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A novel synthetic approach to fluorine-containing acetylenic compounds based on Nicholas reaction

Tsutomu Konno *, Go Nagai, Takashi Ishihara

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

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Abstract

The fluorine-containing dicobalthexacarbonyl complex, prepared readily from γ-fluoroalkylated propargyl acetates and $Co_2(CO)_8$, reacted smoothly with various nucleophiles at the propargylic position, followed by oxidative decomplexation under the influence of $Fe(NO_3)_3$, to afford fluoroalkylated alkynes bearing various types of alkyl side chains in good to high yields.

Keywords: Fluorine-containing alkynes; Propargyl acetates; Dicobaltoctacarbonyl; Nicholas reaction

1. Introduction

Fluorine-containing compounds are of current interest in the research areas of polymer, pharmaceutical, and agricultural chemistry due to the unique properties of fluorine atom(s), such as the highest electronegativity, the relatively close size to a hydrogen atom, the increase in oxidative, hydrolytic, and thermal stability [1]. Consequently, much effort has been devoted to developing novel synthetic methods for various types of fluorinated substances [2].

Out of such compounds, fluoroalkylated acetylenic compounds **1** (Fig. 1) are recognized as one of the most valuable synthetic intermediates in fluorine chemistry, as described in the precedent studies on their synthetic applications, such as the regio- and stereo-selective synthesis of various types of fluoroalkylated alkenes via the hydrometallation and carbometallation reactions of **1** [3], the one-pot synthesis of fluoroalkylated heterocyclic compounds (indoles, benzofurans, and isoquinolines) via the carbopalladation reactions of **1** [4], and so on [5].

The fluoroalkylated acetylenic compounds **1A** or **1B** having an aromatic or alkenyl side chain as R in **1** can easily be prepared via the palladium-catalyzed coupling reaction of the corresponding fluoroalkylated metal acetylides with various aryl or alkenyl halides (Fig. 2) [6]. Additionally, γ-fluoroalkylated propargylic alcohols **1C** can also be synthesized by the nucleophilic addition reaction of fluoroalkylated metal acetylides with various carbonyl compounds [7]. In sharp contrast, there have been quite limited studies on the preparation of the fluorine-containing alkynes **1D** having an aliphatic side chain as R. The only reported synthetic method for **1D** is that via β-elimination of vinyl halides **2** which can be prepared by the radical addition reaction of RfI into the corresponding terminal alkynes [6a,8]. However, this method sometimes suffers from HF-elimination from **2** followed by further reactions of the resultant fluorinated compounds, leading to the formation of the desired acetylenes **1D** in very low yields.

In this article, we wish to disclose a new, efficient access to such types of acetylenic compounds **1D** through the cobalt-mediated nucleophilic substitution reaction of γ-fluoroalkylated propargylic alcohol derivatives with hydride (n-Bu_3SnH) or various carbon nucleophiles, such as silyl enol ethers, enamine, and so on.

2. Results and discussion

Generally, acetylenic compounds readily react with dicobaltoctacarbonyl ($Co_2(CO)_8$) to form the corresponding alkyne-dicobalthexacarbonyl ($Co_2(CO)_6$) complexes quantitatively, in

* Corresponding author.
E-mail address: konno@chem.kit.ac.jp (T. Konno).

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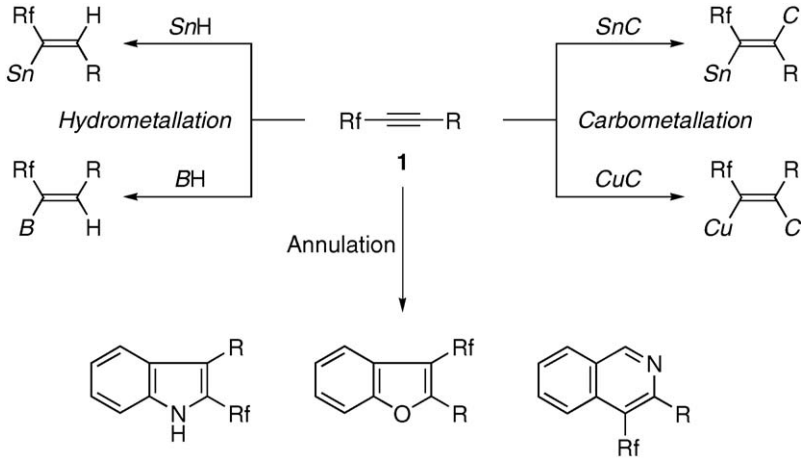


Fig. 1. Fluoroalkylated acetylenic compounds and their synthetic applications.

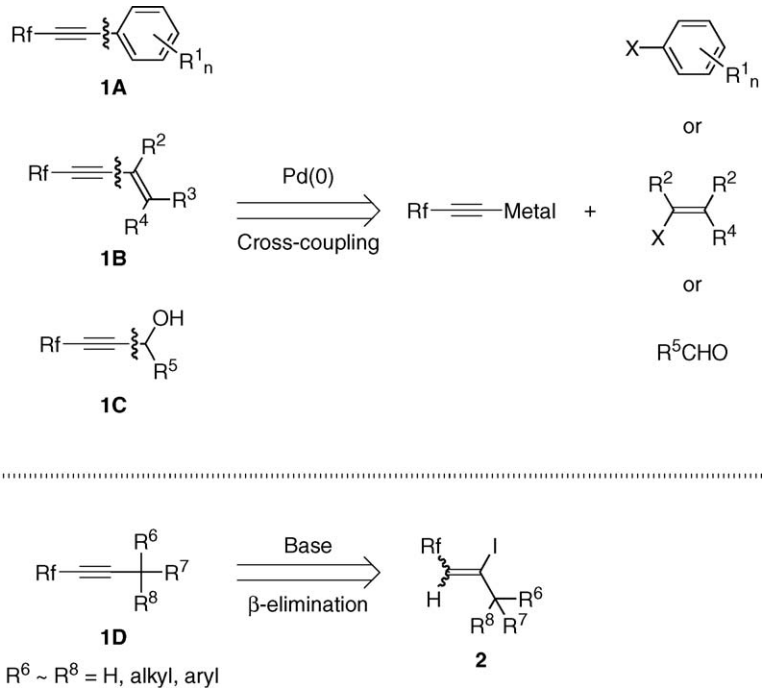


Fig. 2. Various acetylenic compounds and their synthetic methods.

which a $Co_2(CO)_6$ group effectively stabilizes a propargyl cation (Fig. 3). These cobalt complexes can react with a wide variety of nucleophiles, followed by oxidative demetallation, to yield the corresponding internal alkynes [9]. This reaction sequence, commonly referred to as the Nicholas reaction, has recently been used for the synthesis of intricate biologically active compounds [10].

