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Regioselectivity of the ring opening of propene oxides bearing electron-withdrawing substituents at the methyl group with Olah's reagent

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Abstract

The regiochemistry of the hydrofluorination of terminal epoxides with Olah's reagent (Py·9HF) is dependent on the electron-withdrawing character of the β-substituents. Phenoxy ethers with different substitution patterns of the aromatic ring and several *N*-heterocycles were examined as β-substituents.

Keywords: Terminal epoxides; Hydrofluorination; Regiochemistry; Olah's reagent

1. Introduction

The regioselectivity of the formal addition of HX (X=Br, Cl, I) to terminal epoxides and the synthesis of β-halohydrins have been the topics of several papers [1,2]. Cleavage of terminal epoxides with nucleophilic agents proceeds via polar transition states and the nucleophile attacks at the terminal carbon atom (S_N2-like reaction) [3]. On the other hand, ring opening in the presence of Lewis acids such as metal-halides affords a regioselective formation of 2-halohydrins (S_N1-like reaction) [4]. The regioselectivity depends on the Lewis acid character of the metal halide. Highly regioselective syntheses for both isomers have been described in the literature [5,6].

For regioselective syntheses of vicinal fluorohydrins, these considerations had to be modified as anhydrous HF is usually not a useful source of fluoride ions for ring opening reactions of epoxides. However, anhydrous HF can be combined with organic bases like amines [7–9] (e.g. Py·9HF, $Et_3N·3HF$). The regioselectivity of the ring opening using such reagents depends on the amount and the identity of the amine, which influences the nucleophilicity of the fluorinating species [10–12]. With reagents which contain stronger nucleophilic species like $Et_3N·3HF$ [12], *i*-$Pr_2NH·2HF$ [11] or KHF_2-complexes [13–15] the ring opening of epoxides occurs in an S_N2-like manner and mainly terminally fluorinated compounds are formed.

In ring opening reactions with Olah's reagent (Py·9HF) as HF-source the regioisomer derived from the more stable carbocation is formed (S_N1-like reaction) though there is no evidence for the formation of a free cationic center [16,11]. Showing the dependence on the substrate it is possible to shift the regioisomeric ratio in favor of the terminally fluorinated alcohol [11]. We now want to show that in similar molecules it is also possible to change the favored attack of fluoride in an acidic, hence less nucleophilic, medium as a result of the electron-withdrawing character of functional groups.

2. Results

In initial reactions with Olah's reagent we saw that allylbenzene oxide **1** gave exclusively the fluorohydrin **2** (primary alcohol) [17], while terminal epoxides with phenoxy groups **3** as β-substituents yielded mixtures of regioisomeric vicinal fluorohydrins **4** and **5** (Scheme 1).

On the other hand, ring opening of **3a** (R=H) with KHF_2 in the presence of catalytic amounts of $Bu_4N^+H_2F_3^-$ gave **4a** exclusively [18], while the reaction of **1** with KHF_2 gave a 1:9 mixture of **2** and its regioisomer [12].

The pharmacologically interesting starting materials **3** can be easily prepared by reaction of epichlorohydrin with the corresponding phenols under basic conditions. Thus, it is

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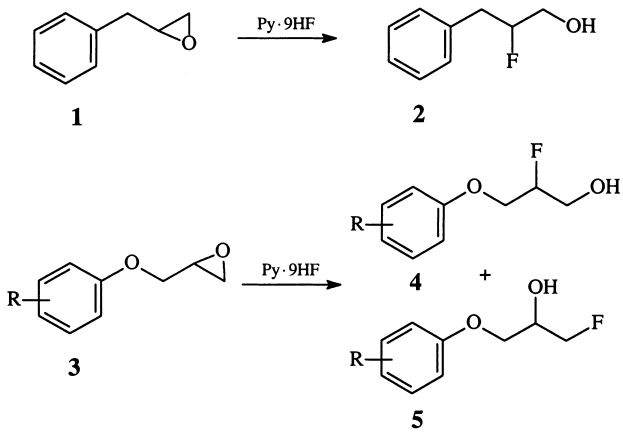
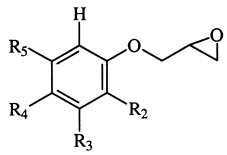


Scheme 1. Hydrofluorination of β-substituted epoxides.

possible to generate a great variety of phenoxyethers with different substitution patterns on the aromatic ring by known procedures [19,20].

