A view through novel process windows

A View Through Novel Process Windows

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Abstract
This mini-review discusses some of the recent work on Novel Process Windows by the group of Micro Flow Chemistry and Process Technology at the Eindhoven University of Technology, and their associates. Novel Process Windows consist of unconventional approaches to boost chemical production, often requiring harsh reaction conditions at short to very short time-scales. These approaches are divided into six routes: the use of high temperatures, high pressures, and high concentrations (or solvent-free), new chemical transformations, explosive conditions and process simplification and integration. Microstructured reactors, due to their inherent safety, short time-scales and the high degree of process control, are the means that make such extreme chemistry possible.

Keywords: Microreactors; Flow Chemistry; Green Chemistry; Novel Process Windows; Process Intensification

1. Introduction

Chemical industry is continuously being pushed towards more efficient production due to factors, such as, the increasing costs of natural resources and the increasing environmental restrictions placed on chemical processes through regulations.[1,2] In the recent decade, both have seen drastic enforcement, together with a growing number of production facilities opening in Asia. Accordingly, this places strong emphasis on process development, requiring more drastic improvements than can be achieved through conventional process optimization. In contrast, Novel Process Windows aim to boost chemical production through unconventional chemistry, utilizing harsh reaction conditions.[3–7] At the core of this approach is the notion that the intrinsic kinetics behind many chemical processes can be very fast, if the right conditions are applied. Since such conditions are not commonly found in today's laboratories, intrinsic kinetics are typically much lower however. This is further reduced by limitations to mass- and heat transfer, finally providing the effective kinetics. Microstructured reactors have vastly improved mass- and heat transfer, thus allowing operation under intrinsic kinetics. Furthermore, the inherent safety and the high degree of control provided by microstructured reactors removes the need for any artificial restraint on the conditions, thus making intensified intrinsic kinetics obtainable.[8–11] Novel Process Windows exploit these characteristics of microstructured reactors to reconsider chemical processes from scratch, potentially increasing performance step-change wise, i.e. several orders of magnitude increase in conversion rates.

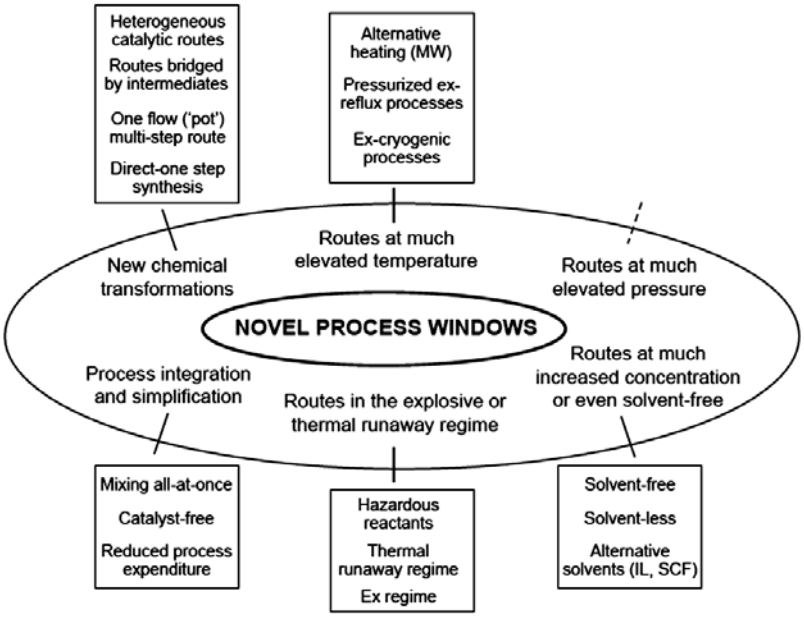


Figure 1**.** *Six pathways to Novel Process Windows proposed by Hessel (2009)*[3] *(by courtesy of Wiley-VCH)*

For the concept of Novel Process Windows as proposed by Hessel (2009)[3], six pathways were identified: routes using high temperatures, high pressures, and high concentrations (or solvent-free), new chemical transformations, explosive conditions and process simplification and integration. These six pathways are a combination of routes based on chemical intensification and those based on process design intensification, see Figure 1, and are further divided into specific approaches.

2. Chemical Intensification

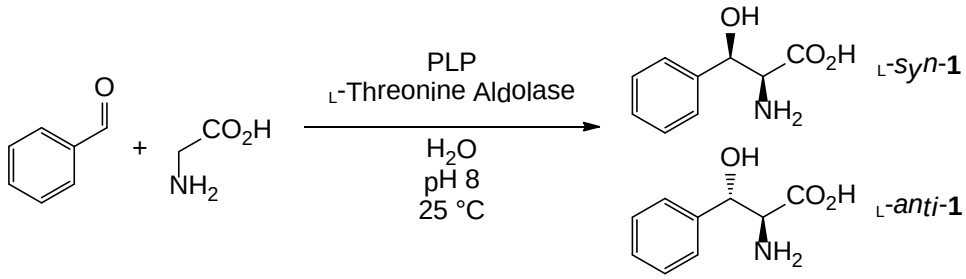
Four of the six routes to Novel Process Windows are focused on chemical intensification: new chemical transformations, routes at elevated temperature, routes at elevated pressure and routes at increased concentration. The aim of these routes is to boost reaction chemistry by operating at reaction conditions outside the range normally found in industry. New chemical transformations, when applied as an alternative to more extensive processing, are at the core of process design intensification.

