Addition of organolithium reagents to α-(trifluoromethyl)styrene: concise synthesis of functionalised *gem*-difluoroalkenes

Jean-Pierre Bégué, Danièle Bonnet-Delpon * and Michael H. Rock

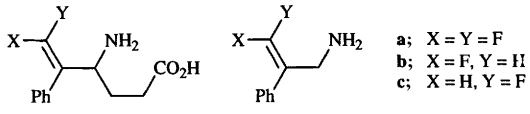
BioCIS-CNRS, Centre d'Etudes Pharmaceutiques, Rue J. B. Clément, F-92296 Châtenay-Malabry, France

The treatment of α-(trifluoromethyl)styrene with organolithium reagents results in the selective formation of *gem*-difluoroalkenes in good-to-excellent yields. This reaction has been applied to the synthesis of 3-*gem*-difluoro-2-phenylallylic amines and other functionalised *gem*-difluoroalkenes.

Introduction

There is considerable interest in the synthesis of compounds containing one or two fluorines at key sites in a molecule.[1] In particular much attention has been focused on the synthesis of molecules containing the difluoromethylene (CF_2) group since it is isopolar and isosteric with an ether oxygen.[2] The CF_2 group can be prepared by the fluorination of a suitable functional group, for example the DAST (diethylaminosulfur trifluoride) fluorination of ketones.[3]

An alternative approach for synthesis of compounds containing the difluoromethylene group is through the elaboration of an appropriate fluorinated building synthon. *gem*-Difluoroalkenes have been demonstrated to be versatile building blocks for the synthesis of compounds containing the CF_2 moiety. They have been shown to undergo Diels–Alder reactions,[4] 1,3-dipolar cycloadditions,[5] and radical additions.[6] *gem*-Difluoroallylic alcohols have been utilised for the formation of the CF_2 group through 3,3-sigmatropic rearrangements[7] and 2,3-Wittig rearrangements.[8]



1 **2**

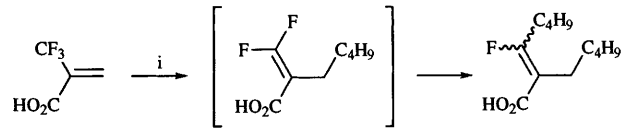
a; X = Y = F
b; X = F, Y = H
c; X = H, Y = F

In addition to this synthetic versatility, *gem*-difluoroalkenes and in particular difluoroallylic amines can exhibit biological activity.[9] For example 6,6-difluoro-4-amino-5-phenylhex-5-enoic acid **1a** is an irreversible inhibitor of γ-aminobutyric acid (GABA)-transaminase in the mammalian brain,[9b] and the 2-phenylallylamine **2a** and related monofluoro compounds **2b** and **c** exhibit irreversible inhibition of monoamine oxidases.[9c]

Results and discussion

A variety of different synthetic strategies has been reported for the synthesis of *gem*-difluoroalkenes. The direct conversion of aldehydes or ketones by the Wittig reaction with a difluoromethylenephosphorane[10] or by the Wadsworth–Emmons reaction with a difluorophosphonate anion.[11] Other successful approaches have included the trapping of stabilised difluorovinyl anions derived from 1,1,1-trifluoroethanol,[12] the Reformatsky reaction of 4-chloro-4,4-difluorocrotonate,[13] and treatment of chlorodifluoromethylepoxy ethers[14] or epoxides with butyllithium.[15]

A little utilised approach involves the reaction of organolithium reagents with trifluoromethyl alkenes which can result in the formation of difluoroalkenes through a formal addition of the organolithium reagent followed by the elimination of lithium fluoride. This strategy has only been applied successfully to the reaction of 1,1,1-trifluoropropene with such reagents as butyllithium,[16] dimethyl(phenyl)silyllithium[17] and more interestingly with lithium ester enolates.[18] The reaction can be limited by multiple additions of the organolithium reagent, due to the fact that the formed difluoroalkenes are themselves reactive towards organolithium reagents.[19a] For example, treatment of 2-(trifluoromethyl)-acrylic acid **3** with one mole equivalent of butyllithium does not result in the desired 3,3-difluoro-2-pentylacrylate **4** but in the formation of the monofluoroalkenes **5** where a fluorine atom has been displaced by a butyl group through an addition/elimination process[19b] (Scheme 1). This result indicates that the

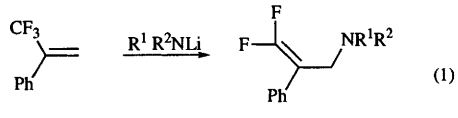


3 **4** **5** 23%

Scheme 1 *Reagent:* i, BuLi

reactivity of the initial product **4** is greater than that of the starting alkene **3** towards the organolithium reagent.

