solvias

(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

solvias

- Background

  The Molecule, the situation, possible approaches

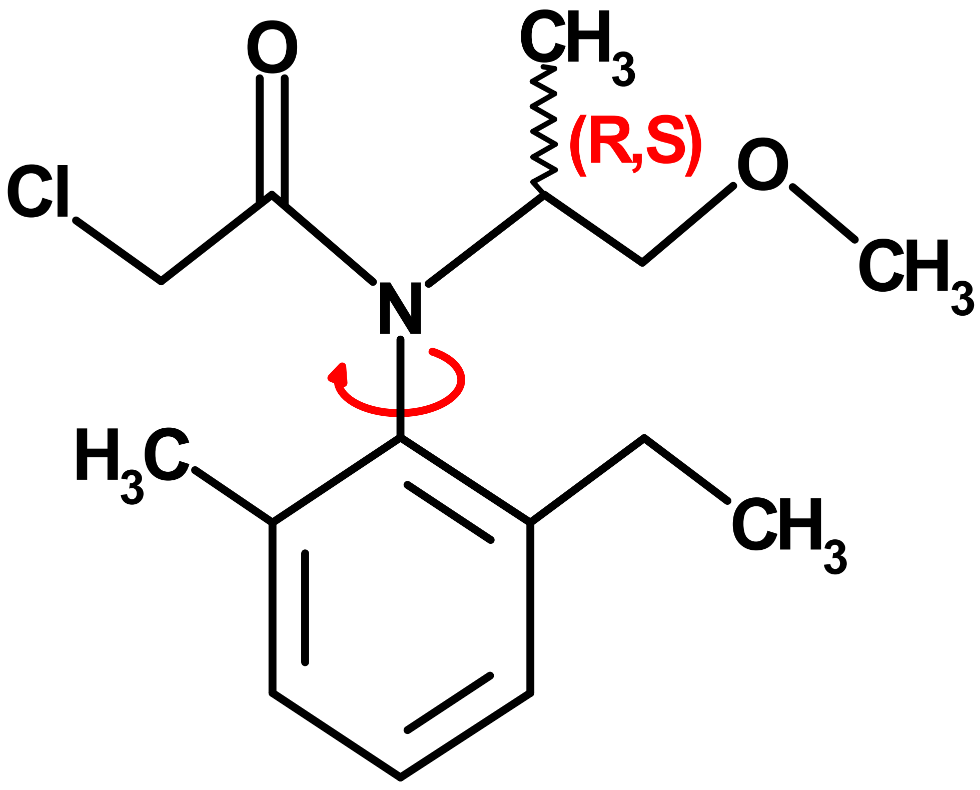
- In Search of the Ideal Catalyst

  “Moving in a Labyrinth (in the Fog)”

- The Technical Process

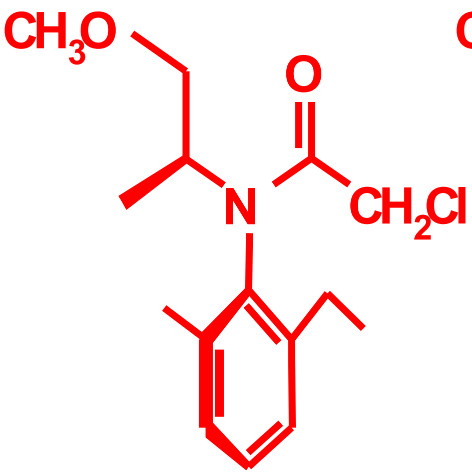
  Ligand Scale-up, Imine Synthesis, Choice of Reactor,

Metolachlor
The Molecule

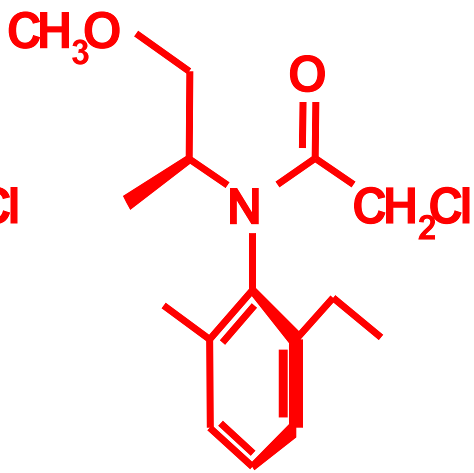


- Herbicide for maize
- > 20’000 t/y
- Only (S)-enantiomers active
  - Ca. 35% less loading for enriched form

