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Chloro, Difluoromethylation and Chloro, Carbomethoxydifluoromethylation: Reaction of Radicals Derived from R_fSO_2Cl with Unactivated Alkenes under Metal-Free Conditions

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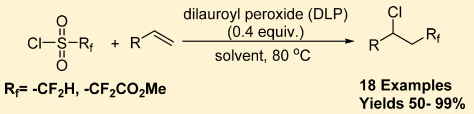
Supporting Information

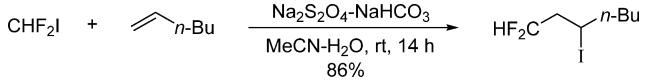
ABSTRACT: Difluoromethyl and carbomethoxydifluoromethyl radicals were generated from their respective sulfonyl chlorides under mild, metal-free conditions leading to efficient atom transfer radical additions (ATRA) to unactivated alkenes to form chloro, difluoromethylated and chloro, carbomethoxydifluoromethylated products.



In 1945, Kharasch and co-workers reported that halocarbons such as CCl_4 could add to olefins through a radical chain process.[1] Since then, atom transfer radical addition (ATRA) reactions have been elaborated extensively to allow the addition of a multitude of halocarbons to olefins in the process of developing useful applications in organic synthesis. Since fluorinated substituents are recognized to impart significant changes to a molecule's physical, chemical, and biological properties,[2] it is not surprising that ATRA reactions have found considerable application with respect to the addition of fluorinated groups to olefins.[3,4]

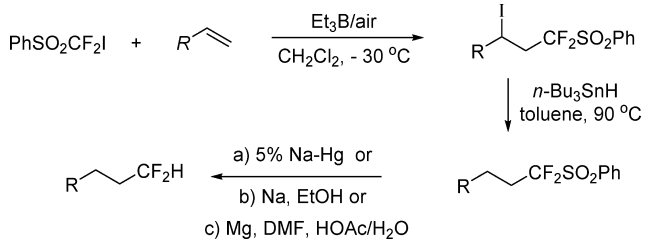
Recently, free radical processes have been frequently used to effect the incorporation of a CF_3 group into molecules, using Togni's reagent, Umemoto's reagent, Langlois' reagent, $ClSO_2CF_3$, or other trifluoromethylating reagents via ATRA type reactions,[5−10] and a new method for adding $\cdot CF_2Cl$ radicals to alkenes by the use of xanthates has just appeared.[11] Despite such recent advances in this field, use of free radical chemistry to incorporate partially fluorinated substituents has remained relatively underdeveloped and the discovery of new approaches to accomplish this are therefore always welcomed by the synthetic community. Incorporation of the difluoromethyl group is of particular interest to pharmaceutical and agrochemical researchers, because it has been shown to affect the membrane permeability, bioavailability, binding affinity, and lipophilicity of molecules.[12] Baran has made significant contributions with regard to radical-based, CF_2H functionalization of heteroaromatic compounds using his recently developed $Zn(SO_2CFH$ reagent.[13] In the past, the only ATRA-type reaction that has been reported to *directly* introduce the CF_2H group by addition to alkenes is the reaction of CHF_2I with alkenes, reported by Chen's group in 1994 (Scheme 1).[14] However, CHF_2I is not available commercially, and by our own experience, it is not easily or inexpensively prepared or convenient to use as it is a highly volatile compound (bp ∼20 °C).

Scheme 1. Chen's Study of the Addition of CHF_2I to Alkenes



In the absence of direct methods, a number of two-step procedures for the introduction of a CF_2H group by free radical additions to alkenes have been developed over the years. These methods involve the free radical additions of $\cdot CF_2X$ radicals to alkenes, followed by conversion of the X groups to H. Thus far, the X groups that have been found to be effective are Br, Cl, SPh, and, in particular, $PhSO_2$ (Scheme 2).[15]

Scheme 2. Sulfones as Indirect Difluoromethylation Reagents[16]



Similarly, the CF_2CO_2R group is important because it allows the potential for further functionalization once it is incorporated.[17] Previous halo, carboalkoxydifluoromethylations have been limited to the use of ethyl or methyl halo- or xanthodifluoroacetates (XCF_2CO_2R) as precursors of the carboalkoxydifluoromethyl radical, where X = Br, I, or SCOSR, with these reactions proceeding via atom transfer radical addition (ATRA) processes (Scheme 3).[18]

Although the previously reported methods to accomplish difluoromethylation and carboalkoxydifluoromethylation clearly have their merits, there is plenty of incentive for the development of new methodologies. In the present paper, we report mild, metal-free conditions for carrying out chloro,

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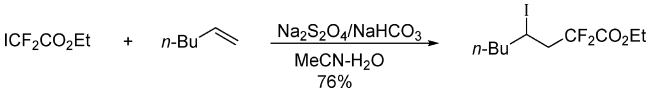
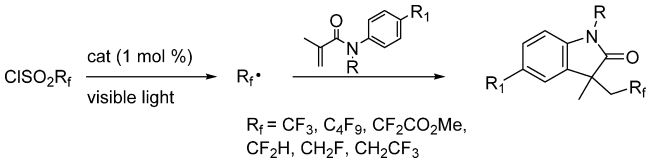
Scheme 3. Example of Halo, Carboethoxydifluoromethylation Using ICF_2CO_2Et[18h]



difluoromethylations and chloro, carbomethoxydifluoromethylations of unactivated alkenes by the use of sulfonyl chlorides, CHF_2SO_2Cl and $CH_3O_2CCF_2SO_2Cl$, as the respective radical precursors.

