Addition of α,α-Difluoroiodomethyl Ketones to Alkenes with a Copper Catalyst

Kyung Chell Kwak, Woo-Yiel Lee, Quan Zheshan,[†] Young Hang Lee, Young-Gab Yun,[‡] Gyu Beum Kwak,[§] Hun-Taeg Chung,[#] Tae-Oh Kwon,[¶] and Kyu Yun Chai[*]

Department of Bionanochemistry and Basic Sciences Research Institute, Wonkwang University, Iksan, Chonbuk 570-749, Korea
[*]E-mail: geuyoon@wonkwang.ac.kr
[†]College of Pharmacy, Yanbian University, Yanji 133000, China
[‡]Department of Prescription, School of Oriental Medicine, Wonkwang University, Iksan, Chonbuk 570-749, Korea
[§]Department of New Material Science, Chonbuk National University, Jeonju, Chonbuk 561-756, Korea
[#]Medicinal Resources Research Center of Wonkwang University, Iksan, Chonbuk 570-749, Korea
[¶]College of Life Science and Natural Resources, Wonkwang University, Iksan, Chonbuk 570-749, Korea
Received July 20, 2004

The addition reactions of α,α-difluoroiodomethyl *n*-butyl ketone, α,α-difluoroiodomethyl cyclohexyl ketone, or α,α-difluoroiodomethyl phenyl ketone to alkenes were successfully accomplished in good yields in the presence of copper powder. The reaction was also applicable to alkenes containing a variety of functional groups such as ester, trimethylsilyl, or ether group. Acetonitrile was determined to be the best solvent in the present study and the reaction was performed at 55 °C for 15-22 h. This reaction provides a new, efficient and general method for the synthesis of α,α-difluoro functionalized ketones.

Key Words : α,α-Difluoroiodomethyl ketone derivatives, Copper catalyst

Introduction

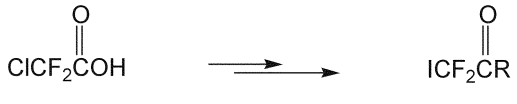
The organic compounds with selectively introduced difluoromethylene group have been known to exhibit important biological properties such as the inhibitory effects on various enzymes,[1] antibiotic,[2] anti-human immunodeficiency virus (HIV),[3] anticancer and antihypertensive effects.[4]

Difluoromethylene group has been generally introduced to organics by the methods previously reported as follows. The addition of perfluoroalkyl iodide to alkenes was performed in the presence of various catalysts such as titanium,[5] benzoylperoxide,[6] sodium dithionite[7] and organophosphines.[8] The Reformatsky reaction was used to prepare α,α-difluoro-β-hydroxy carbonyl compounds from the reaction of aldehydes with α-chloro-α,α-difluoromethyl ketones[9] or α-bromo-α,α-difluoro acetates.[10] The addition of ethyl bromodifluoroacetate to alkenes was carried out using nikel chloride or copper powder as a catalyst.[11] The transformation of carbonyl group to difluoromethylene group utilizing (diethylamino)sulfur trifluoride (DAST) was reported.[12] In addition, difluoromethylene ketone was recently reported to be introdued to the electron-deficient olefins using UV irradiation,[13] while palladium catalyst was used for the addition to electron-rich olefins.[14]

However, since the experimental procedure required for the photoreaction involving the repeated freezing under liquid nitrogen and degassing processes is complicated, this method could be limited in general utilization. Moreover, palladium is expensive and limited numbers of method are available for the addition of difluoromethylene group to electron-rich olefins. As a preliminary result, we briefly described the addition of α,α-difluoroiodomethyl cyclohexyl ketone to alkenes in the presence of copper.[15] We report here the detailed results concerning the addition of α,α-difluoroiodomethyl phenyl ketone, α,α-difluoroiodomethyl cyclohexyl ketone and α,α-difluoroiodomethyl *n*-butyl ketone to alkenes, respectively, with a variety of functional groups such as trimethylsilyl, ether and ester group in the presence of copper.

Results and Discussion

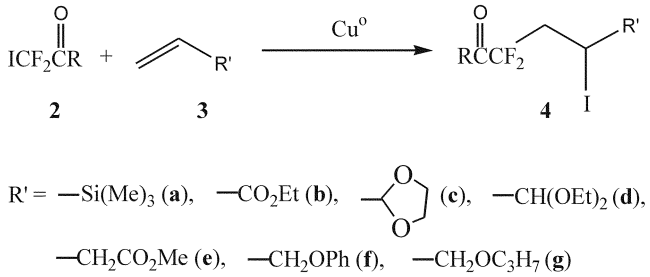
The starting compounds in this study, α,α-difluoroiodomethyl phenyl ketone (**2a**), α,α-difluoroiodomethyl cyclohexyl ketone (**2b**) and α,α-difluoroiodomethyl *n*-butyl ketone (**2c**), are readily obtained from chlorodifluoroacetic acid (**1**) using the Grignard reaction followed by the Reformatsky reaction[16] (Scheme 1). The difluoroiodomethyl ketone compounds were reacted with alkenes having various functional groups (Scheme 2) such as vinyltrimethylsilane (**3a**), ethyl acrylate (**3b**), vinyl-1,3-dioxolane (**3c**), 3,3-diethoxy-1-propene (**3d**), methyl 3-butenoate (**3e**), allyl phenyl ether (**3f**) and allyl propyl ether (**3g**). The addition of 1.2 to 2 equivalents of olefins to α,α-difluoroiodomethyl ketones (**1a**, **1b**, **1c**) was successfully carried out in acetonitrile at 55 °C for 15 to 22 h in the presence of 30 mole



1 **2**

R: Phenyl (**2a**), Cyclohexyl (**2b**), *n*-Butyl (**2c**)

Scheme 1



Scheme 2

Table 1. Copper-catalyzed addition of difluoroiodomethyl ketones to alkene derivatives

