JOC The Journal of Organic Chemistry

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Copper-Catalyzed Reductive Ring-Cleavage of Isoxazoles: Synthesis of Fluoroalkylated Enaminones and Application for the Preparation of Celecoxib, Deracoxib, and Mavacoxib

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Cite This: *J. Org. Chem.* 2021, 86, 4557−4566 Read Online

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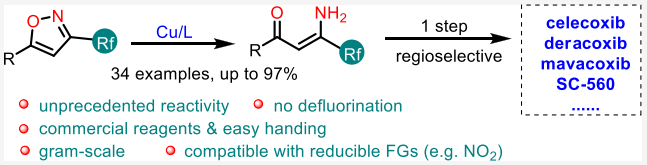
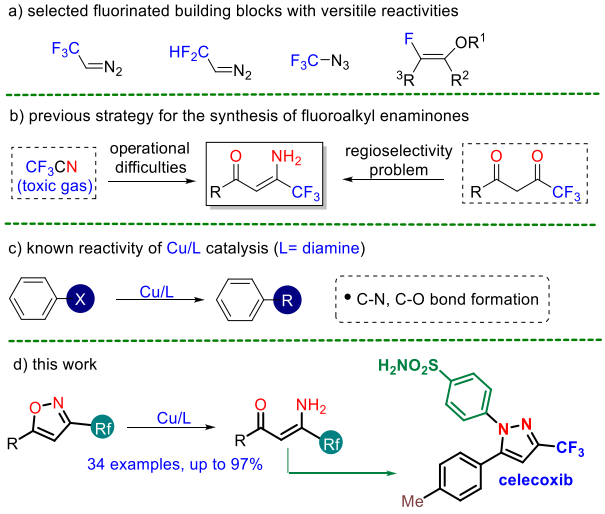
ABSTRACT: We have identified a new reactivity of copper/diamine catalysis for the reductive ring-cleavage of isoxazoles to yield fluoroalkylated enaminones. This protocol has the advantage of using commercially available reagents, ease of setting up, broad tolerance of functionality, and is regiospecific and free of defluorination and reduction of reducible functional groups. The utility was demonstrated by a one-step, regioselective synthesis of fluoroalkylated pyrazole-based drugs such as celecoxib, deracoxib, and mavacoxib.



INTRODUCTION

The modification of molecules with fluorinated units is an important means in drug development to optimize the properties of lead compounds.[1] Whereas more efforts have been devoted to introducing these units by direct fluorination or fluoroalkylation, the importance of approaches utilizing fluorinated building blocks can never be underestimated.[2] For example, fluorinated intermediates such as diazoalkanes, azides, and enol ethers have been successfully applied for the synthesis of various high-value compounds,[3] some of which are not easy or even impossible to synthesize with direct fluoroalkylation approaches (Scheme 1a).

Scheme 1. Previous Research and This Work



Enaminone compounds are highly versatile intermediates in organic synthesis.[4] However, literature surveys show that the application of their fluoroalkylated counterparts remains largely underdeveloped (Scheme 1b), which could be attributed to the synthesis difficulties.[5,6] For instance, trifluoromethylated enaminones can be synthesized from CF_3CN. However, CF_3CN is a toxic gas, and the reaction needs to use highly acidic and basic reagents.[5] Alternatively, they can be prepared from corresponding diketones. However, regioselectivity could be a problem.[6]

On the basis of our previous work,[7a,b] we envisioned that the reductive ring-cleavage of fluoroalkylated isoxazoles could provide a convenient access to fluoromethylated enaminones. The reductive cleavage of N−O bond of isoxazoles could be achieved by hydrogenolysis in the presence of Raney-nickel,[8a,b] Pd/C,[8c] or aged NMP/$FeCl_3$;[8d] alternatively, it could be realized by the reductive ring opening promoted by metal reagents or catalysts including Na,[9a] SmI_2,[9b] EtMgBr/Ti(Oi-Pr)$_4$,[9c] $Mo(CO)_6$,[9d,e] Fe/Cu/HCl,[9f] or Fe(II)Cl_2.[9g] Though methods are well documented, our optimization showed that it was not a trivial job to achieve the ring-opening of fluoroalkyl isoxazoles (vide infra).

Herein, we report an unexpected reactivity of copper/diamine system (Scheme 1c),[10] that is, the cleavage of N−O bond of isoxazole, which allows an easy and general access to the fluoroalkyl enaminones (Scheme 1d). This method avoids the reduction of functional groups and the unexpected

Received: December 19, 2020
Published: February 15, 2021

https://dx.doi.org/10.1021/acs.joc.0c02980
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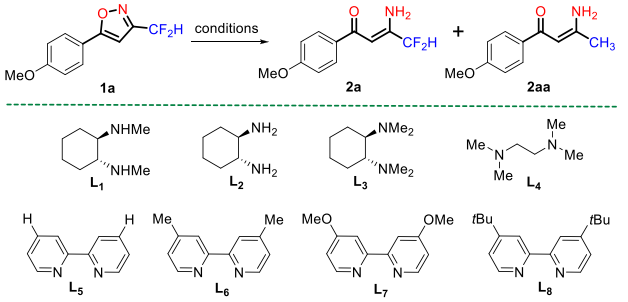
Table 1. Reaction Optimization[a]



entry	reagents/solvent/temp (°C)	yields (%) of **2a**
1	Pd/C (20 wt %)/MeOH/35	n.d.
2	Pd/C (20 wt %)/MeOH/80	n.d.
3	Raney-Ni (20 wt %)/MeCN/35	38
4	Raney-Ni (20 wt %)/EtOH/35	42
5[c]	Raney-Ni (20 wt %)/MeOH/35	62
6	Raney-Ni (20 wt %)/MeOH/0	8
7	$FeCl_2$ (400 mol %)/MeCN/90	n.d.
8	$Mo(CO)_6$ (50 mol %)/MeCN/85	21
9	$Mo(CO)_6$ (50 mol %)/MeCN/140	77
10	CuI (30 mol %)/L1 (20 mol %)/dioxane/140	12
11	CuI (30 mol %)/L1 (200 mol %)/dioxane/140	92
Variation of the copper catalyst		
12	CuCl (30 mol %)/L1 (200 mol %)/dioxane/140	80
13	CuBr (30 mol %)/L1 (200 mol %)/dioxane/140	71
14	CuTC (30 mol %)/L1 (200 mol %)/dioxane/140	27
15	**$Cu(OAc)_2$(30 mol %)/L1 (200 mol %)/dioxane/140**	**90**
16	$CuCl_2$ (30 mol %)/L1 (200 mol %)/dioxane/140	58
17	$Cu(acac)_2$ (30 mol %)/L1 (200 mol %)/dioxane/140	74
Variation of the ligand		
18	CuI (30 mol %)/L2 (200 mol %)/dioxane/140	80
19	CuI (30 mol %)/L3 (200 mol %)/dioxane/140	67
20	CuI (30 mol %)/L4 (200 mol %)/dioxane/140	17
21	CuI (30 mol %)/L5 (200 mol %)/dioxane/140	31
22	CuI (30 mol %)/L6 (200 mol %)/dioxane/140	52
23	CuI (30 mol %)/L7 (200 mol %)/dioxane/140	12
24	CuI (30 mol %)/L8 (200 mol %)/dioxane/140	21
Variation of the solvent		
25	CuI (30 mol %)/L2 (200 mol %)/THF/140	53
26	CuI (30 mol %)/L2 (200 mol %)/MeOH/140	41
27	CuI (30 mol %)/L2 (200 mol %)/toluene/140	66
28	CuI (30 mol %)/L2 (200 mol %)/DMF/140	74
Variation of other parameters		
29	CuI (30 mol %)/L1 (50 mol %)/dioxane/140	52
30	CuI (30 mol %)/L1 (100 mol %)/dioxane/140	67
31	CuI (30 mol %)/L1 (150 mol %)/dioxane/140	80
32	CuI (30 mol %)/L1 (200 mol %)/dioxane/120	70
33	CuI (30 mol %)/L1 (200 mol %)/dioxane/100	52
Control experiments		
34	CuI (30 mol %)/L1 (200 mol %) + H_2O (100 mol %) /dioxane/140	90
35	CuI (30 mol %)/L1 (100 mol %) + H_2O (100 mol %) /dioxane/140	55
36	CuI (30 mol %)/L1 (200 mol %) + HCO_2H (100 mol %)/dioxane/140	56
37	CuI (30 mol %)/L1 (200 mol %) + AcOH (100 mol %)/dioxane/140	65
38	CuI (30 mol %)/dioxane/140	n.d.
39	L1 (200 mol %)/dioxane/140	n.d.

