

**Afscheidsrede prof.dr. R.A. Sheldon
hoogleraar Biokatalyse en Organische Chemie
December 7, 2007**

**'E Factors, Green Chemistry and Catalysis:
Records of the Travelling Chemist'**

Green Chemistry

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

Sustainability

**Meeting the needs of the present generation
without compromising the needs of future
generations to meet their own needs**

is the goal

“What we need is more imagination not more knowledge”

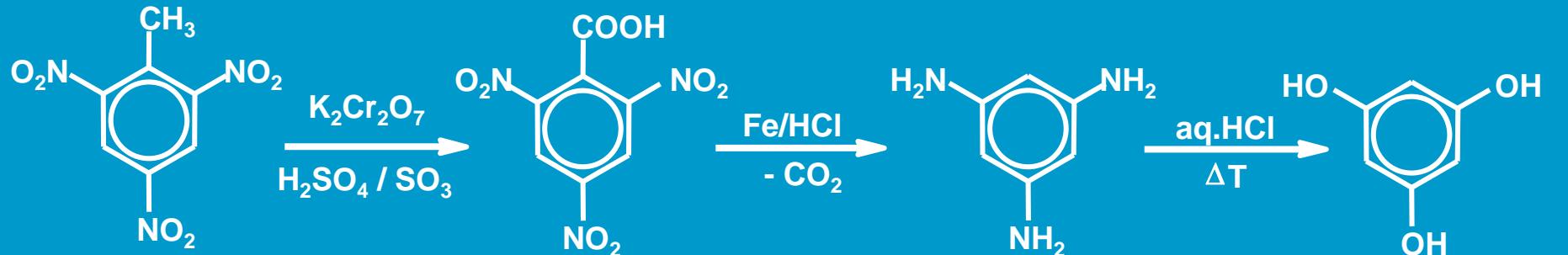
Albert Einstein

Do politicians understand the issues?

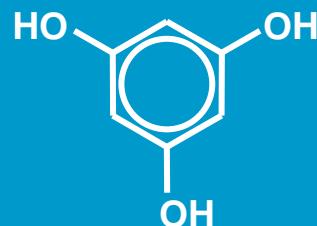
It's not pollution that is the problem it's the impurities in our air and water.

Dan Quayle

Phloroglucinol Synthesis



Ca. 40kg of solid waste per kg phloroglucinol



MW = 126

product

+ $Cr_2(SO_4)_3$ + $2KHSO_4$ + $9FeCl_2$ + $3NH_4Cl$ + CO_2 + $8H_2O$

392 272 1143 160 44 144

byproducts

Atom Utilisation = $126/2282 = \text{ca. } 5\%$

E Factor = ca. 40

“ To measure is to know ” Lord Kelvin

Syn gas utilisation (1983)

Atom for Atom

Oxygen utilisation (1990)



100%



44%

Oxidant

H₂O₂

% Active O

47

t-BuOOH

18

CH₃COOOH

22

NaOCl

22

KIO₄

Byproduct

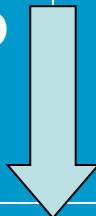
H₂O

t-BuOH

CH₃COOH

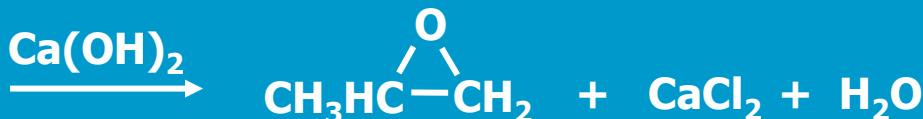
NaCl

KIO₃



Atom utilisation (1991)

1. PO : Chlorohydrin process



25% atom utilisation

2. PO : Catalytic Oxidation



76% atom utilisation

See Chem. Eng. Progr. 1991, 87(12), 11

See also Trost, Science, 1991, 254, 1471

E Factors

E Factor = kg waste/kg product

	Tonnage	E Factor
Bulk Chemicals	$10^4\text{-}10^6$	<1 - 5
Fine chemical Industry	$10^2\text{-}10^4$	5 - >50
Pharmaceutical Industry	$10\text{-}10^3$	25 - >10

“Another aspect of process development mentioned by all pharmaceutical process chemists who spoke with C&EN, is the need for determining an E Factor”.

A. N. Thayer, *C&EN*, August 6, 2007, pp.11-19.

Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Volume 9 | Number 12 | December 2007 | Pages 1261–1384

The E Factor: 15 years on

I Factor = 4.19

ISSN 1463-9262

RSC Publishing

Sheldon
The E Factor: fifteen years on
Cozzi and Zoli
Nucleophilic substitution of
ferrocenyl alcohols

Fleckenstein and Plenio
Aqueous cross-coupling
Qi and Jiang
Efficient synthesis of β -oxocarbonyl-
carbamates



1463-9262(2007)9;12;1-R

The E Factor

- Is the actual amount of **all waste** formed in the process, including solvent losses and waste from energy production
(c.f. atom utilisation is a theoretical nr.)
- $E = [\text{raw materials-product}]/[\text{product}]$
- A good way to quickly show (e.g. **to students**) the enormity of the waste problem
- Undergraduate Course : “**Green Chemistry & Sustainable Technology**”

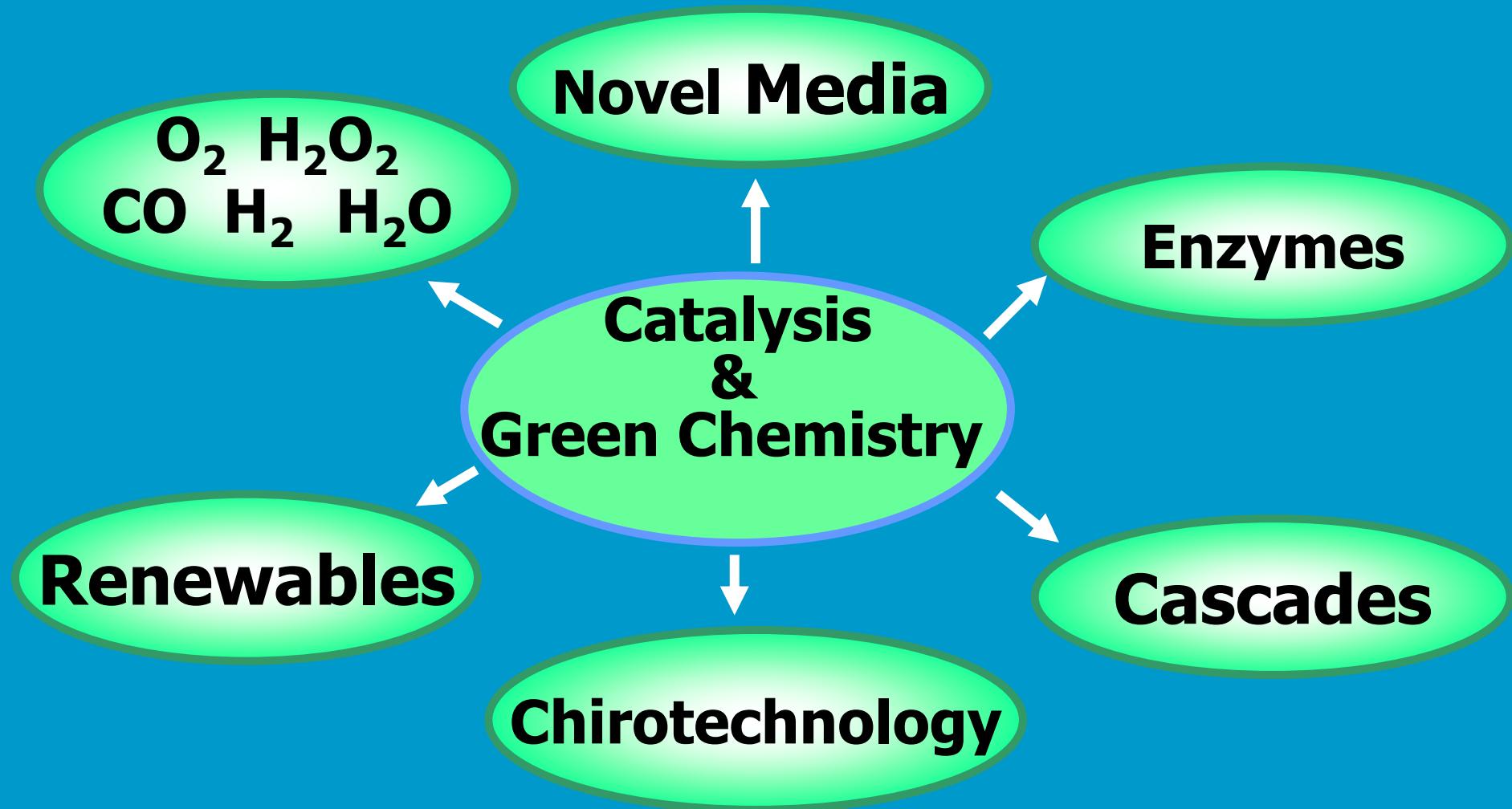
Major Sources of Waste

- STOICHIOMETRIC ACIDS & BASES
- STOICHIOMETRIC OXIDANTS & REDUCTANTS
 - $\text{Na}_2\text{Cr}_2\text{O}_7$, KMnO_4 , MnO_2
 - LiAlH_4 , NaBH_4 , Zn , Fe/HCl
- SOLVENT LOSSES
 - Air emissions & aqueous effluent

The Solution is Catalytic

- Substitution of conventional Bronsted & Lewis acids by recyclable, non-corrosive solid acids e.g zeolites
- Atom efficient catalytic processes:
 - hydration (H_2O) reduction (H_2), oxidation (O_2, H_2O_2)
 - carbonylation (CO), hydroformylation (CO/H_2)
 - amination (NH_3), reductive amination (NH_3 / H_2)
with olefins and (alkyl)aromatics as raw materials
- Alternative reaction media / biphasic catalysis
- Biocatalysis, naturally

