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Scalable Continuous Flow Process for the Synthesis of Eflornithine using Fluoroform as Difluoromethyl Source

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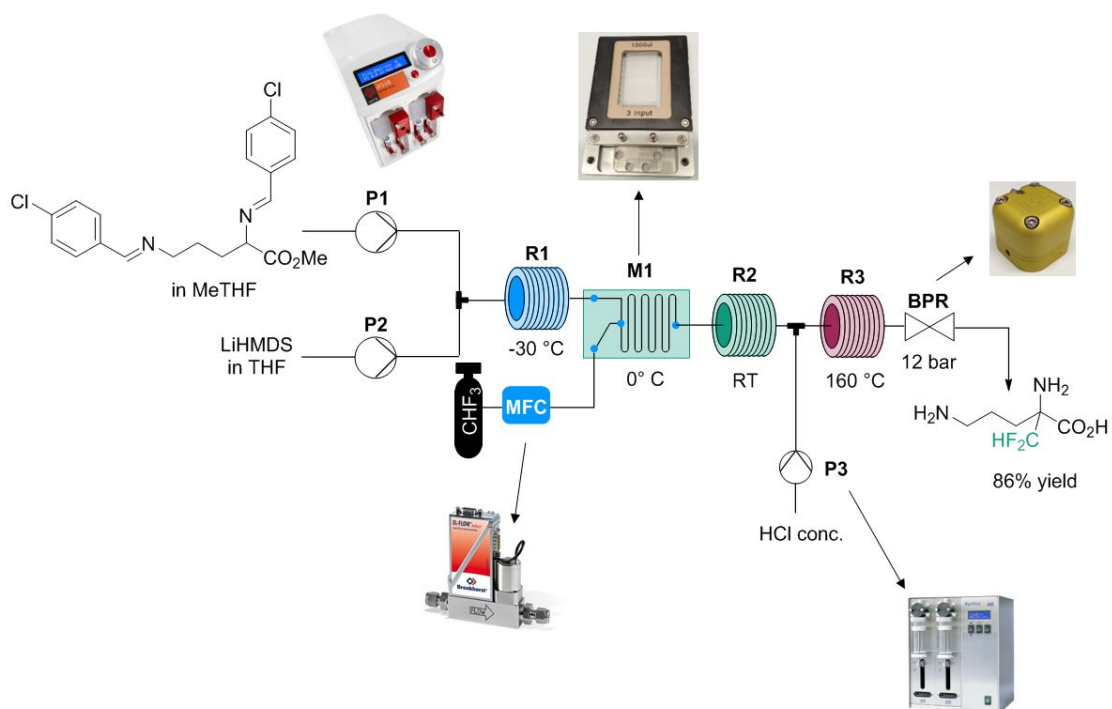
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Abstract

The development of a scalable telescoped continuous flow procedure for difluoromethylation of a protected amino acid with fluoroform (CHF_3, R-23) gas and subsequent high temperature deprotection to provide eflornithine, an important Active Pharmaceutical Ingredient (API), is described. Eflornithine is used for the treatment of sleeping sickness and hirsutism, and is on the World Health Organization's list of essential medicines. Fluoroform is produced in large quantities as a side product in the manufacture of polytetrafluoroethylene (PTFE, Teflon®). Fluoroform is an ozone-benign and nontoxic gas, but its release into the environment is forbidden under the Kyoto protocol owing to its high global warming potential. The existing manufacturing route to eflornithine uses chlorodifluoromethane ($CHClF_2$, R-22) which will be phased out under the Montreal protocol, therefore the use of the fluoroform presents a viable cost effective and more sustainable alternative. The process parameters and equipment setup were optimized on laboratory scale for the two reaction steps to improve product yield and scalability. The telescoped flow process utilizing fluoroform gas was operated for 4 h to afford the target molecule in 86 % isolated yield over two steps with a throughput of 24 mmol/h.

INTRODUCTION

Eflornithine, also known as α-difluoromethylornithine (DFMO, **1**), is an Active Pharmaceutical Ingredient (API) on the World Health Organization's list of essential medicines. DFMO is used to treat the second stage of African trypanosomiasis (sleeping sickness). In addition, DFMO is also used to treat opportunistic infections with *Pneumocystis carinii pneumonia*, a form of pneumonia found in people with a weak immune system suffering from conditions such as acquired immunodeficiency syndrome (AIDS).[1] It has also been explored as chemopreventive agent in cancer therapy with minor success.[2] Today, its main use is to treat excessive facial hair growth on women (hirsutism). The topical cream (Vaniqa®) significantly reduces the psychological burden of those affected.[3]
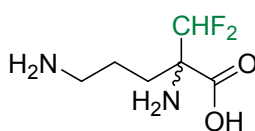
D,L-α-difluoromethylornithine (DFMO, **1**)

Figure 1. Structure of D,L-α-difluoromethylornithine (elfornithine, DFMO, **1**) as free base. Topical administrations use eflornithine hydrochloride monohydrate.[3]

Eflornithine's mechanism of action is well understood.[4] It acts as a "suicide inhibitor" of ornithine decarboxylase (ODC), an enzyme responsible for the committed step in polyamine biosynthesis. Eflornithine irreversibly binds to the active site of ODC, which results in the suppression of catalytic activity for conversion of the natural substrate. The polyamines produced by OCD are associated with growth processes and reduced apoptosis.[2]

Currently, the employed manufacturing strategy for eflornithine **1** (Scheme 1)[5] commences by condensing diethylmalonate and acrylonitrile to afford diethyl 2-(2-cyanoethyl)malonate (**2**). The afforded malonate is then difluoromethylated by chlorodifluoromethane ($CHClF_2$, R-22) under basic conditions.[5,6] Subsequent hydrogenolysis of nitrile **3** provides the lactam **4** which is transformed to the amide **5** through treatment with ammonia gas. The following Hofmann rearrangement and hydrolysis affords **1**. The Hoffmann rearrangement poses safety challenges caused by the possibility of a run-away reaction.[7] The reported overall yield is ~26 % for this

synthetic route.[5] Alternative routes, which still utilize chlorodifluoromethane, reported yields in the range of 37% to 40%.[8]
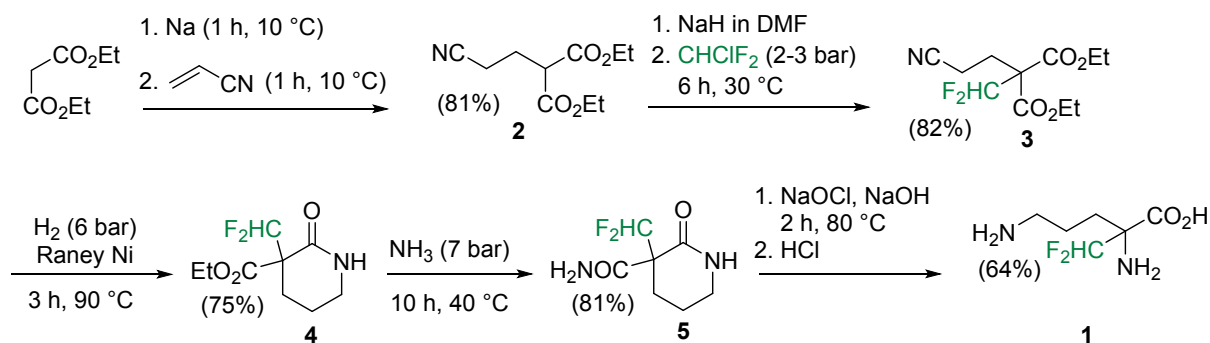
Scheme 1. Industrial synthesis of eflornithine starting from diethylmalonate.[5]

There are challenges associated with using gases such as NH_3, H_2 and R-22 in batch reactors, in particular in terms of mass transfer and safety. Furthermore, R-22 will be completely phased out under the Montreal protocol because of its ozone depleting potential.[9] The Montreal protocol is an international treaty to ensure protection of the earth´s ozone layer by phasing out the production of compounds that are responsible for ozone depletion such as chlorofluorohydrocarbons (CFCs). The phasing out of R-22 will have a significant impact on its production, availability and cost, particularly in industrialized countries. Therefore, we aimed to identify a more cost-effective and sustainable difluoromethyl source as an alternative to R-22, and subsequently design an industrial relevant process for the synthesis of eflornithine utilizing the new difluoromethyl source.