[a]Conditions: **1a** (0.1 mmol), solvent (3 mL) for 36 h. [b]Yields were determined by ^{19}F NMR analysis using 3,5-bis(trifluoromethyl)-bromobenzene as an internal standard. [c]**2a** and **2aa** were isolated in 62% and 18% yield, respectively.

defluorination side reaction, which would be encountered by conventional methods for the reductive ring-cleavage of isoxazoles (vide infra).[8,9] The usefulness of fluoroalkyl enaminones was demonstrated by a one-step, regioselective synthesis of nonsteroidal drugs such as celecoxib, deracoxib, mavacoxib, and related lead compounds.

RESULTS AND DISCUSSION

As shown in Table 1, The Pd/C catalyzed hydrogenolysis of **1a** could hardly afford the desired product even at elevated temperature (Entries 1−2), reflecting that **1a** has a lower reactivity compared to reported nonfluorinated isoxazoles.[8c] With freshly activated Raney-Ni, expected β-enaminone **2a** was obtained in 38−62% yields in different solvents (Entries 3−5), but the reaction was plagued by the defluorination byproduct **2aa** in various amounts (e.g., 18% for Entry 5), which was not easy to separate from **2a**. Lowering the temperature could avoid the above side reaction, but the yield was only 8% (Entry 6). Whereas the reductive method using $Fe(II)Cl_2$[9g] afforded no desired product (Entry 7), the reaction of $Mo(CO)_6$ under the reported conditions (in CH_3CN at 85 °C),[9d,e] one of the most used protocols, gave **2a** in a low yield of 21%, again indicating the sluggish reactivity of fluorinated isoxazoles. Although increasing the temperature to 140 °C could push the reaction to completion, the yield was not ideal (77%) and some unidentified polar byproducts were observed. Furthermore, it is not desirable to use this reagent at this temperature, because $Mo(CO)_6$ is a dangerous source of volatile metal as well as CO.[11] Fortuitously, we found that the copper/diamine could yield the desired product in 12% yield at 140 °C, and no trace of **2aa** was observed (Table 1, Entry 10).[12] Interestingly, when increasing the loading of L_1 (1*R*,2*R*)-*N1*,*N*2-dimethylcyclohexane-1,2-diamine (*t*-DMACH) to a two molar ratio, the desired product **3a** was isolated in 92% yield (Entry 11). Further screening showed that the reaction could occur under various copper(I)/copper(II) catalysts (Entries 12−17), with $Cu(OAc)_2$ (Entry 15) being equally efficient to that with CuI (Entry 11). Different diamine- and bis-pyridine-ligands were then tested, which showed that *t*-DMACH was the most suitable one for this reaction (Entries 18−24). The reaction could occur in solvents other than dioxane, but with lower efficiencies (Entries 25−28 vs Entry 11). Variation of the ligand loading showed that the reaction requires at least two equivalents of *t*-DMACH (Entries 29−31). Lower yields were obtained when the temperature was dropped to 120 or 100 °C (Entries 32−33). Though water does not affect the reaction efficiency, it could not replace L_1,[9d,e] indicating that *t*-DMACH may act as both the hydrogen source and the ligand (Entries 34−35).[13] The addition of organic acids lowered the yield significantly (Entries 36−37), indicating that the high loading of *t*-DMACH is not due to the competitive coordination of enaminone **2a** to the copper catalyst. Finally, control experiments proved that both the copper catalyst and the

https://dx.doi.org/10.1021/acs.joc.0c02980
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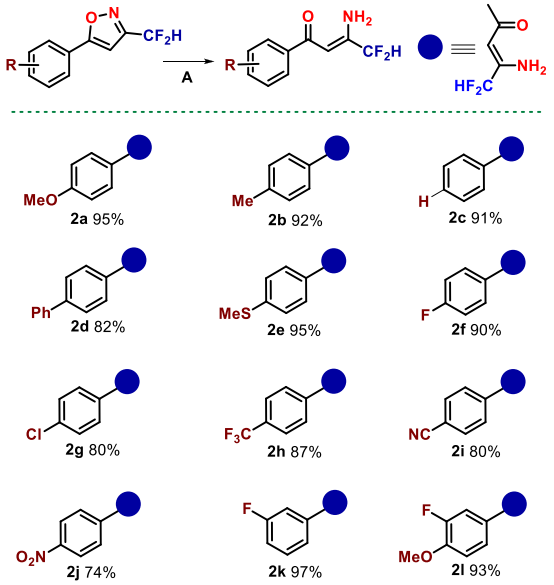
ligand *t*-DMACH are essential for this reaction (Entries 38–39).

Having identified the optimal reaction conditions (Table 1, entry 11), the generality of the reaction with respect to the substituent on the aromatic ring of difluoromethylated isoxazoles was explored (Table 2). Alkyl, hydrogen, and

Table 2. Substrate Scope of CF_2-Isoxazoles[a]

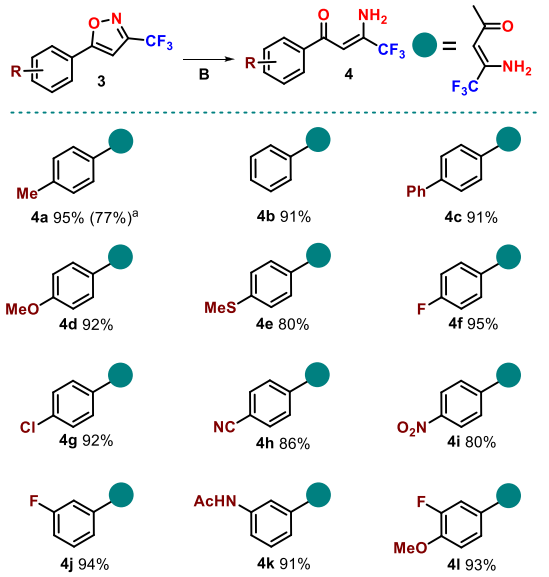


[a]Conditions A: **1** (0.1 mmol), CuI (0.03 mmol)/*t*-DMACH (0.2 mmol), dioxane (3 mL), 140 °C, 36 h.

phenyl substituted compounds (**2b**–**2d**) are viable substrates, affording the desired products in good yields. Isoxazoles bearing electron-donating groups exhibited excellent reactivity, affording the corresponding product in >90% yields (**2a**, **2e**). Halogens (**2f**–**2g**) were tolerated under the reaction conditions, which leaves a reactive handle for further derivatization. Isoxazoles bearing electron-withdrawing groups (**2h**–**2j**) underwent the reaction successfully, yielding the products in good yields. In contrast to previous methods, easily reducible groups (e.g., CN, NO_2) were intact in this work (**2i**–**2j**). Finally, *meta*-substitution and disubstitution were compatible under the reaction conditions, and **2k** and **2l** were obtained in 97% and 93% yield, respectively. The structures of **2i** and **2j** were confirmed unambiguously by means of X-ray crystallographic analysis (CCDC 1577900, 2038891, and Supporting Information).

Next, we proceed to test the limit of this transformation with respect to the CF_3-isoxazoles (Table 3). Interestingly, the introduction of another fluorine makes the reaction more sluggish under previous conditions (with CuI, Table 1, entry 11). Fortunately, after slight adjustment, the reaction could occur smoothly with a higher loading (50 mol %) of copper acetate (Table 1, entry 11). Generally, the reaction shows equally excellent tolerance of functionalities to that with CF_2-counterparts and the yields (80–95%) are a little higher than those listed in Table 2. Note that the reaction could be run on gram scale, and **4a** was obtained in 77% yield. The structures of **4a** and **4h** were confirmed unambiguously by means of X-ray crystallographic analysis (CCDC 2038890, 2041334, and Supporting Information).

