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Synthesis of Trifluoromethyl Ketones via Tandem Claisen Condensation and Retro-Claisen C−C Bond-Cleavage Reaction

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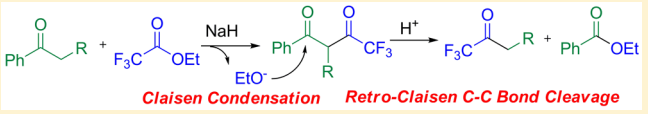
Supporting Information

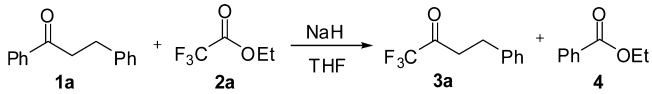
ABSTRACT: A highly efficient, operationally simple approach to trifluoromethyl ketones has been developed that builds on the use of a tandem process involving Claisen condensation and retro-Claisen C−C bond cleavage reaction. Enolizable alkyl phenyl ketones were found to react readily with ethyl trifuoroacetate under the promotion of NaH to afford trifluoroacetic ester/ketone exchange products, trifluoromethyl ketones, which were quite different from the general Claisen condensation products, β-diketones. This procedure uses readily available starting materials and can be extended to the preparation of perfluoroalkyl ketones in excellent yield.



The trifluoromethyl group has versatile influences on pharmaceuticals, agrochemicals, and materials due to its high hydrophobicity, metabolic stability, and electrowithdrawing character.[1−3] Brilliant and considerable progress has thus been made toward the development of trifluoromethylation methods.[4−11] Among numerous trifluoromethyl-containing compounds, trifluoromethyl ketones (TFMKs) constitute an important structural motif of many biologically active compounds[12−14] and intermediates for the synthesis of other trifluoromethyl-substituted compounds.[15−18] While successful strategies for the preparation of trifluoromethyl aryl ketones have been established, the synthesis of trifluoromethyl alkyl ketones still remains a challenging task. Thus, synthesis of TFMKs, especially trifluoromethyl alkyl ketones, has received much attention, and the approaches involve the reactions of organometallic reagent like Grignard reagent or alkyllithium with trifluoromethyl acid, acetate, or their salts,[19,20] nucleophilic trifluoromethylation of ester or amide with $TMSCF_3$[21,22] or $Et_3GeNa/PhSCF_3$,[23] treatment of carboxylic acid chlorides with pyridine and trifluoroacetic anhydride,[24,25] sulfone-mediated synthesis of TFMKs from alkyl and alkenyl bromides,[26] oxidation of trifluoromethylcarbinols,[27−29] catalytic aerobic oxidative decarboxylation of trifluoromethylhydroxy acids,[30] and conversion of trifluoroethylamines by the treatment of NBS/DBU.[31] Notably, Reeves and co-workers reported an efficient and general conversion of enolizable carboxylic acids to TFMKs via enediolate trifluoroacetylation/decarboxylation,[32] and the employment of cheap reagents makes it a practical method for the preparation of TFMKs. However, most of the previous methods require multiple steps or a large excess (3−6 equiv) of trifluoromethyl agents or use expensive reagents. A scalable synthesis of TFMKs from cheap reagents is still highly desirable.

When we carried out the Claisen condensation of 1,3-diphenyl-1-propanone (**1a**) with ethyl trifluoroacetate (**2a**) in the presence of NaH, 1,1,1-trifluoro-4-phenyl-2-butanone (**3a**) and ethyl benzoate (**4**) were unexpectedly observed as the exclusive products (Scheme 1). Although the formation of TFMK and benzoate in a similar reaction had been observed in an earlier report,[33] there was no further report on the application of such transformation in the preparation of TFMKs. In contrast, replacing MeONa with NaH in our protocol increased the reactivity and selectivity dramatically. The results are also different from the ring cleavage of 2-perfluoroalkanoylcycloalkanones to afford fluorinated oxo esters reported by Trabelsi,[34] which involved a multistep procedure. We are aware that this procedure may supply us a practical method to prepare TFMKs. Herein, we report the procedure to obtain TFMKs in high yield from enolizable alkyl phenyl ketones and ethyl trifluoroacetate.

