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Direct Nucleophilic Difluoromethylation of Enolizable Ketones with CHF_2TMS/HMPA

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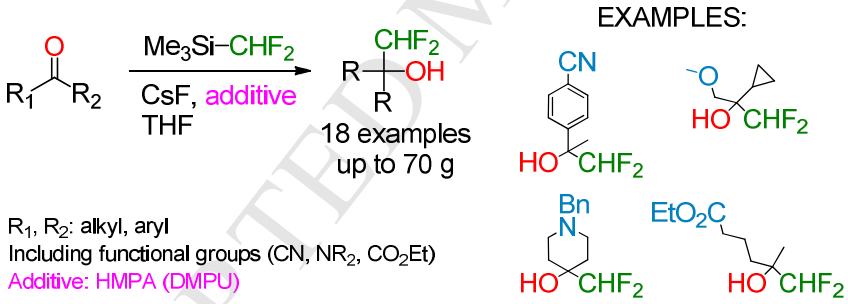
Abstract

Easily available difluoromethylating reagent Me_3SiCF_2H enables multigram synthesis of difluoromethyl alcohols in good yields under mild conditions from a number of aldehydes and ketones in the presence of HMPA. This additive makes possible the previously challenging nucleophilic difluoromethylation of enolizable ketones. DMPU can be used as a non-toxic alternative to the HMPA in the difluoromethylation reaction, albeit the yields were slightly lower in this case. The method works well with cyclic, acyclic, aryl ketones and tolerates various functional groups.



Key words: addition, catalysis, fluorine, ketones, nucleophilic difluoromethylation.

Introduction

Incorporation of fluorine in organic molecules modulates their pharmacological properties and has become almost a standard practice in medicinal chemistry. The unique properties of fluorine such as high electronegativity, excellent NMR parameters, low abundance in biosphere, ability to mimic hydrogen and block metabolic processes, increased lipophilicity and bioavailability of fluoroorganic molecules has made fluorine the "second-favourite heteroatom" after the nitrogen in drug design.[1] It is estimated that 30–40% of agrochemicals and 20% of pharmaceuticals contain fluorine.[2] The difluoromethyl group (CF_2H) has a great potential in the design of pharmaceuticals, agrochemicals, and materials. In the area of medicinal chemistry, the CF_2H groups prove to be a useful bioisostere of a hydroxy group, mainly because it is a lypophilic hydrogen bond donor, offering a potential for

improved membrane permeability.[3] Recently, the CF_2H group has been used as a non-reactive –SH bioisostere in the design of cysteine-containing hexapeptide analogues, leading to potent inhibitors of NS3/4A protease.[4] It is therefore not surprising that the number of studies on synthetic methods of the CF_2H-containing compounds has been dramatically increased in the last decade.[5]

In the course of the work on the synthesis of new fluorinated building blocks[6] we became interested in α-difluoromethyl alcohols. Several methods have been described in the literature for their synthesis, most of them applicable to either aldehydes or ketones as the starting compounds.[7] The most frequently used methods involved the use of the nucleophilic reagents possessing the CF_2 fragment connected to auxiliary groups which stabilize the carbanion, *e.g.* (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$),[8] diethyl difluoromethylphosphonate anion ($(EtO)_2OPCF_2^-$),[9] difluoro(phenylthio)methyl anion ($PhSCF_2^-$),[10] N-tert-butyldimethylsilyl-S-difluoromethyl-S-phenylsulfoximine anion ($PhSO(NTBS)CF_2^-$),[11] etc. Application of these reagents to the difluoromethylation of carbonyl compounds requires strong alkali reagents (e.g. LDA, MeONa, t-BuOK, Na/Hg) and an additional step to remove the auxiliary group.

In the search for a cheaper and milder difluoromethylating method, we decided to use the trimethylsilyldifluoromethane (Me_3SiCF_2H) as a CF_2H group source. Me_3SiCF_2H is commercially available, and can also be prepared in a laboratory by the $NaBH_4$ reduction of Me_3SiCF_3.[12] Recently it was reported as a convenient source of the CF_2H group by several authors.[13] Notably, use of this reagent could allow direct, one-pot conversion of ketones to α-difluoromethyl alcohols, like in the case of the more common Ruppert-Prakash reagent (Me_3SiCF_3).[14] Me_3SiCF_2H adds to the aldehydes and non-enolizable ketones in high yields, but nucleophilic addition to enolizable ketones is often accompanied by side reactions, leading to low yields and contaminated products. Fuchikami *et al.* reported that although Me_3SiCF_2H and $PhMe_2SiCF_2H$ converted aldehydes to difluoromethyl alcohols in good yields (in the presence of KF in DMF at 100 ºC), their reaction with ketones proceeded with low yields (20–25%).[15] More recently, similar results were obtained by other authors who used various bases in DMF or THF at ambient or low temperatures.[16, 17] Clearly, there was a need for a practical, general approach for Me_3SiCF_2H addition to ketones.[i] Here, we disclose a convenient protocol for direct difluoromethylation of enolizable ketones.

