DOI: 10.1002/ejoc.201000887

The Reaction of Carboxylic Acid Esters with R_fMgBr: A Convenient Synthesis of Perfluoroalkyl Ketones

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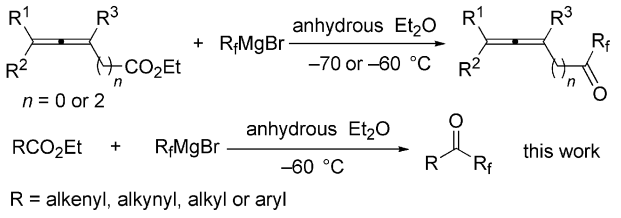
Keywords: Esters / Grignard reaction / Fluorine / Perfluoroalkanes / Ketones

An efficient method for the preparation of the synthetically attractive perfluoroalkyl ketones through the reaction of readily available alkenoates, alkynoates, or regular carboxylic esters with perfluoroalkyl Grignard reagents at –70 to –60 °C in diethyl ether with moderate to good yields was developed. The reaction stopped at the ketone stage, with no further reaction to form the tertiary alcohols being observed. DFT calculations confirmed that the perfluoroalkyl-substituted ketones are less electrophilic as compared to ordinary ketones.

Introduction

Perfluoroalkyl ketones are important intermediates in organic synthesis, materials science, and the pharmaceutical industry.[1] A literature survey shows that perfluoroalkyllithium reagents (R_fLi) have been extensively used in perfluoroalkylation reactions with amides, anhydrides, and carboxylic esters, etc.[2–6] In most cases, a mixture of perfluoroalkyl ketones and diperfluoroalkyl-substituted tertiary alcohols were obtained.[2,7] Reports on the preparation of perfluoroalkyl ketones through the reactions of perfluoroalkyl Grignard reagents (R_fMgX) with carboxylic esters are very limited.[8–10] Recently, we have developed an efficient method for the synthesis of perfluoroalkyl allenyl ketones through the 1,2-addition/elimination reaction of allenoates with R_fMgX.[11] As a meaningful extension of this field, we have focused our attention on the reactions of alkenoates, alkynoates, and nonfluorinated carboxylic esters with R_fMgBr and on a theoretical study on the reactivities of perfluoroalkyl ketones (Scheme 1).



Scheme 1. Reactions of R_fMgBr with allenoates (previous work[11]) and alkenoates, alkynoates, and nonfluorinated carboxylic esters (this work).

Results and Discussion

According to the established reaction conditions,[11] we conducted the reaction of ethyl (*E*)-2-methyl-3-phenyl-2-propenoate [(*E*)-**1a**] with 3.5 equiv. of *n*-C_4F_9MgBr in anhydrous Et_2O at –60 °C. As a result, perfluorobutyl (1*E*)-1-phenylprop-1-en-2-yl ketone [(*E*)-**2a**] was formed in an isolated yield of 85% (Table 1, Entry 1). *n*-C_4F_9MgBr was prepared by the I/Mg exchange reaction of *n*-C_4F_9I with EtMgBr in anhydrous Et_2O at –70 °C.[12] We attempted to reduce the amount of R_fMgBr, but the reaction with 2.0, 2.5 and 3.0 equiv. of the Grignard reagents led to incomplete conversions (Table 1, Entries 2–4). Furthermore, it is interesting to note that only 5% of ketone (*E*)-**2a** was observed when tetrahydrofuran (THF) was used as the solvent (determined by ^1H NMR spectroscopic analysis); the reaction in toluene afforded ketone (*E*)-**2a** in 74% yield with 26% recovery of (*E*)-**1a**.

As the starting materials are easily available, we then started to explore the scope of this reaction with the optimized reaction conditions (Table 2). A conjugated carbon–carbon double bond in the starting material remained untouched in the reaction. The experimental results showed that for 2-monosubstituted (Table 2, Entries 3 and 4) and 2,3-disubstituted (Table 2, Entries 1 and 2) ethyl 2-alkenoates, the reaction proceeded smoothly with yields ranging from 82 to 85%. However, when 3-monosubstituted ethyl 2-alkenoate (**1c**) was subjected to the same reaction conditions, considerable amounts of starting material were also recovered (Table 2, Entry 5).

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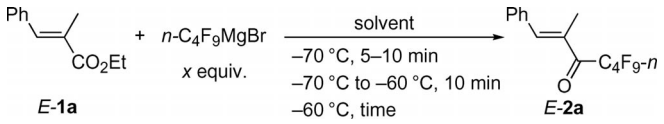
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000887.

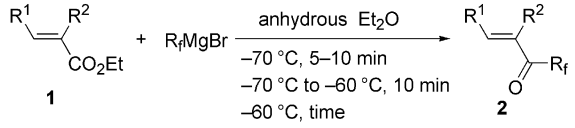
Table 1. Optimization of the reaction of ethyl (*E*)-2-methyl-3-phenyl-2-propenoate with *n*-C_4F_9MgBr.



Entry	*x* [equiv.]	Solvent	Time [h]	NMR yield of (*E*)-**2a** [%]	Recovery of (*E*)-**1a** [%]
1	3.5	Et_2O	11	85[a]	0
2	2.0	Et_2O	48	51	39
3	2.5	Et_2O	48	68	30
4	3.0	Et_2O	48	81	14
5	3.5	THF	24	5	94
6	3.5	toluene	24	74	26

[a] Isolated yield.

Table 2. Reaction of alkenoates with perfluoroalkyl Grignard reagents.



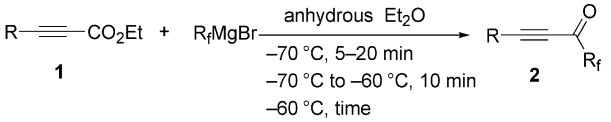
Entry	R^1	R^2	R_f (equiv.)	Time [h]	Yield of **2** [%][a]
1	Ph	Me [(*E*)-**1a**]	*n*-C_4F_9 (3.5)	11	85 [(*E*)-**2a**]
2	Ph	Me [(*E*)-**1a**]	*n*-C_6F_{13} (4.0)	11	85 [(*E*)-**2b**]
3	H	Bn (**1b**)	*n*-C_4F_9 (3.5)	11	82 (**2c**)
4	H	Bn (**1b**)	*n*-C_6F_{13} (4.0)	11	84 (**2d**)
5	Ph	H [(*E*)-**1c**]	*n*-C_4F_9 (3.5)	24	51 [(*E*)-**2e**][b]

[a] Isolated yield. [b] Starting material [(*E*)-**1c**] was recovered (28%).

