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Sulfur Assisted Tandem Electrophilic Fluorinative Deacylation: Synthesis of α-Fluoro β-Ketosulfides

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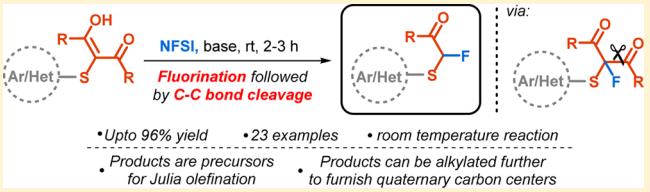
Supporting Information

ABSTRACT: A successful synthesis of α-fluoro-β-ketosulfides using an electrophilic fluorination method has been reported for the first time. The reaction proceeds via an electrophilic fluorination of α-sulfenyl-β-diketones followed by an unexpected tandem deacylation. The resulting products, α-fluoro-β-ketosulfides, are easily oxidized to the corresponding α-fluoro-β-ketosulfones, which can be used for further useful olefination reactions.



INTRODUCTION

Incorporation of fluorine into organic molecules is an active research area in organic synthesis because fluorine containing organic compounds are found in many biologically active compounds, pharmaceuticals, agrochemicals, and materials (Figure 1).[1,2]

A plethora of methods is available in the literature for incorporation of fluorine into organic molecules to obtain a variety of structurally diverse molecular scaffolds.[3] However, controlled monoelectrophilic fluorination at the α-position of an electron withdrawing group still remains a challenge in organic synthesis.[4] This problem becomes compounded when a sulfide group is present at α-position to an electron withdrawing moiety. Several attempts toward synthesizing α-fluoro-β-ketosulfides via electrophilic fluorination method by various groups have resulted in the formation of undesired or overfluorinated products (Scheme 1).[4b−d] This is probably due to (i) the strong affinity between sulfur and fluorine to form S−F/S → F bond, which leads to undesired side reactions, and (ii) the presence of a sulfur atom at α-position increases the acidity of α-C−H bond and results in rapid uncontrolled fluorination. The methods for the formation of α-fluoro-β-ketosulfides are limited to a few β-ketosulfide derivatives that bear the substitution at the α-position.[4d]

In contrast to electrophilic fluorination, the controlled nucleophilic fluorination of β-ketosulfides was successfully achieved by electrochemical methods (eq 1, Scheme 2).[5]

The only chemical method known to obtain α-fluoro-β-ketosulfides is the nucleophilic fluorination of sulfoxide with DAST (diethyl amino sulfurtrifluoride) in the presence of catalytic amount of ZnI_2 (eq 2, Scheme 2).[6a] However, the nucleophilic substitution of α-bromofluorocarbonyl compounds with thiols provides the expected α-fluoro-β-ketosulfides (eq 3, Scheme 2).[6b,c]

On the other hand, several reports of deacylation of β-dicarbonyl compounds such as classical acetoacetic ester synthesis are well-documented in the literature.[6d−g] In recent years, the release of trifluoro acetate groups from the fluorinated β-dicarbonyl compounds has been shown as an important reaction in organic synthesis.[6h−k] When the α-position of β-dicarbonyl compounds is substituted with sulfides, the deacylation is relatively facile.[7] The deacylation of β-ketoesters is facile in the presence of nucleophilic base at ambient temperature.[7b] However, the deacylation of β-diketones generally requires transition-metal catalysts and oxidants, and the reaction is performed at higher temperature.[7c,d] A report for the electrophilic halogenative (+Cl and +Br) deacylation of nonsulfide bearing β-dicarbonyl compounds is known in the literature.[7e] Distinct from these reports, the present work involves an unexpected tandem deacylation of α-fluoro sulfenyl β-diketones in mild reaction conditions to synthesize α-fluoro-β-ketosulfides (eq 4, Scheme 2). To the best of our knowledge, to date, (i) a controlled fluorination leading to monoelectrophilic fluorination of β-ketosulfides and (ii) a successful synthesis of α-fluoro-β-ketosulfides via electrophilic fluorination method are unknown.

RESULTS AND DISCUSSION

Optimization Studies. Initially, we performed a fluorination of α-sulfenyl-β-diketone (**1a**, 1 equiv) using NFSI (*N*-fluorobenzenesulfonimide, 1.1 equiv) as a fluorinating reagent and K_2CO_3 (1.2 equiv) as a base in CH_3CN (2 mL). The initial reaction furnished a mixture of fluorinated product **2a** and the corresponding deacylated product **3a** in 54 and 43% yields, respectively (determined by ^1H NMR, Table 1, entry 1). Extending the reaction time to 1 h led to the formation of **2a** and **3a** in 44 and 56% yields, respectively (entry 2).

Further extension to 2 h led to the formation of a mixture of **2a** and **3a** in 10 and 90% yields, respectively (entry 3). On purification, we were able to isolate exclusively deacylated product **3a** in 96% isolated yield (entry 3), indicating that the

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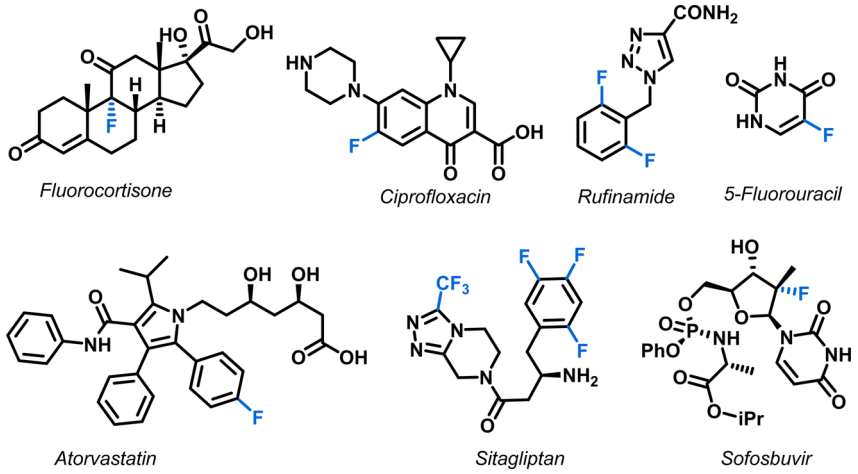
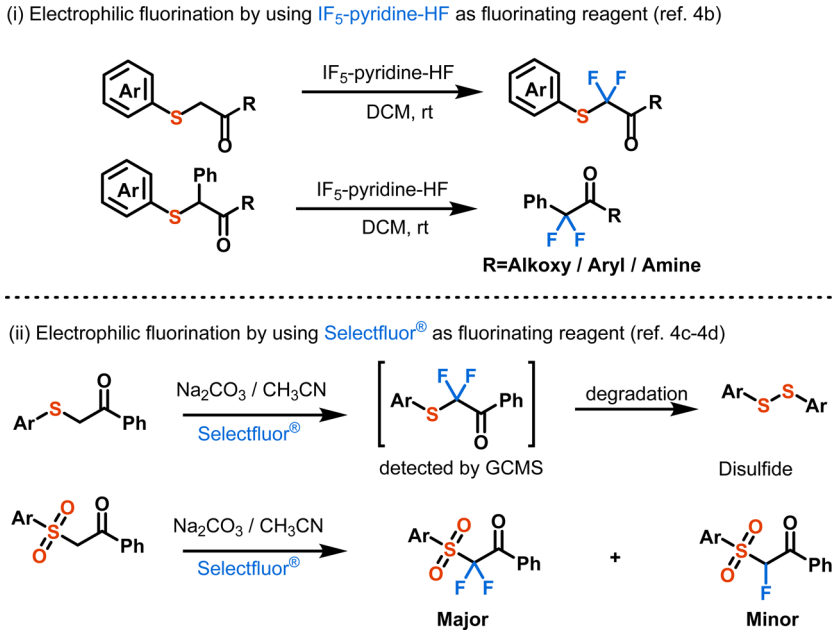


Figure 1. Examples of fluorine containing drug molecules.

Scheme 1. Undesired/Uncontrolled Electrophilic Fluorination



fluorinated product **2a** underwent deacylation under the chromatographic conditions (see the Supporting Information, SI3 and 4). Further, reaction of **1a** using solvents such as THF and acetone resulted in the formation of a mixture of **2a** and **3a** (entries 4−6). The reaction of **1a** with NFSI in EtOAc (1 h) furnished the products **2a** and **3a** in 22 and 78% yields, respectively (entry 7). Further, when the reaction was carried out in EtOAc for 2 h, it furnished exclusively deacylated product **3a** in almost quantitative yield (entry 8). Reactions with solvents such as CH_2Cl_2 and toluene led to a mixture of **2a** and **3a** (entries 9 and 10, respectively). Furthermore, the reaction in MeOH formed a complex mixture, whereas the reaction in H_2O was not successful (entries 11 and 12). The reaction performed using Na_2CO_3 gave **2a** and **3a** in 59 and 23% yields, respectively (entry 13), whereas the reaction using Cs_2CO_3 proceeded smoothly to furnish only **3a** in quantitative yield (entry 14).

Substrate Scope. Under the established optimized reaction conditions A (entry 8, Table 1), the scope and limitations of this fluorinative deacylation reaction were explored (Scheme 3). As seen in Scheme 3, a variety of α-benzoxazole-2-sulfenyl acetylacetone derivatives bearing alkyl/aryl/halo substitution on benzoxazole ring (**1a**−**1g**) and unsubstituted α-benzoxazole-2-sulfenyl acetylactone (**1h**) underwent smooth electrophilic fluorination followed by deacetylation, furnishing products **3a**−**3h** in moderate to excellent yields (96, 92, 89, 80, 93, 69, 44, and 98%, respectively). Further, a facile deacylation was observed even in the case of α-benzoxazole-2-sulfenyl-3,5-heptanediones (**1i** and **1j**), and the expected products **3i** and **3j** were obtained in good yields (70 and 73%, respectively). Under the optimal conditions, the benzothiazole derivative (**1k**) furnished the expected product **3k** in excellent yield (96%). However, α-benzothiazole-2-sulfenyl 3,5-heptanediones (**1l**) furnished an inseparable mixture of **2l** and **3l** in 12 and 77% yields, respectively (based on ^{1}H NMR ratio). The fluorinative deacylation reaction of α-oxazole-2-sulfenylacetylacetone (**1m**) furnished only 30% of the desired product **3m** after column purification. The compound **1n**, which has the unsymmetrical diketone moiety, underwent fluorinative deacylation to give the mixture of **2n**, **3n**, and **3a** in a ratio of 40:36:24. The compounds **3n** and **3a** were isolated in 40 and 35% yields, respectively, whereas the

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Scheme 2. Reaction Development

