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Base-promoted double-bond-migration/hydrolysis/isomerization of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates: a metal-free approach to *β*-trifluoromethyl ketones

Yuhan Zhou,*[a] Chunxia Zhang,[a] Yilong Zhao,[a] Dong Li,[a] Jinfeng Zhao,[a] Zhaotian Wang,[a] and Jingping Qu[a]

Abstract: A method for the synthesis of *β*-trifluoromethyl ketones promoted by a base is described. In the presence of DBU, 1-aryl-4,4,4-trifluoromethylbutanones with various functional groups were obtained through the reaction of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates with water in moderate to excellent yields. The reaction underwent a double-bond-migration/hydrolysis/isomerization pathway, and 1-aryl-4,4,4-trifluorobut-2-en-1-ols were determined as the key intermediates. Both electron-withdrawing and electron-donating groups, such as fluoro, chloro, bromo, ester, cyano, trifluoromethyl, alkyl, and alkoxy, were tolerated well in this reaction.

Introduction

Trifluoromethyl-containing compounds are widely used in pharmaceuticals, agrochemicals, and functional materials owing to the strong electron-withdrawing nature, superior lipophilicity and metabolic stability of trifluoromethyl group.[1] Among them, *β*-trifluoromethyl ketones constitute an important structural motif of many biologically active molecules and are intermediates for the preparation of trifluoromethylated compounds (Figure 1).[2] Thus, the synthetic approaches to *β*-trifluoromethyl ketones have drawn much attention.

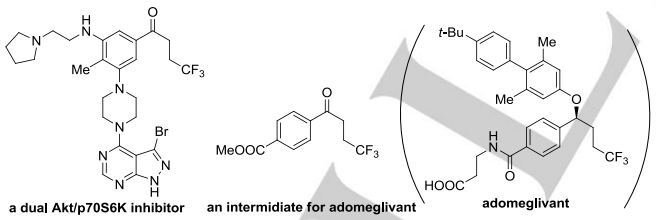

Figure 1. Applications of *β*-trifluoromethyl ketones

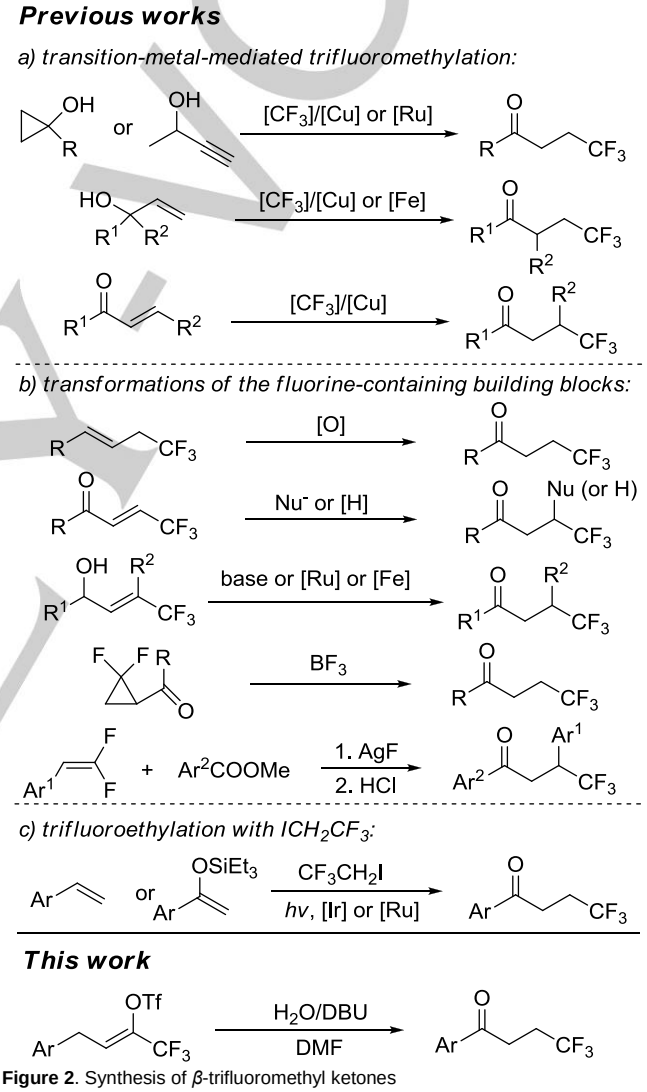

Figure 2. Synthesis of *β*-trifluoromethyl ketones

The first and foremost, *β*-trifluoromethyl ketones have been prepared successfully through the transition-metal-mediated trifluoromethylation of various substrates (Figure 2, a), such as copper-catalyzed ring-opening trifluoromethylation of cyclopropanols,[3] copper-catalyzed or photoredox trifluoromethylation of propargylic alcohols,[4] copper or iron catalyzed trifluoromethylation/semipinacol rearrangement of allylic alcohols,[5] copper-catalyzed trifluoromethylation of *α*,*β*-unsaturated ketones.[6] Additionally, the transformations of the fluorine-containing building blocks can afford *β*-trifluoromethyl

[a] State Key Laboratory of Fine Chemicals, School of Pharmaceutical Science and Technology
Dalian University of Technology
Linggong road 2, Dalian 116024, PR China
E-mail: zhouyh@dl.cn

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ketones (Figure 2, b), for example the Wacker-type oxidation of allylic trifluoromethyl-substituted alkenes,[7] hydrogenation or nucleophilic addition of *β*-trifluoromethyl-substituted enones,[8] isomerization of trifluoromethylated allylic alcohols,[9] boron trifluoride promoted ring-opening of *gem*-difluorocyclopropyl ketones,[10] AgF-mediated fluorination with concomitant cross-coupling/hydrolysis between *gem*-difluoroolefins and *α*-methoxyalkenes.[11] Furthermore, the oxidative coupling of vinylarenes with ICH_2CF_3[12] and the trifluoroethylation of silyl enol ethers (Figure 2, c) [13] also leaded to *β*-trifluoromethyl-substituted ketones.

