Universität Bielefeld

FET-OPEN: ONE-FLOW

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Working packages related to cascade 4

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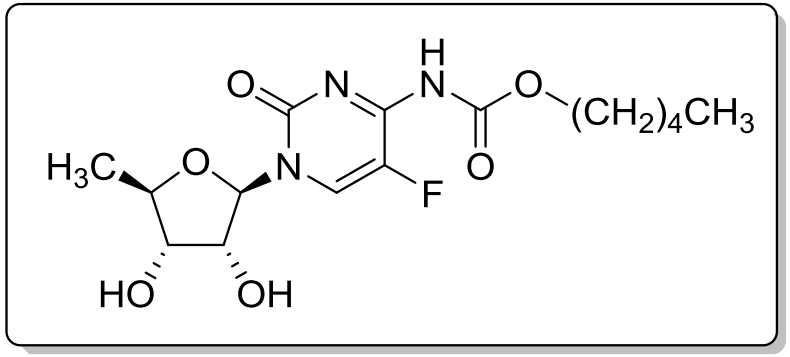
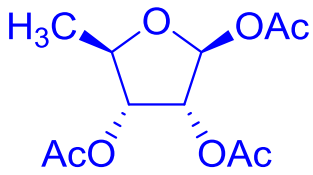
ONE-FLOW-KickOff-Meeting, Eindhoven January 18, 2017

ONE-FLOW cascade no. 4

Target molecule:
Key intermediate of the oncology drug Capecitabine



Capecitabine



chiral
key intermediate

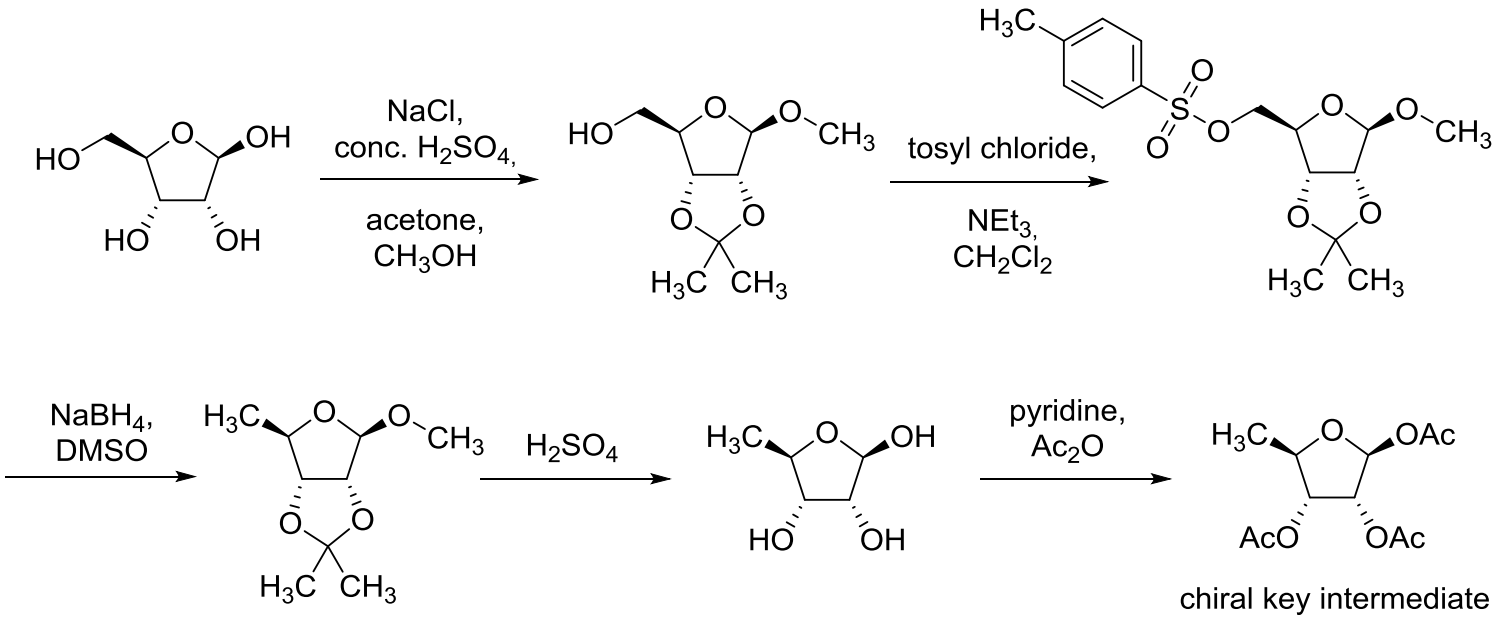
- Listed in the WHO´s “World Health Organization's List of Essential Medicines”
- Capecitabine is a prodrug being converted to 5-fluorouracil in the body
- Use against, e.g., metastatic breast cancer, gastric cancer and colorectal cancer
- Capecitabine belongs to the Top 100 US Pharmaceutical products of, e.g., the year 2013 (in terms of retail sales)

