Green Chemistry & Catalysis for the Production of Flavours & Fragrances

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Green Chemistry

Technologies that are energy efficient,minimise or preferably eliminate the formation of waste, avoid the use of toxic and/or hazardous solvents and reagents and, where possible,utilise renewable raw materials.

Primary Pollution Prevention not Remediation

E Factors

E Factor = **amount** of waste/kg product

	Tonnage	E Factor
• Bulk Chemicals	10^4-10^6	<1 - 5
• Fine chemical Industry	10^2-10^4	5 - >50
• Pharmaceutical Industry	10-10^3	25 - >10

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

The E Factor

- Is the actual amount of waste formed in the process, including solvent losses, acids and bases used in work-up,process aids, and,in principle,waste from energy production (c.f. atom efficiency is a theoretical nr.)

- Can be derived from amount of raw materials purchased /amount of product sold :

E= [raw materials-product]/[product]

- A good way to quickly show (e.g.,to students)the enormity of the waste problem

Major Sources of Waste

- STOICHIOMETRIC BRONSTED & LEWIS ACIDS & BASES
  - Acid promoted rearrangements, e.g. Beckmann (H_2SO_4)
  - Friedel-Crafts acylation ($AlCl_3$, $ZnCl_2$, BF_3)
  - Base promoted condensations, e.g. Aldol (NaOH, NaOMe)

- STOICHIOMETRIC OXIDANTS & REDUCTANTS
  - $Na_2Cr_2O_7$, $KMnO_4$, 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)

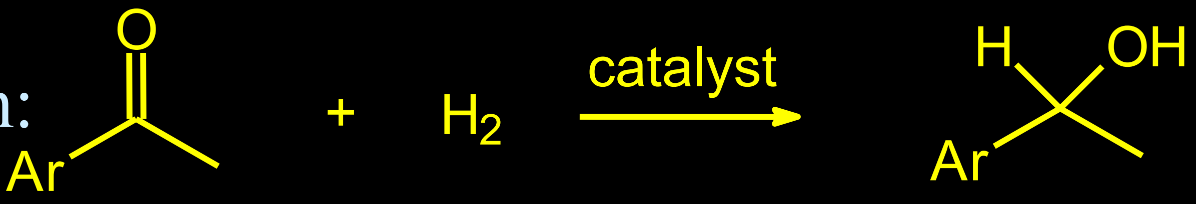
  with olefins and (alkyl)aromatics as basic raw materials

- Alternative reaction media / biphasic catalysis

- Biocatalysis, naturally

Atom Efficient Processes

Hydrogenation:

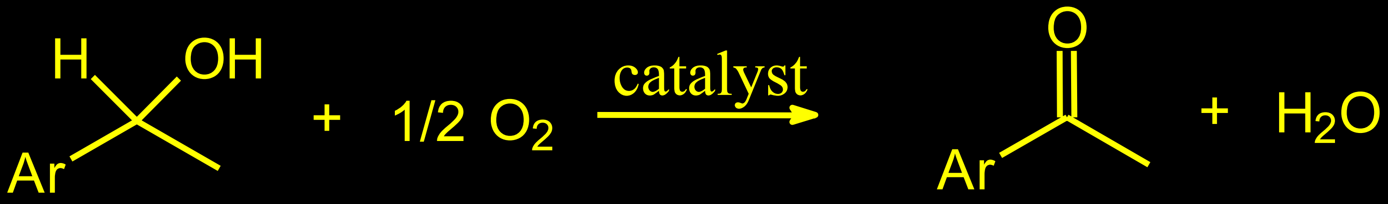


100% atom efficient

Carbonylation:

100% atom efficient

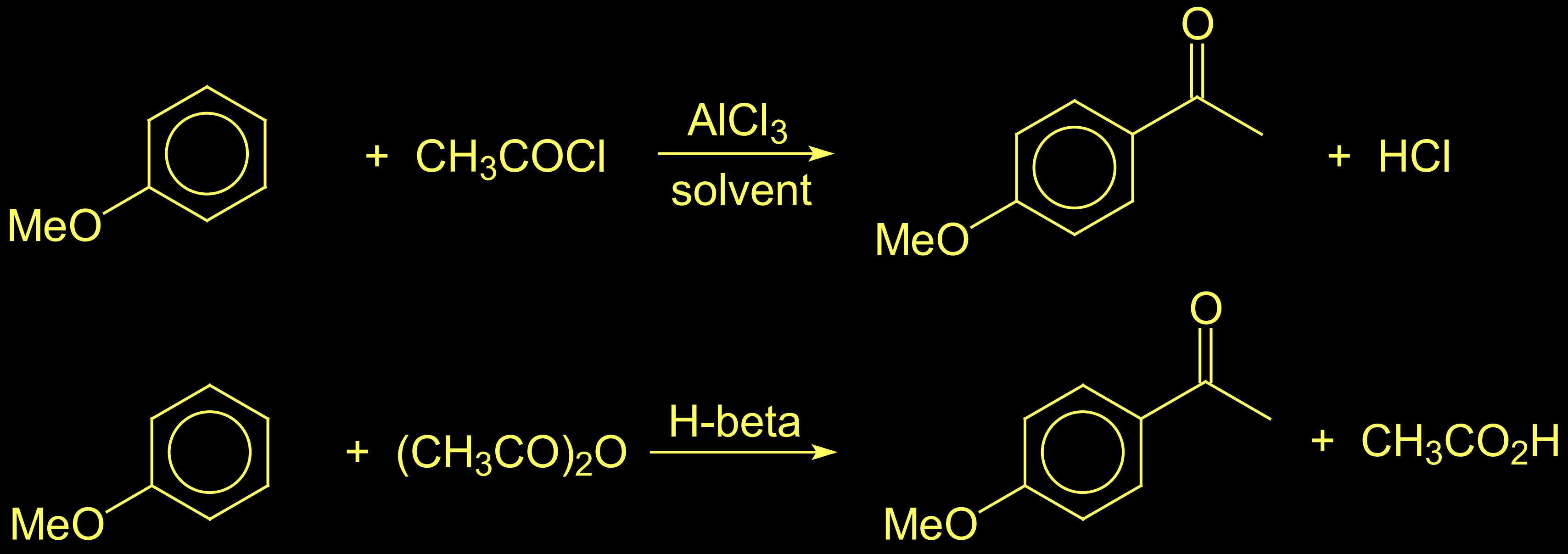
Oxidation:



87% atom efficient

Heterogeneous Catalysis

Zeolite Catalyzed Friedel Crafts Acylation

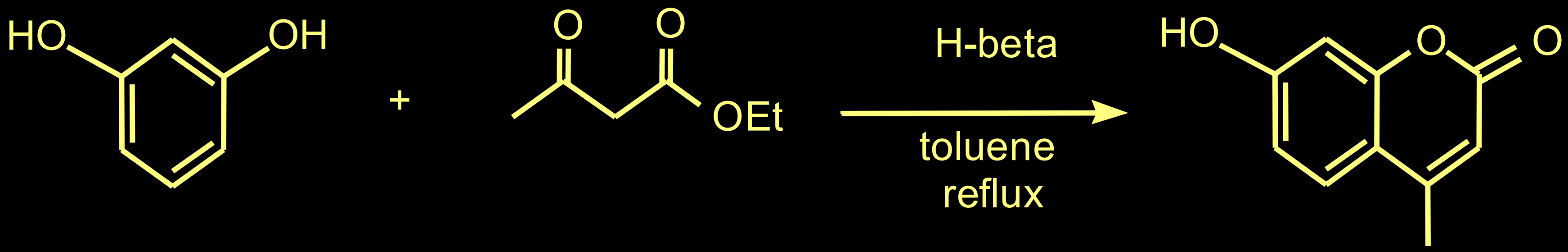


Homogeneous	**Heterogeneous**
$AlCl_3$ >1 equivalent	H-beta, catalytic & regenerable
Solvent (recycle)	No solvent
Hydrolysis of products	No water necessary
85-95% yield	>95% yield /higher purity
4.5 kg aqueous effluent per kg	0.035 kg aqueous effluent per kg

12 unit operations **3 unit operations**

S. Ratton, *Chem. Today (Chim. Oggi)*, March/April, 1998, 33

Zeolite Catalyzed Coumarin Synthesis



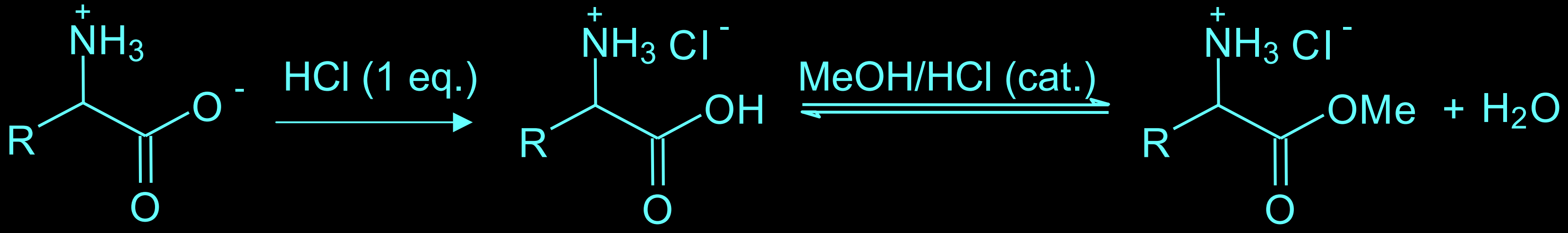
methylumbelliferone
70-80% yield

perfumery ingredient

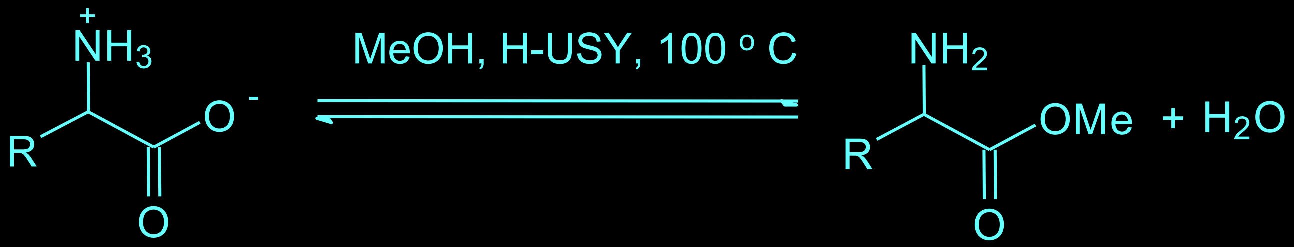
H van Bekkum et al. Recl Trav Chim Pays-Bas 115 226-230 1996

Salt-Free Esterification of Amino Acids

CONVENTIONAL :



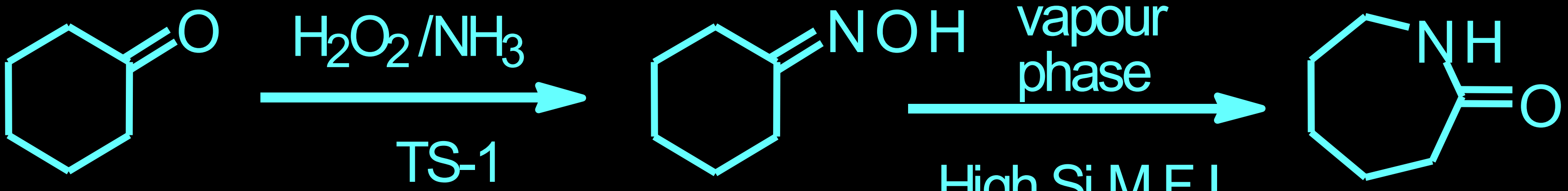
ZEOLITE-CATALYZED :



- R = $PhCH_2$ (aspartame intermediate); S/C = 20 (w/w), 83% yield (TON = 180)
- Naphtha cracking catalyst (H-USY)
- Opt. Active amino acids undergo racemization