There is a plethora of difluoromethylation agents available, including CHF_2OTf, $TMSCF_2Br$, $(EtO)_2POCF_2Br$ and $PhCOCF_2Cl$.[10] These reagents cover the needs for small scale laboratory synthesis very well, but generally are impractical for large scale industrial processes because of their limited commercial availability, low atom economy and high cost per mole. Fluoroform (CHF_3, R-23), on the other hand, is a large-volume gaseous side product in the production of polytetrafluoroethylene (PTFE, Teflon®) which can potentially serve as alternative to R-22. Fluoroform is an ozone-benign and nontoxic gas (bp. $= -83\ °C$). However, the release of fluoroform into the environment is forbidden under the Kyoto protocol due to its high global

warming potential (GWP). Fluoroform's global warming potential is 14 800 times higher than CO_2 over a century.[11] Consequently, fluoroform needs to be converted to less harmful substances before release into the environment. Currently, this is achieved mainly through destructive means such as thermolysis, plasmolysis or catalytic hydrolysis.[12,13] The more preferable option would be to use fluoroform as a feedstock for industrial scale manufacturing of difluoro- or trifluoromethylated fine chemicals or APIs. Nevertheless, this has been an unyielding endeavor for a long time, partially caused by the very low reactivity of the gas (pK_a = 25–28 in water).[13] Recently the first synthetically valuable transformations using fluoroform as CF_3-source[13-16] and CHF_2-source[17,18] have been reported.[18b] Trifluoromethylation reactions were conducted by deprotonating fluoroform with either an electrogenerated[14] or a strong base and trapping of CF_3^- (trifluoromethyl anion) with a suitable acceptor (TMSCl,[13] DMF[14,15] or Cu(I)[16]). The formed intermediates were then reacted with a variety of electrophiles. Most notably, Mikami and co-workers reported the treatment of a variety of carbonyl compounds with strong lithium bases such as lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LiHMDS) and fluoroform to afford their corresponding difluoromethylated analogue.[17] The mechanism presumably involves the formation of an electrophilic singlet difluorocarbene formed by rapid α-elimination of fluoride from CF_3^-.

The described literature protocols using fluoroform gas operate mostly in batch mode. Scaling up a gas-liquid batch reaction to production quantities, however, poses unique challenges. To establish the required stoichiometry, a sufficient amount of gas must be dissolved in the reaction media. The solubility of a gas increases as a function of pressure (Henry's law), therefore reactors have to be pressurized to ensure sufficient gas dissolution. However, pressurizing a huge inventory of gas and reaction media poses significant safety risks. Commercial batch reactors can typically operate at up to 6 bar, higher pressures require more specialized equipment. Therefore gas-liquid reactions can benefit massively from a safety and process operation viewpoint by using continuous processing.[19] Historically, the fine chemicals and pharmaceutical industry operated by using flexible multipurpose batch plants, but recently there has been a paradigm shift from batch manufacturing to continuous processing.[20] This shift has been driven by a need to lower operating costs, increase safety, achieve higher product quality and lower solvent usage for API and fine chemical manufacturing. Continuous processing meets those goals by providing excellent control over process parameters such as residence time, temperature and mixing

because of the small channel dimensions used. The small reactor volume minimizes the risks associated with handling hazardous chemistry thus making gas-liquid reactions inherently safer and more controlled.

Recently, efforts have been made to utilize fluoroform gas within continuous flow reactors. Grushin and co-workers developed a continuous flow protocol for the cupration of fluoroform to $CuCF_3$, which they demonstrated as a trifluoromethylating agent.[21] Ley and coworkers monitored fluoroform consumption in real-time by using a benchtop flow ^{19}F NMR for a continuous-flow nucleophilic trifluoromethylation.[22] Our group has reported using fluoroform in a 3D printed stainless steel continuous flow reactor for the difluoromethylation of diphenylacetonitrile,[23] a reaction which was originally developed by Mikami and co-workers.[17] Most relevant to the present work, we recently communicated a general continuous flow strategy for the difluoromethylation of protected amino acids (Scheme 2).[24] We achieved this by deprotonation of benzylidene protected amino acid esters at $-30\,°C$ with LiHMDS (2 equiv) and subsequent reaction with excess of fluoroform (3 equiv) at $-15\,°C$ in a continuous flow system. After warming to room temperature the reaction mixture was quenched with water. The process was performed at 12 bar to ensure complete dissolution of fluoroform. The obtained protected difluoromethylated amino acid esters were hydrolyzed in a microwave reactor using superheated HCl and isolated by precipitation. Although successful, this approach had certain limitations from a process chemistry perspective, such as the excess of fluoroform employed - necessary to cope with pressure fluctuations of the system. The highly viscous substrates used were only bench-stable for ~24 h. Additionally, we were unable to demonstrate scalability of the process due to precipitation inside the back pressure regulator (BPR) which prevented operation over longer times.
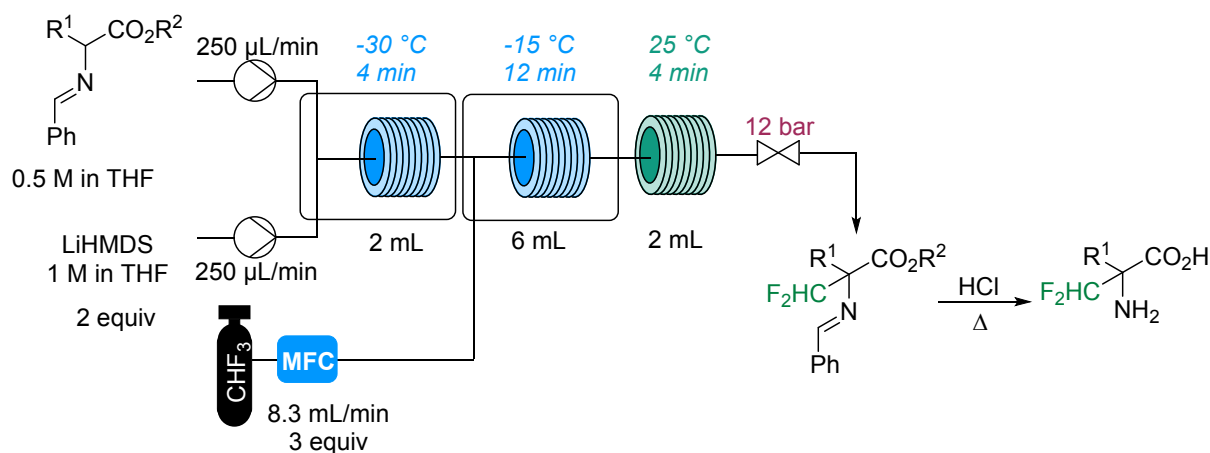
Scheme 2. Continuous flow C$^\alpha$-difluoromethylation with fluoroform (previous work).[24]

The aim of the research described in this article is to address the challenges associated with our preliminary difluoromethylation approach described above (Scheme 2), and develop a scalable continuous difluoromethylation protocol using fluoroform with an attached telescoped high-T/p deprotection reaction with higher throughput. Furthermore, we were interested in increasing the sustainability of the process by finding alternatives to the use of THF and CHCl$_3$ as solvents as they are classified as highly hazardous and problematic, respectively.[25]

RESULTS AND DISCUSSION

Pressure Stabilization Experiments. One of the main objectives of this work was to reduce the fluoroform input and, more importantly, the fluoroform remaining at the end of the process, because its discharge into the environment is strictly regulated. The main reason for using 3 equiv of fluoroform in our previous report[24] was the pressure fluctuation caused by accumulation of inorganic precipitate inside the Swagelok backpressure regulator (BPR). The pressure fluctuation resulted in a variation in the fluoroform flow rate over the course of the reaction. We proposed three approaches to handle the excess use of fluoroform: (a) the use of gas-liquid membrane separation technology, based on a gas permeable and liquid impermeable membrane,[26] to remove and recycle the surplus fluoroform; (b) improved pressure control in order to prevent fluoroform flow rate fluctuation; or (c) decrease the fluoroform input to a minimum and react the surplus with base to more benign compounds. Although intriguing at first, we decided against using a membrane separation technique because of almost certain membrane fouling caused by the precipitate and the high solubility of fluoroform in THF.

We commenced our investigation by utilizing our previously reported flow setup (Scheme 2).[24] The flow setup comprised of two syringe pumps to introduce a 0.5 M solution of substrate in THF (Feed 1, 2 mL sample injection loop), and a commercial 1 M solution of LiHMDS in THF (Feed 2, 4 mL sample injection loop). Feed 1 and 2 were mixed in a Y-shaped connector submerged within a cooling bath at −30 °C. The substrate was converted to the enolate in a 2 mL residence time loop (reactor 1). Subsequently, the enolate was reacted with fluoroform, which was introduced through a second Y-shaped connector. The amount of fluoroform added was controlled using a calibrated mass flow controller (MFC, Bronkhorst-EL). The combined mixture then passed through a second cooled residence time loop at −15 °C (reactor 2) and then through a third residence loop at room temperature (reactor 3). Cooling of reactor 2 was necessary due to increased solubility of fluoroform at lower temperatures and the delayed precipitation of LiF. The system pressure was maintained by using an adjustable back pressure regulator (BPR, Swagelok). At pressures of 5 bar or above and temperatures below 25 °C for reactor 2, the fluoroform dissolved completely in the liquid feed under the flow rates employed. Higher temperatures at 5 bar pressure resulted in a gas-liquid segmented flow regime. As a result of the large inner volume (~1 mL) and small aperture of the outlet, the BPR (Swagelok, 0 to 26 bar) clogged periodically from accumulation of precipitated solids formed in the reaction media, most notably LiF. The formation of solids resulted in pressure fluctuations of ±2 bar (Table 1, entry 2) and an unsteady delivery of fluoroform into the reaction mixture, therefore the stoichiometry could not be carefully controlled. The problem became even more severe when using an Upchurch Scientific BPR with a fixed back pressure of 100 psi/6.89 bar (Table 1, entry 1), as even the slightest precipitation stopped the flow through the narrow channels of the BPR entirely. To fulfill our requirements, a BPR with a small dead volume, precise pressure control and large enough channel width to ensure a smooth flow without clogging seemed to be most appropriate. The flow reaction performed most consistently with a Zaiput BPR. The Zaiput BPR is pressurized to the correct setpoint by filling a gas chamber with a membrane on the bottom. The reaction fluid needs to work against the compressed gas inside the chamber to flow out on the other side. Pressure fluctuations were decreased to only ±0.1 bar with no clogging (Table 1, entry 3), therefore the fluoroform flow rate did not fluctuate to compensate for pressure changes. The reaction was successfully operated to give the product in 80% yield.

