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IN THE BLIND SPOT OF DIFFUSION CONTROL : 2-FLUOROALLYL CATIONS AND THEIR VARIOUS POSSIBILITIES FOR STABILIZATION

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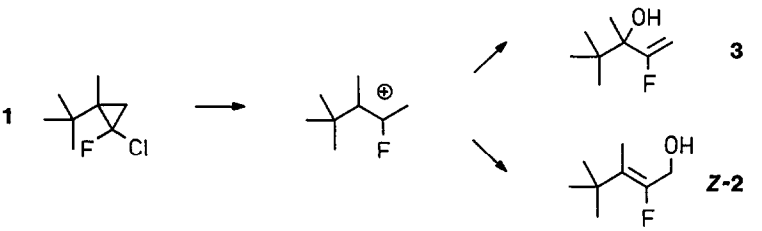
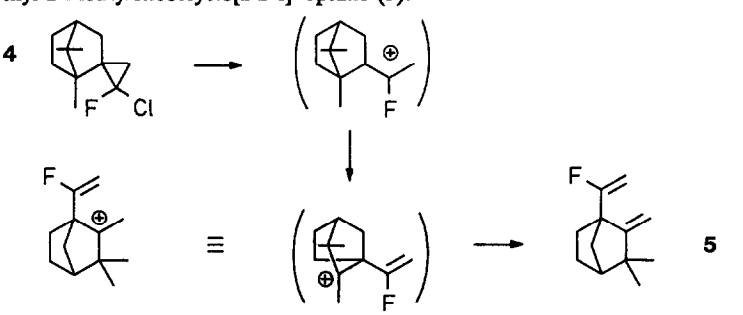
Summary : Three new model substrates of the chlorofluorocyclopropane type (**6**, **11** and **14**) were submitted to silver ion-assisted ring opening. No rearrangement, but only fragmentation or direct solvolysis was found to take place. In the latter case, primary rather than tertiary 2-fluoroallyl alcohols are formed almost exclusively. Nucleophilic attack at the unsubstituted terminus of the 2-fluoroallyl cation is apparently favored for steric reasons

A systematic investigation of the ring-opening solvolysis of *gem*-chlorofluorocyclopropanes has revealed a striking difference between the campher derived model compound **4** and a monocyclic analogon **1** [1] Upon treatment with silver nitrate in the presence of aqueous pyridine the *syn* diastereomer of 2-*tert*-butyl-1-chloro-1-fluoro-2-methylcyclopropane (**1**) generated a 2-fluoroallyl cation which upon addition of water afforded a 1 : 3 mixture of (*Z*)-2-fluoro-3,4,4-trimethyl-2-penten-1-ol (*Z*-**2**) and 2-fluoro-3,4,4-trimethyl-1-penten-3-ol (**3**).

