

ILLUMINATE

Cascade reactions in flow: a novel process window in fine chemicals synthesis*

Thomas H. Rehm¹, Michaela Müller,² Greta Nölke,³ Bettina Herbig⁴

¹ Fraunhofer Institute for Microengineering and Microsystems IMM, Carl-Zeiss-Straße 18-20, 55129 Mainz, Germany

² Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Nobelstraße 12, 70569 Stuttgart, Germany

³ Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Forckenbeckstr. 6, 52074 Aachen, Germany

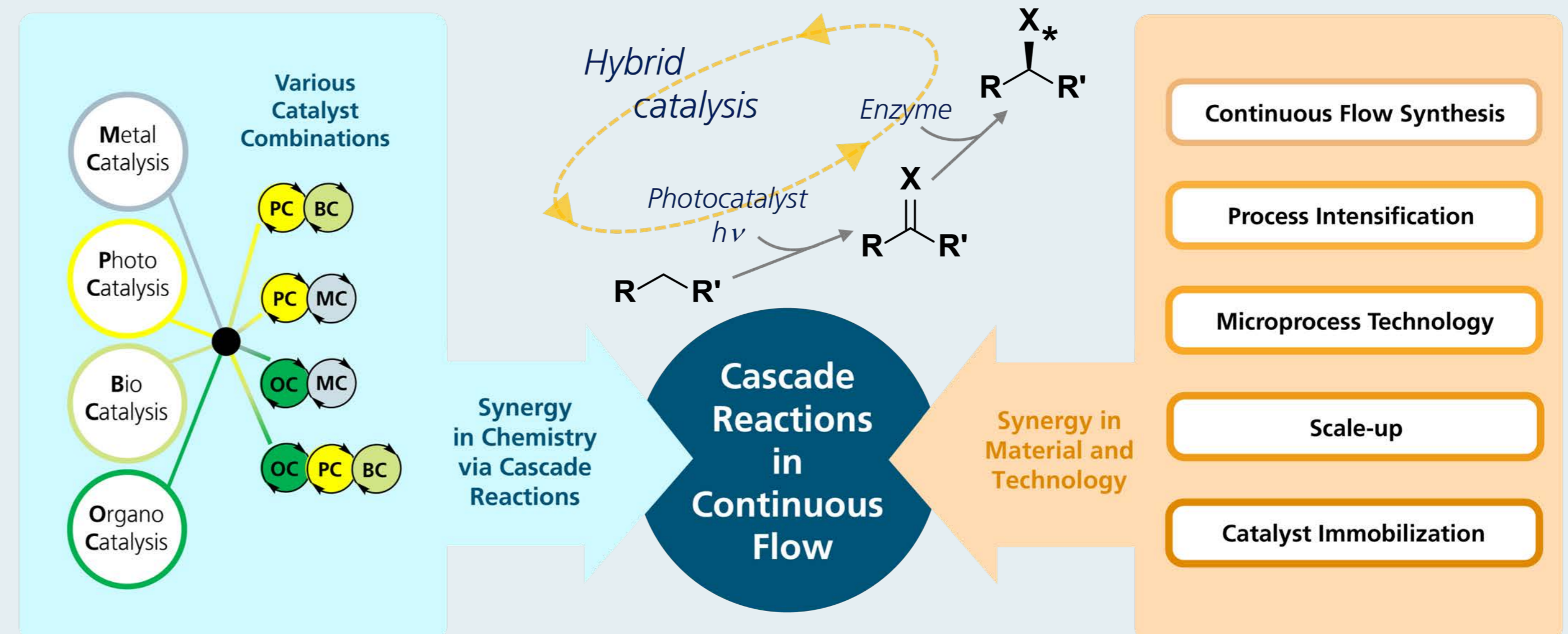
⁴ Fraunhofer Institute for Silicate Research ISC, Neunerplatz 2, 97082 Würzburg, Germany

* <https://www.cascade-reactions.de>



Relevance of research

In recent years, cascade reactions have become a highly interesting topic of academic research. Such multi-step chemical transformations have the potential of high synergy by combining different catalysis methods within one reaction sequence. A particular interesting synergy results from the combination of photocatalysis and biocatalysis as both methods perform under mild process conditions and can provide reactive intermediates via photocatalysis with subsequent usage in the enzymatic step. In the ILLUMINATE project, a consortium of four Fraunhofer institutes investigates the transfer of photo- and biocatalyzed cascade reactions from batch to flow by developing novel multi-step catalyst materials and continuous flow reactors.[1]



A modular platform technology for cascade reactions

- Catalysts**
 - Selection and development of catalysts
 - Hybrid catalysts
 - Immobilization on surfaces
 - Scale-up
- Flow reactors**
 - Development of customer & process specific reactor systems
 - Reactor scale-up
- Synthesis plants**
 - Development of customer & process specific plants
 - Integration of analytics and control elements
- Process development**
 - Process evaluation
 - Transfer from batch to flow mode
 - Cascade reactions

On the way to cascade reactions in flow Photocatalytic reaction

graphitic carbonitrile $\xrightarrow{\text{blue light}}$ benzaldehyde $\xrightarrow[\text{KCN}]{\text{HNL}}$ cyanohydrin

H₂O₂ generation
- tricine buffer, 1 Vol.% MeOH

| Wavelength (nm) | H ₂ O ₂ generation (µM) |
|-----------------|---|
| 405 | ~1000 |
| 365 | ~500 |
| 450 | ~200 |
| 520 | ~100 |

The catalyst technology 1 – Supraparticles for capillary reactors

Photocatalytic building block + Biocatalytic building block or other building blocks

Photocatalytic supraparticle, Hybrid catalytic supraparticle, Biocatalytic supraparticle

Capillary photoreactor

On the way to cascade reactions in flow Enzymatic reaction

graphitic carbonitrile $\xrightarrow{\text{blue light}}$ benzaldehyde $\xrightarrow[\text{KCN}]{\text{HNL}}$ cyanohydrin

OD 280 nm

| Time (s) | BA in 50 mM citrate buffer pH 5 | BA + HNL Type 1 + KCN in 50 mM citrate pH 5 | BA + HNL Type 2 + KCN in 50 mM citrate pH 5 |
|----------|---------------------------------|---|---|
| 0 | ~2.0 | ~2.0 | ~2.0 |
| 200 | ~2.0 | ~1.8 | ~1.8 |
| 400 | ~2.0 | ~1.8 | ~1.8 |
| 600 | ~2.0 | ~1.8 | ~1.8 |
| 800 | ~2.0 | ~1.8 | ~1.8 |
| 1000 | ~2.0 | ~1.8 | ~1.8 |
| 1200 | ~2.0 | ~1.8 | ~1.8 |
| 1400 | ~2.0 | ~1.8 | ~1.8 |

The catalyst technology 2 – Polymeric foils for a FFMR

Transparent foil \rightarrow Functionalized foil

Immobilization of catalysts

Foil with photocatalytic building block, Foil with hybrid catalysts, Foil with biocatalytic building block

Falling film microreactor

Outlook

- Immobilization of enzymes on carrier particles and polymeric foils
 - Process optimization with hybrid catalysts in continuous flow
 - Scale-up of catalyst material
 - Flow reactor characterization utilizing cascade reactions
 - Technology and catalyst transfer to other industrial relevant syntheses of fine chemicals and APIs
-

[1] Funded by the Fraunhofer Society and the Federal Ministry of Education and Research BMBF (ILLUMINATE Project, Grant # 031B1121).