We then explored the reaction of a range of substituted ethyl 2-alkynoates with R_fMgBr. Alkyl- and aryl-substituted ethyl 2-alkynoates could be readily converted into the corresponding 1-alkynyl perfluoroalkyl ketones upon addition of R_fMgBr with good to excellent yields (Table 3, Entries 1–3). The substituents on the aryl ring had no significant effect on the reaction (Table 3, Entries 4–9). It should be noted that for substrates substituted with a heteroaromatic group (e.g., ethyl 3-thienylpropiolate; **1i**), the expected target products could also be obtained in yields ranging from 87 to 94% (Table 3, Entries 10 and 11).

As reported previously, usually, a mixture of ketones and tertiary alcohols are produced when perfluoroalkyllithium reagents are added to normal carboxylic esters.[7,8] We therefore attempted to carry out the reaction of ethyl *n*-octanoate (**1j**) with 3.5 equiv. of *n*-C_4F_9MgBr under our reaction conditions (Table 4, Entry 1) and were surprised to find that the starting material was converted into *n*-heptyl nonafluorobutyl ketone (**2q**) completely. Aryl and alkyl carboxylates could readily be transformed into the corresponding perfluoroalkyl ketones without the formation of

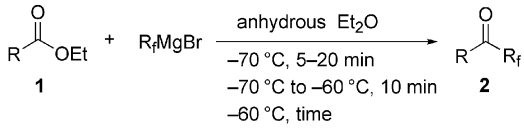
Table 3. Reaction of alkynoates with perfluoroalkyl Grignard reagents.



Entry	R	R_f (equiv.)	Time [h]	Yield of **2** [%][a]
1	*n*-C_4H_9 (**1d**)	*n*-C_6F_{13} (4.0)	11	94 (**2f**)
2	Ph (**1e**)	*n*-C_4F_9 (3.5)	14.5	91 (**2g**)
3	Ph (**1e**)	*n*-C_6F_{13} (4.0)	11	89 (**2h**)
4	4-$MeOC_6H_4$ (**1f**)	*n*-C_4F_9 (4.0)	18	83 (**2i**)
5	4-$MeOC_6H_4$ (**1f**)	*n*-C_6F_{13} (4.0)	18	75 (**2j**)
6	4-*n*-PrC_6H_4 (**1g**)	*n*-C_4F_9 (3.5)	11	97 (**2k**)
7	4-*n*-PrC_6H_4 (**1g**)	*n*-C_6F_{13} (4.5)	21.5	96 (**2l**)
8	4-FC_6H_4 (**1h**)	*n*-C_4F_9 (3.5)	17	79 (**2m**)
9	4-FC_6H_4 (**1h**)	*n*-C_6F_{13} (4.0)	17	75 (**2n**)
10	3-thienyl (**1i**)	*n*-C_4F_9 (3.5)	12	87 (**2o**)
11	3-thienyl (**1i**)	*n*-C_6F_{13} (4.0)	21.5	94 (**2p**)

[a] Isolated yield.

Table 4. Reaction of nonfluorinated carboxylic esters with perfluoroalkyl Grignard reagents.

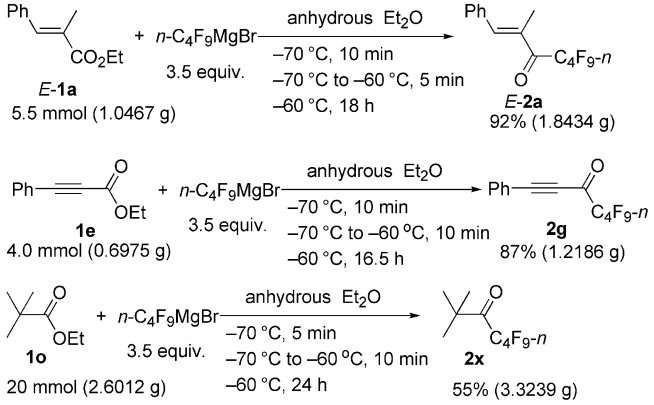


Entry	R	R_f (equiv.)	Time [h]	Yield of **2** [%][a]
1	*n*-C_7H_{15} (**1j**)	*n*-C_4F_9 (3.5)	16.5	87 (**2q**)
2	*n*-C_7H_{15} (**1j**)	*n*-C_6F_{13} (4.0)	15.5	82 (**2r**)
3	Ph (**1k**)	*n*-C_4F_9 (3.5)	14.5	61 (**2s**)
4	Ph (**1k**)	*n*-C_6F_{13} (4.0)	16	86 (**2t**)[b]
5	cyclohexyl (**1l**)	*n*-C_6F_{13} (4.0)	24	77 (**2u**)
6	cumyl (**1m**)	*n*-C_4F_9 (3.5)	13	86 (**2v**)
7	adamantyl (**1n**)	*n*-C_4F_9 (3.5)	24	82 (**2w**)

[a] Isolated yield. [b] Starting material was also recovered (3.5%).

tertiary alcohols (Table 4, Entries 2–4). The reactions of R_fMgBr with secondary and tertiary alkyl carboxylates, such as cyclohexyl, cumyl, and adamantyl carboxylates (Table 4, Entries 5–7) also afforded the expected products **2u**–**w** in rather good yields. These results indicate that the relatively weaker nucleophilicity of R_fMgBr compared to R_fLi enables the reaction to stop at the ketone stage completely.

The reaction could also be carried out on a scale of 4.0–20 mmol to afford the corresponding perfluoroalkyl ketones (*E*)-**2a**, **2g**, and **2x** in 92, 87, and 55% yields, respectively (Scheme 2).

