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

Grundlagen Feinchemikalien; industrielle Aspekte der Katalyse; Chiralität; katalytische Prozesse

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland

Amazing where you can go

Inhalt

- Feinchemikalien und Katalyse (Definition, Eigenheiten)
- Chirale Moleküle (Eigenschaften, selektive Synthesemethoden)
- Enantioselektive Processe

Fine Chemicals Definition

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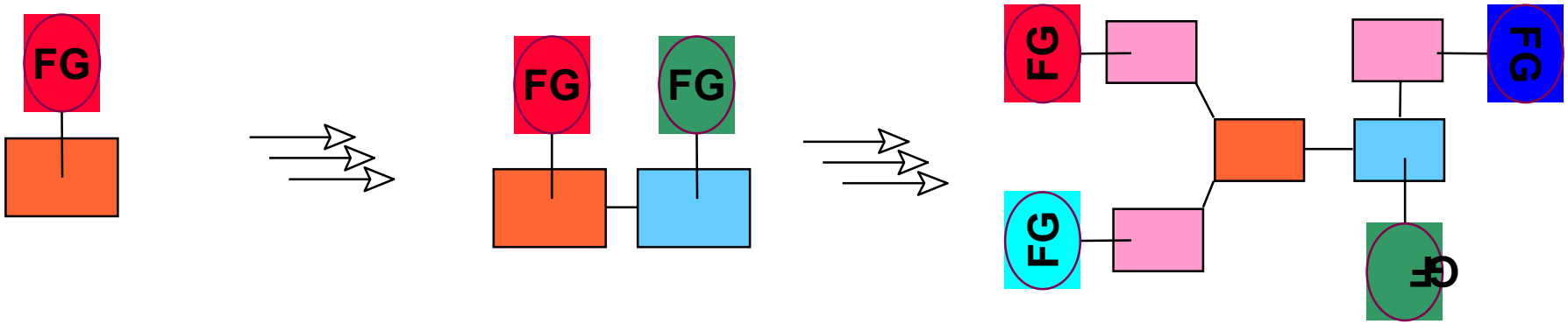
BULK CHEMICALS

FINE CHEMICALS



Small, mono-functionalized

Large, poly-functionalized

low	**number of compounds**	**high**
process / catalyst	**patents**	**compound**
high / low	**volume / added value**	**low / high**

Fine Chemicals: Characteristics

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Molecules

- stereoisomers,
- functional groups

- limited thermal stability
- low volume (1-10'000 t/y)
- limited life time

Synthesis

- multi step procedures
- classical organic reactions, catalysis as exception

- batch processes in solution
- multi purpose equipment

- short development time, low budget

Catalysts

- high chemo-, regio- and stereoselectivity
- fit into overall synthesis scheme

- good activity at low T
- batch reactors, simple technology

- commercial catalysts, limited time for catalyst development

Catalysis for Fine Chemicals

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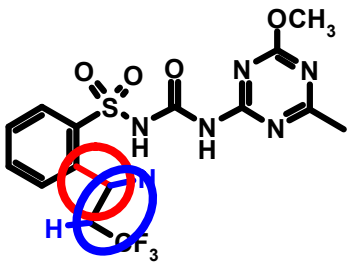

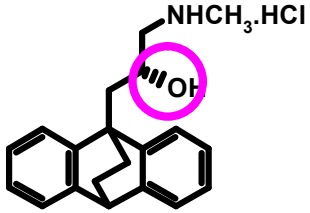

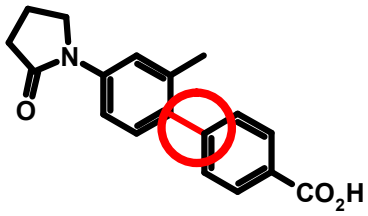

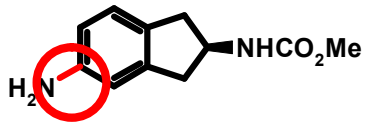

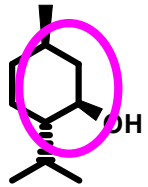

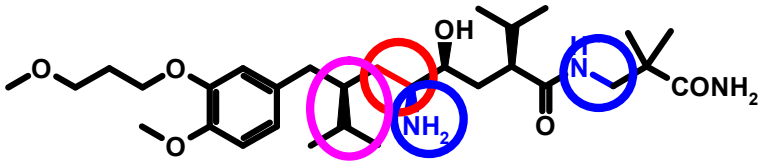

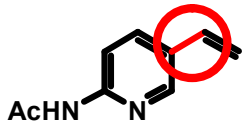

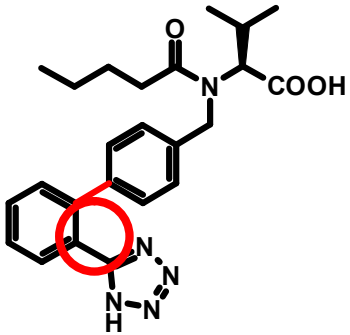

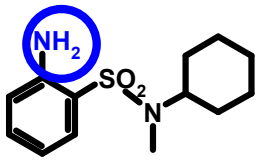

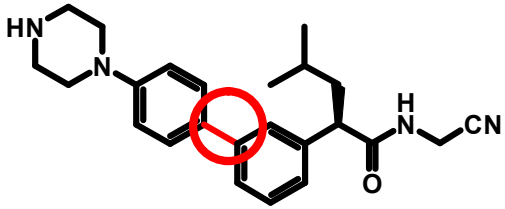

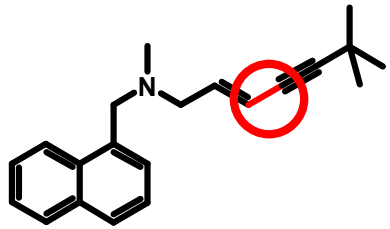

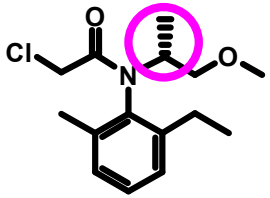

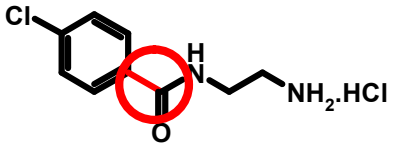

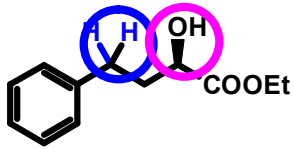

catalytic C-C coupling

heterogeneous hydrogenation

enantioelective catalysis

Fine Chemicals vs Bulk Chemicals

	Fine Chemicals	Bulk Chemicals
number of different products	large	small
volume	small / medium	large
patents	product	process
life time	short / medium	long
development time	short	long
consequences for catalysis	- processes must be flexible and competitive - development must be fast	process must be the best

“Quality” of Synthesis (Catalysis)

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Not important

discovery synthesis

pharma (agro)

- high fail rate
- multi parallel methods

important but not critical

new active compounds

pharma (agro)

- % cost of goods of marketed product low
- low to medium production volume

decisive

Generica

Bulk chemicals

- % cost of goods of marketed product high
- medium to very high production volume

The E-factor (kg by-products / kg product)

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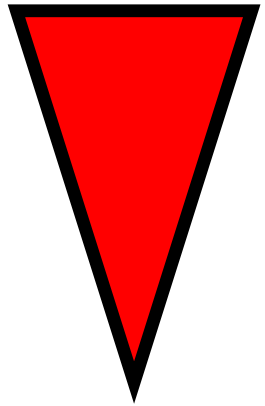
Use of Catalytic methods

Industry	Tonnage	E-factor
Oil refining	10^6 - 10^8	ca 0.1
Bulk chemicals	10^4 - 10^6	< 1-5
Fine chemicals	10^2 - 10^4	5 - >50
Pharmaceuticals	10 - 10^3	25 - >100
Bechamp Red.	10^2 - 10^4	ca. 15
Catalytic Hydrog.	10^2 - 10^4	< 1



R.A. Sheldon, Chem.&Ind., 1992

Report Deutsches Umweltamt

Waste Prevention by Using Catalytic Methods

"Abfallvermeidung bei Produktionen für organische Spezialchemikalien durch den Einsatz hochspezifischer Katalysatoren (Using highly specific catalysis to prevent waste when producing organic fine chemicals)"

Deutsches Umweltbundesamt, 2003

Analysis of patents	➔	Possible catalytic systems with industrial potential
Interviews with experts	➔	potential for waste reduction by using catalysis

Conclusions

Waste Prevention by Using Catalytic Methods

- Potential waste reduction within 10 years
  - → **Over-all ca. 9-14%**
  - → In Germany: 370.000 tons / year!
- Waste reduction within 10 years **ca. 30 – 60%** for
  - → Pesticides
  - → Pharmaceuticals
  - → Vitamines
  - → Organic pigments

Waste Prevention by Using Catalytic Methods: Conclusions 2

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- Reaction types with high prevention potential

  - → Oxidation (diols, epoxides, aromatics, alcohols)
  - → Reduction (hydrides, metals)
  - → Functionalization of aromatics (Friedel Craft, amination)
  - → Aliphatic amination, amino acids

  - → Chemistry without protecting groups
  - → Improved asymmetric reactions

Catalysis for Fine Chemicals Opportunities

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New transformations

- **C-C coupling reactions (e.g. Heck, Hydroformylation)**
- **Benzylic oxidation**

New selectivities

- **Enantioselective hydrogenation**
- **(Enantioselective) epoxydation**
- **Regioselective addition of HCN to C=C**

New reactants or catalysts

- **H_2 instead of metals or metal hydrides**
- **Replace toxic oxides or peracids with O_2, H_2O_2 or ROOH**
- **Solid acids and basis instead of aqueous chemistry**
- **Replace $AlCl_3$ by zeolites or clays**

Inhalt

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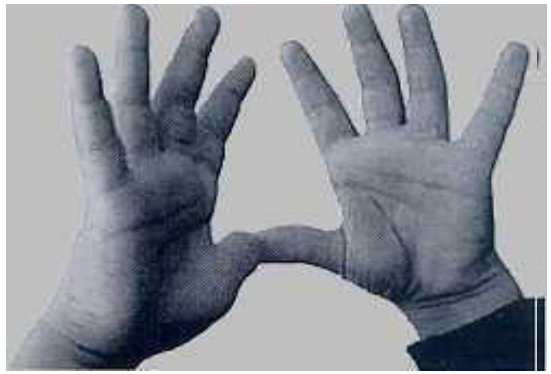
- Enantioselektive Processe

Chirality in the nature

Living organisms are chiral!!

Normally, only one enantiomer is produced in Nature

biological material recognizes enantiomers



Biological Effect vs. Absolute Configuration

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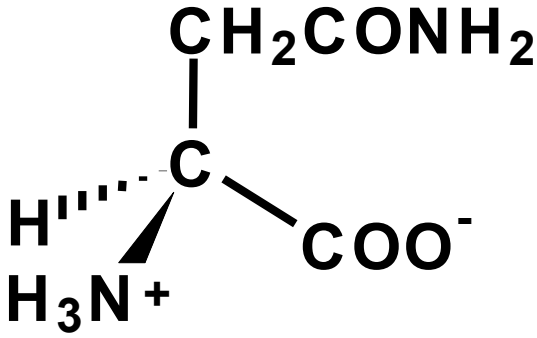
The most frequent cases

- **All stereoisomers possess nearly identical qualitative and quantitative biological activity**
- **The stereoisomers have qualitatively similar activities but quantitatively different properties**
- **The stereoisomers have qualitatively different biological activities (biological activity in one stereoisomer)**

G.M. Ramos, D. Bellus et al. Angew. Chem 103 (1991) 219; Bull. Soc. Chim. Belg. 103 (1994)

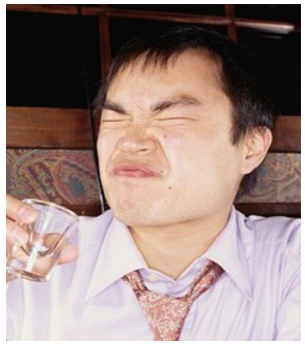
G.M. Ramos Tombo, H. U. Blaser, "Chirality in Agrochemistry: An Established Technology and its Impact on the Development of Industrial Stereoselective Catalysis" in "Pesticide Chemistry and Bioscience" G.T. Brooks, T.R. Roberts (eds.), Royal Society of Chemistry, Cambridge, 1999, p. 33.

