Article

Halogenative difluorohomologation of ketones

Oleg V. Fedorov, Mikhail D. Kosobokov, Vitalij V. Levin, Marina I. Struchkova, and Alexander D. Dilman

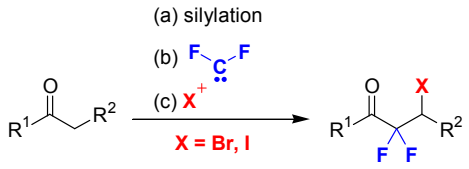
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b00904 • Publication Date (Web): 12 May 2015

Halogenative difluorohomologation of ketones

Oleg V. Fedorov, Mikhail D. Kosobokov, Vitalij V. Levin, Marina I. Struchkova, Alexander D. Dilman*

N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation

adil25@mail.ru



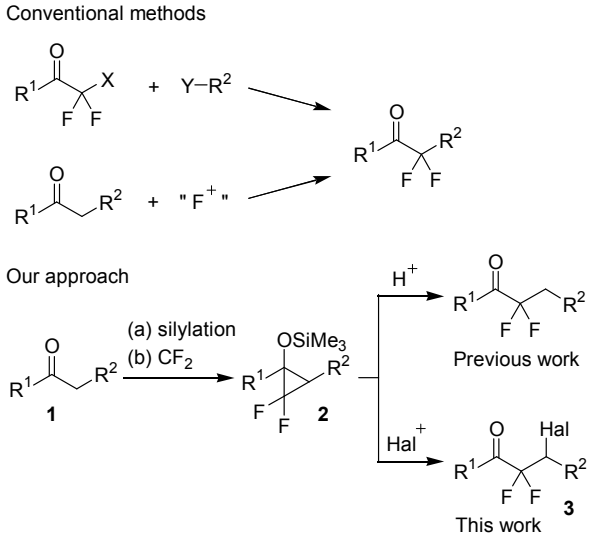
Abstract. A method for the difluorohomologation of ketones accompanied by halogenation of a C-H bond is described. The reaction involves silylation, difluorocarbene addition using Me_3SiCF_2Br activated by bromide ion, and halogenation of intermediate cyclopropanes with *N*-bromo- or *N*-iodosuccinimide. The whole process is performed without isolation of intermediates. The resulting α,α-difluoro-β-halo-substituted ketones can be readily converted into fluorine containing pyrazole derivatives and oxetanes.

Introduction

α,α-Difluoroketones represent an important subclass of organofluorine compounds, useful for medicinal chemistry,[1,2] and other fields.[3] Due to significant electron withdrawing effect of two fluorine atoms, the carbonyl group can react with water to form hydrate adducts. The hydration not only alters the polarity of the starting molecule, but also changes the shape of the carbonyl functionality from planar to tetrahedral. The hydrate adducts can mimic the transition state of peptide hydrolysis thereby serving as inhibitors of proteases. This phenomenon has been exploited for the identification of inhibitors of various enzymes.[2a-c] Moreover, other mechanisms of biological activities of α,α-difluorinated carbonyl compounds have been discovered.[2d,e]

Conventional methods for the synthesis of α,α-difluoroketones involve functionalization of difluorocarbonyl fragment[4] or electrophilic fluorination of parent ketones and their derivatives[5] (Scheme 1). Recently, we proposed a concept for difluorohomologation of ketones **1** based on generation of silyloxy-substituted cyclopropanes **2** followed by their protonation.[6] Herein we report that cyclopropanes **2** may undergo halogenation leading to β-halogen-substituted α,α-difluoroketones **3**, and demonstrate the utility of the latter for the preparation of other *gem*-difluorinated products.

Scheme 1. Synthesis of α,α-difluoroketones.



The halogenation of non-fluorinated cyclopropanols and their derivatives was well documented,[7] and frequently employed in combination with subsequent halogen elimination to afford α,β-unsaturated ketones.[7,8] While halogen elimination is facile in non-fluorinated series,[9] it is not feasible for products **3** due to the presence of two fluorine atoms. However, for halogenation of fluorinated cyclopropyl ethers, the data available in the literature are scarce. Thus, in a single example, the reaction of a cyclopropane, derived from difluorocarbene addition to 2-methoxypropene, with an excess of bromine in water was reported to afford a tribromo-substituted product (the primary ring-opened product underwent subsequent dibromination at methyl group).[10] On the other hand, perfluorinated cyclopropyl ethers reacted with bromine at very harsh conditions (temperatures exceeding 150 °C, long reaction times).[11]

Cyclopropanes **2** can be accessed by difluorocarbene addition to silyl enol ethers. However, the limited stability of cyclopropanes **2** is a key problem determining the scope of their applications.[6] Indeed, compounds **2** are prone to transformation into α-fluoroenones, and this process can proceed either at elevated temperatures,[12] or under neutral or basic conditions even at room temperature.[13] Conventional chromatographic isolation of **2** may also be problematic.[6a] Therefore, compounds **2** must be generated under mildest conditions possible, and subsequently immediately employed, preferably in the same reaction flask.

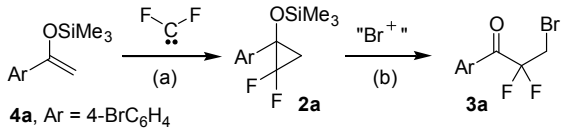
Results and Discussion

Wide variety of reagents for the generation of difluorocarbene have been described in the literature.[14] However, a silicon reagent, (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br), was selected for our study on the following reasons: (a) it can effect difluorocyclopropanation of alkenes under virtually non-basic and anhydrous conditions;[15,16] (b) it is air-stable and easy-to-handle compound;[17] (c) it is now commercially available from several suppliers, or can be prepared in one or two steps from readily available (trifluoromethyl)trimethylsilane.[15a,17a]

Silyl enol ether **4a**, derived from *p*-bromoacetophenone, was selected as a model substrate. First, enol ether **4a** was converted into cyclopropane **2a** using Me_3SiCF_2Br and hexamethylphosphoramide (HMPA) according to previously developed procedure,[6a] followed by addition of bromine (Table 1). However, there was only 19% conversion of **2a** to **3a** within 10 minutes, which did not increase with time even on mild heating (entry 1). The use of *N*-bromosuccinimide (NBS) gave similar result (entry 2). Presumably, Lewis basic HMPA inhibits bromination reaction.[18] Then we switched to cyclopropanation conditions involving bromide ion as an activator of the silicon reagent. It was reported that combination of Me_3SiCF_2Br with catalytic amounts (3 mol %) of Bu_4NBr works well at 110 °C for various alkenes.[15a] In our case, the moderate stability of cyclopropane **2a** prompted us to employ lower temperatures with concomitant increase of concentration of the bromide activator. When the reaction was performed in hot 1,2-dichloroethane (82 °C) using Me_3SiCF_2Br and 0.2 equiv of Bu_4NBr, the cyclopropane was formed

in about 60% yield. Surprisingly, ^{19}F NMR analysis indicated the formation of less reactive Me_3SiCF_2Cl, which likely originates from initial Br/Cl exchange between bromide ion and dichloroethane followed by Br/Cl exchange between appeared chloride ion and Me_3SiCF_2Br.[19] Nevertheless, subsequent addition of NBS gave rapid conversion of **2a** into **3a** (entry 3). To exclude halogen exchange, acetonitrile was used as a solvent, with the cyclopropanation being complete within 1.5 h at 80 °C. After cooling to room temperature, NBS was added that within 10 minutes effected clean conversion of **2a** into product **3a** finally isolated in 89% yield (entry 4).

