Addition of Organometallic Compounds to 2-Chloro-1,1-difluoro-3-hydroxy-1-alkenes. A New Synthesis of α,β-Unsaturated α-Chloro Aldehydes and Ketones

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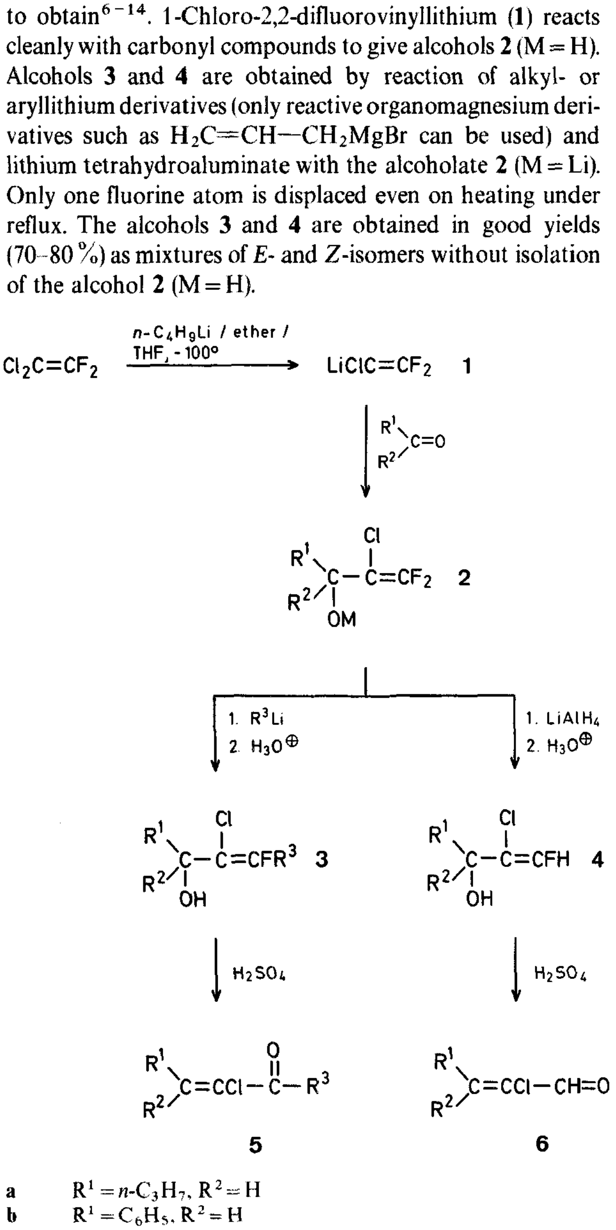
1-Chloro-2,2-difluorovinyllithium (**1**) has been prepared in moderate yields from $F_2C{=}CClH$[1] and from $F_2C{=}CCl_2$[2,3]. We have now found that better (>85%) yields of **1** can be obtained by reaction of $F_2C{=}CCl_2$ with *n*-butyllithium in ether at low temperature in the presence of a molar equivalent of tetrahydrofuran (in the absence of tetrahydrofuran the yield is 40%[2], with 2 equivalents it is 75%, and with 8 equivalents, 30%).

Using a similar sequence of reactions to that described for the preparation of α,β-unsaturated α-fluoro derivatives[4,5] we now report a useful synthesis of linear α,β-unsaturated α-chloro carbonyl compounds which are otherwise difficult to obtain[6–14]. 1-Chloro-2,2-difluorovinyllithium (**1**) reacts cleanly with carbonyl compounds to give alcohols **2** (M = H). Alcohols **3** and **4** are obtained by reaction of alkyl- or aryllithium derivatives (only reactive organomagnesium derivatives such as $H_2C{=}CH{-}CH_2MgBr$ can be used) and lithium tetrahydroaluminate with the alcoholate **2** (M = Li). Only one fluorine atom is displaced even on heating under reflux. The alcohols **3** and **4** are obtained in good yields (70–80%) as mixtures of *E*- and *Z*-isomers without isolation of the alcohol **2** (M = H).



a $R^1 = n\text{-}C_3H_7$, $R^2 = H$
b $R^1 = C_6H_5$, $R^2 = H$
c $R^1 = R^2 = CH_3$
d $R^1 = R^2 = -(CH_2)_5-$

It is interesting to note that the $-CCl{=}CF_2$ group of the alcoholate **2** (M = Li) is more electrophilic than the $-CF{=}CF_2$ group of the corresponding alcoholate since phenyllithium does not add to the trifluoroalcoholate[4] and lithium tetrahydroaluminate brings about reduction more slowly[5].

