Asymmetric Catalysis for Fine Chemicals Synthesis

Monday, 8h15 – 10h00, GR A3 30
http://moodle.epfl.ch/
https://www.epfl.ch/labs/lcso/Teaching/
https://epfl.zoom.us/j/83387556644?pwd=Sy9JRCtlSFdGNzc1YTRnc0kwcFVuUT09
https://mediaspace.epfl.ch/channel/CH-435+Catalytic+asymmetric+reactions+in+organic+chemistry/29624

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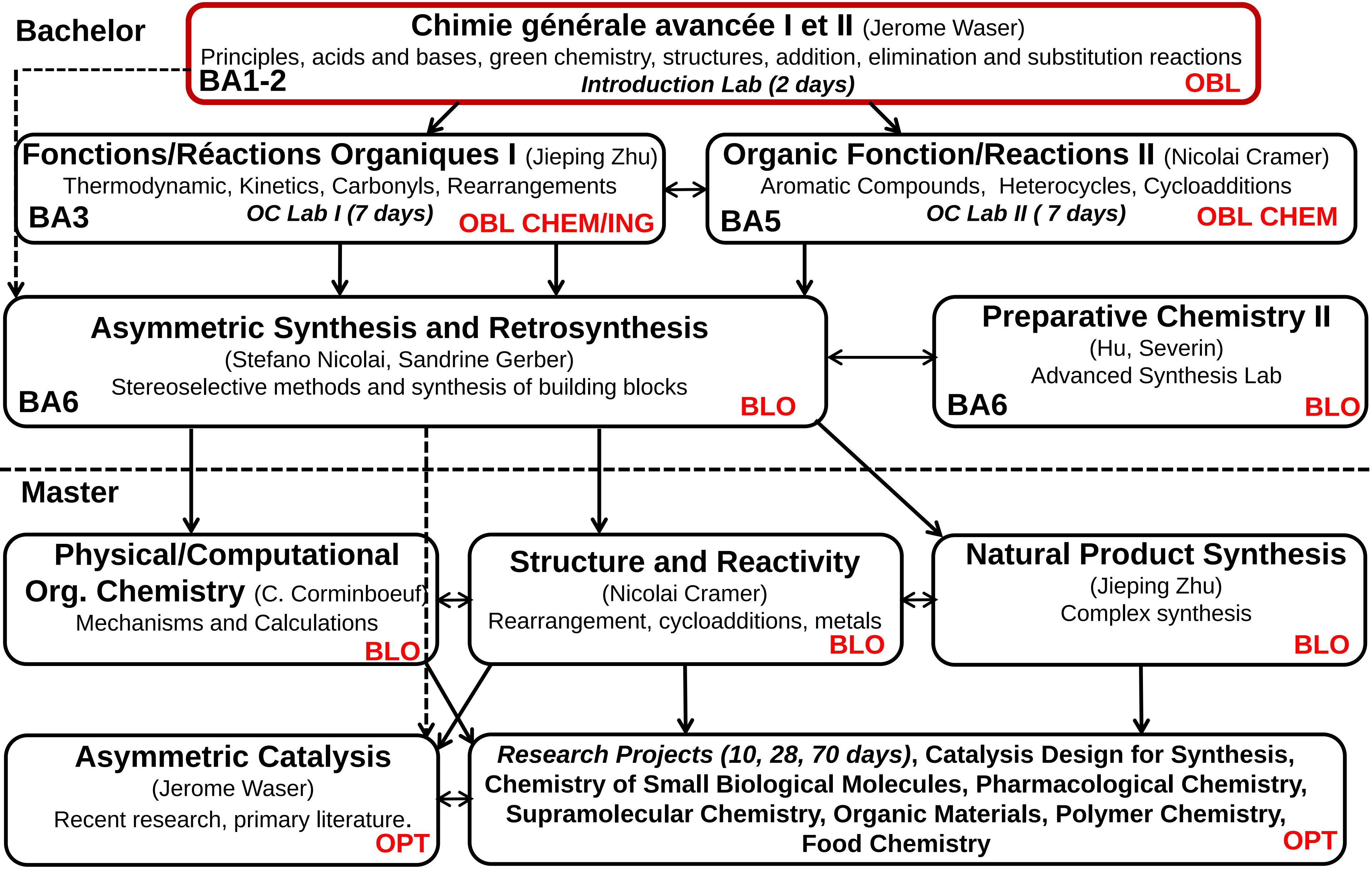
Organic Chemistry at EPFL



Bachelor

Chimie générale avancée I et II (Jerome Waser)
Principles, acids and bases, green chemistry, structures, addition, elimination and substitution reactions
BA1-2
Introduction Lab (2 days)
OBL

Fonctions/Réactions Organiques I (Jieping Zhu)
Thermodynamic, Kinetics, Carbonyls, Rearrangements
BA3
OC Lab I (7 days)
OBL CHEM/ING

Organic Fonction/Reactions II (Nicolai Cramer)
Aromatic Compounds, Heterocycles, Cycloadditions
BA5
OC Lab II (7 days)
OBL CHEM

Asymmetric Synthesis and Retrosynthesis
(Stefano Nicolai, Sandrine Gerber)
Stereoselective methods and synthesis of building blocks
BA6
BLO

Preparative Chemistry II
(Hu, Severin)
Advanced Synthesis Lab
BA6
BLO

Master

Physical/Computational Org. Chemistry (C. Corminboeuf)
Mechanisms and Calculations
BLO

Structure and Reactivity
(Nicolai Cramer)
Rearrangement, cycloadditions, metals
BLO

Natural Product Synthesis
(Jieping Zhu)
Complex synthesis
BLO

Asymmetric Catalysis
(Jerome Waser)
Recent research, primary literature.
OPT

***Research Projects (10, 28, 70 days)*, Catalysis Design for Synthesis, Chemistry of Small Biological Molecules, Pharmacological Chemistry, Supramolecular Chemistry, Organic Materials, Polymer Chemistry, Food Chemistry**
OPT

Lecture Structure

- Power point presentation
- First hour: 10+5 min presentation of recent publication
- Second hour: 10 min mechanism exercise
- Content: principles for catalysis in organic chemistry, reactions and ligands introduced on the way
- Classical examples and new developments
- Bridging gap between classics and current research

Lecture Structure: The Presentation

- Power point presentation by 2-3 students (10 min) Answering the exam questions on a recent publication:
    - Which reaction?
    - Reactivity analysis (nucleophile-electrophile)
    - Principle of catalysis
    - The complete catalytic cycle
    - Specifics of the publication: scope, conditions, applications
    - Critical analysis of novelty, practicability and sustainability
- Questions are given by me to the class before presentation
- Discussion in the class after presentation

