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α-Trifluoromethylation of Secondary and Sterically Hindered Carboxylates with Use of BrF_3

Aviv Hagooly and Shlomo Rozen*

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

rozens@post.tau.ac.il

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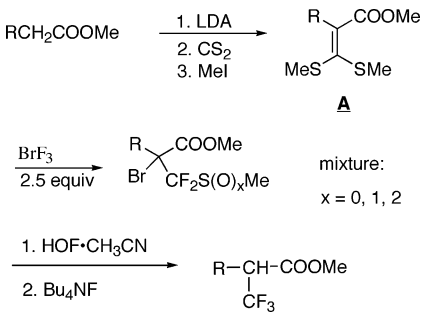
Secondary esters and those with sterical hindrance at the β carbon were reacted with base, carbon disulfide, and methyl iodide to produce methyl 2-carboalkoxydithioalkenoate (**2**). These compounds were reacted with BrF_3, forming the corresponding α-trifluoromethyl esters (**3**) along with 1,1-difluoro-2-trifluoromethyl-2-alkyl ethers (**4**). The products of type **4** have been transformed to derivatives of type **3**, thus raising the overall yields of the target respective α-trifluoromethyl esters to 65−80%. The reaction is tolerant to different functional groups such as halogens, protected alcohols, esters, and lactones.

Frequently, the biological activity of organic substrates is strongly influenced by the trifluoromethyl group. This phenomenon is usually explained by the increased lipophilicity and hydrolytic stability of the corresponding organic substrates. Many articles and reviews are devoted to compounds possessing this group. They deal with the whole spectrum of properties, from pharmacological aspects to synthetic methods devised for the incorporation of the CF_3 moiety into various specific sites of organic molecules.[1]

A general method for introducing the trifluoromethyl group into the α position of carboxylic acids was, however, conspicuously missing. Only a few unique α-trifluoromethyl carboxylates have been described. Purrington achieved trifluoromethylation of malonic acids using CF_2Br_2 followed by nucleophilic displacement of bromine by fluoride.[2] Tellier performed some sigmatropic shifts with vinyl alcohols and 2H perfluoropropene,[3] Lassaletta developed a route for constructing α-alkoxy-α-trifluoromethyl acids,[4] and Allmendinger prepared α-trifluoromethyl-α,β-unsaturated acids.[5] Kitazume reacted methyl β,β,β-trifluoropropionate with allylic carbamates obtaining eventually some functionalized α-trifluoromethyl carboxylates.[6] Recently Cahard described a procedure for electrophilic trifluoromethylation on the highly nucleophilic carbon of β-ketocarboxylates.[7] Attempting α-alkylation of β,β,β-trifluoropropionates was proved to be impractical since a facile defluorination takes place even at −78 °C: $CF_3CH_2COOR + B^- \rightarrow CF_2{=}CHCOOR$.[8] Recently, we developed a general method for constructing straight-chain α-trifluoromethyl carboxylates using CS_2 and BrF_3 (Scheme 1).[9] These two reagents are the cornerstone also for the present work, which describes a general preparation of secondary, as well as sterically hindered, α-trifluoromethyl carboxylic acids. Although the reaction with this family of compounds proceeds differently from what is described in Scheme 1, the basic roles of the reagents remained the same. The carbon atom of the CF_3 group originated in carbon disulfide, while BrF_3 was the supplier of the fluorine atoms.

SCHEME 1. Synthesis of Straight-Chain α-Trifluoromethyl Carboxylates[9]



Most specific reactions with BrF_3[10] were made possible because of the tendency of the soft acidic electrophilic bromine to complex itself with soft basic heteroatoms, such as nitrogen and sulfur, bringing the naked nucleo-

* Address correspondence to this author. Fax: 972-3-6409293.

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(2) Everett, T. S.; Purrington, S. T.; Bumgardner, C. L. *J. Org. Chem.* **1984**, *49*, 3702.

(3) Tellier, F.; Audouin, M.; Sauvetre, R. *J. Fluorine Chem.* **2002**, *113*, 167.

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(5) Allmendinger, T.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 339.