Nevertheless we envisaged that the reaction of N-lithiated amines with α-(trifluoromethyl)styrene **6** would give a concise synthesis of 3-*gem*-difluoro-2-phenylallylic amines **7** [eqn. (1)].[20] The addition of lithium diisopropylamide (LDA) to α-



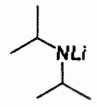
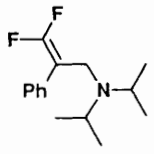
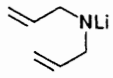
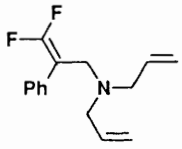
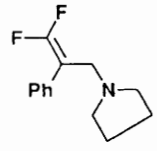
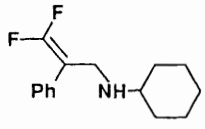
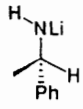
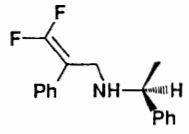
6 **7** (1)

(trifluoromethyl)styrene **6** in tetrahydrofuran (THF) at −78 °C and subsequent warming to −20 °C resulted in exclusive formation of the corresponding 3-*gem*-difluoro-2-phenylallylic amine **7a** (Table 1).

The absence of monofluorinated compounds prompted us to try the more practical addition of compound **6** to the preformed LDA at −78 °C, and even under these conditions no monofluorinated alkenes were detected. We then investigated this reaction with a range of N-lithiated species derived from primary and secondary amines (Table 1). Yields were excellent for N-lithiated secondary amines: sterically demanding, functionalised, cyclic and aromatic amines were introduced. Primary amines were also successfully introduced but in a lower yield.

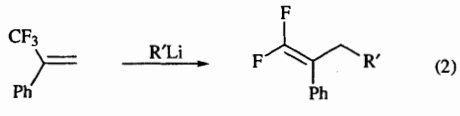
The high selectivity obtained with the N-lithiated species prompted us to extend this study to other organolithium

Table 1 Addition of N-lithiated amines to α-(trifluoromethyl)styrene **6**

Entry	R^1R^2NLi	Products **7a–e**	Yield (%)
a			90
b			85
c			90
d			66
e			60

reagents.[21] We performed our initial investigations with simple commercial organolithium reagents. The addition of compound **6** to a solution of butyllithium (1.2 mol equiv.) in THF at −78 °C, followed by warming to −20 °C, resulted in the formation of a mixture of the desired *gem*-difluoroalkene and monofluoroalkenes. To prevent the occurrence of this process, the order of addition was reversed and the number of mole equivalents reduced to exactly one. In all cases the reaction of α-(trifluoromethyl)styrene **6** with the organolithium reagents (butyl-, *tert*-butyl-, methyl-, phenyl-lithium) gave only the desired difluoroalkenes in excellent yield (Table 2, entries 1–4), indicating that compound **6** is more reactive than the difluoroalkene product.

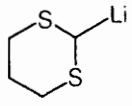
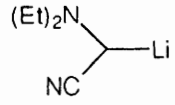
We then investigated the reactivity of functionalised organolithium reagents as a route to functionalised *gem*-difluoroalkenes. For these reagents, products arising from the reaction of the desired *gem*-difluoroalkene with a second molecule of the organolithium reagent were not detected even when compound **6** was added to a preformed solution of the organolithium reagent. The order of addition chosen was thus the more practical addition of compound **6** to the preformed organolithium at −78 °C. The reaction was successful with organolithium reagents containing phosphonate, sulfone, or sulfoxide functions and the desired *gem*-difluoroalkenes were isolated in excellent yields [Table 2, eqn. (2)]. A masked



6 **8–16** (2)

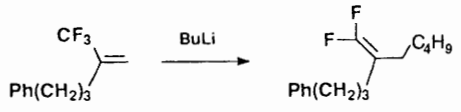
aldehyde in the form of a 1,3-dithiane and the more readily deprotected diethylaminoacetonitrile was also introduced in high yield. However, unlike 1,1,1-trifluoropropene,[18] α-(trifluoromethyl)styrene **6** did not react with lithium ester enolates even after prolonged reaction times.

Table 2 Addition of organolithium reagents to α-(trifluoromethyl)-styrene **6**

Entry	R′–Li	Solvent	% Yield	(Compound)
1	MeLi	THF	90[a]	(**8**)
2	BuLi	THF	93[a]	(**9**)
3	Bu′Li	THF	92[a]	(**10**)
4	PhLi	Et_2O	90[a]	(**11**)
5	$(EtO)_2P(O)CH_2Li$	Et_2O	85[b]	(**12**)
6	$PhS(O)CH_2Li$	THF	83[b]	(**13**)
7	$PhS(O_2)CH_2Li$	THF	80[b]	(**14**)
8		THF	90[b]	(**15**)
9		Et_2O	86[b]	(**16**)

[a] Organolithium reagent added to a solution of **6**. [b] Compound **6** added to a solution of preformed organolithium reagent.

