

An Efficient and General Method for the Reformatsky-Type Reaction of Chlorodifluoromethyl Ketones with Carbonyl Compounds Giving α,α -Difluoro- β -hydroxy Ketones¹⁾

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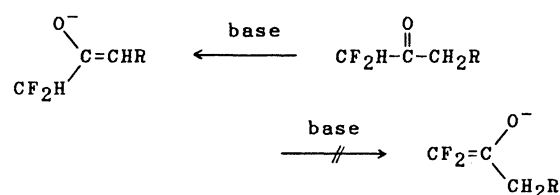
Chlorodifluoromethyl ketones CF_2ClCOR , where R is an alkyl, aryl, and 1-alkynyl group, underwent the Reformatsky-type aldol reaction with a wide variety of aldehydes or ketones in the presence of acid-washed zinc dust and copper(I) chloride or silver acetate to give the corresponding α,α -difluoro- β -hydroxy ketones in good to excellent yields. Specific activation of zinc metal with the metal salt is essential to achieve high efficiency of the reaction, depending upon the structures of the chlorodifluoromethyl ketones and the carbonyl compounds employed. In-situ formed intermediates in these reactions were successfully detected by ^{19}F NMR spectroscopy, which suggests that their structure is not an α -metallo ketone but an oxygen-metallated species possessing the zinc(II) metal as counter cation.

β -Hydroxy carbonyl compounds are very versatile intermediates in organic synthesis, particularly in the synthesis of a variety of naturally occurring substances. General access to these β -hydroxy carbonyl compounds has been accomplished by employing the well-established aldol reactions²⁾ of metal enolates or related reactive species with aldehydes and ketones. On the other hand, α -fluorinated β -hydroxy carbonyl compounds have been attracting much attention in recent years, because they are successfully applied to the fluorine-containing analogues³⁾ of biochemically important compounds such as sugars, nucleosides, amino acids, or fatty acids, which often exhibit dramatic changes in biological activities.⁴⁾ Among methods for the synthesis of α -fluorinated β -hydroxy carbonyl compounds, the most advantageous and direct method is to utilize the aldol reactions of enolates bearing fluorine(s) on the carbon terminus in their ambident anionic structure. These reactions are a fundamental and valuable transformation in organic synthesis as well as in organofluorine chemistry and, therefore, a number of studies relating to this subject have been undertaken^{5–12)} since the McBee's report⁵⁾ on the Reformatsky reaction of ethyl bromofluoroacetate.

Recently Welch et al. succeeded in generating enolates of fluoroacetates^{7b–d)} and fluoroacetamides^{7e)} by use of deprotonation with an amide base, and developed the high-yield method for their directed aldol reactions with various aldehydes or ketones. They also observed^{7a)} that the lithium enolate of 1-fluoro-3,3-dimethyl-2-butanone underwent aldol reaction with aldehydes with relatively high threo selectivity. The chemistry of enolates generated via reductive dehalogenation of bromodifluoro- or iododifluoroacetate has been exploited by Hallinan and Fried⁹⁾ and Kobayashi et al.,¹⁰⁾ respectively, who thereby applied them to the synthesis of several *gem*-difluorinated counterparts of natural compounds. Lang and Schaub¹¹⁾ reported that the aldol reactions of ethyl chlorodifluoroacetate as well as of chlorodifluoro-

methyl ketones proceed well in *N,N*-dimethylformamide to give the corresponding α,α -difluoro- β -hydroxy carbonyl compounds in moderate to good yields.

At the outset of our present work, however, little had been investigated about the generation and applications of enolates of α,α -difluorinated carbonyl compounds except our study^{8a)} concerning the synthesis of 2,2-difluoroethenyl silyl ethers. Our preliminary experiments¹³⁾ revealed that on treatment of 1,1-difluoro-2-alkanone with a base, the abstraction of proton-3 occurs exclusively rather than that of proton-1 to result in formation of the undesired enolate of type $\text{RCH}=\text{C}(\text{O}^-)\text{CF}_2\text{H}$. Accordingly, we decided to



investigate the Reformatsky-type aldol reactions¹⁵⁾ of chlorodifluoromethyl ketones (**1–3**), prepared from commercially available chlorodifluoroacetic acid or its ester,¹⁶⁾ with various aldehydes and ketones in order to get α,α -difluoro- β -hydroxy ketones (**4–8**). In this paper, we wish to describe our results of these reactions, together with the spectral data of intermediate zinc enolates of difluoromethyl ketones.

Results and Discussion

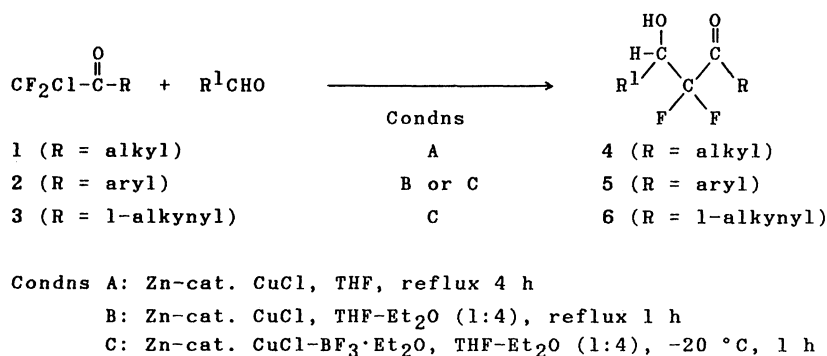
The starting chlorodifluoromethyl alkyl (**1**) or aryl ketones (**2**) were obtained in good yields by the reaction of chlorodifluoroacetic acid with the corresponding Grignard reagent according to a slightly modified procedure of the reported method.¹⁷⁾ Chlorodifluoromethyl 1-alkynyl ketones (**3**) were readily synthesized by the reaction between methyl chlorodifluoroacetate and lithium acetylide.¹⁸⁾

When thus-prepared chlorodifluoromethyl alkyl ketone **1** was treated with an aldehyde in the presence

of acid-washed zinc dust¹⁹) in refluxing tetrahydrofuran (THF), the expected α,α -difluoro- β -hydroxy ketone **4** was produced only in either low or variable yield, and in some cases unexpectedly long reaction time was required for completion of the reaction. For example, 1-chloro-1,1-difluoro-2-octanone (**1a**) was allowed to react with benzaldehyde under the influence of acid-washed zinc dust (3 equiv) in refluxing THF for 24 h to afford 2,2-difluoro-1-hydroxy-1-phenyl-3-nonanone (**4g**) in a 49% yield. These unsat-

isfactory results prompted us to explore the reaction conditions capable of efficiently promoting the desired Reformatsky-type reaction of chlorodifluoromethyl ketones.

Some recent reports demonstrate²⁰) that zinc metal can be activated in situ by simple treatment with a small quantity of transition metal salt and that the resulting zinc metal is very active towards the alkylation of aldehydes and ketones. We examined whether or not the use of the metal salt is effective for



Scheme 1.