(6) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369.

(7) Ma, J. A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726.

(8) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987.

(9) Hagooly, A.; Rozen, S. *Chem. Commun.* **2004**, 594.

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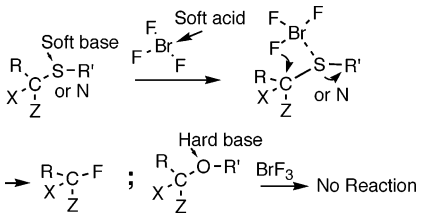
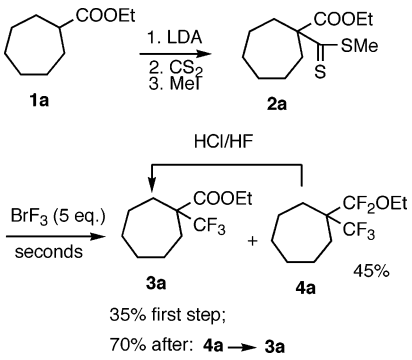
SCHEME 2. General Mechanism of BrF_3 Reacting with Electron-Rich Centers



SCHEME 3



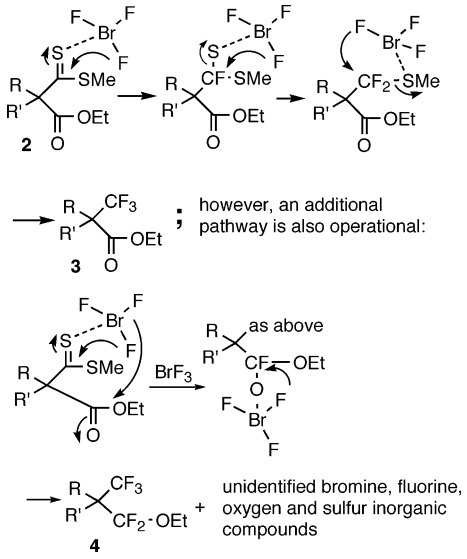
philic fluorides near the reaction center. This proximity reduces undesirable radical reactions and enables relatively clean substitution of the heteroatoms for fluorides (Scheme 2). It should be noted that the soft bromine will not complex itself with hard oxygen atoms. No specific reactions were observed when BrF_3 was brought in contact with any type of carbonyl, including malonates, which resemble compounds of type **2** (see below).

Results and Discussion

The chain of reactions that starts with ethyl cycloheptylcarboxylate (**1a**) can serve as an illustrative example for introducing the CF_3 group at the α-position of secondary acid derivatives. When **1a** was reacted with LDA, CS_2, and MeI, methyl 2-carboethoxydithiocycloheptanoate (**2a**) was obtained in very good yield. Unlike the intermediate **A** in Scheme 1, no carbon−carbon double bond could be formed around which the usual first step of most reactions with BrF_3 takes place. Still, we found that this reagent reacted successfully with **2a** although a larger excess of up to 5 mol equiv was needed. After a few seconds the desired ethyl 2-trifluoromethylcycloheptanoate (**3a**) was formed, although in 35% yield only. It was accompanied by additional major product (45% yield) that proved to be 1-(difluoromethylene ethyl ether)-1-trifluoromethylcycloheptane (**4a**) (Scheme 3).

These results indicate that the reaction mechanism is somewhat similar to the one described for the reaction of BrF_3 with nitriles.[11] While the electrophilic bromine is complexed around the sulfur atoms the nucleophilic fluorides get close to the adjacent carbonyl forming, in addition to the CF_3 group, an α,α-difluoro ether moiety shown in Scheme 4. In the past we have made intentionally similar α,α-difluoro ethers by reacting bromine trifluoride with thioesters.[12] At that time we found that these ethers are not very stable and tend to decompose slowly back to the corresponding esters. To facilitate this last transformation, we treated **4a** with an aqueous−alcoholic mixture of HCl/HF for a few hours regenerating the ester moiety in higher than 80% yield, raising the overall yield of **3a** to 70% (see also Scheme 3).

