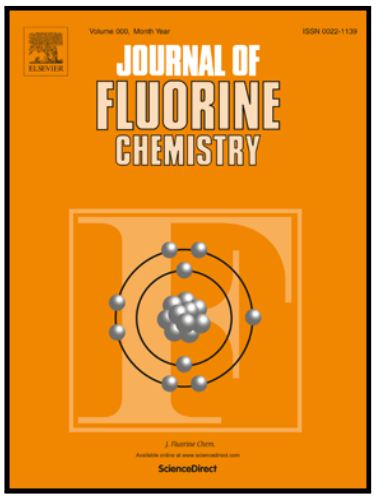

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Efficient Protocol for the SO_2F_2-Mediated Deoxyfluorination of Aliphatic Alcohols

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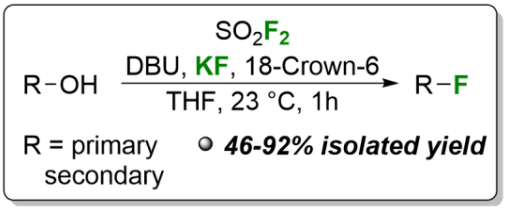
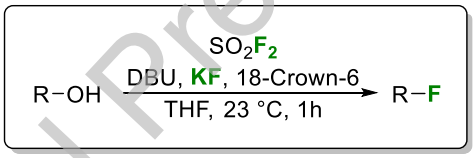
Graphical abstract



Highlights

- New, mild SO_2F_2-mediated deoxyfluorination reaction.
- Efficient for both primary and secondary alcohols.
- The alkyl fluorides can be accessed at room temperature in an hour.
- Net inversion of configuration is observed with only minor deterioration of the ee.

Abstract:



Alkyl fluorides are prevalent in both the pharmaceutical and agrochemical industries. As such, there has been significant interest over the past 40 years in the development of new synthetic methods to access these important fluorinated motifs. Herein we report the sulfuryl fluoride-mediated deoxyfluorination of alcohols using room temperature reaction conditions in only an hour. A wide range of primary aliphatic alcohols were efficiently converted to the corresponding fluoride in 46-70% isolated yields. Secondary alcohols were also effectively deoxyfluorinated in 50-92% yields. Chiral secondary alcohols were cleanly converted to the corresponding alkyl fluoride with only a minor deterioration of the enantioenrichment. A steroid derivative also underwent deoxyfluorination in 50% yield and 5.9:1 dr, with the major product resulting from net inversion of the stereocenter.

Keywords
Sulfur(VI) fluorides, sulfuryl fluoride, alkyl fluoride, deoxyfluorination, *ex situ* gas generation.

1. Introduction

Fluorine incorporation into pharmaceuticals and agrochemicals is a common method to modulate and tune a molecule's physicochemical properties, including lipophilicity, acidity,[1] and metabolic stability.[2] Because of the utility of organofluorine molecules, they are now

prevalent in both industries. Between 1991 and 2019, 18% of all pharmaceuticals on the market contained fluorine, [3] including three out of the five top-selling drugs. [4] For pesticides alone, 16% are fluorine-containing agrochemicals. [5] While many different fluorinated motifs are utilized in both of these industries, alkyl fluorides are prevalent (Fig. 1). The importance of these fluoroalkyl motifs has motivated the development of numerous methods for their synthesis. Of particular interest are the methods that promote the direct deoxyfluorination of alcohols in a single synthetic step. Numerous nitrogen-, [6–8] carbon-, [9] and sulfur-based reagents [10–17] have been developed over the past forty years to effect deoxyfluorinations, but there are limitations with many of the aforementioned methods, such as long reaction times, harsh reaction conditions, and high reagent expense.

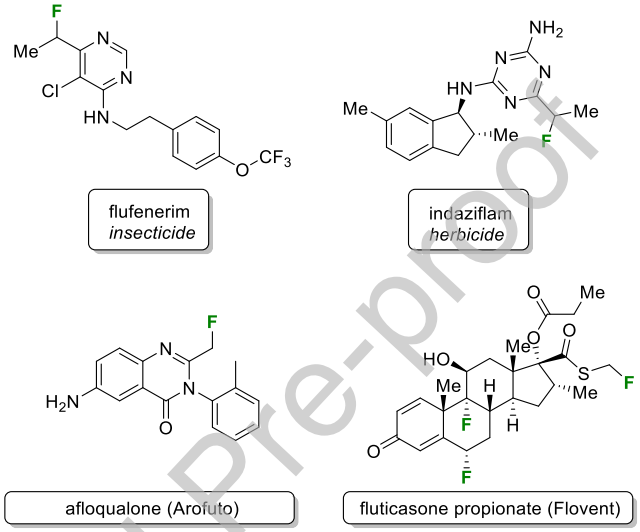


Fig. 1. Representative examples of fluoroalkyl pharmaceuticals and agrochemicals.

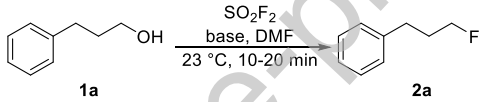
We were intrigued by the possibility of developing a general method for the deoxyfluorination of alcohols using sulfuryl fluoride (SO_2F_2), a commodity chemical that is widely used as a fumigant but has not been extensively applied to organic synthesis. Sulfuryl fluoride is an attractive reagent as it can either be directly purchased or readily synthesized on-demand. [18–20] Furthermore, the by-products of sulfuryl fluoride-based methods are typically sulfates that can readily be removed. There are few patents by Ishii and coworkers that describe SO_2F_2-promoted deoxyfluorination. [21–27] Unfortunately, this method has several disadvantages, such as requiring low temperatures (–40 to –78 ˚C), moderate to high pressures (up to 2 MPa), long reaction times (20 to 40 h), and highly variable yields. Our goal was to develop a more efficient and mild protocol for SO_2F_2-mediated deoxyfluorination.

2. Results and discussion

Our study began by applying our previously developed aliphatic alcohol activation methods for deoxyfluorination,[19,20] but nether provided high yields of the desired product. We then investigated different bases in the SO_2F_2-mediated deoxyfluorination of primary alcohols (Table

1). 3-Phenyl-1-propanol (**1a**) was selected as a model substrate as the alcohol is not activated, and the corresponding alkyl fluoride (**2a**) has a sufficiently high molecular weight that it is not highly volatile. We started by examining the reaction with 1.5 equivalents of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) with sulfuryl fluoride in DMF, which afforded the desired alkyl fluoride (**2a**) in only 26% isolated yield (entry 1). Increasing the amount of DBU resulted in a modest decrease in the isolated yield (entry 2). Replacing DBU with the weaker bases triethylamine (Et_3N) or *N*,*N*-diisopropylethylamine (DIPEA) resulted in 30% (entry 3) and 6% isolated yield (entry 4), respectively. The addition of catalytic amounts of 4-dimethylaminopyridine (DMAP) or tetrabutylammonium iodide (TBAI) had a negligible effect on the reaction yield (entries 5-7). While tetrabutylammonium fluoride (TBAF) did not improve the reaction with DIPEA (entry 8), it led to a significant increase in yield when DBU was utilized (entry 9). Changing the fluoride source to KF led to a slight decrease in yield (entry 10), but addition of KF and 18-crown-6 with sulfuryl fluoride and DBU afforded **2a** in 52% isolated yield (entry 11).

