Grundlagen
Feinchemikalien; industrielle Aspekte der Katalyse; Chiralität; katalytische Prozesse

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland
Inhalt

- Feinchemikalien und Katalyse (Definition, Eigenheiten)
- Chirale Moleküle (Eigenschaften, selektive Synthesemethoden)
- Enantioselektive Prozesse
**Fine Chemicals Definition**

**BULK CHEMICALS**
- Small, mono-functionalized
  - Low number of compounds
  - Low process / catalyst
  - Low volume / added value

**FINE CHEMICALS**
- Large, poly-functionalized
  - High number of compounds
  - High process / catalyst
  - High volume / added value
  - High patents / low compound

<table>
<thead>
<tr>
<th>low</th>
<th>number of compounds</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>process / catalyst</td>
<td>patents</td>
<td>compound</td>
</tr>
<tr>
<td>high / low</td>
<td>volume / added value</td>
<td>low / high</td>
</tr>
</tbody>
</table>
# Fine Chemicals: Characteristics

## Molecules
- stereoisomers,
- functional groups
- limited thermal stability
- low volume (1-10,000 t/y)
- limited life time

## Synthesis
- multi step procedures
- classical organic reactions, catalysis as exception
- batch processes in solution
- multi purpose equipment
- short development time, low budget

## Catalysts
- high chemo-, regio- and stereoselectivity
- fit into overall synthesis scheme
- good activity at low T
- batch reactors, simple technology
- commercial catalysts, limited time for catalyst development
Catalysis for Fine Chemicals

catalytic C-C coupling
heterogeneous hydrogenation
enantioselective catalysis
## Fine Chemicals vs Bulk Chemicals

<table>
<thead>
<tr>
<th></th>
<th>Fine Chemicals</th>
<th>Bulk Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of different products</td>
<td>large</td>
<td>small</td>
</tr>
<tr>
<td>volume</td>
<td>small / medium</td>
<td>large</td>
</tr>
<tr>
<td>patents</td>
<td>product</td>
<td>process</td>
</tr>
<tr>
<td>life time</td>
<td>short / medium</td>
<td>long</td>
</tr>
<tr>
<td>development time</td>
<td>short</td>
<td>long</td>
</tr>
</tbody>
</table>

### Consequences for Catalysis

- Processes must be flexible and competitive
- Development must be fast
- Process must be the best
“Quality” of Synthesis (Catalysis)

Not important

discovery synthesis
pharma (agro)

important but not critical

new active compounds
pharma (agro)

decisive

Generica
Bulk chemicals

• high fail rate
• multi parallel methods

• % cost of goods of marketed product low
• low to medium production volume

• % cost of goods of marketed product high
• medium to very high production volume
### The E-factor (kg by-products / kg product)

<table>
<thead>
<tr>
<th>Industry</th>
<th>Tonnage</th>
<th>E-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refining</td>
<td>$10^6 - 10^8$</td>
<td>ca 0.1</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4 - 10^6$</td>
<td>&lt; 1-5</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^2 - 10^4$</td>
<td>5 - &gt;50</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>$10 - 10^3$</td>
<td>25 - &gt;100</td>
</tr>
<tr>
<td>Bechamp Red.</td>
<td>$10^2 - 10^4$</td>
<td>ca. 15</td>
</tr>
<tr>
<td>Catalytic Hydrog.</td>
<td>$10^2 - 10^4$</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

R.A. Sheldon, Chem.&Ind., 1992

Use of Catalytic methods
"Abfallvermeidung bei Produktionen für organische Spezialchemikalien durch den Einsatz hochspezifischer Katalysatoren (Using highly specific catalysis to prevent waste when producing organic fine chemicals)"

Deutsches Umweltbundesamt, 2003

Analysis of patents ➔ Possible catalytic systems with industrial potential

Interviews with experts ➔ Potential for waste reduction by using catalysis
Conclusions
Waste Prevention by Using Catalytic Methods

- Potential waste reduction within 10 years
  - Over-all ca. 9-14%
  - In Germany: 370,000 tons / year!

