The Combinatorial Approach to Asymmetric Hydrogenation.

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DSM Pharma Chemicals
and
University of Groningen

IASOC 2004, Ischia
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2. Homogeneous catalysis for fine chemicals
3. HTE approach; ligand libraries
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6. Mechanism
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DSM Pharma Chemicals

DSM
The specialty company
Life science products
Polymeric materials
Industrial Chemicals
DSM. A century of change

Evolution

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Life Science Products
Performance Materials
Petro-Chemicals
Sustainability
Customer intimacy

DSM Pharma Chemicals

Strategic impact Petrochem & Roche deals

DSM 2002

- Petro
- LSP
- IC
- PM

DSM 2003

- IC
- Vitamins
- PM
- LSP

Total sales ~ € 7 bn
Specialties from ~ 50% to > 80%

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Homogeneous Catalysis for Fine Chemicals

Important technologies

- Asymmetric hydrogenation (olefins, ketones, imines, enamides)
- Asymmetric transfer hydrogenation (ketones)
- Asymmetric epoxidation
- Aromatic substitution
  - Heck
  - Suzuki/Negishi
  - Sonogashira
  - Amination
  - Cyanation
- CO chemistry (hydroformylation, carbonylation, amidocarbonylation)
- Isomerisation and racemisation
- Oxidation
  - benzylic and allylic oxidation
  - alcohols to aldehydes or acids
  - olefins to epoxides

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Asymmetric Hydrogenation

- Nobel prize winning chemistry
- Several hundred ligands known
- Many thousands examples on lab-scale

Till about 5 years ago the use of this technology for the production of fine chemicals was scarce.

Why?

Reviews

Obstacles that need to be overcome

1. Time to market constraints in pharmaceuticals production leads to very short development time
2. Competing technologies
3. Cost
   - Cost of metal (Rh or Ru)
   - Cost of ligand
   - Activity of the catalyst.
   - Stability of the catalyst
   - Recovery or recyclability
4. Availability of catalysts on short notice
5. Patents and high cost of licensing
6. Reliability, real or perceived

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Combinatorial / HTE approach to asymmetric hydrogenation

Goal: Find catalytic solution for customer requests within 3 weeks

Requirements:
- Hardware
  - Endeavor (8 high pressure reactors)
  - Two proprietary reactors for high pressure (96 and 28 vessels)
- HTE Analysis
  - GC
  - HPLC (including chiral HPLC)
  - Flow-NMR
- Libraries of ligands

Libraries of ligands

- Libraries of phosphine ligands are not easy to prepare.
- Phosphoramidites on the contrary are easily prepared in 2 steps:

\[
\text{Cn} \quad \begin{array}{c}
\text{O} \\
\text{P} - \text{NR}^1 \text{R}^2 \\
\text{O}
\end{array}
\]

- Diversity from both diol and amine part.
- Chirality from BINOL or TADDOL skeleton or chiral amine.
- Very successful in copper catalysed asymmetric 1,4 addition of \( \text{Et}_2\text{Zn} \) to cyclic enones (B. Feringa et al, RUG)
- Not known for asymmetric hydrogenation!

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Easy synthesis of phosphoramidites

- \( \text{OH} \quad \text{OH} \quad + \quad \text{PCl}_3 \quad \rightarrow \quad \text{OP} - \text{Cl} \quad \rightarrow \quad \text{RR'}\text{NH}/\text{Base} \)
- \( \text{RR'}\text{NH} \quad + \quad \text{PCl}_3 \quad \rightarrow \quad \text{Cl} - \text{P} - \text{N} - \text{R} \quad \rightarrow \quad \text{OH} \quad \text{OH} \quad \rightarrow \quad \text{RR'}\text{NH} \quad + \quad \text{HMPT} \quad \rightarrow \quad \text{OP} - \text{N(Me)}_2 \quad \rightarrow \quad \text{RR'}\text{NH} \quad \text{cat. tetrazole} \)

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Strong solvent effect but highly enantioselective!

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<th>Entry</th>
<th>Solvent</th>
<th>Temp</th>
<th>e.e.</th>
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<td>CH₃OH</td>
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<tr>
<td>2.</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>95%</td>
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<tr>
<td>3.</td>
<td>CH₂Cl₂</td>
<td>5°C</td>
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<td>4.</td>
<td>THF</td>
<td>RT</td>
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</tr>
<tr>
<td>5.</td>
<td>Acetone</td>
<td>RT</td>
<td>92%</td>
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<tr>
<td>6.</td>
<td>PrOCH₂CH₂OH</td>
<td>RT</td>
<td>77%</td>
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Asymmetric hydrogenations with MonoPhos™

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Solvent</th>
<th>e.e. (RT)</th>
<th>e.e. (0°C)</th>
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<tr>
<td>1.</td>
<td>Ph</td>
<td>Me</td>
<td>CH₂Cl₂</td>
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<td>97%</td>
</tr>
<tr>
<td>2.</td>
<td>Ph</td>
<td>H</td>
<td>EtOAc</td>
<td>97%</td>
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<tr>
<td>3.</td>
<td>H</td>
<td>Me</td>
<td>EtOAc</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>4.</td>
<td>H</td>
<td>H</td>
<td>EtOAc</td>
<td>&gt;99%</td>
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WO 02/04466

DSM Pharma Chemicals
MonoPhos can be prepared in a single step from commercially available BINOL (Compare with DPHOS: 6 steps).

