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# Synthesis of Medicinally Interesting Polyfluoro Ketones via Perfluoroalkyl Lithium Reagents

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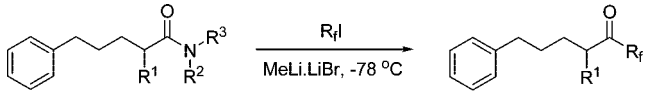


The addition of (pentafluoroethyl)- and (heptafluoropropyl)lithium to various acyl derivatives was studied. Weinreb and morpholine amides led to polyfluoro ketones in high to quantitative yields in short reaction times. Derivatives of 2-fluorocarboxylic acids may produce 1,1,1,2,2,4-hexafluoro ketones and 1,1,1,2,2,3,3,5-octafluoro ketones. The methodology can provide inhibitors for various lipolytic enzymes, including phospholipase $A_2$.

In contemporary medicinal chemistry, fluorine substituents have gained special attention since they may affect either the drug metabolic stability or the binding affinity in protein−ligand complexes.[1,2] The latter can be a direct effect by interaction of the fluorine with the protein, or an indirect effect by modulation of the polarity of other groups of the ligand that interact with the protein. Since the early report on the design of di- and trifluoromethyl ketones as inhibitors of serine proteases,[3] a great variety of trifluoromethyl ketones have been synthesized and studied as inhibitors of various enzymes.[4] Furthermore, peptidyl pentafluoroethyl ketones have been reported to inhibit various enzymes, for example, elastase[5] and hepatitis C virus N53 protease.[6,7] Some fluoroketone inhibitors of proteases have entered clinical trials.[8] In the course of our studies for the development of selective inhibitors for the various phospholipase $A_2$ classes,[9] most recently we have found that 1,1,1,2,2-pentafluoro-7-phenylheptan-3-one (FKGK11) is a potent and selective inhibitor of human calcium-independent phospholipase $A_2$ (GVIA iPLA$_2$)[10] that exhibits a very interesting therapeutic activity in experimental autoimmune encephalomyelitis, the animal model of multiple sclerosis, and is a valuable tool to understand the role of intracellular phospholipase $A_2$ in peripheral nerve injury.[11] Since we have observed that the pentafluoroethyl ketone functionality favors GVIA iPLA$_2$ inhibition, we were interested in developing synthetic methods leading to the synthesis of FKGK11 and other related pentafluoroethyl ketones in high yields. In the present work, we present our studies on the synthesis of pentafluroethyl and heptafluoropropyl ketones through the nucleophilic addition of organolithium reagents to various acyl derivatives.

The synthesis of 1,1,1,2,2-pentafluoro-7-phenylheptan-3-one[10] was accomplished by conversion of 5-phenylpentanoic acid to the corresponding chloride followed by treatment with pentafluoropropionic anhydride in the presence of pyridine, according to a method[12] widely used for the synthesis of trifluoromethyl ketones. However, this method led to a moderate yield.[10] In literature, methods for the synthesis of pentafluoroethyl ketones include the treatment of phosphonium ylides with perfluoroalkyl anhydrides[13] or esters,[14] the addition of phenyllithium to ethyl pentafluoroacetate,[15] and the addition of (pentafluoroethyl)lithium to an aldehyde followed by oxidation.[16] Gassman has shown that (pentafluoroethyl)lithium adds to aldehydes and ketones producing the corresponding secondary and tertiary alcohols in high yields, while in the case of esters either ketones or tertiary alcohols are produced in high yields.[17] Peptidyl pentafluoroethyl ketones have been prepared by treatment of peptidyl Weinreb amides with (pentafluoroethyl)lithium.[5−7,18] The synthesis of peptidyl pentafluoroethyl and heptafluoropropyl ketones through the reaction of peptide esters with (perfluoroalkyl)lithium reagents has also been reported.[19] In addition, trifluoromethyl and pentafluoroethyl ketones have

