Outline

• Importance of asymmetric synthesis
• Organocatalysis and organocatalysts
• Comparison with conventional catalysis
• Advantages of organocatalysts
• Large scale organocatalytic reaction processes
Why asymmetric synthesis?

• Different enantiomers or diastereomers of a molecule often have different biological activity.

• Synthesis of chiral drugs - $18 billion annually (growing @ 9.04% p.a.)

• Predicted that 75% of the drugs will be sold as single enantiomers in the coming years.
Why asymmetric synthesis?

Chiral Resolution  Chiral agent  Chiral product

(up to 50% yield and 100% ee)
Why asymmetric synthesis?

(Chiral Resolution)  (Chiral agent)  (Chiral product)

(up to 50% yield and 100% ee)

(Chiral Synthesis)  (Chiral catalysis)  (Chiral product)

(up to 100% yield and 100% ee)
Asymmetric catalysis

- Organometallic catalysis
- Enzyme catalysis

organocatalysis
What is Organocatalysis?

• A concatenation of the terms “organic” and “catalyst”

• In organic chemistry, the term Organocatalysis refers to a form of catalysis, whereby the rate of a chemical reaction is increased by an organic catalyst consisting (mainly) of carbon hydrogen, sulfur, nitrogen, oxygen and phosphorus.

• “Metal free catalysis”
What is an Organocatalyst?

• An organocatalyst is an organic molecule that does not contain a metal which in substoichiometric amounts accelerates the reaction

• Usually a low molecular weight compound

• Two types:
  – Achiral
  – Chiral
Few examples...

- **L-proline**
- **quinine**
- **DMAP**
- **Nobin**
- **BOPHOZ**
- **Macmillan’s catalyst**
Increasing popularity

Number of articles per year focusing on number of the use of organocatalytic concept
Primary attractions of 
organocatalysis

• Usually robust
• Inexpensive
• Readily available
• Non-toxic
• Able to bring about transformations that were not known earlier
Primary attractions of organocatalysis

• Inertness towards moisture and oxygen

• Demanding reaction conditions (inert atmospheres, low temperatures, absolute solvents etc.) are usually not required

• Absence of transition metals – attractive for synthesis of pharmaceutical products
<table>
<thead>
<tr>
<th>Type</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organometallic catalysis</td>
<td>Wide substrate scope</td>
<td>Tedious process, potential heavy metal pollution</td>
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<tr>
<td></td>
<td>high catalytic activity</td>
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</tr>
<tr>
<td>Enzyme catalysis</td>
<td>High selectivity &amp; catalytic activity</td>
<td>Limited substrate scope</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually single enantiomer</td>
</tr>
<tr>
<td>Organocatalysis</td>
<td>Simple structure, inexpensive, natural molecules, nontoxic.</td>
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Mission:
To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally.
Brainstorm Output

- **Organocatalysis**
  - Asymmetric Hydrocyanation
  - Aldehyde or Ketone + NH$_3$ + “X” to give a chiral amine
  - N-Centred chemistry avoiding azides, hydrazines etc
  - Asymmetric Hydrolysis of nitriles
  - Asymmetric Hydrogenation of unfunctionalised olefins/enamines/imines
  - Asymmetric Hydroformylation
  - C-H activation of aromatics
  - C-H activation of alkyl groups
  - New Green Fluorination Methods
  - Oxygen Nucleophiles with high reactivity
  - Green sources of electrophilic Nitrogen
  - Asymmetric Hydroamination of olefins

- **New Green Fluorination Methods**
  - Green Mitsunobu Reactions
  - Reduction of amides avoiding LAH and Diborane
  - Bromination Reactions
  - Sulfonation reactions
  - Amide Formation avoiding poor atom economy reagents
  - Nitration reactions
  - F/C Reactions on unactivated substrates
  - Demethylation Reactions
  - Ester Hydrolysis
  - OH activation for nucleophillic substitution
  - Epoxidation
  - Oxidation
  - Wittig Chemistry without (Ph$_3$PO)
  - Radical Chemistry without Bu$_3$SnH
Large –scale Organocatalytic Reaction Processes

• General considerations:
  
  • Economy of the catalyst (Price and availability)
    – Readily available from nature’s “Chiral pool” or their derivatives
    – Cheap
  
  • Stability of the catalysts and handling issues
    – Not moisture sensitive (serious issue for chiral metal complexes)
    – No special equipments for handling not required
  
  • Enantioselectivity, conversion and catalyst loading
Large-scale Organocatalytic Reaction Processes

• General considerations:
  
  • Recycling: Immobilization of Organocatalysts
    – Leaching problems do not occur due to covalent bonding with the support unlike metal complexes

Very efficient over 10 reaction cycles
Yield: 96-98%    ee: 92-93%

Results superior to those obtained with analogous “free” solution-phase catalyst
Large-scale Organocatalytic Reaction Processes

- Epoxydation of Chalcones
- Alkylation of Cyclic Ketones
Epoxydation of Chalcones

Advantages

• Use of H$_2$O$_2$
• Use of organocatalyst
• Recyclability of catalyst
• High enantioselectivity

Disadvantages

• Large excess of catalyst (up to 200%)
• Preactivation of catalyst needed (6hrs)
• Long reaction times (1-5 days)
Epoxydation of Chalcones

- Potential applications
Epoxydation of Chalcones

H₂O₂ : 1.3 eq, NaOH: 1.3eq, cat: 0.35-0.7mol%, PTC: 11mol% at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standard poly-L-leu</td>
<td>90</td>
<td>2% conversion, ee not evaluated</td>
</tr>
<tr>
<td>2</td>
<td>ht-Poly-L-leu</td>
<td>90</td>
<td>59% conversion, ee = 91%</td>
</tr>
<tr>
<td>3</td>
<td>ht-Poly-L-leu + TBAB</td>
<td>7</td>
<td>&gt;99% conversion, ee = 94%</td>
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</tbody>
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tetrabutylammonium bromide
Epoxydation of Chalcones

Chemzyme Membrane Reactor (CMR)

membrane

chalcone

urea-H₂O₂

chiral epoxide

molecular weight enlarged homogeneous catalyst

Chemzyme Membrane Reactor (CMR)
Alkylation of Cyclic Ketones

- Synthesis of Indacrinone
Alkylation of Cyclic Ketones

- First highly asymmetric PTC-catalyzed alkylation
- First organocatalytic synthesis applied on a large scale
- Highly efficient (100% yield, 94% ee)
Conclusion

• Asymmetric organocatalysis has matured in the recent few years into a very powerful, practical and broadly applicable third methodological approach in the catalytic asymmetric synthesis.

• Process development and scale up already achieved for several organocatalytic reactions have shown that organocatalysis can be a valuable tool for industrial-scale solutions.

• Broad variety of efficient syntheses will contribute to an increasing number of organocatalytic large-scale reactions in the future.
References

- http://www.organic-chemistry.org/topics/organocatalysis.shtml
- http://portal.acs.org/portal/acs/corg/content
- Albrecht Berkessel, Harald Gröger, Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis, New York, Wiely, 2005
- http://www.epa.gov/greenchemistry/pubs/principles.html
Thank you!