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Novel Innovation Systems for a Cellular Approach to Continuous Process Chemistry from Discovery to Market

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Abstract:

Continuous processing of liquid/liquid synthesis and microreaction technology are shown to reduce the cost of process development and manufacturing of active pharmaceutical ingredients and other functional molecules on a commercial scale. Combinatorial synthesis systems for continuous chemistry are introduced, and their applications are described. Reactions within these systems scale seamlessly in standardized commercial continuous synthesis equipment allowing rapid access to kilogram quantities of advanced intermediates. Chemical and process development within such systems are illustrated by a case study of a continuous multistep process. Additionally, another case study shows the benefit of microreaction technology in the manufacture of high value added functional chemicals.

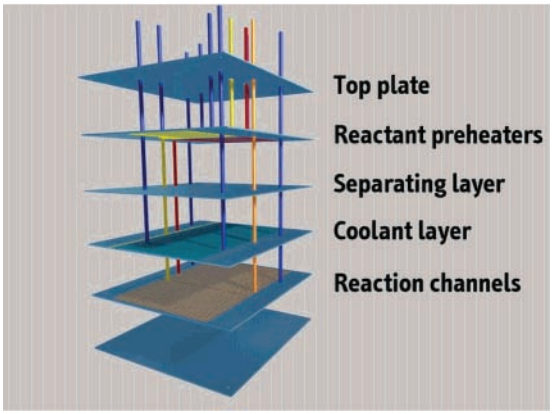

Figure 1. **A microreactor integrating thermal conditioning, mixing, and thermal reaction control into one module.**

1. Introduction

Recent technological innovation in the field of microreaction technology or process intensification has combined with an economically driven search for the benefit of continuous chemical processing in the field of high value added compounds, in particular active pharmaceutical ingredients (API). Continuous processing predominates in many industries, where it is perceived to generate lower operating cost and enhanced process safety.

Moreover there is now general consensus that continuous processes are operationally more stable and reproducible and hence yield more consistent product quality. However, in chemicals manufacturing, continuous processes have mostly been applied in dedicated production facilities. In such a highly inflexible setup capital investment is comparatively large. Further, a significant adaptation to varying output rates is difficult. By contrast, traditional batch production plants have been flexible towards product changes, requiring lower capital investment and utilizing small discrete steps to the changing of manufacturing quantity schemes. Therefore, from a manufacturing perspective there is a challenge to evolve with a new continuous processing answer[1] to the target of uniting the traditional logistic convenience of batch production with the advantages of continuous processing. A significant boundary condition for a continuous manufacturing strategy for compounds demands that a manufacturing process can be set up before quality specification such as those required in the drug master file. In these stages of synthesis development, process materials are scarce, time is of the essence, and hence extensive sourcing of process development material is counterproductive. Consistently implemented microreaction[2] technology[3] enables a solution to these challenges: A broad synthetic applicability of standard microreactors[4] (Figure 1) permits even difficult reactions.[5] Low internal volumes and optimized flow profiles enable fast process development at small compound consumption.

Parallel reactor arrays can give access to commercial scale manufacturing quantities. In summary, microreaction technology enables continuous processing for high value added chemicals. In this contribution we wish to give an overview of the basics of the technology and their utilization in synthesis. Experimental procedures are given for new applications.[6]

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(1) (a) Behr, A.; Brehme, V. A.; Ewers, C. L. J.; Grön, H.; Kimmel, T.; Küppers, S.; Symietz, I. *Chem. -Ing. -Tech.* **2003**, *75*, 417. (b) Ewers, C. L. J.; Küppers, S. *Nachr. Chem., Tech. Lab.* **2002**, *50*, 1255.

(2) Floyd, T. M.; Kopp, M. W.; Firebaugh, S. L.; Jensen, K. F.; Schmidt, M. A. In *Proceedings of the 3rd International Conference on Microreaction Technology (IMRET 3)*, Frankfurt/Main; Ehrfeld, W., Ed.; Springer: Berlin, 1999; p 171.

(3) (a) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406. (b) Schwalbe, T.; Autze, V.; Wille, G. *Chimia* **2002**, *56*, 636.

(4) The broad applicability of such systems results from an integration of a thermal conditioner for starting materials, a mixer for these, and an integrated heat exchanger for thermal reaction control. This patented integration is commercially available as CYTOS.

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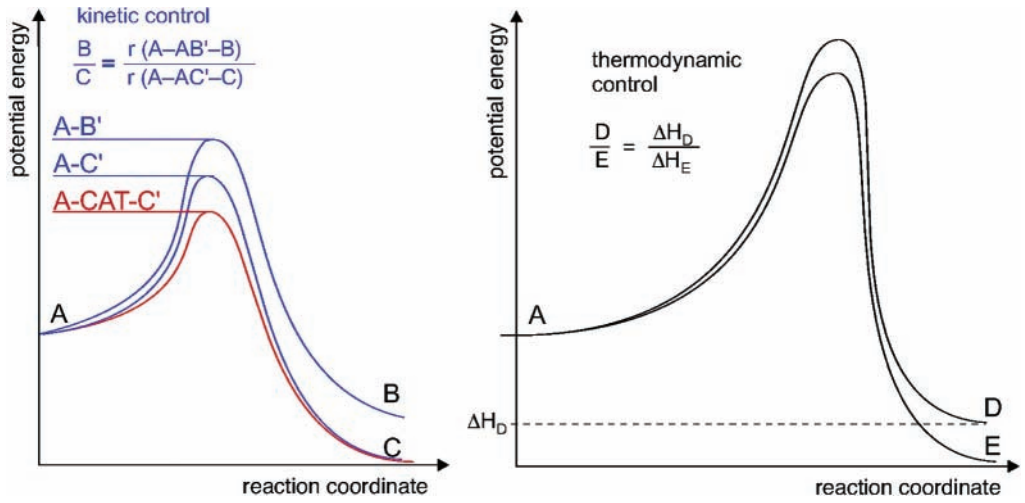


Figure 2. **Potential energy profile: kinetic reaction vs thermodynamic reaction, catalysis.**

2. Generic Benefits from Integrated Microreactors in Synthesis

Microreactors (MRs) possess certain advantageous engineering features,[7] for example, fast diffusive mixing[8] and high heat transfer rates. Further, a tightened residence time distribution can lead to elution profiles that more closely approximate plug flow than, for instance, the elution profiles susceptible to macroscopic flow tubes. Finally, practically any reaction operated in a microreactor of suitable dimension can be immediately operated to yield kilogram quantities of synthetic material at a day's notice. However, one problematic aspect connected with the handling of the systems should be mentioned. In some cases, preceding optimization is essential before submitting a reaction from the conventional mode to the microreactor. Since the microchannels are restricted to reactions in a liquid/liquid, liquid/gas, or gas/gas phase system, solid reagents have to be replaced by soluble alternatives. This process may require additional time for the optimization of conditions. In addition, the time saving effect of continuously operating synthesis may be compensated by standard workup protocols that are mostly still based on conventional methods. Due to the efficient mixing in a microreactor, for the rest of the discussion we can assume mixing is nearly ideal. Under these conditions it is appropriate to focus the discussion of reactions on the potential energy profile as related to reaction temperature along the reaction coordinate and in passing through transition states (Figure 2, lit.[9]). On the left side of Figure 2, a reaction is shown to proceed under kinetic control, and the formation of product C is favored if the activation energy provided by the reaction is limited. These reactions are most favorably run in MRs. A reversible reaction path allows for the predominant formation of the more stable product through reversible reaction conduct (thermodynamic control, right). Whilst such reactions can in principle be run in a MR, there are few cases where we would expect incrementally beneficial results.

From an experimental operating perspective the continuous conduct of microreactor experimentation avoids dosing times, yet it is due to the integration of conditioning heat exchangers into microreactors that undesired side reactions such as thermal decomposition or reactive aggregation such as polymerization of starting materials can be largely avoided. In the conceptual view of a reaction profile, this conditioning works in a direction *as if* the reaction compo-

(5) The breadth of applicability of microreactors was reported: (a) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883. (b) DeWitt, S. H.; *Curr. Opin. Chem. Biol.* **1999**, *3*, 350. (c) Okamoto, H. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 805. (d) Krummradt, H.; Kopp, U.; Stoldt, J. In *Proceedings of the 3rd International Conference on Microreaction Technology (IMRET 3)*, Frankfurt/Main; Ehrfeld, W., Ed.; Springer: Berlin, 1999; p 181. (e) Autze, V.; Kleemann, A.; Golbig, K. *Nachr. Chem., Tech. Lab.* **2000**, *48*, 683. (f) Example reactions are listed at: www.cpc-net.com. (g) Förster, A. *Chem. -Ing. -Tech. plus* **2001**, *4*, 28. (h) Hessel, V.; Löwe, H.; *Chem. -Ing. Tech.* **2002**, *74*, 186. (i) Wörz, O.; Jäckel, K. P.; Richter, K. P.; Wolf, A. *Chem. Eng. Technol.* **2001**, *24*, 138. (k) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun.* **2001**, 391. (l) Watts, P.; Wiles, Ch.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2002**, *58*, 5427. (m) Fletcher, P. D. I.; Haswell, S. J.; E. Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735.

(6) All experiments described in the CYTOS Lab System, unless otherwise indicated, were carried out in the CYTOS microreactor developed by CPC − Cellular Process Chemistry Systems GmbH, Germany. Schwalbe, Th.; Golbig, K.; Hohmann, M.; Georg, P.; Oberbeck, A.; Dittmann, B.; Stasna, J.; Oberbeck, S. Eur. Pat. Appl. EP 1 123 734, 2001; *Chem. Abstr.* **2001**, *135*, 154468b. The effective reaction volume of the CYTOS microreactor is 1.2 mL; however, along with the feed lines inside the cell the total volume results in 2.0 mL. Additional reaction volume is provided by equipping the microreactor with up to three residence time units with a 15 mL volume each in the standard configuration. Further information is available on the Internet: www.cpc-net.com. CYTOS is registered by CPC-Systems GmbH.

(7) Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652.