SCHEME 4. The Proposed Reaction Mechanism



Similarly, the aliphatic ethyl 2-propylpentanoate (**1b**) was converted to methyl 2-carboethoxy-2-propyldithiopentanoate (**2b**), which was then reacted with BrF_3. Both ethyl 2-propyl-2-trifluoromethylpentanoate (**3b**) and 1-ethoxy-1,1-difluoro-2-propyl-2-trifluoromethylpentane (**4b**) were formed. The latter was converted to **3b** in good yield (see Table 1). Primary esters with strong steric hindrance at the *β*-position can also be manipulated as described above. Butyl neopentanoate (**1c**) and methyl 2-norbornyl acetate (**1d**) gave, after treatment with base, CS_2 and MeI, the corresponding **2c** and **2d**. Reacting these compounds with BrF_3 resulted in the respective α-trifluoromethyl esters **3c** and **3d** accompanied by the pentafluoro derivatives **4c** and **4d**. Here too, these pentafluoro compounds were transformed back to **3c** and **3d**, considerably increasing the overall yield of the desired α-trifluoromethyl esters.

To explore the scope and limitations of this method we repeated the above chain of reactions with compounds bearing additional functionalities. It seems that the presence of common aromatic rings is not compatible with the reaction since BrF_3 readily brominates these rings.[13] Other functional groups, however, are tolerated. While it is known that BrF_3 can substitute chlorine with fluorine[14] we found that the reaction at the sulfur center is much faster. 3-Chloropropyl cyclohexylcarboxylate (**1e**) was easily converted to **2e.** This compound was reacted

(10) For some recent reactions with the still rarely used BrF_3 see: (a) Rozen, S.; Mishani, E.; Bar-Haim, A. *J. Org. Chem.* **1994**, *59*, 2918. (b) Rozen, S.; Ben-David, I. *J. Org. Chem.* **2001**, *66*, 496. (c) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769. (d) Hagooly, A.; Sasson, R.; Rozen, S. *J. Org. Chem.* **2003**, *68*, 8287. (e) Hagooly, A.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2002**, *67*, 8430.

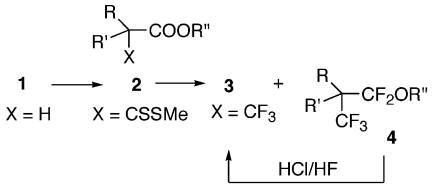
(11) Rozen, S.; Rechavi, D.; Hagooly, A. *J. Fluorine Chem.* **2001**, *111*, 161.

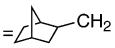
(12) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761.

(13) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.

(14) Rozov, L. A.; Huang, C. G.; Halpern, D. F.; Vernice, G. G.; Ramig K. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3023.

TABLE 1.



		3 (%)	4 (%)
b:	R = R' = Pr R" = Et	70[a] (30)[b]	55
c:	R = *t*-Bu; R' = H R" = Bu	75[a] (35)[b]	45
d:	R =  R' = H; R" = Me	75[a] (35)[b]	50
e:	R = R' = cyclohexyl R" = $(CH_2)_3Cl$	80[a] (25)[b]	60
f:	R = Et; R' = Me R" = CH_2CH_2OCOt-Bu	65[a] (30)[b]	55

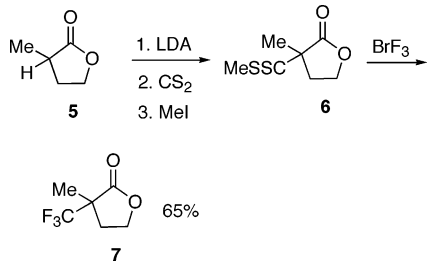
[a] Total overall yield. [b] Yield before converting **4** to **3**.

