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Regioselective synthesis of β-fluoro-α,β-unsaturated ketones by the reaction of β-diketones with DFMBA

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ABSTRACT

The deoxyfluorination reaction of β-diketones with *N,N*-diethyl-α,α-difluoro-*m*-methylbenzylamine (DFMBA) gave β-fluoro-α,β-unsaturated ketones in good yields. The reaction proceeded regioselectively, and only one regioisomer was obtained from the unsymmetrical 1-aryl-1,3-diketones. The reaction is applicable to diketones with a trifluoromethyl group, obtaining good yields of 3,4,4,4-tetrafluorobutenones. We used the resulting β-fluoro-α,β-unsaturated ketones for the reaction with lithium dialkyl cuprates.

1. Introduction

β-Fluoro-α,β-unsaturated ketones have been conveniently used as a building-block for the synthesis of fluorinated cyclic compounds via Diels–Alder reaction [1] and the synthesis of the heterocyclic compounds [2]. The β-fluoro-α,β-unsaturated ketones were previously prepared by the hydrofluorination of alkynyl ketones [3], the alkylation of β-fluoro-α,β-unsaturated carboxylic acid chlorides [4], the alkylation of β,β-difluoro-α,β-unsaturated ketones [5], or the elimination of HF from β,β-difluoroalkyl ketones [2a,b]. However, the starting materials, alkynyl ketones, β-fluoro-α,β-unsaturated carboxylic acid chlorides, β,β-difluoro-α,β-unsaturated ketones, and β,β-difluoroalkyl ketones are not easily available in those methods. The corresponding chlorides, β-chloro-α,β-unsaturated ketones, can be easily prepared from β-diketones with chlorination reagents [6], but the reaction of β-diketones with fluorination reagents such as DAST or deoxofluor gave poly-fluorinated products, so β-fluoro-α,β-unsaturated ketones could not be directly prepared from β-diketones [7]. Recently, we reported the fluorination of alcohols [8], epoxides [9], aldehydes [10], diols [11], and amino alcohols [12] using *N,N*-diethyl-α,α-difluoro-*m*-methylbenzylamine (DFMBA). During the course of our study of the fluorination reaction using DFMBA, we found that β-fluoro-α,β-unsaturated ketones **2** can be prepared from β-diketones **1** by the reaction with DFMBA (Scheme 1).

2. Result and discussion

The reaction of undecane-5,7-dione **1a** with DFMBA was completed at 30 °C in 24 h and 7-fluoro-6-undecen-5-one **2a** was obtained in a 79% yield as a mixture of stereoisomers (*E*:*Z* = 73:27) (entry 1 in Table 1). A two equivalent of DFMBA to **1a** is necessary, and with a smaller amount of DFMBA, the yield of **2a** decreased considerably. As for the solvent, 1,4-dioxane, DMF, and CH_2Cl_2 are appropriate and hydrocarbon such as hexane is not suitable for this reaction. When 1-phenylbutane-1,3-dione **1b** was used, the deoxyfluorination reaction occurred regioselectively at the carbonyl group of C3 to give 3-fluoro-1-phenyl-2-buten-1-one **2b**, but its regioisomer, 4-fluoro-4-phenyl-3-buten-2-one, did not form (entry 2). Such regioselectivity was always observed in the reaction with unsymmetrical 1-aryl-1,3-alkadiones (R^1 = Ar, R^2 = H, R^3 = alkyl) (entries 2, 4–9). In contrast, a poor stereoselectivity of the generated double bond in the products was observed in most of the cases, and mixtures of the stereoisomers were obtained (entries 1–3, and 5–9). When the diketone **1d** with a bulky substituent (R^3 = *tert*-Bu) was used, the product (*Z*)-**2d** was obtained stereo- and regioselectively (*E*:*Z* = 1:99) (entry 4). The reactions of diketones **1c**, **1d** and **1i** were sluggish and required higher reaction temperatures for completion (entries 3, 4, and 9). In the reaction of the diketone **1j** with an α-substituent, we applied a microwave irradiation condition without solvent to optimize the

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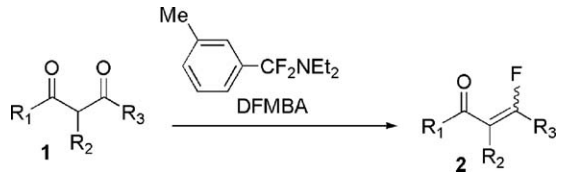
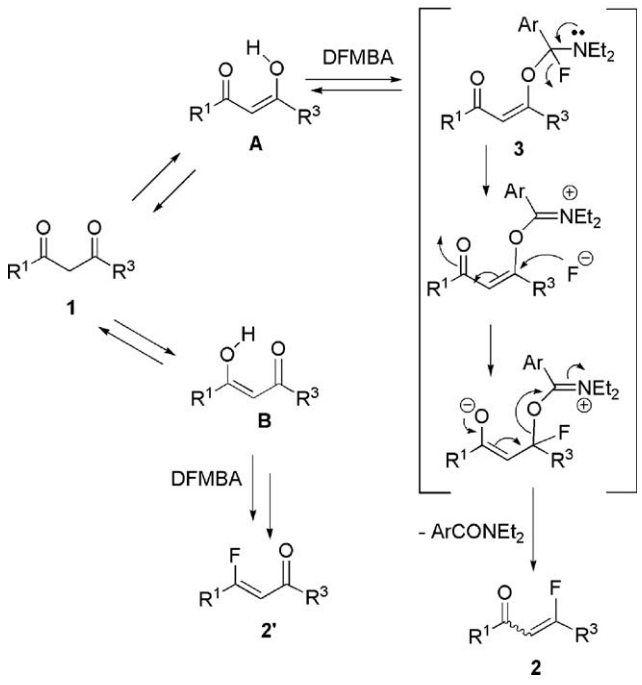


