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FULL PAPER

Synthesis of novel cyclic nitrones with *gem*-difluoroalkyl side chains through cascade reactions

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Abstract: New five-membered cyclic nitrones with *gem*-difluoroalkyl groups in γ-position have been prepared by a 3-step sequence starting from propargylic alcohols. This domino process involves a base-mediated isomerization reaction to enones, which are trapped *in situ* by nitroalkane anions. In a final step, starting from these key precursors, a reduction-cyclization process affords the target molecules. Mono- and bicyclic nitrones have been prepared by this route which allows, as well, the synthesis of nitrones with functional groups in terminal position of the side chain.

Introduction

Nitrones are presently the most used spin traps to characterize free radicals in biological systems,[1-5] with Phenyl-*N*-tertiobutyl Nitrone (PBN) and Dimethyl-Pyrrolidine-N-oxide (DMPO, Figure 1) being the most representative examples for such uses. However, due to the variety of radical types to be studied with large differences in physical, chemical and biological properties, there is a constant need to design and develop novel nitrones.[6] Further, nitrones have been employed also as therapeutic agents in the treatment of diseases related to oxidative stress such as neurodegeneration,[7,8] ischemic stroke,[9,10] cardiovascular diseases,[11] and cancer.[12-15] In addition, nitrones are valuable intermediates in organic synthesis affording efficiently various types of useful heterocyclic, as well as acyclic molecules.[16] On the other hand, it is well recognized that introduction of fluorine in organic molecules can be used for a fine tuning of their physical, chemical and biological properties.[17] Relatively few fluorinated nitrones have been described to date, mostly with fluorine atoms on the phenyl group of PNB,[18] or with CF_3 or CHF_2 groups on the nitrone.[19] In the case of fluorinated nitrones, ^{19}F NMR could be also a very useful tool for monitoring biophysical and biochemical studies.[20] Therefore, the goal of this paper is to describe short and efficient syntheses of new nitrones bearing *gem*-difluoroalkyl side chains in γ-position. More precisely, we will first develop our strategy for the preparation of type ***A*** model nitrones (Figure 1). Then, we will extend it to molecules ***B*** with functional groups in terminal position of the alkyl chains. Such groups (ester, azide, alcohol, tosylate, and protected alcohol) could be of much use to adjust the physicochemical and biological properties of these nitrones. Further, these groups could be also employed to graft easily various types of labels eventually required for in depth *in vivo* biological studies. Finally, starting from the same intermediates, we will report the preparation of the bicyclic analogues ***C***. All these new nitrones will be prepared in short sequences (2-3 steps) from the easily available type-***D*** *gem*-difluoroalkyl propargylic alcohols.[21]

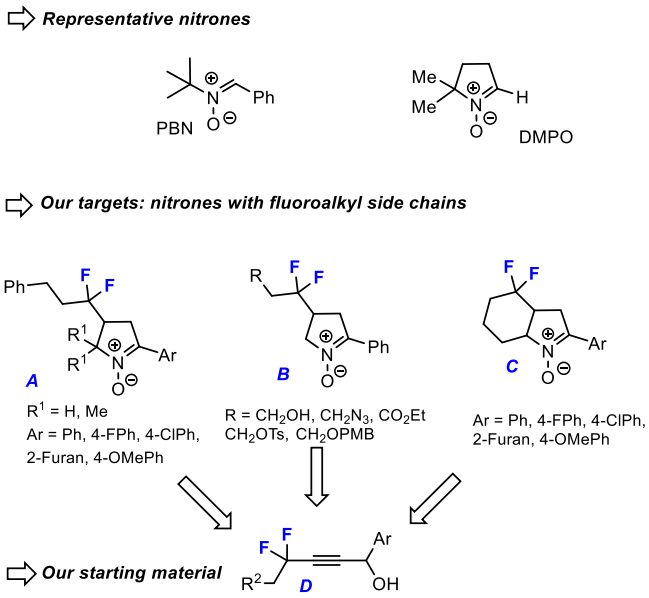

Figure 1. Our Target molecules starting from *gem*-difluorinated propargylic alcohols **D**.

Results and Discussion

In order to prepare the first series of representative nitrones, we started from the known [21, 22] *gem*-difluoro propargylic derivative **1**. After reaction with *n*-BuLi at -90 °C, followed by addition of different aldehydes **2a-e**, the *gem*-difluorinated alcohols **3a-e** were obtained (Scheme 1, Table 1). The reactions with nitromethane, or 2-nitropropane, in the presence of DBU afforded in fair to good yields the nitro intermediates **4a-e** and **5a-e** respectively. In agreement with previous results, the first step of this domino process is likely the base-mediated isomerization of the propargylic alcohols into the corresponding (non-isolated) enones **3'a-e** which are trapped *in situ* by the nitroalkane anions to give the desired molecules **4** or **5**. [22]

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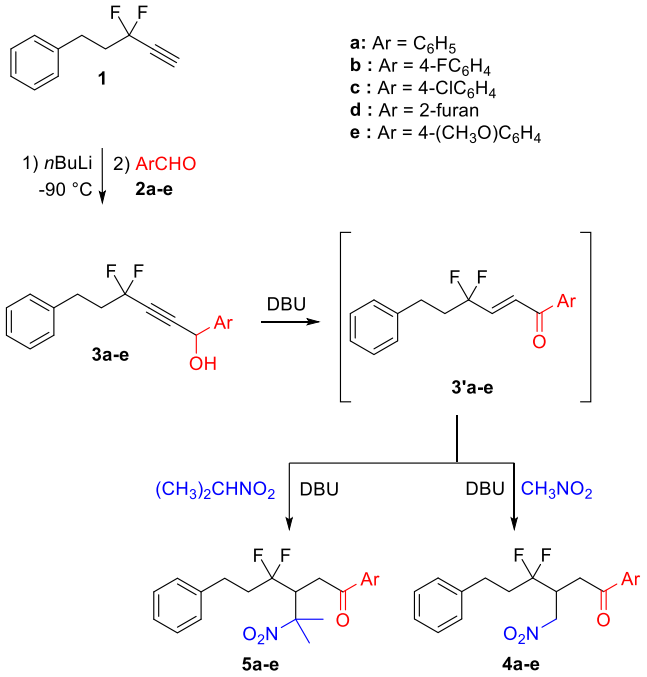


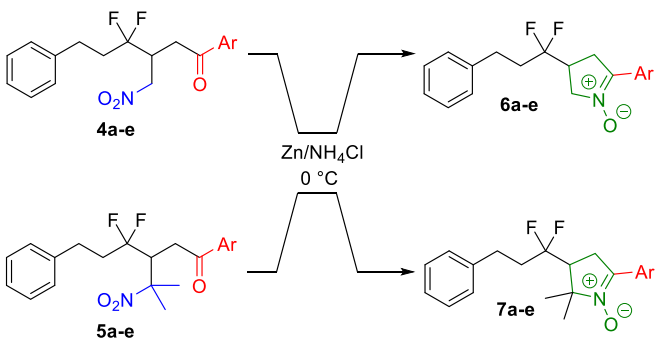
Scheme 1. The synthesis of nitro intermediates **4a-e** and **5a-e**

Table 1. The synthesis of nitro intermediates **4a-e** and **5a-e**

			Yield (%)[a]		
Entry	SM	Ar	3	4	5
1	**2a**	Ph	**3a**: 73 [b]	**4a** : 72	**5a** : 69
2	**2b**	4-FC_6H_4	**3b** : 81	**4b** : 74	**5b** : 69
3	**2c**	4-ClC_6H_4	**3c** : 60	**4c** : 69	**5c** : 73
4	**2d**	2-furan	**3d** : 64	**4d** : 71	**5d** : 72
5	**2e**	4-$(CH_3O)C_6H_4$	**3e** : 67	**4e** : 76	**5e** : 60

[a] Isolated yields; [b] Reported previously. [23]

Several attempts were done to reduce the nitro group in **4a** using $Pd(OH)_2$ and H_2 gas to afford the nitrone **6a** but unfortunately the yield was very low (15%). Similarly, $NiCl_2.6H_2O$ in the presence of $NaBH_4$ gave a poor yield (30%), and even lower yield (10%) was obtained by using ammonium formate in the presence of Pd/C at 60°C. However, upon using Zn powder in the presence of NH_4Cl in water and THF at 0°C, the nitrones **6a-e** and **7a-e** were successfully prepared, as shown in Scheme 2 and Table 2.



Scheme 2. Synthesis of the nitrones **6a-e** and **7a-e**

Table 2. Synthesis of the nitrones **6a-e** and **7a-e**

		Yield (%)[a]		Yield (%)[a]
Entry	SM	6	SM	7
1	**4a**	**6a** : 65	**5a**	**7a** : 90
2	**4b**	**6b** : 61	**5b**	**7b** : 55
3	**4c**	**6c** : 71	**5c**	**7c** : 54
4	**4d**	**6d** : 73	**5d**	**7d** : 70
5	**4e**	**6e** : 69	**5e**	**7e** : 85

[a] Isolated yields

All these derivatives have spectral and analytical data in agreement with the proposed structures (See experimental section and SI). In addition, the structure of the nitrone **6e** was confirmed by X-Ray analysis (Figure 2). [24]

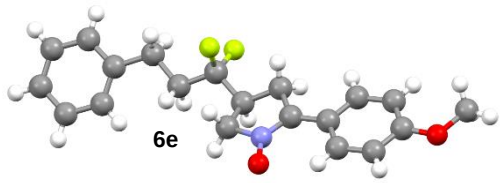
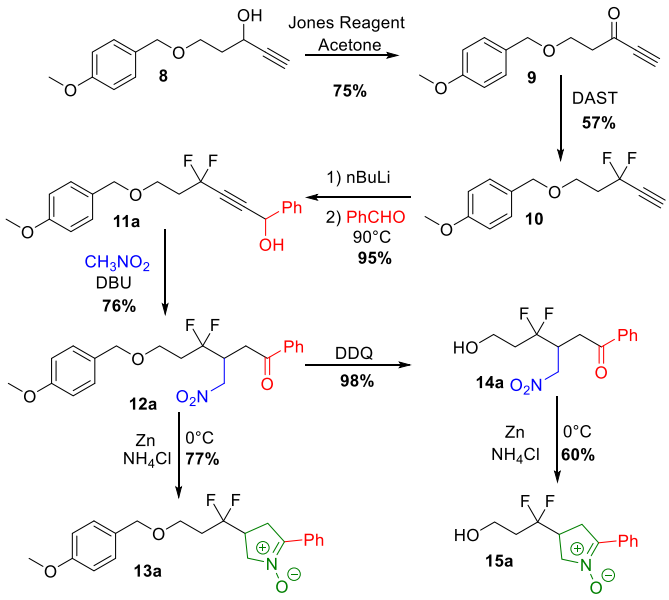


Figure 2. X-Ray structure analysis of **6e**.

Then, to expand the methodology to compounds having a functional group on the terminal position of the side chain, we started from the known [25] ynol **8** (Scheme 3). After oxidation with Jones reagent at 0°C the ynone **9** was obtained in 75% yield and it was reacted with Diethylaminosulfurtrifluoride (DAST) to give the *gem*-difluoro propargylic intermediate **10** in 57% yield. The same sequence of reactions as before allowed us to prepare the alcohol **11a** in 95% yield, the nitromethane adduct **12a** with 76% yield and finally the nitrone **13a** in 77% yield**.** On the other hand, the deprotection of **12a** afforded the alcohol **14a** in excellent yield, and the final reduction gave in 60% yield the nitrone **15a** with a free primary alcohol group (Scheme 3).



Scheme 3. Synthesis of the nitrones **13a** and **15a**.

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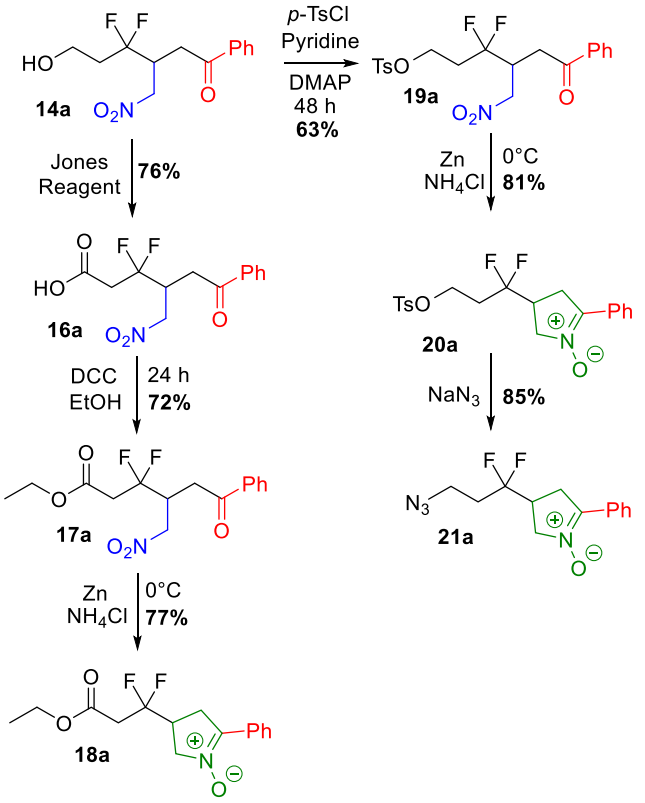
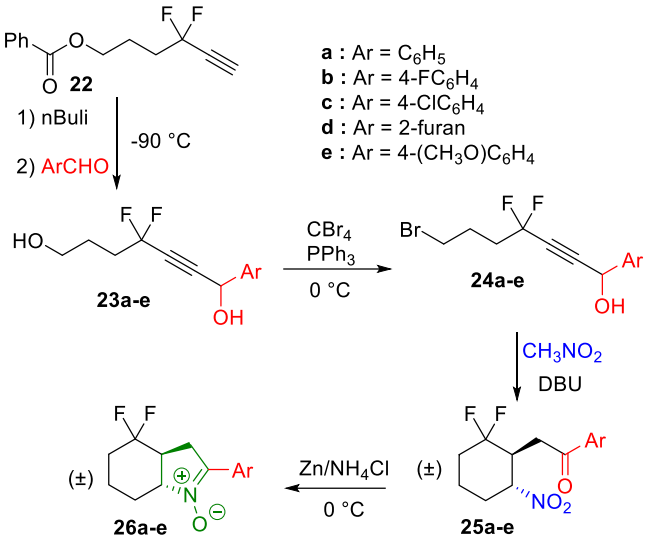


Scheme 4. Synthesis of the nitrones, **18a**, **20a**, and **21a.**

To complete this strategy and extend the range of functional groups in the terminal position of the side chain, alcohol **14a** was first transformed into the acid **16a** by Jones reagent. After Steglich esterification of this acid, the ester **17a** was obtained and the reduction of the nitro group under the same conditions as above gave the nitrone with a terminal ester group **18a**, in 42% overall yield from **14a**. On the other hand, the tosylation of the alcohol **14a** afforded compound **19a** which was readily reduced to the nitrone with a tosylate group **20a** in 51% overall yield from **14a**. Then displacing this tosylate group with sodium azide afforded the nitrone with a terminal azide **21a** in 85% yield (Scheme 4). These new nitrones, with different functional groups in the terminal position of the side chain, offer many potentialities for further applications in chemistry and in studies of biological problems.

