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Microreactor Technology

Intelligent Microflow: Development of Self-Optimizing Reaction Systems**

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Chemical synthesis methods are undergoing a period of rapid change. The introduction of general platforms to perform reactions under continuous-flow conditions rather than in batch mode has led to improvements in safety and sustainability. Microreactor technology offers many advantages over classical approaches through the miniaturization of structural features down to the micrometer regime. Many reactions can benefit from the physical properties of microreactors, such as short diffusion distances, improved mass and heat transfer as a result of large surface-to-volume ratios, and regular flow profiles leading to improved yields, increased selectivities, and better reproducibility. Strict control over thermal and concentration gradients within the microreactor can result in new methods for efficient chemical transformations with high space–time yields. Substrates and reagents can be mixed under highly controlled conditions leading to improved protocols and can enable novel and diverse applications.[1]

The improvement and optimization of chemical reactions and processes have always been important aspects of research. Unoptimized reactions are expensive and require extensive efforts in purification and the removal of by-products. When a reaction is optimized such that a by-product becomes a major product, a novel reaction may be discovered. Even small increases in yield or selectivity help to save money and resources, especially in a production environment. Because of the limitations of batch chemistry, usually only a small set of reaction conditions is investigated. For this reason it cannot be ensured that the global optimum for a reaction is found by monodimensional optimization (optimization of only one reaction parameter, then keeping this optimized value and changing a second one). This is illustrated in Figure 1 by an example described by Yoshida and co-workers. In the contour plot the yield of **2** following lithiation and protonation of **1** is dependent on temperature and reaction time (numbers in the plot correspond to yields). A first optimization of the temperature at $t^R = 10^{-2}$ s would result in $T = -27\,^\circ\mathrm{C}$ (①) as the optimal reaction, and an increase in reaction time would only lower the yield. Reaction conditions leading to higher yields (②) would not be found.[2]

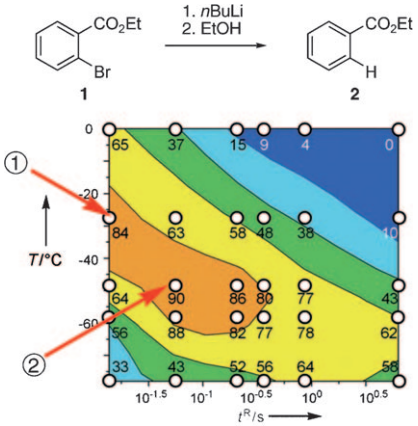

Figure 1. Yields of the lithiation–protonation of **1** as a contour plot with varying reaction time and reaction temperature.

Various factors should be considered when reactions are optimized. Organic reactions are usually influenced by changes in the concentrations of substrates and reagents, the reaction time, and the temperature. In batch chemistry, optimization usually is a time- and material-consuming exercise but improvements have been made. Robotic systems for faster batch chemistry have been developed.[3] Buchwald, Jensen, and co-workers have now addressed the disadvantages of batch optimization by using microreactor technology.[4] In microflow chemistry, reaction parameters such as concentration and reaction time are controlled by the flow rates of solvents and solutions. If a reaction could be analyzed directly (online) after a defined reaction time, instant feedback and evaluation of the reaction conditions with respect to a given output parameter (yield, selectivity) would be possible. A schematic setup is shown in Figure 2.

The first online analysis and even on-chip methods for the determination of yields and selectivities have been reported.[5] In other areas of chemistry, related approaches have been used to control reactions although in different timeframes. In the quest to steer more complex systems, an adaptive optimal femtosecond laser pulse can be used to "teach" a light beam

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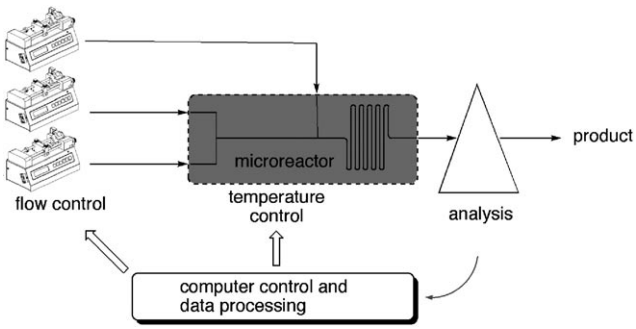
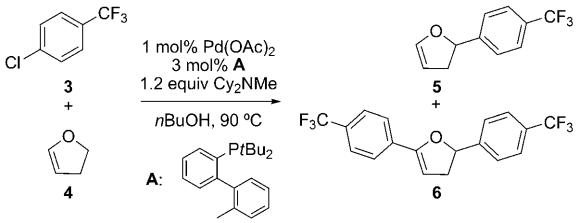


Figure 2. Microflow system with intelligent computer control.

in order to optimize the yield of a specific product.[6] For the synthesis of CdSe nanoparticles the fluorescent spectra of the product has been used to influence reaction conditions.[7]

Jensen et al. used online HPLC analysis to determine the yields of the Heck reaction shown in Scheme 1. The results of the analysis were then used to directly influence the reaction



Scheme 1. Heck reaction used for the self-optimization protocol. Cy = cyclohexyl.

parameters (concentration, reaction time, temperature) without any additional input. Different algorithms such as evolutionary (genetic) and stochastic algorithms can be used for the automated optimization. Jensen et al. selected the Nelder-Mead (simplex-based) search algorithm, which requires no initial reaction or gradient information.[8] Certain boundaries were introduced to prevent large excesses of substrates or reagents. Heck reactions have already been performed in microreactors under homogeneous as well as heterogeneous reaction conditions, although these investigations were limited to the more reactive aryl iodides and aryl bromides.[9] The reaction shown in Scheme 1 was selected as the product **5** is known to react readily with excess aryl chloride to give product **6**.[10] Therefore, the yield of **5** is highly dependent on the substrate concentrations.

The advantage of microfluidic systems in rapidly measuring and influencing parameters made it possible to quickly determine multiple points in the multidimensional "reaction space", where the dimensions correspond to concentration and reaction time. In the experiments the temperature was not varied and remained constant at 90 °C. The automated system maximized the yields of **5** by varying the ratio of **3**/**4** and the residence time. Under the optimized conditions (ratio **3**/**4** = 5:1, reaction time: 5.5 min) **5** was obtained in a yield of 82 %; these conditions were then transferred to a 50-fold larger flow reactor. Further experimentation resulting in similar yields confirmed the successful transfer to the larger system. Offline analysis has already been used for rapid optimization in microreactors and the reaction conditions have been transferred successfully to larger scale reactions.[11]

The combination of microreactors and online analysis can provide information very rapidly not only on the concentration of products, but also on the regiochemical and (with appropriate compounds) even the stereochemical outcome of a reaction when pseudo-enantiomers are analyzed.[12] The integration of automation into microreactor systems is envisaged to be suitable for a wide range of reactions. The quick and efficient optimization of multiple reaction parameters using microreactors requires only small amounts of solvents and chemicals and, as these conditions scale directly to larger systems, should also reduce the time needed to develop new processes.

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