JOC The Journal of Organic Chemistry

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Scissoring Enaminone C=C Double Bond by Free Radical Process for the Synthesis of α-Trifluoromethyl Ketones with CF_3SO_2Na

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c02431 Read Online

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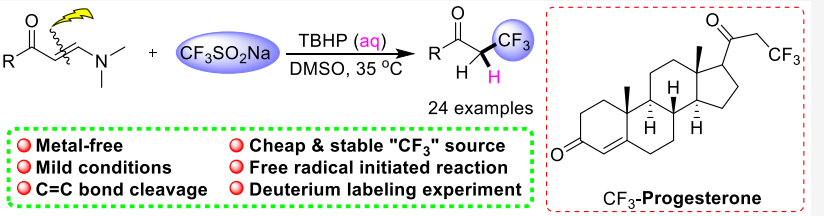

ABSTRACT: The C=C double bond cleavage on tertiary enaminones, enabling the formation of a new C−CF_3 bond, has been realized as a practical method for the synthesis of α-trifluoromethyl ketones with only the promotion of TBHP and ambient heating. Control experiments support that the reactions proceed via a featured free radical process. The deuterium labeling experiment employing D_2O indicates that water participated in the product formation by donating the hydrogen atom for the newly generated α-C−H bond in the product.

The trifluoromethyl group is a well-documented moiety that is capable of providing new biological functions or enhancing the bioactivity of organic molecules, which finds widespread application in the discovery of pharmaceuticals and lead compounds.[1] Owing to the scarce availability of trifluoromethyl in the natural world, the synthesis of CF_3-functionalized molecules via a trifluoromethylation reaction thus constitutes the predominant tool to access trifluoromethyl-functionalized organic compounds.[2] Under the driving force of the high application potential and promise of trifluoromethyl compounds, a great number of different trifluoromethyl-functionalized products have been synthesized over the past decades.[3] Among the numerous trifluoromethyl compounds reported in the literature, the α-trifluoromethyl ketones are inarguably a class of highly important and useful compounds for not only the versatile biological profiles associated with them but also their distinctive utilities in the synthesis of other diverse trifluoromethylated molecules by acting as the key building blocks.[4] Typically, the trifluoromethylation of activated ketones such as silyl enol ethers,[5] enol acetates/triflates,[6] α-haloketones,[7] and α-ketocarboxylic acids[8] has been proven to be applicable methods for α-trifluoromethyl ketone synthesis. In addition, the direct C−H trifluoromethylation of methyl ketones[9] and the difunctionalization of alkynes,[10] alkenes,[11] or their functionalized derivatives[12] have also been developed. Generally, the employment of a noble metal catalyst or expensive or sensitive trifluoromethyl reagent and/or the requirement of prior functionalization to activate the ketone substrates are yet the restrictions in known methods, which implies that more efforts are yet desirable to develop a complementary method for the synthesis of α-trifluoromethyl ketones.

As easily available and highly useful organic substrates, enaminones have in recent years exhibited widespread applications in organic synthesis.[13] Particularly, the featured C=C double bond cleavage of enaminones has been identified as a powerful tool toward the synthesis of structurally diverse products. Under proper reaction conditions, such C=C double bond cleavage takes place via different pathways and leads to the synthesis of α-aminoesters,[14] 1,2-diketones,[15] α-ketoamides/thioamides/ketoesters,[16] carbamoyl-functionalized enaminones,[17] amidines, and diazoketones[18] as well as ketones bearing various heteroatom functional structures.[19] With the encouragement for these successful examples on the diverse products initiated by the enaminone C=C bond cleavage as well as our longstanding interest in enaminone chemistry, we envisage that a new method for the synthesis of α-trifluoromethyl ketones by employing enaminone C=C double bond functionalization should be feasible. Herein, we report our recent results on the α-trifluoromethyl ketone synthesis via the TBHP-promoted reactions of *N*,*N*-dimethylenaminones with cheap CF_3SO_2Na as the trifluoromethyl

Received: October 14, 2020

https://dx.doi.org/10.1021/acs.joc.0c02431
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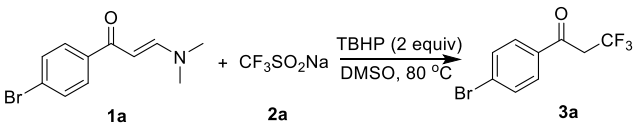
source by stirring at 35 °C without employing any transition metal reagent.

