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gem-Difluoromethylation of α- and γ-ketoesters: preparation of *gem*-difluorinated α-hydroxyesters and γ-butyrolactones

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Abstract—$PhSCF_2SiMe_3$ has been demonstrated as difluoromethyl carbanion synthon ($^-CF_2H$). It reacts chemoselectively with α- and γ-ketoesters at the keto group in the presence of a catalytic amount of TBAF in THF to give the corresponding α-hydroxy ester adducts as well as γ-*gem*-difluorophenylsulfanylmethylated-γ-butyrolactones in good yields. Reductive cleavage of the phenylsulfanyl group of these products employing Bu_3SnH/AIBN gives the corresponding *gem*-difluoromethylated α-hydroxyesters and γ-butyrolactones in good yields.

1. Introduction

Organofluorine compounds have received remarkable interest due to their utilities in several fields, such as medicinal, biological, and agricultural chemistry.[1] These compounds have been found to display interesting biological effects, which are attributed to the unique properties of the fluorine atom. Because of the potential applications in many fields, the fluorine-containing analogues of natural products as well as development of new synthetic methods for the incorporation of fluorine atom(s) into organic molecules have been extensively investigated.[2] Of particular interest is the introduction of a *gem*-difluoromethyl moiety into organic molecules. It has been reported that the difluoromethyl group (CF_2H) is isosteric and isopolar to a CH_2OH group.[1b,3] Direct methods for the preparation of *gem*-difluorinated compounds by reacting appropriate substrates with fluorinating agents such as DAST,[4] SF_4,[5] TBAF,[6] BrF_3,[7] Selectfluor[8] or NFSI[9] have been reported. Several nucleophilic *gem*-difluoromethylation building blocks employing difluoromethylphenylsulfone ($PhSO_2CF_2H$),[10] bromodifluoromethylphenylsulfone ($PhSO_2CF_2Br$),[11] (trifluoromethyl)trimethylsilane (CF_3SiMe_3),[12] [(difluoromethyl)(phenylsulfonyl)]trimethylsilane ($PhSO_2CF_2SiMe_3$),[13] [(difluoromethyl)(phenylsulfanyl)]trimethylsilane ($PhSCF_2SiMe_3$) (**1**),[14] and [difluoro(phenylseleno)methyl]trimethylsilane ($PhSeCF_2SiMe_3$)[15] have been extensively studied.

The report by Prakash et al.,[13,14b] Hu,[14c] and our recent complementary studies[14a] on the use of **1** as the *gem*-difluoromethylated building block with carbonyl compounds demonstrated the versatility of this strategy. We envisaged that with α-, β-, and γ-ketoesters as the carbonyl components, this technology would lead to high functionalized *gem*-difluoromethylated derivatives. We are pleased to report that such studies have been successful. Additionally, the chemoselectivity of **1** with γ-ketoesters led to γ-butyrolactones possessing *gem*-difluoromethyl group at γ-position.

2. Results and discussion

Initially, the reaction of **1** with methyl benzoate catalyzed by TBAF was studied. It was found that no expected benzoylated product, α,α-difluoro-α-phenylsulfanylacetophenone, could be detected. Methyl benzoate was completely recovered. Prakash[4b,16] reported that the same reaction using tetrabutylammonium triphenyldifluorosilicate (TBAT) provided a moderate yield of the expected benzoylated product. The reaction employing TBAF implied that the reaction of **1** toward ketoesters might be chemoselective providing the adducts arisen from the addition to only the keto functional group. Indeed, the treatment of α-ketoester **2a** with 1 equiv of **1** in the presence of 10 mol % of TBAF in THF at −78 °C to room temperature afforded the expected adduct **3a** in 68% yield after chromatography (Scheme 1 and Table 1, Entry 1). The best result was observed when 2 equiv of **1** was employed under the same conditions; **3a** was isolated in 87% yield (Table 1, Entry 1). Following the standard conditions, a variety of adducts of type **3** were prepared in good yields from a wide range of α-ketoesters (Scheme 1). The results are summarized in Table 1. Having the adducts **3** in hands, reductive cleavage of the phenylsulfanyl group to

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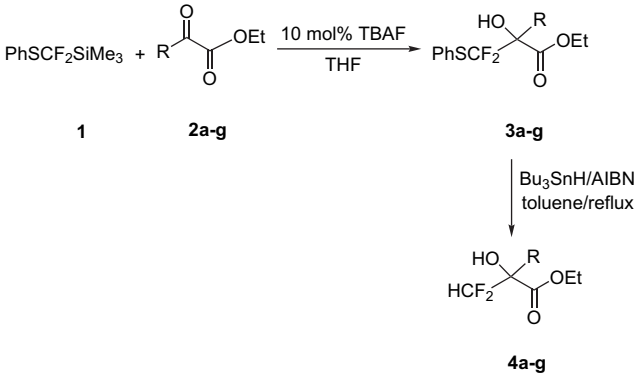
the corresponding *gem*-difluorinated compounds **4** was achieved by treatment with Bu_3SnH/AIBN in refluxing toluene for 15 h (Table 1).

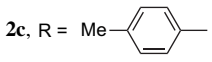
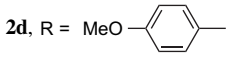
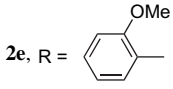
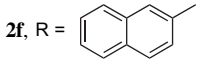
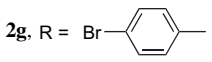
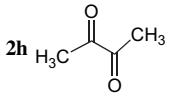
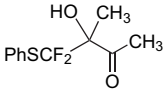


Scheme 1.

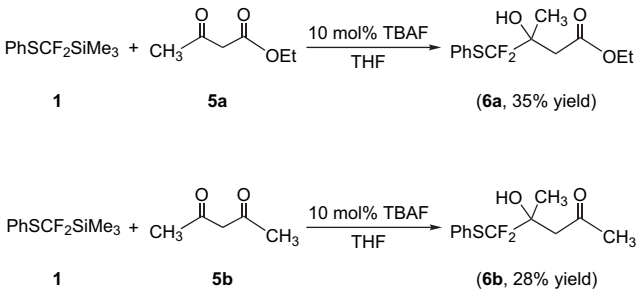
To investigate the generality of the reaction, we studied the reaction of **1** with β-ketoesters and β-diketones, which contain highly acidic methylene protons. The reaction of **1** with highly enolizable ethyl acetoacetate (**5a**) and 2,4-pentanedione (**5b**) under the standard conditions provided low yields of the corresponding adducts **5a** and **5b** (Scheme 2). The results may be due to competitive proton abstraction of the methylene protons of ethyl acetoacetate (**5a**) and 2,4-pentadione (**5b**) during the reaction.