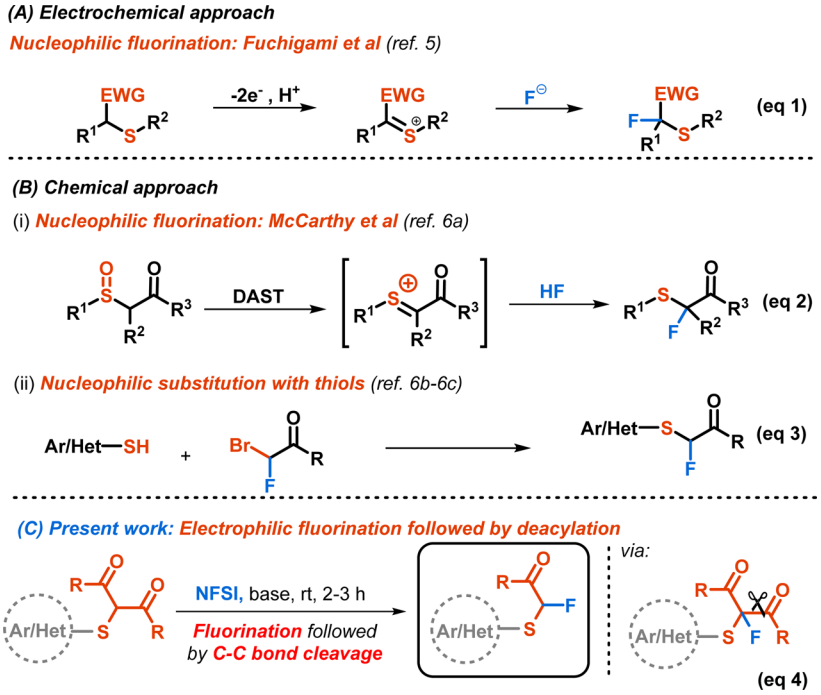
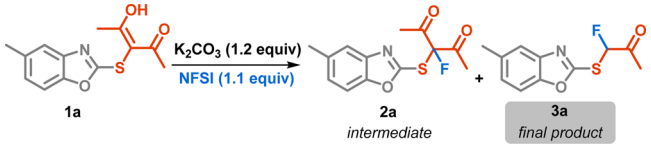


Table 1. Screening Studies (Standard Conditions A)[a]



			^{1}H NMR yield (%) for crude reaction mixture[b]	
entry	solvent (mL)	time (h)	2a	3a
1	CH_3CN	0.75	54	43
2	CH_3CN	1	44	56
3	CH_3CN	2	10	90 (96)[e]
4	THF	1	57	43
5	THF	2	nd	100
6	acetone	2	18	82
7	EtOAc	1	22	78 (92)[e]
8	**EtOAc**	**2**	**nd**	**100 (96)**[e]
9	DCM	2	50	50
10	toluene	2	41	51
11	MeOH	2	nd	nd
12	H_2O	2	nr	nr
13[c]	EtOAc	2	59	23
14[d]	EtOAc	2	nd	100

[a]Reaction conditions A: **1a** (0.1 mmol) and K_2CO_3 (1.2 equiv) in solvent (1 mL) were prestirred for 60–90 min; then, NFSI (1.1 equiv) was added, and the reaction mixture was stirred for the given time. [b]^{1}H NMR yields (determined by using terephthaldehyde as internal standard). [c]Na_2CO_3 (1.2 equiv). [d]Cs_2CO_3 (1.2 equiv). [e]Values in the parentheses are isolated yields of **3a** after passing through a silica gel column (**2a** converts to **3a** in the column).

compound **2n** underwent deacylation on silica gel column. Hence, the increment in the isolated yields of **3n** and **3a** was observed.

The compound **1o**, which preferentially exists in diketone form (due to bulky carbonyl groups) bearing a relatively less acidic proton,[7a] did not furnish the expected product **3o**, and starting material was intact (based on ^{1}H NMR spectrum, Scheme 4). The starting materials **1p** and **1q** did not furnish the α-alkylthio-β-diketones (Scheme 4).[8a] Further, when the starting material **1a** was allowed to react with NCS/NBS/NIS instead of NFSI, the reaction produced a complex inseparable mixture (Scheme 4).

Optimization for Aryl-Substituted Sulfdes. Under the optimized reaction conditions A, 3-(phenylthio)pentane-2,4-dione (**4a**) did not undergo complete deacylation and instead furnished a mixture of nondeacylated and deacylated fluorine compounds. Therefore, further optimization study was under taken to enhance the deacylation process (entries 1–5, Table 2). During this optimization study, we found that increasing the concentration of the reaction mixture (0.5 mmol of **4** in 2 mL of CH_3CN) in the presence of a strong base (Cs_2CO_3, 1.2 equiv) resulted in complete deacylation (entry 5, optimized reaction condition B; Table 2).

Substrate Scope. Under the reaction conditions B, α-thiophenyl acetyl acetone **4a** and its derivatives **4b–4h** underwent smooth reaction, which upon purification on a silica gel column furnished exclusively deacylated fluorine compounds **6a** (88%), **6b** (83%), **6c** (62%), **6d** (65%), **6e** (82%), **6f** (78%), **6g** (88%), **6h** (87%), and **6i** (82%) (Scheme 5). The α-sulfenyl β-ketoester **4i** furnished the mixture of **5j** and **6j** in 38 and 42% yields, respectively (^{1}H NMR yield, see the Supporting Information, SI 87 and 88). However, our attempt to isolate **5j** and **6j** was not successful as the crude compound degraded on the silica gel column.

α-Fluoro-β-ketosulfones are important starting materials in Julia–Kocienski fluoro-olefination reaction for synthesizing fluoro-olefins.[6b,c,10] Further, the sulfones have great utility in organic synthesis as well as in pharmaceutical chemistry.[4b,6b,c,9] The general reaction sequences used for the synthesis of α-fluoro-β-ketosulfones are cumbersome and have multiple problems (eq 1, Scheme 6).[6b,c,10a–c] Hu et al. reported an

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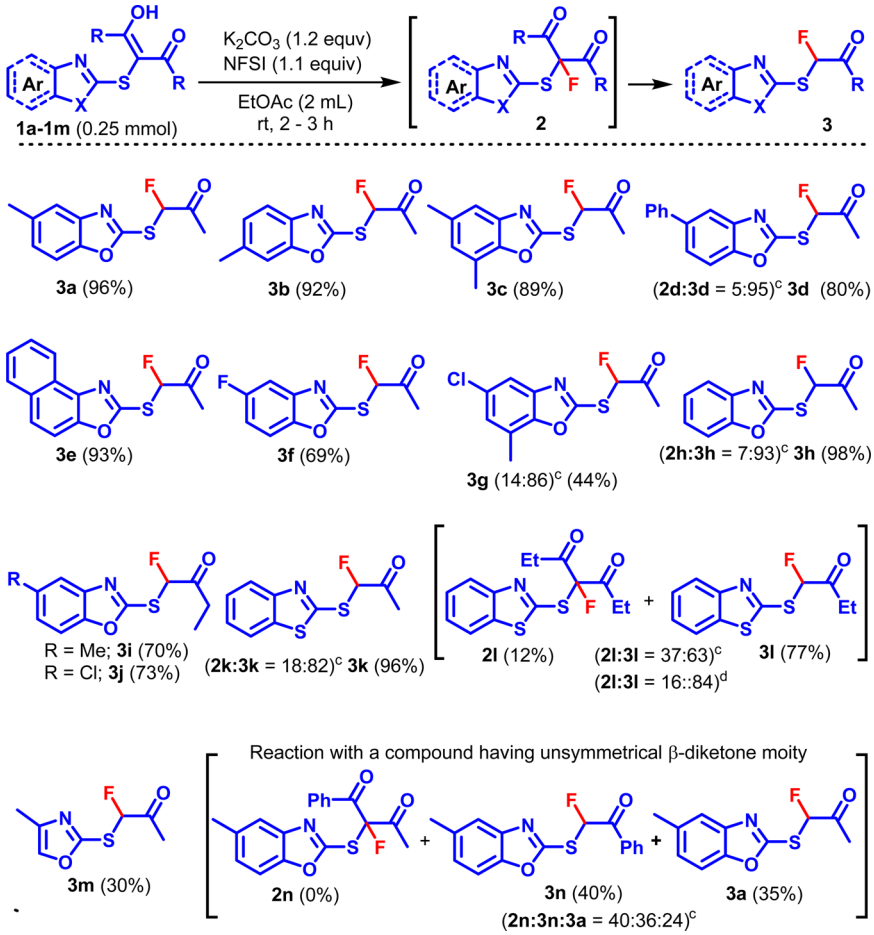
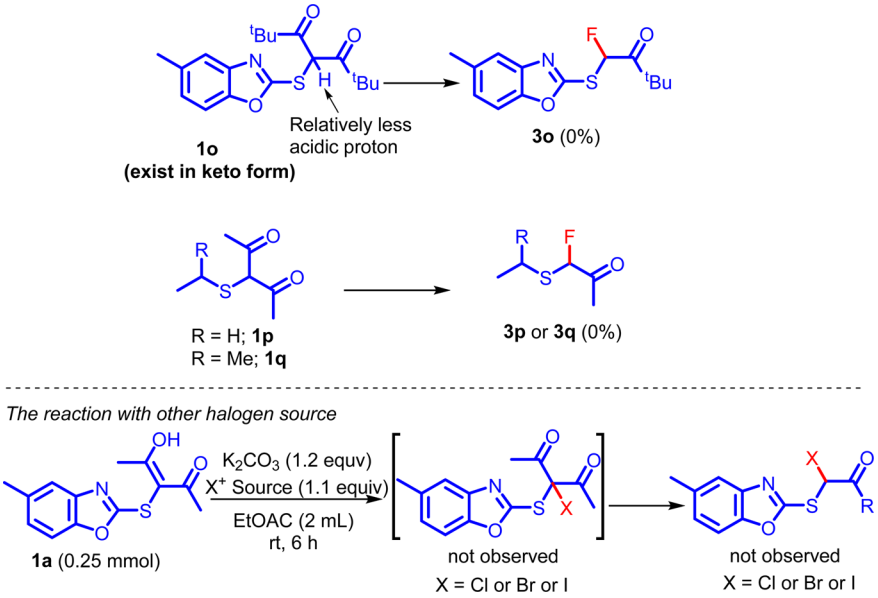
Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.25 mmol) and K_2CO_3 (1.2 equiv), were prestirred for 60−90 min in EtOAc (2 mL), then NFSI (1.1 equiv) was added and reaction mixture was stirred at rt for further 2−3 h. [b]Values in the parentheses are isolated yields. [c]^{1}H NMR ratio of products before column purification. [d]^{1}H NMR ratio of products after column purification.

Scheme 4. Unsuccessful Reaction under Optimized Reaction Conditions A



alternate strategy which avoids the overfluorination (eq 2, Scheme 6).[9b]

To address these synthetic challenges, we thought that α-fluoro-β-ketosulfides would be suitable substrates for synthesiz-

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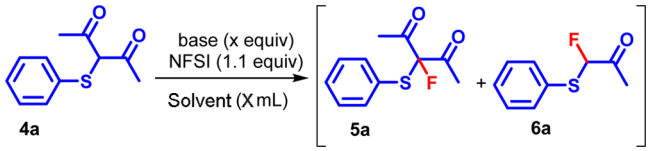
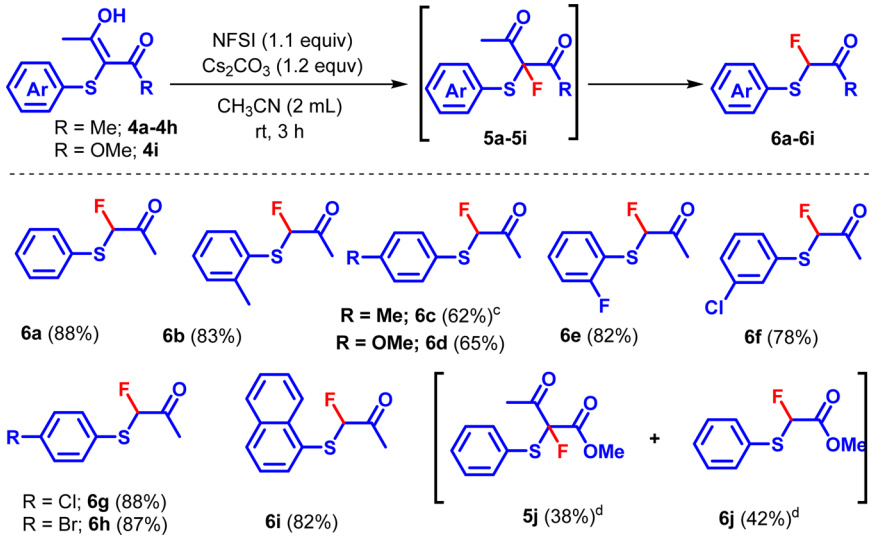
Table 2. Optimization for Aryl Substituted Sulfides (6a–6i) (Standard Conditions B)[a]



entry	**4a** (mmol)	solvent (mL)	base (equiv)	conversion ratios in crude reaction mixture[b] **5a:6a**	ratios after subjecting to column purification[c,d] **5a:6a**
1	0.25	EtOAc (2.0)	K_2CO_3 (1.2)	68:32	30:70 **5a** (19%); **6a** (60%)
2	0.5	EtOAc (4.0)	K_2CO_3 (3.0)	38:62	8:92 **5a** (6%); **6a** (82%)
3	0.5	EtOAc (2.0)	Cs_2CO_3 (1.2)	25:75	7:93 **5a** (5%); **6a** (91%)
4	0.25	CH_3CN (2.0)	K_2CO_3 (1.2)	34:66	
5	**0.5**	**CH_3CN (2.0)**	**Cs_2CO_3 (1.2)**	**3:97**	**0:100 5a** (0%); **6a** (88%)

