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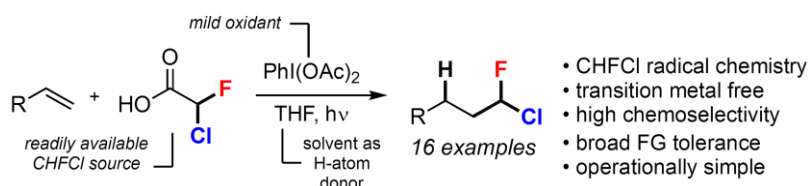
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Hydrochlorofluoromethylation of Unactivated Alkenes with Chlorofluoroacetic Acid

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ABSTRACT

An operationally simple method enabling hydrochlorofluoromethylation of unactivated alkenes under visible light activation is reported. The procedure has various benefits. It uses commercially available and inexpensive chlorofluoroacetic acid and phenyliodine(III) diacetate for the generation of the required chlorofluoromethyl radical, it converts feedstock olefins into attractive 1-chloro-1-fluoroalkanes, and it tolerates a broad variety of functional groups. The chlorofluoromethyl radical has a reactivity profile towards alkenes similar to the difluoromethyl radical, an indicator of its nucleophilic behavior.

Keywords:

Fluorine, Chlorofluoromethyl radical, Hypervalent Iodine, Photochemistry

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1. Introduction

Organofluorine compounds are widely used in medicinal chemistry as well as in material sciences.¹ Specifically, fluorine substitution is a common strategy in pharmaceutical drug development as the presence of fluorine within a molecule can alter properties such as conformation, lipophilicity and metabolic stability.² In recent years, new methods have appeared for the installation of various fluorine-containing motifs into organic molecules; amongst those, numerous radical-based reactions demonstrate excellent functional group tolerance and suitability for applications beyond discovery scale.³ In 2018, Stephenson and co-workers reported a radical C-H chlorodifluoromethylation of (hetero)arenes using chlorodifluoroacetic anhydride (Figure 1A).⁴ Simultaneously, Sodeoka and co-workers disclosed a method using this same reagent for the allylic and amino-chlorodifluoromethylation of alkenes.⁵ These reactions exploit the reactivity of the chlorodifluoromethyl radical ($\bullet\text{CF}_2\text{Cl}$) and afford products amenable to further functionalization. In this context, we opted to investigate the reactivity of chlorofluoromethyl radical ($\bullet\text{CHFCl}$) onto alkenes to form products resulting from net hydrochlorofluoromethylation. The chlorofluoromethyl radical was first characterized in 1979 by Andrews and co-workers using infrared spectroscopy.⁶ Later, Marshall and co-workers calculated and compared the physical properties of a series of chlorofluoromethyl radicals.⁷ This investigation was conducted to enable accurate modeling of these species in simulations of the role of haloethanes in atmospheric and combustion processes.

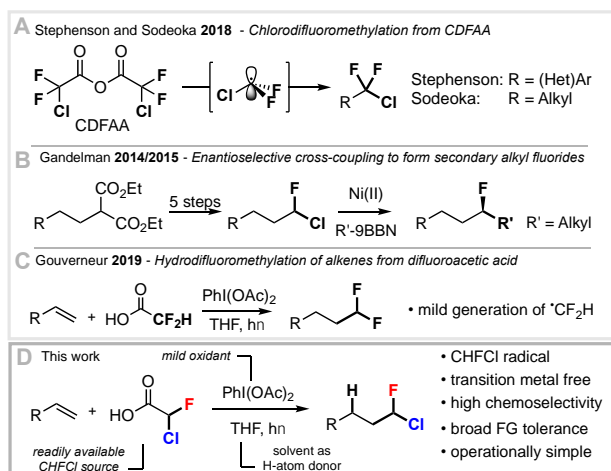


Fig. 1. A-B. Selected routes towards chloro(di)fluoroalkanes. C-D. Hydrodifluoro- and hydrochlorofluoromethylation of alkenes.

In contrast to these fundamental studies, the chemistry of the chlorofluoromethyl radical has not been investigated. This is surprising for two reasons; mechanistically, there is value in probing the reactivity of $\bullet\text{CHFCl}$ with respect to $\bullet\text{CF}_2\text{H}$ and $\bullet\text{CF}_2\text{Cl}$; synthetically, molecules featuring a chlorofluoromethyl group are high value building blocks considering the rich downstream chemistry that this motif could bring for synthesis. For example, Gandelman and co-workers have demonstrated the utility of 1-chloro-1-fluoroalkanes for Suzuki cross-coupling reactions, a process affording secondary alkyl fluorides in high yields (Figure 1B).⁸ One drawback of this elegant transformation is the five-step synthesis required to access the necessary starting materials. Building on our recently disclosed hydrodifluoromethylation of alkenes with inexpensive difluoroacetic acid (Figure 1C),⁹ we report herein a reaction that gives direct access to 1-chloro-1-fluoroalkanes from feedstock olefins and commercially available reagents in a single step procedure (Figure 1D). Specifically, we propose that the

treatment of chlorofluoroacetic acid with PIDA under blue light irradiation would release $\bullet\text{CHFCl}$ that can add regioselectively to the alkene. The resulting secondary C-centered radical would be intercepted by tetrahydrofuran (THF), the solvent of the reaction that also serves as the hydrogen atom donor source. The validation of this process is the object of this report.

