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Visible Light Induced Oxydifluoromethylation of Styrenes with Difluoromethyltriphenylphosphonium Bromide

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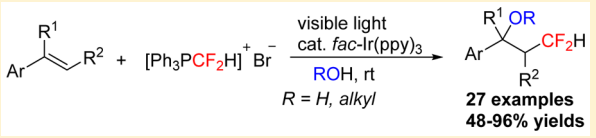
Supporting Information

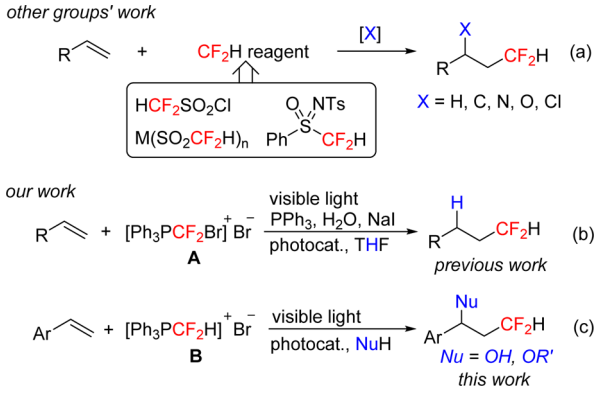
ABSTRACT: A convenient, visible light induced oxidifluoromethylation of styrenes was developed. This protocol employs the readily prepared difluoromethyltriphenylphosphonium bromide as the difluoromethylating reagent and alcohols/water as the nucleophiles, affording difluoromethyl(CF_2H)-containing alcohols and ethers in moderate to excellent yields.



INTRODUCTION

The difluoromethyl (CF_2H) substituent has emerged as an important functional group for the modulation of the physical properties in new pesticides and pharmaceuticals candidates,[1] due to the lipophilicity and hydrogen-bonding potency of the difluoromethyl group.[2] However, there had been few methods reported for the direct synthesis of difluoromethylated compounds before 2010 probably because of the lack of efficient and easily handled difluoromethylating reagents.[3] Over the past several years, with the advent of new difluoromethylating reagents and difluoromethylation reactions, great progress has been made in the direct incorporation of the CF_2H group into organic compounds.[4] Especially, the transition-metal-mediated/catalyzed[5] and radical[6] difluoromethylations of (hetero)aromatic compounds have been intensively studied. Recently, the selective transfer of the CF_2H group to alkenes has emerged as a hot research topic with increased interest. Dolbier,[7] Tan,[8] and Hu[9] as well as Koike and Akita[10] have developed the simultaneous incorporation of a CF_2H group and another functional group (H,[7e] C,[7a,8,9] N,[7d] O,[10] and Cl[7b,c]) into alkenes (Scheme 1a). These difunctionalization reactions allow convenient access to a variety of CF_2H-containing compounds. However, the employed difluoromethylating reagents including HCF_2SO_2Cl, $Zn(SO_2CF_2H)_2$, HCF_2SO_2Na, and *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine are not easy to prepare.[11] Very recently, we disclosed an unprecedented visible light induced hydrodifluoromethylation of alkenes with the readily prepared bromodifluoromethyltriphenylphosphonium bromide (**A**) using H_2O and THF as the hydrogen sources (Scheme 1b).[12] This work disclosed a new application of reagent **A**, the well-known difluorocarbene precursor, as a fluoroalkylating reagent. To extend the application of fluoroalkylphosphonium salts, we became interested in the use of other fluoroalkylphosphonium salts, such as difluoromethyltriphenylphosphonium bromide (**B**), for the preparation of difluoromethylated compounds. In

Scheme 1. Difunctionalization-Type Difluoromethylation of Alkenes



continuation of our research interest in difunctionalization-type fluoroalkylation of alkenes,[12,13] herein we describe the reaction of styrenes and reagent **B** using alcohols and H_2O as the nucleophiles under visible light conditions (Scheme 1c). It was noteworthy that during the preparation of this manuscript, Koike and Akita reported a photocatalyic oxidifluoromethylation of styrenes using *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine as the difluoromethylating reagent.[10]

RESULTS AND DISCUSSION

Reagent **B** was developed by Burton from the reaction of PPh_3, CF_2Br_2, and H_2O in THF (Scheme 2a).[14] Although this reagent has been known for more than 30 years, its application has been largely unexplored. Due to the acidity of the proton in the CF_2H group, reagent **B** easily undergoes deprotonation to give

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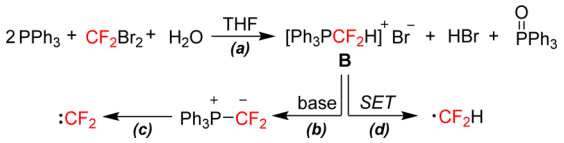
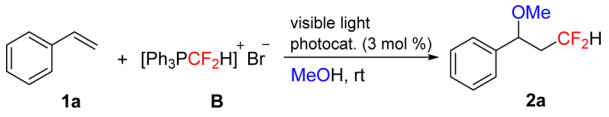
Scheme 2. Preparation and Reactions of Reagent B



difluoromethylene phosphonium ylide (Scheme 2b), which could undergo a Wittig reaction with aldehydes[15a] or release difluorocarbene (Scheme 2c).[15b] We envisaged that the appropriate choice of reaction conditions might find new applications of reagent **B**. Inspired by the recent achievements in visible light photoredox catalyzed fluoroalkylation reactions,[16] we hypothesized that reagent **B** could be reduced to generate the CF_2H radical under visible light promoted single-electron-transfer (SET) processes (Scheme 2d).