In order to expand the strategy to fused bicyclic nitrones, we started from the known,[22] *gem*-difluorinated propargylic compound **22**. After reaction with *n*-BuLi and different aromatic aldehydes, the propargylic alcohols **23a-e** were obtained in good yields (Table 3). Substitution of the terminal primary alcohol by bromine gave the derivatives **24a-e** in fair to good yields. Then, reaction with nitromethane in the presence of DBU gave directly the cyclohexyl derivatives **25a-e**, as single diastereoisomers (control of the crude reaction mixture using ^{19}F NMR). Based on our previous studies,[22,26] in this cascade process, three steps are likely to occur sequentially: isomerization of the propargylic alcohol to the enone then nucleophilic substitution of the bromine by the nitromethane anion, and finally intramolecular Michael addition of the nitro anion onto this enone to give **25a-e** as *trans* isomers (Scheme 5).



Scheme 5. Synthesis of the bicyclic nitrones **26a-e**

Table 3. Synthesis of the bicyclic nitrones **26a-e**

			Yield (%)[a]			
Entry	SM	Ar	**23**	**24**	**25**	**26**
1	**22a**	Ph	72[a]	72[a]	76	56
2	**22b**	4-FC$_6$H$_4$	70	88	66	70
3	**22c**	4-ClC$_6$H$_4$	86	61	70	60
4	**22d**	2-furan	90	51	52	80
5	**22e**	4-(CH$_3$O)C$_6$H$_4$	95	77	49	75

[a] Isolated yields; [b] Reported previously [22]

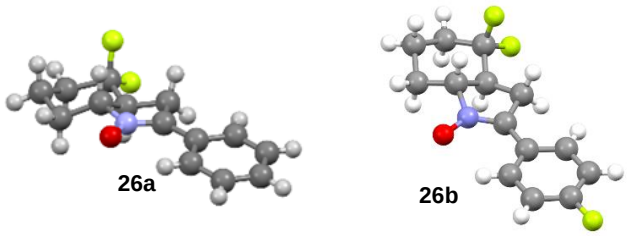


Figure 3. X-Ray structure analysis of **26a** and **26b**.

In a last step, the desired bicyclic nitrones were obtained using the same reduction procedure as above to give compounds **26a-e** in good yields (Table 3). The structure of **26a** and **26b**, including the *trans* ring junction, were unambiguously established using X-Ray crystallography (Figure 3).[24]

Conclusion

Novel mono- and bicyclic nitrones with a CF_2R group in γ position have been efficiently prepared from *gem*-difluoro propargylic alcohols. Biological properties of these new nitrones are under active study and corresponding results will be reported in due course.

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Experimental Section

General informations: see ref. 22

General procedure 1 for the synthesis of *gem*-difluoropropargylic alcohols 3

To a solution of *n*-butyllithium 2.5 M (1.44 mL, 3.61 mmol) in anhydrous THF (25 mL) cooled to -90°C, was added under nitrogen, a solution of **1** (500 mg, 2.77 mmol). The mixture was stirred for 30 min at -90°C. Then, aldehyde **2** (1.3 equiv) in anhydrous THF (10 mL) was added at - 90°C, stirred for 45 min, then the reaction mixture was allowed to warm to r.t. within 2h. The mixture was then treated with a saturated ammonium chloride solution and extracted with ethyl acetate (3x40 mL). The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. After purification by chromatography on silica gel, the propargylic alcohols **3** were obtained.

4,4-difluoro-1-(4-fluorophenyl)-6-phenylhex-2-yn-1-ol 3b

Pale yellow oil, yield 684 mg (81%). R_f = 0.5 (hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 2H), 7.32 – 7.10 (m, 5H), 7.09 – 6.97 (m, 2H), 5.44 (t, $^3J_{H-H}$ = 3.9 Hz, 1H), 2.90 – 2.76 (m, 2H), 2.45 – 2.24 (m, 2H), 2.32 – 2.10 (bs, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C-F}$ = 247.9 Hz), 139.8, 134.9, 128.7, 128.6 (d, $^3J_{C-F}$ = 8.4 Hz), 128.5, 126.6, 115.9 (d, $^2J_{C-F}$ = 21.8 Hz), 114.2 (t, $^1J_{C-F}$ = 233.6 Hz), 86.8 (t, $^3J_{C-F}$ = 6.7 Hz), 79.6 (t, $^2J_{C-F}$ = 41.0 Hz), 63.6, 41.0 (t, $^2J_{C-F}$ = 26.2 Hz), 29.1 (t, $^3J_{C-F}$ = 4.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.75 (s), -112.77 (s). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{18}H_{15}OF_3Na$) = 327.0967; found: 327.0970 (1 ppm).

1-(4-chlorophenyl)-4,4-difluoro-6-phenylhex-2-yn-1-ol 3c

Yellow oil, yield 534 mg (60%). R_f = 0.2 (hexane / Ethyl Acetate: 9/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 4H), 7.35 – 7.27 (m, 2H), 7.26 – 7.16 (m, 3H), 5.49 (bs, 1H), 2.94 – 2.83 (m, 2H), 2.49 – 2.31 (m, 2H), 2.27 (bs, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 137.5, 135.0, 129.2, 128.8, 128.5, 128.1, 126.6, 114.2 (t, $^1J_{C-F}$ = 233.7 Hz), 86.6 (t, $^3J_{C-F}$ = 6.7 Hz), 79.7 (t, $^2J_{C-F}$ = 41.0 Hz), 63.6, 40.9 (t, $^2J_{C-F}$ = 26.1 Hz), 29.1 (t, $^3J_{C-F}$ = 4.0 Hz). ^{19}F {H} NMR {H} (282 MHz, $CDCl_3$) δ -83.81 (s). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{18}H_{15}OF_2{}^{35}ClNa$) = 343.0671; 343.0672 (0 ppm).

4,4-difluoro-1-(furan-2-yl)-6-phenylhex-2-yn-1-ol 3d

Black oil, yield 490 mg (64%). R_f = 0.3 (hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, $^3J_{H-H}$ = 1.9, $^3J_{H-H}$ = 0.8 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 6.44 (dd, $^3J_{H-H}$ = 3.3 Hz, $^3J_{H-H}$ = 0.8 Hz, 1H), 6.35 (dd, $^3J_{H-H}$ = 3.3 Hz, $^3J_{H-H}$ = 1.9 Hz, 1H), 5.49 (t, $^5J_{H-F}$ = 3.9 Hz, 1H), 2.92 – 2.81 (m, 2H), 2.68 (bs, 1H, OH), 2.46 – 2.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 143.6, 139.9, 128.7, 128.5, 126.5, 114.2 (t, $^1J_{C-F}$ = 233.7 Hz), 110.7, 108.6, 84.7 (t, $^3J_{C-F}$ = 6.8 Hz), 78.6 (t, $^2J_{C-F}$ = 41.1 Hz), 57.9 (t, $^4J_{C-F}$ = 1.8 Hz), 41.0 (t, $^2J_{C-F}$ = 26.0 Hz), 29.1 (t, $^3J_{C-F}$ = 4.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -84.02 (s). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{16}H_{14}O_2F_2Na$) = 299.0854; found: 299.0857 (1 ppm).

4,4-difluoro-1-(4-methoxyphenyl)-6-phenylhex-2-yn-1-ol 3e

Pale yellow oil, yield 588 mg (67%). R_f = 0.2 (Petroleum Ether / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.96 – 6.89 (m, 2H), 5.47 (t, $^5J_{H-F}$ = 3.9 Hz, 1H), 3.82 (s, 3H), 2.92 – 2.85 (m, 2H), 2.48 – 2.31 (m, 2H), 2.28 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 139.9, 131.4 (t, $^5J_{C-F}$ = 1.6 Hz), 128.7, 128.5, 128.2, 126.5, 114.3, 114.2 (t, $^1J_{C-F}$ = 233.4 Hz), 87.3 (t, $^3J_{C-F}$ = 6.8 Hz), 79.2 (t, $^2J_{C-F}$ = 40.9 Hz), 63.9 (t, $^4J_{C-F}$ = 2.0 Hz), 55.5, 41.0 (t, $^2J_{C-F}$ = 26.2 Hz), 29.1 (t, $^3J_{C-F}$ = 4.0 Hz). ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -83.61 (s). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{18}O_2F_2Na$) = 339.1167; found: 339.1169 (1 ppm).

General procedure 2 for the synthesis of *gem*-difluoronitro-ketones 4 and 5

Representative procedure: Synthesis of 4,4-difluoro-3-(nitromethyl)-1,6-diphenylhexan-1-one 4a

To the difluoropropargylic alcohol **3a** (150 mg, 0.52 mmol) was added nitromethane (56 µL, 1.04 mmol) and DBU (310 µl, 2.10 mmol) in THF (3 ml). The reaction mixture was stirred at room temperature overnight. At the end saturated NH_4Cl (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3x20 mL). The organic layers were separated, washed with water (1x10 mL), dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, **4a** (131 mg, 72%) was obtained as white solid. R_f = 0.2 (hexane / Ethyl Acetate: 9/1). mp = 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 2H), 7.67 – 7.57 (m, 1H), 7.54 – 7.44 (m, 2H), 7.34 – 7.15 (m, 5H), 4.74 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 6.1 Hz, 1H), 4.52 (dd, $^2J_{H-H}$ = 13.6 Hz, $^2J_{H-H}$ = 5.5 Hz, 1H), 3.83 – 3.62 (m, 1H), 3.41 (dd, $^2J_{H-H}$ = 18.5 Hz, $^2J_{H-H}$ = 4.6 Hz, 1H), 3.24 (dd, $^2J_{H-H}$ = 18.5 Hz, $^2J_{H-H}$ = 8.1 Hz, 1H), 2.94 – 2.82 (m, 2H), 2.33 – 2.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 140.0, 136.1, 134.0, 129.0, 128.8, 128.4, 128.3, 126.6, 124.1 (t, $^1J_{C-F}$ = 245.7 Hz), 73.9 (t, $^3J_{C-F}$ = 4.8 Hz), 39.3 (t, $^2J_{C-F}$ = 24.5 Hz), 37.0 (t, $^2J_{C-F}$ = 24.6 Hz), 35.4 (t, $^3J_{C-F}$ = 3.6 Hz), 28.0 (t, $^3J_{C-F}$ = 5.1 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.95 (AB system, $^2J_{F-F}$ = 248.9 Hz), -104.05 (AB system, $^2J_{F-F}$ = 248.9 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{19}NO_3F_2Na$) = 370.1225; found: 370.1230 (1 ppm).

4,4-difluoro-1-(4-fluorophenyl)-3-(nitromethyl)-6-phenylhexan-1-one 4b

Yellow solid, yield 133 mg (74%) from 150 mg (0.49 mmol) of **3b**. R_f = 0.4 (hexane / Ethyl Acetate: 9/1). mp = 129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 – 7.98 (m, 2H), 7.48 – 7.08 (m, 7H), 4.80 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.9 Hz, 1H), 4.58 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.6 Hz, 1H), 3.87 – 3.63 (m, 1H), 3.45 (dd, $^2J_{H-H}$ = 18.5 Hz, $^3J_{H-H}$ = 4.6 Hz, 1H), 3.29 (dd, $^2J_{H-H}$ =18.4 Hz, $^3J_{H-H}$ = 8.0 Hz, 1H), 3.09 – 2.81 (m, 2H), 2.39 – 2.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 166.3 (d, $^1J_{C-F}$ = 256.3 Hz), 139.9, 132.5 (d, $^4J_{C-F}$ = 3.0 Hz), 131.0 (d, $^3J_{C-F}$ = 9.5 Hz), 128.8, 128.4, 124.0 (t, $^1J_{C-F}$ = 245.8 Hz), 116.2 (d, $^2J_{C-F}$ = 22.1 Hz), 73.8 (t, $^3J_{C-F}$ = 4.9 Hz), 39.3 (t, $^2J_{C-F}$ = 24.5 Hz), 36.9 (t, $^2J_{C-F}$ = 24.6 Hz), 35.2 (t, $^3J_{C-F}$ = 3.7 Hz), 28.0 (t, $^3J_{C-F}$ = 5.1 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -103.00 (**A**B system, $^2J_{F-F}$ = 248.8 Hz), -103.52 (s), -139.95 (A**B** system, $^2J_{F-F}$ = 248.8 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{18}NO_3F_3Na$) = 388.1131; found: 388.1131 (0 ppm).

1-(4-chlorophenyl)-4,4-difluoro-3-(nitromethyl)-6-phenylhexan-1-one 4c

White solid, yield 123 mg (69%) from 150 mg (0.47 mmol) of **3c**. R_f = 0.3 (hexane / Ethyl Acetate: 9/1). mp = 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H), 7.52 – 7.42 (m, 2H), 7.34 – 7.12 (m, 5H), 4.73 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.9 Hz, 1H), 4.51 (dd, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 5.6 Hz, 1H), 3.79 – 3.54 (m, 1H), 3.37 (dd, $^2J_{H-H}$ = 18.5 Hz, $^3J_{H-H}$ = 4.6 Hz, 1H), 3.22 (dd, $^2J_{H-H}$ = 18.5 Hz, $^3J_{H-H}$ = 8.0 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.33 – 2.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 140.6, 139.9, 134.4, 129.7, 129.3, 128.8, 126.6, 124.0 (t, $^1J_{C-F}$ = 245.7 Hz), 73.8 (t, $^3J_{C-F}$ = 4.9 Hz), 39.3 (t, $^2J_{C-F}$ = 24.5 Hz), 36.9 (t, $^2J_{C-F}$ = 24.7 Hz), 35.3 (t, $^3J_{C-F}$ = 3.6 Hz), 28.0 (dd, $^3J_{C-F}$ = 5.8 Hz, $^3J_{C-F}$ = 5.0 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -103.0 (**A**B system, $^2J_{F-F}$ = 249.2 Hz), -103.6 (**A**B system, $^2J_{F-F}$ = 249.2 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{18}NO_3F_2{}^{35}ClNa$) = 404.0835; found: 404.0832 (1 ppm).

