Concise stereoselective synthesis of 1-perfluoroalkyl enamines *via* the addition of *N*-lithiated amines to enol ethers and their subsequent metalation to form new functionalized enamines

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Addition of lithium amides derived from a range of cyclic, sterically demanding, and chiral amines, to trifluoromethyl (*Z*)-enol ethers 1 and 4, provides stereoselectively the corresponding (*Z*)-enamines 3a–e and 7 in good yields. This reaction has been extended to the perfluoroalkyl and chlorofluoroalkyl enol ethers (CF_2Cl, C_2F_5). The enamines can react with Bu^{t}Li to give vinylic anions and, after quenching with aldehydes and ethyl chloroformate, provide new functionalized enamines 12–16.

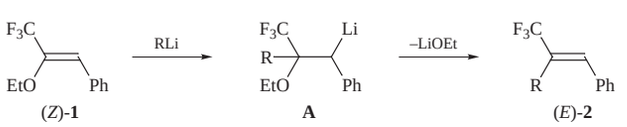
Introduction

Organofluorine compounds have found increasing use in the areas of agrochemicals, pharmaceuticals, polymers and new materials.[1] The fluorine atom brings specific chemical and physical properties to molecules. In the pharmaceutical field, molecules containing CF_2 or CF_3 can offer a significant change in biological activity, compared to their non fluorinated analogs. For example, the enzyme inhibitory activity of trifluoromethyl ketones has been widely proved.[2] The interest in molecules containing the CF_3 group entailed the development of new and efficient synthetic methodologies. Direct trifluoromethylation[3] and synthesis using fluorine-containing building blocks[4] are two major approaches which have gained considerable improvement in recent years. For the latter approach, the elaboration of new versatile building blocks is required. Perfluoroalkylated enamines are precursors of ketones and amines, and are versatile building blocks for the synthesis of complex fluorinated compounds. For their preparation, we have previously developed a Wittig reaction with amides, which was limited to trifluoroacetamides.[5] Other described preparations are the amination of fluoroalkyl ketones[6] and in particular examples, the addition of an amine to fluoroalkynes,[7] the nucleophilic displacement of a vinylic fluoride by a lithium amide,[8] and a direct trifluoromethylation of pyrrolidinones.[9] Most of these preparations are not stereoselective. We report here a new and stereoselective access to functionalized perfluoroalkyl enamines from the corresponding enol ethers.

Results and discussion

We have previously reported the synthetic utility of CF_3 enol ethers which can be involved in electrophilic reactions such as epoxidation and bromination, to give the corresponding epoxy ethers[10] and vinyl bromides.[11] We then exploited their electrophilicity in reactions involving organolithium reagents. CF_3 Enol ethers **1** can undergo addition of alkyllithium reagents but with a regioselectivity opposite to that of CF_3-substituted terminal olefins,[12] giving stereoselective access to trifluoromethyl alkenes **2** (Scheme 1).[13]

We proposed that this formal substitution of the ethoxy group by the alkyl group occurs through a *syn*-addition of the organolithium reagent to the double bond giving the intermediate **A** followed by a *trans*-elimination of LiOEt.



(*Z*)-**1** **A** (*E*)-**2**

Scheme 1

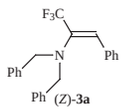
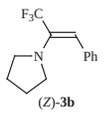
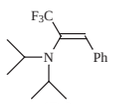
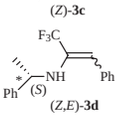
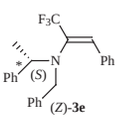
Those results prompted us to investigate the reactivity of CF_3 enol ether **1** towards lithium amides. The treatment of enol ether **1** with one equivalent of lithium dibenzyl amide at −78 °C in THF, and stirring for 3 h at 0 °C, resulted in the stereoselective formation of the (*Z*)-trifluoromethyl-substituted enamine **3a** accompanied by starting material. Two equivalents of lithium amide were required to drive the reaction to completion and to obtain the enamine in high yield (Scheme 2, Table 1). This unusual reaction of addition of lithium amides to a double bond occurs at the opposite site of that expected in Michael-type reactions, and is quite different to reaction with CF_3 substituted terminal olefins.[12] The reaction has been successfully extended to *N*-lithiated species derived from a cyclic amine and the sterically demanding diisopropylamine. The reaction occurred in high yield with complete stereoselectivity. The configuration of double bonds has been determined using an established empirical rule based on $^3J_{CF}$ coupling constants in the ^{13}C NMR spectra.[14] Their values, higher than 4 Hz, demonstrate the *Z*-configuration of the double bonds which was confirmed by NOE experiments performed on the enamine **3a**. After complete assignments of the protons by COSY heteronuclear multiple-quantum coherence (HMQC), and heteronuclear multiple bond coherence (HMBC), irradiation of the benzylic protons resulted in a 6% signal enhancement of the *ortho*-aromatic protons, indicating their spatial proximity.

