

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/231389908>

Increasing Productivity of Microreactors for Fast Gas–Liquid Reactions: The Case of Direct Fluorination of Toluene

ARTICLE *in* INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH · DECEMBER 2008

Impact Factor: 2.59 · DOI: 10.1021/ie801232d

CITATIONS

30

READS

17

4 AUTHORS, INCLUDING:



Axel Guenther

University of Toronto

67 PUBLICATIONS 2,746 CITATIONS

SEE PROFILE

Increasing Productivity of Microreactors for Fast Gas–Liquid Reactions: The Case of Direct Fluorination of Toluene

Nuria de Mas,^{†,§} Axel Günther,^{†,||} Martin A. Schmidt,[‡] and Klavs F. Jensen^{*,†}

Department of Chemical Engineering, and Microsystems Technology Laboratories, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

The throughput of a single-channel microreactor used for a fast gas–liquid reaction was increased by up to one order of magnitude relative to previously published results by simultaneously increasing the superficial gas and liquid velocities. Superficial gas and liquid velocities varied between 2.9–14.6 m/s and 0.012–0.061 m/s, respectively. The direct fluorination of toluene in acetonitrile, selected as a model reaction, was performed at room temperature in microchannels formed in a silicon substrate, coated with thermally grown silicon oxide and evaporated nickel, and capped by Pyrex. With faster velocities the toluene conversion increased from 63% to 76%, while the combined selectivity of *ortho*-, *meta*-, and *para*-fluorotoluene isomers remained constant at 26%. Operating at faster gas and liquid velocities appeared to enhance the contacting between the two phases, thus outweighing the reduced liquid residence time.

1. Introduction

Over the past decade, microreactors have showed significant benefits over their macroscopic counterparts to perform a wide variety of single- and multiphase chemical reactions.^{1–3} Microreactors have been developed to handle highly exothermic reactions (e.g., direct fluorination)^{4–6} and explore reaction spaces difficult to access in conventional reactors with minimal consumption of reagents (e.g., aminocarbonylation).⁷ Gas–liquid segmented flows have been used to enhance mixing and minimize axial dispersion in microchannels (e.g., synthesis of colloidal silica and quantum dots).^{8,9} Microreactors are new chemical synthesis tools that may be used in discovery and development laboratories of fine chemical and pharmaceutical companies. For this purpose, microreactors should be ideally stand-alone units, easy to operate and clean or inexpensive to fabricate if disposable, and able to produce on the order of gram quantities of material per day. The throughput of microreactors has previously been increased by scale-out, that is, by operating multiple reaction channels in parallel, and examples have been reported for direct fluorinations.^{4,10} This approach requires proper design and precise fabrication of flow distribution channels that dominate the overall pressure drop across the reactor and, hence, ensure even flow distribution of reactants across all reaction channels.¹¹

This article describes a new, complementary approach to achieving higher throughputs in microreactors used to perform fast gas–liquid reactions. The throughput of a single-channel reactor was increased by up to one order of magnitude relative to previously published results⁶ by simultaneously increasing the superficial gas and liquid velocities. The direct fluorination of toluene was selected as a model reaction, and experiments previously performed in a dual-channel device were employed as a benchmark.⁶ The same reaction was conducted in a 20-

channel device, described elsewhere,¹¹ at the same superficial velocities used in the dual-channel device.

2. Experimental Section

2.1. Fluorine Delivery System. A 25 vol % mixture of fluorine in nitrogen was used as supplied (Spectra Gases, fluorine purity 99.0%, connected to a Monel pressure regulator) and diluted with research-grade nitrogen as appropriate using mass flow controllers (Unit Instruments). All piping used in the fluorine delivery system was made of electropolished 316 stainless steel. A Monel pressure gauge was installed on the gas line to detect any significant changes in pressure drop that might result from a reactor failure. Prior to use in reaction experiments, the entire manifold was leak-tested, thoroughly dried, and passivated by slowly increasing the fluorine-to-nitrogen flow rate ratio until the concentration reached operating conditions. After use, the lines were first purged of any unreacted fluorine using a corrosion-service vacuum pump (60 mTorr), and then pressurized with nitrogen (3 bar). The evacuation/pressurization cycle was repeated two more times. A perfluorinated polyether (Krytox, DuPont Co. or Fomblin, Solvay Solexis, Inc.) was used for pump lubrication. The manifold was maintained under a positive pressure of dry nitrogen when not in use to minimize the formation of HF from water and maximize the durability of the lines and other equipment.

2.2. Microreactor Packaging. The packaging scheme implemented to interface the single- and 20-channel microreactor chips (Figure 1) with the macroscale gas and liquid manifolds has been previously described.⁶ The silicon chip was compressed between a plexiglass plate, to allow viewing of the microreactor chip, and a Kalrez (DuPont perfluoroelastomer, 0.75 mm thick) gasket with punched holes matching the inlet and outlet ports of the microreactor chip to form a fluidic seal on a stainless steel base. Stainless steel fittings (Valco Instruments, TX) and fluidic lines (1/16 in. o.d. and 1/8 in. o.d. for the single- and 20-channel microreactors, respectively) machined into the stainless steel base were used to deliver the reactants. Stainless steel or Teflon tubing (Valco Instruments) from the microreactor base was used to collect the products. The toluene solution was held in gastight glass syringes (50 mL, Hamilton) and metered at the desired flow rate by a syringe pump (Harvard Apparatus

* To whom correspondence should be addressed. Fax: (617) 258-8992. E-mail: kfjensen@mit.edu.

[†] Department of Chemical Engineering.

[‡] Microsystems Technology Laboratories.

[§] Current address: Process R&D, Bristol-Myers Squibb Co., New Brunswick, NJ 08901.