Compounds **3a–k** were converted with Py·9HF (Table 1). They include both electron-withdrawing (*o*-, *p*-NO_2) and electron-donating (*o*-, *m*-, *p*-CH_3) groups. For the halogen-substituted compounds (*p*-F, *o*-, *p*-Cl, *p*-Br) we expected rather non-uniform results ($-I/+M$-effect).



3a-k

To get the most original information about the regioisomeric ratio we chose integration of the ^{19}F NMR spectra of the worked-up but unpurified reaction mixture. In order to determine also small amounts of fluorinated compounds we used proton-decoupled ^{19}F NMR spectra. However, the nuclear overhauser effect (NOE) causes a stronger amplification than would have been expected from the multiplets [21]. The intensification factor is dependent on the corresponding gyromagnetic ratio of the considered nuclei (^1H, ^{19}F).

$$\eta = \frac{\gamma_H}{2\gamma_F} \quad \text{(H saturated, F observed)},$$

$$\eta \cong 0.5 \quad \text{for } \gamma_H = 26.752 \times 10^7 \,\text{rad}\,\text{T}^{-1}\,\text{s}^{-1},$$

$$\gamma_F = 25.167 \times 10^7 \,\text{rad}\,\text{T}^{-1}\,\text{s}^{-1},$$

$$I = (1+\eta)I_0,$$

with I_0 the intensity without NOE, I the total intensity, $1+\eta$ the intensification factor

$$\Rightarrow I = 1.5\,I_0 \quad \text{for } \eta = 0.5.$$

The theoretical intensification of the signals in a proton-decoupled ^{19}F NMR spectrum caused by NOE is calculated to a maximum of 50%. However, the error from the integration of primary and secondary fluorohydrins is much lower. Moreover, in this paper the results of the ring opening experiments are compared to each other so that in this case the NOE can be neglected. The determination of the regioisomeric ratio from the proton-decoupled ^{19}F NMR spectrum is therefore a good method to quantify the electronic influence of the substituents in the phenyl ring during the hydrofluorination.

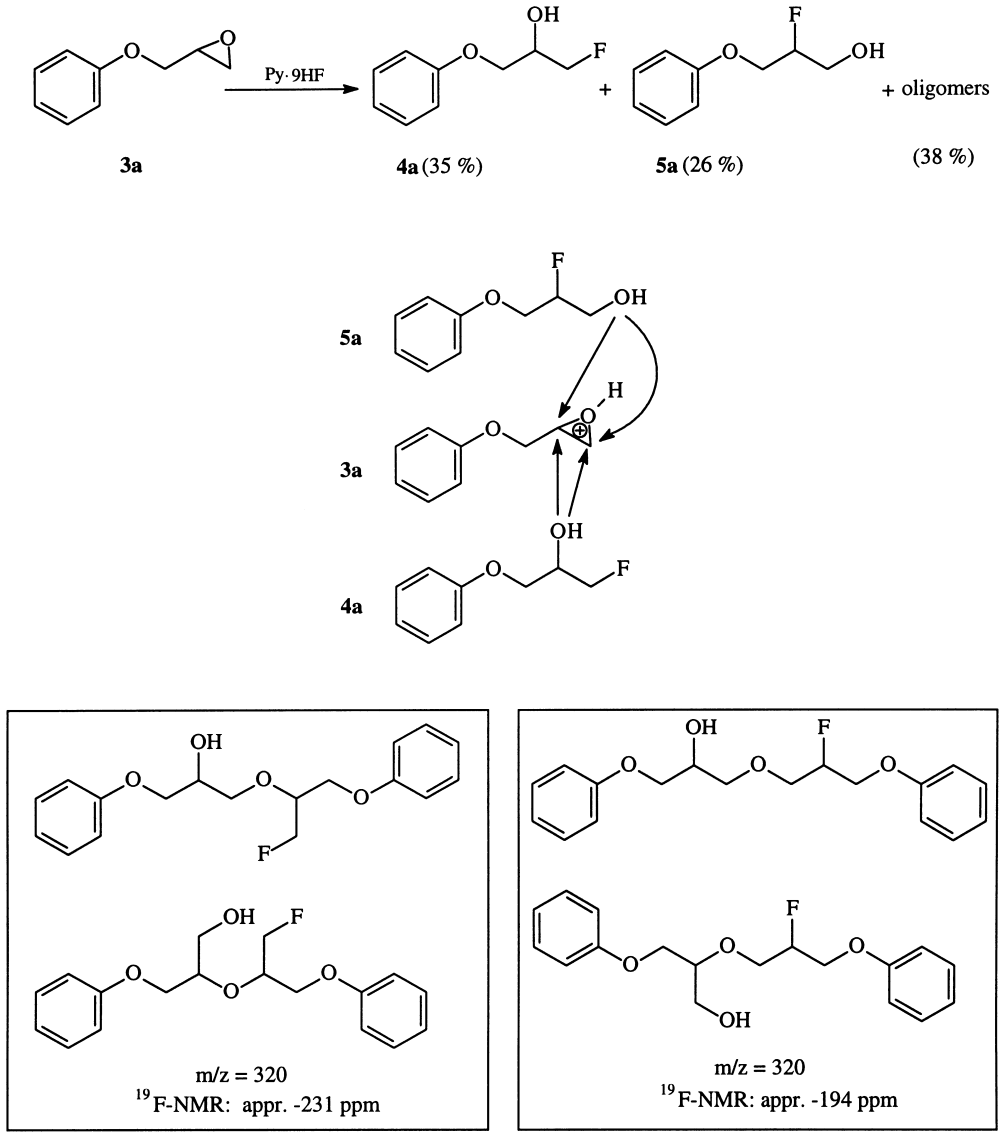
However, the conversion of **3a–k** with Olah's reagent showed beside the expected fluorohydrins a significant amount of fluorinated side products. Identification of them by mass spectrometry showed that under the acidic conditions of the hydrofluorination a competitive acid-catalyzed cleavage of the educt by the already formed regioisomeric fluorohydrins occurred. This is shown in Scheme 2 using the unsubstituted phenoxyether **3a** as an example.

