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$CuSO_4$-Mediated Decarboxylative Difluoroacetamidation of α,β-Unsaturated Carboxylic Acids

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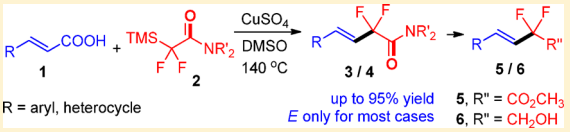
Supporting Information

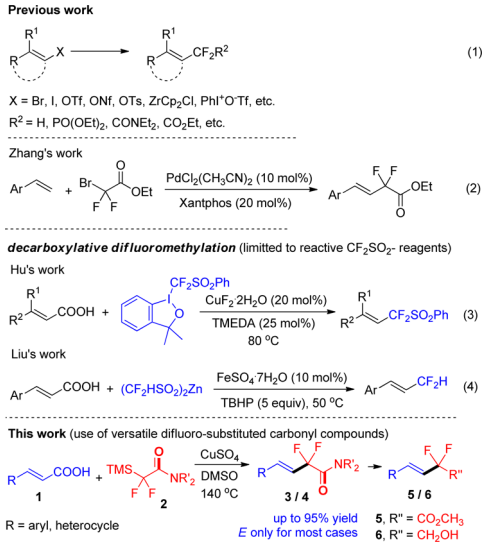
ABSTRACT: The first example of decarboxylative difluoroacetamidation of α,β-unsaturated carboxylic acids by using difluoromethyl-substituted carbonyl compounds was disclosed. The procedure, which was mediated by low-cost and benign $CuSO_4$, furnished a broad range of difluorinated alkenes in remarkable yields with only the *E* configuration in most of the cases. Moreover, the product could be smoothly transformed to the corresponding difluorofunctionalized ester and alcohol in high yields.



The introduction of fluorine into organic compounds can dramatically improve the metabolic stability and bioavailability and can increase the strength of the interaction with target proteins.[1] Owing to the unique properties of the CF_2 moiety,[2] the past few years has witnessed a rapid development in the incorporation of this moiety into various compounds.[3] Until now, transition-metal-catalyzed (or mediated) difluoromethylation/difluoroalkylation of aryl halides or aryl boronic acids for the synthesis of CF_2 contained arenes have been intensively studied.[4] However, reliable methods for the construction of difluoromethylated alkenes have not been well developed and are still highly desired.[5] Previously reported approaches to this kind of compounds mainly rely on the reactions between difluoromethylation agents and prefunctionalized alkenes, such as alkenyl halides, alkenyl triflates, alkenylzirconium, alkenyl hypervalent iodines, etc. (Scheme 1, eq 1).[6] Very recently, Zhang and co-workers reported a Heck-type reaction for the synthesis of difluoromethylated alkenes using valuable Pd catalyst and phosphorus ligand (Scheme 1, eq 2).[7a] Despite these excellent achievements, other types of reactions with more available surrogates and cheaper mediators are scarce. In view of the practicability and economy, it is ideal to eliminate the use of phosphorus ligand and replace the catalyst by inexpensive metals, such as Cu salts.[7]

Transition-metal-catalyzed decarboxylative cross coupling has been proven to be a powerful and effective method for the construction of C−C bonds.[8] α,β-Unsaturated carboxylic acids, which are commercially available, inexpensive, and diversiform, are ubiquitous starting materials in decarboxylative reactions. In 2012, Hu and co-workers disclosed a decarboxylative difluoromethylation reaction of alkenes by using an electrophilic hypervalent iodine reagent (Scheme 1, eq 3).[9] Although the starting materials were not cheap and multiple steps were necessary for the synthesis of the difluoromethyl hypervalent iodine agent, the high yields of the obtained difluoromethylated alkenes demonstrated the high efficiency of this method. Subsequently, an iron-catalyzed decarboxylative difluoromethylation of alkenes using Baran's reagent $(CF_2HSO_2)_2Zn$ was achieved by the group of Liu (Scheme 1, eq 4).[10] However, only electron-rich difluoromethyl-substituted alkenes were provided in relatively low to moderate yields (35−68%). To the best of our knowledge, existing strategies for decarboxylative alkene difluoroalkylations are limited to the use of highly reactive CF_2SO_2-containing reagents, which restricted the further functionalization of the CF_2 moiety.[9,10] Compared with $-CF_2SO_2R$ groups, difluoromethyl-substituted carbonyl compounds have versatile synthetic utilities and could be derivatized to obtain many functional products.[6g,7a,11] In spite of the attention received by the synthetic community, the application of CF_2-substituted carbonyl compounds in the

Scheme 1. Previous Works and This Work for Alkene Difluoroalkylation



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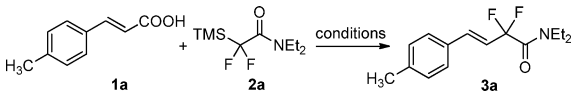
decarboxylative difluoromethylation of alkenes has not been documented and still remains a challenge. In this paper, we disclosed the first example of decarboxylative difluoroacetamidation of alkenes by using the low-cost and benign $CuSO_4$ as metal mediator under ligand-free conditions. The preliminary mechanistic study indicated that a radical pathway might be involved in this transformation. Notably, the coupling product could be smoothly transformed to the corresponding difluorofunctionalized ester and alcohol in high yields, which could not be obtained by traditional decarboxylative alkene difluoroalkylations.

Our investigation was initiated by using 4-methylcinnamic acid **1a** and α,α-difluoro-α-(trimethylsilyl)acetamide **2a** as substrates (Table 1). In the first several trials, several silver salts as well as copper salts were applied to the decarboxylative reaction, and CsF was employed as an activator of the enolate **2a** (entries 1−9). Disappointedly, the reactions gave very little of the desired product **3a**, leaving a large proportion of cinnamic acid **1a** untouched. We envisioned that a radical process was also possibly involved in this transformation rather than the participation of α,α-difluoroacetamide enolates. The reaction was then conducted in the absence of CsF and using $CuBr_2$ as metal promoter. To our delight, the yield of the product was significantly improved (entry 10 vs 7). Other metal salts were subsequently subjected to the decarboxylative difluoroacetamidation reaction (entries 11−16; see the Supporting Information for details), and the yield of **3a** was improved to 90% when $CuSO_4$ was employed (entry 14).[12] The amount of $CuSO_4$ could be reduced to 1.2 equiv with the yield of the product decreased slightly (entry 17). However, the combination of a catalytic amount of $CuSO_4$ (0.2 equiv) and oxidants, such as $PhI(OAc)_2$, $Na_2S_2O_8$, BQ (1,4-benzoquinone), DDQ (dichloro-5,6-dicyanobenzoquinone), and O_2, all failed to give good results (entries 18−22). Since $CuSO_4$ is water-soluble and extremely cheap, it can be considered as an ideal mediator. The solvent screen indicated that dimethyl sulfoxide (DMSO) was the best medium for this transformation (entry 23). Other solvents, such as DCE, dioxane, NMP, and DMAC, were less effective (see the Supporting Information for details). It is worth noting that the yield of **3a** decreased significantly at lower reaction temperatures (entries 24 and 25).

