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

Entwickeln von katalytischen Prozessen

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland

Amazing where you can go

Time Constraints

Two different cases:

- Process for known building block
- Asymmetric process for commercial racemic compound (chiral switch)

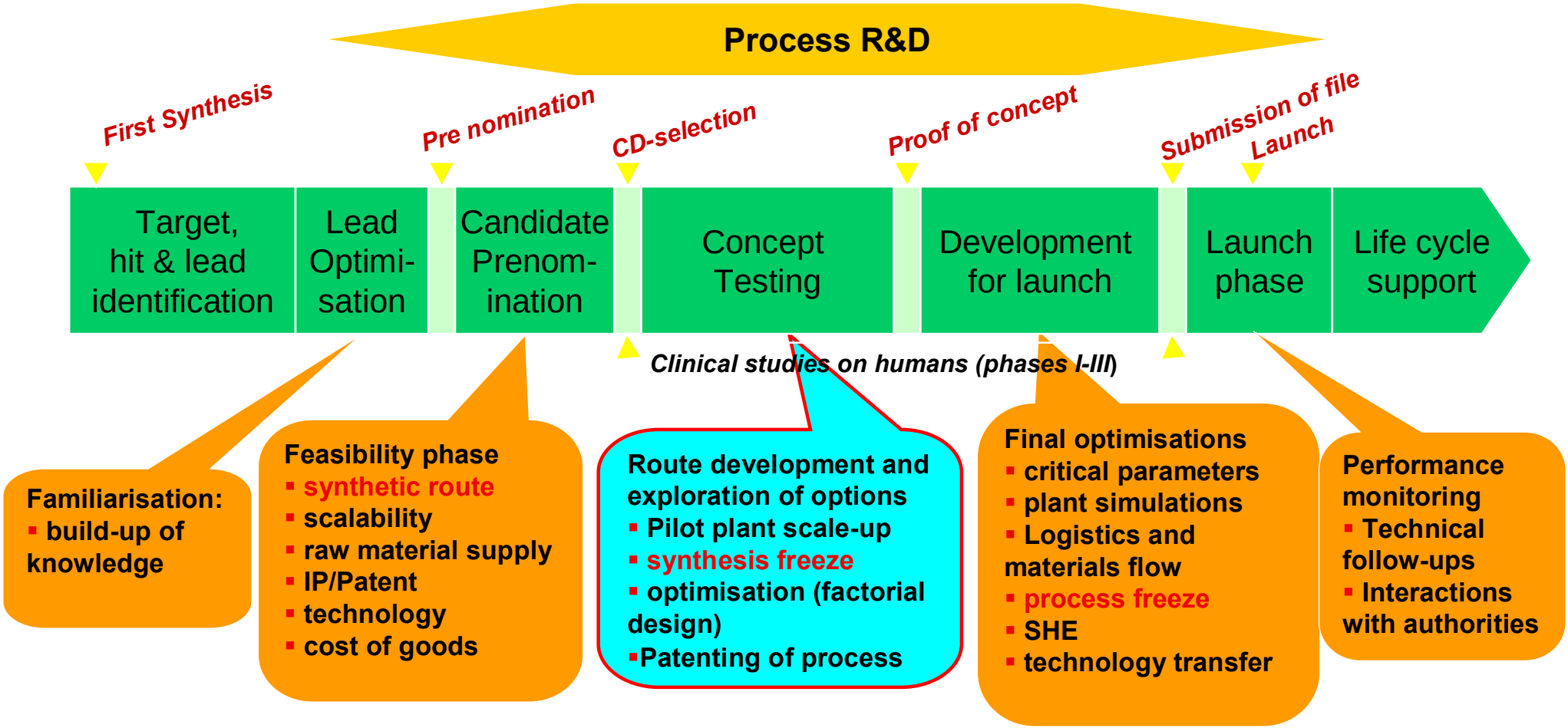
➢ **Development time and effort not critical**

- Asymmetric process for new active compound

➢ **Development time and effort very critical**

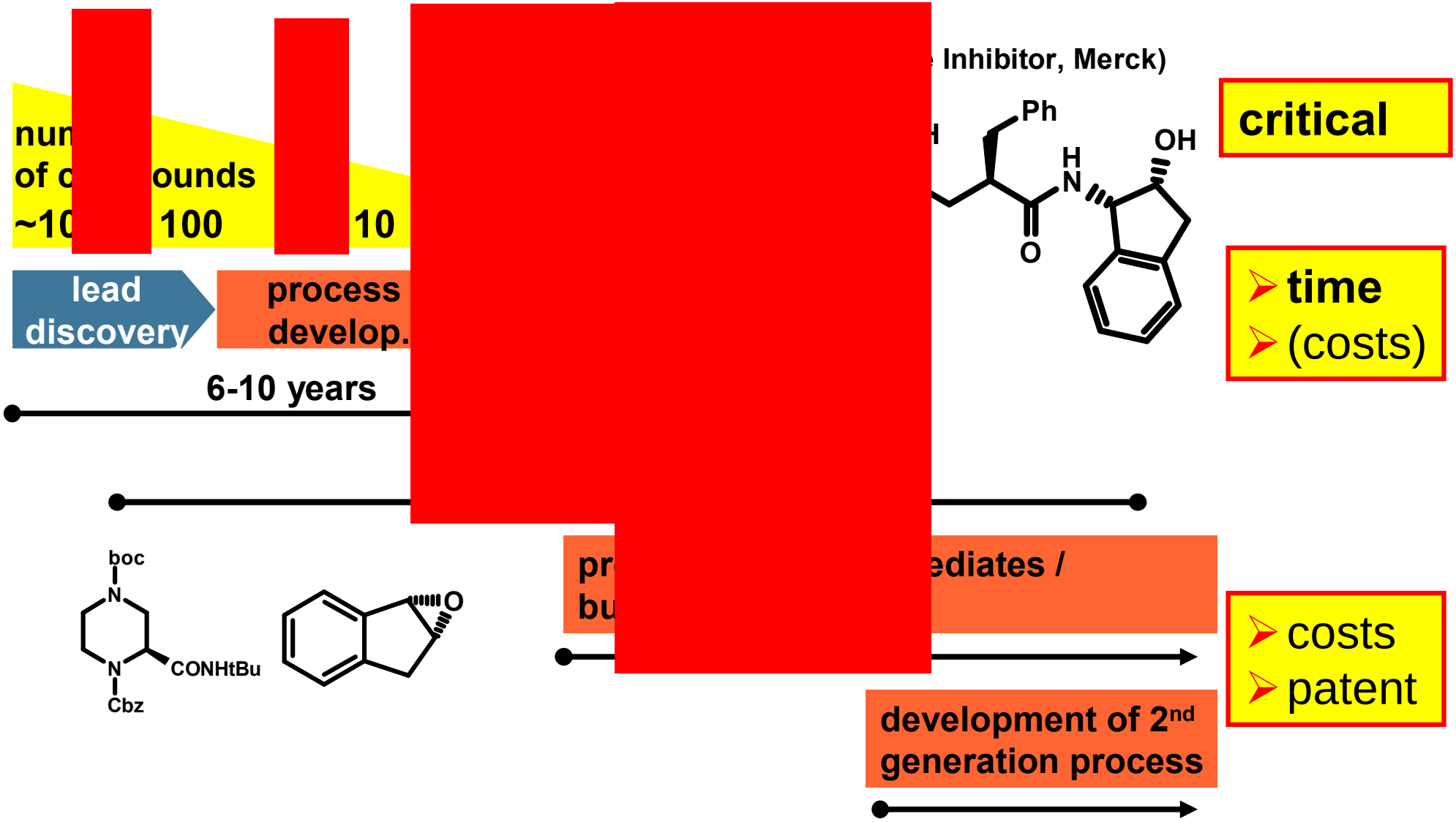
Time Factor

Development Phases in the Pharma Industry



Hans-Jürgen Federsel, AstraZeneca PR&D

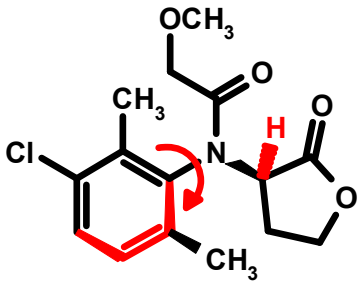
Life Cycle Pharmaceutical
Opportunities for Catalysis



