Strategies for Accelerating the Development of Catalytic Enantioselective Reactions

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland

Singapore Catalysis Forum, 17. April 2008

Amazing where you can go

Solvias
A Technology Company

1970-1996 Central Research Center of Ciba-Geigy AG

1997 Scientific Services of Novartis AG

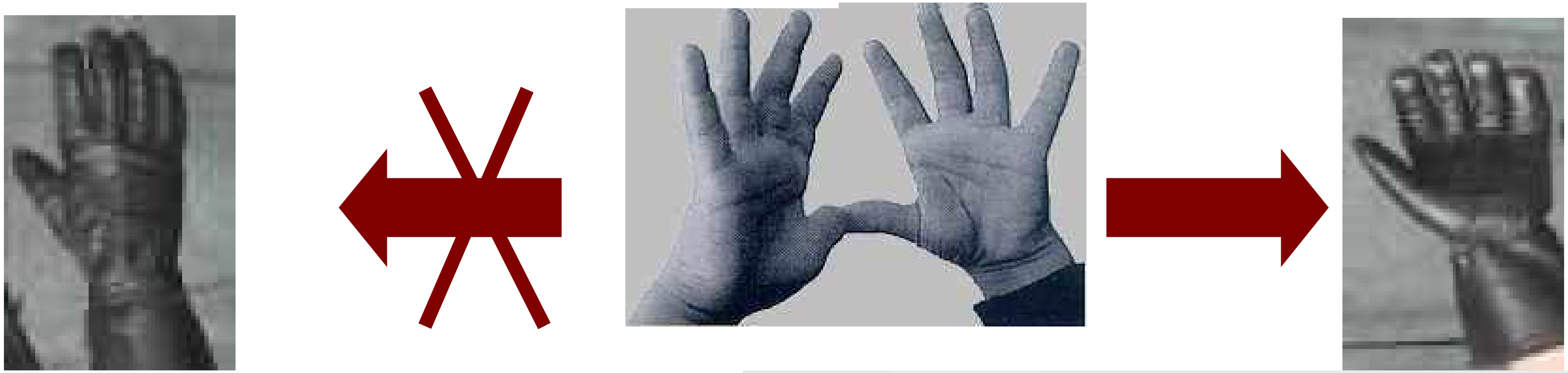
1 Oct.1999: Start as fully autonomous and independent technology company

- **Our Expertise**
  - **Chemical, physical and biological analytics**
  - **Synthesis with emphasis on (enantioselective) catalysis**
  - **Service related products (chiral ligands)**

Outline

- Background
- Developing Enantioselective Processes
- HTS at Solvias (Hydrogenation)
- Conclusions

Chirality and Nature (Handedness)



Living organisms are chiral!!
Normally, only one enantiomer is produced in Nature

biological material recognizes enantiomers

Chiral Aminoacids

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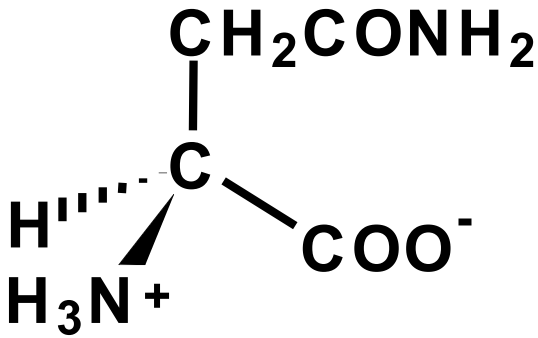
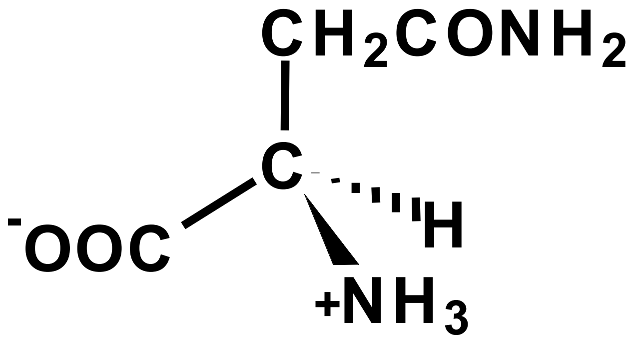
Image



***S*-aspargine**

bitter

Mirror image



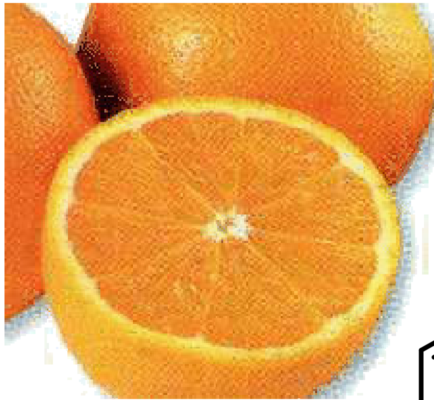
***R*-aspargine**

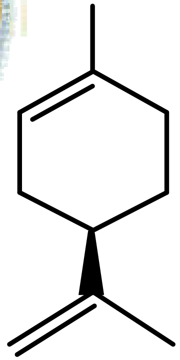
sweet

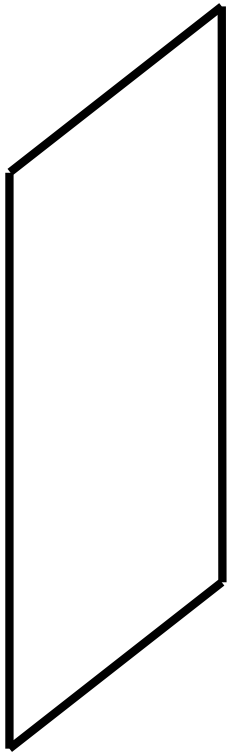
Enantiomers

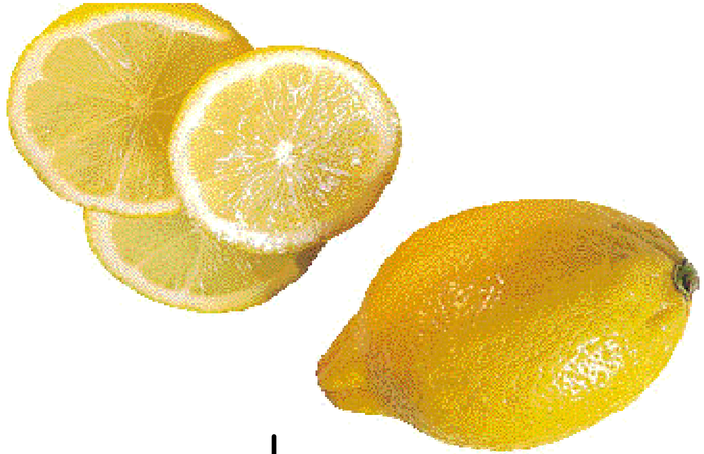
Carmen Claver

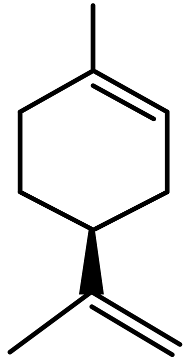
It smells....











