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Fundamentals of Green Chemistry: Efficiency in Reaction Design

A Tutorial Review

Roger A. Sheldon

Department of Biotechnology

Delft University of Technology

r.a.sheldon@tudelft.nl

r.sheldon@clea.nl

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Fundamentals of Green Chemistry: Efficiency in Reaction Design

Outline

1. Introduction: Efficiency in Organic Synthesis
2. Alcohol Oxidation
3. Enantioselective Ketone Reduction
4. Biocatalysis
5. Enzyme Immobilization
6. Conclusions & Take Home Message

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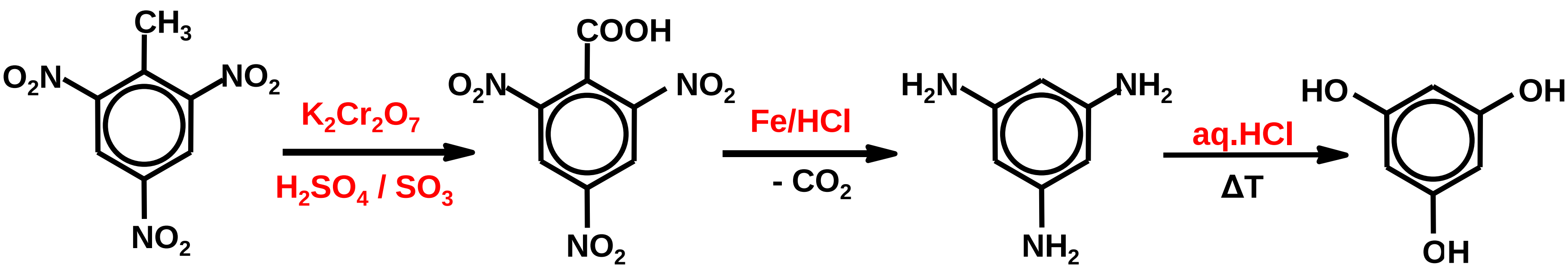
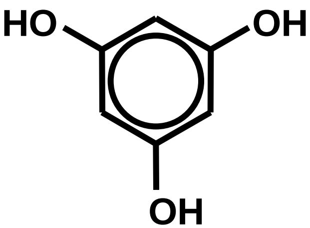
Phloroglucinol Synthesis anno 1980



TNT

phloroglucinol

Ca. 40kg of solid waste per kg phloroglucinol



product

MW = 126

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

392 272 1143 160 44 144

byproducts

Atom Utilisation = 126/2282 = ca. 5 %

E Factor = ca. 40

> 90 % yield
Selective?
Efficient?

" To measure is to know " Lord Kelvin

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Reaction Stoichiometry and Atom Economy

$$C_7H_5N_3O_6 + K_2Cr_2O_7 + 5\,H_2SO_4 + 9\,Fe + 21\,HCl \longrightarrow$$

$$C_6H_6O_3 + Cr_2(SO_4)_3 + 2\,KHSO_4 + 9\,FeCl_2 + 3\,NH_4Cl + CO_2 + 8\,H_2O$$

126 392 272 1143 161 44 144

Atom economy = 126/2282 = ca. 5 %

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Conclusion?

A new paradigm was needed for efficiency in organic synthesis.

From the traditional one of chemical yield

to one that assigns value to waste elimination and avoiding toxic/hazardous materials.

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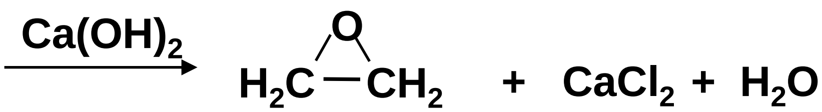
Atom Economy of Ethylene Oxide Manufacture

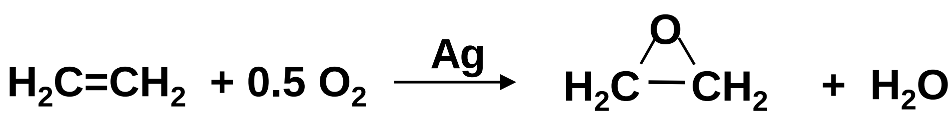
1. Chlorohydrin process

$$H_2C{=}CH_2 + Cl_2 + H_2O \longrightarrow ClCH_2CH_2OH + HCl$$



25 % atom utilisation

2. Direct Oxidation



100 % atom utilisation

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E Factor = kg waste/kg product

	Tonnage	E Factor
Oil Refining	10^6-10^8	<0.1
Bulk Chemicals	10^4-10^6	<1 - 5
Fine chemical Industry	10^2-10^4	5 - >50
Pharmaceutical Industry	10-10^3	25 - >100

"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

R.A.Sheldon, Chem & Ind, 1992, 903 ; 1997, 12

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The E factor

(E)verything but the Product

- 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 = [kgs raw materials- kgs product]/[kgs product]
- A good way to quickly show (e.g. to students) the enormity of the waste problem

What about the process water?

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Sustainability

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

Brundtland Report, 'Our Common Future', 1987

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The Great Law of the Iroquois Confederacy

'In our every deliberation, we must consider the impact of our decisions on the next seven generations.'

http://www.iroquoisdemocracy.pdx.edu

www.seventhgeneration.com

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The Twelve Principles of Green Chemistry

1. Prevention instead of Remediation
2. Atom Efficiency
3. Less Hazardous Chemicals
4. Design Safer Chemical Products
5. Safer Solvents & Auxiliaries
6. Energy Efficient by Design

P.T.Anastas & J.C.Warner,Green Chemistry : Theory & Practice ,Oxford Univ. Press,New York,1998

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The Twelve Principles of Green Chemistry

7. Renewable Raw Materials
8. Shorter Syntheses
9. Catalytic Methodologies
10. Design for Degradation
11. Analysis for Pollution Prevention
12. Inherently Safer Chemistry

P.T.Anastas & J.C.Warner,Green Chemistry : Theory & Practice ,Oxford Univ. Press,New York,1998

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A Mnenomic for the Spirit of Green Chemistry

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

S. L. Y. Tang, R. L. Smith and M. Poliakoff, *Green Chem*., **2005**, *7*,761.

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Green (Clean) 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.

Anastas & Warner, Green Chemistry : Theory & Practice ,Oxford Univ. Press,New York,1998

Sheldon, Arends and Hanefeld , Green Chemistry and Catalysis, Wiley, New York, 2007

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Metrics of Green Chemistry

E factor

$$E = \frac{\text{Total mass of waste}}{\text{Mass of final product}}$$

Atom efficiency (AE)

$$AE\,(\%) = \frac{\text{m.w of product} \times 100}{\Sigma \text{ m.w. of reactants}}$$

Mass intensity (MI)

$$MI = \frac{\text{Total mass in process}}{\text{Mass of product}}$$

Reaction mass efficiency (RME)

$$RME(\%) = \frac{\text{Mass of product C} \times 100}{\text{Mass of A + Mass of B}}$$

Mass Productivity (MP)

$$MP = \frac{\text{Mass of product}}{\text{Total mass in process}}$$

Carbon efficiency (CE)

$$CE(\%) = \frac{\text{Carbon in product} \times 100}{\text{Total carbon in reactants}}$$

Effective mass yield (EMY)

$$EMY(\%) = \frac{\text{Mass of product} \times 100}{\text{Mass of hazardous reagents}}$$

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The Environmental Impact EQ

EQ = E(kg waste) × Q

Q = Unfriendliness Multiplier

e.g. NaCl : Q = 1 (arbitrary)

Cr salts : Q = 1000?

There are many shades of green!

R.A.Sheldon, Chem & Ind, 1992, 903 ; 1997, 12

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Major Sources of Waste

- Stoichiometric Reagents
  - Acids & Bases (e.g H_2SO_4 and NaOH)
  - Oxidants & reductants (e.g. $K_2Cr_2O_7$ & Fe/HCl)
- Solvent losses (85% of non-aqueous mass)
  - Air emissions & aqueous effluent
- Multistep syntheses

The Solution :
Atom & step economic catalytic processes
in alternative reaction media (H_2O, $scCO_2$, ILs)
(the best solvent is no solvent)

What about process water?
Only counts if it needs to be treated?

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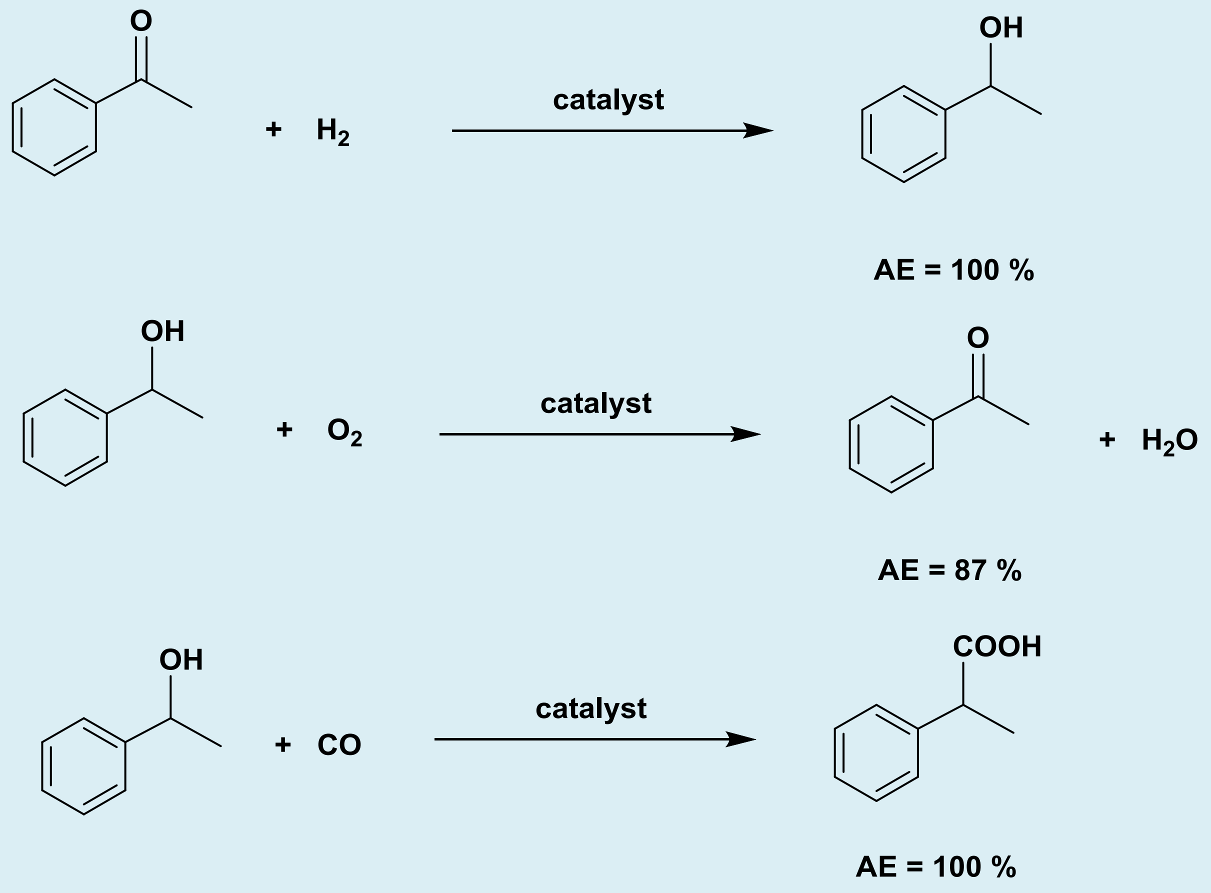
Atom Economy of Catalytic Processes



The Ideal Synthesis

100% Yield

One Step

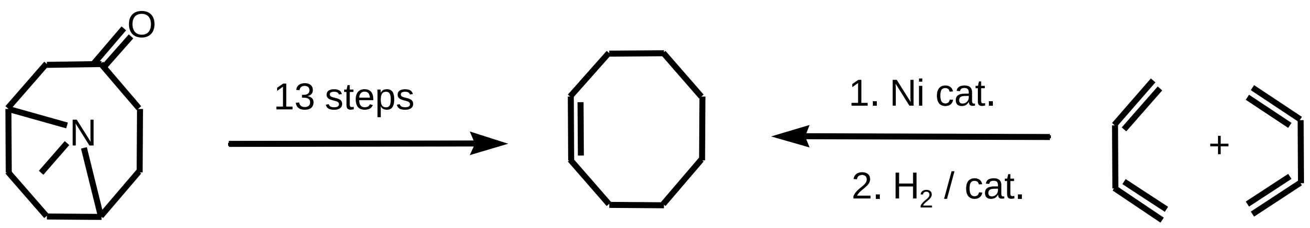
Simple & Safe

Economical in Time & Waste

Environmentally Acceptable

- atom economy

- step economy



The Ideal Process

"The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole"

Sir John Cornforth (Nobel Prize 1975)

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Solvent Selection Guide

- Pentane
- Hexane(s)
- Di-isopropyl ether
- Diethyl ether
- Dichloromethane
- Dichloroethane
- Chloroform
- NMP
- DMF
- Pyridine
- DMAc
- Dioxane
- Dimethoxyethane
- Benzene
- Carbon Tetrachloride

→

- Cyclohexane
- Toluene
- Methylcyclohexane
- TBME
- Isooctane
- Acetonitrile
- 2-MeTHF
- THF
- Xylenes
- DMSO
- Acetic Acid
- Ethylene Glycol