- Waste reduction within 10 years ca. 30 – 60% for
  - Pesticides
  - Pharmaceuticals
  - Vitamins
  - Organic pigments
Reaction types with high prevention potential

- Oxidation (diols, epoxides, aromatics, alcohols)
- Reduction (hydrides, metals)
- Functionalization of aromatics (Friedel Craft, amination)
- Aliphatic amination, amino acids
- Chemistry without protecting groups
- Improved asymmetric reactions
Catalysis for Fine Chemicals Opportunities

New transformations
- C-C coupling reactions (e.g. Heck, Hydroformylation)
- Benzylic oxidation

New selectivities
- Enantioselective hydrogenation
- (Enantioselective) epoxydation
- Regioselective addition of HCN to C=C

New reactants or catalysts
- H₂ instead of metals or metal hydrides
- Replace toxic oxides or peracids with O₂, H₂O₂ or ROOH
- Solid acids and basis instead of aqueous chemistry
- Replace AlCl₃ by zeolites or clays
Inhalt

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- Chirale Moleküle (Eigenschaften, selektive Synthesemethoden)
- Enantioselektive Prozesse
Chirality in the nature

Living organisms are chiral!!

Normally, only one enantiomer is produced in Nature

biological material recognizes enantiomers

Carmen Claver
Biological Effect vs. Absolute Configuration

The most frequent cases

- All stereoisomers possess nearly identical qualitative and quantitative biological activity
- The stereoisomers have qualitatively similar activities but quantitatively different properties
- The stereoisomers have qualitatively different biological activities (biological activity in one stereoisomer)


Chiral Aminoacids

S-asparagine bitter

\[ \text{S} - \text{asparagine} \]

\[ \text{CH}_2\text{CONH}_2 \]

\[ +\text{COO}^- \]

\[ \text{H}_3\text{N}^+ \]

R-asparagine sweet

\[ \text{R} - \text{asparagine} \]

\[ \text{CH}_2\text{CONH}_2 \]

\[ -\text{OOC} \]

\[ \text{+NH}_3 \]

enantiomers

Carmen Claver
It smells....

(R)-limonene  (S)-limonene
orange        lemon

Carmen Claver
Chirality: Different properties of enantiomers

Permetrinic acid insecticide is active, whereas the inactive version is shown.

S-metolachlor herbicide has a high toxicity of $10^4$ tm/year, while R-metolachlor is inactive.
Thalidomid (Contergan)

R-Thalidomid (Schlafmittel)

S-Thalidomid (teratogen)
Thalidomid (Contergan)

Thalidomid ist der Wirkstoff des Schlaf- und Beruhigungs-mittels Contergan, das Ende der 1950er Jahre zu zahlreichen schweren Schädigungen an ungeborenem Leben führte. Thalidomid wurde in Form des racemischen Gemischs der beiden Enantiomere auf den Markt gebracht.

Zunächst wurde angenommen, dass für die Fehlbildungen (die teratogene Wirkung) allein das (S)-Enantiomer verantwortlich sei und nur das (R)-Enantiomer die gewünschte beruhigende Wirkung hervorrufe.

Da die Enantiomere bei Thalidomid im Körper allerdings racemisieren, kann keinem der beiden Enantiomere eine beruhigende bzw. teratogene Wirkung zugesprochen werden. Die Gabe eines reinen Thalidomid-Enantiomers hätte die Contergan-Katastrophe also nicht verhindern können.
Optically pure agrochemicals
Herbicidal Activity of Metolachlor Stereoisomers

H. Moser, G. Rihs, H.P. Sauter 1982

H. Moser, G. Rihs, H.P. Sauter 1982
Clozylacon Stereoisomers In-Vitro Fungicidal Activity

(average of 5 pathogens)
CGA 29’212: Complimentary Biological Activity

Herbicidal activity (average 8 grasses)

Fungicidal activity downy mildew on grapes

![Chemical structure](image)