Encouraged by the above results, we expected that when a γ-ketoester **7** was reacted under the same reaction conditions,

Table 1. Preparation of adducts **3** by fluoride-catalyzed addition of $PhSCF_2SiMe_3$ (**1**) to α-ketoesters **2** and their reduction to *gem*-difluorinated adducts **4**

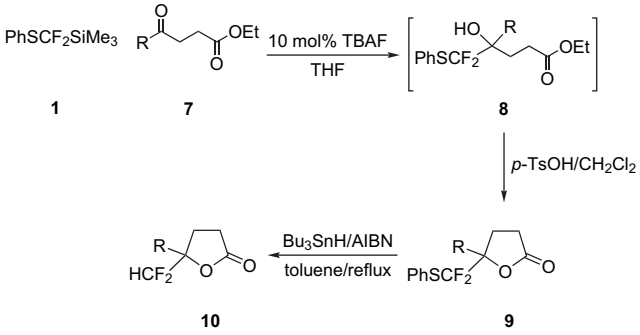
Entry	α-Ketoesters **2**	Adducts **3**[a,b] (%)	Products **4**[a] (%)
1	**2a**, R=CH_3	**3a**, 87 (68)[c]	**4a**, —[d]
2	**2b**, R=Ph	**3b**, 77 (60)[c]	**4b**, 74
3	**2c**, R = 	**3c**, 91 (65)[c]	**4c**, 80
4	**2d**, R = 	**3d**, 98	**4d**, 88
5	**2e**, R = 	**3e**, 98	**4e**, 91
6	**2f**, R = 	**3f**, 77	**4f**, 89
7	**2g**, R = 	**3g**, 96	**4g**, 90
8	**2h** 	**3h**, 80 (77)[c] 	—[d]

[a] Isolated yields by preparative thin-layer chromatography on silica gel.
[b] Two equivalents of **1** was employed.
[c] Yields given in parentheses are of the products obtained from the reaction using 1 equiv of **1**.
[d] The reductive product could not be isolated due to its volatility.



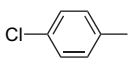
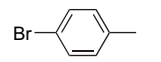
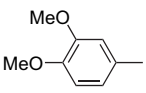
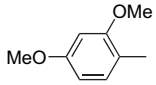
Scheme 2.

high chemoselectivity of the reaction leading to an adduct of type **8** would be obtained. Lactonization of the adduct **8** would furnish the corresponding γ-butyrolactone **9** containing *gem*-difluoro moieties (Scheme 3). As expected, fluoride-catalyzed addition reaction of **1** (2 equiv) with γ-ketoester **7a** proceeded with high chemoselectivity to give a mixture of adduct **8a** and γ-butyrolactone **9a**, which was treated with a catalytic amount of *p*-TsOH in CH_2Cl_2 to furnish γ-butyrolactone **9a** in 90% yield. The results for the preparation of γ-butyrolactones **9** are summarized in Table 2. Treatment of **9a** with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene for 15 h afforded *gem*-difluorinated adduct **10a** in 76% yield. Under the same conditions, *gem*-difluorinated adducts **10** were prepared in good yields as summarized in Table 2.



Scheme 3.

Table 2. Preparation of *gem*-difluorinated γ-butyrolactones **9** and **10**

Entry	γ-Ketoesters **7**	**9**[a] (%)	**10**[a] (%)
1	**7a**, R=Ph	**9a**, 90	**10a**, 76
2	**7b**, R = 	**9b**, 72	**10b**, 74
3	**7c**, R = 	**9c**, 75	**10c**, 80[b] (R=Ph)
4	**7d**, R = 	**9d**, 93	**10d**, 85
5	**7e**, R = 	**9e**, 72	**10e**, 82

[a] Isolated yields by preparative thin-layer chromatography on silica gel.
[b] Both C–S and C–Br bonds were cleaved.

3. Conclusion

In conclusion, we have demonstrated a general and efficient *gem*-difluoromethylation of α-, β-, and γ-ketoesters by a two-step fluoride-catalyzed (phenylsulfanyl)difluoromethylation employing $PhSCF_2SiMe_3$ and reductive cleavage of the phenylsulfanyl group strategy. $PhSCF_2SiMe_3$ can be considered as a versatile difluoromethyl carbanion equivalent ($^-CF_2H$).

4. Experimental

4.1. General methods

The ^1H NMR spectra were recorded on either Bruker DPX-300 (300 MHz) or Bruker Avance-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker Avance-500 (470 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane (δ=0) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on an MS Micromass model VQ-TOF2. Elemental analyses were performed by a Perkin Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Buechi 501 Melting Point Apparatus and uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dry dichloromethane (CH_2Cl_2) and dry *N*,*N*-dimethylformamide (DMF) were obtained by distilling over phosphorous pentoxide and calcium hydride, respectively, and stored over molecular sieves (4 Å). Other common solvents (hexanes, ethyl acetate, methanol, and acetone) were distilled before use. All glasswares and syringes were oven dried and kept in a dessicator before use. Radial chromatography (chromatotron) and column chromatography were performed by using Merck silica gel 60 F_{254} (Art. 7749) and silica gel 60H (Art. 7736), respectively.