N. Shimma, I. Umeda, M. Arasaki, C. Murasaki, K. Masubuchi, Y. Kohchi, M. Miwa, M. Ura, N. Sawada, H. Tahara, I. Kuruma, I. Horii, H. Ishitsuka, *Bioorg. Med. Chem*. **2000**, *8*, 1697-1706.

J.-T. Zhang, S.-P. Peng, J.-M. Feng, D.-W. Liu, L.-J. Tang, X.-J. Wang, S.-P. Huang, *Adv. Mater. Res*. **2013**, *781-784*, 1184-1186.

The benchmark process for Capecitabine

Lengthy multi-step approach starting from D-ribose



- Methylol functionality has to be converted into a simple methyl group, which requires activation and reduction steps
- Costs for the starting material D-ribose (produced on industrial scale through fermentation), which has a relatively high market price of ca. 20-30$/Kg:

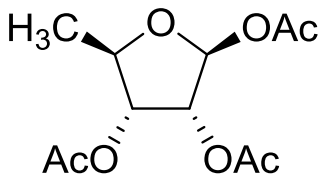
R. D. Woodyer; N. J. Wymer, F. Racine, S. N. Khan, B. C. Saha, *Appl. Environm. Microbiol.* **2008**, *74*, 2967-2975.

ONE-FLOW cascade no. 4

Target process:
Chemoenzymatic one-flow approach toward Capecitabine

Readily available starting materials

chemoenzymatic synthetic approach



chiral
key intermediate

- Starting materials: readily available and cheap industrial building blocks
- Tailor-made construction of the stereogenic centers from building blocks available in bulk quantities
- Chemoenzymatic reaction sequence
- Various options for processes running in a flow-mode are conceivable

Working packages in ONE-FLOW

WP number 2:
Chemoenzymatic synthesis of Capecitabine

- Study of individual reaction steps
- Process development for desired key steps
- Study of compatibility of the individual reaction steps
- Combination of steps in a batch-process (as benchmark for flow process)

WP number 3:
Flow processes for Capecitabine synthesis

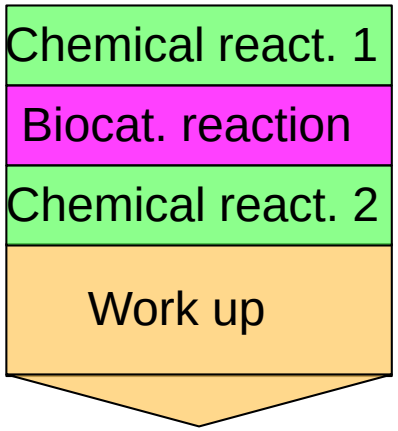
- Solvent studies & solvent engineering of individual reaction steps
- Process development for desired key steps with prioritized solvents
- Study of downstream-processing
- Contributions to applications in a one-flow cascade

Example for combinations of tolerant chemo- & biocatalysis

Selected examples for one-pot process combinations:

organocatalysis (aldol reaction)	Pd-catalysis (Suzuki reaction)
alcohol dehydrogenase	alcohol dehydrogenase
Angew. Chem. **2009**, *121*, 9519. *Angew. Chem.* **2011**, *123*, 8092.	*Angew. Chem.* **2008**, *120*, 9693.
Fe-catalysis (Cofactor-oxid.)	Ru-catalysis (metathesis)
glucose & alcohol dehydrogenase	hydrolase
Angew. Chem. **2011**, *123*, 2445.	*Adv. Synth. Catal.* **2011**, *353*, 2363.