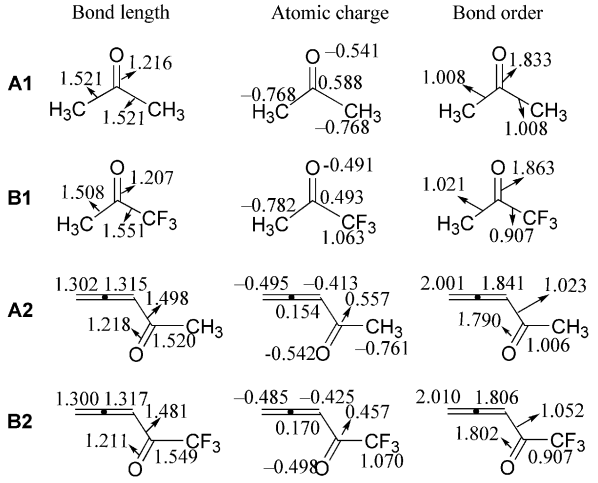


Scheme 2. Larger scale reactions of **1a**, **1e**, and **1o** with *n*-C_4F_9MgBr.

Theoretical Studies on the Reactivity of Methyl Ketones versus Trifluoromethyl Ketones

The experimental results presented above, together with our previous observations,[11] point to the fact that the perfluoroalkyl group in a perfluoroalkyl ketone $R_fC(O)R$ helps stabilize the carbonyl moiety, preventing it from further reactions towards the R_fMgBr reagent. To better understand this stabilization effect, we performed density functional theory (DFT) calculations by using the B3LYP functional on four different perfluoroalkyl ketones (Scheme 3).

Scheme 3 shows the bond lengths, atomic charges, and bond orders calculated for two methyl ketones, **A1** and **A2**, as well as two trifluoromethyl ketones, **B1** and **B2**. The atomic charges and bond orders, which are Wiberg bond indices[13] and a measure of bond strength, were obtained by using the natural bond orbital (NBO) analysis.[14] The DFT results clearly show that the trifluoromethyl group enhances the C=O bonding interaction. The C=O bond in **B1** is noticeably shorter than that in **A1**, and its bond order is larger. A similar trend can also be observed for **B2** when compared with **A2**. The atomic charges calculated for the carbonyl carbon atoms in **B1** and **B2** are less positive than those in **A1** and **A2**, respectively, implying that the carbonyl carbon atoms in the perfluoroalkyl ketones are less electrophilic. The atomic charges calculated for the carbonyl carbon atom in the allenyl ketones **A2** and **B2** were determined to be less positive than those in their corresponding alkyl ketones **A1** and **B1**, respectively. The greater conjugation in **A2** or **B2** increases the inertness of their carbonyl moieties toward nucleophiles.



Scheme 3. Comparsion of methyl ketones with trifluoromethyl ketones.

Conclusions

We have developed an efficient method with which to prepare perfluoroalkyl ketones through the reaction of alkenoates, alkynoates, or nonfluorinated carboxylic esters with perfluoroalkyl Grignard reagents. The results of the DFT calculations are consistent with the experimental observation of less electrophilic carbonyl moieties in the perfluoroalkyl ketones as compared to those of nonfluorinated ketones. In the perfluoroalkyl ketones, the charge density loss at the carbonyl carbon atom to the perfluoroalkyl group is apparently more compensated for by π-electron donation from the carbonyl oxygen atom, leading to a more inert carbonyl moiety. Due to the ready availability of the starting materials and to the relative convenience of R_fMgBr compared to the corresponding R_fLi reagents, this approach will provide a convenient method for introducing perfluoroalkyl groups into organic molecules.

Experimental Section

General: Et_2O was distilled from Na/benzophenone. EtMgBr was produced freshly just before the reaction. The other commercially available chemicals were purchased and used without additional purification. Petroleum ether with a boiling range of 30–60 °C was used. Flash-column chromatography was carried out on silica gel H (10–40 μm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AM-300 spectrometer. IR spectra were recorded with a Perkin–Elmer 983 spectrometer. Mass spectra were recorded with an HP 5989A spectrometer.

***n*-Perfluorobutyl (1*E*)-1-Phenylprop-1-en-2-yl Ketone [(*E*)-2a]. Typical Procedure I:** To a dried Schlenk tube were added *n*-C_4F_9I (0.36 mL, d = 2.01 g/mL, 0.72 g, 2.09 mmol) and anhydrous Et_2O (2.5 mL). The resulting mixture was cooled to –70 °C with a cooling bath, and a solution of EtMgBr (0.48 mL, 3.0 M in Et_2O,

1.44 mmol) was added dropwise at –70 °C with stirring. After the addition, anhydrous Et_2O (0.75 mL) was applied to rinse the remaining EtMgBr. The resulting mixture was stirred at –70 °C for 1.5 h. A solution of (*E*)-**1a** (76.5 mg, 0.40 mmol) in anhydrous Et_2O (1 mL) was then added to this resulting mixture dropwise at –70 °C within 10 min with stirring, and the mixture was warmed to –60 °C within 10 min and stirred at –60 °C for 11 h (reaction monitored by TLC analysis). The mixture was quenched with saturated aqueous NH_4Cl (5 mL) at –60 °C. After warming slowly to room temp., H_2O (5 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (5 mL) and dried with anhydrous Na_2SO_4. Filtration, concentration, and purification by chromatography on silica gel (petroleum ether, boiling range 30–60 °C) afforded (*E*)-**2a** (124.0 mg, 85%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H, C=CH), 7.50–7.38 (m, 5 H, ArH), 2.17 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.7 (t, J = 24.3 Hz), 145.8 (app. tt, J = 5.4 Hz), 134.8, 132.7 (t, J = 2.1 Hz), 130.3, 129.9, 128.7, 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.0 to –81.1 (m, 3 F), –110.2 to –110.3 (m, 2 F), –121.6 to –121.9 (m, 2 F), –125.0 to –125.2 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 1690, 1616, 1577, 1492, 1449, 1395, 1354, 1327, 1236, 1164, 1137, 1066, 1006 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 365 (6.34) [M$^+$ + 1], 364 (38.19) [M]$^+$, 117 (100). HRMS: calcd. for $C_{14}H_9F_9O$ [M]$^+$ 364.0510; found 364.0512.