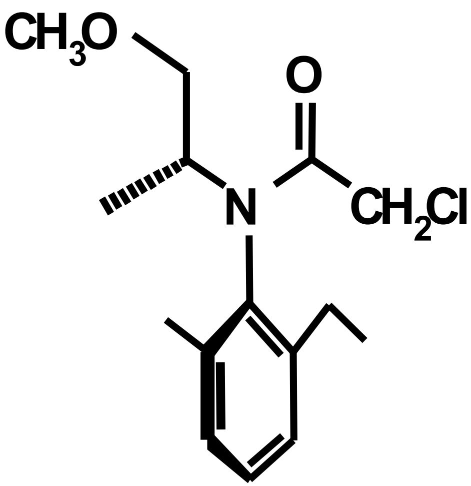
The Four Stereoisomers of Metolachlor



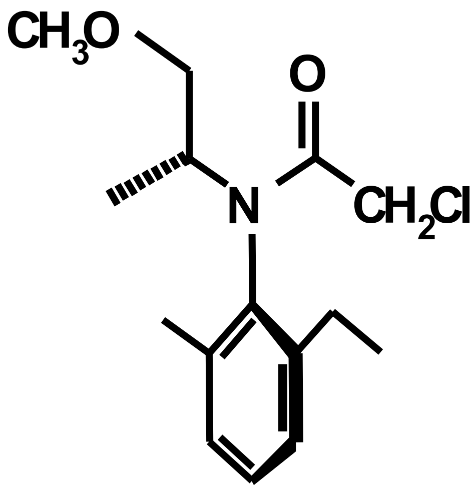
αR,1'S



αS,1'S



αR,1'R



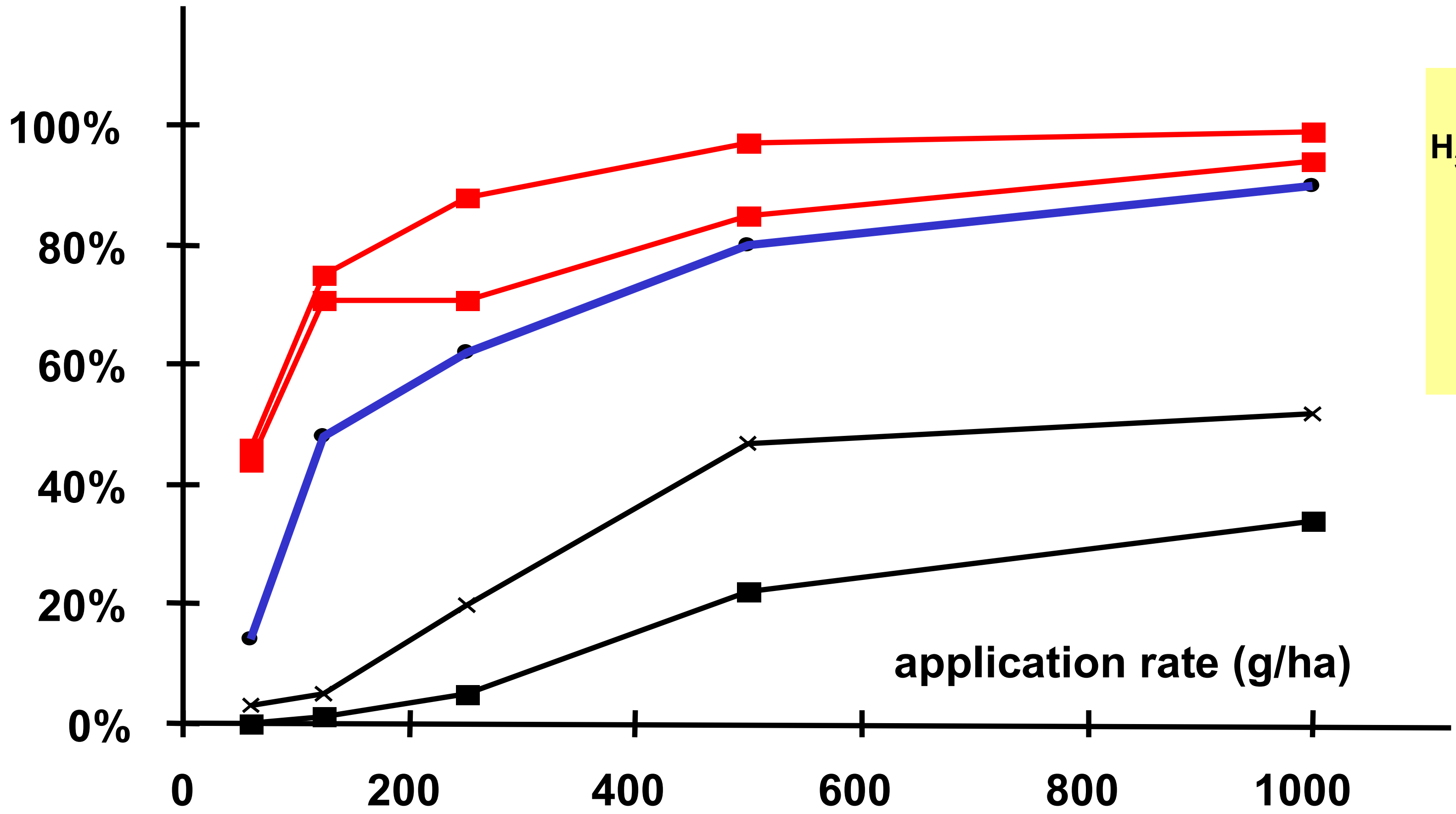
αS,1'R

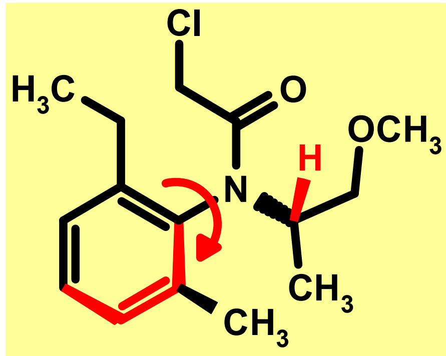
2 active stereoisomers

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

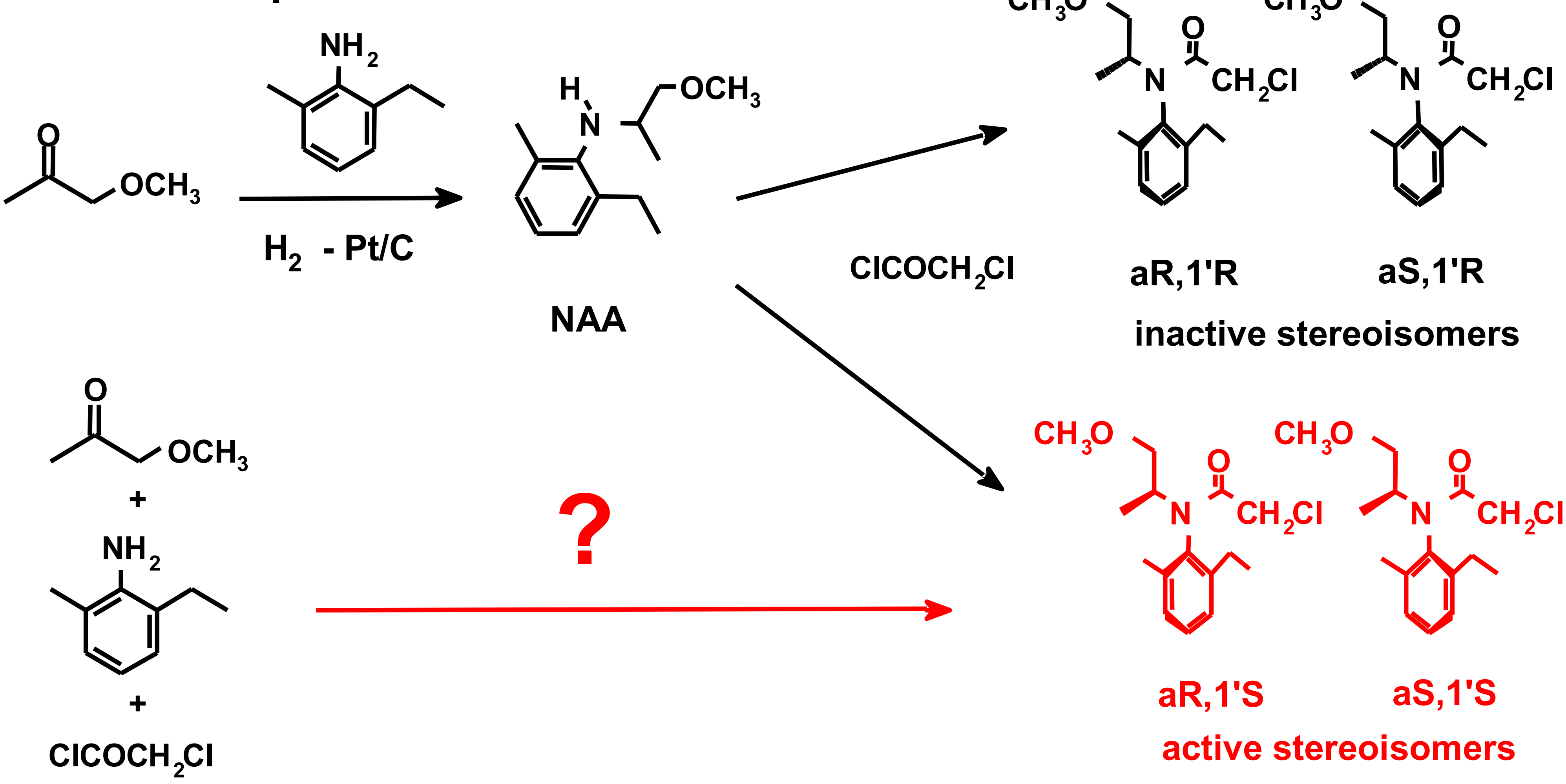
solvias

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

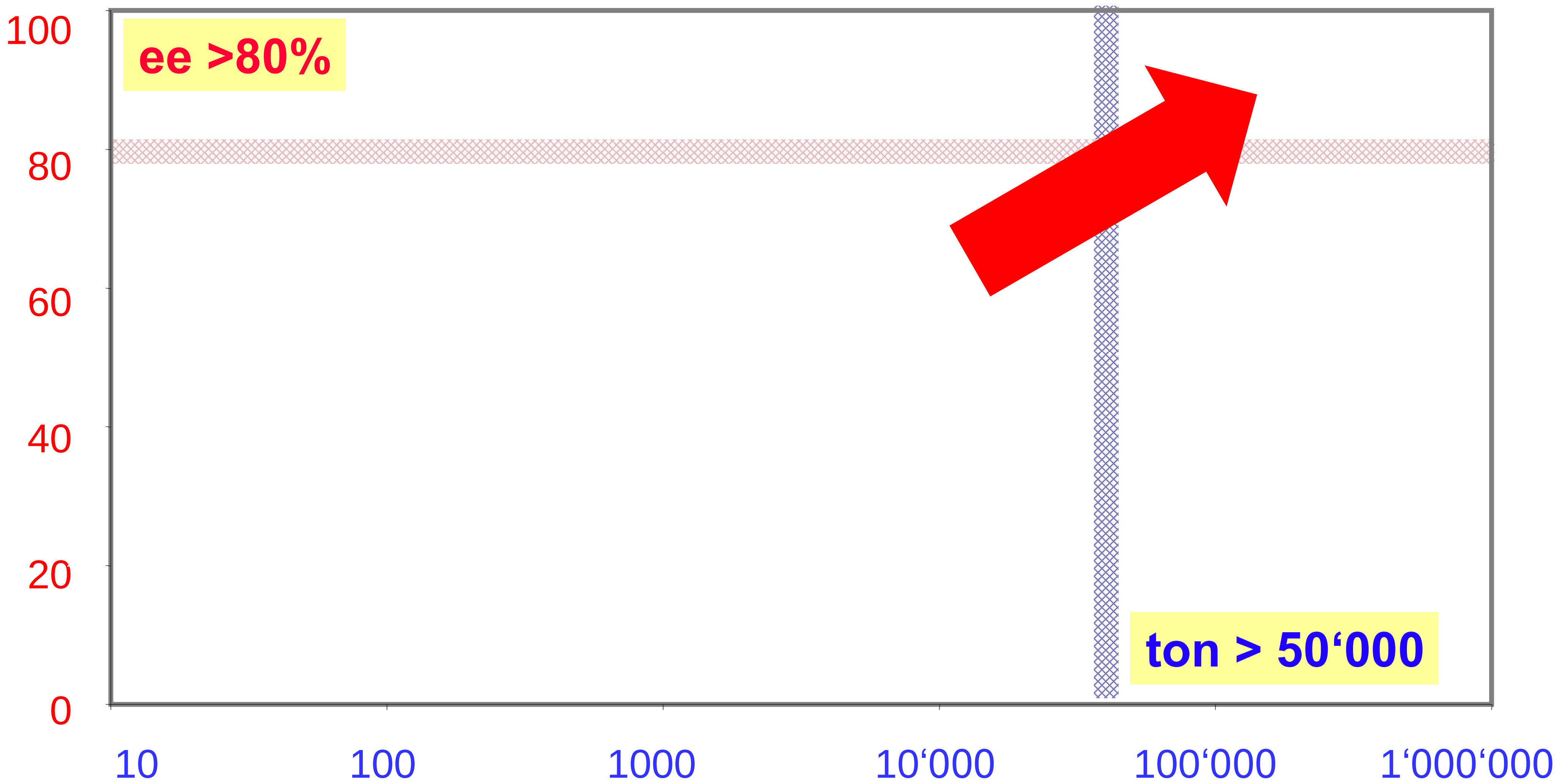


(S)-Metolachlor
The Challenge

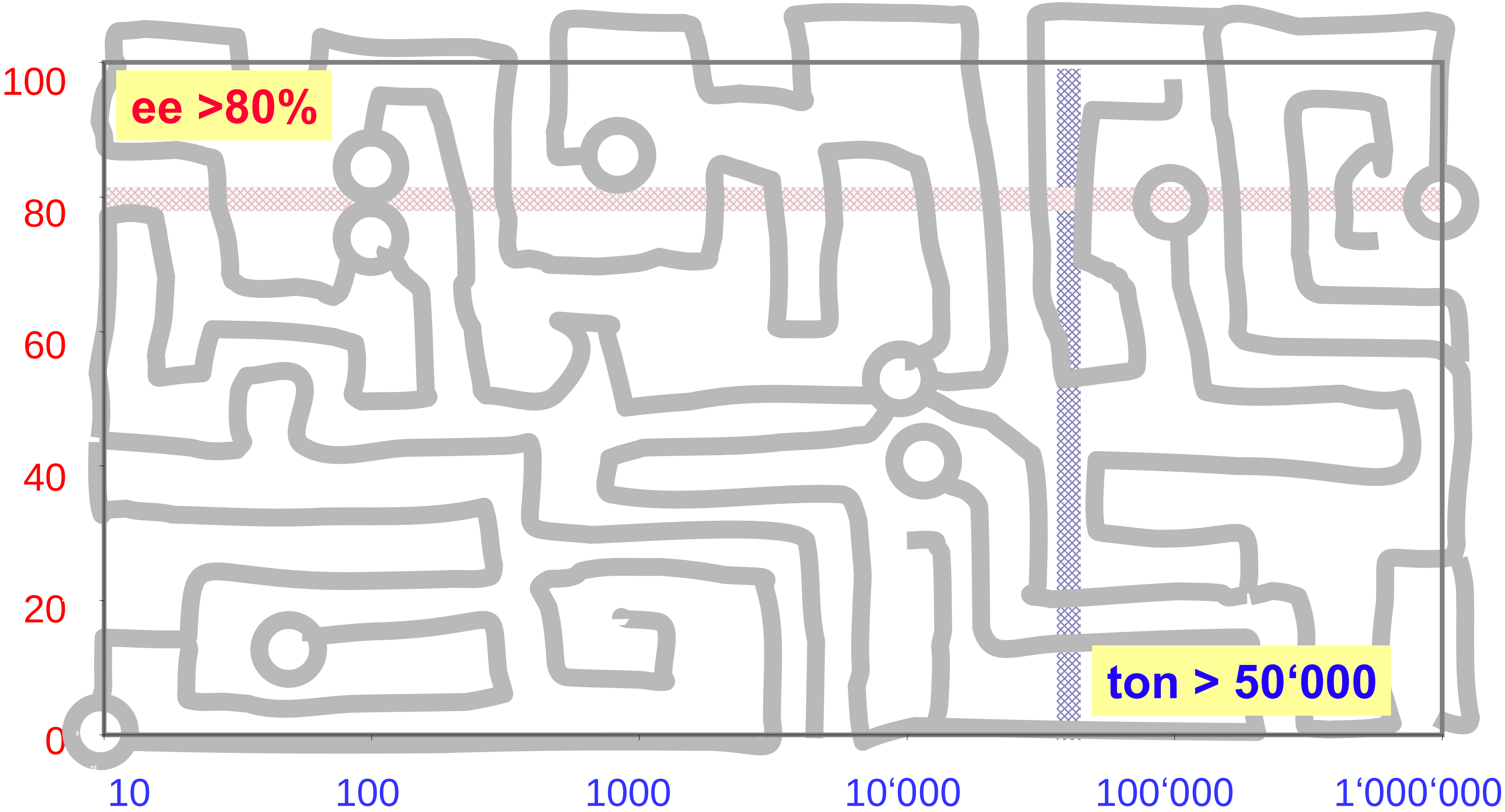
solvias

	Production process	Minimum requirements
Enantioselectivity	-	ee >80%
Catalyst productivity (ton)	>1'000'000 (70 recycles)	>50'000 (s/c ratio)
Catalyst activity (tof)	>4000/h at 50°C, 5 bar	>10'000/h
Space-time yield	very high	high

Moving in the "ee – ton" Space



Moving in the "ee – ton" Space
A Labyrinth!



Development Phases for EPC Synthesis

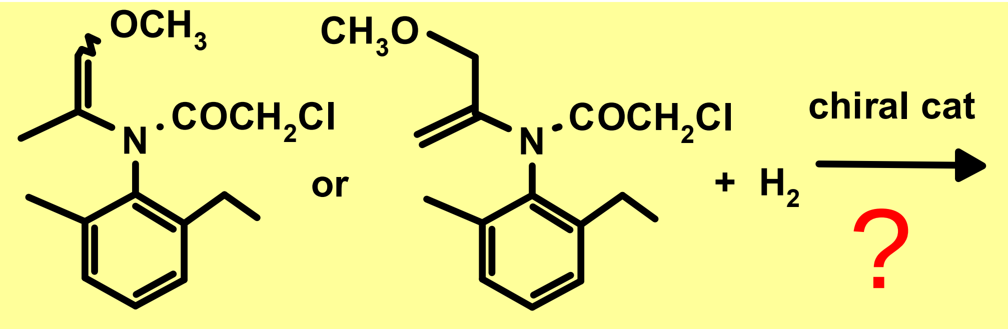
solvias

- **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

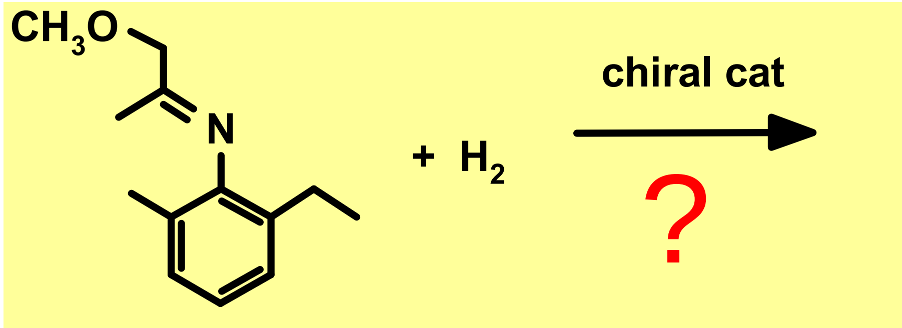
Routes to (S)-Metolachlor

solvias

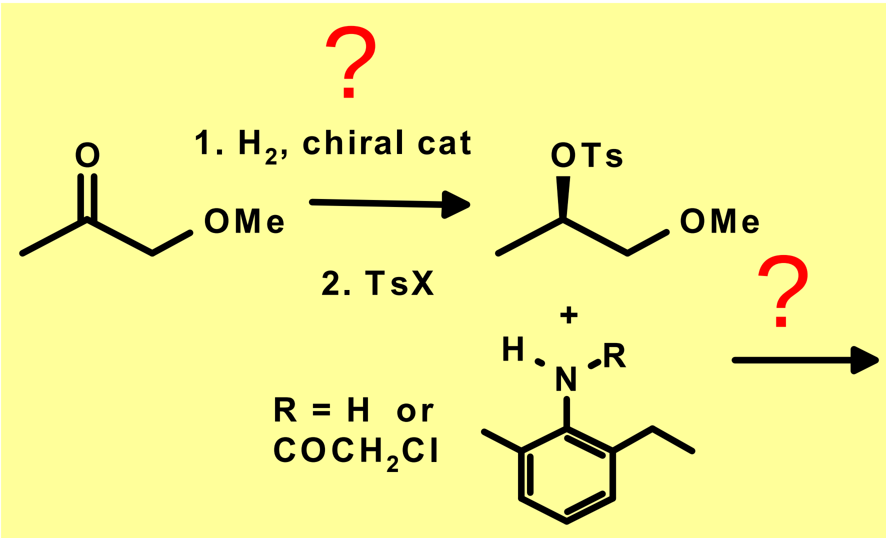
Hydrogenation of enamide (isomers)



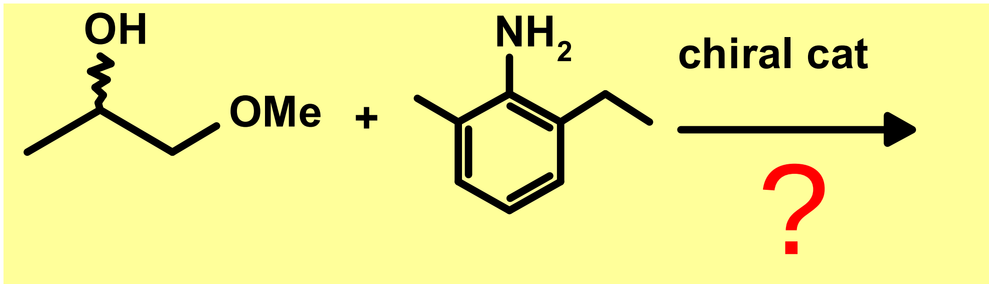
Hydrogenation of imine (isomers)



Hydrogenation / substitution



Direct alkylation



(S)-Metolachlor
Route Assessment

route	catalytic step
enamide	close analogy ee >90%
substitution	weak analogy ee >80%
imine	weak analogy ee <30%
direct alkylation	no precedent

(S)-Metolachlor:
Route Assessment

solvias

route	catalytic step	other steps
enamide	close analogy ee >90%	enamide synthesis difficult
substitution	weak analogy ee >80%	substitution difficult
imine	weak analogy ee <30%	as in current process
direct alkylation	no precedent	as in current process

(S)-Metolachlor: Route Assessment

route	catalytic step	other steps	cost (ecology)	priority
enamide	close analogy ee >90%	enamide synthesis difficult	high (medium)	1
substitution	weak analogy ee >80%	substitution difficult	high (bad)	2
imine	weak analogy ee <30%	as in current process	medium (good)	3
direct alkylation	no precedent	as in current process	low (very good)	4

Development Phases for EPC Synthesis

solvias

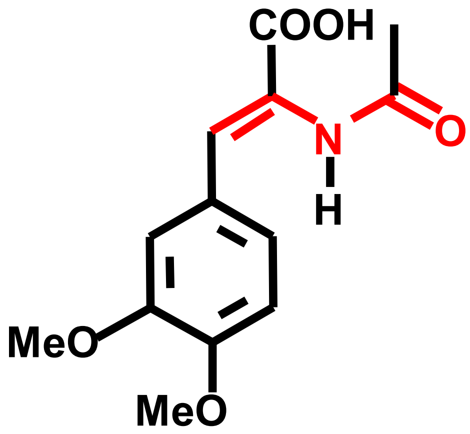
- **Phase 1:** Design and assessment of synthetic routes
- **Phase 2: Demonstrating chemical feasibility**
- **Phase 3:** Optimizing the key (catalytic) reaction(s)
- **Phase 4:** Optimizing the over-all process

The Enamide Route

The Analogy

L-Dopa
Rh-dipamp

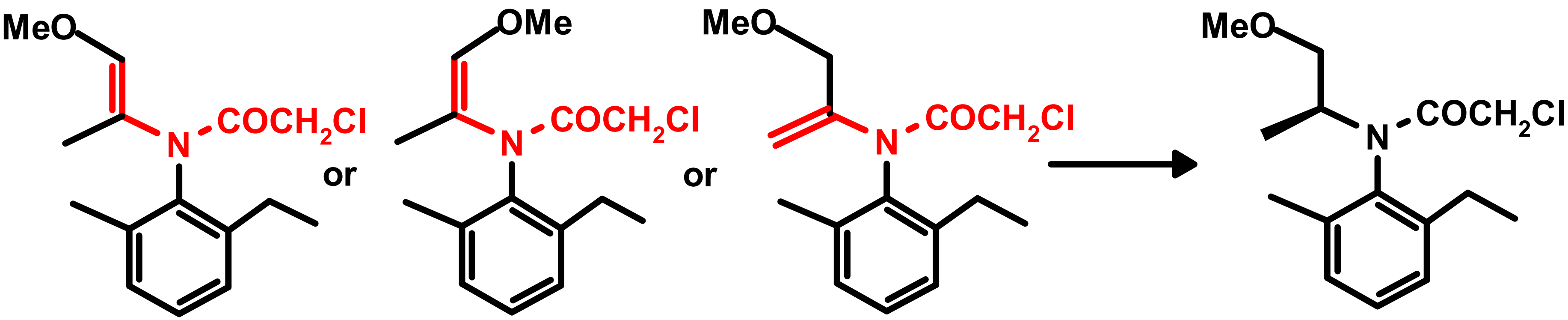
(Monsanto)



ee 96%
ton 10‘000

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

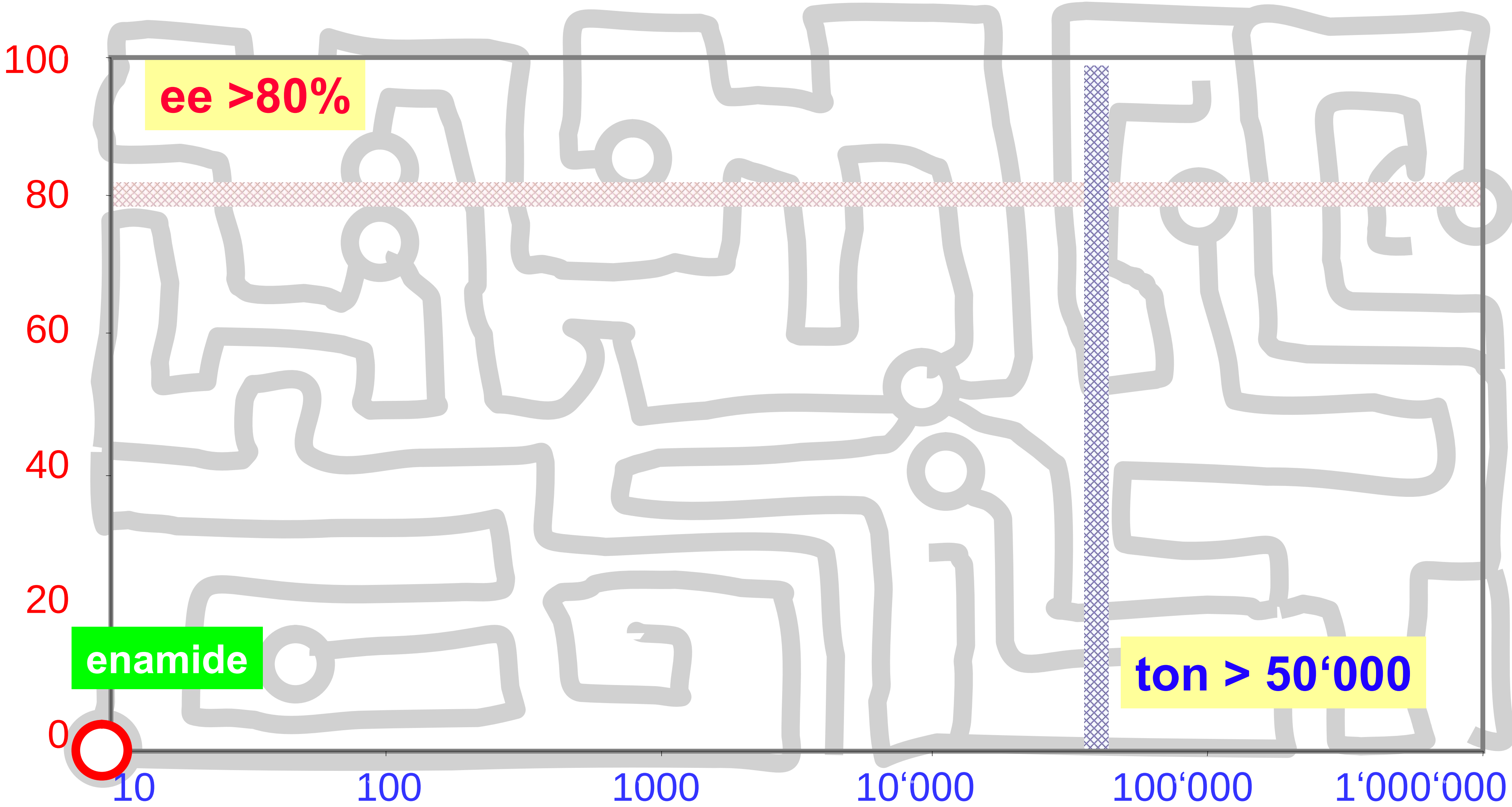
NO activity at all!!