2.1 New Chemical Transformations

In industry, the synthesis routes that pass the process design stage, towards an industrial process, do not have to be those that are most ideal from a chemistry perspective. For an industrial process, other contributing factors have to be considered as well, most of these related to the problems of scaling-up. Above all, safety must be sufficiently guaranteed, but also heat- and mass transfer issues must be resolved. Microstructured reactors do not suffer from any scale-up problems, relying on numbering-up or smart scale-out towards mini-flow technology instead.[12] Thus new potential applications are opened up for synthesis routes that have so far been disregarded. If this concerns not only substituting one reaction alternative by another, but replacing several conventional steps by a single one, then a completely new “direct route” is opened. This also

has major consequences for the setup of the whole plant (process design intensification); i.e. directly affecting costs and sustainability.[13–16]

Enzymes are biocatalysts that can operate under mild conditions and that provide exceptionally high selectivity. These properties translate into low energy consumption, high quality products and less down-stream processing, which explains the considerable interest for their application in industrial processing.[17,18] Unfortunately, the long-term operational stability of enzymes is limited and their homogeneous nature makes recovery a challenge.[19] Since enzymes are costly, this severely limits their application in industrial processing.[19]To overcome these drawbacks, enzymes can be immobilized in microchannels, an approach that has already shown great promise.[20–24] A crucial point is still the investigation of new supports and immobilization methods.[19] Towards this end, threonine aldolase (TA) immobilization on innovative Nanosprings[25] and commercial Eupergit CM[26] supports was investigated, see Scheme 1.[27] TA is an enzyme used for carbon-carbon bond formation of amino acids and enables the direct synthesis of enantiomers and diastereomers. The highest activity retention (89.4%) was reported by immobilization on Eupergit CM via an indirect method. In addition, immobilization on Eupergit CM also slowed the rate of TA deactivation, see Figure 2. Activity retention reported for immobilization on Nanosprings was comparatively low (13.2%) and thermal stability was not enhanced. However, unlike Eupergit CM, Nanosprings should be better suited for use in flow, as their open structure should not create a diffusion barrier. Finally, a cost analysis of a process using Nanosprings-immobilized enzymes in micro flow indicates that it would be economically viable in the case of high added-value products. The prerequisite would be that the immobilized enzyme can be reused sufficiently, up to 100 times.



Scheme 1. Synthesis of phenylserine from benzaldehyde and glycine with TA, using pyrodoxal-L-phosphate as a co-factor.