Large-Scale Reaction for the Synthesis of *n*-Perfluorobutyl (1*E*)-1-Phenylprop-1-ene-2-yl Ketone [(*E*)-2a]. Typical Procedure II: To an oven-dried, three-necked, round-bottom flask were added *n*-C_4F_9I (5.0 mL, *d* = 2.01 g/mL, 10.05 g, 29.05 mmol) and anhydrous Et_2O (34 mL). After the mixture was cooled in a –70 °C cooling bath, a solution of EtMgBr (6.4 mL, 3.0 M in Et_2O, 19.2 mmol) was added dropwise at –70 °C with stirring for 15 min. After the addition, anhydrous Et_2O (12 mL) was applied to rinse the remaining EtMgBr. The resulting mixture was stirred at –70 °C for 1.5 h. A solution of (*E*)-**1a** (1.0467 g, 5.5 mmol) in Et_2O (12 mL) was then added dropwise with stirring at –70 °C within 10 min, and the mixture was warmed to –60 °C within 5 min and stirred at –60 °C for 18 h (reaction monitored by TLC, eluted with pure petroleum ether twice). The mixture was quenched with saturated aqueous NH_4Cl (25 mL) at –60 °C, and, after the mixture had been warmed slowly to room temp., H_2O (15 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 × 20 mL). The combined organic extracts were washed with brine (15 mL) and dried with anhydrous Na_2SO_4. Filtration, concentration, and purification by chromatography on silica gel (petroleum ether, boiling range 30–60 °C) afforded (*E*)-**2a** (1.8434 g, 85%) as a liquid.

***n*-Perfluorohexyl (1*E*)-1-Phenylprop-1-en-2-yl Ketone [(*E*)-2b]:** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C, afforded the Grignard reagent, which was treated with (*E*)-**1a** (74.9 mg, 0.39 mmol) in Et_2O (1 mL) at –60 °C for 11 h to afford (*E*)-**2b** (156.2 mg, 85%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1 H, =CH), 7.51–7.37 (m, 5 H, ArH), 2.17 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.6 (t, J = 24.5 Hz), 145.8 (app. tt, J = 6.2 Hz), 134.8, 132.7 (t, J = 2.1 Hz), 130.3, 129.9, 128.6 (d, J = 5.7 Hz), 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.2 (m, 3 F), –110.0 to –110.3 (m, 2 F), –120.7 to –121.3 (m, 4 F), –122.8 to –123.1 (m, 2 F), –126.1 to –126.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3064, 3031, 2931, 1690, 1617, 1577, 1493, 1449, 1395, 1363, 1313, 1240, 1145, 1124, 1070, 1024, 1006 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 465 (4.37) [M$^+$ + 1], 464 (22.73) [M]$^+$, 117 (100). HRMS: calcd. for $C_{16}H_9F_{13}O$ [M]$^+$ 464.0446; found 464.0438.

***n*-Perfluorobutyl 3-Phenylprop-1-en-2-yl Ketone (2c):** According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1b** (76.5 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 11 h to afford **2c** (120.0 mg, 82%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 3 H, ArH), 7.19–7.13 (m, 2 H, ArH), 6.43 (d, J = 0.6 Hz, 1 H, =CH), 6.05 (s, 1 H, =CH), 3.66 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.7 (app. td, J_1 = 25.1, J_2 = 1.3 Hz), 143.2 (t, J = 2.2 Hz), 137.1, 132.6 (app. tt, J = 3.7 Hz), 129.1, 128.7, 126.8, 37.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.1 (m, 3 F), –112.0 to –112.2 (m, 2 F), –121.9 to –122.1 (m, 2 F), –125.2 to –125.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3033, 2928, 1706, 1497, 1455, 1439, 1355, 1238, 1138, 1096, 1075, 1047 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 365 (6.47) [M$^+$ + 1], 364 (45.01) [M]$^+$, 145 (100). HRMS: calcd. for $C_{14}H_9F_9O$ [M]$^+$ 364.0510; found 364.0519.

***n*-Perfluorohexyl 3-Phenylprop-1-en-2-yl Ketone (2d):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1b** (77.6 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 11 h to afford **2d** (158.7 mg, 84%) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.12 (m, 5 H, ArH), 6.42 (s, 1 H, =CH), 6.05 (s, 1 H, =CH), 3.66 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.7 (t, J = 25.2 Hz), 143.3 (t, J = 1.8 Hz), 137.1, 132.6 (app. tt, J = 6.5 Hz), 129.2, 128.7, 126.8, 37.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.1 (m, 3 F), –111.8 to –112.1 (m, 2 F), –120.9 to –121.5 (m, 4 F), –122.7 to –123.1 (m, 2 F), –126.1 to –126.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3067, 3033, 2927, 1705, 1605, 1497, 1455, 1439, 1364, 1316, 1241, 1206, 1146, 1075, 1031, 1008 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 465 (5.86) [M$^+$ + 1], 464 (32.76) [M]$^+$, 145 (100). HRMS: calcd. for $C_{16}H_9F_{13}O$ [M]$^+$ 464.0446; found 464.0452.

***n*-Perfluorobutyl (*E*)-Styryl Ketone [(*E*)-2e]:**[3b] According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.46 mL, *d* = 2.01 g/mL, 0.92 g, 2.67 mmol) with EtMgBr (0.60 mL, 3.0 M in Et_2O, 1.80 mmol) in Et_2O (3.0 mL) at –70 °C, afforded the Grignard reagent, which was treated with (*E*)-**1c** (70.6 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 24 h, to afford (*E*)-**2e** (72.3 mg, 51%) as a liquid, with recovery of (*E*)-**1c** (28% by ^{1}H NMR analysis). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 [d, J = 15.6 Hz, 1 H, =C(Ph)-H], 7.72–7.63 (m, 2 H, ArH), 7.55–7.41 (m, 3 H, ArH), 7.13 [d, J = 15.9 Hz, 1 H, =C(CO)H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.0 (t, J = 25.3 Hz), 150.0, 133.3, 132.4, 129.4, 129.2, 116.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.1 (m, 3 F), –121.1 to –121.4 (m, 2 F), –123.2 to –123.5 (m, 2 F), –125.7 to –126.0 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3066, 3032, 1712, 1609, 1577, 1497, 1452, 1339, 1306, 1235, 1206, 1136, 1084, 1012 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 351 (4.31) [M$^+$ + 1], 350 (29.66) [M]$^+$, 131 (100). HRMS: calcd. for $C_{13}H_7F_9O$ [M]$^+$ 350.0353; found 350.0355.