H.U. Blaser, F. Spindler 1983

From Dream to Process
Important Milestones (1983)

solvias

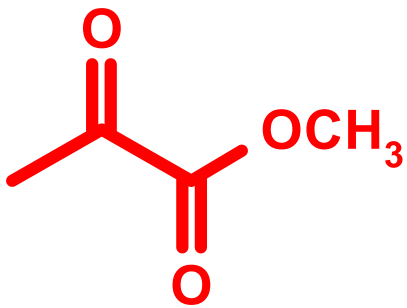


Substitution Route
Heterogeneous Hydrogenation

solvias

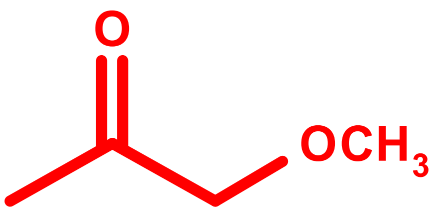
<u>The Analogy</u>: Pt/Al_2O_3-Cinchonidine

(Orito, 1979)

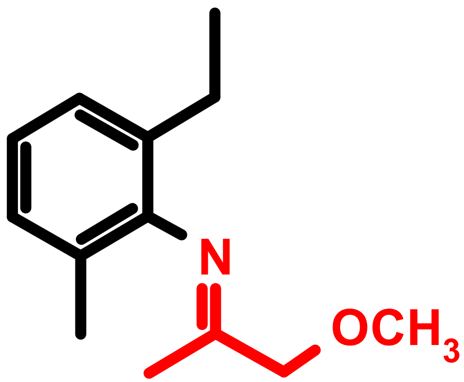


ee >85%

<u>The Result</u>: Pt/Al_2O_3-Cinchonidine



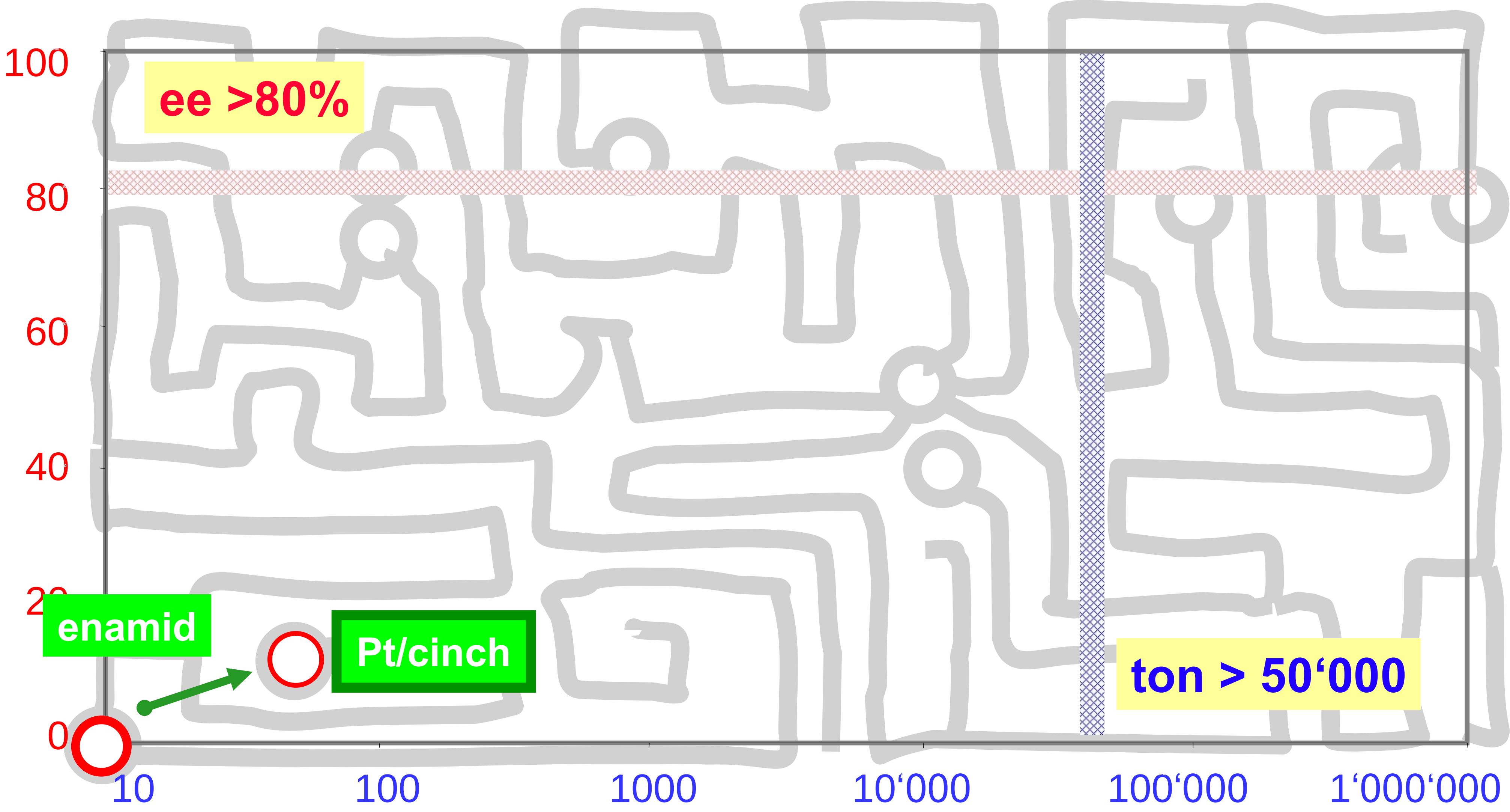
activity ok
ee 12%!!



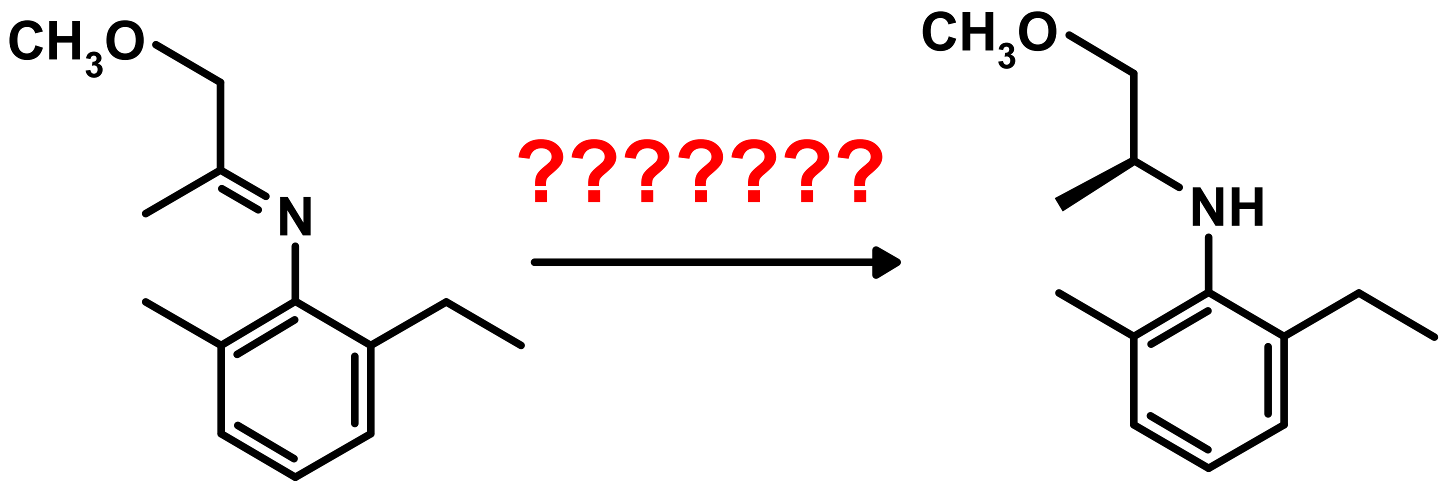
ee 0%!!

H.U. Blaser, H.P. Jalett 1983

From Dream to Process
Important Milestones (1983)

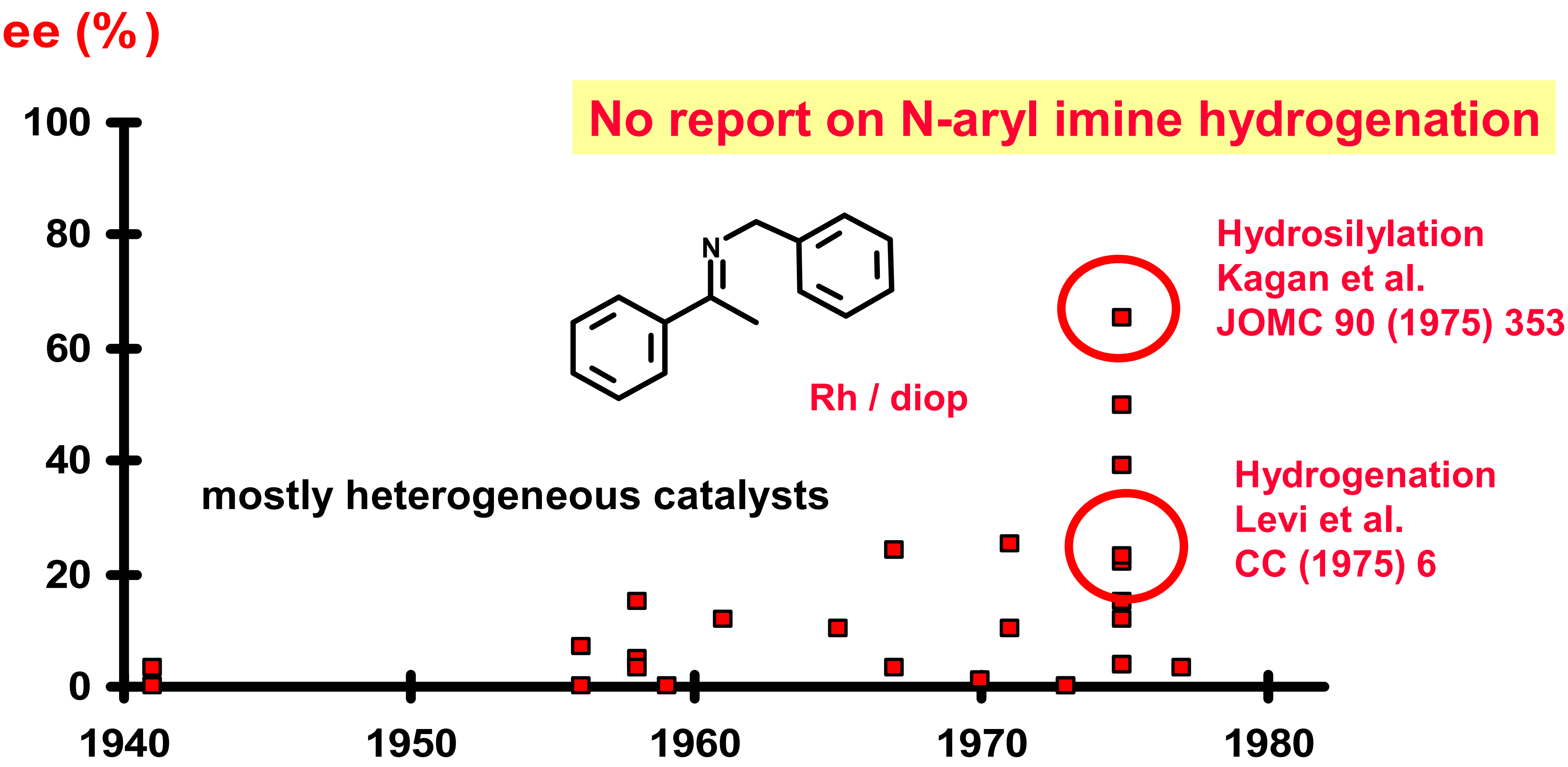


Imine Hydrogenation



Enantioselective C=N Reduction
State of the Art Around 1982

solvias



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.)**

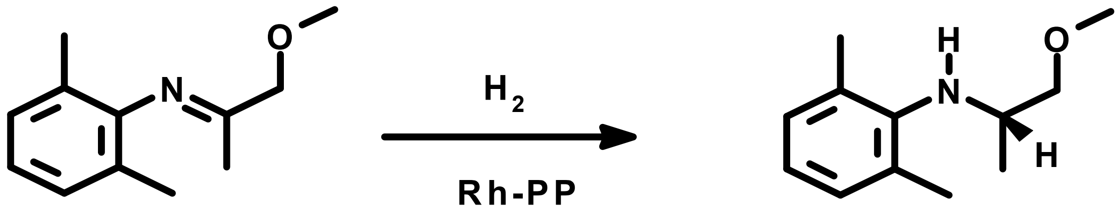
Search for a catalyst

• **ULP Strasbourg (J.A. Osborn)**

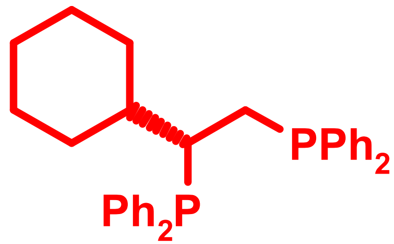
Investigate Ir-diphosphine catalysts (active species, deactivation behavior)

UBC: Rh-Cycphos
A First Success

solvias



DMA-imine

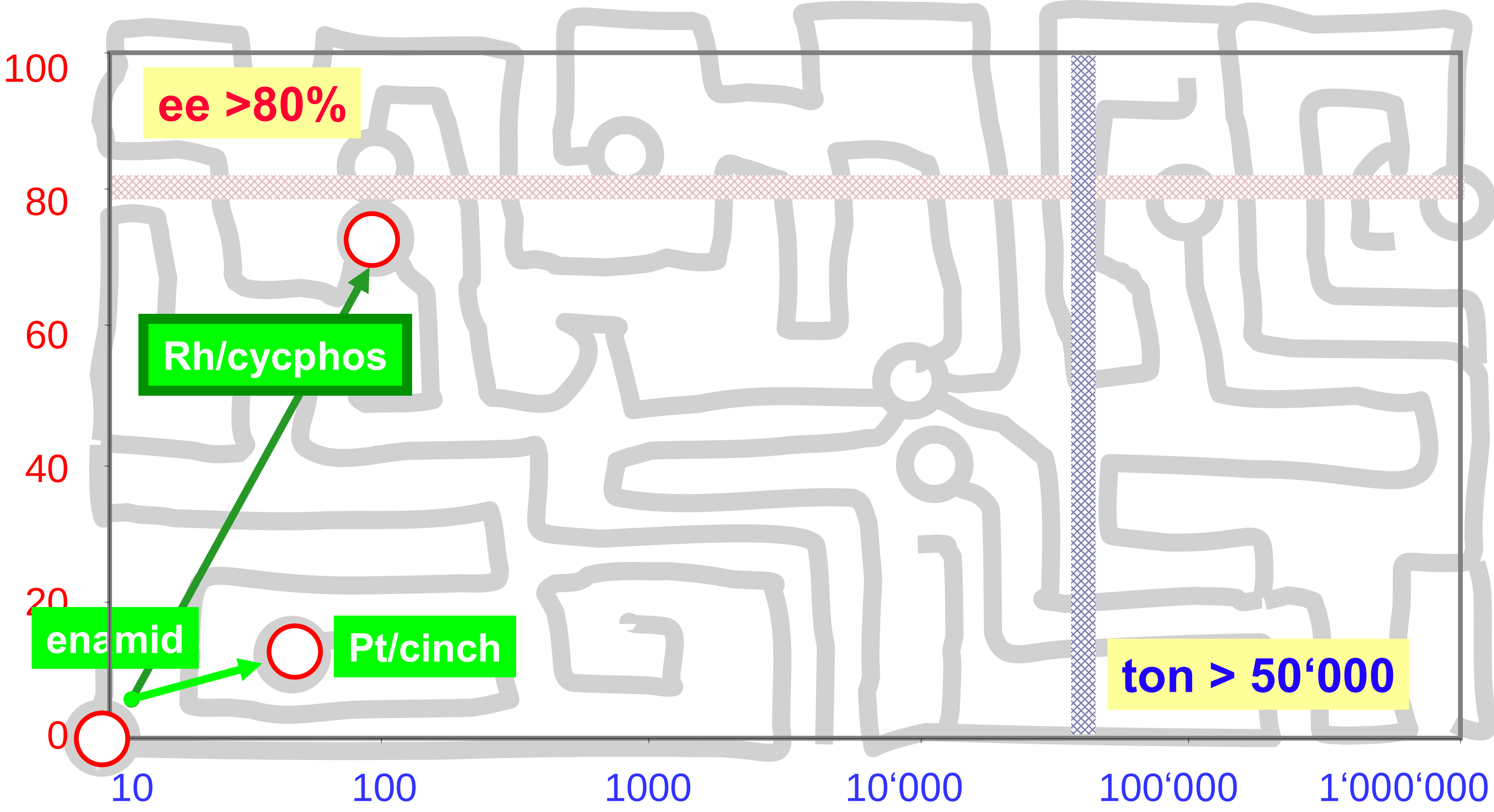


(R)-cycphos

s/c	Temperature [°C]	t [hrs.]	Conv. [%]	tof [h^{-1}]	ee [%]
100	20	44	99	2.3	53
100	-10	20	100	5	69
1000	-10	168	67	4	69
100	-25	70	100	1.4	73

Cullen, Fryzuk, James, Kutney, et al. UBC Vancouver 1984-89

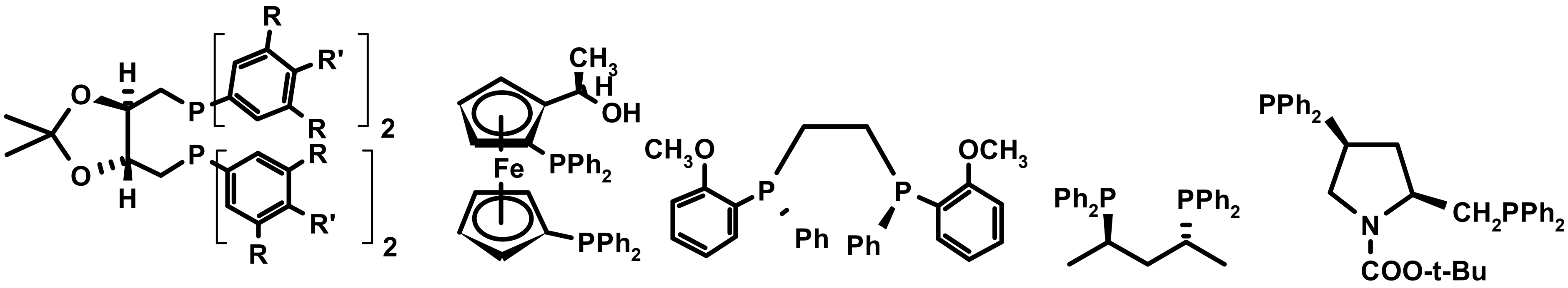
From Dream to Process
Important Milestones (1985)



New Idea: Ir - P^P Complexes

Ligand	tof (4h)	tof (24h)	ee
diop	165	32	61
subst-diop	89-146	28-32	56-61
bppm (tBuOMe)		6	79
bppm (MeOH)		30	6
dipamp		19	7
bppfoh		21	28
bdpp	114	26	78
*p*N(Me)$_2$-bdpp		31	rac

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

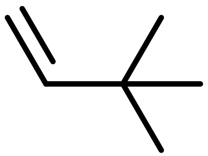
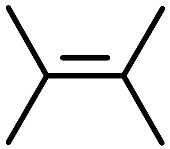


substituted diop   bppfoh   dipamp   bdpp (skewphos)   bppm

F. Spindler 1986

Why Iridium?