**Graphs:**
- **Herbicidal activity**:
  - x-axis: kg/ha
  - y-axis: %
  - Data points for (R), (S), and (R,S) forms

- **Fungicidal activity**:
  - x-axis: ppm
  - y-axis: %
  - Data points for (R) and (S) forms
### Chiral Agrochemicals of Novartis (ca. 1999)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioactive ingredients</td>
<td>77</td>
</tr>
<tr>
<td>Chiral compounds</td>
<td>18</td>
</tr>
<tr>
<td>Mixture of isomers</td>
<td>13</td>
</tr>
<tr>
<td>Pure isomers</td>
<td>3</td>
</tr>
<tr>
<td>Enriched isomers</td>
<td>2</td>
</tr>
</tbody>
</table>
Chiral Pesticides 1997

- Insecticides
- Fungicides
- Herbicides
- Various

Categories: achiral, chiral, single isomer
Some Numbers

Market value for chiral fine chemicals (2000)

Total 6.6x10⁹ $  
Pharmaceutical application 5.4x10⁹ $  
Other applications (agrochemicals, flavors etc) 1.2x10⁹ $

Strong growth expected

➤ Need for effective production methods

Motivations for Improved Production Methods

- Regulations, especially in pharma
- Ecological pressure, especially in agro
- Economical pressure, mainly for chiral intermediates but also for agro and generics
Inhalt

- Feinchemikalien und Katalyse (Definition, Eigenheiten)
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- Enantioselektive Prozesse
Syntheses of Enantiomerically Pure Compounds (EPC)

* Synthesis ("chiral pool")
* Fermentation
* Enantiomer separation
* Stoichiometric
* Asymmetric Synthesis / Catalysis

Chiral chromatography
Diastereomer separation
Kinetic resolution

* Biocatalyst
* Chemical catalyst
Syntheses of Enantiomerically Pure Compounds (EPC)

- Separation of enantiomers via classical resolution, i.e., crystallisation of diastereomeric adducts, still accounts for the production of more than 50% of enantioenriched drugs. An emerging technology is separation by chiral high performance liquid chromatography (HPLC) using moving simulated bed technology.

- The chiral pool approach uses chiral building blocks originating from natural products. Depending on the commercial availability of the starting material, it can also be used for large-scale products.

- Enantioselective syntheses are performed with the help of covalently bound chiral auxiliaries (often from the chiral pool). These are not incorporated in the target molecule but are removed after the stereogenic centres have been established and must be either recycled or discarded.

- In many respects the most elegant approach is enantioselective catalysis where prochiral starting materials are transformed to enantiomerically pure products with the help of chiral catalysts. Effective catalysts are either man-made (chemical catalysis) or can be of natural origin (biocatalysis).

## Syntheses of Enantiomerically Pure Compounds (EPC)

<table>
<thead>
<tr>
<th></th>
<th>Chemical catalysis</th>
<th>Biocatalysis</th>
<th>Chiral pool</th>
<th>Crystallisation</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enantioselectivity</td>
<td>1-2</td>
<td>1</td>
<td>1</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Activity and productivity</td>
<td>1-2</td>
<td>2-3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Availability and diversity</td>
<td>1-2</td>
<td>2-3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Substrate specificity</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Work-up and ecology</td>
<td>1-2</td>
<td>2-3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Development time and effort</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1-2</td>
<td>1</td>
</tr>
<tr>
<td>Application in the lab</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1-2</td>
<td>1</td>
</tr>
<tr>
<td>Application in development</td>
<td>1-2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Small-scale production</td>
<td>1-2</td>
<td>1-2</td>
<td>1</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td>Large-scale production</td>
<td>1</td>
<td>2</td>
<td>2-3</td>
<td>1-2</td>
<td>3</td>
</tr>
</tbody>
</table>

## Catalysis in Pharma Development
Some Statistics (1999)

K.G. Gadamasetti, Ed. "Approaches to pharmaceutical process development" (Case Histories), Marcel Dekker, 1999