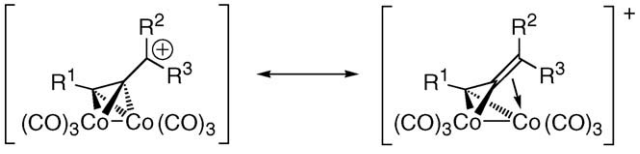
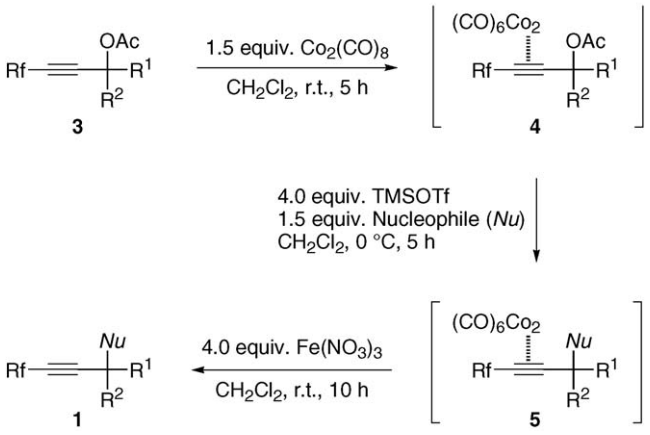
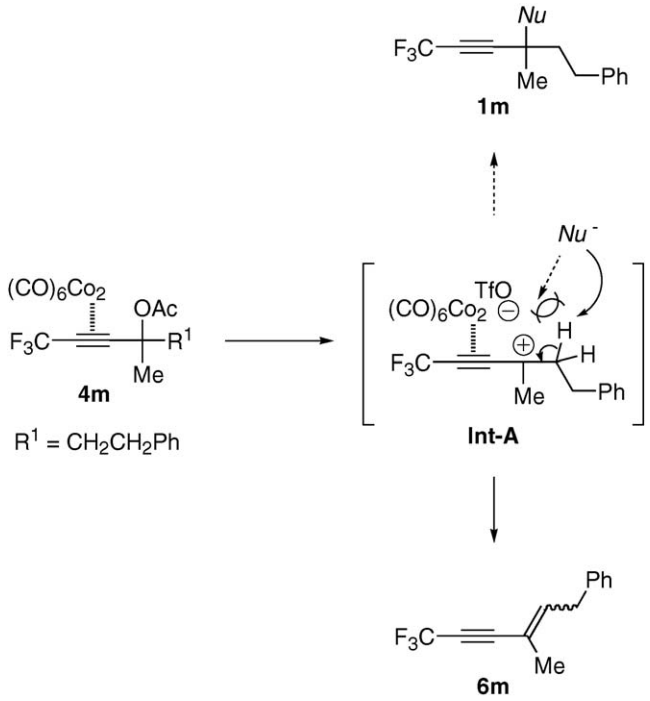


Fig. 3. Stabilization of the propargylic cation.

Then, the Nicholas reaction of trifluoromethylated propargylic alcohol derivatives **3a** (Rf = CF_3, R^1 = *p*-$MeOC_6H_4$, R^2 = H) with *n*-Bu_3SnH was chosen for our initial investigation for the synthesis of the fluorine-containing acetylenic compounds **1** having an alkyl side chain (Scheme 1). Thus, the treatment of **3a** with 1.5 equiv. of $Co_2(CO)_8$ in CH_2Cl_2 at room temperature for 5 h gave the corresponding cobalt complex **4a** quantitatively, as a dark-purple liquid. Subsequently, **4a** was subjected to the Nicholas reaction conditions, such as 4.0 equiv. of TMSOTf and 1.5 equiv. of *n*-Bu_3SnH in CH_2Cl_2 at 0 °C for 5 h, to afford the corresponding substitution product **5a**. After flash column chromatography, **5a** was allowed to decomplex under the influence of $Fe(NO_3)_3$ in CH_2Cl_2 at room temperature for 10 h, the corresponding



Scheme 1. The Nicholas reaction.



Scheme 2. The reaction mechanism.

fluoroalkylated internal alkyne **1a** having an alkyl side chain being obtained in 89% overall yield. These reaction conditions were next applied for various types of fluoroalkylated propargylic alcohol derivatives **3b–m**, as shown in Table 1.

As shown in entries 1–3, a *p*-$MeOC_6H_4$ substituent was found to be very effective, the desired reduction products **1a–c** being provided in excellent yields without any influence of a fluoroalkyl group. However, the position of a MeO group on the aromatic ring significantly affected the efficiency of the reaction and, **1d** and **1e** were given in only 52% and 51% yields, respectively, (entries 4 and 5). The use of the alkynes having an aromatic ring substituted by a Me or Cl group at the *para* position resulted in a slight increase of the yield, compared with those of **1d** and **1e** (entries 6 and 7). The substrate **3i** bearing a 2-furyl group did not give any desired compound at all, the cobalt complex **4i** being obtained in almost quantitative yield (entry 9). Additionally, the reactions of **3j–l** carrying a 2-thienyl or alkyl group as R^2 proceeded somewhat sluggishly to afford the corresponding products in moderate yields (entries 10–12). Interestingly, the substrate **3m** having two alkyl groups as R^1 and R^2 led to the enyne product **6m** in 44% yield, and any substitution product **1m** could not be detected at all (entry 13). This may be explained by preferential β-elimination on **Int-A** rather than nucleophilic attack to the sterically hindered tertiary carbon (Scheme 2).

Table 1
The Nicholas reaction of propargylic alcohol derivatives **3** using *n*-Bu_3SnH as a nucleophile (Nu = H)

Entry	Rf	R^1	R^2	Yield[a]/% of **1**
1	CF_3	H	*p*-$MeOC_6H_4$ (**a**)	89
2	CHF_2	H	*p*-$MeOC_6H_4$ (**b**)	97
3	$HCF_2CF_2CF_2$	H	*p*-$MeOC_6H_4$ (**c**)	99
4	CF_3	H	*m*-$MeOC_6H_4$ (**d**)	52
5	CF_3	H	*o*-$MeOC_6H_4$ (**e**)	51
6	CF_3	H	*p*-MeC_6H_4 (**f**)	64
7	CF_3	H	*p*-ClC_6H_4 (**g**)	63
8	CF_3	H	1-Naphthyl (**h**)	78
9	CF_3	H	2-Furyl (**i**)	0
10	CF_3	H	2-Thienyl (**j**)	47
11	CF_3	H	$PhCH_2CH_2$ (**k**)	41
12	CF_3	H	$PhCH(CH_3)$ (**l**)	54
13	CF_3	Me	$PhCH_2CH_2$ (**m**)	44[b]

[a] Isolated yields.
[b] The isomerization product **6m** was obtained in 44% yield.