The starting compound $PhSCF_2SiMe_3$ (**1**) was prepared according to the literature procedure.[10e]

4.2. Preparation of compounds 3 by fluoride-catalyzed condensation of compound 1 with α-ketoesters

4.2.1. Preparation of ethyl 3,3-difluoro-2-hydroxy-2-methyl-3-(phenylsulfanyl)propanoate (3a). *General procedure*. To a mixture of compound **1** (0.928 g, 4.0 mmol) and ethyl pyruvate (**2a**) (0.232 g, 2.0 mmol) in THF (5 mL) was added 10 mol % TBAF (0.4 mL, 0.4 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C to room temperature overnight, quenched with 1 M HCl (3 mL), and extracted with EtOAc (3×25 mL). The combined organic phases were washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by radial chromatography (SiO_2, 10% EtOAc in hexanes) to give a white solid of **3a** (0.240 g, 87% yield, mp=55–57 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=7.0 Hz, 2H, Ar*H*), 7.45–7.31 (m, 3H, Ar*H*), 4.40–4.30 (m, 2H, CH_2), 4.00 (br s, 1H, O*H*), 1.65 (s, 3H, CH_3), 1.35 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C=O), 136.7 (CH), 129.9 (CH), 129.0 (2×CH), 128.9 (t, *J*=289.0 Hz, CF_2), 128.8 (CH), 125.5 (C), 78.0 (t, *J*=25.5 Hz, C), 63.2 (CH_2), 20.0 (CH_3), 13.8 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.74 (d, *J*=205.7 Hz, 1F), −83.48 (d, *J*=205.7 Hz, 1F). IR ($CHCl_3$): ν_{max} 3510 (OH), 1733 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 276 (M^+, 11), 231 (7), 203 (4), 185 (20), 183 (22), 159 (100), 109 (19), 77 (20). Anal. Calcd for $C_{12}H_{14}F_2O_3S$: C, 52.16; H, 5.11. Found: C, 52.34; H, 4.99.

4.2.2. Ethyl 3,3-difluoro-2-hydroxy-2-phenyl-3-(phenylsulfanyl)propanoate (3b). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl 2-oxo-2-phenylacetate (**2b**) (0.356 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3b** (0.260 g, 77% yield, mp=62–64 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 2H, Ar*H*), 7.54–7.50 (m, 2H, Ar*H*), 7.35–7.33 (m, 4H, Ar*H*), 7.30–7.28 (m, 2H, Ar*H*), 4.60 (br s, 1H, O*H*), 4.47–4.37 (m, 1H, CH*H*), 4.35–4.28 (m, 1H, C*H*H), 1.35 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (C=O), 136.8 (CH), 134.8 (C), 134.1 (CH), 130.0 (C), 129.8 (CH), 129.1 (CH), 128.9 (2×CH), 128.3 (t, *J*=290.9 Hz, CF_2), 128.0 (2×CH), 127.3 (CH), 125.9 (CH), 80.5 (t, *J*=25.7 Hz, C), 64.0 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.08 (d, *J*=205.6 Hz, 1F), −80.24 (d, *J*=205.6 Hz, 1F). IR (Nujol): ν_{max} 3475 (OH), 1719 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 339 (M^+, 6), 319 (24), 301 (17), 300 (13), 299 (59), 257 (43), 217 (26), 209 (25), 197 (18), 185 (15), 179 (23), 105 (100), 77 (25). Anal. Calcd for $C_{17}H_{16}F_2O_3S$: C, 60.34; H, 4.77. Found: C, 60.73; H, 4.81.

4.2.3. Ethyl 3,3-difluoro-2-hydroxy-3-(phenylsulfanyl)-2-*p*-tolylpropanoate (3c). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*p*-tolylacetate (**2c**) (0.380 g, 2.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3c** (0.320 g, 91% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.50 (d, *J*=7.3 Hz, 2H, Ar*H*), 7.38–7.22 (m, 3H, Ar*H*), 7.15 (d, *J*=8.2 Hz, 2H, Ar*H*), 4.60 (br s, 1H, O*H*), 4.45–4.30 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.35 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (C=O), 136.6 (2×CH), 131.1 (C), 129.6 (CH), 128.7 (2×CH), 128.6 (2×CH), 128.4 (t, *J*=290.9 Hz, CF_2), 128.3 (C), 127.1 (2×CH), 125.7 (C), 80.3 (t, *J*=25.6 Hz, C), 63.7 (CH_2), 20.8 (CH_3), 13.6 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.89 (d, *J*=205.5 Hz, 1F), −79.99 (d, *J*=205.5 Hz, 1F). IR (neat): ν_{max} 3475 (OH), 1728 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 352 (M^+, 6), 316 (22), 315 (100), 313 (34), 287 (10), 271 (25), 231 (11), 119 (23). HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_3SNa$ $[M+Na]^+$: 375.0842; found: 375.0832.

4.2.4. Ethyl 3,3-difluoro-2-hydroxy-2-(4-methoxyphenyl)-3-(phenylsulfanyl)propanoate (3d). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*p*-methoxyphenylacetate (**2d**) (0.382 g, 2.0 mmol) in THF (5 mL) afforded a yellow liquid of **3d** (0.360 g, 98% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.8 Hz, 2H, Ar*H*), 7.70 (d, *J*=7.2 Hz, 2H,

Ar*H*), 7.50–7.45 (m, 1H, Ar*H*), 7.40–7.35 (m, 2H, Ar*H*), 7.04–7.00 (m, 2H, Ar*H*), 4.75 (br s, 1H, O*H*), 4.50–4.40 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (C=O), 160.0 (C), 136.9 (C), 136.6 (CH), 130.6 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (t, J=290.7 Hz, CF_2), 125.9 (C), 113.3 (CH), 80.2 (t, J=25.7 Hz, C), 63.7 (CH_2), 54.9 (CH_3), 13.7 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.08 (d, J=205.4 Hz, 1F), −80.20 (d, J=205.4 Hz, 1F). IR (neat): ν_{max} 3479 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 368 (M^+, 0.1), 275 (2), 247 (9), 209 (29), 159 (3), 136 (9), 135 (100), 109 (2), 108 (3), 107 (4), 77 (10). HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_4SNa$ $[M+Na]^+$: 391.0792; found: 391.0782.