Concept of one-pot process



Product

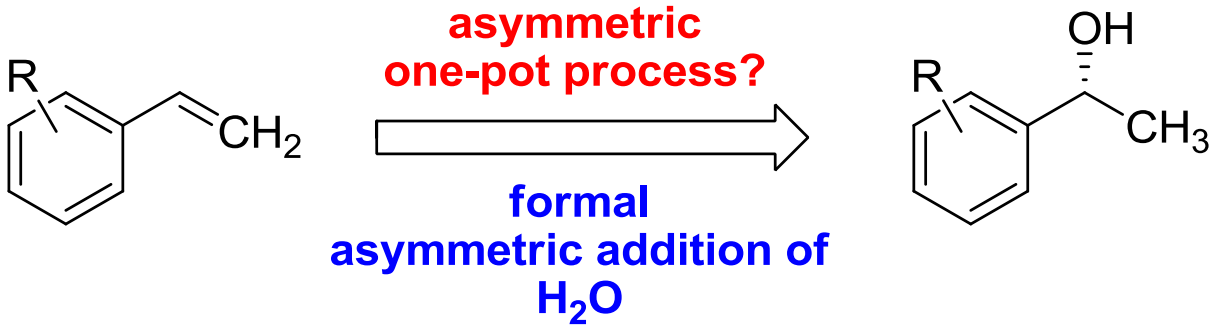
Current topics in chemoenzymatic one-pot processes

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

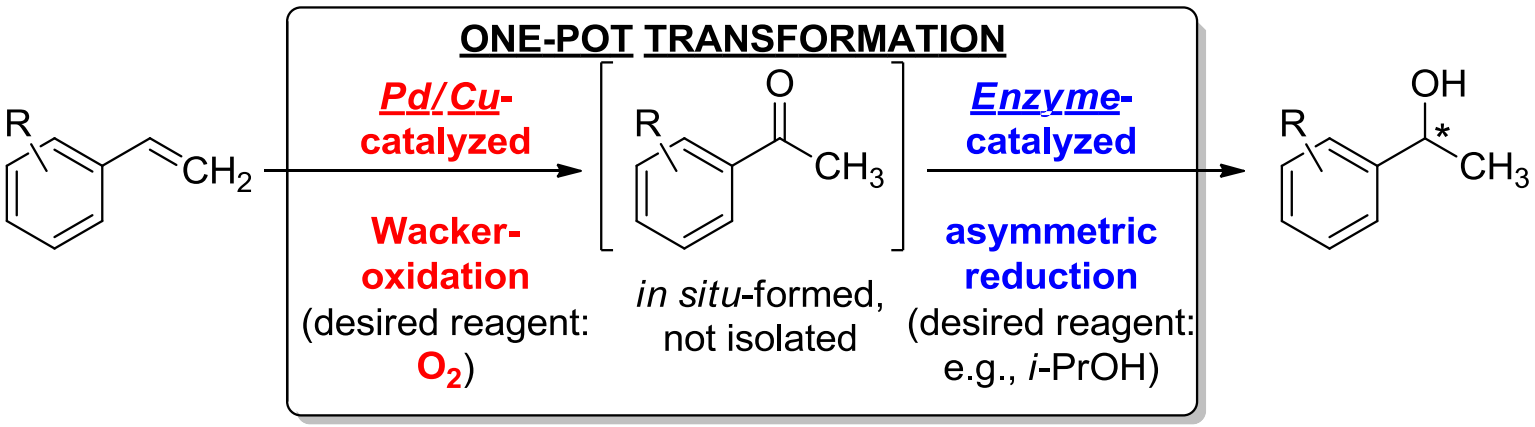


Joint project with
Prof. Hummel
(University of Düsseldorf)