We next investigated the Nicholas reaction of **3a** with various types of carbon nucleophiles, as summarized in Table 2. As shown in entries 1–3, methallylstannane, allylstannane, and allylsilane were found to be less nucleophilic, so that the coupling products **1aA**, **1aB** were given in moderate yields (49–63%). Particularly, the reaction of **3a** with methallylstannane gave an isomeric mixture of $\mathbf{1aA_1}$ and $\mathbf{1aA_2}$ in a ratio of 3:1. In contrast, more nucleophilic silyl enol ethers derived from ketones, such as acetophenone, pinacolone, and cyclohexanone, underwent the smooth Nicholas reaction, **1aC–1aE** being afforded in excellent yields (entries 4, 6, and 7). Enamine and silyl ketene acetal could also participate very well in the present reaction, leading to high yields of the coupling products **1aC** and **1aF** (entries 5 and 8). It should be noted that a fluoroalkyl group in the substrate **3** did not affect the Nicholas reaction at all. The reactions of **3b** (Rf = CHF_2) and **3c** (Rf = $HCF_2CF_2CF_2$) with silyl enol ether took place efficiently to give rise to the corresponding coupling products **1bC** and **1cC** in 96% and 87% yields, respectively, (entries 9 and 10).

3. Conclusion

In summary, we have developed a novel method for the preparation of various types of fluorine-containing alkynes bearing an alkyl side chain via the Nicholas reaction. Various fluorine-containing propargyl acetates underwent the smooth

Table 2
The Nicholas reaction with various carbon nucleophiles

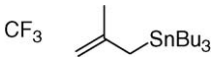
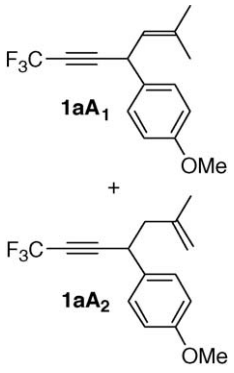
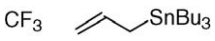
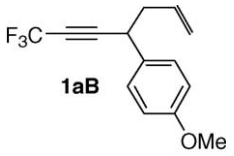
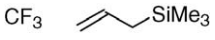
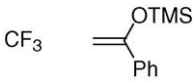
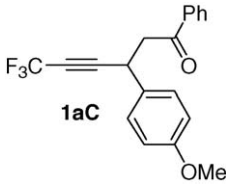
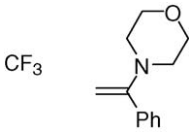
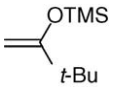
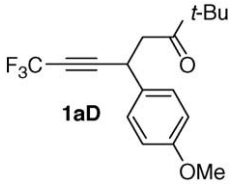
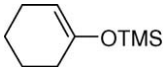
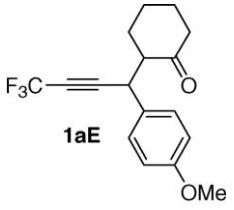
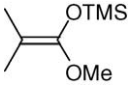
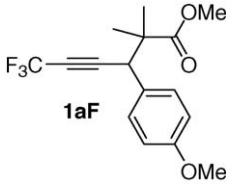
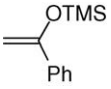
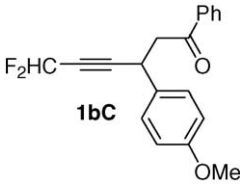
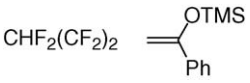
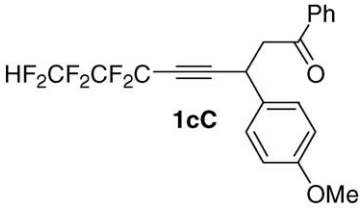
Entry	Rf	Nucleophile	Product	Yield[a]/% of **1**
1	CF_3			49 (**1aA$_1$**:**1aA$_2$** = 3:1)
2	CF_3			63
3	CF_3			59
4	CF_3			88
5	CF_3			89
6	CF_3			99
7	CF_3			88[b]
8	CF_3			96

Table 2 (*Continued*)

Entry	Rf	Nucleophile	Product	Yield[a]/% of **1**
9	CHF_2		 **1bC**	96
10	$CHF_2(CF_2)_2$		 **1cC**	87

[a] Isolated yields.
[b] 1:1 Diastereomer mixture.

Nicholas reaction with *n*-Bu_3SnH, leading to the reduction products. Additionally, various carbon nucleophiles, such as allylstannane, allylsilane, silyl enol ethers, silyl ketene acetals, enamine, and so on, could participate nicely in the Nicholas reaction, the desired alkynes being obtained in good to excellent yields.

4. Experimental

4.1. General methods

^1H NMR spectra were measured with a Bruker DRX (500.13 MHz) spectrometer in a chloroform-*d* ($CDCl_3$) solution with Me_4Si as an internal reference. ^{13}C NMR spectra were recorded on a Bruker DRX (125.77 MHz) spectrometer. A JEOL JNM-EX90 (84.21 MHz, FT) spectrometer was used for determining NMR yields by the use of internal C_6F_6. ^{19}F NMR spectra were determined with a JEOL JNM-EX90 spectrometer in a $CDCl_3$ solution with internal $CFCl_3$. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-700 instrument.

Dicobaltoctacarbonyl was purchased from Kanto Chemical Co. Inc., CH_2Cl_2 was freshly distilled from calcium hydride. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin layer chromatography was done with Merck silica gel 60 F_{254} plates and column chromatography was carried out with Wako gel C-200. All propargyl alcohols were prepared according to the literature procedure [7].

4.2. General procedure for the synthesis of fluoroalkylated propargyl acetate **3**

To a solution of the corresponding propargyl alcohol (10 mmol) in CH_2Cl_2 (15 mL) was added Ac_2O (1.2 mL, 12 mmol) and pyridine (1.0 mL, 12 mmol) at 0 °C and the mixture was allowed to warm to room temperature, and then stirred for 12 h. The reaction was quenched with NH_4Cl aqueous solution and the resulting mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel to afford the corresponding acetate **3** (35–95% yield).

4.2.1. 4,4,4-Trifluoro-1-(4-methoxyphenyl)-2-butynyl acetate (**3a**)

Yield 79%; ^1H NMR δ (ppm) 2.11 (3H, s), 3.82 (3H, s), 6.47 (1H, q, J = 2.88 Hz), 6.92–6.94 (2H, m), 7.40–7.43 (2H, m); ^{13}C NMR δ (ppm) 20.8, 55.3, 63.9, 73.3 (q, J = 53.2 Hz), 83.3 (q, J = 6.5 Hz), 113.9 (q, J = 257.8 Hz), 114.3, 126.7, 129.4, 160.6, 169.3; ^{19}F NMR δ (ppm) −54.7 (3F, s); IR (neat) 2914, 2841, 2272, 1749, 1612, 1516 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{13}H_{11}F_3O_3$ 272.0660, found 272.0660.