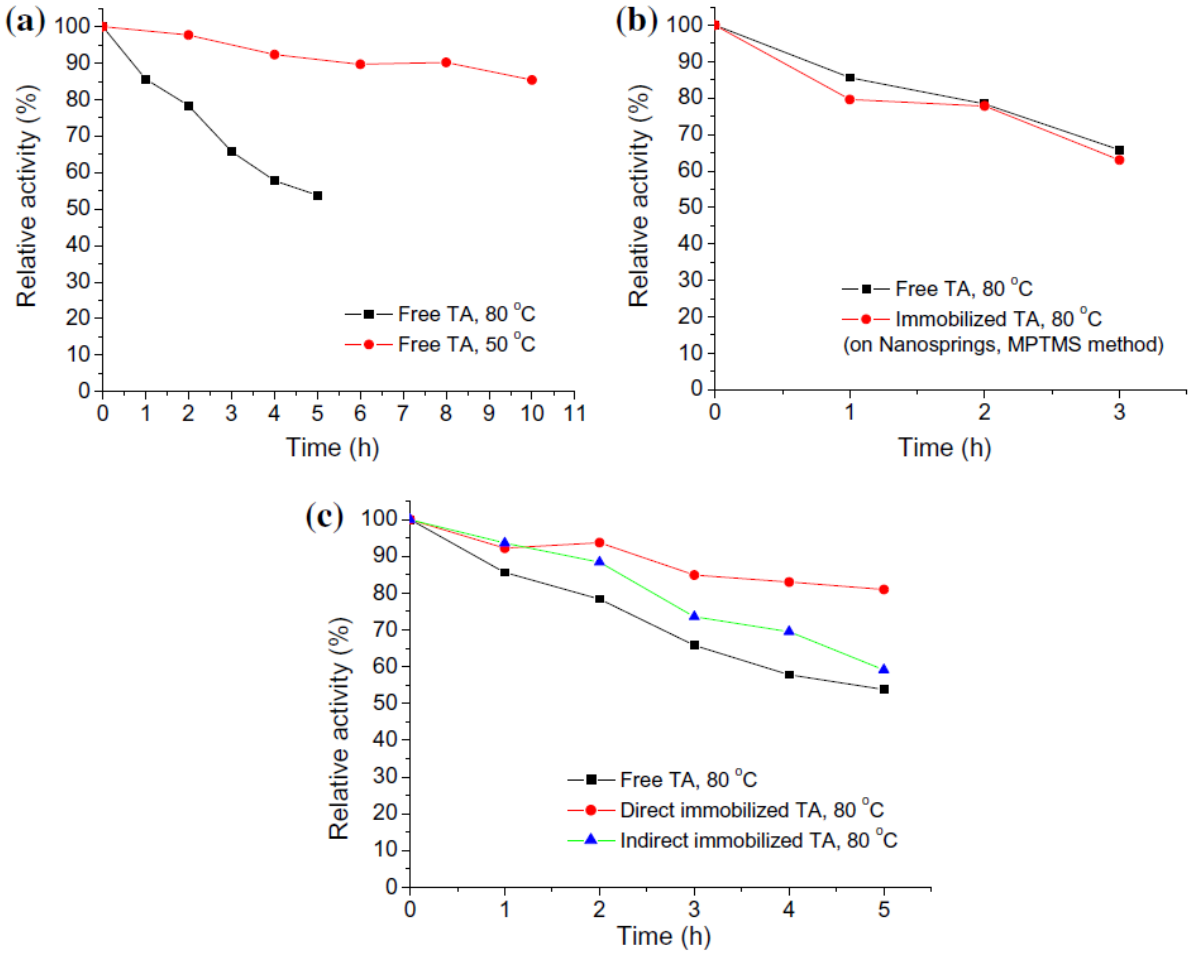


Figure 2. *Effect of support on TA thermal stability for a) free TA at 50 °C and 80 °C, b) free TA and TA immobilised on Nanosprings at 80 °C and c) free TA and TA immobilised directly (without spacer) and indirectly on Eupergit CM. Fu et al*[27]*. (by courtesy of Elsevier)*

Also investigated was the productivity of an enzyme microreactor for the transesterification of ethyl butyrate and 1-butanol to butyl butyrate with Novozym 435.[28] In comparison with the same reaction in batch, the enzyme microreactor provided a higher yield of butyl butyrate in the same reaction time, see Figure 3. In microflow, more than twice the amount of enzyme could be used, which may account for the increased reaction rate. Using a similar amount of enzymes in batch was not possible, due to the enzymes sticking to the wall of the reactor vessel.

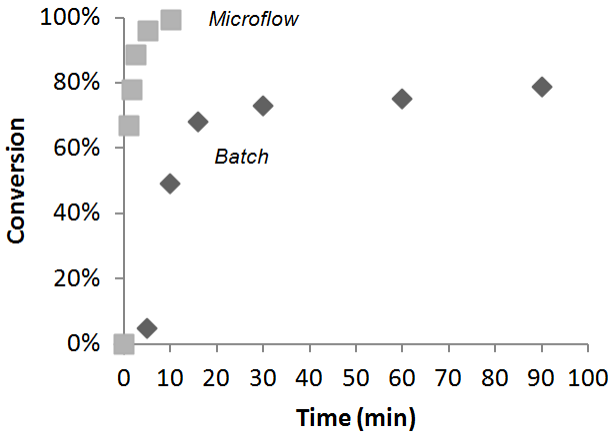
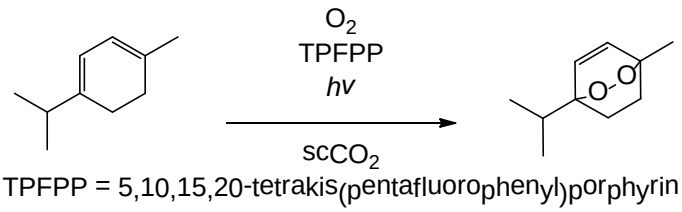


Figure 3. *Productivity of an enzyme microreactor versus a batch reactor*[28]

2.2 High Concentration / Tailored Solvents

Solvents in chemical industry represent 80 to 90% of the total mass used and contribute considerably to the energy consumption and waste that is generated in chemical processes.[29,30] Reducing or eliminating the use of solvents would therefore be a large step towards decreasing this waste generation. However, the use of solvents serves several important purposes. Firstly, diluting the reaction mixture can mitigate temperature fluctuations when the heat produced in the reaction cannot be removed quickly enough otherwise. Secondly, the use of a solvent is required for reactions involving solid reagents and products that could otherwise not be processed. Finally, solvents also affect the course of the reaction directly by influencing the rate of the reaction and the selectivity, primarily through the dielectric constant (solvent polarity). In a microreactor, the excellent heat transfer would eliminate the need for a solvent to dilute the reaction's heat production. Microreactors are also beneficial when operating at the elevated temperatures required for the solid reagents and products to become liquid. New tailored, innovative solvents such as ionic liquids, supercritical fluids and fluorous solvents offer many new possibilities for enhancing the reaction environment, especially when combined with the process control provided by micro flow systems. An examples is the use of reactive ionic liquids in the Kolbe-Schmitt synthesis[31]. When a capillary reactor with microwave heating was combined with reactive ionic liquids, a record yield of 59% (180 °C, 35 bar, 0.17 L/h, 130 s) was attained.[32] Supercritical CO_2 ($scCO_2$) was used by Poliakoff, George et al. in the photo-catalytic oxidation with singlet O_2 in microflow, see Scheme 2.[33,34] In this process, the singlet oxygen is stabilized by the $scCO_2$, enhancing the rate of reaction.



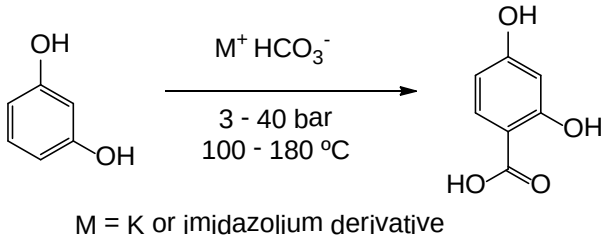
TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin

Scheme 2. *Photo-oxidation of α-terpinene to ascaridole in $scCO_2$*

2.3 High Temperature

The relationship between temperature and kinetics is described by the Arrhenius equation, which shows us that an increase in temperature will lead to an increase in the reaction rate constant. At a higher temperature, thermodynamic equilibrium will thus be reached faster. In practice however, the operating temperature is quite often lowered due to some process restriction. Higher temperatures often require the operation of a pressurized system, which limits the possibilities with typical glass-based laboratory equipment. Another reason for operating at a lower temperature is to improve process control. For exotic reactions, the high reaction rate may provide more heat production than the system can deal with and cause temperature variations, leading to the formation of undesired by-products. Increased control over the process may also be required from a safety perspective. All such limitations are overcome by using a microstructured reactor, which has no issues with the increased pressure necessary to raise the boiling point and has excellent mass- and heat transfer characteristics. For processes that already operate at high temperatures, the use of a microstructured reactor can further simplify and improve the process.