→

- Water
- Acetone
- Ethanol
- 2-Propanol
- 1-Propanol
- Heptane
- Ethyl Acetate
- Isopropyl acetate
- Methanol
- MEK
- 1-Butanol
- *t*-Butanol

P. Dunn et al, Green Chem. 2008, 10, 31-36

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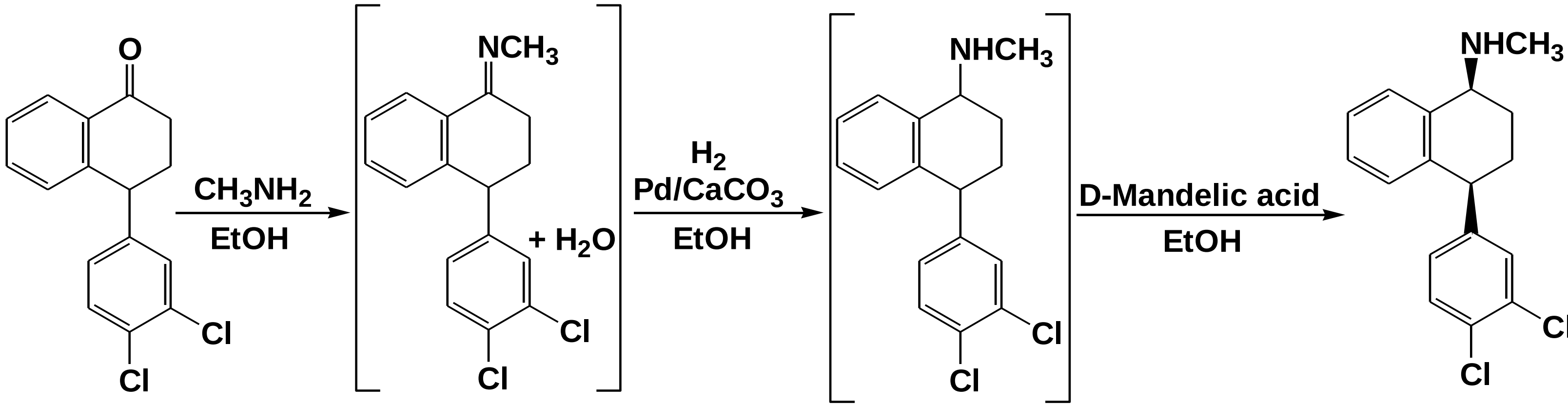
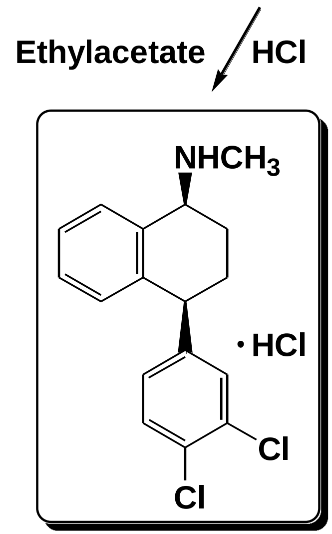
New Sertraline Process (Pfizer's Antidepressant) is Greener





Sertraline · HCl

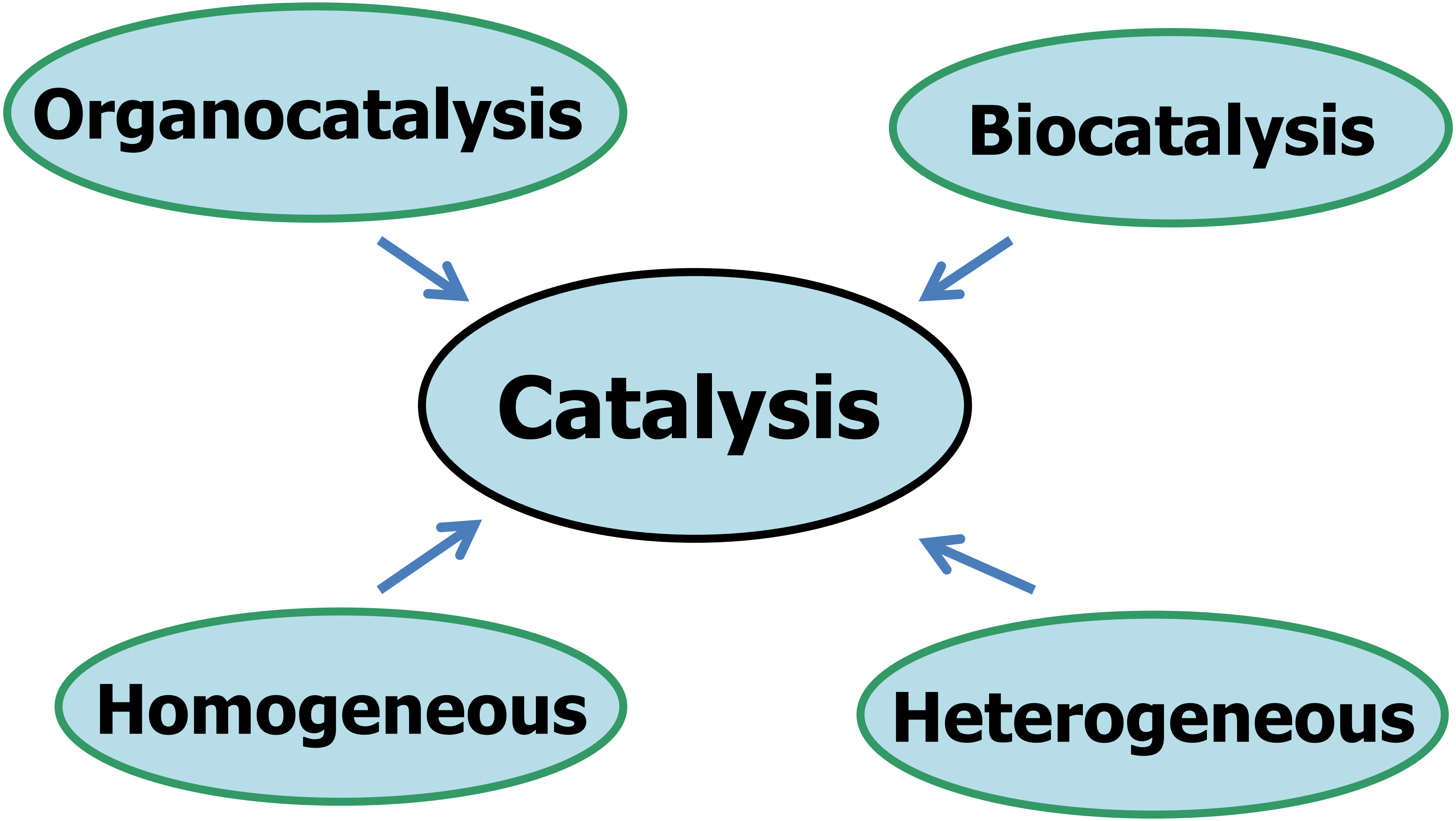
Three step process
Introduction of EtOH as solvent
Replacement of Pd/C with $Pd/CaCO_3$ - higher yields

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

Catalysis & Green Chemistry



Sheldon, Arends and Hanefeld , Green Chemistry And Catalysis, Wiley, New York, 2007

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Organic chemistry & Catalysis: Bridging the Gap

J. J. Berzelius 1779-1848

Organic Chemistry (1807)	Catalysis (1835)
Urea synthesis (Wöhler) 1828	ca. 1900 Catalysis definition (Ostwald)
	Catalytic Hydrogenation (Sabatier)
First synthetic dye 1856: Aniline purple (Perkin)	ca. 1920 Petrochemicals
↓	↓
Dyestuffs Industry (based on coal-tar)	1936 Catalytic cracking
	1949 Catalytic reforming
	1955 Ziegler-Natta catalysis
↓	↓
Fine Chemicals	Bulk Chemicals & Polymers

→ Catalysis in Organic Synthesis ←

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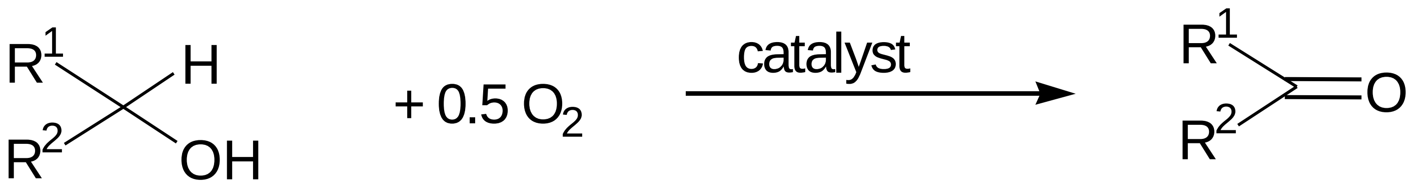
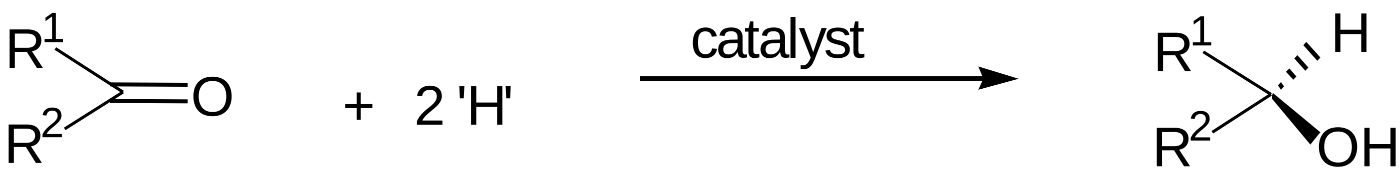
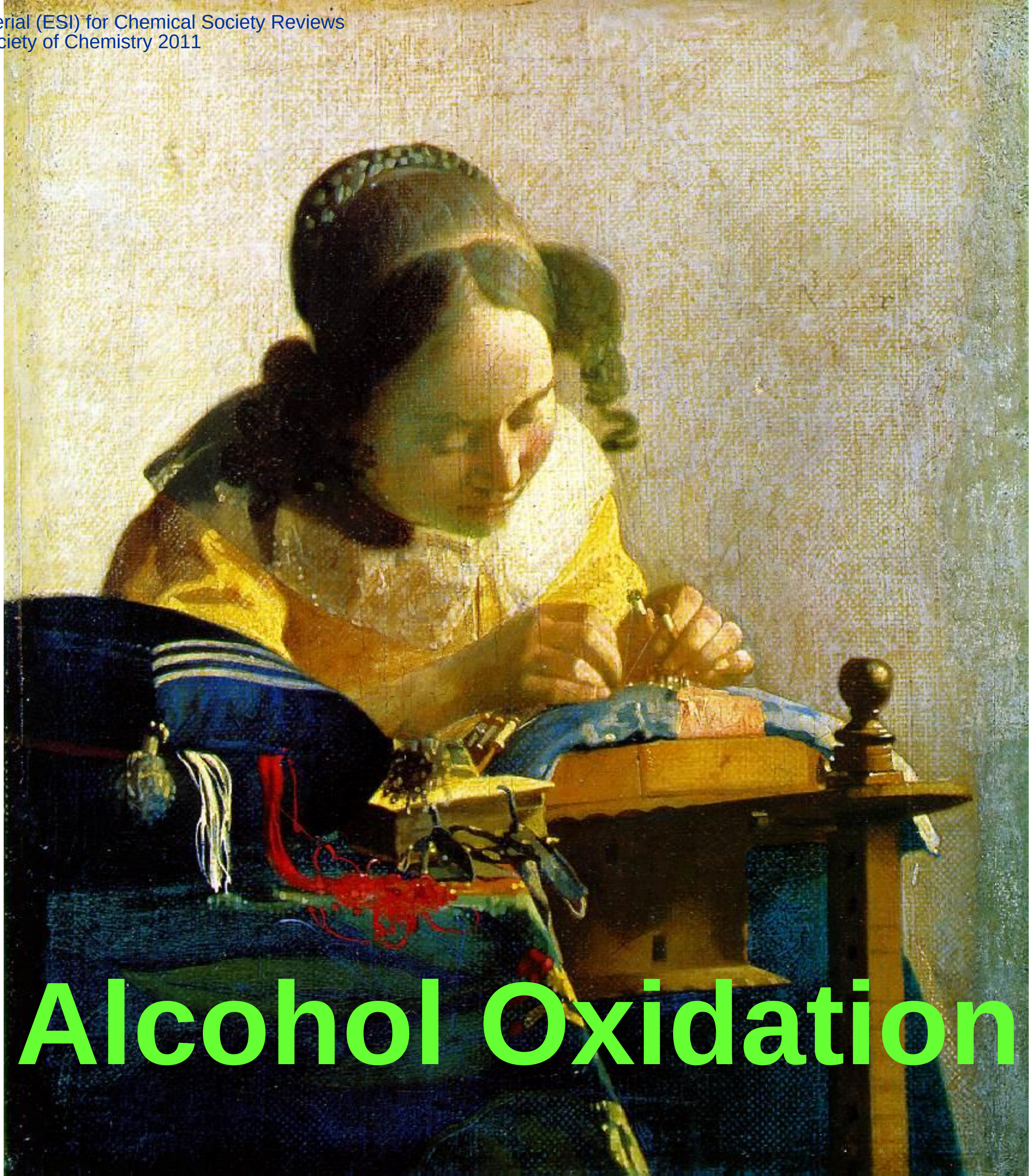
Pivotal Reactions in Organic Synthesis