^{||} Current address: Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, Ontario M5S 3G8, Canada.

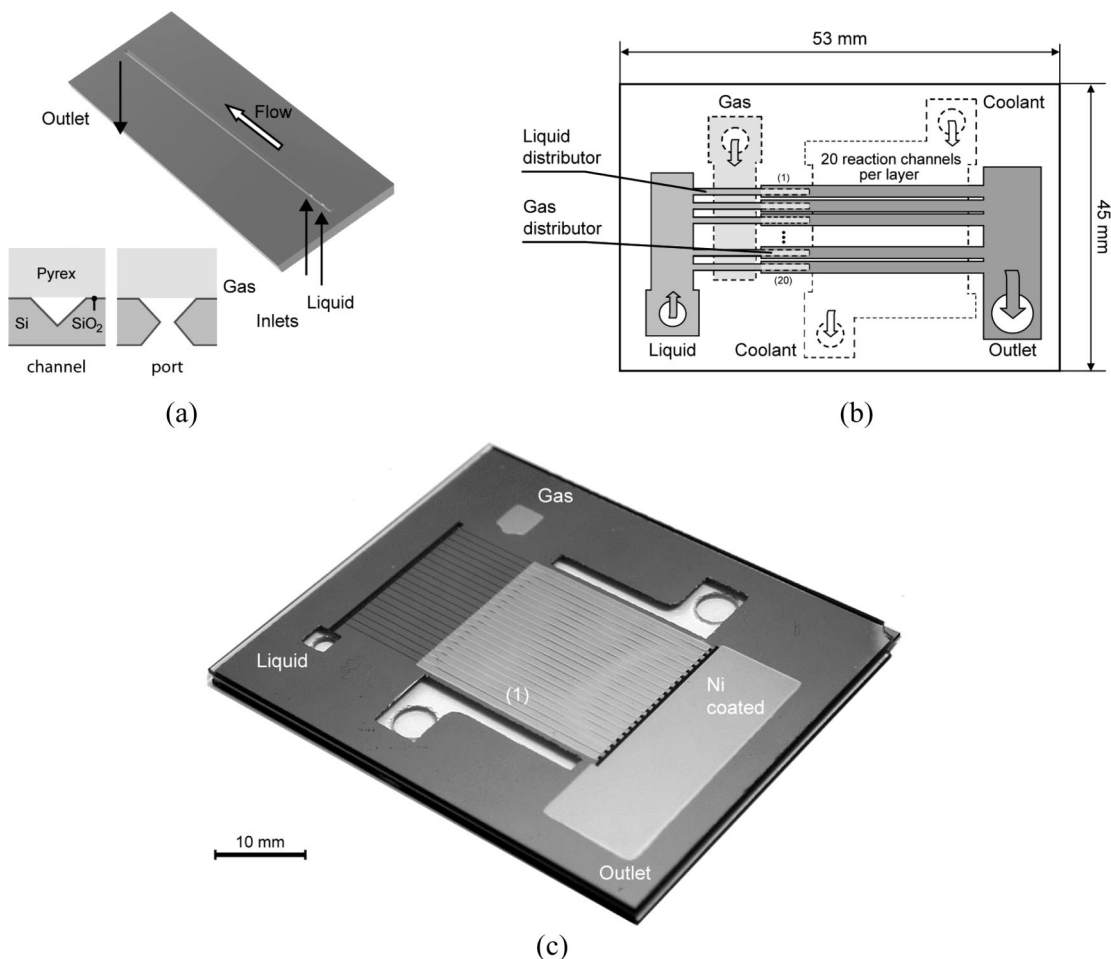


Figure 1. (a) Schematic of single-channel reactor with triangular cross section, $415\ \mu\text{m}$ wide ($d_h = 215\ \mu\text{m}$) and $20\ \text{mm}$ long (nickel coating and Pyrex cap not shown), along with channel and port cross sections. (b) Schematic of 20-channel reactor with liquid-inlet channel, liquid pressure-drop channels, reaction channels ($W = 484\ \mu\text{m}$, $d_h = 250\ \mu\text{m}$, $L = 20\ \text{mm}$), and outlet slit on the front side, and gas-inlet channel, gas pressure-drop channels, coolant-inlet channel, coolant-inlet slit, and cooling channels on the back side. (c) Photograph of the front side of the 20-channel reactor used for direct fluorination experiments. Its channels are formed in a silicon substrate and capped by Pyrex. The areas of the reactor wetted by fluorine or the reaction mixture, including the gas-inlet port, gas-inlet slit (on the back side), reaction channels (1), and outlet slit, are coated with silicon oxide and nickel. The uncoated downstream end of the reaction channels permits qualitative visualization of the gas-liquid flow.

PHD2000). The temperature of the silicon chip was monitored using thermocouples ($0.25\ \text{mm}$, type K, Omega) inserted between the plexiglass and the stainless steel base and in contact with the silicon chip near the gas-inlet port. Heat removal from the reactor was facilitated by heat conduction through the packaging assembly, which was heat sunk to a metallic holder via the silicon substrate, the gasket material, and the stainless steel base.

Gas-liquid flow regimes have been mapped in (uncoated, no nickel) single- and 20-channel microreactors by continuous wave and pulsed-laser fluorescence microscopy as well as by using integrated velocimetry sensors.^{6,11} In addition, an uncoated portion of the Pyrex cover of the 20-channel microreactor at the downstream end of the reaction channels permitted visual confirmation of the presence of gas-liquid flow across all channels before and after performing reactions (Figure 1c).

