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New functionalized, differently fluorinated building-blocks via Michael addition to γ-fluoro-α-nitroalkenes

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Abstract

The Michael addition of ketone-derived enamines, metalated methylene active compounds and *N*-methyl pyrroles to γ-fluoro-α-nitroalkenes provided in moderate to good isolated yields the corresponding β-fluoroalkyl nitro compounds, which represent new interesting, highly functionalized building blocks in organofluorine chemistry.

Keywords: Michael additions, Nitroalkenes, Enamines

1. Introduction

One of the key issues in organofluorine chemistry is the availability of suitably functionalized fluorinated building blocks to be used in the synthesis of more complex fluorinated molecular structures.

γ-Fluoro-α-nitroalkenes **1** (Fig. 1) have been so far scarcely studied and exploited in the synthesis of functionalized fluoroorganic molecules, despite the fact that they constitute a very promising, highly reactive, yet easy-to-handle class of fluorinated building blocks. Surprisingly, among the differently fluorinated compounds **1a–d**, only 3,3,3-trifluoro-1-nitropropene **1a** has been hitherto described in the literature [1].

Within the frame of a project aimed at the synthesis of fluorinated peptidomimetics via aza-Michael reactions, we became interested in the chemistry of γ-fluoro-α-nitroalkenes **1** [2], thus we decided to undertake a research programme on the synthetic opportunities offered by these interesting fluorinated building-blocks in the preparation of fluoroorganic molecules having potential interest in biomedicinal chemistry and materials science.

Here we describe in full details the synthesis of compounds **1b–d**, and the results of a study on the Michael addition of ketones **2a–c** (and their reactive derivatives such as enamines and silyl enolethers) to **1a–d**, that allows for an efficient entry to β-fluoroalkyl γ-nitroketones **3** (see Scheme 3) and the corresponding carbinols **4** (see Scheme 4) [3,4]. In addition, we describe the Michael reaction of **1a–c** with metalated methylene active compounds **9a–c** and *N*-methyl azoles.

2. Results and discussion

The reactivity of compounds **1** is nearly unexplored, as only a handful of papers describing some examples of Diels–Alder [5] and 1,3-dipolar reactions [6], Friedel–Crafts [7], aza-Michael [2,8] and Michael reactions with methylene active compounds [5] is present in the literature. More recently, in a study on the enantioselective Michael addition of carbonyl compounds catalyzed by chiral enamines, **1a** was marginally mentioned as a ''difficult'' substrate featuring low yields, and low enantioselectivity as well [9].

The key γ-fluoro-α-nitroalkenes **1** were prepared in moderate to good yields by Henry (nitroaldol) reaction of nitromethane with the corresponding fluoroaldehydes (Scheme 1) [10], followed by P_2O_5 promoted dehydration of the intermediate β-nitroalcohols **5**.

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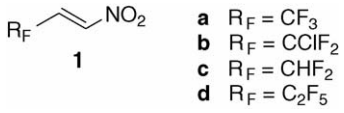
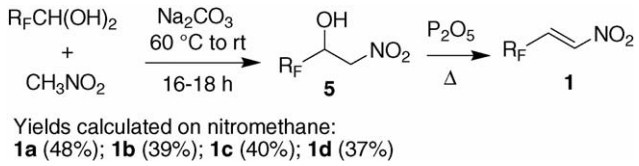
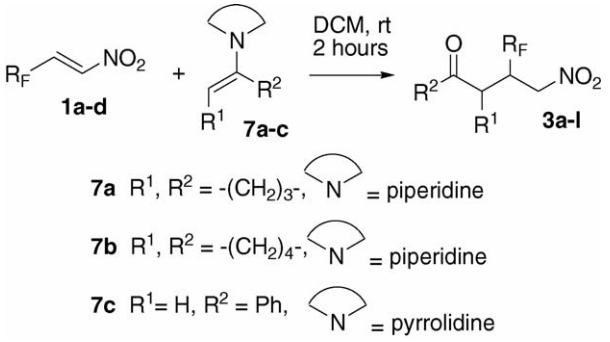


Fig. 1. Fluorinated nitroalkenes 1a–d.



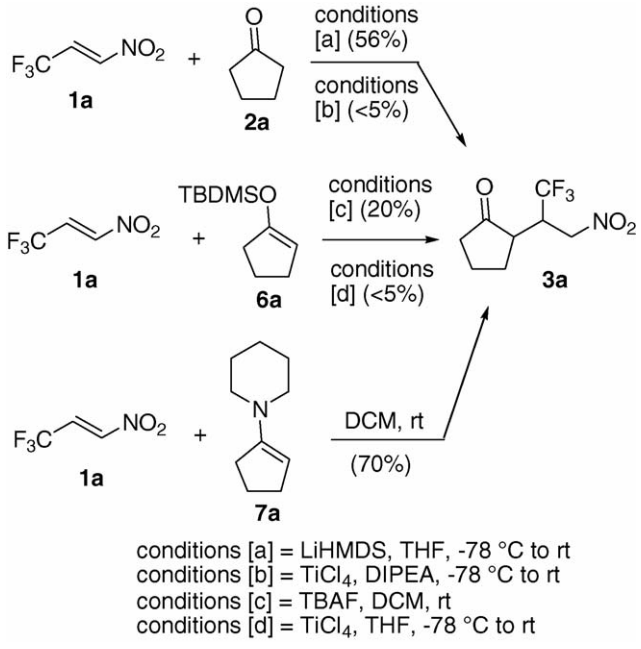
Scheme 1. Preparation of 3-fluoro-1-nitroalkenes.



Scheme 3. Michael reactions of nitroalkenes 1a–d with enamines 7a–c.

The Michael reaction between cyclopentanone and **1a** was chosen as a model, in order to identify the best conditions for the synthesis of the β-trifluoromethyl γ-nitroketone **3a** (Scheme 2).

The reaction of lithiated **2a** with **1a** (conditions [a]) delivered the target product **3a** in fair yields (56%), as a nearly equimolar mixture of the two possible diastereomers. Attempts to react the titanium enolate of **2a** (conditions [b]) afforded negligible amounts of **3a**, whereas extended decomposition was observed instead. The silyl enolether **6a** [11] failed to afford satisfactory yields of the desired product **3a** both using tetrabutylammonium fluoride (TBAF) as a promoter (conditions [c]) and Mukaiyama-like conditions [d] [12]. In fact using conditions [c] slow reaction and formation of complex mixtures upon prolonged reaction times were observed, whereas using conditions [d] extended decomposition was observed by TLC monitoring. Rewardingly, the enamine derivative **7a** [13] reacted with **1a** affording good yields of the target product **3a** (70%). Also in this case no diastereocontrol was observed. We therefore decided to use enamines **7a–c** as reagents of choice in the Michael addition to α-fluoro-γ-nitroalkenes **1a–d**.