M.Wegman, et al, *Green Chem.*, 3,61,2001

Green Caprolactam Process : Sumitomo

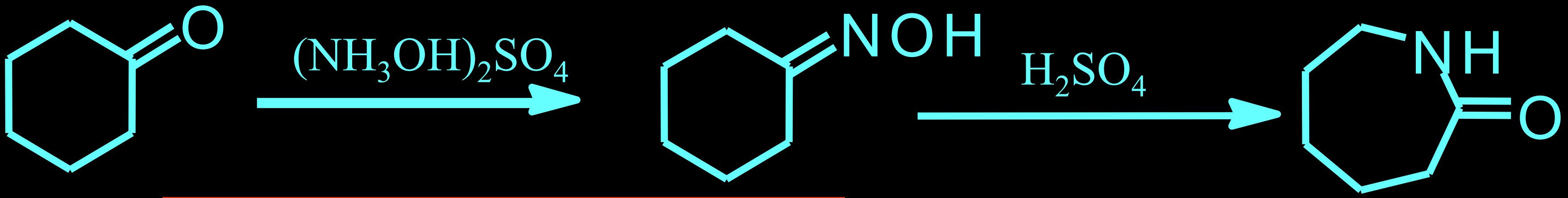


Ammoximation

Beckmann rearrangement

$$C_6H_{10}O + H_2O_2 + NH_3 \longrightarrow C_6H_{11}NO + 2H_2O$$

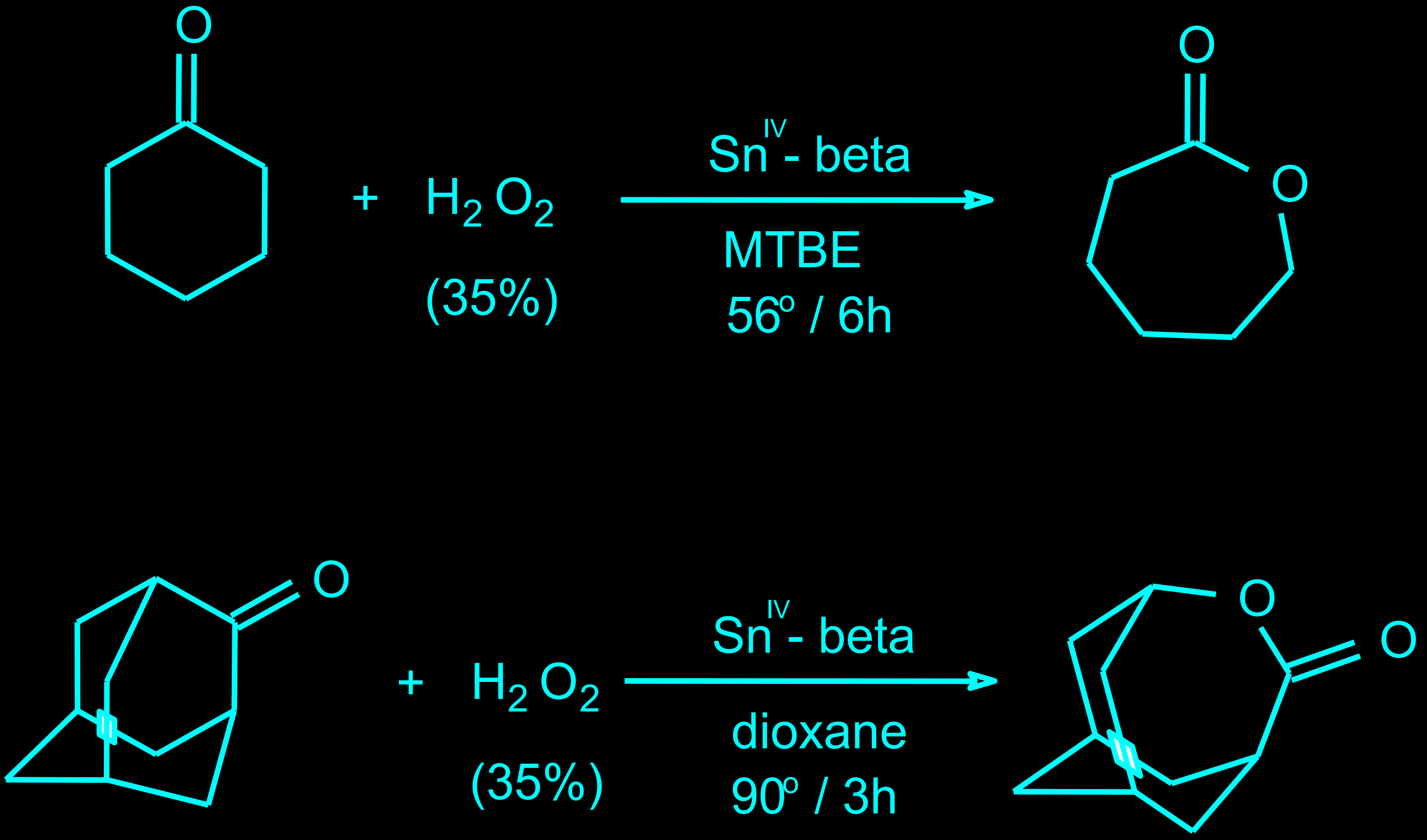
Atom efficiency = 75% ; E = 0.32 (<0.1)



Atom efficiency =29% ; E = 4.5

H.Ichihashi and M.Kitamura,Catal.Today,73,23,2002

A Heterogeneous Catalyst for Baeyer Villiger Oxidation with H_2O_2



94% yiel
>98% sel.

52% yiel
>98% sel.

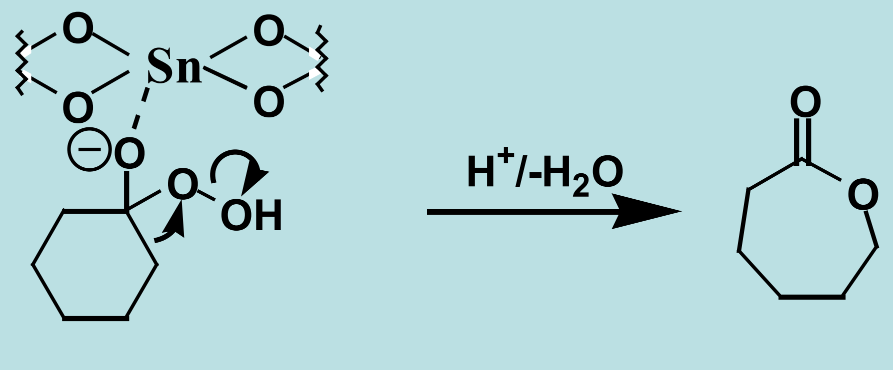
S / C = 150

1.6 w% Sn in zeolite beta

Corma, J. T Nemeth, M Renz and S Valencia, *Nature*, 2001, 412, 423

HETEROGENEOUS Sn-CATALYST :

- Tetrahedral incorporation of Sn^{IV} in Al-free beta demonstrated by ^{119}Sn-NMR (δ = -445 ppm)
- Filtration test showed no residual activity
- Recycling of catalysts displayed no considerable loss.
- Homogeneous $SnCl_4$ exhibits > 10x lower activity
- SnO_2 on surface not active as catalyst

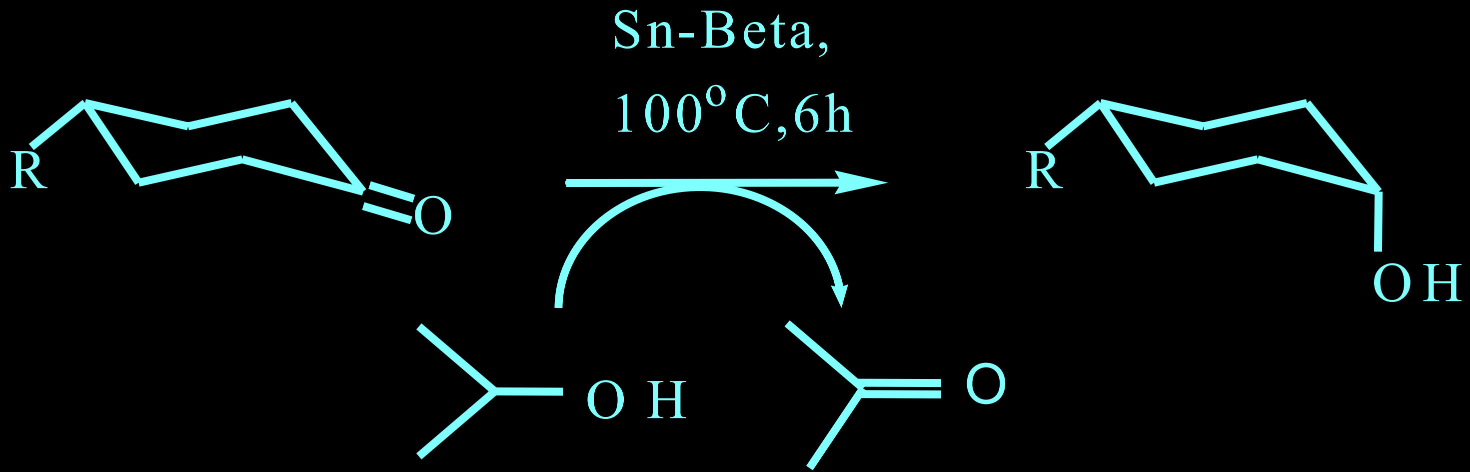


Criegee adduct

Lewis-acid activates carbonyl group not H_2O_2

A.Corma, L.T.Nemeth, M.Renz and S.Valencia, *Nature*, 2001, 412, 423
M. Renz et al. Chem. Eur. J., 8 (2002) 4708

Sn-Beta Catalyzed MPV reduction of Alkylcyclohexanones



- IPA/sub= 60/1
  60mmol sub/75mg cat.
  2% Sn-Beta

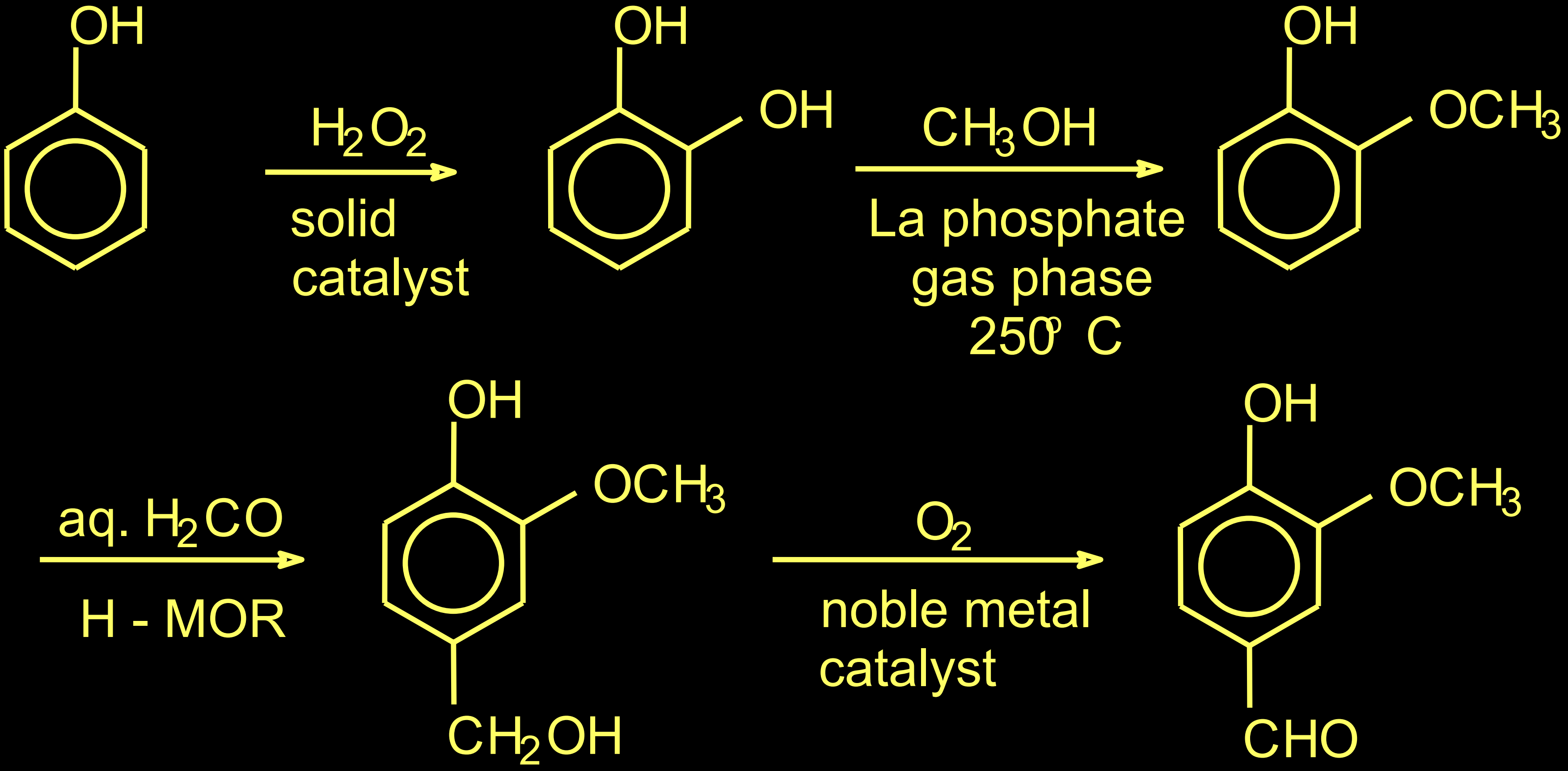
- Also with Al-Beta & Ti-Beta
  (H.van Bekkum et al)

