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Synthesis of α-Halo-α,α-difluoromethyl Ketones by a Trifluoroacetate Release/Halogenation Protocol

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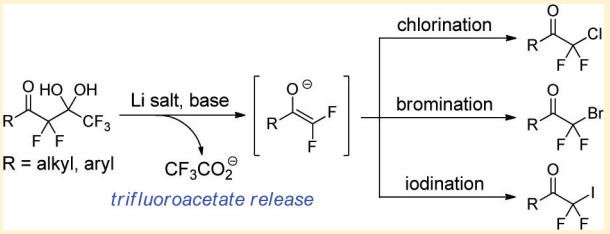
Supporting Information

ABSTRACT: Three series of α-halo-α,α-difluoromethyl ketones are prepared from highly α-fluorinated gem-diols by exploiting the facile release of trifluoroacetate, followed by immediate trapping of the liberated α,α-difluoroenolate with an electrophilic chlorine, bromine, or iodine source. The products are typically isolated in good yields, even in the case of sensitive, α-iodo-α,α-difluoromethyl ketones. Also, we demonstrate that an α-iodo-α,α-difluoromethyl ketone will participate in a copper-promoted reaction to forge a new carbon−carbon bond.



Fluorinated organic compounds have attracted considerable attention from the pharmaceutical, chemical, and agrochemical industries.[1,2] Although multiple synthetic methods are available to introduce fluorine or a trifluoromethyl group, fewer methods are available to install a difluoromethylene group.[3−7] Typically, α-halo-α,α-difluoroacetates are used as building blocks to prepare compounds with difluoromethylene groups.[8−11] Unfortunately, there are very few synthetic methods that can be used to assemble α-halo-α,α-difluoroacetates or other α-halo-α,α-difluoro centers adjacent to carbonyl groups, especially α-halo-α,α-difluoromethyl ketones.[8−15] Existing synthetic strategies to assemble α-halo-α,α-difluoromethyl ketones rely heavily on halogenating α,α-difluoroenoxysilanes[13,14] or adding Grignard reagents into α-bromo-α,α-difluoroacetates or α-chloro-α,α-difluoroacetates (Figure 1).[8,9] Typically, α,α-difluoroenoxysilanes arise from

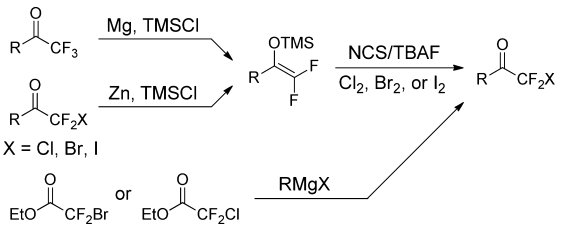


Figure 1. Three common methods to prepare α-halo-α,α-difluoromethyl ketones.

the silylation of a metalloenolate formed after carbon−halogen fragmentation on a α-halo-α,α-difluoromethyl group or on a trifluoromethyl group adjacent to a carbonyl group. Our synthetic plan is an alternative method to assemble α-halo-α,α-difluoromethyl ketones by halogenation of the α,α-difluoroenolate generated by the facile release of trifluoroacetate and does not require α,α-difluoroenoxysilanes, their precursors, or α-halo-α,α-difluoroacetates.

The strategy to release trifluoroacetate is based on a report in 1968 that hexafluoroacetone hydrate fragments to eliminate trifluoroacetate.[16] We have recently demonstrated that this fragmentation can be used to generate α,α-difluoroenolates from highly α-fluorinated gem-diols under very mild conditions (i.e., LiBr/Et_3N) and subsequently used in aldol reactions.[17] The major benefits of using this approach are that it is mild, versatile, and typically finished after 3 min at room temperature. The release of trifluoroacetate is rarely explored in synthesis, but other difficult transformations can be accomplished.[18] We now aim to extend this method and trap the difluoroenolate with electrophilic halogenation reagents (Figure 2). We

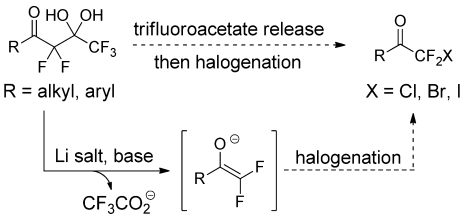


Figure 2. Trifluoroacetate release/halogenation strategy.