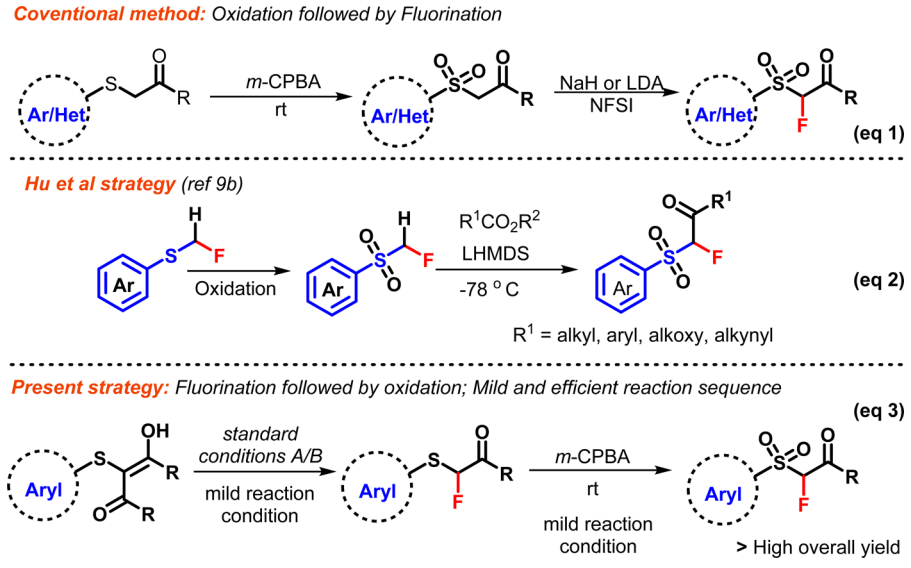
[a]Reaction conditions: **4a** (1 equiv) and base (*x* equiv) were prestirred for 2 h; then, NFSI (1.1 equiv) was added, and the reaction mixture was stirred at room temperature for 3 h. [b]^{1}H NMR ratio of products. [c]^{1}H NMR ratio of products after silica gel column purification. [d]Values in the parentheses are the isolated yield of an inseparable mixture of products **5a** and **6a**.

Scheme 5. Substrate Scope under the Optimized Reaction Conditions B[a,b]



[a]Reaction conditions: **4** (0.5 mmol) and Cs_2CO_3 (1.2 equiv) were prestirred for 2 h in CH_3CN (2 mL), NFSI was added (1.1 equiv), and the reaction mixture was stirred at rt for further 3 h. [b]Values in the parentheses are isolated yields. [c]Reaction time: 6 h. [d]^{1}H NMR yield (determined by using terephthaldehyde as internal standard; see SI 87 and 88) of the compounds that degraded during isolation.

Scheme 6. Reaction Development for the Synthesis of Fluorosulfones



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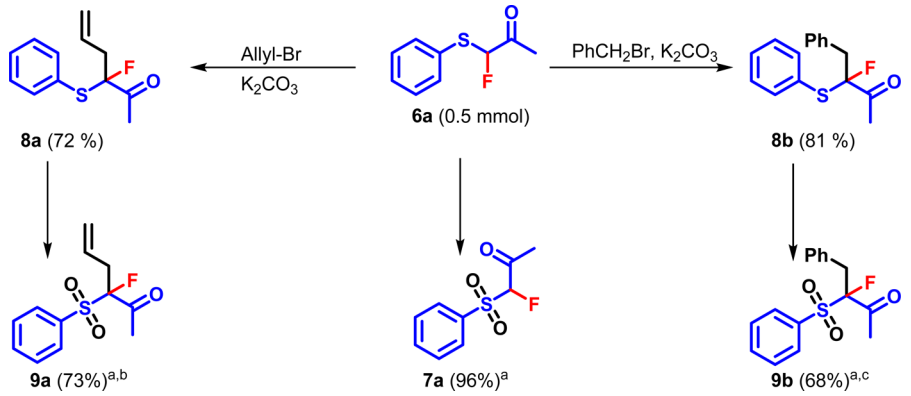
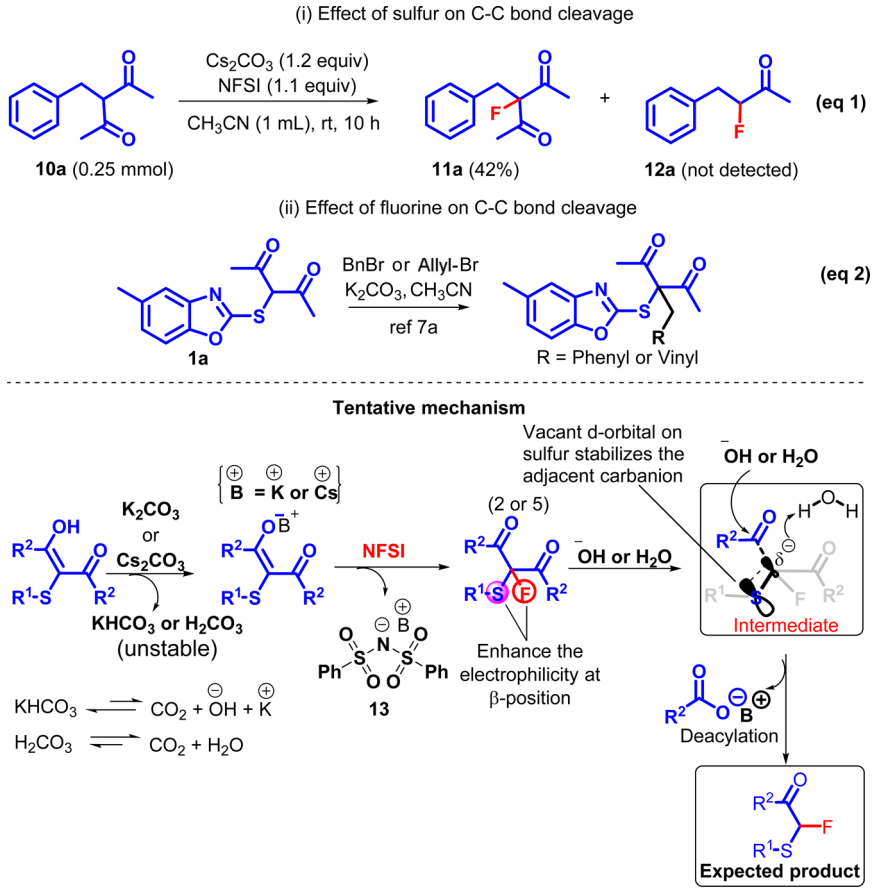
Scheme 7. Synthetic Application



[a]Reaction conditions: mCPBA (4 equiv), CH_2Cl_2 (5 mL), rt, 6 h (values in the parentheses are isolated yields). [b]**8a** (0.36 mmol). [c]**8b** (0.4 mmol).

Scheme 8. Establishment of Mechanism



ing α-fluoro-β-ketosulfones (eq 3, Scheme 6). Hence, the compound **6a** was chosen as the model substrate for the oxidation, and sulfones **7a**, **9a**, and **9b** were synthesized in good to excellent yields (96, 73, and 68%, respectively Scheme 7) from the starting material **6a** under mild reaction conditions using *m*-CPBA as an oxidant.[8b] To demonstrate further synthetic utility, both allylation and benzylation of **6a** were performed, in which only the products **8a** and **8b** were obtained from **6a** (see the Supporting Information, SI 92 and 96).

Control Experiments. To understand the effect of sulfur on deacylation reaction, the compound **10a** was fluorinated under optimized reaction conditions B, which furnished only the nondeacylated product **11a** in 42% yield (eq 1, Scheme 8, see SI 106 and SI 107). This result clearly indicates the necessity of the sulfur moiety for deacylation of α-fluoro-β-diketones. Earlier, we reported a reaction in which the active methine position of **1a** is substituted (allylation and benzylation reactions) to form the nondeacylated products (eq 2, Scheme 8).[7a] This result clearly suggests the necessity of fluorine moiety for deacylation of α-sulfenyl β-diketones. Hence, these two results clearly indicate that the presence of both sulfur and fluorine at α-position of β-dicarbonyl is essential for facile deacylation. On the basis of these observations, a tentative mechanism has been proposed (Scheme 8). Fluorine being the most electronegative element, its

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substitution at α-position of β-dicarbonyl enhances the electrophilicity of the carbonyl carbons, thereby facilitating a even weak nucleophile to attack carbonyl carbons.[11a,b] On the other hand, the vacant d-orbital of sulfur stabilizes the adjacent carbanion[11b,c] (Scheme 8), thereby favoring the deacylation.

Therefore, the electronegativity factor as well as carbanion stabilization operate together, causing the deacylation. Further, the residue that forms after the reaction has been identified as the potassium/cesium salt of benzenesulfonimide, and that of **4a** was found to be cesium salt of benzenesulfonimide (compound **13**, determined by ^{1}H NMR in D_2O, Scheme 8). This indicates that the anion of benzenesulfonimide has probably no role in deacylation. Further, in addressing the substrate scope of the present work, the inherent instability of α-sulfenyl-β-dicarbonyl to undergo deacylation[7] limits the substrate scope as synthesizing the starting materials is cumbersome. α-Sulfenyl-β-ketoesters are especially prone to undergo deacylation and decompose during isolation. However, we believe that the significance of the present fluorinative deacylation methodology and the application of α-fluoro β-ketosulfides overcomes the limitation of the substrate scope.

CONCLUSION

In conclusion, we developed an unprecedented tandem electrophilic fluorinative deacylation method for synthesizing α-fluoro-β-keto sulfides under mild basic reaction conditions at room temperature. The unexpected deacylation upon fluorination of α-sulfenyl β-dicarbonyls is the salient feature of this method. The synthetic potential of the methodology has been demonstrated by synthesizing a series of sulfones which can be used for synthesizing fluoro olefins.

EXPERIMENTAL SECTION

General Experimental. All of the reactions were carried out using commercially available AR grade solvents without further distillation. Unless otherwise noted, starting materials and solvents obtained from commercial suppliers were used without further purification. Reactions were monitored by using precoated silica TLC plates. Column chromatography was performed on silica gel 100−200 mesh. Distilled petroleum ether was used for column chromatography. The starting materials α-sulfenyl β-diketones (**1a**−**1n**) were prepared as described in our earlier reports,[7a,12] and α-sulfenyl β-diketones (**3a**−**3h**) were prepared as described in the literature[13] with necessary modifications (see the given procedure and note 1). NMR spectra were recorded at 400 MHz using $CDCl_3$. For the spectra recorded in $CDCl_3$, TMS (tetramethylsilane) or residual $CHCl_3$ served as internal standard for ^{1}H NMR (0.00 ppm or 7.26), and solvent signal was used as reference signal for ^{13}C NMR (77.00 ppm). IR spectra were measured using an FT-IR spectrometer. Mass spectra were measured using Q-TOF (ESI-HRMS).

