Addition of α,α-Difluoroiodomethylcyclohexyl Ketone to Alkenes under Copper Catalyst

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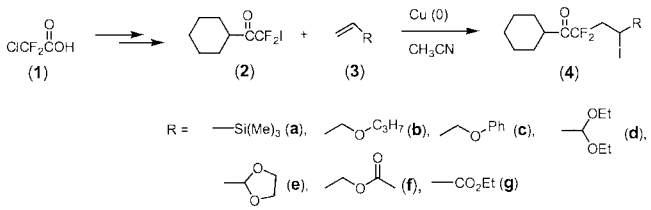
Fluorinated organic compounds often exhibit important biological properties.[1] This is mainly due to strong carbon and fluorine bond, the function of fluorine as a hydrogen-bond acceptor, increased lipid solubility, and the similarity between C-F and C-O bond lengths.[2] It is also well known that the organic compounds with selectively introduced difluoromethylene unit are particularly useful in pharmaceutical, agrochemical, and industrial fields. The documented biological activities of these types of compounds include inhibitory effects on various enzymes,[3] antibiotic,[4] anticancer,[5] anti-HIV,[6] and antihypertensive[7] effects.

Introduction of difluoromethylene group into organics has been generally accomplished by following methods: the addition of perfluoroalkyl iodide to alkenes in the presence of various catalysts such as titanium,[8] benzoylperoxide,[9] sodium dithionite,[10] and organophosphines;[11] the addition of ethyl bromodifluoroacetate to alkenes using nickel chloride[12] or copper powder[13] as a catalyst; and the transformation of carbonyl group to difluoromethylene group utilizing DAST [(diethylamino)sulfur trifluride].[14] In addition, Burton *et al.* recently reported the addition of difluoroiodomethyl ketone to the electron-deficient olefins using UV irradiation,[15] while palladium catalyst was used for the addition to electron-rich olefins.[16] However, the rather complicated experimental procedure for photoreaction such as repeated freezing at low temperature (under liquid nitrogen) and degassing processes could limit the utilization of the method. Moreover, limited numbers of method are available for the addition to electron-rich olefins. Thus, we describe herein an efficient method for the addition of difluoroiodomethylcyclohexyl ketone to both electron-rich and electron-deficient olefins utilizing copper powder, which is cheap and requires only mild reaction conditions.

The starting compound in this method, α,α-difluoroiodomethylcyclohexyl ketone (**2**), could be readily obtained by Grignard reaction, followed by Reformasky reaction from chlorodifluoroacetic acid (**1**).[17] Addition of 1.2 to 2 equiv of olefins to **2** in the presence of 15 mol% of copper powder in acetonitrile at 60 °C for 15 to 22 h afforded the corresponding adducts **4** in good yields (Scheme 1). These results were summarized in Table 1.

The reaction products **4** were obtained with 52% to 90%



Scheme 1

yields. It is noteworthy that electron-deficient olefin, ethyl acrylate (**3g**) could only afford lower yield (52%) of the adduct (5-cyclohexyl-4,4-difluoro-2-iodo-5-oxopentanoate, **4g**) even in the presence of larger amount of **3g** (2.0 equiv) and longer reaction time (22 h). On the other hand, 1-cyclohexyl-2,2-difluoro-4-iodo-4-trimethylsilylbutanone (**4a**) was obtained with highest yield (90%) from vinyltrimethylsilane (**3a**) with 1.2 equiv of **3a** and 15 h of reaction time. The effect of solvents was examined for the reaction. When methylene chloride, ethyl acetate, THF, DMF, and acetonitrile were employed for the reaction, acetonitrile gave the highest yields of the products (data not shown). The products **4** were identified by analysis of the ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and MS spectra. Since two fluorines in the products are non-equivalent due to the presence of γ-positioned chiral center, a typical AB splitting pattern is always observed in the ^{19}F NMR spectra. The peaks due to two fluorines were observed at $\delta \cong -107$ and $\delta \cong -103$ with coupling constants of $^{2}J_{FF} \cong 278$ Hz, $^{3}J_{FH} \cong 21$ Hz, and $^{3}J_{FH} \cong 11$ Hz.