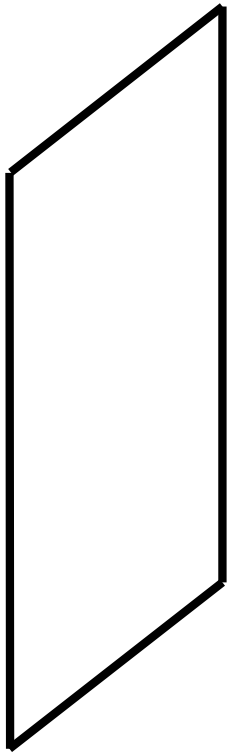
Chiral Aminoacids



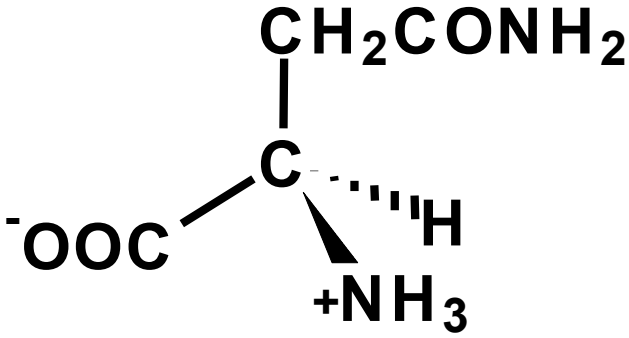
S-aspargine

bitter





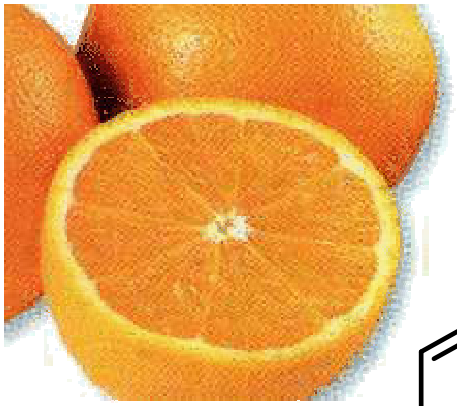
enantiomers

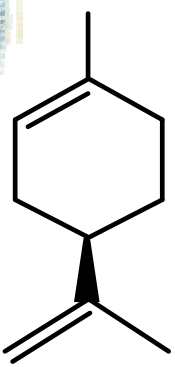


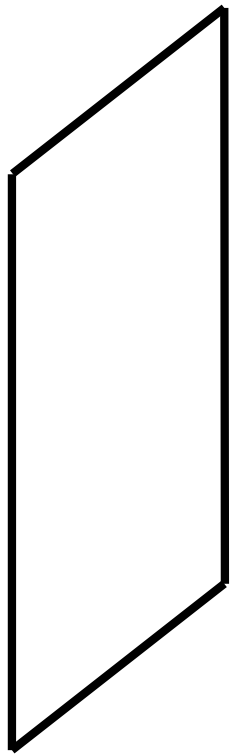
***R*-aspargine**

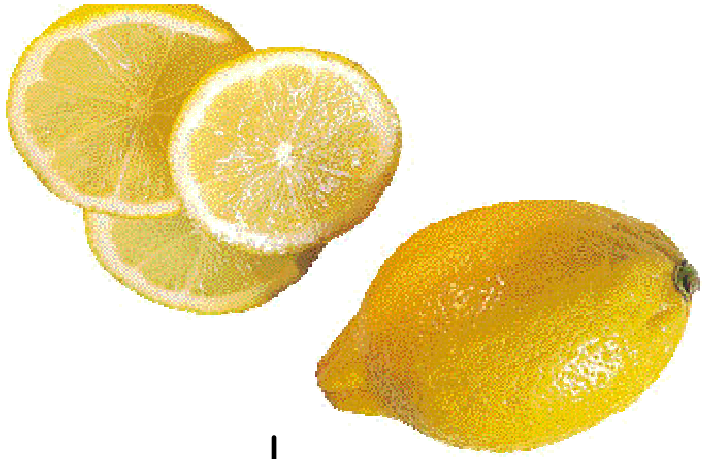
sweet

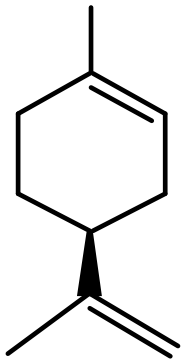
It smells….











(R)-limonene
orange

(S)-limonene
lemon

Chirality: Different properties of enantiomers

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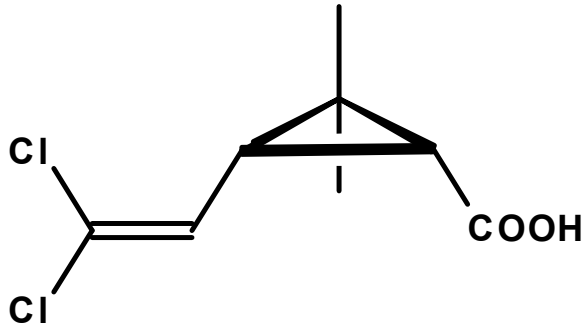
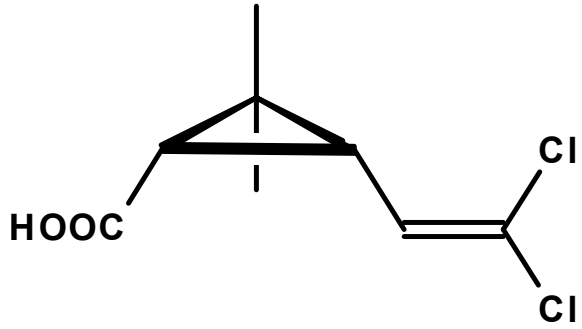
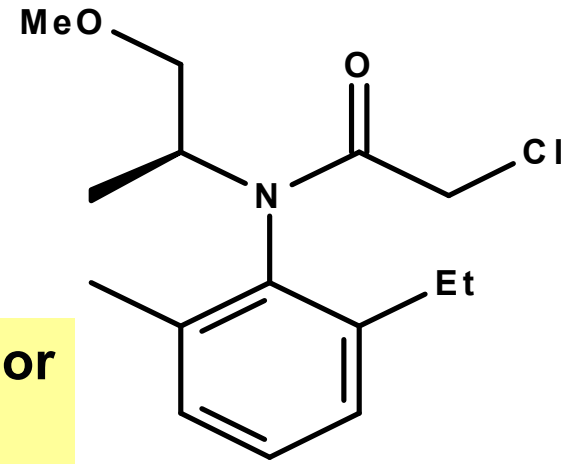


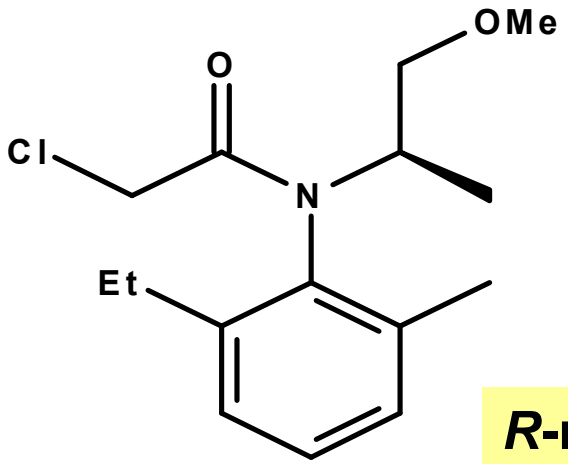
permetrinic acid insecticide



inactive

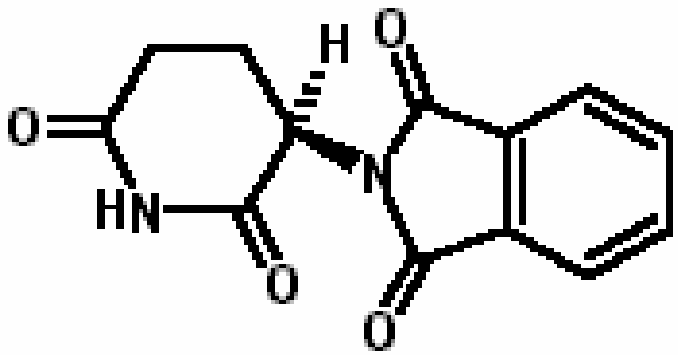


***S*-metolachlor herbicide 10^4 tm/year**

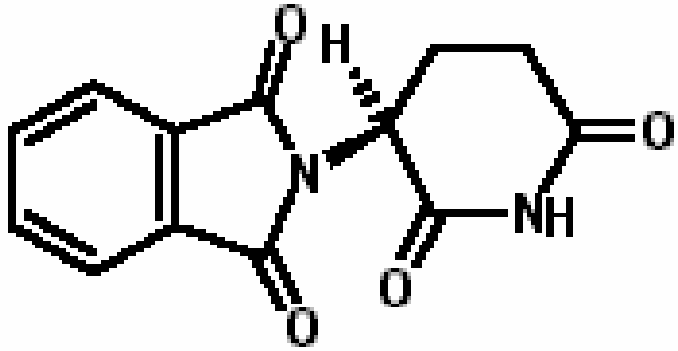


***R*-metolachlor inactive**

Thalidomid (Contergan)



R-Thalidomid
(Schlafmittel)



S-Thalidomid
(teratogen)

Thalidomid (Contergan)

Thalidomid ist der Wirkstoff des Schlaf- und Beruhigungs-mittels Contergan, das Ende der 1950er Jahre zu zahlreichen schweren Schädigungen an ungeborenem Leben führte. Thalidomid wurde in Form des racemischen Gemischs der beiden Enantiomere auf den Markt gebracht.

Zunächst wurde angenommen, dass für die Fehlbildungen (die teratogene Wirkung) allein das (S)-Enantiomer verantwortlich sei und nur das (R)-Enantiomer die gewünschte beruhigende Wirkung hervorrufe.

Da die Enantiomere bei Thalidomid im Körper allerdings racemisieren, kann keinem der beiden Enantiomere eine beruhigende bzw. teratogene Wirkung zugesprochen werden. Die Gabe eines reinen Thalidomid-Enantiomers hätte die Contergan-Katastrophe also nicht verhindern können.

