

# Improved conditions for the synthesis of tertiary fluorides using a $\text{KF}/\text{H}_2\text{SO}_4$ combination.

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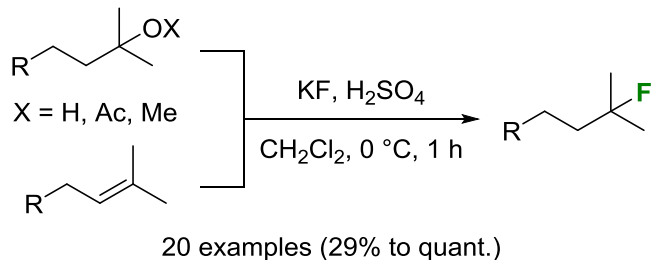
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## ABSTRACT:

In this paper, we report the deoxyfluorination of tertiary alcohol using a simple combination of potassium fluoride and sulfuric acid. These cheap and widely available reagents allow for the synthesis of tertiary fluorides in good to excellent yields. Extension of the reaction to other functional groups such as alkenes, acetates and ethers have also been studied.

**KEYWORDS:** Deoxyfluorination, Hydrofluorination, Potassium fluoride, Alcohol,  
Alkenes

## GRAPHICAL ABSTRACT:



- Simple purification
- Short reaction time
- Cheap and readily available reagents

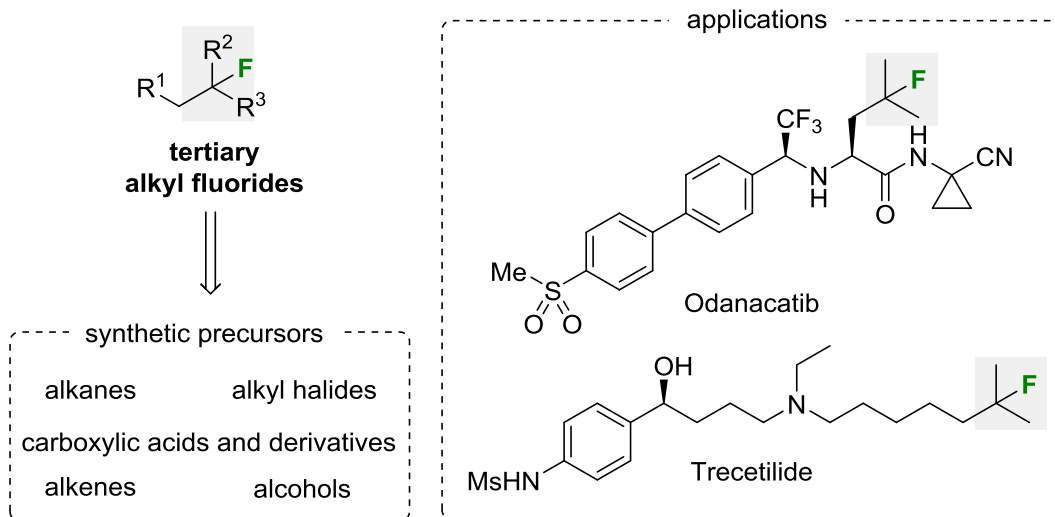
## 1. Introduction

Organofluorine compounds display interesting applications in a wide range of industry [1]. Notably, more than 20% of all FDA-approved drugs contain at least one fluorine atom [2]. While fluoroarenes remain the dominating functional group amongst fluorinated pharmaceuticals, other motifs are also present [2a]. One of them is the tertiary alkyl fluoride, which can be found in compounds such as Odanacatib [3] or Trecetilide [4] (Scheme 1a). Although this motif can be obtained from many precursors such as alkanes [5], alkenes [6], halides [7], carboxylic acids [8], as well as others [9] (Scheme 1a), there is a particular interest in the deoxyfluorination reaction, that is substituting an alcohol by a fluoride [10]. This is due to the great commercial availability of alcohol-containing molecules, as well as the ease of preparation of this functional group. Most of these transformations are done using deoxyfluorination reagents that are based on the S–F bond, such as the traditional DAST and DeoxoFluor or the more recently developed XtalFluor-E [11], PyFluor [12], AlkylFluor [13] and Fluolead [14]. Even though these reagents work very well with primary and secondary alcohols, they tend to give limited

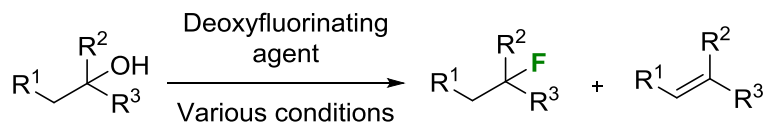
yields for tertiary alcohols, mainly due to the formation of the alkene through an elimination side reaction (Scheme 1b). Alternative reactions have been developed over the last few years in an effort to solve this issue [15]. We have also recently reported a direct ionic deoxyfluorination reaction to obtain tertiary fluorides using a combination of potassium bifluoride and methanesulfonic acid (Scheme 1c) [16]. Notably, the elimination products, i.e. the corresponding alkenes, were not detected under the reaction conditions. In an effort to make this reaction potentially applicable to radiofluorination [17], we have investigated the use of potassium fluoride [18], one of the most common  $^{18}\text{F}$  source for nucleophilic fluorination, and the results are reported herein (Scheme 1d).