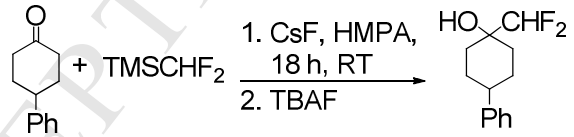
Results and discussion

Our initial attempts to induce nucleophilic difluoromethylation with enolizable ketones were focused on Me_3SiCF_2H as a source of the difluoromethyl anion and CsF as the fluoride ion source. Under conditions similar to those reported previously for the nucleophilic addition to aldehydes (CsF, THF),[16] no reaction occurred either with cyclohexanone or 4-phenylcyclohexanone as model

[i] Igoumnov *et al.* (*Fluorine Notes* **2011**, 5, 78) reported that aldehydes and ketones behave similar in direct difluoromethylation reaction. However, we were not able to reproduce these results.

substrates. Obviously, CsF generated only a low concentration of fluoride ions due to its low solubility in THF; the reaction rate was very slow under these conditions. Increasing the fluoride ion concentration by performing reaction in DMF,[16] DMSO or using a soluble fluoride ion source, e.g. tetramethylammonium fluoride (TMAF) in THF allowed us to increase the reaction rate, but the yields of the desired alcohols were still low (~ 20% by ^{19}F NMR). It should be noted that the main problem, in this case, was the formation of a number of unidentified and non-separable by-products (shown by ^{1}H NMR and GSMS of crude reaction mixture, see the Supporting Information), presumably due to substantial enolization and subsequent condensation reaction of the ketone. We hypothesized that maintaining a low concentration of the fluoride ions is the key to achieve clean transformation. This led us to an idea of performing the synthesis in THF in the presence of a polar additive, *e.g.* HMPA or DMPU in order to accelerate the reaction and at the same time generate a low concentration of the "naked" fluoride ions. The first experiment we performed with in the presence of HMPA in THF showed that the nucleophilic addition took place smoothly, but the conversion was ~50%. The only detectable products in the reaction mixture (in the case of cyclohexanone) were difluoromethyl alcohol (d, δ_F –134.8 ppm), its silyl ether (d, δ_F –132.8 ppm) and CH_2F_2 (t, δ_F –143.8 ppm). Formation of CH_2F_2 can be explained taking into account the enolization of ketones through the difluoromethyl anion species. Indeed, use of 2,2,6,6-tetradeuterocyclohexanone as a carbonyl component led to the formation of a small amount of $CHDF_2$ (shown by ^{19}F NMR). As expected, when TMAF was used as the fluoride ion source, no detectable effect of the HMPA addition on the reaction yield was observed. Further optimization experiments were performed using 4-phenylcyclohexanone, which proved to be more convenient model substrate because its low volatility (Table 1).

Table 1 Optimization of reaction conditions

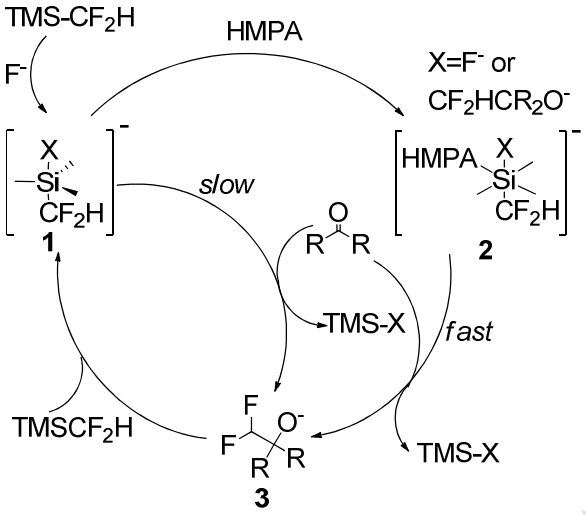


Entry	Equiv. $TMSCF_2H$	Equiv. HMPA	Equiv. CsF	Conversion (%)
1	2	5	0.1	46
2	2	5	0.2	93
3	2	5	0.3	96
4	2	5	0.4	96
5	2	5	1	96
6	2	1	0.2	52
7	2	3	0.2	66
8	2	4	0.2	81
9	2	5	0.2	93
10	1	5	0.1	30
11	1.5	5	0.1	37
12	2	5	0.1	45
13	3	5	0.1	49

Varying the reaction conditions showed that increase in the amount of CsF had beneficial effect on the yield of the reaction. Although CsF is almost insoluble in THF/HMPA, the increased quantity of CsF led to higher conversion of the ketone. The optimal amount of CsF was determined to be about 30 mol% (Table 1, entry 1–4). The same is true for HMPA: 5 equivalents of the additive provided the best conversion of the starting material (Table 1, entry 5–10). It is worth mentioning that performing the reaction in neat HMPA or at higher concentration of HMPA led to low yields and unidentified byproducts. Addition of DMPU instead of HMPA to the reaction medium gave similar results but the conversion was somewhat less (DMPU – 57%, HMPA – 76% yield by ^{19}F NMR). Nevertheless, it was demonstrated that at least in case of cyclohexanone, DMPU can be used instead of HMPA. This possibility might be useful for large-scale preparation of α-difluoromethyl alcohols. Finally, the use of excess Me_3SiCF_2H was important to achieve good conversion; it was obvious from the experiments with 10 mol% of CsF (Table 1, entries 10–13). The optimal amount of Me_3SiCF_2H was determined to be 2 equivalents; it gave the highest conversion of the ketone and was at the same time economical. It should be noted, however, that in some cases the use of more than 2 equivalents of Me_3SiCF_2H could lead to better yields of the difluoromethyl alcohols. In case of 4-phenylcyclohexanone elevated temperatures did not lead to increase in the conversion of the starting material. In summary, the optimal general conditions we propose for the difluoromethylation reaction are the following: 2 equivalents of Me_3SiCF_2H, 5 equivalents of HMPA and 30 mol% of CsF in THF at room temperature. The reaction was not particularly fast and took about a day to achieve 95% conversion.

From a mechanistic point of view, the overall process seems to be similar to the addition of the well-known Me_3SiCF_3 reagent.[14] A plausible reaction mechanism explaining the experimental facts is illustrated in Scheme 1. In the first step, the base (the fluoride or alcoxy anion, X) coordinates with the silicon atom of Me_3SiCF_2H to form **1**. The rate of its addition to ketone seems to be relatively slow as compared to the rate of side reactions, e.g., enolization and condensation of the ketone. Coordination of **1** with HMPA might lead to another hypervalent silicon species, compound **2**, which is more reactive towards ketones.[17,18] The addition product could react with Me_3SiCF_2H to complete the catalytic cycle. The role of additional amount of insoluble CsF is unclear, but could be rationalized assuming that it allows generation of low concentration of fluoride ion on the surface of the CsF during the course of the reaction. We speculate that it is the low concentration of the fluoride ions that allows for Me_3SiCF_2H activation without significant enolization of the ketone, and therefore, avoiding the side reactions.

