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Radical trifluoromethylation of Ti ate enolate: possible intervention of transformation of Ti(IV) to Ti(III) for radical termination

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Abstract

The radical trifluoromethylation of ketone Ti ate enolates gave α-CF_3 ketones in good yields. The use of excess amount of LDA and $Ti(O^iPr)_4$ in the preparation of Ti ate enolates is the key to the efficient radical trifluoromethylation. Theoretical studies on the spin density of the Ti(IV) ate ketyl radical intermediate suggest the involvement of transformation from Ti(IV) ate ketyl radical intermediates to Ti(III) species in a radical termination step.

Keywords: Trifluoromethylation; Ti ate enolate; α-CF_3 ketone; Radical addition

1. Introduction

Introduction of fluorine functionality, especially CF_3 unit, into an organic molecule has attracted much attention, because those molecules exhibit specific physical and biological properties [1]. We have been exploring the synthesis and reaction of α-CF_3 carbonyl compounds [2], which are, in principle, one of the most useful synthetic intermediates for constructing CF_3 containing organic molecules. A radical trifluoromethylation of enolates is one of the simplest ways to synthesize α-CF_3 carbonyl compounds. However, there are only limited examples especially in the case of ketones [3–7]. It has been reported that the synthetic difficulty is due to a defluorination of the α-CF_3 ketone product by the parent enolate or a base during the reaction (Scheme 1) [8]. To avoid defluorination of α-CF_3 ketone products, less reactive enolate equivalents such as silyl or germyl enol ethers have been used for radical trifluoromethylation [4]. However, we have already reported the radical trifluoromethylation of Ti ate enolates [2(d)] based on our successful discovery of stable Ti enolate of α-CF_3 ketone which suppress defluorination by the linearity of Ti–O–C bond [2(c)]. Further investigation and the limitation of this reaction are herein reported.

2. Results and discussion

First, several Ti enolates of cyclohexanone (**1a**) were investigated (Table 1). The enolates were reacted with CF_3 radical generated by CF_3I and Et_3B [9]. The yield was determined by ^{19}F NMR using BTF as an internal standard. No α-CF_3 product was obtained by the radical trifluoromethylation of the $TiCl_3$ enolate, which was generated by $TiCl_4/Et_3N$ at −78 °C. However, more electron rich $Ti(O^iPr)_3$ enolate gave the α-CF_3 product (**2a**) in 23%. Further enrichment of the electron density by the use of Ti ate type enolate ($Ti^-(O^iPr)_4Li^+$) increased the product yield to 56% yield.

The radical trifluoromethylation of Ti enolates of 3,3-dimethyl-4-phenyl-2-butanone (**1b**) was also investigated (Table 2). The same tendency was observed in the case of the reaction of $Ti(O^iPr)_3$ enolate and Ti ate enolate ($Ti^-(O^iPr)_4Li^+$). Ti ate enolate gave the product (**2b**) in 50% yield (entry 2). On the other hand, relatively electron poor $Ti(O^iPr)_3$ enolate gave the product in only 4% yield (entry 1). Several species of Ti ate type enolate was investigated for this substrate (entries 3–8). For the alkoxide ligand, $-O^iPr$ (entry 2), $-O^tBu$ (entry 4), –OEt (entry 5), and $-NMe_2$ (entry 6) were investigated and $-O^iPr$ gave the highest yield (50%). For $Ti(O^tBu)_4$, the Ti ate enolate might not be formed based on the color of the solution; normally the color changes to slightly yellow upon formation of Ti ate enolates. For $Ti(OEt)_4$ and $Ti(NMe_2)_4$, the reason for the low yields are not clear;