*Experimental Procedures for the Synthesis of Starting Materials. Typical Experimental Procedure for the Synthesis of (E)-3-(Ethylthio)-4-hydroxypent-3-en-2-one (**1p**).*[13] To a well-stirred, ice cold mixture of ethyl thiol (10 mmol) and α-chloro acetylacetone (10 mmol) was added pyridine slowly (11 mmol) for a period of 1 min. The reaction mixture was stirred vigorously at room temperature for 12 h. Then, the diethyl ether (15 mL) was added to the reaction mixture; crude compound was filtered through the sintered funnel, and the filtrate containing crude compound was adsorbed on silica gel (100−200 mesh size) and purified on a silica gel column using EtOAc:petroleum ether (2:98−5:95) as eluent to obtain the expected α-sulfenyl β-diketone **1p**.

*Typical Experimental Procedure for the Synthesis of (E)-4-Hydroxy-3-(isopropylthio)pent-3-en-2-one (**1q**).*[13] To a well-stirred, ice cold mixture of isopropyl thiol (10 mmol) and α-chloro acetylacetone (10 mmol) was added pyridine slowly (11 mmol) for a period of 1 min. The reaction mixture was stirred vigorously at room temperature for 12 h. After, the reaction mixture was diluted with 3−4 mL of diethyl ether and directly transferred onto a silica gel column and purified using EtOAc:petroleum ether (2:98−5:95) as eluent to obtain the expected α-sulfenyl β-diketone **1q**.

* We observed, the starting materials **1p** and **1q** are low boiling point liquids

*General Experimental Procedure for the Synthesis of Starting Materials (**4a**−**4i**).*[13] To a well-stirred, ice cold mixture of thiol (10 mmol) and α-chloro acetylacetone (10 mmol) was added pyridine slowly (11 mmol) for a period of 1 min (please see note 1). The reaction mixture was stirred vigorously at room temperature for 12 h. Then, diethyl ether (15 mL) was added to the reaction mixture, and crude compound was filtered through sintered funnel, and the filtrate containing crude compound was adsorbed on silica gel (100−200 mesh size) and purified on a silica gel column using EtOAc:petroleum ether (0:100−4:96) as eluent to obtain the expected α-sulfenyl β-diketone.

Note 1: When thiols are liquid, no solvent was used in the reaction. When thiols are solid, the reaction was performed in diethyl ether (15 mL); i.e., pyridine was added to the ice cold solution of thiol and α-chloro acetylacetone in diethyl ether.

*Typical Experimental Procedure for the Synthesis of Starting Material **4j**.*[13] To a well-stirred, ice cold mixture of thiophenol (10 mmol) and α-chloro methyl acetoacetate (10 mmol) was added pyridine slowly (11 mmol) for a period of 1 min. The reaction mixture was stirred vigorously at room temperature for 12 h. Then, the diethyl ether (15 mL) was added to the reaction mixture; crude compound was filtered through sintered funnel, and the filtrate containing crude compound was adsorbed on silica gel (100−200 mesh size) and purified on a silica gel column using EtOAc:petroleum ether (0:100−5:95) as eluent to obtain the expected product **4j**.

*Experimental Procedures for the Synthesis of the Products. General Experimental Procedure for the Synthesis of α-Fluoro β-Ketosulfides (**3a**−**3n**).* To a well-stirred solution of α-sulfenyl β-diketone (**1**, 0.25 mmol) in EtOAc (2 mL) was added anhydrous K_2CO_3 (1.2 equiv). The reaction mixture was stirred at room temperature until it turned into a white turbid heterogeneous reaction mixture (generally 60−90 min). The round-bottom flask was then placed under the ice bath, and NFSI (1.1 equiv) was added slowly to the cold reaction mixture. After 5 min of complete addition of NFSI, the ice bath was removed, and stirring was continued at room temperature for 3 h. Then, the crude compound was filtered through sintered funnel, and the residue was washed with EtoAc (5 mL × 2). The filtrate was adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (0:100−5:95) as the eluent to obtain the expected α-fluoro β-ketosulfides (**3a**−**3n**).

*General Experimental Procedure for the Synthesis of α-Fluoro β-Ketosulfides (**6a**−**6i**).* To a well-stirred solution of α-sulfenyl β-diketone (**4**, 0.5 mmol) in CH_3CN (2.0 mL) was added anhydrous Cs_2CO_3 (1.2 equiv). The reaction mixture was stirred at room temperature until it turned into a white turbid heterogeneous reaction mixture (generally 2 h). The round-bottom flask was then placed under the ice bath, and NFSI (1.1 equiv) was added slowly to the cold reaction mixture. After 5 min of complete addition of NFSI, the ice bath was removed, and stirring was continued at room temperature for 3 h. Then, the crude compound was filtered through sintered funnel, and the residue was washed with EtOAc (5 mL × 2). The filtrate was adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (0:100−5:95) as the eluent to obtain the expected α-fluoro β-ketosulfides (**6a**−**6i**).

Note 2: For optimization studies, the following workup procedure was followed: The crude compound in EtOAc (10 mL) was taken in separating funnel; water (10 mL) was added, and then the mixture was shaken well to form white turbid mixture. To this white turbid mixture was added the brine solution (3−5 mL) to obtain a clear bilayer of organic and aqueous mixture. The organic layer was separated, and the aqueous layer was washed with EtOAc (5 mL × 2). The combined organic fraction was dried over anhydrous Na_2SO_4, and ^{1}H NMR yield was determined by using terephthaldehyde as internal standard.

Note 3: Other than in the reaction medium, we also observed the deacylation process on silica gel column. Under the standard reaction

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conditions, in some cases the complete monodeacylation of fluorinated compound did not occur. Therefore, retaining of a small amount of nondeacylated compounds, i.e., α,α-fluoro sulfenyl β-diketones, was observed after the workup (found by ^{1}H and ^{19}F NMR). However, such nondeacylated fluorinated compounds (**2** or **5**) underwent deacylation on silica gel column during purification to give an additional amount of expected product. As we observed, the α,α-fluoro sulfenyl β-diketones containing heteroaryl sulfenyl moiety showed a high propensity to undergo deacylation. In these cases, irrespective of the ratio of deacylated and nondeacylated products obtained from the reaction media, the complete monodeacylated compounds were obtained after silica gel column chromatography. However, α,α-fluoro sulfenyl β-diketones containing aryl sulfenyl moiety showed less propensity to undergo deacylation on the silica gel column.

Note 4: As silica gel also influenced the deacylation process, 100−200 mesh sized silica gel columns with fixed size of 5 × 20 cm^2 were preferred for purification of all the crude compounds.

*Typical Experimental Procedure for the Synthesis of 1-Fluoro-1-(phenylsulfonyl)propan-2-one (**7a**)*[4d,9c]. To a well-stirred solution of 1-fluoro-1-(phenylthio)propan-2-one (**6a**, 0.5 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (55−70%, 4 equiv) at room temperature, and the reaction mixture was stirred at room temperature for 6 h. Then, the saturated aqueous sodium sulfite solution was added to the reaction mixture, and stirring was continued at room temperature for further 2 h. The crude compound was extracted into CH_2Cl_2 (10 mL × 3) and dried over anhydrous Na_2SO_4. The crude compound in CH_2Cl_2 was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (20:80−40:60) as eluent to obtain the 1-fluoro-1-(phenylsulfonyl)propan-2-one (**7a**) in 96% (104 mg) yield.

*Typical Experimental Procedure for the Synthesis of 3-Fluoro-3-(phenylthio)hex-5-en-2-one (**8a**).* To a well-stirred, heterogeneous mixture of 1-fluoro-1-(phenylthio)propan-2-one (**6a**, 0.5 mmol) and anhydrous K_2CO_3 (4.0 equiv) in CH_3CN (4 mL) was added allyl bromide (6 equiv) at room temperature, and the reaction mixture was refluxed for 24 h. Then, the crude compound was filtered through sintered funnel, and the residue was washed with EtOAc (5 mL). The filtrate was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (0:100−2:98) as the eluent to obtain the allylated product **8a** in 72% (81 mg) yield.

Note 5: The ^{1}H NMR of the crude compound showed the presence of the only allylated product **8a**.

*Typical Experimental Procedure for the Synthesis of 3-Fluoro-4-phenyl-3-(phenylthio)butan-2-one (**8b**).* To a well-stirred, heterogeneous mixture of 1-fluoro-1-(phenylthio)propan-2-one (**6a**, 0.5 mmol) and anhydrous K_2CO_3 (4.0 equiv) in CH_3CN (4 mL) was added benzyl bromide (2 equiv) at room temperature, and the reaction mixture was refluxed for 24 h. Then, the crude compound was filtered through sintered funnel, and the residue was washed with EtOAc (5 mL). The filtrate was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (0:100−2:98) as the eluent to obtain the benzylated product **8b** in 81% (112 mg) yield.

Note 6: The ^{1}H NMR spectrum of the crude compound showed the presence of only the benzylated product **8b.**

*Typical Experimental Procedure for the Synthesis of 3-Fluoro-3-(phenylsulfonyl)hex-5-en-2-one (**9a**).*[4,9c] To a well-stirred solution of 1-fluoro-1-(phenylthio)propan-2-one (**8a**, 0.36 mmol) in CH_2Cl_2 (5 mL) was added mCPBA (55−70%, 4 equiv) at room temperature, and the reaction mixture was stirred at room temperature for 6 h. Then, the saturated aqueous sodium sulfite solution was added to the reaction mixture, and stirring was continued at room temperature for further 2 h. The crude compound was extracted into CH_2Cl_2 (10 mL × 3) and dried over anhydrous Na_2SO_4. The crude compound in CH_2Cl_2 was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column flash chromatography by using EtOAc:petroleum ether (20:80−40:60) as eluent to obtain the α-fluoro-β-ketosulfone **9a** in 73% yield.

*Typical Experimental Procedure for the Synthesis of 3-Fluoro-4-phenyl-3-(phenylsulfonyl)butan-2-one (**9b**).*[4d,9c] To a well-stirred solution of 1-fluoro-1-(phenylthio)propan-2-one (**8b**, 0.4 mmol) in CH_2Cl_2 (5 mL) was added mCPBA (55−70%, 4 equiv) at room temperature, and the reaction mixture was stirred at room temperature for 6 h. Then, the saturated aqueous sodium sulfite solution was added to the reaction mixture, and stirring was continued at room temperature for further 2 h. The crude compound was extracted into CH_2Cl_2 (10 mL × 3) and dried over anhydrous Na_2SO_4. The crude compound in CH_2Cl_2 was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column flash chromatography by using EtOAc:petroleum ether (20:80−40:60) as eluent to obtain the α-fluoro-β-ketosulfone **9b** in 68% yield.

