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Electrophilic Amination of Fluoroalkyl Groups on Azodicarboxylate Derivatives

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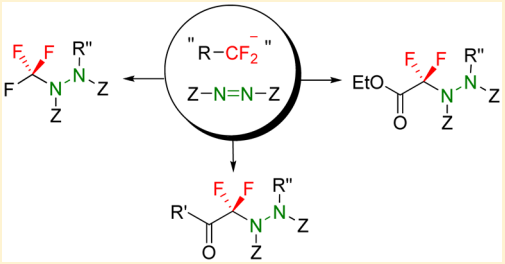
Supporting Information

ABSTRACT: The formation of an NCF_3 bond or an NCF_2R bond still remains scarce. An efficient direct electrophilic amination of fluoroalkyl groups was developed. Difluoroenoxysilanes reacted easily on azodicarboxylate derivatives. These results led to a novel family of NCF_3 and NCF_2 hydrazine derivatives.

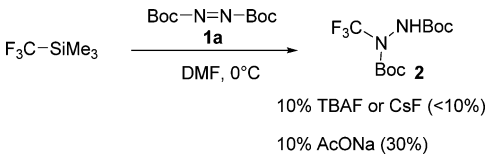


Fluorinated molecules are increasingly present in pharmaceuticals, materials, and polymers.[1] Therefore, it is still necessary to develop new methods for the incorporation of fluorinated groups. In recent years, compounds having the fluorinated groups on a heteroatom such as RCF_2S and RCF_2O moieties have attracted special interest.[2] This approach is challenging and much less developed. Because of their high hydrophobic parameters,[3] these groups are potentially important targets and are now present in the pharmaceutical and agrochemical fields.[1,2] However, the synthesis of fluorinated groups on nitrogen such as NCF_3 and NCF_2H is understudied, even less NCF_2R, and remains a challenge. Furthermore, these compounds should be markedly different from nonfluorinated analogues in order to exploit them wisely in different fields of research.

The general method to incorporate the CF_3 group on nitrogen[4] in comparison to other ways of fluorination[5] is the oxidative desulfurization−fluorination of dithiocarbamates using fluoride sources. More recently, some groups described the direct electrophilic incorporation of the CF_3.[6] On the other hand, the main approaches to introduce the CF_2H group were performed using different reagents, such as chlorodifluoromethane,[7] chlorodifluoroacetic acid derivatives,[8] chlorodifluoromethyl phenyl sulfone,[9] $TMSCF_2Br$,[10] and $TMSCF_3$.[11] We report here an efficient route to NCF_3 and NCF_2R groups where R is an acyl or a carboalkoxyl, by direct electrophilic amination of fluorinated groups on azodicarboxylate derivatives. These latter have been widely used to yield a wide variety of amino compounds.[12]

First, we investigated the addition on azodicarboxylate derivatives of the "CF_3^-" entity, which is generated in situ from the Ruppert−Prakash reagent. From the di-*tert*-butyl azodicarboxylate **1a**, reactions with various fluoride catalysts (TBAF, CsF, TBAT...) in DMF afforded a mixture of compounds with low yield (<10%) of the desired compound **2**. As we expected, the main compounds resulted from the trifluoromethylation of the ester groups. Several pics were observed in ^{19}F NMR with a chemical shift window from −76 to −86 ppm attributable to ketones, ketals, and amino ketal derivatives. However, the best conditions are the use of AcONa (10%) in DMF at 0°C (Scheme 1). Unfortunately, from the dibenzyl azodicarboxylate **1b**, reaction afforded only traces of compounds.

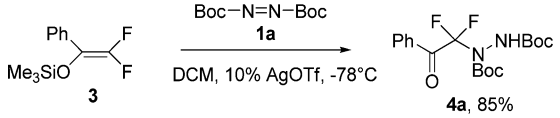
Scheme 1. Trifluoromethylation of Di-*tert*-butyl Azodicarboxylate 1a



The CF_3 hydrazide compound **2** was isolated in 30% from the di-*tert*-butyl azodicarboxylate **1a** accompanied of previous side products. Despite screening of different conditions (toluene or DCM as solvent, copper or silver salts as catalyst), the yield of the reaction could not be improved. The product **2** is a very stable white powder (several months).

We next considered the addition of the phenyl-difluoroenoxysilane **3**[13] on the di-*tert*-butyl azodicarboxylate **1a** (Scheme 2). After several unsuccessful trials with various catalysts ($BF_3{\cdot}Et_2O$, $Yb(OTf)_3$), the use of silver triflate (10%)

Scheme 2. Electrophilic Amination



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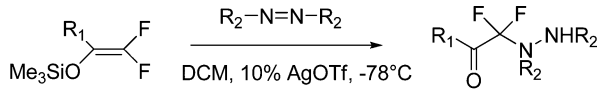
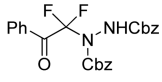
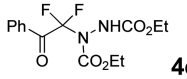
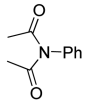
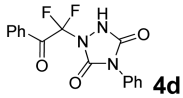
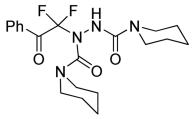
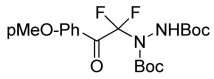
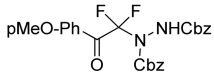
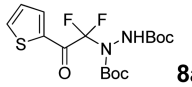
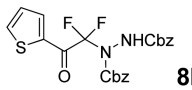
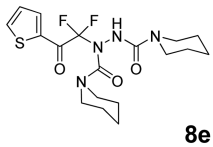
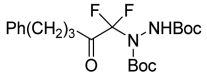
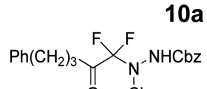
in dichloromethane at −78 °C led to the difluorohydrazide derivative **4a** in good yield (85%) with a complete chemoselectivity on the nitrogen.[14] The present reaction occurs exclusively on nitrogen of the azo group rather than on the carbonyl carbon. The silver catalyst is necessary for performing the reaction. When the reaction was carried out with 10% of triflic acid, the conversion is low and a mixture of products is observed.

The scope and limitations of the reaction were then investigated with other difluoroenoxysilanes and azodicarboxylates. The results are reported in Table 1.

Table 1. Addition of Difluoroenoxysilanes on Azodicarboxylates[a]



Entry	R_1	R_2	Product	Yield (%)[a]
1	Ph, **3**	Cbz, **1b**	 **4b**	80
2	**3**	CO_2Et, **1c**	 **4c**	99
3	3	 **1d**	 **4d**	86
4	3	 **1e**	 **4e**	74
5	*p*-$MeOC_6H_4$ **5**	Boc, **1a**	 **6a**	94
6	**5**	Cbz, **1b**	 **6b**	90
7	 **7**	Boc, **1a**	 **8a**	99
8	**7**	Cbz, **1b**	 **8b**	98
9	**7**	 **1e**	 **8e**	60
10	$Ph(CH_2)_3$ **9**	Boc, **1a**	 **10a**	30
11	**9**	Cbz, **1b**	 **10b**	30

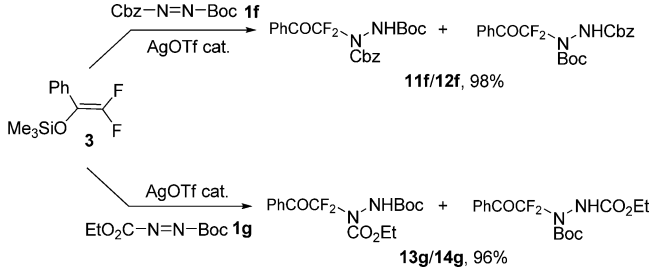
[a]Isolated yields.

