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Indium-mediated reduction of β-aminovinyl chloro-difluoromethylated ketones in the presence of heteroaryl aldehydes A mild entry to novel difluoromethylene enaminone derivatives

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Dedicated to Professor Kenji Uneyama with friendship and deepest recognition on the occasion of his receipt of the 2007 ACS Award for Creative Work in Fluorine Chemistry.

Abstract

The synthesis of new β-aminovinyl chloro-difluoromethylated ketones **1** and **2** is presented. In some of them the activation of the C–Cl bond was achieved, under mild conditions, using indium powder. The corresponding difluoro-enolates were trapped with a series of aromatic and heterocyclic aldehydes, to furnish the corresponding difluoromethylene aldol products **3** and **4**, in moderate to good yields. The present synthetic methodology provides a convenient approach for the preparation of novel difluoromethylene functionalized enaminone derivatives.

Keywords: Indium; Enaminones; Nucleophilic addition; Electron transfer

1. Introduction

Difluoromethylene derivatives are an important class of compounds because of their synthetic and biological importance [1]. One of the most common ways to prepare complex molecules bearing a CF_2 moiety is based on the ''building block'' approach, i.e., starting from a difluoromethylene-containing starting material [2]. For some years we have been interested to develop new synthetic approaches to prepare fluorinated organic molecules, especially those having a CF_2 moiety. Among the recent studies developed in our laboratories, we have shown that a series of halogeno-difluoromethyl aromatics and heterocycles could be successfully engaged in anionic and radical coupling reactions giving access to novel difluoromethylene derivatives [3]. Trifluoromethylated β-aminovinyl ketones are known and have been frequently used as valuable building blocks, to prepare various trifluoromethylated aromatics and heterocycles [4]. Some chloro-difluoromethylated analogs were also prepared in these studies, but the synthetic potential that could be derived from the chemoselective activation of the C–Cl bond, has been rarely investigated [5]. As part of a research program directed to the synthesis of novel fluorinated heterocycles with potential biological applications, we presented the indium activation of some aromatic chloro-difluoromethylated enaminones in the presence of a series of heteroaryl aldehydes [6]. Indium closely resembles zinc in several aspects and its first ionization potential (5.8 eV) is the lowest relative to other metal elements near in the periodic table [7]. Its synthetic use in organofluorine chemistry is recent [8] and most of the work reported in the literature is related to allylation reactions of fluorinated compounds or indium-mediated cross-coupling reactions of a

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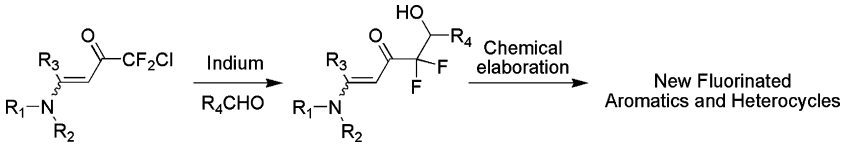
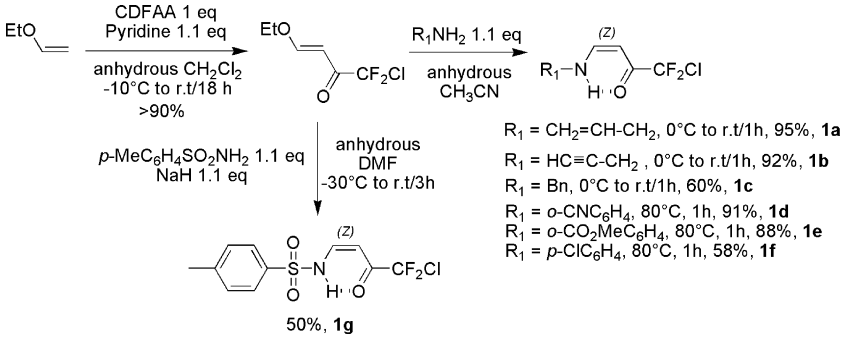


Scheme 1.



Scheme 2.

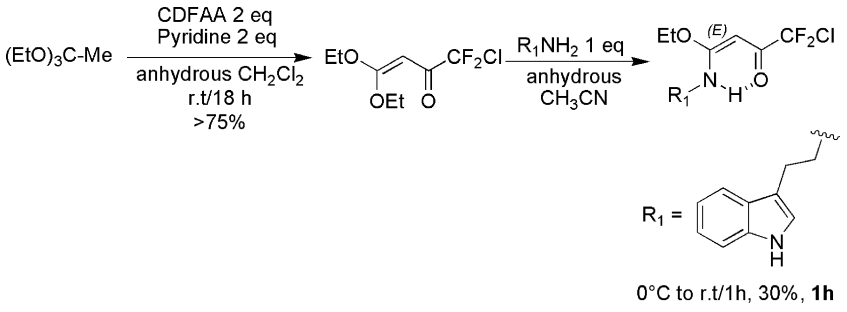
gem-difluoropropargyl starting material that generate a stable difluoroallenyl indium species.

This paper is an extension of our previous report [6], that describes indium as a potential synthetic electron transfer reagent, to promote C–C coupling reactions with some new β-aminovinyl chloro-difluoromethylated ketones and a series of heteroaryl aldehydes (Scheme 1). The coupling adducts are envisaged as potential building blocks to prepare new fluorinated aromatics and heterocycles.

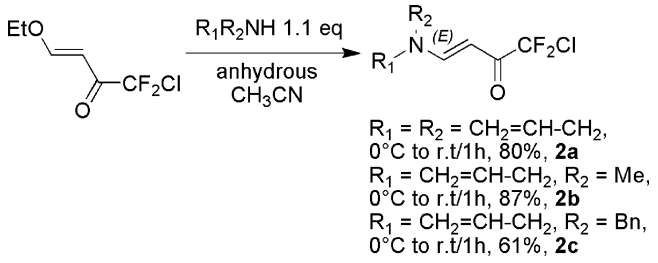
2. Results and discussion

Starting materials of the general structure **1** were prepared in good yields in two steps: chloro-difluoroacetylation of commercially available ethyl vinyl ether [chloro-difluoroacetic anhydride (CDFAA)/pyridine in anhydrous dichloromethane], followed by O–N exchange reaction of the resulting crude (*E*)-1-chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one, with the corresponding amines (slight excess) in anhydrous acetonitrile (Scheme 2). The allylic, propargylic and benzylic substrates **1a–c** were obtained in moderate to good yields (60–95%) through the dropwise addition of the amines to a cooled (0 °C) anhydrous acetonitrile solution containing the crude (*E*)-1-chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one, followed by warming the reaction mixture to room temperature for one hour. The aromatic substrates **1d,e** [6] and **1f** [9] were also obtained in very good yields under refluxing conditions for 1 h (TLC monitoring). The substrate **1g** was obtained in a modest 50% isolated yield after silica gel chromatography by means of using *p*-toluenesulfonamide (1.1 equiv.) in the presence of NaH (1.1 equiv.) in anhydrous DMF (−30 °C to room temperature over 3 h). Substrate **1h** was prepared by adding tryptamine to crude 1-chloro-4,4-diethoxy-1,1-difluorobuten-3-en-2-one [10] and was obtained in a 30% isolated yield (not optimized, Scheme 3). The free NH substrates **1a–g** were obtained as *Z* isomers (and *E* isomer for **1h**), as determined by ^{1}H NMR (small coupling constant of the olefinic protons of 6–8 Hz and a deshielded peak of the amino proton $\delta_H > 10.0$ ppm) due to hydrogen bonding between NH and C=O. Compounds **1a–b** were obtained as yellowish liquids and are pure enough to be used for the next steps, whereas **1c** (yellowish liquid) was purified by silica gel chromatography. **1d–g** were obtained as solids and were recrystallized from the crude product. Tryptamine derivative **1h** precipitated during the reaction and was recovered as a white solid after a simple filtration.

Starting materials of general structure **2a–c** were obtained by adding secondary amines R_1R_2NH to the crude (*E*)-1-chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one in anhydrous acetonitrile using the same conditions for the synthesis of **1** (Scheme 4). *N*-Allylbenzylamine was prepared as described in



Scheme 3.



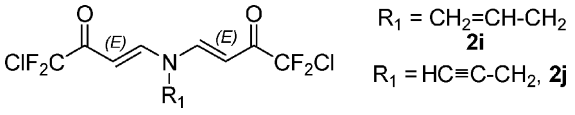
Scheme 4.

[11], but the other secondary amines (*N*,*N*-diallylamine and *N*-methylallylamine) were commercially available.

Protection of the free NH of substrates **1** was achieved with Boc_2O and tosyl chloride (TsCl) in moderate to excellent yields (Scheme 5). The introduction of the Boc moiety into **1a**, was achieved with Boc_2O and pyridine as the base and solvent, to furnish the corresponding enaminone **2d** in a 95% isolated yield. The reaction conditions (Boc_2O/$NaHCO_3$/Toluene/Δ) used to make derivatives **2g**,**h** [6] did not give satisfactory yields with **1a**. Enaminone derivatives with a tosyl protecting group **2e**,**f** were obtained in moderate yields using anhydrous potassium carbonate and tosyl chloride in toluene at 70 °C. A minor impurity was often observed during these tosylation reactions, identified as the bis-enaminone derivatives **2i** and **2j** (Scheme 6).

It is worth to mention that, while attempting to improve the yield of **2f** using NaH and TsCl in anhydrous DMF, the enaminone derivative **2j** was obtained as the major product in a 48% isolated yield, along desired **2f** in 19% isolated yield (Scheme 7). Probably, part of the anion generated by the deprotonation of the free NH with NaH gave rise a Michael addition with **2f** giving, after an N-N exchange reaction, product **2j** as a *E*,*E* isomer, as determined by ^{1}H NMR.

Examination by cyclic voltammetry of the reduction potential of substrates **1** and **2** showed that these compounds were reduced at potentials between −1.25 and −1.95 V *versus* SCE (first peak potentials measured in DMF/NBu_4PF_6 0.1 M); the free NH enaminones **1a–c** and **2a–c** are the most difficult to reduce, while the enaminones **1d–g** (and **2g**,**h**) were the easiest compounds to be reduced in the series. These data indicate that these enaminones might be good candidates for useful single coupling reactions using suitable electron transfer reagents.