Table 1. Reformatsky Reaction of Chlorodifluoromethyl Ketones 1–3 with Aldehydes

Entry	Chlorodifluoromethyl ketone	Condns ^{a)}	Aldehyde	Yield /% ^{b)}
1	$\text{CF}_2\text{ClC}(\text{CH}_2)_5\text{CH}_3$ (1a)	A	CH ₃ CH ₂ CHO	4a , 100
2	1a	A	CH ₃ (CH ₂) ₂ CHO	4b , 100
3	1a	A	(CH ₃) ₂ CHCHO	4c , 81
4	1a	A	(CH ₃) ₃ CCHO	4d , 60
5	1a	A	(<i>E</i>)-CH ₃ CH=CHCHO	4e , 85
6	1a	A	(<i>E</i>)-CH ₃ CH=C(CH ₃)CHO	4f , 100
7	1a	A	C ₆ H ₅ CHO	4g , 90
8	$\text{CF}_2\text{ClCC}_6\text{H}_{11-c}$ (1b)	A	CH ₃ (CH ₂) ₂ CHO	4h , 81
9	1b	A	(CH ₃) ₂ CHCHO	4i , 86
10	1b	A	(<i>E</i>)-CH ₃ CH=CHCHO	4j , 77
11	1b	A	(<i>E</i>)-CH ₃ CH=C(CH ₃)CHO	4k , 93
12	1b	A	C ₆ H ₅ CHO	4l , 93
13	$\text{CF}_2\text{ClCCH}_2\text{C}_6\text{H}_5$ (1c)	A	CH ₃ (CH ₂) ₂ CHO	4m , 70
14	1c	A	(<i>E</i>)-CH ₃ CH=CHCHO	4n , 93
15	1c	A	C ₆ H ₅ CHO	4o , 90
16	$\text{CF}_2\text{ClCC}_6\text{H}_5$ (2)	B	CH ₃ (CH ₂) ₂ CHO	5a , 70
17	2	C	CH ₃ (CH ₂) ₂ CHO	5a , 80
18	2	B	(<i>E</i>)-CH ₃ CH=CHCHO	5b , 100
19	2	B	C ₆ H ₅ CHO	5c , 88
20	2	C	C ₆ H ₅ CHO	5c , 86
21	$\text{CF}_2\text{ClCC}=\text{C}(\text{CH}_2)_5\text{CH}_3$ (3a)	C	C ₆ H ₅ CHO	6a , 74
22	$\text{CF}_2\text{ClCC}=\text{CC}_6\text{H}_5$ (3b)	C	CH ₃ (CH ₂) ₂ CHO	6b , 84
23	3b	C	CH ₃ (CH ₂) ₅ CHO	6c , 86
24	3b	C	C ₆ H ₅ CHO	6d , 82

a) See Scheme 1 and the Experimental section. b) Yields refer to pure isolated products.

Experimental

All boiling points are uncorrected. Infrared spectra (IR) were taken either on a Shimadzu IR-400 or on a JASCO IR-810 infrared spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz), XL-200 (200 MHz), or a JEOL JNM-PMX60SI (60 MHz) spectrometer for solutions in deuteriochloroform (CDCl_3). A JEOL FX90Q computer-controlled spectrometer was used to measure ^{19}F NMR spectra in CDCl_3 solutions. Proton and fluorine chemical shifts are given in ppm downfield from tetramethylsilane and trichlorofluoromethane (CFCl_3), respectively, as an internal standard. Mass spectra (MS) were obtained by use of a Shimadzu GCMS-QP1000 instrument operating at an ionization potential of 20 eV. Column chromatography was carried out with Wako silica gel C-200 (100–200 mesh) at an atmospheric pressure.

Materials. Ether and THF were freshly distilled from lithium aluminium hydride prior to use. Chlorodifluoroacetic acid and methyl chlorodifluoroacetate were purchased from Aldrich Chemical Company. Aldehydes and ketones were distilled (or vacuum-distilled) from calcium hydride and stored under argon. Alkyl halides for Grignard reagents and 1-alkynes for lithium acetylides were purified in the conventional manner. Zinc dust was washed successively with 5% HCl, water, methanol, and with ether, and then dried under vacuum. Butyllithium (1.57 mol dm^{-3} hexane solution) and chlorodiethylaluminium (1 mol dm^{-3} hexane solution) were commercially available from Aldrich Chemical Company and from Kanto Chemical Company, respectively. All other chemicals are of reagent grade and used without further purification.

Preparation of Chlorodifluoromethyl Ketones 1 and 2. Hexylmagnesium bromide was prepared from 1-bromohexane (20.6 g, 125 mmol) and magnesium (3.65 g, 150 mmol) in ether (50 cm^3). A solution of chlorodifluoroacetic acid (6.52 g, 50 mmol) in ether (15 cm^3) was gradually added under argon to the Grignard reagent at such a rate that the temperature did not rise above -10°C . After stirring for 12 h at -20°C ,²⁹ the reaction mixture was hydrolyzed with aqueous HCl (6 mol dm^{-3} , 50 cm^3) below 0°C and stirred for 1 h at room temperature. The resulting mixture was extracted with ether (50 $\text{cm}^3 \times 3$) and the ethereal extracts were washed with a saturated NaHCO_3 aqueous solution (50 $\text{cm}^3 \times 2$) and brine (50 $\text{cm}^3 \times 2$), dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The oily residue was distilled under reduced pressure to give 1-chloro-1,1-difluoro-2-octanone (**1a**) (8.63 g) in 87% yield: bp $86\text{--}87^\circ\text{C}$ (25 mmHg);³⁰ IR (neat) 2956 (s), 2864 (s), 1760 (vs), 1462 (m), 1408 (m), 1380 (w), 1210 (m), 1148 (vs), 1116 (s), 1042 (s), 912 (s), 720 (w), and 660 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=2.72$ (t, $J=7.5$ Hz, 2H), 1.67 (t, $J=7.5$ Hz, 2H), 1.5–1.1 (m, 6H), and 0.88 (t, $J=5.4$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-68.80$ (s, 2F). Found: C, 48.11; H, 6.29%. Calcd for $\text{C}_8\text{H}_{13}\text{ClF}_2\text{O}$: C, 48.37; H, 6.60%.

2-Chloro-1-cyclohexyl-2,2-difluoro-1-ethanone (1b): 84% yield; bp $74\text{--}75^\circ\text{C}$ (28 mmHg);³⁰ IR (neat) 2946 (vs), 2856 (vs), 1756 (vs), 1452 (s), 1378 (w), 1248 (m), 1216 (s), 1182 (m), 1148 (vs), 1132 (vs), 1090 (m), 1058 (m), 995 (vs), 934 (vs), 918 (vs), 880 (m), 844 (m), 796 (m), 752 (m), 710 (m), and 660 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=3.1\text{--}2.7$ (m, 1H) and 2.1–0.9 (m, 10H); ^{19}F NMR (CDCl_3) $\delta=-68.05$ (s, 2F). Found: C, 48.69; H, 5.36%. Calcd for $\text{C}_8\text{H}_{11}\text{ClF}_2\text{O}$: C, 48.87; H, 5.64%.

1-Chloro-1,1-difluoro-3-phenyl-2-propanone (1c): 80% yield; bp $92\text{--}93^\circ\text{C}$ (19 mmHg);³⁰ IR (neat) 3064 (w), 3040 (m), 2900 (w), 1762 (vs), 1604 (w), 1498 (m), 1456 (w), 1406 (m), 1342 (w), 1224 (s), 1142 (vs), 1076 (s), 1032 (vs), 1000 (m), 942 (s), 912 (s), 865 (s), 822 (w), 772 (m), 718 (vs), 692 (s), and 660 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=7.5\text{--}7.0$ (m, 5H) and 3.97 (s, 2H); ^{19}F NMR (CDCl_3) $\delta=-68.05$ (s, 2F). Found: C, 52.81; H, 3.40%. Calcd for $\text{C}_9\text{H}_7\text{ClF}_2\text{O}$: C, 52.83; H, 3.45%.