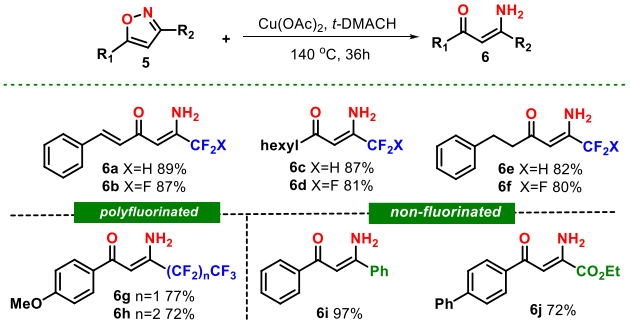
Table 3. Substrate Scope of CF_3-Isoxazoles[b]



[a]On gram-scale. [b]Conditions B: **3** (0.1 mmol), $Cu(OAc)_2$ (0.05 mmol)/*t*-DMACH (0.2 mmol), dioxane (3 mL), 140 °C, 36 h.

As shown in Table 4, fluoroalkylated isoxazoles with other substituents instead of aryls are viable compounds. For

Table 4. Reductive Ring-Cleavage of Other Representative Isoxazoles Including Non-Fluorinated Ones[a]



[a]Conditions: **5** (0.1 mmol), $Cu(OAc)_2$ (0.05 mmol)/*t*-DMACH (0.2 mmol), dioxane (3 mL), 140 °C, 36 h.

example, **6a** and **6b** with a styrene group could be obtained in 89% and 87% yield, respectively. As observed before, the reducible double bond was not affected under the reaction conditions. Alkyl-substituted compounds also underwent the reaction successfully, and **6c**–**6f** were all obtained in high yields. Note that **6c** and **6d** are very volatile and need to be handled with care. Isoxazoles were viable substrates (**6g**, **6h**), thus demonstrating the utility of this method for the preparation of polyfluorinated enaminones. Finally, the reaction is also suitable for the ring-opening of nonfluorinated compounds, yielding the products (**6i**, **6j**) in 97% and 72% yield, respectively. These two experiments, along with our earlier observation in the reaction optimization section, indicate the utility of this method in a broader perspective.

In a preliminary demonstration of the utility of the fluoroalkylated enaminones, we attempted to transform them into fluoroalkylated 1,5-diarylpyrazoles, which are privileged cores in medicinal chemistry.[14] For example, celecoxib is a

https://dx.doi.org/10.1021/acs.joc.0c02980
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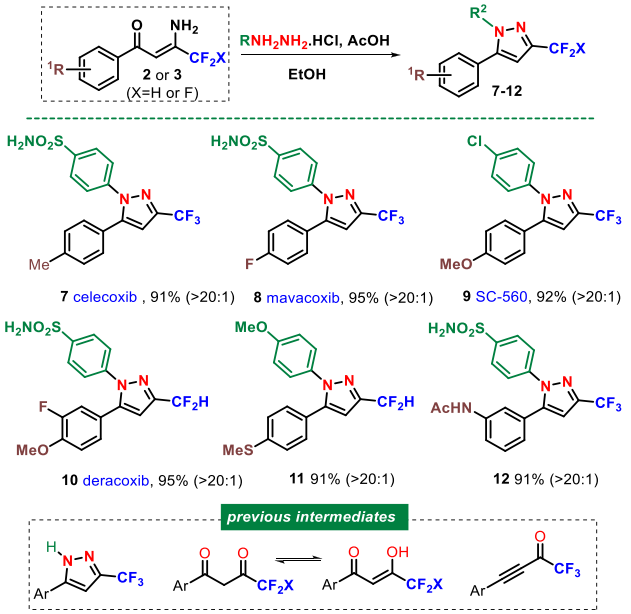
cyclooxygenase-2 (COX-2) inhibitor and nonsteroidal anti-inflammatory drug and among the most prescribed medications in the United States. After some optimization (Supporting Information, Table S1), celecoxib (**7**), mavacoxib (**8**), SC-560 (**9**), deracoxib (**10**), and **11** were obtained regioselectively in high yields by the reaction of the above-obtained enaminones with corresponding aryl hydrazines in ethanol with 3 equiv of acetic acid. Although these compounds can be prepared from fluoroalkylated pyrazoles,[15] β-diketones,[14,16] and ynones,[17] our method provides a high-yielding, regioselective alternative to obtain them. Importantly, whereas demonstrating comparable efficiency, all the enaminones listed in Tables 2, 3, and 5 are solid and stable, and thus more convenient to handle than corresponding fluoroalkylated diketones; furthermore, this reaction is complementary in synthesizing certain compounds of interest and could provide pyrazoles (e.g., **12**) that are not accessible from fluoroalkyl β-diketones.[18] Finally, it is worth noting that using fluoroalkylated enaminones as key intermediates enables a high yielding, 3-steps access to these fluoroalkylated pyrazoles from commercially available reagents based on our previous work.[7a]

Table 5. Synthesis of Celecoxib-Related Pyrazoles[a]



[a]Conditions: **2** or **3** (0.1 mmol), $ArNH_2NH_2$·HCl (0.15 mmol), AcOH (0.3 mmol), EtOH (2 mL), 80 °C, 10 h. The isomer ratios in the parentheses were determined by ^{19}F NMR analysis using 2,2,2-trifluoroacetophenone as an internal standard.

CONCLUSIONS

In summary, we have identified a new reactivity of copper/diamine catalysis for the reductive ring-cleavage of isoxazoles, and provided a general and efficient method for the synthesis of CF_2- and CF_3-substituted enaminones. This protocol has the advantage of using commercially available reagents, ease of setting up, broad tolerance of functionality, and is regiospecific and free of defluorination and reduction of reducible functional groups. Furthermore, the method is also suitable for the reductive ring-cleavage of polyfluorinated as well as non-fluorinated isoxazoles. The utility of fluoroalkylated enaminones was demonstrated by the one-step, regioselective synthesis of fluoroalkylated pyrazole-based drugs and lead compounds such as celecoxib, deracoxib, and mavacoxib. We anticipate that the easy access of fluoroalkylated enaminones, coupled with their favorable physical properties (e.g., solid and stable) and potentially versatile reactivity, should promote more research using them for the synthesis of high-value compounds in future.

EXPERIMENTAL SECTION

General Information. All solvents were dried over activated 4 Å molecular sieves. Difluoroethylamine and trifluoroethylamine were purified by distillation. Chromatographic purification of products was carried out by flash column chromatography on silica gel (300−400 mesh). NMR spectra were measured in $CDCl_3$ (TMS, ^1H δ = 0; $CDCl_3$, ^1H δ = 7.26, ^{13}C δ = 77.16) or DMSO-d_6 (TMS, ^1H δ = 0; DMSO-d_6, ^1H δ = 2.50, ^{13}C δ = 39.52) on a Bruker AV 400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) magnetic resonance spectrometer. HRESI mass spectra were recorded on an AB Sciex Triple-TOF 5600+ mass instrument.

General Procedure for the Synthesis of Isoxazoles. 1a−1l, 3a−3l, 5a−5n were synthesized according to our previous method.[7a]

General Procedure for the Raney-Ni Catalyzed Ring-Opening of Fluoroalkylated Isoxazoles. A reaction vessel charged with isoxazole **1a** (0.2 mmol, 45 mg, 1 equiv), Raney-Ni catalyst (20 wt %), and MeOH (3 mL) were evacuated and backfilled with hydrogen (1 atm) three times. The reaction mixture was stirred under a hydrogen balloon at 35 °C on a heating mantle. Upon completion, the mixture was filtered over a plug of Celite (AcOEt as the eluent) and concentrated under reduced pressure. The resulting mixture was purified by flash column chromatography on silica gel to afford the compound **2a** and **2aa**.

General Procedures for the Synthesis of 2a−2l, 4a−4l, and 6a−6j. A solution of 1,4-dioxane (3 mL) and (1*R*,2*R*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (*t*-DMACH) (0.2 mmol, 32 μL, 2 equiv) was added to a 15 mL Schlenk tube charged with CuI (30 mmol %, 5.7 mg for **2a−2l**; $Cu(OAc)_2$, 50 mmol %, 10 mg for **4a−4l** and **6a−6j**), isoxazole **1** (0.1 mmol, 1 equiv), and a magnetic stirring bar under nitrogen atmosphere. The mixture was stirred at 140 °C for 36 h on a heating mantle, then cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to afford the desired products.