2. Results and Discussion

Initial efforts focused on identifying reaction conditions for the hydrochlorofluoromethylation of alkenes (Table 1).

Table 1. Optimization studies for the hydrochlorofluoromethylation of alkenes.^a

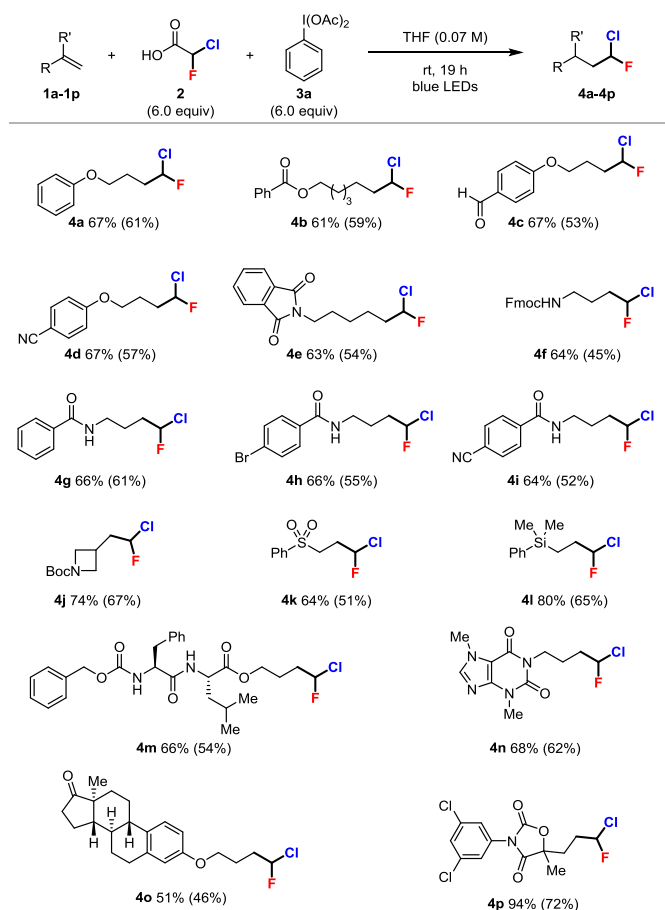
Entry	Solvent	Oxidant	Yield (%)
1	THF	3a	57
2	THF	3b	7
3 ^b	THF	3c	14
4 ^c	THF	3a	67
5 ^c	DMF	3a	30
6 ^c	1,4-dioxane	3a	16
7 ^d	THF	3a	18

^a**1a** (0.1 mmol), **2** (0.6 mmol), **3a** or **3b** (0.6 mmol), solvent (1.5 mL), blue LED irradiation ($\lambda = 470$ nm), rt, 19 h. The mixture was analyzed by ^{19}F NMR using trifluorotoluene as an internal standard. ^b**3c** (0.2 mmol) was used in the absence of **2**. ^cOxidant **3a** was added in two batches (0.3 mmol each). Second batch was added after a reaction time of 5 h. ^dReaction performed in absence of light.

When reacting model alkene **1a** with the oxidant phenyliodine(III) diacetate (PIDA) and chlorofluoroacetic acid in THF under blue light irradiation ($\lambda = 470$ nm), the desired hydrochlorofluoromethylated compound was formed in 57% yield along with unreacted **1a** (Table 1, entry 1). Exchanging PIDA with [bis(trifluoroacetoxy)iodo]-benzene **3b** (PIFA) or [bis(chlorofluoroacetoxy)iodo]benzene **3c** proved detrimental (Table 1, entry 2-3). When **3a** was added in two batches, the yield increased to 67% (Table 1, entry 4). Changing the solvent did not afford **4a** in higher yield (Table 1, entries 5-6). A control experiment performed in absence of light gave **4a**, albeit in significantly lower yield (Table 1, entry 7).