(8) To practically benefit from the use of microreactors in synthesis, it is worthwhile to conceptually separate the effects of mass transfer from thermal effects onto a reaction. For practical synthetic considerations, diffusive mixing in microreactors is significantly faster than reacting. This has been amply discussed in the literature, and mixing in microreactors is commonly characterized by the Villermaux/Dushman (Fournier, M. C.; Falk, L.; Villermaux, K. *J. Chem. Eng. Sci.* **1996**, *51*, 5187) reaction. Further well-designed microreactors demonstrate a stable mixing performance over a wide range of flows. By and large limitations to the comparative value of this characterization only surface with the occurrence of multiple phases as well as with widely differing viscosities, hence mixing energy requirements in the starting media or changes of viscosity after mixing. Hence, alternative characterization reactions have been proposed (Panic, S.; Antes, J.; Richert, B.; Boskovic, D.; Tuercke, T.; Schnuerer, F.; Marioth, E.; Loebbecke S. In *Abstracts of Papers*, 7th International Conference on Microreaction Technology (IMRET 7); Lausanne, Switzerland; DECHEMA-Gesellschaft für in Chemische Technik und Biotechnologie: Frankfurt/Main, Germany, 2003; p 236.

(9) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 4th ed.; Allyn and Bacon: Boston, MA, 1983.

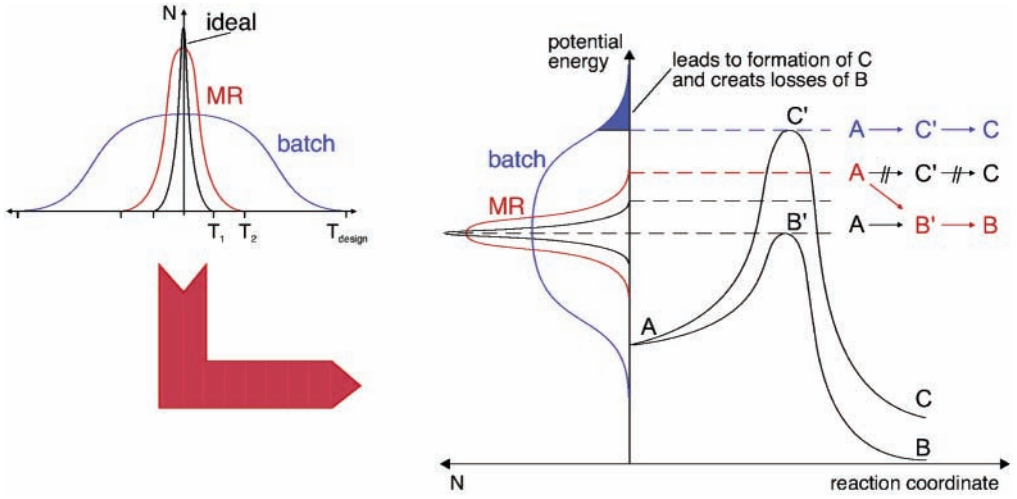
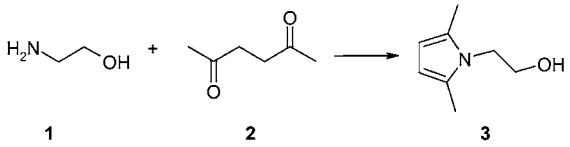


Figure 3. **Temperature and activation energy, temperature quality, and activation energy.**

Scheme 1. **Paal−Knorr synthesis of pyrrole 3**



1 2 3

Table 1. **Preconditioning reagents for accelerated reaction times in the Paal−Knorr synthesis**

residence time	5.2 min
total flow rate	6.1 mL/min
reaction temperature	65 °C
throughput of product	260 g/h
yield [%]	91

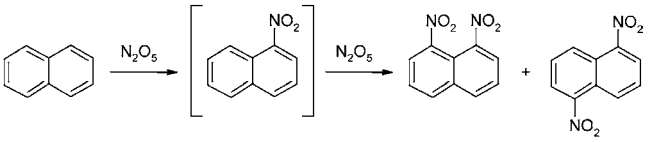
nents were entering the reaction coordinate and contacting just at the transition structure energy level.

One example for the preconditioning of reaction intermediates is the Paal−Knorr condensation[10] of ethanolamine (**1**) and acetonylacetone (**2**, Scheme 1; Table 1; for experimental details see section 8).

In the exothermic synthesis of pyrrole **3**, the decelerated dosing of the starting material to the reaction mixture adds significantly to the total process time. The design of the microreactor enables the synthesis of pyrrole **3** directly from the neat material in a chemical yield of 91% (process yield[11] 87%) saving significant amounts of solvent with high throughput rates of 260 g/h.

In Figure 3, a normal distribution of particles at certain temperatures is vertically turned and imposed upon the reaction profile (taken from Figure 2) of competing reactions hence transition structures. Here it is illustrated that increasing temperature quality can be used to increase selectivity under the kinetic control of reactions. Alternatively, or in combination, the increase in temperature control can be used to increase the technical reaction target temperature level and hence increase time/space yield.

Scheme 2. **Discrimination between the double-nitrated products 6 and 7 according to Loebbecke et al.[a]**



4 5 6 7

[a] Ratio (batch): **6**/**7** = 1:3.6. Ratio (microreactor): **6**/**7** = 1:2.8.

An application example for this consideration in this discussion is given for increasing the second step selectivity of the nitration of naphthalene (**4**) by Loebbecke et al.[15a] (Scheme 2). The authors mentioned that "the isomeric ratio" of 1,5-dinitronaphthalene (**6**) and 1,8-dinitronaphthalene (**7**) was found to be almost constant in macroscopic batch reactions at different process conditions: 1,5-dinitro/1,8-dinitro ≈ 1:3.6. By applying microreactors the amount of the unfavored 1,5-dinitro isomer could be significantly increased resulting in an isomeric ratio of 1,5-dinitro/1,8-dinitro ≈ 1:2.8.

Selectivity gains or potential increases of reaction temperatures are amplified by simultaneous gains in control of temperature and concentration. High concentration and temperature gradients in microstructure reactors are again drivers

(10) (a) Buu-Hoi, Ng. P. *J. Org. Chem.* **1955**, *20*, 639. (b) Bishop, W. S. *J. Am. Chem. Soc.* **1945**, *67*, 2261.

(11) The chemical yield refers to the material exclusively isolated from steady-state conditions. In contrast to this, the overall amount of the consumed material is taken into account in the process yield which includes also the prerun. Upon enhanced operating periods of the microreaction system, the lack of yield in the process yield is increasingly negligible.

(12) Fukuyama, T.; Nishitani, S.; Yamaura, R.; Sato, M.; Ryu, I. In *Abstracts of Papers*, 7th International Conference on Microreaction Technology (IMRET 7); Lausanne, Switzerland; DECHEMA-Gesellschaft für Chemische Technik und Biotechnologie; Frankfurt/Main: Germany, 2003; p 236.

(13) Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, 2827.

(14) Dale, J. D.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.

(15) For related investigations into nitration reactions, see also: (a) Antes, J.; Tuerecke, T.; Marioth, E.; Schmid, K.; Krause, H.; Loebbecke, S. In *Topical Conference Proceedings, 4th International Conference on Microreaction Technology (IMRET 4)*; Rinard, I., Ed.; AIChE Spring National Meeting, Atlanta, GA, 2000; p 194. (b) Burns, J. R.; Ramshaw, C. In *Topical Conference Proceedings, 4th International Conference on Microreaction Technology (IMRET 4)*; Rinard, I., Ed.; AIChE Spring National Meeting, Atlanta, GA, 2000; p 133. (c) Burns, J. R.; Ramshaw, C. *Trans. Inst. Chem. Eng.* **1999**, *77*, 206.

(16) Schmalz, H. G.; Schwalbe, Th.; Sakamoto, Y.; Matsumoto, K.; Goto, S. Germ. Patent DE 103 33 174.3, 2003.

(17) (a) Baldyga, J.; Bourne, J. R. *Turbulent Mixing and Chemical Reactions*, 1st ed.; John Wiley & Sons: New York, NY, 1999. (b) Borune, J. R. *Org. Process Res. Dev.* **2003**, *7*, 471.

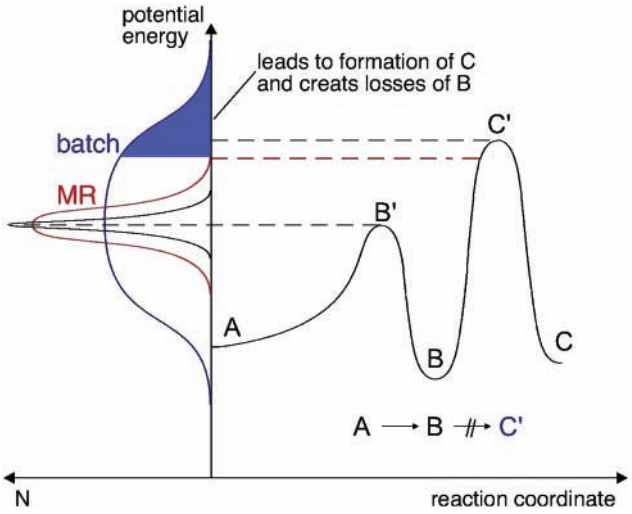
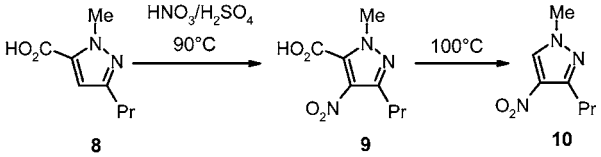


Figure 4. **Suppression of follow-up reactions by exact adjustment of the inner temperature in a two-stage process.**

Scheme 3. **Nitration of 8**



of tight control. Since tighter concentration and temperature control allows a closer tune of reactions to conversion or selectivity requirements, the reaction control works similar to (and combined synergistic with) catalysis.[12]

In a recently published example[13] for the practical applicability of this reaction design benefit, the pyrrazole nitration reaction **8**, a precursor in the Sildenafil synthesis (Scheme 3), is the crucial reaction. This highly exothermal reaction has proved difficult to scale;[14] upon addition of the nitration mixture to the starting material, it was difficult to maintain a target reaction temperature of 70 °C, since the reaction heats the mixture to above 100 °C, a temperature at which the product **9** decarboxylates under the reaction conditions forming the undesired follow-up product **10**. The reaction could be converted into a microreactor and safely run at a higher temperature of 90 °C, thus avoiding decarboxylation. The effect of the energy distribution inside the microsystem on the product profile is outlined in Figure 4.[15]

Shortened mixing times and tightened residence time distribution, plug flow, beneficially discriminate against follow-up reactions in certain practical cases. They both work *as if* the reaction coordinate of two subsequent reactions (Figure 5) could be intersected right after the formation of the desired product.