Wikipedia

Optically pure agrochemicals

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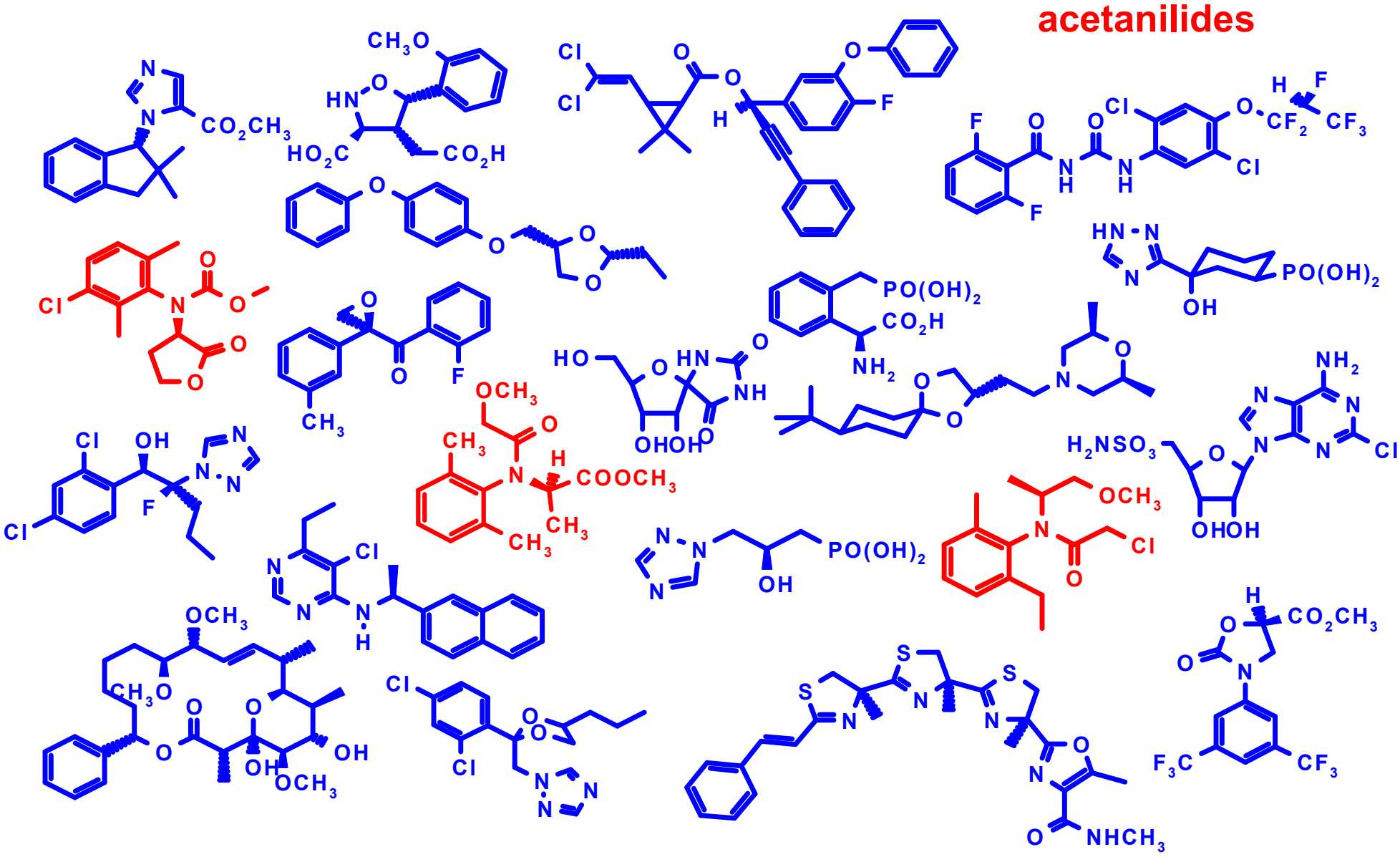
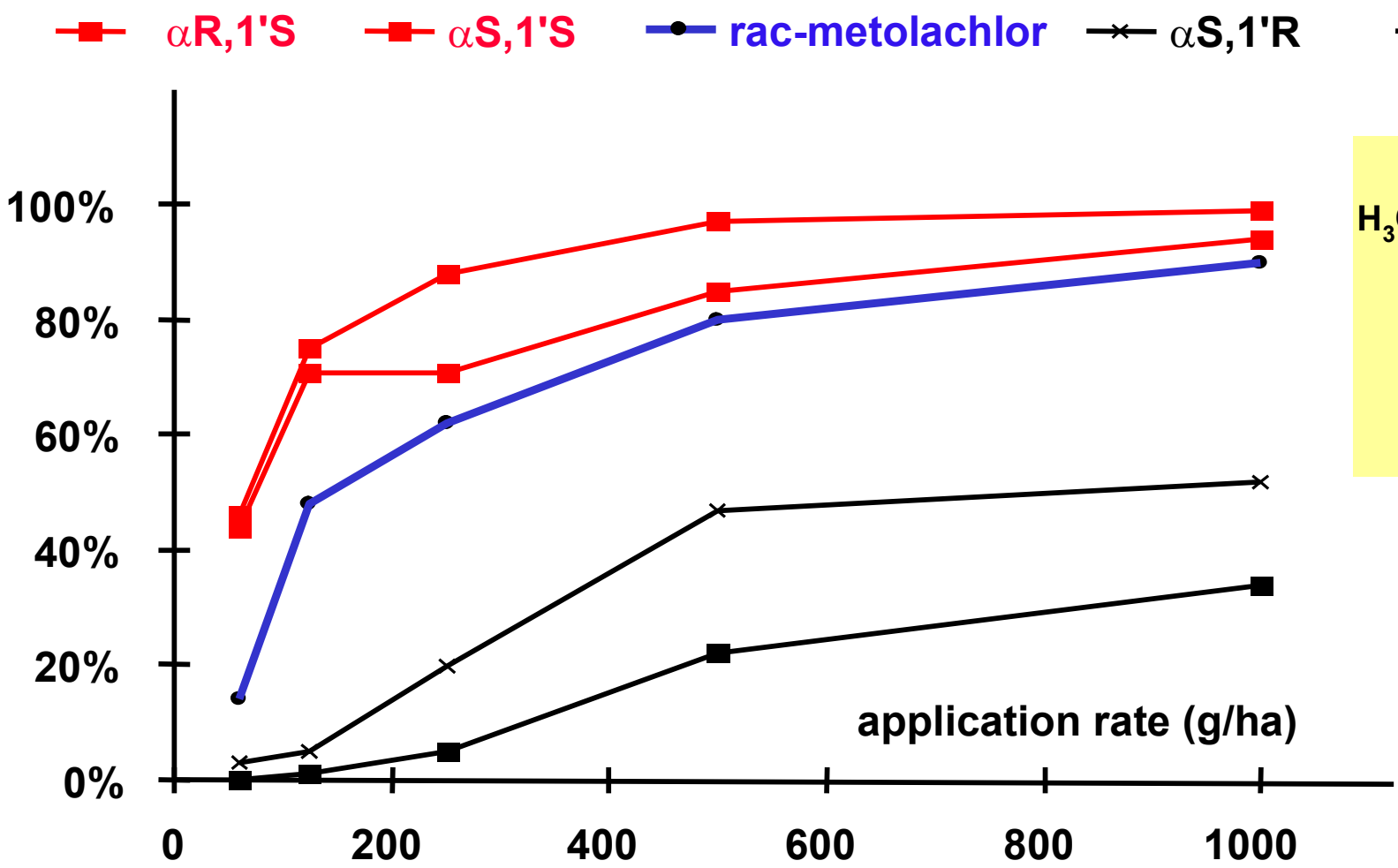
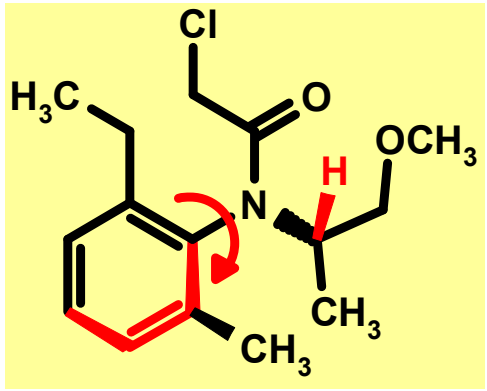


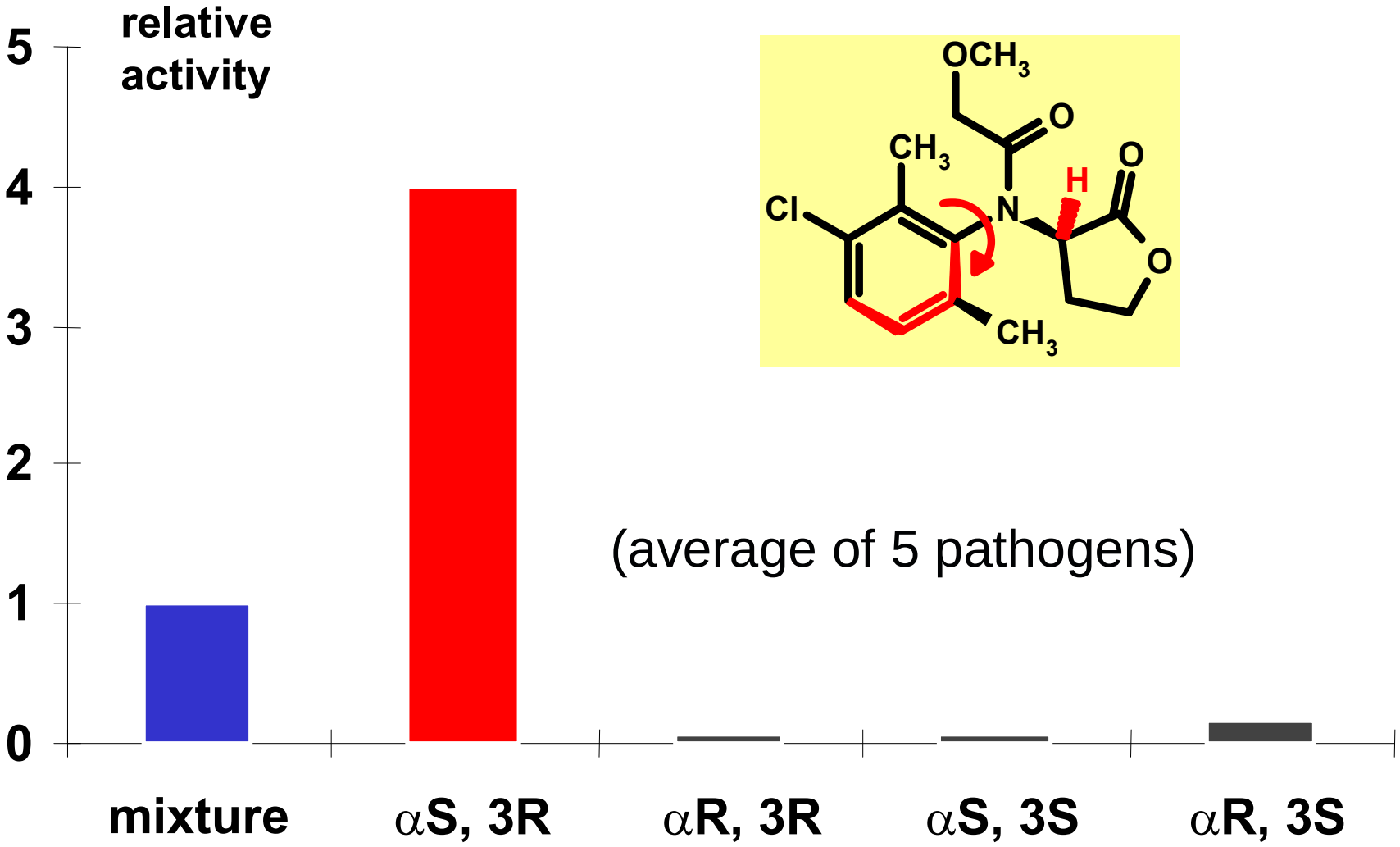
Herbicidal Activity of Metolachlor Stereoisomers





H. Moser, G. Rihs, H.P. Sauter 1982

Clozylacon Stereoisomers In-Vitro Fungicidal Activity



CGA 29'212: Complimentary Biological Activity

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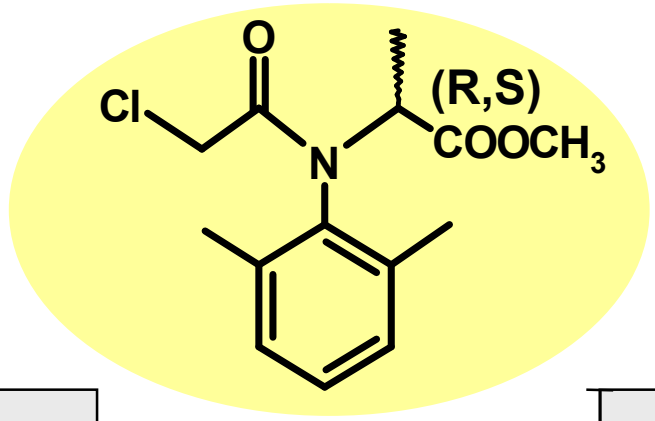
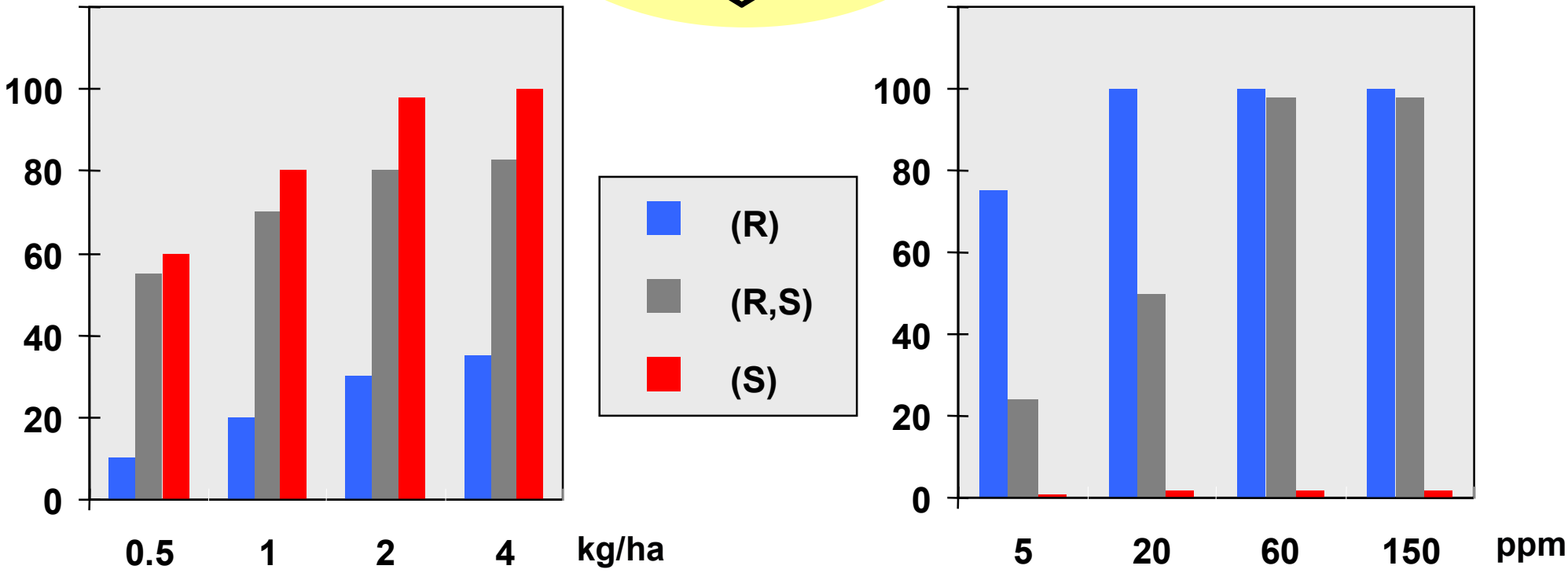
Herbicidal activity
(average 8 grasses)



