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A new flexible strategy for the synthesis of *gem*-difluoro-bisarylic derivatives and heterocyclic analogues

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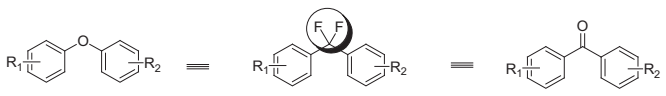
ABSTRACT

A new strategy has been designed for the preparation of *gem*-difluoro-bisarylic derivatives. It starts from easily accessible and reactive *gem*-difluoro-propargylic intermediates and elaborates the aromatic rings by a Diels–Alder-aromatization sequence. Heterocyclic systems can be also obtained by 1,3 dipolar cycloadditions, affording mixed aromatic/heteroaromatic derivatives with CF_2 as a linker. Since this motif is a bioisostere of O and CO, corresponding bisarylic scaffolds could be of use to prepare chemical libraries of fluorinated analogues of bioactive natural products and/or drugs.

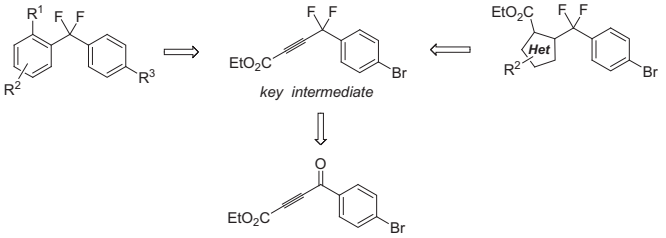
1. Introduction

Diaryl ethers are recognized as important moieties since they are key parts of many natural products,[1] and also very often used in bioorganic and medicinal chemistry.[2] Similarly, diarylketones are also frequently found in the core structures of natural products, drugs or agrochemicals.[3] On the other hand, it is well known that introduction of fluorine in organic molecules strongly modifies their physical, chemical and biological activities and this has been also of much use in fluorobiorganic chemistry.[4] Since CF_2 is usually considered as a bioisostere of the oxygen atom, as well as of a carbonyl group,[5] it would be of much interest to have easy access to *gem*-difluoro-bisarylic derivatives (Scheme 1).



Scheme 1. Diaryl ethers, benzophenones and *gem*-difluoro-bisarylic derivatives.

However, the *gem*-difluorination of benzophenones is a difficult operation, involving usually two-step processes through some intermediates (thioketones or thioketals) and harsh reaction conditions and/or reagents.[6] Moreover, direct fluorination of benzophenones using nucleophilic fluorinating agents, such as Deoxofluor®, has important limitations since it is very sensitive to the nature of substituents on the aromatic systems.[6] Therefore it appeared of interest to develop new strategies to access such attractive molecules. Towards this goal, our design was to build one of the aromatic rings starting from a propargylic *gem*-difluoride as a key intermediate (Scheme 2).



Scheme 2. A new synthetic strategy towards *gem*-difluoro-bisarylic derivatives and mixed aryl-heteroaryl systems.

This new approach takes advantage of the easy access and the good reactivity of such intermediates[7,8] and, further, should allow the preparation of many other carbo- and hetero-cycles through cycloaddition reactions. Moreover, provided appropriate substituents and/or functional groups are introduced on these skeletons, it should also allow the preparation of designed chemical libraries of new fluorinated molecules.

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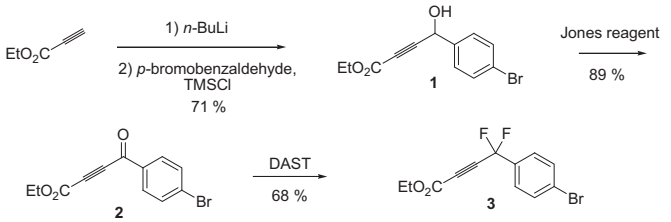
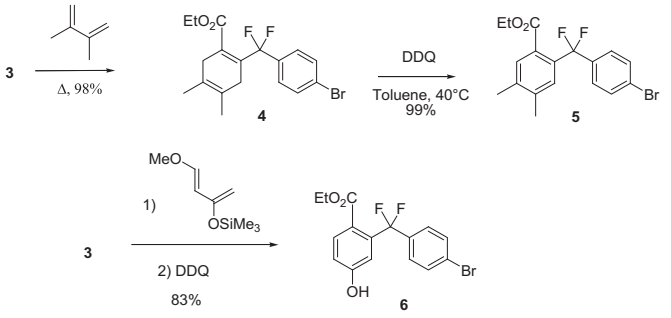
2. Results and discussion

The synthesis of the key *gem*-difluoro intermediate **3** is reported in Scheme 3. Metallation of ethylpropiolate at strictly controlled temperature (≤−80 °C)[9] followed by trapping with *p*-bromobenzaldehyde and then by TMSCl, afforded propargylic alcohol **1** in 71% yield. Oxidation with Jones reagent gave ketone **2** in 89% yield. Due to the presence of the propargylic system[10] and the ester function, this ketone reacted efficiently with diethylaminosulfurtrifluoride (DAST) to afford **3** in 68% yield. Therefore this new *gem*-difluoro-propargylic key intermediate was obtained in three steps and 43% overall yield from ethylpropiolate.



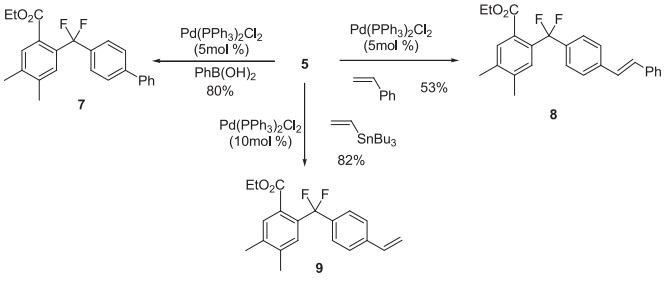
Scheme 3. Synthesis of *gem*-difluoro intermediate **3**.

Starting from intermediate **3** two representative aromatic derivatives have been obtained by a classical Diels–Alder-aromatization sequence, as indicated in Scheme 4. Reaction with excess dimethylbutadiene at reflux giving **4**, followed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) mediated aromatization afforded a first *gem*-difluoro-bisaryl derivative **5** in 96% overall yield. On the other hand, reaction with Danishefsky's diene,[11] followed by DDQ aromatization gave the second *gem*-difluoro-bisarylic molecule **6** in 83% overall yield. In this cycloaddition a single isomer was obtained and the regioselectivity was easily established by extensive NMR analysis.