Scheme 1 Possible mechanism for HMPA promoted difluoromethylation.



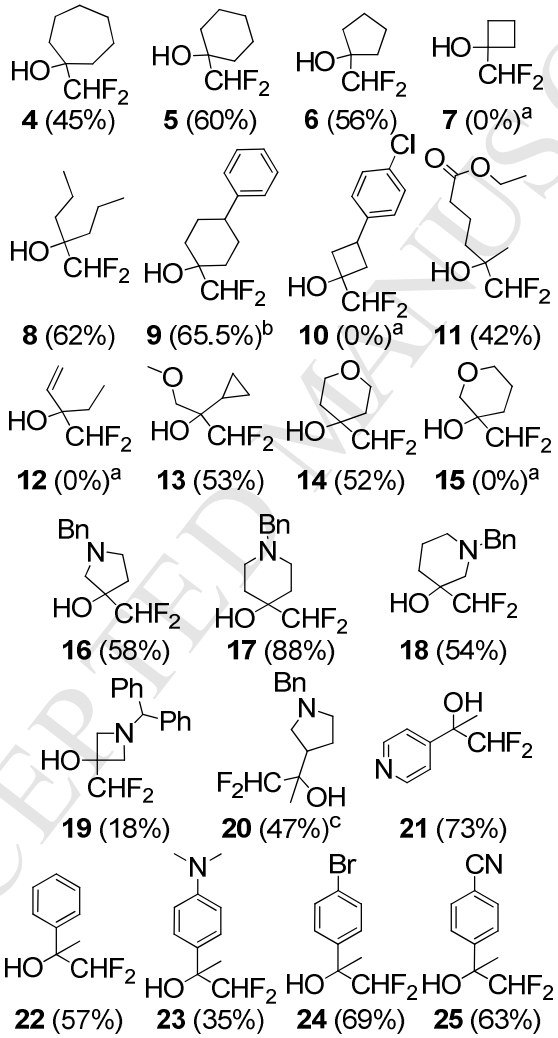
In order to test if the reaction is autocatalytic, we performed model studies using sodium difluoroethylate (CF_2HCH_2ONa) as an initiator. CF_2HCH_2ONa has similar nucleophilicity to the intermediate anion **3**, produced in the difluoromethylation reaction. Indeed, in this case the difluoromethylation reaction of cyclohexanone in THF proceeded with moderate yield (as determined by ^{19}F NMR) of the corresponding difluoromethyl alcohol without (36%) or in the presence (54%) of HMPA. Hence, CF_2HCH_2ONa was found to be rather good initiator, despite some unidentified by-products were formed. In contrast to previous studies,[16] these experiments clearly demonstrated the autocatalytic nature of the ketone difluoromethylation reaction.

Applying the general procedure to a representative set of ketones led to a number of difluoromethyl alcohols (Figure 1). In general, the yields of the corresponding difluoromethyl alcohols were good, their purification were simple and straightforward. We found that acyclic ketones, seven-, six-, and five-membered cyclic ketones reacted well, whereas cyclobutanone formed unidentified mixture of compounds, presumably due to fast enolization and subsequent aldol reaction (compounds **4**–**10**). Other highly enolizable ketones (ethyl pyruvate and 3-pyranone) also failed to give the desired products **12** and **15**, an exothermic reaction leading to a mixture of unidentified compounds occurred upon addition of CsF instead. In the case of ketones containing a basic nitrogen atom, the yields were usually better (compounds **16**–**21**). Thus, even the four-membered azetidinone derivative formed the product **19**, albeit in low yield. Aryl ketones gave good yields of the difluoromethyl alcohols **21**–**25**. Notably, aryl ketones demonstrated better conversion at elevated temperatures.

Finally, as can be seen from the **Fig. 1**, the ester, nitro, cyano and protected amino groups in the substrates tolerated the difluoromethylation reaction conditions. In general, the method worked well in preparations of difluoromethyl alcohols on a relatively large scale (up to 70 g, see the experimental procedures for the compounds **16** and **17**).

In conclusion, we have developed a new protocol for the direct difluoromethylation reaction of enolizable ketones with Me_3SiCF_2H. Using a base with low solubility in THF (CsF) and addition of HMPA as a promoter is crucial for the reaction efficiency. Various alicyclic and acyclic difluoromethyl alcohols can be prepared in one step in moderate to good yields. Moreover, DMPU can be used instead of HMPA as a non-toxic substitute. Reaction conditions are mild and tolerate various functionalities. We believe that the overall simplicity of the procedure, scalability and accessibility of starting materials will make this method a preferred alternative to indirect difluoromethylation reaction.

Figure 1 Difluoromethyl alcohols and their isolated yields.



[a]No product was obtained. [b]Combined yield for two isomers. Diastereomers were separated by column chromatography. [c]Obtained as ca. 1:1 mixture of diastereomers.

Supporting Information for this article is available online. It includes the copies of ^{1}H, ^{13}C,^{19}F NMR spectra and additional details of the experiments.

Experimental section

Solvents were purified according to the standard procedures. Starting materials were supplied from Enamine LTD. Melting points were measured on an automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C, ^{19}F NMR, and 2D NMR spectra were recorded on either Bruker Avance 500 spectrometer at 499.9 (^{1}H), 124.9 (^{13}C) and 470 (^{19}F) MHz, or on Varian Unity Plus 400 spectrometer at 400 (^{1}H), 101 (^{13}C) and 377 (^{19}F) MHz. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as an internal standard. HRMS analyses were performed on a Surveyor HPLC system interfaced to an LTQ Orbitrap (Bremen, Germany), equipped with electrospray (ESI) ion source. Infrared spectra were measured on a Perkin Elmer Spectrum 100 FTIR and are reported in reciprocal centimeters (cm^{-1}). All compound names were generated using ChemBioDraw.