With the optimized conditions in hand (Table 1, entry 23), we next examined the scope of the decarboxylative reaction with respect to α,β-unsaturated carboxylic acids. As shown in Table 2, the substrates bearing both electron-rich and electron-poor groups on the aromatic ring were well tolerated in this process, resulting in the corresponding difluoroacetamidated alkenes with good to outstanding yields (**3a−l**). It is noteworthy that the reactions of 2-, 3-, and 4-chlorocinnamic

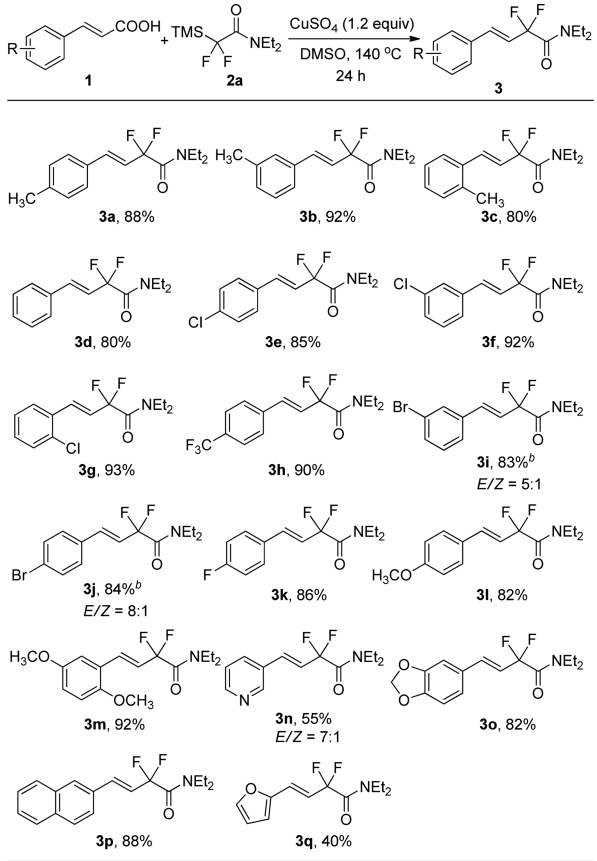
Table 1. Selected Results for the Screening of Reaction Conditions[a]



entry	metal mediator	additive	solution	yield[b] (%)
1	AgOAc	CsF	DMF	12
2	Ag_2O	CsF	DMF	0
3	$AgNO_3$	CsF	DMF	32
4	Ag_2CO_3	CsF	DMF	0
5	$Cu(OAc)_2$	CsF	DMF	38
6	$Cu(OTf)_2$	CsF	DMF	8
7	$CuBr_2$	CsF	DMF	41
8	CuI	CsF	DMF	12
9	$CuCl_2{\cdot}2H_2O$	CsF	DMF	<5
10	$CuBr_2$		DMF	71
11	$AgNO_3$		DMF	89
12	CuF_2		DMF	44
13	$Cu(OAc)_2$		DMF	73
14	$CuSO_4$		DMF	90
15	CuBr		DMF	67
16	$FeCl_3$		DMF	0
17[c]	$CuSO_4$		DMF	88
18[d]	$CuSO_4$	$PhI(OAc)_2$	DMF	41
19[d]	$CuSO_4$	$Na_2S_2O_8$	DMF	<5
20[d]	$CuSO_4$	BQ	DMF	<5
21[d]	$CuSO_4$	DDQ	DMF	trace
22[d,e]	$CuSO_4$	O_2	DMF	trace
23[c]	$CuSO_4$		DMSO	95 (88)[f]
24[c,g]	$CuSO_4$		DMSO	46
25[c,h]	$CuSO_4$		DMSO	<5

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), metal mediator (0.1 mmol), additive (0.1 mmol), 1 mL of solvent, 140 °C, 24 h, under argon. [b]Yield determined by GC. [c]1.2 equiv of $CuSO_4$ was used. [d]0.2 equiv of $CuSO_4$ was used. [e]Under 1 atm of O_2 atmosphere. [f]Isolated yield of a 0.3 mmol scale reaction in 3 mL of DMSO. [g]120 °C. [h]100 °C.

Table 2. Scope of α,β-Unsaturated Carboxylic Acids[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $CuSO_4$ (0.36 mmol), 3 mL of DMSO, 140 °C, 24 h, under argon. Yield refers to isolated yield. Only the *E* configuration was detected, unless otherwise noted. [b]DMF was used instead of DMSO.

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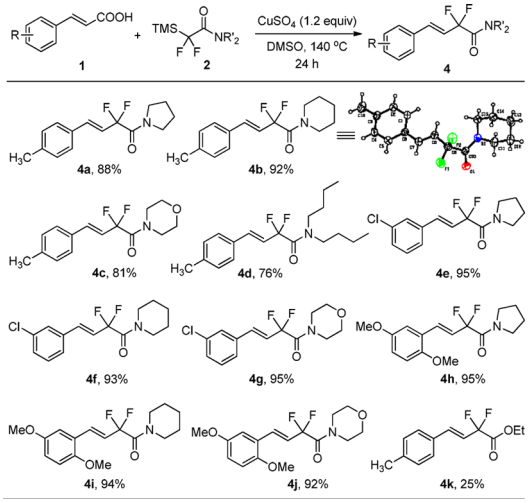
acid or 4-bromocinnamic acid with **2a** all efficiently proceeded to form the decarboxylative products, with the halogen substituents untouched during the reactions, which renders the coupling products good candidates for further transformations such as transition-metal-catalyzed functionalization of the carbon−halogen bond. In all attempted cases, electronic effects and steric hindrance showed very little effect on the outcome of this difluoroacetamidation reaction. Disubstituted and sterically hindered α,β-unsaturated carboxylic acids also underwent the transformation with good yields (**3m**, **3o**, and **3p**). However, heteroaryl-substituted carboxylic acids led to a dramatically lower yield of the desired products (**3n** and **3q**).