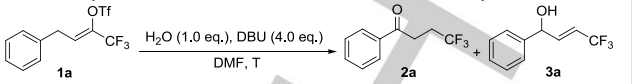
Recently, our group also committed to the preparation of organic fluorides.[14] It is worth mentioning that the useful fluorinated building blocks, (*Z*)-trifluoromethyl alkenyl triflates, were prepared and utilized successfully for the synthesis of various trifluoromethyl derivatives such as alkynes, diarylethylenes, enynes, benzofurans, allyl azides, and azirines. During the exploration of the reaction of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates in the presence of a base and water, 1-aryl-4,4,4-trifluorobutanones were detected. That offered us a practical method to *β*-trifluoromethyl ketones (Figure 2). And this metal-free reaction shows its merit for the strict restriction on the residual amount of heavy metals in pharmaceuticals and some functional materials. In this context, we describe the base-promoted synthesis of *β*-trifluoromethyl ketones from (*Z*)-trifluoromethyl alkenyl triflates.

Results and Discussion

4-Phenyl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonate (**1a**) was selected as the model substrate for optimization of the reaction conditions. 1-Phenyl-4,4,4-trifluorobutan-1-one (**2a**) and 1-phenyl-4,4,4-trifluorobut-2-en-1-ol (**3a**) were formed in the reaction of **1a** with water promoted by DBU in DMF. The preliminary results indicated that the temperature has a significant effect on the selectivity of **2a** to **3a**. Thus, the effect of the temperature was investigated initially (Table 1). When the reaction was carried out at a low temperature, **3a** was determined as the major product without the generation of **2a** (Table 1, entries 1 and 2). Raising the temperature, the ratio of **2a** to **3a** was increased (Table 1, entry 3). When the reaction was performed at room temperature, **2a** was obtained in 68% yield without **3a** (Table 1, entry 4).

We proposed that **3a** is an intermediate in the formation of **2a** (see Scheme 1), and lower temperature is in favor of the transformation of **1a** to **3a**, while higher temperature is in favor of the transformation of **3a** to **2a**. Gratifyingly, a two-step procedure was found to give better result. In other words, initiate the reaction at a low temperature (-40 °C), after the starting materials is consumed, raise it to a higher temperature. The disappearance of **3a** and the generation of **2a** at higher temperature support our suggestion. And in the second step, reacting at 80 °C for 3 h gave the best result (Table 1, entry 13). Increasing the amount of water to 2 equivalents has no effect on the reaction (Table 1, entry 15). In most of the reactions, a small amount of unknown tarry byproduct was formed.

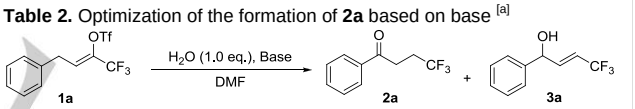
Table 1. Optimization of the formation of **2a** based on temperature [a]



Entry	T (°C)	Yield (%)[b]	
		2a	**3a**
1	-40 °C 7 h	0	85
2	-20 °C 7 h	0	78
3	0 °C 7 h	61	20
4	25 °C 7 h	68	0
5	80 °C 7 h	61	0
6	-40 °C 5 h, 40 °C 7 h	80	0
7	-40 °C 5 h, 60 °C 7 h	81	0
8	-40 °C 5 h, 80 °C 7 h	84	0
9	-40 °C 5 h, 90 °C 7 h	84	0
10	-40 °C 5 h, 100 °C 7 h	82	0
11	-40 °C 5 h, 120 °C 7 h	79	0
12	-40 °C 5 h, 80 °C 2 h	67	0
13	-40 °C 5 h, 80 °C 3 h	85	0
14	-40 °C 5 h, 80 °C 12 h	80	0
15[c]	-40 °C 5 h, 80 °C 7 h	84	0

[a] Reaction conditions: **1a** (0.2 mmol), DBU (4.0 eq.), and H_2O (1.0 eq.) in DMF (1 mL). [b] The yield was determined by ^1H NMR with dimethyl terephthalate as an internal standard. [c] H_2O (2.0 eq.).

Table 2. Optimization of the formation of **2a** based on base [a]



Entry	Base	Conv. (%) [b]	Yield (%)[b]	
			2a	**3a**
1	DBN (4 eq.)	100	68	0
2	Et_3N (4 eq.)	100	43	42
3	$EtN(i\text{-}Pr)_2$ (4 eq.)	100	49	40
4	Pyridine (4 eq.)	88	<10	70
5	K_2CO_3 (4 eq.)	100	43	15
6	$KHCO_3$ (4 eq.)	100	17	39
7	NaOH (4 eq.)	100	0	0
8	DBU (4 eq.)	100	85	0
9	DBU (0.5 eq.)	56	<10	0
10	DBU (3 eq.)	100	80	0
11	DBU (5 eq.)	100	79	0

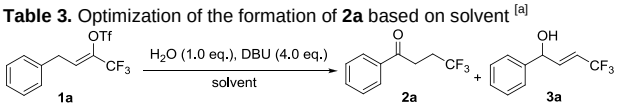
[a] Reaction conditions: **1a** (0.2 mmol), base, and H_2O (1.0 eq.) in DMF (1 mL) was stirred at -40 °C for 5 h, then at 80 °C for 3 h. [b] The yield was determined by ^1H NMR with dimethyl terephthalate as an internal standard.