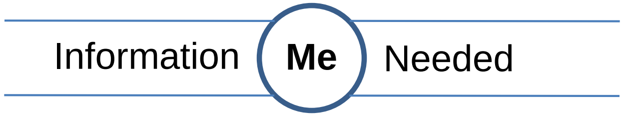
Lecture Structure: Mechanism exercise

- On the spot catalytic cycle analysis
- Critical analysis

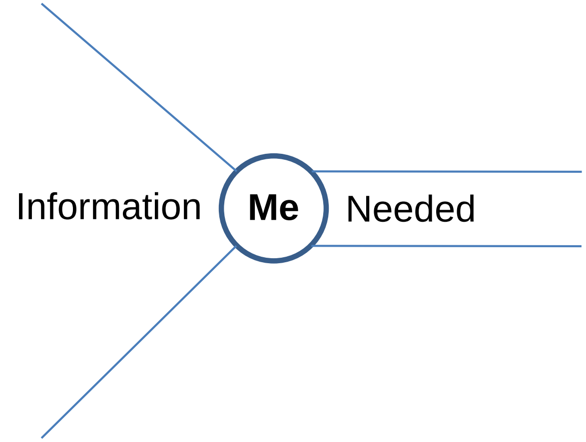
Exam and Grading

- Grading system: 20% on presentation, 80% oral exam
- Oral exam on a recent publication with 20 min reading time
- Answering the same questions as asked for presentations

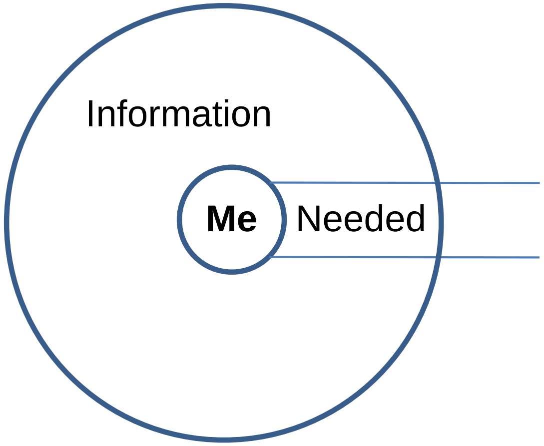
Didactic Goal: Learning to Deal with Information Overflow



Bachelor, 1. Master Lecture



Advanced Master Lecture



Real Life

Didactic Goal: Getting the Maximum from Oral Presentations

- Information content on one slide very low
- Learn to identify the key information
- Nearly no text on the slides: learn to take notes!
- Learn to summarize a topic

Scientific Goals

- Key concepts in organic, coordination and stereo chemistry
- Catalysis and Sustainability (9th Principle of Green Chemistry)[1]
- In direct contact with current research
- Principles of catalysis (activation, whole catalytic cycle)
- Principles of asymmetric induction
- Reading and analyzing scientific primary literature
- Important research groups in the World and Switzerland

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(1) Anastas, P. T.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301.

Why care about asymmetric catalysis?

- Pharmaceutical industry want to escape “flatland”[1,2]

- Enantiomers have different bioactivity

- In 2020, 20 out of 35 new small molecule pharmaceuticals accepted by FDA were chiral[3]

- Drug complexity is constantly increasing[4]

- In theory, asymmetric catalysis is “the sustainable solution”: a small amount of chiral element leads to nearly enantiopure products

- However, the impact of asymmetric catalysis in chemical production is still low compared to investment in research: why?

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(1) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (2) Lovering, F. *MedChemComm* **2013**, *4*, 515. (3) Jarvis, L.M. *Chem. Eng. News* **2021**, 99. (4) https://sites.arizona.edu/njardarson-lab/top200-posters/