4.2.2. 4,4-Difluoro-1-(4-methoxyphenyl)-2-butynyl acetate (**3b**)

Yield 45%; ^1H NMR δ (ppm) 2.69 (3H, s), 3.80 (3H, s), 6.24 (1H, dt, J = 1.00, 54.42 Hz), 6.46 (1H, t, J = 4.27 Hz), 6.90–7.44 (4H, m); ^{13}C NMR δ (ppm) 20.8, 55.3, 64.3, 77.5 (t, J = 34.6 Hz), 85.5 (t, J = 7.2 Hz), 103.5 (t, J = 233.2 Hz), 114.2, 127.4, 129.3, 160.4, 169.4; ^{19}F NMR δ (ppm) −107.3 (2F, d, J = 56.5 Hz); IR (neat) 2939, 2841, 2312, 2257, 1747, 1612 cm^{-1}; HRMS (FAB) calcd. for (M^+ matrix-m-NBA) $C_{13}H_{12}F_2O_3$ 254.0755, found 254.0762.

4.2.3. 4,4,5,5,6,6-Hexafluoro-1-(4-methoxyphenyl)-2-hexynyl acetate (**3c**)

Yield 54%; ^1H NMR δ (ppm) 2.10 (3H, s), 3.82 (3H, s), 6.02 (1H, tt, J = 5.35, 52.10 Hz), 6.47 (1H, t, J = 4.25 Hz), 6.93 (2H, d, J = 8.72 Hz), 7.42 (2H, d, J = 8.71 Hz); ^{13}C NMR δ (ppm)

20.7, 55.3, 64.2, 72.8 (t, J = 36.9 Hz), 89.3 (t, J = 6.4 Hz), 107.7 (tt, J = 31.4, 253.3 Hz), 104.9–110.8 (m), 114.3, 126.6, 129.4, 160.7, 169.4; ^{19}F NMR δ (ppm) −137.1 (2F, dquint., J = 8.5, 50.8 Hz), −130.9 (2F, m), −100.9 (2F, m); IR (neat) 2941, 2843, 2266, 1749, 1715 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{15}H_{12}F_6O_3$ 354.0691, found 354.0691.

*4.2.4. 4,4,4-Trifluoro-1-(3-methoxyphenyl)-2-butynyl acetate (**3d**)*

Yield 72%; ^{1}H NMR δ (ppm) 2.14 (3H, s), 3.83 (3H, s), 6.49 (1H, q, J = 2.82 Hz), 6.94–7.07 (3H, m), 7.34 (1H, t, J = 7.90 Hz); ^{13}C NMR δ (ppm) 20.7, 55.3, 64.0, 73.5 (q, J = 53.6 Hz), 83.5 (q, J = 6.4 Hz), 113.3, 113.8 (q, J = 258.3 Hz), 115.1, 119.8, 130.1, 135.9, 159.94, 169.2; ^{19}F NMR δ (ppm) −53.0 (3F, s); IR (neat) 2943, 2841, 2272, 1755, 1605, 1493, 1458 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{13}H_{11}F_3O_3$ 272.0660, found 272.0669.

*4.2.5. 4,4,4-Trifluoro-1-(2-methoxyphenyl)-2-butynyl acetate (**3e**)*

Yield 77%; ^{1}H NMR δ (ppm) 2.12 (3H, s), 3.85 (3H, s), 6.86 (1H, q, J = 2.92 Hz), 6.92 (1H, q, J = 8.15 Hz), 7.02 (1H, dt, J = 0.79, 7.56 Hz), 7.38 (1H, dt, J = 1.66, 7.88 Hz), 7.54 (1H, dd, J = 1.58, 7.61 Hz); ^{13}C NMR δ (ppm) 20.7, 55.6, 59.2, 72.5 (q, J = 53.0 Hz), 84.0 (q, J = 6.5 Hz), 111.00, 113.9 (q, J = 258.0 Hz), 120.8, 122.7, 128.6, 131.0, 156.6, 169.2; ^{19}F NMR δ (ppm) −53.8 (3F, s); IR (neat) 2945, 2843, 2270, 1755, 1716, 1605 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{13}H_{11}F_3O_3$ 272.0660, found 272.0666.

*4.2.6. 4,4,4-Trifluoro-1-(4-methylphenyl)-2-butynyl acetate (**3f**)*

Yield 82%; ^{1}H NMR δ (ppm) 2.13 (3H, s), 2.39 (3H, s), 6.51 (1H, br q, J = 2.65 Hz), 7.24 (2H, d, J = 7.84 Hz), 7.40 (2H, d, J = 7.87 Hz); ^{13}C NMR δ (ppm) 20.7, 21.2, 64.1, 73.3 (q, J = 53.2 Hz), 83.8 (q, J = 6.5 Hz), 113.9 (q, J = 257.8 Hz), 127.7, 129.6, 131.6, 139.8, 169.2; ^{19}F NMR δ (ppm) −51.2 (3F, s); IR (neat) 2930, 2870, 2270, 1751, 1616, 1516 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{13}H_{11}F_3O_2$ 256.0711, found 256.0706.

*4.2.7. 1-(4-Chlorophenyl)-4,4,4-trifluoro-2-butynyl acetate (**3g**)*

Yield 63%; ^{1}H NMR δ (ppm) 2.14 (3H, s), 6.48 (1H, q, J = 2.83 Hz), 7.39–7.44 (4H, m); ^{13}C NMR δ (ppm) 20.7, 63.5, 73.8 (q, J = 53.3 Hz), 83.0 (q, J = 6.5 Hz), 113.8 (q, J = 258.4 Hz), 129.1, 129.3, 133.1, 135.8, 169.1; ^{19}F NMR δ (ppm) −52.6 (3F, s); IR (neat) 2939, 2272, 1751, 1599, 1491 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_{12}H_8{}^{35}ClF_3$ 276.0165, found 276.0167.

*4.2.8. 4,4,4-Trifluoro-1-(1-naphthyl)-2-butynyl acetate (**3h**)*

Yield 49%; mp 72–74 °C; ^{1}H NMR δ (ppm) 2.17 (3H, s), 7.21 (1H, q, J = 2.90 Hz), 7.51–8.15 (7H, m); ^{13}C NMR δ (ppm) 20.6, 62.6, 74.0 (q, J = 53.2 Hz), 83.6 (q, J = 6.4 Hz), 113.9 (q, J = 257.9 Hz), 123.0, 125.1, 126.3, 126.9, 127.1, 129.0, 129.8, 130.2, 130.8, 134.0, 169.3; ^{19}F NMR δ (ppm) −51.2 (3F, s); IR (KBr) 3070, 2962, 2272, 1744, 1601 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{16}H_{11}F_3O_2$ 292.0711, found 292.0701.