(1) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.
(2) Bohm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643.
(3) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813–1817.
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(5) Angelastro, M. R.; Baugh, L. E.; Bey, P.; Burkhart, J. P.; Chen, T.-M.; Durham, S. L.; Hare, C. M.; Huber, E. W.; Janusz, M. J.; Koehl, J. R.; Marquart, A. L.; Mehdi, S.; Peet, N. P. *J. Med. Chem.* **1994**, *37*, 4538–4554.
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(7) Perni, R. B.; Pitlik, J.; Britt, S. D.; Court, J. J.; Courtney, L. F.; Deininger, D. D.; Farmer, L. J.; Gates, C. A.; Harbeson, S. L.; Levin, R. B.; Lin, C.; Lin, K.; Moon, Y.-C.; Luong, Y.-P.; O'Malley, E. T.; Rao, B. G.; Thomson, J. A.; Tung, R. D.; Van Drie, J. H.; Wei, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1441–1446.
(8) For a review see: Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341.
(9) Six, D. A.; Barbayianni, E.; Loukas, V.; Constantinou-Kokotou, V.; Hadjipavlou-Litina, D.; Stephens, D.; Wong, A. C.; Magrioti, V.; Moutevelis-Minakakis, P.; Baker, S.; Dennis, E. A.; Kokotos, G. *J. Med. Chem.* **2007**, *50*, 4222–4235, and references cited therein.
(10) Baskakis, C.; Magrioti, V.; Cotton, N.; Stephens, D.; Constantinou-Kokotou, V.; Dennis, E. A.; Kokotos, G. *J. Med. Chem.* Submitted for publication.
(11) Lopez-Vales, R.; Navarro, X.; Shimizu, T.; Baskakis, C.; Kokotos, G.; Constantinou-Kokotou, V.; Stephens, D.; Dennis, E. A.; David, S. *Brain*. doi 10.1093/brain/awn188.
(12) Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573–2584.
(13) Qui, W. M.; Shen, Y. C. *J. Fluorine Chem.* **1988**, *38*, 249–256.
(14) Begue, J. P.; Bonnet-Delpon, D.; Mesureur, D.; Nee, G.; Wu, S. W. *J. Org. Chem.* **1992**, *57*, 3807–3814.
(15) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1981**, *18*, 117–129.
(16) Ueda, T.; Kam, C.-M.; Powers, J. C. *Biochem. J.* **1990**, *265*, 539–545.
(17) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481–2490.
(18) Angelastro, M. R.; Burkhart, J. P.; Bay, P.; Peet, N. P. *Tetrahedron Lett.* **1992**, *33*, 3265–3268.
(19) Cregge, R. J.; Curran, T. T.; Metz, W. A. *J. Fluorine Chem.* **1998**, *88*, 71–77.

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been synthesized by treatment of the lithium salts of tetrapeptides with perfluoroalkyl anhydrides.[20] Thus, we decided to study the reaction of (pentafluoroethyl)lithium and (heptafluoropropyl)lithium with various acyl derivatives, including unactivated and activated esters, acyl fluoride, anhydrides, and amides.

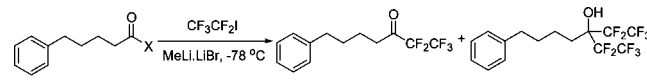
5-Phenylpentanoic acid was chosen as a model substrate and was converted into the corresponding fluoride, pentafluorophenyl ester, Weinreb amide, and morpholine amide according to known methods. The symmetric anhydride of 5-phenylpentanoic acid as well as the mixed anhydride with monoisobutyl carbonate were prepared and used in situ. In all cases organolithium reagents were prepared in situ by reaction of pentafluoroethyl or heptafluoropropyl iodide with MeLi·LiBr at −78 °C. The results of the addition of (pentafluoroethyl)lithium on the various acyl derivatives are summarized in Table 1.

The methyl ester of 5-phenylpentanoic acid led to a separable mixture (approximately equimolar) of the corresponding ketone **2** and the tertiary alcohol **3** after 30 min (entry 1, Table 1), whereas prolonged reaction time led exclusively to tertiary alcohol **3** (entry 2, Table 1). Direct reaction of the carboxylic acid with (pentafluoroethyl)lithium produced ketone **2** as a sole product in low yield, only after 20 h (entries 3 and 4, Table 1). Activated pentafluorophenyl ester gave tertiary alcohol **3** in high yield, even after 3 min (entries 5 and 6, Table 1). After 90 min, alcohol **3** was obtained from acyl fluoride, whereas in short reaction time the conversion was low and a negligible amount of ketone **2** was isolated (entries 7 and 8, Table 1). Symmetric anhydride led to mixtures of **2** and **3** after either 90 or 20 min (entries 9 and 10, Table 1).