Table 1
Base and additive optimization of sulfuryl fluoride-mediated deoxyfluorinations.[a]



entry	variation from standard conditions	NMR yield of **2a** (%)
1	DBU (1.5 equiv.)	26
2	DBU (4 equiv.)	18
3	Et_3N (4 equiv.)	30
4	DIPEA (4 equiv.)	6
5	DIPEA (4 equiv.), DMAP (0.1 equiv.)	12
6	DIPEA (4 equiv.), TBAI (0.1 equiv.)	12
7	DBU (4 equiv.), TBAI (0.1 equiv.)	20
8	DIPEA (4 equiv.), TBAF (in THF, 1 equiv.)	12
9	DBU (4 equiv.), TBAF (in THF, 1 equiv.)	49
10	DBU (2 equiv.), KF (3 equiv.)	32
11	DBU (2 equiv.), KF (3 equiv.), 18-crown-6 (3 equiv.)	52

[a]Reaction conditions: To a solution of the base, 3-phenyl-1-propanol (0.6 mmol), and DMF (1.8 mL) was bubbled *ex situ*-generated SO_2F_2 (general procedure A). The yield was determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

Despite extensive subsequent optimization, the isolated yields of **2a** never exceeded 52%. We hypothesized that the problem may be due to the competing reaction of alcohol **1** with the key reactive intermediate, fluorosulfate **3** (Fig. 2) to form dialkyl sulfate **4**, which is known to be less reactive towards substitution.[28,29] This hypothesis was confirmed as analysis of the crude reaction mixture using ^{1}H NMR spectroscopy revealed that a significant amount of dialkyl sulfate **4** (Fig. 2) was forming under the reaction conditions and, once formed, it did not react with fluoride in solution. Thus, disfavoring the dialkyl sulfate pathway is essential to achieve high yields of the desired alkyl fluoride product (**2**).

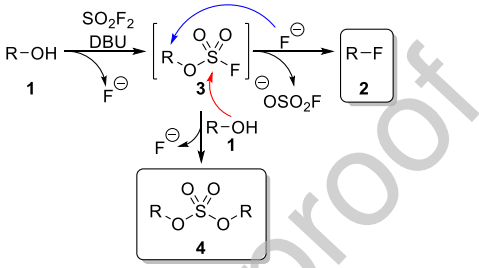
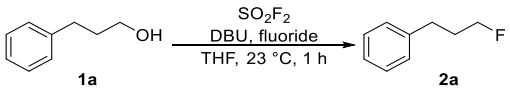


Fig. 2. One-pot deoxyfluorination mediated by SO_2F_2 (blue; top) and the associated undesired reaction pathway to the formation of dialkylsulfate **4** (red; bottom).

One strategy to disfavor the formation of dialkyl sulfate **4** is to keep the concentration of alcohol low compared to sulfuryl fluoride. This increases the likelihood of the desired reaction between fluorosulfate **3** and fluoride compared to the reaction of **3** with the alcohol (**1**). To minimize the concentration of alcohol during the course of the reaction, we examined reverse addition conditions, where the alcohol was slowly added to a pre-saturated solution of SO_2F_2 (Table 2). [30] After a brief screen, THF was identified as the most promising solvent for the reversed addition conditions.[31] The desired alkyl fluoride (**2a**) was obtained in 39% and 41% yields (Table 2, entries 1 and 2), which is notably higher than the 32% yield that was achieved using the former protocol (Table 1, entry 9). Increasing the amount of KF to 3 equivalents gave 48% of the target product **2a**. The reaction afforded either comparable or modestly higher yields when CsF, tetramethylammonium fluoride (TMAF), or potassium bifluoride were used as fluoride additives (Table 2, entries 4-6). The addition of 18-crown-6 led to a slight increase in yield for both CsF and KF (entries 7,8). We selected KF over KHF_2 for further optimization as 18-crown-6 is more commonly utilized in conjunction with KF. Increasing the amount of the KF/18-crown-6 to 4 equivalents led to 70% yield of the desired alkyl fluoride (entry 9), but further increasing the amount of fluoride did not influence the reaction (entry 10).

Table 2
Optimization of the fluoride additive using reversed addition conditions[a]



entry	fluoride	DBU (equiv.)	fluoride (equiv.)	NMR yield (%)
1	KF	1	3	39
2	KF	2	3	41
3	KF	3	3	48
4	CsF	3	3	45
5	TMAF	3	3	54
6	KHF_2	3	3	54
7	CsF/18-crown-6	3	3	54
8	KF/18-crown-6	3	3	55
9	KF/18-crown-6	3	4	70
10	KF/18-crown-6	3	5	69

[a]Reaction conditions: To a solution of the sulfuryl fluoride in THF (6 mL) was added base, 3-phenyl-1-propanol (0.3 mmol), and the fluoride additive (general procedure B). The yield was determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

