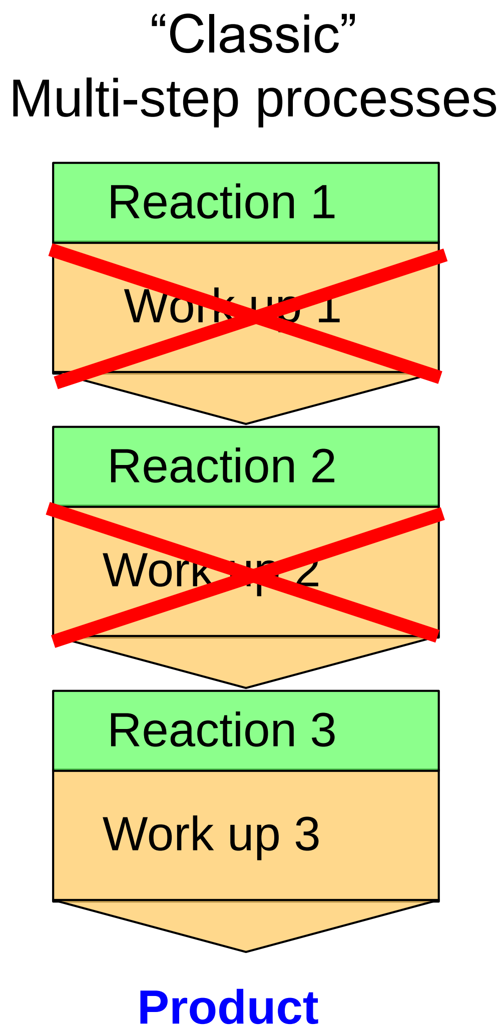
Integration of Biotransformations in Chemical Multi-Step Processes for Fine and Bulk Chemicals

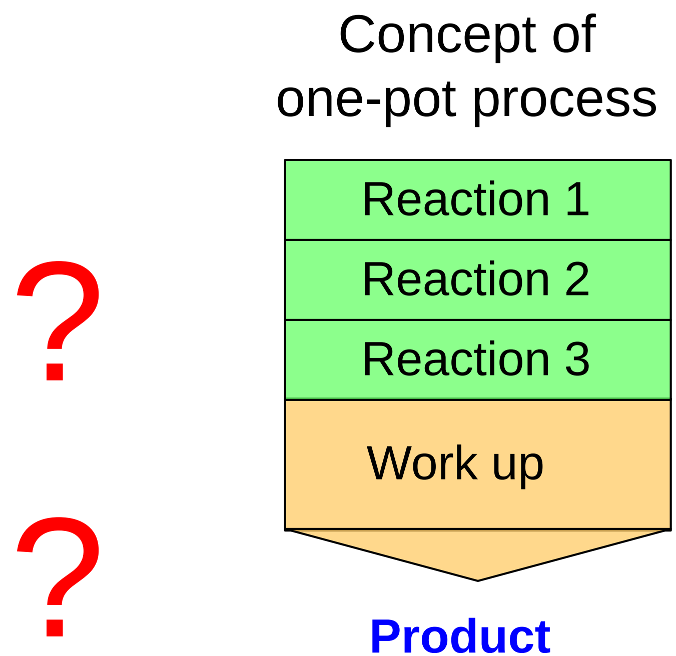
Prof. Dr. Harald Gröger

Chair of Organic Chemistry I
Faculty of Chemistry
Bielefeld University

DECHEMA PRAXISforum "Enzymes for Industrial Applications",
Frankfurt am Main, November 8-9, 2016

Why one-pot multi-step strategies?





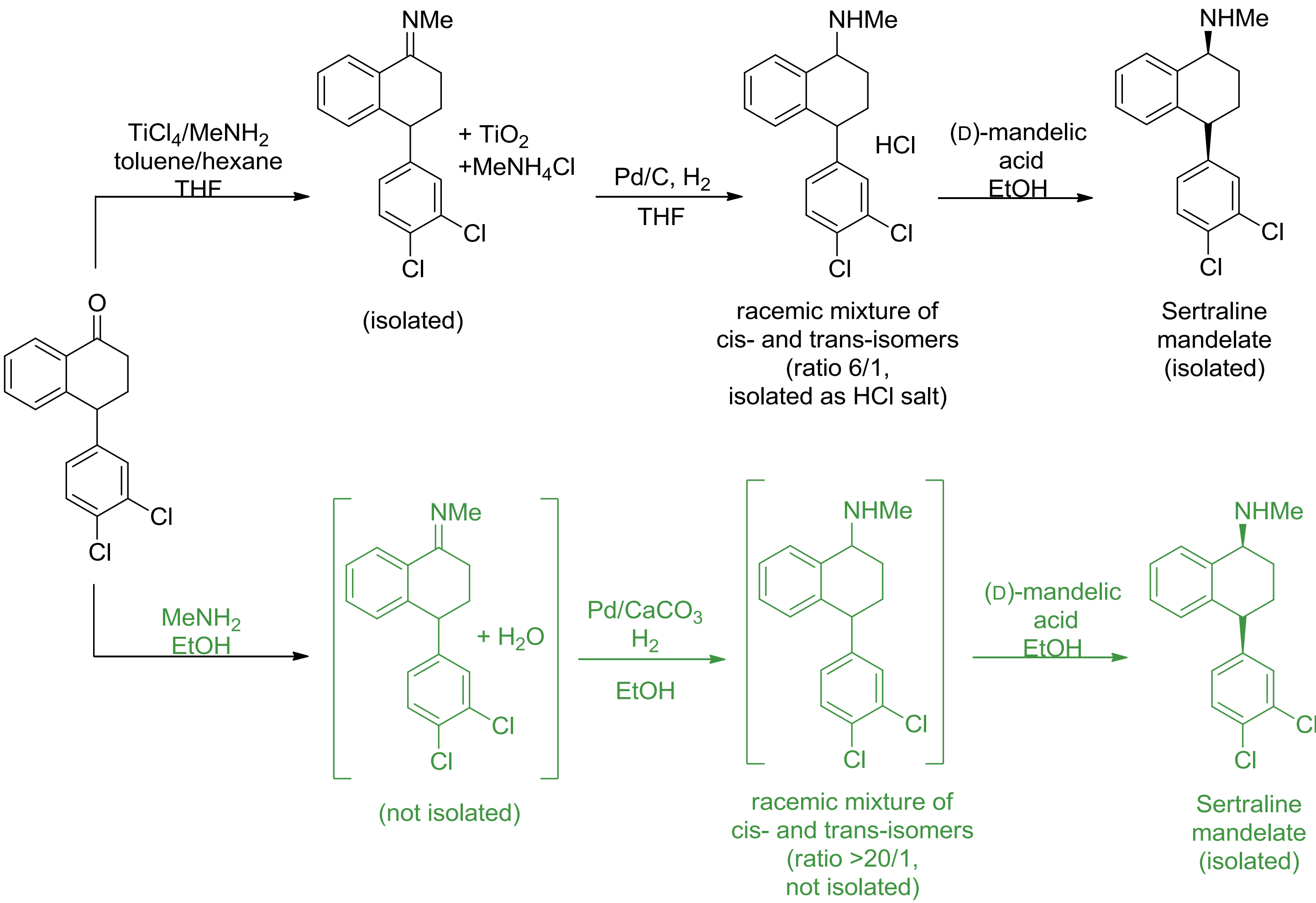
Potential strategies:

-Tandem reactions

- Subsequent synthetic steps
- Compartimentation of steps

“Green Chemistry” in industry

Case study: Pfizer´s process for Sertraline (Zoloft®)

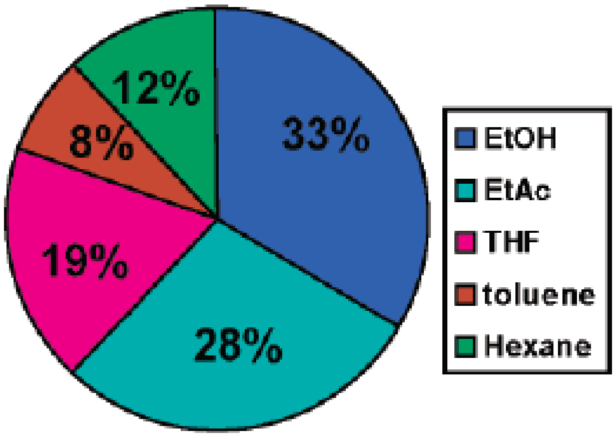


G. P. Taber, D. M. Pfisterer, J. C. Colberg, *Org. Proc. Res. Developm*. **2004**, *8*, 385-388.

“Green Chemistry” in industry

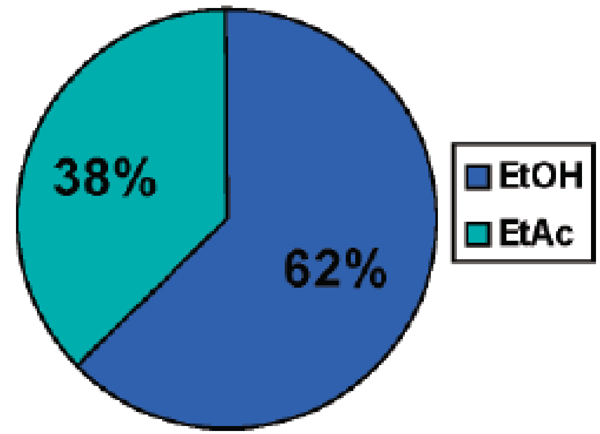
Key feature: Overall amount of used solvents / Compatibiliy of reactions

Sertraline Hydrochloride First Commercial Route



•EtOH	34,000 L
•EtAc	28,400 L
•THF	19,000 L
•Toluene	8,000 L
•Hexane	12,000 L
Total	101,400 L