Entry	Substrate	Reactant (R')	Reaction time (h)	Product	Yield (%)
1	**1a**	**3a**	15	**4aa**	97
2	**1a**	**3b**	22	**4ab**	42
3	**1a**	**3c**	18	**4ac**	89
4	**1a**	**3d**	18	**4ad**	73
5	**1a**	**3e**	18	**4ae**	78
6	**1a**	**3f**	15	**4af**	95
7	**1a**	**3g**	18	**4ag**	81
8	**1b**	**3a**	15	**4ba**	90
9	**1b**	**3b**	22	**4bb**	52
10	**1b**	**3c**	18	**4bc**	80
11	**1b**	**3d**	18	**4bd**	72
12	**1b**	**3e**	18	**4be**	82
13	**1b**	**3f**	22	**4bf**	66
14	**1b**	**3g**	22	**4bg**	70
15	**1c**	**3a**	15	**4ca**	94
16	**1c**	**3b**	22	**4cb**	55
17	**1c**	**3c**	18	**4cc**	85
18	**1c**	**3d**	18	**4cd**	74
19	**1c**	**3e**	18	**4ce**	75
20	**1c**	**3f**	18	**4cf**	88
21	**1c**	**3g**	18	**4cg**	80

% copper powder. The reaction products were obtained with 40 to 97% yields (Table 1).

All the products were identified using ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MS spectra. ^{19}F NMR spectra of all the adducts showed typical AB splitting patterns, because the two fluorines are not equivalent due to the presence of the γ-positioned chiral center. For example, the ^{19}F NMR of 2,2-fluoro-4-iodo-1-phenyl-4-trimethylsilylbutanone had doublets at −109.2 and −103.8 ppm with coupling constants of $^{2}J_{FF}$ = 261.0, $^{3}J_{FF}$ = 16.1 and $^{3}J_{FF}$ = 16.1 Hz.

The addition products formed from the reaction of α,α-difluoromethylphenyl ketone with various alkenes with the exception of ethyl acrylate were obtained with slightly higher yields (3-5%) than those formed from α,α-difluoro-iodomethyl cyclohexyl ketone or α,α-difluoromethyl *n*-butyl ketone. Considering the functional groups of alkene, the reaction with the electron-rich olefin (**3a**) having trimethyl-silyl group gave the addition product in the highest yield (> 90%). By contrast, the electron-deficient olefin (**3b**) afforded the lower yields of the adducts in the reaction with the difluoroiodomethyl ketones (**2**). These results indicate that the mechanism of addition reaction has a similarity to that suggested for the reaction of iododifluoromethyl ketones with normal alkenes using Pd(0) catalyst.[14,17] Therefore, electron scavengers or radical inhibitors are expected to inhibit the addition reaction including a single electron transfer process. The radical mechanism was supported by the observation that **2a** was not reacted with **3a** under the same reaction conditions in the presence of 30 mole % dinitrobenzene. The detail mechanism of the current reactions has been proposed in Figure 1.

In order to improve the yield of addition, the reaction of α,α-difluoroiodomethyl phenyl ketone (**2a**) with trimethyl-silane (**3a**) in presence of copper was allowed in a variety of solvents. When methylene chloride, acetonitrile, *n*-hexane, THF, DMDO, DMF and ethyl acetate were employed for the reaction, acetonitrile was determined to be the best solvent. It is noteworthy that the coordinating solvents such as DMSO, DMF and THF gave low yields (Table 2).

Scince the fluorination of biologically important mole-cules has resulted in dramatic changes and distintive modifi-cations in their biological activities,[18] many efforts have been made to design the efficient methods for the synthesis of selectively fluorinated compounds. Although the recent methods using Pd(0) catalyst and UV irradiation may be general ways to prepare the adducts of difluoroiodomethyl

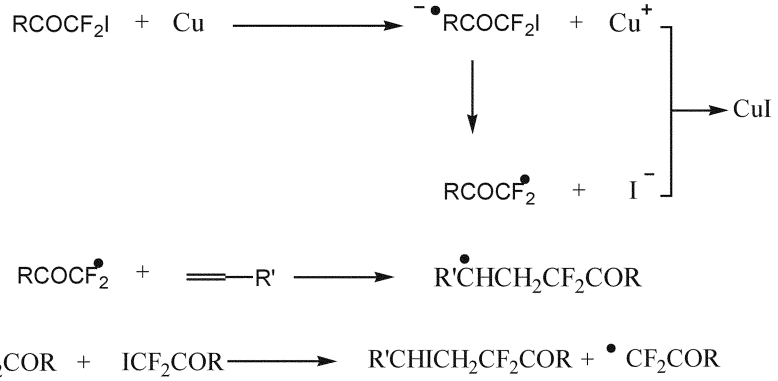


Figure 1. The proposed mechanism of the addition of α,α-difluoroiodomethyl alkyl ketones to alkenes in the presence of copper catalyst.

Table 2. Investigation of solvent effect

No	Solvent	Time (h)	Yield (%)
1	CH_3CN	18	99
2	MC	18	60
3	THF	18	30
4	DMSO	6	40
5	DMF	6	30
6	EA	18	< 5
7	*n*-Hexane	24	NR

ketones with olefins, this method provides a simple and more efficient approach to the introduction of α,α-difluoromethylene group to various olefins.

Experimental Section

General experimental procedures. NMR spectra were recorded in $CDCl_3$ using a JEOL Eclipse 500-MHz spectrometer, and ^1H and ^{13}C chemical shifts were referenced relative to the corresponding residual solvent signals (δ 7.24/77.0). ^{19}F NMR spectra were referenced relative to an internal $CFCl_3$. All mass spectra analyses were performed at 70 eV in electron impact mode. The IR spectra were obtained on a JASCO FT/IR-5300.