Considering the significant role of the base in this transformation, different bases were examined (Table 2). If a weak base, such as Et_3N, K_2CO_3 or $KHCO_3$, was used, **3a** was found in the reaction mixture (Table 2, entries 2-6). When NaOH was used, the reaction gave complicated mixture (Table 3, entry 7). The

results suggested that a stronger base was beneficial to the generation of **2a**, and 4 equivalent of DBU gave the best results (Table 2, entry 8). Raising or reducing the amount of DBU resulted in a decreased yield of **2a** (Table 2, entries 9-11).

Then, the effect of the solvent was also explored (Table 3). Although the reaction proceeded smoothly in most solvents, polar solvents were more favorable. When THF or Et_2O were used as solvents, the reaction gave complicated mixture (Table 3, entries 2 and 3). DMF was shown to be a better choice (Table 3, entry 8).

Table 3. Optimization of the formation of **2a** based on solvent [a]

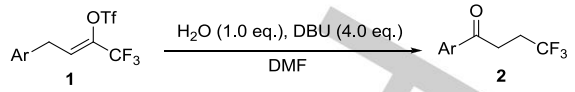


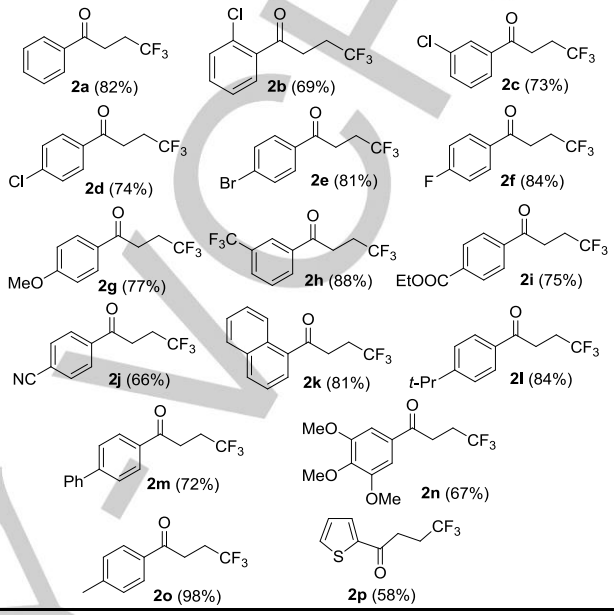
Entry	Solvent	Conv. (%) [b]	Yield (%)[b]	
			2a	3a
1	toluene	100	53	0
2	THF	100	<10	0
3	Et_2O	86	<10	0
4	CH_2Cl_2	100	56	0
5	$CHCl_3$	100	68	0
6	CH_3CN	100	82	0
7	DMSO	100	69	0
8	DMF	100	85	0

[a] Reaction conditions: **1a** (0.2 mmol), DBU (4.0 eq.), and H_2O (1.0 eq.) in solvent (1 mL) was stirred at -40 °C for 5 h, then at 80 °C for 3 h. [b] The yield was determined by ^1H NMR with dimethyl terephthalate as an internal standard.

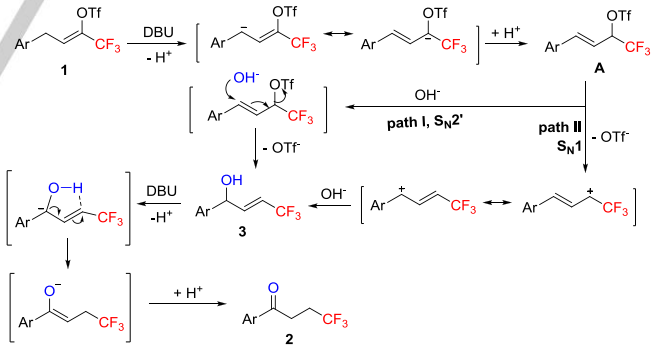
With the optimum reaction conditions in hand, the scope in terms of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates (**1**) was explored (Table 4). A series of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates bearing either electron-withdrawing or electron-donating groups on the aromatic ring underwent this transformation, and the desired products were obtained in moderate to excellent yields. Halo substituted molecules gave good yields in this reaction (**2b**-**2f**). And 2-chlorophenyl substrate gave similar result with 3- and 4-chloro ones (**2b**-**2d**). Trifluoromethyl, ester and cyano groups were also tolerated well (**2h-2j**). In addition, naphthyl and biphenyl substitutes (**2k** and **2m**) also showed efficiency as well as multi-substituted substrate (**2n**). It is noteworthy that methyl-substituted 4-phenyl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonate gave an excellent yield (**2o**) while thienyl substitute gave moderate yield (**2p**). 4-Alkyl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates, for example (*Z*)-1,1,1-trifluoroundec-2-en-2-yl trifluoromethanesulfonate, was also examined. Unfortunately, the conversion and the yield were very low.

