# The Story of *(S)*-Metolachlor

## *An Industrial Odyssey*

## *in*

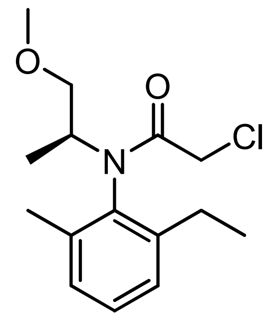
## *Asymmetric Catalysis*

A Literature Presentation

Aman Desai

04.10.09

# The Glory of the Odyssey – Reasons Behind the Talk




(*S*)-Metolachlor

- *(S)*-metolachlor is the active ingredient in Dual Magnum®, one of the most important grass herbicides for use in maize.
- >20,000 ton/year market of the herbicide.
- Key step in synthesis – an Ir-catalyzed asymmetric hydrogenation.
- A 14 year odyssey of development.
- Operated on a >10,000 ton/year scale since 1996.
- This is to date the largest application of asymmetric catalysis.
- The Ir-Xyliphos is the most active and productive catalyst till date (>7,000,000 TON and >2,000,000 TOF).
- Developed during the incipient years of asymmetric hydrogenation – a historical case study.

Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.
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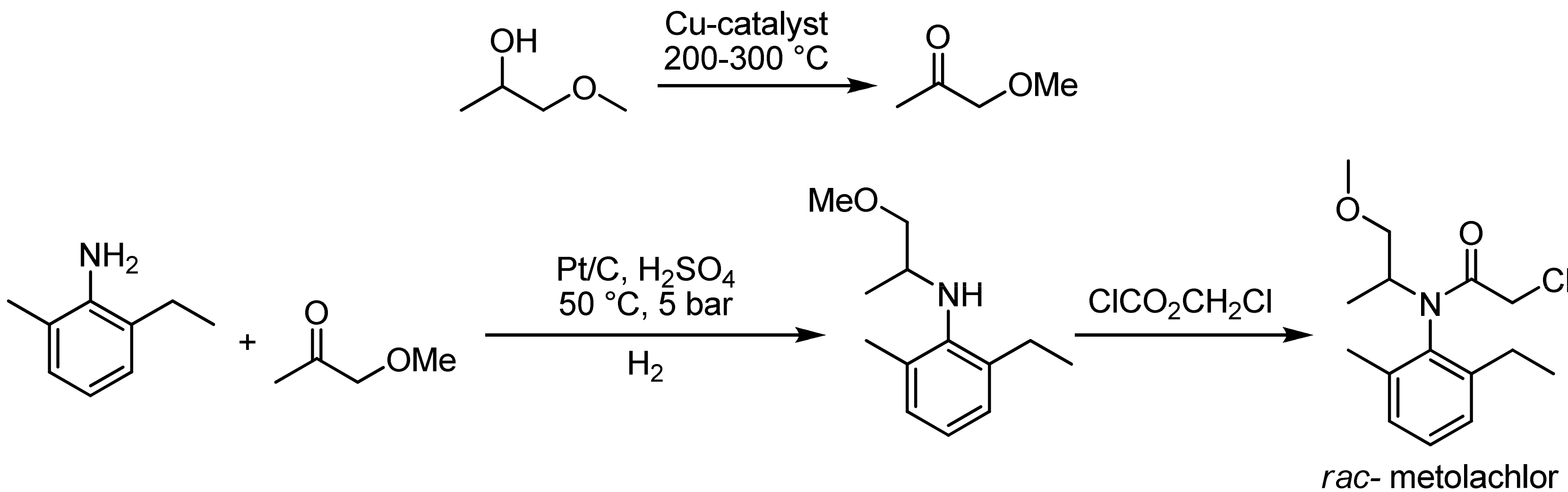
# The Initial Process for *rac*- Metolachlor

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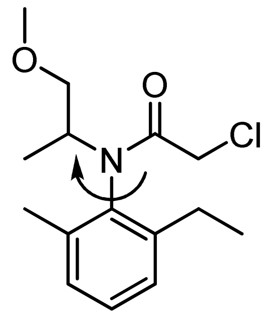
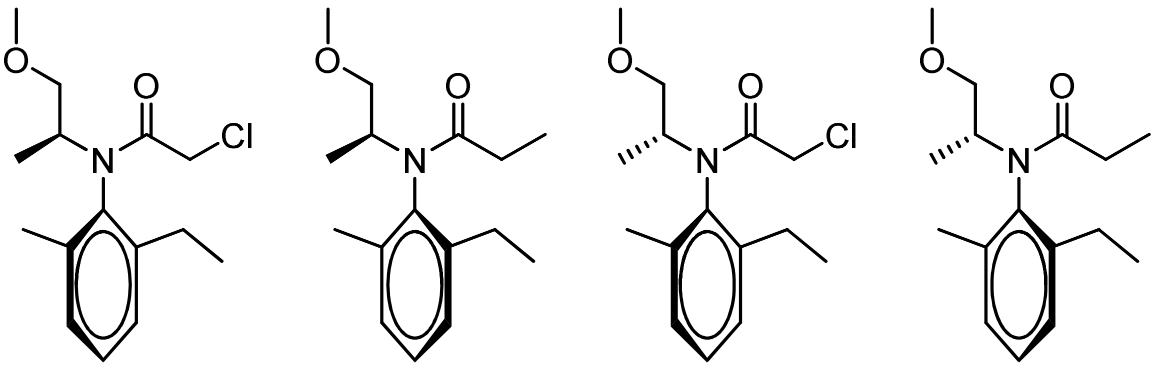
# Discovery of the Active and Inactive Stereoisomers




*rac*- metolachlor




*αR, 1'S* *αS, 1'S* *αR, 1'R* *αS, 1'R*

the active stereoisomers the inactive stereoisomers

95% of herbicidal activity resides in the two *(1'S)*-diastereomers.

Thus, same biological effect could be produced at ~60% of the use rate of the racemic product.

*Not a small matter considering the >20,000 t/y market!*

The quest for a viable commercial catalyst for the asymmetric manufacture had started!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# The First Assessment and The Four Routes Considered

