Synthesis of α-Fluorocarboxylates from the Corresponding Acids Using Acetyl Hypofluorite

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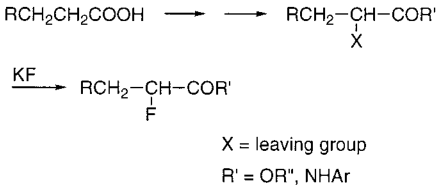
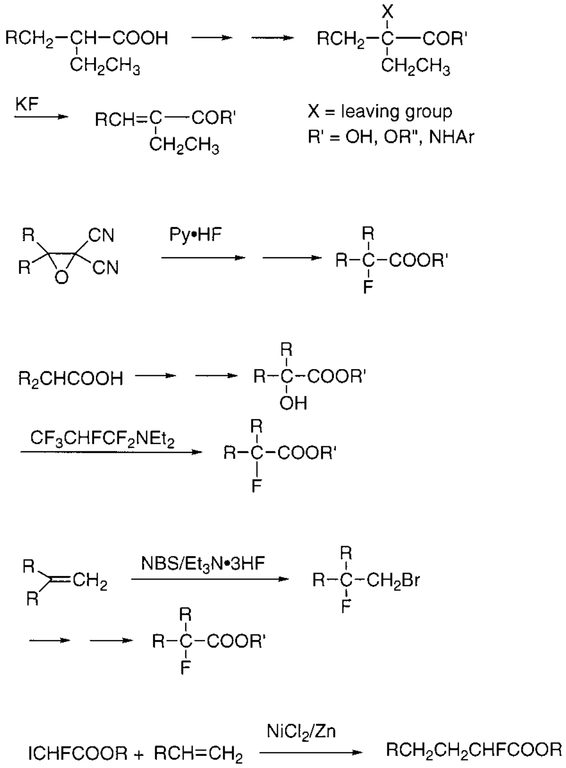
α-Fluorocarboxylic esters and acids were synthesized in good yields. The corresponding esters and acids were converted to their ketene acetals, and these enol derivatives reacted with AcOF made directly from fluorine. This route circumvents the problems associated with nucleophilic fluorinations such as various eliminations and rearrangements. α- and *β*-branched carboxylic acid derivatives that cannot be directly fluorinated gave by this electrophilic fluorination the corresponding α-fluoro derivatives in good yield. Both the fluorination reaction and the preparation of AcOF are fast and suitable for [18]F incorporation into acids and esters needed for working with PET. α-Fluoroibuprofen (**20**) and methyl 2-fluoro-3,3,3-triphenylpropionate (**32**) are two examples of this general reaction.

The biological importance of fluorine-containing compounds is already common knowledge and underlined in practically any introduction of the relevant papers. Fluorocarboxylic acids are no exception. The interest in these compounds first arose in the 1950s when it was found that straight-chain *ω*-fluoro acids with an even number of carbons are almost as toxic as fluoroacetic acid itself.[1] Since that time, many papers appeared dealing with the synthesis and biological importance of α-fluorocarboxylic acids. The main method of preparation was based on the displacement of a leaving group α to the carboxylate moiety by a nucleophilic fluoride usually in a form of KF (Scheme 1).[2] Because of the basicity of the reagent, however, such an approach results, along with the desired α-fluoroacids, in elimination reactions or various rearrangements. These two types of side reactions become dominant whenever α- or *β*-branched carboxylic acids are the target molecules. Such limitations encouraged alternative, multistep routes, such as opening epoxides,[3] reacting α-hydroxy acids with DAST[4] or Ishikawa reagent,[5] reacting alkenes with [BrF] agents, prepared from HF and a source of electrophilic bromine,[6] or building the target α-fluoro acid by combining two fragments, one of which already contains the fluorine atom (Scheme 2).[7]

Scheme 1



Scheme 2



Fluorination on anionic centers α to a carboxylate, using several "NF" reagents such as *N*-fluorobis[(trifluo-