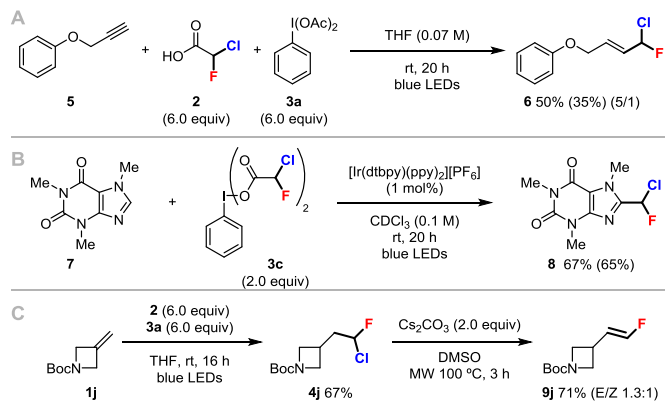
With the optimized conditions in hand, the scope of this reaction was investigated (Scheme 1). In general, $\bullet\text{CHFCl}$ displayed a reactivity profile towards alkenes similar to the nucleophilic radical $\bullet\text{CF}_2\text{H}$, with the best results obtained for electron-deficient as well as electron-neutral alkenes.^{9a,10} A variety of terminal and *gem*-disubstituted alkenes were converted to the hydrochlorofluoromethylated products. Ether **4a** and ester **4b** were obtained in moderate to good yield. Substrates containing aldehyde and nitrile functionalities were well tolerated and afforded products **4c,d,i** with yields averaging 57%. Secondary and tertiary amides as well as carbamates also underwent hydrochlorofluoromethylation in good yields (**4e-i**).

Furthermore, the *gem*-disubstituted alkene **1j** afforded the azetidine **4j** isolated in 67% yield. The electron-deficient alkene **1k** was suitable for this transformation affording **4k** in 51% yield. Moreover, vinyl silane **1l** was also amenable to regioselective hydrochlorofluoro-methylation. We further investigated alkene-containing biologically active molecules. The dipeptide **4m** was isolated in moderate yield, and interestingly *N*-allyl caffeine was transformed as expected and did not undergo competing C-H chlorofluoromethylation (**4n**). The estrone and vinclozolin derivatives **4o** and **4p** were isolated in 46% and 72% yield, respectively.



Scheme 1. Hydrochlorofluoromethylation of alkenes. Reaction conditions: alkene **1a-p** (0.3 mmol), **2** (1.8 mmol), **3a** (0.9 mmol), THF (4.5 mL), blue LED irradiation ($\lambda = 470$ nm), rt, 19 h. After 5 h a second portion of **3a** (0.9 mmol) was added. Yields determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard; yields of isolated products in brackets.

Next, the method was applied to two representative radical acceptors other than alkenes. Alkyne **5** underwent regioselective hydrochlorofluoromethylation to give allyl chloride **6** as a 5:1 mixture of geometrical isomers; this is a remarkably expedited route to a class of compounds that may have direct use, for example in Tsuji-Trost allylic substitution (Scheme 2A). C-H Chlorofluoromethylation was also possible as illustrated with caffeine **7** (Scheme 2B). This latter reaction required substantial modifications of our standard reaction conditions to proceed. Specifically, **7** was treated with [bis(chlorofluoroacetoxy)iodo]benzene **3c** in the presence of the photoredox catalyst $[\text{Ir}(\text{dtbpy})(\text{ppy})_2][\text{PF}_6]$ in CDCl_3 under blue LEDs irradiation for 20 h at room temperature, a protocol affording **8** isolated in 65% yield (Scheme 2B). Furthermore, we demonstrated that subjecting **4j** to hydrochlorofluoromethylation followed by HCl elimination afforded fluoroalkene **9j** in 71% yield, albeit as a mixture of geometrical isomers (Scheme 2C).



Scheme 2. A) Hydrochlorofluoromethylation of alkyne **5**. B) C-H Chlorofluoromethylation of the heteroarene caffeine **7**. C) Sequential hydrochlorofluoromethylation then elimination for the conversion of **1j** into fluoroalkene **9j**.

3. Conclusion

We have developed a practical and mild method for the hydrochlorofluoromethylation of alkenes exploiting the nucleophilic character of the $\cdot\text{CH}_2\text{FCl}$ radical. The protocol employs inexpensive chlorofluoroacetic acid and PIDA, and tolerates a wide range of functional groups. Furthermore, we have demonstrated the feasibility of hydrochlorofluoromethylation on a representative alkyne, and of C-H chlorofluoromethylation on caffeine.