with bromine trifluoride to give the desired 3-chloropropyl 2-trifluoromethylcyclohexanoate (**3e**) along with the pentafluoro derivative **4e**. The crude reaction mixture was heated with 3-chloropropanol/HF/HCl to give **3e** in high yield. Alcohols are easily oxidized by BrF_3 to the corresponding acyl fluorides,[15] but when protected the reaction proceeds smoothly. Thus, the hydroxy group of ethyleneglycyl 2-methylbutanoate was protected as a pivaloate **1f**. The reason for choosing this protecting group is the absence of any acidic hydrogen α to the carbonyl, a necessity when a strong base is applied. Methyl 2-(2-pivaloylcarboethoxy)-2-methyldithiobutanoate (**2f**) was thus obtained in very good yield and after the reaction with bromine trifluoride the pentafluoro derivative **4f** was found to be the major product. The crude reaction mixture was treated with HCl/HF and we obtained the 2-pivaloylethyl 2-methyl-2-trifluoromethylbutanoate **3f** in good yield. It should be noted that unlike the carbonyl near the dithioesters that was attacked by the nucleophilic fluorine atoms of the reagent, the remote carbonyl of the pyvaloyl group was not affected by BrF_3, another support for the proposed mechanism of the reaction as presented in Schemes 2 and 4.

Lactones are also suitable derivatives for this reaction and α-methyl-γ-butyrolactone (**5**) can serve as an example. The preparation of the dithioester α-methyl-α-(methyldithioformate)-γ-butyrolactone (**6**) proceeded as usual, but when reacted with BrF_3 the only compound isolated was the desired α-methyl-α-trifluoromethyl-γ-butyrolactone (**7**) in 65% yield (Scheme 5). While we do not have a solid explanation for the absence of the corresponding pentafluoro derivative in this case, a probable factor may be the greater distance of the methyl dithioester from the carbonyl moiety compared with other 2-carboalkoxydithioalkanoates.

(15) Rozen, S.; Ben-David, I. *J. Fluorine Chem*. **1996**, *76*, 145.

SCHEME 5



In conclusion, this work, along with that described in ref 9, covers the general preparation of the whole spectrum of the potentially important α-trifluoromethyl carboxylic acid derivatives. In addition it should be stressed once again that when properly used, bromine trifluoride can serve as an excellent fluorinating agent for hard to prepare fluorinated compounds.

Experimental Section

^1H NMR spectra were recorded on a 200-MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. Only the relevant and characteristic peaks are reported. The ^{19}F NMR spectra were measured at 188.1 MHz and are reported upfield from CFCl3, 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 and Me_4Si as an internal standard. IR spectra were recorded in $CHCl_3$ solution on a FTIR spectrophotometer. Silica gel 60H (Merck) and petroleum ether/ethyl acetate were used in the flash chromatography when the purification of the product was desired. Most compounds described in this work were purified and their spectral data recorded. However, only the α-trifluoromethyl carboxylates were analytically purified. Their purity was confirmed also by elemental microanalysis.

Preparing and Handling BrF_3. Although commercially available, we usually prepare our own BrF_3 by passing 0.6 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor and cooled to 0−10 °C. Under these conditions the higher oxidation state, BrF_5, will not be formed in any appreciable amount. The product can be stored in Teflon containers indefinitely. BrF_3 is a strong oxidizer and tends to react very exothermically with water and oxygenated organic solvents such as acetone or THF. Alkanes, like petroleum ether, cannot serve as solvents either since they also react fast with BrF_3. Any work with BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised. It is recommended that a face shield and comfortable, yet heavy-duty gloves should be wear when working with this reagent.

General Procedure for the Preparation of Methyl 2-Carboalkoxydithioalkenoate Derivatives 2.[16] A 10-mmol sample of the ester **1** was dissolved in 100 mL of dry THF and cooled to −78 °C. Lithium diisopropylamide (12.5 mmol) (LDA, 1.5 M solution in cyclohexane) was added, the cooling bath was removed, and the mixture was stirred for 2 h. The reaction was cooled again to −78 °C and carbon disulfide (about 40 mmol) was added. The brown solution was stirred for another hour and cooled again to −78 °C, then methyl iodide (about 40 mmol) was added. After another 2 h the reaction was warmed to room temperature, poured into water, extracted with ether, and dried over $MgSO_4$, then the solvent was removed. The product (of type **2**) was isolated by flash chromatography as a brown-orange oil.