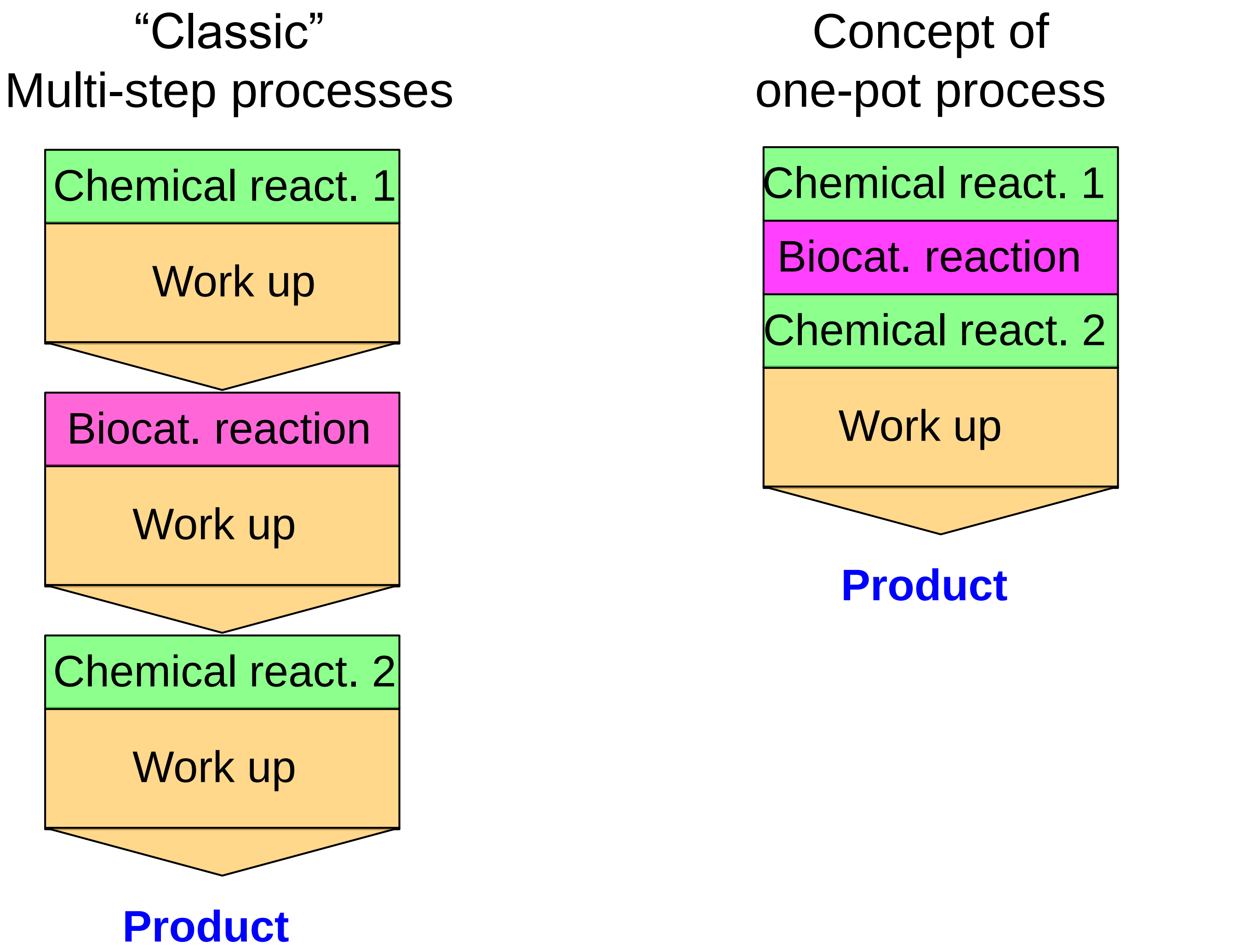
Sertraline Hydrochloride New Route



•EtOH	15,000 L
•EtAc	9,000 L
Total	24,000 L

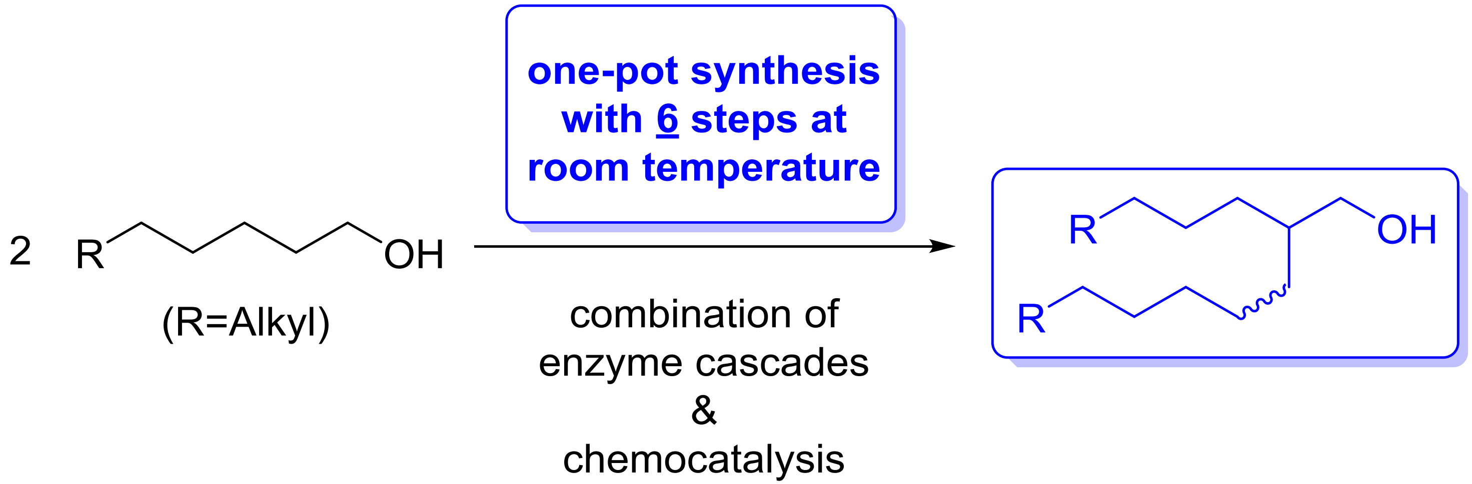
G. P. Taber, D. M. Pfisterer, J. C. Colberg, *Org. Proc. Res. Developm*. **2004**, *8*, 385-388.

Integration of biocatalysis in multi-step drug synthesis



Combination of chemo- and biocatalysis for alternative Guerbet alcohol synthesis

Process scheme:



**Joint project with
Prof. Hummel
(University of Düsseldorf)**

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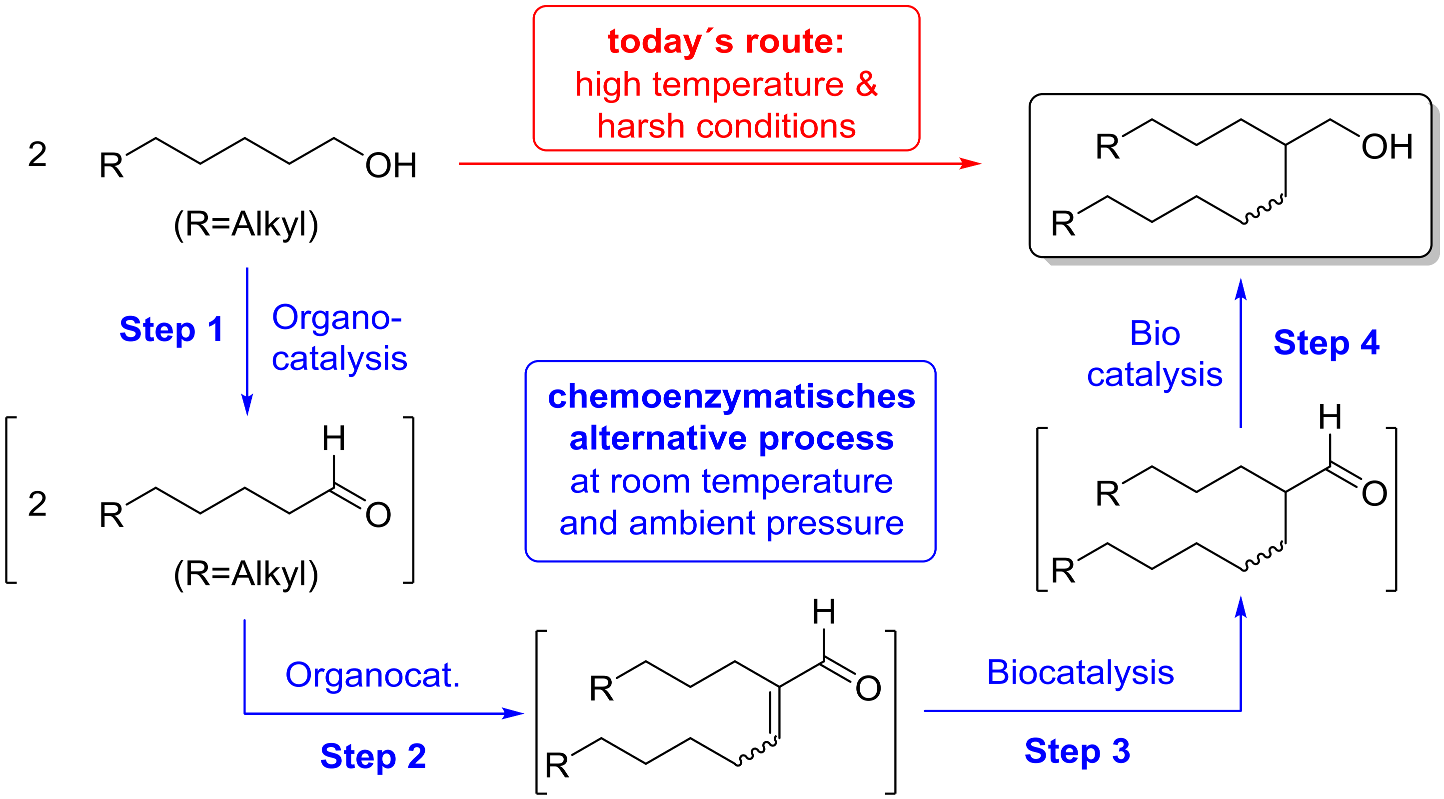
für Bildung
und Forschung

Synthesis of Guerbet-alcohols

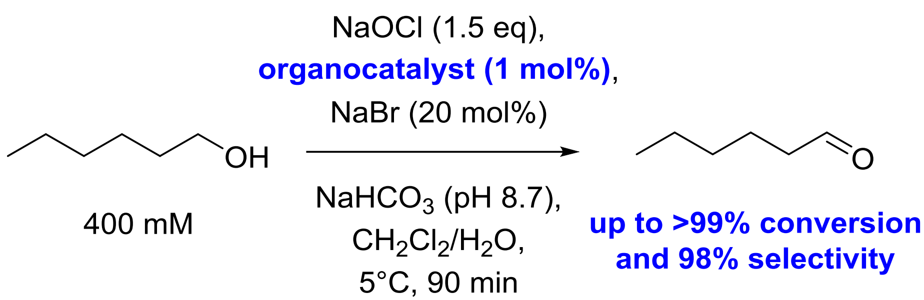
Today´s state of the art and potential alternatives:

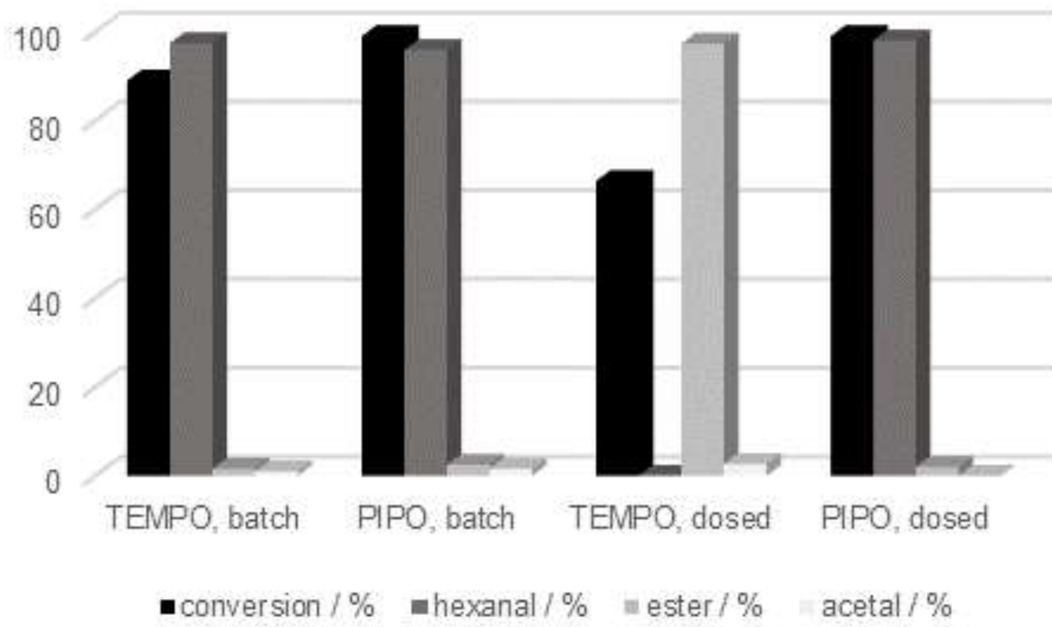


M. Biermann, H. Gruß, W. Hummel, H. Gröger, *ChemCatChem* **2016**, *8*, 895-899.

Organocatalytic oxidation of alcohols (step 1)

