JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b01590 • Publication Date (Web): 24 Aug 2015

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Nucleophilic Iododifluoromethylation of Aldehydes Using Bromine/Iodine Exchange

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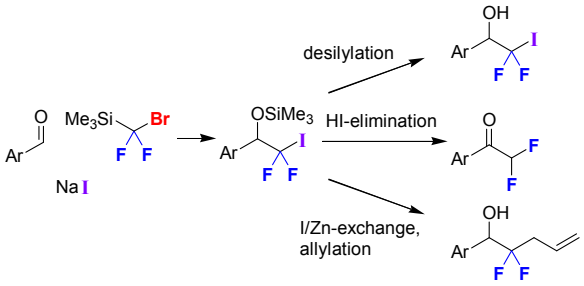


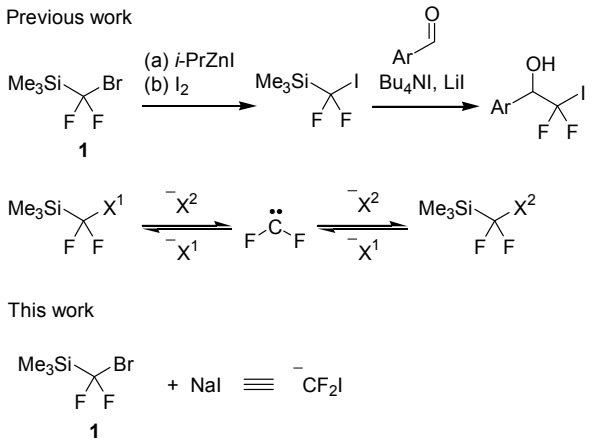
Abstract. A method for the iododifluoromethylation of aromatic aldehydes using (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br) is described. The selective formation of CF_2I group is based on using sodium iodide, with the sodium serving as a scavenger of bromide, and iodide serving as a nucleophile with respect to difluorocarbene. The primary CF_2I-addition products can undergo HI-elimination or iodine/zinc exchange followed by allylation in a one-pot manner.

Despite significant advances in the methodology for the synthesis of organofluorine compounds,[1] some structural fragments are still difficult to access. For example, in contrast to trifluoromethylation reactions, which have enjoyed great attention,[2] approaches for the direct introduction of valuable mixed fluorinated groups CF_2X are limited. In a series of interhalogen substituents CF_2X (X = Cl, Br, I), iododifluoromethyl group occupies a special position due to opportunities for its functionalization. Indeed, relatively facile activation of carbon-iodine bond in a

free-radical or electron-transfer processes can be exploited for the synthesis of various difluoromethylenated products.[3] Furthermore, ability of the CF_2I group to engage in halogen bonding can be used in crystal engineering and medicinal chemistry.[4]

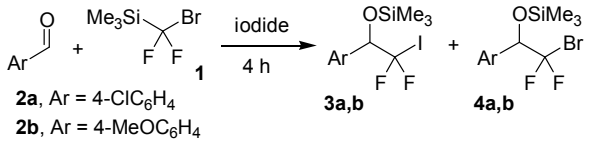
Methods for the synthesis of compounds with the CF_2I group involve radical atom-transfer processes starting from CF_2I_2,[5] or Br/I exchange in the CF_2Br group which is typically performed by organozinc formation followed by iodination,[3b,6] or, in rare cases, using direct nucleophilic substitution.[7] Iododifluoromethylation of aldehydes was also achieved by a halogenative Julia-Kocienski reaction with subsequent deprotection.[8] Recently we reported on a nucleophilic iododifluoromethylation of aldehydes and iminium ions using corresponding silicon reagent Me_3SiCF_2I,[9] which has to be prepared from Me_3SiCF_2Br (**1**) using zincation/iodination sequence (Scheme 1). At the same time, it has been noted that in the presence of halide ion, silicon reagents can undergo reversible halogen exchange.[9a,10] To synthesize chloro-substituted silane, Hu and co-workers applied stoichiometric amount of silver salt to shift the equilibrium from bromine (X^1) to chlorine (X^2) (Scheme 1). Herein we demonstrate that nucleophilic iododifluoromethylation reaction can efficiently be carried out with readily available bromo-substituted silane **1**[11,12] by using iodide ion in combination with sodium counter-ion.