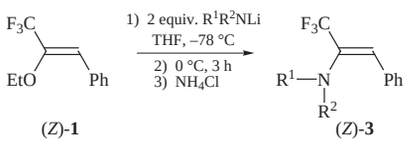
The reaction most likely occurs under kinetic control since the enamines **3** possess the same configuration as the starting material whatever the bulkiness of substituents of the double bond, and since, when an isomerisation can occur, a *Z*/*E* mixture was obtained as in the case of enamine **3d** (Table 1, Entry 4).

We then studied the addition of chiral amines and first chose the (*S*)-phenethyl amine (Table 1, entry 4). However, although the reaction was successful with this monoalkyl lithium amide, it was not stereoselective, leading to a 55:45 mixture of *Z*:*E* isomers. A facile prototropy is probably responsible for the isomerisation of the *Z*-enamine to the less hindered *E*-isomer. When performed with a chiral dialkyl lithium amide, the reaction provided stereoselectively the chiral *Z*-enamine **3e** (Table 1, entry 5).

As in the carbolithiation reaction of enol ethers, the limitation of this reaction is the presence of a conjugated β-substituent which can stabilize an intermediate anionic species. With the enol ether **4**, the reaction still occurs in high yield, although the *p*-methoxyphenyl substituent renders the double

Table 1 Addition of *N*-lithiated amines to enol ether **1**

Entry	R^1R^2NLi	Products **3a**–**e**	Yield (%)
1		 (*Z*)-**3a**	84
2		 (*Z*)-**3b**	78
3		 (*Z*)-**3c**	80
4		 (*Z*,*E*)-**3d**	85
5		 (*Z*)-**3e**	87



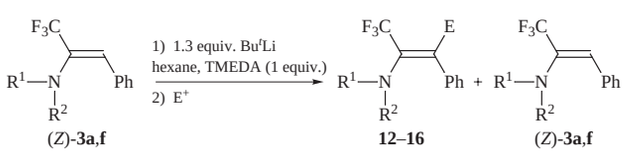
(*Z*)-**1** (*Z*)-**3**

Scheme 2

bond less electrophilic. In contrast, the enol ether **5**, substituted with an alkyl group, was completely unreactive towards lithium diisopropylamide (LDA) (Table 2).

The generality of this reaction was investigated by studying the reactivity of other fluoroalkyl enol ethers. C_2F_5- and $ClCF_2$-Substituted enol ethers **6** and **7**[15] reacted under the same conditions with lithium amides to provide the corresponding enamines **9**, **10** and **11**. The reaction between the enol ether **6** and LDA to provide **10** in good yield confirms the insensitivity of the reaction to steric hindrance and is a good alternative to the Wittig reaction.[5]

In these experiments, we have checked, by performing the reaction in the presence of trimethylsilyl chloride, that the excess of LDA does not allow a vinylic metalation to occur. In order to generate these vinyllithium reagents, we thus used the more basic *tert*-butyllithium reagent (Bu^{t}Li) under the conditions which have been successful for the metalation of CF_3-substituted olefins.[13] Enamines **3c** and **3f**[15] reacted at room temperature with 1.3 equiv. of Bu^{t}Li in hexane in the presence of tetramethylethylenediamine (TMEDA), and, after a few minutes, trapping by one equivalent of propanal, followed by hydrolysis, provided the allylic alcohols **12** and **13** respectively (*E*-isomers), accompanied with about 60% of starting enamines (Scheme 3). These results confirm that, in the absence of



(*Z*)-**3a**,**f** **12**–**16** (*Z*)-**3a**,**f**

Scheme 3

a leaving group, the addition of organolithium reagents of CF_3-substituted double bonds does not occur.[13] Since partial recovering of the enamine could be the result of an incomplete formation of the vinylic anions, we investigated the influence of two parameters, the number of equivalents of Bu^{t}Li, and the