To test our hypothesis, we initially chose styrene (**1a**) as the model substrate to react with reagent **B** in MeOH under photoredox conditions (Table 1). Among the commonly

Table 1. Screening of Different Photocatalysts[a]



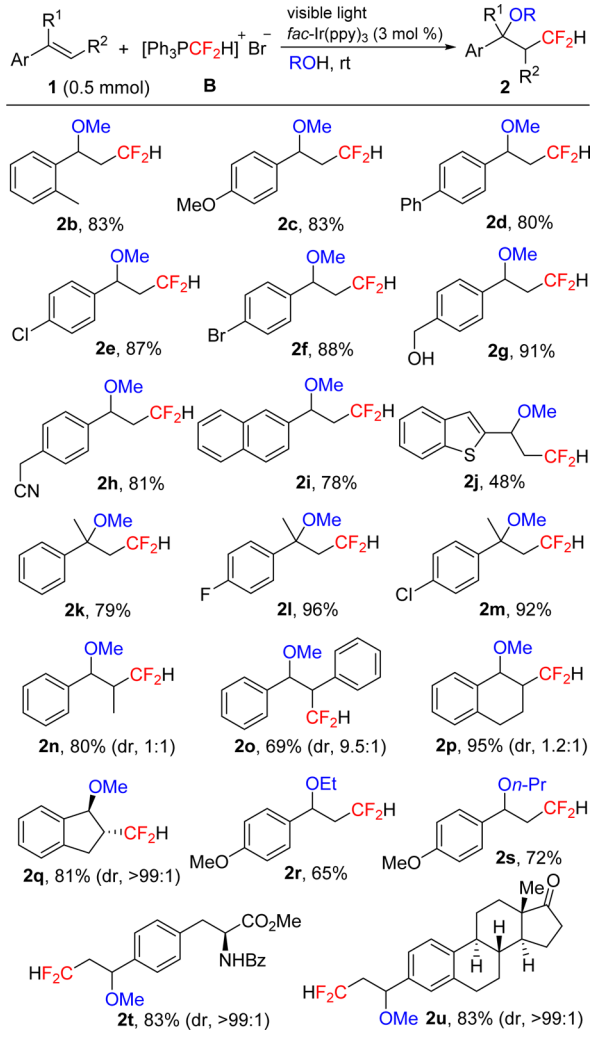
entry	photocatalyst	yield (%)[b]
1	$Ru(bpy)_3Cl_2·6H_2O$	trace
2	*fac*-Ir(ppy)$_3$	99 (96[c])
3	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$	trace
4	$[Ir(dtbpy)(ppy)_2]PF_6$	trace
5	Eosin Y	trace

[a]Reaction conditions: **1a** (0.1 mmol), difluoromethyltriphenylphosphonium bromide **B** (0.15 mmol), photocatalyst (0.003 mmol), MeOH (2.0 mL), rt, under N_2, 10 h. [b]Yields determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c]Isolated yield.

employed visible light photocatalysts including polypyridyl complexes of ruthenium and iridium as well as the organic dye (Eosin Y), only *fac*-Ir(ppy)$_3$ could promote this reaction, affording oxidifluoromethylated product **2a** in 96% yield (entry 2). This is probably because *fac*-Ir(ppy)$_3$ has a stronger reducing excited state ($E_{1/2}^{IV/*III} = -1.73$ V vs SCE) than other photocatalysts.[17]

With the optimized conditions in hand, the substrate scope of this oxidifluoromethylation reaction was examined next (Scheme 3). Styrenes **1b–i** bearing different aryl groups underwent the desired transformation, affording the corresponding products **2b–i** in moderate to excellent yields. A variety of functional groups were tolerated, including alcohol, ether, nitrile, chloro, and bromo groups. The pyridine-containing substrates were not compatible, whereas benzo[*b*]-thiophene derivative **1j** was viable for this protocol. Several disubstituted alkenes **1k–m** participated in this reaction effectively to give products **2k–m**. This oxidifluoromethylation reaction could also be applied to internal alkenes **1n–q**, and the desired products **2n–q** were isolated in high yields. However, trisubstituted styrenes were converted into other CF_2H-containing byproducts, probably because of the steric hindrance of the substrates. When other alcohols including ethanol and *n*-propanol were used as the solvents, the reactions proceeded well to afford the expected products **2r** and **2s** in good yields.

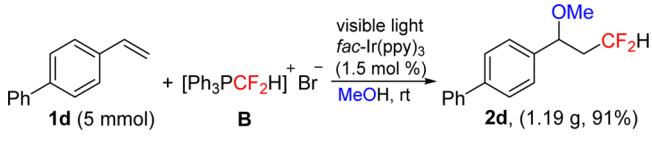
Scheme 3. Substrate Scope of Oxydifluoromethylation[a]



[a]Reaction conditions: **1** (0.5 mmol), difluoromethyltriphenylphosphonium bromide **B** (0.75 mmol), *fac*-Ir(ppy)$_3$ (0.015 mmol), ROH (10.0 mL), rt, under N_2, 10 h. Yields are those of the isolated products. The diastereomeric ratio was determined by ^{19}F NMR spectroscopy of the reaction mixture.

To demonstrate the application of this reaction further, two complex molecules including vinylestrine **1t** and vinyl-*N*-benzoyl-L-tyrosine ethyl ester **1u** were tested. Both of the oxidifluoromethylated products **2t** and **2u** were obtained in 83% yield with excellent diastereoselectivities,[10,13f] which indicated that this protocol might be applicable to "late-stage oxydifluoromethylation" of natural products and drugs. It was noteworthy that the current reaction conditions were amenable to a large-scale reaction. As shown in Scheme 4, the reaction of **1d** (5 mmol) and reagent **B** gave 1.19 g of **2d** in 91% yield. Interestingly, the yield of a 5 mmol scale reaction is even higher than that of a 0.5 mmol scale reaction in Scheme 3.

Scheme 4. Scalability of Oxydifluoromethylation



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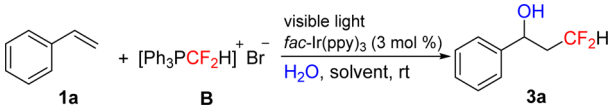
The next part of this work was to investigate the hydroxydifluoromethylation of styrenes with water as the nucleophile. We still chose styrene (**1a**) as the model substrate to optimize the reaction conditions. We directly used *fac*-Ir(ppy)$_3$ as the photocatalyst and mainly examined the effect of different solvents (Table 2). Among the common organic solvents, acetone was superior to other solvents such as DMF, DMSO, CH_2Cl_2, and EtOAc, affording product **3a** in 99% yield (entry 4).