Scheme 1.



First, the reaction of *p*-chlorobenzaldehyde **2a** with silane **1** was evaluated under previously described conditions (heating in propionitrile, *ca.* 100 °C),[9a] but involving tetrabutylammonium and lithium iodides (Table 1, entry 1). Virtually equimolar mixture of **3a** and **4a** was formed reflecting rapid halogen exchange. When sodium iodide was used instead of lithium iodide, the portion of iodinated product **3a** increased (entry 2), while the use of 1.5 equiv of sodium salt gave **3a** contaminated with only 2% of **4a** (entry 3). Application of sodium iodide taken in excess amount (2.5 equiv) provided iodinated product exclusively, though at incomplete conversion. Switching to 1,2-dymethoxyethane (glyme, DME), which serves as a better solvent for sodium salts, caused some rate acceleration that allowed to decrease the temperature to 80 °C and reduce the amount of silane **1** from 3 to 1.5 equiv (entry 5). Finally, addition of a lithium salt, which is believed to effect a Lewis acidic activation of the aldehyde, would be helpful. Despite the fact that lithium iodide would be a good candidate, it is usually supplied in the hydrate form, and its drying in the reaction flask is inconvenient on small scale. Rewardingly, addition of only 0.3 equiv of lithium bromide gave good yield of iodinated product **3a** (entry 6). Notably, the bromide ion from lithium salt does not lead to brominated product **4a**, likely because it is counterbalanced by sodium cation (*vide infra*). *p*-Anysaldehyde proved to be less reactive under the same conditions (entry 7), and increased loading of the reagents was required (entry 8).

Table 1. Optimization studies.



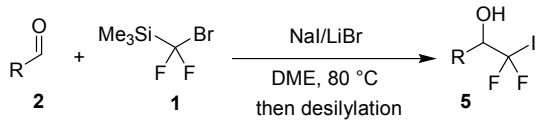
no.	**2**	**1** (equiv)	iodide (equiv)	conditions[a]	**3** : **4**[a]	Yield of **3**,%[b]
1	**2a**	3	Bu_4NI (1.1), LiI (0.5)	EtCN, Δ	1:1.2	45
2	**2a**	3	Bu_4NI (1.1), NaI (0.5)	EtCN, Δ	1.7:1	58
3	**2a**	3	Bu_4NI (1.1), NaI (1.5)	EtCN, Δ	50:1	72
4	**2a**	1.5	NaI (2.5)	EtCN, Δ	> 99:1	44
5	**2a**	1.5	NaI (2.5)	DME, 80 °C	> 99:1	61
6	**2a**	1.5	NaI (2.5), LiBr (0.3)	DME, 80 °C	> 99:1	95
7	**2b**	1.5	NaI (2.5), LiBr (0.3)	DME, 80 °C	> 99:1	59
8	**2b**	2.4	NaI (3.6), LiBr (1.0)	DME, 80 °C	> 99:1	87

[a] Reaction time 4 h.

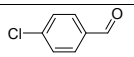
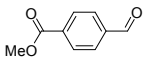
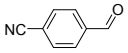
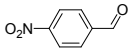
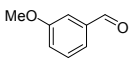
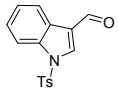
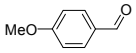
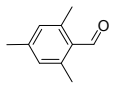
[b] Determined by ^{19}F NMR of reaction mixtures.

Under the optimized conditions, a series of aldehydes were iododifluoromethylated with silane **1** using methods A or B differing in excess of the reagents (Table 2). As a rule, 1.5 equiv of silane **1** was sufficient for aldehydes bearing electron withdrawing groups (method A), whereas for electron reach substrates a bit more forcing conditions were required (method B). In reaction of cinnamaldehyde, a small amount of a difluorocyclopropane (*ca.* 15%) arising from cyclopropanation of iododifluoromethylation product was formed that led to a decreased 69% yield of expected product **5m** (entry 13). Hydrocinnamaldehyde provided complex mixture containing less than 30% of the target product, presumably, due to propensity of the aldehyde to enolization. In this case, generation of enol ether fragment from enolizable aldehydes and ketones would lead to fast difluorocarbene addition to the electron reach double bond[12c,d] thereby consuming the carbonyl substrate irreversibly.[13]

Table 2. Iododifluoromethylation of aldehydes.



