International Collaborations in the Field of Laboratory- and Pilot-scale Micro-reactor Plants

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Abstract

As micro-reactor technology is an interdisciplinary topic all fields of expertise hardly can be covered by a single group. Examples of IMM's international collaboration with other research groups as well as of contract research with industrial partners from Europe, Asia and the United States are given. These collaborations vary from the simple supply of a micro device, assistance by scientific evaluation and training to process development in the laboratory, pilot and production scale and even the development and delivery of plants for these processes.

1 Introduction

Micro-reactor technology is an interdisciplinary topic, involving skills from simulation, mechanical engineering, chemical engineering, chemistry, catalysis, and many more scientific fields. Such fields of expertise hardly can be covered by a single group today. Rather, collaborations and networking are an essential part of the business to bring the research developments into industrial application. Essential world-class scientific or industrial achievements are made, when crossing borders between the disciplines. For example, the high loading and large turnover in micro structured catalytic reactors demand for the development of new, highly active catalysts, rendering joint efforts of catalyst and micro fabrication experts superior to isolated strategies based on simple supply of commercial material. In this paper, some successful examples about such joint activities of IMM with both academia and industry will be given. Typically, laboratory-scale developments are made in scientific investigations, while such results are exploited with industry currently up to the pilot-scale level. The following chart gives an overview about the different ways of IMM's collaboration with academia and industrial partners.

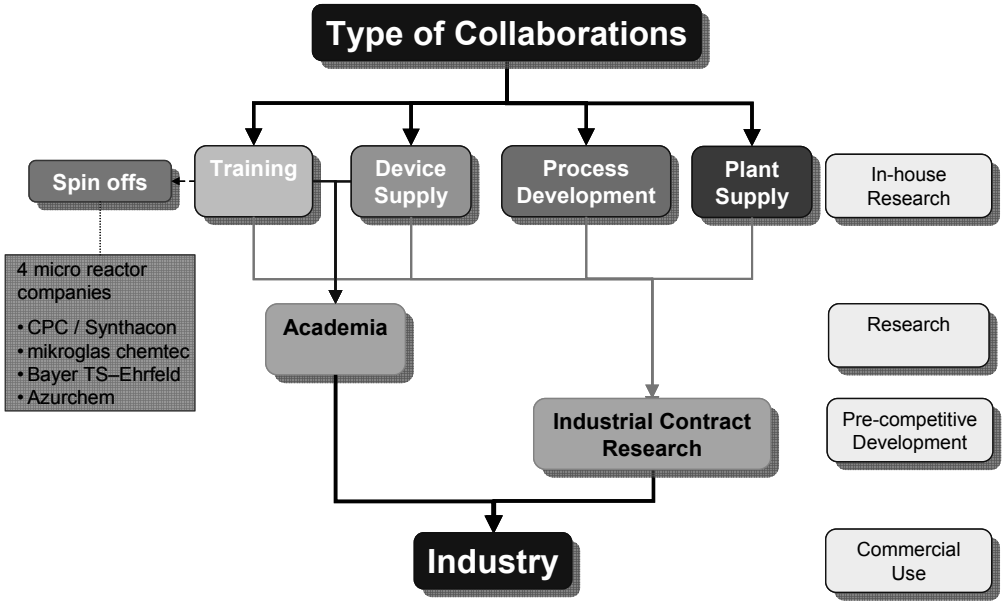


Figure 1. Types of collaborations of IMM with academia and industry

2 Collaboration with academia

2.1 Continuous micro-flow screening process - CPE/CNRS / France

IMM stands for know-how in simulation, micro device manufacturing and assembly, and chemical micro-reactor and process engineering. An R&D project of the European Community gave the chance of merging the expertises in homogeneous catalysis of the French institute CPE/CNRS (Villerbanne-Lyon) and of liquid-liquid and gas-liquid micro-reactor processing at IMM. In this way, a novel continuous micro flow screening process was developed, enabling a fast testing of libraries of substrates and catalysts for the allyl alcohol isomerization [3] and asymmetric hydrogenation of cinnamic acid esters. [1], [2]

