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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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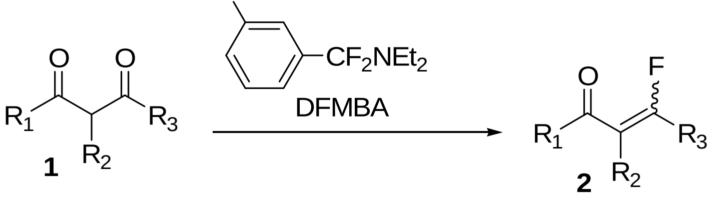
β-diketone
N,N-diethyl-α,α-difluoro-*m*-methylbenzylamine
deoxyfluorination
regioselective

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).

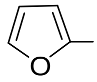
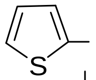
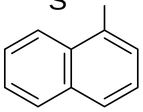


Scheme 1

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 micro-wave irradiation condition without solvent to optimize the 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].

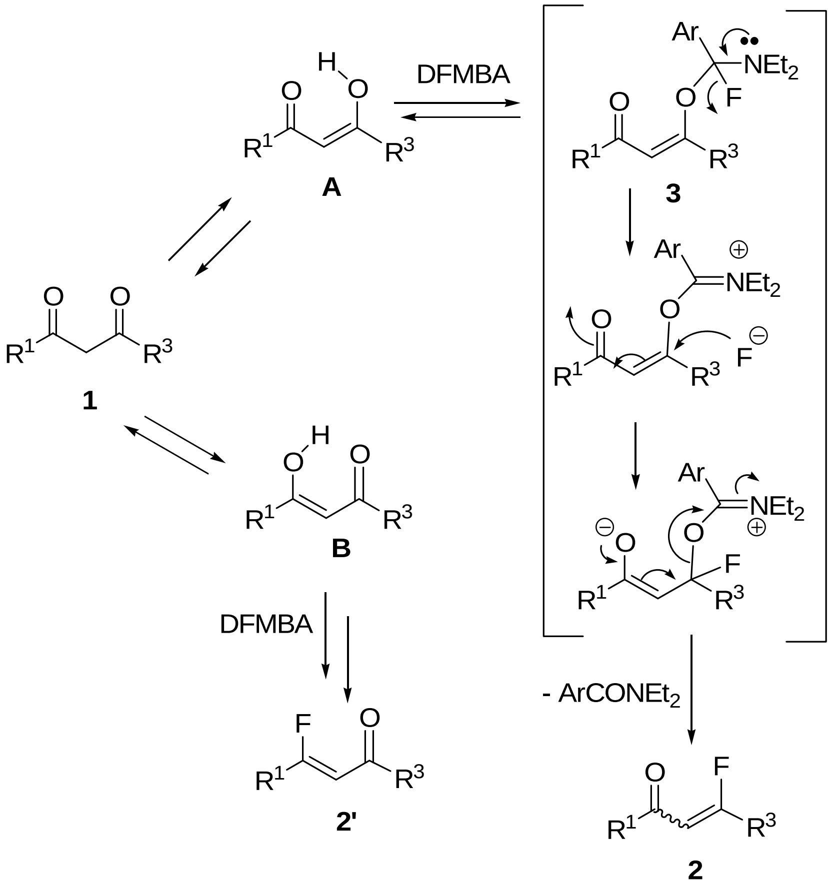
Table 1
Reaction of β-diketones with DFMBA[a].

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	${}^tBu$	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	**1i**	Ph	Me	Me	90 °C	0.5 h	74 (86 : 14)
10[d]	**1j**	$-(CH_2)_2\underset{\overset{\mid}{{}^tBu}}{C}HCH_2-$		Me	30 °C	12 h	74

[a] If otherwise not mentioned, the reaction was carried out in 1,4-dioxane using 2 eq 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}FNMR yield.

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

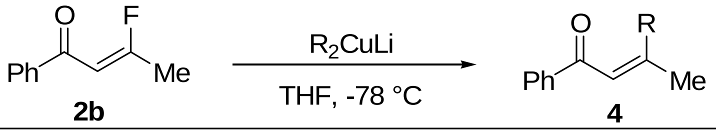
DFMBA, respectively. However, in the present deoxyfluorination reaction, only one regioisomer **2** was formed from the unsymmetrical diketones (**1b**, **1d**-**1i**). In the chlorination of the unsymmetrical β-diketones with Vielsmerer's reagent, the similar regioselectivity was observed and the selectivity 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.

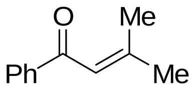
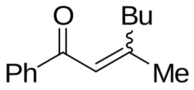


Scheme 2.