General procedure used to prepare the addition products (4). To a solution of α,α-difluoroiodomethyl ketone (**2**, 0.1 mol) and activated copper powder (0.015 mol) in dry acetonitrile (100 mL), olefin (**3**, 0.12 to 0.20 mol) was dropped under N_2 gas (Scheme 2), and the mixture was heated at 60 °C for 15 to 22 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The resulting residue was partitioned between diethyl ether and water, and the diethyl ether layer was dried with $MgSO_4$. After the solvent was evaporated under reduced pressure, the residue was applied onto a silica gel column to afford compound **4**.

2,2-Difluoro-4-iodo-1-phenyl-4-trimethylsilyl-1-butanone (4aa). ^1H NMR ($CDCl_3$, TMS): δ 8.11 (d, *J* = 7.79 Hz, 2H), 7.64 (t, *J* = 7.33 Hz, 1H), 7.50 (t, *J* = 7.79 Hz, 2H), 3.25 (dd, *J* = 10.54, 2.75 Hz, 1H), 2.75 (m, 2H), 0.20 (s, 9H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −108.14 (ddd, *J* = 264.37, 17.04, 17.0 Hz, 1F) δ −104.78 (ddd, *J* = 264.37, 17.04, 17.0 Hz, 1F). ^{13}C NMR ($CDCl_3$, TMS): δ 189.4 (t, *J* = 30.7 Hz), 134.6 (s), 132.2 (s), 130.5 (s), 128.9 (s), 119.3 (t, *J* = 256.2 Hz), 38.3 (t, *J* = 23.0 Hz), 4.4 (s). GC-MS (m/e, relative intensity): 382 (M^+, 1.03), 105 (48.34), 77 (96.60), 73 (100). IR (CCl_4): 3067, 2955, 2926, 2854, 1701, 1599, 1450, 1251, 1417, 1179 cm^{-1}

Ethy1-4,4-difluoro-2-iodo-5-oxo-5-phenylpentanoate (4ab). ^1H NMR ($CDCl_3$): δ 8.05 (d, *J* = 8.25 Hz, 2H), 7.62 (t, *J* = 7.33 Hz, 1H), 7.47 (t, *J* = 7.79 Hz, 2H), 4.63 (dd, *J* = 10.77, 3.44 Hz, 1H) 4.20 (q, *J* = 7.10 Hz, 2H) 3.36 (m, 1H) 2.85 (m, 1H), 1.17 (t, *J* = 7.10 Hz, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −109.27 (ddd, *J* = 261.48, 17.01, 17.01 Hz, 1 F) δ −104.32 (ddd, *J* = 261.48, 17.01, 17.01 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 187.93 (t, *J* = 30.23 Hz), 134.74 (s), 131.35 (s), 130.26 (t, *J* = 3.84 Hz) 128.85 (s), 118.35 (t, *J* = 256.24 Hz), 62.26 (s), 41.21 (t, *J* = 23.09 Hz) 13.69 (s), 7.99 (t, *J* = 3.84 Hz). IR (CCl_4): 3422, 1740, 1449 cm^{-1}. GC-MS (m/e, relative intensity): 382 (M^+, 0.45), 337 (24.26), 309 (27.24), 255 (87.67), 182 (29.36), 162 (44.04), 133 (17.65), 105 (100).

2,2-Difluoro-4-(1,3-dioxolan-2-yl)-4-iodo-1-phenyl-1-butanone (4ac). ^1H NMR ($CDCl_3$): δ 8.10 (d, *J* = 7.79 Hz, 2H), 7.64 (t, *J* = 7.33 Hz, 1H), 7.51 (t, *J* = 7.79 Hz, 2H), 4.68 (d, *J* = 3.21 Hz 1H), 4.38 (m, 1H), 4.11 (m.2H), 3.97 (m, 2H), 3.02, (dddd *J* = 18.83 Hz, 18.83 Hz, 6.88 Hz, 6.88 Hz 2H). ^{19}F NMR ($CFCl_3$): δ −107.34 (ddd, *J* = 273.04, 16.07, 16.07 Hz, 1F), δ −104.42 (ddd, *J* = 273.04, 16.07, 16.07 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 188.53 (t, *J* = 31.67 Hz), 134.53 (s), 131.75 (s), 130.27 (t, *J* = 2.88 Hz), 128.80 (s), 118.67 (t, *J* = 256.24 Hz), 104.22 (s), 66.16 (s), 65.59 (s), 38.99 (t, *J* = 22.07 Hz), 21.86 (s). GC-MS (m/e, relative intensity): 207 (0.22), 150 (0.77), 132 (1.96), 127 (0.11), 106 (8.11), 105 (100.00), 77 (42.63), 57 (23.50), 51 (23.20). IR (CCl_4): 3065, 2928, 2856, 1720, 1599, 1452, 1375 cm^{-1}.

5,5-Diethoxy-2,2-difluoro-4-iodo-1-phenyl-1-pentanone (4ad). ^1H NMR ($CDCl_3$): δ 8.10 (d, *J* = 7.79 Hz, 2H), 7.64 (t, *J* = 7.79 Hz, 1H), 7.50 (t, *J* = 7.79 Hz, 2H), 4.31 (m, 2H), 3.72 (m, 2H), 3.58 (m, 2H), 3.16 (m, 1H), 2.87 (m, 1H), 1.22 (q, *J* = 7.33, 4H), 0.86 (m, 6H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −107.53 (ddd, *J* = 278.64, 17.08, 17.08 Hz, 1F) δ −104.27 (ddd, *J* = 278.64, 17.08, 17.08 Hz, 1F) ^{13}C NMR ($CDCl_3$): δ 188.52 (t, *J* = 31.72 Hz),134.47 (s), 131.72 (s), 130.28 (t, *J* = 2.88 Hz), 128.78 (s), 118.68 (t, *J* = 256.72 Hz), 104.04 (s), 64.19 (s), 62.86 (s), 38.82 (t, *J* = 21.08 Hz), 30.78 (s), 15.15 (s), 15.13 (s). GC-MS (m/e, relative intensity): 373 (0.5), 309 (0.02), 291 (0.21), 271 (0.12), 245 (0.35), 225 (0.49), 180 (0.73), 155 (0.26), 149 (0.56), 127 (0.59), 104 (56.10), 103 (100. 00), 83 (38.56), 77 (5.81), 75 (52.17), 59 (13. 59), 55 (64.39). IR (CCl_4): 3048, 2988, 2928, 1712, 1599, 1450, 1376 cm^{-1}.