Research Themes

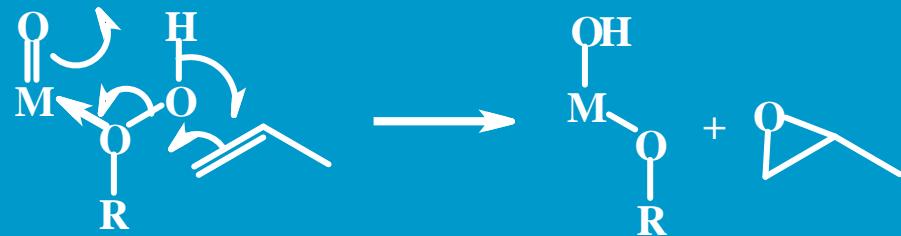


Heterogeneous Catalysis

Shell SMPO process 1973



Peroxometal mechanism 1973



Sheldon and van Doorn, *J.Catal.* 31, 427, 1973

Metal Catalyzed Epoxidation



Headwaters/Evonik 2006

Sheldon, *Rec.Trav.Chim.Pays-Bas*, 92, 253, 1973

Mimoun, Sharpless



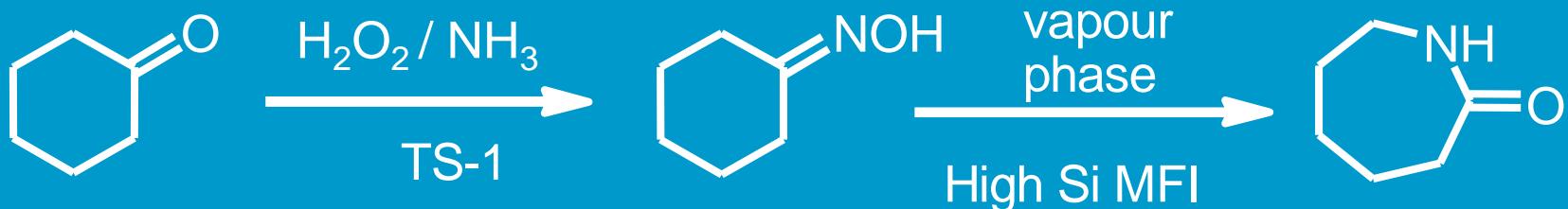
Enichem 1985

Ti-beta, Ti-MCM41, Ti-ITQ, etc
van Bekkum, Corma
Dakka, Sato, LeBars



Redox Molecular Sieves (Zeozymes)

Green Caprolactam Process : Sumitomo



Ammoxidation



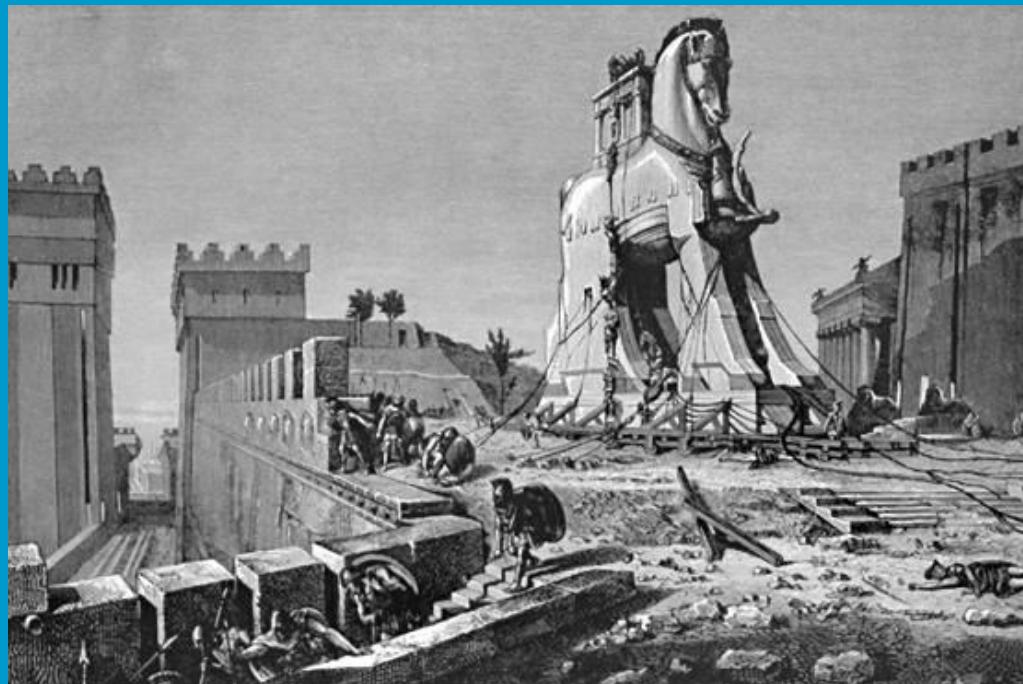
Beckmann rearrangement

Atom efficiency = 75% ; E = 0.32 (<0.1)



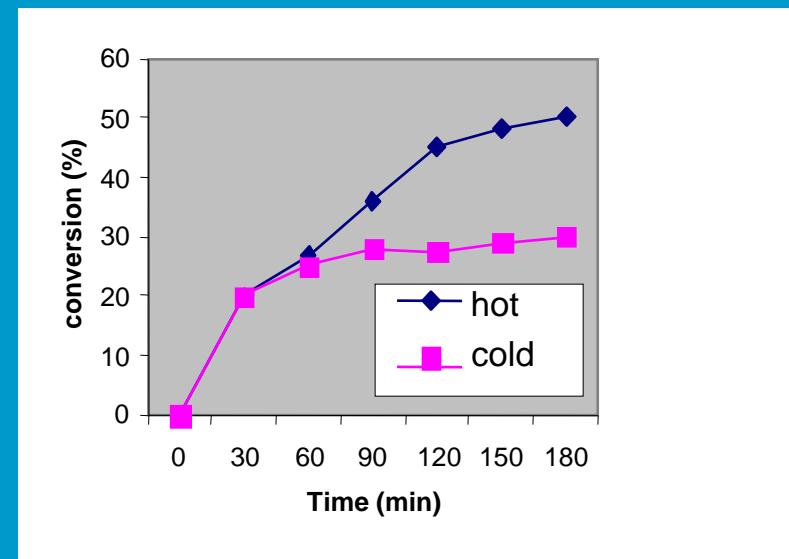
Atom efficiency = 29% ; E = 4.5

Redox Molecular Sieves : Philosophers' Stones or Trojan horses ?



Chen (1995), Elings (1997), Plyuto, Schuchardt

Filtration Test for Heterogeneity:



Lempers (1998)

Sheldon, Wallau, Arends and Schuchardt,
Acc. Chem. Res., 31 (1998) 485-493.

Homogeneous Catalysis

Catalysis in Non-conventional Reaction Media

Two challenges :

- Toxicity and/or hazards of atmospheric and ground water pollution by conventional solvents
- Separation/recycling of homogeneous catalysts

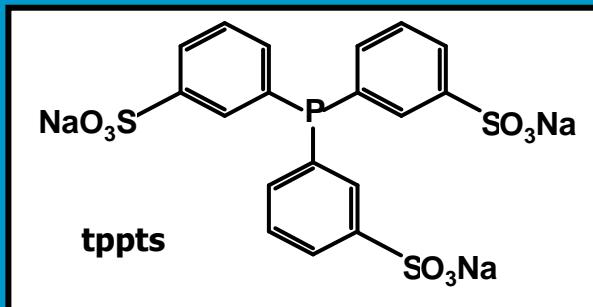
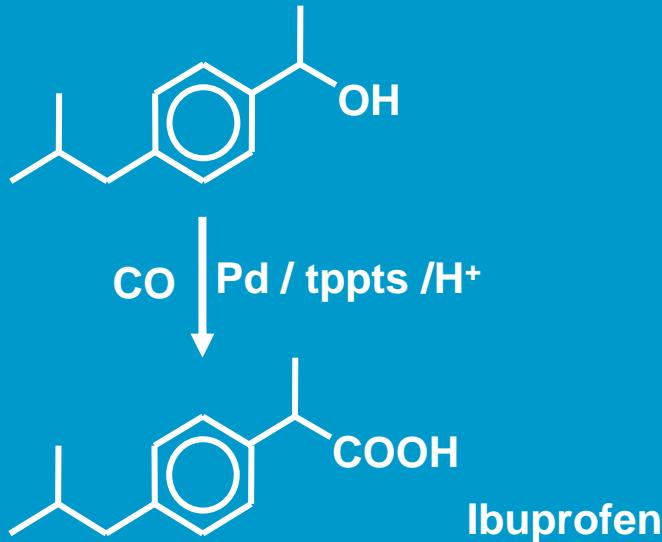


- (Biphasic) catalysis in non-conventional media
 - water
 - supercritical carbon dioxide (**Martyn Poliakoff**)
 - ionic liquids (**Ken Seddon**)
 - fluororous biphasic (**Istvan Horvath**)

“The best solvent is no solvent”

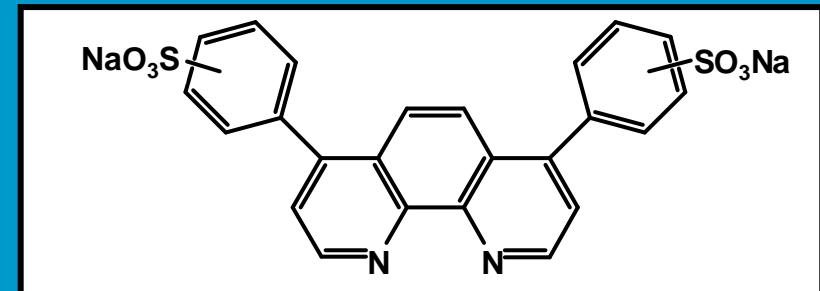
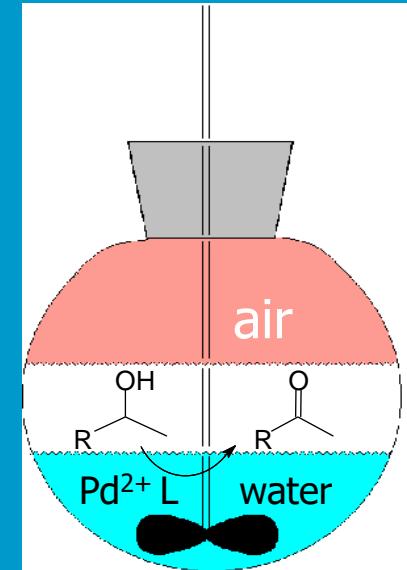
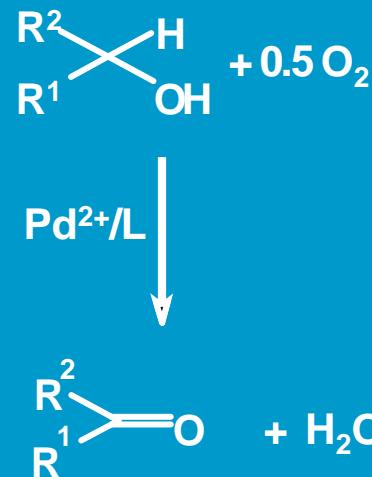
Aqueous Biphasic Cataysis