hypothesize that this strategy will be compatible with common halogenation reagents and allow isolation of these sensitive, highly halogenated products. Herein, we describe a versatile, high-yielding protocol that can be used to assemble α-halo-α,α-difluoromethyl ketones that is based on the novel halogenation of α,α-difluoroenolates generated by the facile release of trifluoroacetate. Reaction conditions for chlorination, bromina-

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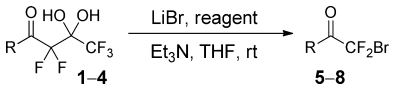
tion, and iodination are described, and the trihalogenated products are isolated in good yields. Also, we demonstrate that an α-iodo-α,α-difluoromethyl ketone, which is a highly sensitive organic compound, will participate in a copper-promoted reaction to forge a new carbon−carbon bond.

We have previously reported an efficient, two-step synthesis of highly α-fluorinated gem-diols from methyl ketones.[17] This method was based on the fluorination work of Ley and co-workers.[19] Using the α-fluorinated gem-diols, we discovered that trifluoroacetate release provided the desired brominated product after the starting material was treated with LiBr, Et_3N, and Br_2. Even though the reagent bromine served to brominate the difluoroenolate generated in situ, a significant excess of base (i.e., Et_3N) was needed to execute the reaction, likely because of the presence of acidic impurities in bromine. Therefore, we surveyed other electrophilic sources of bromine as part of our optimization efforts but found that the common brominating reagent, NBS, did not provide a brominated product after trifluoroacetate release. Ultimately, we identified the protocol of Shreeve using LiBr/Selectfluor to be an ideal source of electrophilic bromine.[20] Using gem-diols **1**−**4**, the combination of LiBr/Selectfluor/Et_3N routinely provided high yields of the respective α-bromo-α,α-difluoroketones **5**−**8** (Table 1).

Table 1. Strategy for α-Bromo-α,α-difluoromethyl Ketones

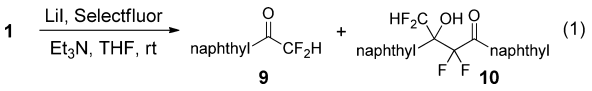


entry	substrate	reagent	major product	yield[a]
1	**1**	Selectfluor	**5**	87%
2	**1**	Br_2	**5**	80%
3	**2**	Selectfluor	**6**	75%
4	**3**	Selectfluor	**7**	81%
5	**3**	Br_2	**7**	81%
6	**4**	Selectfluor	**8**	72%

[a]Isolated yields.

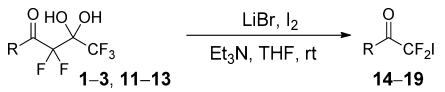
Bromination on the aromatic rings in substrates **1**−**4** was not observed under these conditions. Indeed, the substrates have very limited exposure to the halogen source because trifluoroacetate release is complete after 30 min at room temperature. Also, evidence of the exclusive release of trifluoroacetate from these substrates was obtained, as trifluoroacetate was observed in the crude reaction mixture by ^{19}F NMR (data not shown).

Amides with an α,α-difluoro-α-iodomethyl group adjacent to the carbonyl group are synthetically useful because of their propensity to participate in metal-mediated reactions.[21,22] For example, in 2010, copper-mediated cross-coupling with difluoroiodoacetamides was demonstrated by Hu and co-workers.[21] When we attempted trifluoroacetate release/iodination with **1**, the combination of LiI/Selectfluor/Et_3N did not provide a high conversion to the α,α-difluoro-α-iodomethyl ketone as expected. Instead, the additional formation of the α,α-difluoromethyl ketone **9** along with the self-aldol condensation product **10** was observed (eq 1). The



formation of product **10** demonstrates that the protonation of the difluoroenolate to **9** and subsequent reaction by additional difluoroenolate will commence if an appropriate electrophile is not present. Also, LiI/I_2/Et_3N gave similar results. However, by substituting LiBr for LiI and using I_2 and Et_3N, the gem-diols **1**−**3** and **11**−**13** provided the α,α-difluoro-α-iodomethyl ketones **14**−**19** in good yields (Table 2). The iodinated

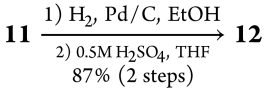
Table 2. Strategy for α,α-Difluoro-α-iodo-methyl Ketones



entry	substrate	major product	yield[a]
1	**1**	**14**	73%
2	**2**	**15**	65%
3	**3**	**16**	79%
4	**11**	**17**	67%
5	**12**[b]	**18**	83%
6	**13**	**19**	66%

