Umweltverträgliche Chemie mittels effizienter Syntheseplanung

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Concepts

- What this talk is about.
- Main metrics
- An example
- Application of metrics in industry
- Metrics easily obtained.
- Industrial case study
- Environmental assessment: Env. index (EHS-metric)
- Outlook (new assessment concept)
- Summary

What this talk is about.

Performance metrics of syntheses or synthesis sequences.

➔ Information about

Raw material utilization

Waste production

Cost drivers (materials)

Volume of recycle loops

Problematic substances

Quantification
Visualization

➔ Objective and clear
identification of weak-points.
comparison with alternative synthesis routes.
documentation of the efficiency of scale-up efforts.

Main metrics

$$\text{Mass index} \quad S^{-1} = \frac{\sum \text{Raw material [kg]}}{\text{Product [kg]}} \quad \begin{cases} \dfrac{\text{Substrates [kg]}}{\text{Product [kg]}} \\ \dfrac{\text{Solvents (total) [kg]}}{\text{Product [kg]}} \\ \dfrac{\text{Solvents (recycling) [kg]}}{\text{Product [kg]}} \\ \dfrac{\text{Water [kg]}}{\text{Product [kg]}} \end{cases}$$

....

$$\text{Environmental factor} \quad E = \frac{\sum \text{Waste [kg]}}{\text{Product [kg]}}$$

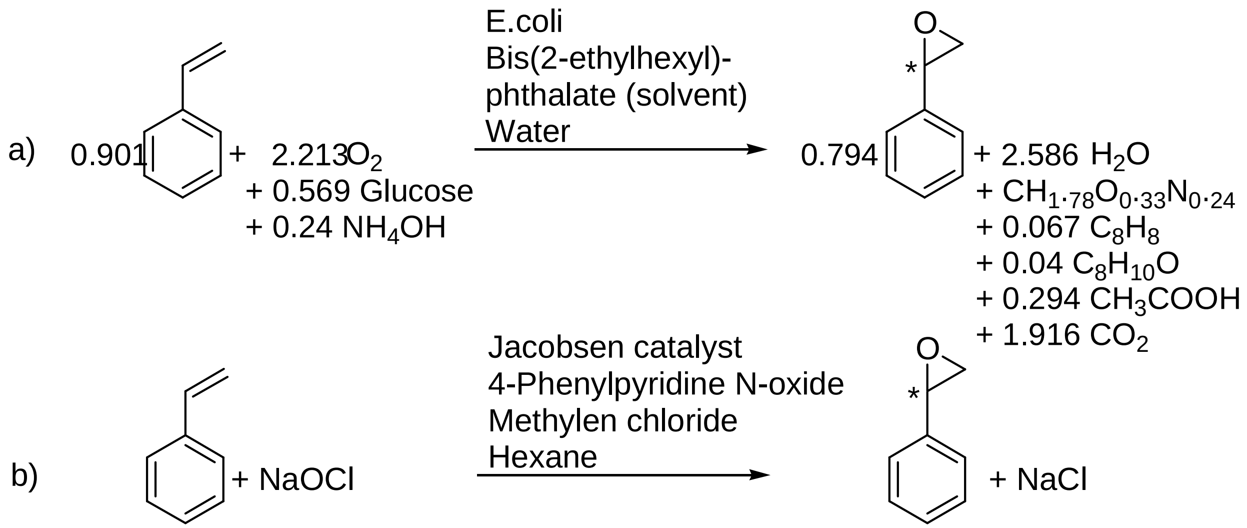
$$\text{Cost index} \quad CI = \frac{\sum \text{Raw material [EURO]}}{\text{Product [kg]}}$$

An example

Enantioselective Epoxidation

Biochemical (E.coli)

Chemical (Jacobsen)



88% yield

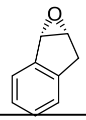
(99% ee)

71% yield

(86% ee)

a) S. Panke, M. Held, M. G. Wubbolts, B. Witholt, A. Schmid, *Biotechnology and Bioengineering* **2002**, *80*, 33-41

b) According to J. F. Larrow, E. Roberts, T. R. Verhoeven, K. M. Ryan, C. H. Senanayake, P. J. Reider, E. N. Jacobsen, *Organic Syntheses*, *76*, 46.

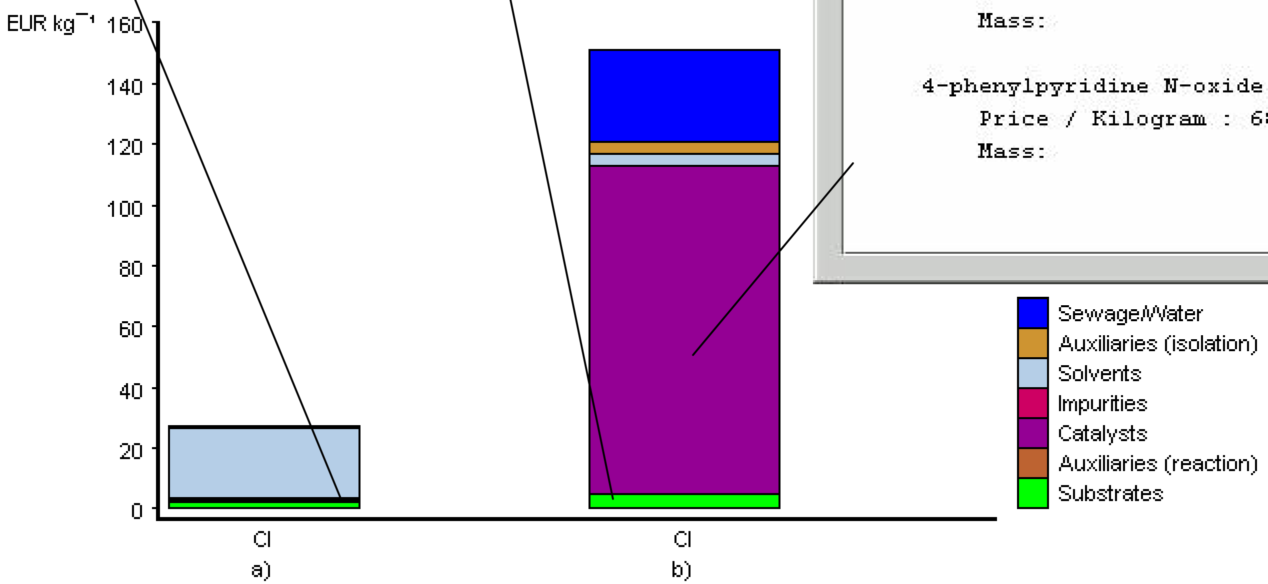


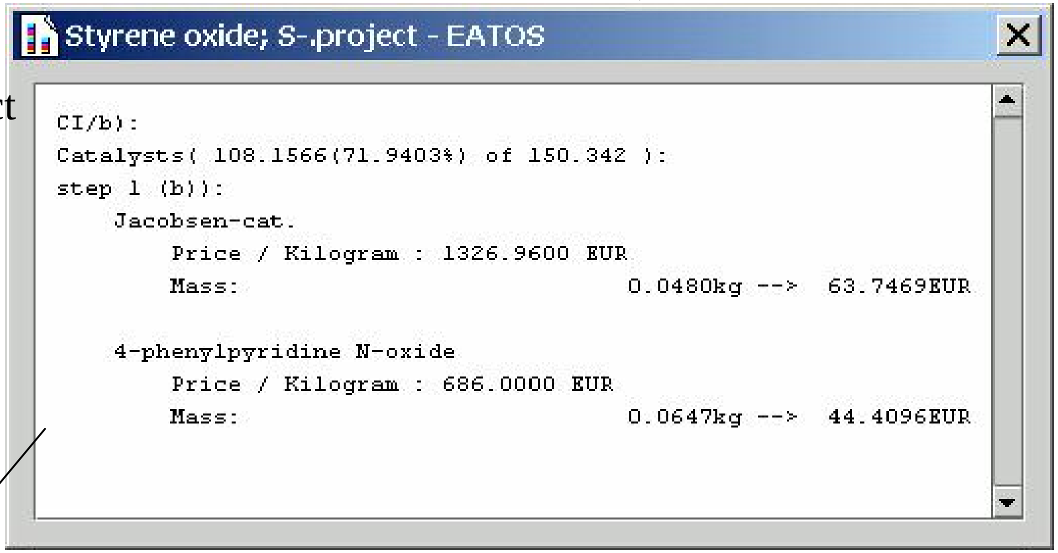
An example

Cost index **CI** (presented by means of the software EATOS)

Substrates:
4.28 EUR / kg Product

Substrates:
1.46 EUR / kg Product





biochemical   chemical

EATOS: M. Eissen, J. O. Metzger, Environmental Performance Metrics for Daily Use in Synthetic Chemistry, *Chem. Eur. J.* **2002**, *8*, 3580-3585.

Market prices, except Jacobsen catalyst
and 4-phenylpyridine N-oxide ➔ Aldrich price / 10 was applied

Application of metrics in industry

Company 1 | Company 2

In order to not infringe a copyright two figures similar to the one on slide 6 were deleted.

Application of metrics in industry

My impression: (MFA = material flow analysis X = fitness for use)

	Remark	Stage of development	Synthesis design	Process design	Operation
Merck	MFA	mature			
BASF I	Eco-efficiency	mature			
BASF II	MFA	in development			
Bayer I	Eco-check	mature			
Bayer II	MFA	in development			
Clariant	MFA	in development (Excel)			
Schering	MFA	in development (Excel)			
Aventis	MFA	in development (Excel)			
Syngenta uses Excel calc.					

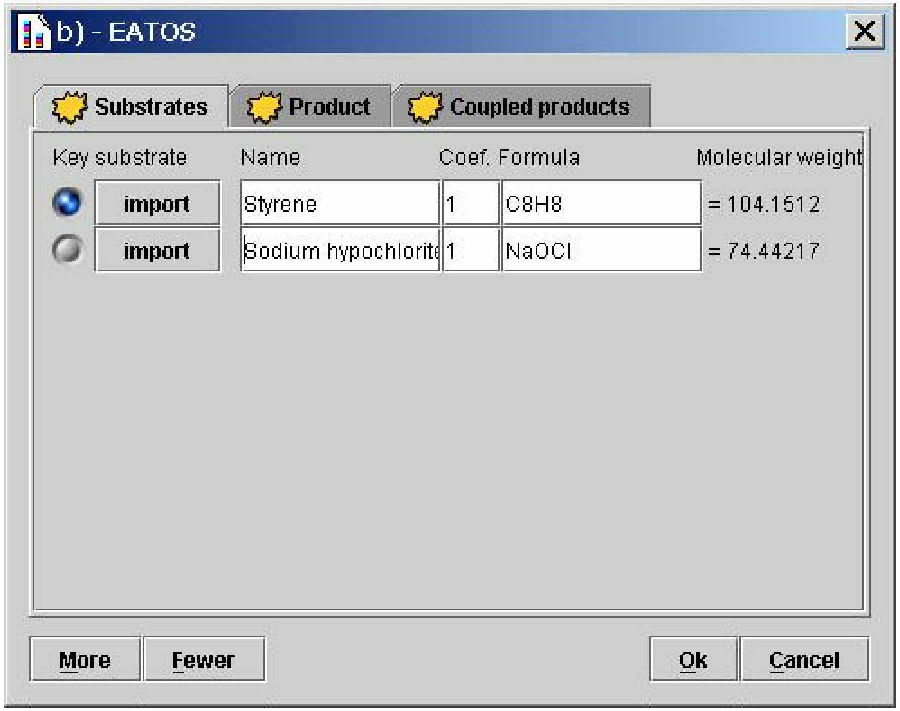
The rating may be out of date. Therefore it was deleted.

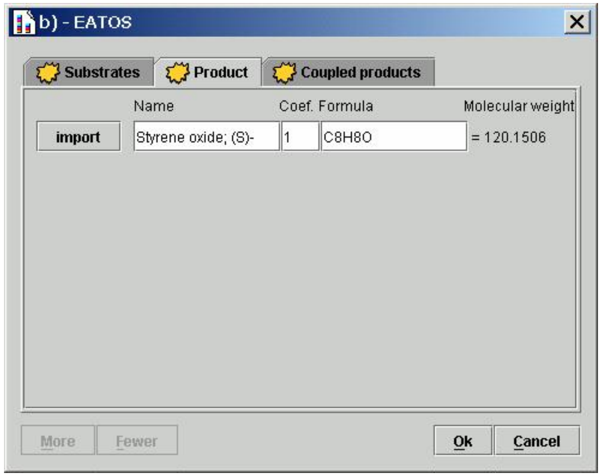
Metrics easily obtained.

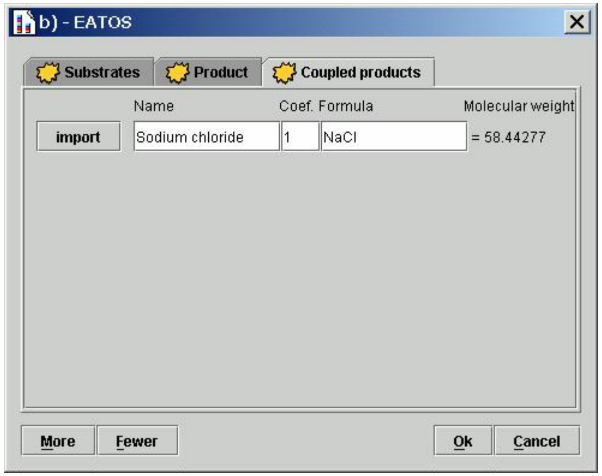
How can calculations be performed.