4.2.5. Ethyl 3,3-difluoro-2-hydroxy-2-(2-methoxyphenyl)-3-(phenylsulfanyl)propanoate (3e). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*o*-methoxyphenylacetate (**2e**) (0.382 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3e** (0.361 g, 98% yield, mp=89–91 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, J=7.9, 1.3 Hz, 1H, Ar*H*), 7.70–7.65 (m, 2H, Ar*H*), 7.45–7.30 (m, 4H, Ar*H*), 7.02 (ddd, J=7.9, 7.9, 1.3 Hz, 1H, Ar*H*), 6.85 (dd, J=8.3, 0.9 Hz, 1H, Ar*H*), 4.80 (br s, 1H, O*H*), 4.38–4.25 (m, 2H, CH_2), 3.75 (s, 3H, CH_3), 1.25 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2 (C=O), 157.5 (C), 136.9 (2×CH), 130.3 (2×CH), 129.2 (2×CH), 129.0 (2×CH), 128.6 (t, J=290.6 Hz, CF_2), 124.7 (C), 120.5 (CH), 111.7 (CH), 80.5 (t, J=25.0 Hz, C), 62.9 (CH_2), 55.6 (OCH_3), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −76.31 (d, J=208.2 Hz, 1F), −78.85 (d, J=208.2 Hz, 1F). IR (neat): ν_{max} 3451 (OH), 1747 (C=O) cm^{-1}. MS: m/z (%) relative intensity 368 (M^+, 0.2), 209 (13), 136 (9), 135 (100), 123 (7), 109 (5), 107 (4), 77 (28). Anal. Calcd for $C_{18}H_{18}F_2O_4S$: C, 58.69; H, 4.92. Found: C, 58.44; H, 4.92.

4.2.6. Ethyl 3,3-difluoro-2-hydroxy-2-(naphthalene-2-yl)-3-(phenylsulfanyl)propanoate (3f). According to the general procedure, the reaction of **1** (1.392 g, 6.0 mmol) with ethyl α-oxo-β-naphthylacetate (**2f**) (0.678 g, 3.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3f** (0.895 g, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H, Ar*H*), 8.00 (d, J=8.8 Hz, 1H, Ar*H*), 7.79–7.78 (m, 1H, Ar*H*), 7.77–7.76 (m, 2H, Ar*H*), 7.55–7.53 (m, 4H, Ar*H*), 7.45–7.40 (m, 1H, Ar*H*), 7.35–7.30 (m, 2H, Ar*H*), 4.70 (br s, 1H, O*H*), 4.50–4.43 (m, 1H, C*H*H), 4.41–4.35 (m, 1H, CH*H*), 1.35–1.30 (m, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0 (C=O), 136.8 (2×CH), 133.4 (C), 132.8 (C), 131.6 (C), 130.9 (C), 129.8 (CH), 128.9 (2×CH), 128.8 (CH), 128.6 (t, J=246.5 Hz, CF_2), 127.6 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 124.6 (CH), 80.7 (t, J=26.0 Hz, C), 64.1 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.78 (d, J=205.9 Hz, 1F), −79.72 (d, J=205.9 Hz, 1F). IR (neat): ν_{max} 3472 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 388 (M^+, 2), 351 (6), 307 (3), 278 (3), 267 (5), 259 (4), 247 (6), 229 (13), 156 (13), 155 (100), 128 (13), 127 (41), 126 (4), 77 (3). Anal. Calcd for $C_{21}H_{18}F_2O_3S$: C, 64.93; H, 4.67. Found: C, 65.03; H, 4.63.

4.2.7. Ethyl 2-(4-bromophenyl)-3,3-difluoro-2-hydroxy-3-(phenylsulfanyl)propanoate (3g). According to the general procedure, the reaction of **1** (1.392 g, 6.0 mmol) with ethyl α-oxo-*p*-bromophenylacetate (**2g**) (0.768 g, 3.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3g** (1.190 g, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.55 (d, J=8.8 Hz, 2H, Ar*H*), 7.50–7.42 (m, 4H, Ar*H*), 7.35–7.33 (m, 1H, Ar*H*), 7.25–7.23 (m, 2H, Ar*H*), 4.48 (br s, 1H, O*H*), 4.37–4.30 (m, 1H, C*H*H), 4.27–4.23 (m, 1H, CH*H*), 1.25 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5 (C=O), 136.8 (2×CH), 133.0 (C), 131.2 (2×CH), 129.9 (CH), 129.2 (2×CH), 128.9 (2×CH), 128.1 (t, J=290.9 Hz, CF_2), 125.6 (C), 123.7 (C), 80.2 (t, J=26.2 Hz, C), 64.3 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.21 (d, J=206.6 Hz, 1F), −80.37 (d, J=206.6 Hz, 1F). IR (neat): ν_{max} 3470 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 415 (M^+, 5), 397 (5), 381 (13), 379 (25), 376 (15), 337 (17), 335 (15), 309 (14), 307 (13), 259 (12), 257 (25), 256 (74), 224 (22), 185 (100), 183 (99), 159 (10), 155 (12). Anal. Calcd for $C_{17}H_{15}BrF_2O_3S$: C, 48.93; H, 3.62. Found: C, 49.02; H, 3.53.

4.2.8. 4,4-Difluoro-3-hydroxy-3-methyl-4-(phenylsulfanyl)butan-2-one (3h). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with 2,3-butanedione (**2h**) (0.17 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3h** (0.394 g, 80% yield, mp=55–58 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=7.1 Hz, 2H, Ar*H*), 7.45–7.32 (m, 3H, Ar*H*), 4.55 (br s, 1H, O*H*), 2.35 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1 (C=O), 136.8 (CH), 133.1 (CH), 130.0 (CH), 129.3 (CH), 129.2 (C), 129.0 (CH), 125.5 (t, J=285.3 Hz, CF_2), 81.7 (t, J=25.7 Hz, C), 25.1 (CH_3), 20.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −79.80 (d, J=208.0 Hz, 1F), −81.50 (d, J=208.0 Hz, 1F). IR ($CHCl_3$): ν_{max} 3442 (OH), 1717 (C=O) cm^{-1}. MS: m/z (%) relative intensity 246 (M^+, 40), 203 (57), 159 (31), 121 (50), 110 (100), 109 (34), 77 (26). Anal. Calcd for $C_{11}H_{12}F_2O_2S$: C, 53.65; H, 4.91. Found: C, 53.64; H, 4.81.

