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Synthesis of α-Fluoroketones Based on Palladium-Catalyzed Decarboxylation Reactions of Allyl β-Keto Carboxylates

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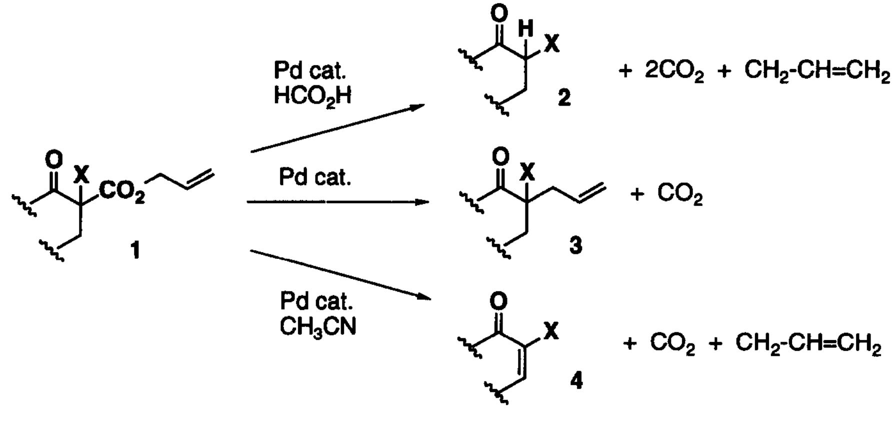
Abstract: Fluorination of allyl β-keto carboxylates using N-fluoro-2,4,6-pyridinium triflate gave allyl α-fluoro-β-keto carboxylates. Reaction of allyl α-fluoro-β-keto carboxylates with formic acid in the presence of palladium-phosphine catalyst gave α-fluoro ketones. When the palladium-catalyzed reaction was carried out without formic acid, the decarboxylation-allylation took place to give α-fluoro-allylketones. Decarboxylation-dehydrogenation to afford α-fluoro-α,β-unsaturated ketones was carried out with palladium catalysts in acetonitrile.

Owing to unique features of fluorine atom numerous efforts have been made for introduction of fluorine atoms into organic molecules in order to enhance biological and / or physical properties.1) Although α-fluoroketones occupy an important position for synthesis of various fluorinated compounds, only a few practical synthetic methods are reported. Fluorination of acidic hydrogen of β-keto esters are carried out easily using N-fluoropyridinium triflates.2) However, decarboxylation of α-fluoro-β-keto esters to the corresponding ketones is difficult owing to acyl fission reaction (retro-Claisen condensation) during hydrolysis.3) From the easily accessible α-fluoro-β-keto esters if decarboxylation is carried out selectively, it would provide a useful synthetic method for α-fluoroketones. We have reported that various decarboxylation reactions of allylic esters of β-keto carboxylic acids proceeds to various ketones with palladium catalysts as shown in Scheme 1.4) Namely, simple decarboxylation to α-fluoroketones is carried out by the palladium-catalyzed hydrogenolysis with formic acid (**1**→**2**),5) α-allylketones are obtained by palladium-catalyzed decarboxylation allylation (**1**→**3**),6) and α,β-unsaturated ketones are obtained by decarboxylation dehydrogenation (**1**→**4**).7) We wish to report here synthetic methods for various α-fluoroketones from allyl β-keto carboxylates based on the palladium-catalyzed decarboxylation reactions.8) (Scheme 1, X=F)

