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Reactivity of 1-bromo-1,1-difluoro-2-alkenes: synthesis of 1,1-difluoroolefins

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Abstract

The treatment of 1-bromo-1,1-difluoro-2-alkenes with organometallic reagents in the presence of copper and lithium salts leads to 1,1-difluoroolefins.

Keywords: 1-Bromo-1,1-difluoro-2-alkenes; Organometallic reagents; Allylic rearrangement; 1,1-Difluoroolefins

1. Introduction

Fluorinated organic molecules attract much attention due to their unique biological properties. The replacement of hydrogen by fluorine atoms in biological molecules causes a relatively small steric perturbation but leads to major changes in hydrophobicity and polarity factors [1–3]. The 1,1-difluorovinylic group is critical for certain mechanism-based enzyme inhibitors [4–7], and can function as a bioisostere for aldehydes and ketones [8].

Some methods for the preparation of 1,1-difluoro-1-alkenes have been described. The most versatile method allowing incorporation of the terminal difluorocarbon is the Wittig olefin synthesis [9–16]. Electrophilic mono or difluorination from mono or non fluorinated precursors offers alternative methods to 1,1-difluoroolefins [17,18]. Other methods require incorporation of two terminal difluoroolefin carbons onto a precursor. These include the addition of stabilized difluorovinyl anions to electrophiles [19–25] or to aryl and alkenyl iodides by palladium catalysis [26–32], and the addition of ethyl-4-chloro-4,4-difluorocrotonate to aldehydes via the Reformatsky reaction [33].

Although some synthetic methods are hitherto recorded, we wish to add a new procedure widely applicable to prepare compounds having a difluoromethylene group from ketones and aldehydes.

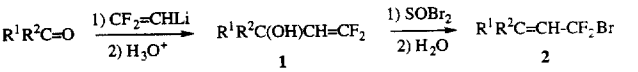
2. Results and discussion

In a previous paper, we have described the synthesis of 1-bromo-1,1-difluoro-2-alkenes **2** through the reaction of thionyl bromide with 1,1-difluoro-1-alken-3-ols **1** [34,35] (readily obtained by addition of difluorovinyllithium to carbonyl compounds [9vi]) (Scheme 1).

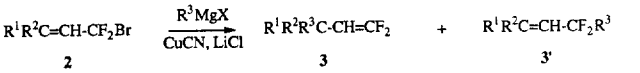
We now show that these brominated compounds **2** react with Grignard reagents in the presence of copper and lithium salts to give in most cases the corresponding alkenes **3**, 1,1-difluorinated and trisubstituted in an allylic position (Scheme 2). The reaction proceeds in THF in 30 min at the temperature indicated in the table.

The results of this reaction are summarized in Table 1 and from the latter, the following comments may be made.

With regard to the substrate **2**, the nature of substituents R^1 and R^2 have no or a very light influence on the rate of reaction and on the ratio of S_N2' and S_N2 substitution products. We note that there are no electronic effects: whether R^1 and R^2 are electron-donating or -withdrawing group (compare entries 3 and 9), the S_N2'/S_N2 ratio is similar. We can



Scheme 1.



Scheme 2.

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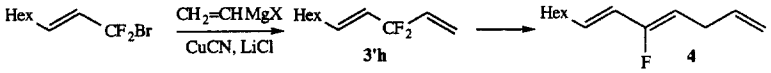
Table 1

Entry	R^1	R^2	R^3	Experimental conditions, n/°C [a]	Products: yield [b] (%)	3:3′ [c]
1	*n*-Hex	H	Me	2/+10	[**3a**+**3′a**]: 70	98:2
2	*n*-Hex	H	*n*-Bu	1.2/−20	[**3b**]: 96	100:0
3	*n*-Hex	H	*i*-Pr	1.2/−20	[**3c**]: 92	100:0
4	*n*-Hex	H	*t*-Bu	1.2/−20	[**3d**]: 93	100:0
5	*n*-Hex	H	Benzyl	2/−20	[**3e**+**3′e**]: 80	92:8
6	*n*-Hex	H	Allyl	1.5/−20	[**3f**+**3′f**]: 80	85:15
7	*n*-Hex	H	Phenyl	2/−20	[**3′g**]: 30 [d]	0:100
8	*n*-Hex	H	Vinyl	2/−20	[**3h**+**3′h**]: 50 [d]	5:95
9	Phenyl	H	*i*-Pr	1.6/−30	[**3i**]: 90	100:0
10	Phenyl	H	*t*-Bu	1.6/−30	[**3j**+**3′j**]: 85	97:3
11	$(CH_2)_5$		*n*-Bu	1.6/−30	[**3k**+**3′k**]: 87	97:3
12	$(CH_2)_5$		*i*-Pr	1.6/−30	[**3l**+**3′l**]: 85	97:3

[a] Number of equivalents of R^3MgX and reaction temperature.
[b] Yield in isolated products [**3**+**3′**].
[c] S_N2'/S_N2 ratio determined by NMR spectroscopy.
[d] See Section 2.



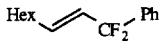
Scheme 3.

also note that if a disubtituted product **2** (entry 12) is used instead of a monosubstituted one (entry 3), a small amount of S_N2 product is obtained. This means that there is thus a very little steric effect.