Scheme 1.

result (entry 10). This reaction is applicable to the diketones **1e**–**h** with a trifluoromethyl group (R^1 = Ar, R^2 = H, R^3 = CF_3) and 1-aryl-3,4,4,4-tetrafluoro-2-buten-1-ones **2e**–**h** were obtained in good yields (entries 5–8). 1-Phenyl-3,4,4,4-tetrafluoro-2-buten-1-one **2e** was previously prepared from 1-phenyl-3,3,4,4,4-pentafluorobutan-1-one by elimination of HF, and used as a building-block for the synthesis of various organofluorine compounds [2a,b]. However, the starting material of our reaction, 1-phenyl-4,4,4-trifluorobutane-1,3-dione **1e**, is commercially available and more accessible than 1-phenyl-3,3,4,4,4-pentafluorobutan-1-one. Therefore, our method is more useful for the synthesis of 1-aryl-3,4,4,4-tetrafluoro-2-buten-1-ones than the previous method. In the reaction of 4-*tert*-butyl-2-acetylcyclohexanone **1j**, a double bond was formed at *exo*-position selectively and 4-*tert*-butyl-2-(1-fluoroethylidene)cyclohexanone **2j** was obtained as a single isomer [13].

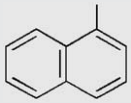
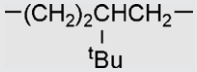
The presumed reaction mechanism of the present deoxyfluorination reaction is shown in Scheme 2. The β-diketones **1** exist as an equilibrium mixture of keto and enol forms [14] and DFMBA reacted with the enol form to give the intermediate **3**. From **3**, elimination of the fluoride, attack of the fluoride at the β-carbon, and the elimination of an amide took place successively to give β-fluoro-α,β-unsaturated ketones **2**. In the reaction of unsymmetrical diketones (R^1 = Ar, R^3 = alkyl or CF_3), two kinds of enol forms (**A** and **B**) exist, and they could give regioisomers **2** and **2′** via the reaction with DFMBA, respectively. However, in the present



Scheme 2.

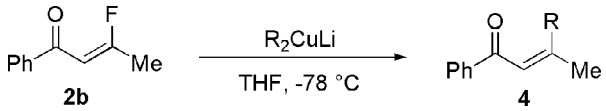
deoxyfluorination reaction, only one regioisomer **2** was formed from the unsymmetrical diketones (**1b**, **1d**–**1i**). In the chlorination of the unsymmetrical β-diketones with Vielsmerer's reagent, the similar regioselectivity was observed and the selectivity was explained by the difference in nucleophilicity of the hydroxy oxygen (A > B: R^1 = Ar, R^3 = alkyl) [6]. Therefore, the enol form **A** is more reactive towards DFMBA than **B**, and the reaction proceeded through the intermediate **3** to give product **2** selectively.

Table 1
Reaction of β-diketones with DFMBA[a].

Entry	Substrate	R^1	R^2	R^3	Reac. cond.	Yield (%)[b]
1	**1a**	Bu	H	Bu	30 °C, 24 h	79 (73:27)
2	**1b**	Ph	H	Me	30 °C, 24 h	89 (62:38)
3	**1c**	Ph	H	Ph	80 °C, 5 h	78 (56:44)
4	**1d**	Ph	H	^{t}Bu	80 °C, 5 h	82 (1:99)
5[d]	**1e**	Ph	H	CF_3	20 °C, 24 h	86 (16:84)
6[d]	**1f**		H	CF_3	20 °C, 24 h	91[e] (21:79)
7[d]	**1g**		H	CF_3	20 °C, 24 h	89[e] (29:71)
8[d]	**1h**		H	CF_3	20 °C, 24 h	94 (19:81)
9[c]	**1i**	Ph	Me	Me	90 °C, 0.5 h	74 (86:14)
10[d]	**1j**			Me	30 °C, 12 h	74

[a] If otherwise not mentioned, the reaction was carried out in 1,4-dioxane using 2 equiv. of DFMBA.
[b] Isolation yield based on diketone used. In parentheses, *E*:*Z* ratio.
[c] The reaction was carried out under microwave irradiation without solvent.
[d] CH_2Cl_2 was used as solvent.
[e] ^{19}F NMR yield.

Table 2
The reaction of **2b** with R_2CuLi[a]



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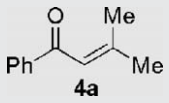
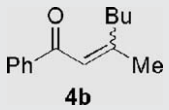
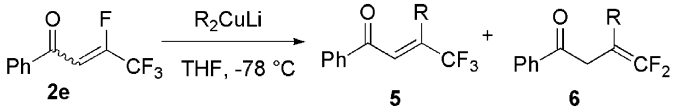
Entry	Substrate	R_2CuLi	Product	Yield (%)[b]
1	(*E*)-**2b**	Me_2CuLi	 **4a**	93
2	(*E*)-**2b**	Bu_2CuLi	 **4b**	82 (24:76)
3	(*Z*)-**2b**	Bu_2CuLi	**4b**	76 (30:70)

[a] The reaction was performed in THF using 2 equiv. of R_2CuLi.
[b] Isolation yield based on **2b**. In parentheses, isomer ratio (*E*:*Z*).

