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Articles

Application of Microreactor Technology in Process Development

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Abstract:

The microreactor technology is an efficient tool for kilogram-scale syntheses in continuous mode and is particularly effective for hazardous reactions that do not allow scale-up in conventional reactors. Applications to several classes of reactions including highly exothermic reactions, high-temperature reactions, reactions with unstable intermediates, and reactions involving hazardous reagents are described herein.

Introduction

A microreactor is generally defined as a miniaturized reactor with characteristic dimensions in micrometers and reaction volumes in the nanoliter-to-microliter range. In recent years, research on microreactors has become well established,[1] resulting in increased number of publications in various areas including high throughput synthesis,[2] multiphasic chemical reactions,[3a] catalytic reactions,[3] electrochemical reactions,[4] as well as reactions involving reactive and potentially hazardous chemicals.[2a,5] With the availability of commercial continuous microreactors,[6] the technology has drawn increased attention from industry in addition to academia.[7]

CYTOS system is a benchtop continuous reactor using microreactor technology (Figure 1, chiller not shown).[6] The microreactor plate, the core structure of this system, consists largely of a series of extremely thin stainless steel plates placed one on top of the other. These plates contain fine microchannels and predefined feed lines that allow chemicals and cooling agents to pass from one plate to the other. The microchannels are where the reactions take place. The residence volume can be adjusted by number of the residence modules used. This unique design offers much higher surface-to-volume ratio compared to the conventional reactors, and thus, the heat- and mass-transfer coefficients exceed those of conventional reactors by an order of magnitude.[6]

The continuous mode of operation offers several advantages over a batch process such as simplified operations, reduced reaction time, precise process control, higher reproducibility, and in some cases, even enhanced reaction selectivity.[8] Hazardous intermediates can be prepared and converted directly to more advanced nonhazardous product. The immediate separation of products from the reaction mixtures eliminates possible side products that may result from secondary reactions. The continuous mode may also offer a means to replace large reactors, which are costly and take up expensive laboratory or chemical plant space. In addition to the above benefits, microreactors offer their own unique advantages over traditional continuous processing systems including the highly efficient heat transfer and small reaction volumes that allow safer handling of exothermic reactions, reactions involving explosive and toxic materials, and other hazardous reactions that are normally difficult to scale up. Making increased amounts of materials becomes a matter of simply "numbering up" the microreactor systems.[6] This may ultimately lead to fast and low-cost kilogram-scale synthesis by simply bypassing the time-consuming process optimization from lab to pilot scales. However, the utilization of this technology in process research and scale-up has been limited.[7,9]

Our group is constantly engaged in chemical process research and development and the synthesis of early clinical drug candidates. We manage a large number of projects with high attrition rate. Our goal is to prepare kilogram quantities of drug substances for early clinical studies without fully developed commercial processes in a very short time. We believe that technologies, like the microreactor, provide tools

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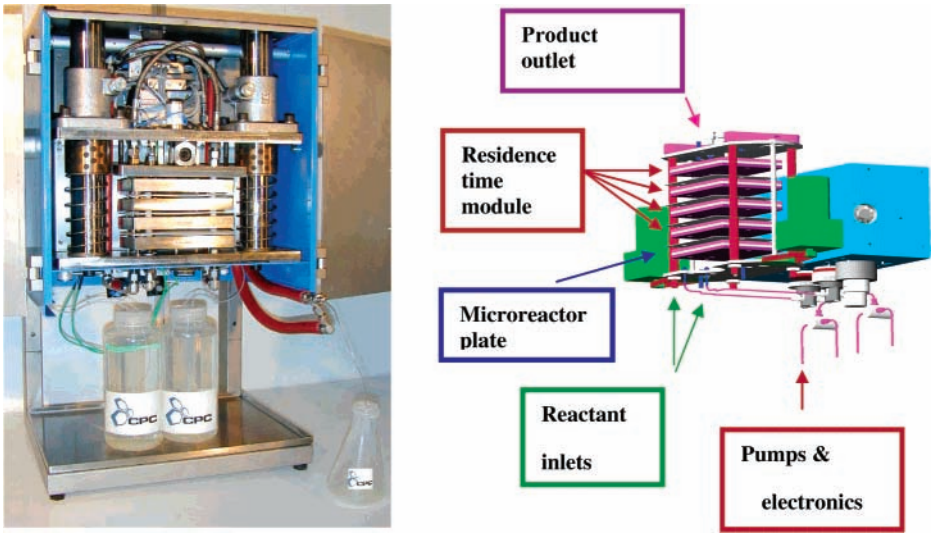