Scheme 2. Reaction of **1a** with cyclopentanone and derivatives.

Table 1
Michael addition of enamines **7** to γ-fluoro-α-nitroalkenes **1**[a]

Entry	α-Fluoro-γ-nitroalkene	Enamine	Product	Yield (%)[b]
1	**1a**	**7a**	**3a**	70[c]
2	**1b**	**7a**	**3b**	40[d]
3	**1c**	**7a**	**3c**	57
4	**1d**	**7a**	**3d**	75
5	**1a**	**7b**	**3e**	60
6	**1b**	**7b**	**3f**	63
7	**1c**	**7b**	**3g**	58
8	**1d**	**7b**	**3h**	58
9	**1a**	**7c**	**3i**	78
10	**1b**	**7c**	**3j**	65
11	**1c**	**7c**	**3k**	55
12	**1d**	**7c**	**3l**	68

[a] Products **3a–h** were obtained as nearly equimolar mixtures of diastereomers.
[b] Isolated yields.
[c] About 15% of by-product **8a** (Fig. 2) was formed.
[d] About 30% of by-product **8b** (Fig. 2) was formed.

As portrayed in Scheme 3 and Table 1, the reaction provided moderate to good yields of a wide range of differently fluorinated β-fluoroalkyl γ-nitroketones **3a–l**, demonstrating the viability of the method, which should be of rather general scope.

In the case of entries 1 and 2, relevant amounts of by-products **8a** and **8b** (Fig. 2) arising by double Michael addition of the enamine **7a** to nitroalkenes **1a** and **1b**, respectively, were formed. The structure of **8a** was confirmed by X-ray diffraction.[1] This racemic by-product is rather interesting, as it is formed as a largely predominant diastereomer having three stereogenic centers with the relative configuration portrayed in Fig. 2.

The molecular geometry and the atomic numbering of **8a** are shown in Fig. 3a. The two trifluoropropyl-nitro fragments show a different attachment to the central pentene ring, owing to the presence of the endocyclic double bond. The C5–C1–C11–C13 and C5–C1–C11–C13 torsion angles have values of 169.1(2)° and 130.4(2)°, respectively. The reciprocal position of the NO_2 and CF_3 groups on each side of the molecule is well defined by

[1] CCDC 294989 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposi@ccdc.cam.ac.uk).

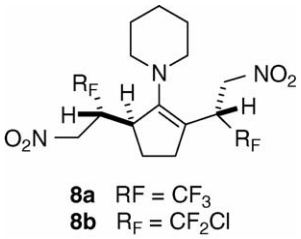
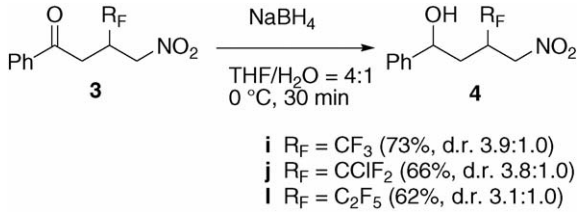
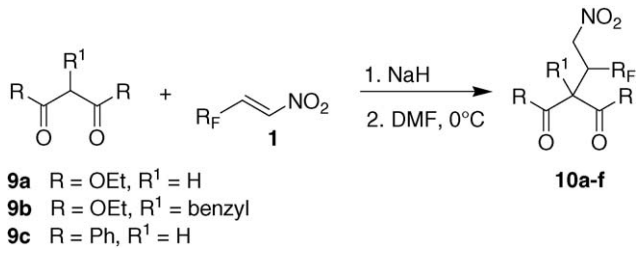


Fig. 2. Byproducts of the Michael reactions of 1a and b with enamine 7a.



Scheme 4. Reduction of γ-nitroketones **3** to carbinols **4**.



Scheme 5. Reaction of nitroalkenes **1** with methylene active compounds **10**.

the torsion angles C16–C14–C15–N2 [−71.5(2)°] and C13-C4-C12-N1 [−161.4(2)°]. The pentene ring assumes an envelop conformation, with the C4 atom 0.214(3) Å out of the mean C1/C2/C3/C5 plane. The piperidine ring shows a regular chair conformation. In the crystal, the supramolecular structure is governed only by short non-bonded C–H···O contacts. The C4 atom of each molecule acts as hydrogen bond donor towards the nitro O1 atom [C4···O1′ = 3.225(3) Å, H(C4)···O1′ = 2.342(3) Å, C4–H···O1′ = 154(1)°] of a symmetry related [$x - 1/2$, $3/2 - y$, z] molecule, building up an infinite zig-zag chain running along the *a* axis (Fig. 3b). This hydrogen bond pattern may be described in terms of graph set C(8) [14].

Attempts to generate the enamines in situ by adding a catalytic (and even stoichiometric) amount of L-proline to a mixture of nitroalkene **1** and ketone **2** gave no trace of the target molecules **3**, instead we observed products arising from irreversible aza-Michael addition of proline to **1**.

We next explored the possibility to reduce the ketones **3** to the corresponding carbinols **4** (Scheme 4). Thus, **3i**, **3j** and **3l** were treated with $NaBH_4$ delivering the target β-fluoroalkyl γ-nitroalcohols **4** in satisfactory yields and fair diastereocontrol.

Next, we explored the Michael addition of nitroalkenes **1** with sodium derivatives of methylene active compounds **9** (Scheme 5).

The reactions took place in DMF at 0 °C affording the target products **10a–f** in moderate to low yields. It should be noticed (Table 2) that the main problem in these reactions is the apparently poor stability of the acceptors **1** in strongly basic environment. Therefore, if the Michael additions do not take place very rapidly, the nitroalkenes decompose, lowering the reaction yields.

Finally, we explored the Friedel–Crafts type reactivity of nitroalkenes **1** with activated electronrich heteroaromatics, such as *N*-methyl-pyrrole and *N*-methyl indole (Scheme 6). The reactions took place without catalysis, providing fair yields of the desired products **11** and **12**.

Attempts to improve the reactions performance by using *N*,*N*′-di[3,5-di(trifluoromethyl)phenyl]urea as catalyst [15] did not show any detectable difference with respect to the uncatalyzed reactions. This is probably due to the poor hydrogen-bond acceptor properties of the nitro group of **1**, that prevents an effective hydrogen bond formation with the urea.