The probability of attack of both **4** and **5** at the two carbon atoms of the epoxides **3** leads to four constitutional isomers distinguished by different shifts in the proton-decoupled ^{19}F NMR spectra (Scheme 3). Diastereomers could not be discovered in the ^{19}F NMR spectra.

The very small peaks could be explained by the fact that the free hydroxyl-function of the "dimeric" products can react again with the epoxide. Corresponding fragments of

Table 1
Regioisomeric ratio of the hydrofluorination of **3a–k** with Olah's reagent

Educt **3**	R_2	R_3	R_4	R_5	Primary fluorohydrin **4**	Secondary fluorohydrin **5**	Primary oligomer fluorohydrins	Secondary oligomer fluorohydrins	Σ primary fluorohydrins	Σ secondary fluorohydrins
a	H	H	H	H	35.2	26.4	11.9	26.4	47	53
b	CH_3	H	H	H	38.6	36.9	7.7	16.9	46	54
c	H	CH_3	H	H	35.8	30.4	12.4	21.4	48	52
d	H	H	CH_3	H	35.1	29.5	10.8	24.6	46	54
e	H	CH_3	H	CH_3	49.4	19.6	13.5	17.5	63	37
f	H	H	F	H	36.1	23.5	15.9	24.5	52	48
g	Cl	H	H	H	32.0	20.0	18.5	29.5	51	49
h	H	H	Cl	H	36.6	23.0	15.1	25.3	52	48
i	H	H	Br	H	37.1	24.1	14.5	24.3	52	48
j	NO_2	H	H	H	45.7	15.9	20.1	18.3	66	34
k	H	H	NO_2	H	43.8	14.3	26.1	15.8	70	30



Scheme 2. Products formed from **3a** with Olah's reagent.

"trimeric" products were also found in the mass spectra of the crude product mixture.