## Scheme 1. Tertiary alkyl fluorides

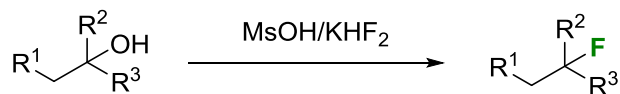
(a) Tertiary alkyl fluorides: applications and synthesis



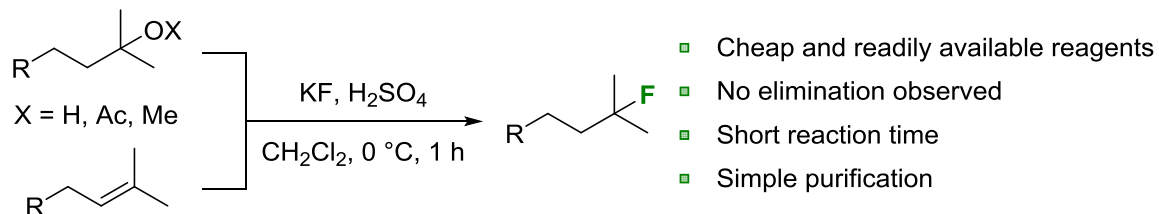
(b) Side-product of tertiary alcohol deoxyfluorination



(c) Direct deoxyfluorination of tertiary alcohols – Previous work



(d)  $\text{H}_2\text{SO}_4/\text{KF}$  promoted synthesis of tertiary fluorides – This work

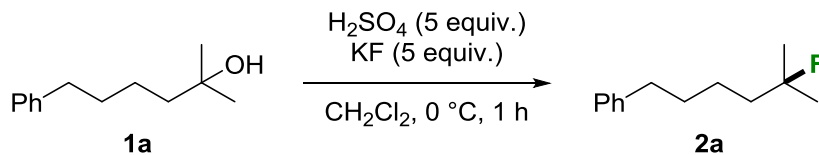


## 2. Results and discussion

Starting with the deoxyfluorination conditions used in our previous studies as the starting point,[16] we rapidly identified the optimized conditions with potassium fluoride. Indeed, using sulfuric acid (5 equiv.) and potassium fluoride (5 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 1 h afforded the desired fluoride in an excellent 95% yield (Table 1, entry 1). Surprisingly, sodium fluoride gave a very poor yield of 5% while calcium fluoride[19] gave a modest yield of 49% (Table 1, entries 2-3). An organic source of fluoride, i.e., Et<sub>3</sub>N·3HF also gave a very good yield (Table 1, entry 4), but KF was still selected as its cheaper and safer to handle. In a previous study [16] we had found that methanesulfonic acid gave excellent yield for the deoxyfluorination of alcohols in the presence of potassium bifluoride. However, in this study, it was found that this acid did not perform as well, yielding the desire product in only 45% (Table 1, entry 5). Finally, other solvents were tested, but did not perform as well (Table 1, entries 6-7).

**Table 1. Optimization of the reaction conditions for the deoxyfluorination of alcohol**

**1a.**



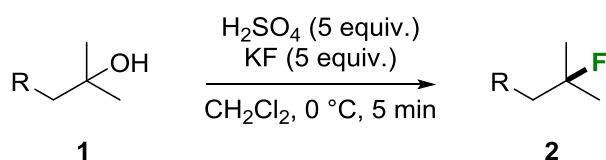
Entry	Deviation from standard conditions	Yield of <b>2a</b> (%) <sup>[a]</sup>
1	None	95
2	NaF instead of KF	5
3	CaF <sub>2</sub> instead of KF	49
4	Et <sub>3</sub> N·3HF instead of KF	85
5	MsOH instead of H <sub>2</sub> SO <sub>4</sub>	45
6	CHCl <sub>3</sub> instead of CH <sub>2</sub> Cl <sub>2</sub>	67
7	Toluene instead of CH <sub>2</sub> Cl <sub>2</sub>	21
8	5 minutes reaction time	93

[a] Estimated by <sup>19</sup>F NMR analysis of the crude mixture after workup using 2-fluoro-4-nitrotoluene as the internal standard.

We were pleased to see that the reaction proceeded in only 5 minutes without any loss in the yield (Table 1, entry 8). However, when starting to examine the scope of the reaction, we observed that some substrates, the ones bearing heteroatoms, did not show complete conversion within this very short reaction time as they reacted slower. As can

be seen in Table 2, alcohols **1a**, **1c** and **1d** afforded the corresponding fluorides in excellent conversions in only five minutes, while alcohols bearing a benzoate (**1e**) or a phthalimide (**1h**) showed significantly lower conversions of 18% and 33% respectively. Therefore, we continued this study with a one-hour reaction time for all substrates. A possible explanation for this effect might be the presence of a basic function (i.e., esters or phthalimide) that can hinder the protonation of the alcohol which slows the reaction.