With regard to the nucleophile, the results obtained show that if the nucleophilic substituents are sp^3-hybridized (namely unstable) (entries 2, 3, 4 and 9), they attack on one side alone and lead to the alkenes **3**, namely the S_N2'-like substitution products (the entry 1 with R^3 = Me cannot be compared with the others because in this case the reaction being more difficult, the temperature must be higher). When the nucleophiles are stabilized by resonance (entries 5 and 6), a small amount (10 to 15%) of the alkenes **3′**, namely the S_N2-like substitution products, are present. Finally, when the nucleophiles used are sp^2-hybridized (R^3 = phenyl and vinyl) (entries 7 and 8), they are still more stabilized than the two groups previously cited and only the products **3′** (S_N2-type) are obtained.

In fact, the results of the entries 7 and 8 are more complex than the other studied cases. These two reactions have given a complex mixture of several fluorinated products. Column chromatography (silica-cyclohexane) does not allow us to completely separate the different compounds but nevertheless the more important products could be identified. After a detailed study of NMR spectra of the different collected fractions, we may make the following remarks.

(1) the S_N2' product **3** (easily identifiable by ^1H NMR spectrum, the proton H^2 being characterized by a multiplet (ddd) at 3.9 ppm) is not present (entry 7) or only in very small amount (entry 8). The absence of **3** could be explained by the fact that it could react again in the mixture to give other products. We think that this idea must be wrong because in the other studied cases, the products **3** are stable in our experimental conditions in presence of an excess of organometallic.



3′g

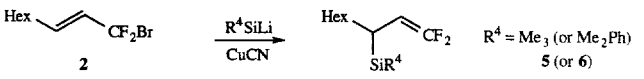
Scheme 4.

(2) we mainly obtain the product **3′** (S_N2-type) in an estimated yield of about 50% (R^3 = vinyl) or 30% (R^3 = phenyl).

When R^3 = vinyl, the result is clear. An amount of **3′h** is attacked again by the organometallic to give in the reaction crude, a product identified as **4** (**4** is obtained in an estimated yield of 10–20%) (Scheme 3). In contrast to the product **3**, **3′h** can continue to react in the reaction mixture. That is due to the fact that **3′h** is reactive because of its fluorine atoms which are in an bis-allylic position hence very mobile. We think that the rates of reaction of **2** and **3′h** with R^3MgX are similar. The Grignard reagent mainly attacks **3′h** on the less hindered side. The attack inside the molecule (on the carbon C^5) cannot be confirmed with certainty among the minor signals of the ^{19}F NMR spectrum, but we do not exclude it. Recently, this type of reattack on a difluoroallylic moiety has been observed and reported [36,37].

When R^3 = phenyl, the reaction gives as main fluorinated product, the S_N2-type product (**3′g**) (Scheme 4). The other fluorinated products obtained are present in very small amount and cannot be identified (an important amount of biphenyl which cannot be completely removed, hinders the study of ^1H and ^{13}C NMR spectra).

In conclusion, the mechanism of this reaction has not been fully determined, but the results obtained suggest that the substitution process involves a transition state with a significant carbocation character [38,39].



Scheme 5.

Scheme 6.

A similar process using organosilicon intermediates which are prepared via cuprates, allows us to prepare difluorovinylic compounds bearing a silyl group, $SiMe_3$ or $SiMe_2Ph$, in an allylic position with good yields (about 75%) (only the S_N2'-like substitution products are obtained) (Scheme 5). Herein is reported the first synthesis of the fluoroallylsilanes **5** and **6**.

The allylsilanes are well recognized as useful building blocks in organic synthesis. They can react with various electrophiles and therefore be potent intermediate synthons for the construction of more elaborate molecules. To this end, we have examined the behavior of **5** and **6** in reaction with electrophilic reagents.

The organo-silanes **5** and **6** in the presence of benzaldehyde and *t*-BuOK in DMPU [40] after 1 h at room temperature lead to the corresponding alcohol **7** in good yield (70%) and high regioselectivity (in the case of allylsilanes, exclusive attack on the allylic terminal position is observed [41,42]) but without stereoselectivity ($E/Z = 1/1$) (Scheme 6).

With Bu_4NF as reaction promotor, we obtain the same alcohols **7** but in lower yield (40%), because the reaction leads also to an important amount of the protodesilylated product (1,1-difluoro-2-nonene). On the other hand, the organo-silanes do not react with the aldehyde if the catalyst used is a Lewis acid ($AlCl_3$, $TiCl_4$).

Several methods to synthesize molecules with the entity [C=C–CF_2–C(OH)] have been previously published [40,43–49]. The process described here has the advantage of allowing the preparation of alcohols substituted in position 4.

Then, we have examined the reactivity of the organo-silanes **5** and **6** with ketones (acetone and cyclohexanone) in presence of *t*-BuOK–DMPU or Bu_4NF–THF. These reactions mainly lead to the protodesilylated product. The desired alcohols are present in the reaction crude but only in small amount.

The fluoroallylsilane **5** reacts with acetyl chloride (or acetic anhydride) in presence of $AlCl_3$ in CH_2Cl_2, not to give the desired 3,3-difluoro-4-undecen-2-one **8** (which has not been seen) but the fluoroenone **9** (Scheme 7).