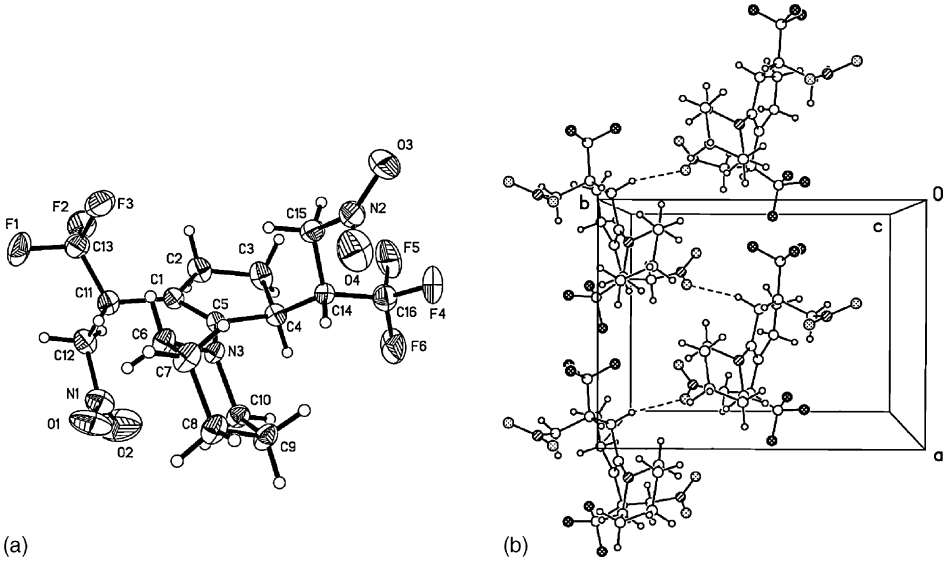
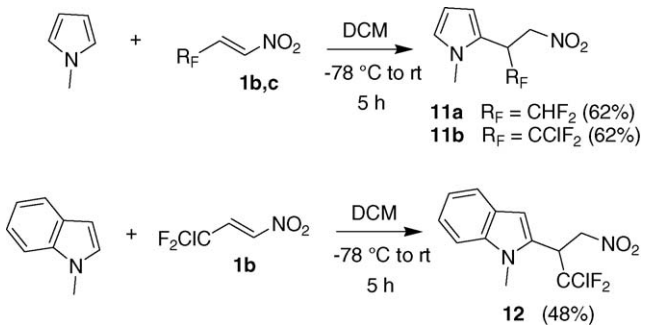


Fig. 3. (a) ORTEP drawing of **8a**, showing 20% probability thermal ellipsoids. (b) Part of the crystal structure of **8a** showing the infinite zig-zag-chain of molecules connected by C–H···O interactions.

Table 2
Michael reactions of nitroalkenes 1a–c with methylene active compounds 9a–c

Entry	α-Fluoro-γ-nitroalkene	Methylene active compound	Product	Yield (%)[a]
1	**1a**	**9a**	**10a**	43
2	**1b**	**9a**	**10b**	63
3	**1a**	**9b**	**10c**	22
4	**1c**	**9b**	**10d**	53
5	**1a**	**9c**	**10e**	25
6	**1c**	**9c**	**10f**	20

[a] Isolated yields.



Scheme 6. Friedel–Crafts type reactions.

Very slow reactions were observed in the reactions of **1b** with electronrich aromatics, such as 1-(*N*,*N*-diethylamino)-naphthalene and 4-(2-propenyl)anisole.

3. Conclusion

In summary, the reactivity of fluorinated nitroalkenes **1a–d**, three of them prepared for the first time (**1b–d**), has been investigated, in particular the Michael addition of ketone-derived enamines **7a–c** and methylene active compounds **9**, as well as the Friedel–Crafts reaction with *N*-methyl pyrrole and -indole. The reduction of β-fluoroalkyl γ-nitroketones **3i**, **3j**, and **3l** to β-fluoroalkyl γ-nitroalcohols **4i**, **4j**, and **4l** was also explored. The reactions above afforded a wide range of differently fluorinated building blocks, that might represent useful starting materials for biologically interesting molecules.

4. Experimental section

4.1. General details

Commercially available reagent-grade solvents were employed without purification. All reactions where an organic solvent was employed were performed under nitrogen atmosphere, after flame-drying of the glass apparatus. Melting points (m.p.) are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck. Flash chromatographies (FC) were performed with silica gel 60 (60–200 μm, Merck). ^{1}H, ^{13}C, and ^{19}F NMR spectra were run at 250, 400 or 500 MHz. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and $\delta_C = 0.00$), while C_6F_6 was used as external standard ($\delta_F - 162.90$) for ^{19}F.

4.2. General procedure for the preparation of γ-fluoro-α-nitroalkenes *1*. Synthesis of *1b*

Chlorodifluoroacetaldehyde hydrate tech. (5.04 g, 38.0 mmol), nitromethane (2.11 g, 34.6 mmol) and sodium carbonate (241 mg, 2.28 mmol) were mixed at room temperature under vigorous stirring. The mixture was heated at 60 °C (in a few min a dark red coloration appeared) for 3 h and then stirred at room temperature overnight. The mixture was extracted with diethyl ether, the organic layer was dried on anhydrous Na_2SO_4 and then filtered. The organic solvent was carefully removed in vacuo at low temperature. The resulting dark red oil was treated with P_2O_5 (5.2 g, 36.8 mmol) added in one portion and the mixture submitted to fractional distillation at atmospheric pressure. Nitroalkene **1b** was obtained as a green-yellow liquid distilled at 103–105 °C (2.11 g, 39%).

Nitroalkenes **1c** and **1d** were obtained by bulb to bulb distillation using a Kugelrohr apparatus (temperature 80–90 °C).

1a: analytical and spectroscopic data matched those described in Ref. [5].

1b: ^{1}H NMR ($CDCl_3$): $\delta = 7.37$ (m, 1H), 7.25 (m, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -54.69$ (d, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 142.9$, 131.4, 122.1 (t, $J = 291.0$ Hz). Anal. Calcd for $C_3H_2ClF_2NO_2$: C, 22.88; H, 1.28. Found: C, 23.02; H, 1.34.