Note 7: For synthesis of sulfones, mCPBA was dried under reduced pressure (4−5 h) before being used in the reaction

*Typical Experimental Procedure for the Synthesis of 3-Benzyl-3-fluoropentane-2,4-dione (**11a**).* To a well-stirred solution of 3-benzylpentane-2,4-dione (**7a**, 0.25 mmol) in CH_3CN (1.5 mL) was added anhydrous Cs_2CO_3 (1.2 equiv). The reaction mixture was stirred at room temperature until it turned into a white turbid heterogeneous reaction mixture (4−5 h). The round-bottom flask was then placed under the ice bath, and NFSI (1.1 equiv) was added slowly to the cold reaction mixture. After 5 min of complete addition of NFSI, the ice bath was removed, and stirring was continued at room temperature for 8 h. Then, the crude compound was filtered through sintered funnel, and the residue was washed with EtOAc (5 mL × 2). The filtrate was then adsorbed on silica gel (100−200 mesh size) and purified on silica gel (100−200 mesh size) column by using EtOAc:petroleum ether (2:98−5:95) as the eluent to obtain only the nondeacylated product **11a** in 42%.

Note 8: The ^{1}H NMR and ^{19}F NMR (single peak) of the crude compound showed only the presence of **11a**.

*Potassium or Cesium Salt of Benzenesulfonamide (**13a** or **13b**).* These compounds are the residues obtained by filtration of the crude reaction mixture of the fluorinative deacylation reaction of **1** or **4** under the respective optimized reaction conditions.

*Experimental Data for Starting Materials. (E)-3-(Ethylthio)-4-hydroxypent-3-en-2-one (**1p**).*[13] Colorless liquid; yield: 66% (1.06 g); R_f (5% EtoAc/Pet ether) 0.6; IR (Neat, cm^{-1}): 1587, 1407, 1259, 1014; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.40 (brs, 1H), 2.54 (q, J = 7.2 Hz, 2H), 2.43 (s, 6H), 1.22 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 104.0, 30.4, 24.5, 14.1; ESI-HRMS (m/z): calcd for $C_7H_{12}O_2SNa$ (M + Na): 183.0456, found (M + Na): 183.0453.

*(E)-4-Hydroxy-3-(isopropylthio)pent-3-en-2-one (**1q**).*[13] Yellow liquid; yield: 24% (417 mg); R_f (5% EtoAc/Pet ether) 0.6; IR (Neat, cm^{-1}): 2360, 2335, 1628, 1446, 1180, 1128, 1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (septet, J = 6.8 Hz, 1H), 2.42 (s, 6H), 1.22 (d, J = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 104.2, 39.6, 24.7, 24.6; ESI-HRMS (m/z): calcd for $C_8H_{14}O_2SNa$ (M + Na): 197.0612, found (M + Na): 197.0614.

*(E)-4-Hydroxy-3-(phenylthio)pent-3-en-2-one (**4a**).*[13−15] Yellow liquid; yield: 82% (1.7 g); R_f (Pet ether) 0.2; IR (Neat, cm^{-1}): 1582, 1477, 1404, 1255, 1081, 1018, 909; ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.26 (brs, 1H), 7.29−7.25 (m, 2H), 7.13−7.08 (m, 3H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 137.7, 129.2, 125.2, 124.6, 101.5, 24.3. ESI-HRMS (m/z): calcd for $C_{11}H_{12}O_2SNa$ (M + Na): 231.0456, found (M + Na): 231.0459.

*(E)-4-Hydroxy-3-(o-tolylthio)pent-3-en-2-one (**4b**).* White solid; yield: 80% (1.78 g); mp: 67−69 °C R_f (Pet ether) 0.25; IR (KBr, cm^{-1}): 1573, 1458, 1386, 1255, 1044, 1003, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.10 (m, 2H), 7.06−7.02 (m, 1H), 6.83 (d, J = 7.6 Hz, 1 H), 2.38 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 136.5, 134.3, 130.3, 126.7, 124.7, 122.7, 100.7, 24.2, 19.6; ESI-HRMS (m/z): calcd for $C_{12}H_{14}O_2SNa$ (M + Na): 245.0612, found (M + Na): 245.0611.

*(E)-4-Hydroxy-3-(p-tolylthio)pent-3-en-2-one (**4c**).*[14,15] Low melting yellow crystalline solid; yield: 82% (1.82 g); R_f (Pet ether) 0.25; IR (Neat, cm^{-1}): 1729, 1674, 1589, 1492, 1413, 1376, 1252, 1014; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, J = 7.2 Hz, 2H), 6.99 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 2H), 2.34 (s, 6 H), 2.30 (s, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 198.2, 135.1, 134.2, 129.9, 124.9, 102.1, 24.4, 20.8; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{14}O_2SNa$ (M + Na): 245.0612, found (M + Na): 245.0609.

(E)-4-Hydroxy-3-((4-methoxyphenyl)thio)pent-3-en-2-one (**4d**).[14,15] White crystalline solid; mp: 87−89 °C; yield: 72% (1.71 g); R_f (Pet ether) 0.3; IR (Neat, cm^{-1}): 1576, 1490, 1403, 1290, 1241, 1173, 1024; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 9.2 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 2.36 (S, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 157.9, 128.4, 126.9, 114.9, 103.0, 55.4, 24.4; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{14}O_3SNa$ (M + Na): 261.0561, found (M + Na): 261.0562.

(E)-3-((2-Fluorophenyl)thio)-4-hydroxypent-3-en-2-one (**4e**). Pale yellow crystalline solid; mp: 54−56 °C; yield: 70% (1.58 g); R_f (Pet ether) 0.2; IR (KBr, cm^{-1}): 1585, 1544, 1394, 1343, 1265, 1194, 1133, 1057, 1012, 909, 850, 811; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16−7.11 (m, 1 H), 7.09−7.03 (m, 2 H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 2.34 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 159.3 (d, ^1J (CF) = 242 Hz), 126.82 (d, ^3J (CF) = 8 Hz), 126.13 (d, ^4J (CF) = 1 Hz), 124.91 (d, ^2J (CF) = 16 Hz), 124.75 (d, ^3J (CF) = 4 Hz), 115.69 (d, ^2J (CF) = 21 Hz), 99.7, 24.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −113.5; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{11}O_2FSNa$ (M + Na): 249.0361, found (M + Na): 249.0364.

(E)-3-((3-Chlorophenyl)thio)-4-hydroxypent-3-en-2-one (**4f**). Yellow liquid; yield: 78% (1.89 g); R_f (Pet ether) 0.2; IR (Neat, cm^{-1}): 1573, 1460, 1403, 1256, 1113, 1073, 1016, 910; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1 H), 6.96 (d, *J* = 8.0 Hz, 1H), 2.33 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 140.0, 135.3, 130.2, 125.4, 124.3, 122.6, 101.8, 24.3; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{11}O_2SClNa$ (M + Na): 265.0066, found (M + Na): 265.0064.

(E)-3-((4-Chlorophenyl)thio)-4-hydroxypent-3-en-2-one (**4g**).[15] White solid; yield: 83% (2.0 g); R_f (Pet ether) 0.25; IR (KBr, cm^{-1}): 1554, 1466, 1385, 1087, 1001, 907; ^1H NMR (400 MHz, $CDCl_3$): δ 17.27 (brs, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 136.4, 131.1, 129.3, 125.9, 101.3, 24.3; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{11}O_2SClNa$ (M + Na): 265.0066, found (M + Na): 265.0065.

(E)-3-((4-Bromophenyl)thio)-4-hydroxypent-3-en-2-one (**4h**).[14,15] White crystalline solid; yield: 87% (2.5 g); R_f (Pet ether) 0.25; IR (KBr, cm^{-1}): 1548, 1465, 1379, 1244, 1079, 997, 905, 803; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.96 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H), 2.32 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 137.0, 132.1, 126.1, 118.7, 101.1, 24.3; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{11}O_2SBrNa$ (M + Na): 308.9561, found (M + Na): 308.9562, (M + 2 + Na): 310.9602.

(E)-4-Hydroxy-3-(naphthalen-1-ylthio)pent-3-en-2-one (**4i**). White solid; yield: 75% (1.93 g); mp: 92−94 °C; R_f (Pet ether) 0.25; IR (KBr, cm^{-1}): 1538, 1496, 1393, 1265, 1058, 1012, 905, 850, 810, 744; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.48−7.39 (m, 3 H) 7.26−7.24 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 135.3, 133.9, 131.5, 128.9, 127.8, 126.8, 125.4, 123.6, 121.8, 101.5, 24.4; ESI-HRMS (*m*/*z*): calcd for $C_{15}H_{14}O_2SNa$ (M + Na): 281.0612, found (M + Na): 281.0612.

(E)-4-Hydroxy-3-(phenylthio)pent-3-en-2-one (**4j**).[13] Brown liquid; yield: 40% (896 mg); R_f (5% EtOAc/Pet ether) 0.5; IR (Neat, cm^{-1}): 1633, 1589, 1441, 1338, 1254, 1070; ^1H NMR (400 MHz, $CDCl_3$): δ 13.80 (brs, 1H), 7.27−7.24 (m, 2H), 7.13−7.09 (m, 3H), 3.76 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.2, 173.4, 137.8, 132.5, 128.9, 125.1, 125.0, 91.5, 52.7, 20.9; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{12}O_3SNa$ (M + Na): 247.0405, found (M + Na): 247.0403.

*Experimental Data for the Products (**3a**−**3n**). 1-Fluoro-1-((5-methylbenzo[d]oxazol-2-yl)thio)propan-2-one* (**3a**). Colorless liquid; yield: 96% (57 mg); R_f (5% EtOAc/hexane) 0.25; IR (Neat, cm^{-1}): 1738, 1508, 1479, 1423, 1359, 1256, 1220, 1151, 1104, 1030; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.78 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.49 (d, ^4J (CH_3−F) = 3.2 Hz, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9 (d, ^2J (CF) = 25.0 Hz), 158.9, 150.4, 141.4, 134.7, 126.0, 119.2, 109.6, 97.1 (d, ^1J (CF) = 238.0 Hz), 26.3, 21.4; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.3; calcd for $C_{11}H_{10}NO_2SFNa$ (M + Na): 262.0310, found (M + Na): 262.0315.

1-Fluoro-1-((6-methylbenzo[d]oxazol-2-yl)thio)propan-2-one (**3b**). White solid; yield: 92% (55 mg); R_f (5% EtOAc/hexane) 0.25; IR (KBr, cm^{-1}): 1698, 1627, 1527, 1422, 1332, 1214; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.1 Hz, 1H), 7.29 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.77 (d, ^2J (CH−F) = 50.5 Hz, 1H), 2.484 (d, ^4J (CH_3−F) = 3.2 Hz, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4 (d, ^2J (CF) = 25.4 Hz), 158.2, 152.5, 139.2, 135.5, 126.0, 118.6, 110.5, 97.1 (d, ^1J (CF) = 238.3 Hz), 26.3, 21.7; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.2; HRESI-MS (*m*/*z*): calcd for $C_{11}H_{10}NO_2SFNa$ (M + Na): 262.0314, found (M + Na): 262.0312.

1-((5,7-Dimethylbenzo[d]oxazol-2-yl)thio)-1-fluoropropan-2-one (**3c**). White solid paste; yield: 89% (56 mg); R_f (5% EtOAc/hexane) 0.1; IR (KBr, cm^{-1}): 2924, 1732, 1633, 1511, 1151, 1116, 1018; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.92 (s, 1H), 6.78 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.486 (d, ^4J (CH_3−F) = 3.2 Hz, 3H), 2.44 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9 (d, ^2J (CF) = 26.0 Hz), 158.5, 149.8, 141.1, 134.6, 127.2, 120.2, 116.5, 97.1 (d, ^1J (CF) = 238 Hz), 26.3, 21.3, 14.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.3; HRESI-MS (*m*/*z*): calcd for $C_{12}H_{12}NO_2SFNa$ (M + Na): 276.0470, found (M + Na): 276.0468.