Enter stoichiometry

1 Styrene + 1 NaOCl ➔ 1 (*S*)-Styrene oxide + 1 NaCl



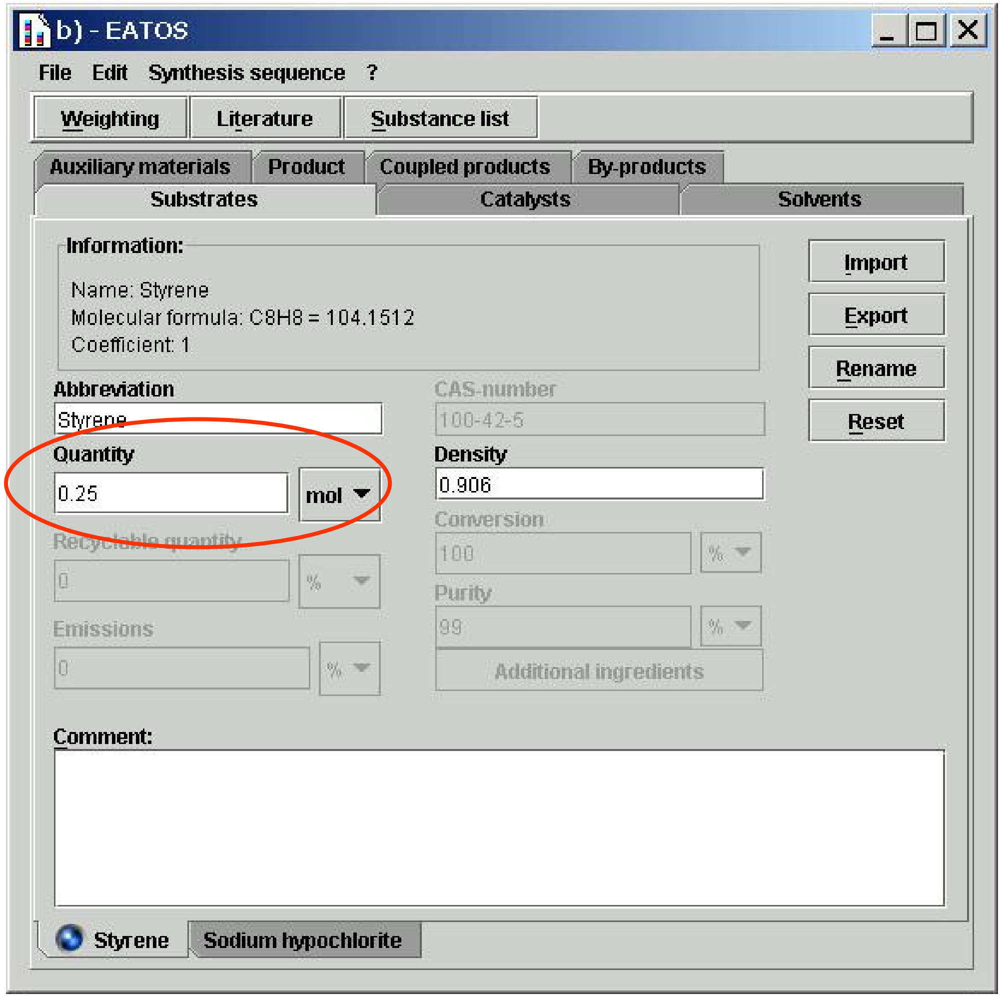




Metrics easily obtained.

How can calculations be performed.

Enter quantities

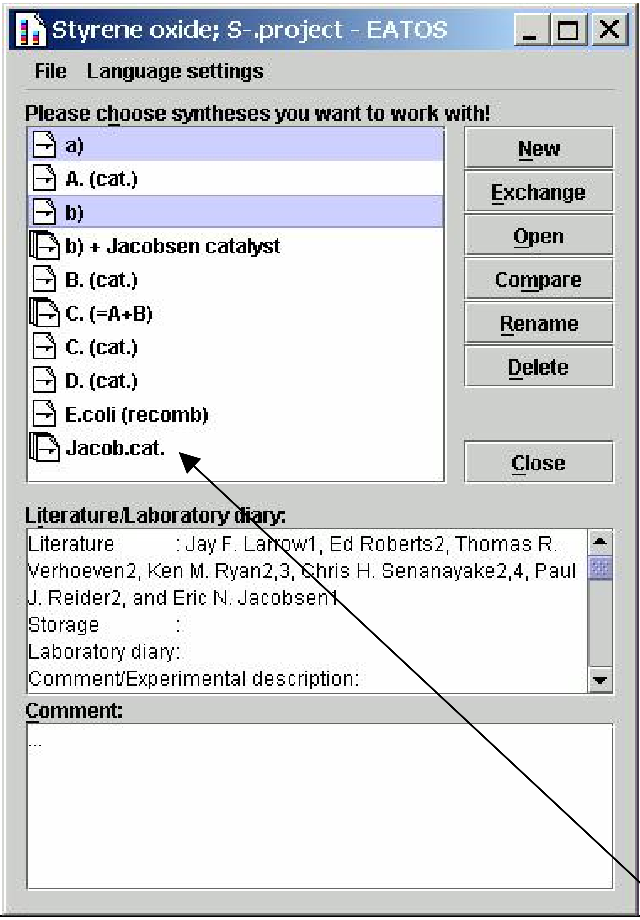


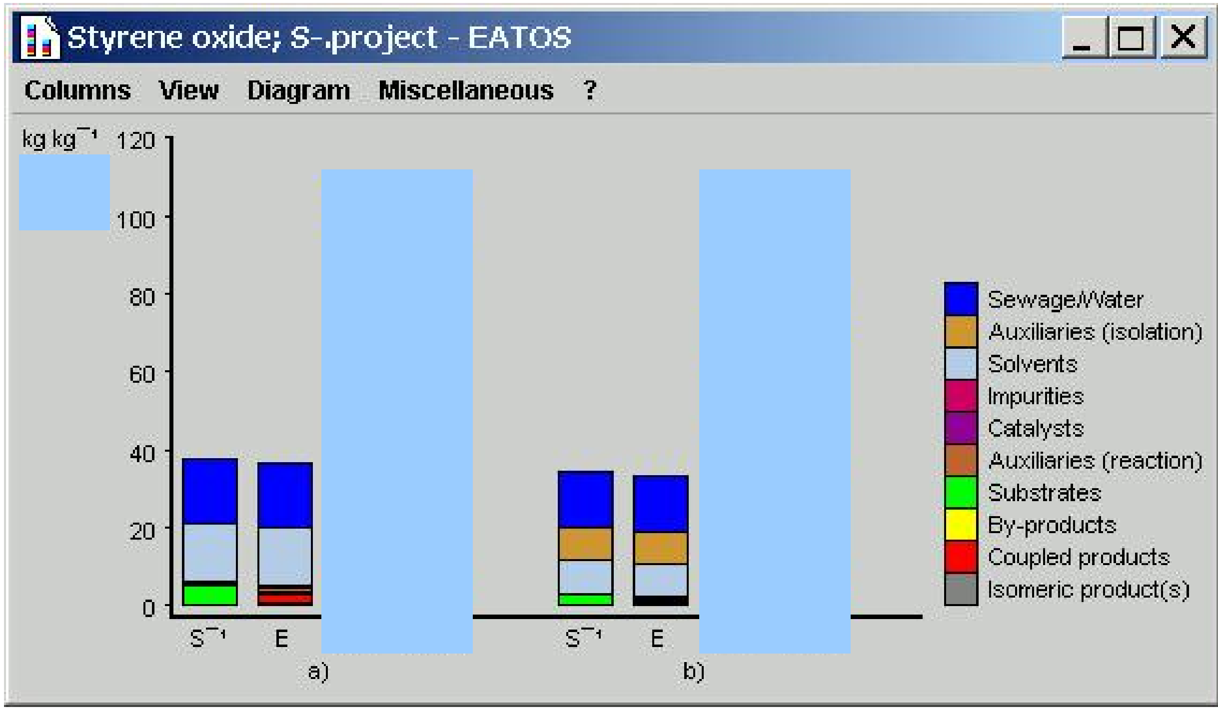
Metrics easily obtained.

How can calculations be performed.

voilà

Press ‚Compare‘





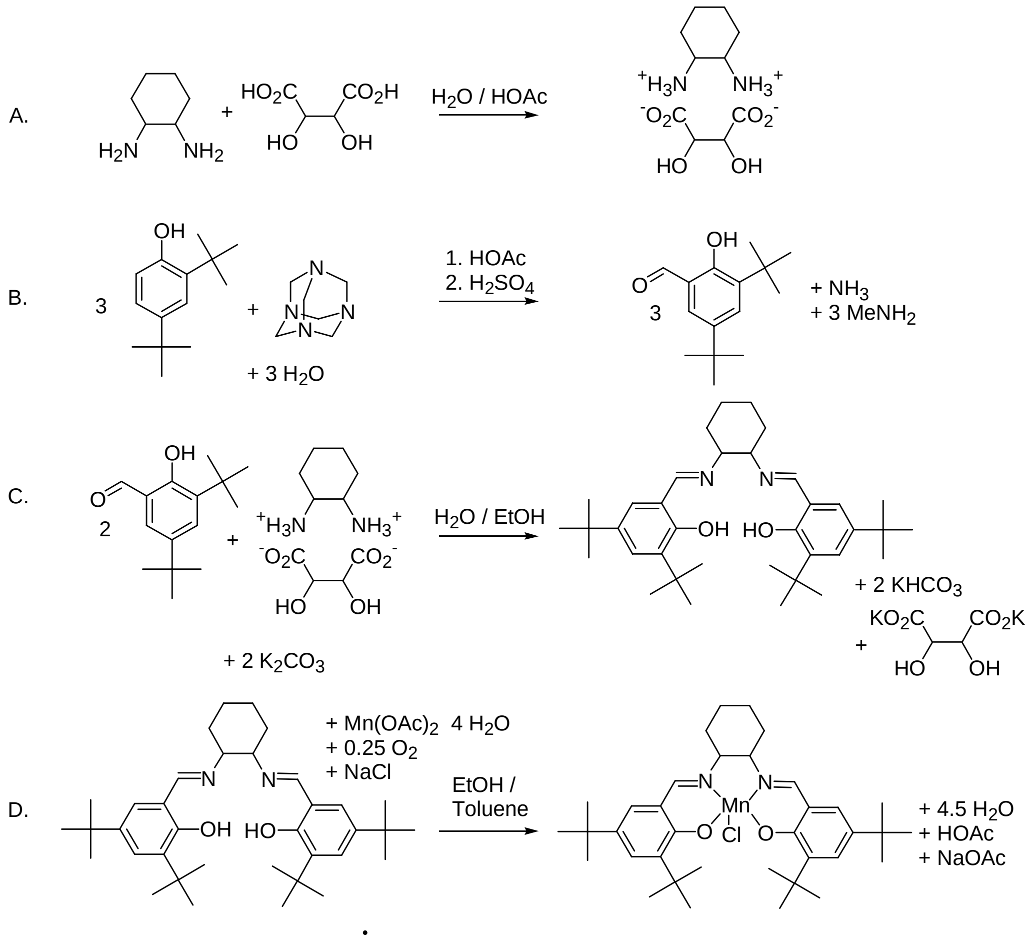
Click segments for details.

To examine complex synthesis sequences press ‚Import‘ to import a preceding synthesis.

Example: ‚Jacobsen.cat.‘ = A.(cat.) ∞ B.(cat.) ∞ C.(cat.) ∞ D.(cat.)

Metrics easily obtained.

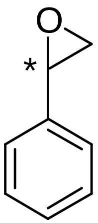
Integrate, in case you want, the preparation of the Jacobsen catalyst



J. F. Larrow, E. N. Jacobsen, *Organic Syntheses*, *75*, 1.

Metrics easily obtained.

To assess the production of



(*S*) - Styrene oxide

three metrics were used:

S^{-1}	E	CI
Quantities		**Costs**
[kg / kg]		**[EUR / kg]**
Input / Output		Input

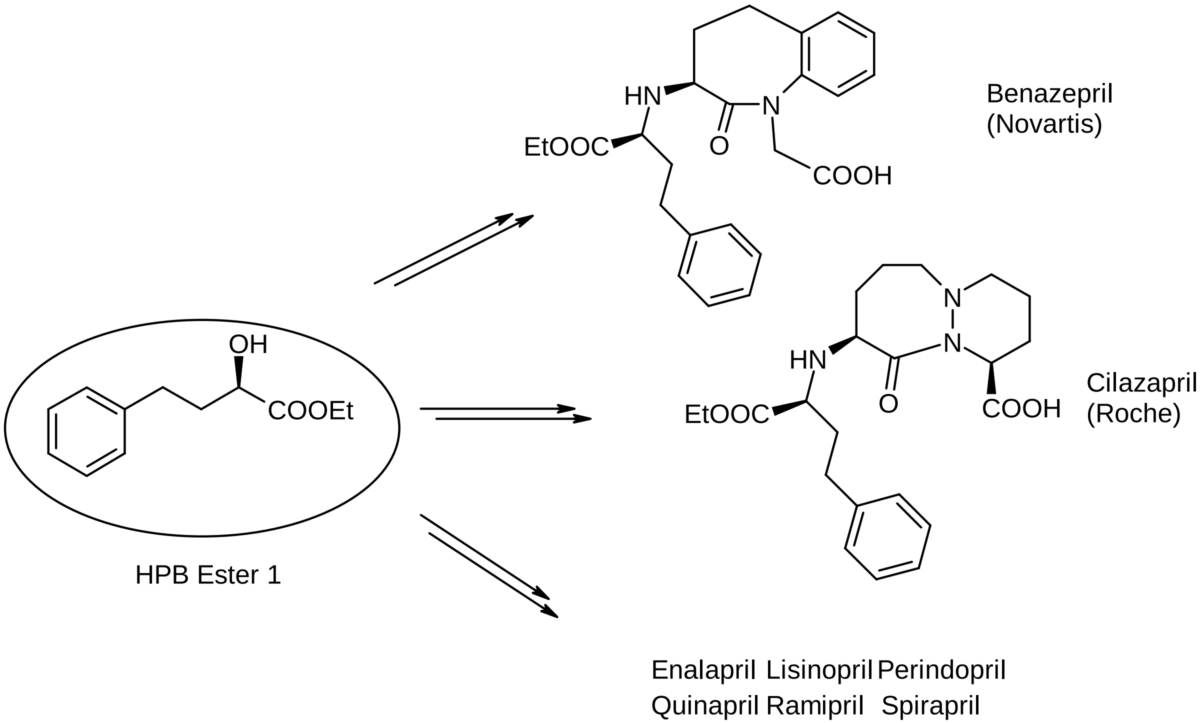
(Mass index; Environmental factor; Cost index**)**

In the following two case studies, it will be presented how these metrics were applied.

