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Organocatalytic Reactions of α-Trifluoromethylated Esters with Terminal Alkenes at Room Temperature

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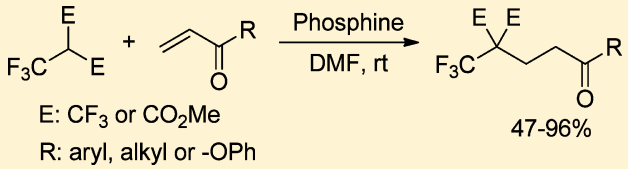
Supporting Information

ABSTRACT: CF_3-containing esters smoothly reacted with electron-deficient alkenes in the presence of a phosphine (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) organocatalyst at room temperature in an aerobic atmosphere. These Michael reactions efficiently provided products with a CF_3 quaternary carbon center.



INTRODUCTION

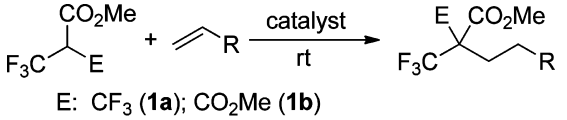
Quaternary carbon centers are frequently found as an important structural motif in various naturally occurring, biologically active compounds, so synthetic studies of such units have been extensively performed in recent years.[1] Fluorinated compounds have also attracted great interest because fluorine often endows organic molecules with many important properties such as high lipophilicity, bioavailability, and metabolic stability.[2,3] However, very few methods for the construction of trifluoromethylated all-carbon quaternary centers have been reported,[3−6] possibly because β-defluorination occurs, forming an alkene, when an anion is generated α to a CF_3 group. Until now, there have been a few examples of reactions that successfully prevent the defluorination of α-CF_3 carbanions and their equivalent building blocks,[7] including reactions with aldehydes at low temperature,[8] enol-mediated reactions,[9] palladium-catalyzed allylic alkylation,[6c−f,10] and iridium/ruthenium-catalyzed Michael addition.[6g] Despite these efforts, versatile reactions that require mild conditions are still much needed.

Unlike the case of nonfluorinated nucleophiles such as dimethyl malonate, alkylation at the methide position of the trifluoromethylated malonate **1b** is hard because β-elimination of fluoride occurs when a carbanion is formed. Ishikawa and Yokozawa reported the successful methylation of **1b** using MeI in the presence of a large excess of CsF. However, higher temperatures were required for the slightly less reactive benzyl and allyl bromides.[6a] Fuchigami and Nakagawa improved the procedure by using electrogenerated bases with a quaternary ammonium cation and extended the reaction to CH_3I, *n*-BuI, $PhCH_2Br$, *p*-$NO_2C_6H_4CH_2Br$, *p*-$NO_2C_6H_4CH_2Cl$, and $CH_2{=}CHCH_2Br$.[6b] A high-temperature pyridine-promoted Michael reaction of **1b** with methyl vinyl ketone (**2m**) was reported.[6a] The substrate was extended to the reaction of acrylonitrile and **2m** using an iridium catalyst.[6g] The scope of the alkylation of **1b** is extremely narrow, probably because of the lack of suitable conditions.

Organic synthesis using metal-free low-molecular-weight organic molecules as catalysts, which is now commonly known as organocatalysis, has developed rapidly in the past decade.[11] Organocatalysts are readily accessible, insensitive to oxygen and moisture, and nontoxic, so they have become important complements to metal catalysts. In 2009, we reported that trifluoromethylated compounds reacted with alkenes under catalysis by iridium or ruthenium complexes, giving adducts in good to excellent yields.[6g] Interestingly, when we conducted some control experiments to exclude some reaction pathways, we found that *i*-Pr_3P also promoted the reaction, although much less efficiently. This observation encouraged us to optimize the conditions by using organocatalysis for the same transformation (Scheme 1).[12]

It is assumed that the addition reaction proceeds through nucleophilic addition to the alkene of a CF_3-containing

Scheme 1. Design of Organocatalyzed Michael Reactions of CF_3-Containing Esters



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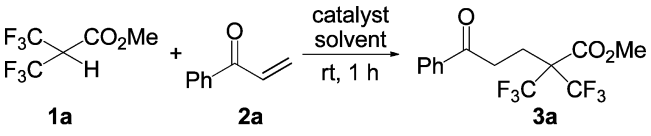
carbanion; β-fluoride elimination from the carbanion is a competing side reaction, and this seems to be hard to avoid.[6a,b,7] However, theoretically, the generation of a β-fluorinated carbanion is faster than its defluorination.[13] We therefore wondered if it is possible to optimize the reaction conditions to prohibit the β-fluoride elimination pathway. In this article, we report the results of our work on phosphine-catalyzed Michael reactions of CF_3-containing esters. To the best of our knowledge, this is the first example of a room-temperature Michael reaction with α-trifluoromethylated nucleophiles, catalyzed by neutral organocatalysts.[14]

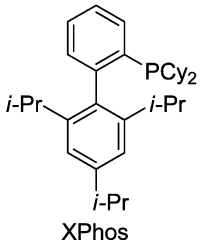
RESULTS AND DISCUSSION

We began by screening the reaction conditions of **1a** with phenyl vinyl ketone (**2a**) at room temperature (Table 1). After extensive screening of organic bases and solvents, we found that 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) promoted the reaction with extremely high efficiency, with 100% conversion of starting fluorinated material and 98% yield based on ^{19}F NMR spectroscopic monitoring (Table 1, entry 1). Other phosphines such as trimethylphosphine, tri-*n*-butylphosphine, and triphenylphosphine were less effective (Table 1, entries 2–4). The weak nucleophilicity of XPhos may prevent telomerization of the alkene. We also tested some other bases such as triethylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), and *tert*-butoxide, which promoted the reactions but gave much lower conversions and/or much lower yields (Table 1, entries 5–8). The low yields may be the result of ready β-defluorination of substrate **1a** under the effects of these bases. Reactions in polar solvents such as DMF, acetonitrile, dichloromethane, and methanol gave higher yields than those in less polar solvents such as THF and toluene (Table 1, entries 9–13). Reaction in an aerobic atmosphere was as effective as that under N_2, and anhydrous DMF was not necessary (Table 1, entry 1). These results mean that the reaction is easy to handle.