| route | catalytic step | other steps | cost | ecology |
|---|---|---|---|---|
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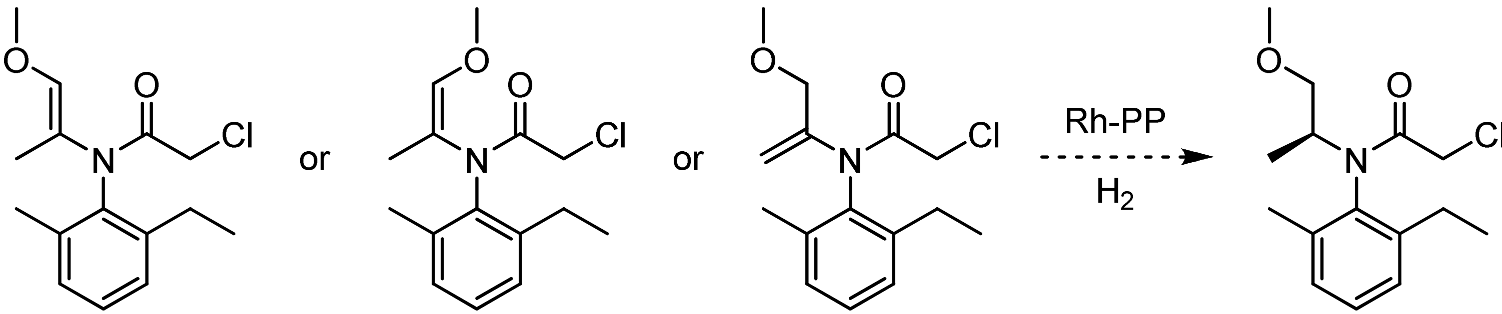
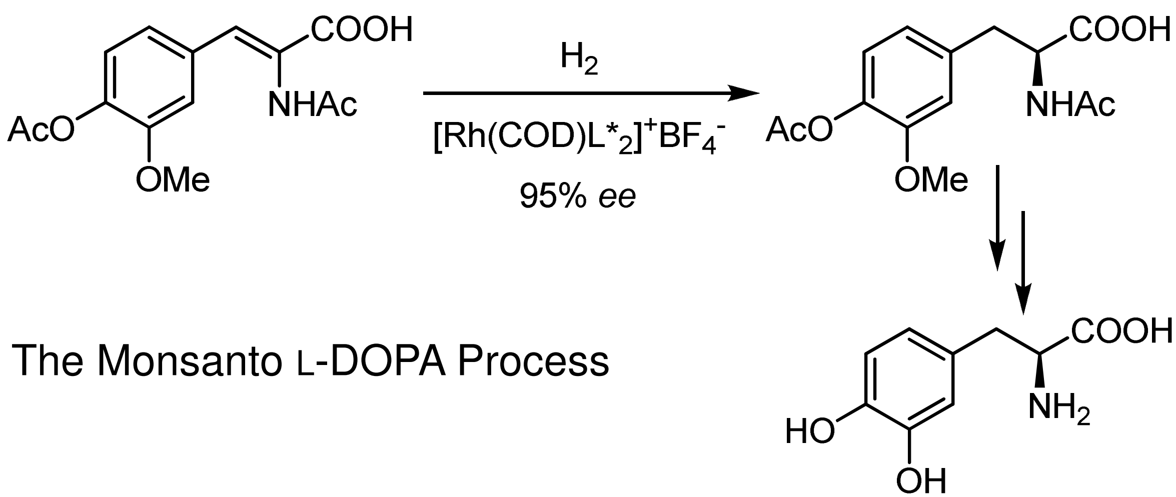
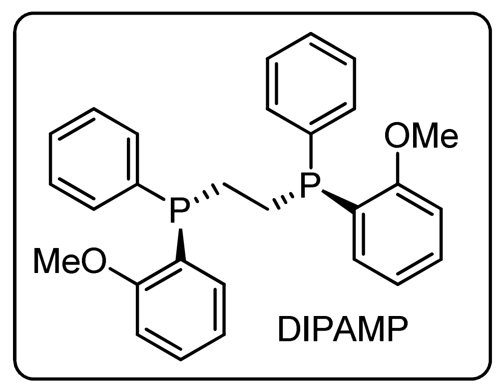



(*S*)-metolachlor




The Monsanto L-DOPA Process





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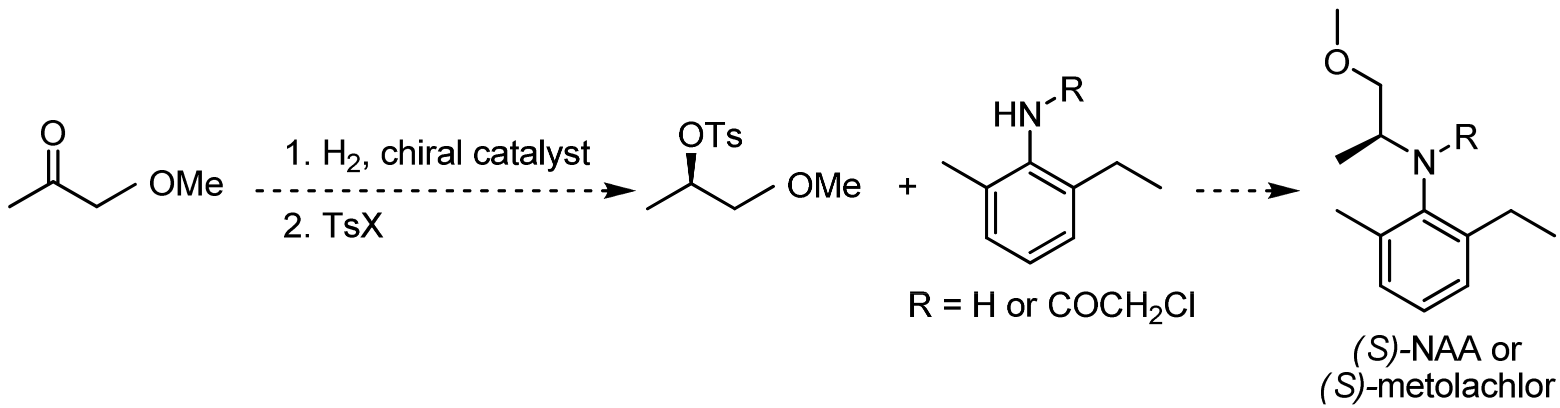


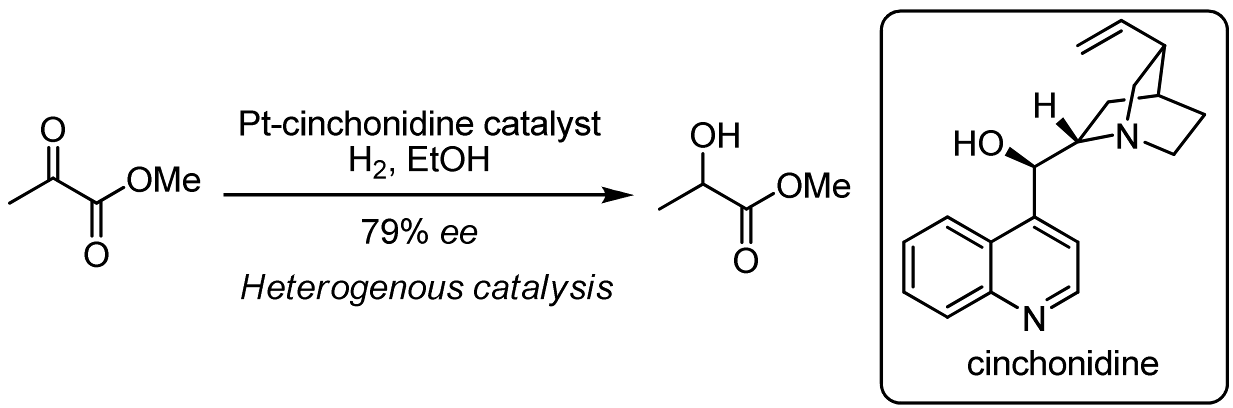


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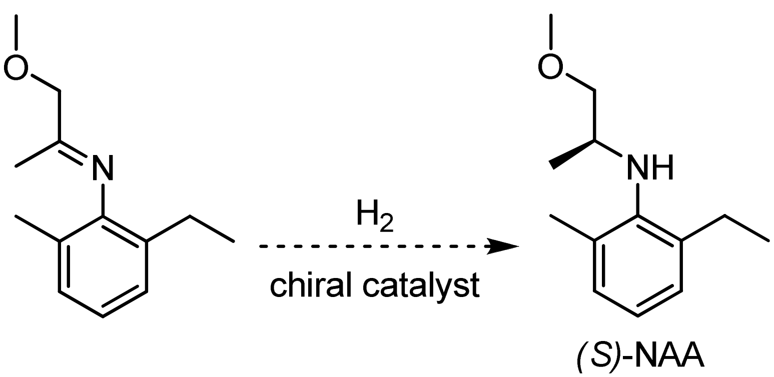