1-Fluoro-1-((5-phenylbenzo[d]oxazol-2-yl)thio)propan-2-one (**3d**). Pale yellow gummy solid; yield: 80% (60 mg); R_f (5% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1737, 1507, 1466, 1419, 1359, 1258, 1141, 1105, 1023; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.52 (s, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.38−7.34 (m, 1H), 6.81 (d, ^2J (CH−F) = 50 Hz, 1H), 2.503 (d, ^4J (CH_3−F) = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8 (d, ^2J (CF) = 25.0 Hz), 159.8, 151.6, 141.9, 140.6, 138.7, 128.8, 127.4 (2 peaks), 124.4, 117.6, 110.2, 97.1 (d, ^1J (CF) = 238.0 Hz), 26.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.3; HRESI-MS (*m*/*z*): calcd for $C_{16}H_{12}NO_2FSNa$ (M + Na): 324.0471, found (M + Na): 324.0481.

1-Fluoro-1-(naphtho[1,2-d]oxazol-2-ylthio)propan-2-one (**3e**). Yellow liquid; yield: 93% (60 mg); R_f (5% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1737, 1499, 1374, 1190, 1139, 1028; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 8.2 Hz, 1H), 7. 94 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.67−7.62 (m, 2H), 7.54 (dd, J_1 = J_2 = 8.0 Hz, 1H), 6.77 (d, ^2J (CH−F) = 52.0 Hz, 1H), 2.544 (d, ^4J (CH_3−F) = 3.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0 (d, ^2J (CF) = 25.0 Hz), 156.94 (d, ^3J (CF) = 2.0 Hz), 149.8, 137.0, 131.1, 128.5, 127.2, 126.0, 125.71, 125.69, 122.1, 110.3, 97.3 (d, ^1J (CF) = 239.0 Hz), 26.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.1; HRESI-MS (*m*/*z*): calcd for $C_{14}H_{10}NO_2FSNa$ (M + Na): 298.0316, found (M + Na): 298.0318.

1-Fluoro-1-((5-fluorobenzo[d]oxazol-2-yl)thio)propan-2-one (**3f**). White gummy solid; yield: 69% (42 mg); R_f (5% EtOAc/hexane) 0.1; IR (KBr, cm^{-1}): 1726, 1471, 1433, 1362, 1330, 1238, 1127, 1045, 951; ^1H NMR (400 MHz, $CDCl_3$): δ 7. 42 (dd, J_1 = 9.0 Hz, J_2 = 4.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.04 (ddd, J_1 = J_2 = 9.0 Hz, J_3 = 2.0 Hz, 1H), 6.79 (d, ^2J (CH−F) = 50.0 Hz, 1H), 2.505 (d, ^4J (CH_3−F) = 3.2 Hz, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8 (d, ^2J (CF) = 25.0 Hz), 161.3 160.1 (d, ^1J (CF) = 233.0 Hz), 148.5, 142.1 (d, ^3J (CF) = 14.0 Hz), 112.46 (d, ^2J (CF) = 26.0 Hz), 110.57 (d, ^3J (CF) = 11.0 Hz), 105.87 (d, ^2J (CF) = 26.0 Hz), 97.0 (^1J (CF) = 239.0 Hz), 26.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −117.0, −162.5; HRESI-MS (*m*/*z*): calcd for $C_{10}H_7NO_2F_2SNa$ (M + Na): 266.0063, found (M + Na): 266.0063.

1-((5-Chloro-7-methylbenzo[d]oxazol-2-yl)thio)-1-fluoropropan-2-one (**3g**). Pale yellow liqid; yield: 44% (30 mg); R_f (20% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1737, 1503, 1464, 1220, 1130, 1020; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.11 (s, 1H), 6.77 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.509 (d, ^4J (CH_3−F) = 3.6 Hz, 3H), 2.47 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9 (d, ^2J (CF) = 26.0 Hz), 160.5, 150.1, 141.7, 130.1, 126.1, 122.0, 116.5, 97.0 (d, ^1J (CF) = 239 Hz), 26.4, 14.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.9; HRESI-MS (*m*/*z*): calcd for $C_{11}H_9NO_2FSClNa$ (M + Na): 295.9924, found (M + Na): 295.9925.

1-(Benzo[d]oxazol-2-ylthio)-1-fluoropropan-2-one (**3h**). Colorless liquid; yield: 98% (56 mg); R_f (5% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1778, 1735, 1509, 1481, 1452, 1359, 1135; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J_1 = 6.0 Hz, J_2 = 2.4 Hz, 1H), 7.49 (dd, J_1 = 5.8 Hz, *J*

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$_2$ = 2.0 Hz, 1H), 7.34 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 6.80 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.504 (d, ^4J (CH_3−F) = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9 (d, ^2J (CF) = 26.0 Hz), 159.2, 152.1, 141.3, 124.9, 124.8, 119.2, 110.3, 97.1 (d, ^1J (CF) = 238.0 Hz), 26.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −162.4; HRESI-MS (m/z): calcd for $C_{10}H_8NO_2FSNa$ (M + Na): 248.0157, found (M + Na): 248.0157.

*1-Fluoro-1-((5-methylbenzo[d]oxazol-2-yl)thio)butan-2-one (**3i**).* Colorless liquid; yield: 70% (45 mg); R_f (5% EtOAc/hexane) 0.3; IR (Neat, cm^{-1}): 1733, 1623, 1462, 1427, 1310, 1238, 1077; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.81 (d, ^2J (CH−F) = 50.8 Hz, 1H), 2.93−2.77 (m, 2H), 2.45 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9 (d, ^2J (CF) = 24.0 Hz), 159.2, 150.4, 141.5, 134.7, 125.9, 119.1, 109.6, 97.0 (d, ^1J (CF) = 238.0 Hz), 32.2, 21.5, 7.08; ^{19}F NMR (377 MHz, $CDCl_3$): δ −163.6; calcd for $C_{12}H_{12}NO_2FSNa$ (M + Na): 276.0470, found (M + Na): 276.0469.

*1-((5-Chlorobenzo[d]oxazol-2-yl)thio)-1-fluorobutan-2-one (**3j**).* Colorless liquid; yield: 73% (50 mg); R_f (5% EtOAc/hexane) 0.3; IR (Neat, cm^{-1}): 1735, 1504, 1450, 1140, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7. 62 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.82 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.96−2.97 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.80 (d, ^2J (CF) = 24.0 Hz), 161.3, 150.7, 142.3, 130.4, 125.1, 119.2, 110.9, 97.0 (d, ^1J (CF) = 239.0 Hz), 32.3, 7.0; ^{19}F NMR (377 MHz, $CDCl_3$): δ −163.9; HRESI-MS (m/z): calcd for $C_{11}H_9NO_2FSClNa$ (M + Na): 295.9924, found (M + Na): 296.0000.

*1-(Benzo[d]thiazol-2-ylthio)-1-fluoropropan-2-one (**3k**).* Colorless liquid; yield: 96% (58 mg); R_f (5% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1743, 1464, 1426, 1358, 1310, 1164; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.1 Hz, J_2 = 2.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.0 Hz, 1H), 7.37 (dd, J_1 = J_2 = 8.0 Hz, 1H), 6.80 (d, ^2J (CH−F) = 50.4 Hz, 1H), 2.465 (d, ^4J (CH_3−F) = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0 (d, ^2J (CF) = 25.4 Hz), 159.5 (d, ^3J (CF) = 2.5 Hz), 152.5, 136.2, 126.5, 125.3, 122.4, 121.2, 97.2 (d, ^1J (CF) = 237.8 Hz), 26.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ −161.8; HRESI-MS (m/z): calcd for $C_{10}H_8NOFS_2$ Na (M + Na): 263.9929, found (M + Na): 263.9928.

*Mixture of 4-(Benzo[d]thiazol-2-ylthio)-4-fluoroheptane-3,5-dione (**2l**) and 1-(Benzo[d]thiazol-2-ylthio)-1-fluorobutan-2-one (**3l**).* Colorless liquid; R_f (5% EtOAc/hexane) 0.2. 4-(Benzo[d]thiazol-2-ylthio)-4-fluoroheptane-3,5-dione (**2l**): yield: 12% (9 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 0.19 H), 7.80 (d, J = 8.0 Hz, 0.19 H), 7.49−7.44 (m, 0.19 H), 7.37 (t, J = 8.0 Hz, 0.19 H), 3.03−2.70 (m, 0.76 H), 1.11 (t, J = 7.2 Hz, 1.14 H); ^{19}F NMR (377 MHz, $CDCl_3$): δ −139.9; ESI-HRMS (m/z): calcd for $C_{14}H_{14}NO_2FS_2Na$ (M + Na): 334.0348, found (M + Na): 334.0348. IR (Neat, cm^{-1}) from the mixture of compounds (**2l** and **3l**): 1733, 1462, 1427, 1310, 1077.

*1-(Benzo[d]thiazol-2-ylthio)-1-fluorobutan-2-one (**3l**).* Yield: 77% (49 mg); R_f (5% EtOAc/hexane) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ. (ppm) 7.93 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.49−7.44 (m, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.82 (d, ^2J (CH−F) = 50.8 Hz, 1H), 2.86−2.80 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1 (d, ^2J (CF) = 24.0 Hz), 159.7, 152.6, 136.1, 126.5, 125.3, 122.4, 121.2, 97.2 (d, ^1J (CF) = 237.8 Hz), 32.2, 7.30; ^{19}F NMR (377 MHz, $CDCl_3$): δ −163.2; ESI-HRMS (m/z): calcd for $C_{11}H_{10}NOFS_2Na$ (M + Na): 278.0086, found (M + Na): 278.0086.

*1-Fluoro-1-((4-methyloxazol-2-yl)thio)propan-2-one (**3m**).* Colorless liquid; yield: 30% (14 mg); R_f (5% EtOAc/hexane) 0.1; IR (Neat, cm^{-1}): 1642, 1499, 1365, 1284, 1156, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 6.46 (d, ^2J (CH−F) = 50.8 Hz, 1H), 2.40 (d, ^4J (CH_3−F) = 3.2 Hz, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.76 (d, ^2J (CF) = 26.0 Hz), 153.5, 138.7, 137.7, 97.2 (d, ^1J (CF) = 239.0 Hz), 26.1, 11.5; ^{19}F NMR (377 MHz, $CDCl_3$): δ −161.2; calcd for $C_7H_8NO_2FSNa$ (M + Na): 212.0157, found (M + Na): 212.0154.

*2-Fluoro-2-((5-methylbenzo[d]oxazol-2-yl)thio)-1-phenylethan-1-one (**3n**).* Colorless liquid; yield: 40% (30 mg); R_f (5% EtOAc/hexane) 0.4; IR (Neat, cm^{-1}): 1699, 1627, 1508, 1447, 1258, 1219, 1020; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.6 Hz, 2H), 7.86 (d, ^2J (CH−F) = 51 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.49 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.60 (d, ^2J (CF) = 22.0 Hz), 159.8, 150.5, 141.5, 134.84 (d, ^3J (CF) = 12.0 Hz), 129.3, 129.3, 129.0, 125.9, 119.2, 109.7, 96.3 (d, ^1J (CF) = 235.0 Hz), 21.5; ^{19}F NMR (377 MHz, $CDCl_3$): δ −160.1; calcd for $C_{16}H_{12}NO_2SFNa$ (M + Na): 324.0470, found (M + Na): 324.0473.

*Experimental Data for the Products (**6a**−**6h**). 1-Fluoro-1-(phenylthio)propan-2-one (**6a**).*[5] Colorless liquid; yield: 88% (81 mg); R_f (5% EtOAc/hexane) 0.5; IR (Neat, cm^{-1}): 1733, 1476, 1438, 1359, 1221, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.53 (m, 2H), 7.39−7.33 (m, 3H), 5.99 (d, ^2J (CH−F) = 52.4 Hz, 1H), 2.123 (d, ^4J (CH_3−F) = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.22 (d, ^2J (CF) = 27.0 Hz), 133.855 (d, ^4J (CF) = 1.0 Hz), 129.3, 129.3, 129.2, 99.38 (d, ^1J (CF) = 235.0 Hz), 26.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −158.7; ESI-HRMS (m/z): calcd for C_9H_9OFSNa (M + Na): 207.0256, found (M + Na): 207.0257.