Table 2. Screening of Different Solvents[a]

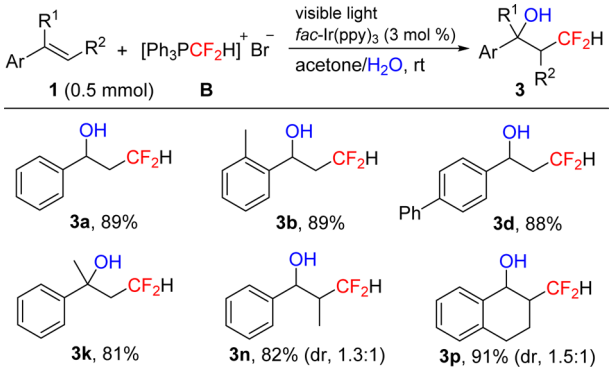


entry	solvent	yield (%)[b]
1	DMF	90
2	DMSO	55
3	CH_2Cl_2	trace[c]
4	acetone	99
5	EtOAc	trace[c]

[a]Reaction conditions: **1a** (0.1 mmol), difluoromethyltriphenylphosphonium bromide **B** (0.15 mmol), *fac*-Ir(ppy)$_3$ (0.003 mmol), H_2O (0.2 mL), solvent (2.0 mL), rt, under N_2, 10 h. [b]Yields determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c]Some side reactions, such as hydrodifluoromethylation and 1,2-bis(difluoromethylation), happened.

The substrate scope of hydroxydifluoromethylation under optimized reaction conditions (Table 2, entry 4) was then examined. As shown in Scheme 5, a series of styrenes including

Scheme 5. Substrate Scope of Hydroxydifluoromethylation[a]

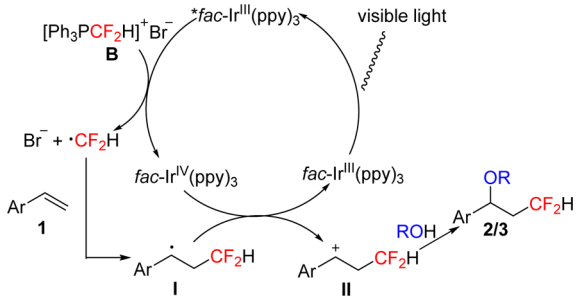


[a]Reaction conditions: **1** (0.5 mmol), difluoromethyltriphenylphosphonium bromide **B** (0.75 mmol), *fac*-Ir(ppy)$_3$ (0.015 mmol), H_2O (1.0 mL), acetone (10.0 mL), under N_2, 10 h. Yields are those of the isolated products. The diastereomeric ratio was determined by ^{19}F NMR spectroscopy of the reaction mixture.

monosubstituted alkenes **1b,d**, disubstituted alkene **1k**, and internal alkenes **1n,p** underwent this transformation, affording the corresponding hydroxydifluoromethylated products **3a–p** in 81–91% yields.

Finally, several control experiments were carried out to gain insight into the reaction mechanism. No reaction took place in the absence of visible light or *fac*-Ir(ppy)$_3$. Furthermore, the oxytrifluoromethylation reaction was completely inhibited in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a known radical scavenger. Based on these results, this transformation appears to proceed through a mechanism (Scheme 6) similar to those of the reported photocatalyzed

Scheme 6. Proposed Reaction Mechanism



oxytrifluoromethylation[18] and oxidifluoromethylation[10] of alkenes. First, irradiation with visible light excites *fac*-Ir^{III}(ppy)$_3$ into a strong reducing species **fac*-Ir^{III}(ppy)$_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE). Among those common photocatalysts in Table 1, only *fac*-Ir(ppy)$_3$ has such a strongly reducing excited state, which is capable of reducing reagent **B** to a CF_2H radical.[19] Then, the addition of the CF_2H radical to styrenes **1** generates radical intermediate **I**, which can be easily oxidized to the corresponding cation intermediate **II**. Finally, the nucleophilic attack of cation **II** by alcohols or water affords the oxidifluoromethylated products **2** and **3**. Although the Br anion exists in the reaction system, no bromodifluoromethylated product could be detected in the presence of a large excess of more nucleophilic alcohols or water.

CONCLUSION

We have developed an efficient and practical oxidifluoromethylation of styrenes by visible light photoredox catalysis. This method is highlighted by use of the readily prepared difluoromethyltriphenylphosphonium bromide (**B**) as the difluoromethylating reagent and alcohols/water as the nucleophiles. The cheapness of the reagents and mild reaction conditions make this protocol attractive in the preparation of CF_2H-containing alcohols and ethers.

EXPERIMENTAL SECTION

General Experimental Methods. ^1H NMR (TMS as the internal standard) and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Substrates were purchased from commercial sources or were prepared according to literature procedures.[20]

General Procedure for Oxidifluoromethylation of Styrenes. A 50 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with difluoromethyltriphenylphosphonium bromide **B** (295.0 mg, 0.75 mmol, 1.5 equiv) and *fac*-Ir(ppy)$_3$ (9.8 mg, 0.015 mmol, 3 mol %). Then styrene **1** (0.5 mmol, 1.0 equiv) and alcohol (10 mL) were added. The flask was sealed with 3M vinyl electrical tape. The mixture was degassed three times according to the freeze–pump–thaw procedure before it was stirred at room temperature for 1 h. The flask was placed at a distance of 2 cm from the blue LEDs. The mixture was stirred under a nitrogen atmosphere and irradiated by blue LEDs for 10 h. After the reaction was complete, 30% H_2O_2 (1 mL) was added to the reaction mixture,

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and then the reaction mixture was concentrated under vacuum. The residue was purified with silica gel column chromatography to provide the desired product.

*(3,3-Difluoro-1-methoxypropyl)benzene (**2a**).* Compound **2a** was obtained as a light yellow liquid (89.1 mg, 96%), Hexane/Et_2O = 50:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.39−7.24 (m, 5H), 6.09−5.78 (m, 1H), 4.33−4.30 (m, 1H), 3.23 (s, 3H), 2.39−2.23 (m, 1H), 2.14−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.5, 128.9, 128.3, 126.6, 116.0 (t, J = 236.6 Hz), 78.8−78.6 (m), 56.7, 42.9 (t, J = 21.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −115.7 to −118.9 (m, 2F); IR (thin film) ν 3031, 2935, 2827, 1494, 1426, 1401, 1117, 1092, 760, 701 cm^{-1}; MS (EI): m/z (%) 186 (M^+), 155 (100); HRMS (EI-TOF) calculated for $C_{10}H_{12}F_2O$: 186.0856; found: 186.0860.