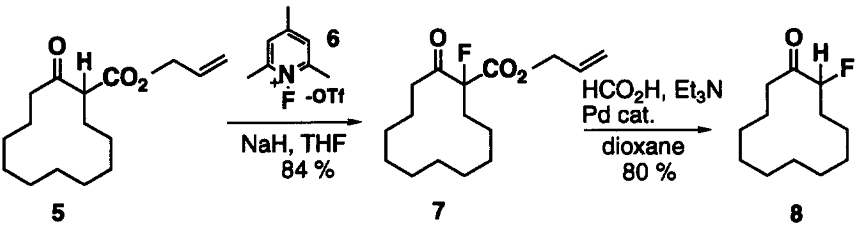
Scheme 1



Results and Discussion

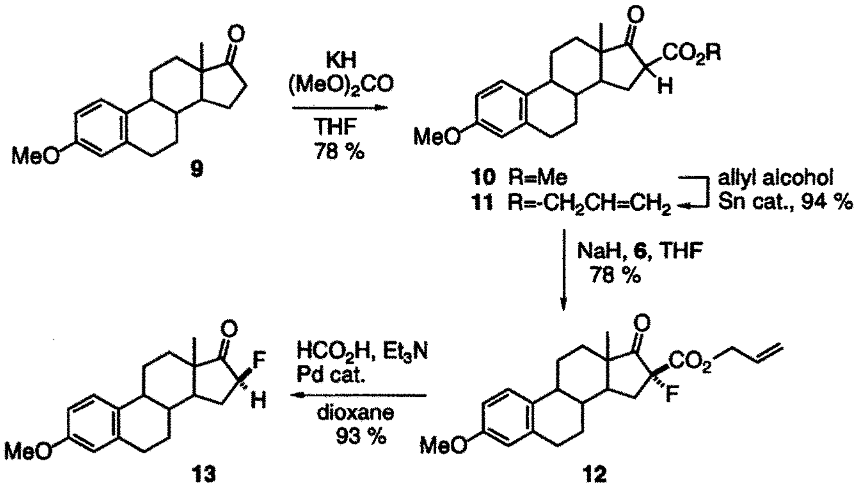
Fluorination of allyl β-keto carboxylates was carried out using N-fluoro-2,4,6-trimethylpyridinium triflate (**6**) at 0 °C in 51-84% yields.[2] The simple decarboxylation of allyl 1-fluoro-2-cyclododecanonecarboxylate (**7**) to 2-fluorocyclododecanone (**8**) was carried out in 80 % yield using formic acid in the presence of palladium-phosphine catalyst.

Scheme 2



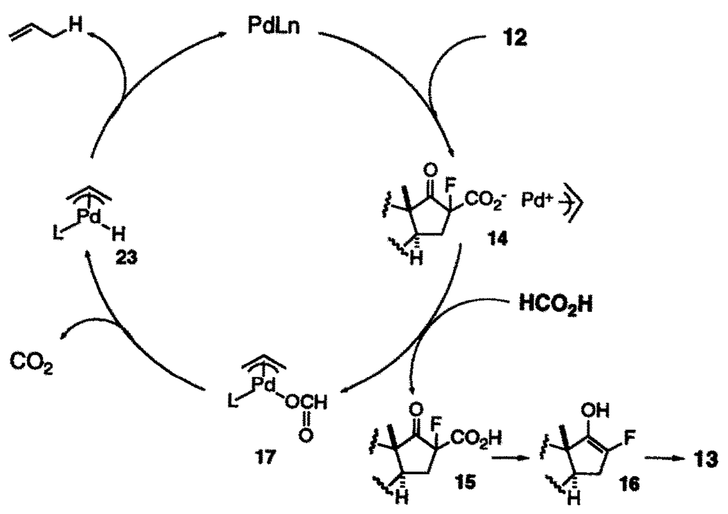
This decarboxylation method was applied to synthesis of 16β-fluoroestrone methyl ester (**13**)[9]. Methoxycarbonylation of **9** at C16 followed by transesterification of **9** with allylic alcohol using the stanoxane catalyst, $Cl(n\text{-}Bu)_2Sn\text{-}O\text{-}Sn(n\text{-}Bu)_2OH$,[10] gave **11**, which was fluorinated to give **12** as a single stereoisomer. Decarboxylation of **12** gave 16β-fluoroestrone methyl ether (**13**) in 93% yield. (Scheme 3) The stereochemistry at C16 of **13** was determined by comparison of its ^1H and ^{19}F NMR data with the known data in the literatures.[9]

Scheme 3



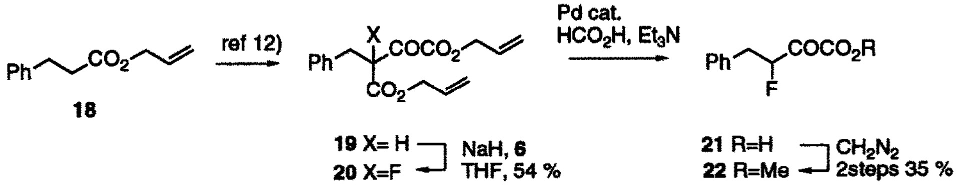
Mechanisms of decarboxylation and the stereochemical outcome of **13** are explained as shown in Scheme 4. Oxidative addition of the allylic ester **12** to palladium(0)-phosphine complexes gives the π-allylpalladium carboxylate **14**, which reacts with formic acid to form the π-allylpalldium formate **17** and the *β*-keto acid **15**. Thermal decomposition of **15** via the enol **16** give the α-fluoroketone **13**. Protonation at C16 position from the α-side of enol of 17-keto steroid is preferential to the *β*-side attack.[11] Finally the π-allylpalladium formate **17** decomposes to propene and palladium(0) species **11**, forming the catalytic cycle.[12]