Scheme 1. Formation of TFMK and Benzoate



Our study began with the investigation into the general reaction conditions with **1a** as the model substrate. The reaction was found to be highly dependent on the basicity of the base (Table 1). Weak bases gave poor yield or even no reaction (entries 9−13), while strong bases afforded excellent results (entries 2−4, 6, and 7). With NaH powder or 60% NaH dispersion in mineral oil, similar results were obtained (entries 2 and 3). Compound **4** was determined by GC with a similar yield of **3a** in all cases. When MeONa was used as the base (entry 9), a mixture containing **1a**, **4**, **3a**, and 4,4,4-trifluoro-2-benzyl-1-phenyl-1,3-butanedione was obtained, and the yield of **3a** was only 15% after 4 h. Concerning the price and convenience of operation, NaH is a better choice.

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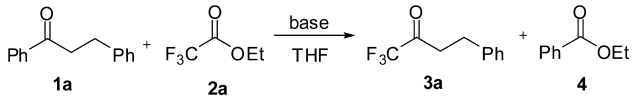
Table 1. Optimization of Base for the Reaction[a]



				yield[b] (%)	
entry	base	temp (°C)	time (h)	3a	4
1	LiH	reflux	10	84	85
2[c]	NaH	reflux	3	98	99
3[d]	NaH	reflux	3	97	99
4	KH	rt	0.5	98	99
5	CaH_2	reflux	6	72	74
6	LDA	rt	0.5	97	99
7	*n*-BuLi	0	0.4	98	99
8	*t*-BuOK	reflux	3.5	87	89
9	MeONa	reflux	4	15	19
10	$KHCO_3$	reflux	24	nr	nr
11	K_2CO_3	reflux	24	nr	nr
12	NaOH	reflux	24	10	15
13	K_3PO_4	reflux	24	trace	trace

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), base (1.2 mmol), THF (2 mL) under argon. [b]Determined by GC with biphenyl as an internal standard. [c]NaH powder was used. [d]60% NaH dispersion in mineral oil was used.

The effect of solvents on the reaction was also explored (Table 2). The reaction proceeded smoothly in most aprotic solvents. Relatively, THF, Et_2O, and benzene gave better results (entries 1, 2, and 5). The reactions proceeded more slowly in polar solvents (entries 4 and 8).

Table 2. Optimization of Solvent for the Reaction[a]

entry	solvent	temp (°C)	time (h)	yield[b] (%)
1	THF	reflux	3	98 (95[c])
2	Et_2O	reflux	3	98
3	1,4-dioxane	60	3	92
4	CH_2Cl_2	reflux	6	72
5	benzene	reflux	5	98
6	*n*-hexane	reflux	4	89
7	cyclohexane	60	3	80
8	DMSO	35	48	87

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), NaH (1.2 mmol, powder), THF (2 mL) under argon. [b]Yield of **3a** determined by GC with biphenyl as an internal standard. [c]Isolated yield.

With the general procedure established, the scope in terms of ketones was explored (Table 3). Various enolizable phenyl ketones were converted smoothly to the corresponding trifluoromethyl alkyl ketones. Substrates with functional groups such as phenyl, chloro, alkoxy, ester, and heterocycles gave the desired products in excellent yield. The relatively low yield of **3b** was attributed to the loss of product during isolation because of its low boiling point. No reaction occurred for the nonenolizable ketones under the same conditions (entries 15 and 16). Acetophenone and cycloketone yielded the corresponding *β*-diketones instead of TFMKs under such conditions (entries 17 and 18).

The reaction afforded trifluoroacetic ester/ketone exchange products, which was quite different from the general Claisen condensation giving 1,3-dicarbonyl products. We postulate that this reaction undergoes a tandem Claisen condensation and retro-Claisen C−C bond cleavage reaction (Scheme 2); the latter has received increasing attention and has been used as a particular tool in organic synthesis recently.[35−38] The enolate of ketone undergoes Claisen condensation to give 1,3-dicarbonyl product and releases ethoxy anion in the section fronts of the reaction. Then, the ethoxy anion attacks the carbonyl group in 1,3-dicarbonyl intermediate and undergoes retro-Claisen C−C bond cleavage to give benzoate and TFMK immediately. Acetophenone (Table 3, entry 17) and cycloketone (Table 3, entry 18) gave common condensation products (*β*-diketones) which indicated that the steric congestion caused by R group was in favor of the C−C bond cleavage.

In addition, the reaction was successfully extended to the synthesis of pentafluoroethyl ketone and *n*-perfluoroheptyl ketone as depicted in Table 4. The same procedure as TFMKs was conducted, except that corresponding ethyl perfluorocarboxylate was used.

