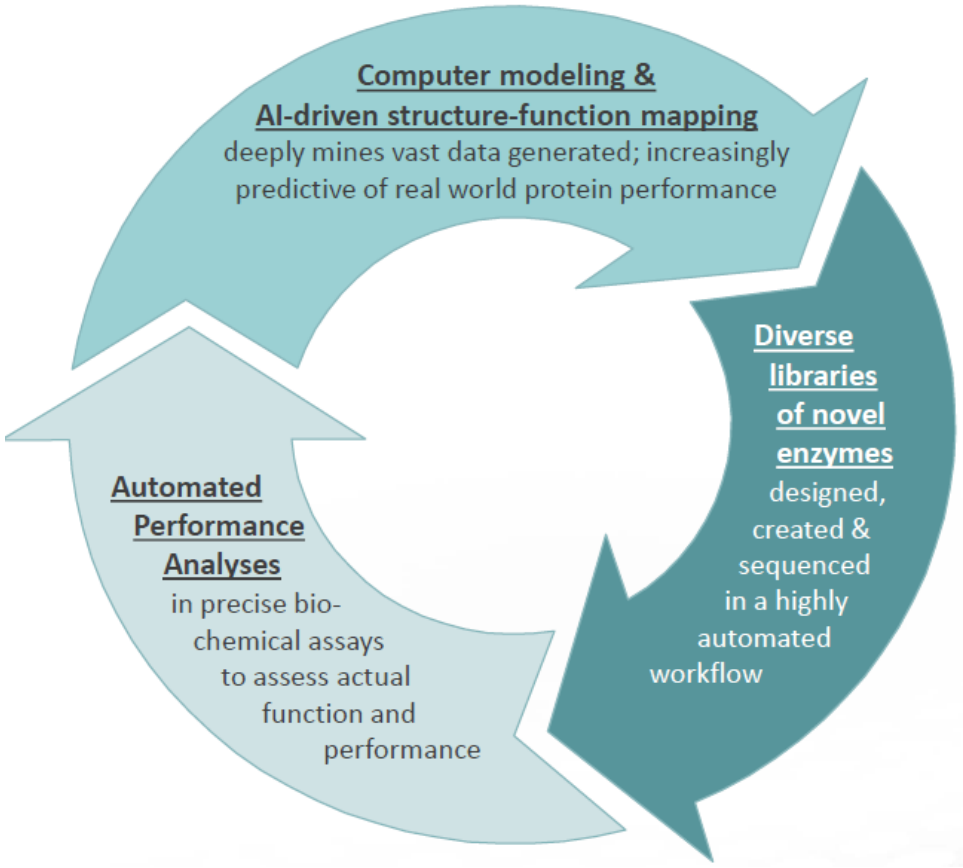
# BIOCATALYSIS

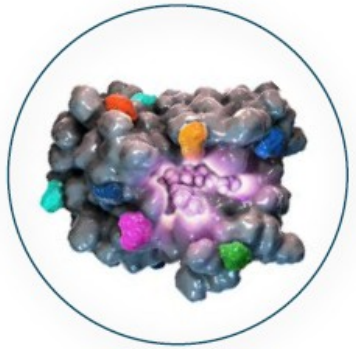
## CODEXIS



**Starting Protein**

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



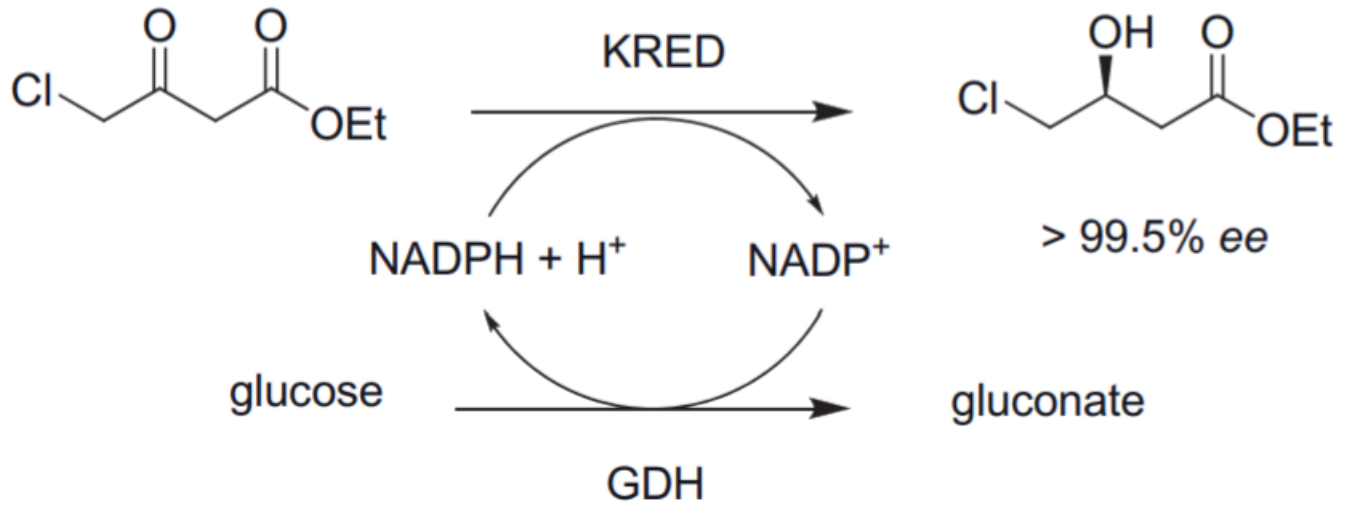
**CodeEvolver® Engineered Protein**

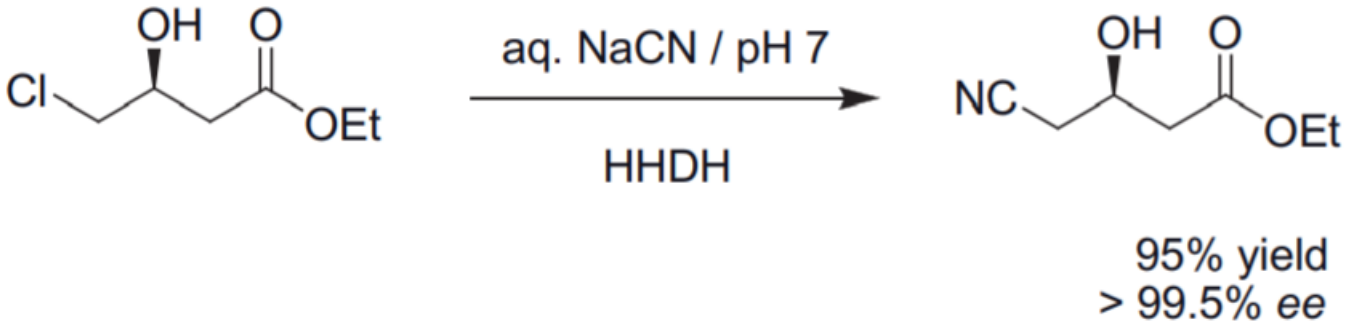