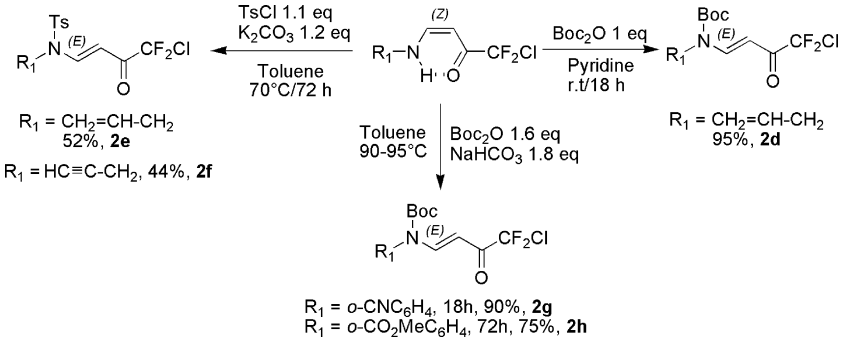


Scheme 6.

As indium might be considered as a possible reductant, we therefore examined the possibility to activate the C–Cl bond of some of these enaminones, using indium in anhydrous THF containing water [6]. The coupling reaction with a series of aromatic and heterocyclic aldehydes was then achieved at room temperature in THF/H_2O (1/4) [6] and the results are presented in Table 1. This combination of solvents was found to be the best medium for these indium-mediated reactions, usually at room temperature. Running the reactions at an elevated temperature (80 °C) did shorten the reaction time but did increase as well the yield of the reduction product **5**. In addition several new fluorinated impurities were detected by ^{19}F NMR. Replacing THF/H_2O by EtOH/H_2O gave similar results, at least at room temperature. The reaction was best monitored by ^{19}F NMR (and TLC when possible) until all the starting material was consumed or when the crude NMR spectrum remained unchanged for a couple of hours.

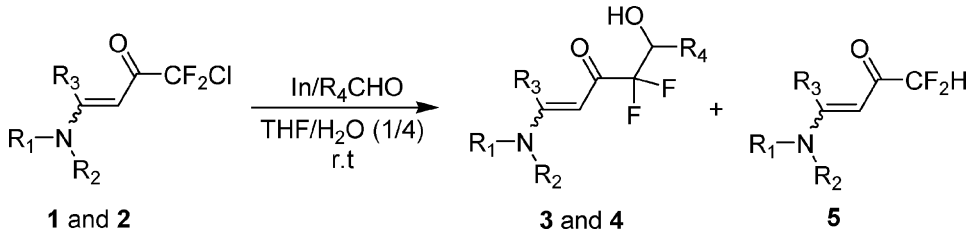
Substrate **1a** was chosen as a model and was engaged in coupling reactions with three aromatic aldehydes: benzaldehyde, 2-bromo benzaldehyde and *p*-trifluoromethyl benzaldehyde. With benzaldehyde and an excess of indium (2.3 equiv., entry 1) the alcohol adduct **3aa** was obtained in a 40% isolated yield (60% by ^{19}F NMR), after three hours of vigorous stirring. Ratio of alcohol/reduction product was close to 2:1; we found that 1.0 equiv. of indium gave a similar yield of **3aa**, although after a longer reaction time period (24 h) and a similar quantity of reduction product **5**. Other aldehydes gave similar yields of adducts **3ab** (entry 2) and **3ac** (entry 3) with good conversions (80–100%). Surprisingly the coupling reaction with *p*-trifluoromethyl benzaldedhyde (entry 3) worked relatively well with no appreciable formation of the pinacol, in contrast to the coupling reactions of **1d** or **1e** with the same aldehyde, where the pinacol was the only product [6].

The coupling reaction of propargylic substrate **1b** with benzaldehyde (entry 4) gave a complex mixture as judged by ^{19}F NMR analysis of the crude reaction, despite the starting material being apparently consumed; no desired alcohol **3ba**



Scheme 5.

Table 1
Indium coupling reactions of β-aminovinyl chloro-difluoromethylated ketones **1–2** with heteroaryl aldehydes[a]



1 and **2** **3** and **4** **5**

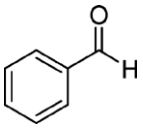
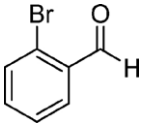
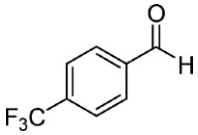
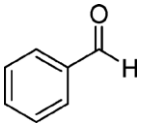
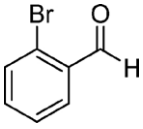
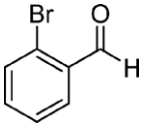
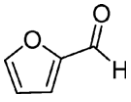
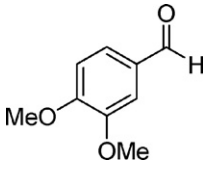
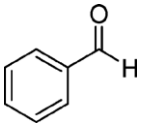
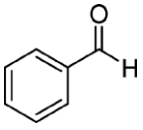
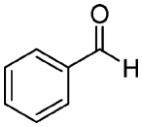
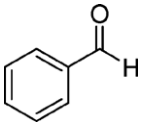
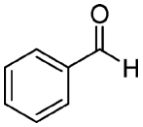
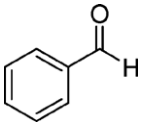
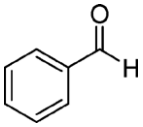
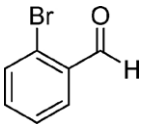
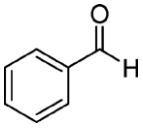
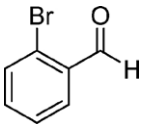
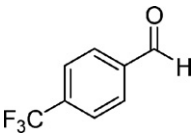
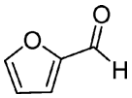
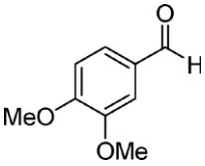
Entry	**1** or **2**	Aldehyde	In (equiv.)	Time (h)	Conversion	Ratio (**3** or **4**):**5**	Yield[b]
1	**1a**		2.3 1.0	3 24	100 97	2:1 2:1	**3aa**; 40 (60) **3aa**; 45 (45)
2	**1a**		1.0	24	80	1:1	**3ab**;50(60)
3	**1a**		1.0	48	90	15:1	**3ac**; 60
4	**1b**		1.0	18	c	nd	**3ba**[c]
5	**1d**		1.5	17	100	9:1	**3db**; 90
6	**1e**		1.0	36	98	8:1	**3eb**; 78
7	**1e**		1.3	48	95	5:3	**3ed**;34
8	**1e**		1.0	24	30	5:2	**3ee**;(11)
9	**1f**		1.2	24	95	2.5:1	**3fa**; 59
10	**1g**		2.0	27	100	50:1	**3ga**; (36)[d]

Table 1 (*Continued*)

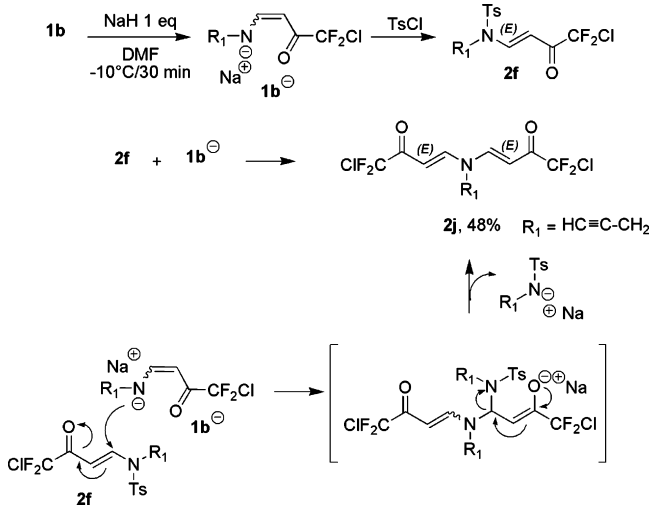
Entry	**1** or **2**	Aldehyde	In (equiv.)	Time (h)	Conversion	Ratio (**3** or **4**):**5**	Yield[b]
11	**1h**		3.0	430	50	3:2	**3ha**; (14)
12	**2a**		1.0	4	100	3:2	**4aa**; 30
13	**2b**		1.2	15	100	3:2	**4ba**; 56
14	**2c**		1.0	4	100	2: 1	**4ca**; 55
15	**2d**		1.0	18	100	1:0	**4da**; 60
16	**2d**		1.0	48	92	1:0	**4db**; 53
17	**2e**		2.3	24	100	1:0	**4ea**; 70
18	**2e**		1.0	24	100	1:0	**4eb**;(74)
19	**2e**		1.0	48	100	30:1	**4ec**; 30
20	**2e**		1.0	24	75	15:1	**4ed**; 24 (82)
21	**2e**		1.0	48	100	50:1	**4ee**; 41

[a] Substrate **1** or **2** (1 mmol) was first dissolved in freshly distilled THF (1 mL) followed by the addition of the aldehyde (1–2 mmol). The mixture was stirred gently and then H_2O (4 mL) was added dropwise. Indium was finally added at once and the whole mixture was vigorously stirred and monitored by ^{19}F NMR (and TLC) for the indicated time. Mixture was then filtrated over Celite® and the filter cake washed with EtOAc and H_2O. Extraction and purification by recrystallization or silica gel chromatography gave the desired alcohol adduct.

[b] Isolated yields (in parentheses, ^{19}F NMR yield).

[c] Complex reaction mixture.

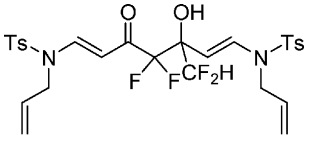
[d] Alcohol adduct was unstable during silica gel chromatography purification.



Scheme 7.

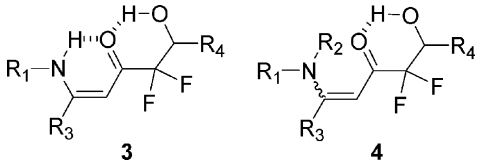
could be isolated. Other free NH enaminones **1d** (entry 5), **1e** (entries 6 and 7), **1f** (entry 9) gave usually good yields of alcohols, with good conversions with the exception of reaction of **1e** with 3,4-dimethoxyphenyl benzaldehyde (entry 8) and **1h** with benzaldehyde (entry 11). Alcohol adduct **3ga** (entry 10), resulting from the coupling reaction of **1g** and benzaldehyde needed 2 equiv. of indium but was too unstable to be isolated by silica gel chromatography. In addition ^{19}F NMR analysis of the crude reaction mixture revealed that for some reactions (with **1a**, **1g** and **1h**) a substantial loss of mass balance was observed. The reaction between **1h** and benzaldehyde was found to take place very slowly, even with an excess of indium (3 equiv.) and with a modest conversion; the tryptamine derived adduct **3ha** was obtained in only 14% (^{19}F NMR yield). In general in the free NH enaminone series, the substrates having an aryl moiety (**1d–f**) gave usually better yields of the corresponding alcohol adducts.

