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Nucleophilic Iododifluoromethylation of Aldehydes Using Bromine/Iodine Exchange

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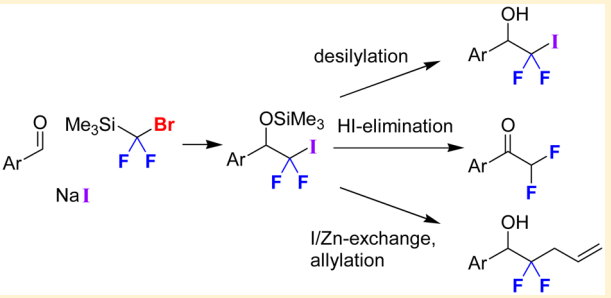
Supporting Information

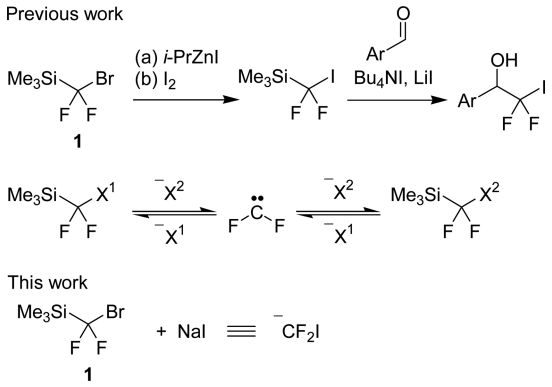
ABSTRACT: A method for the iododifluoromethylation of aromatic aldehydes using (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br) is described. The selective formation of the CF_2I group is based on using sodium iodide, with the sodium serving as a scavenger of bromide and iodide serving as a nucleophile 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), the iododifluoromethyl group occupies a special position due to opportunities for its functionalization. Indeed, relatively facile activation of the carbon−iodine bond in free-radical or electron-transfer processes can be exploited for the synthesis of various difluoromethylenated products.[3] Furthermore, the 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 a zincation/iodination sequence (Scheme 1). At the same time, it has been noted that in the presence of a halide ion, silicon reagents can undergo reversible halogen exchange.[9a,10] To synthesize chloro-substituted silane, Hu and co-workers applied a 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 an iodide ion in combination with the sodium counterion.

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). A 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 the 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 a decrease in the temperature to 80 °C and a reduction in 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,

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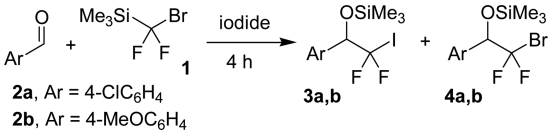
Table 1. Optimization Studies



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

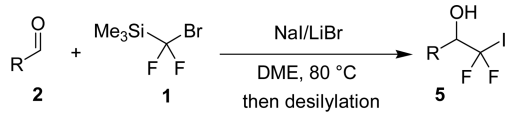
[a]Reaction time of 4 h. [b]Determined by ^{19}F NMR of reaction mixtures.

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 a 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 the 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).

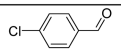
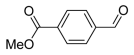
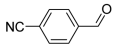
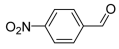
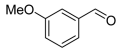
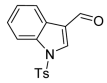
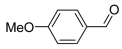
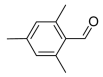
Under the optimized conditions, a series of aldehydes were iododifluoromethylated with silane **1** using method A or B differing in excess of the reagents (Table 2). As a rule, 1.5 equiv of silane **1** was sufficient for aldehydes bearing electron-withdrawing groups (method A), whereas for electron-rich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

Concerning the reaction mechanism, first of all, the opportunity for formation of iodo-substituted product **3a** by Br/I exchange after a 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 the NaI/LiBr combination does take place and proceeds even at room temperature (see table in Scheme 2). However, attempts to shift the equilibrium between silanes **1** and **6** toward **6** using an excess of NaI (without LiBr) were unsuccessful. We believe that the ability of the sodium ion to

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.

bind bromide better than iodide is the key factor responsible for the bromine/iodine selectivity for the product formation.[14] After the initial attack of the halogen on the silicon atom of reagent **1** or **6**, carbanionic species **7** and **8** are formed. The sodium ion can decrease the concentration of carbanion **7** by abstracting the bromide. Furthermore, bromide present in the reaction mixture is associated with sodium more tightly compared to the case of iodide, and as a result, iodide outperforms bromide in nucleophilic reactivity toward difluorocarbene. The role of the lithium ion is likely to activate