4. Experimental section

4.1. General information

All NMR spectra were recorded on a Bruker DPX-400 or a Bruker Avance II HD spectrometer with standard pulse sequences operating at 400 and 500 MHz, respectively. ^1H and ^{13}C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to CFCl_3 in CDCl_3 . Coupling constants (J) are measured in hertz (Hz). The following abbreviations are used to describe multiplicities s=singlet, d=doublet, t=triplet, q=quartet, pent=pentet, br=broad, m=multiplet. NMR spectra were processed in MestreNova. High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI) or on an Intuvo GC 9000 - MSD 5977B (Agilent Technologies) using electron impact ionization (EI). Exact masses were calculated with MassWorks software (from Cerno Bioscience) through a correction of the mass with a calibration file. Melting points of solids were measured on a DSC823^c (Differential Scanning Analysis) Mettler Toledo apparatus. IUPAC names were obtained using the ChemDraw service. Weighing was performed with a 4 decimal place balance. All reactions for the hydrochlorofluoromethylation of alkenes were conducted in non-dried glassware with magnetic stirring. All solvents were used as received without further purification. Flash column chromatography was performed over Merck silica gel C60 (40–60 μm) using a gradient system (EtOAc in heptane 0/100 to 100/0). Chlorofluoroacetic acid was purchased from Apollo Scientific. PIDA was purchased from Carbosynth. All commercially available substrates were purchased from commercial suppliers or otherwise synthesized according to literature.^{9a} Reactions were performed in 7 mL vials in a SynLED photoreactor ($\lambda_{\text{max}} = 465\text{--}470$ nm). The yields were

determined by either ^{19}F NMR spectroscopy or by the isolation on SiO_2 gel column chromatography. If the purity of the compounds was not satisfying an analytical sample was further purified by reverse phase HPLC purification.

4.2. General procedure A: Hydrochlorofluoromethylation of alkenes and alkynes

Chlorofluoroacetic acid (133 μL , 1.80 mmol, 6.0 equiv) was added to a suspension of phenyliodine(III) diacetate (290 mg, 0.90 mmol, 3.0 equiv) and alkene (0.30 mmol) in THF (4.5 mL). The mixture was stirred under blue LED irradiation (SynLED photoreactor) at rt for 5 h, after which a second portion of phenyliodine(III) diacetate (290 mg, 1.80 mmol, 3.0 equiv) was added. The suspension was stirred under blue LED irradiation for another 14 h. α,α,α -Trifluorotoluene (123 μL , 1.00 mmol, 3.33 equiv) was added and the mixture was analyzed by ^{19}F NMR spectroscopy. The solvents were removed *in vacuo* and the residue was purified by column chromatography (silica, EtOAc in heptane 0/100 to 100/0) to yield the desired product.

4.2.1. (4-chloro-4-fluorobutoxy)benzene (**4a**)

General procedure A was followed to obtain **4a** (37 mg, 0.18 mmol, 61%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.27 (m, 2H), 6.97 (tt, J = 7.3, 1.1 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.29 (dt, J = 50.8, 5.3 Hz, 1H), 4.03 (t, J = 6.0 Hz, 2H), 2.40 – 2.20 (m, 2H), 2.09 – 1.96 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.8, 129.6, 121.0, 114.6, 102.7 (d, J = 241.4 Hz), 66.7, 36.4 (d, J = 20.3 Hz), 24.2 (d, J = 4.5 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.3 (dt, J = 50.6, 18.5 Hz); HRMS (EI): calculated for $\text{C}_{10}\text{H}_{12}\text{ClFO}^+$ (M^+): 202.0555; observed: 202.0570.

4.2.2. 7-chloro-7-fluoroheptyl benzoate (**4b**)

General procedure A was followed to obtain **4b** (48 mg, 0.18 mmol, 59%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.06 – 8.02 (m, 2H), 7.58 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 6.16 (dt, J = 51.0, 5.4 Hz, 1H), 4.32 (t, J = 6.6 Hz, 2H), 2.20 – 1.97 (m, 2H), 1.85 – 1.74 (m, 2H), 1.58 – 1.38 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 166.6, 132.9, 130.4, 129.5, 128.3, 102.8 (d, J = 241.3 Hz), 64.9, 39.2 (d, J = 20.1 Hz), 28.6, 28.5, 25.9, 24.0 (d, J = 4.4 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -129.7 – -129.9 (m); HRMS (EI): calculated for $\text{C}_{14}\text{H}_{18}\text{ClFO}_2^+$ (M^+): 272.0974; observed: 272.1022.

4.2.3. 4-(4-chloro-4-fluorobutoxy)benzaldehyde (**4c**)

General procedure A was followed to obtain **4c** (37 mg, 0.16 mmol, 53%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 9.89 (s, 1H), 7.89 – 7.79 (m, 2H), 7.02 – 6.96 (m, 2H), 6.29 (dt, J = 50.8, 5.1 Hz, 1H), 4.11 (t, J = 6.0 Hz, 2H), 2.40 – 2.20 (m, 2H), 2.13 – 2.00 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 190.9, 163.8, 132.2, 130.3, 114.9, 102.4 (d, J = 241.5 Hz), 67.2, 36.1 (d, J = 20.6 Hz), 23.9 (d, J = 4.4 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.5 (dt, J = 50.8, 18.4 Hz); HRMS (ESI-TOF): calculated for $\text{C}_{11}\text{H}_{13}\text{ClFO}_2^+$ ($[\text{M}+\text{H}]^+$): 231.0588, observed: 231.0586.

