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Synthesis of Pentafluorinated β-Hydroxy Ketones

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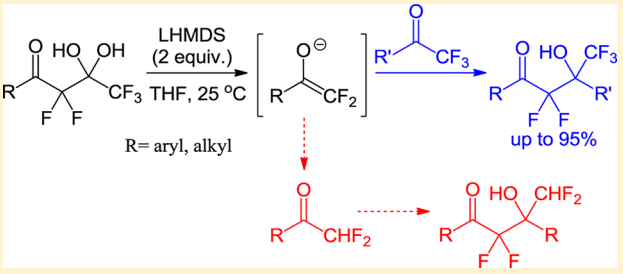
Supporting Information

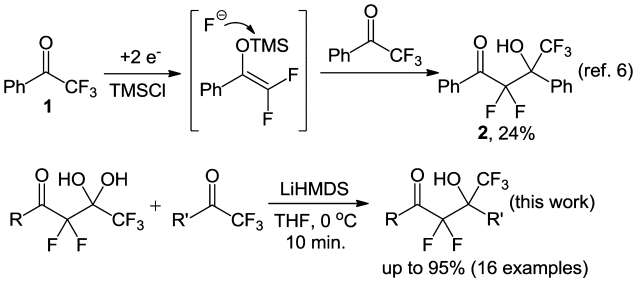
ABSTRACT: The LHMDS-promoted in situ generation of difluoroenolates from readily available 1-aryl and 1-alkyl 2,2,4,4,4-pentafluorobutan-1,3-dione hydrates has been used to produce a series of pentafluorinated β-hydroxy ketones in up to 95% yield. The reaction proceeds under mild conditions, tolerates a wide range of functional groups, and is complete within 10 min. Reduction toward the corresponding 1,3-diol with DIBAL gives quantitative amounts and favors the formation of the *syn*-isomer.



Although few naturally occurring organofluorine compounds are known, about 20% of all pharmaceuticals contain at least one carbon−fluorine bond. In 2011, 30% of the 10 best-selling drugs and 20% of newly approved entities contained fluorine.[1] The steadily growing popularity of fluorinated compounds stems from a variety of beneficial effects of the fluorine moiety on the physiochemical properties and pharmacological profiles of drugs.[2] Fluorine incorporation typically increases a compound's lipophilicity which improves partitioning into membranes and bioavailability.[3] It also enhances oxidative and thermal stability and resistance to metabolic degradation due to the strength of the C−F bond. The placement of more than one fluorine atom at the same site can have dramatic effects on both the structure and function of biologically active compounds. The high electronegativity of fluorine often leads to increased dipole moments, conformational changes, carbonyl hydration, and reduced pK_a values of adjacent functionalities.[4] The difluoromethylene unit has been recognized as a unique electronic mimic and bioisostere of an ether function because it places the two fluorine atoms in the same direction as the lone electron pairs of the ether oxygen and is capable of serving as a weak hydrogen bond acceptor.

The chemistry of trifluoromethyl ketones has received significant attention in recent years which is mostly a consequence of the increasing pharmaceutical utility of organofluorines. Several strategies for the difluoromethylation of aldehydes and ketones, for example with sulfur-derived fluoroalkylating reagents, are known.[5] In contrast, a practical synthetic method for the nucleophilic addition of difluoroenolates to trifluoromethyl ketones,[6] which would provide pentafluorinated β-hydroxy ketones, has not been introduced to date. Uneyama and co-workers were able to produce difluoroenolates via electroreductive defluorination of trifluoromethyl ketones and showed that the silyl enol ether obtained from α,α,α-trifluoroacetophenone, **1**, reacts with another equivalent of **1** to produce 2,2,4,4,4-pentafluoro-3-hydroxy-1,3-diphenylbutan-1-one, **2**, in 24% yield.[7] In a similar two-step synthesis Ishihara et al. prepared **2** in 47% overall yield.[8] Generally, few examples of aldol type reactions with intermediate difluoroenolates have been reported in the literature.[9] Prager and Colby, however, have demonstrated that the mild cleavage of hexafluoroacetone and its derivatives with an excess of base, metal salts, and other additives affords fluorinated nucleophiles suitable for effective carbon−carbon bond formation.[10,11] Encouraged by these findings we have developed a method for the fast and high-yielding synthesis of a wide range of pentafluorinated β-hydroxy ketones that occurs via mild in situ formation of α,α-difluoroenolates (Scheme 1).