(R)-limonene
orange

(S)-limonene
lemon

Carmen Claver

Syntheses of Enantiomerically Pure Compounds (EPC)

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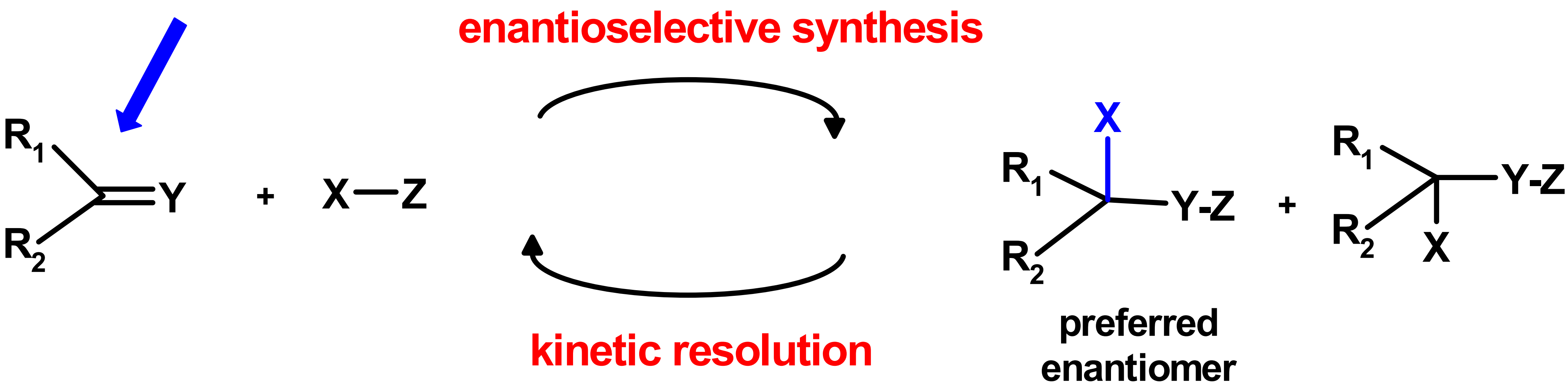
* **Synthesis starting from naturally occurring chiral molecules**

  (e.g. from fermentation)

* **Enantiomer separation** → **Chiral chromatography**
  Diastereomer separation
  Kinetic resolution

* **Stoichiometric**
* **Asymmetric Synthesis / Catalysis** →
  * **Biocatalyst**
  * **Chemical catalyst**

Enantioselective Catalysis
Some Definitions: A Reminder



only possible in presence of a chiral auxiliary

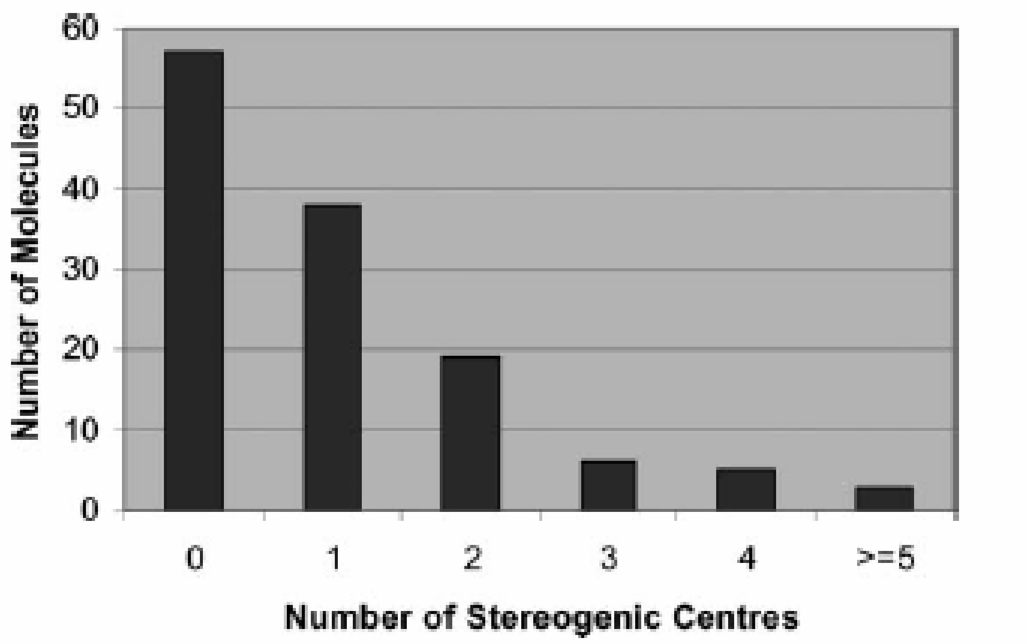
Selectivity: Enantiomeric excess (ee, %(R) - %(S))

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

Chirality

- Of the 128 molecules analyzed, 69 (54%) contained at least one stereogenic center.
- Of the 69 chiral molecules 67 were developed as single stereoisomers, with only two as racemates.



J.S. Carey, D. Laffan, C. Thomson, M.T. Williams, Org. Biomol. Chem. 4 (2006) 2337

Importance of Chiral Compounds

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Market value for chiral fine chemicals (2000)

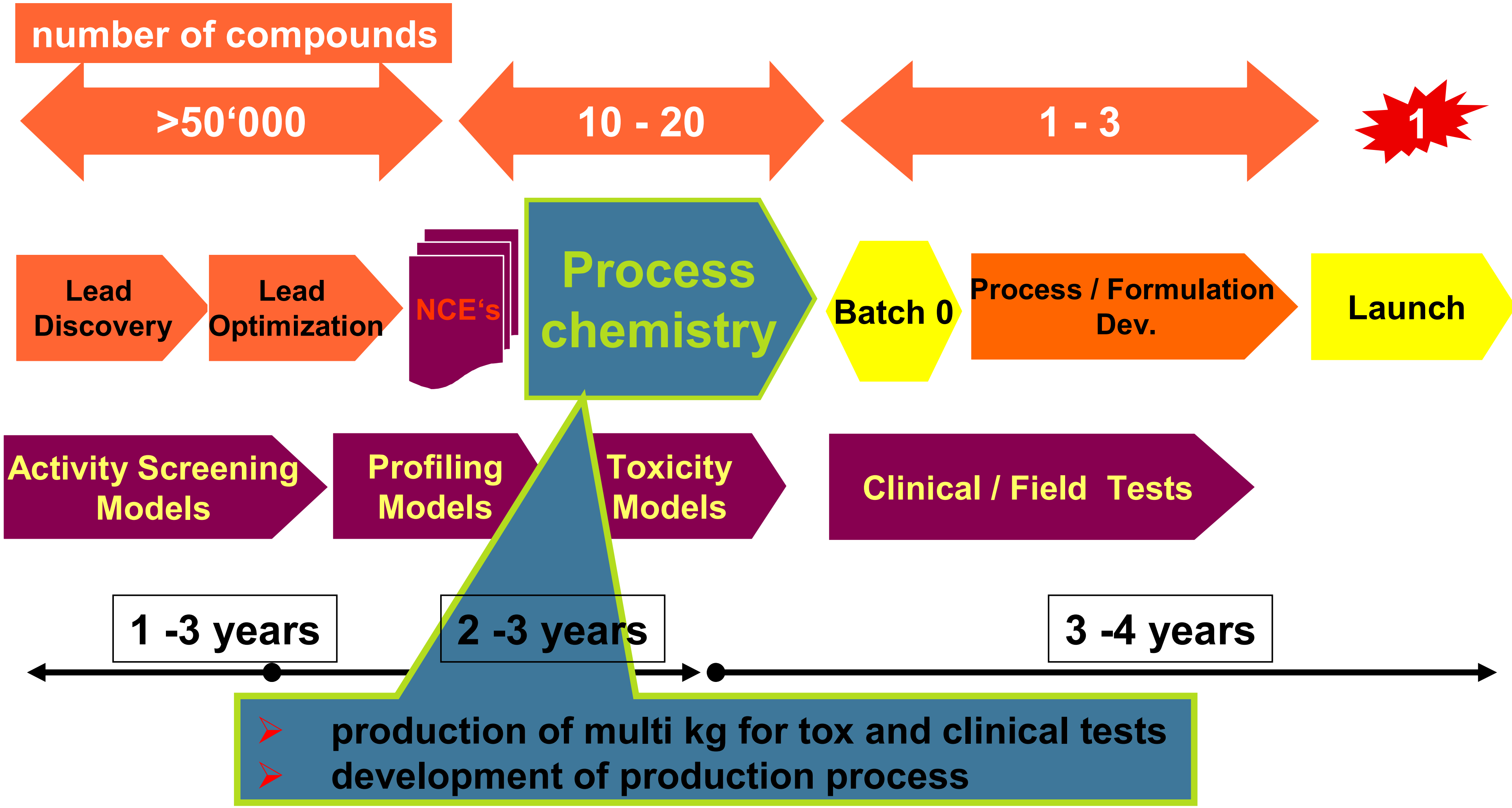
Total	**$6.6x10^9$ $**
Pharmaceutical application	**$5.4x10^9$ $**
Other applications (agrochemicals, flavors etc)	**$1.2x10^9$ $**

