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Fluoropolymer Coated PDMS Microfluidic Devices for Application in Organic Synthesis

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Abstract

In recent years there has been huge interest in the development of microfluidic reactors for the synthesis of small molecules and nanomaterials. Such reaction platforms represent a powerful and versatile alternative to traditional formats since they allow for the precise, controlled and flexible management of reactive processes. To date, the majority of microfluidic reactors used in small molecule synthesis have been manufactured using conventional lithographic techniques, from materials such as glasses, ceramics, stainless steel and silicon. Surprisingly, the fabrication of microfluidic devices from such rigid materials remains ill-defined, complex, and expensive. Accordingly, the microfluidic toolkit for chemical synthesis would significantly benefit from the development of solvent-resistant microfluidic devices that can be manufactured using soft-lithographic prototyping methods. Whilst significant advances in the development of solvent-resistant polymers have been made, only modest steps have been taken towards simplifying their use as microfluidic reactors. Herein, we emphasize the benefits of using a commercially available, amorphous perfluorinated polymer, CYTOP, as a coating with which to transform PDMS into a chemically inert material for use in organic synthesis applications. Its efficacy is demonstrated through the subsequent performance of photooxidation reactions and reactions under extremely acidic or basic conditions.

Introduction

The development of microfluidic devices for chemical synthesis applications has received considerable attention over the past two decades^[1]. The unique properties of small-volume environments provide for a range of basic and pragmatic advantages that can and have been exploited in the synthesis of small molecules and advanced materials^[2]. At a fundamental level, microfluidic activities have been kindled by the fact that physical processes and chemical state functions can be more easily controlled when instrumental dimensions are reduced to the micron scale^[3].

A microfluidic reactor is simply an engineered fluidic device where flow is almost always nonturbulent and thus highly ordered. Normally, this coincides with critical structural dimensions (such as channel widths) on the order of tens to hundreds of microns. For the chemist, the small instantaneous volumes and large surface area-to-volume ratios associated with microfluidic systems, mean that both solute and temperature gradients may be created or homogenized in a rapid and controllable manner. This engenders an exquisite ability to tune reagent concentrations, reaction temperatures and residence times, allowing reactions to proceed in an efficient manner and generating products in higher yield and in shorter periods of time^[4].

Traditionally, the majority of microfluidic reactors have been operated in a continuous flow manner, where a single fluid phase is driven by a hydrodynamic force through a microchannel, yielding a flow that is laminar, symmetric and highly structured. By uniting multiple input streams and then leveraging techniques such parallel lamination and chaotic advection to mix fluids in a rapid and controllable manner, product formation may be optimized, and undesirable side reactions avoided^[5]. Whilst this approach is conceptually seductive, potential interactions between the reactor material and the chemical components passing through it are often highly problematic for the experimentalist. Unsurprisingly, and due to their excellent chemical properties, a wide range of microfluidic reactors have been developed in glass, silicon, ceramics^[6] and thiolene-based resins^[7]. That said, the fabrication of microfluidic devices from such rigid materials remains an ill-defined, complex and expensive process. To address these fabrication- and material-based limitations, much attention has focused on the development of polymeric platforms that can be fabricated in a direct manner and at low cost. In this regard, soft-lithography can be considered an established, simple and precise method for creating three dimensional micronanostructures within elastomeric and polymers. such as

polydimethylsiloxane (PDMS)^[8]. Whilst PDMS remains, by an enormous margin, the most popular substrate material for biological and biochemical applications^[9], its incompatibility with most nonpolar organic solvents severely limits its use in organic synthesis^[10]. To address this issue, recent studies have reported the use of hybrid inorganic/organic polymer coatings^[11], parylene^[12], or sol-gels^[13] to render PDMS surfaces solvent-resistant. Other strategies involve fabrication of microfluidic systems made from fluoroelastomers due to their compatibility with most common organic solvents^[14]. Such devices can be made from either custom-synthesized photocurable perfluoropolyethers (PFPEs)^[15], commercially available perfluoropolyethers (such as Fluorolink MD 70016) or the thermally curable perfluoropolyether SIFEL^{®[16]}. Nevertheless, microfluidic reactors made from these polymers typically involve surprisingly tedious and cost intensive fabrication methods^[17], require polymer feedstocks that are not commercially available^[15-16] and are challenging to interface with world-to-chip-connectors^[17]. Additionally, devices made from Teflon^{®[18]}, Viton^{®[19]}, Dyneon^{®[20]} and PTFE^[21] either require the processing of multiple layers of polymer or specialized equipment for manufacture. This naturally leads to significant increases in the cost and time needed to produce microfluidic devices.