During the course of our study of the photoredox-catalyzed tandem radical cyclization of *N*-arylacrylamides in their reactions with R_fSO_2Cl, where R_f = n-C_4F_9, CF_3, CF_2H, CH_2F, CH_2CF_3, and CF_2CO_2Me, to obtain fluorinated 2-oxindoles (Scheme 4),[19] we discovered that these radical

Scheme 4. Fluorinated Sulfonyl Chlorides As Radical Precursors—Our Previous Work



cyclizations also occurred in the absence of a photoredox catalyst, under thermal conditions using dilauroyl peroxide (DLP) as an initiator and possible oxidant. On the basis of this result, we hypothesized that it might be possible to induce sulfonyl chlorides to participate in atom transfer radical addition reactions with unactivated alkenes under similar conditions.

Our study of this chemistry was initiated by examination of the reaction of 4-phenyl-1-butene with 2 equiv of difluoromethanesulfonyl chloride, using 0.3 equiv of dilauroyl peroxide (DLP) as an initiator, in 1,2 dichloroethane (DCE) at 80 °C for 8 h (Scheme 5). Under these initial conditions, the expected chloro, difluoromethylated product (**3a**) was obtained in 68% yield (Table 1, entry 1). The reaction was then explored with the intent of optimizing the conditions for the most favorable outcome.

AIBN was explored as an alternative initiator, but the reaction proved less efficient (entry 2). Photoredox catalysts (entries 3 and 4) were also examined, but no improvement was observed. At this point, the effects of varying the solvent and temperature of the reaction were examined. It was found that using dichloromethane (DCM) as solvent, in a sealed vessel at 70 °C, with 0.3 equiv of DLP as the initiator provided a 93% yield of **1a** (entry 6) and that essentially quantitative yields were obtained when the amount of DLP was increased to 0.4 equiv (entry 8). Further attempts to improve the reaction by decreasing the amount of sulfonyl chloride or increasing the amount of DLP did not improve yields (entries 9 and 10).

Using the optimized conditions, the scope of this chloro, difluoromethylation reaction was explored, with the results

Table 1. Optimization of the Reaction of Difluoromethanesulfonyl Chloride with 4-Phenyl-1-butene

entry	initiator	solvent	temp (°C)	yield (**1a**)[a]
1	0.3 equiv of DLP	DCE	80	68%
2	0.3 equiv of AIBN	DCE	80	35%
3[b]	0.5% $Cu(dap)_2CI_2$	DCE	90	50%
4[b]	0.5% $Ru(1,10\ phen)_3CI_2{\cdot}xH_2O$	DCE	rt	–
5	0.3 equiv of DLP	DCE	70	60%
6	0.3 equiv of DLP	DCM	70	93%
7	0.3 equiv of DLP	MeCN	70	50%
8	0.4 equiv of DLP	DCM	70	(99%)
9[c]	0.4 equiv of DLP	DCM	70	70%
10	0.5 equiv of DLP	DCM	70	85%

[a]Yields were observed by ^{19}F NMR using $PhCF_3$ as internal standard; parentheses indicates isolated yield. [b]Reaction carried out with 20 mol % K_2HPO_4 and a 120 W bulb to initiate reation. [c]1.5 equiv of sulfonyl chloride used.

being summarized in Table 2. Terminal unfunctionalized alkenes showed great reactivity under these conditions (**1a**–**d**), and alkenes with ether, ester, phthalimide, and even carboxylic acid functional groups also gave the desired products in good to excellent yields (**1f**–**1i**). 1-Phenylcyclohexene, a nonterminal alkene, gave moderate yields of a single regio- and (presumably *E*) stereoisomer (**1e**).

To further extend the scope of this methodology, methyl 2,2-difluoro-2-(chlorosulfonyl)acetate was examined as a source of the carbomethoxy-2,2-difluoromethyl radical under similar conditions. When DLP (0.3 equiv) was used as the initiator in DCE at 80 °C, the desired 4-chloro, carbomethoxydifluoromethyl product (**2a**) was obtained in 59% yield. Similar optimization experiments to those in Table 1 were carried out with very similar results, except that it was found that DCE was the solvent that gave the best results: an 89% yield using 0.4 equiv of DLP at 70 °C for 8 h (Scheme 6).