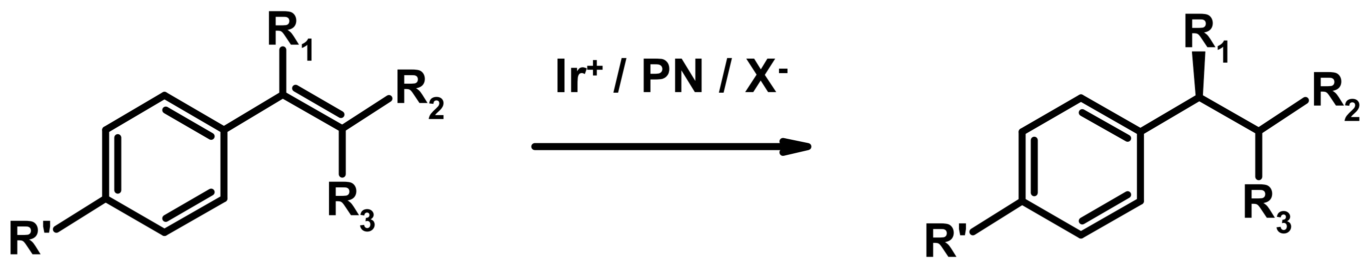
$[Ir(cod)(py)(Pcy_3)]PF_6$: Extremely active catalysts for olefin hydrogenation

Olefin	maximum tof (1/h)
	6400
	8300
	4000

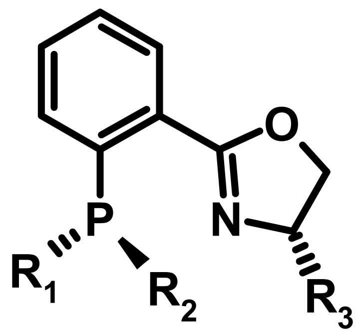
Drawback: Very fast deactivation via dimerization

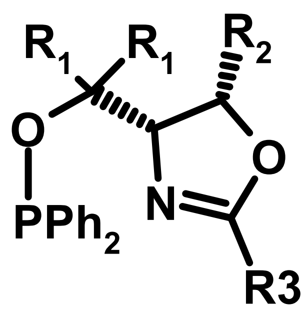
R. Crabtree et al. J. Organomet. Chem. 141 (1977) 205

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



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

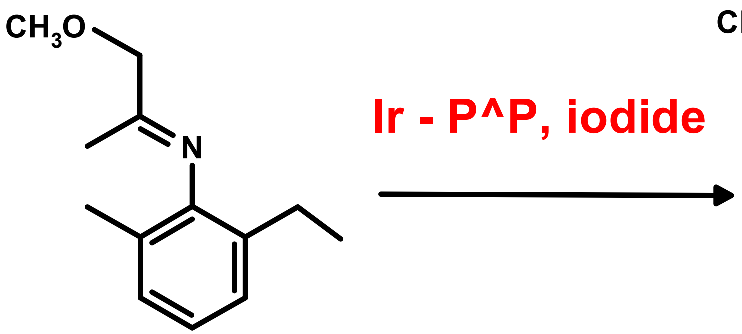


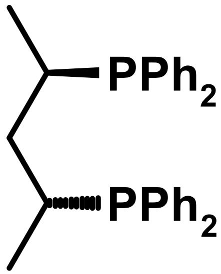


A. Pfaltz

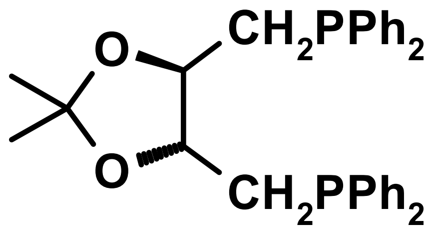
Review: A. Pfaltz, W.J. Drury, Proc. Nat. Acad. Sci. USA 101 (2004) 5723

Iridium: Best Results after Optimization





bdpp



diop

bdpp	ee 84%	ton 100	(at 0°C)
diop	ee 52%	ton 10'000	(at 30°C)

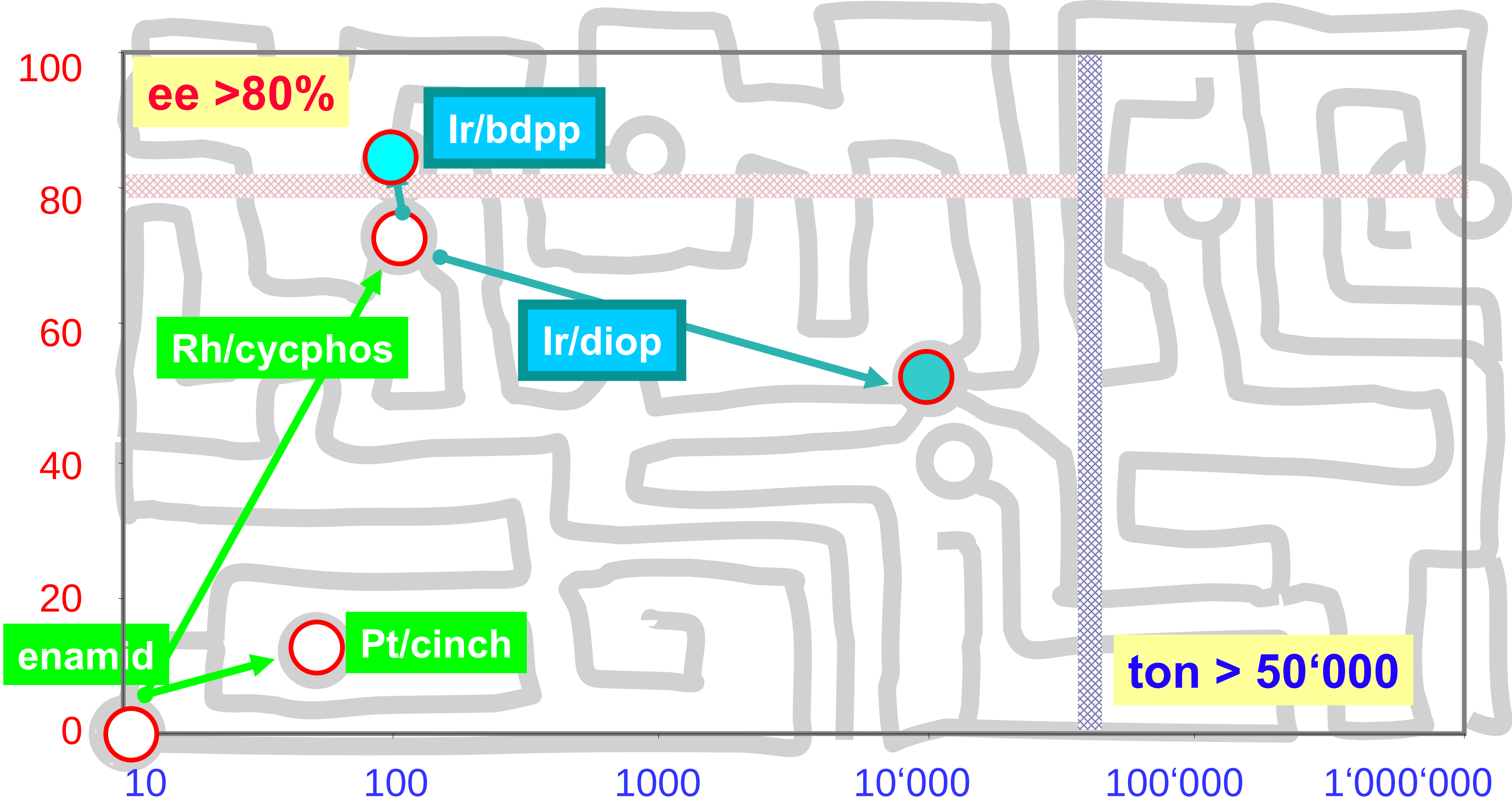
PROBLEM

CATALYST DEACTIVATION

(Dimerization??)

F. Spindler, B. Pugin 1986

From Dream to Process
Important Milestones



Fighting Catalyst Deactivation

Understanding

- Nature of active species: Collaboration with JAO

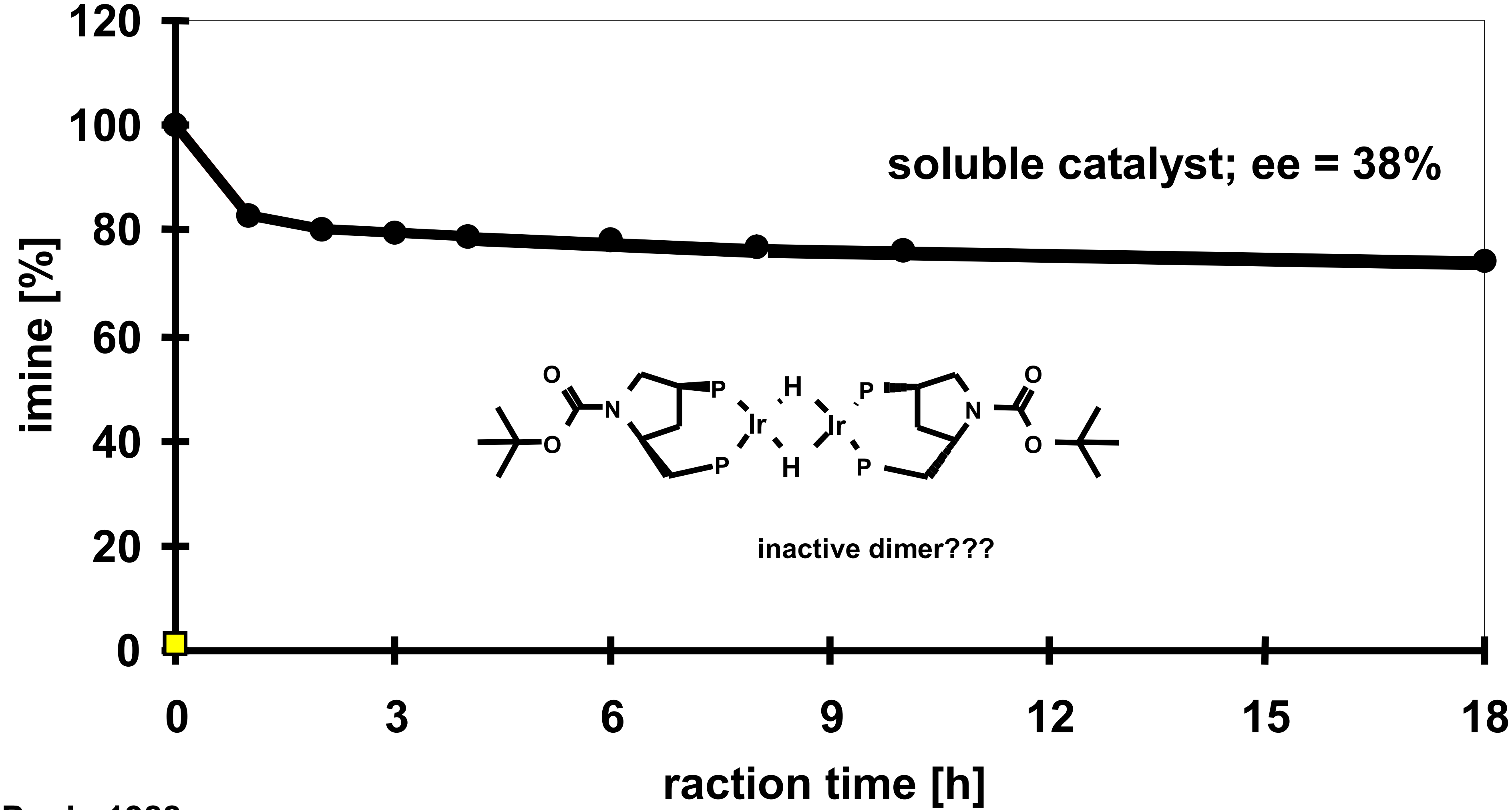
Stabilizing Additives

- Avoid dimerization by complexation

Immobilization

- Avoid dimerization by “site-isolation”

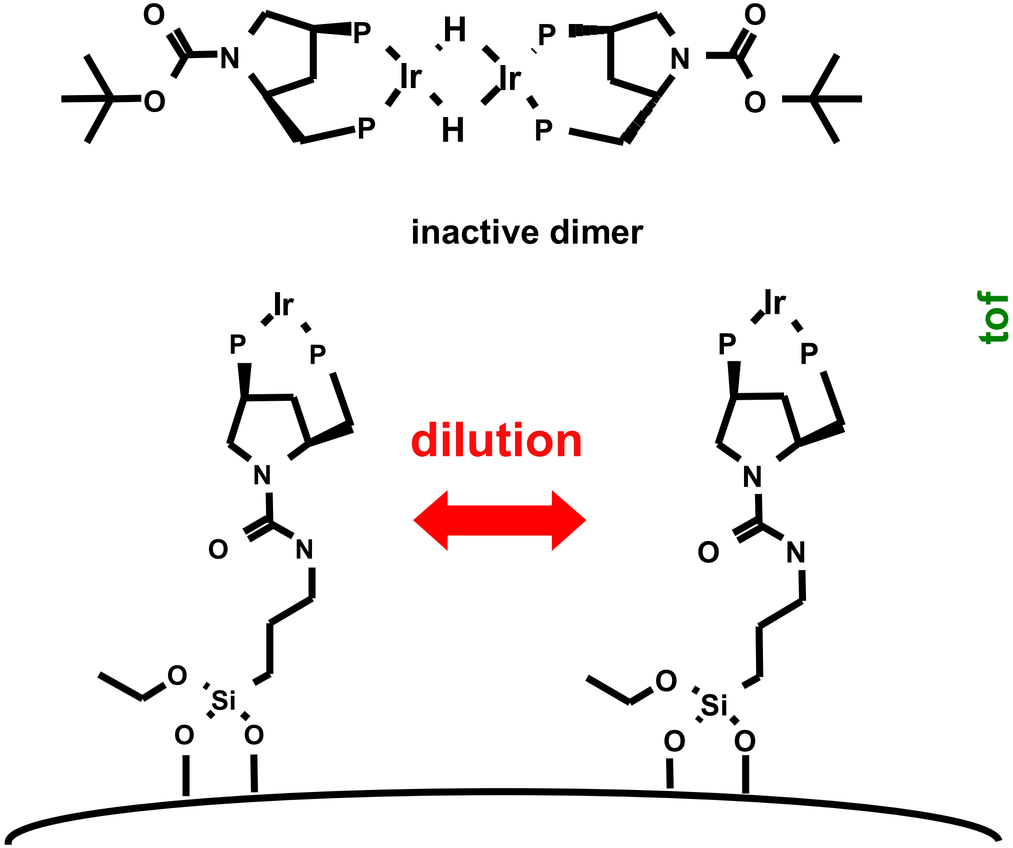
Fighting Deactivation
Immobilization of Ir - bppm