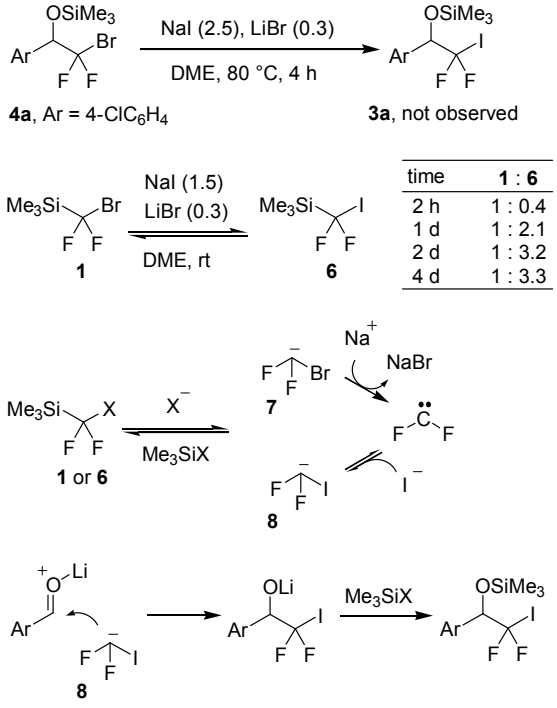
Method A: **1** (1.5 equiv), NaI (2.5 equiv), LiBr (0.3 equiv)
Method B: **1** (2.4 equiv), NaI (3.6 equiv), LiBr (1.0 equiv)

no.	aldehyde	method	time, h	**5**	yield of **5**, %[a]
1		A	4	**5a**	94
2		A	2	**5c**	87
3		A	2	**5d**	74
4		A	2	**5e**	90
5		A	5	**5f**	93
6		A	1	**5g**	97
7		A	3	**5h**	86
8		B	4	**5i**	78
9		B	4	**5j**	88
10		B	4	**5b**	87
11		B	4	**5k**	92
12		B	4	**5l**	74
13		B	4	**5m**	69
14		B	4	**5n**	22

[a] Isolated yield.

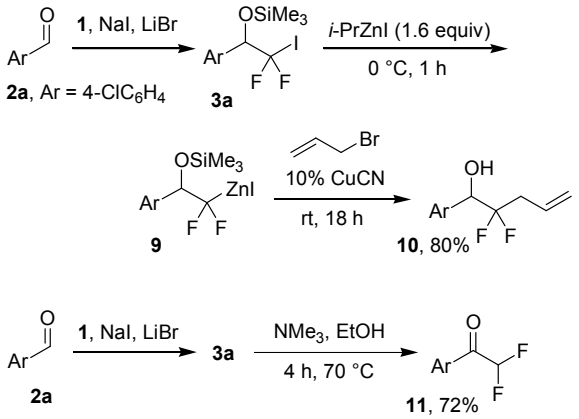
Concerning the reaction mechanism, first of all, the opportunity of formation of iodo-substituted product **3a** by Br/I exchange after carbonyl addition event was discarded, since in a blank experiment no conversion of preformed compound **4a** into **3a** under the reaction conditions was observed (Scheme 2). At the same time, the equilibrium formation of iodo-substituted silane **6** from silane **1** upon reaction with NaI/LiBr combination does take place, and proceeds even at room temperature (see table on Scheme 2). However, attempts to shift the equilibrium between silanes **1** and **6** towards **6** using excess of NaI (without LiBr) were unsuccessful. We believe that the ability of sodium ion to bind bromide better than iodide is the key factor responsible for the bromine/iodine selectivity for the product formation.[14] After initial attack of halogen on the silicon atom of reagent **1** or **6**, carbanionononic species **7** and **8** are formed. Sodium ion can decrease the concentration of carbanion **7** by abstracting the bromide. Furthermore, bromide present in reaction mixture is associated with sodium tighter compared to that of iodide, and, as a result, iodide outperforms bromide in nucleophilic reactivity towards difluorocarbene. The role of lithium ion is likely to activate the carbonyl group towards nucleophilic attack by short-lived intermediate **8** (Scheme 2, bottom equation).

Scheme 2. Mechanistic studies.