2.3. Toluene Fluorination. Starting materials were obtained commercially (Sigma-Aldrich) and used as received unless otherwise specified. The fluorination procedure has been previously described.⁶ Toluene solutions in acetonitrile were dried with activated molecular sieves and filtered (GHP Acrodisc, $0.45\ \mu\text{m}$). During startup, the microreactor assembly and attached tubing were primed with dry nitrogen and anhydrous solvent to remove air and moisture. Under a flow of dry nitrogen, the entire reactor was filled with the liquid solution. The liquid

solution and the fluorine mixture were then passed through the reactor at the prescribed flow rates, and the system was allowed to reach steady state ($\sim 25\ \text{min}$). Once steady state had been reached, liquid products were collected in an ice-cooled round-bottom glass flask containing sodium fluoride, which trapped the byproduct HF in the form of NaHF_2 .¹² The flask was connected to a cooling water West condenser to maximize the recovery of solvent and product vapors from the gas effluent. Samples were typically collected for $30\ \text{min}$. Waste gases were scrubbed in a $15\ \text{wt}\%$ aqueous potassium hydroxide solution before being exhausted.¹² The workup steps included degassing of the sample with dry nitrogen (3 times the volume of the collected mixture) and filtration of the sample through a syringe filter (GHP Acrodisc, $0.45\ \mu\text{m}$). The reaction products were identified by GC-MS (Hewlett-Packard 6890 GC equipped with an HP 5973 mass-selective detector) and quantified by a flame ionization detector (FID) injecting liquid samples of the reaction mixture. An HP-INNOWax column ($0.25\ \mu\text{m}$ film thickness, $0.25\ \text{mm} \times 30\ \text{m}$) was used. Product conversions and yields were calculated from the integrated areas of the FID chromatograms and the response factor of each compound with respect to octafluorotoluene, which was added to the initial toluene solutions and used as an internal standard. The concentration of octafluorotoluene used was at least an order of magnitude lower than that of toluene.

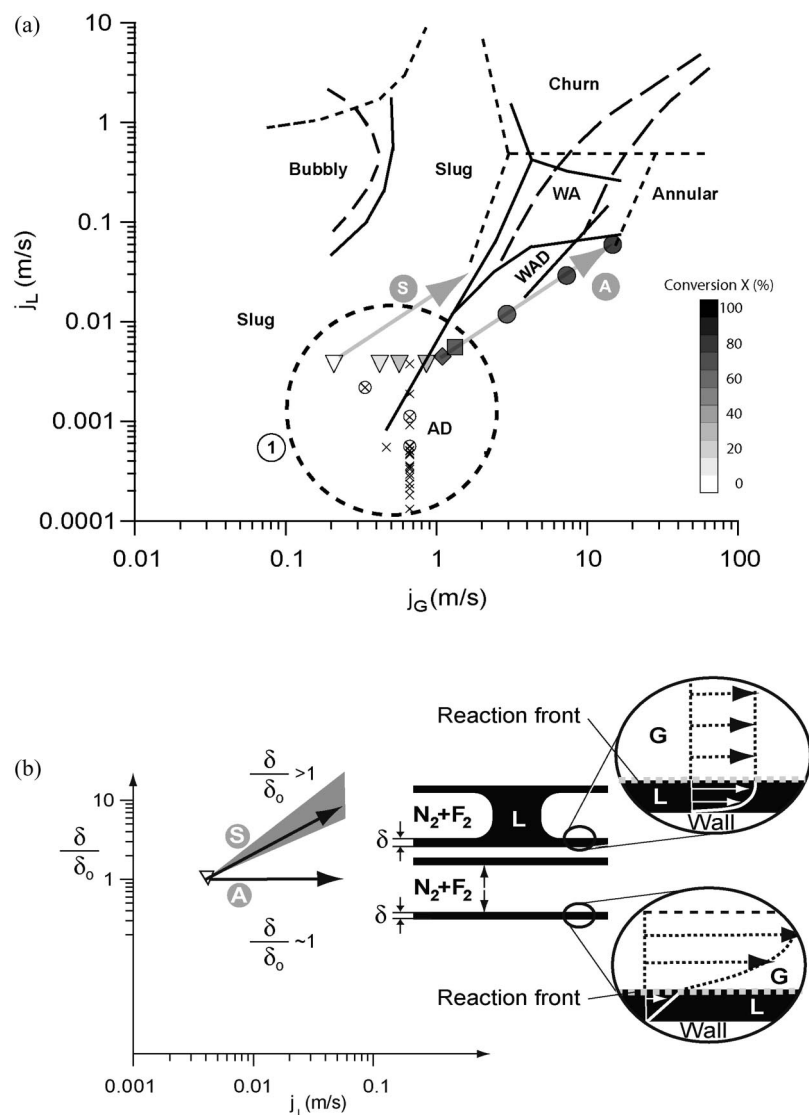


Figure 2. (a) Flow conditions of fluorination studies in triangular microchannels with the nitrogen–acetonitrile system in the single- (○), dual- (□), and 20-channel (◇) devices. Flow regimes for different superficial gas (j_G) and liquid (j_L) velocities are annular, churn, wavy annular (WA), wavy annular-dry (WAD), slug, bubbly, and annular-dry flows. Transition lines for nitrogen–acetonitrile flows in a triangular channel with $d_h = 224 \mu\text{m}$ are shown (—).⁶ Transition lines for air–water flows in triangular channels with $d_h = 1.097$ (---)¹⁴ and 0.866 mm (---)¹⁵ are shown. Region 1 presents flow conditions of previous fluorination studies in rectangular channels for a 32-channel reactor with $d_h = 150 \mu\text{m}$ (▽),⁴ single- and three-channel reactors with $d_h = 500 \mu\text{m}$ (⊗),⁵ and 9-, 18-, and 30-channel reactors with $d_h = 500 \mu\text{m}$ (×).¹⁰ The gray scale legend indicates conversion of toluene. Faster gas and liquid velocities result in higher conversions of toluene. (b) The liquid film thickness in the annular flow regime (“A”) is on the order of δ_o and is not expected to increase at constant j_G/j_L . For a segmented flow case (“S”), however, the film thickness increases proportionally to $j_G^{2/3-4/3}$ (constant j_G/j_L).