Table 1. Preparation of ketone 3a.



4a, Ar = 4-BrC$_6$H$_4$

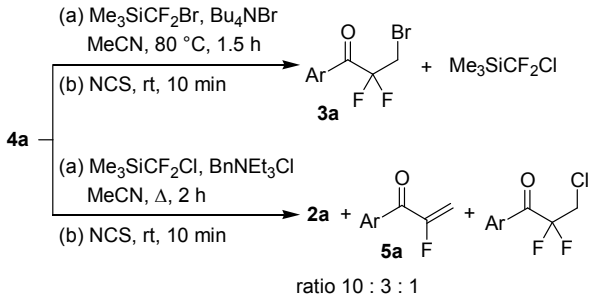
no	Conditions	**2a** : **3a**[a]	Yield of **3a**, %[a]
1	(a) $TMSCF_2Br$ (2 equiv), HMPA (3 equiv), dioxane, rt, 2h (b) Br_2 (1.5 equiv), rt, 10 min	81 : 19	16
2	(a) $TMSCF_2Br$ (2 equiv), HMPA (3 equiv), dioxane, rt, 2h (b) NBS (1.5 equiv), rt, 10 min	75 : 25	13
3	(a) $TMSCF_2Br$ (1.3 equiv), Bu_4NBr (0.2 equiv), dichloroethane, Δ, 2 h (b) NBS 1.3 equiv, rt, 10 min	– : 100	60
4	(a) $TMSCF_2Br$ (1.5 equiv), Bu_4NBr (0.2 equiv); MeCN, 80 °C, 1.5 h (b) NBS 1.3 equiv, rt, 10 min	– : 100	89[b]

[a] Determined by ^{19}F NMR of reaction mixtures.

[b] Isolated yield

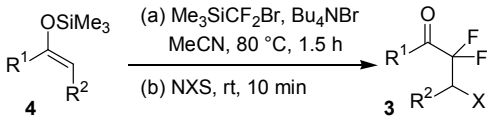
We also attempted chlorination of intermediate cyclopropane **2a** using *N*-chlorosuccinimide (NCS) (Scheme 2). Thus, when NCS was added to the cyclopropane generated from enol ether **4a** under typical conditions, only brominated product along with Me_3SiCF_2Cl were observed by ^{19}F NMR. Apparently, the combination of NCS and bromide ion served as a brominating reagent along with the formation of chloride ion, which reacted with excess of Me_3SiCF_2Br. Unfortunately, use of combination Me_3SiCF_2Cl/chloride/NCS provided a complex mixture containing significant amounts of unreacted cyclopropane **2a** along with its decomposition product — α-fluoroenone **5a**, and a minor amount of expected chlorination compound.

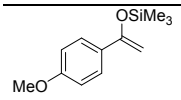
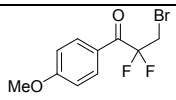
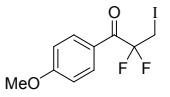
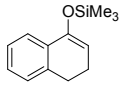
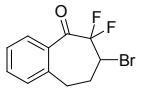
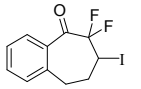
Scheme 2. Reactions using NCS.



Under the optimized conditions, a series of silyl enol ethers **4** were converted into bromo- or iodo-substituted products **3** employing NBS or NIS, respectively (Table 2). High yields of products were obtained from enol ethers derived from *p*-methoxyacetophenone, α-tetralone and cyclohexanone.

Table 2. Synthesis of 3 from silyl enol ethers 4.

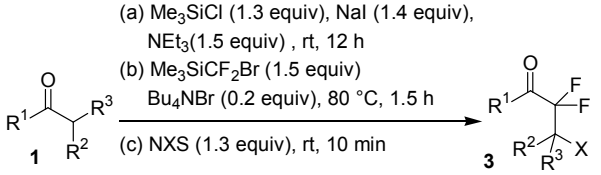


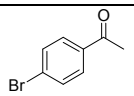
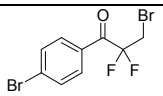
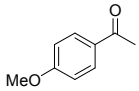
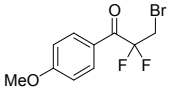
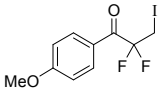
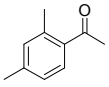
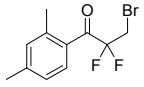
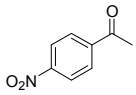
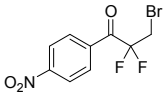
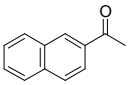
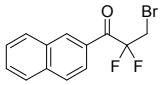
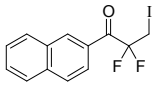
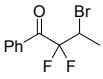
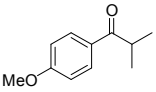
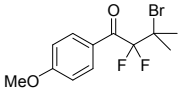
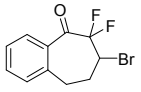
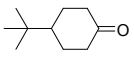
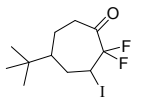
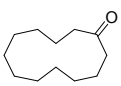
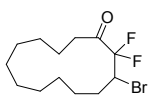
substrate		X	product		yield of **3**, %[a]
	**4b**	Br		**3b**	95
	4b	I		**3c**	82
	**4c**	Br		**3d**	97
	4c	I		**3e**	85
	**4d**	I		**3f**	80

[a] Isolated yield

Despite the fact that silyl enol ethers can be readily prepared from ketones,[20] we decided to perform the whole sequence of transformations of ketones into final products without time-consuming isolation and purification of enol ethers. For this purpose, ketones **1** were silylated using chlorosilane/NaI/NEt_3 combination,[20a] and the crude silyl enol ethers **4**, which were produced in virtually quantitative yields, were subjected to further reactions without purification (Table 3). This halogenative difluorohomologation worked well for acyclic and cyclic ketones affording final products **3** in good overall yields.

Table 3. Synthesis of 3 from ketones 1.



no.	substrate	X	product	yield of **3**, %[a]
1		**1a** Br		**3a** 78
2		**1b** Br		**3b** 89
3		**1b** I		**3c** 80
4		**1e** Br		**3g** 92
5[b]		**1f** Br		**3h** 65
6[c]		**1g** Br		**3i** 56
7		**1h** Br		**3j** 91
8		**1h** I		**3k** 90
9[b]		**1i** Br		**3l** 69
10[b]		**1j** Br		**3m** 71
11		**1c** Br		**3d** 85
12		**1d** I		**3f** 77
13		**1k** I		**3n**[d] 76
14		**1l** Br		**3o** 96

[a] Isolated yield based on ketone **1**.