1c: ^{1}H NMR ($CDCl_3$): $\delta = 7.28$ (m, 1H), 7.10 (m, 1H), 6.40 (td, $J = 53.7$, 3.5 Hz); ^{19}F NMR ($CDCl_3$): $\delta = -118.6$ (dd, $J = 54.7$, 8.2 Hz, 2F); ^{13}C NMR ($CDCl_3$): $\delta = 143.8$, 130.3 (t, $J = 23.8$ Hz), 110.3 (t, $J = 239.4$ Hz).

1d: ^{1}H NMR ($CDCl_3$): $\delta = 7.50$ (m, 1H), 7.15; ^{19}F NMR ($CDCl_3$): $\delta = -85.7$ (s, 3F), -117.8 (m, 2F); ^{13}C NMR ($CDCl_3$): $\delta = 146.4$, 124.9 (t, $J = 31.4$ Hz), the CF_2CF_3 signal was obscured due to its low intensity.

4.3. General procedure for the Michael addition of enamines *7* to γ-fluoro-α-nitroalkenes *1*. Synthesis of *3i*

To a stirred solution of **7c** (110 mg, 0.63 mmol), in dry dichloromethane, under nitrogen, at RT, was added a solution of **1a** (89 mg, 0.63 mmol), in dichloromethane. A dark red-orange color slowly appeared. After 2 h the organic solvent was removed in vacuo, and the crude was purified by flash chromatography (*n*-Hex/EtOAc 8:2), affording 124 mg of **3i** (78%).

3a: $R_f = 0.32$, *n*-Hex/EtOAc 8:2; mixture 1:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): $\delta = 4.95$ (dd, $J = 14.2$, 5.8 Hz, 1H), 4.68 (dd, $J = 14.2$, 6.8 Hz, 1H), 4.60 (dd, $J = 13.7$, 7.2 Hz, 1H), 4.29 (dd, $J = 13.7$, 5.6 Hz, 1H), 3.87 (m, 1H), 3.55 (m, 1H), 2.60 (m, 1H), 2.48–2.02 (overlap, 9H), 1.93–1.74 (m, 3H), 1.68 (m, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -68.3$ (d, $J = 7.4$ Hz), -70.1 (d, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$) (selected signals): $\delta = 194.6$, 125.9 (q, $J = 280.3$ Hz), 72.2, 37.7 (q, $J = 28.9$ Hz), 34.1. Anal. Calcd for $C_8H_{10}F_3NO_3$: C, 42.67; H, 4.48. Found: C, 42.77; H, 4.40.

8a: $R_f = 0.45$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): $\delta = 4.61$ (m, 1H), 4.19 (d, $J = 13.2$ Hz, 1H), 3.54 (m, 1H), 3.38 (m, 1H), 3.11 (m, 2H), 2.82 (m, 2H), 2.44 (m, 1H), 2.27 (m, 1H), 2.02

(m, 1H), 1.62 (m, 7H); ^{19}F NMR ($CDCl_3$): $\delta = -67.5$ (d, $J = 6.4$ Hz, 3F), −70.4 (d, $J = 8.7$ Hz, 3F); ^{13}C NMR ($CDCl_3$): $\delta = 151.7$, 127.0, 124.7, 109.3, 72.7, 69.7, 50.7, 42.9 (q, $J = 26.8$ Hz), 42.0 (q, $J = 27.8$ Hz), 41.4, 28.7, 26.1, 23.9, 21.6. Anal. Calcd for $C_{16}H_{21}F_6N_3O_4$: C, 44.35; H, 4.88. Found: C, 44.21; H, 4.59.

*4.3.1. X-ray structural determination of **8a***

The compound crystallises in the orthorhombic system, *Pna*2(1) space group, with cell parameters: $a = 9.395(1)$ Å, $b = 12.339(1)$ Å, $c = 17.010$ (1) Å, V = 1972(1) Å^3, $Z = 4$, $D_c = 1.460$ g cm^{-3}, $F(0\,0\,0) = 896$. The crystal suitable for X-ray analysis, with approximate dimensions of 0.3 mm × 0.4 mm × 0.5 mm, was obtained upon slow crystallisation from iPr_2O. Intensities data were collected, at room temperature, on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54179 Å), using $\theta/2\theta$ scan technique, voltage 40 kV, current 40 mA. Unit cell parameters were determined using 81 reflections in the range $10.48^\circ \leq 2\theta \leq 63.3^\circ$. A total of 2161 reflections (1714 unique, $R_{int} = 0.036$) were collected up to 130° in 2θ and index range: $-11 \leq h \geq 1$, $-14 \leq k \geq 1$, $-1 \leq l \geq 19$. Three standard reflections, monitored every 100 reflections, showed no intensity decay. No empirical adsorption correction was deemed necessary. The structure was solved by direct method using SIR97 program [16] which revealed the position of all non H-atoms. The refinement was carried out on F^2 by full-matrix least-squares procedure with SHELXL97 [17] for 263 parameters, with anisotropic temperature factors for non-H atoms. H atoms, were placed in geometrically calculated positions and refined in a riding model. The final stage converged to $R = 0.0506$ ($R_w = 0.112$) for 1260 observed reflections (with $I \geq 2\sigma(I)$), and $R = 0.0885$ ($R_w = 0.135$) for all unique reflections. The goodness of fit, *S*, was 1.095. The final difference map showed a maximum and minimum residual peaks of 0.120 and −0.130 e Å^{-3}, respectively.

3b: $R_f = 0.41$, *n*-Hex/EtOAc 8:2; mixture 1.5:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): $\delta = 5.10$ (dd, $J = 13.6$, 6.3 Hz, 1H), 4.75–4.62 (overlap, 3H), 4.29 (dd, $J = 13.6$, 5.4 Hz, 1H), 4.02 (m, 2H), 3.64 (m, 1H), 2.72 (m, 2H), 2.53–2.30 (overlap, 6H), 2.25–2.04 (overlap, 6H), 1.98–1.55 (overlap, 7H); ^{19}F NMR ($CDCl_3$): $\delta = -52.45$ (dd, $J = 10.2$, 168 Hz, 1F) and −53.50 (dd, $J = 10.2$, 168 Hz, 1F) (minor diastereomer), −54.95 (dd, $J = 10.3$, 168 Hz, 1F) and −56.80 (dd, $J = 10.3$, 168 Hz, 1F) (major diastereomer); ^{13}C NMR ($CDCl_3$): $\delta = 215.8$, 214.8, 129.42 (t), 72.2, 71.3, 48.5, 46.6 (t, $J = 28.6$ Hz), 37.6, 36.6, 28.2, 25.1, 20.47, 20.41; MS (70 eV): *e*/*z* (%): 242 [$M^+ + 1$] (20), 195 (40), 109 (70), 77 (100), 55 (90).