Then further metrics will be introduced.

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

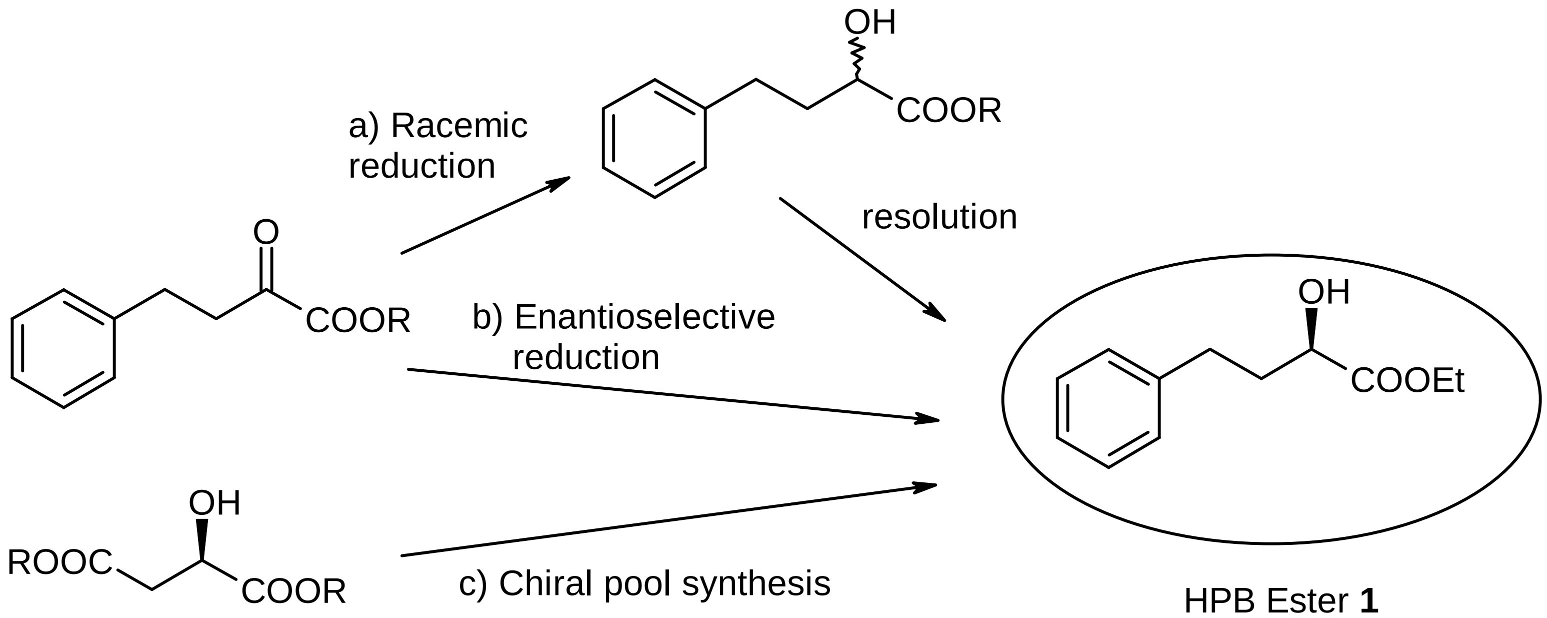


Structures of ethyl (R)-2-hydroxy-4-phenylbutyrate (HBP Ester **1**) and of selected ACE inhibitors

Since the patents for several ACE inhibitors have already expired or will soon do so, the production costs will become very important. This calls for the development of more efficient syntheses both for the ACE inhibitors as well as for the various intermediates.

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

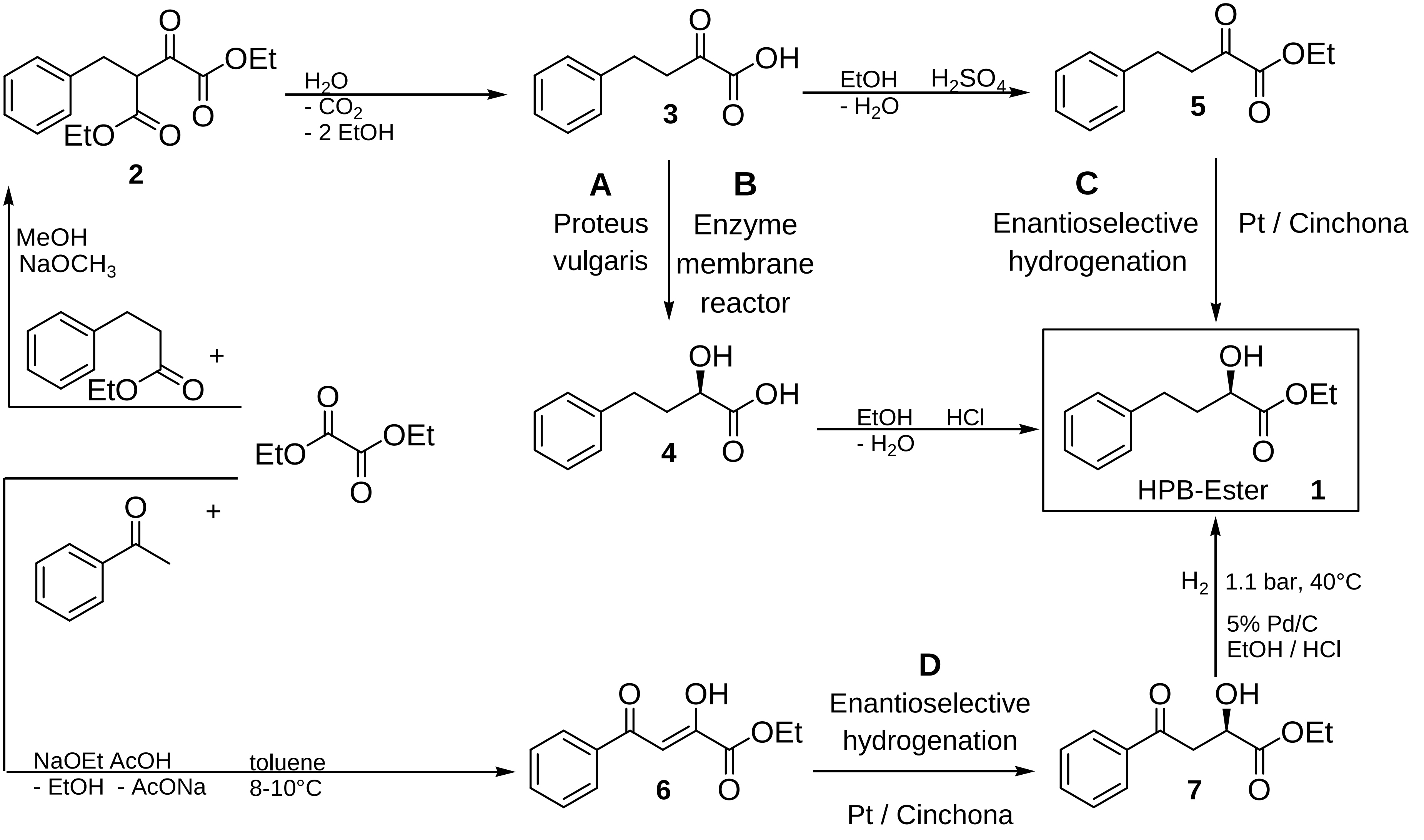


Routes to HPB ester **1**

H.-U. Blaser, M. Eissen, P. F. Fauquex, K. Hungerbühler, E. Schmidt, G. Sedelmeier, M. Studer, Comparison of Four Technical Syntheses of Ethyl (R)-2-Hydroxy-4-Phenylbutyrate, in *Large-Scale Asymmetric Catalysis* (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2003**.

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate



Four enantioselective reduction routes **A** – **D** developed in Ciba-Geigy and Solvias being investigated

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

	A	B	C	D
Number of steps	4	4	4 [a]	3 [a]
Difficult steps	1	1	2	2
Chemical yield in steps 1 – 4 (%)	100/100/99/100	100/100/79/100	100/100/70/73	90/66/96
Over all Chemical yield (%)	**99**	**79**	**46**	**50**
Over all selectivity (%)[c]	12.0 (18.3 [d])	13.0 (20.4[d])	8.4 (17.3 [d])	23.6
Over all atom economy (%)	30.1	33.8	51.0	52.0
Price starting materials	Medium	Medium	Medium	Low
Over all economy	Ok	Ok	Ok	Good

[a] ee upgrading included in the hydrogenation step;
[b] ee upgrading included in the calculation;
[c] Mass of product / Σ mass of substrates;
[d] Mass of product / Σ (mass of substrates – EtOH excess)

Over all comparison of the four routes via **A** – **D**

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

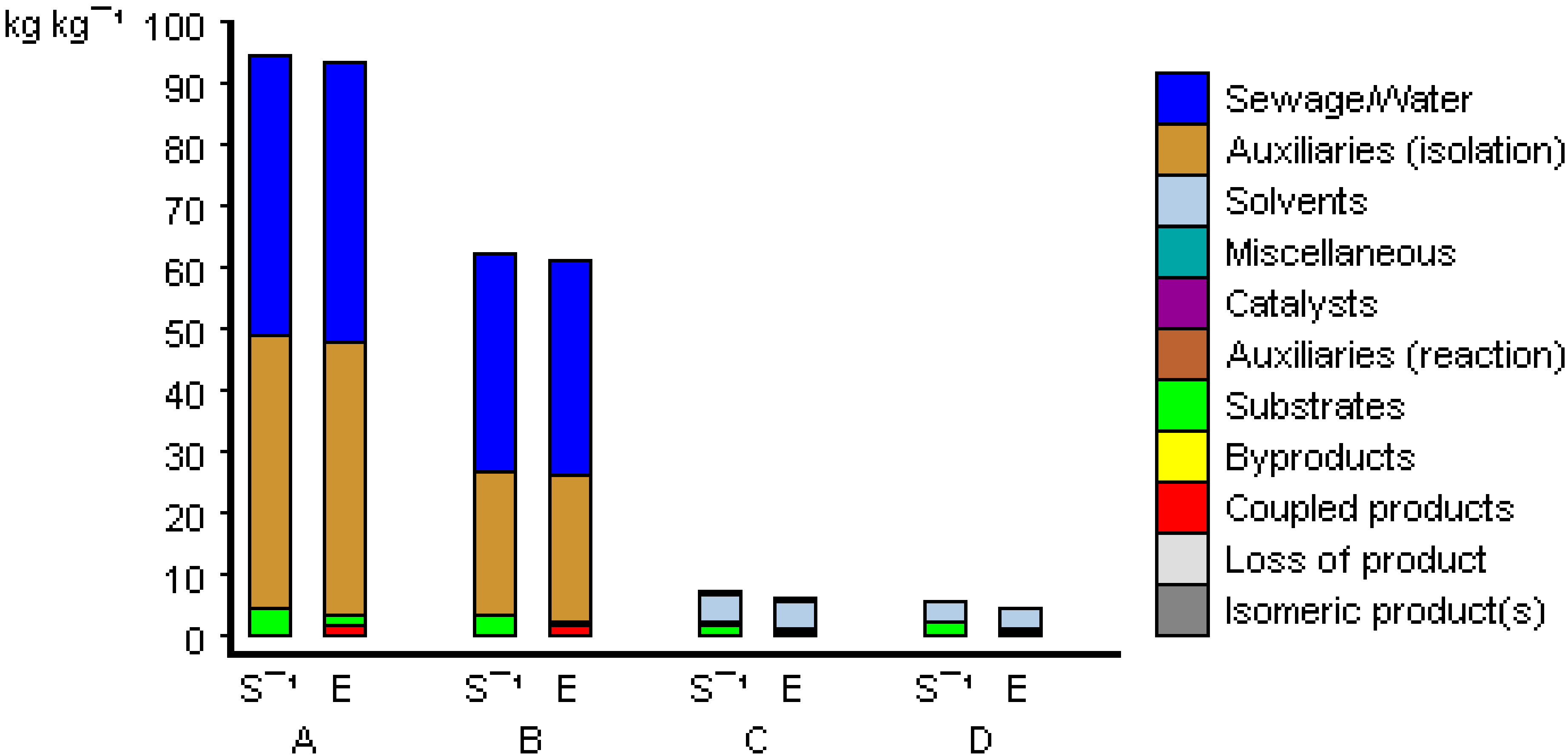
	A	B	C	D
Substrate	3	3	5	6
Enantioselective catalyst	Immobilized proteus vulgaris	Dehydrogenase Enzyme	Pt – cinchona	Pt – cinchona
Reducing agent	HCOOH, viologen	HCOOH, NAD	H_2	H_2
Additives	(Poly)Phosphates	Phosphates	-	-
Solvent	H2O with buffer	H2O with buffer	Toluene or AcOH	Toluene
% ee	> 99	> 99.9	80-92 (82 [a)])	76 – 86 (76 [a)])
S/C (w/w)	50 – 100	25'000	200	40
S/C (mol/mol)	N/A.	N/A.	4000	700
Ton	Living	High	4000	700
tof (h^{-1})	N/A.	N/A.	1000	300
Space / time yield (mol/(l*d))	1.7 – 0.64	1.0	24	12
Production scale	> 20 kg	> 1 kg	> 500 kg	> 100 kg
Problems	Complicated work-up	Complicated work-up	Very sensitive to substrate purity	Very sensitive to substrate purity

[a)] used for the calculations.