From aromatic difluoroenoxysilanes, the products were easily isolated in excellent yields after purification by flash chromatography or crystallization, whatever the electron-withdrawing group on the nitrogen such as Boc, Cbz, ester, triazole dione, and carboxy-piperidine (entries 1−9). In the case of the alkyl difluoroenoxysilane **9**, the products **10a** and **10b** were isolated in low yields (entries 10−11), probably due to the difficulty to obtain **9** cleanly, as reported in the literature.[13]

Given that the product of the reaction led at −78 °C to the *N*-difluorohydrazide derivatives, we carried out thorough structural characterization, both in solution and in the solid state. The obtaining of the X-ray structure of the compound **4a**[15] showed an interesting influence of the CF_2 group on the N−N length, which was 1.387 Å, while, in the nonfluorinated derivatives, the length is around 1.454 Å[16] (Supporting Information). The ^1H and ^{19}F NMR spectra of the product **6a** showed a coalescence. An ^{19}F NMR study at different temperatures was undertaken and showed a mixture of rotamers. At 300 K, the signals of the both rotamers moved even closer but were still detected. Eventually, at 330 K, the two signals coalesced to a single peak at −86.53 ppm (S.I.).

The addition of the difluoroenoxysilane **3** was attempted on the unsymmetrical azodicarboxylates **1f** and **1g**, respectively (Scheme 3).

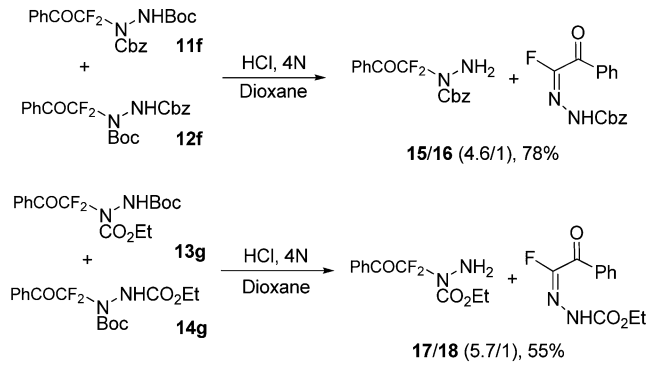
Scheme 3. Additions on Unsymmetrical Azodicaboxylates



Additions led to a mixture of NCF_2 hydrazide derivatives **11f/12f** and **13g/14g**. The addition reaction occurs exclusively on nitrogen with nonregioselectivity, of which the ratio was analyzed after acid-catalyzed hydrolysis of the *tert*-butoxycarbonyl group (4 equiv HCl, 4 N dioxane).

Both products **15**, **16** and **17**, **18** are obtained in a proportion 4.6/1 and 5.7/1, respectively (Scheme 4). Deprotection of the Boc group led to a loss of a fluoride to afford the fluoroimidoyl compounds **16** and **18**, which are very stable. These

Scheme 4. Deprotection Reactions



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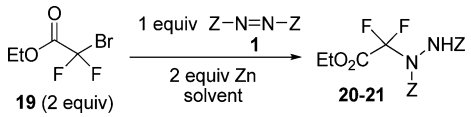
regioselective attacks could be explained by the less steric demand of nitrogen bearing Cbz and CO_2Et groups than that bearing a Boc group.

In the context of our interest in the design of fluorinated peptidomimetics derivatives,[17] we focused our studies on the addition of a difluoroester function on the azodicarboxylates. Faced with the low stability of the difluoroenoxysilane ether,[18] we turned to the addition of the organozinc difluoroester[19] on azodicarboxylate derivatives. First, the Reformatsky reaction was carried out in a one-pot manner with the ethyl bromodifluoroacetate **19** and **1a**. Unfortunately, only the reduction of the di-*tert*-butyl azodicarboxylate **1a** into hydrazide was observed. Thus, the reaction was performed in two steps: first, preparation of the organozinc difluoroester, which was then added on the di-*tert*-butyl azodicarboxylate **1a**.[20] Different conditions have been tested and are reported in Table 2.

Table 2. Addition of Organozinc on Azodicarboxylate 1a



entry	solvent	cat.	1, Z	conditions	yield (%)[b]
1	THF		**1a**, Boc	reflux, 2 h	33[a]
2	DMF		**1a**, Boc	rt, 19 h	30
3	DMF	0.5 equiv AgOTf	**1a**, Boc	rt, 1 h 30	59
4	DMF	0.5 equiv AgOTf	**1b**, Cbz	rt, 1 h 30	40

[a]Side products are reduction of the **1a** and dimerization of the organozinc derivative. [b]Isolated yields.

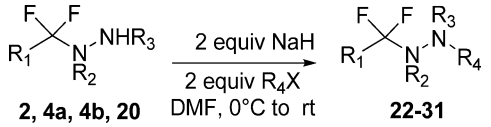
In THF or DMF as solvent with activated zinc powder, compound **20** could be obtained in moderate yield, 33% and 30%, respectively. By carrying out the reaction with 0.5 equiv of AgOTf in DMF (entry 3), the reaction time was shorter, and the yield reached 59%. These latter conditions were also efficient on dibenzyl azodicarboxylate **1b** to afford the *N*-difluorohydrazido ester **21** in 40% yield.

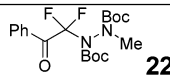
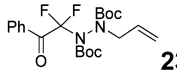
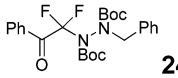
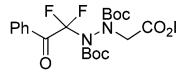
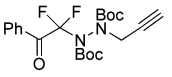
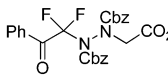
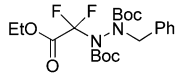
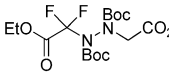
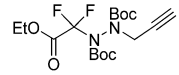
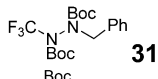
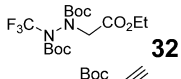
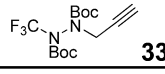
With the new interesting family of *N*-fluoroalkyl hydrazide derivatives, we conducted preliminary studies on their reactivity and, in particular, the alkylation reaction. Whatever the fluoroalkyl groups, the alkylation of the *N*-fluoro-hydrazides **2**, **4a**, and **20** was performed successfully (Table 3). A wide range of functionalized alkyl halides were introduced such as, for example, allyl bromide, propargyl bromide, and ethyl iodoacetate. Despite basic conditions, N-fluorinated hydrazides were very stable without decomposition and loss of fluorine.

Furthermore, some compounds such as **25**−**27**, **29**−**30**, and **32**−**33** were ready to use in order to be incorporated in molecules. For example, to illustrate the high potential of these NCF_3 and NCF_2 building blocks, compounds **26**, **30**, and **33** could react easily with the azide methylester to afford triazoles **34**−**36** in excellent yields (Scheme 5).

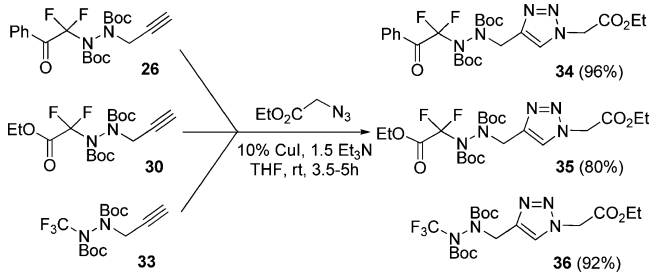
In conclusion, we have demonstrated that nucleophile fluoroalkyl derivatives easily add on electrophilic amines such as azodicarboxylate derivatives. These results extend to a new interesting family of NCF_3 and NCF_2-hydrazino derivatives. Furthermore, their easy handling and their stability made them accessible to new innovative compounds in different fields of research.