For fast reaction sequences wherein the reaction rate of both the first and the second reaction are of the magnitude of the mixing time of traditional mixers,[16] faster mixing in microreactors diminishes the impact of mass transfer constraints.[17] For sequences of a fast and a considerably slower reaction, the sharpened concentration profile of plug flow helps in avoiding, for example, decomposition or overreaction.

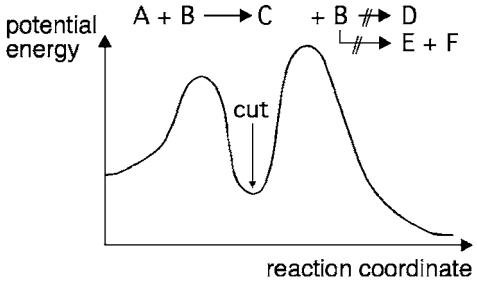


Figure 5. **Avoiding follow-up reactions.**

The selective monoalkylation of a *N*-acyliminiumion **11** with an electron-rich aryltriether **12** in an academic prototype mixer as a case of potential subsequent reactions with kinetics in the range of mixing times was reported by Yoshida and co-workers (Scheme 4).[18] In this case efficient mixing ensured that each aryl compound instantly interacts with an electrophilic reaction partner and that each electrophile is quenched by an unreacted aryl compound. This reaction conduct resulted in a 96:4 selectivity in favor of the monoalkylated product **13**. It was benchmarked against a batch as well as a T-piece flow experiment, both of which led to the formation of approximately similar amounts of mono- and dialkylated product **14**.

In another example, the nucleophilic addition of C_2F_5-MgCl (**16**) to benzophenone (**17**)[19] serves as a case of a discriminated somewhat slower subsequent reaction (Scheme 5; for experimental details see section 8).[20]

In the conventional reaction sequence, intermediate **16** was formed by a metal−halide exchange reaction at −78 °C. The instability due to the elimination of MgXF or LiF from such kind of perfluorinated organometal-reagents is known to occur even at low temperatures.[21] As a consequence of the limited half-life of these intermediates (even at −78 °C in minute range) and extended dosing times, the scale-up of this reaction is very difficult.

Upon operating the reaction in a two-stage microreaction system, both the temperature of the formation of **16** and the temperature of the nucleophilic addition reaction could be increased by approximately 70 K. Since the sensitive organometallic intermediate C_2F_5MgCl was submitted directly to the second stage, presuming full conversion of **15**, its decomposition was suppressed significantly. In addition to this, the competing addition reaction of R−M (used in

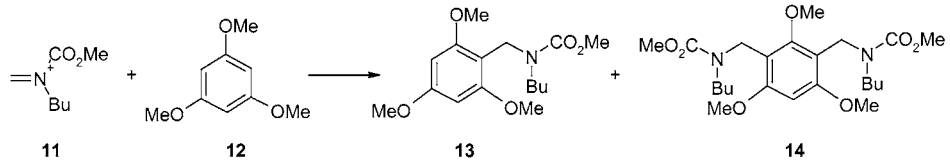
(18) (a) Suga, S., Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (b) Yoshida, J.; Nagaki, A.; Suga, S. In *Abstracts of Papers*, 7th International Conference on Microreaction Technology (IMRET 7); Lausanne, Switzerland; DECHEMA-Gesellschaft für Chemische Technik und Biotechnologie: Frankfurt/Main, Germany, 2003; p 1.

(19) In previous papers, the target compound $Ph_2(C_2F_5)COH$ **18a** was synthesized from flourinated propionic esters and 2 equiv of Ph−M (M = Li, MgX). See: (a) Kaluszyner, A. *J. Am. Chem. Soc.* **1955**, *77*, 4164. (b) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Flourine Chem.* **1981**, *18*, 117.

(20) To the best of our knowledge, the transfer of perfluorinated ethyl groups using C_2F_5MgX has not been reported yet. Some applications for C_2F_5Li have been published for nucleophilic additions to carbonyl groups: (a) Kuroboshi, K.; Hiyama, T. *Chem. Lett.* **1990**, *9*, 1607. (b) Nelson, D. W.; O'Reilly, N. J.; Speier, J.; Gassman, P. G. *J. Org. Chem.* **1994**, *59*, 8157.

(21) Examples for the decomposition rate of *n*-C_3H_7MgBr have been published: McBee, E. T. *Proc. Indiana Acad. Sci.* **1954/55**, *64*, 108. Addition of *n*-C_3H_7MgBr to a macrocyclic ketone was found to yield 60% at −78 to −20 °C: Bartsch, R. A.; Bitalac, L. P.; Cowey, C. L.; Elshani, S.; Goo, M.-J.; Huber, V. J.; Ivy, S. N.; Jang, Y.; Johnson, R. J.; Kim, J. S.; Luboch, E. *J. Heterocycl. Chem.* **2000**, *37*, 1337.

Scheme 4. **Selective electrophilic monosubstitution as reported by Yoshida et al.[a]**



[a] Reaction conditions: −78 °C, CH_2Cl_2.

Scheme 5. **Formation of a short-living organometallic compound 16 (R−M = BuLi, MeMgCl) and its addition to benzphenone (17) in a two-stage microreaction system**

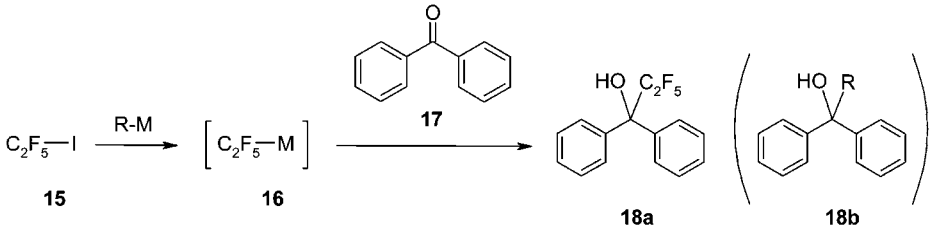


Table 2. **Reaction conditions for the two-step addition of C_2F_5−M to 17**

entry	reagent R−M	*T* (°C) stage 1	*T* (°C) stage 2	ratio R−M/C_2F_5I/**17**	*t* stage 1 (min)	*t* stage 2 (min)	amount **17** [%]	amount **18a** [%]	amount **18b** [%]
1 batch	*n*-BuLi	−78	0	2.8:3.1:1	10	>10	86	14	
2	*n*-BuLi	−61	−10	2.8:3.1:1	4	17	14	51	35
3 batch	MeMgCl	−30	0	2.5:2.8:1	10	>60	84	15	1
4	MeMgCl	2	−4	3.9:4.3:1	0.9	<10	65	25	10
5	MeMgCl	1	−4	3.9:2.7:1	0.9	<10	13	80	7
6	MeMgCl	−6	−4	3.9:2.7:1	0.9	8	9	86	5
7	MeMgCl	−8	−6	5.4:2.7:1	0.7	<10	7	82	11
8	MeMgCl	−6	−4	7.8:7.8:1	0.8	<10	28	72	

Residence time* in the batch mode describes the reaction time of the lithium−halide exchange (stage 1, formation of C_2F_5−M) followed by the nucleophilic reaction after the addition of **17 (stage 2, formation of **18a**).

excess) to the carbonyl (formation of **18b**) was reduced to a minimum (Table 2, entry 6). This demonstrates the advantages of a reaction conducted in a two-stage system that enables the generation of C_2F_5MgCl from C_2F_5I and R−M in the absence of the competing electrophile **17**. The results from Table 2 will be discussed in more detail.

Treatment of **15** with BuLi for a total reaction time of 20 min at −78 °C (entry 1) in the batch mode yielded a very low conversion. In the microreactor at −61 °C, within 4 min of residence time in the first stage the desired product **18a** was formed in 51% yield (entry 2) alongside **18b** (R═Bu) that was formed in 35%. In this experiment, the halogen−lithium exchange did not proceed completely and significant amounts of BuLi were left unconsumed (side reaction generating **18b**).

The benchmark experiment for MeMgCl (entry 3) at −30 °C (stage 1) in the conventional mode gave almost the same results that were obtained with *n*-BuLi at −78 °C (entry 1). The initial experiment under "typical" reaction conditions in the microreactor (residence time in stage 1 of less than 1 min in combination with an elevated temperature) gave little improvement to a 25% yield (entry 4). However, upon changing the MeMgCl/C_2F_5I ratio to an excess of MeMgCl, the yield was improved to 80% (entry 5). Before performing all these experiments, an organometallic reagent was used in sub-stoichiometric amounts in order to suppress the formation of the addition product **18b**. After complete consumption of C_2F_5I in the first stage of experiment 5, obviously the addition rate of C_2F_5MgCl towards **17** is much higher than that of MeMgCl. The optimum with 86% yield (entry 6) was found by decreasing the reaction temperature in the first stage to −6 °C (residence time and molar excess left unchanged). The methylation of the benzophenone was minimized to 5%. Further enhancement of the stoichiometric amounts of MeMgCl and C_2F_5I even had negative effects on the yield and the product profile (entries 7 and 8).[22]

The latter reaction is an example of the capability of today's commercial microreactor systems to be operated in a serial sequence of up to 5 reactor units that are suitable for multistep synthesis. The lithium−halide exchange reaction of 3-bromo-anisole (**19**) (Scheme 6; Table 3; for experimental details see section 8) is another example for the direct connection of two microreaction systems.

Due to the known instability of **20** at elevated temperatures,[23] the microsystem appeared to be an ideal tool for improving its performance. In a preceding experimental

(22) The optimization of the throughput (around 10 g/h for experiment 6) was not part of this project. However, since the required residence times have been realized using low flow rates and small reaction volumes, there is potential for improvement.

Scheme 6. **Lithium−halide exchange of 19 and formylation with DMF in a two-stage microreaction system**

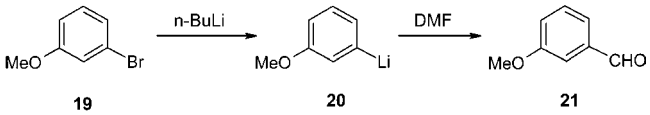


Table 3. **Dual-step synthesis in microreactor systems: lithium−halide exchange of 19 followed by DMF quench**

residence time, stage 1	0.19 min
total flow rate, stage 1	10.8 mL/min
reaction temperature, stage 1	0 °C
residence time, stage 2	0.15 min
total flow rate, stage 2	13.2 mL/min
reaction temperature, stage 2	0 °C
total throughput of product	59 g/h

Table 4. **Previous investigation for the kilogram synthesis of 3-methoxybenzaldehyde**[a]

entry	*T* [°C]	scale [mol]	yield [%]
1	<−65	0.04	quant
2	<−60	0.8	85/76
3	−50	4.8	60
4	−40	4.8	24

[a] Yields were determined by GC except isolated material.

investigation in the batch mode, we examined the effect of the temperature on the formation of 3-methoxy-phenyllithium (**20**). An additional focus of this series of experiments was on scaling up. This was expected to cause problems, due to the temperature sensitivity of **20** along with its exothermic formation and accordingly extended dosing times.