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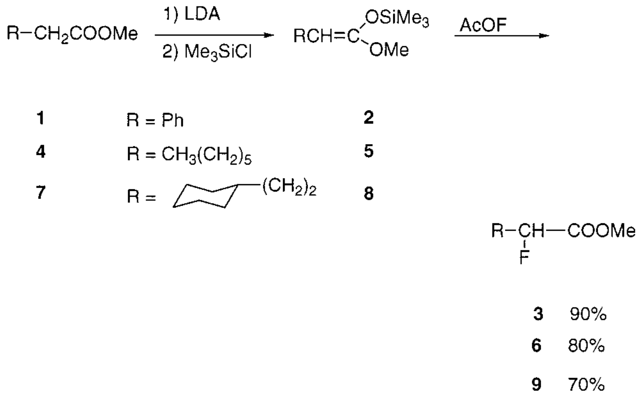
romethyl)sulfonyl]imide,[8] *N*-fluorosultams,[9] and Selectfluor,[10] have also been carried out. Such reactions are still very few and require anhydrous conditions. The reagents, prepared from F_2, have to be isolated and purified in order to function properly. What is more, because of the relatively long fluorination reaction times, as well as the time required for the reagent preparation, none of the above methods is suitable for the incorporation of the [18]F isotope in biologically interesting molecules needed for work with positron-emitting tomography (PET).

Clearly, an additional method that does not suffer from the secondary reactions associated with the basic fluoride is desirable. Such a route should also shorten the multistep construction of both reagents and starting materials needed to obtain the α-fluoro acids.

Acetyl hypofluorite (AcOF) was developed by us 20 years ago.[11] Solutions of this reagent are easily prepared by passing commercially available nitrogen-diluted fluorine through a suspension of sodium acetate in either trichlorofluoromethane or acetonitrile. The reagent solution is stable for a few hours at 0−20 °C and does not need any isolation or purification prior to its use.[12] In a sense, it is a mild carrier of F_2. Because AcOF possesses an electrophilic fluorine, all the disadvantages associated with nucleophilic fluorination are eliminated. Since this reagent reacts smoothly with most kinds of double bonds,[13] and since we have had a successful experience with electrophilic hydroxylations of trimethylsilyl ketene acetals using $HOF{\cdot}CH_3CN$ complex,[14] we decided to investigate the reaction of these enol derivatives with AcOF.

Methyl 2-fluorophenylacetate (**3**) is easily obtained by several methods (see, for example, refs 2c and 3b) so we chose it as a test case. Methyl phenylacetate (**1**) was converted to its known trimethylsilyl ketene acetal (**2**)[15] and reacted with AcOF for a few minutes forming **3** in 90% yield. Nonbenzylic carboxylic acids are also suitable, and methyl octanoate (**4**) or methyl 4-cyclohexylbutanoate (**7**) can serve as examples. Their trimethylsilyl ketene derivatives (**5**) and (**8**) are easy to make, and consecutive reactions with AcOF produce methyl 2-fluorooctanoate (**6**)[16] and the unknown methyl 2-fluoro-4-cyclohexylbutanoate (**9**) in high yields (Scheme 3). It is worth noting that the enolic double bond of **8** reacts much faster than the tertiary hydrogen, which is a potential reaction center whenever electrophilic fluorine is involved.[17]

Scheme 3



The strength of this method is demonstrated with branched carboxylic acids that cannot be converted to their corresponding α-fluoro derivatives by nucleophilic fluorination.[2b] By using AcOF, we synthesized in 90% yield methyl 2-propyl-2-fluoropentanoate (**12**) from methyl 2-propylpentanoate (**10**), which was first converted to its trimethylsilyl ketene acetal **11**. These types of compounds seem to be very promising anticonvulsants and antiepileptics.[1d] Methyl cycloheptanoate (**13**) was also reacted in this manner, and the reaction between its trimethylsilyl ketene acetal **14** and AcOF produced the novel methyl α-fluorocycloheptanoate (**15**). Similar results were obtained with methyl 2-phenylbutanoate (**16**), whose trimethylsilyl ketene acetal (**17**) was reacted with acetyl hypofluorite to form methyl 2-fluoro-2-phenylbutanoate (**18**).

Ibuprofen, 2-(4-isobutylphenyl)propionic acid (**19**), is a powerful analgetic drug. Schlosser prepared its α-fluoro derivative **20** by a multiple-step reaction, starting with 4-isobutylphenyl methyl ketone, which was cyanohydrated, and after a few additional steps the fluorine atom was introduced with DAST.[4] Our approach needed only two steps, so methyl 2-fluoro-2-(4-isobutylphenyl) propionate (**23**) was obtained in 70% yield by reacting AcOF with the trimethylsilyl ketene acetal **22**, easily made from the parent methyl 2-(4-isobutylphenyl) propionate (**21**) (Scheme 4).