***n*-Hex-1-yn-1-yl *n*-Perfluorohexyl Ketone (2f):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.53 mL, *d* = 2.063 g/mL, 1.09 g, 2.45 mmol) with EtMgBr (0.53 mL, 3.0 M in Et_2O, 1.59 mmol) in Et_2O (3.0 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1d** (62.6 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 11 h, to afford **2f** (164.4 mg, 94%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (t, J = 6.9 Hz, 2 H, C≡CCH_2), 1.70–1.58 (m, 2 H, CH_2), 1.53–1.39 (m, 2 H, CH_3CH_2), 0.95 (t, J = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0 (t, J = 30.3 Hz), 106.2, 77.0, 29.1, 21.8, 19.2, 13.3 ppm.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.7 to –80.9 (m, 3 F), –118.4 to –118.7 (m, 2 F), –121.4 to –122.0 (m, 4 F), –122.7 to –123.1 (m, 2 F), –126.1 to –126.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2932, 2215, 1708, 1458, 1240, 1205, 1147 cm^{-1}. MS (ESI): *m*/*z* = 427 $[M - H]^-$. HRMS (ESI): calcd. for $C_{13}H_8F_{13}O^-$ $[M - H]^-$ 427.0373; found 427.0357.

***n*-Perfluorobutyl Phenylacetylenyl Ketone (2g):** According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1e** (69.8 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 14.5 h, to afford **2g** (127.3 mg, 91%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 2 H, ArH), 7.62–7.55 (m, 1 H, ArH), 7.50–7.43 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (t, *J* = 30.8 Hz), 134.0, 132.6, 129.0, 118.1, 101.5, 84.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.0 (m, 3 F), –118.5 to –118.7 (m, 2 F), –122.6 to –122.8 (m, 2 F), –125.6 to –125.8 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2927, 2855, 2200, 1701, 1597, 1491, 1446, 1354, 1310, 1238, 1138, 1084, 1028, 1008 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 348 (3.34) $[M]^+$, 129 (100). HRMS: calcd. for $C_{13}H_5F_9O$ $[M]^+$ 348.0197; found 348.0197.

Large-Scale Preparation of *n*-Perfluorobutyl Phenylacetylenyl Ketone (2g): According to Typical Procedure II, the reaction of *n*-C_4F_9I (3.6 mL, *d* = 2.01 g/mL, 7.24 g, 20.91 mmol) with EtMgBr (4.8 mL, 3.0 M in Et_2O, 14.4 mmol) in Et_2O (32 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1e** (0.6975 g, 4.0 mmol)/Et_2O (10 mL) at –60 °C for 16.5 h, to afford **2g** (1.2186 g, 87%) as a liquid.

***n*-Perfluorohexyl Phenylacetylenyl Ketone (2h):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.53 mL, *d* = 2.063 g/mL, 1.09 g, 2.45 mmol) with EtMgBr (0.53 mL, 3.0 M in Et_2O, 1.59 mmol) in Et_2O (3.0 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1e** (67.9 mg, 0.39 mmol) in Et_2O (1 mL) at –60 °C for 11 h, to afford **2h** (154.8 mg, 89%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.64 (m, 2 H, ArH), 7.61–7.54 (m, 1 H, ArH), 7.50–7.41 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (t, *J* = 30.7 Hz), 134.0, 132.6, 129.0, 118.1, 101.5, 84.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.1 (m, 3 F), –118.4 to –118.7 (m, 2 F), –121.4 to –122.0 (m, 4 F), –122.8 to –123.2 (m, 2 F), –126.2 to –126.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3068, 2957, 2930, 2197, 1701, 1597, 1491, 1446, 1364, 1319, 1240, 1146, 1084, 1037 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 448 (1.53) $[M]^+$, 129 (100). HRMS: calcd. for $C_{15}H_5F_{13}O$ $[M]^+$ 448.0133; found 448.0135.

(4-Methoxyphenyl)acetylenyl *n*-Perfluorobutyl Ketone (2i): According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.42 mL, *d* = 2.01 g/mL, 0.84 g, 2.44 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3 mL) at –70 °C, afforded the Grignard reagent, which was treated with **1f** (77.1 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 18 h, to afford **2i** (126.9 mg, 83%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.60 (m, 2 H, ArH), 6.98–6.92 (m, 2 H, ArH), 3.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (t, *J* = 30.6 Hz), 163.4, 136.4, 114.8, 109.7, 103.5, 85.1, 55.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.1 (m, 3 F), –118.5 to –118.6 (m, 2 F), –122.7 to –123.0 (m, 2 F), –125.7 to –126.0 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3014, 2939, 2847, 2188, 1691, 1601, 1567, 1511, 1466, 1444, 1421, 1355, 1301, 1237, 1172, 1138, 1083, 1030 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 379 (2.09) $[M^+ + 1]$, 378 (13.49) $[M]^+$, 159 (100). HRMS: calcd. for $C_{14}H_7F_9O_2$ $[M]^+$ 378.0302; found 378.0302.

(4-Methoxyphenyl)acetylenyl *n*-Perfluorohexyl Ketone (2j): According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1f** (76.2 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 18 h, to afford **2j** (144.2 mg, 75%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 2 H, ArH), 6.99–6.92 (m, 2 H, ArH), 3.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (t, *J* = 30.4 Hz), 163.4, 136.4, 114.8, 109.8, 103.5, 85.1, 55.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.1 (m, 3 F), –118.2 to –118.6 (m, 2 F), –121.4 to –122.1 (m, 4 F), –122.7 to –123.1 (m, 2 F), –126.1 to –126.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3010, 2961, 2941, 2847, 2186, 1694, 1602, 1568, 1511, 1466, 1445, 1364, 1240, 1145, 1083, 1035 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 479 (2.40) $[M^+ + 1]$, 478 (13.47) $[M]^+$, 159 (100). HRMS: calcd. for $C_{16}H_7F_{13}O_2$ $[M]^+$ 478.0238; found 478.0241.