Table 3
The reaction of **2e** with R_2CuLi[a]



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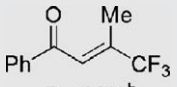
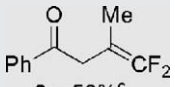
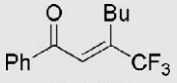
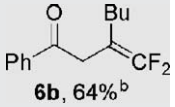
R_2CuLi	Product	
Me_2CuLi	 **5a**, 23%[b]	 **6a**, 53%[c]
Bu_2CuLi	 **5b**, 8%[c]	 **6b**, 64%[b]

[a] The reaction was performed in THF using 2 equiv. of R_2CuLi.
[b] Isolation yield based on **2e**.
[c] ^{19}F NMR yield.

β-Halo- [15], β-alkylthio- [15b], and β-acetoxy-α,β-unsaturated ketones [16] have been used for the reaction with dialkyl cuprates to introduce an alkyl group onto the double bond via the substitution with the hetero atom. β-Fluoro-α,β-unsaturated ketones were also used for the reaction with dialkyl cuprates for the synthesis of β,β-dialkyl-α,β-unsaturated ketones [5]. We also applied **2b** and **2e** to the reaction with dialkyl cuprates. The reaction of (*E*)-**2b** with Me_2CuLi proceeded at −78 °C and 3-methyl-1-phenyl-2-buten-1-one **4a** was obtained in high yield (entry 1 in Table 2). However, when Bu_2CuLi was used for the reaction with (*E*)-**2b**, 3-methyl-1-phenyl-2-hepten-1-one **4b** was obtained as a mixture of stereoisomers (*E*:*Z* = 24:76) (entry 2). As **4b** was also formed as a mixture of stereoisomers (*E*:*Z* = 30:70) in the reaction with (*Z*)-**2b** (entry 3), the reaction of **2b** with lithium dialkyl cuprates proceeded non-stereoselectively as reported previously [5] (Table 3).

In the reaction of 1-phenyl-3,4,4,4-tetrafluoro-2-buten-1-one **2e** (a mixture of *E* and *Z* isomers) with Me_2CuLi, the expected product, (*E*)-3-methyl-1-phenyl-4,4,4-trifluoro-2-buten-1-one **5a**, was obtained as a minor product, and the unexpected 4,4-difluoro-1-phenyl-3-methyl-3-buten-1-one **6a** was obtained as a major product. The unexpected product **6a** must be formed by the reduction of **5a** with the copper reagent [17]. The result was not dependent on the stereochemistry of the starting material **2e**, and from pure (*Z*)-**2e**, the same result was obtained. In the reaction of **2e** with Bu_2CuLi, 4,4-difluoro-1-phenyl-3-butyl-3-buten-1-one **6b** was also obtained in a 64% yield, whereas (*E*)-3-butyl-1-phenyl-4,4,4-trifluoro-2-buten-1-one **5b** was formed as a minor product (8% yield).

3. Conclusion

We performed the reaction of DFMBA with various β-diketones including trifluoro diketones and obtained the β-fluoro-α,β-unsaturated ketones in good yields. The reaction proceeded regioselectively and only one regioisomer was obtained from the unsymmetrical diketones. The resulting β-fluoro-α,β-unsaturated ketones were used for the alkylation reactions with lithium dialkyl cuprates.

4. Experimental

4.1. General

The melting points were measured with a Yanagimoto micro-melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (^1H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. DFMBA was donated from Mitsubishi Gas Chemical Company, Inc. Microwave irradiation was carried out using an IDX microwave oven for organic synthesis (0–300 W, IMCR-25003) with temperature control.

4.2. Reaction of β-diketones with DFMBA

4.2.1. 7-Fluoro-6-undecen-5-one (2a)

A mixture of undecane-5,7-dione **1a** (184 mg, 1 mmol), DFMBA (426 mg, 2 mmol), and 1,4-dioxane (1 mL) in a reaction vessel made of Teflon™ FEP with a tight screw cap was stirred at 30 °C for 24 h. The mixture was poured into water, neutralized with sat aq $NaHCO_3$, and extracted with ether (20 mL × 3). The combined

organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave **2a** (147 mg) in 79% yield as a mixture of stereoisomers (*E*:*Z* = 73:27, they are separable by column chromatography); (*E*)-**2a**; clear oil: IR (neat): 2960, 1672 cm^{-1}. ^1H NMR δ 5.94 (d, *J* = 20.5 Hz, 1H, =C*H*), 2.78 (dt, *J* = 26.2, 7.3 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.63–1.50 (m, 4H), 1.44–1.26 (m, 4H), 0.95–0.88 (m, 6H) {lit. [18] 5.94 (d, *J* = 20.5 Hz, 1H, =C*H*)}. ^{13}C NMR δ 198.88 (d, *J* = 19.5 Hz), 176.31 (d, *J* = 280.9 Hz), 107.03 (d, *J* = 20.1 Hz), 44.54 (d, *J* = 4.5 Hz), 29.90, 29.58, 28.01, 26.13, 22.22 (d, *J* = 2.2 Hz), 13.84, 13.70. ^{19}F NMR δ −76.40 (dt, *J* = 23.0, 23.0 Hz, 1F). HRMS (EI): calcd for $C_{11}H_{19}OF$ (M^+): 186.1420, found: 186.1413. (*Z*)-**2a**; clear oil: IR (neat): 2960, 1672 cm^{-1}. ^1H NMR δ 5.32 (d, *J* = 39.0 Hz, 1H), 2.64 (dt, *J* = 2.3, 7.6 Hz, 2H), 2.29 (dt, *J* = 17.4, 7.2 Hz, 2H), 1.63–1.50 (m, 4H), 1.45–1.26 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H) {lit. [18] 5.32 (d, *J* = 38.8 Hz, 1H, =C*H*)}. ^{13}C NMR δ 199.86 (d, *J* = 2.3 Hz), 170.71 (d, *J* = 283.6 Hz), 108.46 (d, *J* = 7.8 Hz), 43.10 (d, *J* = 5.4 Hz), 32.61 (d, *J* = 25.1 Hz), 27.70 (d, *J* = 1.9 Hz), 26.05 (d, *J* = 1.6 Hz), 22.33, 21.93, 13.86, 13.62. ^{19}F NMR δ −80.07 to −80.28 (m, 1F).

4.2.2. 3-Fluoro-1-phenyl-2-buten-1-one (2b)

The reaction was carried out as described above using 1-phenylbutane-1,3-dione **1b** at 30 °C for 24 h. Purification by column chromatography (silica gel/hexane-ether) gave **2b** in 89% yield as a mixture of stereoisomers (*E*:*Z* = 62:38, they are separable by column chromatography); (*E*)-**2b**; clear oil: IR (neat): 3062, 1679, 1627, 1164 cm^{-1}. ^1H NMR δ 7.93–7.89 (m, 2H), 7.60–7.44 (m, 3H), 6.72 (d, *J* = 21.1 Hz, 1H, =C*H*), 2.47 (d, *J* = 19.7 Hz, 3H). ^{13}C NMR δ 190.02 (d, *J* = 20.1 Hz), 174.66 (d, *J* = 276.5 Hz), 138.48 (d, *J* = 5.0 Hz), 132.84, 128.58 (2C), 127.88 (2C), 104.71 (d, *J* = 22.3 Hz), 17.19 (d, *J* = 24.2 Hz). ^{19}F NMR δ −64.50 (dq, *J* = 20.1, 20.1 Hz, 1F). HRMS (EI): calcd for $C_{10}H_9OF$ (M^+): 164.0637, found: 164.0623. (*Z*)-**2b**; white solid; m.p. 49–51 °C: IR (KBr): 3081, 1632, 1246 cm^{-1}. ^1H NMR δ 7.91–7.88 (m, 2H), 7.58–7.42 (m, 3H), 6.09 (d, *J* = 33.3 Hz, 1H, =C*H*), 2.14 (d, *J* = 16.7 Hz, 3H). ^{13}C NMR δ 188.49, 167.74 (d, *J* = 284.9 Hz), 138.12, 132.75, 128.45 (2C), 128.25 (2C), 104.34 (d, *J* = 5.0 Hz), 19.45 (d, *J* = 26.7 Hz). ^{19}F NMR δ −74.35 (dq, *J* = 33.0, 16.5 Hz, 1F).

4.2.3. 3-Fluoro-1,3-diphenyl-2-propen-1-one (2c)

The reaction was carried out as described above using 1,3-diphenylpropane-1,3-dione **1c** at 80 °C for 5 h. Purification by column chromatography (silica gel/hexane-ether) gave **2c** in 78% yield as a mixture of stereoisomers (*E*:*Z* = 56:44, they are separable by column chromatography); (*E*)-**2c**; white solid; m.p. 36–38 °C: IR (KBr): 3056, 1670, 1626, 1246 cm^{-1}. ^1H NMR δ 7.96–7.93 (m, 2H), 7.71–7.68 (m, 2H), 7.58–7.35 (m, 6H), 6.77 (d, *J* = 21.8 Hz, 1H, =C*H*). ^{13}C NMR δ 189.77 (d, *J* = 17.9 Hz), 168.47 (d, *J* = 267.0 Hz), 137.98 (d, *J* = 4.2 Hz), 133.13, 131.32 (d, *J* = 1.7 Hz, 2C), 128.80, 128.71, 128.58 (2C), 128.49 (2C), 128.07 (2C), 106.07 (d, *J* = 26.3 Hz). ^{19}F NMR δ −79.44 (d, *J* = 22.0 Hz, 1F). HRMS (EI): calcd for $C_{15}H_{11}OF$ (M^+): 226.0794, found: 226.0799. (*Z*)-**2c**; white solid; m.p. 59–60 °C (lit. [3b] 61 °C): IR (KBr): 3041, 1665, 1605, 1214 cm^{-1}. ^1H NMR δ 7.99–7.96 (m, 2H), 7.78–7.74 (m, 2H), 7.62–7.45 (m, 6H), 6.80 (d, *J* = 34.2 Hz, 1H, =C*H*). ^{13}C NMR δ 188.81, 165.21 (d, *J* = 278.1 Hz), 138.57, 132.85, 131.58 (2C), 128.89 (d, *J* = 1.8 Hz), 128.53 (2C), 128.29 (d, *J* = 0.7 Hz, 2C), 125.85, 125.74 (2C), 101.70 (d, *J* = 6.8 Hz). ^{19}F NMR δ = −97.16 (d, *J* = 34.2 Hz, 1F) {lit. [3b] −98.7 (d, *J* = 35 Hz, 1F)}.