Apart from α-branched carboxylic acids that cannot be fluorinated at the α position by conventional nucleophilic fluorination, compounds branched at the *β*-position are equally resistant because steric effects prevent the typical formation of the S_N2 transition state. Thus, for example, derivatives of α-bromoisovaleric (**24**), α-bromo-*β*,*β*,*β*-triphenylpropionic (**25**), and α-bromo-*β*,*β*,*β*-trimethylpropionic acid (**26**) were all reacted in the past with dry KF in diethyleneglycol at 125 °C for 2.5 h as described in ref 2b, resulting in typical carbonium ion reactions. These led to HBr elimination in the case of **24**, HBr elimination accompanied with phenyl rearrangement in the case of **25**, and no reaction when such a rearrangement is not very favorable as in the case of **26** (Scheme 5).[18]

These difficulties can easily be avoided with the electrophilic fluorination method using AcOF. Methyl 2-norbornaneacetate (**27**) is similar to isovaleric acid in exhibiting a strong steric hindrance on the α position. It was easily converted to the corresponding trimethylsilyl ketene acetal **28**, reacted with AcOF, and formed in minutes the novel methyl 2-fluoro(2-norbornane)acetate (**29**). Even more impressive results were achieved with

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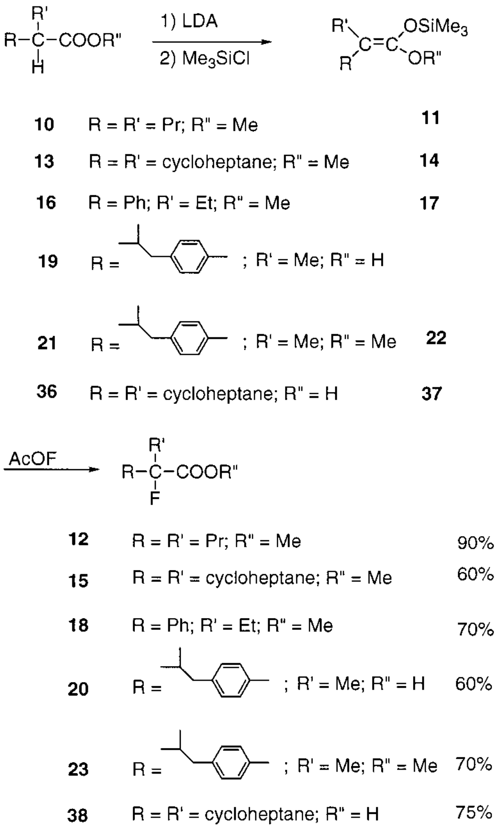
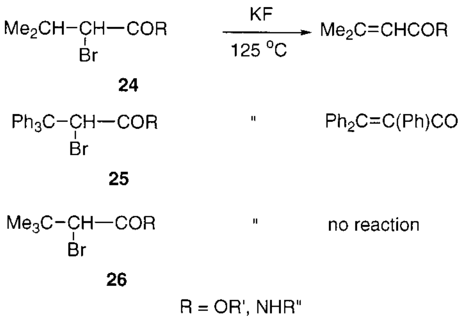
[18] These side reactions occurred with many types of derivatives including various amides. Esters, in addition to these typical SN1 reactions, suffered also from trans esterefication problems. Rozen, S. Unpublished Results.

Scheme 4



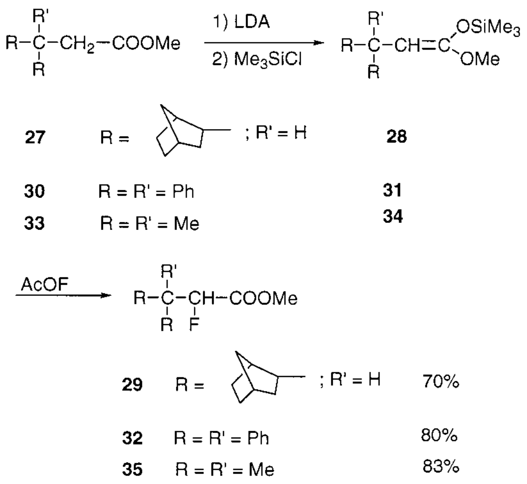
Scheme 5



methyl 3,3,3-triphenylpropionate (**30**) and methyl 3,3,-dimethylbutyrate (**33**), which were converted to their respective trimethylsilyl ketene acetals **31** and **34** and reacted with AcOF. The unknown methyl 2-fluoro-3,3,3-triphenylpropionate (**32**) and methyl 2-fluoro-3,3,-dimethylbutyrate (**35**) were produced, both in excellent yields (Scheme 6).