1. Carbonylation



Papadogianakis, Verspui (2001)

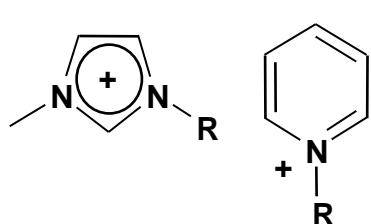
2. Aerobic Oxidation



Moiseev

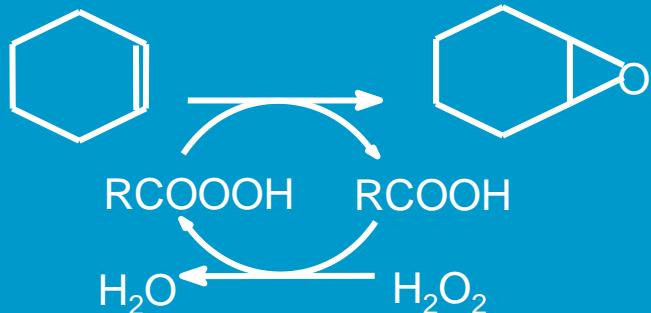
ten Brink (2001)

Catalysis in Ionic Liquids



Anions : BF_4^- , PF_6^- , RCO_2^- , H_2PO_4^- , NO_3^- , $\text{HOCH}_2\text{CO}_2^-$

- Negligible vapour pressure
- Designer solvents
- Catalytic hydroformylation, carbonylation, hydrogenation and **biocatalysis**

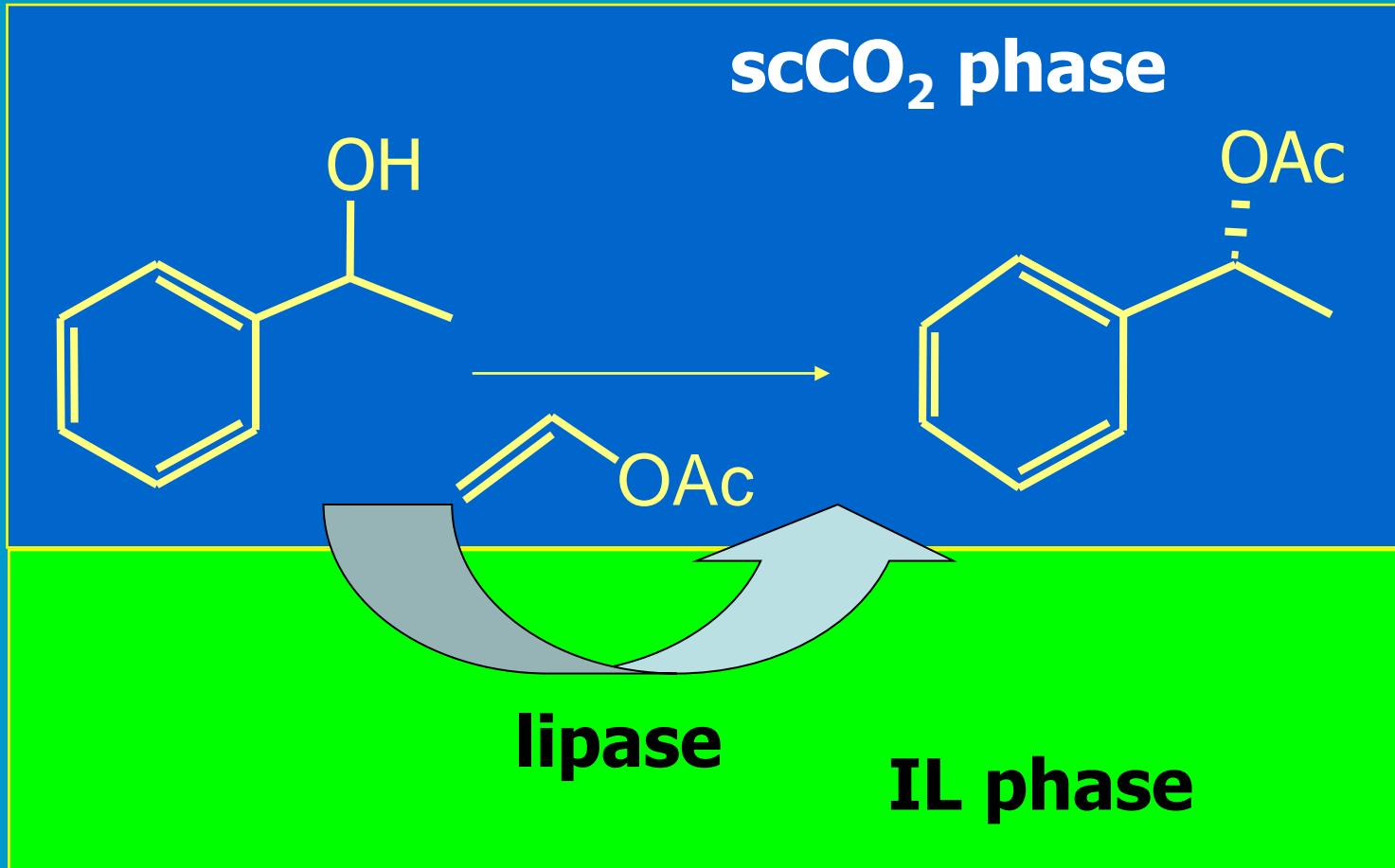


CaLB in $[\text{bmim}][\text{BF}_4^-]$ and $[\text{bmim}][\text{PF}_6^-]$

Madeira Lau (2003) Seddon

Product recovery?

