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Flash Chemistry Extensively Optimized: High-Temperature Swern–Moffatt Oxidation in an Automated Microreactor Platform

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Abstract: The generally accepted benefits of small lateral dimensions of microreactors (1 μm to 1 mm) enable a different way of performing synthetic chemistry: Extremely short contact times in the millisecond range can circumvent the need for performing highly exothermic and fast reactions at very low temperatures. In order to fully exploit this technology, such fast processes need to be redesigned and investigated for optimal reaction conditions, which can differ drastically from the ones traditionally applied. In a comprehensive study, we optimized the selective Swern–Moffatt oxidation of benzyl alcohol to benzaldehyde by varying five experimental parameters, including reaction time and temperature. Employing an ultrashort mixing and reaction time of only 32 ms, the optimal temperature was determined to be 70 °C, approximately 150 °C higher than in the conventional batch conditions. This remarkable difference shows both the potency of continuous-flow chemistry as well as the urgency of a paradigm shift in reaction design for continuous-flow conditions.

Keywords: experimental design · flash chemistry · flow chemistry · microreactors · oxidation

Introduction

Microreactor technology is rapidly becoming a valuable tool in synthetic organic chemistry.[1–6] It is estimated that 20% of all synthetic reactions in the pharmaceutical and fine chemical industries could directly benefit in terms of yield, selectivity, and efficiency from being carried out in microreactors or, more generally, flow reactors.[7,8] The generally accepted benefits of small lateral dimensions of microreactors (1 μm to 1 mm), such as efficient heat and mass transfer, enable a different way of performing synthetic chemistry: Extremely short contact times in the millisecond range can circumvent the need for performing highly exothermic and fast reactions at very low temperatures. This concept of process intensification, aptly termed 'flash chemistry' by Yoshida,[9] opens up a whole new toolbox for the organic chemist.

In order to fully exploit this toolbox, such fast processes and reactions need to be redesigned and therefore reinvestigated to identify optimal reaction conditions, which can differ drastically from the ones traditionally applied. Currently, high flow-through microreactors are generally used for reaction screening and optimization. Smaller devices, however, with typical flow rates in the $\mu L\,min^{-1}$ range and hence requiring significantly smaller amounts of material, are intrinsically considerably more attractive for this purpose.[10,11] Once optimal reaction conditions have been determined on a small scale, flow chemistry allows a scaling-out procedure due to the high level of reproducibility of the process.

The Swern–Moffatt oxidation is potentially a highly relevant reaction for industry, because this selective oxidation of primary alcohols to aldehydes does not require heavy metals. This reaction, however, is traditionally carried out at temperatures around −78 °C, which limits its viability for high-volume manufacturing. In the conventional procedure, the activator trifluoroacetic anhydride (TFAA) is first mixed with dimethylsulfoxide (DMSO) at −78 °C. After the reactive sulfonium species **2** has been formed (Scheme 1), reactant **1** (a primary or secondary alcohol) is added to initiate the oxidation. In the final step a tertiary amine base

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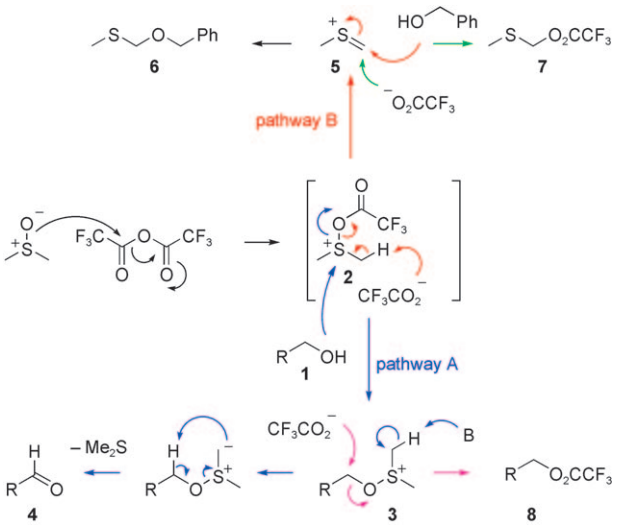

Scheme 1. Proposed reaction scheme for the Swern–Moffatt oxidation of primary alcohol **1** to aldehyde **4**.