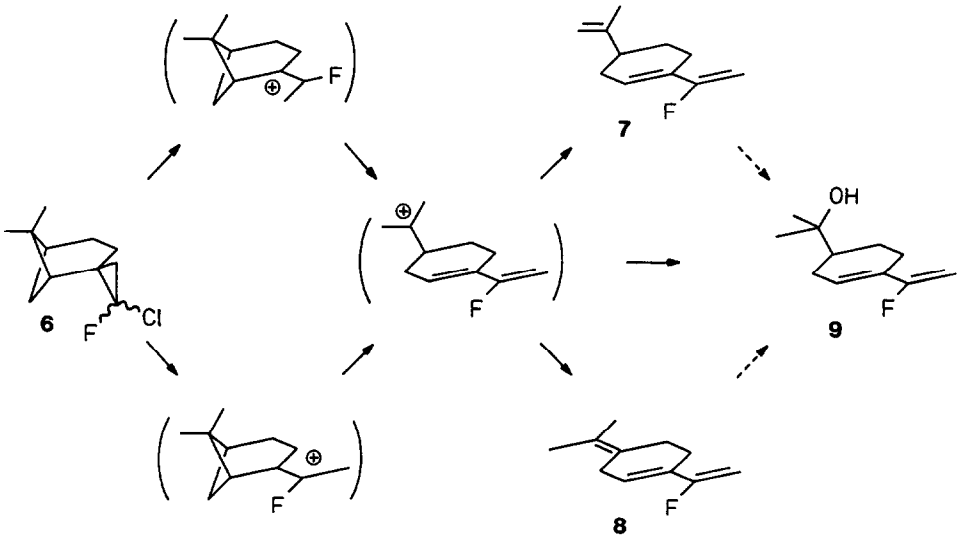


In contrast, the spiro compound **4**, prepared by Wittig methylenation of camphor and subsequent addition of chlorofluorocarbene, produced a 2-fluoroallyl cation which immediately underwent a Wagner-Meerwein type rearrangement giving rise to a *tert*-alkyl cation. The latter became stabilized by proton loss to afford 1-(1-fluorovinyl)-3,3-dimethyl-2-methylenebicyclo[2 2 1]heptane (**5**). [1]

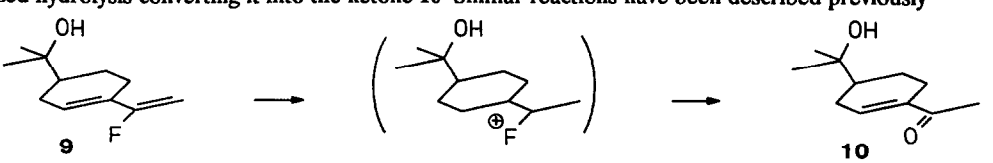


Initially we attempted to rationalize this divergent behavior by postulating concertedness between ring opening and alkyl migration in the case of the spiro compound **4** and stepwise reaction of the monocyclic analog **1** The latter was assumed to suffer from a conformational discrimination Inspection of molecular models, however, did not support this view The ring strain of the bornyl skeleton is probably the true reason why the campher derived 2-fluoroallyl cation rearranges faster than it adds water This strain is substantially attenuated at the transition state of the alkyl migration. We wondered now whether this driving force would be powerful enough to bring about the rearrangement of the 2-fluoroallyl cation intermediate also in cases where only a *secondary* carbenium ion can result We would expect such an isomerization to be still exothermal In the gas phase at least, the hydride affinity of an allyl cation is somewhat higher than that of secondary alkyl cations [2]. The fluorine substituent at the nodal position should further destabilize the positively charged entity

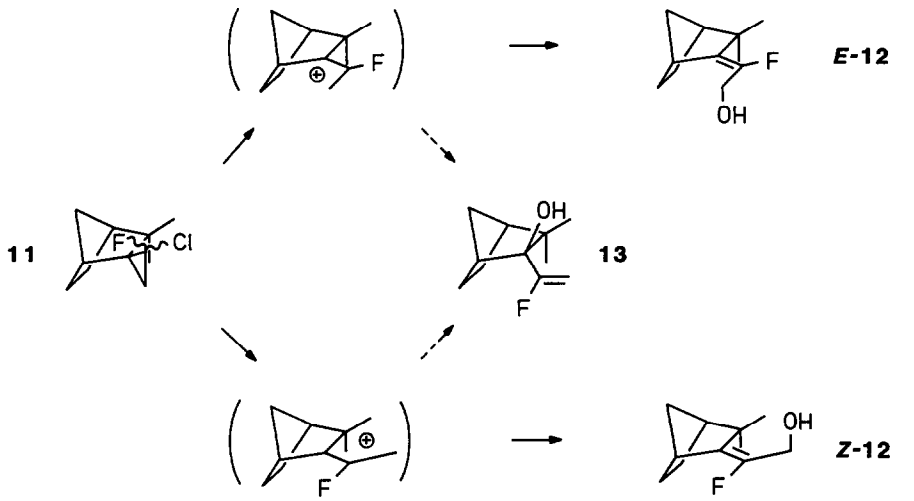
As the first example of this kind we studied the solvolysis of diastereomeric chlorofluorocyclopropanes **6** prepared from β-pinene Neither straightforward hydrolysis nor rearrangement to a secondary alkyl cation but rather a stepwise fragmentation was observed Bond scission between the *gem*-dimethyl substituted bridge and the chain adjacent bridge-head position produced again a tertiary carbocation The latter underwent stabilization by deprotonation, leading to a mixture of fluorotrienes **7** and **8** (together 28%), and concomitant addition of water to give the alcohol **9** (51%) The proportion of the latter product increased at the expense of the fluorohydrocarbons **7** and **8** with time