Table 1. Pressure Fluctuations Using Different Back Pressure Regulators for Difluoromethylation.
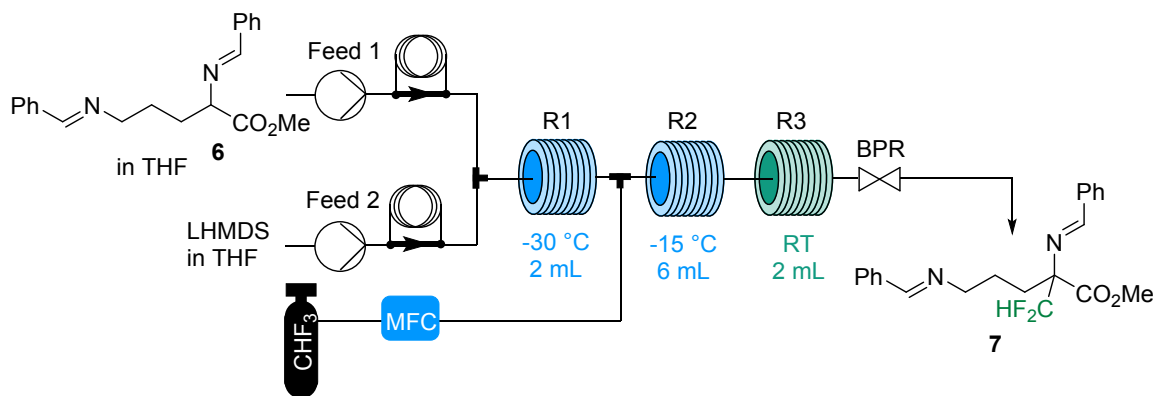
entry	BPR type	fluoroform (equiv)	pressure fluctuation [%]	yield [%][a]
1	Upchurch	3	-	no throughput
2	Swagelok	3	±2 bar	81
3	Zaiput	3	±0.1 bar	80

Conditions: Feed 1 = 0.5 M solution of **6** in THF, F1 = 0.25 µL/min. Feed 2 = 1 M solution of LiHMDS in THF, F2 = 0.25 µL/min. [a] Analyzed by ^{19}F NMR (α, α, α,-trifluorotoluene as internal standard)

Process Optimization Experiments. With a more reliable BPR in hand, we investigated the influence of flow rate, residence time and fluoroform equivalents on the product yield. To ensure full conversion to the corresponding lithium enolate at higher flow rates, reactor 1 was changed from a 2 mL to a 4 mL coil to allow access to a longer residence time. Furthermore, to enable improved mixing we exchanged the Y-shaped connector after reactor 1 for a 2 mL borosilicate static glass mixer plate (Uniqsis). An increase of flow rates and shorter residence time resulted in a considerable drop in yield to just 16% of product **7** (Table 2, entry 3). We could improve the yield back to acceptable levels (87%) without changing the setup by increasing the amount of base from two to three equivalents (Table 2, entries 5, 6 and 8). Although a dilution of the 0.5 M solution of **6** to 0.25 M gave full conversion to the desired product, we opted for the higher concentrated substrate solution because an acceptable conversion and double space time yield could be achieved. During the course of this study, we observed that cooling of the second loop was unnecessary at higher flow rates, because the reaction medium was still sufficiently cold (0 °C) to ensure complete dissolution of the gas, and to achieve a similar yield. Subsequently, the reaction was also investigated by using 2-methyltetrahydrofuran (2-MeTHF) as the solvent for the substrate feed. The substrate displayed slightly better solubility in 2-MeTHF. Using 2-MeTHF also helped with phase separation during the aqueous workup owing to its limited water miscibility. Although currently more costly than THF, prices for 2-MeTHF are predicted to fall

considerably over time as production has been greatly expanded and more suppliers are offering this solvent.[27] In addition, the overall sustainability of the process benefits as 2-MeTHF can be derived from renewable resources, such as corncobs and bagasse. In addition, 2-MeTHF is dried more easily than THF due to the formation of an azeotrope rich in water.[27] Notably, in contrast to THF, 2-MeTHF is not classified as CMR-substance (carcinogenic, mutagenic and toxic for reproduction).

Table 2. Process Throughput Optimization for Difluoromethylation using Fluoroform.
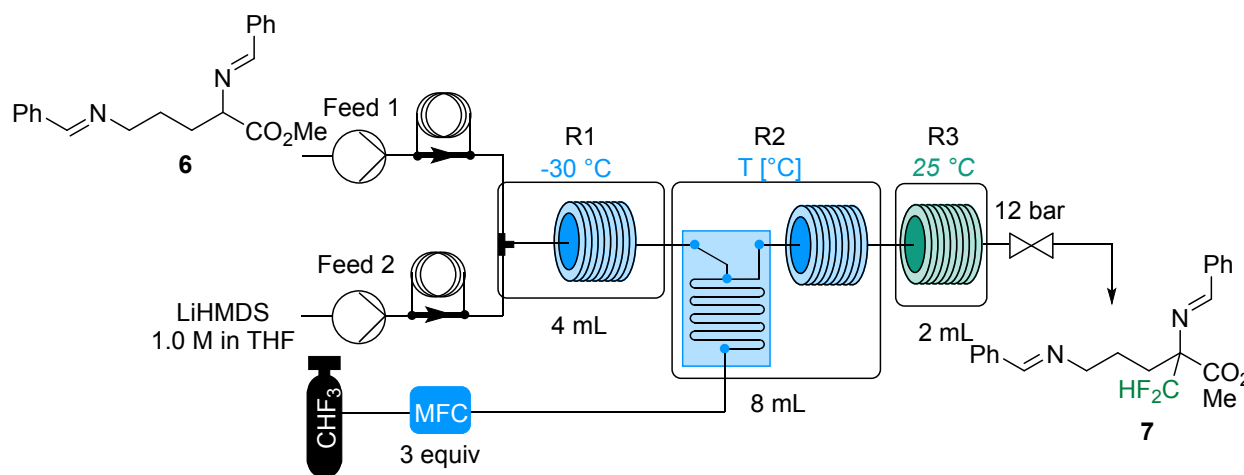
| entry	6 feed conc [mol/L]	feed 1 [mL/min]	feed 2 [mL/min]	temperature R2 [°C]	yield [%][b]
1	0.5	0.25	0.25	−15	80
2	0.5	0.5	0.5	−15	62
3	0.5	1	1	−15	16
4	0.5	1.33	0.66	−15	1
5	0.5	0.8	1.2	−15	87
6	0.5	0.8	1.2	25	85
7	0.25	0.8	1.2	25	quantitative
8[a]	0.5	0.8	1.2	25	86

Conditions: Back pressure = 12 bar. [a] Feed 1 solution of **6** in 2-MeTHF, Volume of R2+R3 = 16 mL. [b] Analyzed by ^{19}F NMR (α, α, α,-trifluorotoluene as internal standard)

Base Screening. The use of LiHMDS clearly contributes most to the overall cost of the process, therefore we tried to replace it with a more cost effective alternative. Unfortunately all our attempts employing *n*-BuLi, LDA, KO*t*Bu and LiO*t*Bu were largely unsuccessful and yielded only negligible amounts of product (1-2% in the case of LDA). The outcome of those

experiments is very much in line with the published literature on these transformations.[17] Notably, Mikami and coworkers proposed a S_N2-type mechanism to explain the need for this specific base.[28] Best results apart from LiHMDS could be obtained by using 5 equiv of LiN(cyHex)$_2$ which afforded compound **7** in 10% yield (Table S1).[29]

Fluoroform Input. We next investigated the influence of decreasing the amount of fluoroform on product yield. For these experiments the substrate solution and LiHMDS were introduced to the reactor via sample injection loops (Table 3). To measure quantitatively how much fluoroform was still dissolved immediately after the difluoromethylation, we decreased the residence time through decreasing the volume of reactor 2 (R2) to 4 mL which resulted in lower yield but a cooled (~0 °C) output solution stream which kept virtually all the fluoroform in solution. Immediately after quenching the cold output stream with cold water, the organic phase was transferred into an NMR tube, which was sealed to avoid loss of fluoroform through gassing out, and subsequently analyzed by ^{19}F NMR. The gassing out of fluoroform in case of 2 equiv and 3 equiv (Table 3) could not be completely avoided. Gratifyingly, decreasing the amount of fluoroform to equimolar amounts only had a small effect on yield (Table 3). The use of 1.25 equiv of fluoroform afforded the highest yield with the product formed in 67% yield.

