SYNFLOW concept and objectives

SYNFLOW aims at developing the basis for **new and widely applicable sustainable production technologies** in low to medium scale chemical and pharmaceutical production. **The vision** of SYNFLOW **is to shift paradigm from batch-wise** processes comprising many separate unit operations **to** highly integrated, and yet flexible **catalytic continuous-flow processing**.
In an ideal continuous flow processes, the substrates flow into the reactor, get in contact with the catalyst immobilized in the reactor, undergo a chemical transformation under well defined process conditions and residence time and finally leave the reactor in a pure form, ready for further use without further separation or purification steps.
This ambitious goal can be achieved by an **integrated development** of **molecular catalysts, immobilization strategies and reaction engineering concepts** for continuous-flow reactions. An **interdisciplinary team** of 13 academic and 6 industrial partners **from all over Europe** has collaborated in the SYNFLOW project.

In order to overcome the limitations of the traditional linear work flow for the development of medium to small scale processes, SYNFLOW aimed at a conceptually new approach based on an **integrative design of molecular catalysts, their synthetic application, and the reaction engineering concepts**. This new paradigm has been developed and demonstrated on the basis of **selected industrial case studies** to provide a well-defined basis for its generic application.

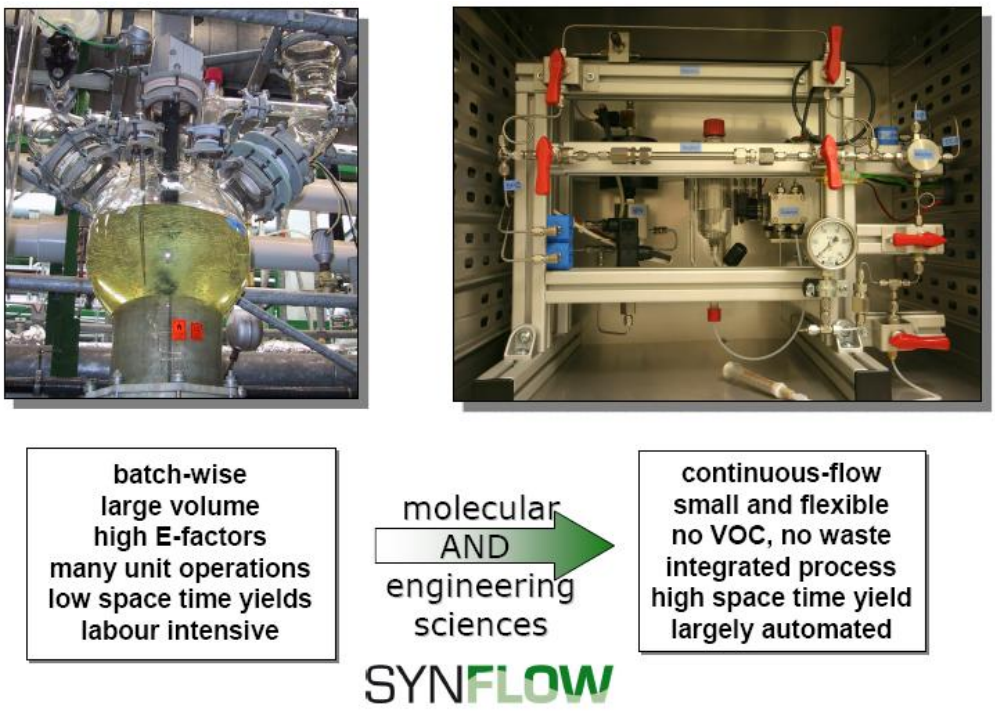

Figure 1: SYNFLOW concept

SYNFLOW Industrial case studies

The industrial sectors addressed in the SYNFLOW project, namely fine and specialty chemicals industry and pharmaceutical industry are characterised by a large diversity in synthetic problems and targeted chemical structures. In order to demonstrate the generality and broad impact of the SYNFLOW concept, the case studies were chosen as prototypical examples for generic challenges in these fields. The current commercial processes represent reaction types such as C-N bond formation, C-C coupling, or stoichiometric reductions, which are notorious for the waste generation and inefficient resource and energy utilisation in the fine chemicals and pharmaceutical sector. These case examples provide the raw models to develop and establish the design process of the SYNFLOW concept, which can then be directly transferred to other transformations or classes of transformations.

6 industrial case studies defined by the industrial partners Bayer Technology Services, AstraZeneca and Evonik have been investigated in the SYNFLOW project:

Pharmaceutical Sector

- Buchwald-Hartwig Reaction; development of a flexible flow methodology for the formation of C-N bonds in a range of target molecules
- Amide Reduction; use of molecular hydrogen as "cleanest" reducing agent, generating only water as a by-product
- Suzuki Couplings; Pd-catalysed cross coupling processes are widely used in the pharmaceutical industry for C-C bond formation
- Asymmetric hydrogenation; Catalytic asymmetric reduction has become an extremely important transformation in the toolkit of process chemists in the pharmaceutical industry

Chemical Sector

- Nitrile synthesis - development of flow processes for the synthesis of aromatic and longer chain aliphatic nitriles, commonly used in the manufacture of agrochemicals, dyes and pharmaceuticals
- Atom-efficient olefin coupling; C-C coupling of C2 and C4 olefins via dimerisation and telomerisation

SYNFLOW results at a glance

Main demonstrator case studies

The **Buchwald-Hartwig case study** provided by AstraZeneca was successfully demonstrated thereby meeting all of the required success criteria. The demonstrator work has clearly proven the feasibility of the continuous process for the case study reaction on kg scale. The process achieves excellent values with respect to process performance indicators and the metal content in the final product. Telescoping the demonstrated reaction step with previous or subsequent steps in the synthesis of the final desired molecule would obviously increase the benefit of such a process even more. Approximately 20 % of small molecule pharmaceuticals contain a structural motif that could be made using this methodology, therefore the potential for beyond the specifically investigated case study is significant.