2-Chloro-2,2-difluoro-1-phenyl-1-ethanone (2): 84% yield; bp $92\text{--}94^\circ\text{C}$ (33 mmHg);³⁰ IR (neat) 3060 (w), 1970 (w), 1910 (w), 1818 (w), 1718 (vs), 1600 (m), 1580 (w), 1452 (m), 1324 (w), 1310 (w), 1282 (m), 1272 (m), 1158 (vs), 1100 (m), 1044 (m), 1032 (m), 1002 (s), 982 (vs), 932 (w), 886 (vs), 832 (m), 778 (w), 708 (s), 682 (s), and 668 (s) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=8.2\text{--}8.0$ (m, 2H) and 7.8–7.3 (m, 3H); ^{19}F NMR (CDCl_3) $\delta=-61.30$ (s, 2F). Found: C, 50.51; H, 2.59%. Calcd for $\text{C}_8\text{H}_5\text{ClF}_2\text{O}$: C, 50.42; H, 2.64%.

Preparation of Chlorodifluoromethyl 1-Alkynyl Ketones 3. A hexane solution (1.57 mol dm^{-3}) of butyllithium (7.0 cm^3 , 11.0 mmol) was added dropwise to a solution of 1-octyne (1.21 g, 11.0 mmol) in THF (50 cm^3) at -78°C under argon. To this mixture, after 1 h, was slowly added a THF (5 cm^3) solution of methyl chlorodifluoroacetate (1.45 g, 10.0 mmol) at -78°C . The reaction mixture was stirred for 2 h at the same temperature, and then poured into a saturated NH_4Cl aqueous solution (50 cm^3). The resultant mixture was extracted with ether (50 $\text{cm}^3 \times 3$) and the extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was chromatographed on a column of silica gel to afford 1-chloro-1,1-difluoro-3-decyn-2-one (**3a**) (1.91 g) in 86% yield: IR (neat) 2956 (vs), 2930 (vs), 2860 (s), 2210 (vs), 1715 (vs), 1468 (m), 1460 (m), 1381 (w), 1348 (w), 1328 (w), 1260 (m), 1163 (vs), 1132 (vs), 984 (s), 946 (m), 876 (m), 838 (m), and 720 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=2.46$ (t, $J=6.3$ Hz, 2H), 1.9–1.1 (m, 8H), and 0.88 (t, $J=5.9$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-67.23$ (s, 2F). Found: C, 53.82; H, 5.68%. Calcd for $\text{C}_{10}\text{H}_{13}\text{ClF}_2\text{O}$: C, 53.94; H, 5.89%.

1-Chloro-1,1-difluoro-4-phenyl-3-butyn-2-one (3b): 83% yield; IR (neat) 3060 (w), 2926 (w), 2852 (w), 2194 (vs), 2090 (w), 1707 (vs), 1598 (m), 1491 (m), 1446 (m), 1305 (m), 1212 (m), 1153 (s), 1057 (vs), 1026 (m), 1000 (m), 938 (vs), 800 (m), 757 (vs), 716 (m), 686 (s), 637 (s), and 613 (vs) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=7.7\text{--}7.1$ (m, 5H); ^{19}F NMR (CDCl_3) $\delta=-66.8$ (s, 2F). Found: C, 56.02; H, 2.30%. Calcd for $\text{C}_{10}\text{H}_5\text{ClF}_2\text{O}$: C, 55.97; H, 2.35%.

Typical Procedure for the Reformatsky-Type Reaction of 1 with Aldehydes. Conditions A. In a 50- cm^3 three-necked flask, which had been purged with argon, were placed acid-washed zinc dust (0.196 g, 3.0 mmol), copper(I) chloride (0.030 g, 0.3 mmol), and THF (5 cm^3). After this suspension was stirred for 0.5 h at room temperature, propanal (0.064 g, 1.1 mmol) and **1a** (0.199 g, 1.0 mmol) were added thereto by use of a syringe. Then the mixture was refluxed with stirring for 4 h. After being cooled to room temperature, the reaction mixture was filtered through a pad of Celite 545 and the filtrate was concentrated in vacuo. Column chromatography of the crude product on silica gel eluting with hexane-ethyl acetate (3:1) provided 4,4-difluoro-3-hydroxy-5-undecanone (**4a**) (0.220 g): IR (neat) 3422 (br, s), 2956 (vs), 2932 (vs), 2858 (s), 1740 (vs), 1648 (w), 1637 (w), 1459 (s), 1401 (s), 1379 (m), 1307 (m), 1221 (s), 1110 (vs), 1074 (s), 1046 (s), 986 (s), 893 (w), 810 (m), 757 (w), 713 (m), and 664 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=4.3\text{--}3.5$ (m,

1H), 2.9—2.3 (m, 1H), 2.69 (t, $J=6.0$ Hz, 2H), 2.0—1.2 (m, 10H), 1.04 (t, $J=6.8$ Hz, 3H), and 0.89 (t, $J=6.2$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-114.32$ (dd, $J=274.7$, 6.1 Hz, 1F) and -125.73 (dd, $J=274.7$, 15.9 Hz, 1F); MS m/z (rel intensity) 222 (M^+ ; 0.1), 113 (100), 85 (55), and 42 (42). Found: C, 59.41; H, 8.93%. Calcd for $\text{C}_{11}\text{H}_{20}\text{F}_2\text{O}_2$: C, 59.44; H, 9.07%.

5,5-Difluoro-4-hydroxy-6-dodecanone (4b): IR (neat) 3408 (br, m), 2958 (vs), 2932 (vs), 2872 (s), 1740 (vs), 1467 (m), 1401 (m), 1380 (m), 1261 (m), 1194 (m), 1115 (s), 1065 (s), 988 (m), and 802 (w) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=4.4-3.5$ (m, 1H), 2.9—2.0 (m, 3H), 2.0—1.1 (m, 8H), 0.96 (t, $J=5.4$ Hz, 3H), and 0.87 (t, $J=5.4$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-114.43$ (dd, $J=273.4$, 6.1 Hz, 1F) and -125.78 (d, $J=273.4$ Hz, 1F); MS m/z (rel intensity) 236 (M^+ ; 0.1), 113 (100), 85 (38), and 73 (20). Found: C, 61.08; H, 9.37%. Calcd for $\text{C}_{12}\text{H}_{22}\text{F}_2\text{O}_2$: C, 60.99; H, 9.38%.