The scope of the reaction was then examined using a variety of structurally diverse alkenes (Table 3). Once again, terminal alkenes were the most reactive (**2a**–**e**). Alkenes with ether, ester, and phthalimide functional groups also provided very good yields of products **2g**–**2i**. A nonterminal alkene, cyclohexene, was also an effective substrate, yielding 73% of product, consisting of an approximately 1:1 mixture of the two stereoisomers (**2f**).

Unfortunately, electron-deficient alkenes, such as acrylates, acrylamides, or α,β unsaturated ketones, were not good substrates in reactions with either of the sulfonyl chlorides.

In conclusion, a method has been developed for metal-free chloro, difluoromethylation and chloro, carbomethoxydifluoromethylation of a variety of unactivated alkenes using sulfonyl chlorides CF_2HSO_2Cl and $MeO_2CCF_2SO_2Cl$ as the radical precursors. This mild and efficient protocol enables the addition of HCF_2 or MeO_2CCF_2 groups and Cl to alkenes in a highly regioselective manner.

Scheme 5. Initial Results

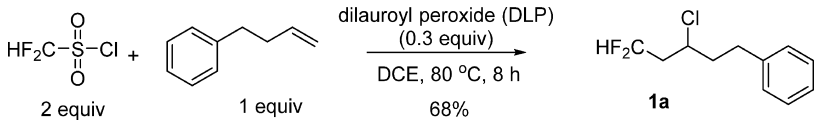


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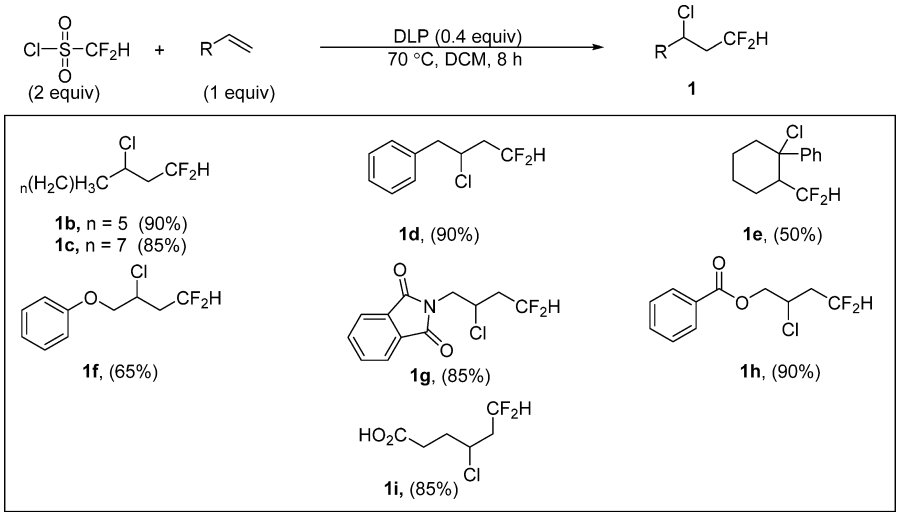
Table 2. Scope of the Reaction of Difluoromethanesulfonyl Chloride with Alkenes



Scheme 6. Optimal Conditions for the Reaction of Methyl 2,2-Difluoro-2-(chlorosulfonyl) Acetate with 4-Phenyl-1-butene

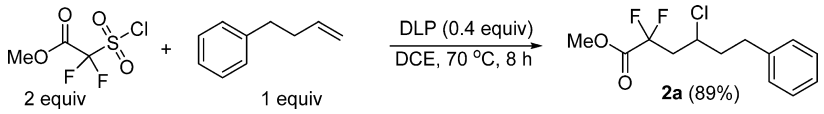
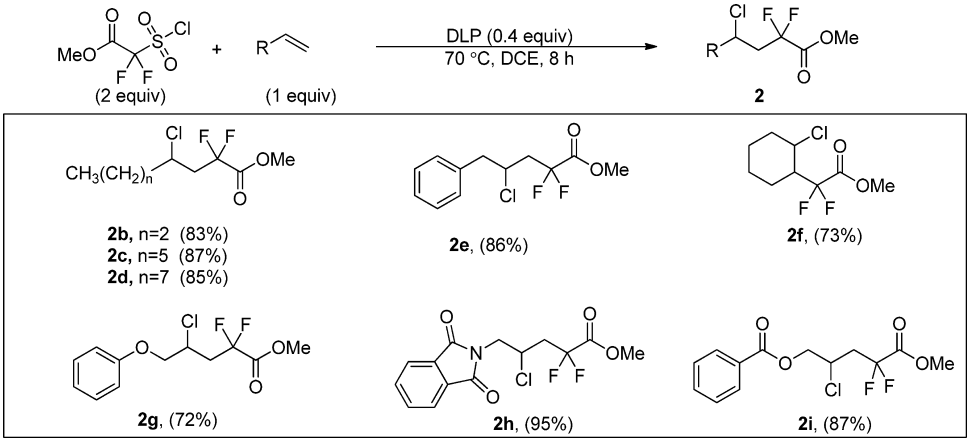