**Table 2. Effect of functional groups on the conversion of alcohol to fluoride**



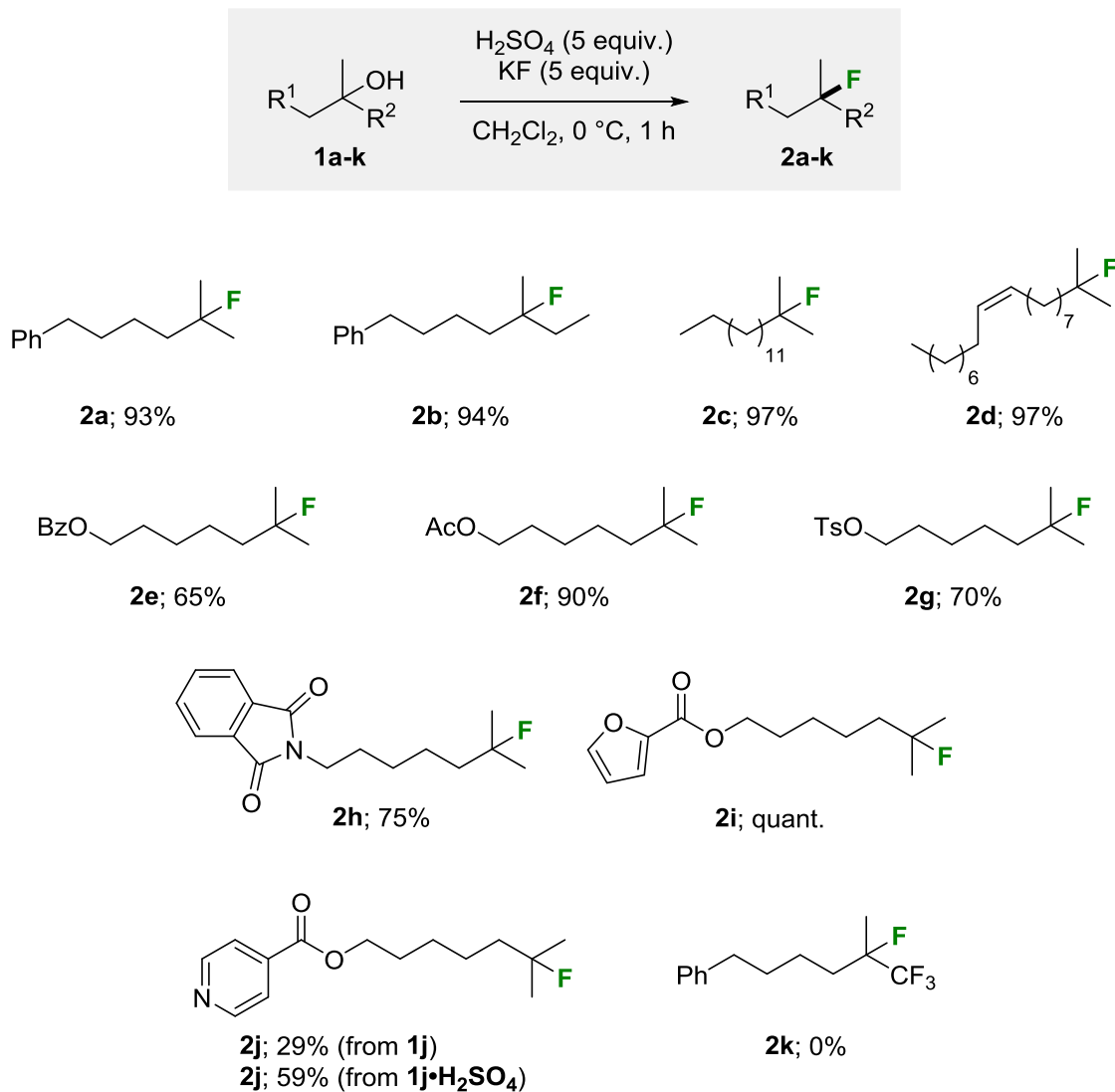
Starting alcohol	Conversion of <b>1</b> (%) <sup>[a]</sup>
<p style="text-align: center;"><b>1a</b></p>	93
<p style="text-align: center;"><b>1c</b></p>	>97
<p style="text-align: center;"><b>1d</b></p>	>97
<p style="text-align: center;"><b>1e</b></p>	18
<p style="text-align: center;"><b>1h</b></p>	33

[a] Conversion estimated by <sup>1</sup>H NMR analysis of the crude mixture based on the ratio of alcohol and fluoride as no other products were formed.

With the optimized conditions in hand, we applied them to a series of tertiary alcohols (Scheme 2) [20]. Simple alcohols such as **1a**, **1b** and **1c** afforded the corresponding fluorides **2a**, **2b** and **2c** in 93%, 94% and 97% yield respectively. The fluorination of an alcohol derived from oleic acid (**1d**) afforded product **2d** in an excellent 97% yield, without fluorination or isomerization of the 1,2-disubstituted alkene. Common protecting groups were also tested and showed good compatibility with the reaction. The benzoate (**1e**), acetate (**1f**) and tosylate (**1g**) gave good to excellent yields of the corresponding fluorides (**2e-g**). A phthalimide protected amine (**1h**) could also be used in this reaction providing **2h** in 75% yield. Heteroaromatic esters were also engaged in the reaction conditions. The tertiary fluoride containing a furan (**2i**) was obtained in a quantitative yield, while the pyridine derivative **2j** was obtained in a 29% yield. While the latter yield is low, it is worth noting that the pyridine was not compatible with our previously conditions [16]. This could be caused by a similar effect as observed in Table 2 with the pyridine acting as a buffer for the protonation. To try to circumvent this issue, we generated the pyridinium salt by adding one equivalent of sulfuric acid prior to the reaction. To our delight, we were able to obtain the corresponding fluoride **2j** in a 59% yield. However, alcohol **1k**, bearing a strong electron-withdrawing group *i.e.*, a CF<sub>3</sub>, did not convert to the desired product **2k**.



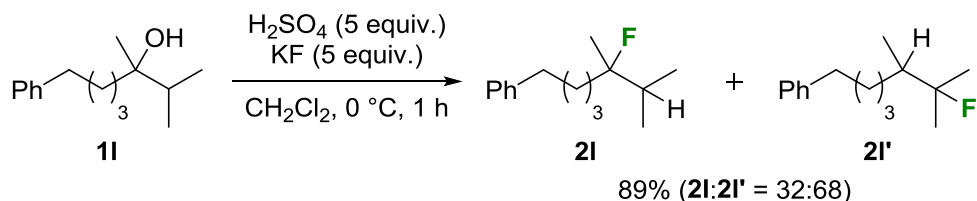
## Scheme 2. Scope of the deoxyfluorination of tertiary alcohols



Based on mechanistic studies performed in our previous study [16], we presume that the transformation first proceeds through an elimination reaction to form the alkene; followed by a hydrofluorination to give the fluorinated products. This is supported by the deoxyfluorination of alcohol **11** which produced the two regioisomers **21** and **21'** in a 32:68 ratio (Scheme 3) with an overall yield of 89%. This is explained by the formation