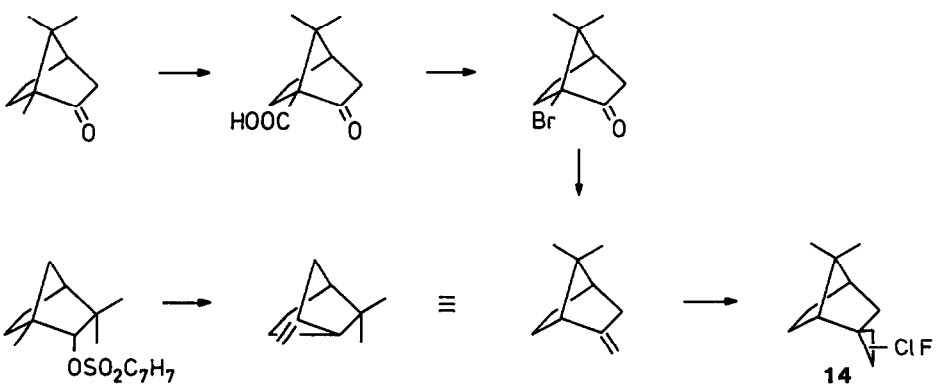
On the other hand, some of the alcohol **9** was progressively consumed by polymerization and more of it by acid-catalyzed hydrolysis converting it into the ketone **10** Similar reactions have been described previously [3]



The camphene derived diastereomeric chlorofluorocyclopropanes **11** opened smoothly the three-membered ring to set free a pair of geometrically isomeric 2-fluoroallyl cations which lack any attractive mode of fragmentation. On the other hand, they could be transformed into a secondary or tertiary carbocation by methylene or methyl migration, respectively Neither type of rearrangement did really occur. The only products isolated were (*Z*)- and (*E*)-2-(3,3-dimethyl-2-bicyclo[2.2.1]heptylidene)-2-fluoroethanol (*Z*- and *E*-**12**, 14% and 55%, respectively) and trace amounts of *endo*-2-(1-fluorovinyl)-3,3-dimethyl-*exo*-2-bicyclo[2 2 1]heptanol (**13**, 2%).

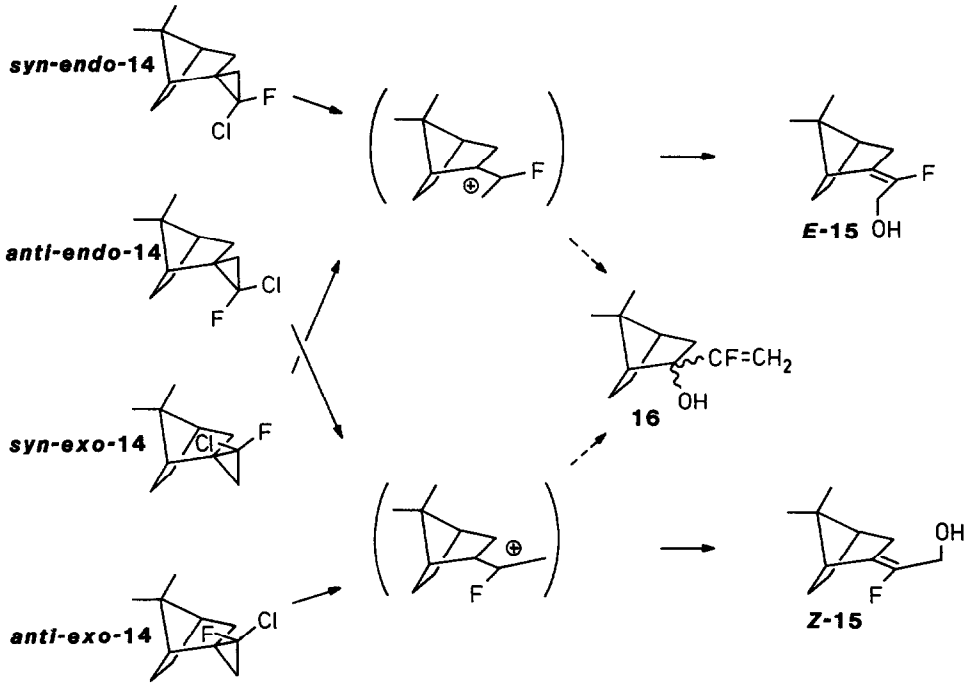


An analogous outcome was noticed when the isomeric chlorofluorocyclopropane **14** was submitted to the silver ion-assisted solvolysis. Substrate **14** was prepared by addition of chlorofluorocarbene to 7,7-dimethyl-2-methylenebicyclo[2.2 1]heptane ("α–fenchene"). This starting material is directly accessible by solvolytic elimination of *endo*-fenchyl *p*-toluolsulfonate [4] or on a more lengthly route starting with campher and proceeding *via* 1-bromo-7,7-dimethyl-2-bicyclo[2.2 1]heptanone [5]