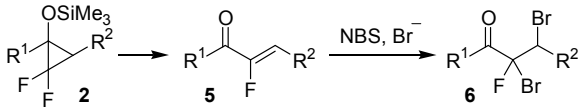
[b] Cyclopropanation conditions: 70 °C, 2.5 h.

[c] Cyclopropanation conditions: Me_3SiCF_2Br (2 equiv), Bu_4NBr (0.3 equiv), 80 °C, 2 h.

[d] Mixture of isomers 5:1.

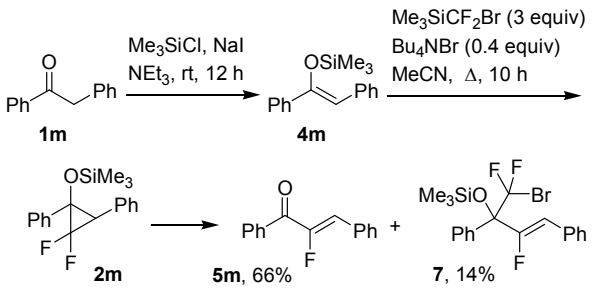
The key possible side reaction for the difluorohomologation process is the known rearrangement of cyclopropanes **2** into fluoroenones **5**[12] (Scheme 3). This rearrangement is favored by temperature and proceeds during difluorocarbene addition step, whereas formed fluoroenones **5** undergo bromination at the next step leading to by-products **6**, which are difficult to get rid of by flash chromatography. In particular, this side reaction was feasible for cyclopropanes **2** derived from acyclic alkyl substituted ketones (R^2 = Alk, entries 9 and 10). Similar processes were noted when difluorocarbene addition is disfavored by sterics (R^1 is *ortho*-substituted aryl group, entry 5) or electronic effects (R^1 contains *p*-nitro group, entry 6). For this reason, difluorocarbene addition for substrates **1f,i,j** (entries 5, 9, 10) was carried out at a bit milder conditions (70 °C, 2.5 h). For *p*-nitroacetophenone **1g**, cyclopropanation was slow and, for complete conversion of silyl enol ether, higher loading of Me_3SiCF_2Br and Bu_4NBr was used (entry 6). In the latter case, fluoroenone formation cannot be suppressed, and corresponding dibrominated by-product **6a** was also isolated in 7% yield (see Scheme 3, structure **6**, R^1 = 4-$NO_2C_6H_4$, R^2 = H).

Scheme 3. Side reaction.



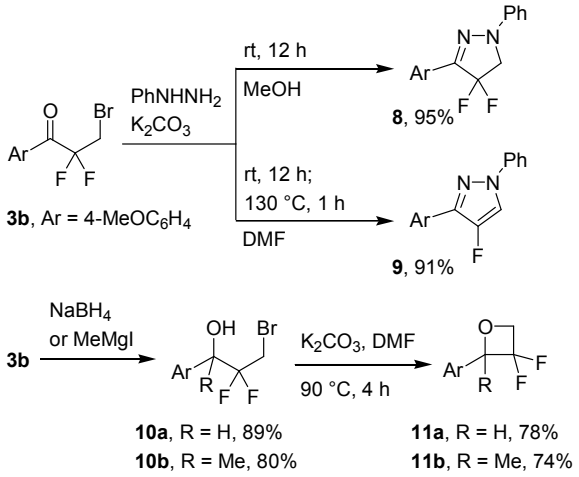
For silyl enol ether **4m**, derived from deoxybenzoin **1m**, cyclopropane **2m** was unstable under the cyclopropanation conditions (Scheme 4). As a result, the reaction of enol ether **4m** afforded fluoroenone **5m** and product **7**. The latter was formed from enone **5m** by nucleophilic addition of CF_2Br-anion at the carbonyl group.[17d]

Scheme 4. Reaction of substrate 1m.



Compounds **3** may provide easy access to fluorine-substituted heterocycles, as was exemplified by reactions of ketone **3b** (Scheme 5). Thus, treatment of **3b** with phenylhydrazine and potassium carbonate afforded either pyrazoline **8** or pyrazole **9** depending on reaction conditions. Addition of a hydride or a Grignard reagent to the carbonyl group furnished alcohols **10**, which under basic conditions were cyclized into *gem*-difluorinated oxetanes **11**. It should be pointed out that no methods have been described in the literature for the synthesis of 3,3-difluorinated oxetanes of this type, whereas by our approach these interesting products[21] can be straightforwardly obtained starting from simple ketones.

Scheme 5. Synthesis of heterocycles.



In summary, a practical method for halogenative difluorohomologation of ketones is described. The process efficiency is determined by difluorocarbene addition step, which is performed in warm acetonitrile by using a silicon reagent as a difluorocarbene source. At the same time, halogenation of the cyclopropanes occurs rapidly and selectively affording ring-opened products. The whole sequence can be conveniently performed without isolation of intermediate compounds. The products of halogenative difluorohomologation can be converted into valuable fluorine substituted heterocycles.

Experimental section

General Methods. All reactions were performed under an argon atmosphere. Acetonitrile was distilled from CaH_2 and stored over MS 4A. Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled under vacuum from CaH_2 and stored over MS 4A. Column chromatography was carried out employing silica gel (230-400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. (Bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br)[17a] and compounds **4a-d,m**[20a] were prepared according to literature procedures.

Reactions of silyl enol ethers 4a-d (General Procedure 1). Me_3SiCF_2Br (305 mg, 1.5 mmol, 1.5 equiv) and Bu_4NBr (64.5 mg, 0.2 mmol, 0.2 equiv) were added to a solution of silyl enol ether **4** (1 mmol, 1 equiv) in MeCN (1 mL) at room temperature, and the mixture was stirred for 1.5 h at 80 °C. Then the mixture was cooled to room temperature, and NBS or NIS (1.3 mmol, 1.3 equiv) was added, and the mixture was stirred for 10 min at room temperature. For the workup, the mixture was diluted with water (8 mL) and aqueous phase was extracted with hexane (3×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

Reactions of ketones 1a-h,i-l (General Procedure 2).

Preparation of silyl enol ether. NaI (210 mg, 1.4 mmol, 1.4 equiv) was placed in a tube, and dried under vacuum using heat gun. After cooling to room temperature, the tube was filled with argon. Then, MeCN (1 mL), ketone **1** (1 mmol, 1 equiv), and Et_3N (152 mg, 1.5 mmol, 1.5 equiv) were successively added. The mixture was cooled with ice/water bath, and Me_3SiCl (1.66 mL, 13 mmol, 1.3 equiv) was added at 0 °C. The cooling bath was removed, and the mixture was stirred for 12 h at room temperature. Then, volatile components were evaporated under vacuum [the vacuum of about 10-20 Torr was applied with heating in water bath at about 50 °C]. The solid residue was washed with hexane (3×15 mL) [the hexane layers were decanted and filtered through a cotton

plug]. The combined filtrates were concentrated under vacuum using rotary evaporator, furnishing silyl enol ether which was used without purification.

