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New Fluorine-containing Building Blocks from Trifluoroethanol. 2.

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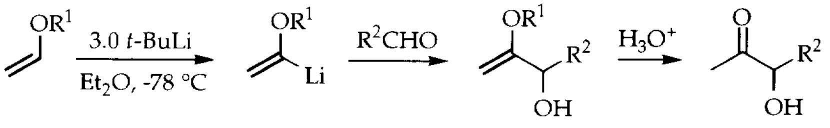
Abstract: *A new fluorine containing acyl anion equivalent 1,1-difluoro-2-lithio-2-[(N,N-diethylcarbamato)-ethene* **9** *has been prepared and trapped with a number of electrophiles in good yields. Transacylation of the first formed lithium alkoxides releases a difluoroenolate, affording difluoromethylketones upon work-up.*

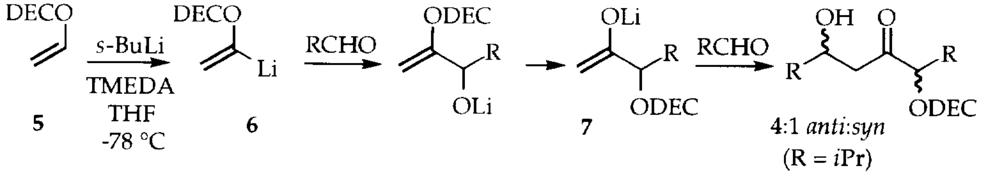
Seminal papers by Schöllkopf[1] and Baldwin[2] showed that the α-metallation of vinyl ethers **1** occurred readily and the newly-formed vinyllithium species **2** could be trapped with carbonyl and alkyl halide electrophiles. Furthermore, acidic hydrolysis of the adduct vinyl ethers **3** released methyl ketones **4**, formed by a reverse polarity or Umpolung route (**Scheme 1**).



1; R^1 = Me, Et.   2   3   4

Scheme 1

The literature contains many applications of the Schöllkopf/Baldwin procedure, applied to acyclic[3] and cyclic[4] substrates and deployed in the total synthesis of natural products.[5] Many structural variations on the theme of the vinyl ether have been explored.



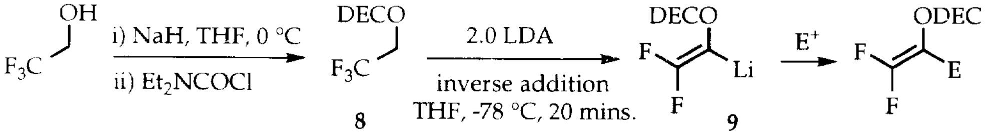
5   6   7

(DEC = CONEt$_2$)

Scheme 2

In particular, metallated enol carbamates display an extremely appealing and versatile range of reactions.[6] In 1990, Sengupta and Snieckus described the metallation of enol carbamate **5**, formed from acetaldehyde enolate (**Scheme 2**).[7] The reactive vinylmetal reagent **6** underwent a range of alkylation reactions and intercepted suitable carbonyl electrophiles. The first-formed alkoxides underwent a rapid transacylation reaction, releasing a lithium enolate **7** which competed with **6** for the carbonyl electrophile leading to the formation of aldol products.[8] Our work in synthetic organofluorine chemistry aspires to the development of useful and general synthetic methods appropriate to the synthesis of densely-functionalised molecules containing a limited number of fluorine atoms.[9] The generation of metallated difluoroenol derivatives from trifluoroethanol is well known,[10] but we became interested in the carbamate chemistry because it held the promise of some tandem chemistry, allowing both carbon atoms of trifluoroethanol to be utilised in a single synthetic operation. In this paper, we wish to describe in full[11] our findings concerning a metallated difluoroenol carbamate, and its reactions with carbonyl, and other, electrophiles.

Carbamate **8** was prepared by the treatment of the sodium salt of trifluoroethanol with *N,N*-diethylcarbamyl chloride in THF at 0 °C. Fractional distillation of the product afforded material suitable for the dehydrofluorination/metallation reaction, though the carbamate could also be distilled from calcium hydride. The slow addition of **8** to a solution of freshly-prepared LDA in THF at -78 °C led to the formation of **9** in an exothermic reaction (**Scheme 3**).

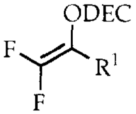


Scheme 3

The thermal stability of **9** is moderate; decomposition occurred above -65 °C so the slow addition rate was essential. The reaction mixture remained homogeneous throughout the procedure, but underwent an interesting range of colour changes. A yellow colour developed towards the end of the addition, deepening through orange to red upon prolonged stirring at -78 °C.[12] Quenching with methanolic ammonium chloride led to the formation of difluoroalkene **10** in high yield. Other effective electrophiles included silicon and tin halides (**Table 1**). Vinyl silane **11** and stannane **12** were obtained in 69 % and 70 % yields upon treating the metallated enol carbamate with trimethylsilyl chloride and tributyltin chloride respectively. However, we were unable to alkylate **9** with iodomethane. No reaction occurred at low temperature (-78 °C); allowing the mixture to warm led to decomposition. This behaviour contrasts with that displayed by **6** which reacted with both iodomethane, and the more demanding and typical iodohexane, in good yield (82 % and 70 % respectively).

A number of sulfur electrophiles have been explored. Treatment of **9** with tosyl fluoride failed to lead to sulfone **13**. Instead, difluoroenol carbamate **10** was isolated upon work-up. Tosic anhydride afforded a similar result. The more reactive **6** reacted with tosyl fluoride to afford a good (75 %) yield of an interesting captodative (sulfonyl)enol carbamate.[7] With diphenyldisulfide, we isolated monofluoro bis sulfides **14a** and **14b** as an inseparable mixture (66 %). The first formed sulfide was attacked by thiophenolate anion, resulting in elimination of fluoride ion. With phenylsulfenyl chloride a complex mixture of products was obtained. The desired vinyl sulfide **15** was identified as one of the conponents in the GC mass spectrum. Recent publications by Ishihara and co-workers have shown that β,β-difluoroenones are useful building blocks for highly substituted unsaturated carbonyl compounds.[13] We therefore attempted the direct preparation of related ketones, esters and amides. However we were unable to isolate addition products from the reactions of **9** with diethylcarbamyl chloride, benzoyl chloride, dimethyl acetamide or dimethyl formamide. Only the addition of solid carbon dioxide afforded an isolable product; unstable acid **16** was isolated in good (75 %) yield after extractive work-up.