R	conv.(%)	cis/trans (%)
Me	96	100/0
t-Bu	97	99/0.5

Shape selectivity as a result of reaction in the pores

.Corma,M.E.Domine,L.Nemeth and S.Valencia,JACS,124,3194,2002

Catalytic Vanillin Synthesis: Rhodia Process

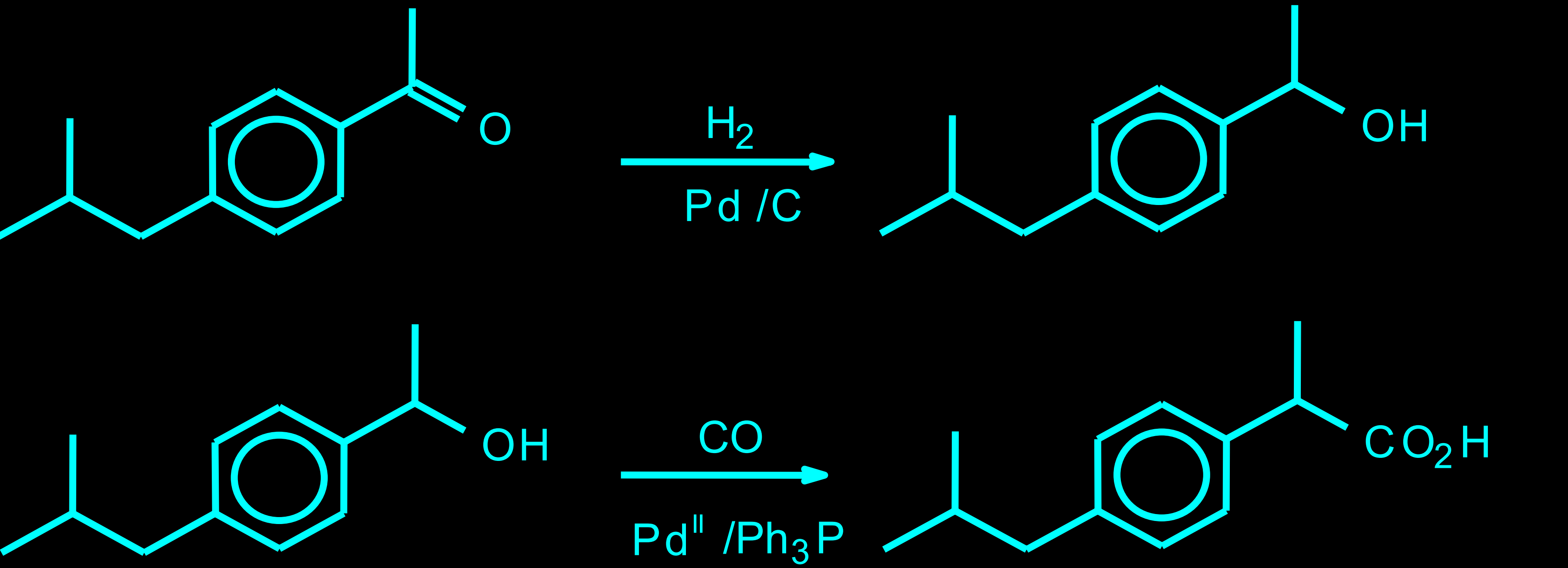


4 steps, all employing a heterogeneous catalyst

S.Ratton, *Chem. Today*, March / April, 1998, p.33

Homogeneous Catalysis

Palladium Catalyzed Carbonylation : BHC Ibuprofen Process



Ibuprofen
3500 tpa

99% conv.
96% sel.
TOF = 375 h^{-1}

☺ 100% atom efficiency

☹ Cumbersome catalyst recovery /product contamination

V. Elango et al, US Patent 4981995 (1991) to Hoechst Celanese

Homogeneous vs Heterogeneous Catalysis

	Homogeneous	Heterogeneous
Advantages	- Mild reaction conditions - High activity & selectivity - Efficient heat transfer	- Facile separation of catalyst and products - Continuous processing
Disadvantages	- Cumbersome separation & recycling of catalyst - Not readily adapted to a continuous process	- Heat transfer problems - Low activity and / or selectivity

→ **Homogeneous liquid / liquid biphasic catalysis**

The Question of Solvents : The Problem

- Toxicity / atmospheric emissions of volatile solvent (e.g. chlorinated hydrocarbons)
- Toxicity / ground water contamination by non-volatile, polar solvents

- Solvents contribute ca.85% of non-aqueous mass in processes in the pharma industry.
- Current recovery efficiencies typically 50-80%.

(Alan Curzons,GSK)

The Question of Solvents : The Solution

- Solvent-free (catalytic)processes (the best solvent is no solvent)
- Aqueous biphasic catalysis
- Supercritical carbon dioxide
- Fluorous biphasic catalysis
- Ambient temperature ionic liquids

Catalyst in
separate phas
(recyclable)

.A.Sheldon,Green Chemistry, 7, 267-278 (2005)

Water as a Reaction Medium

Economically & Environmentally attractive

- Inexpensive and abundantly available
- Non-inflammable and non-toxic
- Odourless and colourless

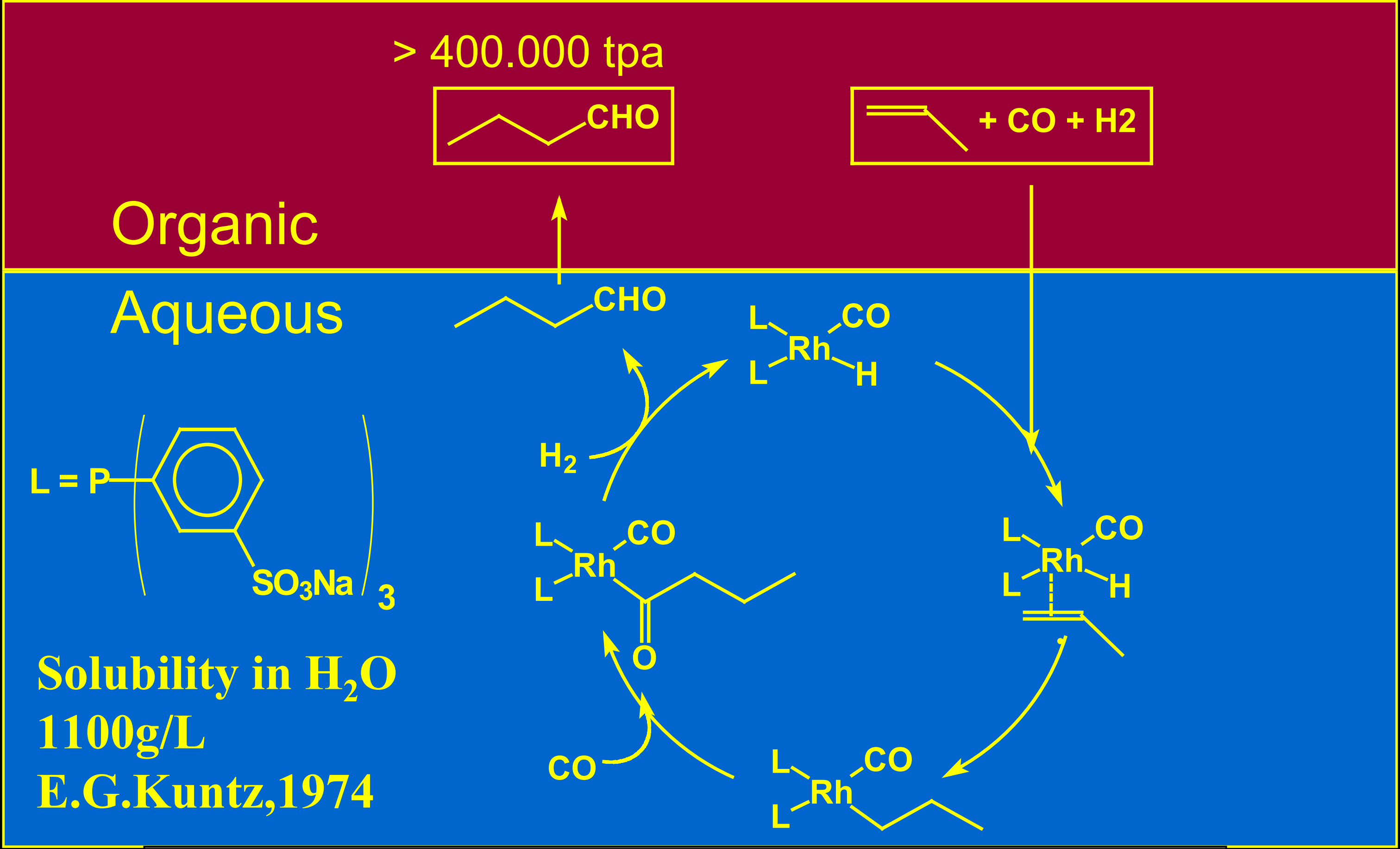
Highly polar reaction medium

- Novel reactivity of organometallic complexes
- Facile product separation/catalyst recycling
- Reduced product contamination

. Papadogianakis, R.A. Sheldon, *New J. Chem.*, 20 (1996) 175-184

Papadogianakis and R.A. Sheldon, *Catalysis*, 13 (1997) 114-193

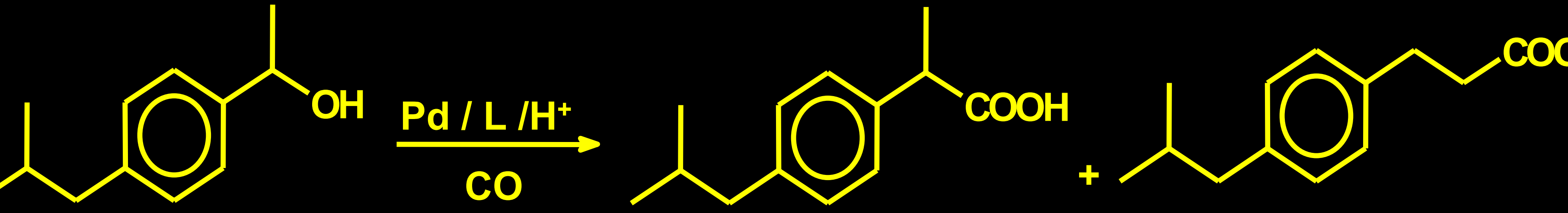
The Ruhrchemie/Rhône Poulenc hydroformylation process



Solubility in H_2O
1100g/L
E.G.Kuntz,1974

Rhodium loss: only 1 kg per 10^9 kg product

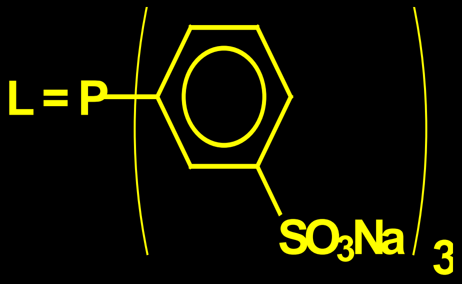
Ibuprofen via Biphasic Carbonylation



IBPE

Ibuprofen

3-IPPA



conversion: 83%

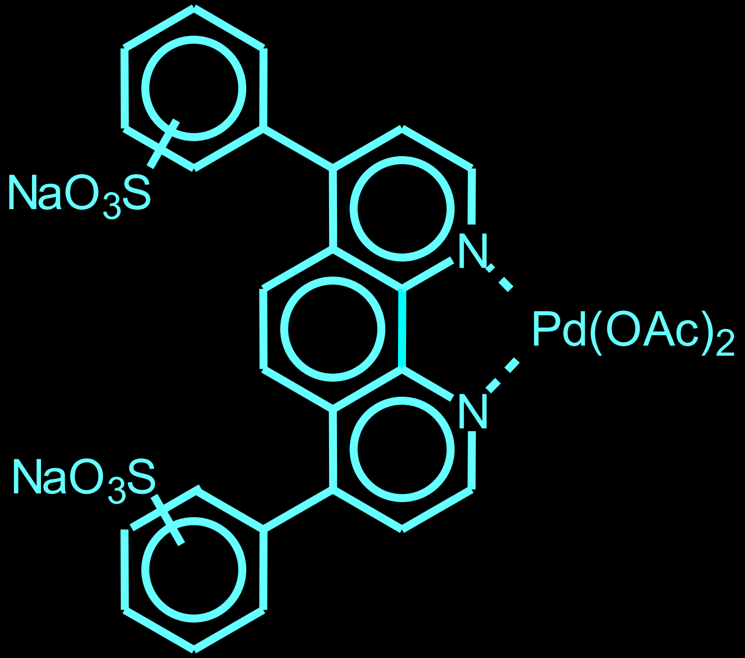
selectivity to ibuprofen: 82%

low activity (TOF = 2.3 h^{-1})