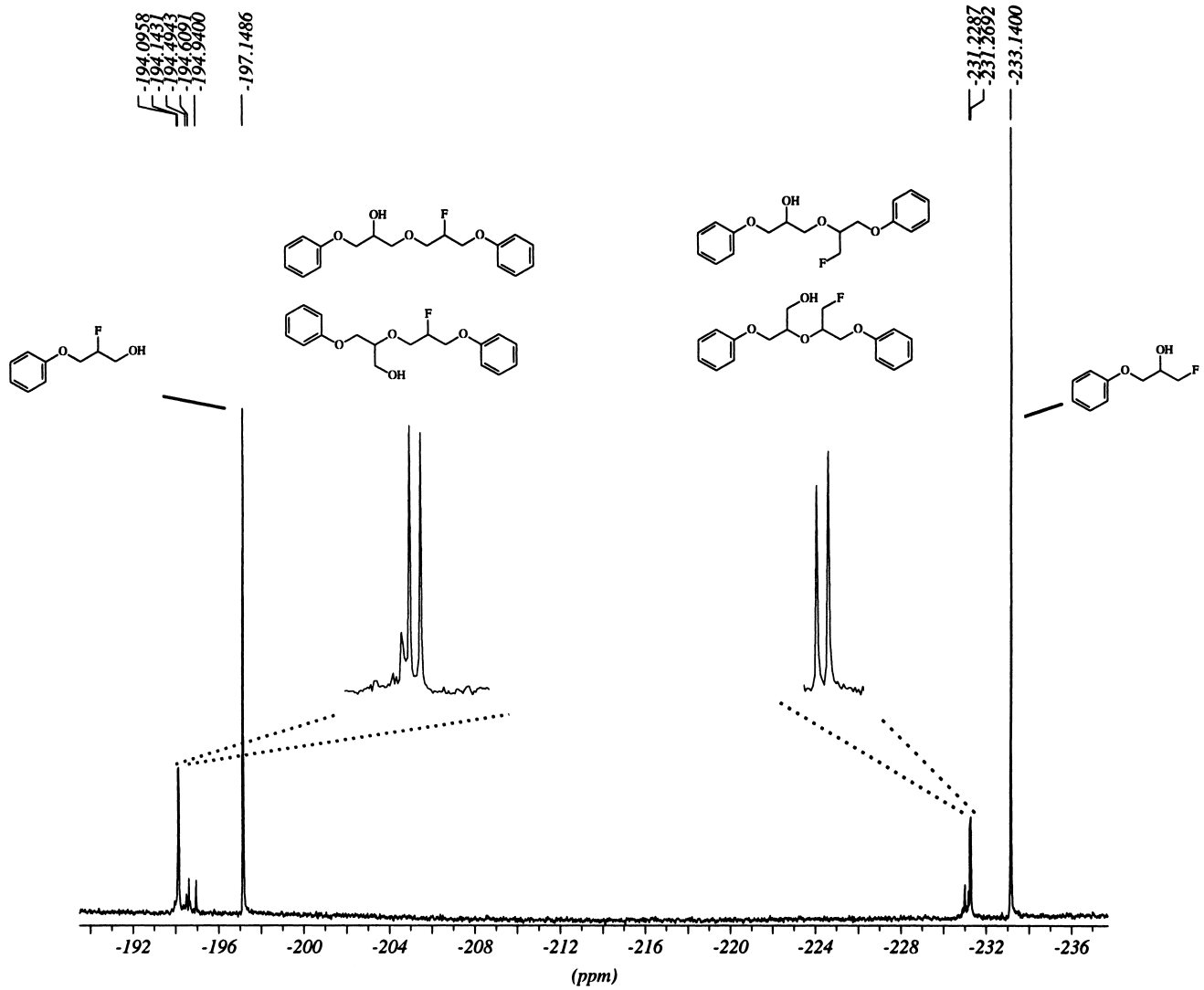
The evaluation of the serial investigation was therefore done by integration of the signals between −193 and −198 ppm for the secondary fluorinated compounds and from −230 to −234 ppm for the primary ones. The sum of the integrals in these areas gives the ratio of the primary formed regioisomers **4** and **5** (Table 1).

The ratio of regioisomers is almost uninfluenced by one single electron-donating substituent (*o*-, *m*-, *p*-methyl, **3b–d**) on the phenyl ring, while two methyl groups in 3- and 5-position (**3e**) yielded predominantly terminally fluorinated compounds, for which we have no explanation at present.

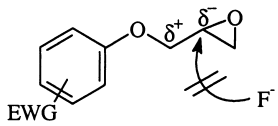
The negative inductive effect of the halogens of the halogen-substituted phenoxyethers (**3f–i**) causes a stronger electron-withdrawing character of the β-substituent, which leads to a slight increase in yield of the primary fluorinated compound. For the various halogens no difference is observed. The inference of this result coincides with the positive value of the substituent constant σ_{para} for halogens (σ_{para} (F)=0.06, σ_{para} (Cl)=0.22, σ_{para} (Br)=0.22) [22,23].