Treatment of alcohols **3** and **4** with 96% sulfuric acid at −30 to −20° causes isomerisation to ketones **5** or aldehydes **6** in good (70%) yields. Alcohols **3b** ($R^3 = C_2H_5$), **3c** ($R^3 = C_6H_5$) and **4b** are not sufficiently stable for distillation and are isomerised without prior purification. Alcohol **3a** ($R^3 = H_2C{=}CH{-}CH_2{-}$) gave rise to a mixture of unidentifiable products.

^{13}C-N.M.R. spectra of the carbonyl compounds **5a** ($R^3 = C_2H_5$, C_6H_5), **5b** ($R^3 = C_6H_5$), **6a**, and **6b** show that these consist of only 1 isomer which was assigned the *Z* structure on the basis of the ^1H-N.M.R. spectra (see Tables 4, 5, and 6).

Preparation of 1-Chloro-2,2-difluorovinyllithium (1):
n-Butyllithium (50 mmol) in ether (30 ml) is added under nitrogen with stirring to 1,1-dichloro-2,2-difluoroethene (53 mmol) dissolved in tetrahydrofuran (5 ml, 62 mmol) and ether (95 ml) at −120°. After the addition is complete (10 min), the temperature is raised to −90° for 5 min; the solution is then used directly.

Preparation of 2-Chloro-1,1-difluoro-3-hydroxy-1-alkenes 2:
These alcohols are prepared following the procedure given in Ref. [2]; for yields and physical properties see Table 1.

Preparation of Alcohols 3:
The carbonyl compound (50 mmol) in ether (15 ml) is added dropwise to a solution of **1** (50 mmol) at −120° in 5 min and the temperature is then allowed to rise to −70°. The organolithium derivative or allylmagnesium bromide (~75 mmol) is added rapidly and the mixture is allowed to warm to room temperature. (With ethyllithium the reaction time is 1 h, with methyl- and phenyllithium, 3 h at 25°, and with allylmagnesium bromide 1 h at reflux). The mixture is then hydrolysed by addition of 6 normal sulfuric acid (50 ml), extracted with ether (2 × 70 ml), the ether extracts are washed with saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, and distilled under vacuum after addition of solid sodium hydrogen carbonate (0.3 g). For physical properties and spectral data see Table 2.

Preparation of Alcohols 4:
The carbonyl compound (50 mmol) in ether (15 ml) is added dropwise to a solution of **1** (50 mmol) at −120° in 5 min and the temperature is allowed to rise to −30°. Lithium tetrahydroaluminate powder (25 mmol) is then added in one portion. The temperature of the mixture rises slowly (sometimes external cooling is necessary to prevent overheating). The reaction mixture is stirred at room temperature for 30 min for **4a**, for 10 min for **4b** and **4d**. Work up as described above gives the alcohols **4**. For yields and physical data see Table 3.

Preparation of α,β-Unsaturated α-Chloro Ketones 5 and Aldehydes 6:
The neat alcohol **3** or **4** (40 mmol) is added during 10 min to a stirred mixture of 96% sulfuric acid (50 ml) and ether (10 ml) at −30°. Stirring is continued for 5 min at −20° (−10° for **4a**) and the mixture is poured on to crushed ice (200 g). The resultant mixture is extracted with ether (2 × 50 ml), the extract is washed with saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, the solvent removed under reduced pressure, and the residue distilled. For yields and physical data see Table 4 for ketones **5** and Table 5 for Aldehydes **6**.

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Table 1. 2-Chloro-1,1-difluoro-3-hydroxy-1-alkenes **2**[a]

Product No.	R^1	R^2	Yield [%]	b.p./torr	n_D^{20}	Molecular formula[b] or Lit. b.p./torr	I.R. (neat) $\nu_{C=C}$ [cm^{-1}]	^1H-N.M.R. (CCl_4) δ [ppm]	^{19}F-N.M.R. ($CCl_4/C_6H_5CF_3$) δ [ppm], J [Hz]
2b	C_6H_5	H	82	63–64°/0.05	1.5110	$C_9H_7ClF_2O$ (204.6)	1740	5.50 (m, 1H)	−25.0 (d), −29.1 (d), $^2J_{FF}=41$
2c	CH_3	CH_3	70	37–40°/13	1.4160	$C_5H_7ClF_2O$ (156.6)	1730	1.45 (2s, 6H)	−20.2 (d), −23.2 (d), $^2J_{FF}=45$
2d	$-(CH_2)_5-$		86	44–45°/0.05	1.4630	68–72°/8[3]	1725	1.4–1.8 (m, 10H)	−18.7 (d), −22.7 (d), $^2J_{FF}=43$

[a] For compound **2a** ($R^1=n$-C_3H_7, $R^2=H$) see Ref. [2].