*1-(3,3-Difluoro-1-methoxypropyl)-2-methylbenzene (**2b**).* Compound **2b** was obtained as a colorless liquid (83.3 mg, 83%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.37−7.14 (m, 4H), 6.15−5.84 (m, 1H), 4.62−4.59 (m, 1H), 3.19 (s, 3H), 2.33 (s, 3H), 2.33−2.14 (m, 1H), 2.10−1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.4, 135.3, 130.7, 127.7, 126.6, 125.6, 116.0 (t, J = 237.0 Hz), 75.2−75.0 (m), 56.5, 41.9 (t, J = 21.1 Hz), 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.5 to −119.1 (m, 2F); IR (thin film) ν 3024, 2937, 1463, 1399, 1190, 1117, 1027, 759, 727 cm^{-1}; MS (EI): m/z (%) 200 (M^+), 169 (100); HRMS (EI-TOF) calculated for $C_{11}H_{14}F_2O$: 200.1013; found: 200.1008.

*1-(3,3-Difluoro-1-methoxypropyl)-4-methoxybenzene (**2c**).* Compound **2c** was obtained as a light yellow liquid (90.2 mg, 83%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.21 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.06−5.75 (m, 1H), 4.28−4.24 (m, 1H), 3.70 (s, 3H), 3.16 (s, 3H), 2.36−2.25 (m, 1H), 2.08−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.6, 132.3, 127.8, 114.1, 115.9 (t, J = 237.0 Hz), 78.2−78.0 (m), 56.3, 55.3, 42.7 (t, J = 21.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −118.8 (m, 2F); IR (thin film) ν 2997, 2938, 2838, 1613, 1514, 1399, 1251, 1118, 834 cm^{-1}; MS (EI): m/z (%) 216 (M^+), 151 (100); HRMS (EI-TOF) calculated for $C_{11}H_{14}F_2O_2$: 216.0962; found: 216.0961.

*4-(3,3-Difluoro-1-methoxypropyl)-1,1′-biphenyl (**2d**).* Compound **2d** was obtained as a light yellow liquid (105.0 mg, 80%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.64−7.61 (m, 4H), 7.49−7.36 (m, 5H), 6.17−5.86 (m, 1H), 4.39−4.24 (m, 1H), 3.29 (s, 3H), 2.44−2.34 (m, 1H), 2.20−2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.3, 140.7, 139.4, 128.9, 127.6, 127.5, 127.1, 127.0, 115.9 (t, J = 237.0 Hz), 78.5−78.3 (m), 56.7, 42.8 (t, J = 21.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.6 to −118.7 (m, 2F); IR (thin film) ν 3030, 2936, 2825, 1487, 1398, 1118, 1030, 804, 698 cm^{-1}; MS (EI): m/z (%) 262 (M^+), 197 (100); HRMS (EI-TOF) calculated for $C_{16}H_{16}F_2O$: 262.1169; found: 262.1166.

*1-Chloro-4-(3,3-difluoro-1-methoxypropyl)benzene (**2e**).* Compound **2e** was obtained as a light yellow liquid (95.6 mg, 87%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.08−5.77 (m, 1H), 4.31−4.27 (m, 1H), 3.17 (s, 3H), 2.32−2.21 (m, 1H), 2.06−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.9, 134.0, 129.0, 127.8, 115.6 (t, J = 237.0 Hz), 78.0−77.9 (m), 56.6, 42.7 (t, J = 21.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.8 to −119.0 (m, 2F); IR (thin film) ν 2993, 2937, 2827, 1491, 1427, 1399, 1094, 1030, 830 cm^{-1}; MS (EI): m/z (%) 220 (M^+), 155 (100); HRMS (EI-TOF) calculated for $C_{10}H_{11}ClF_2O$: 220.0466; found: 220.0469.

*1-Bromo-4-(3,3-difluoro-1-methoxypropyl)benzene (**2f**).* Compound **2f** was obtained as a light yellow liquid (117.3 mg, 88%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.08−5.77 (m, 1H), 4.30−4.26 (m, 1H), 3.18 (s, 3H), 2.32−2.20 (m, 1H), 2.08−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.5, 132.0, 128.2, 122.1, 115.6 (t, J = 237.0 Hz), 78.1−77.9 (m), 56.7, 42.7 (t, J = 21.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.8 to −119.0 (m, 2F); IR (thin film) ν 2991, 2937, 2826, 1486, 1398, 1118, 1082, 1071, 825 cm^{-1}; MS (EI): m/z (%) 264 (M^+), 199 (100); HRMS (EI-TOF) calculated for $C_{10}H_{11}BrF_2O$: 263.9961; found: 263.9959.

*(4-(3,3-Difluoro-1-methoxypropyl)phenyl)methanol (**2g**).* Compound **2g** was obtained as a light yellow liquid (98.0 mg, 91%), hexane/ethyl acetate = 2:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.07−5.77 (m, 1H), 4.67 (s, 2H), 4.33−4.29 (m, 1H), 3.18 (s, 3H), 2.40−2.21 (m, 1H), 2.09−2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.0, 139.7, 127.4, 126.7, 115.8 (t, J = 237.0 Hz), 78.4−78.3 (m), 64.9, 56.5, 42.7 (t, J = 21.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −118.8 (m, 2F); IR (thin film) ν 3395, 2937, 2880, 1424, 1400, 1188, 1118, 1061, 844 cm^{-1}; MS (EI): m/z (%) 216 (M^+), 151 (100); HRMS (EI-TOF) calculated for $C_{11}H_{14}F_2O_2$: 216.0962; found: 216.0965.

*2-(4-(3,3-Difluoro-1-methoxypropyl)phenyl)acetonitrile (**2h**).* Compound **2h** was obtained as a light yellow liquid (91.6 mg, 81%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.35−7.30 (m, 4H), 6.08−5.77 (m, 1H), 4.34−4.30 (m, 1H), 3.74 (s, 2H), 3.20 (s, 3H), 2.33−2.20 (m, 1H), 2.07−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 140.5, 130.0, 128.4, 127.3, 117.7, 115.7 (t, J = 237.0 Hz), 78.2−78.0 (m), 56.7, 42.7 (t, J = 21.2 Hz), 23.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −118.9 (m, 2F); IR (thin film) ν 2993, 2937, 2827, 2251, 1423, 1117, 1029, 921, 810 cm^{-1}; MS (EI): m/z (%) 225 (M^+), 160 (100); HRMS (EI-TOF) calculated for $C_{12}H_{13}F_2NO$: 225.0965; found: 225.0966.