4.2.4. 4-(4-chloro-4-fluorobutoxy)benzonitrile (**4d**)

General procedure A was followed to obtain **4d** (39 mg, 0.17 mmol, 57%) as a white solid. m.p. 31 – 33 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 7.63 – 7.57 (m, 2H), 6.98 – 6.92 (m, 2H), 6.29 (dt, J = 50.7, 5.1 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 2.37 – 2.23 (m, 2H), 2.11 – 2.01 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.1, 134.2, 119.3, 115.3, 104.4, 102.3 (d, J = 241.5 Hz), 67.2, 36.0 (d, J = 20.5 Hz), 23.8 (d, J = 4.4 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.6 (dt, J = 50.5, 18.6 Hz); HRMS (EI): calculated for $\text{C}_{11}\text{H}_{11}\text{ClFNO}^+$ (M^+): 227.0508; observed: 227.0430.

4.2.5. 2-(6-chloro-6-fluorohexyl)isoindoline-1,3-dione (**4e**)

General procedure A was followed to obtain **4e** (46 mg, 0.16 mmol, 54%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.85 – 7.77 (m, 2H), 7.73 – 7.66 (m, 2H), 6.13 (dt, J = 50.9, 5.4 Hz, 1H), 3.67 (t, J = 7.2 Hz, 2H), 2.14 – 1.94 (m, 2H), 1.73 – 1.64 (m, 2H), 1.60 – 1.46 (m, 2H), 1.44 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.6, 134.1, 132.3, 123.3, 102.8 (d, J = 241.6 Hz), 39.2 (d, J = 19.8 Hz), 37.8, 28.5, 26.2, 23.8 (d, J = 4.2 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -129.8 – -130.0 (m). Data consistent with literature values.¹⁵

4.2.6. (9H-fluoren-9-yl)methyl (4-chloro-4-fluorobutyl)carbamate (**4f**)

General procedure A was followed to obtain **4f** (47 mg, 0.14 mmol, 45%) as a white solid. m.p. 116 – 119 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (td, J = 7.5, 1.2 Hz, 2H), 6.20 (dt, J = 50.7, 5.1 Hz, 1H), 4.82 (br s, 0.8H), 4.64 (br s, 0.2H), 4.55 (br s, 0.2H), 4.44 (br d, J = 6.7 Hz, 1.8H), 4.21 (t, J = 6.8 Hz, 1H), 3.25 (q, J = 6.7 Hz, 1.7H), 3.01 (s, 0.3H), 2.17 – 2.02 (m, 1.7H), 1.90 (br s, 0.3H), 1.80 – 1.67 (m, 1.7H), 1.50 (br s, 0.3H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.6, 144.0, 141.5, 127.8, 127.2, 125.1, 120.1, 102.4 (d, J = 241.5 Hz), 66.7, 47.4, 40.2, 36.4 (d, J = 20.3 Hz), 24.8 (d, J = 4.0 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.2 (dt, J = 50.9, 18.6 Hz); Compound **4f** was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

4.2.7. N-(4-chloro-4-fluorobutyl)benzamide (**4g**)

General procedure A was followed to obtain **4g** (42 mg, 0.18 mmol, 61%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.78 – 7.73 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.38 (m, 2H), 6.47 (br s, 1H), 6.22 (dt, J = 50.8, 5.2 Hz, 1H), 3.50 (q, J = 6.8 Hz, 2H), 2.23 – 2.06 (m, 2H), 1.90 – 1.79 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.9, 134.5, 131.7, 128.7, 127.0, 102.4 (d, J = 241.5 Hz), 39.1, 36.6 (d, J = 20.3 Hz), 24.5 (d, J = 4.1 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.2 (dt, J = 51.0, 19.0 Hz); HRMS (ESI-TOF): calculated for $\text{C}_{11}\text{H}_{12}\text{ClFNO}^+$ ($[\text{M}+\text{H}]^+$): 228.0591; observed: 228.0589.

4.2.8. 4-bromo-N-(4-chloro-4-fluorobutyl)benzamide (**4h**)

General procedure A was followed to obtain **4h** (51 mg, 0.17 mmol, 55%) as a white solid. m.p. 85 – 88 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.60 (m, 2H), 7.59 – 7.53 (m, 2H), 6.32 (s, 1H), 6.23 (dt, J = 50.8, 5.1 Hz, 1H), 3.50 (q, J = 6.9 Hz, 2H), 2.25 – 2.05 (m, 2H), 1.94 – 1.80 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.9, 133.3, 132.0, 128.6, 126.4, 102.4 (d, J = 241.6 Hz), 39.3, 36.6 (d, J = 20.4 Hz), 24.4 (d, J = 4.0 Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -130.3 (dt, J = 50.8, 18.7 Hz); HRMS (ESI-TOF): calculated for $\text{C}_{11}\text{H}_{11}\text{BrClFNO}^+$ ($[\text{M}+\text{H}]^+$): 305.9697; observed: 305.9692.