Major user: Life Science Industry

- **Strong growth expected**

S.C. Stinson, Chemical & Engineering News, May 14, 2001, p. 45

Life Science Industry
Product Development Process



Outline

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Phases in Process Development

1. Choice of synthetic route: With or without catalysis?

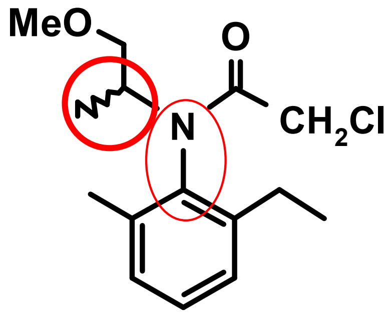
2. Find effective catalytic system (ee; ton; tof)

3. Process optimization (catalytic step, overall synthesis)

4. Scale up, technical process

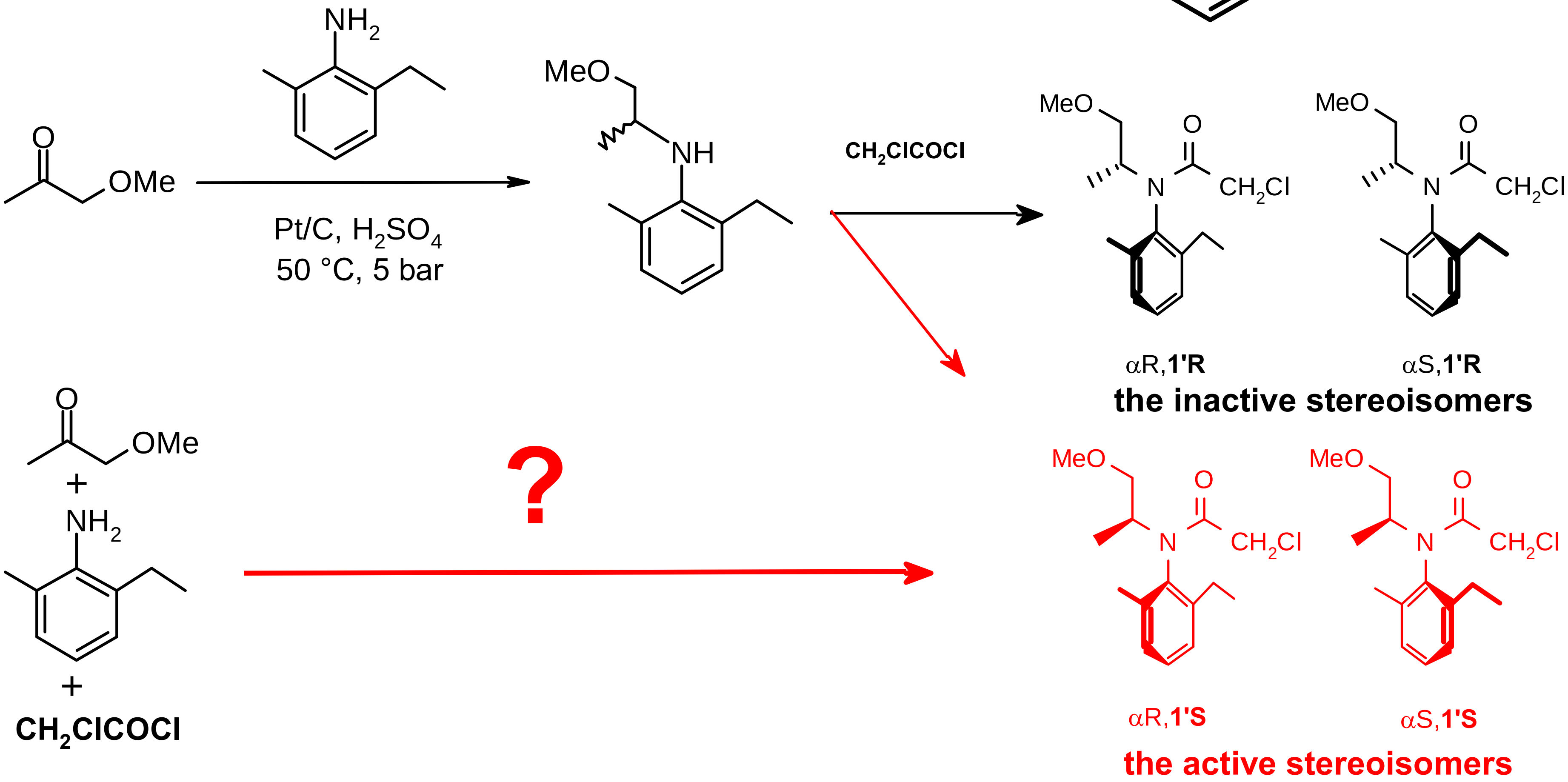
5. Manufacture (trouble shooting)

The *(S)*-Metolachlor Problem
(Ciba-Geigy/Syngenta/Solvias)



metolachlor herbicide >30,000 t/y

Production process for racemate



The (*S*)-Metolachlor Problem
(Ciba-Geigy/Syngenta/Solvias)

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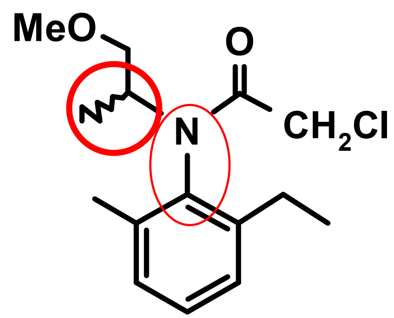
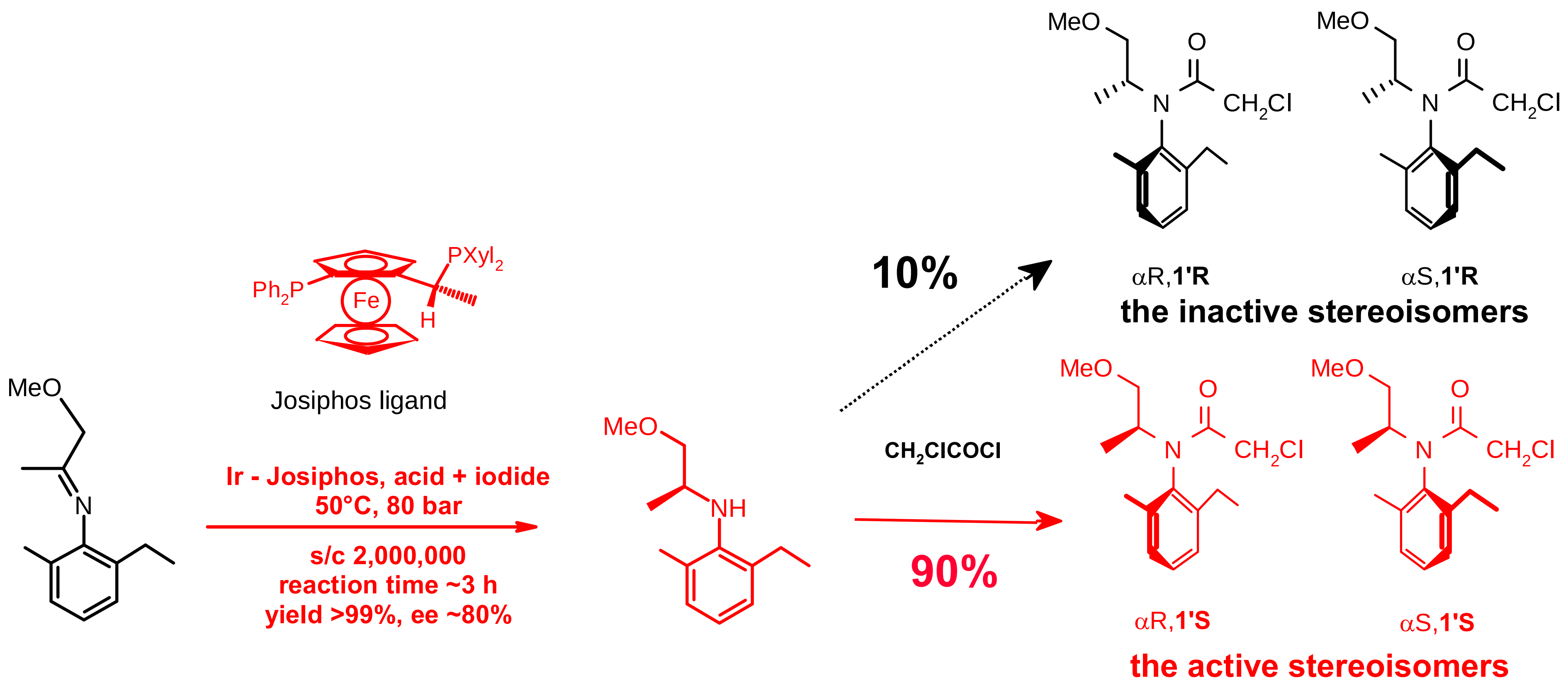
Production process for enriched (S)-metolachlor