All reactions described above involved the ester moiety, but it is as easy to react free acids. The only difference is using twice as much base and Me$_3$SiCl in order to convert the acids into ketene bis(trimethylsilyl acetals). It should be pointed out, however, that the yields of these enol derivatives are somewhat lower (around 70−80%) than the ones obtained from esters. Thus, the ketene bis(trimethylsilyl acetal) **37** of cycloheptyl carboxylic acid (**36**) was reacted with AcOF to produce the α-fluorocycloheptyl carboxylic acid (**38**) in higher than 75% yield. Similarly, ibuprofen (**19**) itself was converted to the 2-fluorinated free acid **20** in 60% yield (Scheme 4). The free α-fluorocarboxylic acids could also be obtained by basic hydrolysis (5% NaOH in EtOH/H$_2$O at 70 °C for about 1 h) in nearly quantitative yields.

Scheme 6



In the past, we have stated that AcOF is a relatively mild carrier of elemental fluorine and its reactions better controlled. In part, this is due to the fact that, unlike F$_2$, acetyl hypofluorite is completely soluble in organic solvents so its concentration is controllable at any given time during the reaction. The present study confirms this statement once again. When we passed dilute fluorine through silyl enol derivatives described above, the yields of the α-fluoroesters dropped to around 20%. Although the preparation of this hypofluorite seems at first to be an extra step, it really is not. The preparation is fast, the reagent does not need any manipulations such as isolation or purification, and essentially, it is a one-pot reaction.

Experimental Section

^{1}H NMR spectra were recorded using a 200 MHz machine with CDCl$_3$ as a solvent and Me$_4$Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz and are reported in parts per million upfield from CFCl$_3$ serving as an internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded at 50.2 MHz. Here too, CDCl$_3$ served as a solvent with TMS as an internal standard. MS and GC−MS spectra were usually measured under EI conditions. Chemical ionization (CI) protocol was used for more sensitive samples. In extreme cases where neither EI nor CI methods could detect the molecular ion, we have used a supersonic GC−MS developed in our department.[19] IR spectra were recorded as neat films, in CHCl$_3$ solution on an FTIR spectrophotometer. The spectral properties of all products presented in this work are in excellent agreement with their structure, and where relevant, with the ones described in the literature.

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and a corrosive material. In organic chemistry, it is mostly used after dilution with nitrogen or helium. Such dilution can be achieved by using an appropriate vacuum line constructed in a well-ventilated area. A detailed description for such a setup has appeared lately.[20] Despite hundreds of papers found in the literature dealing with its reactions with organic compounds, working with F$_2$ is still viewed by some as something extraordinary that should be avoided almost by any cost. The situation, however, is much simpler, and if elementary precautions are taken, work with F$_2$ is simple and can be carried in regular glassware. We have

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run numerous reactions with it and never had any problem. For the occasional user, a prediluted 10% fluorine in nitrogen solution is commercially available, making the whole process very simple indeed.

Preparation of AcOF and Its Reaction with the Enol Form of the Esters and Acids. A mixture of 10−15% F_2 in N_2 was bubbled into a cold (−45 °C) suspension of 2 g of AcONa·AcOH dispersed in 100 mL of CH_3CN and 10 mL of AcOH placed in a standard glass vessel. The solvated salt could be made by leaving anhydrous AcONa over AcOH in a closed desiccator for at least 24 h. The amount of the AcOF thus obtained could be easily determined by reacting aliquots of the reaction mixture with aqueous KI solution and titrating the liberated iodine. A concentration of up to 0.35 M (60 mmol) AcOF was thus achieved in about 1.5−2 h.