In summary, we have developed an operational simple, highly efficient procedure for the synthesis of trifluoromethyl alkyl ketones via a tandem Claisen condensation and retro-Claisen C−C bond cleavage reaction. Using only a slight excess of cheap trifluoromethylation reagent, simple operation and mild conditions make it a practical method for preparation of this important class of chemicals.

EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were performed under Ar atmosphere in oven-dried glassware with magnetic stirring. Anhydrous solvents were freshly distilled from sodium and benzophenone or calcium hydride. Column chromatography was performed on silica gel (100−200 mesh) using petroleum ether/EtOAc (100:0−70:30) as an eluant. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^{1}H), 100 MHz (^{13}C), and 376 MHz (^{19}F) on a spectrometer. Chemical shift (δ) were reported in parts per million (ppm) relative to the residual solvent signal. High-resolution mass spectra (HRMS) were performed on a Q-TOF mass spectrometer in positive electrospray ionization (ESI^+) mode. Enolizable ketones were purchased from commercial sources (**1a−d,g−i,p−s**) or prepared from corresponding acetophenone and aldehydes, reduced by Pd/C-catalyzed hydrogenation according to the literature (**1e,f,j−o**).[39]

General Procedure for the Preparation of TFMKs (3). Under Ar atmosphere in a dry Schlenk tube, a mixture of NaH (6.0 mmol) and trifluoroacetate (6.0 mmol) was stirred in THF (5 mL) at room temperature for 10 min. To this mixture were added enolizable ketones (5.0 mmol) in THF (5 mL) dropwise at 0 °C under Ar atmosphere. After being stirred for 2−6 h at reaction temperature, the reaction solution was cooled to 0 °C again and quenched with five drops of 1 M HCl. After being stirred for an additional 15 min, the mixture was neutralized with saturated $NaHCO_3$ solution. After usual workup, the residue was purified by chromatography on silica gel to afford the trifluoromethylalkyl ketone products.

*1,1,1-Trifluoro-4-phenylbutan-2-one (**3a**).* yield 95% (960 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.25 (m, 5H), 2.7−3.1 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (q, J = 35.0 Hz), 139.5, 128.6, 128.3, 126.7, 115.7 (q, J = 291.0 Hz), 38.0, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.8; HRMS (ESI) m/z calcd for $C_{10}H_9F_3O$ 202.0605, found 202.0606. These spectroscopic data correspond to previously reported data.[22]

*1,1,1-Trifluorohexan-2-one (**3b**).* A 10 g portion of **1b** was used, and the product was isolated as a colorless oil by distillation: yield 48% (4.5 g); bp 91−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (t, J = 7.2 Hz, 2H), 1.67 (m, 2H), 1.39 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7(q, J = 34.5 Hz), 116.0 (q, J = 289.9 Hz), 36.2, 24.6, 22.1, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.1; MS (ESI) m/z 125, 112, 85, 69, 57. These data correspond to previously reported data.[19]

*1,1,1-Trifluorotridecan-2-one (**3c**).* colorless oil; yield 97% (1.22 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (t, J = 7.2 Hz, 2H), 1.65−1.69

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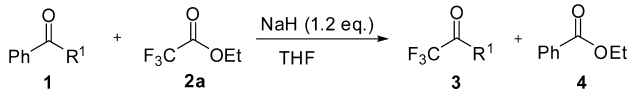
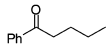
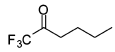
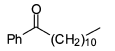
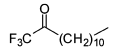
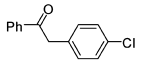
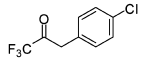
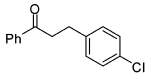
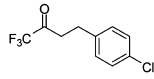
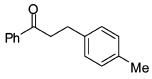
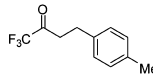
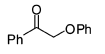
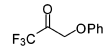
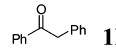
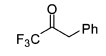
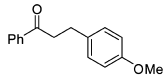
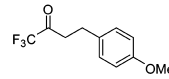
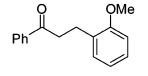
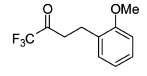
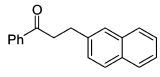
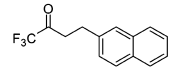
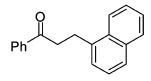
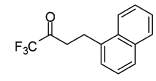
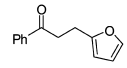
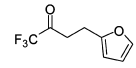
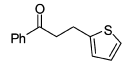
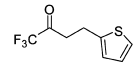
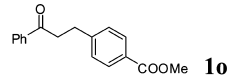
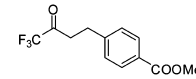
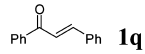
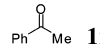
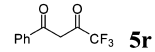
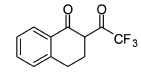
Table 3. Synthesis of TFMKs Mediated by NaH[a]