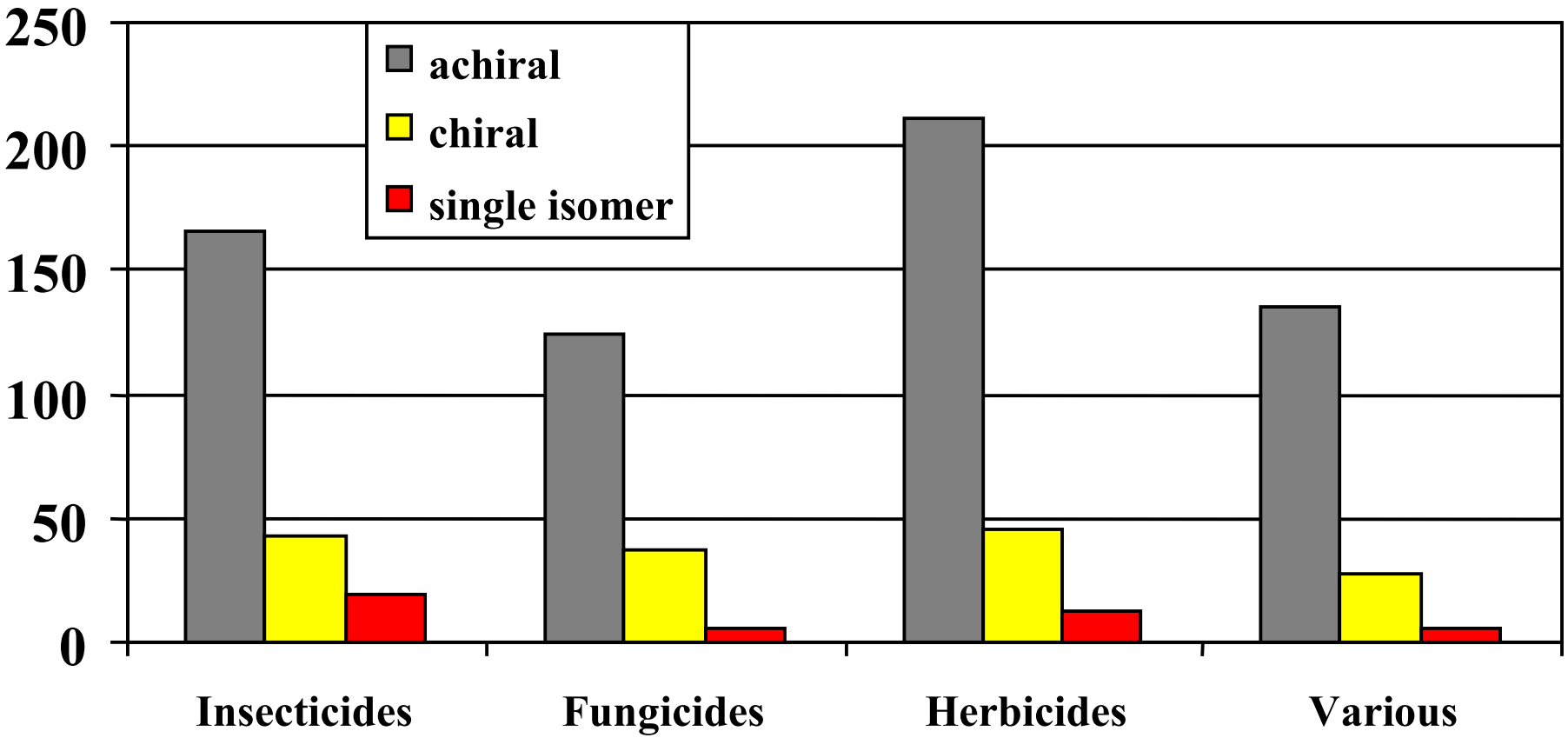
Fungicidal activity
downy mildew on grapes



Chiral Agrochemicals of Novartis (ca. 1999)

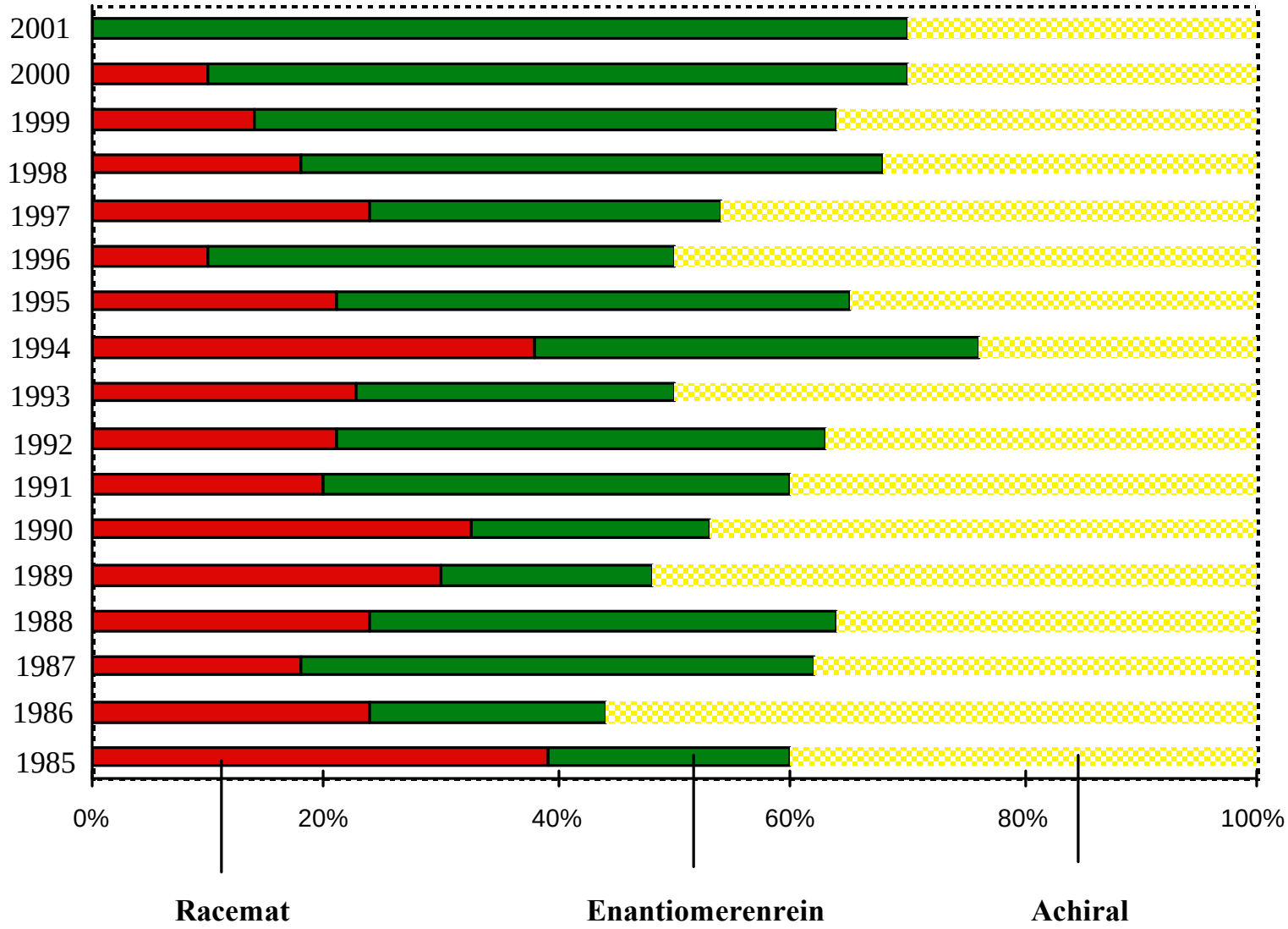
Bioactive ingredients	**77**
Chiral compounds	**18**
Mixture of isomers	**13**
Pure isomers	**3**
Enriched isomers	**2**

Chiral Pesticides 1997



Pesticide Manual 11th Ed., 1997

Chiral Drugs



C&N, May 2003

Carmen Claver

Some Numbers

Market value for chiral fine chemicals (2000)

Total	6.6×10^9 $
Pharmaceutical application	5.4×10^9 $
Other applications (agrochemicals, flavors etc)	1.2×10^9 $

Strong growth expected

➢ Need for effective production methods

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

Motivations for Improved Production Methods

- Regulations, especially in pharma
- Ecological pressure, especially in agro
- Economical pressure, mainly for chiral intermediates but also for agro and generics

Inhalt

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- Chirale Moleküle (Eigenschaften, selektive Synthesemethoden)
- Enantioselektive Processe

Syntheses of Enantiomerically Pure Compounds (EPC)

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* **Synthesis ("chiral pool")**

* **Fermentation**

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

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

Syntheses of Enantiomerically Pure Compounds (EPC)

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- *Separation of enantiomers* via classical resolution, ie crystallisation of diastereomeric adducts, still accounts for the production of more than 50% of enantioenriched drugs. An emerging technology is separation by chiral high performance liquid chromatography (HPLC) using moving simulated bed technology.

- The *chiral pool approach* uses chiral building blocks originating from natural products. Depending on the commercial availability of the starting material, it can also be used for large-scale products.

- *Enantioselective syntheses* are performed with the help of covalently bound chiral auxiliaries (often from the chiral pool). These are not incorporated in the target molecule but are removed after the stereogenic centres have been established and must be either recycled or discarded.

- In many respects the most elegant approach is *enantioselective catalysis* where prochiral starting materials are transformed to enantiomerically pure products with the help of chiral catalysts. Effective catalysts are either man-made (chemical catalysis) or can be of natural origin (biocatalysis).