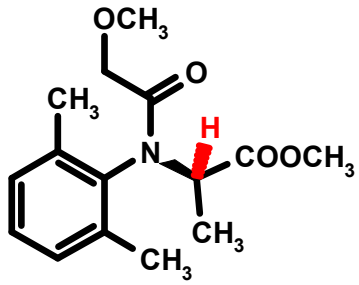
Development Phases for EPC Synthesis

- **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

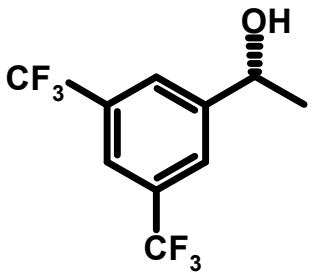
Three Case for Illustration



clozylacon **Buser, Pugin, Spindler 1990 - 91**



metalaxyl **Buser, Pittelkow, Spindler 1993**



(R)-BTMPE **Spindler, Naud 2005**

Development Phases for EPC Synthesis

- **Phase 1:** Design and assessment of synthetic routes

Assessing Routes

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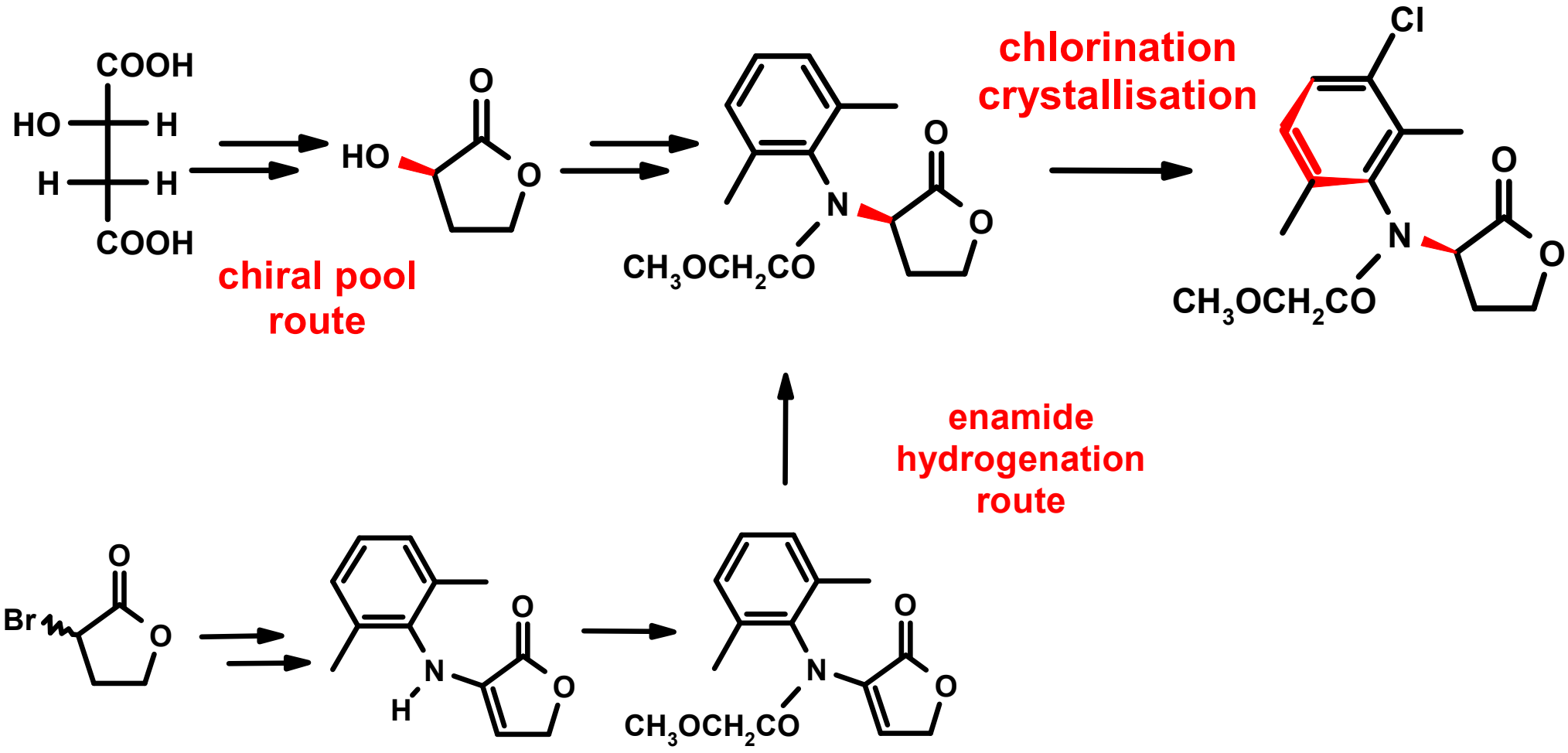
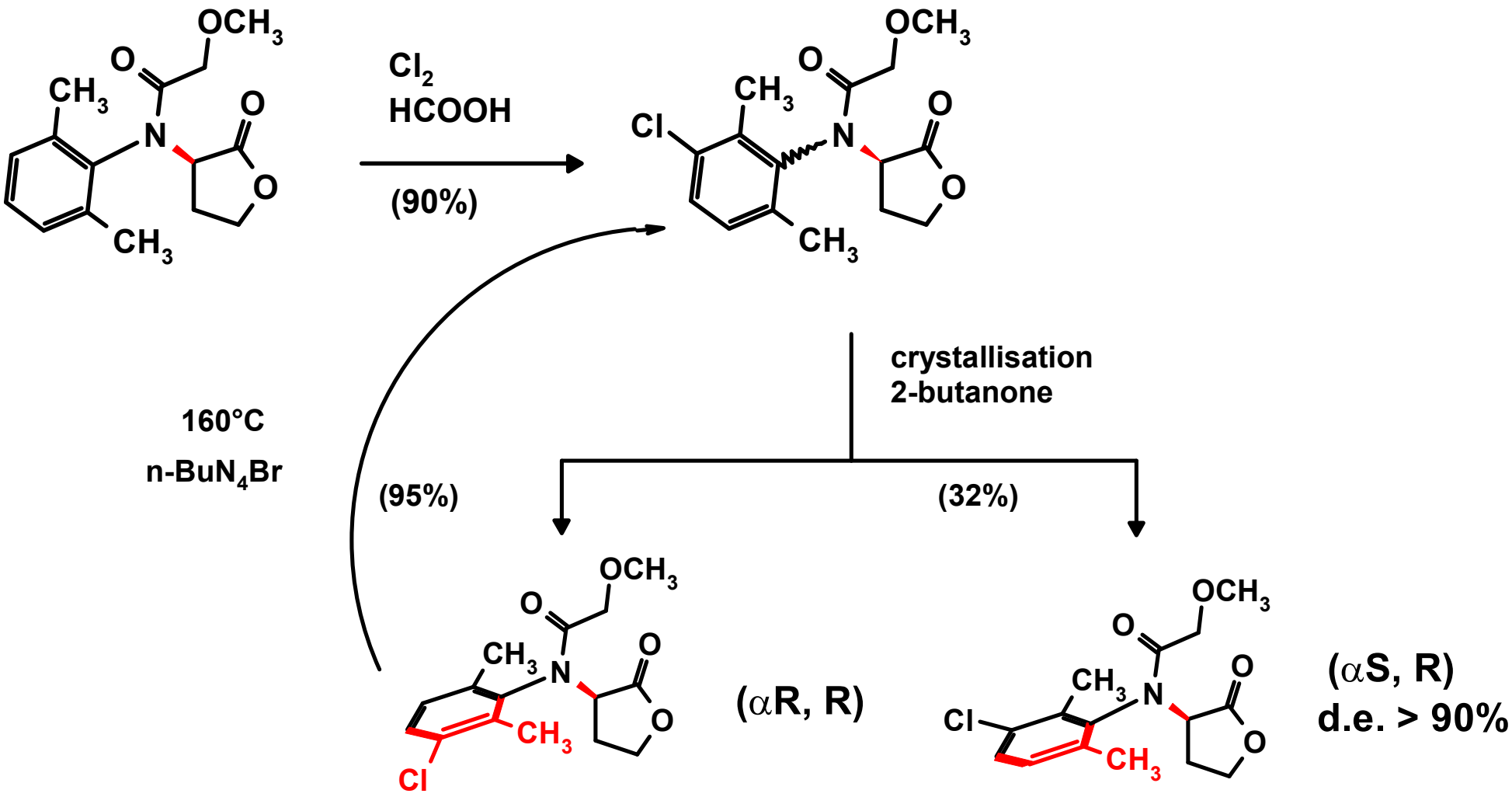
- Chances of success for the key (catalytic) steps (precedents, experience, intuition)
- Number and perceived difficulty of the non-catalytic steps
- First approximations for costs and ecology of the over-all synthesis