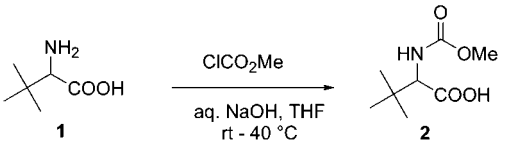
Figure 1.

with great potential to aid our research and development efforts to synthesize drug candidates more efficiently. We studied numerous classes of organic reactions on the microreactor system to evaluate its potential in applications to chemical process research. In the following section we include examples from this evaluation and discussion of our preliminary findings.

Results and Discussion

A main goal in chemical process research is to eliminate any safety concerns and hazardous conditions while maintaining efficiency and ease of operation. As a result considerable time and efforts are spent to address these concerns and to design viable safer alternatives. Typical alerts and concerns are usually raised when dealing, for example, with highly exothermic reactions, reactions carried out at high temperatures, reactions involving unstable intermediates and reactions employing hazardous reagents. With minimum process improvements, many of these reactions can be carried out both safely and effectively on microreactors. We studied several classes of reactions on the CYTOS system to evaluate its utilities in process research. The following typically unsafe reactions are examples we carried out to demonstrate the advantage of this technology in preparation of different products on kilogram scale in a continuous mode with minimum safety concerns.

Exothermic Reactions. Formation of methyl carbamates by reaction of methyl chloroformate with amines is usually exothermic. In a batch reaction (1 g scale), the preparation of *N*-methoxycarbonyl-L-*tert*-leucine (**2**), (eq 1)[10] was accompanied by a significant temperature rise upon addition of methyl chloroformate to L-*tert*-leucine (**1**) in THF in the presence of aqueous NaOH.

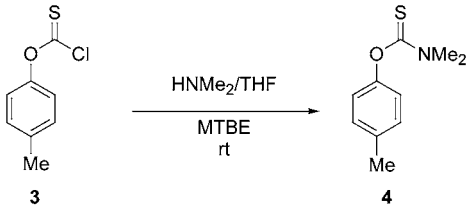


(1)

Reaction calorimetry results using Mettler RC-1 reaction calorimeter confirmed that the addition of methyl chloroformate to L-*tert*-leucine is an exothermic addition (Figure 2). The heat release rate is primarily feed-controlled, as is evident from the square shape of the heat flow (red) curve. There is minimal heat left (approximately 7%) once the addition stops as displayed by the graph of the thermal conversion (yellow line) and methyl chloroformate addition (green line) curves in Figure 2. On the basis of the calculated worst-case temperature rise (T_{ad} = 37.3 °C), the reaction will heat up and approach the solvent reflux temperature if loss of cooling and stirring occurs. Therefore, a potential chemical reaction hazard exists for this addition step. Careful, controlled addition of the methyl chloroformate is recommended so as to match or control the heat-release rate and maintain the desired reaction temperature.

When we examined the reaction in the microreactor, using the temperature and stoichiometry established on the 1-g scale batch reactions, the reaction proceeded very smoothly in 91% yield with only 7-min residence time. We can easily prepare more than 1 kg of *N*-methoxycarbonyl-L-*tert*-leucine within 12 h under these conditions.

Likewise, the amidation of *p*-tolyl chlorothionoformate (**3**) with dimethylamine to form methylphenyl dimethylthiocarbamate (**4**) (eq 2) exhibits temperature rise in batch reactions.[11] This reaction was scaled up directly on the microreactor without a safety evaluation or further process optimization to give the product in 96% yield which is comparable to the yield observed in batch reaction. With 1.4 min residence time at 40 °C, we can achieve a throughput of 155 g of product **4** per hour.