Table 3. Optimization of Fluoroform Input Using ^{19}F NMR with α, α, α,-Trifluorotoluene as Internal Standard.
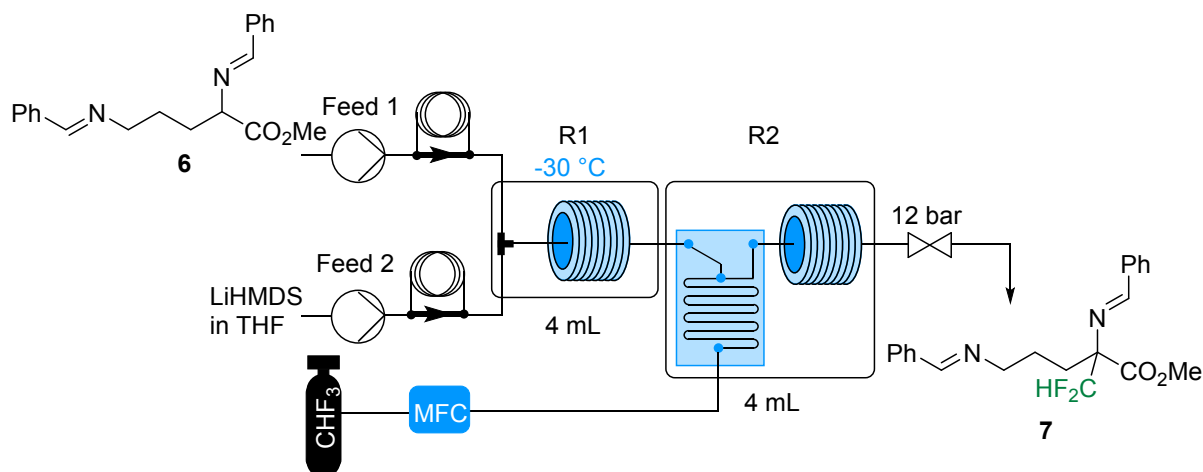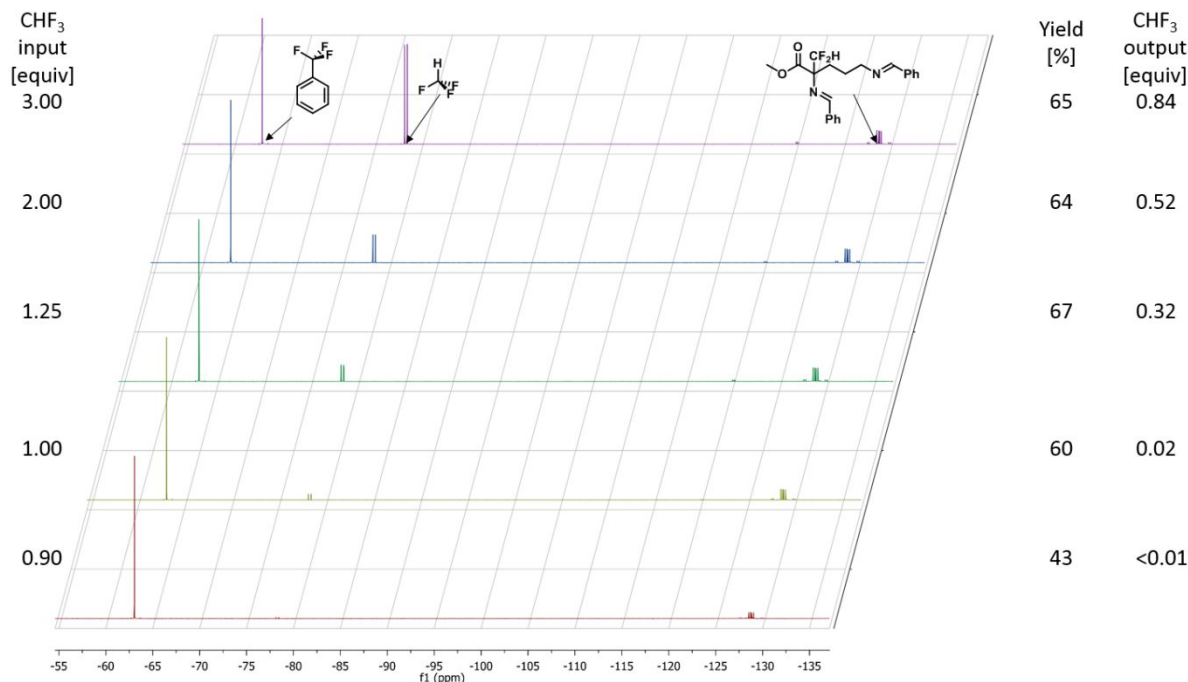
Conditions: Feed $1 = 0.5$ M solution of **6** in 2-MeTHF, $F1 = 0.8$ mL/min. Feed $2 = 1$ M solution of LiHMDS in THF, $F2 = 1.2$ mL/min. Residence time 4 min, back pressure 12 bar. Output stream had a temperature of 0 °C and was quenched with cold water. A sample of 200 µL was diluted to 700µL with CDCl$_3$ and analyzed by ^{19}F NMR (α, α, α,-trifluorotoluene as internal standard) at 282 MHz.

Protection Group Screening. Bisimine **6** is an unstable and highly viscous liquid, therefore we decided to screen for a more suitable protecting group for the amino residue. The optimal substrate would be bench stable, crystalline, easy to synthesize and soluble in 2-MeTHF. For this reason a series of substituted benzaldehydes was tested to form the corresponding bisimine derivatives of ornithine methyl ester through standard condensation reaction. Only four of the 13 tested benzaldehydes produced solid products (Table S2). The most promising candidate was methyl (*S*)-2,5-bis(((*E*)-4-chlorobenzylidene)amino)pentanoate (**8**) formed by condensation of ornithine methyl ester with 4-chlorobenzaldehyde in anhydrous CH$_2$Cl$_2$ in the presence of triethylamine. 4-Chlorobenzaldehyde was also the most cost efficient aromatic aldehyde (apart from benzaldehyde) in this series of aromatic aldehydes. Slow addition of trimethylamine base (~1 h) at 0 °C played a crucial role in obtaining a pure sample of **8**, as deviating from these conditions resulted in the formation of significant quantities of lactam **9**. Lactam **9** was the only side product formed during the condensation reaction in about 2-4% yield (Scheme 3). It should be noted that the solvent used in the condensation reaction was changed from chloroform[24] to dichloromethane. Although dichloromethane is not a green solvent, it is preferable to other

chlorinated solvents as it is not classified as a cancerogen.[25] Structural details of **8** and **9** were elucidated by X-ray crystallography (see Supporting Information for details). Notably, bisimine **8** could be stored for prolonged periods of time under argon at low temperatures (−30 °C) without degradation (Figure S2) and was bench stable at room temperature for at least 2 weeks. The water content of a sample of **8** was determined by Karl Fischer titration (Table S3). A concentration of 1475 ppm H_2O was found, which could in theory hydrolyze 1.48% of **8**.
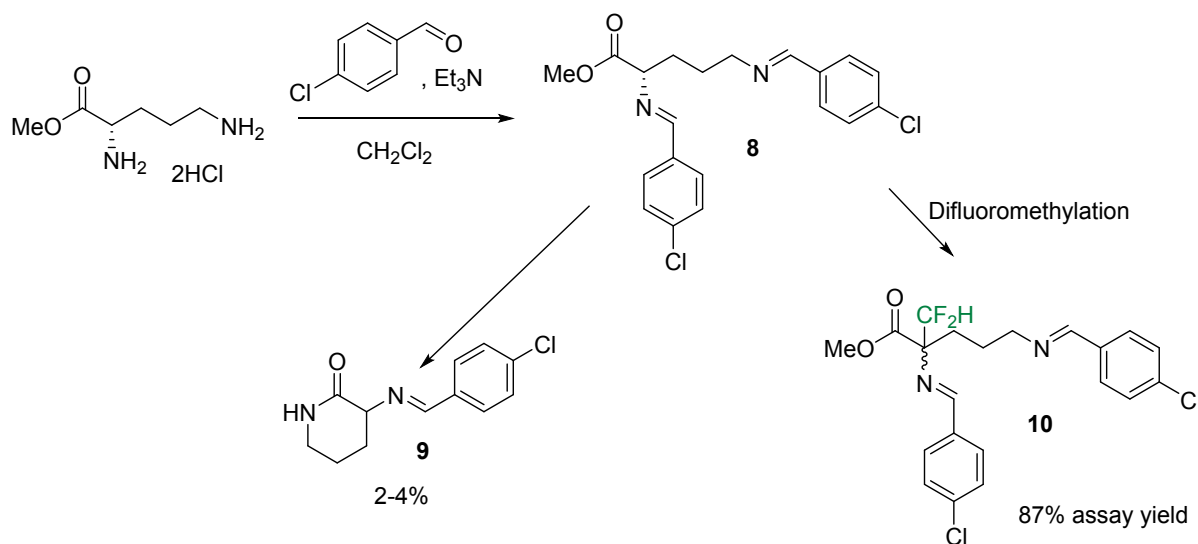
Scheme 3. Formation of **8** and byproduct **9** and subsequent transformation to **10** with optimized difluoromethylation conditions.

Bisimine **8** was converted to its difluoromethylated analogue **10** using the conditions described in Table 2, entry 8 in 87% assay yield (based on an average of 3 measurements, determined by ^{19}F NMR) over a 60 min run time. The collected mixture was used for the optimization experiments for the deprotection procedure. The mixture was diluted with toluene and stored under argon to avoid formation of a gel-like precipitate.