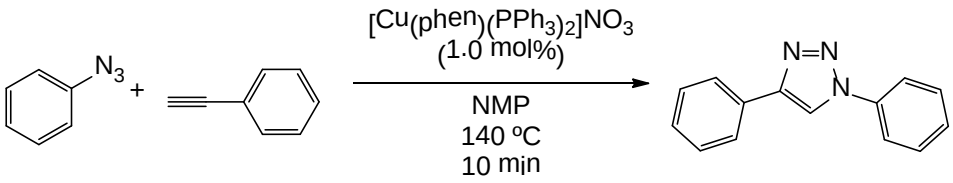
To our best knowledge, the first reaction to be carried out in a capillary reactor under superheated conditions was the Kolbe-Schmitt synthesis of 2,4-dihydroxybenzoic acid from resorcinol, see Scheme 3.[31,35,36] In comparison with a batch reaction carried out in a flask, the space-time yield in a capillary reactor was increased by a factor of 1000. This process has been combined with the use of reactive ionic liquids for solvent-free operation, which could further improve the space-time yield of the capillary reactor.[31] In an attempt to improve on this by increasing the heating rate, the Kolbe-Schmitt synthesis in a capillary reactor was successfully combined with microwave heating.[32] Due to the improved heating a yield of 52% (at 160 °C, 8 bar, 1 L/h, 90 s)) was achieved, 5% higher than with conventional heating using an oil bath (at 140 °C, 40 bar, 84 mL/h, 390s).



Scheme 3. *High temperature Kolbe-Schmitt synthesis in a microreactor achieved by microwave heating (Hessel et al.)*[32]

The Cu(I)-catalyzed azide-alkyne cycloaddition reaction is a well known example of Click chemistry, which is of importance to the pharmaceutical industry.[37] However, the use of azides in this reaction poses an explosion hazard. Such a risk can be greatly diminished by performing the reaction in microflow[38–44], yet it has been shown by Kappe et al. that leaching of the immobilized Cu(I) catalyst arises as a new problem.[44] To circumvent this problem, a homogeneous $[Cu(phen)(PPh_3)_2]NO_3$ catalyst was used in combination with an in-line extraction process, see Scheme 4.[45] At a reaction temperature of 180 °C, a 92% yield was obtained after 10 min, which exceeded the productivity of a similar reaction using a copper tube, see Figure 4. At higher temperature the yield was observed to decline again. Additionally, the high activity of the homogeneous Cu(I) catalyst meant that only a small amount of catalyst was required. By in-line

extraction with a copper scavenger the Cu(I) concentration could be reduced to only 14 ppm, which is below the concentration limit that has been set for active pharmaceutical ingredients.[45]



Scheme 4. *Azide-alkyne cycloaddition in microflow using a homogeneous Cu(I) catalyst*

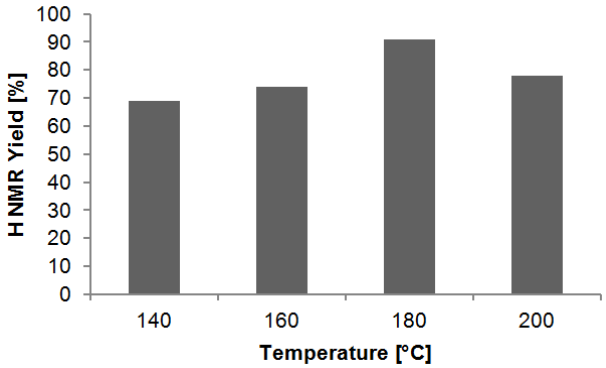


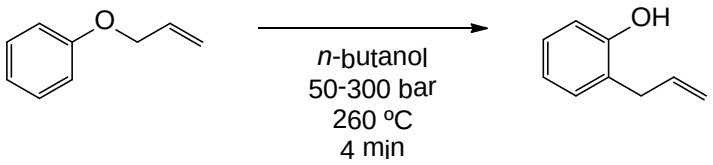
Figure 4. *Yield versus temperature for azide-alkyne cycloaddition in microflow using a homogeneous Cu(I) catalyst*

2.4 High Pressure

Another approach to chemical intensification is the application of high pressures. For reactions that undergo a reduction in volume, the compression of the reaction mixture will lead to an increase in the rate of reaction.[46] A high degree of compression also affects the energy levels of electrons and, as a result, will influence the selectivity of a reaction.[47] Furthermore, high pressure can reduce intermolecular distances of liquids and solids by half, shifting selectivity towards reactions that require the least amount of atomic and molecular displacement.[48,49] Finally, pressure affects a number of properties such as solubility, viscosity and the dielectric constant, effects that can all be exploited to enhance chemistry.[50,51] Unfortunately, for safety reasons the use of high pressure in industrial processes is usually limited. Large pressurized volumes equal a large amount of potential energy that will be released in case of an accident. In a microreactor, such is not the case. The small internal volume of the microreactor results in a limited amount of potential energy, which means less risk and reduced stress on the reactor. Recently, this process was applied in a microreactor for the first time.[52]