General procedure A for difluoromethylation of ketones:

CsF (1.39 g, 9.17 mmol) was added to a solution of ketone (31 mmol) and HMPA (26.7 mL, 155 mmol) in 65 mL of THF under an Ar atmosphere. Me_3SiCF_2H (7.6 g, 61 mmol) was then added, and the mixture was stirred at room temperature for 24 h. A solution of TBAF (31 mL, 1 M in THF) was added at the end of this period, and the mixture was stirred for another 1 h. Then the mixture was poured into water (200 mL). The product was extracted with a mixture of hexanes-ethyl acetate (1:1, 3×70 mL), and the combined organic phase was washed with water (2×70 mL), dried over Na_2SO_4, and evaporated. The products contaminated with unreacted ketone were purified as described below.

A solution of crude difluoromethyl alcohol in methanol (30 mL) was added to a solution of semicarbazide hydrochloride (2 g, 18 mmol) and sodium acetate (2.2 g, 27 mmol) in water (10 mL) at room temperature and stirred for 10 h. Methanol was evaporated, water (50 mL) was added, and the obtained solution was extracted with hexanes (3×50 mL), dried over Na_2SO_4 and evaporated to afford sufficiently pure difluoromethyl alcohol. It could be further purified either by distillation or by column chromatography.

General procedure B for difluoromethylation of ketones (for water-soluble difluoromethyl alcohols):

CsF (1.39 g, 9.17 mmol) was added to a solution of ketone (31 mmol) and HMPA (26.7 mL, 155 mmol) in 65 mL of THF under an Ar atmosphere. Me_3SiCF_2H (7.6 g, 61 mmol) was then added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water (200 mL). The product was extracted with a mixture of hexanes-ethyl acetate (1:1, 3×70 mL), and the combined organic phase was washed with water (2×70 mL) and dried over Na_2SO_4. The drying agent was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in methanol (50

mL), conc. HCl was added to pH 2. The mixture was then stirred for 1 h at r.t. and methanol was removed by rotatory evaporation. The crude product was purified either by distillation or by column chromatography.

General procedure C for difluoromethylation of ketones at elevated temperature:

CsF (1.39 g, 9.17 mmol) was added to a solution of ketone (31 mmol) and HMPA (26.7 mL, 155 mmol) in 65 mL of THF under an Ar atmosphere. Me_3SiCF_2H (7.6 g, 61 mmol) was then added, and the mixture was stirred at reflux for 24 h. A solution of TBAF (31 mL, 1 M in THF) was then added, and the mixture was stirred for another 1 h, and was then poured into water (200 mL). The product was extracted with a mixture of hexanes-ethyl acetate (1:1, 3×70 mL), and the combined organic phase was washed with water (2×70 mL), dried over $NaSO_4$. The drying agent was filtered off and the filtrate was evaporated to dryness. The crude products were purified either by distillation or by column chromatography.

1-(Difluoromethyl)cycloheptanol 4 was prepared according to general procedure A. The product was purified by distillation (25 mbar, 89–92 ºC). Colorless crystals; 2.28 g (yield 45%)**;** m.p. 35–36 ºC; ν_{max}(KBr) 3500-3200 (br), 2933, 2863, 1464, 1448, 1130, 1106, 1062, 1047, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.47 (t, *J* = 56.7 Hz, 1H), 1.88-1.73 (m, 3H), 1.73-1.57 (m, 6H), 1.58-1.45 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 118.5 (t, *J* = 248.2 Hz), 75.4 (t, *J* = 20.0 Hz), 34.4 (s), 29.8 (s), 21.8 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -132.8 (d, *J* = 56.8 Hz); Anal. calcd. for $C_8H_{14}F_2O$: C, 58.52; H, 8.59. Found: C, 58.35; H, 8.83.

1-(Difluoromethyl)cyclohexanol 5 was prepared according to general procedure A. The product was purified by distillation (25 mbar, 82–85 ºC). Colorless crystals; 2.80 g (yield 60%)**;** m.p. 38–39 ºC; ν_{max}(KBr) 3500-3250 (br), 2939, 2866, 1450, 1286, 1191, 1143, 1093, 1083, 1052 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.46 (t, *J* = 56.6 Hz, 1H), 1.77-1.56 (m, 8H), 1.55-1.41 (m, 2H), 1.30-1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 118.0 (t, *J* = 247,3 Hz), 71.8 (t, *J* = 19,8 Hz), 30.1, 25.6, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.8 (d, *J* = 56.6 Hz); Anal. calcd. for $C_7H_{12}F_2O$: C, 55.99; H, 8.05. Found: C, 56.18; H, 7.96.

1-(Difluoromethyl)cyclopentanol 6 was prepared according to general procedure A. The product was purified by distillation (25 mbar, 75–78 ºC). Colorless liquid; 2.36 g (yield 56%); ν_{max}(KBr) 3595, 3560-3200 (br), 2960, 2877, 1633, 1442, 1386, 1193, 1110, 1056, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.66 (t, *J* = 56.4 Hz, 1H), 2.11 (s, 1H), 1.91-1.77 (m, 4H), 1.74-1.55 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 117.1 (t, *J* = 244.9 Hz), 82.0 (t, *J* = 21.7 Hz), 34.6 (s), 24.3 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -130.3 (d, *J* = 56.6 Hz); Anal. calcd. for $C_6H_{10}F_2O$: C, 52.93; H, 7.40. Found: C, 53.17; H, 7.68.