Table 1. Reaction Results from Toluene Direct Fluorination in the Dual-Channel Microfabricated Reactor^a

experiment	superficial gas velocity, j_G (m/s)	superficial liquid velocity, j_L (m/s)	conversion (%)	yield (%)	selectivity (%)	substitution pattern
exp. 1	1.4	5.6×10^{-3}	58	14	24	3.8:1.0:2.1
exp. 2 ^b	1.4	5.6×10^{-3}	64	15	24	3.9:1.0:2.2

^a Gas flow rate = 10 sccm, liquid flow rate = 45 $\mu\text{L}/\text{min}$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv.

^b Experiment 2 is a replicate of the previously reported experiment 1.⁶ It was conducted to validate the experimental setup and fluorination procedure prior to scaling out the reaction. Conversion for experiment 2 was 6% higher than that for experiment 1, while yield and selectivity were consistent.

2.4. Reactor Design and Fabrication. The single-channel reactor consists of a channel with a triangular cross section, $415 \mu\text{m}$ wide, $290 \mu\text{m}$ deep, and 2 cm long. The channel hydraulic diameter d_h (4 times the cross-sectional area divided by the wetted perimeter) is $215 \mu\text{m}$, and the volume of the reactor is $1.2 \mu\text{L}$. The inlet region consists of one liquid port and one gas port that is located 3 mm downstream from the liquid port. The outlet region consists of one single port. Figure 1a is a schematic representation of the reactor along with its channel and port cross sections. The channel was formed in a

silicon wafer by potassium hydroxide etching (low-stress silicon nitride served as the etching mask). Silicon oxide (200 nm thick) was thermally grown over the silicon, and nickel films (200 nm thick) were evaporated over the wetted areas of the channel to protect them from corrosion. Nickel-coated Pyrex was anodically bonded to the silicon to cap the channel.⁶

The design and fabrication of the 20-channel reactor has been previously described.¹¹ It consists of 20 reaction channels that have the same cross section and channel length as those of the single-channel reactor (the actual channel width was $W = 484$

Table 2. Reaction Results from Toluene Direct Fluorination in the Single-Channel Microfabricated Reactor for Various Superficial Gas and Liquid Velocities and in the 20-Channel Microfabricated Reactor at the Base Values of the Superficial Gas and Liquid Velocities

superficial gas velocity, j_G (m/s)	superficial liquid velocity, j_L (m/s)	conversion (%)	yield (%)	selectivity (%)	substitution pattern
Single-Channel Reactor ^a					
2.9	1.2×10^{-2}	63	18	28	3.7:1.0:2.1
7.3	3.1×10^{-2}	71	18	25	3.8:1.0:2.2
14.6	6.1×10^{-2}	76	20	27	4.0:1.0:2.3
20-Channel Reactor ^b					
1.1	4.5×10^{-3}	66	18	27	3.8:1.0:2.1

^a Gas flow rates = 10, 25, and 50 sccm; liquid flow rates = 45, 112, and 223 $\mu\text{L}/\text{min}$. $j_G/j_L = 239$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv. ^b Gas flow rate = 100 sccm, liquid flow rate = 0.45 mL/min. $j_G/j_L = 239$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv.

μm because of undercut of the feature during etching,¹¹ $d_h = 250 \mu\text{m}$). The reaction channels as well as the gas and liquid flow distributors were formed in a silicon substrate. The reaction channels and liquid distributors were formed on the front side of the silicon, while the gas distributors were formed on the back side. Both sides of the silicon layer were capped by Pyrex. The architecture of this reactor is schematically shown in Figure 1b. Gas and liquid are introduced to the reactor through single inlet ports in the bottom Pyrex layer, enter inlet slits on the silicon layer, and are distributed to the reaction channels through individual gas and liquid distributors (one gas distributor and one liquid distributor per reaction channel) that create pressure drops of up to 25 and 50 times larger, respectively, than that across the two-phase reaction channels. The cooling channels below the reaction channels were not used in the reaction experiments because heat conduction through the packaging assembly was sufficient to dissipate the heat of reaction. Figure 1c shows a photograph of the 20-channel reactor. The uncoated section at the downstream end of the reaction channels was used to verify the presence of gas–liquid flow across all reaction channels before and after performing reactions.

All channels of the 20-channel reactor were formed in a silicon wafer by nested potassium hydroxide etching (silicon oxide and low-stress silicon nitride served as etching masks). Silicon oxide (200 nm thick) was thermally grown over the silicon, and nickel films (200 nm thick) were evaporated over the areas wetted by fluorine or the reaction mixture to protect them from corrosion. The liquid inlet slit and liquid pressure drop channels were not coated. Shadow masks fabricated by deep reactive ion etching were used to define the areas to be coated with nickel. Nickel-coated Pyrex was bonded at the die level to the front and back sides of the silicon to cap the channels.