Oxidation



Reduction





Alcohol Oxidation

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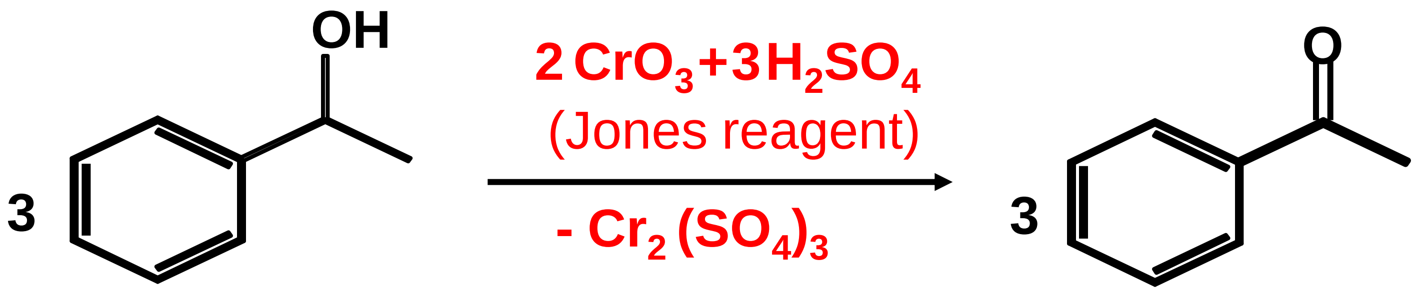
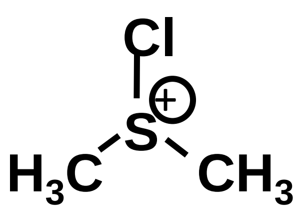
Classical Alcohol Oxidations



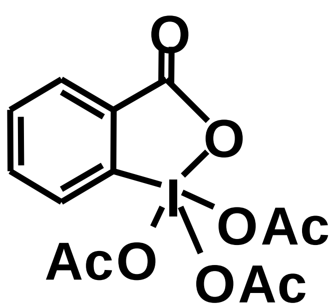
> "It's hexavalent chromium, highly toxic, highly carcinogenic. Gets into your DNA, so you pass the trouble along to your kids."
>
> Julia Roberts in 'Erin Brokovich'

Atom Utilisation = 44%
E = > 3

Other reagents favoured by organic chemists



Swern



Dess-Martin

- Poor atom economy
- Hazardous reagents

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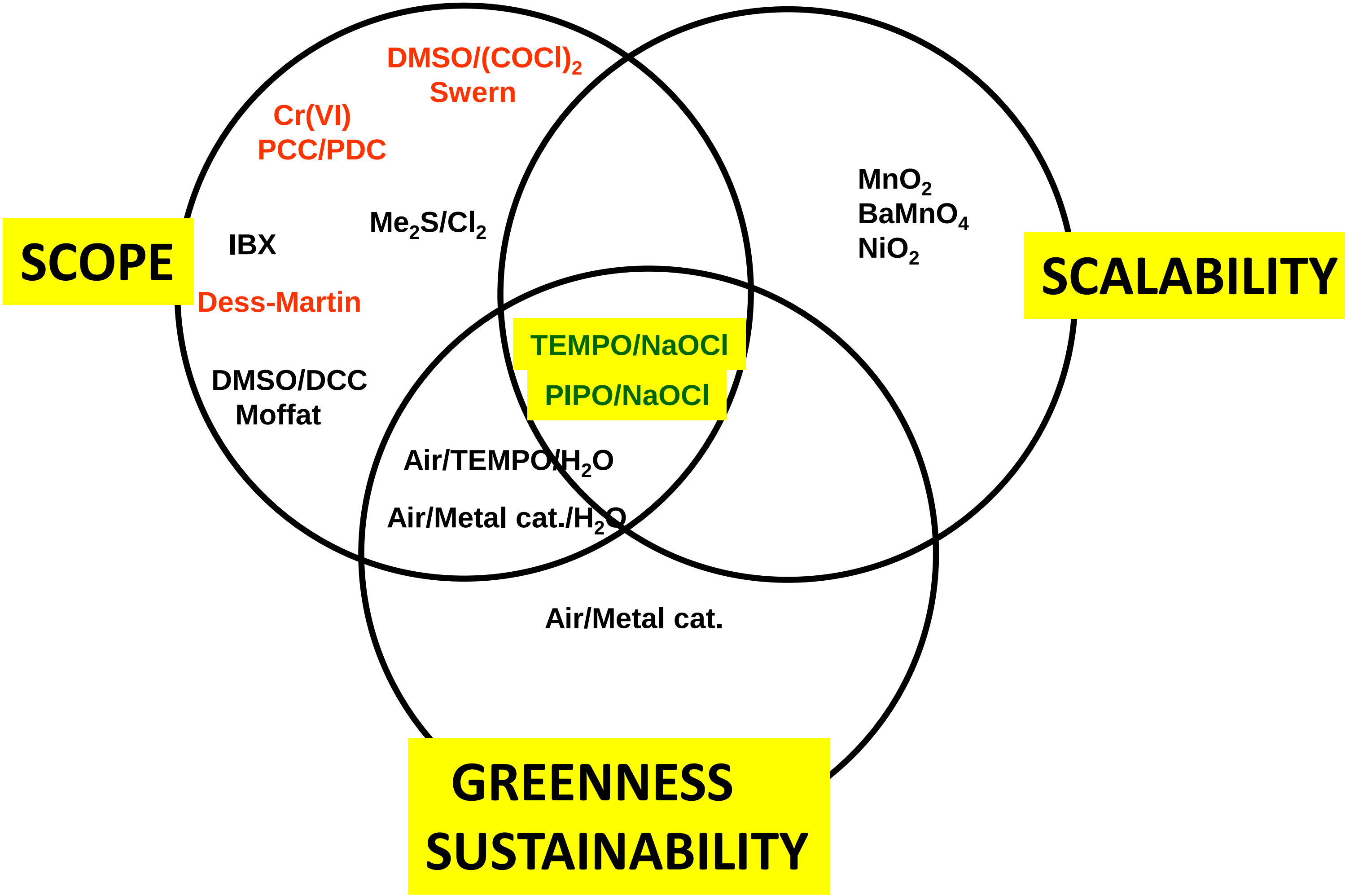
Venn and the Art of Green Chemistry



Oxidation of Primary Alcohol to Aldehyde

P. Dunn et al, Green Chem. 2008, 10, 31-36

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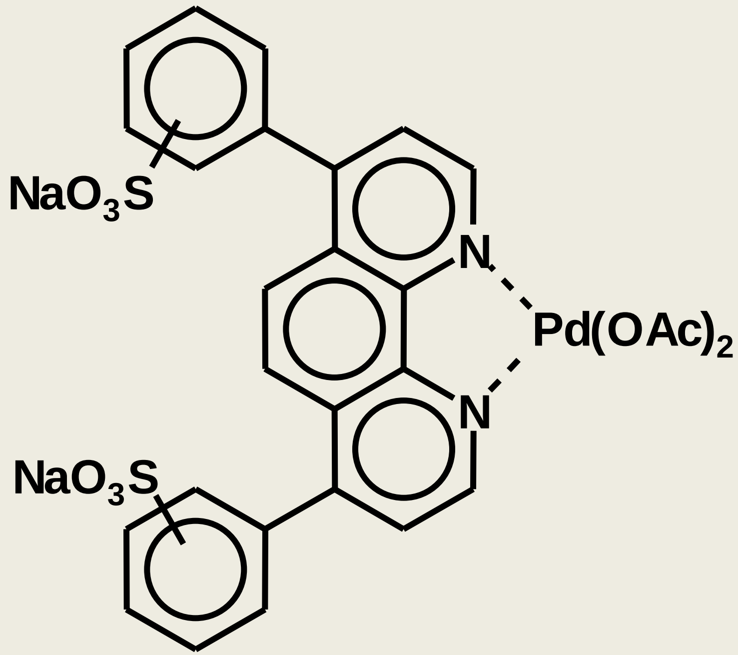
Catalytic Oxidations in Water

Water

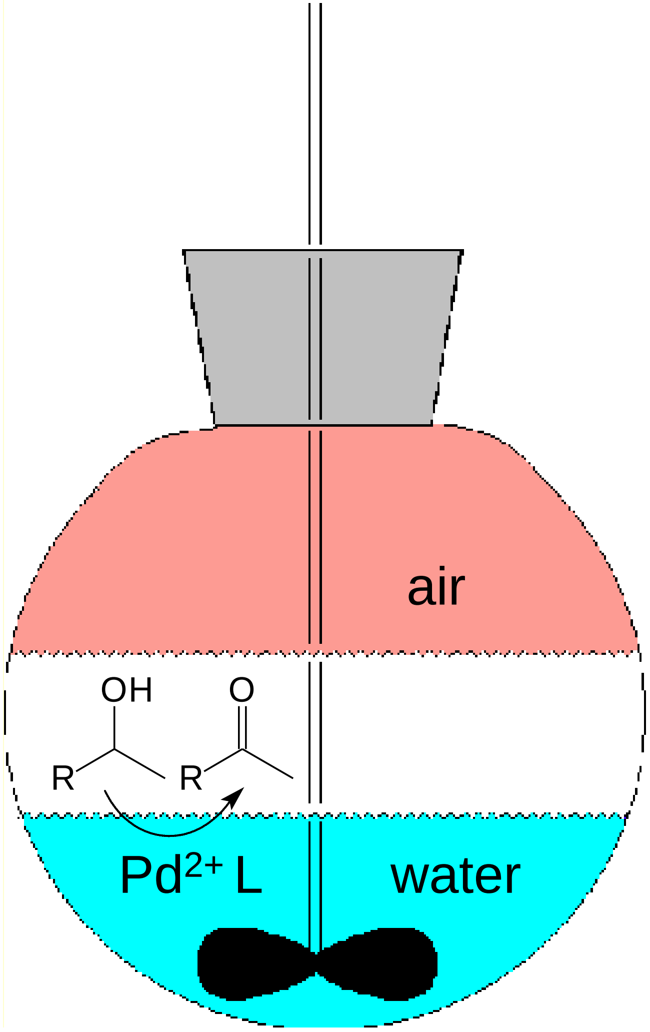
- Polar, inert and clean solvent
- Facile product separation
- Cheap and widely available
- Non-flammable and non-toxic
- Odourless and colourless

Recycling of catalyst

Green, Catalytic Alcohol Oxidations



Pd^{2+}-bathophenanthroline (L)



- **Air as oxidant**
- **No organic solvent**
- **Catalyst recycling via phase separation (recycled 4 times without activity loss)**

G.J. ten Brink, I.W.C.E. Arends and R.A. Sheldon, Science 287 (2000) 1636-9.

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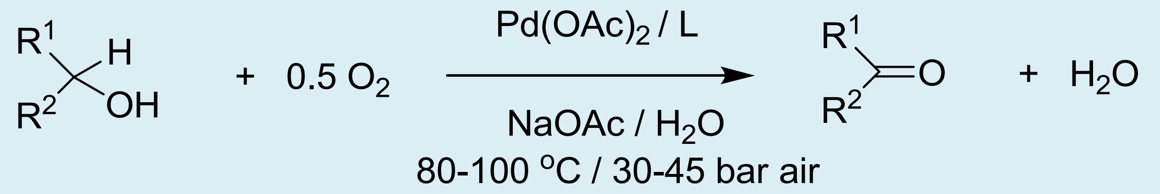
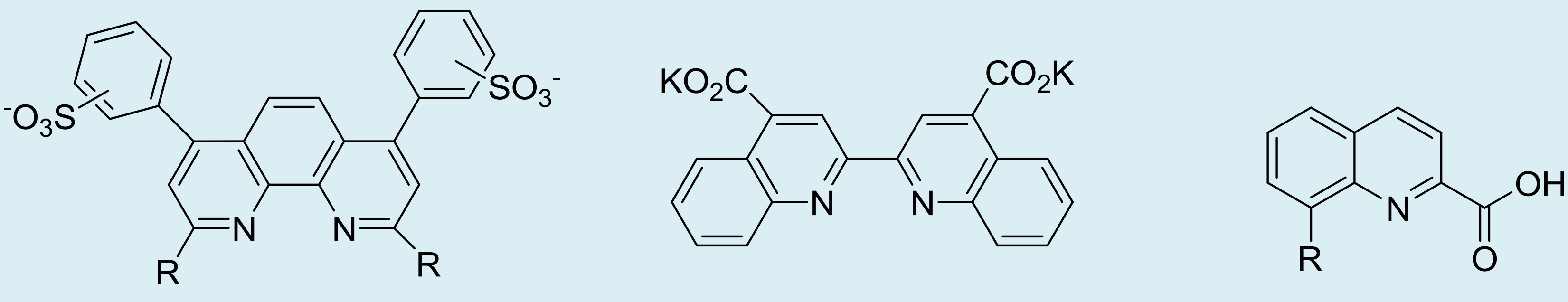
Aerobic Oxidation of Alcohols with Pd(II) – Diamine Catalysts





(*1*) (*2*) (*3*)

R = H, OH

(*1*) G.J. ten Brink, I.W.C.E. Arends and R.A. Sheldon, Science 287 (2000) 1636
(*2*) B. P. Buffin, N. L. Belitz, S. L. Verbeke, *J. Mol. Catal. A: Chemical*, 2008, *284*, 149
(*3*) D. S. Bailie, G. M. A. Clendenning, L.McNamee and M. J. Muldoon, *Chem. Commun.,* 2010, *46*, 7238