Table 3. Alkylation of Hydrazine Derivatives



Entry	R_4X	product	Yield (%)
1	MeI	 **22**	90
2		 **23**	95
3		 **24**	90
4		 **25**	98
5		 **26**	92
6		 **27**	99
7		 **28**	89
8		 **29**	99
9		 **30**	76
10		 **31**	99
11		 **32**	99
12		 **33**	86

Scheme 5. [3 + 2] Cycloaddition Reactions of NCF_3 and NCF_2 Hydrazides



EXPERIMENTAL SECTION

General Methods. All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The usual solvents were purchased from commercial sources. Tetrahydrofuran (THF) was distilled on sodium/benzophenone.

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Reagents were used without further purification as received from a commercial supplier. TLC was performed on silica gel, 60F-250 (0.26 mm thickness) plates. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of $KMnO_4$ in water. Flash chromatography (FC) was performed on 60 silica gel (230−400 mesh). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on ^1H (300 MHz, 200 MHz), ^{13}C (75 MHz), and ^{19}F (188 MHz) spectrometers. Unless otherwise stated, NMR data were obtained under ambient temperature conditions and $CDCl_3$ was used as solvent. Chemical shifts δ are in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet doublet (dd), triplet (t), quintuplet (quint), multiplet (m) and broad singlet (brs). High-resolution mass spectra were obtained on a spectrometer in ESI mode using a TOF mass analyzer.

Synthetic Procedures. *General Procedure to Prepare the Di-tert-butyl 1-(Trifluoromethyl)hydrazine-1,2-dicarboxylate (**2**).* To a mixture of the di-*tert*-butylazodicarboxylate (1 equiv) and trifluoromethyl trimethylsilane (2 equiv) in DMF (1 M) at room temperature was added sodium acetate (0.2 equiv) under nitrogen. After 3 h of strirring, the reaction was stopped by adding a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **2** as a white solid (45 mg, 0.15 mmol, 30%). m.p.: 80 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −59.76 (brs, 3F). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.49−6.03 (brs, 1H), 1.52 (brs, 9H), 1.49 (brs, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 150.4, 118.5 (q, $^1J_{(C,F)}$ = 261.3 Hz, CF_3), 84.8, 82.3, 27.9, 27.7. HRMS (ESI-TOF) m/z $C_{11}H_{19}F_3N_2O_4$ $[M + Na]^+$ cal. 323.1196, found 323.1195.

*General Procedure to Prepare Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)hydrazine-1,2-dicarboxylate (**4a**).* The azodicarboxylate derivative (1 equiv) was dissolved in DCM (0.5 M), and AgOTf (10 mol %) was added. The solution was cold at −78 °C, and a solution of the corresponding eneoxysilane in DCM (1.5 equiv, 0.38 M) was slowly added. The mixture was stirred under an argon atmosphere for 3 h. The reaction was stopped by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by recrystallization in DCM/Cyclohexane to provide **4a** as a white solid (985 mg, 2.55 mmol, 85%). m.p.: 125 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −84.77 to −89.99 (m, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55−7.41 (brs, 2H), 7.66−7.55 (m, 1H), 7.55−7.41 (m, 2H), 6.61 (brs, 1H), 1.52 (brs, 9H), 1.26 (brs, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.2 (t, $^2J_{(C,F)}$ = 30.0 Hz), 157.7, 151.2, 134.1, 132.2, 130.0, 128.7, 112.8 (t, $^1J_{(C,F)}$ = 257 Hz), 86.2, 82.4, 28.2, 27.6. HRMS (ESI-TOF) m/z $C_{18}H_{24}F_2N_2O_5$ $[M + Na]^+$ cal. 409.1549, found 409.1551.

*Dibenzyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)hydrazine-1,2-dicarboxylate (**4b**).* The product was obtained following the general procedure in 3 h. The crude was purified by recrystallization in DCM/Cyclohexane to provide **4b** as a white solid (985 mg, 2.55 mmol, 85%). m.p.: 134 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −85.30 to −88.68 (m, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37−7.89 (m, 2H), 7.68−7.06 (m, 13H), 6.86 (brs, 1H), 5.33−5.12 (m, 2H), 5.12−4.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9 (t, $^2J_{(C,F)}$ = 32.0 Hz), 155.6, 152.7, 135.2, 134.2−128.3 (Car), 112.8 (t, $^1J_{(C,F)}$ = 259.5 Hz), 69.8, 68.6. HRMS (ESI-TOF) m/z $C_{24}H_{20}F_2N_2O_5$ $[M + H]^+$ cal. 455.1412, found 455.1413; $[M + NH_4]^+$ cal. 472.1678, found 472.1679; $[M + Na]^+$ cal. 477.1228, found 477.1232.

*Diethyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)hydrazine-1,2-dicarboxylate (**4c**).* The product was obtained following the general procedure (II) in 2 h. The crude was purified by recrystallization in DCM/Cyclohexane to provide **4c** as a white solid (145 mg, 0.49 mmol, 98%). m.p.: 80−85 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −87.30 (brs, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.30 (brs, 2H), 7.60 (t, $^3J_{(H,H)}$ = 7.4 Hz, 1H), 7.49 (t, $^3J_{(H,H)}$ = 7.6 Hz, 2H), 7.07 (brs, 1H), 4.45−4.20 (m, 2H), 4.10 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 1.46−1.21 (m, 3H), 1.09 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.0 (t, $^2J_{(C,F)}$ = 29.3 Hz), 155.9, 152.7, 134.2, 132.0, 129.8, 128.8, 112.8 (t, $^1J_{(C,F)}$ = 258.0 Hz), 64.6, 63.0, 14.4, 13.8. HRMS (ESI-TOF) m/z $C_{14}H_{16}F_2N_2O_5$ $[M + H]^+$ cal. 331.1100, found 331.1103; $[M + Na]^+$ cal. 353.0916, found 353.0919.

*1-(1,1-Difluoro-2-oxo-2-phenylethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (**4d**).* The product was obtained following the general procedure in 6 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **4d** as a white solid (142 mg, 0.43 mmol, 86%). m.p.: 156 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −87.25 (s, 2F). ^1H NMR (300 MHz, $CDCl_3$) δ = 8.12 (d, $^3J_{(H,H)}$ = 6.9 Hz, 2H), 7.69 (t, $^3J_{(H,H)}$ = 7.4 Hz, 1H), 7.58−7.36 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.0 (t, $^2J_{(C,F)}$ = 32.6 Hz), 154.1, 152.3, 135.4−125.9 (Car), 114.1 (t, $^1J_{(C,F)}$ = 267.00 Hz). HRMS (ESI-TOF) m/z $C_{16}H_{11}F_2N_3O_3$ $[M + Na]^+$ cal. 354.0665, found 354.0666.