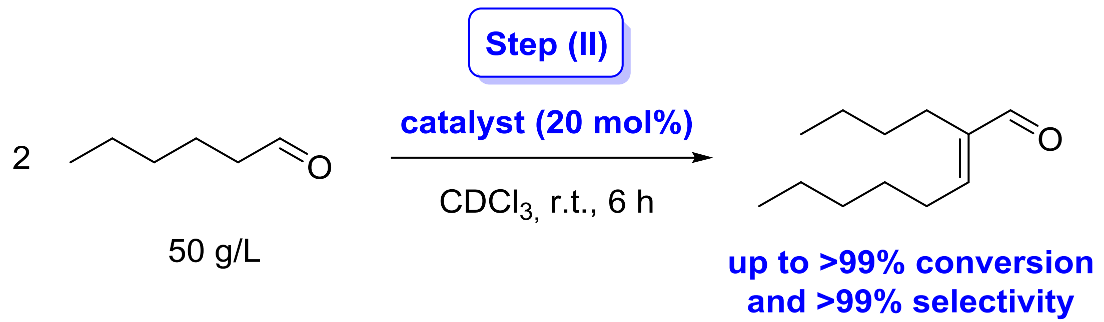
Step (I)

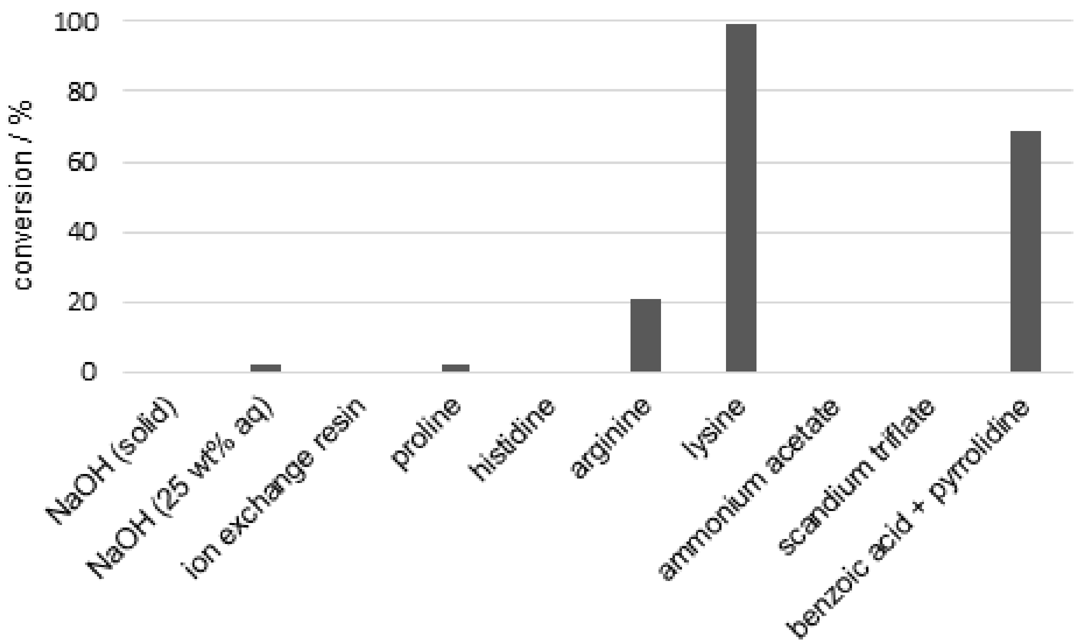




M. Biermann, H. Gruß, W. Hummel, H. Gröger, *ChemCatChem* **2016**, *8*, 895-899.

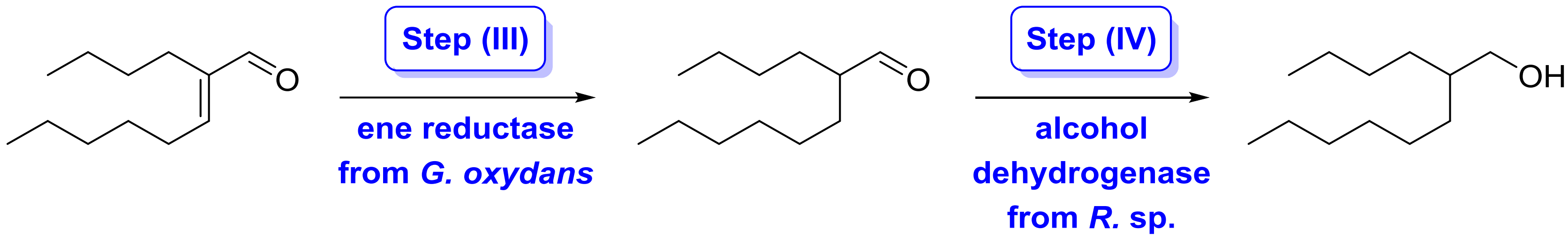
Organocatalytic homo-aldol condensation (step 2)

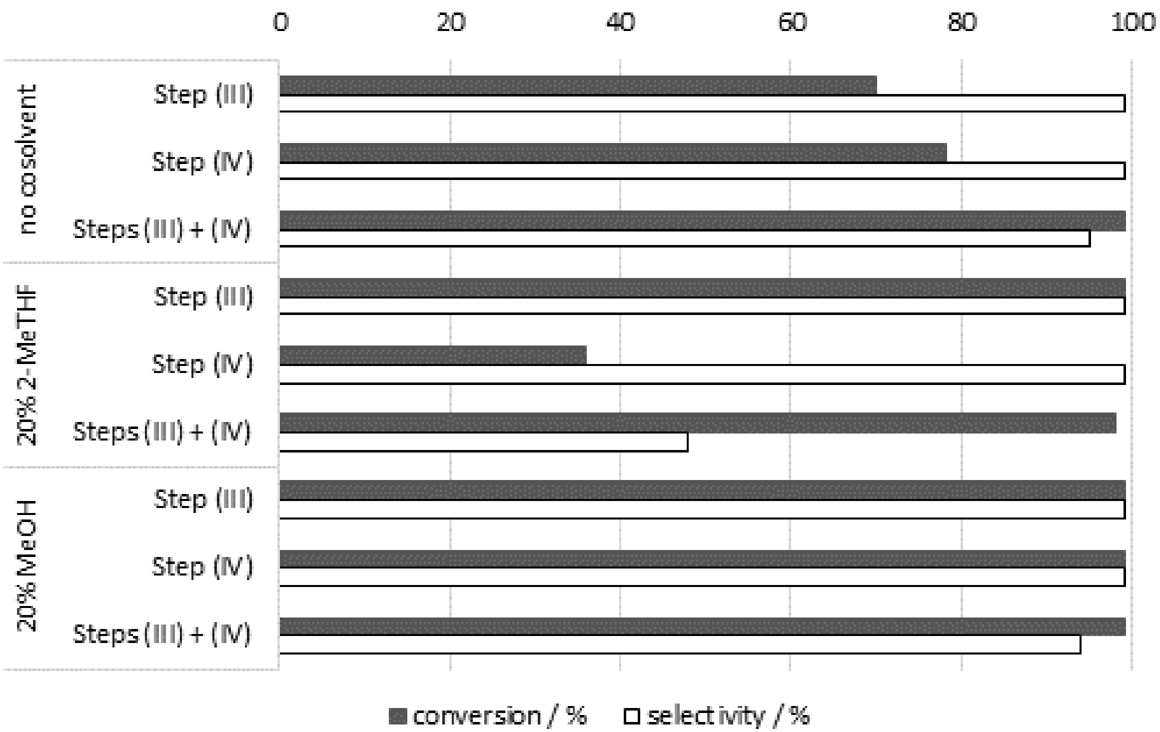




M. Biermann, H. Gruß, W. Hummel, H. Gröger, *ChemCatChem* **2016**, *8*, 895-899.

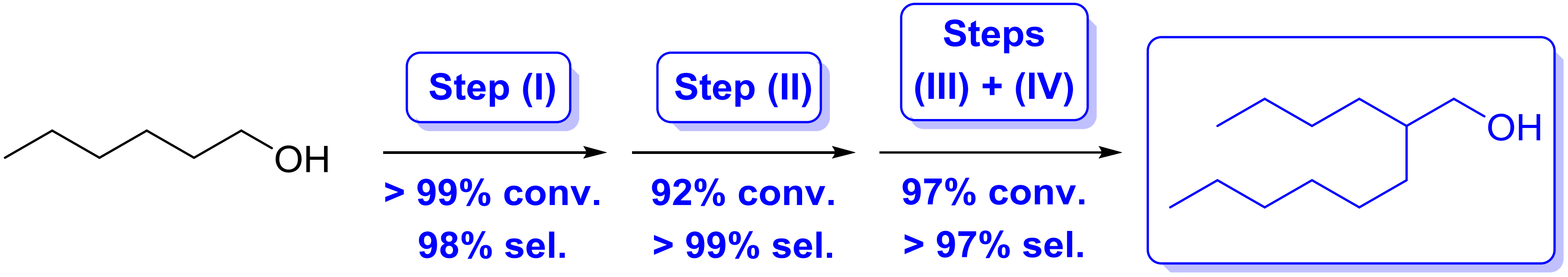
Biocatalytic double reduction (steps 3 & 4)





M. Biermann, H. Gruß, W. Hummel, H. Gröger, *ChemCatChem* **2016**, *8*, 895-899.

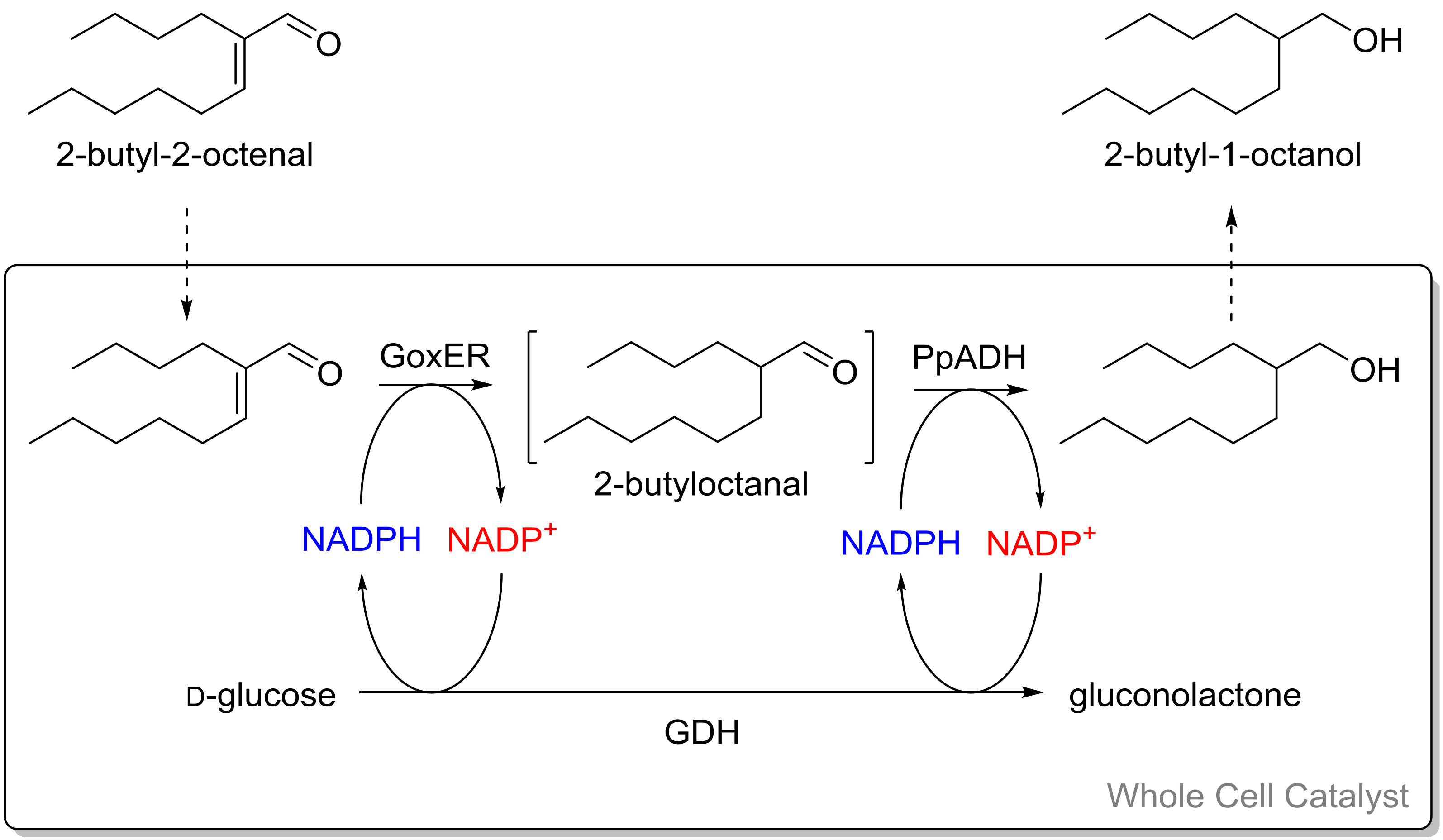
Combination of all reaction steps



M. Biermann, H. Gruß, W. Hummel, H. Gröger, *ChemCatChem* **2016**, *8*, 895-899.

Process development towards a “double reduction”