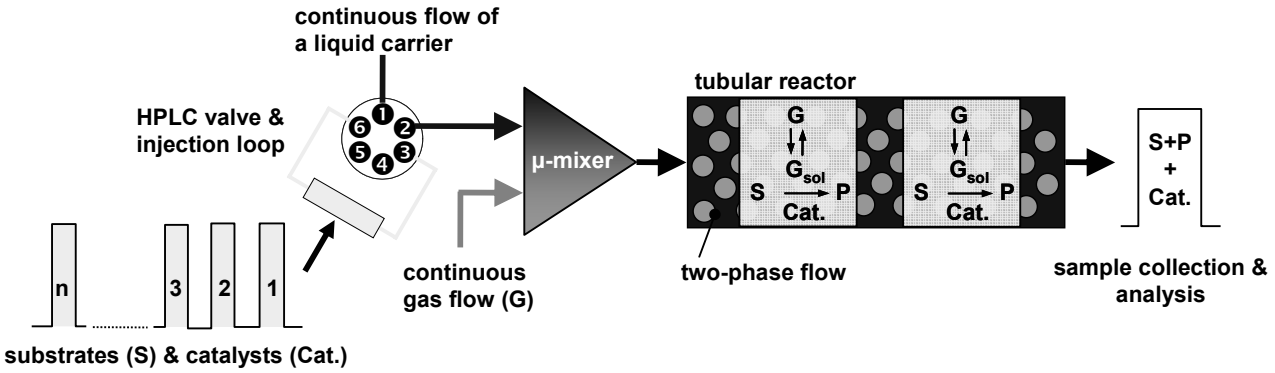


Figure 2. Micromixer tubular reactor for multi-phase transient screening

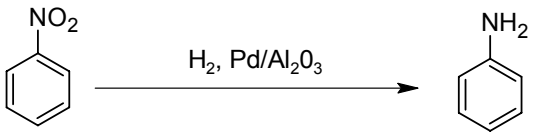
The continuous micro flow screening process consists of three steps: The introduction of a pulse containing substrate and catalyst into the continuous liquid flow, the dispersion of this pulse by the micro mixer whereas the generated two-phase flow acts like a carrier and conveys the reacting segment along the tubular reactor.
As a model reaction for gas-liquid processes the enantioselective hydrogenation of a cinnamic acid derivative was investigated. The advantages of the described process - less amount of catalyst, higher throughput testing frequency and the possibility of a complete automation – may be extracted from table 1.

Table 1. Comparison of the micro mixer-based screening set-up with mini-batch [1]

Feature	**Mini-Batch**	**Micro**
reaction volume [ml]	10	0.1
average amount of Rh/experiment [μg]	500-1000	5-20
typical amount of ligand/experiment [μmol]	10	0.1
temperature range [°C]	20-100	20-80
pressure range [bar]	1-100	1-11
residence time	>10 min	1-30
actual max. throughput testing frequency [d-1]	3	40
range of solvents	large	restricted
automation of reagents/catalyst injection	no	yes
automation of sample collection	no	yes

2.2 Nitrobenzene hydrogenation in a micro structured falling film reactor – UCL / UK

A co-operation between the University College London (UCL) and IMM brought together expertise in simulation, hydrodynamics, catalyst testing and gas-liquid processing, respectively. In this way, for the first time a gas-liquid-solid micro-reactor process, the hydrogenation of nitrobenzene over supported noble metal catalysts (Pd/Al_2O_3), was realized using a micro structured falling film reactor.



This process was chosen as model reaction, because nitro aromatics are of great importance in organic synthesis of pharmaceuticals, for instance. They are intermediates for the generation of the respective anilines by hydrogenation. [6] The hydrogenations of nitro aromatics have high intrinsic reaction rates, which however cannot be exploited by conventional reactors as they are unable to cope with the large heat releases due to the large reaction enthalpies (500 - 550 kJ/mol). [4] This demands restricted hydrogen supply thereby controlling the reaction rate. For the hydrogenation of nitrobenzene a range of preparation procedures for the palladium catalyst were investigated, such as incipient wetness, wet-impregnation, UV-decomposition of precursors and sputtering. The best performance of all catalysts investigated was found for an incipient-wetness palladium catalyst. Having initially more than 90% conversion, a 75%-conversion at selectivity of 80% was reached for long times on stream. Particular concern was given to achieve stable catalysts and how to re-activate them. [4] In addition, hydrodynamic measurements to determine the film shape were done and compared with film theory. Despite the large mass transfer coefficient which was estimated (based on the film thickness in the middle of the channels) to be within the range of 3 - 8 s^{-1}, analysis of the results indicated that the system was operating in between mass transfer and kinetic control regimes. [5]