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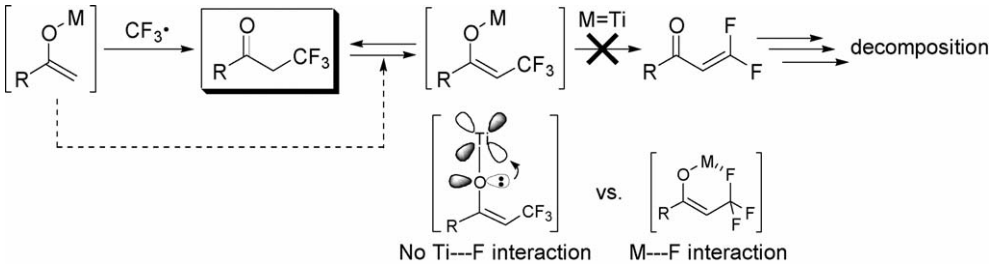
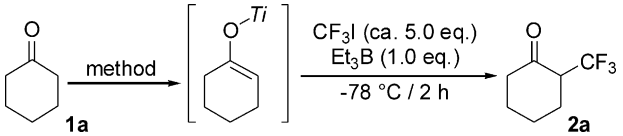


Scheme 1. Radical trifluoromethylation.

Table 1
Radical trifluoromethylation of various Ti enolates of cyclohexanone



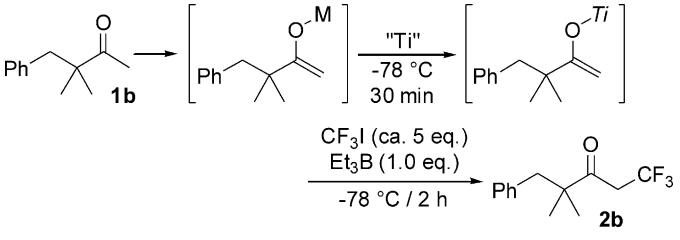
Entry	Method	Ti	Yield (%)
1	$TiCl_4/Et_3N$ at −78 °C in CH_2Cl_2	$TiCl_3$	0
2	(1) LDA, (2) $TiCl(O^iPr)_3$ at −78 °C in THF	$Ti(O^iPr)_3$	23
3	(1) LDA, (2) $Ti(OiPr)_4$ at −78 °C in THF	$Ti^-(O^iPr)_4Li^+$	56

$Ti^-(OEt)_4Li^+$ enolate is insufficiently nucleophilic to react with CF_3 radical. $Ti^-(NMe_2)_4Li^+$ enolate is so basic to decompose the α-CF_3 product.

When 12-crown-4 was added to the reaction system of $Ti^-(O^iPr)_4Li^+$ enolate, the yield did not change (entry 3), compared to the reaction without 12-crown-4 (entry 2). These results indicate that Li cation is not involved in the reaction. Different counter cation (K) was also investigated. The parent K enolate was prepared by treatment of the ketone with KH in THF at r.t. for 1 h. The yield decreased to 17% (entry 7). Addition of $^iPr_2NH$ (by-product of Li enolate formation) had no significant effect (entry 8).

From the discussion above, the highest yielding Ti ate enolate is $Ti^-(O^iPr)_4Li^+$ enolate. We further investigated the amount of LDA and $Ti(O^iPr)_4$ in the preparation of Ti ate enolates (Table 3). When the Ti ate enolate of cyclohexanone (**1a**) was formed by 1.0 eq. of LDA and 1.0 eq. of $Ti(O^iPr)_4$, the α-CF_3 product (**2a**) was formed in 56% yield (entry 1). When 1.6 eq. of LDA and 1.6 eq. of $Ti(O^iPr)_4$ were used, the yield increased up to 81% (entry 3). Use of 1.0 eq. of LDA and 1.6 eq. of $Ti(O^iPr)_4$ gave the α-CF_3 ketone (**2a**) in almost the same yield as in entry 1 (52%, entry 5). The same tendency was observed in the case of 3,3-dimethyl-4-phenyl-2-butanone (**1b**). The use of 1.0 eq. of LDA and $Ti(O^iPr)_4$ in the preparation of Ti ate enolate gave the product in 50% yield (entry 6), and the use of 1.6 eq. of LDA and $Ti(O^iPr)_4$ gave the product in 65% yield (entry 8). Therefore, both LDA and $Ti(O^iPr)_4$ should be used in excess amount.

