(S)-Metolachlor

From Dream to Production Process

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland

Uni Rostock, Gastvorlesung Asymmetrische Katalyse, 7.-8. Dez. 2007

Amazing where you can go
Outline

• Background
  The Molecule, the situation, possible approaches

• In Search of the Ideal Catalyst
  “Moving in a Labyrinth (in the Fog)”

• The Technical Process
  Ligand Scale-up, Imine Synthesis, Choice of Reactor,
Metolachlor
The Molecule

- Herbicide for maize
- > 20’000 t/y
- Only (S)-enantiomers active
- Ca. 35% less loading for enriched form
The Four Stereoisomers of Metolachlor

2 active stereoisomers

2 inactive stereoisomers

H. Moser, G. Rihs, H.P. Sauter 1982
Herbicidal Activity of Metolachlor Stereoisomers

H. Moser, G. Rihs, H.P. Sauter 1982
The History of rac-Metolachlor and (S)-Metolachlor

1970    Discovery of biological activity
1978    Full-scale plant >20’000 t/y
1982    Bioactivity of (S) enantiomers detected
1983    First attempts to make (S)-metolachlor
1985    Rh - cycphos (UBC Vancouver)
1987    Ir - diphosphine (F. Spindler; J.A. Osborn)
1993    Ir - ferrocenyl diphosphine catalysts
1993/4  Patents of rac. metolachlor expired
1995/6  Pilot results: e.e. 79%, ton 1’000’000, tof >200’000/h
16. Nov. 1996  First production batch
Metolachlor: The Problem

Production process for racemate

\[ \text{H}_2 - \text{Pt/C} \]

\[ \text{OCH}_3 \text{COCH}_3 + \text{NH}_2 \text{C}_6\text{H}_4 \text{CH}_3 \rightarrow \text{NAA} \]

\[ \text{NAA} + \text{ClCOCH}_2\text{Cl} \rightarrow \text{active stereoisomers} \]

\[ \text{aR,1'R aS,1'R} \]

\[ \text{inactive stereoisomers} \]

\[ \text{CH}_3\text{O} \text{N} \text{O} \text{CH}_2\text{Cl} + \text{CH}_3\text{O} \text{N} \text{O} \text{CH}_2\text{Cl} \rightarrow \text{aR,1'S aS,1'S} \]

active stereoisomers
### (S)-Metolachlor The Challenge

<table>
<thead>
<tr>
<th></th>
<th>Production process</th>
<th>Minimum requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enantioselectivity</strong></td>
<td>&gt;1'000'000</td>
<td>ee &gt;80%</td>
</tr>
<tr>
<td><strong>Catalyst productivity (ton)</strong></td>
<td>&gt;1'000'000 (70 recycles)</td>
<td>&gt;50'000 (s/c ratio)</td>
</tr>
<tr>
<td><strong>Catalyst activity (tof)</strong></td>
<td>&gt;4000/h at 50°C, 5 bar</td>
<td>&gt;10'000/h</td>
</tr>
<tr>
<td><strong>Space-time yield</strong></td>
<td>very high</td>
<td>high</td>
</tr>
</tbody>
</table>
Moving in the "ee – ton" Space

- ee > 80%
- ton > 50'000
Moving in the "ee – ton" Space
A Labyrinth!

- ee > 80%
- ton > 50'000
Development Phases for EPC Synthesis

- **Phase 1:** Design and assessment of synthetic routes
- **Phase 2:** Demonstrating chemical feasibility
- **Phase 3:** Optimizing the key (catalytic) reaction(s)
- **Phase 4:** Optimizing the over-all process
Routes to (S)-Metolachlor

Hydrogenation of enamide (isomers)

\[
\text{OCH}_3 \quad \text{CH}_3\text{O} \quad \text{N} \cdot \text{COCH}_2\text{Cl} \quad \text{or} \quad \text{CH}_3\text{O} \quad \text{N} \cdot \text{COCH}_2\text{Cl} \quad + \quad \text{H}_2 \quad \text{chiral cat}
\]