Table 3. Scope of the Reaction of Methyl 2,2-Difluoro-2-(chlorosulfonyl)acetate with Alkenes



EXPERIMENTAL SECTION

General Information. All reactions were carried out under a N_2 atmosphere. All anhydrous solvents were purchased from commercial sources and stored over 4 Å molecular sieves. Reagents were purchased at commercial quality and were used without further purification. All NMR spectra were run using $CDCl_3$ as solvent, unless otherwise specified. ^{1}H NMR spectra were recorded at 300 MHz, and chemical shifts are reported in ppm relative to TMS. ^{19}F NMR spectra were recorded at 282 MHz, and chemical shifts are reported in ppm relative to $CFCl_3$ as the external standard. ^{13}C NMR spectra were recorded at 75 MHz with proton decoupling, and chemical shifts are reported in ppm relative to $CDCl_3$ (−77.0 ppm) as the reference. All HRMS data were obtained on a DSQ MS instrument. HCF_2SO_2Cl and $MeOOCCF_2SO_2Cl$ were prepared according to literature procedures.[19]

Representative Procedures for Converting Alkenes to Chloro, Difluoromethylated and Chloro, Carbomethoxydifluoromethylated Products. *Chloro, Difluoromethylation. Preparation of (3-Chloro-5,5-difluoropentyl)benzene (**1a**).* To an oven-dried 17 mm × 60 mm (8 mL) borosilicate vial equipped with a magnetic stirrer were added 0.25 mmol (33 mg) of 4-phenyl-1-butene, 0.1 mmol (40 mg, 40 mol %) of DLP, 1 mL of DCM, and 0.5 mmol (75 mg, 2 equiv) of HCF_2SO_2Cl. The vial was flushed with nitrogen, sealed, and protected by parafilm. The reaction mixture was stirred for 8 h at 70 °C. After 8 h, the mixture was diluted with DCM and washed with water. The organic layer was collected and washed with brine (2 × 20 mL) and concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (9:1) as the eluent to provide 43 mg (99%) of liquid product, 3-chloro-5,5-difluoropentyl)benzene,**1a.**

*(3-Chloro-5,5-difluoropentyl)benzene (**1a**).* 54 mg (99%); ^{1}H NMR, δ 7.19 (d, J = 4 Hz, 2H), 7.08 (d, J = 4 Hz, 3H), 5.93 (tt, $^2J_{H,F}$ = 57 Hz, J = 3 Hz, 1H), 3.87 (m, 1H), 2.79−2.58 (m, 2H), 2.18−2.04 (m, 2H), 1.97−1.90 (m, 2H); ^{19}F NMR, δ −116.2 (ddt, $^2J_{F,F}$ = 288 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 11.3 Hz, 1F), −118.2 (ddt, $^2J_{F,F}$ = 288 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 19.7 Hz, 1F); ^{13}C NMR δ 140.3, 128.4, 126.2, 115.6 (t, $^1J_{C,F}$ = 237.8 Hz), 55.8, 42.6 (t, $^2J_{C,F}$ = 23.3 Hz), 40.0, 32.19, 29.6; HRMS (GC−CI) m/z calcd for $C_{11}H_{12}F_2Cl$ 217.0596 $[M - H]^+$; found 217.0594

*3-Chloro-1,1-difluorononane (**1b**).* 45 mg (90%); ^{1}H NMR, δ 6.05 (tt, $^2J_{H,F}$ = 55.8 Hz, J = 3 Hz, 1H) 4.02 (m, 1H), 2.29−2.18 (m, 2H), 1.80−1.76 (m, 2H), 1.56−1.30 (m, 8H), 0.90 (t, J = 3 Hz, 3H); ^{19}F

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NMR, δ −118.9 (ddt, $^2J_{F,F}$ = 289 Hz, $^2J_{H,F}$ = 56.1 Hz, $^3J_{H,F}$ = 11.7 Hz, 1F), −120.8 (dddd, $^2J_{F,F}$ = 288 Hz, $^2J_{H,F}$ = 58.4 Hz, $^3J_{H,F}$ = 22.5 Hz, $^3J_{H,F}$ = 15.9 Hz, 1F); ^{13}C NMR δ 115.8 (t, $^1J_{C,F}$ = 238.7 Hz), 56.6, 42.7 (t, $^2J_{C,F}$ = 22.5 Hz), 31.5, 28.6, 26.0, 22.6, 22.5, 14.1; HRMS (GC−CI) m/z calcd for $C_9H_{16}F_2Cl$ $[M - H]^+$197.0909; found 197.0913.