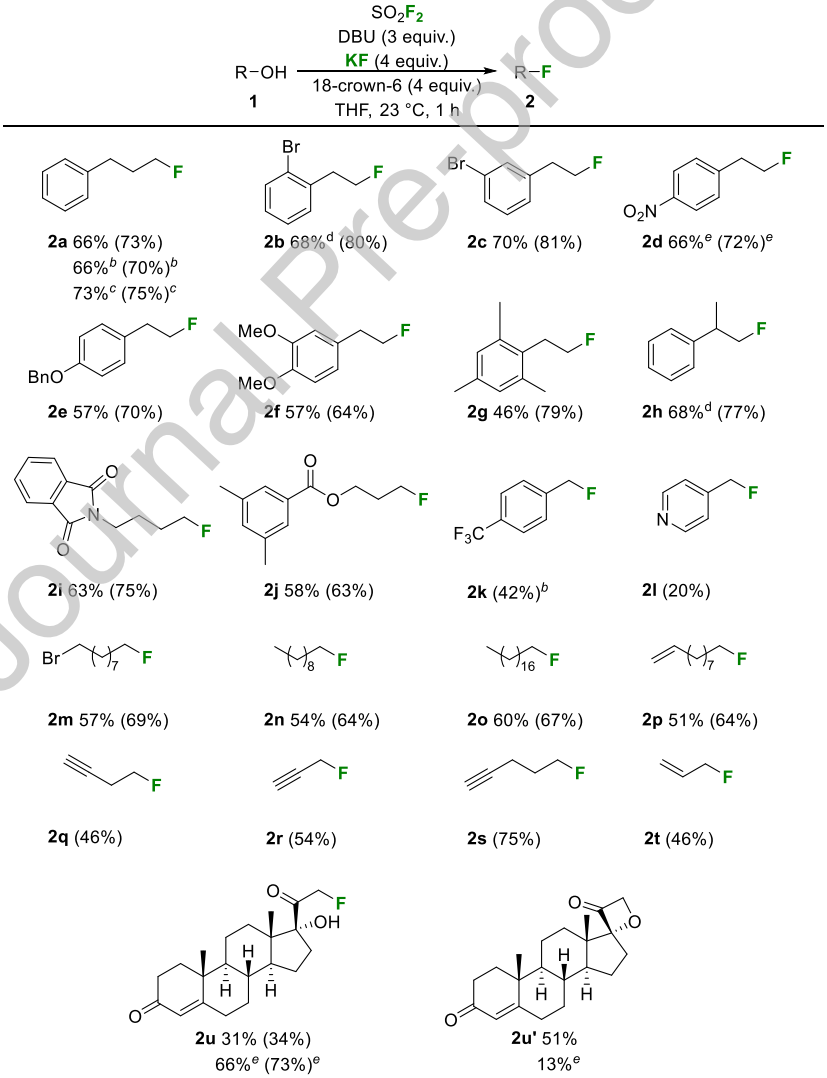
With optimized conditions in hand, we next examined the substrate scope with primary alcohols (Table 2). The reaction with 3-phenyl-1-propanol on both 0.6 mmol and 1 mmol scales afforded the desired alkyl fluoride (**2a**) in 66% isolated yield. The reaction with 3-phenyl-1-propanol on a gram-scale provided **2a** in 73% isolated yield. The reaction was insensitive to bromine on the arene, with both *ortho*- and *meta*-bromophenethyl alcohols converted to the corresponding fluorides (**2b** and **2c**) in 68% isolated yields. The optimized conditions led to significant elimination of nitro derivative **1d** to 1-nitro-4-vinylbenzene. However, when the amount of DBU was decreased to 1 equivalent, the desired alkyl fluoride could be isolated in 66% yield. The reaction was also compatible with electron-donating groups on the arene, with *para*-(benzyloxy)phenethyl alcohol (**1e**) and dimethoxy derivative **1f** both converted to **2e** and **2f** in 57% isolated yields. Trimethyl derivative **1g** was effective under the reaction conditions, affording **2g** in 79% NMR yield. The reaction was not significantly impacted when extra steric bulk was added to the beta-position as alkyl fluoride **2h** was isolated in 68% yield. Phthalimides and esters were also tolerated under the reaction conditions, with **2i** and **2j** isolated in 63% and 58% yield, respectively. Linear primary aliphatic alcohols **1m**-**1p** were successfully converted to the corresponding alkyl fluorides (**2m**-**2p**) in good yields. Notably, **2n** was obtained in 21% yield under Ishii's conditions [27] while our protocol afforded the same substrate in 54% yield. Alkyne-containing primary alkyl alcohol derivative **1q** was only converted to the corresponding alkyl fluoride in 46% NMR yield, presumably due to elimination of the fluorosulfate intermediate (**3**). Two other alkyne-containing primary alkyl alcohol derivatives, **1r** and **1s**,

afforded **2r** and **2s** in 54% and 75% NMR yields. Allylic alcohol gave 3-fluoroprop-1-ene (**2t**) in 46% NMR yield.

Benzyl alcohols were generally not effective under these reaction conditions, possibly due to the competing reaction between the base and activated fluorosulfate intermediate **3**.[32] Only a benzyl alcohol derivative with an electron withdrawing group, trifluoromethyl derivative **1k**, was converted to the corresponding benzylic fluoride (**2k**). Pyridinyl derivative **1l** was converted to the corresponding alkyl fluoride (**2l**) in 20% NMR yield. Under the optimized conditions, steroid **2u** was isolated in a low yield due to the formation of **2u'**. By decreasing the amount of base to 1 equivalent, **2u** could be isolated in 66% yield and only 13% yield of the undesired side product was obtained. The reaction is not expected to be tolerant of phenols or carboxylic acids as they are known to rapidly convert to fluorosulfates [33] and acyl fluorides, [34] respectively, in the presence of SO_2F_2.

Table 3

Deoxyfluorination substrate scope for primary alcohols.

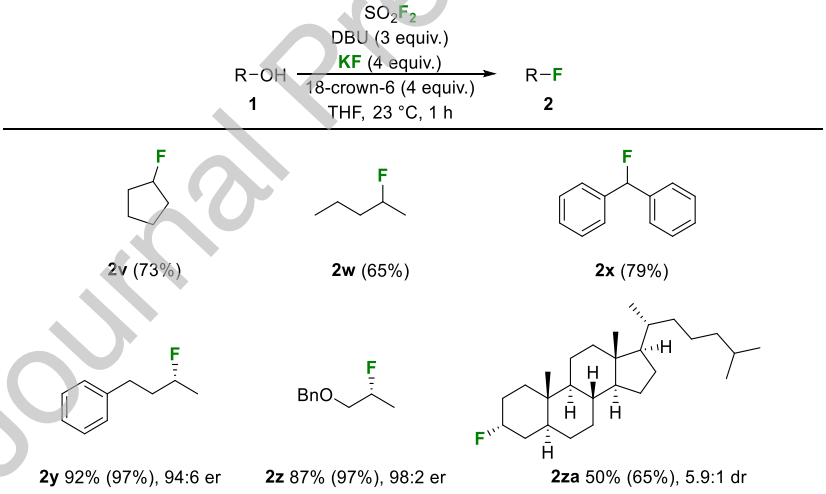


[a] Isolated yields of acyl fluorides are reported using 0.6 mmol of alcohol **1** following the reversed addition protocol (general procedure C). [19]F NMR yields are reported in parentheses. [b]1 mmol scale. [c]1 gram-scale (10 mmol). [d]Due to the volatility of the product, some residual solvent remained after purification. The reported yield has been corrected for these minor impurities. [e]1 equiv. of base.