Scheme 4



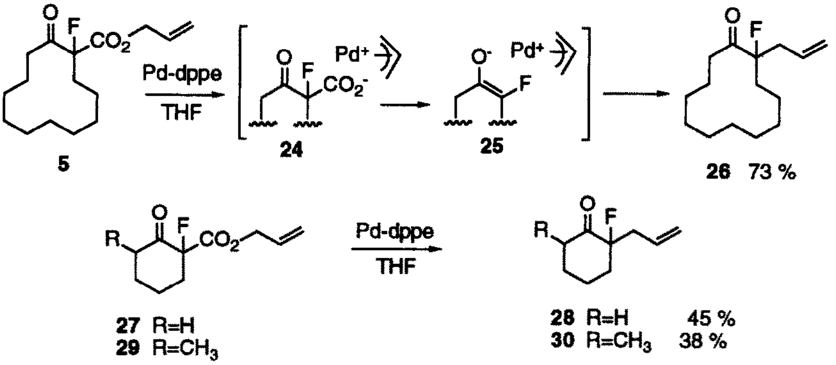
The decarbonylation reaction proceeds under very mild conditions; therefore the method is applicable to synthesis of unstable α-keto acids.[13] Fluorination of **19** was carried out similarly to give **20** in 54% yield and was followed by the reaction with HCO_2H using Pd catalyst to give **22** in 35% yield after esterification of **21** with diazomethane.

Scheme 5



When the reaction of **5** was carried out without using formic acid, decarboxylation-allylation took place to give the α-allylketone **26**. Similarly **27** was converted to **28** in 45 % yield. The decarboxylation-allylation proceeds with high regioselectivity. Thus, reaction of 2-fluoro-6-methylcyclohexanone-2-carboxylate **29** gave 2-allyl-2-fluoro-6-methylcyclohexanone **30** in 66% yield. The decarboxylation-allylation proceeds via π-allylpalladium enolate which generates by decarboxylation of π-allylpalladium carboxylate formed in situ by oxidative addition of **5** to Pd(0) species (**5**→**24**→**25**→**26**).

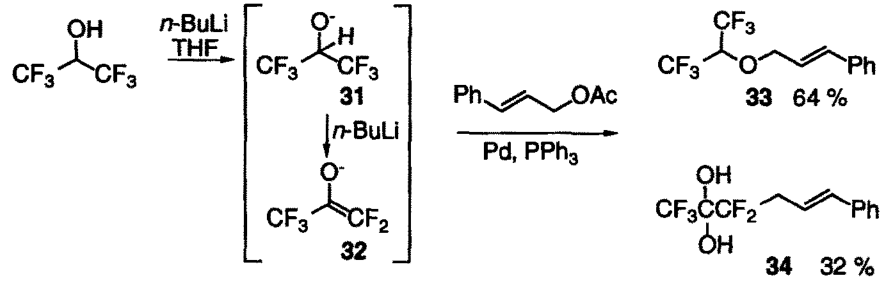
Scheme 6



Although C-alkylation of fluorine substituted ketones via their enolates is difficult, as mentioned above the enolate trap with π-allylpalladium complexes proceeds smoothly to give α-fluoro-α-allyl ketones. We have thought that the palladium catalyzed allylation method may be applied to the C-alkylation of perfluoroacetone. Indeed, reaction of enolate of perfluoroacetone prepared from 1,1,1,3,3,3-hexafluoropropanol according to Nakai's method[14] with cinnamyl acetate in the presence of $Pd(OAc)_2$-PPh_3 catalyst gave the hydrate form of α-cinnamylpentafluoroacetone (**34**) in 32%. In this method considerable amount of hexafluoroisopropyl cinnamyl ether (**33**) was also obtained as a side-product (64 %), which was formed by attacking of alkoxide **31** to π-