Comparison of reduction methods **A** - **D**

Case study

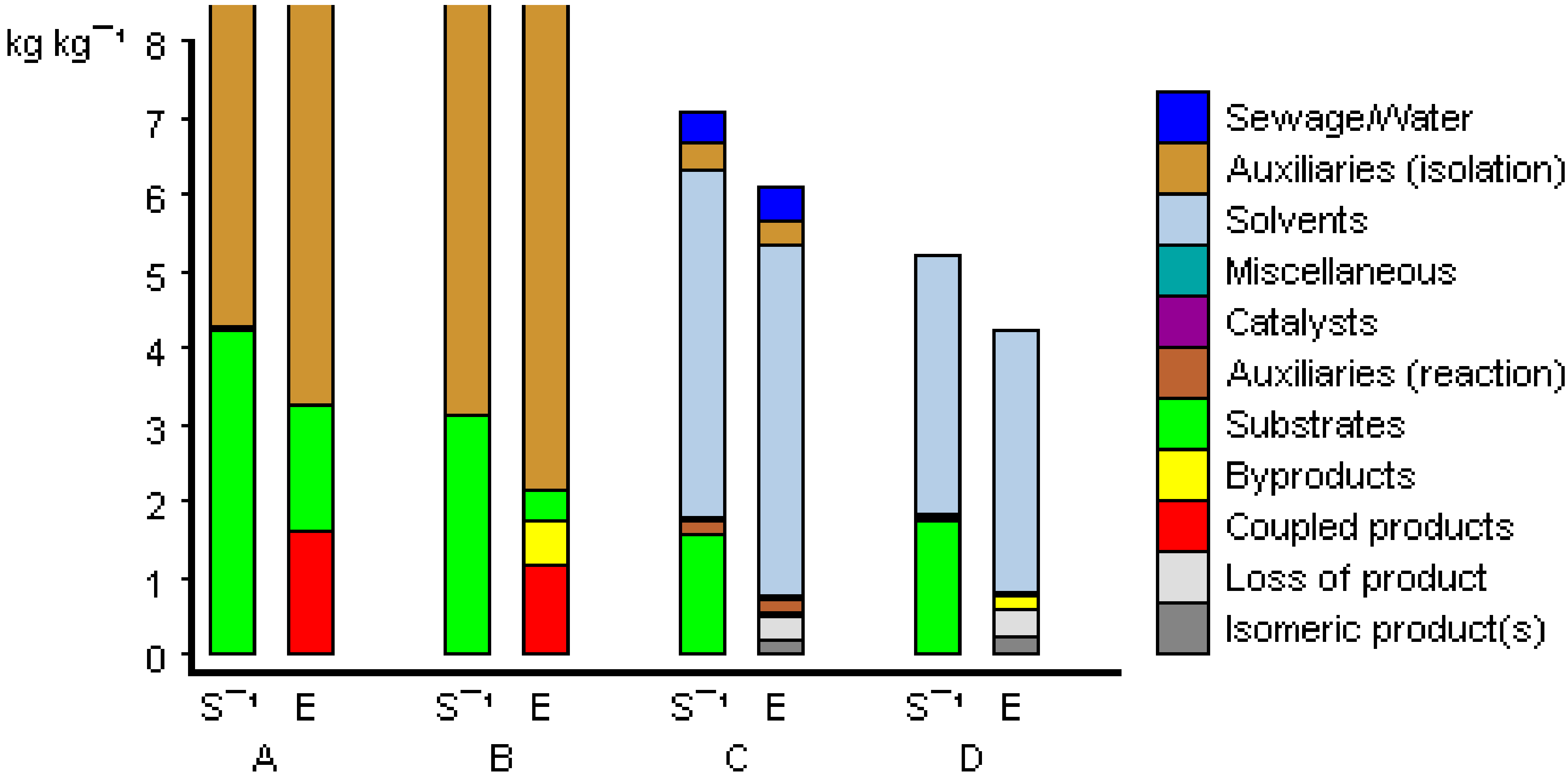
Ethyl (R)-2-Hydroxy-4-Phenylbutyrate



Mass index S^{-1} and environmental factor E of the <u>reductions steps A – D</u>

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

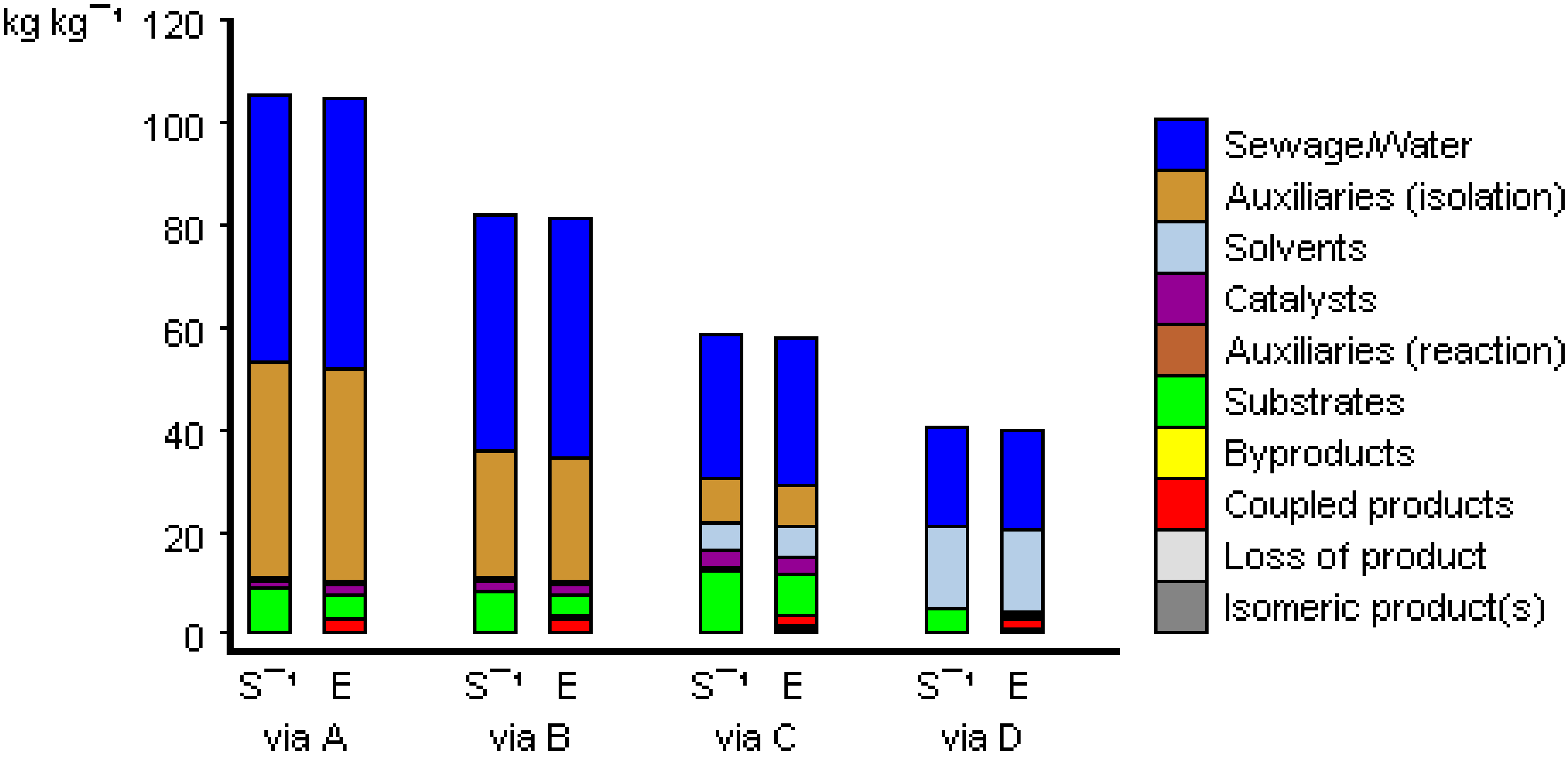


Mass index S^{-1} and environmental factor E of the reductions steps A – D

(Detailed view)