In the case of the acid chloride, the ratio E/Z isomer varies with the experimental procedure (after 2 h at 0°C, yield = 70%, $Z/E = 3/1$; after 1 h at 20°C, yield = 50%, $Z/E = 1/0$). In the case of the anhydride, the reaction is slower, taking 12 h at 20°C for completion and shows only the *Z* isomer (yield = 50%). If the temperature is lower at 0°C for acid chloride and at 20°C for anhydride, the reaction will not take place. Moreover, the isomer *E* is destroyed in the reaction mixture, if the temperature exceeds 0°C. As previously mentioned above for **3'h**, the product **8** is another example of a very reactive compound towards nucleophiles: its two fluorine atoms being both allylic and α to a carbonyl group, are very mobile. **8** is easily attacked by a chloride ion ($AlCl_4^- \rightarrow AlCl_3 + Cl^-$) present in the reaction mixture and undergoes a S_N2' reaction to give the corresponding monofluorinated vinylic compound **9**. The organo-silane **5** can react with an acid chloride (or an anhydride) only when the reaction promotor reaction used is $AlCl_3$ (Bu_4NF–THF, *t*-BuOK–DMPU, $TiCl_4$–CH_2Cl_2 and BF_3–Et_2O are inefficient).

The organo-silane **5**, in the presence of $AlCl_3$, can also react with *t*-butyl chloride to give an unstable product (it cannot be correctly isolated and thus identified) and if the organo-silane **6** is used with $AlCl_3$ as catalyst, the electrophilic reagent (CH_3COCl, *t*-BuCl) will give exclusive attack on the aromatic group.

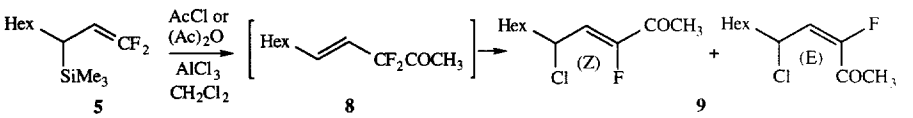
In conclusion, this route appears to provide a general and highly regioselective methodology for the introduction of a difluorovinylic group. Moreover, the fluoroallylsilanes prepared constitute useful precursors for synthesizing more complex fluorinated molecules. Nevertheless, we may remark that the silanes **5** and **6** are less reactive than their non fluorinated analogs.

3. Experimental details

^1H NMR and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer [$CDCl_3$: δ (ppm) from TMS, *J* (Hz)] and ^{19}F NMR spectra on a Jeol FX 90 spectrometer [$CDCl_3$: δ (ppm) from $CFCl_3$, *J* (Hz)]. Infrared spectra were measured on a Perkin-Elmer 397 spectrometer (neat, cm^{-1}).

3.1. Preparation of the intermediate difluorinated alcohols 1

To a solution of $F_2C{=}CH_2$ (2.4 g, 37.5 mmol) in THF (60 ml) and Et_2O (15 ml) were added 30 mmol of *s*-BuLi in cyclohexane at −100°C. The reaction mixture was stirred



Scheme 7.

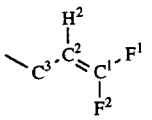
at −90°C for 20 min, and then a solution of the carbonyl compound (25 mmol) in Et_2O (10 ml) was added at −100°C. After 30 min at −90°C, the temperature was raised to 0°C (over 20 min). The solution was hydrolyzed by the addition of H_2SO_4 solution (1 N) and extracted with Et_2O. The organic phase was successively washed with saturated aqueous solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. After evaporation of the solvents, the corresponding alcohols were obtained. The alcohols **1** are unstable in the pure state but they can be stored without any problem in Et_2O solution (with the addition of a small amount of $NaHCO_3$) at −20°C.

3.2. Preparation of the bromodifluorinated alkenes 2

$SOBr_2$ (1.94 ml, 25 mmol) was added (over 5 min) at −80°C to a solution of crude alcohol **2** (prepared from 25 mmol of the carbonyl derivative) in Et_2O (50 ml). After 15 min, the temperature was allowed to warm up to 20°C (over 15 min). The reaction mixture was stirred for 1 h (R^1, $R^2=(CH_2)_5$) or 3 h (R^1=Hex, R^2=H and R^1=Phenyl, R^2=H) and then hydrolyzed by the addition of H_2O (30 ml) at −10°C and extracted with Et_2O. The organic phase was successively washed with sat. aq. $NaHCO_3$ and NaCl solutions. It was then dried over $MgSO_4$ and concentrated in vacuo. To the crude product thus obtained was quickly added 30 ml of a mixture of pentane and Et_2NH in a 95/5 ratio. After 2 min, this solution was filtered through a small column packed with silica. The solvent was evaporated to afford the desired product **2**. In the case of R^1=Hex, R^2=H, the residue was distilled over $NaHCO_3$ (b.p. 38–42°C/0.5 Torr). If R^1=Phenyl, R^2=H and R^1, $R^2=(CH_2)_5$, the bromides were used crude.

3.3. Preparation of the 1,1-difluoroalkenes 3

To a solution of bromoalkene **1** (5 mmol, 1 equiv.) in THF (40 ml) were added at −30°C, CuCN (0.045 g, 0.5 mmol) and LiCl (0.021 g, 0.5 mmol), followed by the Grignard reagent (the number of equivalents of this reagent and the reaction temperature are indicated in Table 1). After stirring for 30 min, the mixture was hydrolyzed with NH_4Cl/NH_4OH solution, filtered on celite and extracted with Et_2O. The combined organic layers were washed with sat. aq. NaCl solution and dried over $MgSO_4$. The solvents were removed and the crude residue was filtered through a small column packed with silica (pentane for R^1=Hex, R^2=H, cyclohexane for R^1=Phenyl, R^2=H and R^1, $R^2=(CH_2)_5$).



