Green Chemistry & Catalysis for Sustainable Organic Synthesis

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Lecture given at University Pierre et Marie Curie,
Paris, May 12, 2004

Sustainability:
Meeting the needs of the present generation without compromising the needs of future generations

is the goal

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.

is the means

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Primary Pollution Prevention not (End-of Pipe)Remediation

Do politicians understand the issues?

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

Dan Quayle

The E Factor

Amount of waste/kg product:

	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 - >100

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

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,i.e., from the mass balance: E= [raw materials-product]/product

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

WHERE DOES ALL THIS WASTE ORIGINATE?

1. STOICHIOMETRIC BRONSTED ACIDS & BASES
   - Aromatic nitrations with H_2SO_4 / HNO_3
   - Acid promoted rearrangements, e.g. Beckmann (H_2SO_4)
   - Base promoted condensations, e.g. Aldol (NaOH, NaOMe)
2. STOICHIOMETRIC LEWIS ACIDS
   - Friedel-Crafts acylation ($AlCl_3$, $ZnCl_2$, BF_3)
3. STOICHIOMETRIC OXIDANTS & REDUCTANTS
   - $Na_2Cr_2O_7$, $KMnO_4$, MnO_2
   - $LiAlH_4$, $NaBH_4$, Zn, Fe/HCl
4. HALOGENATION & HALOGEN REPLACEMENT
   - Nucleophilic substitutions
5. SOLVENT LOSSES
   - Air emissions & aqueous effluent

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ATOM EFFICIENCY: STOICHIOMETRIC VS CATALYTIC OXIDATION

Stoichiometric: The Jones Reagent (Sir Ewart Jones)

$$3\ PhCH(OH)CH_3 + 2\ CrO_3 + 3\ H_2SO_4 \longrightarrow 3\ PhCOCH_3 + Cr_2(SO_4)_3 + 6\ H_2O$$

Atom efficiency = 360 / 860 = 42%

E_{theor} = ca. 1.5

Catalytic:

$$PhCH(OH)CH_3 + 1/2\ O_2 \xrightarrow{\text{Catalyst}} PhCOCH_3 + H_2O$$

Atom efficiency = 120/138 = 87%

Byproduct: H_2O

E_{theor} = ca. 0.1(0)

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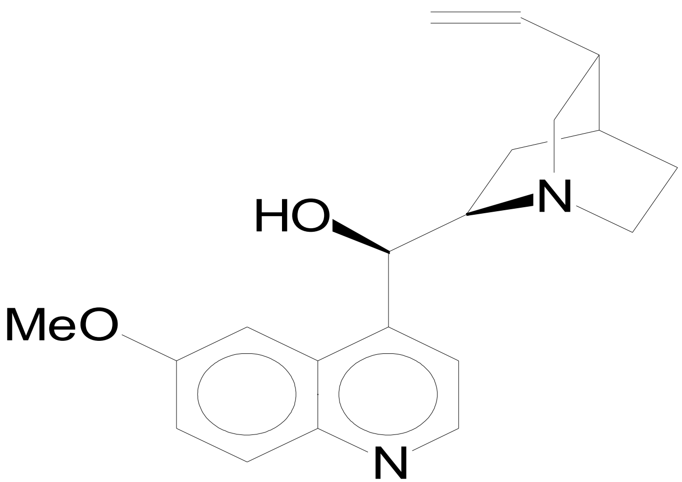
CHROMIUM(VI): THE ORGANIC CHEMIST'S FAVOURITE OXIDANT

1856 : Attempted synthesis of quinine (W.H.Perkin)

$$2\ C_{10}H_{13}N \quad + \quad 3\ O \xrightarrow{K_2Cr_2O_7} C_{20}H_{24}N_2O_2 \quad + \quad H_2O$$

allyltoluidine quinine



quinine

- Led to the serendipitous synthesis of the first synthetic dyestuff mauveine (aniline purple)

2000 : Julia Roberts in "Erin Brokovich"

"It's hexavalent chromium, highly toxic, highly carcinogenic.

Gets into your DNA, so you pass the trouble along to your kids."

ATOM EFFICIENT PROCESSES

Hydrogenation:

100% atom efficient

Carbonylation:

100% atom efficient

Oxidation:

87% atom efficient

(Ar = C_6H_5)

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The Environmental Impact EQ

EQ

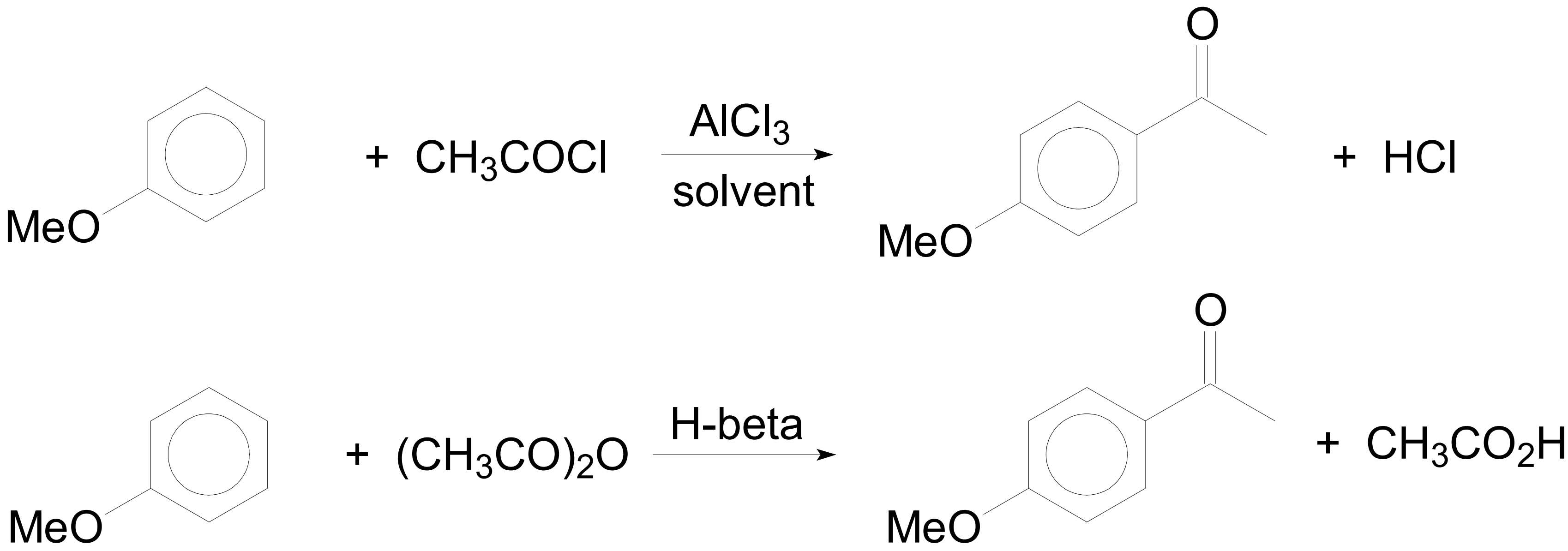
E(kg waste) × Q (Unfriendliness)

e.g. NaCl=1 (arbitrary)

Cr salts= 1000?

Solid Acid Catalysts

ZEOLITE-CATALYZED FRIEDEL-CRAFTS ACYLATION



Homogeneous

$AlCl_3$ >1 equivalent
Solvent (recycle)
Hydrolysis of products
85-95% yield
4.5 kg aqueous effluent per kg
12 unit operations

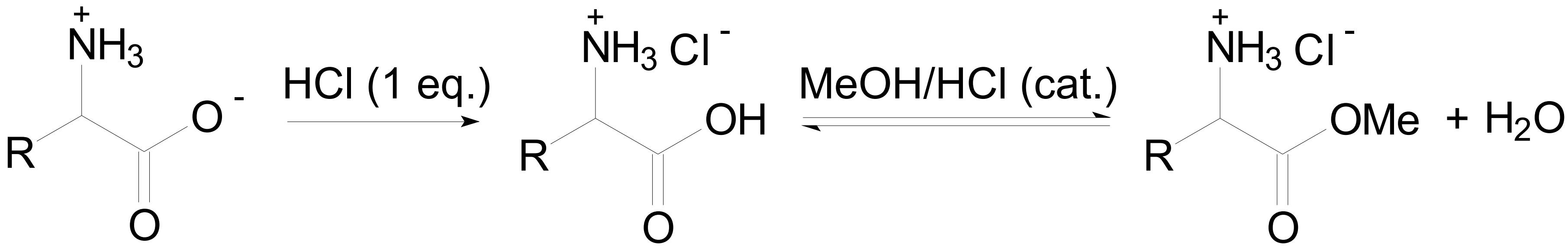
Heterogeneous

H-beta, catalytic & regenerable
No solvent
No water necessary
>95% yield /higher purity
0.035 kg aqueous effluent per kg
3 unit operations

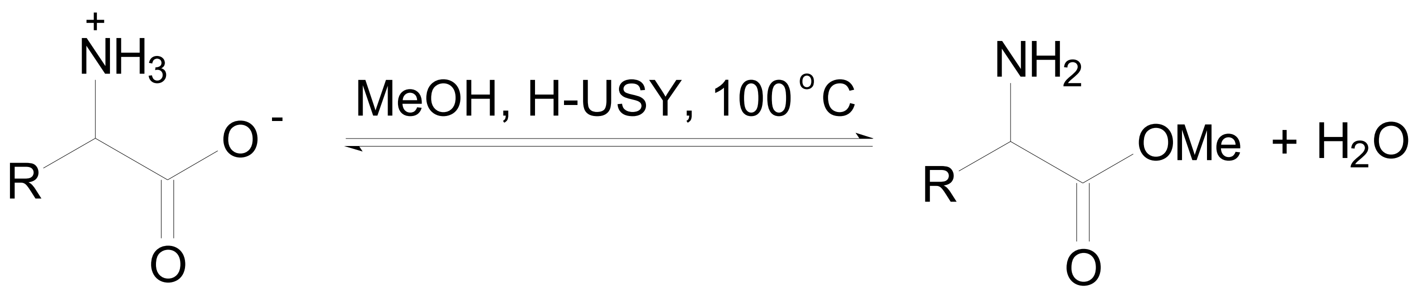
S. Ratton, *Chem. Today (Chim. Oggi)*, March/April, 1998, 33

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 (partially) racemized

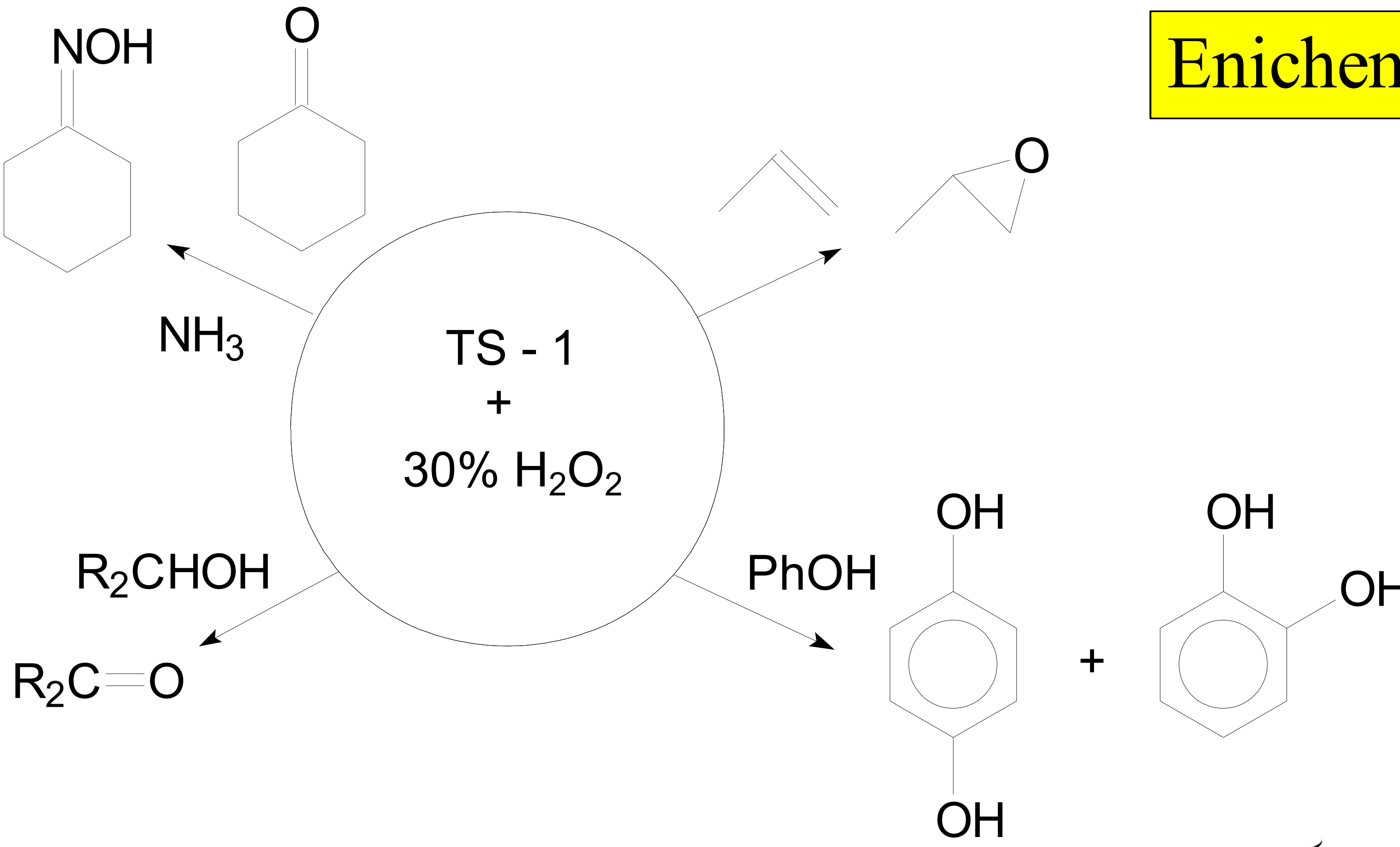
M.Wegman, J.M.Elzinga, E.Neeleman, F.van Rantwijk and R.A.Sheldon, *Green Chem.*, 3,61,2001

Catalytic Oxidations

TS-1 CATALYZED OXIDATIONS WITH H_2O_2

Hydrophobic molecular sieve (5.6 x 5.3Å) / HI (X_{octane} / X_{H2O}) TS-1=3.4 ; Ti / SiO_2=0.1

Enichem



B.Notari, *Stud. Surf. Sci. Catal.*, 37 , 431 (1988)

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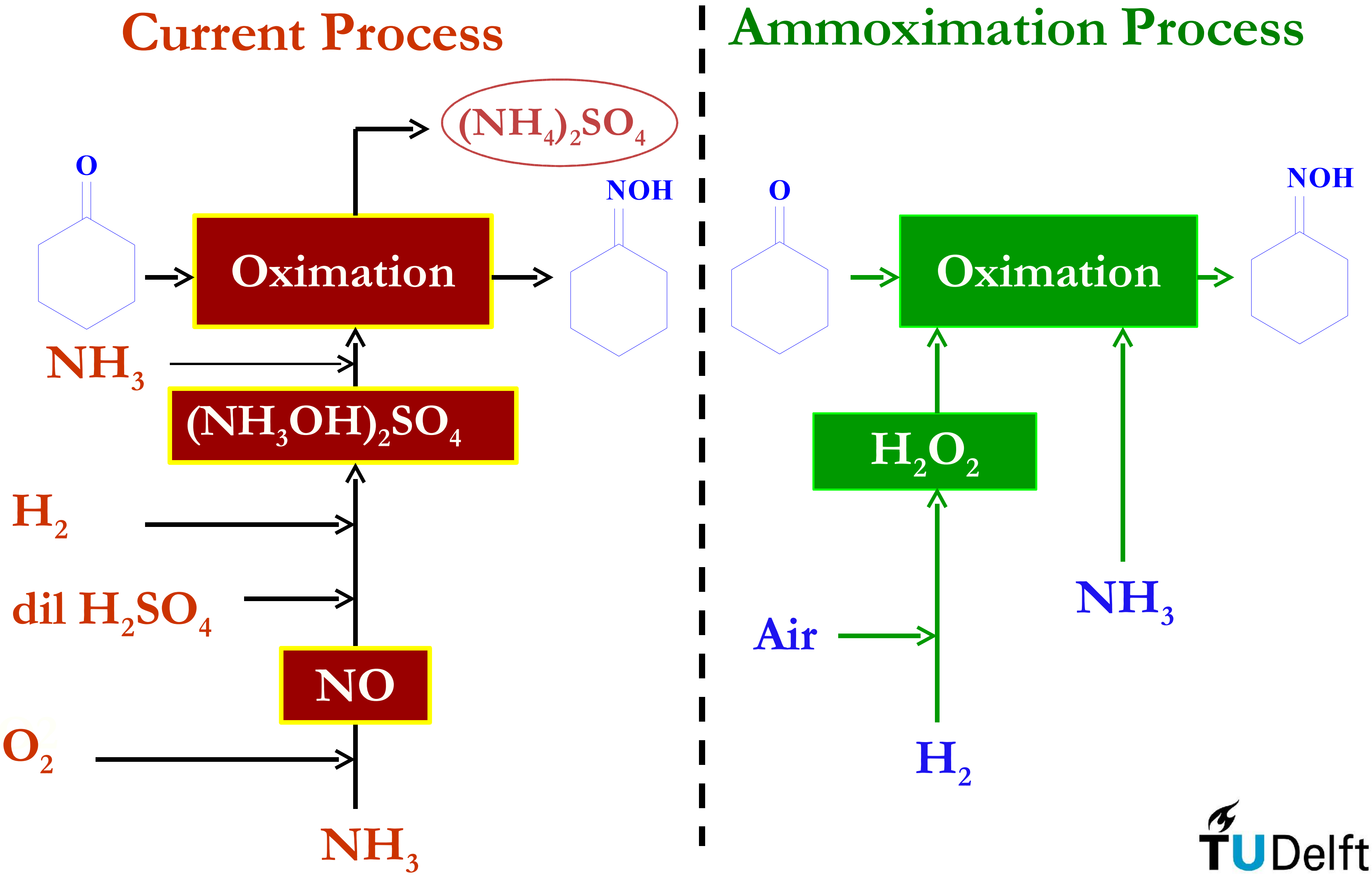
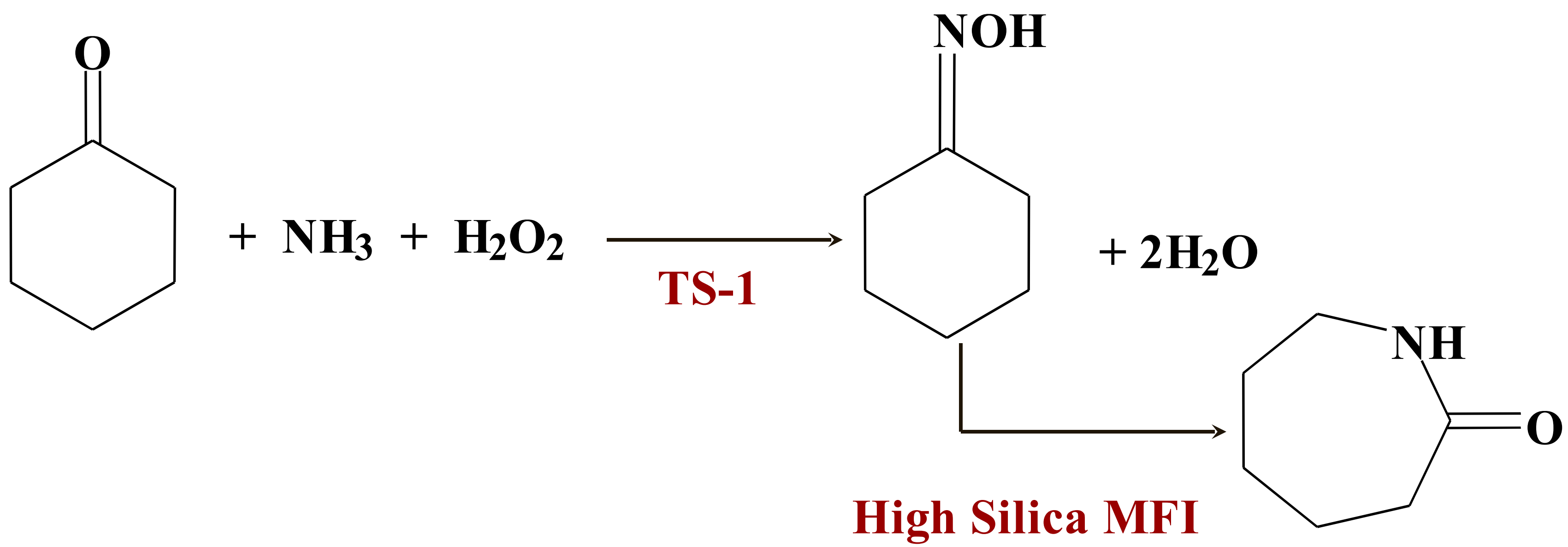
Cyclohexanone Oxime Manufacturing Process