4.2.4. (Z)-3-Fluoro-1-phenyl-4,4-dimethyl-2-penten-1-one (2d)

The reaction was carried out as described above using 1-phenyl-4,4-dimethylpentane-1,3-dione **1d** at 80 °C for 5 h. Purification by column chromatography (silica gel/hexane-ether) gave **2d** in 82% yield (*Z*:*E* = 99:1); clear oil: IR (neat): 2972, 1681, 1627, 1280, 1222 cm^{-1}. ^1H NMR δ 7.89–7.86 (m, 2H), 7.58–7.43 (m, 3H), 6.06 (d, *J* = 35.6 Hz, 1H, =C*H*), 1.26 (s, 9H). ^{13}C NMR δ 189.60, 177.15 (d, *J* = 289.3 Hz), 138.47, 132.65, 128.38 (2C), 128.27 (2C), 100.38 (d, *J* = 7.2 Hz), 36.02 (d, *J* = 21.7 Hz), 26.92 (d, *J* = 2.8 Hz, 3C). ^{19}F NMR δ −90.01 (d, *J* = 36.0 Hz, 1F). HRMS (EI): calcd for $C_{13}H_{15}OF$ (M^+): 206.1107, found: 206.1101.

4.2.5. 3,4,4,4-Tetrafluoro-1-phenyl-2-buten-1-one (2e)

The reaction was carried out as described above using 1-phenyl-4,4,4-trifluorobutane-1,3-dione **1e** in CH_2Cl_2 at 20 °C for 24 h. Purification by column chromatography (silica gel/hexane-ether) gave **2e** in 86% yield as a mixture of stereoisomers (*E*:*Z* = 16:84, only (*Z*)-isomer is isolable as pure form); (*Z*)-**2e**; clear oil: IR (neat): 3068, 1707, 1296, 1208, 1156 cm^{-1}. ^1H NMR δ 7.94–7.91 (m, 2H), 7.68–7.50 (m, 3H), 6.72 (d, *J* = 31.3 Hz, 1H, =C*H*). ^{13}C NMR δ 186.46, 151.06 (dq, *J* = 283.9, 39.6 Hz), 136.18, 134.35, 128.96 (2C), 128.70 (2C), 117.78 (dq, *J* = 41.2, 273.1 Hz), 107.80–107.68 (m). ^{19}F NMR δ −73.78 (d, *J* = 9.7 Hz, 3F), −117.52 (dq, *J* = 31.1, 9.8 Hz, 1F) {lit. [2b] δ −73.64 (d, *J* = 10 Hz, 3F), −117.5 (dt, *J* = 31, 10 Hz, 1F)}. HRMS (EI): calcd for $C_{10}H_6OF_4$ (M^+): 218.03546, found: 218.03524. (*E*)-**2e**; ^1H NMR δ 6.72 (d, *J* = 18.9 Hz, 1H, C=C*H*). ^{19}F NMR δ −69.79 (d, *J* = 10.7 Hz, 3F), −119.58 (dq, *J* = 18.2, 9.1 Hz, 1H).

4.2.6. 3,4,4,4-Tetrafluoro-1-(furan-2-yl)-2-buten-1-one (2f)

The reaction was carried out as described above using 1-(furan-2-yl)-4,4,4-trifluorobutane-1,3-dione **1f** in CH_2Cl_2 at 20 °C for 24 h. ^{19}F NMR analysis using fluorobenzene as internal standard showed that **2f** was formed in 91% yield as a mixture of stereoisomers (*E*:*Z* = 21:79, only (*Z*)-isomer is isolable as pure form by column chromatography (silica gel/hexane-ether)); (*Z*)-**2f**; white solid: m.p. 30–31 °C: IR (KBr): 3137, 1712, 1646, 1317 cm^{-1}. ^1H NMR δ 7.67 (d, *J* = 1.8 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 30.0 Hz, 1H, =C*H*), 6.64 (dd, *J* = 3.6, 1.8 Hz, 1H). ^{13}C NMR δ 173.35, 152.55 (dq, *J* = 288.9, 39.8 Hz), 152.16, 147.71, 119.22, 117.62 (dq, *J* = 40.1, 273.7 Hz), 113.22, 105.96 (q, *J* = 2.9 Hz). ^{19}F NMR δ −74.07 (d, *J* = 9.0 Hz, 3F), −115.66 (dq, *J* = 29.5, 8.9 Hz, 1F). HRMS (EI): calcd for $C_8H_4F_4O_2$ (M^+): 208.0147, found: 208.0151. (*E*)-**2f**; ^1H NMR δ 7.68 (brs, 1H), 7.30 (d, *J* = 3.6 Hz, 1H), 6.73 (d, *J* = 19.0 Hz, 1H, C=C*H*), 6.64–6.62 (m, 1H). ^{19}F NMR δ −69.51 (d, *J* = 8.5 Hz, 3F), −115.9 (brs, 1F).