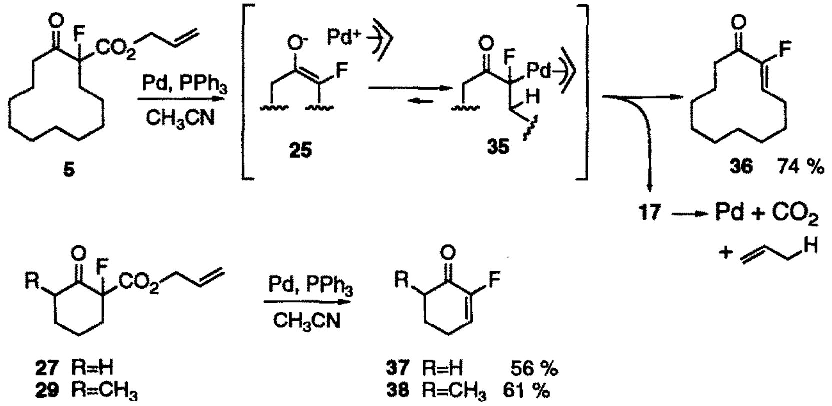
allylpalladium intermediates. Although the selectivity of the reaction is not satisfactory, it is noteworthy that as far as we know this is the only example of C-alkylation of fluorinated enolates.[15)]

Scheme 7



We have reported that α,β-unsaturated ketones are obtained when the palladium-catalyzed reaction of allylic β-ketocarbonylates is carried out in CH_3CN. The reaction is considered to proceed by β-elimination of Pd-H from α-palladaketone **35** which is in equibrium with the enolate **25**. Reaction of **5** in CH_3CN in the presence of $Pd_2(dba)_3CHCl_3$ and PPh_3 in a 1:1 ratio of Pd-phosphine gave (*E*)-2-fluorocyclododec-2-enone **36** in 74% yield. Similarly cyclohexanones **37** and **38** were obtained regioselectively from **27** and **29** in 56% and 61 % yields respectively.

Scheme 8



Conclusion

The palladium-catalyzed reactions of allyl esters of β-fluorocarboxylates proceeds under mild conditions, the methods are useful for preparation of α-fluoroketones, α-allyl-α-fluoroketones, and α-fluoro-α,β-unsaturated ketones.

Acknowledgements: We thank Dr. Umemoto for helpful discussion about the fluorination method. This research was financially supported from the ministry of Education, Science and Culture, and the Asahi Glass Foundation.

Experimental

General: Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. All reactions using palladium catalyst or base were carried out under argon atmosphere. THF and dioxane were distilled over benzophenonekethyl. Triphenylphosphine and 1,2-bis(diphenylphosphino)ethane (dppe) were purified through recrystallization prior to use. Tris(dibenzylideneacetone)chloroform dipalladium ($Pd_2(dba)_3CHCl_3$) was prepared by the published procedure.16) ^1H NMR spectra were recorded in CCl_4 or $CDCl_3$ solution at 60.0 MHz with a Hitachi R-24 or a JEOL PMX60, and in $CDCl_3$ solution at 90.0 MHz with a Hitachi R/90H. Chemical shifts are expressed in ppm down field from internal tetramethylsilane and ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in Hertz, and number of protons. ^{19}F NMR spectra were recorded in $CDCl_3$ at 84.7 MHz with a Hitachi R/90H. Chemical shifts are expressed in ppm down field from internal fluoro trichloromethane ($CFCl_3$). ^{19}F NMR data are tabulated in order: multiplicity and coupling constant in Hertz. Infrared spectra were determined with a Shimadzu IR-400 and high resolution mass spectra (HRMS) were taken with a JEOL JMS-DX300. Column chromatography was performed using Wakogel C-200 and a mixture of ether and hexane as the eluent.

Allyl 1-fluoro-2-oxocyclododecanecarboxylate (7). To a suspension of NaH (55% in mineral oil, 0.13 g, 3.1 mmol) in THF (5 mL), a solution of **5** (0.75 g, 2.8 mmol) in THF (5 mL) was added at 0 °C. The resulting mixture was added to a suspension of **6** (0.90 g, 3.1 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Saturated aqueous $NaHCO_3$ solution was added to the mixture and the mixture was extracted with ether. The extract was washed with 1N HCl solution and brine. The mixture was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on SiO_2 to give **7** (0.67 g, 84%):^1H NMR (CCl_4, 60 MHz) δ 1.10-2.87 (m, 20H), 4.58 (d, J=5.5 Hz, 2H), 5.04-5.45 (m, 2H), 5.54-6.23 (m, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -166.29 (d, J=26.2 Hz);IR (neat) 1758 and 1731 cm^{-1}; HRMS Calcd for $C_{16}H_{25}O_3F$ 284.1788, Found 284.1801.