Routes to (αS,3R)-Clozylacon

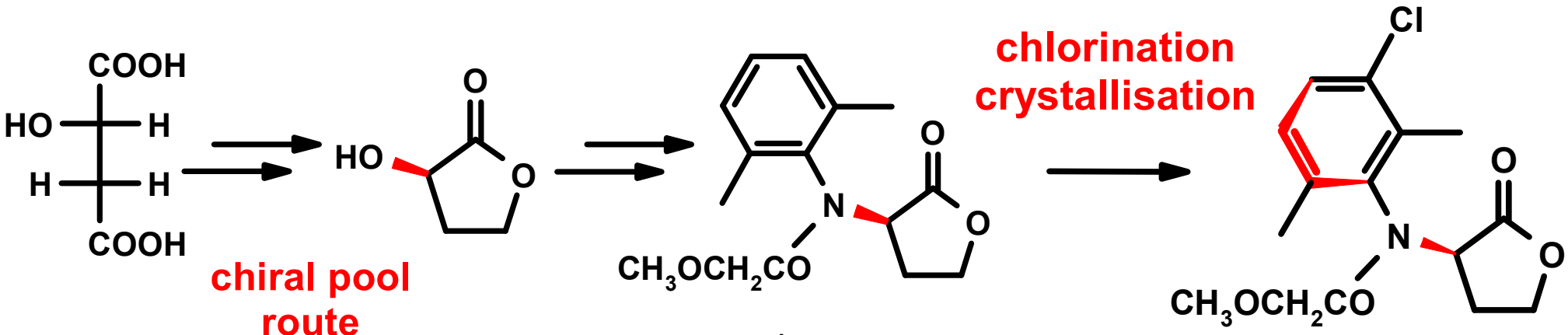


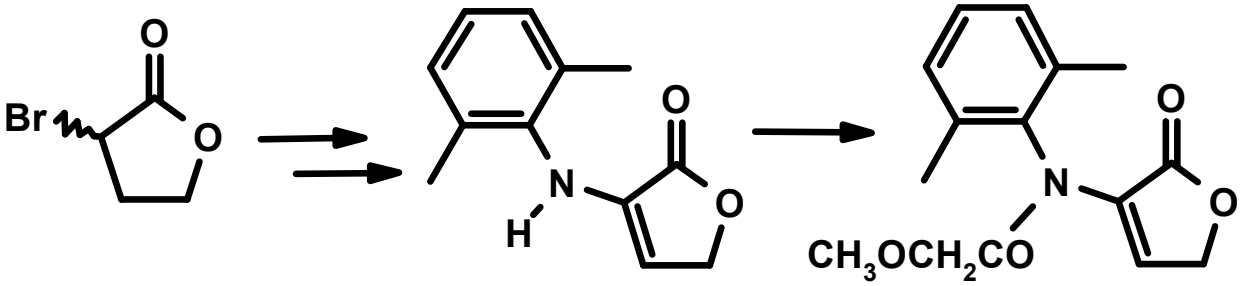
Clozylacon: Separation of Diastereomers Already Solved



Routes to (αS,3R)-Clozylacon

High chances for success; more steps





low chances for success; probably more economical

The Enamide Route

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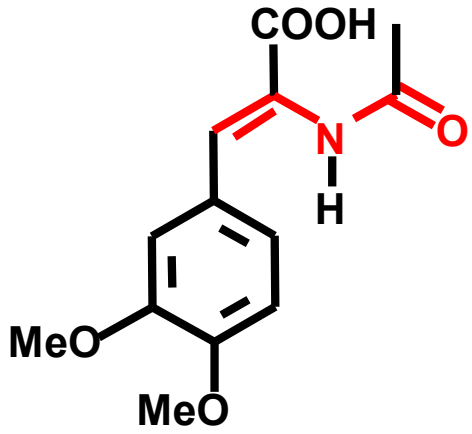
The Analogy

L-Dopa
Rh-dipamp

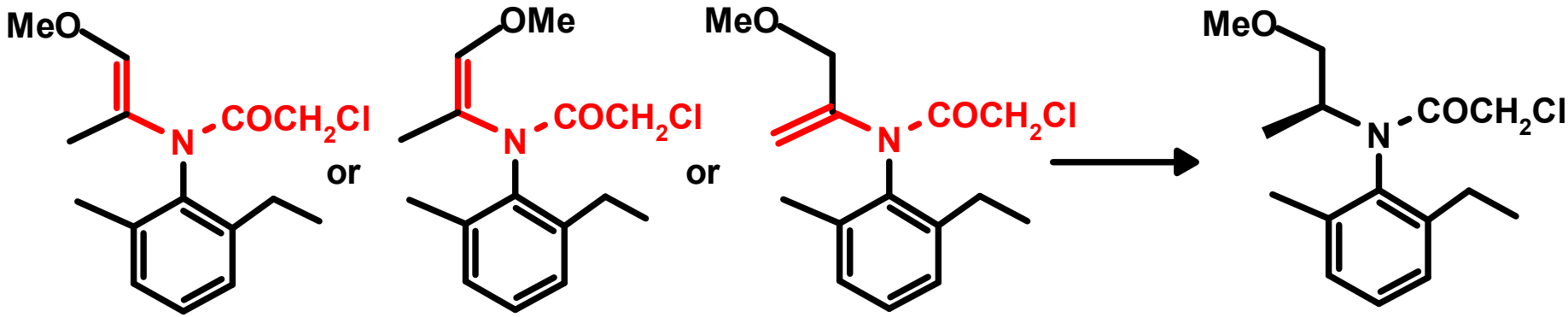
(Monsanto)



ee 96%
ton 10‘000

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

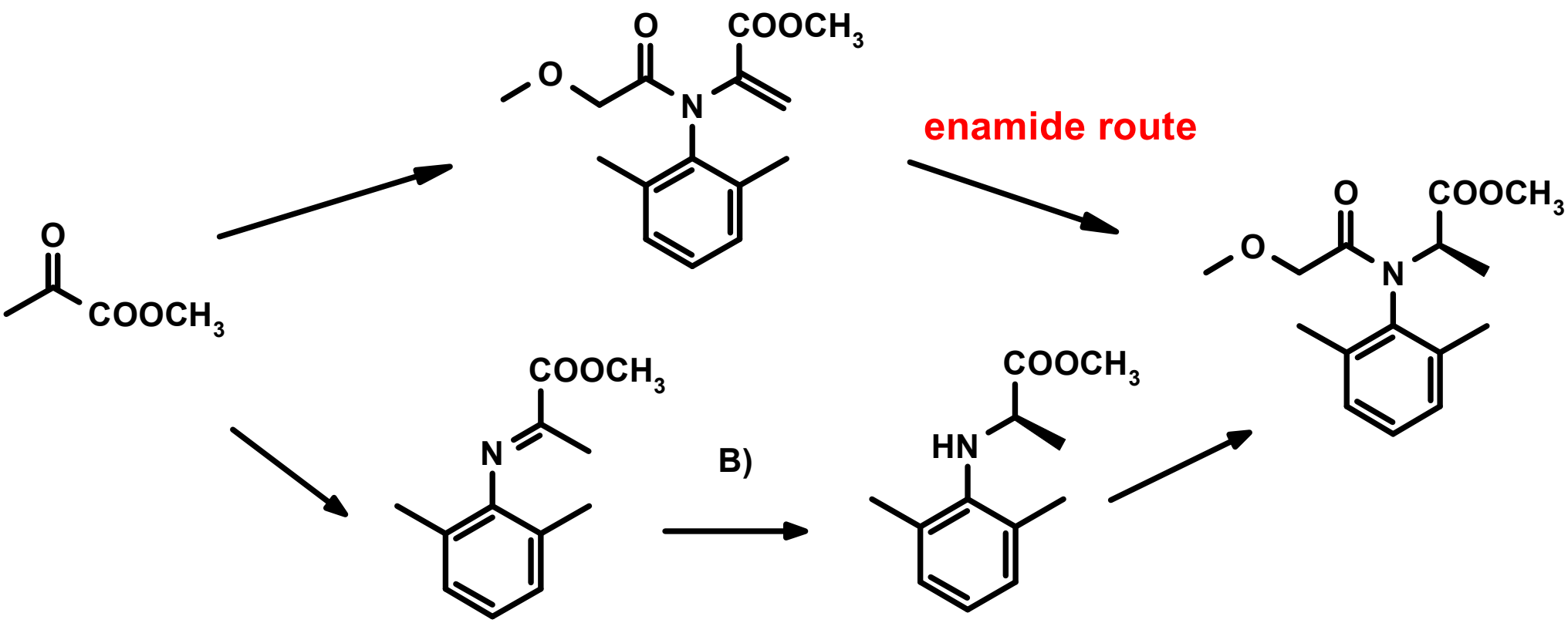
NO activity at all!!