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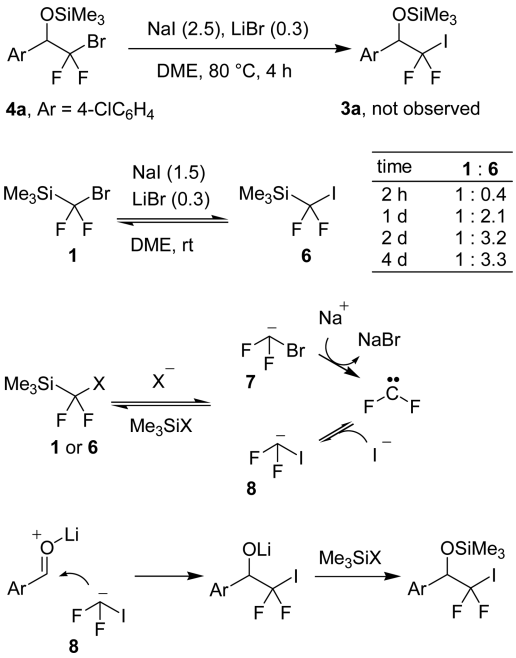
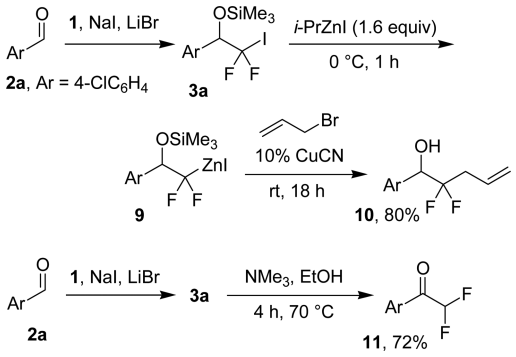
Scheme 2. Mechanistic Studies



the carbonyl group toward nucleophilic attack by short-lived intermediate **8** (Scheme 2, bottom equation).

Compounds **5** can be employed in the synthesis of organofluorine compounds. Thus, addition of isopropylzinc iodide to initially formed addition product **3a** led to organozinc species **9** (Scheme 3). This organozinc intermediate is

Scheme 3. Synthesis of Fluorinated Compounds



reasonably stable, and upon storage at room temperature for 24 h its decomposition did not exceed 5%. Organozinc **9** was allylated with allyl bromide 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]

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 an iodo-substituted addition product, with the sodium cation playing the role of a binder for the bromide counterion.

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 mmHg) using a heat gun for 3 min. After the mixture cooled 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 workup, ethanol (0.75 mL) and CF_3CO_2H (3 mmol, 231 μL) were added, and the mixture was stirred for 1 h 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 and 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 mmHg) using a heat gun for 3 min. After the mixture cooled to room temperature, glyme (1.0 mL), aldehyde (1.0 mmol), and $TMSCF_2Br$ (490 mg, 2.4 mmol) were added, and the mixture was stirred at 80 °C for 4 h and then cooled to room temperature.

Workup 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 h. Then, EtOAc (5.0 mL), saturated aqueous Na_2CO_3 (2.0 mL) and sodium thiosulfate pentahydrate (250 mg, 1.0 mmol) were added, and stirring was continued for 5 min. The 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.

Workup 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. The liquid phase was separated with a Pasteur pipet, and the solid residue was 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 nonpolar 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 h 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

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(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{^{1}H} 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). ^{1}H 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). ^{1}H 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{^{1}H} 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). ^{1}H 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{^{1}H} 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). ^{1}H 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 (300 MHz, $CDCl_3$) 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 (300 MHz, $CDCl_3$) 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 (300 MHz, $CDCl_3$) 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 (300 MHz, $CDCl_3$) 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**.* The reaction mixture obtained from reaction of 4-chlorobenzaldehyde **2a** with Me_3CF_2Br according to Method A was cooled to −30 °C. A solution of *i*-PrZnI (2.0 M in THF, 2.5 mmol, 1.25 mL) was added at −30 °C, and the reaction flask was immersed into an ice/water bath and stirred for 1 h 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 h at 0 °C. The cooling bath was removed, and the mixture was stirred for 18 h at room temperature. For the workup, water (5 mL) and hexane (10 mL) 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 min. Then, water (7 mL) was added, and the mixture was extracted with hexane (3 × 5 mL). The combined organic layers were filtered through Na_2SO_4 and 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 to Method A, at room temperature, were successively added ethanol (0.75 mL) and a 50% aqueous solution of

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Me_3N (7.5 mmol, 1.03 mL). The reaction vessel was tightly closed, and the mixture was heated at 70 °C for 4 h 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).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01590.

Copies of NMR spectra for all compounds (PDF)

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Notes

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