2-Fluorocyclododecanone (8). To a mixture of $Pd_2(dba)_3CHCl_3$ (20 mg, 0.019 mmol) and PPh_3 (5 mg, 0.019 mmol) in dioxane (10 mL), a mixture of HCO_2H (88%, 0.143 mL, 3.31 mmol) and Et_3N (0.208 mL. 1.5 mmol) in dioxane (5 mL) was added at room temperature. A solution of **7** (0.214 g, 0.750 mmol) in dry dioxane (5 mL) was added to the mixture and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and the resulting mixture was extracted with ether. The usual work up and purification by chromatography on SiO_2 gave **8** (0.120 g, 80%): ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10–1.60 (16H),1.61-2.16 (m, 3H), 2.43-2.79 (m, 1H), 4.86 (ddd, J=49.0, 7.0 Hz, and 4.3, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 34.4, 95.5 (d, J=184.5 Hz), 208.5 (d, J=21.4 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ (-188.67)-(-189.74) (m); IR (neat) 1721 cm^{-1}; HRMS Calcd for $C_{12}H_{21}OF$ 200.1577, Found 200.1558.

16β-Allyloxycarbonyl-16α-fluoroestrone methyl ether (12). To a suspension of KH (35 % in mineral oil, 3.4 g) in THF (10 mL) was added a solution of **9** (0.410 g, 1.44 mmol) in THF (5 mL). Dimethyl carbonate (0.65 mL) was added to the resulting mixture and the mixture was refluxed for 3h. The usual work up and purification by column chromatography gave **10** (0.387 g, 78 %). A mixture of **10** (0.224 g, 0.654 mmol), Cl(*n*-Bu)$_2$SnOSn(*n*-Bu)$_2$OH (3.9 mg), allyl alcohol (0.5 mL) in toluene (7 mL) was refluxed for 4 h. After evaporation of the solvent the residue was chromatographed to give **11** (0.229 g, 94 %). The allylic ester **11** (132 mg, 0.354 mmol) was fluorinated by a similar procedure as **7** to give **12** (106 mg, 78 %): ^{1}H NMR (CCl_4, 60 MHz) δ 1.09 (s, 3H), 1.22-3.04 (m, 13H), 3.69 (s, 3H), 4.66 (d, J=5.5 Hz, 2H), 5.06-5.49 (m, 2H), 5.56-6.25 (m, 1H), 6.60 (bs, 1H), 6.66 (d, J=9.5 Hz, 1H), 7.14 (J=9.5 Hz, 1H);^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 55.11, 66.60, 95.28 (d, J=201.1 Hz), 111.58, 113.80, 119.20, 126.09, 130.35, 131.24, 137.28, 157.58, 167.37 (d, J=26.3), 207.88 (d, J=15.9 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz), δ -161.23 (t, J=16.2 Hz); HRMS Calcd for $C_{23}H_{27}O_4F$ 386.1894, Found 386.1896.

16β-Fluoroestrone methyl ether (13) was obtained by a similar procedure as **8** in 93% yield. ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.02 (s, 3H), 1.17-3.12 (m, 13H), 3.75 (s, 3H), 4.73 (dt, J=49.9, 7.5 Hz, 1H), 6.60 (bs, 1H), 6.68 (d, J=9.5, 1H), 7.16 (d, J=9.5, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 54.94, 91.40 (d, J=194.8 Hz), 111.43, 113.66, 125.92, 131.30, 173.22, 157.46, 212.63 (d, J=11.6 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -184.86 (dd, J=49.9, 21.4 Hz).