H.U. Blaser, F. Spindler 1983

Routes to (R)-Metalaxyl

low chances for success; 2 steps



better chances for success; 3 steps

Development Phases for EPC Synthesis

- **Phase 2:** Demonstrating chemical feasibility

Criteria for an Industrial Catalyst (Hydrogenation)

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Enantiomeric excess, ee

>99% (pharma); >80% (agro or if further enrichment easy)

Catalyst productivity, ton ⇒ catalyst cost

>1000 (small scale, high value); >50‘000 (large scale, low price)

Catalyst activity, tof ⇒ production capacity

>500/h (small scale); >10‘000/h (large scale)

Key Problems

- Find the right catalyst type
  - Analogies
  - Screen existing catalysts
  - Develop / synthesize new catalysts / ligands
- Optimize / modify / promote catalyst
- Optimize process (solvent, p, T, etc.)
- Identify catalyst poisons

Toolbox for Fast Development

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- Library of chiral ligands / metal precursors
- Experimental setup for fast testing
- Reaction data bases (internal and literature)
- Analytical procedures
- Experienced chemists

Screening Trends

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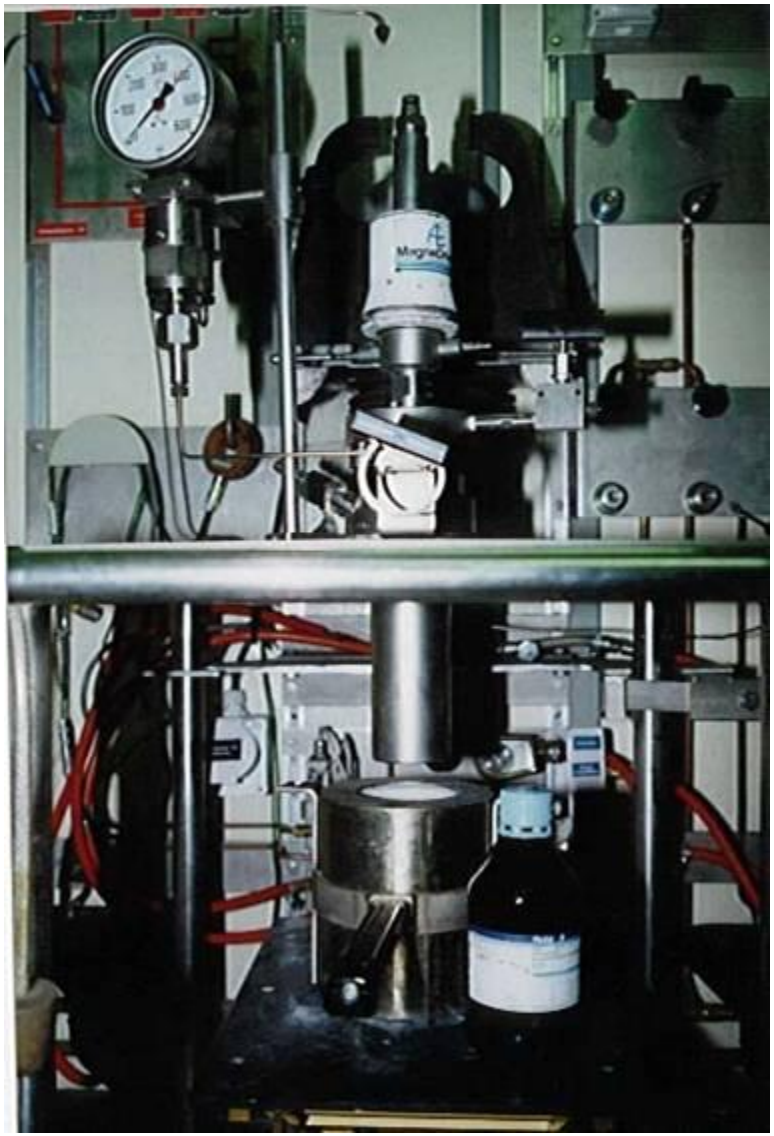
- Faster response / higher efficiency necessary
- Smaller amounts of substances available
- More catalysts available (ligands, precursors, ...)
- Data mining becomes more important
- Progress in Automation / data processing
- New equipment available

- Triumph of high throughput philosophy

Screening a Few Years Ago



series of 50 ml autoclaves

300 ml autoclave

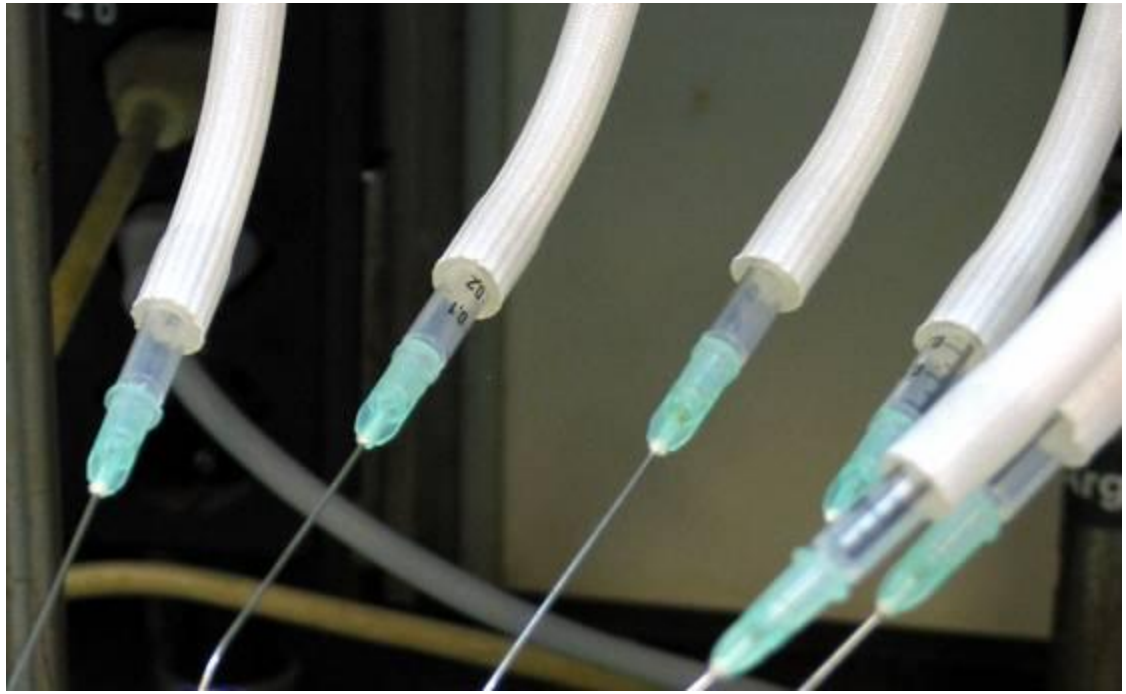
Screening Now

Chemspeed robot (3 x 16 vials)