MonoPhos is an order of magnitude cheaper than currently available bisphosphines.

The hydrogenation rate can be increased by increasing the H\textsubscript{2} pressure without loss in enantioselectivity!

At S/C ratio of 2000 full conversion in 2 h at 10 bar.

Method of choice for asymmetric olefin hydrogenation.

Large library of ligands available.
Subtle ligand effects in enamide hydrogenation

- Synthesis of precursors: Z/E mixtures with predominantly Z
- Asymmetric hydrogenation of E is facile.
- Asymmetric hydrogenation of Z is difficult. For R = aryl so far only a few successful catalyst systems known: Ru-BINAPO, Tangphos (X. Zhang et al.)
- Two strategies can be developed:
  - find good ligand for Z
  - synthesis of only E
Beta-amino acids

\[
\begin{align*}
\text{H}_2\text{C} & \text{N} - \text{R} \rightarrow \text{CO}_2\text{Me} \\
\text{H}_3\text{C} & \text{N} - \text{R} \rightarrow \text{CO}_2\text{Me}
\end{align*}
\]

\[
\text{Rh(COD)}_2\text{BF}_4 / \text{Ligand}
\]

\[
\text{H}_2 \ 10 \text{ bar}, \text{ solvent}
\]

Substrate | Ligand | Solvent | e.e. |
--- | --- | --- | --- |
\(E-\ R = \text{CH}_3\) | MonoPhos | \(\text{CH}_2\text{Cl}_2\) | 95% |
\(E-\ R = \text{CH}_3\) | 1 | \(\text{CH}_2\text{Cl}_2\) | 99% |
\(Z-\ R = \text{CH}_3\) | 2 | \(i\text{PrOH}\) | 95% |
\(Z-\ R = \text{Ph}\) | 2 | \(i\text{PrOH}\) | 92% |

D. Peña et al, 

Cocktails anyone?

- What happens if you mix ligands?

\[
\begin{align*}
\text{Rhl}^1\text{L}^1 & \leftrightarrow \text{Rhl}^1\text{L}^2 \\
\text{Rhl}^1\text{L}^2 & \leftrightarrow \text{Rhl}^2\text{L}^2
\end{align*}
\]
Combinatorial Catalysis with Mixtures of Monodentate Ligands

(S)-1, $R^1 = Me, R^2 = R^3 = H$
(S)-2, $R^1 = R^2 = Me, R^3 = H$
(S)-3, $R^1 = Me, R^2 = H, R^3 = Br$
(S)-4, $R^1 = Bn, R^2 = R^3 = H$

$\text{NHAc}$

$R^2 CO_2Et$

\[
\text{Rh(COD)$_2$BF$_4$}
\]

ligand

7, $R = Me$ Blue bars
8, $R = Ph$ Red bars

9, $R = Me$
10, $R = Ph$

Combinatorial catalysis.....

- From NMR: Almost exclusive formation of mixed complex in case of e.e. enhancement.
- Most tested combinations gave lower enantioselectivity than the homo-catalysts.
- Significantly increases the scope of asymmetric hydrogenation.
- Also shown to work with monodentate phosphites. (M.Reetz et al. Angew. Chem. Int. Ed. 2003, 42, 790.)
New low-cost monodentate ligand families

- They can all be synthesized in 1-2 steps
- Other applications besides hydrogenation: Asymmetric Heck, hydroarylation, hydrosilylation, allylic substitution.

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The combinatorial approach to ligand finding

- So far ligand libraries have been made manually. Each ligand synthesised and purified separately.
- Can we make ligands in a robot?
- What about purification?
96 New ligands in 1 day, tested the next day

![Diagram of reaction process]

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**Conversion**

<table>
<thead>
<tr>
<th>10-20</th>
<th>20-30</th>
<th>40-50</th>
<th>60-70</th>
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<th>20-30</th>
<th>40-50</th>
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**E.e.**

<table>
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<th>60-65</th>
<th>70-75</th>
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**Conversion**

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<th>Ee (%)</th>
<th>Conv (%)</th>
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<td>NEt₂</td>
<td>8</td>
<td>46</td>
<td>11</td>
<td>41</td>
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<tr>
<td>Piperidine</td>
<td>11</td>
<td>55</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>NH-α-MeBenz</td>
<td>96</td>
<td>94</td>
<td>51</td>
<td>88</td>
</tr>
<tr>
<td>NHHiPr</td>
<td>100</td>
<td>95</td>
<td>95</td>
<td>92</td>
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</table>

**Comparison**

- **Purified ligands**
  - Conv: Conversion
  - Ee: Enantiomeric Excess

- **Library ligands**
  - Conv: Conversion
  - Ee: Enantiomeric Excess

**DSM Pharma Chemicals**
This HTE approach enables a very fast synthesis of a wide range of phosphoramidites and their screening in asymmetric olefin hydrogenation of

Also less easy accessible N-H ligands can be tested.

