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Featured Article

Trifluoromethylthiolation, Trifluoromethylation, and Arylation Reactions of Difluoro Enol Silyl Ethers

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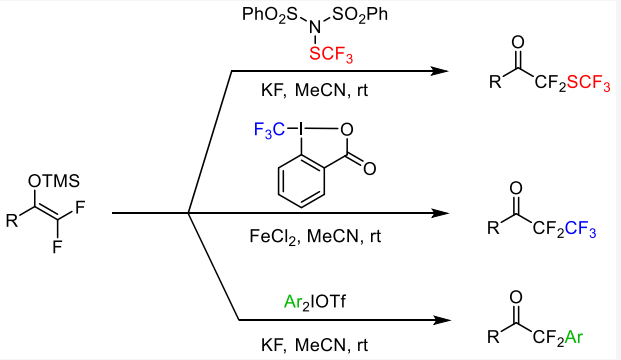
ABSTRACT: This study reports a new application area of difluoro enol silyl ethers, which can be easily obtained from trifluoromethyl ketones. The main focus has been directed to the electrophilic fluoroalkylation and arylation methods. The trifluoromethylthiolation of difluoro enol silyl ethers can be used for the construction of a novel trifluoromethylthio-α,α-difluoroketone ($-COCF_2SCF_3$) functionality. The $-CF_2SCF_3$ moiety has interesting properties due to the electron-withdrawing, albeit lipophilic, character of the SCF_3 group, which can be combined with the high electrophilicity of the difluoroketone motif. The methodology could also be extended to difluoro homologation of the trifluoromethyl ketones using the Togni reagent. In addition, we presented a method for transition-metal-free arylation of difluoro enol silyl ethers based on hypervalent iodines.



INTRODUCTION

Organofluorine compounds have found many important applications in several areas of life sciences. The high metabolic stability, ability to modify the lipophilicity, acid−base properties, and overall reactivity/bioavailability of small molecules[1] led to a widespread application of organofluorines especially in medicinal chemistry[2] and agrochemistry.[3] As a consequence, expanding the chemical space of new organofluorine compounds has attracted great attention in industrial and academic research.[4] An important class of druglike molecules is based on α-fluorinated ketone motifs (Figure 1). Due to the strong electron-withdrawing character of di-, tri-, and perfluoro alkyl groups, the electrophilicity of the neighboring keto functionality is enhanced. As a consequence, nucleophilic functionalities of enzymes, such as the hydroxy group of serine or other residues, readily interact with the low lying $\pi^*(C{=}O)$ orbitals forming (covalently bound) ketal/hemiketal-type products.[5] Thus, α-fluorinated ketones are important pharmacophores for serine proteases and related enzymes (Figure 1). For instance, small molecules with β-amino-α,α-difluoroketone motifs (Figure 1a) are selective inhibitors of human renin (protease regulating blood pressure).[6] Certain types of α,α-difluoroketones (Figure 1b) interact with the hydroxy methylglutaryl binding domain of coenzyme A (HMG CoA) reductase and are thus efficient inhibitors of these enzymes.[7] Phospholipase A_2 ($iPLA_2$) enzymes, which are involved in inflammatory disorders (such as arthritis and autoimmune diseases), can be efficiently inhibited by perfluoroethyl ketones (Figure 1c).[8] Human neutrophil elastase (HNE) is a serine protease, which can also be involved in pathophysiological states (such as cystic fibrosis and chronic bronchitis) and inhibited by trifluoromethyl ketones (Figure 1d).[9] The binding properties to HNE can be improved by variation of the

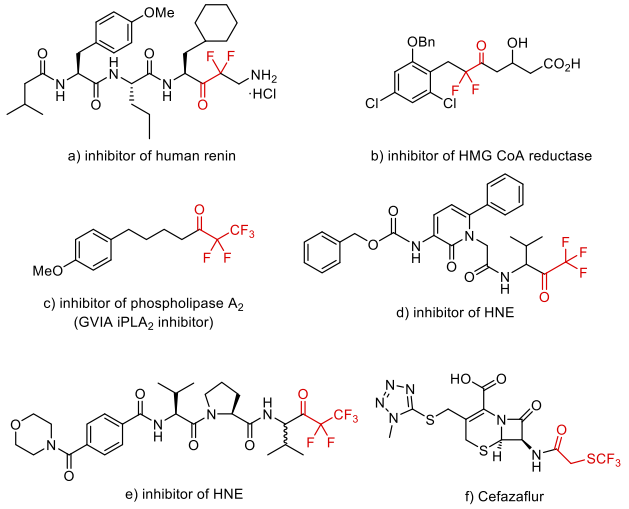


Figure 1. Bioactive small molecules with α-fluoro and related pharmacophores.

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fluorinated carbonyl activating group.[10] Thus, perfluoroethyl ketones (Figure 1e) have also been considered as HNE inhibitors.[9b,10,11] Application of the α-trifluoromethylthio ketones is less common in druglike molecules than the fluoro or fluoroalkyl analogues, which might be the consequence of synthetic limitations. This pharmacophore occurs, for example, in cefazaflur (Figure 1f), which is a cephalosporin antibiotic.[12]

Difluoro enol silyl ethers are useful synthons for introduction of the α,α-difluoro carbonyl functional group.[13] These compounds can be prepared from trifluoroketones (**1**) by Mg-mediated cleavage of one of the C−F bonds (Figure 2a).[14] This reaction affords fairly stable difluoro enol silyl

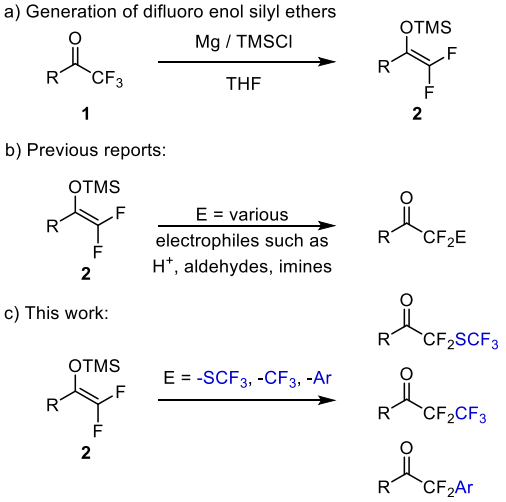


Figure 2. Synthesis and electrophilic transformations of difluoro enol silyl ethers.

ethers (**2**), which are difficult to isolate, and therefore, derivatives of **2** are usually reacted with various electrophiles without purification. The standard applications[13a] involve aldol reactions,[14a,15] Mannich reactions,[16] protonation,[14b] halogenation,[17] and arylation[18] reactions (Figure 2b).

As a part of our organofluorine chemistry program,[19] we sought to expand the reagent scope of difluoro enol silyl ethers (**2**) to reactions with new types of electrophiles. Our interest was 2-fold: (i) testing electrophilic reagents for the introduction of (S)CF_3 groups and (ii) studying the application of hypervalent iodine-based electrophiles (Figure 2c) in C−C bond-forming reactions with **2**.