4 vials per 50 ml autoclave

➢ **Know Scope and Limitations!!**

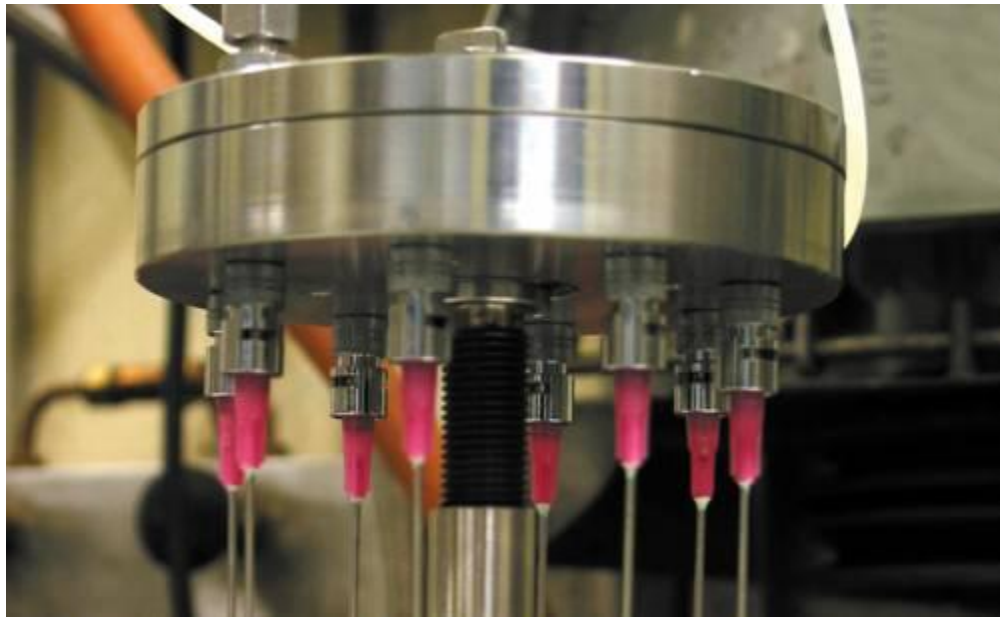
The Solvias Octoclave



Loading under inert conditions

- **8 parallel runs with gaseous reactants**
- **very good mixing**

The Solvias Octoclave



Under pressures up to 100 bar

Seamless Scale-up

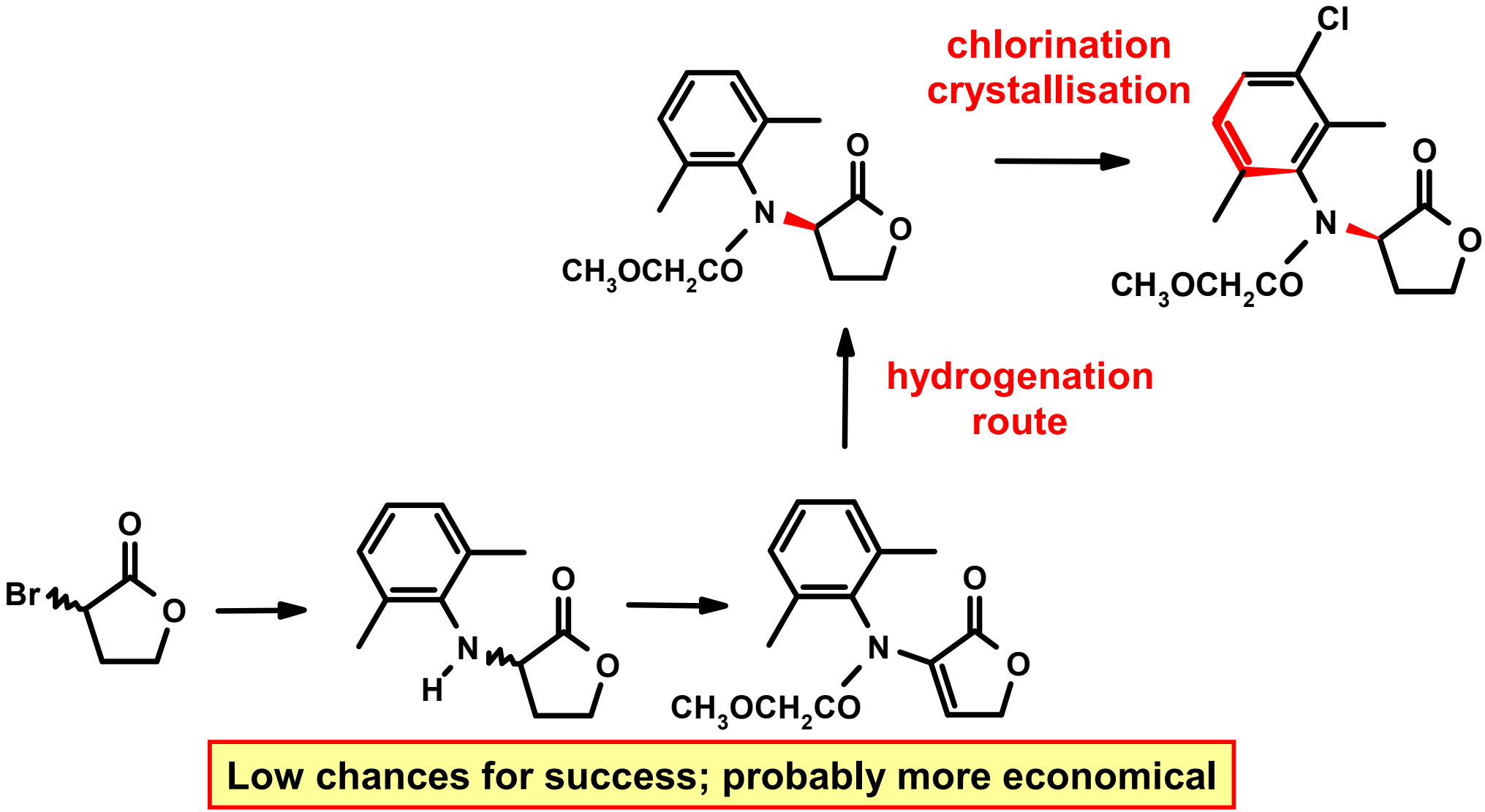
100 ml to 1 l
(various alloys)

8 l to 16 l
(Hast C, 300bar)

50 l
(100bar)

Scale up to 50 l directly or in steps
(300ml, 1 l, 2 l, 6.3 l, 8 l, 16 l)
Transfer to Production facility

Routes to (αS,3R)-Clozylacon



Low chances for success; probably more economical

Clozylacon Catalyst/Ligand Screening

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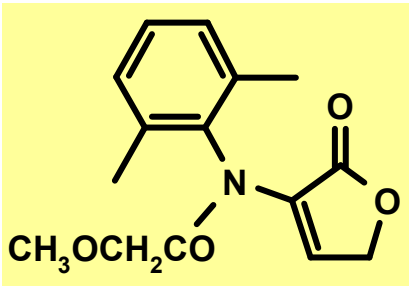
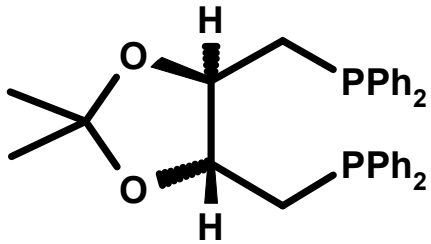
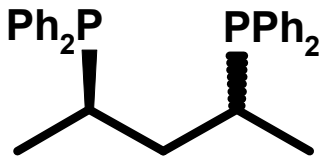


11 of 15 available catalysts tested

$[Rh(nbd)(PP)]BF_4$



diop



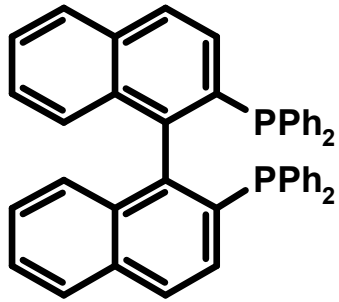
bdpp

ton	**50 - 200**	**50**
ee	**46 - 85 %**	**75 %**

➢ **Catalyst productivity too low**

Buser, Pugin, Spindler 1990

$[Ru(OAc)_2(S)\text{-binap}]$



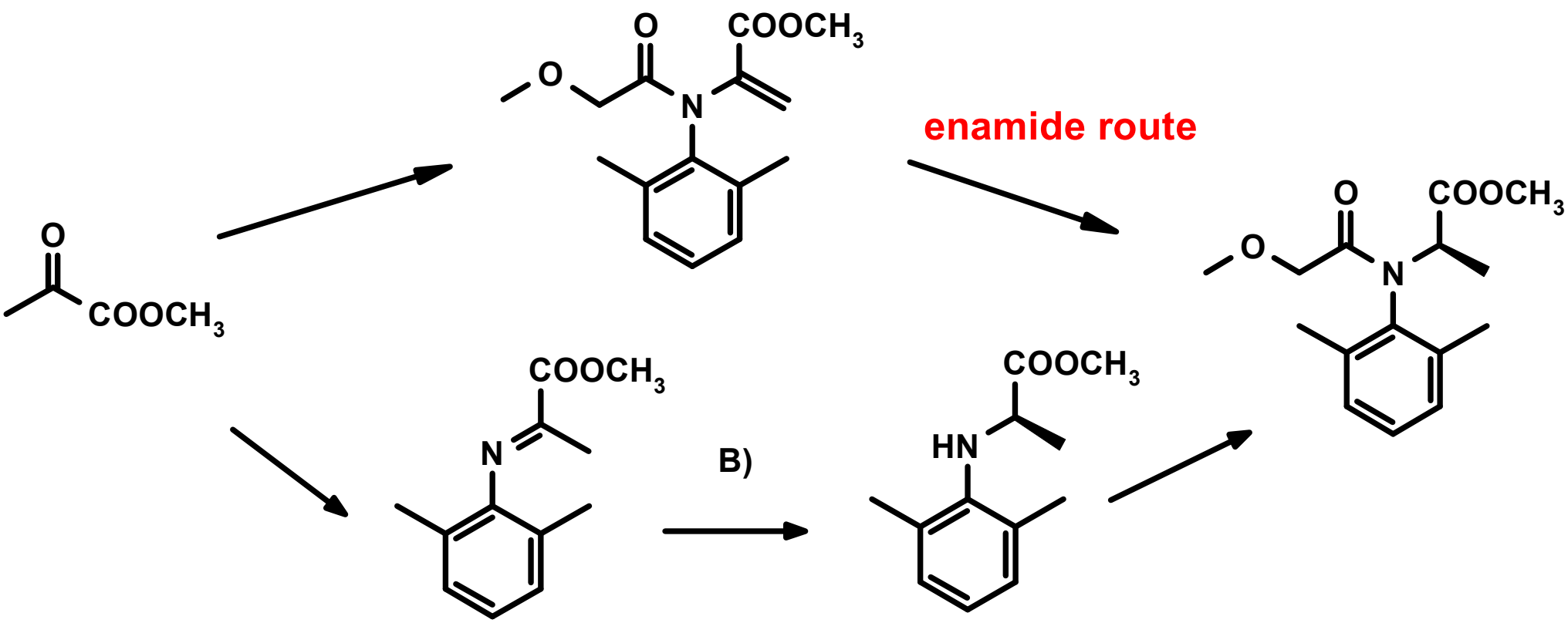
200 - 4,000

66 - 67 % (> 99 % after cryst.)