*4.2.9. 4,4,4-Trifluoro-1-(2-furyl)-2-butynyl acetate (**3i**)*

Yield 95%; ^{1}H NMR δ (ppm) 2.12 (3H, s), 6.40 (1H, dd, J = 1.44, 3.31 Hz), 6.56 (1H, d, J = 3.33 Hz), 6.58 (1H, q, J = 2.84 Hz), 7.46 (1H, d, J = 1.28 Hz); ^{13}C NMR δ (ppm) 20.4, 57.2, 72.8 (q, J = 53.4 Hz), 81.1 (q, J = 7.3 Hz), 110.8, 111.2, 113.7 (q, J = 258.3 Hz), 144.3, 146.7, 169.1; ^{19}F NMR δ (ppm) −51.5 (3F, s); IR (neat) 2277, 1760, 1500, 1373, 1279 cm^{-1}.

*4.2.10. 4,4,4-Trifluoro-1-(2-thienyl)-2-butynyl acetate (**3j**)*

Yield 35%; ^{1}H NMR δ (ppm) 2.12 (3H, s), 6.77 (1H, q, J = 2.78 Hz), 7.01–7.03 (1H, m), 7.26–7.27 (1H, m), 7.39 (1H, dd, J = 1.15, 5.11 Hz); ^{13}C NMR δ (ppm) 20.5, 59.3, 73.0 (q, J = 53.4 Hz), 82.7 (q, J = 6.4 Hz), 113.8 (q, J = 258.3 Hz), 126.9, 127.9, 128.5, 136.6, 169.0; ^{19}F NMR δ (ppm) −51.5 (3F, s); IR (neat) 2936, 2279, 1755, 1433, 1371, 1279 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{10}H_7F_3O_2{}^{32}S$ 248.0119, found 248.0104.

*4.2.11. 4,4,4-Trifluoro-1-(2-phenylethyl)-2-butynyl acetate (**3k**)*

Yield 56%; ^{1}H NMR δ (ppm) 2.11 (3H, s), 2.13–2.22 (2H, m), 2.78 (2H, t, J = 7.81 Hz), 5.14 (1H, oct., J = 2.90 Hz), 7.18–7.33 (5H, m); ^{13}C NMR δ (ppm) 20.6, 31.0, 35.2, 61.9, 72.5 (q, J = 53.2 Hz), 84.3 (q, J = 6.4 Hz), 113.8 (q, J = 261.4 Hz), 126.5, 128.3, 128.6, 139.7, 169.4; ^{19}F NMR δ (ppm) −54.5 (3F, s); IR (neat) 3030, 2936, 2868, 2274, 1751 cm^{-1}; HRMS (CI) calcd. for (M + H) $C_{14}H_{14}F_3O_2$ 271.0946, found 271.0945.

*4.2.12. 4,4,4-Trifluoro-1-(1-phenylethyl)-2-butynyl acetate (**3l**)*

Yield 70%; ^{1}H NMR δ (ppm) 1.44 (3H, d, J = 7.09 Hz), 2.10 (3H, s), 3.23 (1H, quint., J = 6.94 Hz), 5.53 (1H, sex., J = 2.96 Hz), 7.24–7.36 (5H, m); ^{13}C NMR δ (ppm) 16.2, 20.6, 43.1, 66.8, 73.2 (q, J = 53.2 Hz), 83.6 (q, J = 6.5 Hz), 113.7 (q, J = 257.6 Hz), 127.6, 128.0, 128.5, 140.0, 169.4; ^{19}F NMR δ (ppm) −53.4 (3F, s); IR (neat) 3034, 2980, 2939, 2883, 2272, 1753 cm^{-1}; HRMS (FAB) calcd. for (M + Na) $C_{14}H_{13}F_3NaO_2$ 293.0765, found 293.0760.

*4.2.13. 3-(6,6,6-Trifluoro-3-methyl-1-phenyl-4-hexynyl) acetate (**3m**)*

Yield 69%; ^{1}H NMR δ (ppm) 1.76 (3H, s), 2.05 (3H, s), 2.14–2.20 (1H, m), 2.25–2.31 (1H, m), 2.74–2.86 (2H, m), 7.20–7.32 (5H, m); ^{13}C NMR δ (ppm) 21.4, 25.6, 30.3, 42.4, 72.7 (q, J = 52.7 Hz), 73.0, 86.8 (q, J = 6.6 Hz), 114.1 (q, J = 257.7 Hz), 126.2, 128.4, 128.5, 140.5, 168.9; ^{19}F NMR δ (ppm) −52.8 (3F, s); IR (neat) 3065, 3030, 2932, 2868, 2278, 1751 cm^{-1}.

4.3. General procedure for the Nicholas reaction with n-Bu_3SnH

$Co_2(CO)_8$ (0.51 g, 1.5 mmol) was added to a solution of acetate **3** (1.0 mmol) in CH_2Cl_2 (5.0 mL) at room temperature. After stirring for 5 h, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was passed through a silica gel column to give a crude complex **4** which was used for the next reaction without further purification.

To a solution of the crude cobalt complex **4** in CH_2Cl_2 (15 mL) was added TMSOTf (0.89 g, 4.0 mmol) and *n*-Bu_3SnH (0.44 g, 1.5 mmol) at 0 °C, and the whole was stirred for 5 h. The reaction was quenched with $NaHCO_3$ aqueous solution and the resultant mixture was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was passed through a short silica gel column to afford the crude product **5**.

A solid of $Fe(NO_3)_3{\cdot}9H_2O$ (1.62 g, 4 mmol) was added to the crude cobalt complex **5** in CH_2Cl_2 (10 mL) and the whole was stirred until a red color of the reaction mixture disappeared (∼10 h). The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding fluoroalkylated acetylene derivative **1**.

4.3.1. 1,1,1-Trifluoro-4-(4-methoxyphenyl)-2-butyne (**1a**)

Yield 89%; ^{1}H NMR δ (ppm) 3.66 (2H, q, J = 3.66 Hz), 3.81 (3H, s), 6.89 (2H, d, J = 8.62 Hz), 7.21 (2H, d, J = 8.54 Hz); ^{13}C NMR δ (ppm) 23.6, 55.3, 69.8 (q, J = 52.4 Hz), 87.0 (q, J = 6.2 Hz), 114.2 (q, J = 255.1 Hz), 114.3, 125.3, 129.0, 158.9; ^{19}F NMR δ (ppm) −53.6 (3F, s); IR (neat) 2916, 2841, 2260, 1610 cm^{-1}; HRMS (FAB) calcd. for (M − H) $C_{11}H_8F_3O$ 213.0527, found 213.0528.