Bundesministerium
für Bildung
und Forschung

Alternative concept: chemoenzymatic one-pot synthesis

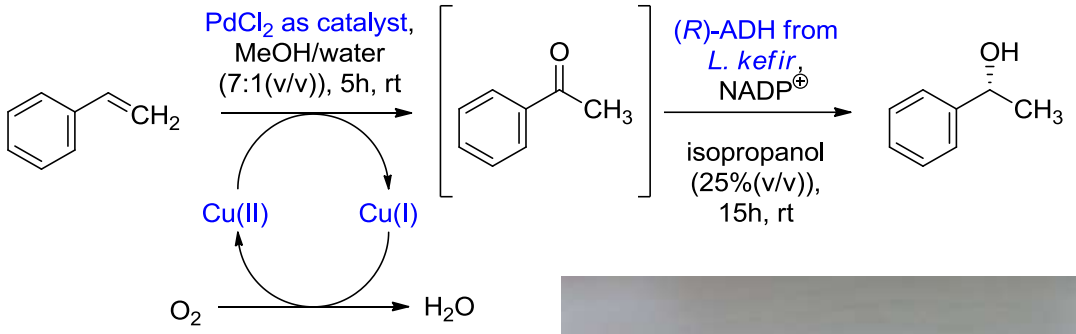
Direct transformation of styrenes into chiral phenylethan-1-ols: Formal addition of water *via* chemoenzymatic one-pot process

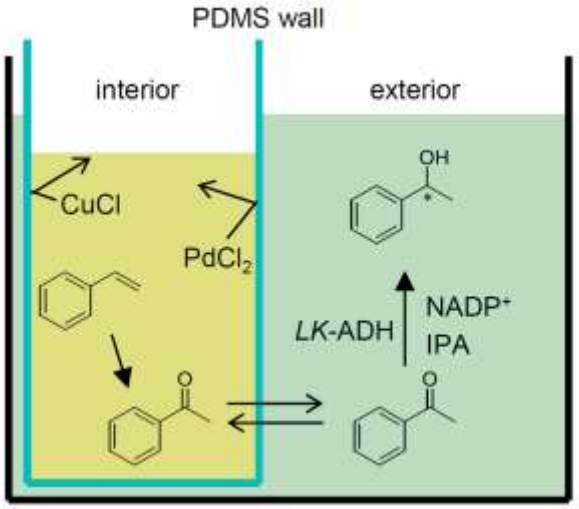


H. Sato, W. Hummel, H. Gröger,
Angew. Chem. **2015**, *127*, 4570-4574; *Angew. Chem. Int. Ed.* **2015**, *54*, 4488-4492.

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

Cooperative chemo- and biocatalysis through compartmentation

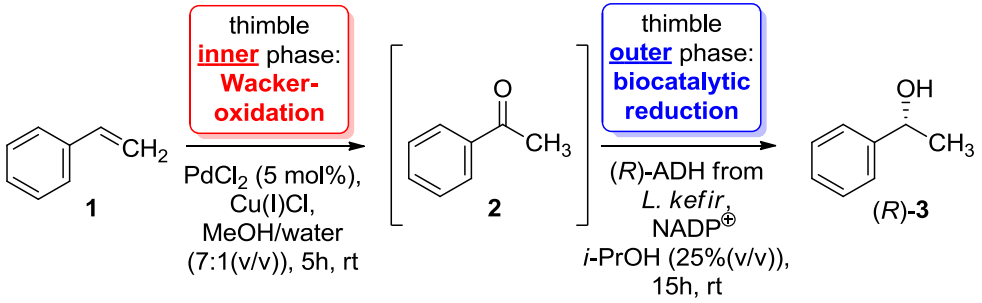




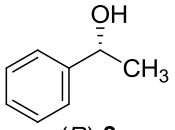
H. Sato, W. Hummel, H. Gröger,
Angew. Chem. **2015**, *127*, 4570-4574; *Angew. Chem. Int. Ed.* **2015**, *54*, 4488-4492.