*3-chloro-1,1-difluoroundecane (**1c**).* 48 mg (85%); ^{1}H NMR, δ 6.07 (tt, $^2J_{H,F}$ = 56 Hz, J = 3 Hz, 1H), 4.03 (m, 1H), 2.30−2.24 (m, 2H), 1.79−1.74 (m, 2H), 1.57−1.29 (m, 12 H), 0.90 (t, J = 3 Hz, 3H); ^{19}F NMR, δ −117.1 (ddt, $^2J_{F,F}$ = 290 Hz, $^2J_{H,F}$ = 54.7 Hz, $^3J_{H,F}$ = 13.0 Hz, 1F), −118.9 (dddd, $^2J_{F,F}$ = 287 Hz, $^2J_{H,F}$ = 55.3 Hz, $^3J_{H,F}$ = 24.0 Hz, $^3J_{H,F}$ = 14.1 Hz, 1F); ^{13}C NMR δ 115.8 (t, $^1J_{C,F}$ = 236.3 Hz), 56.8, 42.7 (t, $^2J_{C,F}$ =22.5 Hz), 38.5, 31.8, 29.4, 28.9, 26.0, 22.6, 14.09; HRMS (GC−CI) m/z calcd for $C_{11}H_{20}F_2Cl$ $[M - H]^+$ 225.1222; found 225.1211.

*(2-Chloro-4,4-difluorobutyl)benzene (**1d**).* 46 mg (90%); ^{1}H NMR, δ 7.25 (d, J = 4 Hz, 3H), 7.17 (d, J = 6 Hz, 2H), 5.99 (tt, $^2J_{H,F}$ = 57 Hz, J = 3 Hz, 1H), 4.15 (m, 1H), 3.08−2.94 (m, 2H), 2.23−2.08 (m, 2H); ^{19}F NMR, δ −117.4 (ddt, $^2J_{F,F}$ = 289 Hz, $^2J_{H,F}$ = 55.8 Hz, $^3J_{H,F}$ = 11.0 Hz, 1F), −119.3 (dddd, $^2J_{F,F}$ = 289 Hz, $^2J_{H,F}$ = 56.1 Hz, $^3J_{H,F}$ = 29.6 Hz, $^3J_{H,F}$ = 13.5 Hz, 1F); ^{13}C NMR δ 136.5, 129.4, 128.7, 128.6, 127.2, 115.7 (t, $^1J_{C,F}$ = 236.3), 56.4, 44.8, 41.7 (t, $^2J_{C,F}$ =22.5 Hz); HRMS (GC−CI) m/z calcd for $C_{10}H_{11}F_2Cl$ 204.0517 M^+; found 204.0510.

*(1-Chloro-2-(difluoromethyl)cyclohexyl)benzene (**1e**).* 31 mg (50%); ^{1}H NMR, δ 7.29 (m, 4H), 6.10 (s, 1H), 5.7 (t, $^2J_{H,F}$ = 57 Hz, 1H), 3.16 (m, 1H), 2.22−1.68 (m, 7H); ^{19}F NMR, −121.9 (ddd, $^2J_{F,F}$ = 275 Hz, $^2J_{H,F}$ = 56.1 Hz, $^3J_{H,F}$ = 8.5 Hz, 1F), −124.6 (ddd, $^2J_{F,F}$ = 275 Hz, $^2J_{H,F}$ = 56.7 Hz, $^3J_{H,F}$ = 25.4 Hz, 1F); ^{13}C NMR δ 131.1, 128.4, 127.3, 126.3, 117.1 (t, $^1J_{C,F}$ = 241.5 Hz), 40.0 (t, $^2J_{C,F}$ = 19.5 Hz), 25.5, 21.0, 19.2; HRMS (EI) m/z calcd for $C_{13}H_{14}F_2$ $[M - HCl]^+$ 208.1064; found 208.1069.

*(2-Chloro-4,4-difluorobutoxy)benzene (**1f**).* 36 mg (65%); ^{1}H NMR, δ 7.23 (m, 2H), 6.92 (t, J = 4 Hz), 6.84 (d, J = 9 Hz), 6.03 (tt, $^2J_{H,F}$ = 57 Hz, J = 3 Hz), 4.26−4.17 (m, 1H), 4.13−4.01 (m, 2H), 2.46−2.21 (m, 2H); ^{19}F NMR, δ −117.4 (ddt, $^2J_{F,F}$ = 291 Hz, $^2J_{H,F}$ = 58.9 Hz, $^3J_{H,F}$ = 14.7 Hz, 1F), −119.3 (dddd, $^2J_{F,F}$ = 292 Hz, $^2J_{H,F}$ = 53.5 Hz, $^3J_{H,F}$ = 24.8 Hz, $^3J_{H,F}$ = 13.3 Hz, 1F); ^{13}C NMR, δ 129.6, 121.7, 115.4 (t, $^1J_{C,F}$ = 252 Hz), 114.7, 71.0, 52.5, 39.5 (t, $^2J_{C,F}$ = 22.5 Hz); HRMS (GC−CI) m/z calcd for $C_{10}H_{12}OF_2Cl$ 221.0545 $[M + H]^+$; found 221.0540