4.2.7. 3,4,4,4-Tetrafluoro-1-(thien-2-yl)-2-buten-1-one (2g)

The reaction was carried out as described above using 1-(thien-2-yl)-4,4,4-trifluorobutane-1,3-dione **1g** in CH_2Cl_2 at 20 °C for 24 h. ^{19}F NMR analysis using fluorobenzene as internal standard showed that **2g** was formed in 89% yield as a mixture of stereoisomers (*E*:*Z* = 29:71, only (*Z*)-isomer is isolable as pure form by column chromatography (silica gel/hexane-ether)); (*Z*)-**2g**; white solid: m.p. 38–40 °C: IR (KBr): 3100, 1701, 1629, 1167 cm^{-1}. ^1H NMR δ 7.79 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.74 (d, *J* = 3.8 Hz, 1H), 7.20 (dd, *J* = 4.9, 4.0 Hz, 1H), 6.65 (d, *J* = 30.1 Hz, 1H, =C*H*). ^{13}C NMR δ 178.00, 151.32 (dq, *J* = 286.9, 40.0 Hz), 143.62, 136.20, 133.68, 128.60, 117.67 (dq, *J* = 40.0, 273.7 Hz), 107.17–107.07 (m). ^{19}F NMR δ −73.90 (d, *J* = 10.7 Hz, 3F), −116.80 (dq, *J* = 30.4, 9.6 Hz, 1F). HRMS (EI): calcd for $C_8H_4F_4OS$: 223.9919, found: 223.9921. (*E*)-**2g**; ^1H NMR δ 7.80 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.70 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.20 (dd, *J* = 4.9, 4.0 Hz, 1H), 6.71 (d, *J* = 18.6 Hz, 1H, C=C*H*). ^{19}F NMR δ −69.54 (d, *J* = 9.0 Hz, 3F), −118.71 (dq, *J* = 18.0, 8.9 Hz, 1F).

4.2.8. 3,4,4,4-Tetrafluoro-1-(naphth-2-yl)-2-buten-1-one (2h)

The reaction was carried out as described above using 1-(naphth-2-yl)-4,4,4-trifluorobutane-1,3-dione **1h** in CH_2Cl_2 at 20 °C for 24 h. Purification by column chromatography (silica gel/hexane-ether) gave **2h** in 94% yield as a mixture of stereoisomers

(*E*:*Z* = 19:81, only (*Z*)-isomer is isolable as pure form); (*Z*)-**2h**; yellow solid: m.p. 62–63 °C: IR (KBr): 1702, 1650, 1213, 1139 cm^{-1}. ^1H NMR δ 8.40 (s, 1H), 8.02–7.90 (m, 4H), 7.69–7.58 (m, 2H), 6.87 (d, *J* = 31.3 Hz, 1H, =C*H*). ^{13}C NMR δ 186.09, 150.99 (dq, *J* = 283.3, 39.3 Hz), 135.95, 133.45, 132.21, 131.09, 129.64, 129.21, 128.91, 127.79, 127.10, 123.36, 117.82 (dq, *J* = 41.0, 273.7 Hz), 107.78–107.67 (m). ^{19}F NMR δ −73.70 (d, *J* = 9.0 Hz, 3F), −117.70 (dq, *J* = 30.5, 10.2 Hz, 1F). HRMS (EI): calcd for $C_{14}H_8OF_4$ (M^+): 268.05112, found: 268.05123. (*E*)-**2h**; ^1H NMR δ 6.85 (d, *J* = 18.7 Hz, 1H, C=C*H*). ^{19}F NMR δ −69.74 (d, *J* = 9.0 Hz, 3F), −119.62 (dq, *J* = 19.7, 8.9 Hz, 1F).

4.2.9. 3-Fluoro-2-methyl-1-phenyl-2-buten-1-one (2i)

To a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, 2-methyl-1-phenylbutane-1,3-dione **1i** (176 mg, 1 mmol) and DFMBA (426 mg, 2 mmol) were introduced. The open end of the tube was connected to a reflux condenser. Then, the reaction mixture was submitted for 30 min to microwave irradiation and during the irradiation, the temperature was kept at 90 °C. After cooling, the reaction mixture was poured into sat aq $NaHCO_3$. The product was extracted with ether (20 mL × 3) and the combined ethereal layer was dried over $MgSO_4$. Purification by column chromatography (silica gel/hexane-ether) gave **2i** (132 mg) in 74% yield as a mixture of stereoisomers (*E*:*Z* = 86:14, they are separable by column chromatography); (*E*)-**2i**; clear oil: IR (neat): 2926, 1811, 1651, 1284 cm^{-1}. ^1H NMR δ 7.86–7.82 (m, 2H), 7.58–7.41 (m, 3H), 2.09 (d, *J* = 18.4 Hz, 3H), 1.90 (brs, 3H). ^{13}C NMR δ 196.42 (d, *J* = 2.2 Hz), 157.98 (d, *J* = 257.9 Hz), 137.84 (d, *J* = 1.6 Hz), 132.85, 128.95 (d, *J* = 1.6 Hz, 2C), 128.35 (2C), 113.01 (d, *J* = 14.2 Hz), 15.45 (d, *J* = 29.8 Hz), 14.14 (d, *J* = 4.2 Hz). ^{19}F NMR δ −84.38 to −84.75 (m, 1F). HRMS (EI): calcd for $C_{11}H_{11}FO$ (M^+): 178.0794, found: 178.0792. (*Z*)-**2i**; clear oil: IR (neat): 2927, 1655, 1320 cm^{-1}. ^1H NMR δ 7.82–7.79 (m, 2H), 7.59–7.45 (m, 3H), 1.95–1.85 (m, 6H). ^{13}C NMR δ 197.69 (d, *J* = 12.6 Hz), 161.53 (d, *J* = 263.8 Hz), 137.64 (d, *J* = 3.3 Hz), 132.98, 129.08 (2C), 128.64 (2C), 115.11 (d, *J* = 16.5 Hz), 17.23 (d, *J* = 28.9 Hz), 12.62 (d, *J* = 7.4 Hz). ^{19}F NMR δ −85.91 to −86.06 (m, 1F).

