A Continuous Flow Process for the Defluorosilylation of HFC-23 and HFO-1234yf

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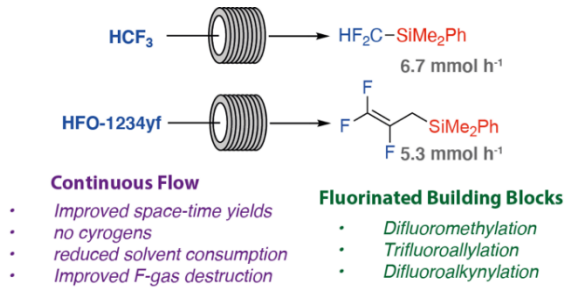

ABSTRACT: A continuous flow process has been developed for the defluorosilylation of trifluoromethane (HFC-23) and 2,3,3,3-propene (HFO-1234yf) through reaction with lithium silanide reagents under inert conditions. Design of experiment optimization improved process conditions including productivity, yields, reduction of solvent use, and gas destruction. The small chain fluorinated organosilane products R_3SiCF_2H and $R_3SiCH_2C(F)=CF_2$ were competent nucleophiles in the fluoride-catalyzed difluoromethylation of aldehydes, and trifluoroallylation of aldehydes, ketones, and imines. Stepwise treatment of $R_3SiCH_2C(F)=CF_2$ with KHMDS and IPrCuCl gave IPrCuC≡C–CF_2H, which reacted with allyl and acyl halides to transfer the fluorinated propyne motif.

The use of hydrofluorocarbons (HFCs) and hydrofluoroolefins (HFOs) as fluorinated building blocks for synthetic chemistry is an attractive strategy.[1] These fluorinated gases are produced on large scales due to their application as refrigerants, propellants and blowing agents and, as such, are readily available. For example, HCF_3 is produced on-scale as a byproduct of PTFE production, while HFO-1234yf is manufactured for use in air-conditioning units in the automotive sector. HFCs and HFOs typically contain between 1-4 carbon atoms and 1-6 fluorine atoms, meaning they are useful sources of small, fluorinated carbon chains, which are privileged fragments across the pharmaceutical, agrochemical, materials, and energy sectors.[2–6] Moreover, there are established networks for recovery and purification of HFCs as they are controlled substances due to their high global warming potentials and known detrimental impact on the environment. While HFOs have lower global warming potentials and are not currently recovered on scale, there is increasing concern over the fate of HFOs which contain CF_3 groups as they breakdown into trifluoroacetic acid in the environment.[7,8] There is also the potential that certain HFCs and HFOs may be classed as per- or poly-fluorinated alkyl substances (PFAS) under newly proposed EU regulatlation.[9]

Recently there has been a growth in the reports of synthetic transformations involving HFCs and HFOs as small chain fluorinated building blocks.[10–17] Despite these advances, scale-up of the new methodology continues to be challenging. HFCs and HFOs are often available in the form of low-pressure gas reservoirs. Scaling up reactions

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in batch is impractical due to the large volumes of gases involved, and potential for extreme exotherms. Continuous flow methods offer a key enabling technology to solve these problems. Flow methods allow safe scale-up and process optimization, through efficient liquid-gas mixing, increased heat dissipation, and reduction of reactor volumes.[18–20]

One of the first continuous flow processes that used HFCs was reported by Grushin and coworkers in 2014.[21] They demonstrated that 'ligandless' [$CuCF_3$] could be prepared from HCF_3, CuCl, KOtBu in DMF using $Et_3N{\cdot}3HF$ as a stabilising agent to slow degradation. [$CuCF_3$] itself is a versatile trifluoromethylating agent that has been applied in a series of carbon–carbon bond forming reactions.[22] Since this breakthrough, HCF_3 has been used as trifluoromethylating agent under flow conditions in base-mediated (e.g. KOtBu, KHMDS) reactions with aldehydes and ketones,[23,24] imines,[25] and esters.[26] Kappe and coworkers have reported the difluoromethylation of enolisable esters with HCF_3 in the presence of a base.[27] This methodology has been applied to a scalable continuous flow process for the synthesis of Eflornithine with production rates of 24 mmol h^{-1}.[28] A similar approach has been used for the difluoromethylation of enolisable nitriles, albeit with the design of a specialist reactor to control the temperature in flow.[29] To the best of our knowledge, continuous flow methods have yet to be applied to synthetic transformations of HFOs.