4,4-Difluoro-3-hydroxy-2-methyl-5-undecanone (4c): IR (neat) 3442 (br, m), 2958 (vs), 2930 (vs), 2860 (s), 1741 (s), 1468 (s), 1401 (m), 1376 (m), 1215 (m), 1119 (s), 1061 (s), 1030 (s), 985 (m), 961 (w), 919 (w), and 880 (w) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=4.2-3.4$ (br d, $J=19.5$ Hz, 1H), 2.67 (t, $J=6.2$ Hz, 2H), 2.5—1.2 (m, 10H), 1.01 (d, $J=6.4$ Hz, 6H), and 0.87 (t, $J=5.8$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-110.81$ (d, $J=274.7$ Hz, 1F) and -124.58 (dd, $J=274.7$, 19.5 Hz, 1F); MS m/z (rel intensity) 236 (M^+ ; 0.1), 113 (100), 85 (54), and 73 (6). Found: C, 60.76; H, 8.99%. Calcd for $\text{C}_{12}\text{H}_{22}\text{F}_2\text{O}_2$: C, 60.99; H, 9.38%.

4,4-Difluoro-3-hydroxy-2,2-dimethyl-5-undecanone (4d): IR (neat) 3484 (br, s), 2956 (vs), 2930 (vs), 2872 (vs), 1740 (vs), 1483 (s), 1468 (s), 1401 (s), 1370 (s), 1279 (m), 1236 (s), 1195 (s), 1172 (s), 1119 (s), 1106 (s), 1071 (vs), 1021 (s), 983 (m), 934 (w), 895 (w), 795 (w), 770 (w), and 706 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=3.73$ (ddd, $J=22.0$, 6.0, 6.0 Hz, 1H), 2.67 (t, $J=7.0$ Hz, 2H), 2.5—2.1 (br s, 1H), 1.9—1.1 (m, 8H), 1.03 (s, 9H), and 0.90 (t, $J=5.4$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-105.83$ (d, $J=271.0$ Hz, 1F) and -124.79 (dd, $J=271.0$, 22.0 Hz, 1F); MS m/z (rel intensity) 250 (M^+ ; 0.1), 113 (68), 85 (46), and 57 (100). Found: C, 62.43; H, 9.69%. Calcd for $\text{C}_{13}\text{H}_{24}\text{F}_2\text{O}_2$: C, 62.38; H, 9.66%.

(E)-5,5-Difluoro-4-hydroxy-2-dodecen-6-one (4e): IR (neat) 3418 (br, s), 2954 (vs), 2926 (vs), 2858 (vs), 1740 (vs), 1675 (m), 1452 (s), 1402 (s), 1379 (s), 1207 (s), 1122 (s), 1092 (vs), 1070 (vs), 1031 (s), 967 (vs), 927 (m), 830 (m), 724 (m), and 663 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=6.1-5.1$ (m, 2H), 4.7—4.0 (m, 1H), 2.63 (t, $J=7.2$ Hz, 2H), 2.5—2.1 (br s, 1H), 2.0—1.0 (m, 8H), 1.71 (d, $J=6.4$ Hz, 3H), and 0.85 (t, $J=5.0$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-114.42$ (dd, $J=269.8$, 6.1 Hz, 1F) and -123.90 (dd, $J=269.8$, 14.7 Hz, 1F); MS m/z (rel intensity) 234 (M^+ ; 0.3), 113 (80), 85 (52), and 71 (100). Found: C, 61.51; H, 8.43; F, 16.17%. Calcd for $\text{C}_{12}\text{H}_{18}\text{F}_2\text{O}_2$: C, 61.52; H, 8.60; F, 16.22%.

(E)-5,5-Difluoro-4-hydroxy-3-methyl-2-dodecen-6-one (4f): IR (neat) 3448 (br, s), 2928 (vs), 2858 (vs), 1740 (vs), 1669 (w), 1460 (s), 1401 (s), 1381 (s), 1204 (s), 1161 (m), 1102 (vs), 1075 (vs), 977 (m), 934 (m), 847 (w), 790 (m), 758 (m), 718 (m), and 664 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=5.55$ (q, $J=6.2$ Hz, 1H), 4.38 (dd, $J=17.1$, 8.5 Hz, 1H), 2.63 (t, $J=7.2$ Hz, 2H), 2.7—2.0 (br s, 1H), 1.9—1.0 (m, 8H), 1.70 (s, 3H), 1.63 (d, $J=6.2$ Hz, 3H), and 0.87 (t, $J=5.8$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-113.23$ (dd, $J=264.9$, 8.5 Hz, 1F) and -122.40 (dd, $J=264.9$, 17.1 Hz, 1F); MS m/z (rel intensity) 248 (M^+ ; 0.3), 230 (0.5), 113 (12), and 85 (100). Found: C, 63.09; H, 8.98%. Calcd for $\text{C}_{13}\text{H}_{22}\text{F}_2\text{O}_2$: C, 62.88; H, 8.93%.

2,2-Difluoro-1-hydroxyl-1-phenyl-3-nonanone (4g): IR (neat) 3448 (br, s), 3064 (m), 3032 (m), 2952 (vs), 2928 (vs), 2858 (s), 1960 (w), 1888 (w), 1814 (w), 1739 (vs), 1495 (m), 1455 (s), 1400 (s), 1379 (m), 1341 (m), 1202 (s), 1159 (s), 1107 (vs), 1064 (vs), 1028 (s), 981 (m), 912 (w), 844 (m), 819 (m), 728 (s), 712 (s), 698 (vs), 664 (m), and 612 (vs) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=7.26$ (s, 5H), 5.03 (dd, $J=15.9$, 7.3 Hz, 1H), 3.1—2.5 (br s, 1H), 2.53 (t, $J=7.2$ Hz, 2H), 1.8—1.0 (m, 8H), and 0.83 (t, $J=6.0$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-113.60$ (dd, $J=268.6$, 7.3 Hz, 1F) and -123.47 (dd, $J=268.6$, 15.9 Hz, 1F); MS m/z (rel intensity) 270 (M^+ ; 2.5), 113 (68), 107 (100), and 85 (48). Found: C, 66.66; H, 7.42; F, 14.10%. Calcd for $\text{C}_{15}\text{H}_{20}\text{F}_2\text{O}_2$: C, 66.65; H, 7.46; F, 14.06%.

1-Cyclohexyl-2,2-difluoro-3-hydroxy-1-hexanone (4h): IR (neat) 3446 (br, s), 2932 (vs), 2856 (vs), 1731 (vs), 1452 (s), 1400 (m), 1381 (m), 1317 (m), 1292 (m), 1275 (m), 1249 (m), 1220 (s), 1174 (m), 1137 (s), 1115 (vs), 1064 (vs), 1039 (s), 981 (s), 943 (m), 922 (w), 892 (w), 859 (w), 814 (w), 789 (w), 749 (m), 707 (m), and 663 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=4.4-3.6$ (m, 1H), 3.2—2.5 (m, 1H), 2.4—2.1 (m, 1H), 2.1—1.1 (m, 8H), and 1.1—0.7 (m, 3H); ^{19}F NMR (CDCl_3) $\delta=-113.81$ (dd, $J=279.5$, 6.1 Hz, 1F) and -125.39 (dd, $J=279.5$, 15.9 Hz, 1F); MS m/z (rel intensity) 234 (M^+ ; 0.1), 214 (0.5), 111 (100), and 84 (64). Found: C, 61.67; H, 8.61%. Calcd for $\text{C}_{12}\text{H}_{20}\text{F}_2\text{O}_2$: C, 61.52; H, 8.60%.