Table 2 Addition of *N*-lithiated amines to enol ethers **4**–**7**

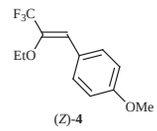
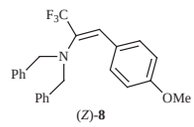
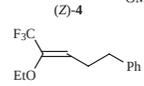
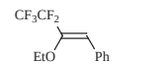
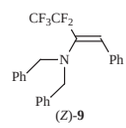
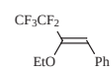
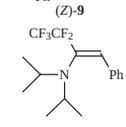
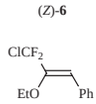
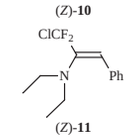
Entry	Enol ethers **4**–**7**	R^1R^2NLi	Enamines **8**–**11**	Yield (%)
1	 (*Z*)-**4**		 (*Z*)-**8**	73
2	 (*Z*)-**5**		No reaction	0
3	 (*Z*)-**6**		 (*Z*)-**9**	70
4	 (*Z*)-**6**		 (*Z*)-**10**	75
5	 (*Z*)-**7**		 (*Z*)-**11**	71

Table 3

t/min[a]	Yield of **12** (%)	Yield of **3a** (%)
7	42	58
10	50	50
15	77	23
20	43	57

[a] *t* = time between Bu^{t}Li and aldehyde additions.

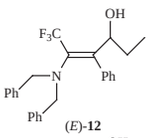
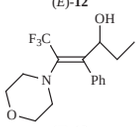
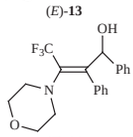
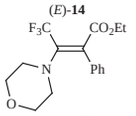
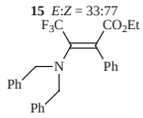
time before introduction of the aldehyde. The former had no significant influence on the results. Conversely, the proportion of allylic alcohols and starting enamines was highly dependent on the time (*t*) between addition of Bu^{t}Li and the aldehyde (Table 3). Experiments performed with **3a** showed that 15 min was required for the optimal formation of the vinylic anion. This anion then rapidly underwent protonation in the reaction medium. Under these conditions, the proportion of allylic alcohols **12** and **13** could be improved and after separation from starting material, they could be isolated in 65% yield (Table 4). With benzaldehyde the reaction occurred in a lower yield (55%). Vinylic anions generated from **3a** and **3f** have also been quenched with ethyl chloroformate leading to the corresponding enamino esters **15** (58%) and **16** (55%) but without stereoselectivity ($E:Z \sim 30:70$). Since no isomerisation of the vinyl anions is observed in reactions with aldehydes, the lack of stereoselectivity is explained by mesomeric forms of enamino esters.

The *E*-configuration of the trisubstituted enamine **14** was demonstrated by a hetero NOE experiment. Irradiation of the fluorine atoms resulted in a 9% enhancement of the signal of the proton *geminal* to the hydroxy group. The spatial proximity between these atoms is confirmed by a through space $^4J_{CF}$ coupling constant of 3.5 Hz, observed for the ^{13}C NMR signal of the hydroxy-substituted carbon. Similar $^4J_{CF}$ were observed for enamines **12** and **13**.

Conclusions

We have developed a method for the preparation of CF_3-substituted enamino alcohols and enamino esters in two steps from enol ethers. The first step involves addition of lithium amides to CF_3-substituted enol ethers, giving stereoselective access to the corresponding enamines in high yields. Lithium amides derived from a range of amines, including chiral ones, were all reactive towards enol ethers. This good alternative to

Table 4 Preparation of enamines **12**–**16** from enamine **3a** and **3f**

Entry	Electrophile	Products **12**–**16**	Yield (%)
1	C_2H_5CHO	 (*E*)-**12**	65
2	C_2H_5CHO	 (*E*)-**13**	65
3	PhCHO	 (*E*)-**14**	57
4	$ClCO_2Et$	 **15** *E*:*Z* = 33:77	58
5	$ClCO_2Et$	 **16** *E*:*Z* = 30:70	55

the Wittig reaction performed on trifluoroacetamide, can be applied to other fluoroalkyl enol ethers. The second reaction is metalation of the (*Z*)-enamine in the presence of *tert*-butyllithium, and subsequent condensation with electrophiles. These new functionalized enamines can be useful precursors of γ amino alcohols and amino acids.