(triethylamine or *N*,*N*-diisopropylethylamine (DIPEA)) is added to terminate the reaction, creating the desired aldehyde or ketone, and to quench unreacted TFAA. The low temperatures are required to prevent an important side reaction: the Pummerer rearrangement. Both reaction intermediates trifluoroacetoxy dimethylsulfonium salt **2** and the alkoxy dimethylsulfonium salt **3** rearrange at higher temperatures, forming either the trifluoroacetyl ester **8** or thiomethyl ether **6**.

Abstract in Dutch: De algemeen geaccepteerde voordelen van de zijdelingse dimensies van microreactoren (1 μm tot 1 mm) maken een nieuwe manier van het uitvoeren van synthetische reacties mogelijk: extreem korte contacttijden in de orde van milliseconden kunnen de noodzaak van het uitvoeren van zeer exotherme reacties bij lage temperaturen omzeilen. Om deze technologie ten volle te benutten, moeten dergelijke snelle processen opnieuw worden ontworpen, en moet opnieuw worden gezocht naar optimale reactiecondities, die nu drastisch kunnen verschillen van de conventionele omstandigheden. In een uitgebreide studie hebben we de selectieve Swern–Moffatt oxidatie van benzylalcohol naar benzaldehyde geoptimaliseerd door vijf experimentele parameters te variëren, waaronder reactietijd en temperatuur. Door gebruik te maken van zeer korte meng- en reactietijden, zoals 32 ms, is vastgesteld dat de optimale reactietemperatuur 70 °C bedraagt, ongeveer 150 °C hoger dan onder gebruikelijke condities. Dit opmerkelijke verschil reflecteert enerzijds het potentieel van flowchemie, maar toont anderzijds ook de noodzaak aan van een drastische verandering in denkwijze bij het ontwerpen van continue flowchemie.

It was previously shown by Yoshida et al. that it is possible to perform the Swern–Moffatt oxidation in a microreactor at room temperature.[12] Using a continuous-flow setup, and by drastically reducing the time between the addition of TFAA and the alcohol (on the order of 100 ms) the reaction at room temperature gave results comparable to conventional procedures. In addition, a broad study of Swern–Moffatt oxidations with a range of primary and secondary alcohols was performed by Van der Linden et al.,[13] demonstrating that premixing DMSO with the alcohol prior to reacting it with TFAA inside the microreactor led to similar or even better aldehyde yields and selectivities than conventional conditions. It can be reasoned that if the alcohol substrate is present in the DMSO solution, the reactive intermediate will react in situ with the alcohol so that one mixing step can be eliminated.

Since these studies indicate that the traditional barriers for the Swern–Moffatt oxidation have disappeared by applying microreactor technology, it is now of interest to find the optimal reaction conditions for this reaction. Herein we describe a comprehensive study to systematically screen Swern–Moffatt oxidation parameters using a microreactor device (internal reactor volume 140 nL), which generates a large amount of chemical information with only minute amounts of starting compound. The oxidation of benzyl alcohol (**1**, R = Ph) to benzaldehyde was chosen as the model reaction, because the intermediate alkoxysulfonium salt **3** is most prone to undesired solvolytic attack.

Since the effect of multiple parameters was investigated, multivariate screening was employed instead of the more commonly used univariate screening. Earlier examples of employing multivariate screening using microreactor flow chemistry were demonstrated by Yoshida et al.[14] The benefit of a multivariate approach includes the detection of possible dependency between parameters. Because multivariate experiments tend to require a large number of experiments when all possible combinations of settings would be screened, experimental design methodology should be used. In this paper, D-optimal designs were employed,[15] based on linear models containing up to cubic terms. Using linear regression, nonsignificant terms were removed from the equation in a stepwise fashion, which eventually was refit using only relevant terms. This method was used for visualization and determination of the optimal reaction conditions. The selected and simultaneously screened reaction parameters are listed in Table 1. The yield of the aldehyde was chosen as the actual goal of the optimization. In commercial chemical manufacturing, other goals for optimization are typically space–time yield and overall production rate versus costs. However, we felt that for simplicity reasons, yield would be a more appropriate choice for demonstration of the method's viability. After optimization, the optimal reaction conditions were applied to a larger continuous-flow reactor to validate the scalability.