entry	ketone	temp (°C)	time(h)	product	yield[b] (%)
1[c]	 **1b**	rt	2	 **3b**	48
2	 **1c**	rt	3	 **3c**	97
3	 **1d**	reflux	4	 **3d**	90
4	 **1e**	reflux	3	 **3e**	96
5	 **1f**	reflux	3.5	 **3f**	94
6	 **1g**	reflux	2	 **3g**	93
7	 **1h**	reflux	3	 **3h**	95
8	 **1i**	reflux	2	 **3i**	95
9	 **1j**	reflux	2	 **3j**	99
10	 **1k**	reflux	2	 **3k**	94 (71[d])
11	 **1l**	reflux	3	 **3l**	90
12	 **1m**	reflux	2.5	 **3m**	90
13	 **1n**	rt	4	 **3n**	91
14	 **1o**	rt	4	 **3o**	91
15	Ph_2CO **1p**	reflux	10	nr	-
16	 **1q**	reflux	10	nr	-
17	 **1r**	reflux	2	 **5r**	98
18	 **1s**	reflux	2	 **5s**	98

[a]Reaction conditions: **1** (5.0 mmol), **2a** (6.0 mmol), NaH (6.0 mmol, powder), THF (10 mL) under argon. [b]Isolated yield. [c]10 g of **1b** was used. [d]Isolated yield by freezing crystallization.

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Scheme 2. Proposed Reaction Mechanism

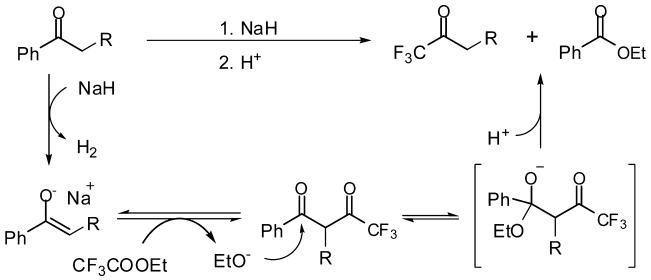
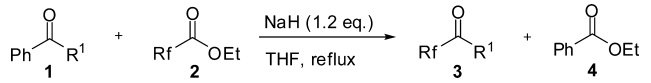
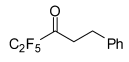
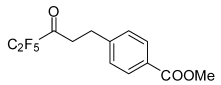
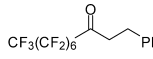


Table 4. Synthesis of Perfluoroalkyl Ketones[a]



entry	time(h)	product	yield[b](%)
1	3	 **3p**	99
2	2.5	 **3q**	97
3	4	 **3r**	98

[a]Reaction conditions: **1** (5.0 mmol), **2** (6.0 mmol), NaH (6.0 mmol, powder), THF (10 mL) under argon. [b]Isolated yield.

(m, 2H), 1.26−1.34 (m, 16H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3 (q, J = 36.6 Hz), 115.7 (q, J = 290.2 Hz), 36.3, 32.0, 29.6, 29.44, 29.42, 29.3, 28.8, 22.7, 22.4, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.4; HRMS (ESI) m/z calcd for $C_{13}H_{23}F_3O$ 252.1701, found 252.1699. These spectroscopic data correspond to previously reported data.[29]

*1,1,1-Trifluoro-3-(4-chorophenyl)propan-2-one (**3d**):* colorless oil; yield 90% (1.0 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (q, J = 35.0 Hz), 134.4, 131.3, 129.5, 129.0, 116.0 (q, J = 290.6 Hz), 42.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.8; HRMS (ESI) m/z calcd for $C_9H_6ClF_3O$ 222.0060, found 222.0059. These spectroscopic data correspond to previously reported data.[40]

*1,1,1-Trifluoro-4-(4-chorophenyl)butan-2-one (**3e**):* white power; yield 96% (1.13 g); mp 36−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (q, J = 35.1 Hz), 137.9, 132.6, 129.8, 128.9, 115.6 (q, J = 289.9 Hz), 37.9, 27.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.8; HRMS (ESI) m/z calcd for $C_{10}H_8ClF_3O$ 236.0216, found 236.0212. These spectroscopic data correspond to previously reported data.[41]