[a]Isolated yields. Products are not stable to storage. [b]Synthesized from **11** (see eq 2).

products were not stable to storage, as expected,[23] but would readily participate in subsequent coupling reactions (see below). During these investigations, additional stability data for highly α-fluorinated gem-diols was gathered, as the α,β-unsaturated substrate **11** was reduced in high yield to the saturated alkyl derivative **12** (eq 2). Although trace amounts of the ethanol-derived hemiacetal were formed, dilute acid provided the gem-diol **12** (for subsequent iodination to **18**).



(2)

For the preparation of α-chloro-α,α-difluoromethyl ketones, chlorine gas was not investigated because of its hazardous nature. A survey of alternative reagents to promote the trifluoroacetate release/chlorination was conducted, and finally, the combination of LiCl/NCS/Et_3N was found to be optimal (Table 3). This strategy minimized the formation of both the α,α-difluoromethyl ketone and the self-aldol condensation

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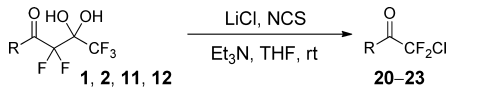
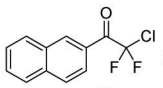
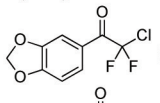
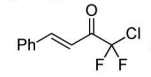
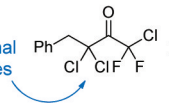
Table 3. Strategy for α-Chloro-α,α-difluoromethyl Ketones



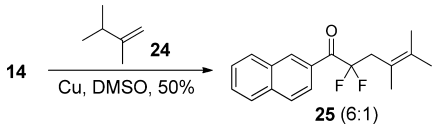
entry	substrate	major product	yield[a]
1	1	 20	80%
2	2	 21	83%
3	11	 22	63%
4	12	additional chlorines  23	73%

[a]Isolated yields.

product as previously observed during the iodination studies (see eq 1). The α-chloro-α,α-difluoromethyl ketones **20**–**23** were isolated in good yields using this process. However, the incorporation of two additional chlorines at the other α-position of the carbonyl group was observed with the alkyl substrate **12**. Clearly, these two protons in **12** are highly acidic; therefore, enolate formation and subsequent chlorination are also favorable under these reaction conditions. On the other hand, overiodination was not prevalent when **12** was subjected similar conditions (see Table 2), so perhaps other factors, such as sterics or the nature of the electrophile, may contribute. Indeed, adding a large excess of I_2 along with LiBr and Et_3N to substrate **12** did not promote the formation products from overiodination (analogous to overchlorination in **23**); instead, benzylic iodination was observed.

With efficient access to α-halo-α,α-difluoromethyl ketones, we next sought to explore new synthetic roles for these compounds. On the basis of previous literature precedent with α,α-difluoro-α-iodoacetamides[21,22] and α-bromo-α,α-difluoroacetates,[24] we examined copper-promoted reactions with α-iodo-α,α-difluoromethyl ketone **14** (Scheme 1). To our knowledge,

Scheme 1. Copper-Mediated Reaction



such reactions with copper have not been applied to α-halo-α,α-difluoromethyl ketones, and only reactions initiated by UV-irradiation and $Pd(Ph_3)_4$ have been described.[23,25,26] Upon treatment of α-iodo-α,α-difluoromethyl ketone **14** and olefin **24** with Cu in DMSO followed by heating, the difluoroketone **25** was isolated as the major isomer in a 6:1 mixture with the terminal olefin isomer. Although a modest yield of **25** was obtained (i.e., 50%), this yield correlates well with previous work with acetamides[21] and avoids the isolation of an iodinated product unlike prior work.[23,25,26] Indeed, additional synthetic strategies for difluoroketones are quite valuable because of the diverse biological activities of these fluorinated compounds.[27]

In conclusion, we have successfully demonstrated that synthetically valuable α-halo-α,α-difluoromethyl ketones can be formed under mild reaction conditions with high yields using a trifluoroacetate release/halogenation protocol. These data correlate well with our previous findings that trifluoroacetate release is a quick, powerful, yet mild reaction to generate reactive intermediates[17] and to synthesize sensitive compounds.[17,18] Also, we have demonstrated that an α-iodo-α,α-difluoromethyl ketone will participate in a copper-promoted reaction to forge a new carbon−carbon bond. Additional studies to elucidate the scope of trifluoroacetate release are underway and will be reported in due course.