The chlorofluorocyclopropane **14** was obtained as an inseparable mixture of diastereomers with relative amounts of 10 : 40 : 10 : 40. The individual signals in the ^{19}F-nmr spectrum were well resolved and, on the basis of chemical shifts and ^{5}J or ^{6}J coupling constants, *syn-endo*, *anti-endo*, *syn-exo* and *anti-exo* configurations were

tentatively assigned. The solvolytic ring opening of the mixture gave, besides very little of the tertiary alcohol **16** (< 1%), (*Z*)- and (*E*)-3-(7,7-dimethyl-2-bicyclo[2.2.1]heptylidene)-2-fluoro-2-propen-1-ol (*Z*- and *E*-**15**; 79%) in the approximate ratio of 1 : 2.



Since the solvolytic opening of three-membered rings follows a disrotatory inversion mode [6], we would have expected the (*Z*) and (*E*) isomers of **15** to emerge in a 1 · 4 rather than 1 : 2 ratio. For the moment we have no convincing explanation for this discrepancy We have considered the possibility of an acid catalyzed isomerization of initially formed **16** to **15** (and, by analogy, of **13** to **12**), but have provisionally rejected it on the basis of indirect evidence.

The addition of water to a reactive carbocation is generally considered to be a diffusion controlled process having a negligeable activation barrier ($E_a \leq 3$ kcal/mol). Indeed the 3,4,4-trimethyl-2-penten-1-yl cation which results from the ionization of the chlorofluorocyclopropane **1** undergoes hydration faster than methyl migration although the latter process should require an activation energy of not more than 2 or 3 kcal/mol as estimated by analogy. [7] Therefore, the general preference [3] for the tertiary (or secondary) rather than the primary fluoroallyl alcohol appears not to be the outcome of an ordinary competition arbitrated by two up-hill potentials of different height. The fixation of a water molecule at the substituted, more positively charged terminus of the allyl moiety causes the least perturbation of the electron distribution and notably the C,C bond distances. Thus it should be favored for probability reasons ("principle of the least motion" [8]). The ordinary regioselectivity of nucleophilic addition may, however, be altered if severe steric hindrance overrides other effects. This is obviously the case with the cations derived from the chlorofluorocyclopropanes **1**, **11** and **14**

EXPERIMENTAL PART

1 General

Nuclear magnetic resonance spectra of hydrogen nuclei (^{1}H-NMR) were recorded at 60 MHz or, if marked with an asterisk, at 250 or 360 MHz, those of fluorine nuclei (^{19}F-NMR) at 84.7 MHz or, if marked with an asterisk, at 188 MHz. Chemical shifts are given relative to the signal of tetramethylsilane and trifluoromethylbenzene, respectively For other details see articles on related topics [9]

2 Chlorofluorocyclopropanes

General procedure [10] A round-bottom flask was cooled to 0 °C and filled with benzyltriethylammonium chloride (2 3 g, 10 mmol), potassium hydroxide pellets (20 g, 0 36 mol), the olefin (0.10 mol) and precooled dichlorofluoromethane ("Freon-21", 0.10 L, 0 14 kg, 1.4 mol) The flask was closed with a dry ice/methanol condenser and placed in the cavity of an ultrasonicator which was put in action. After 10 h, the remaining haloform was condensed into a collector bottle, Celite (kieselgur, diatomite) was added, the mixture was triturated with diethyl ether (0 10 L) and filtered with suction. The filtrate was concentrated. The product was isolated by distillation under reduced pressure