The coupling reactions with disubstituted enaminones **2** gave also moderate to good yields of adducts, with usually good conversions and within a comparable reaction time period. For substrate **2e** ^{19}F NMR analysis of the crude reaction mixture indicated the presence of a new fluorinated product (~2–5%) besides the formation of alcohol adducts (**4ea**, **4eb**, **4ec**, **4ed** and **4ee**; entries 17–21) and reduction product **5**. This impurity was identified as the cross aldol product of type **6** by ESI-MS [m/z = 1282.8 $(2M + Na)^+$, 653.1 $(M + Na)^+$, 630.9 (MH^+)]; this impurity was only observed with the substrate **2e**.



6

All the coupling reactions gave as by-product the corresponding reduced enaminone **5** which can be separated by silica gel chromatography, with the exception of the reactions using **2d** benzaldehyde and 2-bromo benzaldehyde (entries 15 and 16) and reaction using **2e** and benzaldehyde (entry 17), which gave no hydrogenolysis product. The



Scheme 8.

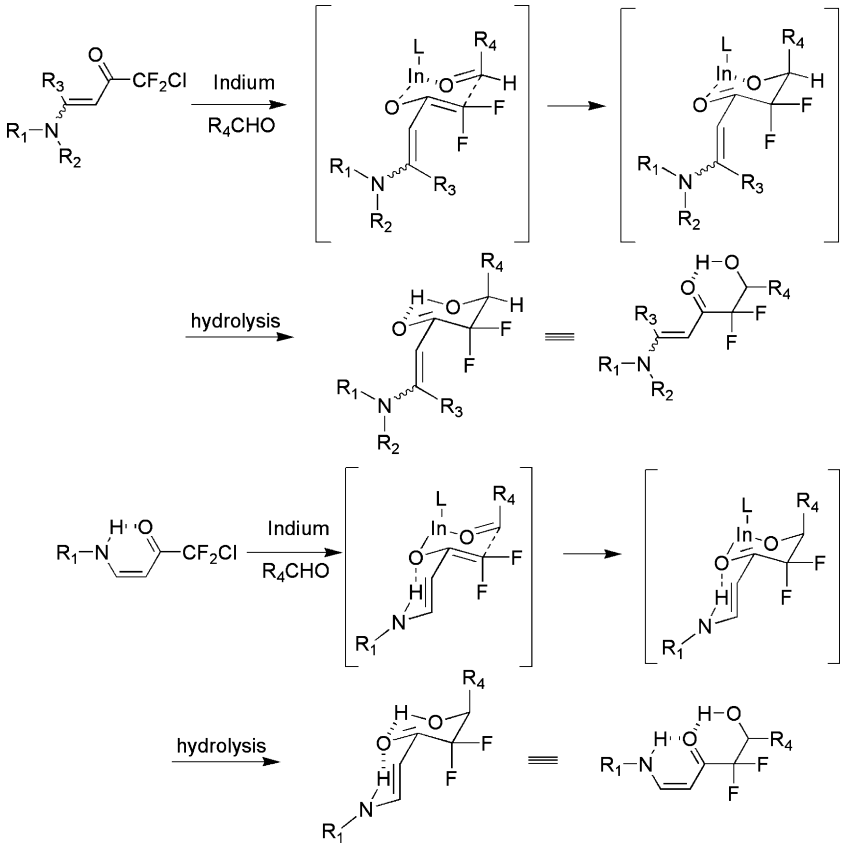
coupling products of the general structure **3** and **4** usually show a relatively large ΔJ_{F-H} for the two geminal fluorines which indicates an intramolecular hydrogen bonding between the C=O and the OH [12]. For compounds **3** they may adopt a "pincer" type structure owing to the two hydrogen bonds (NH···O=C, OH···O=C). Therefore adducts **3** and **4** may be possibly drawn as in Scheme 8.

Some of the isolated yields reported in Table 1 are sometimes modest, and this is mainly due to difficulties to remove efficiently some gel formation obtained during the work-up procedure. Usually the ^{19}F NMR yields (when available) before the work-up, are relatively good. Also for some of the reactions presented in this paper (entries 1, 8, 10 and 11), we did observe that the balance material was not good. Optimization of the reaction conditions and of the work-up procedure is actively pursued in our laboratory. For one alcohol adduct (**3fa**), it was shown that this molecule may exist as a mixture of *Z* and *E* isomers in DMSO, because of a favourable solvent–solute hydrogen bonding. It may be a general trend for all the enaminones **1**, **2**, **3** and **4** synthesized in this work.

3. Conclusions

In this study we demonstrated that indium is an effective reagent to promote the coupling reactions of a series of new β-aminovinyl chloro-difluoromethyl ketones with a series of aromatic and heterocyclic aldehydes. Although the mechanism of this reaction still remains to be elucidated, indium species is likely to act as an electron-transfer reagent generating a reactive difluoro-enolate. What we already know is that the coupling reactions using indium are greatly accelerated in the presence of the aldehyde; for example mixing substrate **1a** (as a model substrate) and 2.2 equiv. of indium at room temperature for 24 h gave little conversion to the corresponding reduction product **5**, while the same reaction with benzaldehyde was completed after only 3 h. We propose that a six-membered Zimmerman–Traxler transition state model might be involved in these coupling reactions to give the desired alcohol after hydrolysis (Scheme 9). $InCl_3$ might be formed after the possible two-electron reduction of the C–Cl bond that can eventually act also as a Lewis acid activator of the aldehyde.

A series of new compounds were prepared under mild conditions and these new difluoromethylene enaminones are currently utilized as useful building blocks to prepare libraries of new functionalized cyclic and heterocyclic structures. We made significant progress in this area and the results will be presented in our forthcoming papers. Recently some new β-aminovinyl chloro-difluoromethylated ketones were prepared and will be soon engaged in these coupling reactions. Finally



Scheme 9.

other electrophiles than heteroaryl aldehydes, especially ketones, enones, α-keto esters, potentially useful to prepare more complex structures, will be soon tested in our laboratory.

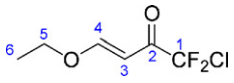
4. Experimental

4.1. General comments

Solvents were distilled before use. Reagents were obtained commercially and used without further purification except for 3,4-dimethoxybenzaldehyde which was recrystallized from petroleum ether (bp 45–60 °C) and benzylamine which was distilled. *N*-Allylbenzylamine was prepared as described in [11]. Compounds **1d–e** were already described in [6] and **1c** and **1f** were already described in [9]. ^{1}H, ^{19}F and ^{13}C NMR were recorded with a Bruker Avance 300 spectrometer (in $CDCl_3$ or DMSO-d_6) at 300, 282 and 75 MHz, respectively. Chemical shifts are given in ppm relative to residual peak of solvent (δ_H = 7.26 ppm for $CHCl_3$, δ_H = 2.50 ppm for Me_2SO, δ_C = 77.0 ppm for $CDCl_3$ and δ_C = 39.52 ppm for Me_2SO-d_6) or $CFCl_3$ (^{19}F). Coupling constants are given in Hertz. Silica gel chromatography was performed on Macherey–Nagel Silica gel 60 M (0.04–0.063 mm). Solvents for chromatography and work-up are: ethyl acetate (EA), diethyl ether (ether), and petroleum ether (PE). Mass spectra were recorded using a FINIGAN MAT 95 [EI, CI (CH_4 or NH_3) and ESI]. Melting points (uncorrected) were determined in capillary tubes on a Buchi apparatus.

4.2. General procedure for the synthesis of *1a–b* and *2a–c*

4.2.1. (E)-1-Chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one

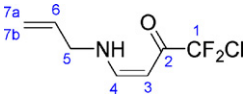


To a stirred solution of ethyl vinyl ether (3.8 mL, 40 mmol) and pyridine (3.6 mL, 44 mmol) in anhydrous dichloromethane (10 mL), was added dropwise an anhydrous dichloromethane solution (20 mL) containing chloro-difluoroacetic anhydride (7 mL, 40 mmol) with cooling (−10 °C). When the addition was finished (30 min), the reaction mixture was slowly warmed-up to room temperature and stirred at this temperature for 18 h. The solution was quenched with H_2O (20 mL) and extracted with dichloromethane (2 mL × 20 mL). The combined organic layers were washed with an aqueous solution of 1N HCl (2 mL × 20 mL) and water (2 mL × 20 mL) and dried over $MgSO_4$. Evaporation of the solvent left a yellowish oil (7.02 g, 36 mmol, 90%) as crude product. ^{13}C NMR ($CDCl_3$): δ 181.1 (t, J = 28.8, C-2), 168.1 (C-4), 120.4 (t, J = 304.9, C-1), 96.7 (C-3), 69.0 (C-5), 14.4 (C-6). ^{1}H NMR ($CDCl_3$): δ 7.85 (1H, d, J = 12.2, H-4), 5.82 (1H, d, J = 12.2, H-3), 4.07 (2H, q, J = 7.0, H-5), 1.35 (3H, t, J = 7.0, H-6). ^{19}F NMR ($CDCl_3$): δ −67.78.

To a stirred solution of (*E*)-1-chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one (1.81 g, 9.8 mmol) in anhydrous acetonitrile (30 mL) was added dropwise the appropriate amine (10.8 mmol) at 0 °C. The solution solution turned red or pink and was

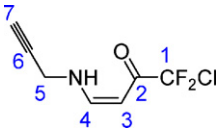
stirred at room temperature (**1a–c**, **2a–c**) or heated at reflux for 1 h (**1d–f**). The solvent was removed under reduced pressure and the residue was pure enough (**1a–b**, **2a**, **2c**) for the next steps, purified by silica gel chromatography (**1c**, **2b**) or recrystallized (**1d–f**).