*2-(3,3-Difluoro-1-methoxypropyl)naphthalene (**2i**).* Compound **2i** was obtained as a light yellow liquid (91.5 mg, 78%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.89−7.43 (m, 7H), 6.14−5.83 (m, 1H), 4.52−4.48 (m, 1H), 3.24 (s, 3H), 2.48−2.37 (m, 1H), 2.22−2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.8, 133.4, 133.3, 128.9, 128.0, 127.8, 126.5, 126.3, 126.0, 123.9, 115.9 (t, J = 237.0 Hz), 78.8−78.7 (m), 56.7, 42.7 (t, J = 21.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.6 to −118.7 (m, 2F); IR (thin film) ν 3057, 2990, 2936, 1399, 1371, 1189, 1117, 1030, 820 cm^{-1}; MS (EI): m/z (%) 236 (M^+), 171 (100); HRMS (EI-TOF) calculated for $C_{14}H_{14}F_2O$: 236.1013; found: 236.1012.

*2-(3,3-Difluoro-1-methoxypropyl)benzo[b]thiophene (**2j**).* Compound **2j** was obtained as a light yellow liquid (116.2 mg, 48%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.82−7.84 (m, 1H), 7.73−7.75 (m, 1H), 7.31−7.39 (m, 2H), 7.25 (s, 1H), 5.82−6.13 (m, 1H), 4.67−4.71 (m, 1H), 3.32 (s, 3H), 2.45−2.55 (m, 1H), 2.24−2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.8, 139.2, 124.7, 124.6, 123.7, 122.7, 115.5 (t, J = 237.0 Hz), 74.8−74.9 (m), 56.8, 55.3, 42.7 (t, J = 21.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −119.0 (m, 2F); IR (thin film) ν 3059, 2992, 2936, 2826, 1459, 1400, 1195, 1106, 749 cm^{-1}; MS (EI): m/z (%) 242 (M^+), 177 (100); HRMS (EI-TOF) calculated for $C_{12}H_{12}F_2OS$: 242.0577; found: 242.0568.

*(4,4-Difluoro-2-methoxybutan-2-yl)benzene (**2k**).* Compound **2k** was obtained as a light yellow liquid (79.6 mg, 79%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.38−7.24 (m, 5H), 5.97−5.67 (m, 1H), 3.08 (s, 3H), 2.39−2.17 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.7, 128.6, 127.5, 125.9, 116.0 (t, J = 236.0 Hz), 76.5−76.4 (m), 50.3, 47.4 (t, J = 20.4 Hz), 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −111.1 to −113.7 (m, 2F); IR (thin film) ν 3061, 2989, 2932, 1447, 1399, 1115, 1073, 1035, 702 cm^{-1}; MS (EI): m/z (%) 200 (M^+), 169 (100); HRMS (EI-TOF) calculated for $C_{11}H_{14}F_2O$: 200.1013; found: 200.1018.

*1-(4,4-Difluoro-2-methoxybutan-2-yl)-4-fluorobenzene (**2l**).* Compound **2l** was obtained as a light yellow liquid (104.3 mg, 96%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.35−7.02 (m, 4H), 5.97−5.66 (m, 1H), 3.06 (s, 3H), 2.33−2.15 (m, 2H), 1.61(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.5 (d, J = 244.3 Hz), 139.6 (d, J = 2.9 Hz), 127.7 (d, J = 8.0 Hz), 115.4 (d, J = 21.2 Hz), 115.8 (t, J = 237.0

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Hz), 76.1−76.0 (m), 50.2, 47.5 (t, J = 20.4 Hz), 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −111.3 to −113.8 (m, 2F), −115.3 to −115.4 (m, 1F); IR (thin film) ν 2987, 2941, 2831, 1603, 1510, 1425, 1117, 1097, 837, 608 cm^{-1}; MS (EI): m/z (%) 218 (M^+), 187 (100); HRMS (EI-TOF) calculated for $C_{11}H_{13}F_3O$: 218.0918; found: 218.0924.

*1-Chloro-4-(4,4-difluoro-2-methoxybutan-2-yl)benzene (**2m**).* Compound **2m** was obtained as a light yellow liquid (108.2 mg, 92%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40−7.28 (m, 4H), 5.97−5.67 (m, 1H), 3.07 (s, 3H), 2.31−2.17 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.4, 133.4, 128.7, 127.4, 115.7 (t, J = 236.2 Hz), 76.2−76.1 (m), 50.3, 47.3 (t, J = 20.4 Hz), 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −111.3 to −113.7 (m, 2F); IR (thin film) ν 2987, 2831, 1490, 1399, 1117, 1098, 1082, 829, 747 cm^{-1}; MS (EI): m/z (%) 234 (M^+), 169 (100); HRMS (EI-TOF) calculated for $C_{11}H_{13}ClF_2O$: 234.0623; found: 234.0624.

*(3,3-Difluoro-1-methoxy-2-methylpropyl)benzene (**2n**).* Compound **2n** was obtained as a colorless liquid (79.8 mg, 80%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38−7.24 (m, 5H), 6.32−6.03 (m, 0.5H), 5.74−5.44 (m, 0.5H), 4.29 (d, J = 5.6 Hz, 0.5H), 3.97 (d, J = 10.0 Hz, 0.5H), 3.23 (s, 1.5H), 3.13 (s, 1.5H), 2.30−2.04 (m, 1H), 0.98 (d, J = 6.8 Hz, 1.5H), 0.70 (d, J = 6.8 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.2, 139.1, 128.54, 128.52, 128.50, 128.3, 127.8, 127.60, 127.57, 126.8, 118.0 (t, J = 239.1 Hz), 117.0 (t, J = 240.6 Hz), 84.1 (t, J = 2.2 Hz), 82.0 (t, J = 5.8 Hz), 57.1, 56.5, 44.9 (t, J = 19.0 Hz), 43.6 (t, J = 39.4 Hz), 7.4−7.2 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −120.9 to −121.8 and −126.6 to −127.5 (m, 1F), −124.4 to −125.3 and −133.2 to −134.2 (m, 1F); IR (thin film) ν 3065, 2986, 2942, 1455, 1395, 1128, 1074, 996, 703 cm^{-1}; MS (EI): m/z (%) 200 (M^+), 121 (100); HRMS (EI-TOF) calculated for $C_{11}H_{14}F_2O$: 200.1013; found: 200.1006.