4.2.9. N-(4-chloro-4-fluorobutyl)-4-cyanobenzamide (**4i**)

General procedure A was followed to obtain **4i** (40 mg, 0.16 mmol, 52%) as a white solid. m.p. 120 – 122 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 7.88 – 7.84 (m, 2H), 7.75 – 7.71 (m, 2H), 6.48 (s, 1H), 6.24 (dt, J = 50.7, 5.0 Hz, 1H), 3.53 (q, J = 6.7 Hz, 2H), 2.22 – 2.09 (m, 2H), 1.92 – 1.82 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.9, 138.3, 132.5, 127.6, 118.0, 115.1, 102.2 (d, J = 241.6 Hz), 39.3, 36.4 (d, J = 20.3 Hz), 24.2 (d, J = 3.8 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.4 (dt, J = 51.2, 19.0 Hz); HRMS (ESI-TOF): calculated for $\text{C}_{12}\text{H}_{11}\text{ClFN}_2\text{O}^+$ ($[\text{M}+\text{H}]^+$): 253.0544; observed: 253.0538.

4.2.10. *tert*-butyl 3-(2-chloro-2-fluoroethyl)azetidine-1-carboxylate (**4j**)

General procedure A was followed to obtain **4j** (48 mg, 0.20 mmol, 67%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 6.16 (dt, $J = 50.4$, 5.0 Hz, 1H), 4.08 (t, $J = 8.5$ Hz, 2H), 3.67 (ddd, $J = 8.3$, 5.8, 1.9 Hz, 2H), 2.88 – 2.77 (m, 1H), 2.46 – 2.30 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.3, 101.2 (d, $J = 241.8$ Hz), 79.7, 54.4 (br s), 43.3 (d, $J = 19.9$ Hz), 28.5, 24.7 (d, $J = 3.9$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -131.8 (br s); HRMS (EI): calculated for $\text{C}_{10}\text{H}_{17}\text{ClFNO}_2^{++}$ (M^{++}): 237.0926; observed: 237.0869.

4.2.11. ((3-chloro-3-fluoropropyl)sulfonyl)benzene (**4k**)

General procedure A was followed to obtain **4k** (36 mg, 0.15 mmol, 51%) as a white solid. m.p. 45 – 47 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.96 – 7.89 (m, 2H), 7.73 – 7.67 (m, 1H), 7.64 – 7.57 (m, 2H), 6.34 (dt, $J = 50.3$, 4.8 Hz, 1H), 3.38 – 3.23 (m, 2H), 2.60 – 2.44 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 138.6, 134.3, 129.7, 128.1, 100.0 (d, $J = 242.5$ Hz), 50.8 (d, $J = 3.9$ Hz), 32.5 (d, $J = 22.1$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -132.5 – -132.7 (m); HRMS (EI): calculated for $\text{C}_9\text{H}_9\text{ClFO}_2\text{S}^{++}$ (M^{++}): 236.0069; observed: 236.0016.

4.2.12. (3-chloro-3-fluoropropyl)dimethyl(phenyl)silane (**4l**)

General procedure A was followed to obtain **4l** (45 mg, 0.20 mmol, 65%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.53 – 7.49 (m, 2H), 7.41 – 7.36 (m, 3H), 6.08 (dt, $J = 51.2$, 5.2 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.01 – 0.87 (m, 2H), 0.32 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 138.1, 133.6, 129.4, 128.1, 104.5 (d, $J = 243.4$ Hz), 34.3 (d, $J = 20.4$ Hz), 10.1 (d, $J = 3.0$ Hz), -3.1; ^{19}F NMR (471 MHz, CDCl_3) δ -130.0 (dt, $J = 51.2$, 17.8 Hz); Compound **4l** was found to be unstable under various ionisation techniques and HRMS could therefore not be obtained.

4.2.13. 4-chloro-4-fluorobutyl ((benzyloxy)carbonyl)-L-phenylalanyl-L-leucinate (**4m**)