Reaction of silyl enol ethers. The crude silyl enol was transferred into a reaction tube, the tube was evacuated and filled with argon. Then, MeCN (1 mL), Me_3SiCF_2Br (305 mg, 1.5 mmol, 1.5 equiv) and Bu_4NBr (64.5 mg, 0.2 mmol, 0.2 equiv) were successively added at room temperature. The mixture was stirred for 1.5 h at 80 °C (for substrates **1a-e,h,k,l**) or 2.5 h at 70 °C (for substrates **1f,i,j**), and then cooled to room temperature. NBS or NIS (1.3 mmol, 1.3 equiv) was added, and the mixture was stirred for 10 min at room temperature. For the workup, the mixture was diluted with water (8 mL) and aqueous phase was extracted with hexane (3×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

*3-Bromo-1-(4-bromophenyl)-2,2-difluoropropan-1-one (**3a**).* General procedure 1, yield 292 mg (89%). General procedure 2, yield 257 mg (78%). Colorless crystals. Mp 45–46 °C. R_f 0.39 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, 2H, J = 8.2 Hz), 7.66 (d, 2H, J = 8.2 Hz), 3.89 (t, 2H, J_{H-F} = 14.7 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 28.9 (t, J = 28.1 Hz), 115.3 (t, J = 256.4 Hz), 130.3 (t, J = 3.4 Hz), 130.7, 131.7 (t, J = 3.4 Hz), 132.4, 186.9 (t, J = 31.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –100.5 (t, 2F, J = 14.7 Hz). Calcd for $C_9H_7Br_2F_2O$ (327.95): C, 32.96; H, 1.84. Found: C, 32.93; H, 1.91.

*3-Bromo-2,2-difluoro-1-(4-methoxyphenyl)propan-1-one (**3b**).* General procedure 1, yield 265 mg (95%). General procedure 2, yield 248 mg (89%). Colorless crystals. Mp 47–48 °C. R_f 0.36 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 3.89 (t, J_{H-F} = 14.7 Hz, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 29.7 (t, J = 28.2 Hz), 55.7, 114.3, 115.4 (t, J = 256.5 Hz), 124.4 (t, J = 3.3 Hz), 132.9 (t, J = 3.3 Hz), 165.0, 185.9 (t, J = 29.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –100.3 (t, 2F, J = 14.7 Hz). Calcd for $C_{10}H_9BrF_2O_2$ (279.08): C, 43.04; H, 3.25. Found: C, 42.74; H, 3.36.

*2,2-Difluoro-3-iodo-1-(4-methoxyphenyl)propan-1-one (**3c**).* General procedure 1, yield 267 mg (82%). General procedure 2, yield 262 mg (80%). Colorless crystals. Mp 55–56 °C. R_f 0.33 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.75 (t, $J_{H\text{-}F}$ = 16.1 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 1.3 (t, *J* = 27.6 Hz), 55.8, 114.3, 115.9 (t, *J* = 255.1 Hz), 124.4 (t, *J* = 3.0 Hz), 133.0 (t, *J* = 3.5 Hz), 165.0, 185.3 (t, *J* = 31.1 Hz). ^{19}F NMR (300 MHz, $CDCl_3$) δ: –94.8 (t, 2F, *J* = 16.1 Hz). Calcd for $C_{10}H_9F_2IO_2$ (326.08): C, 36.83; H, 2.78. Found: C, 36.77; H, 2.90.

*7-Bromo-6,6-difluoro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**3d**).* General procedure 1, yield 267 mg (97%). General procedure 2, yield 235 mg (85%). Yellow oil. R_f 0.32 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 4.69–4.46 (m, 1H), 3.37 (dd, *J* = 16.5, 11.0 Hz, 1H), 2.94 (dd, *J* = 16.5, 7.3 Hz, 1H), 2.70–2.37 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 30.8, 33.3 (t, *J* = 2.3 Hz), 49.5 (dd, *J* = 27.6, 23.0 Hz), 115.6 (dd, *J* = 253.4, 255.7 Hz), 127.3,130.2, 130.3, 133.2, 134.3, 140.5, 191.3 (dd, *J* = 28.8, 31.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –99.3 (dd, *J* = 243.7, 6.4 Hz), –106.4 (dd, *J* = 243.7, 14.8 Hz). Calcd for $C_{11}H_9BrF_2O$ (275.09): C, 48.03; H, 3.30. Found: C, 48.04; H, 3.31.

*6,6-Difluoro-7-iodo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**3e**).* General procedure 1, yield 274 mg (85%). Yellow oil. R_f 0.30 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 4.77–4.56 (m, 1H), 3.30–3.11 (m, 1H), 3.04–2.85 (m, 1H), 2.63–2.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 27.0 (t, *J* = 24.2 Hz), 32.6, 35.4 (t, *J* = 4.6 Hz), 116.3 (t, *J* = 253.4 Hz), 127.2, 130.2, 130.3, 133.1, 134.2, 140.9, 190.0 (t, *J* = 27.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –95.1 (dd, *J* = 238.5, 6.3 Hz), –97.8 (dd, *J* = 238.5, 19.1 Hz). Calcd for $C_{11}H_9F_2IO$ (322.09): C, 41.02; H, 2.82. Found: C, 41.11; H, 2.91.

*2,2-Difluoro-3-iodocycloheptanone (**3f**).* General procedure 1, yield 219 mg (80%). General procedure 2, yield 210 mg (77%). Colorless oil. R_f 0.29 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 4.32 (dddd, J_{H-F} = 21.1 Hz, J = 8.3, 4.1, 2.3 Hz), 2.94–2.74 (m, 1H), 2.73–2.53 (m, 1H), 2.43–2.26 (m, 1H), 2.25–2.06 (m, 1H), 1.96–1.66 (m, 3H), 1.58 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 22.0, 26.6 (dd, J = 26.1, 23.9 Hz), 27.0, 36.1 (t, J = 2.8 Hz), 38.3, 116.2 (dd, J = 255.6, 254.4 Hz), 197.9 (dd, J = 29.0, 26.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –92.47 (d, J = 241.6 Hz), –110.04 (dd, J = 241.6, 21.1 Hz). Calcd for $C_7H_9F_2IO$ (274.05): C, 30.68; H, 3.31. Found: C, 30.51; H, 3.19.

