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

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:

<table>
<thead>
<tr>
<th>Product tonnage</th>
<th>E Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^4$-$10^6$</td>
<td>&lt;1 - 5</td>
</tr>
<tr>
<td>$10^2$-$10^4$</td>
<td>5 - &gt;50</td>
</tr>
<tr>
<td>$10$-$10^3$</td>
<td>25 - &gt;100</td>
</tr>
</tbody>
</table>

- Bulk Chemicals
- Fine chemical Industry
- Pharmaceutical Industry

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: \[ E = \frac{\text{[raw materials} - \text{product]}}{\text{product}} \]

• 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 $\text{H}_2\text{SO}_4 / \text{HNO}_3$
   - Acid promoted rearrangements, e.g. Beckmann ($\text{H}_2\text{SO}_4$)
   - Base promoted condensations, e.g. Aldol (NaOH, NaOMe)

2. STOICHIOMETRIC LEWIS ACIDS
   - Friedel-Crafts acylation ($\text{AlCl}_3$, $\text{ZnCl}_2$, $\text{BF}_3$)

3. STOICHIOMETRIC OXIDANTS & REDUCTANTS
   - $\text{Na}_2\text{Cr}_2\text{O}_7$, $\text{KMnO}_4$, $\text{MnO}_2$
   - $\text{LiAlH}_4$, $\text{NaBH}_4$, Zn, Fe/HCl

4. HALOGENATION & HALOGEN REPLACEMENT
   - Nucleophilic substitutions

5. SOLVENT LOSSES
   - Air emissions & aqueous effluent
Stoichiometric: The Jones Reagent (Sir Ewart Jones)

\[ 3 \text{PhCH(OH)CH}_3 + 2 \text{CrO}_3 + 3 \text{H}_2\text{SO}_4 \rightarrow 3 \text{PhCOCH}_3 + \text{Cr}_2(\text{SO}_4)_3 + 6 \text{H}_2\text{O} \]

Atom efficiency = \( \frac{360}{860} = 42\% \)

\( E_{\text{theor}} = \text{ca. 1.5} \)

Catalytic:

\[ \text{PhCH(OH)CH}_3 + \frac{1}{2} \text{O}_2 \xrightarrow{\text{Catalyst}} \text{PhCOCH}_3 + \text{H}_2\text{O} \]

Atom efficiency = \( \frac{120}{138} = 87\% \)

\( E_{\text{theor}} = \text{ca. 0.1(0)} \)

Byproduct: \( \text{H}_2\text{O} \)
1856: Attempted synthesis of quinine (W.H. Perkin)

\[
2 \text{C}_{10}\text{H}_{13}\text{N} + 3 \text{O} \xrightarrow{\text{K}_2\text{Cr}_2\text{O}_7} \text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2 + \text{H}_2\text{O}
\]

- Led to the serendipitous synthesis of the first synthetic dyestuff, mauveine (aniline purple)
CHROMIUM(VI): THE ORGANIC CHEMIST’S FAVOURITE OXIDANT

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:

\[
\text{Ar} \quad \xrightarrow{\text{catalyst}} \quad \text{Ar} \quad \xrightarrow{100\% \text{ atom efficient}} \quad \text{H}_2 \quad + \quad \xrightarrow{\text{catalyst}} \quad \text{Ar} \quad + \quad \text{H}_2\text{O}
\]

Carbonylation:

\[
\text{Ar} \quad + \quad \text{CO} \quad \xrightarrow{\text{catalyst}} \quad \text{Ar} \quad + \quad \text{Ar} \quad \xrightarrow{100\% \text{ atom efficient}} \quad \text{CO}_2\text{H}
\]

Oxidation:

\[
\text{Ar} \quad + \quad \frac{1}{2} \text{O}_2 \quad \xrightarrow{\text{catalyst}} \quad \text{Ar} \quad + \quad \xrightarrow{87\% \text{ atom efficient}} \quad \text{H}_2\text{O}
\]