Further expansion of the substrate scope was focused on α,α-difluoro-α-(trimethyl)silylacetamides that participated in the difluoroacetamidation reaction. The results are summarized in Table 3. As expected, the reaction between cyclic amides and

Table 3. Scope of α,α-Difluoro-α-(trimethylsilyl)acetamides and α,β-Unsaturated Carboxylic Acids[a]

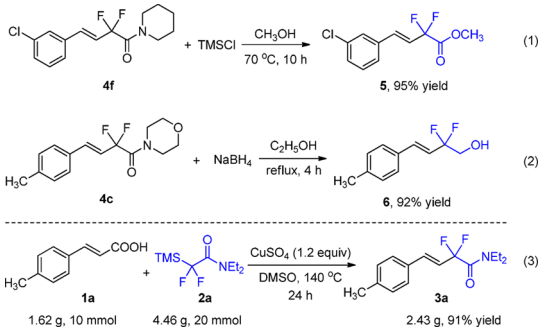


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $CuSO_4$ (0.36 mmol), 3 mL of DMSO, 140 °C, 24 h, under argon. Yield refers to isolated yield. Only the *E* configuration was detected.

1a furnished the difluoroacetamidated alkenes **4a−c** in good to excellent yields. Nevertheless, the *N,N*-dibutylacetamide showed a relatively lower reactivity and provided the corresponding product **4d** in 76% yield. The cyclic amides were also subjected to the coupling reactions with electronically varied unsaturated carboxylic acids. Gratifyingly, the reactions proceeded smoothly and delivered **4e−j** in splendid results. The α-silyldifluoroacetate was tested under the established conditions. We were not surprised to find that only a poor yield of **4k** was achieved. $TMSCF_2PO(OEt)_2$ even failed to participate in this kind of reaction. The structure of the products was determined by X-ray crystal structure analysis of compound **4b** (see the Supporting Information).[13]

An important feature of carboxylic acid derivatives is the ability to convert one of the functional groups to another and to reduce them to the corresponding alcohols. Amides are known to be poor electrophiles, which is typically attributed to the resonance stability of the amide bond.[14] However, with the assistance of the two fluorine atoms on the α carbon, the carbonyl group in α,α-difluoroacetamide is more electrophilic than their nonfluorinated congener. Although the α-silyldifluoroacetates failed to undergo the decarboxylative difluoroalkylation with satisfying results, the difluorofunctionalized ester could be obtained almost in quantitative yield from the corresponding amide (Scheme 2, eq 1). The α-styrene-α,α-

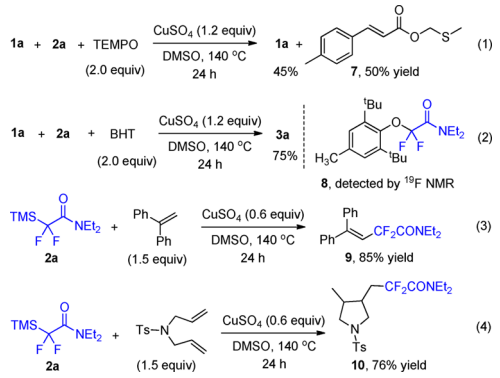
Scheme 2. Transformations of α-Styrene-α,α-difluoroacetamides and Large-Scale Reaction



difluoroacetamide could also be reduced to 2-styrene-2,2-difluoroethanol in excellent yield (Scheme 2, eq 2). It should be noted that the yield of the desired product was maintained when the reaction was conducted on a gram-scale under standard conditions (Scheme 2, eq 3).

In order to gain some information on the reaction mechanism, radical inhibition experiment was examined (Scheme 3). When radical scavenger TEMPO (2 equiv) was

Scheme 3. Mechanistic Studies



added under the standard conditions, the reaction was completely suppressed with 45% **1a** recovered. It is interesting that a methylthiomethyl ester **7** was isolated in 50% yield (Scheme 3, eq 1).[15] The addition of BHT (2,6-di-*tert*-butyl-4-methylphenol, 2 equiv) to the reaction mixture caused a small decrease of the reaction efficiency. Nevertheless, ^{19}F NMR analysis demonstrated the formation of BHT−CF_2CONEt_2 (**8**) adduct (Scheme 3, eq 2). The use of a radical clock, such as ethene-1,1-diyldibenzene and *N,N*-diallyl-4-methylbenzenesulfonamide, gives the desired product (Scheme 3, eqs 3 and 4). These results suggested that a radical pathway was involved in the current reaction (for details, see the Supporting Information).

Based on the above investigations and previous work,[10,16] we proposed a hypothesis for the reaction mechanism (Scheme 4). First, the α,α-difluoro-α-(trimethylsilyl) acetamide **2** reacted with Cu^{II} to form a Cu^{III} intermediate **A** and released a trimethylsilyl radical under heating conditions. Cu^{III} was then reduced to Cu^{II}, and gave the difluoroacetamidated radical **B**. Meanwhile, a Cu^{II} carboxylate **C** was generated from the

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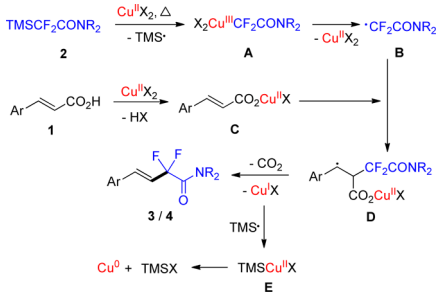
Scheme 4. Proposed Reaction Mechanism



incorporation of α,β-unsaturated carboxylic acid **1** and copper sulfate. Addition of the difluoroacetamidated radical at the α-position of the double bond in **C** formed the benzylic radical **D** with a single bond at the α,β-position, which could result in isomerization during the following double-bond formation step. The subsequently elimination of CO_2 and Cu^I delivered the desired product **3** or **4**. The Cu^I was then oxidized to form the Cu^{II} intermediate **E** through a single electronic-transfer process, which would be further reduced to give the metal byproduct copper(0).

In conclusion, we have developed an efficient and practical protocol for the preparation of difluorinated alkenes. The procedure, which started from readily available α,β-unsaturated carboxylic acids and versatile silicon enolates of α,α-difluoroacetamides, mediated by low-cost $CuSO_4$, furnished a broad range of difluorinated alkenes in good to excellent yields. It is the first example of decarboxylative difluoroacetamidation of α,β-unsaturated carboxylic acids by using difluoromethyl-substituted carbonyl compounds. Moreover, the difluoroacetamidation reactions were found to be stereoselective, with only the *E* configuration detected in most of the reactions. A primary mechanistic investigation suggested the involvement of a radical species.

EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used without further purification unless otherwise stated. All solvents were dried according to established procedures. Reactions were monitored by thin-layer chromatography (TLC). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on 300, 75, and 282 MHz instruments, respectively. Data are presented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), and coupling constant (in hertz (Hz)). High-resolution mass spectra (HRMS) were obtained by ESI (TOF) ionization sources. α,α-Difluoro-α-(trimethylsilyl)acetamides **2** were prepared according to the previously reported procedures.[11a] Cinnamic acids **1** and other reagents were commercially available.

General Procedure for the Synthesis of 3 and 4. To a 25 mL Schlenk tube were added cinnamic acid **1** (0.3 mmol) and $CuSO_4$ (0.36 mmol, 1.2 equiv). The Schlenk tube was capped and then evacuated and backfilled with argon (3×). DMSO (3 mL) and α,α-difluoro-α-(trimethylsilyl)acetamide **2** (0.6 mmol, 2 equiv) were added subsequently. After being stirred at 140 °C for 24 h, the reaction mixture was quenched with H_2O (0.5 mL) and extracted with EtOAc. The organic phase was concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc = 15:1−10:1) to give product **3** or **4**.

(E)-N,N-Diethyl-2,2-difluoro-4-p-tolylbut-3-enamide (***3a***)*:* yellow solid (70.5 mg, 88%, mp 41−42 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.94 (dt, J = 16.3, 2.7 Hz, 1H), 6.41 (dt, J = 16.3, 10.8 Hz, 1H), 3.53−3.37 (m, 4H), 2.36 (s, 3H), 1.26−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (t, J = 30.1 Hz), 139.5, 135.2 (t, J = 9.8 Hz), 131.6, 129.5, 127.3, 119.4 (t, J = 24.9 Hz), 115.4 (t, J = 248.6 Hz), 42.1 (t, J = 4.9 Hz), 41.4, 21.3, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.3; HRMS (ESI) $C_{15}H_{20}F_2NO$ $[M + H]^+$ calcd 268.1507, found 268.1515.

(E)-N,N-Diethyl-2,2-difluoro-4-m-tolylbut-3-enamide (***3b***)*:* yellow oil (73.4 mg, 92%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.20 (m, 3H), 7.18−7.12 (m, 1H), 6.94 (dt, J = 16.3, 2.7 Hz, 1H), 6.45 (dt, J = 16.3, 10.8 Hz, 1H), 3.53−3.37 (m, 4H), 2.35 (s, 3H), 1.26−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (t, J = 30.0 Hz), 138.4, 135.4 (t, J = 9.8 Hz), 134.3, 130.2, 128.6, 127.9, 124.5, 120.3 (t, J = 24.9 Hz), 115.3 (t, J = 248.8 Hz), 42.1 (t, J = 4.9 Hz), 41.4, 21.3, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.6; HRMS (ESI) $C_{15}H_{20}F_2NO$ $[M + H]^+$ calcd 268.1507, found 268.1517.

(E)-N,N-Diethyl-2,2-difluoro-4-o-tolylbut-3-enamide (***3c***)*:* yellow oil (64.3 mg, 80%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.46 (m, 1H), 7.29−7.14 (m, 4H), 6.36 (dt, J = 16.2, 10.6 Hz, 1H), 3.54−3.38 (m, 4H), 2.36 (s, 3H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (t, J = 30.0 Hz), 136.5, 133.4, 133.1 (t, J = 9.8 Hz), 130.5, 129.1, 126.3, 126.1, 121.8 (t, J = 24.9 Hz), 115.3 (t, J = 248.5 Hz), 42.0 (t, J = 4.8 Hz), 41.3, 19.6, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.3; HRMS (ESI) $C_{15}H_{20}F_2NO$ $[M + H]^+$ calcd 268.1507, found 268.1518.

(E)-N,N-Diethyl-2,2-difluoro-4-phenylbut-3-enamide (***3d***)*:* light yellow oil (60.8 mg, 80%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.6, 1.9 Hz, 2H), 7.42−7.29 (m, 3H), 6.98 (dt, J = 16.3, 2.7 Hz, 1H), 6.47 (dt, J = 16.3, 10.8 Hz, 1H), 3.54−3.38 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1−162.3 (m), 135.2 (t, J = 9.8 Hz), 134.4, 129.3, 128.7, 127.3, 120.5 (t, J = 24.9 Hz), 115.3 (t, J = 249.0 Hz), 42.1 (t, J = 5.0 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.7; HRMS (ESI) $C_{14}H_{18}F_2NO$ $[M + H]^+$ calcd 254.1351, found 254.1362.

(E)-4-(4-Chlorophenyl)-N,N-diethyl-2,2-difluorobut-3-enamide (***3e***)*:* yellow solid (73.2 mg, 85%, mp 57−58 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.30 (m, 4H), 6.94 (dt, J = 16.3, 2.6 Hz, 1H), 6.46 (dt, J = 16.3, 11.0 Hz, 1H), 3.56−3.37 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (t, J = 30.2 Hz), 135.1, 133.7 (t, J = 9.8 Hz), 132.9, 129.0, 128.5, 121.2 (t, J = 24.6 Hz), 115.2 (t, J = 248.6 Hz), 42.0 (t, J = 5.2 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.2; HRMS (ESI) $C_{14}H_{17}ClF_2NO$ $[M + H]^+$ calcd 288.0961, found 288.0967.

(E)-4-(3-Chlorophenyl)-N,N-diethyl-2,2-difluorobut-3-enamide (***3f***)*:* light yellow oil (79.0 mg, 92%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.37−7.24 (m, 3H), 6.92 (dt, J = 16.3, 2.6 Hz, 1H), 6.50 (dt, J = 16.3, 11.0 Hz, 1H), 3.56−3.37 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (t, J = 29.9 Hz), 136.2, 134.7, 133.5 (t, J = 9.8 Hz), 130.0, 129.2, 127.2, 125.5, 122.1 (t, J = 24.6 Hz), 115.1 (t, J = 250.4 Hz), 42.0 (t, J = 5.2 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.4; HRMS (ESI) $C_{14}H_{17}ClF_2NO$ $[M + H]^+$ calcd 288.0961, found 288.0967.