Cooperative catalysis via compartmentation

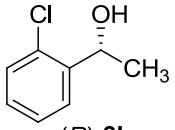
Substrate scope:



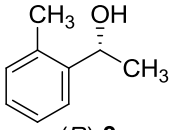
Synthetic examples



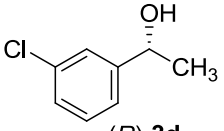
(*R*)-**3a**
>95% overall conv.
(87% conv. to **2a**)
85% conv. to (*R*)-**3a**
99% ee



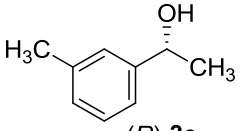
(*R*)-**3b**
>95% overall conv.
(90% conv. to **2b**)
79% conv. to (*R*)-**3b**
98% ee



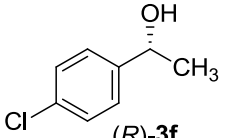
(*R*)-**3c**
>95% overall conv.
(93% conv. to **2c**)
3% conv. to (*R*)-**3c**
ee not determined



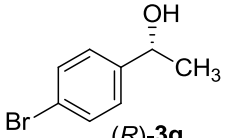
(*R*)-**3d**
>95% overall conv.
(94% conv. to **2d**)
84% conv. to (*R*)-**3d**
98% ee



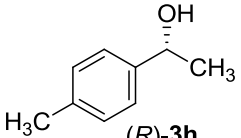
(*R*)-**3e**
>95% overall conv.
(83% conv. to **2e**)
70% conv. to (*R*)-**3e**
99% ee



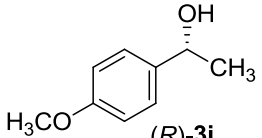
(*R*)-**3f**
>95% overall conv.
(93% conv. to **2f**)
91% conv. to (*R*)-**3f**
98% ee



(*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

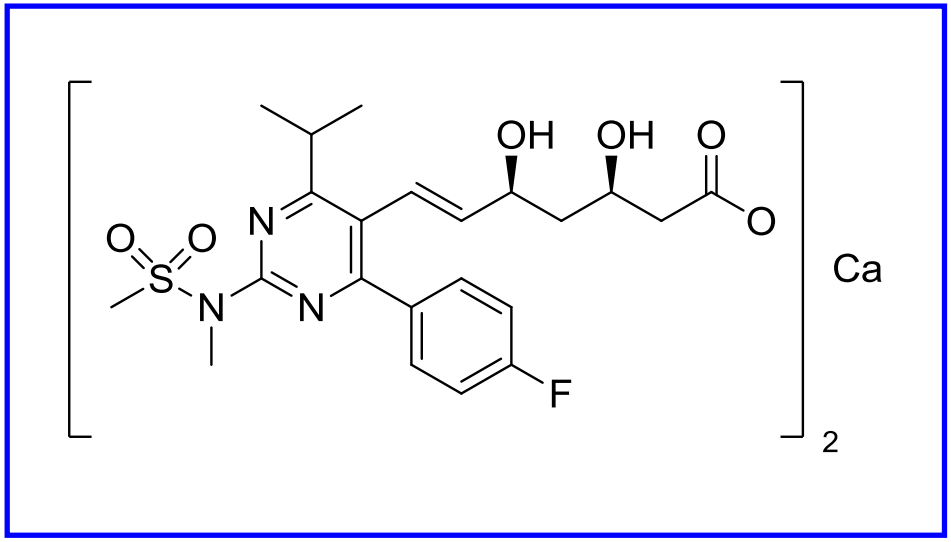


(*R*)-**3i**
>95% overall conv.
(93% conv. to **2i**)
70% conv. to (*R*)-**3i**
98% ee