Experimental

^{19}F NMR chemical shifts (δ_F) are reported in ppm, negative upfield relative to internal $CFCl_3$, ^1H NMR and ^{13}CNMR chemical shifts (δ_H, δ_C) are reported in ppm, positive downfield relative to internal Me_4Si; spectra were recorded in $CDCl_3$ at 200 MHz (Bruker AC200) and 400 MHz (Bruker ARX 400). *J* Values are in Hz. Infrared spectra (ν/cm^{-1}; neat) were recorded on a Perkin-Elmer 841 spectrophotometer. Elemental analyses were performed by the Service de Microanalyses of the Centre d'Etudes Pharmaceutiques, Châtenay-Malabry. All reactions were performed in an oven-dried apparatus under an inert atmosphere of argon. THF and diethyl ether were distilled from sodium benzophenone ketyl, and amines were distilled from calcium hydride prior to use. All other reagents were used without further purification. Column chromatography was performed on SiO_2 (70–230 or 230–400 Mesh Merck).

General procedure for the synthesis of the enamines 3a–e, 8–11

An enol ether (1 mmol) was added at −78 °C under argon to an *N*-lithiated amine prepared at −30 °C from *n*-butyllithium (2 equiv., 1.5 M in hexane) and the appropriate amine (2 equiv.) in THF (25 cm^3). The colored solution was stirred for 15 min at −78 °C and then was allowed to warm to 0 °C over a period of 1 h. After 1 to 3 h, the brown solution was poured into saturated aq. ammonium chloride, the layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 cm^3). The combined organics were dried ($MgSO_4$) and evaporated to afford a brown oil. The final enamine was purified by chromatography on SiO_2 (eluent pentane). Enamines prepared from dialkyl amines were obtained with traces of starting material which could not be separated.

(*Z*)-2-Dibenzylamino-1-phenyl-3,3,3-trifluoropropene 3a. From enol ether **1** (0.22 g, 1 mmol) and *N*-lithiated dibenzylamine (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; dibenzylamine 0.4 g, 2 mmol), after purification, compound **3a** was obtained as an oil (0.30 g, 84%); ν(neat)/cm^{-1} 1631 (C=C); δ_F −62.6; δ_H 3.9 (4H, s), 6.5 (1H, s), 6.8 (2H, m), 7.2 (13H, m); δ_C 54.7, 118.5 (q, $^3J_{CF}$ 4.6), 122.5 (q, $^1J_{CF}$ 279), 126.9, 128.1, 128.7, 134.3, 134.5 (q, $^2J_{CF}$ 29), 137.3, 139.7 (Found: C, 75.29; H, 5.58; N, 3.90. $C_{23}H_{20}F_3N$ requires C, 75.18; H, 5.50; N, 3.81%).

(*Z*)-1-Phenyl-2-pyrrolidinyl-3,3,3-trifluoropropene 3b. From enol ether **1** (0.22 g, 1 mmol) and *N*-lithiated pyrrolidine (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; pyrrolidine 0.14 g, 2 mmol), after purification, compound **3b** was obtained in 96% purity (0.19 g, 78%); ν(neat)/cm^{-1} 1634 (C=C); δ_F −64.7; δ_H 1.7 (4H, m), 3.05 (4H, m), 6.15 (1H, s), 7.3 (m, 5H); δ_C 25.6, 50.3, 110.2 (q, $^3J_{CF}$ 5), 122.6 (q, $^1J_{CF}$ 279), 126.6, 127.9, 129.3, 133.7 (q, $^2J_{CF}$ 28), 135.9.

(*Z*)-2-Diisopropylamino-1-phenyl-3,3,3-trifluoropropene 3c. From enol ether **1** (0.22 g, 1 mmol) and LDA (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; diisopropylamine 0.2 g, 2 mmol), after purification, compound **3c** was obtained in 98% purity (0.23 g, 80%); ν(neat)/cm^{-1} 1665 (C=C); δ_F −62.3; δ_H 1.1 (12H, d, *J* 6.6), 3.54 (2H, m), 6.9 (1H, s), 7.3 (3H, m), 7.95 (2H, m); δ_C 20.47 (CH_3), 48.2 (CH), 124.0 (q, $^1J_{CF}$ 285), 128.0, 129.0, 130.5, 134.5, 132.5 (q, $^2J_{CF}$ 28.2).