4,4-difluoro-1-(furan-2-yl)-3-(nitromethyl)-6-phenylhexan-1-one 4d

Black solid, yield 130 mg (71%) from 150 mg (0.54 mmol) of **3d**. R_f = 0.4 (hexane / Ethyl Acetate: 8/2). mp = 79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, $^3J_{H-H}$ = 1.7 Hz, $^4J_{H-H}$ = 0.8 Hz, 1H), 7.46 – 7.15 (m, 6H), 6.65 (dd, $^3J_{H-H}$ = 3.6 Hz, $^3J_{H-H}$ = 1.7 Hz, 1H), 4.80 (dd, $^2J_{H-H}$ = 13.7 Hz, $^3J_{H-H}$ = 6.1 Hz, 1H), 4.59 (dd, $^2J_{H-H}$ = 13.7 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H), 3.90 – 3.59 (m, 1H),

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3.35 (dd, $^2J_{H-H}$ = 18.1 Hz, $^3J_{H-H}$ = 4.9 Hz, 1H), 3.16 (dd, $^2J_{H-H}$ = 18.1 Hz, $^3J_{H-H}$ = 7.9 Hz, 1H), 3.00 – 2.75 (m, 2H), 2.46 – 2.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 152.1, 147.1, 140.0, 128.8, 128.4, 126.5, 124.0 (t, $^1J_{C-F}$ = 245.8 Hz), 118.0, 112.8, 73.7 (t, $^3J_{C-F}$ = 4.9 Hz), 39.0 (t, $^2J_{C-F}$ = 24.6 Hz), 36.8 (t, $^2J_{C-F}$ = 24.6 Hz), 35.1 (t, $^3J_{C-F}$ = 3.8 Hz), 27.9 (t, $^3J_{C-F}$ = 5.1 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.94 (**A**B system, $^2J_{F-F}$ = 248.6 Hz), -104.39 (A**B** system, $^2J_{F-F}$ = 248.6 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{17}H_{17}NO_4F_2Na$) = 360.1018; found: 360.1019 (0 ppm).

4,4-difluoro-1-(4-methoxyphenyl)-3-(nitromethyl)-6-phenylhexan-1-one 4e

White solid, yield 130 mg (76%) from 150 mg (0.47 mmol) of **3e**. R_f = 0.5 (Petroleum Ether / Ethyl Acetate: 8/2). mp = 107 ˚C.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.87 (m, 2H), 7.42 – 7.10 (m, 5H), 7.01 – 6.91 (m, 2H), 4.73 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 6.2 Hz, 1H), 4.52 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.3 Hz, 1H), 3.88 (s, 3H), 3.80 – 3.62 (m, 1H), 3.35 (dd, $^2J_{H-H}$ = 18.3 Hz, $^3J_{H-H}$ = 4.5 Hz, 1H), 3.18 (dd, $^2J_{H-H}$ = 18.3 Hz, $^3J_{H-H}$ = 8.2 Hz, 1H), 2.94 – 2.81 (m, 2H), 2.32 – 2.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 164.2, 140.0, 130.6, 129.1, 128.8, 128.4, 126.5, 124.2 (t, $^1J_{C-F}$ = 245.7 Hz), 114.1, 73.9 (t, $^3J_{C-F}$ = 4.8 Hz), 55.7, 39.4 (t, $^2J_{C-F}$ = 24.3 Hz), 36.9 (t, $^2J_{C-F}$ = 24.6 Hz), 34.9 (dd, $^3J_{C-F}$ = 4.1, $^3J_{C-F}$ = 3.1 Hz), 28.0 (t, $^3J_{C-F}$ = 5.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.83 (**A**B system, $^2J_{F-F}$ = 248.6 Hz), -104.10 (A**B** system, $^2J_{F-F}$ = 248.6 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{20}H_{21}NO_4F_2Na$) = 400.1331; found: 400.1333 (0 ppm).

4,4-difluoro-3-(2-nitropropan-2-yl)-1,6-diphenylhexan-1-one 5a

Yellow solid, yield 136 mg (69%) from 150 mg (0.47 mmol) of **3a**. R_f = 0.3 (hexane / Ethyl Acetate: 9/1). mp = 71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.94 (m, 2H), 7.68 – 7.59 (m, 1H), 7.58 – 7.42 (m, 2H), 7.32 – 7.07 (m, 5H), 4.40 (ddt, $^3J_{H-F}$ = 25.6 Hz, $^3J_{H-F}$ = 4.7 Hz, $^3J_{H-H}$ = 4.7 Hz, 1H), 3.24 (dd, $^1J_{H-H}$ = 19.3 Hz, $^3J_{H-H}$ = 4.4 Hz, 1H), 3.09 (dd, $^1J_{H-H}$ = 19.2 Hz, $^3J_{H-H}$ = 5.2 Hz, 1H), 2.99 – 2.70 (m, 2H), 2.21 – 1.96 (m, 2H), 1.78 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 140.2, 135.9, 134.0, 129.0, 128.6, 128.4, 128.3, 126.3, 125.3 (t, $^1J_{C-F}$ = 247.8 Hz), 89.2 (d, $^3J_{C-F}$ = 1.8 Hz), 45.0 (t, $^2J_{C-F}$ = 21.6 Hz), 38.6 (t, $^2J_{C-F}$ = 24.9 Hz), 35.8 (t, $^3J_{C-F}$ = 4.5 Hz), 28.0 (dd, $^3J_{C-F}$ = 6.3 Hz, $^3J_{C-F}$ = 4.4 Hz), 27.2 (d, $^4J_{C-F}$ = 1.5 Hz), 22.5 (t, $^4J_{C-F}$ = 3.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -100.15 (**A**B system, $^2J_{F-F}$ = 247.3 Hz), -102.16 (A**B** system, $^2J_{F-F}$ = 247.3 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{21}H_{23}NO_3F_2Na$) = 398.1538; found: 398.1534 (1 ppm).

4,4-difluoro-1-(4-fluorophenyl)-3-(2-nitropropan-2-yl)-6-phenylhexan-1-one 5b

Pale yellow solid, yield 134 mg (69%) from 150 mg (0.49 mmol) of **3b**. R_f = 0.4 (hexane / Ethyl Acetate: 9/1). mp = 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.93 (m, 2H), 7.34 – 7.07 (m, 7H), 4.35 (ddt, $^3J_{H-F}$ = 25.3 Hz, $^3J_{H-F}$ = 4.8 Hz, $^3J_{H-H}$ = 4.8, 1H), 3.20 (dd, $^1J_{H-H}$ = 19.2 Hz, $^3J_{H-H}$ = 4.4 Hz, 1H), 3.03 (dd, $^1J_{H-H}$ = 19.2 Hz, $^1J_{H-H}$ = 5.1 Hz, 1H), 2.95 – 2.68 (m, 2H), 2.17 – 1.93 (m, 2H), 1.76 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 166.3 (d, $^1J_{C-F}$ = 256.3 Hz), 140.2, 132.4 (d, $^4J_{C-F}$ = 3.0 Hz), 131.0 (d, $^3J_{C-F}$ = 9.5 Hz), 128.7, 128.4, 126.4, 125.2 (t, $^1J_{C-F}$ = 247.8 Hz), 116.2 (d, $^2J_{C-F}$ = 22.0 Hz), 89.2 (d, $^3J_{C-F}$ = 1.5 Hz), 45.1 (t, $^2J_{C-F}$ = 21.7 Hz), 38.6 (t, $^2J_{C-F}$ = 24.9 Hz), 35.7 (t, $^3J_{C-F}$ = 4.5 Hz), 28.0 (dd, $^3J_{C-F}$ = 6.1 Hz, $^3J_{C-F}$ = 4.6 Hz), 27.0, 23.2, 22.7. ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -100.05 (**A**B system, $^2J_{F-F}$ = 247.5 Hz), -102.15 (A**B** system, $^2J_{F-F}$ = 247.5 Hz), -103.55 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{21}H_{22}NO_3F_3Na$) = 416.1444; found: 416.1443 (0 ppm).

1-(4-chlorophenyl)-4,4-difluoro-3-(2-nitropropan-2-yl)-6-phenylhexan-1-one 5c

Yellow oil, yield 140 mg (73%) from 150 mg (0.47 mmol) of **3c**. R_f = 0.6 (hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H), 7.58 – 7.51 (m, 5H), 7.38 – 7.15 (m, 2H), 4.41 (ddt, $^3J_{H-F}$ = 25.3 Hz, $^3J_{H-F}$ = 4.8 Hz, $^3J_{H-H}$ = 4.8 Hz, 1H), 3.27 (dd, $^2J_{H-H}$ = 19.3 Hz, $^3J_{H-H}$ = 4.4 Hz, 1H), 3.09 (dd, $^2J_{H-H}$ = 19.3 Hz, $^3J_{H-H}$ = 5.1 Hz, 1H), 3.02 – 2.74 (m, 2H), 2.24 – 2.01 (m, 2H), 1.83 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 140.6, 140.2, 134.2, 129.7, 129.4, 128.7, 128.4, 126.4, 125.2 (t, $^1J_{C-F}$ = 248.2 Hz), 89.2 (d, $^3J_{C-F}$ = 1.6 Hz), 45.1 (t, $^2J_{C-F}$ = 21.6 Hz), 38.6 (t, $^2J_{C-F}$ = 24.9 Hz), 35.8 (t, $^3J_{C-F}$ = 4.5 Hz), 28.0 (dd, $^3J_{C-F}$ = 6.2 Hz, $^3J_{C-F}$ = 4.5 Hz), 23.9, 22.8 (t, $^4J_{C-F}$ = 3.0 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -100.0 (**A**B system, $^2J_{F-F}$ = 247.7 Hz), -102.2 (A**B** system, $^2J_{F-F}$ = 247.7 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{21}H_{22}NO_3F_2{}^{35}ClNa$) = 432.1149; found: 432.1150 (0 ppm).

4,4-difluoro-1-(furan-2-yl)-3-(2-nitropropan-2-yl)-6-phenylhexan-1-one 5d

Yellow oil, yield 117 mg (72%) from 150 mg (0.44 mmol) of **3d**. R_f = 0.4 (hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, $^3J_{H-H}$ = 1.7 Hz, $^4J_{H-H}$ = 0.7 Hz, 1H), 7.39 – 7.18 (m, 6H), 6.66 (dd, $^3J_{H-H}$ = 3.6 Hz, $^3J_{H-H}$ = 1.7 Hz, 1H), 4.33 (ddt, $^3J_{H-F}$ = 25.2 Hz, $^3J_{H-F}$ = 4.8 Hz, $^3J_{H-H}$ = 4.8 Hz, 1H), 3.16 (dd, $^2J_{H-H}$ = 19.2 Hz, $^3J_{H-H}$ = 4.5 Hz, 1H), 3.05 (dd, $^2J_{H-H}$ = 19.2 Hz, $^3J_{H-H}$ = 5.2 Hz, 1H), 3.00 – 2.75 (m, 2H), 2.25 – 2.06 (m, 2H), 1.83 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 152.0, 147.0, 140.3, 128.7, 128.5, 126.4, 125.2 (t, $^1J_{C-F}$ = 245.3 Hz), 118.0, 112.9, 89.2 (d, $^3J_{C-F}$ = 1.5 Hz), 44.7 (t, $^2J_{C-F}$ = 21.8 Hz), 38.6 (t, $^2J_{C-F}$ = 24.9 Hz), 35.6 (t, $^3J_{C-F}$ = 4.6 Hz), 28.0 (dd, $^3J_{C-F}$ = 6.1 Hz, $^3J_{C-F}$ = 4.6 Hz), 27.3 (d, $^4J_{C-F}$ = 1.2 Hz), 22.4 (dd, $^4J_{C-F}$ = 2.7, $^3J_{C-F}$ = 0.6 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -100.45 (**A**B system, $^2J_{F-F}$ = 247.3 Hz), -102.24 (A**B** system, $^2J_{F-F}$ = 247.3 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{19}H_{21}NO_4F_2Na$) = 388.1331; found 388.1333 (0 ppm).

4,4-difluoro-1-(4-methoxyphenyl)-3-(2-nitropropan-2-yl)-6-phenylhexan-1-one 5e

Pale yellow solid, yield 115 mg (60%) from 150 mg (0.47 mmol) of **3e**. R_f = 0.5 (Petroleum Ether / Ethyl Acetate: 8/2). mp = 111 ˚C.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.92 (m, 2H), 7.31 – 7.17 (m, 2H), 7.23 – 7.09 (m, 3H), 7.02 – 6.92 (m, 2H), 4.38 (ddt, $^3J_{H-F}$ = 25.7 Hz, $^3J_{H-F}$ = 4.7 Hz, $^3J_{H-H}$ = 4.7 Hz, 1H), 3.89 (s, 3H), 3.16 (dd, $^2J_{H-H}$ = 19.0 Hz, $^3J_{H-H}$ = 4.4 Hz, 1H), 3.01 (dd, $^2J_{H-H}$ = 19.1 Hz, $^3J_{H-H}$ = 5.2 Hz, 1H), 2.98 – 2.67 (m, 2H), 2.20 – 1.94 (m, 2H), 1.76 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 164.2, 140.3, 130.6, 129.0, 128.7, 128.5, 126.3, 125.4 (t, $^1J_{C-F}$ = 247.6 Hz), 114.2, 89.2 (d, $^3J_{C-F}$ = 1.8 Hz), 55.7, 45.0 (t, $^2J_{C-F}$ = 21.5 Hz), 38.6 (t, $^2J_{C-F}$ = 24.9 Hz), 35.4 (dd, $^3J_{C-F}$ = 5.0 Hz, $^3J_{C-F}$ = 3.8 Hz), 28.0 (dd, $^3J_{C-F}$ = 6.3 Hz, $^3J_{C-F}$ = 4.4 Hz), 27.3 (d, $^4J_{C-F}$ = 1.4 Hz), 22.5 (t, $^4J_{C-F}$ = 2.9 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -100.30 (**A**B system, $^2J_{F-F}$ = 247.1 Hz), -101.94 (A**B** system, $^2J_{F-F}$ = 247.1 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{22}H_{25}NO_4F_2Na$) = 428.1644; found: 428.1650 (1 ppm).