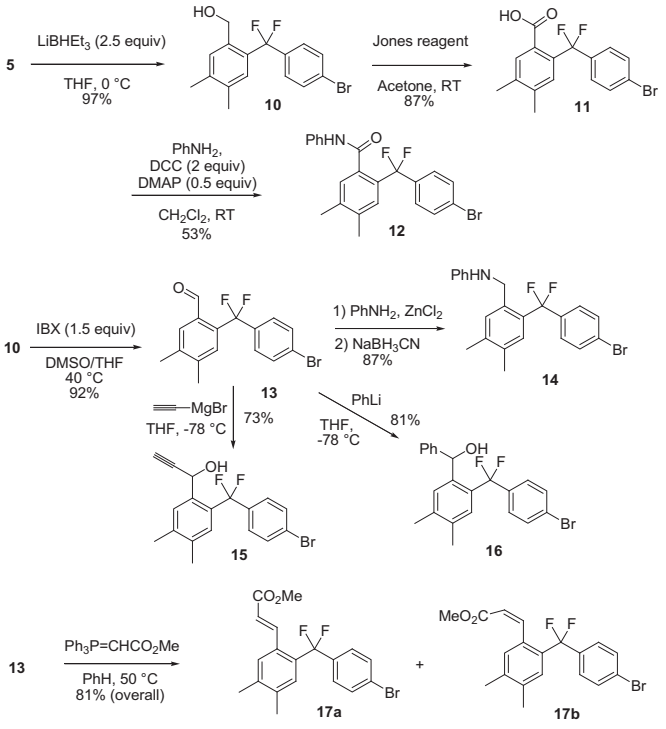
Scheme 4. Synthesis of *gem* - difluoro-bisarylic derivatives **5** and **6**.

The next step was to demonstrate the possibility of using the *p*-bromo substituent in some palladium-catalyzed reactions. Three representative examples, using *gem*-difluoro-bisaryl derivative **5** as a model substrate, are indicated in Scheme 5. First a Suzuki–Miyaura coupling,[12] with phenylboronic acid, afforded biphenyl-type compound **7** in 80% yield. Then Heck reaction,[13] gave the stilbene-type product **8** in 53% yield while Stille cross coupling,[14] afforded styrene-type derivative **9** in 82% yield.



Scheme 5. Palladium-catalyzed reactions on aromatic intermediate **5**.

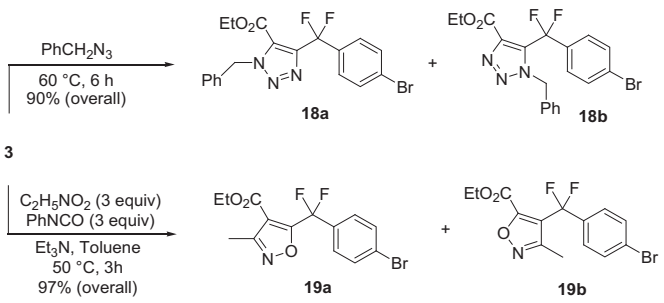
These data indicate that this bromide can be of much use to build designed chemical libraries around this skeleton.[15] However it was of interest to examine the possibility of using the ester group as a second point of molecular diversity. This was performed in several ways, as indicated in Scheme 6. Since saponification of ester group in compound **5** was unsuccessful under various reaction conditions, the acid **11** was prepared in a two steps sequence: reduction with $LiBEt_3H$ affording alcohol **10** in 97% yield, followed by oxidation with Jones reagent gave desired acid **11** in 87% yield. A classical coupling reaction with DCC and DMAP and aniline afforded model amide **12** in 53% yield. Then oxidation of alcohol **10** by 2-iodoxybenzoic acid (IBX) furnished, in 92% yield, the key aldehyde **13**, which was used for several transformations: reductive amination with aniline gave amino derivative **14** in 87% yield. On the other hand, reaction with alkynyl Grignard and phenyl lithium afforded the adducts **15** and **16** in 73% and 81% yields, respectively. Finally, a Wittig reaction with carbomethoxymethylenetriphenylphosphorane gave the alkenes **17a** and **17b** as an 8/1 mixture in 81% overall yield. These isomers were easily separated by silica gel chromatography. These results demonstrate that, on such *gem*-difluoro-bisarylic derivatives, both the bromo substituent and the ester function can be used to introduce new groups and/or functions and therefore such scaffolds are of interest regarding the preparation of chemical libraries for biological studies.



Scheme 6. Synthesis of *gem*-diaryl derivatives **10**–**17**.

The next step was to demonstrate the possibility of using the same propargylic intermediates for the preparation of mixed aromatic/heteroaromatic derivatives with a CF_2 group as linker. This was performed on two representative examples of 1,3 dipolar cycloadditions (Scheme 7). Reaction of **3** with benzyl azide afforded in 90% overall yield a 1/2 mixture of triazoles **18a** and **18b**, separated by silica gel chromatography. The regioselectivity was established based on ^{13}C NMR data: for **18b** there is a small J_{CF} coupling constant (4.5 Hz) between the carbon of the CH_2Ph group with the two fluorine atoms, coupling which do not exist for **18a**. On the other hand, nitrile oxide cycloaddition, using nitroethane under

Mukaiyama's conditions,[16] gave an inseparable (2/1) mixture of isoxazoles **19a** and **19b** in 97% overall yield. The regioselectivity of the cycloaddition was also established by NMR: for **19b** there is a small J_{HF} coupling constant (1.9 Hz) between the two fluorine atoms and the protons of the CH_3 group together with a small J_{CF} coupling constant (3.1 Hz) with the carbon of this CH_3. Such coupling constants are not present in **19a**.



Scheme 7. Synthesis of mixed *gem*-difluoro aromatic/heteroaromatic derivatives **18** and **19**.

3. Conclusion

In conclusion, this study confirms the versatility of propargylic fluorides in the synthesis of useful building blocks for further applications in organic and medicinal chemistry. A functionalized *gem*-difluoro-propargylic intermediate **3**, with a CF_2Ar group, has been prepared for the first time. Through cycloadditions, it afforded versatile scaffolds, which could be developed in many different ways. In particular intermediates of this type could easily generate chemical libraries of bisaromatic or mixed aromatic/heteroaromatic molecules with fluorinated linkers, of interest in bioorganic and medicinal chemistry. Development of this chemistry, as well as preparation of other heterocycles starting from propargylic fluorides, are under active study in our group and will be reported in due course.