4.3.2. 1,1-Difluoro-4-(4-methoxyphenyl)-2-butyne (**1b**)

Yield 97%; ^{1}H NMR δ (ppm) 3.62 (2H, t, J = 5.61 Hz), 3.78 (3H, s), 6.20 (1H, t, J = 55.28 Hz), 6.84–7.25 (4H, m); ^{13}C NMR δ (ppm) 23.8 (t, J = 2.6 Hz), 55.2, 73.7 (t, J = 33.8 Hz), 88.5 (t, J = 7.2 Hz), 103.9 (t, J = 231.5 Hz), 114.1, 126.4, 128.9, 158.7; ^{19}F NMR δ (ppm) −105.0 (2F, dt, J = 5.7, 56.5 Hz); IR (neat) 2910, 2839, 2324, 2255, 1612, 1587, 1514 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{11}H_{10}F_2O$ 196.0700, found 196.0697.

4.3.3. 4,4,5,5,6,6-Hexafluoro-1-(4-methoxyphenyl)-2-hexyne (**1c**)

Yield 99%; ^{1}H NMR δ (ppm) 3.66 (2H, t, J = 5.54 Hz), 3.77 (3H, s), 5.99 (1H, tt, J = 5.45, 52.25 Hz), 6.87 (2H, d, J = 8.57 Hz), 7.19 (2H, d, J = 8.49 Hz); ^{13}C NMR δ (ppm) 23.9, 55.2, 69.1 (t, J = 36.1 Hz), 92.7 (t, J = 6.4 Hz), 107.9 (tt, J = 31.4, 253.3 Hz), 105.2–110.2 (m), 114.3, 125.3, 128.9, 159.0; ^{19}F NMR δ (ppm) −137.1 (2F, dquint., J = 8.5, 50.8 Hz), −131.1 (2F, m), −98.9 (2F, m); IR (neat) 2912, 2841, 2264, 1612, 1587, 1514 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{13}H_{10}F_6O$ 296.0636, found 296.0641.

4.3.4. 1,1,1-Trifluoro-4-(3-methoxyphenyl)-2-butyne (**1d**)

Yield 52%; ^{1}H NMR δ (ppm) 3.69 (2H, q, J = 3.67 Hz), 3.81 (3H, s), 6.82–6.89 (3H, m), 7.26 (1H, t, J = 7.87 Hz); ^{13}C NMR δ (ppm) 24.4, 55.2, 70.1 (q, J = 52.2 Hz), 86.4 (q, J = 6.4 Hz), 112.7, 114.1 (q, J = 256.6 Hz), 113.7, 120.2, 129.9, 134.8, 160.0; ^{19}F NMR δ (ppm) −52.2 (3F, s); IR (neat) 2928, 2841, 2262, 1603 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{11}H_9F_3O$ 214.0605, found 214.0607.

4.3.5. 1,1,1-Trifluoro-4-(2-methoxyphenyl)-2-butyne (**1e**)

Yield 51%; ^{1}H NMR δ (ppm) 3.72 (2H, q, J = 3.72 Hz), 3.88 (3H, s), 6.92 (1H, d, J = 8.21 Hz), 7.02 (1H, d, J = 7.48 Hz), 7.33 (1H, t, J = 7.86 Hz), 7.41 (1H, d, J = 7.44 Hz); ^{13}C NMR δ (ppm) 19.0, 55.3, 69.6 (q, J = 52.1 Hz), 87.1 (q, J = 6.4 Hz), 110.3, 114.3 (q, J = 256.4 Hz), 120.7, 121.9, 128.7, 128.8, 156.7; ^{19}F NMR δ (ppm) −54.2 (3F, s); IR (neat) 2943, 2841, 2260, 1603, 1495 cm^{-1}; HRMS (FAB) calcd. for (M − H) $C_{11}H_8F_3O$ 213.0527, found 213.0518.

4.3.6. 1,1,1-Trifluoro-4-(4-methylphenyl)-2-butyne (**1f**)

Yield 64%; ^{1}H NMR δ (ppm) 2.36 (3H, s), 3.68 (2H, q, J = 3.69 Hz), 7.16–7.21 (4H, m); ^{13}C NMR δ (ppm) 21.0, 24.1, 69.9 (q, J = 52.1 Hz), 86.9 (q, J = 6.4 Hz), 114.2 (q, J = 256.4 Hz), 127.8, 129.6, 130.3, 137.1; ^{19}F NMR δ (ppm) −50.2 (3F, s); IR (neat) 2928, 2858, 2260, 1705, 1605 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_{11}H_9F_3$ 198.0656, found 198.0650.

4.3.7. 4-(4-Chlorophenyl)-1,1,1-trifluoro-2-butyne (**1g**)

Yield 63%; ^{1}H NMR δ (ppm) 3.69 (2H, q, J = 3.64 Hz), 7.24 (2H, d, J = 8.50 Hz), 7.33 (2H, d, J = 8.44 Hz); ^{13}C NMR δ (ppm) 23.9, 70.4 (q, J = 52.5 Hz), 85.9 (q, J = 6.4 Hz), 114.0 (q, J = 256.6 Hz), 129.0, 129.2, 131.8, 133.4; ^{19}F NMR δ (ppm) −52.1 (3F, s); IR (neat) 2930, 2856, 2262, 1682, 1591 cm^{-1}; HRMS (FAB) calcd. for (M − H) $C_{11}H_5{}^{35}ClF_3$ 217.0032, found 217.0031.

4.3.8. 1,1,1-Trifluoro-4-(1-naphthyl)-2-butyne (**1h**)

Yield 78%; mp 32–34 °C; ^{1}H NMR δ (ppm) 4.10 (2H, q, J = 3.66 Hz), 7.48–7.95 (7H, m); ^{13}C NMR δ (ppm) 22.3, 70.8 (q, J = 52.3 Hz), 86.3 (q, J = 6.3 Hz), 114.2 (q, J = 256.5 Hz), 122.8, 125.5, 126.0, 126.1, 126.6, 128.4, 128.9, 129.2, 131.1, 133.8; ^{19}F NMR δ (ppm) −50.2 (3F, s); IR (KBr) 3068, 2303, 2262, 1599 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_{14}H_9F_3$ 234.0656, found 234.0666.

4.3.9. 1,1,1-Trifluoro-4-(2-thienyl)-2-butyne (**1j**)

Yield 47%; ^{1}H NMR δ (ppm) 3.90 (2H, q, J = 3.36 Hz), 6.97–6.98 (2H, m), 7.23 (1H, dd, J = 1.38, 4.90 Hz); ^{13}C NMR δ (ppm) 19.4, 69.8 (q, J = 52.4 Hz), 85.4 (q, J = 6.4 Hz), 114.0 (q, J = 256.9 Hz), 125.0, 126.1, 127.1, 135.1; ^{19}F NMR δ (ppm) −50.5 (3F, s); IR (neat) 2928, 2260, 1715, 1439, 1416 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_8H_5F_3{}^{32}S$ 190.0064, found 190.0067.