General procedure 3 for the synthesis of difluoronitrones 6 and 7

Representative procedure: 3-(1,1-difluoro-3-phenylpropyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 6a

To the difluoronitro-ketone **4a** (75 mg, 0.22 mmol) was added NH_4Cl (35 mg, 0.65 mmol) in THF (2 ml) and water (1 ml) at 0 °C. The reaction mixture was stirred for 5 mn then Zn powder (212 mg, 3.24 mmol) was added over 15 mn and very slowly. The reaction was monitored using TLC each 5 mn. Prolonged reaction times will lead to the total reduction of the nitro groups into amines. At the end the reaction mixture was filtrated on celite, concentrated under vacuum, and purified by chromatography on silica gel, **6a** (44 mg, 65%) was obtained as yellow solid. R_f = 0.3 (hexane / Ethyl Acetate: 6/4). mp = 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 8.18 (m, 2H), 7.49 – 7.39 (m, 3H), 7.37 – 7.27 (m, 2H), 7.27 – 7.13 (m, 3H), 4.36 (dd, $^2J_{H-H}$ = 14.3 Hz, $^3J_{H-H}$ = 7.8 Hz, 1H), 4.25 (dd, $^2J_{H-H}$ = 14.3 Hz, $^3J_{H-H}$ = 9.7 Hz, 1H), 3.25 (d, $^3J_{H-H}$ = 8.1 Hz, 2H), 3.12 – 2.93 (m, 1H), 2.93 – 2.79 (m, 2H), 2.32 – 2.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 139.4, 130.7, 128.8, 128.7, 128.6, 128.3, 127.3, 126.6, 123.3 (t, $^1J_{C-F}$ = 244.0 Hz), 64.2 (dd, $^3J_{C-F}$ = 5.5 Hz, $^3J_{C-F}$ = 3.8 Hz), 37.0 (t, $^2J_{C-F}$ = 24.9 Hz), 36.5 (t, $^2J_{C-F}$ = 26.4 Hz), 31.4 (dd, $^3J_{C-F}$ = 5.6 Hz, $^3J_{C-F}$ = 4.3 Hz), 27.9 (t, $^3J_{C-F}$ =

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4.7 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -106.75 (d, *J* = 246.0 Hz), -107.87 (d, *J* = 246.0 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{19}NOF_2Na$) = 338.1327; found: 338.1330 (1 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(4-fluorophenyl)-3,4-dihydro-2H-pyrrole 1-oxide 6b

Pale yellow solid, yield 42 mg (61%) from 75 mg (0.20 mmol) of **4b**. R_f = 0.1 (hexane / Ethyl Acetate: 6/4). mp = 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 – 8.27 (m, 2H), 7.38 – 7.28 (m, 2H), 7.28 – 7.07 (m, 5H), 4.44 – 4.18 (m, 2H), 3.43 – 3.16 (m, 2H), 3.16 – 2.94 (m, 1H), 2.94 – 2.80 (m, 2H), 2.32 – 2.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (d, $^1J_{C\text{-}F}$ = 252.8 Hz), 140.0, 138.7, 129.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 128.9, 128.4, 126.7, 125.1, 123.3 (t, $^1J_{C\text{-}F}$ = 244.1 Hz), 115.8 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 64.2, 37.2 (t, $^2J_{C\text{-}F}$ = 24.9 Hz), 36.5 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 31.4, 28.0 (t, $^3J_{C\text{-}F}$ = 4.6 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -106.86 (**A**B system, $^2J_{F\text{-}F}$ = 246.1 Hz), -107.32 (s), -108.00 (A**B** system, $^2J_{F\text{-}F}$ = 246.1 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{18}NOF_3Na$) = 356.1233; found: 356.1235 (1 ppm).

5-(4-chlorophenyl)-3-(1,1-difluoro-3-phenylpropyl)-3,4-dihydro-2H-pyrrole 1-oxide 6c

Pale white solid, yield 52 mg (71%) from 75 mg (0.20 mmol) of **4c**. R_f = 0.1 (Petroleum Ether / Ethyl Acetate: 6/4). mp = 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.20 (m, 2H), 7.45 – 7.37 (m, 2H), 7.36 – 7.15 (m, 5H), 4.36 (dd, $^2J_{H\text{-}H}$ = 14.4 Hz, $^3J_{H\text{-}H}$ = 7.8 Hz, 1H), 4.24 (dd, $^2J_{H\text{-}H}$ = 14.4 Hz, $^3J_{H\text{-}H}$ = 9.7 Hz, 1H), 3.24 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H), 3.15 – 2.92 (m, 1H), 2.93 – 2.83 (m, 2H), 2.31 – 2.09 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 138.5, 136.4, 128.9, 128.9, 128.6, 128.4, 127.2, 126.7, 123.3 (t, $^1J_{C\text{-}F}$ = 244.2 Hz), 64.3 (t, $^3J_{C\text{-}F}$ = 4.7 Hz), 37.1 (t, $^2J_{C\text{-}F}$ = 24.9 Hz), 36.5 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 31.3 (t, $^3J_{C\text{-}F}$ = 5.0 Hz), 28.0 (t, $^3J_{C\text{-}F}$ = 4.7 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.84 (**A**B system, $^2J_{F\text{-}F}$ = 246.3 Hz), -107.86 (A**B** system, $^2J_{F\text{-}F}$ = 246.2 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{18}NOF_3ClNa$) = 372.0937; found: 372.0939 (0 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(furan-2-yl)-3,4-dihydro-2H-pyrrole 1-oxide 6d

Yellow oil, yield 50 mg (73%) from 75 mg (0.22 mmol) of **4d**. R_f = 0.2 (hexane / Ethyl Acetate: 2/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $^3J_{H\text{-}H}$ = 3.2 Hz, 1H), 7.49 (d, $^3J_{H\text{-}H}$ = 1.1 Hz, 1H), 7.39 – 7.13 (m, 5H), 6.58 (dd, $^3J_{H\text{-}H}$ = 3.4 Hz, $^4J_{H\text{-}H}$ = 1.8 Hz, 1H), 4.36 – 4.06 (m, 2H), 3.38 – 3.14 (m, 2H), 3.15 – 2.92 (m, 1H), 2.92 – 2.77 (m, 2H), 2.33 – 2.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 143.9, 140.0, 133.5, 128.8, 128.4, 126.6, 123.3 (t, $^1J_{C\text{-}F}$ = 244.1 Hz), 115.0, 112.6, 62.3 (dd, $^3J_{C\text{-}F}$ = 5.3 Hz, $^3J_{C\text{-}F}$ = 4.0 Hz), 37.6 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 37.0 (t, $^2J_{C\text{-}F}$ = 24.9 Hz), 29.3 (t, $^3J_{C\text{-}F}$ = 5.0 Hz), 28.0 (t, $^3J_{C\text{-}F}$ = 4.7 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -106.02 (**A**B system, $^2J_{F\text{-}F}$ = 246.1 Hz), -108.38 (A**B** system, $^2J_{F\text{-}F}$ = 246.1 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{17}H_{17}NO_2F_2Na$) = 328.1120; found: 328.1121 (0 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrole 1-oxide 6e

Pale yellow solid, yield 55 mg (80%) from 75 mg (0.20 mmol) of **4e**. R_f = 0.4 (Petroleum Ether / Ethyl Acetate: 6/4). mp = 126 ˚C.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 8.25 (m, 2H), 7.38 – 7.25 (m, 2H), 7.29 – 7.15 (m, 3H), 6.98 – 6.91 (m, 2H), 4.39 – 4.15 (m, 2H), 3.84 (s, 3H), 3.26 – 3.19 (m, 2H), 3.12 – 2.93 (m, 1H), 2.91 – 2.84 (m, 2H), 2.30 – 2.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 140.0, 139.3, 129.3, 128.8, 128.4, 126.6, 123.4 (t, $^1J_{C\text{-}F}$ = 245.2 Hz) , 121.6, 113.9, 63.7 (t, $^3J_{C\text{-}F}$ = 4.7 Hz), 55.4, 37.1 (t, $^2J_{C\text{-}F}$ = 24.9 Hz), 36.5 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 31.4 (t, $^3J_{C\text{-}F}$ = 5.0 Hz), 28.0 (t, $^3J_{C\text{-}F}$ = 4.7 Hz). ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -106.9 (**A**B system, $^2J_{F\text{-}F}$ = 246.0 Hz), -107.7 (A**B** system, $^2J_{F\text{-}F}$ = 246.0 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{20}H_{21}NO_2F_2Na$) = 368.1433; found: 368.1435 (1 ppm).

3-(1,1-difluoro-3-phenylpropyl)-2,2-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 7a

White solid, yield 62 mg (90%) from 75 mg (0.20 mmol) of **5a**. R_f = 0.4 (hexane / Ethyl Acetate: 6/4). mp =110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 – 8.26 (m, 2H), 7.53 – 7.40 (m, 3H), 7.37 – 7.16 (m, 5H), 3.23 – 3.00 (m, 2H), 3.00 – 2.84 (m, 2H), 2.85 – 2.59 (m, 1H), 2.41 – 2.07 (m, 2H), 1.65 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 136.0, 130.5, 129.4, 128.9, 128.7, 128.5, 127.4, 126.7, 123.7 (t, $^1J_{C\text{-}F}$ = 245.2 Hz), 77.0, 48.5 (t, $^2J_{C\text{-}F}$ = 24.1 Hz), 38.9 (t, $^2J_{C\text{-}F}$ = 25.1 Hz) , 28.5 (dd, $^3J_{C\text{-}F}$ = 7.0 Hz, $^3J_{C\text{-}F}$ = 4.0 Hz), 28.1 (t, $^3J_{C\text{-}F}$ = 5.0 Hz), 27.3 (d, $^4J_{C\text{-}F}$ = 1.2 Hz), 21.0 (t, $^3J_{C\text{-}F}$ = 3.3 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.75 (**A**B system, $^2J_{F\text{-}F}$ = 247.0 Hz), -104.91 (A**B** system, $^2J_{F\text{-}F}$ = 247.0 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{21}H_{23}NOF_2Na$) = 366.1640; found: 366.1644 (1 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(4-fluorophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide 7b

White solid, yield 38 mg (55%) from 75 mg (0.19 mmol) of **5b**. R_f = 0.2 (hexane / Ethyl Acetate: 6/4). mp =119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 – 8.29 (m, 2H), 7.39 – 7.27 (m, 2H), 7.30 – 7.18 (m, 3H), 7.19 – 7.04 (m, 2H), 3.17 – 2.98 (m, 2H), 2.99 – 2.83 (m, 2H), 2.73 (m, 1H), 2.38 – 2.12 (m, 2H), 1.64 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C\text{-}F}$ = 252.7 Hz), 140.2, 135.1, 129.7 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 128.9, 128.4, 126.7, 125.8 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 123.6 (t, $^1J_{C\text{-}F}$ = 245.1 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 76.9, 48.4 (t, $^2J_{C\text{-}F}$ = 24.2 Hz), 38.9 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 28.5 (dd, $^3J_{C\text{-}F}$ = 7.2, $^3J_{C\text{-}F}$ = 4.0 Hz), 28.0 (t, $^3J_{C\text{-}F}$ = 5.0 Hz), 27.3, 21.0 (t, $^4J_{C\text{-}F}$ = 3.6 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.61 (**A**B system, $^2J_{F\text{-}F}$ = 247.3 Hz), -104.92 (A**B** system, $^2J_{F\text{-}F}$ = 247.3 Hz), -108.05 (s). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{21}H_{22}NOF_3Na$) = 384.1545; found: 384.1543 (1 ppm).

5-(4-chlorophenyl)-3-(1,1-difluoro-3-phenylpropyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide 7c

Yellow oil, yield 37 mg (54%) from 75 mg (0.18 mmol) of **5c**. R_f = 0.2 (hexane / Ethyl Acetate: 6/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.27 (m, 2H), 7.43 – 7.39 (m, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.20 (m, 3H), 3.17 – 3.00 (m, 2H), 2.95 – 2.84 (m, 2H), 2.82 – 2.64 (m, 1H), 2.33 – 2.14 (m, 2H), 1.64 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 136.0, 135.4, 128.9, 128.7, 128.4, 128.4, 127.8, 126.7, 123.6 (t, $^1J_{F\text{-}F}$ = 245.3 Hz), 78.8, 48.4 (t, $^2J_{F\text{-}F}$ = 24.2 Hz), 38.9 (t, $^2J_{F\text{-}F}$ = 25.1 Hz), 28.4 (dd, $^3J_{F\text{-}F}$ = 7.1 Hz, $^3J_{F\text{-}F}$ = 4.0 Hz), 28.0 (dd, $^3J_{F\text{-}F}$ = 5.0 Hz, $^3J_{F\text{-}F}$ = 0.1 Hz), 27.2 (d, $^4J_{F\text{-}F}$ = 1.6 Hz), 21.0 (dd, $^3J_{F\text{-}F}$ = 4.2 Hz, $^3J_{F\text{-}F}$ = 3.1 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -102.68 (**A**B system, $^2J_{F\text{-}F}$ = 247.3 Hz), -104.95 (A**B** system, $^2J_{F\text{-}F}$ = 247.3 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{21}H_{22}NOF_2{}^{35}ClNa$) = 400.1250; found: 400.1255 (1 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(furan-2-yl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide 7d

Yellow oil, yield 48 mg (70%) from 75 mg (0.21 mmol) of **5d**. R_f = 0.3 (hexane / Ethyl Acetate: 2/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $^3J_{H\text{-}H}$ = 3.5 Hz, 1H), 7.48 (dd, $^3J_{H\text{-}H}$ = 1.8, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.27 – 7.18 (m, 3H), 6.58 (dd, $^3J_{H\text{-}H}$ = 3.5 Hz, $^3J_{H\text{-}H}$ = 1.8 Hz, 1H), 3.20 – 2.98 (m, 2H), 2.95 – 2.84 (m, 2H), 2.84 – 2.61 (m, 1H), 2.38 – 2.07 (m, 2H), 1.61 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 143.5, 140.1, 130.0, 128.8, 128.4, 126.6, 123.6 (dd, $^1J_{C\text{-}F}$ = 246.0 Hz, $^1J_{C\text{-}F}$ = 244.3 Hz), 114.4, 112.5, 75.6, 49.2 (t, $^2J_{C\text{-}F}$ = 24.1 Hz), 38.8 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 28.0 (dd, $^3J_{C\text{-}F}$ = 5.7 Hz, $^3J_{C\text{-}F}$ = 4.3 Hz), 27.0 (d, $^4J_{C\text{-}F}$ = 1.6 Hz), 26.5 (dd, $^3J_{C\text{-}F}$ = 7.2 Hz, $^3J_{C\text{-}F}$ = 4.1 Hz), 20.9 (dd, $^4J_{C\text{-}F}$ = 4.6 Hz, $^4J_{C\text{-}F}$ = 2.9 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -103.27 (**A**B system, $^2J_{F\text{-}F}$ = 246.8 Hz), -104.94 (A**B** system, $^2J_{F\text{-}F}$ = 246.8 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{19}H_{21}NO_2F_2Na$) = 356.1433; found: 356.1436 (1 ppm).