To start the synthetic investigation, the reaction of *p*-bromophenyl-functionalized enaminone **1a** and CF_3SO_2Na **2a** was conducted under a variety of different conditions (Table 1). Whereas the employment of TBHP (2 equiv) in DMSO and 80 °C heating gave product **3a** in 36% yield (entry 1, Table 1), the variation on oxidant species (entries 2−5, Table 1) and oxidant-free (entry 6, Table 1) operation proved that TBHP was the most proper oxidant. In addition, altering the reaction medium to DMF, toluene, dioxane, or MeCN led to no observation of better medium (entries 7−10, Table 1). An improved result was obtained by varying the TBHP loading to 1.5 equiv (entries 11 and 12, Table 1). Later, slightly increasing the reaction time (entries 13 and 14, Table 1) and modifying the reaction temperature to 35 °C (entries 15 and 16, Table 1) gave further enhanced product yield. Finally, when the loading of substrate **2a** was utilized at 3 equiv, the yield of **3a** was increased to 70% (entries 17−19, Table 1).

Table 1. Optimization of Reaction Conditions[a]



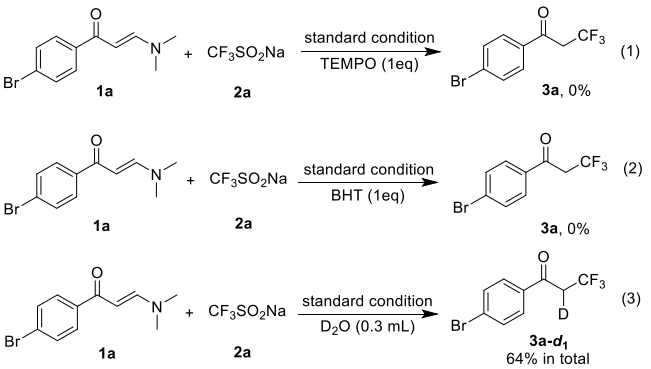
1a **2a** **3a**

entry	variation	yield (%)[b]
1	no	36
2	DTBP as oxidant	20
3	H_2O_2 as oxidant	trace
4	$PhI(OAc)_2$ as oxidant	0
5	$K_2S_2O_8$ as oxidant	0
6	no oxidant	0
7	DMF as medium	25
8	toluene as medium	0
9	1,4-dioxane as medium	0
10	MeCN as medium	0
11	with 1 equiv of TBHP	38
12	with 1.5 equiv of TBHP	41
13	1.5 equiv of TBHP, 16 h	43
14	1.5 equiv of TBHP, 22 h	38
15	1.5 equiv of TBHP, 16 h, 60 °C	44
16	1.5 equiv of TBHP, 16 h, 35 °C	58
17	1.5 equiv of TBHP, 16 h, 35 °C, 0.2 mmol **2a**	49
18	1.5 equiv of TBHP, 16 h, 35 °C, 0.6 mmol **2a**	70
19	1.5 equiv of TBHP, 16 h, 35 °C, 0.8 mmol **2a**	57

[a]General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.4 mmol) in 2 mL of solvent and stirred at 80 °C for 12 h. [b]Isolated yield.

Following the efforts at optimizing the reaction conditions, we then turned to investigate the application scope of this synthetic method toward different α-trifluoromethyl ketones. According to the results from this section, this C═C double bond cleavage protocol was found to be widely applicable in the synthesis α-trifluoromethyl ketones. For benzene-derived enaminone substrates, the functional groups of varied properties, including alkyl, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxyl, as well as sulfonyl (**3a**−**3t**, Table 2) all displayed fine tolerance to the synthesis. According to the results given by those enaminones bearing *para*-substituted phenyl structure, the unsubstituted and electron donating group functionalized phenyl enaminones provided corresponding products with a yield (**3b** and **3c**, Table 2) generally lower than that of equivalent reactions using electron withdrawing group functionalized phenyl enaminones. The electron withdrawing effect in the phenyl of enaminones might enhance the addition selectivity of the electrophilic CF_3 free radical to the nucleophilic enaminone α-site (see Scheme 1) by making the electron in the C═C double bond more polar, which improved product yield from related entries. In addition, the enaminones featured with monosubstituted phenyl at the *meta*-site (**3l**−**3p**, Table 2) and the disubstituted (**3q**−**3t**, Table 2) and trisubstituted (**3u**, Table 2) phenyls were also utilized as substrates for the practical synthesis of related α-trifluoromethyl ketones with moderate to good yields. Furthermore, the fused aryl, such as naphthyl-functionalized enaminone (**3v**, Table 2) and heteroaryl-functionalized enaminone (**3w**, Table 2), was also well tolerated, indicating the general applicability of this method for the titled transformation on aryl-functionalized enaminones. More notably, the enaminone derived from the natural product progesterone was also successfully transformed into corresponding α-trifluoromethyl progesterone with this method (**3x**, Table 2), further demonstrating the important application of the present protocol. The reaction using a methyl-based enaminone (Table 2, R^3 = Me) and CF_3SO_2Na did not provide a corresponding product. As additional efforts, the reactions of enaminones containing a methyl substituent at the α- or β-site with **2a** were also run, but the expected trifluoromethylation was not observed in both entries (Table 2). Furthermore, performing the model experiment at the scale of 4 mmol **1a** gave product **3a** in 38% yield. In the synthesized products, **3j**, **3p**, **3r**−**3u**, and **3x** were new compounds which had not been previously reported in other synthetic methods.