*1-(1,1-Difluoro-2-oxo-2-phenylethyl)hydrazine-1,2-bis(1-piperidinylcarbonyl) (**4e**).* The product was obtained following the general procedure in 25.5 h. The crude was purified by recrystallization in DCM/Cyclohexane to provide **4e** as a white solid (138 mg, 0.37 mmol, 74%). m.p.: 156 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −88.27 to −89.49 (m, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H), 7.56 (t, $^3J_{(H,H)}$ = 8.0 Hz, 1H), 7.46 (t, $^3J_{(H,H)}$ = 8.0 Hz, 1H), 7.24 (brs, 1H), 3.57−3.12 (m, 8H), 1.66−1.30 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.8 (t, $^2J_{(C,F)}$ = 29.3 Hz), 157.5, 155.93, 133.9, 132.2, 130.0, 128.6, 115.3 (t, $^1J_{(C,F)}$ = 257.3 Hz), 46.8, 45.5, 25.7, 25.6, 24.4, 24.3. HRMS (ESI-TOF) m/z $C_{20}H_{26}F_2N_4O_3$ $[M + H]^+$ cal. 409.2054, found 409.2051; $[M + Na]^+$ cal. 431.1876, found 431.1871.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-(4-methoxyphenyl)ethyl)-hydrazine-1,2-dicarboxylate (**6a**).* The product was obtained following the general procedure in 2 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 90/10) to provide **6a** as a white solid (202 mg, 0.48 mmol, 97%). m.p.: 131 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −86.53 (brs, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48−8.00 (brs, 2H), 7.11−6.81 (m, 2H), 6.67−6.30 (brs, 1H), 3.87 (s, 3H), 1.52 (brs, 9H), 1.28 (brs, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.0 (t, $^2J_{(C,F)}$ = 30.0 Hz), 164.5, 154.8, 151.2, 132.6, 125.1, 114.1, 113.0 (t, $^1J_{(C,F)}$ = 257.0 Hz), 86.2, 82.4, 55.7, 28.3, 27.7. HRMS (ESI-TOF) m/z $C_{19}H_{26}F_2N_2O_6$ $[M + Na]^+$ cal. 439.1654, found 439.1657.

*Dibenzyl 1-(1,1-Difluoro-2-oxo-2-(4-methoxyphenyl)ethyl)-hydrazine-1,2-dicarboxylate (**6b**).* The product was obtained following the general procedure in 2 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 90/10) to provide **6b** as a white foam (227 mg, 0.47 mmol, 94%). m.p.: < 50 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −84.00 to −89.00 (m, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.40−7.84 (m, 2H), 7.45−7.20 (m, 8H), 7.20−7.05 (m, 2H), 7.05−6.83 (m, 2H), 6.83−6.37 (m, 1H), 5.34−5.15 (m, 2H), 5.15−4.95 (m, 2H), 3.96−3.70 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.6 (t, $^2J_{(C,F)}$ = 28.9 Hz), 164.4, 155.8, 152.63, 135.5−124.5 (Car), 114.1, 112.9 (t, $^1J_{(C,F)}$ = 261.4 Hz), 69.7, 68.4, 55.6. HRMS (ESI-TOF) m/z $C_{25}H_{22}F_2N_2O_6$ $[M + Na]^+$ cal. 507.1343, found 507.1344.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-(thiophen-2-yl)ethyl)-hydrazine-1,2-dicarboxylate (**8a**).* The product was obtained following the general procedure (II) in 3 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **8a** as a white solid (195 mg, 0.50 mmol, 99%). m.p.: 40−50 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −84.00 to −89.93 (m, 2F). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (brs, 1H), 7.74 (d, $^3J_{(H,H)}$ = 3.0 Hz, 1H), 7.18 (brs, 1H), 6.63 (brs, 1H), 1.50 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (t, $^2J_{(C,F)}$ = 32.0 Hz), 154.8, 151.2, 138.3, 136.4, 135.8, 129.2, 112.7 (t, $^1J_{(C,F)}$ = 258.0 Hz), 86.3, 82.4, 28.2, 27.6. HRMS (ESI-TOF) m/z $C_{16}H_{22}F_2N_2O_5S$ $[M + Na]^+$ cal. 415.1116, found 415.1115.

*Dibenzyl 1-(1,1-Difluoro-2-oxo-2-(thiophen-2-yl)ethyl)hydrazine-1,2-dicarboxylate (**8b**).* The product was obtained following the general procedure in 3 h. The crude was purified by recrystallization in DCM/Cyclohexane to provide **8b** as a white solid (227 mg, 0.49

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mmol, 99%). m.p.: 110 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −82.60 to −91.99 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (brs, 1H), 7.93−7.56 (m, 1H), 7.54−7.05 (m, 11H), 5.30−5.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8 (t, $^2J_{(C,F)}$ = 31.0 Hz), 155.7, 152.7, 137.9−128.3 (Car), 112.7 (t, $^1J_{(C,F)}$ = 260.0 Hz), 69.7, 68.4. HRMS (ESI-TOF) m/z $C_{22}H_{18}F_2N_2O_5S$ $[M + H]^+$ cal. 461.0978, found 461.0977; $[M + NH_4]^+$ cal. 478.1242, found 478.1243; $[M + Na]^+$ cal. 483.0792, found 483.0797.

*1-(1,1-Difluoro-2-oxo-2-(thiophen-2-yl)ethyl)hydrazine-1,2-bis(1-piperidinylcarbonyl) (**8e**).* The product was obtained following the general procedure in 25.5 h. The crude was purified by recrystallization in DCM/Cyclohexane to provide **8e** as a yellow solid (127 mg, 0.31 mmol, 61%, 2 conformers). m.p.: 160 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = 90.78 and −90.85 (2 s, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (dd, $^3J_{(H,H)}$ = 3.9 Hz, $^4J_{(H,H)}$ = 1.1 Hz, 1H), 7.74 (dd, $^3J_{(H,H)}$ = 5.0 Hz, $^4J_{(H,H)}$ = 1.1 Hz, 1H), 7.18 (2d, $^3J_{(H,H)}$ = 5.0 Hz, $^3J_{(H,H)}$ = 3.9 Hz, 1H), 6.80 (s, 1H), 3.60−3.44 (m, 4H), 3.40−3.22 (m, 4H), 1.76−1.37 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8 (t, $^2J_{(C,F)}$ = 31.5 Hz), 157.4, 155.9, 138.2, 136.3, 135.8, 128.9, 115.2 (t, $^1J_{(C,F)}$ = 258.0 Hz), 46.9, 45.5, 25.7, 24.3. HRMS (ESI-TOF) m/z $C_{18}H_{24}F_2N_4O_3S$ $[M + H]^+$ cal. 415.1615, found 415.1615; $[M + Na]^+$ cal. 437.1435, found 437.1435.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-5-phenylpentyl)hydrazine-1,2-dicarboxylate (**10a**).* The product was obtained following the general procedure (II) in 3.25 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **10a** as a colorless oil (63 mg, 0.15 mmol, 30%). ^{19}F NMR (188 MHz, $CDCl_3$): δ = −91.39 to −96.42 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33−7.15 (m, 5H), 6.56−6.15 (m, 1H), 3.02−2.55 (m, 2H), 2.69 (t, $^3J_{(H,H)}$ = 7.7 Hz, 2H), 2.02 (q, $^3J_{(H,H)}$ = 4.4 Hz, 2H), 1.50 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9 (t, $^2J_{(C,F)}$ = 21.8 Hz), 124.3, 152.0, 141.6, 128.6, 128.5, 126.1, 112.4 (t, $^1J_{(C,F)}$ = 261.0 Hz), 85.3, 84.5, 36.3, 34.9, 28.2, 28.0, 24.8. HRMS (ESI-TOF) m/z $C_{21}H_{30}F_2N_2O_5$ $[M + Na]^+$ cal. 451.2023, found 451.2020.