Scheme 1. Synthetic Strategies towards Pentafluorinated β-Hydroxy Ketones



As previously demonstrated by Colby, we observed that the hydrate of 1-phenyl-2,2,4,4,4-pentafluorobutan-1,3-dione, **3**, which is easily prepared from diketone **4** by exhaustive fluorination with Selectfluor, undergoes rapid C−C bond scission and concomitant difluoroenolate release when an excess of a base is added.[11] Initial screening of solvent and additives, including a wide range of amines, organolithium reagents, Schwesinger base, and inorganic salts, showed that the pentafluoro β-hydroxy ketone **2** can be obtained in 68% yield within 10 min when the reaction is carried out in the presence of 2 equiv of KHMDS in THF at 0 °C. Because the enolate

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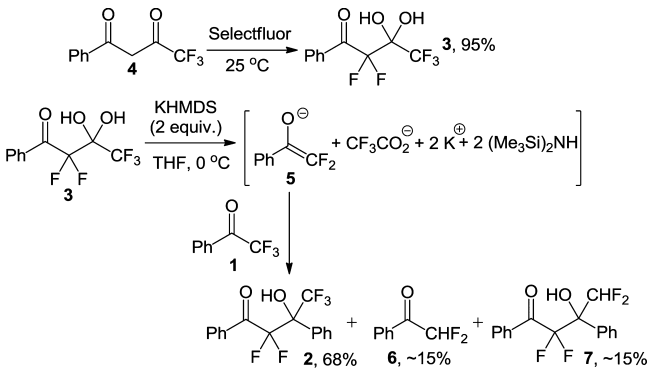
precursor **3** was fully consumed in this reaction we decided to investigate the formation of byproducts. Analysis of the reaction mixture revealed two major byproducts that apparently arise from competing protonation of the intermediate difluoroenolate **5** toward α,α-difluoroacetophenone, **6**, and aldol reaction between **5** and **6** toward the tetrafluorinated hydroxy ketone **7** (Scheme 2).

Scheme 2. Formation of 2 and Byproducts 6 and 7



Fortunately, we observed that the formation of **6** and **7** can be reduced when KHMDS is replaced with LHMDS. Using this base under otherwise identical conditions, the desired product **2** was isolated in 88% yield. We believe that compared to its potassium analogue the use of LHMDS generates a more stable ion pair with the intermediate difluoroenolate **5** and thus impedes protonation toward **6**. Having optimized the base-promoted difluoromethylation protocol by controlling the concentration of **6** which competes with **1** for the reaction with the in situ generated nucleophile **5**, we then continued with the evaluation of the substrate scope (Table 1).

We were pleased to find that a wide range of pentafluorinated β-hydroxy ketones can be generated in very good yields. The employment of enolate precursor **3** and trifluoromethyl ketones **8**, **10**, and **12** in our protocol gave the corresponding products **9**, **11**, and **13** in 85−89% yield (entries 2−4). Similarly, the aldol products **15**, **17**, **19**, **21**, and **23** were obtained from both electron-deficient and -rich ketones **14**, **16**, **18**, **20**, and **22** in 88−95% yield (entries 5−9). The tolerance of several functional groups present in the trifluoromethyl ketones used and the smooth reaction of 2-trifluoroacetyl thiophene, **24**, toward **25** are noteworthy (entry 10). Alternatively, other enolate precursors such as **26** and **28** can be used without compromising the results (entries 12 and 13). When we attempted to use 1,1,1-trifluoro-3-phenylpropan-2-one, **30**, which is highly prone to enolization, we observed a dramatic decrease in yield due to the side reaction discussed above (Scheme 2). A change in the addition sequence or addition of lithium salts did not increase yields with this aliphatic trifluoromethyl ketone. Addition of cerium(III) chloride, however, improved the yields, and we were finally able to prepare **31** in 63% yield (entry 13). As expected, the use of aliphatic enolate precursor **32** is not problematic and the reaction with ketones **1**, **8**, and **14** produced pentafluorinated β-hydroxy ketones **33**−**35** in 84−93% yield (entries 14−16).