Many recent efforts have been undertaken to find new methodologies for selective introduction of the SCF_3 group.[4b,20] This group frequently occurs in drug molecules (e.g., Figure 1f) because of its excellent pharmacochemical properties, such as the strong electron-withdrawing character and an exceptionally high Hansch lipophilicity parameter (π = 1.44).[21] Although α-trifluoromethylthiolation of ketones is described in the literature,[22] introduction of the SCF_3 group in difluoro enol silyl ethers **2** has never been reported. We hypothesized (Figure 3) that reacting **2** with sufficiently reactive electrophilic SCF_3 transfer reagents, such as benzenesulfonimide **3**,[23] a novel perfluoroalkyl ($-COCF_2SCF_3$) functionality could be constructed (**4**). In this way, the difluoro ketone group could be equipped with an electron-withdrawing but lipophilic group allowing, for example, extension of the pharmacochemical space of α-fluorinated ketones (Figure 1). In fact, very few synthetic

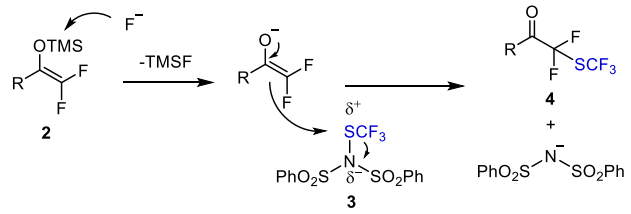


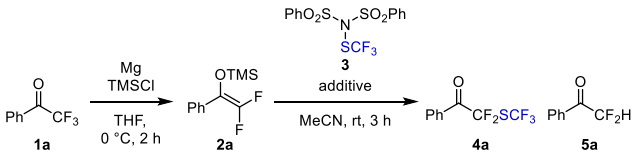
Figure 3. Hypothesis of trifluoromethylthiolation of difluoro enol silyl ethers using *N*-trifluoromethylthiodibenzenesulfonimide and fluoride.

methods have been reported for construction/introduction of the $-CF_2SCF_3$ functionality,[24] while none of these literature methods were suitable for the preparation of $-COCF_2SCF_3$-containing molecules.

RESULTS AND DISCUSSION

In line with our hypothesis (Figure 3), when *N*-trifluoromethylthiodibenzenesulfonimide **3**[23] was reacted with difluoro enol silyl ether **2a** (freshly prepared[14] from trifluoroacetophenone **1a** with Mg and TMSCl) in the presence of KF, $-COCF_2SCF_3$-functionalized product **4a** was obtained (Table 1). The optimal conditions involved application of **2a**, **3**, and

Table 1. Deviation of Reaction Conditions for the Trifluoromethylthiolation of 2a[a]



entry	additive	yield[b] of **4a** (%)	yield[b] of **5a** (%)	recovery[b] of **2a** (%)
1	1.0 equiv of KF	78	3	–
2	1.0 equiv of CsF	61	6	–
3	1.0 equiv of TBAF·3H_2O	15	45	–
4	1.0 equiv of TBAT	41	3	–
5	10 mol % of DABCO	–	–	70
6	10 mol % of $FeCl_2$	8	–	78
7[c]	1.0 equiv of KF	–	–	76
8	–	trace	–	75

[a]General procedure: **2a** (0.1 mmol), **3** (0.1 mmol), and additive were stirred in MeCN (0.5 mL) at room temperature for 3 h. [b]^{19}F NMR yield using $PhCF_3$ as the internal standard. [c]DCM was used as a solvent instead of MeCN.

KF in equimolar amounts in acetonitrile at room temperature for 3 h. Under these conditions, **4a** was obtained in 78% (NMR) yield along with 3% of the protonated analogue **5a** (Table 1, entry 1). Deviation from these conditions led to lower yields and/or extensive formation of **5a**.

When KF was replaced by CsF, the yield slightly decreased (entry 2). Using TBAF as an activator instead of KF proved to be even less effective (entry 3). The reaction proceeded with poor yield (15%) and extensive formation of protonated side product **5a**. Application of TBAT additive (entry 4) led to a higher yield (41%) than use of TBAF. However, the yield was still lower than with KF. Since tertiary amines have been successfully used as activators in aldol reactions of **2**,[15d] we attempted to replace KF with DABCO. However, we could not detect formation of **4a** in the presence of DABCO (entry 5).

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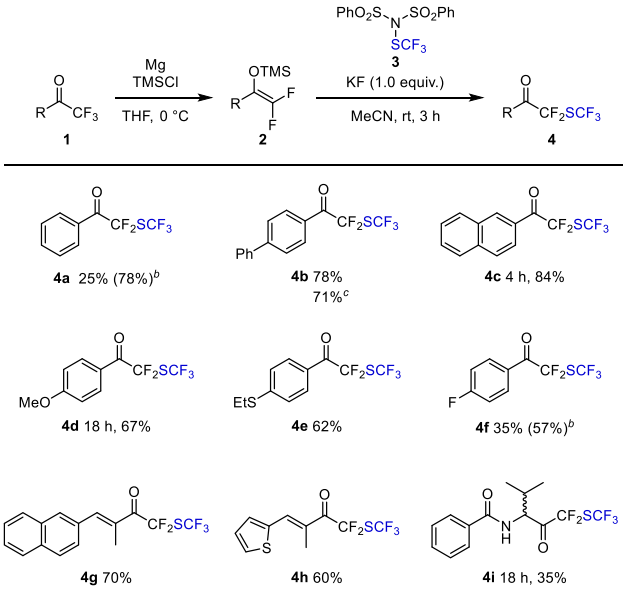
We have also attempted to use $FeCl_2$ as an activator, which proved to be efficient in the analogue trifluoromethylation reaction (see below). However, the trifluoromethylthiolation reaction proceeded with only 8% yield (entry 6). When acetonitrile was replaced with dichloromethane, formation of product **4a** was not observed (entry 7). A possible explanation is the poor solubility of KF in dichloromethane. In the absence of any activator, only traces of **4a** were formed (entry 8).

With the optimized conditions in hand, we explored the substrate scope of the trifluoromethylthiolation of **2** (Table 2).