Table 1. Overview of experimental parameters.

Run	No. of dimensions	No. of experiments	Reaction time [s]	TFFA/substrate stoichiometry	T [°C]	DMSO/substrate stoichiometry	Substrate conc. [M][a]
1	2	126	0.2–20	1.0–9.6	23	5	0.5
2	3	55[b]	0.04–3.55	1.0–8.0	25–70	5	0.5
3	5	180[b]	0.04–3.55	1.0–8.5	25–70	2.5–10	0.15–0.25

[a] In feeding liquid. [b] D-optimal selections.

Results and Discussion

Microreactor Setup

Schematic representations of the microreactor setups are shown in Figure 1. All parts within the dotted line consist of one single glass chip with single-sided wet etched channels of 55×120 μm. The mixing time could be held sufficiently low even without further specific channel geometries: Even at the highest flow rates the time required for diffusive mixing in the straight mixing channels was kept well below the total residence time, mainly owing to low viscosities and fast diffusive properties of the small molecules. The channel volumes determining the reaction time, designated as R1 and R2 in setups 1 and 2, respectively, are indicated in Figure 1.

Run 1: Two-Parameter Optimization: Reaction Time and TFAA Stoichiometry

In the first optimization run at room temperature, setup 1 was used (Figure 1). Reaction time and TFAA stoichiometry relative to the alcohol substrate were simultaneously varied in the range from 0.2 to 20 s and from 2 to 9, respectively, resulting in two-dimensional plots. The results from 126 experiments were visualized by local interpolation and generation of a simple contour plot (Figure 2a). For the calculation of the interpolation, the simple linear algorithm *griddata* in MATLAB (MathWorks, R2007a) with default linear settings was used. However, in order to locate the optimum value for reaction yield, curve fitting was required. Results from third-order two-dimensional curve fitting are shown in Figure 2b. It must be noted that regulating the stoichiometric ratio was performed by varying the flow rates of the benzyl alcohol/DIPEA/DMSO solution and the TFAA solution. One can argue that owing to different flow rates also the

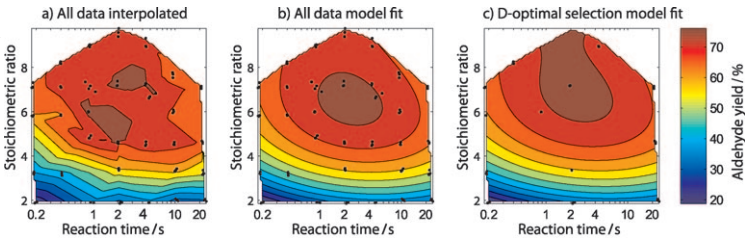

Figure 2. Yield of aldehyde **4** in run 1 at room temperature, shown as contour plots: a) interpolated response, b) third-order curve fitting, c) third-order curve fitting on selection of D-optimal design ($n = 30$ experiments).