3. Results and Discussion

Gas–liquid microreactors have so far been operated at liquid superficial velocities $j_L < 10^{-2}$ m/s, within region 1 of the flow regime diagram shown in Figure 2a. The strategy for scaling out microreactors has been to replicate these reaction conditions across many reaction channels operating in parallel. The superficial gas and liquid velocities, $j_G = \dot{Q}_G/(n_{\text{ch}}A_{\text{ch}})$ and $j_L = \dot{Q}_L/(n_{\text{ch}}A_{\text{ch}})$, are proportional to the gas and liquid volumetric flow rates entering the reactor, \dot{Q}_G and \dot{Q}_L ; n_{ch} is the number of reaction channels, and A_{ch} is the cross-sectional area of one reaction channel. Flow and reaction conditions of previous direct

fluorination studies in microchannels were $j_G = (2.1 \times 10^{-1})$ – (8.7×10^{-1}) m/s and $j_L = 3.8 \times 10^{-3}$ m/s in a 32-channel reactor (∇ , $d_h = 150 \mu\text{m}$, toluene as the substrate, -15°C as the reaction temperature) by Jähnisch et al.,⁴ $j_G = (3.4 \times 10^{-1})$ – (6.8×10^{-1}) m/s and $j_L = (5.6 \times 10^{-4})$ – (2.2×10^{-3}) m/s in single- and three-channel reactors (\otimes , $d_h = 500 \mu\text{m}$, 4-nitrotoluene at 0°C to room temperature and 1,3-dicarbonyl substrates at 5°C) by Chambers et al.,⁵ $j_G = (4.7 \times 10^{-1})$ – (6.7×10^{-1}) m/s and $j_L = (1.3 \times 10^{-4})$ – (3.8×10^{-3}) m/s in 9-, 18-, and 30-channel reactors (\times , $d_h = 500 \mu\text{m}$, ethyl 3-oxobutanoate, 10 – 20°C) by Chambers et al.,¹⁰ and $j_G = 1.4$ m/s and $j_L = 5.6 \times 10^{-3}$ m/s in our dual-channel reactor (\square , $d_h = 224 \mu\text{m}$, toluene, room temperature).⁶

Fluorinations are fast gas–liquid reactions, and gaseous fluorine is only slightly soluble in the liquid phase. For the reaction conditions of the dual-channel reactor, the reaction occurs essentially at the gas–liquid interface, and at steady state the rate of mass transfer of toluene from the bulk liquid phase to this interface is expected to control the rate of reaction, assuming that the solvent and reaction products are inert to fluorine.⁶ Consequently, to achieve full conversion of toluene, gas and liquid superficial velocities must be selected to (a) provide sufficient liquid residence time for liquid mass transfer to take place and (b) satisfy the stoichiometry (fluorine is likely to become the limiting reactant as a result of side reactions; thus, excess fluorine is supplied).

In contrast to previous studies, we explored the opportunity of significantly increasing reactor throughput by proportionally increasing the gas and liquid volumetric flow rates, that is, by changing the flow conditions at a slope of 1 in the flow regime diagram (Figure 2a). Annular flow conditions were considered. Whether the reaction is carried out in a (segmented) slug flow or annular flow regime, fluorine needs to be transported from within the nitrogen core of the microchannel to the liquid film across a distance of $\sim d_h/2$. Flows in the microchannels are laminar; at the reaction conditions presented in this study, the liquid Reynolds number is on the order of 1–10 and the gas Reynolds number is on the order of 10–100. The characteristic diffusion time for fluorine transport toward the gas–liquid interface is 0.6 ms. For the given reactor geometry (reactor length of 2 cm), the reaction is therefore limited by mass transfer in the liquid film as long as the superficial gas velocity is $j_G < 2 \text{ cm}/0.6 \text{ ms} = 33 \text{ m/s}$. Conducting fluorination reactions in the annular flow regime at faster superficial velocities (Figure 2b) has two key advantages:

(1) If j_G is increased at a constant j_G/j_L , the liquid film thickness δ does not increase in the annular flow case (“A” in Figure 2). A force balance shows that, for a constant j_G/j_L , δ depends on the microchannel size and fluid properties only.⁶ For the segmented flow case (“S” in Figure 2), however, the film thickness δ increases with increasing superficial gas velocity j_G , thereby increasing mass transfer limitations within the film. The increase is proportional to $j_G^{2/3-4/3}$ for the considered case of a constant ratio j_G/j_L .¹³ A key difference between the annular and segmented flows is the slip (relative velocity) between the gas and liquid phases: it is very significant in the annular flow and close to unity in the segmented flow.

(2) For the annular gas–liquid flows at the fast superficial velocities considered, the gas–liquid interface is perturbed by interfacial (Kelvin–Helmholtz) instabilities.⁶ These instabilities are not expected to alter the mean film thickness. However, perturbation of the interface likely improves the dynamic wetting behavior of the channel walls in the annular-dry flow regime and enhances the limiting transport of toluene from the bulk of

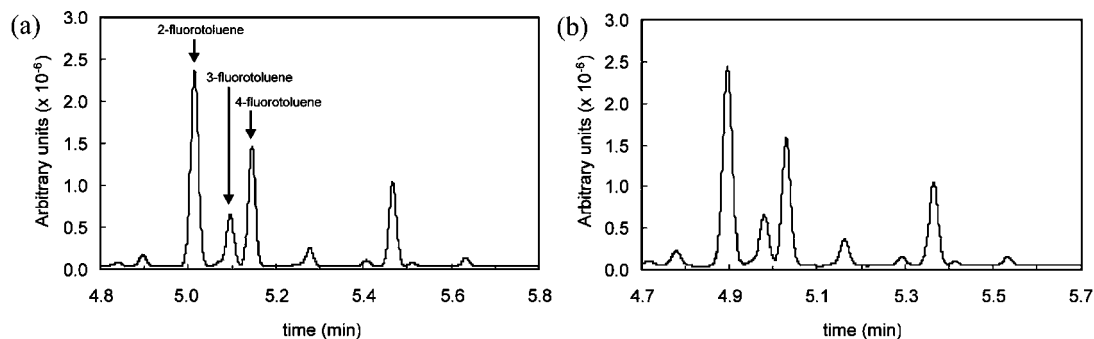


Figure 3. Product chromatograms from the direct fluorination of toluene in the single-channel reactor using (a) $j_G = 2.9$ m/s, $j_L = 1.2 \times 10^{-2}$ m/s and (b) $j_G = 14.6$ m/s, $j_L = 6.1 \times 10^{-2}$ m/s ($j_G/j_L = 239$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv). Products eluting before and after the fluorotoluene isomers correspond to multifluorinated toluenes, including di- and trifluorotoluenes. The product distribution was maintained when the single-channel reactor was operated at faster superficial gas and liquid velocities.