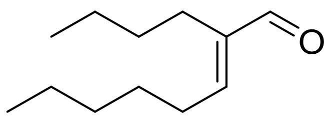
Whole-cell catalyzed C=C- and C=O-reduction:



M. Biermann, D. Bakonyi, W. Hummel, H. Gröger, *Green Chem.* **2016**, in press.

Process development towards a “double reduction”

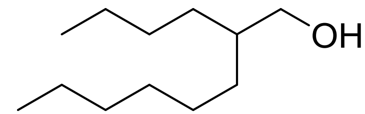
Whole-cell catalyzed C=C- and C=O-reduction:



2-butyl-2-octenal
500 mL @ 18.5 g/L

whole cell catalyst
20 g/L (wet)

2 mol% $NADP^+$, 4 eq D-glucose,
50 mM KPi buffer (pH 7), pH stat,
20% v/v methanol, room temp., 48 h



2-butyl-1-octanol
9.2 g (97% yield)
88% purity (w/o distillation)

Further experiments (same cond. as above)

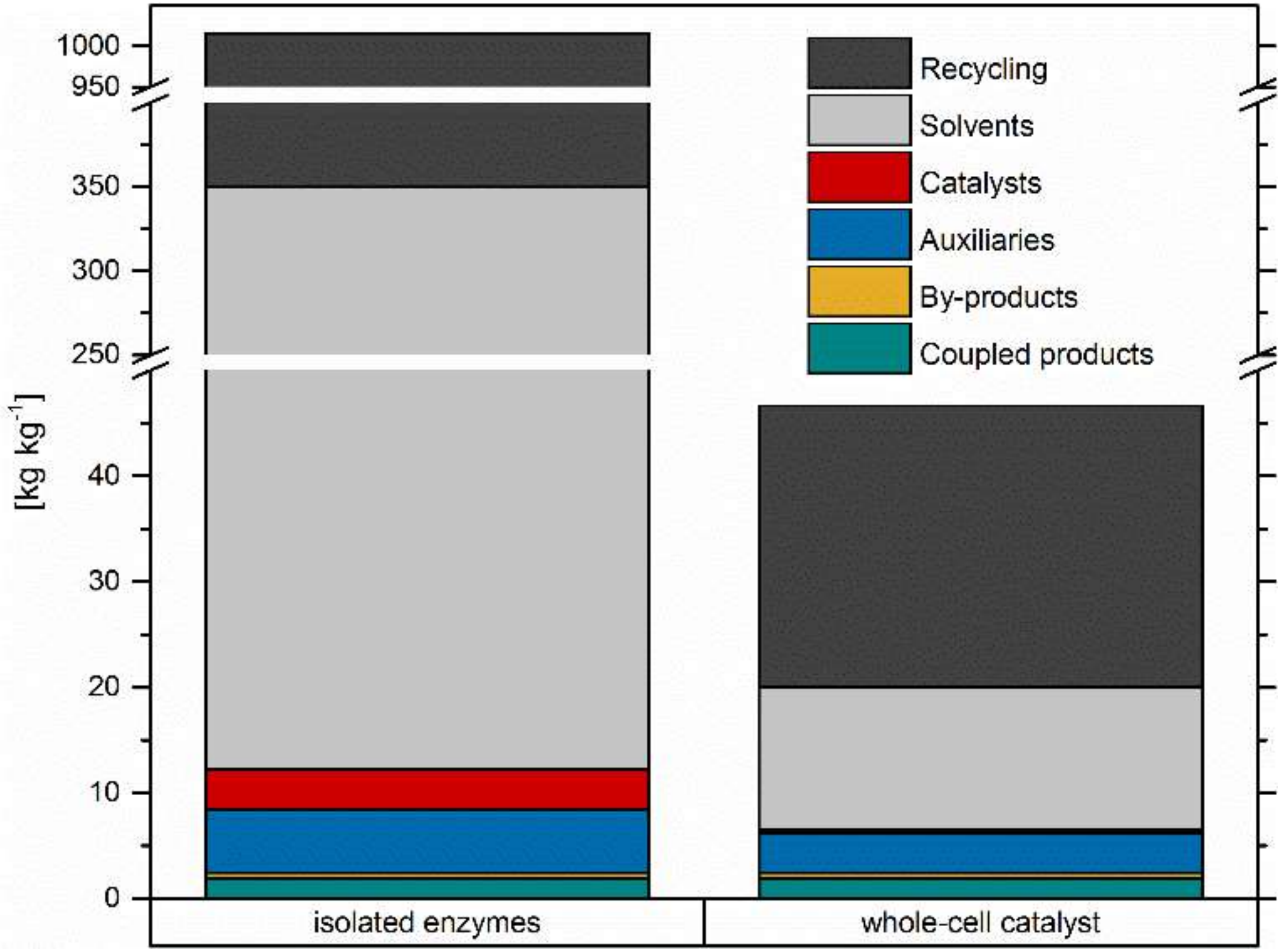
entry	scale [mL]	substrate [g/L]	time[a] [h]	yield [%]
1	25	17.2	16	80
2	25	37.2	48	89
3	25	**93.6**	68	**86**
4	**500**	18.5	48	**97**

[a] time after which the reaction was stopped. Considerably after full conversion was reached.

M. Biermann, D. Bakonyi, W. Hummel, H. Gröger, *Green Chem.* **2016**, in press.

Evaluation of sustainability of overall process

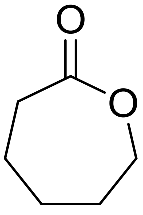
Waste balance and E-factor:



M. Biermann, D. Bakonyi, W. Hummel, H. Gröger, *Green Chem.* **2016**, in press.

Petrochemical polymer poly-ε-caprolactone

The monomer ε-caprolactone



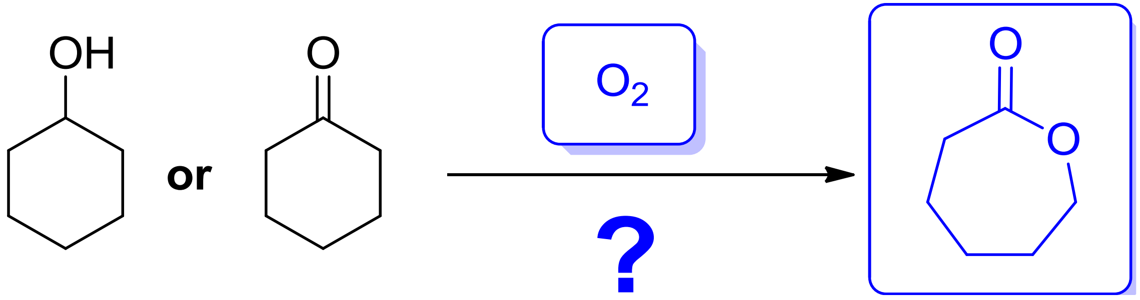
ε-caprolactone

Industrial importance of ε-caprolactone

- bulk chemical with a broad application range
- applications mainly in the field of polymer materials, e.g. polyester polyols, polyurethane
- industrial application fields: glues, coatings, paints
- production volume: multi-10.000 tons per year
- established production technology *via* UCC-process

Alternative synthesis of ε-caprolactone as key step

Basic concept: air as oxidation agent & biocatalysis



Joint project funded by DBU

Prof. Schmid / Dr. Bühler

technische universität dortmund

Prof. Liese

TUHH
Technische Universität Hamburg-Harburg

Prof. Kragl

Universität Rostock
Traditio et Innovatio

Prof. Gröger

Universität Bielefeld

Prof. Bornscheuer

Wi55en lockt.
550 Jahre Universität Greifswald

Dr. Menyes

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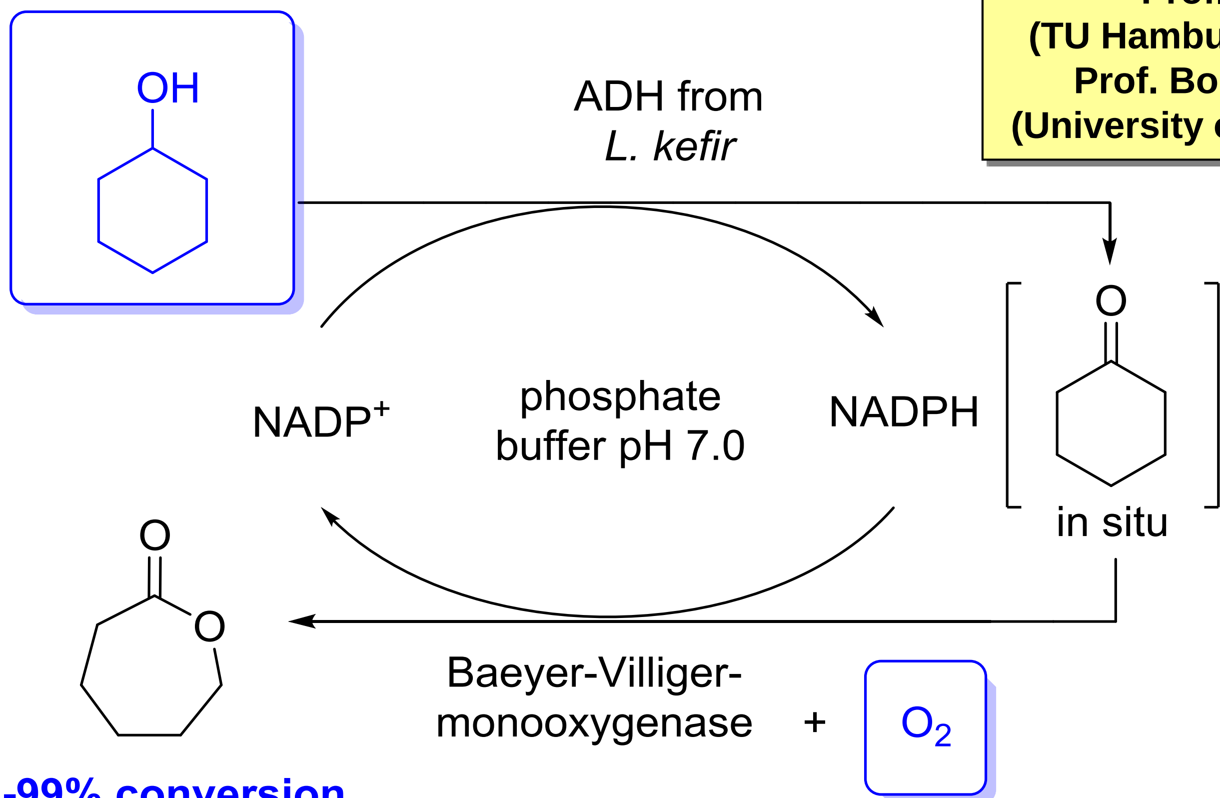
Biocatalytic route towards ε-caprolactone