H.U. Blaser, "Enantioselective Catalysis in Fine Chemicals Production", Chem. Commun. (2003) 293

Syntheses of Enantiomerically Pure Compounds (EPC)

solvias

	Chemical catalysis	Biocatalysis	Chiral pool	Crystalli-sation	HPLC
Enantioselectivity	1-2	1	1	1-2	1-2
Activity and productivity	1-2	2-3	-	-	-
Availability and diversity	1-2	2-3	2	1	1
Substrate specificity	2	3	1	1	2
Work-up and ecology	1-2	2-3	2	2	2
Development time and effort	2	3	1	1-2	1
Application in the lab	2	3	1	1-2	1
Application in development	1-2	2	1	2	2
Small-scale production	1-2	1-2	1	1-2	2
Large-scale production	1	2	2-3	1-2	3

H.U. Blaser, "Enantioselective Catalysis in Fine Chemicals Production", Chem. Commun. (2003) 293

Catalysis in Pharma Development Some Statistics (1999)

solvias

K.G. Gadamasetti, Ed. "Approaches to pharmaceutical process development"(Case Histories), Marcel Dekker, 1999

Transformations	total	catal
Hydrolysis, esterifications, acylations, amidations, mesylations	53	
C=O Reduction ($NaBH_4$, Dibal, BH_3, SnH, Ti^{3+}, SiH, Na/NH_3)	32	2
Nucleophilic substitution reactions (incl. ring opening and closing)	27	
Oxidations, epoxidations (allylic/benzylic bromination, $KMnO_4$, CrO_3, SeO_2, Swern, $CuBr_2$, ozonation, N-oxid, peracid) ($NaBrO_3$/Ru cat, TEMPO)	22	1
Heterogeneous hydrogenolysis (Debenzylation, C-X cleavage)	14	14
Reactions with C=C (Diels Alder, Michael add, ene rxn, elimination, addition, isomeriz.)	13	
Heterogeneous hydrogenations C=C, arom. NO_2, N-N, red alkylation	12	12
Grignard, Lithiation, Li-Br exchange	12	
Reactions with C=O, C=N (Wittig, aldol)	10	
Electrophilic arene substitution (nitration, bromination; Friedel Crafts)	8	
Arene C-C coupling (CN, carbonylation, Heck, Suzuki)	4	3
Total	**206**	**32**

Heterogeneous catalysis (reductions)	26
Homogeneous catalysis (reduction, oxidation, C-C)	4
Biocatalysis (reduction)	2

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

	AstraZeneca	GlaxoSmithKline	Pfizer	Total
Number of syntheses	45	39	44	128
Total number of chemical transformations	371	310	358	1039
Average number of chemical transformations per synthesis	8.2	7.9	8.1	8.1
Number of chiral compounds	25	23	21	69
Number of chiral centres	46	52	37	135
Number of chiral centres generated	22	19	20	61
Number of substituted aromatic starting materials	64	79	63	206
New aromatic heterocycles formed	14	11	29	54

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

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

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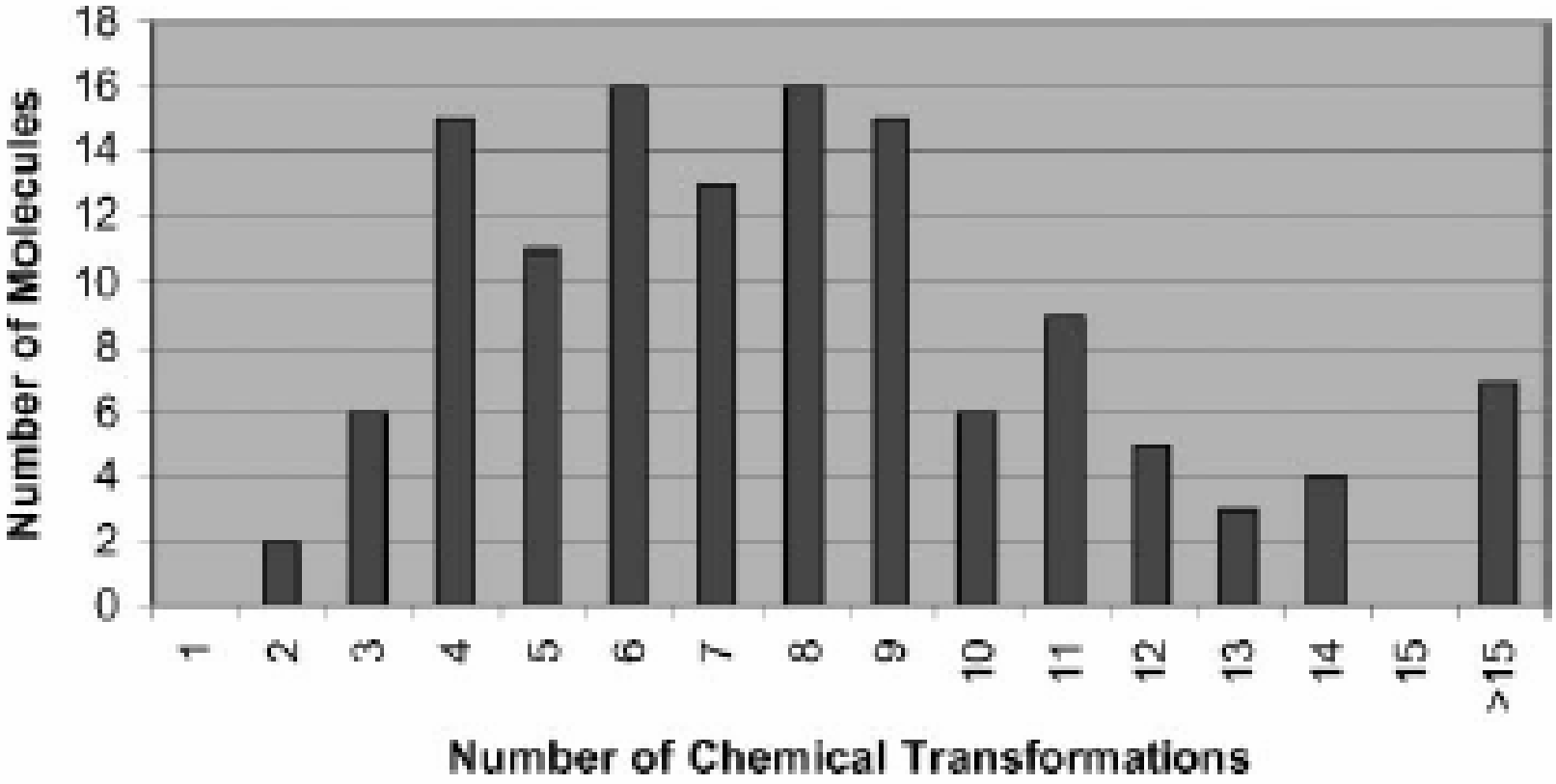
Reaction category	AstraZeneca	GlaxoSmithKline	Pfizer	Total	Percen
Heteroatom alkylation & arylation[a]	87	57	52	196	19%
Acylation[a]	41	37	50	128	12%
C–C bond forming[a]	31	41	44	116	11%
Aromatic heterocycle formation[a]	16	10	26	52	5%
Deprotection[b]	54	56	49	159	15%
Protection[b]	18	16	27	61	6%
Reduction[b]	27	24	43	94	9%
Oxidation[b]	17	7	16	40	4%
Functional group interconversion[b]	43	34	27	104	10%
Functional group addition[b]	13	8	12	33	3%
Resolution[b]	14	8	8	30	3%
Miscellaneous	10	12	4	26	3%
Totals	371	310	358	1039	

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

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)



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

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

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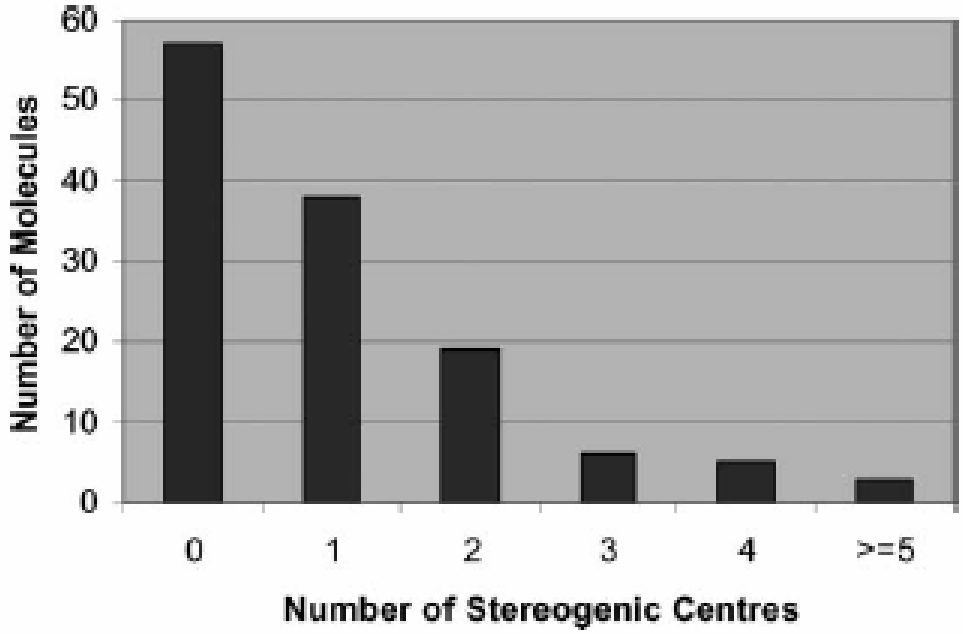
Chirality

- Of the 128 molecules analysed, 69 (54%) are molecules containing at least one stereogenic centre.
- Of the 69 chiral molecules 67 are being developed as single stereoisomers, with only two as racemates.

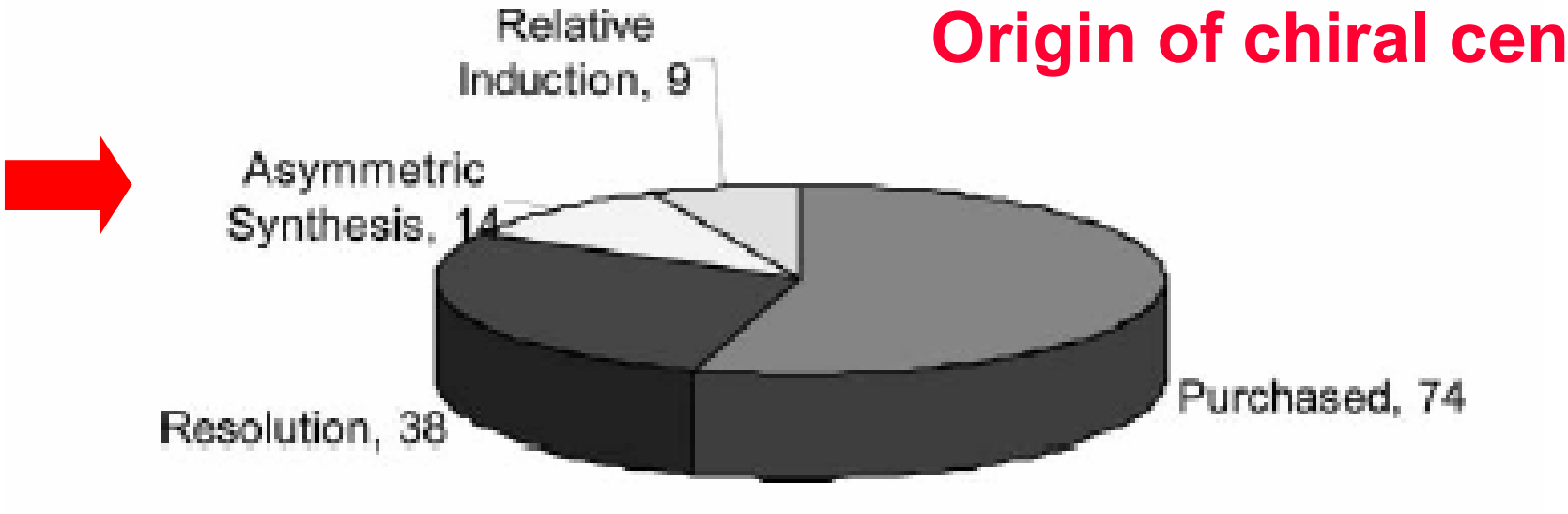


J.S. Carey, D. Laffan, C. Thomson, M.T. Williams, Org. Biomol. Chem. 4 (2006) 2337

Chirality in Pharma Development

AstraZeneca, GlaxoSmithKline, Pfizer (2006)

Origin of chiral centers



- Asymmetric synthesis only accounts for a smaller proportion, approx. 20%, of the chiral centres generated,
- It is noteworthy that the methods applied are catalytic in nature.
- Even for a well developed methodology, such as catalytic asymmetric hydrogenation, application to a moderately complex substrate rarely yields the target enantiomeric purity directly.

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

Industrial Biotransformations

solvias

Total: 134 documented processes

Product classes	
Cabohydrates, nucleotides	20%
Fat derivatives, steroids	10%
Peptides, β-lactams	15%
amino acids	15%
sec-Alcohols	15%
Other chiral	15%
Other non-chiral	5%

Chirality	
Chiral precursor (pool)	40%
Kinetic resolution	27%
Asymmetric synthesis	20%
Not chiral	7-8%

A.J.J. Straathof, S. Panke, A. Schmid, Curr. Opinion Biotechnology, 2002, 13, 548.