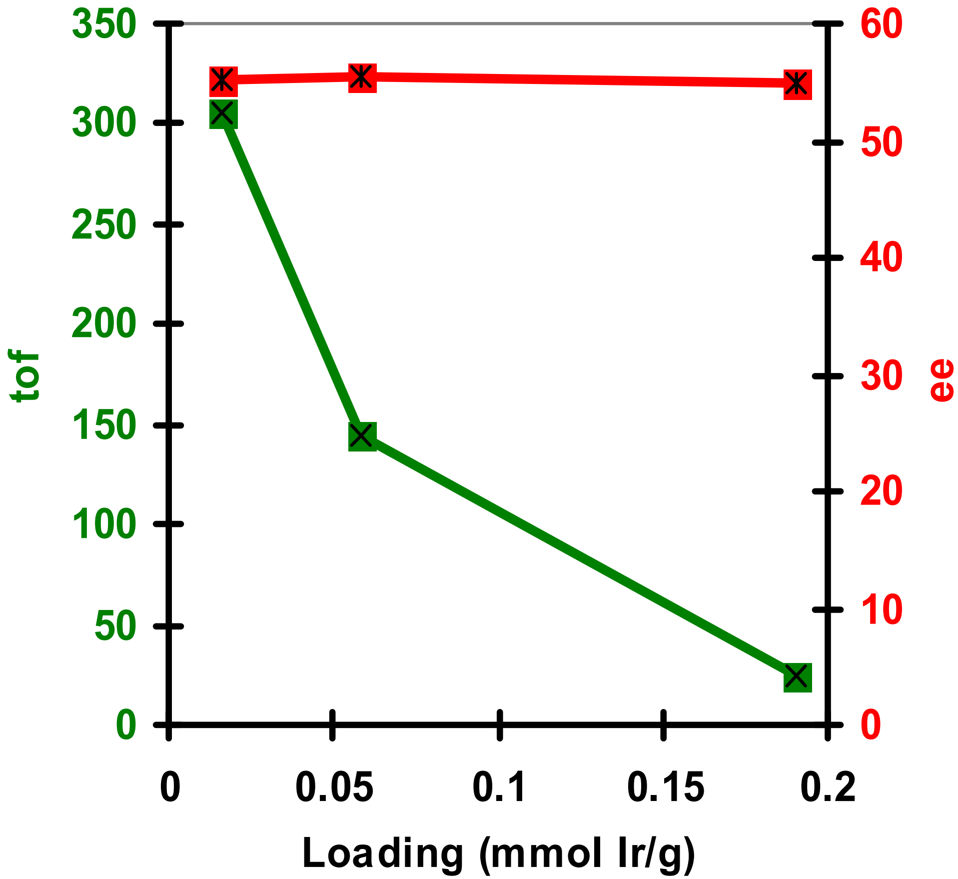


B. Pugin 1988

Fighting Deactivation
Immobilization of Ir - bppm

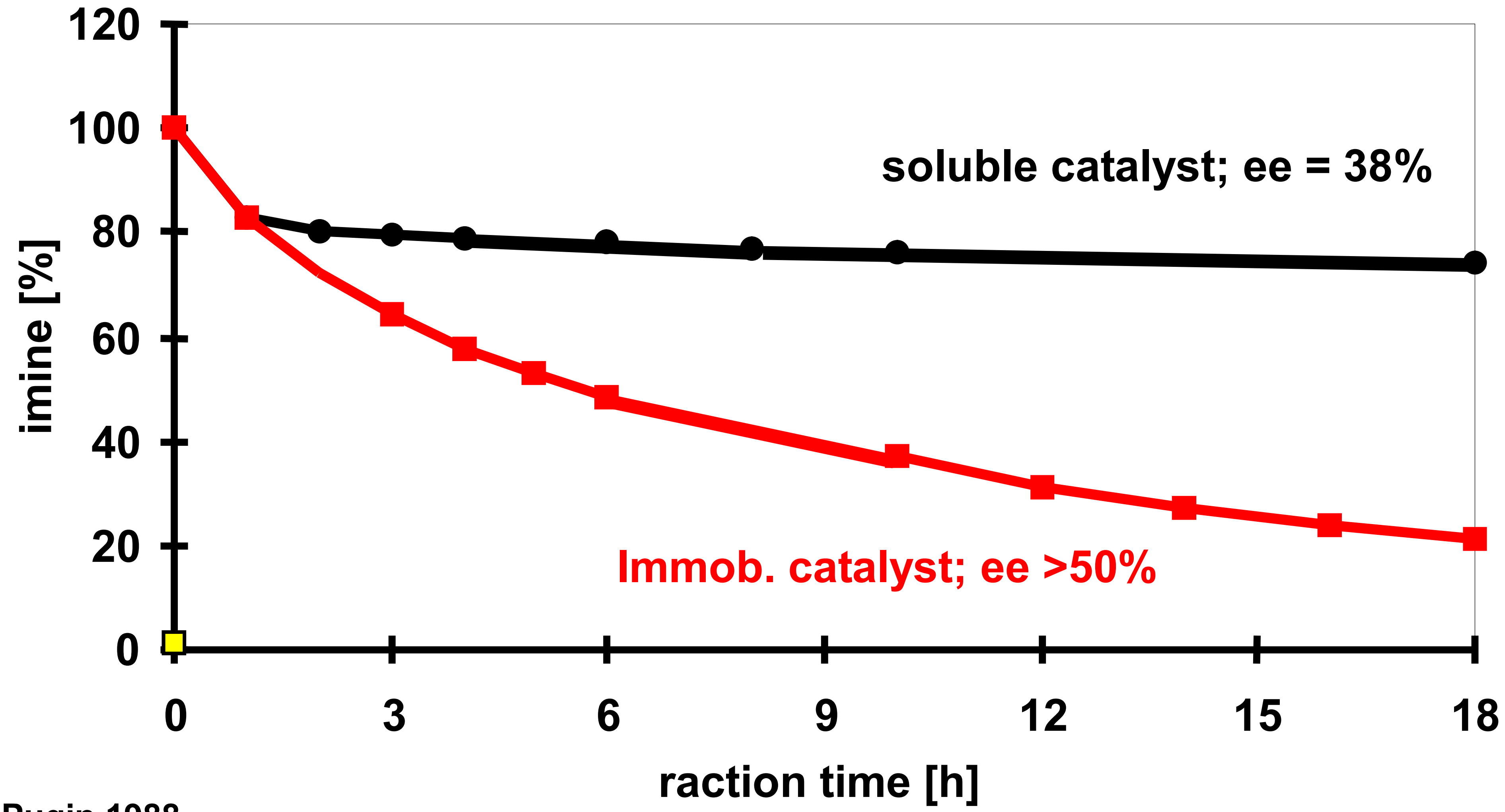
solvias





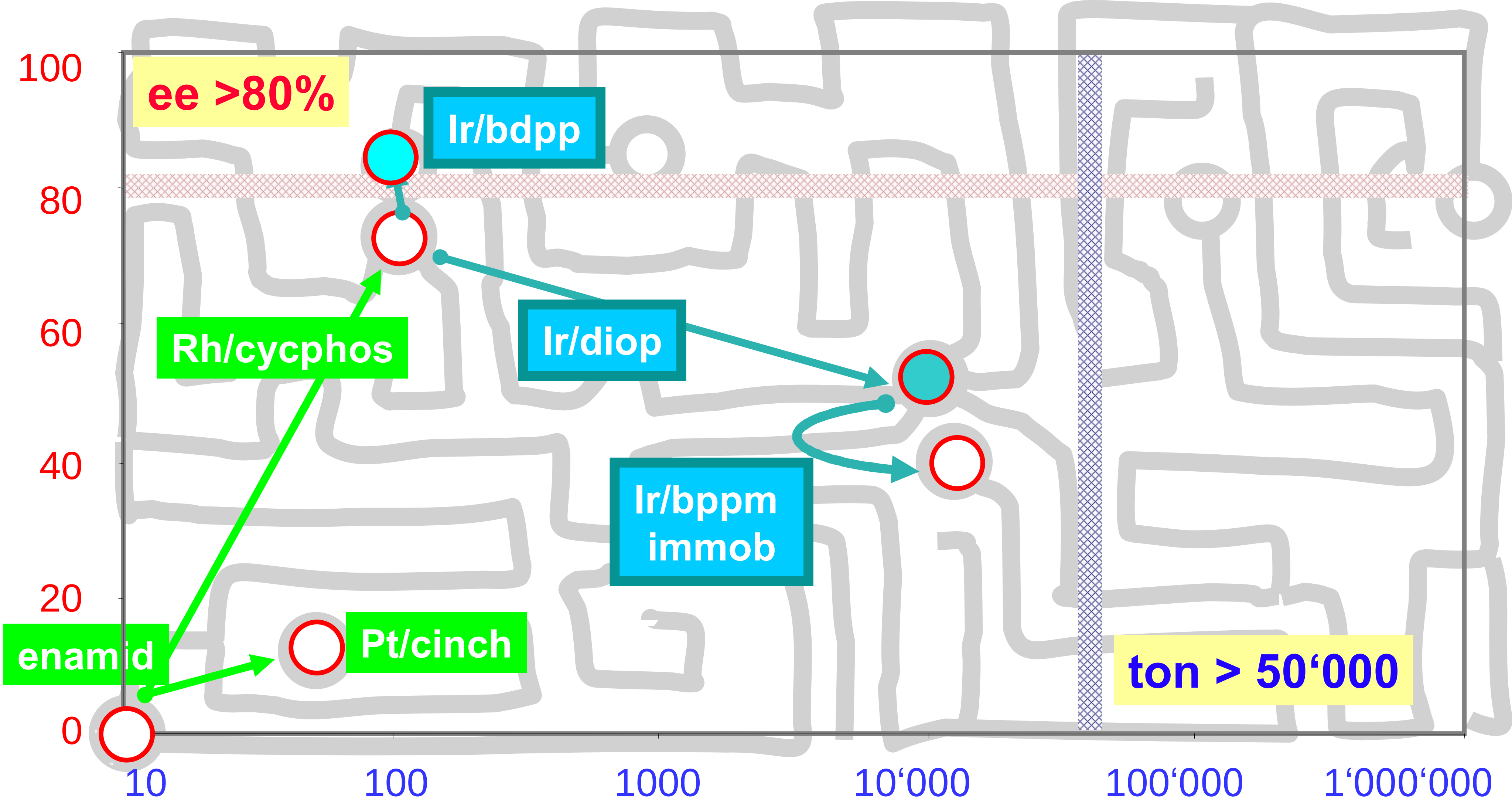
B. Pugin 1988

Fighting Deactivation
Homogeneous Ir – bppm Catalyst



B. Pugin 1988

From Dream to Process
Important Milestones



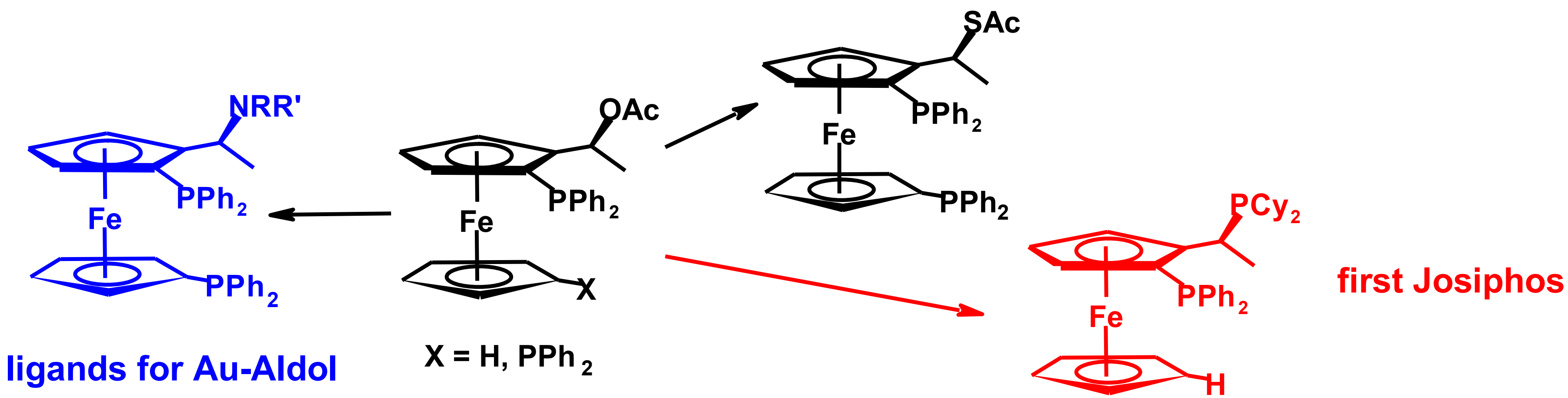
Intermezzo 1988-1992

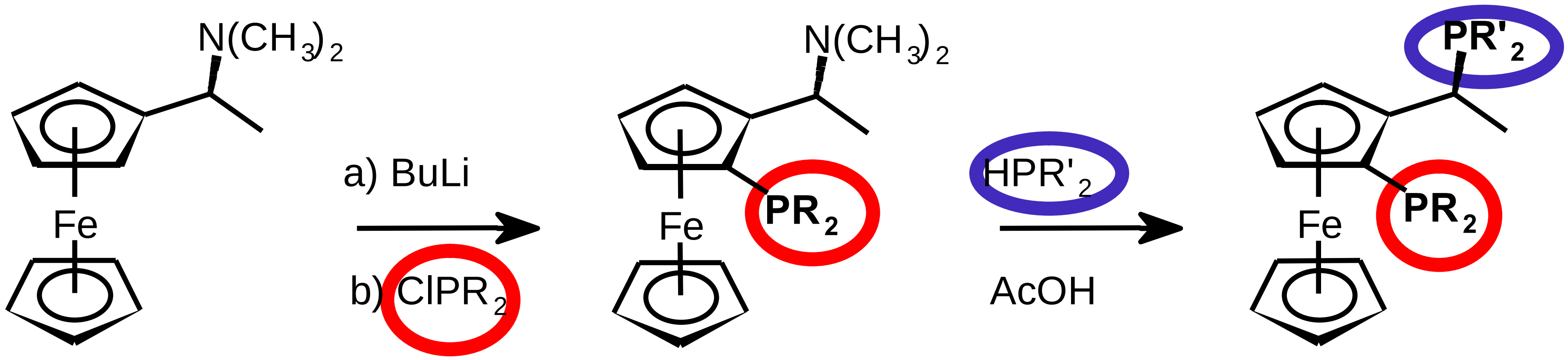
solvias

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



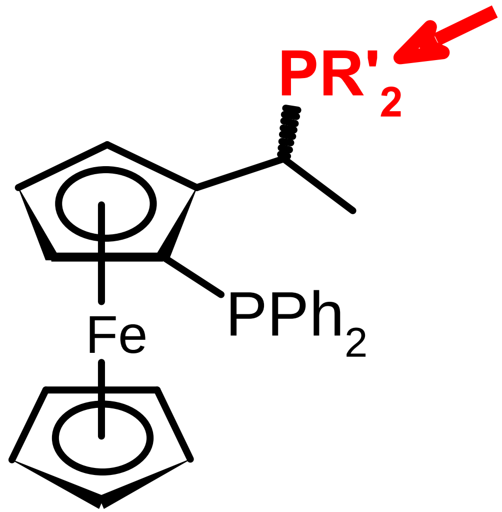


➢ **Modular, tunable ligands**

A. Togni, F. Spindler, B. Pugin

The Final Breakthrough
Ir – Xyliphos / AcOH / Iodide

<u>Best results</u> (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

solvias

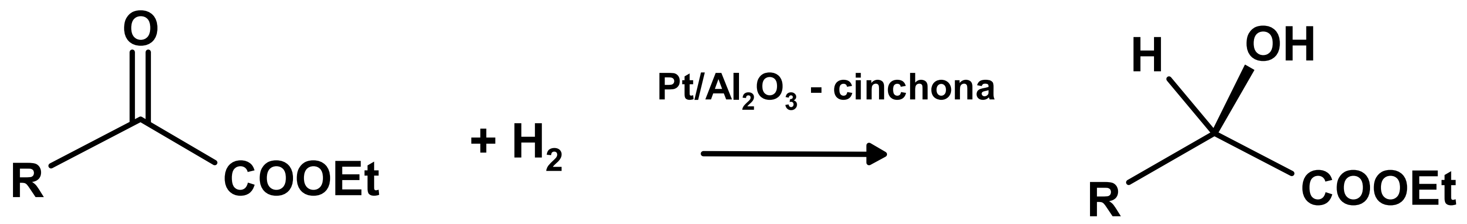
Solvent	t (100%) (h)	initial rate	ee
thf	7	0.3	74
CH_2Cl_2	4	0.3	74
$(CH_3)_3COCH_3$	12	0.2	75
acetone	6	0.4	73
toluene	12	0.4	73
i-PrOH	0.75	1.1	79
t-BuOH	1	1.0	77
CH_3COOEt	8	0.7	72
none	10	0.3	73
CH_3COOH	0.5	1.5	79

Reaction conditions: MEA-Imine; *s/c*: 800; 150 mg TBAI; solvent: 2 ml; 25 bar H_2; 30°C.