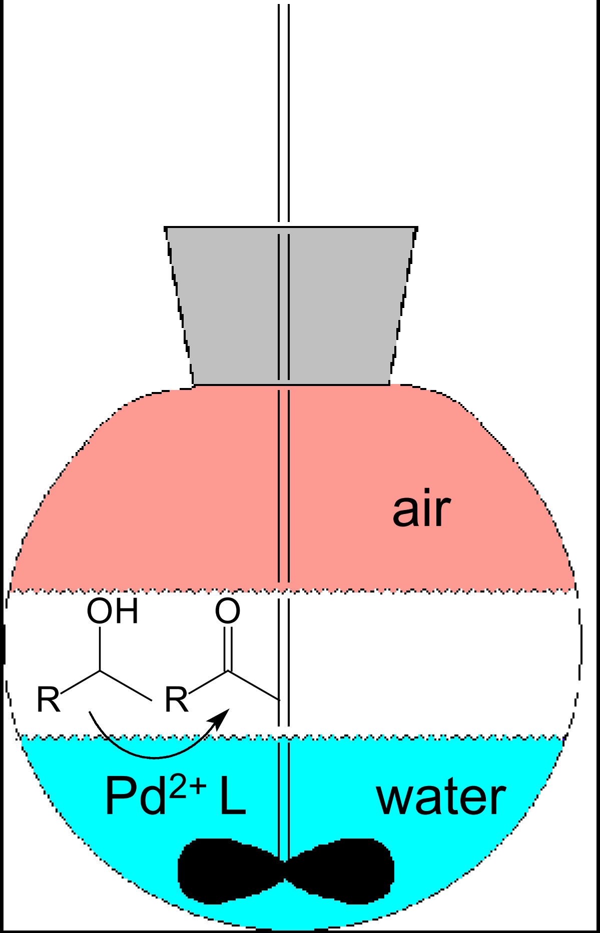
A. Sheldon, L. Maat, G. Papadogianakis, *US Pat.* 5,536,874 (1996) to Hoechst Celanese

Papadogianakis, L. Maat, R.A. Sheldon, *J. Chem. Tech. Biotechnol.*, **70** (1997) 83-91

Green, Catalytic Alcohol Oxidations



Pd^{2+}-bathophenanthroline (L)



- **Air as oxidant**
- **No organic solvent**
- **Catalyst recycling via phase separation**
- **Highly selective for 1^e and 2^e alcohols**

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

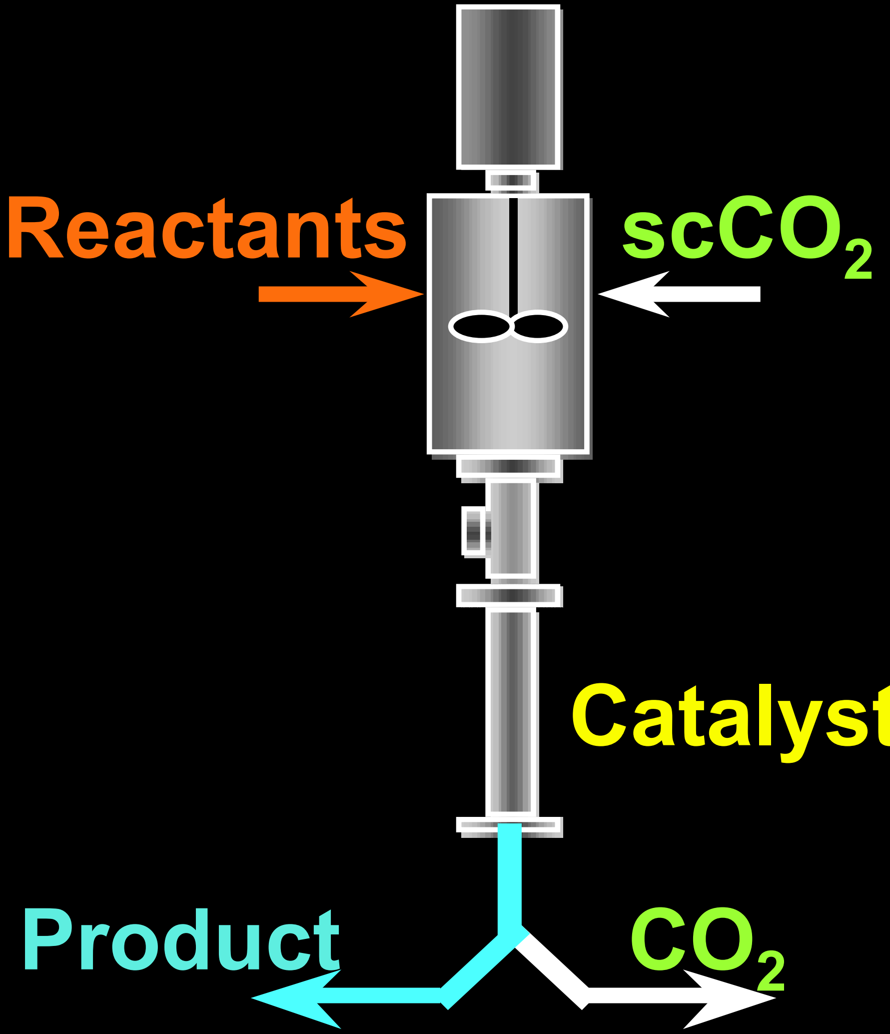
Supercritical CO_2

Supercritical CO_2 as a Reactant Medium

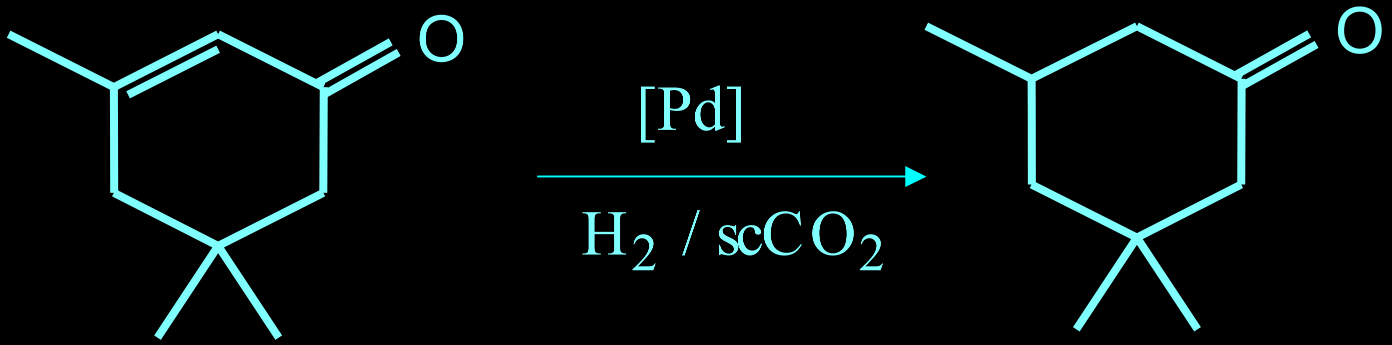
- T_c 31.0 °C, p_c 73.8 bar, d_c 0.477 kg L^{-1}
- Low viscosity (more like a gas than like a liquid)hence, fast mass transfer
- Cheap and abundantly available
- Non-toxic & non-inflammable
- Easy to remove/no net emissions
- Completely miscible with H_2,CO,O_2

Continuous Supercritical Chemistry

- Simple
- Safe
- Efficient
- Selective
- Versatile
- Clean



Continuous Supercritical Hydrogenation



isophorone

(solvent for fragrances)

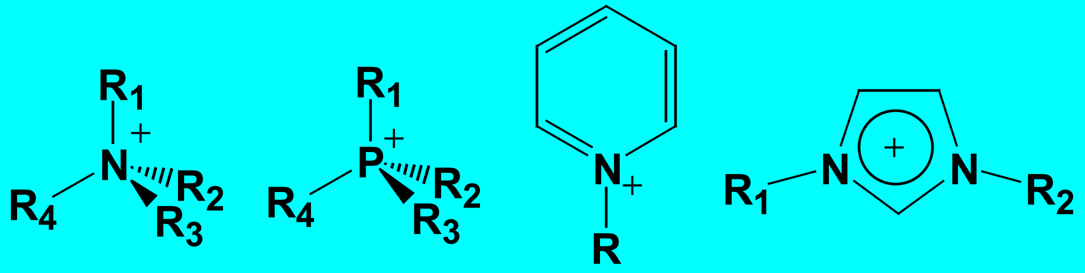
- Quantitative yield , no byproducts
- Small reactor / high throughput/ good safety
- Environmentally “Clean” / reduced waste
- Conventional process requires expensive DSP

M.Poliakoff,et al,Green Chem.,5,99-104,2003

Ionic Liquids

Catalysis in Ionic Liquids

CATIONS



ANIONS

BF_4^-, PF_6^-, SbF_6^-, NO_3^-

$CF_3SO_3^-$, $(CF_3SO_3)_2N^-$,

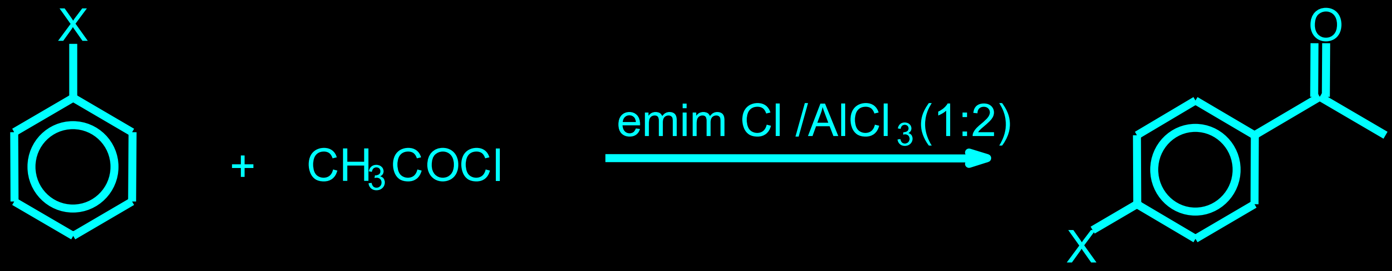
$ArSO_3^-$, $CF_3CO_2^-$, $CH_3CO_2^-$,

$Al_2Cl_7^-$

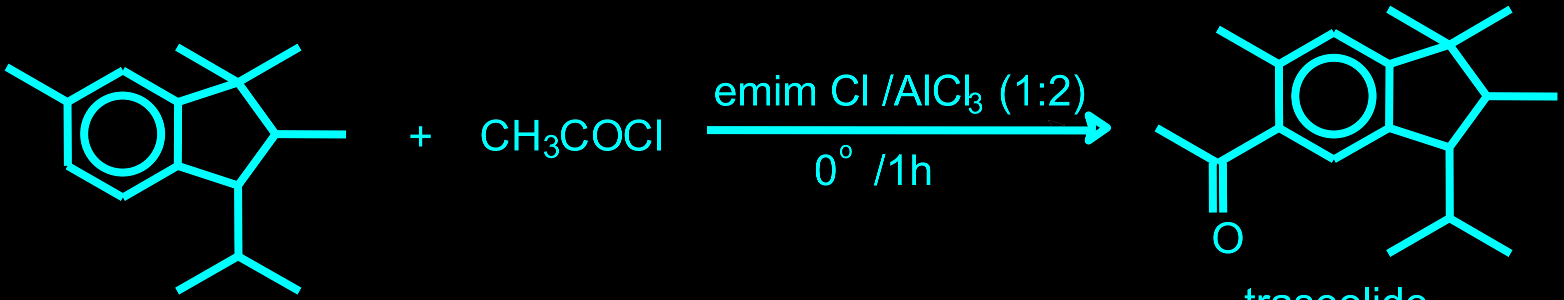
- Liquid at room temperature/no vapor pressure
- Liquid range of 300 °C (c.f. H_2O, 100 °C)
- Designer solvents (hydrophobicity,etc)
- High rate enhancements for ionic intermediates