Table 4. Preparation of 1-aryl-4,4,4-trifluorobutan-1-one derivatives [a]





[a] Reaction conditions: **1** (0.4 mmol), DBU (4.0 eq.), and H_2O (1.0 eq.) in DMF (2 mL) was stirred at -40 °C for 5 h, then at 80 °C for 3 h. Isolated yield.



Scheme 1. Plausible reaction mechanism.

According to the fact that **3a** is an intermediate in the formation of **2a**, the possible mechanism for the synthesis of 1-aryl-4,4,4-trifluoromethylbutanones from 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates was shown in Scheme 1. Firstly, through the double bond isomerization, the intermediate **A** was generated in the presence of DBU. Secondly, the intermediate **A** could be transformed into **3** in two possible pathways. One way was S_N2' substitution, OH^- anion took a conjugate addition over

the double bond, and –OTf group left to afford **3** (path I). And the other way was that the leaving of –TfO in intermediate **A** resulted in the formation of CF_3-allyl cations.[14d,15] Having two resonances, the relative stable CF_3-allyl cations could be captured by OH^- to afford **3** (path II). Finally, the product **2** was formed from **3** after double bond migration under DBU action.[9a]

Conclusions

In summary, a metal-free synthesis of 1-aryl-4,4,4-trifluoromethylbutanones has been developed. Promoted by DBU, 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates were converted into 1-aryl-4,4,4-trifluoromethylbutanones smoothly in moderate to excellent yields. Both electron-withdrawing and electron-donating groups, such as fluoro, chloro, bromo, ester, cyano, trifluoromethyl, alkyl, and alkoxy, were tolerated well in this reaction.

Experimental Section

All ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F NMR (377 MHz or 470 MHz) were recorded on Bruker AVANCE II-400 or Bruker AVANCE III-500 spectrometer with chemical shifts reported as ppm. High resolution mass spectra (HRMS) (ESI) were recorded on a Micromass Waters Q-TOF Microspectrometer. IR spectra were determined by a Thermo Fisher FT-IR spectrometer. Column chromatography was performed on silica gel (200~300 mesh). 4-Aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates (**1**) were prepared following our previous methods.[14a,14d] Other reagents and the substrates were purchased and used as received.

*General procedure for the synthesis of 1-aryl-4,4,4-trifluoromethylbutanones (**2**)*:

To a solution of (*Z*)-trifluoromethyl alkenyl triflates **1** (0.4 mmol) in DMF (5 mL) was added DBU (1.6 mmol) and H_2O (0.4 mmol) at -40 ^{o}C. After the reaction was complete (monitored by TLC), the reaction solution was moved to 80 °C with stirring for 3 h. After the reaction was complete (monitored by TLC), the reaction solvent was poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the product **2**.

*1-Phenyl-4,4,4-trifluorobutan-1-one (**2a**)*:[12a]

2a was prepared according to the general procedure using **1a** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2a** was obtained as a white solid. Yield: 82% (66 mg); mp. 65.3 - 65.6 °C; IR (KBr): $\tilde{\nu}$ = 3442, 1686, 1335, 1128, 750, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 - 7.47 (m, 2H), 3.29 - 3.25 (m, 2H), 2.69 - 2.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.3, 136.1, 133.6, 128.8, 128.0, 127.2 (q, *J* = 276.9 Hz), 31.2 (q, *J* = 2.3 Hz), 28.3 (q, *J* = 29.5 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.47 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{10}H_9F_3O$ [M^+] 202.0605, found: 202.0603.

*1-(2'-Chlorophenyl)-4,4,4-trifluorobutan-1-one (**2b**)*:[12a]

2b was prepared according to the general procedure using **1b** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2b** was obtained as a light yellow liquid. Yield: 69% (66 mg); IR (KBr): $\tilde{\nu}$ = 2965, 1637, 1261, 1098, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 - 7.49 (m, 1H), 7.45 - 7.41 (m, 2H), 7.35 (m, 1H), 3.33 - 3.19 (m, 2H), 2.73 - 2.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.3, 138.3, 132.3, 131.1, 130.7, 129.1, 127.1, 126.9 (q, *J* = 272.7 Hz), 35.4 (q, *J* = 2.7 Hz), 28.43 (q, *J* = 30.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.47 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{10}H_8ClF_3O$ [M^+] 236.0216, found: 236.0206.

*1-(3'-Chlorophenyl)-4,4,4-trifluorobutan-1-one (**2c**)*:[10]

2c was prepared according to the general procedure using **1c** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2c** was obtained as a light yellow liquid. Yield: 73% (69 mg); IR (KBr): $\tilde{\nu}$ = 2964, 1697, 1260, 1101, 802, 681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (t, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.58 - 7.56 (m, 1H), 7.45 -7.41 (m, 1H), 3.36 - 3.17 (m, 2H), 2.72 - 2.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.0, 137.6, 135.2, 133.5, 130.1, 128.1, 127.0 (q, *J* = 276.8 Hz), 126.1, 31.3 (q, *J* = 2.7 Hz), 28.2 (q, *J* = 29.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.49 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{10}H_8ClF_3O$ [M^+] 236.0216, found: 236.0215.