4-(Difluoromethyl)heptan-4-ol 8 was prepared according to general procedure A. The product was purified by distillation (25 mbar, 72–74 ºC). Colorless liquid; 3.19 g (yield 62%); ν_{max}(KBr) 3604,

3550-3300 (br), 2964, 2877, 1467, 1108, 1062, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.60 (t, *J* = 56.3 Hz, 1H), 1.70 (s, 1H), 1.62 – 1.46 (m, 4H), 1.46 – 1.28 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 117.8 (t, *J* = 247.3 Hz), 74.4 (t, *J* = 20.3 Hz), 36.0(s), 16.1 (s), 14.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -133.3 (d, *J* = 56.3 Hz). Anal. calcd. for $C_8H_{16}F_2O$: C, 57.81; H, 9.70. Found: C, 57.97; H, 9.51.

***E*-1-Difluoromethyl-4-phenyl-cyclohexanol *E*-9** was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 3:1, R_f=0.45). White crystals; 2.03 g (yield 29%); m.p. 50-51 ºC; ν_{max}(KBr) 3500-3200 (br), 2950, 2865, 1492, 1452, 1357, 1114, 1101, 1057 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.36 (t, *J* = 7.5 Hz, 2H), 7.31-7.22 (m, 3H), 5.89 (t, *J* = 55.9 Hz, 1H), 2.78 (tt, *J* = 10.6, 3.8 Hz, 1H), 2.25 (s, 1H), 2.14 (d, *J* = 13.2 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.84-1.63 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 145.4 (s), 128.6 (s), 126.9 (s), 126.3 (s), 116.9 (t, *J* = 246.2 Hz), 71.1 (t, *J* = 19.7 Hz), 41.9 (s), 32.4 (s), 29.2 (s).^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.0 (d, *J* = 55.9 Hz). Anal. calcd. for $C_{13}H_{16}F_2O$: C, 69.01; H, 7.13. Found: C, 68.88; H, 7.28.

***Z*-1-Difluoromethyl-4-phenyl-cyclohexanol *Z*-9** was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 3:1, R_f=0.55). White crystals; 2.59 g (yield 37%); m.p. 64–65 ºC; ν_{max}(KBr) 3542, 3500-3350 (br), 2944, 2862, 1494, 1442, 1386, 1168, 1118, 1060, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), δ 5.56 (t, *J* = 56.6 Hz, 1H), 2.56 (tt, *J* = 12.05, 3.0 Hz, 1H), 2.02 – 1.78 (m, 7H), 1.70 (td, *J* = 13.7, 3.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 146.6 (s), 128.5 (s), 126.9 (s), 126.3 (s), 118.0, (t, *J* = 246.9 Hz), 71.2 (t, *J* = 20.9 Hz), 43.7 (s), 30.2 (s), 27.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.1 (d, *J* = 56.6 Hz). Anal. calcd. for $C_{13}H_{16}F_2O$: C, 69.01; H, 7.13. Found: C, 68.91; H, 7.25.

Ethyl 6,6-difluoro-5-hydroxy-5-methylhexanoate 11 was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 5:1, R_f=0.23). Colorless liquid; 2.73 g (yield 42%); ν_{max}(KBr) 3600-3200 (br), 2983, 2944, 1731, 1718, 1465, 1377, 1192, 1093, 1062 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.52 (t, *J* = 56.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 1H), 1.84 – 1.68 (m, 2H), 1.63 – 1.51 (m, 2H), 1.30 – 1.19 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 173.6 (s), 117.7 (t, *J* = 247.6 Hz), 72.6 (t, *J* = 21.5 Hz), 60.6 (s), 34.6 (s), 34.4 (s), 19.8 (s), 18.1 (s), 14.3 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -132.0 (dd, *J* = 279.4, 56.6 Hz, 1F), -133.6 (dd, *J* = 279.4, 56.6 Hz, 1F). HRMS (EI^+) calcd. for $[M]^+$ $C_9H_{16}F_2O_3^+$ 210.1062, found 210.1061.

(1,1-Difluoro-3-methoxy-2-methylpropan-2-yl)cyclopropane 13 was prepared according to general procedure B. The product was purified by distillation (7 mbar, 89–91 ºC). Colorless liquid; 2.73 g (yield 53%); ν_{max}(KBr) 3600-3200 (br), 3093, 3012, 2935, 2900, 2832, 1673, 1456, 1419, 1382, 1189, 1114, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.73 (t, *J* = 56.2 Hz, 1H), 3.63 (d, *J* = 9.6 Hz,

1H), 3.40 (s, 3H), 3.35 (d, *J* = 9.6 Hz, 1H), 2.51 (s, 1H), 0.966-0.847 (m, 1H), 0.656-0.547 (m, 1H), 0.503-0.320 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 116.8 (t, *J* = 247.9 Hz), 74.7 (s), 71.6 (t, *J* = 21.0 Hz), 59.6 (s), 11.0 (s), -0.4 (s), -1.4 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -132.0 (dd, *J* = 282.4, 56.1 Hz, 1F), -136.3 (dd, *J* = 282.5, 56.3 Hz, 1F). Anal. calcd. for $C_7H_{12}F_2O_2$: C, 50.60; H, 7.28. Found: C, 50.89; H, 7.50.

4-(Difluoromethyl)tetrahydro-2H-pyran-4-ol 14 was prepared according to general procedure B. The product was purified by column chromatography (Hexanes : EtOAc = 2:1, R_f=0.3). m.p. 80–81 ºC; White solid; 2.45 g **(**yield 52%); ν_{max}(KBr) 3550-3200 (br), 2972, 2875, 1388, 1288, 1247, 1203, 1132, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.47 (t, *J* = 56.3 Hz, 1H), 3.84 (dd, *J* = 11.4, 5.0 Hz, 2H), 3.75 (dd, *J* = 11.9 Hz, *J* = 11.8 Hz 2H), 2.26 (s, 1H), 1.83 (td, *J* = 13.1, 5.1 Hz, 2H), 1.48 (d, *J* = 13.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 117.2 (t, *J* = 246.7 Hz), 69.6 (t, *J* = 21.5 Hz), 62.5 (s), 30.5 (t, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -135.4 (d, *J* = 56.3 Hz). Anal. calcd. for $C_6H_{10}F_2O_2$: C, 47.37; H, 6.63. Found: C, 47.52; H, 6.39.