With the optimal conditions in hand, the alkene reactant scope was tested (Table 2). The reactions of various aryl vinyl ketones generated the corresponding products in moderate to excellent yields (Table 2, entries 1–16). Electron-donating and electron-withdrawing groups (Cl, Br, NO_2, CF_3, Me, or MeO) at the *para* or *meta* positions of the aryl ring of **2** were tolerated (Table 2, entries 2–9, 14–16). When **1a** ($R^1 = CF_3$) was used, electron-rich aryl vinyl ketones were more reactive as Michael acceptors and gave higher yields than those obtained with electron-deficient aryl vinyl ketones (Table 2, entries 7, 8 vs 4, 5, and 9). However, when **1b** ($R^1 = CO_2Me$) was used, the reactivity was reversed, and the electron-deficient aryl vinyl

Table 1. Screening of Reaction Conditions





entry[a]	catalyst	mol %	solvent	conv (%)[b]	yield (%)[b]
1[c]	XPhos	10	DMF	100	98 (94)
2	Me_3P	10	DMF	53	30
3	nBu_3P	10	DMF	100	76
4	PPh_3	10	DMF	100	83
5	MeONa	100	DMF	54	1[d]
6	Et_3N	100	DMF	89	45
7	DBU	100	DMF	100	15
8	*t*BuOK	10	DMF	70	52
9	XPhos	10	toluene	100	65
10	XPhos	10	CH_2Cl_2	100	88
11	XPhos	10	THF	100	63
12	XPhos	10	MeCN	100	82
13	XPhos	10	MeOH	100	85

[a]The reactions were carried out with **1a** (0.2 mmol) and phenyl vinyl ketone **2a** (0.6 mmol, 3 eqiv) in the presence of a catalyst in 0.4 mL of solvent at room temperature under a nitrogen atmosphere. [b]Conversions and yields were determined by ^{19}F NMR spectroscopy using 4-(trifluoromethyl)anisole as an internal standard. Yield of isolated product is shown in parentheses. [c]Under an aerobic atmosphere. [d]Another unidentified fluorinated product was observed.

Table 2. Michael Addition of Vinyl Ketones and Esters with 1

entry[a]	R^1	R^2	3	yield (%)[b]
1	CF_3 (**1a**)	Ph (**2a**)	**3a**	94
2[c]	CF_3 (**1a**)	4-ClC_6H_4 (**2b**)	**3b**	75
3	CF_3 (**1a**)	4-BrC_6H_4 (**2c**)	**3c**	76
4	CF_3 (**1a**)	4-$NO_2C_6H_4$ (**2d**)	**3d**	68
5	CF_3 (**1a**)	4-$CF_3C_6H_4$ (**2e**)	**3e**	72
6	CF_3 (**1a**)	4-MeC_6H_4 (**2f**)	**3f**	88
7	CF_3 (**1a**)	4-$MeOC_6H_4$ (**2g**)	**3g**	82
8	CF_3 (**1a**)	3-$MeOC_6H_4$ (**2h**)	**3h**	90
9	CF_3 (**1a**)	3-$NO_2C_6H_4$ (**2i**)	**3i**	60
10	CF_3 (**1a**)	2-naphthyl (**2j**)	**3j**	96
11	CF_3 (**1a**)	2-thienyl (**2k**)	**3k**	72
12	CF_3 (**1a**)	2-furyl (**2l**)	**3l**	77
13[c]	CO_2Me (**1b**)	2-naphthyl (**2j**)	**3m**	91
14[c]	CO_2Me (**1b**)	3-$NO_2C_6H_4$ (**2i**)	**3n**	88
15[c]	CO_2Me (**1b**)	4-ClC_6H_4 (**2b**)	**3o**	90
16[c]	CO_2Me (**1b**)	4-$MeOC_6H_4$ (**2g**)	**3p**	47
17[c,d]	CO_2Me (**1b**)	Me (**2m**)	**3q**	89
18[c,e]	CO_2Me (**1b**)	Et (**2n**)	**3r**	53
19[c,e]	CO_2Me (**1b**)	*n*-pent (**2o**)	**3s**	51
20[d]	CF_3 (**1a**)	Me (**2m**)	**3t**	93
21[e]	CF_3 (**1a**)	Et (**2n**)	**3u**	73
22[e]	CF_3 (**1a**)	*n*-pent (**2o**)	**3v**	68
23[d]	CO_2Me (**1b**)	PhO (**2p**)	**3w**	76
24[d]	CF_3 (**1a**)	PhO (**2p**)	**3x**	83

[a]The reactions were carried out with **1a** (0.2 mmol) and phenyl vinyl ketone **2a** (0.6 mmol) in the presence of 10 mol % XPhos in DMF (0.4 mL) at room temperature. [b]Isolated yields. [c]4 equiv of alkene. [d]10 mol % (4-$MeOC_6H_4)_3P$ instead of XPhos. [e]20 mol % (4-$MeOC_6H_4)_3P$ instead of XPhos.