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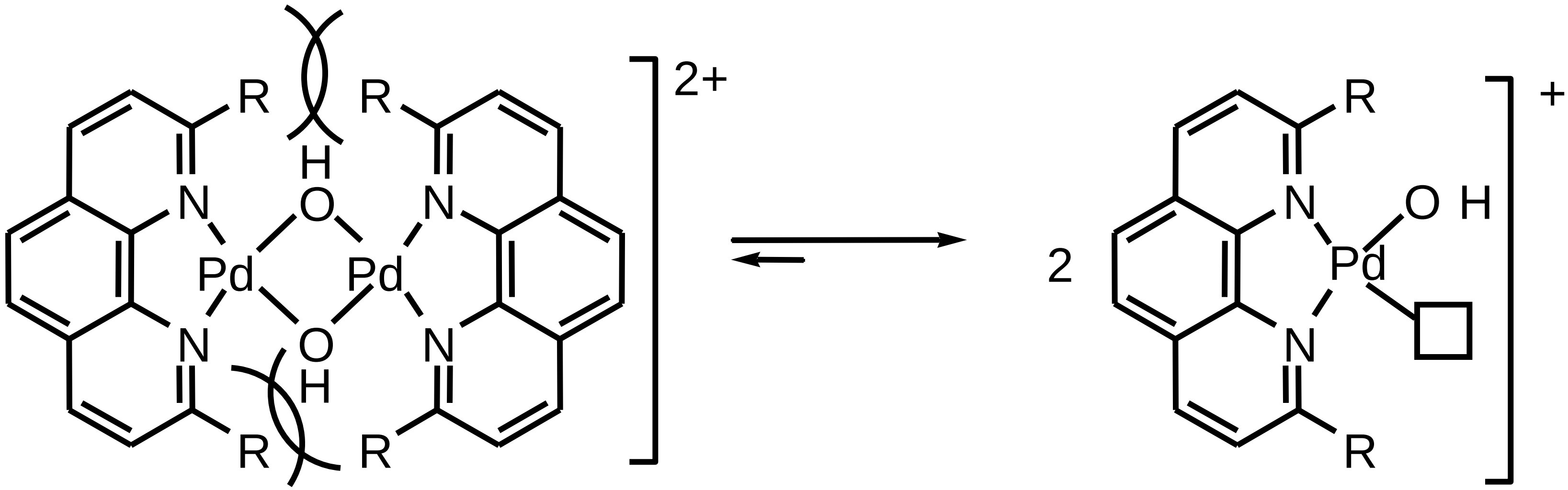
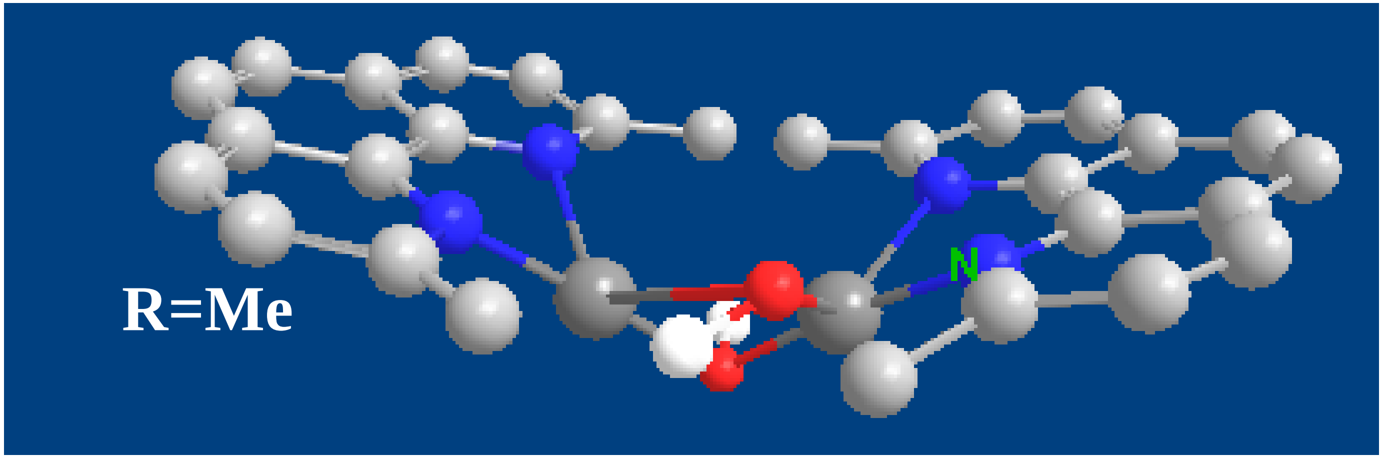
Steric Effects



Structure in aq. solution

Active catalyst



Cup*Pd(OAc)$_2$

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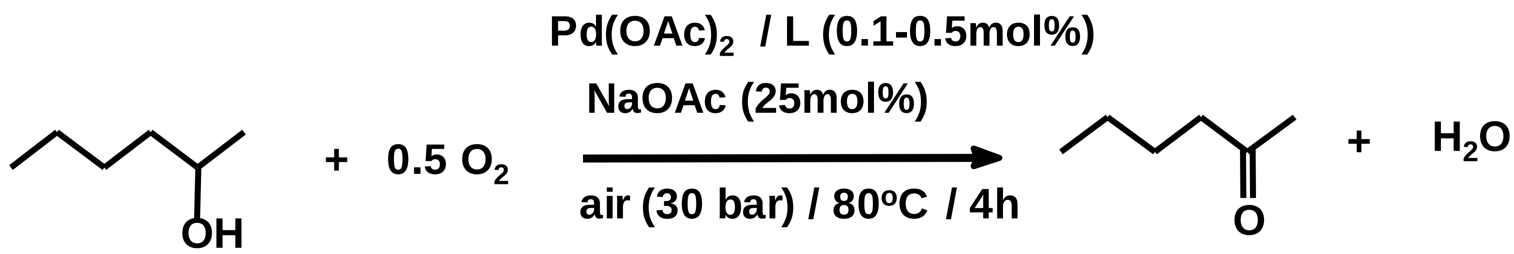
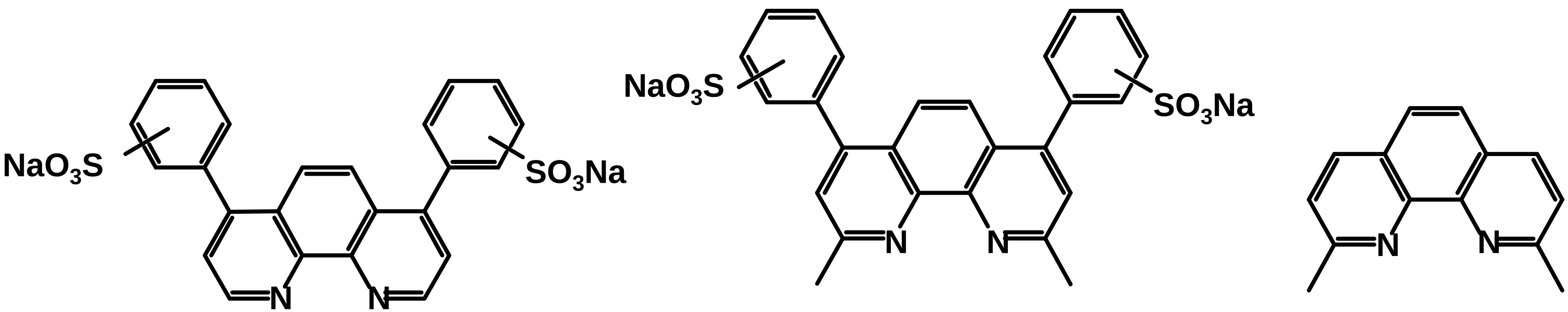
Steric Effects





L	PhenS	BathocuproinS	Cuproin
TOF (h^{-1})	50	150	1800
Solvent	H_2O	H_2O	H_2O / DMSO (1:1)

Cuproin/Pd(OAc)$_2$: Functional Group Tolerance

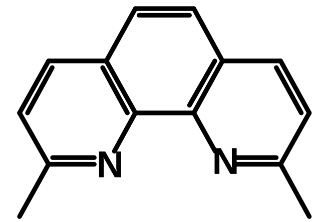
C=C	C=O	acetylene
OR	SR	SiR_3
(O)S=O	SO_3R	NR_2
CN	$CONH_2$	CO_2R

Alcohol (0.3M),0.5m% LPd(OAc)$_2$

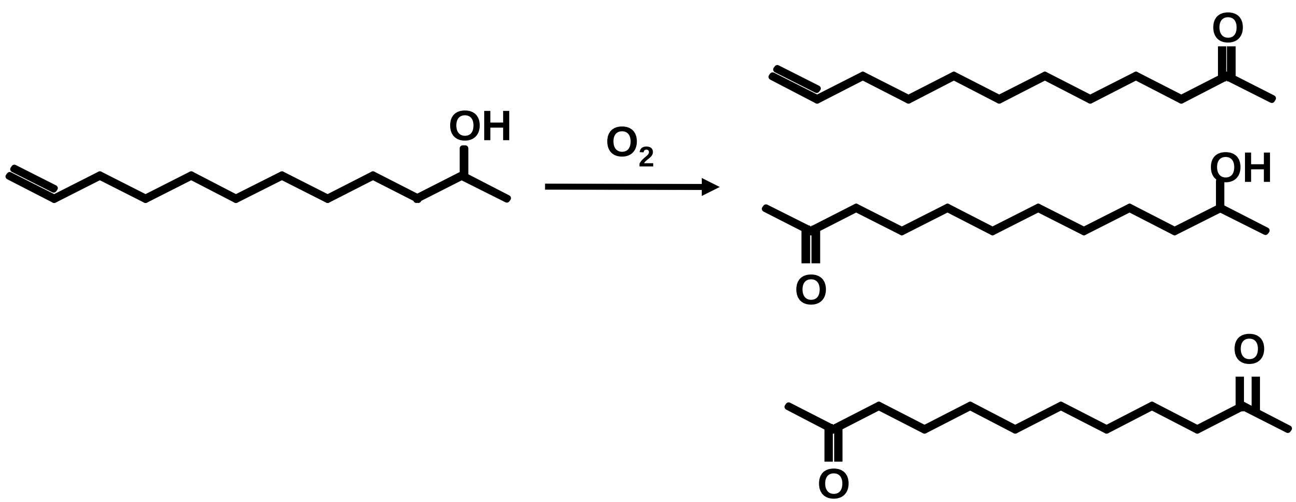
25m % NaOAc in DMSO/H_2O

80^{0}C/30 bar air,4h

L =



L =PhenS	Cuproin
~ 2 %	> 99%
75 %	
8 %	



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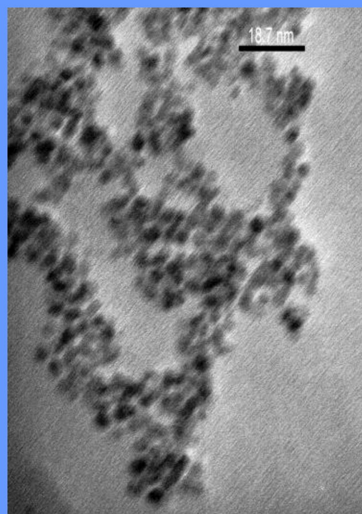
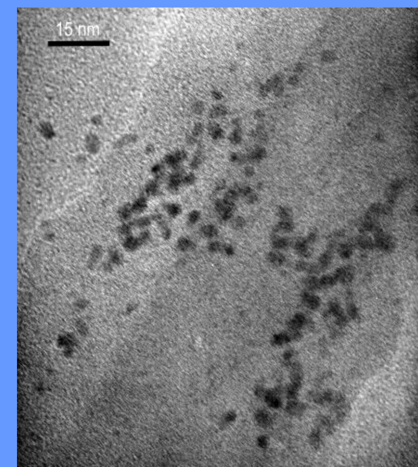
Pd-nanoparticles