*3-Bromo-2,2-difluoro-1-phenylpropan-1-one (**3g**).*[23] General procedure 2, yield 229 mg (92%). Colorless oil. R_f 0.33 (hexane/EtOAc, 25:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, J = 8.2 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 3.91 (t, J_{H-F} = 14.7 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 29.2 (t, J = 27.6 Hz), 115.3 (t, J = 256.5 Hz), 128.9, 130.3 (t, J = 3.3 Hz), 131.7 (t, J = 3.2 Hz), 134.9, 187.7 (t, J =30.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –100.6 (t, J = 14.7 Hz). Calcd for $C_9H_7BrF_2O$ (249.05): C, 43.40; H, 2.83. Found: C, 43.27; H, 2.71.

*3-Bromo-1-(2,4-dimethylphenyl)-2,2-difluoropropan-1-one (**3h**).* General procedure 2, yield 180 mg (65%). Colorless crystals. Mp 38–37 °C. R_f 0.32 (hexane/EtOAc, 12:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, J = 8.2 Hz, 1H), 7.17–7.05 (m, 2H), 3.89 (t, J_{H-F} = 13.7 Hz, 2H), 2.48 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 21.3, 21.7, 29.2 (t, J = 29.3 Hz), 115.2 (t, J = 258.2 Hz), 126.4, 129.1, 130.2 (t, J = 5.7 Hz), 133.2, 141.1, 144.0, 190.4 (t, J = 28.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –100.2 (t, J = 13.7 Hz). Calcd for $C_{11}H_{11}BrF_2O$ (277.11): C, 47.68; H, 4.00. Found: C, 47.54; H, 3.91.

*3-Bromo-2,2-difluoro-1-(4-nitrophenyl)propan-1-one (**3i**)* The reaction of 4-nitroacetophenone **1g** was performed according to General procedure 2 using modified condition at difluorocyclopropanation step: Me_3SiCF_2Br (406 mg, 2 mmol, 2 equiv), Bu_4NBr (96 mg, 0.3 mmol, 0.3 equiv), heating for 2 h at 80 °C. The crude material was separated by column chromatography (hexane/EtOAc, gradient from 4:1 to 2:1) affording compounds **3i** (172 mg) and **6a** (23 mg). Compound **3i** was subsequently distilled in a short path apparatus at 139–141 °C (bath temp.)/0.7 Torr furnishing 165 mg (56%). Colorless oil. R_f 0.31 (hexane/EtOAc, 2:1). ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 8.34 (d, J = 8.5 Hz, 2H), 8.25 (d, J = 8.5 Hz, 2H), 3.91 (t, J_{H-F} = 14.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 28.2 (t, J = 28.1), 115.1 (t, J = 256.4 Hz), 124.0, 131.3 (t, J = 3.4 Hz), 136.1, 151.2, 186.6 (t, J = 32.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –100.5 (t, J = 14.7 Hz). Calcd for $C_9H_6BrF_2NO_3$ (294.05): C, 36.76; H, 2.06; N, 4.76; Found: C, 36.82; H, 2.09; N, 4.74.

*3-Bromo-2,2-difluoro-1-(naphthalen-2-yl)propan-1-one (**3j**).* General procedure 2, yield 272 mg (91%). Colorless crystals. Mp 61–65 °C. R_f 0.30 (hexane/EtOAc, 8:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.97–7.84 (m, 2H), 7.76–7.52 (m, 2H), 3.99 (t, J_{H-F} = 14.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 20.5 (t, J = 28.1 Hz), 115.5 (t, J = 256.4 Hz), 124.7, 124.8, 127.3, 128.0, 128.9, 130.0, 130.3, 132.4, 133.2 (t, J = 4.6 Hz), 136.3, 187.6 (t, J = 30.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –99.9 (t, J = 14.6 Hz). Calcd for $C_{13}H_9BrF_2O$ (299.11): C, 52.20; H, 3.03. Found: C, 52.11; H, 2.98.

*2,2-Difluoro-3-iodo-1-(naphthalen-2-yl)propan-1-one (**3k**).* General procedure 2, yield 311 mg (90%). Colorless crystals. Mp 73–74 °C. R_f 0.29 (hexane/EtOAc, 16:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.94–7.83 (m, 2H), 7.70–7.57 (m, 2H), 3.84 (t, J_{H-F} = 16.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 1.2 (t, J = 27.6 Hz), 115.9 (t, J = 255.4 Hz), 142.7 (t, J = 2.2 Hz), 127.2, 127.9, 128.6 (t, J = 2.8 Hz), 128.8, 129.7, 130.2, 132.3, 133.1 (t, J = 5.0 Hz), 136.2, 186.8 (t, J = 31.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –94.4 (t, J = 16.1 Hz). Calcd for $C_{13}H_9F_2IO$ (346.11): C, 45.11; H, 2.62. Found: C, 45.12; H, 2.51.

*3-Bromo-2,2-difluoro-1-phenylbutan-1-one (**3l**).* General procedure 2, yield 182 mg (69%). Colorless oil. R_f 0.32 (hexane/EtOAc, 20:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J = 7.8 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 4.64 (ddq, J_{H-F} = 14.7 Hz, J = 11.0, 6.4 Hz, 1H), 1.84 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 18.5 (t, J = 3.4 Hz), 43.6 (dd, J = 25.2, 26.7 Hz), 116.3 (t, J = 258.7 Hz), 129.0, 130.2 (t, J = 3.4 Hz), 132.6, 134.6, 188.5 (dd, J = 28.7, 31.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –103.8 (dd, J = 277.1, 11.0 Hz), –108.1 (dd, J = 276.1, 14.7 Hz). Calcd for $C_{10}H_9BrF_2O$ (263.08): C, 45.65; H, 3.45. Found: C, 45.59; H, 3.37.

*3-Bromo-2,2-difluoro-1-(4-methoxyphenyl)-3-methylbutan-1-one (**3m**).* General procedure 2. yield 218 mg (71%). Colorless oil. R_f 0.27 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H), 1.98 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 28.8 (t, *J* = 2.8 Hz), 55.7, 60.9 (t, *J* = 25.2 Hz), 114.0, 117.5 (t, *J* = 261.7 Hz), 126.7 (t, *J* = 2.3 Hz), 133.3 (t, *J* = 4.6 Hz), 164.6, 187.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –103.1 (s). Calcd for $C_{12}H_{13}BrF_2O_2$ (307.13): C, 46.93; H, 4.27. Found: C, 46.84; H, 4.23.