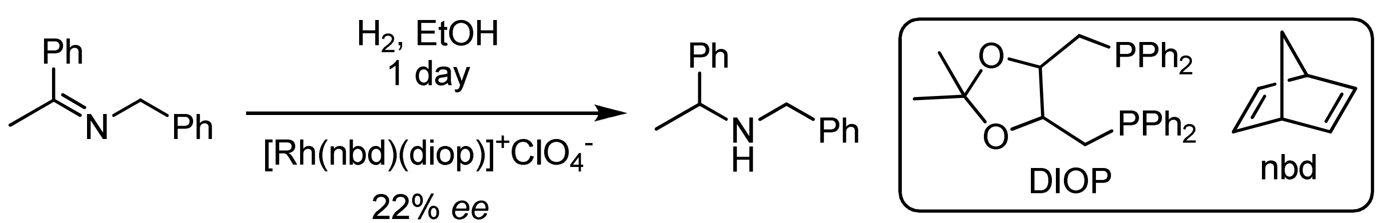


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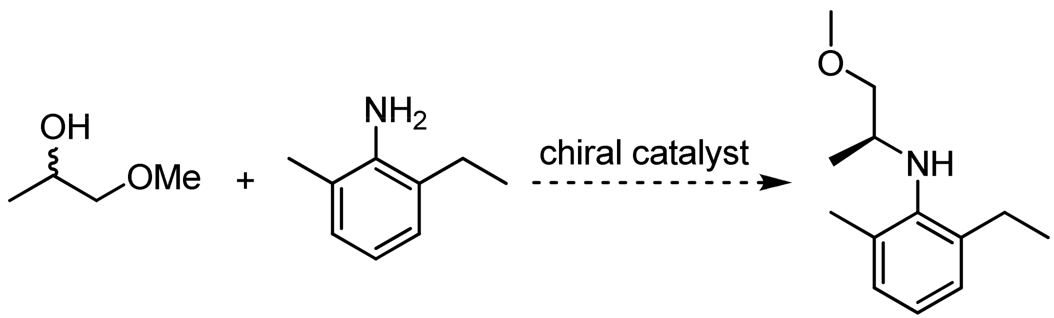
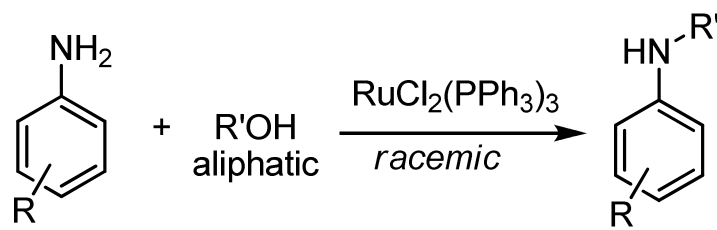



(*S*)-NAA





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# Priorities Assigned to the Routes

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# Proposed Project and Goals

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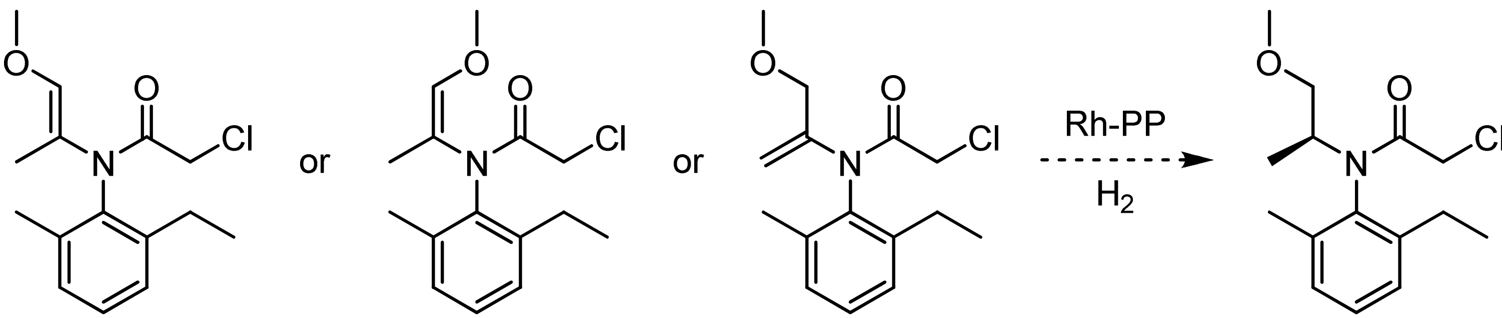
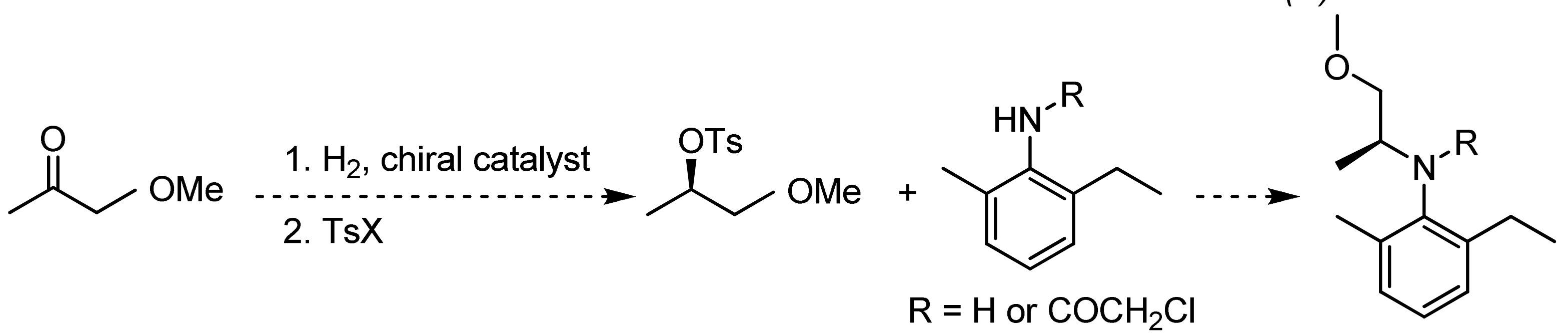



(*S*)-metolachlor




(*S*)-NAA or
(*S*)-metolachlor

Attain >70% *ee*'s; no goal for catalyst activity or productivity

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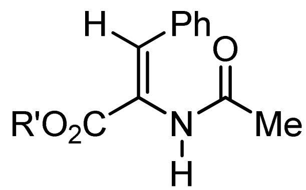
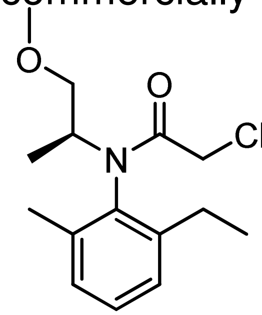
# State of Asymmetric Catalysis in 1981 and at Ciba-Geigy

• Only one industrial process existed – Monsanto's L-DOPA process.