In situ product removal with scCO₂



scCO₂ as mobile phase in batch or continuous operation

The Miscibility Switch

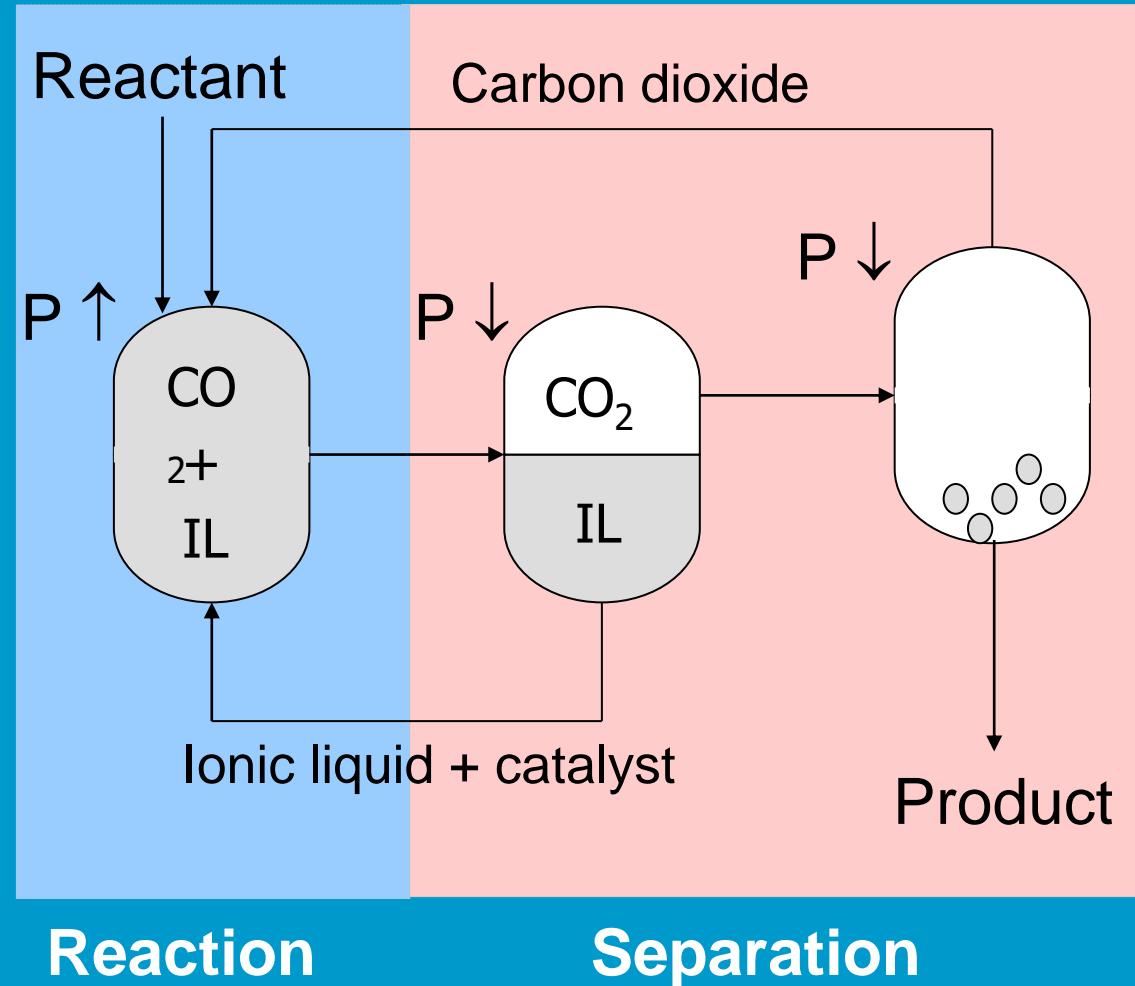
IL
+
Catalyst
+
Reactant
+
 CO_2

CO_2
+
Product

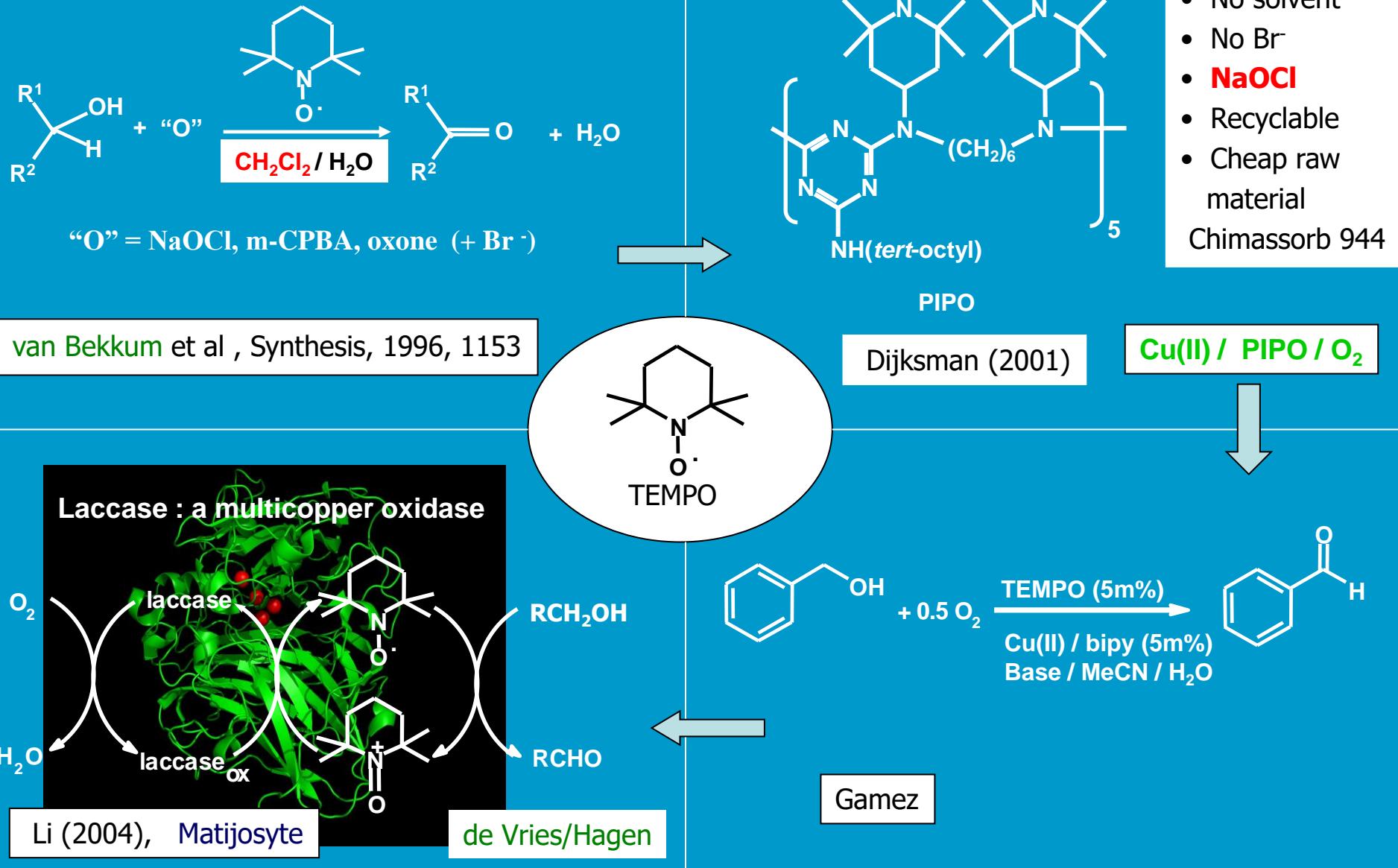
IL
+
Catalyst
+
Product

High p_{CO_2}
one phase

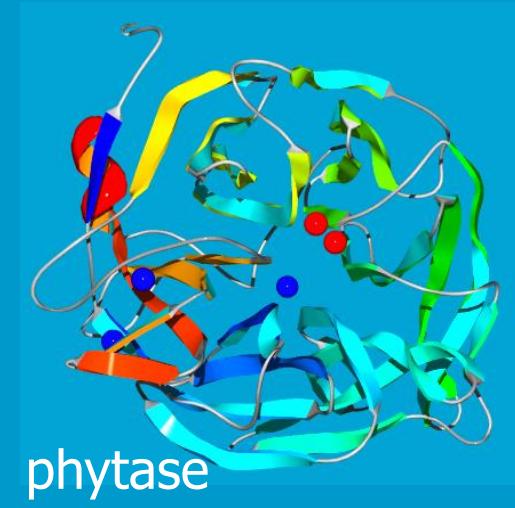
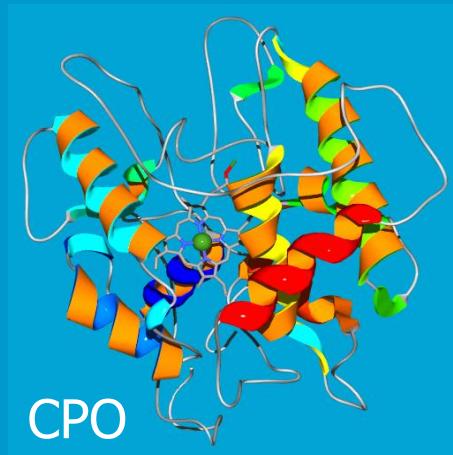
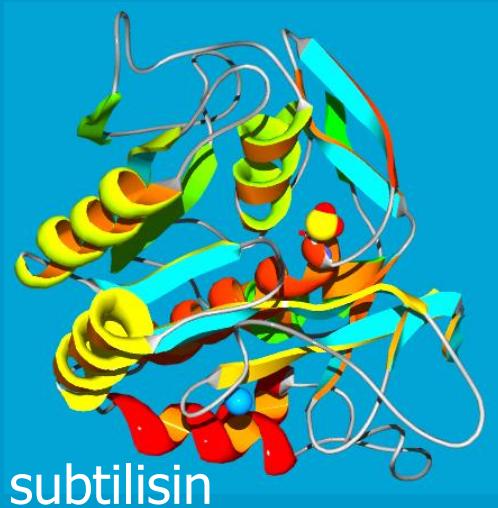
Low p_{CO_2}
two phases



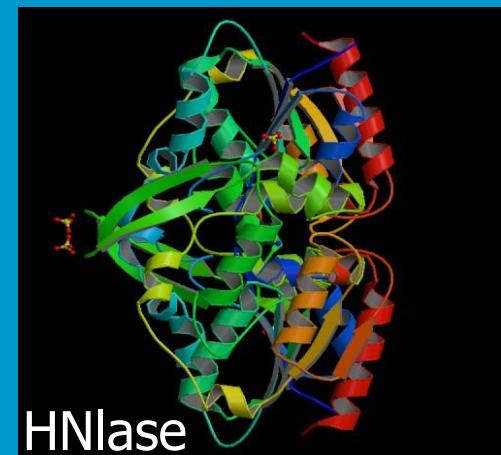
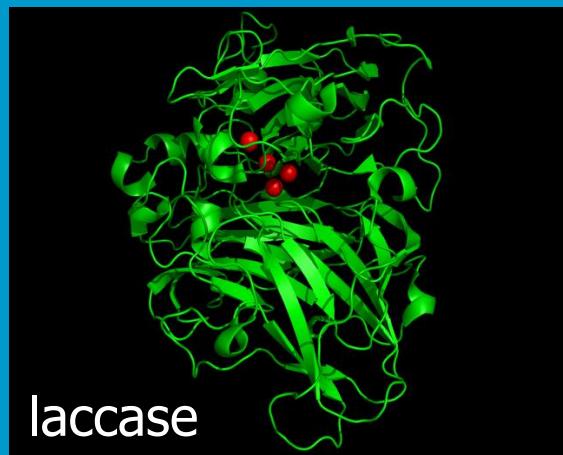
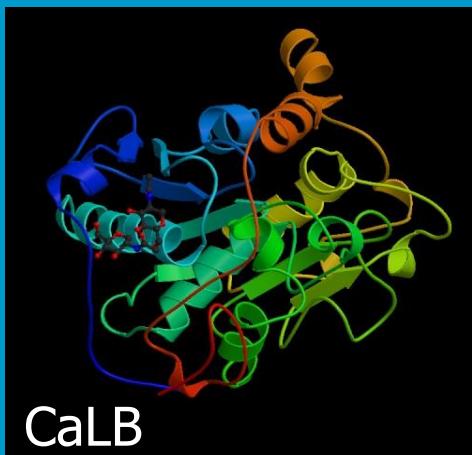
Organocatalysis



Organocatalytic Oxidations



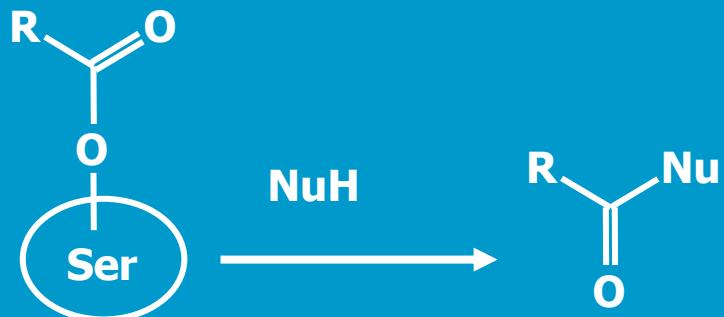
Biocatalysis



Why Biocatalysis?

- **Mild conditions: ambient temperature & pressure in water**
- **Enzymes are derived from renewable sources and are biodegradable**
- **High rates & highly specific : substrate, chemo-, regio-, and enantiospecific**
- **Higher quality product**
- **Green Chemistry (environmental footprint)**

Enzymatic Ammoniolytic



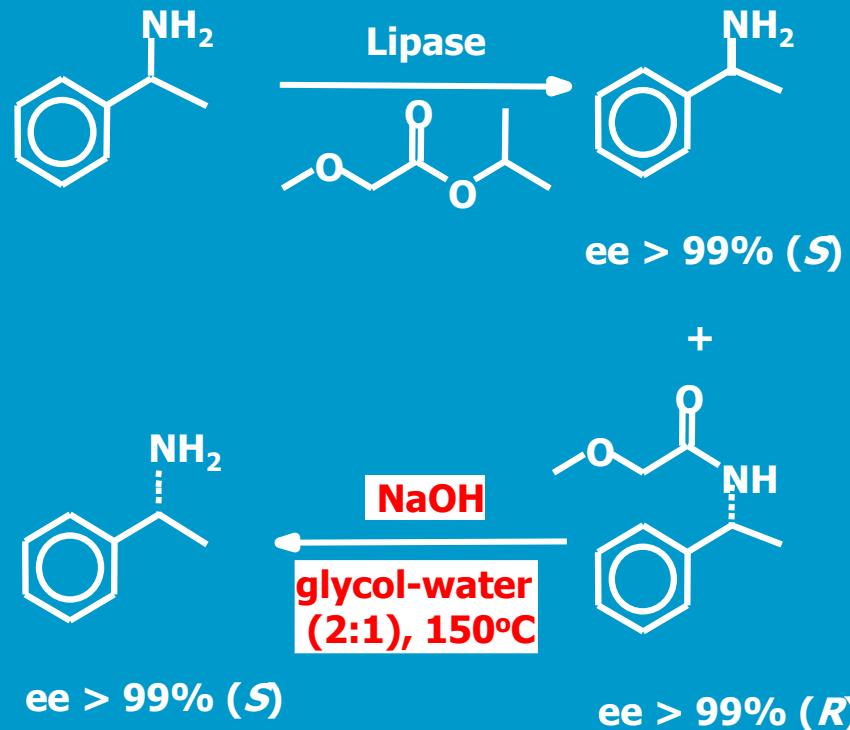
$\text{Nu} = \text{OH}, \text{OR}, \text{NH}_2, \text{RNH}, \text{OOH}, \text{etc}$