(E)-4-(2-Chlorophenyl)-N,N-diethyl-2,2-difluorobut-3-enamide (***3g***)*:* light yellow oil (80.1 mg, 93%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64−7.54 (m, 1H), 7.39 (dq, J = 6.7, 2.9 Hz, 2H), 7.32−7.22 (m, 2H), 6.48 (dt, J = 16.3, 10.5 Hz, 1H), 3.56−3.39 (m, 4H), 1.28−1.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (t, J = 29.7 Hz), 134.0, 132.7, 131.3 (t, J = 10.1 Hz), 130.3, 129.8, 127.4, 127.0, 123.2 (t, J = 25.0 Hz), 115.1 (t, J = 249.5 Hz), 42.0 (t, J = 5.0 Hz), 41.4, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.0; HRMS (ESI) $C_{14}H_{17}ClF_2NO$ $[M + H]^+$ calcd 288.0961, found 288.0968.

(E)-N,N-Diethyl-2,2-difluoro-4-(4-(trifluoromethyl)phenyl)but-3-enamide (***3h***)*:* light yellow oil (86.8 mg, 90%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (q, J = 8.4 Hz, 4H), 7.02 (dt, J = 16.3, 2.5 Hz, 1H), 6.59 (dt, J = 16.3, 11.1 Hz, 1H), 3.53 (q, J = 7.0 Hz, 2H), 3.43 (q, J = 7.1 Hz, 2H), 1.28−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (t, J = 29.9 Hz), 137.9, 133.3 (t, J = 9.8 Hz), 130.9 (q, J = 32.3 Hz), 127.5, 125.7 (q, J = 3.8 Hz), 123.3 (t, J = 24.5 Hz), 122.1 (t, J = 270.5 Hz), 115.1 (t, J = 251.2 Hz), 42.0 (t, J = 5.3 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.8, −96.8; HRMS (ESI) $C_{15}H_{17}F_5NO$ $[M + H]^+$ calcd 322.1225, found 322.1233.

(E)-4-(3-Bromophenyl)-N,N-diethyl-2,2-difluorobut-3-enamide (***3i***)*:* light yellow oil (82.5 mg, 83%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.42−7.28 (m, 1H), 7.23 (t, J =

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7.8 Hz, 1H), 6.91 (dt, J = 16.3, 2.6 Hz, 1H), 6.57−6.39 (m, 1H), 3.56−3.37 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (t, J = 29.9 Hz), 136.5, 133.4 (t, J = 9.8 Hz), 132.1, 130.2, 130.1, 129.3, 128.7, 127.3, 126.0, 122.9, 122.2 (t, J = 24.6 Hz), 115.1 (t, J = 250.5 Hz), 42.0 (t, J = 5.2 Hz), 41.5, 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.4; HRMS (ESI) $C_{14}H_{17}BrF_2NO$ $[M + H]^+$ calcd 332.0456, found 332.0464.

(E)-4-(4-Bromophenyl)-N,N-diethyl-2,2-difluorobut-3-enamide ***(3j)****:* yellow solid (83.5 mg, 84%, mp 45−46 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.92 (dt, J = 16.4, 2.4 Hz, 1H), 6.56−6.39 (m, 1H), 3.55−3.37 (m, 4H), 1.27−1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (t, J = 30.0 Hz), 133.7 (t, J = 9.8 Hz), 133.3, 131.9, 128.8, 123.4, 121.3 (t, J = 24.6 Hz), 115.2 (t, J = 250.2 Hz), 42.0 (t, J = 5.1 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.2; HRMS (ESI) $C_{14}H_{17}BrF_2NO$ $[M + H]^+$ calcd 332.0456, found 332.0464.

(E)-N,N-Diethyl-2,2-difluoro-4-(4-fluorophenyl)but-3-enamide ***(3k)****:* light yellow oil (70.0 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.39 (m, 2H), 7.11−7.00 (m, 2H), 6.95 (dt, J = 16.3, 2.7 Hz, 1H), 6.40 (dt, J = 16.3, 10.9 Hz, 1H), 3.56−3.37 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, J = 249.6 Hz), 162.6 (t, J = 30.1 Hz), 133.8 (t, J = 9.8 Hz), 130.6, 129.1, 129.0, 120.3 (dd, J = 24.6, 22.4 Hz), 115.9, 115.6, 115.3 (t, J = 249.7 Hz), 42.0 (t, J = 5.2 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.9, −111.5; HRMS (ESI) $C_{14}H_{17}F_3NO$ $[M + H]^+$ calcd 272.1257, found 272.1263.

(E)-N,N-Diethyl-2,2-difluoro-4-(4-methoxyphenyl)but-3-enamide ***(3l)****:* light yellow oil (69.5 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 71.42−7.35 (m, 2H), 6.97−6.84 (m, 3H), 6.32 (dt, J = 16.3, 10.7 Hz, 1H), 3.82 (s, 3H), 3.53−3.38 (m, 4H), 1.26−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (t, J = 30.2 Hz), 160.5, 134.8 (t, J = 9.9 Hz), 128.8, 127.0, 118.1 (t, J = 24.9 Hz), 115.5 (t, J = 246.7 Hz), 114.1, 55.3, 42.1 (t, J = 4.8 Hz), 41.4, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.9; HRMS (ESI) $C_{15}H_{20}F_2NO_2$ $[M + H]^+$ calcd 284.1457, found 284.1463.

(E)-4-(2,5-Dimethoxyphenyl)-N,N-diethyl-2,2-difluorobut-3-enamide ***(3m)****:* light yellow oil (86.6 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dt, J = 15.6, 2.9 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 6.90−6.78 (m, 2H), 6.51 (dt, J = 16.5, 10.6 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.52−3.38 (m, 4H), 1.26−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (t, J = 29.9 Hz), 153.4, 152.0, 130.5 (t, J = 10.2 Hz), 123.8, 121.0 (t, J = 25.0 Hz), 115.9, 115.5 (t, J = 246.2 Hz), 112.7, 112.2, 56.0, 55.7, 42.1 (t, J = 4.6 Hz), 41.3, 14.1, 12.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.1; HRMS (ESI) $C_{16}H_{22}F_2NO_3$ $[M + H]^+$ calcd 314.1562, found 314.1568.