4. Experimental section

4.1. 4-(4-Bromophenyl)-4-hydroxybut-2-ynoicacid ethyl ester 1

To a solution of ethylpropiolate (2.1 mL, 0.02 mmol) in anhydrous THF (25 mL) cooled at −90 °C, was added, dropwise under nitrogen, a solution of *n*-BuLi in hexanes (15.3 mL, 1.6 M, 1.2 equiv). The mixture was stirred for 30 min at $t \leq -80$ °C before dropwise addition, of *p*-bromobenzaldehyde (4.26 g, 1.2 equiv) in anhydrous THF (15 mL). After 20 min additional stirring at the same temperature, TMSCl (6.1 mL, 2.5 equiv) was added dropwise. The reaction mixture was stirred for additional 90 min at $t \leq -80$ °C and then in an ice bath for additional 1 h. The mixture was treated with a saturated NH_4Cl solution, extracted by ether (3×80 mL). The combined organic phases were washed with water, dried over $MgSO_4$ and concentrated in vacuo. After purification by chromatography on silica gel, using as eluent a 15/85 ether/pentane mixture, compound **1** was obtained as a yellow oil (4.08 g, 71% yield). R_f=0.16 (Et_2O/pentane, 2/8). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.29 (t, 3H, J=7.1 Hz); 4.22 (q, 2H, J=7.1 Hz); 5.50 (s, 1H); 7.47–7.49 (m, 2H); 7.50–7.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.9; 62.4; 63.4; 77.9; 85.7; 122.8; 128.3; 131.8; 137.5; 153.3. HRMS (ESI) calcd for $C_{12}H_{11}O_3{}^{79}BrNa$: $[M+Na]^+$: m/z 304.9789. Found: m/z 304.9792 (1 ppm).

4.2. 4-(4-Bromophenyl)-4-oxo-but-2-ynoicacid ethylester 2

To alcohol **1** (2.78 g, 9.82 mmol) in acetone (30 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 equiv), the reaction mixture was filtered and the residues were washed with ether. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography on silica gel ketone **2** was obtained as yellow crystals. Mp: 32–34 °C. (2.48 g, 89% yield). R_f=0.26 (Et_2O/pentane, 2/98). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.36 (t, 3H, J=7.1 Hz); 4.34 (q, 2H, J=7.1 Hz); 7.63–7.68 (m, 2H); 7.93–7.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.9; 63.1; 79.2; 80.8; 130.8; 130.9; 132.2; 134.3; 152.0; 175.0. HRMS (ESI) calcd for $C_{12}H_9O_3{}^{79}BrNa$: $[M+Na]^+$: m/z 302.9633. Found: m/z 302.9636 (1 ppm).

4.3. 4-(4-Bromophenyl)-4,4-difluorobut-2-ynoicacid ethylester 3

To propargylic ketone **2** (2.18 g, 7.76 mmol) were added three drops of 95% ethanol and DAST (8.14 mL, 8 equiv). The reaction mixture was stirred at 65 °C for 8 h. After coming back to room temperature, pentane (50 mL) was added, followed by slow addition of a 1% HCl solution. The organic layers were separated, washed with water (3×5 mL), dried over $MgSO_4$ and concentrated under vacuum at 300 mbar pressure. After purification by chromatography on silica gel, ester **3** was obtained as a colourless oil (1.6 g, 68% yield). R_f=0.46 (Et_2O/pentane, 2/98). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.34 (t, 3H, J=7.1 Hz); 4.29 (q, 2H, J=7.1 Hz); 7.50–7.53 (m, 2H); 7.60–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.9; 63.1; 76.3 (t, $^2J_{CF}$=43.9 Hz); 78.7 (t, $^3J_{CF}$=5.9 Hz); 111.1 (t, $^1J_{CF}$=235.5 Hz); 126.0 (t, $^5J_{CF}$=2.3 Hz); 126.9 (t, $^3J_{CF}$=4.8 Hz); 132.1; 133.4 (t, $^2J_{CF}$=27.5 Hz); 151.7 (t, $^4J_{CF}$=2.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −79.69 (s). HRMS (ESI) calcd for $C_{12}H_9O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 324.9652. Found: m/z 324.9652 (0 ppm).

4.4. 2-[(4-Bromophenyl)-difluoromethyl]-5-methylcyclohexa-1,4-dienecarboxylicacid ethylester 4

The difluoro-propargylic ester **3** (1.75 g, 1 equiv) and 2,3-dimethylbutadiene (6.5 mL, 10 equiv) were refluxed neat at 80 °C overnight. After purification by flash chromatography on silica gel, cyclohexadiene **4** was isolated as a colourless oil (2.18 g, 98% yield). R_f=0.68 (Et_2O/pentane, 4/96). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.25 (t, 3H, J=7.1 Hz); 1.58 (s, 3H); 1.64 (s, 3H); 2.53 (m, 2H); 2.92 (m, 2H); 4.20 (q, 2H, J=7.1 Hz); 7.49–7.57 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.9; 17.7; 18.0; 31.6 (t, $^3J_{CF}$=3.2 Hz); 35.5; 61.1; 120.1 (t, $^1J_{CF}$=243.5 Hz); 121.2; 121.6; 124.5 (t, $^5J_{CF}$=2.3 Hz); 127.6 (t, $^3J_{CF}$=5.6 Hz); 128.5 (t, $^2J_{CF}$=25.6 Hz); 130.1 (t, $^3J_{CF}$=4.7 Hz); 131.6; 134.7 (t, $^2J_{CF}$=28.5 Hz); 169.9 (t, $^4J_{CF}$=0.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −92.42 (s). HRMS (ESI) calcd for $C_{18}H_{19}O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 407.0434. Found: m/z 407.0435 (0 ppm).