Over the past few years, we have reported several synthetic approaches for the defluorosilylation and defluoroborylation of HFCs and HFOs.[30–32] This includes the defluorosilylation of industrially relevant HCF_3 (HFC-23) and 2,3,3,3-tetrafluoropropene (HFO-1234yf) under batch conditions using lithium silanide reagents. In the case of HFC-23, the reaction proceeds efficiently over 10 minutes at 25 °C, provided a low concentration of **1·PMDETA** (20 mM) and excess of HCF_3 (approx. 7 equiv.) is used. In the case of HFO-1234yf, cryogenic temperatures of –78 °C and a reaction time of 3 h are required. Both reactions could be performed on a 1 – 3 mmol scale, allowing isolation of products in 68 – 69 % yield (Figure 1).

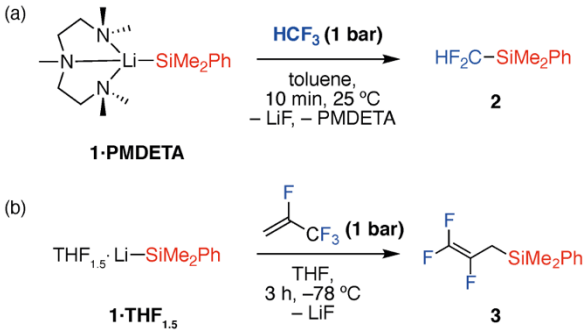

Figure 1. Defluorosilylation of (a) HFC-23 and (b) HFO-1234yf under batch conditions.

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In this paper, we describe a continuous flow method for defluorosilylation of both HFC-23 and HFO-1234yf. The approach allows facile scale-up. Optimal process conditions result in improved production rates and reduced solvent use compared to batch conditions, while also obviating the need for cryogenic temperatures. The new enabling technology provides access to small chain fluorinated building blocks in sufficient quantities to effectively explore their onward chemistry. We demonstrate a broad scope of difluoromethylation and trifluoroallylation of carbonyls, along with the discovery of a method to generate 3,3-difluoroprop-1-yne fragments from HFO-1234yf.

The defluorosilylation of HCF_3 with **1·PMDETA** was conducted in flow using a Vapourtec easy-scholar reactor system (Figure 2a). A reactor coil of length = 495 cm, volume = 3.9 ml was used, leading to residence times of between 30 s - 6 min depending on flow rates used. All reactions were conducted at 25 °C. Flow rates were regulated to initially produce a segmented flow regime directly after the T-junction, however, as the reaction proceeded HCF_3 was consumed resulting in dissipation of the segmented flow. Samples for analysis were collected following dispensing of 1 to 2 reactor volumes under flow. Precipitation of a solid, presumed to be LiF, was observed during reactions but did not cause fouling of the reactor tubing. Formation of **2** was quantified by both ^{19}F NMR spectroscopy and GC-FID analysis.

A Design-of-experiment (DoE) strategy was used to optimise the process and gain a better understanding of which variables had the greatest statistical significance on the outcome. A definitive screen DOE was constructed using 17 initial experiments, augmented by a further 10 experiments to extend the range of each variable beyond the initial conditions. The yield of **2** was measured across an average of three samples per run. All statistical analysis and modelling were performed using JMP™ software. Modelling of the resultant data revealed that concentration of **1·PMDETA** has the greatest statistical influence on yield, followed by gas pressure, then gas flow rate (Figure 2b).