The "proof of concept" for a direct oxidation of cyclohexanol to ε-caprolactone:

Joint project with
Prof. Hummel
(University of Düsseldorf),
Prof. Liese
(TU Hamburg-Harburg),
Prof. Bornscheuer
(University of Greifswald)

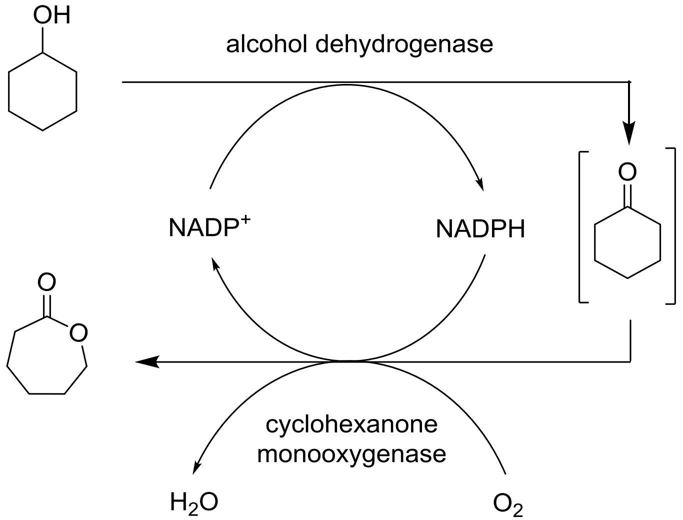


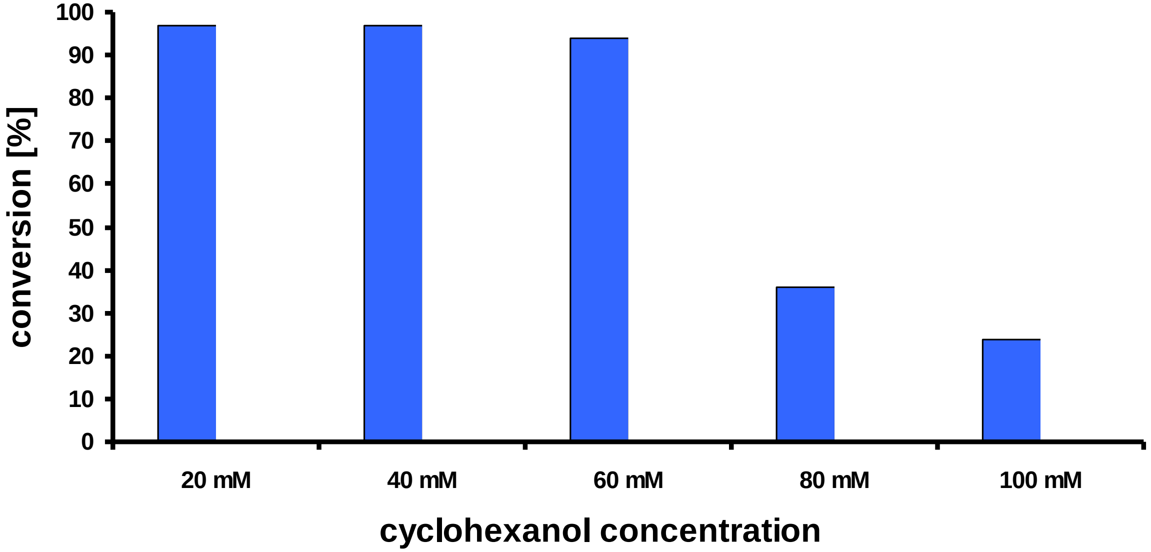
97-99% conversion

S. Staudt, U. T. Bornscheuer, U. Menyes, W. Hummel, H. Gröger, *Enzyme Microbial Technol*. **2013**, *53*, 288-292.

Initial bioprocess development

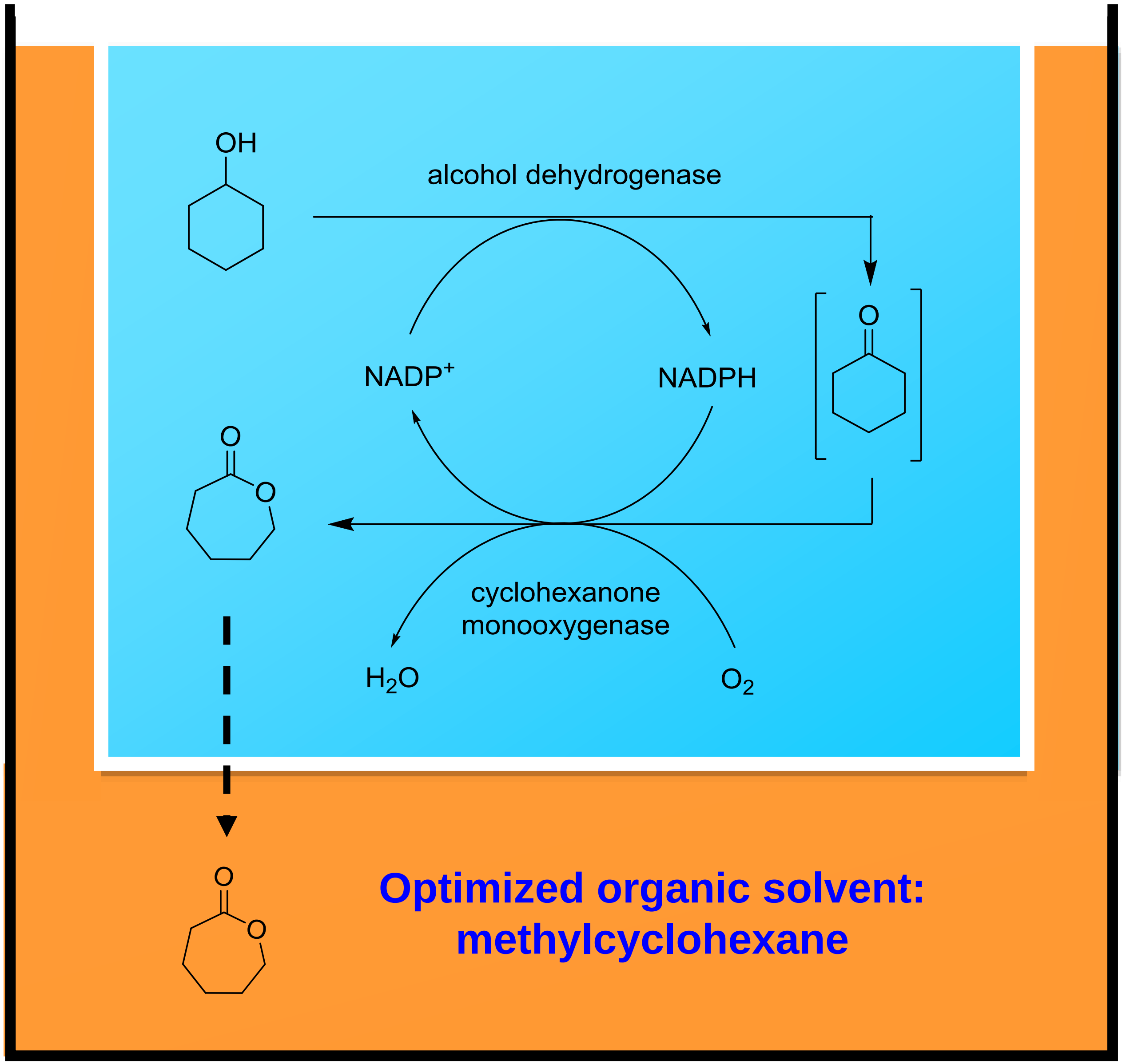
The impact of substrate concentration:





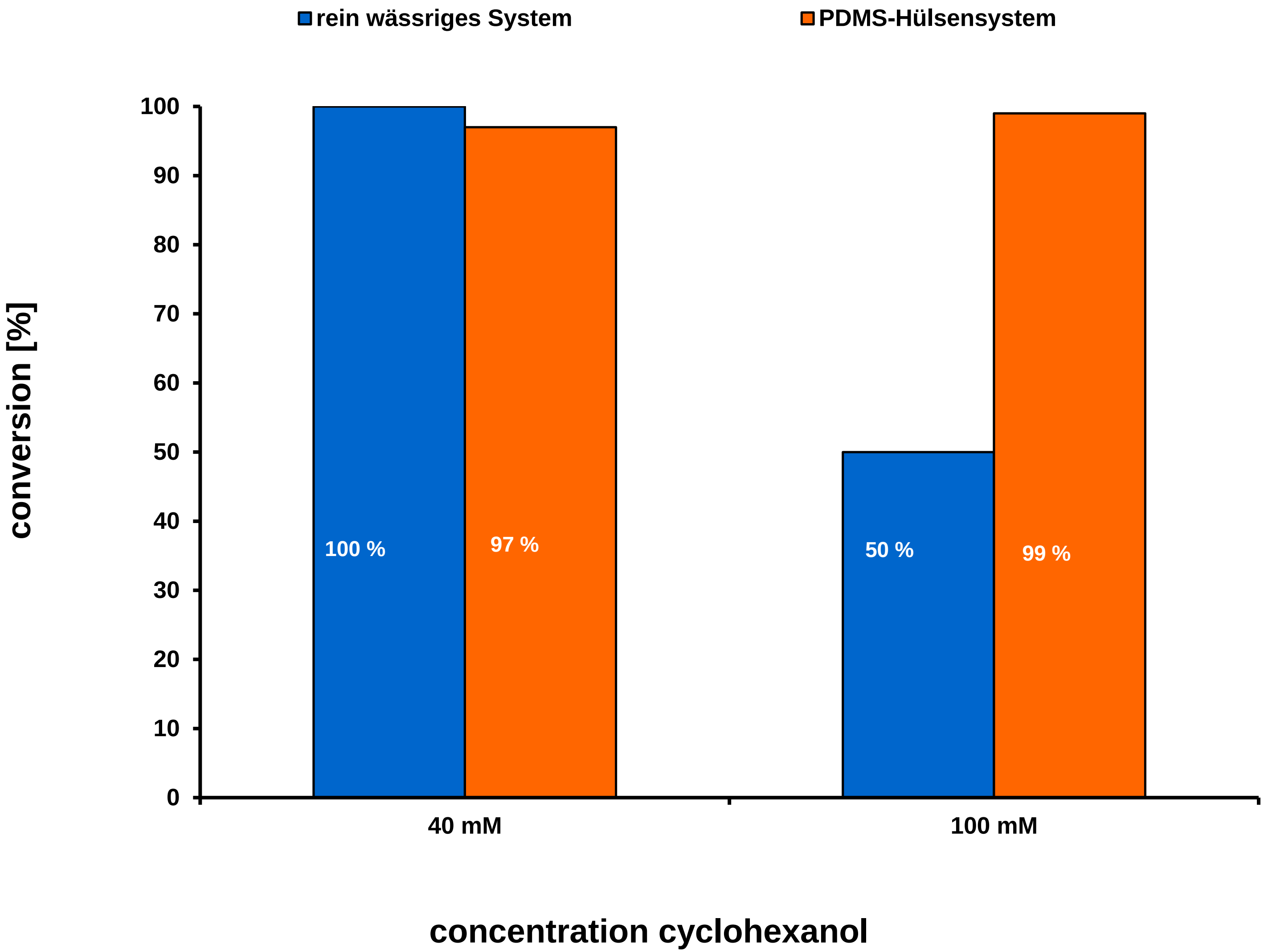
S. Staudt, U.T. Bornscheuer, U. Menyes, W. Hummel, H. Gröger, *Enzyme Microb. Technol.* **2013**, *53*, 288-292.