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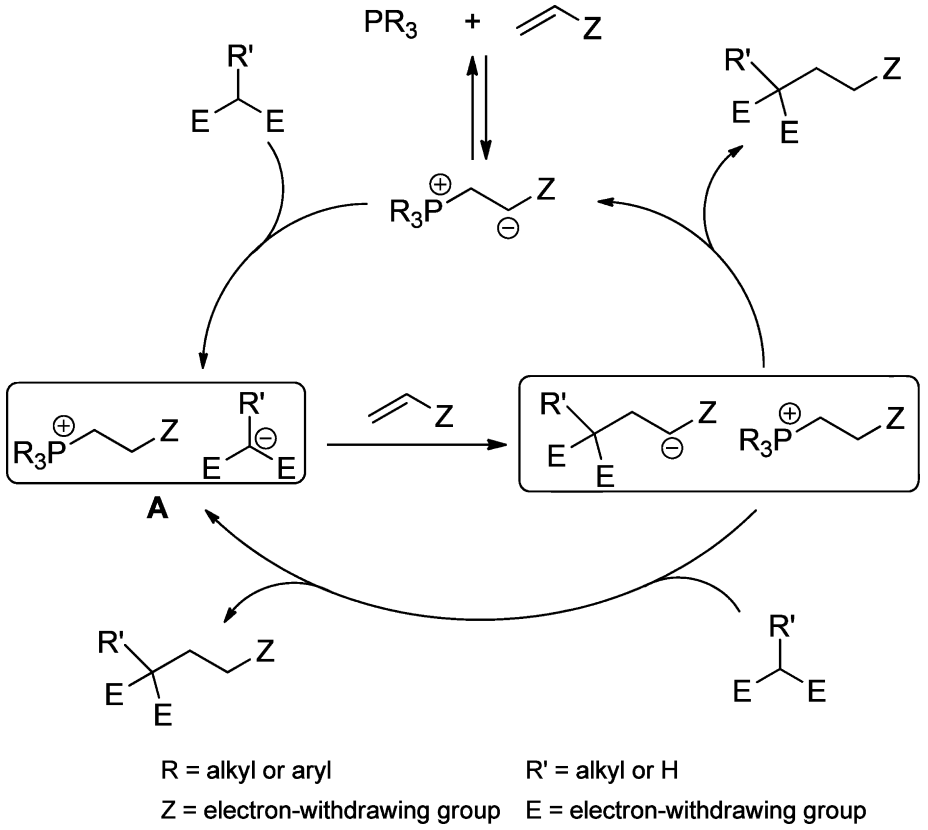
Scheme 2. Proposed Mechanism



ketone gave higher yields (Table 2, entries 14, 15 vs 16). This means that a slight change in structure may affect the results significantly. Functional groups (naphthyl, thienyl, and furyl) were compatible (Table 2, entries 10−13) with the reaction.

Alkyl vinyl ketones were also examined. For these substrates, we found that $(4\text{-}MeOC_6H_4)_3P$ was a better catalyst than XPhos. The yields of the reactions of substrates with long alkyl chains were slightly lower (Table 2, entries 17−22). When *n*-pentyl vinyl ketone was used, the yields decreased to 51% and 68% (Table 2, entries 19 and 22).

The reactions of *α*,*β*-unsaturated ester **2p** proceeded under the optimized conditions to give the adducts in good yields (Table 2, entries 23 and 24).

However, the alkene substrate scope is not wide and is limited to terminal alkenes such as aryl vinyl ketones, alkyl vinyl ketones, and a phenyl acrylate. Poor yields were obtained when methyl acrylate, acrylonitrile, and acrolein were used, probably due to polymerization side reaction. The reactivity of the Michael acceptor is crucial in this reaction. Also, the acidity of the trifluoromethylated nucleophile is important. The reaction did not occur when $CF_3CH_2CO_2Me$, which has low acidity, was used. Overall, this reaction requires a weak phosphine, an extremely active alkene, and a highly acidic nucleophile.

In the reaction catalyzed by an iridium/ruthenium complex, the reaction of **1a**/**1b** with acrylonitrile occurred at room temperature because the cyano group ligand promotes C−H activation. However, the reaction with methyl vinyl ketone required a high temperature.[6g] In contrast, the phosphine-promoted Michael reaction of **1a**/**1b** was successful with many *α*,*β*-unsaturated carbonyl compounds at room temperature. In this sense, the current work is complementary to that using organometallic complex catalysis.

Although phosphine catalysis of Michael additions is known for nonfluorinated nucleophiles,[15] reactions using fluorinated, particularly *α*-trifluoromethylated, nucleophiles have not been researched and discussed. One solution, which increases the lifetime of the fluorinated anion and simultaneously reduces defluorination, is to install electron-withdrawing group(s) to stabilize the anion; another solution is to use bulky counter cations.[7a,16] The metallic counter cations (M^+) of the normal bases used to generate the carbanions of **1a**/**1b** assist defluorination. In contrast, bulky cations impede elimination of fluoride. The phosphine-catalyzed Michael reactions of stabilized nucleophiles have been researched extensively. Initial conjugate addition by a phosphine to an activated alkene results in the formation of a phosphonium carbanion. Proton transfer gives an intermediate carbanion **A**, which reacts with another molecule of alkene to afford the product (Scheme 2).[15] In our study, we rationalize that the fluorinated nucleophilic anion is paired with a bulky quaternary phosphonium cation. Moreover, three electron-withdrawing groups increase the stability of the anions of **1a**/**1b**. As a result of a combination of these two factors, defluorination is suppressed, and the adduct is obtained smoothly.

Quaternary carbon centers exist in many pharmaceutical molecules, for example, gemfibrozil.[17] An acid **4** was obtained after hydrolysis of **3a**, and the $-C(CF_3)_2COOH$ motif of **4** is a fluorinated $-C(CH_3)_2COOH$ unit present in gemfibrozil (Scheme 3). The pK_a of **4** was 4.00 in ethanol/H_2O (3:1 by volume). This acidity is higher than those of most of carboxylic acids because of the electron-withdrawing effect of the two trifluoromethyl groups.[18] The property brought by fluorine atoms[2] is potential for drug design, and further research of biological activity will be done in due course.

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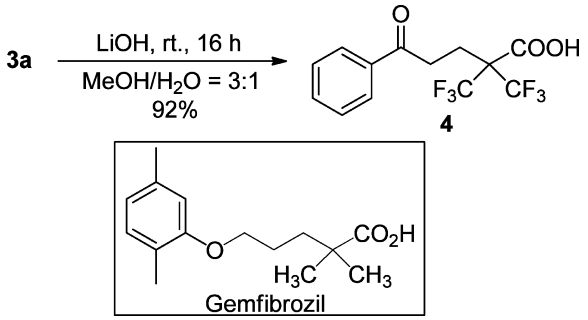
Scheme 3. Transformation of Michael Adduct 3a



CONCLUSION

In conclusion, we have developed phosphine-catalyzed Michael reactions of CF_3-containing esters with alkenes. Although limited to active Michael acceptors and highly acidic trifluoromethylated nucleophiles, these reactions with α,β-unsaturated carbonyl compounds such as (hetero)aryl vinyl ketones, alkyl vinyl ketones, and phenyl acrylate proceeded efficiently at room temperature, providing many fluorinated compounds with a CF_3-containing quaternary carbon center. After our successful use of organometallic catalysis in 2009, we now provide another method of suppressing defluorination of α-trifluoromethylated compounds in C−C bond-forming reactions, using organocatalysis. Future work will focus on enantioselective organocatalytic reactions of α-trifluoromethylated compounds with nonterminal alkenes.