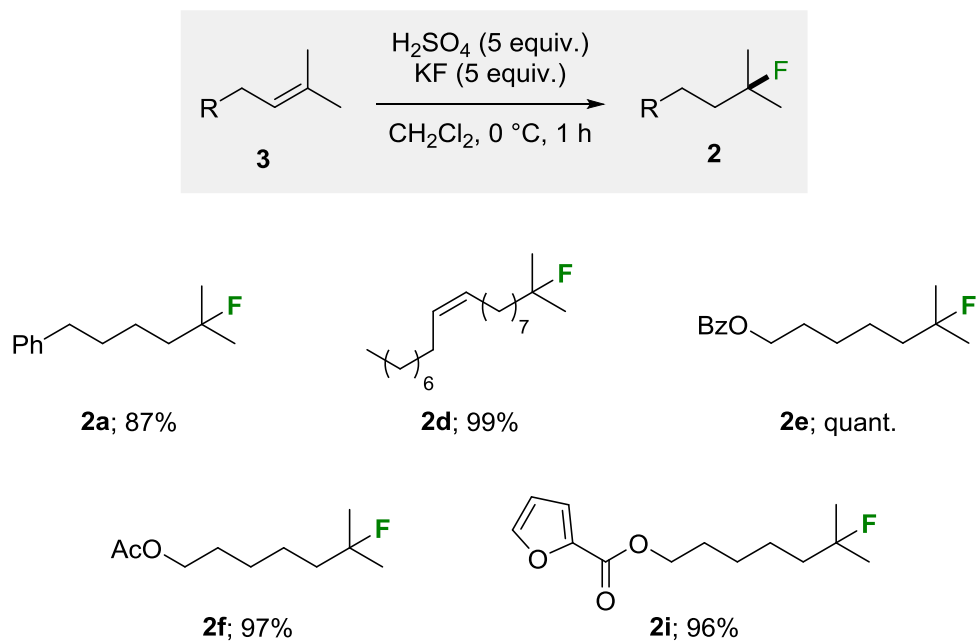
of the tetrasubstituted alkene that can produce both isomers following the hydrofluorination.

### Scheme 3. Further support for an alkene intermediate



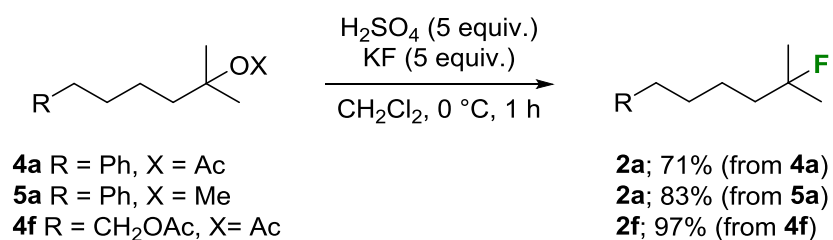
Therefore, we submitted some alkenes to our conditions to see if we could obtain the corresponding fluorides (Scheme 4). The fluorides were obtained in excellent yields, generally higher or similar to their alcohol counterparts. Notably, we were able to selectively perform the hydrofluorination of the trisubstituted alkene of **3d** in the presence of a 1,2-disubstituted alkene. These results are therefore in accordance with the proposed mechanism.

### Scheme 4. Scope of the hydrofluorination of alkenes



Finally, we could also employ these conditions for the fluorination of alcohol derivatives (Scheme 5). Tertiary acetate **4a** gave a good yield of 71%, while the tertiary methyl ether **5a** gave a very good yield of 83%. By using diacetate **4e**, we were able to prove the selectivity of our reaction for the formation of tertiary fluoride as no primary fluoride, resulting from the potential activation of the primary acetate, was observed.

### Scheme 5. Fluorination of alcohol derivatives



### 3. Conclusion

In summary, we have reported an improved method for the deoxyfluorination of tertiary alcohols that uses a KF/H<sub>2</sub>SO<sub>4</sub> as a combination of readily available reagents. Those conditions allow for the direct transformation of tertiary alcohols to the corresponding tertiary fluorides under mild conditions within 60 minutes. Trisubstituted alkenes and tertiary alcohol derivatives (acetate or methyl ether) can also be converted to the fluorides. We envision that the use of potassium fluoride for this reaction is a step forward for the direct conversion of tertiary alcohols into the <sup>18</sup>F-fluorides [8c, 21] as the short reaction time combined with the ease of purification also makes these conditions attractive for the development of a <sup>18</sup>F version of this reaction.

## 4. Experimental

### 4.1 General information

The following includes general experimental procedures, specific details for representative reactions, isolation and spectroscopic information for the new compounds prepared. All commercial compounds were used as received. Solvents were used as purchased unless stated as dry. THF, CH<sub>2</sub>Cl<sub>2</sub> and toluene were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All air and water sensitive reactions were carried out under argon atmosphere. Reactions were monitored by TLC on pre-coated plates (Silicycle silica gel 60 Å F254 230-240 mesh) and products were visualized under 254 nm UV light followed by staining with KMnO<sub>4</sub>, PMA or vanilin when appropriate. Purification by flash column chromatography was carried out on silica gel (Silicycle silica gel 60 Å F254). NMR spectra were recorded on an Agilent DD2 500 MHz spectrometer, on a Varian Inova 400 MHz spectrometer or on a Bruker Ultrashield 300 MHz in the indicated solvent at 298 K. Chemical shifts for <sup>1</sup>H and <sup>13</sup>C spectra are reported on the delta scale in ppm and were referenced to residual solvent references or internal TMS reference. For <sup>19</sup>F spectra, calibration was performed using a unified scale [22]. Resonances are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, nonet = nonaplet, m = multiplet, br. s = broad signal, app. = apparent or a combination of the above), coupling constant (Hz), integration. NMR yields were determined by <sup>19</sup>F NMR analysis of the crude mixture after work-up using 2-fluoro-4-nitrotoluene as the internal standard. High-resolution mass (HRMS) spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI). Infrared

spectra were recorded on an ABB MB3000 FT-IR spectrometer. Alcohols **1a**, **1c-1j**, alkenes **3a** and **3e**, acetate **4a** and methyl ether **5a** were synthesized according to a known procedure [16].