In summary, the adduct **4** *via* the addition of difluoroiodomethylcyclohexyl ketone to alkenes were efficiently obtain-

Table 1. Copper catalyzed addition reaction of α,α-difluoroiodomethylcyclohexyl ketone to alkenes

Entry	Substrate	Reactant	Equiv of **3**	Reaction time (h)	Product	yield, %
1	**2**	**3a**	1.2	15	**4a**	90
2	**2**	**3b**	1.5	18	**4b**	70
3	**2**	**3c**	1.5	18	**4c**	66
4	**2**	**3d**	1.5	18	**4d**	72
5	**2**	**3e**	1.5	18	**4e**	77
6	**2**	**3f**	2.0	22	**4f**	82
7	**2**	**3g**	2.0	22	**4g**	52

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ed with good yields by utilizing copper as a catalyst under mild reaction conditions, and the present method could be applied to the synthesis of various fluorinated compounds. Further work on the application of this method to other system such as α,α-difluoroiodomethylphenyl ketone is in progress.

Experimental Section

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 the electron impact mode. The IR spectrum was recorded on a JASCO FT/IR-5300.

General procedure for the preparation of addition products 4. To a solution of α,α-difluoroiodomethylketone (**2**, 0.1 mol) and activated copper powder (0.015 mol) in dry acetonitrile (100 mL), olefin (**3**, 0.12 to 0.20 mol, see Table 1) was dropped under N_2 gas, and heated at 60 ºC for 15 to 22 h (see Table 1). 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 evaporation of the solvent under reduced pressure, silica gel column chromatography on the residue afforded compounds **4**.

1-Cyclohexyl-2,2-difluoro-4-iodo-4-trimethylsilylbutanone (4a). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.08 (dd, J = 10.5, 3.2 Hz, 1H), 2.96 (m, 1H), 2.60 (m, 2H), 1.15-1.90 (m, 10H), 0.21 (s, 9H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -108.4 (dt, J = 279.5, 16.6 Hz, 1F) -102.7 (dt, J = 279.5, 16.6 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.9 (t, J = 29.8 Hz), 118.2 (t, J = 254.3 Hz), 45.2 (s), 37.2 (t, J = 23.5 Hz), 28.5 (s), 28.3 (s), 25.9(s), 25.7 (s), 25.6 (s), 5.0 (t, J = 2.9 Hz), -2.35 (s); MS *m/z* (relative intensity): 388 (M^+, 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); IR (film): 3393, 2949, 2926, 1738, 1451 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-iodo-5-propoxy-1-pentanone (4b). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.22 (quintet, J = 6.4 Hz, 1H), 3.66 (dd, J = 10.5, 6.4 Hz, 1H), 3.58 (dd, J = 10.5, 6.4 Hz, 1H), 3.41 (m, 2H), 2.87 (m, 2H), 2.62 (m, 1H), 1.56 (sextet, J = 7.3 Hz, 2H), 1.90-1.10 (m, 10H), 0.90 (t, J = 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -106.8 (ddd, J = 282.7, 19.7, 12.1 Hz, 1F), -104.2 (ddd, J = 282.7, 19.7, 12.1 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.1 (t, J = 30.7 Hz), 117.7 (t, J = 255.3 Hz), 75.9 (s), 72.7 (s), 44.9 (s), 39.8 (t, J = 20.0 Hz), 28.4 (s), 28.3 (s), 25.6 (s), 25.5 (s), 25.4 (s), 22.8 (s), 15.3 (s), 10.6 (s); MS *m/z*, (relative intensity): 329 [$(M\text{-}OC_3H_7)^+$, 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 (film): 2934, 2858, 1734, 1450, 1289 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-iodo-5-phenoxypentanone (4c). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (m, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 4.44 (quintet, J = 6.1 Hz, 1H), 4.24 (dd, J = 10.3, 6.1 Hz, 1H), 4.15 (dd, J = 10.3, 6.1 Hz, 1H), 3.03 (m, 1H), 2.92 (m, 1H), 2.78 (m, 1H), 1.90-1.10 (m, 10H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -106.8 (ddd, J = 279.3, 20.1, 10.5 Hz, 1F), -104.3 (ddd, J = 279.3, 20.1, 10.5 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.0 (t, J = 35.0 Hz), 157.9 (s), 129.7 (s), 121.7 (s), 117.6 (t, J = 255.3 Hz), 115.0 (s), 73.1 (s), 44.9 (s), 40.0 (t, J = 23.0 Hz), 28.39 (s), 28.36 (s), 25.6 (s), 25.48 (s), 25.43 (s), 16.2 (s); MS *m/z* (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 (film): 3040, 2932, 2856, 1734, 1559, 1496, 1452, 1240 cm^{-1}.