Following the work on the synthesis of different α-trifluoromethyl ketones, an array of control experiments were then conducted. At first, the model reaction was performed under the standard conditions in the presence of additionally employed free radical scavenger. In the reactions independently employing TEMPO and BHT, no target product (eqs 1 and 2), demonstrating that key free radical generation and transformations were involved in the reactions. On the other hand, when this reaction was conducted under standard conditions with additionally added D_2O (0.3 mL), the α-deuterium-labeled product **3a**-d_1 was observed as the only compound in the chromatography purified sample (eq 3). On the contrary, stirring product **3a** under identical conditions did not provide, such a deuterium-labeled product, confirming that water had participated in the reactions forming α-trifluoromethyl ketones.



https://dx.doi.org/10.1021/acs.joc.0c02431
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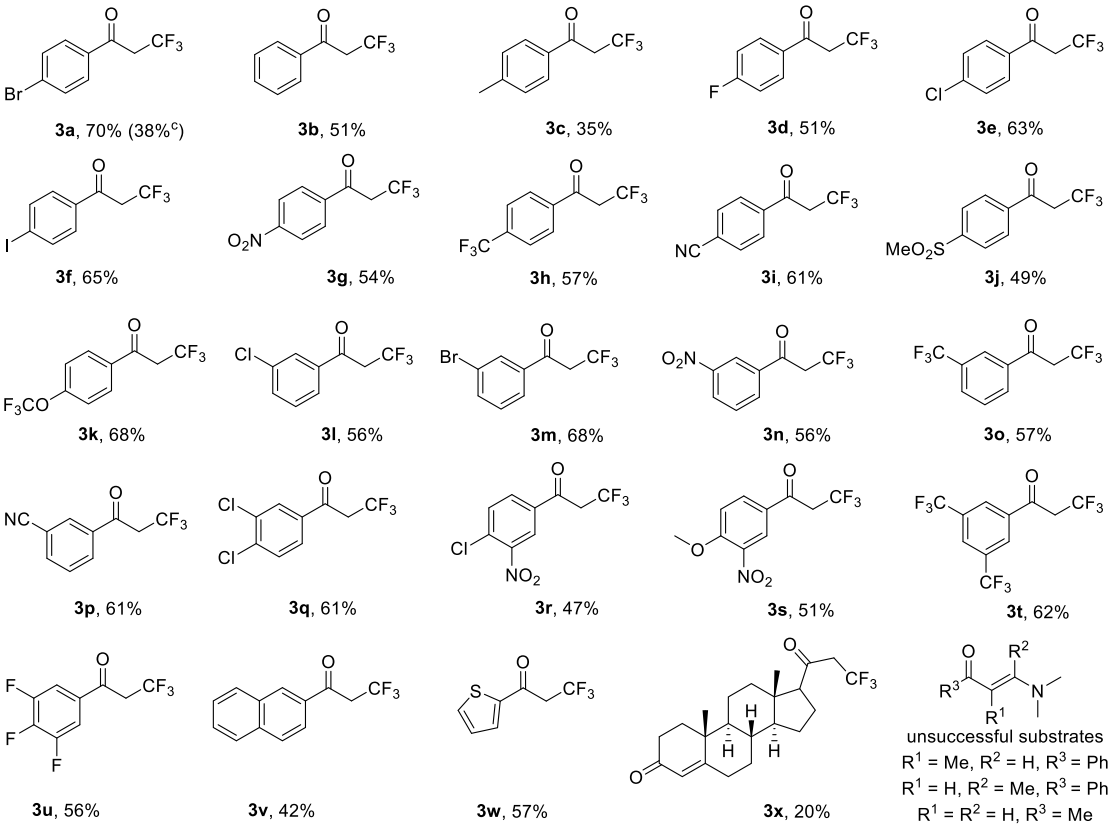
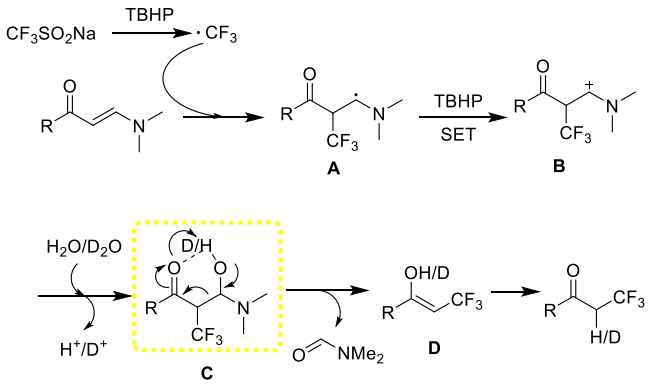
Table 2. Scope of the Synthesis of α-Trifluoromethyl Ketones[a,b]