(2)

Reactions at Elevated Temperature. Most multipurpose conventional reactors have an upper temperature range of about 140 °C. Higher temperature reactions need special

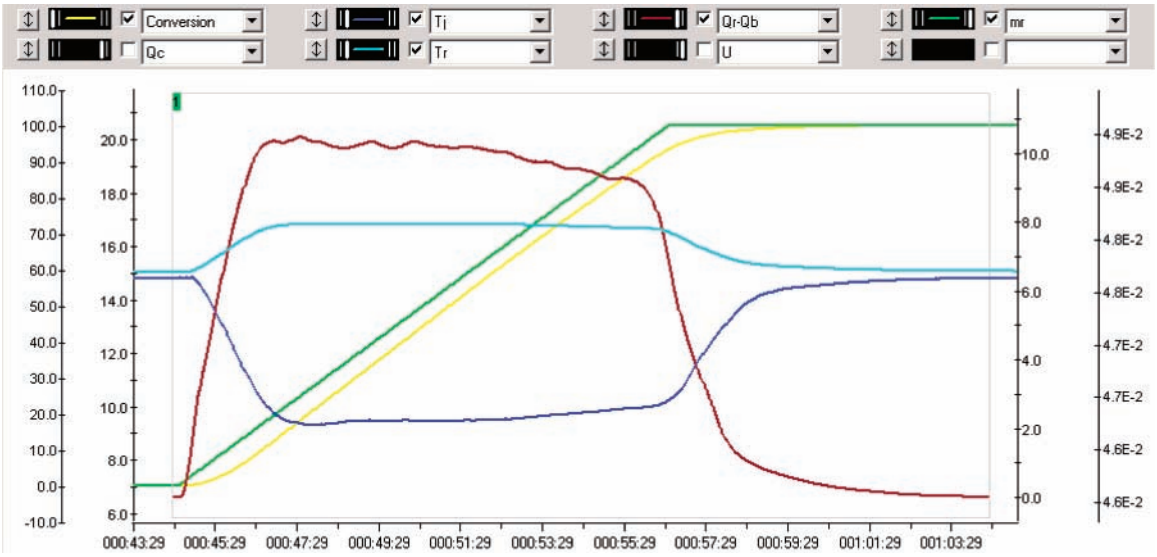
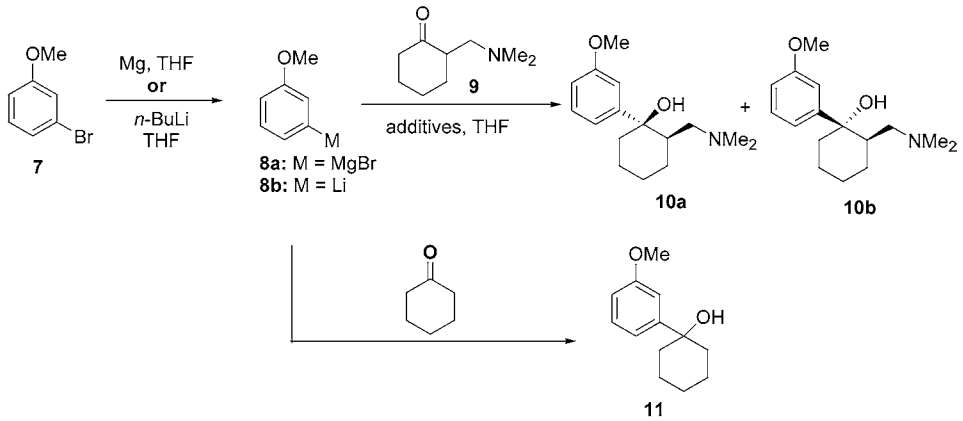
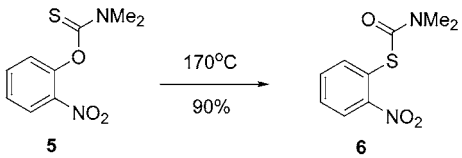


Figure 2. **Reaction calorimetry results from the addition of methyl chloroformate (slight excess) to L-*tert*-leucine.**

Scheme 1



reactors and heat transfer equipment. The CYTOS system can heat to 200 °C, which offers a broader temperature range than conventional reactors. We examined the Newman-Kuart rearrangement involving *O*-(2-nitrophenyl)-*N*,*N*-dimethylthiocarbamate (**5**) as an example of high-temperature reaction. Newman reported 90% yield for the rearrangement of neat *O*-(2-nitrophenyl)-*N*,*N*-dimethylthiocarbamate (**5**) to *S*-(2-nitrophenyl)-*N*,*N*-dimethylcarbamothioate (**6**) at 170 °C in 14 min (eq 3).[11] Using sulfolane as a solvent and applying the same reaction conditions on the microreactor, we effected the same rearrangement quantitatively with a throughput of 34 g of **6** per hour. Under these conditions, the throughput is only limited by the solubility of the starting material in sulfolane.