metolachlor herbicide >30,000 t/y



The History of rac-Metolachlor and (S)-Metolachlor

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1970	Discovery of biological activity
1978	Full-scale plant >20’000 t/y
1982	Bioactivity of (S) enantiomers detected
1983	Route design: 4 variants ⇒ imine hydrogenation
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**

Some Lessons

1. Choice of synthetic route: With or without catalysis?

➢ **Very situation dependent, not easy to accelerate**

Important Factors when Deciding the Application of Catalysis

Product

- availability of competitive alternative routes
- time frame for development
- cost vs added value

Catalytic reaction

- maturity
  - known scope / limitations
  - catalyst availability
  - development time
- IP situation
- required equipment / techniques
- cost

Chemist & Company

- education, acceptance of novel methods
- catalytic know how and facilities

Some Lessons

2. Find effective catalytic system (ee; ton; tof)

- **Very often THE bottle neck**
- **Highest potential for acceleration**

Major hurdles

- **Availability of ligands (catalysts)**
- Testing equipment
- Analytics

Some Lessons

3. Process optimization (catalytic step, overall synthesis)

4. Scale up, technical process

5. Manufacture (trouble shooting)

➢ **Less potential for acceleration**

Major hurdles

- **Availability of ligands on technical scale / IP problems**
- Scale up equipment

Outline

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Find Catalytic System (ee, ton, tof)

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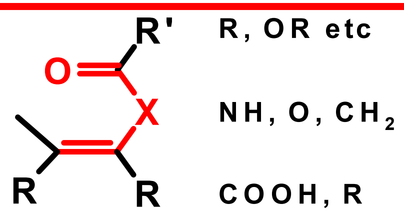
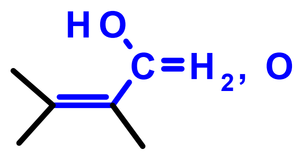
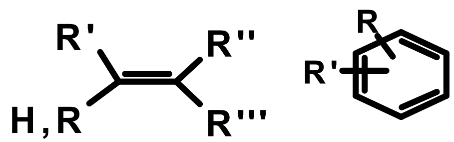
- Choice of catalyst difficult due to high substrate specificity (analogies are often weak)
- Requirements for catalyst performance for economical processes can be very demanding
- Time constraints especially for new chemical entities in the pharma sector (less in agro)

Experience From Model Substrates

easy substrates	α-acyl-dehydro amino acid derivatives itaconates	
good substrates	β-acyl-dehydro amino acid derivatives enol acetates	
	allylic acohol α,β-unsaturated acids	
difficult substrates	no preferred functional groups tetra substituted aromatics (almost unknown)	

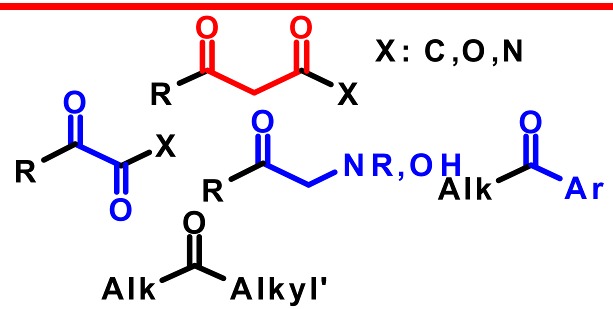






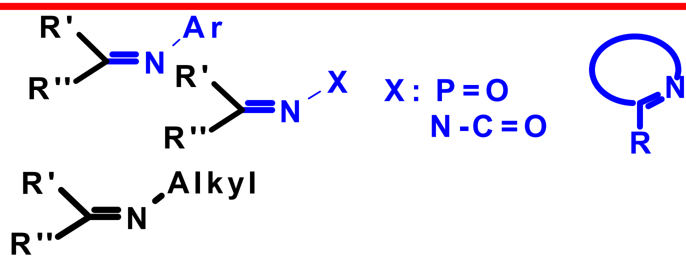
C=C

easy substrates	β-functionalized ketones	
good substrates	α-keto esters α-amino ketones aryl methyl ketones	
difficult substrates	alkyl ketones	