1 2a 3



[a]General conditions: **1** (0.2 mmol), **2a** (0.6 mmol), TBHP (0.3 mmol), 2 mL of DMSO, 35 °C, 16 h, under air. [b]Isolated yield. [c]The yield from the reaction of 4 mmol (1.012 g) **1a**.

Scheme 1. Proposed Reaction Mechanism



Based on the results given by the control experiments, the reaction mechanism involving the free radical addition to the C═C double bond and water-assisted C−C bond decomposition is proposed (Scheme 1). Initially, the reaction of TBHP and CF_3SO_2Na provides a CF_3 free radical, and this free radical adds to the C═C double bond in enaminones to afford free radical intermediate **A**. In the presence of oxidant (TBHP), this free radical can be oxidized to cation intermediate **B** via single electron transfer (SET). The quick cooperation of this cation with water then leads to the CF_3-functionalized *N*,*O*-acetal intermediate **C**. A typical 1,5-proton transfer in **C** takes place to promote the decomposition of the *α*,*β*-C−C bond in this species and yields the CF_3-functionalized enone **D** accompanied by the release of DMF (see Supporting Information for the detection of DMF with GC). The *α*-trifluoromethyl ketones were provided via enone−ketone tautomerization.

In conclusion, by means of a free-radical-initiated C═C bond cleavage, we have disclosed a new method for the synthesis of *α*-trifluoromethyl ketones via the reactions of *N*,*N*-dimethylenaminones and simple CF_3SO_2Na. In addition to enabling the synthesis of highly diverse CF_3-functionalized ketones with this cheap and stable trifluoromethyl source, this method possesses several additional advantages such as the transition-metal-free catalysis, tolerance to moisture, and applicability in the synthesis of deuterium-labeled *α*-trifluoromethyl ketones and CF_3-elaborated natural product.

EXPERIMENTAL SECTION

General Experimental Information. All experiments were carried out under air atmosphere. Enaminones **1** were prepared using methyl ketones via a simple one-step process following a literature process.[20] All other chemicals and solvents used in the experiments were acquired from commercial sources and used directly

https://dx.doi.org/10.1021/acs.joc.0c02431
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without further treatment. The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as the internal standard, and the chemical shifts are reported in parts per million. High-resolution mass spectrometry (HRMS) data for all new products were obtained under ESI model in an apparatus equipped with a TOF analyzer. The melting points were tested with X-4A apparatus without correcting the temperature. Thin-layer chromatography was performed on GF254 plates.

*(E)-1-(4-Chloro-3-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (**1r**):* Brown solid (reaction at 10 mmol scale, 57% yield, 1.45 g); mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 2.0 Hz, 1 H), 7.98 (dd, J = 8.4, 2.0 Hz, 1 H), 7.81 (d, J = 12.0 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 5.56 (d, J = 12.0 Hz, 1 H), 3.14 (s, 3 H), 2.91 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.7, 155.1, 141.5, 133.9, 131.7, 131.2, 129.1, 118.7, 112.3, 91.2, 45.3, 37.5; HRMS (ESI) m/z calcd for $C_{11}H_{12}ClN_2O_3^+$ $[M + H]^+$ 255.0531, found 255.0551.