Hydrogenation of imine (isomers)

\[
\text{CH}_3\text{O} \quad \text{N} \quad + \quad \text{H}_2 \quad \text{chiral cat}
\]

Hydrogenation / substitution

\[
\text{?} \quad \text{1. H}_2, \text{chiral cat} \quad \text{1. H}_2, \text{chiral cat}
\]

Direct alkylation

\[
\text{OH} \quad \text{OMe} \quad + \quad \text{NH}_2 \quad \text{H} \quad \text{or} \quad \text{R} \quad \text{N} \quad \text{chiral cat}
\]
# (S)-Metolachlor Route Assessment

<table>
<thead>
<tr>
<th>route</th>
<th>catalytic step</th>
</tr>
</thead>
<tbody>
<tr>
<td>enamide</td>
<td>close analogy</td>
</tr>
<tr>
<td></td>
<td>ee &gt;90%</td>
</tr>
<tr>
<td>substitution</td>
<td>weak analogy</td>
</tr>
<tr>
<td></td>
<td>ee &gt;80%</td>
</tr>
<tr>
<td>imine</td>
<td>weak analogy</td>
</tr>
<tr>
<td></td>
<td>ee &lt;30%</td>
</tr>
<tr>
<td>direct alkylation</td>
<td>no precedent</td>
</tr>
</tbody>
</table>
(S)-Metolachlor: Route Assessment

<table>
<thead>
<tr>
<th>route</th>
<th>catalytic step</th>
<th>other steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>enamide</td>
<td>close analogy</td>
<td>enamide synthesis difficult</td>
</tr>
<tr>
<td></td>
<td>ee &gt;90%</td>
<td></td>
</tr>
<tr>
<td>substitution</td>
<td>weak analogy</td>
<td>substitution difficult</td>
</tr>
<tr>
<td></td>
<td>ee &gt;80%</td>
<td></td>
</tr>
<tr>
<td>imine</td>
<td>weak analogy</td>
<td>as in current process</td>
</tr>
<tr>
<td></td>
<td>ee &lt;30%</td>
<td></td>
</tr>
<tr>
<td>direct alkylation</td>
<td>no precedent</td>
<td>as in current process</td>
</tr>
</tbody>
</table>
### (S)-Metolachlor: Route Assessment

<table>
<thead>
<tr>
<th>route</th>
<th>catalytic step</th>
<th>other steps</th>
<th>cost (ecology)</th>
<th>priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>enamide</td>
<td>close analogy ee &gt;90%</td>
<td>enamide synthesis difficult</td>
<td>high (medium)</td>
<td>1</td>
</tr>
<tr>
<td>substitution</td>
<td>weak analogy ee &gt;80%</td>
<td>substitution difficult</td>
<td>high (bad)</td>
<td>2</td>
</tr>
<tr>
<td>imine</td>
<td>weak analogy ee &lt;30%</td>
<td>as in current process</td>
<td>medium (good)</td>
<td>3</td>
</tr>
<tr>
<td>direct alkylation</td>
<td>no precedent</td>
<td>as in current process</td>
<td>low (very good)</td>
<td>4</td>
</tr>
</tbody>
</table>
Development Phases for EPC Synthesis

- **Phase 1:** Design and assessment of synthetic routes
- **Phase 2:** Demonstrating chemical feasibility
- **Phase 3:** Optimizing the key (catalytic) reaction(s)
- **Phase 4:** Optimizing the over-all process
The Enamide Route

**The Analogy**
L-Dopa
Rh-dipamp
(Monsanto)

**The Result:** (All) available Rh/P^P
(up to 20 bar / 50°C)

NO activity at all!!