4.2.2. (Z)-4-Allylamino-1-chloro-1,1-difluoro-but-3-en-2-one, ***1a***



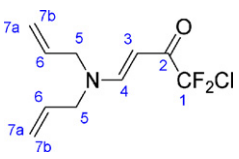
Yield: 99%, red-orange oil. ^{13}C NMR ($CDCl_3$): δ 179.6 (t, J = 27.4, C-2), 158.2 (C-4), 132.8 (C-6), 121.2 (t, J = 303.8, C-1), 117.9 (C-7), 85.7 (C-3), 51.4 (C-5). ^{1}H NMR ($CDCl_3$): δ 10.08 (1H, br s, NH), 7.11 (1H, dd, J = 13.6, 7.2, H-4), 5.87–5.73 (1H, m, H-6), 5.37 (1H, d, J = 7.2, H-3), 5.28 (1H, br d, J = 6.2, H-7a), 5.24 (1H, br s, H-7b), 3.94 (2H, br t, J = 5.8, H-5). ^{19}F NMR ($CDCl_3$): δ −64.92. MS (EI): 195 ($M^{\bullet+}$), 160 ([M − Cl]$^{\bullet+}$), 110 ([M − CF_2Cl]$^{\bullet+}$), 82 ([M − $COCF_2Cl$]$^{\bullet+}$), 41 ($C_3H_5^+$). HRMS (EI): *m/z* calcd for $C_7H_8ClF_2NO$ 195.0262; found: 195.0262.

4.2.3. (Z)-1-Chloro-1,1-difluoro-4-prop-2-ynylamino-but-3-en-2-one, ***1b***



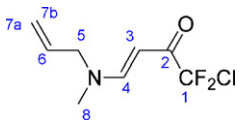
Yield: 89%, yellowish oil. ^{13}C NMR ($CDCl_3$): δ 180.0 (t, J = 27.4, C-2), 157.1 (C-4), 121.1 (t, J = 303.8, C-1), 86.5 (C-3), 76.7 (C-6), 75.4 (C-7), 37.9 (C-5). ^{1}H NMR ($CDCl_3$): δ 10.12 (1H, br s, NH), 7.36 (1H, dd, J = 13.2, 7.3, H-4), 5.46 (1H, d, J = 7.35, H-3), 4.17 (2H, dd, J = 4.5, 2.5, H-5), 2, 50 (1H, d, J = 2.6, H-7). ^{19}F NMR ($CDCl_3$): δ −65.17. MS (EI): 193 ($M^{\bullet+}$), 158 ([M − Cl]$^{\bullet+}$), 108 ([M − CF_2Cl]$^{\bullet+}$), 80 ([M − $COCF_2Cl$]$^{\bullet+}$). HRMS (EI): *m/z* calcd for $C_7H_6ClF_2NO$ 193.0106; found: 193.0105.

4.2.4. (E)-1-Chloro-4-diallylamino-1,1-difluoro-but-3-en-2-one, ***2a***



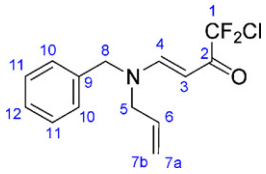
Yield: 80%, silica gel chromatography (PE/EA, 4/1), orange liquid. ^{13}C NMR ($CDCl_3$): δ 179.1 (t, J = 26.9, C-2), 155.8 (C-4), 131.5 and 129.1 (C-6 and C-6′), 121.5 (t, J = 305.6, C-1), 119.9 and 118.6 (C-7 and C-7′), 86.7 (C-3), 58.6 and 50.6 (C-5 and C-5′) ^{1}H NMR ($CDCl_3$): δ 7.89 (1H, d, J = 12.4, H-4), 5.90–5.64 (2H, m, H-6), 5.42–5.15 (5H, m, H-3 and H-7a and H-7b), 3.93 and 3.85 (4H, 2 d br, J = 6.0 and J = 5.5, H-5). ^{19}F NMR ($CDCl_3$): δ −65.58.

4.2.5. (E)-4-(Allyl-methyl-amino)-1-chloro-1,1-difluoro-but-3-en-2-one, ***2b***



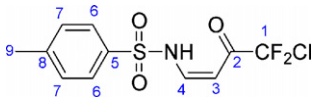
Yield: 87%, silica gel chromatography (PE/EA, 4/1), orange oil. ^{13}C NMR ($CDCl_3$): δ 178.8 (t, J = 26.7, C-2), 156.5 and 156.2 (C-4), 131.3 and 128.6 (C-6), 121.6 (t, J = 305.6, C-1), 119.6 and 118.7 (C-7), 86.2 and 86.0 (C-3), 60.7 and 52.7 (C-5), 43.3 and 35.4 (C-8) ^{1}H NMR ($CDCl_3$): δ 7.74 (1H, d, J = 12.4, H-4), 5.60 (1H, m, H-6), 5.19–5.04 (3H, m, H-3, H-7a and H-7b), 3.82 (2H, d, J = 5.8, H-5), 2.77 (3H, s, H-8). ^{19}F NMR ($CDCl_3$): δ −65.46.

4.2.6. (E)-4-(Allyl-benzyl-amino)-1-chloro-1,1-difluoro-but-3-en-2-one, ***2c*** *(2 rotamers)*



Yield: 61%, pinkish oil (crude product). ^{13}C NMR ($CDCl_3$): δ 179.5 and 179.4 (t, J = 27.0, C-2), 156.5 and 156.2 (C-4), 134.5 and 133.9 (C-9), 131.4 and 129.0 (C-6), 129.1 and 128.3 (C-11), 128.5 and 127.8 (C-10), 127.3 (C-12), 120.3 and 119.0 (C-7), 115.5 (t, J = 305.6, C-1), 87.0 and 86.8 (C-3), 60.1 and 51.7 (C-8), 58.4 and 50.5 (C-5). ^{1}H NMR ($CDCl_3$): δ 8.07 and 8.03 (1H, 2 d, J = 12.6 and J = 12.6, H-4), 7.44–7.31 (3H, m, H-11 and H-12), 7.25–7.14 (2H, m, H-10), 5.85–5.61 (1H, 2 m, H-6), 5.52 and 5.42 (1H, 2 d, J = 12.4 and J = 12.4, H-3), 5.33 and 5.28 (1H, dd, J = 10.1, 1.1, H-7a), 5.24 and 5.17 (1H, dd, J = 17.0, 1.1, H-7b), 4.50 and 4.45 (2H, s br, H-8), 3.91 and 3.77 (2H, 2 br d, J = 6.2 and J = 5.6, H-5). ^{19}F NMR ($CDCl_3$): δ −65.60 (br s). MS (EI): 285 ($M^{\bullet+}$), 250 ([M − Cl]$^{\bullet+}$), 244 ([M − C_3H_5]$^{\bullet+}$), 200 ([M − CF_2Cl]$^{\bullet+}$), 194 ([M − C_7H_7]$^{\bullet+}$), 172 ([M − $COCF_2Cl$]$^{\bullet+}$), 91 ($C_7H_7^{\bullet+}$). HRMS (EI): *m/z* calcd for $C_8H_{10}ClF_2NO$: 285.0732; found: 285.0725.

4.3. (Z)-N-(4-Chloro-4,4-difluoro-3-oxo-but-1-enyl)-4-methyl-benzenesulfonamide, ***1g***

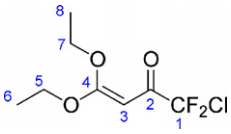


1.1 g (6.5 mmol) of *p*-toluenesulfonamide was dissolved in 10 mL of anhydrous DMF under nitrogen. The solution was cooled to −30 °C and 0.26 g (6.5 mmol) of NaH (60% dispersion in oil) was added portion wise and the reaction mixture stirred during 30 min. A solution of 1.0 g (5.4 mmol) of (*E*)-1-chloro-4-ethoxy-1,1-difluoro-but-3-en-2-one in 10 mL of anhydrous DMF was then added dropwise and the reaction

mixture was slowly warmed-up to room temperature under stirring. After 3 h, the DMF solution was hydrolysed with 20 mL of water, extracted with ethyl acetate (4 mL × 20 mL) and the combined organic layers washed with water (4 mL × 10 mL) and brine (2 mL × 10 mL). The solvent was removed under reduced pressure and the crude product purified by silica gel chromatography. Yield: 50%, silica gel chromatography (PE/EA, 2/1), yellow solid. ^{1}H NMR ($CDCl_3$): δ 10.93 (1H, br s, NH), 7.77 (2H, d, J = 8.5, H-6), 7.45 (1H, d, J = 8.5, H-4), 7.36 (2H, d, J = 8.1, H-7), 5.74 (1H, d, J = 8.3, H-3), 2.45 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −67.48. MS (CI): 310 ($MH^{\bullet+}$), 224 ($[M - CF_2Cl]^{\bullet+}$), 155, 91.

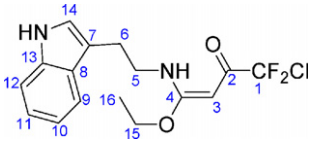
4.4. 1-Chloro-4-ethoxy-1,1-difluoro-4-[2-(1H-indol-3-yl)-ethylamino]-but-3-en-2-one, **1h**

4.4.1. 1-Chloro-4,4-diethoxy-1,1-difluoro-but-3-en-2-one



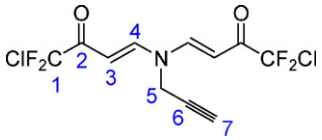
1.8 mL (10 mmol) of 1,1,1-triethoxy-ethane and 1.6 mL (20 mmol) of pyridine were added under nitrogen to 10 mL of anhydrous dichloromethane. The solution was cooled to −30 °C and a 10 mL anhydrous dichloromethane solution containing 3.5 mL (20 mmol) of chloro-difluoroacetic anhydride was added dropwise over 1.5 h under stirring. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. The solution was hydrolysed with 50 mL of a saturated aqueous solution of Na_2CO_3 and extracted with dichloromethane (2 mL × 50 mL). The combined organic layers were washed with a saturated aqueous solution of Na_2CO_3 (1 mL × 20 mL) and water (2 mL × 20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure to give a crude product used without further purification. Yield: 75%, orange liquid. ^{1}H NMR ($CDCl_3$): δ 4.89 (1H, s, H-3), 4.32 (2H, q, J = 7.1, H-7), 4.12 (2H, q, J = 7.0, H-5), 1.40 (3H, t, J = 7.1, H-8), 1.36 (3H, t, J = 7.0, H-6). ^{19}F NMR ($CDCl_3$): δ −65.70.