\( (\text{Ar} = \text{C}_6\text{H}_5) \)
The Environmental Impact EQ

$$EQ \quad E(\text{kg waste}) \times Q$$

(Unfriendliness)

e.g. NaCl=1 (arbitrary)

Cr salts=1000?
Solid Acid Catalysts
ZEOLITE-CATALYZED FRIEDEL-CRAFTS ACYLATION

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{CH}_3\text{COCl} \quad \xrightarrow{\text{AlCl}_3} \quad \text{solvent} \quad \text{MeO} \\
\text{MeO} & \quad + \quad (\text{CH}_3\text{CO})_2\text{O} \quad \xrightarrow{\text{H-beta}} \quad \text{MeO} \\
\end{align*}
\]

Homogeneous

- \( \text{AlCl}_3 >1 \) 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

CONVENTIONAL:

\[
\begin{align*}
\text{NH}_3^+ \text{O}^- & \quad \text{HCl (1 eq.)} \quad \text{NH}_3^+ \text{Cl}^- \\
\text{R} & \quad \text{OH} \quad \text{MeOH/HCl (cat.)} \quad \text{OMe}^+ \text{MeOH} + \text{H}_2\text{O}
\end{align*}
\]

ZEOLITE-CATALYZED:

\[
\begin{align*}
\text{NH}_3^+ \text{O}^- & \quad \text{MeOH, H-USY, 100 °C} \quad \text{NH}_2 \text{OMe} + \text{H}_2\text{O}
\end{align*}
\]

- \( R = \text{PhCH}_2 \) (aspartame intermediate); \( S/C = 20 \) (w/w), 83% yield (TON = 180)
- Naphtha cracking catalyst (H-USY)
- Opt. Active amino acids (partially) racemized

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

Sumitomo Process: Combined Ammoximation and Vapor Phase Beckmann Rearrangement

By-product: $\text{H}_2\text{O}$

Green Chemical Process

Personal communication, H. Ichihashi, Sumitomo
Comparison between the Current and New Processes

Overall reaction of a typical current process

\[
\text{Overall reaction of a typical current process} \\
\text{Atom Economy} = 29\% \quad \text{E-factor} = 2.5
\]

Overall reaction of the new process

\[
\text{Overall reaction of the new process} \\
\text{Atom Economy} = 75\% \quad \text{E-factor} = 0.32
\]
Homogeneous Catalysts
PALLADIUM-CATALYZED CARBONYLATION: BHC IBUPROFEN PROCESS


100% atom efficiency

Cumbersome catalyst recovery /product contamination

Ibuprofen 3500 tpa  99% conv.  96% sel.  TOF = 375 h⁻¹
Asymmetric Catalysis
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”

THE WRONG ISOMER HAS UNDESIRABLE SIDE-EFFECTS

- Teratogen: (S) Thalidomide (R)
- Sedative: (S) Penicillamine (R)
- Anaesthetic: (S) Ketamine (R)
- Hallucinogen: (S) Thalidomide (R)
- Antiarthritic: (S) Penicillamine (R)
- Mutagen: (S,S)-Ethambutol (R,R)
- Tuberculostatic: (S,S)-Ethambutol (R,R)
- Blindness: (S,S)-Ethambutol (R,R)
<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1939</td>
<td>Cinchonine-modified Pt (Lipkin and Stewart)</td>
</tr>
<tr>
<td>1956</td>
<td>Pd modified with silk fibroin (Akabori, Izumi)</td>
</tr>
<tr>
<td>1963</td>
<td>Raney Ni/tartrate (Izumi)</td>
</tr>
<tr>
<td>1966</td>
<td>Asymmetric cyclopropanation catalyzed by a chiral Schiff's base complex, 10% ee</td>
</tr>
<tr>
<td></td>
<td>(Nozaki, Noyori)</td>
</tr>
<tr>
<td>1968</td>
<td>Asymmetric hydrogenation with a rhodium-chiral phosphine complex, 15% ee</td>
</tr>
<tr>
<td></td>
<td>(Knowles and Sabacky; Horner)</td>
</tr>
<tr>
<td>1970</td>
<td>Monsanto L-Dopa process</td>
</tr>
<tr>
<td>1971</td>
<td>DIOP ligand (Kagan)</td>
</tr>
<tr>
<td>1980</td>
<td>Asymmetric epoxidation, Ti/TBHP/tartrate (Sharpless)</td>
</tr>
<tr>
<td>1984</td>
<td>Takasago l-menthol process, Rh-Binap (Otsuka, Akutagawa, Noyori)</td>
</tr>
<tr>
<td>1988</td>
<td>Asymmetric dihydroxylation of olefins, OsO₄/quinine (Sharpless)</td>
</tr>
<tr>
<td>1991</td>
<td>Jacobsen-Katsuki epoxidation</td>
</tr>
<tr>
<td>2001</td>
<td>Nobel prize in Chemistry for Knowles, Noyori and Sharpless</td>
</tr>
</tbody>
</table>
MONSANTO L-DOPA PROCESS