*5-(tert-Butyl)-2,2-difluoro-3-iodocycloheptanone (**3n**).* Mixture of diastereoisomers, 5:1. General procedure 2, yield 251 mg (76%). Colorless oil. R_f 0.28 (hexane/EtOAc, 15:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74–4.58 (m, major) and 4.19–3.98 (m, minor) (1H), 3.06–2.41 (m) and 2.35–2.15 (m) (3H), 2.11–1.77 (m) and 1.69–1.33 (m) (4H), 0.92 (s, major) and 0.88 (s, minor) (9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: Major: 24.2 (d, *J* = 2.8 Hz), 27.0 (t, *J* = 25.7 Hz), 27.6, 33.6, 35.8 (dd, *J* = 4.6, 1.8 Hz), 38.5 (t, *J* = 1.7 Hz), 46.9, 116. 1 (dd, *J* = 256.5, 254.1 Hz), 197.4 (dd, *J* = 27.9, 24.6); Minor: 24.3 (d, *J* = 2.8 Hz), 27.9 (dd, *J* = 25.7, 23.7 Hz), 21.2, 34.2, 37.6 (t, *J* = 1.7 Hz), 39.9 (d, *J* = 5.2 Hz), 50.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: Major: –99.9 (dd, 1F, *J* = 250.0, 4.2 Hz), –101.4 (dd, 1F, *J* = 250.0, 10.6 Hz); Minor: –89.9 (d, *J* = 231.5 Hz), –114.2 (dd, *J* = 231.5, 29.0 Hz). Calcd for $C_{11}H_{17}F_2IO$ (330.15): C, 40.02; H, 5.19. Found: C, 39.97; H, 5.02.

*3-Bromo-2,2-difluorocyclotridecanone (**3o**).* General procedure 2, yield 299 mg (96%). Colorless crystals. Mp 35.5–36.5 °C. R_f 0.29 (hexane/EtOAc, 30:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.28–4.04 (m, 1H), 3.00 (ddt, *J* = 19.2, 10.1, 2.8 Hz, 1H), 2.63 (ddd, *J* = 19.2, 7.3, 2.8 Hz, 1H), 2.01–1.82 (m, 1H), 1.83–1.51 (m, 4H), 1.50–1.05 (m, 13H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 21.2, 23.2, 23.9, 24.2, 24.6, 24.7, 25.5, 26.4, 30.6 (d, *J* = 2.7 Hz), 36.6, 51.1 (dd, *J* = 24.0, 22.2 Hz), 115.1 (dd, *J* = 260.4, 255.3 Hz), 201.2 (dd, *J* = 32.1, 25.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –96.7 (d, *J* = 243.7 Hz), –125.3 (dd, *J* = 243.7, 25.4 Hz). Calcd for $C_{13}H_{21}BrF_2O$ (311.21): C, 50.17; H, 6.80. Found: C, 50.14; H, 6.96.

*2,3-Dibromo-2-fluoro-1-(4-nitrophenyl)propan-1-one (**6a**).* Obtained in reaction of 4-nitroacetophenone **1g** as a by-product to **3i** (see procedure for the synthesis of **3i**). Yield 23 mg

(7%). Colorless crystals. Mp 88–89 °C. R_f. 0.23 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36–8.32 (m, 2H), 8.31–8.25 (m, 2H), 4.47 (dd, J_{H-F} = 29.7 Hz, J = 11.7 Hz, 1H), 4.20 (dd, J = 11.7, 8.1, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 33.7 (d, J = 22.7 Hz), 98.2 (J = 276 Hz), 123.9, 131.6 (d, J = 5.9 Hz), 136.8, 150.9, 187.8 (d, J = 27.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –121.7 (dd, J = 29.7, 8.1 Hz). Calcd for $C_9H_6Br_2FNO_3$ (354.96): C, 30.45; H, 1.70; N, 3.95. Found: C, 30.30; H, 1.81; N, 3.88.

Preparation of compounds 5m and 7. Silyl enol ether **4m** was prepared according to General Procedure 2 from deoxybenzoine **1m** (268 mg, 1 mmol). A solution of crude **4m** in MeCN (1 mL) was treated with Me_3SiCF_2Br (609 mg, 3 mmol, 3 equiv) and Bu_4NBr (128 mg, 0.4 mmol, 0.4 equiv) were successively added at room temperature. The mixture was heated at reflux for 10 h, and then cooled to room temperature. For the workup, the mixture was diluted with water (8 mL) and aqueous phase was extracted with hexane (3×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum. The residue was separated by semi-preparative HPLC (reversed phase column C18-reprosil ultra, 10 μ, 21×250 mm, H_2O/MeCN gradient 30/70 to 70/30). Retention time: **5m,** 9 min; **7**, 12 min.

*(Z)-2-Fluoro-1,3-diphenylprop-2-en-1-one (**5m**).*[22] Yield 149 mg (66%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98–7.36 (m, 10 H), 6.86 (d, J_{H-F} = 36.7 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 120.2 (d, J = 5.7 Hz), 128.6, 129.0, 129.5 (d, J = 3.5 Hz), 130.1 (d, J = 3.5 Hz), 130.8 (d, J = 9.2 Hz), 131.5 (d, J = 4.6 Hz), 133.0, 136.4, 154.6 (d, J = 271.9 Hz), 188.0 (d, J = 28.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –120.1 (d, J = 36.7 Hz). Calcd for $C_{15}H_{11}FO$ (226.25): C, 79.63; H, 4.90. Found: C, 79.67; H, 4.87.

({(2Z)-1-[Bromo(difluoro)methyl]-2-fluoro-1,3-diphenylprop-2-enyl}oxy)(trimethyl)silane (7). Yield 58 mg (14%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.65 (m, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.47–7.29 (m, 7H), 6.27 (d, J_{H-F} = 39.6 Hz), 0.24 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 1.6 (d, J = 1.6 Hz), 84.6 (m), 111.9 (dt, J = 6.9, 2.3 Hz), 125.7 (m), 128.17, 128.23 (t, J = 1.9 Hz), 128.4 (d, J = 2.3 Hz), 128.8, 129.3 (d, J = 8.0 Hz), 129.5, 132.3 (d, J = 2.3 Hz), 137.1,

155.4 (d, J = 269.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –53.3 (dd, J = 162.4, 13.1 Hz), –54.74 (dd, J = 162.4, 4.2 Hz), –111.0 (dd, J = 39.6, 13.1 Hz). Calcd for $C_{19}H_{20}BrF_3OSi$ (429.35): C, 53.15; H, 4.70. Found: C, 53.01; H, 4.71.

*4,4-Difluoro-3-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**8**).* Phenylhydrazine (108 mg, 1.05 mmol, 1.05 equiv) and potassium acetate (300 mg, 3 mmol, 3 equiv) were added to a solution of ketone **3b** (279 mg, 1 mmol, 1 equiv) in methanol (1.5 mL), and the mixture was stirred for 12 h at room temperature. Then, water (9 mL) water was added with stirring, and the mixture was kept without stirring for additional 10 min. The precipitate was filtered and washed with cold ethanol, and dried under vacuum. Yield 274 mg (95%). Yellow crystals. Mp 105–106 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.04–6.92 (m, 3H), 4.24 (t, $J_{H\text{-}F}$ = 21.9 Hz, 2H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 55.5, 56.7 (t, J = 31.0 Hz), 113.0, 114.5, 121.0, 127.4, 128.4 (t, J = 249.4 Hz), 129.5, 141.5 (t, J = 24.1 Hz), 141.8, 143.6, 160.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –92.7 (t, J = 21.9 Hz). Calcd for $C_{16}H_{14}F_2N_2O$ (288.29): C, 66.66; H, 4.89; N, 9.72. Found: C, 66.64; H, 4.90; N, 9.68.