Synthesis of Trimethyl Silyl Enol Derivatives. All enol derivatives (25 mmol) were prepared by standard procedures such as reacting the corresponding esters or acids with commercial LDA followed by trimethylsilyl chloride.[15] The resulting ketene acetals were purified by vacuum distillation, but no attempt was made to obtain analytically pure samples. These silyl enol derivatives can be stored indefinitely under nitrogen at 0 °C. Some spectral properties of the ketene acetals that are not described in the literature are given. Yields of 70% and higher were easily achieved by this method.

General Synthesis of α-Fluoro Esters. A stirred $CHCl_3$ solution (10 mL) of the ketene acetal (usually about 1.3 mmol), obtained as described above, was cooled to −45 °C. AcOF (3.9 mmol) solution was added to it in one portion. After a few minutes, the reaction was terminated by pouring it into 500 mL of $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The products were usually purified by flash chromatography (Merck silica gel 60H) using petroleum ether−chloroform as eluent.

Methyl 2-Fluorophenylacetate (3).[3b] Methyl phenylacetate (**1**) was converted as described above to its trimethylsilyl ketene acetal **2**[15] (*E* and *Z* mixture): oil; $bp_{(0.3mm)}$ 78 °C; ^1H NMR (all peak pairs are due to the *E* and *Z* isomers) 7.47−7.03 (5 H, m), 4.7 and 4.62 (1 H, s), 3.72 and 3.70 (3 H, s), 0.35 and 0.29 ppm (9 H, s). Compound **2** was then reacted with AcOF as described above to give **3** in 90% yield: oil; $bp_{(15\ mm)}$ 100 °C; IR 1760 cm^{-1}; ^1H NMR 7.40 (5 H, m), 5.80 (1 H, d, J = 47 Hz), 3.78 ppm (3 H, s); ^{19}F NMR −180.07 ppm (d, J = 47 Hz); HRMS calcd for $C_9H_9FO_2$ 168.0586 $(M)^+$, found 168.0582.

Methyl 2-Fluorooctanoate (6).[16] Methyl octanoate (**4**) was converted as described above to its trimethylsilyl ketene acetal **5** (mixture of *E* and *Z*): oil; $bp_{(0.1mm)}$ 53 °C; ^1H NMR 3.68 (1 H, t, J = 7 Hz), 3.50 and 3.47 (for *E* and *Z*) (3 H, s), 1.93 (2 H, m), 1.26 (8 H, m), 0.87 (3 H, t, J = 7 Hz), 0.20 and 0.18 ppm (9 H, s). Compound **5** was then reacted with AcOF as described above to give **6** in 80% yield: oil; IR 1765 cm^{-1}; ^1H NMR 4.90 (1 H, dt, J_1 = 50 Hz, J_2 = 6 Hz), 3.79 (3 H, s), 1.88 (2 H, m) 1.35 (8 H, m), 0.87 ppm (3 H, t, J = 7 Hz); ^{19}F NMR −192.5 ppm (dt, J_1 = 50 Hz, J_2 = 25 Hz); ^{13}C NMR 170 (d, J = 22.5 Hz), 88.48 (d, J = 183 Hz), 51.59, 31.95 (d, J = 20.5 Hz), 31.07, 28.29, 23.85 (d, J = 2 Hz), 22.03, 13.45 ppm.

Methyl 2-Fluoro-4-cyclohexylbutanoate (9). Methyl 4-cyclohexylbutanoate (**7**) was converted as described above to its trimethylsilyl ketene acetal **8**: oil; $bp_{(0.2mm)}$ 60 °C; ^1H NMR 3.67 (1 H, t, J = 7 Hz), 3.44 (3 H, s), 2.1−0.75 (15 H, m), 0.18 ppm (9 H, s); ^{13}C NMR 153, 85.05, 54.12, 38.07, 36.69, 32.95, 26.41, 26.10, 21.32, 0.22 ppm. Compound **8** was then reacted with AcOF as described above to give **9** in 70% yield: oil; IR 1756 cm^{-1}; ^1H NMR 4.9 (1 H, ddd, J_1 = 49 Hz, J_2 = 7 Hz, J_3 = 5 Hz), 3.78 (3 H, s), 2.10−1.5 (5 H, m) 1.5−1.0 (8 H, m), 0.87 ppm (2 H, m); ^{19}F NMR −192.6 ppm (dt, J_1 = 49 Hz, J_2 = 25.2 Hz); ^{13}C NMR 170.57 (d, J = 24 Hz), 89.28 (d, J = 183 Hz), 52.22, 37.17, 33.14, 32.95, 31.76, 29.91 (d, J = 21 Hz), 26.50, 26.20 ppm; HRMS (CI) calcd for $C_{11}H_{19}FO_2$ 203.145042 $(MH)^+$, found 203.144733. Anal. Calcd for $C_{11}H_{19}FO_2$: C, 65.32; H, 9.47. Found: C, 65.49; H, 9.38.