1-Cyclohexyl-2,2-difluoro-3-hydroxy-4-methyl-1-pentanone (4i): IR (neat) 3446 (br, s), 2934 (vs), 2856 (vs), 1731 (vs), 1467 (m), 1451 (s), 1390 (m), 1375 (m), 1332 (m), 1318 (m), 1293 (m), 1249 (m), 1220 (s), 1175 (m), 1129 (s), 1114 (s), 1064 (vs), 978 (s), 932 (m), 920 (m), 892 (w), 858 (w), 837 (w), 807 (m), 744 (m), 703 (m), and 663 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=4.2-3.5$ (m, 1H), 3.2—2.6 (m, 1H), 2.6—2.2 (m, 1H), 2.2—0.7 (m, 11H), and 1.01 (t, $J=6.8$ Hz, 6H); ^{19}F NMR (CDCl_3) $\delta=-109.77$ (d, $J=275.9$ Hz, 1F) and -124.60 (dd, $J=275.9$, 19.5 Hz, 1F); MS m/z (rel intensity) 234 (M^+ ; 0.1), 214 (0.5), 111 (100), and 84 (64). Found: C, 61.38; H, 8.42%. Calcd for $\text{C}_{12}\text{H}_{20}\text{F}_2\text{O}_2$: C, 61.52; H, 8.60%.

(E)-1-Cyclohexyl-2,2-difluoro-3-hydroxy-4-hexen-1-one (4j): IR (neat) 3438 (br, s), 3036 (w), 2932 (vs), 2856 (vs), 1732 (vs), 1673 (m), 1656 (w), 1451 (vs), 1379 (s), 1316 (m), 1293 (m), 1249 (m), 1216 (s), 1172 (s), 1132 (s), 1071 (vs), 1040 (s), 993 (m), 967 (vs), 922 (m), 892 (m), 855 (m), 832 (m), 799 (m), 778 (w), 743 (m), and 704 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=6.2-5.2$ (m, 2H), 4.8—4.1 (m, 1H), 3.2—2.6 (m, 1H), 2.6—2.2 (m, 1H), 2.2—0.9 (m, 10H), and 1.72 (d, $J=5.4$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-113.80$ (dd, $J=272.2$, 8.5 Hz, 1F) and -123.44 (dd, $J=272.2$, 14.7 Hz, 1F); MS m/z (rel intensity) 232 (M^+ ; 0.8), 212 (0.8), 162 (27), 111 (92), 84 (100), and 72 (92). Found: C, 62.19; H, 7.88%. Calcd for $\text{C}_{12}\text{H}_{18}\text{F}_2\text{O}_2$: C, 62.05; H, 7.81%.

(E)-1-Cyclohexyl-2,2-difluoro-3-hydroxy-4-methyl-4-hexen-1-one (4k): IR (neat) 3444 (br, s), 2930 (vs), 2856 (vs), 1732 (vs), 1686 (w), 1666 (w), 1451 (vs), 1382 (s), 1352 (w), 1317 (m), 1292 (m), 1249 (m), 1212 (s), 1171 (s), 1134 (s), 1070 (vs), 974 (s), 945 (s), 921 (m), 893 (w), 857 (w), 845 (w), 800 (m), 785 (m), 749 (m), 709 (m), and 665 (m) cm^{-1} ; ^1H NMR (CDCl_3) $\delta=5.56$ (q, $J=7.2$ Hz, 1H), 4.43 (dd, $J=17.7$, 9.2 Hz, 1H), 3.1—2.6 (m, 1H), 2.6—2.2 (m, 1H), 2.1—0.9 (m, 10H), 1.64 (t, $J=7.2$ Hz, 3H), and 0.87 (t, $J=5.8$ Hz, 3H); ^{19}F NMR (CDCl_3) $\delta=-112.40$ (dd, $J=268.6$, 9.2 Hz, 1F) and -122.09 (dd, $J=268.6$, 17.7 Hz, 1F); MS m/z (rel intensity) 246 (M^+ ; 2), 226 (0.8), 162 (12.5), 111 (37.5), 86 (100), and 84 (92). Found: C, 63.65; H, 8.33%. Calcd for $\text{C}_{13}\text{H}_{20}\text{F}_2\text{O}_2$: C, 63.40;

H, 8.18%.

1-Cyclohexyl-2,2-difluoro-3-hydroxy-3-phenyl-1-propanone (4l): IR (neat) 3500 (br, m), 2932 (vs), 2856 (s), 1733 (s), 1497 (w), 1453 (m), 1379 (w), 1195 (w), 1174 (w), 1135 (m), 1083 (m), 1071 (s), 1030 (w), and 966 (w) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.26$ (s, 5H), 5.06 (dd, $J=15.9$, 8.6 Hz, 1H), 3.2–2.7 (m, 1H), 2.7–2.3 (m, 1H), and 2.1–0.6 (m, 10H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-112.58$ (dd, $J=272.2$, 8.6 Hz, 1F) and -123.07 (dd, $J=272.2$, 15.9 Hz, 1F); MS m/z (rel intensity) 268 (M^+ ; 3), 248 (4), 162 (17), 111 (40), 107 (100), and 84 (64). Found: C, 67.24; H, 6.69%. Calcd for $\text{C}_{15}\text{H}_{18}\text{F}_2\text{O}_2$: C, 67.15; H, 6.76%.

3,3-Difluoro-4-hydroxy-1-phenyl-2-heptanone (4m): IR (neat) 3372 (br, s), 3086 (m), 3062 (m), 3030 (m), 2960 (vs), 2872 (vs), 1742 (vs), 1640 (w), 1498 (s), 1455 (s), 1400 (s), 1383 (s), 1343 (s), 1314 (s), 1271 (s), 1205 (vs), 1113 (vs), 1063 (vs), 1032 (vs), 1010 (s), 993 (s), 899 (w), 854 (w), 749 (s), 709 (vs), and 697 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.6$ –6.9 (m, 5H), 4.4–3.7 (m, 1H), 3.97 (s, 1H), 1.9–1.2 (m, 4H), and 0.95 (t, $J=5.8$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-113.65$ (dd, $J=273.4$, 6.1 Hz, 1F) and -124.88 (dd, $J=273.4$, 15.9 Hz, 1F); MS m/z (rel intensity) 242 (M^+ ; 35), 119 (17), and 91 (100). Found: C, 64.36; H, 6.61%. Calcd for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$: C, 64.45; H, 6.66%.

(E)-3,3-Difluoro-4-hydroxy-1-phenyl-5-hepten-2-one (4n): IR (neat) 3404 (s), 3062 (m), 3030 (m), 2916 (m), 1745 (vs), 1671 (w), 1604 (w), 1498 (s), 1455 (s), 1400 (s), 1380 (m), 1341 (m), 1207 (s), 1084 (vs), 1069 (vs), 1031 (vs), 968 (m), 830 (m), 709 (s), and 664 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.4$ –7.0 (m, 5H), 6.2–5.2 (m, 2H), 4.44 (ddd, $J=14.7$, 8.5, 6.8 Hz, 1H), 3.97 (s, 2H), 2.22 (br s, 1H), and 1.73 (d, $J=4.6$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-113.73$ (dd, $J=269.8$, 8.5 Hz, 1F) and -123.02 (dd, $J=269.8$, 14.7 Hz, 1F); MS m/z (rel intensity) 240 (M^+ ; 4), 169 (25), 91 (38), and 72 (100). Found: C, 65.35; H, 5.98%. Calcd for $\text{C}_{13}\text{H}_{14}\text{F}_2\text{O}_2$: C, 64.99; H, 5.87%.