*Dibenzyl 1-(1,1-Difluoro-2-oxo-5-phenylpentyl)hydrazine-1,2-dicarboxylate (**10b**).* The product was obtained following the general procedure in 1.5 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **10b** as a colorless oil (70 mg, 0.14 mmol, 28%). ^{19}F NMR (188 MHz, $CDCl_3$): δ = −93.66 (brs, 2F).^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40−7.10 (m, 15H), 6.94−6.60 (m, 1H), 5.29−4.99 (m, 4H), 2.96−2.48 (m, 4H), 2.08−1.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0 (m, $^2J_{(C,F)}$ = 28.1 Hz), 155.3, 153.04, 141.5−126.1 (C_{ar}), 112.2 (t, $^1J_{(C,F)}$ = 262.9 Hz), 69.7, 68.4, 36.4, 34.8, 24.6. HRMS (ESI-TOF) m/z $C_{27}H_{26}F_2N_2O_5$ $[M + Na]^+$ cal. 519.1708, found 519.1707.

*1-Benzyl, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), 2-tert-Butyl-hydrazine-1,2-dicarboxylate (**11f**) and 1-tert-Butyl, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), 2-Benzyl Hydrazine-1,2-dicarboxylate (**12f**).* The product was obtained following the general procedure in 3 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **11f** and **12f** as a white foam (832 mg, 1.98 mmol, 99%, 2 isomers, 82:18). m.p.: < 50 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −84.00 to −90.00 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53−8.03 (m, 2H), 7.71−7.09 (m, 8H), 6.98 (brs, 1H), 5.39−4.96 (m, 2H), 1.47 (s, 6H), 1.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.2 (t, $^2J_{(C,F)}$ = 27.8 Hz), 181.8 (t, $^2J_{(C,F)}$ = 27.0 Hz), 156.0, 154.4, 152.9, 150.9, 135.4−128.3 (C_{ar}), 112.9 (t, $^1J_{(C,F)}$ = 257.6 Hz), 112.6 (t, $^1J_{(C,F)}$ = 257.6 Hz), 86.7, 83.2, 82.6, 69.5, 68.2, 28.0, 27.4. HRMS (ESI-TOF) m/z $C_{21}H_{22}F_2N_2O_5$ $[M + Na]^+$ cal. 443.1396, found 443.1394.

*1-Ethyl, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), 2-tert-Butyl-hydrazine-1,2-dicarboxylate (**13g**) and 1-tert-Butyl, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), 2-Ethyl Hydrazine-1,2-dicarboxylate (**14g**).* The product was obtained following the general procedure in 4 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **13g** and **14g** as a colorless oil (886 mg, 2.47 mmol, 99%, 2 isomers, 85:15). ^{19}F NMR (188 MHz, $CDCl_3$): δ = −85.05 to −89.57 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47−8.07 (m, 2H), 7.68−7.56 (m, 1H), 7.56−7.44 (m, 2H), 6.75−6.25 (m, 1H), 4.39−4.23 (m, 0.34H), 4.21−4.05 (m, 1.63H), 1.53 (brs, 7.71H), 1.40−1.29 (m, 0.57H), 1.25 (brs, 1.44H), 1.21−1.08 (m, 2.33H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.2 (t, $^2J_{(C,F)}$ = 29.1 Hz), 181.5 (t, $^2J_{(C,F)}$ = 28.6 Hz), 156.2, 154.8, 154.6, 152.8, 150.8, 134.0, 133.9, 131.9, 131.8, 129.6, 129.3, 128.5, 112.6 (t, $^1J_{(C,F)}$ = 258.5 Hz), 112.4 (t, $^1J_{(C,F)}$ = 256.1 Hz), 86.2, 82.9, 82.1, 77.6, 77.2, 76.7, 64.0, 62.4, 27.8, 27.1, 26.7, 14.2, 13.5. HRMS (ESI-TOF) m/z $C_{16}H_{20}F_2N_2O_5$ $[M + Na]^+$ cal. 381.1238, found 381.1239.

General Procedure for the Deprotection of Dissymmetric *N*-Difluoromethyl Hydrazide Derivatives. To a solution of the corresponding protected hydrazine derivative (1 equiv) in DCM (0.6 M) was added a solution of hydrogen chloride in dioxane (4 M, 10 equiv) at room temperature. When the reaction was completed, solvent was removed under vacuum and the crude product was directly purified by column chromatography in appropriate solvents.

*Hydrazinecarboxylic Acid, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), Benzyl Ester (**15**) and 3-Phenyl Propanehydrazonoyl Fluoride, N-Benzyl Carboxylate (**16**).* The product was obtained following the general procedure after one night. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **15** and **16** as a colorless oil (434 mg, 1.43 mmol, 78%, 4.6:1). *Major product* **15**: ^{19}F NMR (188 MHz, $CDCl_3$) δ = −85.24 (brs, 2F). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.06−7.95 (m, 2H), 7.63−7.56 (m, 1H), 7.48−7.41 (m, 2H), 7.36−7.25 (m, 5H), 5.19 (brs, 2H), 4.13 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.75 (t, $^2J_{(C,F)}$ = 30.5 Hz), 155.09, 134.56, 133.98, 132.22, 129.48, 128.75, 128.71, 128.34, 114.26 (t, $^1J_{(C,F)}$ = 259.9 Hz), 69.35. HRMS (ESI-TOF) m/z $C_{16}H_{14}F_2N_2O_3$ $[M + Na]^+$ cal. 343.0870, found 343.0883. *Minor product* **16**: m.p.: = 126 °C. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −74.58 (brs, 1F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.85 (brs, 1H), 8.31−8.20 (m, 2H), 7.65−7.55 (m, 1H), 7.50−7.31 (m, 7H), 5.27 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8 (d, $^2J_{(C,F)}$ = 29.2 Hz), 152.4, 139.6 (d, $^1J_{(C,F)}$ = 329.9 Hz), 135.1, 134.1, 134.0, 133.9, 130.8, 128.7, 128.5, 128.4, 68.5. HRMS (ESI-TOF) m/z $C_{16}H_{13}FN_2O_3$ $[M + Na]^+$ cal. 323.0808, found 323.0811.

*Hydrazinecarboxylic Acid, 1-(1,1-Difluoro-2-oxo-2-phenylethyl), Ethyl Ester **17** and 3-Phenyl Propanehydrazonoyl Fluoride, N-Ethyl Carboxylate (**18**).* The product was obtained following the general procedure in 4 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **17** and **18** as a colorless oil (169 mg, 0.66 mmol, 55%, 5.7:1). *Major product* **17**: ^{19}F NMR (188 MHz, $CDCl_3$) δ = −85.71 (brs, 2F). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.01 (d, $^3J_{(H,H)}$ = 7.4 Hz, 2H), 7.61−7.52 (m, 1H), 7.51−7.38 (m, 2H), 4.23−4.06 (m, 2H), 4.17 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 1.18 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.77 (t, $^2J_{(C,F)}$ = 30.6 Hz), 155.04, 133.93, 132.24, 129.37, 128.68, 114.13 (t, $^1J_{(C,F)}$ = 259.0 Hz), 63.94, 14.00. HRMS (ESI-TOF) m/z $C_{11}H_{12}F_2N_2O_3$ $[M + Na]^+$ cal. 281.0714, found 281.0715. *Minor product* **18**: ^{19}F NMR (188 MHz, $CDCl_3$) δ = −75.26 (brs, 1F). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.78 (brs, 1H), 8.28−8.19 (m, 2H), 7.63−7.51 (m, 1H), 7.51−7.38 (m, 2H), 4.28 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 1.30 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9 (d, $^2J_{(C,F)}$ = 29.4 Hz), 152.4, 134.0, 130.7, 128.5, 63.0, 14.3. NB: CF not observed

General Procedure to Prepare Ethyl Ester *N*-Difluoromethyl Derivatives. Preparation of Bromozinc-α,α-difluoroacetate. To a suspension of zinc turning (1 equiv) in anhydrous DMF (5 M) was added a drop of TMSCl under nitrogen at room temperature. After 5 min, the ethyl bromodifluoroacetate (1 equiv) diluted in DMF (1.25 M) was added, and the mixture was stirred until the flask warmed (ca. 5−10 min). The solution was stirred for another 1 h and directly used for the following reaction.