(3)

Reactions with Unstable Intermediates. An early synthesis of tramadol (**10a**) was accomplished via addition of the Grignard reagent, 3-methoxyphenylmagnesium bromide (**8a**), to ketone **9** (Scheme 1). This addition typically results in formation of the *cis*-isomer (**10a**) and *trans*-isomer (**10b**) in about 4:1 ratio.[12] Further studies of this reaction resulted in several improvements in the stereoselectivity of the Grignard addition[13] as well as the separation of the two isomeric products.[14] It was determined that a higher ratio of the desired isomer **10a** is achieved when aryllithium **8b** was used instead of the Grignard reagent at low temperatures.[15]

We studied this reaction extensively, trying to increase the stereoslectivity under various reaction conditions.[16] Through the use of reaction calorimetry we found that both

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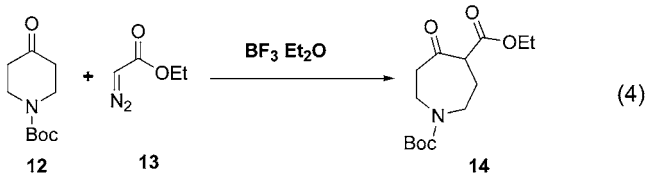
steps, the formation of 3-methoxyphenyllithium (**8b**) and its addition to ketone **9**, are quite exothermic in batch reactions with worst case temperature rise (T_{ad}) of 61.9 and 133 °C, respectively. Very low reaction temperatures are required due to the instability of 3-methoxyphenyllithium intermediate. We concluded then that a continuous reaction may be a good alternative to batch synthesis to improve the reaction yield and to minimize the safety concerns of the reaction sequence. Consequently, we built a benchtop continuous reactor utilizing HPLC pumps and tubing to carry out this reaction in a continuous mode. However, we were unsuccessful due to the inefficient heat transfer in this system. Recently, with the availability of the microreactor system, we revisited this reaction and reexamined the continuous process using unsubstituted cyclohexanone as a model compound.[17]

First, we carried out the reaction on a small scale in batch mode at −10 and −65 °C and obtained 32 and 80% yield of the expected tertiary alcohol **11**, respectively. Clearly, low temperature is preferred due to the instability of lithium intermediate **8b** at high temperatures. The CYTOS system offers two low-temperature ranges, −20 °C with a conventional chiller, and −65 °C with a more powerful chiller. With two successive microreactor systems, we would be able to carry out both reaction steps in a continuous mode with precise control. However, with only one system available and a regular chiller, we chose to study the metal−halogen exchange step on the microreactor at −14 °C with 17 s residence time, and then react the resulting lithium intermediate **8b** with cyclohexanone in batch mode at −40 °C. We achieved 87% yield and a throughput of 54 g of product per hour.

Reactions Involving Hazardous Reagents. In process research, we often encounter reactions involving potentially hazardous reagents such diazo compounds, azides, etc. We often have to devote time and resources to find suitable experimental and engineering designs to safely scale-up these reactions or to design safer alternative syntheses.[18] Since the actual reaction volumes in a microreactor are very small, the safety concerns are minimized. This has been proven when we studied the following ring-expansion reaction (eq 4) on the microreactor system.



12 **13** **14** (4)

The reaction of *N*-Boc-4-piperidone (**12**) with ethyl diazoacetate (**13**) gives 90% crude yield of product **14** when carried out in the presence of $BF_3 \cdot Et_2O$ in ether at −25 °C.[19] In addition to using ether as solvent, such reaction conditions involving the use of ethyl diazoacetate pose safety concerns for large-scale synthesis without the proper safety and engineering controls to mitigate both the chemical and operational hazards associated with the use of this reagent.[20] We investigated this reaction, in a batch mode, on 70-mg scale without any significant safety concerns. Several variables were studied including solvent, reaction temperature, stoichiometry, and order of reagent addition to eliminate the by-products and increase the yield and purity. We found the solvent and reaction temperature are critical for the success of the reaction. Increasing the reaction temperature resulted in more by-products. An 81% yield was obtained when 0.2 equiv of $BF_3 \cdot Et_2O$ was added at <15 °C to a mixture of ethyl diazoacetate (**13**) and *N*-Boc-4-piperidone (**12**) in 1:4 ratio of CH_2Cl_2/MTBE solvent mixture.