Sumitomo Process:Combined Ammoximation and Vapor Phase Beckmann Rearrangement

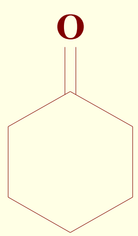


By-product: H_2O
Green Chemical Process

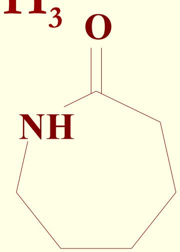
Personal communication,
H.Ichihashi,Sumitomo

Comparison between the Current and New Processes

Overall reaction of a typical current process



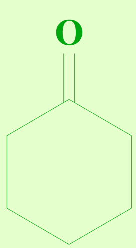
$+ 0.5(NH_3OH)_2SO_4 + 1.5H_2SO_4 + 4NH_3 \longrightarrow$



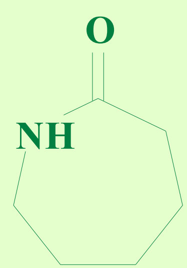
$+ 2(NH_4)SO_4 + H_2O$

Atom Economy = 29%   E-factor = 2.5

Overall reaction of the new process



$+ NH_3 + H_2O_2 \longrightarrow$



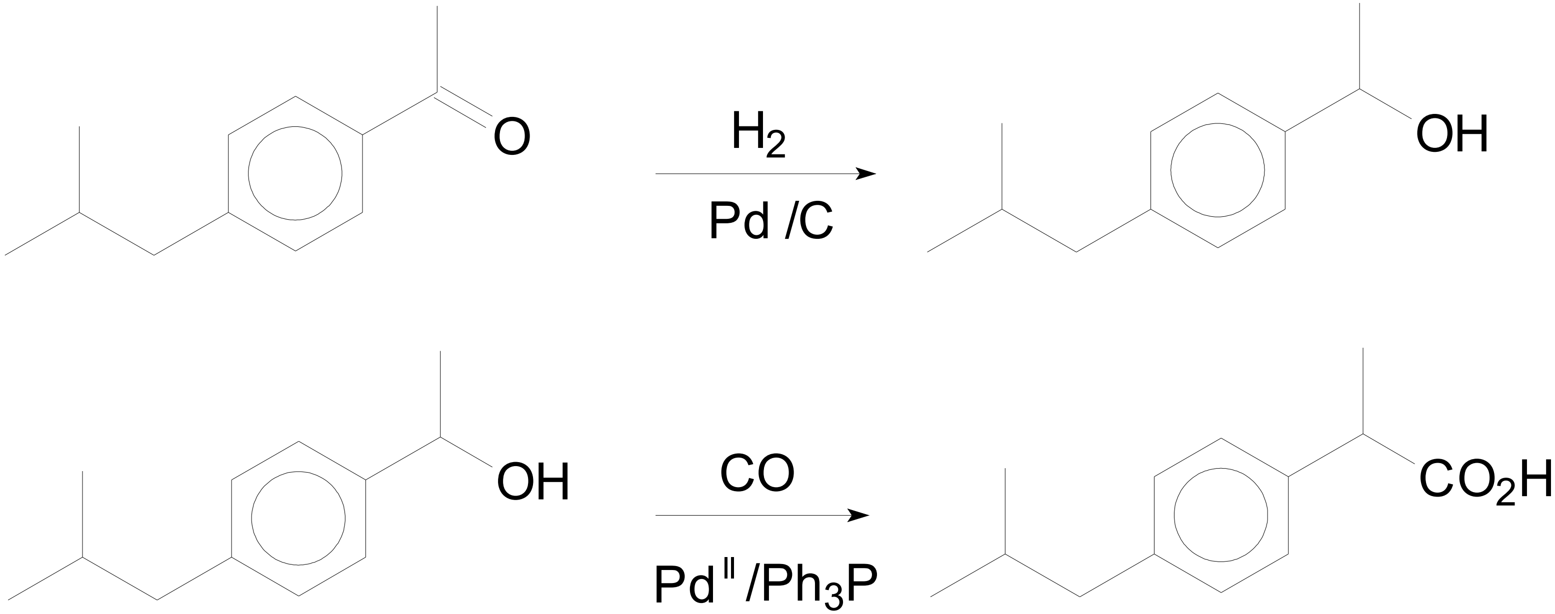
$+ 2H_2O$

Atom Economy = 75%   E-factor = 0.32

H.Ichihashi

Homogeneous Catalysts

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

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Asymmetric Catalysis

PASTEUR'S CHIRAL FORCE

THE ESSENTIAL PRODUCTS OF LIFE ARE ASYMMETRIC AND POSSESS SUCH ASYMMETRY THAT THEY ARE NOT SUPERIMPOSABLE ON THEIR IMAGES?THIS ESTABLISHES PERHAPS THE ONLY WELL-MARKED LINE OF DEMARCATION THAT CAN AT PRESENT BE DRAWN BETWEEN THE CHEMISTRY OF DEAD MATTER AND THE CHEMISTRY OF LIVING MATTER

Louis Pasteur, 1822-1895

HISTORICAL DEVELOPMENT

1848 First separation of a racemate (Pasteur)

1853 First separation of a racemate by diastereomer crystallization (Pasteur)

1858 First racemate separation by fermentation-Penicillium glaucum (Pasteur)

J.H.van ‘t Hoff: Father of Stereochemistry

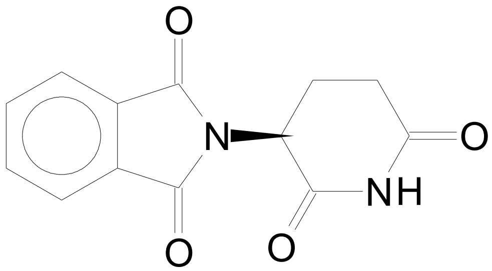
First Nobel Prize in Chemistry,1901

Title of paper written at the age of 22:

“Proposal for the extension of the structural formulae now in use in chemistry into space,together with a related note on the relationship between the optical active power and the chemical constitution of organic compounds”

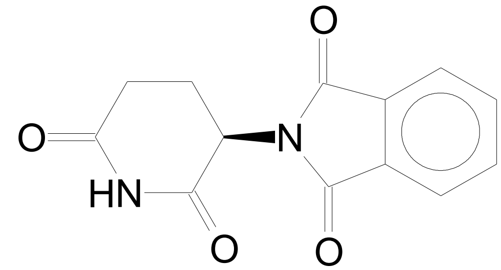
J.H.van ‘t Hoff,Arch.Neerl.Sci.Exacts Nat., 9,445-454,1874

THE WRONG ISOMER HAS UNDESIRABLE SIDE-EFFECTS

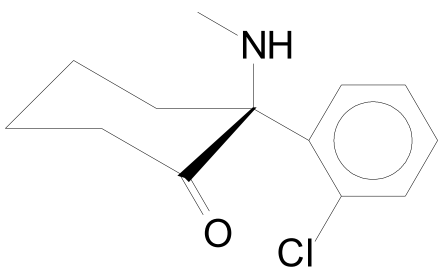


teratogen

(S) Thalidomide (R)

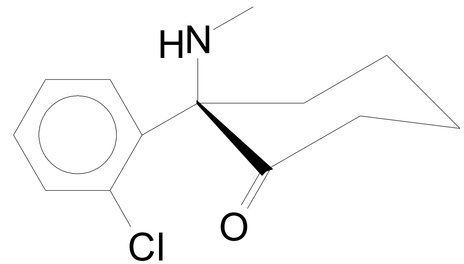


sedative

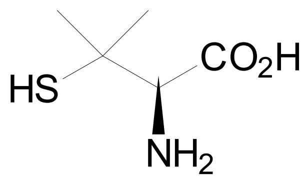


anaesthetic

(S) Ketamine (R)

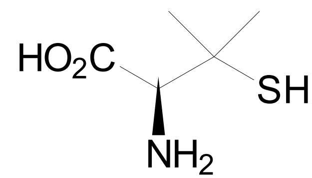


hallucinogen

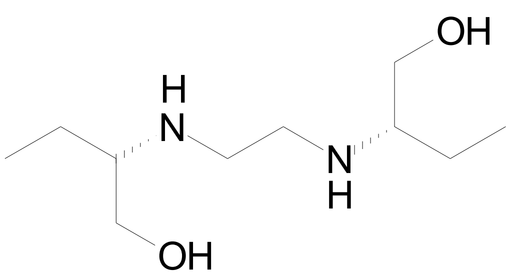


antiarthritic

(S) Penicillamine (R)

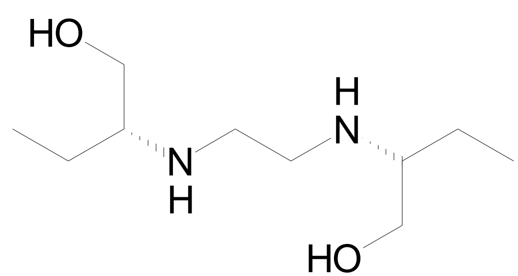


mutagen



tuberculostatic

(S,S)-Ethambutol (R,R)

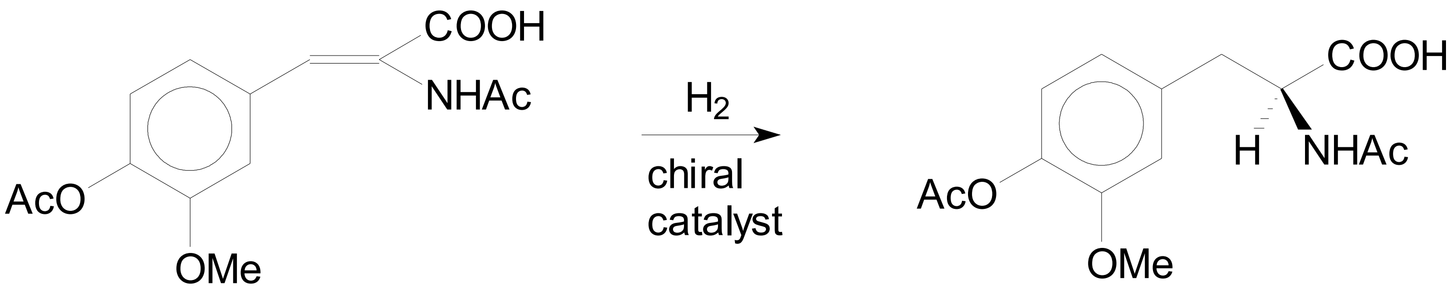


blindness

MILESTONES IN ASYMMETRIC CATALYSIS

1939	Cinchonine-modified Pt (Lipkin and Stewart)
1956	Pd modified with silk fibroin (Akabori, Izumi)
1963	Raney Ni/tartrate (Izumi)
1966	Asymmetric cyclopropanation catalyzed by a chiral Schiff's base complex, 10% ee (Nozaki, Noyori)
1968	Asymmetric hydrogenation with a rhodium-chiral phosphine complex, 15% ee (Knowles and Sabacky; Horner)
1970	Monsanto L-Dopa process
1971	DIOP ligand (Kagan)
1980	Asymmetric epoxidation, Ti/TBHP/tartrate (Sharpless)
1984	Takasago l-menthol process, Rh-Binap (Otsuka, Akutagawa, Noyori)
1988	Asymmetric dihydroxylation of olefins, OsO_4/quinine (Sharpless)
1991	Jacobsen-Katsuki epoxidation
2001	Nobel prize in Chemistry for Knowles,Noyori and Sharpless

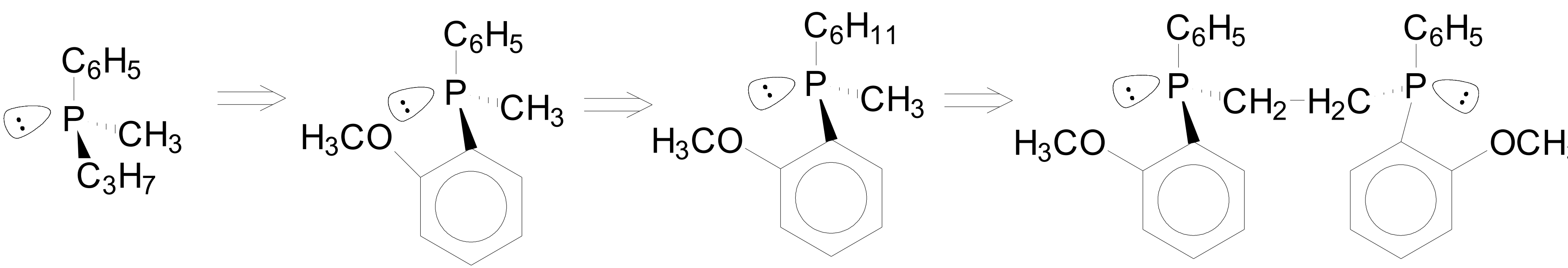
MONSANTO L-DOPA PROCESS



Catalyst = [Rh(COD)L*$_2$]$^+$ BF_4^-

COD = 1,5-cyclooctadiene

L* = chiral phosphine



PMPP
28% ee

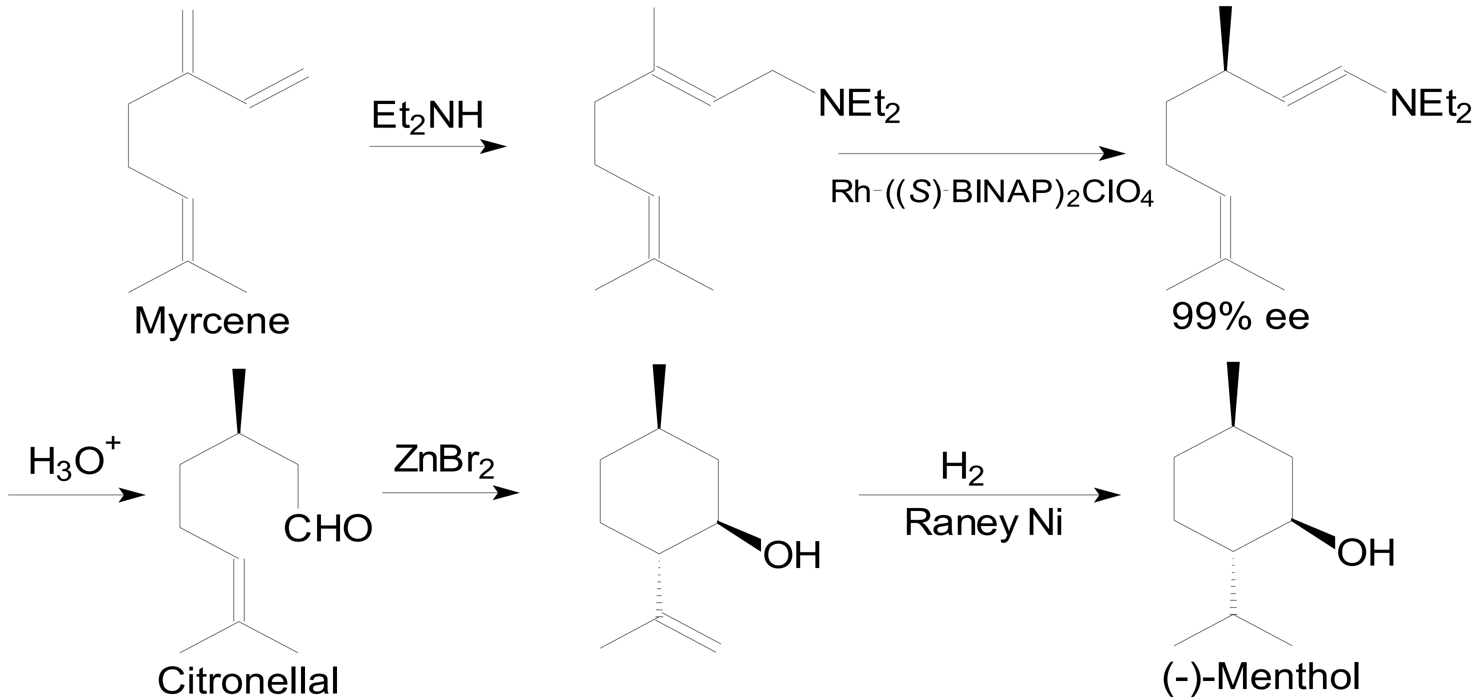
PAMP
60% ee

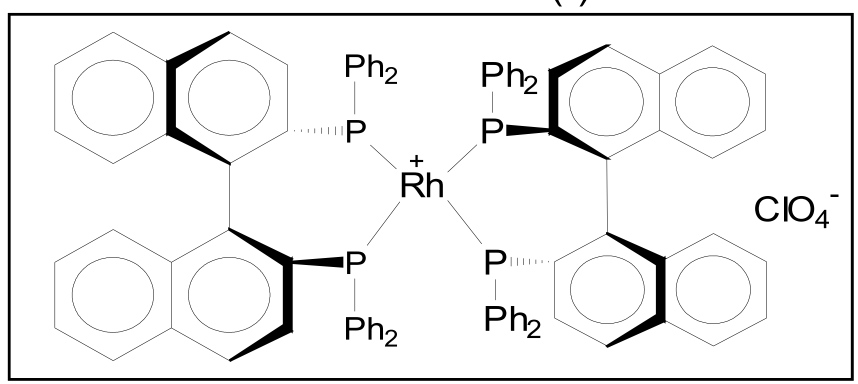
CAMP
85% ee

DIPAMP
95% ee

W.S.Knowles, *Acc. Chem. Res.*, 16, 106-122 (1983); *J. Chem. Educ.*, 63, 222-225 (1986)

TAKASAGO l-MENTHOL SYNTHESIS





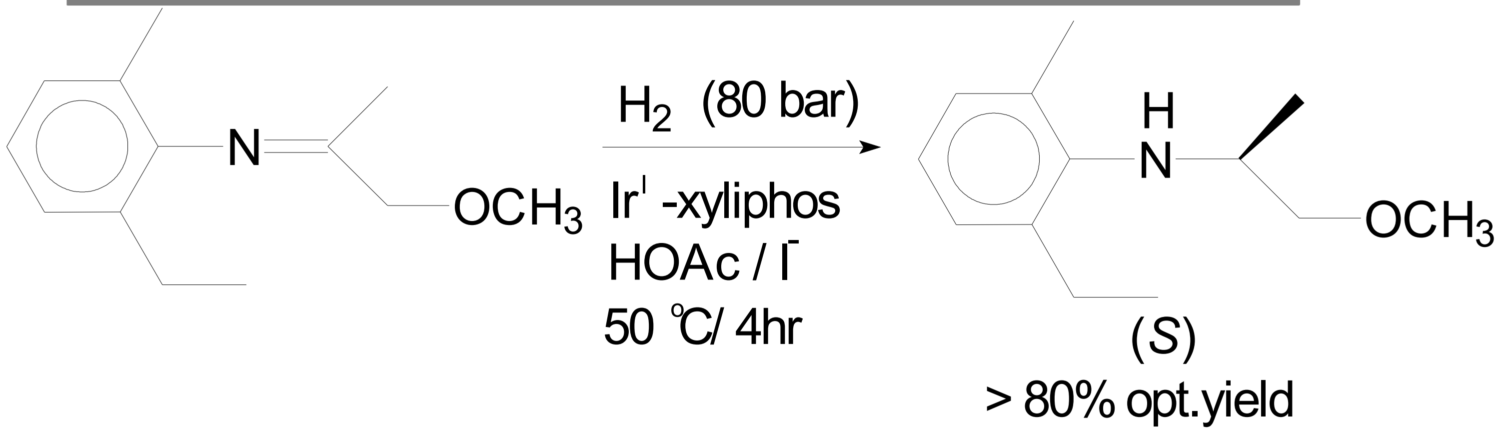
THF solvent, 80 ^{o}C

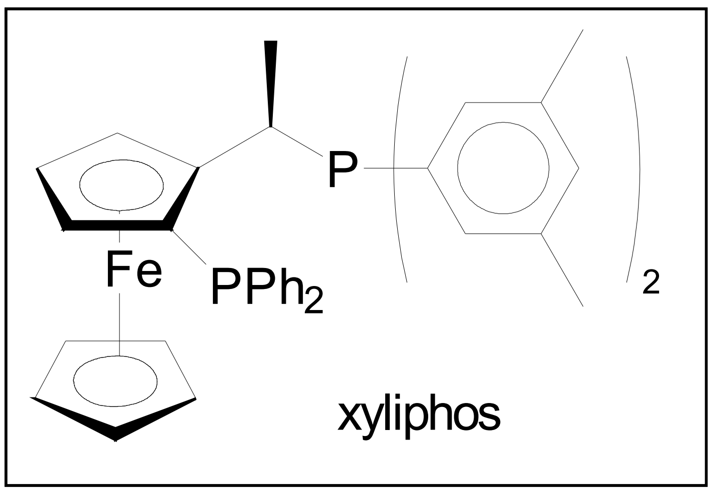
substrate: catalyst ratio = 8000

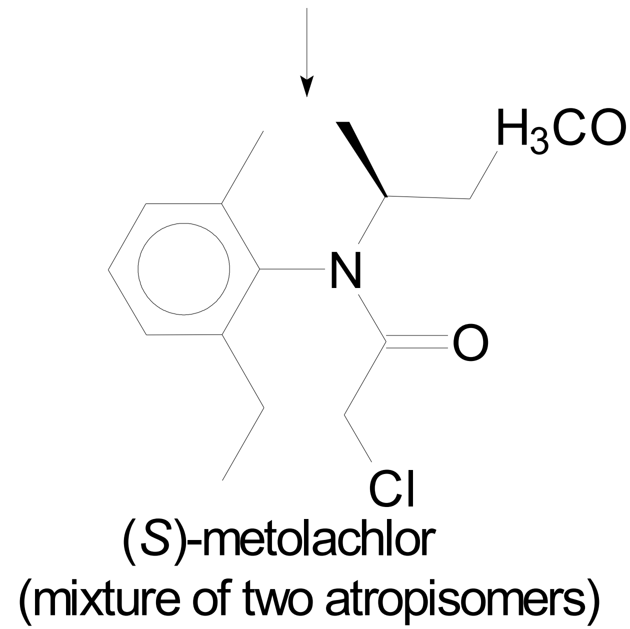
turnover number = 300,000

S.Akutegawa, in Chirality in Industry, pp.313-323; S.Akutegawa and K.Tani, in ‘Catalytic Asymmetric Synthesis’, I.Ojima Ed., VCH, Berlin, 1993, pp.41-61; S.Otsuka and K.Tani, Synthesis, 665 (1991)