- Green amide synthesis
- Enantioselective with amino acid esters

Steverink(1995), Hacking (1999)
Wegman(2001)

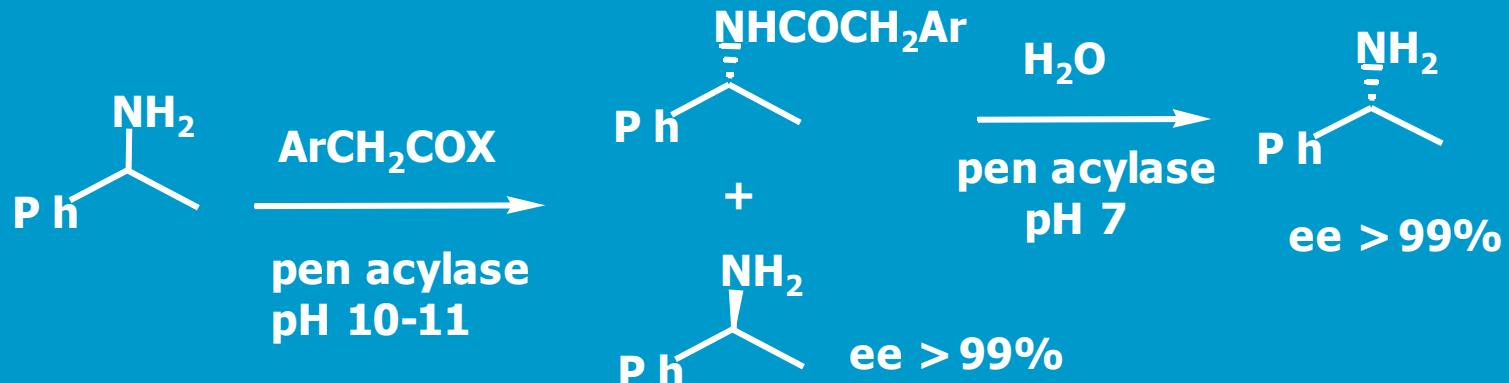
BASF Process



> 3000 tpa

If you want to find something new
you have to DO something new

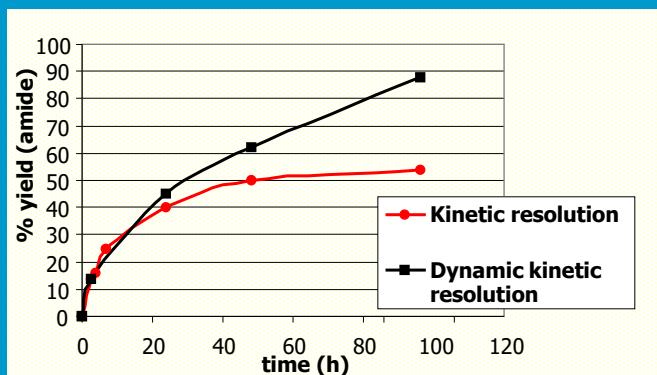
Easy-on-easy-off resolution



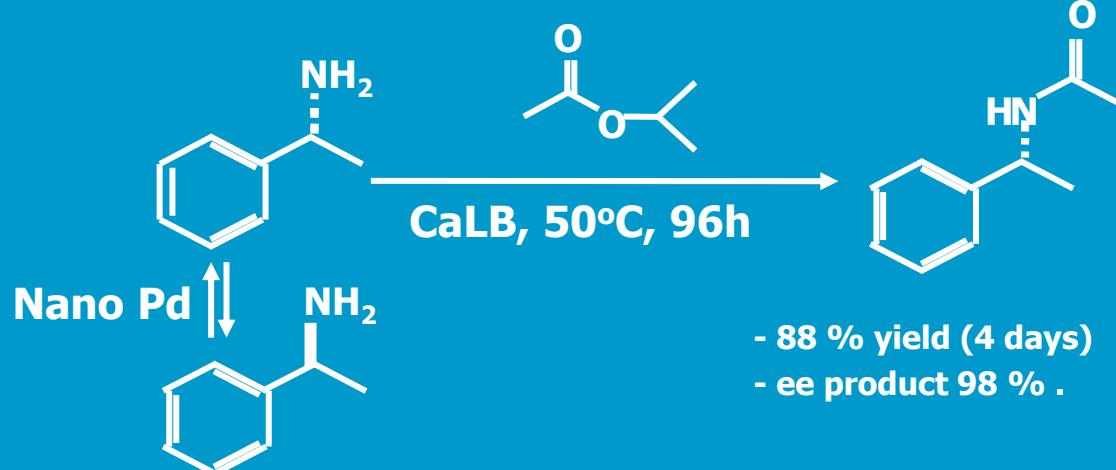
V.Svedas

L.van Langen(2001), R.Madeira Lau(2003), H.Ismail(2007)

Dynamic Kinetic Resolution



H.Ismail(2007)

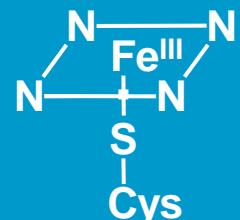


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Pd –catalyzed racemization of 1-phenethylamine :
Murahashi (1983) ; Reetz , DKR (1996).

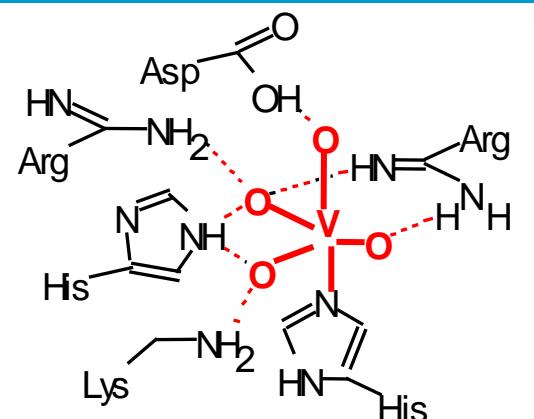


99% yield
>99% ee



Heme
Low stability

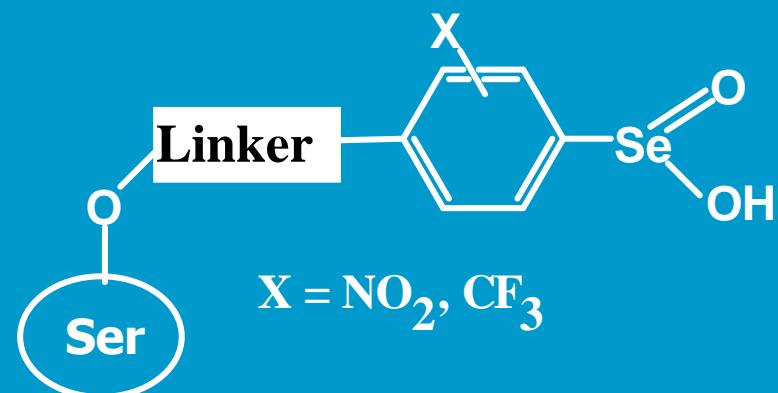
van Deurzen (1996)
van de Velde (2000)