8b: $R_f = 0.45$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): $\delta = 4.61$ (m, 1H), 4.19 (d, $J = 13.2$ Hz, 1H), 3.54 (m, 1H), 3.38 (m, 1H), 3.11 (m, 2H), 2.82 (m, 2H), 2.44 (m, 1H), 2.27 (m, 1H), 2.02 (m, 1H), 1.62 (m, 7H); ^{19}F NMR ($CDCl_3$): $\delta = -52.7$ (dd, $J = 166.7$, 10.2 Hz, 1F), −54.0 (dd, $J = 166.7$, 10.2 Hz, 1F), −54.1 (m, 1F), −57.3 (m, 1F); MS (70 eV): *e*/*z* (%): 465 [$M^+ + 1$] (40), 323 (100), 276 (65), 176 (70), 84 (80), 77 (55).

3c: $R_f = 0.31$, *n*-Hex/EtOAc 8:2; mixture 5:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): $\delta = 6.23$ (m, 1H), 6.00 (m, 1H), 4.76 (m, 2H), 4.63 (dd, $J = 14.6$, 7.6 Hz, 1H), 3.40–3.03 (overlap, 2H), 2.49 (m, 2H), 1.82–1.65 (overlap, 4H); ^{19}F NMR ($CDCl_3$): $\delta = -122.0$ (ddd, $J = 287.5$, 55.9, 10.6 Hz, 1F), −124.4 (ddd, $J = 287.5$, 55.9, 15.9 Hz, 1F), −122.6 (ddd, $J = 287.5$, 55.9, 11.9 Hz, 1F), −126.3 (ddd, $J = 287.5$, 55.9, 17.3 Hz, 1F); ^{13}C NMR ($CDCl_3$) mixture: $\delta = 217.0$, 216.9, 115.5 (t, $J = 250.1$ Hz), 115.3 (t, $J = 243.9$ Hz), 71.4, 72.2, 46.9, 46.2, 41.2, 41.0 (t, $J = 20.7$ Hz), 40.3 (t, $J = 20.7$ Hz), 37.6, 37.3, 27.1, 26.4, 20.6.

3d: ^{1}H NMR ($CDCl_3$): $\delta = 4.64$ (dd, $J = 14.1$, 6.8 Hz, 1H), 4.21 (dd, $J = 14.1$, 4.5 Hz, 1H), 4.01 (m, 1H), 2.61 (m, 1H), 2.38 (m, 2H), 1.86 (m, 2H), 1.65 (m, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -83.5$ (s, 3F) −116.2 (dd, $J = 292.0$, 15.1 Hz, 1F), −119.1 (dd, $J = 292.0$, 12.9 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 70.1$, 47.3, 37.9 (t, $J = 21.9$ Hz), 36.6 25.4, 20.3. Anal. Calcd for $C_9H_{10}F_5NO_3$: C, 39.28; H, 3.66. Found: C, 39.48; H, 3.76.

3e: $R_f = 0.34$, *n*-Hex/EtOAc 8:2; mixture 5:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): major $\delta = 4.83$ (dd, $J = 14.6$, 6.9 Hz, 1H), 4.45 (m, 1H), 4.0 (m, 1H), 3.0 (m, 1H), 2.55–1.94 (m, 5H), 1.78, 1.61 (m, 3H); minor $\delta = 4.52$ (dd, $J = 14.6$, 8.4 Hz, 1H), 4.45 (m, 1H), 3.60 (m, 1H), 2.80 (m, 1H), 2.55–1.94 (m, 5H), 1.78–1.67 (m, 3H); ^{19}F NMR ($CDCl_3$): $\delta = -67.4$ (d, $J = 7.6$ Hz, 3F), −69.5 (d, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$): major $\delta = 207.9$, 126.5 (q, $J = 276.5$ Hz), 70.7, 47.7, 41.7, 39.7 (q, $J = 27.6$ Hz), 28.9, 27.0, 24.9; minor $\delta = 208.4$, 125.9 (q, $J = 276.5$ Hz), 71.9, 48.4, 42.2, 31.5, 27.6, 25.2; MS (70 eV): *e*/*z* (%): 240 [$M^+ + 1$] (40), 193 (100), 165 (55), 55 (90), 41 (60).

3f: $R_f = 0.39$, *n*-Hex/EtOAc 8:2; mixture 1:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): major $\delta = 4.88$ (dd, $J = 14.2$, 5.4 Hz, 1H), 4.45 (m, 1H), 3.69 (m, 1H), 2.87 (m, 1H), 2.58–1.67 (m, 8H); minor $\delta = 4.58$ (dd, $J = 14.8$, 7.4 Hz, 1H), 4.45 (m, 1H), 4.25 (m, 1H), 3.02 (m, 1H), 2.58–1.67 (m, 8H); ^{19}F NMR ($CDCl_3$): major $\delta = -51.8$ (dd, $J = 165.4$, 9.7 Hz, 1F), −52.3 (dd, $J = 165.4$, 9.7 Hz, 1F); minor $\delta = -53.8$ (dd, $J = 166.4$, 11.7 Hz, 1F), −55.1 (dd, $J = 166.4$, 11.7 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 129.4$ (t, $J = 296.2$ Hz), 72.9, 71.3, 49.9, 49.0, 48.3 (t, $J = 23.2$ Hz), 45.5 (t, $J = 23.8$ Hz), 41.8, 32.2, 29.7, 28.8, 27.6, 27.0, 25.0; MS (70 eV): *e*/*z* (%): 256 [$M^+ + 1$] (10), 181 (30), 77 (40), 55 (100), 41 (60).