#### 4.2 Synthesis of starting material

**4.2.1 3-Methyl-7-phenylheptan-3-ol (1b).** A solution of ethylmagnesium chloride (2 M in Et<sub>2</sub>O, 0.75 mL, 1.5 mmol, 1.5 equiv.) was added to a solution of 6-phenylhexan-2-one (176 mg, 1 mmol, 1 equiv.) in THF (3 mL, 0.33 M) at 0 °C. The reaction was brought back to room temperature and stirred for 18 hours. A saturated solution of NH<sub>4</sub>Cl was added and the mixture was extracted with Et<sub>2</sub>O (3x). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The titled compound was obtained as a colorless oil without further purification (184 mg, 0.89 mmol, 89%). Spectroscopic data are in accordance with literature [23]. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.24 (m, 3H), 7.21 – 7.14 (m, 2H), 2.66 – 2.59 (m, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.52 – 1.43 (m, 4H), 1.43 – 1.34 (m, 2H), 1.14 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 3H).

**4.2.2 1,1,1-Trifluoro-2-methyl-6-phenylhexan-2-ol (1k).** Trimethyl(trifluoromethyl)silane (0.3 mL, 3 mmol, 1.5 equiv.) was added to a solution of 6-phenylhexan-2-one (352 mg, 2 mmol, 1 equiv) in THF (2 mL, 1M). The reaction was cooled to 0 °C in an ice bath and TBAF (1 M in THF, 0.2 mL, 0.2 mmol, 0.2 equiv) was added. The reaction was brought back to room temperature and stirred for 2 hours. The reaction was then quenched with HCl 3M and extracted with Et<sub>2</sub>O (3x). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was solubilized in methanol (2 mL) and sodium borohydride (76 mg, 2 mmol) was added to reduce the remaining

ketone. HCl 3M was added to quench the reaction and the product was extracted with Et<sub>2</sub>O (3x). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The titled compound was obtained as a colorless oil (283 mg, 1.15 mmol, 57%) after purification by silica gel chromatography (10% EtOAc/Hexanes). IR (ATR, diamond),  $\nu = 3435, 2943, 1454, 1296, 1153, 1101, 746, 698 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.29 (t,  $J = 7.7 \text{ Hz}$ , 2H), 7.22 – 7.15 (m, 3H), 2.65 (t,  $J = 7.7 \text{ Hz}$ , 2H), 1.80 – 1.76 (m, 1H), 1.73 – 1.62 (m, 4H), 1.56 – 1.45 (m, 2H), 1.33 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  142.3, 128.51, 128.49, 126.6 (q,  $J = 285.4 \text{ Hz}$ ), 125.9, 73.8 (q,  $J = 28.1 \text{ Hz}$ ), 35.9, 35.0, 31.8, 22.3, 20.2 (q,  $J = 1.9 \text{ Hz}$ ); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$  -83.1.; HRMS-ESI calcd for C<sub>13</sub>H<sub>21</sub>F<sub>3</sub>NO [M+NH<sub>4</sub>]<sup>+</sup> 264.1570 found 264.1562.

*4.2.3 2,3-Dimethyl-7-phenylheptan-3-ol (II)*. A solution of isopropylmagnesium chloride lithium chloride complex (1.3 M in THF, 1 mL, 1.3 mmol, 1.3 equiv.) was added to a solution of 6-phenylhexan-2-one (176 mg, 1 mmol, 1 equiv.) in THF (3 mL, 0.33 M) at 0 °C. The reaction was brought back to room temperature and stirred for 18 hours. A saturated solution of NH<sub>4</sub>Cl was added and the mixture was extracted with Et<sub>2</sub>O (3x). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The titled compound was obtained as a colorless oil without further purification (115 mg, 0.52 mmol, 52%). IR (ATR, diamond),  $\nu = 3475, 2937, 1497, 1452, 1371, 1076, 746 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.30 – 7.26 (m, 2H), 7.20 – 7.15 (m, 3H), 2.67 – 2.60 (m, 2H), 1.72 – 1.66 (m, 1H), 1.66 – 1.59 (m, 2H), 1.52 – 1.45 (m, 2H), 1.45 – 1.36 (m, 2H), 1.15 – 1.09 (m, 1H), 1.08 (s, 3H), 0.91 (d,  $J = 6.8 \text{ Hz}$ , 3H), 0.88 (d,  $J = 6.9 \text{ Hz}$ , 3H); <sup>13</sup>C

NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  142.8, 128.5, 128.4, 125.8, 74.8, 39.7, 36.8, 36.1, 32.3, 23.34, 23.26, 17.7, 17.1; HRMS-ESI calcd for C<sub>15</sub>H<sub>28</sub>NO [M+NH<sub>4</sub>]<sup>+</sup> 238.2165 found 238.2151.

*General procedure A: Alkene synthesis*

*para*-Toluenesulfonic acid (1 equiv.) was added to a solution of the corresponding alcohol (1 equiv.) in toluene (0.2 M). The reaction was stirred at reflux in an oil bath for 30 minutes, and then brought back to 20 °C. The reaction was diluted in Et<sub>2</sub>O and washed with a saturated aqueous solution of NaHCO<sub>3</sub> (2x). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. All alkenes are contaminated with up to 10% of the inseparable 1,1-disubstituted isomer.