Procedure for the Gram-Scale Synthesis of Trifluoromethylated β-Enaminones 4a. In a round-bottom flask (250 mL) equipped with a condenser was charged with **3a** (6.6 mmol, 1.5 g, 1 equiv), $Cu(OAc)_2$ (50 mmol %, 660 mg), and purged with nitrogen three times. Then 1,4-dioxane (100 mL) and *t*-DMACH (13.2 mmol, 2.1 mL, 2 equiv) were added and the resulting solution was allowed to stir at 140 °C for 36 h in an oil bath under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was filtered over a plug of Celite (AcOEt as eluent) and the filtrate was washed with saturated aqueous NaCl (30 mL). The two layers were separated and the aqueous layer was extracted with AcOEt and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/AcOEt) to give the desired product **4a** (1.16 g, 77% yield, 93% yield based on the recovery of the starting material).

General Procedure for the Synthesis of Fluorinated Pyrazoles 7−12. A reaction vessel charged with 4-hydrazinobenzene hydrochloride (0.15 mmol, 1.5 equiv), acetic acid (0.3 mmol, 17 μL, 3 equiv), and enaminone (0.1 mmol, 1.0 equiv) in ethanol (2 mL) was stirred at 80 °C on a heating mantle. Upon completion, the solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography.

*5-(4-Methoxyphenyl)-3-(perfluoroethyl)isoxazole (**5g**).* Purified by flash column chromatography (petroleum ether/AcOEt = 200:1), yellow solid, mp 90−92 °C; 726 mg, 62%; ^1H NMR (400

https://dx.doi.org/10.1021/acs.joc.0c02980
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MHz, $CDCl_3$) δ 7.75 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.63 (s, 1H), 3.88 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −84.30 (t, J = 1.85 Hz, 3F), −114.6 (q, J = 1.85 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −84.30 (t, J = 1.85 Hz, 3F), −114.6 (q, J = 1.85 Hz, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 162.1, 155.1 (C−F, $^2J_{C-F}$ = 28.0 Hz), 127.9, 119.9 (C−F, $^1J_{C-F}$ = 285.9, 36.1 Hz), 118.9, 114.8, 109.9 (C−F, $1J_{C-F}$ = 253.8, 40.3 Hz), 96.4, 55.6; HRMS (ESI-TOF) m/z calcd for $C_{12}H_9F_5NO_2^-$ $[M + H]^+$ 294.0548, found 294.0545.

*3-(Difluoromethyl)-5-phenethylisoxazole (**5e**).* Purified by flash column chromatography (petroleum ether/AcOEt = 200:1), colorless oil, 432 mg, 48%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 2H), 7.25−7.21 (m, 1H), 7.19−7.14 (m, 2H), 6.70 (t, J = 53.9 Hz, 1H), 6.15 (s, 1H), 3.13−3.07 (m, 2H), 3.05−2.99 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.19 (d, J = 53.9 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −115.19 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 158.8 (C−F, $^2J_{C-F}$ = 30.0 Hz), 139.7, 128.8, 128.3, 126.7, 109.3 (C−F, $^1J_{C-F}$ = 237.6 Hz), 98.2, 33.5, 28.6; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}F_2NO^-$ $[M + H]^+$ 224.0881, found 224.0884.

*5-Phenethyl-3-(trifluoromethyl)isoxazole (**5f**).* Purified by flash column chromatography (petroleum ether/AcOEt = 200:1), colorless oil, 503 mg, 52%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 2H), 7.27−7.20 (m, 1H), 7.19−7.14 (m, 2H), 6.16 (s, 1H), 3.16−3.10 (m, 2H), 3.07−3.00 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.30 (s, 3F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −63.30 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.3, 155.5 (C−F, $^2J_{C-F}$ = 38.0 Hz), 139.4, 128.8, 128.3, 126.9, 119.9 (C−F, $^1J_{C-F}$ = 271.0 Hz), 99.1, 33.5, 28.6; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{11}F_3NO^-$ $[M + H]^+$ 242.0787, found 242.0791.

*(Z)-3-Amino-4,4-difluoro-1-(4-methoxyphenyl)but-2-en-1-one (**2a**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), off white solid, mp 87−88 °C, 21.6 mg, 95% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (bs, 1H), 7.88 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.11 (t, J = 55.8 Hz, 1H), 5.96 (s, 1H), 5.56 (bs, 1H), 3.83 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.29 (d, J = 55.8 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.29 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.5, 162.8, 152.7 (C−F, $^2J_{C-F}$ = 22.0 Hz), 131.8, 129.6, 113.8, 111.8 (C−F, $^1J_{C-F}$ = 244.0 Hz), 90.9 (C−F, $^3J_{C-F}$ = 6.1 Hz), 55.5; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{10}F_2NO_2^-$ $[M-H]^-$ 226.0685, found 226.0687.

*(Z)-3-Amino-1-(4-methoxyphenyl)but-2-en-1-one (**2aa**).*[19a] Purified by flash column chromatography (petroleum ether/AcOEt = 3:1), yellow solid, 6.8 mg, 18% yield; ^1H NMR (400 MHz, CDCl3) δ 10.13 (bs, 1H), 7.89−7.84 (m, 2H), 6.94−6.88 (m, 2H), 5.71 (s, 1H), 5.09 (bs, 1H), 3.85 (s, 3H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.6, 162.2, 161.8, 132.8, 129.0, 113.4, 91.9, 55.3, 22.9.

*(Z)-3-Amino-4,4-difluoro-1-(p-tolyl)but-2-en-1-one (**2b**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), off white solid, mp 82−84 °C, 19.4 mg, 92% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 6.12 (t, J = 55.2 Hz, 1H), 5.99 (s, 1H), 5.44 (bs, 1H), 2.40 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.34 (d, J = 55.2 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.34 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.4, 153.1 (C−F, $^2J_{C-F}$ = 21.5 Hz), 142.7, 136.4, 129.3, 127.5, 111.7 (C−F, $^1J_{C-F}$ = 242.0 Hz), 91.1 (C−F, $^3J_{C-F}$ = 6.0 Hz), 21.6; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{10}F_2NO^-$ $[M-H]^-$ 210.0736, found 210.0735.

*(Z)-3-Amino-4,4-difluoro-1-phenylbut-2-en-1-one (**2c**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), pale yellow solid, mp 65−68 °C, 17.9 mg, 91% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 7.90 (d, J = 7.4 Hz, 2H), 7.54−7.40 (m, 3H), 6.14 (t, J = 55.0 Hz, 1H), 6.01 (s, 1H), 5.50 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.43 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.43 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.6, 153.4 (C−F, $^2J_{C-F}$ = 22.0 Hz), 139.1, 132.1, 128.6, 127.5, 111.6 (C−F, $^1J_{C-F}$ = 224.0 Hz), 91.1 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_8F_2NO^-$ $[M-H]^-$ 196.0579, found 196.0577.

*(Z)-1-([1,1′-Biphenyl]-4-yl)-3-amino-4,4-difluorobut-2-en-1-one (**2d**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), white solid, mp 127−129 °C, 22.4 mg, 82% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (bs, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz 2H), 7.66−7.60 (m, 2H), 7.47 (t, J = 7.3 Hz, 2H), 7.43−7.36 (m, 1H), 6.16 (t, J = 55.3 Hz, 1H), 6.06 (s, 1H), 5.40 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.43 (d, J = 55.3 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.43 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 153.3 (C−F, $^2J_{C-F}$ = 22.0 Hz), 144.8, 140.2, 137.8, 129.0, 128.1 (2C), 127.4, 127.3, 111.7 (C−F, $^1J_{C-F}$ = 243.7 Hz), 91.2 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{16}H_{12}F_2NO^-$ $[M-H]^-$ 272.0892, found 272.0896.

*(Z)-3-Amino-4,4-difluoro-1-(4-(methylthio)phenyl)but-2-en-1-one (**2e**).* Purified by flash column chromatography (petroleum ether/AcOEt = 8:1), pale brown solid, mp 107−108 °C, 23.2 mg, 95% yield; ^1H NMR (400 MHz, $CDCl_3$)δ 9.46 (bs, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.12 (t, J = 55.0 Hz, 1H), 5.96 (s, 1H), 5.52 (bs, 1H), 2.49 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.27 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.27 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.5, 153.2 (C−F, $^2J_{C-F}$ = 21.9 Hz), 144.3, 135.3, 127.9, 125.2, 111.7 (C−F, $^1J_{C-F}$ = 244.6 Hz), 90.8 (C−F, $^3J_{C-F}$ = 6.0 Hz), 15.0; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{12}ONF_2S^+$ $[M + H]^+$ 244.0602, found 244.0609.