EXPERIMENTAL SECTION

Representative Procedure for the Synthesis of α-Bromo-α,α-difluoromethyl Ketones. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **1**[17] (30 mg, 0.094 mmol) in THF (940 μL) was added LiBr (48 mg, 0.56 mmol) followed by Selectfluor (67 mg, 0.19 mmol). The reaction mixture was stirred for 1 min, and then Et_3N (25 μL, 0.19 mmol) was added. After stirring for 30 min at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was extracted with EtOAc (1 mL × 2), and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (5% Et_2O in hexanes) afforded the 2-bromo-2,2-difluoro-1-(naphthalen-2-yl)-ethanone **5** as a colorless oil (23 mg) in 87% yield.

2-Bromo-2,2-difluoro-1-(naphthalen-2-yl)ethanone 5. See representative reaction procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.69 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.61 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4 (t, J_{CF} = 25.6 Hz, 1C), 136.3, 133.5, 132.1, 130.2, 129.9, 128.9, 127.9, 127.3, 126.3, 124.9, 113.7 (t, J_{CF} = 318 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.2 (s, 2F); IR (film) ν_{max} 1705.3, 1626.7, 1152.6, 1119.3 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_7BrF_2O$ $(M)^+$ 283.9648, found 283.9651.

1-(Benzo[1,3]dioxol-5-yl)-2-bromo-2,2-difluoroethanone 6. See representative reaction procedure. 1-(Benzo[1,3]dioxol-6-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **2**[17] (10 mg, 0.03 mmol), LiBr (16 mg, 0.19 mmol), Selectfluor (22 mg, 0.063 mmol), and Et_3N (9 μL, 0.06 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (6.4 mg) in 75% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7 (t, J_{CF} = 25.5 Hz, 1C), 153.6, 148.4, 128.0, 123.3, 113.6 (t, J_{CF} = 319 Hz, 1C), 110.0, 108.4, 102.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −57.8 (s, 2F); IR (film) ν_{max} 2924.0, 1678.7, 1455.3, 1266.4, 1070.6 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_9H_5BrF_2O_3$ $(M)^+$ 277.9390, found 277.9393.

1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 3. To a −78 °C solution of hexamethyldisilazane (165 mg, 1.01 mmol) in THF (1.5 mL) was added a solution of n-BuLi (400 μL, 2.5 M in hexanes). The mixture was stirred for 30 min at −78 °C, and then a solution of 1-(benzothiophen-3-yl)ethanone (150 mg, 0.85 mmol) in THF (1.5 mL) was added dropwise. After an additional 1 h at −78 °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (250 mg, 1.3 mmol) was added dropwise, and the mixture was stirred for 30 min at the same temperature. Next, the reaction mixture was quenched at −78 °C with 0.1 M H_2SO_4 (3 mL) and allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (3 mL × 2). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product (230 mg). The crude product was dissolved in CH_3CN (6 mL), treated with Selectfluor (750 mg, 2.1 mmol), and stirred at rt for 24 h. The reaction mixture was diluted with EtOAc (6 mL), filtered through a pad of Celite, and concentrated under reduced pressure. The product was dissolved in CH_2Cl_2 (10 mL), washed with H_2O (5 mL × 2) and brine (5 mL), and then concentrated under reduced pressure to provide the 1-(benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3** as a colorless solid (250 mg) in 90% yield: mp 72−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (t, J = 1.6 Hz, 1H), 8.68 (d, J = 8.2 Hz,

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1H), 7.94 (d, J = 8.1 Hz, 1H), 7.58 (m, 1H), 7.53−7.49 (m, 1H), 4.74 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9 (t, J_{CF} = 28.0 Hz, 1C), 144.8 (t, J_{CF} = 10.1 Hz, 1C), 138.7, 136.7, 128.4, 126.8, 126.3, 125.0, 122.5, 120.9 (q, J_{CF} = 287 Hz, 1C), 111.0 (t, J_{CF} = 269 Hz, 1C), 92.8 (qt, J = 27.8, 5.5 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.8 (t, J = 11.0 Hz, 3F), −112.6 (q, J = 10.9 Hz, 2F); IR (film) ν_{max} 3368.3, 1662.9, 1488.3, 1461.0, 1424.5, 1204.7, 1067.2 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_7F_5O_3S$ $(M - H_2O)^+$ 307.9931, found 307.9936.