R.A.Sheldon,Chem.Comm.,2001,2399-2407

Friedel-Crafts Acylation in Ionic Liquids

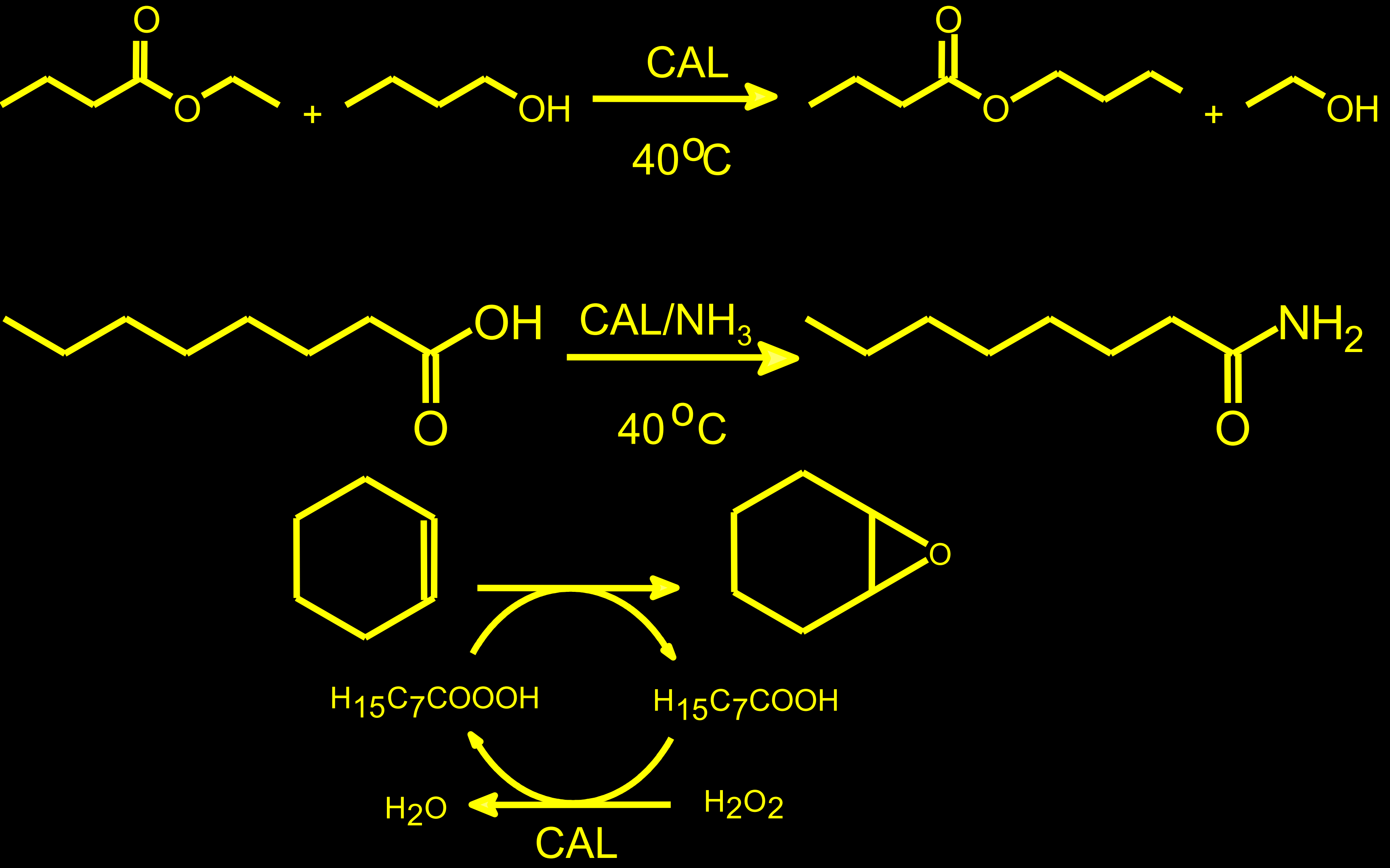


R	Temp (°C)	Time (h)	Yield (%)
MeO	-10	0.25	99
Me	20	1	98
Cl	20	24	97



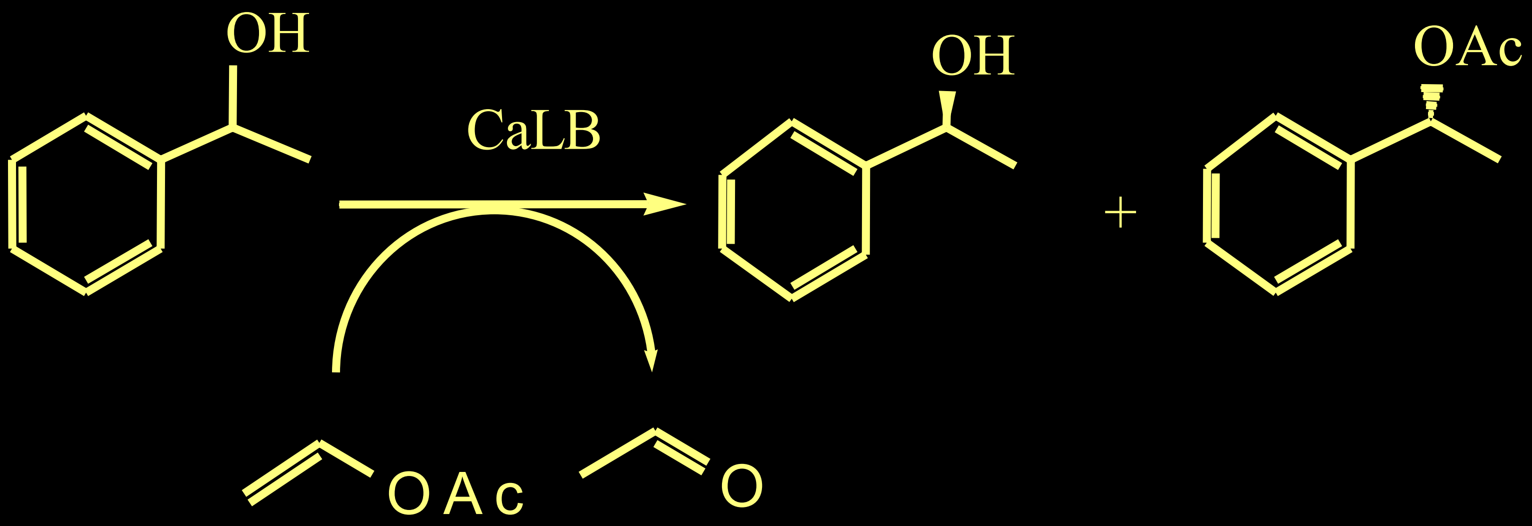
traseolide
99% yield

Enzymes in Anhydrous Ionic Liquids



Madeira Lau,F.van Rantwijk,K.R.Seddon and R.A.Sheldon, Org.Lett., 2 , 4189, 2000

In situ product removal with $scCO_2$

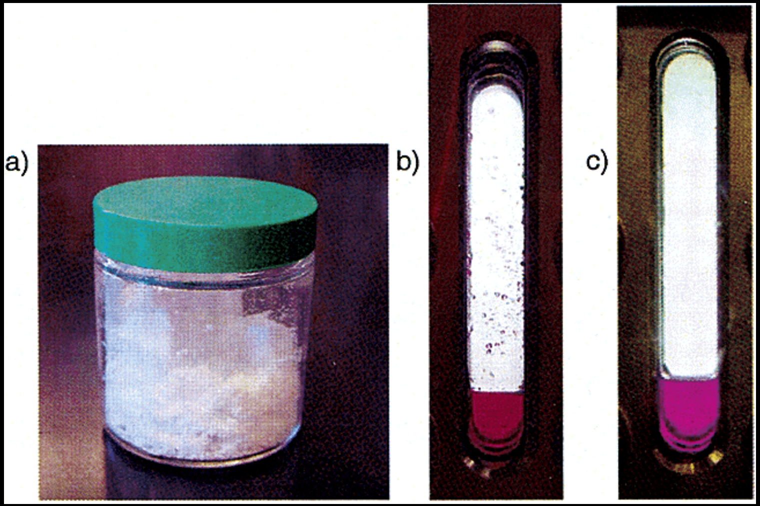


IL = [bmim] or [emim] $[(CF_3SO_2)_2N]^-$

$scCO_2$ as mobile phase in batch or continuous operation

.Lozano et al,Chem.Comm.,2002,692
M.Reetz et al,Chem.Comm.,2002,992

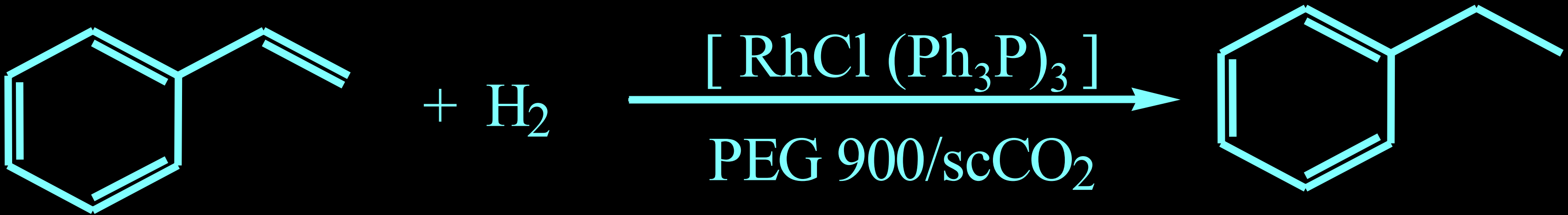
PEG-$scCO_2$ Biphasic System

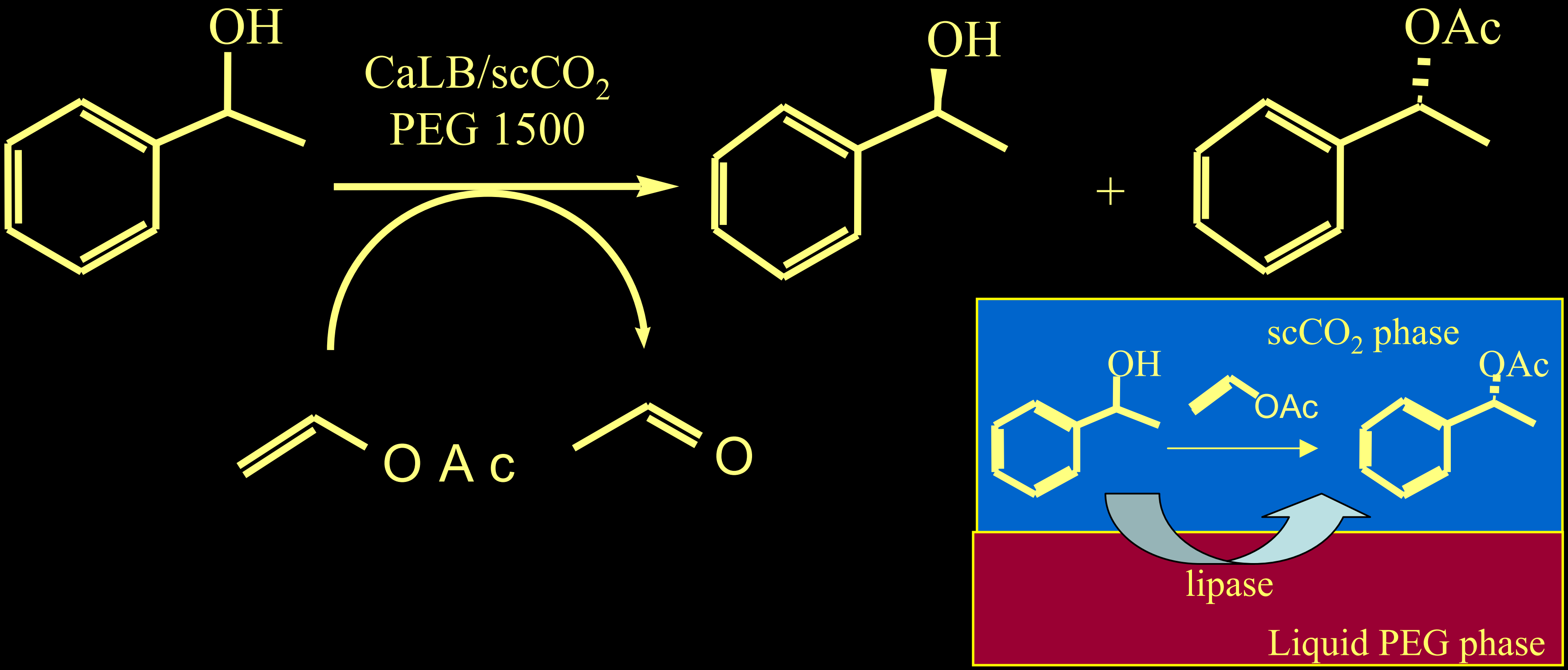


- Non-toxic (food-grade)
- PEGs poorly soluble in $scCO_2$ /expandable with CO_2
- Lower viscosity & m.p.
- Increased diffusion rates
- Increased solubility H_2

D.J.Heldebrant and P.G.Jessop, JACS, 125, 5600-5601,2003

PEG-$scCO_2$ Biphasic System





D.J.Heldebrant and P.G.Jessop, JACS, 125, 5600-5601,2003
M.T.Reetz and W.Wiesenhofer Chem.Comm. 2004 , 2750