EXPERIMENTAL SECTION

General Experiment Details. All reagents were commercially available and used without further purification except aryl vinyl ketones, which were prepared according to a reported method.[19] All reactions were carried out in open vessels under aerobic atmosphere. All solvents were purified according to standard methods prior to use. Melting points were determined by differential scanning calorimetry (DSC) measurements. NMR spectra were obtained on 300 MHz spectrometers and recorded at 25 °C. Chemical shifts for ^{1}H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C NMR spectra are recorded in ppm relative to internal chloroform (δ 77.0 ppm for ^{13}C), and chemical shifts for ^{19}F NMR are reported in ppm downfield from fluorotrichloromethane ($CFCl_3$). Coupling constants (J) are reported in hertz. The terms m, s, d, t, and q refer to multiplet, singlet, doublet, triplet, and quartet, respectively. ^{13}C NMR was broad-band decoupled from hydrogen nuclei. Infrared spectra (IR) were recorded with an infrared spectrometer; absorbance frequencies are given at maximum intensity in cm^{-1}. The mass analyzer type uesd for the HRMS is time-of-flight mass spectrometry (TOF-MS) or Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS). Column chromatography was performed using silica gel (mesh 300−400).

General Procedure of Michael Addition Reaction. To a solution of phosphine (0.01 or 0.02 mmol) in DMF (0.4 mL) were added α-trifluoromethylated compounds (**1**, 0.2 mmol) and α,β-unsaturated ketone or ester (**2**, 0.6 or 0.8 mmol). The mixture was stirred at room temperature for the time indicated. The reaction was monitored by ^{19}F NMR spectroscopy. After that, the reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to yield the desired product.

5-Oxo-5-phenyl-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3a). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-phenylprop-2-en-1-one (**2a**, 79.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 64.2 mg (94%). White solid; mp 42.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.14 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 162.8, 136.3, 133.5, 128.8, 128.0, 122.7 (q, J = 281.0 Hz), 60.4 (m), 54.1, 33.0, 22.9; IR (KBr) ν 2962.7, 2896.2, 1760.1, 1693.1, 1450.0, 1235.9, 1058.9, 747.3, 689.8; MS (ESI) m/z 365 [M + Na]$^+$; HRMS (ESI-FTICR-MS) calcd for $C_{14}H_{12}F_6O_3Na$ [M + Na]$^+$ 365.0583, found 365.0582.

5-Oxo-5-(4-chlorophenyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3b). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(4-chlorophenyl)prop-2-en-1-one (**2b**, 99.6 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 56.4 mg (75%). White solid; mp 61.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 3.92 (s, 3H), 3.11 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 162.8, 140.0, 134.5, 129.4, 129.0, 122.6 (q, J = 282.9 Hz), 60.5 (m), 54.1, 32.9, 22.7; IR (KBr) ν 2934.1, 2856.3, 1758.7, 1693.8, 1589.3, 1300.0, 1193.9, 1056.9, 999.6, 803.0; MS (EI) m/z 376 [M]$^+$; HRMS (EI-TOF-MS) calcd for $C_{14}H_{11}ClF_6O_3$ [M] 376.0301, found 376.0306.

5-Oxo-5-(4-bromophenyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3c). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(4-bromophenyl)prop-2-en-1-one (**2c**, 126.6 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 64.0 mg (76%). White solid; mp 85.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 3.91 (s, 3H), 3.10 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1. 162.6, 134.9, 132.0, 129.5, 128.7, 122.6 (q, J = 282.9 Hz), 60.5 (m), 54.1, 32.9, 22.7; IR (KBr) ν 2971.6, 2886.5, 1760.3, 1693.4, 1576.5, 1299.8, 997.6, 769.4, 663.2; MS (EI) m/z 420 [M]$^+$; HRMS (EI-TOF-MS) calcd for $C_{14}H_{11}BrF_6O_3$ [M] 419.9796, found 419.9795.

5-Oxo-5-(4-nitrophenyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3d). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(4-nitrophenyl)prop-2-en-1-one (**2d**, 106.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 52.6 mg (68%). White solid; mp 116.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.1 Hz, 2H), 3.93 (s, 3H), 3.19 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 162.8, 150.9, 140.6, 129.2, 124.2, 122.8 (q, J = 294.9 Hz), 60.4 (m), 54.4, 33.8, 22.8; IR (KBr) ν 3118.5, 3076.2, 2967.6, 2853.4, 1745.6, 1694.1, 1526.3, 1445.2, 1297.0, 1008.6, 860.1, 808.5, 674.0; MS (ESI) m/z 410 [M + Na]$^+$; HRMS (ESI-FTICR-MS) calcd for $C_{14}H_{11}F_6NO_5Na$ [M + Na]$^+$ 410.0434, found 410.0438.

5-Oxo-5-(4-trifluoromethylphenyl)-2,2-bis(trifluoromethyl)-pentanoic Acid Methyl Ester (3e). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**2e**, 120 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 59.0 mg (72%). White solid; mp 71.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 3.92 (s, 3H), 3.17 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2 (s, 3F), −66.2 (s, 6F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 162.6, 145.4, 138.8, 128.4, 125.8 (q, J = 3.7 Hz), 122.6 (q, J = 277.3 Hz), 122.1 (q, J = 280.2 Hz), 60.2 (m), 54.0, 33.2, 22.5; IR (KBr) ν 2923.9, 2853.5, 1755.4, 1698.7, 1490.3, 1195.3, 1081.8, 856.7, 775.6, 542.9; MS (EI) m/z 410 [M]$^+$; HRMS (EI-TOF-MS) calcd for $C_{15}H_{11}F_9O_3$ [M] 410.0564, found 410.0567.