\[
\text{AcO} - \text{OMe} \quad \text{COOH} \quad \text{NHAc} \quad \xrightarrow{H_2} \quad \text{AcO} - \text{OMe} \quad \text{COOH} \quad \text{NHAc}
\]

Catalyst = \([\text{Rh(COD)\text{L}^*}_2]^+ \text{BF}_4^-\)
COD = 1,5-cyclooctadiene
L* = chiral phosphine

PMPP
28% ee

PAMP
60% ee

CAMP
85% ee

DIPAMP
95% ee

THF solvent, 80 °C
substrate: catalyst ratio = 8000
turnover number = 300,000

ASYMMETRIC HYDROGENATION OF AN IMINE

\[
\text{N}=\overset{\text{OCH}_3}{\text{OCH}_3}
\]

\[
\text{H}_2 \ (80 \text{ bar}) \quad \text{Ir}^\text{I} \ - \text{xyli phosphos} \quad \text{HOAc} / \text{I} \quad 50 \ ^\circ \text{C} / 4 \text{hr}
\]

\[
> 80\% \text{ opt.yield}
\]

\[
\text{HOAc} / \text{I} - \text{H}_2
\]

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

\[
\text{Fe} \quad \text{PPh}_2
\]

\[
\text{xyli phosphos}
\]

\[
\text{(S)}\ - \text{metolachlor}
\]

\[
\text{(S)-metolachlor (mixture of two atropisomers)}
\]

**HIGHLY EFFICIENT ASYMMETRIC HYDROGENATION OF KETONES**

\[
\text{Ar} \text{R} + \text{H}_2 \quad \overset{\text{Ru catalyst}}{\longrightarrow} \quad \text{Ar} \text{R} \quad \text{OH}
\]

Rate 100x faster with preformed complex

e.g. Ar=Ph; R=CH₃

S/C = 2,400,000

30 °C/45 bar/48 h

100% yield; 80%ee

TOF = 228,000 h⁻¹

at 30% conv.

Homogeneous vs Heterogeneous Catalysis

Homogeneous

Advantages
- Mild reaction conditions
- High activity & selectivity
- Efficient heat transfer

Disadvantages
- Cumbersome separation & recycling of catalyst
- Product contamination
- Not readily adapted to
- Continuous processing
- Heat transfer problems
- Low activity

Heterogeneous

Advantages
- Facile separation of catalyst and products
- Continuous processing

Disadvantages
- Heat transfer problems
- Low activity

Homogeneous liquid / liquid biphasic catalysis
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)
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, scCO₂, 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

Three step process
Introduction of EtOH as solvent
Replacement of Pd/C with Pd/CaCO₃ - higher yields

Elimination of titanium chloride, toluene, THF, CH₂Cl₂, 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™)

## Comparison of E factors

<table>
<thead>
<tr>
<th>Industry segment</th>
<th>Prodn (tons)</th>
<th>E-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refining</td>
<td>$10^6\text{–}10^8$</td>
<td>$&lt; 0.1$</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4\text{–}10^6$</td>
<td>$&lt; 1\text{–}5$</td>
</tr>
<tr>
<td>Sildenafil citrate</td>
<td>$30\text{–}40$</td>
<td>6</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^2\text{–}10^4$</td>
<td>$5\text{–}50$</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>$10\text{–}10^3$</td>
<td>$25\text{–}100$</td>
</tr>
</tbody>
</table>
THE QUESTION OF SOLVENTS