Process design & proof of concept



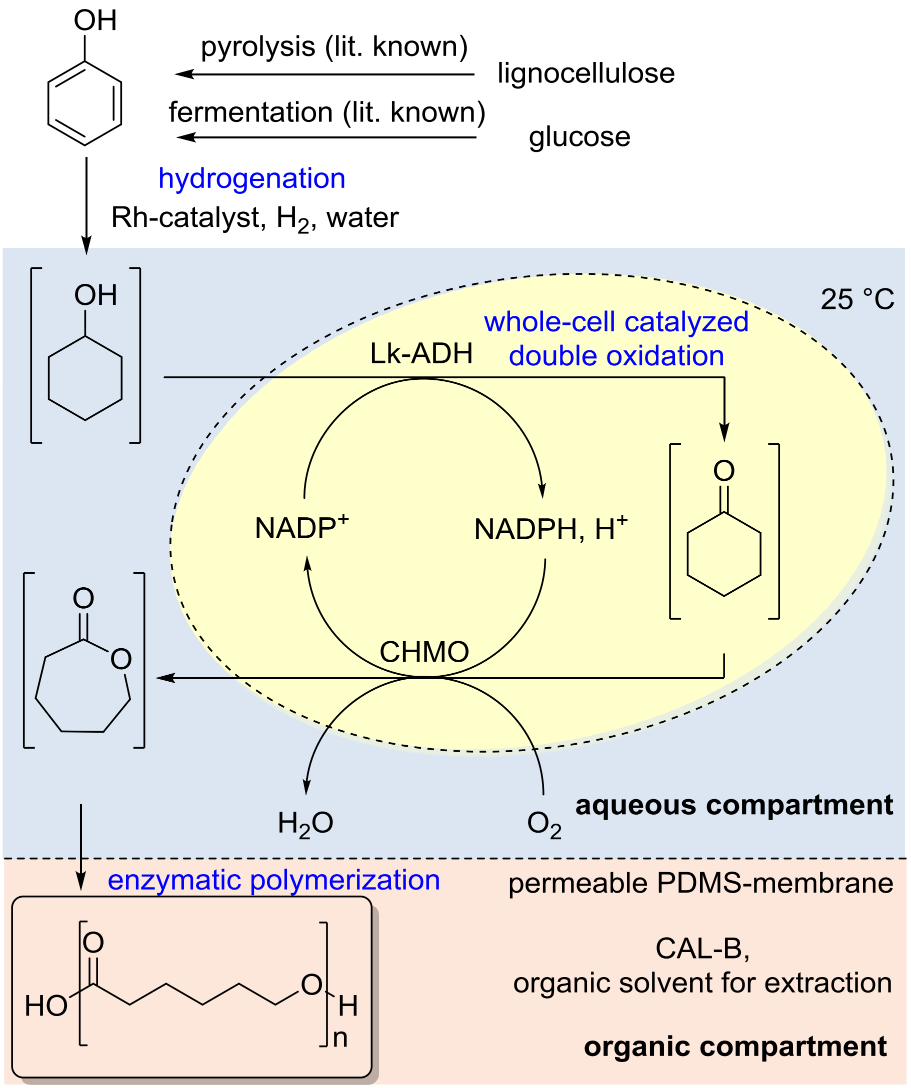
PDMS-thimble

in situ-Product removal by extraction



From biorenewables towards petrochemical polymers

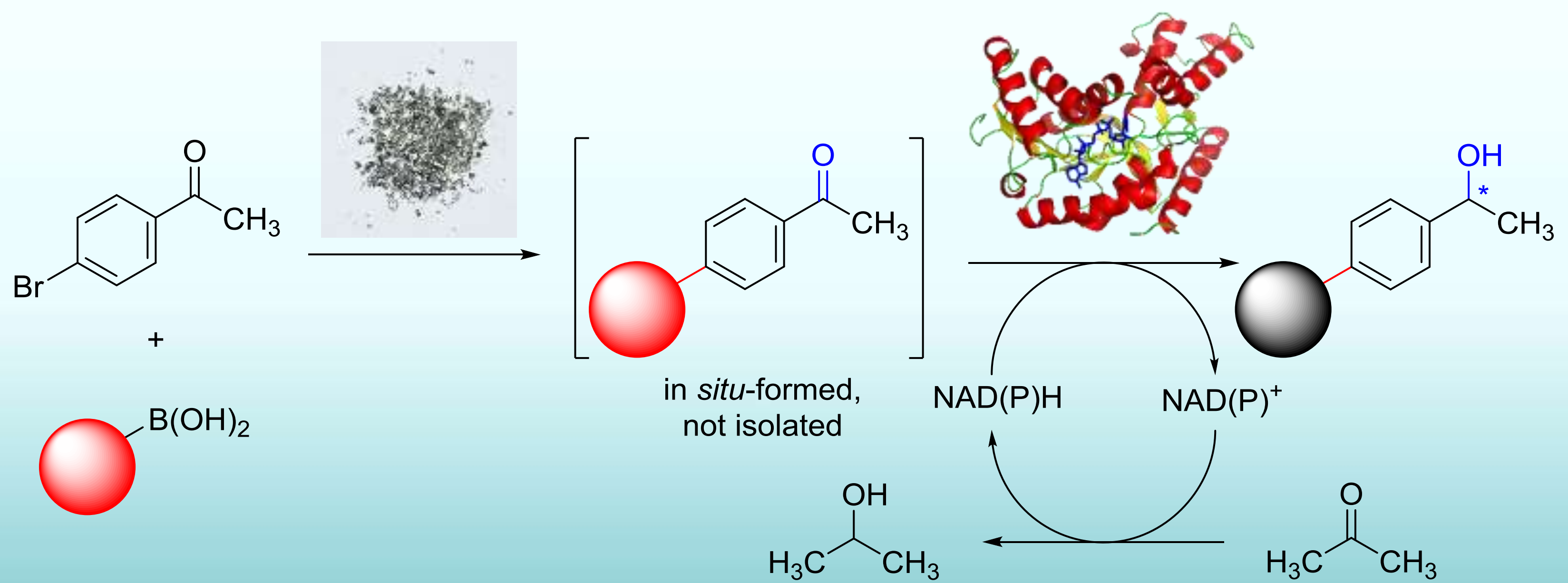
Alternative concept for an approach towards ε-caprolactone:



S. Wedde, P. Rommelmann, C. Scherkus, S. Schmidt, U.T. Bornscheuer, A. Liese, H. Gröger, submitted.

One-pot syntheses of biaryl alcohols in aqueous media

Combining Pd-catalyzed Suzuki-coupling and bioreduction



Joint project with Prof. Hummel (University of Düsseldorf)

E. Burda, W. Hummel, H. Gröger, *Angew. Chem*. **2008**, *120*, 9693-9696; *Angew. Chem. Int. Ed.* **2008**, *47*, 9551-9554.

Examples for one-pot combinations of chemo- & biocatalysis

Selected examples for chemo-enzymatic process combinations:

organocatalysis (aldol reaction)
alcohol dehydrogenase

Angew. Chem. **2009**, *121*, 9519.
Angew. Chem. **2011**, *123*, 8092.

Pd-catalysis (Suzuki / Wacker)
alcohol dehydrogenase

Angew. Chem. **2008**, *120*, 9693.

Fe-catalysis (Cofactor-oxid.)
glucose & alcohol dehydrogenase

Angew. Chem. **2011**, *123*, 2445.

Ru-catalysis (metathesis)
hydrolase

Adv. Synth. Catal. **2011**, *353*, 2363.

Concept of one-pot process

Chemical react. 1
Biocat. reaction
Chemical react. 2
Work up

Product

Current topics in chemoenzymatic one-pot processes

How to combine „non-tolerant“ catalysts?

***De novo*-synthesis of industrial chemicals**

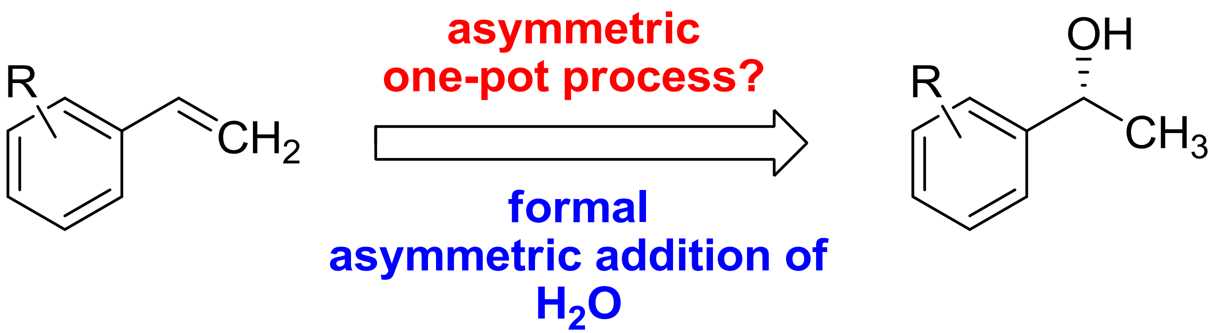
Current topics in chemoenzymatic one-pot processes

How to combine „non-tolerant“ catalysts?

***De novo*-synthesis of industrial chemicals**

Approaches towards chiral alcohols with industrial attractiveness

A “dream reaction”:
direct transformation of styrenes into chiral phenylethan-1-ols



Joint project with
Prof. Hummel
(University of Düsseldorf)

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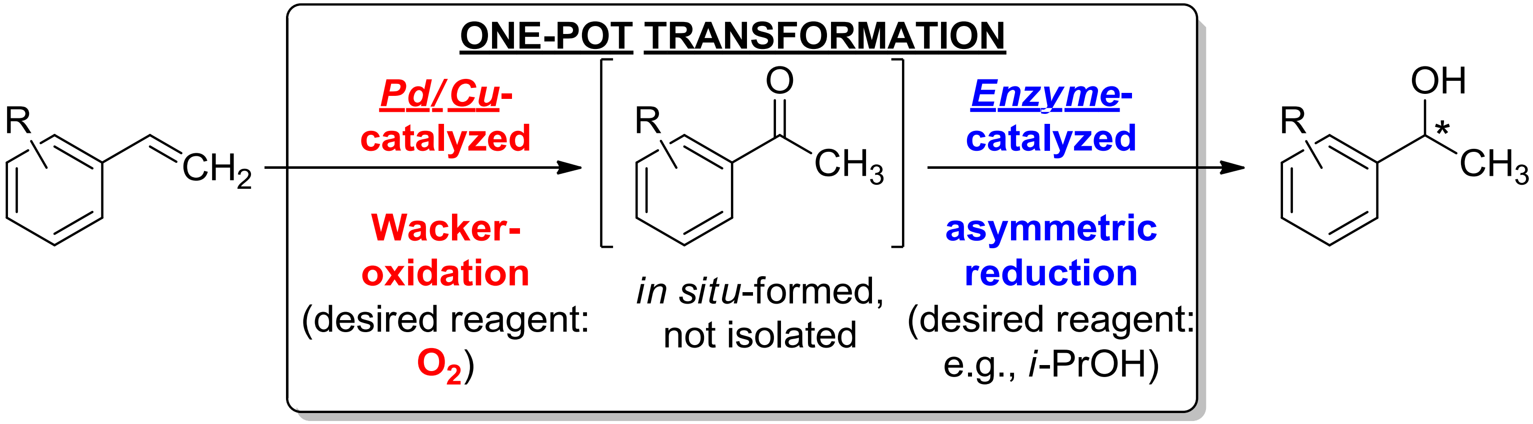
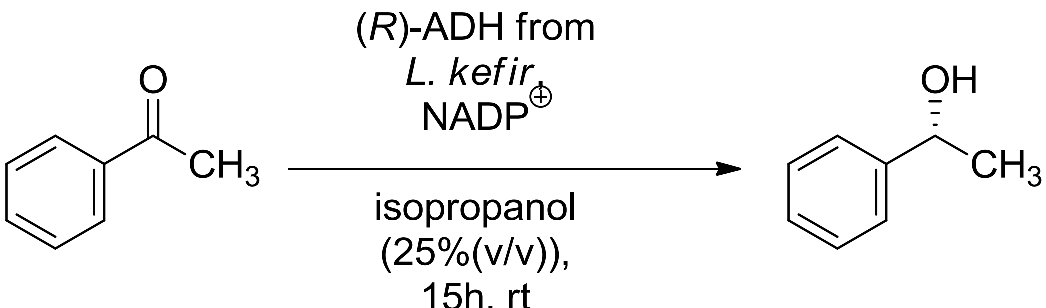
Alternative concept:
chemoenzymatic one-pot synthesis