2-[(1*S*)-1-phenylethylamino]-1-phenyl-3,3,3-trifluoropropene 3d. From enol ether **1** (0.22 g, 1 mmol) and *N*-lithiated (*S*)-(−)-α-methylbenzylamine [*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; (*S*)-(−)-α-methylbenzylamine 0.24 g, 2 mmol], after purification, compound **3d** was obtained as an oil (0.25 g, 85%); ν(neat)/cm^{-1} 3452 (N–H), 1650 (C=C); δ_F −62.9, −68.5 (55 : 45); δ_H 1.35 (3H, d, *J* 6), 1.5 (3H, d, *J* 6), 3.9 (1H), 4.35 (1H, q, *J* 6), 5.4 and 6.0 (2H, s), 7.2 (2 × 5H, m); δ_C 23.1/24.9, 53.6/53.9, 105.6 (q, $^3J_{CF}$ 2.3)/108.7 (q, $^3J_{CF}$ 4), 122.4/122.5 (q, $^1J_{CF}$ 275), 126.2, 128.9, 131.9/132.0 (q, $^2J_{CF}$ 30), 135.1/135.7, 143.5/143.9.

(*Z*)-2-{*N*-Benzyl-*N*-[(1*S*)-1-phenylethyl]amino}-1-phenyl-3,3,3-trifluoropropene 3e. From enol ether **1** (0.22 g, 1 mmol) and *N*-lithiated (*S*)-(−)-α-methyldibenzylamine [*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; (*S*)-(−)-α-methyldibenzylamine 0.42 g, 2 mmol], after purification compound **3e** was obtained (0.25 g, 87%); ν(neat)/cm^{-1} 1631 (C=C); δ_F −60.5; δ_H 1.6 (3H, d, *J* 6.7), 3.75 (1H, d, *J* 14.4) and 4.1 (1H, d, *J* 14.4), 4.7 (1H, q, *J* 6.6), 6.6 (1H), 7.1 (m, 15H); δ_C 20.3 (CH_3), 51.7 (CH_2N), 61.5 (CHN), 123.0 (q, $^1J_{CF}$ 282), 126.5 (q, $^3J_{CF}$ 3.62), 127.7, 128.8, 128.9, 129.7, 133.6 (q, $^2J_{CF}$ 27.5), 134.3, 138.4, 143.2 (Found: C, 75.34; H, 5.82; N, 3.49. $C_{24}H_{22}F_3N$ requires C, 75.56; H, 5.82; N, 3.49%).

(*Z*)-2-Dibenzylamino-1-*p*-methoxyphenyl-3,3,3-trifluoropropene 8. From enol ether **4** (0.25 g, 1 mmol) and *N*-lithiated dibenzylamine (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; dibenzylamine 0.4 g, 2 mmol), after purification, compound **8** was obtained as an oil (0.29 g, 73%); ν(neat)/cm^{-1} 1632 (C=C); δ_F −62; δ_H 3.9 (3H, s), 4.1 (4H, s), 6.6 (s, 1H), 6.8 (2H, d, *J* 9), 7.0 (2H, d, *J* 9), 7.4 (10H, m); δ_C 55.0 (*C*H_2Ph), 55.3 (CH_3O), 113.5, 114.1, 120.0 (q, $^3J_{CF}$ 4.5), 122.5 (q, $^1J_{CF}$ 279), 126.9, 127.5, 128.5, 129.1, 130.6, 131.1, 133.5 (q, $^2J_{CF}$ 28.2), 137.8, 159.3 (Found: C, 72.35; H, 5.68; N, 3.45. $C_{24}H_{22}F_3O$ requires C, 72.52; H, 5.59; N, 3.52%).

(*Z*)-2-Dibenzylamino-3,3,4,4,4-pentafluoro-1-phenylbut-1-ene 9. From enol ether **6** (0.27 g, 1 mmol) and *N*-lithiated dibenzylamine (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; dibenzylamine 0.4 g, 2 mmol), after purification, compound **9** was obtained as an oil (0.29 g, 70%); ν(neat)/cm^{-1} 1621 (C=C); δ_F −83 (CF_3), −107.6 (CF_2); δ_H 3.7 (4H, m), 6.5 (1H, s), 7.2 (15H, m); δ_C 55.3 (*C*H_2Ph), 122.7 (*C*HPh), 127.1, 128.6, 129.5, 134.7 (t, $^2J_{CF}$ 21, CCF_2), 134.8, 137.2 (C_5F_5 not observed) (Found: C, 69.19; H, 4.96; N, 3.43. $C_{24}H_{20}F_5N$ requires C, 69.05; H, 4.84; N, 3.43%).