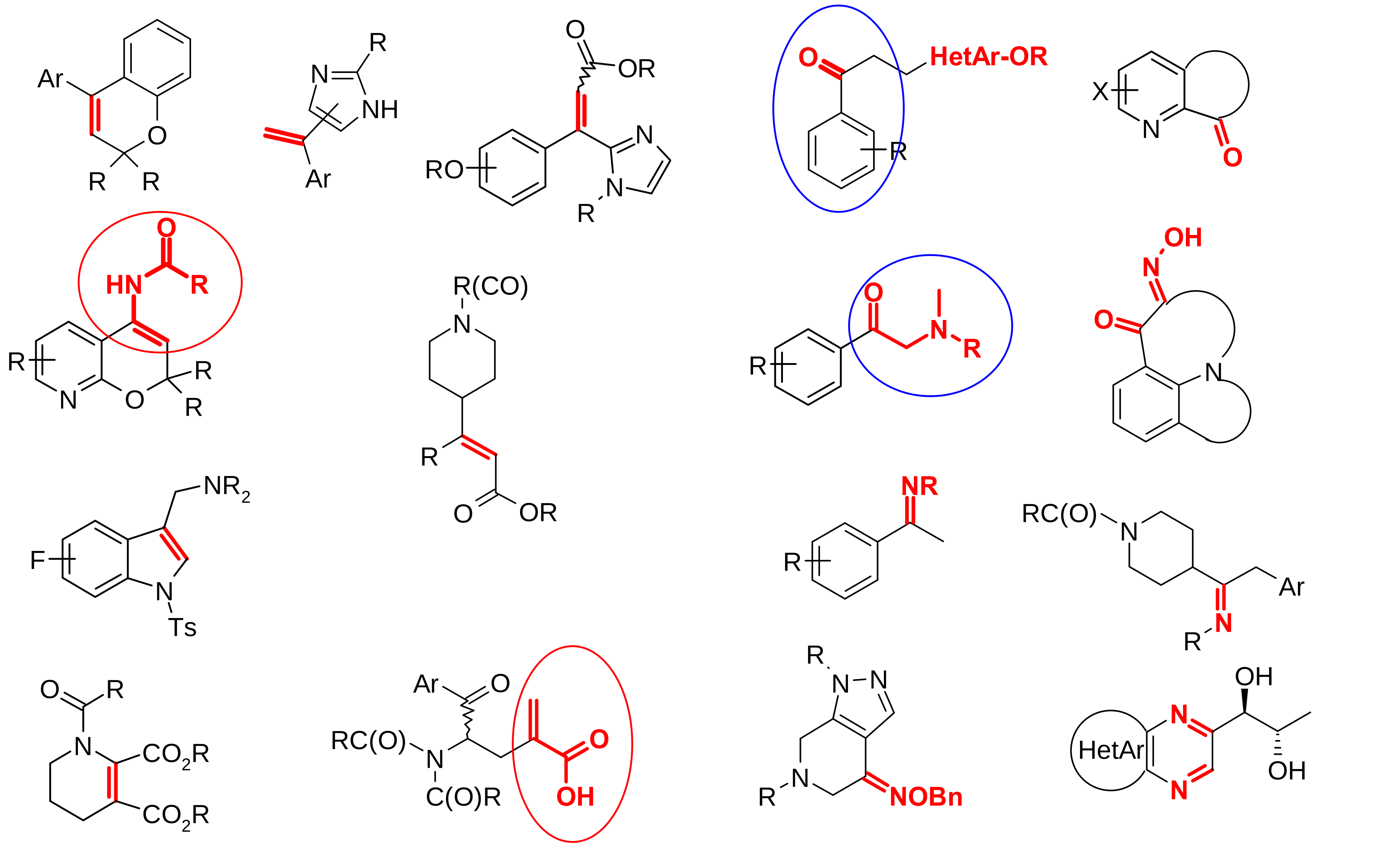
C=O

good substrates	some N-aryl imines some cyclic imines N-functionalized imines	
difficult substrates	simple alkyl imines	



C=N

Selected Customer Problems

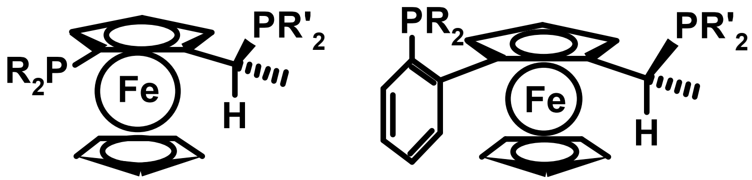


Toolbox for Process Development

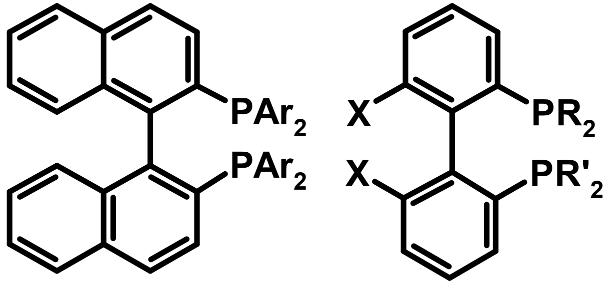
- Library of chiral ligands / metal precursors
- Experimental setup for parallel testing
- Suitable analytical procedures

BUT MOST IMPORTANT: Optimal screening strategy

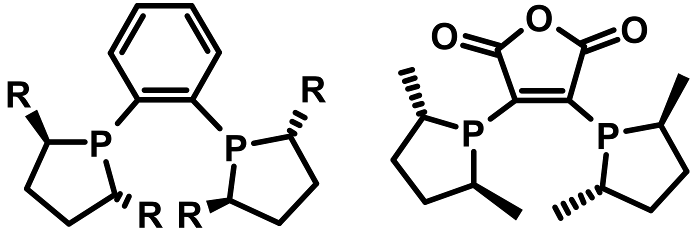
Selection of Chiral Ligands



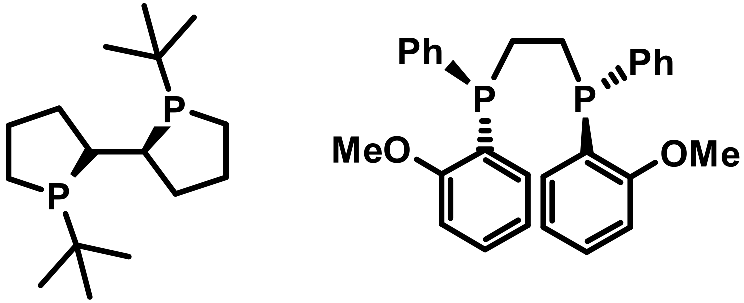
ferrocene based



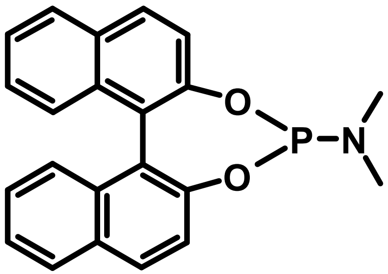
axially chiral / biaryl



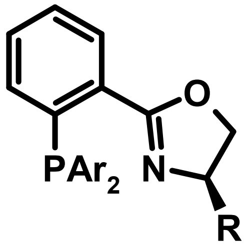
phospholanes



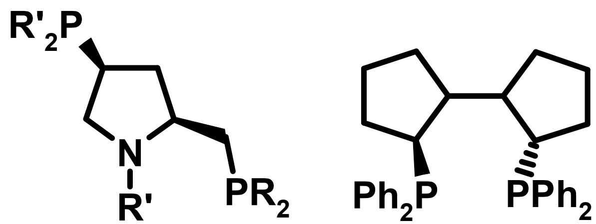
P-chiral



monodentate



P-N ligands



various

HT Screening Strategies

Classical Strategy: Pre-existing library of ligands

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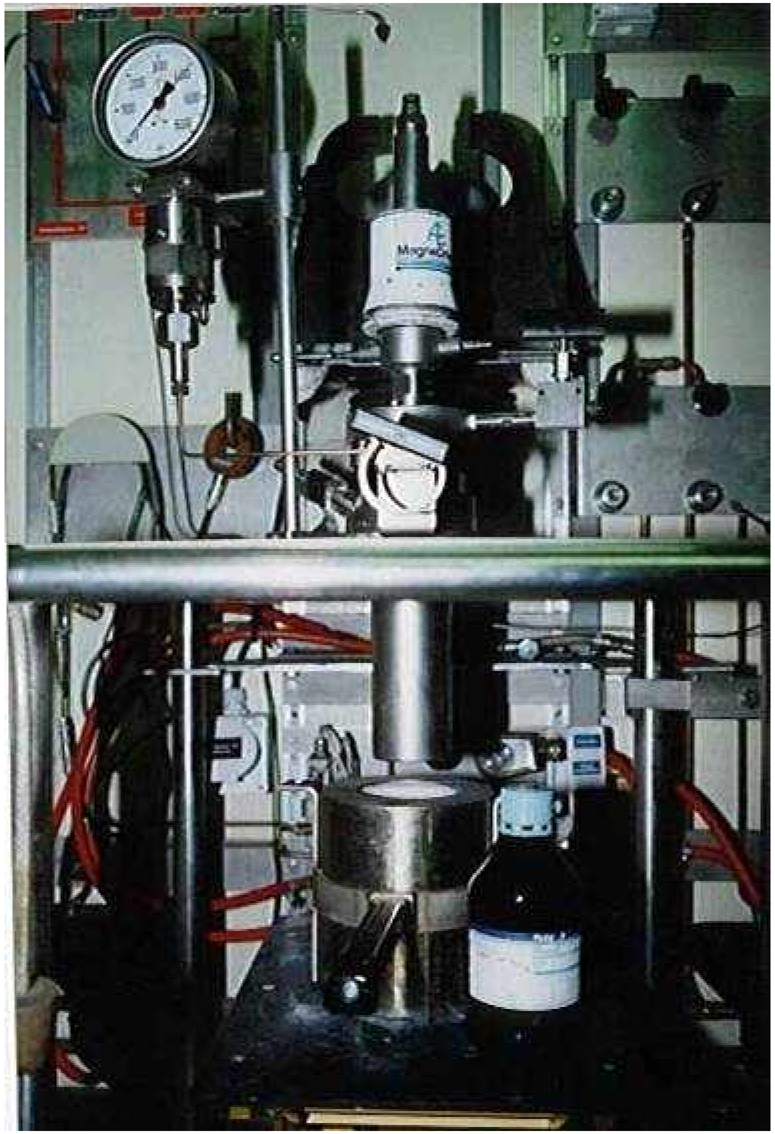
- **>600 chiral ligands (both enantiomers)**
- **65% Solvias owned (mostly modular) ligand families**
- **20% patented ligands of other suppliers**
- **15% patent free ligands**