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

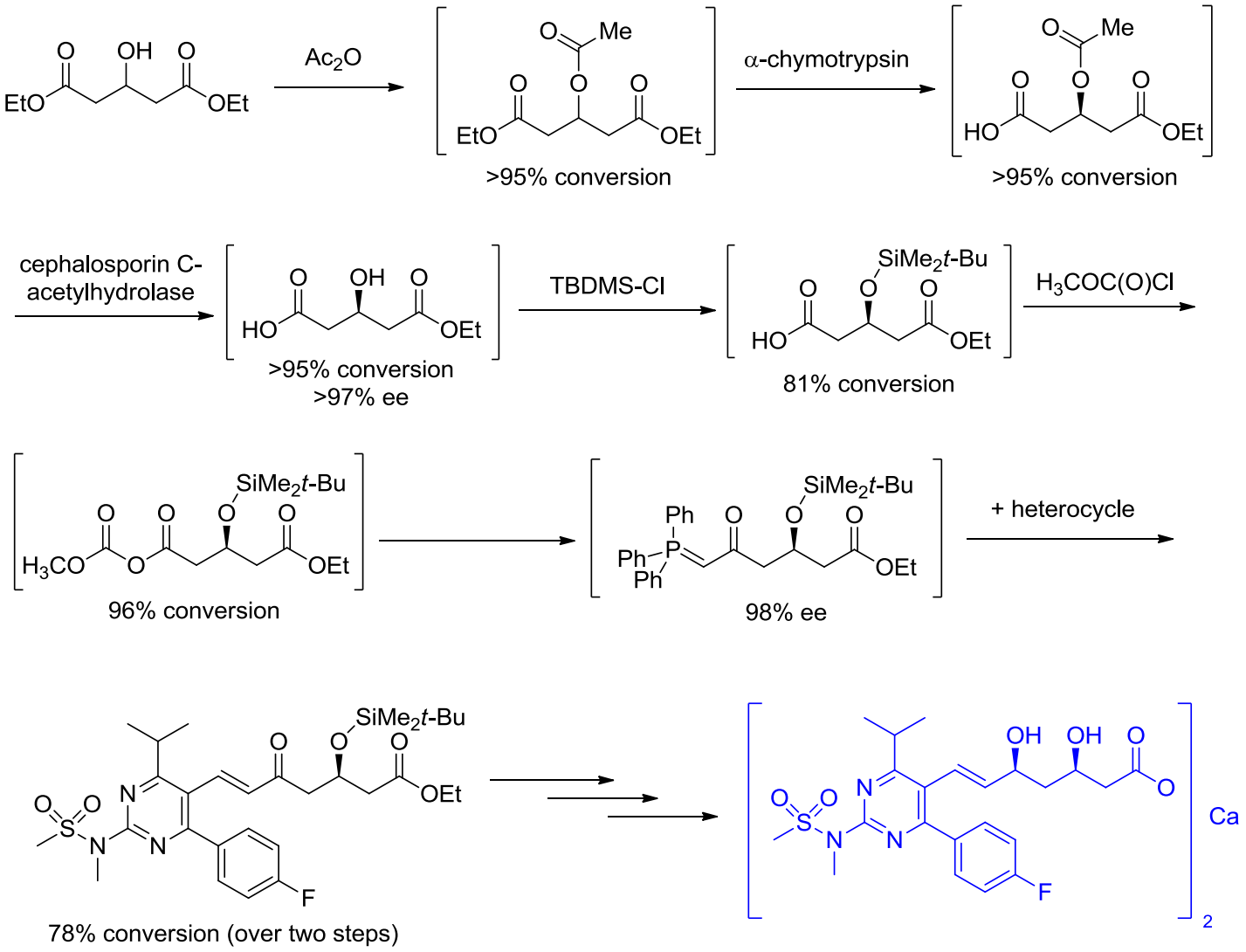
A challenge:
Integration of biocatalysis in multi-step drug synthesis

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



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.