1-(Benzothiophen-3-yl)-2-bromo-2,2-difluoroethanone 7. See representative reaction procedure. 1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3** (10 mg, 0.03 mmol), LiBr (16 mg, 0.19 mmol), Selectfluor (22 mg, 0.063 mmol), and Et_3N (9 μL, 0.06 mmol) were used. Purification by semiprep HPLC (99.9:0.1 hexanes/EtOAc) provided the title compound as a colorless oil (7.2 mg) in 81% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75−8.72 (m, 2H), 7.93 (dt, J = 8.0, 1.0 Hz, 1H), 7.58 (ddd, J = 8.3, 7.1, 1.1 Hz, 1H), 7.50 (ddd, J = 8.2, 7.3, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (t, J_{CF} = 26.2 Hz, 1C), 142.2 (t, J_{CF} = 6.1 Hz, 1C), 139.0, 137.1, 126.6, 126.3, 125.6, 125.3, 122.4, 113.5 (t, J_{CF} = 319 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.1 (s, 2F); IR (film) ν_{max} 1688.0, 1489.5, 1142.7, 1102.0 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{10}H_5BrF_2OS$ $(M)^+$ 289.9213, found 289.9211.

2-Bromo-1-(4-chlorophenyl)-2,2-difluoroethanone 8. See representative reaction procedure. 1-(4-Chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **4**[17] (20 mg, 0.07 mmol), LiBr (16 mg, 0.39 mmol), Selectfluor (47 mg, 0.13 mmol), and Et_3N (18 μL, 0.13 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (12.7 mg) in 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3 (t, J_{CF} = 26.2 Hz, 1C), 142.0, 132.0 (2C), 129.4 (2C), 127.4, 113.3 (t, J_{CF} = 318 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.1 (s, 2F); IR (film) ν_{max} 1713.1, 1589.9, 1489.7, 1276.7, 1159.5 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_8H_4BrClF_2O$ $(M)^+$ 267.9102, found 267.9100.

Representative Procedure for the Synthesis of α,α-Difluoro-α-iodomethyl Ketones. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-3-yl)butan-1-one **1**[17] (10 mg, 0.03 mmol) in THF (310 μL) was added LiBr (16 mg, 0.19 mmol) followed by I_2 (16 mg, 0.062 mmol). The reaction mixture was stirred for 1 min, and then Et_3N (9 μL, 0.06 mmol) was added. After stirring for 30 min at rt, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The mixture was extracted in EtOAc (1 mL × 2), and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by semiprep HPLC (99.9:0.1 hexanes/EtOAc) afforded the 2,2-difluoro-2-iodo-1-(naphthalen-3-yl)ethanone **14** as a pale yellow oil (7.6 mg) in 73% yield.

2,2-Difluoro-2-iodo-1-(naphthalen-2-yl)ethanone 14. See representative reaction procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.68 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.61 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4 (t, J_{CF} = 23.1 Hz, 1C), 136.2, 133.6, 132.2, 130.2, 129.9, 128.9, 127.9, 127.3, 125.6, 125.2, 95.8 (t, J_{CF} = 326 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.6 (s, 2F); IR (film) ν_{max} 1697.2, 1468.5, 1280.4, 1143.4, 1116.0 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_7F_2IO$ $(M)^+$ 331.9510, found 331.9512.

1-(Benzo[1,3]dioxol-5-yl)-2,2-difluoro-2-iodoethanone 15. See representative reaction procedure. 1-(Benzo[1,3]dioxol-6-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **2**[17] (10 mg, 0.03 mmol), LiBr (16 mg, 0.19 mmol), I_2 (16 mg, 0.063 mmol), and Et_3N (9 μL, 0.06 mmol) were used. Purification by semiprep HPLC (99.9:0.1 hexanes/EtOAc) afforded the title compound as a pale yellow oil (6.8 mg) in 65% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7 (t, J_{CF} = 22.9 Hz, 1C), 153.5, 148.3, 128.2, 122.5, 110.1, 108.4, 102.3, 95.5 (t, J_{CF} = 326 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.1 (s, 2F); IR (film) ν_{max} 2910.2, 1692.6, 1606.2, 1504.9, 1447.9, 1354.6, 1267.6, 1093.9 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_9H_5F_2IO_3$ $(M)^+$ 325.9252, found 325.9259.