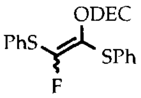
Table 1. Reactions of **9** with non-carbonyl electrophiles.

Electrophile	Product		(Yield, %)
$NH_4Cl/MeOH$		**10**; $R^1 = H$	(92)
Me_3SiCl		**11**; $R^1 = SiMe_3$	(69)
Bu_3SnCl		**12**; $R^1 = SnBu_3$	(70)
p-$TolSO_2F$		**13**; $R^1 = SO_2$*p*-Tol	(0)
PhSSPh		**14**; $R^1 = SPh$	(66)[a]
PhSCl		**15**; $R^1 = SPh$	(-)[b]
CO_2		**16**; $R^1 = CO_2H$	(75)
$ZnBr_2$		**17**; $R^1 = ZnBr$	(-)[c]
I_2		**18**; $R^1 = I$	(75)

a). The yield referred to was obtained for the bis(sulfide) **14a,b**.

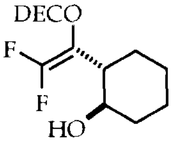
b). Detected in the GCMS and ^{19}F NMR spectra.

c). Converted to **18** without isolation.



14a,b

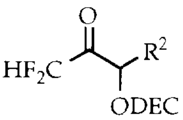
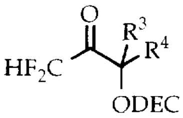
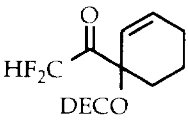
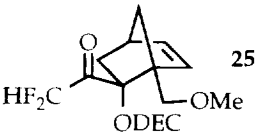
Treatment of **9** with zinc bromide leads to the formation of thermally stable and unreactive zinc reagent **17**. However, exposure to iodine led to the isolation of iodide **18** in 75 % yield. All attempts to deploy stananne **12**, zinc reagent **17** and iodide **18** in Pd(0) catalysed couplings with alkenyl halides, aryl halides, vinyl triflates, vinyl stannanes and vinyl zinc reagents were unsuccessful. These and other transmetallation studies will be reported elsewhere.



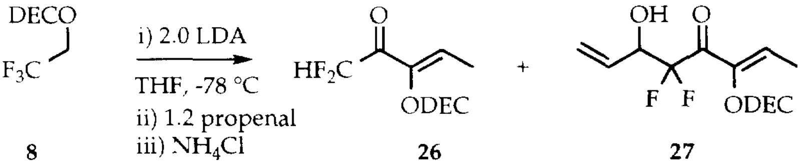
19

All attempts to open cyclohexene oxide with **9** in the presence of boron trifluoride etherate to form **19** were unsuccessful. Products arising from eliminative ring opening were isolated.

Table 2. Reactions of **9** with carbonyl electrophiles

Electrophile	Product		(Yield, %)
Propanal		**20**; $R^2 = CH_2CH_3$	(68)
2-Methylpropanal		**21**; $R^2 = CH(CH_3)_2$	(74)
Trimethylacetaldhyde		**22**; $R^2 = C(CH_3)_3$	(54)
Pentan-3-one		**23**; $R^3 = R^4 = CH_2CH_3$	(72)
2-Cyclohexenone		**24**	(54)
1-(Methoxymethyl)-5-norbornen-2-one		**25**	(56)

However, remetallation of stannane **12** occurred smoothly in THF at -78 °C upon exposure to one equivalent of *n*-butyllithium. Addition of freshly-distilled boron trifluoride etherate followed immediately by a small excess of cyclohexene oxide in a modification of Ganem's procedure,[15] led to the isolation of homoallylic alcohol **19** in good (65 %) yield. The failure of the alcohol to undergo transacylation *via* a six-membered cyclic tetrahedral intermediate is due, presumably, to the low nucleophilicity of the boron alkoxide formed when the epoxide opens.[16] Carbonyl electrophiles reacted efficiently to afford ketones **20-25** (**Table 2**) although a slight decrease in yield was observed as the carbonyl group became more sterically hindered. Primary, secondary and tertiary aldehydes afforded good yields of products. Acyclic and cyclic ketones reacted efficiently and exclusive 1,2-addition occurred with cyclohexenone. All the reactions with carbonyl electrophiles afforded α,α-difluoromethyl ketone products. Good yields were obtained only when the reaction mixture was allowed to warm to 0 °C over one hour. Aldol products were not observed in any of these reactions. Presumably, this is due to the presence of the two fluorine atoms, lowering the nucleophilicity of the enolate. However, the treatment of **9** with propenal led to an interesting observation (**Scheme 4**).



Scheme 4

The formation of **27** in addition to isomerised mono-adduct **26** implies that non-enolisable aldehydes are competent electrophiles for difluoroenolates.[17] The migration of the double bond into conjugation with the carbonyl group presumably occurs during work-up. Only products containing the *E*-configured double bond were isolated.[18]

A profile of the reactivity of **9** is beginning to emerge. The organolithium reagent derived from the fluorinated enol carbamate is clearly less reactive than the desfluoro species **6**. The reaction with iodomethane provides the clearest demonstration of this fundamental difference.[19] We suggest that **9** is also significantly "harder", reacting most efficiently with highly polarised carbonyl electrophiles and reacitve Group (IV) halides, reagents well known for their efficient trapping of unstabilised organometallic reagents.

Though the effect of the fluorine atoms in attenuating the nucleophilic reactivity of **9** restricts the range of useful electrophiles, this has the distinct advantage of limiting the nucleophilic reactivities of the enolates released by the transacylation reaction, avoiding contamination of the product ketones with aldol products.