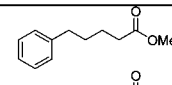
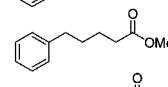
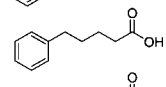
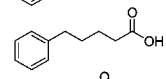
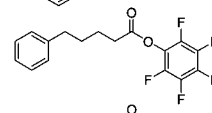
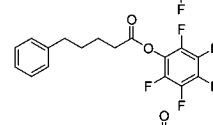
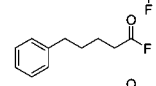
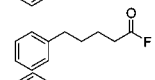
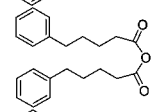
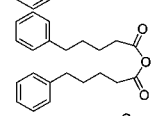
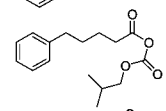
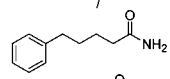
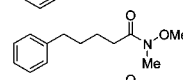
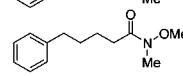
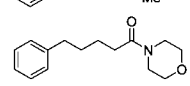
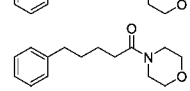
Mixed anhydride led again to a mixture of products (entry 11, Table 1). Primary amide was unable to react within a short time (entry 12, Table 1); however, both Weinreb amide and morpholine amide led to the desired product. Ketone **2** was isolated in almost quantitative yield after 60 to 90 min (entries 13 and 14, Table 1). Also, morpholine amide led to ketone in high yield after 60 min, while prolonged reaction time has as a result the decrease of ketone yield, accompanied by an amount of alcohol **3** (entries 15 and 16, Table 1). As expected, Weinreb and morpholine functionalities stabilize via chelation of the tetrahedral intermediate leading to polyfluoro ketones.

To extend the substrate scope, we studied the reaction of five different amide substrates. Both Weinreb and morpholine amides of oleic acid gave the corresponding ketone **5** in excellent yields in 60 min (entries 1 and 2, Table 2). In the same reaction time, the Weinreb amide of cinnamic acid produced the corresponding ketone in 74% yield. It should be noticed that in the case of α,β-unsaturated carboxylic acids, the synthesis of the corresponding polyfluoro ketones by the general method[12] consisting of the conversion of the acid to chloride and treatment with perfluoroalkyl anhydride is not feasible. We also studied the reaction of amides of 5-(4-hexyloxyphenyl)pentanoic acid, because we had observed that the trifluoromethyl ketone corresponding to this chain is a potent inhibitor of both intracellular GIVA $cPLA_2$ and GVIA $iPLA_2$ enzymes.[10] In both cases, the conversion was low within the reaction time studied and ketone **5** was isolated in low yield (entries 4 and 5, Table 2), indicating that longer reaction times have to be explored, depending on the substrate. In all cases of Table 2, no tertiary alcohol was isolated.

**TABLE 1. Nucleophilic Addition of (Pentafluoroethyl)lithium to Various Acyl Derivatives**




1 2 3

| Entry | Substrate | Time (min) | Ketone **2** (%)[a] | Alcohol **3** (%)[a] |
|---|---|---|---|---|
| 1 |  | 30 | 44 | 46 |
| 2 |  | 240 | 0 | 99 |
| 3 |  | 90 | traces | 0 |
| 4 |  | 1200 | 45 | 0 |
| 5 |  | 90 | 0 | 88 |
| 6 |  | 3 | 0 | 84 |
| 7 |  | 90 | 0 | 79 |
| 8 |  | 20 | 7 | 28 |
| 9 |  | 90 | 21 | 42 |
| 10 |  | 30 | 44 | 17 |
| 11 |  | 90 | 25 | 11 |
| 12 |  | 90 | 0 | 0 |
| 13 |  | 90 | 98 | 0 |
| 14 |  | 60 | 99 | 0 |
| 15 |  | 120 | 84 | 14 |
| 16 |  | 60 | 88 | 0 |

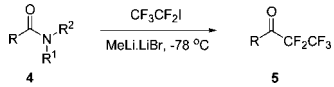
[a] Isolated yield.

On the basis of the successful results described in Table 1, we studied the corresponding reactions with (heptafluoropropyl)lithium. The results in Table 3 show that only Weinreb amides gave excellent yields of the ketones.