<table>
<thead>
<tr>
<th>Transformations</th>
<th>total</th>
<th>catal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrolysis, esterifications, acylations, amidations, mesylations</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>C=O Reduction (NaBH₄, Dibal, BH₃, SnH, Ti³⁺, SiH, Na/NH₃)</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Nucleophilic substitution reactions (incl. ring opening and closing)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Oxidations, epoxidations (allylic/benzylic bromination, KMnO₄, CrO₃, SeO₂, Swern, CuBr₂, ozonation, N-oxid, peracid) (NaBrO₃/Ru cat, TEMPO)</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Heterogeneous hydrogenolysis (Debenzylation, C-X cleavage)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Reactions with C=C (Diels Alder, Michael add, ene rxn, elimination, addition, isomeriz.)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous hydrogenations C=C, arom. NO₂, N-N, red alkylation</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Grignard, Lithiation, Li-Br exchange</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Reactions with C=O, C=N (Wittig, aldol)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Electrophilic arene substitution (nitration, bromination; Friedel Crafts)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Arene C-C coupling (CN, carbonylation, Heck, Suzuki)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>32</td>
</tr>
</tbody>
</table>

- Heterogeneous catalysis (reductions)                                           | 26    |
- Homogeneous catalysis (reduction, oxidation, C-C)                              | 4     |
- Biocatalysis (reduction)                                                       | 2     |
### Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

<table>
<thead>
<tr>
<th></th>
<th>AstraZeneca</th>
<th>GlaxoSmithKline</th>
<th>Pfizer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of syntheses</td>
<td>45</td>
<td>39</td>
<td>44</td>
<td>128</td>
</tr>
<tr>
<td>Total number of chemical transformations</td>
<td>371</td>
<td>310</td>
<td>358</td>
<td>1039</td>
</tr>
<tr>
<td>Average number of chemical transformations per synthesis</td>
<td>8.2</td>
<td>7.9</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Number of chiral compounds</td>
<td>25</td>
<td>23</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>Number of chiral centres</td>
<td>46</td>
<td>52</td>
<td>37</td>
<td>135</td>
</tr>
<tr>
<td>Number of chiral centres generated</td>
<td>22</td>
<td>19</td>
<td>20</td>
<td>61</td>
</tr>
<tr>
<td>Number of substituted aromatic starting materials</td>
<td>64</td>
<td>79</td>
<td>63</td>
<td>206</td>
</tr>
<tr>
<td>New aromatic heterocycles formed</td>
<td>14</td>
<td>11</td>
<td>29</td>
<td>54</td>
</tr>
</tbody>
</table>

Chirality in Pharma Development
AstraZeneca, GlaxoSmithKline, Pfizer (2006)

<table>
<thead>
<tr>
<th>Reaction category</th>
<th>AstraZeneca</th>
<th>GlaxoSmithKline</th>
<th>Pfizer</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heteroatom alkylation &amp; arylation</td>
<td>87</td>
<td>57</td>
<td>52</td>
<td>196</td>
<td>19%</td>
</tr>
<tr>
<td>Acylation</td>
<td>41</td>
<td>37</td>
<td>50</td>
<td>128</td>
<td>12%</td>
</tr>
<tr>
<td>C–C bond forming</td>
<td>31</td>
<td>41</td>
<td>44</td>
<td>116</td>
<td>11%</td>
</tr>
<tr>
<td>Aromatic heterocycle formation</td>
<td>16</td>
<td>10</td>
<td>26</td>
<td>52</td>
<td>5%</td>
</tr>
<tr>
<td>Deprotection</td>
<td>54</td>
<td>56</td>
<td>49</td>
<td>159</td>
<td>15%</td>
</tr>
<tr>
<td>Protection</td>
<td>18</td>
<td>16</td>
<td>27</td>
<td>61</td>
<td>6%</td>
</tr>
<tr>
<td>Reduction</td>
<td>27</td>
<td>24</td>
<td>43</td>
<td>94</td>
<td>9%</td>
</tr>
<tr>
<td>Oxidation</td>
<td>17</td>
<td>7</td>
<td>16</td>
<td>40</td>
<td>4%</td>
</tr>
<tr>
<td>Functional group interconversion</td>
<td>43</td>
<td>34</td>
<td>27</td>
<td>104</td>
<td>10%</td>
</tr>
<tr>
<td>Functional group addition</td>
<td>13</td>
<td>8</td>
<td>12</td>
<td>33</td>
<td>3%</td>
</tr>
<tr>
<td>Resolution</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>30</td>
<td>3%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10</td>
<td>12</td>
<td>4</td>
<td>26</td>
<td>3%</td>
</tr>
<tr>
<td>Totals</td>
<td>371</td>
<td>310</td>
<td>358</td>
<td>1039</td>
<td></td>
</tr>
</tbody>
</table>