Acknowledgements

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EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-300 (300.13 and 75.47 MHz respectively) and Bruker AMX-400 (400.14 and 100.6 MHz respectively) spectrometers. All spectra were recorded relative to tetramethylsilane as the internal standard. ^{19}F-NMR spectra were recorded on JEOL GX-90 (89.70 MHz) or Bruker AMX-400 (376.45 MHz) spectrometers relative to chlorotrifluoromethane as the internal standard. ^{13}C NMR spectra were recorded using the JMOD pulse sequence unless otherwise stated. Mass spectra were recorded on a Kratos MS-80 mass spectrometer with a DS-55 data system or a Kratos MS-580 RF mass spectrometer. Chemical ionisation (CI$^+$) methods used ammonia as the carrier gas. Microanalyses were performed on a Perkin Elmer 240 Elemental Analyser. Fluorine analysis could not be obtained locally. For TLC, precoated aluminium-backed silica gel plates were supplied by E. Merck, A.G. Darmstadt, Germany. (Silica gel 60 F$_{254}$, thickness 0.2 mm). Anisaldehyde staining was employed for visualisation, unless otherwise stated. Column chromatography was performed using silica gel (E. Merck A. G. Kieselgel 60, Art. 9385). Column fractions were collected and monitored by thin layer chromatography.

Gas chromatographic analyses were carried out on a Pye Unicam series 304 chromatograph, fitted with a Pye Unicam computing integrator or on a Carlo-Erba 8000 series chromatograph. The chromatograph was fitted with a wall-coated fused silica capillary column, type CP-SIL-19 CB (50 m). Infra red spectra were obtained from a Perkin Elmer 1600 series FTIR spectrophotometer, in the region 4000-625 cm^{-1}. The samples were run as films.

Tetrahydrofuran was dried by refluxing with sodium metal and benzophenone under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. Trifluoroethanol was purchased from Fluorochem. All electrophiles were purchased from the Aldrich Chemical Company and distilled before use, or freshly prepared by literature procedures.

All products were purified to >98% purity by Kugelrohr distillation or flash column chromatography and analysed immediately. In some cases, product instability prevented satisfactory microanalyses from being obtained.

2,2,2-Trifluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethane (8)

2,2,2-Trifluoroethanol (7.3 ml, 10.0 g, 0.1 mol) was added dropwise over one hour to a suspension of sodium hydride (4.0 g at 60 % dispersion from which the oil had been removed with toluene) in dry THF (20 ml) at 0 °C. The olive green suspension was stirred for one hour, and then diethylcarbamyl chloride (12.7 ml, 0.1 mol) was added dropwise over ninety minutes at 0 °C. The beige suspension was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by the cautious addition of saturated aqueous sodium bicarbonate (50 ml), followed by water (100 ml). The mixture was extracted with diethyl ether (3 x 100 ml), and the combined organic extracts were washed successively with saturated aqueous ammonium chloride (100 ml), saturated aqueous sodium bicarbonate (100 ml) and then water (2 x 150 ml), and dried ($MgSO_4$). The ether was removed *in vacuo*, and the crude product was distilled to yield **carbamate 8** (17.5 g, 88 %) as a colourless liquid; b.p. 62 °C/27 mm Hg; (Found: C, 42.18; H, 6.09; N, 7.10. Calc. for $C_7H_{12}NF_3O_2$: C, 42.21; H, 6.07; N, 7.03%); ν_{max} ($CHCl_3$) 1694 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 4.44 (2H, *q*, $^3J_{H\text{-}F}$ 9.0, CF_3CH_2), 3.34-3.18 (4H, *m*, $N(CH_2CH_3)_2$), 1.10 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(300 MHz; $CDCl_3$) 153.7 , 123.3 (*q*, $^1J_{C\text{-}F}$ 277.2), 60.8 (*q*, $^2J_{C\text{-}F}$ 36.2), 42.3, 41.4, 13.5, 12.9; δ_F(90 MHz, $CDCl_3$) -74.95 (3F, *t*, $^3J_{H\text{-}F}$ 9.0); *m/z* (EI) 199 (M^+, 100 %).

The reaction of (9) with non-carbonyl electrophiles: 1,1-Difluoro-2-(*N,N*-diethylcarbamoyloxy) ethene (10).

In a typical procedure, diisopropylamine (6.60 ml, 50.0 mmol) was dissolved in dry THF (50 ml) and the solution was cooled to -78 °C. *n*-Butyllithium (30 ml of a 1.6 M solution in hexane) was added over five minutes. The mixture was allowed to warm to -30 °C, and then recooled to -78 °C. 2,2,2-Trifluoro-1-(*N,N*-diethylcarbamoyloxy)ethane **8** (3.90 ml, 24.0 mmol) was added over fifteen minutes, and the mixture was stirred for a further twenty minutes. During this time the colour of the mixture changed from colourless to yellow, through orange to red. Methanolic ammonium chloride (5.0 ml) was added in one portion, and stirring was continued for one hour at -78 °C, before the mixture was allowed to warm to room temperature, giving a yellow coloured solution. The reaction was quenched with saturated aqueous ammonium chloride (250 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated cautiously *in vacuo*. Distillation afforded the **enol carbamate 10** (7.73 g, 92 %); b.p. 75 °C/32 mm Hg; (Found: C, 46.82; H, 6.25; N, 7.71. Calc. for $C_7H_{11}F_2NO_2$: C, 46.91; H, 6.19; N, 7.82 %); ν_{max} ($CHCl_3$) 1716 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 6.60 (1H, *dd*, $^3J_{H\text{-}F(trans)}$ 16.0, $^3J_{H\text{-}F(cis)}$ 3.0), 3.26-3.14 (4H, *m*, $N(CH_2CH_3)_2$), 1.10 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(300 MHz; $CDCl_3$) 154.5 (*dd*, $^1J_{C\text{-}F}$ 288.2, 274.6), 150.8, 101.0 (*dd*, $^2J_{C\text{-}F}$ 60.7, 13.3), 42.4, 41.7, 13.8, 13.1; δ_F(90 MHz; $CDCl_3$) -97.8 (1F, *dd*, $^2J_{F\text{-}F}$ 73.2, $^3J_{H\text{-}F\,(trans)}$ 16.0), -118.3 (1F, *d*, $^2J_{F\text{-}F}$ 73.2); *m/z* (CI) 180 ($[M+H]^+$, 100 %) 100 ($[CONEt_2]^+$, 85).