1,1-Difluoro-3-methyl-1-nonene (**3a**): yield, 70%. IR (cm^{-1}): 3020; 2850; 1740 (s); 1450; 1285; 970. ^{19}F NMR δ: −90.9 (dd, F^1, J=51 and 3 Hz); −92.4 (dd, F^2, J=51 and 25 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H, J=6.5 Hz); 1.0 (d, 3H, J=7 Hz); 1.3 (m, 10H); 2.3 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=10 Hz, $J(H^2/F^1)$=3 Hz) ppm. ^{13}C NMR δ: 14.2 (CH_3); 21.5 (CH_3); 22.9 (CH_2); 27.5 (CH_2); 28.5 (d, C^3, J=4 Hz), 29.5 (CH_2); 32.1 (CH_2); 37.7 (CH_2); 84.1 (t, C^2, J=20 Hz), 156.2 (t, C^1, J=286 Hz)) ppm. Analysis: Calc. for $C_{10}H_{18}F_2$: C, 68.15; H, 10.29. Found: C, 68.31; H, 10.44%.

1,1-Difluoro-3-butyl-1-nonene (**3b**): yield, 96%. IR (cm^{-1}): 2920; 2850; 1740 (s); 1460; 1175; 930. ^{19}F NMR δ: −90.1 (d, F^1, J=51 Hz); −92.6 (dd, F^2, J=51 and 26 Hz) ppm. ^1H NMR δ: 0.9 (t, 6H, J=6 Hz); 1.3 (m, 16H); 2.15 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=26 Hz, $J(H^2/H^3)$=10 Hz, $J(H^2/F^1)$=3 Hz) ppm. ^{13}C NMR δ: 14.2 (2 CH_3); 22.81 (CH_2); 22.84 (CH_2); 27.3 (CH_2); 29.46 (CH_2); 29.55 (CH_2); 32.0 (CH_2); 34.0 (d, C^3, J=4 Hz); 35.6 (CH_2); 35.9 (CH_2); 82.7 (t, C^2, J=20 Hz); 156.8 (t, C^1, J=286 Hz) ppm. Analysis: Calc. for $C_{13}H_{24}F_2$: C, 71.52; H, 11.08. Found: C, 71.41; H, 11.15%.

1,1-Difluoro-3-*i*-propyl-1-nonene (**3c**): yield, 92%. IR (cm^{-1}): 2920; 2850; 1740 (s); 1460; 910. ^{19}F NMR δ: −89.3 (d, F^1, J=50 Hz), −92.4 (dd, F^2, J=50 and 25 Hz) ppm. ^1H NMR δ: 0.82 (d, 3H, J=7 Hz); 0.880 (d, 3H, J=7 Hz); 0.884 (t, 3H, J=7 Hz); 1.25 (m, 8H); 1.4 (m, 2H); 1.6 (m, 1H); 2.0 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=11 Hz, $J(H^2/F^1)$=3 Hz) ppm. ^{13}C NMR δ: 14.2 (CH_3); 18.4 (CH_3); 20.9 (CH_3); 22.9 (CH_2); 27.7 (CH_2); 29.5 (CH_2); 32.07 (CH_2); 32.15 (CH); 33.1 (CH_2); 40.2 (d, C^3, J=3 Hz); 80.0 (t, C^2, J=20 Hz); 156.9 (t, C^1, J=285 Hz) ppm. Analysis: Calc. for $C_{12}H_{22}F_2$: C, 70.55; H, 10.85. Found: C, 70.39; H, 10.91%.

1,1-Difluoro-3-*t*-butyl-1-nonene (**3d**): yield, 93%. IR (cm^{-1}): 2950; 2920; 2850; 1740 (s); 1460; 1360; 1285; 1165; 910; 825. ^{19}F NMR δ: −89.4 (d, F^1, J=50 Hz); −92.4 (dd, F^2, J=50 and 25 Hz) ppm. ^1H NMR δ: 0.86 (s,9H); 0.88 (t,3H); 1.3 (m, 8H); 1.5 (m, 2H); 1.9 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=11 Hz, $J(H^2/F^1)$=3 Hz) ppm. ^{13}C NMR δ: 14.2 (CH_3); 22.9 (CH_2); 27.5 (CH_3); 28.4 (CH_2); 29.5 (CH_2); 29.9 (CH_2); 33.1 (CH_2); 33.5 (quat. C); 44.6 (d, C^3, J=3 Hz); 80.1 (t, C^2, J=20 Hz); 157.1 (t, C^1, J=285 Hz) ppm. Analysis: Calc. for $C_{13}H_{24}F_2$: C, 71.52; H, 11.08. Found: C, 71.63; H, 11.27%.

1,1-Difluoro-3-benzyl-1-nonene (**3e**): yield, 80%. IR (cm^{-1}): 3020; 2920; 2850; 1740 (s); 1450; 1170; 745; 695. ^{19}F NMR δ: −89.4 (dd, F^1, J=48 and 3 Hz); −91.6 (dd, F^2, J=48 and 25 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H, J=6.5 Hz); 1.2 (m, 8H); 1.4 (m, 2H); 2.5 (m, 2H); 2.7 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=10 Hz, $J(H^2/F^1)$=3 Hz); 7.1–7.3 (m, 5H) ppm. ^{13}C NMR δ: 14.2 (CH_3); 22.8 (CH_2); 27.3 (CH_2); 29.4 (CH_2); 32.0 (CH_2); 35.1 (CH_2); 35.8 (d, C^3, J=4 Hz), 42.3 (CH_2); 82.0 (t, C^2,

J=20 Hz); 126.1; 128.3; 129.2; 140.0 (arom. C); 156.6 (t, C^1, J=286 Hz) ppm.