The generality of this reaction was investigated by studying the reactivity of a variety of organolithium reagents towards the α-alkyl-α-(trifluoromethyl)alkene **17** which is readily accessible by Wittig olefination of the corresponding ketone. The reaction of compound **17** with a reactive organolithium reagent such as butyllithium to give the corresponding difluoroalkene **18** was successful (Scheme 2) but when the reaction was extended to the less reactive phenyllithium or LDA no reaction was observed.



17 **18** (87%)

Scheme 2

Although the products are formally derived from an addition of the organolithium reagent followed by an elimination of lithium fluoride, the results obtained do not allow the elucidation of the exact mechanism. It is clear that one of the driving forces for this reaction is the presence of a good leaving group in the form of fluoride anion. However, the loss of lithium fluoride can be envisaged to occur through a concerted or a two-step process. The greater reactivity of α-(trifluoromethyl)styrene **6** compared with that of α-alkyl-α-(trifluoromethyl)-alkene **17** indicates that the stabilisation of an incipient carbanion is also a driving force for this process. This latter effect of stabilisation by the phenyl group seems to be more important than the electrophilicity of the double bond since the phenyl group is expected to oppose the electron-withdrawing effect of the CF_3 group in the starting material.

In summary, we have demonstrated that the addition of organolithium reagents to α-substituted (trifluoromethyl)-alkenes is a viable route to *gem*-difluoroalkenes and we have applied this synthetic strategy for the synthesis of a series of functionalised 1-*gem*-difluoro-2-phenylalkenes and 3-*gem*-difluoro-2-phenylallylic amines from α-(trifluoromethyl)styrene **6**.

Experimental

^{19}F NMR chemical shifts (δ_F) are reported in ppm, negative upfield relative to internal $CFCl_3$, ^1H NMR and ^{13}C NMR chemical shifts (δ, 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. IR spectra (ν/cm^{-1}; neat) were recorded on a Perkin-Elmer 841 spectrophotometer. Elemental analyses were performed by the Service de Microanalyses of the Faculté de Pharmacie, Châtenay-Malabry. All the 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). α-(Trifluoromethyl)styrene **6** was prepared according to the literature procedure[22] and α-trifluoromethyl-α-alkylalkene **17** was prepared by Wittig olefination[23] of 1,1,1-trifluoro-5-phenylpentan-2-one.[24]

General procedure for the synthesis of 3-*gem*-difluoro-2-phenylallylic amines

α-(Trifluoromethyl)styrene **6**[22] (0.52 g, 3 mmol) was added at −78 °C over a period of 2 min to N-lithiated amine prepared from butyllithium (1.36 cm^3 of a 2.5 mol dm^{-3} solution in hexanes) and the appropriate amine (0.56 cm^3, 3.5 mmol) in THF (20 cm^3). The pale yellow solution was stirred for 1 h and then was allowed to warm to 0 °C over a period of 1 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 and evaporated to afford a brown oil, which was purified by passage through a short column of silica gel (eluent pentane–diethyl ether 9:1) to give the desired product as a clear oil.

3,3-Difluoro-2-phenylprop-2-enyl(diisopropyl)amine 7a. From α-(trifluoromethyl)styrene **6** (0.52 g, 3 mmol) and LDA (3.5 mmol), after purification compound **7a** was obtained as an oil (0.68 g, 90%), ν_{max}(neat)/cm^{-1} 1731 (C=C); δ_F −88.95 (d, *J* 42.4) and −92.5 (d, *J* 42.4); δ 0.95 (12 H, d, *J* 6.6), 3.05 (2 H, sept, *J* 6.6) 3.45 (2 H, dd, *J* 2.8 and 2.85) and 7.35 (5 H, m); δ_C 15.9, 38.0, 42.2, 87.5 (dd, $^2J_{CF}$ 10.9 and 17.5) 122.6, 123.3, 124.2, 124.5, 129.15 and 150.3 (dd, $^1J_{CF}$ 288 and 290) (Found: C, 70.9; H, 8.0; N, 5.2. $C_{15}H_{21}F_2N$ requires C, 71.15; H, 8.3; N, 5.5%).