*1,1,1-Trifluoro-4-(4-methylphenyl)butan-2-one (**3f**):* colorless oil; yield 94% (1.01 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1(q, J = 35.0 Hz), 136.4, 129.5, 129.2, 128.5, 115.9 (q, J = 290.3 Hz), 38.3, 28.0, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.7; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3O$: 216.0762, found 216.0764. These spectroscopic data correspond to previously reported data.[22]

*1,1,1-Trifluoro-3-(phenoxy)propan-2-one (**3g**):* colorless oil; yield 93% (950 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.34 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.94−7.21 (m, 2H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6 (q, J = 35.0 Hz), 157.3, 130.0, 122.8, 119.8, 114.5 (q, J = 290.0 Hz), 68.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.0; HRMS (ESI) m/z calcd for $C_9H_7F_3O_2$ 204.0398, found 204.0398.

*1,1,1-Trifluoro-3-phenylpropan-2-one (**3h**):* colorless oil; yield 95% (891 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.33 (m, 5H), 3.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3 (q, J = 34.8 Hz), 130.5, 129.7, 128.9, 127.9, 115.9 (q, J = 290.6 Hz), 42.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.9; HRMS (ESI) m/z calcd for $C_9H_7F_3O$ 188.0456, found 188.0449. These spectroscopic data correspond to previously reported data.[42]

*1,1,1-Trifluoro-4-(4-methoxyphenyl)butan-2-one (**3i**):* colorless oil; yield: 95% (1.10 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (q, J = 35.0 Hz), 158.4, 131.3, 129.2, 120.1, 114.1 (q, J = 290.6 Hz), 54.7, 38.1, 27.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.3; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3O_2$: 232.0711, found 232.0710. These spectroscopic data correspond to previously reported data.[22]

*1,1,1-Trifluoro-4-(2-methoxyphenyl)butan-2-one (**3j**):* colorless oil; yield 99% (1.15 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.25 (m, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.84−6.91 (m, 2H), 3.82 (s, 3H), 3.02 (t, J = 6.2 Hz, 2H), 2.98 (t, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2 (q, J = 34.6 Hz), 157.4, 130.1, 128.1, 127.5, 120.6, 115.6 (q, J = 290.5 Hz), 110.3, 55.1, 36.6, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.2; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3O_2$ 232.0711, found 232.0709. These spectroscopic data correspond to previously reported data.[22]

*1,1,1-Trifluoro-4-(2-naphthyl)butan-2-one (**3k**).* The crude product was purified by chromatography on silica gel to afford **3k** as white needle crystal, yield 94% (1.18 g). In a alternative case, after usual workup and remove of solvents, the residue was maintained at −20 °C until needle solid appearing, filtered, and washed with cold petroleum, afforded **3k** as a white needle crystal, yield: 71% (895 mg). mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.83 (m, 3H), 7.65 (s, 1H), 7.43−7.50 (m, 2H), 7.33 (d, J = 8.4 Hz, 1H), 3.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (q, J = 34.9 Hz), 136.8, 133.7, 132.5, 128.6, 127.8, 127.6, 126.8, 126.7, 126.5, 125.9, 115.7 (q, J = 290.2 Hz), 38.1, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.6; HRMS (ESI) m/z calcd for $C_{14}H_{11}F_3O$ 252.0762, found 252.0763.

*1,1,1-Trifluoro-4-(1-naphthyl)butan-2-one (**3l**):* colorless oil; yield 90% (1.14 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.45−7.53 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 3.41 (t, J = 8.0 Hz, 2H), 3.12 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (q, J = 35.0 Hz), 135.3, 134.1, 131.5, 129.2, 127.7, 126.5, 126.2, 125.9, 125.7, 123.0, 115.7 (q, J = 290.2 Hz), 37.3, 25.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.4; HRMS (ESI) m/z calcd for $C_{14}H_{11}F_3O$ 252.0762, found 252.0763.