The initial experiment (Table 4, entry 1) at a 40 mmol scale ($T < -65$°C) provided 3-methoxybenzaldehyde **21**[24] in almost quantitative yield (in process control, IPC, by GC analysis). Upon scale enhancement to 0.8 mol, the IPC yield decreased to 85% (76% isolated). Finally in a 4.8 mol scale (entry 4), the temperature was kept below −40°C but dosing times of 4 h for the *n*-BuLi and 2.5 h for the DMF, respectively, were required. However, in the end of the conversion, the IPC yield was poor[23b] (24%) and the product was accompanied by considerable impurities.

To compliment these findings, both exothermic reactions, the lithium−halide exchange and the formylation, were performed in a two-stage microreaction system. A throughput of 59 g/h was established for approximately 24 h under nearly isothermal conditions. The product **21** was isolated in 88% yield accompanied only by small amounts of side products. The contact time was reduced to a minimum of 11 s (stage 1), which helps to overcome the problem with the intermediates' lifetime, followed by the addition to the carbonyl group within a residence time of 9 s (stage 2). To learn more about

(23) (a) Zhang, X.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455−460. (b) The authors in the latter publication report the conversion at −10 °C in a gram scale flask experiment to provide only 31% yield.

(24) (a) Saboureau, C.; Troupel, M.; Sibille, S.; d'Incan, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 895, (b) Hajipour, A. R.; Mallakpour, S. E.; Samimi, H. A. *Synth. Lett.* **2001**, *11*, 1735.

(25) Schwalbe, Th.; Oberbeck, A.; Taghavi-Moghadam, S.; Golbig, K.; Hohmann, M. U.S. Patent 9,617,068, 2000 and Eur. Patent EP 1 174 184, 2001.

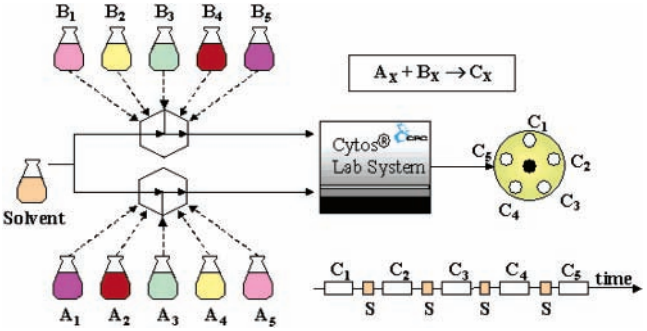


Figure 6. **General simplified scheme for combinatorial experiments in an MR.**

the scope and limitation of the reaction, the flow rate was increased by a factor of 2 in all three pumps resulting in a doubled throughput rate and halved residence times. Apart from a minor drop of the yield (83%), product quality remained constant and adaptations at the microsystem to the set parameters were not required. In conclusion, the straightforward handling of the lithium−halide exchange reaction plus an electrophilic addition was demonstrated without any scale-up risks and at convenient temperatures.

3. Sequential Development of Chemistry Choices in Continuously Conducted Organic Synthesis

The comparative ease of scaling output quantity from synthesis in continuously operated microreactor systems has created the opportunity to apply the same principle to the combinatorial synthesis of discovery compounds as well as to combinatorial process development.

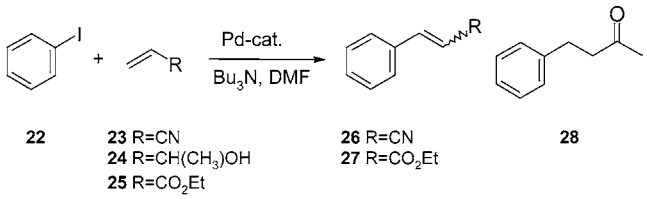
Recently this novel concept[25] for combinatorial experimentation has been commercially introduced (Figure 6). It aims at the synthesis of focused compound libraries and at selecting the right reagent choices for that synthesis. It is organized around the same scaleable process used throughout the chemical synthesis process. Within this concept, variations on starting materials A_x and B_x are sequentially reacted in a microreactor process plant to yield a variety of C_x. The concept enables the unrestricted combination of A_x and B_x.

This new regimen developed by our group lends itself in particular to temperature sensitive reactions, moisture sensitive reactions, kinetically controlled C−C bond formation processes, and homogeneous catalysis[26] in the field of synthesis of targeted (i.e., hypothesis) driven libraries. Further, it is of similar importance to the optimization of solvent and reagent choices from the chemical diversity space. Finally, it allows to scale synthesis output within these experimental phases to any quantity requirement from functional screening methods and thereby allows compounds to be manufactured under the same conditions when desired.

From an operative perspective, experiments are entered into the system in pulse sequence and their elution profile from the reactor is optically analyzed. Different operating and analysis modes have been developed to allow for the

(26) The formation of carbocations in a sequenced manner in microflow systems has been reported: (a) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (b) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2651. Also see: de Bellefon, S.; Tanchoux, N.; Caravieihes, S.; Grenouillet, P.; Hessel V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3342.

Scheme 7. **Heck reaction**



22 **23** R=CN; **24** R=CH(CH$_3$)OH; **25** R=CO$_2$Et → **26** R=CN; **27** R=CO$_2$Et → **28**

fractioned collection of crude products. Individual reaction plugs are separated by a spacer solvent. To ensure the reliability of each experiment, a clear separation of each plug is essential. The overall close to plug flow behaviour is the result of a careful system design.[27]

In the chemical development of applications, the ultimate objective is to capture representative samples for the overall stable process. Hence, steady state fractions are collected according to the selected fractioning conditions. Again careful system design minimizes waste under these conditions. In this field the principle has been demonstrated in an investigation aimed at systematically exploring alternative solvents for diverse organolithium reactions as well as in the continuous process screen of palladium catalyzed reactions.[28,29] In a sequential screening, four palladium complexes were investigated with respect to their conversion rate for the coupling of three arylhalogens (Scheme 7), amongst them iodobenzene and three olefins at three different catalyst concentrations at three different temperatures.[30] In the experiment, olefins and arylhalogens were premixed as one reactor feed and the catalyst solution at preset concentrations was fed as the second feed. The different reaction temperatures were applied after completing each full chemistry cycle.

Table 5 demonstrates a selection of results from this experimental run (for experimental details, see section 8). In agreement with results from other groups,[31] lower concentrations of palladium catalyst were found to give much better results in terms of yield and product profile. Since synthesis in microstructures is bound on particle free solutions, it will prove beneficial to find the lowest permissible concentration of reactive palladium concentration in the continuous microsystem. The full investigation covered a variety of independent experiments (dealing with temperature and several catalyst concentrations which will be published in a later paper).

Table 5. **Heck reactions performed in the sequential microreaction system**

entry	reagent	product	catalyst	catalyst amount [%]	conversion[a] [%]	*T* [°C]
1	23	26	$Pd(OAc)_2$	2.0	32	105
2	23	26	$Pd(OAc)_2$ /P(*t*-Bu)$_3$	2.0/4.0	53	105
3	23	26	$Pd[(PPh_3)]_4$	1.2	76	105
4	23	26	$Pd[(PPh_3)_2Cl_2]$	1.2	76	105

entry	reagent	product	catalyst	catalyst amount [%]	yield [%]	*T* [°C]
5	23	26	$Pd[(PPh_3)_2Cl_2]$	0.6	86 (E/Z 4.3:1)	125
6	24	28[a]	$Pd[(PPh_3)_2Cl_2]$	0.6	57	125
7	25	27	$Pd[(PPh_3)_2Cl_2]$	0.6	94 (E/Z > 98:1)	125

[a] The product in entry 6 undergoes an internal rearrangement.

4. Approach to Maximize Throughput in Continuous Integrated Microreactor Systems

With increasing quantity requirements in the development process of chemicals, there is a requirement to maximize time/space yield in a continuously operated microreactor to access commercial scale manufacture. Recently, an instrument became commercially available that couples a microreactor plant to in-line analytics (Figure 7). Hardware and experimental procedures have been developed to enable a rapid kinetic screening of a reaction and to continuously enhance reagent concentration and temperature. This resulted in a new high-throughput tool for the optimization of continuous reactions. The transient nature of experiments in these setups allows for a rapid adaptation of synthesis towards its optimal conditions.

As an example for a rapid screening of a reaction kinetic, the acylation (Boc protection, Scheme 8; for experimental details see section 8) of benzylamine (**29**) is illustrated. The reaction starts from a residence time $\tau = 0.5$ min and is conducted at 22 °C in 0.8 M (each reactant) concentration, respectively. At a combined flow rate of 4 mL/min (2 × 2 mL/min), the starting materials are reacted and passed through a continuous microreactor system before the flow reaches a switching valve that directs the material to an in-line infrared analyzer flow cell. Changes in the product formation are monitored directly by comparison of the signal intensity at 1711 cm^{-1} (product carbonyl absorbance). After a stable spectrum at a residence time of 0.5 min has been collected, the valve is switched to allow a flow path through an additional reaction time volume container of another 15 mL. After this residence time unit (RTU), the flow again passes through a switching valve to the analyzer flow cell. The flow through that cell is again monitored until a stable spectrum in representation of a 4.3 min reaction time is collected. The cycle of switching additional residence time is repeated until the full set of incremental residence time units (RTUs) has been incorporated as reaction chambers or vice versa either quantitative conversion or maximal product formation has been observed (Table 6). When either or both

(27) Golbig, K.; Kursawe, A.; Hohmann, M.; Taghavi-Moghadam, S.; Schwalbe, Th. *Chem. Eng. Commun*. **2004**, in press.

(28) (a) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (b) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev*. Submitted for publication.

(29) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals;* Beller, M., Bohm C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol 1, p 208.

(30) In this application, different olefins, arylhalogens, catalysts, catalyst concentrations, and reaction temperatures were screened. A suitable setup to investigate all chemistry choices in one sequence at a given temperature prior to changing the temperature was chosen. The primary motive was to investigate the substrate/catalyst suitability. In the event these chemistry choices can be made aforehand, continuous parameter optimization regarding concentration and temperature with in-line analysis is advisable as opposed to discrete experimentation.