$Pd(O_2CCF_3)_2$/neocuproin =1/1
ethylene carbonate in H_2O

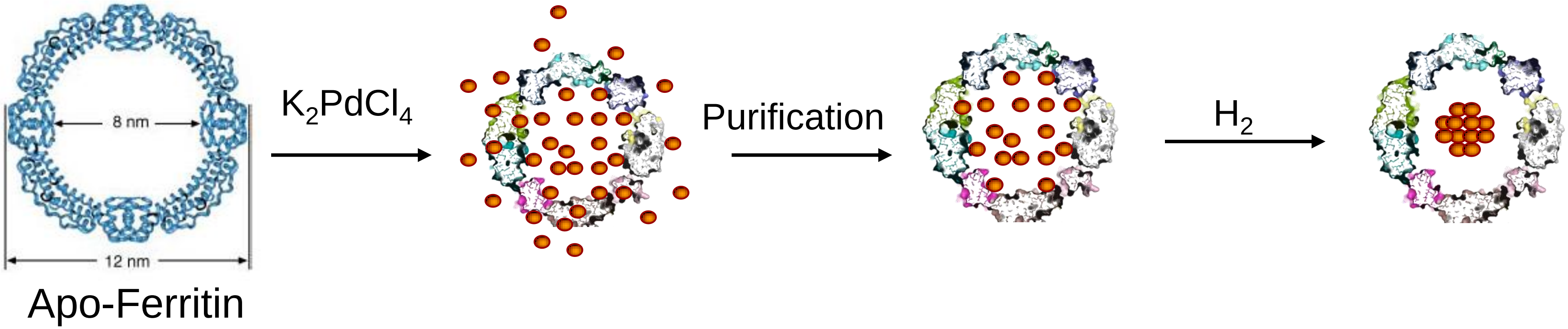
Particle size: 5 nm

$Pd(O_2CCF_3)_2$/neocuproin =1/1
PEG3400 in H_2O

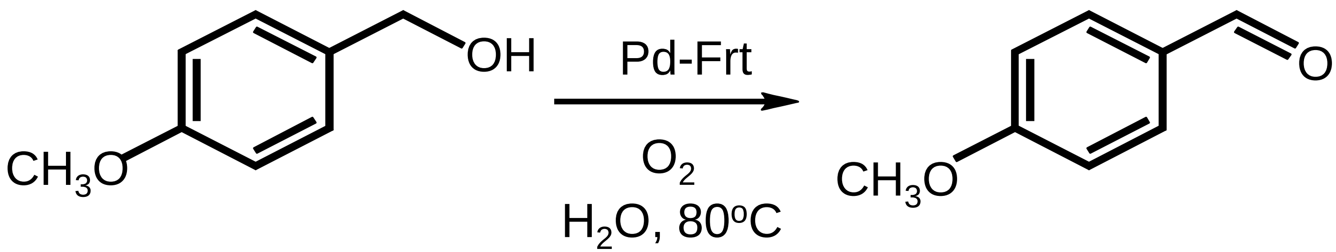
Particle size: 3 nm

See also I. I. Moiseev et al, *Chem. Commun*. 1985, 937-8

Pd-Ferritin as an Oxidation Catalyst



Thermostable Fer from Pyrococcus furiosus



Chemomimetic biocatalysis

Seda Aksu-Kanbak

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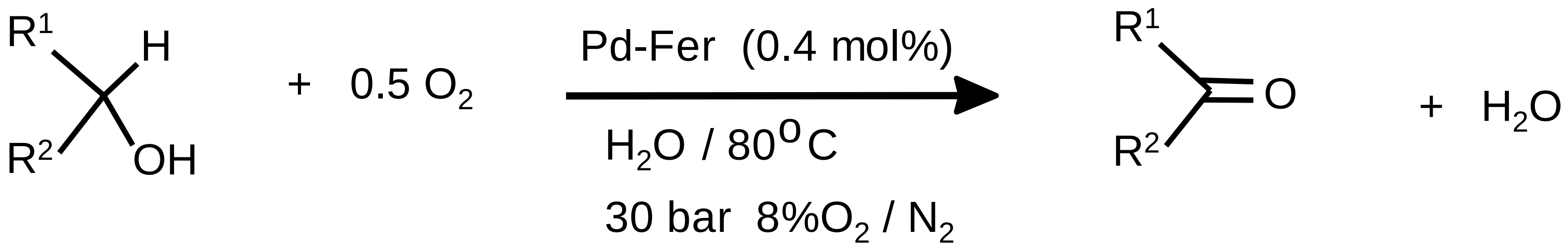
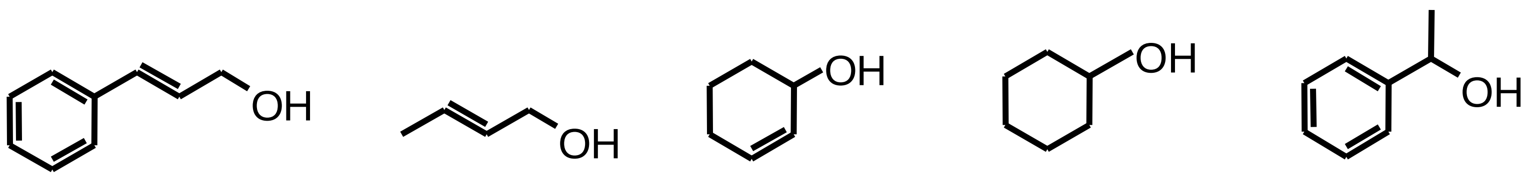
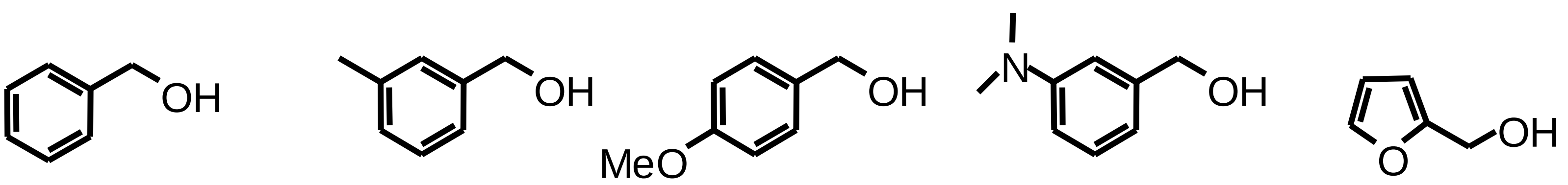
Catalytic Oxidation of Alcohols in Water with Pd-Ferritin





TOF (h^{-1}) 197 36 101 3 3



TOF (h^{-1}) 37 48 138 19 12

N.B. Pd-Fer catalyzes the Suzuki coupling *in aqua*

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Organocatalysis

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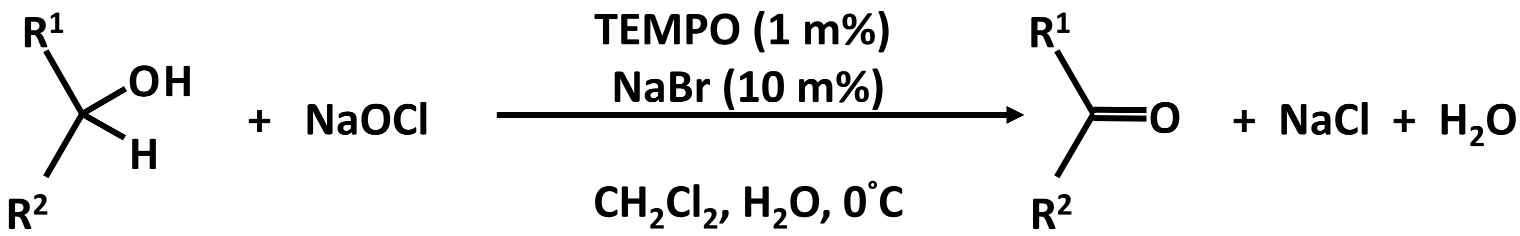
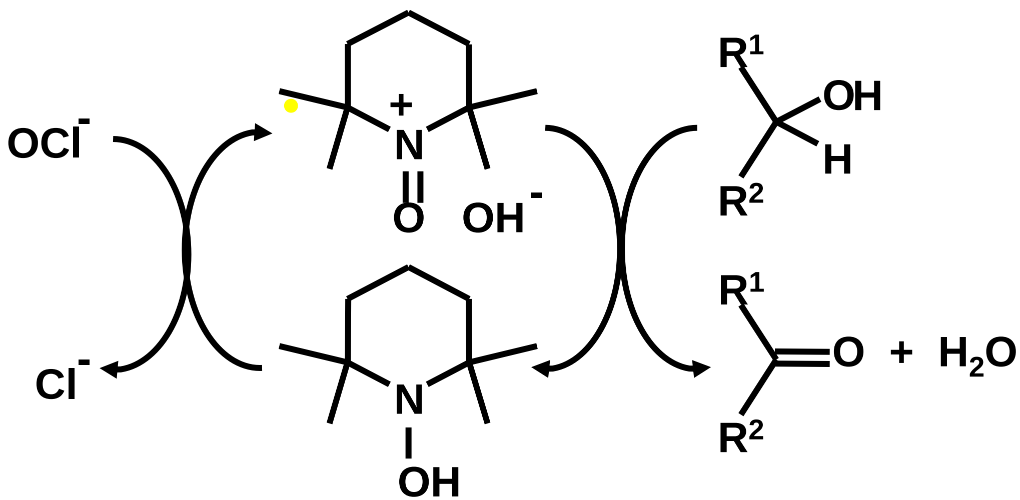
Stable Nitroxyl Radicals:
Versatile Catalysts for Alcohol Oxidations





There are many shades of green!

P.L.Anelli, C.Biffi, F.Montanari, S.Quici,JOC,52,2559 (1987)

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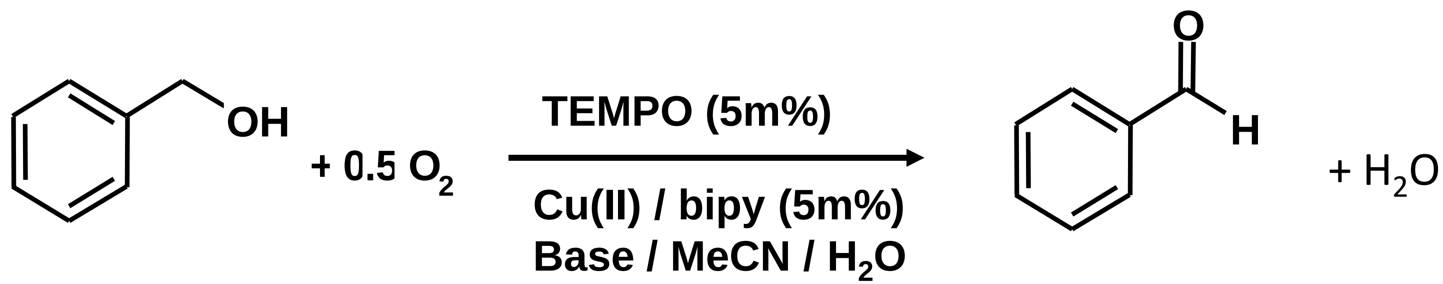
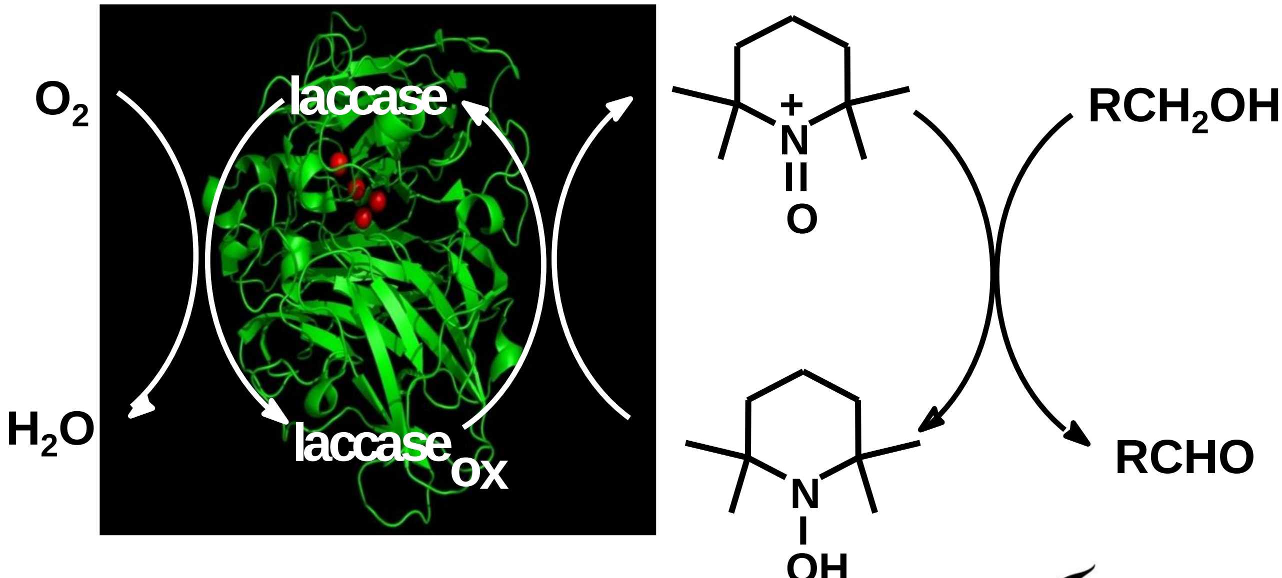
Dioxygen (Air) as Oxidant



Highly selective for 1e alcohols

Laccase : a blue enzyme for green chemistry



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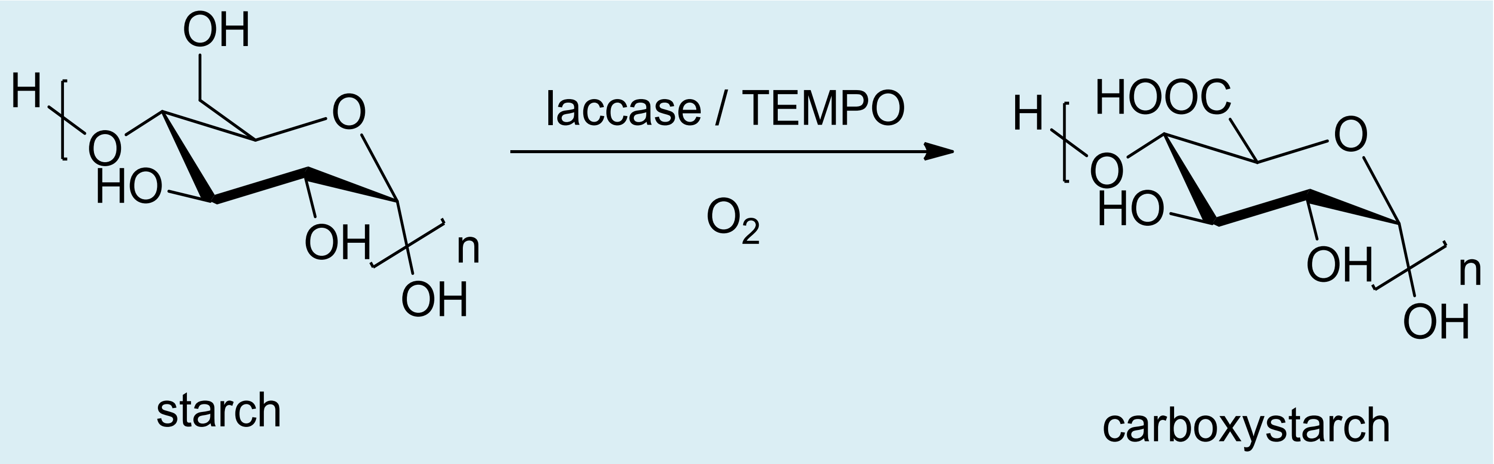
Oxidation of Benzylic Alcohols

$$RCH_2OH \xrightarrow[O_2\text{ , }30°\text{ C}]{\text{laccase/TEMPO}} RCHO$$

Substrate	Product	Conversion % after 4 hour
3-Methoxybenzyl alcohol	3-Methoxybenzaldehyde	100
Veratryl alcohol	3,4-Dimethoxybenzaldehyde	100
4-Methoxybenzyl alcohol	4-Methoxybenzaldehyde	98
3-Phenyl-2-propene-1-ol	Cinnamaldehyde	72
3-(Hydroxymethyl) pyridine	Nicotinaldehyde	98
Benzyl alcohol	Benzaldehyde	90