We next examined the scope of secondary alcohols using our new deoxyfluorination methodology. Gratifyingly, cyclopentanol (**1v**) was efficiently transformed into the volatile alkyl fluoride **2v** in 73% NMR yield. Linear secondary alcohol **1w** could also be converted to the corresponding alkyl fluoride (**2w**) in 65% NMR yield. Secondary benzylic alcohol **1x** was also an effective substrate, affording corresponding alkyl fluoride **2x** in 79% NMR yield.

We next examined whether stereodefined secondary alcohols were viable substrates for the optimized reaction conditions. Chiral secondary alcohol **1y** could be converted to the corresponding alkyl fluoride **2y** in very high yield relative to **2**w. Similarly, the reaction with enantiopure alcohol **1z** afforded very high yields of alkyl fluoride **2z** in 98:2 er. A more complex substrate, 3β-hydroxy-5-cholestene (**1za)**, afforded the desired alkyl fluoride **2za** in 50% isolated yield and 5.9:1 dr. Comparison to the literature confirms that the major product results from net inversion of the stereocenter.[35]

Table 4
Deoxyfluorination substrate scope for secondary alcohols.[a]



[a] Isolated yields of acyl fluorides are reported using 0.6 mmol of alcohol **1** following the reversed addition protocol (general procedure C). [19]F NMR yields are reported in parentheses.

3. Conclusion

We have developed a practical SO_2F_2-mediated deoxyfluorination methodology that affords good to high yields of the desired alkyl fluoride products at room temperature under atmospheric pressure in only an hour. This study is complementary to our previously developed methods, which did not work well for deoxyfluorination.[19,20] The critical aspect of this new work is a

combination of the reversed addition conditions and the specific choice of fluoride salt. The reverse addition strategy, where the alcohol was slowly added to a pre-concentrated solution of sulfuryl fluoride, effectively promoted the deoxyfluorination of primary alcohols with a range of functionalities. Furthermore, the reaction was successfully applied to both symmetric and chiral secondary alcohols, with the latter formed in good enantioselectivity and a net inversion of configuration. Finally, the method was applied to a steroid derivative, which afforded good yield and 5.9:1 dr with the major product resulting from net inversion of the stereocenter.

4. Experimental

4.1. General information

All chemicals were from commercial sources AK Scientific, Alfa Aesar, Fisher Chemical, Oakwood Chemical, Sigma-Aldrich, and Tokyo Chemical Industry (TCI). All reactions were performed in flame-dried disposable scintillation 3.70 mL (15 x 45 mm), 20 mL (28 x 61 mm), or 30 mL (25 x 95 mm) glass vials under nitrogen atmosphere. 1,1'-sulfonyldiimidazole (SDI) was prepared to synthesize sulfuryl fluoride (SO_2F_2) following the procedure reported by De Borggraeve. [18] Screw caps and PTFE/Silicone septa (13 mm x 0.060" and 22 mm x 0.060") were from Chemglass Life Sciences. Polyethylene tubing 100 ft (I.D. 1.57 mm, O.D. 1.14 mm) was from Becton Dickinson. KDS 100 Legacy Single Syringe Infusion Pump was from KD Scientific. Disposable 1 mL syringes (I.D. 4.69 mm), 3 mL Syringes (I.D. 9.65 mm), 5 mL Syringes (I.D. 12.45 mm), and 10 mL Syringes (I.D. 15.9 mm) were from Norm-Ject.

Tetrahydrofuran (THF) was obtained from Sigma-Aldrich, dried by a solvent purification system (SPS), or distilled over sodium and benzophenone. N,N-Dimethylformamide (DMF), dioxane, and ethyl acetate (EtOAc) were dried over 4 Å molecular sieves. Acetonitrile (ACN) and dichloromethane (DCM) were obtained from a solvent purification system (SPS)

Flash column chromatography was performed using Silicycle F60 silica: 230-400 mesh (40-63 μm) silica. TLC's were run on Merck Kieselgel 60 F_{254} aluminum sheets and visualized by UV fluorescence (254 nm) then one of the following: KMnO4, ninhydrin, *p*-anisaldehyde, bromocresol green.

Infrared (IR) spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer or a Perkin Elmer Frontier FT-IR. The spectra are reported in cm^{-1}.

High resolution mass spectra (HRMS) were recorded on a Waters or Micromass LCT spectrometer or a JEOL AccuTOF-GC spectrometer.

Chiral high performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260 infinity LC system with commercially available Daicel Chiralcel® OD-3 (250 x 4.6 mm) chiral columns, with products detected using UV absorbance at 210 nm.

Optical rotations were measured on a Jasco P-2000 polarimeter. The reported value $[\alpha]_D^{23}$ (concentration in g/100 mL, $CHCl_3$) was the average of five runs.

NMR spectra were obtained on a Bruker AV-300 or AV-400 spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm). ^{19}F NMR chemical shifts were referenced to Trichlorofluoromethane ($CFCl_3$, ^{19}F: δ = 0.00 ppm). NMR yields were determined by ^{19}F NMR using a relaxation delay (or recycle delay) of 40 seconds to ensure complete relaxation of all fluorine nuclei. α,α,α-Trifluorotoluene ($PhCF_3$, ^{19}F: δ = -63.72 ppm) was used as an internal standard, unless otherwise specified. The aliquot is diluted with $CDCl_3$ in the quantitative NMR analysis. ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m), doublet of triplets (dt), doublet of quartets (dq), triplet of doublets (td), triplet of triplets (tt), triplet of quartets (tq) and doublet of doublet of triplets (ddt). Coupling constants (J) are reported in Hz. Assignment of peaks was done based on the chemical shifts, multiplicities, and integrals of the peaks. Note: Impurities in the 0.8-1.3 ppm range are visible on the spectra.

CAUTION: Sulfuryl fluoride is a toxic gas and must always be handled with care in a well ventilated fumehood. The excess sulfuryl fluoride can be quenched by passing it through a basic aqueous medium.

4.2. Base and additive optimization of sulfuryl fluoride-mediated deoxyfluorinations

General procedure A: Two 20 mL vials equipped with magnetic stir-bars were capped with septum-fitted vial caps connected by a polyethylene tube. Vial A was charged with SDI (2.64 mmol, 4.4 equiv) and anhydrous KF (7.02 mmol, 11.7 equiv). To vial B was added 3-Phenyl-1-propanol **1a** (0.6 mmol, 1 equiv), DBU (0.9 mmol, 1.5 equiv), DMF (1.8 mL), and additives. The polyethylene tube in vial B was immersed into the solution and then to vial A was added TFA (1.5 mL). Vigorous bubbling of SO_2F_2 and fuming were observed in vial B for a few minutes and when the bubbling subsided, vial B was vented via a needle for 1-2 minutes (this triggered more bubbling of SO_2F_2 through the solution). The tube and needle were then removed and the mixture in vial B was allowed to stir at ambient temperature for 10 minutes. An aliquot was taken for quantitative ^{19}F NMR analysis. Caution: Reaction vials can become pressurized during the generation of SO_2F_2. Note: we have not observed a difference in reactivity when different needle diameters were utilized. As the density of SO_2F_2 is about 3 times larger than the density of air, any air seepage had a minimal impact on the reaction.