*1-(4'-Chlorophenyl)-4,4,4-trifluorobutan-1-one (**2d**)*:[10]

2d was prepared according to the general procedure using **1d** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2d** was obtained as a light yellow liquid. Yield: 74% (70 mg); IR (KBr): $\tilde{\nu}$ = 2987, 1680, 1308, 1096, 825, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 - 7.87 (m, 2H), 7.57 - 7.40 (m, 2H), 3.31 - 3.20 (m, 2H), 2.67 - 2.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.0, 140.1, 134.4, 129.4, 129.1, 127.1 (q, *J* = 275.7 Hz), 31.2 (q, *J* = 5.0 Hz), 28.2 (q, *J* = 29.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.49 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{10}H_8ClF_3O$ [M^+] 236.0216, found: 236.0210.

*1-(4'-Bromophenyl)-4,4,4-trifluorobutan-1-one (**2e**)*:[10]

2e was prepared according to the general procedure using **1e** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2e** was obtained as a white solid. Yield: 81% (91 mg); mp. 84.5 - 84.7 °C; IR (KBr): $\tilde{\nu}$ = 2937, 1688, 1334, 1136, 781, 626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 - 7.77 (m, 2H), 7.67 - 7.57 (m, 2H), 3.24 - 3.20 (m, 2H), 2.68 - 2.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.1, 134.8, 132.1, 129.5, 128.8, 127.1 (q, *J* = 275.7 Hz), 31.2 (q, *J* = 2.6 Hz), 28.2 (q, *J* = 29.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.46 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{10}H_8BrF_3O$ [M^+] 279.9711, found: 279.9708.

*1-(4'-Fluorophenyl)-4,4,4-trifluorobutan-1-one (**2f**)*:[10]

2f was prepared according to the general procedure using **1f** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2f** was obtained as a white solid. Yield: 84% (74 mg); mp. 54.0 - 54.2 °C; IR (KBr): $\tilde{\nu}$ = 2910, 1686, 1332, 1157, 852, 642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 - 7.94 (m, 2H), 7.22 - 7.11 (m, 2H), 3.35 - 3.13 (m, 2H), 2.73 - 2.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 166.0 (d, *J* = 255.6 Hz), 132.6 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 9.4 Hz), 127.1 (q, *J* = 275.7 Hz), 115.9 (d, *J* = 22.0 Hz), 31.1 (q, *J* = 2.7 Hz), 28.3 (q, *J* = 29.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -

66.52 (t, *J* = 10.8 Hz, 3F), *δ* -104.35(s, 1F). HRMS (EI) *m/z*: calcd for $C_{10}H_8F_4O$ [M^+] 220.0511, found: 220.0518.

*1-(4'-Methoxylphenyl)-4,4,4-trifluorobutan-1-one (**2g**)*:[10]

2g was prepared according to the general procedure using **1g** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/5), **2g** was obtained as a white solid; Yield: 77% (72 mg); mp. 63.5 - 64.3 °C; IR (KBr): ῡ = 2933, 1678, 1340, 1140, 835, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 7.87 - 7.84 (m, 2H), 6.99 - 6.89 (m, 2H), 3.85 (s, 3H), 3.26 - 3.14 (m, 2H), 2.65 - 2.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 194.8, 163.9, 130.3, 129.2, 127.3 (q, *J* = 275.7 Hz), 113.9, 55.4, 30.7 (q, *J* = 2.5 Hz), 28.4 (q, *J* = 29.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.45 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{11}H_{11}F_3O_2$ [M^+] 232.0711, found: 232.0713.

*1-(3'-Trifluoromethylphenyl)-4,4,4-trifluorobutan-1-one (**2h**)*:[3b]

2h was prepared according to the general procedure using **1h** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2h** was obtained as a colorless liquid. Yield: 88% (95 mg); IR (KBr): ῡ = 2920, 1636, 1261, 1023, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.26 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 3.42 - 3.35 (m, 2H), 2.74 – 2.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 194.9, 136.6, 131.50 (q, *J* = 33.2 Hz), 131.1, 129.9 (q, *J* = 3.3 Hz), 129.5, 127.0 (q, *J* = 275.7 Hz), 124.8 (q, *J* = 7.6 Hz), 123.6 (q, *J* = 273.7 Hz), 31.4 (q, *J* = 2.7 Hz), 28.2 (q, *J* = 30.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -62.96 (s, 3F), -66.53 (t, *J* = 10.7 Hz, 3F). HRMS (EI) *m/z*: calcd for $C_{11}H_8F_6O$ [M^+] 270.0479, found: 270.0476.

*Ethyl 4-(4',4',4'-trifluorobutyryl)benzoate (**2i**)*:

2i was prepared according to the general procedure using **1i** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/5), **2i** was obtained as a white solid. Yield: 75% (82 mg); mp. 86.8 - 87.0 °C; IR (KBr): ῡ = 2997, 1710, 1687, 1286, 1150, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.14 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.38 - 3.18 (m, 2H), 2.75 - 2.47 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 195.8, 165.5, 139.1, 134.7, 129.8, 127.8, 126.7 (q, *J* = 275.8 Hz), 61.5, 31.5 (q, *J* = 2.6 Hz), 28.2 (q, *J* = 29.9 Hz), 14.1. ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.51 (t, *J* = 10.6 Hz). HRMS (EI) *m/z*: calcd for $C_{13}H_{13}F_3O_3$ [M^+] 274.0817, found: 274.0807.