NCCR Catalysis: Towards Sustainable Chemical Processes

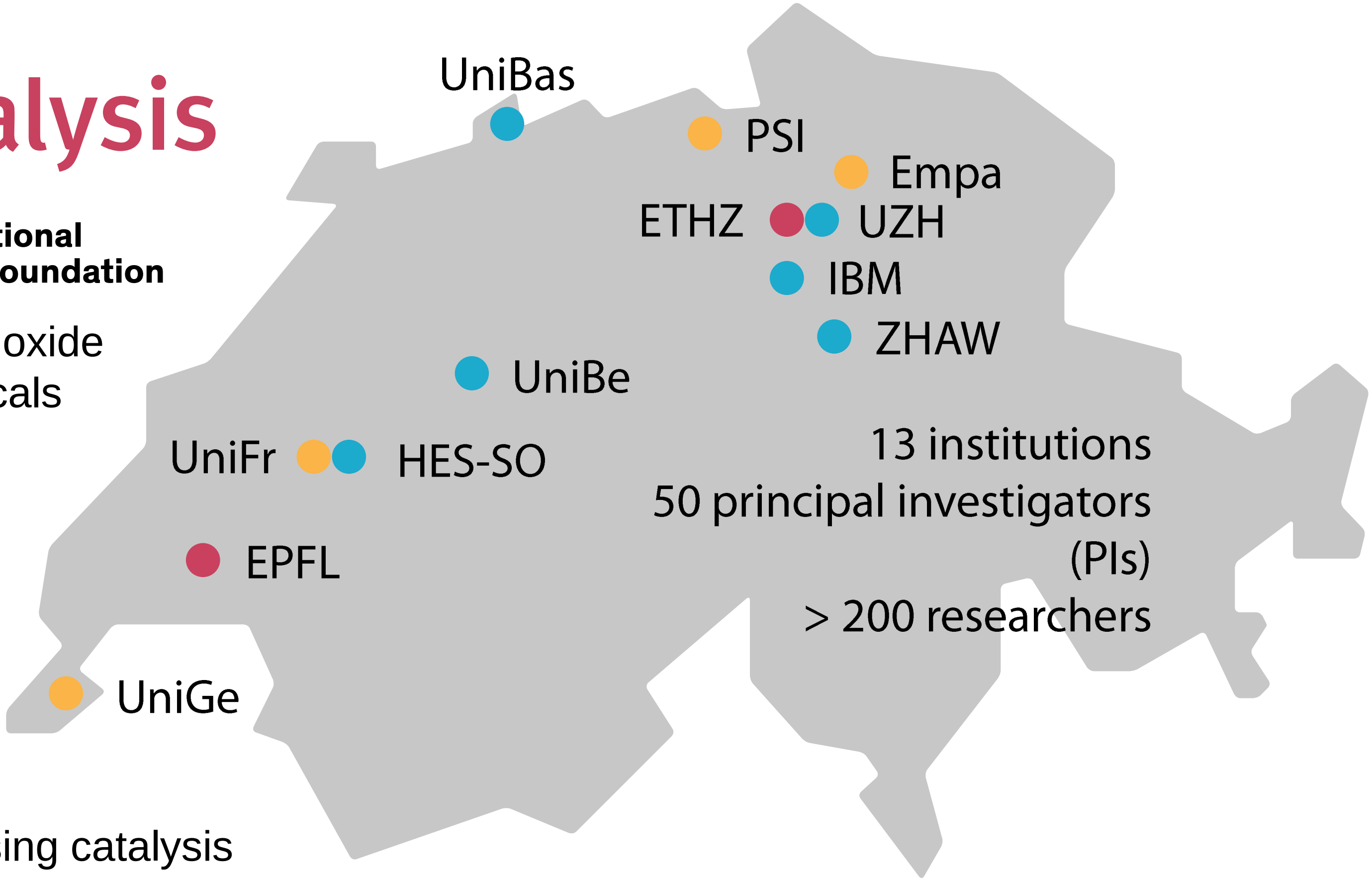
NCCR
Catalysis

Swiss National
Science Foundation

Transforming carbon dioxide
into fuels and chemicals

Computational design of
new catalysts

From nature to drugs using catalysis
and sun light



13 institutions
50 principal investigators
(PIs)
> 200 researchers

From nitrogen in the air to
fertilizers directly on the field

Planetary (plant-to-planet)
assesment of chemicals

https://nccr-catalysis.ch

Bibliography

- *Catalytic Asymmetric Synthesis; Ojima, I. ed.; Wiley-VCH, 2000.* – A good book on the classical developments in the 90's

- *New Frontiers in Asymmetric Catalysis; Mikami, K., Lautens, M., Eds.; Wiley: 2007.* – Collection of reviews on specific reactions

- *Enantioselective Chemical Synthesis: Methods, Logic and Practice*; Corey, E. J.; Kurti, L.; Direct Book Publishing, LLC, Harvard, 2010.

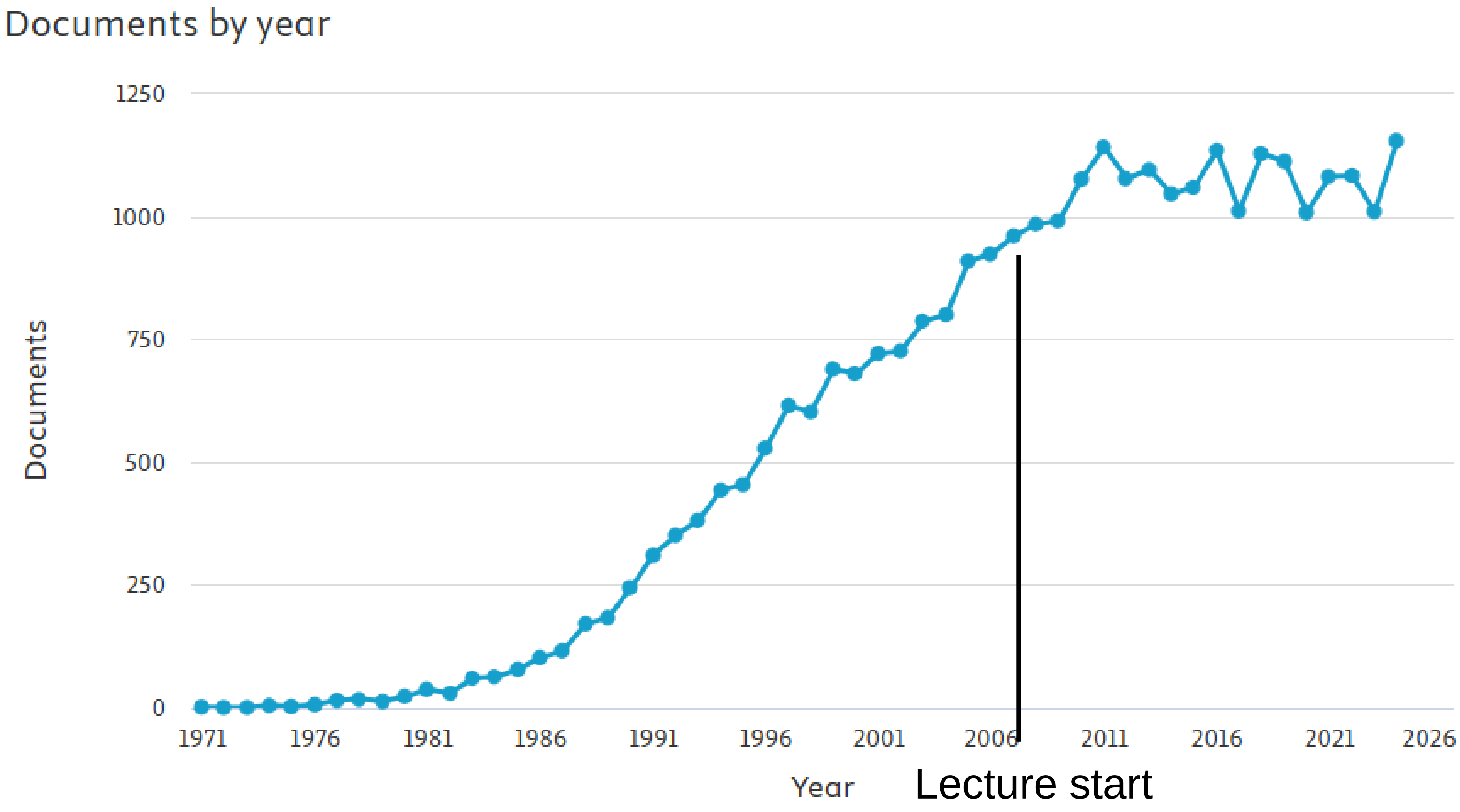
- No really good overview book

- Changing every week and exponentially

- Primary literature is best source: each year the literature list is updated (for future eventual use, not meant to be read!)

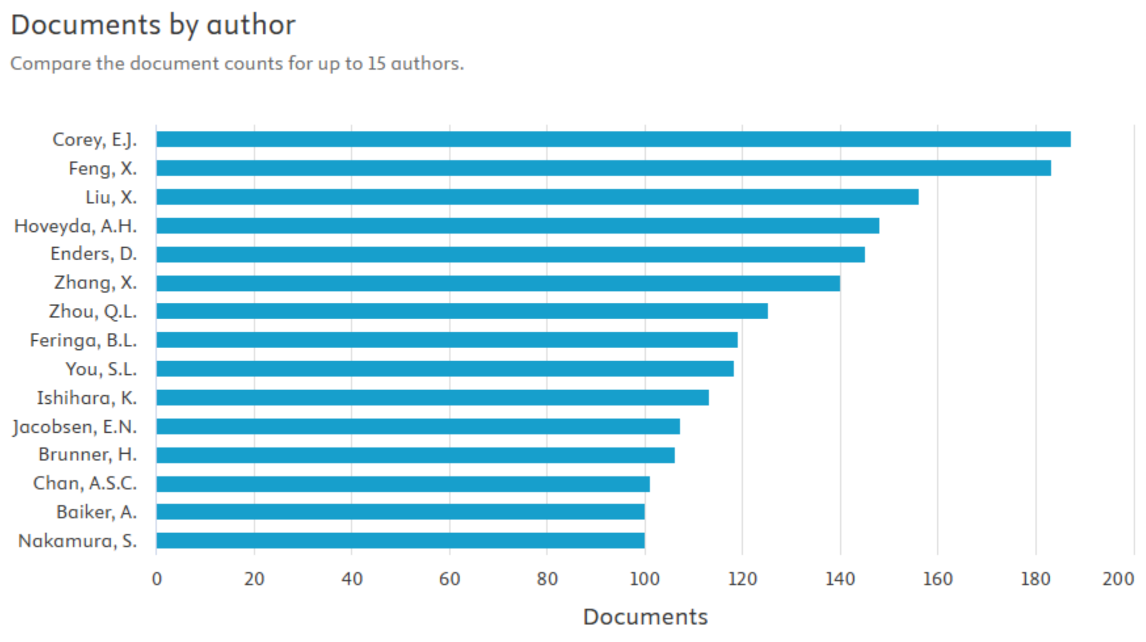
- Organic seminars at EPFL: https://www.epfl.ch/schools/sb/research/isic/news-events/organic_chemistry_seminars/