1-Benzyl-3-(difluoromethyl)pyrrolidin-3-ol 16 was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 1:1+3% triethylamine, R_f=0.5). Colorless liquid; 4.08 g (yield 58%). For the scale-up synthesis, 50 g of 1-benzylpyrrolidin-3-one was used as the starting material and 35 g (54%) of 1-benzyl-4-(difluoromethyl)piperidin-4-ol was obtained according to general procedure A, but using proportional amounts of reactants. In this case the product was purified by distillation (2.7 mbar, 111–113 ºC). ν_{max}(KBr) 3600-3200 (br), 2950, 2811, 1650, 1604, 1454, 1382, 1211, 1135, 1058 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.43 – 7.18 (m, 5H), 5.74 (t, *J* = 56.1 Hz, 1H), 4.14 (s, 1H), 3.63 (dd, *J* = 42.0, 12.7 Hz, 2H), 3.00 – 2.86 (m, 1H), 2.67 (dd, *J* = 25.3, 10.6 Hz, 2H), 2.46 (dd, *J* = 16.4, 8.0 Hz, 1H), 2.28 – 2.15 (m, 1H), 1.92 – 1.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 137.8 (s), 129.1 (s), 128.4 (s), 127.4 (s), 116.2 (t, *J* = 245.0 Hz), 79.8 (t, *J* = 21.7 Hz), 61.2 (s), 60.1 (s), 53.1 (s), 34.5 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -130.7 (dd, *J* = 280.2, 56.1 Hz, 1F), -131.8 (dd, *J* = 280.1, 56.2 Hz, 1F). HRMS (EI^+ + 3NBA) calcd. for $[M+H]^+$ $C_{12}H_{16}F_2NO^+$ 228.1194, found 228.1196.

1-Benzyl-4-(difluoromethyl)piperidin-4-ol 17 was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 1:1+3% triethylamine, R_f=0.5). Colorless liquid; 6.57 g (yield 88%). For the scale-up synthesis, 60 g of N-benzyl-4-piperidone was used as starting material and 68 g (89%) of 1-benzyl-4-(difluoromethyl)piperidin-4-ol was obtained according to general procedure A, but using proportional amounts of reactants. ν_{max}(KBr) 3550-3150 (br), 2954, 2819, 1652, 1602, 1454, 1365, 1305, 1197, 1122, 1058 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.41 – 7.23 (m, 5H), 5.51 (t, *J* = 56.4 Hz, 1H), 3.57 (s, 2H), 2.77 (d, *J* = 11.3 Hz, 2H), 2.37 (td, *J* = 11.7, 2.0 Hz, 2H), 1.89 (s, 1H), 1.83 (td, *J* = 13.3, 4.4 Hz, 2H), 1.60 (d, *J* = 12.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 138.4 (s), 129.2 (s), 128.4 (s), 127.2 (s), 117.6 (t, *J* = 246.5 Hz), 70.1 (t, *J* = 21.1 Hz), 63.1 (s), 47.9 (s), 30.2 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.46 (d, *J* = 56.4 Hz). HRMS (EI^+ + 3NBA) calcd. for $[M+H]^+$ $C_{13}H_{18}F_2NO^+$ 242.1351, found 242.1349.

1-Benzyl-3-(difluoromethyl)piperidin-3-ol 18 was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 1:1+3% triethylamine, R_f=0.5). Colorless liquid; 4.03 g (yield 54%). Alternatively, the product can be purified by distillation (2.7 mbar, 119–120 ºC); ν_{max}(KBr) 3600-3200 (br), 2948, 2806, 1662, 1585, 1454, 1371, 1297, 1147, 1105, 1058 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.35-7.19 (m, 5H), 5.61 (t, J = 55.9 Hz, 1H), 3.55 (s, 2H), 3.31 (s, 1H), 2.76 (d, J = 10.7 Hz, 1H), 2.67 (d, J = 11.2 Hz, 1H), 2.22 (d, J = 11.0 Hz, 1H), 2.07 (td, J = 11.3, 3.2 Hz, 1H), 1.89-1.74 (m, 1H), 1.73 – 1.55 (m, 2H), 1.50 (dt, J = 13.1, 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$), δ: 137.52 (s), 129.0 (s), 128.4 (s), 127.4 (s), 116.7 (t, J = 245.6 Hz), 70.5 (t, J = 21.6 Hz), 62.7 (s), 57.4 (t, J = 3.9 Hz), 53.2 (s), 28.2 (s), 20.5 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.90 (d, J = 56.0 Hz). Anal. calcd. for $C_{13}H_{17}F_2NO$: C, 64.71; H, 7.10; N, 5.81. Found: C, 64.96; H, 7.29; N, 6.01.

1-Benzhydryl-3-(difluoromethyl)azetidin-3-ol 19 was prepared according to general procedure C. The product was purified by column chromatography (Hexanes : EtOAc = 2:1, R_f=0.55). Yellow oil; 1.61 g (yield 18%); ν_{max}(KBr) 3600-3200 (br), 3062, 3027, 2958, 2848, 1806, 1599, 1492, 1452, 1226, 1095, 1068, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.50 – 7.15 (m, 10H), 6.01 (t, J = 55.6 Hz, 1H), 4.45 (s, 1H), 3.47 (d, *J* = 9.4 Hz, 2H), 3.17 (s), 3.11 (d, *J* = 9.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 141.6 (s), 128.7 (s), 127.49 (s), 115.5 (t, *J* = 243.6 Hz), 77.5 (s), 69.5 (t, *J* = 23.1 Hz), 60.3 (t, *J* = 3.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ: -134.17 (d, *J* = 55.7 Hz). HRMS (EI^+ + 3NBA) calcd. for $[M+H]^+$ $C_{17}H_{18}F_2NO^+$ 290.1351, found 290.1350.