*(Z)-3-Amino-4,4-difluoro-1-(4-fluorophenyl)but-2-en-1-one (**2f**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), pale yellow solid, mp 70−72 °C, 19.4 mg, 90% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (bs, 1H), 7.95−7.87 (m, 2H), 7.06−7.05 (m, 2H), 6.13 (t, J = 54.8 Hz, 1H), 5.95 (s, 1H), 5.47 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.46 to −107.54 (m, 1F), −122.57 (d, J = 54.8 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −107.49 (s, 1F), −122.57 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.1, 165.2 (C−F, $^1J_{C-F}$ = 253.2 Hz), 153.5 (C−F, $^2J_{C-F}$ = 22.0 Hz), 135.3 (C−F, $^4J_{C-F}$ = 2.9 Hz), 129.9 (C−F, $^3J_{C-F}$ = 9.7 Hz), 115.6 (C−F, $^2J_{C-F}$ = 21.2 Hz), 111.5 (C−F, $^1J_{C-F}$ = 244.1 Hz), 90.7 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_7F_3NO^-$ $[M-H]^-$ 214.0485, found 214.0490.

*(Z)-3-Amino-1-(4-chlorophenyl)-4,4-difluorobut-2-en-1-one (**2g**).* Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow solid, mp 85−86 °C, 18.5 mg, 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (bs, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 6.13 (t, J = 55.0 Hz, 1H), 5.94 (s, 1H), 5.53 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.65 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.65 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.2, 153.8 (C−F, $^2J_{C-F}$ = 22.3 Hz), 138.3, 137.4, 128.9, 128.8, 111.5 (C−F, $^1J_{C-F}$ = 243.9 Hz), 90.6 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_7ClF_2NO^-$ $[M-H]^-$ 230.0189, found 230.0198.

*(Z)-3-Amino-4,4-difluoro-1-(4-(trifluoromethyl)phenyl)but-2-en-1-one (**2h**).* Purified by flash column chromatography (petroleum ether/AcOEt = 8:1), white solid, mp 86−87 °C, 23.1 mg, 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (bs, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 6.16 (t, J = 55.0 Hz, 1H), 5.98 (s, 1H), 5.52 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.96 (s, 3F), −122.81 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −62.96 (s, 3F), −122.81 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.2, 154.4 (C−F, $^2J_{C-F}$ = 21.9 Hz), 142.0, 133.4 (C−F, $^2J_{C-F}$ = 32.5 Hz), 127.8, 125.6 (C−F, $^3J_{C-F}$ = 3.8 Hz), 123.9 (C−F, $^1J_{C-F}$ = 272.4 Hz), 111.3 (C−F, $^1J_{C-F}$ = 244.1 Hz), 90.7 (C−F, $^3J_{C-F}$ = 5.9 Hz); HRMS (ESI-TOF) m/z calcd for $C_{11}H_7NF_5O^-$ $[M-H]^-$ 264.0453, found 264.0457.

*(Z)-4-(3-Amino-4,4-difluorobut-2-enoyl)benzonitrile (**2i**).* Purified by flash column chromatography (petroleum ether/AcOEt = 5:1), pale brown solid, mp 138−140 °C, 17.8 mg, 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 6.17 (t, J = 55.0 Hz, 1H), 5.96 (s, 1H), 5.65 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.95 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.95 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.4, 154.8 (C−F, $^2J_{C-F}$ = 22.4 Hz), 142.5, 132.5, 127.9, 118.4, 115.2, 111.1 (C−F, $^1J_{C-F}$ = 245.0 Hz), 90.6 (C−F, $^3J_{C-F}$ = 5.6 Hz); HRMS (ESI-TOF) m/z calcd for $C_{11}H_7N_2F_2O^-$ $[M-H]^-$ 221.0532, found 221.0532.

https://dx.doi.org/10.1021/acs.joc.0c02980
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(Z)-3-Amino-4,4-difluoro-1-(4-nitrophenyl)but-2-en-1-one ***(2j)***. Purified by flash column chromatography (petroleum ether/AcOEt = 5:1), yellow solid, mp 123−125 °C, 17.9 mg, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (bs, 1H), 8.29 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.5 Hz, 2H), 6.19 (t, J = 55.0 Hz, 1H), 5.99 (s, 1H), 5.65 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.01 (d, J = 55.0 Hz, 2F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −123.01 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.1, 154.9 (C−F, $^2J_{C-F}$ = 22.4 Hz), 144.1, 128.4, 123.9, 111.1 (C−F, $^1J_{C-F}$ = 246.0 Hz), 90.8 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_7N_2F_2O_3^-$ [M−H]$^-$ 241.0430, found 241.0431.

(Z)-3-Amino-4,4-difluoro-1-(3-fluorophenyl)but-2-en-1-one ***(2k)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow solid, mp 76−78 °C, 20.9 mg, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (bs, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61−7.55 (m, 1H), 7.44−7.37 (m, 1H), 7.20 (tdd, J = 8.3, 2.7, 1.0 Hz, 1H), 6.14 (t, J = 54.8 Hz, 1H), 5.94 (s, 1H), 5.55 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.33 to −112.41 (m, 1F), −122.65 (d, J = 54.8 Hz, 2F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −112.37 (s, 1F), −122.65 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.0 (C−F, $^4J_{C-F}$ = 2.2 Hz), 163.0 (C−F, $^1J_{C-F}$ = 247.4 Hz), 154.0 (C−F, $^2J_{C-F}$ = 22.0 Hz), 141.3 (C−F, $^3J_{C-F}$ = 6.3 Hz), 130.2 (C−F, $^3J_{C-F}$ = 7.7 Hz), 123.1 (C−F, $^4J_{C-F}$ = 3.0 Hz), 119.0 (C−F, $^2J_{C-F}$ = 21.5 Hz), 114.4 (C−F, $^2J_{C-F}$ = 22.5 Hz), 111.4 (C−F, $^1J_{C-F}$ = 244.1 Hz), 90.8 (C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_7F_3NO^-$ [M−H]$^-$ 214.0485, found 214.0488.

(Z)-3-Amino-4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)but-2-en-1-one ***(2l)***. Purified by flash column chromatography (petroleum ether/AcOEt = 6:1), pale yellow solid, mp 75−76 °C, 22.8 mg, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$)δ 9.41 (bs, 1H), 7.63−7.60 (m, 2H), 6.93 (t, J = 8.5 Hz, 1H), 6.12 (t, J = 55.0 Hz, 1H), 5.88 (s, 1H), 5.62 (bs, 1H), 3.89 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.35 (d, J = 55.0 Hz, 2F), −134.72 to −134.78 (m, 1F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.35 (s, 2F), −134.75 (s, 1F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.2 (C−F, $^4J_{C-F}$ = 1.7 Hz), 153.4 (C−F, $^2J_{C-F}$ = 22.0 Hz), 152.1 (C−F, $^1J_{C-F}$ = 236.8 Hz), 150.8 (C−F, $^2J_{C-F}$ = 10.8 Hz), 132.1 (C−F, $^3J_{C-F}$ = 5.2 Hz), 124.3 (C−F, $^3J_{C-F}$ = 3.3 Hz), 115.1 (C−F, $^2J_{C-F}$ = 19.2 Hz), 112.4 (C−F, $^4J_{C-F}$ = 1.7 Hz), 111.6 (C−F, $^1J_{C-F}$ = 244.0 Hz), 90.3 (C−F, $^3J_{C-F}$ = 6.0 Hz), 56.2;HRMS (ESI-TOF) m/z calcd for $C_{11}H_{11}O_2NF_3^+$ [M + H]$^+$ 246.0736, found 246.0726.