The following were also obtained by this general procedure:

2,2-Difluoro-1-(*N,N*-diethylcarbamoyloxy)-1-(trimethylsilyl)ethene (11)

Trimethylsilyl chloride was used as the electrophile (1.1 equivalents) and the mixture was quenched with aqueous ammonium chloride at -30 °C. The usual work-up afforded the crude silane which was purified by filtration through an alumina column (Brockmann, Activity 1) with toluene. Removal of the solvent *in vacuo* afforded **silane 11** (69 %); (Found C, 47.81; H, 7.49; N, 5.63. Calc. for $C_{10}H_{19}NO_2F_2Si$: C, 47.79; H, 7.57; N, 5.58 %); ν_{max} ($CHCl_3$) 1716 cm^{-1} (C=O);

δ_H(300 MHz; CDCl$_3$) 3.20 (4H, *q*, ^3J $_{H\text{-}H}$ 7.5, N(C*H*$_2$CH$_3$)$_2$), 1.10 (*t*, 6H, ^3J $_{H\text{-}H}$ 7.0, N(CH$_2$C*H*$_3$)$_2$), 0.15 (9H, *s*, Si(C*H*$_3$)$_3$); δ_C(300 MHz; CDCl$_3$) 159.4 (*dd*, ^1J $_{C\text{-}F}$ 311.0, 279.0), 154.1, 111.8 (*dd*, ^2J $_{C\text{-}F}$ 61.8, 5.43), 42.4, 41.9, 13.9, 13.2, -2.2; δ_F(90 MHz; CDCl$_3$) -82.6 (1F, *d*, ^2J $_{F\text{-}F}$ 49.0), -103.5 (1F, *d*, ^2J $_{F\text{-}F}$ 49.0); *m/z* (CI) 257 ([M+H]$^+$, 67 %), 100 ([CONEt$_2$]$^+$, 100).

2,2-Difluoro-1-(*N,N*-diethylcarbamoyloxy)-1-(tributylstannyl)ethene (12)

Tributyltin chloride was used as the electrophile (1.1 equivalents) and the mixture was quenched with aqueous ammonium chloride at -30 °C. The usual work-up afforded the crude stannane which was purified by filtration through an alumina column (Brockmann, Activity 1) with toluene. Removal of the solvent *in vacuo* afforded **stannane 12** (70 %); ν_{max} (CHCl$_3$) 1716 cm^{-1} (C=O); δ_H(300 MHz; CDCl$_3$) 3.25 (4H, *q*, ^3J $_{H\text{-}H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$), 1.60-0.93 (27H, *envelope*, Sn(C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_3$)$_3$), 0.93 (6H, *t*, ^3J $_{H\text{-}H}$ 7.0, N(CH$_2$C*H*$_3$)$_2$); δ_C(300 MHz; CDCl$_3$) 158.2 (*dd*, ^1J $_{C\text{-}F}$ 311.1, 277.0), 154.5, 112.8 (*dd*, ^2J $_{C\text{-}F}$ 81.9, 13.5), 42.3, 41.8, 28.8, 27.3, 14.0, 13.7, 13.4, 11.5; δ_F(90 MHz; CDCl$_3$) -84.2 (1F, *d*, ^2J $_{F\text{-}F}$ 64.1), -110.8 (1F, *d*, ^2J $_{F\text{-}F}$ 64.1); HRMS (Found: 470.1861. Calc. for $C_{19}H_{37}NO_2F_2Sn$: 470.1893); *m/z* (CI) 471 ([M+H]$^+$, 10 %), 100 ([CONEt$_2$]$^+$, 100).

Attempted preparation of 1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(tolylsulfonyl)ethene (13)

p-Toluenesulfonyl fluoride (1.1 equivalents added as a 1.0 M solution in dry THF) was used as the electrophile. The mixture was stirred at -78 °C for 6 hours then allowed to warm to -30 °C and quenched with aqueous ammonium chloride. The usual extractive work-up (with diethyl ether) and examination of the crude product by ^{19}F NMR revealed the presence of **10** and unreacted sulfonyl fluoride as the sole fluorine-containing materials.

***E*- and *Z*-(2-(*N,N*-diethylcarbamoyloxy)-1-fluoro-1,2-bis(thiophenyl)ethene (14a) and (14b)**

Diphenyldisulfide (1.1 equivalents) was used as the electrophile. The mixture was stirred at -78 °C for 6 hours then allowed to warm to -30 °C and quenched with aqueous ammonium chloride. The usual extractive work-up (with diethyl ether) afforded the crude mixture of bis(sulfides) which was purified by flash column chromatography (R$_f$ 0.12, 10 % EtOAc/Hexane) to afford **bis(sulfides) 14a** and **14b** as an inseparable mixture (66 %). Major isomer; ν_{max} (CHCl$_3$) 1716 cm^{-1} (C=O); δ_H(300 MHz; CDCl$_3$) 7.51-7.20 (10H, *m*, C_6H_5S x 2), 3.24 (4H, *q*, ^3J $_{H\text{-}H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$), 1.06 (6H, *t*, ^3J $_{H\text{-}H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$); δ_C(CDCl$_3$; 300 MHz) 151.8, 151.4 (*d*, ^1J $_{C\text{-}F}$ 294.3), 135.4 (*d*, ^2J $_{C\text{-}F}$ 36.8), 131.0, 130.8, 129.0, 128.0, 127.9, 42.5, 41.9, 13.8, 13.1; δ_F(90 MHz, CDCl$_3$) -102.48 (*s*); *m/z* (CI) 378 ([M+H]$^+$, 85 %), 100 ([CONEt$_2$]$^+$, 100). Minor isomer; ν_{max} (CHCl$_3$) 1716 cm^{-1} (C=O); δ_H(300 MHz; CDCl$_3$) 7.51-7.20 (10H, *m*, C_6H_5S x 2), 3.04 (4H, *q*, ^3J $_{H\text{-}H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$), 0.93 (6H, *t*, ^3J $_{H\text{-}H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$); δ_C(CDCl$_3$; 300 MHz) 151.9 (C-3), 149.6 (*d*, ^1J $_{C\text{-}F}$ 294.3), 135.4 (*d*, ^2J $_{C\text{-}F}$ 36.8), 131.0, 129.7, 129.4, 129.1, 128.9, 127.7, 42.5, 41.9, 13.8, 13.1; δ_F(90 MHz, CDCl$_3$) -91.3 (*s*); *m/z* (CI) 378 ([M+H]$^+$, 85 %), 100 ([CONEt$_2$]$^+$, 100). Satisfactory microanalyses could not be obtained for these compounds.