However, reaction calorimetry results using the Mettler RC-1 reaction calorimeter show that the addition of the $BF_3 \cdot Et_2O$ solution to a mixture of *N*-Boc-4-piperidone (**12**) and ethyl diazoacetate (**13**) is very exothermic (Figure 3). The heat release rate with this mode of addition is not feed-controlled, and an initiation period is observed. The reaction is very sluggish, and the majority of the reaction occurs en mass once 60% of the material has been added. Also, it is at this point that the majority of the gas release takes place. On the basis of the calculated worst case temperature rise (T_{ad} = 45.63 °C), the reaction would quickly heat up and approach the solvent reflux temperature, depending on the starting reaction temperature, possibly spewing the contents of the reactor if loss of cooling or stirring occurred with full accidental mischarge of all the $BF_3 \cdot Et_2O$. Even using the RC-1, the reaction temperature was difficult to control as the reaction quickly progressed. Although the T_{ad} result showed that the decomposition temperature of ethyl diazoacetate would not be reached, a chemical reaction hazard still exists for this addition and mode of operation due to evolution of large amounts of nitrogen gas as the reaction proceeds, which could result in over-pressurization of the reaction vessel. Scaling this reaction to kilogram scales safely in a conventional reactor is not recommended because of these reasons.

However, using the microreactor, we were able to reduce the time-consuming process research to find optimal safe conditions. Applying the conditions established on the 70-mg scale reaction in batch mode, without any further optimization, the reaction proceeded smoothly and safely with precise control on the microreactor system to form the desired product in 89% yield. This is a rapid reaction with only 1.8 min residence time. Under these conditions, we achieved a throughput of 91 g per hour. This reaction

(16) Unpublished results.

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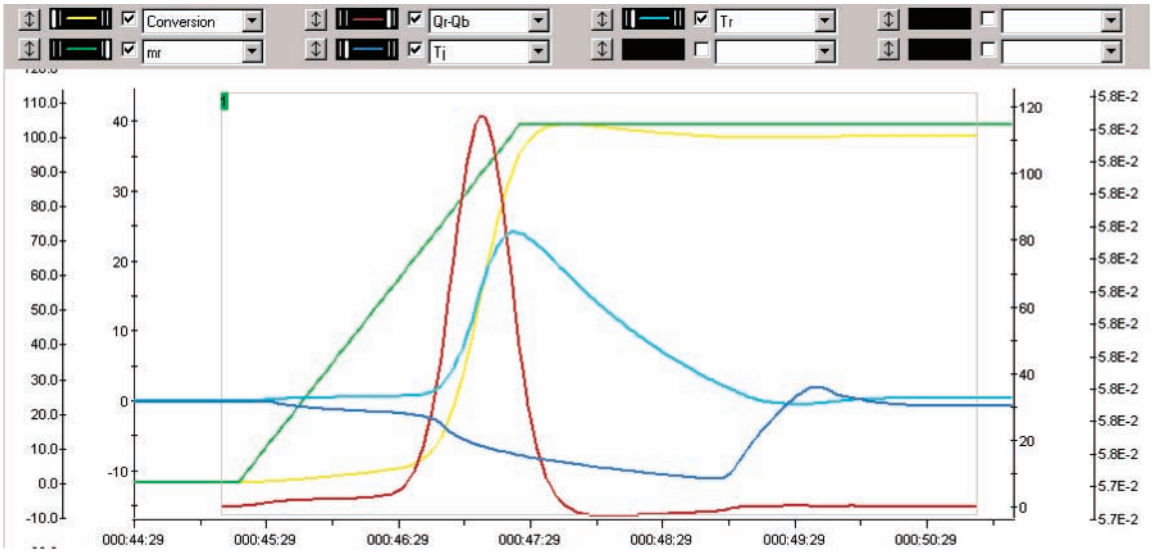

Figure 3. **Addition of BF_3 Et_2O to *N*-Boc-4-piperidone and ethyl diazoacetate**

demonstrates the effectiveness and potential of microreactor technology in large-scale synthesis in a continuous mode.