(E)-N,N-Diethyl-2,2-difluoro-4-(pyridin-3-yl)but-3-enamide ***(3n)****:* yellow oil (42.1 mg, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 4.7 Hz, 1H), 7.78−7.65 (m, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 7.5, 4.9 Hz, 1H), 7.11−6.90 (m, 2H), 3.55−3.37 (m, 4H), 1.27−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (t, J = 29.8 Hz), 152.7, 149.8, 136.7, 134.6 (t, J = 9.5 Hz), 124.7 (t, J = 25.1 Hz), 123.6, 123.2, 115.1 (t, J = 249.3 Hz), 42.1 (t, J = 4.9 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.8; HRMS (ESI) $C_{13}H_{17}F_2N_2O$ $[M + H]^+$ calcd 255.1303, found 255.1309.

(E)-4-(Benzo[d][1,3]dioxol-5-yl)-N,N-diethyl-2,2-difluorobut-3-enamide ***(3o)****:* yellow solid (73.4 mg, 82%, mp 64−66 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 1.6 Hz, 1H), 6.93−6.82 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.28 (dt, J = 16.2, 10.8 Hz, 1H), 5.99 (s, 2H), 3.53−3.37 (m, 4H), 1.26−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (t, J = 30.1 Hz), 148.7, 148.2, 134.9 (t, J = 9.9 Hz), 128.7, 122.9, 118.5 (t, J = 24.8 Hz), 115.4 (t, J = 246.8 Hz), 108.4, 106.1, 101.4, 42.1 (t, J = 5.0 Hz), 41.4, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.1.; HRMS (ESI) C15H18F2NO3 $[M + H]^+$ calcd 298.1249, found 298.1257.

(E)-N,N-Diethyl-2,2-difluoro-4-(naphthalen-2-yl)but-3-enamide ***(3p)****:* light yellow oil (80.3 mg, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.03 (m, 1H), 7.90−7.82 (m, 2H), 7.78 (dt, J = 16.1, 2.8 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.60−7.43 (m, 3H), 6.54 (dt, J = 16.0, 10.8 Hz, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.47 (q, J = 7.1 Hz, 2H), 1.30−1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ162.7 (t, J = 29.8 Hz), 133.5, 132.5 (t, J = 9.9 Hz), 132.0, 131.1, 129.6, 128.7, 126.6, 126.1, 125.5, 124.7, 123.6 (t, J = 24.5 Hz), 123.3, 115.2 (t, J = 247.9 Hz), 42.1 (t, J = 4.9 Hz), 41.4, 14.3, 12.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.7; HRMS (ESI) $C_{18}H_{20}F_2NO$ $[M + H]^+$ calcd 304.1507, found 304.1514.

(E)-N,N-Diethyl-2,2-difluoro-4-(furan-2-yl)but-3-enamide ***(3q)****:* light yellow oil (29.2 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.77 (dt, J = 16.0, 2.6 Hz, 1H), 6.48−6.29 (m, 3H), 3.53−3.36 (m, 4H), 1.26−1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (t, J = 29.9 Hz), 150.3, 143.7, 122.9 (t, J = 10.4 Hz), 118.5 (t, J = 25.1 Hz), 115.2 (t, J = 247.1 Hz), 112.2, 111.8, 42.1 (t, J = 5.0 Hz), 41.5, 14.2, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.9; HRMS (ESI) $C_{12}H_{16}F_2NO_2$ $[M + H]^+$ calcd 244.1144, found 244.1147.

(E)-2,2-Difluoro-1-(pyrrolidin-1-yl)-4-p-tolylbut-3-en-1-one ***(4a)****:* white crystals (70.0 mg, 88%, mp 97−99 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.98 (dt, J = 16.3, 2.6 Hz, 1H), 6.38 (dt, J = 16.3, 11.2 Hz, 1H), 3.66 (t, J = 6.5 Hz, 2H), 3.57 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H), 2.01−1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (t, J = 31.3 Hz), 139.6, 135.5 (t, J = 9.7 Hz), 131.6, 129.5, 127.3, 118.7 (t, J = 24.7 Hz), 115.1 (t, J = 246.8 Hz), 47.5, 46.7 (t, J = 5.5 Hz), 26.5, 23.3, 21.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.0; HRMS (ESI) $C_{15}H_{18}F_2NO$ $[M + H]^+$ calcd 266.1351, found 266.1355.

(E)-2,2-Difluoro-1-(piperidin-1-yl)-4-p-tolylbut-3-en-1-one ***(4b)****:* white crystals (77.3 mg, 92%, mp 80−81 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.95 (dt, J = 16.3, 2.7 Hz, 1H), 6.39 (dt, J = 16.3, 10.7 Hz, 1H), 3.66−3.55 (m, 4H), 2.36 (s, 3H), 1.69−1.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (t, J = 29.9 Hz), 139.6, 135.3 (t, J = 9.8 Hz), 131.5, 129.5, 127.3, 119.3 (t, J = 24.9 Hz), 115.4 (t, J = 246.6 Hz), 47.0 (t, J = 5.1 Hz), 44.4, 26.3, 25.6, 24.4, 21.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.6; HRMS (ESI) $C_{16}H_{20}F_2NO$ $[M + H]^+$ calcd 280.1507, found 280.1516.

(E)-2,2-Difluoro-1-morpholino-4-p-tolylbut-3-en-1-one ***(4c)****:* light yellow solid (68.3 mg, 81%, mp 81−83 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.97 (dt, J = 16.3, 2.7 Hz, 1H), 6.39 (dt, J = 16.3, 11.0 Hz, 1H), 3.76−3.65 (m, 8H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (t, J = 30.5 Hz), 139.8, 135.7 (t, J = 9.8 Hz), 131.3, 129.5, 127.3, 118.7 (t, J = 24.4 Hz), 115.3 (t, J = 247.1 Hz), 66.7, 66.6, 46.6 (t, J = 5.0 Hz), 43.4, 21.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.8; HRMS (ESI) $C_{15}H_{18}F_2NO_2$ $[M + H]^+$ calcd 282.1300, found 282.1307.

(E)-N,N-Dibutyl-2,2-difluoro-4-p-tolylbut-3-enamide ***(4d)****:* light yellow oil (73.7 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.94 (dt, J = 16.3, 2.6 Hz, 1H), 6.40 (dt, J = 16.3, 10.8 Hz, 1H), 3.42−3.32 (m, 4H),, 2.36 (s, 3H), 1.66−1.51 (m, 4H), 1.40−1.22 (m, 5H), 0.99−0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (t, J = 30.0 Hz), 139.5, 135.1 (t, J = 9.8 Hz), 131.6, 129.4, 127.2, 119.5 (t, J = 24.8 Hz), 115.4 (t, J = 248.8 Hz), 47.6 (t, J = 4.6 Hz), 46.8, 31.0, 29.1, 21.3, 20.2, 19.9, 13.8, 13.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.1; HRMS (ESI) $C_{19}H_{28}F_2NO$ $[M + H]^+$ calcd 324.2133, found 324.2143.