4.4.2. 1-Chloro-4-ethoxy-1,1-difluoro-4-[2-(1H-indol-3-yl)-ethylamino]-but-3-en-2-one, **1h**



0.69 g (3.0 mmol) of 1-chloro-4,4-diethoxy-1,1-difluoro-but-3-en-2-one was dissolved in 10 mL of anhydrous acetonitrile under nitrogen. 0.48 g (3.0 mmol) of tryptamine was then added portion wise at 0 °C over 5 min under stirring. The solution turned pink and was allowed to warm to room temperature and stirred for 1 h. A white solid precipitated and was filtrated and dried. Yield: 30%, white solid, mp: 190 °C. ^{13}C NMR (DMSO-d_6): δ 174.7 (t, J = 29.1, C-2), 169.4 (C-4), 136.4 (C-13), 127.0 (C-8), 123.2 (C-14), 122.3 (t, J = 303.8, C-1), 121.1 (C-10), 118.4 (C-11), 118.3 (C-9), 111.5 (C-12), 110.7 (C-7), 70.5 (t, J = 2.2, C-3), 65.8 (C-15), 40.8 (C-5), 25.1 (C-6), 14.0 (C-16). 1H NMR ($CDCl_3$): δ 10.43 (1H, br s, NH), 8.16 (1H, br s, NH), 7.57 (1H, d, J = 7.9, H-9), 7.37 (1H, d, J = 7.9, H-12), 7.23–7.18 (1H, m, H-9), 7.15–7.10 (2H, m, H-10 and H-14), 5.03 (1H, s, H-3), 4.05 (2H, q, J = 7.0, H-15), 3.65 (2H, td, J = 6.9, 5.9, H-5), 3.05 (2H, t, J = 6.9, H-6), 1.30 (3H, t, J = 7.0, H-16). ^{19}F NMR ($CDCl_3$): δ −63.99. MS (EI): 342 ($M^{\bullet+}$), 307 ($[M - Cl]^{\bullet+}$), 257 ($[M - CF_2Cl]^{\bullet+}$), 212 ($[M - C_9H_8N]^{\bullet+}$), 184 ($[C_6H_7ClF_2O_2]^{\bullet+}$), 130 ($[C_9H_8N]^{\bullet+}$). HRMS (EI): m/z calcd for $C_{16}H_{17}ClF_2N_2O_2$: 342.0947; found: 342.0946.

4.5. 1-Chloro-1,1-difluoro-4-[(4-chloro-4,4-difluoro-3-oxo-but-1-enyl)-prop-2-2-ynyl-amino]-but-3-en-2-one, **2j**

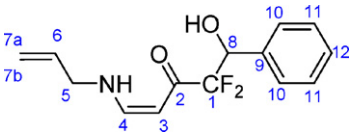


Under nitrogen 0.118 g (3.1 mmol) of NaH (60% dispersion in oil) was added portion wise to an anhydrous cooled (−30 °C) DMF (15 mL) solution containing 0.59 g (3.1 mmol) of **1b**. The initial orange solution became gradually dark and then after 30 min of stirring at this temperature, 0.65 g (3.4 mmol) of tosyl chloride dissolved in 15 mL of anhydrous DMF was added dropwise. After the addition was finished, the clear solution was slowly warmed-up to room temperature overnight. Solution was quenched with water (20 mL) and extracted with ethyl acetate (4 mL × 10 mL), the combined organic phases washed with brine (4 mL × 10 mL) and water (2 mL × 10 mL). After drying over $MgSO_4$, the solvent was removed under reduced to yield a brown oil as crude product which was purified by silica gel chromatography. Yield: 48%, silica gel chromatography (EA/PE, 9/1 → EA), pale yellow solid, mp: 78 °C. 1H NMR ($CDCl_3$): δ 7.83 (2H, d, J = 13.57, H-3), 6.05 (2H, d, J = 13.57, H-4), 4.36 (2H, d, J = 2.4, H-5), 2.48 (^{1}H, t, J = 2.4, H-7). ^{19}F NMR ($CDCl_3$): δ −67.82.

4.6. General procedure to prepare **3** and **4**

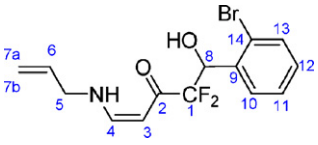
Substrate **1** or **2** (1 mmol) was first dissolved in freshly distilled THF (1 ml) followed by the addition of the aldehyde (1–2 mmol). The mixture was stirred gently and then H_2O (4 ml) was added dropwise. Indium (100 mesh) was finally added at once and the whole mixture was vigorously stirred and monitored by ^{19}F NMR (and TLC) for the indicated time in Table 1. Mixture was then filtrated over Celite® and the filter cake washed with ethyl acetate and water. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 mL × 25 mL), the combined organic layers washed with water (2 mL × 25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product purified either by recrystallization or silica gel chromatography.

4.6.1. (Z)-1-Allylamino-4,4-difluoro-5-hydroxy-5-phenyl-pent-1-en-3-one, ***3aa***



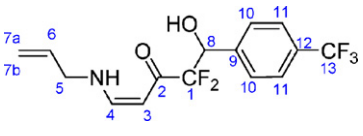
Yield: 45%, silica gel chromatography (PE/EA, 9/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 179.6 (dd, J = 27.9, 26.3, C-2), 157.3 (C-4), 136.0 (C-9), 133.1 (C-6), 128.5 (C-10), 128.1 (C-11), 128.0 (C-12), 118.0 (C-7), 114.9 (dd, J = 259.6, 254.7, C-1), 89.1 (C-3), 73.8 (dd, J = 28.6, 24.7, C-8), 51.4 (C-5). ^{1}H NMR ($CDCl_3$): δ 10.23 (1H, br s, NH), 7.44 (2H, m, H-11), 7.33 (3H, m, H-10 and H-12), 6.94 (1H, dd, J = 13.4, 7.2, H-4), 5.90–5.77 (1H, m, H-6), 5.36 (1H, d, J = 7.2, H-3), 5.27–5.19 (2H, m, H-7a and H-7b), 5.16 (1H, dd, J = 16.6, 7.6, H-8), 4.26 (1H, br s, OH), 3.85 (2H, t, J = 5.65, H-5). ^{19}F NMR ($CDCl_3$): δ −112.7 (1F, dd, J = 262.2, 7.6), −121.3 (1F, dd, J = 262.2, 16.6). MS (EI): 267 ($M^{\bullet+}$), 247 ([M − HF]$^{\bullet+}$), 226 ([M − C_3H_5]$^{\bullet+}$), 110 ($C_6H_8NO^{\bullet+}$), 107 ($C_7H_7O^{\bullet+}$), 82 ($C_5H_8N^{\bullet+}$), 41 ($C_3H_5^{\bullet+}$). HRMS (EI): m/z calcd for $C_{14}H_{15}F_2NO_2$: 267.1071, found: 267.1069.

4.6.2. (Z)-1-Allylamino-5-(2-bromo-phenyl)-4,4-difluoro-5-hydroxy-pent-1-en-3-one, ***3ab***



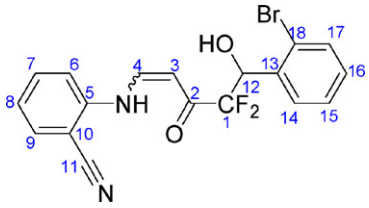
Yield: 50%, yellow solid, mp: 84 °C (CH_2Cl_2/pentane). ^{13}C NMR ($CDCl_3$): δ 187.5 (t, J = 27.7, C-2), 157.6 (C-4), 135.5 (C-9), 133.0 (C-6), 132.7 (C-13), 130.3 (C-10), 130.2 (C-12), 127.5 (C-11), 124.4 (C-14), 118.4 (C-7), 114.5 (dd, J = 261.0, 256.6, C-1), 88.9 (t, J = 1.9, C-3), 73.8 (dd, J = 29.6, 23.6, C-8), 51.7 (C-5). ^{1}H NMR ($CDCl_3$): δ 10.32 (1H, br s, NH), 7.69 (1H, dm, J = 7.9, H-10), 7.56 (1H, dd, J = 7.9, 1.1, H-13), 7.36 (1H, m, H-11), 7.19 (1H, m, H-12), 6.94 (1H, dd, J = 13.6, 7.2, H-4), 5.88 (1H, m, H-6), 5.74 (1H, dd, J = 18.5, 3.8, H-8), 5.46 (1H, d, J = 7.2, H-3), 5.36–5.19 (3H, m, H-7a, H-7b and OH), 3.85 (2H, t, J = 5.65, H-5). ^{19}F NMR ($CDCl_3$): δ −111.1 (1F, dd, J = 267.5, 2.9), −122.4 (1F, dd, J = 267.3, 18.4). MS (EI): 345 ($M^{\bullet+}$), 325 ($M^{\bullet+}$ − HF), 266 ($M^{\bullet+}$ − Br), 246 ($M^{\bullet+}$ − Br-HF), 185 ($C_7H_6BrO^+$), 110 ($C_6H_8NO^{\bullet+}$), 41 ($C_3H_5^+$). HRMS (CI): m/z calcd for $C_{14}H_{14}BrF_2NO_2$ (MH$^+$): 346.0176, found: 346.0254.