Methyl 5,5-difluoro-3-iodo-6-oxo-6-phenylhexanoate (4ae). ^1H NMR ($CDCl_3$): δ 8.10 (d, *J* = 7.79 Hz, 2H), 7.65 (t, *J* = 7.10 Hz, 1H), 7.51 (t, *J* = 7.56 Hz, 2H), 4.48 (m, 2H), 4.28 (m, 1H), 3.01 (m, 2H), 2.06 (s, 3H). ^{19}F NMR ($CFCl_3$, $CDCl_3$): δ −108.76 (ddd, *J* = 284.17, 14.04, 14.04 Hz, 1F) δ −104.24 (ddd, *J* = 284.17, 14.04, 14.04 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 188.27 (t, *J* = 30.71 Hz), 170.22 (s), 134.72 (s), 131.50 (s), 130.33 (t, *J* = 2.88 Hz), 128.86 (s), 118.61 (t, *J* = 256.24 Hz), 68.91 (s), 41.06 (t, *J* = 24.04 Hz), 20.77 (s), 15.03 (t, *J* = 3.84 Hz). IR (CCl_4): 3055, 2924, 2854, 1751, 1703, 1450, 1383 cm^{-1}. GC-MS (m/e, relative intensity): 382 (M^+. 0.15), 351 (1.04), 323 (2.85), 255 (23.45), 105 (100.00), 77 (43.05).

2,2-Difluoro-4-iodo-5-phenoxy-1-phenyl-1-hexanone (4af). ^1H NMR ($CDCl_3$): δ 8.08 (d, *J* = 7.79 Hz 2H), 7.64 (t, *J* = 7.79 Hz 1H), 7.49-6.98 (m, 7H), 4.59 (quintet, *J* = 6.87 Hz 1H), 4.31 (dd, *J* = 10.31, 5.24 Hz 1H), 4.21 (dd, *J* = 10.31, 6.87Hz 1H), 3.14 (dddd, *J* = 16.27 Hz, 16.27 Hz, 6.87 Hz, 6.87 Hz 2H). ^{19}F NMR ($CFCl_3$): δ −106.77 (ddd, *J* = 283.15, 16.27, 16.17 Hz, 1F) δ −104.38 (ddd, *J* = 283.15, 16.27, 16.17 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 188.40 (t, *J* =

30.71 Hz), 157.79 (s), 135.09 (s), 134.61 (s), 130.33 (t, *J* = 2.88 Hz), 129.64 (s), 128.82 (s), 121.67 (s), 118.74 (t, *J* = 255.28 Hz), 114.93 (s), 73.02 (s), 41.03 (t, *J* = 22.07 Hz), 16.03 (s). GC-MS (m/e, relative intensity): 329 (11.54), 311 (0.56), 309 (0.79), 291 (1.51), 261 (0.47), 247 (1.65), 217 (1.21), 183 (3.21), 163 (3.22), 139 (5.69), 127 (1.20), 119 (8.16), 105 (7.53), 93 (42.16), 90 (12.28), 83 (50.52), 77 (21.65), 65 (32.46), 55 (100.00), 51 (21.20). IR (CCl_4): 3067, 3040, 2986, 2924, 2866, 1703, 1649, 1599, 1494, 1454 cm^{-1}.

2,2-Difluoro-4-iodo-1-phenyl-5-propanoxy-1-pentanone (4ag). ^{1}H NMR ($CDCl_3$): δ 8.10 (d, *J* = 7.79 Hz , 2H), 7.64 (t, *J* = 7.33 Hz 1H), 7.50 (t, *J* = 7.79 Hz 2H), 4.41 (quintet, *J* = 6.42 Hz 1H), 3.71 (dd, *J* = 10.54. 5.50 Hz, 1H), 3.64 (dd, *J* = 10.54, 6.87 Hz, 1H), 3.42 (m, 2H), 3.17 (m, 1H), 2.87 (m, 1H),1.53 (sextet, *J* = 7.33 Hz, 2H) 0.89 (t, *J* = 7.33 Hz. 3H). ^{19}F NMR. ($CDCl_3$, $CFCl_3$): δ –108.88 (ddd, *J* = 284.21, 17.21, 17.21 Hz, 1F) δ –106.47 (ddd, *J* = 284.21, 17.21, 17.21 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 188.51 (t, *J* = 30.71 Hz), 134.49 (s), 130.29 (t, *J* = 2.88 Hz), 128.78 (s), 75.89 (s), 72.67 (s), 40.95 (t, *J* = 22. 55Hz), 29.79 (s), 22.79 (s), 18.05 (t, *J* = 2.88 Hz), 14.21 (s), 10.64 (s). GC-MS (m/e, relative intensity): 323 (0.44), 255 (5.21), 213 (10.28), 176 (4.20), 156 (0.84), 149 (4.78), 147 (3.64), 127 (3.50), 105 (100.00), 77 (61.82), 57 (8.68), 51 (33.68). IR (CCl_4): 3055, 2924, 2854, 1703, 1599, 1581, 1450, 1377 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-iodo-4-trimethylsilyl-1-butanone (4ba). ^{1}H NMR ($CDCl_3$): δ 3.08 (dd, *J* = 10.54, 3.21 Hz, 1H), 2.96 (dddd, *J* = 11.91, 11.92, 3.21, 3.21 Hz, 1H), 2.60 (m, 2H), 1.30-1.85 (m, 10H), 0.21 (s, 9H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –108.38 (ddd, *J* = 279.45, 16.55, 16.55 Hz, 1F) δ –102.70 (ddd, *J* = 279.45, 16.55, 16.55 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 203.90 (t, *J* = 29.75 Hz), 118.20 (t, 254.32 Hz), 45.20 (s), 37.24 (t, *J* = 23.51 Hz), 28.49 (s), 28.31 (s) , 25.87 (s), 25.70 (s), 25.60 (s), 5.03 (t, *J* = 2.88 Hz), –2.35 (s). IR: 3393, 2949, 2926, 1738, 1451 cm^{-1}. GC-MS (m/e, relative intensity): 389 (0.17), 388 (0.89), 373 (0.82), 261 (3.41), 177 (0.12), 169 (10.16), 127 (2.20), 111 (17.17), 83 (100.00), 73 (55.33), 55 (76.79), 53 (10.58).