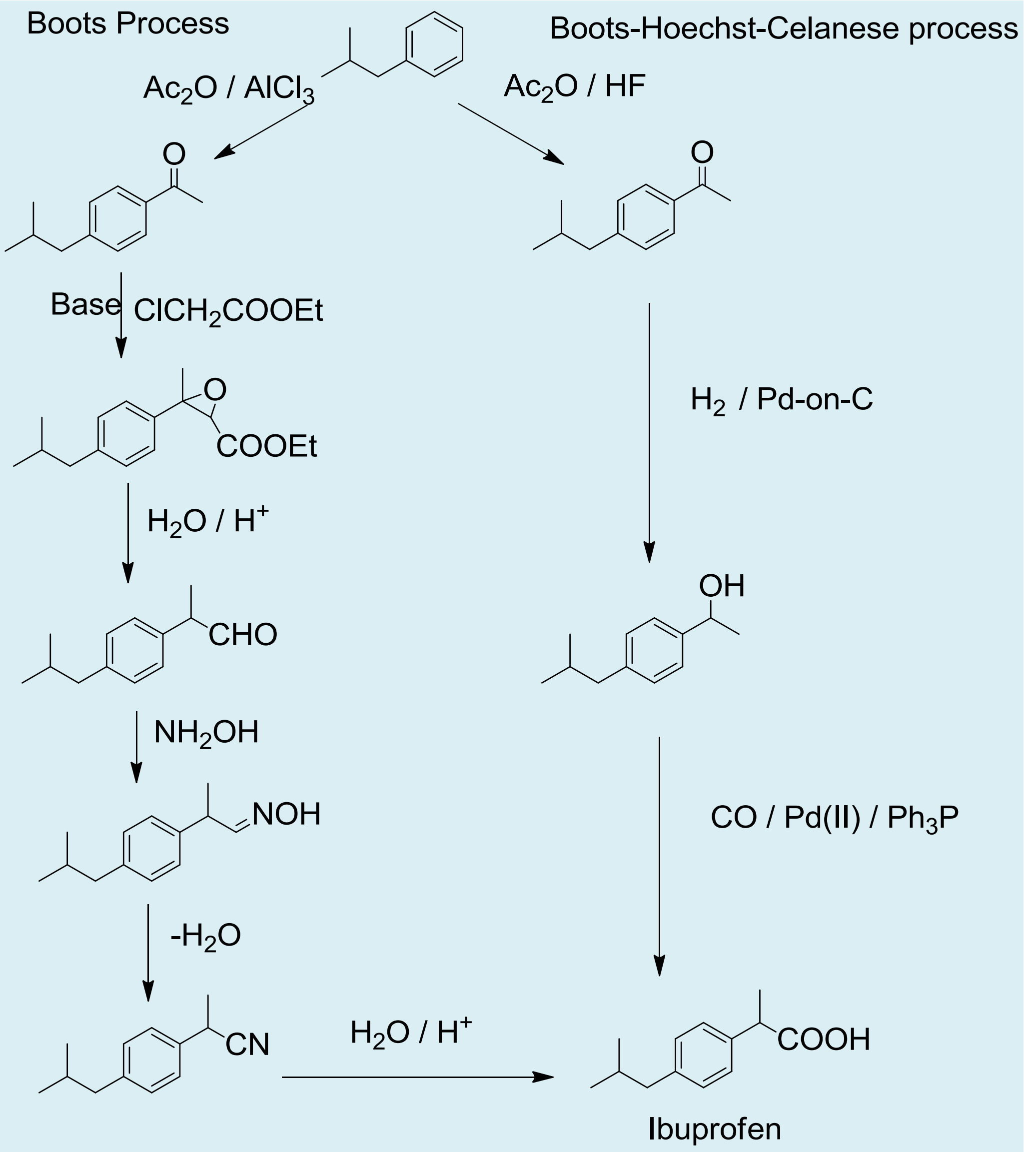
1.6 mmol substrate, Lacc/Subs: 62.5 U/mmol,
TEMPO (9.4 mol%), 0.1 M phosphate buffer (pH 4)

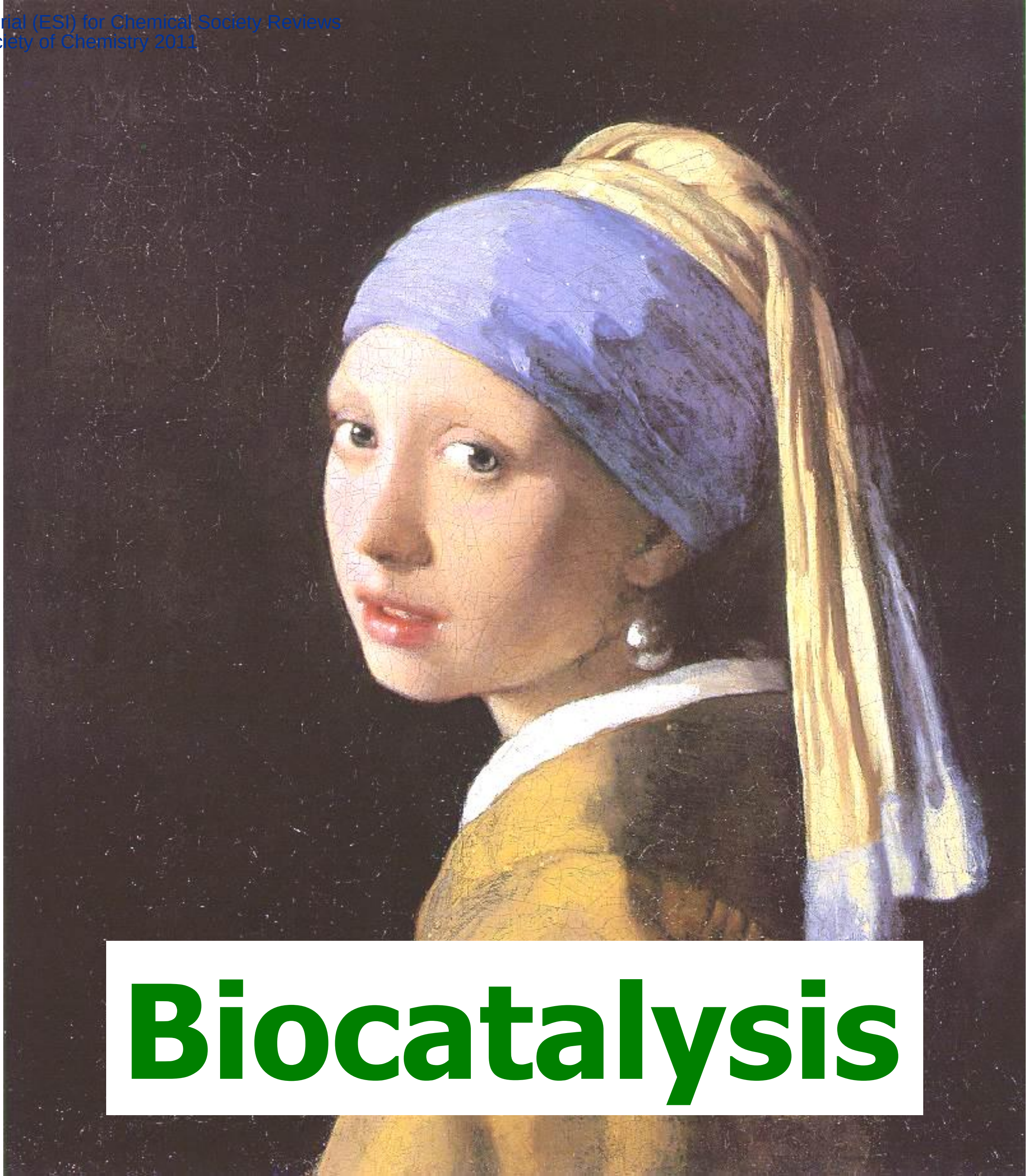
A Green Product: Carboxystarch



- A biodegradable water super absorbent
- To replace poorly biodegradable polyacrylates
- Laccase immobiliized as a CLEA for improved performance

Efficiency in C-C Bond Formation: Carbonylation





Biocatalysis

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Biocatalysis is Green & Sustainable

- **Enzymes are derived from renewable resources and are biodegradable**
- **Avoids use of (and product contamination by) scarce precious metals**
- Mild conditions: ambient T & P in water
- High rates & highly specific : substrate, chemo-, regio-, and enantiospecific
- Higher quality product
- No special equipment needed

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Biocatalysis : why now ?

1. Genome sequencing (> 5000)
   (more enzymes)

2. Directed evolution technologies
   (better enzymes)

3. Immobilization technologies
   (better formulation)

4. Green & Sustainable
   (small environmental footprint)

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Two Types of Biotransformations

- Free enzymes
  - isolated (purified)
  - whole cells (not growing)
  - can be very high STY

- Fermentations (growing microbial cells)
  - less expensive (no enzyme isolation needed)
  - often dilute solution / low STY
  - water footprint /energy intensive
  - byproducts from enzyme impurities

E Factors of Fermentations

Product	E Factor	E factor (incl. water)
Citric acid	1.4	17
Bioethanol	1.1	42[a]
Rec. insulin	6600	50,000

[a] Includes water and carbon dioxide

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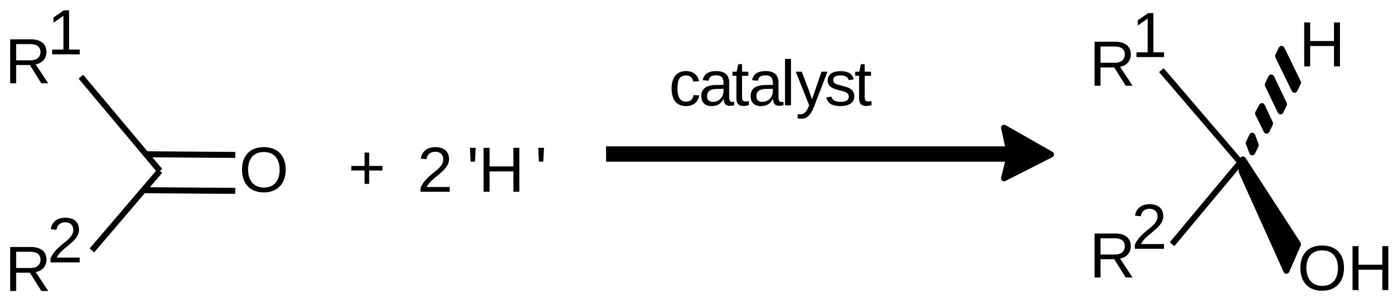
Asymmetric Ketone Reduction