Biocatalysis

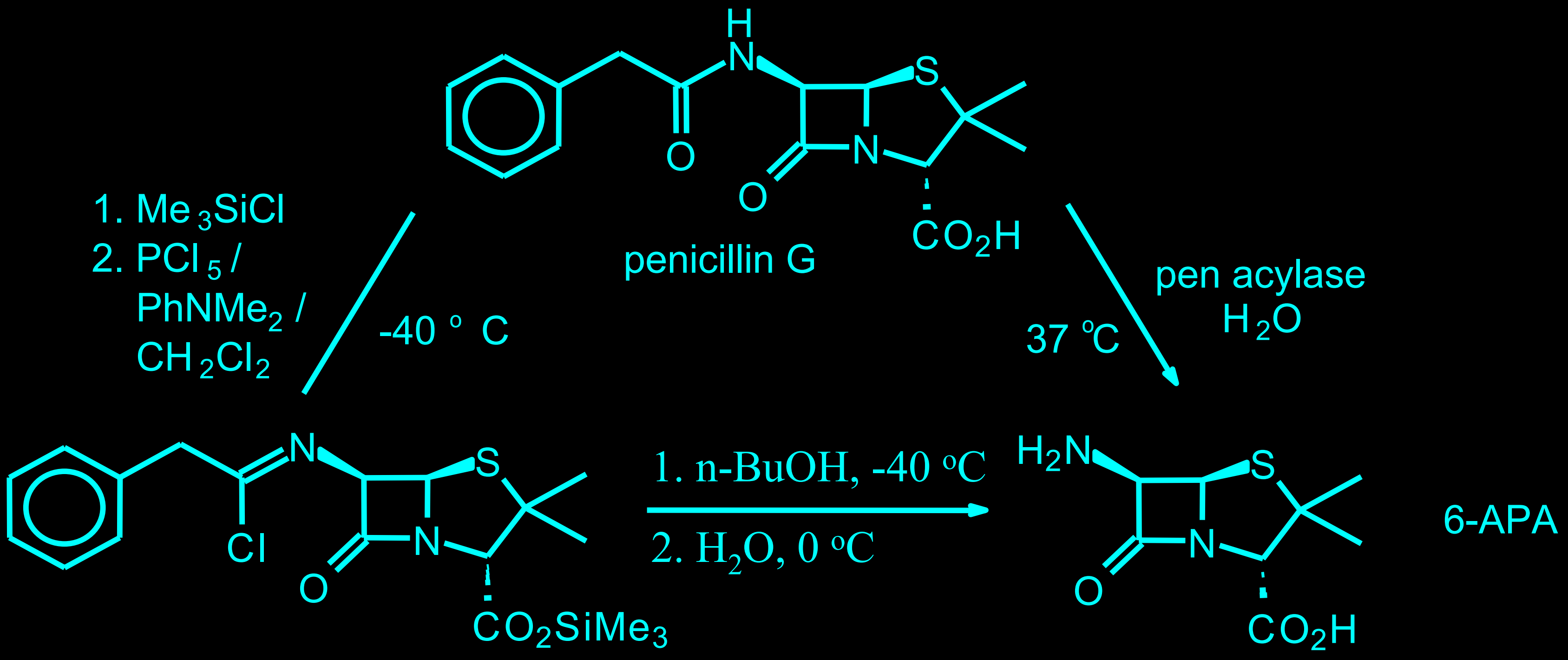
Why Biocatalysis?

- Mild conditions: ambient temperature /pressure and physiological pH
- Fewer steps (avoidsprotection/ deprotection steps)
- Largely avoids toxic/hazardous reagents & solvents
- High chemo-,regio- and stereoselectivities

SyntheticBiotransformations:Opportunities

- ENVIRONMENTALLY BENIGN SYNTHESES
  Fine chemicals & certain commodities
- CHIRALITY & BIOLOGICAL ACTIVITY
  Pharmaceuticals & Agrochemicals
- NATURAL VS SYNTHETIC
  Food ingredients (flavours & fragrances)
  Nutraceuticals
  Personalcare(fragrances,skincreams,shampoos,etc)

Enzymatic vs Chemical Process for 6-APA


penicillin G

1. Me_3SiCl
2. PCl_5 / $PhNMe_2$ / CH_2Cl_2

-40 °C

pen acylase H_2O

37 °C

1. n-BuOH, -40 °C
2. H_2O, 0 °C

6-APA

Process	**Chemical**	**Enzymatic**
Reagents (kg/ kg 6-APA)	Me_3SiCl (0.6) PCl_5 (1.2) $PhNMe_2$ (1.6) n-BuOH (8.4 ltr), NH_3 (0.2)	Pen acylase (1-2) NH_3 (0.09)
Solvent (ltr/kg 6-APA)	CH_2Cl_2 (8.4)	H_2O (2)

Bioesters via Lipase Catalyzed (trans)Esterification

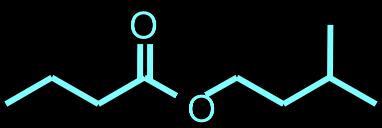
emollients / emulsifiers in personal care products:

$$R^1CO_2R + R^2OH \xrightarrow{\text{lipase}} R^1CO_2R^2 + ROH$$

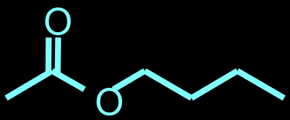
$R^1 = n\text{-}C_{14}H_{29}$; $n\text{-}C_{16}H_{33}$

$R^2 = i\text{-}C_3H_7$; $CH_3(CH_2)_3CH(C_2H_5)CH_2$

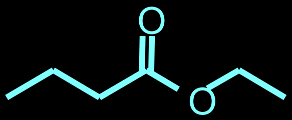
flavour esters



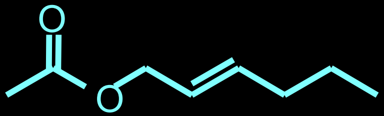
banana



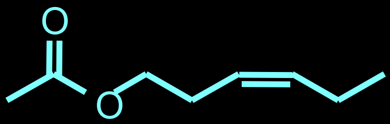
apple



pineapple



fruity



fruity/green tea

-solvent free

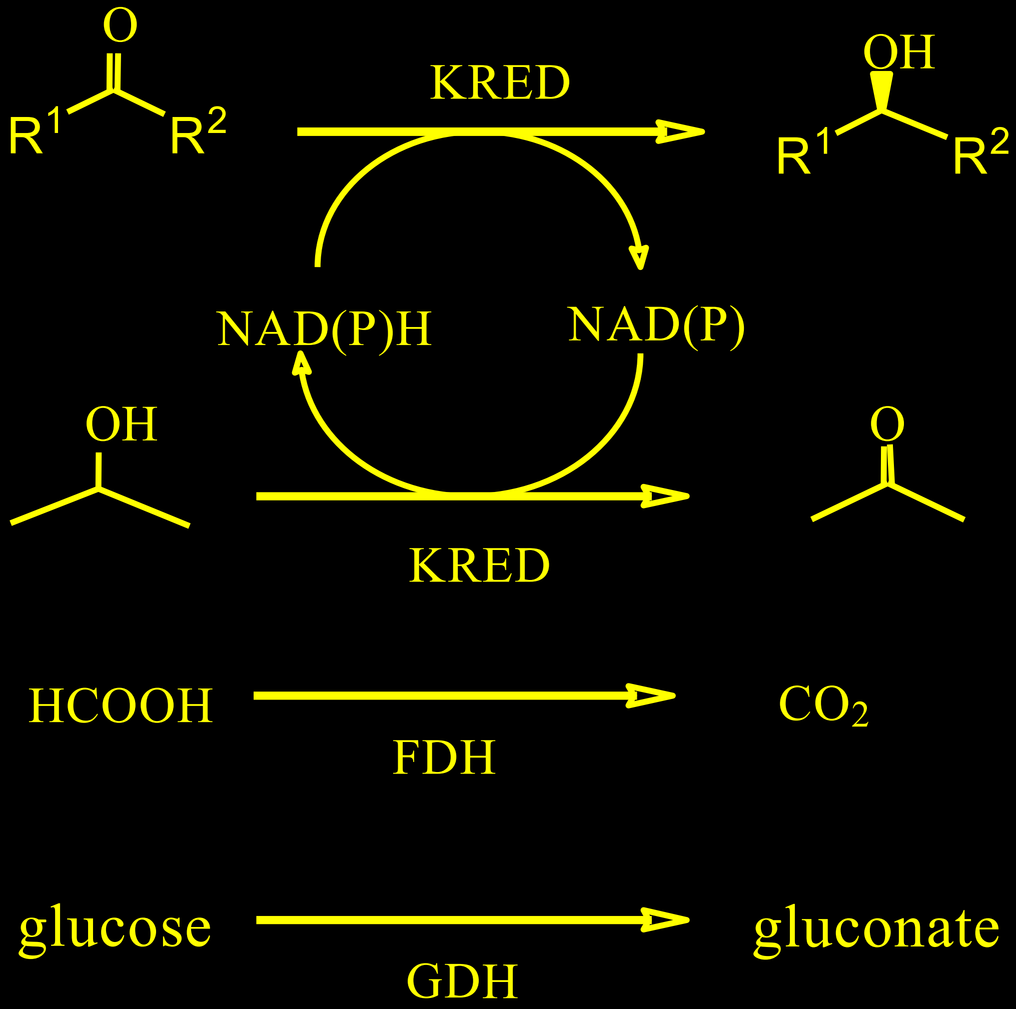
- in $scCO_2$[1]

- gas phase[2]

[1] G.Madras et al,Ind.Eng.Chem.Res. 41 , 1940-5 , 2002

[2] M.D.Legoy et al, J.Mol.Catal.B:Enzymatic, 32 , 53-59 , 2004

Cofactor Regeneration:Substrate or Enzyme Couple



KRED

NAD(P)H

NAD(P)

Substrate coupled

KRED

Enzyme coupled

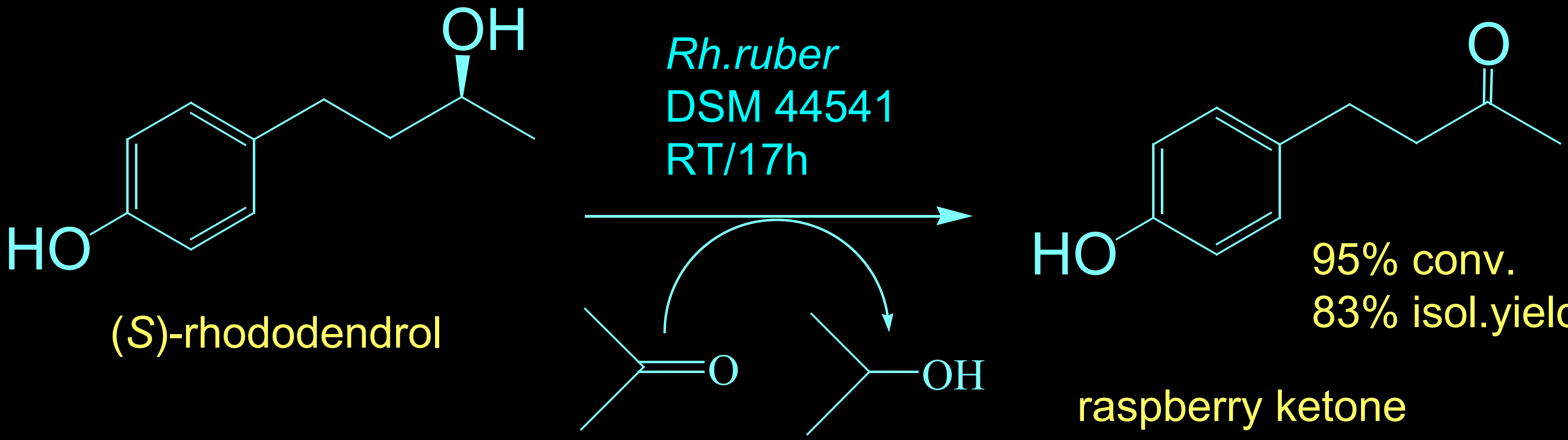
HCOOH → CO_2

FDH

glucose → gluconate

GDH

Microbial Oppenauer Oxidation



Rh.ruber
DSM 44541
RT/17h

(*S*)-rhododendrol

95% conv.
83% isol.yield

raspberry ketone

Natural : Eur 600-2000/kg
Synthetic: Eur 10/kg

- 0.88g substrate
- 1g dry cells
- 15ml 50mM phosphate buffer (0.13g)
- 3.1ml acetone

- Vol.yield = 40g/l
- STY = 60g/l/day
- Productivity = ca.1g/g/day
- E = 4.5

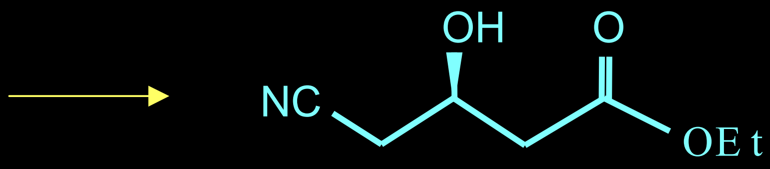
W.Kroutil et al.Tetrahedon.59.9517(2003)

Asymmetric Reduction of beta Keto Esters

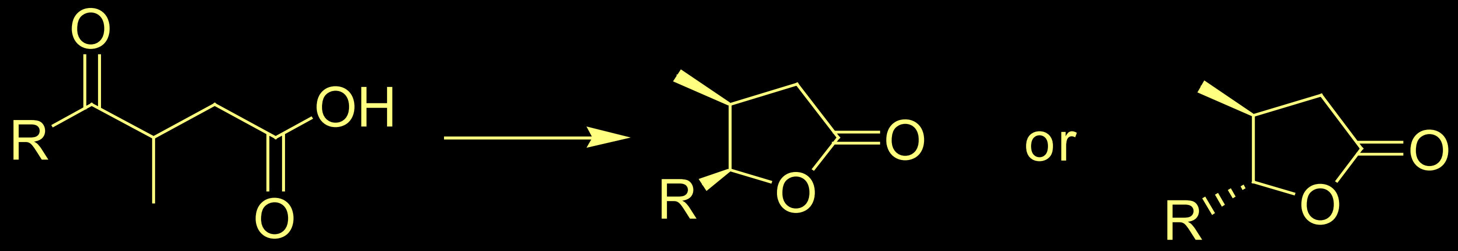
H_2 / (*S*)- BINAP/Ru

EtOH,100 bar,
100°C,5 min

97% ee (*R*)