3-(1,1-difluoro-3-phenylpropyl)-5-(4-methoxyphenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide 7e

White solid, yield 59 mg (85%) from 75 mg (0.18 mmol) of **5e**. R_f = 0.3 (Petroleum Ether / Ethyl Acetate: 7/3). mp = 152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 – 8.26 (m, 2H), 7.37 – 7.28 (m, 2H), 7.27 – 7.15 (m, 3H),

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6.98 – 6.88 (m, 2H), 3.81 (s, 3H), 3.07 – 2.97 (m, 2H), 2.96 – 2.81 (m, 2H), 2.79 – 2.57 (m, 1H), 2.35 – 2.10 (m, 2H), 1.62 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 140.1, 135.7, 129.2, 128.7, 128.3, 126.5, 123.6 (dd, $^1J_{C\text{-}F}$ = 245.4 Hz, $^1J_{C\text{-}F}$ = 244.6 Hz), 122.1, 113.8, 76.2 (d, $^3J_{C\text{-}F}$ = 1.1 Hz), 55.3, 48.2 (t, $^2J_{C\text{-}F}$ = 24.1 Hz), 38.7 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 28.3 (dd, $^3J_{C\text{-}F}$ = 7.0 Hz, $^3J_{C\text{-}F}$ = 3.9 Hz), 27.9 (dd, $^4J_{C\text{-}F}$ = 5.5 Hz, $^4J_{C\text{-}F}$ = 4.4 Hz), 27.1 (d, $^4J_{C\text{-}F}$ = 1.5 Hz), 20.8 (dd, $^3J_{C\text{-}F}$ = 4.3 Hz, $^3J_{C\text{-}F}$ = 2.9 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -102.74 (**A**B system, $^2J_{F\text{-}F}$ = 246.9 Hz), -104.68 (A**B** system, $^2J_{F\text{-}F}$ = 246.9 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{22}H_{25}NO_2F_2Na$) = 396.1745; found: 396.1745 (0 ppm).

Synthesis of 5-((4-methoxybenzyl)oxy)pent-1-yn-3-one 9

To the propargylic alcohol **8** (3 g, 13.62 mmol) in acetone (20 mL) was added dropwise under magnetic stirring at room temperature, a concentrated (5.4 M) solution of Jones reagent until disappearance of the starting material (TLC analysis). After addition of isopropanol (5.0 equiv), the reaction mixture was filtered and the filtrate was extracted with ethyl acetate (3x40mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. After purification by chromatography on silica gel, 5-((4-methoxybenzyl)oxy)pent-1-yn-3-one **9** was obtained as colorless oil (2.08 g, 70%). R_f = 0.6 (Petroleum Ether/ Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 2H), 6.94 – 6.77 (m, 2H), 4.45 (s, 2H), 3.82 – 3.75 (m, 5H), 3.23 (d, $^5J_{H\text{-}H}$ = 0.8 Hz, 1H), 2.85 (td, $^3J_{H\text{-}H}$ = 6.2 Hz, $^5J_{H\text{-}H}$ = 0.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 159.4, 130.0, 129.5, 113.9, 81.3, 79.1, 73.0, 64.3, 55.4, 45.7. HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{14}O_3Na$) = 241.0835; found: 241.0837 (1 ppm).

Synthesis of 1-(((3,3-difluoropent-4-yn-1-yl)oxy)methyl)-4-methoxybenzene 10

To the propargylic ketone **9** (2 g, 9.16 mmol) one drop of 95% ethanol and DAST (2.42 mL, 18.32 mmol, 2 equiv) were added. The reaction mixture was stirred at 58 °C for 8 h. After coming back to room temperature and hydrolysis, the reaction mixture was extracted with CH_2Cl_2 (3x40 mL). The organic layers were separated, washed with water (3x20 mL), dried over $MgSO_4$ then filtrated on silica. After purification by chromatography on silica gel, the 1-(((3,3-difluoropent-4-yn-1-yl)oxy)methyl)-4-methoxybenzene **10** was obtained as a yellow oil (1.25 g, 57%). R_f = 0.4 (Petroleum Ether/ Ethyl Acetate: 9/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 3H), 6.95 – 6.81 (m, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.70 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 2H), 2.78 (t, $^3J_{H\text{-}F}$ = 5.1 Hz, 1H), 2.41 (tt, $^3J_{H\text{-}F}$ = 14.7 Hz, $^3J_{H\text{-}H}$ = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.1, 129.5, 114.0, 113.0 (t, $^1J_{C\text{-}F}$ = 233.3 Hz), 76.4 (t, $^2J_{C\text{-}F}$ = 40.5 Hz), 75.7 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 73.0, 63.9 (t, $^3J_{C\text{-}F}$ = 4.8 Hz), 55.4, 39.4 (t, $^2J_{C\text{-}F}$ = 25.7 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -82.75 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{14}O_2F_2Na$) = 263.0854; found: 263.0856 (1 ppm).

Synthesis of 4,4-difluoro-6-((4-methoxybenzyl)oxy)-1-phenylhex-2-yn-1-ol 11a

The reaction was carried out with 1-(((3,3-difluoropent-4-yn-1-yl)oxy)methyl)-4-methoxybenzene **10** (1 g, 4.16 mmol) with Benzaldehyde (550 µL, 5.41 mmol) according to the general procedure 1. After purification by chromatography on silica gel, **11a** was obtained as yellow oil (1.35 g, 95%). R_f = 0.4 (Petroleum Ether/ Ethyl Acetate: 7.5/2.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.34 (m, 5H), 7.29 – 7.19 (m, 2H), 6.94 – 6.81 (m, 2H), 5.48 (bs, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.69 (td, $^3J_{H\text{-}H}$ = 6.8 Hz, $^4J_{H\text{-}F}$ = 0.6 Hz, 2H), 2.57 (bs, 1H), 2.42 (tt, $^3J_{H\text{-}F}$ = 14.0 Hz, $^3J_{H\text{-}H}$ = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 139.1 (t, $^5J_{C\text{-}F}$ = 1.6 Hz), 130.0, 129.5, 129.0, 128.9, 126.7, 114.0, 113.5 (t, $^1J_{C\text{-}F}$ = 233.3 Hz), 87.2 (t, $^3J_{C\text{-}F}$ = 6.7 Hz), 79.2 (t, $^2J_{C\text{-}F}$ = 40.5 Hz), 72.9, 64.2 (t, $^4J_{C\text{-}F}$ = 2.0 Hz), 63.9 (t, $^3J_{C\text{-}F}$ = 4.8 Hz), 55.4, 39.5 (t, $^2J_{C\text{-}F}$ = 26.1 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -81.73 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{20}H_{20}O_3F_2Na$) = 369.1272; found: 369.1272 (0 ppm).

Synthesis of 4,4-difluoro-6-((4-methoxybenzyl)oxy)-3-(nitromethyl)-1-phenylhexan-1-one 12a

The reaction was carried out with 4,4-difluoro-6-((4-methoxybenzyl)oxy)-1-phenylhex-2-yn-1-ol **11a** (1 g, 2.88 mmol) according to the general procedure 2. After purification by chromatography on silica gel, **12a** was obtained as a colorless oil (0.89 g, 76%). R_f = 0.3 (Petroleum Ether/ Ethyl Acetate: 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.65 – 7.55 (m, 1H), 7.52 – 7.43 (m, 2H), 7.25 – 7.17 (m, 2H), 6.87 – 6.80 (m, 2H), 4.73 (dd, $^2J_{H\text{-}H}$ = 13.4 Hz, $^3J_{H\text{-}H}$ = 5.9 Hz, 1H), 4.59 (dd, $^2J_{H\text{-}H}$ = 13.4 Hz, $^3J_{H\text{-}H}$ = 5.0 Hz, 1H), 4.43 (s, 2H), 3.78 (s, 3H), 3.65 (t, $^3J_{H\text{-}H}$ = 5.9 Hz, 2H), 3.43 (dd, $^2J_{H\text{-}H}$ = 18.4 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 3.24 (dd, $^2J_{H\text{-}H}$ = 18.4 Hz, $^3J_{H\text{-}H}$ = 8.9 Hz, 1H), 2.39 – 2.21 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 159.3, 136.1, 133.7, 129.5, 129.5, 128.8, 128.1, 124.2 (d, $^1J_{C\text{-}F}$ = 244.9 Hz), 113.9, 73.5 (t, $^3J_{C\text{-}F}$ = 4.6 Hz), 73.2, 63.4 (t, $^3J_{C\text{-}F}$ = 6.3 Hz), 55.3, 39.3 (t, $^2J_{C\text{-}F}$ = 24.3 Hz), 35.3 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 34.9 (t, $^3J_{C\text{-}F}$ = 3.6 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -99.53 (**A**B system, $^2J_{F\text{-}F}$ = 253.2 Hz), -100.47 (A**B** system, $^2J_{F\text{-}F}$ = 253.2 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{21}H_{23}NO_5F_2Na$) = 430.1437; found: 430.1439 (1 ppm).

Synthesis of 3-(1,1-difluoro-3-((4-methoxybenzyl)oxy)propyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 13a

The reaction was carried out with 4,4-difluoro-6-((4-methoxybenzyl)oxy)-3-(nitromethyl)-1-phenylhexan-1-one **12a** (75 mg, 0.18 mmol) according to the general procedure 3. After purification by chromatography on silica gel, **13a** was obtained as colorless oil (53 mg, 77%). R_f = 0.1 (Petroleum Ether/ Ethyl Acetate: 6/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 – 8.21 (m, 2H), 7.49 – 7.40 (m, 3H), 7.26 – 7.19 (m, 2H), 6.95 – 6.81 (m, 2H), 4.44 (s, 2H), 4.41 – 4.20 (m, 2H), 3.79 (s, 3H), 3.64 (t, $^3J_{H\text{-}H}$ = 5.9 Hz, 2H), 3.36 – 3.05 (m, 3H), 2.33 – 2.13 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 139.9, 130.8, 129.7, 129.5, 128.8, 128.6, 127.4, 123.5 (t, $^1J_{C\text{-}F}$ = 243.4 Hz), 114.1, 73.2, 64.4 (dd, $^3J_{C\text{-}F}$ = 6.1 Hz, $^3J_{C\text{-}F}$ = 3.7 Hz), 63.5 (t, $^3J_{C\text{-}F}$ = 6.3 Hz), 55.4, 36.3 (t, $^2J_{C\text{-}F}$ = 25.8 Hz), 35.8 (t, $^2J_{C\text{-}F}$ = 25.4 Hz), 31.5 (dd, $^3J_{C\text{-}F}$ = 6.2, $^3J_{C\text{-}F}$ = 4.1 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -103.73 (**A**B system, $^2J_{F\text{-}F}$ = 249.2 Hz), -104.83 (A**B** system, $^2J_{F\text{-}F}$ = 249.2 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{21}H_{23}NO_3F_2Na$) = 398.1538; found: 398.1538 (0 ppm).

Synthesis of 4,4-difluoro-6-hydroxy-3-(nitromethyl)-1-phenylhexan-1-one 14a

To protected nitro compound **12a** (0.5 g, 1.22 mmol) in DCM (20 mL) and water (1 mL) was added under magnetic stirring at room temperature, DDQ (420 mg, 1.84 mmol) until disappearance of the starting material (TLC analysis). Then water was added and the reaction mixture was extracted with DCM (3x20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuum. After purification by chromatography on silica gel, 4,4-difluoro-6-hydroxy-3-(nitromethyl)-1-phenylhexan-1-one **14a** was obtained as yellow oil (345 mg, 98%). R_f = 0.4 (Petroleum Ether/ Ethyl Acetate: 6/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H), 7.65 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 4.75 (dd, $^2J_{H\text{-}H}$ = 13.5 Hz, $^3J_{H\text{-}H}$ = 5.9 Hz, 1H), 4.55 (dd, $^2J_{H\text{-}H}$ = 13.5 Hz, $^3J_{H\text{-}H}$ = 5.5 Hz, 1H), 3.90 (t, $^3J_{H\text{-}H}$ = 5.9 Hz, 2H), 3.87 – 3.69 (m, 1H), 3.45 (dd, $^2J_{H\text{-}H}$ = 18.5 Hz, $^3J_{H\text{-}H}$ = 4.5 Hz, 1H), 3.25 (dd, $^2J_{H\text{-}H}$ = 18.5 Hz, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H), 2.23 (tt, $^3J_{H\text{-}F}$ = 17.1 Hz, $^2J_{H\text{-}H}$ = 5.9 Hz, 2H), 2.08 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$δ 196.5, 136.0, 134.0, 128.9, 128.2, 124.5 (t, *J* = 245.1 Hz), 73.7 (t, *J* = 4.9 Hz), 56.5 (t, *J* = 6.0 Hz), 39.5 (t, *J* = 24.2 Hz), 37.3 (t, *J* = 24.1 Hz), 35.2 (dd, *J* = 4.2, 3.3 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -100.56 (**A**B system, $^2J_{F\text{-}F}$ = 252.5 Hz), -101.43 (A**B** system, $^2J_{F\text{-}F}$ = 252.5 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{15}NO_4F_2Na$) = 310.0861; found: 310.0863 (0 ppm).