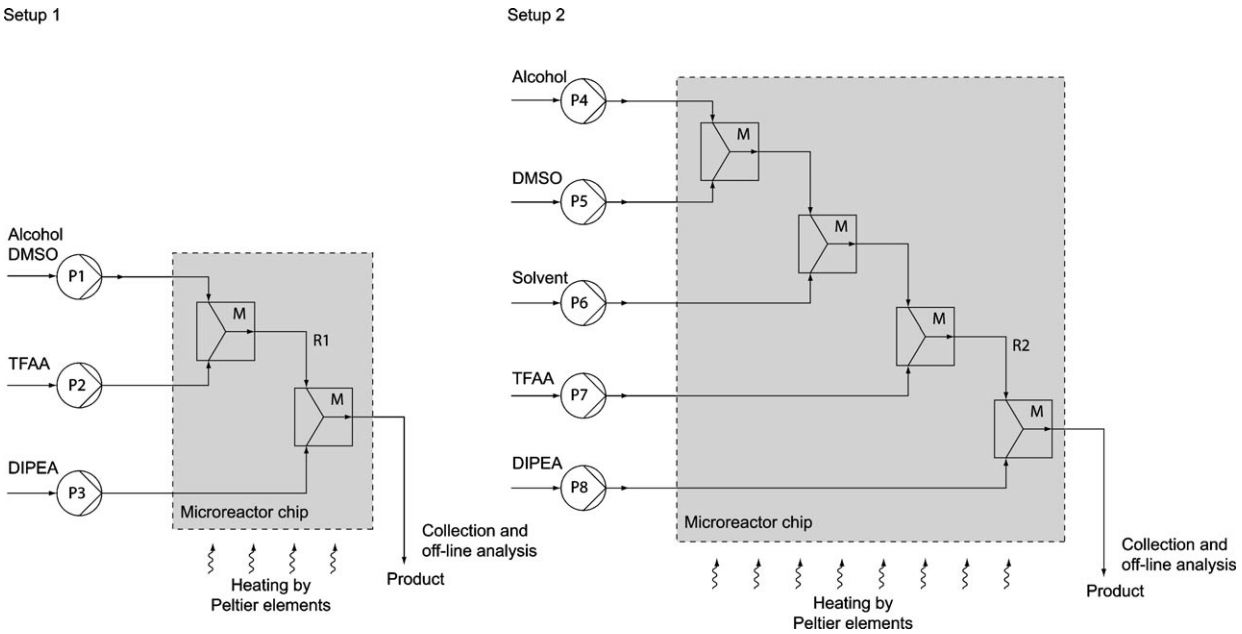

Figure 1. Microreactor setups 1 and 2, with relevant reactor volumes designated 'R1' and 'R2'.

two reagent streams occupied different volumes in the microreactor. This could have an influence on the diffusion time and hence the reaction efficiency. However, repeating the experiment with different TFAA concentrations but identical overall stoichiometric ratios yielded similar results (data not shown). Subsequently, a polynomial model was prepared from a D-optimal selection of the experimental data (30 experiments), resulting in a very similar plot (Figure 2c). This confirms the hypothesis that a D-optimal experimental design can be applied to perform multidimensional reaction screening, thereby drastically decreasing the required number of experiments.

Run 2: Three-Parameter Optimization: Reaction Time, TFAA Stoichiometry, and Temperature

In the next step, reaction temperature was investigated as a third parameter. Conventionally, the Swern–Moffatt oxidation is performed at low temperatures, typically around −78 °C. While it was previously shown that the reaction temperature could be raised to room temperature while retaining chemoselectivity, we aimed to increase the reaction temperature even further and evaluate the reaction performance in terms of yield and selectivity.

In Figure 3, the modelled aldehyde yield for experiment 2 is shown, clearly indicating optimal reaction parameters near 0.5 s reaction time, a TFAA stoichiometry of 7, and a temperature of 45 °C. For the linear interpolation the MATLAB algorithm *interp3* with default linear settings was used. It must be noted that the optimum in reaction time in this case is somewhat different than observed in the previous experiment. As shown in the slice plot, however, the reaction yield is stable over a rather broad range of different reaction times, from approximately 0.3 s up to several seconds. Thus, it can be concluded that although fast mixing and a short reaction time are required to prevent the reactive intermediate **2** from decomposing, the alkoxysulfonium salt **3** is stable on the timescale of a second, even at elevated temperatures.

Run 3: Five-Parameter Optimization, Including DMSO Stoichiometry, and Substrate Concentration

In the final part of the experiment, any possible influences of DMSO stoichiometry relative to alcohol substrate and the concentration of the alcohol substrate were also taken into account, leading us to a five-dimensional optimization run. A total number of 180 experiments were run. The results were again modelled following a cubic polynomial approach. Optimal values for all parameters were found, and are listed in Table 2.

Table 2. Overview of optimal reaction conditions.

Temperature	70 °C
Reaction time	0.032 s
Substrate concentration in reactor	0.17 M
TFAA stoichiometry	6
DMSO stoichiometry	9
Residence time unit dimensions (diameter × length)	0.125 × 40 mm
Total substrate throughput	0.50 g h^{-1}

These optimal settings were used to visualize the actual model of the aldehyde yield (Figure 4, upper matrix for aldehyde yield). Each contour plot represents a two-dimensional cross-section of the five-dimensional space. All other parameters were fixed at the optimal settings.