H.P. Jalett, F. Spindler

Why Acetic Acid

solvias



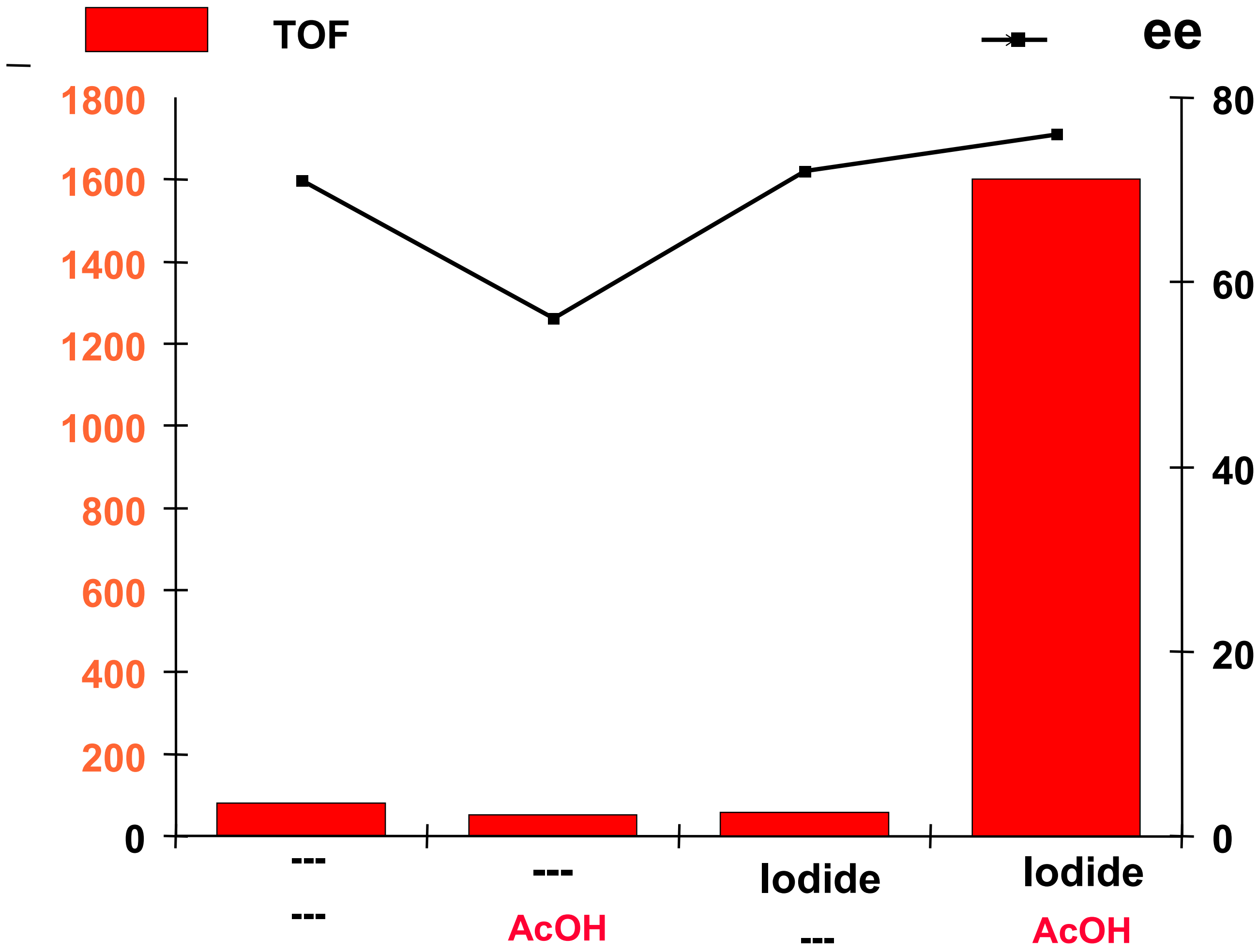
R = CH_3 and $PhCH_2CH_2$

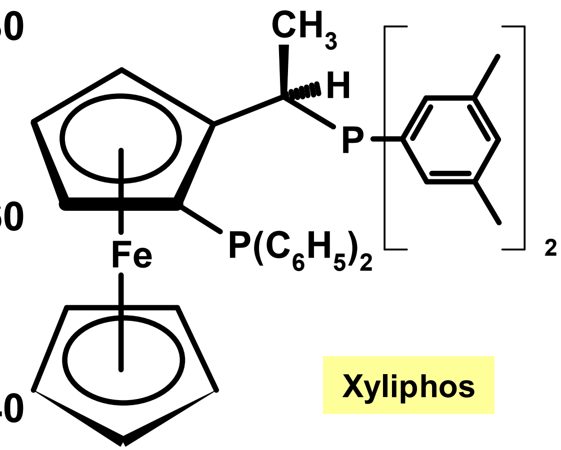
R-hydroxyester

solvent	ee
EtOH	82%
toluene	87%
acetic acid	92-94%

H.P. Jalett, H.U. Blaser, Wiehl 1991

Ir - Xyliphos
Effect of AcOH and I^-





Xyliphos

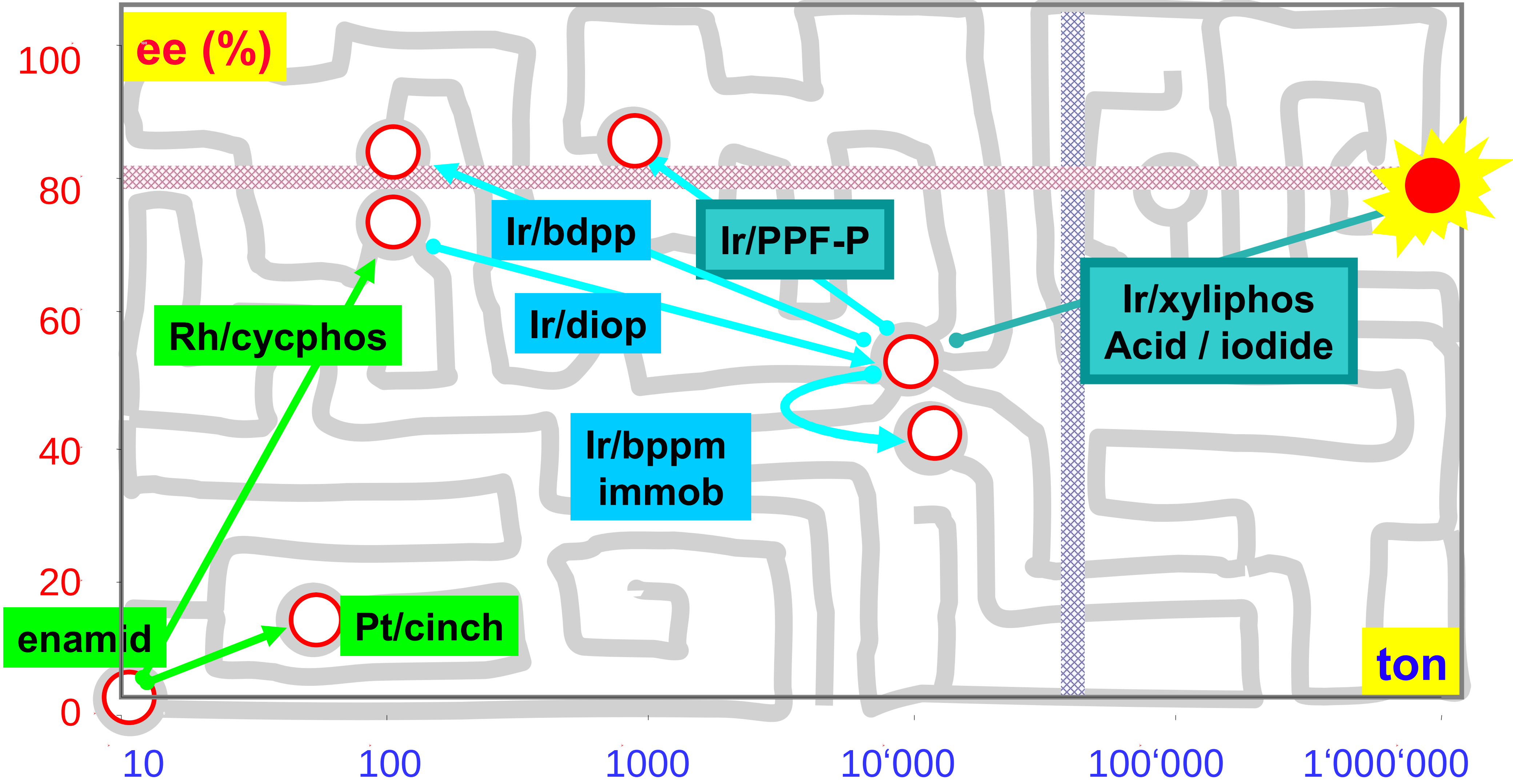
<u>General acid effect:</u>

- **CF_3COOH**
- **H_2SO_4**

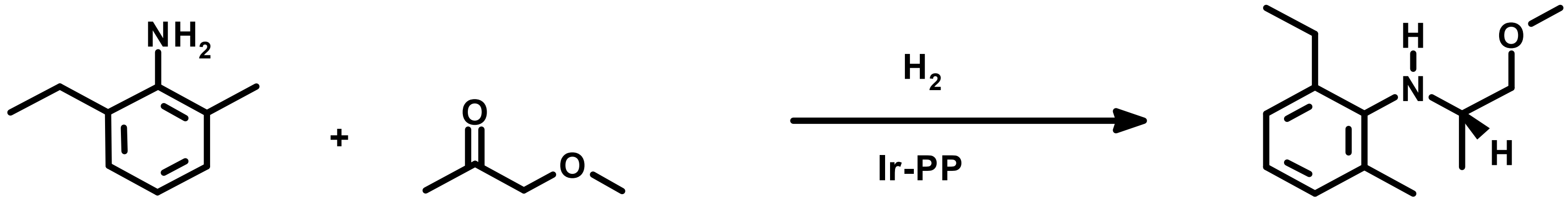
H.P. Jalett, F. Spindler 1993

From Dream to Process
Important Milestones

ee	≥80%
ton	>50‘000
tof	>10‘000/h



Reductive Alkylation of MEA
Ir-xyliphos, AcOH: Solvent Effect



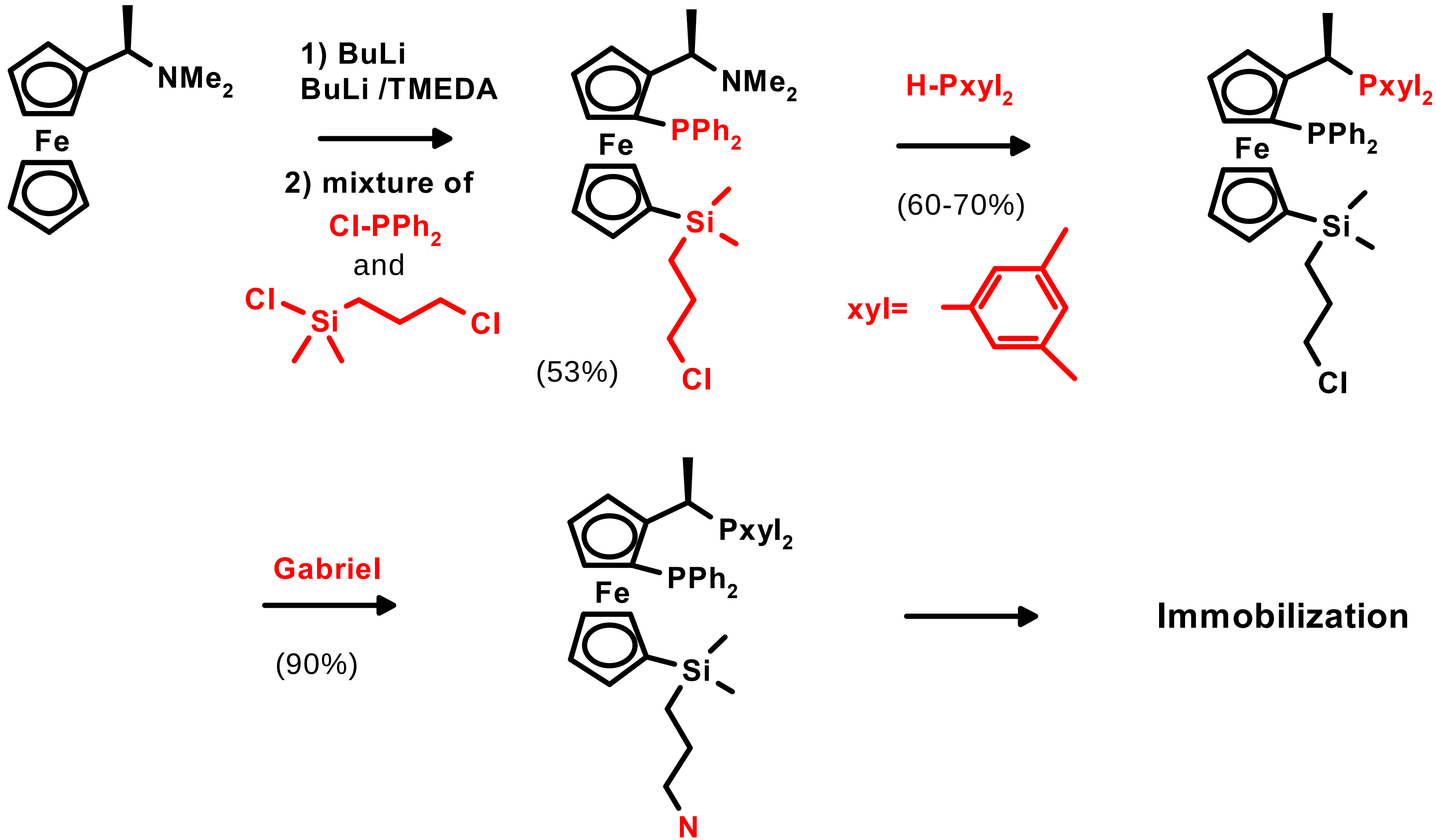
MEA MOA ***s/c* 10'000** *S*-NAA

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

Reaction conditions: 0.1 mol MEA; 0.12 mol MOA (dry); AcOH: 2.5 ml; 20 mg TBAI; 80 bar H_2; 50°C.

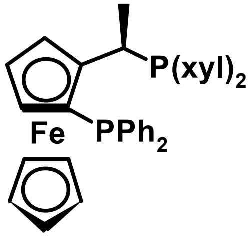
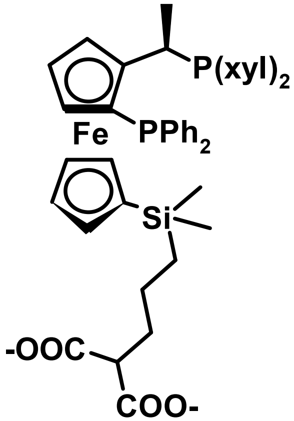
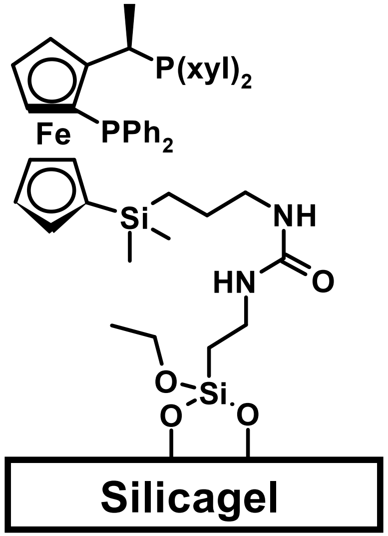
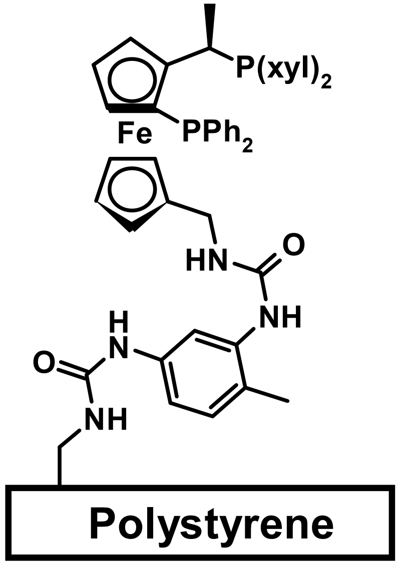
H.U. Blaser, H.P. Jalett

Functionalization of Xyliphos



B. Pugin, H. Landert 1995

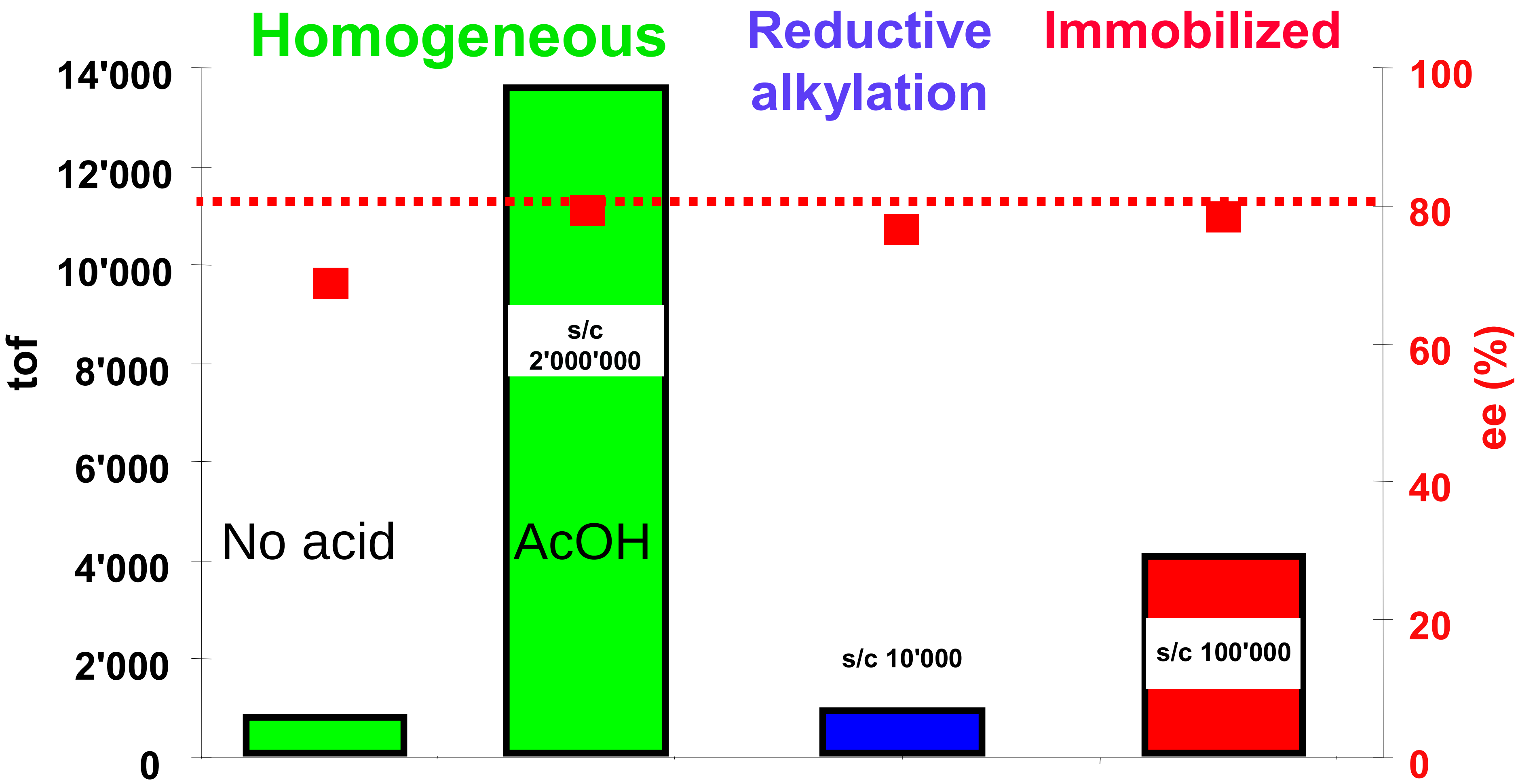
Metolachlor: Recycling??

