A Facile and Mild Approach for Stereoselective Synthesis of α-Fluoro-α,β-unsaturated Esters from α-Fluoro-β-keto Esters via Deacylation

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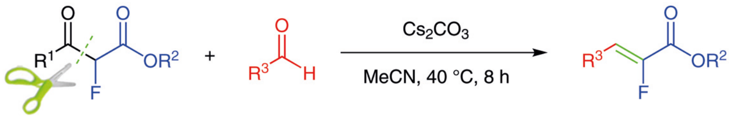


- mild reaction conditions
- high yield and stereoselectivity
- simple material

18 examples
Z/E up to 99:1

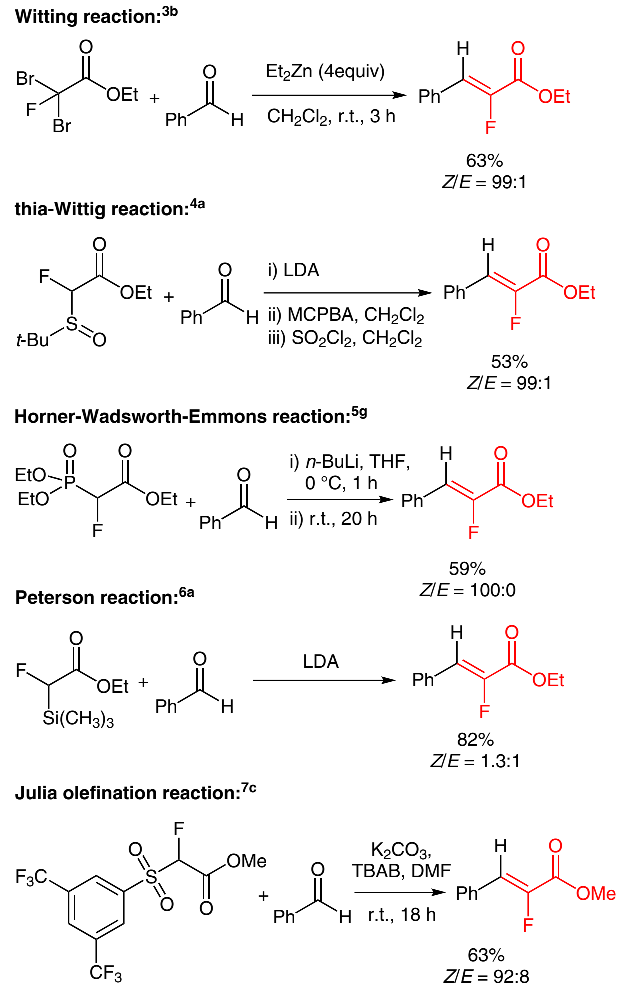
Received: 02.08.2014
Accepted after revision: 09.10.2014