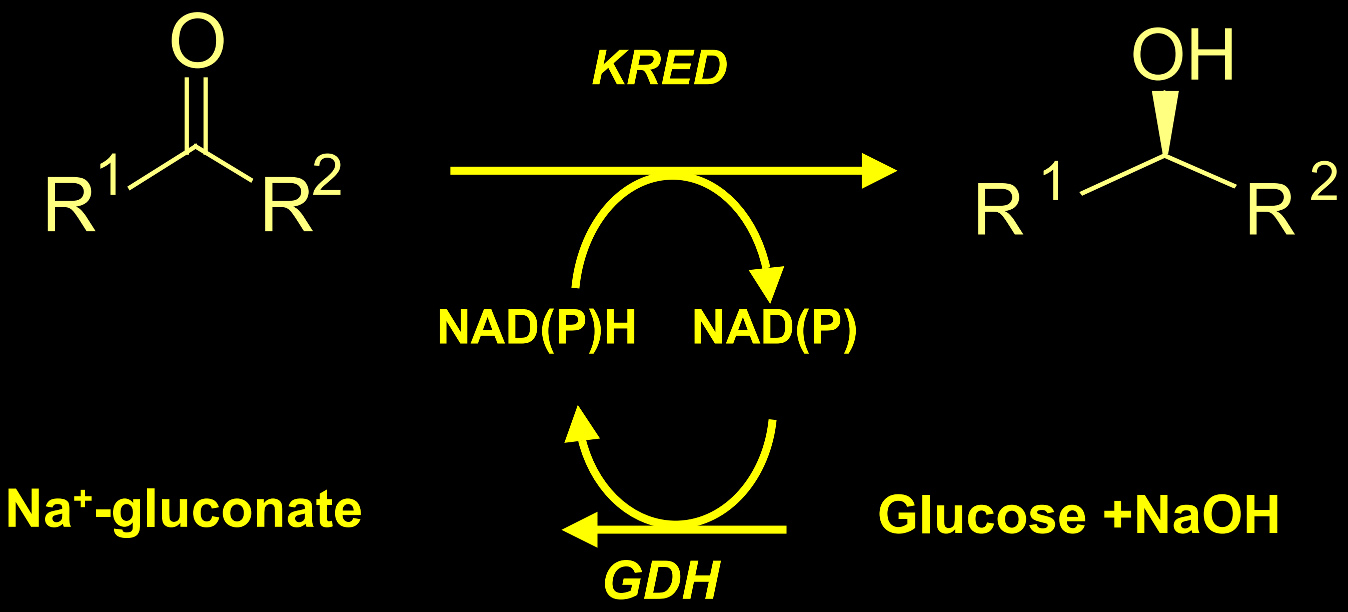
Lipitor intermediate
Sales in 2004 > $ 10mio



R = n-C_4 whisky lactones
R = n-C_5 cognac lactones

.Kitamura,T.Ohkuma,H.Takaya and R.Noyori,Tet.Lett29,1555,1988

Enantioselective Ketone Reduction



KRED

NAD(P)H NAD(P)

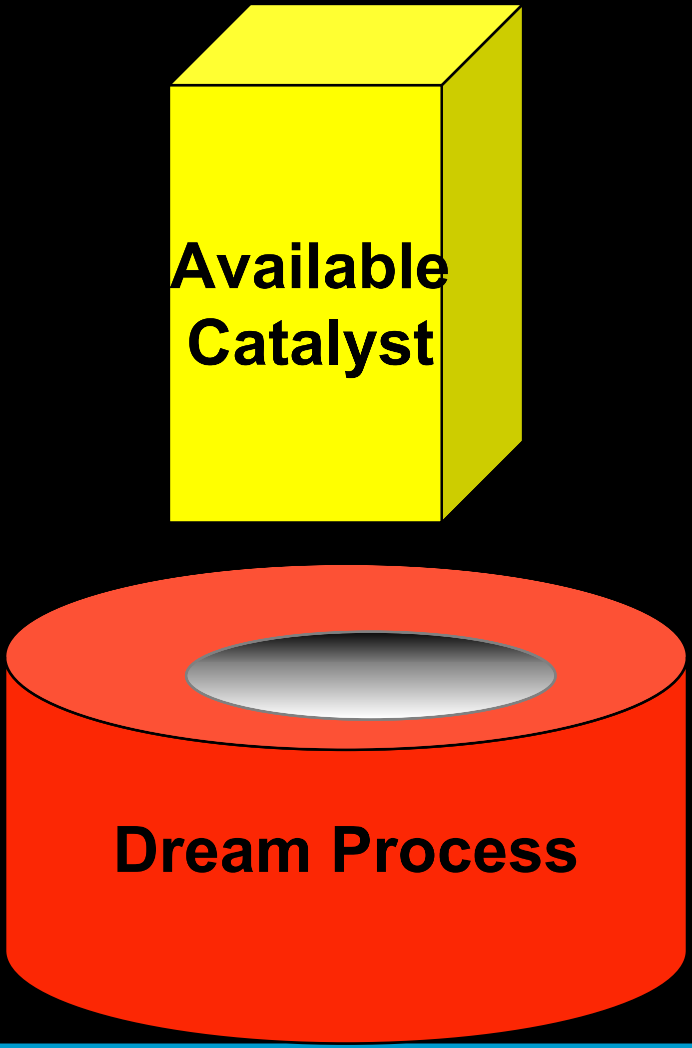
Na$^+$-gluconate

Glucose +NaOH

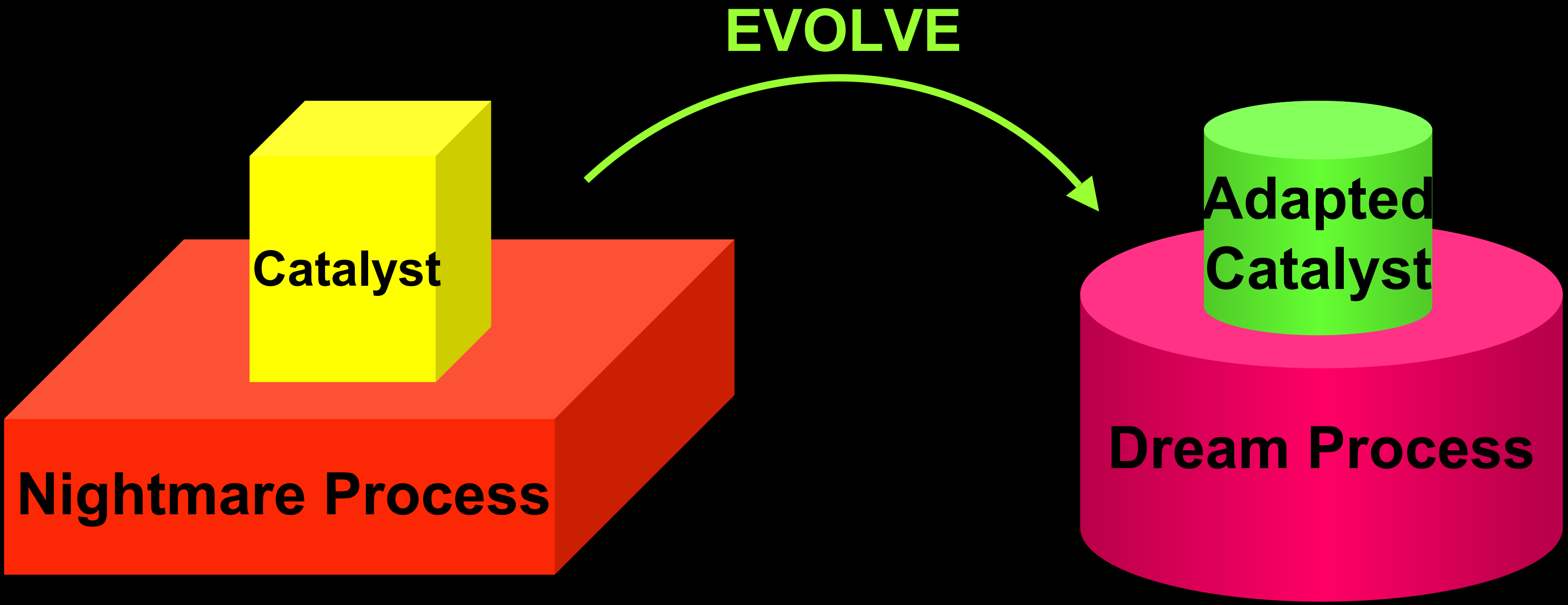
GDH

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

Historically:Adapt Process to fit Catalyst



Future: Adapt Catalyst to fit Ideal Process



EVOLVE

Catalyst

Nightmare Process

Adapted Catalyst

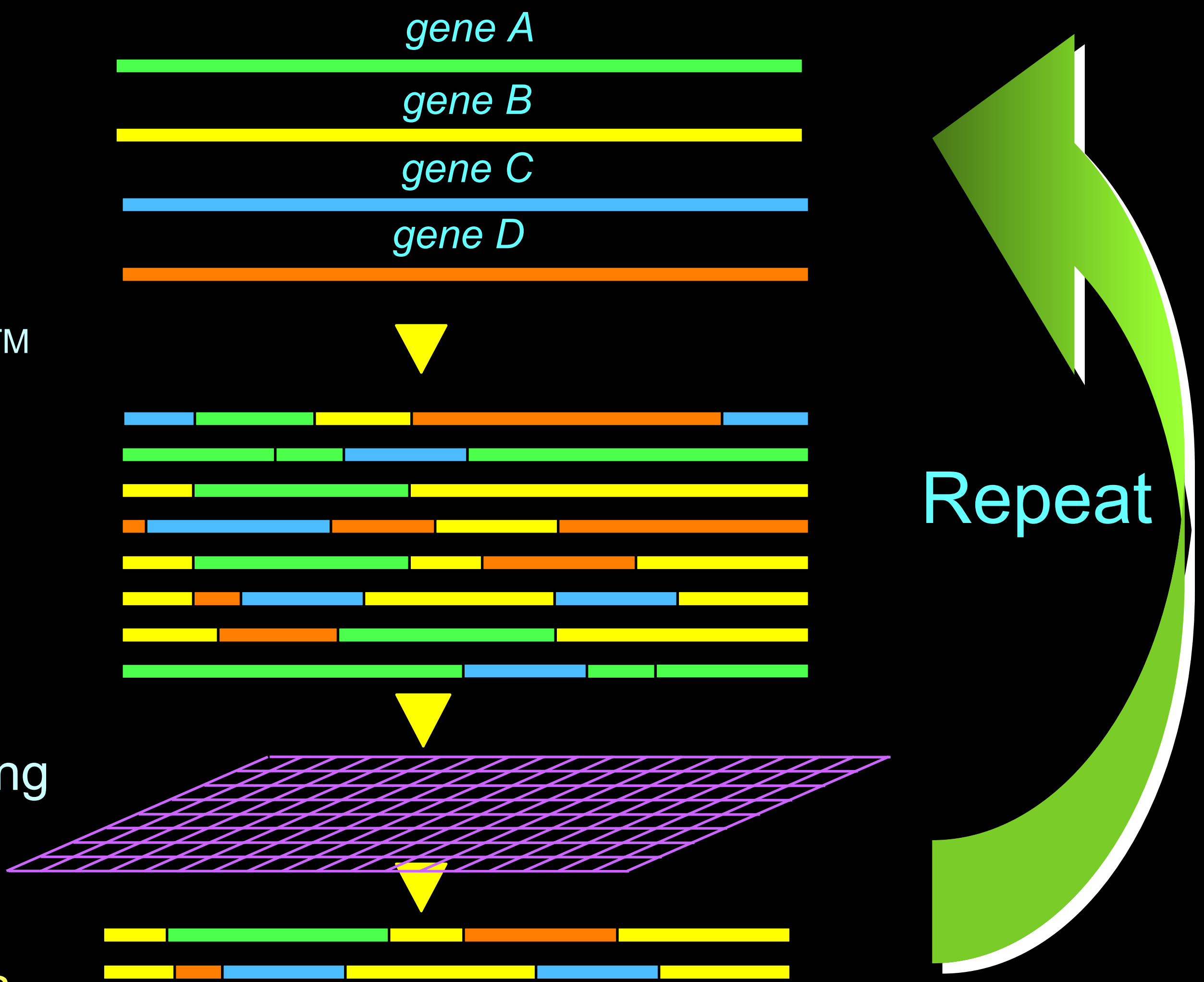
Dream Process

Compromise process to accommodate catalyst

Adapt catalyst to optimum process

Directed Evolution

DNA Shuffling : Evolution in the Fast Lane



Genes
From Nature

DNA Shuffling™

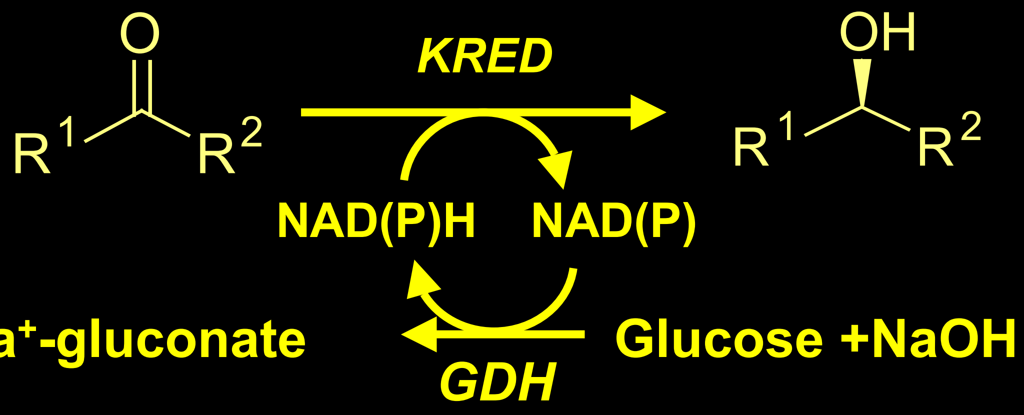
Library of
Novel Genes

HTP Screening

Novel Genes

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

Ketone Reduction with Shuffled KREDs : Codexis



Wild type enzyme	Shuffled enzyme
0 g/L KRED/GDH; 80 g/L Substrate	<1 g/L KRED/GDH; 160 g/L Substrat
Reaction time: 24 hrs	Reaction time 10 hrs.
Phase separation >1 hour	Phase separation ~1 minute
Isolated yield ~80% / ee 99.8%	Isolated yield >95% / ee >99.9%