Attempted preparation of 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-1-(thiophenyl)ethene (15)

Freshly-distilled phenylsulfenyl chloride[20] (1.1 equivalents) was used as the electrophile . The mixture was stirred at -78 °C for 4 hours then allowed to warm to -30 °C and quenched with aqueous ammonium chloride. The usual extractive work-up (with diethyl ether) and examination of the crude product by ^{19}F NMR revealed the presence of a complex mixture of products which contained signals consistent with the presence of **15**. All attempts to separate the constituents of the product mixture (Kugelrohr distillation and column chromatography) were unsuccessful. For **15**; δ_F(90 MHz, $CDCl_3$) -84.10 (*d*, $^2J_{F\text{-}F}$ 27.5), -95.73 (*d*, $^2J_{F\text{-}F}$ 27.5); *m/z* (CI) 288 ($[M+H]^+$, 15 %), 100 ($[CONEt_2]^+$, 100).

1,1-Difluoro-2-(*N*,*N*-diethyl carbamoyloxy)prop-1-enoic acid (16)

2,2,2-Trifluoro-1-(N,N-diethylcarbamoyloxy)ethane **8** was added dropwise over twenty minutes to a solution of LDA (generated from the slow addition of *n*-butyllithium (3 ml of a 1.6 M solution in hexane) to diisopropylamine (0.66 ml, 5.0 mmol) in dry THF (5 ml) at -78 °C). The mixture was stirred for a further twenty minutes at -78 °C, and then added *via* cannula into a dry flask containing solid CO_2 (0.17 g, 3.60 mmol). On completion of the addition, the mixture was stirred at -78 °C until any excess solid CO_2 had evaporated. The resulting solution was quenched (Caution!) with water, followed by hydrochloric acid (1M, 25 ml). The mixture was extracted with diethyl ether (3 x 30 ml) and the combined organic extracts were washed successively with saturated aqueous ammonium chloride solution (100 ml) and sodium bicarbonate solution (100 ml), then dried ($MgSO_4$). After filtration the ether was removed *in vacuo* to yield **acid 16** as an unstable semi-solid (75 %); ν_{max} (KBr) 1716 (carbamate C=O), 1670-1620 (acid C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 9.22 (1H, *br. s*, CO_2H), 3.32-3.15 (4H, *m*, $N(CH_2CH_3)_2$) 1.20-0.97 (6H, *m*, $N(CH_2CH_3)_2$); δ_C (300 MHz, $CDCl_3$) 164.1 (*dd*, $^1J_{C\text{-}F}$, 335.1, 317.5), 162.9, 152.7, 107.1 (*dd*, $^2J_{C\text{-}F}$, 32.6, 32.5), 42.8, 42.5, 13.8, 13.2; δ_F(90 MHz; $CDCl_3$) -77.1 (1F, *s*), -82.0 (1F, *s*). All attempts to obtain mass spectra or microanalyses for this compound were unsuccessful.

2,2-Difluoro-1-(*N*,*N*-diethylcarbamoyloxy)-1-iodoethene (18) (*via* zinc reagent (17))

Zinc bromide (2.4 ml of a 1.0 M solution in diethyl ether) was added in one portion to a solution of the metallated difluoroenol carbamate (2.4 mmol), and the mixture immediately became yellow in colour. Stirring was maintained at -78 °C for a further hour, and then the mixture was warmed to 0 °C. A saturated solution of iodine (0.61g, 4.8 mmol) in dry THF (2 ml) was added in one portion with subsequent addition of dry THF washings (3 x 2 ml), to the reaction mixture. Stirring was maintained at this temperature for one hour. The reaction was allowed to warm to room temperature overnight and was then quenched with saturated aqueous ammonium chloride (25 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were washed with saturated aqueous sodium sulfite solution (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil. Distillation afforded **iodide 18** (0.622 g, 74 %) as a colourless oil; b.p. 50 °C/2 mm Hg (Kugelrohr); (Found: C, 27.78; H, 3.35; N, 4.36. Calc. for $C_7H_{10}NO_2F_2I$: C, 27.54; H, 3.31; N, 4.59 %); δ_H(300 MHz; $CDCl_3$) 3.33-3.17 (4H, *m*, $N(CH_2CH_3)_2$), 1.11 (3H, *t*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)_2$), 1.09 (3H, *t*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(300 MHz; $CDCl_3$) 153.8 (*dd*, $^1J_{C-F}$ 298.0, 279.8), 151.2, 60.7 (*dd*, $^2J_{C-F}$ 58.0, 27.2), 42.9, 42.0, 14.1, 13.1; δ_F(90 MHz; $CDCl_3$) -85.8 (1F, *d*, $^2J_{F-F}$ 42.7), -99.3 (1F, *d*, $^2J_{F-F}$ 42.7); *m/z* (CI) 323 ($[M+NH_4]^+$, 10 %), 306 ($[M+H]^+$, 50), 100 ($[CONEt_2]^+$, 100).