Synthesis of 3-(1,1-difluoro-3-hydroxypropyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 15a

The reaction was carried out with 4,4-difluoro-6-hydroxy-3-(nitromethyl)-1-phenylhexan-1-one **14a** (75 mg, 0.26 mmol) according to the general

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procedure 3. After purification by chromatography on silica gel, **15a** was obtained as white solid (40 mg, 60%). R_f = 0.1 (Petroleum Ether/ Ethyl Acetate: 2.5/7.5). mp= 147 ˚C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.37 – 8.27 (m, 2H), 7.56 – 7.42 (m, 3H), 4.46 – 4.18 (m, 2H), 3.78 (t, $^3J_{H-H}$ = 6.3 Hz, 2H), 3.57 – 3.32 (m, 3H), 2.31 – 2.14 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 144.8, 132.5, 129.6, 129.5, 129.2, 125.3 (t, $^1J_{C-F}$ = 242.8 Hz), 65.0 (dd, $^3J_{C-F}$ = 6.1 Hz, $^3J_{C-F}$ = 4.0 Hz), 56.5 (t, $^3J_{C-F}$ = 6.2 Hz), 38.5 (t, $^2J_{C-F}$ = 24.2 Hz), 37.4 (t, $^2J_{C-F}$ = 25.8 Hz), 32.8 (dd, $^3J_{C-F}$ = 6.4 Hz, $^3J_{C-F}$ = 4.1 Hz). ^{19}F {H} NMR (471 MHz, CD_3OD) δ -105.95 (**A**B system, $^2J_{F-F}$ = 248.4 Hz), -107.81 (A**B** system, $^2J_{F-F}$ = 248.4 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{15}NO_2F_2Na$) = 278.0963; found: 278.0961 (1 ppm).

3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexanoic acid 16a

The reaction was carried out with 4,4-difluoro-6-hydroxy-3-(nitromethyl)-1-phenylhexan-1-one **14a** (200 mg, 0.70 mmol) based on the same procedure of the synthesis of compound **9**. After purification by chromatography on silica gel, **16a** was obtained as white solid (160 mg, 76%). R_f = 0.2 (Petroleum Ether/ Ethyl Acetate/methanol: 4.5/5/0.5). mp= 130 ˚C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.1 – 8.0 (m, 2H), 7.7 – 7.6 (m, 1H), 7.6 – 7.5 (m, 2H), 4.9 (dd, $^2J_{H-H}$ = 14.2 Hz, $^3J_{H-H}$ = 6.8 Hz, 1H), 4.7 (dd, $^2J_{H-H}$ = 14.2 Hz, $^3J_{H-H}$ = 4.6 Hz, 1H), 4.2 – 4.0 (m, 1H), 3.6 (ddd, $^2J_{H-H}$ = 18.7 Hz, $^3J_{H-H}$ = 3.8 Hz, $^4J_{H-F}$ = 0.9 Hz, 1H), 3.5 (dd, $^2J_{H-H}$ = 18.7 Hz, $^3J_{H-H}$ = 9.2 Hz, 1H), 3.4 – 3.1 (m, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 197.0, 167.9 (dd, $^3J_{C-F}$ = 8.9 Hz, $^3J_{C-F}$ = 4.6 Hz), 137.4, 134.3, 129.5, 129.0, 123.8 (t, $^1J_{C-F}$ = 245.1 Hz), 74.2 (t, $^3J_{C-F}$ = 4.5 Hz), 40.2 (t, $^2J_{C-F}$ =26.8 Hz), 39.7 (t, $^2J_{C-F}$ = 23.4 Hz), 36.1 (dd, $^3J_{C-F}$ = 4.9 Hz, $^3J_{C-F}$ = 2.6 Hz). ^{19}F {H} NMR (471 MHz, $(CD_3)_2CO$) δ -98.03 (**A**B system, $^2J_{F-F}$ = 254.8 Hz), -100.29 (A**B** system, $^2J_{F-F}$ = 254.7 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{11}NO_5F_2Na$) = 300.0689; found: 300.0684 (2 ppm).

ethyl 3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexanoate 17a

To 3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexanoic acid **16a** (100 mg, 0.33 mmol), N, N′-Dicyclohexylcarbodiimide "DCC" (137 mg, 0.66 mmol), and ethanol (39 µL, 0.66 mmol), were added and mixed in 4 ml DCM for 24 h. The reaction was monitored by TLC. At the end concentrated NH_4Cl (2 mL) was added and the reaction mixture was extracted with DCM (3x10mL). The organic layers were separated, washed with water (1x10mL), dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, **17a** (78 mg, 72%) was obtained as pale yellow oil. R_f = 0.6 (Petroleum Ether / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.66 – 7.57 (m, 1H), 7.53 – 7.45 (m, 2H), 4.80 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.7 Hz, 1H), 4.62 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 5.1 Hz, 1H), 4.21 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 4.02 – 3.78 (m, 1H), 3.45 (dd, $^2J_{H-H}$ = 18.4 Hz, $^3J_{H-H}$ = 4.7 Hz, 1H), 3.34 (dd, $^2J_{H-H}$ = 18.4 Hz, $^3J_{H-H}$ = 8.3 Hz, 1H), 3.11 (dd, $^2J_{H-H}$ = 15.1 Hz, $^3J_{H-H}$ = 4.1 Hz, 1H), 3.05 (dd, $^2J_{H-H}$ = 15.1 Hz, $^3J_{H-H}$ = 3.7 Hz, 1H), 1.29 (t, $^3J_{H-H}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 166.2 (t, $^3J_{C-F}$ = 7.4 Hz), 136.1, 134.0, 129.0, 128.3, 121.8 (t, $^1J_{C-F}$ = 246.9 Hz), 73.6 (t, $^3J_{C-F}$ = 4.8 Hz), 61.9, 40.7 (t, $^2J_{C-F}$ = 27.6 Hz), 39.1 (t, $^2J_{C-F}$ = 23.8 Hz), 34.8 (t, $^3J_{C-F}$ = 3.7 Hz), 14.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ -97.24 (**A**B system, $^2J_{F-F}$ = 257.7 Hz), -97.93 (A**B** system, $^2J_{F-F}$ = 257.7 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{15}H_{17}NO_5F_2Na$) = 352.0967; found: 352.0972 (1 ppm).

3-(3-ethoxy-1,1-difluoro-3-oxopropyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 18a

The reaction was carried out with ethyl 3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexanoate **17a** (60 mg, 0.18 mmol) according to the general procedure 3. After purification by chromatography on silica gel, **18a** was obtained as pale yellow oil (42 mg, 77%). R_f = 0.1 (Petroleum Ether/ Ethyl Acetate: 5/5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 – 8.22 (m, 2H), 7.50 – 7.36 (m, 3H), 4.38 – 4.29 (m, 2H), 4.20 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 3.61 – 3.15 (m, 3H), 3.10 – 2.85 (m, 2H), 1.28 (t, $^3J_{H-H}$ = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (t, $^3J_{C-F}$ = 8.0 Hz), 139.3, 130.8, 128.7, 128.6, 127.3, 121.1 (t, $^3J_{C-F}$ = 245.3 Hz), 64.0 (dd, $^3J_{C-F}$ = 5.7 Hz, $^3J_{C-F}$ = 3.5 Hz), 61.8, 40.8 (t, $^2J_{C-F}$ = 28.2 Hz), 35.5 (t, $^2J_{C-F}$ = 25.1 Hz), 31.3 (dd, $^3J_{C-F}$ = 6.1 Hz, $^3J_{C-F}$ = 4.1 Hz), 14.1. ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -101.23 (d, **A**B system, $^2J_{F-F}$ = 253.8 Hz), -102.47 (A**B** system, $^2J_{F-F}$ = 253.8 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{15}H_{17}NO_3F_2Na$) = 320.1069; found: 320.1071 (1 ppm).

3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexyl 4-methylbenzenesulfonate 19a

To 4,4-difluoro-6-hydroxy-3-(nitromethyl)-1-phenylhexan-1-one **14a** (150 mg, 0.52 mmol), *p*-toluenesulfonyl chloride (200 mg, 1.04 mmol), pyridine (84 µL, 1.04 mmol), and catalytic amount of DMAP were added and mixed in 5 ml DCM for 48 h. The reaction was monitored by TLC. At the end saturated NH_4Cl (2 mL) was added and the reaction mixture was extracted with DCM (3x10 mL). The organic layers were separated, washed with water (1x10 mL), dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, **19a** (145 mg, 63%) was obtained as white solid. R_f = 0.3 (Petroleum Ether / Ethyl Acetate: 8/2). mp = 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H), 7.82 – 7.71 (m, 2H), 7.66 – 7.55 (m, 1H), 7.54 – 7.42 (m, 2H), 7.39 – 7.28 (m, 2H), 4.67 (dd, $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ = 6.2 Hz, 1H), 4.48 (dd, $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ = 5.2 Hz, 1H), 4.34 – 4.15 (m, 2H), 3.74 – 3.51 (m, 1H), 3.35 (dd, $^2J_{H-H}$ = 18.6 Hz, $^3J_{H-H}$ = 4.5 Hz, 1H), 3.21 (dd, $^2J_{H-H}$ = 18.6 Hz, $^3J_{H-H}$ = 8.1 Hz, 1H), 2.43 (s, 3H), 2.42 – 2.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 145.4, 135.9, 134.1, 132.4, 130.1, 128.9, 128.2, 128.0, 123.1 (t, $^1J_{C-F}$ = 246.0 Hz), 73.3 (t, $^3J_{C-F}$ = 4.8 Hz), 63.3 (t, $^3J_{C-F}$ = 5.9 Hz), 39.3 (t, $^2J_{C-F}$ = 23.7 Hz), 35.1 (dd, $^3J_{C-F}$ = 4.3 Hz, $^3J_{C-F}$ = 3.0 Hz), 34.5 (t, $^2J_{C-F}$ = 24.8 Hz), 21.7. ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -101.54 (A**B** system, $^2J_{F-F}$ = 253.2 Hz), -102.91 (A**B** system, $^2J_{F-F}$ = 253.2 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{20}H_{21}NO_6F_2SNa$) = 464.0950; found: 464.0956 (1 ppm).

3-(1,1-difluoro-3-(tosyloxy)propyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 20a

The reaction was carried out with 3,3-difluoro-4-(nitromethyl)-6-oxo-6-phenylhexyl 4-methylbenzenesulfonate **19a** (100 mg, 0.23 mmol) according to the general procedure 3. After purification by chromatography on silica gel, **20a** was obtained as colorless oil (75 mg, 81%). R_f = 0.3 (Petroleum Ether/ Ethyl Acetate: 2.5/7.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.23 (m, 2H), 7.82 – 7.73 (m, 2H), 7.48 – 7.40 (m, 3H), 7.39 – 7.31 (m, 2H), 4.34 – 4.17 (m, 4H), 3.51 – 2.88 (m, 3H), 2.44 (s, 3H), 2.41 – 2.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 139.3, 132.4, 130.8, 130.2, 128.6, 128.0, 127.3, 122.4 (t, $^1J_{C-F}$ = 244.3 Hz), 63.9 (dd, $^3J_{C-F}$ = 5.7 Hz, $^3J_{C-F}$ = 3.5 Hz), 63.4 (t, $^3J_{C-F}$ = 5.9 Hz), 36.3 (t, $^2J_{C-F}$ = 25.6 Hz), 34.8 (t, $^2J_{C-F}$ = 25.7 Hz), 31.3 (t, $^3J_{C-F}$ = 5.0 Hz), 21.8. ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -104.66 (**A**B system, $^2J_{F-F}$ = 250.8 Hz), -106.45 (A**B** system, $^2J_{F-F}$ = 250.9 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{20}H_{21}NO_4F_2SNa$) = 432.1052; found: 432.1058 (2 ppm).

3-(3-azido-1,1-difluoropropyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide 21a

To 3-(1,1-difluoro-3-(tosyloxy)propyl)-5-phenyl-3,4-dihydro-2H-pyrrole 1-oxide **20a** (60 mg, 0.15 mmol), sodium azide (15 mg, 0.22 mmol) was added in 2 mL DMF. The reaction was monitored by TLC. At the end saturated NH_4Cl (2 mL) was added and the reaction mixture was extracted with DCM (3x 5 mL). The organic layers were separated, washed with water (1x 5 mL), dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, **21a** (35 mg, 85%) was obtained as colorless oil (75 mg, 81%). R_f = 0.3 (Petroleum Ether/ Ethyl Acetate: 2.5/7.5). mp= 72 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.24 (m, 2H), 7.54 – 7.42 (m, 3H), 4.39 – 4.32 (m, 2H), 3.61 (t, $^3J_{H-H}$ = 6.8 Hz, 2H), 3.44 – 3.02 (m, 3H), 2.30 – 2.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 130.9, 128.7, 128.6, 127.4, 122.7 (t, $^1J_{C-F}$ = 244.2 Hz), 64.1 (dd, $^3J_{C-F}$ = 5.5 Hz, $^3J_{C-F}$ = 3.9 Hz), 44.7 (t, $^3J_{C-F}$ = 5.3 Hz), 36.6 (t, $^2J_{C-F}$ = 25.9 Hz),

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34.6 (t, $^2J_{C\text{-}F}$ = 25.2 Hz), 31.4 (dd, $^3J_{C\text{-}F}$ = 5.8 Hz, $^3J_{C\text{-}F}$ = 4.4 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -101.23 (**A**B system, $^2J_{F\text{-}F}$ = 253.9 Hz), -102.47 (A**B** system, $^2J_{F\text{-}F}$ = 253.9 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{14}N_4OF_2Na$) = 303.1027; found: 303.1027 (0 ppm).

General procedure 4 for the synthesis of difluoropropargylic alcohols 23

To a solution of *n*-butyllithium 2.5 M (2.77 mL, 6.92 mmol) in anhydrous THF (40 mL) cooled to -90°C, was added under nitrogen, a solution of **22** (500 mg, 2.10 mmol). The mixture was stirred for 30 min at -90°C. Then, aldehyde **2** (1.3 equiv) in anhydrous THF (10 mL) was added at - 90°C, stirred for 45 min, then the reaction mixture was allowed to warm to r.t. within 2h. The mixture was then treated with a saturated NH_4Cl solution and extracted with ethyl acetate (3x40 mL). The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, the propargylic alcohols **23** were obtained.