The simplest approach for realizing solvent-resistant elastomeric devices is the direct modification or coverage of PDMS with a solvent resistant material. A variety of PDMS surface treatments for have been proposed in the literature^[22], but most require elaborate fabrication steps and/or the ability to control of thickness of the coated material. The amorphous, perfluorinated polymer polyperfluoro-butenylvinylether (CYTOP) has proven to be a promising material as a solvent resistant coating on PDMS surfaces due to its strong chemical resistance^[23] and optical properties^[24]. However, despite these efforts, CYTOP has yet to be used as a solvent resistant coating for organic synthesis reactions due to its short-term stability^[23]. Herein, we demonstrate for the first time that CYTOP is particularly well-suited for use in various chemical applications, due to its chemical resistance and high optical transparency in the UV, visible and near IR regions of the electromagnetic spectrum^[25]. In spite of its excellent optical characteristics, and to the best of our knowledge, the use of CYTOP as a reactor coating for organic syntheses has yet to be explored. Accordingly, we propose and demonstrate a simple two step procedure for fabricating solvent-resistant microfluidic devices. To demonstrate the efficacy of CYTOP-based chemistries, we use these chemically resistant microfluidic reactors to perform photooxidations and reactions under extremely acidic or basic conditions.

Materials and Methods

Materials

CYTOP fluoropolymer solution (CTX-809AP2) and its associated solvent (CT-SOLV180) were purchased from AGC Chemicals Europe (Thornton-Cleveleys, United Kingdom) and 3aminopropyltriethoxysilane 99% (APTES) was purchased from Acros Organics (Geel, Belgium). α -terpinene was procured from Tokyo Chemical Industry (Eschborn, Germany). Tetraphenylporphyrin and tetrakis(triphenylphosphine)palladium(0) (99.9%) were bought from ABCR-Chemicals (Karlsruhe, Germany). All other chemicals and solvents were bought from Sigma-Aldrich (St. Louis, USA) and used without further purification.

Fabrication of fluoropolymer coated microfluidic reactors

Microfluidic circuits were designed using AutoCAD® 2014 (Autodesk, San Rafael, USA) and printed onto a high-resolution film photomask (Micro Lithography Services Ltd, Chelmsford, UK). Master structures were subsequently fabricated on a SU-8 (Microchem Corporation, Westborough, USA) coated silicon wafer via conventional photolithographic methods. Microfluidic devices were manufactured using standard soft-lithographic techniques. Briefly, a 10:1 (wt/wt) mixture of polydimethylsiloxane (PDMS) base and curing agent (Sylgard 184; Dow Corning, Midland, USA) was poured over the master structure and cured in an oven at 70°C for at least 4 hours. The cured PDMS structure was then peeled off the wafer, and inlet and outlet ports formed using a hole-punch (Technical Innovations, West Palm Beach, USA). The structured PDMS substrate and a 3 mm thick flat PDMS bottom layer were subsequently exposed to an oxygen plasma (EMITECH K1000X, Quorum Technologies, East Sussex, United Kingdom) for one minute and then immersed in a 5% (v/v) ethanolic APTES solution for 30 minutes (Figure 1a). Both PDMS layers were then rinsed with ethanol and dried in a stream of nitrogen. CYTOP solutions (CTX-809AP2 and CT-SOLV180) of defined concentration were spin coated onto the APTES modified surface of both PDMS substrates at different spin speeds so as to control layer thickness (Figure S2). For example, to generate a 4 µm thick coating using CTX-809AP2, substrates were spun at 500 rpm for 10 seconds, followed by spinning at 900 rpm for 30 seconds. Subsequently, each PDMS substrate was placed on a hot plate at 70°C for 30 minutes to ensure the complete removal of solvent by evaporation. Finally, the coated substrates were aligned and thermally bonded at 180°C. This involved increasing the temperature from ambient to 180°C at a rate of 5°C per minute and holding for 2 hours. To aid bonding, a 500-gram weight was placed on top of the aligned substrates for the duration of the process. It is significant to note that since CYTOP is a thermoplastic and PDMS is heat-curable, thermal fusion bonding between CYTOP layers can be realized without deformation or destruction of any fine structures within the PDMS layer. To confirm the hydrophobicity of the fluoropolymer coating, water-in-oil droplet formation was performed (**Figure S1a**) with light mineral oil as the continuous phase and deionized water as the discrete phase (both delivered at a flow rate of 8 μ L/min). Blue ink (Waterman, Paris, France) was added to water phase to aid imaging of droplet formation. Precision syringe pumps (neMESYS, Cetoni GmbH, Korbussen, Germany) coupled to 1 mL gastight syringes (Hamilton, Bonaduz, Switzerland) were used to deliver the fluids into the microfluidic reactor, via polytetrafluoroethylene (PTFE) tubing (250 μ m ID, Upchurch Scientific, Oak Harbor, USA).