4.3.10. 1,1,1-Trifluoro-6-phenyl-2-hexyne (**1k**)

Yield 41%; ^{1}H NMR δ (ppm) 1.92 (2H, quint., J = 7.53 Hz), 2.32 (2H, oct., J = 3.70 Hz), 7.18–7.33 (5H, m); ^{13}C NMR δ

(ppm) 17.4, 28.7, 34.5, 68.8 (q, J = 52.2 Hz), 88.8 (q, J = 6.2 Hz), 114.1 (q, J = 256.0 Hz), 126.2, 128.46, 128.52, 140.6; ^{19}F NMR δ (ppm) −54.1 (3F, s); IR (neat) 2932, 2864, 2264, 1716 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_{12}H_{11}F_3$ 212.0813, found 212.0810.

4.3.11. 1,1,1-Trifluoro-5-phenyl-2-hexyne (**1l**)

Yield 54%; ^{1}H NMR δ (ppm) 1.40 (3H, d, J = 7.01 Hz), 2.48–2.62 (2H, m), 3.05 (1H, sex., J = 7.03 Hz), 7.21–7.26 (3H, m), 7.31–7.34 (2H, m); ^{13}C NMR δ (ppm) 20.6, 27.3, 38.1, 69.6 (q, J = 51.9 Hz), 87.7 (q, J = 6.4 Hz), 114.1 (q, J = 256.5 Hz), 126.7, 126.9, 128.6, 144.4; ^{19}F NMR δ (ppm) −51.7 (3F, s); IR (neat) 2968, 2932, 2856, 2258, 1495 cm^{-1}; HRMS (CI) calcd. for (M^+) $C_{12}H_{11}F_3$ 212.0813, found 212.0808.

4.3.12. 6,6,6-Trifluoro-3-methyl-1-phenyl-2-hexen-4-yne (**6m**)

Yield 44%; ^{1}H NMR δ (ppm) 1.95 (3H, s), 3.50 (2H, d, J = 7.64 Hz), 6.34 (1H, t, J = 7.56 Hz), 7.15–7.33 (5H, m); ^{13}C NMR δ (ppm) 16.1, 34.7, 72.9 (q, J = 52.1 Hz), 89.2 (q, J = 6.4 Hz), 114.9 (q, J = 256.4 Hz), 115.21, 115.23, 126.6, 128.4, 128.7, 138.5, 142.68, 142.70; ^{19}F NMR δ (ppm) −51.9 (3F, s); IR (neat) 3030, 2962, 2928, 2239, 1605 cm^{-1}; HRMS (EI) calcd. for (M^+) $C_{13}H_{11}F_3$ 224.0813, found 224.0813.

4.4. General procedure for the Nicholas reaction with various carbon nucleophiles

The reaction was carried out according to the same procedure as described for the Nicholas reaction with n-Bu_3SnH by using the corresponding carbon nucleophiles (1.5 equiv.) in place of n-Bu_3SnH.

4.4.1. 7,7,7-Trifluoro-4-(4-methoxyphenyl)-2-methyl-1-hepten-5-yne (**1aA$_1$**)

Yield 49%; ^{1}H NMR δ (ppm) 1.79 (3H, s), 2.49 (1H, q, J = 6.40, 13.91 Hz), 2.58 (1H, q, J = 8.80, 13.93 Hz), 3.85 (3H, s), 3.87 (1H, m), 4.80 (1H, s), 4.90 (1H, s), 6.92–6.95 (2H, m), 7.26–7.30 (2H, m); ^{13}C NMR δ (ppm) 22.3, 24.3, 35.3, 45.6, 70.7 (q, J = 52.1 Hz), 90.2 (q, J = 6.5 Hz), 114.3 (q, J = 256.3 Hz); ^{19}F NMR δ (ppm) −51.7 (3F, s); IR (neat) 2926, 2841, 2257, 1610 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{15}H_{15}F_3O$ 268.1075, found 268.1078.

4.4.2. 7,7,7-Trifluoro-4-(4-methoxyphenyl)-2-methyl-2-hepten-5-yne (**1aA$_2$**)

Yield 49%; ^{1}H NMR δ (ppm) 1.81 (6H, s), 3.84 (3H, s), 4.66 (1H, m), 5.30 (1H, dm, J = 9.12 Hz), 6.92–6.95 (2H, m), 7.26–7.30 (2H, m); ^{13}C NMR δ (ppm) 18.1, 25.6, 34.7, 55.3, 69.8 (q, J = 52.2 Hz), 89.5 (q, J = 6.5 Hz), 114.4 (q, J = 256.6 Hz); ^{19}F NMR δ (ppm) −51.9 (3F, s); IR (neat) 2926, 2841, 2257, 1610 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{15}H_{15}F_3O$ 268.1075, found 268.1078.

4.4.3. 7,7,7-Trifluoro-4-(4-methoxyphenyl)-1-hepten-5-yne (**1aB**)

Yield 63%; ^{1}H NMR δ (ppm) 2.52–2.56 (2H, m), 3.75 (1H, oct., J = 3.54 Hz), 3.81 (3H, s), 5.08–5.12 (2H, m), 5.73–5.81 (1H, m), 6.88–6.90 (2H, m), 7.20–7.26 (2H, m); ^{13}C NMR δ (ppm) 36.5, 41.4, 55.3, 70.9 (q, J = 52.2 Hz), 89.9 (q, J = 6.5 Hz), 114.2, 114.3 (q, J = 256.6 Hz), 118.2, 128.4, 130.3, 133.9, 158.9; ^{19}F NMR δ (ppm) −51.9 (3F, s); IR (neat) 3082, 2914, 2839, 2264, 1612, 1514 cm^{-1}; HRMS (FAB) calcd. for (M − H) $C_{14}H_{12}F_3O$ 253.0840, found 253.0845.

4.4.4. 6,6,6-Trifluoro-3-(4-methoxyphenyl)-1-phenyl-4-hexyn-1-one (**1aC**)

Yield 63%; ^{1}H NMR δ (ppm) 3.44 (1H, q, J = 6.60, 17.46 Hz), 3.58 (1H, q, J = 7.27, 17.45 Hz), 3.80 (3H, s), 4.52 (1H, oct., J = 3.40 Hz), 6.88–7.93 (9H, m); ^{13}C NMR δ (ppm) 31.3, 46.0, 55.3, 70.1 (q, J = 52.6 Hz), 89.9 (q, J = 6.3 Hz), 114.0 (q, J = 256.9 Hz), 114.4, 128.1, 128.6, 128.7, 130.3, 133.6, 136.2, 159.1, 195.7; ^{19}F NMR δ (ppm) −50.1 (3F, s); IR (neat) 2912, 2839, 2264, 1688 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{19}H_{15}F_3O_2$ 332.1024, found 332.1027.