• Asymmetric enamide hydrogenation: High *ee*'s (>95%), low TON's (<2300), <10 chiral phosphines commercially available (small quantities).




most investigated model




(*S*)-metolachlor

• Modified heterogeneous catalysts were the most active catalysts for C=O groups. *ee*'s upto 85%.

• No history of asymmetric catalysis at Ciba-Geigy.

• No hydrogenation equipment for homogenous catalysis.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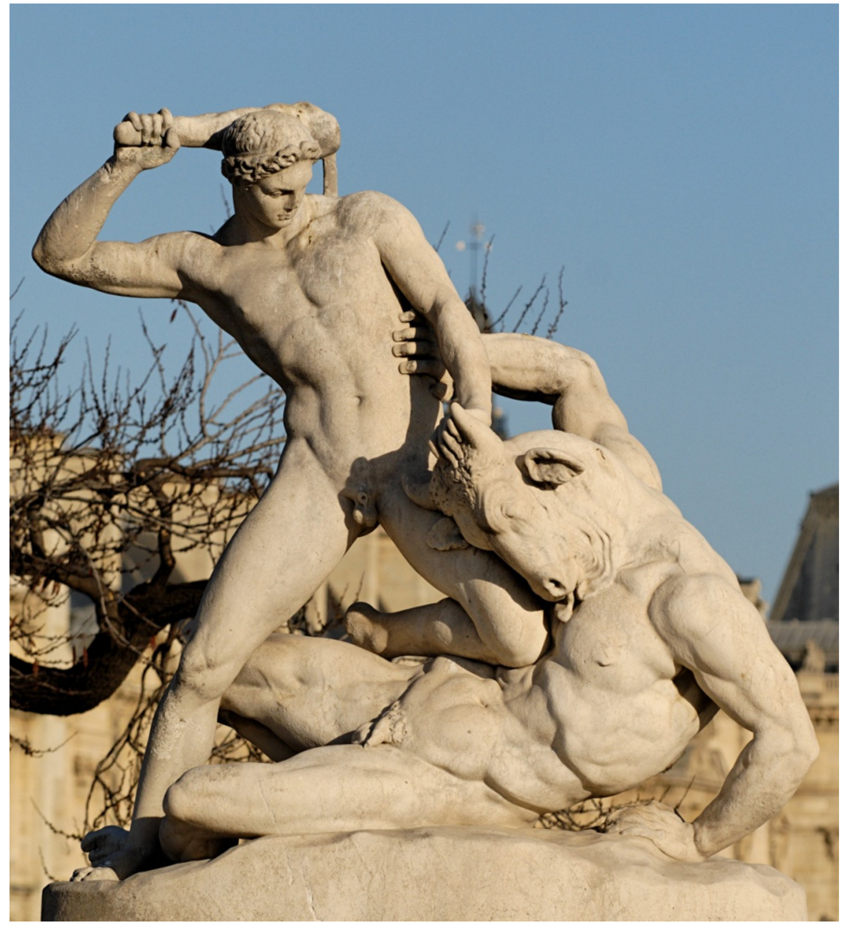
# The “Theseus-Minotaur” Greek Legend



*Theseus fighting the Minotaur*
by Jean-Etienne Ramey, marble, 1826
Tuilereis Gardens, Paris

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www.wikipedia.com

# The ee-TON Labyrinth is the same as the Theseus-Minotaur one


The successful route shown

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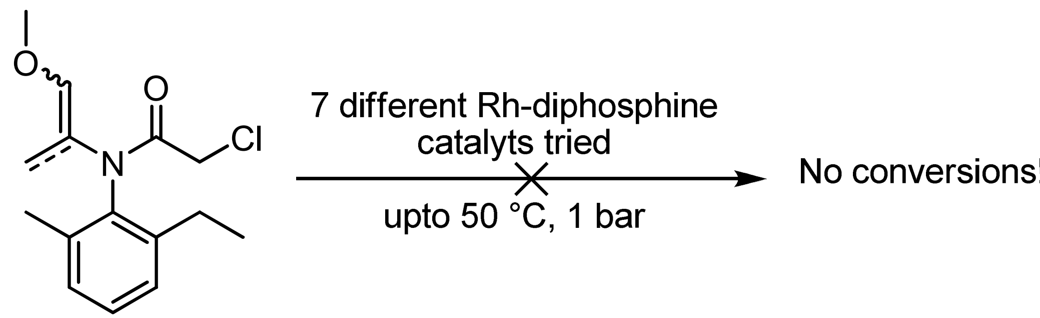
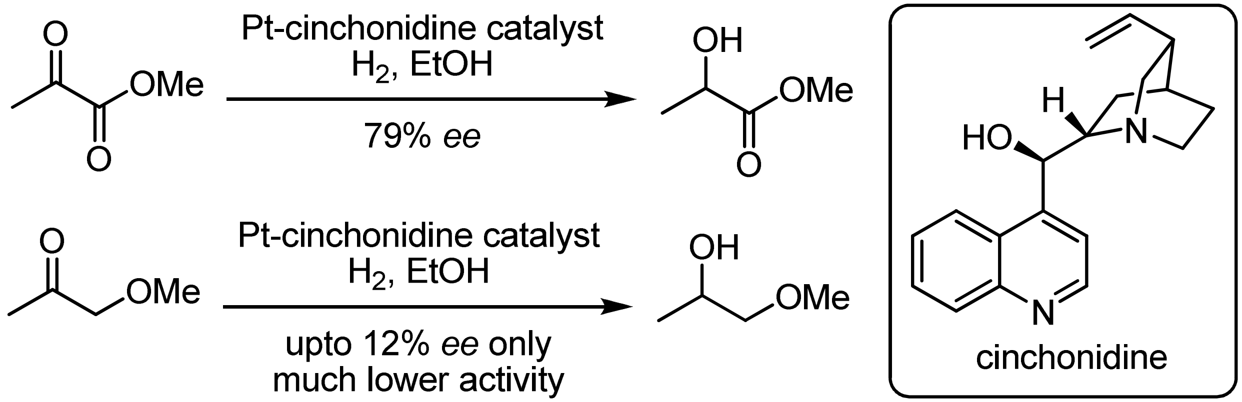
# The First Steps in the Labryinth – the First Disappointments