4.2.9. Ethyl 4,4-difluoro-3-hydroxy-3-methyl-4-(phenylsulfanyl)butanoate (6a). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl acetoacetate (**5a**) (0.26 g, 2.0 mmol) in THF (5 mL) afforded a colorless liquid of **6a** (0.163 g, 28% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J=7.0 Hz, 2H, Ar*H*), 7.35–7.30 (m, 1H, Ar*H*), 7.29–7.26 (m, 2H, Ar*H*), 4.75 (br s, 1H, O*H*), 4.25–4.15 (m, 2H, CH_2), 2.80 (d, J=15.9 Hz, 1H, C*H*H), 2.50 (d, J=15.9 Hz, 1H, CH*H*), 1.50 (s, 1H, CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1 (C=O), 136.8 (2×CH), 131.5 (t, J=285.8 Hz, CF_2), 129.8 (CH), 128.9 (2×CH), 125.9 (C), 77.0 (t, J=24.1 Hz, C), 61.3 (CH_2), 39.3 (CH_2), 23.3 (CH_3), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.80 (d, J=204.9 Hz, 1F), −84.28 (d, J=204.9 Hz, 1F). IR (neat): ν_{max} 3441 (OH), 1714 (C=O) cm^{-1}. MS: m/z (%) relative intensity 290 (M^+, 1), 197 (11), 177 (16), 149 (18), 135 (12), 131 (100), 110 (10), 109 (12), 103 (26), 85 (58). HRMS (ESI-TOF) calcd for $C_{13}H_{16}F_2O_3SNa$ $[M+Na]^+$: 313.0686; found: 313.0688.

4.2.10. 5,5-Difluoro-4-hydroxy-4-methyl-5-(phenylsulfanyl)pentan-2-one (6b). According to the general procedure,

the reaction of **1** (0.928 g, 4.0 mmol) with 2,4-pentanedione (**5b**) (0.2 g, 2.0 mmol) in THF (5 mL) afforded a colorless liquid of **6b** (0.184 g, 35% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64–7.62 (m, 2H, Ar*H*), 7.45–7.25 (m, 1H, Ar*H*), 7.40–7.37 (m, 2H, Ar*H*), 3.12 (d, J=16.9 Hz, 1H, C*H*H), 2.60 (d, J=16.9 Hz, 1H, CH*H*), 2.44 (s, 3H, CH_3), 1.60 (br s, 1H, O*H*), 1.50 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.4 (C=O), 137.5 (CH), 133.0 (t, J=286.0 Hz, CF_2), 130.7 (2×CH), 129.9 (2×CH), 127.2 (C), 76.9 (t, J=23.9 Hz, C), 47.9 (CH_2), 32.3 (CH_3), 22.7 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.86 (d, J=204.2 Hz, 1F), −83.82 (d, J=204.2 Hz, 1F). IR ($CHCl_3$): ν_{max} 3020 (OH), 1705 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 260 (M^+, 2), 202 (6), 160 (23), 159 (18), 110 (16), 109 (18), 101 (100), 77 (16), 65 (14), 59 (63). HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_2SNa$ $[M+Na]^+$: 283.0580; found: 283.0571.

4.3. Preparation of compounds 9 by fluoride-catalyzed condensation of compound 1 with γ-ketoesters

4.3.1. 5-(Difluoro(phenylsulfanyl)methyl)-5-phenyldihydrofuran-2(3*H*)-one (9a). *General procedure*. To a mixture of compound **1** (0.696 g, 3.0 mmol) and ethyl 4-oxo-4-phenylbutanoate (**7a**) (0.412 g, 2.0 mmol) in THF (5 mL) was added 10 mol % TBAF (0.3 mL, 0.3 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C to room temperature overnight (15 h), quenched with 1 M HCl (3 mL), and extracted with EtOAc (3×25 mL). The organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was treated with *p*-TsOH in CH_2Cl_2 at 0 °C. The resulting mixture was stirred at room temperature overnight (15 h) and extracted with EtOAc (3×20 mL). The combined organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by radial chromatography (SiO_2, 30% EtOAc in hexanes) to give a pale yellow solid of **9a** (0.578 g, 90% yield, mp=75–78 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59–7.55 (m, 2H, Ar*H*), 7.51–7.48 (m, 2H, Ar*H*), 7.43–7.37 (m, 4H, Ar*H*), 7.33–7.29 (m, 2H, Ar*H*), 3.18–3.09 (m, 1H, C*H*H), 2.80–2.72 (m, 1H, CH*H*), 2.58–2.50 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7 (C=O), 136.7 (2×CH), 130.0 (CH), 129.9 (C), 129.2 (CH), 129.1 (t, J=286.9 Hz, CF_2), 129.0 (2×CH), 128.4 (2×CH), 126.4 (2×CH), 122.7 (C), 88.3 (t, J=24.2 Hz, C), 30.2 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.30 (d, J=209.4 Hz, 1F), −85.29 (d, J=209.4 Hz, 1F). IR (KBr): ν_{max} 1802 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 321 (M^+, 1), 162 (12), 161 (100), 133 (19), 117 (4), 115 (10), 106 (3), 105 (19), 77 (8). HRMS (ESI-TOF) calcd for $C_{17}H_{14}F_2O_2SNa$ $[M+Na]^+$: 343.0580; found: 343.0579.

4.3.2. 5-(4-Chlorophenyl)-5-(difluoro(phenylsulfanyl)methyl)dihydrofuran-2(3*H*)-one (9b). According to the general procedure, the reaction of **1** (0.464 g, 2.0 mmol) with ethyl 4-(chlorophenyl)-4-oxobutanoate (**7b**) (0.238 g, 1.0 mmol) in THF (3 mL) afforded a white crystal of **9b** (0.263 g, 72% yield, mp=102–104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J=7.8 Hz, 4H, Ar*H*), 7.35–7.31 (m, 3H, Ar*H*), 7.28–7.22 (m, 2H, Ar*H*), 3.09–3.01 (m, 1H, C*H*H), 2.76–2.68 (m, 1H, CH*H*), 2.53–2.38 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4 (C=O), 136.7 (2×CH), 135.5 (C), 131.3 (C), 130.1 (CH), 129.0 (2×CH), 128.7 (2×CH), 127.9 (2×CH), 126.7 (t, J=223.1 Hz, CF_2), 124.9 (C), 88.0 (t, J=26.6 Hz, C), 30.2 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.41 (d, J=210.1 Hz, 1F), −85.43 (d, J=210.1 Hz, 1F). IR (Nujol): ν_{max} 1799 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 355 (M^+, 2), 197 (33), 196 (11), 195 (100), 169 (10), 167 (11), 161 (5), 151 (8), 149 (16), 141 (20), 139 (64), 115 (10), 111 (23), 75 (9). Anal. Calcd for $C_{17}H_{13}ClF_2O_2S$: C, 57.55; H, 3.69. Found: C, 57.31; H, 3.41.