Bibliography: Statistics



Scopus search on 1.02.2025 for articles with «enantioselective» in title

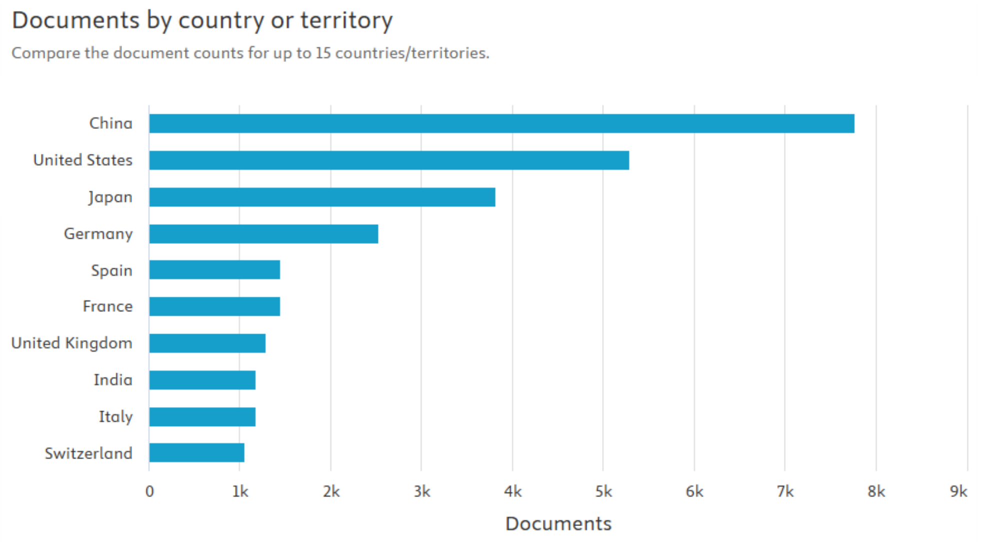
Bibliography: Statistics


Documents by author

Compare the document counts for up to 15 authors.

In Switzerland:

1. Cramer (EPFL, 70)
2. Zhu (EPFL, 69)
3. Alexakis (Geneva, 68)
4. Carreira (ETHZ, 67)


Documents by country or territory

Compare the document counts for up to 15 countries/territories.

Table of Content

1. Introduction

- Vocabulary and concepts in asymmetric catalysis
- Classification problem: ligands, metals, reactions or principles?

2. LUMO Activation

2.1. Lewis and Brønsted acids activation of carbonyl and imines

2.2. Lewis and Brønsted acids activation of extended π- systems of carbonyl and imines

2.3. Catalysis via iminium formation

2.4. Activation of electrophiles other than carbonyl/imines

2.5. Activation of allylic systems

2.6. Direct activation of C-C double bond

2.7. Chiral acylation

Table of Content

Table of Content

1. Introduction

Key Parameters for Catalysis

Catalysis is the acceleration of a chemical reaction by means of a substance called a **catalyst**, which is itself not consumed by the overall reaction.[1]

Parameters for Efficiency in Catalysis

Turnover number (TON): number of catalytic cycles (until deactivation)

Turnover frequency (TOF): number of catalytic cycles in one time unit

Catalyst Loading (usually in mol%)

Typical digits in academia: 5 mol% catalyst, TON = 20, TOF = 5/h

Desired in industry: < 0.01 mol% catalyst, TON = 10^5-10^6, TOF = 10^5 !