4.3. Optimization of the fluoride additive using reversed addition conditions

General procedure B: A 3.7 mL vial A and a 30 mL vial B were equipped with magnetic stir-bars, were capped with septum-fitted vial caps and connected by a polyethylene tube. Under nitrogen, Vial A was charged with SDI (2.77 mmol, 9.22 equiv) and anhydrous KF (7.36 mmol, 24.5 equiv). To vial B was added THF (6 mL). A 3 mL syringe filled with excess of TFA (1.50 mL, 19.6 mmol) was added into the vial A at a rate of 9 mL/hr by a syringe pump. The tube in vial B was immersed into the solution after the first bubbles of SO_2F_2 appeared. Once bubbling of SO_2F_2 subsided, into vial B was inserted an empty balloon to increase the bubbling rate. When the bubbling had almost stopped, 6M NaOH (1.5 mL) was slowly added into vial A. After completing generation of SO_2F_2, the tube was removed. Without opening the

vial B, trifluorotoluene (1 equiv) was added by a syringe into vial B as an internal standard. Without opening the vial B, an aliquot was taken by a syringe for quantitative ^{19}F NMR analysis to confirm no TFA contaminant and quantify the amount of SO_2F_2 (Note: the chemical shift of the two equivalent fluorines of SO_2F_2 appear at 33.8 ppm. Typically, about 1.5 to 2.5 equivalents of SO_2F_2 were calculated to be in THF prior to addition of the other reagents). KF (4 equiv) and 18-crown-6 (4 equiv) were added into vial B. A reaction mixture of 3-Phenyl-1-propanol **1a** (0.3 mmol, 1 equiv), THF (2.0 mL), and DBU (0.9 mmol, 3 equiv) were added into vial B at 4 mL/hr by a syringe pump. An aliquot was taken for quantitative ^{19}F NMR analysis after stirring for one hour (note: the amount of the aliquot is less than 0.1 mL which is less than 2% of the reaction solution). Caution: Reaction vials can become pressurized during the generation of SO_2F_2. Note: Picture of the assembly is available in the SI.

4.4. 0.6 mmol scale one-pot deoxyfluorination of alcohols

General procedure C: A 20 mL vial A and a 30 mL vial B were equipped with magnetic stir-bars, were capped with septum-fitted vial caps and connected by a polyethylene tube. Under nitrogen, Vial A was charged with SDI (5.53 mmol, 9.22 equiv) and anhydrous KF (14.7 mmol, 24.5 equiv). To vial B was added THF (12 mL). A 3 mL syringe filled with excess of TFA (3.0 mL, 39.2 mmol) was added into the vial A at a rate of 9 mL/hr by a syringe pump. The tube in vial B was immersed into the solution after the first bubbles of SO_2F_2 appeared. Once bubbling of SO_2F_2 subsided, into vial B was inserted an empty balloon to increase the bubbling rate. When the bubbling had almost stopped, 6M NaOH (3.0 mL) was slowly added into vial A. After completing generation of SO_2F_2, the tube was removed. Without opening the vial B, trifluorotoluene (1 equiv) was added by a syringe into vial B as an internal standard. Without opening the vial B, an aliquot was taken by a syringe for quantitative ^{19}F NMR analysis to confirm no TFA contaminant and quantify the amount of SO_2F_2 (Note: the chemical shift of the two equivalent fluorines of SO_2F_2 appear at 33.8 ppm. Typically, about 1.5 to 2.5 equivalents of SO_2F_2 were calculated to be in THF prior to addition of the other reagents). KF (4 equiv) and 18-crown-6 (4 equiv) were added into vial B. A reaction mixture of 3-Phenyl-1-propanol **1a** (0.6 mmol, 1 equiv), THF (4.0 mL), and DBU (1.8 mmol, 3 equiv) were added into vial B at 4 mL/hr by a syringe pump. An aliquot was taken for quantitative ^{19}F NMR analysis after stirring for one hour (note: the amount of the aliquot is less than 0.1 mL which is less than 1% of the reaction solution). Caution: Reaction vials can become pressurized during the generation of SO_2F_2. Note: Picture of the assembly is available in the SI.

(3-fluoropropyl)benzene (2a)

Compound **2a** was prepared on 0.6 mmol, 1.0 mmol and 10 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% pentane as eluent) to leave (3-fluoropropyl)benzene as a colorless liquid (55.0 mg, 66% for 0.6 mmol scale and 91.1 mg, 66% for 1.0 mmol scale, 100.8 mg, 73% for 10 mmol scale). The spectroscopic data were consistent with those previously published. [36] ^1H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 2H), 7.25 – 7.14 (m, 3H), 4.54 (t, *J* = 6.0 Hz, 1H), 4.38 (t, *J* = 6.0 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.13 – 1.90 (m, 2H).$^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 141.3, 128.6, 128.6, 126.2, 83.3 (d, *J* = 164.7 Hz), 32.2 (d, *J* = 19.8 Hz), 31.5 (d, *J* = 5.4 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -220.4 (tt, *J* = 47.4, 25.2 Hz).

1-Bromo-2-(2-fluoroethyl)benzene (2b)

Compound **2b** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-bromo-2-(2-fluoroethyl)benzene as a colorless liquid (85.3 mg, 70% yield contaminated with approx. 2% petroleum ether leading to 82.8 mg, 68% corrected yield). The spectroscopic data were consistent with those previously published. [37] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.18 – 7.06 (m, 1H), 4.66 (dt, *J* = 47.0, 6.5 Hz, 2H), 3.18 (dt, *J* = 22.5, 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 136.5 (d, *J* = 6.3 Hz), 133.1, 131.5, 128.6, 127.7, 124.7, 82.6 (d, *J* = 169.2 Hz), 37.2 (d, *J* = 21.0 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -217.2 (td, *J* = 46.9, 23.0 Hz).

1-bromo-3-(2-fluoroethyl)benzene (2c)

Compound **2c** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-bromo-3-(2-fluoroethyl)benzene as a colorless liquid (85.1 mg, 70%).^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.43 – 7.34 (m, 2H), 7.23 – 7.13 (m, 2H), 4.62 (dt, *J* = 47.0, 6.4 Hz, 2H), 2.98 (dt, *J* = 24.2, 6.3 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 139.7 (d, *J* = 5.4 Hz), 132.1, 130.2, 130.0, 127.8, 122.7, 83.7 (d, *J* = 169.6 Hz), 36.6 (d, *J* = 20.7 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -216.5 (td, *J* = 47.2, 23.6 Hz). HRMS-EI (m/z) calculated for C_8H_8BrF: 201.9793. Found: 201.9799. IR (cm^{-1}): 3064, 2966, 1568, 1473, 1428.