(31) (a) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. *Org. Lett*. **2003**, *5*, 3285. (b) Also see: Laird, T.; Hermitage, S.; Tilstam, U. *Org. Process Res. Dev*. **2004**, *8*, 2.

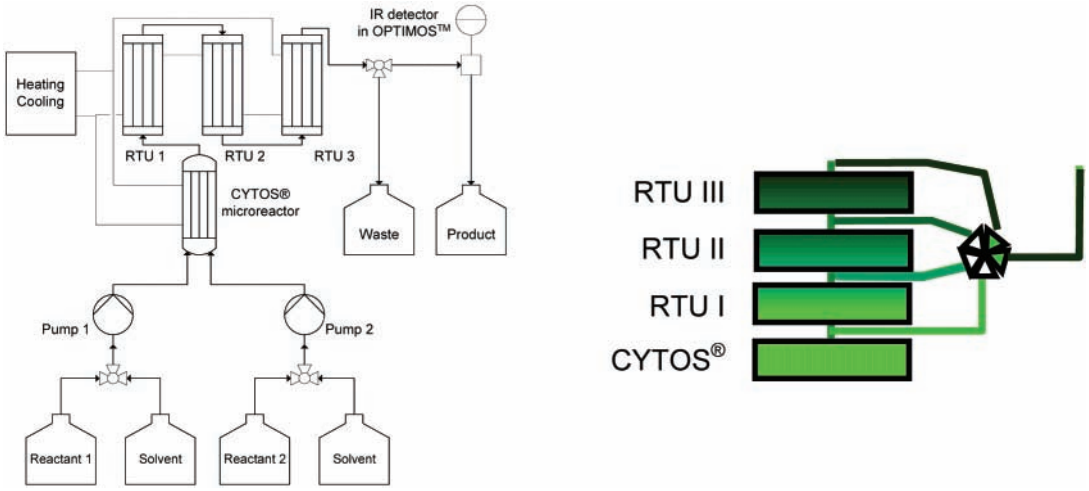
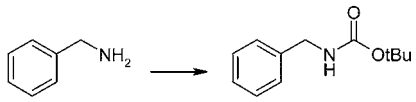


Figure 7. **General system setup for an optimization system with in-line analyzer (left) and switchable residence time units (right).**

Scheme 8. **Boc protection of benzylamine (29)**



29 **30**

Table 6. **Conversion rates of the Boc-protection of benzylamine (29)**

residence time τ [min]	conversion [%]
0.5	70
4.3	93
8.0	97
11.8	98

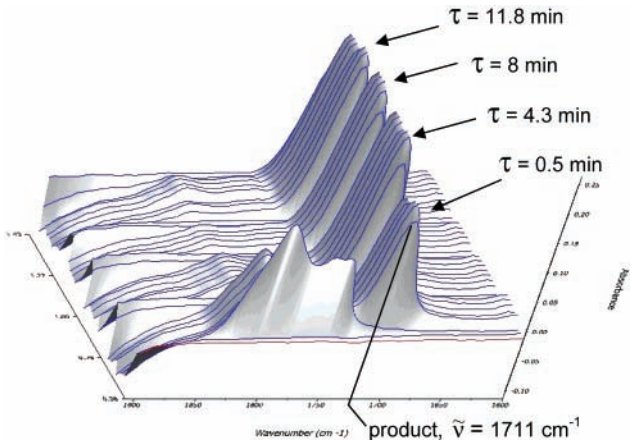


Figure 8. **Inline IR analysis of the Boc protection (initial experiment). Carbonyl absorbances: 30, 1711 cm^{-1}; Boc_2O, 1750, 1800 cm^{-1}.**

of these criteria are fulfilled, both flow rates are enhanced by 20% and the eluant is allowed to stabilize as analyzed by the sequence of spectra observed within approximately 1.4 times the new resulting residence time. With a stable composition of the eluant from the maximal residence time, the switching valves are operated in reverse sequence and product formation is observed after 11.8, 8.0, 4.3, and 0.5 min respectively. Thus, an eight-point isothermal kinetic curve is experimentally determined. In cases where the initial flow rate and the total reaction volume were chosen such that upon switching the maximum reaction volume complete conversion could not be obtained, the flow rate would be lowered in 20% steps to a minimal combined flow rate of 1 mL and the analysis completed as described before.

This methodology allows the continuous manipulation of reagent concentration and reaction temperature in a similar manner. Further applications using these manipulations will be reported elsewhere. A screenshot of the in-line IR spectra series for the acylation of **29** is given in Figure 8.[32] The diagram outlines the first set of residence time screenings before intensification of the flow rates. The gaps between the individual measurements originate from solvent leftovers inside the RTUs, which were removed prior to product sampling and gave no IR absorbance in the carbonyl area. Unconsumed amounts of the reagent Boc_2O are visible at 1800 and 1750 cm^{-1}. The smooth conversion was verified by GC. Apart from small impurities, only starting material and product were found in the individual samples. The yield of the optimized experiment (residence time 11.8 min) was determined to be 92% from product crystallization of a defined sample.[33]

5. A Case Study on Optimising Processes with an Emphasis on Minimal Compound Consumption and Shortened Learning Cycles

A recent case study conducted in collaboration between GlaxoSmithKline and CPC-Systems aimed at establishing a continuous multistep process route for the synthesis of an advanced pharmaceutical intermediate. The objective of the study was to demonstrate the feasibility of continuous processing in this context with a particular emphasis on a

(32) Theoretical considerations suggested and benchmark experiments verified 1.4 residence times as an sufficient forerun for synthesis under steady-state conditions. From this point, switching to the next residence time unit would be advisable to make the parameter screening after that period as efficient as possible. However, each measurement in Figure 8 was kept for an enhanced period in order to demonstrate the constant level of the product formation clearly.

(33) Yield in the conventional experiment: 96% (dioxane, 90 °C, 4 h, chromatography). Padwa, A.; Dean, D. C.; Fairfax, D. J.; Simon, L. X. *J. Org. Chem.* **1993**, *58*, 4646.

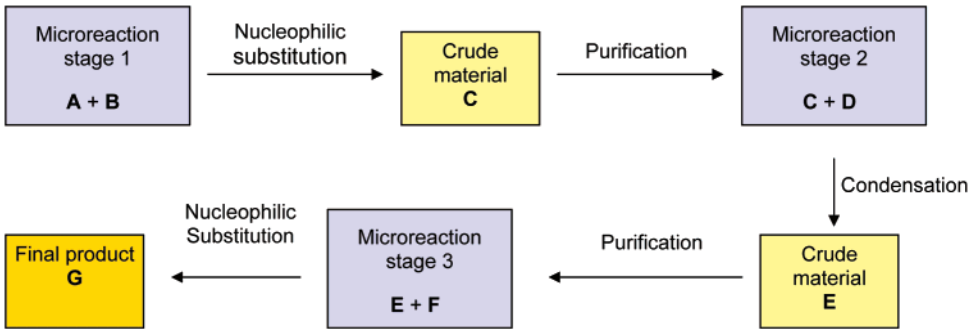


Figure 9. **Synthesis scheme of the three-stage microreaction plant.**

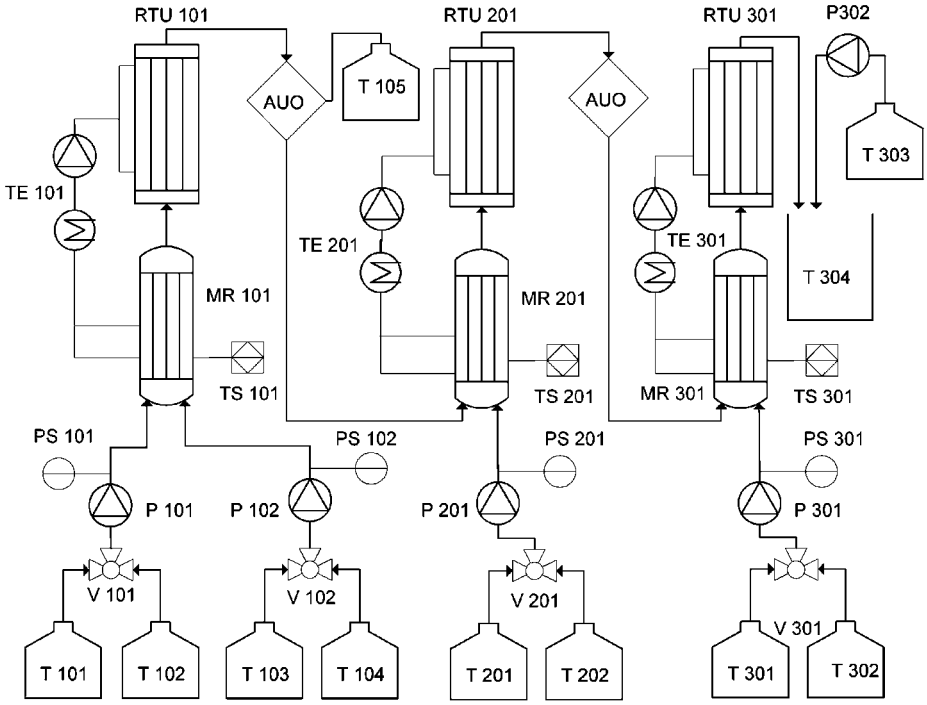


Figure 10. **Process flow diagram. Abbreviations: AUO, additional unit operation; MR, microreactor; P, pump; PS, pressure sensor; RTU, residence time unit; T, tank; TE, thermo element, TS, thermo sensor; V, valve.**

short process optimization time. An intent to minimize material consumption was pragmatically balanced by a target process output of a medium-sized double digit gram per hour production rate. The underlying synthesis was comprised of three steps and included two purification steps (Figure 9).