Diallyl 2-benzyl-2-fluoro-3-oxosuccinate (20) was prepared by a similar procedure as **7** from **19** in 54% yield. ^{1}H NMR (60 MHz, CCl_4) δ 3.41 (d, J=26.0 Hz, 2H), 4.53 (d, J=5.5 Hz, 2H), 5.70 (d, J=5.5 Hz, 2H), 5.06-6.27 (m, 6H), 7.15 (s, 5H); IR (neat) 1754, 1740, 1496, 1452, 1428, 1367, 1273, 1113, 1087, 1044, 941, 741, and 706 cm^{-1}.

Methyl 3-fluoro-2-oxo-4-phenylbutanoate (22). By a similar procedure as **8**, reaction of **20** (0.32 g, 1.00 mmol) with HCO_2H (0.43 mL) and Et_3N (0.5 mL) in the presence of $Pd_2(dba)_3CHCl_3$ (26 mg) and PPh_3 (7 mg) in THF and the usual work up gave the crude keto acid **21**, which was taken up in ether (20 mL) and THF (20 mL). To the resulting solution, an ethereal solution of diazomethane (dried over KOH) was added at 0 °C until persistence of the yellow color of diazomethane. The excess diazomethane was destroyed with acetic acid. The mixture was washed with NaOH solution (10%), $NaHCO_3$ solution, and NH_4Cl solution. The organic phase was dried over $MgSO_4$ and concentrated. The residue was chromatographed on SiO_2 to give **22** (73 mg, 35%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.00 (t, J=6.4 Hz, 2H), 3.75 (s, 3H), 5.09 (ddd, J=4.1, 6.4, 49.5 Hz, 1H), 7.26 (s, 5H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 89.3 (d, J=188.6 Hz), 184.9 (d, J=282.4 Hz), 206.6; ^{19}F NMR δ (84.7, MHz, $CDCl_3$) δ (-190.20)-(-192.92) (m).

2-Allyl-2-fluorocyclododecanone (26). To a refluxing mixture of $Pd_2(dba)_3CHCl_3$ (15 mg, 14 mmol) and dppe (23 mg, 56 mmol) in THF (10 mL), a solution of **5** (0.16 g, 0.561 mmol) in THF (10 mL) was added. The mixture was refluxed for an additional 1 h. The reaction mixture was poured into brine and extracted with ether. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on SiO_2 to give **26** (98 mg, 73%): ^{1}H NMR (CCl_4, 60 MHz) δ 4.83-6.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 34.5, 39.8 (d, J=22.1 Hz), 102.4 (d, J=185.2 Hz), 118.8, 130.8 (d, J=3.6 Hz), 210.0 (d, J=26.3 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ (-160.72)-(-161.68) (m); IR (neat) 1719, 1472, 992, 917 cm^{-1}; HRMS Calcd for $C_{15}H_{25}OF$ 240.1890 Found 240.1906.

Allyl 1-fluoro-2-oxocyclohexanecarboxylate (27) was prepared by fluorination of allyl 2-oxocyclohexanonecarboxylate in 60% yield by a similar procedure as **5**.:^{1}H NMR (CCl_4, 60 MHz) δ 1.6-3.0 (m, 8H), 4.65 (d=5.5 Hz, 2H), 5.12-5.50 (m, 2H), 5.62-6.23 (m, 1H);^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -160.72 (s);IR (neat) 1759, 1728, 1453, 1367, 1279, 1223, 1149, 1098, 1074, 1054, 992, 943; HRMS Calcd for $C_{10}H_{13}FO_3$ 200.0849, Found 200.0868.

2-Allyl-2-fluorocyclohexanone (28). By a similar procedure as **26**, **27** was converted to **28** in 45% yield.:^{1}H NMR (CCl_4, 60 MHz) δ 4.83-5.04 (m, 1H), 5.15 (bs, 1H) 5.43-6.11 (m, 1H).; ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ (-157.61)-(-158.61) (m).; IR (neat) 1728, 1432, 1127, 923. HRMS Calcd for $C_9H_{13}FO$ 156.0951 found 156.0958.

Allyl 1-fluoro-3-methyl-2-oxocyclohexanecarboxylate (29) was prepared from allyl 3-methyl-2-oxocyclohexanecarboxylate in 38% yield.; ^1H NMR (CCl_4, 60 MHz) δ 0.95 (d, J=6.5 Hz, 3H), 1.10-2.50 (m, 7H), 4.53 (d, J=5.5 Hz, 2H), 5.10-5.50 (m, 2H), 5.63-6.27 (m, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -163.63 (d, J=45.2 Hz); IR (neat) 1741, 1452, 1373, 1261, 982, 923, 796; HRMS Calcd for $C_{11}H_{15}FO_3$ 214.1005 Found 214.0983.