Table 2. Substrate Scope of the Trifluoromethylthiolation Reaction of Difluoro Enol Silyl Ethers[a]

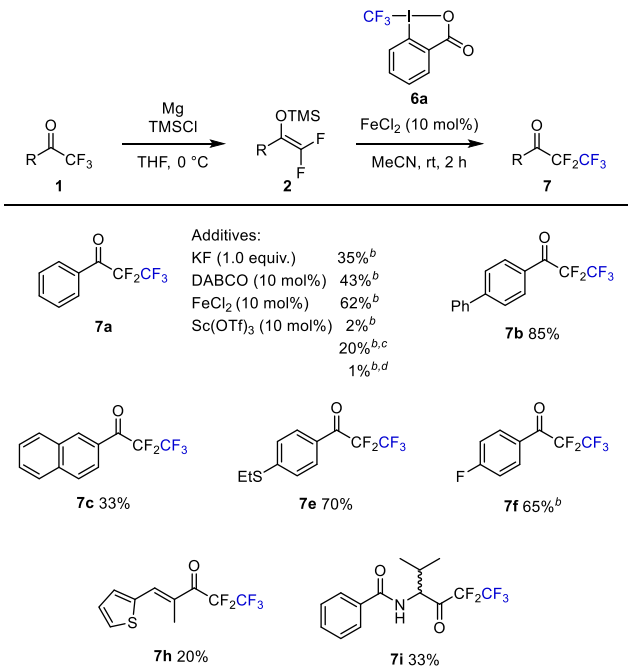


[a]General procedure: **2** (0.1 mmol), **3** (0.1 mmol), and KF (0.1 mmol) were stirred in MeCN (0.5 mL) at room temperature for 3 h. [b]^{19}F NMR yield using $PhCF_3$ as the internal standard. [c]Reaction conducted on 1.0 mmol scale.

As mentioned above, the reaction of **2a** proceeds with high NMR yield (78%), but because of the volatility of **4a** only 25% of the product could be isolated. The volatility of the products could not be decreased by hydration of the difluoro-keto groups. *p*-Phenyl-substituted ketone **4b** formed smoothly and could be isolated in 78% yield. The reaction of naphthyl enol silyl ether **2c** afforded **4c** in 84% yield within 4 h. Reactions using substrates with electron-withdrawing substituents in the aromatic ring gave the corresponding products **4d,e** with 67% and 62% yield, respectively. The difluoro enol silyl ether with an electron-withdrawing fluoro group also reacted smoothly, affording product **4f** in 57% NMR yield. However, because of the volatility of **4f**, it could be isolated only in 35% yield. Alkenyl difluoromethyl enolates could also be trifluoromethylthiolated with good yields, as **4g** and **4h** are obtained in 70% and 60% yields, respectively. We were also able to prepare the $-CF_2SCF_3$ analogue of the synthetic intermediate of the HNE inhibitor[25] presented in Figure 1d. Compound **4i** formed with 35% yield. The reaction could be scaled up to 1.0 mmol scale (**4b**) without significant change of the yield (71%).

We were able to extend the above methodology to trifluoromethylation of difluoro enol silyl ethers **2** (Table 3). Using Togni reagent[4c] **6a** (instead of **3**), difluoro homologation of trifluoromethyl ketones (**1**) could be achieved. The

Table 3. Substrate Scope of the Trifluoromethylation Reaction of Difluoro Enol Silyl Ethers[a]



[a]General procedure: **6a** (0.1 mmol), **2** (0.1 mmol), and $FeCl_2$ (0.01 mmol) were stirred in MeCN (0.5 mL) at room temperature for 2 h. [b]^{19}F NMR yield using $PhCF_3$ as the internal standard. [c]With trifluoromethylbenziodoxole **6b** instead. [d]With Umemoto reagent instead of **6a**.

trifluoromethylation of difluoro enol silyl ether **2a** proceeded with poor NMR yield (35%) in the presence of KF as the mediator (Table 3). However, when catalytic amounts of DABCO or $FeCl_2$ were used the yield could be improved to 43% and 62%, respectively. Application of $Sc(OTf)_3$ led to formation of **7a** with 2% yield. When the other type of Togni reagent[4c] (1-trifluoromethyl-3,3-dimethyl-1,2-benziodoxole, **6b**) was used, the yield dropped to 20%. With Umemoto reagent 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate,[26] only 1% of **7a** was obtained. Considering these results, further reactions were carried out with **6a** in the presence of $FeCl_2$ catalyst.[27] Similar to the SCF_3 analog (**4a**), compound **7a** was volatile, and therefore, the yield was not determined. However, perfluoroethyl compound **7b** with a phenyl substituent on the aromatic ring could be isolated in 85% yield. The naphthyl analogue was obtained in 33% yield. However, **7e**, with the electron-donating EtS group on the aromatic ring, formed in high yield (70%). In the presence of the electron-withdrawing fluoro substituent, the reactions still proceeded smoothly, affording **7f** with 65% NMR yield. Product **7f** was also volatile, and therefore, it was not isolated. Trifluoromethyl vinyl ketone **1h** also underwent difluorohomologation via **2h**, affording **7h** in 20% yield. Similarly to the trifluoromethyltiolation (**4i**), the drug intermediate of HNE inhibitors (Figure 1d), **1i**, could be converted to its perfluoroethyl analogue **7i** in 33% yield.

Interestingly, the above trifluoromethylation and trifluoromethylthiolation reactions could also be performed in a sequence (Figure 4). Thus, **7b** (obtained from **1b** by trifluoromethylation) may undergo a subsequent trifluoromethylthiolation with **3** via enolate **2j** to afford **4j** in 86% yield.

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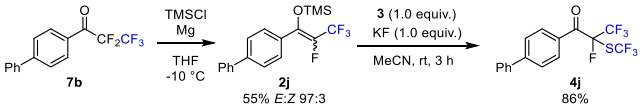
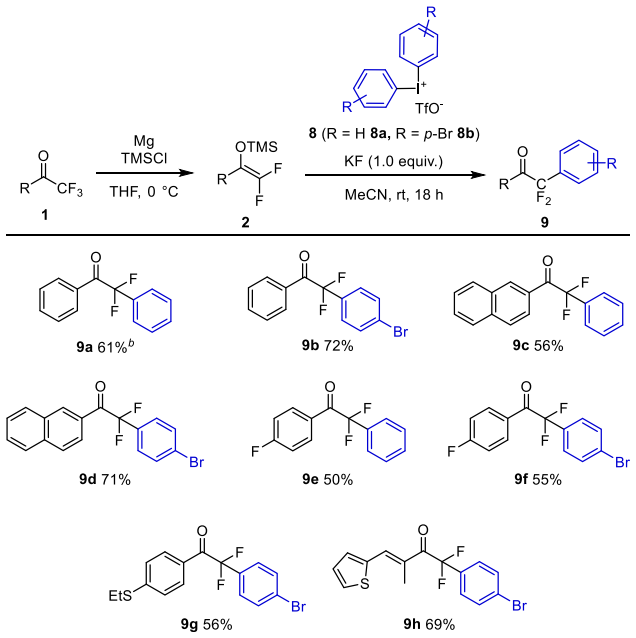


Figure 4. Trifluoromethylthiolation of **2j**.

The interesting feature of **4j** is that all three functional groups, which are widely used in organofluorine chemistry, are attached to the same carbon center.