4.6.3. 1-Allylamino-4,4-difluoro-5-hydroxy-5-(4-trifluoromethyl-phenyl)-pent-1-en-3-one, ***3ac***



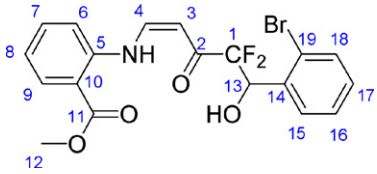
Yield: 60%, yellow pellets, mp: 77 °C (CH_2Cl_2/pentane). ^{13}C NMR ($CDCl_3$): δ 187.1 (dd, J = 28.0, 26.3, C-2), 157.6 (C-4), 140.0 (C-9), 132.9 (C-6), 130.7 (q, J = 32.4, C-12), 128.4 (C-10), 125.1 (q, J = 3.8, C-11), 124.1 (q, J = 272.1, C-13), 118.4 (C-7), 114.4 (dd, J = 260.7, 255.8, C-1), 89.0 (dd, J = 2.2, 1.6, C-3), 73.4 (dd, J = 28.8, 24.9, C-8), 51.6 (C-5). ^{1}H NMR ($CDCl_3$): δ 10.28 (1H, br s, NH), 7.66–7.55 (4H, m, H10 and H-11), 7.03 (1H, dd, J = 13.4, 7.2, H-4), 5.88 (1H, m, H-6), 5.40 (1H, dt, J = 7.2, 1.3, H-7a), 5.32–5.18 (3H, m, H-3, H-7b and H-8), 4.00 (1H, d, J = 4.2, OH), 3.93 (2H, tm, J = 5.75, H-5). ^{19}F NMR ($CDCl_3$): δ −63.1 (3F, s), −111.9 (1F, dd, J = 268.5, 5.7), −120.6 (1F, dd, J = 268.5, 16.6). MS (EI): 335 ($M^{\bullet+}$), 315 ($M^{\bullet+}$ − HF), 360 ($M^{\bullet+}$ − Br), 175 ($C_8H_6F_3O^{\bullet+}$), 145 ($C_7H_4F_3^{\bullet+}$), 110 ($M^{\bullet+}$ − $C_9H_6F_5O$), 41 ($C_3H_5^{\bullet+}$). HRMS (EI): m/z calcd for $C_{15}H_{14}F_5NO_2$: 335.0945, found: 335.0943.

4.6.4. 2-[5-(2-Bromophenyl)-4,4-difluoro-5-hydroxy-3-oxopent-1-enylamino]benzonitrile, ***3db***



Yield: 90%, ochre powder, mp: 143 °C (CH_2Cl_2/pentane). ^{1}H NMR (DMSO-d_6): δ 12.05 (1H, br d, J = 12.33, NH, isomer Z), 10.55 (1H, br s, NH, isomer E), 8.26–8.05 (1H, m, H-4, both isomers), 7.90–7.57 (5H, m, H-7, H-9, H-14, H-16 and H-17, both isomers), 7.54–7.37 (1H, m, H-15, both isomers), 7.37–7.20 (2H, m, H-6 and H-8, both isomers), 6.61 (1H, dd, J = 5.9, 1.2, OH, Z or E), 6.53 (1H, br d, J = 5.8, OH, Z or E), 6.30 (1H, d, J = 13.1, H-3, isomer E), 5.84 (1H, dd, J = 7.8, 2.6, H-3, isomer Z), 5.69–5.48 (1H, m, H-12, both isomers). ^{19}F NMR ($CDCl_3$): δ −110.3 (1F, dd, J = 276.5, 3.4), −123.8 (1F, dd, J = 276.5, 19.0).

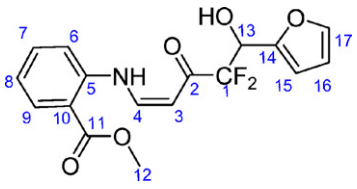
4.6.5. (Z)-2-[5-(2-Bromo-phenyl)-4,4-difluoro-5-hydroxy-3-oxo-pent-1-enylamino]-benzoic acid methyl ester, ***3eb***



Yield: 78%, yellow powder, mp: 126 °C ($CHCl_3$). ^{13}C NMR (DMSO-d_6): δ 187.2 (dd, J = 30.1, 24.1, C-2), 166.4 (C-11), 146.1 (C-4), 141.3 (C-5), 137.0 (C-19), 134.8 (C-18), 132.2 (C-15), 131.5 (C-9), 130.7 (C-8), 130.3 (C-7), 127.6 (C-17), 123.5 (C-14), 123.2 (C-16), 116.2 (J = 264.3, 251.1, C-1), 115.7 (C-10), 115.6 (C-6), 93.4 (C-3), 69.7 (dd, J = 30.8, 21.8, C-13), 52.5 (C-12). ^{1}H NMR ($CDCl_3$): δ 13.21 (1H, br d, J = 13.0, NH), 8.09 (1H, dd, J = 7.9, 1.5, H-9), 7.72 (1H, dm, J = 7.7, H-7), 7.67–7.49 (3H, m, H-4, H-15 and H-18), 7.41–7.30 (2H, m, H-6 and H-17), 7.24–7.11 (2H, m, H-8 and H-16), 5.95–5.77 (2H, m, H-3 and H-13), 4.03 (3H, s, H-12), 3.66 (1H, br d, J = 3.4, OH). ^{19}F NMR ($CDCl_3$): δ −109.9 (1F, dd, J = 268.5,

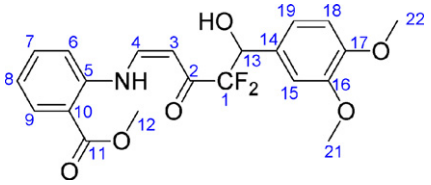
3.4), −124.9 (1F, dd, J = 268.5, 20.1). ^{19}F NMR (DMSO-d_6): δ −107.5 (1F, d, J = 254.7), −126.9 (1F, dd, J = 254.7, 21.3). MS (EI): 439 ($M^{\bullet+}$), 419 ($M^{\bullet+}$ − HF), 360 ($M^{\bullet+}$ − Br), 284 ($M^{\bullet+}$ − C_6H_4Br), 204 ($M^{\bullet+}$ − $C_8H_6BrF_2O$), 185 ($C_7H_6BrO^{\bullet+}$). $^{+}$). HRMS (EI): m/z calcd for $C_{19}H_{16}BrF_2NO_4$: 439.0231, found: 439.0230.

4.6.6. (Z)-Methyl 2-(4,4-difluoro-5-furan-2-yl-5-hydroxy-3-oxo-pent-1-enylamino)-benzoate, ***3ed***



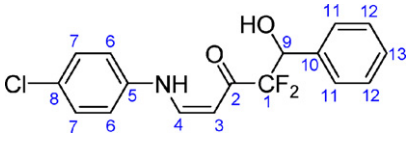
Yield: 34%, silica gel chromatography (PE/EA, 4/1), orange powder, mp: 111 °C. ^{13}C NMR ($CDCl_3$): δ 188.5 (dd, J = 28.6, 26.3, C-2), 167.2 (C-11), 149.5 (C-14), 145.6 (C-4), 143.4 (C-17), 141.8 (C-5), 134.8 (C-7), 132.5 (C-9), 123.7 (C-8), 117.1 (C-10), 115.0 (C-6), 114.7 (dd, J = 261.3, 256.3, C-1), 110.8 (C-16), 110.1 (C-15), 93.6 (C-3), 68.2 (dd, J = 29.7, 25.3, C-13), 53.0 (C-12). ^{1}H NMR ($CDCl_3$): δ 13.21 (1H, br d, J = 12.8, NH), 8.05 (1H, dd, J = 7.9, 1.5, H-9), 7.60–7.50 (2H, m, H-4 and H-7), 7.41 (1H, m, H-17), 7.30 (1H, d, J = 8.3, H-6), 7.12 (1H, m, H-8), 6.48 (1H, d, J = 3.0, H-15), 6.35 (1H, dd, J = 3.3, 1.8, H-16), 5.80 (1H, dd, J = 8.0, 1.5, H-3), 5.37 (1H, dd, J = 16.4, 6.8, H-13), 3.99 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −113.0 (1F, dd, J = 263.9, 8.0), −122.2 (1F, dd, J = 263.9, 17.2). MS (ESI): 724.9 ($2M$ + Na)$^+$, 374.1 (M + Na)$^+$, 352.0 (MH)$^+$, 204.0 ([M − $C_6H_5F_2O_2$]$^+$), 172.1. HRMS (EI): calcd for $C_{17}H_{15}F_2NO_5$ 351.0918, found: 351.0917.

4.6.7. (Z)-Methyl-2-[5-(3,4-dimethoxyphenyl)-4,4-difluoro-5-hydroxy-3-oxopent-1-enylamino]-benzoate, ***3ee***



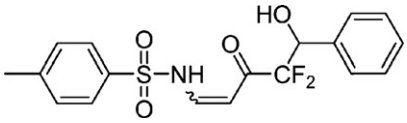
Yield (^{19}F NMR): 11%. ^{19}F NMR ($CDCl_3$): δ −112.4 (1F, dd, J = 266.1, 6.6), −122.6 (1F, dd, J = 266.1, 16.8).

4.6.8. 1-(4-Chloro-phenylamino)-4,4-difluoro-5-hydroxy-5-phenyl-pent-1-en-3-one, ***3fa***



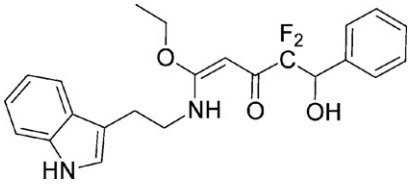
Yield: 59%, yellow powder, mp: 156 °C (EA/pentane). ^{13}C NMR (DMSO-d_6): δ 188.1 (dd, J = 28.3, 25.5, C-2, Z or E), 186.6 (dd, J = 28.1, 25.1, C-2, Z or E), 148.3 (C-4, Z or E), 146.1 (C-4, Z or E), 139.6 (C-5, Z or E), 138.7 (C-5, Z or E), 137.8 (C-10), 129.7 (C-6), 128.3 (C-11), 128.0 (C-12), 128.0 (C-13), 127.3 (C-8), 118.9 (C-7, Z or E), 117.9 (C-7, Z or E), 117.0 (dd, J = 261.2, 252.6, C-1), 96.1 (C-3, Z or E), 92.4 (C-3, Z or E), 71.9 (dd, J = 28.6, 23.7, C-9). ^{1}H NMR ($CDCl_3$): 11.85 (1H, d, J = 12.3, NH), 7.60–7.27 (9H, m, H-4, H-7, H-11, H-12, H-13 and OH), 7.11-6.96 (2H, m, H-6), 5.66 (1H, d, J = 7.6, H-3), 5.23 (1H, dd, J = 15.9, 7.5, H-9) δ ^{19}F NMR ($CDCl_3$): δ −113.9 (1F, dd, J = 257.0, 8.0), −122.8 (1F, dd, J = 257.0, 16.1). MS (ESI): 696.9 ($2M$ + Na)$^+$, 360.0 (M + Na)$^+$, 338.0 (MH)$^+$, 180.2 ([M − $C_8H_7F_2O$]$^+$). HRMS (EI): m/z calcd for $C_{17}H_{14}ClF_2NO_2$ 337.0681, Found 337.06801.