It is clear that DMSO and TFAA stoichiometry have a dramatic effect on the reaction rate. The same can be concluded from the reaction time. The two other parameters, overall reaction concentration and temperature, seem to have much less effect on the reaction efficiency. Furthermore, significant parameter dependencies between TFAA and DMSO stoichiometry on the one hand and TFAA stoichiometry and reaction time on the other hand are observed, demonstrating the need for simultaneous multidimensional screening. Reaction time and temperature as single parameters show that the actual optimal setting is on the edge of the parametric domain chosen. This means that

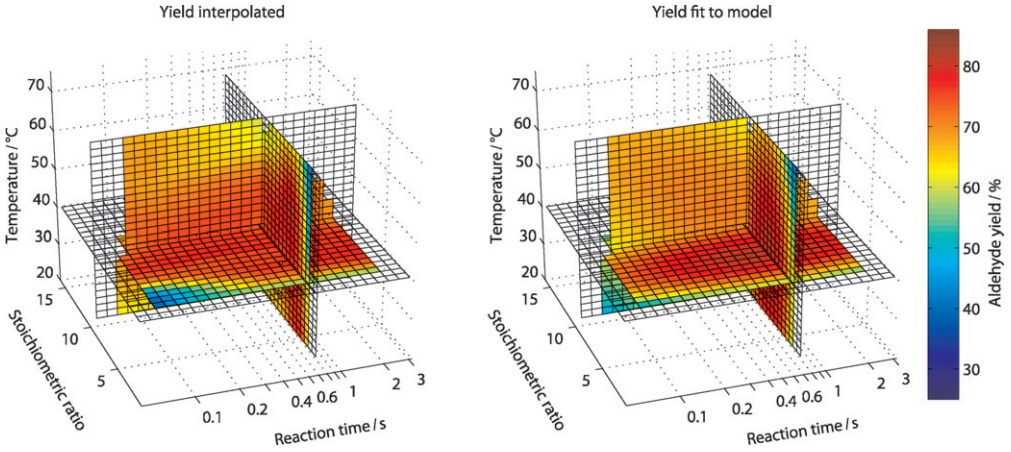

Figure 3. Yield of aldehyde **4** in run 2, shown as a three-dimensional slice plot: locally interpolated data (left) and model fit (right).