3g: $R_f = 0.32$, *n*-Hex/EtOAc; mixture 1:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): major $\delta = 6.10$ (td, $J = 56.3$, 3.81 Hz, 1H), 4.78 (dd, $J = 14.4$, 5.5 Hz, 1H), 4.45 (dd, $J = 14.4$, 3.8 Hz, 1H), 3.13 (m, 1H), 2.76 (m, 1H), 2.47 (m, 1H), 2.36 (m, 1H), 2.22 (m, 1H), 2.15 (m, 1H), 2.00 (m, 1H), 1.67 (overlap 2H); minor $\delta = 4.60$ (dd, $J = 14.4$, 7.2 Hz, 1H), 4.50 (dd, $J = 14.4$, 5.1 Hz, 1H), 3.33 (m, 1H), 2.80 (m, 1H), 2.52 (m, 1H), 2.36 (m, 1H), 2.22 (m, 1H), 2.15 (m, 1H), 1.97 (m, 1H), 1.67 (m, 2H); ^{19}F NMR ($CDCl_3$): major $\delta = -120.3$ (ddd, $J = 288.2$, 56.8, 18.8 Hz, 1F), −122.6 (ddd, $J = 288.2$, 56.8, 8.5 Hz, 1F); minor $\delta = -120.8$ ^{13}C NMR ($CDCl_3$): major $\delta = 115.7$ (t, $J = 247.3$ Hz), 71.5, 48.4, 42.1, 40.4 (t, $J = 20.3$ Hz), 30.7, 29.6, 27.4; minor $\delta = 115.7$ (t, $J = 247.3$ Hz), 71.51, 48.39, 41.8, 30.77, 27.4; MS (70 eV): *e*/*z* (%): 222 [$M^+ + 1$] (20), 175 (70), 55 (100), 41 (50).

3h: $R_f = 0.37$, *n*-Hex/EtOAc 8:2; mixture 2:1 of two diastereomers. ^{1}H NMR ($CDCl_3$): major $\delta = 5.04$ (dd, $J = 14.6$, 5.0 Hz, 1H), 4.67 (m, 1H), 3.60 (m, 1H), 2.86 (m, 1H), 2.60–1.40 (m, 8H); minor $\delta = 4.59$ (dd, $J = 14.0$, 6.7 Hz, 1H), 4.44 (dd, $J = 14.0$, 7.9 Hz, 1H), 4.14 (m, 1H), 2.94 (m, 1H), 2.60–1.40 (m, 8H); ^{19}F NMR ($CDCl_3$): major $\delta = -84.7$ (s, 3F), -115.9 (dd, $J = 277.0$, 15.7 Hz, 1F), -117.3 (dd, $J = 277.0$, 15.7 Hz, 1F); minor $\delta = -84.2$ (s, 3F), -115.4 (dd, $J = 277.0$, 15.7 Hz, 1F), -119.9 (dd, $J = 277.0$, 15.7 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 208.1$, 117.6, 74.5, 71.1, 70.3, 58.4, 48.9, 47.8, 41.9, 41.7, 37.1, 36.9 (t, $J = 20.1$ Hz), 31.5, 29.1, 26.9, 25.2, 24.8.

3i: $R_f = 0.35$, *n*-Hex/EtOAc 8:2. FT-IR (film): $\nu_{max} = 3063$, 2971, 1690, 1566, 1425, 1380, 1176, 1125, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.95$ (d, $J = 7.6$ Hz, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 4.70 (dd, $J = 13.8$, 6.8 Hz, 1H), 4.62 (dd, $J = 13.8$, 4.1 Hz, 1H), 3.93 (m, 1H), 3.46 (dd, $J = 17.7$, 3.4 Hz, 1H), 3.33 (dd, $J = 17.7$, 9.1 Hz, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -71.9$ (d, $J = 7.4$ Hz, 3F); ^{13}C NMR ($CDCl_3$): $\delta = 194.7$, 135.6, 134.1, 128.9, 128.1, 126.1 (q, $J = 276.8$ Hz), 72.4, 37.9 (q, $J = 28.6$ Hz), 34.2; MS (ESI): 283.8 [M^+ + Na]. Anal. Calcd for $C_{11}H_{10}F_3NO_3$: C, 50.58; H, 3.86. Found: C, 50.44; H, 3.59.

3j: $R_f = 0.37$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): $\delta = 7.96$ (d, $J = 7.2$ Hz, 2H), 7.62 (m, 1H), 7.50 (m, 2H), 4.75 (dd, $J = 13.9$, 6.4 Hz, 1H), 4.62 (dd, $J = 13.9$, 4.6 Hz, 1H), 4.08 (m, 1H), 3.54 (dd, $J = 18.2$, 3.4 Hz, 1H), 3.34 (dd, $J = 18.2$, 8.9 Hz, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -56.1$ (dd, $J = 166.7$, 8.9 Hz, 1F), -56.9 (dd, $J = 166.7$, 8.9 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 194.7$, 135.7, 134.1, 129.6 (t, $J = 296.7$ Hz), 128.9, 128.1, 73.4, 44.0 (t, $J = 24.7$ Hz), 35.8.

3k: $R_f = 0.37$, *n*-Hex/EtOAc 8:2. FT-IR (film): $\nu_{max} = 3022$, 2924, 1687, 1560, 1379, 1217, 1138, 1060, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.94$ (d, $J = 7.6$ Hz, 2H), 7.61 (m, 1H), 7.48 (m, 2H), 6.16 (td, $J = 55.6$, 2.85 Hz, 1H), 4.71 (dd, $J = 13.3$, 5.2 Hz, 1H), 4.61 (dd, $J = 13.3$, 5.2 Hz, 1H), 3.44 (m,1H); ^{19}F NMR ($CDCl_3$): $\delta = -124.4$ (ddd, $J = 284.2$, 55.0, 13.5 Hz, 1F), -126.5 (ddd, $J = 284.2$, 55.0, 13.5 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 196.0$, 135.9, 133.9, 128.8, 128.0, 115.5 (t, $J = 243.7$ Hz), 72.6, 37.4 (t, $J = 21.3$ Hz), 33.9; ESI: 265.8 [M + Na].

3l: $R_f = 0.37$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): $\delta = 7.94$ (d, $J = 7.4$ Hz, 2H), 7.61 (m, 1H), 7.24 (m, 2H), 4.77 (dd, $J = 13.8$, 6.0 Hz, 1H), 4.58 (dd, $J = 13.8$, 5.1 Hz, 1H), 4.08 (m, 1H), 3.50 (dd, $J = 18.5$, 4.5 Hz, 1H), 3.35 (dd, $J = 18.5$, 8.1 Hz, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -83.4$ (s, 3F), -118.3 (dd, $J = 275.3$, 10.1 Hz, 1F), -120.2 (dd, $J = 275.3$, 14.8, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 194.6$, 135.6, 128.9, 128.0, 118.8 (qt, $J = 287.21$, 35.20 Hz, 2F), 115.0 (tq, $J = 255.7$, 37.1 Hz, 3F), 72.1, 35.3 (t, $J = 20.1$ Hz), 34.2; ESI: 333.8 [M + Na] (100%). Anal. Calcd for $C_{12}H_{10}F_5NO_3$: C, 46.31; H, 3.24. Found: C, 46.33; H, 3.42.