E.e's are slightly lower than for the conventional reaction. However, the order is representative.

Can also be applied to other monodentate ligand families

Can also be applied in other catalytic chemistry (C-C bond formation)

**Effect of Ligand/Rh ratio**

The chemical reaction and its graphical representation show the dependence of ee on the MonoPhos/Rh ratio. The graph illustrates the ee at different MonoPhos/Rh ratios over time.

**How many ligands on rhodium**

- Asymmetric Amplification!
- More than 1 ligand on rhodium?
If the "racemic" catalyst is slower than the enantiopure catalysts the e.e. will be higher than expected; positive asymmetric amplification.

If the "racemic" catalyst is faster than the enantiopure catalysts: e.e. will be lower than expected; negative asymmetric amplification.

This experiment proves the existence of RhL₂.

But......

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Possible equilibria in solution

- ...it does not rule out the existence of catalytically active RhL.
- NMR, MS and kinetic studies needed.

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Experiment with 5 mol% Rh followed over time with ES-MS (cationic mode):

After 30 min: RhL$_2$(nbd), RhL$_2$(Substrate), RhL$_3$, RhL$_3$(Substrate)
After 60 min: RhL$_2$(nbd), RhL$_2$(Substrate), RhL$_3$, RhL$_4$
After 120 min: RhL$_2$(Substrate), RhL$_3$, RhL$_4$

Conclusions:
• No RhL derived complexes found
• RhL$_3$ and RhL$_4$ cannot lead to products
• From results with mixtures of ligands: Only RhL$_2$ (not RhL) is an active catalyst!
• A large part of the rhodium is tied up in inproductive complexes.

$^{31}$P NMR
Complex made from Rh(COD)$_2$BF$_4$ + 2 MonoPhos; slowly added
Rh(MonoPhos)$_2$(COD)BF$_4$

$^{31}$P NMR in CD$_2$Cl$_2$ at various temperatures

$^{31}$P NMR Rh(MonoPhos)$_2$(COD)BF$_4$ in CD$_2$Cl$_2$ at 211K
complex 'a' of Rh(MonoPhos)$_2$(COD)BF$_4$ is presumed to have the following structure

Coordination sites of the cyclooctadiene, COD omitted for clarity

complex 'b' of Rh(MonoPhos)$_2$(COD)BF$_4$ is presumed to have the following structure

Coordination sites of the cyclooctadiene, COD omitted for clarity
Chiral catalysis: Enzymes vs transition metals

- Transition metal catalysed reactions very good for:
  - Hydrogenation
  - C-C bond formation
  - Oxidation
- Enzymes are very good in:
  - Hydrolytic reactions
  - Chiral induction
  - Enormous diversity readily available in large numbers!
- Can we wed the best properties of both?
- Prior art: Whitesides and Ward (biotin linked catalysed bound to Avidin)

Artificial co-factors

- Combine homogeneous catalysts that are good in hydrogenation and hydroformylation with an enzyme!
- Enzyme-Ligand-Metal
- Unfavourable weight ratio demands highly active catalyst
- Catalyst needs to be stable in aqueous environment
- Attachment at single position in enzyme for reproducibility.
- Start: Papain plus rhodium/phosphite complexes
  - Enzyme-S-linker-O-P(OR)_2Rh-(COD)BF_4
Ligand system

1. $-\text{CH}_3$
2. $-\text{C}($CH$_3)_3$
3. $-\text{OCH}_3$
4. $-\text{O}($CH$_2$CH$_2$O)$_3$CH$_3$

Selective binding of ligand to enzyme on Cys-SH
Binding of ligand to papain is monitored by activity assay

After treatment of the ligated enzyme with [Rh(COD)$_2$]BF$_4$ and purification only a single Rh is bound to the enzyme!

Mass Spectroscopy

After treatment of the ligated enzyme with [Rh(COD)$_2$]BF$_4$ and purification only a single Rh is bound to the enzyme!
• Product N-Ac-Ala-OH is racemic.
• Native papain reacted with Rh-precursor and purified in the same manner shows no reactivity.
• Next step: other enzymes and substrates.

*Lavinia Panella, unpublished results*

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**Conclusions**

• Monodentate phosphoramidites are excellent ligands for enantioselective olefin hydrogenation.
• Monophos is at least an order of magnitude cheaper than existing bisphosphine ligands.
• A library of 96 phosphoramidite ligands can be made in a single day and screened in catalysis the next day.
• Monophos™ and other phosphoramidites are available in research quantities via STREM.
• Combination of transition metal catalysts with enzymes is a promising new field.
# Acknowledgements

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