Enamide hydrogenation route:



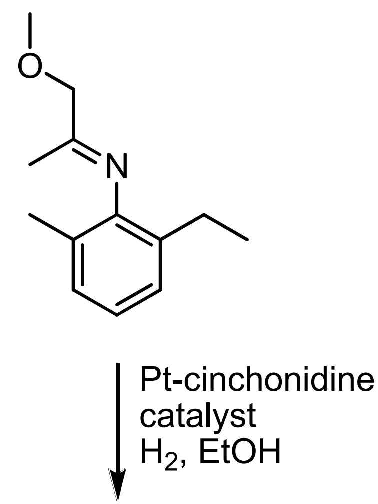

3 enamide isomers

Methoxyacetone reduction route:




cinchonidine

Imine reduction route:




racemic products only

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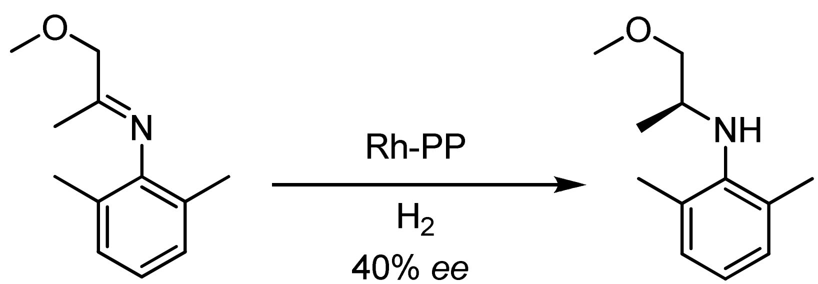
# A Second Chance and the First Breakthrough

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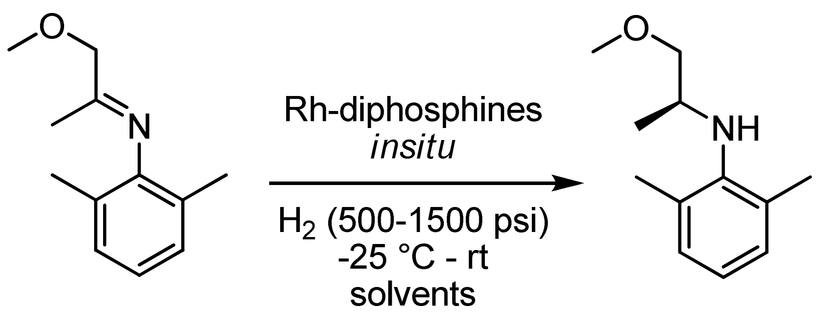
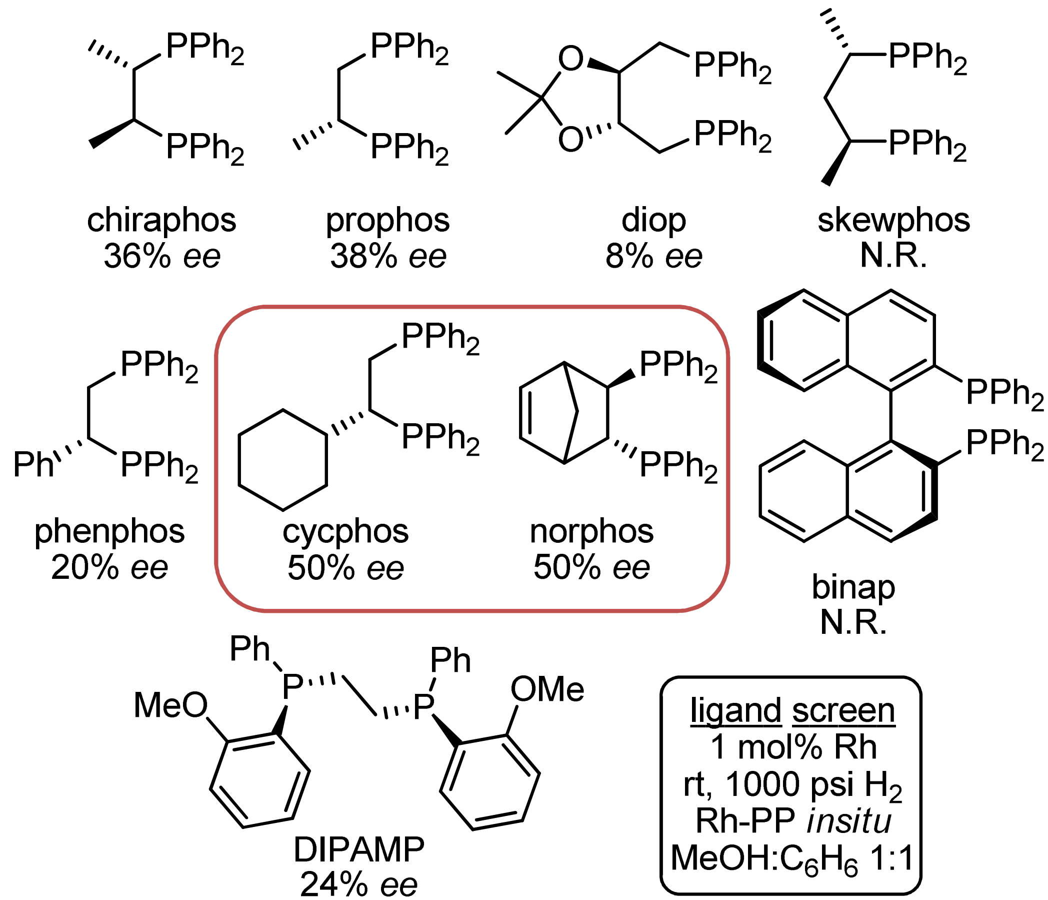
# The U. British-Columbia – Ciba-Geigy Study




a thorough study

0.1 mol% Rh, 0.2 mol% cycphos catalyst *insitu*
-25 °C, 1500 psi $H_2$, 70 h, 2:1 MeOH:toluene

69% *ee*, 100% conversion
TOF = 15 $h^{-1}$, TON = 1000




Cullen, W. R.; Fryzuk, M.D.; James, B. R.; Kutney, J. P.; Kang, G-J.; Herb, G.; Thorburn, I. S.; Spogliarich, R. *J. Mol. Cat.* **1990**, *62*, 243-254.

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# The Switch to Iridium Complexes

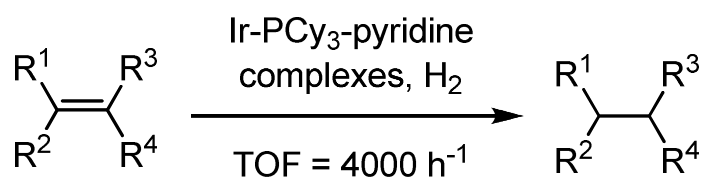
It was thought that Rh-diphosphine complexes would never be active enough.

Best results with Rh – 69% ee, 1000 TON, 70 h

Requirements for a technical process: ≥80% ee, >50,000 TON, <8 h

Risks with iridium – very little known, Ir-catalyzed reactions were very rare and none was asymmetric.