4.5. 2-[(4-Bromophenyl)difluoromethyl]-4,5-dimethylbenzoicacid ethylester 5

A solution of the cyclohexadiene **4** (790 mg, 1 equiv) and DDQ (559 mg, 1.2 equiv) in toluene (2 mL) was stirred at 40 °C for 2 h. The reaction mixture was filtered on silica gel and the residues were washed with ether. The organic phase was concentrated in vacuo and the product **5** was isolated by flash chromatography on silica as yellow crystals (776 mg, 99% yield). Mp: 83–85 °C. R_f=0.60 (Et_2O/pentane, 4/96). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.10 (t, 3H, J=7.1 Hz); 2.33 (s, 3H); 2.34 (s, 3H); 4.12 (q, 2H, J=7.1 Hz); 7.33–7.36 (m, 2H); 7.42 (s, 1H); 7.46 (s, 1H); 7.49–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.7; 19.4; 19.8; 61.2; 120.3 (t, $^1J_{CF}$=241.5 Hz); 124.2 (t, $^5J_{CF}$=2.5 Hz); 127.9 (t, $^3J_{CF}$=4.9 Hz); 128.5 (t, $^3J_{CF}$=7.7 Hz); 129.0 (t, $^3J_{CF}$=3.4 Hz); 130.8; 131.2; 131.8

(t, $^{2}J_{CF}$=26.8 Hz); 137.1 (t, $^{2}J_{CF}$=28.5 Hz); 139.0 (t, $^{4}J_{CF}$=1.5 Hz); 139.7; 167.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −81.93 (s). HRMS (ESI) calcd for $C_{18}H_{17}O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 405.02778. Found: m/z 405.0278 (0 ppm).

4.6. 2-[(4-Bromo-phenyl)-difluoro-methyl]-4-hydroxy-benzoic acid ethyl ester 6

A mixture of difluoro-propargylic ester **3** (100 mg, 0.33 mmol) and Danishefsky's diene (0.19 mL, 3 equiv), was stirred neat overnight at 70 °C. After addition of DDQ (90 mg, 1.2 equiv) and toluene (1 mL), the mixture was stirred for 3 h at 40 °C. The reaction mixture was filtered and the residues were washed with ether. The combined organic phases were concentrated in vacuo. After purification by flash chromatography on silica gel, the product **6** was isolated as yellow crystals (101 mg, 83% yield). Mp: 130–132 °C. R_f=0.34 (Et_2O/pentane, 30/70). ^{1}H NMR (acetone-d_6, 300 MHz) δ, ppm: 1.06 (t, 3H, J=7.1 Hz); 3.19 (br s, 1H); 4.05 (q, 2H, J=7.1 Hz); 7.08 (dd, 1H, J=8.5 Hz, J=2.5 Hz); 7.25 (d, 1H, J=2.5 Hz); 7.42–7.45 (m, 2H); 7.63–7.66 (m, 2H); 7.70 (d, 1H, J=8.5 Hz). ^{13}C NMR (acetone-d_6, 75 MHz) δ, ppm: 15.0; 62.4; 116.2 (t, $^{3}J_{CF}$=8.7 Hz); 118.6 (t, $^{5}J_{CF}$=1.3 Hz); 122.1 (t, $^{1}J_{CF}$=241.0 Hz); 124.4 (t, $^{3}J_{CF}$=3.3 Hz); 125.5 (t, $^{5}J_{CF}$=2.5 Hz); 129.9 (t, $^{3}J_{CF}$=5.0 Hz); 133.1; 134.4; 138.4 (t, $^{2}J_{CF}$=26.8 Hz); 139.0 (t, J=28.0 Hz); 161.6; 168.3. ^{19}F NMR (acetone-d_6, 282 MHz) δ, ppm: −82.73 (s). HRMS (ESI) calcd for $C_{16}H_{13}O_3F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 392.9914. Found: m/z 392.9911 (1 ppm).

4.7. 2-(Biphenyl-4-yl-difluoro-methyl)-4,5-dimethyl-benzoic acid ethyl ester 7

A solution of bromo-ester **5** (150 mg, 0.39 mmol), phenylboronic acid (96 mg, 2 equiv), palladium dichlorobis(triphenylphosphine) (14 mg, 5 mol %) and potassium carbonate (108 mg, 2 equiv) in a 5/1 mixture of dioxane and water (3 mL) was stirred at 90 °C for 22 h. After addition of $MgSO_4$ and filtration, the residues were washed with ether and the solution concentrated in vacuo. After purification by chromatography on silica gel, the product **7** was isolated as white crystals (120 mg, 80% yield). Mp: 79–81 °C. R_f=0.27 (Et_2O/pentane, 5/95). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.09 (t, 3H, J=7.1 Hz); 2.34 (s, 3H); 2.36 (s, 3H); 4.14 (q, 2H, J=7.1 Hz); 7.34–7.63 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.6; 19.4; 19.9; 61.2; 120.8 (t, $^{1}J_{CF}$=240.9 Hz); 126.6 (t, $^{3}J_{CF}$=4.9 Hz); 126.8; 127.2; 127.7; 128.6 (t, $^{3}J_{CF}$=7.5 Hz); 128.8; 129.2 (t, $^{3}J_{CF}$=3.3 Hz); 130.6; 132.3 (t, $^{2}J_{CF}$=27.1 Hz); 136.9 (t, $^{2}J_{CF}$=28.1 Hz); 138.8 (t, $^{5}J_{CF}$=1.5 Hz); 139.5; 140.3; 142.6 (t, $^{5}J_{CF}$=2.0 Hz); 168.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −81.43 (s). HRMS (ESI) calcd for $C_{24}H_{22}O_2F_2Na$: $[M+Na]^+$: m/z 403.1485. Found: m/z 403.1483 (1 ppm).

4.8. 2-[Difluoro-(4-styryl-phenyl)-methyl]-4,5-dimethyl-benzoic acid ethyl ester 8

DMF (2 mL) was first degassed by bubbling argon. Then were added successively: bromo-compound **5** (100 mg, 0.26 mmol), palladium (dichlorobistriphenylphosphine) (9 mg, 5 mol %), potassium carbonate (72 mg, 2 equiv) and styrene (0.15 mL, 5 equiv). The reaction mixture was stirred under argon at 120 °C for 3 days. After addition of ether (25 mL) the reaction mixture was washed with water (3×5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. After purification by chromatography on silica gel the product **8** was isolated as white crystals (56 mg, 53% yield). Mp: 73–75 °C. R_f=0.29 (Et_2O/pentane, 1/9). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.10 (t, 3H, J=7.1 Hz); 2.34 (s, 3H); 2.35 (s, 3H); 4.13 (q, 2H, J=7.1 Hz); 7.11 (d, 1H, J=16.4 Hz); 7.15 (d, 1H, J=16.4 Hz); 7.27–7.54 (m, 11H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 13.7; 19.3; 19.8; 61.2; 120.7 (t, $^{1}J_{CF}$=240.9 Hz); 126.1; 126.5 (t, $^{3}J_{CF}$=5.0 Hz); 126.6; 127.7; 127.9; 128.6 (t, $^{3}J_{CF}$=7.5 Hz); 128.7; 129.3 (t, $^{23}J_{CF}$=3.2 Hz); 130.0; 130.6; 132.3 (t, $^{2}J_{CF}$=27.1 Hz); 136.9; 137.0 (t, $^{2}J_{CF}$=28.0 Hz); 138.7; 138.8 (t, $^{5}J_{CF}$=2.0 Hz); 139.5; 168.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −81.47 (s). HRMS (ESI) calcd for $C_{26}H_{24}O_2F_2Na$: $[M+Na]^+$: m/z 429.1642. Found: m/z 429.1638 (1 ppm).