The above results with the Togni reagent **6a** suggested that other hypervalent iodines[28] can also be useful electrophiles for the functionalization of difluoro enol silyl ethers **2**. Indeed, we have found that **2** reacted smoothly with diphenyl iodonium salt **8a** (Table 4) in the presence of KF under conditions very

Table 4. Substrate Scope of the Arylation Reaction of Difluoro Enol Silyl Ethers[a]



[a]General procedure: **8** (0.1 mmol), **2** (0.1 mmol), and KF (0.1 mmol) were stirred in MeCN (0.5 mL) at room temperature for 18 h. [b]When $FeCl_2$ (10 mol %) or DABCO (10 mol %) was used instead, no **9a** was detected.

similar to those of the above trifluoromethylthiolation reactions (Table 2). The reaction afforded **9a** with 61% yield using KF as mediator, while formation of **9a** was not observed with DABCO or $FeCl_2$ as mediators (instead of KF). The bromo analogue **8b** reacted with an even higher yield of 72%. The synthesis of aryl bromide products proceeded smoothly under the applied transition-metal-free conditions. Thus, both phenyl- and bromophenyl-containing difluoroketones **9c**–**9g** could be easily obtained in 50–71% yields. Not only aryl ketones but also vinyl ketone **1h** could be converted to bromophenyl derivative **9h** (69%) via enolate **2h**. We attempted to use alkynyl derivatives of hypervalent iodine reagents,[29] but formation of the corresponding difluoroketone product was not observed.

CONCLUSIONS

In summary, we have presented a new method for the functionalization of difluoro enol silyl ethers with electrophilic alkyl fluoride and aryl-transfer reagents. Using trifluoromethylthiolation reagent **3**, $-COCF_3$ functionalities could be converted to $-COCF_2SCF_3$ groups. The electron-withdrawing but lipophilic $-CF_2SCF_3$ group is an interesting new modifier for the reactivity of the keto groups in bioactive compounds (Figure 1). We have also presented two extensions of the methodology using hypervalent iodine-based electrophiles. By use of Togni reagent **6a**, difluoro homologation of the $-COCF_3$ group can be performed. This way of construction of a perfluoroethyl group can be used as an alternative method for the introduction of $-CF_2CF_3$ moiety to ketones.[30] In addition, we have shown that transition-metal-free arylation of difluoro enol silyl ethers can be performed using hypervalent iodines as aryl source. This method complements the reported transition-metal-catalyzed cross-coupling and other related arylation reactions to obtain $-COCF_2Ar$ functionality.[18,31] Overall, the new methodology is suitable for the expansion of the synthetic space of difluoro ketone based compounds including bioactive molecules.

EXPERIMENTAL SECTION

General Information. The difluoro enol silyl ethers **2** were freshly prepared (and used without purification) from the corresponding trifluoroketones according to the literature procedures reported by the Olah/Prakash[14b] and the Uneyama[14a,32] groups. Trifluoromethylthiolating reagent **3** was synthesized according to a procedure by Shen and co-workers.[23] Trifluoromethylating reagent **6a** (trifluoromethylbenziodoxolone) and **6b** (trifluoromethylbenziodoxole) were synthesized according to the reported literature procedures.[27,33] Anhydrous acetonitrile was purchased from Sigma-Aldrich and stored in an argon-filled glovebox. KF was dried by heating with a heat gun (550 °C) for about 2 min under vacuum and kept under Ar before use in the glovebox. All other chemicals, including diaryliodonium salts **8a** and **8b**, were obtained from commercial sources and used as received. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ (internal standard: 7.26 ppm, ^1H; 77.0 ppm, ^{13}C) using 400 or 500 MHz spectrometers. High-resolution mass data (HRMS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer. For column chromatography, silica gel (35–70 μm) was used. Unless otherwise stated, the reactions were conducted under Ar atmosphere.

*(E)-1,1,1-Trifluoro-3-methyl-4-(naphthalen-2-yl)but-3-en-2-one (**1g**).* The trifluoromethylenone was synthesized according to a literature procedure[34] using 2-naphthaldehyde. The product was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 115/1) to afford ketone **1g** as a pale yellow solid (1.12 g, 85% yield); mp 78.6–79.8 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.95–7.84 (m, 4H), 7.61–7.51 (m, 3H), 2.27 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −68.80; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 182.3 (q, J_{CF} = 33.1 Hz), 145.9 (q, J_{CF} = 3.5 Hz), 133.6, 132.9, 132.1, 131.01, 130.95, 128.6, 128.4, 127.74, 127.66, 126.9, 126.8, 116.9 (q, J_{CF} = 291.7 Hz), 13.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{12}F_3O$ 265.0835, found 265.0837.

*(E)-1,1,1-Trifluoro-3-methyl-4-(thiophene-2-yl)but-3-en-2-one (**1h**).* The trifluoromethylenone was synthesized according to a literature procedure[34] using thiophene-2-carbaldehyde. The product was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 100/1) to afford the desired ketone **1h** as a yellow oil (1.00 g, 91% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 3.7 Hz, 1H), 7.22 (dd, J = 5.1, 3.7 Hz, 1H), 2.25 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −68.64; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 181.4 (q, J_{CF} = 33.1 Hz), 138.4, 138.2 (q, J_{CF} = 3.7 Hz), 135.2, 132.8, 128.0, 126.8, 117.0 (q, J_{CF} = 291.8 Hz), 13.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_9H_8F_3OS$ 221.0242, found 221.0243.

*((1-([1,1′-Biphenyl]-4-yl)-2,3,3,3-tetrafluoroprop-1-en-1-yl)oxy)-trimethylsilane (**2j**).* The difluoro enol silyl ether **2j** was synthesized according to the literature procedure.[32] A round-bottom flask

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containing a stir bar was charged with magnesium turnings (0.74 mmol, 2.1 equiv) activated by heating under vacuum. The flask was cooled to −10 °C, and dry THF (1.4 mL) was added, followed by TMSCl (1.5 mmol, 4.2 equiv). To the mixture was added dropwise a solution of the ketone **7b** (0.35 mmol, 1.0 equiv) in THF (0.4 mL). The reaction mixture was stirred at −10 °C for 3 h, and then the solvent and the excess of TMSCl were evaporated, and pentane was added to the residue. The mixture was filtered through a pad of Celite and washed with pentane. The solvent was removed under reduced pressure to obtain the yellow liquid **2j** in 55% yield as a mixture of *E*/*Z* isomers (97:3 by ^{19}F NMR): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68−7.59 (m, 6H), 7.49−7.44 (m, 2H), 7.41−7.36 (m, 1H), 0.13 (s, 9H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ (*E* isomer, major) −65.54 (d, J_{FF} = 10.4 Hz), −165.81 (q, J_{FF} = 10.5 Hz); (*Z* isomer, minor) −63.80 (d, J_{FF} = 13.2 Hz), −153.45 (q, J_{FF} = 13.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (*E* isomer) 142.9 (dq, J_{CF} = 30.5, 2.6 Hz), 142.7, 140.1, 138.0 (dq, J_{CF} = 241.6, 36.8 Hz), 131.7 (d, J_{CF} = 5.1 Hz), 128.9, 128.5 (d, J_{CF} = 5.7 Hz), 127.9, 127.1, 126.9, 120.4 (dd, J_{CF} = 271.4, 37.4 Hz), 0.2.