General Procedure for Reacting 2 with BrF_3: The Preparation of 2-Trifluoromethyl Esters 3. The methyl

(16) Konen, D. A.; Pfeffer, P. E.; Silbert, L. S. *Tetrahedron* **1976**, *32*, 2507.

2-carboalkoxydithioalkenoate derivative **2** (usually 1 mmol) was dissolved in 10−15 mL of dry $CFCl_3$ and cooled to 0 °C. About 5 mmol of BrF_3 was dissolved in 10 mL of the same solvent, cooled to 0 °C, and added dropwise, over 1−2 min, to the above solution. Upon completion, the reaction was quenched with saturated aqueous Na_2SO_3 and washed until colorless. The aqueous layer was extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography gave the desired product **3** in 25−45% yields and **4** in 45−60% yields. All compounds of type **4** can be transformed to alkyl 2-trifluoromethyl esters (**3**) by heating them (100 °C, oil bath) for 6−14 h in 10 mL of the same alcohol as the alcoholic part of the ester (R″OH) and 5 mL of water containing 0.5 mL of HCl (32%) and 0.5 mL HF (40%). The regeneration of the ester was monitored by GC and stopped at about 90% conversion. The aqueous layer was extracted with ether, the organic solvent dried over $MgSO_4$ and evaporated, and the residue purified by flash chromatography. The desired products **3** were obtained in 65−90% yields (based on the pentafluoro derivative) increasing the overall yields of **3** to 65−80%.

Methyl 2-carboethoxydithiocycloheptanoate (2a) was prepared from **1a** as described above in 90% yield: oil; IR 1724 cm^{-1}; ^1H NMR δ 4.12 (2 H, q, J = 7 Hz), 2.58 (3 H, s), 1.18 ppm (3 H, t, J = 7 Hz); ^{13}C NMR δ 241.6, 172.7, 70.2, 61.0, 38.1, 29.4, 24.1, 19.9, 13.7 ppm.

Methyl 2-carboethoxy-2-propyldithiopentanoate (2b) was prepared from **1b** as described above in 90% yield: oil; IR 1725 cm^{-1}; ^1H NMR δ 4.12 (2 H, q, J = 7 Hz), 2.60 (3 H, s), 1.18 (3 H, t, J = 7 Hz), 0.89 ppm (3 H, t, J = 7 Hz); ^{13}C NMR δ 239.9, 172.3, 69.3, 61.0, 37.9, 19.8, 17.4, 14.4, 13.7 ppm.

Methyl 2-carbobutoxy-3,3-dimethyldithiobutanoate (2c) was prepared from **1c** as described above in 90% yield: oil; IR 1737 cm^{-1}; ^1H NMR 4.26 (1 H, s), 4.08 (2 H, t, J = 7 Hz), 2.62 (3 H, s), 1.16 (9 H, s), 0.89 ppm (3 H, t, J = 7 Hz); ^{13}C NMR δ 229.8, 168.2, 75.2, 64.7, 35.1, 30.3, 28.1, 20.7, 19.0, 13.5 ppm.

Methyl 2-carbomethoxy-2-norbornyldithioethanoate (2d) was prepared from **1d** as described above. The two diastereoisomers were obtained in 90% yield: oil; IR 1736 cm^{-1}; ^1H NMR δ 4.01 and 3.95 (1 H, d, J = 2 Hz), 3.72 and 3.69 (3 H, s), 2.67 and 2.64 ppm (3 H, s); ^{13}C NMR (only the relevant picks) δ 231.3 and 230.2, 169.1 and 168.7, 71.2 and 70.9, 52.4 ppm.

Methyl 2-(3-chlorocarbopropoxy)dithiocyclohexanoate (2e) was prepared from **1e** as described above in 90% yield: oil; IR 1723 cm^{-1}; ^1H NMR δ 4.28 (2 H, t, J = 7 Hz), 3.55 (2 H, t, J = 7 Hz), 2.61 ppm (3 H, s); ^{13}C NMR δ 240.4, 171.3, 67.5, 61.8, 41.2, 36.1, 31.3, 25.2, 23.5, 19.9 ppm.