The pentafluorinated β-hydroxy ketone **2** can be effectively reduced to 2,2,4,4,4-pentafluoro-1,3-diphenyl-1,3-butanediol, **36**. We first observed that heterogeneous hydrogenation with 10 mol % palladium on carbon affords the 1,3-diol in quantitative yields as a 1:1 *syn*/*anti*-mixture.[12] Following a procedure previously developed by Kuroboshi and Ishihara,[13] we were able to improve the stereoselectivity using DIBAL and produced the two diastereomers in a 3.1:1 ratio in an overall 98% yield (Scheme 3).[14] We were able to grow a single crystal of the minor isomer by slow evaporation of a solution in chloroform. Crystallographic analysis proved that it was *anti*-**36** (see Supporting Information).

In summary, we have developed an LHMDS-promoted aldol reaction that utilizes readily available difluoroenolate precursors for fast addition reactions with trifluoromethyl ketones under mild conditions. The careful in situ generation of difluoroenolates provides superior results compared to previously reported methods and provides practical access to a series of new pentafluoro β-hydroxy ketones. With the exception of aliphatic substrates, the yields generally range from 83 to 95% and the reaction tolerates several functional groups. The use of enolizable trifluoromethyl ketones is possible in the presence of cerium chloride, but yields drop significantly due to the increased protonation of the intermediate difluoroenolate and subsequent aldol reaction of the corresponding difluoromethyl ketone. The feasibility of diastereoselective quantitative reduction of these unprecedented ketones with DIBAL favoring formation of pentafluorinated *syn*-1,3-diols has also been demonstrated.

EXPERIMENTAL SECTION

General Methods. All commercially available reagents and solvents were used without further purification. Anhydrous THF was used as purchased and not dried any further. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 32−63 μm).

General Procedure for the Preparation of Pentafluoro β-Hydroxy Ketones. To a solution of LiHMDS (0.8 mL, 1.0 M in THF, 0.8 mmol) was added 1 mL of anhydrous THF under nitrogen at 0 °C. Then, a solution of the enolate precursor (0.4 mmol) and the trifluoromethyl ketone (1.2 equiv, 0.48 mmol) dissolved in 1.5 mL of THF was added dropwise, and the mixture was stirred at room temperature for 10 min. After completion of the reaction, several drops of saturated ammonium chloride solution were added. The solvents were removed, and the crude residue was loaded directly onto a silica gel column and purified by flash chromatography as described below.

Preparation of 1-Phenyl-2,2,4,4,4-pentafluorobutan-1,3-dione, 3.[11] To a solution of diketone **4** (4.32 g, 20 mmol) in 40 mL of acetonitrile was added Selectfluor (15.576 g, 2.2 equivalents, 44 mmol) under a nitrogen atmosphere at room temperature. The mixture was stirred overnight and then filtrated and washed with dichloromethane. The solvents were removed, and the residue was dissolved in dichloromethane and extracted with brine. The combined organic layers were concentrated in vacuum. Purification by column chromatography using EtOAc/hexanes = 1:3 as the mobile phase gave 1-phenyl-2,2,4,4,4-pentafluorobutan-1,3-dione, **3** (5.157 g, 19.1 mmol), in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.57 (s, 2H), 7.54 (dd, J = 7.9 Hz, 7.9 Hz, 2H), 7.72 (dd, J = 7.5 Hz, 7.5 Hz, 1H), 8.10 (d, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 92.8 (m), 111.5 (t, J_{C-F} = 268.6 Hz), 117.3 (q, J_{C-F} = 288.4 Hz), 128.8, 130.5, 131.6, 135.6, 191.6 (t, J_{C-F} = 29.1 Hz).

Reduction Procedure. A solution of **2** (99 mg, 0.3 mmol) in 2 mL of anhydrous THF was cooled to −78 °C. Then, DIBAL (1.0 M in THF, 0.9 mL, 0.9 mmol) was added dropwise and the mixture was stirred at this temperature for 1 h. After completion of the reaction, several drops of saturated ammonium chloride solution were added and the mixture was allowed to come to room temperature. The solvents were removed, and the residue was dissolved in dichloromethane and extracted with brine. The combined organic layers were concentrated in vacuo. Column chromatography using dichloromethane/hexanes = 3:2 as the