DOI: 10.1055/s-0034-1378917; Art ID: st-2014-w0647-l

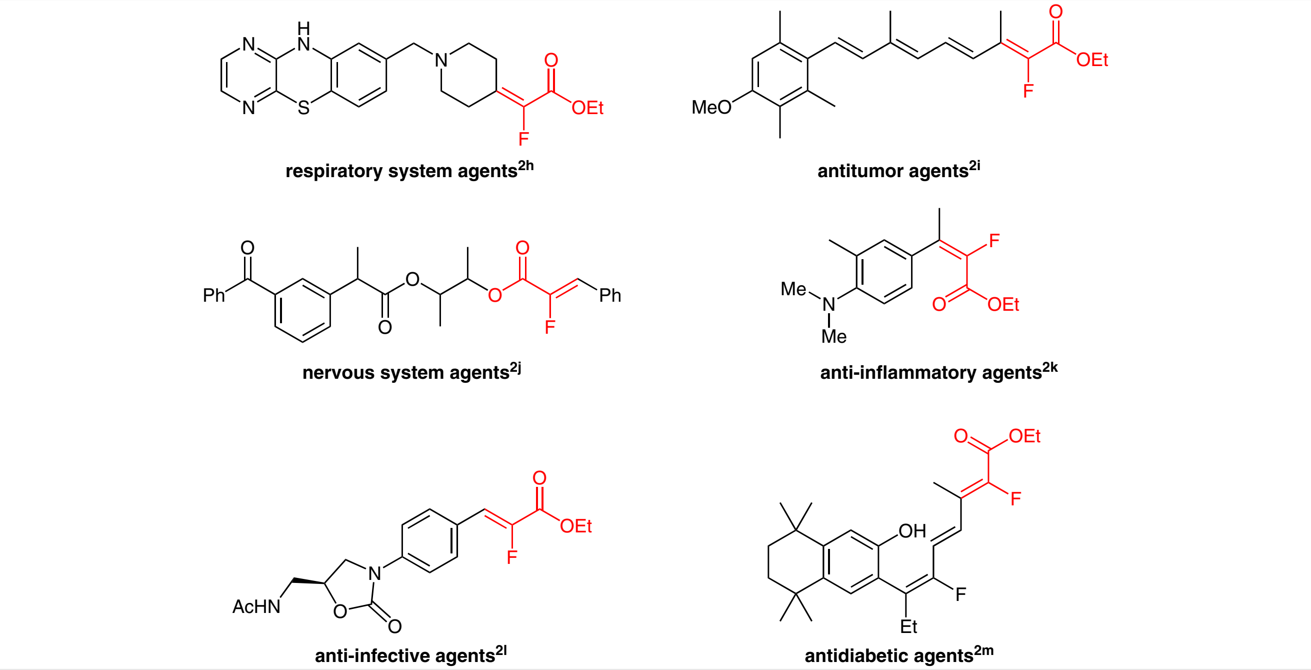
Abstract The highly stereoselective olefination reaction of α-fluoro-β-keto esters for the synthesis of α-fluoro-α,β-unsaturated esters has been developed. The olefination combines nucleophilic addition, intramolecular nucleophilic addition, and elimination in one step, as well as provides a facile synthetic approach to α-fluoro-α,β-unsaturated esters which are important units in many biologically active compounds and useful precursors in a variety of functional-group transformations.

Key words olefination, highly stereoselective, deacylation, fluoro-olefins, carbon–carbon bond cleavage

Organofluorine compounds have experienced considerable growth in academic interest in recent years due to their growing importance in drug development purposes and crop protection.[1] In particular, α-fluoro-α,β-unsaturated esters are well known as precursors to biologically active compounds and have been successfully used to prepare a new generation of modified pheromones, herbicides, and medicines[2] (selected bioactive structures are shown in Figure 1). The traditional approaches for the preparation of these compounds are based on the Wittig,[3] thia-Wittig,[4] Horner–Wadsworth–Emmons (HWE),[5] Peterson,[6] or fluorous Julia[7] olefination reactions (Scheme 1). Most of these procedures generally suffer from several major drawbacks including the requirement of metal catalysts,[3] harsh reaction conditions,[4,5] low selectivity,[6] and the use of expensive or complex starting materials.[5–8]



Scheme 1 Traditional approach for the preparation of α-fluoro-α,β-unsaturated esters



respiratory system agents[2h]

antitumor agents[2i]

nervous system agents[2j]

anti-inflammatory agents[2k]

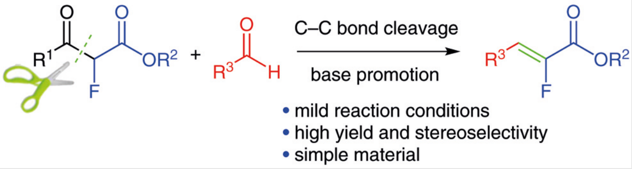
anti-infective agents[2l]

antidiabetic agents[2m]

Figure 1 Selected bioactive structures

Owing to the stability of carbon–carbon bonds, their cleavage has long remained a great challenge for organic chemists.[9] Decarboxylation[10b,c] and deacylation[10a,d] are two types of the most prevailing methods to fulfill this purpose because of their efficiency informing reactive intermediates that successively promote the bond cleavage under mild conditions.[10] The descriptions of this potentially useful and versatile molecule for the synthesis of α-functionalized α,β-unsaturated carbonyl compounds date back to 1978, in which Tsuboi's group reported the synthesis of 5,5,5-trichloro-3-penten-2-one by the reaction of chloral with 2,4-pentanedione via deacylation process.[11] In 2004, they continuously developed this method for the synthesis of α-chloro-α,β-unsaturated esters by the reaction of chlorinated ethyl acetoacetates with aldehydes.[12]

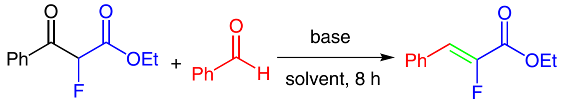
Along this line, we herein reported the first example of the synthesis of α-fluoro-α,β-unsaturated esters from α-fluoro-β-keto esters and aldehydes through deacylation process (Scheme 2). This process successfully combines nucleophilic addition, intramolecular nucleophilic addition, and elimination in one step. This protocol also provides a practical, simple, and mild synthetic approach to α-fluoro-α,β-unsaturated carbonyl compounds.