From Dream to Process
Important Milestones (1983)

ee >80%

enamide

ton > 50‘000
Substitution Route
Heterogeneous Hydrogenation

The Analogy: Pt/Al₂O₃-Cinchonididine
(Orito, 1979)

The Result: Pt/Al₂O₃-Cinchonididine

H.U. Blaser, H.P. Jalett 1983
From Dream to Process
Important Milestones (1983)

- ee > 80%
- Pt/cinch
- enamid
- ton > 50'000
Imine Hydrogenation

\[
\text{CH}_3\text{O} \quad \text{CH}_3\text{O}
\]

\[
\text{??\quad ??}
\]

\[
\text{??\quad ??}
\]
Enantioselective C=N Reduction
State of the Art Around 1982

No report on N-aryl imine hydrogenation

mostly heterogeneous catalysts

Hydrosilylation
Kagan et al.
JOMC 90 (1975) 353

Hydrogenation
Levi et al.
CC (1975) 6
Industry’s Approaches for Solving Difficult Problems

- Do-it-yourself
- Outsource to a specialized department
- Outsource to a specialized company (Solvias!)
- Collaboration with universities

- UBC Vancouver (Cullen, Fryzuk, James, Kutney et al.)

  Search for a catalyst

- ULP Strasbourg (J.A. Osborn)

  Investigate Ir-diphosphine catalysts (active species, deactivation behavior)
### UBC: Rh-Cycphos A First Success

**Chemical Structures:**
- DMA-imine
- (R)-cycphos

<table>
<thead>
<tr>
<th>s/c</th>
<th>Temperature [°C]</th>
<th>t [hrs.]</th>
<th>Conv. [%]</th>
<th>tof [h⁻¹]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>20</td>
<td>44</td>
<td>99</td>
<td>2.3</td>
<td>53</td>
</tr>
<tr>
<td>100</td>
<td>-10</td>
<td>20</td>
<td>100</td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>1000</td>
<td>-10</td>
<td>168</td>
<td>67</td>
<td>4</td>
<td>69</td>
</tr>
<tr>
<td>100</td>
<td>-25</td>
<td>70</td>
<td>100</td>
<td>1.4</td>
<td>73</td>
</tr>
</tbody>
</table>

Cullen, Fryzuk, James, Kutney, et al. UBC Vancouver 1984-89
From Dream to Process Important Milestones (1985)

- ee > 80%
- ton > 50,000

- Rh/cycphos
- enamid
- Pt/cinch
New Idea: Ir - P^P Complexes

<table>
<thead>
<tr>
<th>Ligand</th>
<th>tof (4h)</th>
<th>tof (24h)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>diop</td>
<td>165</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>subst-diop</td>
<td>89-146</td>
<td>28-32</td>
<td>56-61</td>
</tr>
<tr>
<td>bppm ( tBuOMe)</td>
<td></td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>bppm (MeOH)</td>
<td></td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>dipamp</td>
<td></td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>bppfoh</td>
<td></td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>bdpp</td>
<td>114</td>
<td>26</td>
<td>78</td>
</tr>
<tr>
<td>(\rho\text{N(Me)}_2)-bdpp</td>
<td></td>
<td>31</td>
<td>rac</td>
</tr>
</tbody>
</table>

10-20 °C, 30-80 bar, conversion: 17-96%

F. Spindler 1986
**Why Iridium?**

[\text{Ir(cod)(py)(Pcy}_3\text{)]PF}_6\text{: Extremely active catalysts for olefin hydrogenation}

<table>
<thead>
<tr>
<th>Olefin</th>
<th>maximum tof (1/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![olefin1]</td>
<td>6400</td>
</tr>
<tr>
<td>![olefin2]</td>
<td>8300</td>
</tr>
<tr>
<td>![olefin3]</td>
<td>4000</td>
</tr>
</tbody>
</table>

**Drawback: Very fast deactivation via dimerization**

1997: Chiral Iridium – PN Catalysts: Effective for C=C Hydrogenation

\[
\text{Ir}^+ / \text{PN} / X^- \rightarrow \text{product}
\]

ee up to >99%
ton >5000
tof 1250 h\(^{-1}\)

Iridium: Best Results after Optimization

bdpp  ee 84%  ton 100  (at 0°C)

diop  ee 52%  ton 10'000  (at 30°C)

F. Spindler, B. Pugin 1986
From Dream to Process Important Milestones

- ee >80%
- ton > 50'000
- Rh/cycphos
- Ir/bdpp
- Ir/diop
- Pt/cinch
- enamid
Fighting Catalyst Deactivation

Understanding
◆ Nature of active species: Collaboration with JAO

Stabilizing Additives
◆ Avoid dimerization by complexation

Immobilization
◆ Avoid dimerization by “site-isolation”
Fighting Deactivation
Immobilization of Ir - bppm

soluble catalyst; ee = 38%

inactive dimer???