Evaluation of the resistance of CYTOP-coated surfaces to organic solvents

Coating thicknesses were evaluated using a DektakXT stylus profiler (Bruker, Fällanden, Switzerland), with the morphology of the fluoropolymer coated channel being assessed by scanning electron microscopy (ULTRA 55, Carl Zeiss, Oberkochen, Germany). To determine the stability of the bond between the fluoropolymer coating and the PDMS channel, a microfluidic device (**Figure S1b**) incorporating an 18 cm long, 300 μ m wide and 50 μ m high channel was connected to a 10 mL gastight syringe. neMESYS pumps were then used to deliver water through the channel at flow rates between 100 μ L/min and 1.5 mL/min. The long-term stability of the coated microfluidic reactor to non-polar organic solvents was assessed by delivering toluene or chloroform through the microfluidic device at a volumetric flow rate of 20 μ L/min for 3 hours. Identical experiments were also performed using uncoated PDMS devices, with brightfield images being used to assess and compare any variations in channel structure, geometry and integrity. In addition, the transmittance of a 4 μ m thick fluoropolymer coating on a 3 mm thick PDMS slide was determined (for wavelengths between 300 and 600 nm) using a FluoroMax 4 spectrophotometer (HORIBA Scientific, Northampton, UK).

Application of fluoropolymer coated microfluidic reactors to organic synthesis

To assess the performance and utility of fluoropolymer coated microfluidic channels under a variety of conditions encountered in small molecule synthesis, we conducted reactions involving strongly acidic conditions (toluene nitration), strongly basic conditions (Heck

coupling of iodobenzene to methyl acrylate at 85°C) and aggressive organic solvents (photooxidation of α -terpinene in chloroform). The main microfluidic channel used to process all reactions was 35 cm long, 300 μ m wide and 80 μ m high (Figure **S1a**). In all experiments, polytetrafluoroethylene tubing was used to connect 10 mL gastight syringes (Hamilton, Bonaduz, Switzerland) to the inlets of the microfluidic device. A 3 cm long section of PTFE tubing was used to connect the outlet to a collection vial.

The nitration of toluene was conducted at room temperature in a segmented flow manner^[26]. 68% (w/w) nitric acid and 98% (w/w) sulfuric acid were mixed off-chip to yield 63% sulfuric and 25% nitric acid in water (w/w). This solution and toluene were subsequently delivered to inlet 2 and inlet 1 of the microfluidic reactor (**Figure S1a**) at flow rates of 25 μ L/min and 5 μ L/ min respectively. This leads to the generation of a segmented flow, where toluene acts as the continuous carrier fluid. Once the segmented flow was stable, product was collected for one hour, with the reaction being quenched with a cold, saturated NaHCO₃ solution in water. The crude solution was extracted with ethyl acetate and extracts dried over MgSO₄. Finally, extracts were concentrated to remove solvent and analysed using gas chromatography and ¹H NMR.

Singlet oxygen addition to α -terpinene was performed using a mixture of 0.61 M α -terpinene and 2.6 mM tetraphenylporphyrin (TPP)^[27] in chloroform. The reactant solution was introduced into inlet 1 (**Figure S1a**, with inlet 3 being blocked) at a flow rate of 2 µL/min. Pure oxygen was introduced into inlet 2 at a flow rate of 15 µL/min using an EL-FLOW[®] mass flow controller (Bronkhorst AG, Reinach, Switzerland). The resulting gas/liquid segmented flow was formed at the T junction and the entire microfluidic device then exposed to a 700 mW collimated beam at 420 nm. The reaction was quenched by diluting product with diethyl ether over ice and in the dark. The product was then filtered through a short silica plug to remove residual TPP sensitizer. The crude material was then concentrated and analysed by gas chromatography and ¹H NMR.