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



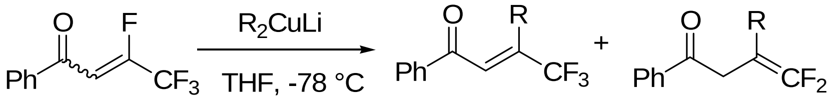
Entry	Substrate	R_2CuLi	Product	Yield (%)[b]
1	(*E*)-**2b**	Me_2CuLi	 **4a**	93
2	(*E*)-**2b**	Bu_2CuLi	 **4b**	82 (24:76)
3	(*Z*)-**2b**	Bu_2CuLi	**4b**	76 (30:70)

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

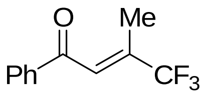
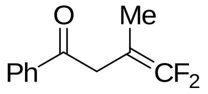
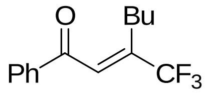
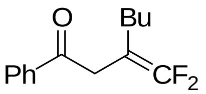
In the reaction of 1-phenyl-3,4,4,4-tetrafluoro-2-buten-1-one **2e** (a mixture of *E* and *Z* isomers) with Me_2CuLi, the expected product,

(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).

Table 3
The reaction of **2e** with R_2CuLi^a.



2e **5** **6**

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 eq of R_2CuLi.
[b] Isolation yield based on **2e**.
[c] ^{19}F NMR 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 ^{1}H 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 (^{1}H, ^{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 Mitubishi Gas Co. Ltd. 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<u>H</u>), 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<u>H</u>)}. ^{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<u>H</u>)}. ^{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<u>H</u>), 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; mp 49–51 °C: IR (KBr): 3081, 1632, 1246 cm^{-1}. ^{1}H NMR δ 7.91–7.88 (m, 2H), 7.58–7.42 (m, 3H), 6.09 (d, *J* = 33.3 Hz, 1H, =C$\underline{H}$), 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 ºC 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; mp 36–38 °C: IR (KBr): 3056, 1670, 1626, 1246 cm^{-1}. ^{1}H NMP 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$\underline{H}$). ^{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; mp 59–60 °C (lit.[3b] 61 °C): IR (KBr): 3041, 1665, 1605, 1214 cm^{-1}. ^{1}H 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$\underline{H}$). ^{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}. ^{1}H NMR δ 7.89–7.86 (m, 2H), 7.58–7.43 (m, 3H), 6.06 (d, $J = 35.6$ Hz, 1H, =C<u>H</u>), 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}. ^{1}H NMR δ 7.94–7.91 (m, 2H), 7.68–7.50 (m, 3H), 6.72 (d, $J = 31.3$ Hz, 1H, =C<u>H</u>). ^{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**; ^{1}H NMR δ 6.72 (d, $J = 18.9$ Hz, 1H, C=C<u>H</u>). ^{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: mp 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$\underline{H}$), 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$\underline{H}$), 6.64–6.62 (m, 1H). ^{19}F NMR δ –69.51 (d, *J* = 8.5 Hz, 3F), –115.9 (brs, 1F).

*4.2.6. 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: mp 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, =CH). ^{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**; ^{1}H 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=CH). ^{19}F NMR δ –69.54 (d, *J* = 9.0 Hz, 3F), –118.71 (dq, *J* = 18.0, 8.9 Hz, 1F).

*4.2.7. 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: mp 62–63 °C: IR (KBr):1702, 1650, 1213, 1139 cm^{-1}. ^{1}H 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, =CH). ^{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**; ^{1}H NMR δ 6.85 (d, *J* = 18.7 Hz, 1H, C=CH). ^{19}F NMR δ –69.74 (d, *J* = 9.0 Hz, 3F), –119.62 (dq, *J* = 19.7, 8.9 Hz, 1F).

*4.2.7. 3-Fluoro-2-methyl-1-phenyl-2-buten-1-one (**2i**)*

To a Teflon^{TM} 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 micro-wave 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 X 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).

4.2.8. 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 X 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}. ^{1}H 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, $C\underline{H}_3$), 2.02 (d, J = 1.1 Hz, 3H, $C\underline{H}_3$) {lit. [19] 2.23 (d, J = 1.14 Hz, 3H, $C\underline{H}_3$), 2.04 (d, J = 1.28 Hz, 3H, $C\underline{H}_3$)}. ^{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 X 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, $C\underline{H_3}$), 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, $C\underline{H_3}$)}. ^{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 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}. ^{1}H 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}. ^{1}H 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 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}. ^{1}H 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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