*4.2.4 (Z)-2-Methylnonadeca-2,10-diene (3d)*. Following general procedure A on a 0.5 mmol scale using **1d**, the titled compound was obtained was a colorless oil (83.7 mg, 0.30 mmol, 60%) after purification by silica gel chromatography (100% hexanes). IR (ATR, diamond),  $\nu$  = 2957, 2922, 2853, 1462, 1456, 966, 887, 721 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.41 – 5.31 (m, 2H), 5.12 (t, *J* = 7.2 Hz, 1H), 2.06 – 1.92 (m, 6H), 1.69 (s, 3H), 1.60 (s, 3H), 1.35 – 1.25 (m, 20H), 0.88 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  131.3, 130.1, 130.0, 125.1, 32.8, 32.1, 30.0, 29.94, 29.91, 29.85, 29.82, 29.7, 29.5, 29.4, 28.2, 27.4, 25.9, 22.8, 17.8, 14.3; HRMS-APPI calcd for C<sub>20</sub>H<sub>38</sub> [M\*]<sup>+</sup> 278.2968 found 278.2961.

*4.2.5 6-Methylhept-5-en-1-yl acetate (3f)*. Following general procedure A on a 1 mmol scale using **1f**, the titled compound was obtained was a colorless oil (140 mg, 0.82 mmol,

82%) without further purification. IR (ATR, diamond),  $\nu = 2961, 2932, 2858, 1740, 1452, 1366, 1234, 1040, \text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.13 – 5.06 (m, 1H), 4.06 (t,  $J = 6.7$  Hz, 2H), 2.04 (s, 3H), 2.00 (q,  $J = 7.4$  Hz, 2H), 1.69 (s, 3H), 1.66 – 1.55 (m, 5H), 1.38 (p,  $J = 7.7$  Hz, 2H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 132.0, 124.3, 64.7, 28.4, 27.7, 26.3, 25.9, 21.2, 17.8; HRMS-ESI calcd for  $\text{C}_{10}\text{H}_{19}\text{O}_2$   $[\text{M}+\text{H}]^+$  171.1380 found 171.1374.

*4.2.6 6-Methylhept-5-en-1-yl furan-2-carboxylate (3i)*. Following general procedure A on a 0.66 mmol scale using **1i**, the titled compound was obtained was a colorless oil (145.3 mg, 0.65 mmol, 99%) without further purification. IR (ATR, diamond),  $\nu = 2962, 2932, 2858, 1717, 1582, 1474, 1398, 1292, 1178, 1117, 1013, 885, 760 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (dd,  $J = 1.9, 0.9$  Hz, 1H), 7.16 (dd,  $J = 3.5, 0.9$  Hz, 1H), 6.50 (dd,  $J = 3.5, 1.7$  Hz, 1H), 5.11 (tt,  $J = 7.2, 1.5$  Hz, 1H), 4.30 (t,  $J = 6.7$  Hz, 2H), 2.03 (q,  $J = 7.4$  Hz, 2H), 1.83 – 1.70 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.45 (p,  $J = 7.6$  Hz, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 146.3, 145.0, 132.1, 124.2, 117.8, 111.9, 65.2, 28.4, 27.7, 26.2, 25.8, 17.8; HRMS-ESI calcd for  $\text{C}_{13}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$  223.1329 found 223.1321.

*4.2.7 6-Methylheptane-1,6-diyl diacetate (4f)*. Acetic anhydride (2.8 mL, 30 mmol, 6 equiv.), pyridine (1.2 mL, 15 mmol, 3 equiv.) and DMAP (61 mg, 0.5 mmol, 0.1 equiv) were added on a solution of 6-methylheptane-1,6-diol (730 mg, 5 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL, 0.5 M) at 0 °C. The reaction was allowed to warm back to 20 °C and stirred for 18 hours. Aqueous HCl (1 M) was added and the mixture was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced



pressure to afford the titled compound (300 mg, 1.3 mmol, 26%) as a colorless oil as well as alcohol **1e** (652 mg, 3.5 mmol, 69 %) after purification by silica gel chromatography (10% to 40% EtOAc/hexanes). Spectroscopic data are in accordance with literature [24].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.05 (t,  $J = 6.7$  Hz, 2H), 2.05 (s, 3H), 1.97 (s, 3H), 1.77 – 1.71 (m, 2H), 1.67 – 1.60 (m, 2H), 1.42 (s, 6H), 1.38 – 1.29 (m, 4H).

### 4.3 Fluorination reactions

#### *General procedure B: Fluorination of alcohols and alkenes*

Potassium fluoride (58,1 mg, 1.0 mmol, 5 equiv.) was added at 0 °C on a solution of the corresponding starting substrate (0.2 mmol) in dichloromethane (1 mL, 0.2 M) in a conical polypropylene tube (critical for the reaction to work as glass vessels completely shut down the reaction). Sulfuric acid (54  $\mu\text{L}$ , 1.0 mmol, 5 equiv.) was added dropwise and the reaction was vigorously stirred for 1 h at 0 °C. The reaction was then quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3x). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure.

4.3.1 *(5-Fluoro-5-methylhexyl)benzene (2a)*. Following general procedure B, the titled compound was obtained as a colorless oil:

From alcohol **1a** (36.1 mg, 0.186 mmol, 93%) without further purification.

From alkene **3a** (33.9 mg, 0.174 mmol, 87%) without further purification.

From acetate **4a** (27.5 mg, 0.142 mmol, 71%) after purification by silica gel chromatography (100 % hexanes).