The Solution

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

Rhodium Catalyzed Hydroformylation; Union Carbide Process

100 - 300 psi CO/H₂, 100°C, P:Rh = 1000

RCH=CH₂ + CO + H₂ → RC₃H₇CH₂COH + R(H₃C)₂CHCOH

**Normal**

**Iso**

**Advantages**
High catalytic activity
Good n/i selectivity

**Disadvantages**
Separation of the catalyst from Cₙ-aldehydes (n>8) is difficult
Sodium salt of tri-\textit{m}\textendash sulfonatotriphenylphosphine (tppts)

- Solubility in water: 1100 g / L

E.G. Kuntz, 1974
The Ruhrchemie/Rhône Poulenc hydroformylation process

> 400,000 tpa

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

G. Verspui et al., Chem. Commun. 1363 (2000)
$^{17}\text{O}$-, $^{31}\text{P}$- and $^{35}\text{Cl}$ NMR study of the redox reaction between PdCl$_2$, tppts and H$_2$O

Biphasic carbonylation of 1-(4-isobutylphenyl)ethanol

IBPE + CO → Ibuprofen + 3-IPPA

conversion: 83%
selectivity to ibuprofen: 82%
Low activity (TOF = 2.3 h⁻¹)

Green, Catalytic Alcohol Oxidations

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

Fluorous Biphasic Catalysis
The Principle of Fluorous Phase Catalysis

- 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

Evolution of Rhodium Hydroformylation Catalysts

\[
\begin{align*}
\text{R} & \quad \text{H} \quad \text{R} \quad \text{h} \quad (\text{C}_3\text{H}_6)_3 \quad \text{O} \quad [\text{P} \quad \text{R} \quad \text{H} \quad \text{C} \quad \text{O} \quad \text{H}] \\
\text{Gas Phase} & \quad \Rightarrow \quad \text{Hydrocarbon Phase} & \quad \Rightarrow \quad \text{Aqueous Phase} & \quad \Rightarrow \quad \text{Fluorous Phase}
\end{align*}
\]

PPh₃

\[
\begin{align*}
P(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3
\end{align*}
\]

Limitations

Separation of catalysts from Cₙ>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?

A Supercritical Fluid is a state of matter that occurs when the pressure and temperature exceed the critical point, represented by the critical point (P_c, T_c) on a phase diagram. In this state, the fluid exhibits properties of both a liquid and a gas, with the ability to dissolve and transport substances efficiently. This state is often used in processes such as supercritical fluid extraction (SFE) and supercritical fluid chromatography (SFC) due to its unique properties.
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

Reactants $\rightarrow$ Catalyst $\rightarrow$ Product

$\text{scCO}_2$ $\rightarrow$ $\text{CO}_2$
$\text{H}_2$ and scCO$_2$ Completely Miscible

$T < T_c$

$T > T_c$
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$_2$

- n/iso 35 - 50
- No loss of activity over several days
- Turnover frequency, compared with toluene:
  - $4 \times$ faster than immobilised catalyst
  - $0.5 \times$ the rate of the homogeneous catalyst

Rhodium complex catalyst, chemically anchored to a silica surface to prevent leaching
Ionic Liquids
CATALYSIS IN IONIC LIQUIDS

- Liquid at room temperature/no vapor pressure
- Liquid range of 300 °C (c.f. H₂O, 100 °C)
- Designer solvents, e.g. bmim BF₄ hydrophilic, bmim PF₆ hydrophobic

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

NIEUWS
Miljoen voor Screentec

INTERVIEW
Dow en de Nederlandse katalyse

ISO 9000
Tevreden klant is de norm

SUBSIDIES
Helpen ze eigenlijk wel?