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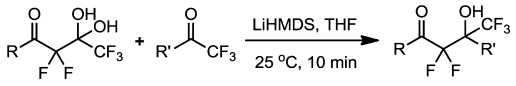
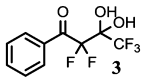
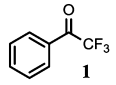
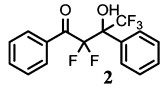
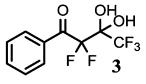
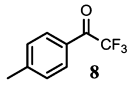
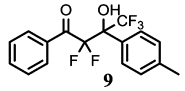
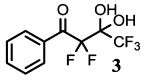
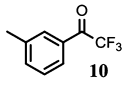
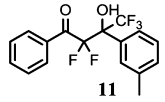
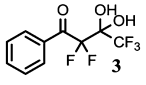
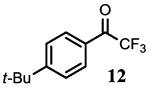
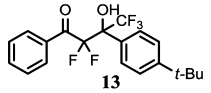
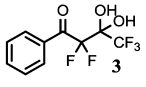
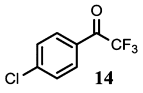
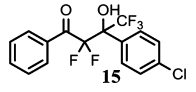
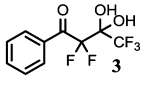
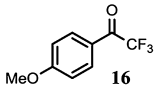
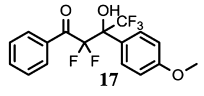
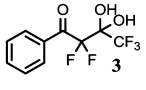
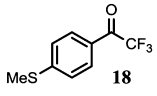
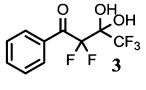
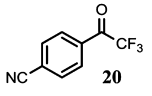
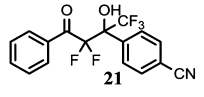
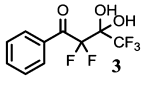
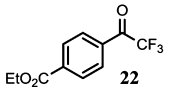
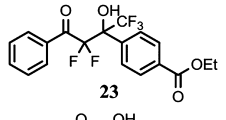
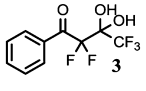
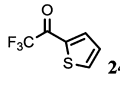
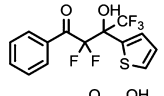
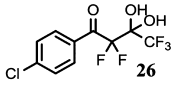
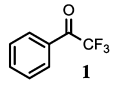
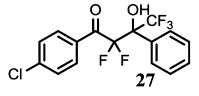
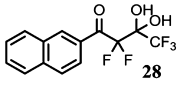
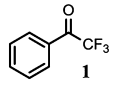
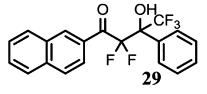
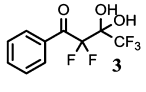
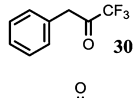
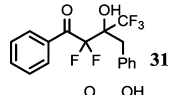
Table 1. Transformation of Trifluoromethyl Ketones to Pentafluorinated β-Hydroxy Ketones



Entry	Enolate Precursor	Ketone	Product	Yield[a]
1	 **3**	 **1**	 **2**	88
2	 **3**	 **8**	 **9**	85
3	 **3**	 **10**	 **11**	88
4	 **3**	 **12**	 **13**	89
5	 **3**	 **14**	 **15**	94
6	 **3**	 **16**	 **17**	88
7	 **3**	 **18**	 **19**	93
8	 **3**	 **20**	 **21**	92
9	 **3**	 **22**	 **23**	95
10	 **3**	 **24**	 **25**	83
11	 **26**	 **1**	 **27**	95
12	 **28**	 **1**	 **29**	93
13	 **3**	 **30**	 **31**	63[b]
14	**32**	**1**	**33**	93
15	**32**	**8**	**34**	86
16	**32**	**14**	**35**	84

[a]Isolated yields. [b]2 equiv of **30** and 2 equiv of $CeCl_3$ were used.

mobile phase gave 74 mg (0.23 mmol) of *syn*-**36** and 24 mg (0.08 mmol) of *anti*-**36** as colorless solids in 98% overall yield.