(Z)-3-Amino-4,4,4-trifluoro-1-(p-tolyl)but-2-en-1-one ***(4a)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), pale blue solid, mp 85−87 °C, 21.8 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 6.23 (s, 1H), 2.41 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{19}F{1H} NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.6, 148.5 (C−F, $^2J_{C-F}$ = 33.1 Hz), 143.2, 136.2, 129.4, 127.7, 120.7 (C−F, $^1J_{C-F}$ = 276.3 Hz), 90.5 (C−F, $^3J_{C-F}$ = 3.3 Hz), 21.7; HRMS (ESI-TOF) m/z calcd for $C_{11}H_9F_3NO$- [M−H]$^-$ 228.0641, found 228.0639.

(Z)-3-Amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one ***(4b)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), pale green solid, mp 64−66 °C, 19.6 mg, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.7 Hz, 2H), 7.62−7.37 (m, 3H), 6.25 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.9, 148.8 (C−F, $^2J_{C-F}$ = 33.0 Hz), 138.7, 132.4, 128.7, 127.6, 120.6 (C−F, $^1J_{C-F}$ = 274.6 Hz), 90.5 (C−F, $^3J_{C-F}$ = 3.3 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_7F_3NO^-$ [M−H]$^-$ 214.0485, found 214.0486.

(Z)-1-([1,1′-Biphenyl]-4-yl)-3-amino-4,4,4-trifluorobut-2-en-1-one ***(4c)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), yellow solid, mp 138−140 °C, 26.5 mg, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.68−7.61 (m, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.44−7.38 (m, 1H), 6.31 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.47 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.47 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.4, 148.7 (C−F, $^2J_{C-F}$ = 33.0 Hz), 145.2, 140.1, 137.5, 129.1, 128.2 (2C), 127.4 (2C), 120.6 (C−F, $^1J_{C-F}$ = 277.7 Hz), 90.5 (C−F, $^3J_{C-F}$ = 3.5 Hz); HRMS (ESI-TOF) m/z calcd for $C_{16}H_{11}F_3NO^-$ [M−H]$^-$ 290.0798, found 290.0798.

(Z)-3-Amino-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-one ***(4d)***. Purified by flash column chromatography (petroleum ether/AcOEt = 30:1), yellow solid, mp 80−81 °C, 22.5 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.20 (s, 1H), 3.86 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.52 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.52 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.6, 163.1, 148.2 (C−F, $^2J_{C-F}$ = 33.0 Hz), 131.6, 129.7, 120.7 (C−F, $^1J_{C-F}$ = 277.5 Hz), 113.9, 90.3 (C−F, $^3J_{C-F}$ = 3.5 Hz), 55.5; HRMS (ESI-TOF) m/z calcd for $C_{11}H_9F_3NO_2^-$ [M−H]$^-$ 244.0591, found 244.0587.

(Z)-3-Amino-4,4,4-trifluoro-1-(4-(methylthio)phenyl)but-2-en-1-one ***(4e)***. Purified by flash column chromatography (petroleum ether/AcOEt = 1:1), pale yellow solid, mp 109−110 °C, 20.9 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.20 (s, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.52 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.52 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.8, 148.6 (C−F, $^2J_{C-F}$ = 33.6 Hz), 145.0, 135.0, 128.0, 125.3, 120.2 (C−F, $^1J_{C-F}$ = 276.4 Hz), 90.3, 15.0; HRMS (ESI-TOF) m/z calcd for $C_{11}H_9F_3NOS^-$ [M−H]$^-$ 260.0362, found 260.0361.

(Z)-3-Amino-4,4,4-trifluoro-1-(4-fluorophenyl)but-2-en-1-one ***(4f)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), white solid, mp 65−67 °C, 22.1 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.88 (m, 2H), 7.12 (t, J = 8.6 Hz, 2H), 6.18 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.56 (s, 3F), −106.65 to −106.85 (m, 1F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.56 (s, 3F), −106.79 (s, 1F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.3, 165.5 (C−F, $^1J_{C-F}$ = 253.3 Hz), 149.0 (C−F, $^2J_{C-F}$ = 33.3 Hz), 135.0 (C−F, $^4J_{C-F}$ = 3.0 Hz), 130.0 (C−F, $^3J_{C-F}$ = 9.2 Hz), 120.5 (C−F, $^1J_{C-F}$ = 277.5 Hz), 115.7 (C−F, $^2J_{C-F}$ = 21.9 Hz), 90.1 (C−F, $^3J_{C-F}$ = 3.5 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_6F_4NO^-$ [M−H]$^-$ 232.0391, found 232.0391.

(Z)-3-Amino-1-(4-chlorophenyl)-4,4,4-trifluorobut-2-en-1-one ***(4g)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), yellow solid, mp 81−83 °C, 22.9 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.18 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.54 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.5, 149.2 (C−F, $^2J_{C-F}$ = 33.2 Hz), 138.8, 137.1, 129.0 (2C), 120.5 (C−F, $^1J_{C-F}$ = 276.0 Hz), 90.1 (C−F, $^3J_{C-F}$ = 3.5 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_6ClF_3NO^-$ [M−H]$^-$ 248.0095, found 248.0093.

(Z)-4-(3-Amino-4,4,4-trifluorobut-2-enoyl)benzonitrile ***(4h)***. Purified by flash column chromatography (petroleum ether/AcOEt = 5:1), white solid, mp 164−166 °C, 20.6 mg, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 6.18 (s, 1H), 5.54 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.51 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.51 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.8, 149.1 (C−F, $^2J_{C-F}$ = 33.4 Hz), 141.1, 131.6, 127.1, 119.3 (C−F, $^1J_{C-F}$ = 277.0 Hz), 117.3, 114.5, 89.0 (C−F, $^3J_{C-F}$ = 3.4 Hz); HRMS (ESI-TOF) m/z calcd for $C_{11}H_6F_3N_2O^-$ [M−H]$^-$ 239.0437, found 239.0436.

(Z)-3-Amino-4,4,4-trifluoro-1-(4-nitrophenyl)but-2-en-1-one ***(4i)***. Purified by flash column chromatography (petroleum ether/AcOEt = 5:1), yellow solid, mp 140−142 °C, 20.8 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (bs, 1H), 8.29 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 6.20 (s, 1H), 5.66 (bs, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.51 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.51 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.6, 150.2 (C−F, $^2J_{C-F}$ = 33.5 Hz), 150.0, 143.6, 128.6, 124.4, 120.2 (C−F, $^1J_{C-F}$ = 276.0 Hz), 90.1 (C−F, $^3J_{C-F}$ = 3.3 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_6F_3N_2O_3^-$ [M−H]$^-$ 259.0336, found 259.0335.

(Z)-3-Amino-4,4,4-trifluoro-1-(3-fluorophenyl)but-2-en-1-one ***(4j)***. Purified by flash column chromatography (petroleum ether/AcOEt = 50:1), yellow solid, mp 63−65 °C, 21.9 mg, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.7 Hz, 1H), 7.62−7.56 (m,

https://dx.doi.org/10.1021/acs.joc.0c02980
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1H), 7.46−7.38 (m, 1H), 7.25−7.19 (m, 1H), 6.18 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.55 (s, 3F), −112.11 to −112.18 (m, 1F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −71.55 (s, 3F), −112.15 (s, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.3 (C−F, $^4J_{C-F}$ = 2.3 Hz), 163.1 (C−F, $^1J_{C-F}$ = 247.4 Hz), 149.4 (C−F, $^2J_{C-F}$ = 33.6 Hz), 140.9 (C−F, $^3J_{C-F}$ = 6.2 Hz), 130.3 (C−F, $^3J_{C-F}$ = 7.6 Hz), 123.2 (C−F, $^4J_{C-F}$ = 3.0 Hz), 120.5 (C−F, $^1J_{C-F}$ = 276.7 Hz), 119.3 (C−F, $^2J_{C-F}$ = 21.5 Hz), 114.5 (C−F, $^2J_{C-F}$ = 22.4 Hz), 90.2 (C−F, $^3J_{C-F}$ = 3.4 Hz); HRMS (ESI-TOF) m/z calcd for $C_{10}H_6F_4NO^-$ $[M-H]^-$ 232.0391, found 232.0392.

(Z)-N-(3-(3-Amino-4,4,4-trifluorobut-2-enoyl)phenyl)acetamide ***(4k)***. Purified by flash column chromatography (petroleum ether/AcOEt = 2:1), white solid, mp 142−144 °C, 24.8 mg, 91% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.11 (s, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.12 (s, 1H), 2.06 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −69.60 (s, 3F); $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −69.60 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 189.7, 168.6, 149.0 (C−F, $^2J_{C-F}$ = 32.6 Hz), 139.7, 139.0, 129.1, 122.5, 121.8, 120.5 (C−F, $^1J_{C-F}$ = 276.5 Hz), 117.5, 87.5 (C−F, $^3J_{C-F}$ = 3.5 Hz), 24.0; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{10}F_3N_2O_2^-$ $[M-H]^-$ 271.0700, found 271.0698.