Milestones for Enantioselective Catalysis

solvias

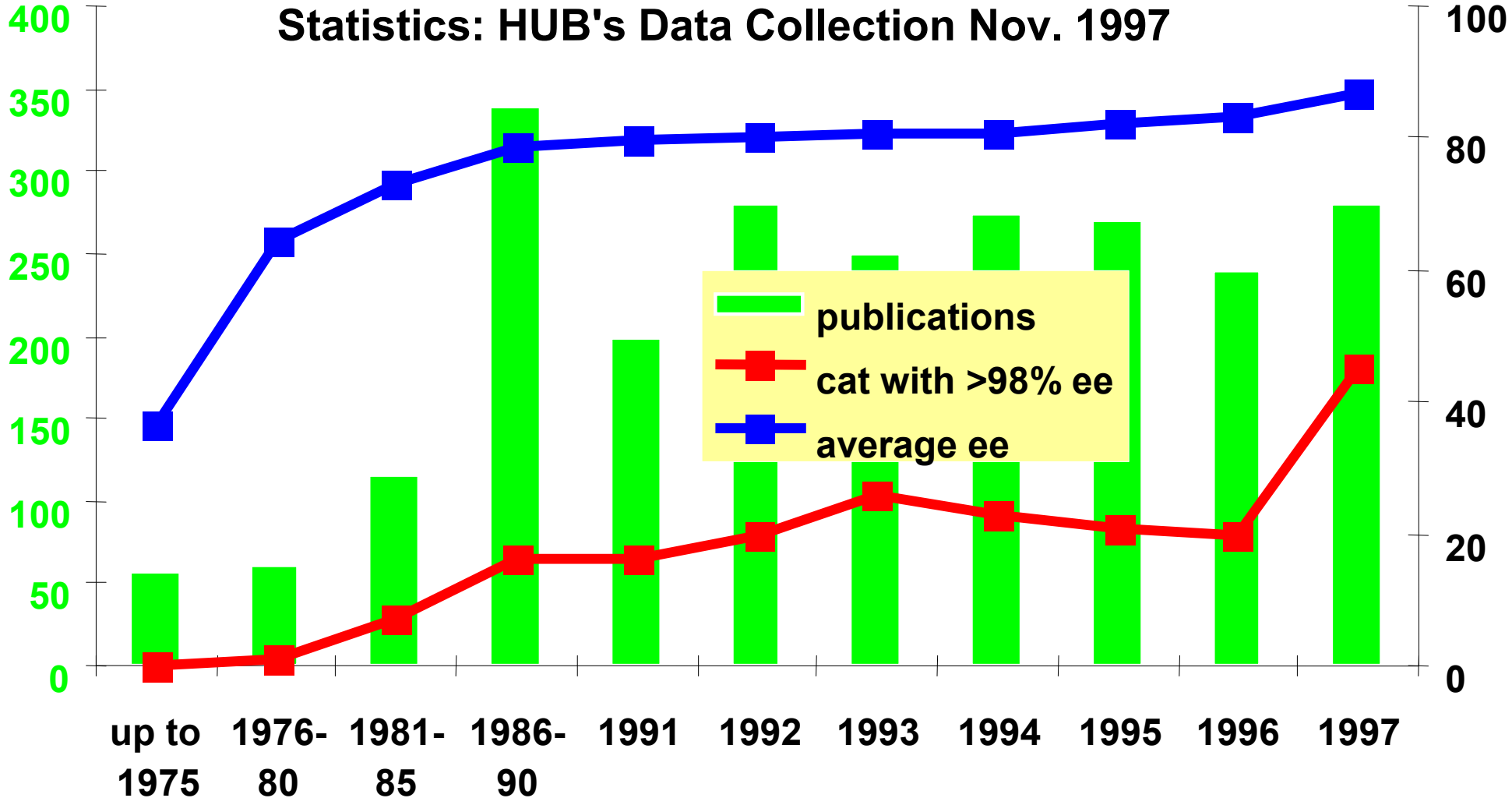
year	milestone	chiral catalyst	ee (%)
1912	HCN addition to PhCHO	quinine	<10
1940	hydrogenation of C=N	chiral acid on Pt black	18
1956	hydrogenation of C=C	Pd on silk fibroin	(66)
1966	cyclopropanation	Cu - Schiff' base	10
1968	hydrogenation of enamides	Rh - chiral phosphine	15
1978	hydrogenation of β-keto esters	Ni-tartrate-NaBr	89
1979	hydrogenation of α-keto esters	cinchona on Pt	80
1980	epoxidation of allylic alcohols	Ti-tartrate complex	>90
1980	binap ligand	Rh, Ru complexes	high
1988	dihydroxylation	Os-cinchona complex	>95
1991	epoxidation of C=C	Mn salen complex	>95
1995	epoxide ring opening	Cr salen complex	>95

Milestones for Enantioselective Catalysis

solvias

year	milestone	chiral catalyst	ee (%)
1912	organic catalyst	quinine	<10
1940	modified heterogeneous catalyst	chiral acid on Pt black	18
1956	chiral support	Pd on silk fibroin	(66)
1966	homogeneous catalyst	Cu - Schiff' base	10
1968	homogeneous catalyst	Rh - chiral phosphine	15
1978	modified heterogeneous catalyst	Ni-tartrate-NaBr	89
1979	modified heterogeneous catalyst	cinchona on Pt	80
1980	homogeneous catalyst	Ti-tartrate complex	>90
1980	homogeneous catalyst	Rh, Ru complexes	high
1988	homogeneous catalyst	Os-cinchona complex	>95
1991	homogeneous catalyst	Mn salen complex	>95
1995	homogeneous catalyst	Cr salen complex	>95

Some Numbers
Catalysts with High Enantioselectivity



Reactions with Very High Enantioselectivity (ee>98%)

Hydrogenation C=C	20
R-Me addition to RCH=O, RCH=NR	17
Reduction C=O, C=N (>10% cat)	16
Aminohydroxylation, Dihydroxylation	14
Hydrogenation C=O	13
Allylic alkylation	11
Aldol, ene, Micheal reactions	10
C-C Coupling , Cyclopropanation, Heck	10
Diels-Alder	8
Hydrosilylation C=C, C=O	6
Epoxidation	6

Source: HUB Data collection, Nov. 1997

Milestones for Industrial Enantioselective Catalysis

solvias

1970’s L-Dopa, enamide hydrogenation (Monsanto)

1980’s L-Menthol, C=C isomerization (Takasago)

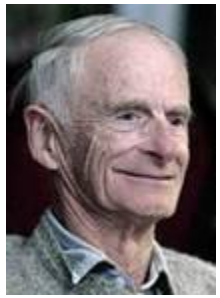
1990’s Glycidol, Sharpless epoxidation (Arco)

S-Metolachlor (Ciba-Geigy/Novartis/Solvias)

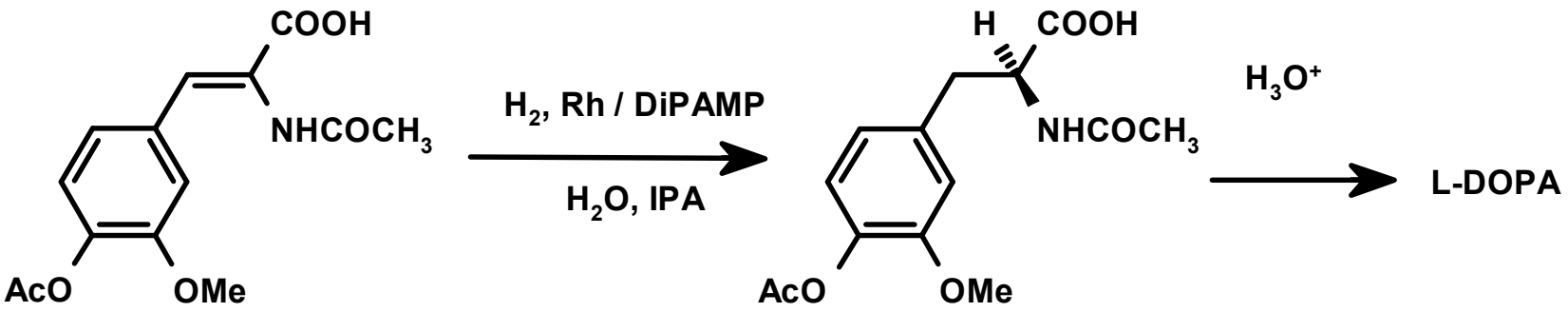
2000’s Epoxide ring opening (Rhodia/Chirex)

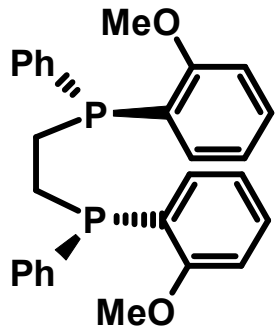
"Routine" application of enantioselective hydrogenation

L-DOPA (Monsanto)



solvias





dipamp

Catalyst performance 95% ee, ton 10-20'000, tof 1000/h

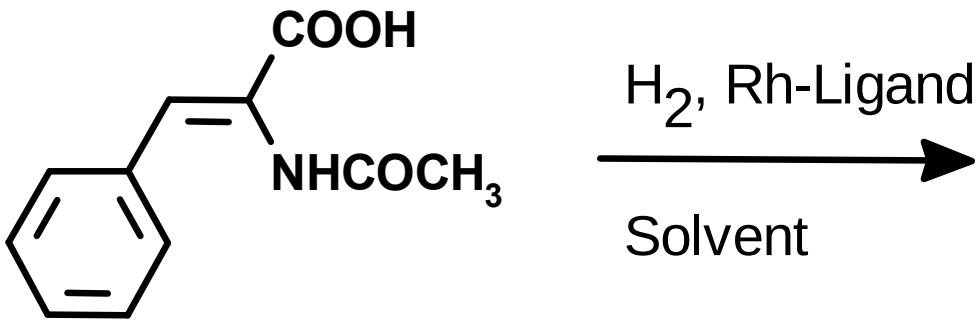
Important features Pure product (100% ee) crystallizes

- separation from catalyst and undesired racemate

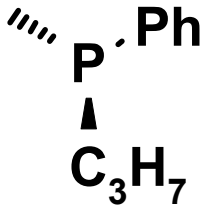
Knowles et al.

L-DOPA: Impact on Science

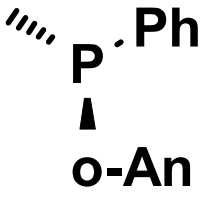
For many years enamides most important test substrate



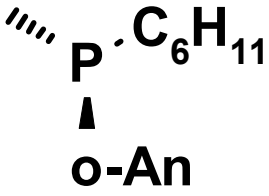
P chiral / bidentate / C_2 symmetric (Kagan)



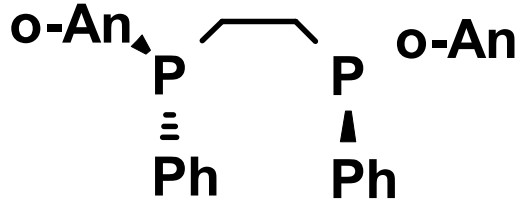
28%



PAMP 55%

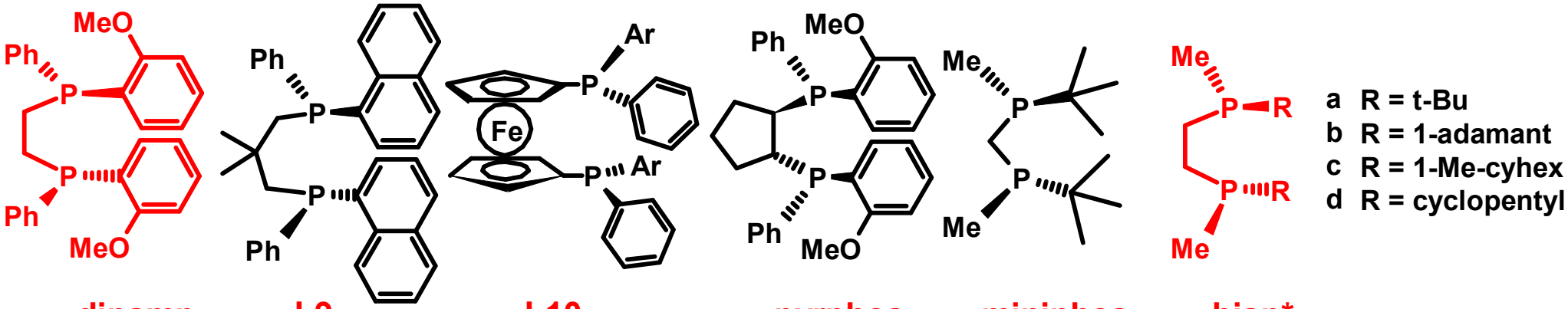


CAMP 84%



DiPAMP 95%

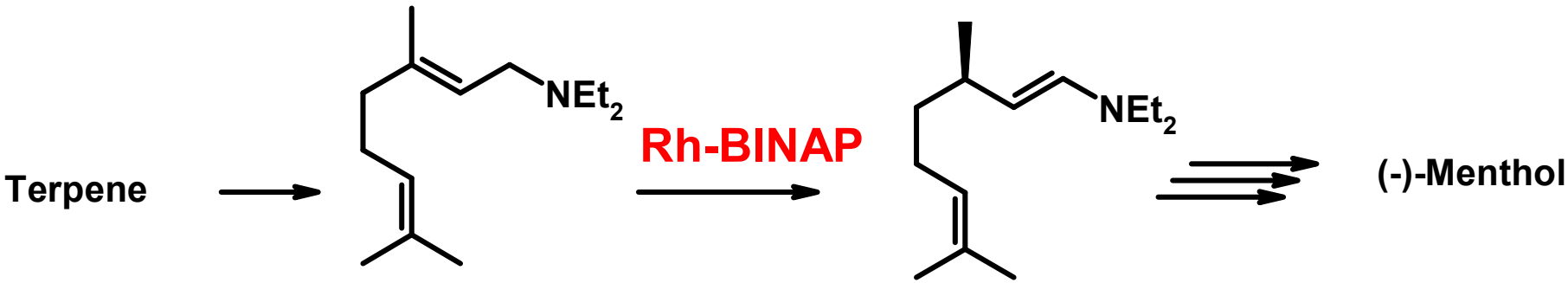
P-Chiral Ligands (2003)