Ethyl 5-cyclohexyl-4,4-difluoro-2-iodo-5-oxopentanoate (4bb). ^{1}H NMR ($CDCl_3$): δ 4.52 (dd, *J* = 10.54, 3.67 Hz, 1H), 4.21 (q, *J* = 7,10 Hz, 2H), 3.10 (m, 1H), 2.84 (m, 1H), 2.66 (m, 1H), 1.90-1.25 (m, 10H), 1.27 (t, *J* = 7.33 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 202.63 (t, *J* = 29.75 Hz), 170.80 (s), 117.04 (t, *J* = 255.28 Hz), 62.27 (s), 44.77 (s), 40.32 (t, *J* = 23.03 Hz), 28.33 (s), 28.20 (s), 25.59 (s), 25.43 (s), 25.39 (s), 17.72 (s), 7.38 (t, *J* = 4.32 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –107.18 (ddd, 278.44, 21.32, 11.29 Hz, 1F) δ –103.47 (ddd, 278.44, 21.32, 11.29 Hz, 1F) IR (CCl_4): 2931, 2857, 1749, 1601, 1484, 1283 cm^{-1}. GC-MS (m/e, relative intensity): 388 (M^+, 0.25), 342 (0.85), 323 (1.45), 241 (28.25), 111 (100), 83 (72.45).

1-Cyclohexyl-2,2-difluoro-4-(1.3-dioxolan-2-yl)-4-iodo-1-butanone (4bc). ^{1}H NMR ($CDCl_3$): δ 4.61 (d, *J* = 3.21 Hz, 1H), 4.21 (ddd, *J* = 8.02, 5.27, 3.21 Hz, 1H), 4.08 (m, 2H), 3.95 (m, 2H), 2.87 (m, 2H), 2.69 (m, 1H), 1.78 (m, 4H), 1.29 (m, 6H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –107.61 (ddd, *J* = 272.14, 20.36, 10.32 Hz, 1F) δ –103.22 (ddd, *J* = 272.14, 20.36, 10.32 Hz, 1F). ^{13}C NMR ($CDCl_3$, TMS): δ 203.00 (t, *J* = 30.23 Hz), 117.58 (t, *J* = 255.28 Hz), 104.14 (s), 66.11 (s), 65.93 (s), 44.86 (s), 38.01 (t, *J* = 23.03 Hz), 28.37 (s), 28.33 (s), 25.65 (s), 25.49 (s), 25.42 (s), 22.08 (s). GC-MS (m/e, relative intensity): 261 (0.74), 241 (0.17), 168 (0.14), 155 (0.42), 127 (0.57), 111 (3.62), 106 (1.20), 99 (3.04), 83 (21.51), 77 (2.48), 74 (3.40), 73 (100.00), 55 (30.53), 51 (2.01). IR (CCl_4): 2978, 2934, 1735, 1695, 1598, 1450, 1378 cm^{-1}.

1-Cyclohexyl-5,5-diethoxy-2,2-difluoro-4-iodo-1-pentanone (4bd). ^{1}H NMR ($CDCl_3$): δ 4.28 (d, *J* = 3.67 Hz, 1H), 3.70 (q, *J* = 7.33 Hz, 2H), 3.57 (q, *J* = 7.33 Hz, 2H), 2.91 (m, 2H), 2.67 (m, 1H), 1.92-1.83 (m, 6H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –107.21 (ddd, *J* = 272.24, 21.32, 10.35 Hz, 1F) δ –103.46 (ddd, *J* = 272.24, 21.32, 10.35 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 203.29 (t, *J* = 30.48 Hz), 117.87 (t, *J* = 254.32 Hz), 104.09 (s), 64.19 (s), 63.91 (s), 45.01 (s), 37.48 (t, *J* = 23.03 Hz), 28.44 (s), 28.31 (s), 25.66 (s), 25.53 (s), 25.43 (s), 21.34 (s), 15.17 (s). GC-MS (m/e, relative intensity): 373 (0.56), 291 (0.27), 225 (0.46), 180 (0.84), 177 (0.33), 149 (0.60), 135 (0.75), 127 (0.62), 111 (4.25), 103 (100.00), 87 (8.55), 83 (46.24), 77 (4.46), 75 (55.10), 67 (5.68), 55 (66.76). IR (CCl_4): 2976, 2934, 1734, 1691, 1599, 1450, 1375, 1275 cm^{-1}.