Optimal conditions for maximising the formation of product were found to be 1.2 ml min^{-1} liquid flow rate of a 20 mM solution of **1·PMDETA**, with 2.4 ml min^{-1} gas flow-rate of HCF_3 at 2.5 bar forming **2** in 74 % yield, corresponding to a production rate of 1.1 mmol h^{-1}. With a space-time yield of 0.27 mol l^{-1} h^{-1} this corresponds to a 10-fold increase from the previously reported batch conditions. A multi-response model was then fit using productivity, solvent usage, and calculated gas destruction to accurately predict within experimental error the optimal process conditions. The optimal process conditions were found to be a 2.0 ml min^{-1} liquid flow-rate of a 110 mM solution of **1·PMDETA**, 2.5 ml min^{-1} gas flow-rate of HCF_3 at 3.1 bar forming **2** at a predicted 53 % yield (Figure 2d). These conditions were tested on a 3 g scale to give a confirmed 51% in situ yield corresponding to a production rate of 6.7 mmol h^{-1}, and space-time yield of 1.5 mol l^{-1} h^{-1}. Comparison of these optimal process conditions to those in batch reveals a dramatic reduction in solvent use (74 ml $mmol^{-1}$ in batch; 18 ml $mmol^{-1}$ in flow) and equivalents of HCF_3 required (7 equiv. in batch; 1.4 equiv. in flow), with a 56-fold improvement in space-time yield (0.026 mol l^{-1} h^{-1} in batch; 1.5 mol l^{-1} h^{-1} in flow).

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The same Vapourtec system can be adapted for the defluorosilylation of HFO-1234yf, forming **3** successfully at room temperature (Figure 2c). This is the first example of applying flow methods to upgrade HFOs through synthesis. Optimal process conditions were found to be a 1.3 ml min^{-1} liquid flow-rate of a 110 mM solution of **1·THF$_{1.5}$**, 3.0 ml min^{-1} gas flow-rate of HCF_3 at 1.4 bar leading to 62 % yield of **3** with a production rate of 5.3 mmol h^{-1}. The reaction proceeds selectively at room temperature, with just 1.2 equivalents of gas and a residence time of 2.5 minutes, compared to a 3 hour reaction time in batch. This reaction could also be effectively run for an extended period using crude **1·THF$_{1.5}$** allowing removal of a purification step from the overall procedure. The flow methodology offers a marked increase in space-time yield of 1.05 mol l^{-1} h^{-1}, an 86-fold improvement compared to batch.