2.3 Investigation of free and controlled styrene radical polymerization - ECPM / France

The experience of IMM in mixing with micro structured mixers and the competence of ECPM (Strasbourg) both in polymer reaction kinetics and polymer synthesis / characterization was bundled for the investigation of free and controlled (living) styrene radical polymerization. In this way improved molecular weight distributions close to the ideal values, verified both by experiment and theory, could be achieved. A numerical study investigated and compared three different types of micro mixers (used as polymerization reactors), concerning their ability to the mentioned polymerization reaction. Both the high pressure interdigital micro mixer (HPIMM) and the SuperFocus interdigital micro mixer (SFIMM) were designed by IMM and were compared with a T-junction combined with a tube reactor. Thermal and mass transfer, hydrodynamics and reaction are coupled and influence the micro reactor's geometry. Thus the system was simulated by the simultaneous solving of the related partial differential equations. It was determined, that the so-called SuperFocus interdigital micro mixer allows the best control over the polymerization regarding fast mixing, narrow residence time distribution and heat transfer to guarantee almost isothermal conditions. Also the variation of the polydispersity index with respect to the diffusion coefficient led to the SuperFocus mixer giving the best results for the range investigated. [7] To verify the simulation experimental trials were carried out. It could clearly be shown that the HPIMM micro mixer gives nearly ideal polydispersity indices for radical polymerizations near to 1.5, both being predicted and confirmed by experiments. Results of the investigations with an IMM SuperFocus mixer are not yet reported.

Table 2. Model validation - Comparison with experimental results

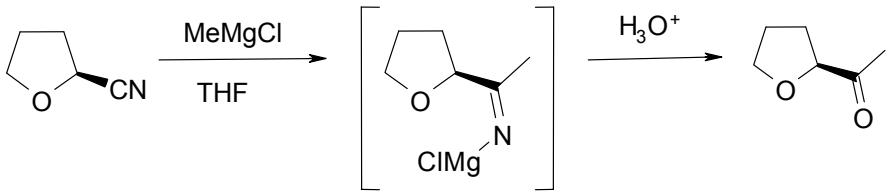
Solvent		*20 %*		*30 %*	
		Experimental	*Modeled*	*Experimental*	*Modeled*
X_M	Flask	59 %		56 %	
	T-Junction + Tube	55 %	54 %	50 %	51%
	HPIMM + Tube	56 %			
Mn	Flask	48000		38000	
	T-Junction + Tube	49000	46000	34000	32000
	HPIMM + Tube	42000		33500	
PDI	Flask	1.98		1.92	
	T-Junction + Tube	1.52	1.56	1.60	1.54
	HPIMM + Tube	1.56		1.52	

3 Contract research with chemical industry

3.1 Synthesis of (S)-2-acetyl tetrahydrofuran (ATHF) - SK Corporation / Korea

IMM has a number of different collaborations with industry. They vary from the simple supply of a micro device, assistance by scientific evaluation and training to process development in the laboratory, pilot and production scale and even the development and delivery of plants for these processes.

An example of the advantages that may result even from simple device delivery is the investigation of the synthesis of (s)-2-acetyl tetrahydrofuran (ATHF) performed by SK Corporation (Korea) using an IMM reactor. [8]



In the (S)-2-acetyl tetrahydrofuran (ATHF) synthesis, the Grignard reagent MeMgCl is very reactive and not easy to handle on a large scale. Therefore safety and hazardous problems at industrial scale may arise. There are also issues of chirality conservation. The α-hydrogen of the starting material is unstable under basic conditions. Consequently, racemization may occur. Using the micro-reactor, the optical purity of the product was increased to 98.4% as compared to 97.9% at batch level. Further, there are selectivity issues. The over-alkylation to tertiary alcohol must be avoided. The individual impurity level must be less than 0.2 %. The micro-reactor impurity was 0.18% through minimization of back mixing while the batch impurity was 1.56% (see Table 2). Accordingly, with fine thermal and flow control, the productivity and economics of this process are increased.

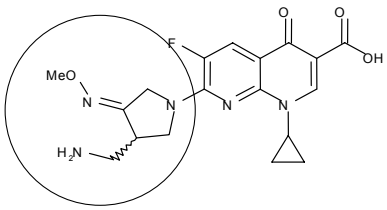
Table 3. Comparison of batch and micro reaction technology (MRT) processes for ATHF synthesis manufacture [8]

Reaction Type	Individual Impurity	Optical Purity
Batch	1.56 %	97.9 %
MRT	**0.18 %**	98.4 %