2,2,4,4,4-Pentafluoro-3-hydroxy-1,3-diphenylbutan-1-one, 2.[7] Chromatographic purification (EtOAc/hexanes = 1:10) gave 123

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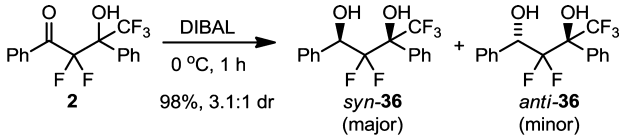
Scheme 3. DIBAL Reduction of 2



mg (0.37 mmol, 93%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.84 (s, 1H), 7.35−7.45 (m, 5H), 7.60 (dd, J = 7.4 Hz, 7.4 Hz, 1H), 7.70−7.74 (m, 2H), 8.04 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 79.0 (m), 113.9 (t, J_{C-F} = 269.1 Hz), 123.3 (q, J_{C-F} = 287.9 Hz), 127.0, 128.4, 128.7, 129.7, 130.1, 131.5, 132.3, 134.9, 190.8 (t, J_{C-F} = 30.2 Hz).

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-tolyl)-1-phenylbutan-1-one, 9. Chromatographic purification (DCM/hexanes = 1:4 to 1:2) gave 117 mg (0.34 mmol, 85%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 4.77 (s, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 8.1 Hz, 8.1 Hz, 2H), 7.57−7.92 (m, 3H), 7.92 (d, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.0, 78.5 (m), 113.8 (t, J_{C-F} = 269.0 Hz), 123.4 (q, J_{C-F} = 287.6 Hz), 126.8, 128.5, 128.6, 129.2, 130.3, 132.4, 134.9, 139.7, 190.8 (t, J_{C-F} = 29.4 Hz). Anal. Calcd for $C_{17}H_{13}F_5O_2$: C, 59.31; H, 3.81. Found: C, 59.26; H, 3.77.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(3-tolyl)-1-phenylbutan-1-one, 11. Chromatographic purification (DCM:hexanes =1:4 to 2:3) gave 121 mg (0.35 mmol, 88%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 4.78 (s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.26 (dd, J = 7.7 Hz, 7.7 Hz, 1H), 7.41 (ddd, J = 1.5 Hz, 7.6 Hz, 7.6 Hz, 2H), 7.48−7.54 (m, 2H), 7.69 (dddd, J = 1.2 Hz, 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H), 7.89 (dd, J = 1.2 Hz, 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 78.8 (m), 114.0 (t, J_{C-F} = 269.1 Hz), 123.1 (q, J_{C-F} = 287.7 Hz), 124.0, 127.6, 128.3, 128.7, 130.2, 130.5, 131.4, 132.4, 134.9, 138.2, 190.8 (t, J_{C-F} = 29.3 Hz). Anal. Calcd for $C_{17}H_{13}F_5O_2$: C, 59.31; H, 3.81. Found: C, 59.14; H, 3.62.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-*tert*-butylphenyl)-1-phenylbutan-1-one, 13. Chromatographic purification (DCM/hexanes = 1:4 to 1:1) gave 137 mg (0.36 mmol, 89%) of a white solid, mp 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.29 (s, 9H), 4.76 (s, 1H), 7.35−7.40 (m, 4H), 7.57 (dd, J = 7.5 Hz, 7.5 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 31.1, 34.5, 78.5 (m), 114.3 (t, J_{C-F} = 268.8 Hz), 123.4 (q, J_{C-F} = 287.7 Hz), 125.4, 126.7, 128.3, 128.6, 130.1, 132.5, 134.7, 152.7, 190.7 (t, J_{C-F} = 29.1 Hz). Anal. Calcd for $C_{20}H_{19}F_5O_2$: C, 62.17; H, 4.96. Found: C, 61.78; H, 5.04.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-chlorophenyl)-1-phenylbutan-1-one, 15. Chromatographic purification (DCM:hexanes =1:5 to 1:1) gave 137 mg (0.38 mmol, 94%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.01 (s, 1H), 7.36 (ddd, J = 2.1 Hz, 2.1 Hz, 8.9 Hz, 2H), 7.45 (dd, J = 7.8 Hz, 7.8 Hz, 2H), 7.62−7.69 (m, 3H), 7.94 (dd, J = 1.2 Hz, 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 78.6 (m), 113.5 (t, J_{C-F} = 268.2 Hz), 123.1 (q, J_{C-F} = 289.3 Hz), 128.6, 128.8, 129.5, 130.0, 132.2, 132.0, 135.2, 136.1, 189.9 (t, J_{C-F} = 29.4 Hz). Anal. Calcd for $C_{16}H_{10}ClF_5O_2$: C, 52.69; H, 2.76. Found: C, 52.43; H, 2.46.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylbutan-1-one, 17. Chromatographic purification (DCM/hexanes = 2:3) gave 126 mg (0.35 mmol, 88%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.78 (s, 3H), 4.82 (s, 1H), 6.89 (d, J = 9.1 Hz, 2H), 7.42 (dd, J = 8.2 Hz, 8.2 Hz, 2H), 7.58−7.65 (m, 3H), 7.90 (d, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.2, 78.5 (m), 113.8, 113.9 (t, J_{C-F} = 268.8 Hz), 123.2, 123.4 (q, J_{C-F} = 287.6 Hz), 128.4, 128.6, 130.2, 132.4, 134.9, 160.5, 190.9 (t, J_{C-F} = 29.2 Hz). Anal. Calcd for $C_{17}H_{13}F_5O_3$: C, 56.67; H, 3.64. Found: C, 56.72; H, 3.56.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-methylthiophenyl)-1-phenylbutan-1-one, 19. Chromatographic purification (DCM/hexanes = 1:3 to 1:1) gave 140 mg (0.38 mmol, 93%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.45 (s, 3H), 4.87 (s, 1H), 7.23 (d, J = 8.9 Hz, 2H), 7.43 (dd, J = 8.3 Hz, 8.3 Hz, 2H), 7.58−7.64 (m, 3H), 7.91 (dd, J = 1.1 Hz, 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.0, 78.6 (m), 113.8 (t, J_{C-F} = 269.5 Hz), 123.3 (q, J_{C-F} = 287.6 Hz), 125.7, 127.4, 127.8, 128.7, 130.2, 132.3, 135.0, 140.0, 190.8 (t, J_{C-F} = 29.4 Hz). Anal. Calcd for $C_{17}H_{13}F_5O_2S$: C, 54.25; H, 3.48. Found: C, 54.08; H, 3.27.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-cyanophenyl)-1-phenylbutan-1-one, 21. Chromatographic purification (EtOAc/hexanes = 1:8) gave 131 mg (92%, 0.37 mmol) of a white solid, mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.30 (s, 1H), 7.50 (dd, J = 7.6 Hz, 7.6 Hz, 2H), 7.67−7.73 (m, 3H), 7.90 (d, J = 8.4 Hz, 2H), 7.97 (dd, J = 1.1 Hz, 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 78.7 (m), 113.4 (t, J_{C-F} = 268.2 Hz), 113.7, 118.0, 122.9 (q, J_{C-F} = 291.3 Hz), 128.0, 128.9, 130.3, 131.8, 132.0, 135.4, 136.2, 190.2 (t, J_{C-F} = 28.7 Hz). Anal. Calcd for $C_{17}H_{10}F_5NO_2$: C, 57.47; H, 2.84; N, 3.94. Found: C, 57.47; H, 2.88; N, 3.92 .