(*Z*)-2-Diisopropylamino-3,3,4,4,4-pentafluoro-1-phenylbut-1-ene 10. From enol ether **6** (0.27 g, 1 mmol) and LDA (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; diisopropylamine 0.2 g, 2 mmol), after purification, compound **10** was obtained in 97% purity (0.23 g, 75%); ν(neat)/cm^{-1} 1641 (C=C); δ_F −81 (CF_3), −107.4 (CF_2); δ_H 1.1 (12H, d, *J* 6.4), 3.6 (2H, septet, *J* 6.4), 6.8, 7.3, 7.9 (5H); δ_C 20.9, 48.9, 113.9 (tq, $^1J_{CF}$ 220, $^2J_{CF}$ 37, CF_2),

119.5 (qt, $^1J_{CF}$ 288, $^2J_{CF}$ 40, CF_3), 128.0, 129.2, 130.2, 132.3 (t, $^2J_{CF}$ 23.2), 134.5, 136.0.

(*Z*)-3-Chloro-3,3-difluoro-2-dimethylamino-1-phenylpropene 11. From enol ether **7** (0.27 g, 1 mmol) and *N*-lithiated diethylamine (*n*-butyllithium 1.32 cm^3, 1.5 M in hexane; diethylamine 0.14 g, 2 mmol), after purification, compound **11** was obtained in 98% purity (0.17 g, 71%); ν(neat)/cm^{-1} 1628 (C=C); δ_F −48.2; δ_H 1.0 (6H, t, *J* 6), 2.9 (4H, q, *J* 6), 6.5 (s, 1H), 7.2, 7.5 (5H); δ_C 13.5, 46.5, 121.0 (q, $^3J_{CF}$ 4.5), 126.9 (t, $^1J_{CF}$ 297.5), 128.0, 129.0, 134.7, 139.5 (t, $^2J_{CF}$ 22.1).

General procedure for preparation of enamines 12–16

tert-Butyllithium (1.5 M in hexane, 1.3 equiv.) was added at room temperature under argon to a solution of enamine **3a** or **3f** (1 mmol) in hexane (15 cm^3) in the presence of TMEDA (1.3 equiv.). A red color appeared. The mixture was stirred 15 min at room temperature before the addition of the electrophile (1 equiv.). The solution was then treated with saturated aq. ammonium chloride. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organics were dried ($MgSO_4$) and evaporated to afford a brown oil. The final enamine was separated by chromatography (eluent pentane–diethyl ether, 9:1).

(*E*)-2-Dibenzylamino-4-hydroxy-3-phenyl-1,1,1-trifluorohex-2-ene 12. From enamine **3a** (0.37 g, 1 mmol) and *tert*-butyllithium (0.86 cm^3, 1.5 M in hexane, 1.3 equiv.), after addition of propanal (0.06 g, 1 mmol) and purification, compound **12** was obtained (0.27 g, 65%); δ_F −53.6; δ_H 0.7 (3H, t, *J* 6), 0.8 (m, OH), 1.2 (2H, m), 3.7 (4H, s), 4.6 (1H, m), 7.0 (15H, m); δ_C 9.9, 27.6, 55.6, 71.0 (q, $^4J_{CF}$ 3.2), 124.0 (q, $^1J_{CF}$ 276), 127.1, 128.0, 129.1, 129.2, 133.2 (q, $^2J_{CF}$ 32.7), 135.6, 137.7, 148.3 (q, $^3J_{CF}$ 28.2) (Found: C, 71.62; H, 6.55; N, 2.94. $C_{26}H_{26}F_3NO$ requires C, 73.41; H, 6.11; N, 3.29%).

(*E*)-4-Hydroxy-2-morpholino-3-phenyl-1,1,1-trifluorohex-2-ene 13. From enamine **3f** (0.26 g, 1 mmol) and *tert*-butyllithium (0.86 cm^3, 1.5 M in hexane, 1.3 equiv.) after addition of propanaldehyde (0.06 g, 1 mmol) compound **13** was obtained after purification (0.2 g, 65%); ν(neat)/cm^{-1} 3442 (OH), 1687 (C=C); δ_F −56.7; δ_H 0.9 (3H, t, *J* 7.4), 1.4 (2H, q, *J* 7.4), 1.7 (s, OH), 2.45 (4H, m), 3.3 (4H, m), 4.7 (1H, td, *J* 6.4, *J* 1.47), 7.1–7.3 (5H, m); δ_C 9.44, 28.6, 51.3, 67.0, 70.8, 123.0 (q, $^1J_{CF}$ 282), 127.0, 128.0, 129.0, 135.0, 137.0 (q, $^2J_{CF}$ 29.4), 144.0 (Found: C, 60.83; H, 6.47; N, 4.29. $C_{16}H_{20}O_2F_3N$ requires C, 60.76; H, 6.35; N, 4.44%).