*(3,3-Difluoro-1-methoxypropane-1,2-diyl)dibenzene (**2o**).* Compound **2o** was obtained as a light yellow solid (90.2 mg, 69%), hexane/Et_2O = 50:1 as eluent for the column chromatography. Mp: 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.24−7.04 (m, 10H), 6.59−5.86 (m, 1H), 4.69−4.51 (m, 1H), 3.40−3.29 (m, 1H), 3.22 (s, 2.3H), 3.19 (s, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.7, 133.31, 133.29, 130.2, 130.1, 128.6, 128.5, 128.3, 128.21, 128.18, 128.1, 128.0, 127.9, 127.6, 127.5, 127.1, 118.0 (t, J = 239.1 Hz), 116.2 (t, J = 239.2 Hz), 83.7−83.6 (m), 77.2, 56.6−56.2 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −120.4 to −121.3 and −122.6 to −123.5 (m, 1F), −121.9 to −122.8 and −122.6 to −127.6 (m, 1F); IR (thin film) ν 3064, 3032, 2934, 1455, 1129, 1104, 1072, 988, 689 cm^{-1}; MS (EI): m/z (%) 262 (M^+), 121 (100); HRMS (EI-TOF) calculated for $C_{16}H_{16}F_2O$: 262.1169; found: 262.1175.

*2-(Difluoromethyl)-1-methoxy-1,2,3,4-tetrahydronaphthalene (**2p**).* Compound **2p** was obtained as a light yellow liquid (100.7 mg, 95%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38−7.11 (m, 4H), 6.09−5.73 (m, 1H), 4.47−4.30 (m, 1H), 3.37 (s, 1.5H), 3.33 (s, 1.5H), 3.01−2.75 (m, 2H), 2.49−1.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.4, 136.9, 134.9, 133.7, 130.2, 129.5, 128.7, 128.7, 128.3, 127.9, 126.2, 125.3, 118.5 (t, J = 237.0 Hz), 76.5−75.5 (m), 56.6, 56.0, 44.0 (t, J = 26.4 Hz), 42.3 (t, J = 19.0 Hz), 27.5, 27.0, 18.7 (t, J = 5.2 Hz), 17.4 (t, J = 5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −120.7 to −121.6 and −126.1 to −127.0 (m, 1F), −123.7 to −124.6 and −126.4 to −127.4 (m, 1F); IR (thin film) ν 3023, 2941, 2824, 1458, 1114, 1079, 1053, 769, 745 cm^{-1}; MS (EI): m/z (%) 212 (M^+), 129 (100); HRMS (EI-TOF) calculated for $C_{12}H_{14}F_2O$: 212.1013; found: 212.1016.

*2-(Difluoromethyl)-1-methoxy-2,3-dihydro-1H-indene (**2q**).* Compound **2q** was obtained as a light yellow liquid (80.3 mg, 81%), hexane/Et_2O = 100:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39−7.22 (m, 4H), 6.26−5.95 (m, 1H), 4.68−4.67 (m, 1H), 3.34 (s, 3H), 3.17−3.10 (m, 1H), 2.96−2.90 (m, 1H), 2.85−2.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.8, 141.0, 129.2, 126.4, 125.5, 125.4, 117.3 (t, J = 234.8 Hz), 83.1 (d, J = 10.2 Hz), 56.4, 48.3 (t, J = 21.1 Hz), 31.3 (d, J = 8.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −115.6 to −124.1(m, 2F); IR (thin film) ν 2990, 2928, 2824, 1404, 1117, 1090, 1072, 1036, 759 cm^{-1}; MS (EI): m/z (%) 198 (M^+), 167 (100); HRMS (EI-TOF) calculated for $C_{11}H_{12}F_2O$: 198.0856; found: 198.0853.

*1-(1-Ethoxy-3,3-difluoropropyl)-4-methoxybenzene (**2r**).* Compound **2r** was obtained as a light yellow liquid (74.6 mg, 65%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 6.08−5.77 (m, 1H), 4.39−4.35 (m, 1H), 3.79 (s, 3H), 3.38−3.22 (m, 2H), 2.35−2.24 (m, 1H), 2.08−1.99 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.4, 133.1, 127.6, 114.1, 116.0 (t, J = 236.3 Hz), 76.2−76.1 (m), 63.9, 55.3, 42.9 (t, J = 21.1 Hz), 15.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.9 to −119.0 (m, 2F); IR (thin film) ν 2976, 2874, 2839, 1513, 1249, 1118, 1037, 834, 594 cm^{-1}; MS (EI): m/z (%) 230 (M^+), 165 (100); HRMS (EI-TOF) calculated for $C_{12}H_{16}F_2O_2$: 230.1118; found: 230.1115.

*1-(3,3-Difluoro-1-propoxypropyl)-4-methoxybenzene (**2s**).* Compound **2s** was obtained as a light yellow liquid (88.3 mg, 72%), hexane/Et_2O = 50:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.11−5.80 (m, 1H), 4.39−4.35 (m, 1H), 3.80 (s, 3H), 3.28−3.13 (m, 2H), 2.36−2.23 (m, 1H), 2.10−1.98 (m, 1H), 1.58−1.49 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.4, 133.1, 127.6, 114.0, 116.0 (t, J = 237.0 Hz), 76.4−76.3 (m), 70.2, 55.2, 43.0 (t, J = 20.4 Hz), 22.9, 10.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.9 to −119.1 (m, 2F); IR (thin film) ν 3000, 2996, 2887, 2839, 1613, 1513, 1118, 1096, 833, 594 cm^{-1}; MS (EI): m/z (%) 244 (M^+), 137 (100); HRMS (EI-TOF) calculated for $C_{13}H_{18}F_2O_2$: 244.1275; found: 244.1278.

*(2S)-Methyl 2-Benzamido-3-(4-(3,3-difluoro-1-methoxypropyl)-phenyl)propanoate (**2t**).* Compound **2t** was obtained as a dark yellow liquid (162.3 mg, 83%), hexane/ethyl acetate = 1:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71−7.12 (m, 9H), 6.60 (d, J = 6.8 Hz, 1H), 6.06−5.76 (m, 1H), 5.10−5.05 (m, 1H), 4.29−4.26 (m, 1H), 3.75 (s, 3H), 3.32−3.15 (m, 5H), 2.35−2.22 (m, 1H), 2.09−2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.1, 166.9, 139.3, 136.0, 133.9, 131.9, 129.8, 128.6, 127.0, 126.8, 115.8 (t, J = 237.0 Hz), 78.3−78.2 (m), 56.6, 53.5, 52.4, 42.9−42.5 (m), 37.6 (t, J = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −118.8 (m, 2F); IR (thin film) ν 3322, 2993, 2935, 1745, 1645, 1533, 1217, 1118, 714 cm^{-1}; MS (EI): m/z (%) 391 (M^+), 105 (100); HRMS (EI-TOF) calculated for $C_{21}H_{23}F_2NO_4$: 391.1595; found: 391.1601.