3.2 Synthesis of a pharmaceutical intermediate of quinolone antibiotics - LG Chem / Korea

LG Chem, the leading chemical company in Korea, used an IMM interdigital micro mixer for studies regarding the synthesis of intermediate to yield a quinolone antibiotic drug named Gemifloxacin (FACTIVE®). [9]

Gemifloxacin (FACTIVE®)



IMM supported LG Chem by providing training in micro reaction technology, delivery of micro-reactor tools and also by developing another process. Using this knowledge and in-house expertise, five different types of reactors, including tube reactors, static mixers and a micro structured reactor, were tested. Among these, the micro structured reactor was successfully applied to the synthesis of the pharmaceutical intermediate via a fast exothermic Boc protecting reaction step. The reaction temperature was isothermally controlled at 15°C. The heat of reaction was completely removed using the micro structured reactor. So virtually no byproducts were produced during the reaction and further purification steps were not necessary. Conversions as high as 96% could achieved. The micro-reactor operation can be compared with other reactors, however, which need to be operated at 0°C or –20°C to avoid side reactions.

3.3 Improvements of dye properties of the AZO Pigment Yellow 12 - Trust Chem / China

Developments with Trust Chem Co., Ltd., one of the biggest producers of specialty chemicals in China, were concerned with improving the azo pigment Yellow 12 synthesis. Changing such synthesis from batch to a semi-continuous process using mixing and precipitation with IMM micro structured mixers led to smaller particle sizes and narrower particle size distributions. Consequently, pigment and other particulate syntheses could be improved. In this way, finer particles with more uniform size distribution were yielded for the commercial azo pigment Yellow 12. The particles formed in the micro structured mixer had better optical properties such as glossiness or transparency at similar tinctorial power. Since the micro mixer made pigments have more intense colour, lower contents of the costly raw material in the commercial dye products can now be employed which increases the profitability of the pigment manufacture.

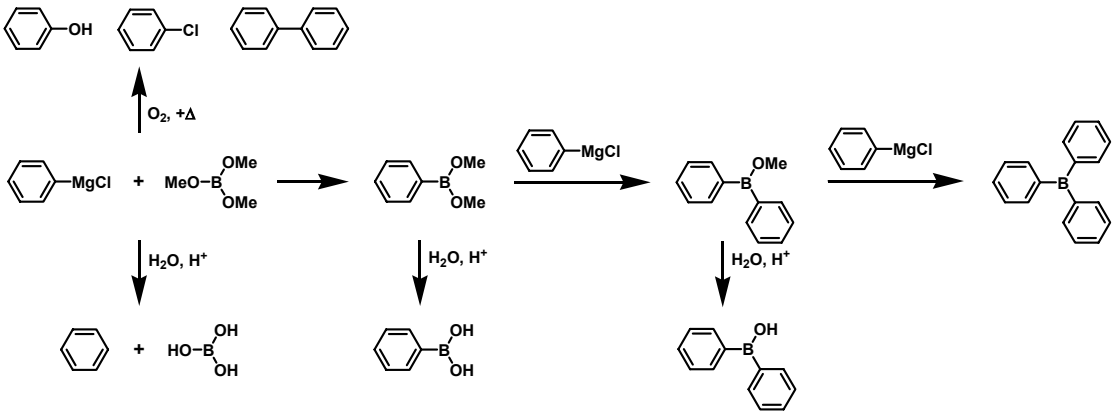
In comparison to the Yellow 12 standard
- the glossiness was increased by 73% and
- the transparency by 66%

in connection with an unchanged tinctorial power. [10]

Currently, this co-operation is continued with more demanding particle syntheses, performed by several European researchers at the industrial site in China.

3.4 Process intensification for the synthesis of phenyl boronic acid - Clariant / Germany

Clariant (Frankfurt), a leading fine- and functional-chemicals manufacturer, wanted to achieve process intensification for the synthesis of phenyl boronic acid as an intermediate for electronic materials. [11]



The previous production method required harsh cooling conditions (cryo operation) and nonetheless led to several side and consecutive products. By improving the mixing with micro structured devices the development of a better controlled process under more convenient operation conditions was expected. Using the respective synergies between Clariant and IMM, the synthesis process could be successfully changed and a pilot plant with a micro mixer could be realized.