2,2-Difluoro-1-phenyl-3-decene (**3'e**): ^{19}F NMR δ: −94.0 (dt, 2F, J=15 and 13 Hz) ppm. ^1H NMR δ: 3.15 (t, H^1, J=15 Hz) ppm.

1,1-Difluoro-3-allyl-1-nonene (**3f**): yield, 80%. IR (cm^{-1}): 3070; 2920; 2850; 1740 (s); 1640; 1460; 1285; 1170; 985; 910; 810. ^{19}F NMR δ: −89.3 (dd, F^1, J=50 and 3 Hz); −91.6 (dd, F^2, J=50 and 25 Hz) ppm. ^1H NMR δ: 0.9 (t,3H); 1.3 (m, 8H); 1.4 (m, 2H); 2.0–2.3 (m, 4H); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=10 Hz, $J(H^2/F^1)$=3 Hz); 5.0 (2dd, 2H, J=10 and 1 Hz and, J=17 and 1 Hz); 5.7 (ddt, 1H, J=17, 10 and 7 Hz) ppm. ^{13}C NMR δ: 14.2 (CH_3); 22.8 (CH_2); 27.3 (CH_2); 29.4 (CH_2); 32.0 (CH_2); 33.8 (d, C^3, J=4 Hz); 35.2 (CH_2); 40.2 (CH_2); 82.1 (t, C^2, J=20 Hz); 116.4 (CH_2); 136.3 (CH); 156.6 (t, C^1, J=286 Hz) ppm.

4,4-Difluoro-1,5-dodecadiene (**3'f**): ^{19}F NMR δ: −94.8 (dt, 2F, J=15 and 12 Hz) ppm. ^1H NMR δ: 2.25 (m, 2H); 2.7 (td, H^3, J=15 and 7 Hz); 5.2 (m, 2H); 6.1 (m, 1H) ppm. ^{13}C NMR δ: 42.1 (t, C^3, J=28 Hz); 120.1 (C^1); 124.8 (t, C^5, J=26 Hz) ppm.

(*E*)-1,1-Difluoro-1-phenyl-2-nonene (**3'g**): ^{19}F NMR δ: −90.6 (dq, J=9 and 3 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.1–1.5 (m, 8H); 2.05 (m, 2H); 5.8 (dtt, H^2, $J(H^2/H^3)$=16 Hz, $J(H^2/F$=9 Hz, $J(H^2/H^4)$=1 Hz); 5.95 (dtt, H^3, $J(H^2/H^3)$=16 Hz, $J(H^3/H^4)$=7 Hz, $J(H^3/F)$=3Hz); 7–7.5 (m, 5H) ppm. ^{13}C NMR δ: 14.2; 22.7; 28.5; 28.9; 31.7; 31.9; 119.9 (t, C^1, J=237 Hz); 137.4 (t, C^3, J=9 Hz) ppm.

(*E*)-3,3-Difluoro-1,4-undecadiene (**3'h**): ^{19}F NMR δ: −93.5 (m) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.3 (m, 6H); 1.4 (m, 2H); 2.1 (q, 2H^6, J=7 Hz); 5.4 (dd, H^1, $J(H^1/H^2)$=11 Hz, $J(H^1/H^{1'})$=1 Hz); 5.6 (dtt, H^4, $J(H^4/H^5)$=16 Hz, $J(H^4/F)$=8 Hz, $J(H^4/H^6)$=2 Hz); 5.6 (dtd, $H^{1'}$, $J(H^{1'}/H^2)$=17 Hz, $J(H^{1'}/F)$=3 Hz, $J(H^1/H^{1'})$=1 Hz); 5.9 (ddt, H^2, $J(H^{1'}/H^2)$=17 Hz, $J(H^1/H^2)$=11 Hz, $J(H^2/F)$=10 Hz); 6.1 (dtt, H^5, $J(H^4/H^5)$=16 Hz, $J(H^5/H^6)$=7 Hz, $J(H^5/F)$=3 Hz) ppm. ^{13}C NMR δ: 14.2; 22.7; 28.5; 28.9; 31.8; 32.0; 118.2 (t, C^3, J=235 Hz); 119.5 (t, C^1, J=9 Hz); 124.6 (t, C^4, J=28.5 Hz); 133.2 (t, C^2, J=30 Hz); 137.4 (t, C^5, J=9 Hz) ppm.

(*Z,E*)-5-Fluoro-1,4,6-tridecatriene (**4**): ^{19}F NMR δ: −123.8 (dd, J=36 and 24 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.15–1.5 (m, 8H); 2.1 (q, 2H^8, J=7 Hz); 2.9 (t, 2H^3, J=7 Hz); 4.7 (dt, H^4, $J(H^4/F)$=36 Hz, $J(H^4/H^3)$=7 Hz); 5.0 (dq, H^1, $J(H^1/H^2)$=10 Hz, $J(H^1/H^{1'})$=2 Hz, $J(H^1/H^3)$=2 Hz); 5.05 (dq, $H^{1'}$, $J(H^{1'}/H^2)$=17 Hz, $J(H^1/H^{1'})$=2 Hz, $J(H^{1'}/H^3)$=2 Hz); 5.75 (ddt, H^2, $J(H^{1'}/H^2)$=17 Hz, $J(H^1/H^2)$=10 Hz, $J(H^2/H^3)$=7 Hz); 5.78 (ddt, H^6, $J(H^6/F)$=24 Hz, $J(H^6/H^7)$=14 Hz, $J(H^6/H^8)$=2 Hz); 5.95 (dt, H^7, $J(H^6/H^7)$=14 Hz, $J(H^7/H^8)$=7 Hz) ppm. ^{13}C NMR δ: 14.2; 22.7; 29.0; 29.1; 31.8; 31.9; 32.4 (C^3); 105.3 (d, C^4, J=16 Hz); 115.1 (C^1); 121.9 (d, C^6, J=24 Hz); 131.5 (d, C^7, J=3 Hz); 136.2 (C^2); 156.8 (d, C^5, J=249 Hz) ppm.