1-(Benzothiophen-3-yl)-2,2-difluoro-2-iodoethanone 16. See representative reaction procedure. 1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3** (10 mg, 0.03 mmol), LiBr (16 mg, 0.19 mmol), I_2 (16 mg, 0.063 mmol), and Et_3N (9 μL, 0.06 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a pale yellow oil (8.1 mg) in 79% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74−8.71 (m, 2H), 7.92 (dt, J = 8.2, 0.9 Hz, 1H), 7.57 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.49 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5 (t, J_{CF} = 23.5 Hz, 1C), 142.0 (t, J_{CF} = 6.8 Hz, 1C), 138.9, 137.2, 126.6, 126.2, 125.4, 124.6, 122.3, 95.6 (t, J_{CF} = 326 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.1 (s, 2F); IR (film) ν_{max} 3116.1, 1678.3, 1488.8, 1459.3, 1360.7, 1228.5, 1096.8 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{10}H_5F_2IOS$ $(M)^+$ 337.9074, found 337.9077.

(*E*)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one 11. To a −78 °C solution of hexamethyldisilazane (265 mg, 1.64 mmol) in THF (3 mL) was added a solution of *n*-BuLi (650 μL, 2.5 M in hexanes). The mixture was stirred for 30 min at −78 °C, and then a solution of (*E*)-4-phenylbut-3-en-2-one (200 mg, 1.37 mmol) in THF (3 mL) was added dropwise. After an additional 1 h at −78 °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (400 mg, 2.05 mmol) was added dropwise, and the mixture was stirred for 30 min at the same temperature. Next, the reaction mixture was quenched at −78 °C with 0.1 M H_2SO_4 (6 mL) and allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (6 mL × 2). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product (335 mg). The crude product was dissolved in CH_3CN (5 mL), treated with Selectfluor (1.24 g, 3.50 mmol), and stirred at rt for 24 h. The reaction mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite, and concentrated under reduced pressure. The product was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (10 mL × 2) and brine (10 mL), and then concentrated under reduced pressure to provide the 4,4,6,6,6-pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **11** as a colorless solid (400 mg) in 99% yield: mp 68−70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 15.9 Hz, 1H), 7.68 (d, J = 7.3 Hz, 2H), 7.53−7.50 (m, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 15.9 Hz, 1H), 4.61 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4 (t, J_{CF} = 28.1 Hz, 1C), 150.9, 133.3, 132.6, 129.6 (2C), 129.3 (2C), 120.8 (q, J_{CF} = 288 Hz, 1C), 116.8, 110.0 (t, J_{CF} = 266 Hz, 1C), 92.6 (qt, J = 27.0, 5.8 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.3 (t, J = 10.3 Hz, 3F), −120.8 (q, J = 10.1 Hz, 2F); IR (film) ν_{max} 3398.9, 1697.1, 1594.9, 1575.0, 1451.5, 1206.0, 1072.3 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_9F_5O_3$ $(M - H_2O)^+$ 278.0366, found 278.0363.

(*E*)-1,1-Difluoro-1-iodo-4-phenylbut-3-en-2-one 17. See representative reaction procedure. (*E*)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **11** (10 mg, 0.03 mmol), LiBr (17.5 mg, 0.20 mmol), I_2 (17 mg, 0.067 mmol), and Et_3N (10 μL, 0.07 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a pale yellow oil (7.0 mg) in 67% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 15.8 Hz, 1H), 7.65 (dd, J = 7.7, 1.5 Hz, 2H), 7.51−7.44 (m, 3H), 7.09 (dt, J = 15.8, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9 (t, J_{CF} = 23.3 Hz, 1C), 149.9, 133.6, 132.1, 129.2 (4C), 114.2, 96.9 (t, J_{CF} = 326 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.2 (s, 2F); IR (film) ν_{max} 3055.5, 3032.0, 2923.7, 1703.6, 1608.0, 1496.0, 1449.3, 1343.5, 1206.6, 1053.0 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{10}H_7F_2IO$ $(M)^+$ 307.9510, found 307.9508.