The Crabtree inspiration:

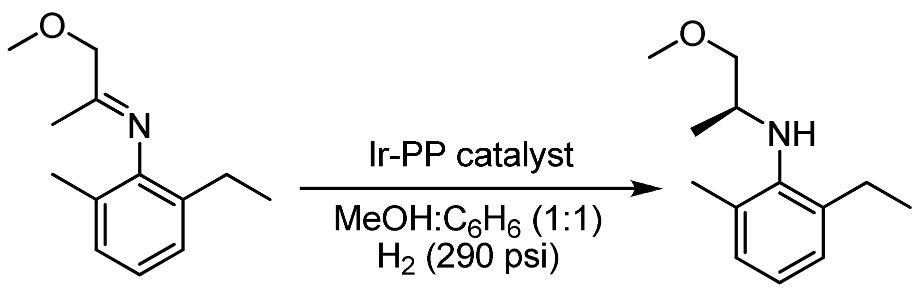


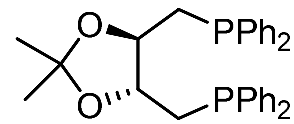

A full study undertaken like the UBC rhodium study.


Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.
Crabtree, R.; Felkin, H; Fellebeen-Khan, G. *J. Organometal. Chem.* **1979**, *168*, 183.

# Good results with Ir – but are they good enough?

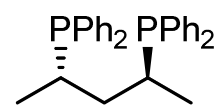
$[Ir(COD)Cl]_2$ + 2.2 eq PP + 4 eq TBAI $\xrightarrow{MeOH:C_6H_6\ (1:1)}$ Ir-PP catalyst *insitu*




diop

25 °C, 50 h
62% *ee*
TON = 10,000

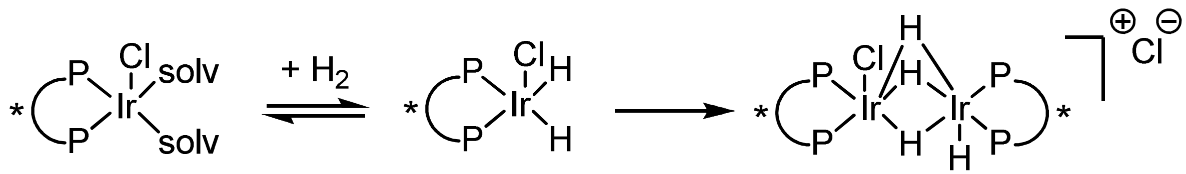



bdpp

0 °C, 16 h
84% *ee*
TON = 100

Requirements for a technical process: ≥80% ee, TON = 40,000, <8 h

Irreversible catalyst deactivation – a major problem.




active complex

inactive dimer
(irreversible)

This was the best enantioselective imine hydrogenation at that time…

….yet, a new approach was needed.


Splinder, F.; Pugin, B.; Blaser, H-U. *Angew. Chem. Int. Ed. Eng.* **1990**, *29*, 588-589.
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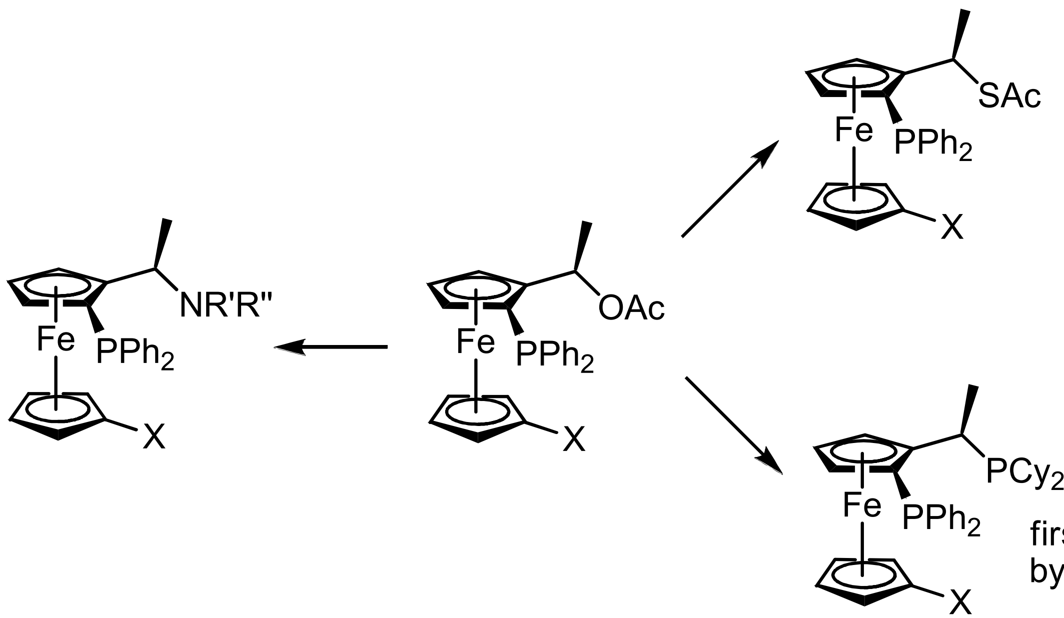
Blaser, H-U.; Pugin, B.; Splinder, F.; Thommen, M.; *Acc. Chem. Res.* **2007**, *40*, 1240-1250.

# Josiphos Ligands – A New Family at Ciba-Geigy

Extremely modular and tunable diphosphine ligands.



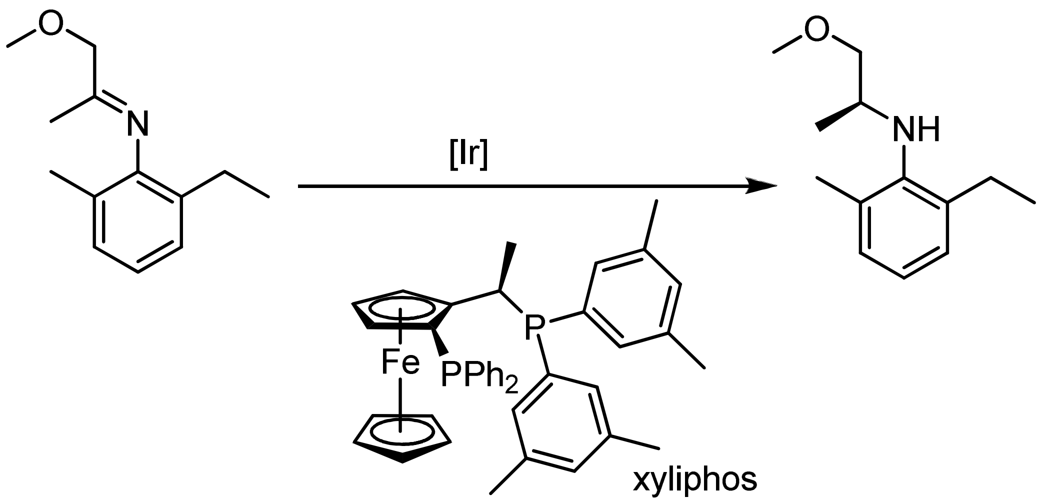

first Josiphos
by Josi Puleo
X = H

From the first try, these ligands were very efficient and were used for several commercial applications.