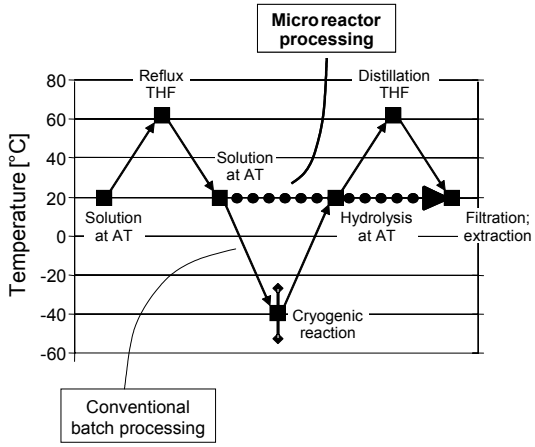


Figure 3. Temperature profile of the phenyl boronic acid synthesis along the major steps of the process flow scheme [11]

Energy savings were both given by shifting the former cryogenic process to room temperature and by achieving a highly pure crude product, thereby rendering the former energy consuming distillation step unnecessary (see Figure 3). Thus, having higher selectivity did not only affect the reaction itself but also downstream purification.

3.5 Direct synthesis of hydrogen peroxide in the explosive regime - UOP / USA

The direct synthesis of hydrogen peroxide from the elements in the explosive regime was the aim of a contract research done for UOP (Chicago), a company licensing petrochemical processes and respective catalysts.

$$H_2 + O_2 \longrightarrow H_2O_2$$

UOP's interest was to have this direct route in the framework of propylene oxide manufacture. Important were here IMM's skills in safe plant operation within the explosive regime with micro structured devices. Laboratory-scale peroxide testing at IMM used a hydrogen peroxide selective catalyst placed within a mini trickle bed reactor equipped with a micro mixer. In this way, a safe direct route to hydrogen peroxide at reduced pressure (30 bar), favorable O_2 /H_2 ratios close to 1, and high space-time yields was developed, accompanied by determination of CAPEX and OPEX costs.

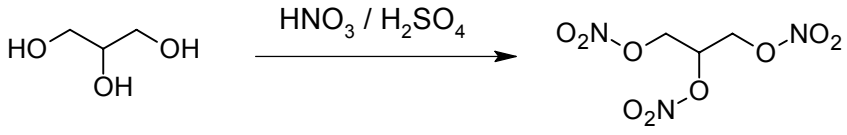
Table 4. Specifications of the direct hydrogen-peroxide micro-reactor process benchmarked

	Published	IMM-UOP Test
Pressure, bar	124	30
Temperature, °C	35	50
O_2 : H_2	6.8	3
'Space velocity', g H_2/(g_{CAT} h)	2.6	1.8
H_2O_2 concentration (max), wt%	5.2	1.7*
Yield, g H_2O_2/(g_{CAT} h)	1.5	2.0

A basic engineering was made for a plant in the range of more than 150,000 t/a. Based on micro structured mixing units embedded in traditional large-scale fixed-bed plant architecture, the new process was realized by direct contacting of hydrogen and oxygen (without inert gas) in the presence of a heterogeneous catalyst. The key to achieving a high selectivity was to have a noble metal catalyst in a partially oxidized state. Otherwise, only water was formed or no reaction took place. [12]

3.6 Continuously working nitro-glycerin production plant - HAC / China

The Chinese Class I big state-owned enterprise Xi'an Huian Chemical Industry Co., Ltd. (HAC), situated near Xi'an, is a large-scale producer of fine, specialty and bulk chemicals. The company is engaged mainly in the products cellulose and its ramification, paints and organic solvents. HAC and IMM decided to establish a long term co-operation to explore possible applications of micro reaction technology for the production of fine chemicals and specialties and signed a R&D agreement this year. [13] This co-operation started with developing a continuously working nitro-glycerin production using IMM pilot plant technique with integrated micro mixer-heat exchangers.



The plant has been installed and is currently started up [14]. The manufactured nitroglycerin will be used as medicine for acute cardiac infarction. Therefore, the product quality must be of highest grade and the plant installation tests already revealed higher selectivity and purity than given for the former batch process. The plant was found to operate safely in the initial trials and is foreseen to be fully automated later. As a second step, a plant for downstream purification, of notably larger size and complexity as the reactor plant, is going to be developed. Environmental pollution will be excluded in a follow-up project ready for

signature by advanced waste water treatment and a closed water cycle. Thus, the purification plant will have parts for washing and drying of the nitroglycerin and, in a final stage, also encompass formulation and packaging.

4 Conclusions

By means of three respectively six different examples regarding IMM's collaboration with academia and contract research with industry the results and advantages of these collaborations were demonstrated. Micro-reactor technology is a fast developing field which enters more and more industry. This process was substantially promoted by international collaborations between research groups and with industrial partners.

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