At elevated temperature (>200 °C) and atmospheric pressure, the Claisen rearrangement typically requires several hours to reach full conversion.[53] Previously it has been shown by that at high pressure and further increased temperature, conditions made possible in a microreactor, the reaction time can be reduced to several minutes.[54–56] The application high pressures in the Claisen rearrangement was further investigated by Hessel *et al.*, see Scheme 5.[57] At a pressure from 50 to 300 bar, the yield for the Claisen rearrangement was enhanced from 50% to 67%; an increase of 3.4% yield every 50 bar. In addition it was observed that the reaction is enhanced by the use of

protic solvents, probably due to the catalyzing effect of hydrogen bonding. As discussed previously, the use of solvents above their boiling point requires high pressure, another point in favor of micro flow systems. Although the Claisen rearrangement was investigated up to 300 bar, commonly even higher pressure is required; from 1-10 kbar.[58]



Scheme 5. *Claisen rearrangement of an allyl phenyl ether using high temperature and pressure (Hessel et al.)*[57]

3. Process Design Intensification

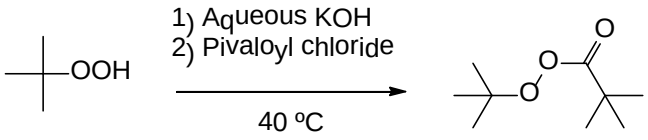
The second category of Novel Process Windows focuses on process design intensification: routes in the explosive and thermal runaway regime and process simplification and integration. The aim of these routes is to reconsider existing industrial processes in the light of advances through Novel Process Windows and flow-based transport intensification. Although such process design intensification could provide step-change improvements, the design focus is typically on individual units due the lack of standard modules, the focus on reaction optimization, the fact that components cannot simply be plugged into a plant and the rarity of systems that allow an integrated design.[59]

3.1 Explosive and Thermal Runaway Regime

Without sufficient control over a process, accidents are guaranteed to occur. Therefore, chemical processes involving hazardous chemicals are designed to operate outside of the explosive- or thermal runaway regime. A very effectively way of ensuring these conditions is by restricting the concentration of the hazardous reagent, typically by slowly adding the reagent over a period of time. Unfortunately, operating at a low reagent concentration will also limit the reaction kinetics, often lowering the effective reaction rate and severely hampering the use of the reagent concentration for influencing selectivity. The key to this issue lies in the fact that the hazard is not merely determined by the concentration of the hazardous reagent, but also depends on the hold-up. A process that involves only small amounts of the reaction mixture could safely operate at reagent concentrations well in the explosive- or thermal runaway regime. In case of an explosive reaction or thermal runaway, only a limited amount of energy can be released. More importantly however, at the scale of a microreactor, kinetic quenching of the runaway reaction mechanism occurs, thus ensuring inherent safety.[10] Microreactors, given their small internal volume, are therefore ideally suited for such an approach. The excellent heat transfer characteristics of a microreactor will further prevent conditions that would lead to an explosion or thermal runaway.

The synthesis of organic peroxides is a challenging process due to their thermal instability and the associated risk of explosion.[60–62] Illg *et al.* demonstrated the successful application of an orifice microreactor for the continuous flow synthesis of *tert*-butyl peroxypivalate, see Figure 5.[63] The production of *tert*-butyl peroxypivalate is a two-step process, in which the second step is the most challenging.[64] This step involves a biphasic reaction between reactants that are both thermally

unstable and corrosive. The industrial batch process, which has poor mass- and heat transfer, is not ideal for such a reaction and has a space-time yield of only 190 L^{-1} h^{-1}. In comparison, a space-time yield of 420,000 g L^{-1} h^{-1} was achieved at 40 °C in a 9 orifice microreactor. By serial placement of the orifices, the onset of mass-transfer limitations through droplet coalescence can be overcome. When the number of orifices is increased beyond 9, a further increase in yield is observed, but this also reduces heat transfer efficiency, thereby causing undesired side reactions.



Scheme 6. *Tert-butyl peroxypivalate synthesis in a microreactor (Illg et al.)*[63]