1,1-Difluoro-3-*i*-propyl-3-phenyl-1-propene (**3i**): yield, 90%. IR (cm^{-1}): 2950; 1735 (s); 1270; 1180; 910; 750; 695. ^{19}F NMR δ: −89.3 (dt, F^1, J=46.5 and 3 Hz); −91.1 (dd, F^2, J=46.5 and 24 Hz) ppm. ^1H NMR δ: 0.8 (d, 3H, J=7 Hz); 0.9 (d, 3H, J=7 Hz); 1.9 (dhept, H^4, J=7 and 8 Hz); 3.1 (dd, H^3, J=11 and 8 Hz); 4.4 (ddd, H^2, $J(H^2/F^2)$=24.5 Hz, $J(H^2/H^3)$=11 Hz, $J(H^2/F^1)$=3 Hz); 7.1–7.3 (m, 5H) ppm. ^{13}C NMR δ: 20.05 (CH_3); 21.05 (CH_3); 33.8 (s, C^4); 47.3 (d, C^3, J=4 Hz); 81.2 (t, C^2, J=20 Hz); 126.5; 127.7; 128.6; 143.6 (arom. C); 156.3 (t, C^1, J=287 Hz) ppm. Analysis: Calc. for $C_{12}H_{14}F_2$: C, 73.45; H, 7.19. Found: C, 73.34; H, 7.05%.

1,1-Difluoro-3-*t*-butyl-3-phenyl-1-propene (**3j**): yield, 85%. IR (cm^{-1}): 2960; 1735 (s); 1360; 1290; 1190; 1160; 920; 780; 730; 700. ^{19}F NMR δ: −89.0 (ddd, F^1, J=45.5, 4 and 2 Hz); −90.2 (dd, F^2, J=45.5 and 23 Hz) ppm. ^1H NMR δ: 0.9 (s,9H); 3.2 (dd, H^3, J=11 and 2 Hz); 4.7 (ddd, H^2, $J(H^2/F^2)$=24 Hz, $J(H^2/H^3)$=11 Hz, $J(H^2/F^1)$=3 Hz); 7.1–7.3 (m, 5H) ppm. ^{13}C NMR δ: 27.7 (CH_3); 34.6 (quat. C); 50.4 (d, C^3, J=4 Hz); 79.5 (t, C^2, J=21 Hz); 126.6; 127.9; 129.1; 141.6 (arom. C); 156.1 (t, C^1, J=287 Hz) ppm. Analysis: Calc. for $C_{13}H_{16}F_2$: C, 74.26; H, 7.67. Found: C, 74.41; H, 7.69%.

1,1-Difluoro-2-(-1-butylcyclohexyl)-1-ethene (**3k**): yield, 87%. IR (cm^{-1}): 2925; 2855; 1735 (s). ^{19}F NMR δ: −87.2 (m) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.15–1.65 (m, 16H); 3.9 (dd, H^2, J=27 and 10 Hz) ppm. ^{13}C NMR δ: 14.1 (CH_3); 22.6 (CH_2); 23.4 (CH_2); 25.9 (CH_2); 26.3 (CH_2); 36.2 (CH_2); 36.9 (CH_2); 42.1 (C^3); 84.9 (t, C^2, J=17 Hz), 155.0 (t, C^1, J=292 Hz) ppm. Analysis: Calc. for $C_{12}H_{20}F_2$: C, 71.25; H, 9.97. Found: C, 71.31; H, 10.12%.

1,1-Difluoro-2-(-1-*i*-propylcyclohexyl)-1-ethene (**3l**): yield, 85%. IR (cm^{-1}): 2930; 2850; 1730 (s); 1220; 1190; 1165; 1130; 1005; 910; 890. ^{19}F NMR δ: −85.8 (dd, F^1, J=52 and 7 Hz); −87.7 (dd, F^2, J=52 and 30 Hz) ppm. ^1H NMR δ: 0.8 (d, 6H, J=7 Hz); 1.1–1.8 (m, 11H); 3.8 (dd, H^2, J=30 and 7 Hz) ppm. ^{13}C NMR δ: 17.3 (CH_3); 23.0 (CH_2); 26.4 (CH_2); 34.58 (CH_2); 34.62 (CH_2); 38.3 (C^4); 39.9 (C^3); 83.3 (dd, C^2, J=20 and 15 Hz); 155.7 (dd, C^1, J=293 and 283 Hz) ppm. Analysis: Calc. for $C_{11}H_{18}F_2$: C, 70.18; H, 9.64. Found: C, 70.27; H, 9.75%.