Chirality in Pharma Development
AstraZeneca, GlaxoSmithKline, Pfizer
(2006)

Chirality

- Of the 128 molecules analysed, 69 (54%) are molecules containing at least one stereogenic centre.
- Of the 69 chiral molecules 67 are being developed as single stereoisomers, with only two as racemates.

Asymmetric synthesis only accounts for a smaller proportion, approx. 20%, of the chiral centres generated.

It is noteworthy that the methods applied are catalytic in nature.

Even for a well developed methodology, such as catalytic asymmetric hydrogenation, application to a moderately complex substrate rarely yields the target enantiomeric purity directly.

## Industrial Biotransformations

Total: 134 documented processes

<table>
<thead>
<tr>
<th>Product classes</th>
<th>Chirality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabohydrates, nucleotides</td>
<td>Chiral precursor (pool) 40%</td>
</tr>
<tr>
<td>Fat derivatives, steroids</td>
<td>Kinetic resolution 27%</td>
</tr>
<tr>
<td>Peptides, $\beta$-lactams</td>
<td>Asymmetric synthesis 20%</td>
</tr>
<tr>
<td>amino acids</td>
<td>Not chiral 7-8%</td>
</tr>
<tr>
<td>sec-Alcohols</td>
<td></td>
</tr>
<tr>
<td>Other chiral</td>
<td></td>
</tr>
<tr>
<td>Other non-chiral</td>
<td></td>
</tr>
</tbody>
</table>

### Milestones for Enantioselective Catalysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
<th>Chiral Catalyst</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1912</td>
<td>HCN addition to PhCHO</td>
<td>quinine</td>
<td>&lt;10</td>
</tr>
<tr>
<td>1940</td>
<td>hydrogenation of C=N</td>
<td>chiral acid on Pt black</td>
<td>18</td>
</tr>
<tr>
<td>1956</td>
<td>hydrogenation of C=C</td>
<td>Pd on silk fibroin</td>
<td>(66)</td>
</tr>
<tr>
<td>1966</td>
<td>cyclopropanation</td>
<td>Cu - Schiff' base</td>
<td>10</td>
</tr>
<tr>
<td>1968</td>
<td>hydrogenation of enamides</td>
<td>Rh - chiral phosphine</td>
<td>15</td>
</tr>
<tr>
<td>1978</td>
<td>hydrogenation of β-keto esters</td>
<td>Ni-tartrate-NaBr</td>
<td>89</td>
</tr>
<tr>
<td>1979</td>
<td>hydrogenation of α-keto esters</td>
<td>cinchona on Pt</td>
<td>80</td>
</tr>
<tr>
<td>1980</td>
<td>epoxidation of allylic alcohols</td>
<td>Ti-tartrate complex</td>
<td>&gt;90</td>
</tr>
<tr>
<td>1980</td>
<td>binap ligand</td>
<td>Rh, Ru complexes</td>
<td>high</td>
</tr>
<tr>
<td>1988</td>
<td>dihydroxylation</td>
<td>Os-cinchona complex</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1991</td>
<td>epoxidation of C=C</td>
<td>Mn salen complex</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1995</td>
<td>epoxide ring opening</td>
<td>Cr salen complex</td>
<td>&gt;95</td>
</tr>
<tr>
<td>year</td>
<td>milestone</td>
<td>chiral catalyst</td>
<td>ee (%)</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td>1912</td>
<td>organic catalyst</td>
<td>quinine</td>
<td>&lt;10</td>
</tr>
<tr>
<td>1940</td>
<td>modified heterogeneous catalyst</td>
<td>chiral acid on Pt black</td>
<td>18</td>
</tr>
<tr>
<td>1956</td>
<td>chiral support</td>
<td>Pd on silk fibroin</td>
<td>(66)</td>
</tr>
<tr>
<td>1966</td>
<td>homogeneous catalyst</td>
<td>Cu - Schiff’ base</td>
<td>10</td>
</tr>
<tr>
<td>1968</td>
<td>homogeneous catalyst</td>
<td>Rh - chiral phosphine</td>
<td>15</td>
</tr>
<tr>
<td>1978</td>
<td>modified heterogeneous catalyst</td>
<td>Ni-tartrate-NaBr</td>
<td>89</td>
</tr>
<tr>
<td>1979</td>
<td>modified heterogeneous catalyst</td>
<td>cinchona on Pt</td>
<td>80</td>
</tr>
<tr>
<td>1980</td>
<td>homogeneous catalyst</td>
<td>Ti-tartrate complex</td>
<td>&gt;90</td>
</tr>
<tr>
<td>1980</td>
<td>homogeneous catalyst</td>
<td>Rh, Ru complexes</td>
<td>high</td>
</tr>
<tr>
<td>1988</td>
<td>homogeneous catalyst</td>
<td>Os-cinchonha complex</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1991</td>
<td>homogeneous catalyst</td>
<td>Mn salen complex</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1995</td>
<td>homogeneous catalyst</td>
<td>Cr salen complex</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>
Some Numbers
Catalysts with High Enantioselectivity