*(8R,9S,13S,14S)-3-(3,3-Difluoro-1-methoxypropyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]-phenanthren-17-one (**2u**).* Compound **2u** was obtained as a light yellow liquid (150.6 mg, 83%), hexane/ethyl acetate = 3:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29−7.00 (m, 3H), 6.07−5.76 (m, 1H), 4.26−4.23 (m, 1H), 3.18 (s, 3H), 2.93−2.89 (m, 2H), 2.53−1.93 (m, 9H), 1.67−1.39 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.6, 139.8, 137.7, 136.9 (d, J = 3.6 Hz), 127.0 (d, J = 9.5 Hz), 125.7 (d, J = 3.0 Hz), 123.9 (d, J = 14.6 Hz), 115.9 (t, J = 237.0 Hz), 78.2−78.5 (m), 56.6, 50.6, 48.0, 44.4, 43.0−42.5 (m), 38.1, 35.8, 31.6, 29.4 (d, J = 3.7 Hz), 25.7 (d, J = 2.2 Hz), 21.6, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.7 to −118.8 (m, 2F); IR (thin film) ν 2932, 2868, 2825, 1740, 1498, 1398, 1117, 1030, 841 cm^{-1}; MS (EI): m/z (%) 362 (M^+), 297 (100); HRMS (EI-TOF) calculated for $C_{22}H_{28}F_2O_2$: 362.2057; found: 362.2059.

General Procedure for Hydroxydifluoromethylation of Styrenes. A 50 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with difluoromethyltriphenylphosphonium bromide **B** (295.0 mg, 0.75 mmol, 1.5 equiv) and *fac*-Ir(ppy)$_3$ (9.8 mg, 0.015 mmol, 3 mol %). Then styrene **1** (0.5 mmol, 1.0 equiv), H_2O (1 mL), and alcohol (10 mL) were added. The flask was sealed with 3M vinyl electrical tape. The mixture was degassed three times by the freeze−pump−thaw procedure before it was stirred at room temperature for 1 h. The flask was placed at a distance of 2 cm from the blue LEDs. The mixture was stirred under a nitrogen atmosphere and irradiated by blue LEDs for 10 h. After the reaction was complete, the reaction mixture was concentrated under vacuum.

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The residue was purified with silica gel column chromatography to provide the desired product.

*3,3-Difluoro-1-phenylpropan-1-ol (**3a**).* Compound **3a** was obtained as a light yellow liquid (76.9 mg, 89%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39−7.30 (m, 5H), 6.12−5.81 (m, 1H), 4.92−4.89 (m, 1H), 2.36−2.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.0, 128.9, 128.3, 125.7, 116.1 (t, J = 237.0 Hz), 69.6−69.5 (m), 43.1 (t, J = 20.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.4 to −118.3 (m, 2F); IR (thin film) ν 3415, 3033, 2993, 1403, 1119, 1053, 761, 701, 542 cm^{-1}; MS (EI): m/z (%) 172 (M^+), 107 (100); HRMS (EI-TOF) calculated for $C_9H_{10}F_2O$: 172.0700; found: 172.0702.

*3,3-Difluoro-1-(o-tolyl)propan-1-ol (**3b**).* Compound **3b** was obtained as a light yellow liquid (82.4 mg, 89%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48−7.14 (m, 4H), 6.19−5.88 (m, 1H), 5.16 (d, J = 9.2 Hz, 1H), 2.33 (s, 3H), 2.29−2.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.2, 134.3, 130.7, 127.9, 126.6, 124.9, 116.2 (t, J = 237.8 Hz), 65.9−65.8 (m), 42.2 (t, J = 20.4 Hz), 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.3 to −118.6 (m, 2F); IR (thin film) ν 3420, 3026, 2974, 1490, 1402, 1118, 1061, 760, 727 cm^{-1}; MS (EI): m/z (%) 186 (M^+), 121 (100); HRMS (EI-TOF) calculated for $C_{10}H_{12}F_2O$: 186.0856; found: 186.0862.

*1-([1,1′-Biphenyl]-4-yl)-3,3-difluoropropan-1-ol (**3d**).* Compound **3d** was obtained as a light yellow solid (109.6 mg, 88%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. Mp: 63−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.61−7.36 (m, 9H), 6.18−5.87 (m, 1H), 4.98−4.95 (m, 1H), 2.41−2.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.0, 141.2, 140.6, 128.9, 127.6, 127.2, 126.2, 116.2 (t, J = 237.0 Hz), 69.4−69.2 (m), 43.1 (t, J = 20.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −116.3 to −118.2 (m, 2F); IR (thin film) ν 3416, 3030, 2996, 1487, 1401, 1119, 1059, 765, 697 cm^{-1}; MS (EI): m/z (%) 248 (M^+), 183 (100); HRMS (EI-TOF) calculated for $C_{15}H_{14}F_2O$: 248.1013; found: 248.1020.

*4,4-Difluoro-2-phenylbutan-2-ol (**3k**).* Compound **3k** was obtained as a light yellow liquid (75.5 mg, 81%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44−7.24 (m, 5H), 5.93−5.63 (m, 1H), 2.45−2.32 (m, 2H), 2.14 (s, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 146.5, 128.6, 127.3, 124.4, 116.3 (t, J = 237.0 Hz), 72.3 (t, J = 5.9 Hz), 47.4 (t, J = 19.7 Hz), 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −112.7 to −113.0 (m, 2F); IR (thin film) ν 3602, 3455, 2985, 1447, 1402, 1118, 1031, 853, 701 cm^{-1}; MS (EI): m/z (%) 186 (M^+), 121 (100); HRMS (EI-TOF) calculated for $C_{10}H_{12}F_2O$: 186.0856; found: 186.0852.