*4.4. General procedure for the reduction of oxo-compounds **3** to alcohols **4***

To a solution of **3i** in THF/H_2O (4:1), under N_2, at 0 °C, $NaBH_4$ was added. The resulting mixture was stirred at that temperature for 30 min, then HCl 1N was added. The mixture was extracted twice with EtOAc; the organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo.

The crude was purified by flash chromatography (*n*-Hex 100% to *n*-Hex/EtOAc 9:1), affording 428 mg of **4i** (mixture of two diastereomers) (73%).

4i: $R_f = 0.37$, *n*-Hex/EtOAc 8:2; mixture of two diastereomers 3.9:1.0 in ratio. ^{1}H NMR ($CDCl_3$): major distereomer $\delta = 7.35$ (m, 5H), 4.85 (m, 1H), 4.65 (m, 2H), 3.39 (m, 1H), 2.41 (br, s, 1H), 2.17 (m, 1H), 1.91 (m, 1H), minor diastereomer; ^{19}F NMR ($CDCl_3$): minor diastereomer $\delta = -54.6$ (d, $J = 8.5$ Hz, 3F), major diastereomer -55.0 (d, $J = 8.9$ Hz, 3F); ^{13}C NMR ($CDCl_3$): major diastereomer $\delta = 142.7$, 128.8, 128.60, 128.3, 126.5 (q, $J = 281.0$ Hz), 125.5, 72.8, 70.7, 39.1 (q, $J = 26.9$ Hz), 34.6; minor distereomer 143.4, 128.8, 128.3, 125.47, 73.5, 72.8, 40.4 (q, $J = 27.6$ Hz), 35.15; MS ESI: 285.8 [M + Na] (100%). Anal. Calcd for $C_{11}H_{12}F_3NO_3$: C, 50.19; H, 4.60. Found: C, 50.03; H, 4.65.

4j: $R_f = 0.37$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): major $\delta = 7.38$ (m, 5H), 4.91 (m, 1H), 4.71 (m, 2H), 3.57 (m, 1H), 2.27 (m, 1H), 1.95 (m, 1H), 1.54 (br s, 1H); minor 7.38 (m, 5H), 4.76 (m, 2H), 3.66 (m, 1H), 2.16 (m, 1H), 2.00 (br, s, 1H), 1.89 (m, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -56.2$ (m, 2F); ^{13}C NMR ($CDCl_3$): major diastereomer $\delta = 142.7$, 130.0 (t, $J = 293.0$ Hz), 128.9, 128.4, 125.5, 73.9, 71.0, 45.0 (t, $J = 23.3$ Hz), 36.3; minor diastereomer $\delta = 143.4$, 130.1 (t, $J = 292.7$ Hz), 128.9, 128.4, 125.5, 74.6, 73.2, 46.6 (t, $J = 23.3$ Hz), 36.8; MS ESI: 301.8 [M + Na] (100%). Anal. Calcd for $C_{11}H_{12}ClF_2NO_3$: C, 47.24; H, 4.32. Found: C, 46.99; H, 4.22.

4l: $R_f = 0.37$, *n*-Hex/EtOAc 8:2. ^{1}H NMR ($CDCl_3$): $\delta = 7.36$ (m, 5H), 4.90 (m, 1H), 4.76 (m, 2H), 3.60 (m, 1H), 2.22 (m, 1H), 2.02 (br, s, 1H), 1.94 (m, 1H); ^{19}F NMR ($CDCl_3$): major diastereomer $\delta = -83.0$ (s, 3F), -116.6 (dd, $J = 275.7$, 9.1 Hz, 1F), -121.5 (dd, $J = 275.7$, 18.3 Hz); minor diastereomer $\delta = -82.8$, -117.9 (dd, 1F), -121.2 (dd, $J = 275.7$, 9.1 Hz, 1F), -121.5 (dd, $J = 275.7$, 18.3 Hz, 1F); ^{13}C NMR ($CDCl_3$): $\delta = 142.7$, 128.97, 128.94, 128.92, 128.5, 128.45, 125.4, 70.9, 37.8 (t, $J = 21.4$ Hz), the CF_2CF_3 signal was obscured due to its low intensity; MS ESI: 335.8 [M + Na] (100%).

*4.5. General procedure for the reaction of **1** with malonates **9** to afford **10***

To a solution of 2-benzyl-malonic acid diethyl ester **9b** in DMF, at 0 °C, under nitrogen, NaH was added. The solution was stirred at that temperature for 40 min, then, 3,3-difluoro-1-nitro-propene **1c** was added. The mixture was warmed to room temperature and stirred for 2 h. Water was added (a white slurry formed), and the suspension was extracted with EtOAc. The collected organic layers were dried with sodium sulphate and filtered. Finally the solvent was removed in vacuo and the crude purified by FC (*n*-Hex/EtOAc 0–10%), affording 80 mg (53%) of **10d**.

10a: analytical and spectroscopic data matched those described in Ref. [7].

10b: ^{1}H NMR ($CDCl_3$): $\delta = 5.03$ (dd, $J = 13.5$, 4.3 Hz, 1H,), 4,81 (dd, $J = 13.5$, 7.5 Hz, 1H), 4.23 (m, 5H), 3.91 (d, $J = 4.00$ Hz, 1H), 1.32 (m, 6H).

10c: R_f = 0.37, *n*-Hex/EtOAc 8:2. FT-IR (film): ν_{max} = 3021, 1736, 1568, 1379, 1216, 1136, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.41–7.33 (m, 5H), 5.18 (d, J = 12.2 Hz, 1H), 5.15 (d, J = 12.2 Hz, 1H), 4.64 (dd, J = 13.5, 4.3 Hz, 1H), 4.52 (dd, J = 13.5, 7.5 Hz, 1H), 3.91 (m, 1H), 3.32 (d, J = 5.3 Hz, 1H), 2.04 (m, 1H), 1.94 (br, s, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.87(d, J = 6.5 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ = −75.8 (d, J = 7.7 Hz); MS (ESI): 414.2 [M + Na] (100%).