	homogeneous			heterogeneous		
	free		extractable	immobilized silicagel		immobilized polystyrene
						
S/C	50'000	120'000	120'000	50'000	120'000	50'000
time	1h	2.1h	3h	8h	10h	30h
ee	79%	80%	79%	78%	78%	74%
separation	distillation		extraction > 90%	filtration 95%		filtration 95%

B. Pugin, H. Landert, F. Spindler, H.U. Blaser, Adv. Synth. Catal. 344 (2002) 974

Hydrogenation of Imine
Best Ir / Xyliphos Systems

solvias



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

Development Phases Metolachlor Imine Route

solvias

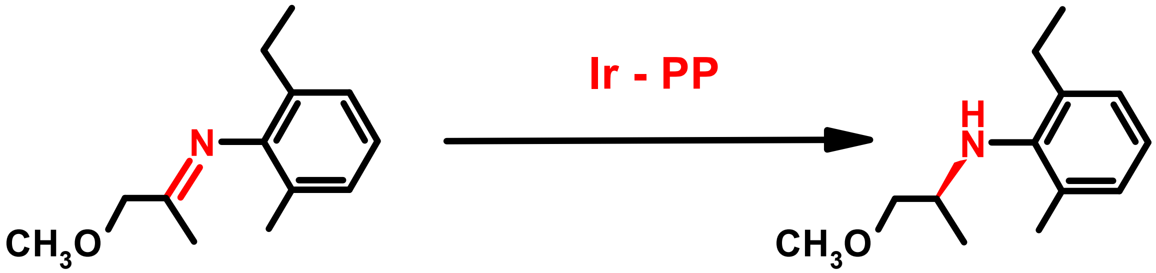
- **Phase 1:** Assessing synthetic routes
- **Phase 2:** Demonstrating chemical feasibility
- **Phase 3: Optimizing the key (catalytic) reaction(s)**
- **Phase 4:** Optimizing the over-all process

Process Optimization

- Ligand fine tuning
- Optimization of reaction conditions
- Strategy for the development of the 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

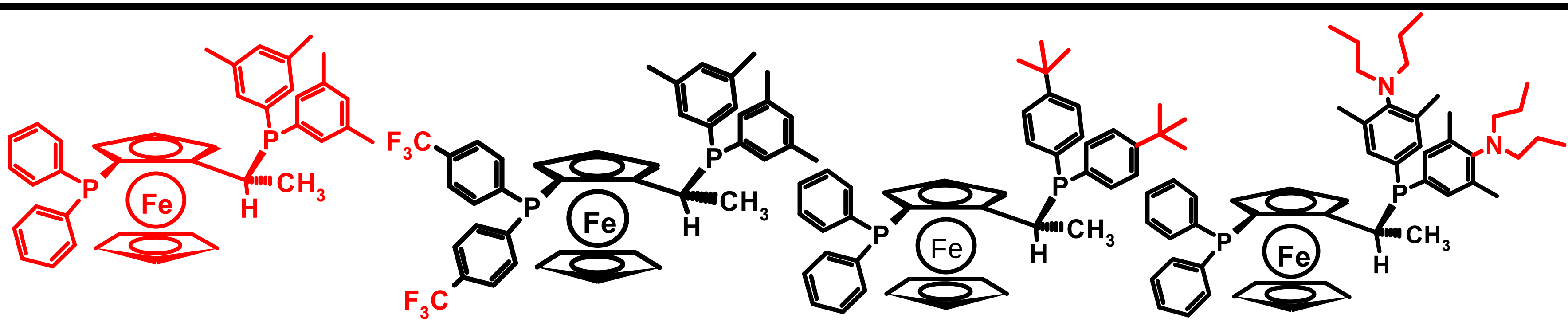
Fine Tuning

(S)-Metolachlor Process



MEA imine (S) -NAA

Catalyst: $[Ir(COD)Cl]_2$, NaI, H_2SO_4, (R)-(S)-R_2PF-PR'$_2$; $p(H_2)$, 80 bar, 50°C

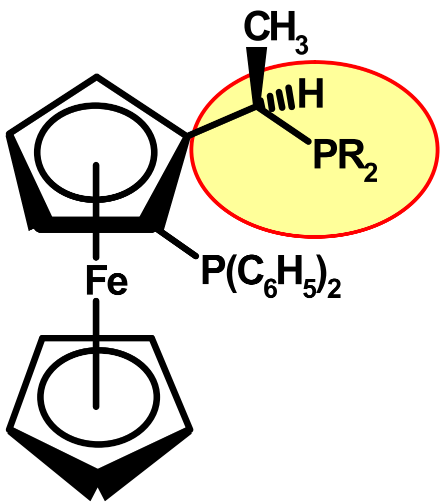


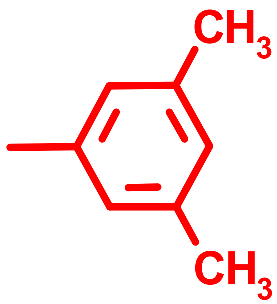
ee %	79	82	87	83
ton	2'000'000	800	5'000	100'000
tof [h^{-1}]	>400'000	400	80	28'000

F. Spindler

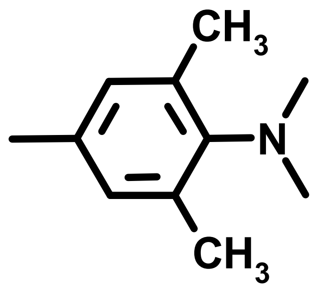
Ligand Finetuning:
N Substituents at Xylyl Group

solvias

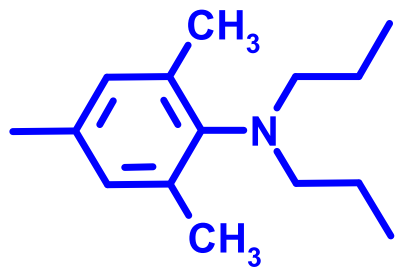




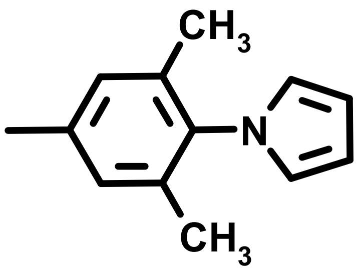
e.e.: 76%
rate: 26 mmol/min



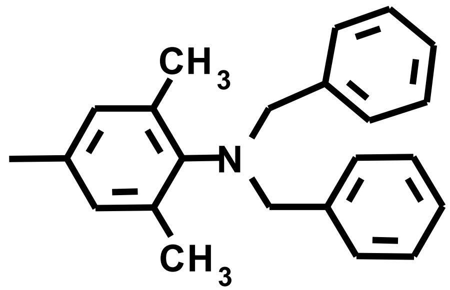
e.e.: 80%
rate: 25 mmol/min



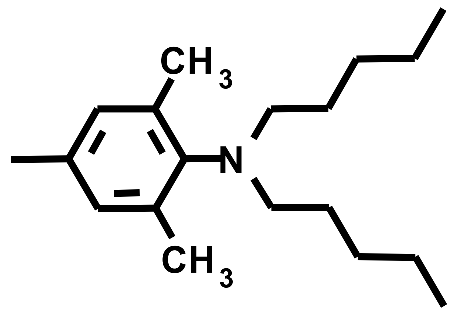
e.e.: 83%
rate: 1 mmol/min



e.e.: 69%
rate: 10 mmol/min



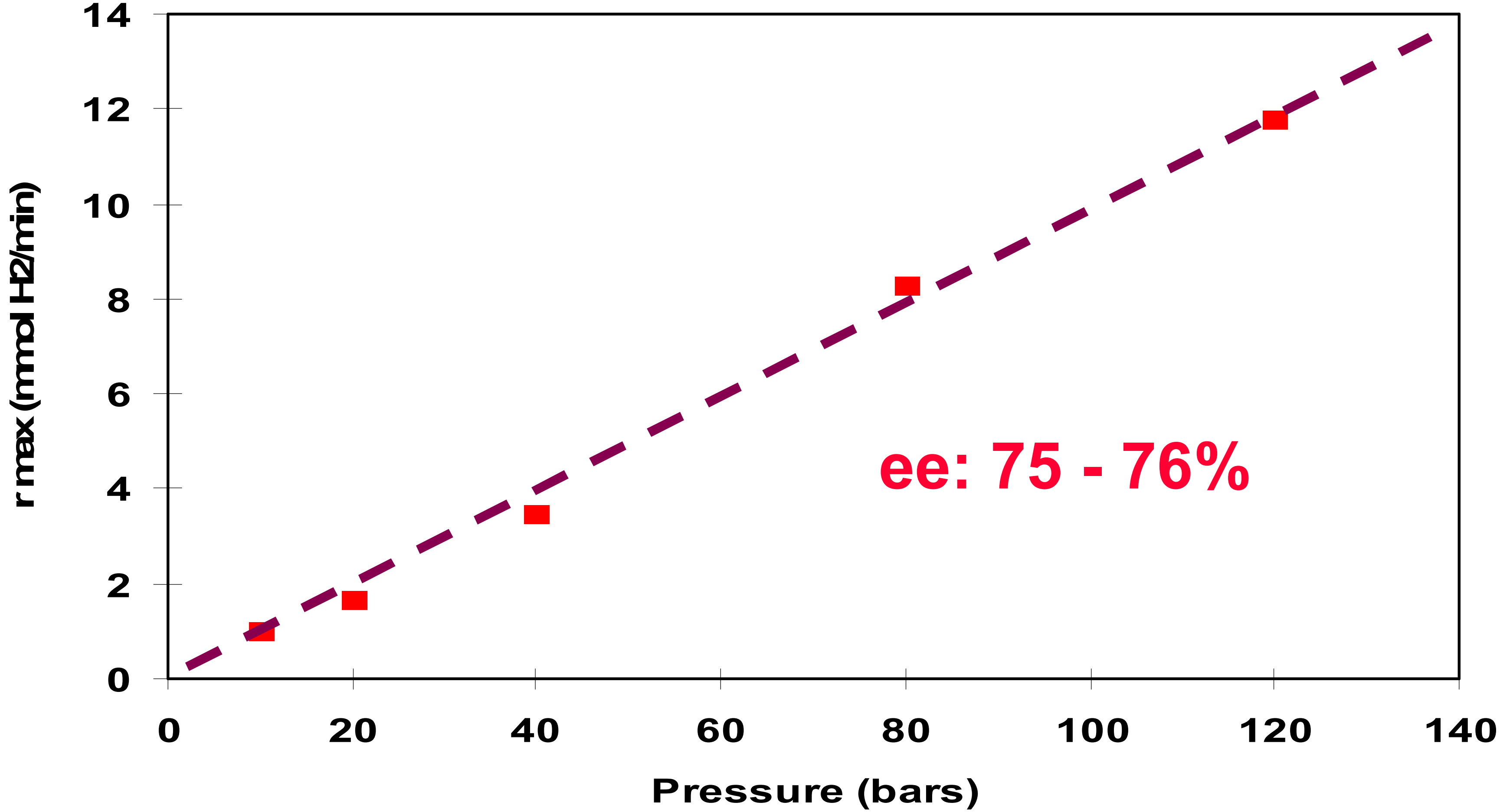
e.e.: 76%
rate: 2 mmol/min



e.e.: 82%
rate: 0.5 mmol/min

F. Spindler, H.P. Buser 1994

Reaction Conditions
Effect of H_2 Pressure



F. Spindler, H.P. Jalett 1994

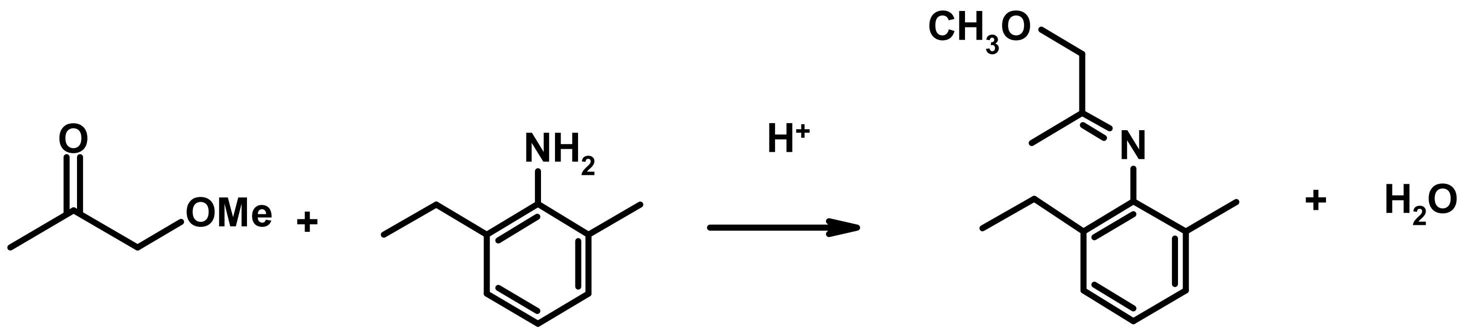
Development Phases for EPC Synthesis

- **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 over-all 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



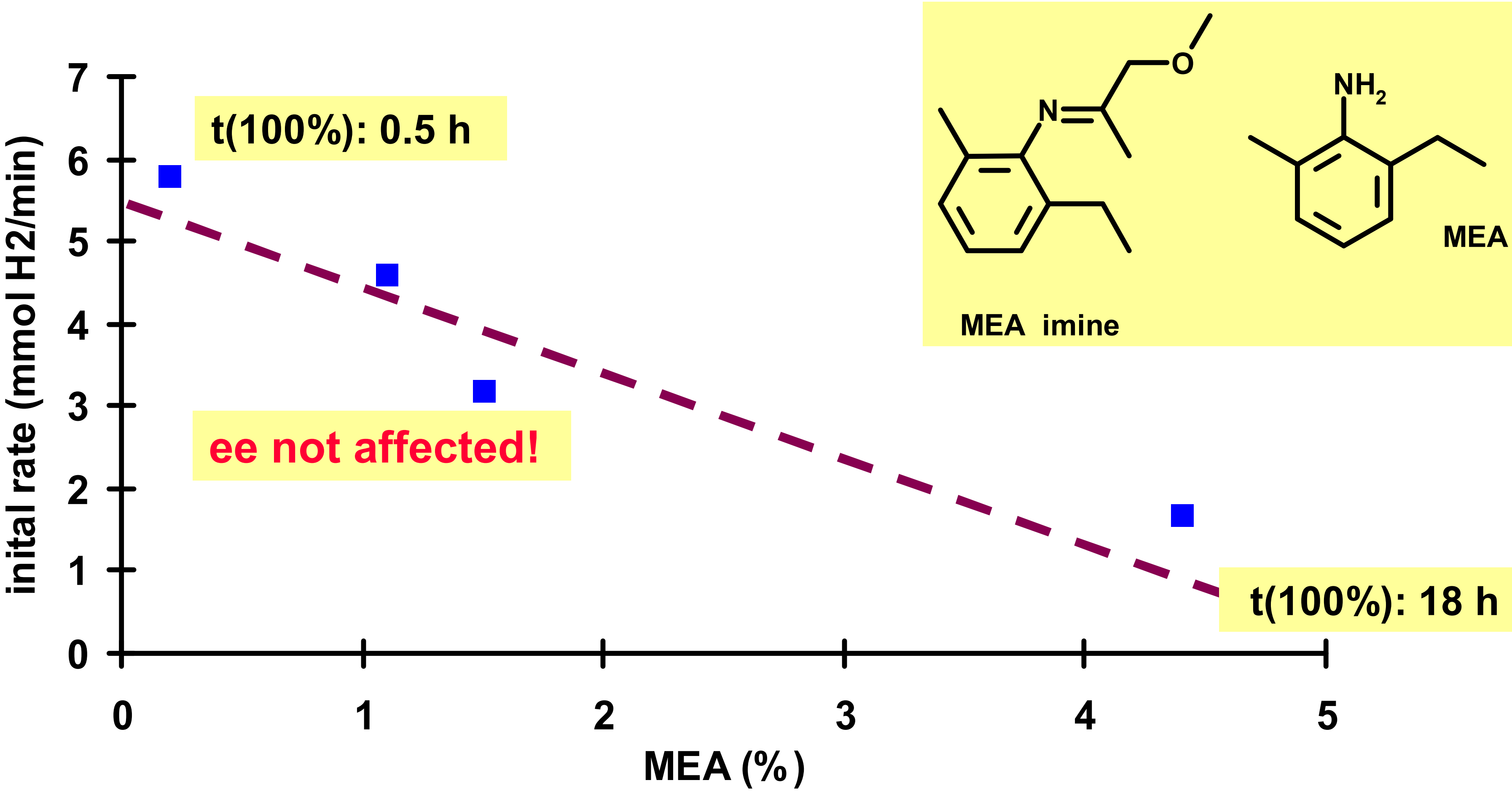
Simple chemistry

BUT

- Scale up difficult due to thermal instability of the imine
  - ➢Fast removal of water neccessary
- Significant catalyst deactivation
  - ➢High purity required