Methyl 2-(2-pivaloylcarboethoxy)-2-methyldithiobutanoate (2f) was prepared from **1f** as described in about 90% yield: oil; IR 1728 cm^{-1}; ^1H NMR δ 4.29−4.23 (4 H, m), 2.62 (3 H, s), 2.21 (2 H, q, J = 7 Hz), 1.65 (3 H, s), 1.20 (9 H, s), 0.91 ppm (3 H, t, J = 7 Hz); ^{13}C NMR δ 239.9, 178.1, 172.5, 66.4, 62.9, 61.8, 32.5, 27.0, 23.5, 20.9, 19.9, 9.0 ppm.

α-Methyl-α-(methyl dithioformate)-γ-butyrolactone (6) was prepared from **5** as described above in 90% yield: oil; IR 1769 cm^{-1}; ^1H NMR δ 4.36−4.29 (2 H, m), 3.21−2.95 (1 H, m), 2.64 (3 H, s), 2.51−2.28 (1 H, m), 1.79 ppm (3 H, s); ^{13}C NMR δ 235.9, 176.5, 65.5, 62.4, 39.1, 24.9, 20.4 ppm.

1-(Difluoromethylene ethyl ether)-1-trifluoromethylcycloheptane (4a) was obtained from **2a** as described above in 45% yield: oil; ^1H NMR δ 3.90 (2 H, q, J = 7 Hz), 1.20 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −72.2 (3 F, t, J = 11 Hz), −80.5 ppm (2 F, q, J = 11 Hz); ^{13}C NMR 127.2 (q, J = 284 Hz), 125.5 (t, J = 271 Hz), 59.5 (t, J = 7 Hz), 53.7 (six, J = 24 Hz), 31.9, 29.4, 24.1, 14.7 ppm; MS (CI) m/z 259 $(M - H)^+$. **4a** was transformed to **3a** as described above (6 h of heating in EtOH/H_2O/HCl/HF) in 80% yield.

1-Ethoxy-1,1-difluoro-2-propyl-2-trifluoromethylpentane (4b) was obtained from **2b** as described above in 55% yield: oil; ^1H NMR δ 3.95 (2 H, q, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz), 0.90 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −68.1 (3 F, t, J = 11 Hz), −76.5 ppm (2 F, q, J = 11 Hz); ^{13}C NMR δ 126.4 (q, J = 285 Hz), 124.4 (t, J = 270 Hz), 59.3 (t, J = 8 Hz), 54.4 (six, J = 23 Hz), 31.3, 16.9, 14.8 ppm; MS (CI) m/z 261 $(M - H)^+$. **4b** was transformed to **3b** as described above (10 h of heating in EtOH/H_2O/HCl/HF) in 75% yield.

1-Butoxy-1,1-difluoro-3,3-dimethyl-2-trifluoromethylbutane (4c) was obtained from **2c** as described above in 45% yield: oil; ^1H NMR δ 3.93 (2 H, t, J = 7 Hz), 2.81−2.53 (1 H, m), 1.18 (9 H, s), 0.91 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −60.1 (3 F, qm, J = 11 Hz), −62.5 to −68.5 ppm (2 F, m); ^{13}C NMR δ 125.4 (q, J = 282 Hz), 123.2 (t, J = 268 Hz), 63.0 (t, J = 7 Hz), 57.4 (six, J = 25 Hz), 32.7, 31.0, 29.4, 19.0, 13.4 ppm. **4c** was transformed to **3c** as described above (6 h of heating in BuOH/H_2O/HCl/HF) in 85% yield.

1,1-Difluoro-1-methoxy-2-norbornyl-2-trifluoromethylethane (4d) was obtained from **2d** as described above. The two diastereoisomers were obtained in 50% yield: oil; ^{19}F NMR δ −63.4 and −64.1 (3 F, qm, J = 11 Hz), −71.5 to −75.6 ppm (2 F, m); MS (CI) m/z 257 $(M - H)^+$. **4d** was transformed to **3d** as described above (14 h of heating in BuOH/H_2O/HCl/HF) in 80% yield.