3,3-Difluoro-4-hydroxy-1,4-diphenyl-2-butanone (4o): IR (neat) 3554 (vs), 3446 (w), 3086 (m), 3062 (m), 3030 (m), 3004 (w), 2960 (m), 2914 (m), 1953 (w), 1892 (w), 1733 (vs), 1497 (m), 1455 (vs), 1401 (s), 1352 (s), 1254 (m), 1215 (s), 1205 (vs), 1154 (s), 1080 (vs), 1056 (vs), 1026 (m), 1006 (w), 983 (m), 920 (w), 904 (w), 818 (m), 767 (m), and 617 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.6$ –6.8 (m, 10H), 4.96 (dd, $J=17.1$, 6.1 Hz, 1H), 3.80 (s, 2H), and 3.6–3.1 (br s, 1H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-112.76$ (ddd, $J=267.3$, 6.1, 6.1 Hz, 1F) and -123.13 (dd, $J=267.3$, 17.1 Hz, 1F). Found: C, 69.66; H, 5.09%. Calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2$: C, 69.56; H, 5.11%.

Typical Procedure for the Reformatsky-Type Reaction of 2 with Aldehydes. Conditions B. A suspension of acid-washed zinc dust (0.196 g, 3.0 mmol) and copper(I) chloride (0.030 g, 0.3 mmol) in ether (4 cm^3) and THF (1 cm^3) was stirred for 0.5 h at room temperature under argon. To this suspension were added butanal (0.080 g, 1.1 mmol) and **2** (0.191 g, 1.0 mmol) via a syringe. After stirring under reflux for 1 h, followed by cooling to room temperature, the reaction mixture was filtered through a pad of Celite 545. The filtrate was concentrated under reduced pressure to leave an oily residue, which was subjected to column chromatography on silica gel eluting with hexane–ethyl acetate (3:1) to give 2,2-difluoro-3-hydroxy-1-phenyl-1-hexanone (**5a**) (0.160 g): IR (neat) 3372 (br, s), 3086 (m), 3062 (m), 3030 (m), 2960 (vs), 2872 (vs), 1742 (vs), 1604 (w), 1498 (s), 1455 (s), 1400 (s), 1383 (s), 1343 (s), 1314 (s), 1271 (s), 1205 (vs), 1113 (vs), 1063 (vs), 1032 (vs), 1010 (s), 993 (s), 899 (w), 854 (m), 749

(s), 709 (vs), and 697 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.6$ –6.9 (m, 5H), 4.4–3.7 (br s, 1H), 3.97 (s, 2H), 1.9–1.2 (m, 4H), and 0.85 (t, $J=5.8$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-113.65$ (dd, $J=273.4$, 6.1 Hz, 1F) and -124.88 (dd, $J=273.4$, 15.9 Hz, 1F); MS m/z (rel intensity) 288 (M^+ ; 0.2), 123 (22), 105 (100), and 77 (42). Found: C, 63.01; H, 6.09; F, 16.42%. Calcd for $\text{C}_{12}\text{H}_{14}\text{F}_2\text{O}_2$: C, 63.15; H, 6.18; F, 16.65%.

(E)-2,2-Difluoro-3-hydroxy-1-phenyl-4-hexen-1-one (5b): IR (neat) 3400 (br, s), 3060 (m), 3034 (m), 2966 (m), 2942 (m), 2918 (m), 2856 (m), 1697 (vs), 1598 (vs), 1579 (m), 1449 (vs), 1397 (m), 1380 (m), 1282 (s), 1230 (m), 1181 (vs), 1122 (vs), 1089 (vs), 1069 (vs), 1028 (s), 1001 (m), 968 (vs), 919 (s), 825 (s), 790 (m), 715 (vs), 686 (vs), and 664 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=8.2$ –7.8 (m, 2H), 7.5–7.1 (m, 3H), 6.2–5.3 (m, 2H), 4.63 (ddd, $J=15.8$, 8.5, 7.8 Hz, 1H), 3.0–2.5 (br s, 1H), and 1.75 (d, $J=5.6$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-107.25$ (dd, $J=288.1$, 8.5 Hz, 1F) and -116.07 (dd, $J=288.1$, 15.9 Hz, 1F); MS m/z (rel intensity) 226 (M^+ ; 0.2), 155 (90), and 105 (100). Found: C, 63.88; H, 5.40%. Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{O}_2$: C, 63.71; H, 5.35%.

2,2-Difluoro-3-hydroxy-1,3-diphenyl-1-propanone (5c): IR (neat) 3448 (br, s), 3062 (m), 3032 (m), 2976 (m), 2926 (m), 1694 (vs), 1598 (vs), 1579 (m), 1495 (m), 1450 (vs), 1389 (m), 1340 (m), 1324 (m), 1285 (s), 1239 (s), 1182 (vs), 1123 (vs), 1066 (vs), 1028 (s), 1001 (m), 922 (s), 838 (m), 809 (m), 773 (m), 733 (vs), 713 (vs), 697 (vs), 686 (vs), 671 (vs), and 608 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=8.1$ –7.7 (m, 2H), 7.5–7.0 (m, 8H), 5.23 (dd, $J=18.3$, 6.1 Hz, 1H), and 3.5–2.9 (m, 1H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-105.23$ (dd, $J=288.1$, 6.1 Hz, 1F) and -116.91 (dd, $J=288.1$, 18.3 Hz, 1F); MS m/z (rel intensity) 262 (M^+ ; 5), 155 (100), 107 (56), 105 (80), and 77 (10). Found: C, 68.81; H, 4.62; F, 14.38%. Calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}_2$: C, 68.70; H, 4.61; F, 14.49%.

Typical Procedure for the Reformatsky-Type Reaction of 2 or 3 with Aldehydes. Conditions C. A suspension of acid-washed zinc dust (0.196 g, 3.0 mmol) and copper(I) chloride (0.030 g, 0.3 mmol) in ether (4 cm^3) and THF (1 cm^3) was stirred for 0.5 h at room temperature under argon. To the mixture, which had been cooled to -20°C , were added successively benzaldehyde (0.117 g, 1.1 mmol), **3a** (0.223 g, 1.0 mmol), and boron trifluoride diethyl etherate (0.156 g, 1.1 mmol). After being stirred for 1 h at -20°C , the reaction mixture was filtered through a pad of Celite 545 and the filtrate was concentrated under vacuum. The residual oil was chromatographed on a column of silica gel with hexane–ethyl acetate (3:1) as eluent to furnish 2,2-difluoro-1-hydroxy-1-phenyl-4-undecyn-3-one (**6a**) (0.298 g): IR (neat) 3424 (br, m), 3064 (m), 3034 (m), 2954 (vs), 2930 (vs), 2858 (s), 2210 (vs), 1693 (vs), 1497 (w), 1456 (s), 1417 (m), 1381 (m), 1321 (m), 1259 (m), 1179 (s), 1111 (s), 1069 (s), 1028 (m), 963 (w), 908 (w), 834 (w), 800 (w), 718 (s), 698 (s), and 665 (m) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.25$ (br s, 5H), 5.08 (dd, $J=15.9$, 8.6 Hz, 1H), 3.7–3.2 (br s, 1H), 2.35 (t, $J=6.4$ Hz, 2H), 1.8–1.1 (m, 8H), and 0.87 (t, $J=5.4$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-112.34$ (dd, $J=263.7$, 8.6 Hz, 1F) and -121.68 (dd, $J=263.7$, 15.9 Hz, 1F); MS m/z (rel intensity) 294 (M^+ ; 2), 274 (3), 217 (3), 187 (70), and 107 (100). Found: C, 69.52; H, 6.89%. Calcd for $\text{C}_{17}\text{H}_{20}\text{F}_2\text{O}_2$: C, 69.37; H, 6.85%.