Effect of MEA Concentration

Ir/xyliphos, Acetic Acid, TBAI



F. Spindler, H.P. Jalett

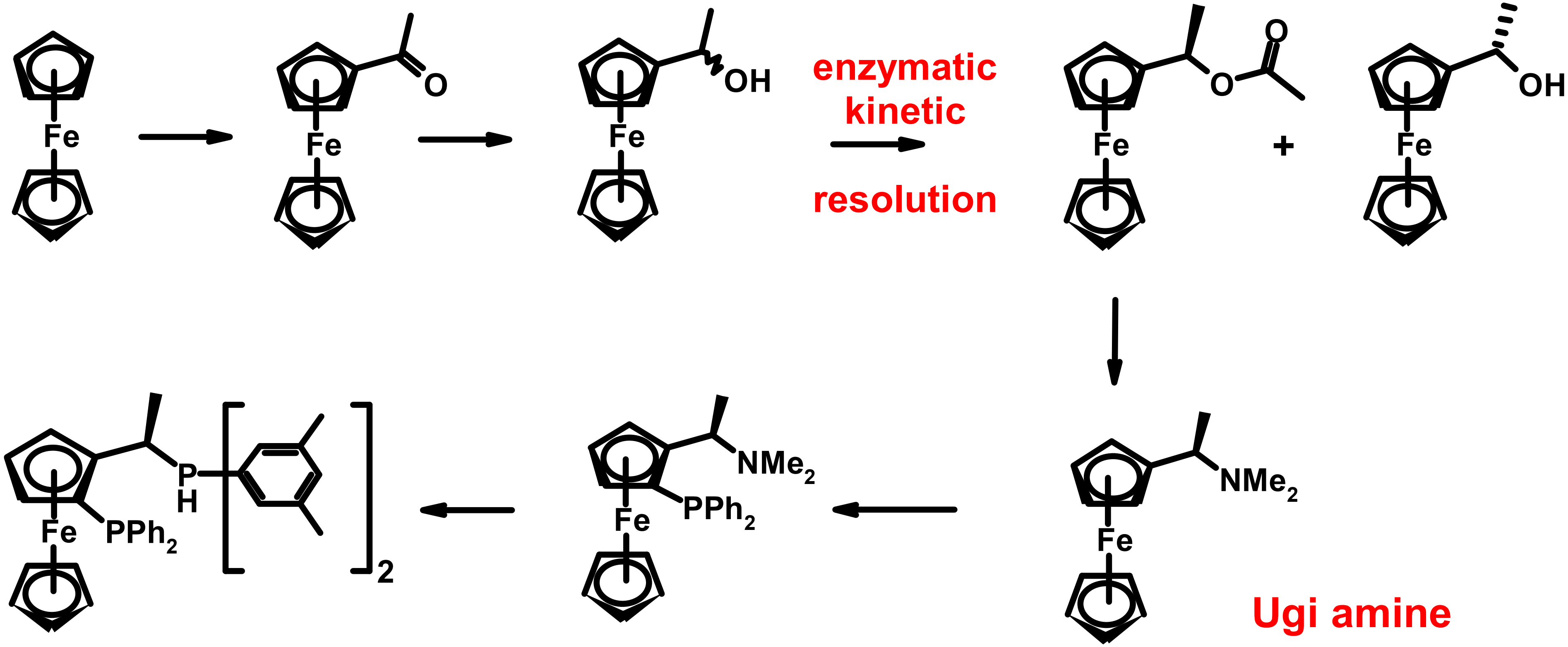
Imine Production: Water Separators

Process Development

solvias

- **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**

Technical Ligand Synthesis



30 Kg scale unproblematic

Process Development

solvias

- 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

Choice of Reactor Technology

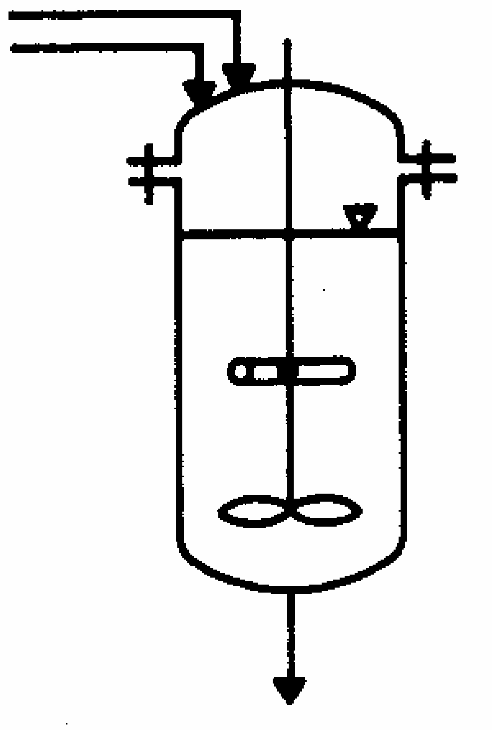
Issues

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

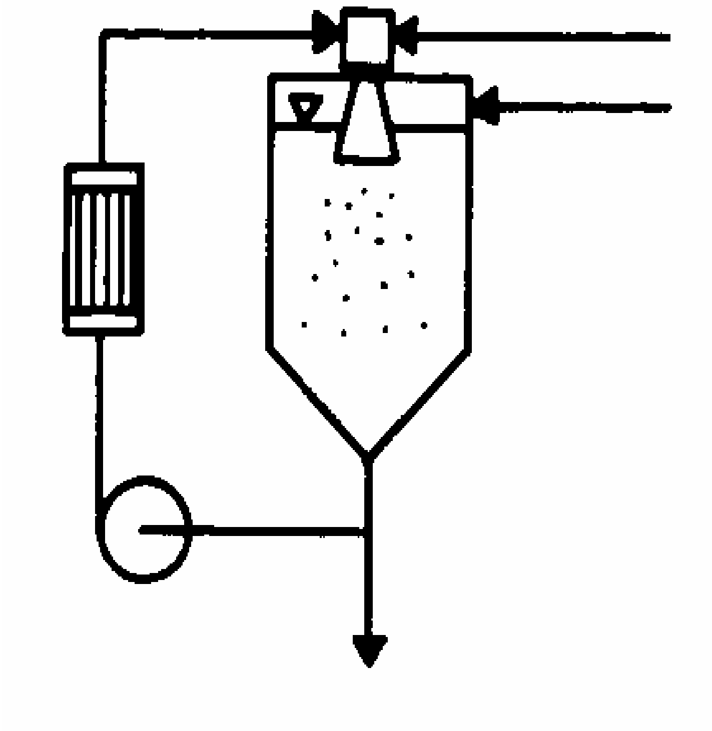
Alternatives

- Stirred tank reactor
- Loop reactor

Coice of Reactor

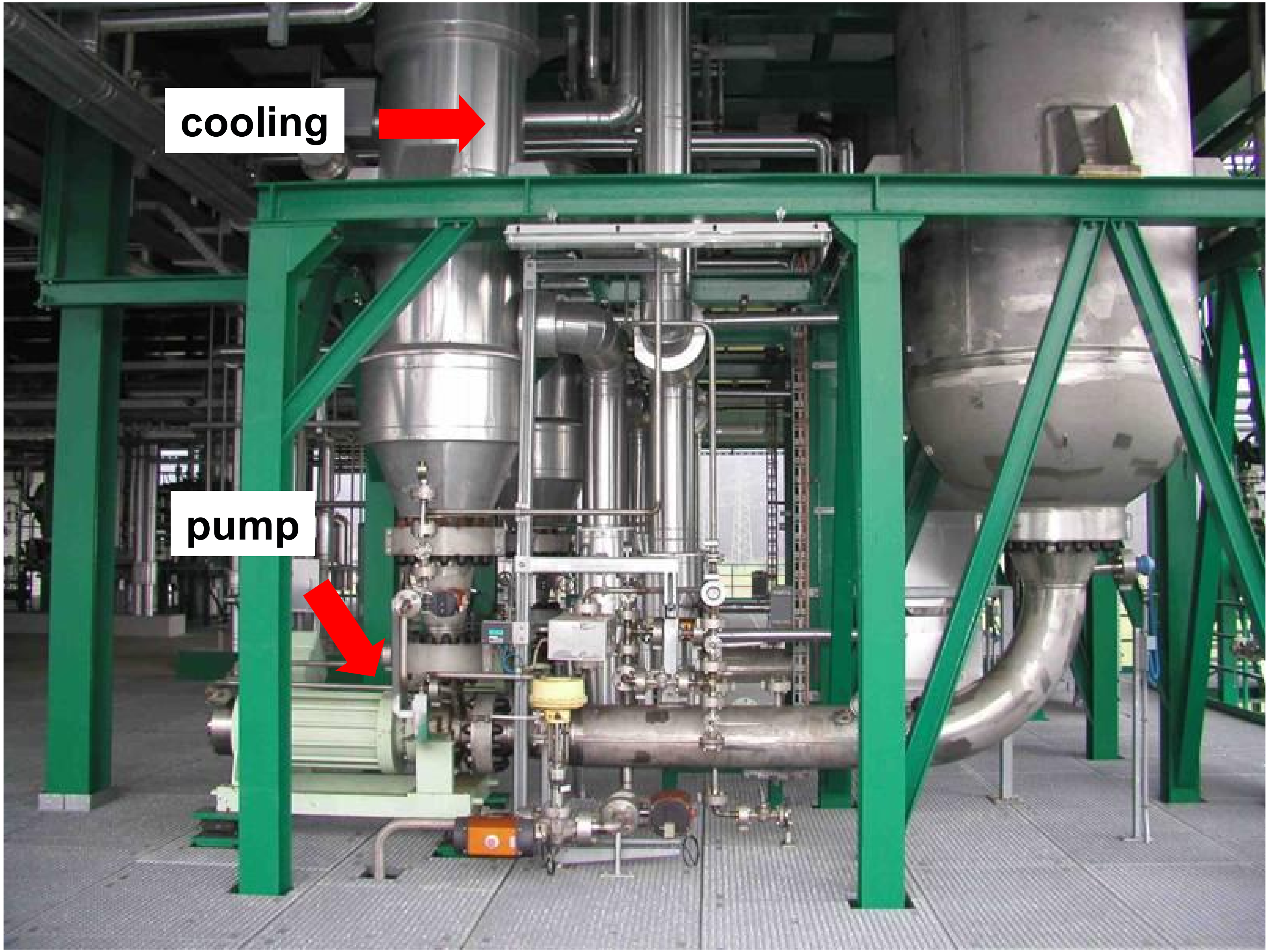


stirred tank



loop reactor

Coice of Reactor

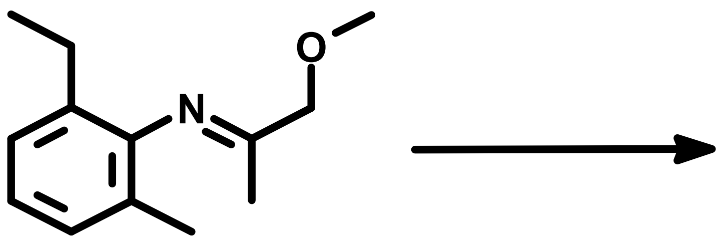


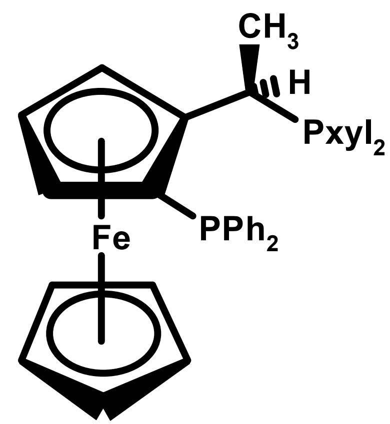
Process Development

solvias

- 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

16. November 1996
Happy End: First Production Batch





	amount	mol
MEA-imine	**10'000 kg**	**48'700**
$[Ir(COD)Cl]_2$	**34 g**	**0.05**
Ligand	**68 g**	**0.11**
NaI	**92.5 g**	**0.6**
H_2SO_4	**250 g**	**0.5**

reaction time 2h

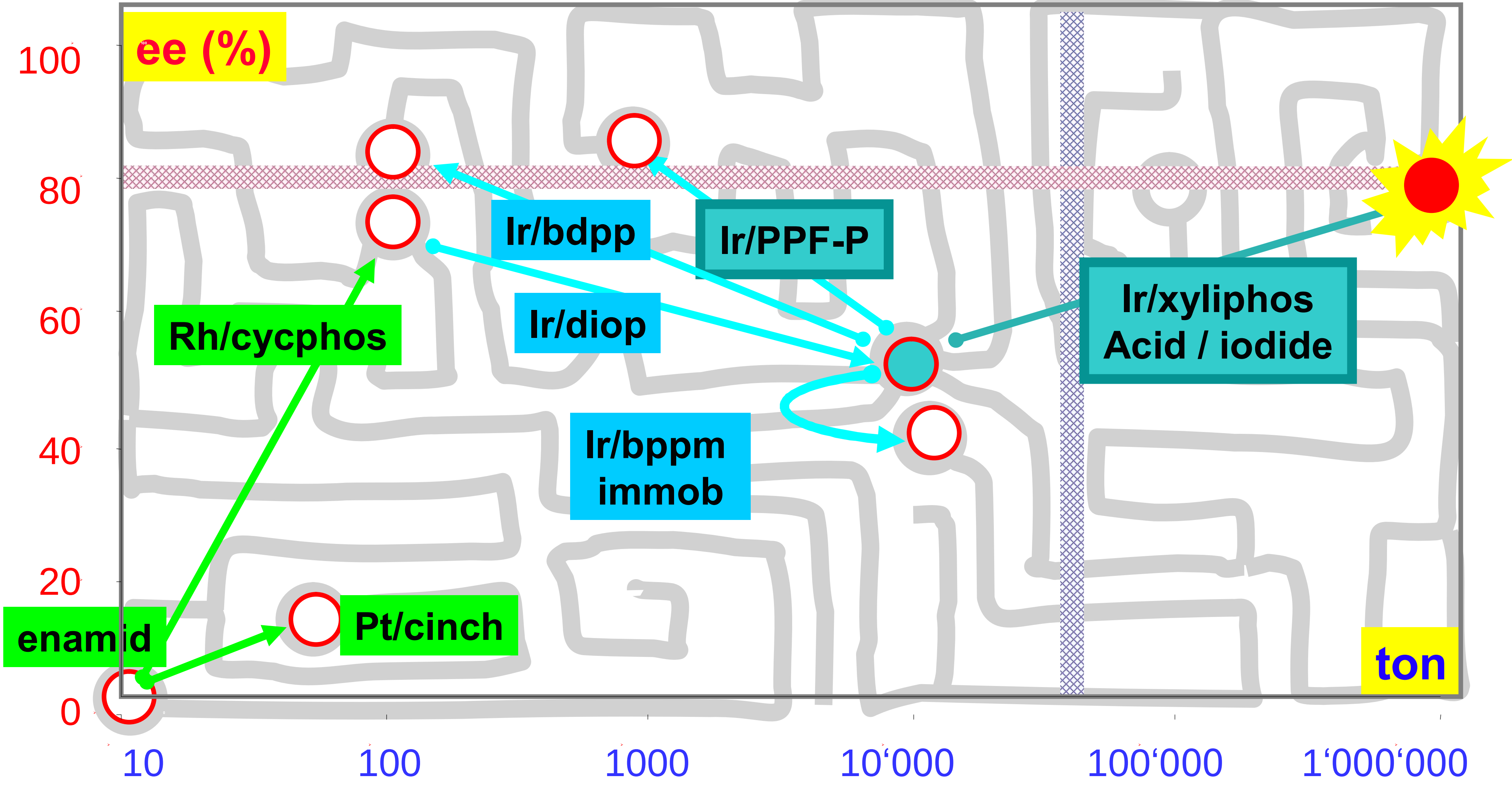
conversion 99.6%

ee 79%

N. Pericles, R. Hanreich

From Dream to Process
Important Milestones

ee	≥80%
ton	>50'000
tof	>10'000/h



Some Lessons

solvias

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

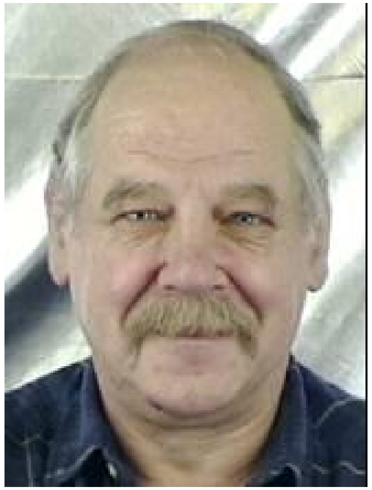
- Parallel screening equipment

NO SUCCESS WITHOUT TOP EXPERTISE

The Key Players

F. Spindler

B. Pugin



H.P. Jalett

solvias

Think catalytic!

Amazing where you can go