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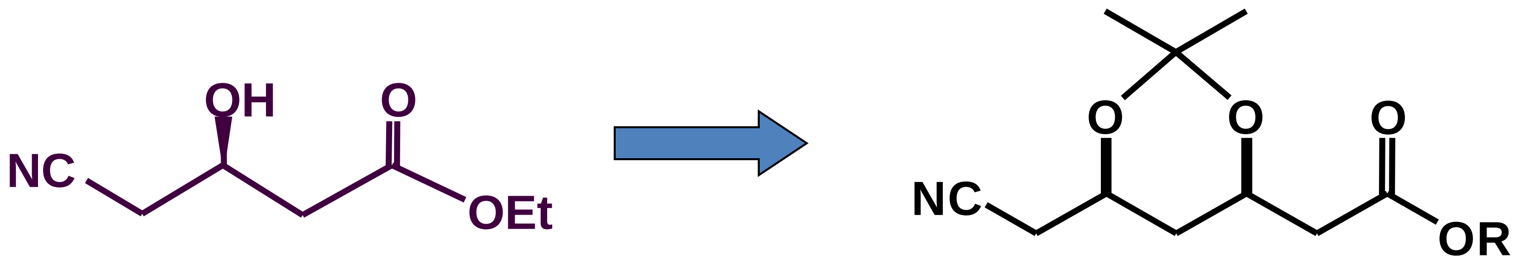
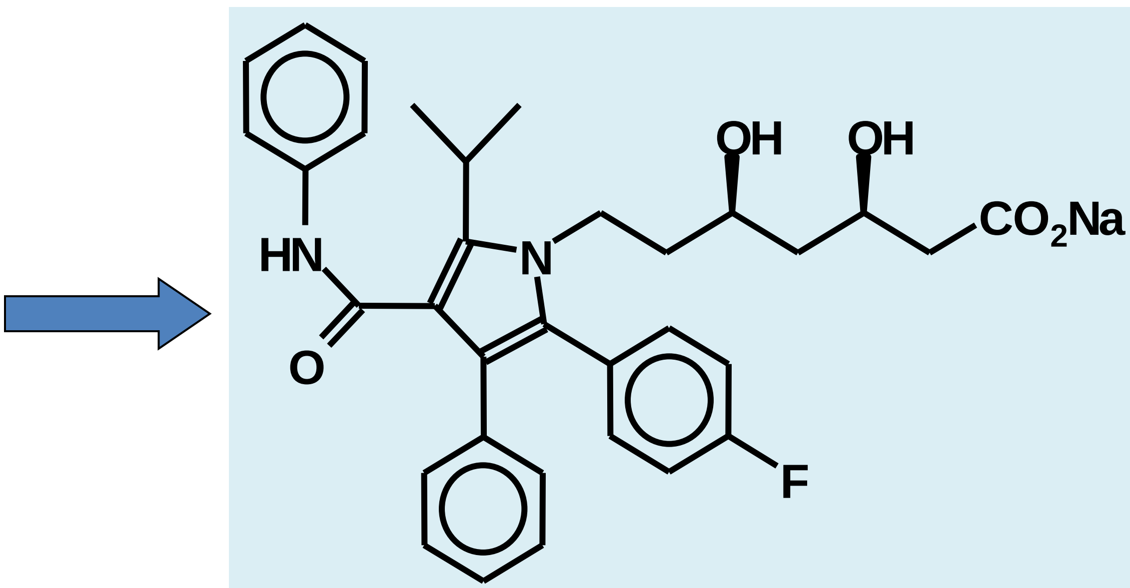
Production of Lipitor Intermediates





Lipitor (Pfizer)

Sales in 2009: $14 bio

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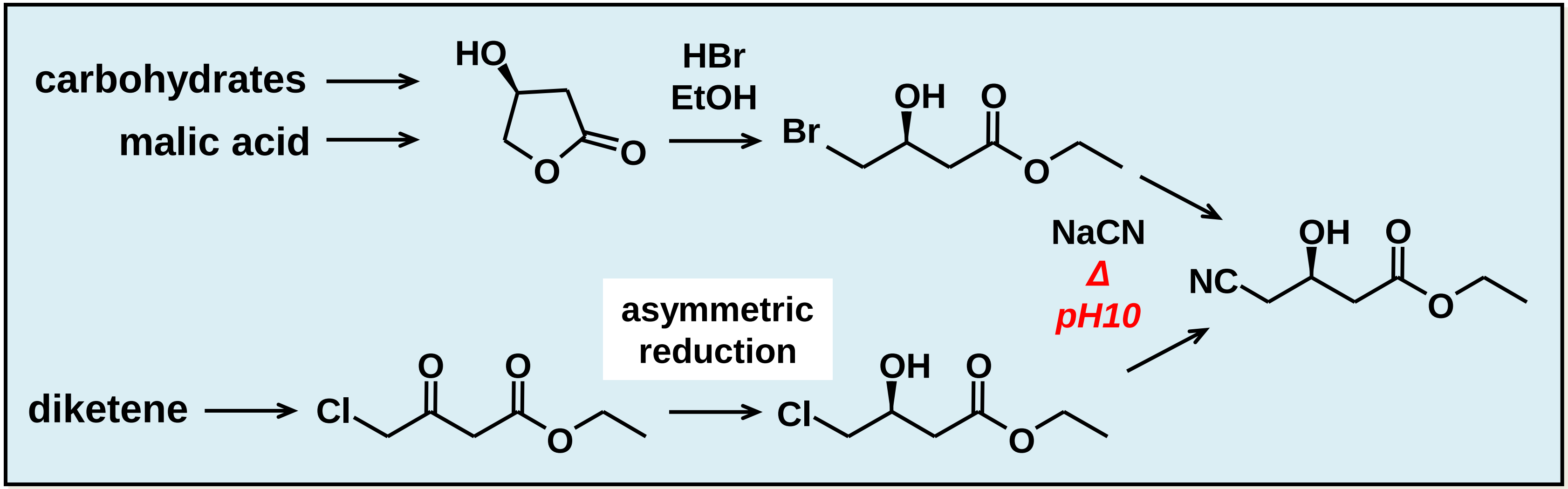
Existing Processes for Hydroxynitrile

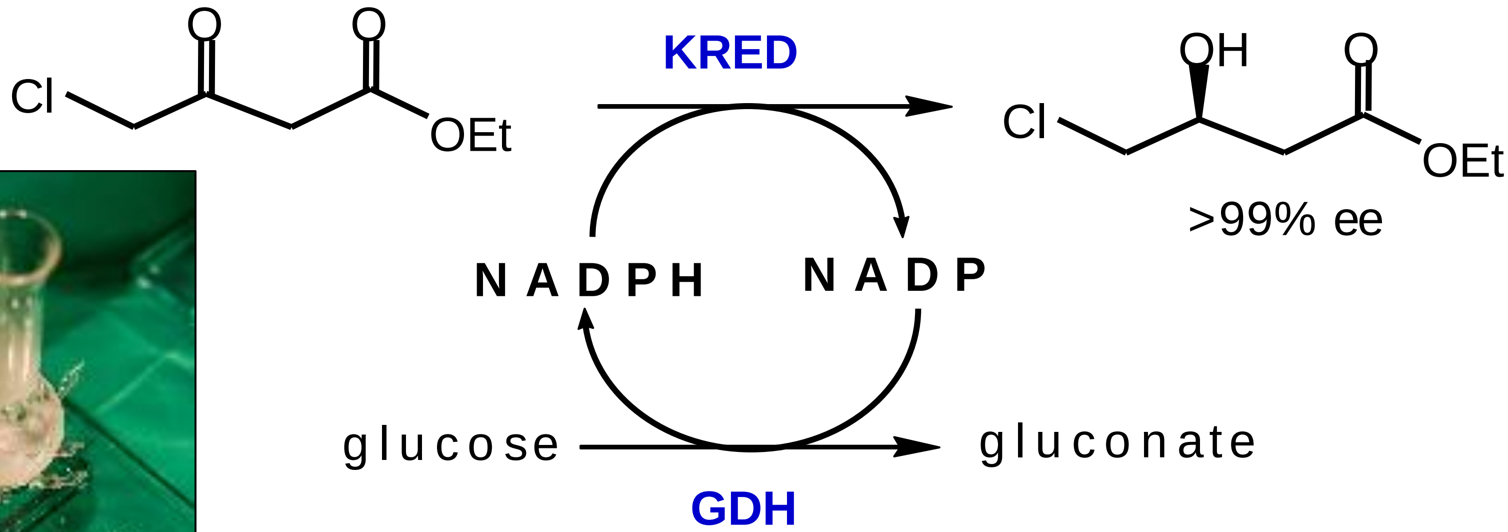


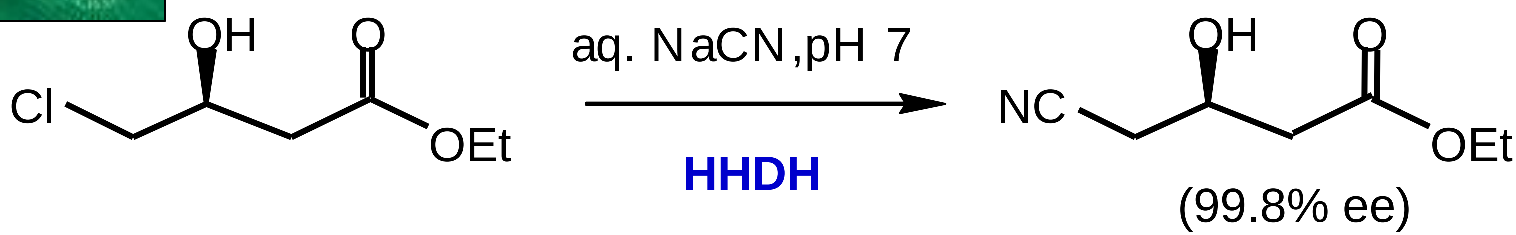
- Forcing conditions for cyanation result in base-catalyzed side reactions,
- Purification requires problematic, high vacuum fractional distillation.

→***Understanding the problem is key (chem. and opt. purity >99%)***

→***Cyanation at neutral pH and RT (with an enzyme)***

Enzymatic Synthesis of Lipitor Intermediate





KRED = keto reductase ; GDH = glucose dehydrogenase

HHDH = halohydrin dehalogenase (non-natural nucleophile)

R.J.Fox, S.C.Davis,R.A.Sheldon, G.W.Huisman, et al
Nature Biotechnology, *25* (2007) 338-344

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Directed Evolution for Improved Performance

Features of the Wild-Type Enzymes:

- high enantioselectivity
- mild (ambient) conditions
- no metal catalysts required
- no need for dedicated equipment
- low productivities

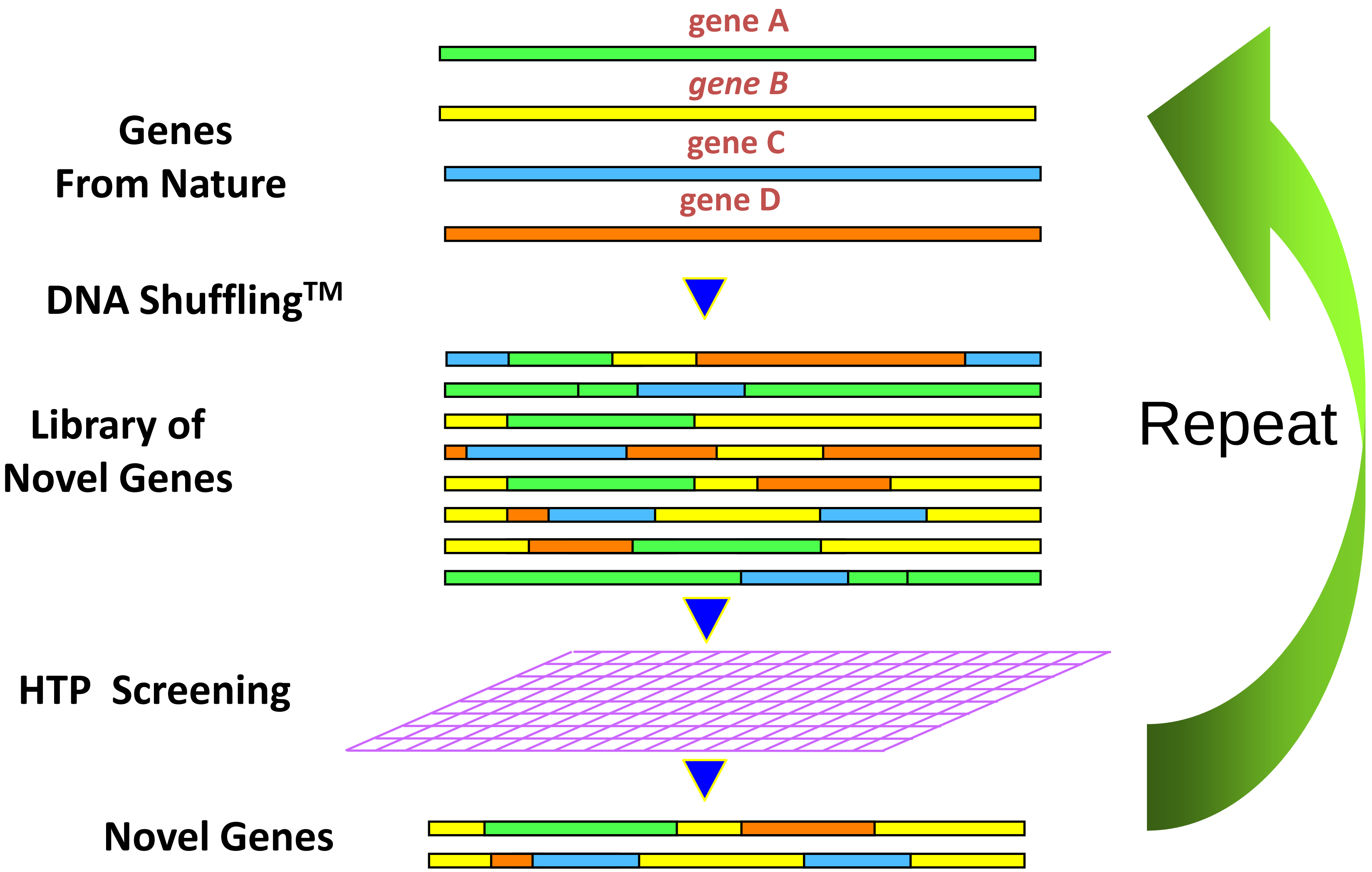
Productivities of all three enzymes improved by directed evolution using gene shuffling technology

W.P.C.Stemmer,Nature,370,389-391,1994

CLEA Technologies

Electronic Supplementary Material (ESI) for Chemical Society Reviews

Gene Shuffling : Evolution in the Fast Lane



W.P.C.Stemmer,Nature,370,389-391,1994

CLEA Technologies

E factor of the Codexis Three-Enzyme Process

Presidential Green Chemistry Challenge Award 2006

Waste	Quantity (kg per kg HN)	% contribution to E (excluding water)	% contribution to E (including water)
ECAA losses (8%)	0.08	<2%	<1%
Triethanolamine	0.04	<1%	<1%
NaCl and Na_2SO_4	1.29	**22%**	ca. 7%
Na-Gluconate	1.43	**ca. 25%**	ca. 9%
BuOAc (85%recycle)	0.46	**ca. 8%**	ca. .3%
EtOAc (85%recycle)	2.50	**ca. 43%**	ca. 14%
Enzymes	0.023	**<1%**	<1%
NADP	0.005	**0.1%**	<0.1%
Water	12.25	-	67%
E Factor	**5.8 (18)**		