Fluoride Determination. The inorganic fluoride content of the reaction mixture after difluoromethylation was determined, since the formation of HF during the acidic hydrolysis is a potential safety risk. HF also contributes towards corrosion of certain reactor materials, such as

stainless steel or glass. A 3 mL sample, corresponding to approximately 2 mmol of fluoride, was extracted with H_2O (3 × 25 mL). Ion chromatography was used to quantify the amount of fluoride dissolved in the aqueous phase. The fluoride amount measured by ion chromatography was 1.5 mmol in the aqueous analyte. This value corresponds to a maximum concentration of HF in the reaction mixture of <1 wt% after extraction into the aqueous phase, which poses no risk to health and safety but may contribute to corrosion of steel and glass.

Microwave-Assisted Deprotection. After preparing a sufficient amount of the protected intermediate **10**, we proceeded to optimize the envisioned deprotection approach with aqueous HCl. We opted for the acidic hydrolysis of compound **10** as simultaneous deprotection of the imine and ester functionality is possible, although ester hydrolysis is considerably slower. The deprotection was performed in a high-T/p range employing sealed vessel microwave heating technology. Optimized microwave batch conditions can subsequently be conveniently translated to (conventionally heated) continuous-flow processes to provide scalability ("microwave-to-flow" paradigm).[30] The optimization was mainly conducted to minimize the hydrolysis time and achieve high conversion. The translation of the previously published protocol (6 M aqueous HCl at 150 °C for 45 min)[24] to a continuous flow approach would have required a large internal volume for the heated coil (135 mL for a total flow rate of 3 mL/min), and operation at high pressure and temperature was deemed a safety risk. Starting from our previously published approach, we attempted to shorten the deprotection time without loss of conversion (Table 4, entry 1-3) but were unsuccessful employing 6 M HCl. We thus opted for concentrated HCl (12 M) instead and could achieve full conversion to the dihydrochloride salt of DFMO (**1**) in 10 min at 160 °C with 12 bar internal pressure (Table 4, entry 11).

Table 4. Microwave Optimization of Acidic Hydrolysis Conditions.
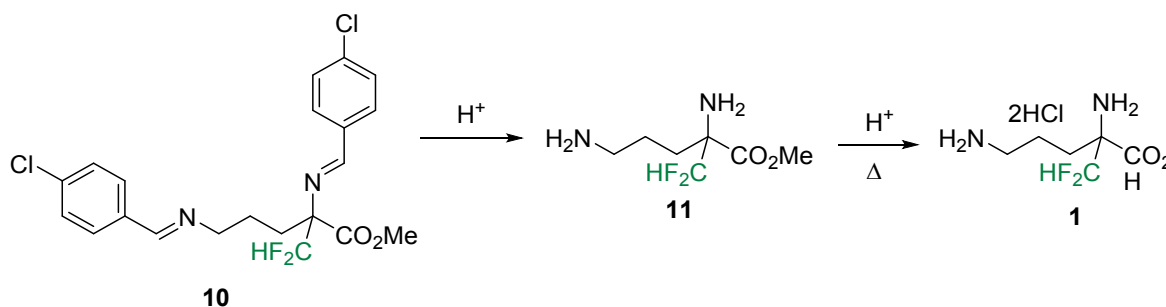
| entry	HCl concentration	temperature [°C]	time [min]	pressure [bar]	conversion [%][a]
1	6 M	140	45	5	>99
2	6 M	150	45	8	>99
3	6 M	150	30	8	85
4	12 M	140	30	5	>99
5	12 M	140	20	5	82
6	12 M	150	30	8	>99
7	12 M	150	20	8	>99
8	12 M	150	10	8	95
9	12 M	160	30	11	>99
11	12 M	160	10	11	>99

Conditions: 3 mL of difluoromethylation reaction mixture (0.15 M solution of **10** in 2-MeTHF/THF/toluene) and 3 mL of HCl were heated in sealed 25 mL microwave vessels. [a] Analyzed by ^{1}H NMR by integrating base line separated CHF_2-peaks of **10** and **1**

Continuous Flow Deprotection Experiments. After having identified optimal conditions for the acidic hydrolysis of the protected intermediate **10**, a continuous flow reactor was assembled. The flow setup consisted of two syringe pumps (Syrris Asia and HighTec Zang Syrdos) with one 2 mL sample injection loop (SL) to introduce a sample of difluoromethylated reaction mixture and a second stream to introduce 12 M HCl directly through the pump. The two feeds were mixed in a T-shaped connector. The mixing of the two feeds results in precipitation, which subsequently dissolved within a few seconds. Thus, a short 2 mL premixing coil was used before introducing the stream into a 10 mL perfluoroalkoxy alkanes (PFA) coil which was submerged within a stirred heated oil bath. The back pressure was adjusted depending on temperature to avoid formation of gas segments. PFA was used as small amounts of hydrofluoric acid might form during the addition of HCl which corrodes steel coils over time. A safety evaluation was

conducted to ensure that the PFA tubing used (1/8 in. o.d.; 0.8 mm i.d) has sufficient wall thickness to withstand the high temperatures and pressure applied.[31]

**Table 5. Acidic Hydrolysis Optimization in Continuous Flow Mode.**
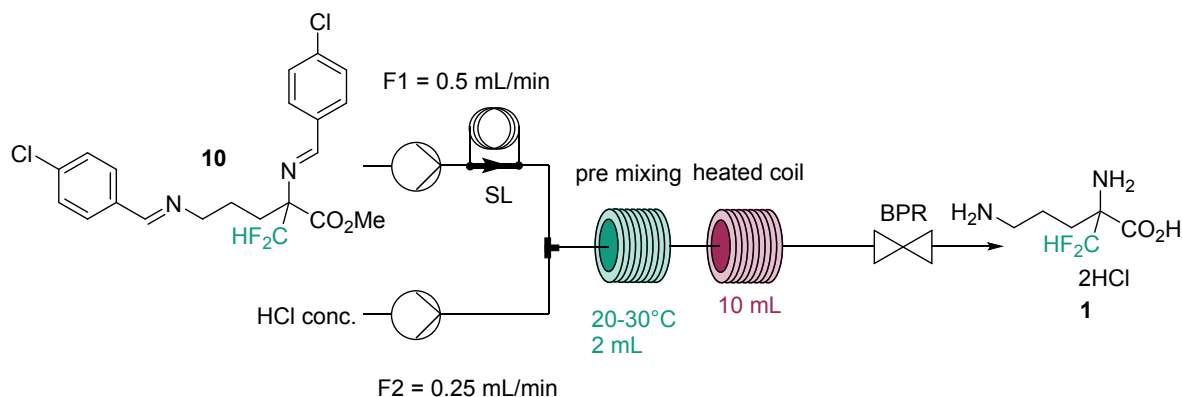
entry	temperature [°C]	back pressure	conversion [%][a]
1	140	7	88
2	150	9	93
3	160	11	>99

Conditions: Feed 1 = 0.5 M solution of 0.15 M solution of **10** in 2-MeTHF/THF/toluene, F1 = 0.5 mL/min. Feed 2 = conc. aq. HCl, F2 = 0.25 mL/min. 16 min residence time was used. [a]Analyzed by ^{1}H NMR by integrating base line separated CHF_2-peaks of **10** and **1**.

Telescoped Continuous Flow experiments. To achieve our ultimate goal, a scalable telescoped difluoromethylation procedure with subsequent deprotection in continuous flow, we connected the two continuous flow setups described above. The previously used 2 mL static glass mixer was exchanged for a smaller 1 mL static glass mixer with narrower channels which could be submerged within a cooled water bath to ensure an improved temperature control. The heated coil was exchanged for a 40 mL PFA coil and submerged within a heated stirred oil bath, so that a higher total flow rate (3 mL/min) could be used in order to provide a higher throughput. Precipitation after mixing the difluoromethylation feed and HCl feed (feed 3) was minimized due to faster mixing from the higher overall flow rates used. First, two runs using sample injection loops were performed to proof feasibility of the telescoped reaction (Table 6, entry 1). An amount

of 1.05 equiv of fluoroform was used and fully consumed (determined by ^{19}F NMR of aqueous and organic layer). To assess scalability we conducted a 4 h long run experiment with a throughput of 24 mmol/h (using conditions from Table 6, entry 2). The substrate solution (0.5 M in 2-MeTHF) and LiHMDS (1.0 M in THF) were directly pumped through the syringe pumps and the injection loops were not used. The employed back pressure rose from 12 to 15 bar. This pressure increase might stem from warming of the BPR and expansion of the gas inside the gas chamber which would result in a higher back pressure. From this protocol the target compound eflornithine hydrochloride monohydrate (DFMO, **1**) was prepared in 86% (19.48 g) isolated yield after purification.