Scheme 2 Reaction of α-fluoro-β-keto esters with aldehydes

The starting material ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**1a**) was easily prepared by stirring the corresponding β-keto ester with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor$^{\text{TM}}$) according to the literature procedure.[13] Our initial study on olefination study started with the reaction of **1a** and benzaldehyde (**2a**). A variety of parameters was summarized in Table 1. With regard to the influence of reaction temperature, it was found that the yield of the product **3aa** increased from 56% at room temperature (Table 1, entry 1) to 80% at 40 °C (Table 1, entry 4) by using cesium carbonate as the base, whereas the yield had a significant reduction when the reaction conducted at 60 °C and 80 °C (Table 1, entries 2 and 3). Beside the cesium carbonate, other cesium salts (CsF and CsOAc) were tested, but only low efficiency were obtained (Table 1, entries 5 and 6). The reaction did not work in the presence of Na$_2$CO$_3$, NaOH, KOH, or KO*t*-Bu (Table 1, entries 7–13). Further studies indicated that the superior result was available by using acetonitrile compared with other solvents (Table 1, entries 4, 14–19). Based on the ^{1}H NMR data and comparison with the reported experimental data,[3b,e] it was to our delight that a high ratio (up to 99:1) of *Z* stereoisomer was identified.

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3aa**

Entry	Base	Solvent	Temp (°C)	Yield (%)[b]	Z/E[c]
1[d]	Cs_2CO_3	MeCN	r.t.	56	97:3
2	Cs_2CO_3	MeCN	60	64	95:5
3	Cs_2CO_3	MeCN	80	39	95:5
4	Cs_2CO_3	MeCN	40	80	96:4
5	CsF	MeCN	40	24	95:5
6	CsOAc	MeCN	40	5[e]	–
7	Na_2CO_3	MeCN	40	7[e]	–
8	K_2CO_3	MeCN	40	20	91:9
9	NaOH	MeCN	40	0	–
10	KOH	MeCN	40	0	–
11	Et_3N	MeCN	40	0	–
12	pyridine	MeCN	40	0	–
13	KO*t*-Bu	MeCN	40	0	–
14	Cs_2CO_3	THF	40	62	96:4
15	Cs_2CO_3	dioxane	40	45	99:1
16	Cs_2CO_3	$CHCl_3$	40	56	96:4
17	Cs_2CO_3	DMF	40	31	97:3
18	Cs_2CO_3	DMSO	40	25	99:1
19	Cs_2CO_3	toluene	40	60	99:1

[a] Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), base (1 mmol).
[b] Isolated yields.
[c] Relative ratio of the crude determined by ^{1}H NMR spectroscopy.
[d] Reaction for 48 h.
[e] GC yield based on **2a**.

With a set of optimized conditions in hand, the scope of α-fluoro-β-keto esters **1** and aldehydes **2** were investigated (Table 2).[14] The reactions of α-fluoro-β-keto esters with aryl aldehydes bearing electron-withdrawing substituents (Table 2, entries 4–10) was more effective than electron-donating ones (Table 2, entries 2 and 3), and could be smoothly transformed into the desired products in excellent yields. Aromatic aldehydes with substituents at different positions of the aryl ring (*para*, *meta*, and *ortho* position) reacted well under the standard conditions (Table 2, entries 8–10). In addition, 1-naphthaldehyde, furfural, 2-thienaldehyde, and 2-pyridinecarboxaldehyde had good yields in this transformation, generating **3am**, **3ak**, **3ao** and **3ap** in 81%, 77%, 75%, and 93% yield, respectively (Table 2, entries 11–14). Alkyl aldehydes also worked well in high yields (Table 2, entries 15 and 16). α-Fluoro-β-keto esters derivates **1b–d** produced the corresponding α-fluoro-α,β-unsaturated esters in moderate to high yields (Table 2, entries 17–20), and indicated that electron-withdrawing substituents make deacylation proceed slightly more efficiently [NO_2/H/OMe = 87:80:63 (%)]. More economical α-fluoro-β-keto ester **1e** gave poor yields in the reaction (Table 2, entries 21, 22). It should be noteworthy that the *Z*/*E* ratios of this transformation are extremely high. X-ray crystal-structure analysis confirmed the structure and selectivity of product **3ag** (Figure 2).