4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one 12. To a solution of (*E*)-4,4,6,6,6-pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **11** (100 mg, 0.34 mmol) in EtOH (3.5 mL) was added Pd/C (17 mg, 0.17 mmol). The reaction mixture was stirred under a H_2 atmosphere for 12 h. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in 1:1 mixture of THF/0.5 M H_2SO_4 (10 mL) and vigorously stirred for 24 h at rt. The reaction mixture was extracted with EtOAc (5 mL × 2), and the organics were dried over Na_2SO_4 and concentrated under reduced pressure to

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provide the 4,4,6,6,6-pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one **12** as a colorless oil (86.6 mg) in 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.30 (m, 2H), 7.25−7.19 (m, 3H), 4.19 (br s, 2H), 3.18 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6 (t, J_{CF} = 28.8 Hz, 1C), 139.3, 128.7 (2C), 128.3 (2C), 126.6, 120.6 (q, J_{CF} = 288 Hz, 1C), 109.5 (t, J_{CF} = 267 Hz, 1C), 92.3 (qt, J = 27.4, 5.9 Hz, 1C), 39.6, 28.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.1 (t, J = 10.2 Hz, 3F), −120.8 (q, J = 10.2 Hz, 2F); IR (film) ν_{max} 3462.1, 1742.2, 1209.8, 1171.9, 1069.0 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_{11}F_5O_3$ (M − H_2O)$^+$ 280.0523, found 280.0525.

1,1-Difluoro-1-iodo-4-phenylbutan-2-one 18. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one **12** (10 mg, 0.036 mmol), LiBr (17 mg, 0.20 mmol), I_2 (17 mg, 0.067 mmol), and Et_3N (10 μL, 0.07 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a pale yellow oil (8.6 mg) in 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5H), 3.16 (t, J = 7.5 Hz, 2H), 3.02 (t, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3 (t, J_{CF} = 24.6 Hz, 1C), 139.5, 128.7 (2C), 128.4 (2C), 126.6, 94.7 (t, J_{CF} = 334 Hz, 1C), 35.2, 29.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.1 (s, 2F); IR (film) ν_{max} 2929.2, 1748.0, 1585.3, 1496.5, 1454.7, 1134.6, 1049.9 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_9F_2IO$ (M + H)$^+$ 310.9744, found 310.9739.

1-(Adamantan-1-yl)-2,2-difluoro-2-iodoethanone 19. See representative reaction procedure. 1-Adamantyl-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **13**[17] (10 mg, 0.030 mmol), LiBr (16 mg, 0.19 mmol), I_2 (16 mg, 0.063 mmol), and Et_3N (9 μL, 0.06 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a pale yellow oil (7.0 mg) in 66% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07−2.05 (m, 9H), 1.75 (q, J = 12.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3 (t, J_{CF} = 20.7 Hz, 1C), 97.4 (t, J_{CF} = 331 Hz, 1C), 45.4, 38.2 (3C), 36.2 (3C), 27.7 (3C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −54.5 (s, 2F); IR (film) ν_{max} 2908.8, 2854.7, 1722.3, 1453.8, 1213.2, 1117.4 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_{15}F_2IO$ (M + H)$^+$ 341.0214, found 341.0210.

Representative Procedure for the Synthesis of α-Chloro-α,α-difluoromethyl Ketones. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-3-yl)butan-1-one **1**[17] (10 mg, 0.031 mmol) in THF (310 μL) was added LiCl (8 mg, 0.2 mmol) followed by NCS (8 mg, 0.06 mmol). The reaction mixture was stirred for 1 min, and then Et_3N (9 μL, 0.06 mmol) was added. After stirring for 30 min at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was extracted in EtOAc (1 mL × 2), and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (5% Et_2O in hexanes) afforded the 2-chloro-2,2-difluoro-1-(naphthalen-2-yl)ethanone **20** as a colorless oil (6.0 mg) in 80% yield.

2-Chloro-2,2-difluoro-1-(naphthalen-2-yl)ethanone 20. See representative reaction procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.11 (dd, J = 8.7, 1.8 Hz, 1H), 8.02 (dd, J = 8.2, 0.6 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.91 (dd, J = 8.2, 0.5 Hz, 1H), 7.69 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.61 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2 (t, J_{CF} = 28.9 Hz, 1C), 136.3, 133.5, 132.1, 130.2, 130.0, 128.9, 127.9, 127.3, 126.5, 124.8, 120.3 (t, J_{CF} = 305 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −61.2 (s, 2F); IR (film) ν_{max} 1709.0, 1155.0, 989.8, 818.7, 752.5 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_{12}H_7ClF_2O$ (M)$^+$ 240.0154, found 240.0153.