*(E)-3-(Dimethylamino)-1-(4-methoxy-3-nitrophenyl)prop-2-en-1-one (**1s**):* Yellow solid (reaction at 10 mmol scale, 65% yield, 1.63 g); mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1 H), 8.17 (dd, J = 8.8, 2.0 Hz, 1 H), 7.84 (d, J = 12.0 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 1 H), 5.66 (d, J = 12.0 Hz, 1 H), 4.01 (s, 3 H), 3.18 (s, 3 H), 2.97 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.6, 154.8, 139.0, 133.5, 132.8, 125.0, 113.0, 90.7, 56.7, 45.2, 37.5; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O_4^+$ $[M + H]^+$ 251.1026, found 251.1039.

*(E)-3-(Dimethylamino)-1-(3,4,5-trifluorophenyl)prop-2-en-1-one (**1u**):* Yellow solid (reaction at 10 mmol scale, 62% yield, 1.43 g); mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 12.0 Hz, 1 H), 7.62−7.46 (m, 2 H), 5.57 (d, J = 12.0 Hz, 1 H), 3.19 (s, 3 H), 2.96 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.1, 155.2, 150.9 (ddd, $^1J_{C-F}$ = 252.7, $^2J_{C-F}$ = 10.4, $^3J_{C-F}$ = 3.4 Hz), 140.2 (t, $^2J_{C-F}$ = 15.1), 136.3 (t, $^3J_{C-F}$ = 4.7), 111.7 (m), 90.6, 45.3, 37.4; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3NO^+[M + H]^+$ 230.0787, found 230.0801.

General Procedure for the Synthesis of α-CF_3 Ketones. Enaminone **1** (0.2 mmol), CF_3SO_2Na **2** (0.6 mmol), TBHP (0.3 mmol, 70 wt % aqueous solution), and DMSO (2 mL) were charged in a 25 mL round-bottom flask equipped with stirring bar. Then the mixture was stirred at 35 °C under air atmosphere for 16 h. After being cooled to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were collected and washed with a small amount of water three times. After being dried with anhydrous Na_2SO_4, the solid was filtered and the solvent was removed at reduced pressure. The residue obtained therein was subjected to flash silica gel column chromatography to provide pure products with the elution of mixed petroleum ether/ethyl acetate (v/v = 50:1).

Procedure for the Synthesis of 3a at 4 mmol Scale. Enaminone **1a** (4 mmol, 1.012g), CF_3SO_2Na (12 mmol, 1.970g), TBHP (6 mmol, 70 wt % aqueous solution), and DMSO (15 mL) were charged in a 50 mL round-bottom flask equipped with stirring bar. Then the mixture was stirred at 35 °C under air atmosphere for 16 h. After being cooled to room temperature, 45 mL of water was added, and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic phases were collected and washed with a small amount of water three times. After being dried with anhydrous Na_2SO_4, the solid was filtered and the solvent was removed at reduced pressure. The resulting residue was subjected to flash silica gel column chromatography to provide **3a** (404 mg, 38% yield) with the elution of mixed petroleum ether and ethyl acetate (v/v = 50:1).

*1-(4-Bromophenyl)-3,3,3-trifluoropropan-1-one (**3a**):*[11e] White solid (37 mg, 70%); mp 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 3.77 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.8, 134.5, 132.3, 129.8, 123.8 (q, $^1J_{C-F}$ = 275.2 Hz), 42.1 (q, $^2J_{C-F}$ = 28.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.01(t, J = 3.0 Hz).

*3,3,3-Trifluoro-1-phenylpropan-1-one (**3b**):*[11e] White solid (19 mg, 51% yield); mp 38−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.0 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 3.80 (q, J = 10.0 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.7, 135.8, 134.2, 128.9, 128.3, 124.0 (d, $^1J_{C-F}$ = 275.3 Hz), 42.1 (q, $^2J_{C-F}$ = 28.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.05.

*3,3,3-Trifluoro-1-p-tolylpropan-1-one (**3c**):*[11e] White solid (14 mg, 35% yield); mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 3.77 (q, J = 10.1 Hz, 2 H), 2.44 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.3, 145.3, 133.4, 129.6, 128.5, 124.1 (d, $^1J_{C-F}$ = 275.2 Hz), 42.0 (q, $^2J_{C-F}$ = 28.2 Hz), 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.00.

*3,3,3-Trifluoro-1-(4-fluorophenyl)propan-1-one (**3d**):*[11c] Pale yellow solid (21 mg, 51% yield); mp 32−33 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.96 (m, 2 H), 7.19 (t, J = 8.5 Hz, 2 H), 3.78 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.1, 166.4 (d, $^1J_{C-F}$ = 255.5 Hz), 132.3, 131.1 (d, $^3J_{C-F}$ = 9.5 Hz), 123.9 (q, $^1J_{C-F}$ = 275.1 Hz), 116.2 (d, $^2J_{C-F}$ = 20.0 Hz), 42.1 (q, $^2J_{C-F}$ = 28.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.03, −102.92.