(Z)-3-Amino-4,4,4-trifluoro-1-(3-fluoro-4-methoxyphenyl)but-2-en-1-one ***(4l)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow solid, mp 84−86 °C, 24.4 mg, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.63 (m, 2H), 6.98 (t, J = 8.3 Hz, 1H), 6.14 (s, 1H), 3.93 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.56 (s, 3F), −134.35 to −134.45 (m, 1F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −71.56 (s, 3F), −134.4 (s, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.5, 152.2 (C−F, $^1J_{C-F}$ = 247.0 Hz), 151.3 (C−F, $^2J_{C-F}$ = 10.9 Hz), 148.7 (C−F, $^2J_{C-F}$ = 33.1 Hz), 131.9 (C−F, $^3J_{C-F}$ = 5.1 Hz), 124.5 (C−F, $^3J_{C-F}$ = 3.2 Hz), 120.6 (C−F, $^1J_{C-F}$ = 275.7 Hz), 115.4 (C−F, $^2J_{C-F}$ = 19.2 Hz), 112.5 (C−F, $^4J_{C-F}$ = 1.9 Hz), 89.9 (C−F, $^3J_{C-F}$ = 3.5 Hz), 56.4; HRMS (ESI-TOF) m/z calcd for $C_{11}H_8F_4NO_2^-$ $[M-H]^-$ 262.0496, found 262.0497.

5-Amino-6,6-difluoro-1-phenylhexa-1,4-dien-3-one ***(6a)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), pale yellow solid, mp 73−75 °C, 19.9 mg, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.51 (m, 3H), 7.42−7.33 (m, 3H), 6.74 (d, J = 16.0 Hz, 1H), 6.08 (t, J = 55.0 Hz, 1H), 5.53 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.51 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.51 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.0, 152.8 (C−F, $^2J_{C-F}$ = 22.5 Hz), 140.6, 135.2, 130.1, 129.0, 128.2, 127.6, 111.5 (C−F, $^1J_{C-F}$ = 245.3 Hz), 94.9 C−F, $^3J_{C-F}$ = 6.0 Hz); HRMS (ESI-TOF) m/z calcd for $C_{12}H_{10}F_2NO^-$ $[M-H]^-$ 222.0736, found 222.0733.

(1E,4Z)-5-Amino-6,6,6-trifluoro-1-phenylhexa-1,4-dien-3-one ***(6b)***. Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), pale green solid, mp 79−81 °C, 20.9 mg, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.52 (m, 3H), 7.42−7.34 (m, 3H), 6.76 (d, J = 15.9 Hz, 1H), 5.77 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.58 (s, 3F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −71.58 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.3, 148.3 (C−F, $^2J_{C-F}$ = 33.0 Hz), 141.3, 135.0, 130.3, 129.0, 128.3, 127.4, 120.5 (C−F, $^1J_{C-F}$ = 276.4 Hz), 94.1; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{11}F_3NO^-$ $[M + H]^+$ 242.0787, found 242.0790.

(Z)-2-Amino-1,1-difluorodec-2-en-4-one ***(6c)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), colorless oil, 17.8 mg, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (t, J = 55.0 Hz, 1H), 5.26 (s, 1H), 2.35 (t, J = 7.4 Hz, 2H), 1.62−1.51 (m, 2H), 1.32−1.22 (m, 6H), 0.90−0.79 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.47 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.47 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, CDC1$_3$) δ 202.4, 151.4 (C−F, $^2J_{C-F}$ = 22.0 Hz), 111.6 (C−F, $^1J_{C-F}$ = 243.5 Hz), 94.3 (C−F, $^3J_{C-F}$ = 6.0 Hz), 43.2, 31.7, 29.1, 25.3, 22.6, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{16}F_2NO^-$ $[M-H]^-$ 204.1205, found 204.1205.

(Z)-2-Amino-1,1,1-trifluorodec-2-en-4-one ***(6d)***. Purified by flash column chromatography (petroleum ether/AcOEt = 20:1), colorless oil, 18.1 mg, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H), 2.41 (t, J = 7.5 Hz, 1H), 1.53−1.67 (m, 2H), 1.25−1.35 (m, 6H), 0.81−0.91 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.75 (s, 3F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −71.75 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.7, 147.0 (C−F, $^2J_{C-F}$ = 33.0 Hz), 120.5 (C−F, $^1J_{C-F}$ = 276.0 Hz), 93.7, 43.5, 31.8, 29.1, 25.1, 22.6, 14.2; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{15}F_3NO^-$ $[M-H]^-$ 222.1111, found 222.1105.

(Z)-5-Amino-6,6-difluoro-1-phenylhex-4-en-3-one ***(6e)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), colorless oil, 18.5 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 2H), 7.22−7.15 (m, 3H), 5.96 (t, J = 55.0 Hz, 1H), 5.27 (s, 1H), 2.93 (t, J = 8.2 Hz, 2H), 2.71 (t, J = 8.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.51 (d, J = 55.0 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −122.51 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.7, 151.6 (C−F, $^2J_{C-F}$ = 22.2 Hz), 141.3, 128.6, 128.4, 126.1, 111.5 (C−F, $^1J_{C-F}$ = 245.0 Hz), 94.3 (C−F, $^3J_{C-F}$ = 5.9 Hz), 44.5, 31.0; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}F_2NO^-$ $[M-H]^-$ 224.0892, found 224.0886.

(Z)-5-Amino-6,6,6-trifluoro-1-phenylhex-4-en-3-one ***(6f)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), blue solid, mp 56−58 °C, 19.4 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (q, J = 7.6 Hz, 2H), 7.21−7.14 (m, 3H), 5.50 (s, 1H), 2.93 (t, J = 7.8 Hz, 2H), 2.74 (t, J = 7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.70 (s, 3F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −71.70 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.1, 147.2 (C−F, $^2J_{C-F}$ = 33.0 Hz), 141.2, 128.6, 128.4, 126.2, 120.4 (C−F, $^1J_{C-F}$ = 279.0 Hz), 93.6, 44.7, 30.8; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{11}F_3NO^-$ $[M-H]^-$ 242.0798, found 242.0794.

(Z)-3-Amino-4,4,5,5,5-pentafluoro-1-(4-methoxyphenyl)pent-2-en-1-one ***(6g)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow solid, mp 90−92 °C, 22.7 mg, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.16 (s, 1H), 3.86 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −84.15 (t, J = 1.8 Hz, 3F), −122.84 (q, J = 1.8 Hz, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −84.15 (t, J = 1.8 Hz, 3F), −122.84 (q, J = 1.8 Hz, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.3, 163.2, 147.5 (C−F, $^2J_{C-F}$ = 23.9 Hz), 131.6, 129.8, 118.5 (C−F, $^2J_{C-F}$ = 37.1 Hz, 284.5 Hz), 113.9, 110.4 (C−F, $^1J_{C-F}$ = 258.0 Hz, 38.9 Hz), 92.0 (C−F, $^3J_{C-F}$ = 6.1 Hz), 55.6; HRMS (ESI-TOF) m/z calcd for $C_{12}H_9F_5NO_2^-$ $[M-H]^-$ 294.0559, found 294.0556.

(Z)-3-Amino-4,4,5,5,6,6,6-heptafluoro-1-(4-methoxyphenyl)hex-2-en-1-one ***(6h)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow oil, 24.8 mg, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.15 (s, 1H), 3.86 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.3 (t, J = 9.9 Hz, 3F), −120.0 to −120.1 (m, 2F), −126.9 (s, 2F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −80.3 (t, J = 9.9 Hz, 3F), −120.0 to −120.1 (m, 2F), −126.9 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.2, 163.2, 147.5 (C−F, $^2J_{C-F}$ = 24.3 Hz), 131.6, 129.8, 122.1, 119.2 (C−F, $^1J_{C-F}$ = 288.2, 33.5 Hz), 113.5 (m), 109.2 (m), 92.3 (C−F, $^3J_{C-F}$ = 5.8 Hz), 55.5; HRMS (ESI-TOF) m/z calcd for $C_{13}H_9F_7NO_2^-$ $[M-H]^-$ 344.0527, found 344.0525.