65% ee

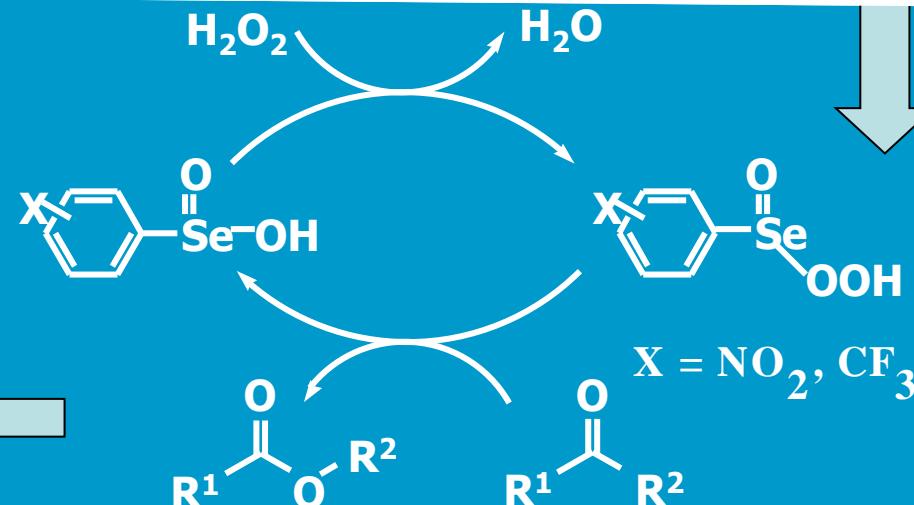
vanadate phytase

van de Velde
Aksu-Kanbak
Correia



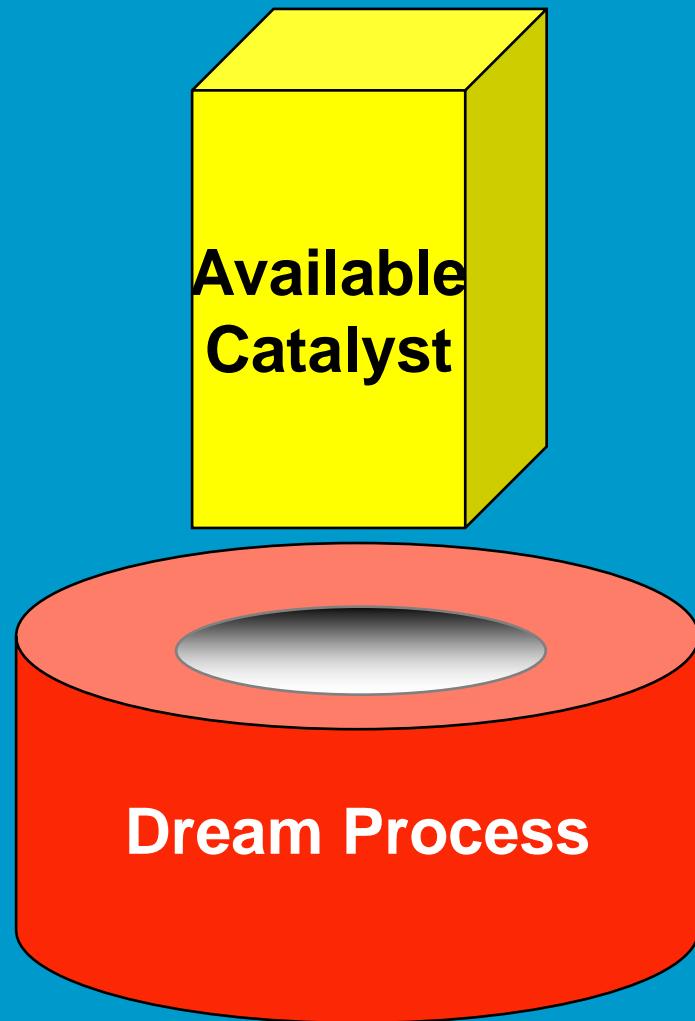
subtilisin

van der Toorn

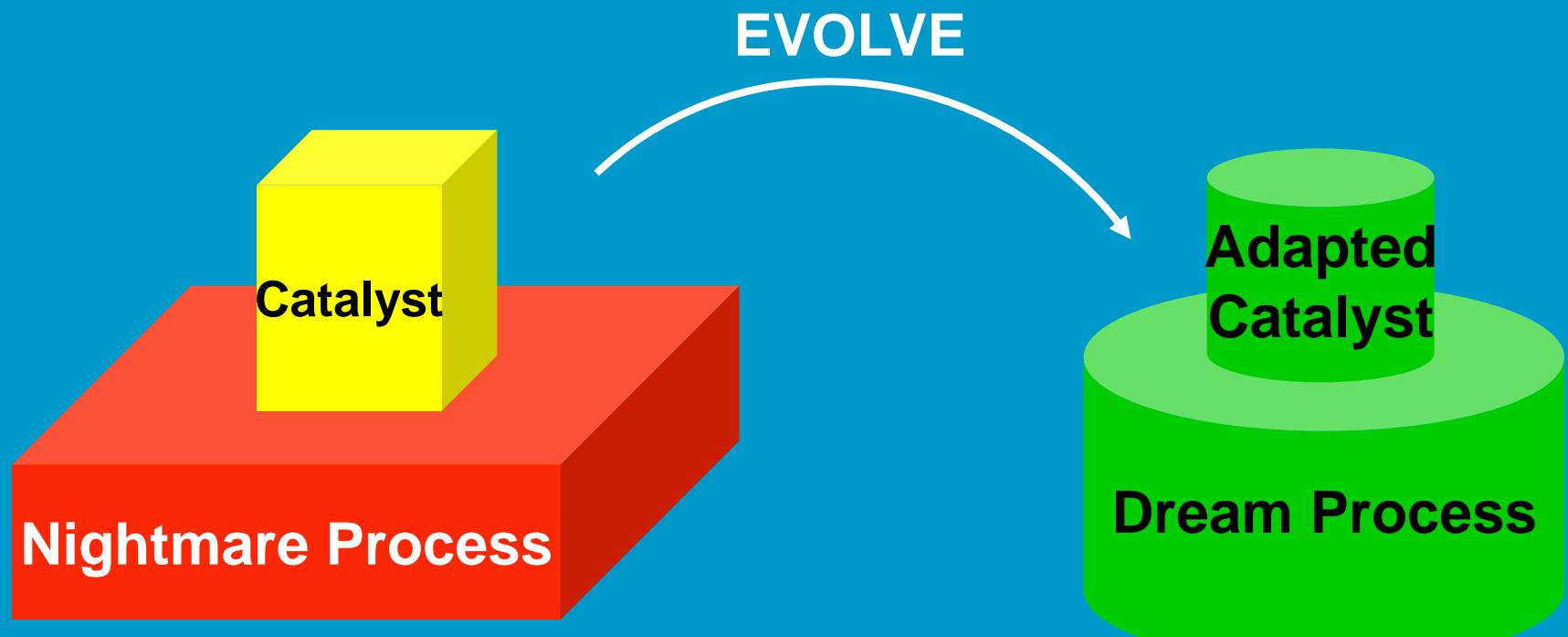


ten Brink (2001)

Historically: Adapt Process to fit Catalyst



Future: Adapt Catalyst to fit Ideal Process

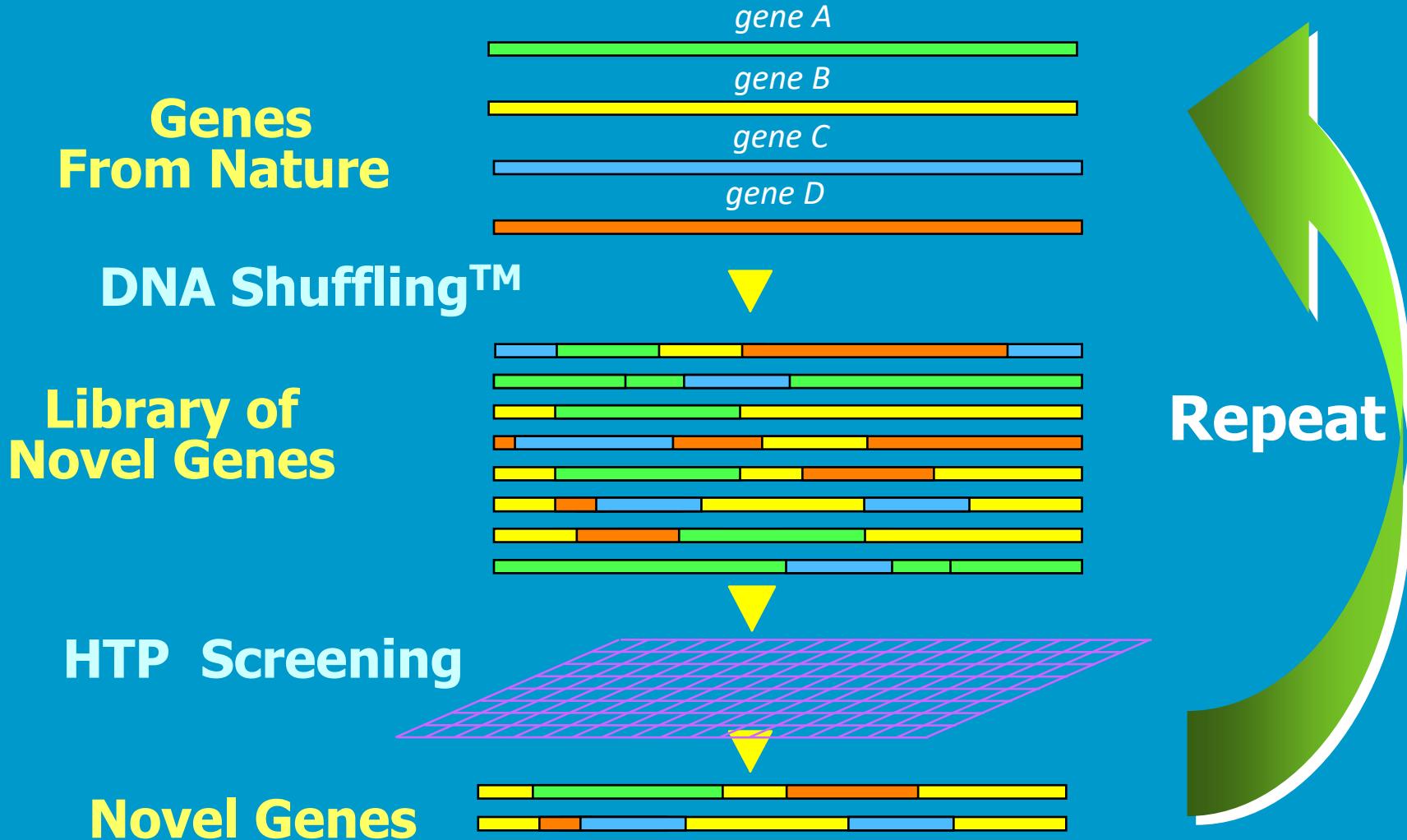


Compromise process to
accommodate catalyst

Adapt catalyst to
optimum process

Directed Evolution

DNA Shuffling : Evolution in the Fast Lane



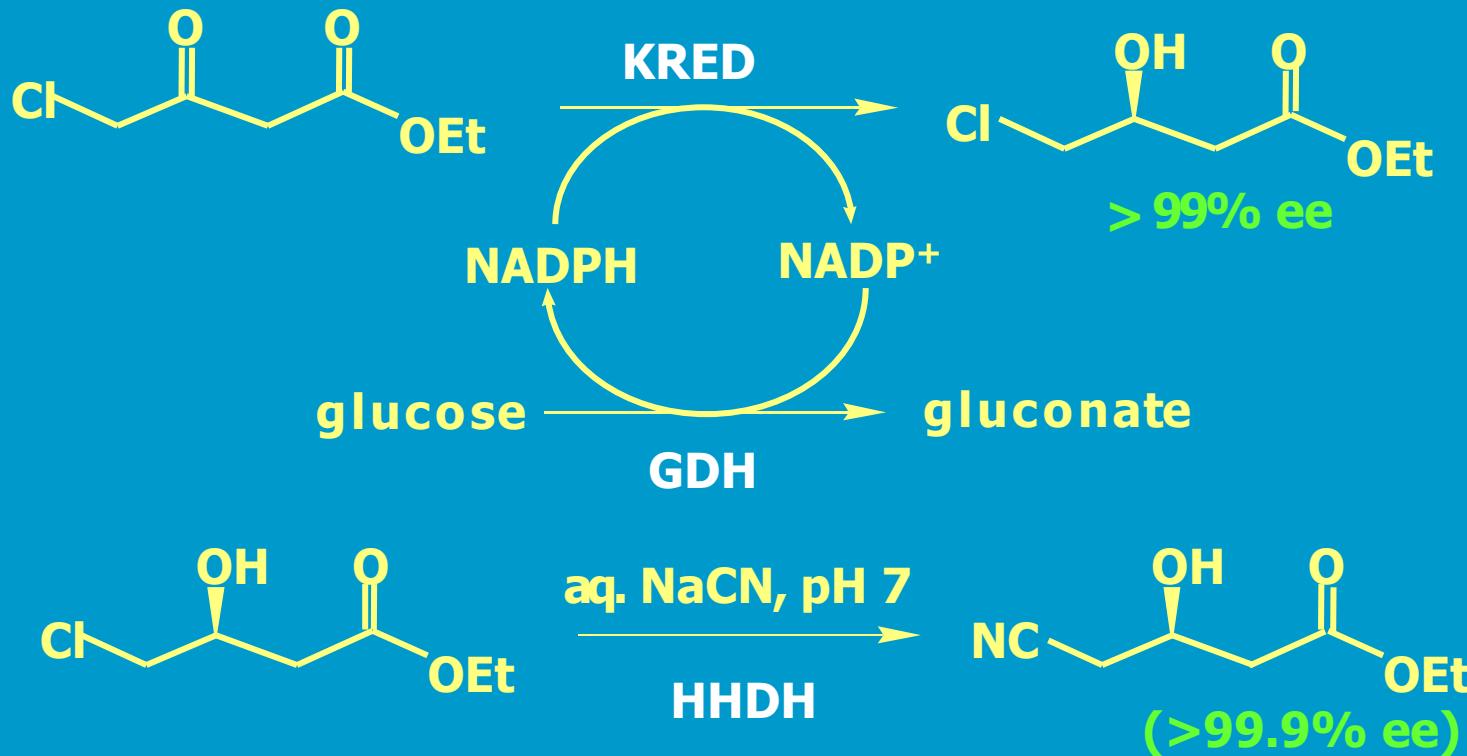
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Stemmer, Nature, 370, 389-391, 1994; Huisman et al (Codexis)

See also Reetz, Advan. Catal. 2006, 1-69.