Addition on Azodicarboxylate. To a solution of the azodicarboxylate derivative (1 equiv) and AgOTf (0.5 equiv) in DMF (0.5 M) at 0 °C was added a solution of bromozinc-α,α-difluoroacetate (2 equiv) in DMF (1 M). After several hours, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography in appropriate solvents.

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*Di-tert-butyl 1-(2-Ethoxy-1,1-difluoro-2-oxoethyl)hydrazine-1,2-dicarboxylate (**20**).* The product was obtained following the general procedure in 4 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **20** as a white solid (744 mg, 2.9 mmol, 59%). m.p.: 68 °C. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −86.46 to −94.99 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.48−6.01 (m, 1H), 4.36 (2 q, $^3J_{(H,H)}$ = 7.0 Hz, $^3J_{(H,H)}$ = 7.0 Hz, 2H), 1.49 (s, 9H), 1.48 (s, 9H), 1.35 (t, $^3J_{(H,H)}$ = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (t, $^2J_{(C,F)}$ = 36.0 Hz), 154.2, 151.5, 111.0 (t, $^1J_{(C,F)}$ = 257.0 Hz), 84.9, 82.4, 63.5, 28.1, 28.0, 13.9. HRMS (ESI-TOF) m/z $C_{14}H_{24}F_2N_2O_6$ $[M + NH_4]^+$ cal. 372.1942, found 372.1941; $[M + Na]^+$ cal. 377.1494, found 377.1495.

*Dibenzyl 1-(2-Ethoxy-1,1-difluoro-2-oxoethyl)hydrazine-1,2-dicarboxylate (**21**).* The product was obtained following the general procedure (IV) in 4.5 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **21** as a colorless oil (84 mg, 0.2 mmol, 40%). ^{19}F NMR (188 MHz, $CDCl_3$): δ = −90.62 (brs, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 10H), 6.81 (brs, 1H), 5.18 (brs, 4H), 4.23 (q, $^3J_{(H,H)}$ = 7.0 Hz, 2H), 1.25 (t, $^3J_{(H,H)}$ = 7.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0 (t, $^2J_{(C,F)}$ = 35.2 Hz), 155.2, 152.6, 135.3−128.4 (C_{ar}), 110.8 (t, $^1J_{(C,F)}$ = 259.1 Hz), 69.6, 68.4, 63.9, 13.7. HRMS (ESI-TOF) m/z $C_{20}H_{20}F_2N_2O_6$ $[M + Na]^+$ cal. 445.1187, found 445.1187.

General Procedure to Prepare Tetrasubstituted Hydrazine Derivatives. To a suspension of sodium hydride (2 equiv, previously washed with 3 × 2 mL of cyclohexane) in DMF (0.25 M) was added a solution of the *N*-difluoromethyl hydrazine derivative (1 equiv) in DMF (0.25 M) at 0 °C. The mixture was stirred for 10 min; then the halogenoalkyl derivative (2 equiv) was added. After 20 min at room temperature, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over $MgSO_4$. After filtration and evaporation, the crude product was purified by column chromatography in appropriate solvents.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)-2-methylhydrazine-1,2-dicarboxylate (**22**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **22** as a colorless oil (105 mg, 0.26 mmol, 90%, 2 conformers). ^{19}F NMR (188 MHz, Methanol-d_4) δ = −80.93 to −91.19 (m, 2F). ^{1}H NMR (300 MHz, Methanol-d_4) δ = 8.46−8.17 (m, 1H), 8.10 (d, $^3J_{(H,H)}$ = 7.7 Hz, 1H), 7.74−7.59 (m, 1H), 7.59−7.40 (m, 2H), 3.24 and 3.20 (2 s, 3H), 1.53 and 1.52 (2 s, 9H), 1.32 (brs, 9H). ^{13}C NMR (75 MHz, Methanol-d_4): δ = 183.5 and 183.3 (2 t, $^2J_{(C,F)}$ = 30.0 Hz and $^2J_{(C,F)}$ = 29.3 Hz), 156.6, 151.8, 135.9−128.7 (C_{ar}), 114.9 (t, $^1J_{(C,F)}$ = 258.0 Hz), 86.6, 83.6, 39.6, 38.3, 28.5, 28.0. HRMS (ESI-TOF) m/z $C_{19}H_{26}F_2N_2O_5$ $[M + Na]^+$ cal. 423.1700, found 423.1707.

*Di-tert-butyl 1-Allyl-2-(1,1-difluoro-2-oxo-2-phenylethyl)-hydrazine-1,2-dicarboxylate (**23**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **23** as a colorless oil (104 mg, 0.24 mmol, 95%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −77.42 to −93.11 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 (brs, 1H), 8.10 (d, $^3J_{(H,H)}$ = 6 Hz, 1H), 7.66−7.54 (m, 1H), 7.53−7.40 (m, 2H), 6.12−5.90 (m, 1H), 5.46−5.05 (m, 2H), 4.35−4.02 (m, 2H), 1.55 and 1.53 (2 s, 9H), 1.33 (brs, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.8 (t, $^2J_{(C,F)}$ = 31.1 Hz), 182.7 (t, $^2J_{(C,F)}$ = 31.1 Hz), 154.4, 151.4, 135.1−127.4 (C_{ar} and N-CH_2-CH=CH_2), 118.3, 118.0, 113.5 (dd, $^1J_{(C,F)}$ = 264.9 Hz, $^1J_{(C,F)}$ = 254.1 Hz), 84.8, 84.85, 56.2, 54.5, 28.2, 27.7. HRMS (ESI-TOF) m/z $C_{21}H_{28}F_2N_2O_5$ $[M + Na]^+$ cal. 449.1868, found 449.1864.

*Di-tert-butyl 1-Benzyl-2-(1,1-difluoro-2-oxo-2-phenylethyl)-hydrazine-1,2-dicarboxylate (**24**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **24** as a colorless oil (108 mg, 0.23 mmol, 99%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −78.78 to −91.44 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35−8.23 (m, 1H), 8.03 (m, 1H), 7.73−7.38 (m, 5H), 7.40−7.27 (m, 3H), 5.16−4.34 (m, 2H), 1.55 and 1.49 (2 s, 9H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.6 (m), 154.6, 151.7, 138.0−126.2 (C_{ar}), 113.9 (t, $^1J_{(C,F)}$ = 259.5 Hz), 84.3, 82.5, 82.3, 56.5, 54.4, 28.2, 27.4. HRMS (ESI-TOF) m/z $C_{25}H_{30}F_2N_2O_5$ $[M + Na]^+$ cal. 499.2021, found 499.2020.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)-2-(2-ethoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**25**).* The product was obtained following the general procedure in 6 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **25** as a colorless oil (122 mg, 0.26 mmol, 98%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −78.05 to −95.73 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (d, $^3J_{(H,H)}$ = 7.2 Hz, 1H), 8.08 (d, $^3J_{(H,H)}$ = 7.0 Hz, 1H), 7.65−7.49 (m, 1H), 7.43 (q, $^3J_{(H,H)}$ = 8.5 Hz, 2H), 4.56 and 4.43 (2 d, $^3J_{(H,H)}$ = 17.1 Hz, $^3J_{(H,H)}$ = 17.4 Hz, 1H), 4.18 and 4.17 (2 q, $^3J_{(H,H)}$ = 7.1 Hz, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 3.85 and 3.82 (2d, $^3J_{(H,H)}$ = 17.4 Hz, $^3J_{(H,H)}$ = 17.2 Hz, 1H), 1.52 and 1.47 (2 s, 9H), 1.33−1.15 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.5 (t, $^2J_{(C,F)}$ = 30.0 Hz), 182.4 (t, $^2J_{(C,F)}$ = 30.0 Hz), 167.8, 167.6, 154.4, 153.7, 150.4, 135.4−126.2 (C_{ar}), 113.3 (t, $^1J_{(C,F)}$ = 258.0 Hz), 85.8, 83.0, 61.1, 54.9, 53.8, 28.1, 27.9, 27.6, 27.5, 14.1, 14.0. HRMS (ESI-TOF) m/z $C_{22}H_{30}F_2N_2O_7$ $[M + Na]^+$ cal. 495.1916, found 495.1919.