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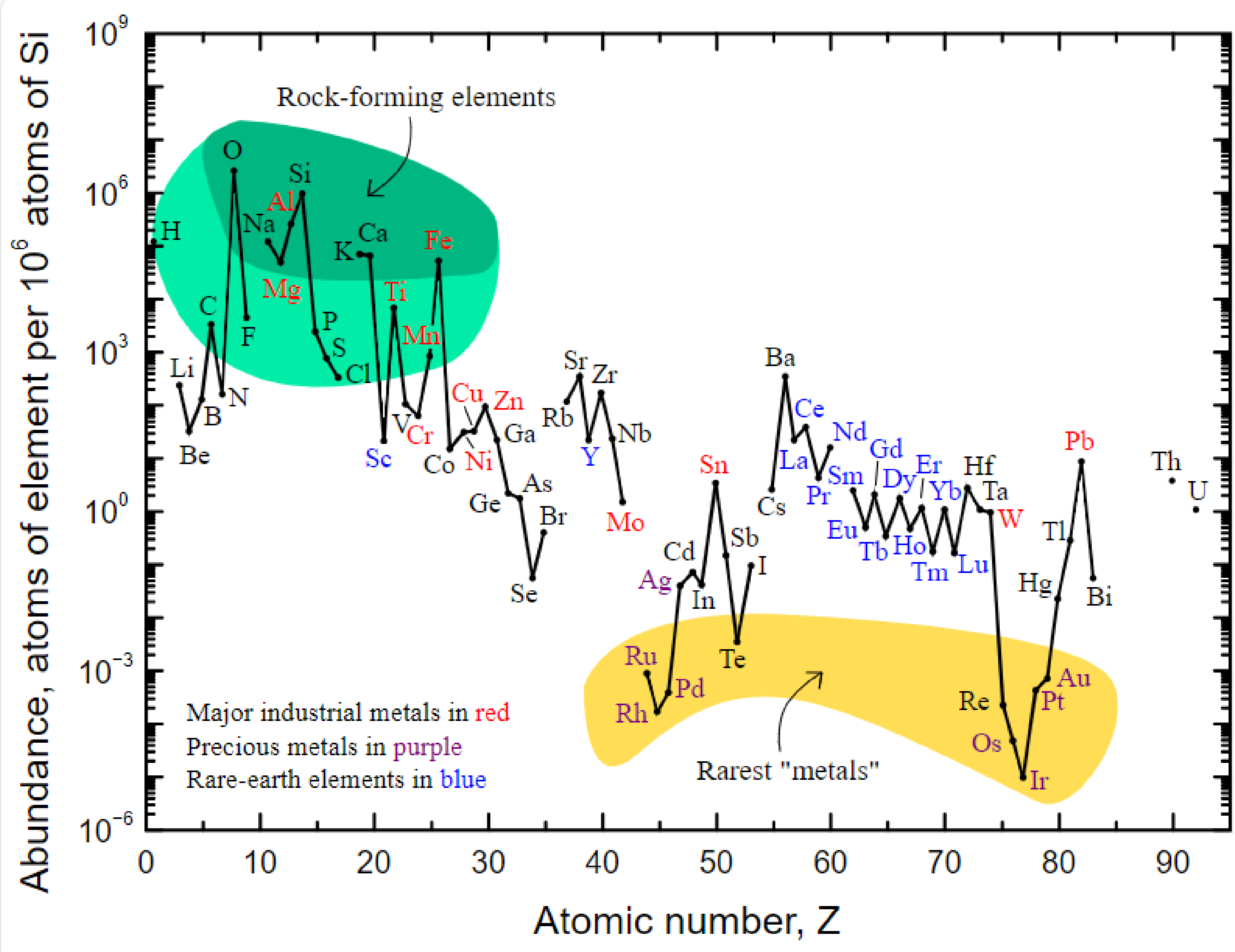
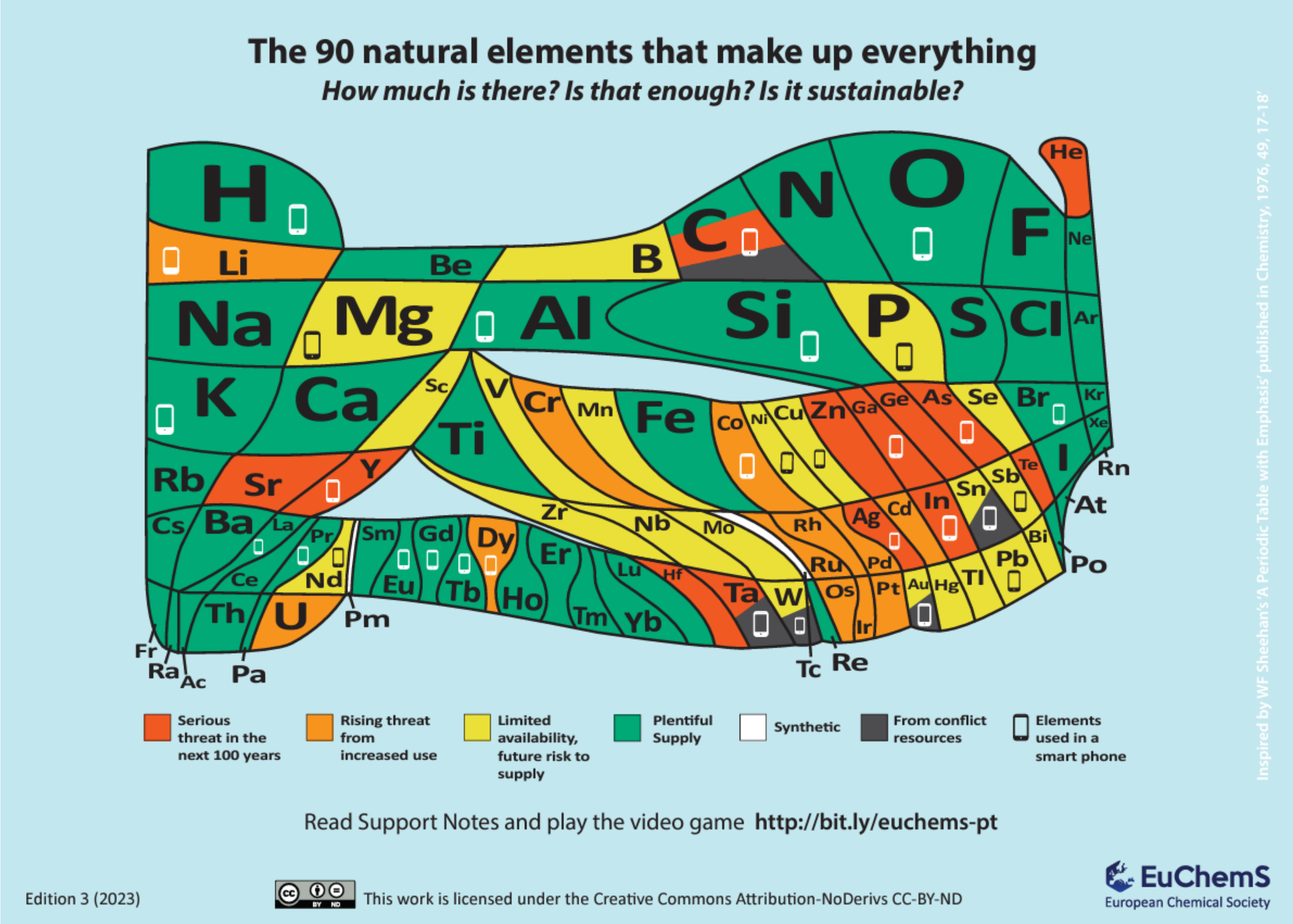
(1) Definition from Wikipedia

Which elements are abundant?



(1) Picture from Wikipedia

Which elements are sustainable?



The 90 natural elements that make up everything

How much is there? Is that enough? Is it sustainable?

🟥 Serious threat in the next 100 years

🟧 Rising threat from increased use

🟨 Limited availability, future risk to supply

🟩 Plentiful Supply

⬜ Synthetic

⬛ From conflict resources

📱 Elements used in a smart phone

Inspired by WF Sheehan's 'A Periodic Table with Emphasis' published in Chemistry, 1976, 49, 17-18'

Read Support Notes and play the video game **http://bit.ly/euchems-pt**

Edition 3 (2023)

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EuChemS
European Chemical Society

(1) https://www.euchems.eu/euchems-periodic-table/

Key Parameters for Asymmetric Catalysis

In asymmetric catalysis, a chiral catalyst is able to induce chirality in the product.