4.6.9. (Z)-N-(4,4-Difluoro-5-hydroxy-3-oxo-5-phenyl-pent-1-enyl)-4-methyl-benzenesulfonamide, ***3ga***



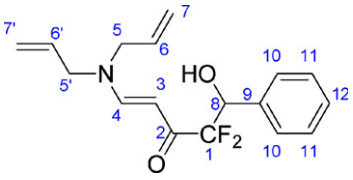
Yield (^{19}F NMR): 36%. Unstable over silica gel. ^{19}F NMR ($CDCl_3$): δ −114.0 (1F, dd, J = 261, 7.5), −123.7 (1F, dd, J = 262, 17.5).

4.6.10. 1-Ethoxy-4,4-difluoro-5-hydroxy-1-[2-(1H-indol-3-yl)-ethylamino]-5-phenyl-pent-1-en-3-one, ***3ha***



Yield (^{19}F NMR): 14%. ^{19}F NMR ($CDCl_3$): δ −111.5 (1F, d, J = 258.1), −123.7 (1F, dd, J = 258.1, 16.7).

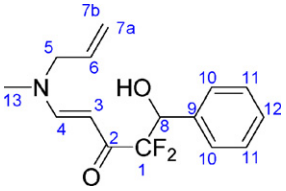
4.6.11. (E)-1-Diallylamino-4,4-difluoro-5-hydroxy-5-phenyl-pent-1-en-3-one, ***4aa***



Yield: 30%, silica gel chromatography (PE/ EA, 9:1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 187.3 (dd, J = 27.7, 26.1, C-2), 155.4 (C-4), 136.1 (C-9), 131.8 and 128.4 (C-6 and C-6′), 128.4 (C-10), 128.1 (C-11), 128.0 (C-12), 120.1 and 118.9 (C-7 and C-7′), 115.3 (dd, J = 261.8, 255.8, C-1), 90.1 (br s, C-3), 73.6 (dd, J = 28.5, 24.7, C-8), 58.6 and 50.7 (C-5 and C-5′). ^{1}H NMR ($CDCl_3$): δ 7.81 (1H, d, J = 12.4, H-4), 7.48–7.45 (2H, m, H-11), 7.37–7.29 (3H, m, H-10 and H-12), 5.80–5.56 (2H, m, H-6 and H-6′), 5.40 (1H, d, J = 12.4, H-3), 5.30–5.05 (5H, m,

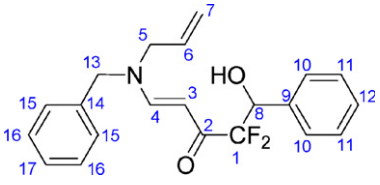
H-7 and H-7′ and H-8), 4.33 (1H, br s, OH), 3.83 and 3.73 (4H, 2 br d J = 6.0 and J = 5.3, H-5 and H-5′). ^{19}F NMR ($CDCl_3$): δ −112.0 (1F, d, J = 265.0), −121.5 (1F, dd, J = 266.2, 11.5). MS (EI): 307 ($M^{\bullet+}$), 287 ($[M - HF]^{\bullet+}$), 200 ($C_{10}H_{12}F_2NO^{\bullet+}$), 150 ($C_9H_{12}NO^{\bullet+}$), 122 ($C_8H_{12}N^{\bullet+}$), 96 ($C_6H_{10}N^{\bullet+}$), 41 ($C_3H_5^{\bullet+}$). HRMS (EI): m/z calcd for $C_{17}H_{19}F_2NO_2$: 307.1384, found: 307.1383.

4.6.12. (E)-1-(Allyl-methyl-amino)-4,4-difluoro-5-hydroxy-5-phenyl-pent-1-en-3-one, **4ba** (2 rotamers)



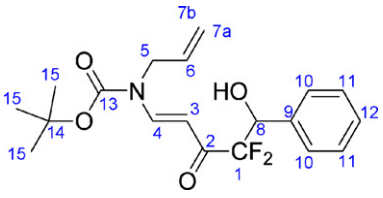
Yield: 56%, silica gel chromatography (PE/EA, 2/1), yellow-orange oil. ^{13}C NMR ($CDCl_3$): δ 200.2 and 186.9 (2 dd, J = 27.9, 26.3, C-2), 156.1 and 155.8 (C-4), 135.9 and 135.0 (C-9), 128.9 (C-10), 128.3 (C-11), 127.9 (C-12), 119.7 and 118.9 (C-7), 114.8 (dd, J = 261.8, 254.6, C-1), 88.6 (C-3), 73.6 and 72.8 (2 dd, J = 28.8, 24.1 and J = 28.8, 24.7, C-8), 60.8 and 52.7 (C-5), 43.8 and 36.0 (C-13). ^{1}H NMR ($CDCl_3$): δ 8.21–8.04 (1H, dm, J = 12.2, H-4), 7.51–7.39 (2H, m, H-11), 7.38–7.27 (3H, m, H-10 and H-12), 5.84–5.55 (1H, m, H-6), 5.45 (1H, d, J = 12.1, H-3), 5.35–5.08 (3H, m, H-7 and H-8), 3.91 and 3.78 (2H, 2 br d, J = 6.2 and J = 5.6, H-5), 3.15 and 2.85 (3H, 2 s, H-13). ^{19}F NMR ($CDCl_3$): δ −110.4 and −110.7 (1F, 2 br d, J = 263.9 and J = 262.7), −122.1 and −122.4 (1F, 2 dd, J = 262.7, 18, and J = 263.9, 16). MS (EI): 281 ($M^{\bullet+}$), 261 ($[M - HF]^{\bullet+}$), 326 ($[M - C_3H_5]^{\bullet+}$), 124 ($C_7H_{10}NO^{\bullet+}$), 41 ($C_3H_5^{\bullet+}$). HRMS (EI): m/z calcd for $C_{15}H_{17}F_2NO_2$ 281.1227, found: 281.1223.

4.6.13. (E)-1-(Allyl-benzyl-amino)-4,4-difluoro-5-hydroxy-5-phenyl-pent-1-en-3-one, **4ca** (2 rotamers)



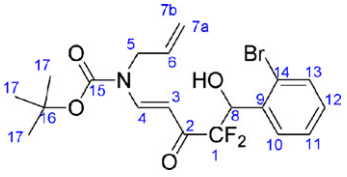
Yield: 55%, silica gel chromatography (PE/ EA, 9/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 187.3 (m, C-2), 155.9 and 155.6 (C-4), 136.2 and 134.2 (C-14), 134.8 (C-9), 131.6 and 129.2 (C-6), 129.0 (C-16), 128.5 (C-15), 128.3 (C-10), 128.0 (C-11), 127.9 (C-12), 127.4 (C-17), 120.2 and 118.9 (C-7), 115.5 (dd, J = 261.8, 256.3, C-1), 90.1 (br s, C-3), 73.4 (m, C-8), 59.8 and 51.3 (C-13), 58.0 and 50.2 (C-5). ^{1}H NMR ($CDCl_3$): δ 8.01 and 7.94 (1H, 2 d, J = 12.4 and J = 12.4, H-4), 7.49 (2H, m, H-11), 7.40–7.27 (6H, m, H-10, H-12, H-16 and H-17), 7.20–7.13 and 7.12–7.05 (2H, 2 m, H-15), 5.79–5.43 (2H, m, H-6 and H-3), 5.30–5.01 (3H, m, H-7 and H-8), 4.76–4.48 (1H, br s, OH), 4.38 and 4.31 (2H, br s and d, J = 2.6, H-13), 3.78 and 3.64 (2H, 2 br d, J = 6.2 and J = 5.6, H-5). ^{19}F NMR ($CDCl_3$): δ −112.4 and −112.7 (1F, 2 br d, J = 265.0 and J = 260.4), −121.5 and −121.8 (1F, 2 br d, J = 260.4 and J = 265.0).

4.6.14. (E)-Allyl-(4,4-difluoro-5-hydroxy-3-oxo-5-phenyl-pent-1-enyl)-carbamic acid tert-butyl ester, **4da**



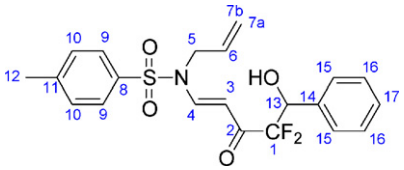
Yield: 60%, silica gel chromatography (PE/EA, 9/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 189.4 (dd, J = 29.1, 26.9, C-2), 151.5 (C-13), 145.9 (C-4), 135.4 (C-9), 130.2 (C-6), 128.6 (C-10), 128.1 (C-11), 127.9 (C-12), 117.4 (C-7) 115.5 (dd, J = 261.8, 255.8, C-1), 99.6 (C-3), 84.3 (C-14), 73.1 (dd, J = 28.0, 24.2, C-8), 46.9 (C-5), 27.8 (C-15). ^{1}H NMR ($CDCl_3$): δ 8.37 (1H, d, J = 13.9, H-4), 7.45–7.36 (2H, m, H-11), 7.35–7.26 (3H, m, H-10 and H-12), 5.73 (1H, d, J = 13.9, H-3), 5.61 (1H, m, H-6), 5.24–5.07 (2H, m, H-7a and H-8), 5.02 (1H, d, J = 17.3, H-7b), 4.16–3.79 (3H, m, H-5 and OH), 1.48 (9H, s, H-15). ^{19}F NMR ($CDCl_3$): δ −113.8 (1F, dd, J = 262, 8.0), −122.6 (1F, dd, J = 262, 16.1). MS (EI): 367 ($M^{\bullet+}$), 352 ($[M - CH_3]^{\bullet+}$), 326 ($[M - C_3H_5]^{\bullet+}$), 311 (M^+-isobutene), 210 ($[M^{\bullet+}$-isobutene-PhCHOHCF$_2$), 57 ($C_4H_9^+$), 41 ($C_3H_5^+$). HRMS (EI): m/z calcd for $C_{19}H_{23}F_2NO_4$: 367.1595, found: 367.1598.