3.4. Synthesis of 1,1-difluoro-3-trimethylsilyl-1-nonene 5

MeLi (3 ml, 5 mmol) was added dropwise at −20°C to a solution of hexamethyldisilane (0.91 g, 6.25 mmol) in a mixture of Et_2O (3 ml) and HMPA (3 ml) [50]. After 15 min at −10°C, $(Me)_3SiLi$ was ready. To this solution were successively added at −20°C, CuCN (0.22 g, 2.5 mmol) and after stirring for 30 min at this temperature, the bromide (0.6 g, 2.5 mmol). After 1 h at −20°C, the mixture was hydrolyzed with aq. sat. NH_4Cl solution, filtered on celite and extracted with Et_2O. The combined organic layers were successively washed with sat. aq. HCl (1N), $NaHCO_3$ and NH_4Cl solutions and dried over $MgSO_4$. The solvent was

evaporated and the crude residue distilled to afford the desired silylated product.

B.p. 30°C/0.1 Torr. Yield, 78%. IR (cm^{-1}): 2960; 2920; 2950; 1735; 1460; 1340; 1245; 1230; 1200; 1145; 910; 870; 830. ^{19}F NMR δ: −90.9 (d, F^1, J=55 Hz); −93.7 (dd, F^2, J=55 and 27 Hz) ppm. ^1H NMR δ: −0.01 (s,9H); 0.9 (t, 3H, J=7 Hz); 1.1–1.55 (m, 11H); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=12 Hz, $J(H^2/F^1)$=3 Hz) ppm. ^{13}C NMR δ: −3.2 (3 CH_3); 14.2 (CH_3); 22.6 (CH); 22.9 (CH_2); 29.2 (CH_2); 29.5 (CH_2); 29.6 (CH_2); 32.0 (CH_2); 79.7 (t, C^2, J=21 Hz); 156.1 (t, C^1, J=284 Hz) ppm. m/z: 45; 55; 67; 73 (100%); 85; 99; 113; 149; 160; 234 $[M]^+$. Analysis: Calc. for $C_{12}F_2H_{24}Si$: C, 61.49; H, 10.32. Found: C, 61.57; H, 10.08%.

3.5. Synthesis of 1,1-difluoro-3-dimethylphenylsilyl-1-nonene 6

$Me_2PhSiLi$ (6.5 ml, 5 mmol) was added at −20°C to CuCN (0.22 g, 2.5 mmol) in THF (20 ml). After stirring at this temperature for 15 min, 0.6 g (2.5 mmol) of bromide was added. After 5 h at −20°C, the mixture was hydrolyzed with aq. NH_4Cl solution, filtered on celite and extracted with Et_2O. The organic phase was washed with sat. aq. $NaHCO_3$ and NH_4Cl solutions and dried over $MgSO_4$. The solvents were removed and 0.56 g of silylated product was obtained after purification by silica-gel chromatography (cyclohexane). Yield: 75%. IR (cm^{-1}): 2960; 2920; 2850; 1735 (s); 1425; 1340; 1250; 1110; 910. ^{19}F NMR δ: −89.8 (d, F^1, J=52 Hz); −93.3 (dd, F^2, J=52 and 24 Hz) ppm. ^1H NMR δ: 0.3 (s,6H); 0.9 (t, 3H, J=7 Hz); 1.1–1.5 (m, 10H); 1.7 (m, H^3); 3.9 (ddd, H^2, $J(H^2/F^2)$=25 Hz, $J(H^2/H^3)$=12 Hz, $J(H^2/F^1)$=3 Hz); 7.3–7.5 (m, 5H) ppm. ^{13}C NMR δ: −5.1; −4.4 (2 CH_3); 14.2 (CH_3); 22.4 (CH); 22.8 (CH_2); 29.0 (CH_2); 29.4 (CH_2); 29.5 (CH_2); 31.9 (CH_2); 79.5 (t, C^2, J=21 Hz); 127.9; 129.3; 134.1; 137.2 (arom. C); 156.2 (t, C^1, J=285 Hz) ppm. m/z: 41; 43; 55; 77; 91; 105; 107; 129; 135 (100%); 198; 211; 296 $[M]^+$. Analysis: Calc. for $C_{17}H_{26}F_2Si$: C, 68.87; H, 8.84. Found: C, 69.05; H, 8.63%.

3.6. Synthesis of 2,2-difluoro-1-phenyl-3-decen-1-ol 7

To a mixture of silylated product **5** (or **6**) (2 mmol) and benzaldehyde (0.21 g, 2 mmol) in DMPU (10 ml) was added at 0°C a solution of *t*-BuOK (0.022 g, 0.2 mmol) in DMPU (2 ml). The reaction mixture was stirred for 1 h at room temperature, then hydrolyzed with HCl solution (1N) and extracted with Et_2O. The organic phase was successively washed with sat. aq. HCl, $NaHCO_3$ and NaCl solutions. It was then dried over $MgSO_4$ and concentrated in vacuo. 0.39 g of alcohol was obtained after purification by silica-gel chromatography (hexane/Et_2O: 90/10).