3,3-Difluoro-2-phenylprop-2-enyl(diprop-2-enyl)amine 7b. From (1,1,1,-trifluoromethyl)styrene **6** (0.52 g, 3 mmol) and N-lithiated diallylamine (0.34 g, 3.5 mmol), after purification compound **7b** was obtained as an oil (0.64 g, 85%), ν_{max}(neat)/cm^{-1} 1850 (C=CH$_2$) and 1731 (C=CF$_2$); δ_F −88.7 (d, *J* 38) and −89.8 (d, *J* 38); δ 3.1 (4 H, dt, *J* 6.4 and 1.2, 1′- and 1″-H$_2$), 3.4 (2 H, dd, $^4J_{HFa}$ 1.7, J_{HFb} 3.0, 1-H$_2$), 5.1 (2 H, ddt *J* 10.4, 1.7 and 1.2, 3′- and 3″-H), 5.13 (2 H, ddt, *J* 16.9, 1.7 and 1.7, 3′- and 3″-H), 5.7 (2 H, tdd, *J* 6.4, 16.9 and 10.4, 2′ and 2″-H) and 7.1–7.5 (5 H, m); δ_C 50.4 (d, $^3J_{CF}$ 4, C-1), 56.4, 90.75 (dd, $^2J_{CF}$ 12 and 18), 117.4, 127.2, 128.1, 128.5, 133.4 (dd, $^3J_{CF}$ 3.1 and 3.5) and 135.6 and 154.8 (dd $^1J_{CF}$ 1, 293) (Found: C, 72.3; H, 6.9; N, 5.85. $C_{15}H_{17}F_2N$ requires C, 72.3; H, 6.8; N, 5.6%).

***N*-(3,3-Difluoro-2-phenylprop-2-enyl)pyrrolidine 7c.** From (1,1,1-trifluoromethyl)styrene **6** (0.52 g, 3 mmol), and N-lithiated pyrrolidine (0.25 g, 3.5 mmol), after purification compound **7c** was obtained as an oil (0.6 g, 90%), ν_{max}(neat)/cm^{-1} 1732 (C=C); δ_F −89.3 [br d ($w_{\frac{1}{2}}$ 3 Hz), *J* 36.4] and −89.8 [br d ($w_{\frac{1}{2}}$ 2 Hz), *J* 36.4]; δ 1.83 (4 H, m), 2.60 (4 H, m), 3.52 (2 H, dd, *J* 3.2 and 2.0) and 7.4 (5 H, m); δ_C 23.5 and 52.8 (d, $^3J_{CF}$ 3.6), 53.6 and 91.3 (dd, $^2J_{CF}$ 18, 12), 127.1, 128.2, 128.3 and 133.9 (t, $^4J_{CF}$ 3), 154.9 (dd, $^1J_{CF}$ 289 and 292) (Found: C, 69.9; H, 6.8; N, 6.4. $C_{13}H_{15}F_2N$ requires C, 69.9; H, 6.8; N, 6.3%).

Cyclohexyl-(3,3-difluoro-2-phenylprop-2-enyl)amine 7d. From (1,1,1-trifluoromethyl)styrene **6** (0.52 g, 3 mmol) and N-lithiated cyclohexylamine (0.34 g, 3.5 mmol), after purification compound **7d** was obtained as an oil (0.49 g, 66%), ν_{max}(neat)/cm^{-1} 3510 (NH) and 1728 (C=C); δ_F −90.2 [br d ($w_{\frac{1}{2}}$ 4.5 Hz), *J* 40] and −90.7 (dt, *J* 2.2 and 40); δ 1.1–1.5 (6 H, m), 1.55–1.95 (5 H, m), 2.5 (1 H, m), 3.5 (2 H, t, *J* 2.2) and 7.1–7.4 (5 H, m); δ_C 25.3, 26.1, 33.2, 43.2 (d, $^3J_{CF}$ 1.5), 55.3, 91.75 (dd, $^2J_{C-F}$ 11.2 and 20.5), 127.9, 128.1, 128.3 and 132.6 (t, $^4J_{C-F}$ 2.8) and 154.4 (dd, $^1J_{C-F}$ 288 and 293).

3,3-Difluoro-2-phenylprop-2-enyl[(*S*)-1-phenylethyl]amine 7e. From (1,1,1-trifluoromethyl)styrene **6** (0.52 g, 3 mmol) and N-lithiated (*S*)-(−)-α-methylbenzylamine (0.6 g, 3.5 mmol), after purification compound **7e** was obtained as an oil (0.49 g, 60%), ν_{max}(neat)/cm^{-1} 3500 (NH) and 1735 (C=C); δ_F −89.6br s; δ 1.2 (3 H, d, *J* 6.7), 1.6 (1 H, br s), 3.5 (2 H, t, *J* 2.9), 3.7 (1 H, q, *J* 6.7) and 7.1–7.4 (5 H, m); δ_C 24.0, 44.2, 57.0, 91.5 (dd, $^2J_{C-F}$ 14.0 and 18), 125.9–128.5 (aromatic) and 132.5, 145.0 and 154.2 (t, $^1J_{C-F}$ 290.1) (Found: C, 69.9; H, 6.8; N, 6.3. $C_{13}H_{15}F_2N$ requires C, 69.9; H, 6.8; N, 6.3%).