General Procedure A: Trifluoromethylthiolation Reaction of Difluoro Enol Silyl Ethers. To a mixture of the difluoro enol silyl ether **2** (0.1 mmol), *N*-trifluoromethylthiodibenzenesulfonimide **3** (39.7 mg, 0.1 mmol, 1.0 equiv), and KF (5.8 mg, 0.1 mmol, 1.0 equiv) was added 0.5 mL of dry MeCN in a glovebox. Unless otherwise stated, the reaction mixtures were stirred at room temperature for 3 h. After evaporation, the product was isolated by silica gel column chromatography.

*2,2-Difluoro-1-phenyl-2-((trifluoromethyl)thio)ethan-1-one (**4a**).* The title compound **4a** was prepared according to the general procedure A. The NMR yield (78%) was determined by ^{19}F NMR (with ^{1}H decoupling, using 3s of delay time in 32 scans) with $PhCF_3$ as the internal standard. The product was purified by silica gel column chromatography (eluent: pentane) to afford **4a** as a volatile pale yellow oil (6.3 mg, 25% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17−8.11 (m, 2H), 7.78−7.72 (m, 1H), 7.62−7.55 (m, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.12 (t, J_{FF} = 8.9 Hz), −70.49 (q, J_{FF} = 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.1 (t, J_{CF} = 27.9 Hz), 135.8, 130.5 (t, J_{CF} = 2.9 Hz), 129.3 (t, J_{CF} = 2.9 Hz), 129.1, 128.3 (q, J_{CF} = 309.0 Hz), 126.6 (t, J_{CF} = 299.5 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_9H_6F_5OS$ 257.0054, found 257.0058.

*1-([1,1′-Biphenyl]-4-yl)-2,2-difluoro-2-((trifluoromethyl) thio)-ethan-1-one (**4b**).* The title compound **4b** was prepared according to the general procedure A above and purified by silica gel column chromatography (eluent: pentane) to afford **4b** as a white solid (26.0 mg, 78% yield): mp 49.6−50.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.80−7.74 (m, 2H), 7.68−7.63 (m, 2H), 7.54−7.48 (m, 2H), 7.48−7.42 (m, 1H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.10 (t, J_{FF} = 8.9 Hz), −70.28 (q, J_{FF} = 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 183.7 (t, J_{CF} = 27.2 Hz), 148.5, 139.1, 131.1 (t, J_{CF} = 2.8 Hz), 129.1, 129.0, 128.3 (q, J_{CF} = 309.0 Hz), 127.8 (t, J_{CF} = 2.9 Hz), 127.7, 127.4, 126.8 (t, J_{CF} = 298.5 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}F_5OS$ 333.0367, found 333.0369.

*Synthesis of **4b** on 1.0 mmol Scale.* To a mixture of the difluoro enol silyl ether **2b** (0.30 g, 1.0 mmol), *N*-trifluoromethylthiodibenzenesulfonimide **3** (0.40 g, 0.1 mmol, 1.0 equiv), and KF (58 mg, 1.0 mmol, 1.0 equiv) was added 5.0 mL of dry MeCN in a glovebox. The reaction mixture was stirred at room temperature for 3 h. After evaporation, the product was isolated by silica gel column chromatography (eluent: pentane) to afford **4b** as a white solid (0.24 g, 71% yield).

*2,2-Difluoro-1-(naphthalen-2-yl)-2-((trifluoromethyl) thio)-ethan-1-one (**4c**).* The title compound **4c** was prepared according to the general procedure A above with a reaction time of 4 h and purified by silica gel column chromatography (eluent: pentane) to afford **4c** as a white solid (25.6 mg, 84% yield): mp 63.1−64.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (s, 1 H), 8.07 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.74−7.67 (m, 1 H), 7.66−7.59 (m, 1 H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.11 (t, J_{FF} = 8.9 Hz), −69.48 (q, J_{FF} = 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 184.1 (t, J_{CF} = 27.7 Hz), 136.6, 133.7 (t, J_{CF} = 4.1 Hz), 132.2, 130.31, 130.25, 129.2, 128.4 (q, J_{CF} = 308.7 Hz), 127.9, 127.5, 127.0 (t, J_{CF} = 298.5 Hz), 126.4 (t, J_{CF} = 2.8 Hz), 124.4; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8F_5OS$ 307.0211, found 307.0208.

*2,2-Difluoro-1-(4-methoxyphenyl)-2-((trifluoromethyl)thio)-ethan-1-one (**4d**).* The title compound **4d** was prepared according to the general procedure A above with a reaction time of 18 h. Compound **4d** was purified by silica gel column chromatography (eluent: pentane/EA = 150/1) to afford **4d** as a yellow oil (19.2 mg, 67% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, *J* = 9.1 Hz, 2H), 7.06−7.00 (m, 2H), 3.94 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.32 (t, J_{FF} = 8.9 Hz), −69.54 (q, J_{FF} = 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 182.5 (t, J_{CF} = 27.2 Hz), 165.7, 133.2 (t, J_{CF} = 2.9 Hz), 128.4 (q, J_{CF} = 308.7 Hz), 127.2 (t, J_{CF} = 299.0 Hz), 121.9 (t, J_{CF} = 3.0 Hz), 114.5, 55.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8F_5O_2S$ 287.0160, found 287.0161.

*2,2-Difluoro-1-(4-(ethylthio)phenyl)-2-((trifluoromethyl) thio)-ethan-1-one (**4e**).* The title compound **4e** was prepared according to the general procedure A above and purified by silica gel column chromatography (eluent: pentane) to afford **4e** as a pale yellow solid (19.7 mg, 62% yield): mp 54.3−55.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 3.06 (q, *J* = 7.4 Hz, 2H), 1.41 (t, *J* = 7.4 Hz, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.21 (t, J_{FF} = 8.9 Hz), −70.02 (q, J_{FF} = 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 183.0 (t, J_{CF} = 27.5 Hz), 149.7, 130.7 (t, J_{CF} = 2.9 Hz), 128.4 (q, J_{CF} = 308.7 Hz), 127.0 (t, J_{CF} = 300.0 Hz), 125.8, 125.1 (t, J_{CF} = 2.9 Hz), 25.6, 13.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}F_5OS_2$ 317.0088, found 317.0096.

*2,2-Difluoro-1-(4-fluorophenyl)-2-((trifluoromethyl)thio)ethan-1-one (**4f**).* The title compound **4f** was prepared according to the general procedure A. The NMR yield (57%) was determined by ^{19}F NMR (with ^{1}H decoupling, using 3s of delay time in 32 scans) with $PhCF_3$ as the internal standard. The product was purified by silica gel column chromatography (eluent: pentane) to afford **4f** as a volatile colorless oil (10.2 mg, 35% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21−8.13 (m, 2H), 7.28−7.19 (m, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.08 (t, J_{FF} = 8.9 Hz), −70.35 (q, J_{FF} = 8.9 Hz), 98.86 to −98.94 (m); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 182.7 (t, J_{CF} = 27.9 Hz), 167.3 (d, J_{CF} = 260.6 Hz), 133.5 (dt, J_{CF} = 10.1 Hz, J_{CF} = 3.1 Hz), 128.2 (q, J_{CF} = 308.3 Hz), 126.6 (t, J_{CF} = 300.0 Hz), 125.7−125.6 (m), 116.7 (d, J_{CF} = 22.2 Hz); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_9H_5F_6OS$ 274.9960, found 274.9963.