*2-(2-Chloro-4,4-difluorobutyl)isoindoline-1,3-dione (**1g**).* 58 mg (85%); ^{1}H NMR, δ 7.90 (m, 2H), 7.76 (m, 2H), 6.09 (tt, $^2J_{H,F}$ = 57 Hz, J = 3 Hz, 1H), 4.41 (m, 1H), 4.11−3.89 (m, 2H), 2.39−2.30 (m, 2H); ^{19}F NMR, δ −116.2−119.4 (m, 2F); ^{13}C NMR, δ 167.8, 134.4, 131.6, 123.7, 115.1 (t, $^1J_{C,F}$ = 231 Hz), 52.4, 43.7, 40.2 (t, $^2J_{C,F}$ = 24 Hz); HRMS (GC−CI) m/z calcd for $C_{12}H_{11}NO_2F_2Cl$ $[M + H]^+$ 274.0446; found 274.0441.

*2-Chloro-4,4-difluorobutyl benzoate (**1h**).* 56 mg (90%); ^{1}H NMR, δ 8.02 (t, J = 6 Hz, 2H), 7.53 (t, J = 6 Hz, 1H), 7.40 (d, J = 2 Hz, 2H), 6.05 (t, $^2J_{H,F}$ = 57 Hz, 1H), 4.51−4.39 (m, 2H), 4.30 (m, 1H), 2.37−2.21 (m, 2H); ^{19}F NMR, δ −117.1 (ddt, $^2J_{F,F}$ = 285 Hz, $^2J_{H,F}$ = 54.4 Hz, $^3J_{H,F}$ = 11.3 Hz, 1F), −118.7 (dddd, $^2J_{F,F}$ = 289 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 24.8 Hz, $^3J_{H,F}$ = 13.8 Hz, 1F); ^{13}C NMR, δ 197.8, 133.6, 129.8, 129.7,128.7,128.5.115.2 (t, $^1J_{C,F}$ = 239 Hz), 67.3, 52.4 39.5 (t, $^2J_{C,F}$ = 22.5 Hz), 29.5; HRMS (GC−CI) m/z calcd for $C_{11}H_{12}O_2F_2Cl$ 249.0494 $[M + H]^+$; found 249.0487.

*4-Chloro-6,6-difluorohexanoic Acid (**1i**).* 40 mg (85%); ^{1}H NMR, δ 5.98 (t, $^2J_{H,F}$ = 57 Hz, 1H), 4.03 (m, 1H), 2.59−2.49 (m, 3H), 2.27−1.51 (m, 4H); ^{19}F NMR, −117.4 (ddt, $^2J_{F,F}$ = 289 Hz, $^2J_{H,F}$ = 57.8 Hz, $^3J_{H,F}$ = 11.3 Hz, 1F), −119.3 (dddd, $^2J_{F,F}$ = 288 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 24.5 Hz, $^3J_{H,F}$ = 14.1 Hz, 1F); ^{13}C NMR, δ 178.4, 115.3 (t, $^1J_{C,F}$ = 245.0 Hz), 55.4, 42.7 (t, $^2J_{C,F}$ = 23.0 Hz), 33.0, 30.4; HRMS (GC−CI) m/z calcd for $C_6H_9F_2O_2$ $[M - Cl]^+$ 151.0571; found 151.0575

*Chloro, Carbomethoxydifluoromethylation. Preparation of Methyl 4-Chloro-2,2-difluoro-6-phenylhexanoate (**2a**).* To an oven-dried 17 mm × 60 mm (8 mL) borosilicate vial equipped with a magnetic stirrer were added 0.25 mmol (33 mg) of 4-phenyl-1-butene, 0.1 mmol (40 mg, 40%) of DLP, 1 mL of DCE, and 0.5 mmol (104 mg, 2 equiv) of $MeCO_2CF_2SO_2Cl$. The vial was flushed with nitrogen, sealed, and protected by parafilm. The reaction mixture was stirred for 8 h at 70 °C. After 8 h, the mixture was diluted with DCM and washed with water. The organic layer was collected and washed with brine (2 × 20 mL) and concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (9:1 to 7:3) as the eluent to provide 49 mg (89%) of liquid product, methyl 4-chloro-2,2-difluoro-6-phenylhexanoate, **2a.**

*Methyl 4-Chloro-2,2-difluoro-6-phenylhexanoate (**2a**).* 62 mg (89%); ^{1}H NMR, δ 7.19 (d, J = 4.0 Hz, 2H), 7.1 (d, J = 4.0 Hz, 3H), 3.97 (m, 1H), 3.75 (s, 3H), 2.79−2.43 (m, 4H), 2.00−1.94 (m, 2H); ^{19}F NMR, δ −102.9 (dt, $^2J_{F,F}$ = 265 Hz, $^3J_{F,H}$ = 14.1 Hz), −108.8 (ddd, $^2J_{F,F}$ = 265 Hz, $^3J_{F,H}$ = 19.7, 16.9 Hz); ^{13}C NMR, δ 164.0, 140.2, 128.6, 128.5, 126.3, 114.6 (t, $^1J_{C,F}$ = 252 Hz), 54.6, 53.5, 43.5 (t, $^2J_{C,F}$ = 24.8 Hz), 40.1, 32.1; HRMS (GC−CI) m/z calcd for $C_{13}H_{15}O_2F_2Cl$ $[M + H]^+$: 276.0729; found 276.0735.