*4-Fluoro-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**9**).* Phenylhydrazine (108 mg, 1.05 mmol, 1.05 equiv) and K_2CO_3 (300 mg, 3 mmol, 3 equiv) were added to a solution of ketone **3b** (279 mg, 1 mmol, 1 equiv) in DMF (1.5 mL), and the mixture was stirred for 12 h at room temperature and for 1 h at 130 °C. The mixture was cooled to room temperature, diluted with water (9 mL), and extracted with diethyl ether (3×4 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography. Yield 244 mg (91%). Colorless crystals. Mp 102–103 °C. R_f 0.27 (hexane/EtOAc, 7:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.7 Hz, 2H), 7.85 (d, $J_{H\text{-}F}$ = 4.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.6, 2H), 7.30 (t, J = 7.6, 1H), 7.02 (t, J = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 55.4, 114.1 (d, J = 29.8 Hz), 114.2, 118.5, 123.6 (d, J = 3.4 Hz), 126.4, 127.7 (d, J = 3.4 Hz), 129.5, 139.0 (d, J = 6.9 Hz), 140.2, 148.8 (d, J = 252.4 Hz), 159.8. ^{19}F NMR (282 MHz,

$CDCl_3$) δ: –173.6 (d, *J* = 4.6 Hz). Calcd for $C_{16}H_{13}FN_2O$ (268.29): C, 71.63; H, 4.88; N, 10.44. Found: C, 71.48; H, 4.77; N, 10.34.

*3-Bromo-2,2-difluoro-1-(4-methoxyphenyl)propan-1-ol (**10a**).* $NaBH_4$ (57 mg, 1.5mmol, 3 equiv) was added to a solution of ketone **3b** (140 mg, 0.5 mmol, 1 equiv) in ethanol (5 mL), and the mixture was stirred for 3 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (6 mL), and the mixture as concentrated under vacuum to 1/3 of its volume. The resulting mixture was diluted with water (3 mL) followed by extraction with methyl *tert*-butyl ether (3×4 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography. Yield 125 mg (89%). Colorless oil. ^{1}H NMR (300 MHz, DMSO-d6) δ: 7.34 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 5.8 Hz, 1H), 4.92 (dt, $J_{H\text{-}F}$ = 16.4, 5.8 Hz, 2H), 4.05–3.77 (m, 2H), 3.75 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d6), δ: 31.3 (dd, *J* =29.8, 26.4 Hz), 55.1, 71.7 (dd, *J* =29.8, 25.2 Hz), 113.4, 119.4 (dd, *J* =248.4, 245.0 Hz), 128.9, 129.4, 159.3. ^{19}F NMR (282 MHz, DMSO-d6) δ: –107.7 (ddt, 1F, *J* = 241.7, 23.3, 8.5 Hz), –112.9 (dddd, 1F, *J* = 241.7, 38.1, 16.4, 5.8 Hz). Calcd for $C_{10}H_{11}BrF_2O_2$ (281.09): C, 42.73; H, 3.94. Found: C, 42.75; H, 4.04.

*4-Bromo-3,3-difluoro-2-(4-methoxyphenyl)butan-2-ol (**10b**).* MeMgBr (3M in diethyl ether, 400 µl, 1.5 mmol, 1.5 equiv) was added dropwise to a solution of ketone **3b** (279 mg, 1 mmol, 1 equiv) in THF (400 µL) at 0 °C. The cooling bath was removed, and the mixture was stirred for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL) by extraction with diethyl ether (3×4 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography. Yield 236 mg (80%). Colorless crystals. 70–71 °C. R_f 0.29 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.78 (dddd, $J_{H\text{-}F}$ = 29.0 Hz, *J* = 12.4, 3.0, 0.8 Hz, 2H), 3.19 (dddd, $J_{H\text{-}F}$ = 29.0, 12.4, 3.0, 0.8 Hz, 1H), 2.31 (s, 1H), 1.75 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 24.4 (t, *J* = 2.8 Hz), 30.4 (t, *J* =26.5 Hz), 55.4, 76.0 (dd, *J* = 26.9, 26.0 Hz), 114.0, 120.0 (t, *J* = 251.0 Hz), 127.2, 132.2 (d, *J* = 3.3 Hz), 159.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –

111.6 (dd, 1F, J = 243.7, 29.0 Hz), –114.9 (dd, 1F, J = 243.7, 29.0 Hz). Calcd for $C_{11}H_{13}BrF_2O_2$ (295.12): C, 44.77; H, 4.44. Found: C, 44.67; H, 4.46.

Synthesis of oxetanes 11a,b. K_2CO_3 (336 mg, 3 mmol, 3 equiv) was added to a solution of alcohol **10** (1 mmol, 1 equiv) in DMF (2 mL) at room temperature, and the mixture was stirred for 4 h at 90°C. The mixture was cooled to room temperature, diluted with water (8 mL), and extracted with diethyl ether (3×4 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

*3,3-Difluoro-2-(4-methoxyphenyl)oxetane (**11a**).* Yield 157 mg (78%). Colorless oil. R_f 0.29 (hexane/EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 9.2 Hz, 2H), 5.80 (t, $J_{H\text{-}F}$ = 11.0 Hz, 1H), 5.01–4.75 (m, 2H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 55.4, 78.7 (dd, J =26.4,24.1 Hz), 91.7 (dd, J =26.4, 23.0 Hz), 114.1, 118.0 (dd, J = 282.3, 280.0 Hz), 125.7 (t, J = 2.9 Hz), 128.6, 160.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –99.5 (dq, J = 192.9, 11.0 Hz, 1F), –112.4 (ddt, J = 192.9, 17.1, 11.0 Hz, 1F). Calcd for $C_{10}H_{10}F_2O_2$ (200.18): C, 60.00; H, 5.04. Found: C, 59.84; H, 4.92.

*3,3-Difluoro-2-(4-methoxyphenyl)-2-methyloxetane (**11b**).* Yield 158 mg (74%). Colorless oil. R_f 0.33 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 4.88–4.65 (m, 2H), 3.83 (s, 3H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 23.2, 55.4, 76.5 (t, J = 26.0 Hz), 95.2 (t, J = 23.2Hz), 113.9, 118.6 (dd, J = 284.4, 282,6 Hz), 126.4, 131.2, 159.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –108.3 (dt, J = 187.5, 12.7 Hz, 1F), –113.5 (dt, J = 187.5, 12.7 Hz, 1F). Calcd for $C_{11}H_{12}F_2O_2$ (214.21): C, 61.68; H, 5.65. Found: C, 61.76; H, 5.71.