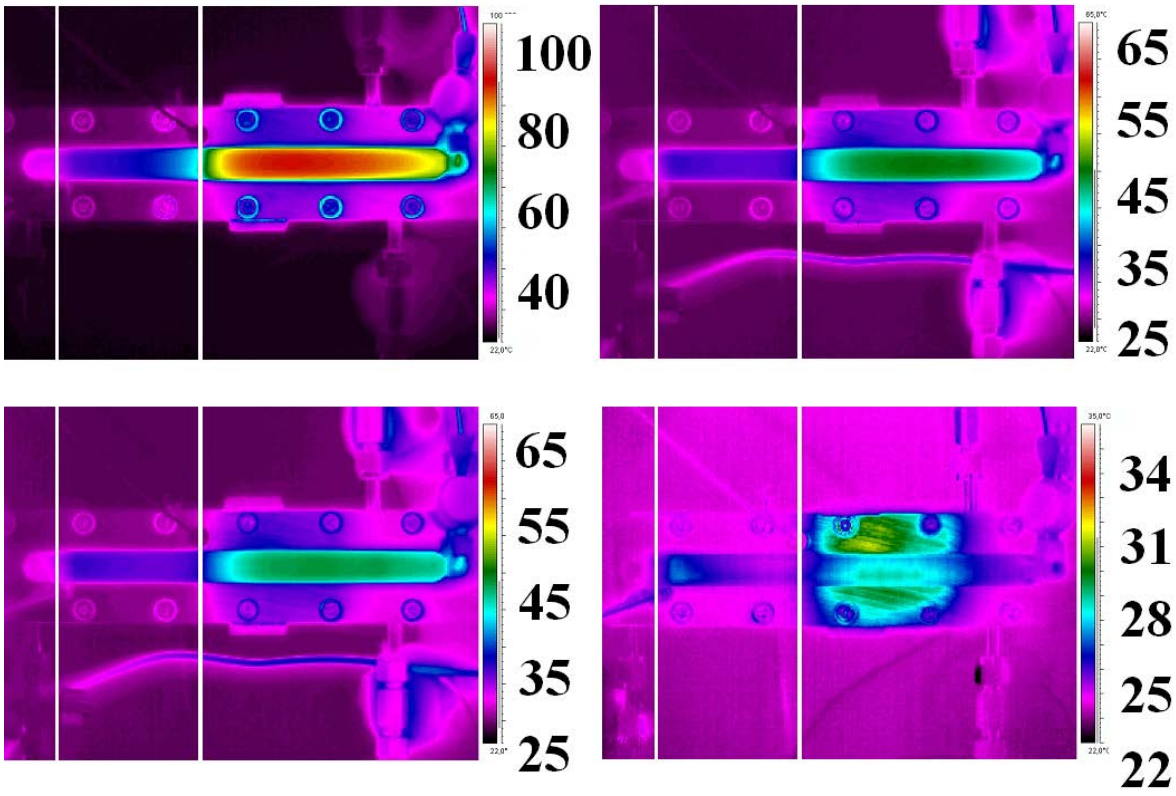


Figure 5. *IR images of the microreactor during ter-butyl peroxypivalate synthesis, showing the microreactor temperature in ºC for a cooling water flow of 0 mL/min (top left), 21 mL/min (top right), 40 mL/min (bottom left) and 9 L/min (bottom right).*

3.2 Process Simplification and Integration

To meet the demands that are placed on chemical industry by both society and the environment requires more than improving the chemistry and the chemical reactor; it requires innovation that spans the entire production process.[65] Traditionally, process improvement is achieved by process optimization, but this approach can never surpass the maximum efficiency of the individual process steps. Process simplification and integration instead aims to respectively reduce and combine these individual steps. New synthesis routes provided by Novel Process Windows can lead to a simpler

process design, eliminating the inefficiency of more elaborate routes. Smart integration of individual process steps reduces the number of unit operations, further improving efficiency.

Adipic acid is an important intermediate product that is used for the production of Nylon 6,6 and polyesters.[66] In industry, adipic acid is typically produced from cyclohexane in a two-step process, but unfortunately this process suffers from several serious drawbacks.[67] In the first step of the process, cyclohexane is converted by air oxidation to yield a mixture of cyclohexanone and cyclohexanol (the so-called KA-oil). For this reaction step, a high selectivity (85-90%) can only be achieved by operating at a very low conversion (4-8%). Consequently, a high amount of unconverted cyclohexane needs to be recycled, requiring the operation of large energy intensive distillation units. In the second step, oxidation of the cyclohexanone/cycohexanol-mixture with concentrated (50-60%) nitric acid finally gives the adipic acid product in a 92-96% yield. Due to its corrosiveness, the handling of such large amounts of nitric acid presents a serious problem. In addition, large quantities of the nitric acid is oxidized to N_2O and NO_x and released into the atmosphere. N_2O is a greenhouse gas for which 5-8% of global emissions can be attributed to adipic acid production.[68]

An alternative route to adipic acid is the direct oxidation of cyclohexene over Na_2WO_2 by 30% H_2O_2, using $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ as a phase transfer catalyst.[69] This reaction has a high yield (93%), with only water as a byproduct, and does not require any solvent or the use of halogens. The issues with this route are the risks associated with the use of H_2O_2 and the limitations to mass transfer due to the biphasic system, but such issues can be overcome by the use of a microreactor. Also, it should be mentioned the production of cyclohexene, by dehydrogenation of cyclohexane, is not yet an established process.

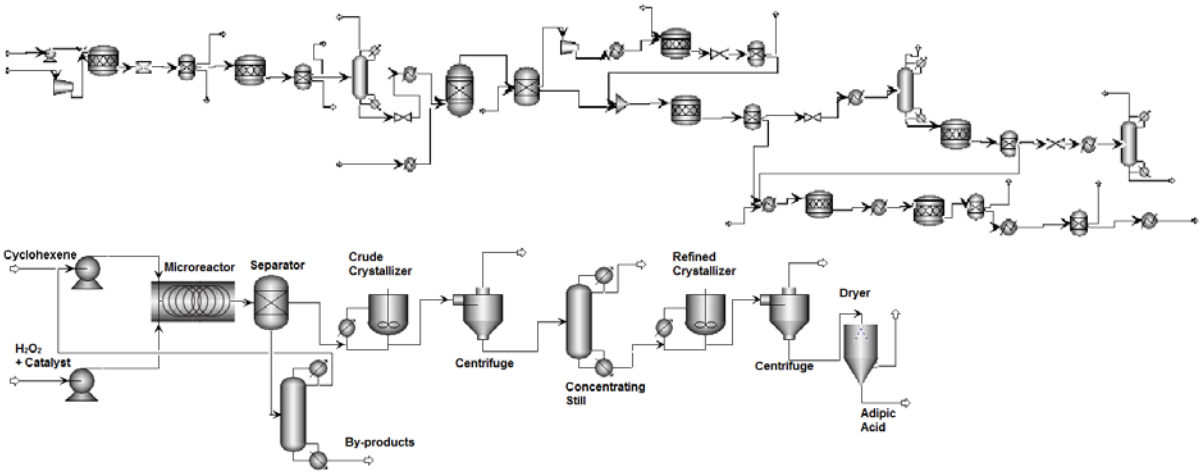


Figure 6. *Comparison of flow routes for the adipic acid process; industrial 2-step process (top) and direct oxidation process (bottom) (Hessel et al.)*[70] *(by courtesy of Wiley-VCH)*