trans-2-([2'N,N-Diethylcarbamoyloxy]-1'1'-difluoroethenyl)-cyclohexan-1-ol (19)

n-Butyllithium (2.14 ml of a 1.6M solution in hexane) was added at -78 °C to a stirred solution of 2,2-difluoro-1-(*N*,*N*-diethylcarbamoyloxy)-1-tributylstannyl ethene **12** (1.5 ml, 3.43 mmol) in dry THF (6.5 ml) over five minutes. The blue coloured suspension was stirred for one hour at -78 °C and then boron trifluoride etherate (0.84 ml, 6.86 mmol) was added in one portion, followed immediately by cyclohexene oxide (0.38 ml, 1.1 equivalents). The mixture became green in colour and was stirred at -78 °C for two hours, then allowed to warm to -20 °C. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and extracted with ethyl acetate (2 x 30 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (35 ml), water (35 ml) and dried ($MgSO_4$). After filtration, the solvents were removed *in vacuo* to afford an orange oil. Purification by flash column chromatography (R_f 0.38, 20 % EtOAc/Hexane) yielded **homoallylic alcohol 19** (0.618 g, 65 %) as a colourless oil; ν_{max} (KBr) 3585-3220 (O-H), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 4.15 (1H, *s*, O*H*), 3.29-3.18 (4H, *m*, $(NCH_2CH_3)_2)$), 3.18-3.08 (1H, *m*, C(OH)*H*), 2.20-1.13 (*envelope*, 9H, cyclohexyl), 1.06 (6H, *q*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(300 MHz; $CDCl_3$) 156.4 (*dd*, $^1J_{C-F}$ 282.4, 50.0), 154.4, 112.3 (*dd*, $^2J_{C-F}$ 43.5, 13.7), 68.8, 45.3, 42.7, 42.0, 33.2, 28.0, 25.1, 24.5, 13.8, 13.0; δ_F(90 MHz; $CDCl_3$) -97.3 (*d*, $^2J_{F-F}$ 58.0), -111.0 (d, $^2J_{F-F}$ 58.0); HRMS (Found: 278.1575. Calc. for $C_{13}H_{21}NO_3F_2$: 278.1568); *m/z* 278 (CI) ($[M+H]^+$, 100 %), 100, ($[CONEt_2]^+$, 95).

The reaction of 9 with carbonyl electrophiles: 1,1-Difluoro-3-(*N*,*N*-diethylcarbamoyloxy)pentan-2-one (20)

In a typical procedure, diisopropylamine (0.66 ml, 5.0 mmol) was dissolved in dry THF (5 ml) and the solution was cooled to -78 °C. *n*-Butyllithium (3 ml of a 1.6 M solution in hexane) was added over five minutes. The mixture was allowed to warm to -30 °C, and then recooled to -78 °C. 2,2,2-Trifluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethane **8** (0.39 ml, 2.4 mmol) was added over fifteen minutes, and the mixture stirred for a further twenty minutes. During this time the colour of the mixture changed from colourless to yellow, through orange to red. Propanal (0.19 ml, 2.64 mmol) was added in one portion, and stirring was continued for one hour at -78 °C, before the mixture was allowed to warm to room temperature, giving a yellow coloured solution. The reaction was quenched with saturated aqueous ammonium chloride (25 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvents were removed *in vacuo*. Distillation (Kugelrohr) afforded **ketone 20** (0.387 g, 68 %) as a colourless oil; b.p. 85 °C/1 mm Hg; ν_{max} ($CDCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 5.92, (1H, *t*, $^2J_{H\text{-}F}$ 51.0, *H*CF_2), 5.00 (1H, ***ddd***, ^3J H-H 7.0, ^3J H-H 4.5, ^4J H-F 1.0, C*H*CH_2CH_3), 3.32-3.10 (4H, *m*, N(C*H*$_2$$CH_3$)$_2$), 1.90-1.65 (2H, m, CHC*H*$_2$$CH_3$), 1.10 (6H, *t*, $^3J_{H\text{-}H}$ 7.0, N(CH_2C*H*$_3$)$_2$), 0.93 (3H, *t*, ^3J H-H 7.0, $CHCH_2$C*H*$_3$); δ_C(300 MHz; $CDCl_3$) 196.7 (*t*, ^2J C-F 22.7), 155.1, 109.3 (*t*, ^1J C-F 251.4), 76.0, 42.1, 41.6, 23.4 , 13.7, 13.1, 9.4; δ_F(90 MHz; $CDCl_3$) -129.4 (1F, *d*, $^2J_{H\text{-}F}$ 51.0), -129.8 (1F, *d*, $^2J_{H\text{-}F}$ 51.0); HRMS (Found: 237.1256. Calc. for $C_{10}H_{17}NF_2O_3$: 237.1255); *m/z* (CI) 238 ([M+H]$^+$, 100 %), 100 ([CONEt$_2$]$^+$, 82).

The following ketones were prepared using the general procedure described above. A slight excess of ketone (1.1 equivalents) was used in all cases. The yields quoted are for reactions on a 5 mmol scale.

1,1-Difluoro-3-(*N*,*N*-diethylcarbamoyloxy)-4-methyl pentan-2-one (21)

2-Methylpropanal was used as the electrophile. Usual work-up followed by distillation afforded the **ketone 21** (74 %) as a colourless oil; b.p. 115 °C/1 mmHg (Kugelrohr); ν_{max} ($CDCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 6.00 (1H, *t*, ^2J H-F 50.0, *H*F_2C), 5.00 (1H, *dd*, ^3J Ha-Hb 15.0, ^4J H-F 5.0, C*H*CH(CH_3)$_2$), 3.35-3.17 (4H, *m*, N(C*H*$_2$$CH_3$)$_2$), 2.30-2.17 (1H, *m*, C*H*(CH_3)$_2$), 1.15 (3H, *t*, ^3J H-H 7.0, N(CH_2C*H*$_3$)$_2$), 1.07 (3H, *t*, ^3J H-H 7.0, N(CH_2C*H*$_3$)$_2$), 1.01 (3H, *d*, ^3J H-H 7.0, CHCH(C*H*$_3$)$_2$), 0.96 (3H, *d*, ^3J H-H 7.0, CHCH(C*H*$_3$)$_2$); δ_C(300 MHz; $CDCl_3$) 197.2 (*t*, ^2J C-F 22.1), 155.2, 109.3 (*t*, ^1J C-F 252.0), 79.0, 42.2, 41.7, 29.4, 17.3, 13.9, 13.3; δ_F(90 MHz; $CDCl_3$) -129.2 (1F, *d*, ^2J F-F 50.0), -129.9 (1F, *d*, ^2J F-F 50.0); HRMS (Found: 252.1374. Calc. for $C_{11}H_{19}NO_3F_2$: 252.1374); *m/z* (CI) 252 ([M+H]$^+$, 100 %).