4,4-Difluoro-5-hydroxy-1-phenyl-1-octyn-3-one (6b): IR (neat) 3438 (br, s), 3062 (w), 2962 (vs), 2934 (s), 2874 (s), 2194 (vs), 1961 (w), 1893 (w), 1803 (w), 1685 (vs), 1597 (m), 1491 (s), 1468 (m), 1459 (m), 1446 (s), 1384 (m), 1310 (s), 1272 (m), 1221 (s), 1164 (s), 1115 (vs), 1071 (vs), 1029 (vs), 1011 (vs), 996 (vs),

955 (s), 925 (w), 901 (w), 857 (w), 817 (m), 758 (vs), 716 (m), 687 (vs), 669 (m), and 637 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.7$ – 7.0 (m, 5H), 4.4 – 3.8 (m, 1H), 2.8 – 2.4 (br s, 1H), 2.0 – 1.3 (m, 4H), and 0.94 (t, $J=6.4$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-114.10$ (dd, $J=264.9$, 8.5 Hz, 1F) and -122.84 (dd, $J=264.9$, 14.7 Hz, 1F); MS m/z (rel intensity) 252 (M^+ ; 0.8), 179 (5), and 129 (100). Found: C, 66.71; H, 5.44%. Calcd for $\text{C}_{14}\text{H}_{14}\text{F}_2\text{O}_2$: C, 66.66; H, 5.59%.

4,4-Difluoro-5-hydroxy-1-phenyl-1-undecyn-3-one (6c): IR (neat) 3368 (br, m), 3058 (w), 2952 (s), 2924 (vs), 2856 (s), 2194 (vs), 1685 (vs), 1648 (w), 1597 (m), 1571 (w), 1560 (w), 1491 (m), 1466 (m), 1459 (m), 1445 (m), 1379 (w), 1307 (m), 1232 (m), 1210 (m), 1161 (m), 1120 (s), 1087 (s), 1033 (m), 992 (m), 757 (s), 715 (m), and 686 (s) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.7$ – 7.0 (m, 5H), 4.4 – 3.8 (m, 1H), 3.1 – 2.5 (br s, 1H), 1.9 – 1.1 (m, 10H), and 0.89 (t, $J=5.4$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-114.10$ (dd, $J=264.9$, 7.3 Hz, 1F) and -122.82 (dd, $J=264.9$, 15.9 Hz, 1F); MS m/z (rel intensity) 294 (M^+ ; 0.1), 179 (5), and 129 (100). Found: C, 69.63; H, 7.06%. Calcd for $\text{C}_{17}\text{H}_{20}\text{F}_2\text{O}_2$: C, 69.37; H, 6.85%.

2,2-Difluoro-1-hydroxy-1,5-diphenyl-4-pentyn-3-one (6d): IR (neat) 3426 (br, m), 3062 (m), 3032 (w), 2922 (w), 2192 (w), 11962 (w), 1894 (w), 1685 (vs), 1596 (m), 1571 (w), 1491 (m), 1455 (m), 1445 (m), 1389 (w), 1306 (m), 1200 (m), 1145 (s), 1090 (s), 1063 (s), 1028 (s), 1011 (s), 993 (s), 922 (w), 843 (w), 823 (w), 782 (m), 757 (s), 715 (s), 697 (s), and 686 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.7$ – 7.0 (m, 10H), 5.19 (dd, $J=15.9$, 7.3 Hz, 1H), 3.0 – 2.3 (br s, 1H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-111.93$ (dd, $J=262.5$, 7.3 Hz, 1F) and -121.37 (dd, $J=262.5$, 15.9 Hz, 1F); MS m/z (rel intensity) 286 (M^+ ; 2.5), 268 (2.5), 266 (2.5), 249 (1.5), 180 (100), and 129 (60). Found: C, 71.44; H, 4.20; F, 13.19%. Calcd for $\text{C}_{17}\text{H}_{12}\text{F}_2\text{O}_2$: C, 71.32; H, 4.23; F, 13.27%.

Typical Procedure for the Reformatsky-Type Reaction of 1 with Ketones. Conditions D. Acid-washed zinc dust (0.196 g, 3.0 mmol) and silver acetate (0.017 g, 0.1 mmol) were suspended in THF (5 cm^3) and this suspension was stirred for 0.5 h at room temperature under argon. To the resultant mixture were gradually added 3-pentanone (0.258 g, 3.0 mmol), **1a** (0.199 g, 1.0 mmol), and a hexane solution (1 mol dm^{-3}) of chlorodiethylaluminum (1.1 cm^3 , 1.1 mol). The mixture was stirred for 9 h at reflux temperature and, after cooling to room temperature, was filtered through a pad of Celite 545. The filtrate was concentrated under reduced pressure to leave a crude product, which was purified by column chromatography on silica gel eluting with hexane-ethyl acetate (3:1) to afford 3-ethyl-4,4-difluoro-3-hydroxy-5-undecanone (**7a**) (0.160 g): IR (neat) 3442 (br, s), 2930 (vs), 2858 (vs), 1740 (vs), 1701 (s), 1656 (m), 1612 (m), 1462 (vs), 1403 (s), 1379 (s), 1269 (m), 1208 (m), 1121 (vs), 1063 (s), 980 (s), 933 (m), 852 (w), 817 (w), 793 (w), 771 (w), and 724 (m) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=2.70$ (t, $J=7.2$ Hz, 2H), 2.27 (s, 1H), 1.9 – 1.1 (m, 12H), and 0.93 (t, $J=7.8$ Hz, 9H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-116.12$ (s, 2F); MS m/z (rel intensity) 250 (M^+ ; 0.1), 221 (1.5), 113 (80), and 87 (100). Found: C, 62.67; H, 9.84%. Calcd for $\text{C}_{13}\text{H}_{24}\text{F}_2\text{O}_2$: C, 62.38; H, 9.66%.

1,1-Difluoro-1-(1-hydroxycyclohexyl)-2-octanone (7b): IR (neat) 3448 (br, m), 2956 (vs), 2934 (vs), 2860 (s), 1737 (s), 1703 (s), 1665 (w), 1453 (m), 1402 (m), 1376 (m), 1315 (m), 1264 (vs), 1202 (s), 1153 (vs), 1123 (vs), 1111 (vs), 1060 (vs), 992 (s), 909 (m), 864 (m), 798 (s), 684 (m), and 663 (m) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=2.68$ (t, $J=6.5$ Hz, 2H), 2.11 (s, 1H), 2.1 – 1.4 (m, 10H), 1.4 – 1.1 (m, 8H), and 0.85 (t, $J=5.0$ Hz,

3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-121.23$ (s, 2F); MS m/z (rel intensity) 262 (M^+ ; 0.1), 225 (5), 113 (48), 99 (100), and 85 (30). Found: C, 64.32; H, 9.29%. Calcd for $\text{C}_{14}\text{H}_{24}\text{F}_2\text{O}_2$: C, 64.10; H, 9.22%.