2'-Chloro-2'-fluoro-6,6-dimethylbicyclo[3.1.1]heptane-2-spiro-1'-cyclopropane (6) 85%, bp 58 - 62 °C/0 2 mmHg - ^{1}H-NMR* . 2.3 (2 H, m), 2.0 (3 H, m), 1.80 (~ 0.5 H, td, *J* 5.5, 3.2), 1.67 (~ 0.5 H, t, *J* 5.5), 1.50 (1 H, dd ?, *J* 10 5, 3 2), 1 3 (2 H, m), 1.26 (~ 1.7 H, s), 1 24 (~ 1.3 H, s), 1.09 (~ 0.5 H, dd, *J* ~ 7, ~ 6), 1.04 (~ 0.5 H, dd, *J* 8 0, 7.5), 0 97 (~ 1.3 H, s), 0.95 (~ 1.7 H, s) - ^{19}F-NMR : -61 (dd, *J* 18, 8) and -63 (d, broad, *J* 18) with ~ 1 1 intensities. - Analysis . calc. for $C_{11}H_{16}ClF$ (202.70) C 65.18, H 7 96, found C 65.21, H 7.97%.

2'-Chloro-2'-fluoro-3,3-dimethylbicyclo[2.2.1]heptane-2-spiro-1'-cyclopropane (11) 15% (81% of camphene recovered), bp 61 - 64 °C/0.2 mmHg. - ^{1}H-NMR* : 2 2 - 0 8 (16 H, m, broad, including six sharp, s-like peaks at δ 1 18, 1 13, 1 12, 1 06, 1 02 and 0 90 with approximate relative intensities of 1 1 1 1 . 2 2) - ^{19}F-NMR . -49 (d-like m, *J* ~ 20) and -52 (d, *J* 24) with ~ 1 5 intensities

2'-Chloro-2'-fluoro-7,7-dimethylcyclo[2.2.1]heptane-2-spiro-1'-cyclopropane (14) 60%; bp 85 - 87 °C/11 mmHg - ^{1}H-NMR* 2.1 (1 H, m), 1.6 (7 H, m), 1.18 (0 5 × 3 H, s), 1.15 (0.2 × 3 H, s), 1 05 (0.3 × 3 H, s), 1 00 (3 H, s), 1 0 (2 H, m) - ^{19}F-NMR* . -73.3 (dd, *J* 16 0, 6.2 "*anti-endo*" ?), -74.4 (dt, *J* 16.0, 6 0 "*syn-endo*" ?), -76.0 (dm, *J* 16 0, "*anti-exo*" ?), -76.5 (ddm, *J* 16 0, 6 4 "*syn-exo*" ?). - MS 204 + 202 (14% + 46%, M^+ [^{37}Cl + ^{35}Cl]), 174 (93%), 94 (100%) - Analysis calc for $C_{11}H_{16}ClF$ (202.70) C 65 18, H 7 96, found C 64 97, H 7 74%

3 Ring Opening Reactions

General Procedure The chlorofluorocyclopropane (50 mmol) was added to a solution of silver nitrate (21 0 g, 125 mmol) in pyridine (10 0 mL, 9 8 g, 124 mmol) and water (10.0 mL) The heterogeneous mixture was magnetically stirred and heated to reflux during 24 h (100 h in the case of 14) After centrifugation, the supernatant liquid was decanted from the precipitate which was thoroughly washed with diethyl ether (25 mL). The liquid phase was also extracted with ether (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated. The residue was distilled and the crude products were purified or separated by column chromatography or preparative gas chromatography.

1-(1-Fluoroethenyl)-4-(1-methylethenyl)cyclohexene (7) and **1-(1-fluoroethenyl)-4-(1-methylethylidene)-cyclohexene (8)** 28%; bp 65 - 70 °C/1 mmHg. - Analysis calc. for $C_{11}H_{15}F$ (166.24) C 79.48, H 9.10, found C 78.88, H 9 00% - The two components were separated by preparative gas chromatography (6 m, 20% Carbowax 20 M, 135 °C) - 7 ^{1}H-NMR · 6.28 (1 H, t-like m, *J* ~ 5), 4 77 (2 H, symm. m), 4.61 (1 H, dd, *J* 18, 3), 4.44 (1 H, dd, *J* 51, 3), 2 2 (7 H, m), 1 75 (3 H, t, *J* 1) - ^{19}F-NMR -31 (dd, *J* 51, 18). - 8 :^{1}H-NMR : 6.27 (1 H, t, *J* 4.5), 4.61 (1 H, dd, *J* 18, 3), 4 44 (1 H, dd, *J* 51, 3), 3 0 (2 H, m), 2 3 (4 H, m), 1 70 (6 H, s, broad) - ^{19}F-NMR : -32 (dd, *J* 51, 19).