4.2.10. 4-tert-Butyl-2-(1-fluoroethylidene)cyclohexanone (2j)

The reaction was carried out as in the case of **2e** using 4-*tert*-butyl-2-acetylcyclohexanone **1j** in CH_2Cl_2 at 30 °C for 12 h. Purification by column chromatography (silica gel/hexane-ether) gave **2j** in 74% yield as a single isomer [13]; clear oil: IR (neat): 2975, 1699, 1619 cm^{-1}. ^1H NMR δ 2.88 (d, *J* = 15.7 Hz, 1H), 2.54 (d, *J* = 18.0 Hz, 1H), 2.28 (d, *J* = 22.1 Hz, 3H), 2.32–2.28 (m, 1H), 2.04–1.96 (m, 2H), 1.48–1.42 (m, 2H), 0.93 (s, 9H). ^{13}C NMR δ 202.17 (d, *J* = 14.3 Hz), 166.24 (d, *J* = 271.6 Hz), 116.47 (d, *J* = 14.8 Hz), 44.42 (d, *J* = 1.9 Hz), 41.26 (d, *J* = 5.8 Hz), 32.60, 27.19 (3C), 25.19 (d, *J* = 8.6 Hz), 24.27, 17.38 (d, *J* = 25.7 Hz). ^{19}F NMR δ −73.34 (q, *J* = 20.3 Hz, 1F). HRMS (EI): calcd for $C_{12}H_{19}FO$ (M^+): 198.1420, found: 198.1414.

4.3. Reaction of 2 with dialkyl cuprates

4.3.1. Reaction of 2b with lithium dimethyl cuprate

To a THF solution (5 mL) of CuBr Me_2S (208 mg, 1.01 mmol) was added at 0 °C, 1.6 M ethereal solution of MeLi (1.25 mL, 2 mmol) and the mixture was stirred for 30 min. Then, the mixture was cooled to −78 °C and a THF solution of (*E*)-**2b** (80.2 mg, 0.488 mmol) was added. The mixture was stirred at the temperature for 3 h and quenched by the successive addition of MeOH (5 mL) and sat aq NH_4Cl (10 mL). The mixture was extracted with ether (20 mL × 3) and combined organic layer was washed with brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 3-methyl-1-phenyl-2-buten-1-one **4a** (73 mg) in 93% yield; clear oil: IR (neat): 2912, 1660, 1614, 1248, 1011 cm^{-1}. ^1H NMR δ 7.94–7.92 (m, 2H), 7.55–7.43 (m, 3H), 6.76–6.75 (m, 1H), 2.21 (d, *J* = 1.0 Hz, 3H, CH_3), 2.02 (d, *J* = 1.1 Hz, 3H, CH_3) {lit. [19] 2.23 (d, *J* = 1.14 Hz, 3H, CH_3), 2.04 (d, *J* = 1.28 Hz, 3H, CH_3)}. ^{13}C NMR δ 191.46, 156.65, 139.18, 132.21 (2C), 128.37 (2C), 128.12, 121.12, 27.93, 21.11.

4.3.2. Reaction of 2b with lithium dibutyl cuprate

To a THF solution (5 mL) of CuBr Me_2S (208 mg, 1.01 mmol) was added at −45 °C, 1.6 M hexane solution of BuLi (1.25 mL, 2.0 mmol) and the mixture was stirred for 45 min. Then, the mixture was cooled to −78 °C and a THF solution of **2b** (80.3 mg, 0.489 mmol) was added. The mixture was stirred at the temperature for 3 h and quenched by the successive addition of MeOH (5 mL) and sat aq NH_4Cl (10 mL). The mixture was extracted with ether (20 mL × 3) and combined organic layer was washed with brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 3-methyl-1-phenyl-2-hepten-1-one **4b** (81.0 mg) in 82% yield as mixture of the stereoisomers (*E*:*Z* = 24:76, they are separable by column chromatography). (*Z*)-**4b**; clear oil: IR (neat): 2958, 1661, 1611, 1254 cm^{-1}. ^1H NMR δ 7.94–7.92 (m, 2H), 7.54–7.43 (m, 3H), 6.72 (s, 1H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.01 (d, *J* = 1.3 Hz, 3H), 1.56–1.35 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 191.23, 160.97, 139.30, 132.19, 128.37 (2C), 128.14 (2C), 121.10, 33.98, 30.40, 25.69, 22.92, 13.95. HRMS (EI): calcd for $C_{14}H_{18}O$ (M^+): 202.1358, found: 202.1353. (*E*)-**4b**; clear oil: IR (neat): 2930, 1661, 1611, 1239 cm^{-1}. ^1H NMR δ 7.94–7.92 (m, 2H), 7.55–7.43 (m, 3H), 6.73 (d, *J* = 1.3 Hz, 1H), 2.26 (t, *J* = 7.4 Hz, 2H), 2.20 (d, *J* = 1.0 Hz, 3H, CH_3), 1.59–1.51 (m, 2H), 1.43–1.35 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) {lit. [19] 2.20 (d, *J* = 1.0 Hz, 3H, CH_3)}. ^{13}C NMR δ 191.74, 160.61, 139.39, 132.22, 128.40 (2C), 128.15 (2C), 120.45, 41.24, 29.75, 22.39, 19.75, 13.92.