1-(2-fluoroethyl)-4-nitrobenzene (2d)

Compound **2d** was prepared on 0.6 mmol scale following a modification to general procedure C (1 equiv of base). The crude product was purified by column chromatography on silica (5% ethyl acetate in petroleum ether as eluent) to leave 1-(2-fluoroethyl)-4-nitrobenzene as a pale yellow solid (78.9 mg, 57%). The spectroscopic data were consistent with those previously published. [38] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.24 – 8.13 (m, 2H), 7.47 – 7.36 (m, 2H), 4.77 (t, *J* = 6.0 Hz, 1H), 4.61 (t, *J* = 6.0 Hz, 1H), 3.16 (t, *J* = 6.0 Hz, 1H), 3.08 (t, *J* = 6.0 Hz, 1H).^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 147.1, 145.2 (d, *J* = 4.0 Hz), 130.0, 123.9, 83.2 (d, *J* = 170.3 Hz), 36.8 (d, *J* = 20.7 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -217.4 (tt, *J* = 47.0, 25.8 Hz).

1-(benzyloxy)-4-(2-fluoroethyl)benzene (2e)

Compound **2e** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-(benzyloxy)-4-(2-fluoroethyl)benzene as a colorless liquid (78.9 mg, 57%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 – 7.34 (m, 5H), 7.28 – 7.15 (m, 2H), 7.07 – 6.94 (m, 2H), 5.11 (s, 2H), 4.65 (dt, *J* = 47.2, 6.6 Hz, 2H), 3.02 (dt, *J* = 22.8, 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 157.9, 137.3, 130.2, 129.6 (d, *J* = 6.6 Hz), 128.8, 128.2, 127.7, 115.2, 84.5 (d, *J* = 168.9 Hz), 70.2, 36.3 (d, *J* = 20.3 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -215.1 (td, *J* = 47.0, 23.0 Hz). HRMS-EI (m/z) calculated for $C_{15}H_{15}FO$: 230.1107. Found: 230.1097. IR (cm^{-1}): 3035, 2919, 2247, 1610, 1455, 1237.

4-(2-fluoroethyl)-1,2-dimethoxybenzene (2f)

Compound **2f** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (10% ethyl acetate in petroleum ether as eluent) to leave 4-(2-fluoroethyl)-1,2-dimethoxybenzene as a colorless liquid (62.8 mg, 57%). The spectroscopic data were consistent with those previously published. [32] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.91 – 6.60 (m, 3H), 4.61 (dt, *J* = 47.2, 6.6 Hz, 2H), 3.87 (d, *J* = 4.7 Hz, 6H), 2.96 (dt, *J* = 23.3, 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 149.1, 148.0, 129.8 (d, *J* = 6.4 Hz), 121.0, 112.4, 111.5, 84.4 (d, *J* = 168.8 Hz), 56.0, 56.0, 36.6 (d, *J* = 20.2 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -215.4 (tt, *J* = 47.0, 23.4 Hz).

2-(2-fluoroethyl)-1,3,5-trimethylbenzene (2g)

Compound **2g** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 2-(2-fluoroethyl)-1,3,5-trimethylbenzene as a colorless liquid (46.1 mg, 46%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.89 (s, 2H), 4.52 (dt, *J* = 47.2, 7.5 Hz, 2H), 3.10 (dt, *J* = 17.2, 7.5 Hz, 2H), 2.34 (s, 6H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 137.1, 136.3, 130.0 (d, *J* = 9.5 Hz), 129.2, 82.5 (d, *J* = 170.4 Hz), 30.5 (d, *J* = 20.5 Hz), 21.0, 20.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -213.3 (tt, *J* = 47.2, 17.1 Hz). HRMS-EI (m/z) calculated for $C_{11}H_{15}F$: 166.1158. Found: 166.1155. IR (cm^{-1}): 3004, 2966, 2920, 1613, 1447.

(1-fluoropropan-2-yl)benzene (2h)

Compound **2h** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave (1-fluoropropan-2-yl)benzene as a colorless liquid (60.5 mg, 73% yield contaminated with approx. 5% petroleum ether leading to 56.4 mg, 68% corrected yield). The spectroscopic data were consistent with those previously published. [39] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 2H), 7.31 – 7.19 (m, 3H), 4.67 – 4.32 (m, 2H), 3.17 (dq, *J* = 16.7, 6.9 Hz, 1H), 1.37 (dd, *J* = 7.0, 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 142.2 (d, *J* = 6.2 Hz), 128.6, 127.4, 126.9, 88.1 (d, *J* = 173.0 Hz), 40.4 (d, *J* = 18.9 Hz), 16.9 (d, *J* = 5.7 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -217.3 (td, *J* = 47.3, 16.5 Hz).

2-(4-fluorobutyl)isoindoline-1,3-dione (2i)

Compound **2i** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (15% ethyl acetate in petroleum ether as eluent) to leave 2-(4-fluorobutyl)isoindoline-1,3-dione as a white solid (83.3 mg, 63%). The spectroscopic data were consistent with those previously published. [40] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.77 (m, 2H), 7.77 – 7.63 (m, 2H), 4.47 (dt, *J* = 47.7, 5.7 Hz, 2H), 3.73 (t, *J* = 6.8 Hz, 2H), 1.87 – 1.65 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 168.5, 134.1, 132.2, 123.4, 83.5 (d, *J* = 165.3 Hz), 37.6, 27.9 (d, *J* = 20.2 Hz), 24.7 (d, *J* = 4.9 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -219.2 (tt, *J* = 48.3, 24.6 Hz).

3-fluoropropyl 3,4-dimethylbenzoate (2j)

Compound **2j** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (3% ethyl acetate in petroleum

ether as eluent) to leave 3-fluoropropyl 3,4-dimethylbenzoate as a colorless liquid (73.5 mg, 58%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.65 (s, 2H), 7.19 (s, 1H), 4.62 (dt, *J* = 47.0, 5.5 Hz, 2H), 4.44 (t, *J* = 6.0 Hz, 2H), 2.36 (s, 6H), 2.17 (dt, *J* = 25.5, 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 166.9, 138.2, 134.8, 130.1, 127.4, 80.8 (d, *J* = 165.4 Hz), 60.9 (d, *J* = 5.5 Hz), 30.1 (d, *J* = 20.1 Hz), 21.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -222.4 (tt, *J* = 47.0, 25.5 Hz). HRMS-EI (m/z) calculated for $C_{12}H_{15}FO_2$: 210.1056. Found: 210.1059. IR (cm^{-1}): 3014, 2969, 1716, 1609, 1455, 1308, 1209.