Further development feasible
BUT: Project abandoned

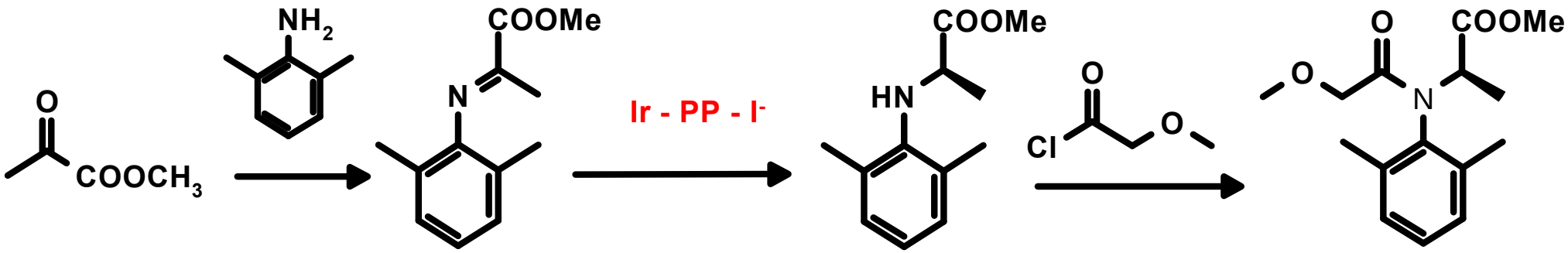
Routes to (R)-Metalaxyl

low chances for success; 2 steps

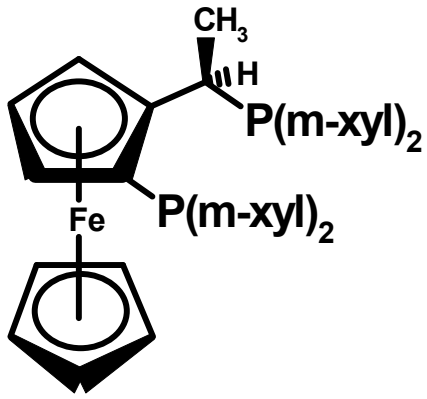


better chances for success; 3 steps

Metalaxyl
Imine Hydrogenation



Best ligand

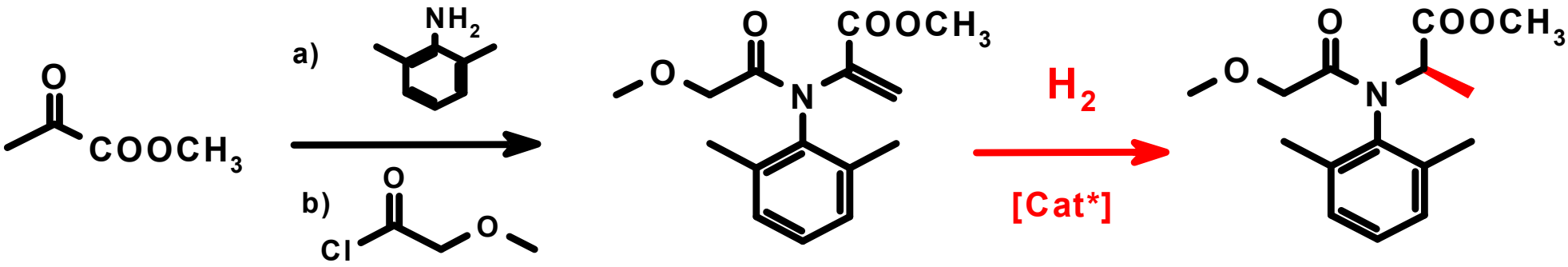


Best result:

ee: 30%

tof: 2 h^{-1}

(R)-Metalaxyl
Enamide Hydrogenation



Metalaxyl: Enamide Route
Catalyst Screening: Best Results

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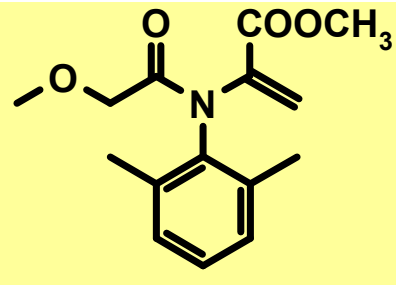
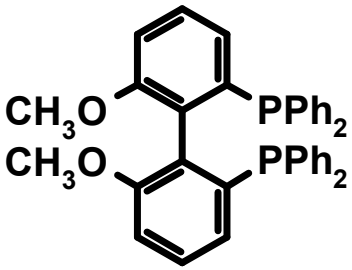
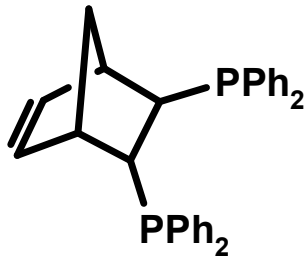


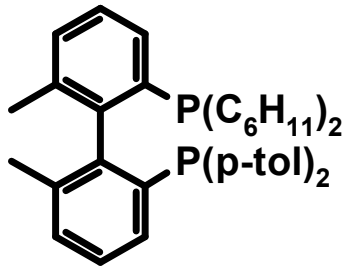
34 of approx. 100 available Rh catalysts tested



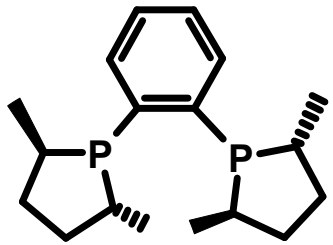
(S)-MeO-biphep



(2S,3S)-norphos



(S)-cy-*p*-tol-biphemp



(R,R)-Me-duphos

ee	**97 (R)**	**94 (R)**	**99 (R)**	**98 (R)**
tof	**55**	**3300**	**4,000**	**4,600**

➢ **Further development feasible**

Buser, Pittelkow, Spindler 1993

Development Phases for EPC Synthesis

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- **Phase 3:** Optimizing the key (catalytic) reaction(s)

Metalaxyl: Enamide Route Bench Scale Process

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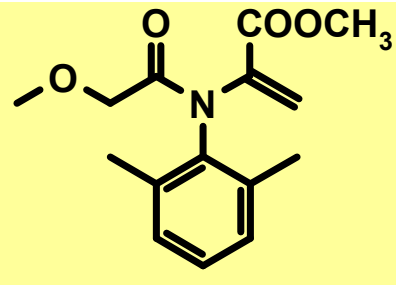
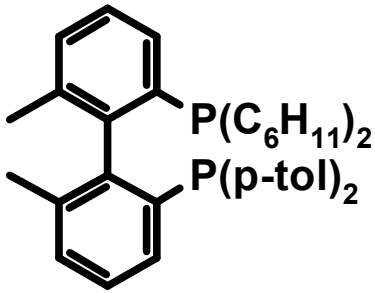
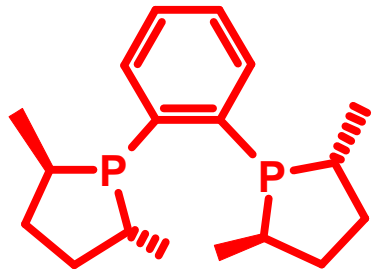


Targets	**ee >95%, ton >50,000; tof >4,000 h^{-1};**
Limitation	**H_2-pressure: < 10 bar**

Catalyst
$[Rh(nbd)(PP)]BF_4$





	***(S)*-cy$_2$-*p*-Tol-biphemp**	***(R,R)*-Me-duphos**
ton / ee	**20,000 / 95%**	**50,000 / 95.5**
tof (h^{-1})	**1,800**	**5,300**

➢ **Rh/Me-duphos catalyst: technically feasible**
BUT: Non-catalytic route chosen

BTMPE – An Important Chiral Building Block

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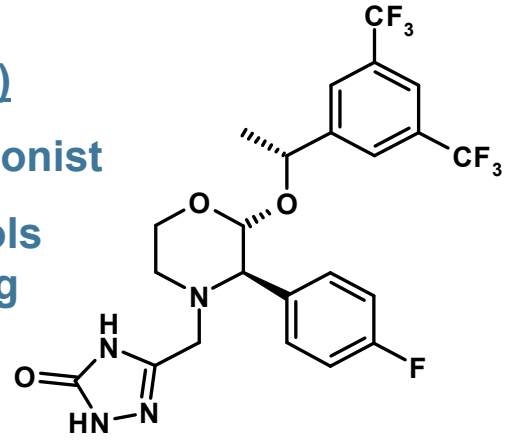
Emend® (Aprepitant)

NK_1 Receptor Antagonist

Prevents and controls nausea and vomiting



Aprepitant

(Merck & Co. Inc.