General procedure for commercial organolithium reagents

The organolithium reagent (4 mmol) was added at −78 °C over a period of 2 min to a solution of α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) in THF (20 cm^3). The pale yellow solution was stirred for 30 min and then allowed to warm to room temperature during 1 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 and evaporated to afford a brown oil, which was purified by passage through a short column of silica gel (eluent pentane) to give the desired product as a clear oil.

1,1-Difluoro-2-phenylbut-1-ene 8. From α-(trifluoromethyl)-styrene **6** (0.7 g, 4 mmol) and methyllithium (2.5 cm^3 of a 1.6 mol dm^{-3} solution in diethyl ether, 4 mmol), after purification compound **8** was obtained as an oil (0.61 g, 90%); ν_{max}(neat)/cm^{-1} 1737 (C=C); δ_F −91.9 (s); δ 1.0 (3 H, t, *J* 7.5), 2.4–2.5 (2 H, m) and 7.1–7.4 (5 H, m); δ_C 12.9, 21.4, 94.0 (dd, $^2J_{CF}$ 15 and 18), 127.4, 128.4, 128.7, 133.8 (d, $^3J_{CF}$ 1.9) and 153.5 (t, $^1J_{CF}$ 288) (Found: C, 71.2; H, 6.25. $C_{10}H_{10}F_2$ requires C, 71.4; H, 6.0%).

1,1-Difluoro-2-phenylhept-1-ene 9. From α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) and butyllithium (1.65 cm^3 of a 2.4 mol dm^{-3} solution in hexanes, 4 mmol), after purification compound **9** was obtained as an oil (0.78 g, 93%); ν_{max}(neat)/cm^{-1} 1737 (C=C); δ_F −91.7 (s); δ 0.8 (3 H, t, *J* 6.8), 1.2–1.5 (6 H, m), 2.3–2.5 (2 H, m) and 7.35–7.42 (5 H, m); δ_C 14.4, 22.9, 28.0, 28.2, 31.8, 93.1 (dd, $^2J_{CF}$ 15.0 and 19), 127.7, 128.8, 128.85, 128.9, 134.6 and 149.3 (t, $^1J_{CF}$ 287.8) (Found: C, 74.45; H, 6.3. $C_{13}H_{16}F_2$ requires C, 74.3; H, 6.2%).

1,1-Difluoro-4,4-dimethyl-2-phenylpent-1-ene 10. From α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) and butyllithium (2.5 cm^3 of a 1.6 mol dm^{-3} solution in pentane, 4 mmol), after purification compound **10** was obtained as an oil (0.77 g, 92%); ν_{max}(neat)/cm^{-1} 1740 (C=C); δ_F −89.55 (d, J_{FF} 41.2) and −92.05 (d, J_{FF} 41.2); δ 0.85 (9 H, s), 2.4 (2 H, dd, $^4J_{HF}$ 2.1 and 2.0) and 7.2–7.3 (5 H, m); δ_C 29.9, 32.8 (t, $^3J_{CF}$ 2.5), 41.4, 91.3 (dd, $^2J_{CF}$ 13.0, 21.4), 126.7, 128.4, 128.7, 128.75 and 135.7 (dd, $^3J_{CF}$ 4.6 and 2.7) and 154.7 (dd, $^1J_{CF}$ 290 and 287.0) (Found: C, 74.1; H, 6.35. $C_{13}H_{16}F_2$ requires C, 74.3; H, 6.2%).

1,1-Difluoro-2,3-diphenylprop-1-ene 11. From α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) and phenyllithium (2.0 cm^3 of a 2 mol dm^{-3} solution in cyclohexane–diethyl ether, 4 mmol), after purification compound **11** was obtained as an oil (0.83 g, 90%), ν_{max}(neat)/cm^{-1} 1739 (C=C); δ_F −90.5 (d, J_{FF} 40.0) and −92.9 (d, J_{FF} 40.0); δ 4.1 (2 H, t, $^4J_{HF}$) and 7.4–7.8 (m, 10 H); δ_C 34.3, 92.2 (dd, $^2J_{CF}$ 13.9 and 21.0), 126.5–129.5 (aromatic), 134.0 (t, $^3J_{CF}$ 3.5), 138.8 and 154.54 (dd, $^1J_{CF}$ 291 and 287) (Found: C, 78.4; H, 5.1. $C_{15}H_{12}F_2$ requires C, 78.25; H, 5.2%).