Yield: 70%. IR (cm^{-1}): 3430; 2950; 2920; 2850; 1670; 1450; 1050; 700. ^{19}F NMR δ: *Z*-isomer: AB system-101.6 (ddd, 1F, J=250, 13 and 11 Hz); −102.3 (ddd, 1F, J=250, 13 and 11 Hz) ppm. *E*-isomer: AB system-105.8 (dt, 1F, J=246 and 10 Hz); −106.9 (dt, 1F, J=246 and 10 Hz) ppm. ^1H NMR δ: 1.1–1.4 (m, 16H); 1.9–2.1 (m, 4H); 7.2–7.4 (m, 10H); *Z*-isomer: 0.86 (t, 3H, J=7 Hz); 2.70 (d, OH, J=3 Hz); 4.79 (td, H^1, J=10 and 3 Hz); 5.3 (tdt, H^3, $J(H^3/F)$=15.5 Hz, $J(H^3/H^4)$=12 Hz, $J(H^3/H^5)$=2 Hz); 5.7 (dtt, H^4, $J(H^3/H^4)$=12 Hz, $J(H^4/H^5)$=8 Hz, $J(H^4/F)$=2 Hz); *E*-isomer: 0.87 (t, 3H, J=7 Hz); 2.65 (d, OH, J=4 Hz); 4.76 (td, H^1, J=9 and 4 Hz); 5.4 (dddt, H^3, $J(H^3/H^4)$=16 Hz, $J(H^3/F)$=13 and 11 Hz, $J(H^3/H^5)$=2 Hz); 5.9 (dtt, H^4, $J(H^3/H^4)$=16 Hz, $J(H^4/H^5)$=7 Hz, $J(H^4/F)$=2 Hz) ppm. ^{13}C NMR δ: 14.1 (CH_3); 22.6 (CH_2); 28.3 (CH_2); 28.7 (CH_2); 28.9 (CH_2); 29.2 (CH_2); 31.6 (CH_2); 31.9 (CH_2); *E*-isomer: 76.1 (t, C^1, J=31 Hz); 119.9 (t, C^2, J=244 Hz); 121.2 (t, C^3, J=25 Hz); 127.7; 128.0; 128.49; 136.4 (arom. C); 138.6 (t, C^4, J=9 Hz); *Z*-isomer: 76.2 (t, C^1, J=30 Hz); 120.5 (t, C^3, J=25 Hz); 121.0 (t, C^2, J=245 Hz); 127.8; 128.0; 128.54; 136.2 (arom. C); 140.7 (t, C^4, J=5 Hz) ppm. m/z: 41; 55; 69; 77; 79; 105; 107 (100%); 157; 268 $[M]^+$. Analysis: Calc. for $C_{16}H_{22}F_2O$: C, 71.61; H, 8.26. Found: C, 71.65; H, 8.27%.

3.7. Synthesis of 5-chloro-3-fluoro-3-undecen-2-one 9

To a solution of $AlCl_3$ (0.6 g, 4.4 mmol) in CH_2Cl_2 (10 ml) were successively added at 0°C, CH_3COCl (0.3 ml, 4 mmol) in CH_2Cl_2 (1 ml) and then at −20°C, the silylated product **5** (0.47 g, 2 mmol) in CH_2Cl_2 (1 ml). After 2 h at 0°C, the mixture was hydrolyzed with an addition of H_2O and extracted with Et_2O. The organic layer was washed with sat. aq. $NaHCO_3$ and NaCl solutions and dried over $MgSO_4$. After evaporation of the solvents, the two isomers were obtained, they could be perfectly separated after purification by silica-gel chromatography (hexane/Et_2O: 90/10).

If acetic anhydride was used instead of acetyl chloride, in order that the reaction was completed 5.5 equiv. of $AlCl_3$, 5 equiv. of anhydride and 12 h at room temperature were necessary (only *Z*-isomer was obtained).

E-isomer: Yield: 20%. IR (cm^{-1}): 2950; 2920; 2850; 1710; 1640; 1360; 1180; 1100. ^{19}F NMR δ: −118.6 (dq, 1F, J=18 and 5 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H, J=7 Hz); 1.2–1.5 (m, 8H); 1.7–1.9 (m, 2H); 2.3 (d, 3H, J=5 Hz); 5.5 (dddd, H^5, $J(H^4/H^5)$=11 Hz, $J(H^5/H^6)$=8 and 6 Hz, $J(H^5/F)$=2 Hz); 5.8 (dd, H^4, $J(H^4/F)$=19 Hz, $J(H^4/H^5)$=11 Hz) ppm. ^{13}C NMR δ: 14.2 (CH_3); 22.7 (CH_2); 26.1 (CH_2); 27.8 (CH_3); 28.7 (CH_2); 31.7 (CH_2); 38.8 (CH_2); 54.7 (d, C^5, J=9 Hz); 121.2 (d, C^4, J=21 Hz); 152.7 (d, C^3, J=265 Hz); 194.5 (d, C^2, J=40 Hz) ppm. Analysis: Calc. for $C_{11}H_{18}ClFO$: C, 59.86; H, 8.22. Found: C, 60.02; H, 8.31%.

Z-isomer: Yield: 50%. IR (cm^{-1}): 2950; 2920; 2850; 1715; 1695; 1660; 1465; 1360; 1280; 1210. ^{19}F NMR δ: −124.6 (dq, 1F, J=31 and 3 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H, J=7 Hz); 1.2–1.5 (m, 8H); 1.7–2.0 (m, 2H); 2.3 (d, 3H, J=3 Hz); 4.8 (dt, H^5, $J(H^4/H^5)$=10 Hz, $J(H^5/H^6)$=7 Hz); 6.1 (dd, H^4, $J(H^4/F)$=31 Hz, $J(H^4/H^5)$=10 Hz) ppm. ^{13}C NMR δ: 14.1 (CH_3); 22.6 (CH_2); 25.8 (CH_3);

26.2 (CH_2); 28.6 (CH_2); 31.6 (CH_2); 38.2 (CH_2); 52.8 (d, C^5, $J=5$ Hz); 118.2 (d, C^4, $J=10$ Hz), 153.6 (d, C^3, $J=269$ Hz); 191.4 (d, C^2, $J=33$ Hz) ppm. Analysis: Calc. for $C_{11}H_{18}ClFO$: C, 59.86; H, 8.22. Found: C, 60.07; H, 8.28%.

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