ASYMMETRIC HYDROGENATION OF AN IMINE



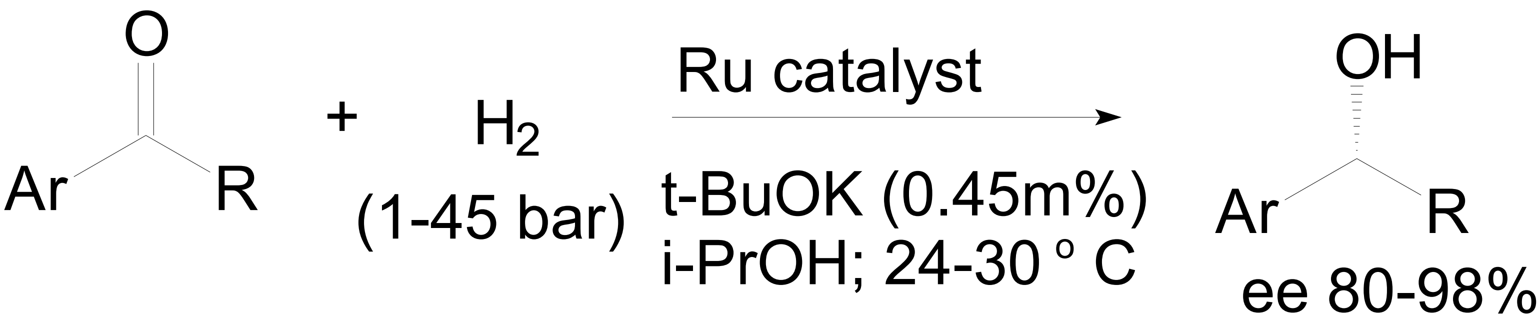


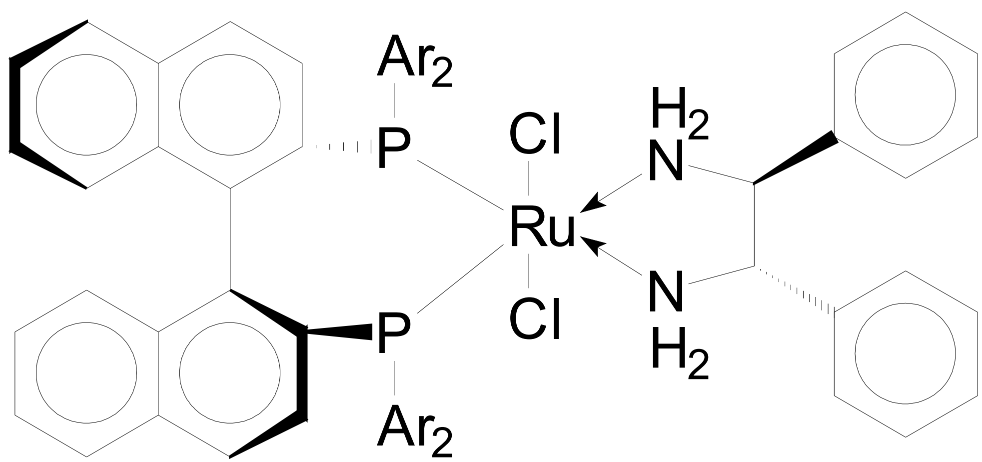


- S/C=750,000
- TOF (initial)=$1.8 \times 10^6 h^{-1}$ (1 mio turnovers in 6 hrs)

R.R.Bader and H.U.Blaser, *4th Int.Symp.Het.Catalysis & Fine Chemicals*, Basel, 1996

HIGHLY EFFICIENT ASYMMETRIC HYDROGENATION OF KETONES





(*S*)-BINAP
(Ar = Ph)

(*S,S*)-DPEN

e.g. Ar=Ph; R=CH_3

S/C = 2,400,000
30 °C/45 bar/48 h
100% yield; 80%ee
TOF =228000 h^{-1}
at 30% conv.

Rate 100x faster with preformed complex

R.Noyori et al., *Angew. Chem. Int. Ed.*, 37, 1703-1707, 1998

Homogeneous vs Heterogeneous Catalysis

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

→ **<u>Homogeneous liquid / liquid biphasic catalysis</u>**

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THE QUESTION OF SOLVENTS

THE PROBLEM:

- Toxicity / emissions of volatile solvents (e.g. chlorinated hydrocarbons)
- Aqueous contamination by non-volatile, polar solvents

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

(Alan Curzons,GSK)

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Restrictions on Solvent Use in the Pharma Industry

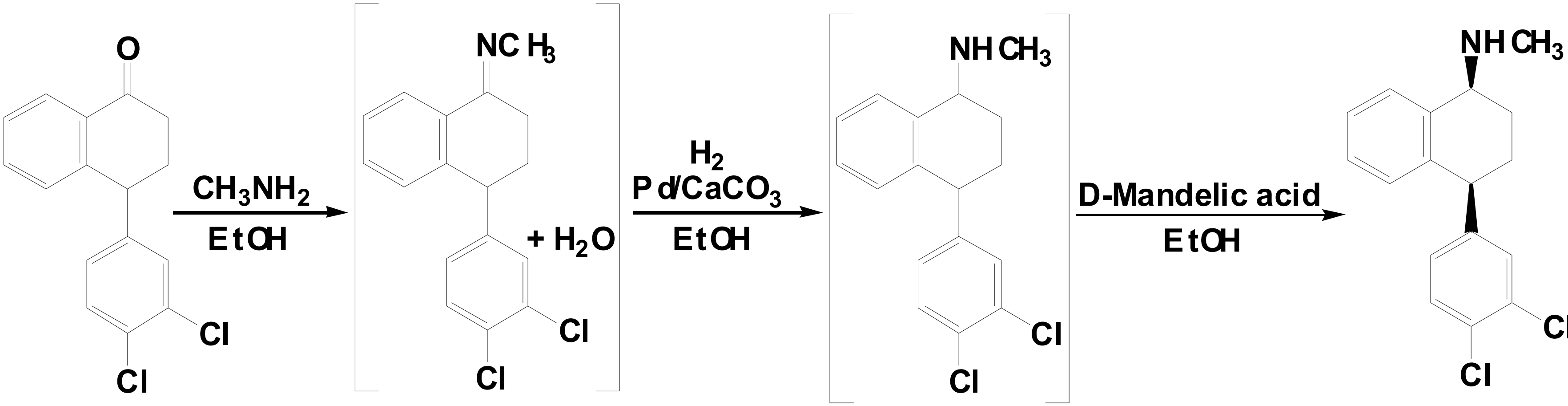
- Driving force: exposure of the user to residual solvents
- Solvents that should never be used: benzene, tetrachlorocarbon, 1,2-dichloroethane, 1,1-dichloroethane,…………
- Solvents that can be used if unavoidable (residues in the product subject to regulations): hexane, toluene, dichloromethane, dioxane, pyridine, methanol, ………….
- Preferred solvents: water, scCO_2, heptane, *tert*-butyl methyl ether, ethyl acetate, *tert*-butyl alcohol, ethanol, ………….

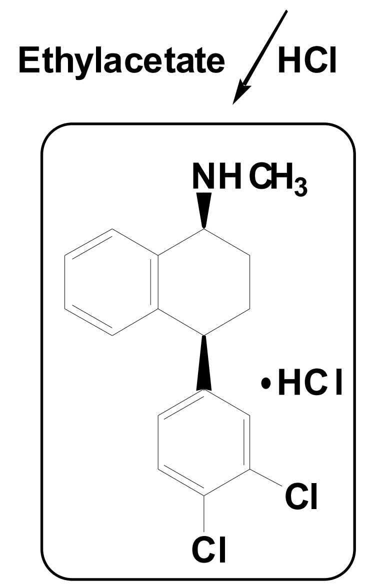
FDA, Q3C - Tables and List (www.fda.gov/cder/guidance/index.htm)

What are Green Solvents?

- Low toxicity
- Easy recyclability (no disposal)
- Further desirable characteristics:
  - -Easy removal from the product
  - -Low reactivity

New Sertraline process (Pfizer's Antidepressant) is Greener





Sertraline •HCl

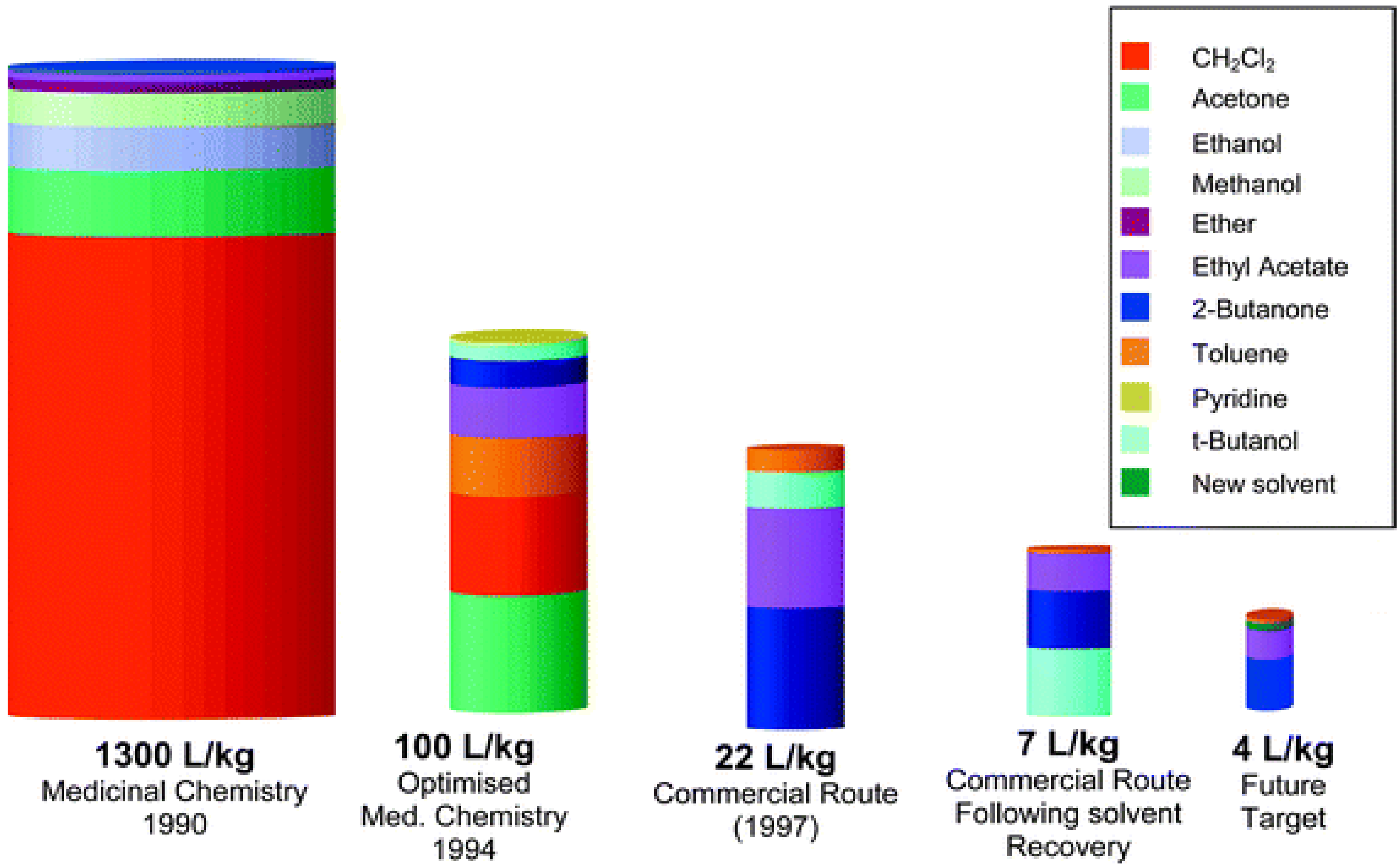
Three step process
Introduction of EtOH as solvent
Replacement of Pd/C with Pd/$CaCO_3$ - higher yields

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

A Green Process for Sildenafil (Viagra™)



P.J.Dunn,S.Galvin and K.Hettenbach,Green Chem. 6,43(2004)

Comparison of E factors

Industry segment	Prodn(tons)	E-factor
Oil refining	10^6–10^8	< 0.1
Bulk chemicals	10^4–10^6	<1–5
Sildenafil citrate	**30–40**	**6**
Fine chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

THE QUESTION OF SOLVENTS

The Solution

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

→ Catalyst in separate phase (recyclable)

Water as a reaction medium

Economically & Environmentally attractive

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

Highly polar reaction medium

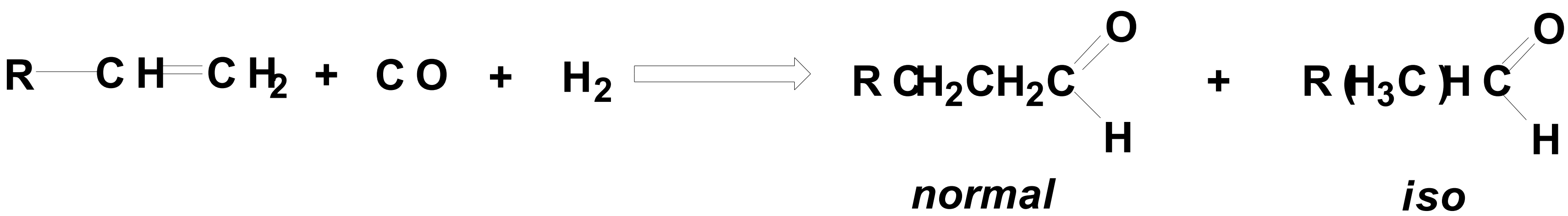
- Novel reactivity of organometallic complexes
- Facile product separation/catalyst recycling
- Reduced product contamination

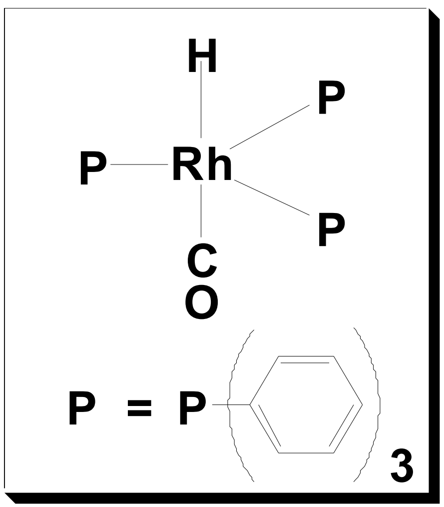
G. Papadogianakis, R.A. Sheldon, *New J. Chem.*, 20 (1996) 175-184

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

Rhodium Catalyzed Hydroformylation;Union Carbide Process

100 - 300 psi CO/H_2, $100^{o}C$, P:Rh = 1000





<u>Advantages</u>

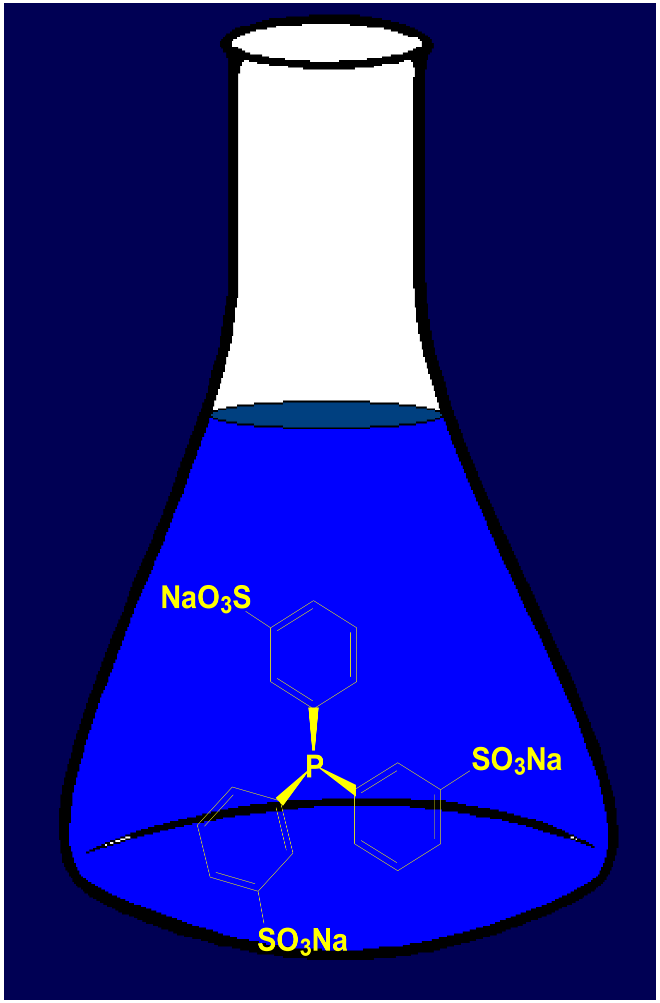
High catalytic activity

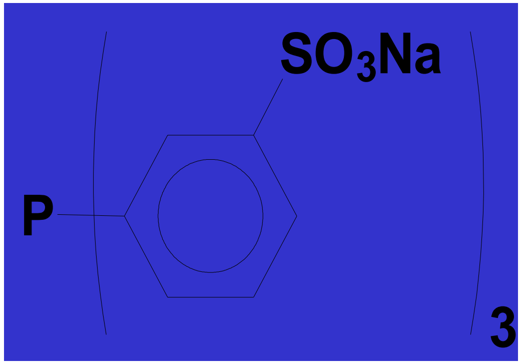
Good n/i selectivity

<u>Disadvantages</u>

Separation of the catalyst from C_n-aldehydes (n>8) is difficult

Sodium salt of tri-*m*-sulfonatotriphenylphosphine (tppts)