4.9. 2-[Difluoro-(4-vinyl-phenyl)-methyl]-4,5-dimethyl benzoic acid ethyl ester 9

A solution of bromo-ester **5** (100 mg, 0.26 mmol), vinyltributylstannane (0.15 mL, 2 equiv), palladium dichlorobis-(triphenylphosphine) (18 mg, 10 mol %) in dioxane (2 mL), was stirred under argon, at 90 °C for 24 h. After filtration, the residues were washed with Et_2O and the solution was concentrated in vacuo. After purification by chromatography on silica gel the product **9** was isolated as white crystals (71 mg, 82% yield). Mp: 62–64 °C. R_f=0.26 (Et_2O/pentane, 5/95). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.08 (t, 3H, J=7.1 Hz); 2.32 (s, 3H); 2.33 (s, 3H); 4.10 (q, 2H, J=7.1 Hz); 5.30 (d, 1H, J=10.9 Hz); 5.78 (d, 1H, J=17.6 Hz); 6.72 (dd, 1H, J=17.6, 10.9 Hz); 7.42–7.44 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.6; 19.4; 19.9; 61.2; 115.2; 120.7 (t, $^{1}J_{CF}$=240.8 Hz); 125.8; 126.4 (t, $^{3}J_{CF}$=5.0 Hz); 128.6 (t, $^{3}J_{CF}$=7.6 Hz); 129.2 (t, $^{3}J_{CF}$=3.3 Hz); 130.6; 132.6 (t, $^{2}J_{CF}$=27.1 Hz); 136.1; 137.3 (t, $^{2}J_{CF}$=27.9 Hz); 138.8 (t, $^{5}J_{CF}$=1.4 Hz); 138.9 (t, $^{5}J_{CF}$=2.1 Hz); 139.5; 168.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −81.63 (s). HRMS (ESI) calcd for $C_{20}H_{20}O_2F_2Na$: $[M+Na]^+$: m/z 353.1329. Found: m/z 353.1328 (0 ppm).

4.10. {2-[(4-Bromophenyl)difluoromethyl]-4, 5-dimethylphenyl}methanol 10

To the ester **5** (276 mg, 0.72 mmol) in anhydrous THF (3 mL) was added, dropwise under magnetic stirring and under N_2 at 0 °C, a 1 M solution of $LiBEt_3H$ in THF (1.8 mL, 2.5 equiv). The reaction mixture was stirred at room temperature for 30 min and then quenched by addition of a saturated NH_4Cl solution and two drops of 2 N HCl. The organic phase was separated, washed with a saturated Na_2CO_3 solution, dried ($MgSO_4$) and concentrated in vacuo. After purification by flash chromatography on silica gel the alcohol **10** was isolated as white crystals (238 mg, 97% yield). Mp: 85–87 °C. R_f=0.27 (Et_2O/pentane, 15/85). ^{1}H NMR (acetone-d_6, 300 MHz) δ, ppm: 2.30 (s, 3H); 2.32 (s, 3H); 4.14 (t, 1H, J=5.6 Hz); 4.50 (d, 2H, J=5.6 Hz); 7.32 (s, 1H); 7.42–7.44 (m, 2H); 7.56 (s, 1H); 7.65–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 19.4; 19.5; 62.0 (t, $^{4}J_{CF}$=3.4 Hz); 121.3 (t, $^{1}J_{CF}$=241.1 Hz); 124.6 (t, $^{5}J_{CF}$=2.4 Hz); 127.8 (t, $^{3}J_{CF}$=5.2 Hz); 127.9 (t, $^{3}J_{CF}$=7.9 Hz); 130.6 (t, $^{2}J_{CF}$=26.3 Hz); 130.9; 131.7; 135.7; 136.2 (t, $^{3}J_{CF}$=2.1 Hz); 136.5 (t, $^{2}J_{CF}$=28.8 Hz); 139.5 (t, $^{5}J_{CF}$=1.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −83.13 (s). HRMS (ESI) calcd for $C_{16}H_{15}OF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 363.0172. Found: m/z 363.0172 (0 ppm).

4.11. 2-[(4-Bromophenyl)-difluoromethyl]-4, 5-dimethylbenzoic acid 11

To a solution of alcohol **10** (100 mg, 0.29 mmol) in acetone (1 mL) was added dropwise at room temperature, a concentrated (5.4 M) solution of Jones reagent until TLC showed the completion of reaction. Then isopropanol (5 equiv) was added to the reaction mixture, which was filtered and the residues were washed with ether. The organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. After purification by flash chromatography on silica gel, the acid **11** was isolated as white crystals (90 mg, 87% yield). Mp: 188–190 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ, ppm: 2.28 (s, 3H); 2.30 (s, 3H); 7.37–7.70 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ, ppm: 18.8; 19.2; 120.4 (t, $^{1}J_{CF}$=241.5 Hz); 123.4 (t, $^{5}J_{CF}$=2.3 Hz); 127.6 (t, $^{3}J_{CF}$=7.7 Hz); 127.8 (t, $^{3}J_{CF}$=5.0 Hz); 129.6 (t, J=3.3 Hz); 130.0; 130.7 (t, $^{2}J_{CF}$=27.0 Hz); 131.2; 136.6 (t, $^{2}J_{CF}$=28.5 Hz); 139.0 (t, $^{5}J_{CF}$=1.3 Hz);

139.2; 168.6. ^{19}F NMR (DMSO-d_6, 282 MHz) δ, ppm: −76.81 (s). HRMS (ESI) calcd for $C_{16}H_{13}O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 376.9965. Found: m/z 376.9966 (0 ppm).