*1-(4-Chlorophenyl)-3,3,3-trifluoropropan-1-one (**3e**):*[11c] Yellow solid (28 mg, 63% yield); mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 2 H), 7.40 (d, J = 7.6 Hz, 2 H), 3.69 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.5, 140.9, 134.1, 129.7, 129.3, 123.8 (d, $^1J_{C-F}$ = 275.2 Hz), 42.1 (q, $^2J_{C-F}$ = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.98.

*1-(4-Iodophenyl)-3,3,3-trifluoropropan-1-one (**3f**):*[6b] Yellow solid (41 mg, 65% yield); mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 3.75 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.1, 138.3, 135.1, 129.6, 123.8 (q, $^1J_{C-F}$ = 276.4 Hz), 102.5, 42.1 (q, $^2J_{C-F}$ = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.98.

*3,3,3-Trifluoro-1-(4-nitrophenyl)propan-1-one (**3g**):*[11c] Yellow solid (25 mg, 54% yield); mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.4 Hz, 2 H), 8.12 (d, J = 8.4 Hz, 2 H), 3.88 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.4, 150.9, 140.0, 129.5, 124.1, 123.5 (q, $^1J_{C-F}$ = 275.9 Hz), 42.7 (q, $^2J_{C-F}$ = 28.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.94.

*3,3,3-Trifluoro-1-(4-(trifluoromethyl)phenyl)propan-1-one (**3h**):*[6b] White solid (29 mg, 57% yield); mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 2 H), 3.83 (q, J = 9.7 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.8, 138.4, 135.4 (d, $^2J_{C-F}$ = 32.6 Hz), 128.7, 126.0 (q, $^3J_{C-F}$ = 3.7 Hz), 123.7 (d, J = 275.5 Hz), 123.3 (d, $^1J_{C-F}$ = 271.4 Hz), 42.5 (q, J = 28.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.00, −63.37.

*4-(3,3,3-Trifluoropropanoyl)benzonitrile (**3i**):*[11c] White solid (26 mg, 61% yield); mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 3.83 (q, J = 9.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.5, 138.6, 132.8, 128.8, 123.6 (q, $^1J_{C-F}$ = 275.4 Hz), 117.5, 117.5, 42.5 (q, $^2J_{C-F}$ = 28.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.96.

*3,3,3-Trifluoro-1-(4-(methylsulfonyl)phenyl)propan-1-one (**3j**):* White solid (26 mg, 49% yield); mp 168−169 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.23 (d, J = 8.4 Hz, 2 H), 8.12 (d, J = 8.4 Hz, 2 H), 4.52 (q, J = 10.6 Hz, 2 H), 3.31 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.1 (d, $^3J_{C-F}$ = 2.6 Hz), 145.4, 139.6, 129.7, 127.9, 125.3 (q, $^1J_{C-F}$ = 274.7 Hz), 43.6, 42.6 (q, $^2J_{C-F}$ = 26.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.11; HRMS (ESI) m/z calcd for $C_{10}H_{10}F_3O_3S^+$ $[M + H]^+$ 267.0297, found 267.0306.

*3,3,3-Trifluoro-1-(4-(trifluoromethoxy)phenyl)propan-1-one (**3k**):*[21] Yellow liquid (37 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.92 (m, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 3.79 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.2, 153.4 (d, $^3J_{C-F}$ = 17.0 Hz), 133.9, 130.5,123.8 (q, $^1J_{C-F}$ = 275.3 Hz), 120.6, 120.2 (q, $^1J_{C-F}$ = 257.8 Hz), 42.2 (q, $^2J_{C-F}$ = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.66, −62.03.

*1-(3-Chlorophenyl)-3,3,3-trifluoropropan-1-one (**3l**):*[6b] Yellow liquid (25 mg, 56% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.46 (t, J = 7.9 Hz, 1 H), 3.78 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.5, 137.3, 135.4, 134.1, 130.3, 128.4, 126.4, 123.7 (q, $^1J_{C-F}$ = 275.3 Hz), 42.3 (q, ^2J = 29.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.04.

https://dx.doi.org/10.1021/acs.joc.0c02431
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*1-(3-Bromophenyl)-3,3,3-trifluoropropan-1-one (**3m**):*[11c] Yellow liquid (36 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.85 (d, J = 7.6 Hz, 1 H), 7.77 (d, J = 8.8 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 3.78 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.4, 137.4, 137.1, 131.3, 130.5, 126.9, 123.8 (q, $^1J_{C-F}$ = 275.5 Hz), 123.3, 42.2 (q, $^2J_{C-F}$ = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.04.