*1-(4'- Cyanophenyl)-4,4,4-trifluorobutan-1-one (**2j**)*:

2j was prepared according to the general procedure using **1j** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/5), **2j** was obtained as a white solid. Yield: 66% (60 mg); mp. 79.8 - 80.6 °C; IR (KBr): ῡ = 3240, 2234, 1697, 1138, 983, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.07 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 3.37 - 3.24 (m, 2H), 2.80 - 2.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 195.0, 138.9, 132.7, 128.5, 126.9 (q, *J* = 278.1 Hz), 117.7, 116.9, 31.6 (q, *J* = 2.7 Hz), 28.2 (q, *J* = 30.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.34 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{11}H_8F_3NO$ [M^+] 227.0558, found: 227.0552.

*1-(1'-Naphthyl)-4,4,4-trifluorobutan-1-one (**2k**)*:

2k was prepared according to the general procedure using **1k** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2k** was obtained as a yellow solid. Yield: 81% (82 mg); mp. 59.1 - 59.3 °C; IR (KBr): ῡ = 2995, 1686, 1320, 1256, 1139, 976, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.71 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.74 (s, 1H), 7.72 (s, 1H),7.67 - 7.63 (m, 1H), 7.61 - 7.56 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 3.38 - 3.34 (m, 2H), 2.86 - 2.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 199.9, 134.6, 134.0, 133.4, 130.2, 128.6, 128.3, 128.1, 127.3 (q, *J* = 276.9 Hz), 126.7, 125.7, 124.3, 34.2 (q, *J* = 2.2 Hz), 28.7 (q, *J* = 29.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.24 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{14}H_{11}F_3O$ [M^+] 252.0762, found: 252.0758.

*1-(4'-Isopropylphenyl) -4,4,4-trifluorobutan-1-one (**2l**)*:[4b]

2l was prepared according to the general procedure using **1l** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2l** was obtained as a white solid. Yield: 84% (82 mg); mp. 48.8 - 49.8 °C; IR (KBr): ῡ = 2965, 1686, 1140, 978, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 7.90 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.35 - 3.15 (m, 2H), 2.94 (dt, *J* = 6.9 Hz, 1H), 2.72 - 2.45 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 195.9, 155.2, 134.0, 128.3, 127.2 (q, *J* = 275.6 Hz), 126.8, 34.3, 31.0 (q, *J* = 2.5 Hz), 28.4 (q, *J* = 29.7 Hz), 23.6. ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.47 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{13}H_{15}F_3O$ [M^+] 244.1075, found: 244.1074.

*1-(4'-Phenylphenyl)-4,4,4-trifluorobutan-1-one (**2m**)*:[3b]

2m was prepared according to the general procedure using **1m** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2m** was obtained as a white solid. Yield: 72% (80 mg); mp. 127.1 - 127.6 °C; IR (KBr): ῡ = 2977, 1683, 1337, 1140, 977, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.04 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.51 - 7.47 (m, 2H), 7.46 - 7.40 (m, 1H), 3.35 - 3.23 (m, 2H), 2.73 - 2.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 195.9, 146.3, 139.7, 134.8, 129.0, 128.6, 128.4, 127.4, 127.3, 127.0 (q, *J* = 215.6 Hz), 31.2 (q, *J* = 5.1 Hz), 28.4 (q, *J* = 29.7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.49 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_{16}H_{13}F_3O$ [M^+] 278.0918, found: 278.0915.

*1-(3',4',5'-Trimethoxylphenyl)-4,4,4-trifluorobutan-1-one (**2n**)*:

2n was prepared according to the general procedure using **1n** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/3), **2n** was obtained as a light yellow solid. Yield: 67% (78 mg); mp. 63.1 - 63.4 °C; IR (KBr): ῡ = 2951, 1682, 1349, 1137, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 7.12 (s, 2H), 3.84 (s, 9H), 3.25 - 3.04 (m, 2H), 2.56 - 2.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 195.0, 153.2, 143.1, 131.3, 127.2 (q, *J* = 275.8 Hz), 105.5, 60.9, 56.3, 30.9 (q, *J* = 5.0 Hz), 28.4 (q, *J* = 29.7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.40 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{13}H_{15}F_3O_4$ [M^+] 292.0922, found: 292.0926.

*4,4,4-Trifluoro-1-p-tolylbutan-1-one (**2o**)*:[12a]

2o was prepared according to the general procedure using **1o** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2o** was obtained as a white solid. Yield: 98% (85 mg); mp. 68.8 - 69.4 °C; IR (KBr): ῡ = 3281, 1637, 1227, 1009, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* = 7.79 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 3.16 - 3.10 (m, 2H), 2.56 - 2.41 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* = 196.0, 144.4, 133.7, 129.4, 128.1, 127.3 (q, *J* = 276.7 Hz), 31.0 (q, *J* = 5.3 Hz), 28.3 (q, *J* = 30.3 Hz), 21.6. ^{19}F NMR (470 MHz, $CDCl_3$) *δ* = -66.48 (t, *J* = 10.9 Hz). HRMS (EI) *m/z*: calcd for $C_{11}H_{11}F_3O$ [M^+] 216.0762, found: 216.0760.