*Methyl 4-Chloro-2,2-difluoroheptanoate (**2b**).* 45 mg (83%); ^{1}H NMR, δ 4.11 (m, 1H), 3.88 (s, 3H), 2.70−2.46 (m, 2H), 1.79−1.72 (m, 2H), 1.58−1.49 (m, 2H), 0.94 (t, 6 Hz); ^{19}F NMR, δ −101.3 (dt, $^2J_{F,F}$ = 265.1 Hz, $^3J_{F,H}$ = 14.1 Hz), −107.6 (ddd, $^2J_{F,F}$ = 265.1, $^3J_{F,H}$ = 22.6 Hz, $^3J_{F,H}$ = 14.1 Hz); ^{13}C NMR, δ 163.7, 114.7 (t, $^1J_{C,F}$ = 252 Hz), 54.6, 53.4, 43.3 (t, $^2J_{C,F}$ = 23.3 Hz), 40.6, 19.2, 13.2; HRMS (GC−CI) m/z calcd for $C_8H_{14}O_2F_2Cl$ $[M + H]^+$: 215.0650; found 215.0644.

*Methyl 4-Chloro-2,2-difluorodecanoate (**2c**).* 56 mg 87%); ^{1}H NMR, δ 4.10 (m, 1H), 3.89 (s, 3H), 2.68−2.47 (m, 2H), 1.79−1.73(m, 2H) 1.79 (m, 8H), 0.89 (t, 4 Hz, 3H); ^{19}F NMR, δ −102.3 (dt, $^2J_{F,F}$ = 265.1 Hz, $^3J_{F,H}$ = 14.1 Hz), −108.6 (ddd, $^2J_{F,F}$ = 265.1, $^3J_{F,H}$ = 22.6 Hz, $^3J_{F,H}$ = 14.1 Hz); ^{13}C NMR, δ 163.7, 114.7 (t, $^1J_{C,F}$ = 252 Hz), 54.9, 53.5, 43.2 (t, $^2J_{C,F}$ = 24.0 Hz), 38.6, 31.6, 28.5, 25.9, 22.5, 14.0; HRMS (GC−CI) m/z calcd for $C_{11}H_{20}O_2F_2Cl$ $[M + H]^+$: 257.1120; found 257.1115.

*Methyl 4-Chloro-2,2-difluorododecanoate (**2d**).* 60 mg (85%); ^{1}H NMR, δ 4.09 (m, 1H), 3.88(s, 3H), 2.70−2.46 (m, 2H), 1.78−1.74 (m, 2H), 1.27 (m, 12H), 0.88 (t, 6 Hz, 3H); ^{19}F NMR, δ −100.7 (dt, $^2J_{F,F}$ = 262.3 Hz, $^3J_{F,H}$ = 14.1 Hz), −107.0 (ddd, $^2J_{F,F}$ = 265.1 Hz, $^3J_{F,H}$ = 19.4 Hz, $^3J_{F,H}$ =14.1 Hz); ^{13}C NMR, δ 163.6, 114.6 (t, $^1J_{C,F}$ = 248.3 Hz), 54.9, 53.4, 43.2 (t, $^2J_{C,F=}$ 24 Hz), 38.6, 31.8, 29.1, 28.9, 28.8, 25.9, 22.6. 14.1; HRMS (GC−CI) m/z calcd for $C_{13}H_{24}O_2F_2Cl$: 285.1433 $[M + H]^+$; found 285.1428.

*Methyl 4-Chloro-2,2-difluoro-5-phenylpentanoate (**2e**).* 57 mg (86%); ^{1}H NMR, δ 7.25 (d, J = 6 Hz, 3H), 7.12 (d, J = 9 Hz), 4.24 (m, 1H), 3.78 (s, 3H), 3.01 (d, J = 6 Hz), 2.49 (m, 2H); ^{19}F NMR, δ −100.5 (dt, $^2J_{F,F}$ = 268.0 Hz, $^3J_{F,H}$ = 14.1 Hz), −106.7 (ddd, $^2J_{F,F}$ = 268.0 Hz, $^3J_{F,H}$ = 22.6 Hz, $^3J_{F,H}$ = 14.1 Hz); ^{13}C NMR, δ 164.0, 136.4, 129.4, 128.6, 129.5, 127.2, 114.6 (t, $^1J_{C,F}$ = 248.6 Hz), 54.7, 53.5, 42.2 (t, $^2J_{C,F}$ = 23.3 Hz); HRMS (DART) m/z calcd for $C_{12}H_{17}ClF_2NO_2^+$ $[M + NH_4]^+$: 280.0910; found 280.0915.