4.4.5. 8,8,8-Trifluoro-5-(4-methoxyphenyl)-2,2-dimethyl-6-octyn-3-one (**1aD**)

Yield 99%; ^{1}H NMR δ (ppm) 1.06 (9H, s), 2.90 (1H, q, J = 6.87, 17.16 Hz), 3.07 (1H, q, J = 7.39, 17.19 Hz), 3.79 (3H, s), 4.35 (1H, m), 6.87 (2H, d, J = 8.56 Hz), 7.24 (2H, d, J = 8.54 Hz); ^{13}C NMR δ (ppm) 25.7, 31.4, 43.9, 44.4, 55.2, 69.8 (q, J = 52.3 Hz), 90.0 (q, J = 6.6 Hz), 114.1 (q, J = 256.5 Hz), 114.3, 128.5, 130.2, 159.0, 211.3; ^{19}F NMR δ (ppm) −50.2 (3F, s); IR (neat) 2972, 2839, 2264, 1711, 1612, 1585, 1514, 1466, 1445 cm^{-1}; HRMS (FAB) calcd. for (M + H) $C_{17}H_{20}F_3O_2$ 313.1415, found 313.1415.

4.4.6. 2-[4,4,4-Trifluoro-1-(4-methoxyphenyl)-2-butynyl]-cyclohexanone (**1aE**)

Combined yield 88%; Diastereomeric ratio = 1:1.

Diastereomer 1: ^{1}H NMR δ (ppm) 1.56–2.59 (9H, m), 3.79 (3H, s), 4.48 (1H, m), 6.87 (2H, d, J = 8.49 Hz), 7.22 (2H, d, J = 8.46 Hz); ^{13}C NMR δ (ppm) 24.8, 27.3, 29.4, 35.2, 42.0, 55.2, 56.2, 71.8 (q, J = 52.1 Hz), 88.5 (q, J = 6.6 Hz), 114.08, 114.13 (q, J = 256.7 Hz), 128.9, 129.5, 158.9, 208.9; ^{19}F NMR δ (ppm) −49.9 (3F, s); IR (neat) 2939, 2866, 2258, 1715 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{17}H_{17}F_3O_2$ 310.1181, found 310.1180.

Diastereomer 2: ^{1}H NMR δ (ppm) 0.87–2.81 (9H, m), 3.80 (3H, s), 4.16 (1H, m), 6.86 (2H, d, J = 8.29 Hz), 7.22 (2H, d, J = 8.28 Hz); ^{13}C NMR δ (ppm) 25.0, 27.7, 31.3, 35.4, 42.2, 55.2, 56.0, 69.6 (q, J = 52.1 Hz), 90.4 (q, J = 6.3 Hz), 114.0, 114.2 (q, J = 256.5 Hz), 128.1, 129.7, 159.0, 209.2; ^{19}F NMR δ (ppm) −49.9 (3F, s); IR (neat) 2939, 2866, 2255, 1713 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{17}H_{17}F_3O_2$ 310.1181, found 310.1180.

4.4.7. Methyl 6,6,6-trifluoro-3-(4-methoxyphenyl)-2, 2-dimethyl-4-hexynoate (**1aF**)

Yield 96%; ^{1}H NMR δ (ppm) 1.15 (3H, s), 1.33 (3H, s), 3.66 (3H, s), 3.79 (3H, s), 4.21 (1H, q, J = 3.60 Hz), 6.86 (2H, d, J = 8.64 Hz), 7.17 (2H, d, J = 8.63 Hz); ^{13}C NMR δ (ppm) 21.5, 23.2, 44.6, 47.4, 52.0, 55.2, 71.7 (q, J = 52.3 Hz), 88.3 (q, J = 6.4 Hz), 113.7, 114.1 (q, J = 256.8 Hz), 126.6, 130.3, 159.3, 175.8; ^{19}F NMR δ (ppm) −50.0 (3F, s); IR (neat) 2955, 2841, 2260, 1734 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{16}H_{17}F_3O_3$ 314.1130, found 314.1133.

4.4.8. 6,6-Difluoro-3-(4-methoxyphenyl)-1-phenyl-4-hexyn-1-one (**1bC**)

Yield 96%; ^{1}H NMR δ (ppm) 3.39 (1H, q, J = 6.44, 17.34 Hz), 3.56 (1H, q, J = 7.46, 17.36 Hz), 3.77 (3H, s), 4.48 (1H, quint., J = 6.13 Hz), 6.17 (1H, t, J = 55.21 Hz), 6.86–7.92 (9H, m); ^{13}C NMR δ (ppm) 31.6, 46.3, 55.2, 74.1 (t, J = 33.9 Hz), 91.4 (t, J = 7.1 Hz), 103.8 (t, J = 231.8 Hz), 114.2, 128.0, 128.5, 128.6, 131.1, 133.4, 136.3, 158.9, 196.1; ^{19}F NMR δ (ppm) −105.3 (2F, d, J = 53.7 Hz); IR (neat) 2839, 2251, 1688, 1612 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{19}H_{16}F_2O_2$ 314.1118, found 314.1127.

4.4.9. 6,6,7,7,8,8-Hexafluoro-3-(4-methoxyphenyl)-1-phenyl-4-octyn-1-one (**1cC**)

Yield 87%; ^{1}H NMR δ (ppm) 3.44 (1H, q, J = 6.32, 17.43 Hz), 3.58 (1H, q, J = 7.68, 17.46 Hz), 3.80 (3H, s), 4.54 (1H, quint., J = 6.43 Hz), 6.04 (1H, tt, J = 5.54, 52.18 Hz), 6.88–7.93 (9H, m); ^{13}C NMR δ (ppm) 31.8, 46.1, 55.3, 69.6 (t, J = 36.7 Hz), 95.7 (t, J = 6.6 Hz), 107.8 (tt, J = 31.2, 253.2 Hz), 107.1–110.1 (m), 114.4, 128.0, 128.5, 128.7, 130.1, 133.6, 136.2, 159.1, 195.8; ^{19}F NMR δ (ppm) −137.2 (2F, dquint., J = 8.5, 50.8 Hz), −131.6 (2F, m), −99.6 (2F, m); IR (neat) 2912, 2839, 2257, 1688, 1612 cm^{-1}; HRMS (FAB) calcd. for (M^+) $C_{21}H_{16}F_6O_2$ 414.1054, found 414.1057.

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