From methyl ether **5a** (32.2 mg, 0.166 mmol, 83%) after purification by silica gel chromatography (5% EtOAc/Hexanes)

Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.25 (m, 2H), 7.22 – 7.12 (m, 3H), 2.66 – 2.59 (m, 2H), 1.69 – 1.58 (m, 4H), 1.47 – 1.38 (m, 2H), 1.33 (d,  $J = 21.5$  Hz, 6H).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.2 (app. nonet,  $J = 21.2$  Hz).

4.3.2 (5-Fluoro-5-methylheptyl)benzene (**2b**). Following general procedure B using alcohol **1b**, the desired product was obtained as a colorless oil (47.3 mg, 0.194 mmol, 94%) without further purification. IR (ATR, diamond),  $\nu = 3026, 2926, 1605, 1464, 1379, 1180, 1030, 743$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.26 (m, 2H), 7.20 – 7.17 (m, 3H), 2.66 – 2.61 (m, 2H), 1.67 – 1.57 (m, 6H), 1.48 – 1.39 (m, 2H), 1.28 (d,  $J = 21.8$  Hz, 3H), 0.92 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  142.7, 128.5, 128.4, 125.8, 97.9 (d,  $J = 166.9$  Hz), 39.0 (d,  $J = 22.9$  Hz), 36.0, 32.3 (d,  $J = 23.7$  Hz), 32.0, 23.9 (d,  $J = 24.8$  Hz), 23.5 (d,  $J = 5.7$  Hz), 8.1 (d,  $J = 6.7$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -145.6 (app. octet,  $J = 21.5$  Hz); HRMS-ESI calcd for  $\text{C}_{14}\text{H}_{21}\text{F}$  [ $\text{M}^*$ ] $^+$  208.1622 found 208.1616.

4.3.3 2-Fluoro-2-methylpentadecane (**2c**). Following general procedure B using alcohol **1c**, the desired product was obtained as a colorless oil (47.3 mg, 0.194 mmol, 97%) without further purification. Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62 – 1.54 (m, 2H), 1.39 – 1.26 (m, 28H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -136.9 (app. nonet,  $J = 21.3$  Hz).

4.3.4 *(Z)*-18-Fluoro-18-methylnonadec-9-ene (*2d*). Following general procedure B, the titled compound was obtained as a colorless oil:

From alcohol **1d** (58.1 mg, 0.195 mmol, 97%) without further purification.

From alkene **3d** (59.4 mg, 0.199 mmol, 99%) without further purification.

Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.37 – 5.33 (m, 2H), 2.04 – 1.97 (m, 4H), 1.68 – 1.53 (m, 2H), 1.39 – 1.20 (m, 28H), 0.88 (t,  $J = 6.6$  Hz, 3H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.0 (app. nonet,  $J = 20.9$  Hz).

4.3.5 *6*-Fluoro-6-methylheptyl benzoate (*2e*). Following general procedure B, the titled compound was obtained as a colorless oil:

From alcohol **1e** (32.9 mg, 0.130 mmol, 65%) after purification by silica gel chromatography (5% EtOAc/Hexanes).

From alkene **3e** (50.5 mg, 0.2 mmol, quant.) without further purification.

Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 – 8.03 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 4.33 (t,  $J = 6.6$  Hz, 2H), 1.79 (q,  $J = 6.7$  Hz, 2H), 1.69 – 1.59 (m, 2H), 1.47 (dt,  $J = 7.7, 3.6$  Hz, 4H), 1.34 (d,  $J = 21.4$  Hz, 6H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.6 (app. nonet,  $J = 20.8$  Hz).

4.3.6 *6*-Fluoro-6-methylheptyl acetate (*2f*). Following general procedure B, the titled compound was obtained as a colorless oil:

From alcohol **1f** (34.2 mg, 0.180 mmol, 90%) without further purification.

From alkene **3f** (36.9 mg, 0.194 mmol, 97 %) without further purification.

From acetate **4f** (37.0 mg, 0.194 mmol, 97%) without further purification.

Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.06 (t,  $J = 6.7$  Hz, 2H), 2.05 (s, 3H), 1.67 – 1.56 (m, 4H), 1.46 – 1.36 (m, 4H), 1.33 (d,  $J = 21.5$  Hz, 6H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.7 (app. nonet,  $J = 20.8$  Hz).

*4.3.7 6-Fluoro-6-methylheptyl 4-methylbenzenesulfonate (2g).* Following general procedure B using alcohol **1g**, the titled compound was obtained as a colorless oil (42.4 mg, 0.140 mmol, 70%) after purification by silica gel chromatography (10% EtOAc/Hexanes). Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 – 7.77 (m, 2H), 7.37 – 7.32 (m, 2H), 4.02 (t,  $J = 6.5$  Hz, 2H), 2.45 (d,  $J = 1.0$  Hz, 3H), 1.70 – 1.61 (m, 2H), 1.57 – 1.50 (m, 2H), 1.35 – 1.26 (m, 10H).;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -138.0 (app. nonet,  $J = 20.9$  Hz).

*4.3.8 2-(6-Fluoro-6-methylheptyl)isoindoline-1,3-dione (2h).* Following general procedure B using alcohol **1h**, the titled compound was obtained as a white solid (41.7 mg, 0.150 mmol, 75%) after purification by silica gel chromatography (100%  $\text{CH}_2\text{Cl}_2$ ). Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 – 7.80 (m, 2H), 7.75 – 7.66 (m, 2H), 3.68 (t,  $J = 7.3$  Hz, 2H), 1.70 (p,  $J = 6.9$  Hz, 2H), 1.64 – 1.52 (m, 2H), 1.49 – 1.23 (m, 10H);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.6 (app. nonet,  $J = 21.0$  Hz).

*4.3.9 6-Fluoro-6-methylheptyl furan-2-carboxylate (2i).* Following general procedure B, the titled compound was obtained as a colorless oil:

From alcohol **1i** (48.5 mg, 0.2 mmol, quant.) without further purification.