STUDENT
Een van de eerste AIO's

PRIMEUR:
ENZYMREACTIES IN WATERVRIJE MEDIA
Friedel-Crafts Acylation in Ionic Liquid

\[
\text{X} + \text{CH}_3\text{COCl} \rightarrow \text{CH}_3\text{CO}_{\text{X}}^{-}
\]

\[
\text{emim Cl} / \text{AlCl}_3 (1:2)
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>-10</td>
<td>0.25</td>
<td>99</td>
</tr>
<tr>
<td>Me</td>
<td>20</td>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>Cl</td>
<td>20</td>
<td>24</td>
<td>97</td>
</tr>
</tbody>
</table>

Asymmetric Hydrogenation in Ionic Liquids

\[
\text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array} + H_2 \xrightarrow{\text{Ru(S)-BINAP}} \text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array}
\]

(S)-naproxen, 80% ee

\[
\text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array} + H_2 \xrightarrow{\text{Ru(OAc)}_2(R)-tolBINAP} \text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array}
\]

100% conversion
99% ee

\[
\text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array} + H_2 \xrightarrow{\text{Ru(OAc)}_2 \text{tolBINAP}} \text{MeO}\begin{array}{c}
\text{OH} \\
\text{CO}
\end{array}
\]

(S)-ibuprofen, 85% ee
Palladium Catalysed Heck Arylation in Ionic Liquid Medium

Workup:
• Add cyclohexane and water
• Separate the triphasic mixture
• Recycle IL layer with catalyst

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

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 (Ph₃P)₃RhCl

- Catalyst 18 × recycled without loss

Thermoregulated Biphasic Catalysis: Inverse Temperature Dependence

- 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

$M_w = 1100 - 4400$

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**

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Me₃SiCl (0.6)</th>
<th>PCl₅ (1.2)</th>
<th>PhNMe₂ (1.6)</th>
<th>NH₃ (0.09)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(kg/ kg 6-APA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-BuOH (8.4 ltr), NH₃ (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solvent</th>
<th>CH₂Cl₂ (8.4)</th>
<th>H₂O (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ltr/kg 6-APA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BIOCATALYTIC PRODUCTION OF ACRYLAMIDE: MITSUBISHI

\[
\text{CN} + \text{H}_2\text{O} \xrightarrow{\text{NHase}} \text{C} = \text{O} \text{NH}_2
\]

conv. > 99.99%
sel. > 99.99%

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

BIOCATALYTIC HYDROLYSIS OF NITRILES

DuPont

\[
\text{NC-} + \text{H}_2\text{O} \xrightarrow{\text{NHase}} \text{NC-} + \text{H}_2\text{O} \xrightarrow{5 \degree \text{C}} \text{NH}2
\]

• Immobilized whole cells of \textit{P. chlororaphis} B23
• Catalyst consumption 0.006 kg/kg product
• Higher conv./sel. than chemical process (MnO}_2\text{ cat. /130 \degree \text{C})


Lonza

\[
\text{CN-} + \text{H}_2\text{O} \xrightarrow{\text{NHase}} \text{CN-} + \text{H}_2\text{O} \xrightarrow{\text{Rh.rhodocrous J1}} \text{CN-} + \text{H}_2\text{O} \xrightarrow{\text{NHase}} \text{NH}_2
\]

100% yield/ 1465 g·l^{-1}/3000

Enzymes in Ionic Liquids

Two phase

- IL
- H$_2$O
- Whole dissolved cells
- Isolated enzyme (dissolved in aqueous phase)

Single phase

- E E E
- 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

\[
\text{CAL} \quad 40 \, ^\circ \text{C}
\]

Reaction conditions:
40 mM ethyl butanoate, 200 mM \text{butan-1-ol}, 25 mg \text{Novozym 435}
in 1 ml solvent at 40°C

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]

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?