1-(3-Chloropropoxy)-1,1-difluoro-2-trifluoromethylcyclohexane (4e) was obtained from **2e** as described above in 60% yield: oil; ^1H NMR δ 4.07 (2 H, t, J = 7 Hz), 3.63 ppm (2 H, t, J = 7 Hz); ^{19}F NMR δ −69.1 (3 F, t, J = 13 Hz), −78.7 ppm (2 F, q, J = 13 Hz); ^{13}C NMR δ 126.6 (q, J = 283 Hz), 124.5 (t, J = 272 Hz), 60.1 (t, J = 8 Hz), 49.8 (six, J = 23 Hz), 40.8, 32.0, 24.7, 24.1, 20.8 ppm; MS (CI) m/z 293 $(M - H)^+$. **4e** was transformed to **3e** as described above (10 h of heating in 3-chloropropanol/H_2O/HCl/HF) in 90% yield.

1,1-Difluoro-2-methyl-1-(2-pivaloylethoxy)-2-trifluoromethylbutane (4f) was prepared from **2f** as described above in 55% yield: oil; ^1H NMR δ 4.28−4.02 (4 H, m), 1.80 (2 H, q, J = 7 Hz), 1.27 (3 H, s), 1.21 (9 H, s), 0.95 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −71.4 (3 F, t, J = 11 Hz), −79.7 to −80.1 ppm (2 F, m); ^{13}C NMR 178.2, 126.4 (q, J = 283 Hz), 124.3 (t, J = 270 Hz), 61.9, 61.5 (t, J = 7 Hz), 50.4 (six, J = 25 Hz), 38.7, 27.0, 24.1, 14.0, 8.4 ppm; MS (CI) m/z 321 $(MH)^+$. **4f** was transformed to **3f** as described above (6 h of heating in ethylene glycol/H_2O/HCl/HF) in 65% yield.

Ethyl 2-trifluoromethylcycloheptanoate (3a) was prepared from **2a** as described above in 70% overall yield: oil; IR 1731 cm^{-1}; ^1H NMR δ 4.22 (2 H, q, J = 7 Hz), 1.24 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −73.3 ppm (s); ^{13}C NMR δ 170.2, 127.7 (q, J = 283 Hz), 61.6, 55.8 (q, J = 23 Hz), 30.4, 30.0, 23.3, 13.8 ppm; HRMS (CI) (m/z) calcd for $C_{11}H_{18}F_3O_2$ 239.1258 $(MH)^+$, found 239.1262. Anal. Calcd for $C_{11}H_{17}F_3O_2$: C, 55.45; H, 7.19. Found: C, 54.98; H, 7.10.

Ethyl 2-propyl-2-trifluoromethylpentanoate (3b) was prepared from **2b** as described above in 70% overall yield: oil; IR 1734 cm^{-1}; ^1H NMR δ 4.23 (2 H, q, J = 7 Hz), 1.34 (3 H, t, J = 7 Hz), 0.90 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −68.6 ppm (s); ^{13}C NMR δ 169.6, 126.4 (q, J = 284 Hz), 61.3, 55.6 (q, J = 24 Hz), 34.5, 17.5, 14.5, 13.9 ppm; HRMS (CI) (m/z) calcd for $C_{11}H_{20}F_3O_2$ 241.1415 $(MH)^+$, found 241.1412. Anal. Calcd for $C_{11}H_{19}F_3O_2$: C, 54.99; H, 7.97. Found: C, 54.43; H, 7.65.

Butyl 3,3-dimethyl-2-trifluoromethylbutanoate (3c) was prepared from **2c** as described above in 75% overall yield: oil; IR 1739 cm^{-1}; ^1H NMR δ 4.17 (2 H, t, J = 7 Hz), 3.02 (1 H, q, J = 9 Hz), 1.14 (9 H, s), 0.92 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −61.7 ppm (d, J = 9 Hz); ^{13}C NMR 167.2, 125.1 (q, J = 282 Hz), 65.1, 59.3 (q, J = 25 Hz), 32.8, 30.4, 28.5, 19.0, 13.5 ppm; HRMS (CI) (m/z) calcd for $C_{11}H_{20}F_3O_2$ 241.1415 $(MH)^+$, found 241.1406. Anal. Calcd for $C_{11}H_{19}F_3O_2$: C, 54.99; H, 7.97. Found: C, 54.71; H, 7.88.