Compounds **5** can be employed in the synthesis of organofluorine compounds. Thus, addition of isopropylzinciodide to initially formed addition product **3a** led to organozinc species **9** (Scheme 3). This organozinc intermediate is reasonably stable, and upon storage at room temperature for 24 hours its decomposition did not exceed 5%. Organozinc **9** was allylated with allylbromide in the presence of copper cyanide furnishing alcohol **10** in 80% yield based on aldehyde **2a**. Iodide in compound **3a** can suffer elimination when the reaction mixture was treated with trimethylamine in ethanol affording difluoroketone **11**.[15] The latter transformation constitutes a convenient one-pot protocol for a formal insertion of CF_2 fragment into C-H bond of the aldehyde.[16]

Scheme 3. Synthesis of fluorinated compounds.



In summary, a method for nucleophilic iododifluoromethylation using a readily available silicon reagent is described. The use of sodium iodide is crucial for selective formation of iodo-substituted addition product, with the sodium cation playing a role of a binder for the bromide counter-ion.

Experimental section

General Methods. All reactions were performed under an argon atmosphere. 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 aq. $KMnO_4$ solution. Me_3SiCF_2Br (**1**)[12a] and 2,2-dimethyl-3-oxopropyl benzoate (**2n**)[12e] were obtained according to literature procedures.

Iododifluoromethylation of aldehydes.

Method A (General Procedure). A mixture of NaI (3.75 mmol, 563 mg) and LiBr (0.5 mmol, 44 mg) was dried under vacuum (0.5 mm Hg) using heat gun for three minutes. After cooling to room temperature, glyme (1.5 mL), Me_3SiCF_2Br (2.25 mmol, 457 mL), and aldehyde (1.5 mmol) were added, and the mixture was stirred at 80 °C for the time given in Table 2, and then cooled to room temperature. For the work-up, ethanol (0.75 mL) and CF_3CO_2H (3 mmol, 231 μL) were added, and the mixture was stirred for 1 hour at room temperature. Then, water (7 mL) was added, and the product was extracted with hexane/EtOAc (2/1, 3×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

Method B (General Procedure). Lithium bromide (87 mg, 1.0 mmol) and sodium iodide (540 mg, 3.6 mmol) were dried under vacuum (0.5 mm Hg) using heat gun for three minutes. After cooling to room temperature, glyme (1.0 mL), aldehyde (1.0 mmol) and $TMSCF_2Br$ (490 mg, 2.4 mmol), and the mixture was stirred at 80 °C for 4 hours, cooled to room temperature.

*Work-up for compounds **5b,i,j,k,m**:* Trifluoroacetic acid (0.27 mL, 3.6 mmol) and KHF_2 (140 mg, 1.8 mmol) were added to the reaction mixture and stirring was continued for 1 hour. Then, EtOAc (5.0 mL) and saturated aqueous Na_2CO_3 (2.0 mL) and sodium thiosulphate pentahydrate (250 mg, 1.0 mmol) were added and stirring was continued for 5 min. Organic layer was separated, and the aqueous layer was washed with EtOAc (2×3 mL). The combined organic layers were, concentrated, and the residue was purified by column chromatography.

*Work-up for compounds **5l,n**:* The reaction mixture was diluted with hexane (6 mL) with stirring, then the stirring was discontinued and inorganic solids were allowed to settle down. Liquid phase was separated with a Pasteur pipette and solid residue were washed with hexane (2×6 mL). The combined organic layers were concentrated, and the residue was subjected to column chromatography on silica gel (CH_2Cl_2/hexane, 1/1) collecting non-polar fractions (R_f >0.8 for **5l**; R_f >0.4 for **5n**). Solvents were evaporated, the residue was dissolved in glyme (1.0 mL) and methanol (0.5 mL), and treated with trifluoroacetic acid (0.075 mL, 1.0 mmol). After completion of desilylation (TLC control; 15 hours for **5l**; 3 days for **5n**,), solvents were removed under vacuum, and the residue was purified by column chromatography.