Acknowledgement

This work was supported by the Ministry of Science (project MD-3256.2015.3), Russian Foundation for Basic Research (projects 15-33-20133, 14-03-00293), and the Russian Academy of Sciences.

Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons: Chichester, 2009. (b) Begue, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine* **2008**, Wiley-VCH, Weinheim.

(2) (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813–1817. (b) Silva, A. M.; Cachau, R. E.; Sham, H. L.; Erickson, J. W. *J. Mol. Biol.* **1996**, *255*, 321–340. (c) Schirlin, D.; Baltzer, S.; Altenburger, J. M.; Tarnus, C.; Remy, J. M. *Tetrahedron* **1996**, *52*, 305–318. (d) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456–2465. (e) Ginzburg, R.; Ambizas, E. M. *Expert Opin. Drug Metab. Toxicol.* **2008**, *4*, 1091–1097.

(3) (a) Codelli, J. A.; Baskin, J. M.; Agard, N. J.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 11486–11493. (b) O'Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. *Pure Appl. Chem.* **2012**, *84*, 1587–1595.

(4) (a) Yang, M.-H.; Orsi, D. L.; Altman, R. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 2361–2365. (b) Ge, S.; Chaladaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149–4152. (c) Guo, C.; Wang, R.-W.; Qing, F.-L. *J. Fluorine Chem.* **2012**, *143*, 135–142. (d) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802–5805. (e) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583–3585. (f) Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, *114*, 127–131. (g) Qiu, Z.-M.; Burton, D. J. *Tetrahedron Letters* **1993**, *34*, 3239–3242.

(5) (a) Peng, W.; Shreeve, J. M. *J. Org. Chem.* **2005**, *70*, 5760–5763. (b) Pravst, I.; Zupan, M.; Stavber, S. *Synthesis* **2005**, 3140–3146. (c) Differding, E.; Rüegg, G. M.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 1779–1782. (d) Stavber, S.; Zupan, M. *Synlett* **1996**, 693–694.

(6) (a) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2015**, *17*, 760–763. (b) For a relevant work, see: Kageshima, Y.; Suzuki, C.; Oshiro, K.; Amii, H. *Synlett* **2015**, *26*, 63–66.

(7) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597–2632.

(8) For a recent application in process chemistry, see: Young, I. S.; Haley, M. W.; Tam, A.; Tymonko, S. A.; Xu, Z.; Hanson, R. L.; Goswami, A. *Org. Proc. Res. Dev.* **2015**, asap, DOI: 10.1021/op500135x.

(9) (a) Raiman, M. V.; Pukin, A. V.; Tyvorskii, V. I.; Kimpe, N. D.; Kulinkovich, O. G. *Tetrahedron* **2003**, *59*, 5265–5272. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Zh. Org. Khim.* **1991**, *27*, 1431–1433 [*J. Org. Chem. USSR (Engl. Transl.)* **1991***, 27,* 1251–1253]. (b) Markovic, M.; Duranova, M.; Koos, P.; Szolcsanyi, P.; Gracza, T. *Tetrahedron* **2013**, *69*, 4185–4189. (d) DePuy, C. H.; Arney, W. C.; Gibson, D. *J. Am. Chem. Soc.* **1968**, *90*, 1830–1840.

(10) Gassen, K. R.; Bielefeldt, D.; Marhold, A.; Andres, P. *J. Fluorine Chem.* **1991**, *55*, 149–162.

(11) (a) Yang, Z.-Y. *J. Org. Chem.* **2003**, *68*, 4410–4416. (b) Hung, M.-H.; Long, L.; Yang, Z.-Y. *J. Org. Chem.* **2004**, *69*, 198–201. (c) Yang, Z.-Y.; Krusic, P. J.; Smart, B. E. *J. Am. Chem. Soc.* **1995**, *117*, 5397–5398.

(12) (a) Song, X.; Chang, J.; Zhu, D.; Li, J.; Xu, C.; Liu, Q.; Wang, M. *Org. Lett.* **2015**, *17*, 1712–1715. (b) Wu, S.-H.; Yu, Q. *Acta Chim. Sinica* **1989**, *7*, 253–257.

(13) (a) The stability of compounds **2** depends on their structure. Cyclopropanes **2** derived from acetophenones are sensitive even to aqueous work-up, while cyclopropanes **2** derived from cyclic ketones can be distilled under vacuum. (b) For similar instability of difluorinated cyclopropanols generated under basic conditions, see: Crabbe, P.; Cervantes, A.; Cruz, A.; Galeazzi, E.; Iriarte, J.; Velarde, E. *J. Am. Chem. Soc.* **1973**, *95*, 6655–6665. (c) Kobayashi, Y.; Taguchi, T.; Mamada, M.; Shimizu, H.; Murohashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 3123–3129.

(14) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842–863.

(15) (a) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394. (b) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411–2413.

(16) Tsymbal, A. V.; Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 7831–7835.

(17) For various applications of Me_3SiCF_2Br reported by our group, see: (a) Kosobokov, M. D.; Dilman, A. D.; Levin, V. V.; Struchkova, M. I. *J. Org. Chem.* **2012**, *77*, 5850–5855. (b) Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2013**, *15*, 917–919. (c) Kosobokov, M. D.; Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Korlyukov, A. A.; Arkhipov, D. E.; Dilman, A. D. *Org. Lett.* **2014**, *16*, 1438–1441. (d) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2014**, *16*, 3784–3787. (e) Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 818–822. (f) Smirnov, V. O.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 11819–11823.

(18) (a) For complex formation between Br_2 and HMPA, see: Ozari, Y.; Jagur-Grodzinski, J. *J. Chem. Soc., Dalton Trans.* **1973**, 474–477. (b) For complexes of *N*-halosuccinimides with Lewis basic molecules, see: (c) Castellote, I.; Moron, M.; Burgos, C.; Alvarez-Builla, J.; Martin, A.; Gomez-Sal, P.; Vaquero, J. J. *Chem. Commun.* **2007**, 1281–1283. (d) Raatikainen, K.; Rissanen, K. *CrystEngComm* **2011**, *13*, 6972–6977. (e) Wang, Y.; Chen, X.; Zou, J.; Yu, Q. *Chem. Res. Chinese U.* **2007**, *23*, 355–359.

(19) The exchange of halogen X between Me_3SiCF_2X and halide ion (X = Cl, Br) was described, see: Wang, F.; Li, L.; Ni, C.; Hu, J. *Beilstein J. Org. Chem.* **2014**, *10*, 344–351.

(20) (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075–2088. (b) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1–26.

(21) Oxetanes have recently emerged as valuable fragments in drug discovery, see: Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052–9067.

(22) Yamada, S.; Kato, M.; Komori, Y.; Konno, T.; Ishihara, T. *Org. Biomol. Chem.* **2011**, *9*, 5493–5502.

(23) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476–3482.