*(E)-1,1-Difluoro-3-methyl-4-(naphthalen-2-yl)-1-((trifluoromethyl)thio)but-3-en-2-one (**4g**).* The title compound **4g** was prepared according to the general procedure A above and purified by silica gel column chromatography (eluent: pentane) to afford **4g** as a yellow solid (24.2 mg, 70% yield): mp 34.2−35.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (s, 1H), 7.99 (s, 1H), 7.93−7.85 (m, 3H), 7.61−7.53 (m, 3H), 2.27 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.60 (t, J_{FF} = 9.0 Hz), −67.13 (q, J_{FF} = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 185.9 (t, J_{CF} = 25.9 Hz), 147.1 (t, J_{CF} = 5.6 Hz), 133.7, 132.9, 132.0, 131.3, 130.1 (t, J_{CF} = 2.6 Hz), 128.7, 128.4 (q, J_{CF} = 309.0 Hz), 128.4, 127.81, 127.75, 127.5 (t, J_{CF} = 299.0 Hz), 126.9, 126.8, 13.7; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{16}H_{12}F_5OS$ 347.0524, found 347.0531.

*(E)-1,1-Difluoro-3-methyl-4-(thiophen-2-yl)-1-((trifluoromethyl)thio)but-3-en-2-one (**4h**).* The title compound **4h** was prepared according to the general procedure A above and purified by silica gel column chromatography (eluent: pentane) to afford **4h** as a yellow oil (18.0 mg, 60% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 7.74 (d, *J* = 5.1 Hz, 1H), 7.50 (d, *J* = 3.7 Hz, 1H), 7.23 (dd, J_1 = 5.1 Hz, J_2 = 3.8 Hz, 1H), 2.24 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −36.73 (t, J_{FF} = 9.0 Hz), −66.70 (q, J_{FF} = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 185.0 (t, J_{CF} = 26.0 Hz), 139.3 (t, J_{CF} = 6.0 Hz), 138.4, 135.7, 133.4, 128.5 (q, J_{CF} = 309.0 Hz), 128.1, 127.9 (t, J_{CF} = 300.5 Hz), 125.7 (t, J_{CF} = 2.7 Hz), 13.5; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8F_5OS_2$ 302.9931, found 302.9928.

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*N-(1,1-Difluoro-4-methyl-2-oxo-1-((trifluoromethyl)thio)pentan-3-yl)benzamide (**4i**).* The title compound **4i** was prepared according to the general procedure A above with a reaction time of 18 h. Compound **4i** was purified by silica gel column chromatography (eluent: pentane/ethyl acetate = 20/1 for the first round, pentane/Et_2O = 20/1 for the second round) to afford **4i** as a white solid (12.3 mg, 35% yield): mp 74.1−75.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82−7.76 (m, 2H), 7.58−7.53 (m, 1H), 7.50−7.44 (m, 2H), 6.49 (d, J = 7.7 Hz, 1H), 5.36−5.29 (m, 1H), 2.50−2.40 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −35.50 (t, J_{FF} = 8.9 Hz), −79.01 (ddq, J = 806.8, 231.6, 8.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 194.4 (dd, J_{CF} = 30.0, 26.1 Hz), 167.5, 133.2, 132.2, 128.8, 127.1, 127.9 (q, J_{CF} = 309.3 Hz), 123.1 (t, J_{CF} = 297.5 Hz), 58.6, 30.0, 20.0, 16.8; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{14}F_5NO_2SNa$ 378.0558, found 378.0561.

*1-([1,1′-Biphenyl]-4-yl)-2,3,3,3-tetrafluoro-2-((trifluoromethyl)-thio)propan-1-one (**4j**).* The title compound **4j** was prepared according to the general procedure A above with a reaction time of 3 h. Compound **4j** was purified by silica gel column chromatography (eluent: pentane) to afford **4j** as a colorless oil (32.8 mg, 86% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dd, J = 8.6, 1.9 Hz, 2H), 7.78−7.72 (m, 2H), 7.67−7.62 (m, 2H), 7.53−7.42 (m, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −35.16 (dq, J_{FF} = 9.6, 4.8 Hz), −73.88 (dq, J_{FF} = 9.7, 4.8 Hz), −146.80 to −147.02 (m); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 187.4 (d, J_{CF} = 24.2 Hz), 147.9, 139.1, 131.2 (d, J_{CF} = 4.0 Hz), 131.0 (d, J_{CF} = 7.8 Hz), 129.1, 128.9, 127.7 (q, J_{CF} = 311.6 Hz), 127.4 (d, J_{CF} = 1.2 Hz), 127.3, 120.5 (qd, J_{CF} = 287.2, 29.9 Hz), 102.6 (dq, J_{CF} = 260.0, 34.0 Hz). Despite repeated attempts, we were not able to obtain high-resolution mass data for **4j**. The probable reason is the difficult ionization of the molecule bearing a −COCF(CF_3)-(SCF_3) group.

General Procedure B: Trifluoromethylation of Difluoro Enol Silyl Ethers. To a mixture of trifluoromethylbenziodoxolone **6a** (31.6 mg, 0.1 mmol, 1.0 equiv) and $FeCl_2$ (1.3 mg, 0.01 mmol, 10 mol %) was added 0.5 mL of dry MeCN and a difluoro enol silyl ether **2** (0.1 mmol), in a glovebox. The reaction mixture was stirred at room temperature for 2 h. After evaporation, the product was isolated by silica gel column chromatography.