The biggest effect is observed with the strongly electron-withdrawing nitro group (*o*-, *p*-NO_2, σ_{para}=0.78). The primary fluorinated compound is formed 23% more from **3k** than from the non-substituted phenoxy compound **3a**. A possible change of the regioisomeric ratio due to steric reasons (**3j** and **3k**) is not observed. On the contrary, the observed bigger influence of the *p*-nitro substituent clearly shows that the regioisomeric ratio is determined by the electronic influence of the aromatic π-system (Scheme 4).

Electron-withdrawing substituents on the phenyl ring obviously strengthen the polarization by the ethereal oxygen of the C–C bond in the epoxide ring. Therefore a secondary carbocationic center is even more destabilized and the



Scheme 3. Proton-decoupled ^{19}F NMR spectrum of the crude product mixture after the hydrofluorination of **3a**.



Scheme 4. Electron-withdrawing groups on the phenyl ring increase the electron-attracting effect of the ethereal oxygen.

hydrofluorination yields predominantly terminally fluorinated compounds.

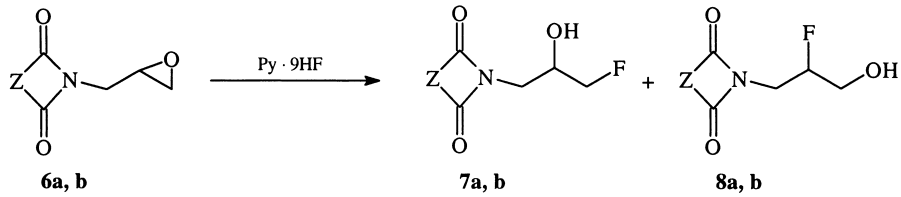
In order to underline this thesis we chose other substrates, in which the electronic structure is even more evident, such as *N*-substituted imides or aromatic nitrogen heterocycles (Scheme 5 and Table 2).

These two results show by the shift of the regioisomeric ratio that the electron-attracting effect of the imide is very strong. No other fluorinated products were formed. The aromatic ring in **6b** has no additional effect in this case.

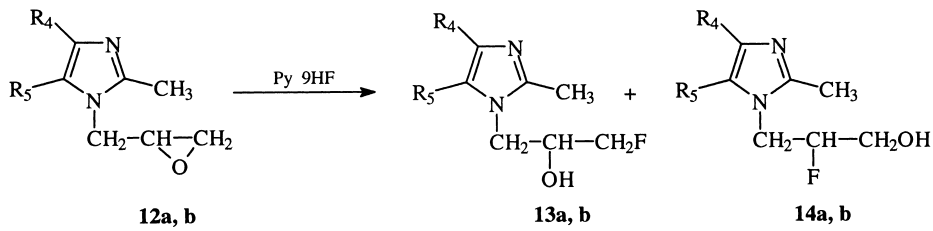
Table 2
Regioisomeric ratio of the hydrofluorination of imides **6a** and **6b** with Olah's reagent

Educt **6**	Z	Primary fluorohydrin **7**	Secondary fluorohydrin **8**
a	C_2H_4	84	16
b		85	15

Combining the electron-withdrawing effect of a nitro group with that of an aromatic nitrogen heterocycle it is possible to obtain almost complete regiocontrol of the hydrofluorination of epoxides. As already described [24] it is possible to get exclusively terminally fluorinated secondary alcohols from β-nitroimidazolyl-epoxides (Scheme 6 and Table 3).



Scheme 5. Products of the hydrofluorination of imides **6a** and **6b** with Olah's reagent.



Scheme 6. Products of the hydrofluorination of the nitroimidazoles **12a** and **12b** with Olah's reagent.

Table 3
Regioisomeric ratio of the hydrofluorination of the nitroimidazoles **12a** and **12b** with Olah's reagent

Educt **12**	R_4	R_5	Primary fluorohydrin **13**	Secondary fluorohydrin **14**
a	NO_2	H	98.5	1.5
b	H	NO_2	98	2

In contrast to the hydrofluorination of the phenoxyethers there was no evidence for the formation of oligomeric side products in the stronger electron-withdrawing nitrogen heterocycles.

These results clearly show that the regiochemistry of hydrofluorination with Olah's reagent is dependent on the nature of the employed epoxides. For a variety of different fluorinating agents this result should also be taken into consideration for the preparative synthesis of monofluorinated compounds.