DSM Strategy: Preparation and screening of "instant" monophos-type ligand libraries

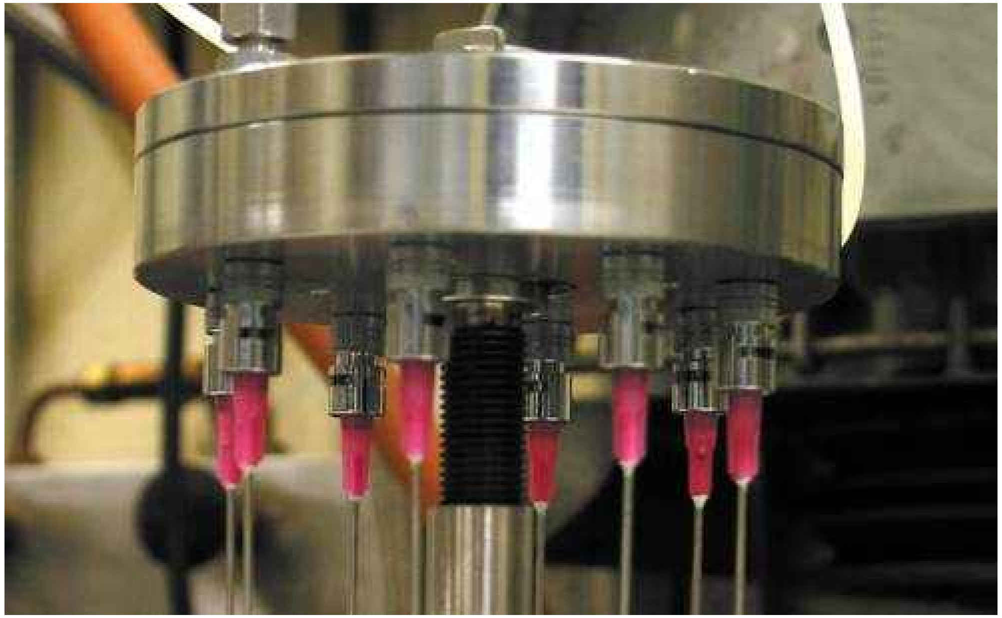
Solvias Screening a Few Years Ago



series of 50 ml autoclaves

300 ml autoclave

The Solvias Octoclave



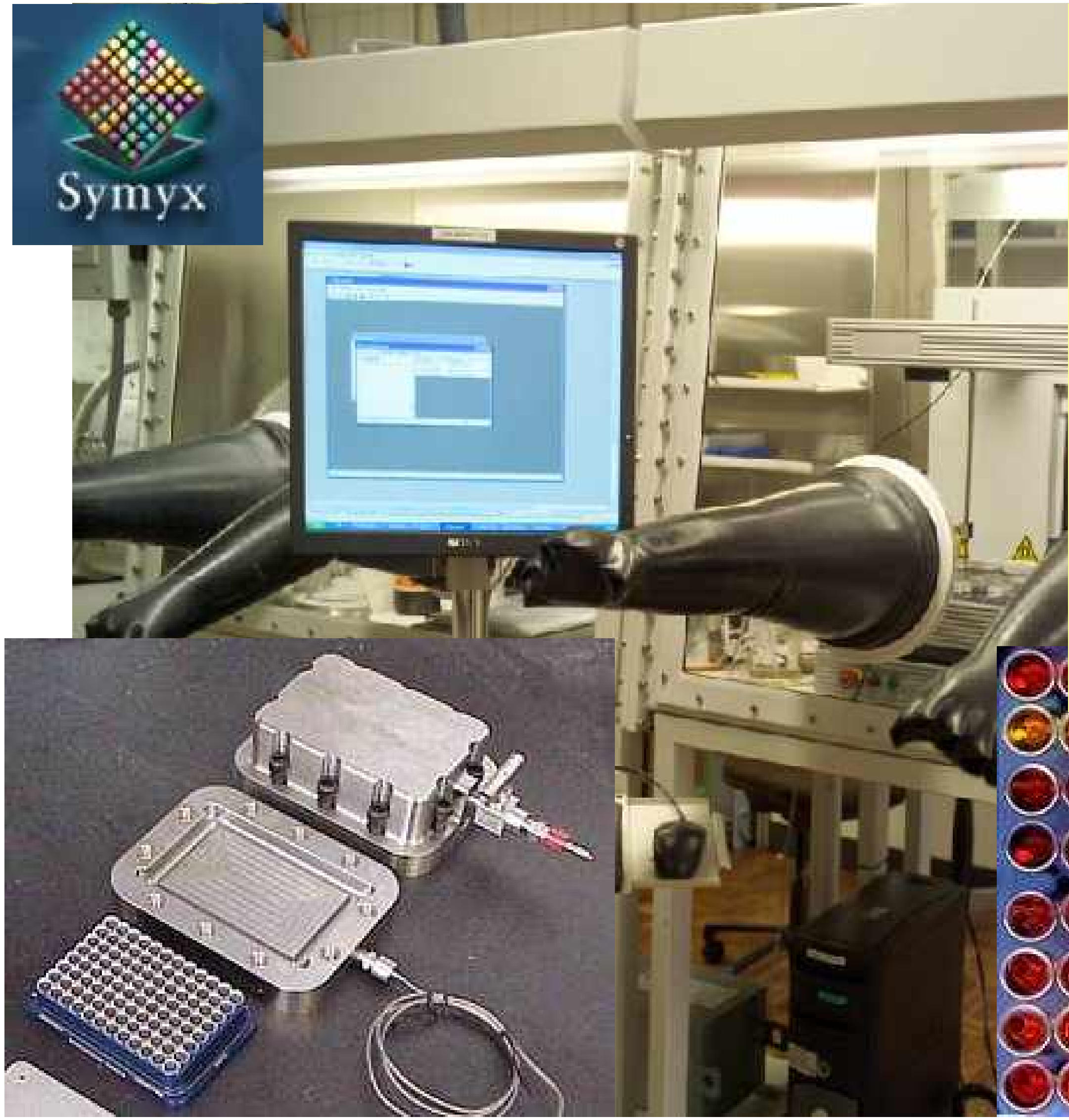
- 8 parallel runs with gaseous reactants
- Very good mixing

- Pressures up to 100 bar

- Loading under inert conditions

Solvias HTS Today

Symyx Based Platform



- **Capacity: 200 react. / day**
- **Fully inert handling**
- **Robotics for set-up**
- **96-well plates, 0.4ml**
- **Up to 100bar (H_2, CO)**
- **Robotics for analytics**
- **(SFC, HPLC, GC)**

Solvias HT Screening Strategy

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Design of Experiments (DoE) done by catalysis expert

- **Combination of experience and serendipity**

Ligands, additives, metals: Test large experimental space

- **Scouting experiments in 50 ml autoclave: ➢ p, T**
- **HTS with s/c 25 (purity of substrate)**