To investigate the direct oxidation route in flow from the perspective of process-design intensification, a comparison of the direct oxidation and the industrial 2-step process was made by doing process simulations.[70,71] In Figure 6 it is shown that adipic acid production through the direct oxidation of cyclohexene can be accomplished with far less unit operations than the current industrial 2-step process. Then, equipment cost estimation was done for the two process alternatives. It was found that total equipment cost for the direct oxidation process is greatly reduced, as can be seen in Figure 7. When share of costs was considered (right), it was seen that the share of the total costs of reactor is 10% in 2-step process compared to 40% in the direct process

due to the higher cost of more advanced flow reactor. Furthermore, energy consumption analysis was carried out. Since the energy intensive separation units are eliminated or simplified in the direct oxidation of cyclohexene, the energy requirement is reduced as well (Figure 8).

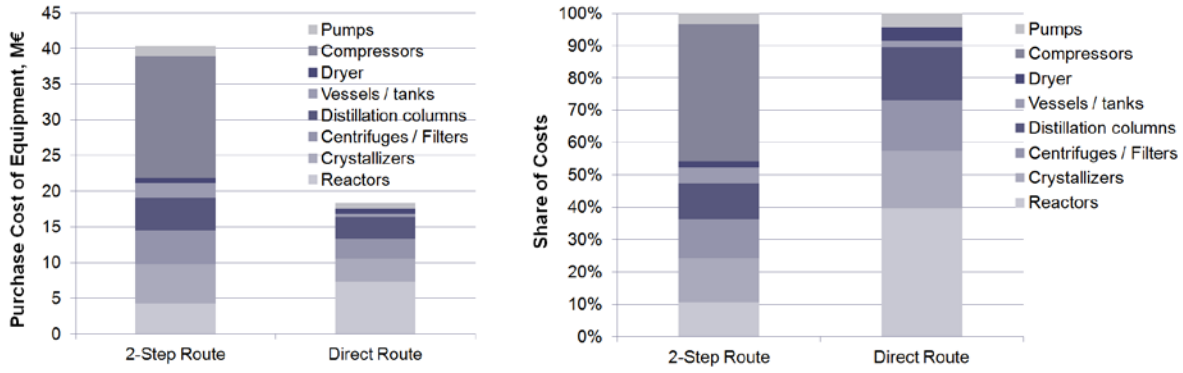


Figure 7. *Comparison of equipment costs (left) and share of costs (right) for the 2-step process and the direct oxidation process*[71]

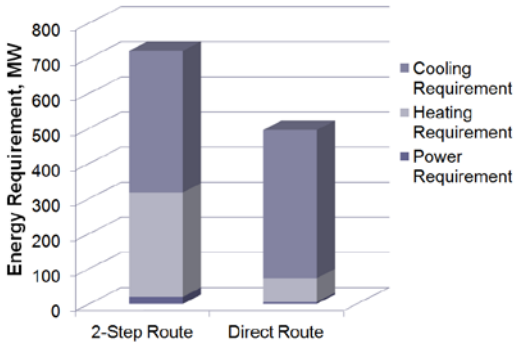


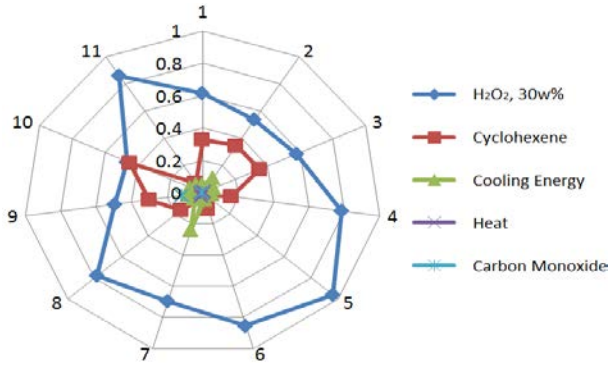
Figure 8. *Energy consumption for the 2-step process and the direct oxidation process*[71]

4. Holistic Evaluation

Novel Process Windows aim to completely redesign existing chemical processes. Thus, the successful application of Novel Process Windows depends on many critical aspects, such as reaction chemistry, catalyst performance and stability, reactor design and down-stream processing, economical feasibility and environmental impact. As this myriad of combinations goes much beyond normal process optimization, bringing these aspects together requires a holistic evaluation of the process, preferably done before the investigation, starting with an ex-ante analysis of all possible alternatives. The methodology for this process analysis was developed for Novel Process Windows by Hessel.[3]

The total environmental impact of the previously mentioned direct oxidation process was investigated with a Life Cycle Assessment (LCA), which looks at the environmental impact over different categories. This revealed, as shown in Figure 9, that H_2O_2 had the largest negative impact on the environment by far, a result of the less sustainable production process for this reagent. Therefore, for a full cradle-to-grave assessment, the production of H_2O_2 via the anthraquinone process should also be included. Further analysis is still in progress and is aimed at a comparison of

the direct oxidation in flow with the 2-step industrial process. This should also include a correction for the fact that cyclohexene production is not an established process.