*1-Phenyl-2,2,3,3,3-pentafluoropropan-1-one (**7a**).* The title compound **7a** was prepared according to the general procedure B above. The NMR yield (62%) was determined by ^{19}F NMR (with ^{1}H decoupling, using 3s of delay time in 32 scans) with $PhCF_3$ as the internal standard. Compound **7a** was purified by silica gel column chromatography (eluent: pentane) to afford the volatile **7a** with pentane: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, J = 8.6 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.56, −115.53. The spectroscopic data is in agreement with the literature values.[35]

*1-([1,1′-Biphenyl]-4-yl)-2,2,3,3,3-pentafluoropropan-1-one (**7b**).* The title compound **7b** was prepared according to the general procedure B above and purified by silica gel column chromatography (eluent: pentane) to afford **7b** as a colorless solid (27.0 mg, 85% yield): mp 42.6−42.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 7.1 Hz, 2H), 7.50 (t, J = 7.3 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.51, −115.48; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 182.7 (t, J_{CF} = 26.6 Hz), 148.2, 139.1, 130.8 (t, J_{CF} = 3.3 Hz), 129.6, 129.1, 128.9, 127.6, 127.4, 118.0 (m), 108.8 (m). The spectroscopic data is in agreement with the literature values.[36]

*1-(Naphthalen-2-yl)-2,2,3,3,3-pentafluoropropan-1-one (**7c**).* The title compound **7c** was prepared according to the general procedure B above and purified by silica gel column chromatography (eluent: pentane) to afford **7c** as a colorless oil (9.0 mg, 33% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 8.11−8.04 (m, 1H), 8.06−7.99 (m, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.70 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.47, −114.82. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 183.1 (t, J_{CF} = 26.6 Hz), 136.4, 133.2 (t, J_{CF} = 4.5 Hz), 132.2, 130.3, 130.1, 129.1, 128.3, 127.9, 127.4, 124.2, 118.9 (qt, J_{CF} = 286.7, 33.8 Hz), 108.9 (tq, J_{CF} = 269.5, 37.1 Hz). The spectroscopic data is in agreement with the literature values.[37]

*1-(4-(Ethylthio)phenyl)-2,2,3,3,3-pentafluoropropan-1-one (**7e**).* The title compound **7e** was prepared according to the general procedure B above and purified by silica gel column chromatography (eluent: petroleum ether to afford **7e** as a yellow oil (19.9 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.7 Hz, 2H), 7.36−7.29 (m, 2H), 3.06 (q, J = 7.4 Hz, 2H), 1.41 (t, J = 7.4 Hz, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.62, −115.44; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 181.9 (t, J_{CF} = 26.4 Hz), 149.2, 130.4 (t, J_{CF} = 3.3 Hz), 127.1, 125.7, 118.0 (qt, J_{CF} = 286.4 Hz, J_{CF} = 33.8 Hz), 108.8 (tq, J_{CF} = 268.0, 37.1 Hz), 25.6, 13.7; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{11}H_{10}F_5OS$ 285.0367, found 285.0366.

*1-(4-Fluorophenyl)-2,2,3,3,3-pentafluoropropan-1-one (**7f**).* The title compound **7f** was prepared according to the general procedure B above. The NMR yield (65%) was determined by ^{19}F NMR (with ^{1}H decoupling, using 3s of delay time in 32 scans) with $PhCF_3$ as the internal standard. The perfluoroethylketone was further purified by silica gel column chromatography (eluent: pentane) to afford the volatile **7f** with traces of pentane: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18−8.09 (m, 2H), 7.27−7.19 (m, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.71, −99.22 to −100.72 (m), −115.58. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 181.6 (t, J_{CF} = 27.0 Hz), 167.1 (d, J_{CF} = 260.1 Hz), 133.2 (dt, J_{CF} = 10.0, 3.4 Hz), 127.4 (d, J_{CF} = 3.0 Hz), 118.0 (qt, J_{CF} = 286.7, 33.7 Hz), 116.54 (d, J_{CF} = 22.2 Hz), 108.7 (tq, J_{CF} = 268.7, 37.3 Hz). The spectroscopic data is in agreement with the literature values.[35]

*(E)-2-Methyl-1-(thiophene-2-yl)-4,4,5,5,5-pentafluoro-pent-1-en-3-one (**7h**).* The title compound **7h** was prepared according to the general procedure B above and purified by silica gel column chromatography (eluent: first run pentane; second run: pentane/Et_2O/triethylamine = 60/1/2) to afford **7h** as a yellow oil (5.5 mg, 20% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (s, 1H), 7.71 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.26−7.19 (m, 1H), 2.25 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.65, −112.52; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 183.6 (t, J_{CF} = 24.9 Hz), 138.4, 138.3 (t, J_{CF} = 6.5 Hz), 135.3, 133.0, 128.0, 127.9, 118.2 (m), 109.1 (m), 13.4. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_8F_5OS$ 271.0211, found 271.0213.

*N-(5,5,6,6,6-Pentafluoro-2-methyl-4-oxohexan-3-yl)benzamide (**7i**).* The title compound **7i** was prepared according to the general procedure B above and purified by silica gel column chromatography (eluent: pentane/ethyl acetate = 20/1) to afford **7i** as a yellow solid (10.5 mg, 33% yield): mp 90.9−92.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83−7.76 (m, 2H), 7.61−7.51 (m, 1H), 7.47 (t, J = 7.5 Hz, 2H), 6.49 (d, J = 6.4 Hz, 1H), 5.38 (ddd, J = 8.7, 4.2, 1.4 Hz, 1H), 2.45 (dq, J = 11.1, 6.8 Hz, 1H), 1.14 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −81.52, −121.43 (dd, J_{FF} = 638.6, 296.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 194.1 (dd, J_{CF} = 28.7, 25.3 Hz), 167.3, 133.3, 132.2, 128.8, 127.1, 117.7 (m), 108.2 (m), 59.3, 29.7, 20.0, 16.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{14}F_5NO_2Na$ 346.0837, found 346.0843. The spectroscopic data is in agreement with the literature values.[38]

General Procedure C: Arylation Reaction of Difluoro Enol Silyl Ethers. To a mixture of the difluoro enol silyl ether **2** (0.1 mmol), diaryliodonium salt **8** (0.1 mmol, 1.0 equiv), and KF (5.8 mg, 0.1 mmol, 1.0 equiv) was added 0.5 mL of dry MeCN in a glovebox. The reaction was stirred at room temperature for 18 h. After evaporation, the product was isolated by silica gel column chromatography.

*2,2-Difluoro-1,2-diphenylethan-1-one (**9a**).* The title compound **9a** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/Et_2O = 200/1) to afford **9a** as a pale yellow oil (14.2 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.00 (m, 2H), 7.65−7.55 (m, 3H), 7.52−7.42 (m, 5H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −97.53; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 189.0 (t, J_{CF} = 31.0 Hz), 134.2, 133.1 (t, J_{CF} = 25.0 Hz), 132.2, 130.9 (t, J_{CF} = 1.9 Hz), 130.3 (t, J_{CF} = 2.9 Hz), 128.8, 128.6, 125.6 (t, J_{CF} = 6.0 Hz), 116.9 (t, J_{CF} = 253.2 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{10}F_2ONa$ 255.0592,

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found 255.0593. The spectroscopic data is in agreement with the literature values.[39]

*2,2-Difluoro-2-(4-bromophenyl)-1-phenylethan-1-one (**9b**).* The title compound **9b** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/EA = 100/1) to afford **9b** as a yellow oil (22.4 mg, 72% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.00 (m, 2H), 7.64−7.57 (m, 3H), 7.51−7.43 (m, 4H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −97.56; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 188.5 (t, J_{CF} = 31.3 Hz), 134.4, 132.1 (t, J_{CF} = 25.5 Hz), 132.1, 131.9 (t, J_{CF} = 1.5 Hz), 130.2 (t, J_{CF} = 3.0 Hz), 128.7, 127.4 (t, J_{CF} = 6.0 Hz), 125.6 (t, J_{CF} = 2.2 Hz), 116.7 (t, J_{CF} = 254.2 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_9{}^{79}BrF_2ONa$ 332.9697, found 332.9693. The spectroscopic data is in agreement with the literature values.[40]