Multistep Syntheses: Nature’s Way

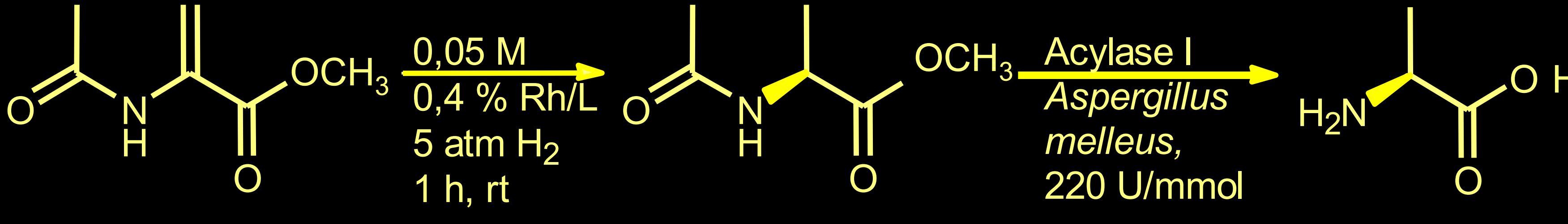
The Cell Factory:

$$A \rightarrow B \rightarrow C \rightarrow D$$

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

Compartmentalisation for compatibility

Chemoenzymatic Synthesis of an Amino Acid

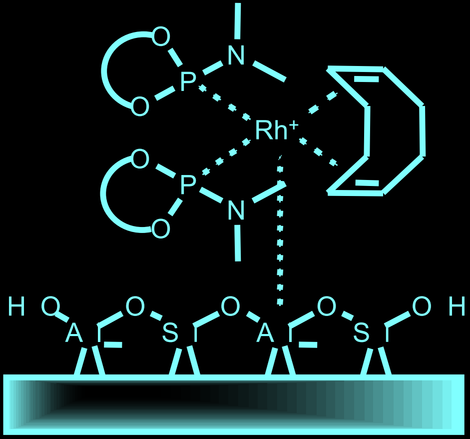


0,05 M
0,4 % Rh/L
5 atm H_2
1 h, rt

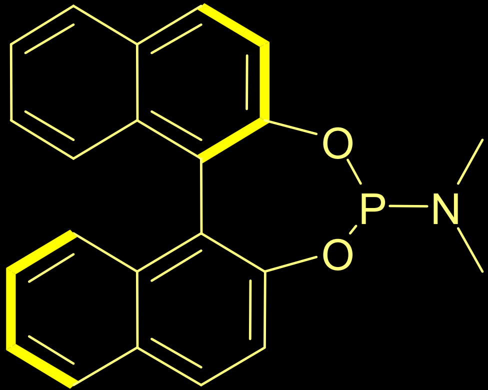
Acylase I
Aspergillus melleus,
220 U/mmol

99% yield / 95% ee

99% yield / > 99%



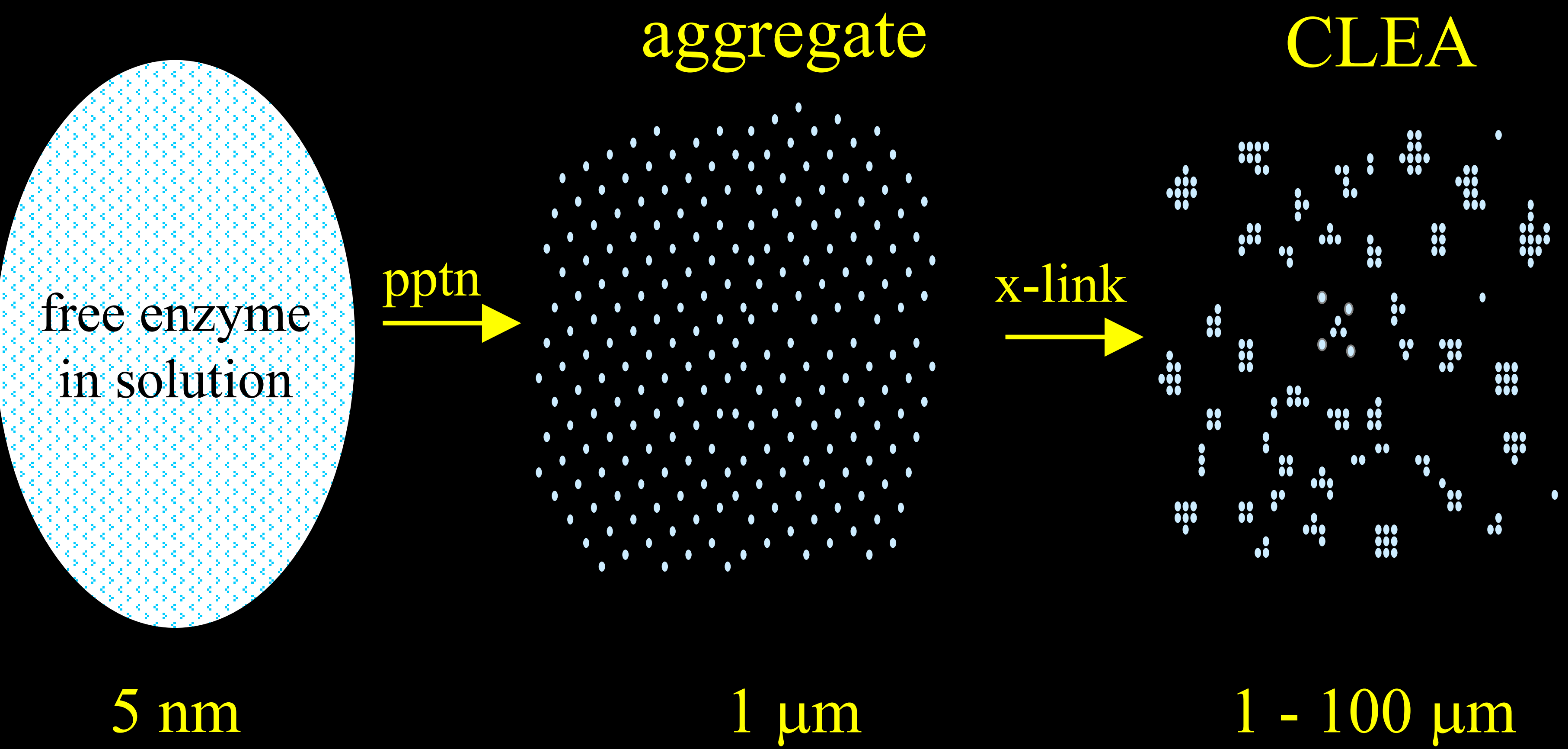
Al TUD-1



L = (*R*) - monophos

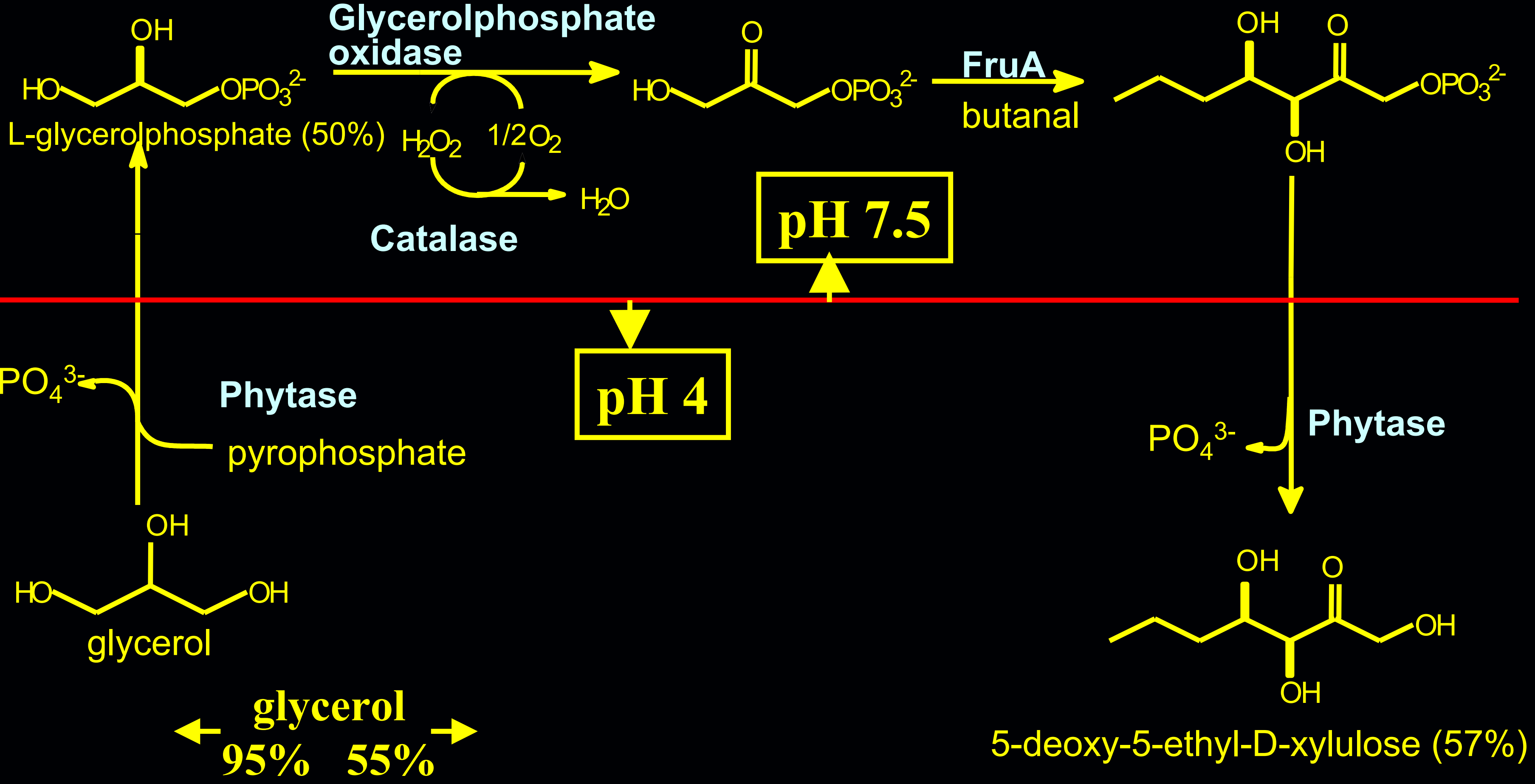
One – pot reaction in water

Cross-Linked Enzyme Aggregates (CLEAs)



L.Cao et al,Org.Lett. 2 , 1361, 2000

Cascade Catalysis:One Pot/Four Enzymes



L-glycerolphosphate (50%)

Glycerolphosphate oxidase

Catalase

FruA

butanal

pH 7.5

pH 4

Phytase

pyrophosphate

Phytase

glycerol

glycerol

95% 55%

5-deoxy-5-ethyl-D-xylulose (57%)

Conclusions & Prospects

- Catalytic methodologies –heterogeneous, homogeneous & enzymatic- and alternative reaction media form the basis for green , sustainable synthesis of flavours & fragrances

- Biocatalysis has many potential benefits and is “natural”

- Holistic approach / integration is the key

- Think Green


Think Green
FEDERAL RESERVE NOTE
THE UNITED STATES OF AMERICA
G 89991297 B
ONE DOLLAR

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