4.12. 2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-*N*-phenyl-benzamide 12

A solution of carboxylic acid **11** (37 mg, 0.10 mmol), DCC (43 mg, 2 equiv), DMAP (7 mg, 0.5 equiv) and aniline (12 μL, 1.2 equiv) was stirred in CH_2Cl_2, at room temperature during 5 h. After addition of a 1% HCl solution, the aqueous and organic phases were separated. The organic phase was washed twice with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by silica gel flash chromatography, the amide **12** was isolated as white crystals (24 mg, 53% yield). Mp: 171–173 °C. R_f=0.32 (Et_2O/pentane, 25/75). ^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm: 2.33 (s, 6H); 7.10–7.15 (m, 1H); 7.29–7.47 (m, 9H); 7.48–7.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 19.4; 19.8; 119.8; 120.6 (t, $^1J_{CF}$=242.3 Hz); 124.5; 124.6 (t, $^5J_{CF}$=2.4 Hz); 127.8 (t, $^3J_{CF}$=5.4 Hz); 128.2 (t, $^3J_{CF}$=7.0 Hz); 129.0; 129.8; 130.8 (t, $^2J_{CF}$=27.2 Hz); 131.5; 133.5 (t, $^3J_{CF}$=3.3 Hz); 136.2 (t, $^2J_{CF}$=28.3 Hz); 137.6; 138.8; 139.5 (t, $^5J_{CF}$=1.7 Hz); 166.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −83.08 (s). HRMS (ESI) calcd for $C_{22}H_{18}NOF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 452.0438. Found: m/z 452.0440 (1 ppm).

4.13. {2-[(4-Bromophenyl)difluoromethyl]-4,5-dimethylbenzaldehyde 13

To a solution of IBX (252 mg, 0.90 mmol, 1.5 equiv) in DMSO (3 mL), was added a solution of alcohol **10** (205 mg, 0.60 mmol) in THF (2 mL) and the reaction mixture was stirred at 40 °C for 1 h. After coming back to room temperature, ice cold water (10 mL) was added. The reaction mixture was filtered and the solid residue washed with ether (10 mL). The organic phase was separated and washed with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by flash chromatography on silica gel, the aldehyde **13** was isolated as white crystals (190 mg, 92% yield). Mp: 78–80 °C. R_f=0.33 (Et_2O/pentane, 2/98). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.36 (s, 6H); 7.30–7.35 (m, 2H); 7.37 (s, 1H); 7.54–7.60 (m, 2H); 7.84 (s, 1H); 10.14 (t, 1H, J=2.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 19.5; 20.3; 120.5 (t, $^1J_{CF}$=242.0 Hz); 125.1 (t, $^5J_{CF}$=2.4 Hz); 127.7 (t, $^3J_{CF}$=5.0 Hz); 128.2 (t, $^3J_{CF}$=7.9 Hz); 130.1; 131.6 (t, $^3J_{CF}$=1.9 Hz); 131.9; 134.9 (t, $^2J_{CF}$=27.6 Hz); 136.6 (t, $^2J_{CF}$=28.1 Hz); 139.8 (t, $^5J_{CF}$=1.5 Hz); 143.2; 190.3 (t, $^4J_{CF}$=3.7 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −78.62 (s). HRMS (ESI) calcd for $C_{16}H_{13}OF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 361.0015. Found: m/z 361.0020 (1 ppm).

4.14. {2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-benzyl}-phenyl-amine 14

A solution of aldehyde **13** (60 mg, 0.18 mmol), aniline (20 μL, 1.2 equiv) and a 1 M solution of zinc chloride (0.23 mL, 1.3 equiv) in THF was stirred at room temperature for 3 h before addition of ethanol (0.5 mL) and sodium cyanoborohydride (33 mg, 3 equiv). The reaction mixture was stirred at room temperature overnight and then quenched by addition of water. The inorganic precipitate was filtered and washed with ethanol. The organic phases were concentrated in vacuo. The crude product was dissolved in ethyl acetate, filtered to remove the remaining inorganic solids and concentrated in vacuo. After purification by flash chromatography on silica gel, the amine **14** was isolated as white crystals (64 mg, 87% yield). Mp: 114–116 °C. R_f=0.37 (Et_2O/pentane, 4/96). ^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm: 2.28 (s, 3H); 2.32 (s, 3H); 3.86 (br s); 4.18 (s, 2H); 6.40–6.43 (m, 2H); 6.68–6.72 (m, 1H); 7.10–7.14 (m, 2H); 7.34 (s, 1H); 7.35–7.38 (m, 2H); 7.39 (s, 1H); 7.52–7.56 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 19.5; 19.7; 45.2 (t, $^4J_{CF}$=3.2 Hz); 112.8; 117.5; 121.2 (t, $^1J_{CF}$=241.8 Hz); 124.6 (t, $^2J_{CF}$=2.5 Hz); 127.9 (t, $^3J_{CF}$=5.1 Hz), 127.9 (t, $^3J_{CF}$=8.1 Hz); 129.2; 130.7; 131.3 (t, $^2J_{CF}$=26.1 Hz); 131.7; 134.8 (t, $^3J_{CF}$=2.3 Hz); 135.4; 136.6 (t, $^2J_{CF}$=28.6 Hz); 139.4 (t, $^5J_{CF}$=1.6 Hz); 147.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ, ppm: −84.64 (s). HRMS (ESI) calcd for $C_{22}H_{20}NF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 438.0645. Found: m/z 438.0646 (0 ppm).

