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A New Route to 1,1-difluoroolefins

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Abstract: A new method for the synthesis of various 1,1-difluoroolefins is described. The key step is the treatment of 1-bromo-1,1-difluoro-2-alkenes with organo-metallic reagents in the presence of copper and lithium salts. © 1997 Elsevier Science Ltd.

Fluorinated organic molecules attract much attention due to their unique biological properties. The replacement of hydrogen atoms by fluorine atoms in biological molecules causes a relatively small steric perturbation but leads to major changes in lipophilicity and polarity factors[1,2]. The 1,1-difluorovinylic group is critical for certain mechanism-based enzyme inhibitors[3-5], and can function as a bioisostere for aldehydes and ketones[6].

Some methods for the preparation of 1,1-difluoro-1-alkenes have been described. The most versatile method allowing to incorporate the terminal difluorocarbon is the Wittig olefin synthesis[7]. Electrophilic mono or difluorination from mono or no fluorinated precursors offers alternative methods to 1,1-difluoroolefins[8]. Other methods require incorporation of the two terminal difluoroolefin carbons into a precursor. These include the addition of stabilized difluorovinyl anions to electrophiles[9] or to aryl and alkenyl iodides by palladium catalysis[10] and, the addition of ethyl-4-chloro-4,4-difluorocrotonate to aldehydes *via* the Reformatsky reaction[11].

Although some synthetic methods have been already recorded, we wish to added a new procedure widely applicable to preparing compounds having difluoromethylene group from ketones and aldehydes.

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**[12] (readily obtained by addition of difluorovinyllithium to carbonyl compounds)[9vi]. We now show that these brominated compounds **2** can react with Grignard reagents in the presence of copper and lithium salts to give the corresponding alkenes **3**, 1,1-difluorinated and trisubstituted in an allylic position.

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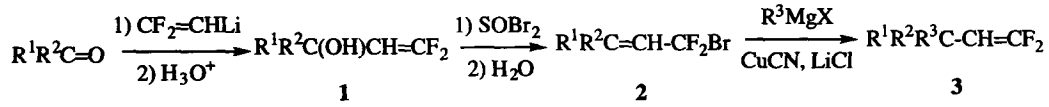
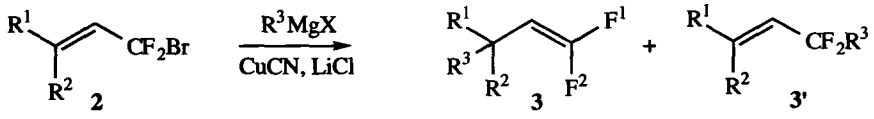


The results of this reaction are summarized in the following table. The reaction proceeds in THF in 30 minutes[13] at the temperature indicated in the table, and affords mainly the alkenes **3**, namely the $S_{N}2'$ substitution products with good yields.

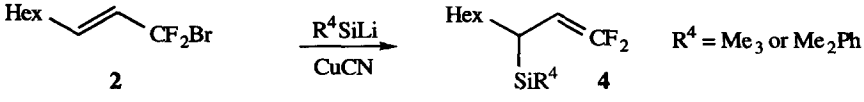


R^1	R^2	R^3	Experimental conditions: n. eq. R^3MgX	temp.[a]	Yield (%)	3/3',[b]	^{19}F NMR (3) δ(ppm)/$CFCl_3$
n-Hex	H	Me	2	+10°C	70	98/2	-90.9, -92.4
"	"	n-Bu	1.2	-20°C	96	100/0	-90.1, -92.6
"	"	i-Pr	"	"	92	100/0	-89.3, -92.4
"	"	t-Bu	"	"	93	100/0	-89.4, -92.4
"	"	Allyl	1.5	"	80	85/15	-89.3, -91.6
"	"	Benzyl	2	"	80	92/8	-89.4, -91.6
Phenyl	"	i-Pr	1.6	-30°C	90	100/0	-89.3, -91.1
"	"	t-Bu	"	"	85	97/3	-89.0, -90.2
	$(CH_2)_5$	n-Bu	"	"	87	97/3	-87.2 (m)
	"	i-Pr	"	"	85	97/3	-85.8, -87.7

a- number of equivalents of organo-metallic and reaction temperature for 30 min

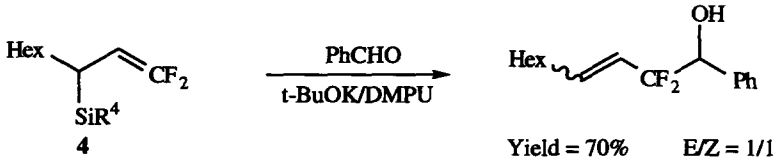
b- $S_{N}2'/S_{N}2$ ratio determined by NMR spectroscopy

Using the process described above from the compound **2** (R^1 = n-Hex, R^2 = H), we have synthesized difluorovinylic compounds bearing silyl group, $SiMe_3$[14] or $SiMe_2Ph$[15] in an allylic position with good yields (about 75%) (only the $S_{N}2'$ products are obtained).