[b] New compounds **2b** and **2c** gave satisfactory microanalyses (C ±0.27, H ±0.14).

Table 2. Alcohols **3**

Product No.	R^3	Yield[a] [%]	b.p./torr	*E*/*Z*-ratio	Molecular formula[b]	I.R. (neat) $\nu_{ClC=CF-}$ [cm^{-1}]	^1H-N.M.R. (CCl_4) δ [ppm]	^{19}F-N.M.R. ($CCl_4/C_6H_5CF_3$) δ [ppm], J [Hz]
3a	C_2H_5	80	43–45°/0.1	9	$C_8H_{14}ClFO$ (180.7)	1685	2.5 (d of q, 2H, $=CF-CH_2$), 4.8 (m, 1H, $-C\underline{H}OH-$)	*E*: −49.1 (t), $^3J_{HF}=23$ *Z*: −36.9 (t), $^3J_{HF}=25$
3a[c]	C_6H_5	80	105°/0.2	9	$C_{12}H_{14}ClFO$ (228.7)	1665	5.1 (d, of t, 1H, $-C\underline{H}OH-$, $^4J_{HF}=3$ Hz)	*E*: −43.6 (s) *Z*: −28.4 (s)
3a	$H_2C=CH-CH_2$	78	60–62°/0.1	6	$C_9H_{14}ClFO$ (192.7)	1680	3.20 (d of d, 2H, $=CF-CH_2$, $^3J_{HF}=23.5$ Hz); 4.82 (d of t, *E*) + 4.40 (d of t, *Z*) total 1H	*E*: −46.3 (t), $^3J_{HF}=23.5$ *Z*: −33.8 (t), $^3J_{HF}=23.5$
3b	C_2H_5	—	decomp.	4	$C_{11}H_{12}ClFO$ (214.7)	1680	2.45 (d of q, 2H); 5.9 (m, 1H)	*E*: −49.1 (t), $^3J_{HF}=23$ *Z*: −36.8 (t), $^3J_{HF}=23$
3c	C_2H_5	60	32–35°/0.2	1.8	$C_7H_{12}ClFO$ (166.6)	1670	2.5 (d of q) + 2.75 (d of q) total 2H	*E*: −43.9 (t), $^3J_{HF}=23$ *Z*: −30.2 (t), $^3J_{HF}=26$
3c	C_6H_5	—	decomp.	10	$C_{11}H_{12}ClFO$ (214.7)	1665	1.6 (2s, 6H)	*E*: −35.2 (s) *Z*: −13.7 (s)
3d	CH_3	70	49–55°/0.05	9	$C_9H_{14}ClFO$ (192.7)	1670	2.15 (d, $^3J_{HF}=18$ Hz) + 2.3 (d, $^3J_{HF}=20$ Hz) total 3H	*E*: −33.8 (q), $^3J_{HF}=18$ *Z*: −17.8 (q), $^3J_{HF}=20$

[a] Yields are based on the starting carbonyl compound.

[b] All new compounds gave satisfactory microanalyses (C ±0.38 %, H ±0.17 %).

[c] The alcohol of (*Z*)-configuration has already been described[2] (^{19}F-N.M.R.: $\delta=-28.4$ ppm); the other isomer is thus of (*E*)-configuration. By analogy with this result (F signal of (*E*)-isomer at higher field) we have assigned the (*E*)- and (*Z*)-configuration of the alcohols described. The (*E*)-isomer is the most abundant and has the shortest G.L.C. retention time on a Carbowax 20M (10 %, 2 m) column.