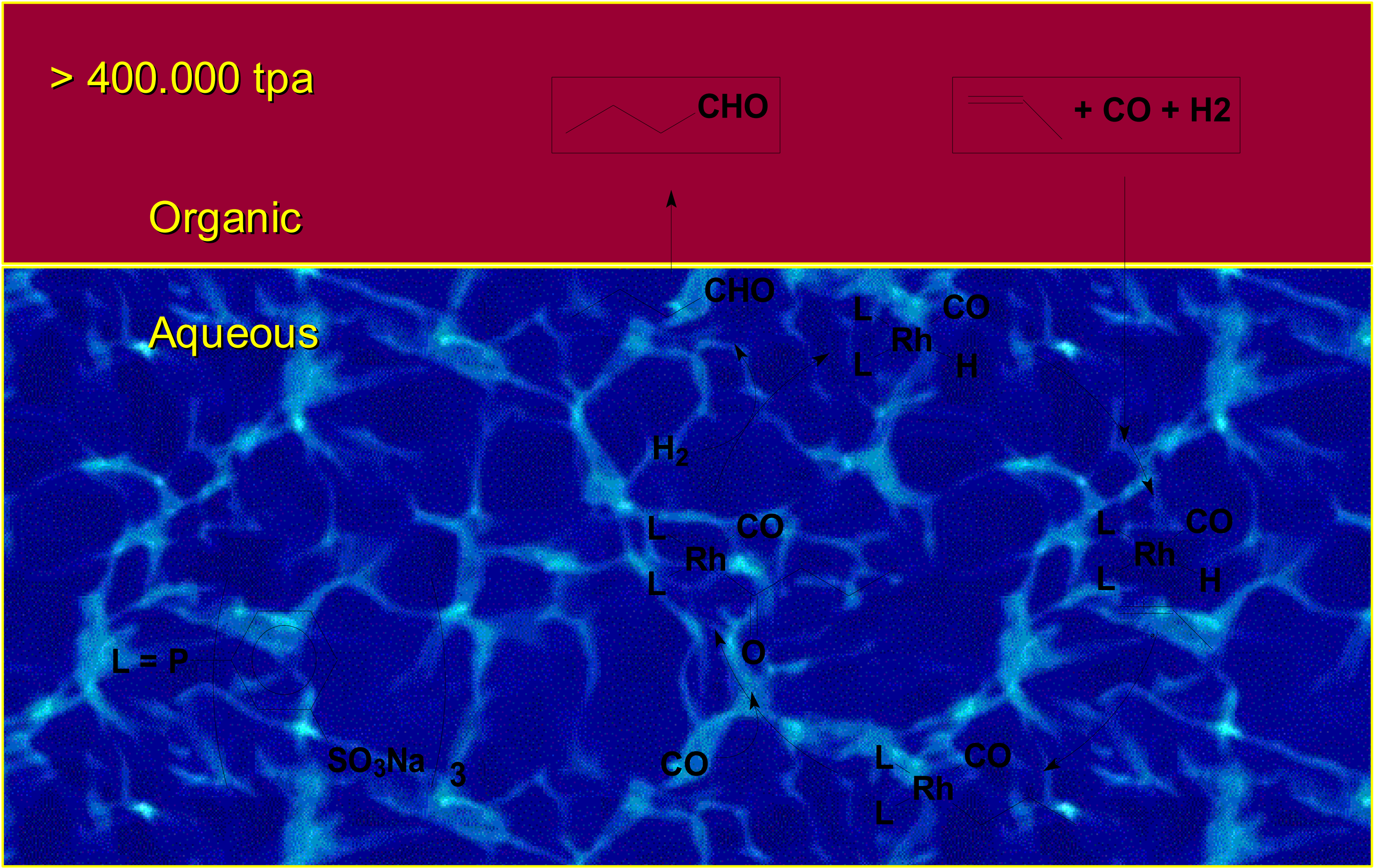




- Solubility in water: 1100 g / L

E.G. Kuntz, 1974

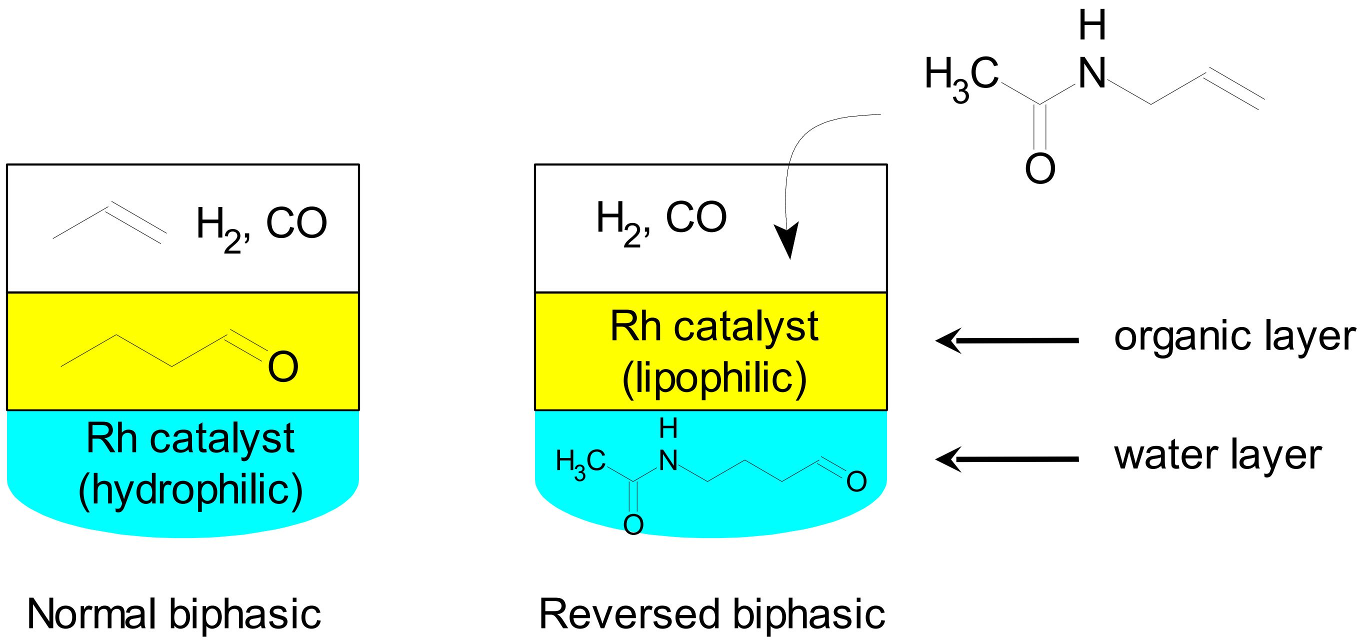
The Ruhrchemie/Rhône Poulenc hydroformylation process



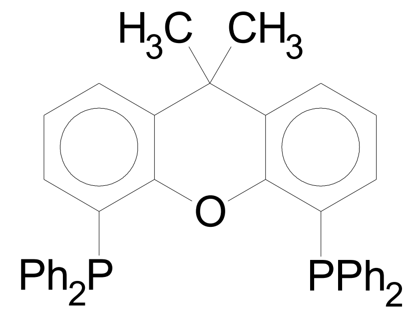
B. Cornils and E. Wiebus, *Chemtech*, 1995, *25*, *33*

Pause

Hydroformylation in a Reversed Biphasic System



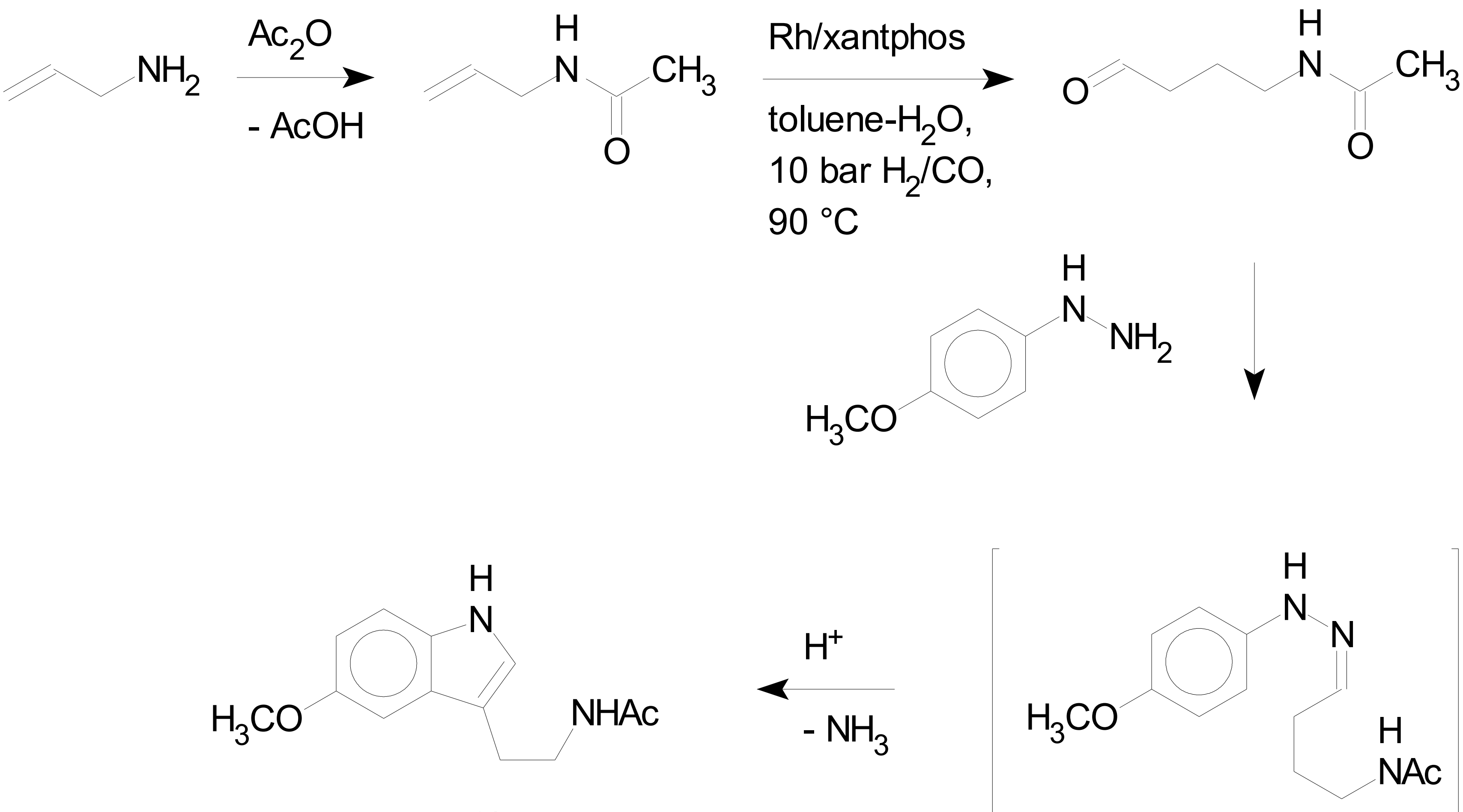
- Hydroformylation in the organic phase is efficient, but ca. 20 × slower than in water (using the tppts ligand)
- The xantphos ligand induces a high (15) n/iso ratio
- No leaching of the catalyst into the aqueous phase (5 × recycle without loss of activity)



Ligand: xantphos

G. Verspui *et al.*, *Chem. Commun.* 1363 (2000)

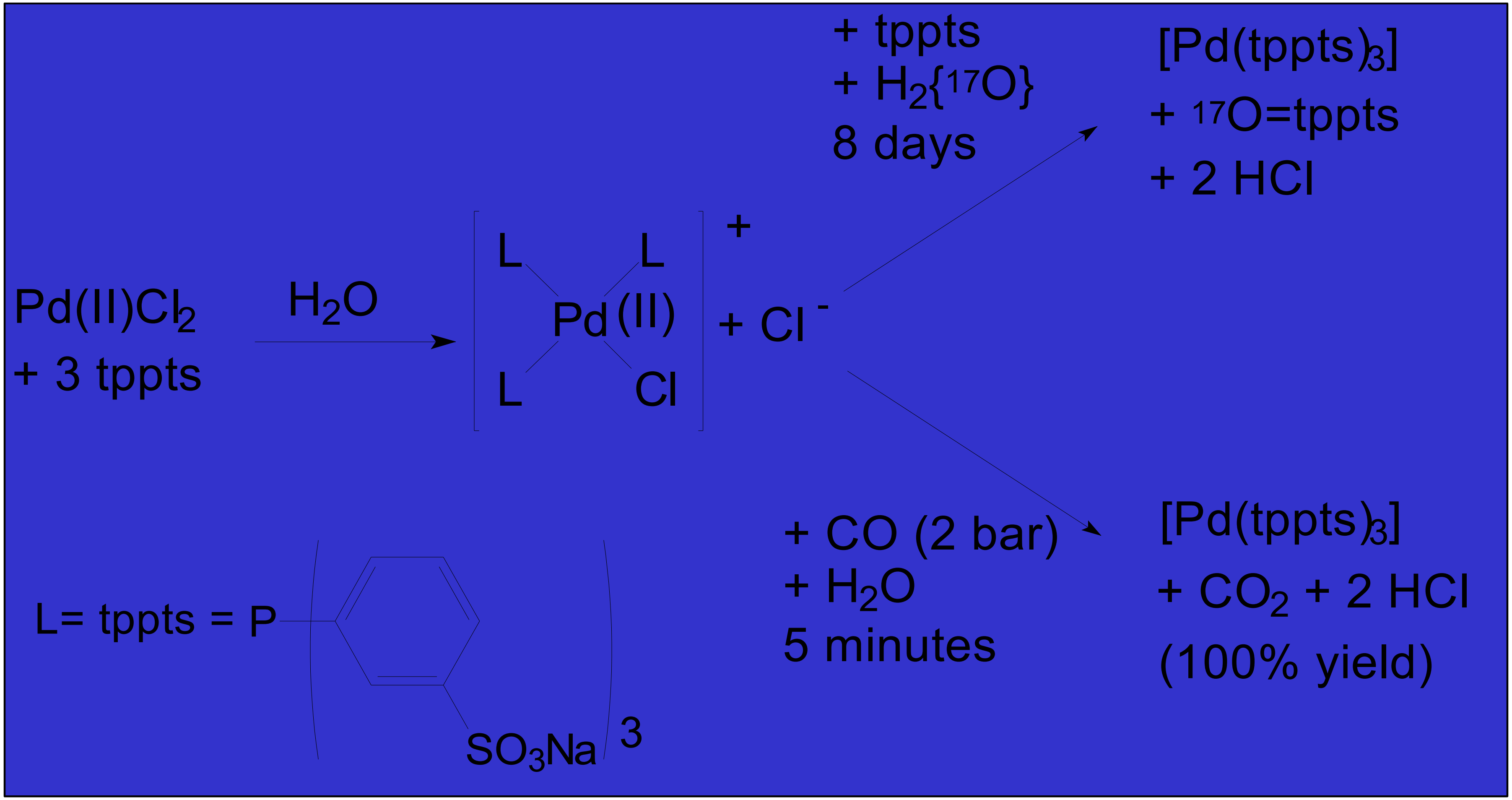
A One-Pot Synthesis of Melatonin



melatonin, 44% yield
(not optimised)

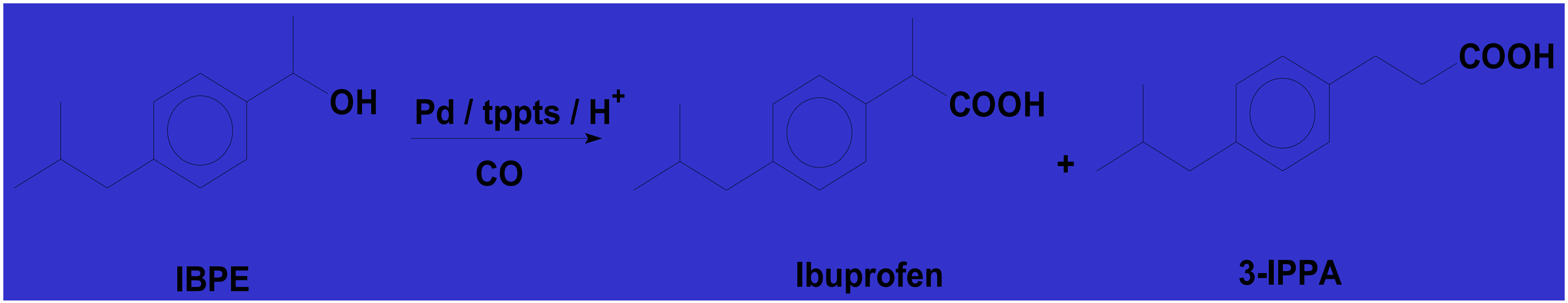
G. Verspui *et al.*, *Chem. Commun.* 1363 (2000)

^{17}O-, ^{31}P- and ^{35}Cl NMR study of the redox reaction between $PdCl_2$, tppts and H_2O



G. Papadogianakis, J.A. Peters, L. Maat and R.A. Sheldon, *Chem. Commun.*, **1995**, 1105
G. Papadogianakis, L. Maat and R.A. Sheldon, *Inorg. Synth.*, **32** (1998) 25-29

Biphasic carbonylation of 1-(4-isobutylphenyl)ethanol



conversion: 83%

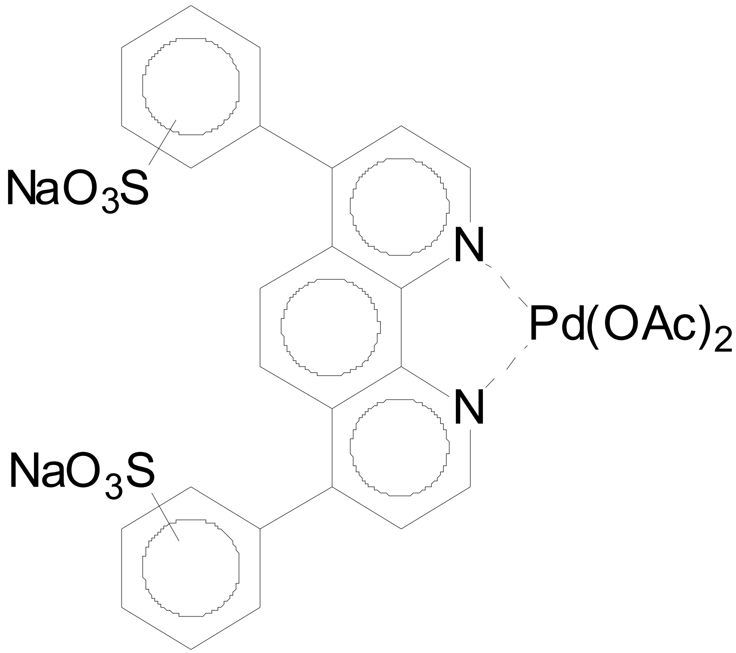
selectivity to ibuprofen: 82%

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

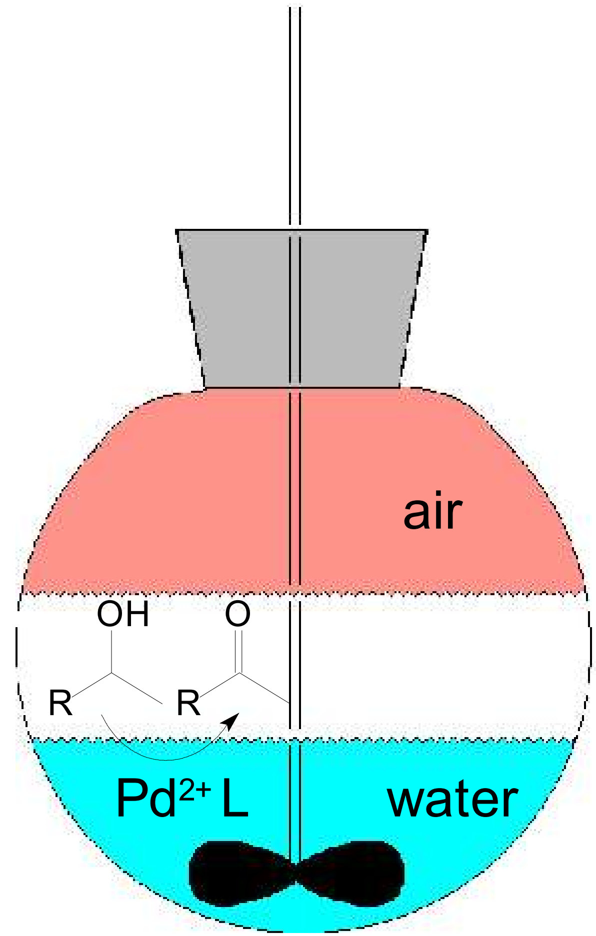
R.A. Sheldon, L. Maat, G. Papadogianakis, *US Patent* 5,536,874 (1996) to Hoechst Celanese Corp.