B. Pugin 1988
Fighting Deactivation Immobilization of Ir - bppm

inactive dimer

dilution

B. Pugin 1988
Fighting Deactivation
Homogeneous Ir – bppm Catalyst

B. Pugin 1988

soluble catalyst; ee = 38%

Immob. catalyst; ee >50%

Reaction time [h]
From Dream to Process Important Milestones

- ee >80%
- Rh/cycphos
- Ir/bdpp
- Ir/diop
- Ir/bppm immob
- enamid
- Pt/cinch
- ton > 50'000
Intermezzo 1988-1992

1988: Project stopped by Agro Division

- A. Togni: Ligands for Au-Aldol reaction
- Enlargement of ligand library
- Systematic immobilization studies
- Technical ligands syntheses
- Various process developments
A. Togni
Ligands Studies: Josiphos

first Josiphos ligands for Au-Aldol

Modular, tunable ligands

A. Togni, F. Spindler, B. Pugin
The Final Breakthrough
Ir – Xyliphos / AcOH / Iodide

Best results (laboratory)

R' = p-tBu-phenyl

| ee | 87% | low tof at -15°C |

R' = 3,5-xylyl

| ee | 76-80% | ton 1'000'000; tof ca. 30'000 h⁻¹ |

BUT:
only on presence of acid AND iodide!!

F. Spindler, H.P. Jalett, H.P. Buser 1992
## Ir - Xyliphos: Effect of Solvent

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$t$ (100%) (h)</th>
<th>initial rate</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>thf</td>
<td>7</td>
<td>0.3</td>
<td>74</td>
</tr>
<tr>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>4</td>
<td>0.3</td>
<td>74</td>
</tr>
<tr>
<td>$(\text{CH}_3)_3\text{COCH}_3$</td>
<td>12</td>
<td>0.2</td>
<td>75</td>
</tr>
<tr>
<td>acetone</td>
<td>6</td>
<td>0.4</td>
<td>73</td>
</tr>
<tr>
<td>toluene</td>
<td>12</td>
<td>0.4</td>
<td>73</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>0.75</td>
<td>1.1</td>
<td>79</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>1</td>
<td>1.0</td>
<td>77</td>
</tr>
<tr>
<td>$\text{CH}_3\text{COOEt}$</td>
<td>8</td>
<td>0.7</td>
<td>72</td>
</tr>
<tr>
<td>none</td>
<td>10</td>
<td>0.3</td>
<td>73</td>
</tr>
<tr>
<td>$\text{CH}_3\text{COOH}$</td>
<td>0.5</td>
<td>1.5</td>
<td>79</td>
</tr>
</tbody>
</table>

Reaction conditions: MEA-lmine; s/c: 800; 150 mg TBAI; solvent: 2 ml; 25 bar $\text{H}_2$; 30°C.

H.P. Jalett, F. Spindler
Why Acetic Acid

\[
\begin{align*}
R & = \text{CH}_3 \text{ and PhCH}_2\text{CH}_2 \\
\text{Pt/Al}_2\text{O}_3 - \text{cinchona} & \\
\text{H}_2 & \\
\rightarrow & \\
R\text{-hydroxyester} & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>solvent</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH</td>
<td>82%</td>
</tr>
<tr>
<td>toluene</td>
<td>87%</td>
</tr>
<tr>
<td>acetic acid</td>
<td>92-94%</td>
</tr>
</tbody>
</table>

Ir - Xyliophos

Effect of AcOH and I⁻

General acid effect:
- CF₃COOH
- H₂SO₄

H.P. Jalett, F. Spindler 1993
From Dream to Process Important Milestones

- **Ir/xyliphos Acid / iodide**
- **Ir/PPF-P**
- **Ir/bdpp**
- **Ir/diop**
- **Ir/bppmimmob**