Table 6. Telescoped Continuous Flow Reaction.
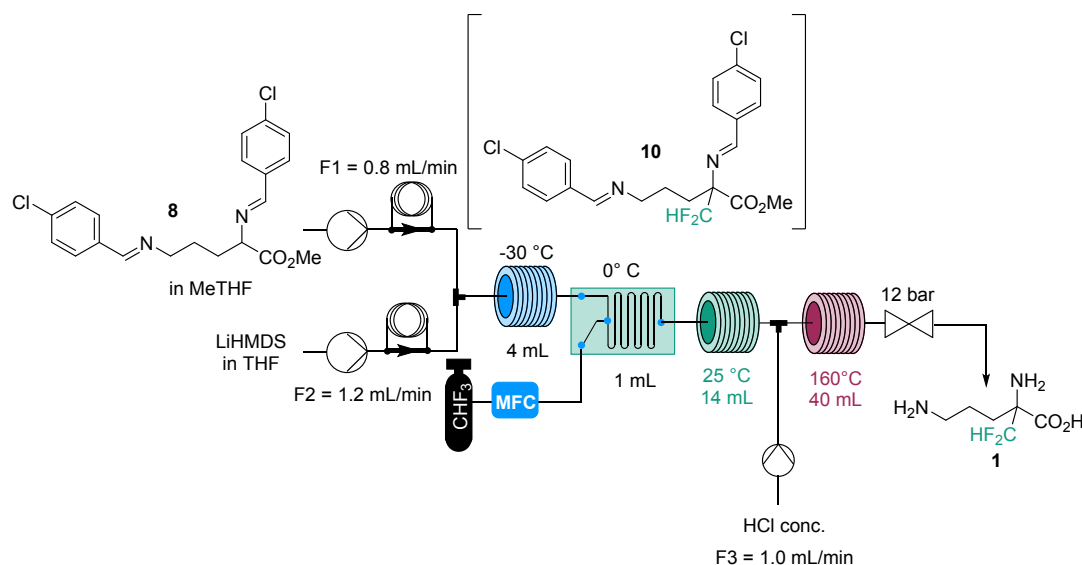
entry	temperature [°C]	back pressure [bar]	conversion [%]
1	150	12	95
2	160	12	<99

Conditions: Feed 1 = 0.5 M solution of **6** in 2-MeTHF, F1 = 0.8 mL/min. Feed 2 = 1 M solution of LiHMDS in THF, F2 = 1.2 mL/min. Feed 3 = 12 M HCl in H$_2$O, F3 = 1 mL/min. Residence time 23 min, back pressure 12 bar (1.05 equiv fluoroform). Conversion from **10** to **1** measured by ^{1}H NMR via integration of base line separated CHF$_2$-peaks of **10** and **1** of dried residue.

CONCLUSION

A telescoped continuous-flow protocol was developed for the preparation of eflornithine. Fluoroform, a large scale industrial by-product of Teflon®, was used as a cost effective reagent. In search of an optimal starting material for the synthesis, we identified the bisimine **8** of commercially available methyl ester of ornithine dihydrochloride and 4-chlorobenzalehyde as a bench stable, crystalline and easy to handle compound. Furthermore, compared to our original preliminary report,[24] the fluoroform input was greatly reduced from 3.00 equiv to 1.05 equiv, without affecting yield. Full consumption of fluoroform was facilitated by using an excess of base. After optimization of deprotection conditions with HCl in a microwave reactor, these conditions were then translated into a continuous flow process. The difluoromethylation and deprotection were connected together as a telescoped process to achieve a throughput of 24 mmol/h. Eflornithine hydrochloride monohydrate was isolated in 86% yield, which is significantly higher than previously reported yields for the less desirable process based on chlorodifluoromethane (37% to 40%).[14,15] The overall processing time was decreased from 23 h in the case of the industrial process to a mere 23.5 min in continuous flow, thus potentially minimizing manufacturing cost.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded on a Bruker 300 MHz or 500 MHz instrument. ^{13}C NMR spectra were recorded on the 300 MHz instrument at 75 MHz. ^{19}F NMR spectra were recorded on the 300 MHz instrument at 282 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet. α, α, α,-Trifluorotoluene was used as internal standard for ^{19}F NMR, nitromethane was used for ^{1}H NMR to determine purity of starting material and yield of reactions. The purity and supplier for each chemical were: (S)-methyl 2,5-diaminopentanoate dihydrochloride (95% purity, Fluorochem), 4-chlorobenzaldehyde (97% purity, Sigma Aldrich), lithium bis(trimethylsilyl)amide (1 M solution in THF, Sigma Aldrich), fluoroform (99.995% purity, Messer), 2-methyltetrahydrofuran anhydrous, ($\geq$99% purity, inhibitor free, Acros Organics), tetrahydrofuran anhydrous ($\geq$99%, Acros Organics) concentrated HCl (35% in water, VWR), dichloromethane (>98% purity, VWR), chloroform (99.2% purity, VWR) and triethylamine ($\geq$99%, Riedel de Haën). Microwave reactions were carried out in a Biotage Initiator+ single mode microwave instrument. Reaction

times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel.

Preparation of 4-Chlorobenzaldehyde Protected Ornithine Methyl Ester 10. The protection protocol was adapted from previously described procedures.[24,32] A dry 2 L round bottom flask with magnetic stirring bar was charged with (*S*)-methyl 2,5-diaminopentanoate dihydrochloride (25.0 g, 114 mmol) and 4-chlorobenzaldehyde (24.2 g, 240 mmol), sealed and flushed with argon three times. Anhydrous dichloromethane (750 mL) was added and then stirred. The colorless reaction mixture was cooled to 0 °C. After addition of triethylamine (33.2 mL, 240 mmol) over 1 h, the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The solvent was removed under reduced pressure. The off-white residue was treated with Et_2O to precipitate $Et_3N \cdot HCl$. The formed colorless precipitate was filtered off and the obtained filtrate was concentrated in vacuo. The obtained off-white residue was recrystallized from petrol ether/EtOAc to provide the desired product **10** as colorless crystalline solid (41.1 g, 105 mmol, 92% yield) mp. 89–92 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, J = 11.6, 5.6 Hz, 2H), 7.75–7.70 (m, 2H), 7.67–7.63 (m, 2H), 7.43–7.35 (m, 4H), 4.06 (dd, J = 8.4, 5.3 Hz, 1H), 3.76 (s, 3H), 3.65 (t, J = 6.7 Hz, 2H), 2.16 – 2.07 (m, 1H), 2.06 – 1.94 (m, 1H), 1.81 – 1.66 (m, 2H) ppm. ^{13}C NMR (75 MHz, CDCl3) δ 172.4, 162.2, 159.9, 137.3, 136.6, 134.7, 134.2, 129.8, 129.3, 129.0, 128.9, 73.3, 61.2, 52.3, 31.3, 27.4 ppm.

Optimized Continuous Flow Procedure for Difluoromethylation (Table 2, Entry 8). The flow setup consisted of two syringe pumps (Asia Syrris) to introduce a solution of substrate **6** (391 mg, 1 mmol) and internal standard (146 mg, 1 mmol) in 2 mL of 2-MeTHF (Feed 1), and a commercial solution of LiHMDS (1.0 M in THF, Sigma-Aldrich) (Feed 2). Injection loops (perfluoroalkoxy alkanes, PFA, 0.8 mm i.d., 1.59 mm o.d.; internal volume: 2.0 mL, Feed 1, and 4 mL, Feed 2) were used to deliver the two feeds. To start the experiment, the complete reactor setup was flushed by pumping dry 2-MeTHF with flow rates of Feed 1 = 800 µL/min and Feed 2 = 1200 µL/min. Fluoroform was introduced into the reactor with a flow rate of 9.23 mL/min (1.05 equiv) using a calibrated Bronkhorst MFC. The internal pressure of the reactor reached the target pressure of 12 bar after approximately 10 min. Substrate **6** (391 mg, 1.00 mmol) and α, α, α,-trifluorotoluene (146 mg, 1 mmol) was dissolved in neat 2-MeTHF and diluted to 2.00 mL in a volumetric flask with 2-MeTHF (Feed 1). A LiHMDS solution (1.0 M, 4 mL) in THF was used as Feed 2. Both solutions were loaded into their corresponding injection loops.

Feed 1 and feed 2 were pumped from the injection loops in a Y-shaped connector (Y Assembly PEEK 1/4-28 0.040 in) in a cooling bath (−30 °C). The combined mixture passed through a first residence loop at −30 °C (1/8 in. o.d.; 0.8 mm i.d.; residence volume V1 = 4.0 mL), before the mixture was combined with fluoroform in a Uniqsis glass static mixer (UQ-5102, 1.8 mL internal volume). The combined mixture then passed through a second residence time loop (1/8 in. o.d.; 0.8 mm i.d.; residence volume V2 = 14 mL) and left the flow system through an adjustable back pressure regulator (Zaiput BPR-10). The effluent was collected in a glass vial and an aliquot taken for determination of yield by ^{19}F NMR. For the 1 h experiment (Scheme 3) fluoroform input was reduced to 9.23 mL/min (1.05 equiv) the substrate solution and LiHMDS were directly pumped through the syringe pumps and the injection loops were not used.