The first reaction of starting materials A and B was a nucleophilic substitution reaction to form crude C. The batch protocol used a high excess of the nucleophilic reagent which required a significant dilution and hence a rather long reaction time. Prior to building the integrated process development plant, the reaction was transferred to a microreactor under reduction of the nucleophile's excess and the dilution. The temperature of the reaction conduct was enhanced slightly, and the reaction time was cut to one-third of the batch reaction time. Eventually, in the pilot plant the crude material C was continuously purified. This reaction step was operated in a coupled manner with the preceding reaction as well as the two subsequent reactions and the second downstream purification. The next reaction step was an intermolecular condensation[34] reaction to yield crude E. Again it required long reaction times due to the azeotropic removal of water in conventional batch processing. In an initial investigative step, the reaction was converted to a continuous microreactor operation through a change of solvent, and the reaction time was reduced to a few minutes. Crude E was again subjected to a purifying unit operation. Purified E was reacted in a nucleophilic reaction to yield G, a reaction that imposed neither any extraordinary inherent conceptual challenge nor any issues of conversion to a continuous microreactor system. Nonetheless, the yield was improved. The entire synthetic work was subordinated to a quantitative benchmark of yield and throughput as well as a quantified qualification based

(34) We would have generally expected difficulties in running condensation reactions in continuous microreactor systems. According to several textbook rules, the product composition is thermodynamically controlled and the equilibrium favors the starting materials over the desired product. Azeotropic water removal is, prior to the use of a dehydrating reagent, a paramount physicochemical means of stirring the equilibrium towards product formation. To our surprise, we found that many condensation reactions work well in microreactors. In many instances (Paal−Knorr synthesis, Guaresky−Thorpe synthesis, generally cyclocondensations yielding conjugated olefins), the equilibrium may well lie by far on the product side. Additionally, in many practical cases, running condensation reactions above the boiling point of water (even when the reaction becomes pressurized to avoid evaporation of lower boiling solvents) ensures close to complete conversion. In this case, the interaction of the solvent with water served the desired role of controlling conversion.

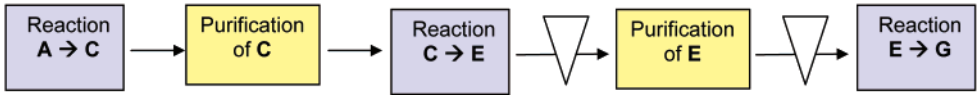


Figure 11. **Serial construction of the multistep plant.**

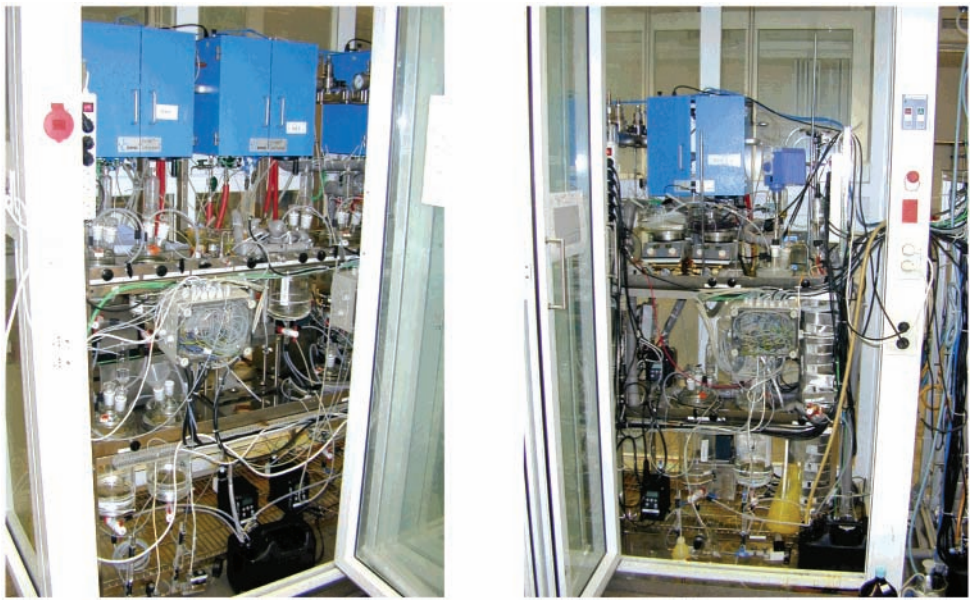


Figure 12. **Photograph of the pilot plant.**

on the final product's conventional processing impurity profile. The synthetic work in the fully coupled completed pilot plant passed all of these criteria.

After the initial reaction transfer from batch to continuous microreactor, a process flow diagram was established (Figure 10).

Three requirements determined the further steps in setting up the pilot plant.[35] First, it was desirable to evolve with an overall plant layout that would enable a rapid response to the parameter changes under investigation throughout the process. Second, the overall process time/yield was set by the pilot plant specification. Third, at this stage it was considered desirable for the general pilot plant start-up to include operating buffer vessels at key points. For further optimization work, these buffer vessels would be bypassed. Thus, the process layout translated into a hold-up scheme that would contain 2.37 L of process material including the buffer and 1.47 L of process material excluding the buffer. The corresponding start-up time of the plant describes both the time it would take from front to end until a stable final product solution would be eluded from the final conversion reaction stage to yield G and the front to end time constant for a process parameter change. This start-up time amounted to 13.7 h including the buffer vessels and 7.7 h excluding the buffer vessels (Table 7, Figure 11).

It is noteworthy that of the latter time requirement 5 h are held within one of the purification steps. The rather low time constants for the reaction step are driven by the extent to which hydrodynamic pulse shaping in the laminar flow regime of microreactors sharpen the elution profile of a tube

(35) Hasebe, S. In *Proceedings, International Workshop on Micro Chemical Plants*; Kaikan, H., Ed.; Micro Chemical Process Technology Research Association:Kyoto, Japan, 2003; p 33.

Table 7. **Hold-up and start-up/response time**

Hold-up [mL]							
stage 1	purification C	stage 2	buffer 1	purification E	buffer 2	stage 3	total
180	20	180	540	1000	360	90	1470 (2370)[a]
Start-up Time [min]							
84	30	35	140	300	180	10	7.7 h (13.7 h)[a]

[a] Including buffer elements.

reactor in the direction of theoretical plug flow. Whilst a tube reactor would require 2.5 τ until a satisfactory elution consistency is achieved, the commercially available microreactor systems used in this case (Figure 12) have been systematically optimized to accomplish a similar consistency within 1.4 τ.

In such a system, material not produced under steady-state conditions does not meet the quality specifications and does not provide information to the process. Assuming similar flow propagation velocity in a microreactor and in a macroscopic tube of 10 mm internal diameter, the compound consumption until a steady state is reached would be an order of magnitude higher for the macroscopic tube. At a minimum, ignoring flow velocity considerations, it would be 40% higher based on the elution profile comparison.

Through detective work in the analytical procedures and protocols that accompanied this work, it was found that the yield of the final product G could be tracked back through the ratio of its starting materials E to F after the purification step to the yield of precursor E. The extent to which this

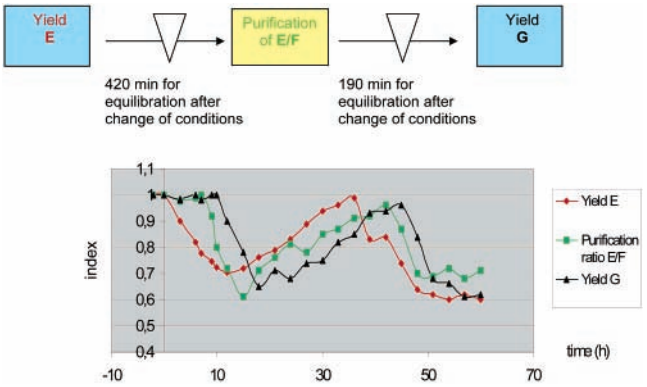


Figure 13. **The yield of E is given along with the purification ratios E/F and yield G on a normalized scale.**

correlation holds is immaterial for the point to be made about the pilot plant. Rather it is essential that the time constants of this tracking phenomenon and the sharp responses coincide with the design (Figure 13).

6. A Case Study on Integrated Microreactor Systems in Multiple Annual Tonnage Production

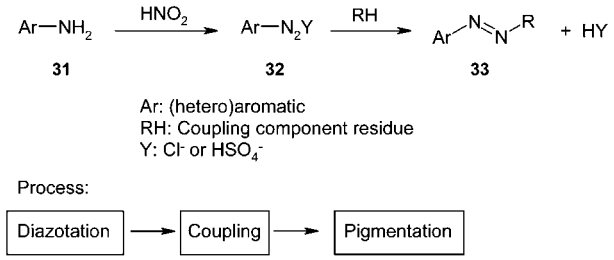
A few cases of applications of microreactors in higher output pilot manufacturing have been referenced,[36] yet detailed reports on their synthesitic objective, quantified performance have not been disclosed thus far.[37] It is therefore appropriate to discuss considerations associated with the building of an advanced pilot or production plant using the example of a three-stage pilot plant built for the synthesis of diazopigments. The synthesis was adapted to continuous microreactor conduct by CPC-Systems for the Clariant company, Switzerland. CPC-Systems built and commissioned the pilot plant under contract.

The important difference that a third party "turn key contract" has compared to a research investigation (aimed at unravelling novel synthesis concepts internally) lies in the financial criteria important to the decision makers. For a manufacturing investment into microreactor plants, such decisions have been based on a priori or smart abductive judgment that confirms three hypotheses.

First, a microreactor plant has satisfactory operating performance. It solves a relevant chemical process challenge reliably. The investigational results are transferable to production and onto a relevant set of chemical products. Roadblocks to plant operating performance and technical availability are removed, or their removal is foreseeable. The plant can be operated safely, conceivably often with a lesser risk exposure over traditional plants.

Second, output and throughput targets are matched. Novel processes can be established with reasonable investigational effort and seamlessly scaled. Time/space yields can be attuned and, in conjunction with throughput enhancing constructive means, brought to manufacturing outputs.

Scheme 9. **Diazopigment synthesis**



Third, a microreactor plant investment is economically valid. The investment generates value to the investor. This value can be modelled. Increased sales expectations compared to the baseline assumption for the noninvestment case and improved cost elements drive such a model. Improved cost may stem from four areas. Lower direct labor cost is commonly associated with continuous manufacturing, lower starting material consumption is expected with enhanced yields, or reduced application cost is expected from higher performance components and lower cost of quality assurance. A few decades ago, a reduction of rejected batches or the cost of blending operations to accomplish commercial specifications might have been involved in assessing such cost reductions.

Understandably, many of the facts that affect decisions in these considerations are considered business sensitive and are inappropriate to be reported here.

CPC-Systems and Clariant reported the conversion of the three synthesis steps for diazopigments into a microreactor (Scheme 9).[38] Notably, in the first step where two solutions were fed into the microreactor, a suspension of the diazonium salt **32** was formed. This suspension could in turn be fed into a second microreactor for the diazocoupling reaction[39] to again form the deeply coloured crude pigment suspension containing **33**. Finally, this suspension was subjected to a final pigmenting step again in a microreactor.