4.3.3. 5-(4-Bromophenyl)-5-(difluoro(phenylsulfanyl)methyl)dihydrofuran-2(3*H*)-one (9c). According to the general procedure, the reaction of **1** (0.930 g, 4.0 mmol) with ethyl 4-(bromophenyl)-4-oxobutanoate (**7c**) (0.568 g, 2.0 mmol) in THF (5 mL) afforded a white crystal of **9c** (0.544 g, 70% yield, mp=103–104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H, Ar*H*), 7.50–7.48 (m, 2H, Ar*H*), 7.45–7.40 (m, 3H, Ar*H*), 7.36–7.31 (m, 2H, Ar*H*), 3.15–3.10 (m, 1H, C*H*H), 2.82–2.76 (m, 1H, CH*H*), 2.60–2.46 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4 (C=O), 136.7 (2×CH), 136.0 (C), 131.7 (2×CH), 130.1 (CH), 129.0 (2×CH), 128.9 (t, J=286.9 Hz, CF_2), 128.2 (2×CH), 124.9 (C), 123.7 (C), 88.0 (t, J=26.6 Hz, C), 30.1 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.46 (d, J=210.3 Hz, 1F), −85.49 (d, J=210.3 Hz, 1F). IR (Nujol): ν_{max} 1799 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 399 (M^+, 2), 242 (11), 241 (100), 240 (13), 239 (97), 213 (16), 211 (16), 185 (18), 183 (19), 116 (10), 77 (44). Anal. Calcd for $C_{17}H_{13}BrF_2O_2S$: C, 51.14; H, 3.19. Found: C, 51.40; H, 3.19.

4.3.4. 5-(Difluoro(phenylsulfanyl)methyl)-5-(2,5-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (9d). According to the general procedure, the reaction of compound **1** (1.92 g, 8.0 mmol) with ethyl 4-(2,5-dimethoxyphenyl)-4-oxobutanoate (**7d**) (1.30 g, 4.0 mmol) in THF (6 mL) afforded a white crystal of **9d** (1.427 g, 93% yield, mp=104–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J=8.0 Hz, 2H, Ar*H*), 7.40 (dd, J=7.0, 1.0 Hz, 1H, Ar*H*), 7.35–7.30 (m, 3H, Ar*H*), 6.95–6.88 (m, 2H, Ar*H*), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.25–3.19 (m, 1H, C*H*H), 2.82–2.69 (m, 2H, CH_2), 2.60–2.50 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2 (C=O), 153.4 (C), 151.1 (C), 136.8 (2×CH), 130.0 (t, J=289.0 Hz, CF_2), 129.8 (CH), 128.9 (2×CH), 125.8 (C), 125.6 (C), 116.1 (CH), 114.5 (CH), 113.4 (CH), 88.5 (d, J=26.8 Hz, C), 56.1 (CH_3), 55.9 (CH_3), 29.5 (CH_2), 28.4 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −80.96 (d, J=205.1 Hz, 1F), −84.15 (d, J=205.1 Hz, 1F). IR (KBr): ν_{max} 1788 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 380 (M^+, 14), 222 (14), 221 (100), 194 (12), 193 (97), 165 (15), 161 (16), 137 (9), 109 (4), 77 (8). Anal. Calcd for $C_{19}H_{18}F_2O_4S$: C, 59.99; H, 4.77. Found: C, 59.69; H, 4.66.

4.3.5. 5-(Difluoro(phenylsulfanyl)methyl)-5-(3,4-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (9e). According to the general procedure, the reaction of **1** (0.464 g, 2.0 mmol) with ethyl 4-(2,5-dimethoxyphenyl)-4-oxobutanoate (**7e**) (0.262 g, 1.0 mmol) in THF (3 mL) afforded a white crystal of **9e** (0.273 g, 72% yield, mp=102–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H, Ar*H*), 7.45–7.40 (m, 1H, Ar*H*), 7.35–7.30 (m, 2H,

ArH), 7.15–7.10 (m, 2H, ArH), 6.90 (d, J=8.4 Hz, 1H, ArH), 3.15–3.08 (m, 1H, CHH), 2.85 (s, 6H, 2×OCH_3), 2.81–2.73 (m, 1H, CHH), 2.62–2.51 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8 (C=O), 149.8 (C), 148.8 (C), 136.6 (2×CH), 131.6 (CH), 129.3 (t, J=286.9 Hz, CF_2), 129.0 (C), 128.9 (2×CH), 125.3 (C), 119.0 (CH), 110.8 (CH), 109.8 (CH), 88.2 (t, J=24.3 Hz, C), 56.1 (CH_3), 55.9 (CH_3), 30.1 (CH_2), 28.1 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.31 (d, J=208.7 Hz, 1F), −85.18 (d, J=208.7 Hz, 1F). IR (Nujol): ν_{max} 1793 (C=O) cm^{-1}. MS: m/z (%) relative intensity 380 (M^+, 4), 266 (15), 222 (13), 221 (100), 193 (7), 192 (5), 166 (6), 165 (42), 125 (5), 91 (9). Anal. Calcd for $C_{19}H_{18}F_2O_4S$: C, 59.99; H, 4.77. Found: C, 60.25; H, 4.75.