3. Experimental

All melting points are reported uncorrected. ^{1}H NMR (300.13 MHz), ^{13}C NMR (75.5 MHz) and ^{19}F NMR (282.3 MHz) were recorded on a Bruker WM 300. Chemical shifts for ^{1}H NMR are reported as δ-values in ppm relative to TMS as internal standard in $CDCl_3$, ^{13}C NMR spectra were calibrated to 77.0 ppm of the $CDCl_3$ triplet, multiplicity was determined by the DEPT operation, and for ^{19}F NMR spectra $CFCl_3$ (δ=0 ppm) was used as an internal standard in $CDCl_3$. For the integration of the ^{19}F NMR spectra decoupled spectra were used. As they were evaluated manually the total error for this procedure amounted to ±1% in ratio. Mass spectra (70 eV) were obtained by GLC/MS using a Varian GC 3400 (quartz capillary column HP1 (0.33 μm) dimensions: 25 m, Ø 0.2 mm) and Finnigan MAT 8230 with the data system SS 300; all marked peaks were listed. Other GLC experiments were performed on a Hewlett-Packard 5890 II gas chromatograph with an SPB-1^{TM} quartz capillary column (0.52 μm) from Supelco, dimensions: 30 m, Ø 0.32 mm. Silica gel (Merck 60, 70–230 mesh) was used for column chromatography, thin layer chromatography was performed with Merck silica gel DC 60 F_{254} plates, detection UV (λ=254 nm).

Olah's reagent (Py·9HF) was obtained from Aldrich, the educt for the 5-nitroimidazoles was partly obtained from Sigma and Hoffmann-La Roche. The used solvents were purified by distillation. All other starting materials and applied reagents were obtained from Acros (Janssen), Merck or Fluka.

3.1. Syntheses of the phenoxyethers

3.1.1. General procedure for the synthesis of the phenoxyethers **3a–i**

According to the literature [25], substituted phenols (0.5 mol) were suspended or dissolved in acetone (100 ml) and stirred overnight with epichlorohydrin (15 ml, 0.2 mol) and potassium carbonate (14 g, 0.1 mol) at 60°C. After cooling to room temperature, the inorganic salts were filtered off, and the acetone was removed under reduced pressure. The residue was taken up in toluene (10–20 ml) and washed with water (100 ml), 1 N aqueous sodium hydroxide solution (2×100 ml) and again with water (2×100 ml). The toluene was dried over magnesium sulfate and removed under reduced pressure. The main product was isolated by column chromatography (silica gel, dichloromethane as mobile phase).

3.1.2. General procedure for the synthesis of the nitro-substituted phenoxyethers **3j** *and* **3k**

According to the literature [26], the nitrophenols (12.6 g, 65 mmol) were suspended in acetone (50 ml). After the

addition of solid sodium hydroxide (4.0 g) the mixture was stirred for 30 min, then epichlorohydrin (10 ml, 0.13 mol) was added and the reaction completed by stirring for 8 h. Finally, the mixture was extracted three times with dichloromethane (100 ml). The organic layer was dried over magnesium sulfate and removed under reduced pressure. The crude product was purified by column chromatography (silicagel, dichloromethane as mobile phase).

The yields obtained were in good accordance with those in the literature; the identification of the phenoxymethyl oxiranes was made by comparison with the published physical and spectroscopic data: **3a–c**, **g**, **h**, **j** [27], **3d** [3], **3e** [28], **3f**, **i** [29], **3k** [30].

3.2. Conversion of the phenoxyethers with Olah's reagent

3.2.1. General procedure

Into a dry polypropylene flask Olah's reagent (Py·9HF, 3 ml, 0.1 mol) was added and cooled to 0°C. Then the corresponding phenoxyether (0.01 mol), dissolved in dichloromethane (10 ml), was carefully added and the mixture was allowed to reach room temperature. After stirring for 2 h, the solution was poured into ice water (50 ml) and neutralized with concentrated ammonia. The organic layer was separated and the aqueous one extracted with dichloromethane (3×10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. This crude reaction mixture was analyzed directly by ^{19}F NMR spectroscopy (2–3 drops in an NMR tube). In order to examine these mixtures by GLC, short column filtration using silica gel (5 g) and cyclohexane/ethyl acetate 1:1 as mobile phase, was carried out. The identification of the fluorinated side products was mostly made from the observation of the molecular ion peak in the mass spectra. The whole spectra are not explicitly presented and only the values of the main products are listed.