Direct transformation of styrenes into chiral phenylethan-1-ols:
Formal addition of water *via* chemoenzymatic one-pot process



Compatibility of Wacker-catalysts and enzymes

The impact of copper ions on enzymatic reduction:



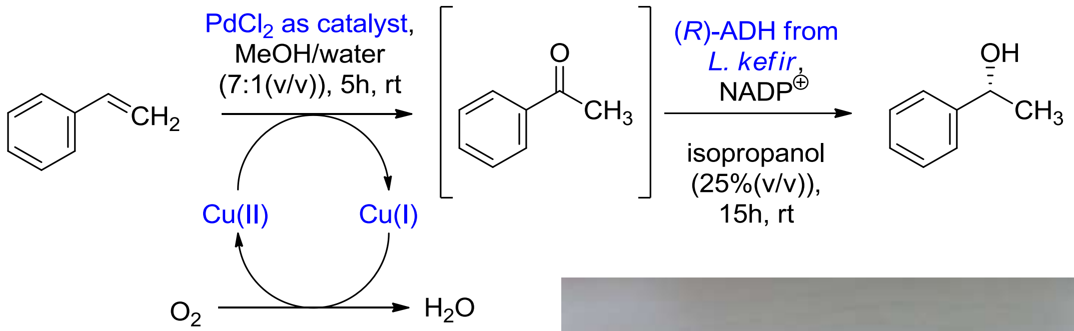
copper salts as an additive

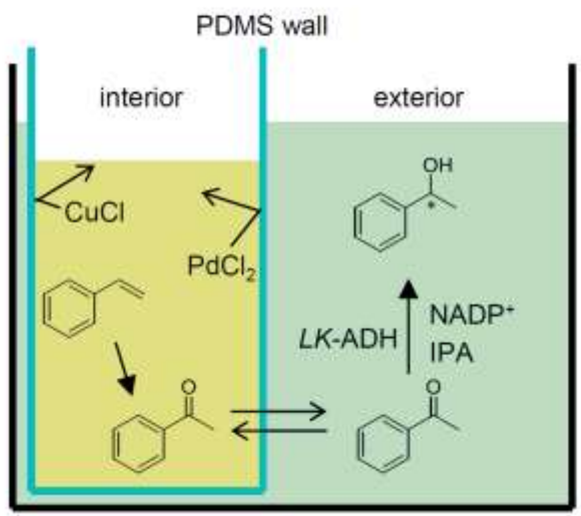
additive	conversion [%]
--	93
$CuCl_2$ (100 mol%)	3
CuCl (100 mol%)	56
CuCl (100 mol%) and $PdCl_2$ (100 mol)	51

H. Sato, W. Hummel, H. Gröger,
Angew. Chem. **2015**, *127*, 4570-4574; *Angew. Chem. Int. Ed.* **2015**, *54*, 4488-4492.

Concept for a one-pot process of non-compatible catalysts

Cooperative chemo- and biocatalysis through compartmentation

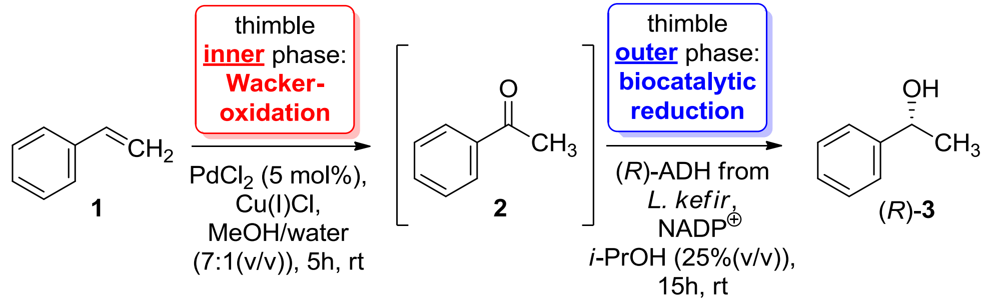




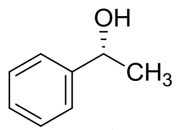
H. Sato, W. Hummel, H. Gröger,
Angew. Chem. **2015**, *127*, 4570-4574; *Angew. Chem. Int. Ed.* **2015**, *54*, 4488-4492.

Cooperative catalysis via compartmentation

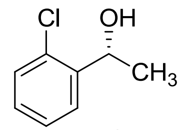
Substrate scope:



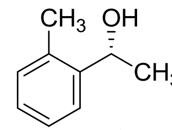
Synthetic examples



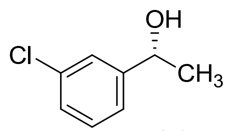
(*R*)-**3a**
>95% overall conv.
(87% conv. to **2a**)
85% conv. to (*R*)-**3a**
99% ee



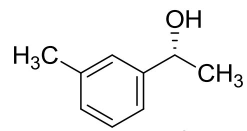
(*R*)-**3b**
>95% overall conv.
(90% conv. to **2b**)
79% conv. to (*R*)-**3b**
98% ee



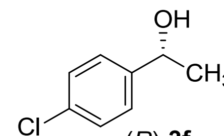
(*R*)-**3c**
>95% overall conv.
(93% conv. to **2c**)
3% conv. to (*R*)-**3c**
ee not determined



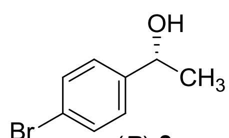
(*R*)-**3d**
>95% overall conv.
(94% conv. to **2d**)
84% conv. to (*R*)-**3d**
98% ee



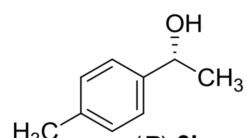
(*R*)-**3e**
>95% overall conv.
(83% conv. to **2e**)
70% conv. to (*R*)-**3e**
99% ee



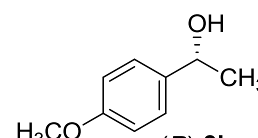
(*R*)-**3f**
>95% overall conv.
(93% conv. to **2f**)
91% conv. to (*R*)-**3f**
98% ee



(*R*)-**3g**
>95% overall conv.
(96% conv. to **2g**)
94% conv. to (*R*)-**3g**
98% ee



(*R*)-**3h**
>95% overall conv.
(94% conv. to **2h**)
87% conv. to (*R*)-**3h**
98% ee

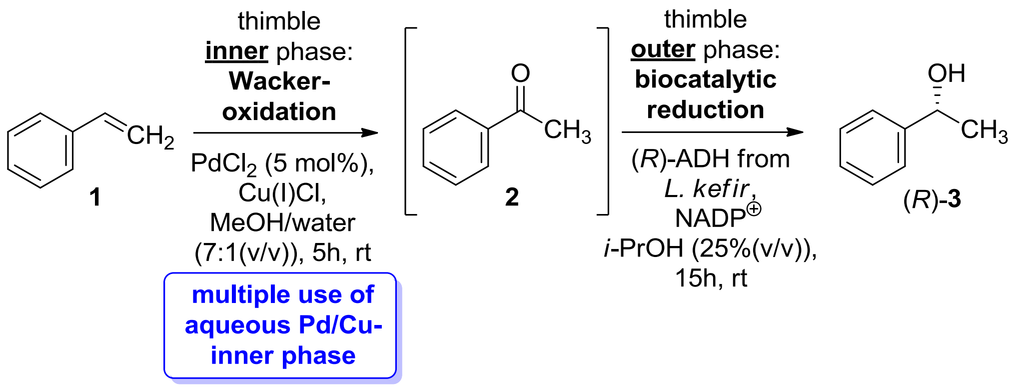


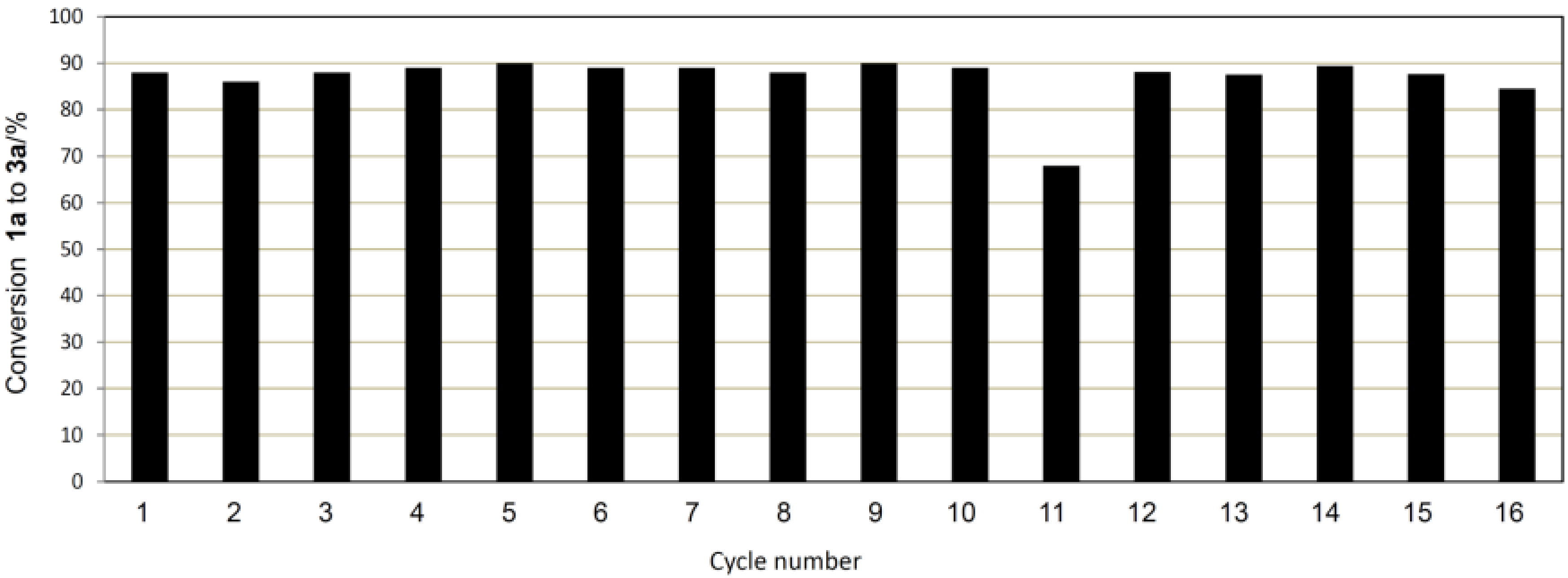
(*R*)-**3i**
>95% overall conv.
(93% conv. to **2i**)
70% conv. to (*R*)-**3i**
98% ee

H. Sato, W. Hummel, H. Gröger, *Angew. Chem.* **2015**, *127*, 4570-4574; *Angew. Chem. Int. Ed.* **2015**, *54*, 4488-4492.