4.4. Preparation of *gem*-difluorinated compounds 4 and 10

4.4.1. Ethyl 3,3-difluoro-2-hydroxy-2-phenylpropanoate (4b). *General procedure*. Argon was bubbled through a solution of **3b** (0.338 g, 1.0 mmol) in dry toluene (5 mL) for 30 min and Bu_3SnH (0.47 mL, 1.75 mmol) was added. Deoxygenation was continued for 5 min. AIBN (25 mg, 0.15 mmol) was added and the solution was refluxed for 15 h. Volatiles were evaporated and the residue was dissolved in EtOAc (5 mL). The solution was stirred overnight with KF/H_2O (30 mg /0.3 mL) and extracted with EtOAc (3×20 mL). The organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by radial chromatography (SiO_2, hexanes then 20% EtOAc in hexanes) to give a colorless liquid of **4b** (0.170 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=7.6 Hz, 2H, ArH), 7.45–7.31 (m, 3H, ArH), 6.25 (t, J=54.4 Hz, 1H, CF_2H), 4.40–4.20 (m, 2H, CH_2), 3.90 (br s, 1H, OH), 1.35 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (C=O), 134.6 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 125.9 (CH), 125.7 (CH), 114.7 (t, J=247.9 Hz, CF_2H), 77.9 (t, J=21.1 Hz, C), 63.5 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.15 (dd, J=278.0, 54.5 Hz, 1F), −133.86 (dd, J=278.0, 54.5 Hz, 1F). IR (neat): ν_{max} 3494 (OH), 1739 (C=O) cm^{-1}. MS: m/z (%) relative intensity 231 (M^+, 88), 214 (16), 213 (100), 194 (14), 193 (50), 179 (11), 109 (10), 105 (16). HRMS (ESI-TOF) calcd for $C_{11}H_{12}F_2O_3Na$ [M+Na]$^+$: 253.0652; found: 253.0649.

4.4.2. Ethyl 3,3-difluoro-2-hydroxy-2-*p*-tolylpropanoate (4c). According to the general procedure, the reaction of **3c** (0.352 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4c** (0.236 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J=8.3 Hz, 2H, ArH), 7.10 (d, J=7.8 Hz, 2H, ArH), 6.12 (t, J=54.4 Hz, 1H, CF_2H), 4.23–4.20 (m, 2H, CH_2), 3.95 (br s, 1H, OH), 2.10 (s, 3H, CH_3), 1.08 (t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (C=O), 138.9 (C), 136.7 (C), 129.6 (CH), 129.4 (CH), 125.8 (CH), 125.5 (CH), 114.8 (t, J=247.6 Hz, CF_2H), 77.8 (t, J=20.9 Hz, C), 63.4 (CH_2), 20.9 (CH_3), 13.8 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.20 (dd, J=276.8, 54.3 Hz, 1F), −134.00 (dd, J=276.8, 54.3 Hz, 1F). IR (neat): ν_{max} 3501 (OH), 1739 (C=O) cm^{-1}. MS: m/z (%) relative intensity 245 (M^+, 4), 228 (13), 227 (100), 209 (7), 207 (22), 193 (10). HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_3Na$ [M+Na]$^+$: 267.0809; found: 267.0810.

4.4.3. Ethyl 3,3-difluoro-2-hydroxy-2-(4-methoxyphenyl)propanoate (4d). According to the general procedure, the reaction of **3d** (0.574 g, 1.5 mmol) with Bu_3SnH (2.6 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4d** (0.338 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60–7.50 (m, 2H, ArH), 7.00–6.80 (m, 2H, ArH), 6.20 (t, J=54.5 Hz, 1H, CF_2H), 4.35–4.20 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 1.30 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (C=O), 160.1 (C), 127.3 (2×CH), 126.5 (C), 114.7 (t, J=248.0 Hz, CF_2H), 114.0 (2×CH), 77.6 (t, J=21.1 Hz, C), 63.5 (CH_2), 55.3 (CH_3), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.96 (dd, J=276.8, 54.5 Hz, 1F), −133.93 (dd, J=276.8, 54.5 Hz, 1F). IR (neat): ν_{max} 3492 (OH), 1739 (C=O) cm^{-1}. MS: m/z (%) relative intensity 260 (M^+, 4), 259 (25), 244 (14), 143 (100), 209 (15), 187 (28), 140 (6), 139 (63), 135 (33), 109 (5), 91 (4), 77 (5). Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.06; H, 5.54.

4.4.4. Ethyl 3,3-difluoro-2-hydroxy-2-(2-methoxyphenyl)propanoate (4e). According to the general procedure, the reaction of **3e** (0.259 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white solid of **4e** (0.170 g, 91% yield, mp=73–75 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J=7.8 Hz, 1H, ArH), 7.35–7.30 (m, 1H, ArH), 7.05 (ddd, J=7.8, 7.8, 1.1 Hz, 1H, ArH), 6.90 (dd, J=8.3, 0.7 Hz, 1H, ArH), 6.52 (t, J=54.5 Hz, 1H, CF_2H), 4.28–4.25 (m, 2H, CH_2), 4.20 (br s, 1H, OH), 3.85 (s, 3H, CH_3), 1.25 (t, J=7.8 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, acetone-d_6): δ 170.6 (C=O), 157.5 (C), 130.8 (CH), 128.7 (CH), 126.2 (C), 121.3 (CH), 115.0 (t, J=243.5 Hz, CF_2H), 112.2 (CH), 77.6 (t, J=21.2 Hz, C), 62.4 (CH_2), 55.9 (OCH_3), 14.2 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.69 (dd, J=280.1, 54.5 Hz, 1F), −132.14 (dd, J=280.1, 54.5 Hz, 1F). IR (Nujol): ν_{max} 3452 (OH), 1716 (C=O) cm^{-1}. MS: m/z (%) relative intensity 260 (M^+, 10), 243 (54), 188 (6), 187 (62), 167 (17), 157 (13), 139 (29), 135 (28), 121 (9), 109 (73), 107 (7), 92 (10), 91 (100), 77 (21), 65 (22). Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.25; H, 5.34.