dipamp L9 L10 pyrphos miniphos bisp*

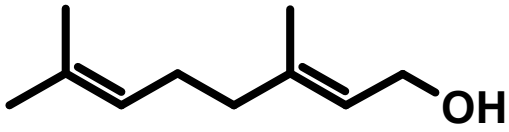
- Most ligands very air sensitive (Rh-complex more stable)
- Generally high ee's for Rh catalyzed hydrogenation of enamides and itaconates

L-Menthol (Takasago)

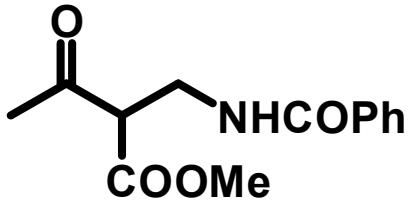


Catalyst performance	97.6% ee, ton 400’000, tof 1300/h
Important features	Active catalyst can be recovered and re-used after distillation Ton increase from 8’000 ➔ 80’000 - 400’000 (optimal work-up).

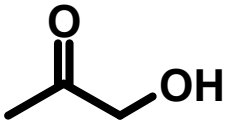
Industrial Applications of Ru – Binap Catalysts



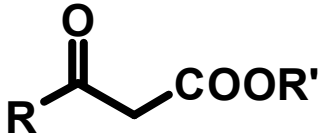
Ru/binap; ee 97%
ton 50'000; tof 500h^{-1}
production process 300 t/y
Takasago



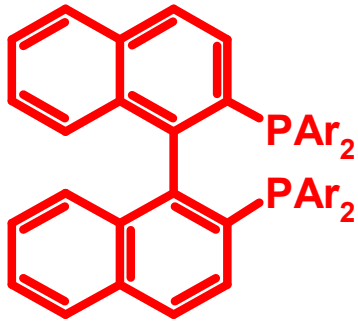
Ru/dmbinap; ee 98%, de >94%
ton 1'000.; tof 200h^{-1}
production process 100 t/y
Takasago



Ru/tolbinap; ee 94%
ton 2'000.; tof 300h^{-1}
medium scale production
Takasago

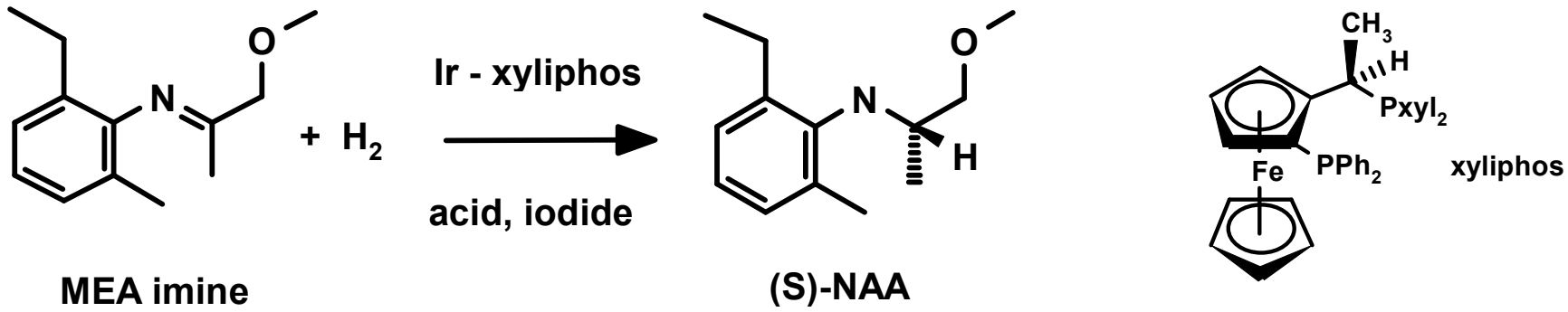


Ru/binap, ee 98-99%
ton 10-20'000; tof 12'000h^{-1}
small scale production
NSC Technologies



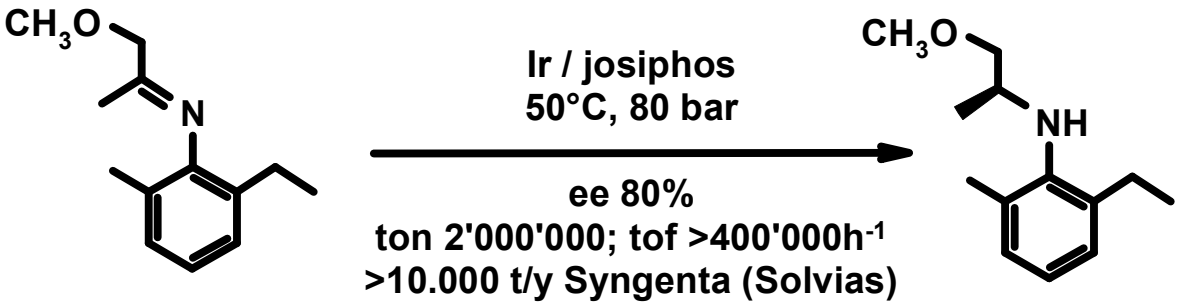
binap Ar: Ph
tolbinap Ar: p-Tol
dmbinap Ar: 2,6-Xyl

S-Metolachlor (Ciba-Geigy/Syngenta)

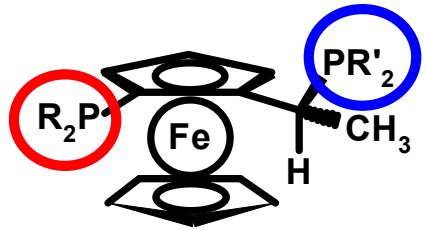


Catalyst performance	80% ee, ton >1'000'000, initial tof >180'000/h
Important features	Extremely active and productive Ir – ferrocenyl diphosphine catalyst. Catalyst separation via distillation Largest enantioselective process (>10'000 t/y)

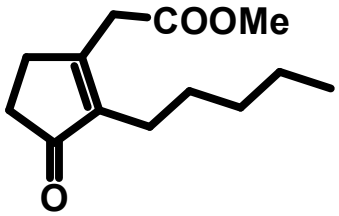
Industrial Applications of Josiphos Ligands



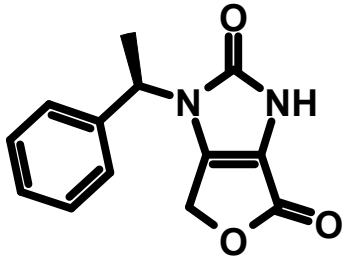
R = Ph
R' = 2,6-Xyl



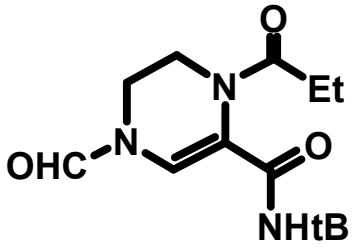
josiphos



Ru/josiphos or duphos; ee 90%
ton 2'000; tof 200h^{-1}
medium scale production
Firmenich



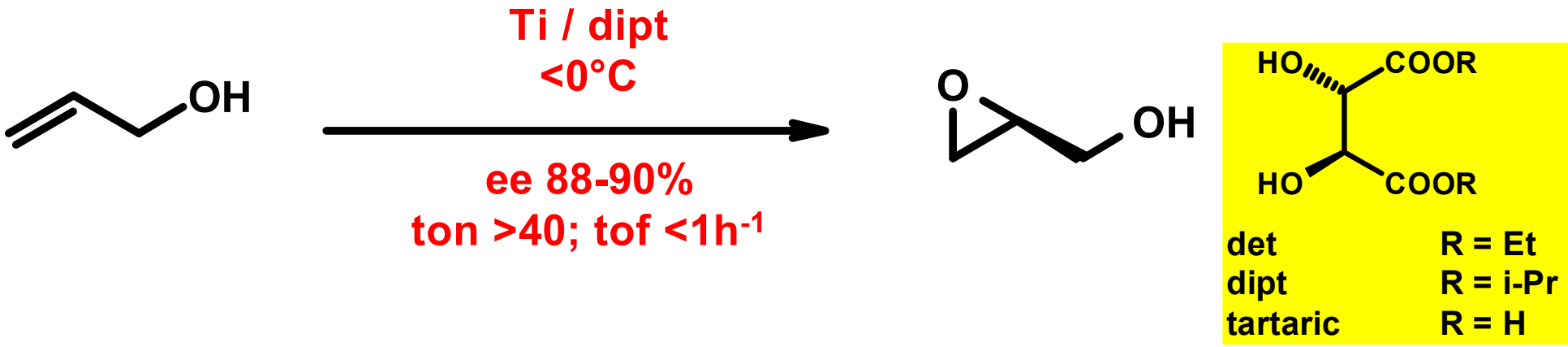
Rh/josiphos; de 99%
ton 2'000; tof n.a.
medium scale production
Lonza



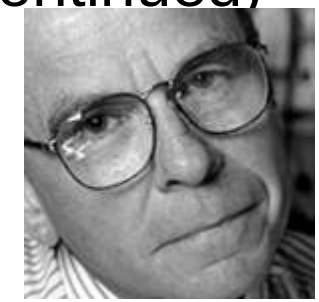
Rh/josiphos; ee 97%
ton 1'000; tof 450h^{-1}
pilot process, >200 kg
Lonza

R = Ph
R' = Cyhex

Sharpless Epoxidation

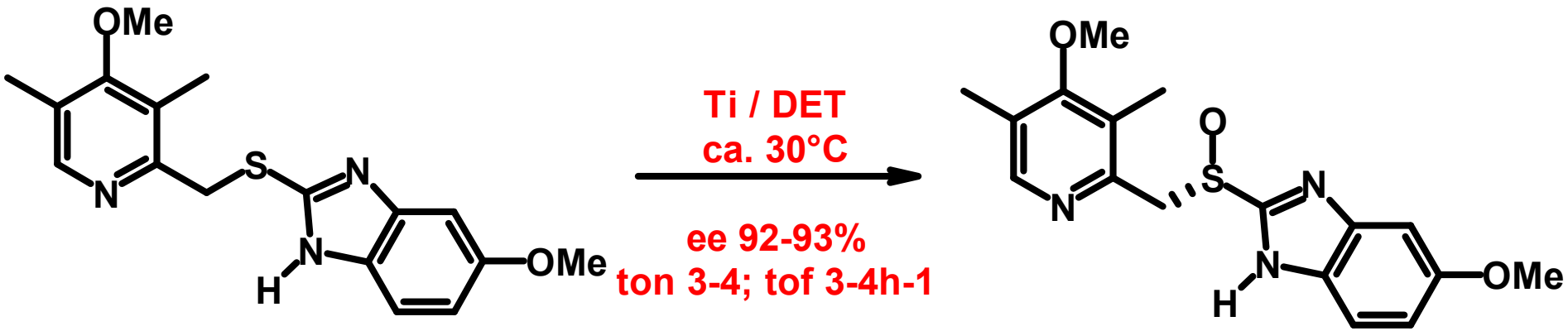


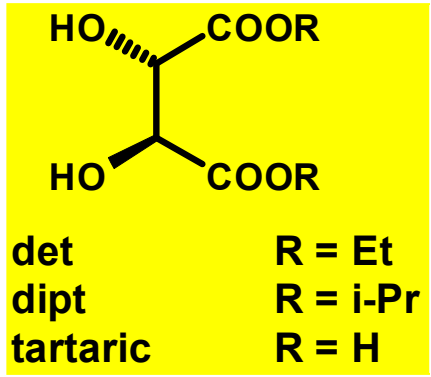
Arco/GGP-Sipsy, chiral building block, multi ton scale (discontinued)