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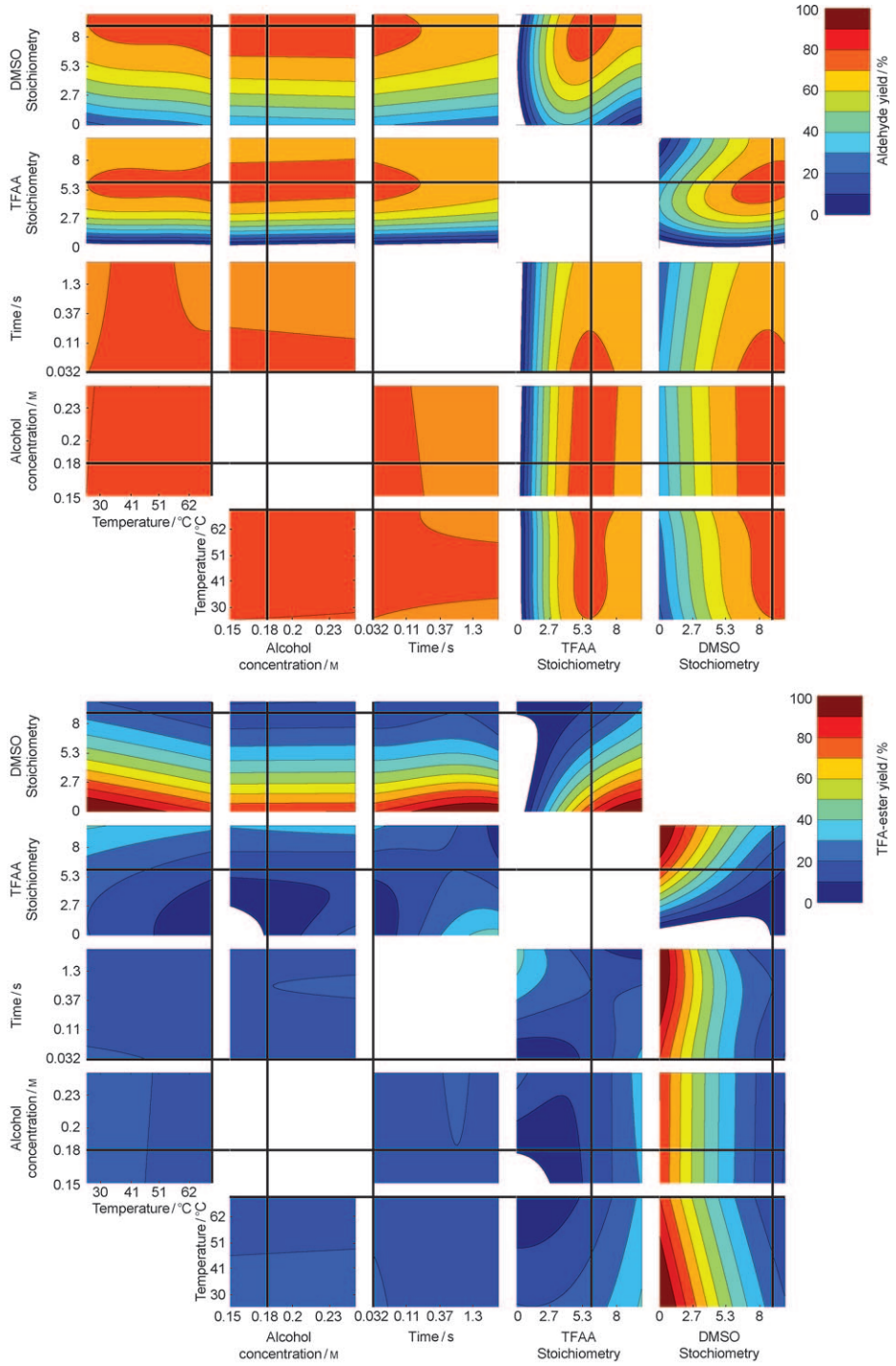

Figure 4. Yields of aldehyde **4** (top) and formation of byproduct **8** (bottom) in run 3, shown as matrix contour plots. Each contour plot is a cross-section of the model space. The set of optimal conditions is used as fixed values for the remaining dimensions in each contour plot, shown as bold lines.

somewhat higher aldehyde yields can be expected at even lower reaction times and higher temperatures. This opens opportunities for further investigations searching for the absolute limit of reaction efficiency.

Very small amounts of thiomethyl ether **6** were observed, approaching the detection limits. Unlike Van der Linden, who reported reduced stability of the trifluoroacetyl ester in samples diluted with THF and water for HPLC, we detected no instability of this analyte when dichloromethane was used as the diluting solvent. The difference can be explained by the sample preparation used by Van der Linden, resulting in an aqueous basic solution in which ester hydrolysis occurs more readily. Because the trifluoracetyl ester **8**, presumably resulting from the Pummerer rearrangement, was detected at significant levels, the ratio between the ester and the desired aldehyde was chosen as a measure for reaction selectivity, while the amount of aldehyde being formed served as the standard yield indicator.

In the bottom part of Figure 4, formation of byproduct **8** is visualized. In most of the experimental domain, **8** was formed in very low amounts, typically less than 2%. At low DMSO and high TFAA concentrations, however, the formation of byproduct **8** steeply increased. Interestingly, these results indicate a pathway of formation of byproduct **8** via direct esterification of the alcohol by TFAA, possibly in combination with esterification of the alcohol by reaction with the Pummerer rearrangement product **7**. It should be noted that Van der Linden did not screen the area of low DMSO and high TFAA concentration, thus avoiding direct esterification of alcohol by TFAA.

Because of the integrated reactor design, both the addition of the alcohol to the activated sulfonium salt **2**, as well as the final deprotonation by the amine base, take place at the same temperature. Since we already observed high yields using this design, further investigation into separating both reaction steps and individually optimizing their temperatures was considered unnecessary at this stage, but remains an interesting topic for future research.