4,4-difluoro-1-(4-fluorophenyl)hept-2-yne-1,7-diol 23b

Colorless oil, yield 380 mg (70%). R_f = 0.2 (Hexane / Ethyl Acetate: 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.39 (m, 2H), 7.12 – 7.01 (m, 2H), 5.48 (t, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 3.68 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.38 – 2.02 (m, 3H), 1.95 – 1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{C\text{-}F}$ = 247.7 Hz), 135.0 (dt, $^4J_{C\text{-}F}$ = 3.3 Hz, $^5J_{C\text{-}F}$ = 1.6 Hz), 128.6 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 114.9 (t, $^1J_{C\text{-}F}$ = 233.0 Hz), 86.9 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 79.5 (t, $^2J_{C\text{-}F}$ = 41.2 Hz), 63.5 (t, $^4J_{C\text{-}F}$ = 2.0 Hz), 61.6, 35.8 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 26.0 (t, $^3J_{C\text{-}F}$ = 3.4 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.16 (s), -112.91 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{13}O_2F_3Na$) = 281.0760; found: 281.0762 (1 ppm).

1-(4-chlorophenyl)-4,4-difluorohept-2-yne-1,7-diol 23c

Yellow oil, yield 496 mg (86%). R_f = 0.2 (hexane / Ethyl Acetate: 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 5.44 (t, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 3.64 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 3.38 (bs, 1H), 2.35 – 2.05 (m, 2H), 1.91 – 1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 134.7, 129.0, 128.1, 114.8 (t, $^1J_{C\text{-}F}$ = 232.9 Hz), 86.8 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 79.4 (t, $^2J_{C\text{-}F}$ = 41.1 Hz), 63.3 (t, $^4J_{C\text{-}F}$ = 1.9 Hz), 61.4, 35.7 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 25.9 (t, $^3J_{C\text{-}F}$ = 3.5 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.07 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{13}O_2F_2{}^{35}ClNa$) = 297.0464; found: 297.0467 (1 ppm).

4,4-difluoro-1-(furan-2-yl)hept-2-yne-1,7-diol 23d

Black oil, yield 435 mg (90%). R_f = 0.1 (hexane / Ethyl Acetate: 7/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, $^3J_{H\text{-}H}$ = 1.8 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 1H), 6.46 (dt, $^3J_{H\text{-}H}$ = 3.3 Hz, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H), 6.37 (dd, $^3J_{H\text{-}H}$ = 3.3 Hz, $^3J_{H\text{-}H}$ = 1.9 Hz, 1H), 5.53 (t, $^3J_{H\text{-}H}$ = 3.9 Hz, 1H), 3.71 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.33 – 2.04 (m, 3H), 1.94 – 1.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5 (t, $^5J_{C\text{-}F}$ = 1.9 Hz), 143.6, 114.8 (t, $^1J_{C\text{-}F}$ = 233.1 Hz), 110.7, 108.5, 84.7 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 78.5 (t, $^2J_{C\text{-}F}$ = 41.3 Hz), 61.6, 57.8 (t, $^4J_{C\text{-}F}$ = 1.8 Hz), 35.8 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 26.0 (t, $^3J_{C\text{-}F}$ = 3.5 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.55. HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{11}H_{12}O_3F_2Na$) = 253.0647; found: 253.0647 (0 ppm).

4,4-difluoro-1-(4-methoxyphenyl)hept-2-yne-1,7-diol 23e

Colorless oil, yield 540 mg (95%). R_f = 0.3 (Petroleum Ether / Ethyl Acetate: 6/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.35 (m, 2H), 6.97 – 6.87 (m, 2H), 5.48 (t, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 3.82 (s, 3H), 3.71 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.32 – 2.06 (m, 2H), 1.90 (bs, 2H, O*H*), 1.89 – 1.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 131.4, 128.3, 114.9 (t, $^1J_{C\text{-}F}$ = 232.8 Hz), 114.3, 87.1 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 79.3 (t, $^2J_{C\text{-}F}$ = 41.0 Hz), 64.0 (t, $^4J_{C\text{-}F}$ = 2.0 Hz), 61.7, 55.5, 35.9 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 26.1 (t, $^3J_{C\text{-}F}$ = 3.5 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -83.13 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{16}O_3F_2Na$) = 293.0960; found: 293.0963 (1 ppm).

General procedure 5 for the synthesis of bromo- compounds 24

Representative procedure: 7-bromo-4,4-difluoro-1-(4-fluorophenyl)hept-2-yn-1-ol 24b

Triphenylphosphine (460 mg,1.76 mmol) in dichloromethane (5 mL) was added dropwise to a vigorously stirred mixture of alcohol **23b** (350 mg, 1.36 mmol) with carbon tetrabromide (585 mg, 1.76 mmol) in dichloromethane (10 mL) at 0 °C under nitrogen. Petroleum ether was added, and the precipitate was then filtered off. Brominated compound **24b** was separated by column chromatography to obtain a yellow oil (383 mg, 88%). R_f = 0.6 (Hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.41 (m, 2H), 7.19 – 6.99 (m, 2H), 5.52 (t, $^3J_{H\text{-}H}$ = 3.9 Hz, 1H), 3.45 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.69 (bs, 1H), 2.50 – 1.92 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C\text{-}F}$ = 248.0 Hz), 134.8 (dt, $^4J_{C\text{-}F}$ = 3.3 Hz, $^5J_{C\text{-}F}$ = 1.6 Hz), 128.6 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 114.2 (t, $^1J_{C\text{-}F}$ = 233.6 Hz), 86.9 (t, $^3J_{C\text{-}F}$ = 6.7 Hz), 79.3 (t, $^2J_{C\text{-}F}$ = 41.0 Hz), 63.6 (t, $^4J_{C\text{-}F}$ = 1.9 Hz), 37.9 (t, $^2J_{C\text{-}F}$ = 26.6 Hz), 32.2, 26.2 (t, $^3J_{C\text{-}F}$ = 3.7 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.23 (s), -112.63(s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{12}OF_3{}^{79}BrNa$) = 342.9915; found: 342.9915 (0 ppm).

7-bromo-1-(4-chlorophenyl)-4,4-difluorohept-2-yn-1-ol 24c

Yellow oil, yield 262 mg (61%) from 350 mg (1.27 mmol) of **23c**. R_f = 0.6 (Hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.41 (m, 2H), 7.41 – 7.27 (m, 2H), 5.52 (t, $^3J_{H\text{-}H}$ = 3.2 Hz, 1H), 3.45 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.70 (bs, 1H), 2.38 – 2.20 (m, 2H), 2.16 – 1.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (t, $^5J_{C\text{-}F}$ = 1.5 Hz), 134.9, 129.2, 128.1, 114.2 (t, $^1J_{C\text{-}F}$ = 233.6 Hz), 86.7 (t, $^3J_{C\text{-}F}$ = 6.7 Hz), 79.4 (t, $^2J_{C\text{-}F}$ = 41.0 Hz), 63.6 (t, $^4J_{C\text{-}F}$ = 1.9 Hz), 37.9 (t, $^2J_{C\text{-}F}$ = 26.6 Hz), 32.2, 26.1 (t, $^3J_{C\text{-}F}$ = 3.7 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.28 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{13}H_{12}OF_2{}^{35}Cl^{79}BrNa$) = 358.9620; found: 358.9621 (0 ppm).

7-bromo-4,4-difluoro-1-(furan-2-yl)hept-2-yn-1-ol 24d

Black oil, yield 227 mg (51%) from 350 mg (1.52 mmol) of **23d**. R_f = 0.5 (Hexane / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, $^3J_{H\text{-}H}$ = 1.9 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 1H), 6.47 (dt, $^3J_{H\text{-}H}$ = 3.3 Hz, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H), 6.38 (dd, $^3J_{H\text{-}H}$ = 3.3 Hz, $^3J_{H\text{-}H}$ = 1.8 Hz, 1H), 5.54 (t, $^3J_{H\text{-}H}$ = 3.9 Hz, 1H), 3.46 (t, $^3J_{H\text{-}H}$ = 6.2 Hz, 2H), 2.81 (bs, 1H), 2.42 – 2.02 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2 (t, $^5J_{C\text{-}F}$ = 2.0 Hz), 143.6, 114.1 (t, $^1J_{C\text{-}F}$ = 233.6 Hz), 110.7, 108.6, 84.8 (t, $^3J_{C\text{-}F}$ = 6.9 Hz), 78.3 (t, $^2J_{C\text{-}F}$ = 41.1 Hz), 57.8 (t, $^4J_{C\text{-}F}$ = 2.0 Hz), 37.9 (t, $^2J_{C\text{-}F}$ = 26.5 Hz), 32.2, 26.1 (t, $^3J_{C\text{-}F}$ = 3.8 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -83.5 (s). HRMS (ESI): calcd. for [M+H]$^+$ ($C_{11}H_{12}O_2F_2{}^{81}Br$) = 294.9962; found: 294.9962 (0 ppm).

7-bromo-4,4-difluoro-1-(4-methoxyphenyl)hept-2-yn-1-ol 24e

Pale yellow oil, yield 332 mg (77%) from 350 mg (1.29 mmol) of **23e**. R_f = 0.4 (Petroleum Ether / Ethyl Acetate: 8/2). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 6.96 – 6.89 (m, 2H), 5.49 (t, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 3.82 (s, 3H), 3.46 (t, $^3J_{H\text{-}H}$ = 6.3 Hz, 2H), 2.36 – 2.07 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 160.2, 131.3 (t, $^5J_{C\text{-}F}$ = 1.6 Hz), 128.3, 114.4, 114.3 (t, $^1J_{C\text{-}F}$ = 233.3 Hz), 87.4 (t, $^3J_{C\text{-}F}$ = 6.7 Hz), 79.0 (t, $^2J_{C\text{-}F}$ = 40.8 Hz), 64.0 (t, $^4J_{C\text{-}F}$ = 2.0 Hz), 55.5, 38.0 (t, $^2J_{C\text{-}F}$ = 26.7 Hz), 32.3, 26.2 (t, $^3J_{C\text{-}F}$ = 3.7 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -83.08 (s). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{15}O_2F_2{}^{81}BrNa$) = 357.0095; found: 357.0095 (0 ppm).

General procedure 6 for the synthesis of cyclic nitro compounds 25

Representative procedure: 2-(2,2-difluoro-6-nitrocyclohexyl)-1-phenylethan-1-one 25a

To the brominated compound **24a** (200 mg, 0.66 mmol) was added nitromethane (71 µl, 1.31 mmol) and DBU (395 µl, 2.63 mmol) in THF (3 ml). The reaction mixture was stirred at room temperature overnight. At the end saturated NH_4Cl (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3x20 mL). The organic layers were separated,

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washed with water (1x10 mL), dried over Na_2SO_4 and concentrated under vacuum. After purification by chromatography on silica gel, **25a** (142 mg, 76%) was obtained as white solid. R_f = 0.5 (Hexane / Ethyl Acetate: 9/1). mp = 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.86 (m, 2H), 7.64 – 7.52 (m, 1H), 7.52 – 7.39 (m, 2H), 4.55 (td, $^3J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.0 Hz, 1H), 3.56 (dd, $^2J_{H-H}$ = 17.8 Hz, $^3J_{H-H}$ = 5.6 Hz, 1H), 3.51 – 3.36 (m, 1H), 2.97 (dd, $^2J_{H-H}$ = 17.8 Hz, $^3J_{H-H}$ = 4.3 Hz, 1H), 2.43 – 1.61 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 136.4, 133.5, 128.8, 128.3, 122.9 (dd, $^1J_{C-F}$ = 249.5 Hz, $^1J_{C-F}$ = 242.4 Hz), 87.0 (d, $^3J_{C-F}$ = 8.5 Hz), 42.6 (dd, $^2J_{C-F}$ = 24.4, $^2J_{C-F}$ = 22.2 Hz), 34.0 (t, $^3J_{C-F}$ = 2.4 Hz), 33.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 22.3 Hz), 30.2 (d, $^4J_{C-F}$ = 1.6 Hz), 19.3 (d, $^3J_{C-F}$ = 10.2 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -95.5 (**A**B system, $^2J_{F-F}$ = 246.6 Hz), -108.2 (A**B** system, $^2J_{F-F}$ = 246.6 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{15}NO_3F_2Na$) = 306.0912; found: 306.0914 (1 ppm).

2-(2,2-difluoro-6-nitrocyclohexyl)-1-(4-fluorophenyl)ethan-1-one 25b

White solid, yield 124 mg (66%) from 200 mg (0.62 mmol) of **24b**. R_f = 0.5 (Hexane / Ethyl Acetate: 9/1). mp = 89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 2H), 7.19 – 7.00 (m, 2H), 4.53 (td, $^3J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.0 Hz, 1H), 3.51 (dd, $^2J_{H-H}$ = 17.6 Hz, $^3J_{H-H}$ = 5.5 Hz, 1H), 3.47 – 3.32 (m, 1H), 2.94 (dd, $^2J_{H-H}$ = 17.6 Hz, $^3J_{H-H}$ = 4.4 Hz, 1H), 2.42 – 1.59 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 166.0 (d, $^1J_{C-F}$ = 255.3 Hz), 132.8 (d, $^4J_{C-F}$ = 3.1 Hz), 131.0 (d, $^3J_{C-F}$ = 9.5 Hz), 122.9 (dd, $^1J_{C-F}$ = 249.4 Hz, $^1J_{C-F}$ = 242.5 Hz), 115.9 (d, $^2J_{C-F}$ = 22.0 Hz), 86.9 (d, $^3J_{C-F}$ = 8.4 Hz), 42.7 (dd, $^2J_{C-F}$ = 24.4 Hz, $^2J_{C-F}$ = 22.2 Hz), 33.9 (t, $^3J_{C-F}$ = 2.4 Hz), 33.2 (dd, $^2J_{C-F}$ = 24.9 Hz, $^2J_{C-F}$ = 22.2 Hz), 30.1 (d, $^4J_{C-F}$ = 1.7 Hz), 19.2 (d, $^3J_{C-F}$ = 10.2 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -95.51 (d, $^2J_{F-F}$ = 246.3 Hz), -104.61 (s), -108.22 (d, $^2J_{F-F}$ = 246.4 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{14}NO_3F_3Na$) = 324.0818; found: 324.0822 (1 ppm).