Enamid

- **Rh/cycphos**

- **Pt/cinch**

**ee (%)**

- ee \(\geq 80\%\)
- ton \(> 50'000\)
- tof \(> 10'000/h\)

**ton**

- 10
- 100
- 1,000
- 10,000
- 100,000
- 1,000,000

\[\text{ee} \geq 80\% \quad \text{ton} > 50'000 \quad \text{tof} > 10'000/h\]
Reductive Alkylation of MEA
Ir-xyliphos, AcOH: Solvent Effect

\[
\begin{align*}
\text{MEA} & \quad + \quad \text{MOA} & \quad \xrightarrow{\text{H}_2, \text{Ir-PP}} \quad S\text{-NAA} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time [h]</th>
<th>Rate [mmol/min]</th>
<th>Conv. [%]</th>
<th>ee [%]</th>
<th>Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>22</td>
<td>0.5</td>
<td>87</td>
<td>76</td>
<td>2 phases</td>
</tr>
<tr>
<td>Cyclohex (10 ml)</td>
<td>21</td>
<td>0.9</td>
<td>92</td>
<td>77</td>
<td>2 phases</td>
</tr>
<tr>
<td>EtOH (10 ml)</td>
<td>18</td>
<td>0.3</td>
<td>24</td>
<td>15</td>
<td>1 phase</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.1 mol MEA; 0.12 mol MOA (dry); AcOH: 2.5 ml; 20 mg TBAI; 80 bar H\(_2\); 50°C.

H.U. Blaser, H.P. Jalett
Functionalization of Xyolphos

1) BuLi /TMEDA

2) mixture of Cl-PPh₂ and Cl₂

(53%)

Gabriel

(90%)

Immobilization

B. Pugin, H. Landert 1995
## Metolachlor: Recycling??

<table>
<thead>
<tr>
<th>homogeneous</th>
<th>heterogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>free</td>
<td>extractable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S/C time</th>
<th>ee</th>
<th>Separation</th>
<th>distillation</th>
<th>extraction &gt; 90%</th>
<th>filtration 95%</th>
<th>filtration 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>50'000</td>
<td>1h</td>
<td>79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120'000</td>
<td>2.1h</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120'000</td>
<td>3h</td>
<td>79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50'000</td>
<td>8h</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120'000</td>
<td>10h</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50'000</td>
<td>30h</td>
<td>74%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hydrogenation of Imine
Best Ir / Xyliphos Systems

F. Spindler, B. Pugin, H.U. Blaser, H.P. Jalett

- Homogeneous
- Reductive alkylation
- Immobilized

Graph showing tof and ee (%) for different conditions:
- No acid
- AcOH
- s/c 2'000'000
- s/c 10'000
- s/c 100'000
Development Phases Metolachlor Imine Route

- **Phase 1:** Assessing synthetic routes
- **Phase 2:** Demonstrating chemical feasibility
- **Phase 3:** Optimizing the key (catalytic) reaction(s)
- **Phase 4:** Optimizing the over-all process
Process Optimization

- Ligand fine tuning
- Optimization of reaction conditions
- Strategy for the development of the overall process
- The Production of the MEA Imine in the Required Quality
- Technical Ligand Synthesis
- Choice of Reactor Technology
- Scale up
- Work-up
- Separation of the Catalyst from the Product
Fine Tuning
(S)-Metolachlor Process

Catalyst: \([\text{Ir(COD)Cl}]_2, \text{NaI, H}_2\text{SO}_4, (R)-(S)-\text{R}_2\text{PF-PR'}_2; \ p(\text{H}_2), 80\text{ bar, 50°C}\)

<table>
<thead>
<tr>
<th>ee %</th>
<th>79</th>
<th>82</th>
<th>87</th>
<th>83</th>
</tr>
</thead>
<tbody>
<tr>
<td>ton</td>
<td>2’000’000</td>
<td>800</td>
<td>5’000</td>
<td>100’000</td>
</tr>
<tr>
<td>tof ([\text{h}^{-1}])</td>
<td>&gt;400’000</td>
<td>400</td>
<td>80</td>
<td>28’000</td>
</tr>
</tbody>
</table>