***If ever possible: In situ* catalyst generation**

- **Highest possible flexibility (metal, precursor type, ligand, counterion)**

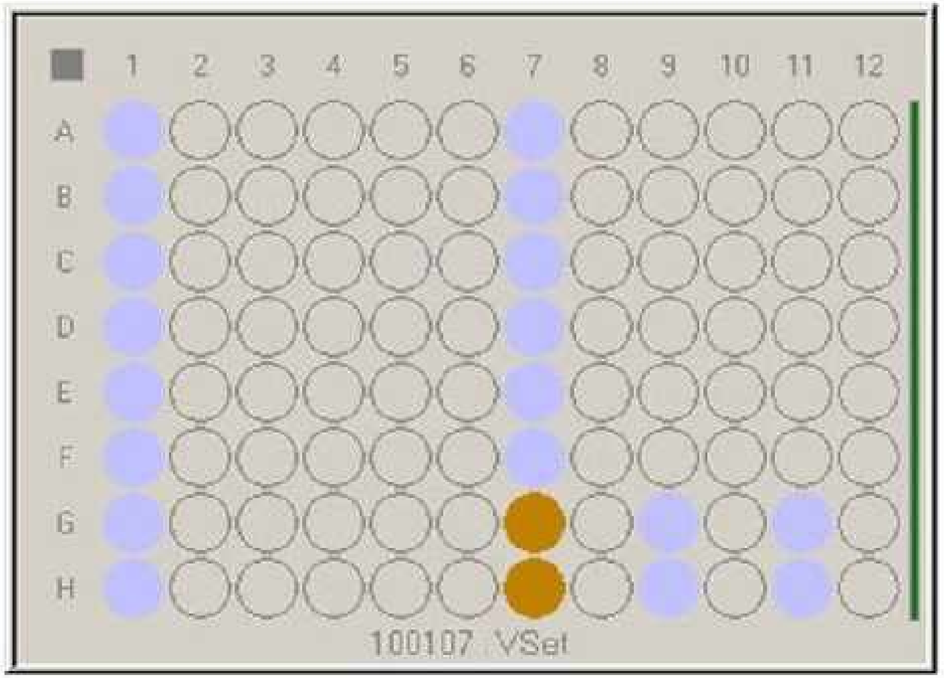
HTS Analytics: Need for speed (rt << 15 min / sample required)

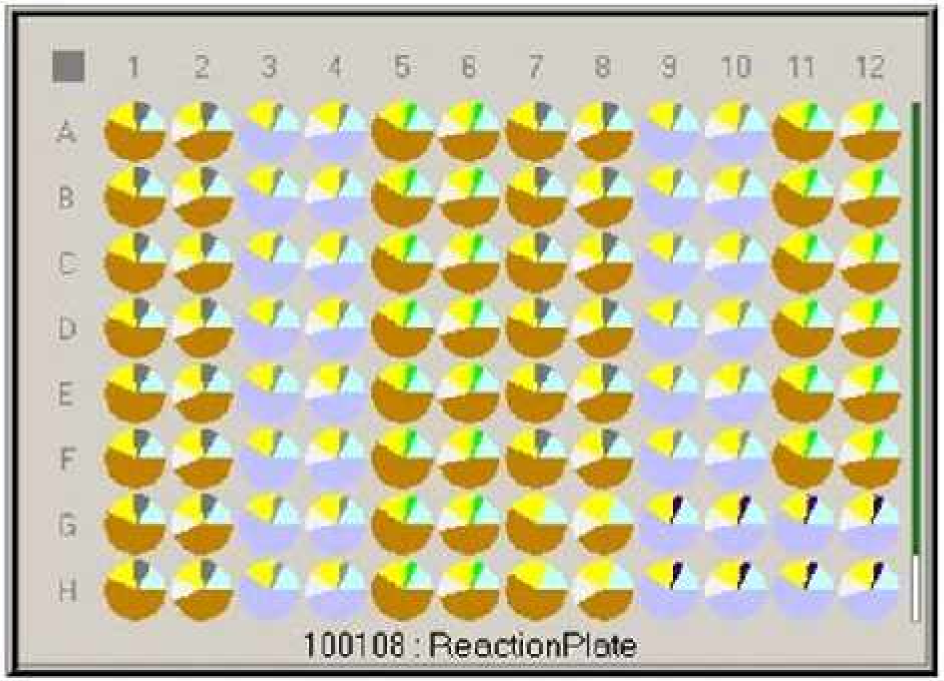
- **SFC, GC, fast HPLC**

Screening Work-Flow

Definition of Ligand

Definition of Reaction





DESIGN

Different ligand classes (Key-, High Priority- and Low Priority Ligands)

Different metal precursors and ratios, different additives, different solvents

Screening Work-Flow

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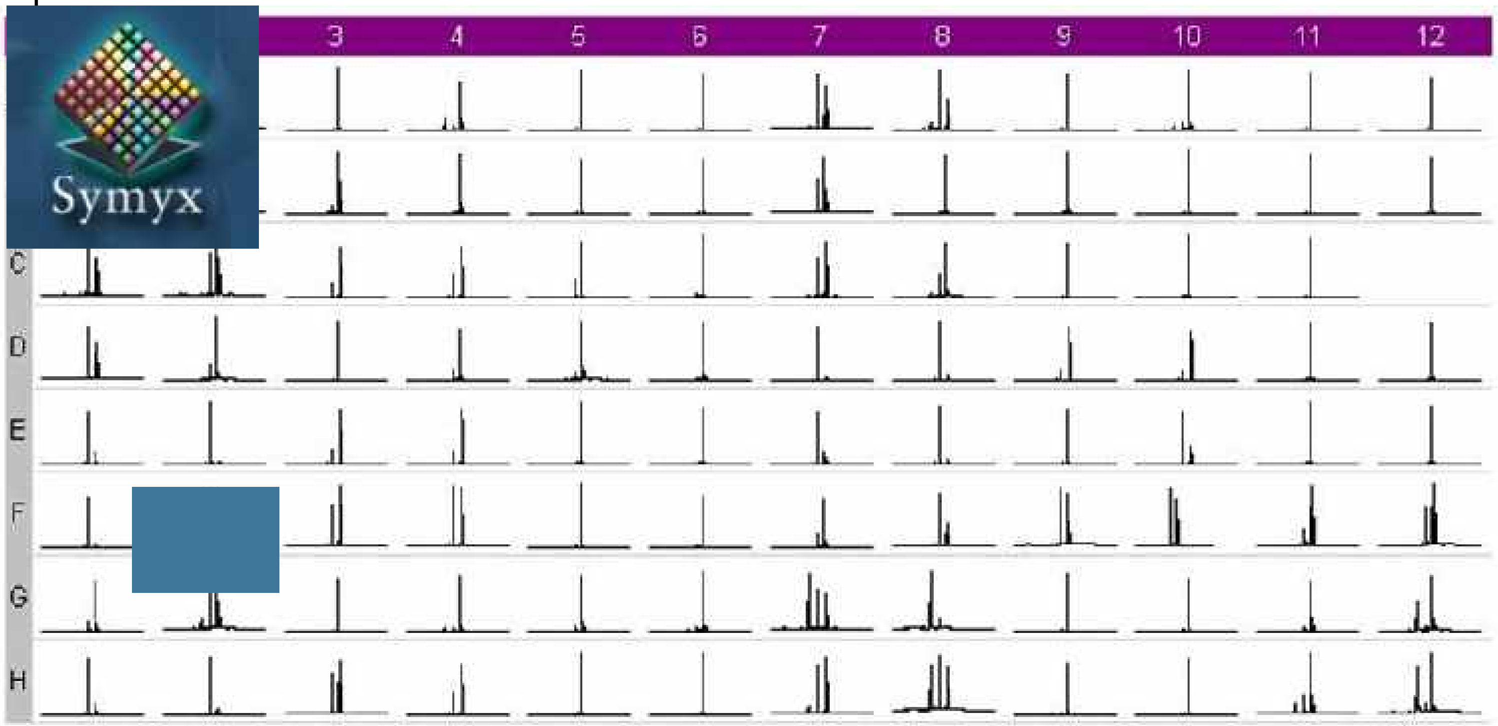