*2,2-Difluoro-1-(naphthalen-2-yl)-2-phenylethan-1-one (**9c**).* The title compound **9c** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/Et_2O/Et_3N = 40/1/2 for two rounds) to afford **9c** as a pale yellow solid (15.7 mg, 56% yield): mp 71.6−72.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H), 8.05 (dd, J = 8.8, 1.5 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.87 (t, J = 8.0 Hz, 2H), 7.70−7.66 (m, 2H), 7.65−7.60 (m, 1H), 7.58−7.52 (m, 1H), 7.51−7.45 (m, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −96.92; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 188.9 (t, J_{CF} = 30.9 Hz), 135.9, 133.3 (t, J_{CF} = 25.0 Hz), 133.0 (t, J_{CF} = 3.9 Hz), 132.2, 130.9 (t, J_{CF} = 1.7 Hz), 130.0, 129.4, 129.3, 128.8, 128.5, 127.7, 127.0, 125.7 (t, J_{CF} = 6.0 Hz), 125.0 (t, J_{CF} = 2.1 Hz), 117.0 (t, J_{CF} = 253.3 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{12}F_2ONa$ 305.0748, found 305.0747. The spectroscopic data are in agreement with the literature values.[40]

*2-(4-Bromophenyl)-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one (**9d**).* The title compound **9d** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/EA = 200/1) to afford **9d** as a white solid (25.6 mg, 71% yield): mp 80.7−81.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 8.5 Hz, 2H), 7.67−7.59 (m, 3H), 7.59−7.50 (m, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −96.91; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 188.4 (t, J_{CF} = 31.2 Hz), 135.9, 133.0 (t, J_{CF} = 4.1 Hz), 132.3 (t, J_{CF} = 25.48 Hz), 132.2, 132.1, 130.0, 129.5, 129.1 (t, J_{CF} = 1.6 Hz), 128.6, 127.8, 127.4 (t, J_{CF} = 6.0 Hz), 127.1, 125.6 (t, J_{CF} = 2.2 Hz), 124.8 (t, J_{CF} = 2.1 Hz), 116.9 (t, J_{CF} = 254.2 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{11}{}^{79}BrF_2ONa$ 382.9854, found 382.9853.

*2,2-Difluoro-1-(4-fluorophenyl)-2-phenylethan-1-one (**9e**).* The title compound **9e** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/Et_2O = 200/1) to afford **9e** as a yellow oil (12.5 mg, 50% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.03 (m, 2H), 7.65−7.55 (m, 2H), 7.53−7.42 (m, 3H), 7.12 (t, J = 8.6 Hz, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −97.46, −102.19 to −102.30 (m); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 187.4 (t, J_{CF} = 31.4 Hz), 166.3 (d, J_{CF} = 257.7 Hz), 133.2 (dt, J_{CF} = 9.6, 3.2 Hz), 132.9 (t, J_{CF} = 25.2 Hz), 131.0 (t, J_{CF} = 1.8 Hz), 128.9, 125.6 (t, J_{CF} = 6.0 Hz), 116.0 (d, J_{CF} = 21.8 Hz), 128.5, 116.9 (d, J_{CF} = 253.2 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_9F_3ONa$ 273.0498, found 273.0506.

*2-(4-Bromophenyl)-2,2-difluoro-1-(4-fluorophenyl)ethan- 1-one (**9f**).* The title compound **9f** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/Et_2O = 200/1) to afford **9f** as a colorless oil (18.2 mg, 55% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.03 (m, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.19−7.10 (m, 2H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −97.45, −101.78 to −101.69 (m); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 187.0 (t, J_{CF} = 31.69 Hz), 166.4 (d, J_{CF} = 258.2 Hz), 133.2 (dt, J_{CF} = 9.7, 3.2 Hz), 132.1, 131.9 (t, J_{CF} = 25.3 Hz), 128.2, 127.4 (t, J_{CF} = 6.0 Hz), 125.7 (t, J_{CF} = 2.2 Hz), 116.7 (t, J_{CF} = 253.9 Hz), 116.1 (d, J_{CF} = 22.0 Hz); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_8{}^{79}BrF_3ONa$ 350.9603, found 350.9607.

*2-(4-Bromophenyl)-1-(4-(ethylthio)phenyl)-2,2-difluoroethan-1-one (**9g**).* The title compound **9g** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane/Et_2O/Et_3N = 60/1/2 for the first round, and pentane/Et_2O = 200/1 for the second round) to afford **9g** as a pale yellow solid (20.9 mg, 56% yield): mp 50.9−52.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.28−7.24 (m, 2H), 3.02 (q, J = 7.4 Hz, 2H), 1.38 (t, J = 7.4 Hz, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −97.36; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 187.3 (t, J_{CF} = 31.0 Hz), 147.4, 132.2 (t, J_{CF} = 25.6 Hz), 132.0, 130.6 (t, J_{CF} = 3.1 Hz), 128.0, 127.4 (t, J_{CF} = 6.0 Hz), 125.7, 125.5 (t, J_{CF} = 2.2 Hz), 116.7 (t, J_{CF} = 254.0 Hz), 25.7, 13.8; HRMS (ESI) m/z [M + Na]$^+$ Calcd for $C_{16}H_{13}{}^{79}BrF_2OSNa$ 392.9731, found 392.9727.

*(E)-1-(4-Bromophenyl)-1,1-difluoro-3-methyl-4-(thiophene-2-yl)-but-3-en-2-one (**9h**).* The title compound **9h** was prepared according to the general procedure C above and purified by silica gel column chromatography (eluent: pentane to pentane/Et_2O = 300/1) to afford **9h** as a yellow oil (24.5 mg, 69% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 1H), 7.65−7.57 (m, 3H), 7.47−7.42 (m, 2H), 7.34 (d, J = 3.7 Hz, 1H), 7.16 (dd, J_1 = 5.1, J_2 = 3.7 Hz, 1H), 2.21 (s, 3H); ^{19}F NMR ($CDCl_3$, 377 MHz) δ −94.74; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 189.2 (t, J_{CF} = 29.6 Hz), 138.7, 137.2 (t, J_{CF} = 5.6 Hz), 134.2, 133.0 (t, J_{CF} = 25.6 Hz), 132.0, 131.8, 128.2, 127.7, 127.1 (t, J_{CF} = 6.0 Hz), 125.3 (t, J_{CF} = 2.2 Hz), 116.9 (t, J_{CF} = 254.4 Hz), 13.9; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{11}{}^{79}BrF_2OSNa$ 378.9574, found 378.9570.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01030.

NMR spectra of all the products (PDF)

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Notes

The authors declare no competing financial interest.

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