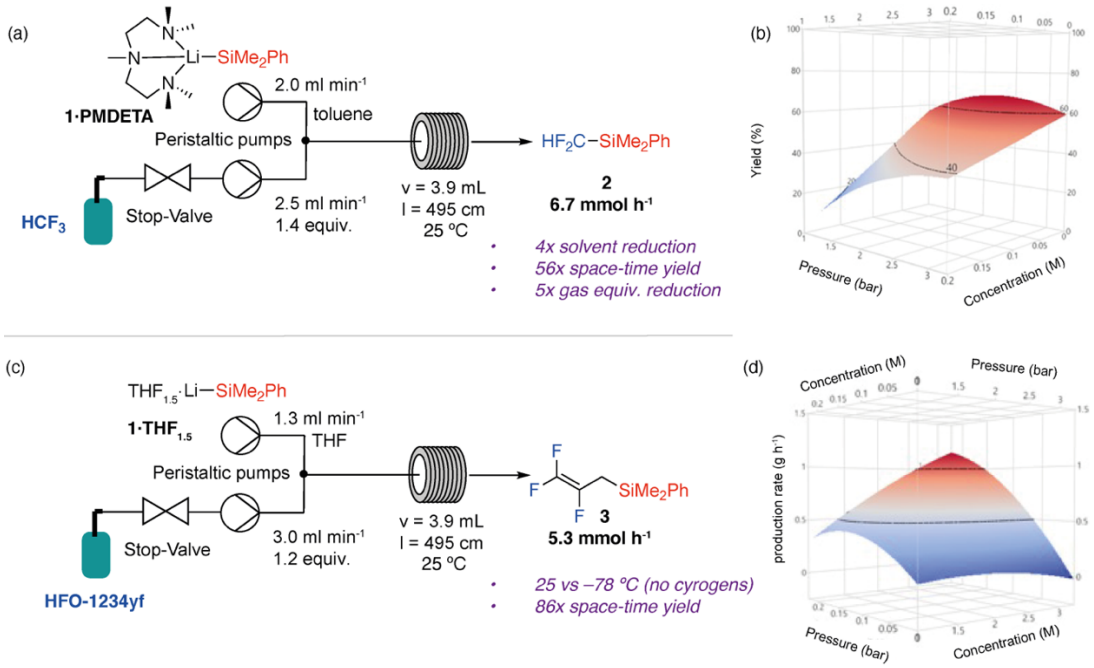

Figure 2. (a) Flow-setup for defluorosilylation of HCF_3 with **1·PMDETA** and (b) DoE surface showing yield response to changes in pressure and concentration of **1·PMDETA**. (c) Flow-setup for defluorosilylation of HFO-1234yf with **1·THF$_{1.5}$** and (d) DoE surface showing production rates response changes in pressure and concentration of **1·PMDETA**.

CF_2HSiMe_3 has previously been demonstrated to be a versatile difluoromethylation agent, reacting with a range of electrophiles in the presence of a fluoride source (e.g. CsF) or base (e.g. KO^{t}Bu).[33] Due to its lower volatility **2** might offer improved ease of handling and storage compared to CF_2HSiMe_3, however its applications in synthesis are limited to difluoromethylation of a range of aromatic and aliphatic aldehydes catalyzed by KF.[34] To further expand the utility of this compound, we investigated reactions with a series of aromatic, α,β-unsaturated, and heteroaromatic aldehydes. Reactions were run at 25 °C using CsF as a catalyst. Once conversion to the silylated alcohols was complete, TBAF was added as a stoichiometric reagent to effect the complete desilylation of the products. Difluoromethylated alcohols **4a-f** were prepared in modest to good yields (Figure 3). The reaction tolerated furyl, pyridyl, benzothiothenyl, and pyrazolyl groups, along with halogens. An analogue of the key intermediate in the preparation of Telotristat Ethyl (a tryptophan hydroxylase inhibitor) in which the CF_3 group has been substituted for a CF_2H group could be prepared.[35] Difluoromethane was observed as a minor by-product in certain cases, most likely arising from the desilylation of **2** with CsF.

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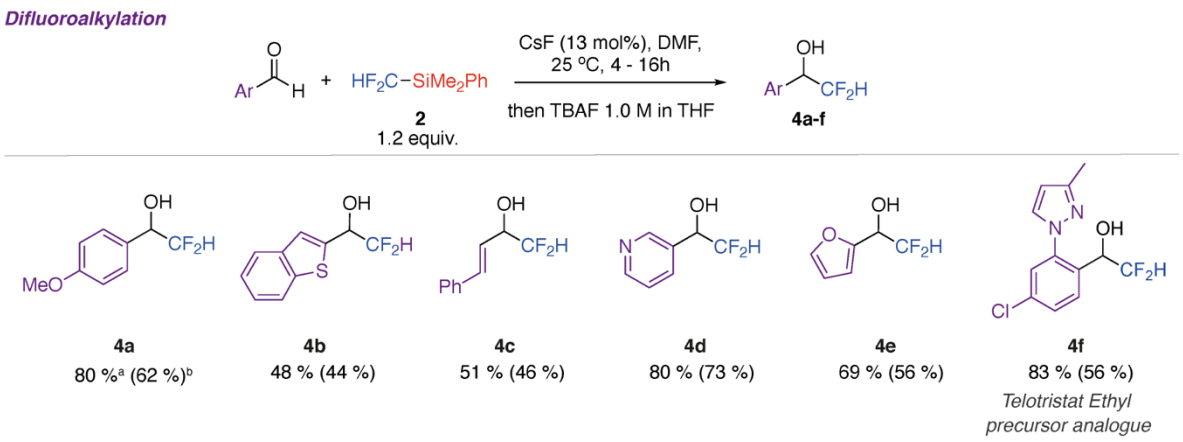