(Z)-3-Amino-1,3-diphenylprop-2-en-1-one ***(6i)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow oil, 21.6 mg, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (bs, 1H), 7.99−7.91 (m, 2H), 7.69−7.60 (m, 2H), 7.53−7.38 (m, 6H), 6.15 (s, 1H), 5.59 (bs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.2, 163.1, 140.4, 137.7, 131.1, 130.8, 129.1, 128.4, 127.3, 126.5, 91.9; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{12}NO^-$ $[M-H]^-$ 222.0924, found 222.0918.

(Z)-1-([1,1′-Biphenyl]-4-yl)-3-aminohex-2-ene-1,4-dione ***(6j)***. Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), yellow oil, 21.2 mg, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (bs, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.71−7.61 (m, 4H), 7.50−7.35 (m, 3H), 6.71 (s, 1H), 6.05 (bs, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.4, 164.0, 147.6, 144.7, 140.3, 138.1, 129.0, 128.1 (2C), 127.4, 127.3, 93.4, 62.8, 14.3; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{16}NO_3^-$ $[M-H]^-$ 294.1135, found 294.1128.

https://dx.doi.org/10.1021/acs.joc.0c02980
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*Celecoxib (**7**).*[19b] Purified by flash column chromatography (petroleum ether/AcOEt = 2:1), white solid, mp 157−159 °C, 34.7 mg, 91% yield (isomer ratio = 40:1); ^{1}H NMR (400 MHz, DMSO-d_6)δ 7.89 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 4H), 7.24−7.20 (m, 4H), 7.18 (s, 1 H), 2.31 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.89 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −60.89 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 145.3, 144.0, 142.2 (C−F, $^2J_{C-F}$ = 38.0 Hz), 141.2, 139.2, 129.5, 128.8, 126.9, 126.0, 125.4, 121.3 (C−F, $^1J_{C-F}$ = 269.0 Hz), 106.2, 20.8.

*Mavacoxib (**8**).*[19b] Purified by flash column chromatography (CH_2Cl_2/MeOH = 50:1), white solid, mp 160−162 °C, 36.6 mg, 95% yield (isomer ratio = 70:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.27−7.20 (m, 2H), 7.09 (t, J = 8.6 Hz, 2H), 6.76 (s, 1H), 4.99 (s, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −62.51 (s, 3F), −110.12 to −110.20 (m, 1F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −62.51 (s, 3F), −110.16 (s, 1F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.4 (C−F, $^1J_{C-F}$ = 251.6 Hz), 144.4 (C−F, $^2J_{C-F}$ = 38.8 Hz), 142.4, 141.7, 131.0 (C−F, $^3J_{C-F}$ = 8.8 Hz), 127.8, 125.7, 124.9 (C−F, $^4J_{C-F}$ = 3.5 Hz), 121.1 (C−F, $^1J_{C-F}$ = 269.4 Hz), 116.5 (C−F, $^2J_{C-F}$ = 22.0 Hz), 106.7 (C−F, $^3J_{C-F}$ = 1.8 Hz).

*SC-560 (**9**).*[19c] Purified by flash column chromatography (petroleum ether/AcOEt = 60:1), colorless oil, 32.4 mg, 92% yield (isomer ratio = 22:1); ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.35−7.30 (m, 2H), 7.29−7.23 (m, 2H), 7.17−7.10 (m, 2H), 6.89−6.84 (m, 2H), 6.69 (s, 1H), 3.82 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.3 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −62.3 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4, 144.8, 143.5 (C−F, $^2J_{C-F}$ = 38.1 Hz), 138.0, 134.3, 130.3, 129.4, 126.7, 121.4 (C−F, $^1J_{C-F}$ = 168.7 Hz), 121.3, 114.4, 105.5, 55.4 (d, J = 2.8 Hz).

*Deracoxib (**10**).*[19d] Purified by flash column chromatography (petroleum ether/AcOEt = 3:2), white crystalline solid,; mp 160−161 °C, 37.7 mg, 95% yield (isomer ratio >185:1); ^{1}H NMR (400 MHz, DMSO-d_6)δ 7.89 (d, J = 8.6 Hz, 2H), 7.54−7.52 (m, 4H), 7.26−7.17 (m, 2H), 7.14 (t, J = 54.0 Hz, 1H), 7.06−7.04 (m, 1H), 6.98 (s, 1H), 3.85 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −111.88 (d, J = 54.0 Hz, 2F), −134.48 (m, 1F); ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −111.88 (s, 2F), −134.48 (s, 1F); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.1 (C−F, $^1J_{C-F}$ = 245.0 Hz), 147.8 (C−F, $^2J_{C-F}$ = 10.2 Hz), 147.2 (C−F, $^2J_{C-F}$ = 29.0 Hz), 143.6, 143.4, 141.3, 126.8, 125.7, 125.6 (C−F, $^3J_{C-F}$ = 3.4 Hz), 121.4 (C−F, $^3J_{C-F}$ = 7.3 Hz), 116.5 (C−F, $^2J_{C-F}$ = 22.3 Hz), 114.0 (C−F, $^4J_{C-F}$ = 2.0 Hz), 111.3 (C−F, $^1J_{C-F}$ = 232.4 Hz), 105.8, 56.1.

*3-(Difluoromethyl)-1-(4-methoxyphenyl)-5-(4-(methylthio)-phenyl)-1H-pyrazole (**11**).*[19e] Purified by flash column chromatography (petroleum ether/AcOEt = 10:1), colorless crystals, mp 100−101 °C, 31.5 mg, 91% yield (isomer ratio = 76:1); ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.22−7.20 (m, 2H), 7.17−7.11 (m, 4H), 6.89−6.86 (m, 2H), 6.76 (t, J = 55.0 Hz, 1H), 6.69 (s, 1H), 3.82 (s, 3H), 2.47 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.51 (d, J = 55.0 Hz, 2F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −111.51 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 147.3 (C−F, $^2J_{C-F}$ = 30.0 Hz), 144.5, 140.0, 132.9, 129.3, 127.1, 126.3, 126.2, 114.6, 111.7 (C−F, $^1J_{C-F}$ = 237.0 Hz), 104.3, 55.9, 15.5.

*N-(3-(1-(4-Sulfamoylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)acetamide (**12**).* Purified by flash column chromatography (CH_2Cl_2/MeOH = 50:1), colorless oil, 38.6 mg, 91% yield (isomer ratio = 36:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.87 (d, J = 8.6 Hz, 2H), 7.67 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50−7.57 (m, 4H), 7.31 (t, J = 7.9 Hz, 1H), 7.18 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 2.02 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.89 (s, 3F); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −60.89 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 168.6, 145.2, 144.0, 142.3 (C−F, $^2J_{C-F}$ = 37.7 Hz), 141.0, 139.8, 129.3, 128.7, 126.8, 125.8, 123.5, 121.2 (C−F, $^1J_{C-F}$ = 268.1 Hz), 119.7, 119.1, 106.5, 24.0; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{16}F_3N_4O_3S^+$ $[M + H]^+$ 425.0890, found 425.0897.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02980.

Experimental procedures, spectroscopic data, and NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1577900, 2038890−2038891, and 2041334 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.CCDC.cam.ac.uk/data_request/cif, or by emailing data_request@CCDC.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Science Foundation of Jiangxi province for funding (20202BABL203006). We also thank Ms. Judy Li at JXNU for the proofreading.

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https://dx.doi.org/10.1021/acs.joc.0c02980
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(13) D_2O and deuterated *t*-DMACH were also used in this reaction to detect where the hydrogens on the nitrogen atom come from. However, no conclusive results could be obtained, mainly because they are not so reliable for integration, and they are also interchangeable with protons from D_2O and the ligand.

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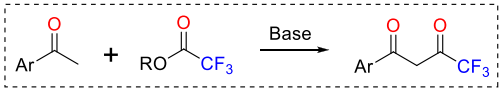
(18) Fluorinated β-diketones are generally prepared via a based mediated process as shown below, which is not compatible with compounds with an activated hydrogen (e.g., NH in **12** in Table 5).



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