*1-(4-Chlorophenyl)-2,2-difluoro-2-iodoethanol (**5a**).*[9a] Method A. Yield 448 mg (94%). Pale yellow oil. Chromatography hexanes/EtOAc 10 : 1 → 5 : 1. R_f 0.32 (hexanes/EtOAc 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.88 (br s, 1H), 4.66 (dd, 1H, *J* = 10.1, 7.8 Hz), 7.33–7.47 (m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –54.2 (dd, 1F, *J* = 182.3, 10.1), –49.2 (dd, 1F, *J* = 182.3, 7.8).

*2,2-Difluoro-2-iodo-1-(4-methoxyphenyl)ethanol (**5b**).*[9a] Method B. Yield 274 mg (87%) Off-white crystals. Mp 63–65 °C (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.83 (br s), 3.83 (s, 3H), 4.64 (dd, 1H, *J* = 10.5, 7.8 Hz), 6.93 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –53.7 (dd, 1F, *J* = 180.2, 10.5 Hz), –49.1 (dd, 1F, *J* = 180.2, 7.8 Hz).

*Methyl 4-(2,2-difluoro-1-hydroxy-2-iodoethyl)benzoate (**5c**).* Method A. Yield 446 mg (87%). Colorless crystals. Mp 82–83 R_f 0.25 (hexane/EtOAc, 4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (d 1H, *J* =4.6 Hz), 3.91 (s, 3H), 4.73 (ddd. 1H, 10.2, 8.0, 5.0 Hz), 7.56 (d, 2H, *J* = 8.2 Hz), 8.01 (d, 2H, *J* = 8.2 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 52.5, 79.5 (t, *J* = 23.5 Hz), 107.2 (dd, *J* = 317.8, 319.5 Hz), 128.2 (t, *J* = 1.5 Hz), 129.6, 130.8, 140.0 (d, *J* = 3.4 Hz), 167.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –53.7 (dd, 1F, *J* = 182.3, 10.2 Hz), –48.7 (dd, 1F, *J* = 182.3, 8.0 Hz). Calcd for $C_{10}H_9F_2IO_3$ (342.08): C, 35.11; H, 2.65; Found C, 35.21; H, 2.69.

*4-(2,2-Difluoro-1-hydroxy-2-iodoethyl)benzonitrile (**5d**).* Method A. Yield 342 mg (74%). Colorless crystals. Mp 106–107 °C. R_f 0.26 (hexane/EtOAc, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ:

3.71 (d, 1H, J = 4.6 Hz), 4.73 (ddd, 1H, J = 9.8, 7.4, 4.8 Hz), 7.60–7.71 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 79.0 (t, J = 24.1 Hz), 106.7 (dd, J = 317.8, 319.5 Hz), 113.0, 118.4, 128.9 (t, J = 1.4), 132.1, 140.0 (d, J = 3.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –54.1 (dd, 1F, J = 184.4, 9.8 Hz), –48.8 (dd, 1F, J = 184.4, 7.4 Hz). Calcd for $C_9H_6F_2INO$ (309.05): C, 34.98; H, 1.96; N, 4.53 Found C, 35.06; H, 2.08; N, 4.36.

*2,2-Difluoro-2-iodo-1-(4-nitrophenyl)ethanol (**5e**).*[9a] Method A. Yield 444 mg (90%). White crystals. Mp 104–106 °C (hexanes). Chromatography hexanes/EtOAc 5 : 1 → 3 : 1. R_f 0.31 (hexanes/EtOAc 3 : 1). ^1H NMR (300 MHz, $CDCl_3$), δ: 3.12 (d, 1H, J = 4.4), 4.81 (ddd, 1H, J = 10.1, 7.4, 4.4), 7.71 (d, 2H, J = 8.5), 8.26 (d, 2H, J = 8.5). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –54.4 (dd, 1F, J = 185.5, 10.1), –49.1 (dd, 1F, J = 185.5, 7.4).

*2,2-Difluoro-2-iodo-1-(3-methoxyphenyl)ethanol (**5f**).* Method A. Yield 438 mg (93%). Colorless crystals. Mp 57–58 °C. R_f 0.18 (hexane/EtOAc, 6/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.10 (d, 1H, J = 4.6 Hz), 4.57 (s, 3H), 4.64 (ddd, 1H, J = 10.6, 7.7, 5.0 Hz), 6.93–7.00 (m, 1H), 7.02–7.09 (m, 2H), 7.31 (t, 1H, J = 7.9 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 55.5, 79.9 (t, J = 23.0 Hz), 107.6 (dd, J = 319.5, 317.2 Hz), 113.7 (t, J = 1.1 Hz), 115.1, 120.5 (t, J = 1.7 Hz), 129.5, 136.2 (d, J = 2.9 Hz), 159.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –53.4 (dd, 1F, J = 181.1, 10.6 Hz), –48.7 (dd, 1F, J = 181.1, 7.7 Hz). Calcd for $C_9H_9F_2IO_2$ (314.07): C, 34.42; H, 2.89; Found C, 34.29; H, 2.87.