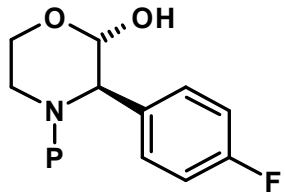
Methods for Preparation of BTMPE:

Asym. Transfer Hydrogenation: Ru/HAI: 91%ee (>99%ee) – 40 kg scale (Merck)

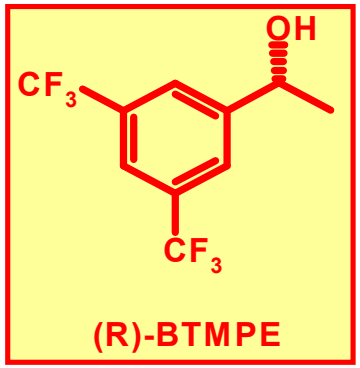
Asym. Hydrogenation: (Ru/PP/NN) ??

Hydride Reduction: >90% ee

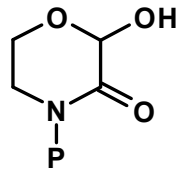
Enzymatic/Microbial Reduction: 99%ee



M. Zhao, et al., JOC, 67, *2002*, 6743.



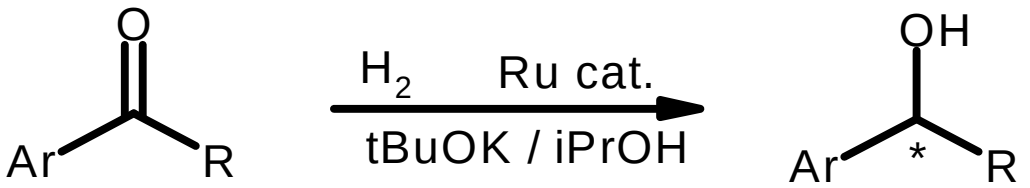
Chiral Building Block

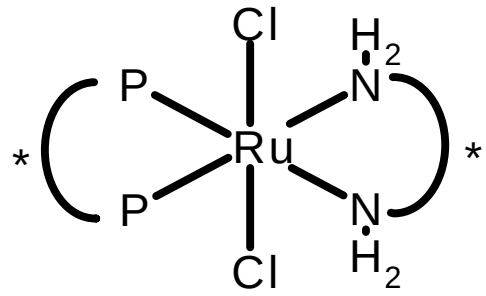


K. Brands, et al., JACS, 125, *2003*, 2129.

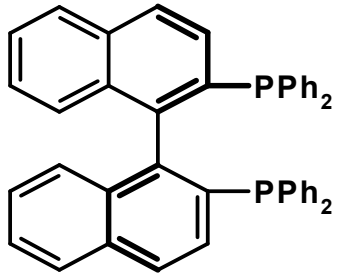
Quest for alternative scalable hydrogenation process

Enantioselective Hydrogenation of Aryl Ketones – State of the Art

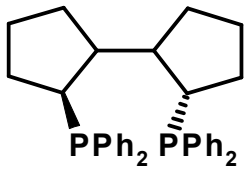




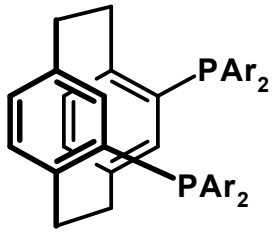
Noyori catalyst



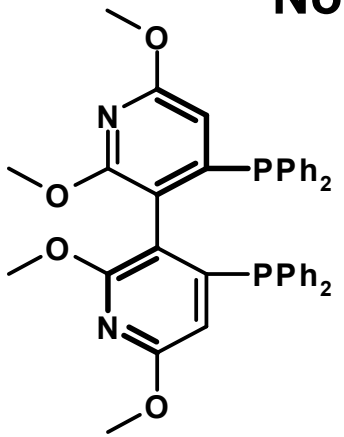
binap **>99%ee**
(R. Noyori, 1998)
ton: 2'400'000 (80%ee)



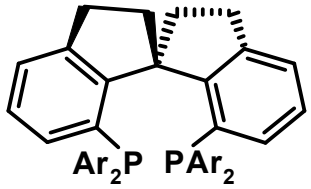
bicp **>90%ee**
(X. Zhang, 1999)



phanephos **>99%ee**
(M. Burk, 2000)



P-phos **>99%ee**
(A. Chan, 2002)



sdp **>99%ee**
(Q.-L. Zhou, 2003)

- **Problem: All catalysts patent-protected**

Enantioselective Hydrogenation of Aryl Ketones – A New Catalyst

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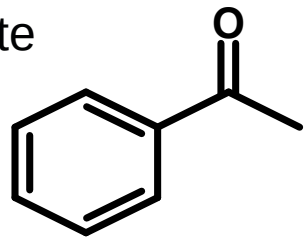
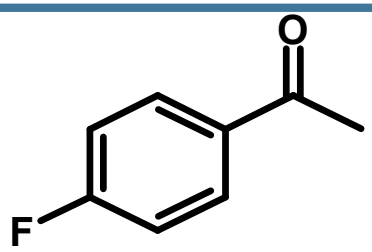
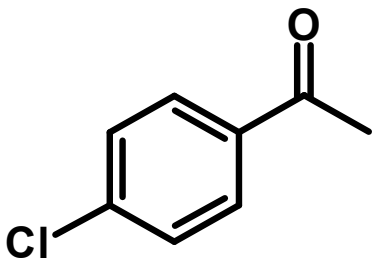
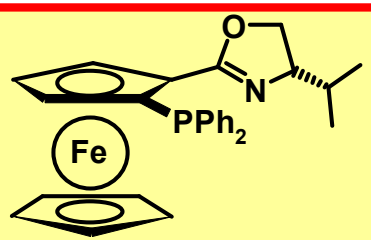
Substrate	 1	 2	 3
Catalyst	 / $RuCl_2(PPh_3)_3$		1kg Substrate 1l Toluene 200mg Ligand 200mg Ru Precursor
Yield [%]	100 in 1h/10'000; 8h/50'000	100 in 2h/5'000	100 in 1.5h/20'000; 6h/50'000
ee (%)	98.5	98	98

➢ **High enantioselectivity AND high activity**

F. Naud, C. Malan, F. Spindler, C. Rüggeberg, A.T. Schmidt, H.U. Blaser, "Ru-(phosphino-oxazoline) complexes as effective, industrially viable catalysts for the enantioselective hydrogenation of aryl ketones", Adv. Synth. Catal. 348 (2006) 47.

Target:
Manufacturing of 200 kg (R)-BTMPE

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Situation and Goals

- **Tough time lines: 2 months for development of process (collaboration with Rohner (CMO))**
- Enantiomeric purity of crude (R)-BTMPE (after hydrogenation): **≥95% ee**
  (Enantiomeric enrichment by re-crystallization (DABCO))
- Enantiomeric purity of isolated (R)-BTMPE: **>98% ee**
- **s/c: ≥20'000**
- Robust process
- **Specific: 20 bar hydrogen pressure; conc.: 10% BTMA (w/v)**
  (4'000 m^3 reactor)

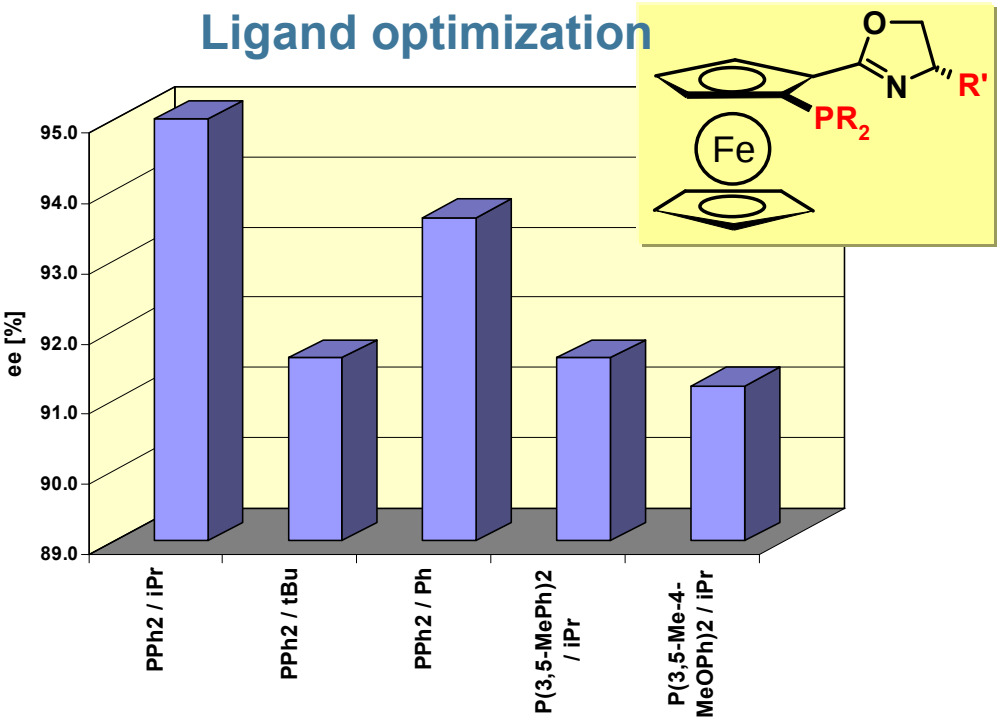
Hydrogenation of BTMA

Optimization of Reaction Parameters – I.