Preparative-Scale Continuous Reaction

The optimal conditions for the 140 nL reactor were transferred to a 500 nL internal volume microreactor in order to conduct the same oxidation on a preparative scale. For this purpose, a standard commercially available stainless steel continuous-flow reactor with an internal diameter of 125 μm was selected and the optimal settings from the screening experiments were applied (Table 2). The reaction fluids were continuously pumped through the reactor for approximately 2 h, with a substrate throughput of 0.5 g h^{-1}. The aldehyde yield of the outflow was monitored at intervals and always appeared greater than 96% with only traces of byproduct based on GC analysis. This confirms that the initially identified optimal oxidation conditions can also be successfully applied to a larger microreactor system, while aldehyde yields compare favorably to those observed by Kawaguchi et al. (75% yield at 20 °C) and Van der Linden (84% at 20 °C). Furthermore, the observation that this particular reaction is easily scaled up to higher diameter tubing is in line with the findings of Van der Linden, indicating that mixing efficiency is not a limitation up to a certain tubing diameter, even for these ultrafast reactions.

Conclusions

We have shown that it is possible to employ an automated microreactor platform to optimize a very fast and exothermic reaction. Five factors (temperature, substrate concentration, stoichiometries of two reagents, and reaction time) were investigated simultaneously in continuous-flow microreactors for optimization of the selective oxidation of benzyl alcohol to benzaldehyde. Employing a very short mixing and reaction time of only 32 ms, the optimal reaction temperature was found to be 70 °C, approximately 150 °C higher than under conventional batch conditions. This remarkable difference shows both the potency of continuous-flow chemistry as well as the urgency of a paradigm shift in the design of chemical reactions when carried out under continuous-flow conditions.

The optimal conditions were also applied to a larger microreactor system to synthesize the aldehyde product on a preparative scale. In conclusion, the oxidation could be performed at around 96% conversion in a continuous-flow microreactor, both on a small and a preparative scale, which clearly underlines the potential of flow chemistry in organic synthesis. Furthermore, efficient multivariate screening is required when dependency between multiple parameters affects reaction efficiency.

Experimental Section

GC analysis: All GC analyses were performed off-line. The effluent of the microreactor was diluted using dichloromethane marked with an internal standard in order to constantly monitor flow rates as previously demonstrated.[16] GC analysis was performed on a Shimadzu GC 2010 GC-FID equipped with a Quadrex 007 1701 column (length: 10 m, internal diameter: 0.1 mm, film thickness: 0.1 μm), using a temperature program starting at 98 °C for 0.85 min with subsequent ballistic heating with a set temperature of 235 °C for 1.0 min, a linear flow rate of 1 m s^{-1}, and a split ratio of 750. An analysis cycle time of approximately 3 min was used.

Microreactor setup: All syringes (Harvard apparatus; high-pressure syringe, 2 mL) mounted on a syringe pump (New Era; type NE-1000 or NE-500) were connected to FEP tubing (1.59 mm OD, 254 μm ID). At the end of each tubing, a special 'flat-bottom headless nut' (Upchurch Scientific; type: M 660) was mounted which pressed down onto a flat bottom ferrule (Upchurch Scientific; type: M 650) to achieve a leak-free fluid connection to the microreactor. The microreactor was placed in a custom-designed chip holder[17] with threaded holes on the top side in which the nuts were screwed. For temperature control, a custom-designed heater (Peltier element) was used, which was slid into the microreactor chip holder and contacted to the microreactor's bottom side. A stainless steel needle (UpChurch Scientific; type U 106 1/100" ID 1/16" OD, custom prepared needle tip) was used as outlet. A sample robot (Gilson 223) was used to dispense all samples during reaction screening. The pumps, robot, and temperature controller were automatically controlled with a custom-designed software program (developed by Fraunhofer IMS, Duisburg, Germany).

Microreactor: The actual microreactor was fabricated from borosilicate glass by Micronit Microfluidics BV, Enschede, The Netherlands (HF etched). Chip dimensions: length 45 mm, width 15 mm, height 2.2 mm. Channel dimensions: width 120 μm, depth 55 μm, total length 26 or 1320 mm, depending on desired residence time. Reaction volumes were 0.14 or 7.02 μL, respectively.