Table 3. 2-Chloro-1-fluoro-3-hydroxy-1-alkenes **4**

Product	Yield[a] [%]	b.p./torr	*E*/*Z*-ratio[b]	Molecular formula[c]	I.R. (neat) $\nu_{-CCl=CFH}$ [cm^{-1}]	^1H-N.M.R. (CCl_4) δ [ppm], J [Hz]	^{19}F-N.M.R. ($CCl_4/C_6H_5CF_3$) δ [ppm], J [Hz]
4a	81	30–35°/0.5	2.3	$C_6H_{10}ClFO$ (152.6)	1675	*E*: 4.75 (d of t, 1H, $^4J_{HF}=3$); 6.75 (d, 1H, $^2J_{HF}=81$) *Z*: 4.1 (t, 1H); 6.95 (d, 1H, $^2J_{HF}=79$)	*E*: −66.6 (d of d, $^2J_{HF}=81$, $^4J_{HF}=3$) *Z*: −68.0 (d, $^2J_{HF}=79$)
4b	—	decomp.	4.5	C_9H_8ClFO (186.6)	1670	*E*: 5.9 (d, 1H, $^4J_{HF}=3$); 6.65 (d, 1H, $^2J_{HF}=80$) *Z*: 5.1 (s, 1H); 6.95 (d, 1H, $^2J_{HF}=78$)	*E*: −66.6 (d of d, $^2J_{HF}=80$, $^4J_{HF}=3$) *Z*: −68.5 (d, $^2J_{HF}=78$)
4d	80	37–55°/0.01	0.8	$C_8H_{12}ClFO$ (178.6)	1670	*E*: 6.7 (d, 1H, $^2J_{HF}=79$) *Z*: 7.15 (d, 1H, $^2J_{HF}=79$)	*E*: −58.8 (d, $^2J_{HF}=79$) *Z*: −71.2 (d, $^2J_{HF}=79$)

[a] Yields are based on the starting carbonyl compound.

[b] Determination of configuration: Alcohols **4a** and **4b**: configuration (*E*) has been assigned to isomers showing a $^4J_{HF}$ coupling constant. Alcohol **4d**: with 0.1 eq. of Eu(fod)$_3$, the smaller shift (0.07 ppm) of the proton geminal to F has been assigned to the (*E*)-isomer and the greater shift (0.27 ppm) to the (*Z*)-isomer. In the three cases the signal of the proton geminal to F in the (*E*)-isomers is at lower field than that of the corresponding (*Z*)-isomers.

[c] All new compounds gave satisfactory microanalyses (C ±0.37 %, H ±0.07 %).

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Table 4. α,β-Unsaturated α-Chloro Ketones **5**

Product No.	R^3	Yield[a] [%]	b.p./torr	n_D^{20}	Molecular formula[b] or Lit. b.p./torr	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4)[c] δ [ppm]
5a	C_2H_5	60	86°/13	1.4655	$C_8H_{13}ClO$ (160.6)	1695 (C=O), 1620 (C=C)	2.35 (d of t, 2H); 2.75 (q, 2H); 7.0 (t, 1H)
5a	C_6H_5	55	96–103°/0.1	1.5470	90–92°/0.01[2]	1670 (C=O), 1620 (C=C)	2.45 (d of t, 2H); 6.65 (t, 1H)
5b	C_2H_5	55	92–93°/0.03 m.p. 36°	—	$C_{11}H_{11}ClO$ (194.7)	1690 (C=O), 1600 (C=C)	2.85 (q, 2H); 7.70 (s, 1H)
5c	C_2H_5	45	58–60°/12	1.4670	$C_7H_{11}ClO$ (146.6)	1690 (C=O), 1600 (C=C)	2.05 (s, 3H); 2.15 (s, 3H); 2.75 (q, 2H)
5c	C_6H_5	62	76.5–78°/0.05	1.5550	75–76°/0.01[2]	1670 (C=O), 1600 (C=C)	1.75 (s, 3H); 2.0 (s, 3H)
5d	CH_3	54	46°/0.05	1.5035	$C_9H_{13}ClO$ (172.6)	1690 (C=O), 1590 (C=C)	2.35 (s, 3H); 2.5 (m, 4H)

[a] Yields are based on the starting carbonyl compound; they are identical with or without isolation of alcohols **3**.

[b] All new compounds gave satisfactory microanalyses (C ±0.35%, H ±0.12%) and showed molecular ion peaks in the mass spectra.

[c] Determination of configuration: With 0.3 eq. of Eu(fod)$_3$ we have found the following shifts ($\Delta\delta$):— methyl *cis* to C=O: $\Delta\delta = 2.80$ ppm for **5c** ($R^3 = C_2H_5$) and 2.10 ppm for **5c** ($R^3 = C_6H_5$)– methyl *trans* to C=O: $\Delta\delta = 1.10$ ppm for **5c** ($R^3 = C_2H_5$) and 0.95 ppm for **5c** ($R^3 = C_6H_5$). For the vinylic CH_2 of **5a** ($R^3 = C_2H_5$) and **5a** ($R^3 = C_6H_5$), we have found respectively $\Delta\delta = 1.10$ and 1.0 ppm; we deduce that these ketones are the (*Z*)-isomers. From these data, the ketone **5a** ($R^3 = C_6H_5$) described in Ref. [2] as (*E*)-should be written as (*Z*), **5b** consists of one isomer which is probably the (*Z*)-one.