(E)-4-(3-Chlorophenyl)-2,2-difluoro-1-(pyrrolidin-1-yl)but-3-en-1-one ***(4e)****:* yellow solid (81.2 mg, 95%, mp 73−74 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.37−7.27 (m, 3H), 6.96 (dt, J = 16.2, 2.6 Hz, 1H), 6.47 (dt, J = 16.2, 11.2 Hz, 1H), 3.68 (t, J = 6.6 Hz, 2H), 3.57 (t, J = 6.9 Hz, 2H), 2.04−1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (t, J = 30.9 Hz), 136.2, 134.7, 134.0 (t, J = 9.6 Hz), 130.0, 129.2, 127.2, 125.6, 121.5 (t, J = 24.7 Hz), 114.7 (t, J = 249.8 Hz), 47.5, 46.6 (t, J = 5.7 Hz), 26.4, 23.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.8; HRMS (ESI) $C_{14}H_{15}ClF_2NO$ $[M + H]^+$ calcd 286.0805, found 286.0812.

(E)-4-(3-Chlorophenyl)-2,2-difluoro-1-(piperidin-1-yl)but-3-en-1-one ***(4f)****:* light yellow oil (83.4 mg, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.37−7.25 (m, 3H), 6.93 (dt, J = 16.3, 2.6 Hz, 1H), 6.48 (dt, J = 16.3, 10.9 Hz, 1H), 3.65−3.58 (m, 4H), 1.73−1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (t, J = 29.7 Hz), 136.2, 134.7, 133.6 (t, J = 9.8 Hz), 130.0, 129.2, 127.2, 125.5, 122.1 (t, J = 24.6 Hz), 115.1 (t, J = 250.1 Hz), 46.9 (t, J = 5.5 Hz), 44.4, 26.4, 25.6, 24.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.7; HRMS (ESI) $C_{15}H_{17}ClF_2NO$ $[M + H]^+$ calcd 300.0961, found 300.0970.

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*(E)-4-(3-Chlorophenyl)-2,2-difluoro-1-morpholinobut-3-en-1-one (**4g**):* light yellow oil (85.8 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.38−7.28 (m, 3H), 6.95 (dt, J = 16.3, 2.6 Hz, 1H), 6.48 (dt, J = 16.3, 11.2 Hz, 1H), 3.77−3.68 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (t, J = 30.4 Hz), 136.0, 134.8, 134.0 (t, J = 9.8 Hz), 130.0, 129.4, 127.3, 125.6, 121.4 (t, J = 24.1 Hz), 115.1 (t, J = 249.2 Hz), 66.7, 46.6 (t, J = 5.4 Hz), 43.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.9; HRMS (ESI) $C_{14}H_{15}ClF_2NO_2$ $[M + H]^+$ calcd 302.0754, found 302.0762.

*(E)-4-(2,5-Dimethoxyphenyl)-2,2-difluoro-1-(pyrrolidin-1-yl)but-3-en-1-one (**4h**):* yellow solid (88.7 mg, 95%, mp 63−64 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, J = 16.4, 2.8 Hz, 1H), 7.00 (d, J = 2.6 Hz, 1H), 6.91−6.79 (m, 2H), 6.48 (dt, J = 16.4, 11.2 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.66 (t, J = 6.6 Hz, 2H), 3.57 (t, J = 6.8 Hz, 2H), 2.02−1.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (t, J = 31.1 Hz), 153.4, 152.0, 130.7 (t, J = 10.0 Hz), 123.8, 120.4 (t, J = 24.6 Hz), 115.9, 115.1 (t, J = 248.2 Hz), 112.8, 112.2, 56.0, 55.7, 47.4, 46.7 (t, J = 5.4 Hz), 26.4, 23.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.2; HRMS (ESI) $C_{16}H_{20}F_2NO_3$ $[M + H]^+$ calcd 312.1406, found 312.1416.

*(E)-4-(2,5-Dimethoxyphenyl)-2,2-difluoro-1-(piperidin-1-yl)but-3-en-1-one (**4i**):* light yellow oil (91.6 mg, 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dt, J = 16.3, 2.9 Hz, 1H), 6.99 (d, J = 2.7 Hz, 1H), 6.91−6.79 (m, 2H), 6.50 (dt, J = 16.5, 10.5 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.67−3.55 (m, 4H), 1.71−1.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (t, J = 29.7 Hz), 153.4, 152.0, 130.7 (t, J = 10.2 Hz), 123.8, 121.0 (t, J = 25.0 Hz), 115.8, 115.5 (t, J = 245.8 Hz), 112.9, 112.2, 55.9, 55.7, 47.0 (t, J = 5.0 Hz), 44.3, 26.1, 25.6, 24.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.4; HRMS (ESI) $C_{17}H_{22}F_2NO_3$ $[M + H]^+$ calcd 326.1562, found 326.1573.

*(E)-4-(2,5-Dimethoxyphenyl)-2,2-difluoro-1-morpholinobut-3-en-1-one (**4j**):* light yellow oil (90.2 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dt, J = 16.5, 2.9 Hz, 1H), 6.99 (d, J = 2.7 Hz, 1H), 6.92−6.79 (m, 2H), 6.48 (dt, J = 16.5, 10.6 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77−3.65 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (t, J = 30.3 Hz), 153.4, 152.0, 131.2 (t, J = 10.2 Hz), 123.5, 120.4 (t, J = 24.7 Hz), 116.0, 115.4 (t, J = 246.1 Hz), 112.9, 112.2, 66.7, 66.5, 55.9, 55.7, 46.7, 43.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.5; HRMS (ESI) $C_{16}H_{20}F_2NO_4$ $[M + H]^+$ calcd 328.1355, found 328.1366.

*(E)-Ethyl 2,2-difluoro-4-(p-tolyl)but-3-enoate (**4k**):* light yellow oil (18.2 mg, 25%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.04 (dt, J = 16.2, 2.5 Hz, 1H), 6.25 (dt, J = 16.2, 11.5 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (t, J = 35.0 Hz), 139.9, 136.7 (t, J = 9.5 Hz), 131.3, 129.5, 127.4, 117.7 (t, J = 25.0 Hz), 112.8 (t, J = 248.3 Hz), 63.1, 21.3, 13.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −103.1; HRMS (ESI) $C_{13}H_{14}F_2NaO_2$ $[M + Na]^+$ calcd 263.0854, found 263.0855.