1. AP: acidification potential
2. GWP 20a: global warming in 20 years
3. EP: Eutrophication potential
4. FAETP 20a: freshwater aquatic ecotoxicity in 20 years
5. HTP 20a: human toxicity in 20 years
6. Land Use
7. Malodours Air
8. MAETP 20a: marine aquatic ecotoxicity in 20 years
9. High NOx POCP : photochemical oxidant creation
10. Depletion of abiotic resources
11. TAETP 20a: terrestrial ecotoxicity in 20 years

Figure 9. *LCA result of direct oxidation process*[71]

As a representative example of a holistic approach, an analysis was performed on the development of a continuous flow process for glucose oxidation, featuring an entirely new class of enzymatic microreactors (see also chapter 1).[72] The challenge in the utilization of glucose as a chemical feedstock is the oxidation of glucose, typically performed in batch by microbial fermentation.[73] Although the used microorganisms are cheap, their performance leaves to be desired; low activity, large amounts of by-products and waste water, high oxygen consumption and the need for a sterile environment.[72] A holistic evaluation on soybean-oil processes was previously done by Kralisch et al.[59] For the oxidation of glucose, alternative processes are based on noble metal catalysts or isolated enzymes, which each have their own challenges. Noble metals, while cheap and easily recovered, require the use of 99% pure glucose, are vulnerable to deactivation and have a low selectivity.[74–76] Enzymes can be used with commercial grade glucose and have both a high selectivity and activity, but are expensive, difficult to recover and their thermal stability is low.[77] The use of noble metal catalysts in a falling film microreactor was predicted as the best option, with a productivity increase by three orders of magnitude over the conventional batch slurry reactor. While enzymes remain interesting, their use will require further investigation to enhance their performance, as outlined in the paper by Fu et al.[27]

5. Conclusion

The field of Novel Process Windows saw its official inception in 2009 and, as a result of numerous research efforts, has since then progressed considerably. This min-review provides a clear and compact introduction into the field of Novel Process Windows and the work done in this field, exemplarily mirrored by the clustered research provided by an ERC Advanced Grant, by the group of Micro Flow Chemistry and Process Technology at the Eindhoven University of Technology, and their associates. The obtained results clearly prove the worth of Novel Process Windows, by realizing higher yields, lower reaction times, higher productivity, new direct routes, less waste (from solvents), improved process control and safety, and thus reducing operating costs and increasing sustainability.

Novel Process Windows are divided into six pathways that serve to focus research efforts. Yet it is clear from the presented work that these pathways are intrinsically connected. Advancements in

one direction may open up new possibilities for other pathways as well. It was shown that through a holistic approach, the total impact of Novel Process Windows on critical aspects of a process can be assessed and monitored, thus providing a means for directing the research.

6. Outlook

6.1 Extension of the given concept

Finally, what will be needed is "fluids structuring" and good catalysts.[78] This will be the focus of the coming work of Stouten on hydroformylation in $scCO_2$, see Figure 10. The compartmenting of reaction steps and ingredients provides enhanced control over the reaction and, in addition, eliminates the need for a separation unit, thus making further intensification possible. This follows the line of focusing on the microreactor's particular strength for fluidic structuring, as stated by Löwe et al.: "A lot of efforts are needed to focus on the essential, to overcome mass- and heat transfer restrictions by pre-structurization and pre-heating of the fluids into micro parts before combining them for reaction."[79] The concept was inspired by the work of Riisager et al. on Supported Ionic Liquid Phase (SILP) catalysts[80] and the development of slippery liquid infused porous coatings (SLIPS) by Wong et al.[81].

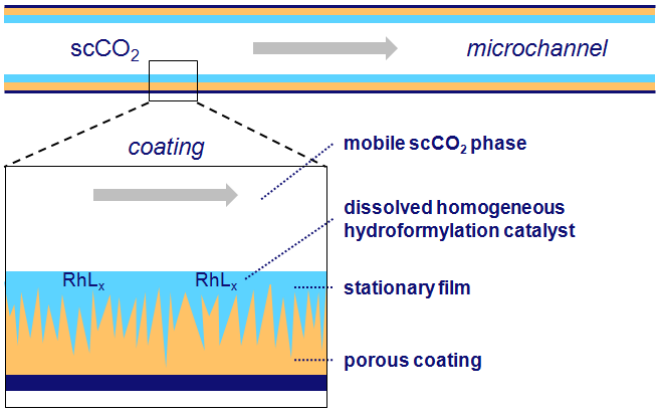


Figure 10. *Flow structuring in microflow for the hydroformylation reaction in supercritical carbon dioxide, using a supported film phase catalyst*

6.2 Flow Chemistry in Australia

Over the last three years, Australia has made its first contribution to the field of flow chemistry, with 16 publications out of about 500 worldwide. Yet this is clearly a first anchoring, given that in total, also about 2800 papers on microreactors were released.[79] The good news is that the majority of these publications featured current and future cutting-edge topics in flow chemistry; photo chemistry, monolithic catalyst supports, nanoparticle synthesis and polymer chemistry, see Table 1. The first of these offers an alternative way of energy provision and the second is seen as a key aspect for new chemical transformations, as given above. Thus, a specific impact is given and the prospects for future contributions from Australia on flow chemistry and Novel Process Windows look promising.

Table 1. *Australian publications on flow chemistry*

Flow topic	Publications
Photo chemistry	5
Organic chemistry	3
Nanoparticle synthesis	2
Monolithic catalyst supports	2
Microfluidics	2
C-C bond forming	1
Polymer chemistry	1

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