*3,3,3-Trifluoro-1-(3-nitrophenyl)propan-1-one (**3n**):*[6d] Yellow solid (26 mg, 56% yield); mp 81−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 8.52 (d, J = 8.0 Hz, 1 H), 8.30 (d, J = 7.6 Hz, 1 H), 7.77 (t, J = 8.0 Hz, 1 H), 3.90 (q, J = 9.7 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 187.8, 148.6, 136.9, 133.8, 130.4, 128.4, 123.2, 123.6 (q, $^1J_{C-F}$ = 275.5 Hz), 123.3, 42.5 (q, $^2J_{C-F}$ = 28.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.97.

*3,3,3-Trifluoro-1-(3-(trifluoromethyl)phenyl)propan-1-one (**3o**):*[11c] White solid (29 mg, 57% yield); mp 41−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 8.13 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 7.68 (t, J = 7.8 Hz, 1 H), 3.84 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.5, 136.3, 131.9, 131.5, 130.6 (d, $^3J_{C-F}$ = 3.4 Hz), 129.7, 125.2 (q, $^3J_{C-F}$ = 3.8 Hz), 123.7 (d, $^1J_{C-F}$ = 275.7 Hz), 123.4 (d, $^1J_{C-F}$ = 270.9 Hz), 42.4 (q, $^2J_{C-F}$ = 28.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.00, −62.97.

*3-(3,3,3-Trifluoropropanoyl)benzonitrile (**3p**):* White solid (26 mg, 61% yield); mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.70 (t, J = 7.8 Hz, 1 H), 3.85 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.0, 137.0, 136.5, 132.2, 132.0, 130.1, 123.6 (d, $^1J_{C-F}$ = 275.4 Hz), 117.5, 113.7, 42.3 (q, $^2J_{C-F}$ = 28.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.99; HRMS (ESI) m/z calcd for $C_{10}H_7F_3NO^+$ $[M + H]^+$ 214.0474, found 214.0474.

*1-(3,4-Dichlorophenyl)-3,3,3-trifluoropropan-1-one (**3q**):*[6b] White solid (31 mg, 61% yield); mp 58−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.75 (d, J = 8.4 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 3.76 (q, J = 9.8 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 187.6, 139.1, 135.3, 133.9, 131.1, 130.3, 127.3, 123.6 (d, $^1J_{C-F}$ = 275.5 Hz), 42.3 (q, $^2J_{C-F}$ = 28.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.99.

*1-(4-Chloro-3-nitrophenyl)-3,3,3-trifluoropropan-1-one (**3r**):* Brown solid (25 mg, 47% yield); mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 2.0 Hz, 1 H), 8.08 (dd, J = 8.4, 2.2 Hz, 1 H), 7.75 (d, J = 8.4 Hz, 1 H), 3.83 (q, J = 9.7 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.8, 134.9, 133.2, 132.9, 132.1, 129.9, 125.4, 123.4 (q, $^1J_{C-F}$ = 275.5 Hz), 42.5 (q, $^2J_{C-F}$ = 28.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.89; HRMS (ESI) m/z calcd for $C_9H_6ClF_3NO_3^+$ $[M + H]^+$ 267.9983, found 267.9981.

*3,3,3-Trifluoro-1-(4-methoxy-3-nitrophenyl)propan-1-one (**3s**):* Yellow solid (27 mg, 51% yield); mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 2.4 Hz, 1 H), 8.18 (dd, J = 8.8, 2.4 Hz, 1 H), 7.22 (d, J = 9.2 Hz, 1 H), 4.07 (s, 3 H), 3.79 (q, J = 9.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.7, 157.0, 139.5, 134.2, 128.2, 126.3, 123.7 (q, $^1J_{C-F}$ = 275.5 Hz), 113.7, 42.1 (q, $^2J_{C-F}$ = 28.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.92; HRMS (ESI) m/z calcd for $C_{10}H_8F_3NO_4Na^+$ $[M + Na]^+$ 286.0298, found 286.0299.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3,3,3-trifluoropropan-1-one (**3t**):* Pale yellow liquid (40 mg, 62% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2 H), 8.15 (s, 1 H), 3.89 (q, J = 9.6 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 187.2, 137.1, 132.9 (q, $^2J_{C-F}$ = 34.0 Hz), 128.3 (d, $^3J_{C-F}$ = 4.0 Hz), 127.3 (q, $^1J_{C-F}$ = 3.5 Hz), 123.4 (q, $^1J_{C-F}$ = 275.5 Hz), 122.6 (q, $^1J_{C-F}$ = 271.4 Hz), 42.5 (q, $^2J_{C-F}$ = 28.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.03, −63.13; HRMS (ESI) m/z calcd for $C_{11}H_6F_9O^+$ $[M + H]^+$ 325.0269, found 325.0287.