Figure 3. Reaction scope of difluoromethylation of aldehydes by **2**.[a] yields by ^{19}F NMR spectroscopy as compared to trifluorotoluene as an internal standard. [b]isolated yields following purification by column chromatography.

The trifluoroallylsilyl reagent **3** was similarly an effective reagent for the trifluoroallylation of carbonyl compounds in the presence of catalytic TBAF yielding **5a-5m** (Figure 4). While allyl silanes are well established allylating reagents, typically under Lewis acidic conditions, the use of fluorinated analogues is under-developed[36] – likely due to the availability of suitable reagents. Electron-deficient and electron-rich aldehydes, along with activated imines, and ketones were all successful electrophiles. Structures of **5a** and **5j** were determined by single crystal X-ray diffraction. 2,3,3-Trifluoroprop-1-ene was observed as a minor side-product in these reactions but is readily separated from the product.

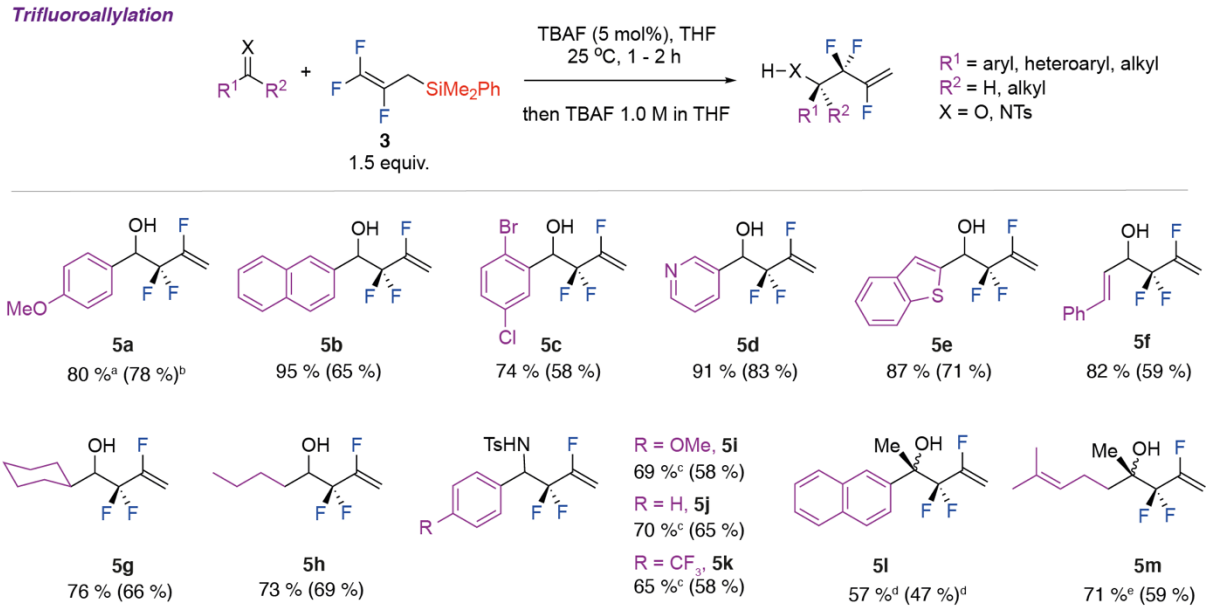

Figure 4. Reaction scope of trifluoroallylation of aldehydes, ketones, and imines by **3**. [a] yields by ^{19}F NMR spectroscopy as compared to trifluorotoluene as an internal standard. [b]isolated yields following purification by column chromatography. [c]reactions performed at 60 °C with 15 mol % portions of TBAF added every 2-3 hours. [d]product was contaminated by 15 % ketone starting material. [e]product contaminated by 8 % ketone starting material.