Methyl-6-cyclohexyl-5,5-difluoro-3-iodo-6-oxohexanoate (4be). ^{1}H NMR ($CDCl_3$): δ 4.32 (m, 2H), 2.91 (m, 1H), 2.76 (m, 2H), 2.11 (s, 3H), 1.89-1.23 (m, 10H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –103.96 (ddd, *J* = 285.25, 21.94, 13.97 Hz, 1F) δ –107.40 (ddd, *J* = 285.25, 21.94, 13.97 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 202.93 (t, *J* = 29.75 Hz), 170.22 (s), 117.76 (t, *J* = 255.43 Hz), 68.83 (s), 4.85 (s), 39.95 (t, *J* = 23.99 Hz), 28.43 (s), 28.33 (s), 25.67 (s), 25.49 (s), 25.42 (s), 20.83 (s), 15.19 (t, *J* = 3.84 Hz). GC-MS (m/e, relative intensity): 367 (0.02), 261 (2.05), 241 (2.00), 201 (0.51), 181 (3.91), 161 (1.34), 127 (0.99), 111 (25.34), 91 (4.31), 83 (100.00), 55 (77.81). IR (CCl_4): 2934, 2856, 1747, 1450, 1381, 1226 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-iodo-5-phenoxy-1-pentanone (4bf). ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 2H), 6.99 (t, *J* = 7.33 Hz, 1H), 6.90 (d, *J* = 7.79 Hz, 2H), 4.44 (5, *J* = 6.42 Hz, 1H), 4.24 (dd, *J* = 10.31,5.27 Hz, 1H), 4.15 (dd, *J* = 10.31, 6.65 Hz, 1H), 3.03 (m, 1H), 2.92 (m, 1H), 2.78 (m, 1H), 1.86 -1.25 (m, 10H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ –106.78 (ddd, *J* = 270.28, 19.40, 10.35 Hz, 1F) δ –104.30 (ddd, *J* = 279.33, 20.69, 10.35 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 202.99 (t, *J* = 35.03 Hz), 157.86 (s), 129.69 (s), 121.73 (s), 114.97 (s), 73.08 (s), 44.87 (s), 39.96 (t, *J* = 23.03 Hz), 28.39 (s), 28.36 (s), 25.63 (s), 25.48 (s), 25.43 (s), 16.19 (s). GC-MS (m/e, relative intensity): 422 (M^+, 0.53), 330 (2.59), 329 (19.55), 291 (2.88), 247 (3.42), 217 (3.05), 183 (5.34), 163 (4.95), 111 (6.81), 94 (34.74), 83 (50.51), 77 (23.80), 65 (28.74), 55 (100.00), 51 (20.65). IR (CCl_4): 3040, 2932, 2856, 1734, 1559, 1496, 1452, 1240 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-iodo-5-propanoxy-1-pentanone (4bg). ^{1}H NMR ($CDCl_3$): δ 4.22 (quintet, *J* = 6.65 Hz, 1H), 3.66 (dd, *J* = 10.54, 5.50 Hz, 1H), 3.58 (dd, *J*=10.54, 6.87 Hz, 1H), 3.41 (t, *J* = 6.87 Hz, 2H), 2.87 (m,

2H), 2.62 (m, 1H), 1.56 (sextet, *J* = 7.33 Hz, 2H), 1.38-1.21 (m, 10H), 0.90 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −106.79 (ddd, *J* = 282.71, 19.71, 12.13 Hz, 1F) δ −104.23 (ddd, *J* = 282.71, 19.73, 12.14 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 203.06 (t, *J*=30.71 Hz), 117.71 (t, *J* = 255.28 Hz), 75.88 (s), 72.70 (s), 44.86 (s), 39.84 (t, *J* = 20.03 Hz), 28.38 (s), 28.30 (s), 25.63 (s), 25.47 (s), 25.40 (s), 22.80 (s), 10.60 (s). GC-MS (m/e, relative intensity): 329 (0.09), 241 (3.42), 181 (3.48), 162 (1.81), 133 (2.28),127 (1.22), 111 (18.09), 83 (97.38), 58 (5.67), 55 (100.00), 52 (10.12). IR (CCl_4): 2934, 2858, 1734, 1450, 1289 cm^{-1}.

Difluoro-1-iodo-1-trimethylsilyl-4-octanone (4ca). ^{1}H NMR ($CDCl_3$) : δ3.08 (dd, *J* = 10.54 Hz, 3.21 Hz, 1H), 2.73 (m, 2H), 2.59 (m, 2H), 1.61 (quintet, *J* = 7.33 Hz, 2H), 1.34 (sextet, *J* = 7.33 Hz, 2H), 0.90 (t, *J* = 7.33 Hz, 3H), 0.12 (s, 9H). ^{19}F NMR ($CFCl_3$): δ −109.15 (ddd, *J* = 261.01 Hz, 16.06, 16.06 Hz) δ −103.79 (ddd, *J* = 261.01 Hz, 16.06, 16.06 Hz). ^{13}C NMR ($CDCl_3$): δ −2.40 (s), 4.89 (s), 13.82 (s), 22.11 (s), 24.76 (s), 36.63 (s), 37.08 (t, *J* = 23.99 Hz), 117.60 (t, *J* = 254.31 Hz), 201.15 (t, *J* = 31.19 Hz). IR (CCl_4) : 2917, 2904, 1706, 1448 cm^{-1}. GC-MS (m/e, relative intensity): 55.00 (54.27), 57.05 (97.45), 73.05 (100.00), 85.10 (54.89), 101.05 (6.33), 143.05 (12.35), 151.05 (10.97), 157.10 (8.31), 185.00 (7.73), 235.20 (2.84), 362.15 (0.75).

Ethyl 4,4-difluoro-2-iodo-5-oxononanoate (4cb). ^{1}H NMR ($CDCl_3$): δ4.51 (dd, *J* = 10.31 Hz, 3.44 Hz, 1H), 4.19 (q, *J* = 7.33 Hz, 2H), 3.10 (m, 2H), 2.63 (t, *J* = 6.42 Hz, 3H), 1.56 (quintet, *J* = 7.33 Hz, 2H), 1.31 (sextet, *J* = 7.33 Hz, 2H), 1.25 (t, *J* = 7.33 Hz, 2H), 0.89 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CFCl_3$): δ −108.37 (ddd, *J* = 272.14, 17.37, 17.37 Hz, 1F). δ −103.54 (ddd, *J* = 272.14, 17.37, 17.37 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 199.94 (t, *J* = 30.71 Hz), 170.77 (s), 116.48 (t, *J* = 255.28 Hz), 62.57 (s), 39.96 (t, *J* = 23.03 Hz), 35.77 (s), 24.64 (s), 22.08 (s), 13.75 (s), 7.69 (t, *J* = 3.84 Hz). GC-MS (m/e, relative intensity): 362 (M^+, 0.03), 316 (0.43), 269 (0.41), 235 (0.40), 215 (5.53), 141 (1.61), 127 (2.47), 122 (2.43), 101 (1.24), 93 (1.83), 85 (69.22), 77 (4.20), 57 (100.00), 55 (24.92), 51 (9.13). IR (CCl_4): 2976, 2935, 1734, 1690, 1597, 1450 cm^{-1}.