- Color-coded bars represent publications, cat with >98% ee, and average ee over the years.

- The graph shows an increasing trend in publications and cat with >98% ee from 1975 to 1997.

- The average ee also shows an increasing trend over the years.
# Reactions with Very High Enantioselectivity (ee>98%)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenation C=C</td>
<td>20</td>
</tr>
<tr>
<td>R-Me addition to RCH=O, RCH=NR</td>
<td>17</td>
</tr>
<tr>
<td>Reduction C=O, C=N (&gt;10% cat)</td>
<td>16</td>
</tr>
<tr>
<td>Aminohydroxylation, Dihydroxylation</td>
<td>14</td>
</tr>
<tr>
<td>Hydrogenation C=O</td>
<td>13</td>
</tr>
<tr>
<td>Allylic alkylation</td>
<td>11</td>
</tr>
<tr>
<td>Aldol, ene, Micheal reactions</td>
<td>10</td>
</tr>
<tr>
<td>C-C Coupling, Cyclopropanation, Heck</td>
<td>10</td>
</tr>
<tr>
<td>Diels-Alder</td>
<td>8</td>
</tr>
<tr>
<td>Hydrosilylation C=C, C=O</td>
<td>6</td>
</tr>
<tr>
<td>Epoxidation</td>
<td>6</td>
</tr>
</tbody>
</table>

Source: HUB Data collection, Nov. 1997
Milestones for Industrial Enantioselective Catalysis

1970’s  L-Dopa, enamide hydrogenation (Monsanto)

1980’s  L-Menthol, C=C isomerization (Takasago)

1990’s  Glycidol, Sharpless epoxidation (Arco)
        S-Metolachlor (Ciba-Geigy/Novartis/Solvias)

2000’s  Epoxide ring opening (Rhodia/Chirex)
        "Routine" application of enantioselective hydrogenation
L-DOPA (Monsanto)

Catalyst performance
95% ee, ton 10-20’000, tof 1000/h

Important features
Pure product (100% ee) crystallizes
➤ separation from catalyst and undesired racemate

Knowles et al.
For many years enamides most important test substrate

P chiral / bidentate / C$_2$ symmetric (Kagan)

28% PAMP 55% CAMP 84% DiPAMP 95%
P-Chiral Ligands (2003)

- Most ligands very air sensitive (Rh-complex more stable)
- Generally high ee's for Rh catalyzed hydrogenation of enamides and itaconates

- dipamp
- L9
- L10
- pyrphos
- miniphos
- bisp*

a. R = t-Bu
b. R = 1-adamant
c. R = 1-Me-cyhex
d. R = cyclopentyl
L-Menthol (Takasago)

Catalyst performance
- 97.6% ee, ton 400’000, tof 1300/h

Important features
- Active catalyst can be recovered and re-used after distillation
- Ton increase from 8’000 ➔ 80’000 - 400’000 (optimal work-up).
Industrial Applications of Ru – Binap Catalysts