Conclusions

To summarize, we demonstrated the successful use of the microreactor technology in several classes of reactions and developed continuous processes for the synthesis of desired molecules. The technology offers an efficient, safe scale-up, shorter process research times, and eventually a reduction in drug development time. Microreactor technology shows promise as an innovative tool to help us fulfill our mission to move new medicines from discovery into patients as quickly as possible.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. Continuous reactions were carried out on the CYTOS system from Cellular Process Chemistry Systems GmbH. The temperature inside the CYTOS system was controlled by an external thermostat (Huber Tango). All solutions were filtered through a medium sintered glass frit funnel. Pumps on the CYTOS system are primed and calibrated with corresponding solutions. The residence time τ was calculated according to the equation: τ (min) = residence volume (mL)/total flow rate (mL/min). Product was collected from the outlet of the system after 1.5 residence times to ensure steady-state conditions.

***N*-Methoxycarbonyl-L-*tert*-leucine (2).** The microreactor with 35 mL residence volume was heated to 35 °C. A solution (200 mL) of L-*tert*-leucine (32.5 g, 0.25 mol) and NaOH (36 g, 0.9 mol) in water was introduced into inlet A at a flow rate of 4 mL/min. A solution (50 mL) of methyl chloroformate (23 mL, 0.3 mol) in THF was introduced into inlet B at a flow rate of 1 mL/min. The product mixture (160 mL) was collected from the reactor outlet over 32 min, and product **2** was extracted from the mixture with CH_2Cl_2. Evaporation of the solvent under reduced pressure gave 60 g of product **2** as a colorless solid (91%). The spectroscopic data are identical to those of the literature report.[10]

Methylphenyl Dimethylthiocarbamate (4). The microreactor with 35 mL residence volume was heated to 40 °C. A solution (35 mL) of *p*-tolyl chlorothionoformate (24.5 mL, 0.16 mol) in THF was introduced into inlet A at a flow rate of 3 mL/min. Dimethylamine in THF (2 M, 193 mL) was diluted to 260 mL with water and introduced into the inlet B at a flow rate of 22.2 mL/min. The biphasic solution (176 mL) was collected from the outlet over 7 min and evaporated under reduced pressure to a suspension. The solid was collected by filtration and dried to give 18.1 g of **4** (96%). The spectroscopic data are identical to those of the literature report.[11]

***S*-(2-Nitrophenyl)-*N*,*N*-dimethylcarbamothioate (6).** The microreactor with a residence volume of 35 mL was heated to 170 °C. A solution (100 mL) of *O*-(2-nitrophenyl)-*N*,*N*-dimethylthiocarbamate (**5**) (22.6 g, 0.1 mol) was prepared in sulfolane at 100 °C and introduced into the reactor at 2.5 mL/min. A sample (42.5 mL) of the product mixture was collected from the reactor outlet over 17 min. HPLC analysis of the product mixture indicated a quantitative conversion of **5** to **6** by comparison with authentic sample prepared in batch reaction.[11]

1-(3-Methoxyphenyl)cyclohexanol (11). The microreactor with 2 mL residence volume was cooled to −14 °C. A solution of *m*-bromoanisole in anhydrous THF (1 M, 100 mL) was prepared and introduced into inlet A under nitrogen at a flow rate of 5 mL/min. *n*-BuLi (2.5 M in hexane, 40 mL) was introduced into inlet B under nitrogen at a flow rate of 2 mL/min. A sample of the resulting solution (70 mL) containing 3-methoxyphenyllithium was collected over 10 min from the microreactor outlet and introduced continuously into a solution of cyclohexanone (1 M in anhydrous THF, 50 mL) at −40 °C under nitrogen. After quenching with saturated aqueous NH_4Cl solution, 9 g of product **11** was obtained (87%) as analyzed by HPLC with comparison to authentic sample prepared in batch reaction.[17a]

***N-tert*-Butoxycarbonyl-5-ethoxycarbonyl-4-perhydroazepinone (14).** The microreactor with 35 mL residence volume was cooled to 10 °C. A solution (400 mL) of *N-tert*-butoxycarbonyl-4-piperidone (**12**) (30.5 g, 0.15 mol) and ethyl diazoacetate (**13**) (21.4 mL, 0.2 mol) in CH_2Cl_2/MTBE (1/4) was introduced into inlet A at a flow rate of 16 mL/min. A solution (100 mL) of BF_3 etherate (4.3 mL, 34.5 mmol) in MTBE was introduced into inlet B at a flow rate of 4 mL/min. The product mixture (400 mL) was collected from the outlet over 20 min and quenched into a 1 M solution of tartaric acid in water (100 mL). The product **14** (30 g) was obtained (89%), as determined by HPLC analysis by comparison with an authentic sample prepared in batch reaction.[19]

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