Table 2 High Stereoselective Olefination Reactions of Different α-Fluoro-β-keto Esters **1** with Different Aldehydes **2**[a]

1 **2** **3**

Entry	R1	R2	R3	Yield (%)[b]	Z/E[c]
1	**1a** Ph	Et	**2a** Ph	**3aa** 80	96:4
2	**1a** Ph	Et	**2b** 4-MeC_6H_4	**3ab** 50	93:7
3	**1a** Ph	Et	**2c** 4-$Me_3OC_6H_4$	**3ac** 54	94:6
4	**1a** Ph	Et	**2d** 4-ClC_6H_4	**3ad** 87	97:3
5	**1a** Ph	Et	**2e** 4-BrC_6H_4	**3ae** 86	98:2
6	**1a** Ph	Et	**2f** 4-FC_6H_4	**3af** 89	98:2
7	**1a** Ph	Et	**2g** 4-$F_3CC_6H_4$	**3ag** 94	99:1
8	**1a** Ph	Et	**2h** 4-$O_2NC_6H_4$	**3ah** 92	99:1
9	**1a** Ph	Et	**2i** 2-$O_2NC_6H_4$	**3ai** 88	97:3
10	**1a** Ph	Et	**2j** 3-$O_2NC_6H_4$	**3aj** 85	99:1
11	**1a** Ph	Et	**2k** 2-furfuryl	**3ak** 77	94:6
12	**1a** Ph	Et	**2l** 1-naphthyl	**3al** 81	96:4
13	**1a** Ph	Et	**2m** 2-thienyl	**3am** 75	94:6
14	**1a** Ph	Et	**2n** 2-pyridyl	**3an** 93	96:4
15	**1a** Ph	Et	**2o** $PhCH_2CH_2$	**3ao** 95	95:5
16	**1a** Ph	Et	**2p** cyclohexyl	**3ap** 87	93:7
17	**1b** 4-C_6H_4	Et	**2a** Ph	**3aa** 63	94:6
18	**1c** 4-$O_2NC_6H_4$	Et	**2a** Ph	**3aa** 87	99:1
19	**1d** 4-FC_6H_4	Me	**2h** 4-$O_2NC_6H_4$	**3dh** 82	99:1
20	**1d** 4-FC_6H_4	Me	**2g** 4-$F_3CC_6H_4$	**3dg** 84	99:1
21	**1e** Me	Et	**2a** Ph	**3aa** 21	93:7
22	**1e** Me	Et	**2g** 4-$F_3CC_6H_4$	**3ag** 34	95:5

[a] Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), Cs_2CO_3 (1.0 mmol).
[b] Isolated yields.
[c] Relative ratio of the crude determined by ^{1}H NMR spectroscopy.

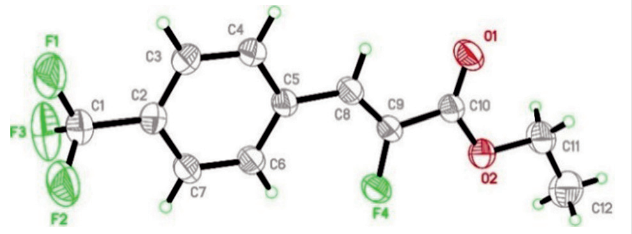
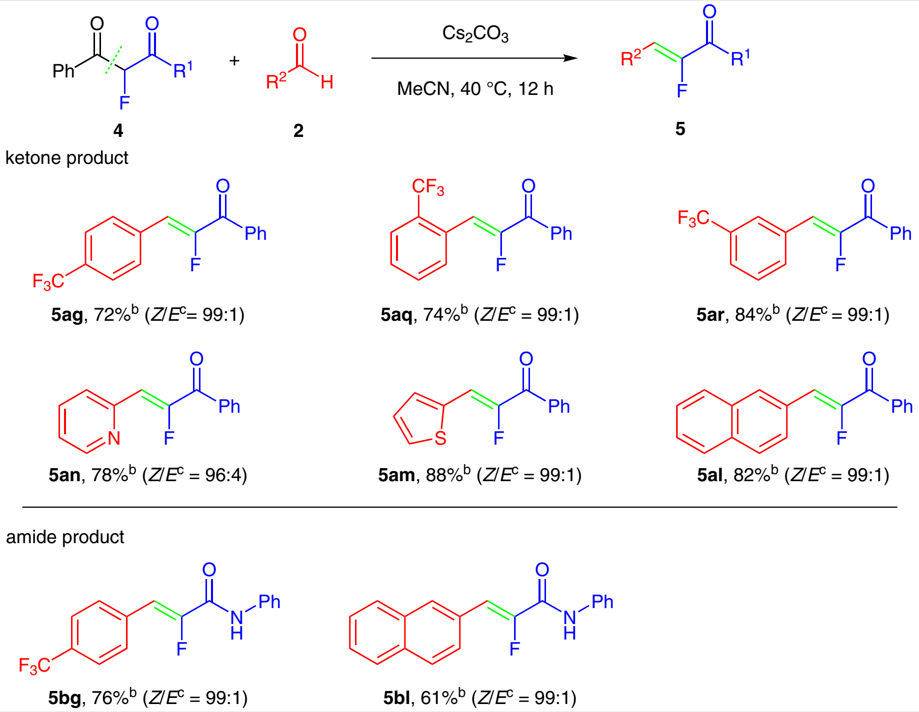