Cyclohexyl-5,5,-diethoxy-2,2-difluoro-4-iodopentanone (4d). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.28 (d, J = 4.0 Hz, 1H), 4.15 (ddd; J = 8.3, 8.3, 4.0 Hz, 1H), 3.70 (m, 2H), 3.57 (m, 2H), 2.91 (m, 2H), 2.67 (m, 1H), 1.92-1.10 (m, 16H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -107.2 (ddd, J = 272.2, 21.3, 10.6 Hz, 1F), -103.5 (ddd, J = 272.2, 21.3, 10.6 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.3 (t, J = 30.5 Hz), 117.9 (t, J = 254.3 Hz), 104.1 (s), 64. 2 (s), 63.9 (s), 45.0 (s), 37.5 (t, J = 23.0 Hz), 28.4 (s), 28.3 (s), 25.7 (s), 25.5 (s), 25.4 (s), 21.3 (s), 15.17 (s), 15.13 (s); MS *m/z* (relative intensity): 373 [$(M\text{-}OC_2H_5)^+$, 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 (film): 2976, 2934, 1734, 1691, 1599, 1450, 1375, 1275 cm^{-1}.

1-Cyclohexyl-2,2-difluoro-4-(1,3-dioxolan-2-yl)-4-iodobutanone (4e). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.61 (d, J = 3.2 Hz, 1H), 4.21 (ddd, J = 8.0, 5.3, 3.2 Hz, 1H), 4.08 (m, 2H), 3.95 (m, 2H), 2.87 (m, 2H), 2.69 (m, 1H), 1.92-1.10 (m, 10H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -107.6 (ddd, J = 272.1, 20.4, 10.3 Hz, 1F), -103.2 (ddd, J = 272.1, 20.4, 10.3 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.0 (t, J = 30.2 Hz), 117.6 (t, J = 255.3 Hz), 104.1 (s), 66.1 (s), 65.9 (s), 44.9 (s), 38.0 (t, J = 23.0 Hz), 28.4 (s), 28.3 (s), 25.7 (s), 25.5 (s), 25.4 (s), 22.1 (s); MS *m/z* (relative intensity): 261 [$(M\text{-}I)^+$, 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 (film): 2978, 2934, 1735, 1695, 1598, 1450, 1378 cm^{-1}.

Methyl 6-cyclohexyl-5,5-difluoro-3-iodo-6-oxohexanoate (4f). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.32 (m, 2H), 4.24 (m, 1H), 2.91 (m, 1H), 2.76 (m, 2H), 2.11 (s, 3H), 1.89-1.23 (m, 10H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -104.0 (ddd, J = 285.3, 21.9, 14.0 Hz, 1F), -107.4 (ddd, J = 285.3, 21.9, 14.0 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.9 (t, J = 29.8 Hz), 170.2 (s), 117.8 (t, J = 255.4 Hz), 68.8 (s), 44.9 (s), 40.0 (t, J = 24.0 Hz), 28.4 (s), 28.3 (s), 25.7 (s), 25.5 (s), 25.4 (s), 20.8 (s), 15.2 (t, J = 3.8 Hz); MS *m/z* (relative intensity): 261 [$(M\text{-}I)^+$, 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 (film): 2934, 2856, 1747, 1450, 1381, 1226 cm^{-1}.

Ethyl 5-cyclohexyl-4,4-difluoro-2-iodo-5-oxohexanoate (4g). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.52 (dd, J = 10.5, 3.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.10 (m, 1H), 2.84 (m, 1H), 2.66 (m, 1H), 1.90-1.15 (m, 10H), 1.27 (t, J = 7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 470.4 MHz): δ -107.2 (ddd, 278.4, 21.3, 11.3 Hz, 1F), -103.5 (ddd, 278.4, 21.3, 11.3 Hz, 1F); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.6 (t, J = 29.8 Hz), 170.8 (s), 117.0 (t, J = 255.3 Hz), 62.3 (s), 44.8 (s), 40.3 (t, J = 23.0 Hz), 28.3 (s), 28.2 (s), 25.6 (s), 25.42 (s), 25.38 (s), 13.7 (s), 7.4 (t, J = 4.3 Hz); MS *m/z* (relative intensity): 388 (M^+, 0.25), 342 (0.85), 323 (1.45), 241 (28.25), 111 (100), 83 (72.45); IR (film): 2931, 2857, 1749, 1601, 1484, 1283 cm^{-1}.

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