***n*-Perfluorobutyl [4-(*n*-Propyl)phenyl]acetylenyl Ketone (2k):** According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C afforded the Grignard reagent, which was treated with **1g** (87.0 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 11 h, to afford **2k** (152.2 mg, 97%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.55 (m, 2 H, ArH), 7.29–7.23 (m, 2 H, ArH), 2.65 (t, *J* = 7.7 Hz, 2 H, $ArCH_2$), 1.73–1.59 (m, 2 H, CH_3CH_2), 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (t, *J* = 30.5 Hz), 148.6, 134.1, 129.2, 115.2, 102.6, 84.5, 38.3, 24.1, 13.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.0 to –81.1 (m, 3 F), –118.6 to –118.7 (m, 2 F), –122.7 to –123.0 (m, 2 F), –125.7 to –126.0 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3036, 2966, 2937, 2877, 2195, 1698, 1605, 1508, 1467, 1414, 1382, 1355, 1311, 1237, 1138, 1083, 1021, 1007 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 391 (1.82) $[M^+ + 1]$, 390 (10.43) $[M]^+$, 171 (100). HRMS: calcd. for $C_{16}H_{11}F_9O$ $[M]^+$ 390.0666; found 390.0667.

***n*-Perfluorohexyl [4-(*n*-Propyl)phenyl]acetylenyl Ketone (2l):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.60 mL, *d* = 2.063 g/mL, 1.24 g, 2.78 mmol) with EtMgBr (0.60 mL, 3.0 M in Et_2O, 1.80 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1g** (87.0 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 21.5 h, to afford **2l** (190.1 mg, 96%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.53 (m, 2 H, ArH), 7.31–7.21 (m, 2 H, ArH), 2.65 (t, *J* = 7.7 Hz, 2 H, $ArCH_2$), 1.74–1.59 (m, 2 H, CH_3CH_2), 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (t, *J* = 30.6 Hz), 148.6, 134.1, 129.2, 115.2, 102.6, 84.5, 38.3, 24.1, 13.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.2 (m, 3 F), –118.3 to –118.6 (m, 2 F), –121.5 to –122.0 (m, 4 F), –122.8 to –123.0 (m, 2 F), –126.1 to –126.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3036, 2966, 2937, 2877, 2192, 1698, 1605, 1508, 1467, 1414, 1364, 1319, 1240, 1146, 1083, 1035, 1021 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 490 (4.21) $[M]^+$, 171 (100). HRMS: calcd. for $C_{18}H_{11}F_{13}O$ $[M]^+$ 490.0602; found 490.0603.

(4-Fluorophenyl)acetylenyl *n*-Perfluorobutyl Ketone (2m): According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C afforded the Grignard reagent, which was treated with **1h** (72.0 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 17 h, to afford **2m** (117.4 mg, 79%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.65 (m, 2 H, ArH), 7.22–7.10 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (t, *J* = 30.9 Hz), 165.2 (d, *J* = 255.7 Hz), 136.5 (d, *J* = 8.4 Hz), 116.7 (d, *J* = 22.1 Hz), 114.3 (d, *J* = 3.5 Hz), 100.3, 84.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.2 (m, 3 F), –102.3 to –102.5 (m, 1 F), –118.6 to –118.8 (m, 2 F), –122.7 to –123.0 (m, 2 F), –125.7 to –126.0 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ =

2201, 1699, 1600, 1509, 1408, 1355, 1311, 1240, 1158, 1138, 1083, 1008 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 366 (1.46) [M]$^+$, 147 (100). HRMS: calcd. for $C_{13}H_4F_{10}O$ [M]$^+$ 366.0102; found 366.0103.

(4-Fluorophenyl)acetylenyl *n*-Perfluorohexyl Ketone (2n): According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1h** (73.0 mg, 0.41 mmol) in Et_2O (1.5 mL) at –60 °C for 17 h, to afford **2n** (144.2 mg, 75%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 2 H, ArH), 7.21–7.11 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (t, *J* = 30.6 Hz), 165.2 (d, *J* = 255.6 Hz), 136.5 (d, *J* = 10.3 Hz), 116.7 (d, *J* = 22.4 Hz), 114.3 (d, *J* = 3.5 Hz), 100.3, 84.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.1 (m, 3 F), –102.3 to –102.5 (m, 1 F), –118.4 to –118.6 (m, 2 F), –121.4 to –122.0 (m, 4 F), –122.7 to –123.4 (m, 2 F), –126.1 to –126.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2198, 1703, 1601, 1509, 1240, 1158, 1146, 1083, 1034 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 466 (2.24) [M]$^+$, 147 (100). HRMS: calcd. for $C_{15}H_4F_{14}O$ [M]$^+$ 466.0039; found 466.0040.

***n*-Perfluorobutyl 3-Thienylacetylenyl Ketone (2o):** According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C afforded the Grignard reagent, which was treated with **1i** (70.7 mg, 0.39 mmol) in Et_2O (1 mL) at –60 °C for 12 h, to afford **2o** (121.0 mg, 87%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.96 (m, 1 H, =CH), 7.43–7.39 (m, 1 H, =CH), 7.33–7.29 (m, 1 H, =CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (t, *J* = 30.9 Hz), 137.5, 130.4, 126.9, 117.6, 96.9, 84.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.1 (m, 3 F), –118.5 to –118.7 (m, 2 F), –122.7 to –122.9 (m, 2 F), –125.7 to –125.9 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3116, 2191, 1698, 1512, 1356, 1237, 1199, 1138, 1089, 1077, 1011 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 354 (12.92) [M]$^+$, 135 (100). HRMS: calcd. for $C_{11}H_3F_9OS$ [M]$^+$ 353.9761; found 353.9761.