Figure 2 X-ray structure of compound **3ag** (CCDC 970020)

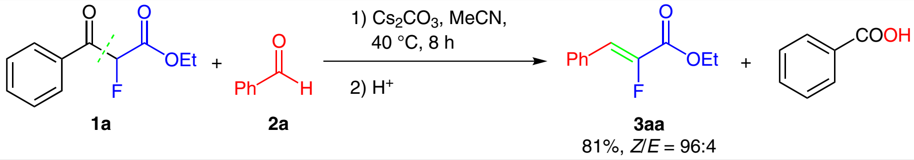
We thought it could be possible to perform deacylation to produce α-fluoro-α,β-unsaturated ketones and amides. It was found that deacylation could be easily achieved by the same method using 2-fluoro-1,3-dione and α-fluoro-β-keto amide compounds (Scheme 3). Thus, reactions of 2-fluoro-1,3-diphenylpropane-1,3-dione (**4a**) or 2-fluoro-3-oxo-*N*,3-diphenylpropanamide (**4b**) with benzaldehydes **2** gave olefination products in 61–88% yields with extremely high *Z*/*E* ratios.

These olefination reactions can be conducted without using Schlenk technique on a larger scale. The olefination of fluorous benzoylacetate **1a** with benzaldehyde (**2a**) on a two-gram scale occurred in a high yield (81%) similar to that of the reaction conducted on a smaller scale (Scheme 4). The benzoic acid was collected for experimental use. Thus, these reactions should be practical for a number of applications in medicinal chemistry.

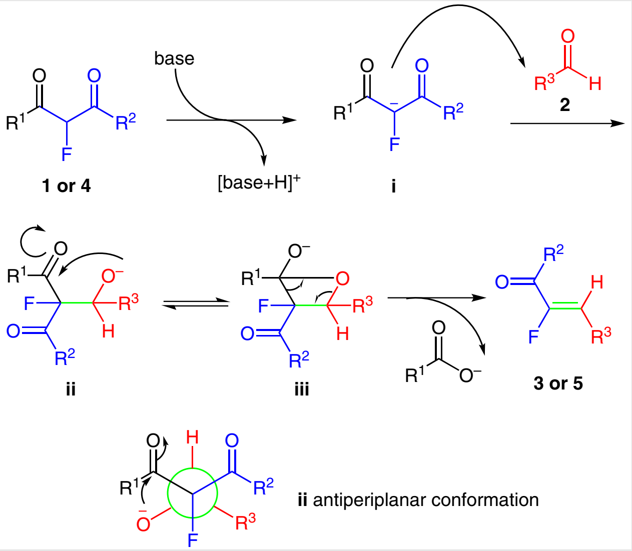
According to the reported literature[11] and experimental points a possible mechanism for this transformation is proposed in Scheme 5, in which Cs_2CO_3 plays an important role as a promoter of nucleophilic addition. Weak bases could not make nucleophilic addition happen. Strong base make the product decompose into (*Z*)-2-fluoro-3-phenylacrylic acid (see the Supporting Information). An intramolecular nucleophilic addition of intermediates **ii** preferentially adopts an antiperiplanar conformation, which is much more thermodynamicly and kineticly stable than its other conformation, and forms a four-membered-ring transition



Scheme 3 Highly stereoselective olefination reaction of α-fluoro-α,β-unsaturated ketone and amide with different aldehydes **2**.[a] [a] **4** (0.55 mmol), **2** (0.5 mmol), Cs_2CO_3 (1 mmol). [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy.