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

Green, Catalytic Alcohol Oxidations



Pd^{2+}-bathophenanthroline (L)

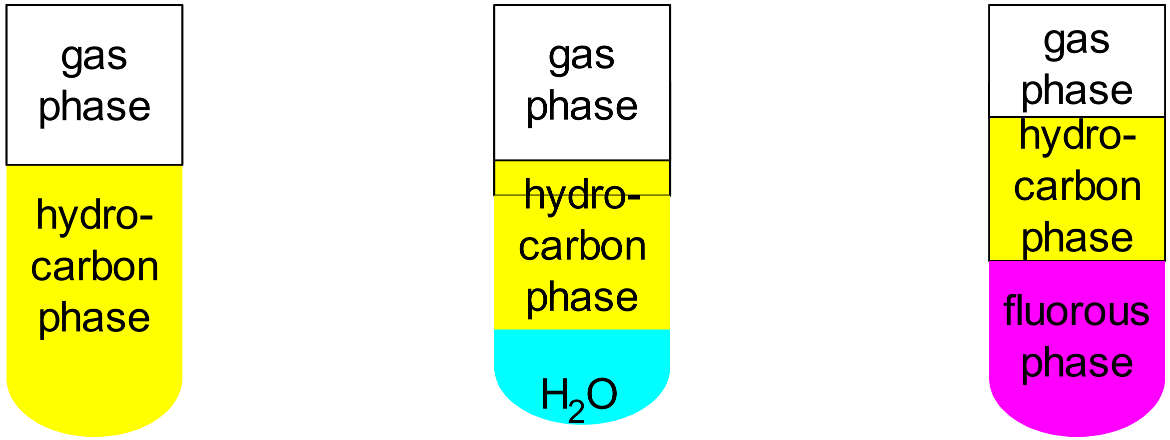


- **Air as oxidant**
- **No organic solvent**
- **Catalyst recycling via phase separation**

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

Fluorous Biphasic Catalysis

The Principle of Fluorous Phase Catalysis



$(Ph_3P)_3(CO)RhH$ $(tppts)_3(CO)RhH$ $((C_nF_{2n-1})P)_3(CO)RhH$

perfluoroalkane,

perfluoroether, etc

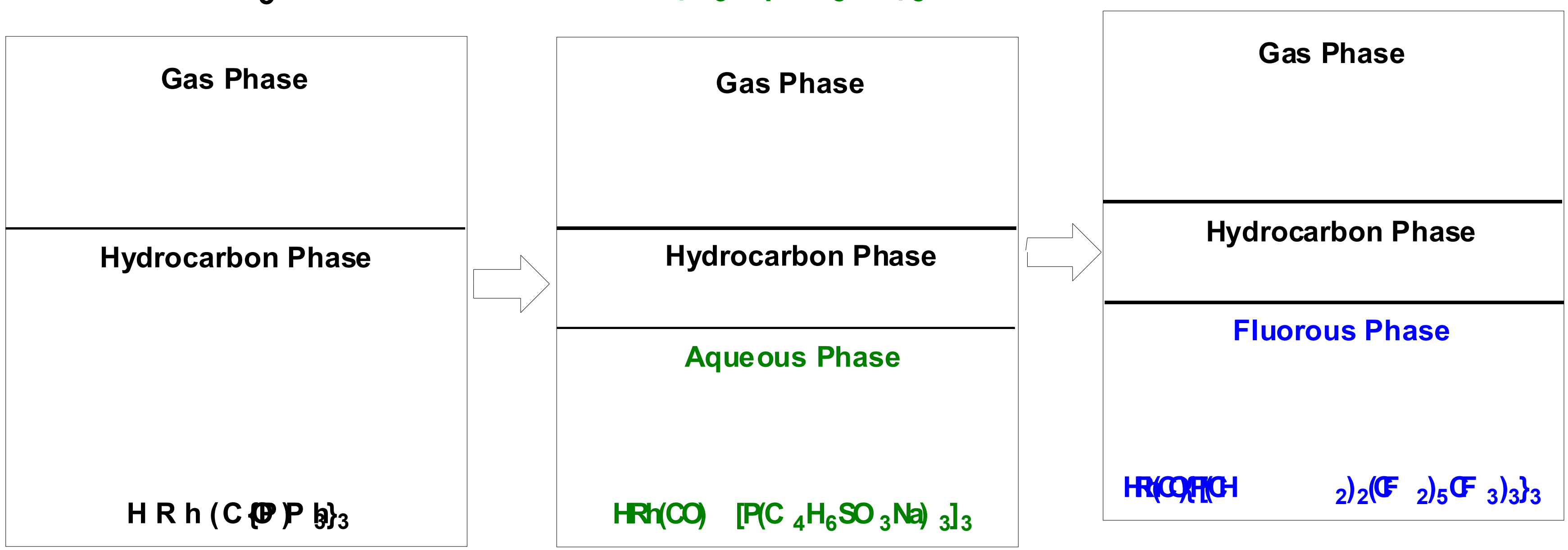
- **Fluorous pony tail fixes the catalyst into the fluorous phase**
- **Fluorous phases dissolve higher olefins better than water**
- **No Rh is carried over into the hydrocarbon phase**

I.T. Horvath, J. Rabai, *Science*, **72**, 266 (1994)

Evolution of Rhodium Hydroformylation Catalysts

$$R{-}CH{=}CH_2 + CO + H_2 \xrightarrow{HRh(CO)[PR_3]_3} R{-}CH_2CH_2CHO + R(CH_3)CH{-}CHO$$

PPh_3 | $P(C_6H_4SO_3Na)_3$ | $P[(CH_2)_2(CF_2)_5CF_3]_3$



Limitations

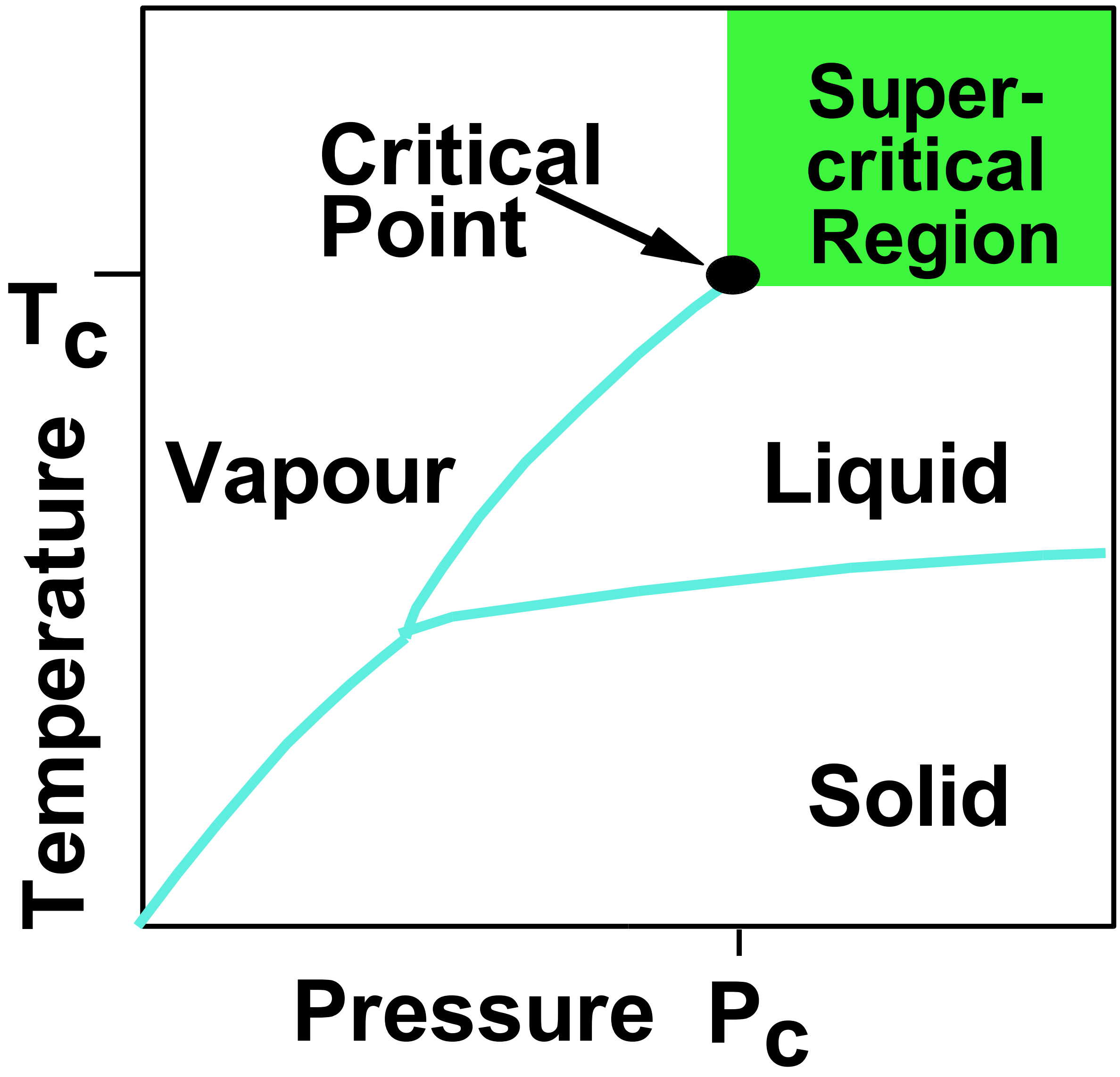
Separation of catalysts from $C_{n>8}$ aldehydes and heavy side-products

Solubility of higher olefins
Side reactions with water

Cost of ligands/solvents
Persistence of fluorocarbons

Supercritical CO_2

What is a Supercritical Fluid?

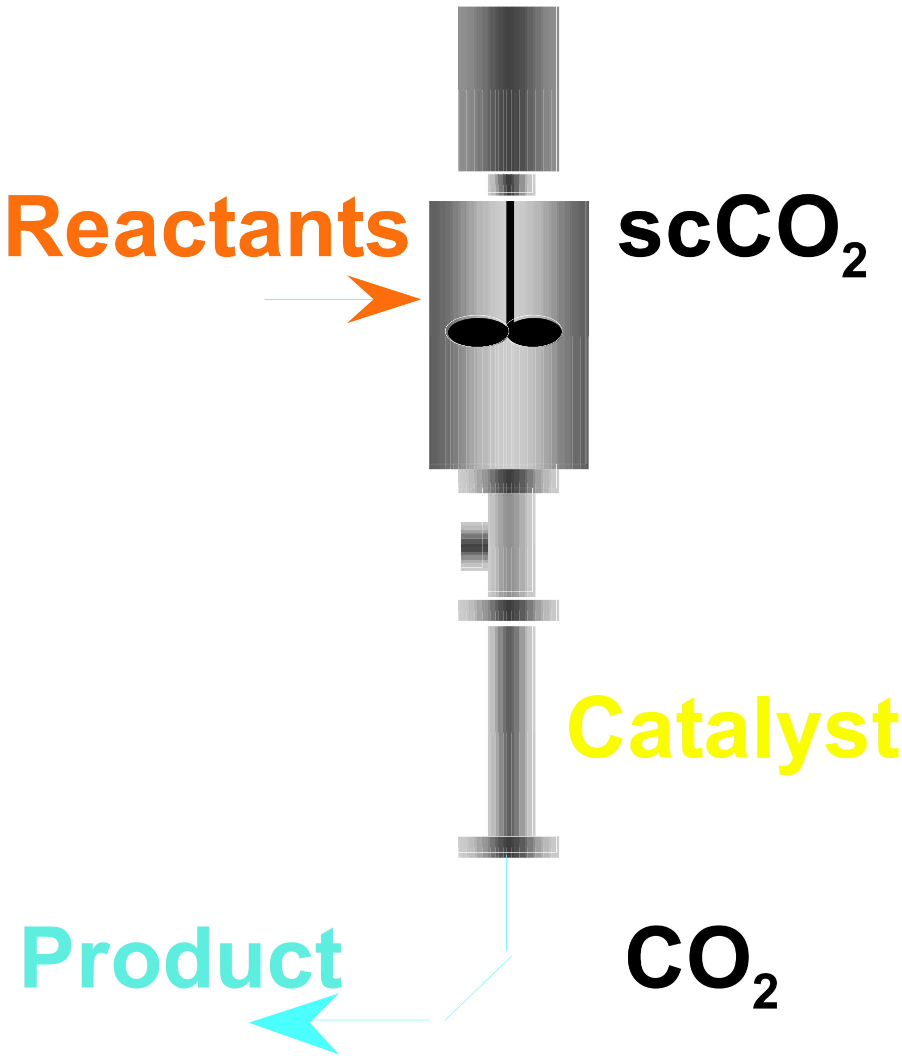


Supercritical CO_2 as a Reaction Medium

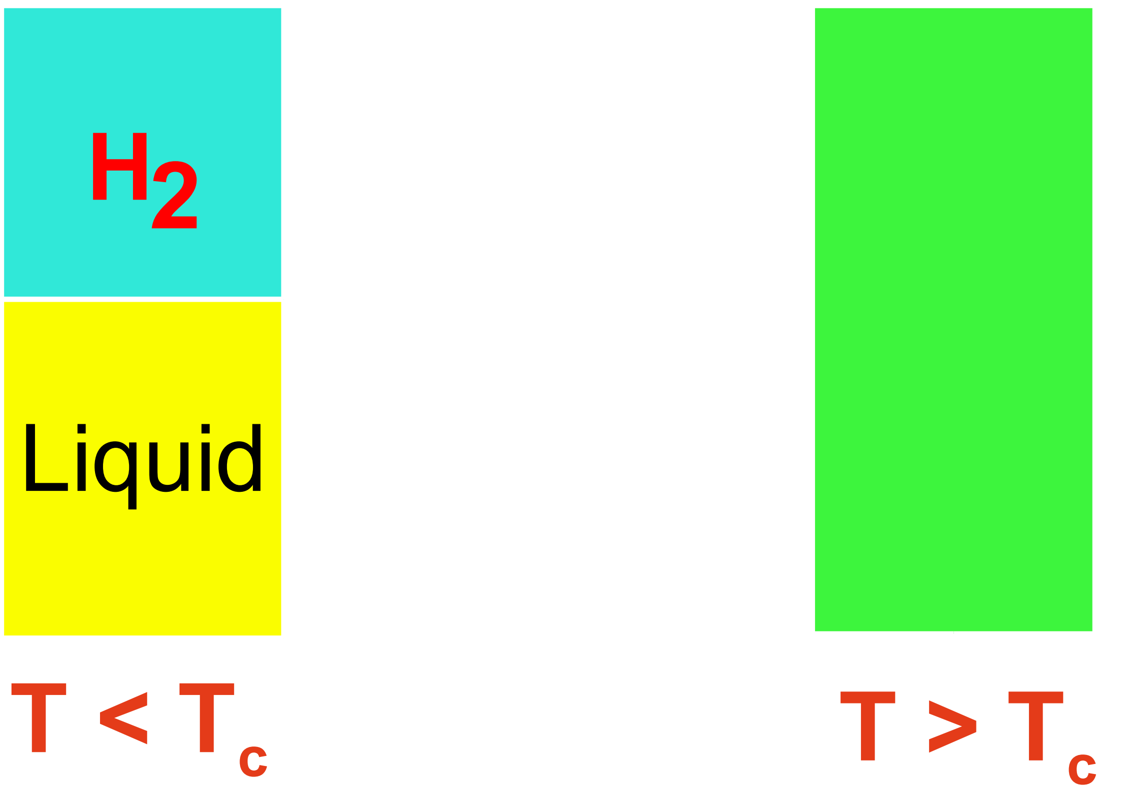
- T_c 31.0 °C, p_c 73.8 bar, d_c 0.477 kg L^{-1}
- Low viscosity (more like a gas than like a liquid); hence, fast mass transfer
- Cheap and abundantly available
- Easy to remove (N.B. no net production of CO_2)
- Non-toxic,non-inflammable,inert

Continuous Supercritical Chemistry

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

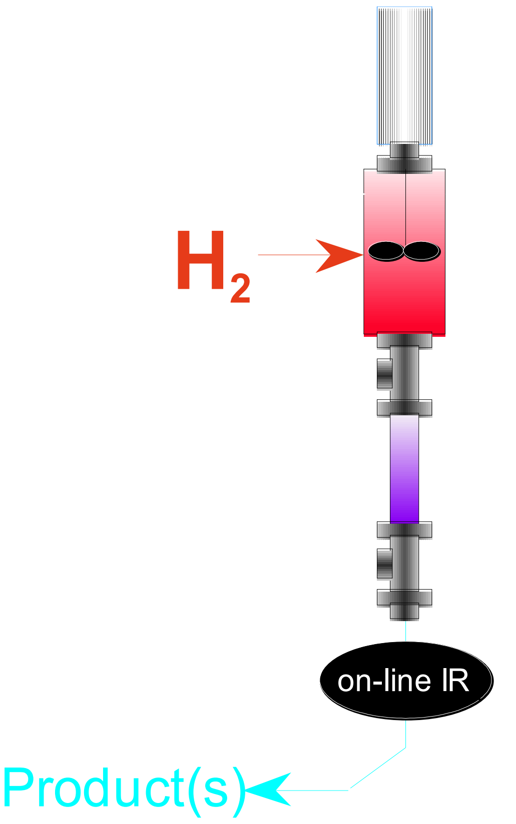


H_2 and $scCO_2$ Completely Miscible

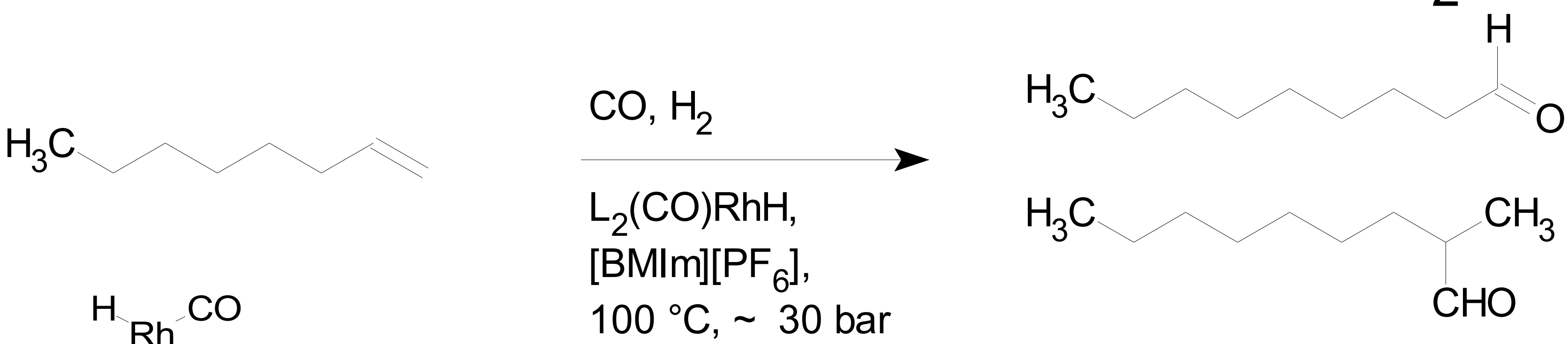


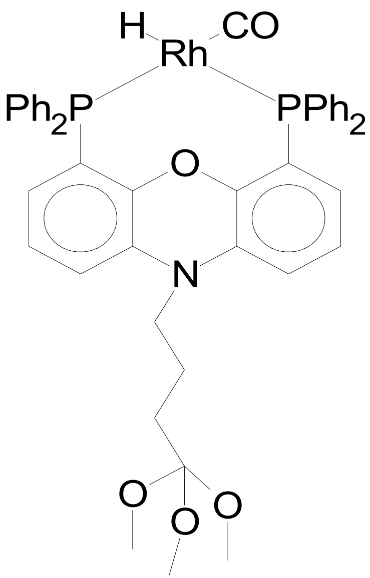
Continuous Supercritical Hydrogenation

- Large number of reactions
  - high conversion
  - high selectivity
- Small reactors:
  - high throughput
  - good safety
- Environmentally “Clean”: **reduced waste**



Continuous Hydroformylation of 1-Octene in $scCO_2$





Rhodium complex catalyst, chemically anchored to a silica surface to prevent leaching

- n/iso 35 - 50
- No loss of activity over several days
- Turnover frequency, compared with toluene:

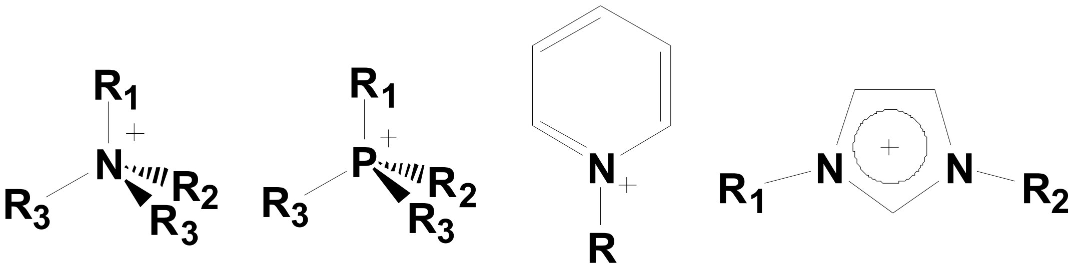
-4 × faster than immobilised catalyst

-0.5 × the rate of the homogeneous catalyst

Ionic Liquids

CATALYSIS IN IONIC LIQUIDS

CATIONS



ANIONS

BF_4^-, PF_6^-, SbF_6^-, NO_3^-
$CF_3SO_3^-$, $(CF_3SO_3)_2N^-$,
$ArSO_3^-$, $CF_3CO_2^-$, $CH_3CO_2^-$,
$Al_2Cl_7^-$

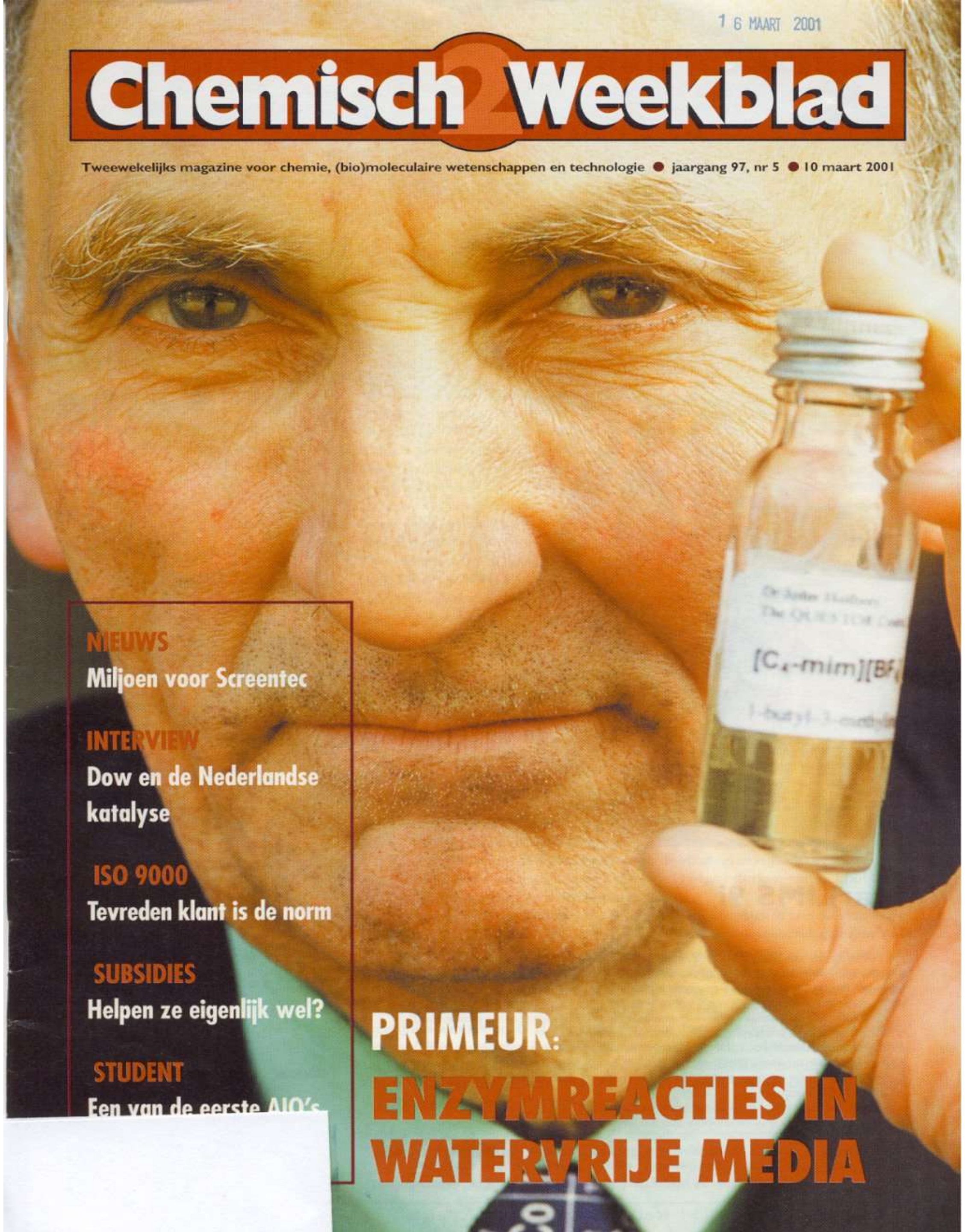
- Liquid at room temperature/no vapor pressure
- Liquid range of 300 °C (c.f. H_2O, 100 °C)
- Designer solvents, e.g. bmim BF_4 hydrophilic, bmim PF_6 hydrophobic

Reactions: hydrogenation,hydroformylation,Heck reactions, dimerization/oligomerization of olefins, etc, **and biocatalysis in ILS**

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

Chemisch2Weekblad

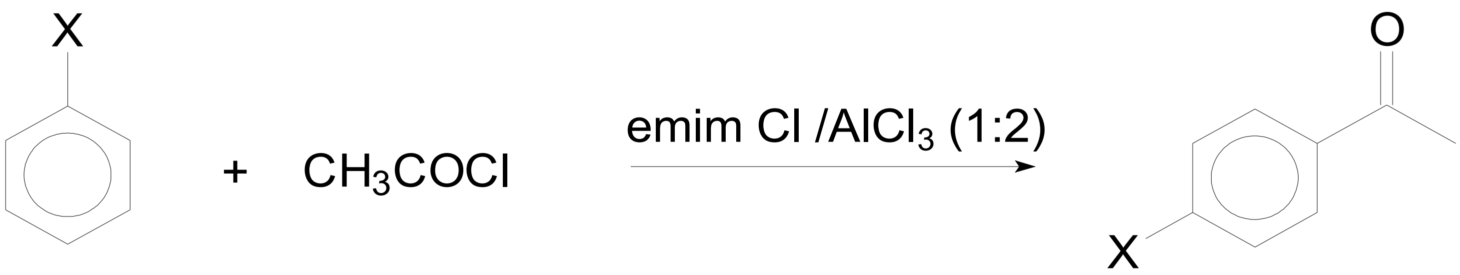
Tweewekelijks magazine voor chemie, (bio)moleculaire wetenschappen en technologie ● jaargang 97, nr 5 ● 10 maart 2001



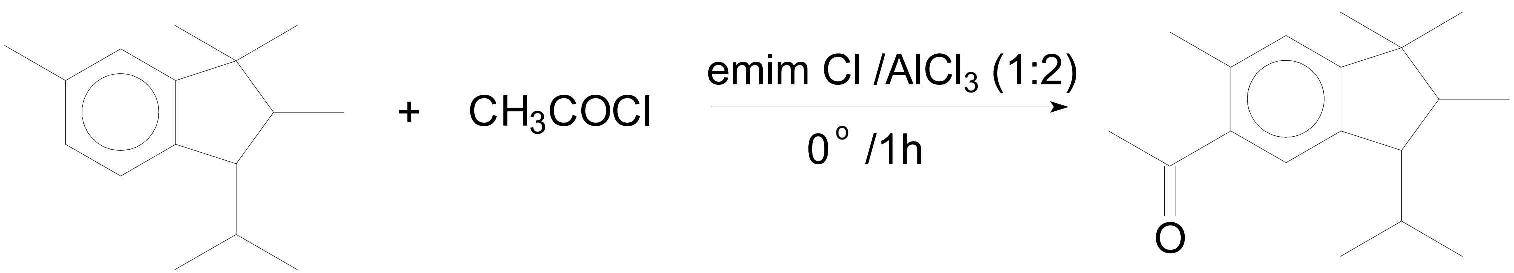
PRIMEUR:

ENZYMREACTIES IN WATERVRIJE MEDIA

Friedel-Crafts Acylation in Ionic Liquid



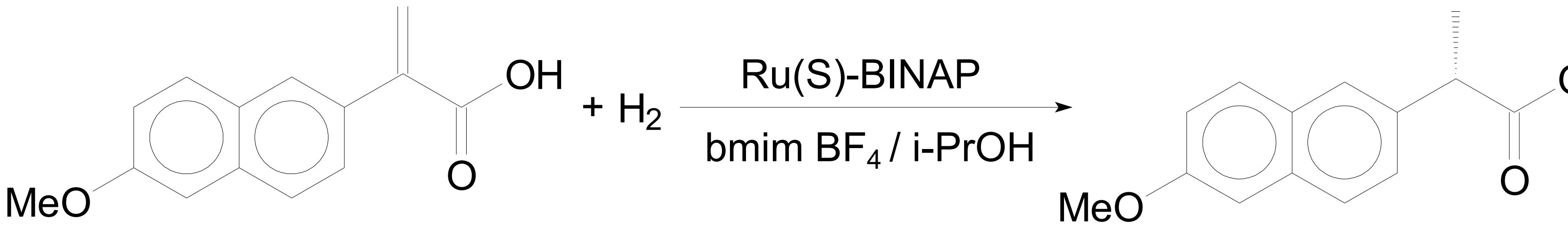
R	Temp (°C)	Time (h)	Yield (%)
MeO	-10	0.25	99
Me	20	1	98
Cl	20	24	97



traseolide
99% yield

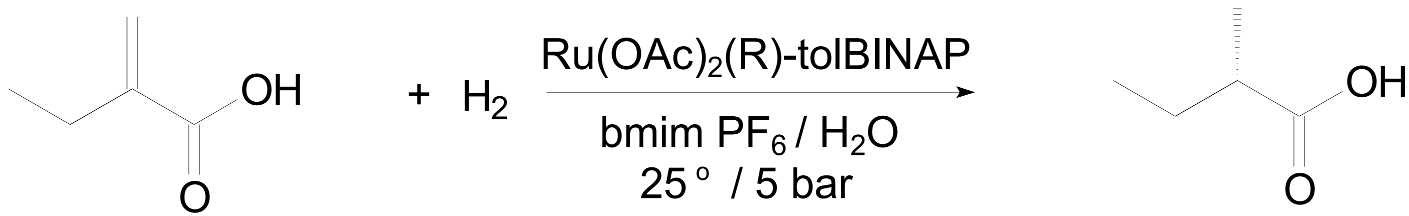
K.R.Seddon et al,Chem.Comm. 2097(1998)

Asymmetric Hydrogenation in Ionic Liquids



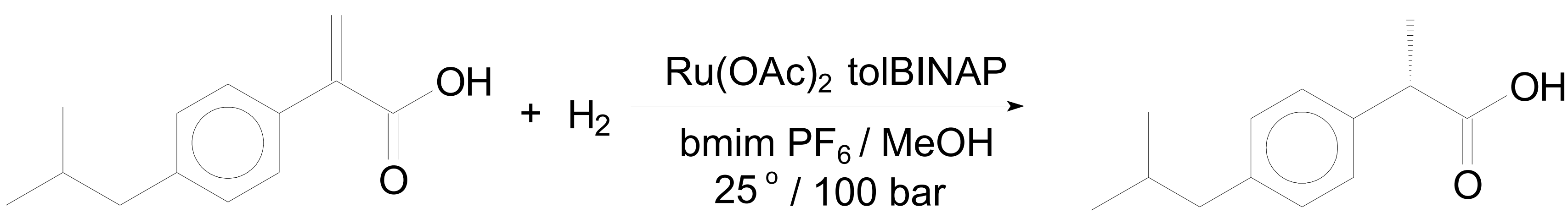
(S)-naproxen, 80% ee

(3)



100% conversion
99% ee

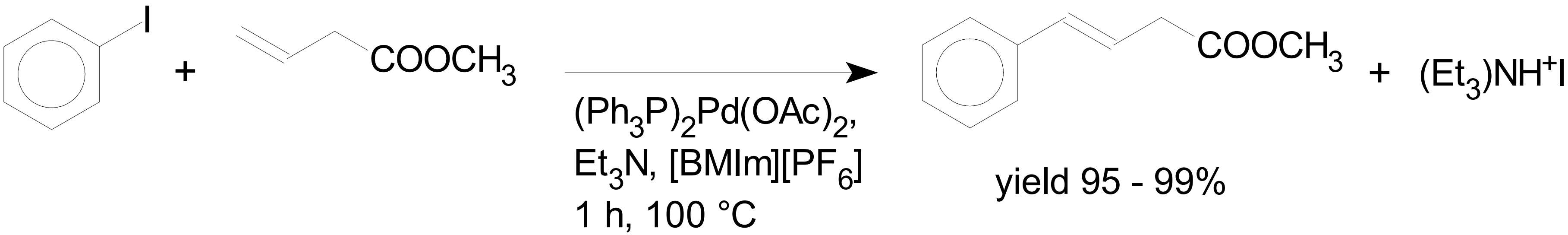
(4)

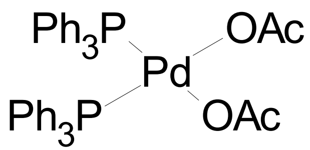


(S)-ibuprofen, 85% ee

(5)

Palladium Catalysed Heck Arylation in Ionic Liquid Medium

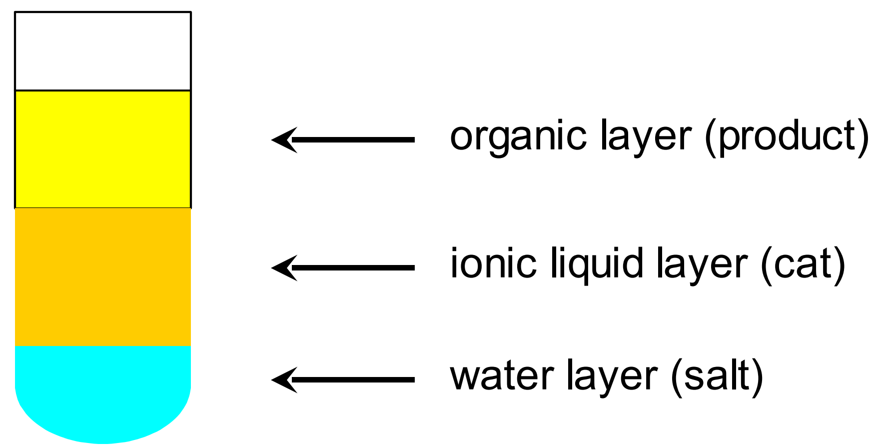




catalyst (4 mol%)

Workup:

- Add cyclohexane and water
- Separate the triphasic mixture
- Recycle IL layer with catalyst



A.J. Carmichael *et al.*, *Org. Lett.* **1**, 997 (1999)

Using Homogeneous Catalysts Efficiently

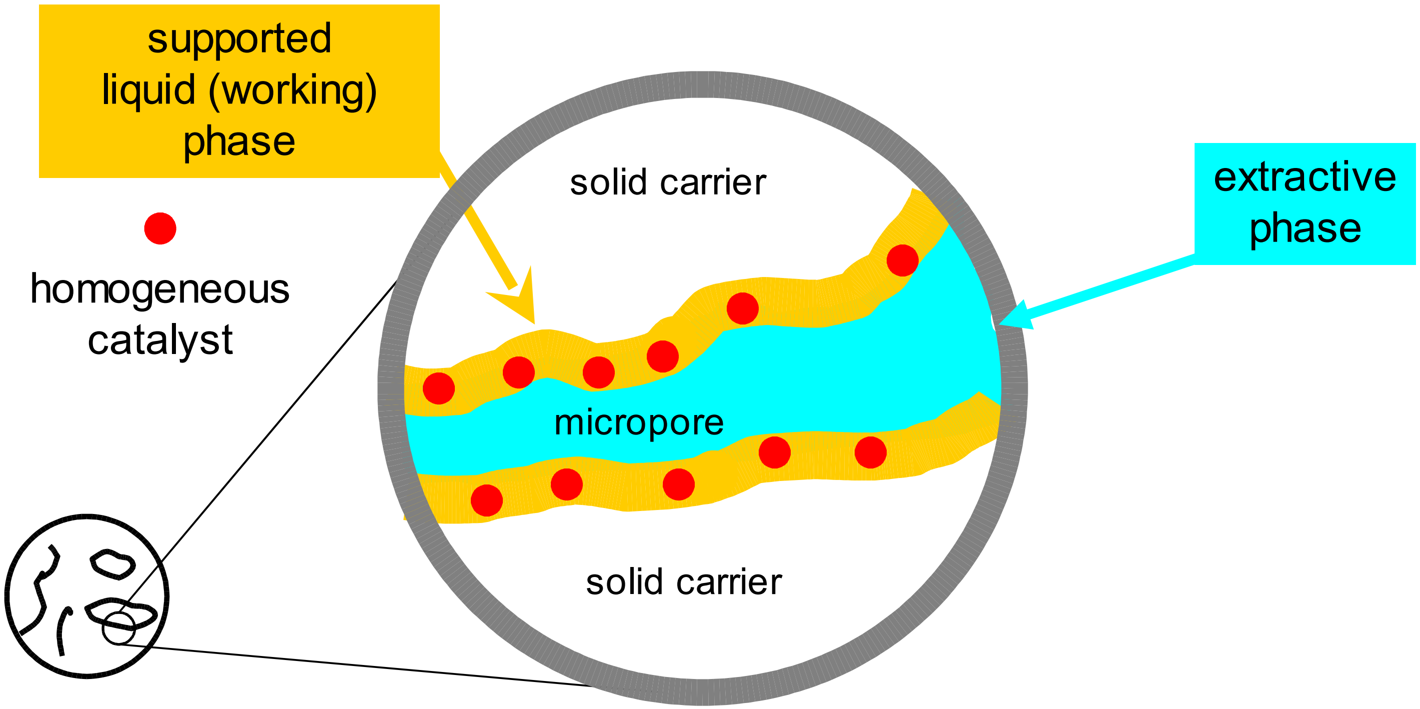
- Biphasic homogeneous catalysis integrates reaction and products and catalyst separation into a single operation

- Other possible solutions:

  -Supported liquid phase catalysis

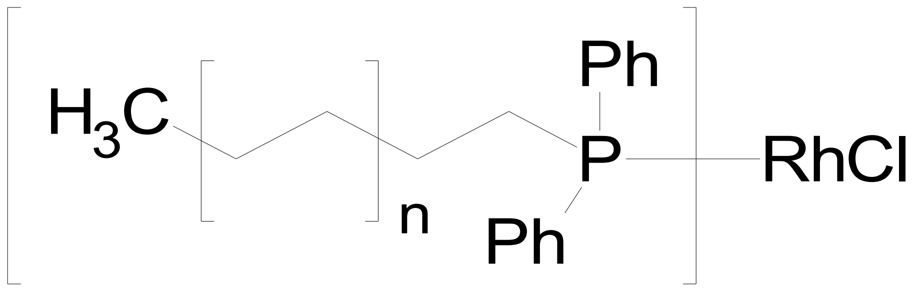
  -Thermoregulated biphasic catalysis

Supported Liquid Phase Catalysis



- Combines advantages of homogeneous and heterogeneous catalysis
- Only a small amount of working phase is present in the reactor
- Particularly suited with ionic liquids as the working phase

Thermoregulated Biphasic Catalysis

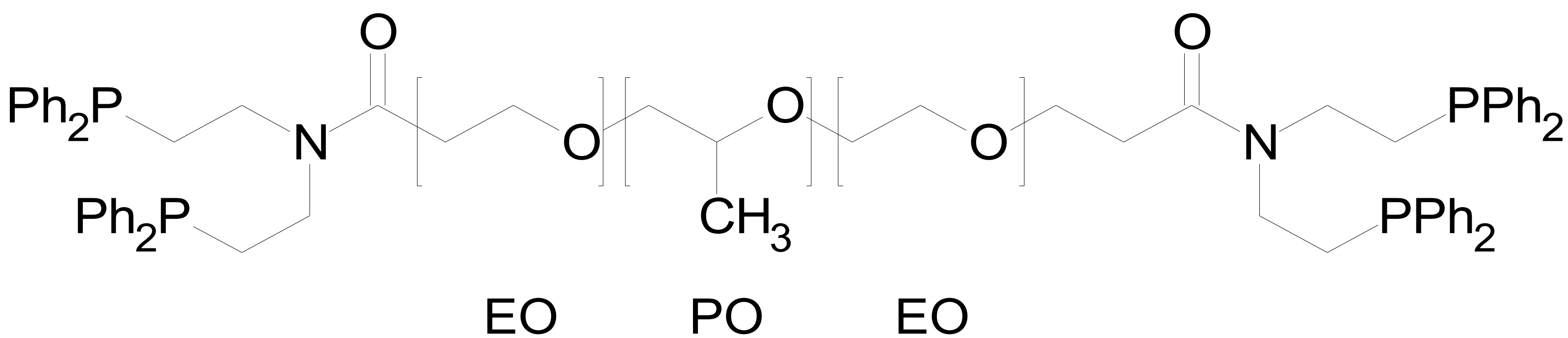


$M_w = 2400$

- The polyethylene ligand is soluble in hydrocarbons at 90 - 110 °C
- Quantitative precipitation at 25 °C
- Demonstrated in olefin hydrogenation in xylene medium
  - Activity is comparable with that of $(Ph_3P)_3RhCl$
  - Catalyst 18 × recycled without loss

D.E. Bergbreiter *et al. J. Am. Chem. Soc.* **109**, 174 (1987)

Thermoregulated Biphasic Catalysis:
Inverse Temperature Dependence



M_w = 1100 - 4400

- The ligand and its Rh complex are soluble in water at 0 °C
- At 40 - 50 °C the complex separates and reaction stops
- Ligand dehydration is the driving force
- Demonstrated in simple hydrogenation