2-Allyl-2-fluoro-6-methylcyclohexanone (30). By a similar procedure as **26**, **29** was converted to **30** in 38% yield.: ^1H NMR (CCl_4, 60 MHz) δ 1.01 (d, J=6.5, 3H), 1.30-2.90 (m, 9H), 4.85-5.06 (m, 1H), 5.16 (s, 1H), 5.40-6.05 (m, 1H). ; ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ (-153.96)-(-154.69) (m); IR (neat) HRMS Calcd for $C_{10}H_{15}FO$ 170.1107 Found 170.1135.

2,2-Dihydroxy-1,1,1,3,3-pentafluoro-6-phenyl-5-hexene (34). To a solution of 1,1,1,3,3,3-hexafluoro-2-propanol (0.63 mL, 6.0 mmol) in THF, *n*-BuLi (1.6 M in hexane, 7.50 mL, 12.0 mmol) was added dropwise at 0 °C and stirred for 15 min at room temperature. The mixture was added to a boiling mixture of $Pd(OAc)_2$ (56 mg, 0.25 mmol) and PPh_3 (0.262 g, 1.0 mmol) in THF (25 mL). To the resulting boiling mixture, cinnamyl acetate (0.839 mL, 5.0 mmol) was added and the mixture was refluxed 2.5 h. The mixture was poured into 1N-HCl and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and condensed in vacuo. The residue was chromatographed on SiO_2 to give **34** (0.451, 32%) and the ether **33** (0.923 g, 65%).**34**: ^1H NMR (CCl_4, 60 MHz) δ 2.96 (dt, J=6.0, 19.0 Hz, 2H), 4.55-5.45 (bs, 2H), 6.11 (dt, J=16.0, 6.0 Hz, 1H), 6.51 (d, J=16.0 Hz, 1H) 7.19 (s. 5H). **33**: ^1H NMR (CCl_4, 60 MHz) δ 4.08 (septet, J=6.0 Hz, 1H) 4.45 (d, J=5.5 Hz, 2H), 6.10 (dt, J=16.0, 5.5 Hz, 1H), 6.61 (d, J=16.0 Hz, 1H), 7.26 (s, 5H).

(*E*)-2-Fluoro-2-cyclododecene (36). A solution of **5** (0.214 g, 0.75 mmol) was added to a refluxing mixture of $Pd_2(dba)_3CHCl_3$ (39 mg, 0.038 mmol) and PPh_3 (10 mg, 0.038 mmol) in CH_3CN (4 mL) and the mixture was refluxed for 2 h. The reaction mixture was cooled and filtered through a celite column with dichloromethane. The eluent was condensed and ether was added to the residue. The ethereal solution was washed with brine , dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on SiO_2 to give **36** (0.111 g, 74%).: ^1H NMR($CDCl_3$, 90 MHz) δ 2.16-2.72 (m, 4H), 6.02 (dt, J=35.5, 8.4 Hz, 1H).; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 37.2 (d, J=1.4 Hz), 119.6 (d, J=12.4) 156.3 (d, J=262.5 Hz), 196.6 (d, J=31.1 Hz).; ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -127.20 (d, J=35.5 Hz); IR (neat) 1713, 1650, 1467, 1445.; HRMS Calcd for $C_{12}H_{19}FO$ 198.1420 Found 198.1408.

2-Fluoro-2-cyclohexenone (37) was prepared in 56% yield by a similar procedure as **36**.: ^1H NMR (CCl_4, 60 MHz) δ 6.31 (dt, J=13.8, 4.0 Hz, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -130.40 (d, J=14.8 Hz); IR (neat) 1693, 1180, 1146, 1112, 893.

2-Fluoro-6-methyl-2-cyclohexenone (38) was prepared in 61% yield by a similar procedure as **36**.: ^1H NMR (CCl_4, 60 MHz) δ 1.14 (d, J=6.5 Hz, 3H), 6.21 (dt, J=15.0, 4.0 Hz, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz) δ -130.66 (d, J=15.0 Hz); IR (neat) 1691, 1453, 1346, 1195, 1180, 1005, 926, 910; HRMS Calcd for C_7H_9FO 128.0637 Found 128.0604.

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