Diethyl 4,4-difluoro-3-phenylbut-1-enephosphonate 12. A solution of diethyl methanephosphonate (0.45 g, 3 mmol) in

THF (5 cm^3) was added at −78 °C over a period of 2 min to LDA prepared from butyllithium (1.36 cm^3 of a 2.5 mol dm^{-3} solution in hexanes) and diisopropylamine (0.65 cm^3, 4 mmol) in THF (20 cm^3). The mixture was stirred for a further 45 min at −78 °C, then α-(trifluoromethyl)styrene **6** (0.52 g, 3 mmol) was added and the mixture was allowed to warm to room temperature over a period of 1 h. The 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 and evaporated to afford an oil, which was purified by passage through a short column of silica gel (eluent pentane–diethyl ether 9:1) to give compound **12** as a clear oil (0.64 g, 85%), ν_{max}(neat)/cm^{-1} 1731 (C=C) and 1050 (C–O–P); δ_F −89.5 (d, J_{FF} 40) and −90.0 (d, J_{FF} 40); δ 1.32 (6 H, t, J 7.1), 2.4–2.6 (2 H, m), 2.8–3 (2 H, m), 3.9 (q, J 7.1), 3.95 (q, J 7.1) and 7.0–7.2 (5 H, m); δ_C 16.3 (d, $^3J_{CP}$ 6), 26.9, 31.6 (d, $^1J_{C-P}$ 142), 61.8 (d, $^2J_{CP}$ 7), 90.3 (ddd, $^2J_{CF}$ 16 and 11, $^3J_{C-P}$ 19), 127.5, 128.32, 128.38, 132.22 and 154.0 (t, $^1J_{CF}$ 290.3); δ_P 29.0 (br s) (Found: C, 67.0; H, 7.5. $C_{14}H_{19}F_2O_2P$ requires C, 67.2; H, 7.6%).

4,4-Difluoro-3-phenylbut-3-enyl phenyl sulfone 13. To a stirred solution of methyl phenyl sulfone (0.62 g, 4 mmol) in diethyl ether (20 cm^3) at 0 °C was added butyllithium (1.8 cm^3 of a 2.5 mol dm^{-3} solution in hexanes). Once the addition was complete the solution was allowed to warm to 20 °C and was stirred for a further 60 min before being cooled to −78 °C. Then α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min, then was allowed to warm to 0 °C (during 1 h). The yellow 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 and evaporated to afford a yellow oil, which was purified by passage through a short column of silica gel (eluent pentane) to give compound **13** as an oil (0.98 g, 80%), ν_{max}(neat)/cm^{-1} 1730 (C=C); δ_F −88.4 (d, J_{FF} 37.0) and −88.7 (d, J_{FF} 37.0); δ 2.5–2.9 (4 H, m), 6.7 (4 H, m) and 7.3–7.8 (6 H, m); δ_C 26.7, 58.4, 88.75 (dd, $^2J_{CF}$ 17.5 and 17.0), 126.1–133.9 (aromatic), 137.5, 140.6 and 153.7 (dd, $^1J_{CF}$ 289.25 and 291.0) (Found: C, 62.65; H, 4.8. $C_{16}H_{14}F_2O_2S$ requires C, 62.3; H, 4.5%).

4,4-Difluoro-3-phenylbut-3-enyl phenyl sulfoxide 14. To a stirred solution of methyl phenyl sulfoxide (0.28 g, 2 mmol) in diethyl ether (20 cm^3) at 0 °C was added butyllithium (0.9 cm^3 of a 2.5 mol dm^{-3} solution in hexanes). Once the addition was complete the solution was allowed to warm to 20 °C and was stirred for a further 60 min before being cooled to −78 °C. Then α-(trifluoromethyl)styrene **6** (0.35 g, 2 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min, then was allowed to warm to 0 °C over a period of 1 h. The yellow 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 and evaporated to afford a yellow oil, which was purified by passage through a short column of silica gel (eluent pentane) to give compound **14** as a mixture of 2 diastereoisomers (0.49 g, 83%), ν_{max}(neat)/cm^{-1} 1740 (C=C); δ_F −88.9 (d, J_{FF} 38) and −89.5 (d, J_{FF} 39) and −89.1 (d, J_{FF} 38) and −89.3 (d, J_{FF} 38); δ 2.4–2.9 (4 H, m) and 7.1–7.6 (10 H, m); δ_C 20.4/22.4, 53.0/54.2, 53.0/54.2, 90.15 (dd, $^2J_{CF}$ 16.0 and 20.0), 124.0–132.2 (aromatic), 143.4 and 153.7 (dd, $^1J_{CF}$ 292 and 290.0) (Found: C, 65.45; H, 5.1. $C_{16}H_{14}F_2OS$ requires C, 65.7; H, 4.8%).