Heck reactions were conducted using a segmented flow approach^[28]. Specifically, a mixture of iodobenzene, methyl acrylate and trimethylamine (Et₃N) in dimethylformamide (DMF) was introduced into inlet 3 shown in **Figure S1a**, at a volumetric flow rate of 4 μ L/min, with tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄) in DMF being delivered though inlet 2 at the same volumetric flow rate. The final concentration of iodobenzene, methyl acrylate, Et₃N

and Pd(PPh₃)₄ was calculated to be 1 mM, 1mM, 0.1mM and 0.1mM respectively within the discrete phase. Light mineral oil (Sigma Aldrich, Buchs, Switzerland) was used as the continuous phase in all experiments and delivered into inlet 1 at a flow rate of 8 μ L/min. The microfluidic reactor was heated to 85°C on a hot plate, with a thermocouple (9211 Module, National Instruments, Austin, USA) in the top PDMS layer being used to estimate on-chip temperatures. Once a uniform flow was established, product was collected for 2 hours in a glass vial placed on ice. The crude material was extracted, with solvent being removed and the product isolated by preparative TLC and analyzed by ¹H NMR.

Results and Discussion

Fabrication of fluoropolymer-coated microchannels

The CTX-809AP2 polymer is functionalized on one end with a carboxylic acid group that can form a covalent bond with the amine group present on an APTES-treated PDMS surface (**Figure 1c**). As previously described, bonding of coated surfaces was thermally controlled, with the bonding temperature (180°C) being significantly above the glass transition temperature (108°C) of the fluoropolymer. As an aside, it was noted that use of bonding temperatures above 180°C improved both bonding stability and spatial homogeneity, but was accompanied by the appearance of a light-yellow discoloration. The hydrophobicity of the fluoropolymer coating was confirmed by the successful and stable generation of water-in-oil droplets at a T-junction as shown in **Figure 1b**.

Evaluation of the resistance of CYTOP-coatings to organic solvents

5% and 9% fluoropolymer solutions were spun at 700, 900, 1000 and 2000 rpm onto clean glass slides and fluoropolymer layer thicknesses measured via surface profilometry (**Figure S2**). We observed good agreement between these measurements and the thickness estimates provided by the vendor. **Figure 2a** shows an SEM image of the cut face of a device containing fluoropolymer-coated microchannels. Inspection of this image confirms the existence a smooth surface when using a 9% CYTOP solution at 900 rpm. The "rough" features visible on the upper and lower channel peripheries are due to stretching and deformation during the cutting process. Furthermore, the rounding of channel corners evident in **Figure 2a** is due to surface tension collecting and accumulating liquid in channel corners during the spinning process^[29]. The thickness of the coating is approximately 4 μ m in all the microfluidic devices used in solvent resistance and bonding strength tests and processing the organic reactions.

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As previously noted, bonding strength and durability were assessed by pumping water at high pressure through a 300 μ m wide, 50 μ m high and 18 cm long microchannel (**Figure S1b**). Pressures of 13.8 bar (corresponding to a volumetric flow rate of 1.5 mL/min) were applied for periods in excess of 40 minutes, with no feature distortion or delamination being observed. Significantly, operation at pressures up to 13.8 bar provides access to a wide range of volumetric flow rates. The long-term stability of the fluoropolymer coating when exposed to common organic solvents condition was subsequently evaluated by flowing either chloroform or toluene through the same microchannel for a period of three hours. Toluene and chloroform are two of the most common solvents used in organic synthesis and are well-recognized to cause significant swelling of PDMS substrates^[10]. **Figures 2b & c** (left and middle panels) illustrate the deformation and distortion of uncoated PDMS channels after only 3 minutes of exposure to either toluene or chloroform. Moreover, after 15 minutes, significant PDMS dissolution and adhesion of channel surfaces could be observed. Conversely, fluoropolymer coated microchannels exhibited no measurable distortion, even after 3 hours of exposure to either chloroform or toluene (**Figure 2d & e**).