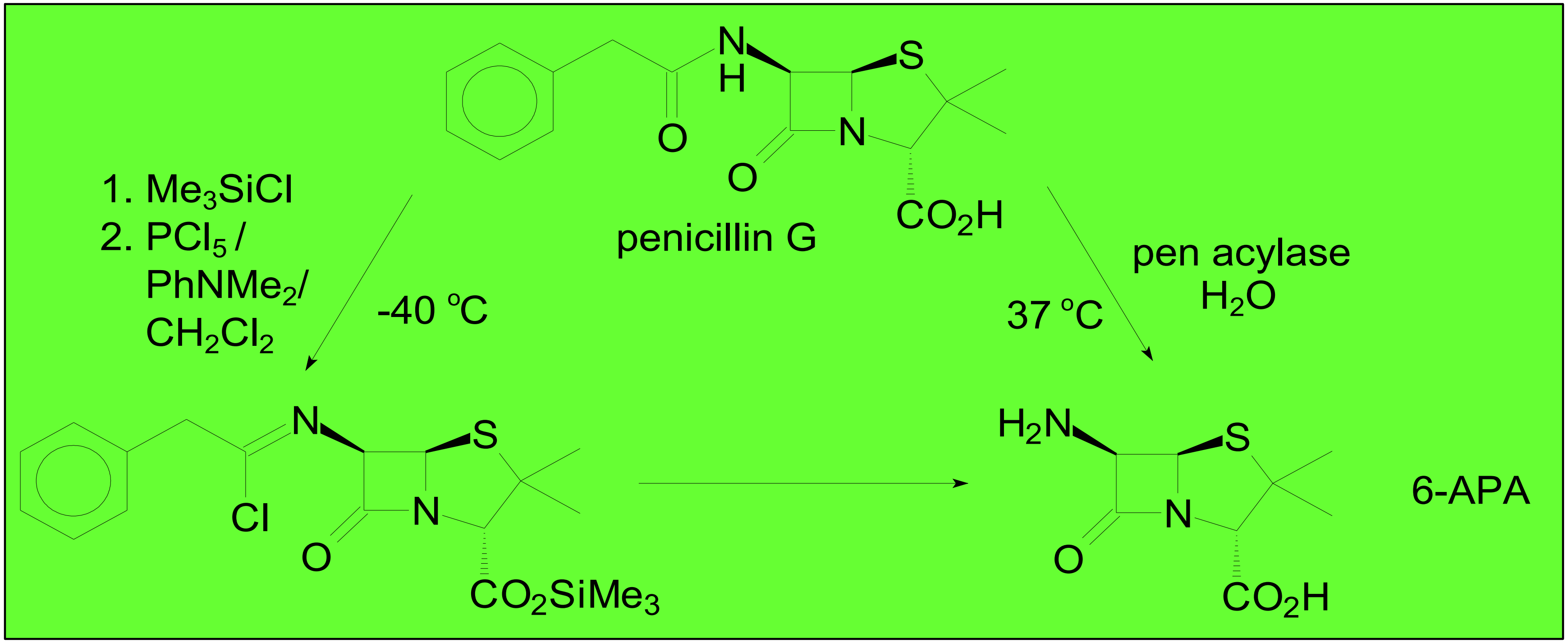
D.E. Bergbreiter *et al. J. Am. Chem. Soc.* **115**, 9295 (1993)

Biocatalysis

Why Biocatalysis?

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

ENZYMATIC vs CHEMICAL PROCESS FOR 6-APA



Key improvements: enhanced enzyme production and immobilization

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)

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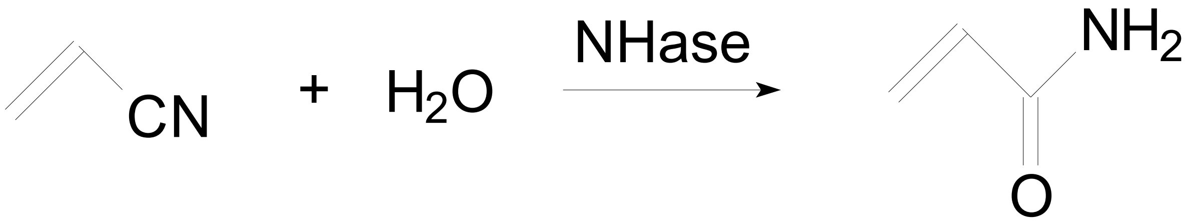
BIOCATALYTIC PRODUCTION OF ACRYLAMIDE: MITSUBISHI



conv. > 99.99%

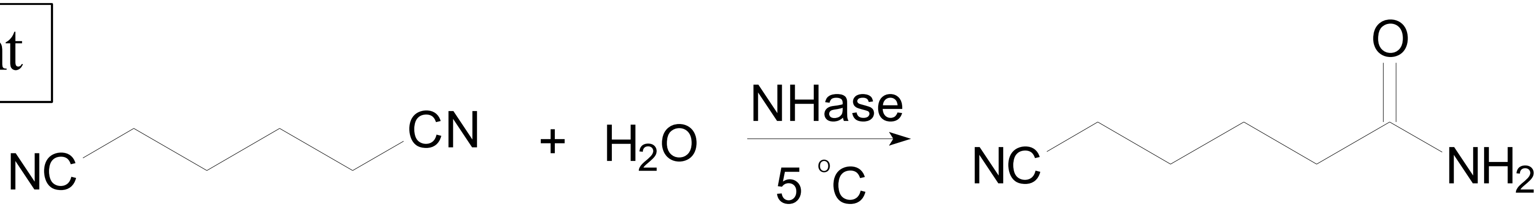
sel. > 99.99%

- 100,000 tons per annum and increasing
- Simpler than chemical process (Cu catalyst)
- Immobilized whole cells of *Rh.rhodocrous* J1
- Mild conditions (5°C); no polymerization inhibitor needed
- >400 $g \cdot l^{-1} \cdot h^{-1}$; higher product quality

A.Liese, K. Seelbach and C. Wandrey, *Industrial Biotransformations*, Wiley-VCH, 2000

BIOCATALYTIC HYDROLYSIS OF NITRILES

DuPont



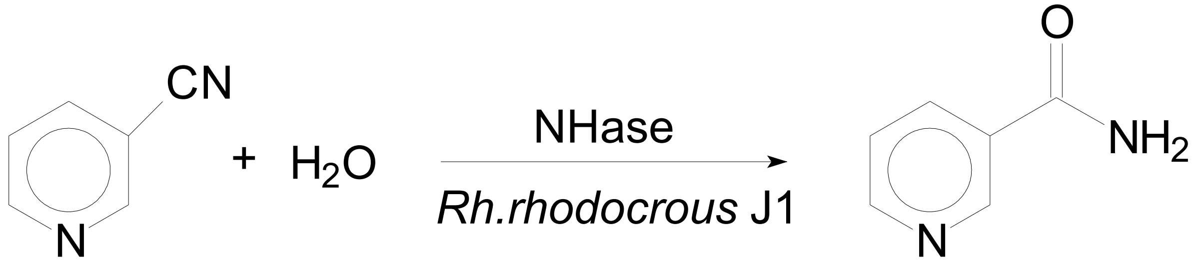
herbicide intermediate

97% conv. / 96% sel.

- Immobilized whole cells of *P. chlororaphis* B23
- Catalyst consumption 0.006 kg/kg product
- Higher conv./sel. than chemical process (MnO_2 cat. /130 °C)

R.Dicosimo et al, *Bioorg. Med Chem*. 1999, 7, 2239

Lonza



100% yield/ 1465 g·l^{-1}/3000 tpa

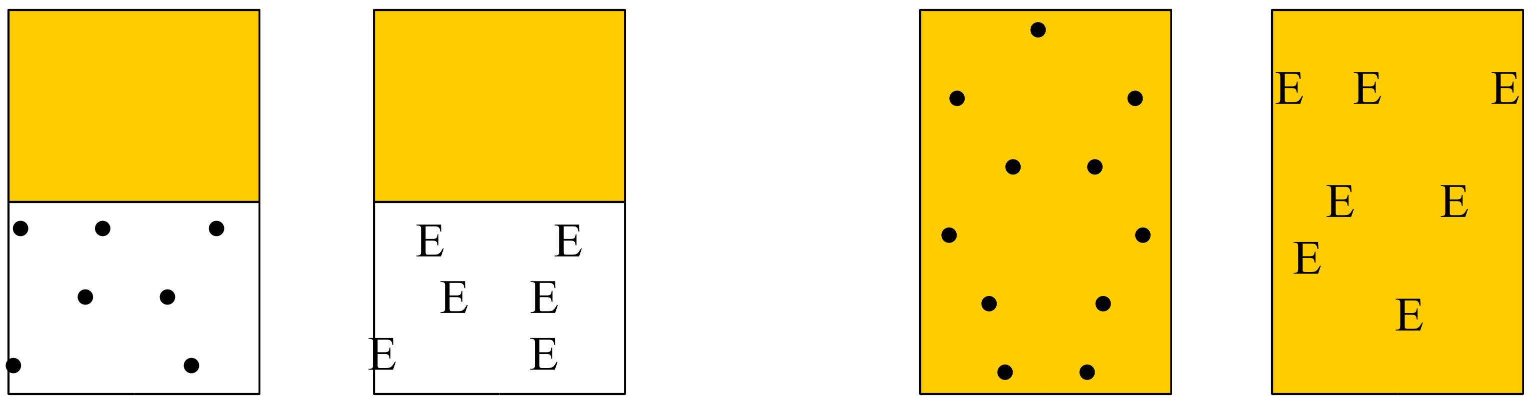
M. Petersen and A. Kiener, *Green Chem*., 1999, 4, 99

Enzymes in Ionic Liquids

Two phase | Single phase

IL

H_2O



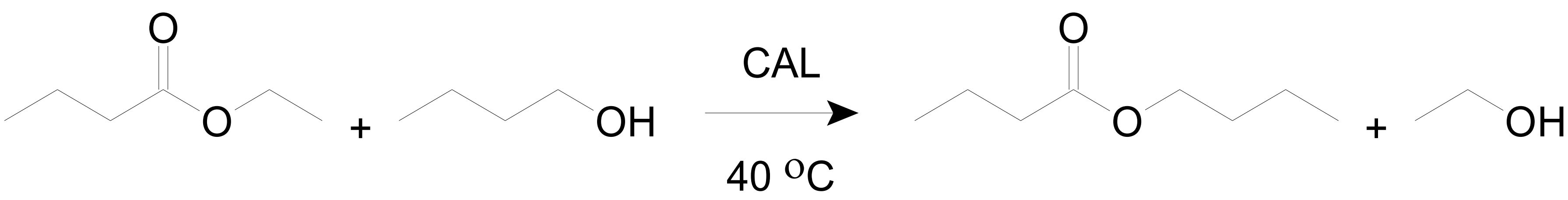
Dissolved

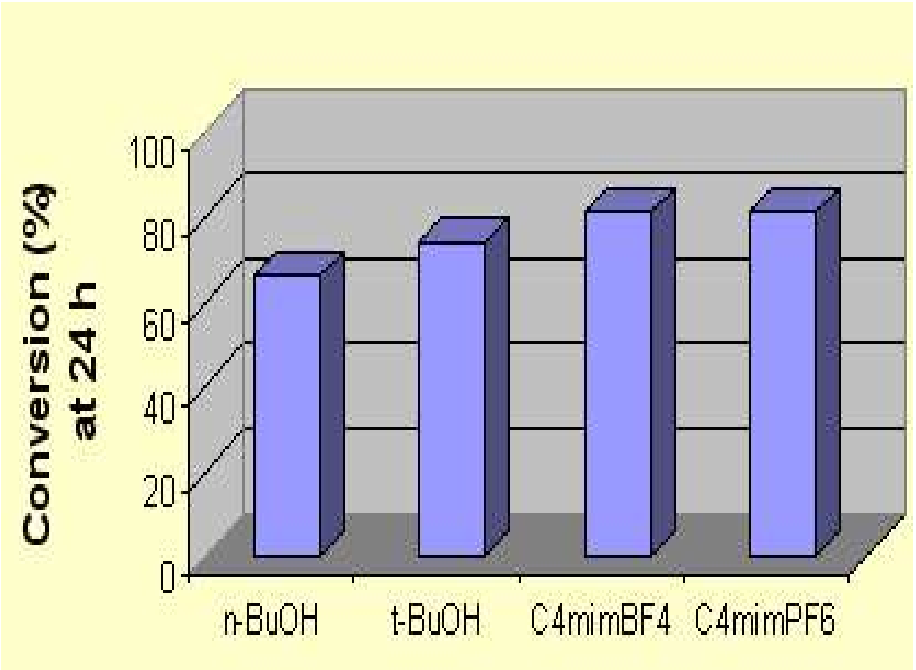
Whole cells | **Isolated enzyme (dissolved in aqueous phase)** | **Suspension (immob. enzyme or whole cells)**

Potential Benefits of Enzymes in Ionic Liquids

- Higher activity compared with organic solvents
- Higher (enantio)selectivity
- Higher operational stability
- Highly polar substrates (e.g. carbohydrates)
- Product separation/catalyst recycling

Organic Solvents vs Ionic Liquids





Reaction conditions:

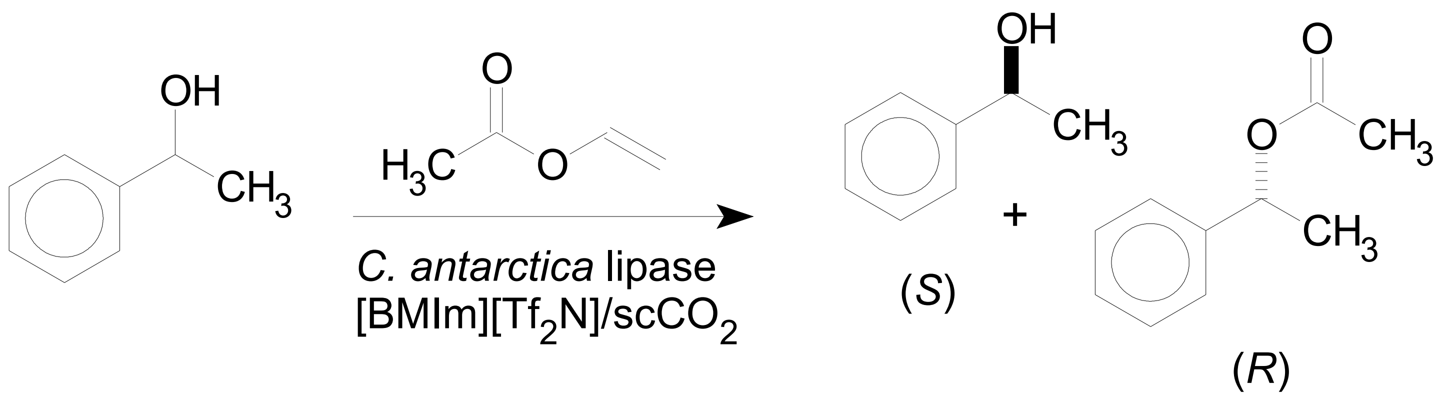
40 mM ethyl butanoate, 200 mM .

butan-1-ol, 25 mg Novozym 435

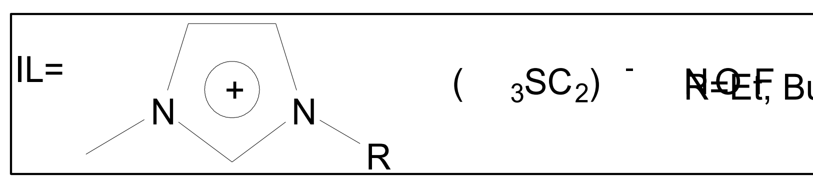
in 1 ml solvent at 40°C

R.Madeira Lau,F.van Rantwijk,K.R.Seddon and R.A.Sheldon,Org.Lett.,2, 4189-91 (2000)

In situ product removal with $scCO_2$



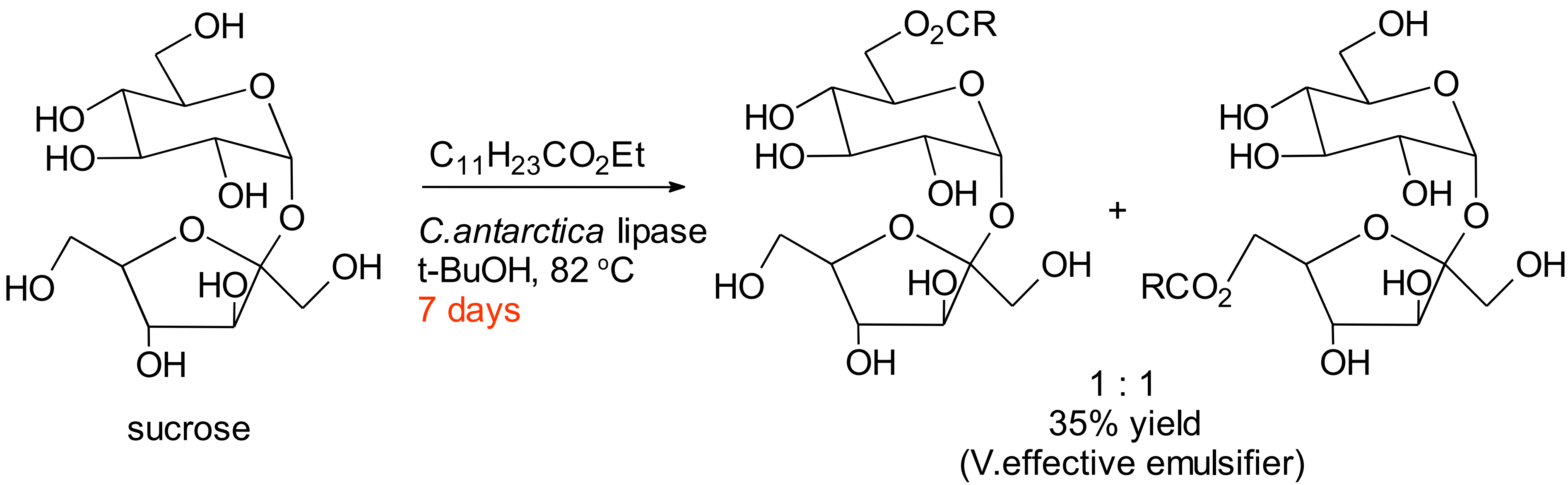
- The ionic liquid containing the biocatalyst was recycled 4 times without loss of activity [1].
- Demonstrated in a continuous mode [1] and with a supported liquid-phase biocatalyst [2]



1. M.T. Reetz *et al.*, *Chem. Commun.* 992 (2002)
2. P. Lozano *et al.*, *Chem. Commun.* 692 (2002)

SWEET'N GREEN: SUGAR-BASED SURFACTANTS

Sucrose fatty acid esters: from canned coffee to cosmetics



- 3 x Green (renewable raw material,biocatalytic process, biodegradable product)
- Current chemical process (Mitsubishi Kagaku)

  yields complex mixture, mono-, di-, etc
- How to increase the rate? Use an ionic liquid medium?