Ru/binap; ee 97%
ton 50'000; tof 500h⁻¹
production process 300 t/y
Takasago

Ru/dmbinap; ee 98%, de >94%
ton 1'000.; tof 200h⁻¹
production process 100 t/y
Takasago

Ru/tolbinap; ee 94%
ton 2'000.; tof 300h⁻¹
medium scale production
Takasago

Ru/binap, ee 98-99%
ton 10-20'000; tof 12'000h⁻¹
small scale production
NSC Technologies

binap  Ar: Ph
tolbinap  Ar: p-Tol
dmbinap  Ar: 2,6-Xyl
S-Metolachlor (Ciba-Geigy/Syngenta)

Extremely active and productive Ir – ferrocenyl diphosphine catalyst. Catalyst separation via distillation. Largest enantioselective process (>10'000 t/y).

Catalyst performance:
- 80% ee, ton >1'000’000, initial tof >180'000/h

Important features:
- Extremely active and productive Ir – ferrocenyl diphosphine catalyst.
- Catalyst separation via distillation.
- Largest enantioselective process (>10'000 t/y).
Industrial Applications of Josiphos Ligands

Ir / josiphos
50°C, 80 bar

R = Ph
R' = 2,6-Xyl

Josiphos

Ru/josiphos or duphos; ee 90%
ton 2'000; tof 200h⁻¹
medium scale production
Firmenich

Rh/josiphos; de 99%
ton 2'000; tof n.a.
medium scale production
Lonza

Rh/josiphos; ee 97%
ton 1'000; tof 450h⁻¹
pilot process, >200 kg
Lonza

R = Ph
R' = Cyhex
Sharpless Epoxidation

\[ \text{Ti / dipt \quad <0^\circ C} \]

ee 88-90%

\[ \text{ton >40; tof <1h}^{-1} \]

Arco/GGP-Sipsy, chiral building block, multi ton scale (discontinued)

- Based on Sharpless technology
- Good enantioselectivity
- Very low ton and tof (addition of molecular sieve necessary)
- Product isolation very difficult (water solubility)
Sulfide Oxidation

AstraZeneca, Esomeprazole (Anti-Ulcer) multi ton scale

- Based on Kagan technology
- Good ee (addition of Hünig base necessary)
- Very low ton and tof
## Industrial Asymmetric Processes


<table>
<thead>
<tr>
<th>Reaction type</th>
<th>substrates / comment</th>
<th>E</th>
<th>WC</th>
<th>H</th>
<th>Het</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-C Coupling</td>
<td>cyanohydrin, cyclopropanation</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hydrogenation C=C</td>
<td>dehydroacylaminoacid, allylic alcohol, tetrasubstituted C=C, enamine</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Hydrogenation / reduction C=O, C=N</td>
<td>a-keto acid derivatives, var. ketones and imines</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Oxidation</td>
<td>alcohol, sulfide</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hydrolysis, acetylation</td>
<td>amide, hydantoin, ester, thioester, nitrile, carbamate, epoxide</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Various</td>
<td>assimilation, carnitine synth.</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>11</td>
<td>11</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

*E* enzyme, *WC* whole cell, *H* homogeneous metal complex, *Het* heterogeneous catalyst
## Industrial Catalytic Asymmetric Processes

**Study: Enantioselective catalysis in fine chemicals production**


<table>
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<tr>
<th>Transformation</th>
<th>production</th>
<th>pilot</th>
<th>bench scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogenation reactions</td>
<td>10</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Oxidation reactions</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Various</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>35</strong></td>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>

**Production processes:**  
- Pharma (generics, NCE) 7
- Agro 2
- Flavors & fragrances 2
- Intermediates (PH, other) 2
- Chiral building blocks 2
Are these Numbers Real?

<table>
<thead>
<tr>
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</table>

Some considerations

- Lack of information (how many did we miss??)
- Some pilot and bench scale processes will (soon?) be applied in production (young technology)

BUT: Not all production processes are still in operation

AND: Many published processes will never be operative
Are these Numbers Real?