*1,1,1-Trifluoro-4-(2-fural)butan-2-one (**3m**):* colorless oil; yield 90% (863 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 1.2 Hz, 1H), 7.27 (dd, J = 2.8, 1.2 Hz, 1H), 6.04 (d, J = 2.8 Hz, 1H), 3.07 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4 (q, J = 35.1 Hz), 152.8, 141.7, 115.7 (q, J = 289.9 Hz), 110.5, 106.1, 35.0, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.9; HRMS (ESI) m/z calcd for $C_8H_7F_3O_2$ 192.0398, found 192.0408. These spectroscopic data correspond to previously reported data.[22]

*1,1,1-Trifluoro-4-(2-thiophenyl)butan-2-one (**3n**):* yellow oil; yield 91% (943 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 2.6 Hz, 1H), 7.15 (m, 1H), 6.84 (d, J = 1.2 Hz, 1H), 3.22 (t, J = 6.8 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (q, J = 35.0 Hz), 141.7, 127.2, 125.3, 124.1, 115.6 (q, J = 290.0 Hz), 38.5, 22.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.8; HRMS (ESI) m/z calcd for $C_8H_7F_3OS$ 208.0170, found 208.0175.

*1,1,1-Trifluoro-4-(4-methoxycarbonyl)phenyl)butan-2-one (**3o**):* colorless oil; yield 91% (1.18 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.2 Hz, 2H), 7.28 (d, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.03 (t, J = 8.0 Hz, 2H), 2.96 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (q, J = 35.0 Hz), 166.8, 144.7, 125.3, 129.9, 128.3, 115.5 (q, J = 290.0 Hz), 51.9, 37.4, 28.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.9; HRMS (ESI) m/z calcd for $C_{12}H_{11}F_3O_3$ 260.0660, found

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260.0658. These spectroscopic data correspond to previously reported data.[43]

*4,4,4-Trifluoro-1-phenylbutane-1,3-dione (**5r**).* This product was isolated in enol form: white needle crystals; yield 98% (1.05 g); mp 35−37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.14 (br, 1H), 7.95 (t, J = 8.4 Hz, 2H), 7.52−7.65 (m, 3H), 6.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 177.3 (q, J = 36.0 Hz), 134.2, 132.9, 129.1, 127.7, 117.4 (q, J = 281.0 Hz), 92.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0. These spectroscopic data correspond to previously reported data.[44]

*2-(2,2,2-Trifluoroacetyl)-3,4-dihydro-2H-naphthalen-1-one (**5s**).* This product was isolated in enol form: white needle crystals; yield 98% (1.18 g); mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.67 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 2.91 (t, J = 8.4 Hz, 2H), 2.76 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 175.1 (q, J = 34.2 Hz), 141.8, 133.8, 129.7, 128.0, 127.3, 126.6, 118.0 (q, J = 283.0 Hz), 104.4, 27.7, 20.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.1. These spectroscopic data correspond to previously reported data.[45]

*1,1,1,2,2-Pentafluoro-5-phenylpentan-3-one (**3p**):* colorless oil; yield 99% (1.25 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.32 (m, 5H), 3.07 (t, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5 (q, J = 26.0 Hz), 139.4, 128.7, 128.3, 126.7, 117.9 (qt, J = 284.0, 33.0 Hz), 107.1 (tq, J = 265.0, 38.0 Hz), 39.1, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.9, −123.3; HRMS (ESI) m/z calcd for $C_{11}H_9F_5O$ 252.0574, found 252.0571. These spectroscopic data correspond to previously reported data.[46]

*1,1,1,2,2-Pentafluoro-5-(4-methoxycarbonyl)phenyl)pentan-3-one (**3q**):* colorless oil; yield 97% (1.50 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 3.70 (s, 3H), 3.14 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2 (q, J = 27.0 Hz), 166.6, 144.6, 129.8, 128.6, 128.2, 117.8 (qt, J = 290.0, 34.0 Hz), 106.9 (tq, J = 270.0, 38.0 Hz), 51.7, 38.2, 28.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −83.0, −124.3; HRMS (ESI) m/z calcd for $C_{13}H_{11}F_5O_3$ 310.0628, found 310.0634.

*Perfluoroheptan(2-phenylethyl)one (**3r**):* colorless oil; yield 98% (2.47 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.33 (m, 5H), 3.08 (t, J = 8.0 Hz, 2H), 2.99 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0 (q, J = 26.0 Hz), 139.4, 128.4, 128.2, 126.8, 106.7−118.8 (m), 39.8, 28.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.9, −121.1−−127.1 (m); HRMS (ESI) m/z calcd for $C_{16}H_9F_{15}O$ 502.0414, found 502.0418.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for **3a**−**r**, **5r**, and **5s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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