Runs 1 and 2 using setup 1: The first syringe was loaded with liquid A containing benzyl alcohol **1** (R = Ph; 1.35 g, 12.5 mmol), DMSO (4.88 g, 62.5 mmol), and 1-bromo-3,5-dimethylbenzene (2.04 g, 11.0 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The second syringe was loaded with liquid B containing TFAA (5.25 g, 25 mmol) and 1,2-dichlorobenzene (1.95 g, 13.3 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The third syringe was filled with DIPEA (liquid C, neat). Liquid D was prepared by dissolving 1-bromonaphthalene (0.1% v/v, internal standard) in dichloromethane. Syringes with liquids A to C were then connected to the microreactor system. Of each reaction mixture, 20 μL was collected in 500 μL of liquid D. Owing to the varying flow rates, sampling times differed for every experiment. All reaction conditions were randomized. All samples were analyzed with GC. Retention times were 0.77, 0.81, 0.91, 1.10, 1.17, and 1.77 min for benzaldehyde **4**, TFA ester **8**, 1,2-dichlorobenzene, benzyl alcohol **1**, 1-bromo-3,5-dimethylbenzene, and 1-bromonaphthalene, respectively.

Run 3 using setup 2: The first syringe was loaded with liquid A containing benzyl alcohol **1** (R = Ph; 2.70 g, 25.0 mmol) and 1-bromo-3,5-dimethylbenzene (2.04 g, 11.0 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The second syringe was loaded with liquid B containing DMSO (9.76 g, 125 mmol) and 1,3,5-trimethylbenzene (1.30 g, 10.8 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The third syringe was loaded with liquid C containing TFAA (21.0 g, 100 mmol) and 1,2-dichlorobenzene (1.95 g, 13.3 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The fourth syringe was loaded with liquid D containing 1,3-dimethylnaphthalene (1.47 g, 9.43 mmol, internal standard) dissolved in dichloromethane (total volume 25 mL). The fifth syringe was filled with DIPEA (liquid E, neat). Liquid F was prepared by dissolving 1-bromonaphthalene (0.1% v/v, internal standard) in dichloromethane. Syringes with solutions A to E were then connected to the microreactor system. Of each reaction mixture, 20 μL was collected in 500 μL of liquid F. Owing to the varying flow rates, sampling times differed for every experiment. All reaction conditions were randomized. All samples were analyzed with GC. Retention times were 0.63, 0.77, 0.81, 0.91, 1.10, 1.17, 1.63, and 1.77 min for 1,3,5-trimethylbenzene, benzaldehyde **4**, TFA ester **8**, 1,2-dichlorobenzene, benzyl alcohol **1**, 1-bromo-3,5-dimethylbenzene, 1,3-dimethylnaphthalene, and 1-bromonaphthalene, respectively.

Reaction in the larger-scale continuous-flow system: A stainless steel tubing microreactor (IDEX, Oak Harbor WA, internal diameter 125 μm, internal volume 0.50 μL between two mixers) was used in combination with two commercially available T-junctions (IDEX, Oak Harbor WA) acting as mixers, analogous to microreactor setup 1. The reactor was submerged in an oil bath and the three inlets of the T-junctions were connected to the syringes. The following solutions were prepared: Liquid A: benzyl alcohol **1** (R = Ph; 3.68 g, 34.1 mmol), DMSO (23.9 g, 306 mmol), and 1,3,5-trimethylbenzene (3.04 g, 25.3 mmol, internal standard) dissolved in dichloromethane (total volume 100 mL). Liquid B: TFAA (42.8 g, 204 mmol) dissolved in dichloromethane (total volume 100 mL). Liquid C: DIPEA, neat. The flow rates of pumps A, B, and C were set to 450, 450, and 300 $\mu L\,min^{-1}$, respectively, corresponding to a total reaction time of 0.032 s. After stabilizing the system for 1 min, the outflow was collected for 127 min. Subsequently, the effluent collected was worked up by the following procedure: The mixture (~150 mL) was diluted with dichloromethane (200 mL) and washed with 1 M HCl (2×200 mL) and brine (150 mL). The organic phase was dried on $MgSO_4$ and concentrated in vacuum. The residue was purified by standard flash chromatography using 3% (v/v) diethyl ether in pentane as eluent and concentrated in vacuum to yield 1.70 g of benzaldehyde (**4**, R = Ph) as a colorless liquid.

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