Numerous new ligands made and screened for *(S)*-metolachlor.


Blaser, H-U.; Brieden, W.; Pugin, B.; Splinder, F.; Studer, M.; Togni, A. *Top. Cat.* **2002**, *19*, 3-16.
Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.

# A Third Chance and a Second Breakthrough – Almost There!




55 °C, 1100 psi $H_2$, 48 h

35,000 TON and 70% ee

Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.
Blaser, H-U.; Pugin, B.; Splinder, F.; Thommen, M.; *Acc. Chem. Res.* **2007**, *40*, 1240-1250.

# Milestones in the History of Metolachlor

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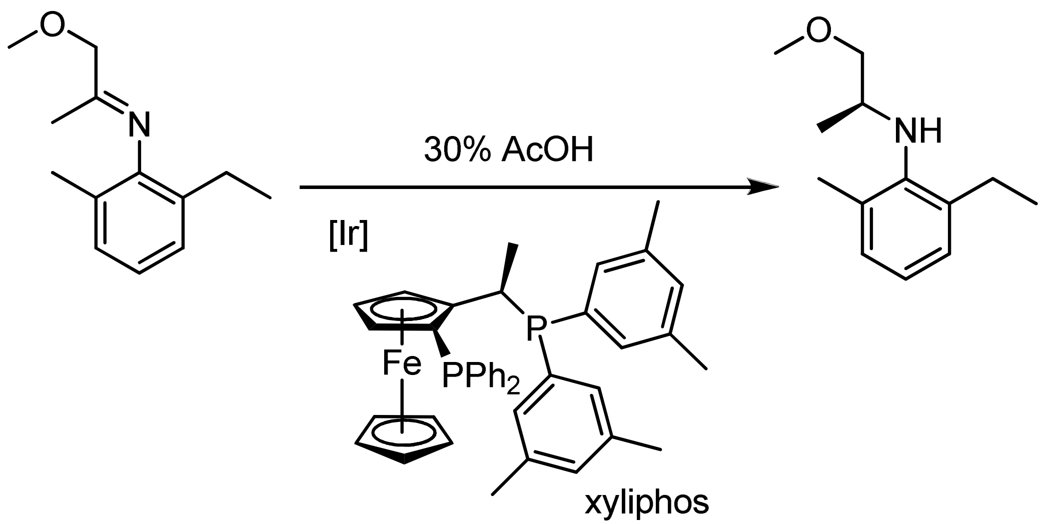
# The Final Breakthrough – The Magic of AcOH




>200,000 TON

75-80% *ee*

Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.
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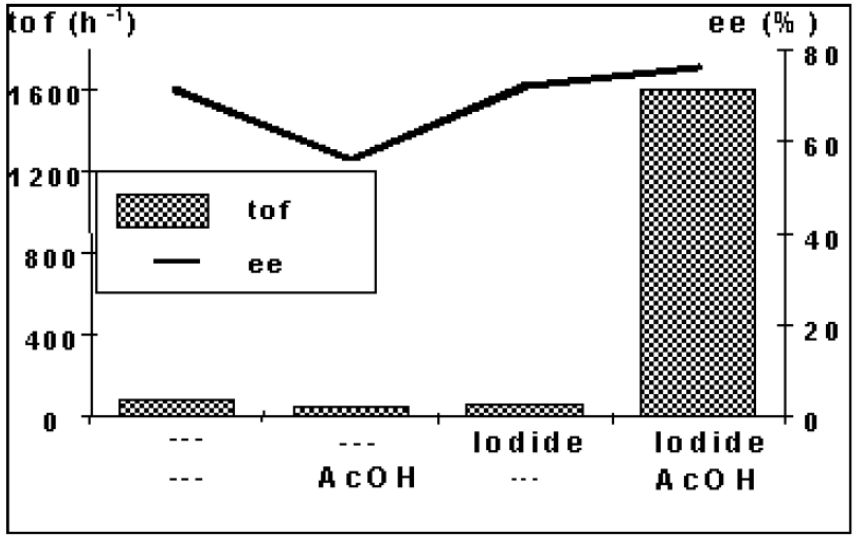
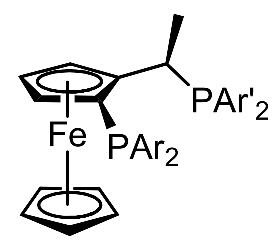
# Exceeding all expectations – by quite a margin!




Over 30 different diphosphine ferrocenyl ligands screened.

| Ar | Ar' | TON | TOF ($h^{-1}$) | *ee* |
|---|---|---|---|---|
| Ph | 3,5-xylyl | 1,000,000 | >200,000 | 79 |
| *p*-$CF_3C_6H_6$ | 3,5-xylyl | 800 | 400 | 82 |
| Ph | 4-$^t$Bu-$C_6H_4$ | 5,000 | 80 | 87 |
| Ph | 4-($^n$Pr)$_2$N-3,5-xylyl | 100,000 | 28,000 | 83 |





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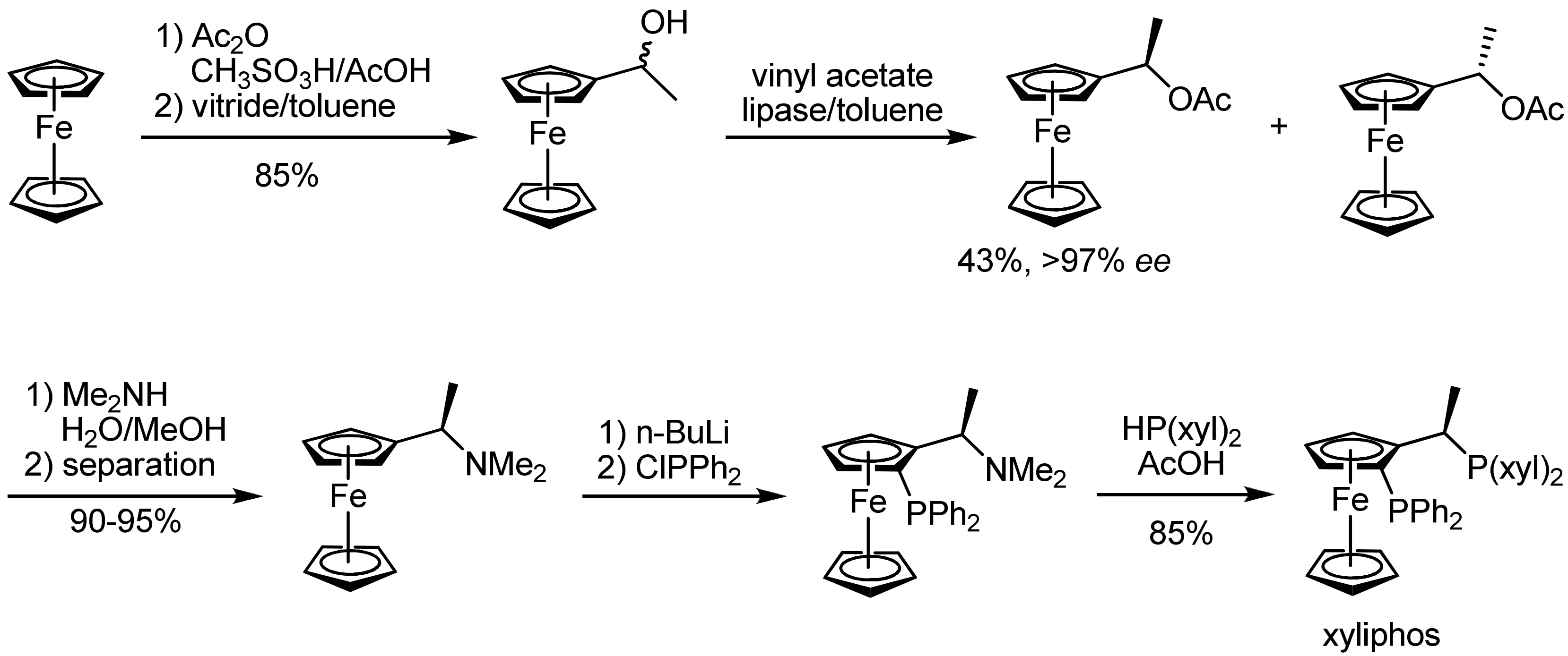
# From Lab to Plant – Technical Ligand Synthesis