5-Oxo-5-(4-methylphenyl)-2,2-bis(trifluoromethyl)-pentanoic Acid Methyl Ester (3f). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-*p*-tolylprop-2-en-1-one (**2f**, 87.6 mg, 0.6 mmol) were used. The mixture was stirred 1 h. Yield: 62.7 mg (88%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 3.91 (s, 3H), 3.11 (t, J = 7.8 Hz, 2H), 2.63 (t,

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J = 7.8 Hz, 2H), 2.42 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 163.0, 144.4, 133.8, 129.4, 128.1, 122.7 (q, J = 288.4 Hz), 60.7 (m), 54.1, 32.7, 23.0, 21.6; IR (KBr) ν 2961.8, 2928.3, 1760.4, 1686.0, 1608.8, 1449.4, 1297.0, 1058.2, 1003.2, 802.4; MS (ESI) m/z 379 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{15}H_{14}F_6O_3Na$ $[M + Na]^+$ 379.0739, found 379.0743.

5-Oxo-5-(4-methoxylphenyl)-2,2-bis(trifluoromethyl)-pentanoic Acid Methyl Ester (3g). XPhos (9.5 mg, 0.04 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(4-methoxyphenyl)prop-2-en-1-one (**2g**, 97.2 mg, 0.6 mmol) were used. The mixture was stirred 1 h. Yield: 61.0 mg (82%). White solid; ; mp 56.6 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); IR (KBr) ν 2928.7, 2963.2, 2843.8, 1759.1, 1682.9, 1601.7, 1512.0, 1300.0, 1246.7, 1173.5, 1056.7, 843.2, 728.0; MS (ESI) m/z 373 $(M + H)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{15}H_{14}F_6O_4Na$ $[M + Na]^+$ 395.0689, found 395.0705.

5-Oxo-5-(3-methoxylphenyl)-2,2-bis(trifluoromethyl)-pentanoic Acid Methyl Ester (3h). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(3-methoxyphenyl)prop-2-en-1-one (**2h**, 97.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 67.0 mg (90%). White solid; mp 74.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.39 (t, J = 8.1 Hz, 1H), 7.39 (d, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.13 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 159.9, 137.7, 129.6, 122.7 (q, J = 287.9 Hz), 120.5, 119.7, 118.1, 112.4, 60.4 (m), 55.3, 53.9, 32.8, 22.8; IR (KBr) ν 3009.5, 2973.1, 2842.3, 1755.1, 1694.5, 1599.7, 1562.0, 1261.1, 1191.3, 1041.9, 955.9, 783.2.0, 684.9, 601.8; MS (ESI) m/z 373 $(M + H)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{15}H_{14}F_6O_4Na$ $[M + Na]^+$ 395.0689, found 395.0694.

5-Oxo-5-(3-nitrophenyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3i). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(3-nitrophenyl)prop-2-en-1-one (**2i**, 106.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 46.4 mg (60%). White solid; mp 79.9 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.46 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.20 (t, J = 7.8 Hz, 2H), 2.67 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 162.6, 137.4, 133.5, 130.2, 127.7, 122.7 (q, J = 285.8 Hz), 60.1 (m), 54.3, 33.3, 22.7; IR (KBr) ν 3080.5, 2971.1, 2928.6, 2886.3, 1760.4, 1690.2, 1538.8, 1355.9, 1243.1, 1114.2, 1070.1, 736.2, 654.5, 519.7; MS (ESI) m/z 410 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{14}H_{11}F_6NO_5Na$ $[M + Na]^+$ 410.0434, found 410.0444.

5-Oxo-5-(naphthalen-2-yl)-2,2-bis(trifluoromethyl)-pentanoic Acid Methyl Ester (3j). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(naphthalen-2-yl)prop-2-en-1-one (**2j**, 109.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 75.2 mg (96%). White solid; mp 80.1 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.01 (t, J = 8.7 Hz, 2H), 7.90 (t, J = 7.2 Hz, 2H), 7.66−7.55 (m, 2H), 3.93 (s, 3H), 3.28 (t, J = 8.1 Hz, 2H), 2.67 (t, J = 8.1 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 163.1, 136.0, 133.7, 132.7, 129.9, 129.8, 128.9, 128.8, 128.0, 127.1, 123.8, 122.9 (q, J = 282.0 Hz), 60.4 (m), 54.3, 33.2, 23.2; IR (KBr) ν 3021.7, 2967.2, 1760.3, 1683.3.2, 1517.6, 1471.4, 1266.1, 1233.1, 1165.6, 1060.7, 764.2, 635.7, 596.7; MS (ESI) m/z 415 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{18}H_{14}F_6O_3Na$ $[M + Na]^+$ 415.0739, found 415.0760.

5-Oxo-5-(2-thienyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3k). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(thiophen-2-yl)prop-2-en-1-one (**2k**, 82.8 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 50.1 mg (72%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 1H), 7.67 (m, 1H), 7.15 (t, J = 4.2 Hz, 1H) 3.92 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 162.8, 143.3, 134.1, 132.1, 128.2, 122.6 (q, J = 287.3 Hz), 60.5 (m), 54.1, 33.5, 22.7; IR (KBr) ν 2994.0, 2898.2, 1750.4, 1668.7, 1553.6, 1406.8, 1225.3, 1065.2, 865.7, 699.5, 553.9; MS (EI) m/z 348 $[M]^+$; HRMS (EI-TOF-MS) calcd for $C_{12}H_{10}F_6O_3S$ $[M]$ 348.0255, found 348.0254.