Table 5. α,β-Unsaturated α-Chloro Aldehydes **6**

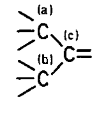
Product[a]	Yield[b] [%]	b.p./torr	Lit. b.p./torr	n_D^{20}	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
6a	60	70–71°/11	60–61°/6[12]	1.4774	1700 (C=O), 1625 (C=C)	2.5 (d of t, 2H); 7.15 (t, 1H); 9.5 (s, 1H)
6b[c]	72	88–89°/0.03	m.p. 34–36°[15]	m.p. 29–32°	1690 (C=O), 1610 (C=C)	7.35 (s, 1H); 9.25 (s, 1H)
6d	58	67–68°/0.01	65°/0.1[11]	1.5340	1685 (C=O), 1600 (C=C)	2.65 (t, 2H); 2.90 (t, 2H); 9.95 (s, 1H)

[a] All compounds showed molecular ion peaks in the mass spectra.

[b] Yields are based on the starting carbonyl compound; they are identical with or without isolation of alcohols **4**.

[c] This aldehyde is identical (^{1}H-N.M.R.) with that previously described as (*Z*)[16].

Table 6. ^{13}C-N.M.R. Data of Characteristic Carbon Atoms in Carbonyl Compounds **5** and **6** (chemical shifts δ [ppm] for $CDCl_3$/TMS solutions)



Carbon Atom	**5a** $R^3 = C_2H_5$	**5a** $R^3 = C_6H_5$	**5b** $R^3 = C_2H_5$	**5c** $R^3 = C_2H_5$	**5c** $R^3 = C_6H_5$	**5d** $R^3 = CH_3$	**6a**	**6b**	**6d**
a	31.8	31.8	133.3	22.6	21.2	31.6	31.8	132.7	30.9
b	—	—	—	24.4	21.4	32.9	—	—	34.3
c	140.7	145.2	135.0	144.4	135.7	149.3	152.7	145.9	162.6
d	134.1	133.5	130.2	126.3	121.8	123.5	136.2	132.1	127.7
e	194.6	190.0	196.1	198.6	191.5	196.4	186.2	186.8	182.0

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[1] F. G. Drakesmith, R. D. Richardson, O. J. Stewart, P. Tarrant, *J. Org. Chem.* **33**, 286 (1968).

[2] D. Masure, R. Sauvêtre, J. F. Normant, J. Villieras, *Synthesis* **1976**, 761.

[3] K. Okuhara, *J. Org. Chem.* **41**, 1487 (1976).

[4] C. Chuit, R. Sauvêtre, D. Masure, M. Baudry, J. F. Normant, J. Villieras, *J. Chem. Res.* **1977**, 104.

[5] R. Sauvêtre, D. Masure, C. Chuit, J. F. Normant, *Synthesis*, **1978**, 128.

[6] L. I. Zakharkin, *Izvest. Akad. Nauk SSSR* **1956**, 313; *C. A.* **50**, 15492 (1956).

[7] D. B. Denney, S. T. Ross, *J. Org. Chem.* **27**, 998 (1962).

[8] E. Elkik, P. Vaudescal, *C. R. Acad. Sci.* **261**, 1015 (1965).

[9] L. Skatteboel, *J. Org. Chem.* **31**, 1554 (1966).

[10] SNPA, *Netherlands Patent Appl.* 6609655; *C. A.* **67**, 81807 (1967).

[11] J. Ficini, J. C. Depezay, *Tetrahedron Lett.* **1968**, 937.

[12] W. E. Parham, K. S. Yong, *J. Org. Chem.* **35**, 683 (1970).

[13] P. Amice, L. Blanco, J. M. Conia, *Synthesis* **1976**, 196.

[14] J. Villieras, P. Perriot, J. F. Normant, *Synthesis* **1978**, 29.

[15] K. V. Auwers, R. Hügel, *J. Prakt. Chem.* **143**, 179 (1935).

[16] C. Beauté, Z. W. Wolkowski, J. P. Merda, D. Lelandais, *Tetrahedron Lett.* **1971**, 2473; and personal communication.

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