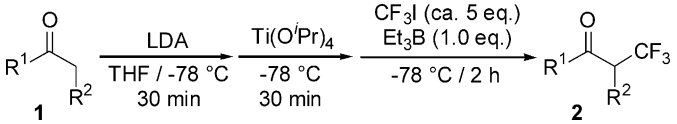
Table 2
Radical trifluoromethylation of various Ti ate enolates

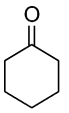
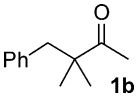


Entry	M	"Ti"	Ti	Yield (%)[a]
1	Li[b]	$TiCl(O^iPr)_3$	$Ti(O^iPr)_3$	4
2		$Ti(O^iPr)_4$	$Ti^-(O^iPr)_4Li^+$	50[c]
3[d]		$Ti(O^iPr)_4$	$Ti^-(O^iPr)_4Li^+$	53[c]
4		$Ti(O^tBu)_4$	$Ti^-(O^tBu)_4Li^+$	30[c]
5		$Ti(OEt)_4$	$Ti^-(OEt)_4Li^+$	4
6		$Ti(NMe_2)_4$	$Ti^-(NMe_2)_4Li^+$	0
7	*K*[e]	$Ti(O^iPr)_4$	$Ti^-(O^iPr)_4K^+$	17
8[f]		$Ti(O^iPr)$	$Ti^-(O^iPr)K^+$	13

[a] Determined by ^1H NMR using 1,4-dioxane as an internal standard.
[b] Li enolate was prepared by the treatment of the ketone with 1.0 eq. of LDA at −78 °C inTHFfor30 min.
[c] The yield of the isolated products.
[d] 1.0 eq. of 12-Crown-4 was added.
[e] K enolate was prepared by the treatment of the ketone with 1.0 eq. of KH at r.t. inTHF for 1 h.
[f] 1.0 eq. of $^iPr_2NH$ was added.

Table 3
Trifluoromethylation of Ti ate enolates

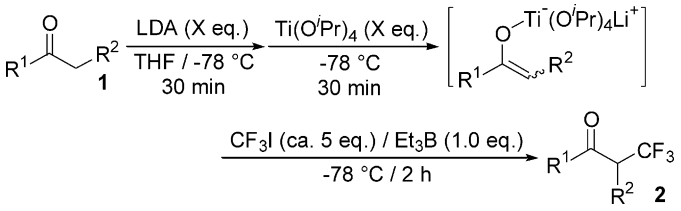


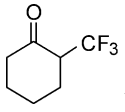
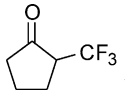
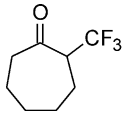
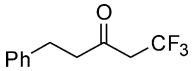
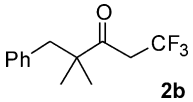
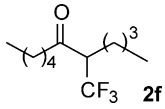
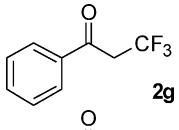
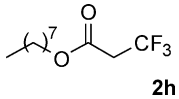
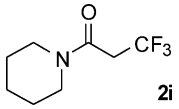
Entry	Substrate	LDA (eq.)	$Ti(O^iPr)_4$ (eq.)	Yield (%)[a]
1	 1a	1.0	1.0	56
2		1.3	1.3	72
3		1.6	1.6	81
4		2.0	2.0	80
5		1.0	1.6	52
6	 1b	1.0	1.0	50[b]
7		1.3	1.3	56[b]
8		1.6	1.6	65[b]

[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] Yield of the isolated product.