The chemical process challenge in these investigations resided in the aggregate characteristics of the diazopigment products. When manufactured in batches, application characteristics such as color strength, brightness, and transparency would depend on a set of more readily quantifiable properties, such as, for instance, the volume density distribution of particles. When manufactured in batch processes, this property would be widely dispersed and vary considerably from batch to batch (Figure 14).

By contrast pigments made in microreactors contained a far tighter distribution of crystal sizes centered around much smaller mean particle sizes. The investigation was extended to cover another pigment, and again application characteristics were improved (Table 8).

A laboratory prepilot system was built and has since been used for further explorative work in the field. Encouraging results from the laboratory process screen and the economic evaluation[40] of the project led to the decision to build a pilot

(36) (a) Schirrmeister, S.; Markowz, G. In *Abstracts of Papers*, 7th International Conference on Microreaction Technology (IMRET 7); Lausanne, Switzerland; DECHEMA-Gesellschaft für Chemische Technik und Biotechnologie: Frankfurt/Main, Germany, 2003; p 49. (b) Schütte, R. Germ. Patent DE 100 02 514 A1.

(37) Matlosz, M.; Jenck, J.; Bayer, Th. *Integrated multiscale process units with locally structured elements (Impulse)*, synopsis, version 3.6, Oct 22, 2002.

(38) Wille, Ch.; Autze, V.; Kim, H.; Nickel, U.; Oberbeck, S.; Schwalbe, Th.; Unverdorben L. In *Conference Proceedings, 6th International Conference on Microreaction Technology (IMRET 6)*; New Orleans, LA, 2002; Baselt, P., Eul, U., Wegeng, R. S., Eds.; AIChE: New York, NY, 2002; p 7.

(39) Wooton, R. C. R.; Fortt, R.; de Mello, A. J. *Lab Chip* **2002**, *2*, 5.

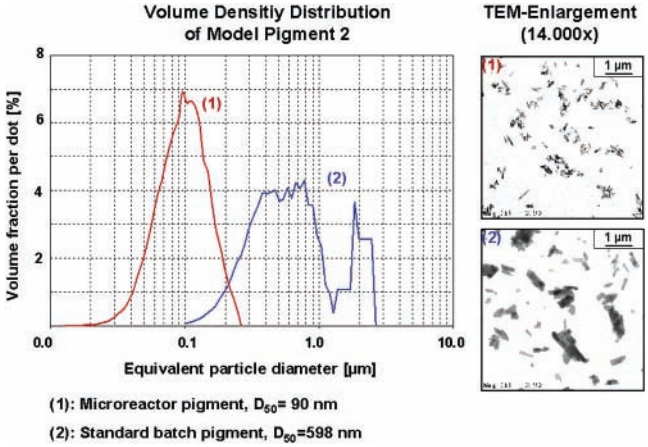


Figure 14. **Comparison of batch and microreactor pigments' crystal size distribution.**

Table 8. **Comparative application characteristics of microreactor manufactured pigments**

	microreactor pigment 1	microreactor pigment 2
color strength [%]	119	139
brightness	5 steps glossier	6 steps glossier
transparency	5 steps more transparent	6 steps more transparent

production plant comprised of all three process steps. The operating safety of this plant was improved by the comparatively small internal volume of a few liters for a 10 tpa output capacity and was shown to significantly enhance the handling of components.

Adequate output of the plant was enabled through numbering up the reaction chamber within the pilot reactor as well as numbering up the reactors by a factor of 3.

7. Summary and Outlook

Recent progress in continuous chemical process and chemistry research has led to versatile microreactor system evolution. Continuous microreactor equipment is now commercially available to cover all aspects of research, development, and manufacturing. More importantly, it is widely accomplishing the objectives of scientists and managers working in these fields.

In the past, many applications for complex organic synthesis in microreactors have been described for the laboratory scale. Since our results described here show the adaptability of microreaction technology in the field of kilogram synthesis (coming from bench scale), it is now clearly the time to apply this technology to its benefit (e.g., transferring the numbering-up concept into a practical approach). In a joint project focusing on the continuous manufacturing of small and large molecules, CPC-Systems along with partners[41] will be operating in the field of small molecule manufacturing in early 2005.

(40) Wille, Ch.; Haller, Th.; Gabski, H.-P.; Kim, H.; Unverdorben, L.; Winter, R. In *Abstracts of Papers*, 7th International Conference on Microreaction Technology (IMRET 7); Lausanne, Switzerland; DECHEMA-Gesellschaft für Chemische Technik und Biotechnologie: Frankfurt/Main, Germany, 2003; p 219.

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8. Experimental Section

General. The CYTOS Lab System (CLS) was filled with solvent by activating the two pumps simultaneously while the temperature was adjusted using an external thermostat (Huber Tango). Prior to synthesis, the pumps A and B of the microreaction system (SEQUOS or standard CLS) were calibrated to the desired flow rates. The residence time τ was calculated according to the equation: τ [min] = system volume [mL]/total flow rate [mL/min]. The temperature inside the microreactor (volume 2 mL) and the attached residence time units (volume 15 mL each) were adjusted. The system was cleaned with the 2-fold installed volume of solvent. A sample of 200 mL of ethanol was evaporated, and the amount of residue was determined (<1 mg) and analyzed by GC. Inorganic impurities from organometallic reactions were removed by an extra run with water. Gas chromatography was performed in a Hewlett-Packard 6890 equipped with an HP 1 column (cross-linked methyl siloxane, 30 m × 0.32 mm × 0.25 mm). Operation method 50 °C, 1 min; 20 °C/min → 250 °C; 250 °C, 10 min. Samples were dissolved in dichloromethane. NMR spectra were recorded on a Bruker AC 300 spectrometer.

2-(2,5-Dimethyl-pyrrol-1-yl)ethanol (3).

reaction conditions	
flow rate A neat ethanolamine	2.1 mL/min (34.8 mmol/min)
flow rate B neat acetonylacetone	4.0 mL/min (34.2 mmol/min)
reaction volume	32 mL
residence time	5.2 min
reaction temperature	65 °C
throughput of product	260 g/h

System Configuration: The synthesis was performed in a standard CLS equipped with one microreactor[6] and two

standard capillary residence time modules (volume 15 mL each). Due to the higher viscosity of the starting materials, the inlet valves were bypassed and the reactants were directly pumped via 1/8" tubing.

Reaction Procedure: After the system was filled with ethanol and the temperature equilibration, the feed vessels (0.5 litre graduated cylinders) were changed from solvents to reactants and the reaction was started. Product sampling began two residence times (10 min) later, and the previously produced material was rejected. The consistency of the flow rate was verified by measuring the consumed volume of starting material in a certain period. IPC was performed every 20 min by GC to monitor constancy of the reaction. Temperature and pressure monitoring verified parameter consistency throughout the entire reaction. After a collection time of 160 min, the inlets were changed back to ethanol. The product was collected for approximately one more residence time (5 min), and then the product valve was switched to waste. The system was cleaned according to the general cleaning procedure.

Workup and Purification: The water formed in the condensation reaction was removed by evaporation in a vacuum to provide 772.0 g of crude product (content >96% according to GC analysis). A sample of 150 g was purified by distillation (bp 74−76 °C, 0.74−0.84 mbar, lit.[10] 106 °C, 5 mbar) to provide 138.8 g of the pyrrole **3** (yield 92.5%, GC purity >99%, residue from the distillation 3.9 g). The process yield was calculated based on extrapolation of the complete run assuming a total mass of 714.2 g. Yield: 91% based on 165 min collecting time (chemical yield) and 86% including 10 min for the prerun (process yield). Total operation time: 185 min, including 10 min start-up time and 10 min for cleaning. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (6H, s, CH_3), 3.75 (2H, br t, J = 7.1 Hz, N−CH_2), 3.91 (2H, q, J = 8.3 Hz, O−CH_2), 5.77 (2H, s, CH_{Ar}).

2,2,3,3,3-Pentafluoro-1,1-diphenylpropan-1-ol (18a).

reaction conditions	
Stage 1	
flow rate A 0.82 M MeMgCl in THF	2.6 mL/min (2.1 mmol/min)
flow rate B 0.75 M C_2F_5I in CH_2Cl_2	2.0 mL/min (2.3 mmol/min)
reaction volume	5 mL
residence time	0.9 min
reaction temperature	−6 °C
Stage 2	
flow rate C 0.62 M benzophenone (**17**) in CH_2Cl_2	1.0 mL/min (0.6 mmol/min)
reaction volume	52 mL
residence time	8.0 min
reaction temperature	−4 °C
total throughput of product	9.7 g/h

(41) One of our partners, ProBioGen, is a leader in mammalian cell line design and a technology promotor for continuous production of monoclonal antibodies based on novel proprietary technology. The company founded, Synthacon GmbH, is located in Leuna, Germany.

System Configuration: The reaction was performed in a two-stage CPC microreaction system consisting of the CYTOS microreactor in both stages equipped with individually designed residence time units of 3 mL (stage 1) and 50 mL (stage 2) of volume, respectively. The temperature inside each stage was controlled independently using two Huber Tango thermostates. All solutions were pumped through the system using rotary piston pumps from graduated cylinders, enabling flow control in regular periods. The storage container of the Grignard reagent was kept in an argon atmosphere, whereas the solution of the C_2F_5I was cooled to 0 °C in order to prevent spontaneous evaporation.

Reaction Procedure: The inlet tubes of stage 1 were changed from solvent to reactants, and the reaction was started by activation of pump A and B (pump C running on solvent). After approximately 2 τ (2 min) elapsed in stage 1, the inlet tube for stage 2 was switched to reactant. After additional 2 τ (18 min) in stage 2, sampling of the final product was initiated. The crude product mixture was collected in a flask under instant quenching with a stirred saturated NaCl solution. During the reaction sequence, both reaction temperature and inside pressure were monitored for each stage. For yield estimation, a defined sample (5 mL) was collected in a separate flask. After finishing the reaction, the entire system was flushed with THF and cleaned according to the general cleaning procedure.

Workup and Yield Estimation: The organic layer was separated after adjusting to a pH of 6 (HOAc), and the aqueous layer was extracted with MTBE (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to provide 1.63 g of solid raw material. The yield of 86% for compound **18a** was calculated by quantitative GC analysis based on the isolated material from experiment 1 (Table 2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (1H, s, COH), 7.32 (3H, m, J = 2.1; 7.5 Hz, CH_{Ar}), 7.54 (2H, br d, J = 2.0; 7.5 Hz, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.84 (COH), 115.12 (CF_x), 117.21 (CF_x), 127.07 ($C_{Ar,\ CH}$), 128.24 ($C_{Ar,\ CH}$), 128.45 ($C_{Ar,\ CH}$), 139.77 ($C_{Ar,\ quart}$). CH assignation in ^{13}C NMR according to DEPT measurements.