1-(Benzo[1,3]dioxol-5-yl)-2-chloro-2,2-difluoroethanone 21. See representative reaction procedure. 1-(Benzo[1,3]dioxol-6-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **2**[17] (10 mg, 0.03 mmol), LiCl (8 mg, 0.19 mmol), NCS (8.5 mg, 0.065 mmol), and Et_3N (10 μL, 0.07 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (6.2 mg) in 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (ddt, J = 8.3, 2.0, 1.1 Hz, 1H), 7.54 (m, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4 (t, J = 28.7 Hz, 1C), 153.7, 148.4, 127.9, 123.6, 120.2 (t, J = 305 Hz, 1C), 109.8, 108.4, 102.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −61.0 (s, 2F); IR (film) ν_{max} 1703.8, 1491.1, 1448.6, 1271.4, 1097.7, 1040.9, 995.4, 744.3 cm^{-1}; HRMS (EI/CI) m/z calcd for $C_9H_5ClF_2O_3$ (M)$^+$ 233.9895, found 233.9894.

(*E*)-1-Chloro-1,1-difluoro-4-phenylbut-3-en-2-one 22. See representative reaction procedure. (*E*)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **11** (30 mg, 0.1 mmol), LiCl (26 mg, 0.60 mmol), NCS (27 mg, 0.20 mmol), and Et_3N (30 μL, 0.20 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (13.7 mg) in 63% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 15.9 Hz, 1H), 7.65 (dd, J = 5.2, 3.2 Hz, 2H), 7.51−7.44 (m, 3H), 7.06 (d, J = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6 (t, J_{CF} = 29.2 Hz, 1C), 150.2, 133.4, 132.2, 129.2 (4C), 120.2 (t, J_{CF} = 305 Hz, 1C), 115.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.5 (s, 2F); IR (film) ν_{max} 2919.4, 1715.7, 1610.4, 1577.0, 1450.7, 1339.6, 1145.0 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_7ClF_2O$ (M + H)$^+$ 217.0232, found 217.0226.

1,3,3-Trichloro-1,1-difluoro-4-phenylbutan-2-one 23. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one **12** (10 mg, 0.033 mmol), LiCl (9 mg, 0.20 mmol), NCS (18 mg, 0.13 mmol), and Et_3N (9 μL, 0.07 mmol) were used. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (7.0 mg) in 73% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 5H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6 (t, J_{CF} = 29.6 Hz, 1C), 131.8, 131.7 (2C), 128.3 (3C), 118.9 (t, J_{CF} = 308 Hz, 1C), 82.3, 48.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.0 (s, 2F); IR (film) ν_{max} 2925.3, 2854.6, 1761.7, 1456.0, 1166.9, 1091.7 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_7Cl_3F_2O$ (M + H)$^+$ 286.9609, found 286.9603.

2,2-Difluoro-4,5-dimethyl-1-(naphthalen-2-yl)hex-4-en-1-one 25. A suspension of 2,2-difluoro-2-iodo-1-(naphthalen-3-yl)-ethanone **14** (26 mg, 0.078 mmol), Cu powder (20 mg, 0.32 mmol), and 2,3-dimethyl-2-butene **24** (100 μL, 0.78 mmol) in DMSO (150 μL) was stirred at 60 °C for 15 h. The reaction mixture was cooled to rt, diluted with H_2O (5 mL), and extracted with EtOAc (2 mL × 2). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (5% Et_2O in hexanes) provided the title compound as a colorless oil (11.2 mg) in 50% yield (6:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.90 (dd, J = 13.8, 8.5 Hz, 2H), 7.64 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.58 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 3.04 (t, J = 18.7 Hz, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2 (t, J_{CF} = 30.9 Hz, 1C), 135.9, 132.7, 132.3, 132.0, 130.1, 129.6, 129.3, 128.5, 127.8, 126.9, 124.9, 120.1 (t, J_{CF} = 256 Hz, 1C), 118.3, 39.0 (t, J_{CF} = 22.9 Hz, 1C), 21.2, 20.9, 20.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.9 (t, J = 18.6 Hz, 2F); IR (film) ν_{max} 2925.6, 1698.2, 1627.9, 1597.1, 1465.9, 1289.7, 1153.7, 1037.2 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{18}F_2O$ (M+Na)$^+$ 311.1223, found 311.1233.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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