Application of fluoropolymer-coated microfluidic reactors in organic syntheses

To evaluate the utility and performance of the fluoropolymer-coated reactors, we initially explored the nitration of toluene (involving a mixture H_2SO_4 and HNO_3) as a model reaction that is both exothermic and proceeds under highly acidic conditions (Figure 3a). At a basic level, the adoption of continuous- or segmented-flow microfluidic reaction format is always accompanied by a significant increase in the surface area-to-volume ratio. This ensures that microfluidic reactors have exceptionally high thermal transfer efficiencies and are able to exert unprecedented control over exothermic or high-temperature reactions^[30]. Interestingly, Burns and Ramshaw reported the direct nitration of toluene in a slug flow and under isothermal conditions using PTFE or stainless steel capillaries^[26], but to our knowledge such reactions have never been successfully performed within polymer-based microfluidic devices. To address this oversight, we used the fluoropolymer-coated device shown in Figure S1a to generate a segmented-flow reaction platform, which intensifies mixing and eliminates axial dispersion^[31]. Specifically, droplets of the aqueous phase are formed at a T-junction (Figure 3b), with toluene acting as the continuous carrier fluid (which preferentially wets the fluoropolymer-coated channels walls). The segmented-flow moves downstream at a linear velocity of 23.74 mm/s, yielding an average residence time of 17 seconds (14 seconds on chip and 3 seconds in the outlet tubing). Highly efficient transformations were achieved within this

17 second time period, with complete (100%) conversion of feedstock by GC area analysis, and yields for 2-nitrotoluene, 4-nitrotoluene and 2, 4-dinitrotoluene of 52.2%, 37.8% and 4.3% respectively (via ¹H NMR analysis, **Figure S4**). Critically, nitration was performed continuously for a period of at least two hours, without any leakage or delamination issues, whilst achieving higher conversions and lower residence times than in previous studies^[26, 32]. These improvements are in large part due to the high surface area-to-volume ratio environment and enhanced diffusion due to rapid internal circulation within the segmented flow.

We subsequently evaluated the utility of our fluoropolymer-coated reactors in photosensitized oxidation reactions, through the gas-liquid, segmented-flow synthesis of ascaridole from α terpinene in chloroform (Figure 4a). In simple terms, the photochemical synthesis of ascaridole proceeds via addition of singlet oxygen to α -terpinene in the presence of an organic sensitizer^[33]. Microfluidic reactors are powerful tools for performing such reactions, due to the facile control of both chemical flows and the optical light path. Indeed, a range of microfluidic reactors have been applied to photosensitized oxygenations over the past decade. For example, Wootton and co-workers demonstrated the safe and efficient generation of singlet oxygen for the synthesis of ascaridole within a planar, glass device^[27b]. In a more recent study, Park and co-workers used a dual-channel PDMS reactor shielded with polyvinylsilazane for a range of photosensitized oxygenations^[34]. This reactor comprised an upper channel for liquid flow and a lower channel for oxygen flow, with sufficient phase contact being effected through the use of a gas permeable (PDMS) membrane. Significantly, the authors reported shorter residence times when compared to standard batch conditions. More recently, Park and colleagues (at Chungnam National University) suggested a continuous flow microfluidic method for the formation of ascaridole using a gas permeable Teflon AF-2400 tube-in-tube reactor^[35]. Critically, this approach engendered a 300-fold increase in product yield when compared to flow systems where the gas and liquid are co-located in the same channel. However, it should be noted that the use of low temperatures (5°C) and a vacuum bath necessitated the use of elaborate safety procedures, even when performing the reaction in a microfluidic environment.

Herein, we adopted a gas-liquid, segmented-flow approach that relies on the generation of micron-sized air slugs within a liquid reaction mixture (**Figure 4 b & c**). The approach has two key advantages over previous experimental formats, namely enhanced reagent mixing within the liquid slugs, and dosing control between bubbles and slugs. The use of alternating slugs of oxygen and α -terpinene dissolved in chloroform provides higher surface area-to-volume ratios,

thus ensuring the enhancement of diffusion across the interface and augmentation of mass transfer. Additionally, it is significant to note that the fluoropolymer layer has excellent optical transparency throughout the visible region of the electromagnetic spectrum (**Figure S3**), and thus effective light penetration into the reactor is maintained constant. The gas-liquid, segmented-flow yielded an average residence time of 30 seconds (of which 26 seconds are onchip and 4 seconds in the outlet tubing). Despite the fact that PDMS swells when exposed to chloroform for extended periods of time, no leakage or delamination was observed over the course (2 hours) of the experiment. More importantly, complete (100%) conversion of α -terpinene occurred within 30 seconds, with an ascaridole yield of 75% (as determined by GC area analysis; **Figures S5 & S6** and ¹H NMR; **Figure S7**). In this respect, the reduced reaction times and high reaction yields suggest appreciable utility of the platform in the scaled-out production of ascaridole.