Case study

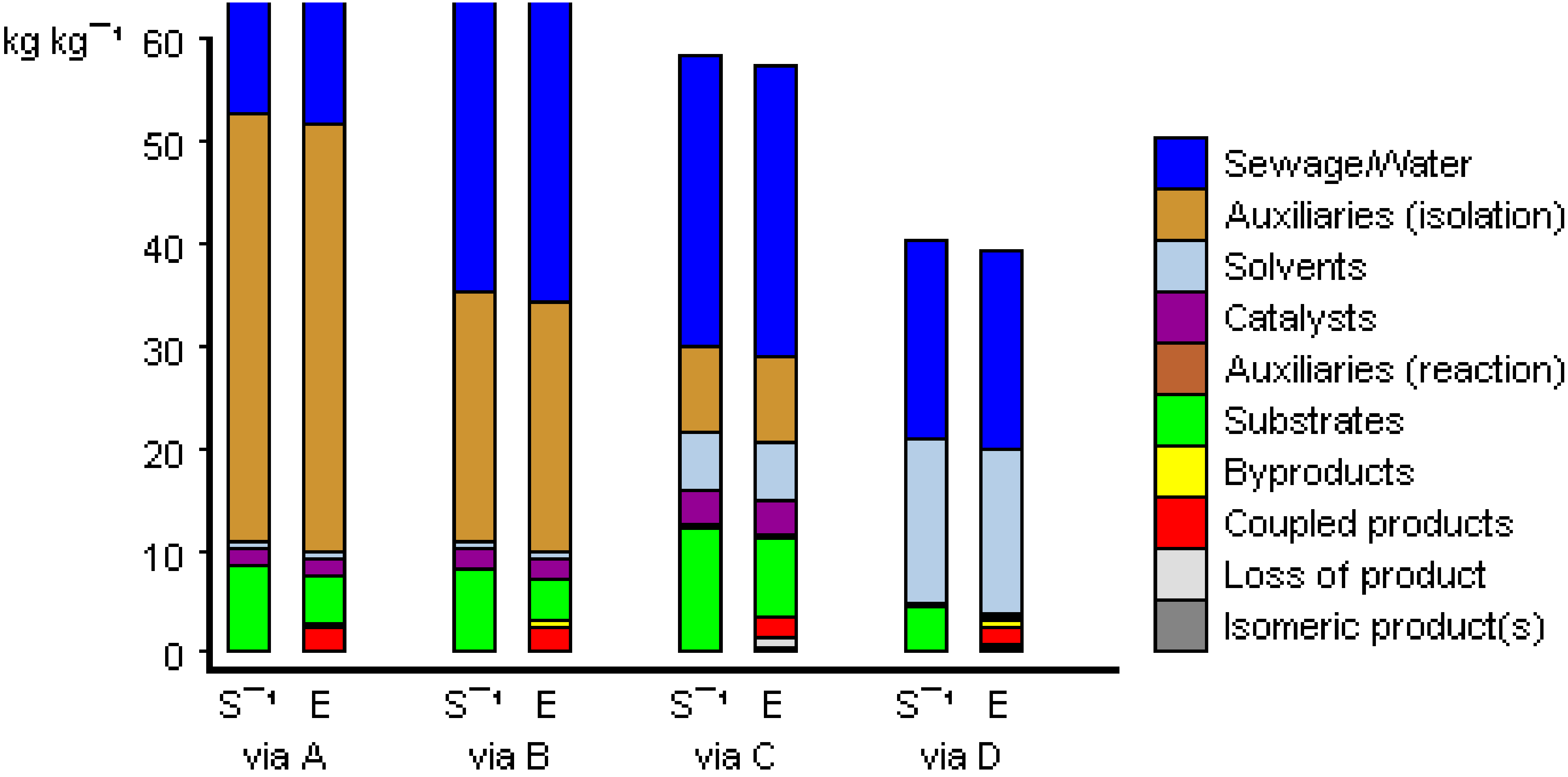
Ethyl (R)-2-Hydroxy-4-Phenylbutyrate



Mass index S^{-1} and environmental factor E of the sequences via A – D

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

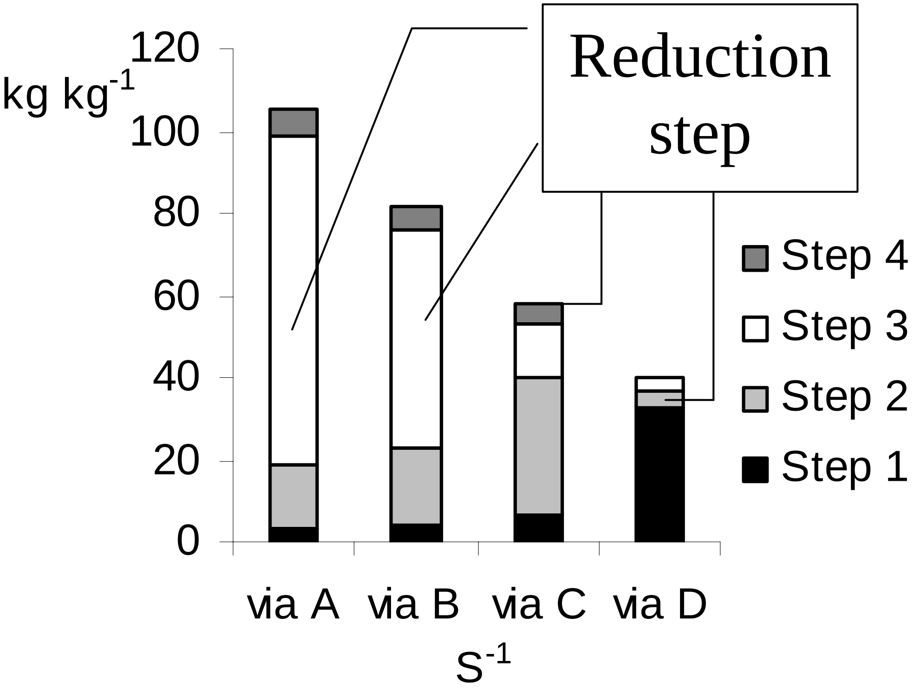


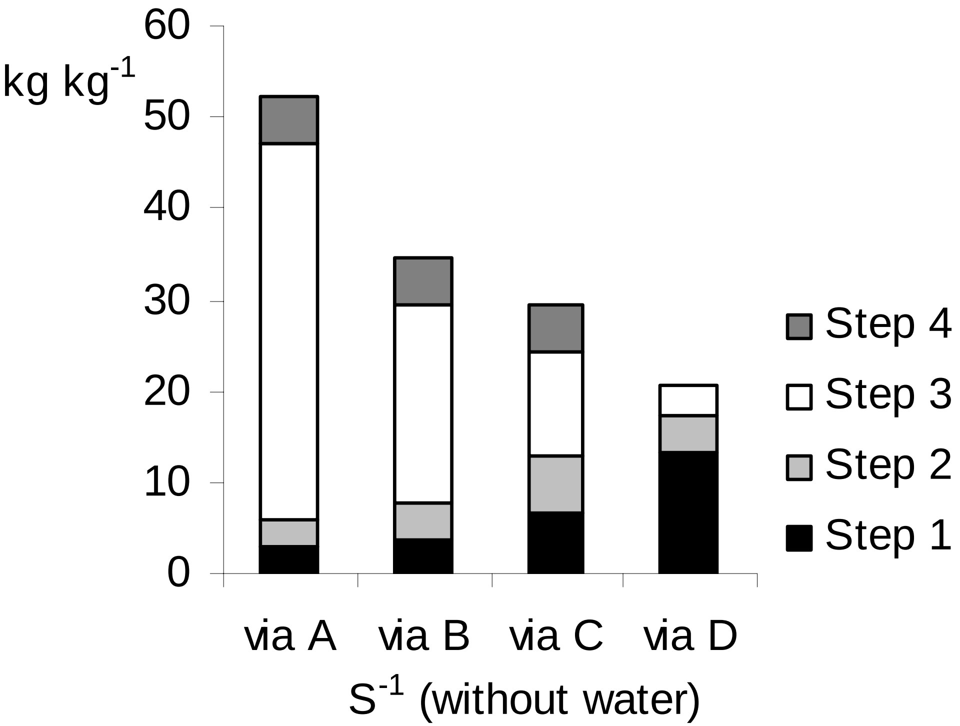
Mass index S^{-1} and environmental factor E of the <u>sequences via A – D</u>

(Detailed view)

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

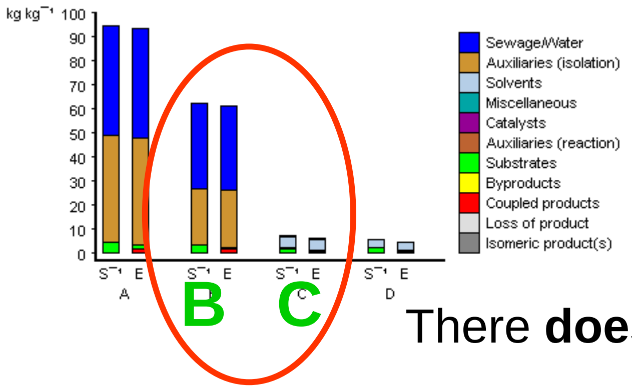




Mass index S^{-1} of the <u>sequences via A – D</u> (Steps)

Case study

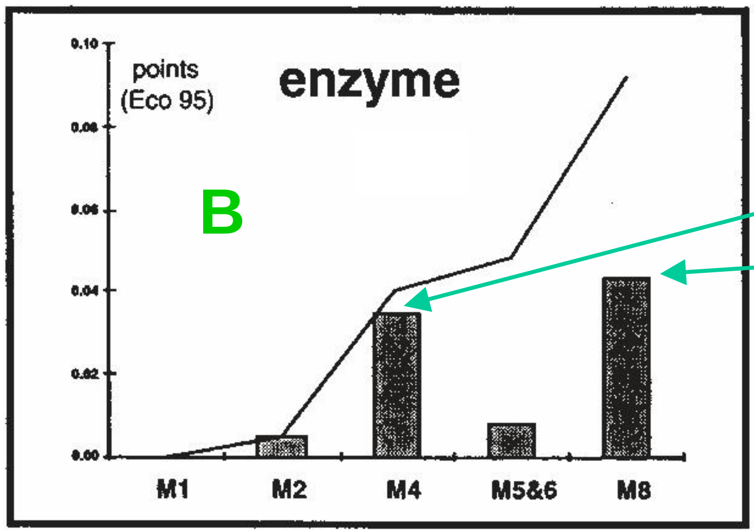
Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

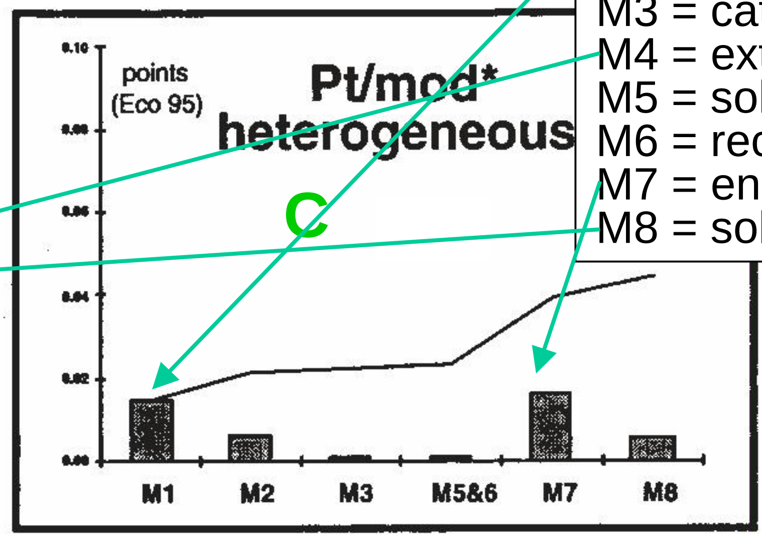


Reduction steps B und C

Mass index S^{-1} und environmental factor E

There **does** already **exist** a **Life Cycle Assessment!**





M1 = catalyst
M2 = reduction
M3 = catalyst removal
M4 = extraction
M5 = solvent drain off
M6 = rectification
M7 = enantiomeric. pur.
M8 = solvent recycling

G. Jödicke, O. Zenklusen, A. Weidenhaupt, K. Hungerbühler, *Journal of Cleaner Production* **1999**, *7*, 159-166.

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

Of course, a Life Cycle Assessment delivers a better assessment than simple mass related metrics. But you only have five minutes per synthesis and not five months.

Fortunately, the preceding slide shows that finally (at least in this special case) Life Cycle Assessment and simple metrics seem to go into the same direction.

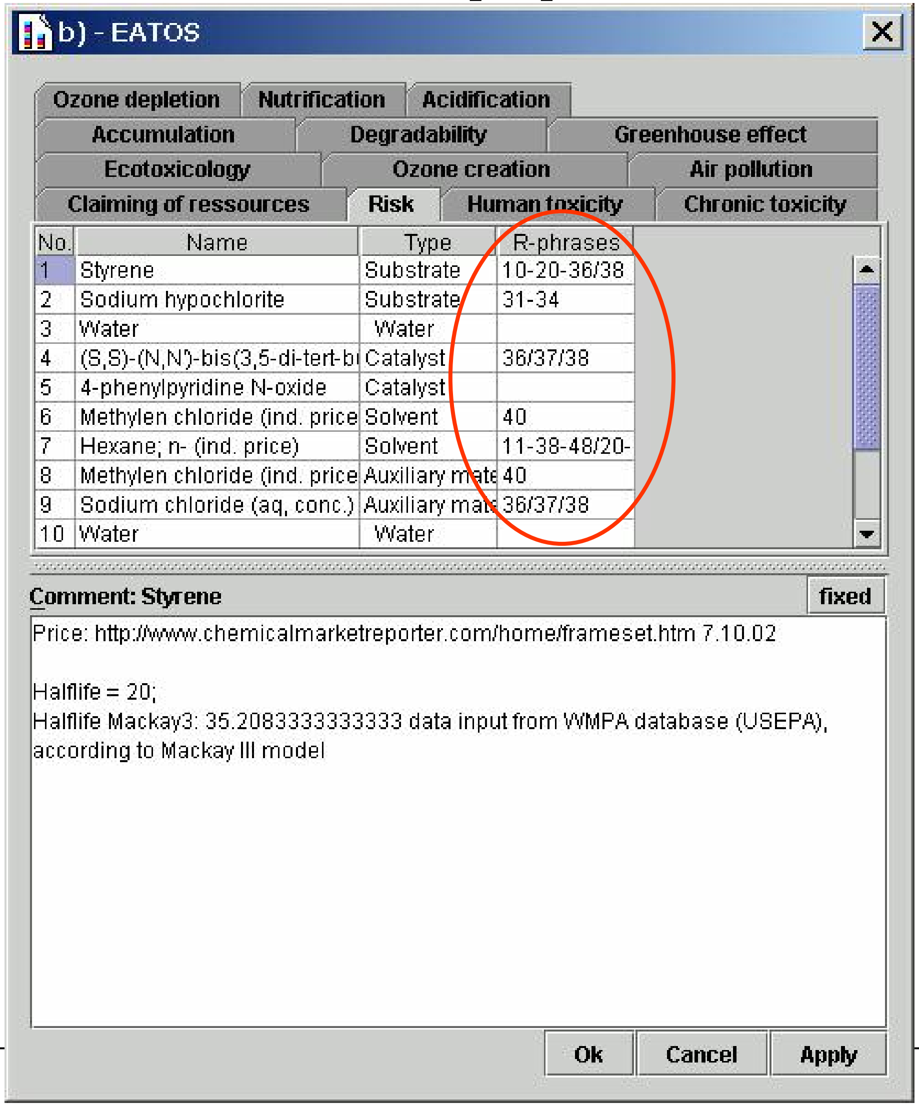
Even Life Cycle Assessment often only considers energy aspects.

But, dealing with chemistry means handling problematic substances.

Environmental index (EHS-metric)

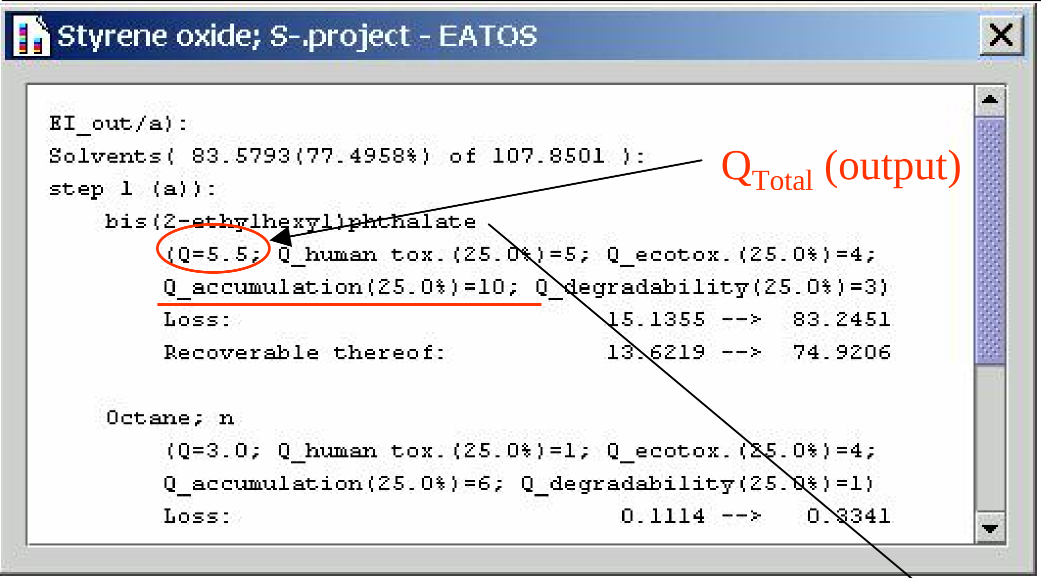
Therefore, if desired:

Enter substance properties



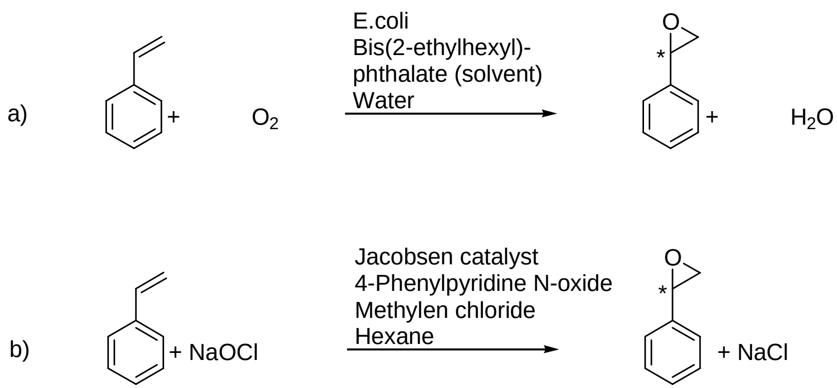
EATOS: M. Eissen, J. O. Metzger, Environmental Performance Metrics for Daily Use in Synthetic Chemistry, *Chem. Eur. J.* **2002**, *8*, 3580-3585.