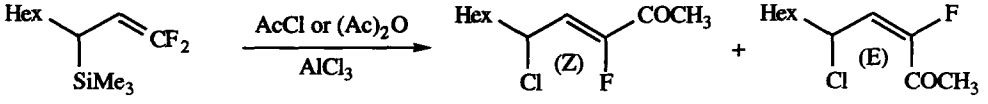


The fluoroallylsilanes obtained can react with various electrophiles and therefore be potent intermediate synthons for the construction of more elaborate molecules. To this end, we have examined the behaviour of **4** in reaction with two electrophilic reagents.

The organo-silanes ($R^4 = Me_3$ or Me_2Ph) in presence of benzaldehyde and t-BuOK in DMPU[16] after 1 h at room temperature leads to the corresponding alcohol with a good yield (70%), a high regioselectivity (only S_N2' substitution product is obtained) but without stereoselectivity (E/Z = 1/1)[17].



The silylated product ($R^4 = Me_3$) reacts with acetyl chloride or acetic anhydride in presence of $AlCl_3$ not to give the desired 3,3-difluoro-4-undecen-2-one but the following ketones[18] (due to a chlorination in a second step by the Lewis acid).



In the case of the acid chloride, the isomer ratio E/Z 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 to be complete and only Z isomer is obtained (yield = 50%).

In conclusion, this route appears to provide a general and highly regioselective methodology for the introduction of a difluorovinylic group. Moreover, the silylated products obtained constitute useful precursors for synthesizing more complex fluorinated molecules.

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13- To the bromide (5 mmol, 1 eq.) in THF (40 ml) are successively added at -30°C CuCN (0.5 mmol) and LiCl (0.5 mmol), and then the Grignard reagent (for the number of eq. see table). Stirring is continued at the temperature indicated in the table for 30 min and the solution is diluted by addition of NH_4Cl/NH_4OH solution. The vinylic difluorinated products obtained are then purified by flash silica-gel chromatography (cyclohexane).
14- MeLi (5 mmol) is added at -20°C to a solution of hexamethyldisilane (6.25 mmol) in Et_2O (3 ml) and HMPA (3 ml)[19]. After 15 min at -10°C, to this solution are successively added at -20°C, CuCN (2.5 mmol) and after 30 min, the bromide (2.5 mmol). After 1h at -20°C, the mixture is hydrolyzed with HCl solution. The allylsilane obtained is purified by distillation. B.p.: 30°C/ 0.1 torr; ^{19}F NMR δ: -90.9 (d, F^1, J = 55 Hz); -93.7 (dd, F^2, J = 55 and 27 Hz) ppm.
15- $Me_2PhSiLi$ (5 mmol) is added at -20°C to CuCN (2.5 mmol) in THF (20 ml) and after stirring at this temperature for 15 min, the bromide (2.5 mmol) is added. After 5 h at -20°C, the solution is diluted by addition of NH_4Cl/NH_4OH solution. The allylsilane is obtained after purification by silica-gel chromatography (cyclohexane). ^{19}F NMR δ: -90.2 (d, F^1, J = 52 Hz); -93.3 (dd, F^2, J = 52 and 24 Hz) ppm.
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17- ^{19}F NMR δ: *Z*-isomer: -101.6 (ddd, 1F, J = 250, 13 and 11 Hz); -102.3 (ddd, 1F, J = 250, 13 and 11 Hz) ppm; *E*-isomer: -105.8 (dt, 1F, J = 246 and 10 Hz); -106.9 (dt, 1F, J = 246 and 10 Hz) ppm.
18- ^{19}F NMR δ: *E*-isomer: -118.6 (dq, J = 18 and 5 Hz) ppm; *Z*-isomer: -124.6 (dq, J = 31 and 3 Hz) ppm.
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