Special Parameters for Asymmetric Catalysis

- Enantiomeric / Diastereomeric Ratio (er, dr)

- Enantiomeric/ Diastereomeric Excess (ee, de)

➡ Difference in % between major and minor enantiomer/diastereomer

$$ee = 100 \cdot \frac{er - 1}{er + 1}$$

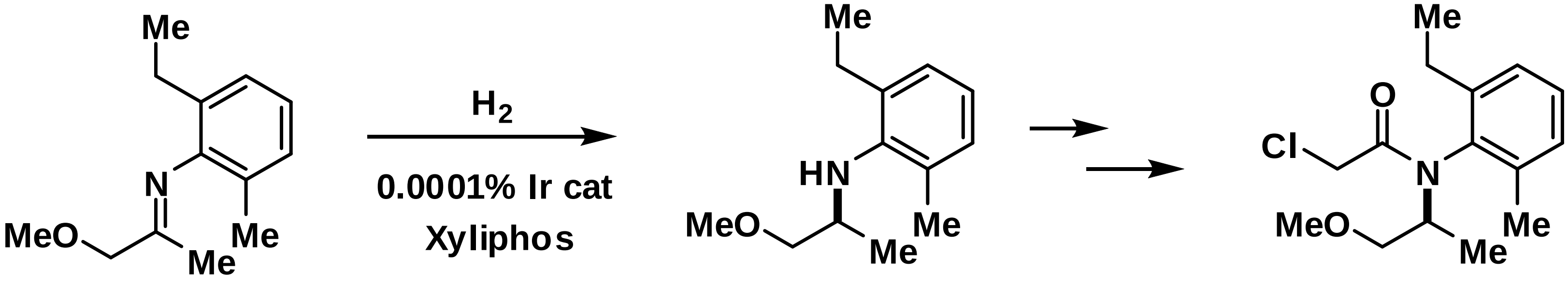
What is a good ee?

➡ Dependent of reaction and physical state of product, often > 90%

Key Parameters for Asymmetric Catalysis

The Gold Standard for Asymmetric Catalysis in Industry

Ciba-Geigy Synthesis of (*S*)-Metolachlor

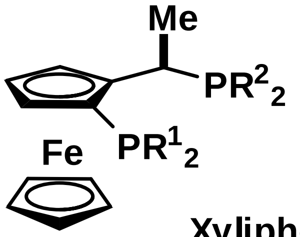


80% ee

(*S*)-Metolachlor

Ciba-Geigy (Novartis)

TON > 1000000
TOF > 180000/h



Xyliphos

R^1 = Xylyl
R^2 = Ph

Key Parameters for Asymmetric Catalysis

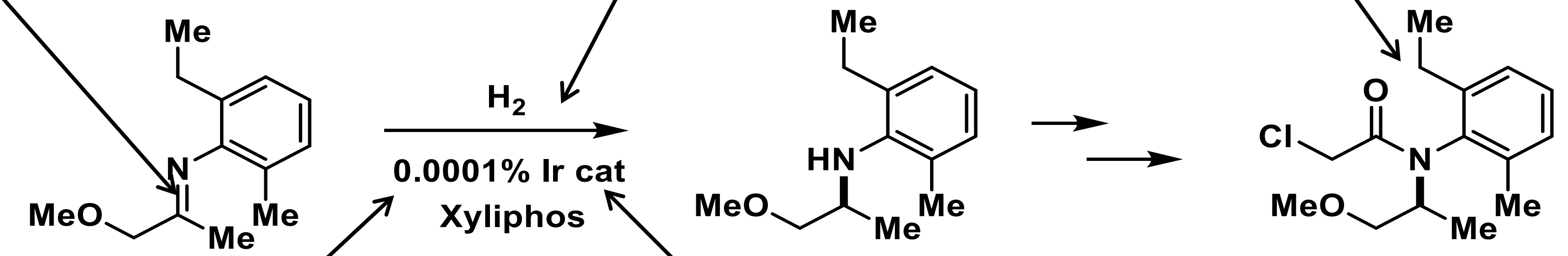
The Gold Standard for Asymmetric Catalysis in Industry

Ciba-Geigy Synthesis of (*S*)-Metolachlor

Imine hydrogenation/reduction: good way to make chiral amine.

Hydrogenation=most atom economical reduction.

Herbicid, agrochemical: synthesis has to be cheap!



80% ee

(*S*)-Metolachlor

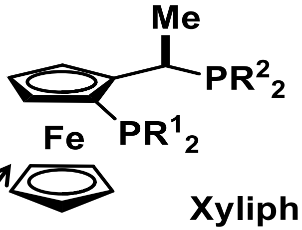
Ciba-Geigy (Novartis)

TON > 1000000
TOF > 180000/h

Exceptionally low loading: 0.1 ppm

Late metal catalysts for hydrogenation (Ru, Rh, Pd, Ir)

Moderate ee: often less important for industry



Xyliphos

R^1 = Xylyl
R^2 = Ph

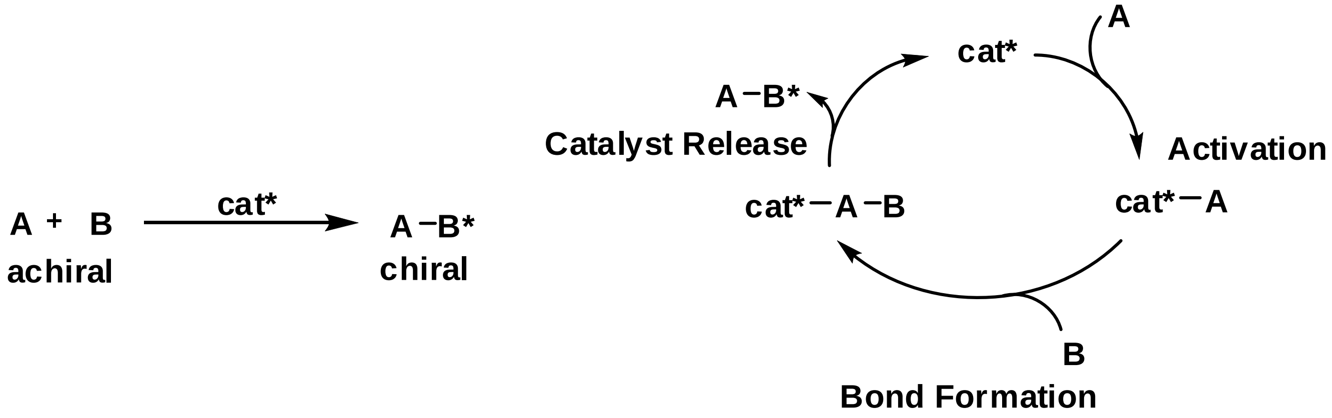
Chiral bisphosphine based on Ferrocene: exceptional ligands for catalysis (A. Togni, Ciba, ETHZ)

Be active, take notes! Now your script should look somewhat like that!