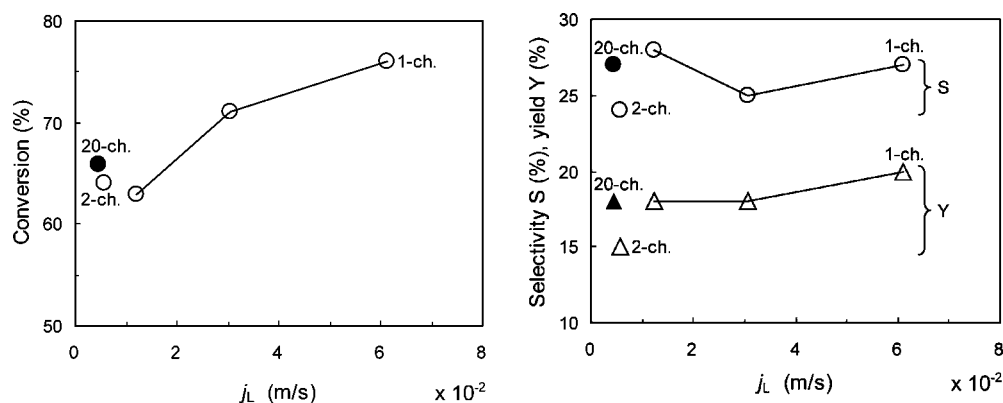


Figure 4. Conversion, selectivity, and yield showing the influence of the liquid superficial velocity in single-, dual-, and 20-channel reactors ($j_G/j_L = 239$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv). Lower-bound (analytical) uncertainties are $\pm 0.4\%$ for conversion and yield, and $\pm 0.5\%$ for selectivity.

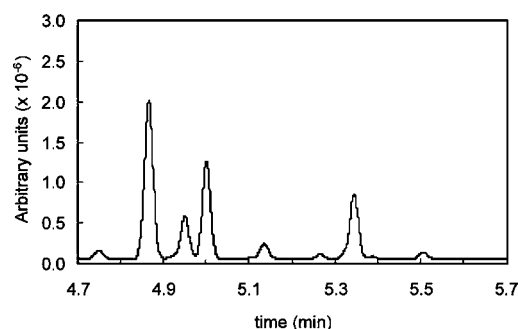


Figure 5. Product chromatogram from the direct fluorination of toluene in the 20-channel reactor ($j_G = 1.1$ m/s, $j_L = 4.5 \times 10^{-3}$ m/s, $j_G/j_L = 239$, room temperature, 0.1 M toluene in acetonitrile, 2.5 vol % F_2/N_2 , 2.5 fluorine equiv). Products eluting before and after the fluorotoluene isomers correspond to multifluorinated toluenes, including di- and trifluorotoluenes.

the liquid film to the gas–liquid interface. Because of the enhanced mass transfer in the liquid phase, it may be possible to operate outside region 1 of the flow regime diagram at fast velocities, $j_L > 10^{-2}$ m/s, while maintaining conversions comparable to those previously obtained within region 1, $j_L = 10^{-4}$ – 10^{-2} m/s.

These findings led us to perform the direct fluorination of toluene at room temperature in the single-channel reactor (○, $d_h = 215$ μm) at three combinations of superficial gas and liquid velocities (j_G, j_L) = (2.9, 1.2×10^{-2} ; 7.3, 3.1×10^{-2} ; 14.6, 6.1×10^{-2}) m/s, which exceed the base values of $j_G = 1.4$ m/s and $j_L = 5.6 \times 10^{-3}$ m/s previously employed in the dual-channel reactor (□, $d_h = 224$ μm) by factors of 2, 5, and 10, respectively. In addition, the same reaction was performed in the 20-channel

reactor at $j_G = 1.1$ m/s and $j_L = 4.5 \times 10^{-3}$ m/s (◇, $d_h = 250$ μm), operating close to the flow conditions of the dual-channel reactor, to demonstrate the traditional scale-out. Note that the fastest superficial gas flow rate of 14.6 m/s is well below the ~ 33 m/s, the maximum gas superficial velocity that ensures diffusion of fluorine from the microchannel core to the surface of the liquid film. The flow conditions selected for the single-channel reactor were annular-dry, annular-dry close to its transition line with wavy-annular, and wavy-annular flows. The 20-channel reactor operated in the annular-dry flow regime. In all reaction experiments, 2.5 fluorine equiv was used. The toluene conversion (X), the combined selectivity of *ortho*-, *meta*-, and *para*-fluorotoluene isomers (S), and the yield (Y) were determined as functions of the reaction conditions. These parameters are defined as follows:

$$X = 1 - \frac{C_{\text{tol},f}/C_{\text{IS},f}}{C_{\text{tol},i}/C_{\text{IS},i}} \quad (1a)$$

$$S = \frac{C_{\text{mF},f}/C_{\text{IS},f}}{(C_{\text{tol},i}/C_{\text{IS},i} - C_{\text{tol},f}/C_{\text{IS},f})} \quad (1b)$$

$$Y = XS \quad (1c)$$

where $C_{\text{tol},i}$ and $C_{\text{tol},f}$ are the molar concentrations of toluene in the initial and final solutions, respectively; $C_{\text{IS},i}$ and $C_{\text{IS},f}$ are the molar concentrations of the internal standard (IS), octafluorotoluene, in the initial and final solutions, respectively; and $C_{\text{mF},f}$ is the sum of the molar concentrations of the *ortho*-, *meta*-, and *para*-fluorotoluene isomers in the final solution.