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(4-ethoxycarbonylphenyl)-1-phenylbutan-1-one, 23. Chromatographic purification (DCM/hexanes = 1:1 to 2:1) gave 152 mg (95%, 0.38 mmol) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.38 (t, J = 7.1 Hz, 3H), 4.37 (q, J = 7.1 Hz, 2H), 5.25 (s, 1H), 7.44 (dddd, J = 1.8 Hz, 1.8 Hz, 7.6 Hz, 7.6 Hz, 2H), 7.62 (dddd, J = 1.2 Hz, 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.94 (dd, J = 1.0 Hz, 8.5 Hz, 2H), 8.06 (ddd, J = 1.9 Hz, 1.9 Hz, 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 61.3, 78.8 (m), 113.5 (t, J_{C-F} = 269.9 Hz), 123.4 (q, J_{C-F} = 287.5 Hz), 127.3, 128.7, 129.4, 130.2, 131.6, 132.1, 135.1, 136.3, 166.0, 190.2 (t, J_{C-F} = 29.4 Hz). Anal. Calcd for $C_{19}H_{15}F_5O_4$: C, 56.72; H, 3.76. Found: C, 56.65; H, 3.49.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-(2-thienyl)-1-phenylbutan-1-one, 25. Chromatographic purification (DCM/hexanes = 1:4 to 1:2) gave 117 mg (0.33 mmol, 83%) of a light yellow solid, mp 59−60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.34 (s, 1H), 7.03 (dd, J = 3.8 Hz, 5.1 Hz, 1H), 7.33 (m, 1H), 7.39 (dd, J = 1.1 Hz, 5.1 Hz, 1H), 7.47 (ddd, J = 1.2 Hz, 7.9 Hz, 7.9 Hz, 2H), 7.65 (ddd, J = 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H), 7.99 (dd, J = 1.2 Hz, 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 78.5 (m), 112.7 (t, J_{C-F} = 268.0 Hz), 123.7 (q, J_{C-F} = 287.5 Hz), 127.4, 127.7, 128.8, 130.0, 132.0, 134.8, 135.2, 191.3 (t, J_{C-F} = 29.3 Hz). Anal. Calcd for $C_{14}H_9F_5O_2S$: C, 50.00; H, 2.70. Found: C, 50.05; H, 2.52.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-phenyl-1-(4-chlorophenyl)butan-1-one, 27. Chromatographic purification (EtOAc/hexanes = 1:20 to 1:10) gave 138 mg (0.38 mmol, 95%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.65 (s, 1H), 7.35−7.40 (m, 5H), 7.70 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 78.6 (m), 114.2 (t, J_{C-F} = 268.8 Hz), 123.3 (q, J_{C-F} = 287.6 Hz), 126.9, 128.5, 129.1, 129.9, 130.6, 131.2, 131.6, 141.8, 189.1 (t, J_{C-F} = 29.4 Hz). Anal. Calcd for $C_{16}H_{10}ClF_5O_2$: C, 52.69; H, 2.76. Found: C, 52.53; H, 2.48.