Modes of Asymmetric Induction

1. Creation of a New Chirality Element During Reaction

General Scheme

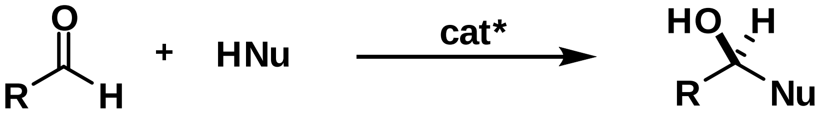


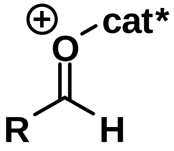
Key Elements:

1. Activation via catalyst (no background, direct reaction)
2. Chirality of catalyst directs stereoselective bond formation
3. Catalyst easily released by product: turnover possible

Modes of Asymmetric Induction

Example of Activation: Addition to Carbonyl

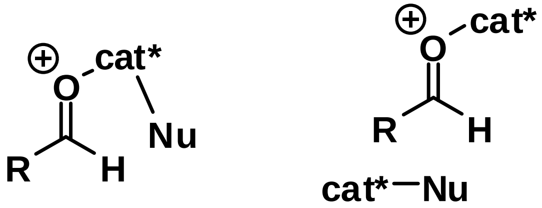




LUMO Activation

cat*—Nu

HOMO Activation



Dual Activation

Possible activation modes:

1. Lowering LUMO: more electrophilic
2. Hightening HOMO: more nucleophilic
3. Dual activation: towards best selectivities

Modes of Asymmetric Induction

2. Kinetic Resolution of Chiral Compounds

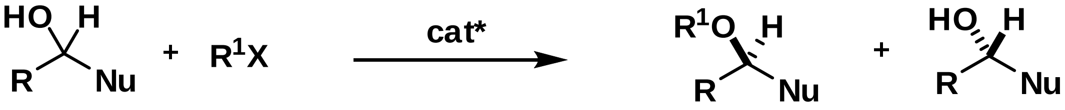
General Scheme

$$A^* + B \xrightarrow{cat^*} A_R{-}B + A_S$$

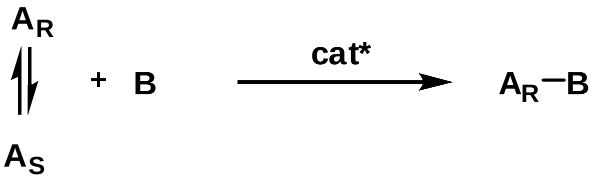
chiral racemic

chiral enantiopure

Resolution of Secondary Alcohols



Dynamic Kinetic Resolution

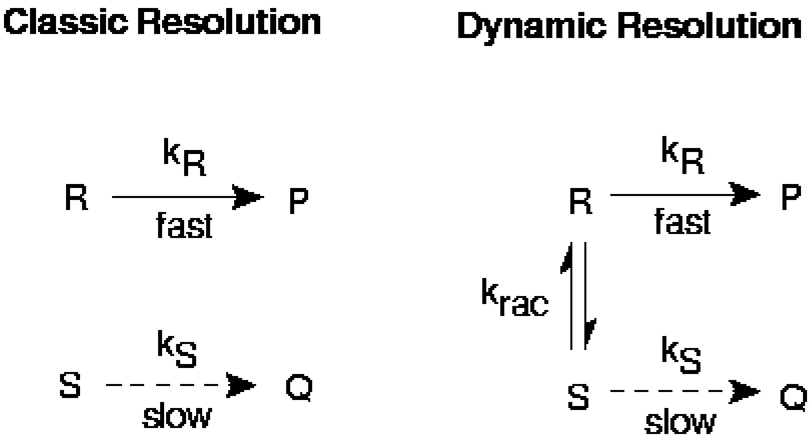


Kinetic resolution: max. 50% enantiopure product and 50% enantiopure starting material.

Dynamic kinetic resolution: max. 100% enantiopure product.

Modes of Asymmetric Induction

Parameters for Kinetic Resolution[1]



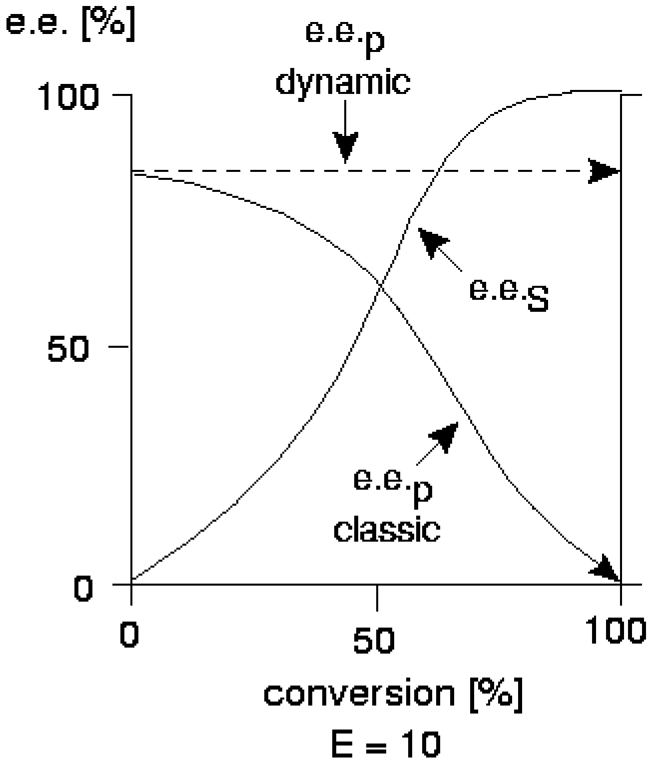
R, S = substrate enantiomers

P, Q = product enantiomers

k_R, k_S = individual rate constants (k_R » k_S)

k_{rac} = racemization constant (k_{rac} • k_R)

E = Enantiomeric Ratio



ee is dependent of the yield if the selectivity is not perfect!

The best parameter to describe the selectivity is E, called S factor, S = k_R/k_S.

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(1) ecsoc2.hcc.ru/ecsoc-2/al001/al001.htm

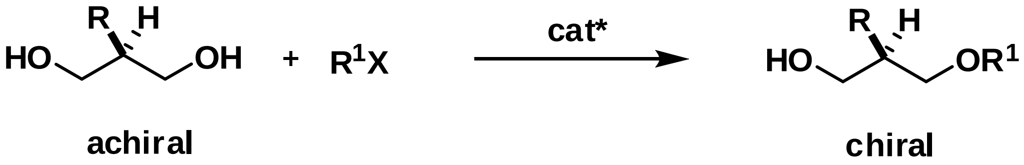
Modes of Asymmetric Induction

3. Desymmetrization

General Scheme

$$\underset{\text{prochiral}}{A + B} \xrightarrow{\text{cat*}} \underset{\text{chiral}}{A{-}B^*}$$