Telescoped Continuous Flow Procedure – Long Run (Table 6, entry 2). The flow setup consisted of three continuous syringe pumps (2 × Asia Syrris, 1 × HighTec Zang Syrdos) to introduce a solution of substrate in 2-MeTHF (Feed 1), a commercial solution of LiHMDS (1.0 M in THF, Sigma-Aldrich) (Feed 2) and concentrated HCl (35% in water) (Feed 3). Feed 1, 2 and 3 were directly pumped through the syringe pumps. To start the experiment, the complete reactor setup was flushed by pumping dry 2-MeTHF with flow rates of Feed 1 = 800 μL/min and Feed 2 = 1200 μL/min. HCl was introduced with Feed 3 = 1000 μL/min. Fluoroform was introduced into the reactor with a flow rate of 9.23 mL/min (1.05 equiv) using a calibrated Bronkhorst MFC. The internal pressure of the reactor reached the target pressure of 12 bar after approximately 10 min. Substrate **10** (100 mmol) was dissolved in neat 2-MeTHF and diluted to 200 mL in two volumetric flasks with 2-MeTHF (Feed 1). A LiHMDS solution (1.0 M, 800 mL) in THF was used as Feed 2. Feed 1 and Feed 2 pumped directly through the syringe pumps were combined in a Y-shaped connector (Y Assembly PEEK 1/4-28 0.040in) in a cooling bath (−30 °C). The combined mixture went through a first residence loop at −30 °C (1/8 in. o.d.; 0.8 mm i.d.; residence volume V1 = 4.0 mL), before the mixture was combined with fluoroform in a Syrris Asia glass static mixer (1 mL internal volume). The mixture then went through a second residence loop at 25 °C (1/8 in. o.d.; 0.8 mm i.d.; residence volume V2 = 14 mL) and were mixed with feed 3 in a T-shaped connector (T Assembly PTFE 1/4-28 0.040in). The combined stream then went through a third residence loop at 160 °C (1/8 in. o.d.; 0.8 mm i.d.; residence volume V3 = 40 mL) and left the flow system through an adjustable back pressure regulator (Zaiput BPR-10). The biphasic mixture was collected for 3.5 h (84 mmol) and the aqueous phase was

washed with Et_2O and concentrated under reduced pressure. The crude product was dissolved in a small amount of H_2O and the pH was adjusted to 4 with Et_3N. The resulting slurry was filtered and washed with cold EtOH abs. and $CHCl_3$. The residue was recrystallized from $EtOH/H_2O$ to give product **1** hydrochloride monohydrate as colourless powder. (17.05 g, 72.3 mmol, 86% yield). Mp. 228 °C; ^1H NMR (300.36 MHz, D_2O): $\delta = 6.46$ (t, $^2J_{HF} = 52.8$ Hz, 1H), 3.05 (t, $^3J_{HH} = 7.6$ Hz, 2H), 2.25-1.97 (m, 2H), 1.96–1.79 (m, 1H), 1.76–1.59 (m, 1H) ppm. ^{13}C NMR (75 MHz, D_2O): $\delta = 167.8$ (d, $^3J_{CF} = 6.4$ Hz), 114.0 (dd, $^1J_{CF} = 249.7$ Hz, $^1J_{CF} = 247.0$ Hz), 64.5 (dd, $^2J_{CF} = 20.4$ Hz, $^2J_{CF} = 18.7$ Hz), 38.8 (d, $^3J_{CF} = 7.3$ Hz), 31.6 (d, $^4J_{CF} = 3.2$ Hz), 20.8 ppm. ^{19}F NMR (282 MHz, D_2O): $\delta = -126.28$ (dd, $^2J_{FF} = 283.5$ Hz, $^2J_{HF} = 52.4$ Hz), -131.76 (dd, $^2J_{FF} = 283.5$ Hz, $^2J_{HF} = 52.4$ Hz) ppm.

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Supporting Information

Description and images of the continuous flow set-up, ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra of all isolated products and X-ray crystallographic data for compound **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1)   (a) Bacchi, C. J.; Goldberg, B.; Garofalo-Hannan, J.; Rattendi, D.; Lyte, P.; Yarlett, N. Fate of Soluble Methionine in African Trypanosomes: Effects of Metabolic Inhibitors. *Biochem. J.* **1995**, *309*, 737–743. (b) Bari, C. Di; Pastore, G.; Roscigno, G.; Schechter, P. J.; Sjoerdsma, A. Late-Stage African Trypanosomiasis and Eflornithine. *Ann. Intern. Med.* **1986**, *105*, 803. (c) Gilman, T. M.; Paulson, Y. J.; Boylen, C. T.; Heseltine, P. N. R.; Sharma, O. P. Eflornithine Treatment of Pneumocystis Carinii Pneumonia in AIDS. *J. Am. Med. Assoc.* **1986**, *256*, 2197.

(2)   (a) Raul, F. Revival of 2-(Difluoromethyl)ornithine (DFMO), an Inhibitor of Polyamine Biosynthesis, as a Cancer Chemopreventive Agent. *Biochem. Soc. Trans.* **2007**, *35*, 353–355. (b) Gerner, E. W.; Meyskens, F. L. Polyamines and Cancer: Old Molecules, New Understanding. *Nat. Rev. Cancer* **2004**, *4*, 781–792. (c) Gunaratna, P. C.; Wilson, G. S.;

Slavik, M. Pharmacokinetic Studies of α-Difluoromethylornithine in Rabbits Using an Enzyme-Linked Immunosorbent Assay. *J. Pharm. Biomed. Anal.* **1994**, *12*, 1249–1257.

(3) Barman Balfour, J. A.; McClellan, K. Topical Eflornithine. *Am. J. Clin. Dermatol.* **2001**, *2*, 197–201.

(4) (a) Phillips, M. A.; Coffinot, P.; Wang, C. C. Cloning and Sequencing of the Ornithine Decarboxylase Gene from Trypanosoma Brucei Implications For Enzyme Turnover and Selective Difluoromethylornithine Inhibition. *J. Biol. Chem.* **1987**, *262*, 8721–8727. (b) Bacchi, C. J.; Garofalo, J.; Mockenhaupt, D.; McCann, P. P.; Diekema, K. A.; Pegg, A. E.; Nathan, H. C.; Mullaney, E. A.; Chunosoff, L.; Sjoerdsma, A.; et al. In Vivo Effects of α-DL-Difluoromethylornithine on the Metabolism and Morphology of Trypanosoma Brucei Brucei. *Mol. Biochem. Parasitol.* **1983**, *7*, 209–225. (c) Vincent, I. M.; Creek, D.; Watson, D. G.; Kamleh, M. A.; Woods, D. J.; Wong, P. E.; Burchmore, R. J. S.; Barrett, M. P. A Molecular Mechanism for Eflornithine Resistance in African Trypanosomes. *PLoS Pathog.* **2010**, *6*, e11001204.

(5) Mettler, H.; Greth, E., *2-Difluormethyl-2-cyanethylmalonsäureniedrigalkylester*, Lonza AG CH672124A5, **1989**.

(6) For a continuous flow process of converting compound **2** into **3** (Scheme 1), see: Gutmann, B.; Hanselmann, P.; Bersier, M.; Roberge, D.; Kappe, C. O. Continuous-Flow Difluoromethylation with Chlorodifluoromethane under Biphasic Conditions. *J. Flow Chem.* **2017**, *7*, 46–51.

(7) Zhu, J.; Chadwick, S. T.; Price, B.; Zhao, S.; Costello, C. A.; Vemishetti, P., *Processes for the Production of Alpha-Difluoromethyl ornithine (DFMO),* WO03020209A2, **2002**.

(8) (a) Seki, M.; Suzuki, M.; Matsumoto, K. Convenient Synthesis of α-Difluoromethylornithine. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1024–1025. (b) Bey P.; Jung M.; Merrell, Toraude et Compagnie, *2-(Difluoromethyl)-2,5-diaminopentanoic acid*, US 4413141, **1983.**

(9) Ozone Secretariat; United Nations Environment Programme. *The Montreal Protocol on Substances That Deplete the Ozone Layer*; Secretariat for The Vienna Convention for the Protection of the Ozone Layer & The Montreal Protocol on Substances that Deplete the Ozone Layer, 2000.

(10) (a) Ni, C.; Hu, J. Recent Advances in the Synthetic Application of Difluorocarbene. *Synthesis* **2014**, *46*, 842–863. (b) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. Difluoromethylation Reactions of Organic Compounds. *Chem. - A Eur. J.* **2017**, *23*, 14676–14701.

(11) Forster, P.; V. Ramaswamy; P. Artaxo; T. Berntsen; R. Betts; D.W. Fahey; J. Haywood; J. Lean; D.C. Lowe; G. Myhre; et al. *Changes in Atmospheric Constituents and in Radiative Forcing. In: Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*; Solomon, S., D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M.Tignor and, H.L. Miller, Eds.; Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, 2007.

(12) Han, W.; Li, Y.; Tang, H.; Liu, H. Treatment of the Potent Greenhouse Gas, CHF_3- An Overview. *J. Fluor. Chem.* **2012**, *140*, 7–16.

(13) Prakash, G. K. S.; Jog, P. V; Batamack, P. T. D.; Olah, G. A. Taming of Fluoroform : Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers. *Science* **2012**, *338*, 1324–1327.

(14) (a) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. A Novel Trifluoromethylation of Aldehydes and Ketones Promoted by an Electrogenerated Base. *J. Org. Chem.* **1991**, *56*, 2–4. (b) Barhdadi, R.; Troupel, M.; Périchon, J. Coupling of Fluoroform with Aldehydes Using an Electrogenerated Base. *Chem. Commun.* **1998**, *0*, 1251–1252.