3.2.2. Phenoxymethyl-oxirane (**3a**) with Py·9HF

^{19}F NMR ($CDCl_3/CFCl_3$) δ: −194.06 to −194.14 (several multiplets) (Σ 19.9%), −194.49 (m), −194.61 (m), −194.93 (m) (Σ 6.6%), −197.14 (m) (26.4% **5a**), −231.23 (m), 231.27 (m) (Σ 11.9%), −233.14 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (35.2% **4a**). MS (GLC–MS, 70 eV) *m/z* (%) **4a**: 171 (8) [M^+ +1], 170 (84) [M^+], 137 (6) [M^+ –CH_2F], 126 (20) [M^+ –C_2H_4O], 119 (10), 108 (6), 107 (40) [M^+ –C_2H_4FO], 95 (38), 94 (100) [$C_6H_6O^+$, Phenol], 79 (18), 77 (78) [$C_6H_5^+$], 66 (15) [$C_6H_6O^+$ –CO], 65 (20) [$C_5H_5^+$], 51 (24) [$C_4H_3^+$], 43 (8) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (17) [$C_3H_3^+$]. **5a**: 171 (7) [M^+ +1], 170 (69) [M^+], 107 (14) [M^+ –C_2H_4FO], 95 (20), 94 (100) [$C_6H_6O^+$, phenol], 79 (6), 77 (32) [$C_6H_5^+$], 66 (16) [$C_6H_6O^+$ –CO], 65 (16) [$C_5H_5^+$], 51 (12) [$C_4H_3^+$], 39 (13) [$C_3H_3^+$].

3.2.3. 2-(2-Methyl-phenoxymethyl)-oxirane (**3b**) with Py·9HF

^{19}F NMR δ: −193.80 (m), −193.86 (m) (Σ 12.0%), −194.29 (m), −194.46 (m) (Σ 4.8%), −195.90 (m) (36.9% **5b**), −230.91 (m) to −231.35 (m) (Σ 7.7%), −232.49 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (38.6% **4b**). MS (GLC–MS, 70 eV) *m/z* (%) **4b**: 185 (5) [M^+ +1], 184 (40) [M^+], 151 (4) [M^+ –CH_2F], 140 (6) [M^+ –C_2H_4O], 121 (16) [M^+ +1 –C_2H_4FO], 109 (14), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (26), 91 (32) [$C_7H_7^+$], 80 (4), 77 (10) [$C_6H_5^+$], 65 (10) [$C_5H_5^+$], 63 (4), 51 (6) [$C_4H_3^+$], 43 (6) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (6) [$C_3H_3^+$]. **5b**: 185 (4) [M^+ +1], 184 (36) [M^+], 133 (2), 121 (4) [$C_8H_9O^+$], 109 (6), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (28), 89 (10), 77 (15) [$C_6H_5^+$], 73 (3), 65 (8), 51 (8) [$C_4H_3^+$], 39 (10) [$C_3H_3^+$].

3.2.4. 2-(3-Methyl-phenoxymethyl)-oxirane (**3c**) with Py·9HF

^{19}F NMR δ: −193.99 (m) to −194.07 (m) (Σ 15.4%), −194.53 (m) (3.1%), −194.88 (m) (2.9%), −196.81 (m) (30.4% **5c**), −230.98 (m) to −231.20 (m) (Σ 12.4%), −232.94 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (35.8% **4c**). MS (GLC–MS, 70 eV) *m/z* (%) **4c**: 185 (6) [M^+ +1], 184 (58) [M^+], 164 (4) [M^+ –HF], 151 (6) [M^+ –CH_2F], 140 (8) [M^+ –C_2H_4O], 121 (24) [$C_8H_9O^+$], 109 (34), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (30), 91 (44) [$C_7H_7^+$], 81 (2), 77 (8) [[$C_6H_5^+$], 76 (4), 65 (10) [$C_5H_5^+$], 63 (4), 51 (5) [$C_4H_3^+$], 43 (4) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (6) [$C_3H_3^+$]. **5c**: 185 (6) [M^+ +1], 184 (42) [M^+], 121 (8) [$C_8H_9O^+$], 109 (10), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (24), 91 (18) [$C_7H_7^+$], 90 (4), 79 (7), 77 (8) [$C_6H_5^+$], 65 (6) [$C_5H_5^+$], 63 (2), 51 (4) [$C_4H_3^+$], 41 (2), 39 (6) [$C_3H_3^+$].