Reaction data obtained in the dual-channel reactor at $j_G = 1.4$ m/s and $j_L = 5.6 \times 10^{-3}$ m/s (Table 1) were compared to the data

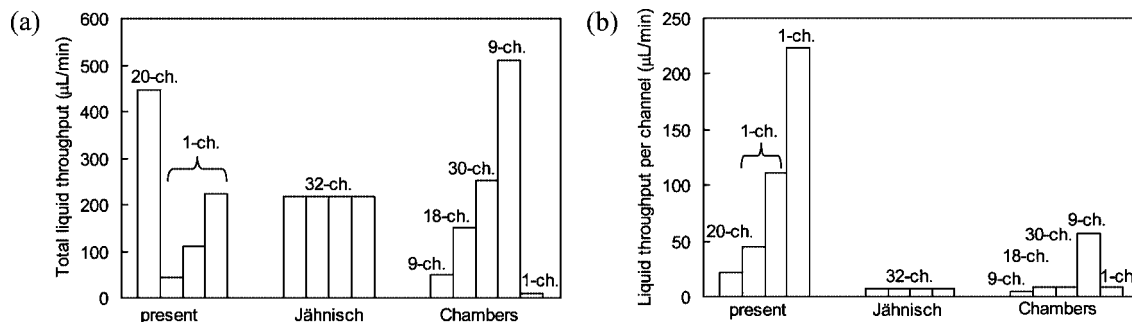


Figure 6. Liquid volumetric throughputs in direct fluorination microreactors given in (a) total liquid throughput and (b) liquid throughput per channel. Data for the present single- and 20-channel microreactors are shown along with data for a 32-channel microreactor by Jähnisch et al.,⁴ as well as 1-, 9-, 18-, and 30-channel microreactors by Chambers et al.^{5,10}

obtained in the single- and 20-channel reactors (Table 2). For the three velocities employed, the single-channel reactor remained at room temperature, and no significant differences in the product distribution were observed. Chromatograms of the product mixture, which contained the unreacted toluene and the *ortho*-, *meta*-, and *para*-fluorotoluene isomers as the main products, are shown in Figure 3. Small amounts of fluoromethylbenzene, difluorotoluenes, trifluorotoluenes, and other unidentified high-boiling compounds were detected, which is expected from the fluorination of mono-substituted precursors such as toluene. The substitution pattern, defined as the ratio of the molar concentrations of the *ortho*-, *meta*-, and *para*-fluorotoluene isomers, was 3.8:1.0:2.2 and was consistent with that observed in the dual-channel reactor. A conversion of 63% and a selectivity of 28% were obtained at the slowest superficial velocities of $j_G = 2.9$ m/s and $j_L = 1.2 \times 10^{-2}$ m/s and were consistent, albeit the selectivity was slightly higher, with those observed in the dual-channel reactor (Figure 4). With faster superficial velocities, conversion increased from 63% to 76%, suggesting enhanced gas–liquid contacting, while selectivity was maintained at 26%, suggesting that the reaction mechanism remained unaltered (the reaction mechanism could become more radical and less electrophilic, for example, at higher temperatures). The maximum yield, 20%, was obtained at the fastest velocities, $j_G = 14.6$ m/s and $j_L = 6.1 \times 10^{-2}$ m/s; at these reactions conditions, the material throughput was 0.12 g toluene/h, which represents a 5-fold increase relative to that of the dual-channel reactor.

The fluorination of toluene was conducted in the 20-channel reactor operating close to the base values of j_G and j_L employed in the dual-channel reactor. The inlet pressure of the reactor was steady (0.2 bar measured at the gas manifold line), and the reactor remained at room temperature. The top nickel-coated Pyrex cover appeared intact after performing the reaction. The product chromatogram with the unreacted toluene and ring-monofluorinated toluenes, shown in Figure 5, as well as the average substitution pattern, 3.8:1.0:2.1, compared well to those observed in the dual-channel reactor. The toluene conversion was 66% and the selectivity was 27%, which are 2% and 3% higher, respectively, than those observed in the dual-channel reactor. Differences in the gas–liquid contacting at the gas inlets may explain the lower yield in the dual-channel reactor. The gas inlets of the 20-channel reactor are located directly underneath each reaction channel (Figure 1b); gas and liquid in the dual-channel reactor, however, first contact about 500 μ m from the upstream end of the interchannel wall, where the channel is 1 mm wide.⁶ The material throughput was 0.25 g toluene/h, which represents a 10-fold increase relative to that of the dual-channel reactor.

Figure 6 shows the total liquid volumetric throughput and the liquid volumetric throughput per channel of our single- and

20-channel reactors and those of previously reported microreactors: a 32-channel microreactor for the direct fluorination of toluene (1 M, -15 °C) by Jähnisch et al.,⁴ and 1-, 9-, 18-, and 30-channel microreactors for the direct fluorination of several substrates (4-nitrotoluene, 0 °C to RT; 1,3-dicarbonyl compounds, 5 °C) by Chambers et al.^{5,10} The total volumetric throughput of the 20-channel reactor, 0.45 mL/min, is similar to that of the 9-channel reactor by Chambers et al., and its material throughput is 1.3 g of fluorinated toluene per day at the velocities and toluene concentration (0.1 M) tested. This throughput may be increased by using higher substrate concentrations (1.0 M solutions have been successfully fluorinated in our dual-channel reactor).⁶ The highest material throughput of the 32-channel reactor by Jähnisch et al. is 3.7 g of fluorinated toluene per day. On the other hand, the largest volumetric throughput per channel of the present single-channel reactor, 0.22 mL/min (0.12 g toluene/h), exceeds that of the nine-channel reactor by Chambers et al. by a factor of 4 and that by Jähnisch et al. by an order of magnitude. According to our results, the fastest superficial velocities used in the single-channel reactor would translate in the 20-channel reactor into gas and liquid flow rates of 1 sL/min and 4.5 mL/min, respectively, and a material throughput of 2.4 g toluene/h (0.1 M solutions), which would generate up to 14 g of ring monofluorinated toluenes per day. From single- and two-phase pressure drop measurements,¹¹ this reactor would operate at gas and liquid inlet pressures of approximately 4 and 3 bar, respectively. The pressure of the fluorine cylinder is 14 bar, the pressure drop across the gas manifold is minimal, and the compression seal used for the reactor chip is good up to 10 bar, so it should be possible to run fluorinations in this reactor.