1-(4-chlorophenyl)-2-(2,2-difluoro-6-nitrocyclohexyl)ethan-1-one 25c

White solid, yield 132 mg (70%) from 200 mg (0.59 mmol) of **24c**. R_f = 0.5 (Hexane / Ethyl Acetate: 9/1). mp = 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.47 – 7.39 (m, 2H), 4.52 (td, $^3J_{H-H}$ = 11.7 Hz, $^3J_{H-H}$ = 4.1 Hz, 1H), 3.50 (dd, $^2J_{H-H}$ = 17.6 Hz, $^3J_{H-H}$ = 5.5 Hz, 1H), 3.46 – 3.32 (m, 1H), 2.94 (dd, $^2J_{H-H}$ = 17.6 Hz, $^3J_{H-H}$ = 4.3 Hz, 1H), 2.40 – 1.62 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 140.0, 134.7, 129.7, 129.1, 122.9 (dd, $^1J_{C-F}$ = 249.4 Hz, $^1J_{C-F}$ = 242.4 Hz), 86.9 (d, $^3J_{C-F}$ = 8.4 Hz), 42.7 (dd, $^2J_{C-F}$ = 24.4 Hz, $^2J_{C-F}$ = 22.2 Hz), 33.9 (t, $^3J_{C-F}$ = 2.4 Hz), 33.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 22.2 Hz), 30.2 (d, $^4J_{C-F}$ = 1.6 Hz), 19.2 (d, $^3J_{C-F}$ = 10.3 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -95.43 (**A**B system, $^2J_{F-F}$ = 246.4 Hz), -108.22 (A**B** system, $^2J_{F-F}$ = 246.4 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{14}NO_3F_2{}^{35}ClNa$) = 340.0522; found: 340.0520 (1 ppm).

2-(2,2-difluoro-6-nitrocyclohexyl)-1-(furan-2-yl)ethan-1-one 25d

White solid, yield 97 mg (52%) from 200 mg (0.68 mmol) of **24d**. R_f = 0.3 (Hexane / Ethyl Acetate: 9/1). mp = 98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, $^3J_{H-H}$ = 1.7 Hz, $^4J_{H-H}$ = 0.8 Hz, 1H), 7.22 (dd, $^3J_{H-H}$ = 3.6 Hz, $^4J_{H-H}$ = 0.8 Hz, 1H), 6.54 (dd, $^3J_{H-H}$ = 3.6 Hz, $^3J_{H-H}$ = 1.7 Hz, 1H), 4.54 (td, $^3J_{H-H}$ = 11.5 Hz, $^3J_{H-H}$ = 4.0 Hz, 1H), 3.49 – 3.19 (m, 2H), 2.89 – 2.76 (m, 1H), 2.40 – 1.54 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 152.1, 146.7, 122.8 (dd, $^1J_{C-F}$ = 249.4 Hz, $^1J_{C-F}$ = 242.5 Hz), 117.6, 112.6, 86.9 (d, $^3J_{C-F}$ = 8.4 Hz), 42.2 (dd, $^2J_{C-F}$ = 24.5 Hz, $^2J_{C-F}$ = 22.3 Hz), 33.6 (t, $^3J_{C-F}$ = 2.5 Hz), 33.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 22.3 Hz), 30.3 (d, $^4J_{C-F}$ = 1.5 Hz), 19.3 (d, $^3J_{C-F}$ = 10.2 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -95.46 (**A**B system, $^2J_{F-F}$ = 246.8 Hz), -108.40 (d, $^2J_{F-F}$ = 246.8 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{12}H_{13}NO_4F_2Na$) = 296.0705; found: 296.0708 (1 ppm).

2-(2,2-difluoro-6-nitrocyclohexyl)-1-(4-methoxyphenyl)ethan-1-one 25e

White solid, yield 92 mg (49%) from 200 mg (0.60 mmol) of **24e**. R_f = 0.4 (Petroleum Ether / Ethyl Acetate: 8/2). mp = 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97 – 7.89 (m, 2H), 6.99 – 6.86 (m, 2H), 4.61 – 4.45 (m, 1H), 3.86 (s, 3H), 3.58 – 3.29 (m, 2H), 2.42 – 1.52 (m, 6H). NMR (75 MHz, $CDCl_3$) δ 194.2, 163.8, 130.6, 129.4, 122.9 (dd, $^1J_{C-F}$ = 249.7 Hz, $^1J_{C-F}$ = 249.5 Hz), 113.9, 87.0 (d, $^3J_{C-F}$ = 8.4 Hz), 55.6, 42.6 (dd, $^2J_{C-F}$ = 24.4 Hz, $^2J_{C-F}$ = 22.2 Hz), 33.5 (t, $^3J_{C-F}$ = 2.3 Hz), 33.2 (dd, $^2J_{C-F}$ = 25.1 Hz, $^2J_{C-F}$ = 22.4 Hz), 30.1 (d, $^4J_{C-F}$ = 1.6 Hz), 19.3 (dd, $^3J_{C-F}$ = 10.2 Hz, $^3J_{C-F}$ = 0.5 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -95.60 (**A**B system, $^2J_{F-F}$ = 246.2 Hz), -108.21 (A**B** system, $^2J_{F-F}$ = 246.6 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{15}H_{17}NO_4F_2Na$) = 336.1018; found: 336.1022 (1 ppm).

Synthesis of 4,4-difluoro-2-phenyl-3a,4,5,6,7,7a-hexahydro-3H-indole 1-oxide 26a

According to the general procedure 3. White solid, yield 37 mg (56%) from 75 mg (0.26 mmol) of **25a**. R_f = 0.2 (Hexane / Ethyl Acetate: 4/6). mp = 206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 – 8.18 (m, 2H), 7.52 – 7.33 (m, 3H), 3.97 (t, $^3J_{H-H}$ = 11.9 Hz, 1H), 3.23 – 3.01 (m, 2H), 2.64 – 2.49 (m, 1H), 2.45 – 2.17 (m, 2H), 2.16 – 1.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 130.5, 129.3, 128.7, 127.2, 122.3 (dd, $^1J_{C-F}$ = 246.9 Hz, $^1J_{C-F}$ = 245.3 Hz), 73.4 (d, $^3J_{C-F}$ = 9.0 Hz), 46.9 (dd, $^2J_{C-F}$ = 25.5 Hz, $^2J_{C-F}$ = 22.6 Hz), 34.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 21.9 Hz), 27.8, 26.5 (d, $^4J_{C-F}$ = 1.6 Hz), 21.2 (d, $^3J_{C-F}$ = 9.5 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -99.88 (A**B** system, $^2J_{F-F}$ = 234.0 Hz), -113.99 (**A**B system, $^2J_{F-F}$ = 234.0 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{15}NOF_2Na$) = 274.1013; found: 274.1013 (0 ppm).

Synthesis of 4,4-difluoro-2-(4-fluorophenyl)-3a,4,5,6,7,7a-hexahydro-3H-indole 1-oxide 26b

According to the general procedure 3. Pale yellow solid, yield 47 mg (70%) from 75 mg (0.25 mmol) of **25b**. R_f = 0.1 (Hexane / Ethyl Acetate: 4/6). mp = 216 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 8.27 (m, 2H), 7.19 – 7.06 (m, 2H), 3.95 (t, $^3J_{H-H}$ = 11.9 Hz, 1H), 3.24 – 2.92 (m, 2H), 2.63 – 2.49 (m, 1H), 2.45 – 2.13 (m, 2H), 2.10 – 1.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C-F}$ = 252.8 Hz), 139.1, 129.5 (d, $^3J_{C-F}$ = 8.3 Hz), 125.8 (d, $^4J_{C-F}$ = 3.3 Hz), 122.3 (dd, $^1J_{C-F}$ = 246.9 Hz, $^1J_{C-F}$ = 245.4 Hz), 115.8 (d, $^2J_{C-F}$ = 21.7 Hz), 73.3 (d, $^3J_{C-F}$ = 8.9 Hz), 46.8 (dd, $^2J_{C-F}$ = 25.5 Hz, $^2J_{C-F}$ = 22.6 Hz), 34.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 21.9 Hz), 27.8, 26.5 (d, $^4J_{C-F}$ = 1.7 Hz), 21.1 (d, $^3J_{C-F}$ = 9.6 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -99.90 (**A**B system, $^2J_{F-F}$ = 234.4 Hz), -107.81 (s), -114.08 (A**B** system, $^2J_{F-F}$ = 234.4 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{14}NOF_3Na$) = 292.0919; found: 292.0918 (1 ppm).

Synthesis of 2-(4-chlorophenyl)-4,4-difluoro-3a,4,5,6,7,7a-hexahydro-3H-indole 1-oxide 26c

According to the general procedure 3. Yellow solid, yield 40 mg (60%) from 75 mg (0.24 mmol) of **25c**. R_f = 0.2 (Hexane / Ethyl Acetate: 4/6). mp = 208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.18 (m, 2H), 7.47 – 7.30 (m, 2H), 3.95 (t, $^3J_{H-H}$ = 12.0 Hz, 1H), 3.22 – 2.97 (m, 2H), 2.64 – 2.49 (m, 1H), 2.43 – 1.97 (m, 3H), 1.90 – 1.46 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 136.0, 128.9, 128.4, 127.8, 122.2 (dd, $^1J_{C-F}$ = 246.9 Hz, $^1J_{C-F}$ = 245.4 Hz), 73.5 (d, $^3J_{C-F}$ = 9.0 Hz), 46.8 (dd, $^2J_{C-F}$ = 25.5 Hz, $^2J_{C-F}$ = 22.6 Hz), 34.2 (dd, $^2J_{C-F}$ = 25.0 Hz, $^2J_{C-F}$ = 21.9 Hz), 27.6, 26.4 (d, $^4J_{C-F}$ = 1.6 Hz), 21.1 (d, $^3J_{C-F}$ = 9.5 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -99.90 (**A**B system, $^2J_{F-F}$ = 234.2 Hz), -113.97 (A**B** system, $^2J_{F-F}$ = 234.2 Hz). HRMS (ESI): calcd. for [M+Na]$^+$ ($C_{14}H_{14}NOF_2{}^{35}ClNa$) = 308.0624; found: 308.0627 (1 ppm).

Synthesis of 4,4-difluoro-2-(furan-2-yl)-3a,4,5,6,7,7a-hexahydro-3H-indole 1-oxide 26d

According to the general procedure 3. Yellow solid, yield 53 mg (80%) from 75 mg (0.27 mmol) of **25d**. R_f = 0.1 (Hexane / Ethyl Acetate: 4/6). mp = 213 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $^3J_{H-H}$ = 3.5 Hz, 1H), 7.49 (d, $^3J_{H-H}$ = 1.7 Hz, 1H), 6.58 (dd, $^3J_{H-H}$ = 3.5 Hz, $^3J_{H-H}$ = 1.8 Hz, 1H), 3.88 (t, $^3J_{H-H}$ = 12.1 Hz, 1H), 3.21 (dd, $^2J_{H-H}$ = 16.1 Hz, $^3J_{H-H}$ = 6.6 Hz, 1H), 3.03 (ddd, $^2J_{H-H}$ = 16.1 Hz, $^3J_{H-H}$ = 11.1 Hz, $^4J_{H-F}$ = 2.8 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.46 – 2.00 (m, 3H), 1.94 – 1.40 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 143.7, 133.7, 122.2 (dd, $^1J_{C-F}$ = 247.0 Hz, $^1J_{C-F}$ = 245.4 Hz), 114.7, 112.7, 72.0 (d, $^3J_{C-F}$ = 9.1 Hz), 47.6 (dd, $^2J_{C-F}$ = 25.5 Hz, $^2J_{C-F}$ = 22.6 Hz), 34.2 (dd, $^2J_{C-F}$ = 25.1 Hz, $^2J_{C-F}$ = 21.9 Hz), 26.3 (d, $^3J_{C-F}$ = 1.6 Hz), 26.0 (d,

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$^4J_{C\text{-}F}$ = 1.0 Hz), 21.2 (d, $^3J_{C\text{-}F}$ = 9.6 Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$) δ -99.8 (**A**B system, $^2J_{F\text{-}F}$ = 234.7 Hz), -113.7 (A**B** system, $^2J_{F\text{-}F}$ = 234.7 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{12}H_{13}NO_2F_2Na$) = 264.0807; found: 264.0810 (1 ppm).

Synthesis of 4,4-difluoro-2-(4-methoxyphenyl)-3a,4,5,6,7,7a-hexahydro-3H-indole 1-oxide 26e

According to the general procedure 3. White solid, yield 51 mg (75%) from 75 mg (0.24 mmol) of **25e**. R_f = 0.1 (Petroleum Ether / Ethyl Acetate: 5/5). mp = 201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.25 (m, 2H), 7.06 – 6.78 (m, 2H), 4.05 – 3.78 (m, 1H), 3.86 (s, 3H), 3.33 – 2.97 (m, 2H), 2.75 – 2.48 (m, 1H), 2.40 – 2.03 (m, 3H), 1.92 – 1.49 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 140.8, 129.4, 127.4, 122.4 (t, $^1J_{C\text{-}F}$ = 246.2 Hz), 114.0, 73.1, 55.5, 47.0 (t, $^2J_{C\text{-}F}$ = 23.8 Hz), 34.3 (dd, $^2J_{C\text{-}F}$ = 25.2 Hz, $^2J_{C\text{-}F}$ = 21.8 Hz), 27.7, 26.6, 21.2 (d, $^3J_{C\text{-}F}$ = 9.5 Hz). ^{19}F {H} NMR (471 MHz, $CDCl_3$) δ -99.85 (**A**B system, $^2J_{F\text{-}F}$ = 234.0 Hz), -113.96 (A**B** system, $^2J_{F\text{-}F}$ = 234.0 Hz). HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{15}H_{17}NO_2F_2Na$) = 304.1120; found: 304.1123 (1 ppm).

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Keywords: fluorine • nitrones • cascade reactions • propargylic fluorides • nitroalkanes

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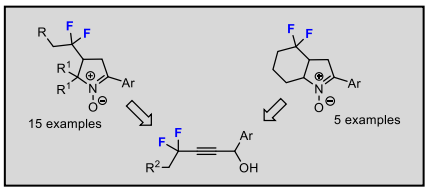

New mono- and bicyclic nitrones containing a CF_2 group have been efficiently synthetized starting from propargylic fluorides. The key steps involve isomerization of propargylic alcohols to enones, followed by nucleophilic addition of nitro alkane anions and then intramolecular Michael additions. The last step is a reductive cyclisation from the nitro group.

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