(15) (a) Folléas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. Fluoroform: An Efficient Precursor for the Trifluoromethylation of Aldehydes. *Tetrahedron* **2000**, *56*, 275–283. (b) Langlois, B. R.; Billard, T. Fluoroform, Fluoral, Trifluoroacetic, and Trifluoromethanesulfinic Acids Derivatives as New Reagents for the Introduction of Polyfluorinated Moieties; *ACS Symposium Series*, Vol. 911 **2005**; 57–86. (c) Folléas, B.; Marek, I.; Normant, J.-F.; Jalmes, L. Saint. Fluoroform: An Efficient Precursor for the Trifluoromethylation of Aldehydes. *Tetrahedron Lett.* **1998**, *39*, 2973–2976. (d) Langlois, B. R.; Billard, T. Some Recent Results in Nucleophilic Trifluoromethylation and Introduction of Fluorinated Moieties. *Synthesis* **2003**, *2*, 185–194. (e) Large, S.; Roques, N.; Langlois, B. R. Nucleophilic Trifluoromethylation of Carbonyl Compounds and Disulfides with Trifluoromethane and Silicon-Containing Bases. *J. Org. Chem.* **2000**, *65*, 8848–8856. (f) Billard, T.; Bruns, S.; Langlois, B. R. New Stable Reagents for the Nucleophilic Trifluoromethylation. 1. Trifluoromethylation of Carbonyl Compounds with *N*-Formylmorpholine Derivatives. *Org. Lett.* **2000**, *2*, 2101–2103.

(16) (a) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. Direct Cupration of Fluoroform. *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913. (b) Novák, P.; Lishchynskyi, A.; Grushin, V. V. Trifluoromethylation of α-Haloketones. *J. Am. Chem. Soc.* **2012**, *134*, 16167–16170. (c) Novák, P.; Lishchynskyi, A.; Grushin, V. V. Fluoroform-Derived $CuCF_3$ for Low-Cost, Simple, Efficient, and Safe Trifluoromethylation of Aryl Boronic Acids in Air. *Angew. Chemie Int. Ed.* **2012**, *51*, 7767–7770.

(17) (a) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. Umpolung of Fluoroform by C-F Bond Activation: Direct Difluoromethylation of Lithium Enolates. *Angew. Chemie - Int. Ed.* **2012**, *51*, 9535–9538. (b) Aikawa, K.; Maruyama, K.; Honda, K.; Mikami, K. α-Difluoromethylation on sp^3 Carbon of Nitriles Using Fluoroform and Ruppert–Prakash Reagent. *Org. Lett.* **2015**, *17*, 4882–4885. (c) Aikawa, K.; Maruyama, K.; Nitta, J.; Hashimoto, R.; Mikami, K. Siladifluoromethylation and Difluoromethylation onto $C(sp^3)$, $C(sp^2)$, and C(sp) Centers Using Ruppert–Prakash Reagent and Fluoroform. *Org. Lett.* **2016**, *18*, 3354–3357.

(18) (a) Okusu, S.; Tokunaga, E.; Shibata, N. Difluoromethylation of Terminal Alkynes by Fluoroform. *Org. Lett.* **2015**, *17*, 3802–3805; for review on the application of fluorofom in synthesis, see: (b) Zhang, C. Application of Fluoroform in Trifluoromethylation and Difluoromethylation Reactions. *Arkivoc* **2017**, part i, 67–83.

(19) (a) Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 327–360. (b) Gemoets, H. P.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël T. Liquid Phase Oxidation Chemistry in Continuous-flow Microreactors. *Chem. Soc. Rev.* **2016**, *45*, 83-117. (c) Gavriilidis, A.; Constantinou, A.; Hellgardt, K.; Hii, K. K.; Hutchings, G. J.; Brett, G. L.; Kuhn, S.; Marsden, S. P. Aerobic Oxidations in Flow: Opportunities for the Fine Chemicals and Pharmaceuticals Industries. *React. Chem. Eng.* **2016**, *1*, 595–612.

(20) (a) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892-4928. (b) Jiménez-González, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B.-S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, R. E.; Dell'Orco, P.; Noorman, H.; et al. Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers. *Org. Process Res. Dev.* **2011**, *15*, 900–911. (c) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology - A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chemie - Int. Ed.* **2015**, *54*, 6688–6728. (d) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017** *117*, 11796-11893. (e) May, S. A. Flow Chemistry, Continuous Processing, and Continuous Manufacturing: A Pharmaceutical Perspective. *J. Flow Chem.* **2017**, *7* 137–145. (f) Pieber, B.; Gilmore, K.; Seeberger, P. H. Integrated Flow Processing - Challenges in Continuous Multistep Synthesis. *J. Flow Chem.* **2017**, *7*, 129–136. (g) Gérardy, R.; Emmanuel, N.; Toupy, T.; Kassin, V. E.; Tshibalonza, N. N.; Schmitz, M.; Monbaliu, J. C. M. Continuous Flow Organic Chemistry: Successes and Pitfalls at the Interface with Current Societal Challenges. *Eur. J. Org. Chem.* **2018**. (h) Jensen, K. F. Flow Chemistry-Microreaction Technology Comes of Age. *AIChE J.* **2017**, *63*, 858–869.

(21) Mazloomi, Z.; Bansode, A.; Benavente, P.; Lishchynskyi, A.; Urakawa, A.; Grushin, V. V. Continuous Process for Production of CuCF$_3$ via Direct Cupration of Fluoroform. *Org. Process Res. Dev.* **2014**, *18*, 1020–1026.

(22) Musio, B.; Gala, E.; Ley, S. V. Real-Time Spectroscopic Analysis Enabling Quantitative and Safe Consumption of Fluoroform during Nucleophilic Trifluoromethylation in Flow. *ACS Sustain. Chem. Eng.* **2018**, *6*, 1489–1495.

(23) Gutmann, B.; Köckinger, M.; Glotz, G.; Ciaglia, T.; Slama, E.; Zadravec, M.; Pfanner, S.; Maier, M. C.; Gruber-Wölfler, H.; Kappe, C. O. Design and 3D Printing of a Stainless Steel Reactor for Continuous Difluoromethylations Using Fluoroform. *React. Chem. Eng.* **2017**, *2*, 919–927.

(24) Köckinger, M.; Ciaglia, T.; Bersier, M.; Hanselmann, P.; Gutmann, B.; Kappe, C. O. Utilization of Fluoroform for Difluoromethylation in Continuous Flow: A Concise Synthesis of α-Difluoromethyl-Amino Acids. *Green Chem.* **2018**, *20*, 108–112.

(25) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. CHEM21 Selection Guide of Classical- and Less Classical-Solvents. *Green Chem.* **2015**, *18*, 288–296.

(26) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. Flow Chemistry: Intelligent

Processing of Gas–Liquid Transformations Using a Tube-in-Tube Reactor. *Acc. Chem. Res.* **2015**, *48*, 349–362.

(27)   (a) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; et al. Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. **2013**. (b) Supporting the Advancement of Chemistry through Sound Environmental, Social & Fiscal Responsibilities   https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma/Brochure/greener_solvent_alternatives.pdf?utm_source=redirect&utm_medium=promotional&utm_campaign=insite_greener_solvent_alternatives (accessed Jul 25, 2018).

(28)   Honda, K.; Harris, T. V.; Hatanaka, M.; Morokuma, K.; Mikami, K. Computational S_N2-Type Mechanism for the Difluoromethylation of Lithium Enolate with Fluoroform through Bimetallic C−F Bond Dual Activation. *Chem. - A Eur. J.* **2016**, *22*, 8796–8800.

(29)   We were unable to reproduce the difluoromethylation protocols reported by Dolbier and co-workers utilizing KOH as base, see: (a) Thomoson, C. S.; Dolbier, W. R. Use of Fluoroform as a Source of Difluorocarbene in the Synthesis of Difluoromethoxy- and Difluorothiomethoxyarenes. *J. Org. Chem.* **2013**, *78*, 8904–8908. (b) Thomoson, C. S.; Wang, L.; Dolbier, W. R. Use of Fluoroform as a Source of Difluorocarbene in the Synthesis of N-CF$_2$H Heterocycles and Difluoromethoxypyridines. *J. Fluor. Chem.* **2014**, *168*, 34–39.

(30)   Glasnov, T. N.; Kappe, C. O. The Microwave-to-Flow Paradigm: Translating High-Temperature Batch Microwave Chemistry to Scalable Continuous-Flow Processes. *Chem. Eur. J.* **2011**, *17*, 11956–11968.

(31)   https://www.adtech.co.uk/products/fluoroplastic-tubing-and-rod/pfa-tube.php, accessed on 18.10.2018.

(32)   (a) Bey, P.; Vevert, J.; Dorsselaer, V. Van; Kolb, M. Direct Synthesis of A-Halogenomethyl-α-Amino Acids from the Parent α-Amino Acids. *J. Am. Chem. Soc.* **1979**, *44*, 2732–2742. (b) Kalyanam, N.; Rapole, K. R.; Rajendran, R.; Majeed, M. A Novel Reaction Cascade Leading to a Spontaneous Intramolecular Dipolar Cycloaddition through Simultaneous Generation of 1,3-Dipole and Dipolarophile. *Tetrahedron Lett.* **2013**, *54*, 5155–5158.