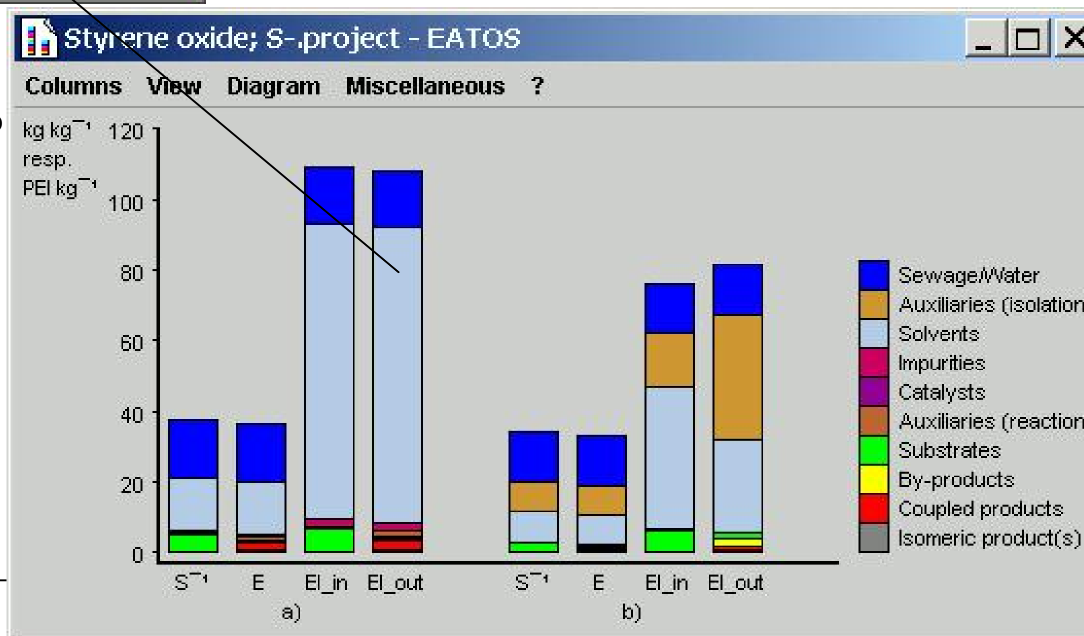
Environmental index (EHS-metric)



„ Phthalates have been detected in every environment in which they have been sought...

The dialkyl phthalate concentrations measured in wastewaters of this chemical industry [Bay of Koper (Gulf of Trieste, Northern Adriatic)] were around 100 mg l^{-1}.“





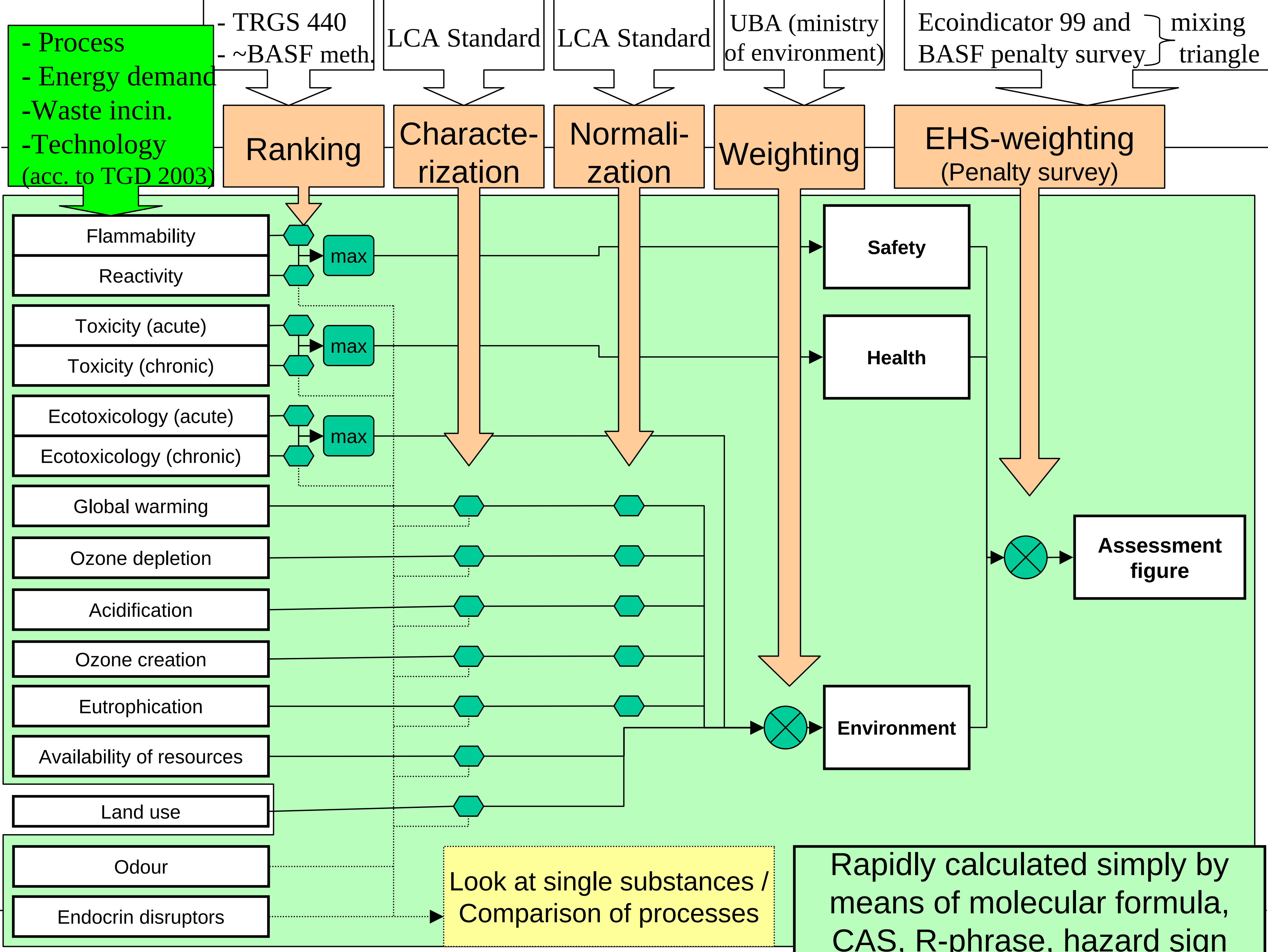
Phthalates-citation in: G. Mailhot, M. Sarakha, B. Lavedrine, J. Cáceres, S. Malato, *Chemosphere* **2002**, *49*, 525–532.

Outlook

Of course, integration of Life Cycle Assessment categories in such a manner is more than rough.

In order to consider all Life Cycle Assessment categories and safety issues for assessment purposes in a scientifically accepted manner, I have developed a new concept which would be an extra talk.

→ Just see an overview on the next slide.


- Process
- Energy demand
-Waste incin.
-Technology
(acc. to TGD 2003)
- TRGS 440
- ~BASF meth.
LCA Standard
LCA Standard
UBA (ministry of environment)
Ecoindicator 99 and BASF penalty survey
mixing triangle
Ranking
Characte-rization
Normali-zation
Weighting
EHS-weighting
(Penalty survey)
Flammability
Reactivity
Toxicity (acute)
Toxicity (chronic)
Ecotoxicology (acute)
Ecotoxicology (chronic)
Global warming
Ozone depletion
Acidification
Ozone creation
Eutrophication
Availability of resources
Land use
Odour
Endocrin disruptors
max
max
max
Safety
Health
Environment
Assessment figure
Look at single substances / Comparison of processes
Rapidly calculated simply by means of molecular formula, CAS, R-phrase, hazard sign

My vision

Database A

Database B

Database C

Database D

Integrated database
(Substance properties)
→ e.g. realized in the group of Hungerbühler (ETHZ)

Enter laboratory log (with an existing computer software)
No data mining!
Automatic calculations!

EHS-Assessment
→ Single substances
→ Aggregation of impacts

Summary

Chemistry metrics

➔ They are already broadly used in industry

(see slides 7-8: *Application of metrics in industry*)

➔ They are easily obtained.

(see slides 9-13: *Metrics easily obtained*)

➔ They make weak-points clear in a comparative fashion.

(see slides 14-25: *Case study*)

Acknowledgements

Discussion on and data from synthetic examples

- (*S*)-Styrene oxide
  Bruno Bühler, Jin Byung Park, Andreas Schmid,
  Institute of Biotechnology, ETHZ
- Benzyl-[1-isopropyl-3-(trimethylsilanyl)-prop-2-ynyl]-amine
  Christian Fischer, Erick M. Carreira, Organic Chemistry, ETHZ
- Ethyl (R)-2-Hydroxy-4-Phenylbutyrate
  Martin Studer, Solvias AG

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Deutsche Bundesstiftung Umwelt
(Osnabrück, Federal Republic of Germany)

DBU
Deutsche Bundesstiftung Umwelt

Programming

Radoslaw Mazur & Karl-Heinz Pennemann

Appendix

- Relevant literature
- Download of Eatos
- Role of chemistry
- Construction details of the ‚unfriendliness quotient‘ Q (regarding the Environmental index (EHS-metric))
- Influence of the catalyst preparation (Styrene oxide example)
- Details of the styrene oxide example
- Details of the reduction steps in the Case study
  Ethyl (R)-2-Hydroxy-4-Phenylbutyrate
- What is your motivation?

Relevant literature

J. O. Metzger, M. Eissen, Concepts on the Contribution of Chemistry to a Sustainable Development - Renewable Raw Materials, *Les Comptes Rendus De L Académie Des Sciences - Chimie* **2004**, *7*, 569-581.

M. Eissen, K. Hungerbühler, S. Dirks, J. O. Metzger, Mass efficiency as metric for the effectiveness of catalysts, *Green Chemistry* **2003**, *5*, G25-G27.

M. Eissen, J. O. Metzger, Environmental Performance Metrics for Daily Use in Synthetic Chemistry, *Chem. Eur. J.* **2002**, *8*, 3580-3585.

M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind,10 Years after Rio – Concepts on the Contribution of Chemistry to a Sustainable Development *Angew. Chem.* **2002**, *114*, 402-425; *Angew. Chem. Int. Ed.* **2002**, *41*, 414-436.

H.-U. Blaser, M. Eissen, P. F. Fauquex, K. Hungerbühler, E. Schmidt, G. Sedelmeier, M. Studer, *Comparison of Four Technical Syntheses of Ethyl (R)-2-Hydroxy-4-Phenylbutyrate*, in *Large-Scale Asymmetric Catalysis* (Eds.: H.-U. Blaser, E. Schmidt), ISBN 3-527-30631-5, Wiley-VCH, Weinheim, **2003**, pp. 91-104, http://www.wiley-vch.de/publish/dt/books/bySubjectNU00/bySubSubjectNU/3-527-30631-5/?sID=d05b.

Download of Eatos

Determination of mass balances and potential environmental impact of chemical syntheses appling the software EATOS

- Download EATOS under http://www.chemie.uni-oldenburg.de/oc/metzger/eatos/
- You have to install the java runtime environment to run the software. Follow the Setup Manual.
- Please note the list of bugs in EATOS.

Role of chemistry

”Chemistry has an important role to play in achieving a sustainable civilization on Earth.”

”The present economy remains utterly dependent on a massive inward flow of natural resources that includes vast amounts of nonrenewables.[...] It has become an imperative that chemists lead in developing the technological dimension of a sustainable civilization.”

T. Collins, Toward Sustainable Chemistry, *Science* **2001**, *291*, 48–49.

“The central theme is the conservation and control of resources. A substantial contribution must be made to this by science, whereby the combination of ecological, economical, and social science needs are consolidated to meet the challenges of the future.“

M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, 10 Years after Rio – Concepts on the Contribution of Chemistry to a Sustainable Development, *Angew. Chem.* **2002**, *114*, 402-425; *Angew. Chem. Int. Ed.* **2002**, *41*, 414-436.

Environmental index (EHS-metric)

In case that substance properties such as

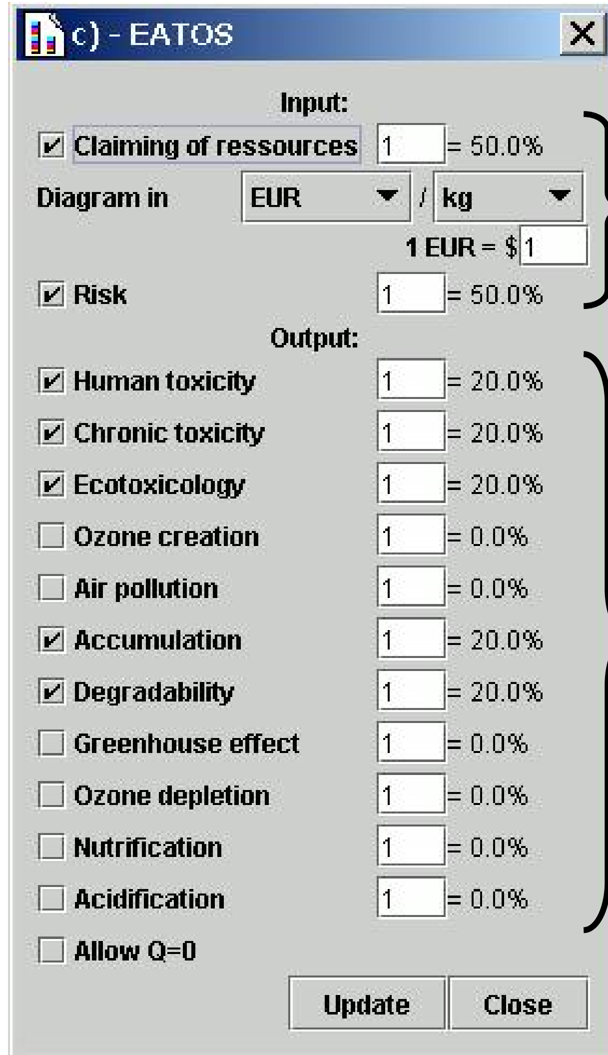
- Toxicity
- Eco-toxicity
- Safety
- etc.

should be assessed, they may be entered to obtain an **‚unfriendliness quotient‘ Q**.

This Q-value will be calculated internally and is between 0 and 10.

(The higher the worse.)

Weighting of mass index and environmental factor with Q_{in} and Q_{out} delivers the environmental indices EI_{in} and EI_{out}.