*2,2-Difluoro-2-iodo-1-(2-nitrophenyl)ethanol (**5g**).* Method A. Yield 479 mg (97%). Yellow oil. R_f 0.28 (hexane/EtOAc, 4/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.67 (d, 1H, J = 5.0 Hz), 5.87–6.01 (m, 1H), 7.52–7.61 (m, 1H), 7.67–7.75 (m, 1H), 7.92–8.02 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 73.9 (dd, J = 25.8, 23.0 Hz). 105.9 (dd, J = 320.1, 318.4 Hz), 125.0, 129.1 (d, J = 2.9 Hz), 130.1 (t, J = 1.1 Hz), 130.3, 133.5, 148.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –54.3 (dd, 1F, J = 184.4, 10.6 Hz), –48.7 (dd, J = 184.4, 6.4 Hz). Calcd for $C_8H_6F_2INO_3$ (329.04): C, 29.20; H, 1.84; N, 4.26 Found C, 29.14; H, 1.72; N, 4.21.

*2,2-Difluoro-1-(2-furyl)-2-iodoethanol (**5h**).* Method A. Yield 353 mg (86%). Yellow oil. R_f 0.23 (hexane/EtOAc, 8/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.07 (d, 1H, J = 7.3 Hz), 4.79 (ddd, 1H, J =

8.7, 8.7, 7.3 Hz), 6.44 (d, 1H, *J* = 3.4, 1.8 Hz), 6.55 (d, 1H, *J* = 3.4 Hz), 7.48 (d, 1H, *J* = 1.8 Hz). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ: 75.3 (t, *J* = 25.2 Hz), 104.8 (t, *J* = 318.9 Hz), 110.7 (t, *J* = 1.2 Hz), 110.9, 143.6, 147.8 (dd, *J* = 3.6, 1.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –53.1 (dd, 1F, *J* = 182.3, 8.7 Hz), –51.4 (dd, 1F, *J* = 182.3, 8.7 Hz). Calcd for $C_6H_5F_2IO_2$ (274.01): C, 26.30; H, 1.84; Found C, 26.19; H, 1.77.

2,2-Difluoro-2-iodo-1-{1-[(4-methylphenyl)sulfonyl]-1H-indol-2-yl}ethanol ***(5i)****.* Method B. Yield 370 mg (78%). Amber viscous oil. R_f 0.26 (CH_2Cl_2). ^{1}H NMR (300MHz, $CDCl_3$) δ: 2.21 (br s, 1H), 2.35 (s, 3H), 4.93 (t, 1H, *J* = 8.7 Hz), 7.20–7.30 (m, 3H), 7.35 (t, 1H, *J* = 7.7 Hz), 7.62 (d, 1H, *J* = 7.7 Hz), 7.78 (d, 2H, *J* = 8.2 Hz), 7.81 (s, 1H), 7.98 (d, 1H, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.7, 75.2 (t, *J* = 25.0 Hz), 108.4 (t, *J* = 318.9 Hz), 113.7, 117.2 (d, *J* = 3.4 Hz), 120.7 (dd, *J* = 2.9, 1.1 Hz), 123.7, 125.3, 126.5, 127.1, 128.7, 130.1, 135.0 (d, *J* = 1.7 Hz), 145.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −52.6 (dd, 1F, *J* = 181.6, 8.7 Hz), −49.1 (dd, 1F, *J* = 181.6, 8.7 Hz). Calcd for $C_{17}H_{14}F_2INO_3S$ (477.27): C, 42.78; H, 2.96; N, 2.93. Found, %: C, 42.54; H, 2.81; N, 2.87.