1,1-Difluoro-3-(*N*,*N*-diethylcarbamoyloxy)-4,4-dimethyl pentan-2-one (22)

Trimethylacetaldehyde was used as the electrophile. Usual work-up followed by flash column chromatography (R_f 0.52, 20 % EtOAc/Hexane) afforded the **ketone 22** as a colourless oil (54 %); (Found: C, 54.30; H, 7.85; N, 5.20. Calc. for $C_{12}H_{21}NO_3F_2$: C, 54.33; H, 7.98; N, 5.28%); ν_{max} ($CDCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 5.92 (1H, *t*, ^2J H-F 52.5, *H*F_2C), 4.75, (1H, *d*, ^4J H-F 1.0, C*H*C(CH_3)$_3$), 3.32-3.10 (4H, *m*, N(C*H*$_2$$CH_3$)$_2$), 1.15-1.08 (6H, *m*, N(CH_2C*H*$_3$)$_2$), 0.99 (9H, *s*, C(C*H*$_3$)$_3$); δ_C(300 MHz; $CDCl_3$) 198.4 (*t*, ^2J C-F 24.4), 155.5, 108.9 (*t*, ^1J C-F 252.5), 79.9 42.2, 41.7, 34.7, 26.7, 14.0, 13.3; δ_F (90 MHz; $CDCl_3$) -126.4 (2F, *d*, ^2J H-F 52.5); *m/z* (CI) 266 ([M+H]$^+$, 85 %), 100 ([CONEt$_2$]$^+$, 100).

1,1-Difluoro-3-(*N*,*N*-diethylcarbamoyloxy)-3-ethyl pentan-2-one (23)

Pentan-3-one was used as the electrophile. Usual work-up followed by distillation afforded the **ketone 23** (72 %) as a colourless oil; b.p. 100 °C/2.5 mmHg; (Found: C, 54.30; H, 7.85; N, 5.20. Calc. for $C_{12}H_{21}NO_3F_2$: C, 54.33; H, 7.98; N, 5.28 %); ν_{max} ($CDCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 5.90 (1H, *t*, ^2J H-F 53.0, *H*F_2C), 3.24 (2H, *q*, ^3J H-H 6.5, N(C*H*$_2$$CH_3$)$_2$), 3.20 (2H, *q*, ^3J H-H 6.5, N(C*H*$_2$$CH_3$)$_2$), 1.99-1.83 (4H, *m*, (C*H*$_2$$CH_3$)$_2$), 1.10 (3H, *t*, $^3J_{H\text{-}H}$ 6.5, N(CH_2C*H*$_3$)$_2$), 1.04 (3H, *t*, $^3J_{H\text{-}H}$ 6.5, N(CH_2C*H*$_3$)$_2$), 0.80 (6H, *t*, $^3J_{H\text{-}H}$ 7.0 (CH_2C*H*$_3$)$_2$); δ_C(300

MHz; $CDCl_3$) 195.7 (*t*, $^2J_{C-F}$ 22.1), 155.0, 108.9 (*t*, $^1J_{C-F}$ 252.0), 85.6, 42.1, 41.7, 24.4, 13.9, 13.1, 6.8; δ_F(90 MHz; $CDCl_3$) -126.6 (2F, *d*, $^2J_{H-F}$ 53.0); *m/z* (CI) 266 ($[M+H]^+$, 99 %).

1-(*N*,*N*-diethylcarbamoyloxy) -1-(2,2-difluoroacetyl)-cyclohex-2-ene (24)

Cyclohexen-2-one was used as the electrophile. Usual work-up followed by flash column chromatography (R_f 0.35, 20 % ethyl acetate/hexane) afforded the **ketone 24** (54%) as a colourless oil; (Found: C, 56.48; H, 7.07; N, 5.23. Calc. for $C_{13}H_{19}NO_3F_2$: C, 56.72; H, 6.96; N, 5.09%); ν_{max} ($CDCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 6.13-6.04 (1H, *m*, CCHC*H*), 6.02 (1H, *t*, $^2J_{H-F}$ 52.0, *H*F_2C), 5.89 (1H, *d*, $^3J_{H-H}$ 9.0, CC*H*CH), 3.34-3.13 (4H, *m*, N(C*H*$_2$CH$_3$)$_2$), 2.15-1.25 (6H, *envelope*, 3 x CH_2), 1.13-1.00 (6H, *m*, N(CH$_2$C*H*$_3$)$_2$); δ_C(300 MHz; $CDCl_3$) 195.1 (*t*, $^2J_{C-F}$ 22.4), 155.4, 135.5, 123.2, 109.0 (*t*, $^1J_{C-F}$ 251.3), 79.7, 42.2, 41.8, 30.1, 24.5, 18.0, 14.0 13.3; δ_F(90 MHz; $CDCl_3$) -126.3 (2F, *d*, $^2J_{H-F}$ 52.0); *m/z* (CI) 276 ($[M+H]^+$, 92 %), 100, ($[CONEt_2]^+$, 76).

1-(Methoxymethyl)-2-(*N*, *N*-diethylcarbamoyloxy)-2-(2',2'-difluoroacetyl)-bicyclo-[2.2.1]-hept-5-ene (25)