Cooperative catalysis via compartmentation

Recycling of the Wacker catalyst under optimized conditions:





H. Sato, W. Hummel, H. Gröger,
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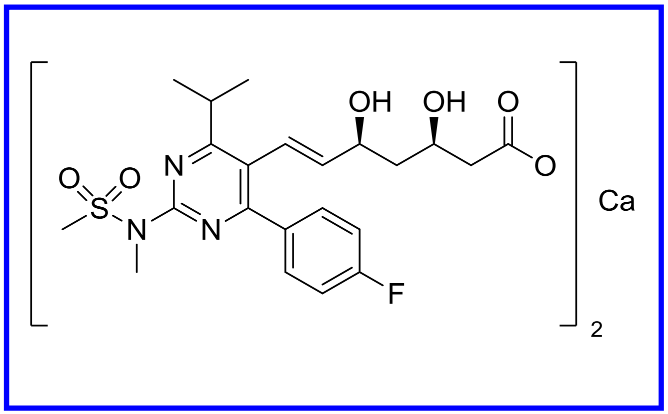
Current topics in chemoenzymatic one-pot processes

How to combine non-compatible catalysts?

***De novo*-synthesis of industrial chemicals**

A challenge:
Integration of biocatalysis in multi-step drug synthesis

An alternative synthetic approach towards Rosuvastatin (Joint project with SANDOZ):



TOP 10 PRODUCTS

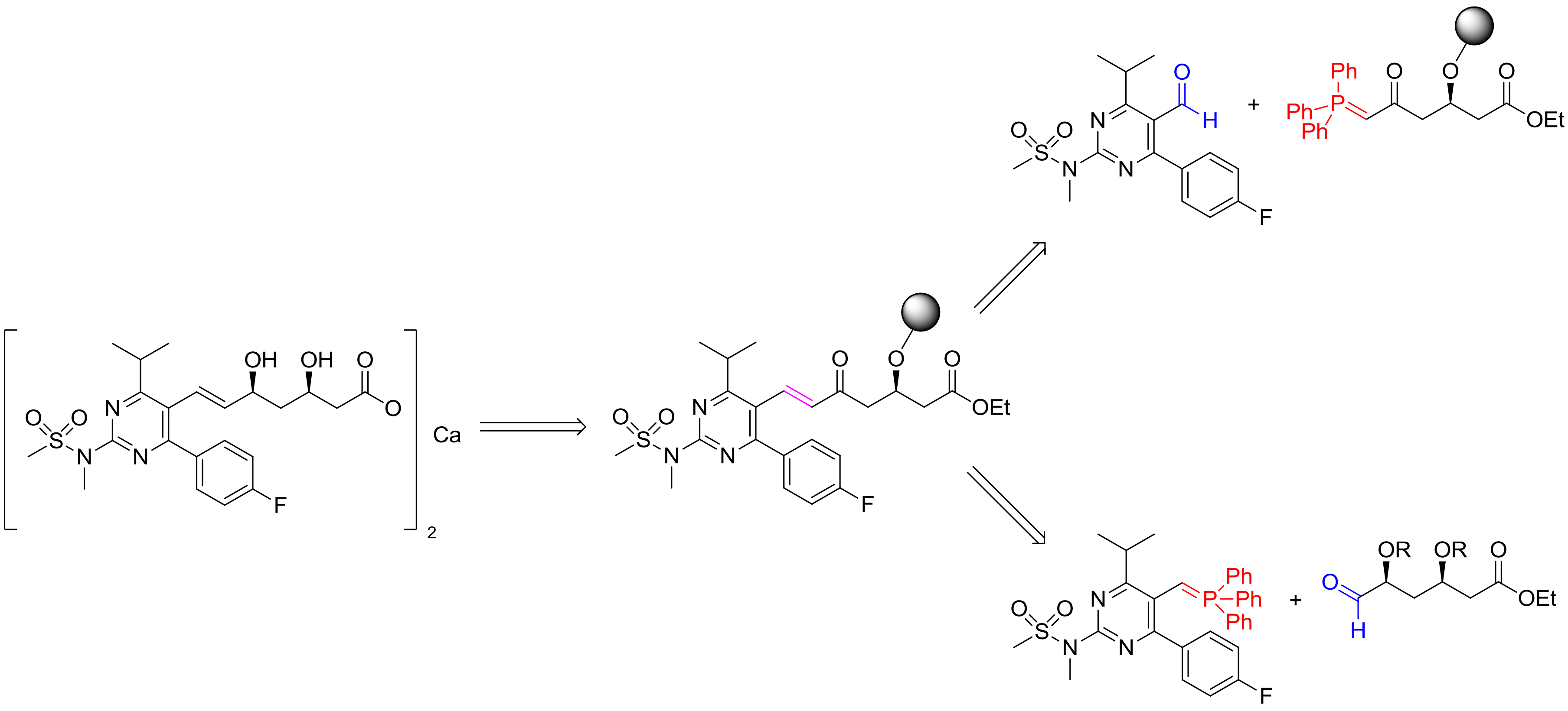
Sales of Lipitor dip as other leading pharmaceuticals see growth

	COMPOUND	MARKETER	INDICATION	SALES TO JUNE 2010 ($ BILLIONS)	12-MONTH CHANGE IN SALES
Lipitor	Atorvastatin	Pfizer	Hypercholesterolemia	[illegible]	[illegible]
Plavix	Clopidogrel	BMS and Sanofi-Aventis	Atherosclerotic events	[illegible]	[illegible]
Nexium	Esomeprazole	AstraZeneca	Acid reflux disease symptoms	[illegible]	5.0
Seretide	Fluticasone and salmeterol	GlaxoSmithKline	Asthma	[illegible]	7.4
[illegible]	[illegible]	AstraZeneca	[illegible]	[illegible]	[illegible]
Crestor	Rosuvastatin	AstraZeneca	Hypercholesterolemia	[illegible]	12.6
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Remicade	Infliximab	Centocor	Crohn's disease, rheumatoid arthritis	[illegible]	[illegible]
Zyprexa	Olanzapine	Eli Lilly & Co.	Schizophrenia	[illegible]	[illegible]
Humira	Adalimumab	Abbott Laboratories	Rheumatoid arthritis	[illegible]	24.2
TOTAL				$75.0	8.7%

NOTE: Sales are for the 12 months ending June 2010. SOURCE: IMS Health

Key building blocks

Key building blocks in dependency on synthetic strategy:



Impact of Green Chemistry metrics program

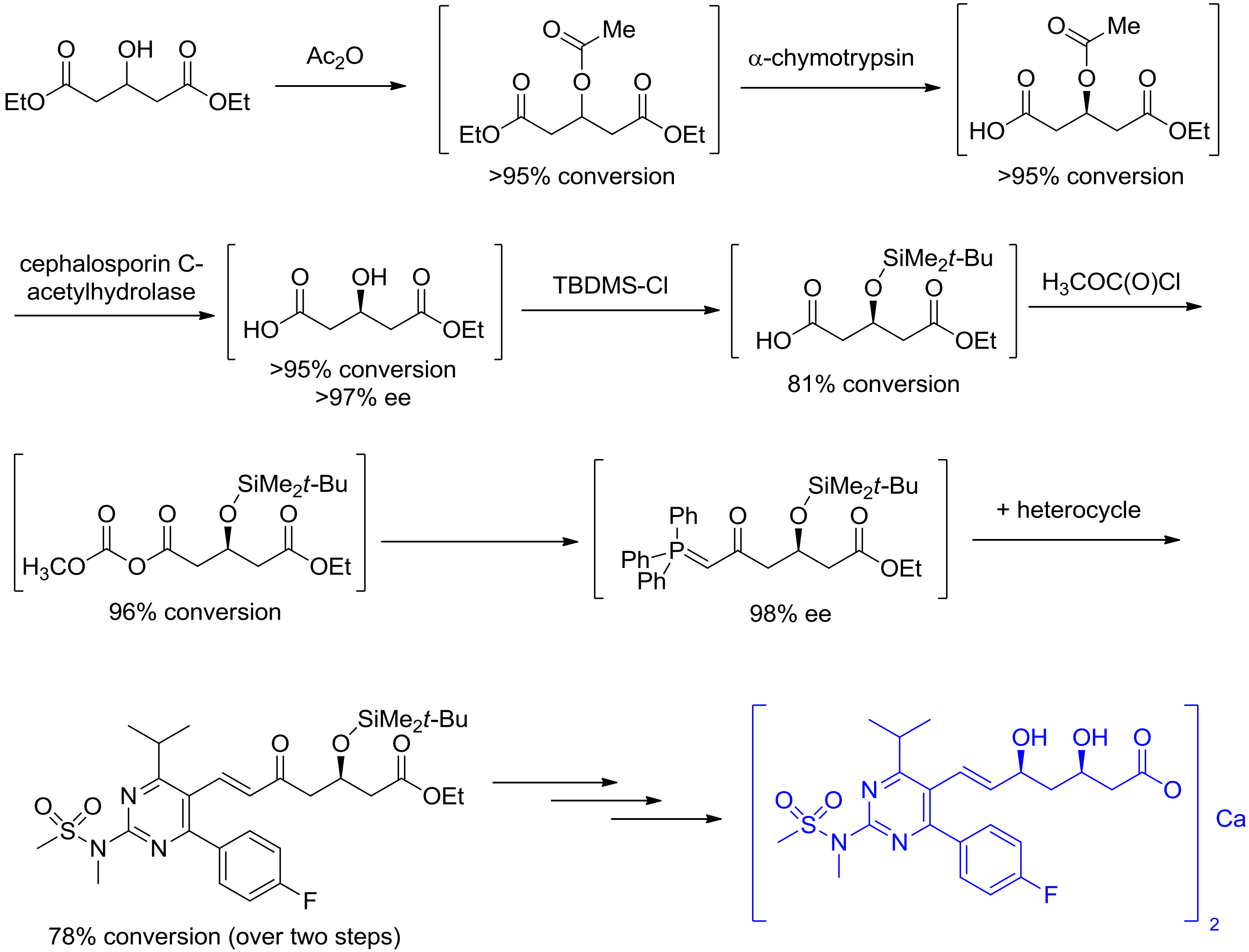
Strategies to achieve reduction goals based on the Green Chemistry metrics program at Pfizer (selected criteria):

- To increase the number of genuine telescoped steps, where the solvent for one reaction is also used for the next reaction, with little or no additional processing.
- To increase the number of reactions carried out in water (especially reactions catalysed by enzymes).
- To run reactions with low heats of reaction in more concentrated solution or suspension after detailed discussion with the process safety laboratory.
- To introduce more efficient intermediate isolations (*e.g.* by direct isolation processes).

G. Assaf, G. Checksfield, D. Critcher, P. J. Dunn, S. Field, J. Harris, R. M. Howard, G. Scotney, A. Scott, S. Mathew, G. M. H. Walker, A. Wilder, *Green Chem*. **2012**, *14*, 123-129.

Alternative retro-synthesis of Rosuvastatin

Total synthesis based on biocatalysis (joint project with SANDOZ):



B. König, F. Wetterich, H. Gröger, R. Metzner (Sandoz AG, Universität Bielefeld), *Eur. Patent Applic*. EP2778229, **2014**,
R. Metzner, W. Hummel, F. Wetterich, B. König, H. Gröger, *Org. Process Res. Dev.* **2015**, *19*, 635-638.

Summary

Enzyme-integrated one-pot processes ...

... provide fast *<u>and</u>* efficient solutions
for challenging syntheses

... shows potential for the development of
industrial production processes

... addresses improvements with respect
to both economy & sustainability

... requires ***<u>interdisciplinarity</u>***
as key success factor:
“Hybridization” of
biology & chemistry & engineering!