2,2-Difluoro-2-iodo-1-phenylethanol ***(5j)****.*[9a] Method B. Yield 249 mg (88%). Colorless oil. Chromatography hexanes/EtOAc 10 : 1 → 5 : 1. R_f 0.4 (hexanes/EtOAc 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.84 (br s, 1H), 4.70 (t, 1H, *J* = 9.9 Hz), 7.37–7.54 (m, 5H). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –53.7 (dd, 1F, *J* = 180.1, 9.9 Hz), –48.8 (dd, 1F, *J* = 180.1, 9.9 Hz).

1-(2-Bromophenyl)-2,2-difluoro-2-iodoethanol ***(5k)****.*[9a] Method B. Yield 335 mg (92%). Pale yellow oil. Chromatography hexanes/EtOAc 10 : 1 → 5 : 1. R_f 0.35 (hexanes/EtOAc 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.97 (d, 1H, *J* = 4.4 Hz), 5.42 (ddd, 1H, *J* = 12.2, 6.9, 4.4 Hz), 7.23–7.33 (m, 1H), 7.35–7.45 (m, 1H), 7.60 (dd, 1H, *J* = 8.1, 1.1 Hz), 7.71 (d, 1H, *J* = 8.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –52.7 (dd, 1F, *J* = 180.1, 12.2 Hz), –49.0 (dd, 1F, *J* = 180.1, 6.9 Hz).

2,2-Difluoro-2-iodo-1-mesitylethanol ***(5l)****.* Method B. Yield 242 mg (74%). Off-white crystals. Mp 73–76 °C. R_f 0.24 (CH_2Cl_2/hexane, 1/1). ^{1}H NMR (300MHz, $CDCl_3$) δ: 2.29 (s, 3H), 2.44 (br s, 6H), 2.86 (br s, 1H), 5.58 (dd, 1H, *J* = 23.3, 2.7 Hz), 6.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:

20.9, 21.45 (d, J = 2.9 Hz), 21.51 (d, J = 3.4 Hz), 79.9 (dd, J = 26.4, 20.7 Hz), 108.0 (dd, J = 328.1, 316.7 Hz), 130.0, 130.7 (br), 138.3 (br), 138.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −48.9 (dd, 1F, J = 174.3, 23.3 Hz), −47.4 (dd, 1F, J = 174.3, 2.7 Hz). Calcd for $C_{11}H_{13}F_2IO$ (326.12): C, 40.51; H, 4.02. Found, %: C, 40.57; H, 3.94.

*(3E)-1,1-difluoro-1-iodo-4-phenylbut-3-en-2-ol (**5m**).* Method B. R_f 0.38 (CH_2Cl_2). After column chromatography, the product was purified by crystallization from hexane (ca. 5 mL) affording 215 mg (69%). White crystals. Mp 66–67 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ: 2.65 (d, 1H, J = 6.0 Hz), 4.19 (qn, 1H, J = 6.5 Hz), 6.18 (dd, 1H, J = 16.0, 6.5 Hz), 6.91 (d, 1H, J = 16.0 Hz), 7.30–7.52 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.7 (dd, J = 24.7, 22.9 Hz), 108.2 (t, J = 318.7 Hz), 122.7 (dd, J = 4.0, 1.2 Hz), 127.0, 128.8, 128.9, 135.7, 136.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −53.8 (dd, 1F, J = 180.1, 6.5 Hz), −49.6 (dd, 1F, J = 180.1, 6.5 Hz). Calcd for $C_{10}H_9F_2IO$ (310.08): C, 38.73; H, 2.93. Found, %: C, 38.85; H, 2.84.

*4,4-Difluoro-3-hydroxy-4-iodo-2,2-dimethylbutyl benzoate (**5n**).* Method B. Yield 86 mg (22%). White crystals. Mp 63–65 °C. R_f 0.27 (CH_2Cl_2). ^{1}H NMR (300MHz, $CDCl_3$) δ: 1.19 (s, 3H), 1.26 (d, 3H, J = 3.3 Hz), 3.09 (br d, 1H, J = 5.5 Hz), 3.95 (br d, 1H, J = 23.1 Hz), 4.01 (d, 1H, J = 11.0 Hz), 4.50 (d, 1H, J = 11.0 Hz), 7.49 (d, 2H, J = 7.5 Hz), 7.61 (t, 1H, J = 7.5 Hz), 8.05 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7 (dd, J = 4.0, 1.1 Hz), 22.2 (dd, J = 5.2, 1.7 Hz), 39.1, 71.8, 81.6 (dd, J = 23.5, 20.1 Hz), 108.9 (dd, J = 328.7, 320.1 Hz), 128.7, 129.7, 129.9, 133.4, 166.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −49.2 (dd, 1F, J = 171.9, 23.4 Hz), −40.4 (d, 1F, J = 171.8 Hz). Calcd for $C_{13}H_{15}F_2IO_3$ (384.16): C, 40.64; H, 3.94. Found, %: C, 40.54; H, 3.99.