1-Benzylpyrrolidin-3-yl-1,1-difluoropropan-2-ol 20 was prepared according to general procedure A. The product was purified by column chromatography (Hexanes : EtOAc = 1:1+3% triethylamine, R_f=0.5). Colorless liquid; 3.71 g (yield 47%); ν_{max}(KBr) 3600-3200 (br), 2973, 2807, 1658, 1454, 1380, 1352, 1211, 1128, 1089, 1061 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.43 – 7.20 (m, 1H), 5.65 (t, *J* = 57 Hz, 0.6H), 5.59 (t, *J* = 56,35 Hz, 0.4H), 3.91 (s, 1H), 3.63 (s, 2H), 2.95 (d, *J* = 7.9 Hz, 0,44H), 2.90 – 2.73 (m, 1.7H), 2.50 (t, *J* = 8.1 Hz, 0.7H), 2.44 – 2.23 (m, 2.6H), 2.06 – 1.86 (m, 2.24H), 1.24 (s, 1.77H), 1.20 (s, 1.35H);^{13}C NMR (126 MHz, $CDCl_3$), δ: 138.5 (s), 138.3 (s), 128.7 (s), 128.7 (s), 128.6 (s), 128.5 (s), 128.4 (s), 127.4 (s), 127.3 (s), 117.9 (t, *J* = 249.28 Hz), 117.2 (t, *J* = 247.38 Hz), 74.0 (t, *J* = 20.39 Hz), 73.7 (s), 73.7 (s), 73.7 (t, *J* = 20.11 Hz), 60.0 (s), 59,8 (s), 55.4 (s), 55.0 (s), 53.3 (s), 52.7 (s), 41.9 (s), 41.1 (s), 24.6 (s), 24.1 (s), 19.1 (s), 18.4 (s); ^{19}F NMR (376 MHz, $CDCl_3$), δ: -127.9 (dd, *J* = 280.2 Hz, 56.3 Hz, 1F), -134.1 (dd, *J* = 280.1, *J* = 56.6 Hz, 1F), -129.0 (dd, *J* = 283.8 Hz, 56.1 Hz, 1F), -136.6 (dd, *J* = 283.8, *J* = 57.2 Hz, 1F). HRMS (EI^+ + 3NBA) calcd. for $[M+H]^+$ $C_{14}H_{20}F_2NO^+$ 256.1507, found 256.1507.

1,1-Difluoro-2-(pyridin-4-yl)propan-2-ol 21 was prepared according to general procedure C. The product was purified by column chromatography (Hexanes : EtOAc = 1:2, R_f=0.3)**.** White solid; 3.91 g (yield 73%); m.p. 84–85 ºC; ν_{max}(KBr) 3300-3000 (br), 2985, 2809, 2636, 1608, 1417, 1384, 1228, 1159, 1106, 1061, 1007 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.53 (d, *J* = 5.9 Hz, 2H), 7.49 (d, *J* = 5.6

Hz, 2H), 5.70 (t, *J* = 56.2 Hz, 1H), 4.98 (s, 1H), 1.64 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$), δ: 150.1 (s), 149.6 (s), 121.3 (s), 116.6 (t, *J* = 250.0 Hz), 73.7 (t, *J* = 22.2 Hz), 22.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$), δ: -129.6 (dd, *J* = 278.9, 56.1 Hz, 1F), -130.5 (dd, *J* = 279, 56.4 Hz, 1F). HRMS (EI^+) calcd. for $[M]^+$ $C_8H_9F_2NO^+$ 173.0647, found 173.0645.

1,1-Difluoro-2-phenylpropan-2-ol 22 was prepared according to general procedure C. The product was purified by distillation (7 mbar, 72–74 ºC). Colorless liquid; 3.04 g (yield 57%); ν_{max}(KBr) 3600-3200 (br), 2939, 2877, 1604, 1448, 1386, 1348, 1203, 1099, 1072, 1057, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$**)**, δ: 7.54 (d, *J* = 7.4 Hz, 2H), 7.48-7.39 (m, 2H), 7.39 – 7.33 (m, 1H), (m, 2H), 5.74 (t, *J* = 56.4 Hz, 1H), 2.55 (s, 1H), 1.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 140.5 (s), 128.5 (s), 128.2 (s), 125.9 (s), 117.0 (t, *J* = 249.2 Hz), 74.3 (t, *J* = 22.0 Hz), 22.4 (s). ^{19}F NMR (376 MHz, $CDCl_3$), δ: -129.46 (dd, *J* = 276.1, 56.1 Hz, 1F), -130.9 (dd, *J* = 276.1, 56.8 Hz, 1F). Anal. calcd. for $C_9H_{10}F_2O$: C, 62.78; H, 5.85. Found: C, 62.53; H, 5.64.

2-(4-(Dimethylamino)phenyl)-1,1-difluoropropan-2-ol 23 was prepared according to general procedure C. The product was purified by column chromatography (Hexanes : EtOAc = 2:1, R_f=0.5)**.** Yellow crystals; 2.33 g (yield 35%); m.p. 42–43 ºC; ν_{max}(KBr) 3550-3100 (br), 2993, 2892, 2856, 1616, 1519, 1484, 1465, 1317, 1199, 1149, 1095, 1062, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.71 (t, *J* = 56.7 Hz, 1H), 2.98 (s, 6H), 2.58 (s, 1H), 1.65 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$), δ: 150.3 (s), 128.1 (s), 126.7 (s), 117.2 (t, *J* = 249.1 Hz), 112.3 (s), 73.9 (t, *J* = 22.0 Hz), 40.5 (s), 22.0 (s).^{19}F NMR (376 MHz, $CDCl_3$), δ: -129.6 (dd, *J* = 274.2, 56.3 Hz, 1F), -130.6 (dd, *J* = 274.1, 57.1 Hz, 1F). HRMS (EI^+) calcd. for $[M]^+$ $C_{11}H_{15}F_2NO^+$ 215.1116, found 215.1118.