5-Oxo-5-(2-furyl)-2,2-bis(trifluoromethyl)pentanoic Acid Methyl Ester (3l). XPhos (9.5 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), 1-(furan-2-yl)prop-2-en-1-one (**2l**, 73.2 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 51.1 mg (77%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.24 (m, 1H), 6.56 (m, 1H) 3.91 (s, 3H), 3.02 (t, J = 7.8 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 162.6, 152.1, 146.5, 122.6 (q, J = 285.8 Hz), 117.2, 112.4, 60.5 (m), 54.1, 32.7, 22.4; IR (KBr) ν 2968.2, 2931.0, 2856.2, 1752.0, 1683.3, 1441.3, 1300.6, 1270.7, 1234.0, 1070.8, 809.1, 755.6, 519.0, 474.1; MS (EI) m/z 332 $[M]^+$; HRMS (EI-TOF-MS) calcd for $C_{12}H_{10}F_6O_4$ $[M]$ 332.0483, found 332.0485.

Dimethyl 2-(3-(Naphthalen-2-yl)-3-oxopropyl)-2-(trifluoromethyl)malonate (3m). XPhos (23.8 mg, 0.05 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), 1-(naphthalen-2-yl)prop-2-en-1-one (**2m**, 364.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 173.8 mg (91%). White solid; mp 100.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.04−7.97 (m, 2H), 7.91−7.86 (m, 2H), 7.64−7.53 (m, 2H), 3.86 (s, 6H), 3.34 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.0 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 165.3, 135.6, 133.7, 132.4, 129.7, 129.6, 128.6, 128.5, 127.7, 126.8, 123.6, 123.5 (q, J = 277.0 Hz), 62.7 (q, J = 25.3 Hz), 53.6, 33.7, 25.2; IR (KBr) ν 3059.8, 2958.0, 2916.1, 1742.2, 1682.9, 1436.8, 1276.9, 1187.6, 1072.0, 794.9; MS (ESI) m/z 383.1 $[M + 1]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{19}H_{18}F_3O_5$ $[M + 1]^+$ 383.1101, found 383.1110.

Dimethyl 2-(3-(4-Nitrophenyl)-3-oxopropyl)-2-(trifluoromethyl)malonate (3n). XPhos (23.8 mg, 0.05 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), 1-(4-nitrophenyl)prop-2-en-1-one (**2n**, 354.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 165.8 mg (88%). White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 6.7 Hz, 2H), 7.44 (d, J = 6.7 Hz, 2H), 3.83 (s, 6H), 3.17 (t, J = 5.7 Hz, 2H), 2.61 (t, J = 5.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.0 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 165.2, 150.4, 140.7, 129.0, 123.9, 123.3 (q, J = 288.9 Hz), 62.4 (q, J = 26.0 Hz), 53.7, 34.3, 29.6; IR (KBr) ν 3059.8, 2952.0, 2922.1, 1739.2, 1676.2, 1626.1, 1468.0, 1278.5, 1181.6, 1123.3, 863.9, 748.1; MS (EI) m/z 377 $[M]^+$; HRMS (EI-TOF-MS) calcd for $C_{15}H_{14}NF_3O_7$ $[M]$ 377.0722, found 377.0724.

Dimethyl 2-(3-(4-Chlorophenyl)-3-oxopropyl)-2-(trifluoromethyl)malonate (3o). XPhos (9.5 mg, 0.05 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100 mg, 0.5 mmol), 1-(4-chlorophenyl)prop-2-en-1-one (**2o**, 332.0 mg, 2 mmol) were used. The mixture was stirred 4 h. Yield: 164.9 mg (90%). White solid; mp 81.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 3.82 (s, 6H), 3.14 (t, J = 7.8 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.0 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 165.3, 139.8, 134.7, 129.4, 129.0, 123.2 (q, J = 270.0 Hz), 62.5 (q, J = 26.0 Hz), 53.6, 33.6, 25.0; IR (KBr) ν 2946.0, 2916.1, 1733.2, 1682.2, 1586.3, 1439.4, 1256.6, 1178.6, 1088.7; MS (ESI) m/z 367.0 $(M + 1)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{15}H_{15}ClF_3O_5$ $[M + 1]^+$ 367.0555, found 367.0558.

Dimethyl 2-(3-(4-Methoxyphenyl)-3-oxopropyl)-2-(trifluoromethyl)malonate (3p). XPhos (23.8 mg, 0.05 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), 1-(4-methoxyphenyl)prop-2-en-1-one (**2p**, 324.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 85.1 mg (47%). White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 6.6 Hz, 2H), 6.93 (d, J = 6.6 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 6H), 3.12 (t, J = 6 Hz, 2H), 2.61 (t, J = 6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 165.2, 163.6, 130.2, 129.4, 123.4 (q, J = 287.0 Hz), 113.7, 62.6 (q, J =

26.0 Hz), 55.4, 53.5, 33.2, 25.2; IR (KBr) ν 2959.3, 2952.8, 1748.4, 1680.1, 1602.0, 1511.8, 1421.1, 1260.3, 1173.5, 1112.3, 1027.5; MS (ESI) m/z 363.0 $(M + 1)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{16}H_{17}F_3O_6Na$ $[M + Na]^+$ 385.0869, found 385.0880.

Dimethyl 2-(3-Oxobutyl)-2-(trifluoromethyl)malonate (3q).[6a] Tris(4-methoxyphenyl)phosphine (17.6 mg, 0.05 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), but-3-en-2-one (**2q**, 140.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 120.2 mg (89%).

Dimethyl 2-(3-Oxopentyl)-2-(trifluoromethyl)malonate (3r). Tris(4-methoxyphenyl)phosphine (35.2 mg, 0.1 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), pent-1-en-3-one (**2r**, 168.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 75.2 mg (53%).Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 6H), 2.57 (t, J = 6.3 Hz, 2H), 2.42−2.35 (m, 4H), 1.02 (t, J = 7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.2 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 165.3, 123.3 (q, J = 278 Hz), 62.4 (q, J = 24 Hz), 53.5, 37.0, 35.8, 24.5, 7.7; IR (KBr) ν 2958.0, 1745.2, 1712.2, 1433.4, 1283.5, 1076.7, 1028.7; MS (ESI) m/z 285.0 $(M + 1)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{11}H_{15}F_3O_5Na$ $[M + Na]^+$ 307.0764, found 307.0773.