(*E*)-Methyl 4-(3-Chlorophenyl)-2,2-difluorobut-3-enoate (5). A 5 mL round-bottom flask with a rubber plug was charged with (*E*)-4-(3-chlorophenyl)-2,2-difluoro-1-(piperidin-1-yl)but-3-en-1-one (**4f**) (59.8 mg, 0.2 mmol), methanol (2 mL), and a magnetic stirring bar. The mixture was cooled to 0 °C, and TMSCl (0.4 mL) was added. The reaction mixture was warmed to 70 °C and stirred for 10 h. The mixture was quenched with H_2O (5 mL) at 0 °C and extracted with EtOAc. The organic phase was concentrated, and the residue was purified with silica gel chromatography (petroleum ether/EtOAc = 20:1) to give the product **5** (46.7 mg, 95% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.32 (s, 3H), 7.02 (dt, J = 16.2, 2.5 Hz, 1H), 6.31 (dt, J = 16.2, 11.3 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (t, J = 35.0 Hz), 135.8, 135.5 (t, J = 9.5 Hz), 134.9, 130.1, 129.6, 127.3, 125.7, 120.2 (t, J = 25.0 Hz), 112.4 (t, J = 248.9 Hz), 53.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −103.5; HRMS (ESI) $C_{11}H_{10}ClF_2O_2$ $[M + H]^+$ calcd 247.0332, found 247.0333.

(*E*)-2,2-Difluoro-4-*p*-tolylbut-3-en-1-ol (6). A 10 mL round-bottom flask was charged with (*E*)-2,2-difluoro-1-morpholino-4-*p*-tolylbut-3-en-1-one (**4c**) (56.2 mg, 0.2 mmol), $NaBH_4$ (113.5 mg, 3 mmol), ethanol (5 mL), and a magnetic stirring bar. The reaction mixture was refluxed for 4 h and then cooled to room temperature. The mixture was quenched with aqueous HCl (1 M) and extracted with EtOAc. The organic phase was concentrated, and the residue was purified with silica gel chromatography (petroleum ether/EtOAc = 10:1) to give product **6** (36.5 mg, 92% yield) as a light yellow solid (mp 55−56 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.97 (dt, J = 16.2, 2.4 Hz, 1H), 6.19 (dt, J = 16.3, 11.4 Hz, 1H), 3.87 (t, J = 12.8 Hz, 2H), 2.35 (s, 3H), 2.17 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 135.5 (t, J = 9.4 Hz), 131.8, 129.5, 127.1, 119.9 (t, J = 240.1 Hz), 119.1 (t, J = 25.4 Hz), 65.1 (t, J = 32.6 Hz), 21.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.8; HRMS (ESI) $C_{11}H_{13}F_2O$ $[M + H]^+$ calcd 199.0929, found 199.0929.

(*E*)-(Methylthio)methyl 3-*p*-tolylacrylate (7): yellow oil (30.0 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 15.9 Hz, 1H), 7.43 (d, J = 7.4 Hz, 2H), 7.20 (d, J = 7.5 Hz, 2H), 6.42 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H), 2.38 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 145.7, 141.0, 131.4, 129.6, 128.2, 116.3, 68.2, 21.5, 15.4; HRMS (ESI) $C_{12}H_{14}NaO_2S$ $[M + Na]^+$ calcd 245.0607, found 245.0609.

2-(2,6-Di-*tert*-butyl-4-methylphenoxy)-*N*,*N*-diethyl-2,2-difluoroacetamide (8): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (s, 2H), 3.39−2.27 (m, 4H), 1.45 (s, 3H), 1.24 (s, 18H), 1.19 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 161.1(t, J = 28.7 Hz), 148.4, 138.3 (t, J = 3.0 Hz), 128.0 (t, J = 1238.1 Hz), 118.3, 46.0 (t, J = 22.8 Hz), 43.1 (t, J = 7.0 Hz), 42.3, 35.0, 32.7 (t, J = 284.6 Hz), 29.3, 20.5 (t, J = 3.9 Hz), 14.8, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −104.6; HRMS (ESI) $C_{21}H_{34}F_2NO_2$ $[M + H]^+$ calcd 370.2552, found 370.2570.

***N*,*N*-Diethyl-2,2-difluoro-4,4-diphenylbut-3-enamide (9):** colorless oil (83.9 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.38−7.28 (m, 6H), 7.28−7.18 (m, 4H), 6.37 (t, J = 12.6 Hz, 1H), 3.36 (q, J = 7.0 Hz, 2H), 3.17 (q, J = 7.1 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (t, J = 30.1 Hz), 149.4 (t, J = 8.2 Hz), 141.1, 137.3, 129.7, 128.8, 128.3, 128.3, 127.8, 127.8, 120.4 (t, J = 26.8 Hz), 114.5 (t, J = 247.4 Hz), 42.1, 41.3, 14.0, 12.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −87.0; HRMS (ESI) $C_{20}H_{22}F_2NO$ $[M + H]^+$ calcd 330.1664, found 330.1671.

***N*,*N*-Diethyl-2,2-difluoro-3-(4-methyl-1-tosylpyrrolidin-3-yl)-propanamide (10):** yellow oil (91.6 mg, 76%, dr = 1.78:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.67 (m, 2H), 7.37−7.27 (m, 2H), 4.01−3.22 (m, 6H), 3.03−2.50 (m, 3H), 2.50−2.19 (m, 5H), 2.19−1.65 (m, 3H), 1.27−1.09 (m, 6H), 0.72 (d, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, C−F coupling not assigned) δ 162.6−161.8 (m), 143.6−143.3 (m), 133.8−132.5 (m), 129.6−129.5 (m), 127.7−127.0 (m), 119.3, 54.5, 53.8, 52.5, 52.0, 51.2, 50.9, 48.7, 46.9, 43.8, 41.7, 41.4, 40.7, 39.0, 37.4, 36.7, 36.4, 36.1, 35.9, 35.6, 35.3, 35.2, 33.3, 33.0, 32.6, 32.0, 31.8, 29.6, 29.2, 29.0, 21.4, 18.3, 15.9, 15.5, 15.4, 14.1, 14.0, 13.3, 12.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.9 to −101.4 (m, 2F); HRMS (ESI) $C_{19}H_{29}F_2N_2O_3S$ $[M + H]^+$ calcd 403.1861, found 403.1863.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00031.

^{1}H and ^{13}C NMR spectra for the products (PDF)

X-ray crystallographic data for **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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