From alkene **3i** (46.6, 0.192 mmol, 96%) without further purification.

Spectroscopic data are in accordance with literature [16].  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (dd,  $J = 1.7, 0.9$  Hz, 1H), 7.17 (dd,  $J = 3.5, 0.9$  Hz, 1H), 6.51 (dd,  $J = 3.5, 1.8$  Hz, 1H), 4.31 (t,  $J = 6.7$  Hz, 2H), 1.81 – 1.74 (m, 2H), 1.67 – 1.57 (m, 2H), 1.48 – 1.41 (m, 4H), 1.33 (d,  $J = 21.5$  Hz, 6H);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.7 (app. nonet,  $J = 20.9$  Hz).

*4.3.10 6-Fluoro-6-methylheptyl isonicotinate (2j)*. Following general procedure B using alcohol **1j**, the titled compound was obtained as a colorless oil (14.5 mg, 0.057 mmol, 29%) after purification by silica gel chromatography (20% EtOAc/Hexanes). From **1j**· $\text{H}_2\text{SO}_4$ : The alcohol **1j** was solubilized in 1 mL of  $\text{CH}_2\text{Cl}_2$  and brought to 0 °C.  $\text{H}_2\text{SO}_4$  (11  $\mu\text{L}$ , 0.2 mmol, 1 equiv.) was added and the mixture was stirred 5 minutes to form **1j**· $\text{H}_2\text{SO}_4$ . General procedure B was then applied to alcohol **1j**· $\text{H}_2\text{SO}_4$ , and the titled compound was obtained as a colorless oil (29.9 mg, 0.118 mmol, 59%) after purification by silica gel chromatography (20% EtOAc/Hexanes). IR (ATR, diamond),  $\nu = 2980, 2941, 1728, 1564, 1279, 1122, 1065, 870, 758, 708$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (d,  $J = 4.7$  Hz, 2H), 7.87 – 7.81 (m, 2H), 4.36 (t,  $J = 6.7$  Hz, 2H), 1.81 (p,  $J = 7.2$  Hz, 2H), 1.67 – 1.61 (m, 2H), 1.51 – 1.44 (m, 4H), 1.34 (d,  $J = 21.4$  Hz, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.3, 150.8, 137.7, 123.0, 95.7 (d,  $J = 164.9$  Hz), 65.9, 41.4 (d,  $J = 22.9$  Hz), 28.7, 26.8 (d,  $J = 24.8$  Hz), 26.5, 23.7 (d,  $J = 4.9$  Hz);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.9 (app. nonet,  $J = 21.2$  Hz). HRMS-ESI calcd for  $\text{C}_{14}\text{H}_{21}\text{FNO}_2$   $[\text{M}+\text{H}]^+$  254.1544 found 254.1551.

4.3.11 (5-Fluoro-5,6-dimethylheptyl)benzene (2l) and (6-fluoro-5,6-dimethylheptyl)benzene (2l'). Following general procedure B using alcohol **11**, a 32:68 mixture of compounds **2l/2l'** was obtained as a colorless oil (39.8 mg, 0.179 mmol, 89%) without further purification. Attempts to separate both regioisomers proved unsuccessful. IR (ATR, diamond),  $\nu = 3026, 2978, 2935, 1497, 1454, 1373, 1151, 849 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 2.68 – 2.56 (m, 2H), 1.96 – 1.85 (m, 0.3H, 2l) 1.70 – 1.56 (m, 4H), 1.52 – 1.41 (m, 1.4H, 2l'), 1.31 – 1.25 (overlapped of m, 4H, 2l' and m, 0.7H, 2l), 1.21 (d,  $J = 22.1 \text{ Hz}$ , 1H, 2l), 1.06 – 1.00 (m, 0.7 H 2l'), 0.94 (d,  $J = 6.9 \text{ Hz}$ , 1H, 2l), 0.89 (overlapped of d,  $J = 6.9 \text{ Hz}$ , 2H, 2l' and d,  $J = 6.9 \text{ Hz}$ , 1H, 2l);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9 (2l'), 142.8 (2l), 128.53 (2l'), 128.52 (2l), 128.42 (2l), 128.39 (2l'), 125.79 (2l), 125.76 (2l'), 99.8 (d,  $J = 169.3 \text{ Hz}$ , 2l), 98.6 (d,  $J = 166.0 \text{ Hz}$ , 2l'), 42.8 (d,  $J = 21.4 \text{ Hz}$ , 2l'), 37.4 (d,  $J = 23.3 \text{ Hz}$ , 2l), 36.08 (2l), 36.07 (2l'), 35.7 (d,  $J = 22.8 \text{ Hz}$ , 2l), 32.11 (2l), 31.83 (2l'), 31.3 (d,  $J = 5.5 \text{ Hz}$ , 2l'), 27.7 (2l'), 24.7 (d,  $J = 25.2 \text{ Hz}$ , 2l'), 23.8 (d,  $J = 25.0 \text{ Hz}$ , 2l'), 23.0 (d,  $J = 4.3 \text{ Hz}$ , 2l), 20.6 (d,  $J = 25.3 \text{ Hz}$ , 2l), 17.6 (d,  $J = 7.2 \text{ Hz}$ , 2l), 17.1 (d,  $J = 5.7 \text{ Hz}$ , 2l), 14.5 (d,  $J = 7.3 \text{ Hz}$ , 2l');  $^{19}\text{F NMR}$  (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -137.2 (m, 0.68F, 2l'), -150.1 (m, 0.32F, 2l).; HRMS-ESI calcd for  $\text{C}_{14}\text{H}_{21}\text{FNO}_2 [\text{M}+\text{H}]^+$  254.1544 found 254.1551.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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