***n*-Perfluorohexyl 3-Thienylacetylenyl Ketone (2p):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1i** (71.7 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 21.5 h, to afford **2p** (169.9 mg, 94%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.96 (m, 1 H, =CH), 7.43–7.39 (m, 1 H, =CH), 7.33–7.29 (m, 1 H, =CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (t, *J* = 31.2 Hz), 137.4, 130.4, 126.9, 117.6, 96.8, 84.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.9 to –81.1 (m, 3 F), –118.4 to –118.6 (m, 2 F), –121.5 to –122.0 (m, 4 F), –122.8 to –123.1 (m, 2 F), –126.2 to –126.5 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3117, 2193, 1698, 1513, 1363, 1318, 1240, 1145, 1089, 1078, 1038, 1020 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 454 (7.01) [M]$^+$, 135 (100). HRMS: calcd. for $C_{13}H_3F_{13}OS$ [M]$^+$ 453.9697; found 453.9699.

***n*-Heptyl *n*-Perfluorobutyl Ketone (2q):** According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C afforded the Grignard reagent, which was treated with **1j** (68.4 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 16.5 h, to afford **2q** (119.6 mg, 87%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 7.2 Hz, 2 H, $COCH_2$), 1.74–1.60 (m, 2 H, CH_2), 1.41–1.20 [m, 8 H, $(CH_2)_4$], 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1 (t, *J* = 25.9 Hz), 37.9, 31.6, 28.9, 28.7, 22.6, 22.4, 14.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.0 to –81.2 (m, 3 F), –120.6 to –120.8 (m, 2 F), –123.3 to –123.6 (m, 2 F), –125.8 to –126.1 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2960, 2932, 2861, 1759, 1467, 1405, 1354, 1237, 1137, 1073 cm^{-1}. MS (ESI): *m*/*z* = 345 [M – H]$^-$. HRMS (ESI): calcd. for $C_{12}H_{14}F_9O^-$ [M – H]$^-$ 345.0906; found 345.0892.

***n*-Heptyl *n*-Perfluorohexyl Ketone (2r):** According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.53 mL, *d* = 2.063 g/mL, 1.09 g, 2.45 mmol) with EtMgBr (0.53 mL, 3.0 M in Et_2O, 1.59 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1j** (69.8 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 15.5 h, to afford **2r** (148.6 mg, 82%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (t, *J* = 7.2 Hz, 2 H, $COCH_2$), 1.73–1.60 (m, 2 H, CH_2), 1.38–1.20 [m, 8 H, $(CH_2)_4$], 0.93–0.82 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1 (t, *J* = 25.8 Hz), 37.9, 31.6, 28.9, 28.7, 22.6, 22.5, 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.0 (m, 3 F), –120.3 to –120.6 (m, 2 F), –121.5 to –121.8 (m, 2 F), –122.2 to –122.5 (m, 2 F), –122.7 to –123.1 (m, 2 F), –126.1 to –126.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2967, 2931, 2865, 1759, 1241, 1206, 1146, 1017 cm^{-1}. MS (ESI): *m*/*z* = 445 [M – H]$^-$. HRMS (ESI): calcd. for $C_{14}H_{14}F_{13}O^-$ [M – H]$^-$ 445.0843; found 445.0823.

***n*-Perfluorobutyl Phenyl Ketone (2s):**[4] According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, *d* = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.25 mL) at –70 °C afforded the Grignard reagent, which was treated with **1k** (61.6 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 14.5 h, to afford **2s** (81.5 mg, 61%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.5 Hz, 2 H, ArH), 7.77–7.67 (m, 1 H, ArH), 7.60–7.50 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2 (t, *J* = 25.8 Hz), 135.4, 131.5 (t, *J* = 2.1 Hz), 130.2 (t, *J* = 3.2 Hz), 129.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.1 (m, 3 F), –112.8 to –113.1 (m, 2 F), –121.8 to –122.1 (m, 2 F), –125.2 to –125.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 1712, 1599, 1451, 1356, 1304, 1237, 1137, 1025 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 324 (0.04) [M]$^+$, 305 (2.59) [M$^+$ – F], 277 (6.48) [M$^+$ – F – CO], 105 (100). HRMS: calcd. for $C_{11}H_5F_9O$ [M]$^+$ 324.0197; found 324.0187.

***n*-Perfluorohexyl Phenyl Ketone (2t):**[5] According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.11 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3.0 mL) at –70 °C afforded the Grignard reagent, which was treated with **1k** (59.1 mg, 0.39 mmol) in Et_2O (1 mL) at –60 °C for 16 h, to afford **2t** (144.5 mg, 86%) as a liquid together with recovery of **1k** (3.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.04 (m, 2 H, ArH), 7.76–7.67 (m, 1 H, ArH), 7.60–7.50 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.3 (t, *J* = 25.6 Hz), 135.4, 131.6 (t, *J* = 2.0 Hz), 130.2 (t, *J* = 3.6 Hz), 129.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.0 (m, 3 F), –112.7 to –112.9 (m, 2 F), –120.9 to –121.4 (m, 4 F), –122.7 to –123.1 (m, 2 F), –126.1 to –126.3 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 1713, 1600, 1452, 1365, 1312, 1240, 1205, 1144, 1126 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 424 (0.02) [M]$^+$, 405 (6.10) [M$^+$ – F], 377 (3.37) [M$^+$ – F – CO], 105 (100). HRMS: calcd. for $C_{13}H_5F_{13}O$ [M]$^+$ 424.0133; found 424.0151.

Cyclohexyl *n*-Perfluorohexyl Ketone (2u): According to Typical Procedure I, the reaction of *n*-$C_6F_{13}I$ (0.54 mL, *d* = 2.063 g/mL, 1.10 g, 2.50 mmol) with EtMgBr (0.54 mL, 3.0 M in Et_2O, 1.62 mmol) in Et_2O (3 mL) at –70 °C afforded the Grignard reagent, which was treated with **1l** (62.7 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 24 h, to afford **2u** (132.5 mg, 77%) as a liquid after purification by column chromatography (*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97–2.83 (m, 1 H, COCH), 1.96–1.78 (m, 4 H, CH_2CH_2), 1.77–1.67 (m, 1 H, CH), 1.53–1.17 (m, 5 H, C_2H_4CH) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 197.4 (t, J = 25.0 Hz), 46.1, 28.2, 25.4, 25.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.8 to –81.0 (m, 3 F), –119.6 to –119.9 (m, 2 F), –121.4 to –121.8 (m, 2 F), –121.9 to –122.2 (m, 2 F), –122.7 to –123.1 (m, 2 F), –126.0 to –126.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2941, 2864, 1751, 1453, 1364, 1316, 1241, 1207, 1146, 1075 cm^{-1}. MS (EI, 70 eV): m/z (%) = 430 (0.07) $[M]^+$, 411 (2.37) $[M^+ – F]$, 131 (7.95) $[C_3F_5^+]$, 111 (30.08) $[M^+ – C_6F_{13}]$, 83 (100). HRMS: calcd. for $C_{13}H_{11}F_{13}O$ $[M]^+$ 430.0602; found 430.0581.