4.15. 1-{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-prop-2-yn-1-ol 15

To a solution of aldehyde **13** (48 mg, 0.14 mmol) in anhydrous THF (1 mL) was added dropwise at 0 °C under nitrogen, a 0.5 M solution of ethynyl magnesium bromide in THF (0.34 mL, 0.17 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h, at 0 °C, before quenching by addition of a saturated NH_4Cl solution. After extraction with diethyl ether, the organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by chromatography on silica gel, the product **15** was isolated as white crystals (38 mg, 73% yield). Mp: 83–85 °C. R_f=0.23 (Et_2O/pentane, 20/80). ^{1}H NMR ($CDCl_3$, 400 MHz) δ, ppm: 2.17 (d, 1H, J=4.2 Hz); 2.29 (s, 3H); 2.34 (s, 3H); 2.53 (d, 1H, J=2.2 Hz); 5.58 (dd, 1H; J=4.2, 2.2 Hz); 7.24 (s, 1H); 7.32–7.34 (m, 2H); 7.54–7.56 (m, 2H); 7.72 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 19.5; 19.6; 60.4 (t, $^4J_{CF}$=3.7 Hz); 74.2; 83.5; 121.0 (t, $^1J_{CF}$=241.0 Hz); 124.9 (t, $^5J_{CF}$=2.4 Hz); 127.8 (t, $^3J_{CF}$=7.7 Hz); 127.9 (t, $^3J_{CF}$=5.0 Hz); 130.2 (t, $^2J_{CF}$=26.2 Hz); 130.3; 131.7; 136.1 (t, $^3J_{CF}$=1.9 Hz); 136.3 (t, $^2J_{CF}$=28.5 Hz); 137.2; 140.1 (t, $^5J_{CF}$=1.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −81.67 (d, J=268. 6 Hz), −80.63 (d, J=268.5 Hz, AB system). HRMS (ESI) calcd for $C_{18}H_{15}OF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 387.0172. Found: m/z 387.0175 (1 ppm).

4.16. {2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-phenyl-methanol 16

To a solution of aldehyde **13** (50 mg, 0.15 mmol) in anhydrous THF (1 mL) was added, dropwise under magnetic stirring and under nitrogen at −70 °C, a 1.5–1.7 M solution of phenyl lithium in a 70/30 mixture of cyclohexane and ether (0.11 mL, 1.2 equiv). The mixture was stirred for 2 h at this temperature, before quenching by addition of a saturated NH_4Cl solution. After extraction with diethyl ether, the organic phases were washed with water, dried ($MgSO_4$) and concentrated in vacuo. After purification by silica gel chromatography, the alcohol **16** was isolated as white crystals (50 mg, 81% yield). Mp: 85–87 °C. R_f=0.38 (Et_2O/pentane, 20/80). ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.06 (s, 1H); 2.26 (s, 3H); 2.31 (s, 3H); 6.03 (s, 1H); 7.19–7.39 (m, 9H); 7.53–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 19.5; 19.7; 70.6 (t, $^4J_{CF}$=2.7 Hz); 121.1 (t, $^1J_{CF}$=241.4 Hz); 124.7 (t, $^5J_{CF}$=2.5 Hz); 126.3; 127.0; 127.4; (t, $^3J_{CF}$=8.1 Hz); 127.9 (t, $^3J_{CF}$=4.9 Hz); 128.1; 130.8; 130.9 (t, $^2J_{CF}$=25.7 Hz); 131.7; 136.2; 136.9 (t, $^2J_{CF}$=28.5 Hz); 139.5 (t, $^3J_{CF}$=2.1 Hz); 139.7 (t, $^5J_{CF}$=1.6 Hz); 143.0. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −82.25 (d, J=266.0 Hz), −79.83 (d, J=266.0 Hz, AB system). HRMS (ESI) calcd for $C_{22}H_{19}OF_2{}^{79}BrNa$: $[M+Na]^+$: m/z 439.0485. Found: m/z 439.0485 (0 ppm).

4.17. 3-{2-[(4-Bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-(*E*)-acrylic acid methyl ester (17a) and 3-{2-[(4-bromo-phenyl)-difluoro-methyl]-4,5-dimethyl-phenyl}-(*Z*)-acrylic acid methyl ester 17b

A solution of aldehyde **13** (50 mg, 0.15 mmol) and Ph_3PCHCO_2Me [100 mg, 2 equiv in benzene (1 mL)] was stirred at 50 °C for 6 h. The reaction mixture was filtered on a short pad of silica gel to remove large part of triphenylphosphine oxide, the residues washed with ether and the solution concentrated in vacuo. The alkenes **17a** and **17b**, obtained in an 8/1 ratio by NMR analysis, were separated by chromatography on silica gel (47 mg, 81% combined yield).

Compound **17a**: white crystals (42 mg, 72% yield). Mp: 122–124 °C. R_f=0.49 (Et_2O/pentane, 20/80). ^1H NMR ($CDCl_3$, 400 MHz) δ, ppm: 2.31 (s, 3H); 2.32 (s, 3H); 3.74 (s, 3H); 6.19 (d, 1H, J=15.8 Hz); 7.30–7.33 (m, 2H); 7.38 (s, 1H); 7.39 (s, 1H); 7.51–7.54 (m, 2H); 7.83 (dt, 1H, J_{HH}=15.8 Hz, J_{HF}=1.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 19.5; 19.8; 51.6; 119.5; 120.6 (t, $^1J_{CF}$=242.4 Hz); 124.6 (t, $^5J_{CF}$=2.3 Hz); 127.8 (t, $^3J_{CF}$=5.1 Hz); 127.9 (t, $^3J_{CF}$=7.9 Hz); 129.1; 130.6 (t, $^3J_{CF}$=2.5 Hz); 131.7; 132.5 (t, $^2J_{CF}$=26.0 Hz); 136.6 (t, $^2J_{CF}$=28.7 Hz); 138.6; 139.3; 142.1 (t, $^4J_{CF}$=2.6 Hz); 166.8. ^{19}F NMR ($CDCl_3$, 376 MHz) δ, ppm: −83.87 (s). HRMS calcd for $C_{19}H_{17}O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 411.0278. Found: m/z 417.0280 (1 ppm). Compound **17b**: White crystals (5 mg, 9% yield). Mp: 63–65 °C. R_f=0.66 (Et_2O/pentane, 20/80). ^1H NMR ($CDCl_3$, 500 MHz) δ, ppm: 2.29 (s, 3H); 2.31 (s, 3H); 3.55 (s, 3H); 5.78 (d, 1H, J=12.0 Hz); 7.04 (d, 1H, J=12.0 Hz); 7.08 (s, 1H); 7.29–7.33 (m, 2H); 7.36 (s, 1H); 7.47–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm: 19.5; 19.7; 51.1; 120.5; 120.7 (t, $^1J_{CF}$=241.8 Hz); 124.4 (t, $^5J_{CF}$=2.3 Hz); 127.3 (t, $^3J_{CF}$=7.5 Hz); 128.1 (t, $^3J_{CF}$=5.0 Hz); 130.8 (t, $^2J_{CF}$=25.2 Hz); 131.4; 131.5; 132.0 (t, $^3J_{CF}$=3.0 Hz); 136.5 (t, $^2J_{CF}$=28.5 Hz); 136.7; 138.4 (t, $^4J_{CF}$=1.4 Hz); 143.0; 165.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ, ppm: −86.03 (s). HRMS (ESI) calcd for $C_{19}H_{17}O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 411.0278. Found: m/z 417.0276 (0 ppm).