Green Synthesis of Lipitor Intermediate (Codexis)

Presidential Green Chemistry Challenge Award 2006



KRED = keto reductase ; GDH = glucose dehydrogenase

HHDH = halohydrin dehalogenase (non-natural nucleophile)

Improving Performance by Directed Evolution: test tube to commercial process with gene shuffling

1. KRED + GDH

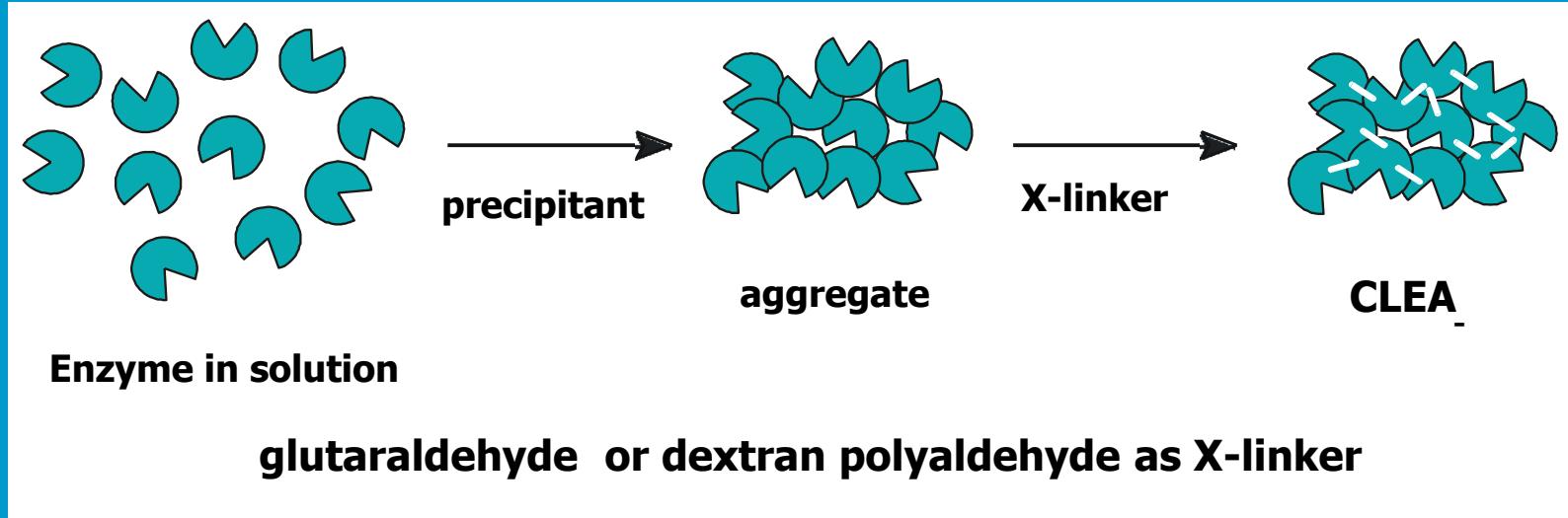
Parameter	Process Design	Initial Performance	Final Performance
Substrate loading	160 g/l	80 g/l	180 g/l
Parameter	Process Design	Initial Performance	Final Performance
Substrate loading	120 g/L	20 g/L	140 g/L
Reaction time	<16 hrs	72 hrs	5 hrs
Enzyme loading	<1.2 g/L	130 g/L	1.2 g/L
Isolated yield	>90%	~60%	92%
Volumetric Productivity	>180 g/L.day	7 g/L.day	670 g/L.day

Disadvantages of Enzymes

- Low operational stability & shelf-life
- Cumbersome recovery & re-use (batch vs continuous operation)
- Product contamination

Solution : Immobilization

Cross-Linked Enzyme Aggregates (CLEAs)



- Enables recycling via filtration
- Higher productivity
- No need for highly pure enzyme
- Simple procedure / widely applicable
- Stability towards denaturation

CLEAS active in:
- scCO₂ (M. Poliakoff)
- ILs (Sheldon)

Examples of Successful CLEAtion

Hydrolases

- Pen. acylases (2)
- Lipases (7)
- Esterases (3)
- Proteases (3)
- Nitrilases (2)
- Aminoacylase
- Phytase
- Galactosidase

Oxidoreductases

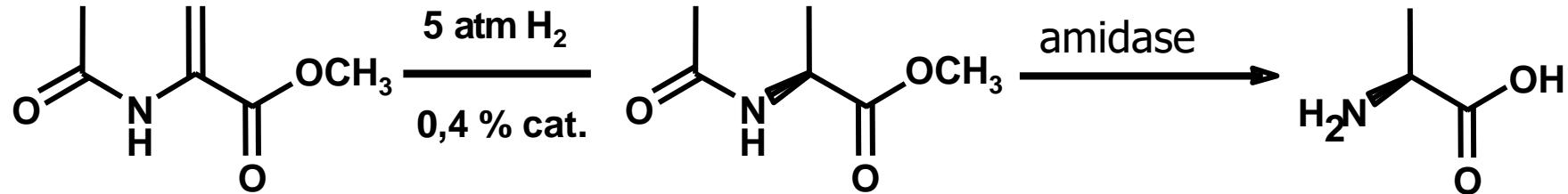
- ADH
- FDH
- Glucose oxidase
- Galactose oxidase
- Laccase
- Catalase
- Chloroperoxidase

Lyases

- R- & S- HnLases
- PDC
- DERA
- Nitrile hydratase

Cao, Lopez-Serrano, Mateo, Perez, van Langen, Sorgedrager
Janssen, Bode, van Pelt, Chmura, Matijosyte, Aksu-Kanbak,

Catalytic Cascade Processes

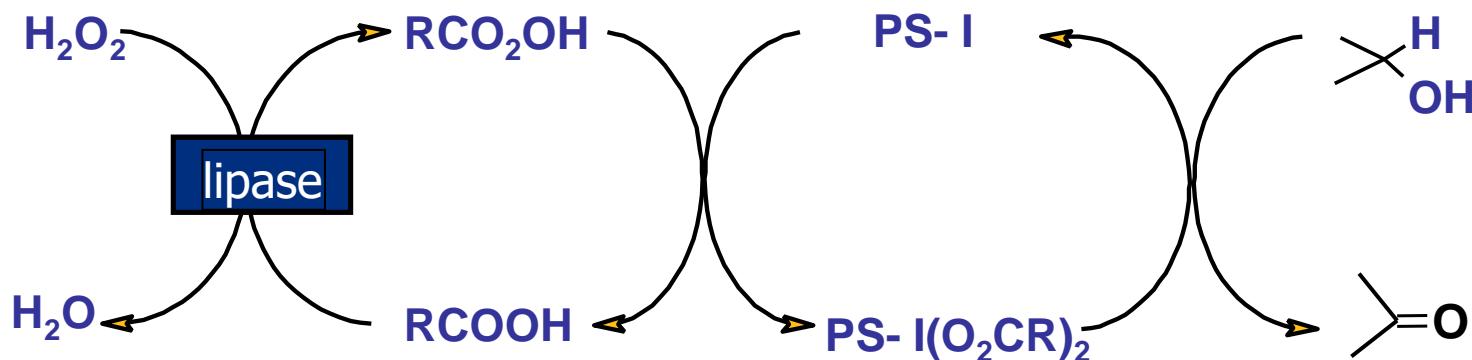


Catalyst :
Rh(monophos) on TUD-1

99% yield / 95% ee

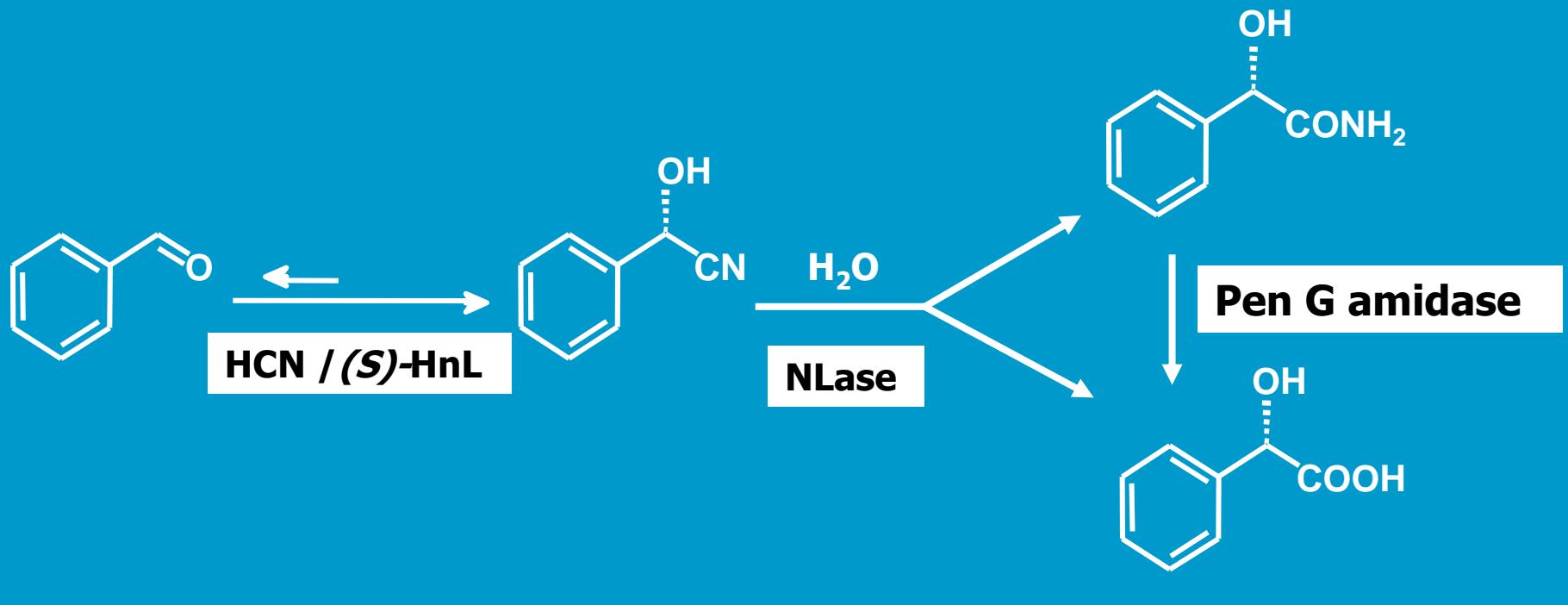
97% yield / > 99% ee

Simons (2007)