4.3.3. Reaction of 2e with lithium dimethyl cuprate

The reaction was carried out as in the case of Section 4.3.1 using **2e** to give (*E*)-4,4,4-trifluoro-3-methyl-1-phenyl-2-buten-1-one **5a** and 4,4-difluoro-3-methyl-1-phenyl-3-buten-1-one **6a**. The yield of **6a** (53%) was determined by ^{19}F NMR using fluorobenzene as an internal standard, and the yield of **5a** (23%) was obtained after isolation by column chromatography (silica gel/hexane-ether); (*E*)-**5a**; clear oil: IR (neat): 1681, 1295, 1181, 1129 cm^{-1}. ^1H NMR δ 7.95–7.93 (m, 2H), 7.64–7.60 (m, 1H), 7.53–7.49 (m, 2H), 7.24–7.23 (m, 1H), 2.16 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR δ 191.10, 139.20 (q, *J* = 30.5 Hz), 137.11, 133.83, 128.87 (2C), 128.56 (2C), 125.76 (q, *J* = 5.4 Hz), 123.39 (q, *J* = 274.0 Hz), 12.82. ^{19}F NMR δ −71.47 (s, 3F) {lit. [20] −71.36 (s, 3F)}. HRMS (EI): calcd for $C_{11}H_9F_3O$ (M^+): 214.0605, found: 214.0602. **6a**; clear oil: IR (neat): 2929, 1765, 1692, 1205 cm^{-1}. ^1H NMR δ 7.98–7.96 (m, 2H), 7.61–7.58 (m, 1H), 7.51–7.47 (m, 2H), 3.64 (t, *J* = 1.8 Hz, 2H), 1.65 (t, *J* = 3.2 Hz, 3H). ^{13}C NMR δ 196.25 (dd, *J* = 3.4, 2.4 Hz), 153.66 (dd, *J* = 282.8, 282.8 Hz), 136.25, 133.40, 128.70 (2C), 128.12 (2C), 80.44 (dd, *J* = 22.9, 19.1 Hz), 38.26 (d, *J* = 2.8 Hz), 12.53 (d, *J* = 1.7 Hz). ^{19}F NMR δ −95.15 (d, *J* = 52.0 Hz, 1F), −94.80 (d, *J* = 51.9 Hz, 1F). HRMS (EI): calcd for $C_{11}H_{10}F_2O$ (M^+): 196.0700, found: 196.0692.

4.3.4. Reaction of 2e with lithium dibutyl cuprate

The reaction was carried out as in the case of Section 4.3.2 using **2e** to give (*E*)-3-trifluoromethyl-1-phenyl-2-hepten-1-one **5b** and 4,4-difluoro-3-butyl-1-phenyl-3-buten-1-one **6b**. The yield of **5b** (8%) was determined by ^{19}F NMR using fluorobenzene as an internal standard and the yield of **6b** (64%) was obtained after isolation by column chromatography (silica gel/hexane-ether), respectively; (*E*)-**5b**; clear oil: IR (neat): 2962, 1677, 1318, 1279, 1176, 1128 cm^{-1}. ^1H NMR δ 7.95–7.93 (m, 2H), 7.64–7.60 (m, 1H), 7.53–7.49 (m, 2H), 7.22 (s, 1H), 2.56–2.52 (m 2H), 1.59–1.51 (m, 2H), 1.41–1.32 (m, 2H), 0.89

(t, J = 7.3 Hz, 3H). ^{13}C NMR δ 191.05, 143.76 (q, J = 28.6 Hz), 137.21, 133.76, 128.85 (2C), 128.52 (2C), 126.30 (q, J = 5.5 Hz), 123.74 (q, J = 275.6 Hz), 30.99, 27.06, 22.84, 13.62. ^{19}F NMR δ −68.92 (s, 3F). HRMS (EI): calcd for $C_{14}H_{15}F_3O$ (M^+): 256.1075, found: 256.1064. **6b**; clear oil: IR (neat): 2959, 1755, 1694, 1273, 1210 cm^{-1}. ^{1}H NMR δ 7.98–7.96 (m, 2H), 7.61–7.57 (m, 1H), 7.50–7.47 (m, 2H), 3.64 (t, J = 1.8 Hz, 2H), 2.08–2.03 (m 2H), 1.39–1.25 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 196.34 (dd, J = 3.1, 2.6 Hz), 154.08 (dd, J = 285.2, 284.2 Hz), 136.34, 133.36, 128.69 (2C), 128.14 (2C), 84.46 (dd, J = 21.9, 16.2 Hz), 36.14 (d, J = 2.9 Hz), 29.24 (dd, J = 2.2, 2.2 Hz), 26.23 (d, J = 1.6 Hz), 22.15, 13.76. ^{19}F NMR δ −93.96 (d, J = 50.2 Hz, 1F), −94.61 (d, J = 50.1 Hz, 1F). HRMS (EI): calcd for $C_{14}H_{16}F_2O$ (M^+): 238.1169, found: 238.1174.

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