2-(4,4-Difluoro-3-phenylbut-3-enyl)-1,3-dithiane 15. To a stirred solution of 1,3-dithiane (0.48 g, 4 mmol) in diethyl ether (20 cm^3) at 0 °C was added butyllithium (1.8 cm^3 of a 2.5 mol dm^{-3} solution in hexanes). Once the addition was complete the solution was allowed to warm to 20 °C and was stirred for a further 60 min before being cooled to −78 °C. Then α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min, then was allowed to warm to 0 °C over a period of 1 h. The yellow 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 and evaporated to afford a yellow oil, which was purified by passage through a short column of silica gel (eluent pentane) to give compound **15** as a pale yellow oil (0.98 g, 90%), ν_{max}(neat)/cm^{-1} 1737 (C=C); δ_F −89.1 (d, J_{FF} 38.0) and −89.8 (d, J_{FF} 38.0); δ 1.6–1.9 (2 H, m), 2.4–2.7 (4 H, m), 2.8 (2 H, br d, J 7.6), 3.75 (1 H, t, J 7.6) and 7.2–7.4 (5 H, m); δ_C 26.7, 29.6, 33.9 (d, $^3J_{CF}$ 2), 44.6 (t, $^4J_{CF}$ 3.3, CH), 89.6 (dd, $^2J_{CF}$ 16.0 and 21) 128.0, 128.6, 128.7, 132.6 (t, $^3J_{CF}$ 3.5) and 154.5 (dd, $^1J_{CF}$ 288.0 and 291.0) (Found: C, 57.4; H, 5.0. $C_{13}H_{14}F_2S_2$ requires C, 57.35; H, 5.1%).

2-Diethylamino-5,5-difluoro-4-phenylpent-4-enenitrile 16. Diethylaminoacetonitrile (0.45 g, 4 mmol) was added at −78 °C over a period of 2 min to LDA prepared from butyllithium (1.8 cm^3 of a 2.5 mol dm^{-3} solution in hexanes) and diisopropylamine (0.73 cm^3, 4.5 mmol) in diethyl ether (20 cm^3). To this was added *N,N,N′,N′*-tetramethylethylenediamine (0.67 cm^3, 45 mmol) and after a further 10 min at −78 °C the mixture was treated with α-(trifluoromethyl)styrene **6** (0.7 g, 4 mmol). The reaction mixture was maintained at −78 °C for 30 min and then was allowed to warm to 0 °C over a period of 1 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 and evaporated to afford a brown oil, which was purified by short-path distillation to give compound **16** as a clear oil (0.9 g, 86%), bp 60 °C at 0.5 mmHg; ν_{max}(neat)/cm^{-1} 1730 (C=C); δ_F −89.6 [br d ($w_{\frac{1}{2}}$ 2 Hz.), J_{FF} 37.5] and −90.0 (td, J_{FF} 37.5, J_{HF} 2.3); δ 0.95 (6 H, t, J 7.1), 2.32 (2 H, dq, J 13 and 6.9), 2.6 (2 H, dq, J 13 and 6.9), 2.8 (2 H, td, J 7.9 and 2.3), 3.5 (1 H, t, J 7.9) and 7.15–7.3 (5 H, m); δ_C 12.95, 30.7, 45.1, 52.1 (t, $^3J_{CF}$ 2.3), 88.7 (dd, $^2J_{CF}$ 17 and 19), 117.5, 128.4, 128.6, 131.9 and 154.5 (dd, $^1J_{CF}$ 289 and 291) (Found: C, 68.5; H, 6.95; N, 11.0. $C_{15}H_{18}F_2N_2$ requires C, 68.2; H, 6.8; N, 10.6%).

1,1-Difluoro-2-(3-phenylpropyl)hept-1-ene 18. From 5-phenyl-2-trifluoromethylpent-1-ene **17** (0.42 g, 2 mmol) and butyllithium (0.825 cm^3 of a 2.4 mol dm^{-3} solution in hexanes, 2 mmol), after purification compound **18** was obtained as an oil (0.41 g, 87%), ν_{max}(neat)/cm $^{-1}$ 1740 (C=C); δ_F −96.8 (s); δ 0.9 (3 H, t, J 7.1), 1.25–1.4 (6 H, m), 1.7–1.75 (2 H, m), 1.95–2.05 (4 H, m), 2.6–2.65 (2 H, m) and 7.35–7.42 (5 H, m); δ_C 14.0, 22.5, 25.7, 26.0, 27.2 (t, $^3J_{CF}$ 2.5), 29.0 (t, $^3J_{CF}$ 2.5), 31.5, 35.2, 88.6 (t, $^2J_{CF}$ 16.7), 126.1, 126.6, 128.85, 129.6, 134.3 and 153.6 (t, $^1J_{CF}$ 283.3).