10d: R_f = 0.37, *n*-Hex/EtOAc 8:2. FT-IR (film): ν_{max} = 2986, 1732, 1565, 1370, 1263, 1215, 1069, 910, 736 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.30 (m, 3H), 7.14 (m, 2H), 6.24 (t, J = 54.8 Hz, 1H), 4.69 (d, J = 16.1 Hz, 1H), 4.60 (dd, J = 16.1, 7.15 Hz, 1H), 4.25 (m, 2H), 4.12 (m, 2H), 3.75 (m, 1H), 3.49 (d, J = 14.9 Hz, 1H), 3.34 (d, J = 14.9 Hz, 1H), 1.27 (t, J = 7.15 Hz, 3H), 1.16 (t, J = 7.15 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ = −120.0 (ddd, J = 291.9, 54.2, 9.3 Hz, 1F), −124.2 (ddd, J = 291.2, 54.2, 22.5 Hz, 1F); ^{13}C NMR ($CDCl_3$): δ = 168.7, 134.3, 129.8, 128.7, 127.8, 114.9 (t, J = 247.7 Hz), 70.8, 62.4, 43.8 (t, J = 25.6 Hz), 38.9, 13.8, 13.6; MS (ESI): 396.2 [M + Na] (100%). Anal. Calcd for $C_{17}H_{21}F_2NO_6$: C, 54.69; H, 5.67. Found: C, 54.89; H, 5.54.

10e: R_f = 0.37, *n*-Hex/EtOAc 8:2. FT-IR (film): ν_{max} = 3022, 1701, 1566, 1379, 1255, 1217, 1130, 909, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.92 (m, 4H), 7.60 (m, 2H), 7.46 (m, 4H), 6.10 (d, J = 4.4 Hz), 5.20 (m, 1H), 4.91(dd, J = 16.3, 7.4 Hz, 1H), 4.21(m, 1H); ^{19}F NMR ($CDCl_3$): δ = −69.5 (J = 7.8 Hz, 3F); ^{13}C NMR ($CDCl_3$): δ = 192.5, 192.1, 135.5, 134.6, 134.5, 134.4, 129.3, 129.1, 128.7, 124.5 (q, J = 281.7 Hz), 70.7, 51.0, 42.6 (q, J = 29.2 Hz); MS ESI: 366.4 [M + 1] (20%), 388.2 [M + Na] (100%).

10f: R_f = 0.37, *n*-Hex/EtOAc 8:2. FT-IR (film): ν_{max} = 3023, 1695, 1561, 1380, 1266, 1071, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.98 (d, J = 7.7 Hz, 2H), 7.89 (d, J = 7.7 Hz, 2H), 7.65 (m, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 6.16 (td, J = 56.0, 4.24 Hz), 5.87 (d, J = 4.24 Hz, 1H), 4.88 (m, 2H), 3.74 (m, 1H); ^{19}F NMR ($CDCl_3$): δ = −120.5 (ddd, J = 288.5, 56.5,14.5 Hz, 1F), −122.4 (ddd, J = 288.5, 56.5, 10.1 Hz, 1F); ^{13}C NMR ($CDCl_3$): δ = 193.72, 193.7, 135.4, 134.9, 134.6, 134.2, 129.3, 129.1, 128.7, 128.6, 115.5 (t, J = 249.1 Hz), 71.3, 52.0, 42.2 (t, J = 23.8 Hz).

*4.6. General procedure for the Friedel–Crafts reaction of **1** with N-methyl heterocycles to afford **11–12***

To a solution of *N*-methyl pyrrole, in dry dichloromethane, at −78 °C, under nitrogen, 3-chloro-3,3-difluoro-1-nitro-propene, dissolved in dichloromethane, was added. The resulting solution was warmed to room temperature and stirred for 5 h, then the solvent was removed in vacuo and the crude purified by flash chromatography (*n*-Hex 100% to *n*-Hex/EtOAc 8:2), affording 139 mg (62%) of **11b**.

11a: R_f = 0.43 (*n*-Hex/EtOAc 8:2). ^1H NMR ($CDCl_3$): δ = 6.64 (m, 1H), 6.13 (m, 2H), 5.92 (td, J = 56.2, 3.38 Hz, 1H), 4.85 (dd, J = 13.5, 5.8 Hz, 1H), 4.67 (dd, J = 13.5, 8.3 Hz, 1H), 4.16 (m, 1H), 3.65 (s, 3H); ^{19}F NMR ($CDCl_3$): δ = −119.8 (ddd, J = 282.7, 55.1, 9.4 Hz, 1F), −123.2 (ddd, J = 282.7, 55.1, 14.5 Hz, 1F); ^{13}C NMR ($CDCl_3$): δ = 123.9, 115.2 (t, J = 248.2 Hz), 108.3, 107.7, 76.6, 39.5 (t, J = 22.1 Hz), 33.8. Anal. Calcd for $C_8H_{10}F_2N_2O_2$: C, 47.06; H, 4.94. Found: C, 46.97; H, 5,04.

11b: R_f = 0.46 (*n*-Hex/EtOAc 8:2). ^1H NMR ($CDCl_3$): δ = 6.66 (m, 1H), 6.27 (m, 1H), 6.15, (m, 1H), 5.00 (dd, J = 13.2, 4.5 Hz, 1H), 4.67 (dd, J = 13.2, 7.9 Hz, 1H), 4.58 (m, 1H), 3.67 (s, 3H); ^{19}F NMR ($CDCl_3$): δ = −55.8 (dd, J = 163.7, 8.9 Hz, 1F), −56.8 (dd, J = 163.7, 11.2 Hz, 1F); ^{13}C NMR ($CDCl_3$): δ = 128.1 (t, J = 296.7 Hz), 124.4, 121.9, 109.1, 107.8, 74.5, 45.7 (t, J = 25.6 Hz,), 33.8 (t, J = 22.1 Hz), 33.8.

12: R_f = 0.40 (*n*-Hex/EtOAc 9:1). ^1H NMR ($CDCl_3$): δ = 6.67 (d, J = 7.58 Hz, 1H), 7.34 (m, 2H), 7.24 (m, 1H), 7.14 (s, 1H), 5.00 (m, 1H), 4.88 (m, 2H), 3.78 (s, 3H); ^{19}F NMR ($CDCl_3$): δ = −60.4 (dd, J = 167.3, 7.6 Hz, 1F), −61.6 (dd, J = 167.3, 7.6 Hz, 1F); ^{13}C NMR ($CDCl_3$): δ = 136.9, 132.1, 128.3, 122.6, 120.3, 118.7, 109.8, 74.9, 46.7 (t, J = 25.1 Hz), 32.9. Anal. Calcd for $C_{12}H_{11}ClF_2N_2O_2$: C, 49.93; H, 3.84. Found: C, 49.90; H, 3.88.

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