Synthesis in 2500 L reactors

Hundreds of kg scale

>99.5% *ee*


Blaser, H-U.; Brieden, W.; Pugin, B.; Splinder, F.; Studer, M.; Togni, A. *Top. Cat.* **2002**, *19*, 3-16.

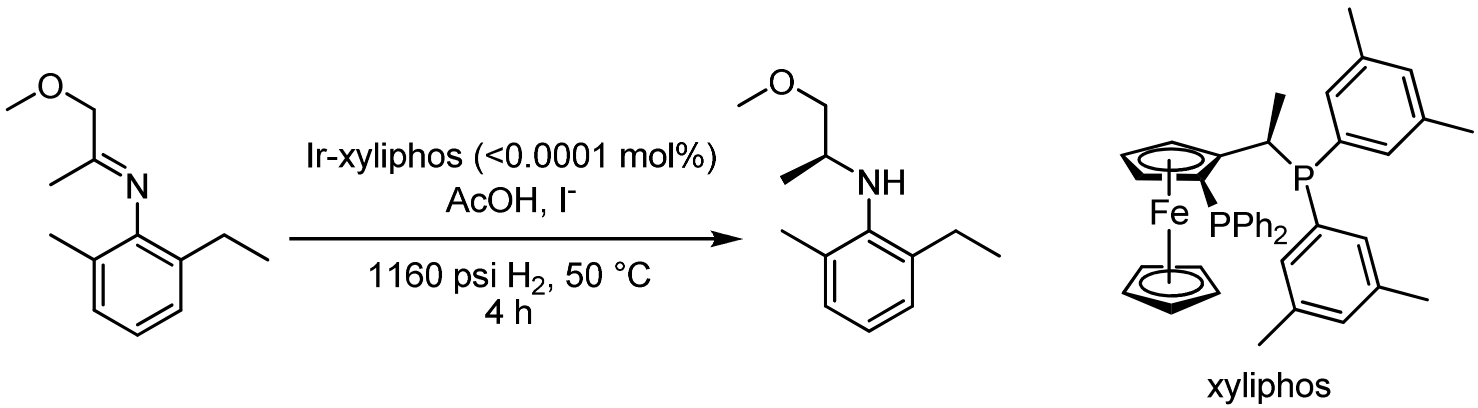
# The Loop Reactor & the Plant, Kaisten, Switzerland (Syngenta)

<u>Post hydrogenation</u>

Continuous aqueous extraction to neutralize and eliminate acid from crude.
Flash distillation to remove residual water.
Subsequent distillation to remove water from catalyst on a thin film evaporator.
Residue – Ir is recovered, ligand is lost.

Hofer, R. *Chimia* **2005**, *59*, 10-12.
Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.

# The Final Production Process




100% conversion
79% ee
>7,000,000 TON
>2,000,000 TOF ($h^{-1}$)

34 g Ir complex + 70 g xyliphos ligand + some acid + some iodide
gives
10,000 kg of hydrogenated product,79% *ee*, 4 h

>10,000 tons/year scale commercial production till date in Switzerland
(Syngenta)


Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.
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# The Key Development Team (top-bottom, left-right)

Benoit Pugin

1981 – PhD, Prof. Venanzi (ETH, Zurich),
1982/3 – Post-doc at Ciba-Geigy
1983… – Ciba-Geigy, Novartis and presently at Solvias
Development of new chiral ligands for asymmetric catalysis

Hans-Ulrich Blaser (the chief)

1971 – PhD, Prof. Eschenmoser (ETH, Zurich)
1971/5 – Post-docs at U. Chicago (J. Halpern), Harvard U. (J. Osborn), Monsanto (Zurich)
1976-96 – Ciba-Geigy.
1996-99 – Novartis
1999… – Solvias
Industrial application of selective catalysts

Felix Splinder

1981 – PhD, Prof. Venanzi (ETH, Zurich)
1983-96 – Ciba-Geigy
1996-99 – Novartis
1999… - Solvias
Homogenous enantioselective hydrogenation

Hans-Peter Jalett

Solvias – Chief technician in Catalysis Section

Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.

# AcOH was the magical key

AcOH as an additive was common in heterogenous catalysis, never investigated in homogenous catalysis.

In fact, Benoit Pugin had found negative effects of AcOH with the Ir-diop ligands in 1986.

Most specialists would have dissuaded Hans-Peter Jalett…

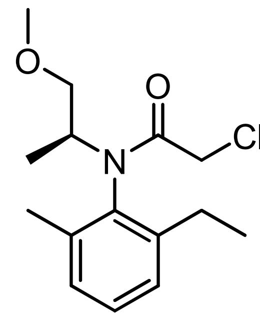
*…but he never asked!*

*"…faced with a decision based solely upon hypothetical arguments, consider all reasons not to perform an experiment, and disregard them."*

– R. B. Woodward
as heard from J. Woods
(2009, Michigan State U.)

Blaser, H-U. *Adv. Synth. Catal.* **2002**, *334*, 17-31.

# The Glory of the *(S)*-Metolachlor Odyssey



*(S)*-Metolachlor

- *(S)*-metolachlor is the active ingredient in Dual Magnum®, one of the most important grass herbicides for use in maize.
- Key step in synthesis – an Ir-catalyzed asymmetric hydrogenation.
- A 14 year odyssey of development.
- Operated on a >10,000 ton/year scale since 1996.
- This is to date the largest application of asymmetric catalysis.
- The Ir-Xyliphos is the most active and productive catalyst till date (>7,000,000 TON and >2,000,000 TOF).
- Developed during the incipient years of asymmetric hydrogenation – a historical case study.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