*1-Fluoro-1-(o-tolylthio)propan-2-one (**6b**).* Colorless liquid; yield: 83% (77 mg); R_f (5% EtOAc/hexane) 0.4; IR (Neat, cm^{-1}); 1730, 1533, 1456, 1355, 1220, 1101, 1049. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 8 Hz, 1 H), 7.32−7.28 (m, 2H), 7.22−7.18 (m, 1H), 5.97 (d, ^2J (CH−F) = 53.2 Hz, 1H), 2.49 (s, 3H), 2.132 (d, ^4J (CH_3−F) = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.76 (d, ^2J (CF) = 27.0 Hz), 141.60, 135.1, 130.8, 129.6, 128.9, 126.8, 99.09 (d, ^1J (CF) = 234.0 Hz), 25.9, 21.0; ^{19}F NMR (377 MHz, $CDCl_3$): δ −158.4; ESI-HRMS (m/z): calcd for $C_{10}H_{11}OFSNa$ (M + Na): 221.0412, found (M + Na): 221.0420.

*1-Fluoro-1-(p-tolylthio)propan-2-one (**6c**).* Colorless liquid; yield: 62% (61 mg) IR (Neat, cm^{-1}): 1723, 1487, 1355, 1323, 1240, 1171, 1023, 955, 806, 724, 621; R_f (5% EtOAc/hexane) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2 H), 7.16 (d, J_1 = 7.6 Hz, 2H), 5.95 (d, ^2J (CH−F) = 52.0 Hz, 1 H), 2.35 (s, 3 H), 2.107 (d, $^4J_1$ (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.54 (d, ^2J (CF) = 26.0 Hz), 139.88, 134.325 (d, ^4J (CF) = 1.0 Hz), 130.12, 125.34, 99.55 (d, ^1J (CF) = 234.0 Hz), 26.17, 21.20; ^{19}F NMR (377 MHz, $CDCl_3$): δ −159.0; ESI-HRMS (m/z): calcd for $C_{10}H_{11}OFSNa$ (M + Na): 221.0412, found (M + Na): 221.0410.

*1-Fluoro-1-(4-methoxythio)propan-2-one (**6d**).* Pale yellow liquid; yield: 65% (70 mg) IR (Neat, cm^{-1}): 1731, 1591, 1494, 1358, 1291, 1249, 1174, 1031; R_f (5% EtOAc/hexane) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.8 Hz, 2 H), 7.87 (d, J = 8.8 Hz, 2 H), 5.90 (d, ^2J (CH−F) = 52 Hz, 1 H), 2.080 (d, ^4J (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.81 (d, ^2J (CF) = 27.0 Hz), 160.9, 136.5, 118.59, 114.9, 99.51 (d, ^1J (CF) = 234.0 Hz), 55.3, 26.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ −159.7; ESI-HRMS (m/z): calcd for $C_{10}H_{11}O_2FSNa$ (M + Na): 237.0361, found (M + Na): 237.0361.

*1-Fluoro-1-((2-fluorophenyl)thio)propan-2-one (**6e**).* Colorless liquid; yield: 92% (92 mg); R_f (5% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1743, 1475, 1359, 1263, 1225, 1042; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dt, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 2 H), 7.42−7.38 (m, 1 H), 7.18−7.12 (m, 2 H), 6.02 (d, ^2J (CH−F) = 51.6 Hz, 1 H), 2.23 (d, ^4J (CH_3−F) = 2.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.54 (d, ^2J (CF) = 25.0 Hz), 162.25 (d, ^1J (CF) = 248.0 Hz), 136.8, 132.0 (d, ^3J (CF) = 8.0 Hz), 124.87 (d, ^4J (CF) = 3.0 Hz), 116.3, 116.1, 115.82 (d, ^2J (CF) = 19.0 Hz), 98.09 (d, ^1J (CF) = 236.0 Hz), 25.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ −160.569 (d, ^5J (F−F coupling) = 1.35 Hz), −106.324 (d, ^5J (F−F coupling) = 1.36 Hz); ESI-HRMS (m/z): calcd for $C_9H_8OF_2SNa$ (M + Na): 225.0162, found (M + Na): 225.0162.

*1-((3-Chlorophenyl)thio)-1-fluoropropan-2-one (**6f**).* Colorless liquid; yield: 78% (85 mg); R_f (5% EtOAc/hexane) 0.25; IR (Neat, cm^{-1}): 1734, 1570, 1462, 1404, 1359, 1223, 1118, 1041; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.53 (m, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.37−7.36 (m, 1 H), 7.30 (d, J = 8 Hz, 1 H), 6.02 (d, ^2J (CH−F) = 52.4 Hz, 1 H), 2.181 (d, ^4J (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.82 (d, ^2J (CF) = 26.0 Hz), 134.9, 133.215 (d, ^4J (CF) = 1.0 Hz), 131.7, 131.3, 130.4, 129.6, 99.21 (d, ^1J (CF) = 236.0 Hz), 26.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ −158.8; ESI-HRMS (m/z): calcd for $C_9H_8OFClSNa$ (M + Na): 240.9869, found (M + Na): 240.9866.

*1-((4-Chlorophenyl)thio)-1-fluoropropan-2-one (**6g**).* Pale yellow liquid; yield: 88% (96 mg); R_f (5% EtOAc/hexane) 0.5; IR (Neat, cm^{-1}): 1733, 1476, 1358, 1222, 1094; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 5.99 (d, ^2J (CH−F) = 52 Hz, 1 H), 2.144 (d, ^4J (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 198.88 (d, ^2J (CF) = 26.0 Hz), 136.0, 135.24 (d, ^4J (CF) = 2.0 Hz), 129.5, 127.5, 99.10 (d, ^1J (CF) = 235.0 Hz), 26.07; ^{19}F NMR (377 MHz, $CDCl_3$): δ −159.3; ESI-HRMS (*m*/*z*): calcd for $C_9H_8OFClSNa$ (M + Na): 240.9865, found (M + Na): 240.9866.

1-((4-Bromophenyl)thio)-1-fluoropropan-2-one (**6h**). Colorless yellow liquid; yield: 87% (75 mg); R_f (5% EtOAc/hexane) 0.4; IR (Neat, cm^{-1}): 2929, 1726, 1560, 1462, 1354, 1238, 1166, 1035; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, $J_1 = J_2 = 7.6$ Hz, 2 H), 7.46 (dd, J_1 = 8.4 Hz, J_2 = 2.0, 2 H), 5.99 (d, ^2J (CH−F) = 52 Hz, 1 H), 2.142 (d, ^4J (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.93 (d, ^2J (CF) = 26.0 Hz), 135.42 (d, ^4J (CF) = 2.0 Hz), 132.5, 128.2, 124.2, 99.02 (d, ^1J (CF) = 235.0 Hz), 26.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ −159.2; ESI-HRMS (*m*/*z*): calcd for $C_9H_8OFBrSNa$ (M + Na): 284.9362, found (M + Na): 284.9361.

1-Fluoro-1-(naphthalen-1-ylthio)propan-2-one (**6i**). Colorless liquid; yield: 82% (96 mg); R_f (3% EtOAc/hexane) 0.4; IR (Neat, cm^{-1}): 1737, 1586, 1499, 1420, 1357, 1223, 1040, 952; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.84−7.80 (m, 3 H), 7.57 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1 H), 7.54−7.50 (m, 2 H), 6.06 (d, ^2J (CH−F) = 52 Hz, 1H), 2.135 (d, ^4J (CH_3−F) = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.37 (d, ^2J (CF) = 26.0 Hz), 133.67 (d, ^4J (CF) = 2.0 Hz), 133.4, 133.2, 133.265 (d, ^4J (CF) = 1.0 Hz), 129.1, 127.8, 127.7, 127.2, 126.9, 126.6, 99.76 (d, ^1J (CF) = 235.0 Hz), 26.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ −158.5; ESI-HRMS (*m*/*z*): calcd for $C_{13}H_{11}OFSNa$ (M + Na): 257.0412, found (M + Na): 257.0414.

1-Fluoro-1-(phenylsulfonyl)propan-2-one (7a).[9b] Colorless liquid; yield: 96% (104 mg); R_f (30% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1739, 1448, 1335, 1214, 1153, 1076; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 2H), 5.50 (d, ^2J (CH−F) = 48.8 Hz, 1H), 2.323 (d, ^4J (CH_3−F) = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.51 (d, ^2J (CF) = 21.0 Hz), 135.3, 134.7, 129.50, 129.47, 101.26 (d, ^1J (CF) = 233.0 Hz), 27.42; ^{19}F NMR (377 MHz, $CDCl_3$): δ −179.7; ESI-HRMS (*m*/*z*): calcd for $C_9H_9O_3FSNa$ (M + Na): 239.0154, found (M + Na): 239.0155.

3-Fluoro-3-(phenylthio)hex-5-en-2-one (**8a**). Colorless liquid; yield: 72% (81 mg), yield: 62% (based on recovery of starting material), R_f (5% EtOAc/hexane) 0.8; IR (Neat, cm^{-1}); 1728, 1642, 1434, 1355, 1099, 1021, 996; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56−7.41 (m, 2H), 7.407−7.32 (m, 3H), 5.84−5.74 (m, 1H), 5.21 (s, 1H), 5.178 (d, *J* = 4.8 Hz, 1H), 2.95−2.76 (m, 2H), 1.853 (d, ^4J (CH_3−F) = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.59 (d, ^2J (CF) = 33.0 Hz), 136.2, 129.8, 129.555 (d, ^3J (CF) = 3.0 Hz), 129.2, 128.1, 120.7, 108.09 (d, ^1J (CF) = 235.0 Hz), 41.10 (d, ^2J (CF) = 22.0 Hz), 27.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ −136.3; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{13}OFSNa$ (M + Na): 247.0569, found (M + Na): 247.0568.

3-Fluoro-4-phenyl-3-(phenylthio)butan-2-one (**8b**). Colorless liquid; yield: 81% (112 mg), R_f (3% EtOAc/hexane) 0.5; IR (Neat, cm^{-1}); 1726, 1493, 1476, 1441, 1354, 1184, 1085, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.41−7.32 (m, 3H), 7.31−7.16 (m, 5H), 3.48 (dd, $^3J_1$ (CH−F) = 28.0 Hz, dd, $^2J_2$ (CH−H) = 14.0 Hz, 1H), 3.35 (dd, $^3J_1$ (CH−F) = 29 Hz, $^2J_2$ (CH−H) = 14.4 Hz, 1H), 1.60 (d, ^4J (CH_3−F) = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.74 (d, ^2J (CF) = 34.0 Hz), 136.4, 133.4, 130.5, 129.7, 129.2, 128.4, 128.1, 127.4, 108.60 (d, ^1J (CF) = 237.0 Hz), 42.70 (d, ^3J (CF) = 22.0 Hz), 27.7; ^{19}F NMR (377 MHz, $CDCl_3$): δ −135.4; ESI-HRMS (*m*/*z*): calcd for $C_{16}H_{15}OFSNa$ (M + Na): 297.0725, found (M + Na): 297.0720.