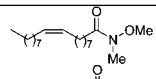
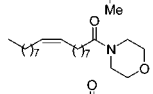
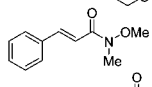
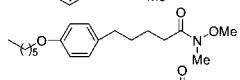
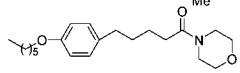
In addition, we studied the synthesis of pentafluoroethyl and heptafluoropropyl ketones through a two-step procedure and the results are summarized in Table 4. Both (pentafluoroethyl)- and (heptafluoropropyl)lithium reacted with 5-phenylpentanal to produce the secondary alcohols **9** in high to quantitative yield (entries 1 and 2, Table 4). Oleyl aldehyde produced the

(20) Jose, B.; Oniki, Y.; Kato, T.; Nishino, N.; Sumida, Y.; Yoshida, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5343–5346.

**TABLE 2. Nucleophilic Addition of (Pentafluoroethyl)lithium to Various Amide Substrates**

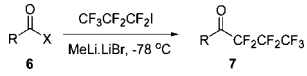



4 5

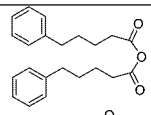
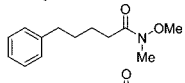
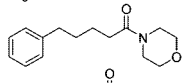
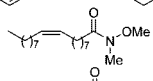
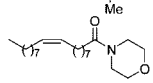
| Entry | Substrate | Time (min) | Ketone **5** (%)[a] |
|---|---|---|---|
| 1 |  | 60 | 86 |
| 2 |  | 60 | 99 |
| 3 |  | 60 | 74 |
| 4 |  | 120 | 44 |
| 5 |  | 150 | 34 |

[a] Isolated yield.

**TABLE 3. Nucleophilic Addition of (Heptafluoropropyl)lithium to Various Acyl Derivatives**



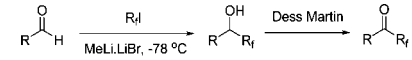

6 7

| Entry | Substrate | Time (min) | Ketone **7** (%)[a] |
|---|---|---|---|
| 1 |  | 60 | 12 |
| 2 |  | 90 | 99 |
| 3 |  | 90 | 54 |
| 4 |  | 90 | 84 |
| 5 |  | 90 | 68 |

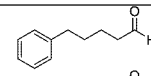
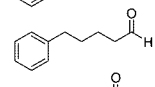
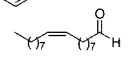
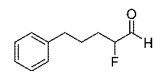
[a] Isolated yield.

corresponding secondary alcohol (entry 3, Table 4). In the case of 2-fluoro-5-phenylpentanal, alcohol **9** was obtained in a short reaction time (entry 4, Table 4). All the secondary alcohols **9** were converted to the desired polyfluoro ketones in high yields by Dess-Martin oxidation (Table 4). 1,1,1,2,2,4-Hexafluoro ketones and 1,1,1,2,2,3,3,5-octafluoro ketones may present special interest as potential enzyme inhibitors and to our knowledge such polyfluoro ketones have not been synthesized and studied up to now. To this end, we studied the addition of (perfluoroalkyl)lithium reagents to Weinreb and morpholine amides of 2-fluoro-5-phenylpentanoic acid. Both amides gave the desired ketones in high yields in 30 to 60 min (entries 1, 2, and 3, Table 5). Even 2-fluoro carboxylic acid was converted to polyfluoro ketone **11** in moderate yield after 4 h. It should be noticed that a 2-fluoro carboxylic acid cannot be converted into the corresponding pentafluoroethyl ketone by conversion to chloride followed by treatment with pentafluoropropionic anhydride in the presence of pyridine, probably because the intermediate ketene required for such a transformation[12] cannot be formed.

**TABLE 4. Nucleophilic Addition of (Perfluoroalkyl)lithium to Aldehydes**

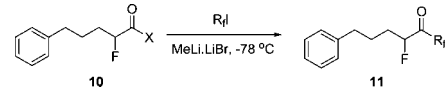



8 9

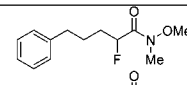
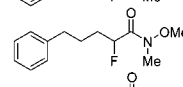
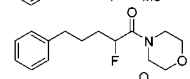
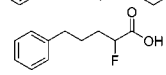
| Entry | Substrate | $R_f$ | Time (min) | Alcohol **9** (%)[a] | Ketone (%)[a] |
|---|---|---|---|---|---|
| 1 |  | $CF_3CF_2$ | 90 | 98 | 87 |
| 2 |  | $CF_3CF_2CF_2$ | 90 | 85 | 86 |
| 3 |  | $CF_3CF_2$ | 90 | 78 | 81 |
| 4 |  | $CF_3CF_2$ | 15 | 73 | 84 |

[a] Isolated yield.