4.6.15. (E)-Allyl-[5-(2-bromo-phenyl)-4,4-difluoro-5-hydroxy-3-oxo-pent-1-enyl]-carbamic acid tert-butyl ester, **4db**



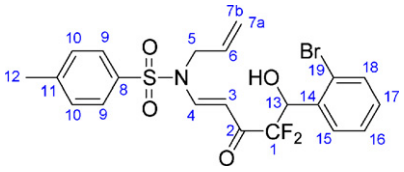
Yield: 53%, silica gel chromatography (PE/EA = 4/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 189.1 (dd, J = 29.9, 27.7, C-2), 151.5 (C-15), 146.6 (C-4), 135.0 (C-9), 132.6 (C-13), 130.4 (C-10), 130.3 (C-12), 130.3 (C-6), 127.6 (C-11), 124.3 (C-14), 117.7 (C-7), 115.1 (dd, J = 263.8, 257.8, C-1), 99.3 (C-3), 84.6 (C-16), 71.4 (dd, J = 29.1, 23.0, C-8), 47.2 (C-5), 28.0 (C-17). ^{1}H NMR ($CDCl_3$): δ 8.48 (1H, d, J = 13.8, H-4), 7.67 (1H, dt, J = 7.7, 1.6, H-10), 7.55 (1H, dd, J = 7.9, 1.1, H-13), 7.35 (1H, td, J = 7.6, 1.1, H-12), 7.20 (1H, m, H-12), 5.84 (1H, d, J = 13.9, H-3), 5.80–5.62 (2H, m, H-6 and H-8), 5.19 (1H, dm, J = 10.4, H-7a), 5.11 (1H, dm, J = 17.3, H-7b), 4.18 (2H, dm, J = 5.1, H-5), 3.52 (1H, d, J = 4.5, OH), 1.52 (9H, s, H-17). ^{19}F NMR ($CDCl_3$): δ −111.3 (1F, d, J = 277.6), −123.7 (1F, dd, J = 262, 18.4).

4.6.16. (E)-N-Allyl-N-(4,4-difluoro-5-hydroxy-3-oxo-5-phenyl-pent-1-enyl)-4-methyl-benzene-sulfonamide, ***4ea***



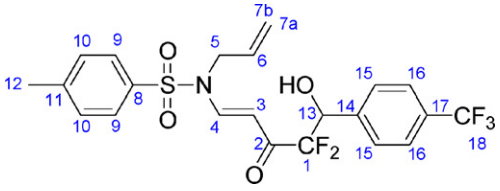
Yield: 70%, silica gel chromatography (PE/EA, 2/1), pale yellow crystals, mp: 50 °C. ^{13}C NMR ($CDCl_3$): δ 188.9 (dd, J = 30.2, 27.4, C-2), 145.7 (C-11), 145.0 (C-4), 135.1 (C-14), 134.6 (C-8), 130.5 (C-10), 129.2 (C-6), 128.9 (C-17), 128.3 (C-15), 128.0 (C-16), 127.6 (C-9), 119.4 (C-7), 115.3 (dd, J = 261.8, 256.3, C-1), 100.0 (C-3), 73.3 (dd, J = 28.3, 24.4, C-13), 48.7 (C-5), 21.7 (C-12). ^{1}H NMR ($CDCl_3$): δ 8.33 (1H, d, J = 13.7, H-4), 7.69 (2H, d, J = 8.3, H-9), 7.43–7.40 (2H, m, H-16), 7.37–7.29 (5H, m, H-10 and H-15 and H-17), 5.67 (1H, d, J = 13.6, H-3), 5.51–5.38 (1H, m, H-6), 5.16 (1H, dd, J = 16.4, 7.7, H-13), 5.12 (1H, dd, J = 9.6, 0.7, H-7a), 5.05 (1H, dd, J = 17.1, 0.7, H-7b), 4.11–3.97 (2H, m, H-5), 3.37 (1H, br s, OH), 2.44 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −113.7 (1F, dd, J = 266.2, 7.4), −121.3 (1F, dd, J = 266.2, 17.2). MS (EI): 421 ($M^{\bullet+}$), 401 ([M − HF]$^{\bullet+}$), 264 ($C_{13}H_{14}NO_3S^{\bullet+}$), 155 ($C_7H_7O_2S^{\bullet+}$), 91 ($C_7H_7^{\bullet+}$). HRMS (EI): m/z calcd for $C_{21}H_{21}F_2NO_4S$: 421.1159, found: 421.1158.

4.6.17. (E)-N-Allyl-N-[5-(2-bromo-phenyl)-4,4-difluoro-5-hydroxy-3-oxo-pent-1-enyl]-4-methyl-benzene-sulfonamide, ***4eb***



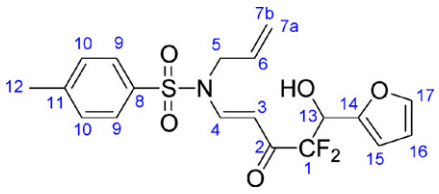
Yield (^{19}F NMR): 74%. Unstable over silica gel. ^{19}F NMR ($CDCl_3$): δ −112.0 (1F, dd, J = 270.5, 4.8), −123.9 (1F, dd, J = 270.5, 17.9).

4.6.18. (E)-N-Allyl-N-[4,4-difluoro-5-hydroxy-3-oxo-5-(4-trifluoromethyl-phenyl)-pent-1-enyl]-4-methyl-benzenesulfonamide, ***4ec***



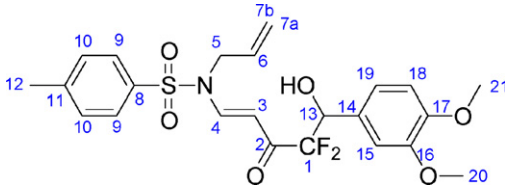
Yield: 30%, silica gel chromatography (PE/EA: 3/1), colourless oil. ^{13}C NMR ($CDCl_3$): δ 188.6 (dd, J = 30.0, 27.6, C-2), 145.8 (C-11), 145.7 (C-4), 139.1 (C-14), 134.6 (C-8), 131.0 (q, J = 32.4, C-17), 130.5 (C-10), 129.2 (C-6), 128.4 (C-15), 127.7 (C-9), 125.2 (q, J = 3.8, C-16), 124.1 (q, J = 272.1, C-18), 119.5 (C-7), 114.7 (dd, J = 262.9, 256.9, C-1), 99.5 (C-3), 72.7 (dd, J = 28.0, 24.7, C-13), 48.8 (C-5), 21.8 (C-12). ^{1}H NMR ($CDCl_3$): δ 8.37 (1H, d, J = 13.7, H-4), 7.71 (2H, d, J = 8.1, H-9), 7.65–7.50 (4H, m, H-15 and H-16), 7.36 (2H, d, J = 8.1, H-10), 5.66 (1H, d, J = 13.7, H-3), 5.57–5.33 (1H, m, H-6), 5.33–5.18 (1H, m, H-13), 5.18–4.98 (2H, m, H-7a and H-7b), 4.10–4.00 (2H, m, H-5), 3.43 (1H, br d, J = 4.3, OH), 2.43 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −62.7 (3F, s), −112.2 (1F, dd, J = 275.4, 6.7), −121.8 (1F, dd, J = 275.4, 16.6).

4.6.19. (E)-N-Allyl-N-(4,4-difluoro-5-furan-2-yl-5-hydroxy-3-oxo-pent-1-enyl)-4-methyl-benzene-sulfonamide, ***4ed***



Yield: 24%, silica gel chromatography (PE/EA: 4/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ : 188.0 (dd, J = 29.5, 27.2, C-2), 148.5 (dd, J = 2.5, 1.5, C-14), 145.5 (C-11), 145.1 (C-4), 143.0 (C-17), 134.4 (C-8), 130.2 (C-10), 129.1 (C-6), 127.4 (C-9), 119.2 (C-7), 114.4 (dd, J = 261.8, 257.5, C-1), 110.5 (C-16), 109.8 (C-15), 99.3 (C-3), 67.7 (dd, J = 29.1, 25.8, C-13), 48.6 (C-5), 21.5 (C-12). ^{1}H NMR ($CDCl_3$): δ 8.37 (1H, d, J = 13.7, H-4), 7.71 (2H, d, J = 8.1, H-9), 7.47–7.28 (3H, m, H-10 and H-17), 6.44 (1H, d, J = 3.3, H-15), 6.35 (1H, dd, J = 3.3, 1.8, H-16), 5.79 (1H, d, J = 13.7, H-3), 5.62–5.39 (1H, m, H-6), 5.30–5.02 (3H, m, H-7a, H-7b and H-13), 4.15–4.05 (2H, m, H-5), 3.24 (1H, br s, OH), 2.44 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −113.1 (1F, dd, J = 270.0, 7.8), −120.9 (1F, dd, J = 270.0, 15.2).

4.6.20. (E)-N-Allyl-N-[5-(3,4-dimethoxy-phenyl)-4,4-difluoro-5-hydroxy-3-oxo-pent-1-enyl]-4-methyl-benzenesulfonamide, ***4ee***



Yield: 41%, silica gel chromatography (PE/ EA = 3/1), yellowish oil. ^{13}C NMR ($CDCl_3$): δ 188.8 (dd, J = 29.6, 27.4, C-2), 149.1 (C-17), 148.5 (C-16), 145.4 (C-11), 144.6 (C-4), 134.4 (C-8), 130.2 (C-10), 128.9 (C-6), 127.4 (C-14), 127.3 (C-9), 120.4 (C-19), 119.1 (C-7), 115.2 (dd, J = 261.1, 255.8, C-1), 110.6 (C-18), 110.5 (C-15), 99.8 (C-3), 72.8 (dd, J = 27.9, 24.4, C-13), 55.7 (C-21), 55.6 (C-20), 48.4 (C-5), 21.5 (C-12). ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, d, J = 13.7, H-4), 7.69 (2H, d, J = 8.4, H-9), 7.34 (2H, d, J = 8.1, H-10), 7.00–6.76 (3H, m, H-15, H-18 and H-19), 5.67 (1H, d, J = 13.7, H-3), 5.57–5.33 (1H, m, H-6), 5.20–4.96 (3H, m, H-7a, H-7b and H-13), 4.10–4.00

(2H, m, H-5), 3.84 (6H, s, H-20 and H-21), 3.16 (1H, br d, $J = 4.3$, OH), 2.43 (3H, s, H-12). ^{19}F NMR ($CDCl_3$): δ −113.6 (1F, dd, $J = 266.2$, 8.0), −121.7 (1F, dd, $J = 266.2$, 15.8).

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H. Eto, Y. Kaneko, T. Sakamoto, Chem. Pharm. Bull. 48 (2000) 982–990.