General procedure A was followed to obtain **4m** (84 mg, 0.16 mmol, 54%) as a white solid. m.p. 80 – 84 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.16 (m, 10H), 6.30 – 6.14 (m, 2H), 5.33 – 5.23 (m, 1H), 5.09 (d, $J = 1.7$ Hz, 2H), 4.52 (td, $J = 8.4$, 5.3 Hz, 1H), 4.44 (q, $J = 7.3$ Hz, 1H), 4.21 – 4.09 (m, 2H), 3.09 (qd, $J = 13.9$, 6.7 Hz, 2H), 2.14 (dddd, $J = 18.4$, 9.3, 6.9, 4.8 Hz, 2H), 1.94 – 1.81 (m, 2H), 1.62 – 1.40 (m, 3H), 0.89 (dd, $J = 6.2$, 4.9 Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 172.4, 170.7, 156.1, 136.3, 136.2, 129.5, 128.8, 128.7, 128.4, 128.2, 127.2, 102.2 (d, $J = 241.9$ Hz), 67.3, 64.2, 56.2, 51.1, 41.6, 38.3, 35.9 (d, $J = 20.7$ Hz), 24.9, 23.4 (d, $J = 4.4$ Hz), 22.8, 22.1; ^{19}F NMR (471 MHz, CDCl_3) δ -130.5 – -130.9 (m); HRMS (ESI-TOF): calculated for $\text{C}_{27}\text{H}_{35}\text{ClFN}_2\text{O}_5^+$ ($[\text{M}+\text{H}]^+$): 521.2219; observed: 521.2216.

4.2.14. 1-(4-chloro-4-fluorobutyl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**4n**)

General procedure A was followed to obtain **4n** (54 mg, 0.19 mmol, 62%) as a white solid. m.p. 111 – 115 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.51 (s, 1H), 6.21 (dt, $J = 50.8$, 5.3 Hz, 1H), 4.05 (t, $J = 7.2$ Hz, 2H), 3.97 (s, 3H), 3.56 (s, 3H), 2.23 – 2.02 (m, 2H), 1.96 – 1.82 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.3, 151.5, 149.0, 141.7, 107.7, 102.4 (d, $J = 241.7$ Hz), 40.3, 36.7 (d, $J = 20.6$ Hz), 33.7, 29.8, 23.0 (d, $J = 4.4$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -130.0 – -130.2 (m); HRMS (ESI-TOF): calculated for $\text{C}_{11}\text{H}_{15}\text{ClFN}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$): 289.0868; observed: 289.0883.

4.2.15. (8R,9S,13S,14S)-3-(4-chloro-4-fluorobutoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-

decahydro-17H-cyclopenta[a]phenanthren-17-one (**4o**)

General procedure A was followed to obtain **4o** (52 mg, 0.14 mmol, 46%) as a white solid. m.p. 107 – 110 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.20 (d, $J = 8.6$ Hz, 1H), 6.70 (dd, $J = 8.6$, 2.8 Hz, 1H), 6.64 (d, $J = 2.7$ Hz, 1H), 6.27 (dt, $J = 50.9$, 5.3 Hz, 1H), 3.99 (t, $J = 6.0$ Hz, 2H), 2.95 – 2.85 (m, 2H), 2.50 (dd, $J = 18.8$, 8.6 Hz, 1H), 2.44 – 1.90 (m, 10H), 1.71 – 1.38 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 221.0, 156.9, 138.0, 132.5, 126.5, 114.7, 112.2, 102.7 (d, $J = 241.3$ Hz), 66.8, 50.6, 48.2, 44.1, 38.5, 36.4 (d, $J = 20.9$ Hz), 36.0, 31.7, 29.8, 26.7, 26.1, 24.2 (d, $J = 4.7$ Hz), 21.7, 14.0; ^{19}F NMR (471 MHz, CDCl_3) δ -130.2 (dt, $J = 51.5$, 18.8 Hz); HRMS (ESI-TOF): calculated for $\text{C}_{22}\text{H}_{29}\text{ClFO}_2^+$ ($[\text{M}+\text{H}]^+$): 379.1840; observed: 379.1839.

4.2.16. 5-(3-chloro-3-fluoropropyl)-3-(3,5-dichlorophenyl)-5-methyloxazolidine-2,4-dione (**4p**)

General procedure A was followed to obtain **4p** (76 mg, 0.21 mmol, 71%) as a sticky oil; d.r. 1:1. ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.44 (m, 2H), 7.44 – 7.42 (m, 1H), 6.35 – 6.15 (m, 1H), 2.38 – 2.05 (m, 4H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 152.1, 135.8, 132.6, 129.3, 123.8, 101.1 (dd, $J = 242.3$, 3.5 Hz), 84.9, 32.9 (d, $J = 21.3$ Hz), 31.1 (d, $J = 4.4$ Hz, 0.5C), 31.0 (d, $J = 4.3$ Hz, 0.5C), 22.5; ^{19}F NMR (471 MHz, CDCl_3) δ -131.5 – -131.7 (m, 0.5F), -131.8 – -132.0 (m, 0.5F); HRMS (ESI-TOF): calculated for $\text{C}_{13}\text{H}_{10}\text{Cl}_3\text{FNO}_3^-$ ($[\text{M}-\text{H}]^-$): 351.9710; observed: 351.9719.