4.18. 3-Benzyl-5-[(4-bromophenyl)-difluoromethyl]-3*H*-[1,2,3]triazole-4-carboxylicacid ethyl ester 18a and 1-benzyl-5-[(4-bromo-phenyl)-difluoromethyl]-1*H*-[1,2,3]triazole-4-carboxylicacid ethyl ester 18b

The difluoro-propargylic ester **5** (195 mg, 0.64 mmol, 1 equiv) and benzyl azide (0.12 mL, 1.5 equiv) were stirred, neat, at 60 °C for 6 h. The adducts **18a** and **18b**, obtained in a 1/2 ratio by NMR analysis, were separated by chromatography on silica gel (251 mg, 90% combined yield). Compound **18a** (83 mg, 30% yield) was obtained as white crystals. Mp: 50–52 °C. R_f=0.41 (Et_2O/pentane, 1/9). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.22 (t, 3H, J=7.1 Hz); 4.27 (q, 2H, J=7.1 Hz); 5.87 (s, 2H); 7.28–7.36 (m, 5H); 7.44–7.46 (m, 2H); 7.56–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.7, 54.1; 62.6; 116.3 (t, $^1J_{CF}$=240.9 Hz); 124.8 (t, $^5J_{CF}$=2.3 Hz); 126.4; 127.6 (t, $^3J_{CF}$=5.6 Hz); 128.0; 128.6; 128.8; 131.5; 134.2; 134.9 (t, $^2J_{CF}$=27.1 Hz); 145.4 (t, $^2J_{CF}$=34.4 Hz); 157.7. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −87.72 (s). HRMS (ESI) calcd for $C_{19}H_{16}N_3O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 458.0292. Found: m/z 458.0288 (1 ppm). Compound **18b** (168 mg, 60% yield) was obtained as white crystals. Mp: 86–88 °C. R_f=0.40 (Et_2O/pentane, 2/8). ^1H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.26 (t, 3H, J=7.1 Hz); 4.27 (q, 2H, J=7.1 Hz); 5.76 (s, 2H); 7.01–7.05 (m, 2H); 7.12–7.15 (m, 2H); 7.22–7.31 (m, 3H); 7.35–7.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, ppm: 13.9; 54.9 (t, $^3J_{CF}$=4.5 Hz); 61.8, 116.7 (t, $^1J_{CF}$=242.7 Hz); 125.5 (t, $^5J_{CF}$=2.5 Hz); 127.1 (t, $^3J_{CF}$=5.0 Hz); 127.7; 128.7; 128.8; 131.6; 133.1 (t, $^2J_{CF}$=26.9 Hz); 133.8, 134.0 (t, $^2J_{CF}$=34.7 Hz); 139.3 (t, $^3J_{CF}$=2.0 Hz); 159.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −83.185 (s). HRMS (ESI) calcd for $C_{19}H_{16}N_3O_2F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 458.0292. Found: m/z 458.0293 (0 ppm).

4.19. 5-[(4-Bromo-phenyl)-difluoro-methyl]-3-methyl-isoxazole-4-carboxylic acid ethyl ester (19a) and 4-[(4-bromo-phenyl)-difluoro-methyl]-3-methyl-isoxazole-5-carboxylic acid ethyl ester (19b)

A solution of fluoro-alkyne **5** (100 mg, 0.33 mmol), $C_2H_5NO_2$ (70 μL, 3 equiv), PhNCO (110 μL, 3 equiv) and three drops of Et_3N in toluene (5 mL) was stirred, at 50 °C during 3 h. The reaction mixture was filtered on silica gel, and concentrated in vacuo. The two isomers **19a** and **19b** were obtained as a 2/1 mixture by NMR analysis. The, inseparable mixture, of **19a** and **19b** was isolated as yellow oil by chromatography on silica gel (115 mg, 97% yield). The analysis of the spectral data could be done on this purified reaction mixture. **19a**: R_f=0.42 (Et_2O/pentane, 10/90). ^1H NMR ($CDCl_3$, 400 MHz) δ, ppm: 1.26 (t, 3H, J=7.1 Hz); 2.45 (s, 3H), 4.25 (q, 2H, J=7.1 Hz); 7.45–7.50 (m, 2H); 7.57–7.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 11.4; 13.9; 61.5; 111.2 (t, $^3J_{CF}$=1.4 Hz); 114.8 (t, $^1J_{CF}$=246.0 Hz); 125.6 (t, $^5J_{CF}$=2.3 Hz); 127.2 (t, $^3J_{CF}$=5.5 Hz); 131.8; 133.0 (t, $^2J_{CF}$=26.9 Hz); 158.8 (t, $^4J_{CF}$=1.2 Hz); 160.8 (t, $^4J_{CF}$=0.7 Hz); 166.3 (t, $^2J_{CF}$=36.4 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −92.27 (s). **19b**: R_f=0.42 (Et_2O/pentane, 10/90). ^1H NMR ($CDCl_3$, 400 MHz) δ, ppm: 1.27 (t, 3H, J=7.1 Hz); 2.40 (t, 3H, J=1.9 Hz); 4.29 (q, 2H, J=7.1 Hz); 7.41–7.43 (m, 2H); 7.54–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ, ppm: 11.6 (t, $^4J_{CF}$=3.1 Hz); 13.7; 62.7; 117.3 (t, $^1J_{CF}$=240.2 Hz); 119.1 (t, $^2J_{CF}$=34.3 Hz); 125.1 (t, $^5J_{CF}$=2.4 Hz); 127.1 (t, $^3J_{CF}$=5.4 Hz); 131.8; 135.0 (t, $^2J_{CF}$=27.9 Hz); 156.1 (t, $^3J_{CF}$=1.2 Hz); 158.0 (t, $^3J_{CF}$=4.8 Hz); 160.0 (t, $^4J_{CF}$=0.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz) δ, ppm: −83.89 (s). HRMS (**19a**+**19b**) (ESI) calcd for $C_{14}H_{12}NO_3F_2{}^{79}BrNa$: $[M+Na]^+$: m/z 381.9866. Found: m/z 381.9868 (0 ppm).

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References and notes

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