Q_{Total} for EI_{in}

Q_{Total} for EI_{out}

M. Eissen, J. O. Metzger

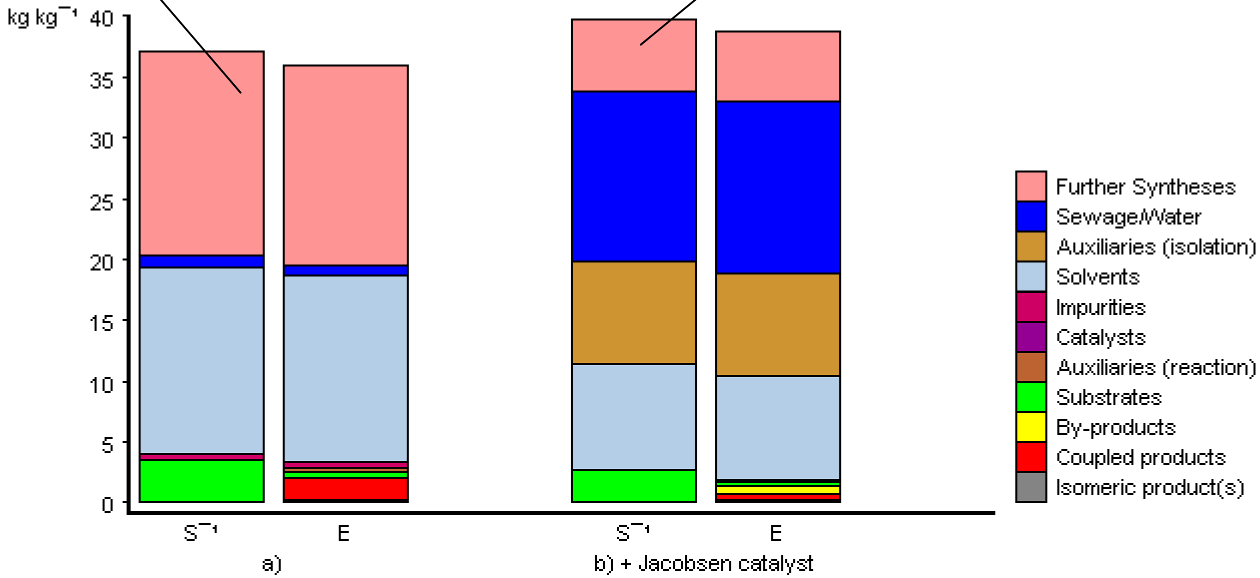
An example

Mass index **S**$^{-1}$ and Environmental factor **E**

Resource requirements due to the production of the Jacobsen catalyst: **5.8** kg,

i.e. 5.8 kg / 0.048 kg catalyst used.

Preparation of *E.coli* solution, mainly water.



biochemical

(Same quantity as before.)

Chemical + Preparation of Jacobsen catalyst

Results

Biocatalysis

Mass index **S^{-1}** and

Environmental factor **E**

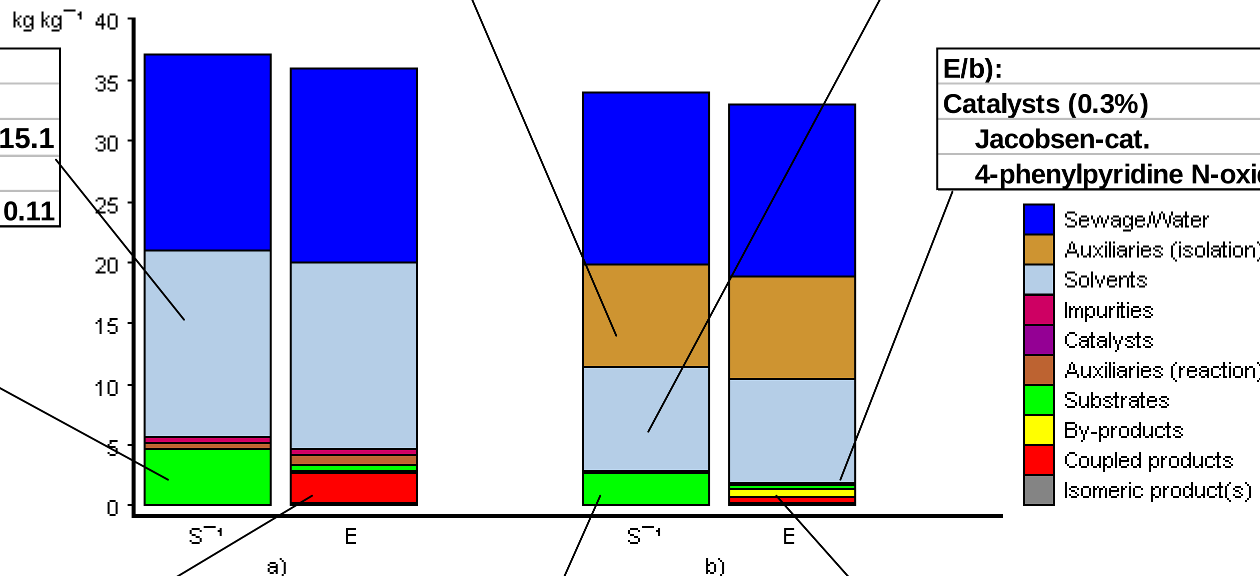
S⁻¹/b):	
Auxiliaries (isolation) (25%)	
Methylen chloride	6.7
Sodium chloride	1.3
Sodium sulfate	0.33
Calcium hydride	0.005

S⁻¹/b):	
Solvents (26%)	
Methylen chloride	2
Hexane; n-	6.6

S⁻¹/a):	
Solvents (41%)	
bis(2-ethylhexyl)	15.1
phthalate	
Octane; n	0.11

S⁻¹/a):	
Substrates (12%)	
Styrene	1
Glucose	2.1
NH4OH	0.27
Oxygen	1.8

E/b):	
Catalysts (0.3%)	
Jacobsen-cat.	0.048
4-phenylpyridine N-oxide	0.065



biochemical

chemical

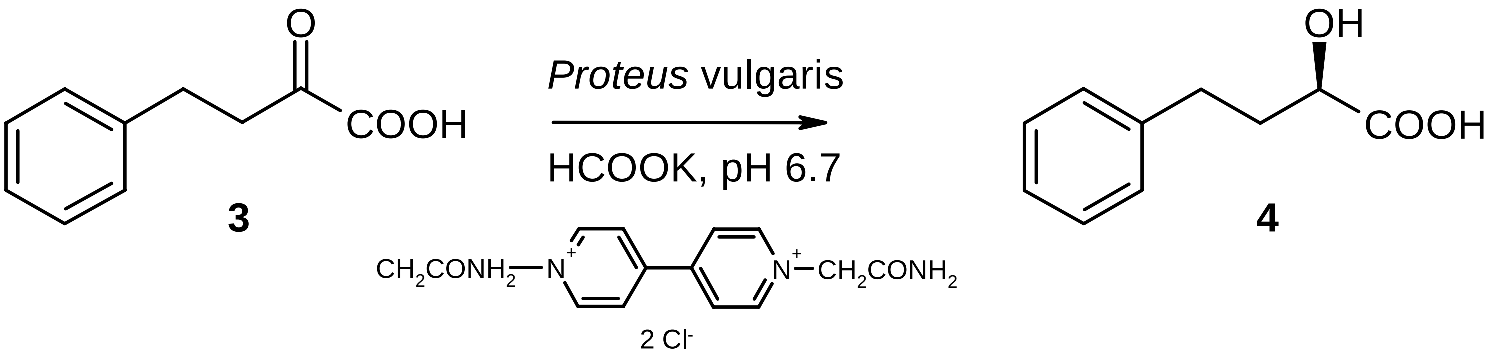
E/a):	
Coupled products (7%)	
Phenyl-ethanol; 2-	0.0517
Styrene	0.0739
E.coli (recomb)	0.2377
Acetic acid	0.1583
Water	0.7977
Carbon dioxide	1.2394

S⁻¹/b):	
Substrates (7.5%)	
Styrene	1.3
Sodium hypochlorite	1.2

E/b):	
Coupled products (1.6%)	
Sodium chloride	0.5

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate

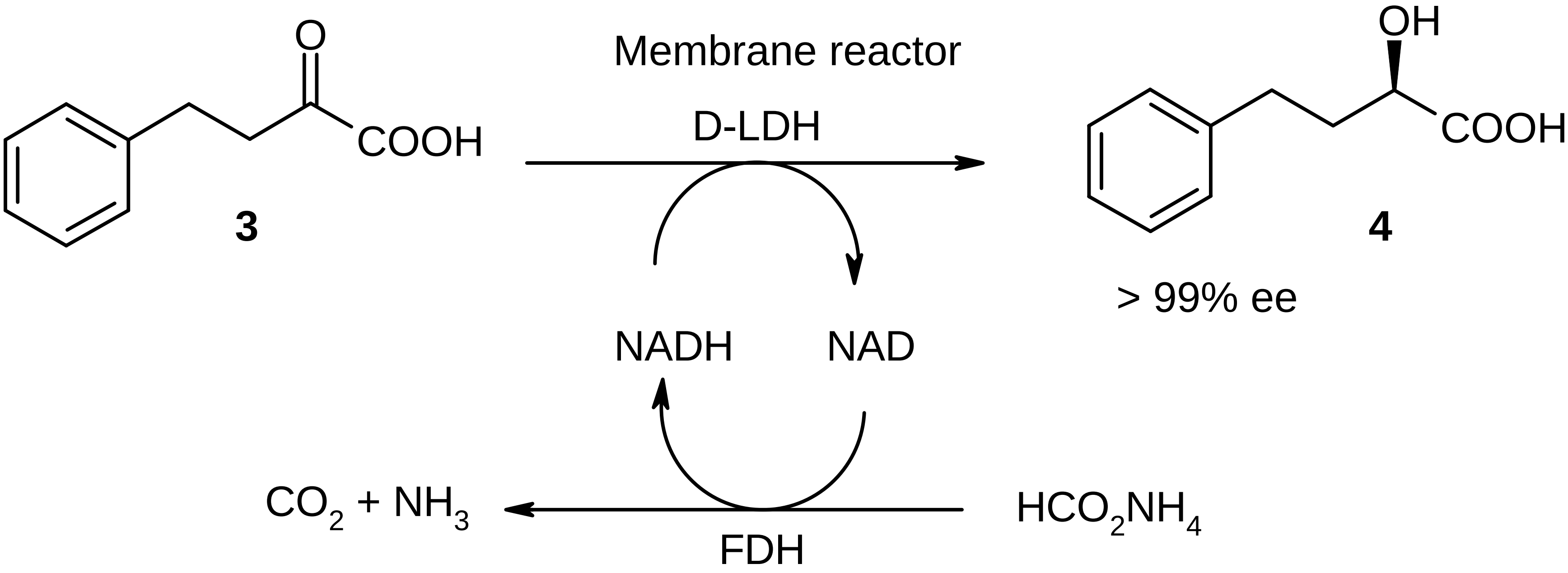


> 99% ee
99% yield

Reduction step in route **A**

Case study

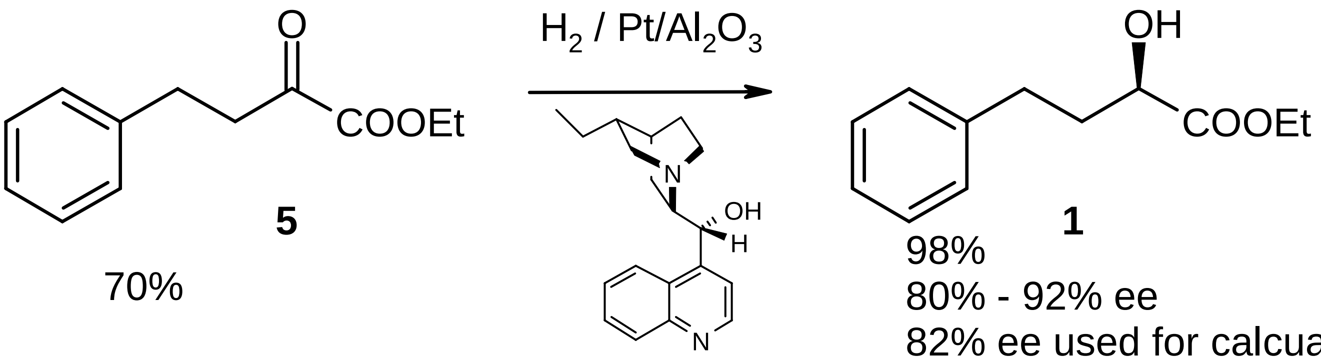
Ethyl (R)-2-Hydroxy-4-Phenylbutyrate



Reduction step in route **B**

Case study

Ethyl (R)-2-Hydroxy-4-Phenylbutyrate



5

70%

1

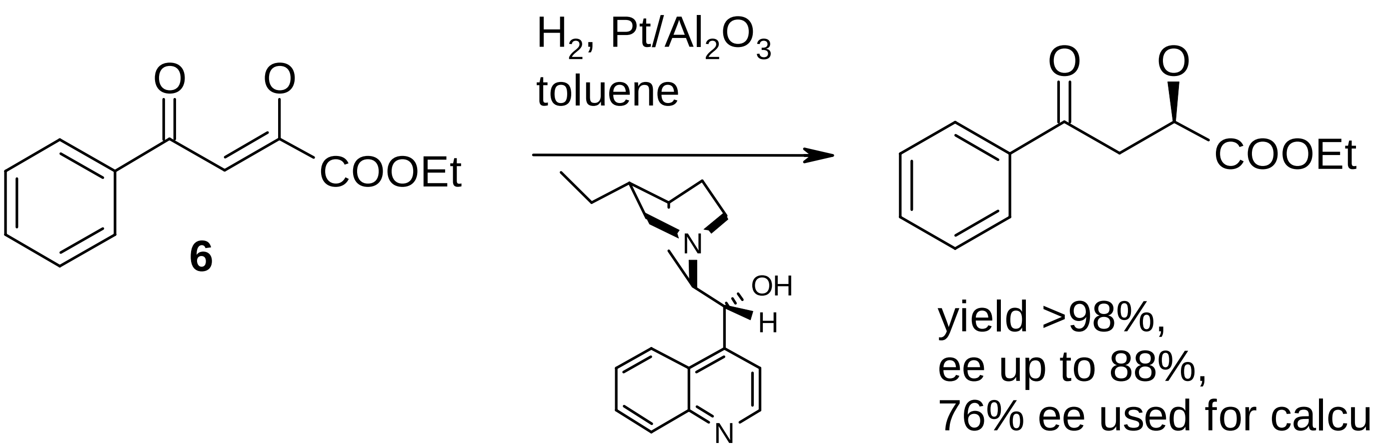
98%

80% - 92% ee

82% ee used for calcuations

Enrichment to >99% ee via nosylate

Reduction step in route **C**



6

7

yield >98%,

ee up to 88%,

76% ee used for calculations

Enrichment by crystallization

Reduction step in route **D**

What is your motivation?