									10	11	12
A	-10.1018	-18.1420	-66.5888	-46.8963	44.53	-57.3142	13.09	33.01	22.53	-8.7711	11.64	-26.7822
B	86.98	48.86	-59.6849	-60.3975	-23.4721	-37.9491	16.34	-16.5701	-70.0818	-47.3240	-25.1872	ND
C	20.92	3.5093	-57.3723	-39.6347	84.57	62.98	-19.2748	55.90	-1.1599	-3.1276	-34.0374	
D	16.76	35.84	-11.7060	36.98	-31.9381	-38.8426	85.06	80.72	-63.7523	-68.7476	-46.8364	-49.8269
E	93.53	94.10	-58.2973	-67.2570	-25.8104	[illegible]	79.36	85.10	-27.8962	46.95	100.00	-16.7083
F	92.83	97.41	[illegible]	-1.0591	15.90	44.82	46.09	41.74	42.81	9.9247	-59.0555	-24.8589
G	8.0135	30.42	-40.0299	-30.6477	-34.6403	-27.9034	3.8388	63.34	26.59	100.00	-61.5051	-43.5927
H	84.43	80.32	-14.3768	-40.7090	-15.6850	-39.4893	-8.7965	10.17	-25.3005	-1.3429	-2.1162	14.92

Case: Hyd

Design and Results of 1st HTS plate

Rational Design Based on Experience

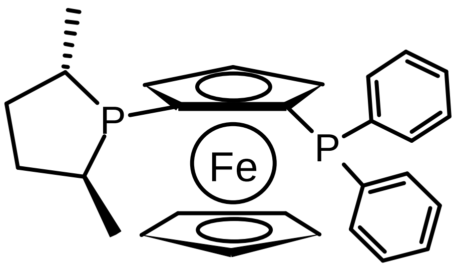
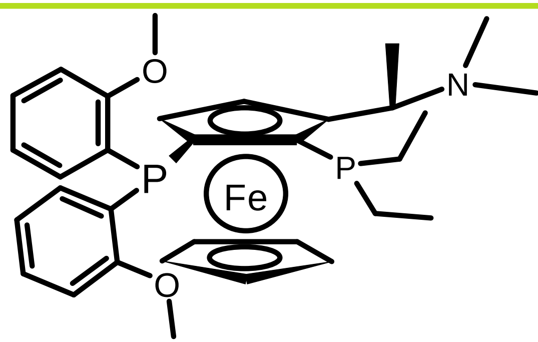
$[Rh(nbd)_2]BF_4$ *in situ* and 3 $[Rh(PP)cod]BF_4$

13 Ligands (Josi-, Ke-Tania-, Wal-, Mandy-, Fengphos, DIPAMP)

MeOH

NEt_3 DMAP

HT Screening: „In situ mixing“, s/c: 25; 1 bar, 25°C, 1h

	Hit 1	**Hit 2**
*Ligand	 **Kephos SL-P053-2**	 **SL-F056-1**
metal **conv.[%]** **ee[%]**	**$[Rh(nbd)_2]BF_4$** **100** **92**	**$[Rh(nbd)_2]BF_4$** **100** **90**

- **ee <95%**
- **experimental ligands**

Felix Spindler (unpublished results)

Design and Results of 2nd HTS plate
"Serendipity added" Design

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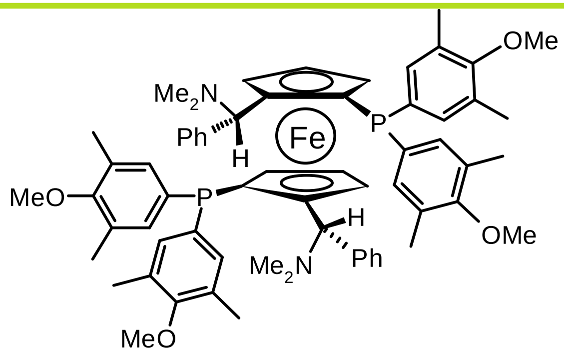
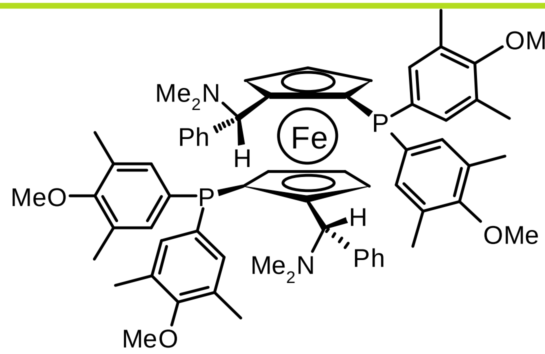
$[Rh(nbd)_2]BF_4$, $[(Rh(cod)Cl]_2$, $[Ir(cod)Cl]_2$ $[Ru(p\text{-}cymene)I_2]_2$	**27 Ligands** (10 Fengphos, 6 Kephos, Tania-, Wal-, Mandy-, Josiphos, BINAP, bppm)	MeOH, DCE, Toluene

HT Screening: „In situ mixing“, s/c: 25; 10 bar, 40 °C, 15 h

	Hit 1: in MeOH	Hit 2: in EtOH/DCE = 2/1
*Ligand	 **Mandyphos SL-M004-1**	 **Mandyphos SL-M004-1**
metal **conv.[%]** **ee[%]**	$[RuI_2(p\text{-}cymene)]_2$ 100 >98 (R)	$[Ir(cod)Cl]_2$ 100 87 (S)

- **ee >95%**
- **Commercial ligand**

Ulrike Nettekoven (unpublished results)

Case: Hydrogenation of Acrylic Acid

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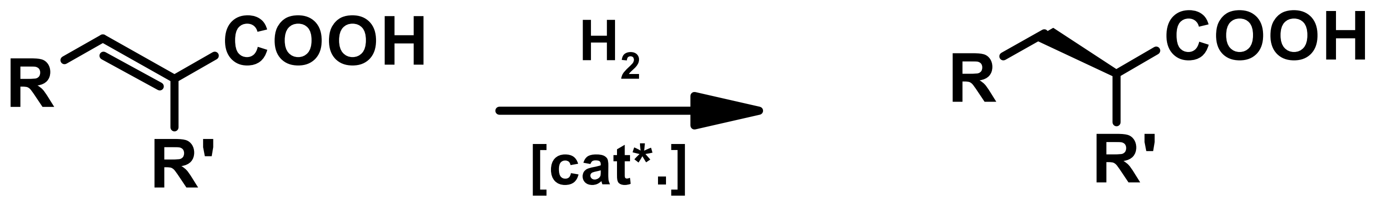

R = alkyl, R' = functionalized alkyl

Targets:

- >95% ee
- 3 kg product delivery within 3 months
- Commercially available ligand

Delivered:

98% ee

s/c 1000, tof 250 h^{-1}

3 kg product delivery within 5 weeks

Commercial ligand (Solvias Portfolio)

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Conclusions

- Process development CAN be accelerated
- Most potential: Screening phase
- High throughput screening set-up very effective
- Suitable screening strategy important
- Essential: EXPERIENCED SCIENTISTS

Conclusions

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- HTS gives reproducible results
- Larger experimental space explored (more leads, faster AND novel solutions)
- Experience AND serendipity important
- BUT: No replacement for classical experimentation

Conclusion

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- Scale up equipment

Acknowledgements

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Walter Weissensteiner, University of Vienna

Armin Börner, Likat Rostock

Albrecht Salzer, RWTH Aachen

Andreas Pfaltz, University of Basel

Antonio Togni, ETH Zürich

Pher Andersson, University of Uppsala

Think catalytic!

Amazing where you can go