(*E*)-4-Hydroxy-2-morpholino-3,4-diphenyl-1,1,1-trifluorobut-2-ene 14. From enamine **3f** (0.26 g, 1 mmol) and *tert*-butyllithium (0.86 cm^3, 1.5 M in hexane, 1.3 equiv.) after addition of benzaldehyde (0.11 g, 1 mmol), and purification, compound **14** was obtained (0.21 g, 57%); ν(neat)/cm^{-1} 3426 (OH), 1620 (C=C); δ_F −56.3; δ_H 2.5 (4H, m), 3.3 (4H, m), 6.1 (1H, s), 6.7–7.2 (10H, m); δ_C 51.5, 67.1, 70.4, 123.5 (q, $^1J_{CF}$ 282), 126.0, 127.0, 128.0, 129.0, 135.0, 136.5 (q, $^2J_{CF}$ 29.4), 140.8, 143.1 (Found: C, 66.16; H, 5.65; N, 3.74. $C_{20}H_{20}F_3NO_2$ requires C, 66.12; H, 5.51; N, 3.86%).

Ethyl 3-morpholino-2-phenyl-4,4,4-trifluorobut-2-enoate 15. From enamine **3f** (0.26 g, 1 mmol) and *tert*-butyllithium (0.86 cm^3, 1.5 M in hexane, 1.3 equiv.) after addition of ethyl chloroformate (0.11 g, 1 mmol) and purification, compound **15** was obtained (0.19 g, 58%); ν(neat)/cm^{-1} 1729 (OH), 1619 (C=C); δ_F −57.8/−62.3 (*E*:*Z* = 33:77); δ_H 1.2/1.25 (3H, t, *J* 6.6), 2.95 (*Z*)/2.62 (4H, m), 3.6 (*Z*)/3.4 (4H, m), 4.1/4.2 (2H, q, *J* 7.1), 7.25 (5H, m); δ_C 13.9, 51.1 (*Z*)/51.0, 61.8 (*Z*)/61.7, 67.0 (*Z*)/67.5, 122.0 (*Z*)/123.0 (q, $^1J_{CF}$ 280), 128.7, 129.0, 132.4, 135.6, 136.2 (*Z*)/137.2 (q, $^2J_{CF}$ 31), 167.1, 167.2 (Found: C, 58.20; H, 5.55; N, 4.11. $C_{16}H_{18}F_3NO_2$ requires C, 58.36; H, 5.47; N, 4.25%).

Ethyl 3-dibenzylamino-2-phenyl-4,4,4-trifluorobut-2-enoate 16. From enamine **3a** (0.37 g, 1 mmol) and *tert*-butyllithium (0.86 cm^3, 1.5 M in hexane, 1.3 equiv.), after addition of ethyl chloroformate (0.11 g, 1 mmol) and purification, compound **16** was obtained (0.24 g, 55%); δ_F −59.4/−57.6 (*E*:*Z* = 30:70); δ_H 1.1 (*Z*)/1.2 (3H, t, *J* 7.1), 3.7 (*Z*)/4.1 (4H, s), 4.15 (2H, q, *J* 7.1), 6.7–7.2 (15H, m); δ_C 14.0 (*Z*)/14.2, 55.6, 56.9, 61.7, 123.0 (q, $^1J_{CF}$ 280.4), 128.4, 128.6, 128.9, 129.1, 134.0 (*Z*)/134.4, 135.0 (q, $^2J_{CF}$ 30.5), 136.9 (*Z*)/137.6, 167.2/167.8 (Found: C, 70.91; H, 5.59; N, 3.16. $C_{26}H_{24}F_3NO_2$ requires C, 71.07; H, 5.47; N, 3.18%).

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References

1 *Organofluorine Chemicals and their Industrial Applications*, ed. R. E. Banks, Halsted Press, New York, 1979; M. Hudlicky, in *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, London, 1992; *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, ed. R. Fuller, Y. Kobayashi and L. Yagupolski, Elsevier, Amsterdam, 1993; *Selective Fluorination in Organic and Bioorganic Chemistry*, ed. J. T. Welch, *ACS Symposium Series 456*, Washington DC, 1991, pp. 164–173; P. N. Edwards, in *Organofluorine chemistry*: *Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994, pp. 501–541.