Finally, we explored the Heck reaction (the palladium(II)-catalysed acrylation reaction of iodobenzene) as a model for reactions performed under strongly basic conditions (>pH 11) and at elevated temperatures (**Figure 5a**)^[36]. Specifically, a mixture of iodobenzene, methyl acrylate and Et_3N in DMF was introduced into inlet 3 of the Y-mixer unit (shown in **Figure S1a**), with Pd(PPh₃)₄ in DMF being delivered though inlet 2 at the same volumetric flow rate. Droplets with a volume of 15 nL were generated at the T-junction, with light mineral oil acting as the continuous phase (**Figure 5b**). Under segmented-flow conditions, at a temperature of 85°C and a residence time in the microreactor of 28 seconds, methyl cinnamate was obtained at a yield of 79% (as determined by ¹H NMR; **Figure S8**). The reaction was processed for a period of 2 hours without any leakage or delamination issues, confirming the chemical stability of the reactor under strongly basic and hot conditions.

Conclusions

We have described the design, fabrication and testing of a novel range of fluoropolymer-coated polymeric devices that exhibit appreciable resistance to non-polar organic solvents. All microfluidic reactors were fabricated using standard PDMS soft lithographic techniques followed by surface treatment with the fluoropolymer CYTOP. CYTOP-PDMS devices were shown to offer significant resistance to non-polar organic solvents when compared to native PDMS devices, with negligible feature distortion, deformation or damage observable over timescales of multiple hours. To demonstrate the efficacy of the approach, fluoropolymer-

coated microfluidic reactors were used to perform photosensitized oxygenations in organic media and organic reactions under strongly acidic or basic conditions. Critically, in all situations conversions, product yields and reaction times were shown to be superior or comparable to contemporary studies involving microfluidic reactors made from alternate materials. Finally, it is important to note that the use of commercially available fluoropolymer precursors allows direct adaptation and use of the presented methodology in a wide range of synthetic applications.

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Keywords: microfluidics, organic synthesis, microreactor, fluoropolymer

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Figure 1 (a) Schematic describing the basic steps involved in the fabrication a CYTOP coated microfluidic reactor. The plasma oxidized PDMS surfaces were treated with APTES and spin coated with CYTOP. After heating the coated slides at 70°C to remove residual solvent, the top and bottom layers were aligned and bonded. (b) Top: Image of an entire CYTOP coated microfluidic reactor containing water-in-oil droplets (scale bar 1 cm). Bottom: Bright field image showing the same droplet formation process in detail (scale bar 600 μ m). (c) Reaction of CYTOP with an APTES coated PDMS surface. Carboxylic acid groups form covalent bonds (amide bonds) with amino groups on the APTES surface.



Figure 2 (a) SEM image of two adjacent fluoropolymer coated channels, 300 μ m wide and 80 μ m high. (b) and (c) show PDMS channels without the CYTOP coating after exposure to chloroform and toluene for 0, 3 and 15 minutes respectively. In both cases channel distortions can be clearly observed at 3 minutes due to swelling. After exposure for 15 minutes, the top and bottom faces of the channel are seen to contact and stick, e.g. the oval feature in the right panel of (b), with channel surfaces becoming rough, e.g. the right panel of (c). (d) and (e) show the fluoropolymer coated channel before and after exposure to chloroform and toluene at a flow rate of 20 μ l/ min for 3 hours. No deformation, distortion or delamination is observed. Scale bars are 100 μ m.



Figure 3 (a) Scheme for the nitration of toluene using a concentrated acid mixture ($HNO_3 + H_2SO_4$) at room temperature with obtained product yields. (b) Schematic of segmented flow reaction format, where toluene acts as the carrier phase and the mixture of acids acts as the discrete phase for the fluoropolymer-coated microfluidic reactor.



Figure 4 (a) Scheme for singlet oxygen addition to α -terpinene to form ascaridole, with associated values for conversion and product yields. (b) Schematic of the gas-liquid segmented flow established within the fluoropolymer-coated microfluidic reactor. (c) Image of the segmented flow, where oxygen slugs are transparent and located between dark purple reactant. Scale bar 100 μ m.



Figure 5 (a) Scheme of the Heck reaction coupling iodobenzene to methyl acrylate at 85°C. (b) Schematic of the segmented flow conditions within the fluoropolymer-coated microfluidic reactor, using light mineral oil as the carrier phase and the reactants as the discrete phase.