3-Fluoro-3-(phenylsulfonyl)hex-5-en-2-one (**9a**). Colorless liquid; yield: 73% (67 mg); R_f (20% EtOAc/hexane) 0.2; IR (Neat, cm^{-1}): 1732, 1629, 1448, 1334, 1158; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 5.55−5.45 (m, 1H), 5.14 (s, 1H), 5.112 (d, *J* = 2.8 Hz, 1H), 2.74−2.66 (m, 2H), 2.047 (d, ^4J (CH_3−F) = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.80 (d, ^2J (CF) = 27.0 Hz), 135.2, 134.1, 130.4, 129.3, 126.955 (d, ^3J (CF) = 3.0 Hz), 122.4, 109.68 (d, ^1J (CF) = 233.0 Hz), 35.13 (d, ^2J (CF) = 20.0 Hz), 27.8; ^{19}F NMR (377 MHz, $CDCl_3$): δ −159.5; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{13}O_3FSNa$ (M + Na): 279.0467, found (M + Na): 279.0466.

3-Fluoro-4-phenyl-3-(phenylsulfonyl)butan-2-one (**9b**). White solid; mp: 78−80 °C; yield: 68% (83 mg); R_f (20% EtOAc/hexane) 0.5; IR (Neat, cm^{-1}): 1730, 1627, 1449, 1333, 1158; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 3.76 (dd, $^3J_1$ (CH−F) = 40.0 Hz, dd, $^2J_2$ (CH−H) = 14.2 Hz, 1H), 3.336 (dd, $^3J_1$ (CH−F) = 14.2 Hz, $^2J_2$ (CH−H) = 10.4 Hz, 1H), 1.74 (d, ^4J (CH_3−F) = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.62 (d, ^2J (CF) = 28.0 Hz), 135.2, 134.4, 130.9, 130.5, 130.4, 129.3, 128.7, 127.8, 109.99 (d, ^1J (CF) = 234.0 Hz), 36.59 (d, ^3J (CF) = 18 Hz), 28.0; ^{19}F NMR (377 MHz, $CDCl_3$): δ −157.7; ESI-HRMS (*m*/*z*): calcd for $C_{16}H_{15}O_3FSNa$ (M + Na): 329.0624, found (M + Na): 329.0622.

3-Benzyl-3-fluoropentane-2,4-dione (**11a**). Colorless liquid; yield: 42% (22 mg); R_f (5% EtOAc/hexane) 0.5; IR (Neat, cm^{-1}): 1745, 1716, 1421, 1357, 1190, 1118, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.25 (m, 3H), 7.18 (d, *J* = 7.2 Hz, 2H), 3.34 (d, ^3J (CH_2−F) = 25.6 Hz, 2H), 2.122 (d, ^4J (CH_3 −F) = 5.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.67 (d, ^2J (CF) = 27.0 Hz), 132.9, 130.3, 128.5, 127.5, 106.26 (d, ^1J (CF) = 199.0 Hz), 40.21 (d, ^2J (CF) = 21.0 Hz), 26.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ −164.8; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{13}O_2FNa$ (M + Na): 231.0797, found (M + Na): 231.0795.

Cesium Salt of Bis(phenylsulfonyl)amide (**13b**). White solid; mp: 208−210 °C; yield: 99% (106 mg); ^{1}H NMR (400 MHz, D_2O): δ 7.59 (d, *J* = 8 Hz, 4H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 104.8, 132.3, 128.8, 126.0.

Experimental Data for the Compounds **5** *and* **6**, *when reaction was performed in EtOAc (see the Supporting Information SI 3 and SI 4). 3-Fluoro-3-(phenylthio)pentane-2,4-dione* (**5a**). Yield: 6% (8 mg: according to the ratio between **5a** and **6a** found by ^{1}H NMR); only the distinguishable ^{1}H NMR and ^{13}C NMR peaks of **5a** are given. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.217 (d, ^4J (CH_3−F) = 3.2 Hz, 0.45 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5; ^{19}F NMR (377 MHz, $CDCl_3$): δ −136.9; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{11}O_2FSNa$ (M + Na): 249.0361, found (M + Na): 249.0363.

1-Fluoro-1-(phenylthio)propan-2-one (**6a**). Yield: 91% (85 mg: according to the ratio between **5a** and **6a** found by ^{1}H NMR).

3-Fluoro-3-(o-tolylthio)pentane-2,4-dione (**5b**). Yield: 19% (23 mg: according to the ratio between **5b** and **6b** found by ^{1}H NMR); only the distinguishable ^{1}H and ^{13}C NMR peaks of **5b** are given. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 0.95 H), 2.176 (d, ^4J (CF) = 1.8 Hz, 1.76H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.50 (d, ^2J (CH_3−F) = 29.0 Hz), 143.2, 131.0, 130.5, 126. 8, 126.0, 109.66 (d, ^1J (CF) = 244.0 Hz), 26.5, 21.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ −136.8; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{13}O_2$ FSNa (M + Na): 263.0518, found (M + Na): 263.0516.

1-Fluoro-1-(o-tolylthio)propan-2-one (**6b**). Yield: 73% (72 mg: according to the ratio between **5b** and **6b** found by ^{1}H NMR).

3-Fluoro-3-(p-tolylthio)pentane-2,4-dione (**5c**). Yield: 26% (31 mg: according to the ratio between **5c** and **6c** found by ^{1}H NMR); only the distinguishable ^{1}H and ^{13}C NMR peaks of **5c** are given. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (d, ^4J (CH_3−F) = 3.6 Hz, 1.33 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5; ESI-HRMS (*m*/*z*): calcd for $C_{12}H_{13}O_2$ FSNa (M + Na): 263.0518, found (M + Na): 263.0520.

1-Fluoro-1-(p-tolylthio)propan-2-one (**6c**). Yield: 70% (69.7 mg: according to the ratio between **5c** and **6c** found by ^{1}H NMR).

3-((4-Bromophenyl)thio)-3-fluoropentane-2,4-dione (**5h**). Yield: 22% (34 mg: according to the ratio between 5h and 6h found by ^{1}H NMR); Only the distinguishable ^{1}H and ^{13}C NMR peaks of **5h** are given. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (d, ^4J (CH_3−F) = 3.2 Hz, 2.40 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4; ^{19}F NMR (377 MHz, $CDCl_3$): δ; −137.3; ESI-HRMS (*m*/*z*): calcd for $C_{11}H_{10}O_2FSBrNa$ (M + Na): 326.9467, found (M + Na): 326.9471.

1-((4-Bromophenyl)thio)-1-fluoropropan-2-one (**6h**). Yield: 67% (87 mg: according to the ratio between **5h** and **6h** found by ^{1}H NMR).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01547.

^{1}H and ^{13}C spectra for all compounds are available (PDF)

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REFERENCES

(1) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. For medicinal and biological application, see (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Gremany, 2004. (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004. (f) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, 2009. For application in material science, see. (g) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847 and references therein..

(2) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceñ a, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. and references therein. (b) Kraemer, W.; Schirmer, U.; Jeschke, P.; Witschel, M. *Modern Crop Protection Compounds*, 2nd ed.; Wiley & Sons: Weinheim, 2012, Vol *1*−*3*. (c) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V. *Chem. Rev.* **2015**, *115*, 973.

(3) (a) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. *J. Org. Chem.* **2015**, *80*, 12137. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (c) Lázaro, R.; Román, R.; Sedgwick, D. M.; Haufe, G.; Barrio, P.; Fustero, S. *Org. Lett.* **2016**, *18*, 948. (d) Ilchenko, N. O.; Cortes, M. A.; Szabo, K. J. *ACS Catal.* **2016**, *6*, 447. and references therein. (e) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219. (f) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943.

(4) (a) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. and references therein. (b) Hara, S.; Monoi, M.; Umemura, R.; Fuse, C. *Tetrahedron* **2012**, *68*, 10145. (c) Loghmani-Khouzani, H.; Poorheravi, M. R.; Sadeghi, M. M.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 7419. (d) Loghmani-Khouzani, H.; Hajiheidari, D. *J. Fluorine Chem.* **2010**, *131*, 561.

(5) (a) Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6074. (b) Fuchigami, T.; Shimojo, M.; Konno, A. *J. Org. Chem.* **1995**, *3459*, 3459. (c) Dawood, K. M.; Higashiya, S.; Hou, Y.; Fuchigami, T. *J. Fluorine Chem.* **1999**, *93*, 159.

(6) (a) McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. *J. Am. Chem. Soc.* **1985**, *107*, 735. (b) Larnaud, F.; Pfund, E; Linclau, B.; Lequeux, T. *Tetrahedron* **2014**, *70*, 5632. (c) Jacobsen, C. B.; Nielsen, M.; Worgull, D.; Zweifel, T.; Fisker, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 7398. For a few examples of deacylation, see (d) Gao, W.-C.; Zhao, J.-J.; Hu, F.; Chang, H.-H.; Li, X.; Wei, W.-L. *RSC Adv.* **2015**, *5*, 25222. (e) Aoyama, T.; Kubota, S.; Takido, T.; Kodomari, M. *Chem. Lett.* **2011**, *40*, 484−485. (f) Gao, Q.; Zhu, Y.; Lian, M.; Liu, M.; Yuan, J.; Yin, G.; Wu, A. *J. Org. Chem.* **2012**, *77*, 9865. (g) Qian, J.; Yi, W.; Lv, M.; Cai, C. *Synlett* **2014**, *26*, 127. (h) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802. (i) Xie, C.; Zhang, L.; Sha, W.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Lett.* **2016**, *18*, 3270. (j) Zhang, P.; Wolf, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7869. (k) Leng, D. J.; Black, C. M.; Pattison, G. *Org. Biomol. Chem.* **2016**, *14*, 1531.

(7) (a) Varun, B. V.; Gadde, K.; Prabhu, K. R. *Org. Lett.* **2015**, *17*, 2944. and references therein. (b) Ogura, K.; Sanada, K.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1982**, *23*, 4035. (c) Zou, L.-H.; Priebbenow, D. L.; Wang, L.; Mottweiler, J.; Bolm, C. *Adv. Synth. Catal.* **2013**, *355*, 2558. (d) He, C.; Guo, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273. (e) Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* **1987**, *28*, 5505.

(8) (a) The products **3p** and **3q** seem to be low boiling liquids such as starting materials; hence, the isolation was not successful for small scale synthesis.. (b) While *m*-CPBA is a widely used reagent for the oxidation of sulfides, our attempts to oxidize the α-fluoro-β-ketosulfones **3a** or **3k** were not successful using *m*-CPBA as the oxidant. However, the methodology for oxidation of the α-fluoro-β-ketosulfides containing heteroaryl moiety is already disclosed with various other oxidizing agents (ref 6b and 6c).

(9) (a) Varun, B. V.; Gadde, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2016**, *14*, 7665. (b) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2009**, *74*, 3767. and references therein. (c) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. and references therein (d) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532. and references therein. (e) Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736.

(10) (a) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689. (b) Zajc, B.; Kake, S. *Org. Lett.* **2006**, *8*, 4457. (c) Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553. (d) Alonso, D. A.; Fuensanta, M.; Gomez-Bengoa, E.; Ná jera, C. *Adv. Synth. Catal.* **2008**, *350*, 1823.

(11) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press: Oxford, 2012 (c) Bernasconi, C. F.; Kittredge, K. W. *J. Org. Chem.* **1998**, *63*, 1944.

(12) Varun, B. V.; Prabhu, K. R. *J. Org. Chem.* **2014**, *79*, 9655.

(13) Yoshida, Z.; Ogoshi, H.; Tokumitsu, T. *Tetrahedron* **1970**, *26*, 2987.

(14) Rashid, M. A.; Rasool, N.; Adeel, M.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 3782.

(15) Liu, Yi-W.; Badsara, S. S.; Liu, Yi-C.; Lee, C-Fa. *RSC Adv.* **2015**, *5*, 44299.

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