**TABLE 5. Nucleophilic Addition of (Perfluoroalkyl)lithium to α-Fluoro Acyl Derivatives**




10 11

| Entry | Substrate | $R_f$ | Time (min) | Ketone **11** (%)[a] |
|---|---|---|---|---|
| 1 |  | $CF_3CF_2$ | 60 | 91 |
| 2 |  | $CF_3CF_2CF_2$ | 60 | 71 |
| 3 |  | $CF_3CF_2$ | 30 | 68 |
| 4 |  | $CF_3CF_2$ | 240 | 49 |

[a] Isolated yield.

In conclusion, we studied the addition of (pentafluoroethyl)- and (heptafluoropropyl)lithium to various acyl derivatives and we ended up with Weinreb and morpholine amides leading to polyfluoro ketones in high to quantitative yields in short reaction times. A synthetic protocol leading to FKGK11 and related compounds in high yields was developed and new hexafluoro and octafluoro ketones were prepared via (perfluoroalkyl)lithium reagents. Thus, the present study provides methodology for the synthesis of potential inhibitors for phospholipase $A_2$ and other lipolytic enzymes, like, for example the enzymes involved in the endocannabinoid system.

## Experimental Section

**General Procedure for the (Perfluoroalkyl)lithium Addition to Carbonyl Compounds.** To a stirring solution of acyl derivative (0.36 mmol) in $Et_2O$ (5 mL) at −78 °C was added pentafluoroiodoethane (1.80 mmol) or heptafluoroiodopropane (1.80 mmol) followed by dropwise addition of a MeLi·LiBr solution 1.6 M in ether (1.80 mmol). The reaction mixture was stirred at −78 °C and monitored by TLC. Once the reaction was finished, the reaction mixture was poured into $H_2O$ and acidified with a 10% solution of $KHSO_4$ (pH 5). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with a 5% solution of $NaHCO_3$ (40 mL) and dried over $MgSO_4$.

The organic solvent was evaporated in vacuo and the residue was purified, when needed, by column chromatography, eluting with the appropriate petroleum ether (40−60 °C):EtOAc mixture.

**1,1,1,2,2-Pentafluoro-7-phenylheptan-3-one.**[10] $R_f$ 0.60 (EtOAc−petroleum ether 5:95); IR (KBr) 1760 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.37−7.09 (5H, m), 2.79 (2H, t, $J$ = 6.2 Hz), 2.67 (2H, t, $J$ = 6.6 Hz), 1.79−1.59 (4H, m); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 194.2 (t, $J$ = 26.0 Hz), 141.6, 128.4, 128.3, 125.9, 117.8 (qt, $J$ = 287.0, 34.0 Hz), 106.8 (tq, $J$ = 267.0, 38.0 Hz), 37.1, 35.5, 30.3, 21.9; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −17.2 (3F, s), −58.6 (2F, s); MS (ESI) $m/z$ (%) 279 ($M^-$, 27), 119 ($C_2F_5^-$, 100).

**1,1,1,2,2-Pentafluoro-7-icos-11-en-3-one.** $R_f$ 0.90 (EtOAc:petroleum ether 3:7); IR (KBr) 1756 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.41−5.21 (2H, m), 2.73 (2H, t, $J$ = 7.0 Hz), 2.07−1.91 (4H, m), 1.74−1.59 (2H, m), 1.41−1.15 (20H, m), 0.87 (3H, t, $J$ = 6.2 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 194.6 (t, $J$ = 26.5 Hz), 130.2, 129.8, 118.1 (qt, $J$ = 284.9, 34.1 Hz), 107.1 (tq, $J$ 264.8, 37.5 Hz), 37.5, 32.1, 30.0, 29.9, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.4, 27.3, 22.9, 22.5, 14.2; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −17.3 (3F, s), −58.7 (2F, s); MS (ESI) $m/z$ (%) 383 ($M^-$, 89), 119 ($C_2F_5^-$, 100). Anal. Calcd for $C_{20}H_{33}F_5O$: C, 62.48; H, 8.65. Found: C, 62.32; H, 8.84.