1-Methoxymethoxy-bicyclo[2.2.1]-hept-2-en-5-one was used as the electrophile. Usual work-up followed by flash column chromatography (R_f 0.33, 20 % EtOAc/Hexane) afforded the **ketone 25** (60%) as a white solid; m.p. 48-49 °C; (Found: C, 58.13; H, 6.86; N, 4.28. Calc. for $C_{16}H_{22}NO_3F_2$: C, 57.98; H, 7.00; N, 4.23%); ν_{max} ($CHCl_3$) 1759 (ketone C=O), 1694 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 6.46 (1H, *ddd*, $^3J_{H-H}$ 5.6, $^4J_{H-H}$ 2.9), 6.10 (1H, *dd*, $^2J_{H-F}$ 54.4, $^2J_{H-F}$ 53.1), 5.85 (1H, *d*, $^3J_{H-H}$, 5.6), 3.85 (1H, *d*, half of an AB quartet, $^3J_{H-H}$ 9.8), 3.59 (1H, *d*, half of an AB quartet, $^3J_{H-H}$ 9.8), 3.40-3.18 [*m* including (3.30 (*s*, OC*H*$_3$), 3.21 (2H, *t*, $^3J_{H-H}$ 1.7), 3.18 (2H, *t*, $^3J_{H-H}$ 1.7), 3.00-2.80 (1H, *m*), 2.00 (1H, *d*, $^3J_{H-H}$ 9.0), 1.40-1.33 (2H, *m*), 1.10 (6H, *t*, $^3J_{H-H}$ 7.0); δ_C(300 MHz; $CDCl_3$) 197.9 (*t*, $^2J_{C-F}$ 23.5), 155.5, 141.3, 134.1, 109.8 (*t*, $^1J_{C-F}$ 253.0), 90.7, 70.3, 64.6, 58.8, 47.9, 44.7, 42.2, 41.6, 41.2, 14.1, 13.4; δ_F(90 MHz; $CDCl_3$) -124.0 (1F, *dd*, half of an AB quartet, $^2J_{F-F}$ 295.0, $^2J_{H-F}$, 54.9), -130.4 (1F, *dd*, half of AB quartet, $^2J_{F-F}$ 295.0, $^2J_{H-F}$ 51.8); *m/z* 222 ($[C_9H_{13}NO_3F_2]^+$, 57 %).

1,1-Difluoro-3-(*N*,*N*-diethylcarbamoyloxy) pent-3-ene-2-one (26) and

4,4-Difluoro-6-(*N*,*N*-diethylcarbamoyloxy) -3-hydroxyoct-1,6-diene-5-one (27).

Prop-2-enal (0.19 ml, 2.64 mmol) was used as the electrophile. Extractive work-up afforded a mixture of fluorine-containing products. Flash column chromatography (20% ethyl acetate/hexane) yielded **ketone 26** (R_f 0.25) as a yellow oil (0.26 g, 47 %); ν_{max} ($CDCl_3$) 1737 (ketone C=O), 1716 (carbamate C=O) cm^{-1}; δ_H(400 MHz; $CDCl_3$) 6.66 (1H, *qt*, $^3J_{H-H}$ 7.0, $^5J_{H-F}$ 1.0, CC*H*CH$_3$), 6.04 (1H, *t*, $^2J_{H-F}$ 53.5, *H*F$_2$C), 3.36 (2H, *q*, $^3J_{H-H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$), 3.28 (2H, *q*, $^3J_{H-H}$ 7.0, N(C*H*$_2$CH$_3$)$_2$), 1.84 (3H, *d*, $^3J_{H-H}$ 7.0, CCHC*H*$_3$), 1.19 (3H, t, $^3J_{H-H}$ 7.0, N(CH$_2$C*H*$_3$)$_2$), 1.12 (3H, *t*, $^3J_{H-H}$ 7.0, N(CH$_2$C*H*$_3$)$_2$); δ_C(300 MHz; $CDCl_3$) 182.4 (*t*, $^2J_{C-F}$ 25.2), 152.7, 143.6, 132.1, 109.8 (*t*, $^1J_{C-F}$ 252.4), 42.4, 42.1, 13.9, 13.1, 11.9; δ_F(90 MHz; $CDCl_3$) -124.2 (*d*, $^2J_{F-H}$ 51.9). **Hydroxyketone 27** was also obtained as a yellow oil (R_f 0.75) (0.16 g, 23 %); ν_{max} ($CDCl_3$) 3550-3140 (O-H), 1737 (ketone C=O), 1716 (carbamate C=O) cm^{-1}; δ_H(300 MHz; $CDCl_3$) 6.80 (1H, *q*, $^3J_{H\text{-}H}$ 7.0, $CCHCH_3$), 5.87 (1H, *ddd*, $^3J_{H\text{-}H}$ 4.5, $^3J_{H\text{-}H\,(trans)}$ 17.0, $^3J_{H\text{-}H(cis)}$ 10.5, $CHCH_2$), 5.48 (1H, *ddd*, $^3J_{H\text{-}H\,(trans)}$ 17.0, $^2J_{H\text{-}H}$ 1.7, $^4J_{H\text{-}H}$ 1.5, $CHCH_2$), 5.34 (1H, *ddd*, $^3J_{H\text{-}H\,(cis)}$ 10.5, $^2J_{H\text{-}H}$ 1.7, $^4J_{H\text{-}H}$ 1.5, $CHCH_2$), 4.52 (1H, *br ddd*, $^3J_{H\ F}$ 17.0, $^3J_{H\text{-}H}$ 4.5, $^3J_{H\text{-}F}$ 6.0, $CHCHCH_2$), 4.15 (1H, *br s*, O*H*), 3.36 (2H, *q*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$) 3.26 (2H, *q*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$), 1.95 (3H, *d*, $^3J_{H\text{-}H}$ 7.0, $CCHCH_3$), 1.17 (3H, t, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$), 1.10 (3H, *t*, $^3J_{H\text{-}H}$ 7.0, $N(CH_2CH_3)_2$); δ_C(300 MHz; $CDCl_3$) 184.6 (*t*, $^2J_{C\text{-}F}$ 28.5), 153.4, 144.0, 132.2, 119.9, 116.4 (*t*, $^1J_{C\text{-}F}$ 262.5), 72.3 (*t*, $^2J_{C\text{-}F}$ 25.9), 60.3, 42.5, 42.2, 13.9, 13.1, 12.0; δ_F(90 MHz; $CDCl_3$) -108.6 (1F, *d*, half of an AB quartet, $^2J_{F\text{-}F}$ 265.5), -120.6 (1F, *dd*, half of an AB quartet, $^2J_{F\text{-}F}$ 265.5, $^3J_{H\text{-}F}$ 15.3); *m/z* ($[M+H]^+$, 95 %), ($[CONEt_2]^+$, 100).

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13. A true test of the synthetic utility of alkylation reactions of vinyl metal reagents is the alkylation with *n*-alkyl iodides, allowing functionalised chains to be attached to the vinylic moiety. For a discussion, see D. W. Knight in *Comprehensive Organic Synthesis*, Ed, B.M. Trost, Pergamon Press, Oxford, 1991, Vol.3, Chapter 2.3.
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