2 K. Brady, A. Wei, D. Ringe and R. H. Abeles, *Biochemistry*, 1990, **29**, 7600; R. P. Dunlap, P. J. Stone and R. H. Abeles, *Biochem. Biophys. Res. Commun.*, 1987, **145**, 509; R. L. Stein, A. M. Strimpler, P. D. Edwards, J. J. Lewis, R. C. Mauger, J. A. Schwartz, M. M. Stein, D. A. Trainor, R. A. Wildonger and M. A. Zottola, *Biochemistry*, 1987, **26**, 2682; C. A. Veale, J. R. Damewood, G. B. Steelman, C. Bryant, B. Gomes and J. C. Williams, *J. Med. Chem.*, 1995, **38**, 86; N. P. Peet, J. P. Burkhart, M. R. Angelastro, E. L. Giroux, S. Mehdi, P. Bey, M. Kolb, B. Neises and D. Schirlin, *J. Med. Chem.*, 1990, **33**, 394; T. Ueda, C. M. Kam and J. C. Powers, *Biochem. J.*, 1990, **265**, 539; H. L. Sham, H. Stein, C. A. Rempel, J. Cohen and J. J. Plattner, *FEBS Lett.*, 1987, **220**, 229; C. Tarnus, M. J. Jung, J. M. Rémy, S. Baltzer and D. Schirlin, *FEBS Lett.*, 1989, **249**, 47; D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, C. A. Free, S. A. Smith and E. W. Petrillo Jr, *J. Med. Chem.*, 1993, **36**, 2431.

3 M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555; R. Krishnamurti and G. K. S. Prakash, *J. Org. Chem.*, 1991, **56**, 984.

4 D. J. Burton, Z. Y. Yang and W. Qiu, *Chem. Rev.*, 1996, **96**, 1641; K. J. Uneyama, *Synth. Org. Chem. Jpn*, 1991, **49**, 612; J. M. Percy, *Contemp. Org. Synth.*, 1995, 251.

5 (*a*) J. P. Bégué and D. Mesureur, *Synthesis*, 1989, 309; (*b*) J. P. Bégué, D. Bonnet-Delpon, D. Mesureur, G. Née and S. W. Wu, *J. Org. Chem.*, 1992, **57**, 3807.

6 V. A. Soloshonok and T. Ono, *Synlett*, 1996, 919; P. Bravo, M. Crucianelli and M. Zanda, *Tetrahedron Lett.*, 1995, **36**, 3043.

7 R. D. Chambers, S. Partington and D. B. Speight, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2673; W. Cen, Y. Ni and Y. Shen, *J. Fluorine Chem.*, 1995, **73**, 161.

8 W. Dmowski, *J. Fluorine Chem.*, 1984, **26**, 379; C. Portella and M. Iznaden, *J. Fluorine Chem.*, 1991, **51**, 1; W. Y. Huang, Y. S. Liu and L. Lu, *J. Fluorine Chem.*, 1994, **66**, 209; L. F. Jalander and J. E. Lönnqvist, *Synth. Commun.*, 1996, **26**, 3549.

9 H. Bürger, T. Dittmar and G. Pawelke, *J. Fluorine Chem.*, 1995, **70**, 89.

10 J. P. Bégué, F. Benayoud and D. Bonnet-Delpon, *J. Org. Chem.*, 1995, **60**, 5029; J. P. Bégué, D. Bonnet-Delpon, N. Fischer-Durand, A. Amour and M. Reboud-Ravaux, *Tetrahedron*: *Asymmetry*, 1994, **5**, 1094; J. P. Bégué, D. Bonnet-Delpon and A. Kornilov, *Synthesis*, 1996, **4**, 529.

11 D. Bonnet-Delpon, D. Bouvet, M. Ourévitch and M. H. Rock, *Synthesis*, 1998, 288.

12 J. P. Bégué, D. Bonnet-Delpon and M. H. Rock, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1409.

13 J. P. Bégué, D. Bonnet-Delpon, D. Bouvet and M. H. Rock, *J. Org. Chem.*, 1996, **61**, 9111.

14 J. P. Bégué, D. Bonnet-Delpon, D. Mesureur and M. Ourévitch, *Magn. Reson. Chem.*, 1991, **29**, 675.

15 For preparation of enol ethers and enamine **3f** see ref. 5(*b*).

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