2,2,4,4,4-Pentafluoro-3-hydroxy-3-phenyl-1-(2-naphthyl)-butan-1-one, 29. Chromatographic purification (DCM/hexanes = 1:3 to 1:1) gave 142 mg (0.37 mmol, 93%) of a light yellow solid, mp 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.93 (s, 1H), 7.35−7.39 (m, 3H), 7.53 (ddd, J = 1.2 Hz, 6.9 Hz, 6.9 Hz, 1H), 7.61 (ddd, J = 1.2 Hz, 6.9 Hz, 6.9 Hz, 1H), 7.75−7.89 (m, 6H), 8.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 79.0 (m), 114.2 (t, J_{C-F} = 269.2 Hz), 123.3 (q, J_{C-F} = 287.4 Hz), 124.9, 127.0, 127.2, 127.7, 128.5, 128.6, 129.4, 129.7, 129.9, 130.2, 131.7, 132.0, 133.4, 136.2, 190.5 (t, J_{C-F} = 29.0 Hz). Anal. Calcd for $C_{20}H_{13}F_5O_2$: C, 63.16; H, 3.45. Found: C, 63.15; H, 3.26.

2,2-Difluoro-3-hydroxy-1,4-diphenyl-3-trifluoromethylbutan-1-one, 31. Procedure was the same as that described above, but 2 equiv of $CeCl_3$ were added prior to LHMDS and 2 equiv of the trifluoromethyl ketone were used. Chromatographic purification (EtOAc/hexanes = 1:20) gave 86 mg (0.25 mmol, 63%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.31 (d, J = 14.5 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 4.33 (s, 1H), 7.28−7.34 (m, 5H), 7.45−7.52 (m, 2H), 7.65 (dddd, J = 1.2 Hz, 1.2 Hz, 7.5 Hz, 7.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 35.5, 78.3 (m), 114.0 (t, J_{C-F} = 264.4 Hz), 124.3 (q, J_{C-F} = 288.5 Hz), 127.7, 128.5, 128.6, 130.4, 131.3, 132.2, 132.5, 134.8, 191.1 (t, J_{C-F} = 28.2 Hz). Anal. Calcd for $C_{17}H_{13}F_5O_2$: C, 59.31; H, 3.81. Found: C, 59.11; H, 3.94.

1,1,1-3,3-Pentafluoro-2-hydroxy-2,6-diphenylhexan-4-one, 33. Chromatographic purification (EtOAc/hexanes = 1:10) gave 134 mg (0.37 mmol, 93%) of a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.35−2.85 (m, 3H), 2.95 (m, 1H), 4.33 (s, 1H), 7.04 (d, J = 7.6 Hz, 2H), 7.16−7.28 (m, 3H), 7.38−7.47 (m, 3H), 7.68 (d, J = 7.3 Hz, 2H).