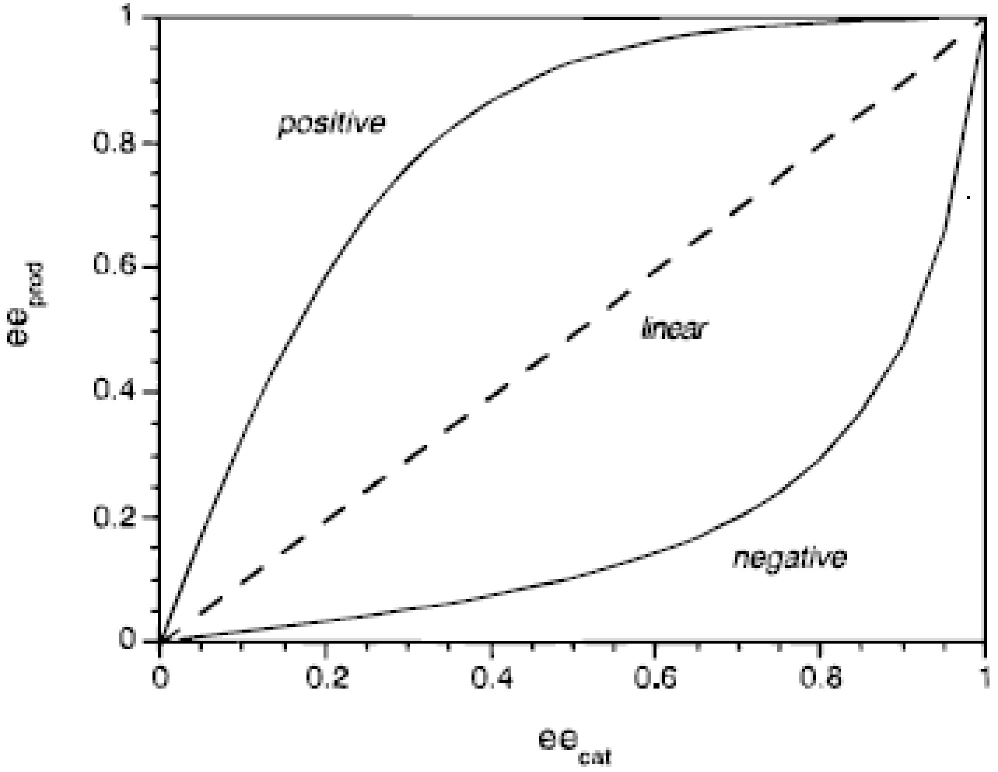
Desymmetrization of Diols



- No chirality element introduced in bond forming event
- Symmetric non-chiral substrates usually easy to prepare

Relationship ee Catalyst ee Product

Non Linear Effect[1]



- Intuitively expected: linear relationship
- How can we explain negative or positive non-linear effects?

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(1) Blackmond, D. G. *Acc. Chem. Res.* ***2000,*** *33, 402-411.*

Relationship ee Catalyst ee Product

Linear relationship: no interaction between enantiomers of catalyst

$$S \xrightarrow[k]{cat_R} P_R$$

$$S \xrightarrow[k]{cat_S} P_S$$

$P_R/P_S = cat_R/cat_S$ (For ideal reaction (100% ee))

Dimerization of Catalyst: NLE possible

$$cat_R + cat_R \overset{K_{RR}}{\rightleftharpoons} (cat_R)_2$$

$$cat_S + cat_S \overset{K_{SS}}{\rightleftharpoons} (cat_S)_2$$

$$cat_R + cat_S \overset{K_{RS}}{\rightleftharpoons} cat_S cat_R$$

- Simplest case: dimers are inactive:
  - $K_{RS} > 1$, $K_{SS} = K_{RR} < 1$: positive NLE (reservoir effect)
  - $K_{RS} < 1$, $K_{SS} = K_{RR} > 1$: negative NLE
- Reality is more complex (no ideal reaction, dimer are active, trimer possible…)

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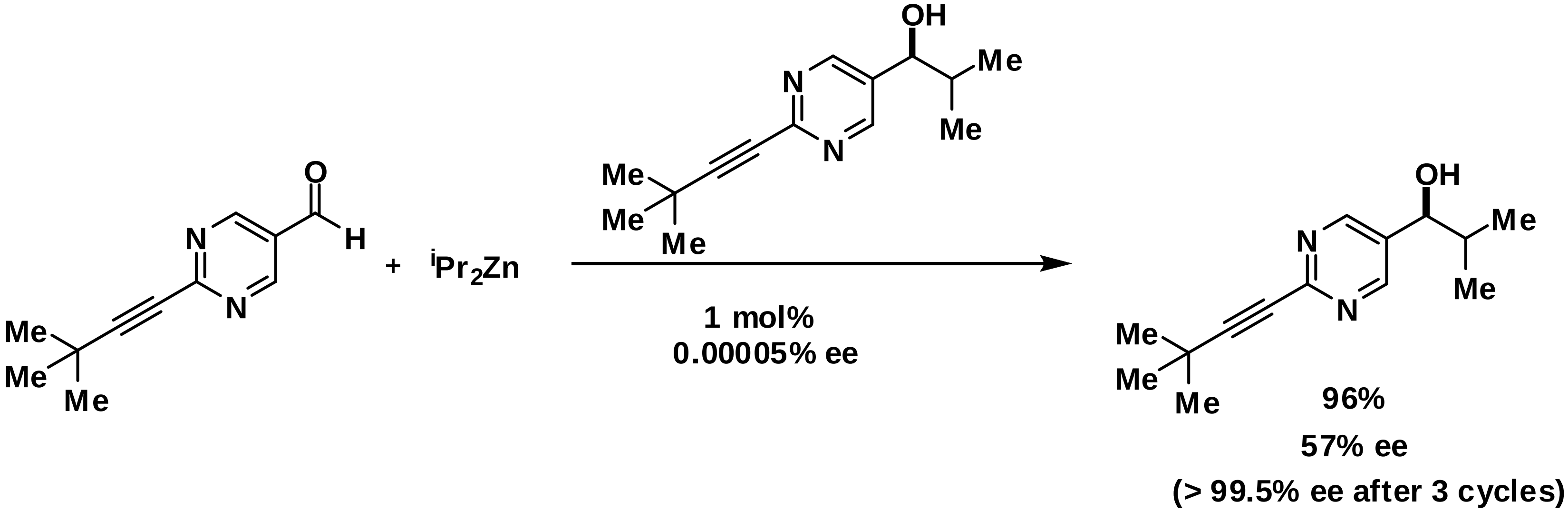
(1) Blackmond, D. G. *Acc. Chem. Res.* **2000,** *33, 402-411.*

Relationship ee Catalyst ee Product

Autocatalysis: The formed product is able to catalyse the reaction.

Special Case: Autocatalysis with strong positive NLE

Soai's system:[1]



1 mol%
0.00005% ee

96%
57% ee
(> 99.5% ee after 3 cycles)

Are similar phenomenes responsible for homochirality in nature?

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(1) Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed*. **2003**, *42,* 315.

Classification of Catalytic Asymmetric Reactions

1. Classification via Catalyst

→ Easy systematic, but not easy for understanding/using

2. Classification via Reaction

→ Good for the laboratory, user

3. Classification via Chiral Element (Ligand)

→ Good for understanding stereoselectivity and ligand design

4. Classification via Catalytic Principles

→ Good for understanding and studying catalysis and enhance creativity

↓

Understanding principles allows to understand current research and design the research of the future!