1-(fluoromethyl)-4-(trifluoromethyl)benzene (2k)

Compound **2k** was prepared on 1.0 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 42%. The spectroscopic data were consistent with those previously published. [41] ^{19}F NMR (377 MHz, Chloroform-*d*) δ -65.8, -216.0 (t, *J* = 47.2 Hz).

4-(fluoromethyl)pyridine (2l)

Compound **2k** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 20%. The spectroscopic data were consistent with those previously published.[42] ^{19}F{^{1}H} NMR (282 MHz, Chloroform-*d*) δ -222.5.

1-bromo-9-fluorononane (2m)

Compound **2m** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-bromo-9-fluorononane as a colorless liquid (77.3 mg, 57%). The spectroscopic data were consistent with those previously published.[43] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.43 (dt, *J* = 47.4, 6.2 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.85 (p, *J* = 6.9 Hz, 2H), 1.67 (ddt, *J* = 24.9, 8.0, 6.1 Hz, 2H), 1.48 – 1.24 (m, 10H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 84.3 (d, *J* = 164.1 Hz), 34.1, 32.9, 30.5 (d, *J* = 19.3 Hz), 29.4, 29.2, 28.8, 28.3, 25.3 (d, *J* = 5.5 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -218.5 (tt, *J* = 47.2, 25.0 Hz).

1-fluorodecane (2n)

Compound **2n** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-fluorodecane as a colorless liquid (52.3 mg, 54%). The spectroscopic data were consistent with those previously published. [44,45] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.43 (dt, *J* = 47.4, 6.2 Hz, 2H), 1.68 (dt, *J* = 24.6, 6.9 Hz, 2H), 1.44 – 1.26 (m, 14H), 0.89 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 84.4 (d, *J* = 164.0 Hz), 32.0, 30.7, 30.4 (d, *J* = 1.9 Hz), 29.6, 29.4 (d, *J* = 3.9 Hz), 25.3 (d, *J* = 5.6 Hz), 22.8, 22.7, 14.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -218.4 (tt, *J* = 48.0, 24.6 Hz).

1-fluorooctadecane (2o)

Compound **2o** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 1-fluorooctadecane as a white solid (98.3 mg, 60%). The spectroscopic data were consistent with those previously published. [9] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.44 (dt, *J*

= 47.4, 6.2 Hz, 2H), 1.68 (ddt, *J* = 24.8, 8.0, 6.2 Hz, 2H), 1.48 – 1.14 (m, 30H), 0.93 – 0.84 (m, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, Chloroform-*d*) δ 84.4 (d, *J* = 164.0 Hz), 32.1, 30.5 (d, *J* = 19.3 Hz), 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 25.3 (d, *J* = 5.5 Hz), 22.8, 14.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -218.3 (tt, *J* = 47.5, 24.6 Hz).

11-fluoroundec-1-ene (2p)

Compound **2p** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 11-fluoroundec-1-ene as a colorless liquid (48.1 mg, 51%). The spectroscopic data were consistent with those previously published. [46] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.14 – 4.83 (m, 2H), 4.44 (dt, *J* = 47.4, 6.2 Hz, 2H), 2.13 – 1.97 (m, 2H), 1.80 – 1.61 (m, 2H), 1.43 – 1.28 (m, 10H). $^{13}C\{^{1}H\}$ NMR (75 MHz, Chloroform-*d*) δ 139.3, 114.3, 84.4 (d, *J* = 164.0 Hz), 33.9, 30.5 (d, *J* = 19.3 Hz), 29.5, 29.3, 29.1, 29.0, 25.3 (d, *J* = 5.6 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -218.1 – -218.8 (m).

4-fluorobut-1-yne (2q)

Compound **2q** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 46%. $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -216.5.

3-fluoroprop-1-yne (2r)

Compound **2r** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 54%. The spectroscopic data were consistent with those previously published.[47] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -218.7.

5-fluoropent-1-yne (2s)

Compound **2s** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 75%. The spectroscopic data were consistent with those previously published.[48] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -222.9.

3-fluoroprop-1-ene (2t)

Compound **2t** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 46%. The spectroscopic data were consistent with those previously published.[47] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -216.9.

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-(2-fluoroacetyl)-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (2u)

Compound **2u** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (10% ethyl acetate in dichloromethane as eluent) to leave (8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-(2-fluoroacetyl)-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one as a white solid (65.5 mg, 31%). Using 1 equivalent base, a white solid (137.1 mg, 66%) was obtained. The spectroscopic data were consistent with those previously published. [49] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.73 (s, 1H), 5.36 (dd, *J* = 47.9, 17.0 Hz, 1H), 5.09 (dd, *J* = 47.7,

17.0 Hz, 1H), 2.82 – 2.68 (m, 1H), 2.51 – 2.23 (m, 4H), 2.09 – 1.99 (m, 1H), 1.94 – 1.28 (m, 12H), 1.19 (s, 3H), 1.13 – 0.91 (m, 2H), 0.74 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, Chloroform-*d*) δ 206.1 (d, *J* = 13.0 Hz), 199.7, 171.0, 124.1, 90.0, 85.2 (d, *J* = 181.0 Hz), 53.4, 50.6, 48.6, 38.7, 35.9, 35.7, 35.0, 34.0, 32.9, 32.1, 30.5, 23.8, 20.7, 17.5, 15.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -231.4 (t, *J* = 47.8 Hz).

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-oxetane]-3,3'(2*H*)-dione (2u')

Compound **2u'** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (10% ethyl acetate in dichloromethane as eluent) to leave (8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-(2-fluoroacetyl)-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one as a white solid (101.7 mg, 52%). Using 1 equivalent base, a white solid (26.2 mg, 13%) was obtained. The spectroscopic data were consistent with those previously published. [49] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.71 (s, 1H), 5.03 (d, *J* = 14.7 Hz, 1H), 4.91 (d, *J* = 14.7 Hz, 1H), 2.43 – 2.22 (m, 5H), 2.14 – 1.99 (m, 2H), 1.89 – 1.79 (m, 2H), 1.72 – 1.53 (m, 4H), 1.49 – 1.21 (m, 4H), 1.17 (s, 3H), 1.13 – 0.93 (m, 2H), 0.86 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, Chloroform-*d*) δ 206.3, 199.5, 170.8, 124.1, 118.6, 85.8, 53.2, 50.3, 48.5, 38.7, 35.8, 35.5, 34.0, 33.4, 32.8, 32.0, 30.5, 24.5, 20.5, 17.6, 13.9. HRMS-EI (m/z) calculated for $C_{21}H_{28}O_3$: 328.2038. Found: 328.2051.

fluorocyclopentane (2v)

Compound **2v** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 73% with, while 65% was obtained without using KF and 18-crown-6. The spectroscopic data were consistent with those previously published. [35,50] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -170.9.