Dimethyl 2-(3-Oxooctyl)-2-(trifluoromethyl)malonate (3s). Tris(4-methoxyphenyl)phosphine (35.2 mg, 0.1 mmol), DMF (1 mL), methyl dimethyl 2-(trifluoromethyl)malonate (**1b**, 100.0 mg, 0.5 mmol), oct-1-en-3-one (**2s**, 252.0 mg, 2 mmol) were used. The mixture was stirred for 4 h. Yield: 83.1 mg (51%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6H), 2.61(t, J = 8.1 Hz, 2H), 2.43 (t, J = 8.4 Hz, 2H), 2.40 (t, J = 7.5 Hz, 2H), 0.91−0.83 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.2 (s); IR (KBr) ν 2959.3, 2856.2, 1748.2, 1715.2, 1437.4, 1284.2, 1047.7, 804.0; MS (ESI) m/z 327.1 $(M + 1)^+$; HRMS (ESI-FTICR-MS) calcd for $C_{14}H_{21}F_3O_5Na$ $[M + Na]^+$ 349.1233, found 349.1227.

5-Oxo-2,2-bis(trifluoromethyl)hexanoic Acid Methyl Ester (3t).[6g] Tris(4-methoxyphenyl)phosphine (7.0 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), but-3-en-2-one (**2q**, 42.0 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 52.1 mg (93%).

5-Oxo-2,2-bis(trifluoromethyl)heptanoic Acid Methyl Ester (3u). Tris(4-methoxyphenyl)phosphine (14.1 mg, 0.04 mmol), DMF (0.4 mL), methyl methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), pent-1-en-3-one (**2r**, 50.4 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 42.9 mg (73%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 2.59 (t, J = 7.2 Hz, 2H), 2.46 (m, 4H), 1.08 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 162.6, 122.6 (q, J = 286.6 Hz), 60.4 (m), 53.9, 36.3, 35.8, 22.3, 7.6; IR (KBr) ν 2982.7, 2913.6, 1761.0, 1452.8, 1235.9, 1093.1, 1026.8; MS (ESI) m/z 317 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{10}H_{12}F_6O_3Na$ $[M + Na]^+$ 317.0583, found 317.0597.

5-Oxo-2,2-bis(trifluoromethyl)nonanoic Acid Methyl Ester (3v). Tris(4-methoxyphenyl)phosphine (14.1 mg, 0.04 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), oct-1-en-3-one (**2s**, 75.6 mg, 0.6 mmol) were uesd. The mixture was stirred for 1 h. Yield: 45.7 mg (68%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 2.57 (t, J = 5.4 Hz, 2H), 2.46 (m, 4H), 1.53−1.64 (m, 2H), 1.36−1.24 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.8 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 162.7, 122.6 (q, J = 284.3 Hz), 60.4 (m), 54.0, 42.7, 36.7, 31.2, 23.4, 22.3, 22.2, 13.8; IR (KBr) ν 2961.1, 2875.1, 1760.5, 1455.0, 1296.7, 1045.6; MS (ESI) m/z 359 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{13}H_{18}F_6O_3Na$ $[M + Na]^+$ 359.1052, found 359.1061.

1-Methyl 5-Phenyl 2-Methoxycarbonyl-2-trifluoromethyl-pentanedioate (3w). Tris(4-methoxyphenyl)phosphine (7.0 mg, 0.02 mmol), DMF (0.4 mL), methyl dimethyl 2-(trifluoromethyl)-malonate (**1b**, 40.0 mg, 0.2 mmol), phenyl acrylate (**2p**, 88.8 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 52.9 mg (76%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, J = 6.0 Hz, 2H), 7.27−7.22 (m, 1H), 7.10 (d, J = 6.0 Hz, 2H), 3.86 (s, 6H), 2.81 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.2, 150.5, 129.4, 125.9, 122.5 (q, J = 286.5 Hz), 121.4, 62.3 (q, J = 26.1 Hz), 53.6, 29.6, 25.7; IR (KBr) ν 3498.0, 3045.7, 2962.6, 2359.8, 1762.7, 1594.2, 1493.8, 1274.2, 1239.7, 1165.0, 1069.3; MS (ESI) m/z 371 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{15}H_{15}F_3O_6Na$ $[M + Na]^+$ 371.0718, found 371.0718.

1-Methyl 5-Phenyl 2,2-Bis(trifluoromethyl)pentanedioate (3x). Tris(4-methoxyphenyl)phosphine (7.0 mg, 0.02 mmol), DMF (0.4 mL), methyl 3,3,3-trifluoro-2-(trifluoromethyl)propanoate (**1a**, 42.0 mg, 0.2 mmol), phenyl acrylate (**2p**, 88.8 mg, 0.6 mmol) were used. The mixture was stirred for 1 h. Yield: 59.4 mg (83%). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 2H), 3.93 (s, 3H), 2.77 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.3 (s); ^{13}C NMR(100 MHz, $CDCl_3$) δ 169.7, 162.5, 150.4, 129.5, 126.1, 122.5(q, J = 286.5 Hz), 121.4, 60.4 (m), 54.2, 29.0, 23.5; IR (KBr) ν 3045.7; 2962.6; 2359.8; 1762.7; 1594.2; 1493.8; 1452.4; 1239.7; 1150.1; 1069.3; 967.6; 811.3; 755.1; 689.4; MS (ESI) m/z 381 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{14}H_{12}F_6O_4Na$ $[M + Na]^+$ 381.0532, found 381.0530.

Procedure of Hydrolysis. LiOH (72.0 mg, 3 mmol) was added to a solution of **3a** (342.0 mg, 1 mmol) in 9 mL of methanol and 3 mL of water. The solution was stirred at room temperature for 16 h. Diluted HCl aqueous solution was added to the reaction mixture. After that, the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to yield the desired product. Yield: 302.0 mg (92%).