*Di-tert-butyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)-2-(prop-2-ynyl)hydrazine-1,2-dicarboxylate (**26**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **26** as a colorless oil (82 mg, 0.19 mmol, 92%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −79.41 to −92.38 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (brs, 1H), 8.14 (d, $^3J_{(H,H)}$ = 7.7, 1H), 7.61 (t, $^3J_{(H,H)}$ = 7.6, 1H), 7.47 (t, $^3J_{(H,H)}$ = 7.7 Hz, 2H), 4.60−4.25 (m, 2H), 2.31 (t, $^3J_{(H,H)}$ = 2.4 Hz, 1H), 1.55 and 1.54 (2 s, 9H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.6 (t, $^2J_{(C,F)}$ = 30.5 Hz), 153.9, 153.5, 151.0, 137.3−125.6 (C_{ar}), 113.5 (dd, $^1J_{(C,F)}$ = 267.0 Hz, $^1J_{(C,F)}$ = 254.5 Hz), 85.5, 83.1, 78.1, 77.8, 73.2, 72.8, 42.5, 40.6, 28.2, 27.7. HRMS (ESI-TOF) m/z $C_{21}H_{26}F_2N_2O_5$ $[M + Na]^+$ cal. 447.1704, found 447.1707.

*Dibenzyl 1-(1,1-Difluoro-2-oxo-2-phenylethyl)-2-(2-ethoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**27**).* The product was obtained following the general procedure in 50 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 80/20) to provide **27** as a white solid (120 mg, 0.22 mmol, 99%, 2 conformers). m.p.: 86 °C. ^{19}F NMR (188 MHz, $CDCl_3$) δ = −83.16 to −88.46 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29−6.93 (m, 15H), 5.29−5.05 (m, 2H), 5.05−4.86 (m, 2H), 4.59 and 4.47 (2 d, $^3J_{(H,H)}$ = 17.4 Hz, $^3J_{(H,H)}$ = 17.8 Hz, 1H), 4.14 and 4.02 (2 m, 2H), 4.14 and 3.90 (2 d, $^3J_{(H,H)}$ = 17.4 Hz, $^3J_{(H,H)}$ = 17.7 Hz, 1H), 1.18 and 1.08 (2 t, $^3J_{(H,H)}$ = 7.1 Hz, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.1 (t, $^2J_{(C,F)}$ = 30.3 Hz), 167.3, 167.2, 155.3, 155.2, 152.0, 135.2−127.9 (C_{ar}), 113.3 (t, $^1J_{(C,F)}$ = 259.8 Hz, CF_2), 113.2 (t, $^1J_{(C,F)}$ = 260.3 Hz), 69.8, 69.7, 69.4, 69.2, 61.5, 54.5, 53.9, 14.1, 14.0. HRMS (ESI-TOF) m/z $C_{28}H_{26}F_2N_2O_7$ $[M + Na]^+$ cal. 563.1602, found 563.1606.

*Di-tert-butyl 1-Benzyl-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-hydrazine-1,2-dicarboxylate (**28**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **28** as a colorless oil (117 mg, 0.26 mmol, 98%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −84.83 to −95.81 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50−7.36 (m, 2H), 7.36−7.27 (m, 3H), 5.19−4.13 (m, 4H), 1.48 (s, 9H), 1.35 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 1.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (t, $^2J_{(C,F)}$ = 35.6 Hz), 154.2, 151.7, 139.9−124.6 (C_{ar}), 111.2 (dd, $^1J_{(C,F)}$ = 251.3 Hz, $^1J_{(C,F)}$ = 265.5 Hz), 83.8, 82.4, 81.9, 63.4, 55.9, 53.4, 28.2, 28.1, 27.5, 13.9. HRMS (ESI-TOF) m/z $C_{21}H_{30}F_2N_2O_6$ $[M + Na]^+$ cal. 467.1971, found 467.1970.

*Di-tert-butyl 1-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-2-(2-ethoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate (**29**).* The product was obtained following the general procedure (V) in 1 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **29** as a colorless oil (114 mg, 0.26 mmol, 99%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −85.87 to −94.19 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.42−4.20 (m, 3H), 4.14 (q, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 3.80 and 3.75 (2 d, $^3J_{(H,H)}$ = 16.5 Hz and $^3J_{(H,H)}$ = 15.0 Hz, 1H), 1.42 and 1.43 (2 s, 18H), 1.28 (t, $^3J_{(H,H)}$ = 7.1 Hz,

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3H), 1.20 (t, $^{3}J_{(H,H)}$ = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167 7, 167.5, 160.3 (t, $^{2}J_{(C,F)}$ = 36.4 Hz), 160.2 (t, $^{2}J_{(C,F)}$ = 35.6 Hz), 154.2, 153.4, 151.0, 150.7, 110.9 (t, $^{1}J_{(C,F)}$ = 251.3 Hz), 84.9, 83.0, 82.7, 63.5, 61.5, 61.0, 55.0, 53.4, 27.9, 14.1, 14.0, 13.8. HRMS (ESI-TOF) m/z $C_{18}H_{30}F_2N_2O_8$ $[M + Na]^+$ cal. 463.1872, found 463.1868.

*Di-tert-butyl 1-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-2-(prop-2-ynyl)hydrazine-1,2-dicarboxylate (**30**).* The product was obtained following the general procedure in 40 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **30** as a colorless oil (111 mg, 0.28 mmol, 76%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −85.87 to −94.19 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.44−4.04 (m, 4H), 2.22 (t, $^{3}J_{(H,H)}$ = 2.4 Hz, 0.9H), 2.18 (t, $^{3}J_{(H,H)}$ = 2.6 Hz, 0.1H), 1.51−1.37 (m, 21H), 1.30 (t, $^{3}J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (t, $^{2}J_{(C,F)}$ = 39.38 Hz), 153.6, 153.1, 151.4, 150.1, 110.9 (t, $^{1}J_{(C,F)}$ = 258.75 Hz), 84.7, 83.5, 83.1, 82.7, 81.8, 73.1, 72.9, 72.5, 63.5, 42.3, 40.1, 38.3, 28.1, 28.0, 27.9, 13.8. HRMS (ESI-TOF) m/z $C_{17}H_{26}F_2N_2O_6$ $[M + Na]^+$ cal. 415.1657, found 415.1661.