4.4.5. Ethyl 3,3-difluoro-2-hydroxy-2-(naphthalene-2-yl)propanoate (4f). According to the general procedure, the reaction of **3f** (0.679 g, 1.8 mmol) with Bu_3SnH (3.15 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4f** (0.437 g, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.10 (d, J=1.2 Hz, 1H, ArH), 7.80–7.76 (m, 3H, ArH), 7.68–7.65 (dd, J=8.8, 1.8 Hz, 1H, ArH), 7.45–7.40 (m, 2H, ArH), 6.27 (t, J=54.3 Hz, 1H, CF_2H), 4.35–4.22 (m, 2H, CH_2), 4.00 (br s, 1H, OH), 1.25 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (C=O), 133.3 (C), 132.9 (C), 131.9 (C), 128.5 (CH), 128.4 (CH), 127.5 (CH), 126.9 (CH), 126.5 (CH), 125.8 (CH), 123.1 (CH), 114.8 (t, J=248.1 Hz, CF_2H), 78.1 (t, J=21.1 Hz, C), 63.6 (CH_2), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.97 (dd, J=277.3, 54.5 Hz, 1F), −133.45 (dd, J=277.3, 54.5 Hz,

1F). IR (neat): ν_{max} 3493 (OH), 1739 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 280 (M^+, 17), 263 (30), 215 (10), 207 (17), 159 (47), 156 (14), 155 (100), 133 (10), 128 (23), 127 (49), 126 (11). Anal. Calcd for $C_{15}H_{14}F_2O_3$: C, 64.28; H, 5.03. Found: C, 64.43; H, 5.05.

4.4.6. 5-(Difluoromethyl)-5-phenyldihydrofuran-2(3*H*)-one (10a). According to the general procedure, the reaction of **9a** (0.354 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **10a** (0.160 g, 76% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (m, 5H, Ar*H*), 5.80 (t, *J*=55.5 Hz, 1H, CF_2H), 2.98–2.93 (m, 1H, C*H*H), 2.82–2.74 (m, 1H, CH*H*), 2.61–2.54 (m, 1H, CH*H*), 2.51–2.45 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C=O), 136.6 (C), 129.1 (2×CH), 128.7 (CH), 125.8 (2×CH), 115.1 (t, *J*=248.8 Hz, CF_2H), 85.4 (t, *J*=23.7 Hz, C), 27.9 (CH_2), 27.7 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.88 (dd, *J*=279.7, 55.7 Hz, 1F), −130.52 (dd, *J*=279.7, 55.7 Hz, 1F). IR (neat): ν_{max} 1794 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 213 (M^+, 5), 162 (12), 161 (100), 133 (28), 117 (5), 105 (37), 91 (3), 77 (14). Anal. Calcd for $C_{11}H_{10}F_2O_2$: C, 62.26; H, 4.75. Found: C, 62.65; H, 4.62.

4.4.7. 5-(4-Chlorophenyl)-5-(difluoromethyl)dihydrofuran-2(3*H*)-one (10b). According to the general procedure, the reaction of **9b** (0.354 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **10b** (0.182 g, 74% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.55–7.40 (m, 4H, Ar*H*), 5.75 (t, *J*=55.7 Hz, CF_2H), 3.00–2.90 (m, 1H, C*H*H), 2.85–2.70 (m, 1H, CH*H*), 2.65–2.55 (m, 1H, C*H*H), 2.50–2.38 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6 (C=O), 135.4 (C), 135.0 (C), 129.0 (2×CH), 127.3 (2×CH), 114.8 (t, *J*=249.0 Hz, CF_2H), 85.0 (t, *J*=23.9 Hz, C), 27.9 (CH_2), 27.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −130.13 (d, *J*=55.4 Hz, 2F). IR (neat): ν_{max} 1799 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 247 (M^+, 6), 197 (34), 196 (12), 195 (100), 167 (24), 149 (7), 141 (13), 139 (33), 115 (5). Anal. Calcd for $C_{11}H_9F_2O_2$: C, 53.57; H, 3.68. Found: C, 53.66; H, 3.58.

4.4.8. 5-(Difluoromethyl)-5-(2,5-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (10d). According to the general procedure, the reaction of **9d** (0.39 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white crystal of **10d** (0.232 g, 85% yield, mp=85–87 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, *J*=2.2, 0.9 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.85–6.80 (m, 2H, Ar*H*), 6.25 (t, *J*=54.2 Hz, CF_2H), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.95 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5 (C=O), 154.0 (C), 149.2 (C), 126.3 (C), 114.2 (t, *J*=245.8 Hz, CF_2H), 112.5 (CH), 122.4 (CH), 112.2 (CH), 85.4 (dd, *J*=21.3, 18.3 Hz, C), 55.9 (2×OCH_3), 29.2 (CH_2), 27.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.53 (dd, *J*=279.7, 54.8 Hz, 1F), −134.03 (dd, *J*=279.7, 54.8 Hz, 1F). IR (Nujol): ν_{max} 1790 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 272 (M^+, 50), 221 (57), 194 (12), 193 (100), 165 (21), 150 (10), 137 (12), 107 (4), 77 (6), 55 (14). Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18. Found: C, 57.48; H, 5.26.

4.4.9. 5-(Difluoromethyl)-5-(3,4-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (10e). According to the general procedure, the reaction of **9e** (0.19 g, 0.5 mmol) with Bu_3SnH (0.88 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white crystal of **10e** (0.112 g, 82% yield, mp=92–94 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.00–6.95 (m, 2H, Ar*H*), 6.90–6.80 (m, 1H, Ar*H*), 5.85 (t, *J*=55.8 Hz, CF_2H), 3.95 (s, 6H, 2×OCH_3), 2.96–2.85 (m, 1H, C*H*H), 2.83–2.75 (m, 1H, CH*H*), 2.64–2.57 (m, 1H, C*H*H), 2.53–2.45 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0 (C=O), 149.7 (C), 149.1 (C), 128.8 (C), 118.3 (CH), 115.1 (t, *J*=248.7 Hz, CF_2H), 111.1 (CH), 109.1 (CH), 85.3 (t, *J*=23.6 Hz, C), 56.0 (OCH_3), 55.9 (OCH_3), 28.0 (CH_2), 27.6 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.65 (dd, *J*=281.1, 56.5 Hz, 1F), −130.30 (dd, *J*=281.1, 56.5 Hz, 1F). IR (Nujol): ν_{max} 1779 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 272 (M^+, 20), 222 (11), 221 (100), 193 (12), 166 (10), 165 (47), 137 (5), 122 (4), 91 (3), 79 (4), 77 (6). Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18. Found: C, 57.59; H, 4.88.

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