4.2.17. ((4-chloro-4-fluorobut-2-en-1-yl)oxy)benzene (**6**)

General procedure A was followed to obtain **6** (21 mg, 0.11 mmol, 35%) as a colourless oil. Mixture of stereoisomers (86:14). ^1H NMR (500 MHz, CDCl_3) δ 7.33 – 7.28 (m, 2H), 7.05 – 7.02 (m, 0.14H), 6.99 (tt, $J = 7.4$, 1.1 Hz, 0.86H), 6.94 – 6.89 (m, 2H), 6.64 – 6.50 (m, 1H), 6.24 – 6.11 (m, 1.86H), 5.97 – 5.93 (m, 0.14H), 4.72 – 4.60 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.2, 130.7 (d, $J = 10.2$ Hz), 129.7, 128.2 (d, $J = 21.2$ Hz), 121.5, 114.8, 99.3 (d, $J = 239.2$ Hz), 66.3; ^{19}F NMR (471 MHz, CDCl_3) δ -128.3 – -128.5 (m); HRMS (EI): calculated for $\text{C}_{10}\text{H}_{10}\text{ClFO}^{++}$ (M^{++}): 200.0399; observed: 200.0364.

4.3. 8-(chlorofluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (**8**)

Chlorofluoroacetic acid (30 μL , 0.40 mmol, 4.0 equiv) was added to a suspension of phenyliodine(III) diacetate (64 mg, 0.20 mmol, 2.0 equiv) in toluene (5 mL). The mixture was concentrated *in vacuo* and azeotropically dried with toluene. To this crude iodine reagent **3c** was added **7** (19 mg, 0.10 mmol, 1.0 equiv), $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2][\text{PF}_6]$ (1 mg, 0.001 mmol, 1 mol%) and CDCl_3 (1.0 mL). The mixture was degassed by nitrogen bubbling for 5 min whilst cooling in a water bath. The mixture was stirred under blue LED irradiation (SynLED photoreactor) at rt for 20 h. α,α,α -Trifluorotoluene (123 μL , 1.00 mmol, 10.0 equiv) was added and the mixture was analyzed by ^{19}F NMR spectroscopy. The solvents were removed *in vacuo* and the residue was purified by column chromatography (silica, EtOAc in heptane 0/100 to 100/0) to yield **8** (17 mg, 0.07 mmol, 65%) as a white solid. m.p. 200 – 202 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.15 (d, $J = 47.3$ Hz, 1H), 4.19 (d, $J = 1.4$ Hz, 3H), 3.55 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.6, 151.6, 146.8, 145.0 (d, $J = 24.9$ Hz), 109.7, 93.4 (d, $J = 240.5$ Hz), 33.3 (d, $J = 3.3$ Hz), 29.9, 28.3; ^{19}F NMR (471 MHz, CDCl_3) δ -135.1 (d, $J = 47.8$ Hz); HRMS (ESI-TOF): calculated for $\text{C}_9\text{H}_{11}\text{ClFN}_4\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 261.0555; observed: 261.0554.

4.4. *tert*-butyl 3-(2-fluorovinyl)azetidine-1-carboxylate (**9j**)

Cs_2CO_3 (165 mg, 0.51 mmol, 2.0 equiv) was added to a solution of **4j** (60 mg, 0.25 mmol, 1.0 equiv) in DMSO (2 mL). The mixture was stirred at 100 °C for 3 h. Water was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, EtOAc in heptane 0/100 to 60/40) to yield **9j** (36 mg, 0.18 mmol, 71%) as a colourless oil. E/Z 57:43; ^1H NMR (500 MHz, CDCl_3) δ 6.55 (ddd, J = 83.5, 11.1, 0.8 Hz, 0.57H), 6.44 (ddd, J = 83.9, 4.8, 1.2 Hz, 0.43H), 5.56 (ddd, J = 17.6, 11.1, 9.6 Hz, 0.57H), 5.00 (ddd, J = 41.5, 9.0, 4.7 Hz, 0.43H), 4.16 – 4.05 (m, 2H), 3.72 – 3.65 (m, 2H), 3.62 – 3.50 (m, 0.43H), 3.17 – 3.02 (m, 0.57H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.3, 156.3, 149.8 (d, J = 258.0 Hz), 148.5 (d, J = 260.6 Hz), 112.9 (d, J = 11.5 Hz), 112.4 (d, J = 4.1 Hz), 79.7, 79.6, 55.1 (br s), 28.5, 28.5, 25.5 (d, J = 10.6 Hz), 23.1 (d, J = 5.4 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -127.6 (dd, J = 84.0, 41.8 Hz, 0.43F), -128.3 (dd, J = 83.5, 17.6 Hz, 0.57F); HRMS (EI): calculated for $\text{C}_{10}\text{H}_{16}\text{FNO}_2^{++}$ (M^{++}): 201.1160; observed: 201.1084.

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10. For details on the similar reactivity of $\bullet\text{CHFCl}$ and $\bullet\text{CF}_2\text{H}$ for substrates other than alkenes, see the Supporting Information.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.