Methyl 2-Propyl-2-fluoropentanoate (12). Methyl 2-propylpentanoate (**10**) was converted as described above to its trimethylsilyl ketene acetal **11**: oil; $bp_{(0.2mm)}$ 45 °C; ^1H NMR 3.49 (3 H, s), 1.91−0.87 (14 H, m), 0.2 ppm (9 H, s); ^{13}C NMR 150, 98, 56.33, 29.40, 20.88, 13.69, 0.50 ppm. Compound **11** was then reacted with AcOF as described above to give **12** in 90% yield: oil; IR 1763 cm^{-1}; ^1H NMR 3.78 (3 H, s), 1.80−1.2 (8 H, m) 0.9 ppm (6 H, t, J = 7 Hz); ^{19}F NMR −166.7 ppm (m); ^{13}C NMR 172.16 (d, J = 23 Hz), 97.93 (d, J = 186 Hz), 52.09, 39.63 (d, J = 23 Hz), 16.67, 13.98 ppm; HRMS calcd for $C_9H_{17}FO_2$ 176.1213 $(M)^+$, found 176.1214. Anal. Calcd for $C_9H_{17}FO_2$: C, 61.34; H, 9.72; F, 10.78. Found: C, 60.90; H, 9.48; F, 10.58.

Methyl α-Fluorocycloheptanoate (15) and α-Fluorocycloheptyl Carboxylic Acid (38). Methyl cycloheptanoate (**13**) was converted as described above to its trimethylsilyl ketene acetal **14**: oil; $bp_{(0.1mm)}$ 50 °C; ^1H NMR 3.45 (3 H, s), 2.12−2.08 (4 H, m), 1.6−1.4 (8 H, m), 0.16 ppm (9 H, s); ^{13}C NMR 149.72, 100.71, 56.55, 29.90, 29.52, 29.00, 28.65, 27.94, 27.80, 1.39 ppm. Compound **14** was then reacted with AcOF as described above to give **15** in 60% yield: oil; IR 1742 cm^{-1}; ^1H NMR 3.75 (3 H, s), 2.10−2.05 (2 H, m) 1.99−1.94 (2 H, m), 1.67−1.58 (4 H, m), 1.24 (2 H, m), 0.85−0.82 ppm (2 H, m); ^{19}F NMR −149.8 ppm (m); ^{13}C NMR 173.71 (d, J = 26 Hz), 97.46 (d, J = 185 Hz), 54.55, 36.77 (d, J = 24 Hz), 29.29, 22.10 ppm; HRMS (CI) calcd for $C_9H_{15}FO_2$ 175.11357 $(MH)^+$, found 175.11343. Anal. Calcd for $C_9H_{15}FO_2$: C, 62.05; H, 8.68. Found: C, 62.25; H, 8.50.

The bis(trimethylsilyl acetal) **37** was obtained from cycloheptyl carboxylic acid (**36**): oil; $bp_{(0.6mm)}$ 75 °C; ^1H NMR 2.12 (4 H, m), 1.48 (8 H, m), 0.18 ppm (18 H, s); ^{13}C NMR 144.75, 98.03, 30.09, 28.47, 0.47 ppm. It was then reacted with AcOF to produce **38** in 75% yield: oil; IR 1723 cm^{-1}; ^1H NMR 8.7 (1 H, bs), 2.13−2.05 (4 H, m) 2.05−2.00 (2 H, m), 1.71−1.64 ppm (6 H, m); ^{19}F NMR −149.7 ppm (quint, 24 Hz); ^{13}C NMR 178.71 (d, J = 27 Hz), 96.93 (d, J = 183 Hz), 36.47 (d, J = 23 Hz), 29.20, 22.04 ppm (d, J = 4 Hz); HRMS (CI) calcd for $C_8H_{13}FO_2$ 161.09778 $(MH)^+$, found 161.09648. Compound **38** was also obtained in 90% yield by heating 40 mg of **15** with 5% aqueous NaOH (6 mL) and 1.5 mL of EtOH at 70 °C for 1 h.