### Solubility of Sucrose in Ionic Liquids

<table>
<thead>
<tr>
<th>Ionic liquid</th>
<th>Solubility (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[bmim][dca]</td>
<td>195</td>
</tr>
<tr>
<td>[hmim][dca]</td>
<td>167</td>
</tr>
<tr>
<td>[omim][dca]</td>
<td>151</td>
</tr>
<tr>
<td>[moemim][dca]</td>
<td>220</td>
</tr>
<tr>
<td>[moemim][Tf$_2$N]</td>
<td>0.13</td>
</tr>
<tr>
<td>[moemim][BF$_4$]</td>
<td>0.4</td>
</tr>
<tr>
<td>[moemim][PF$_6$]</td>
<td>0.7</td>
</tr>
<tr>
<td>[moemim][Tf]</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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
Process Integration
A NEW SALT-FREE CAPROLACTAM PROCESS: RHODIA

Du Pont

\[ \text{ethylene} + 2 \text{HCN} \xrightarrow{\text{Ni catalyst}} \text{caprolactam} \]

Rhodia

\[ \text{caprolactam} + \text{H}_2 \xrightarrow{\text{catalyst}} \text{caprolactam} \]

\[ \text{caprolactam} + \text{NH}_3 \xrightarrow{\text{Al}_2\text{O}_3, 300 \degree \text{C}} \text{caprolactam} \]

overall: \[ \text{ethylene} + 2 \text{HCN} + \text{H}_2\text{O} + \text{H}_2 \xrightarrow{} \text{caprolactam} + \text{NH}_3 \]

> 99% conv.
> 99.5% sel.

The next generation? Biomass fermentation Caprolactam
PROCESS INTEGRATION: LONZA NICOTINAMIDE PROCESS

by-product of Nylon 6,6 manuf.

Overall: $C_6H_8N_2 + \frac{3}{2}O_2 + H_2 \rightarrow C_6H_6N_2O + 2H_2O$

CATALYTIC VANILLIN SYNTHESIS: RHODIA PROCESS

4 steps, all employing a heterogeneous catalyst

Overall: $\text{C}_6\text{H}_6\text{O} + \text{H}_2\text{O}_2 + \text{CH}_3\text{OH} + \text{H}_2\text{CO} + \frac{1}{2} \text{O}_2 \rightarrow \text{C}_6\text{H}_8\text{O}_3 + 3 \text{H}_2\text{O}$

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
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

\[
\text{[RuCl}_2\text{(p-cymene)}]_2 + \text{PhC(CH}_3\text{)(NH}_2\text{)CONH}_2 (1\text{m%}) + \text{K}_2\text{CO}_3 (> 2\text{eq.})}
\]

\[
\begin{array}{ccc}
\text{Catalyst} & \text{Yield} \% & \text{ee (\%)} \\
\text{Backvall catalyst} & 97 & 99 \\
+ \text{PhCOCH}_3 (25\text{m%}) & & \\
\end{array}
\]

G. Verzijl, J.G. de Vries and Q.B. Broxterman, PCT WO 01/90396 A1 (2001) to DSM
Synthesis of a dehydro sugar

D-galactose oxidase
O₂, catalase
water, pH 7

3 steps, 1 pdi
water, pH 7

H₂, Pd/C
water, pH 7

0.1 eq L-proline
70 °C, 5h
water, pH 7

Cascade Catalysis: One Pot/Four Enzymes

L-glycerolphosphate (50%)

\[
\text{DHAP} \xrightarrow{\text{DHAP oxidase}} \text{butanal} \xrightarrow{\text{FruA}} 5\text{-deoxy-5-ethyl-D-xylulose (57%)}
\]

\[
\text{glycerol} \xrightarrow{\text{Catalase}} \xrightarrow{\text{Phytase}} \xrightarrow{\text{Phytase}} \text{glycerol} (95\%)
\]

\[
\text{pyrophosphate} \xrightarrow{\text{Phytase}} \text{PO}_4^{3-}
\]

\[
\text{glycerolphosphate (50%)} \xrightarrow{\text{Glycerolphosphate oxidase}} \text{DHAP} \xrightarrow{1/2 \text{O}_2} \text{butanal}
\]

\[
\text{pH 7.5}
\]

\[
\text{pH 4}
\]

R.A. Sheldon et al.  
Merci beaucoup
Think Green
Fin
Avez-vous des questions?

En Anglais s’il vous plaît