6,6-Difluoro-5-hydroxy-5-methyl-1-undecen-7-one (7c): IR (neat) 3504 (br, s), 3074 (m), 2954 (vs), 2928 (vs), 2856 (vs), 1739 (vs), 1644 (m), 1459 (s), 1402 (s), 1380 (s), 1296 (m), 1260 (m), 1208 (m), 1123 (vs), 1069 (vs), 995 (s), 967 (s), 945 (m), 913 (s), 842 (w), 796 (w), 770 (w), 725 (m), and 665 (m) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=6.2$ – 5.5 (m, 1H), 5.2 – 4.8 (m, 2H), 2.71 (t, $J=7.0$ Hz, 2H), 2.46 (br s, 1H), 2.4 – 1.9 (m, 2H), 1.9 – 1.5 (m, 4H), 1.5 – 1.1 (m, 8H), and 0.87 (t, $J=5.6$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-117.07$ (d, $J=268.6$ Hz, 1F) and -120.47 (d, $J=268.6$ Hz, 1F); MS m/z (rel intensity) 262 (M^+ ; 0.1), 207 (2.5), 113 (100), 99 (58), and 85 (33). Found: C, 64.41; H, 9.48%. Calcd for $\text{C}_{14}\text{H}_{24}\text{F}_2\text{O}_2$: C, 64.10; H, 9.22%.

3,3-Difluoro-2-hydroxy-2-phenyl-4-dodecanone (7d): IR (neat) 3448 (br, s), 3064 (m), 3032 (m), 2952 (vs), 2928 (vs), 2858 (s), 1960 (w), 1888 (w), 1814 (w), 1739 (vs), 1495 (m), 1455 (s), 1400 (s), 1379 (m), 1341 (m), 1202 (s), 1159 (s), 1107 (vs), 1064 (vs), 1028 (s), 981 (m), 912 (w), 844 (m), 819 (m), 728 (s), 712 (s), 698 (vs), 664 (m), and 612 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.26$ (s, 5H), 5.03 (dd, $J=15.9$, 7.3 Hz, 1H), 3.1 – 2.5 (m, 1H), 2.53 (t, $J=7.2$ Hz, 2H), 1.8 – 1.0 (m, 8H), and 0.83 (t, $J=6.0$ Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-113.60$ (dd, $J=268.6$, 7.3 Hz, 1F) and -123.47 (dd, $J=268.6$, 15.9 Hz, 1F); MS m/z (rel intensity) 284 (M^+ ; 0.1), 121 (100), 113 (4), and 107 (27). Found: C, 67.51; 7.56%. Calcd for $\text{C}_{16}\text{H}_{22}\text{F}_2\text{O}_2$: C, 67.59; H, 7.80%.

4-Ethyl-3,3-difluoro-4-hydroxy-1-phenyl-2-hexanone (7e): IR (neat) 3468 (br, m), 3086 (w), 3060 (m), 3028 (m), 2970 (s), 2942 (s), 2884 (m), 1743 (vs), 1700 (s), 1655 (m), 1625 (m), 1618 (m), 1604 (m), 1498 (s), 1456 (vs), 1396 (s), 1341 (s), 1268 (m), 1207 (s), 1091 (vs), 1073 (vs), 1031 (s), 980 (s), 935 (m), 847 (m), 774 (m), 752 (m), 719 (s), and 697 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=7.5$ – 6.9 (m, 5H), 4.03 (s, 2H), 2.10 (br s, 1H), 1.73 (q, $J=7.4$ Hz, 2H \times 2), and 0.93 (t, $J=7.4$ Hz, 3H \times 2); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-115.64$ (s, 2F); MS m/z (rel intensity) 256 (M^+ ; 8), 169 (10), 119 (10), 91 (63), and 88 (100). Found: C, 65.77; H, 6.98%. Calcd for $\text{C}_{14}\text{H}_{18}\text{F}_2\text{O}_2$: C, 65.61; H, 7.08%.

Reformatsky-Type Reaction of 2 with 5-Hexen-2-one. Conditions E. A suspension of acid-washed zinc dust (0.196 g, 3.0 mmol) and silver acetate (0.017 g, 0.1 mmol) in ether (4 cm^3) and THF (1 cm^3) was stirred for 0.5 h at room temperature under argon. 5-Hexen-2-one (0.294 g, 3.0 mmol) and **2** (0.191 g, 1.0 mmol) were added to this suspension by use of a syringe. The mixture was refluxed for 4 h with stirring and, after cooling to room temperature, was filtered through a pad of Celite 545. Evaporation of volatile materials followed by column chromatography on silica gel afforded 2,2-difluoro-3-hydroxy-3-methyl-1-phenyl-6-hepten-1-one (**8**) (0.168 g): IR (neat) 3492 (br, s), 3072 (m), 2922 (vs), 2858 (s), 1693 (vs), 1643 (s), 1618 (w), 1598 (s), 1580 (m), 1560 (w), 1545 (w), 1491 (w), 1450 (vs), 1418 (m), 1379 (s), 1325 (m), 1279 (s), 1188 (s), 1155 (s), 1113 (vs), 1078 (vs), 1028 (m), 1001 (m), 965 (m), 912 (vs), 840 (m), 818 (m), 782 (w), 715 (vs), 685 (vs), and 663 (vs) cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=8.2$ – 7.9 (m, 2H), 7.6 – 7.1 (m, 3H), 6.2 – 5.5 (m, 1H), 5.2 – 4.8 (m, 2H), 2.83 (s, 1H), 2.6 – 2.0 (m, 2H), 2.0 – 1.6 (m, 2H), and 1.41 (dd, $J=1.2$, 1.2 Hz, 3H); $^{19}\text{F NMR}$ (CDCl_3) $\delta=-108.94$ (d, $J=290.5$ Hz, 1F) and -112.6 (d, $J=290.5$ Hz, 1F); MS m/z (rel intensity) 254 (M^+ ; 4.2), 199 (6.2), and 105 (100). Found: C, 66.44; H, 6.56%. Calcd for $\text{C}_{14}\text{H}_{16}\text{F}_2\text{O}_2$: C, 66.13;

H, 6.34%.

Detection of Zinc(II) Enolates 9 and 10 under the Conditions C. A 50-cm³ three-necked flask purged with argon was charged with acid-washed zinc (0.196 g, 3.0 mmol), copper(I) chloride (0.030 g, 0.3 mmol), THF (1 cm³), and ether (4 cm³). To this suspension, after stirring for 0.5 h at room temperature followed by cooling to -20 °C, were added dropwise boron trifluoride diethyl etherate (0.142 g, 1.0 mmol) and **2** (0.191 g, 1.0 mmol) or **3a** (0.223 g, 1.0 mmol). The mixture was stirred for 1 h at the same temperature. An aliquot of the supernatant (about 0.3 cm³) was introduced via a syringe into an argon-purged NMR sample tube, which was immediately subjected to ¹⁹F NMR analysis. Figure 1 depicts the spectra observed in sequential transformation of **2** to **5c** through the enolate **9**. Table 3 lists the ¹⁹F NMR data of **9** and **10**, along with those of the related compounds **11–13**.

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