*Di-tert-butyl 1-Benzyl-2-(trifluoromethyl)hydrazine-1,2-dicarboxylate (**31**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **31** as a colorless oil (104 mg, 0.27 mmol, 99%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −58.93 (brs, 3F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 (brs, 5H), 4.55 (brs, 2H), 1.51 and 1.47 (2 s, 9H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 154.0, 150.1, 149.8, 136.9−126.6 (C_{ar}), 120.5 (2 q, $^{1}J_{(C,F)}$ = 264.5 Hz, $^{1}J_{(C,F)}$ = 265.5 Hz), 84.4, 82.9, 82.4, 55.8, 53.5, 28.2, 28.0, 27.8. HRMS (ESI-TOF) m/z $C_{18}H_{25}F_3N_2O_4$ $[M + Na]^+$ cal. 413.1660, found 413.1664.

*Di-tert-butyl 1-(2-Ethoxy-2-oxoethyl)-2-(trifluoromethyl)-hydrazine-1,2-dicarboxylate (**32**).* The product was obtained following the general procedure (V) in 1 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 85/15) to provide **32** as a colorless oil (94 mg, 0.24 mmol, 99%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −58.68 and −59.26 (2 brs, 3F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.57 and 4.40 (2 d, $^{3}J_{(H,H)}$ = 16.0 Hz and $^{3}J_{(H,H)}$ = 18.0 Hz, 1H), 4.21 and 4.21 (2 q, $^{3}J_{(H,H)}$ = 10.8 Hz, $^{3}J_{(H,H)}$ = 10.7 Hz, 2H), 3.81 and 3.77 (2 d, $^{3}J_{(H,H)}$ = 16.8 Hz and $^{3}J_{(H,H)}$ = 18.0 Hz, 1H), 1.52 and 1.51 (2 s, 9H), 1.48 and 1.46 (2 s, 9H), 1.29 and 1.27 (2 t, $^{3}J_{(H,H)}$ = 8.0 Hz and $^{3}J_{(H,H)}$ = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 153.9, 153.5, 149.8, 149.5, 120.5 (q, $^{1}J_{(C,F)}$ = 263.25 Hz), 120.4 (q, $^{1}J_{(C,F)}$ = 262.5 Hz), 85.1, 83.5, 83.1, 61.2, 54.6, 52.6, 27.9, 27.9, 14.1, 14.0. HRMS (ESI-TOF) m/z $C_{15}H_{25}F_3N_2O_6$ $[M + Na]^+$ cal. 409.1562, found 409.1562.

*Di-tert-butyl 1-(Prop-2-ynyl)-2-(trifluoromethyl)hydrazine-1,2-dicarboxylate (**33**).* The product was obtained following the general procedure in 30 min. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **32** as a colorless oil (249 mg, 0.74 mmol, 86%, 2 conformers). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −59.19 (brs, 3F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.31 (2d, $^{1}J_{(H,H)}$ = 34.4 Hz, $^{1}J_{(H,H)}$ = 18.0 Hz, 1H), 4.13−3.98 (m, 1H), 2.28−2.19 (m, 1H), 1.50−1.29 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 153.1, 149.8, 149.5, 120.4 (q, $^{1}J_{(C,F)}$ = 264.1 Hz), 120.5 (q, $^{1}J_{(C,F)}$ = 262.5 Hz), 84.8, 83.4, 82.9, 76.7, 73.5, 73.3, 41.3, 39.3, 28.0, 27.8. HRMS (ESI-TOF) m/z $C_{14}H_{21}F_3N_2O_4$ $[M + Na]^+$ cal. 361.1351, found 361.1353.

General Procedure for [1−3] Dipolar Cyclization. To a solution of the corresponding di-*tert*-butyl-2-(prop-2-ynyl)hydrazine-1,2-dicarboxylate (1 equiv) in THF (0.08 M) was added ethyl azidoacetate (1.5 equiv, prepared from ethyl bromoacetate), triethylamine (1.5 equiv), and then CuI (0.1 equiv). The reaction was stirred at room temperature and monitored by TLC. When completed, the solution was concentrated under vacuum and the crude product was purified by column chromatography in appropriate solvents.

*Triazole (**34**).* The product was obtained following the general procedure in 5 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **34** as a colorless oil (86 mg, 0.15 mmol, 96%, rotamers mixture).^{19}F NMR (188 MHz, $CDCl_3$) δ = −81.58 to −89.62 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.40−7.79 (m, 3H), 7.59 (t, $^{3}J_{(H,H)}$ = 7.2 Hz, 1H), 7.49 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 3H), 5.36−4.57 (m, 4H), 4.23 (q, J = 7.0 Hz, 2H), 1.62−1.39 (m, 9H), 1.35−1.14 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.5 (t, $^{1}J_{(C,F)}$ = 29.3 Hz), 166.1, 154.1, 151.3, 143.7, 133.7, 132.5, 129.6, 128.5, 125.2, 113.3 (dd, $^{1}J_{(C,F)}$ = 268.8 Hz, $^{1}J_{(C,F)}$ = 251.8 Hz)., 84.7, 82.7, 62.2, 50.8, 47.0, 28.0, 27.4, 13.9. HRMS (ESI-TOF) m/z $C_{25}H_{33}F_2N_5O_7$ $[M + Na]^+$ cal. 576.2246, found 576.2250.

*Triazole (**35**).* The product was obtained following the general procedure in 4 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 60/40) to provide **35** as a colorless oil (116 mg, 0.22 mmol, 80%, rotamers mixture). ^{19}F NMR (188 MHz, $CDCl_3$) δ = −86.27 to −93.83 (m, 2F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72 (brs, 1H), 5.12−5.02 (m, 2H), 4.77 (d, $^{2}J_{(H,H)}$ = 15.1 Hz, 1H), 4.64 (d, $^{2}J_{(H,H)}$ = 15.4 Hz, 1H), 4.34−4.22 (m, 2H), 4.17 (q, $^{3}J_{(H,H)}$ = 7.1 Hz, 2H), 1.44−1.22 (m, 21H), 1.20 (t, $^{3}J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1 (t, $^{1}J_{(C,F)}$ = 33.75 Hz), 160.1, 154.0, 151.3, 143.3, 125.3, 110.7 ($^{1}J_{(C,F)}$ = 255.4 Hz), 84.2, 82.3, 63.4, 62.2, 50.8, 46.1, 27.9, 27.6, 14.0, 13.7. HRMS (ESI-TOF) m/z $C_{21}H_{33}F_2N_5O_8$ $[M + Na]^+$ cal. 544.2195, found 544.2196.

*Triazole (**36**).* The product was obtained following the general procedure in 3.5 h. The crude was purified by flash chromatography (Cyclohexane/Ethyl acetate: 70/30) to provide **36** as a colorless oil (240 mg, 0.51 mmol, 92%, rotamer mixture, 2.3:1). *Major rotamer*: ^{19}F NMR (188 MHz, $CDCl_3$) δ = −59.04 (brs, 3F). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 5.11−5.05 (m, 2H), 4.80 (d, $^{1}J_{(H,H)}$ = 15.4 Hz, 1H), 4.57 (d, $^{1}J_{(H,H)}$ = 15.2 Hz, 1H), 4.17 (q, $^{3}J_{(H,H)}$ = 7.1 Hz, 2H), 1.38 and 1.37 (2s, 18H), 1.20 (t, $^{3}J_{(H,H)}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 153.8, 149.5, 142.7, 125.0, 120.3 (q, $^{1}J_{(C,F)}$ = 262.5 Hz), 84.7, 82.6, 62.3, 50.8, 45.3, 27.8, 27.7, 13.9. HRMS (ESI-TOF) m/z $C_{18}H_{28}F_3N_5O_6$ $[M + Na]^+$ cal. 490.1889, found 490.1889.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds, X-ray diffraction structure of **4a** (CCDC 977875), and CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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