<table>
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Some considerations

- Lack of information (how many did we miss??)
- Some pilot and bench scale processes will (soon?) be applied in production (young technology)
- Not all production processes are still in operation

Why are there so few processes?
Five Hurdles to Success

1. Choice of synthetic route: With or without catalysis?
2. Find effective catalytic system (ee; ton; tof)
3. Beat alternative processes
4. Scale up, technical process, accepted technology
5. Decision to market product
1. Hurdle
Choice of Synthetic Route

Always multi-step synthesis (PH 10-15; AG 4-7)

• Discovery: Often “quick and dirty” preparation; classical organic chemistry is the norm

• Development: Little time for trying “risky” chemistry

• Development chemists often do not know the potential of catalytic methods

• Scale up of catalytic processes and chiral ligands doubtful

⇒ Problem: Recognizing opportunity for catalysis
2. Hurdle
Find Catalytic System (ee, ton, tof)

- Choice of catalyst difficult due to high substrate specificity (analogies are often weak)
- Requirements for catalyst performance for economical processes can be very demanding
- Time constraints especially for new chemical entities in the pharma sector (less in agro)

⇒ Low success rates
Toolbox for Fast Catalyst Screening

- Library of chiral ligands / metal precursors
- Experimental setup for parallel testing
- Reaction data bases (internal and literature)
- Suitable analytical procedures
- Experienced chemists
2. Hurdle
Find Catalytic System (ee, ton, tof)

Issues

• Choice of catalyst difficult due to high substrate specificity (analogies are often weak)

• Requirements for catalyst performance for economical processes can be very demanding

• Time constraints especially for new chemical entities in the pharma sector (less in agro)

⇒ Low success rates
Industrial (Asymmetric) Catalysis
A Multi-Dimensional Task

Chemical factors & Economic factors

- restricted development time
- IP associated with catalyst use
- Activity (tof >500 / 10,000 h\(^{-1}\))
- Productivity (ton >1000 / 50,000)
- catalyst costs
- Ee (for Pharma >90 \(\rightarrow\) >99%)
- catalyst availability, lead times
2. Hurdle
Find Catalytic System (ee, ton, tof)

Issues

• Choice of catalyst difficult due to high substrate specificity (analogies are often weak)

• Requirements for catalyst performance for economical processes can be very demanding

• Time constraints especially for new chemical entities in the pharma sector (less in agro)

⇒ Low success rates
From Discovery to Launch: Product Development Process

- Lead Discovery
- Lead Optimization
- NCE’s
- Synthesis
- Batch 0
- Process / Formulation Dev.
- Launch
- Activity Screening Models
- Profiling Models
- Toxicity Models
- Clinical / Field Tests

- 1 - 3 years
- 2 - 3 years
- 3 - 4 years

Patent
3. Hurdle Beat Alternative Processes

Issues
- **Total costs** of final product are decisive
- Adaptation of overall-synthesis to catalytic step
- Preparation and purification of starting material

Alternatives
- Different catalytic methods (enzymes)
- Different new processes / approaches
- Existing processes
4. Hurdle
Scale up, Technical Process, Acceptance

Issues

• Feasibility of technology (high p, low T, O₂, handling)
• **Commercial availability of chiral ligands, complexes**
• IP rights, licenses, royalties
• Catalyst separation (metal residue; recycling?)
• Production equipment available
• Acceptance of technology by production manager
Commercial Availability

Screening phase
100 mg – 1g samples days - weeks

Pilot phase of process development
Up to 100g within a few weeks – months

First production campaign
Up to kg amounts as soon as 6 months after successful piloting

Regular production
According to production plan; on time; quality assured

➢ Often short lead time for kg amounts of chiral ligands
5. Hurdle
Decision to Market Product

Issue
• Many new pharma products are abandoned at a relatively late stage

What can be done
• NOTHING
Conclusions

Hurdles are of different nature

Psychological

  Prejudice, lack of know how and self confidence

Technical

  Catalyst performance, equipment, availability of catalysts

Commercial

  Product costs, IP rights, time to market, product dies