F. Spindler
Ligand Finetuning:
N Substituents at Xylyl Group

F. Spindler, H.P. Buser 1994

e.e.: 76%
rate: 26 mmol/min

e.e.: 80%
rate: 25 mmol/min

e.e.: 83%
rate: 1 mmol/min

F. Spindler, H.P. Buser 1994
Reaction Conditions
Effect of H₂ Pressure

\[ r_{\text{max}} \text{ (mmol H₂/min)} \]

\[ \text{Pressure (bars)} \]

\[ \text{ee: 75 - 76\%} \]

F. Spindler, H.P. Jalett 1994
Development Phases for EPC Synthesis

- **Phase 1:** Design and assessment of synthetic routes
- **Phase 2:** Demonstrating chemical feasibility
- **Phase 3:** Optimizing the key (catalytic) reaction(s)
- **Phase 4:** Optimizing the overall process
Process Development

- Ligand fine tuning
- Optimization of reaction conditions
- Strategy for the development of the over-all process
- The Production of the MEA Imine in the Required Quality
- Technical Ligand Synthesis
- Choice of Reactor Technology
- Scale up
- Work-up
- Separation of the Catalyst from the Product
Imine Production

\[
\text{Acetone-OMe} + \text{Ammonium Salicylate} \xrightarrow{\text{H}^+} \text{Imine} + \text{H}_2\text{O}
\]

Simple chemistry

**BUT**

- Scale up difficult due to thermal instability of the imine
  - Fast removal of water necessary
- Significant catalyst deactivation
  - High purity required
Effect of MEA Concentration
Ir/xylyphos, Acetic Acid, TBAI

Initial rate (mmol H2/min)

- t(100%): 0.5 h
- t(100%): 18 h

EE not affected!

F. Spindler, H.P. Jalett
Imine Production: Water Separators
Process Development

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Technical Ligand Synthesis

enzymatic kinetic resolution

Ugi amine

30 Kg scale unproblematic
Process Development

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- Work-up
- Separation of the Catalyst from the Product
Choice of Reactor Technology

Issues

- High pressure (80 bar) -> high investment
- Fast exothermic reaction -> heat removal important
- Sensitive catalyst -> handling and loading

Alternatives

- Stirred tank reactor
- Loop reactor
Choice of Reactor

stirred tank

loop reactor
Choice of Reactor

cooling

pump
Process Development

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- Optimization of reaction conditions
- Strategy for the development of the over-all process
- The Production of the MEA Imine in the Required Quality
- Technical Ligand Synthesis
- Choice of Reactor Technology
- Scale up
- Work-up
- Separation of the Catalyst from the Product
Happy End: First Production Batch

\[
\begin{align*}
\text{MEA-imine} & : 10'000 \text{ kg} \quad 48'700 \text{ mol} \\
[\text{Ir(COD)Cl}]_2 & : 34 \text{ g} \quad 0.05 \\
\text{Ligand} & : 68 \text{ g} \quad 0.11 \\
\text{NaI} & : 92.5 \text{ g} \quad 0.6 \\
\text{H}_2\text{SO}_4 & : 250 \text{ g} \quad 0.5
\end{align*}
\]

reaction time 2h
conversion 99.6%
ee 79%

N. Pericles, R. Hanreich
From Dream to Process Important Milestones

- ee (%)
- ton
- tof

- Ir/xyliphos Acid / iodide
- Ir/PPF-P
- Ir/bdpp
- Ir/diop
- Ir/bppmimmob
- Rh/cycphos
- Pt/cinch
- enamid

ee ≥80%
ton >50'000
tof >10'000/h
Some Lessons

Enantioselectivity is not always the major problem
- ton and tof can be just as critical!!

Success often depends on availability of ligands
- Modular ligands are an optimal solution
- Solvias Ligand Kit

Screening capabilities are crucial
- Parallel screening equipment

NO SUCCESS WITHOUT TOP EXPERTISE
The Key Players

F. Spindler

B. Pugin

H.P. Jalett
Think catalytic!

Amazing where you can go