Methyl 2-norbornyl-2-trifluoromethylethanoate (3d) was prepared from **2d** as described above. The two diastereoisomers were obtain in 75% overall yield: oil; IR 1746 cm^{-1}; ^1H NMR δ 3.80 and 3.75 (3 H, s), 3.07−2.89 ppm (1 H, m); ^{19}F NMR δ −65.4 and −65.5 ppm (d, J = 8 Hz); ^{13}C NMR (only the relevant picks) δ 168.1 and 167.8, 125.0 and 124.4 (q, J =

282 Hz), 55.5 and 55.2 (q, J = 24 Hz), 52.3 ppm; HRMS (CI) (m/z) calcd for $C_{11}H_{16}F_3O_2$ 237.1102 $(MH)^+$, found 237.1100. Anal. Calcd for $C_{11}H_{15}F_3O_2$: C, 55.93; H, 6.40. Found: C, 55.81; H, 6.37.

(3-Chloropropyl) 2-trifluoromethylcyclohexanoate (**3e**) was prepared from **2e** as described above in 80% overall yield: oil; IR 1737 cm^{-1}; ^1H NMR δ 4.36 (2 H, t, J = 7 Hz), 3.61 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −75.2 ppm (s); ^{13}C NMR δ 168.6, 125.8 (q, J = 283 Hz), 62.2, 53.1 (q, J = 24 Hz), 40.8, 31.2, 27.3, 24.6, 22.2 ppm; HRMS (CI) (m/z) calcd for $C_{11}H_{17}C_lF_3O_2$ 273.0869 $(MH)^+$, found 273.0868; Anal. Calcd for $C_{11}H_{16}C_lF_3O_2$: C, 48.45; H, 5.91; Cl, 13.00; F, 20.90. Found: C, 48.31; H, 5.93; Cl, 13.11; F, 20.72.

(2-Pivaloylethyl) 2-methyl-2-trifluoromethylbutanoate (**3f**) was prepared from **2f** as described above in 65% overall yield: oil; IR 1744 and 1728 cm^{-1}; ^1H NMR δ 4.38−4.21 (4 H, m), 1.36 (3 H, s), 1.19 (9 H, s), 0.92 ppm (3 H, t, J = 7 Hz); ^{19}F NMR δ −73.4 ppm (s); ^{13}C NMR δ 178.1, 169.4, 126.2 (q, J = 283 Hz), 63.3, 61.7, 52.7 (q, J = 25 Hz), 38.6, 26.9, 26.1, 16.1, 8.5 ppm; HRMS (CI) (m/z) calcd for $C_{13}H_{22}F_3O_4$ 299.1470 $(MH)^+$, found 299.1470. Anal. Calcd for $C_{13}H_{21}F_3O_4$: C, 52.34; H, 7.10. Found: C, 51.89; H, 6.86.

α-Methyl-α-trifluoromethyl-γ-butyrolactone (**7**) was prepared from **6** as described above in 65% yield (the pentafluoro derivative was not formed at all): oil; IR 1782 cm^{-1}; ^1H NMR δ 4.41−4.30 (2 H, m), 2.81−2.51 (1 H, m), 2.40−2.17 (1 H, m), 1.52 ppm (3 H, s); ^{19}F NMR δ −75.3 ppm (s); ^{13}C NMR δ 175.0, 127.4 (q, J = 282 Hz), 66.7, 49.8 (q, J = 28 Hz), 32.7, 19.3 ppm; HRMS (CI) (m/z) calcd for $C_6H_8F_3O_2$ 169.0476 $(MH)^+$, found 169.0474. Anal. Calcd for $C_6H_7F_3O_2$: C, 42.87; H, 4.20. Found: C, 42.67; H, 4.39.

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