Methyl 2-Fluoro-2-phenylbutanoate (18). Methyl 2-phenylbutanoate (**16**) was converted as described above to its trimethylsilyl ketene acetal **17**: oil; $bp_{(0.4mm)}$ 42 °C; ^1H NMR (all pairs for *Z* and *E* isomers) 3.60 and 3.42 (3 H, s), 2.36 (2 H, m), 0.92 (3 H, m), 0.27 and 0.00 ppm (9 H, s); ^{13}C NMR (all pairs for Z and E isomers) 151 and 150, 139−125.08, 103.0 and 102.0, 56.76 and 55.62, 23.32 and 23.01, 13.95 and 13.00, −0.14 and −0.48 ppm. Compound **17** was then reacted with AcOF as described above to give **18** in 70% yield: oil; IR 1734 cm^{-1}; ^1H NMR 7.52−7.24 (5 H, m), 3.75 (3 H, s), 2.39−2.09 (2 H, m), 0.95 ppm (3 H, t, J = 7 Hz); ^{19}F NMR −167.73 ppm (dd, J_1 = 27 Hz, J_2 = 21 Hz); ^{13}C NMR 171.00 (d, J = 27 Hz), 138.59 (d, J = 60 Hz), 127.94, 124.81, 124.62, 97.48 (d, J = 189 Hz), 52.61, 31.55 (d, J = 22 Hz), 7.44 ppm; HRMS calcd for $C_{11}H_{13}FO_2$ 196.08995 $(M)^+$, found 196.08949. Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.33; H, 6.68; Found: C, 67.78; H, 7.03.

Methyl 2-Fluoro-2-(4-isobutylphenyl)propionate (23)[4] **and 2-Fluoro-2-(4-isobutylphenyl)propionic Acid (20).**[4,6b] Methyl 2-(4-isobutylphenyl)propionate (**21**) was converted as described above to its trimethylsilyl ketene acetal **22**: oil; $bp_{(0.2mm)}$ 92 °C; ^1H NMR (for both *E* and *Z* isomers) 7.31−7.26 (4 H, m), 3.62 and 3.51 (3 H, s), 2.43 (2 H, d, J = 8 Hz), 2.10−1.81 (1 H, m), 1.98 and 1.94 (3 H, s), 0.92−0.87 (6 H, m), 0.28 and 0.03 ppm (9 H, s). Compound **22** was then reacted with AcOF as described above to give **23** in 70% yield: oil; IR 1760 cm^{-1}; ^1H NMR 7.4 (2 H, d, J = 8 Hz), 7.16 (2 H, d, J = 8 Hz), 3.77 (3 H, s), 2.47 (2 H, d, J = 7 Hz) 1.94 (3 H, d, J = 22 Hz), 1.86 (1 H, sept, J = 7 Hz), 0.9 ppm (6 H, d, J = 7 Hz); ^{19}F NMR −150.67 ppm (q, J = 22 Hz); HRMS calcd for $C_{14}H_{19}FO_2$ 238.1369 $(M)^+$, found 238.1370.

The bis(trimethylsilyl acetal) of **19** was obtained from the acid: oil; $bp_{(0.3mm)}$ 67 °C; ^1H NMR 7.26 (2 H, d, J = 8 Hz), 7.01 (2 H, d, J = 8 Hz), 2.42 (2 H, d, J = 8 Hz) 1.88 (3 H, s), 1.86−1.76 (1 H, m), 0.88 (6 H, d, J = 6 Hz) 0.26 (9 H, s), −0.06 ppm (9 H, s). It was then reacted with AcOF to produce **20** in 60% yield.[6]