*1-(1'-Thienyl)-4,4,4-trifluorobutan-1-one (**2p**)*:

2p was prepared according to the general procedure using **1p** as the starting material. After purification by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/10), **2p** was obtained as a white solid. Yield: 58% (60 mg); mp. 69.4 - 69.9 °C; IR (KBr) $\tilde{\nu}$ = 3070, 1652, 1385, 1143, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.8 (dd, *J* = 3.7, 0.5 Hz, 1H), 7.67 (d, *J* = 4.9 Hz, 1H), 7.18 - 7.12 (m, 1H), 3.19 (t, *J* = 9.9 Hz, 2H), 2.68 - 2.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 187.4, 141.4, 132.5, 130.4, 126.5, 125.2 (q, *J* = 276.7 Hz), 29.9 (q, *J* = 2.7 Hz), 26.6 (q, *J* = 30.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ = -66.47 (t, *J* = 10.8 Hz). HRMS (EI) *m/z*: calcd for $C_7H_7F_3S$ [$M^{+\cdot}$] 180.0221, found: 180.0161.

*Procedure for the synthesis of 1-phenyl-4,4,4-trifluorobut-2-en-1-ol (**3a**)*:[16]

To a solution of 4-phenyl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonate (**1a**) (0.4 mmol) in DMF (5 mL) was added DBU (1.6 mmol) and H_2O (0.4 mmol) at -40 °C. After the reaction was complete (monitored by TLC), the reaction solvent was poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/5) to afford the product **3a** as a colorless oil. Yield: 78% (63 mg); IR (KBr) $\tilde{\nu}$ = 3566, 1724, 1251, 1142, 973, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.35 (m, 3H), 7.32 - 7.28 (m, 2H), 6.51 - 6.45 (m, 1H), 6.03 - 5.94 (m, 1H), 5.25 - 5.23 (m, 1H), 2.52 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (q, *J* = 6.1 Hz), 140.5, 129.0, 128.7, 126.6, 123.3 (q, *J* = 269.3 Hz), 117.9 (q, *J* = 34.1 Hz), 72.7.^{19}F NMR (377 MHz, $CDCl_3$) δ -64.38 (d, *J* = 6.3 Hz, 3F).

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[1] a) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518; b) C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441–5454; c) T. Hasegawa, *Chem. Rec.* **2017**, *17*, 903–917; d) A. Burriss, A. J. F. Edmunds, D. Emery, R. G. Hall, O. Jacob, J. Schaetzer, *Pest Management Sci.* **2018**, *74*, 1228–1238; e) B. I. Usachev, *J. Fluorine Chem.* **2018**, *210*, 6–45; f) V. G. N. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, *Chem. Rev.* **2015**, *115*, 973–1050; g) X.-Q. Tang, C.-M. Hu, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1039–1043.

[2] a) K. D. Rice, M. H. Kim, J. Bussenius, N. K. Anand, C. M. Blazey, O. J. Bowles, L. Canne-Bannen, D. S.-M. Chan, B. Chen, E. W. Co, S. Costanzo, S. C. DeFina, L. Dubenko, S. Engst, M. Franzini, P. Huang, V. Jammalamadaka, R. G. Khoury, R. R. Klein, A. D. Laird, D. T. Le, M. B. Mac, D. J. Matthews, D. Markby, N. Miller, J. M. Nuss, J. J. Parks, T. H. Tsang, A. L. Tsuhako, Y. Wang, W. Xu, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2693–2697; b) B. A. Czeskis, D. K. Satonin, *J. Label. Compd. Radiopharm* **2017**, *60*, 110–115.

[3] a) D. G. Kananovich, Y. A. Konik, D. M. Zubrytski, I. Järving, M. Lopp, *Chem. Commun.* **2015**, *51*, 8349–8352; b) X.-P. He, Y.-J. Shu, J.-J. Dai, W.-M. Zhang, Y.-S. Feng, H.-J. Xu, *Org. Biomol. Chem.* **2015**, *13*, 7159–7163; c) Y. Li, Z. Ye, T. M. Bellman, T. Chi, M. Dai, *Org. Lett.* **2015**, *17*, 2186–2189.

[4] a) P. Gao, Y.-W. Shen, R. Fang, X.-H. Hao, Z.-H. Qiu, F. Yang, X.-B. Yan, Q. Wang, X.-J. Gong, X.-Y. Liu, Y.-M. Liang, *Angew. Chem. Int. Ed.* **2014**, *53*, 7629–7633; *Angew. Chem.* **2014**, *126*, 7759–7763; b) S. Park, J. M. Joo, E. J. Cho, *Eur. J. Org. Chem.* **2015**, *2015*, 4093–4097.

[5] a) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li, X. Wu, *Angew. Chem. Int. Ed.* **2013**, *52*, 6962–6966; *Angew. Chem.* **2013**, *125*, 7100–7104; b) Z.-M. Chen, W. Bai, S.-H. Wang, B.-M. Yang, Y.-Q. Tu, F.-M. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 9781–9785; *Angew. Chem.* **2013**, *125*, 9963–9967; c) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *Chem. Commun.* **2013**, *49*, 7346–7348.

[6] S. Okusu, Y. Sugita, E. Tokunaga, N. Shibata, *Beilstein J. Org. Chem.* **2013**, *9*, 2189–2193.

[7] M. M. Lerch, B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2014**, *53*, 8654–8658; *Angew. Chem.* **2014**, *126*, 8798–8802.