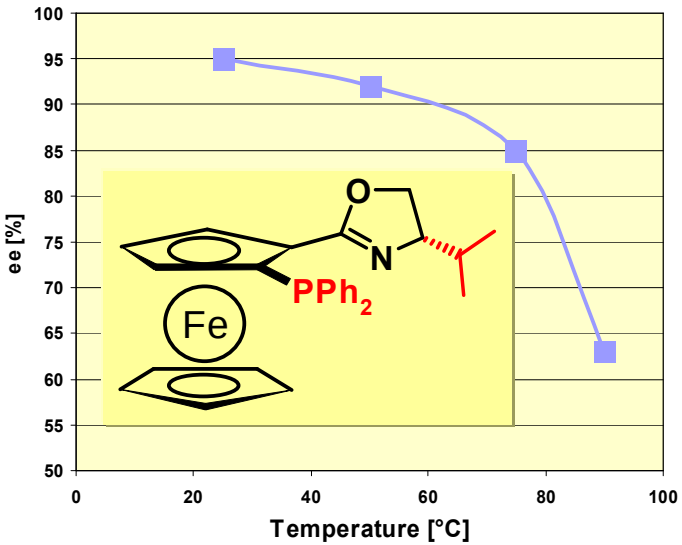
Reaction conditions: 2.3 mmol BTMA; Ru cat.; s/c: 500; 20 bar H_2; Toluene; NaOH (1N, aq)

Catalyst: $[RuCl_2(POx)(PPh_3)]$ or $[RuCl_2(PPh_3)_3]$) + POx;

Ligand optimization



Temperature vs. ee



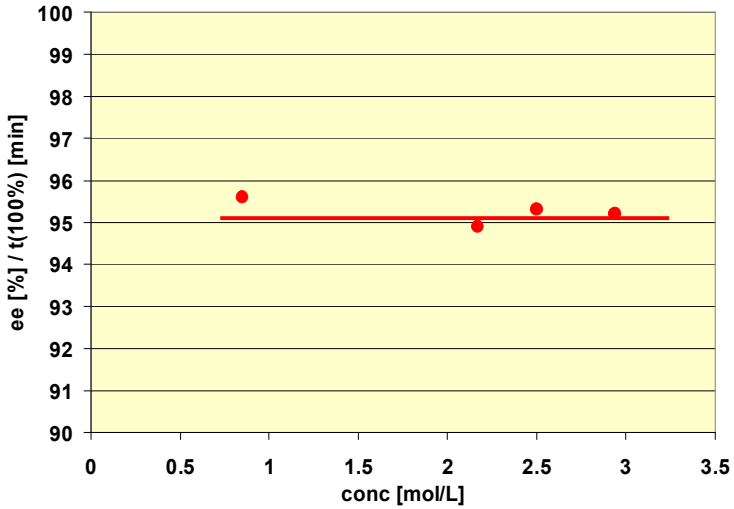
PPh_2Fc-oxa-iPr: Optimum Ligand

20 – 30 °C: Optimum Temperature

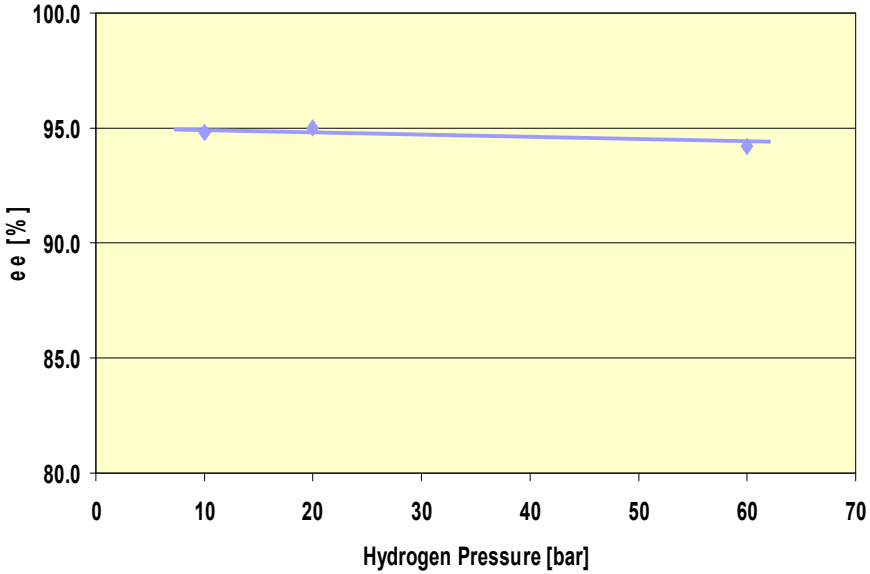
Hydrogenation of BTMA

Optimization of Reaction Parameters – II.

ee independent on concentration



ee only marginally dependent on H_2 pressure



Reaction conditions: 50 mmol BTMA; Ru cat.; s/c: 10'000; 20 bar H_2; Toluene; NaOH (1N, aq)

Catalyst: $[RuCl_2(POx)(PPh_3)]$ or $[RuCl_2(PPh_3)_3]$) + POx;

Development of Robust Processes
Quality Risk Analysis

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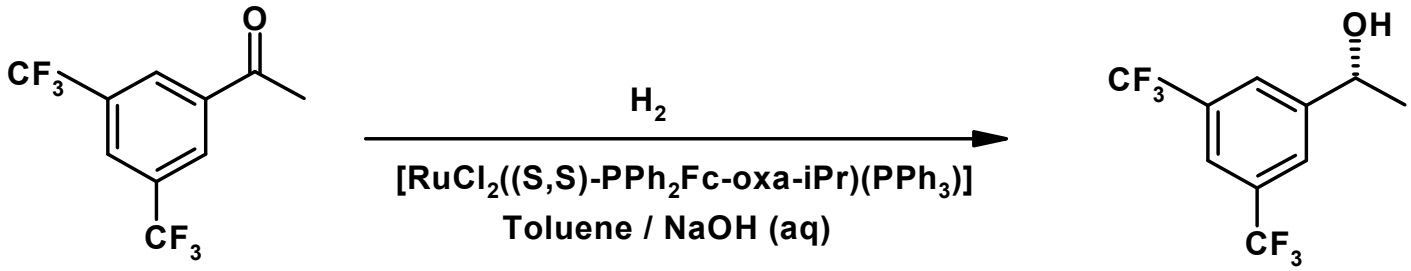
Identification of relevant parameters for a robust process

- **No standard procedure (strongly dependent on catalyst and substrate)**

Typical parameters to investigate

- **Substrate (Impurity profile; Definition of specifications)**
- **Catalyst (Definition of purity; Quality tests: use tests)**
- **Oxygen content (Quality of gases; Purging and degassing procedures)**
- **Scale up effects (Reactor geometry, mass transport effects; Heat flow measurements)**
- **Influence of process failures (Delays during loading procedure; Interrupted stirring; Overpressure; Temporary overheating; etc.)**

Hydrogenation of BTMA
Quality of Starting Material



Producer	Quality	Conv. (%)	ee (%)	
Fluorchem	98%+ (tel quel)	100	94.8	→ pH = 6.7 – 6.9
PacificChem	99% (tel quel)	0	--	→ pH = 3.2 – 3.7
	extr. KOH/tol.	80	93.0	
	extr. KOH/tol.& brine	62	62.8	→ Inhibition by Cl^- ions
	dest. KOH	100	96.0	
Asahi Glass	tel quel	100	95.6	**Disadvantage:** Dest. over KOH Decomposition !

Hydrogenation of BTMA
Production of 200 kg (R)-BTMPE

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1st Batch:

Size	**140 kg**
Yield	**101 kg (71%)**
Purity	**>99 %**
***ee* (crude)**	**95 %**
***ee* (recryst.)**	**98 %**
Ru	**<0.1 ppm**

2nd Batch:

Scale:	**140 kg**
Yield	**100 kg (70%)**
Purity	**>99 %**
***ee* (crude)**	**96 %**
***ee* (recryst.)**	**98 %**
Ru	**<0.1 ppm**

Development Phases for EPC Synthesis

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- **Phase 4:** Optimizing the over-all process