Methyl 2-Fluoro-(2-Norbornane)acetate (29). Methyl 2-norbornaneacetate (**27**) was converted as described above to its trimethylsilyl ketene acetal **28**: oil; bp$_{(0.7\text{mm})}$ 86 °C; ^{1}H NMR 3.61 (1 H, d, $J = 9$ Hz), 3.51 (3 H, s), 2.29−2.17 (2 H, m), 1.91 (1 H, m), 1.61−1.05 (8 H, m), 0.2 ppm (9 H, s); ^{13}C NMR 151.61, 92.34,54.16, 43.33, 39.87, 37.24, 36.11, 35.41, 29.18, 28.15, −0.73 ppm. Compound **28** was then reacted with AcOF as described above to give two diastereoisomers of **29** in 70% yield: oil; IR 1755 and 1711 cm^{-1}; ^{1}H NMR (for the two diastereoisomers) 4.74 (1 H, dd, $J_1 = 50$ Hz, $J_2 = 6$ Hz), 4.54 (1 H, dd, $J_1 = 50$ Hz, $J_2 = 8$ Hz), 3.78 (3 H, s), 2.40−1.8 (4 H, m), 1.6−1.0 ppm (7 H, m); ^{19}F NMR (for the two diastereoisomers) −198.69 (dd, $J_1 = 50$ Hz, $J_2 = 28$ Hz), −188.46 ppm (dd, $J_1 = 50$ Hz, $J_2 = 20$ Hz); ^{13}C NMR (for both diastereoisomers) 169.85 and 169.79 both (d, $J = 22$ Hz), 91.60 and 91.36 both (d, $J = 184$ Hz), 52.01, 44.19 and 44.07 both (d, $J = 20$ Hz), 41.15 and 41.10, 39.20 and 39.17, 36.63 and 36.16, 35.63, 32.33 and 31.31 ppm; HRMS (CI) calcd for $C_{10}H_{15}FO_2$ 187.11362 (MH)$^+$, found 187.11343. Anal. Calcd for $C_{10}H_{15}FO_2$: C, 64.50; H, 8.12. Found: C, 64.83; H, 8.40.

Methyl 2-Fluoro-3,3,3-triphenylpropionate (32). Methyl 3,3,3-triphenylpropionate (**30**) was converted as described above to its trimethylsilyl ketene acetal **31**: oil that could not be distilled because of decomposition at bp; ^{1}H NMR 7.3−7.13 (15 H, m), 4.87 (1 H, s), 2.86 (3 H, s), 0.27 ppm (9 H, s). The crude **31** was then reacted with AcOF as described above to give **32** in 80% yield: oil; IR 1747 cm^{-1}; ^{1}H NMR 7.34−7.15 (15 H, m), 6.41 (1 H, d, $J = 47$ Hz), 3.39 (3 H, s); ^{19}F NMR −187.82 ppm (d, $J = 47$ Hz); ^{13}C NMR 168.24 (d, $J = 24$ Hz), 142.44, 129.47, 127.52, 126.47, 91.76 (d, $J = 194$ Hz), 61.23 (d, $J = 19$ Hz), 51.75 ppm; HRMS (CI) calcd for $C_{22}H_{19}FO_2$ 335.14514 (MH)$^+$, found 335.14473. Anal. Calcd. for $C_{22}H_{19}FO_2$: C, 79.01; H, 5.73, F, 5.69. Found: C, 78.79; H, 5.91; F, 5.49.

Methyl 2-Fluoro-3,3,-dimethylbutyrate (35). Methyl 3,3-dimethylbutyrate (**33**) was converted as described above to its trimethylsilyl ketene acetal **34**: oil; bp$_{(12\text{mm})}$ 60 °C; ^{1}H NMR 3.72 (1 H, s), 3.49 (3 H, s), 1.05 (9 H, s), 0.21 ppm (9 H, s); ^{13}C NMR 152.41, 96.67, 54.09, 31.01, 29.67, −0.4 ppm. Compound **34** was then reacted with AcOF as described above to give **35** in 83% yield: oil; IR 1755 cm^{-1}; ^{1}H NMR 4.55 (1 H, d, $J = 49$ Hz), 3.79 (3 H, s), 1.03 ppm (9 H, s); ^{19}F NMR −194.18 ppm (d, $J = 49$ Hz); ^{13}C NMR 168.87 (d, $J = 25$ Hz), 95.46 (d, $J = 187$ Hz), 51.24, 34.32 (d, $J = 19$ Hz), 24.96 ppm; MS regular measurements such as EI and CI with commercial instruments fail to show any molecular ion peak. Repeating the measurement with an unique supersonic GC−MS developed in our department, using electron ionization of the sample compound while it is vibrationally cooled in a supersonic molecular beam, reveals the molecular ion peak at $m/e = 148$ (M)$^+$. The vibrational cooling considerably enhance the relative abundance of the molecular ion.[19]

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