- Based on Sharpless technology
- Good enantioselectivity
- Very low ton and tof (addition of molecular sieve necessary)
- Product isolation very difficult (water solubility)

Sulfide Oxidation





AstraZeneca, Esomeprazole (Anti-Ulcer) multi ton scale

- Based on Kagan technology
- Good ee (addition of Hünig base necessary)
- Very low ton and tof

Industrial Asymmetric Processes

solvias

Large Scale Asymmetric Catalysis", H.U. Blaser, E. Schmidt (Eds.), Wiley-VCH, 2003

Reaction type	substrates / comment	E	WC	H	Het	
C-C Coupling	cyanohydrin, cyclopropanation	1	-	1	-	2
Hydrogenation C=C	dehydroacylaminoacid, allylic alcohol, tetrasubstituted C=C, enamine	-	-	8	-	8
Hydrogenation / reduction C=O, C=N	a-keto acid derivatives, var. ketones and imines	2	3	3	2	10
Oxidation	alcohol, sulfide	-	1	1	-	2
Hydrolysis, acetylation	amide, hydantoin, ester, thioester, nitrile, carbamate, epoxide	8	4	1	-	13
Various	assimilation, carnitine synth.	-	3	-	-	3
Total		11	11	14	2	38

E enzyme, WC whole cell, H homogeneous metal complex, Het heterogeneous catalyst

Industrial Catalytic Asymmetric Processes

solvias

Study: Enantioselective catalysis in fine chemicals production

H.U. Blaser, F. Spindler, M. Studer, Applied Catalysis: A General 221 (2001) 119.

Transformation	production	pilot	bench scale
Hydrogenation reactions	10	29	20
Oxidation reactions	3	3	6
Various	2	3	1
Total	15	35	27

Production processes:		
	Pharma (generics, NCE)	7
	Agro	2
	Flavors & fragrances	2
	Intermediates (PH, other)	2
	Chiral building blocks	2

Are these Numbers Real?

	production	pilot	bench scale
Total	**15**	**35**	**27**

Some considerations

- Lack of information (how many did we miss??)

- Some pilot and bench scale processes will (soon?) be applied in production (young technology)

BUT: Not all production processes are still in operation

AND: Many published processes will never be operative

Are these Numbers Real?

	production	pilot		ale
Total	**15**	**35**		**27**

Some considerations

- Lack of information (l… did we miss??)

- Some pilot… scale processes will (soon?) be ab… duction (young technology)

- …t all production processes are still in operation

Why are there so few processes?

Five Hurdles to Success

solvias

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

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

3. Beat alternative processes

4. Scale up, technical process, accepted technology

5. Decision to market product

1. Hurdle
Choice of Synthetic Route

solvias

Always multi-step synthesis (PH 10-15; AG 4-7)

- Discovery: Often “quick and dirty” preparation;
  classical organic chemistry is the norm
- Development: Little time for trying “risky” chemistry
- Development chemists often do not know the potential of catalytic methods
- Scale up of catalytic processes and chiral ligands doubtful

$\Rightarrow$ Problem: Recognizing opportunity for catalysis

2. Hurdle
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)

$\Rightarrow$ Low success rates

Toolbox for Fast Catalyst Screening

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

2. Hurdle
Find Catalytic System (ee, ton, tof)

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Issues

- 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)

$\Rightarrow$ Low success rates

Industrial (Asymmetric) Catalysis
A Multi-Dimensional Task

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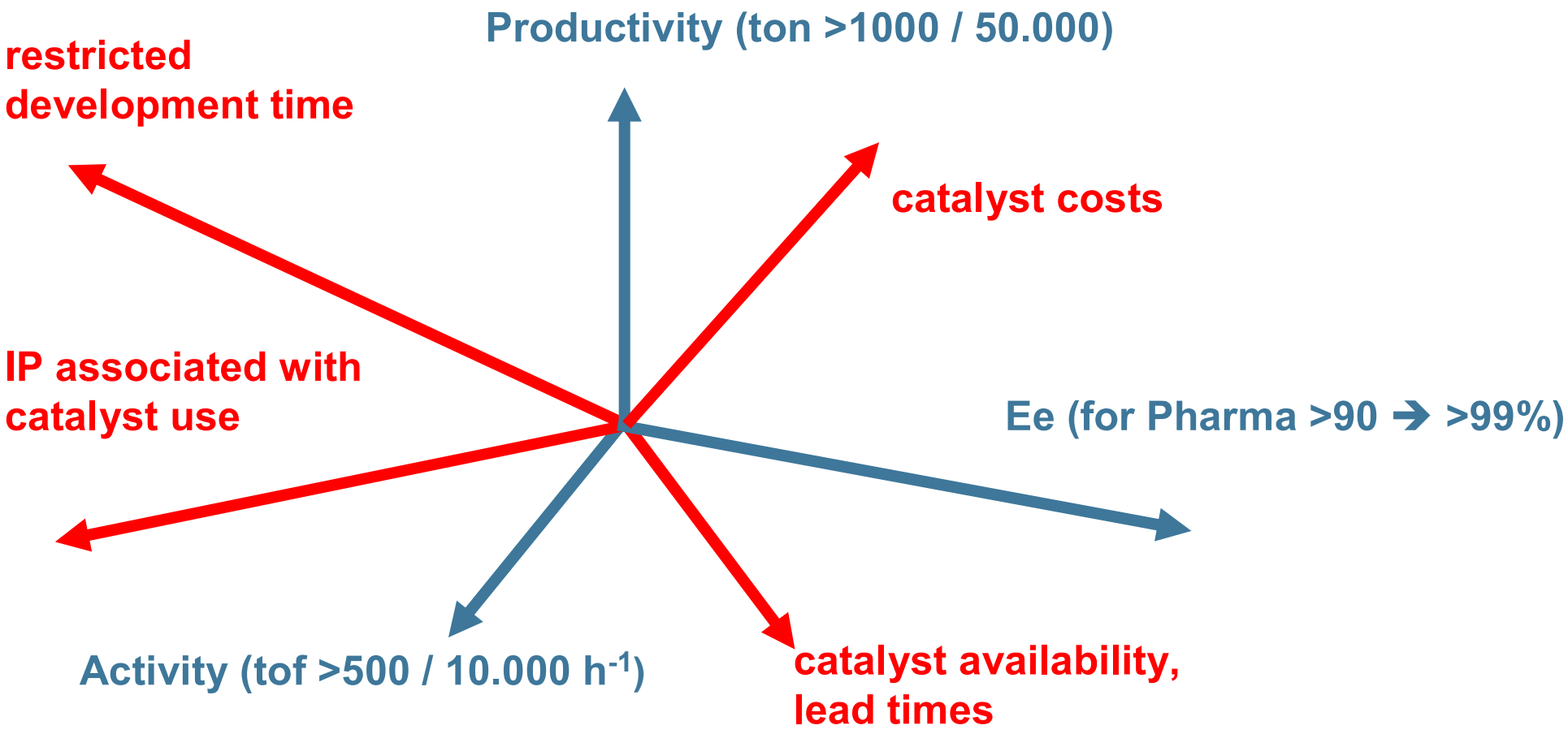
Chemical factors & Economic factors



2. Hurdle
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solvias

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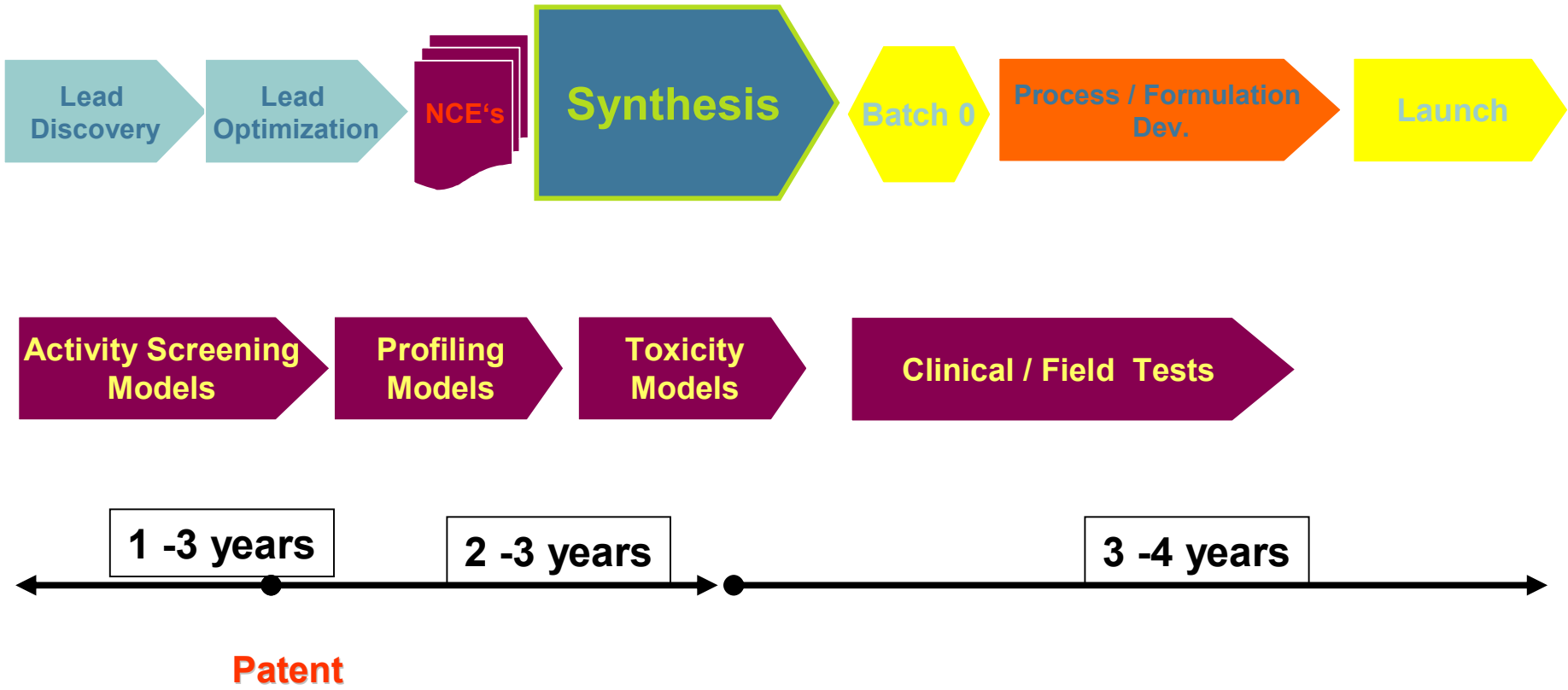
From Discovery to Launch: Product Development Process



3. Hurdle
Beat Alternative Processes

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Issues

- **Total costs** of final product are decisive
- Adaptation of overall-synthesis to catalytic step
- Preparation and purification of starting material

Alternatives

- Different catalytic methods (enzymes)
- Different new processes / approaches
- Existing processes

4. Hurdle

Scale up, Technical Process, Acceptance

Issues

- Feasibility of technology (high p, low T, O_2, handling)
- Commercial availability of chiral ligands, complexes
- IP rights, licenses, royalties
- Catalyst separation (metal residue; recycling?)
- Production equipment available
- Acceptance of technology by production manager

Commercial Availability

Screening phase
100 mg – 1g samples days - weeks

Pilot phase of process development
Up to 100g within a few weeks – months

First production campaign
Up to kg amounts as soon as 6 months after successful piloting

Regular production
According to production plan; on time; quality assured

➢ **Often short lead time for kg amounts of chiral ligands**

5. Hurdle
Decision to Market Product

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Issue

- Many new pharma products are abandoned at a relatively late stage

What can be done

- NOTHING

Conclusions

Hurdles are of different nature

Psychological

Prejudice, lack of know how and self confidence

Technical

Catalyst performance, equipment, availability of catalysts

Commercial

Product costs, IP rights, time to market, product dies