3,3-Difluoro-1-(1,3-dioxolan-2-yl)-1-iodo-4-octanone (4cc). ^{1}H NMR ($CDCl_3$): δ4.65 (d, *J* = 3.21 Hz, 1H), 4.22 (m,1H), 4.10 (m, 2H), 3.96 (m, 2H), 2.88 (m, 1H), 2.73 (m, 1H), 2.70 (t, *J* = 2.87 Hz, 2H), 1.61 (quintet, *J* = 7.33 Hz, 2H), 1.34 (sextet, *J* = 7.33 Hz, 2H), 0.92 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CFCl_3$): δ −106.32 (ddd, *J* = 282.04, 15.78, 15.78 Hz, 1F) δ −104.80 (ddd, *J* = 286.25, 18.75, 17.89 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ200.34 (t, *J* = 30.71 Hz), 117.02 (254.32 Hz), 104.18 (s), 66.13 (s), 65.91 (s), 37.70 (t, *J* = 23.51 Hz), 36.08 (s), 29.78 (s), 22.13 (s), 21.77 (t, *J* = 2.88 Hz), 13.08 (s). GC-MS (m/e, relative intensity): 362 (M^+, 0.10), 235 (0.02), 127 (0.52), 119 (0.26), 99 (3.37), 85 (8.75), 77 (2.34), 74 (4.27), 73 (100.00), 57 (20.96), 55 (9.64), 51 (2.44). IR (CCl_4): 2959, 2928, 1741, 1464, 1379, 1259 cm^{-1}.

1,1-Diethoxy-4,4-difluoro-2-iodo-5-nonanone (4cd). ^{1}H NMR ($CDCl_3$): δ4.30 (d, *J* = 4.12 Hz, 1H), 4.15 (quintet, *J* = 4.35 Hz, 1H), 3.70 (m, 2H), 3.57 (m, 2H), 2.94 (m,1H), 2.69 (t, *J* = 7.33 Hz, 3H), 1.35 (sextet, *J* = 7.33 Hz, 2H), 1.25-1.21 (m, 8H), 0.92 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −107.33 (ddd, *J* = 277.04, 20.89, 13.63 Hz, 1F) δ −105.10 (ddd, *J* = 277.32, 20.88, 13.64 Hz, 1F). ^{13}C NMR ($CDCl_3$,): δ200.54 (t, *J* = 32.63 Hz), 117.33 (t, *J* = 253.36 Hz), 104.12 (s), 64.26 (s), 63.88 (s), 37.27 (t, *J* = 23.99 Hz), 36.26 (s), 29.78 (s), 22.15 (s), 21.17 (t, *J* = 3.84 Hz), 15.17 (s), 15.13 (s), 13.84 (s). GC-MS (m/e, relative intensity): 347 (1.009), 219 (0.43), 191 (0.51), 172 (1.95), 169 (1.35), 134 (1.58), 127 (0.89), 115 (2.20), 105 (5.59), 103 (100.00), 87 (11.43), 85 (31.59), 77 (7.80), 75 (84.06), 57 (76.10), 55 (24.31), 51 (6.73). IR (CCl_4): 2962, 2934, 1736, 1412, 1261 cm^{-1}.

Methyl 5,5-difluoro-3-iodo-6-oxodecanoate (4ce). ^{1}H NMR ($CDCl_3$): 4.35 (m, 2H), 4.29 (dd, *J* = 10.31, 6.42 Hz, 1H), 4.24 (dd, *J* = 10.31, 5.04 Hz, 1H), 2.84-2.74 (m, 2H), 2.70 (t, *J* = 7.33 Hz, 2H), 2.11 (s, 3H), 1.61 (quintet, *J* = 7.33 Hz, 2H), 1.35 (sextet, *J* = 7.33 Hz, 2H), 0.92 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −107.72 (ddd, *J* = 286.58, 20.47, 13.03 Hz, 1F) δ −104.68 (ddd, *J* = 286.49, 20.44, 13.06 Hz, 1F). ^{13}C NMR ($CDCl_3$,): δ 200.23 (t, *J* = 31.15 Hz), 170.22 (s), 116.85 (t, *J* = 255.28 Hz), 68.83 (s), 39.67 (t, *J* = 23.03 Hz), 35.93 (s), 24.73 (s), 22.12 (s), 20.82 (s), 15.01 (t, *J* = 4.32 Hz), 13.81 (s). GC-MS (m/e, relative intensity): 235 (4.38), 155 (2.96), 127 (0.58), 113 (0.72), 90 (4.43), 85 (67.84), 77 (1.67), 71 (2.18), 59 (5.66), 57 (100.00), 51 (6.94). IR (CCl_4): 2961, 2934, 1745, 1461381, 1226, 1037 cm^{-1}.