*3,3-Difluoro-2-methyl-1-phenylpropan-1-ol (**3n**).* Compound **3n** was obtained as a light yellow liquid (75.8 mg, 82%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38−7.24 (m, 5H), 6.32−5.53 (m, 1H), 4.93−4.53 (m, 1H), 2.30−2.04 (m, 2H), 1.00−0.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.9, 128.7, 128.6, 128.4, 127.8, 126.8, 125.9, 118.3 (t, J = 240.6 Hz), 117.2 (t, J = 240.7 Hz), 75.0−74.9 (m), 72.4−72.3 (m), 44.8 (t, J = 18.3 Hz), 44.1 (t, J = 19.7 Hz), 7.7 (t, J = 5.1 Hz), 6.6 (t, J = 5.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −120.9 to −132.6 (m, 2F); IR (thin film) ν 3431, 3032, 2986, 1457, 1396, 1062, 987, 765, 703 cm^{-1}; MS (EI): m/z (%) 186 (M^+), 107 (100); HRMS (EI-TOF) calculated for $C_{10}H_{12}F_2O$: 186.0856; found: 186.0860.

*2-(Difluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**3p**).* Compound **3p** was obtained as a light yellow liquid (90.4 mg, 91%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51−7.10 (m, 4H), 6.22−5.79 (m, 1H), 4.83−4.76 (m, 1H), 3.00−2.75 (m, 2H), 2.16−1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.8, 136.8, 136.32, 136.30, 129.9, 129.3, 128.7, 128.6, 127.7, 127.3, 126.61, 126.57, 118.4 (t, J = 237.7 Hz), 117.2 (t, J = 240.6 Hz), 68.3−68.2 (m), 66.5−66.3 (m), 46.8 (t, J = 19.0 Hz), 44.3 (t, J = 20.4 Hz), 28.1, 27.9, 19.1 (t, J = 4.4 Hz), 17.0−16.9 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm −121.1 to −128.0 (m, 2F); IR (thin film) ν 3364, 3023, 2936, 1458, 1406, 1107, 1052, 775, 741 cm^{-1}; MS (EI): m/z (%) 198 (M^+), 119 (100); HRMS (EI-TOF) calculated for $C_{11}H_{12}F_2O$: 198.0856; found: 198.0860.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00234.

Copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Dibari, C.; Pastore, G.; Roscigno, G.; Schechter, P. J.; Sjoerdsma, A. *Ann. Int. Med.* **1986**, *105*, 83. (b) Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. *J. Agric. Food Chem.* **1991**, *39*, 981. (c) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302. (d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645. (e) Jeschke, P.; Baston, E.; Leroux, F. R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1027.

(2) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. (b) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701. (c) Xu, Y.; Qian, L.; Pontsler, A. V.; McIntyre, T. M.; Prestwich, G. D. *Tetrahedron* **2004**, *60*, 43. (d) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. *J. Med. Chem.* **2009**, *52*, 1525.

(3) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

(4) (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (c) Lu, Y.; Liu, C.; Chen, Q.-Y. *Curr. Org. Chem.* **2015**, *19*, 1638.

(5) (a) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (c) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405. (d) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014**, *1*, 774. (e) Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984. (f) Gu, Y.; Chang, D.; Leng, X.; Gu, Y.; Shen, Q. *Organometallics* **2015**, *34*, 3065. (g) Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44.

(6) (a) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 11868.

(7) (a) Tang, X.-J.; Thomoson, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2014**, *16*, 4594. (b) Tang, X.-J.; Dolbier, W. R., Jr. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246. (c) Thomoson, C. S.; Tang, X.-J.; Dolbier, W. R., Jr. *J. Org. Chem.* **2015**, *80*, 1264. (d) Zhang, Z.; Tang, X.; Thomoson, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2015**, *17*, 3528. (e) Tang, X.-J.; Zhang, Z.; Dolbier, W. R., Jr. *Chem. - Eur. J.* **2015**, *21*, 18961.

(8) Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z. *Eur. J. Org. Chem.* **2014**, *2014*, 3196.

(9) He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 1838.

(10) Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. *Chem. - Eur. J.* **2016**, *22*, 1262.

DOI: 10.1021/acs.joc.6b00234
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(11) For the preparation of HCF_2SO_2Cl, $Zn(SO_2CF_2H)_2$, and $NaSO_2CF_2H$, see refs 7a, 6a, and 9, respectively. For the preparation of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine, see: (a) Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109. (b) Pégot, B.; Urban, C.; Bourne, A.; Le, T. N.; Bouvet, S.; Marrot, J.; Diter, P.; Magnier, E. *Eur. J. Org. Chem.* **2015**, *2015*, 3069.
(12) Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 1479.
(13) (a) Yang, Y.; Jiang, X.-L.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 7538. (b) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (c) Jiang, X.-Y.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 14177. (d) Yu, W.; Xu, X.-H.; Qing, F.-L. *Adv. Synth. Catal.* **2015**, *357*, 2039. (e) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *Org. Biomol. Chem.* **2015**, *13*, 8740. (f) Yang, B.; Xu, X.-H.; Qing, F.-L. *Org. Lett.* **2015**, *17*, 1906.
(14) Burton, D. J. *J. Fluorine Chem.* **1983**, *23*, 339.
(15) (a) Li, Q.; Lin, J.-H.; Deng, Z.-Y.; Zheng, J.; Cai, J.; Xiao, J.-C. *J. Fluorine Chem.* **2014**, *163*, 38. (b) Wei, Y.; Yu, L.; Lin, J.; Zheng, X.; Xiao, J. *Chin. J. Chem.* **2016**, *34*, 481.
(16) (a) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967 and references cited therein. (b) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 539. (c) Rueda-Becerril, M.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2014**, *136*, 2637. (d) Tomita, R.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 12923. (e) Singh, A.; Kubik, J. J.; Weaver, J. D. *Chem. Sci.* **2015**, *6*, 7206. (f) Beatty, J. W.; Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *Nat. Commun.* **2015**, *6*, 7919. (g) Xie, J.; Zhang, T.; Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 2934. (h) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743. (i) Panferova, L. I.; Tsymbal, A. V.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2016**, *18*, 996.
(17) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(18) (a) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (b) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem. - Eur. J.* **2013**, *19*, 6209. (c) Yasu, Y.; Arai, Y.; Tomita, R.; Koike, T.; Akita, M. *Org. Lett.* **2014**, *16*, 780. (d) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240.
(19) The reduction potential of reagent **B** is −1.22 V. For details see the Supporting Information of ref 12.
(20) Yasu, Y.; Koike, T.; Akita, M. *Org. Lett.* **2013**, *15*, 2136.

DOI: 10.1021/acs.joc.6b00234
J. Org. Chem. 2016, 81, 7001−7007