*Methyl 2-(2-Chlorocyclohexyl)-2,2-difluoroacetate (**2f**).* 41 mg (73%); ^{1}H NMR, δ 4.53 (m, 0.3H, cis), 3.95 (m, 0.6H, trans), 3.87 (s, 3H), 2.59−1.87 (m, 2H), 1.83−1.62 (m, 5H), 1.33−1.26 (m, 2H); ^{19}F NMR, δ −105.8 (d, $^2J_{F,F}$ = 252 Hz), −108.5 (t, $^3J_{F,H}$ = 11.3 Hz), −113 (d, J = 14.1 Hz), −118.5 (dd, $^2J_{F,F}$ = 267.9 Hz, $^3J_{F,H}$ = 22.6 Hz); ^{13}C NMR, δ 165.3, 164.8, 115.7 (t, $^1J_{C,F}$ = 248.3 Hz), 115.5 (t, $^1J_{C,F}$ = 248.3 Hz), 53.3, 49.0 (t, $^2J_{C,F}$ = 23.25 Hz), 47.5 (t, $^2J_{C,F}$ = 21.75 Hz), 37.2, 34.5, 25.5, 23.9, 19.6, 19.3; HRMS (GC−CI) m/z calcd for $C_9H_{14}O_2F_2Cl$: 227.0650 $[M + H]^+$; found 227.0647.

*Methyl 4-Chloro-2,2-difluoro-5-phenoxypentanoate (**2g**).* 50 mg (72%); ^{1}H NMR, δ 7.22 (t, J = 9 Hz, 2H), 6.91 (t, J = 6 Hz, 1H), 6.83 (d, J = 9 Hz, 2H), 4.31 (m, 1H), 4.14−4.03 (m, 2H), 3.78 (s, 3H), 2.84−2.59 (m, 2H); ^{19}F NMR, δ −101.4 (dt, $^2J_{F,F}$ = 265.1 Hz, $^3J_{F,H}$ = 14.1 Hz), −105.1 (dt, $^2J_{F,F}$ = 267.9 Hz, $^3J_{F,H}$ = 19.7 Hz); ^{13}C NMR, δ 157.8, 129.6, 129.4, 121.7, 120.9, 114.7, 114.5 (t, $^1J_{C,F}$ = 247.5 Hz), 70.8, 53.6, 51.0, 39.8 (t, $^2J_{C,F}$ = 23.3 Hz); HRMS (GC−CI) m/z calcd for $C_{12}H_{13}O_3F_2Cl$: 278.0521 M^+; found 278.0528.

*Methyl 4-Chloro-5-(1,3-dioxoisoindolin-2-yl)-2,2-difluoropentanoate (**2h**).* 79 mg (95%); ^{1}H NMR, δ 7.88 (m, 2H), 7.75 (m, 2H), 4.51 (m, 1H), 4.03−3.85 (m, 2H), 3.88 (s, 3H), 2.70−2.59 (m, 2H); ^{19}F NMR, δ −110.7 (dt, $^2J_{F,F}$ = 268 Hz, $^3J_{F,H}$ = 14.1 Hz), −105 (dt, $^2J_{F,F}$ = 265 Hz, $^3J_{F,H}$ = 14.1 Hz); ^{13}C NMR, δ 168.2, 167.8, 134.3, 134.0, 131.6, 123.6, 123.2, 114.2 (t, $^1J_{C,F}$ = 248 Hz), 53.6, 50.8,

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43.7, 40.8 (t, $^2J_{C,F}$ = 24.8 Hz); HRMS (GC−CI) *m/z* calcd for $C_{14}H_{13}O_4F_2Cl$ 332.0501 $[M + H]^+$; found 332.0501.

*2-Chloro-4,4-difluoro-5-methoxy-5-oxopentyl benzoate (**2i**).* 67 mg (87%); ^{1}H NMR, δ 7.97 (d, *J* = Hz, 2H), 7.51 (t, *J* = 6 Hz, 1H), 7.38 (t, *J* = 6 Hz, 2H), 4.43−4.36 (m, 2H), 4.35 (m, 1H), 3.81 (s, 3H), 2.70−2.66 (m, 2H); ^{19}F NMR, δ −101.3 (dt, $^2J_{F,F}$ = 270.7 Hz, $^3J_{F,H}$ = 14.1 Hz), −105.9 (dt, $^3J_{F,F}$ = 265.1 Hz, $^3J_{F,H}$ = 16.9 Hz); ^{13}C NMR, δ 165.7, 163.7, 133.4, 129.7, 128.5, 123.3, 114.3 (t, $^1J_{C,F}$ = 248.3 Hz), 67.0, 53.6, 50.8, 39.9 (t, $^2J_{C,F}$ = 24.0 Hz); HRMS (GC−CI) *m/z* calcd for $C_{13}H_{14}O_4F_2Cl$ 307.0549 $[M + H]^+$; found 307.0560.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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