4,4-Difluoro-2-iodo-1-phenoxy-5-nonanone (4cf). ^{1}H NMR ($CDCl_3$): δ7.29 (m, 2H), 6.99 (t, *J* = 7.33 Hz, 1H), 6.89 (d, *J* = 7.79 Hz, 2H), 4.43 (dt, *J* = 11.91, 6.07 Hz, 1H), 4.25 (dd, *J* = 10.08, 5.04, 1H), 4.15 (dd, *J* = 10.08, 6.87, 1H), 3.03 (m, 1H), 2.78 (m, 1H), 2.71 (t, *J* = 7.33 Hz, 2H), 1.58 (quintet, *J* = 7.33 Hz, 2H), 1.33 (sextet, *J* = 7.33 Hz, 2H), 0.91 (t, *J* = 7.33 Hz, 3H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −106.79 (ddd, *J* = 283.25, 17.95, 17.96 Hz, 1F) δ −105.22 (ddd, *J* = 283.25, 17.95, 17.96 Hz, 1F). ^{13}C NMR ($CDCl_3$,): δ 200.25 (t, *J* = 32.15 Hz), 129.70 (s), 121.76 (s), 117.04 (t, *J* = 255.28 Hz), 114.97 (s), 73.07 (s), 39.72 (t, *J* = 23.03 Hz), 35.98 (s), 24.69 (s), 22.12 (s), 16.00 (t, *J* = 4.32), 13.81 (s). GC-MS (m/e, relative intensity): 303 (7.58), 177 (1.17), 156 (28.22), 133 (2.04), 105 (2.96), 94 (61.80), 85 (46.08), 77 (21.03), 64 (34.49), 57 (100.00), 51 (26.26). IR (CCl_4) : 3040, 2961, 2932, 1741, 1599, 1496, 1464, 1383 cm^{-1}.

4,4-Difluoro-2-iodo-1-propanoxy-5-nonanone (4cg). ^{1}H NMR ($CDCl_3$): δ4.25 (m, 1H), 3.67 (dd, *J* = 10.54, 5.50 Hz, 1H), 3.58 (dd, *J* = 10.54, 7.33 Hz, 1H), 3.42 (m, 2H), 2.93 (m, 1H), 2.69 (t, *J* = 7.33 Hz, 2H), 2.66 (m, 1H), 1.59 (m, 4H), 1.35 (sextet, *J* = 7.33 Hz, 2H), 0.92 (t, *J* = 7.33 Hz, 6H). ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −106.63 (ddd, *J* = 281.04, 15.37, 15.37 Hz, 1F) δ −105.28 (ddd, *J* = 281.04, 15.37, 15.37 Hz, 1F). ^{13}C NMR ($CDCl_3$,): δ200.39 (t, *J* = 30.71 Hz), 117.16 (t, *J* = 25.43 Hz), 75.88 (s), 72.72 (s), 39.68 (t, *J* = 23.03 Hz), 36.07 (s), 24.73 (s), 22.82 (s), 22.15 (s), 18.04 (t, *J* = 4.80 Hz), 13.84 (s), 10.63 (s). GC-MS (m/e, relative intensity): 303 (0.17), 235 (1.55), 193 (0.69), 177 (0.83), 173 (4.05), 156 (1.87), 127 (1.75), 111 (4.03), 93 (5.15), 85

(72.28), 77 (2.19), 57 (100.00), 51 (8.59). IR (CCl_4): 2934, 2957, 1734, 1453, 1425, 1361 cm^{-1}.

Acknowledgment. This work was supported by Wonkwang University in 2003.

References

1. Filler, R.; Kobayashi, Y. *Biochemical Aspects of Fluorine Chemistry*; Elsevier Biochemical Press and Kodansha Ltd.: 1982; b) Filler, R. *Biochemistry Involving Carbon-Fluorine Bonds*; ACS: Washington D. C., 1976.
2. Welch, J. J. *Tetrahedron* **1987**, *43*, 3123.
3. Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochem.* **1985**, *24*, 1814.
4. Burkholder, C. R.; Dolbier, W. R.; Medebielle, M. *J. Fluorine Chem.* **2000**, *102*, 369.
5. Davis, C. R.; Burton, D. J.; Yang, Z. Y. *J. Fluorine Chem.* **1995**, *70*, 135.
6. Elsheimer, S.; Dolbier, W. R.; Muria, M. *J. Org. Chem.* **1984**, *49*, 205.
7. (a) Rong, G.; Keese, R. *Tetrahedron Lett.* **1990**, *31*, 5615. (b) Huang, W. Y.; Wang, W.; Hung, B. N. *Acta Chimical Sinia* (*Engl. Ed.*) **1986**, 178.
8. Hung, W. Y.; Zhang, H. J. *J. Fluorine Chem.* **1990**, *50*, 133.
9. Lang, R. W.; Schaud, B. *Tetrahedron Lett.* **1988**, *29*, 2943.
10. Watanabe, S.; Fajita, T.; Sakamoto, M.; Takeda, H.; Kitazume, T.; Yamazaki, T. *J. Fluorine Chem.* **1997**, *82*, 1.
11. (a) Qiu, Z.; Burton, D. J. *J. Org. Chem.* **1995**, *60*, 3465. (b) Yang, Z. Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 170. (c) Yang, Z. Y.; Burton, D. J. *J. Fluorine Chem.* **1989**, *45*, 435.
12. Chen, J.; Hu, C. M. *J. Chem. Soc. Perkin Trans 1* **1994**, 1111.
13. Qiu, Z. M.; Burton, D. J. *Tetrahedron Lett.* **1994**, *35*, 1813.
14. (a) Yang, Z. Y.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 5144. (b) Qiu, Z. M.; Burton, D. J. *Tetrahedron Lett.* **1993**, *34*, 3239.
15. Kwak, K. C.; Oh, H. C.; Yun, Y. G.; Kim, B. H.; Lee, Y. H.; Chai, K. Y. *Bull. Korrean Chem. Soc.* **2002**, *23*(1), 157.
16. (a) Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*, 6481. (b) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 428.
17. Chen, Q. Y.; Yang, Z. Y.; Zhao, C. X.; Qiu, Z. M. *J. Chem. Soc. Perkin Trans 1* **1998**, 563.
18. (a) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS: Washington, DC, 1991. (b) Yang, Z. Y.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 1019. (c) Kitagawa, O.; Miura, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1011.