Scheme 4 Highly stereoselective olefination on gram scale



Scheme 5 Proposed mechanism

state **iii**. The final elimination of unstable transition state **iii** produces the designed product **3**.

In conclusion, a highly stereoselective olefination reaction of α-fluoro-β-keto esters for the synthesis of α-fluoro-α,β-unsaturated esters has been developed. This method provides a practical, simple, and mild synthetic approach to α-fluoro-α,β-unsaturated esters, which are important units in biologically active molecules. The protocol was also used to prepare α-fluoro-α,β-unsaturated ketones and amides. The high stereoselectivity and excellent yields makes this transformation very efficient and practical. Further studies to extend the synthetic applications for fluorinated compound are ongoing in our group.

Acknowledgment

We thank the Fundamental Research Funds for the Central Universities (30920130111002), National Natural Science Foundation of China (21476116), and Natural Science Foundation of Jiangsu (BK20141394). We also thank the Center for Advanced Materials and Technology for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378917.

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(14) **Typical Experimental Procedure for the Fluoroolefins**
The reaction mixture of fluorinated substrates (0.55 mmol), aldehyde (0.5 mmol), Cs$_2$CO$_3$ (1 mmol) and MeCN (1.5 mL) was stirred at 40 °C for the indicated time until complete consumption of the starting material, which was monitored by TLC analysis (6–12 h). The solvents were removed by rotary evaporation to provide raw products. The residue was then chromatographed on silica gel (eluent: hexane–EtOAc), affording the desired fluoroolefins.

Ethyl (*Z*)-2-Fluoro-3-phenylacrylate (3aa)
Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.64 (d, *J* = 6.8 Hz, 2 H), 7.43–7.35 (m, 3 H), 6.92 (d, *J* = 35.2 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (470 MHz, CDCl$_3$): δ = –125.31 (s). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 160.45 (d, *J* = 34.3 Hz), 146.07 (d, *J* = 267.5 Hz), 130.20 (s), 129.30 (d, *J* = 7.2 Hz), 128.68 (s), 127.82 (s), 116.48 (s), 60.89 (s), 13.23 (s). MS (EI): *m/z* = 194.12 [M$^+$].

(*Z*)-2-Fluoro-1-phenyl-3-[2-(trifluoromethyl)phenyl]prop-2-en-1-one (5ar)
Colorless solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.03 (d, *J* = 7.9 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 2 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.63 (t, *J* = 7.5 Hz, 2 H), 7.56–7.47 (m, 3 H), 7.19 (d, *J* = 33.6 Hz, 1 H). ^{19}F NMR (470 MHz, CDCl$_3$): δ = –59.57 (s), –118.61 (s). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 187.69 (d, *J* = 28.3 Hz), 154.69 (d, *J* = 276.2 Hz), 135.67 (s), 133.32 (s), 132.07 (s), 131.51 (d, *J* = 12.1 Hz), 129.47 (d, *J* = 3.6 Hz), 129.32 (s), 129.11 (s), 128.59 (s), 126.22 (q, *J* = 5.5 Hz), 124.96 (s), 122.79 (s), 115.25 (s). MS (EI): *m/z* = 294.15 [M$^+$].

(*Z*)-2-Fluoro-*N*-phenyl-3-[4-(trifluoromethyl)phenyl]acrylamide (5bg)
Colorless solid. ^{1}H NMR (500 MHz, DMSO): δ = 10.47 (s, 1 H), 7.90 (d, *J* = 8.2 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.74 (d, *J* = 7.7 Hz, 2 H), 7.35 (t, *J* = 7.9 Hz, 2 H), 7.20–7.07 (m, 2 H). ^{19}F NMR (470 MHz, DMSO): δ = –61.30 (s), –121.52 (s). ^{13}C NMR (126 MHz, DMSO): δ = 157.26 (d, *J* = 29.8 Hz), 50.89 (d, *J* = 281.5 Hz), 137.26 (s), 134.70 (s), 129.89 (d, *J* = 6.0 Hz), 128.52 (d, *J* = 32.1 Hz), 128.18 (s), 125.22 (s), 24.04 (s), 120.38 (s), 111.49 (s). MS (EI): *m/z* = 309.10 [M$^+$].