3-Methoxybenzaldehyde (21).

reaction conditions	
Stage 1	
flow rate A 1.6 M BuLi in hexane	6.0 mL/min (9.6 mmol/min)
flow rate B 1.9 M 3-bromoanisol in THF	4.7 mL/min (8.9 mmol/min)
reaction volume	2 mL
residence time	0.19 min
reaction temperature	0 °C
Stage 2	
flow rate C 5 M DMF in THF	2.5 mL/min (12.5 mmol/min)
reaction volume	2 mL
residence time	0.15 min
reaction temperature	0 °C
total throughput of product	59 g/h

System Configuration: Synthesis was performed in an assembly of two standard CYTOS Lab Systems connected using a thermocontrolled metal tube ($^1/_{16}$"). Both stage 1 and stage 2 were equipped only with the microreactor. The temperatures of both microreaction systems were controlled independently with individual Huber Tango thermostates. For test purposes special newly developed pressure sensors were used. Due to the higher viscosity of the starting materials, the inlet valves were bypassed and the reactants were directly pumped via $^1/_{16}$" tubing.

Reaction Procedure: The inlet tubes of stage 1 were changed from solvent to reactants, and the reaction was started by activation of pump A and B (pump C running on solvent). After 1 min elapsed in stage 1, the inlet for stage 2 was changed to reactant. After an additional minute in stage 2, the crude product mixture was collected in a flask under instant quenching by stirring with an aqueous solution of 3 M HCl (540 mL of aqueous solution per 90 min of collection). The flasks were exchanged every 90 min, and the quenched material was worked up. The consistency of the flow rate was verified by measuring the consumed volume of starting material during a certain period. During the reaction sequence, both reaction temperature and inside pressure were monitored for each stage. After a collection time of 24 h, the stage 1 inlets were changed back to THF and the product tube was changed to waste. After an additional minute, stage 2 was also changed to THF. The system was cleaned according to the general cleaning procedure.

Workup and Purification: Each fraction was filled directly after finishing collection into a separation funnel, and the layers were separated. The aqueous layer (pH = 0−1) was discarded, and the organic layer was concentrated (50 mbar, 40 °C). The concentrated organic layers were combined (2.81 kg) and purified by distillation (100−109 °C, 13 mbar; lit.[24] 101−103 °C, 10 Torr) to obtain 1.4 kg (88%) of 3-methoxybenzaldehyde (GC-purity > 96%). Total operation time: 24 h 35 min, including 2 min start-up time and 33 min for cleaning. ^{1}H NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (3H, s, OCH_3), 7.18 (1H, m, CH_{Ar}), 7.38 (1H, br d, J = 3.3 Hz, CH_{Ar}), 7.44 (1H, m, CH_{Ar}), 7.46 (1H, m, CH_{Ar}), 10.00 (1H, s, CHO). The isolated material exhibited an identical GC retention time to that of commercially available material of **21** (Fluka catalogue nr. 64780).

Catalyst Screening of the Heck Reaction (Compounds 26−28). *General description* of sequential synthesis in SEQUOS microreaction system: The racks of the feed sampler were loaded with 100 mL septum capped bottles containing the starting material and catalyst solutions. Feeding was performed automatically by switching the reactant valves in a predefined time elapsed mode (volume dependent feeding). After the desired volume of reactant solution had been fed into the system, the inlet valve automatically switched to the spacer solvent (DMF). Fractioning was performed automatically by switching the outlet valve from waste to product after a predefined deviation between the actual and reference spectrum has been exceeded (mode: UV dependent spacing and collecting). After the product flow plug has passed the system (indicated by approximation of the UV absorption to that of the spacer solvent), the collection is stopped, and the next sequence is automatically started. The product solutions were directly quenched in 50 mL septum capped bottles containing 20 mL of 1 M aq HCl each.

Solution A: Phenyliodide **22** (7,65 g, 37.5 mmol), acrylic nitrile **23** (2.19 g, 41.3 mmol), tributylamine (10.43 g, 56.3 mmol) were filled up to 100 mL with dry DMF

Solution B: $Pd[(PPh_3)_2Cl_2]$ (320 mg, 0.46 mmol) dissolved in dry degassed DMF (100 mL).

	reaction conditions B	reaction conditions A
flow rate channel A	1.0 mL/min	1.25 mL/min
flow rate channel B	1.0 mL/min	0.75 mL/min
reaction volume	47 mL	47 mL
residence time	23.5 min	23.5 min
temperature	105 °C	125 °C

Entry 1 (compound **26**): Channel 1, solution A. Channel 2, $Pd(OAc)_2$ (168 mg, 0.75 mmol) in dry degassed DMF (100 mL total vol), reaction conditions A.

Entry 2 (compound **26**): Channel 1, solution A. Channel 2, $Pd(OAc)_2$ (168 mg, 0.75 mmol), P(*t*-Bu)$_3$ (278 mg, 1.5 mmol) in dry degassed DMF (100 mL total vol), reaction conditions A.

Entry 3 (compound **26**): Channel 1, solution A. Channel 2, $Pd(PPh_3)_4$ (527 mg, 0.46 mmol) in dry degassed DMF (100 mL total vol), reaction conditions A.

Entry 4 (compound **26**): Channel 1, solution A. Channel 2, $Pd[(PPh_3)_2Cl_2]$ (320 mg, 0.46 mmol) in dry degassed DMF (100 mL total vol), reaction conditions A.

Entry 5 (compound **26**): Channel 1, phenyliodide **22** (7,65 g, 37.5 mmol), acrylic nitrile **23** (2.19 g, 41.3 mmol), and tributylamine (10.43 g, 56.3 mmol) in dry DMF (100 mL total vol). Channel 2, solution B. Reaction conditions B.

Entry 6 (compound **28**): Channel 1, phenyliodide **22** (7,65 g, 37.5 mmol), 3-buten-2-ol **24** (2.97 g, 41.3 mmol), and tributylamine (10.43 g, 56.3 mmol) in dry DMF (100 mL total vol). Channel 2, solution B. Reaction conditions B.

Entry 7 (compound **27**): Channel 1, phenyliodide **22** (7,65 g, 37.5 mmol), acrylic ester **25** (4.13 g, 41.3 mmol), and tributylamine (10.43 g, 56.3 mmol) in dry DMF (100 mL total vol). Channel 2, solution B. Reaction conditions B.

Workup and Yield Estimation: MTBE (50 mL) was added to the quenched product solution, and the mixture was stirred for 5 min. The phases were separated, and the aqueous layer was extracted with MTBE (2 × 50 mL). The combined organic layers were washed with water and dried ($MgSO_4$), and the solvent was evaporated in a vacuum. For entries 1−4 (compound **26** each), the conversion rate was estimated by GC analysis. The product was identified by coinjection using authentic material from commercial suppliers (cinnamonic nitrile **26**, Fluka catalogue nr. 96415). The yields for entries 5−7 were calculated based on quantitative GC analysis using commercially available material as external standard.

Cinnamonic nitrile **26** (isolated raw material 496 mg, GC purity 80%, yield 86%). The *E*/*Z* ratio of 4.3:1 was

determined by ^{1}H NMR spectroscopy comparing the integrals of the olefinic signals. Cinnamonic ethyl ester (**27**, Fluka catalogue nr. 96 350, isolated raw material 750 mg, GC purity 83%, yield 94%). Only one single isomer was found according to GC analysis and ^{1}H NMR. 4-Phenylbutan-2-on (**28**, Fluka catalogue nr. 13150, isolated raw material 501 mg, GC purity 63%, yield 57%).

***N*-Boc-benzylamine (30)**.

reaction conditions	
channel A	benzylamine **29** (21.41 g, 21.80 mL, 200 mmol), triethylamine (2.02 g, 2.88 mL, 20 mmol) in dry THF (250 mL total vol)
flow rate channel A	2.0 mL/min
channel B	Boc_2O (43.64 g, 200 mmol) in dry THF (250 mL total vol)
flow rate channel B	2.0 mL/min
reaction volume	2, 17, 32 and 47 mL
residence time	0.5, 4.3, 8.0, and 11.8 min
temperature	22 °C

System Configuration: The synthesis was performed in a standard CLS with one microreactor and three standard capillary residence time modules (volume 15 mL each). The microreaction block was equipped with switchable outlets for compound extraction and direct submission of the solution to a Mettler Toldeo React IR 4000 (sample rate 32 scans/30 s). The reaction mixture was quenched instantly in aq HCl (0.05 M, 20 mL).

Reaction Procedure: After the system was filled with THF and temperature equilibration, the reactant valves were changed from solvents to reactants and the reaction started. Recording of the IR spectrum was initiated simultaneously. The solution was passed through the microreactor (experiment 1, $\tau = 0.5$ min) before stepwise hooking up the other RTUs (expt 2, $\tau = 4.3$ min; expt 3, $\tau = 8.0$ min; expt 4, $\tau = 11.8$ min). For a reliable signal estimation, the IR spectrum was recorded for two residence time units plus at least 5 min. The consistency of the flow rate was verified by measuring the consumed volume of starting material during a certain period. After finishing the cycle, the material was removed with THF. The system was cleaned according to the general cleaning procedure.

Workup and Purification: The reaction mixture of experiment 1−4 was quenched instantly in aq HCl (0.05 M, 20 mL) after the IR detection cell. After decomposition of the Boc_2O (stirring for 30 min), the aqueous layer was adjusted to a pH of 8−9 (NaOH, 0.1 M) and extracted with ether (3 × 50 mL). The product profile of the reaction was estimated by GC analysis from the combined organic layers. A sample of 21.7 mL from experiment 4 was collected for quantitative analysis. The aqueous layer (without neutralization, pH 1−2) was extracted with ether (3 × 80 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated, and the product **30** was crystallized from hexane at −20 °C in colorless prisms (1.74 g plus small amounts in the mother liquid, yield 92%). Mp 55−57 °C (lit.[33] 53−55 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (9H, s, CH_3), 4.31 (2H, d, $J = 8.0$ Hz, CH_2), 4.84 (1H, br s, NH), 7.25−7.35 (5H, m, CH_{Ar}).

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