2-fluoropentane (2w)

Compound **2w** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 65%. The spectroscopic data were consistent with those previously published. [47] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -173.5.

(fluoromethylene)dibenzene (2x)

Compound **2x** was prepared on 0.6 mmol scale following the general procedure C. The ^{19}F NMR spectroscopy yield of the desired product was 79%. The spectroscopic data were consistent with those previously published. [51–53] $^{19}F\{^{1}H\}$ NMR (377 MHz, Chloroform-*d*) δ -166.7.

(*R*)-(3-fluorobutyl)benzene (2y)

Compound **2y** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave (*R*)-(3-fluorobutyl)benzene as a colorless liquid (83.8 mg, 92%). The spectroscopic data were consistent with those previously published. [45,54] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 2H), 7.20 (dt, *J* = 9.8, 3.1 Hz, 3H), 4.84 – 4.49 (m, 1H), 2.89 – 2.59 (m, 2H), 2.12 – 1.68 (m, 2H), 1.35 (dd, *J* = 23.9, 6.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, Chloroform-*d*) δ

141.6, 128.6, 126.1, 90.2 (d, *J* = 164.9 Hz), 38.8 (d, *J* = 20.9 Hz), 31.5 (d, *J* = 4.8 Hz), 21.1 (d, *J* = 22.7 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -174.3 – -175.0 (m). $[\alpha]_D^{23}$ = –16.3 (c 1.4, $CHCl_3$, 94% ee) HPLC: Chiralcel® OD-3, Hexane = 100%, Flow rate = 0.6 mL/min, UV = 210 nm, t_R (minor) = 12.5 min and t_R (major) = 12.8 min.

(*R*)-((2-fluoropropoxy)methyl)benzene (2z)

Compound **2z** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (30% dichloromethane in petroleum ether as eluent) to leave (*R*)-((2-fluoropropoxy)methyl)benzene as a colorless liquid (88.2 mg, 87%). The spectroscopic data were consistent with those previously published. [55] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 5.00 – 4.70 (m, 1H), 4.60 (d, *J* = 1.2 Hz, 2H), 3.74 – 3.45 (m, 2H), 1.35 (dd, *J* = 23.6, 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 138.1, 128.6, 127.9, 127.8, 89.7 (d, *J* = 168.2 Hz), 73.6, 73.2 (d, *J* = 21.9 Hz), 17.6 (d, *J* = 22.4 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -179.8 (tq, *J* = 47.3, 23.7 Hz). $[\alpha]_D^{23}$ = –3.2 (c 1.2, $CHCl_3$, 95% ee) HPLC: Chiralcel® OD-3, Hexane : Propan-2-ol = 97% : 3%, Flow rate = 1.0 mL/min, UV = 210 nm, t_R (major) = 5.1 min and t_R (minor) = 6.5 min.

3α-Fluoro-5α-cholestane (2za)

Compound **2za** was prepared on 0.6 mmol scale following the general procedure C. The crude product was purified by column chromatography on silica (100% petroleum ether as eluent) to leave 3α-Fluoro-5α-cholestane as a white solid (117.9 mg, 51%). The spectroscopic data were consistent with those previously published. [35] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.80 (d, *J* = 48.5 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.90 – 1.84 (m, 1H), 1.84 – 1.77 (m, 1H), 1.70 – 1.61 (m, 2H), 1.53 (s, 7H), 1.41 – 1.19 (m, 10H), 1.11 (td, *J* = 14.0, 12.9, 6.8 Hz, 6H), 1.05 – 0.96 (m, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H), 0.64 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 89.7 (d, *J* = 165.6 Hz), 56.6, 56.4, 54.2, 42.7, 40.1, 39.7, 39.5, 36.3, 35.9, 35.8, 35.6, 34.1 (d, *J* = 21.1 Hz), 32.5, 32.1, 28.5, 28.4, 28.1, 27.2 (d, *J* = 22.1 Hz), 24.3, 24.0, 23.0, 22.7, 20.9, 18.8, 12.2, 11.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -178.7 – -183.6 (m).

4.4. Synthesis of alcohols

2-(4-hydroxybutyl)isoindoline-1,3-dione (1i)

4-amino-1-butanol (10 mmol, 1 equiv.), phthalimide (20 mmol, 2 equiv.) and iron (III) nitrate nonahydrate (0.5 mmol, 0.05 equiv.) were suspended in toluene (10 mL). The resulting reaction mixture was stirred under reflux for 17 hours, then allowed to cool down, diluted with ethyl acetate (20 mL) and filtered through celite. The filtrate was concentrated under reduced pressure and the resulting residue was diluted with 3% MeOH/DCM. The undissolved solid (phthalimide) was filtered off and the product **1i** was isolated by flash column chromatography (3% to 5% MeOH/DCM) as a straw-coloured solid (1.69 g, 76% yield). The spectroscopic data match a literature report. [56] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 2H), 7.78 – 7.66 (m, 2H), 3.80 – 3.65 (m, 4H), 1.88 – 1.73 (m, 2H), 1.71 (s, 1H), 1.69 – 1.55 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.6, 134.0, 132.2, 123.3, 62.3, 37.8, 29.9, 25.2.

3-hydroxypropyl 3,5-dimethylbenzoate (1j)

A solution of propane-1,3-diol (45 mmol, 3 equiv.) and Et_3N (30 mmol, 2 equiv.) in DCM (75 mL) was cooled down to 0 °C. To the mixture was added 3,5-dimethylbenzoyl chloride (15 mmol, 1 equiv.) dropwise over 5 minutes. The mixture was warmed up to room temperature and allowed to stir for 17 hours. The solution was transferred to a separatory funnel, diluted with 75 mL of water and the layers were separated. The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organics were washed with brine (75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The product **1j** was isolated via flash column chromatography (50% ethyl acetate/hexanes) as a clear oil (1.73 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.15 (s, 1H), 4.43 (t, *J* = 6.2 Hz, 2H), 3.75 (t, *J* = 6.1 Hz, 2H), 2.89 (bs, 1H), 2.32 (s, 6H), 1.98 (p, *J* = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.4, 138.0, 134.7, 129.9, 127.3, 61.8, 59.0, 31.9, 21.1. LRMS-ESl (m/z): 231.2 $[M+Na]^+$.

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Declaration of Competing Interest

The authors declare no competing financial interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version

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