5-Oxo-5-phenyl-2,2-bis(trifluoromethyl)pentanoic Acid (4). Yellow solid; mp 114.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 3.20 (t, J = 8.4 Hz, 2H), 2.65 (t, J = 8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.2; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 165.5, 136.0, 133.8, 128.8, 128.1, 122.5 (q, J = 282.0 Hz), 60.4 (m), 32.9, 22.9. IR (KBr) ν 3430.8, 3066.8, 2925.4, 1750.6, 1655.2, 1599.9, 1451.4, 1252.4, 1185.3, 1062.4, 1006.1, 747.6, 703.4; MS (ESI) m/z 351 $[M + Na]^+$; HRMS (ESI-FTICR-MS) calcd for $C_{13}H_{10}F_6O_3Na$ $[M + Na]^+$ 351.0426, found 351.0436.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectroscopies for all new compounds. 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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■ REFERENCES

(1) (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (f) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci.*

U.S.A. **2004**, *101*, 5363. (g) Baro, A.; Christoffers, J. *Adv. Synth. Catal.* **2005**, *347*, 1473. (h) Trost, B.; Jiang, C. *Synthesis* **2006**, 369. (i) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (j) Bella, M.; Casperi, T. *Synthesis* **2009**, 1583. (k) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (l) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (m) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (n) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207. (o) Shimizu, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5998. (p) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (q) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.

(2) (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons: West Sussex, 2009. (b) Begue, J. P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: New York, 2008. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) For reports on the biological activities of compounds bearing a trifluoromethylated quaternary all-carbon center, see: (a) Todoriki, Y.; Hirai, N.; Koshimizu, K. *Phytochemistry* **1995**, *38*, 561. (b) Jennings, L. D.; Rayner, D. R.; Jordan, D. B.; Okonya, J. F.; Basarab, G. S.; Amorose, D. K.; Anaclerio, B. M.; Lee, J. K.; Schwartz, R. S.; Whitmore, K. A. *Bioorg. Med. Chem.* **2000**, *8*, 897.

(4) For reports on electrophilic trifluoromethylations of β-ketone esters, see: Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769 and references therein.

(5) For reactions of trifluoromethylated alkenes, see: (a) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Chem. Commun.* **1997**, *16*, 1497. (b) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651. (c) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4959. (d) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983. (e) Nikolaev, V. A.; Supurgibekov, M. B.; Davies, H. M. L.; Sieler, J.; Zakharova, V. M. *J. Org. Chem.* **2013**, *78*, 4239.

(6) For reactions using α-trifluoromethylated nucleophiles, see: (a) Ishikawa, N.; Yokozawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 724. (b) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5277. (c) Sato, K.; Takiguchi, Y.; Yoshizawa, Y.; Iwase, K.; Shimizu, Y.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Chem. Pharm. Bull.* **2007**, *55*, 1593. (d) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037. (e) Li, L.; Huang, D.; Chen, Q.-Y.; Guo, Y. *Synlett* **2013**, *24*, 611. For methods of C−H activation, see: (f) Li, L.; Chen, Q.-Y.; Guo, Y. *Chem. Commun.* **2013**, *49*, 8764. (g) Guo, Y.; Zhao, X.; Zhang, D.; Murahashi, S.-I. *Angew. Chem., Int. Ed.* **2009**, *48*, 2047.

(7) (a) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817 and refrences therein. (b) Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033. (c) Nagaki, A.; Tokuoka, S.; Yamada, S.; Tomida, Y.; Oshiro, K.; Amii, H.; Yoshida, J. *Org. Biomol. Chem.* **2011**, *9*, 7559.

(8) (a) Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4*, 173. (b) Yamauchi, Y.; Kawate, T.; Itahashi, H.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6319.

(9) (a) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174. (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807.

(10) (a) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369. (b) Konno, T.; Kanda, M.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **2005**, *126*, 1517. (c) Zhang, W.; Zhao, Y.; Ni, C.; Mathew, T.; Hu, J. *Tetrahedron Lett.* **2012**, *53*, 6565. (d) Shibata, N.; Fukushi, K.; Furukawa, T.; Suzuki, S.; Tokunaga, E.; Cahard, D. *Org. Lett.* **2012**, *14*, 5366.

(11) Selected reviews: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (g) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526. (h) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (i) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (j) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (k) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

(12) Although phosphines have been studied comprehensively as efficient organocatalysts for carbon−carbon bond-forming reactions, very few fluorine-containing substrates have been used in phosphine-catalyzed reactions. (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (b) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317. (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (d) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (e) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (g) Xu, S.; He, Z. *RSC Adv.* **2013**, *3*, 16885. (h) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588−11619.

(13) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(14) A high-temperature pyridine-promoted Michael reaction of **1b** with **2m** was reported in ref 6a.

(15) Selected examples: (a) White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, *14*, 3597. (b) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598. (c) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943. (d) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

(16) For a reaction with tris(dimethylamino)sulfonium trifluoromethoxide, see: Huang, C.; Liang, T.; Harada, S.; Lee, E.; Ritter, T. *J. Am. Soc. Chem.* **2011**, *133*, 13308.

(17) Gemfibrozil is a member of the class of lipid-regulating drugs known as fibrates. It works by reducing the production of triglycerides in the liver. (a) Rubins, H. B.; Robins, S. J.; Collins, D.; Fye, C. L.; Anderson, J. W.; Elam, M. B.; Faas, F. H.; Linares, E.; Schaefer, E. J.; Schectman, G.; Wilt, T. J.; Wittes, J. *N. Engl. J. Med.* **1999**, *341*, 410. (b) Frick, M. H.; Elo, O.; Haapa, K.; Heinonen, O. P.; Heinsalmi, P.; Helo, P.; Huttunen, J. K.; Kaitaniemi, P.; Koskinen, P.; Manninen, V.; Mäenpää, H.; Mälkönen, M.; Mänttäri, M.; Norola, S.; Pasternack, A.; Pikkarainen, J.; Romo, M.; Sjöblom, T.; Nikkilä, E. A. *N. Engl. J. Med.* **1987**, *317*, 1237.

(18) The pH electrode was calibrated before using. Approximately 45 μmol of acid was dissolved into 50 mL of 75% v/v ethanol/water. This solution was titrated with 0.01 N NaOH by potentiometric titrimeter. The pK_a of the acid was read as the pH value at half volume of ending point of the titration. The pK_a of CF_3CH_2COOH is 5.08 measured by the above method.

(19) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.