Several ketonic substrates were investigated (Table 4). Although cyclohexanone gave α-CF_3 product (**2a**) in 81% yield under LDA = $Ti(O^iPr)_4$ = 1.6 eq. condition (entry 2), cyclopentanone gave poor yield (**2c**) for both LDA = $Ti(O^iPr)_4$ = 1.0 or 1.6 eq. conditions (38 and 33% in entries 3 and 4, respectively). In the case of cycloheptanone, the α-CF_3 product (**2d**) was obtained in good yield (61%) by LDA = $Ti(O^iPr)_4$ = 1.6 eq. condition (entry 6). For acyclic substrates, **1b** and **1f** gave the products in good yield (65 and 64% in entries 10 and 12, respectively). The yield of **2e** was poor in the case that LDA = $Ti(O^iPr)_4$ = 1.6 eq. (entry 8, 14%). Interestingly, however, when the number of equivalents were decreased (LDA = $Ti(O^iPr)_4$ = 1.0 eq.), the yield was increased (38%, entry 7) than with 1.6 eq. for this acyclic substrates. When acetophenone (**1g**) (entry 13), ester (**1h**) (entry 14), and amide (**1i**) (entry 15) were used as substrates, the α-CF_3 product was not obtained at all. The reaction of acetophenone (**1g**) and ester (**1h**) resulted in a complex mixture. For acetophenone (**1g**), it is probably due to the high acidity of α-proton of the α-CF_3 product, which might lead to the decomposition (Scheme 1). For ester (**1h**), the Claisen condensation might be the reason for the complex mixture. The reaction of the amide (**1i**) gave the self-coupling product of the amide enolate.

Table 4
Trifluoromethylation of various substrates (ketone)



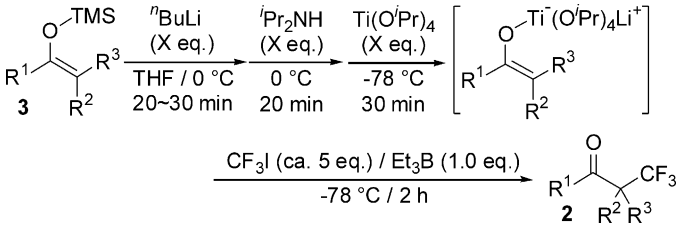
Entry	Product	X (eq.)	Yield (%)[a]
1	 **2a**	1.0	63
2		1.6	81
3	 **2c**	1.0	38
4		1.6	33
5	 **2d**	1.0	49
6		1.6	61
7	 **2e**	1.0	38
8		1.6	14
9	 **2b**	1.0	(50)
10		1.6	69 (65)
11	 **2f**	1.0	32
12		1.6	64
13	 **2g**	1.3	–
14	 **2h**	1.0	–
15	 **2i**	1.3	–

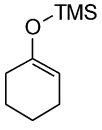
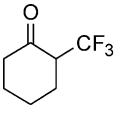
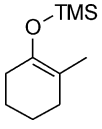
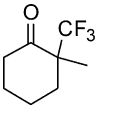
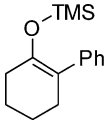
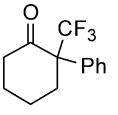
The number in parentheses refer to the yield of the isolated products.
[a] Determined by 19F NMR using BTF as an internal standard.

Although LDA generates only the kinetic Li enolate, the thermodynamic enolate can also be prepared from silyl enol ethers by adding ^{n}BuLi [10]. Therefore, the thermodynamic Ti ate enolate of an α-substituted ketone could be generated by a silyl-to-lithium transmetalation method to construct a quaternary carbon center attached to the CF_3 substituent. In the case of α-Me (**3j**) and α-Ph (**3k**) substituted cyclohexanones, the products were obtained in reasonable yields (42% and 43% yield each) (Table 5).