Synthesis of 1-(4-chlorophenyl)-2,2-difluoropent-4-en-1-ol (10).

*Preparation of organozinc **9**.* Reaction mixture obtained from reaction of 4-chlorobenzaldehyde **2a** with Me_3CF_2Br according Method A was cooled to –30 °C. A solution of *i*-PrZnI (2.0M in THF, 2.5 mmol, 1.25 mL) was added at –30 °C, and the reaction flask was immersed into ice/water bath and stirred for one hour to give a solution of reagent **9**. ^{19}F NMR (282 MHz, THF/DME, 1/1) δ: –110.1 (br d, J = 303 Hz), –112.4 (br d, J = 303 Hz).

*Reaction of organozinc **9***. To a freshly prepared solution of reagent **9**, CuCN (0.15 mmol, 13 mg) was added at 0 °C and stirring was continued for 3 hours at 0 °C. The cooling bath was removed, and the mixture was stirred for 18 h at room temperature. For the work-up, water (5 mL) and hexane (10 mL) of hexane were added, and the mixture was shaken. The organic phase was separated, and concentrated under vacuum. To the residue, MeOH (1.5 mL) and NH_4F (4.5 mmol, 166 mg) were added and the mixture was stirred for 30 minutes. Then, water (7 mL) was added, the mixture 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. Yield 279 mg (80%). Yellow oil. R_f 0.20 (hexane/EtOAc, 8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.37–2.58 (m, 1H), 2.61–2.83 (m,1H), 2.96 (br s, 1H), 4.82 (t, 1H, *J* = 10.4 Hz), 5.19 (dd, 1H, *J* = 17.5, 1.4 Hz) 5.25 (dd, 1H, *J* = 10.9, 1.4 Hz), 5.82 (ddt, 1H, J = 17.1, 10.2, 7.1 Hz), 7.37 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.2 (t, *J* = 24.4 Hz), 74.3 (t, *J* = 28.4 Hz), 120.8, 122.3 (t, *J* = 247.2 Hz), 128.6 (t, *J* = 5.2 Hz), 128.7, 129.0 (t, *J* = 1.3 Hz), 134.8, 135.0 (t, *J* = 2.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –109.9 (dddd. 1F, *J* = 248.0, 19.6, 12.6, 10.6 Hz), –109.1 (dddd, 1F, *J* = 248.0, 19.1, 14.8, 8.5 Hz). Calcd for $C_{11}H_{11}ClF_2O$ (232.65): C, 56.79; H, 4.77; Found C, 56.74; H, 4.97.

1-(4-Chlorophenyl)-2,2-difluoroethanone (11).[17] To a reaction mixture obtained from the reaction of 4-chlorobenzaldehyde **2a** with Me_3CF_2Br according Method A, at room temperature were successively added ethanol (0.75 ml) and 50% aqueous solution of Me_3N (7.5 mmol, 1.03 mL). The reaction vessel was tightly closed and the mixture was heated at 70 °C for 4 hours with stirring. Then, the mixture was cooled to room temperature, water (7 mL) was added, and the product was extracted with pentane (3×5 mL). The combined organic layers were filtered through Na_2SO_4, and pentane was evaporated at atmospheric pressure. The residue was distilled under vacuum in a short-path apparatus, bp 70-80 °C (bath temperature)/4.5 Torr. Yield 205 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.25 (d, 1H, *J* = 53.6 Hz), 7.49 (d, 2H, *J* = 7.8 Hz), 8.01 (d, 2H, *J* = 7.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –122.5 (d, *J* = 53.6 Hz).

Acknowledgement

This work was supported by the Russian Science Foundation (project 14-13-00034).

Supporting Information

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

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