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Compound **3** also proved an effective precursor to generate fluorinated propyne groups. Treatment of **3** with 1.5 equiv. of KHMDS in THF followed by addition of IPrCuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and heating to 60 °C for 18 h resulted in the formation of the copper(I) acetylide complex **6** (Figure 5a). **6** results from a formal elimination of an equivalent of HF from **3** along with isomerization of the unsaturated bond to the internal position. This species was also formed through a direct reaction of IPrCuO^{t}Bu with **3** at 25 °C. **6** demonstrates a diagnostic resonance at δ = −97.20 ppm (d, $^2J_{HF}$ = 57.6 Hz) in the ^{19}F NMR spectrum, coupled to a corresponding signal at δ = 5.97 (t, $^2J_{HF}$ = 57.6 Hz) in the ^{1}H NMR spectrum. Its structure was unambiguously confirmed by single crystal X-ray diffraction. **6** is a competent reagent for the fluoroalkynylation of electrophiles, reacting with benzoyl chloride and allyl bromide to form **7a** and **7b** respectively (Figure 5b).

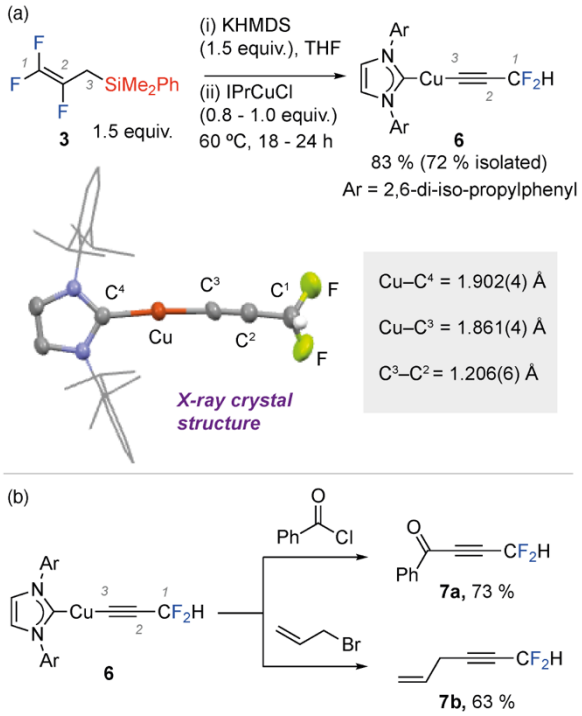

Figure 5. (a) Reaction of **3** with KHMDS and IPrCuCl to form **6** along with (b) onwards reactions that transfer the difluoropropynyl fragment to form **7a-b (**yields by ^{19}F NMR spectroscopy as compared to trifluorotoluene as an internal standard**)**.

In summary, we have developed a continuous flow process for the production of small chain fluorinated building blocks from trifluoromethane (HFC-23) and 2,3,3,3-tetrafluoropropene (HFO-1234yf). Flow conditions offer significant advantages over batch, including: (i) improved production rates, (ii) better control of exotherms (meaning cryogens can be avoided), and (iii) reductions in the volume of solvent and fluorinated gas required for efficient conversion. Accessing building blocks **2** and **3** on ~10 mmol scale has enabled their further development as reagents to install C_1 to C_3 fluorinated motifs into organic molecules. These has been achieved through carbon–carbon bond formation via the difluoromethylation, trifluoroallylation, and difluoroalkynylation of carbonyl and imine functional groups.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org. Synthetic procedures, flow setup and DoE, NMR spectra of all compounds, crystal structures of **x, y** and **6** (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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