When the reaction was carried out by using 0.1 eq. of Et_3B, the yield was only 5% yield. This result implies the existence of a radical termination step which would interrupt the radical cycle. The proposed radical reaction mechanism is shown in Fig. 1. Iseki and coworkers proposed a mechanism in the case of Li imide enolates as path **A** in Fig. 1 [3(b)]. However, this mechanism does not involve any radical termination step. Based on the fact that Ti has a stable oxidation state Ti(III), we

Table 5
Trifluoromethylation of various substrates (silyl enol ether)



Entry	Substrate	Product	X (eq.)	Yield (%)[a]
1	 **3a**	 **2a**	1.0	49
2			1.6	74
3	 **3j**	 **2j**	1.0	30
4			1.6	42
5	 **3k**	 **2k**	1.0	32 (35)
6			1.6	44 (43)

The number in parentheses refer to the yields of the isolated products.
[a] Determined by ^{19}F NMR using BTF as an internal standard.

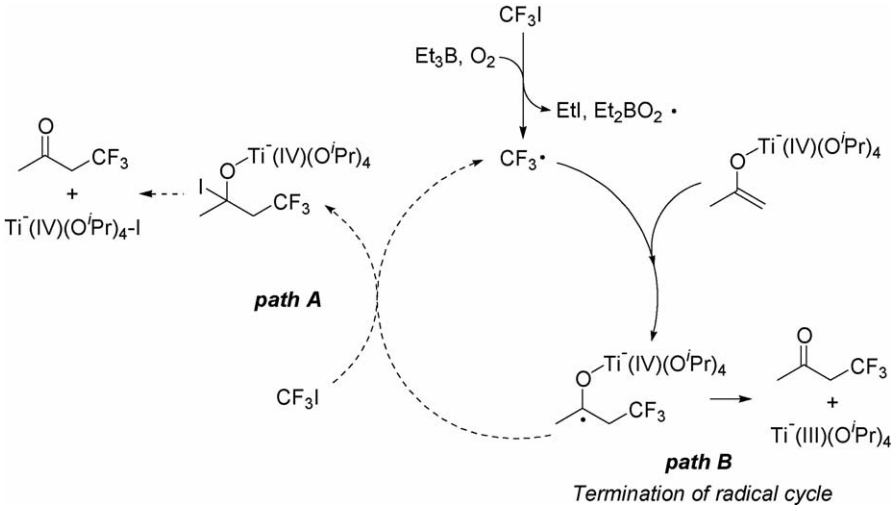


Fig. 1. Radical reaction mechanism.

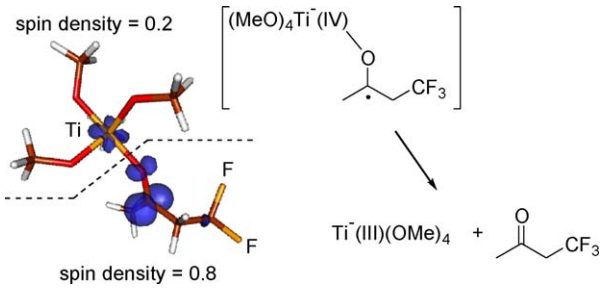


Fig. 2. Spin density of the Ti(IV) ketyl radical intermediate.

propose a radical termination step as path **B**. In fact, calculated spin density of the Ti(IV) ketyl radical intermediate has 20% of its spin on the Ti(IV) part [11,12] to facilitate the elimination of Ti(III) (Fig. 2).

In conclusion, we have developed a radical trifluoromethylation of Ti ate enolates. The key to the success is the use of excess amount of ^{n}BuLi, $^{i}Pr_2NH$ and $Ti(O^{i}Pr)_4$ to generate the Ti ate enolates. A CF_3 substituent can be introduced to various ketones by this method even when quaternary carbon centers are formed. Elimination of Ti(III) from Ti(IV) ketyl radical intermediate is proposed as a termination step of the radical trifluoromethylation.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ^{1}H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta = 77.0$) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard ($\delta = -63.24$) in $CDCl_3$. IR spectrum was measured on JASCO FT/IR-5000 spectrometer. EI Mass spectra were measured on Shimadzu QP-5000 spectrometer. Analytical thin layer chromatography (TLC) was performed on glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F254, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane ethyl acetate mixture as an eluent unless otherwise noted. THF was distilled from benzophenone-kethyl under Ar prior to use. All experiments were carried out under argon atmosphere unless otherwise noted.