Figure 2: Demonstrator unit for the Buchwald-Hartwig case study at INVITE

The **asymmetric hydrogenation case study** of a pharmaceutical substrate provided by Astra Zeneca has been demonstrated on kg scale using two different reaction systems. Extremely stable performances with high conversion and constant high enantioselectivity were achieved fully matching the envisaged success criteria. Very important success is the low metal contamination in the isolated product which is an important driver for continuous-flow process in API manufacturing.

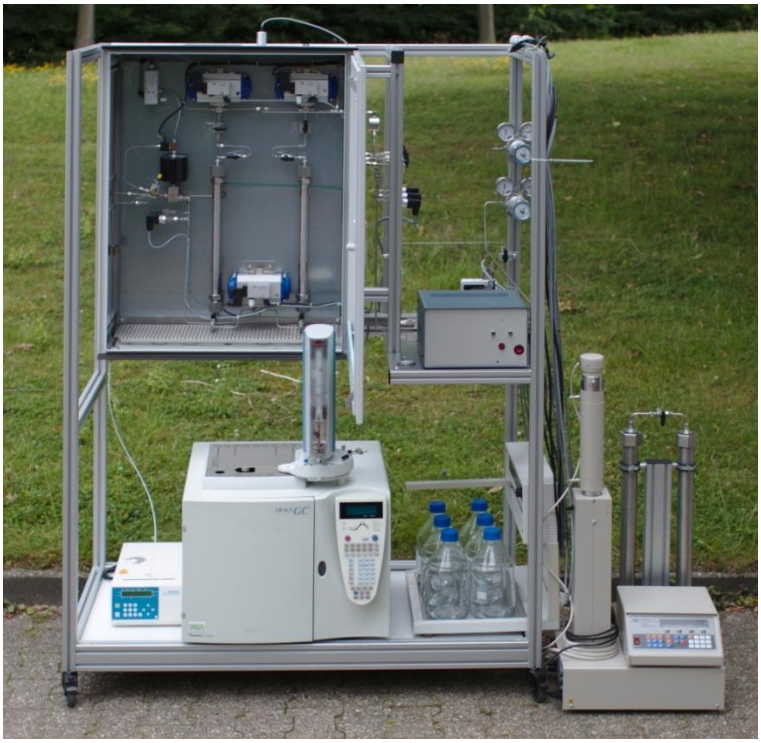

Figure 3: Demonstrator unit for the asymmetric hydrogenation (RWTH)

Two other case studies, the direct hydrogenation of an amide (amide reduction to an amines and a homogeneously catalysed dimerisation (telomerisation) of butadiene have been demonstrated with great success. The other case studies have been investigated at lab scale.

More rational approach to catalytic process design

SYNFLOW partners have developed a range of methodologies during the project to aid catalytic process design, optimisation and implementation. Part of the methodologies is qualitative in nature with the intention to allow rapid identification of lead process options, and dismissal of unfeasible options. The output from the methodology will also identify key data requirements for process optimisation. Another methodology aspect is a rational approach to select the appropriate equipment matching the process requirements.

More quantitative methodologies include a quantitative model-based approach to the design of integrated reaction and separation processes and a reactor design by CFD used to reactor scale-up.

SYNFLOW output

Within SYNFLOW a number of materials have been developed available to an interested community outside the consortium:

- a SYNFLOW training package on the developed methodology, aimed at young chemists and engineers engaged in PhD or postdoctoral research through to more experienced industrial chemists/engineers.
- SYNFLOW case study posters to raise awareness of the concepts developed in the project.
- a SYNFLOW promotional video

All materials will be available on the SYNFLOW website www.synflow.eu, but will also be hosted on the website of the European Technology Platform SusChem www.suschem.org. For this purpose, a dedicated education and project material portal is under construction.

SYNFLOW Partners

RWTH Aachen University (Coordinator)
AstraZeneca
Bayer Technology Services GmbH
Britest Ltd.
Centre National de la Recherche Scientifique - CNRS
DECHEMA - Society for Chem. Engineering
and Biotechnology e.V.
Technical University of Denmark
Evonik Industries AG
Johnson Matthey
University of Bucharest
University of Erlangen-Nuremberg
Gothenburg University
Università degli Studi di Napoli Federico II
University of Nottingham
University of Rennes

Universitat Rovira i Virgili Tarragona
University of St. Andrews
Stockholms Universitet
Cambridge University

Contact

www.synflow.eu