Acknowledgements

This work was supported by CNRS and European Community Network on Synthesis and Molecular Recognition of Selectively Fluorinated Bioactive Molecules (ERBCHRXCT-930279).

References

1 R. Filler and Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Kodansha and Elsevier Biomedical, Tokyo, 1982.
2 K. E. Stremler and C. D. Poulter, *J. Am. Chem. Soc.*, 1987, **109**, 5542.
3 J. A. Wilkinson, *Chem. Rev.*, 1992, **92**, 505.
4 J. M. Percy and M. H. Rock, *Tetrahedron Lett.*, 1992, **33**, 6177.
5 S. T. Purrington and K. W. Sheu, *Tetrahedron Lett.*, 1992, **33**, 3289.
6 M. Suda, *Tetrahedron Lett.*, 1981, **22**, 2395.
7 B. M. Metcalf, E. T. Jarvi and J. P. Burkhart, *Tetrahedron Lett.*, 1985, **26**, 2861; T. Taguchi, T. Morikawa, O. Kitagawa, T. Mishima and Y. Kobayashi, *Chem. Pharm. Bull.*, 1985, **33**, 5137; H. Greuter, R. W. Lang and A. J. Romann, *Tetrahedron Lett.*, 1988, **29**, 3291.
8 S. T. Patel and J. M. Percy, *J. Chem. Soc., Chem. Commun.*, 1992, 1477.
9 (*a*) P. Bey, J. R. McCarthy and I. A. McDonald, *A. C. S. Symposium Series 456*, 1991, pp. 105–133 and references cited therein; (*b*) G. A. Lyles, C. M. S. Marshall, I. A. McDonald, P. Bey and M. G.

Palfreyman, *Biochem. Pharmacol.*, 1987, **36**, 2847; (*c*) M. Kolb, J. Barth, J. G. Heydt and M. J. Jung, *J. Med. Chem.*, 1987, **30**, 267.
10 D. J. Burton and D. G. Naae, *J. Fluorine Chem.*, 1971, **1**, 123.
11 M. Obayashi, E. Ito, K. Mutsui and M. Konodo, *Tetrahedron Lett.*, 1982, **23**, 2323.
12 J. M. Percy, *Tetrahedron Lett.*, 1990, **31**, 3931; A. J. Bennett, J. M. Percy and M. H. Rock, *Synlett*, 1992, 483; S. T. Patel, J. M. Percy and R. D. Wilkes, *Tetrahedron*, 1995, **51**, 9201; J. A. Howarth, W. M. Owton, J. M. Percy and M. H. Rock, *Tetrahedron*, 1995, **51**, 10 289.
13 T. Tsukamoto and T. Kitazume, *Synlett*, 1992, 977.
14 J. P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Tetrahedron Lett.*, 1994, **35**, 6097.
15 J. P. Bégué, D. Bonnet-Delpon, J. M. Percy, M. H. Rock and R. D. Wilkes, *J. Chem. Soc., Chem. Commun.*, 1995, 1854.
16 R. Fontanelli and D. Sianesi, *Ann. Chim. (Rome)*, 1965, **55**, 862.
17 T. Hiyama, M. Obayashi and M. Sawahata, *Tetrahedron Lett.*, 1983, **24**, 4113.
18 D. A. Kendrick and M. Kolb, *J. Fluorine Chem.*, 1989, **45**, 265.
19 (*a*) T. Ishikawa, T. Nakai and S. Hayashi, *Chem. Lett.*, 1980, 935; (*b*) T. Fuchikami, Y. Shibata and Y. Suzuki, *Tetrahedron Lett.*, 1986, **27**, 3173.
20 A preliminary publication has appeared: J. P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Synlett*, 1995, 659.
21 A preliminary publication has appeared: J. P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Tetrahedron Lett.*, 1995, **36**, 5003.
22 P. Tarrant and R. E. Taylor, *J. Org. Chem.*, 1959, **24**, 238.
23 F. Camps, F. J. Sanchez and A. Messeguer, *Synthesis*, 1988, 823.
24 J. P. Bégué, D. Bonnet-Delpon, D. Mesureur, G. Née and S. W. Wu, *J. Org. Chem.*, 1992, **57**, 3807.

Paper 5/07759A
Received 28*th November* 1995
Accepted 12*th February* 1996