Kotlewska

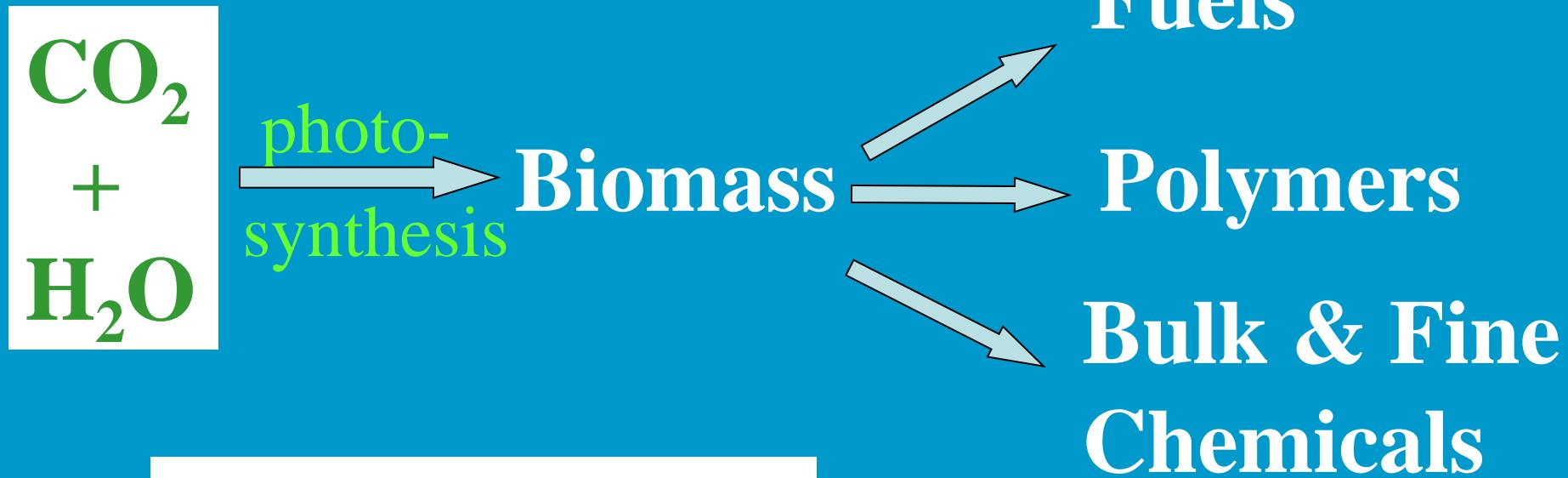
Trienzymatic Cascade with a Triple-Decker combi CLEA



Chmura, Stoltz

Conv. 96% / ee >99%

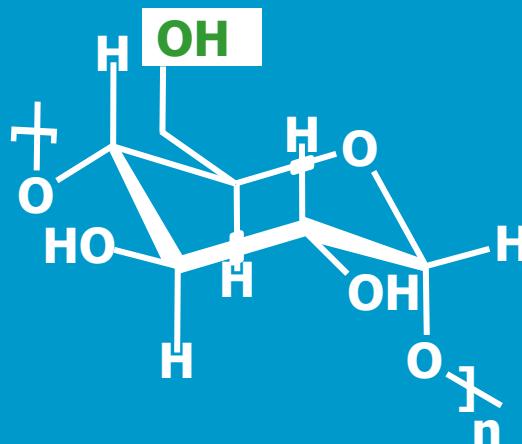
Renewables & Green Chemistry : the Biorefinery



Emons (1992), Arts(1996), Papadogianakis

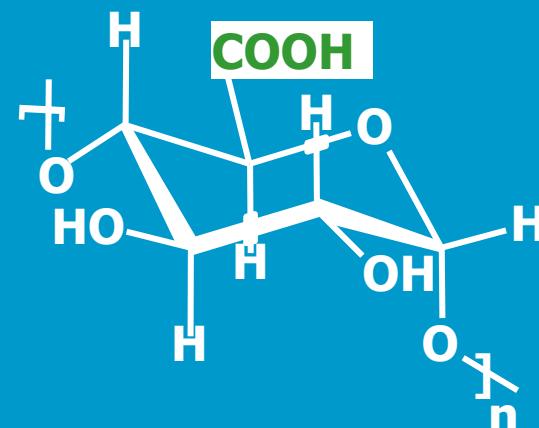
Metrics for renewables ?

Carboxystarch : Safe & Natural Absorbing Polymer (SNAP)



starch

Laccase CLEA
TEMPO/O₂

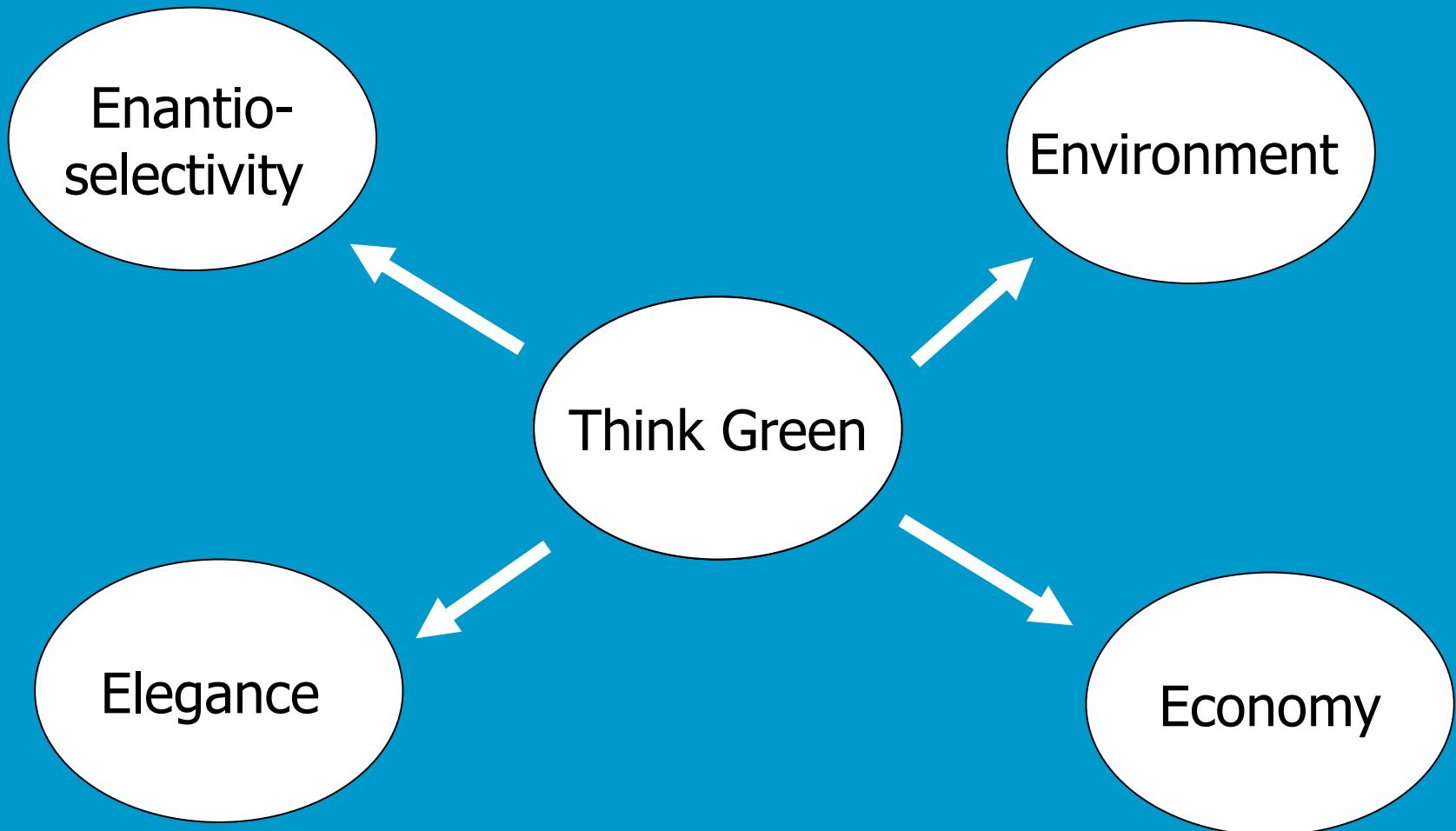


carboxy starch

- Non- toxic & biodegradable
- Green (bio) catalytic process
- Green raw materials

Boumans (TNO)

The plan is nothing, the planning is everything
Mao Zedong



Think Green



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So it goes.....



Collaboration & Funding

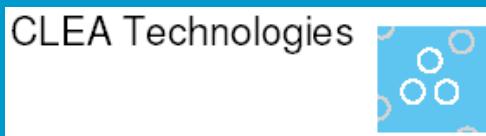
IOP Katalyse



EU



SOLVAY



Unlimited. DSM

AsahiKASEI

SHOWA DENKO

Mitsui Chemicals



Hoechst Celanese



behind every
successful man there is
an astonished woman