[8] a) B. E. Norcross, P. E. Klinedinst Jr, F. H. Westheimer, *J. Am. Chem. Soc.* **1962**, *84*, 797–802; b) X. Xia, M. Wu, R. Jin, T. Cheng, G. Liu, *Green Chem.* **2015**, *17*, 3916–3922; c) V. Bizet, X. Pannecoucke, J.-L. Renaud, D. Cahard, *Adv. Synth. Catal.* **2013**, *355*, 1394–1402; d) B. Huang, C. Li, H. Wang, C. Wang, L. Liu, J. Zhang, *Org. Lett.* **2017**, *19*, 5102–5105; e) M. Tao, W. Zhou, J. Zhang, *Adv. Synth. Catal.* **2017**, *359*, 3347–3353; f) W. Zhou, H. Wang, M. Tao, C.-Z. Zhu, T.-Y. Lin, J. Zhang, *Chem. Sci.* **2017**, *8*, 4660–4665; g) Q. Jiang, T. Guo, Z. Yu, *J. Org. Chem.* **2017**, *82*, 1951–1960.

[9] a) S. Martinez-Erro, A. Sanz-Marco, A. B. Gómez, A. Vázquez-Romero, M. S. G. Ahlquist, B. Martín-Matute, *J. Am. Chem. Soc.* **2016**, *138*, 13408–13414; b) V. Bizet, X. Pannecoucke, J.-L. Renaud, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6467–6470; *Angew. Chem.* **2012**, *124*, 6573–6576; c) Y. Hamada, T. Kawasaki-Takasuka, T. Yamazaki, *Beilstein J. Org. Chem.* **2017**, *13*, 1507–1512; d) V. Bizet, X. Pannecoucke, J.-L. Renaud, D. Cahard, *J. Fluorine Chem.* **2013**, *152* , 56–61; e) T. Kagawa, K. Fujita, K. Kawada, *J. Fluorine Chem.* **2013**, *152* , 77–80.

[10] T.-P. Yang, Q. Li, J.-H. Lin, J.-C. Xiao, *Chem. Commun.* **2014**, *50*, 1077–1079.

[11] B. Gao, Y. Zhao, J. Hu, *Angew. Chem. Int. Ed.* **2015**, *54*, 638–642; *Angew. Chem.* **2015**, *127*, 648–652.

[12] a) N. Yi, H. Zhang, C. Xu, W. Deng, R. Wang, D. Peng, Z. Zeng, J. Xiang, *Org. Lett.* **2016**, *18*, 1780–1783; b) X. Yu, S. M. Cohen, *J. Am. Chem. Soc.* **2016**, *138*, 12320–12323.

[13] a) M. Huang, L. Li, Z.-G. Zhao, Q.-Y. Chen, Y. Guo, *Synthesis* **2015**, 47, 3891–3900; b) T. Umemoto, Y. Gotoh. *Bull Chem. Soc. Jpn.* **1987**, *60*, 3823–3825; c) T. Okano, T. Uekawa, S. Eguchi, *Bull Chem. Soc. Jpn.* **1989**, *62*, 2575–2579; d) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6391–6394.

[14] a) Y. Zhao, Y. Zhou, J. Liu, L. Tao, Y. Liu, X. Dong, J. Liu, J. Qu, *J. Org. Chem.* **2016**, *81*, 4797–4806; b) Y. Zhao, Y. Zhou, C. Zhang, H. Wang, J. Zhao, K. Jin, J. Liu, J. Qu, *Org. Biomol. Chem.* **2017**, *15*, 5693–5700; c) Y. Liu, Y. Zhou, Y. Zhao, J. Qu, *Org. Lett.* **2017**, *19*, 946–949; d) Y. Zhao, Y. Zhou, C. Zhang, P. Sun, J. Li, H. Wang, J. Liu, J. Qu, *J. Org. Chem.* **2018**, *83*, 2858–2868; e) D. Li, Y. Zhou, Y. Zhao, C. Zhang, J. Li, J. Zhao, J. Qu, *J. Fluorine Chem.* **2018**, *212*, 122–129.

[15] A. N. Kazakova, R. O. Iakovenko, I. A. Boyarskaya, V. G. Nenajdenko, A. V. Vasilyev, *J. Org. Chem.* **2015**, *80*, 9506–9517.

[16] T. Yamazaki, M. Ichikawa, T. Kawasaki-Takasuka, S. Yamada, *J. Fluorine Chem.* **2013**, *155*, 151–154.

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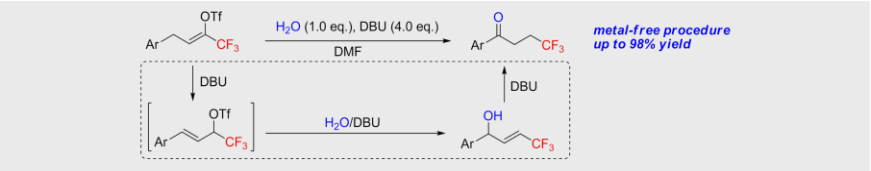

A metal-free synthesis of 1-aryl-4,4,4-trifluoromethylbutanones has been developed. Promoted by DBU, 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates were converted into 1-aryl-4,4,4-trifluoromethylbutanones smoothly in moderate to excellent yields.

***β*-trifluoromethyl ketones**

Yuhan Zhou, Chunxia Zhang, Yilong Zhao, Dong Li, Jinfeng Zhao, Zhaotian Wang, and Jingping Qu*

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Base-promoted double-bond-migration/hydrolysis/isomerization of 4-aryl-1,1,1-trifluorobut-2-en-2-yl trifluoromethanesulfonates: a metal-free approach to *β*-trifluoromethyl ketones