R. A. Sheldon, G. Huisman et al, Green Chem. 2010, 12, 81-86

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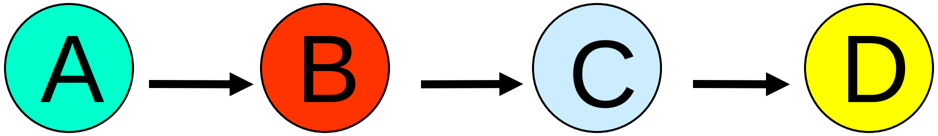
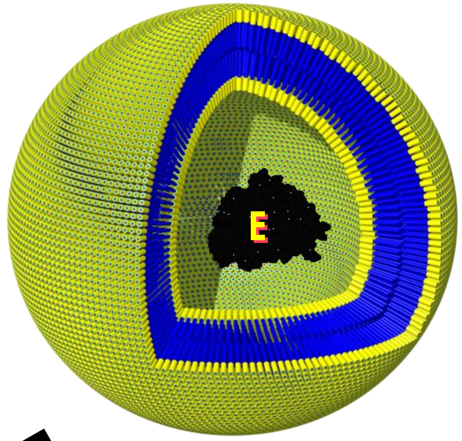
Biocatalyst Engineering

Multistep Syntheses: Nature's Way

The Cell Factory:



Cascade approach in metabolic pathways by enzymatic catalysis in water without isolation of intermediates



Step economy

Compartmentalisation for compatibility

Limitations of Enzymes

- **Low operational stability & shelf-life**
- **Cumbersome recovery & re-use**
- **Product contamination**
- **Allergic reactions of proteins**

The solution: immobilization
an enabling technology

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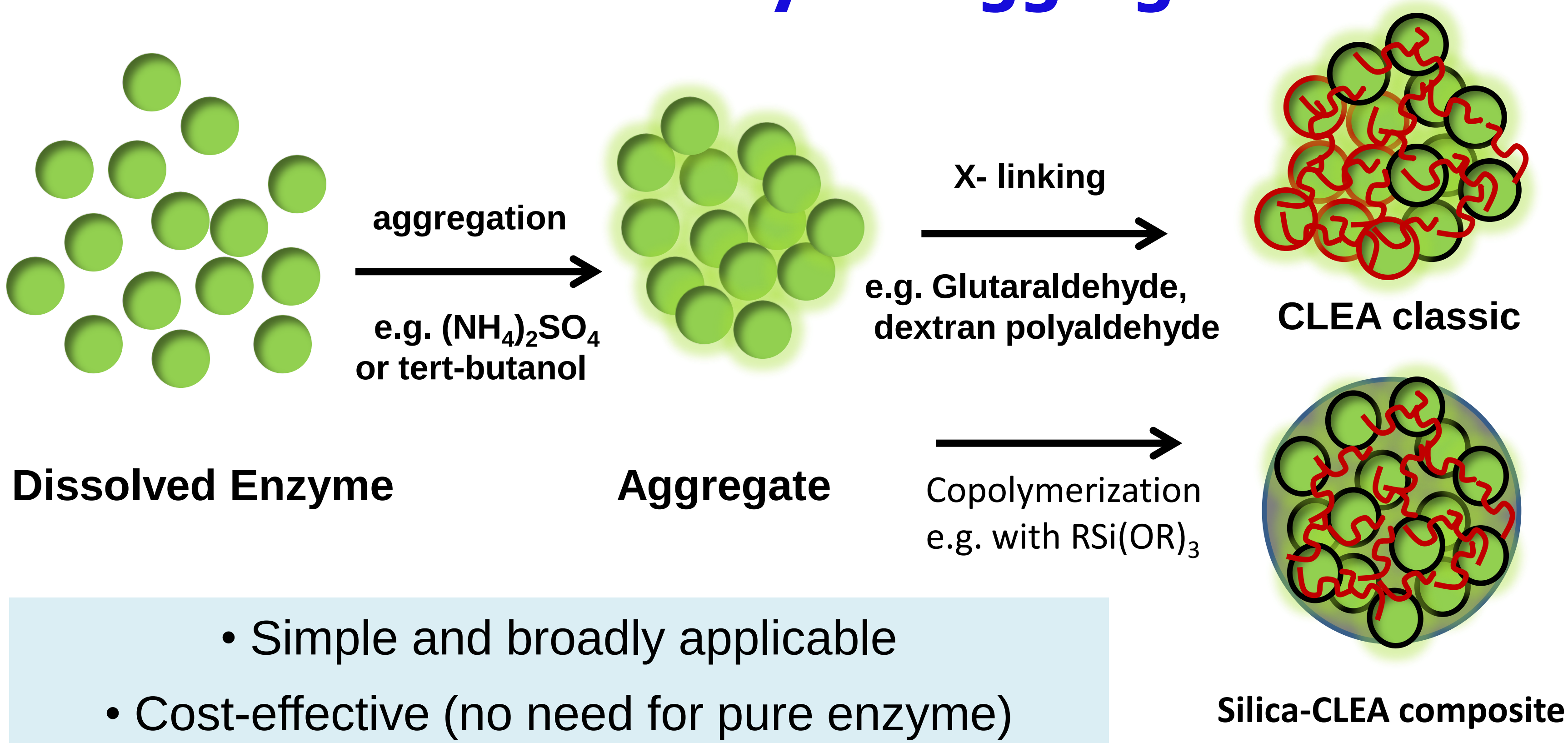
Heterogeneous Catalysis with Cross-Linked Enzyme Aggregates



- Simple and broadly applicable
- Cost-effective (no need for pure enzyme)
- Short time-to-market (low development costs)
- Scalable protocols

www.cleatechnologies.com

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Advantages of CLEAs

1. Improved properties

- better storage and operational stability
- (to heat, organic solvents and autolysis)
- hypoallergenic
- no leaching of enzyme in aqueous media

2. Cost-effective

- no need for highly pure enzyme (crude enzyme extract sufficient)
- easy recovery and recycle (no product contamination)
- high activity recovery and productivity (kg product/kg enzyme)

3. Broad scope & short time to market

- combi CLEAs containing more than one enzyme

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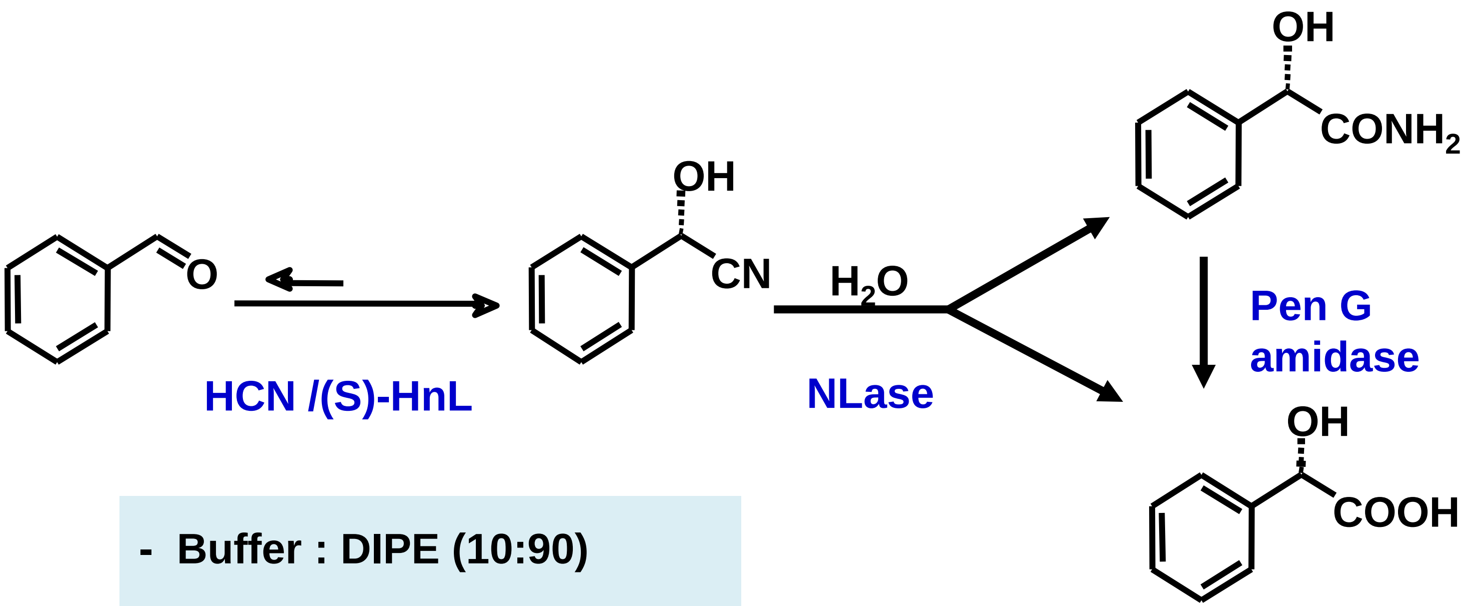
Step Economy a Tri-enzymatic Cascade with a Triple-Decker CLEA

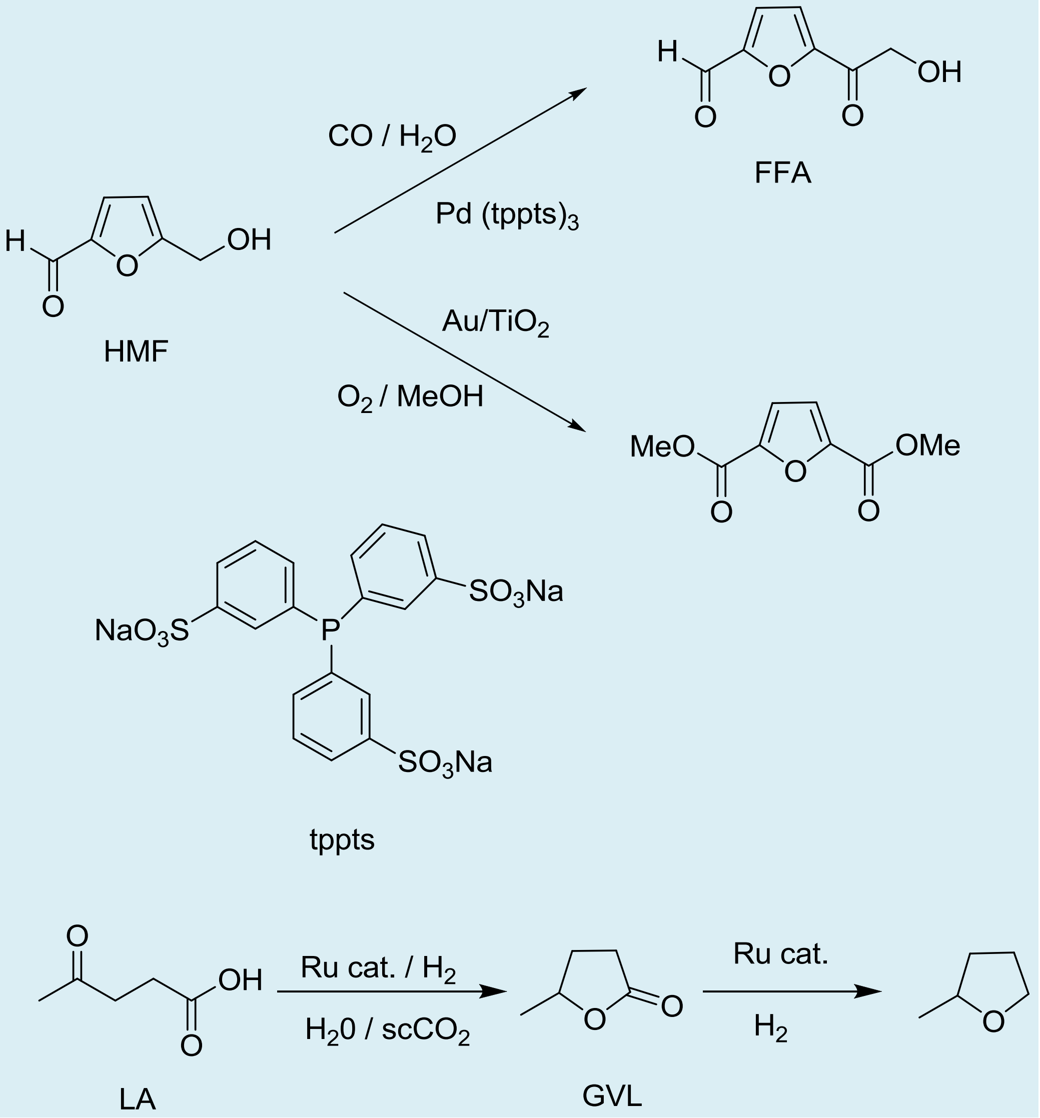


- Buffer : DIPE (10:90)
- pH 5.5 / RT / < 5h
- HnL/ NLase / Pen.acylase combi-CLEA

Conv. 96% / ee >99%

CLEA Technologies

Catalytic Conversion of Renewable Raw Materials



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Take Home Message

Green chemistry & (bio)catalysis merge science and technology with environment and economics on the road to a sustainable society.

Green chemistry is not only good for the environment it is good for business.


Think Green
and Sustainable