You are doing academic research at the university?

Case 1: Your findings are brillant and better than current approaches.

→ use metrics to compare with alternative protocols and prove the superiority of your synthesis

Case 2: Your findings are not necessarily better than current approaches.

→ use metrics to

a) identify relevant weak-points for optimization purposes

b) make clear to the scientific comunity the challenges you see for future research.

c) make clear to the funding organisation the great potential for future improvements, i.e. calculate scenarios.

What is your motivation?

You are doing academic research at the university or in an industry?

Case 3: You have read inspiring literature and have an idea.

→ use metrics to obtain a preview of what you can expect and which benchmark is the challenge.

Case 4: You are examining several parameters, many synthesis protocols or even different synthesis sequences.

→ use metrics to keep the overview of all alternatives in a comparative manner.

What is your motivation?

You are doing research in an industry?

Case 5: You do <u>not</u> use such tools in YOUR research group and you do not only want to rely on your instinct.

→ use metrics to start first optimization efforts in order to reduce costs on the part of the business department. Improve the choice of syntheses that are to be calculated by experts.

Case 6: You already use EXCEL or similar not-tailored software for quantification purposes.

→ save time and energy using our EATOS-Software.

„Several methods at different levels may be necessary for the evaluation. For ordinary chemists and chemical engineers involved in R & D, an easily applicable method is desirable.“

M. Misono, *C.R. Acad. Sci. Paris, Série IIc, Chimie / Chemistry* **2000**, *3*, 471-475

What is your motivation?

You are doing research in an industry?

Case 7: The overwhelming number of possible ideas in literature forces you to disregard many of them.

→ use the software to store data, i.e. to retain an overview also of those syntheses that do not immediately fit well into your experience background. They might become interesting when an early favorite fails.

Case 8: You are engaged in the scale-up process.

→ use metrics to

a) identify the hierarchy of problems.

b) document the improvements in efficiency.

What is your motivation?

You are involved in education?

Case 9: You give a lecture

→ use metrics to

a) give a holistic view of all relevant aspects (solvents, catalyst(preparation), etc.)

b) demonstrate the effect of side reactions on total raw material demand.

c) compare alternative pathways

Case 10: You care for the educational laboratory.

→ use metrics to sensitize students about

a) a responsible way of how to deal with earth‘ resources

b) a self-evident integration of alternative routes.

c) dangers linked with substance specific properties.

(Continuation of the styrene oxid example later in this talk)

Case study from academic research

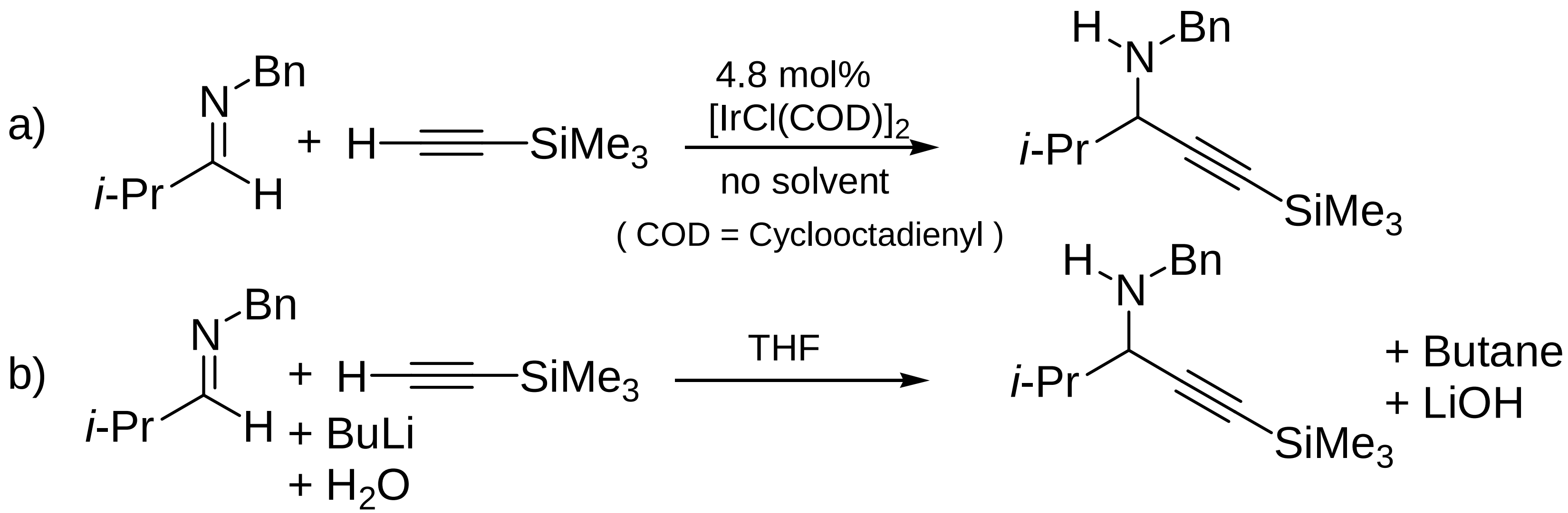
Benzyl-[1-isopropyl-3-(trimethyl-silanyl)-prop-2-ynyl]-amine

Addition of acetylene derivative:

homogeneous catalytic (a)

vs.

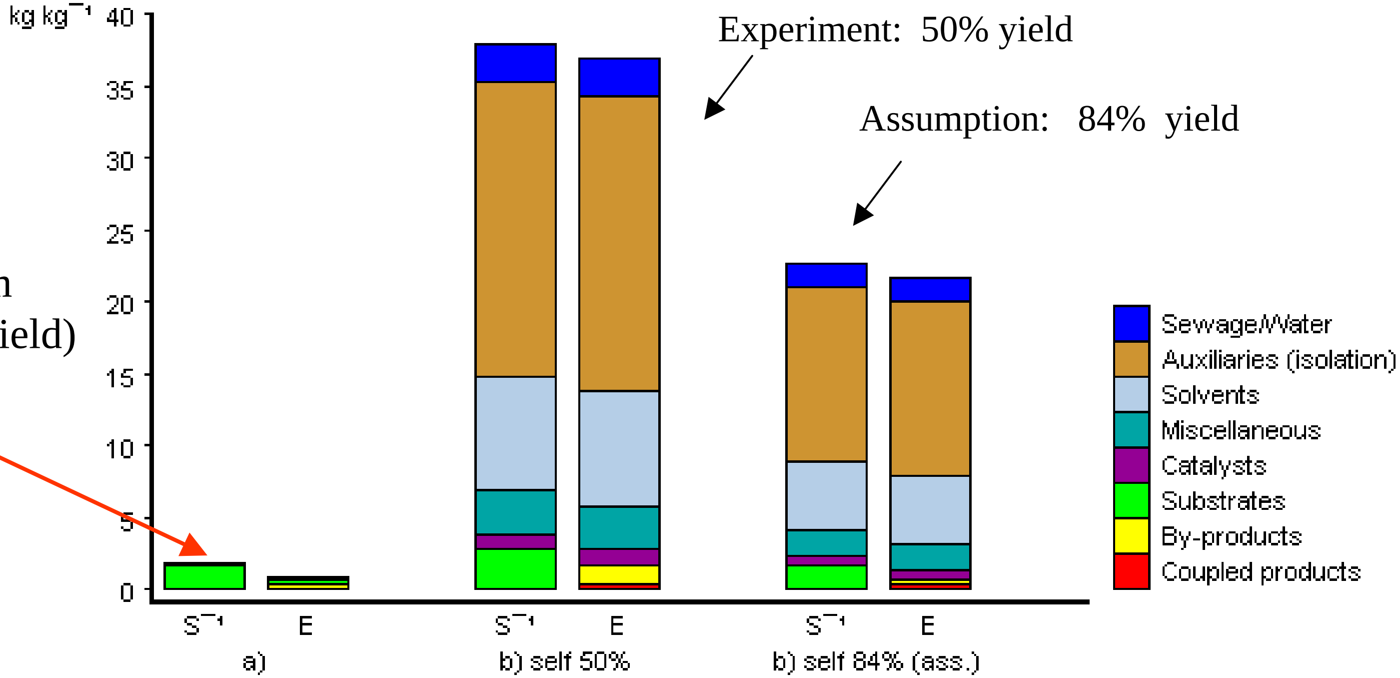
stoichiometric conversion (b)

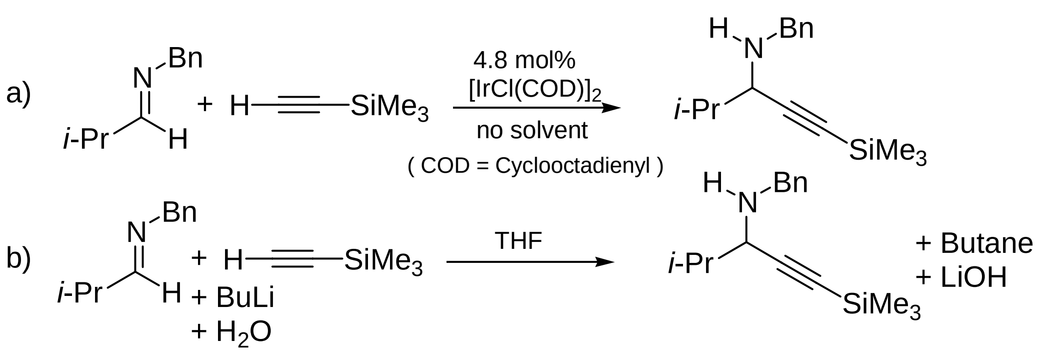


Case study from academic research

Benzyl-[1-isopropyl-3-(trimethyl-silanyl)-prop-2-ynyl]-amine

Concerning resource requirements the Iridium catalyzed procedure (84% yield) is better.



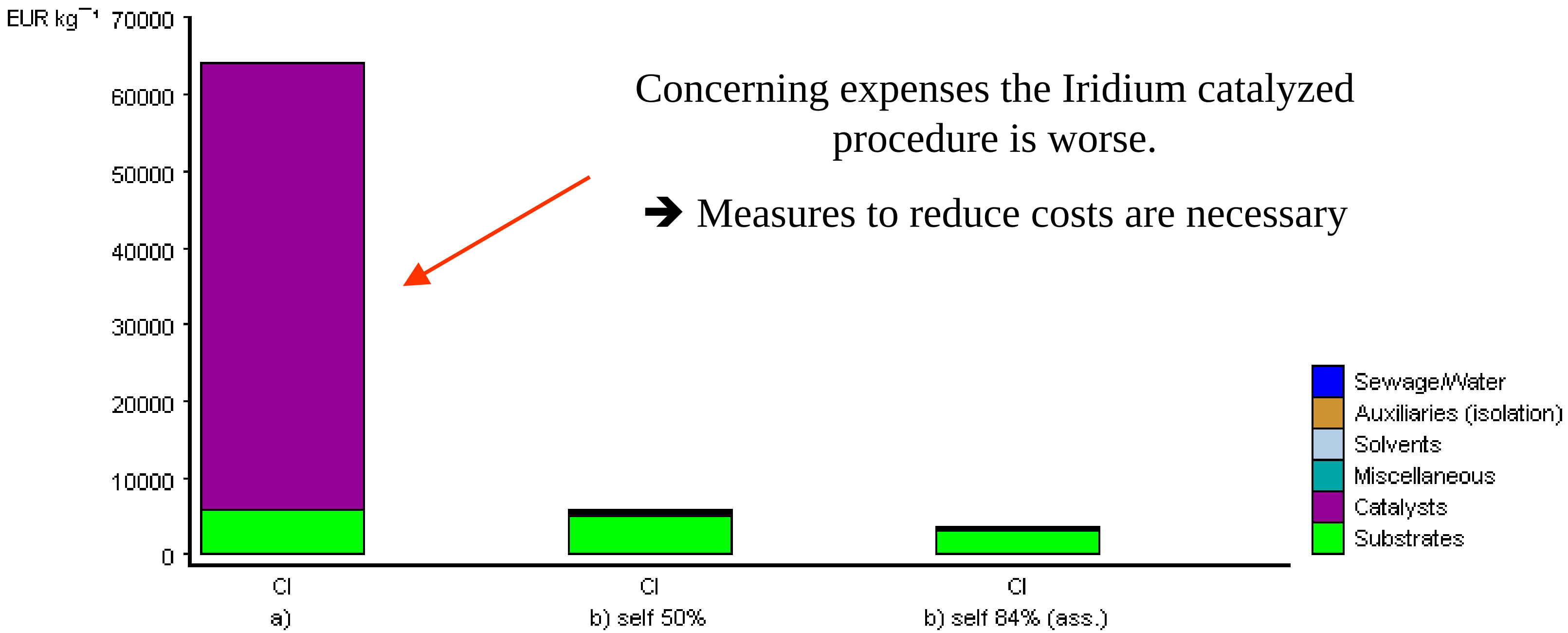


a) C. Fischer, E. M. Carreira, *Organic Letters* **2001**, *3*, 4319-4321.

b) Fischer according to M. Wada, Y. Sakurai, K.-y. Akiba, *Tetrahedron Letters* **1984**, *25*, 1083-1084.

Case study from academic research

Benzyl-[1-isopropyl-3-(trimethyl-silanyl)-prop-2-ynyl]-amine



Concerning expenses the Iridium catalyzed procedure is worse.

➔ Measures to reduce costs are necessary

Cost Index by means of Aldrich and Fluka prices.

a) C. Fischer; b) Fischer according to Wada