4. Conclusions

The throughput of a single-channel direct fluorination microreactor was increased by up to 1 order of magnitude relative to previously published results by operating at faster superficial gas and liquid velocities. The superficial gas and liquid velocities varied between 2.9–14.6 and (1.2×10^{-2}) – (6.1×10^{-2}) m/s, respectively, which correspond to annular-dry and wavy-annular flows. Toluene solutions in acetonitrile were fluorinated at room temperature. Faster velocities appeared to enhance the contacting between the two phases, thus outweighing the corresponding reduced liquid residence time: conversion increased from 63% to 76%, while the combined selectivity of *ortho*-, *meta*-, and *para*-fluorotoluene isomers remained constant at 26%. This approach to increasing microreactor throughputs may be applicable to other fast gas–liquid reactions controlled by liquid mass transfer and may be combined with traditional scale-out to synthesize multigram quantities of material per hour using a

minimal number of microchannels. According to our results, a 20-channel reactor operating at $j_G = 14.6$ m/s and $j_L = 6.1 \times 10^{-2}$ m/s would provide 14 g of ring monofluorinated toluenes per day. These results suggest that for fast reactions, careful design of the gas–liquid contacting in the microchannels may lead to microreactors with high productivity.

Acknowledgment

This research was funded by the Novartis Research Foundation, the MIT Microchemical Systems Technology Center, and the DoD Multidisciplinary University Research Initiative (MURI) program administered by the Army Research Office under Grant DAAD 19-01-1-0566U.S.

Note Added after ASAP Publication: This article was released ASAP on December 30, 2008 with a minor error in the abstract. The correct version was posted on December 31, 2008.

Literature Cited

- (1) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. Chemistry in Microstructured Reactors. *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446.
- (2) Günther, A.; Jensen, K. F. Multiphase Microchemical Systems: From Flow Characteristics to Chemical and Materials Synthesis. *Lab Chip* **2006**, *6*, 1487–1503.
- (3) Song, H.; Chen, D. L.; Ismagilov, R. F. Reactions in Droplets in Microfluidic Channels. *Angew. Chem., Int. Ed.* **2006**, *45*, 7336–7356.
- (4) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. Direct Fluorination of Toluene Using Elemental Fluorine in Gas/Liquid Microreactors. *J. Fluorine Chem.* **2000**, *105*, 117–128.
- (5) Chambers, R. D.; Holling, D.; Spink, R. C. H.; Sandford, G. Elemental Fluorine. Part 13. Gas-Liquid Thin Film Microreactors for Selective Direct Fluorination. *Lab Chip* **2001**, *1*, 132–137.
- (6) de Mas, N.; Günther, A.; Schmidt, M. A.; Jensen, K. F. Microfabricated Multiphase Reactors for the Selective Direct Fluorination of Aromatics. *Ind. Eng. Chem. Res.* **2003**, *42*, 698–710.
- (7) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. Accelerating Reactions with Microreactors at Elevated Temperatures and Pressures: Profiling Aminocarbonylation Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734–1737.
- (8) Khan, S. A.; Günther, A.; Schmidt, M. A.; Jensen, K. F. Microfluidic Synthesis of Colloidal Silica. *Langmuir* **2004**, *20*, 8604–8611.
- (9) Yen, B. K. H.; Günther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G. A Microfabricated Gas-Liquid Segmented Flow Reactor for High-Temperature Synthesis: The Case of CdSe Quantum Dots. *Angew. Chem., Int. Ed.* **2005**, *44*, 5447–5451.
- (10) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. Part 16. Versatile Thin-Film Gas-Liquid Multichannel Microreactors for Effective Scale-Out. *Lab Chip* **2005**, *5*, 191–198.
- (11) de Mas, N.; Günther, A.; Kraus, T.; Schmidt, M. A.; Jensen, K. F. Scaled-out Multilayer Gas-Liquid Microreactor with Integrated Velocimetry Sensors. *Ind. Eng. Chem. Res.* **2005**, *44*, 8997–9013.
- (12) *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995.
- (13) Wong, H.; Radke, C. J.; Morris, S. The Motion of Long Bubbles in Polygonal Capillaries. 1. Thin-Films. *J. Fluid Mech.* **1995**, *292*, 71–94.
- (14) Triplett, K. A.; Ghiaasiaan, S. M.; Abdel-Khalik, S. I.; Sadowski, D. L. Gas-Liquid Two-Phase Flow in Microchannels Part I: Two-Phase Flow Patterns. *Int. J. Multiphase Flow* **1999**, *25*, 377–394.
- (15) Zhao, T. S.; Bi, Q. C. Co-Current Air-Water Two-Phase Flow Patterns in Vertical Triangular Microchannels. *Int. J. Multiphase Flow* **2001**, *27*, 765–782.

Received for review August 11, 2008
Revised manuscript received November 11, 2008
Accepted November 14, 2008

IE801232D