3.2. General procedure: starting from ketone

To a solution of $^{i}Pr_2NH$ (44.9 μl, 0.32 mmol) in THF (2.0 ml) was added ^{n}BuLi (205.1 μl of 1.56 M solution in hexane, 0.32 mmol) at −78 °C. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. To the solution was added cyclohexanone (**1a**) (20.7 μl, 0.2 mmol) and stirred for 30 min at the temperature. Then $Ti(O^{i}Pr)_4$ (94.5 μl, 0.32 mmol) was added to the solution. After stirring for 30 min at −78 °C, gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 h at −78 °C and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at the temperature. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR analysis of the crude mixture (81%) (**2a**).

3.3. General procedure: starting from silyl enol ether

To a solution of 1-(trimethylsilyloxy)cyclohexene (**3a**) (38.9 μl, 0.2 mmol) in THF was added ^{n}BuLi (205.1 μl of 1.56 M solution in hexane, 0.32 mmol) at 0 °C and stirred for

20 min at the temperature. Next, $^{i}Pr_2NH$ (44.9 μl, 0.32 mmol) was added to the solution and stirred for another 20 min. Then, the reaction mixture was cooled to −78 °C. To the mixture was added gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 h at −78 °C and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at the temperature. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR analysis of the crude mixture (74%) (**2a**).

3.4. 2-Trifluoromethyl-cyclohexanone (*2a*)

^{1}H NMR ($CDCl_3$): δ 1.62–1.88 (m, 3H), 1.92–2.14 (m, 2H), 2.24–2.39 (m, 2H), 2.42–2.53 (m, 1H), 2.98–3.13 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 27.1, 27.5 (q, J = 2.4 Hz), 42.2, 53.6(q, J = 25.7 Hz), 124.6(q, J = 279.5 Hz), 203.0. ^{19}F NMR ($CDCl_3$): δ −69.3(d, 7.9 Hz). IR (neat): 2954, 2876, 2364, 1729, 1272, 1170, 1125, 1060 cm^{-1}. EI-MS *m/z*: 166 [$M^{+\bullet}$]

3.5. 1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (*2b*)

^{1}H NMR ($CDCl_3$): δ 1.16 (s, 6H), 2.81 (s, 2H), 3.17 (q, J = 9.9 Hz, 2H), 7.07 (ddd, J = 1.7, 2.1, 6.3 Hz, 2H), 7.19–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 23.8, 41.4 (q, J = 28.1 Hz), 45.3, 48.9, 123.9 (q, J = 277.1 Hz), 126.8, 128.2, 130.2, 136.8, 205.2. ^{19}F NMR ($CDCl_3$): δ −63.0 (t, J = 9.8 Hz). IR (neat): 3034, 2976, 1721, 1369, 1282, 1133, 1100 cm^{-1}. EI-MS *m/z*: 244 [$M^{+\bullet}$].

3.6. 2-Trifluoromethyl-cyclopentanone (*2c*)

^{1}H NMR ($CDCl_3$): δ 1.77–2.00 (m, 1H), 2.01–2.21 (m, 2H), 2.22–2.48 (m, 3H), 2.78–2.97 (qm, J = 9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 20.0, 24.4, 38.5, 51.1 (q, J = 26.9 Hz), 124.6 (q, J = 278.3 Hz), 209.4. ^{19}F NMR ($CDCl_3$): δ −67.9 (d, J = 10.5). IR (neat): 2986, 2896, 2366, 2344, 1758, 1638, 1367, 1313, 1257, 1187, 1151, 1096, 1046 cm^{-1}. EI-MS *m/z*: 152 [$M^{+\bullet}$].