Cumyl *n*-Perfluorobutyl Ketone (2v): According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, d = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.2 mL) at –70 °C afforded the Grignard reagent, which was treated with **1m** (76.5 mg, 0.40 mmol) in Et_2O (1 mL) at –60 °C for 13 h to afford **2v** (125.9 mg, 86%) as a liquid after purification by column chromatography (*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 2 H, ArH), 7.33–7.26 (m, 1 H, ArH), 7.26–7.20 (m, 2 H, ArH), 1.61 (s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.6 (app. tt, J = 24.1 Hz), 139.8, 129.0, 127.7, 125.8, 51.8 (t, J = 1.8 Hz), 24.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.0 to –81.3 (m, 3 F), –111.3 to –111.6 (m, 2 F), –121.5 to –122.0 (m, 2 F), –125.7 to –126.1 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 3065, 3030, 2985, 2938, 1739, 1497, 1475, 1449, 1355, 1295, 1238, 1215, 1136, 1090, 1076 cm^{-1}. MS (EI, 70 eV): m/z (%) = 366 (0.05) $[M]^+$, 347 (0.45) $[M^+ – F]$, 277 (1.10) $[M^+ – CF_3 – HF]$, 219 (1.26) $[C_4F_9^+]$, 119 (100). HRMS: calcd. for $C_{14}H_{11}F_9O$ $[M]^+$ 366.0666; found 366.0653.

Adamantyl *n*-Perfluorobutyl Ketone (2w): According to Typical Procedure I, the reaction of *n*-C_4F_9I (0.36 mL, d = 2.01 g/mL, 0.72 g, 2.09 mmol) with EtMgBr (0.48 mL, 3.0 M in Et_2O, 1.44 mmol) in Et_2O (3.2 mL) at –70 °C afforded the Grignard reagent, which was treated with **1n** (84.9 mg, 0.41 mmol) in Et_2O (1 mL) at –60 °C for 24 h to afford **2w** (128.0 mg, 82%) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.14–2.05 (m, 3 H, CH_2CH), 1.99 (d, J = 3 Hz, 6 H, 3 × CCH_2), 1.84–1.68 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1 (app. tt, J = 23.9 Hz), 47.5 (t, J = 2.2 Hz), 36.8 (t, J = 1.9 Hz), 36.2, 27.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 to –81.3 (m, 3 F), –113.4 to –113.7 (m, 2 F), –121.6 to –121.9 (m, 2 F), –125.0 to –125.3 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2913, 2859, 2683, 2663, 1731, 1455, 1353, 1321, 1236, 1134, 1060, 1036 cm^{-1}. MS (EI, 70 eV): m/z (%) = 382 (0.04) $[M]^+$, 363 (0.78) $[M^+ – F]$, 219 (0.05) $[C_4F_9^+]$, 163 (1.44) $[M^+ – C_4F_9]$, 135 (100). HRMS: calcd. for $C_{15}H_{15}F_9O$ $[M]^+$ 382.0979; found 382.0963.

***tert*-Butyl *n*-Perfluorobutyl Ketone (2x):** According to Typical Procedure II, the reaction of *n*-C_4F_9I (18.1 mL, d = 2.01 g/mL, 36.4 g, 105 mmol) with EtMgBr (23.4 mL, 3.0 M in Et_2O, 70.2 mmol) in Et_2O (140 mL) at –70 °C afforded the Grignard reagent, which was treated with **1o** (2.6012 g, 20 mmol) in Et_2O (10 mL) at –60 °C for 24 h to afford **2x** (3.3239 g, 55%) as a liquid after distillation (b.p. 107–109 °C/760 Torr). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 1.1 Hz, 9 H, 3 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0 (app. tt, J = 24.5 Hz), 44.6 (t, J = 2.4 Hz), 25.6 (t, J = 2.0 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.0 to –81.2 (m, 3 F), –112.8 to –113.2 (m, 2 F), –121.7 to –122.0 (m, 2 F), –125.1 to –125.4 (m, 2 F) ppm. IR (neat): $\tilde{\nu}$ = 2981, 2926, 2886, 2858, 1739, 1484, 1468, 1372, 1355, 1240, 1138, 1090, 1067 cm^{-1}. MS (EI, 70 eV): m/z (%) = 289 (2.18) $[M^+ – CH_3]$, 219 (1.96) $[C_4F_9^+]$, 131 (4.75) $[C_3F_5^+]$, 119 (4.47) $[C_2F_5^+]$, 100 (5.03) $[C_2F_4^+]$, 84(100). HRMS: calcd. for $C_9H_9F_9O$ $[M]^+$ 304.0510; found 304.0513.

Computational Details: Molecular geometries were optimized at the Becke3LYP (B3LYP) level of density functional theory. Frequency calculations at the same level of theory were also performed to identify all stationary points as minima (zero imaginary frequency). The 6-31G* basis set was used for C, O, F, and H atoms. All the calculations were performed with the Gaussian 03 software package.[15] The natural bond orbital (NBO) program,[16] as implemented in Gaussian 03, was also used to obtain the natural population of atoms.

Supporting Information (see footnote on the first page of this article): Copies of ^1H, ^{13}C, and ^{19}F NMR spectra of all compounds.

Acknowledgments

Financial support from the National Natural Science Foundation of China (No. 20732005, 20972135) and the Zhejiang Provincial Natural Science Foundation of China (No. Y4090217) is greatly appreciated. We thank Binjie Guo for reproducing the results presented in Table 2 (Entry 2), Table 3 (Entry 6), and Table 4 (Entry 3]. S. M. is a Qiu Shi Adjunct Professor at Zhejiang University.

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Received: June 21, 2010
Published Online: November 9, 2010