**1,1,1,2,2-Pentafluoro-7-(4-hexyloxyphenyl)heptan-3-one.** $R_f$ 0.90 (EtOAc:petroleum ether 3:7); IR (KBr) 1755 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.06 (2H, d, $J$ = 8.4 Hz), 6.83 (2H, d, $J$ = 8.4 Hz), 3.93 (2H, t, $J$ = 6.6 Hz), 2.75 (2H, t, $J$ = 6.6 Hz), 2.58 (2H, t, $J$ = 6.2 Hz), 1.81−1.57 (6H, m), 1.55−1.21 (6H, m), 0.91 (3H, t, $J$ = 6.8 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 194.5 (t, $J$ = 26.5 Hz), 157.7, 133.7, 129.4, 118.1 (qt, $J$ = 285.3, 33.7 Hz), 114.7, 107.1 (tq, $J$ = 265.2, 37.9 Hz), 68.2, 37.4, 34.8, 31.8, 30.8, 29.5, 26.0, 22.8, 22.1, 14.3; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −17.2 (3F, s), −58.6 (2F, s); MS (ESI) $m/z$ (%) 379 ($M^-$, 100), 119 ($C_2F_5^-$, 26). Anal. Calcd for $C_{19}H_{25}F_5O_2$: C, 59.99; H, 6.62. Found: C, 59.78; H, 6.83.

**1,1,1,2,2,3,3-Heptafluoro-8-phenyloctan-4-one.** $R_f$ 0.60 (EtOAc:petroleum ether 5:95); IR (KBr) 1732 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.33−7.12 (5H, m), 2.77 (2H, t, $J$ = 6.2 Hz), 2.66 (2H, t, $J$ = 6.6 Hz), 1.76−1.57 (4H, m); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 193.9 (t, $J$ = 26.0 Hz), 141.6, 128.4, 128.3, 125.9, 128.2−103.3 (m), 37.7, 35.4, 30.3, 21.9; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −15.9 (3F, t, $J$ = 9.0 Hz), −56.5 (2F, m), −62.0 (2F, s); MS (ESI) $m/z$ (%) 329 ($M^-$, 100), 169 ($C_3F_7^-$, 62). Anal. Calcd for $C_{14}H_{13}F_7O$: C, 50.92; H, 3.97. Found: C, 50.69; H, 4.16.

**1,1,1,2,2,3,3-Heptafluoro-8-henicos-12-en-4-one.** $R_f$ 0.85 (EtOAc:petroleum ether 3:7); IR (KBr) 1735 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.38−5.24 (2H, m), 2.72 (2H, t, $J$ = 7.0 Hz), 2.11−1.85 (4H, m), 1.71−1.56 (2H, m), 1.43−1.03 (20H, m), 0.86 (3H, t, $J$ = 6.2 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 194.4 (t, $J$ = 25.4 Hz), 130.3, 129.8, 129.8−102.8 (m), 38.1, 32.1, 30.0, 29.9, 29.8, 29.7, 29.5, 29.3, 29.2, 28.9, 27.4, 27.3, 22.9, 22.6, 14.3; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −15.9 (3F, t, $J$ = 9.1 Hz), −56.5 (2F, m), −62.0 (2F, s); MS (ESI) $m/z$ (%) 433 ($M^-$, 9), 169 ($C_3F_7^-$, 100). Anal. Calcd for $C_{21}H_{33}F_7O$: C, 58.05; H, 7.66. Found: C, 57.88; H, 7.94.

**1,1,1,2,2,3,3,5-Octafluoro-8-phenyloctan-4-one.** $R_f$ 0.75 (EtOAc:petroleum ether 3:7); IR (KBr) 1766 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.38−7.03 (5H, m), 5.25 (1H, ddd, $J$ = 48.0, 8.2, 3.9 Hz), 2.68 (2H, m), 2.01−1.75 (4H, m); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 190.5 (ddd, $J$ = 27.3, 25.6, 22.3 Hz), 141.0, 128.7, 128.6, 126.4, 119.5−105.6 (m), 92.3 (d, $J$ = 186.7 Hz), 35.2, 30.9 (d, $J$ = 21.2 Hz), 26.2; $^{19}F$ NMR (186 MHz, $CDCl_3$) $\delta$ −15.7 (3F, t, $J$ = 8.9 Hz), −54.7 (2F, dq, $J$ = 78.8, 8.9 Hz), −61.3 (2F, d, $J$ = 7.5 Hz), −131.8 (1F, m); MS (ESI) $m/z$ (%) 347 ($M^-$, 100). Anal. Calcd for $C_{14}H_{12}F_8O$: C, 48.29; H, 3.47. Found: C, 48.07; H, 3.59.

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**Supporting Information Available:** Detailed procedures and characterization data for all compounds and $^1H$ and $^{13}C$ NMR spectra for polyfluoro ketones and polyfluoro alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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