2-(4-Bromophenyl)-1,1-difluoropropan-2-ol 24 was prepared according to general procedure C. The product was purified by distillation (1 mbar, 68–69 ºC). Yellow liquid; 5.37 g (yield 69%); ν_{max}(KBr) 3581, 3550-3200 (br), 2987, 2942, 2879, 1592, 1488, 1402, 1346, 1141, 1074, 1051, 1010 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.52 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 5.67 (t, *J* = 56.4 Hz, 1H), 2.39 (s, 1H), 1.63 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$), δ: 139.4 (s), 131.6 (s), 127.8 (s), 122.6 (s), 116.7 (t, *J* = 249.5 Hz), 74.2 (t, *J* = 22.2 Hz), 22.5 (s).^{19}F NMR (376 MHz, $CDCl_3$), δ: -129.8 (dd, *J* = 277.2, 56.1 Hz, 1F), -130.8 (dd, *J* = 277.2, 56.7 Hz, 1F). Anal. calcd. for $C_9H_9BrF_2O$: C, 43.06; H, 3.61; Br, 31.83. Found: C, 43.32; H, 3.34; Br, 31.55.

4-(1,1-difluoro-2-hydroxypropan-2-yl)benzonitrile 25 was prepared according to general procedure C. The product was purified by column chromatography (Hexanes : EtOAc = 4:1, R_f=0.27)**.** m.p. 68–69 ºC; Yellow crystals; 5.37 g (yield 63%); ν_{max}(KBr) 3500-3300 (br), 2993, 2973, 2240, 1610, 1506, 1411, 1353, 1209, 1159, 1097, 1072, 1057 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.75 – 7.56 (m, 4H), 5.69 (t, *J* = 56.2 Hz, 1H), 2.62 (s, 1H), 1.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 145.6 (s), 132.3 (s), 127.0 (s), 118.6 (s), 116.4 (t, *J* = 250.0 Hz), 112.2 (s), 74.3 (t, *J* = 22.4 Hz), 22.6

(s). ^{19}F NMR (376 MHz, $CDCl_3$), δ: -129.64 (dd, *J* = 278.9, 56.0 Hz, 1F), -130.64 (dd, *J* = 279.0, 56.5 Hz, 1F). HRMS (EI^+) calcd. for $[M]^+$ $C_{10}H_9F_2NO^+$ 197.0647, found 197.0648.

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References

1. (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, K.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, 114, 2432. (b) Ojima, I. Ed. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009.
2. Kirsch, P., Ed. *Modern fluoroorganic chemistry: synthesis, reactivity, applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004.
3. Meanwell, N. A. *J. Med. Chem.* **2011**, 54, 2529.
4. Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, 12, 701.
5. (a) Shen X.; Miao W.; Ni C.; Hu J. *Angew. Chem. Int. Ed.* **2014**, 53, 775. (b) Wang X; Liu G., Xu X.-H.; Shibata N; Tokunaga E.; Shibata N. *Angew. Chem. Int. Ed.* **2014**, 53, 1827. (c) Shen X.; Liu Q.; Luo T.; Hu J. *Chem. - Eur. J.* **2014**, 20, 6795. (d) Levin V. V.; Trifonov A. L.; Zemtsov A. A.; Struchkova M. I.; Arkhipov D. E.; Dilman A. D. *Org. Lett.* **2014**, 16, 6256 (e) Thomoson C. S.; Tang X.-J.; Dolbier W. R. Jr. *J. Org. Chem.* **2015**, 80, 1264.
6. (a) Mykhailiuk, P. K.; Radchenko, D. S.; Komarov, I. V. *J. Fluorine Chem*. **2010**, 131, 221. (b) Mykhailiuk, P.; Tkachenko, A.; Radchenko, D.; Shishkin, O.; Tolmachev, A.; Komarov, I. *Synthesis* **2012**, 44, 903. (c) Radchenko, D. S.; Michurin, O. M.; Chernykh, A. V.; Lukin, O.; Mykhailiuk, P. K. *Tetrahedron Lett.* **2013**, 54, 1897.
7. (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, 52, 8214–8264.
8. Surya Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A. *Eur. J. Org. Chem.* **2005**, 11, 2218.
9. Beier, P.; Alexandrova, A. V.; Zibinsky, M.; Prakash, G. K. *Tetrahedron* **2008**, 64, 10977.
10. Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, 126, 527.
11. Shen, X.; Zhang, W.; Ni, C.; Gu, Y.; Hu, J. *J. Am. Chem. Soc.* **2012**, 134, 16999.
12. Tyutyunov A. A.; Boyko V. E.; Igoumnov S. M. *Fluorine Notes* **2011**, 74, 1.
13. (a) Gu Y.; Leng X.; Shen Q. *Nat. Commun.* **2014**, 5, 5405. (b) Matheis C.; Jouvin K.; Goossen L. *J. Org. Lett.* **2014**, 16, 5984.

14. (a) Ruppert I.; Schlich K.; Volbach W. *Tetrahedron Lett.* **1984**, 25, 2195. (b) Prakash G. K. S.; Yudin A. K. *Chem. Rev.* **1997**, 97, 757.

15. Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 1995, 7, 717.

16. Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, 13, 5342.

17. Du, G.-F.; Wang Y.; Gu C.-Z.; Dai B.; He, L. *RSC Advances* **2015**, 5, 35421.

18. Mizuta, S.; Shibata, N.; Sato, T.; Fujimoto, H.; Nakamura, S.; Toru, T. *Synlett* **2006**, 267.