M.Woudenberg-van Oosterom, F.van Rantwijk and R.A.Sheldon, *Biotechnol. Bioeng*., 49, 328 (1996)

Solubility of Sucrose in Ionic Liquids

Ionic liquid	Solubility (g/L)
[bmim][dca]	195
[hmim][dca]	167
[omim][dca]	151
[moemim][dca]	220
[moemim][Tf_2N]	0.13
[moemim][BF_4]	0.4
[moemim][PF_6]	0.7
[moemim][Tf]	2.1

Preliminary expts showed that the Nov 435-catalyzed acylation of sucrose with dodecanoic acid proceeded smoothly in [bmim][dca]

dca = $(CN)_2N$

Q.Liu,M.Janssen,submitted

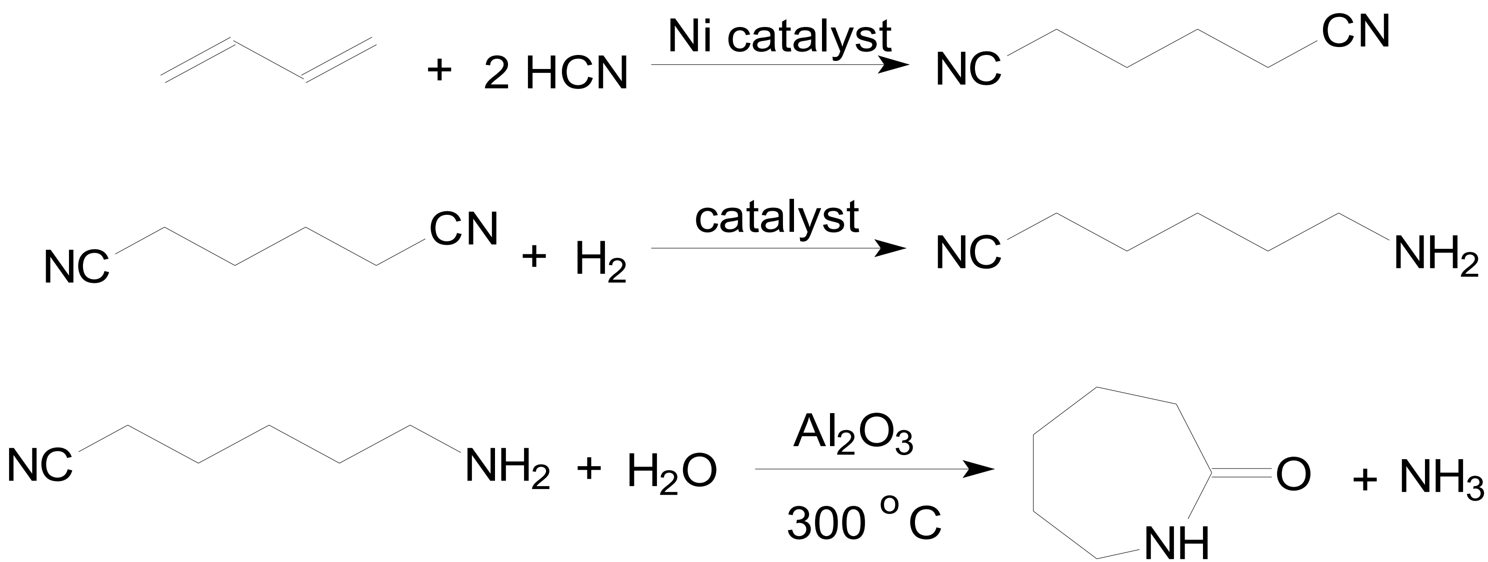
TU Delft

Process Integration

A NEW SALT-FREE CAPROLACTAM PROCESS :RHODIA

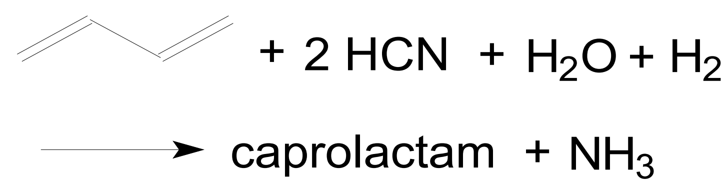
Du Pont

Rhodia



caprolactam
> 99% conv.
> 99.5% sel.

overall:



The next generation? Biomass —fermentation→ Caprolactam

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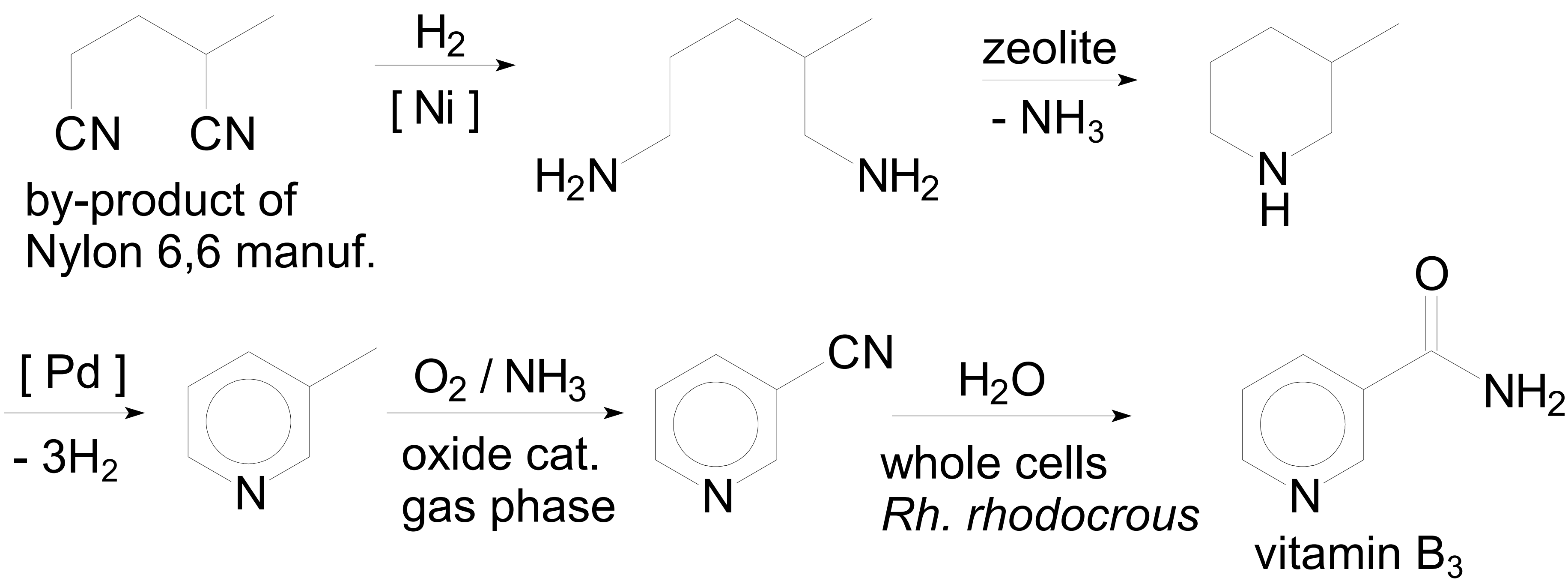
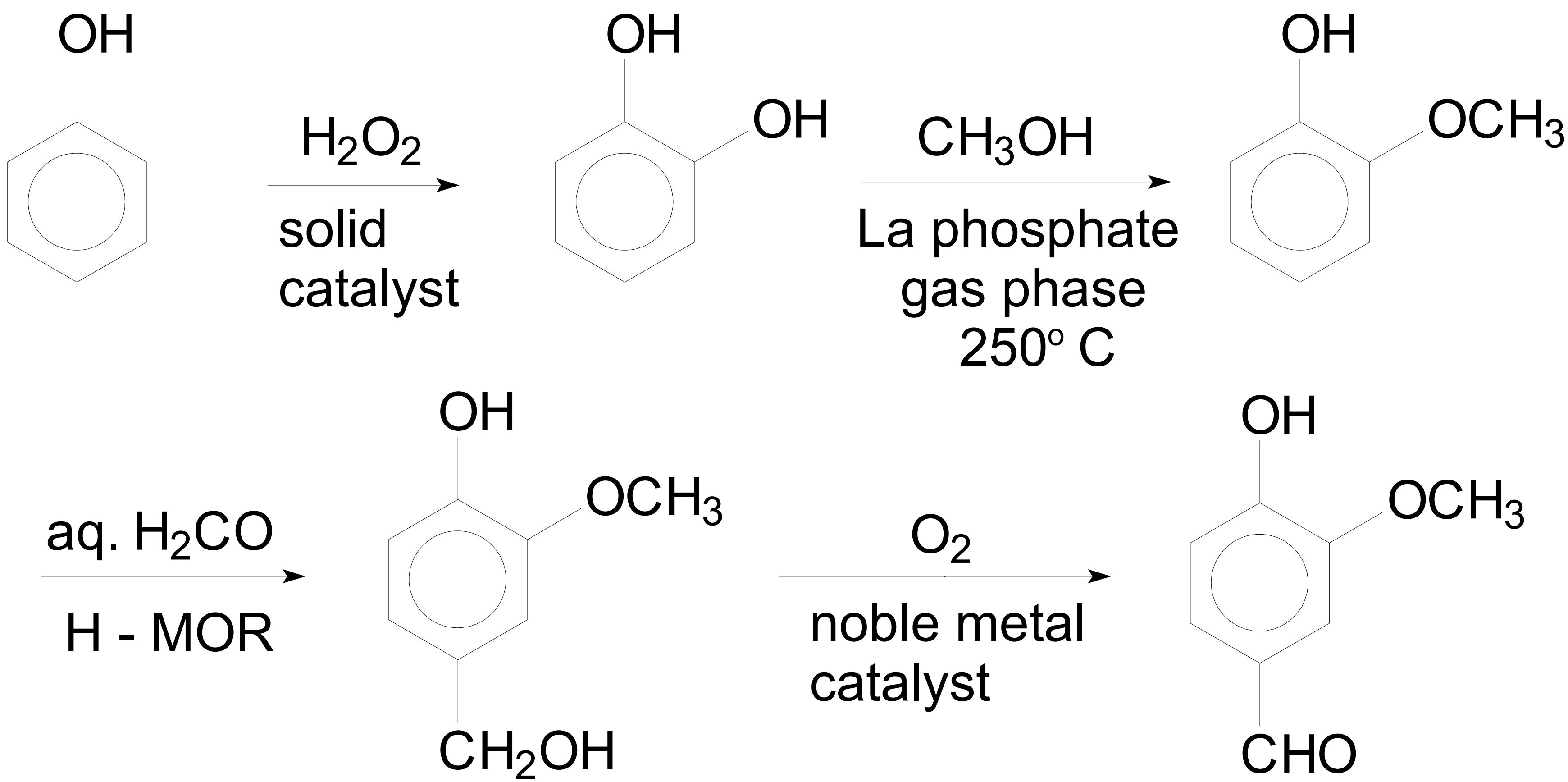
PROCESS INTEGRATION: LONZA NICOTINAMIDE PROCESS



Overall: $C_6H_8N_2 + 3/2\ O_2 + H_2 \rightarrow C_6H_6N_2O + 2\ H_2O$

J. Heveling, *Chimia*, 50, 114 (1996)

CATALYTIC VANILLIN SYNTHESIS: RHODIA PROCESS



4 steps, all employing a heterogeneous catalyst

Overall: $C_6H_6O + H_2O_2 + CH_3OH + H_2CO + 1/2\ O_2 \rightarrow C_6H_8O_3 + 3\ H_2O$

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

Conclusion: the Take-Home Message

- Catalytic processes can be redesigned for eliminating or decreasing the use of hazardous organic solvents

- Downstream processing must be an integral part of the process design

- The resulting procedures are not just greener, but often also better and cheaper

Fine Chemical Processes of the Future

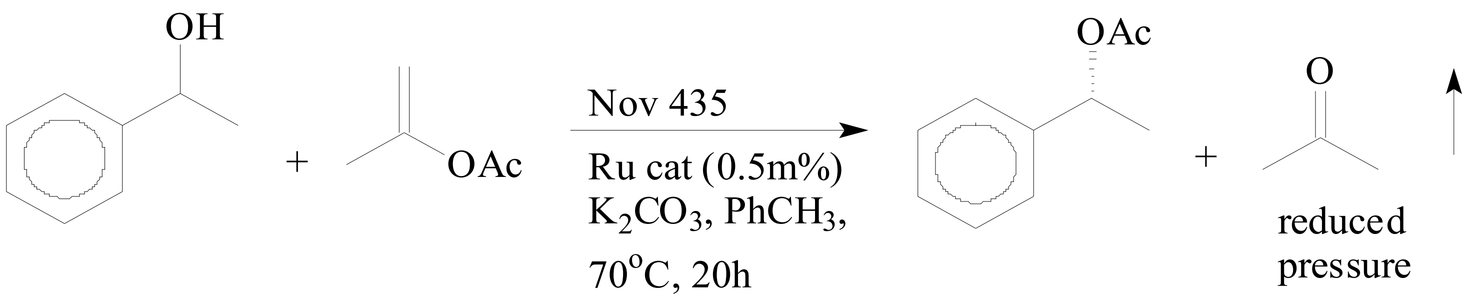
- Generic processes
- Fewer steps/minimum waste
- Inherently safe
- More catalysis
- Continuous operation
- Process intensification(mini-reactors)
- 100% yield/100% ee concept (e.g.DKR)
- Process integration
- Catalytic cascade processes

TU Delft

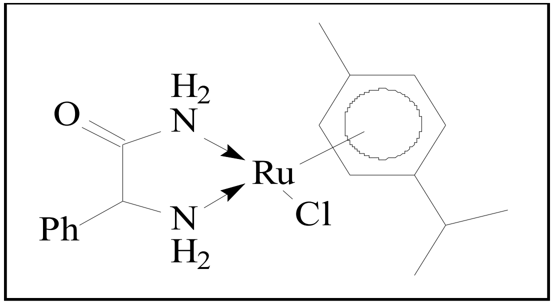
Integration of Chemo- and Biocatalysis:Cascade Catalysis

- Chemoenzymatic syntheses,e.g. dynamic kinetic resolutions.
  100% yield/100% ee concept (the ultimate in efficiency
- One-pot,multi-enzyme cascades (the ultimate emulating Nature)
- Compartmentalization for compatibility (c.f. the living cell)

CHEMOENZYMATIC DKR OF SEC-ALCOHOLS

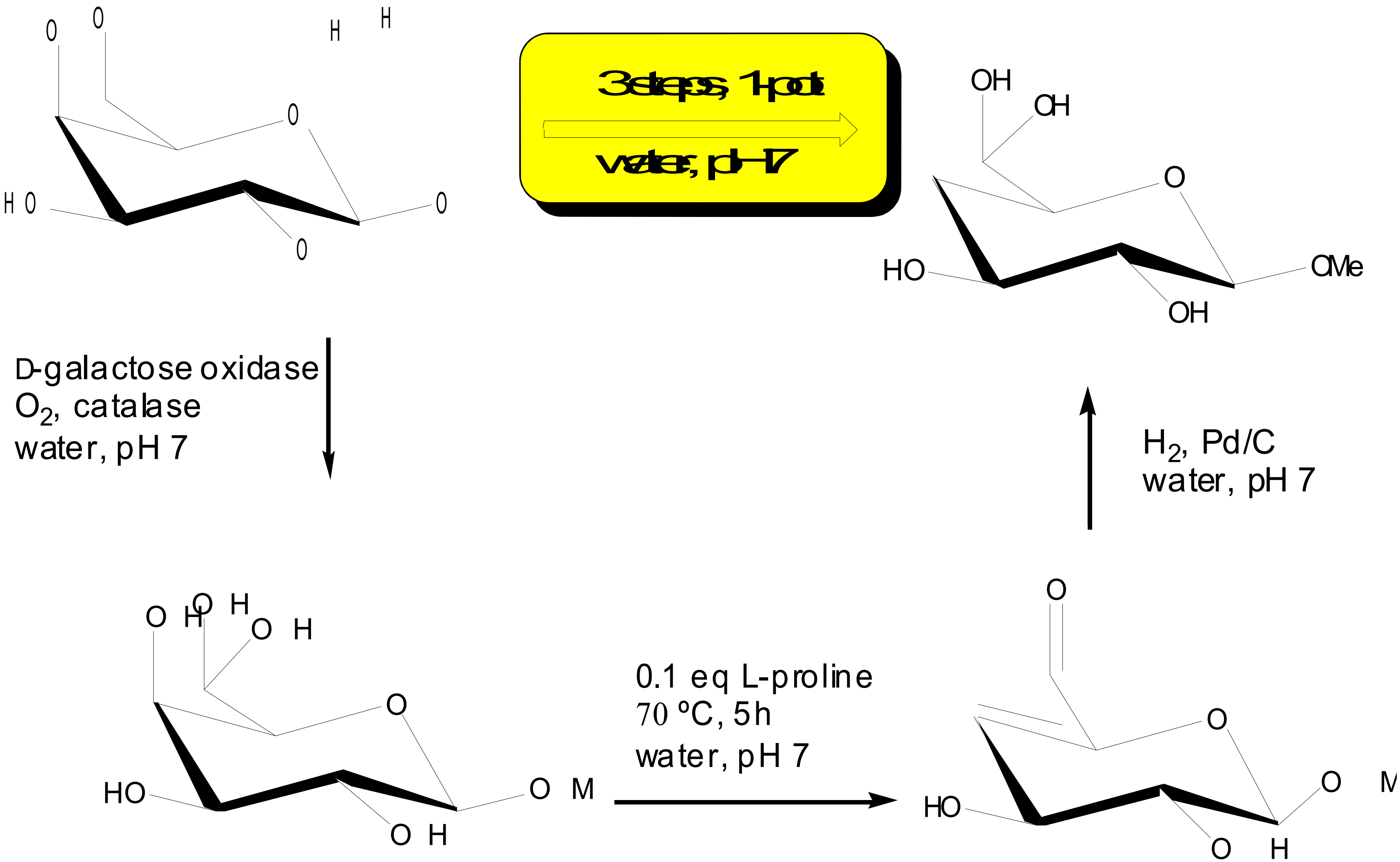


Catalyst	Yield %	ee (%)
Backvall catalyst + $PhCOCH_3$ (25m%)	97	99
$[RuCl_2$ (*p*-cymene)$]_2$ + $PhC(CH_3)(NH_2)CONH_2$ (1m%) + K_2CO_3 (> 2eq.)	82	99



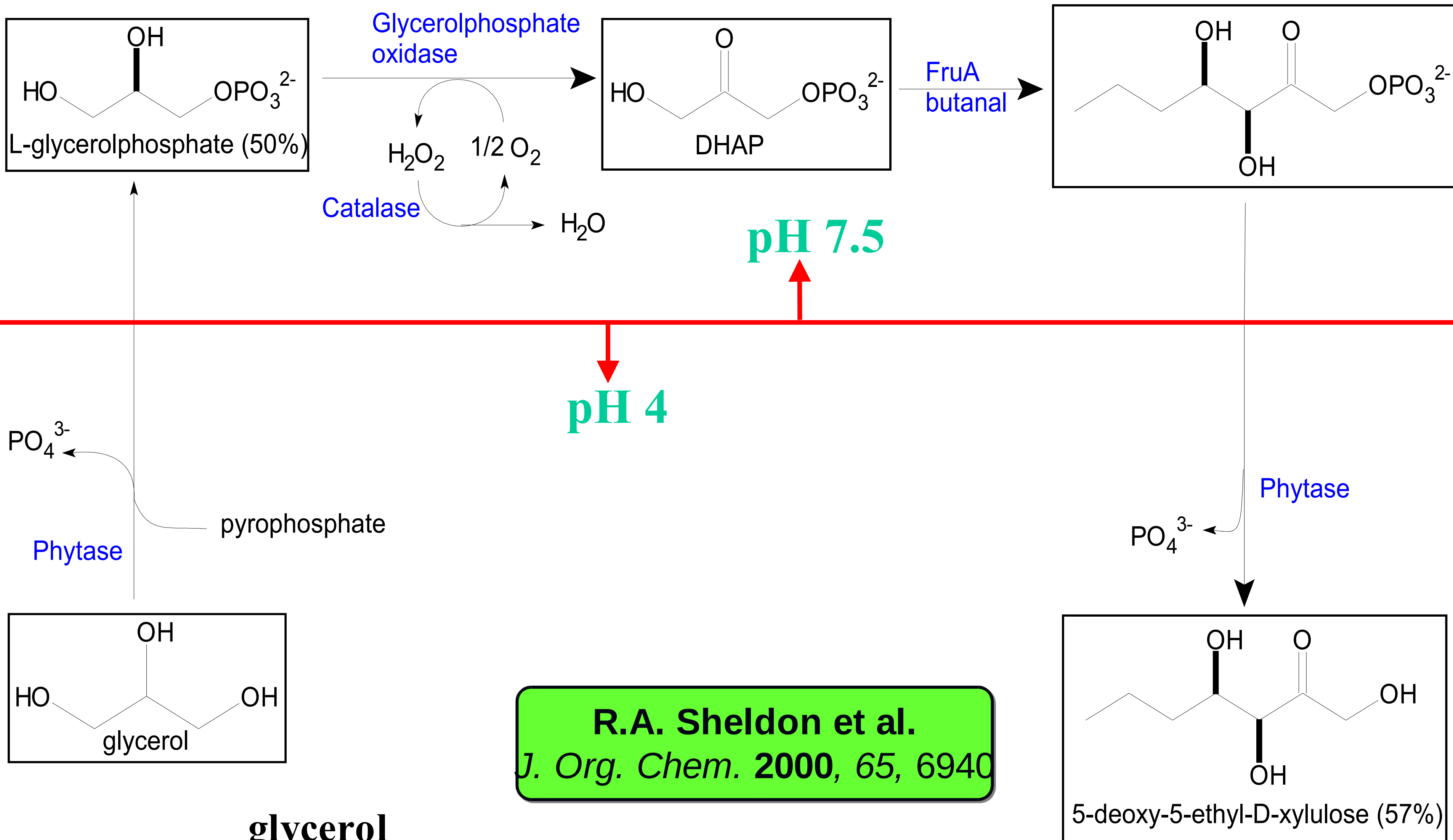
G. Verzijl, J.G. de Vries and Q.B.Broxterman, PCT *WO 01/90396* A1 (2001) to DSM

Synthesis of a dehydro sugar



Schoevaart R., Kieboom T. *Tetrahedron Letters* **2002,** 43, 3399–3400

Cascade Catalysis:One Pot/Four Enzymes



R.A. Sheldon et al.
J. Org. Chem. **2000**, *65*, 6940

glycerol

←95% 55%→

Merci beaucoup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Fin

Avez vous des questions?

En Anglais s'il vous plait