*3,3,3-Trifluoro-1-(3,4,5-trifluorophenyl)propan-1-one (**3u**):* Pale yellow liquid (27 mg, 56% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, J = 6.2 Hz, 2 H), 3.74 (qd, J = 9.7, 1.6 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.3, 151.4 (ddd, $^1J_{C-F}$ = 252.7, $^2J_{C-F}$ = 10.4, $^3J_{C-F}$ = 3.4 Hz), 142.9 (dt, $^1J_{C-F}$ = 260.9, $^2J_{C-F}$ = 15.2 Hz), 131.3 (d, $^3J_{C-F}$ = 3.9 Hz), 123.4 (q, $^1J_{C-F}$ = 275.5 Hz), 113.1 (m), 42.2 (q, $^2J_{C-F}$ = 28.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.04, −130.88, −130.93, −149.80 (t, J_{F-H} = 20.3 Hz); HRMS (ESI) m/z calcd for $C_9H_5F_6O^+$ $[M + H]^+$ 243.0239, found 243.0241.

*3,3,3-Trifluoro-1-(naphthalen-2-yl)propan-1-one (**3v**):*[11c] Pale yellow solid (20 mg, 42% yield); mp 79−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 8.02−7.89 (m, 4 H), 7.67−7.57 (m, 2 H), 3.93 (q, J = 10.0 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.6, 136.0, 133.2, 132.4, 130.6, 129.7, 129.2, 128.9, 127.9, 127.2, 123.5, 124.1 (d, $^1J_{C-F}$ = 275.2 Hz), 42.3 (q, $^2J_{C-F}$ = 28.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.90.

*3,3,3-Trifluoro-1-(thiophen-2-yl)propan-1-one (**3w**):*[11c] Brown liquid (22 mg, 57% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.73 (m, 2 H), 7.19 (dd, J = 4.9, 3.9 Hz, 1 H), 3.71 (d, J = 10.0 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.2, 143.2, 135.7, 133.4, 128.5, 123.7 (d, $^1J_{C-F}$ = 275.6 Hz), 43.0 (q, $^2J_{C-F}$ = 28.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.95.

*(8S,9S,10R,13S,14S)-10,13-Dimethyl-17-(3,3,3-trifluoropropanoyl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-one (**3x**):* White solid (15 mg, 20% yield); mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (s, 1 H), 3.20 (qd, J = 10.2, 3.0 Hz, 2 H), 2.57 (t, J = 8.8 Hz, 1 H), 2.45−2.13 (m, 6 H), 2.07−2.00 (m, 2 H), 1.90−1.84 (m, 1 H), 1.77−1.71 (m, 3 H), 1.60−1.56 (m, 1 H), 1.50−1.43 (m, 2 H), 1.34−1.25 (m, 2 H), 1.19 (s, 3 H), 1.09−0.96 (m, 2 H), 0.71 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.6, 199.3, 170.5, 124.0, 123.6 (d, $^1J_{C-F}$ = 275.3 Hz), 63.3, 56.1, 53.5, 47.0 (q, $^2J_{C-F}$ = 27.2 Hz), 44.6, 38.6, 38.5, 35.7, 35.5, 33.9, 32.7, 31.8, 24.3, 22.9, 21.0, 17.4, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.24; HRMS (ESI) m/z calcd for $C_{22}H_{30}F_3O_2^+$ $[M + H]^+$ 383.2192, found 383.2207.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02431.

^{1}H NMR spectrum of the D-labeled compound **3a**-d_1, ^{1}H, ^{13}C NMR spectra for all products and new enaminone substrates, ^{19}F NMR spectra for all CF_3-functionalized products, and the GC chromatograms on DMF detection (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is financially supported by the National Natural Science Foundation of China (21861019, 21562025) and Natural Science Foundation of Jiangxi Province (20202ACBL203006).

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https://dx.doi.org/10.1021/acs.joc.0c02431
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