1-(1-Fluoroethenyl)-4-(1-hydroxy-1-methylethyl)cyclohexene (9) : 33%; bp 101 - 104 °C/1 mmHg. - ^{1}H-NMR · 6 22 (1 H, t-like m, $J \sim 5$), 4.61 (1 H, dd, J 18, 3), 4.44 (1 H, dd, J 51, 3), 1 91 (1 H, s), 2.1 (4 H, m), 1.4 (3 H, m), 1.15 (6 H, s). - ^{19}F-NMR -32 (dd, J 51, 18).

1-[4-(1-Hydroxy-1-methylethyl)-1-cyclohexenyl]ethanone (10) : 20%; bp 141 - 143 °C/1 mmHg. - ^{1}H-NMR : 6.88 (1 H, t-like m, $J \sim 5$), 2.17 (3 H, s), 2.14 (1 H, s), 2.1 (4 H, m), 1.4 (3 H, m), 1.14 (6 H, s). - Analysis : calc. for $C_{11}H_{18}O_2$ (182 26) C 72 49 H 9.95, found C 72.32, H 9.99%

2-(3,3-Dimethyl-2-bicyclo[2.2.1]heptylidene)-2-fluoroethanol (12) . 66%; bp 91 - 94 °C/1 mmHg. - Analysis : calc. for $C_{11}H_{17}FO$ (184 25) C 71 71, H 9 30; found C 71.90, H 9.33%. - The (*Z*) and (*E*) isomer were present in a 4 1 ratio. The two components were separated by preparative gas chromatography (6 m, 20% Carbowax 20 M, 185 °C) - *Z*-**12** . mp 52 - 53 °C. - ^{1}H-NMR : 4 17 (2 H, d, J 22), 2.79 (1 H, s, broad), 1.92 (1 H, s), 2 1 - 0.9 (7 H, m), 1 19 (3 H, s), 1.15 (3 H, s). - ^{19}F-NMR . -41 (t, J 23). - *E*-**12** : ^{1}H-NMR : 4.50 (2 H, d, J 22), 3.15 (1 H, s, broad), 2.29 (1 H, s), 2.1 - 0 9 (7 H, m), 1.15 (3 H, s), 1.11 (3 H, s). - ^{19}F-NMR : -48 (t, J 23).

The lowest boiling fraction contained a by-product, presumably the tertiary alcohol **13** (1 - 5%), which showed a characteristic 1-fluorovinyl signal ($\delta \sim 4$ 5, 2 × dd, J_{HF} 49, 18)

2-(7,7-Dimethyl-2-bicyclo[2.2.1]heptylidene)-2-fluoroethanol (15) 79%; bp 105 - 110 °C/10 mmHg. - Analysis : calc for $C_{11}H_{17}FO$ (184 25) C 71 71, H 9 30, found C 71 68, H 9 03% - Under standard conditions the (*Z*) and (*E*) isomers were obtained in a 2 1 or 5 2 ratio, attempts to separate the two components failed - ^{1}H-NMR* : 4 20 (0 3 × 2 H, dd, J 21.6, 1.5), 4.15 (0 7 × 2 H, dd, J 21.0, 1.5), 2 50 (0 7 × 1 H, dm, J 4 0), 2 45 (1 H, ddd, J 15.4, 7 0, 3.3), 2 21 (0.3 × 1 H, t, J 3.5), 2.0 (1 H, m), 1 8 (6 H, m), 1.00 (3 H, s), 0.96 (3 H, s) - ^{19}F-NMR* : -62.1 (0.7 F, tm, J 21.0), -63.1 (0 3 F, tm J 21.0). - **Acetate** : bp 225 - 229 °C - Analysis : calc. for $C_{13}H_{19}FO_2$ (226 29) C 69 00, H 8 46; found C 68.78, H 8.52%

The presence of a by-product in the crude reaction mixture is revealed by a ^{1}H-NMR signal typical for the 1-fluorovinyl moiety ($\delta \sim 4.5$, 2 × dd, J_{HF} 49, 18). This may well be caused by trace amounts (< 1%) of the tertiary alcohol **16**

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[10] This protocol is an improved version of former ones [3] which can still be recommended for application in routine cases