tailored for specific end use application

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

# BIOCATALYSIS

## CODEXIS



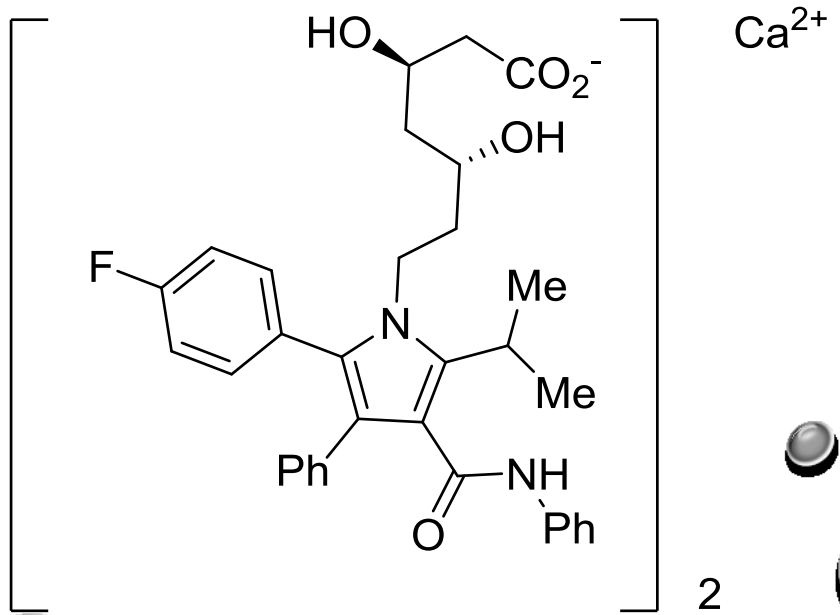




KRED = ketoreductase
GDH = glucose dehydrogenase
HHDH = halohydrin dehalogenase

# 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“**