3.7. 2-Trifluoromethyl-cycloheptanone (*2d*)

^{1}H NMR ($CDCl_3$): δ 1.22–1.48 (m, 2H), 1.48–1.75 (m, 2H), 1.86–2.05 (m, 3H), 2.09–2.20 (m, 1H), 2.54–2.61 (m, 2H), 3.16–3.31 (qdd, J = 4.1, 8.9, 11.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.4, 24.7 (q, J = 2.4 Hz), 27.5, 29.1, 43.1, 55.5 (q, J = 24.5 Hz), 124.9 (q, J = 280.8 Hz), 205.9. ^{19}F NMR ($CDCl_3$): δ −69.0 (d, J = 9.0 Hz). IR (neat): 2940, 2866, 1721, 1178, 1151, 1096 cm^{-1}. EI-MS *m/z*: 180 [$M^{+\bullet}$].

3.8. 1,1,1-Trifluoro-5-phenyl-3-pentanone (*2e*)

^{1}H NMR ($CDCl_3$): δ 2.80–3.00 (m, 4H), 3.19 (q, J = 10.2 Hz, 2H), 7.14–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 29.2, 44.9, 46.5 (q, J = 28.1 Hz), 123.5 (q, J = 277.1 Hz), 126.4, 128.3, 128.6, 140.1, 199.1. ^{19}F NMR ($CDCl_3$): δ -62.9 (t, J = 10.2 Hz). IR (neat): 3068, 3032, 2922, 1734, 1605, 1497, 1456, 1419, 1377, 1261, 1154, 1096, 750, 700 cm^{-1}. EI-MS *m/z*: 216 [$M^{+\bullet}$].

3.9. 7-Trifluoromethyl-6-undecanone (*2f*)

^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 3.9 Hz, 6H), 1.18–1.41 (m, 8H), 1.53–1.65 (m, 2H), 1.65–1.79 (m, 1H), 1.81–1.97 (m, 1H), 2.47 (dt, J = 18.0, 7.2 Hz, 1H), 2.61 (dt, J = 7.4, 18.0 Hz, 1H), 3.11–3.26 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 22.4, 22.7, 25.59, 25.62, 29.0, 31.1, 43.6, 55.6 (q, J = 24.4 Hz), 124.9 (q, J = 280.7 Hz), 204.5. ^{19}F NMR ($CDCl_3$): δ 67.4 (d, J = 9.0 Hz). IR (neat): 2966, 2938, 2870, 1731, 1263, 1164 cm^{-1}. EI-MS *m/z*: 238 [$M^{+\bullet}$].

3.10. 2-Methyl-2-trifluoromethyl-cyclohexanone (*2j*)

^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.70–2.00 (m, 5H), 2.06–2.20 (m, 1H), 2.35–2.58 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.7 (q, J = 2.4 Hz), 20.5, 26.4, 33.5, 39.4, 53.7 (q, J = 23.2 Hz), 126.5 (q, J = 283.2 Hz), 206.2. ^{19}F NMR ($CDCl_3$): δ −73.6 (s). IR (neat): 2936, 2874, 1725, 1274, 1170, 1137 cm^{-1}. EI-MS *m/z*: 180 [$M^{+\bullet}$].

3.11. 2-Phenyl-2-trifluoromethyl-cyclohexanone (*2k*)

^{1}H NMR ($CDCl_3$): δ 1.63–1.86 (m, 3H), 1.89–2.00 (m, 1H), 2.12–2.25 (m, 1H), 2.31–2.40 (m, 2H), 2.91 (qd, J = 3.0, 14.4 Hz, 1H), 7.29–7.35 (m, 2H), 7.35–7.47 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 20.2, 27.4, 29.9 (q, J = 2.4 Hz), 39.8, 62.2 (q, J = 22.0 Hz), 125.1 (q, J = 283.2 Hz), 128.7, 128.8, 129.0, 131.8, 204.7. ^{19}F NMR ($CDCl_3$): δ −72.9 (s). IR (neat): 3066, 2954, 2874, 1725, 1282, 1255, 1176, 1152 cm^{-1}. EI-MS *m/z*: 242 [$M^{+\bullet}$].

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