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^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.2, 40.0, 77.8 (m), 111.9 (t, J_{C-F} = 267.4 Hz), 123.3 (q, J_{C-F} = 287.8 Hz), 126.5, 126.7, 128.2, 128.5, 128.6, 130.0, 130.3, 139.5, 200.3 (t, J_{C-F} = 29.1 Hz). Anal. Calcd for $C_{18}H_{15}F_5O_2$: C, 60.34; H, 4.22. Found: C, 60.12; H, 4.13.

1,1,1-3,3-Pentafluoro-2-hydroxy-2-(4-tolyl)-6-phenylhexan-4-one, 34. Chromatographic purification (EtOAc/hexanes = 1:20 to 1:10) gave 128 mg (0.34 mmol, 86%) of a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 2.63−2.80 (m, 3H), 2.92 (m, 1H), 4.29 (s, 1H), 7.02 (d, J = 7.2 Hz, 2H), 7.15−7.26 (m, 5H), 7.54 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2, 28.2, 40.0, 77.8 (m), 112.8 (t, J_{C-F} = 267.2 Hz), 123.3 (q, J_{C-F} = 287.9 Hz), 126.4, 126.8, 127.5, 128.2, 128.5, 129.4, 139.6, 140.1, 200.2 (t, J_{C-F} = 28.7 Hz). Anal. Calcd for $C_{19}H_{17}F_5O_2$: C, 61.29; H, 4.60. Found: C, 61.22; H, 4.79.

1,1,1-3,3-Pentafluoro-2-hydroxy-2-(4-chlorophenyl)-6-phenylhexan-4-one, 35. Chromatographic purification (EtOAc/hexanes = 6.7%) gave 132 mg (0.34 mmol, 84%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.75−2.87 (m, 3H), 2.99 (m, 1H), 4.53 (s, 1H), 7.05 (d, J = 6.6 Hz, 2H), 7.18−7.30 (m, 3H), 7.34−7.39 (m, 2H), 7.60 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.2, 40.0, 77.5 (m), 112.0 (t, J_{C-F} = 267.2 Hz), 123.1 (q, J_{C-F} = 289.7 Hz), 123.1, 126.5, 128.2, 128.5, 128.6, 128.7, 128.8, 136.4, 139.3, 200.5 (t, J_{C-F} = 30.4 Hz). Anal. Calcd for $C_{18}H_{14}ClF_5O_2$: C, 55.05; H, 3.59. Found: C, 55.04; H, 3.62.

***syn*-2,2,4,4,4-Pentafluoro-1,3-diphenyl-1,3-butanediol, *syn*-36.** Mp 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.99 (d, J = 2.3 Hz, 1H), 5.26 (ddd, J = 3.3 Hz, 3.3 Hz, 22.0 Hz, 1H), 5.45 (s, 1H), 7.30−7.40 (m, 8H), 7.69−7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 75.5 (m), 79.6 (m), 115.7 (dd, J_{C-F} = 254.0 Hz, 261.2 Hz), 124.2 (q, J_{C-F} = 288.2 Hz), 127.3, 128.0, 128.2, 129.4, 129.5, 131.7, 134.9. Anal. Calcd for $C_{16}H_{13}F_5O_2$: C, 57.84; H, 3.94. Found: C, 58.06; H, 3.98.

***anti*-2,2,4,4,4-Pentafluoro-1,3-diphenyl-1,3-butanediol, *anti*-36.** Mp 100−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.54 (d, J = 2.4 Hz, 1H), 4.71 (dd, J = 2.7 Hz, 22.2 Hz, 1H), 4.82 (s, 1H), 7.31−7.38 (m, 5H), 7.48−7.54 (m, 3H), 7.82−7.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 74.5 (m), 79.0 (m), 117.6 (dd, J_{C-F} = 256.5 Hz, 267.1 Hz), 123.2 (q, J_{C-F} = 286.3 Hz), 126.8, 128.1, 128.3, 128.7, 129.4, 129.8, 133.2, 134.3. Anal. Calcd for $C_{16}H_{13}F_5O_2$: C, 57.84; H, 3.94. Found: C, 57.75; H, 4.00.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallography, NMR and X-ray spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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