3.2.5. 2-(4-Methyl-phenoxymethyl)-oxirane (**3d**) with Py·9HF

^{19}F NMR δ: −194.03 to −194.84 (several multiplets) (Σ 24.6%), −196.82 (m) (29.5% **5d**), −230.99 to −231.21 (several multiplets) (Σ 10.8%), −232.92 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (35.1% **4d**). MS (GLC–MS, 70 eV) *m/z* (%) **4d**: 185 (6) [M^+ +1], 184 (44) [M^+], 164 (2) [M^+ –HF], 151 (3) [M^+ –CH_2F], 140 (5) [M^+ –C_2H_4O], 121 (12) [$C_8H_9O^+$], 109 (12), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (35), 91 (29) [$C_7H_7^+$], 80 (3), 77 (9) [$C_6H_5^+$], 76 (2), 65 (9) [$C_5H_5^+$], 63 (3), 51 (4) [$C_4H_3^+$], 43 (16) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (6) [$C_3H_3^+$]. **5d**: 185 (6) [M^+ +1], 184 (42) [M^+], 121 (5) [$C_8H_9O^+$], 109 (8), 108 (100) [$C_7H_8O^+$, methylphenol], 107 (33), 91 (14) [$C_7H_7^+$], 80 (4), 77 (8) [$C_6H_5^+$], 70 (2), 65 (5), 61 (3), 51 (5) [$C_4H_3^+$], 43 (12) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (5) [$C_3H_3^+$].

3.2.6. 2-(3,5-Dimethyl-phenoxymethyl)-oxirane (**3e**) with Py·9HF

^{19}F NMR δ: −193.99 (m), 194.07 (m), 194.11 (m) (Σ 13.8%), −194.63 (m), 195.04 (m) (Σ 3.7%), −197.53 (m) (19.6% **5e**), −231.14 (m), 231.17 (m) (Σ 10.7%), −232.66

(m) (2.8%), −233.60 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (49.4% **4e**). MS (GLC–MS, 70 eV) *m/z* (%) **4e**: 198 (55) [M^+], 178 (4) [M^+ –HF], 165 (6) [M^+ –CH_2F], 154 (5) [M^+ –C_2H_4O], 135 (22) [M^+ –C_2H_4FO], 123 (40), 122 (100) [$C_8H_{10}O^+$, dimethylphenol], 107 (36) [178 – $C_3H_5O_2$], 105 (38), 94 (15) [$C_8H_{10}O^+$ –CO], 91 (13) [$C_7H_7^+$], 79 (14), 77 (20) [$C_6H_5^+$], 65 (6) [$C_5H_5^+$], 63 (5), 51 (5), 43 (7) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF]. **5e**: 198 (70) [M^+], 183 (4), 165 (2), 135 (12) [M^+ –C_2H_4FO], 123 (20), 122 (100) [$C_8H_{10}O^+$, dimethylphenol], 121 (20), 107 (48) [178 –$C_3H_5O_2$], 105 (26), 94 (22) [$C_8H_{10}O^+$ –CO], 79 (20), 77 (30) [$C_6H_5^+$], 67 (2), 65 (8) [$C_5H_5^+$], 63 [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 41 (8), 39 (16) [$C_3H_3^+$].

3.2.7. 2-(4-Fluoro-phenoxymethyl)-oxirane (**3f**) with Py·9HF

^{19}F NMR δ: −122.9 (tt, not completely resolved, Ar–F), −193.94 to −194.01 (several multiplets) (Σ 19.9%), −194.03 to −194.80 (several multiplets) (Σ 4.6%), −196.50 (m) (23.5% **5f**), −230.94 to −231.37 (several multiplets) (Σ 15.9%), −233.60 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (36.1% **4f**). MS (GLC–MS, 70 eV) *m/z* (%) **4f**: 189 (4) [M^+ +1], 188 (34) [M^+], 155 (2) [M^+ –CH_2F], 144 (6) [M^+ –C_2H_4O], 137 (4), 125 (10) [M^+ –C_2H_4FO], 113 (10), 112 (100) [$C_6H_5FO^+$, fluorophenol], 111 (6), 97 (5), 95 (19) [M^+ –$C_3H_6FO_2$], 83 (6), 75 (7), 63 (4), 57 (5) [$C_3H_5O^+$, methyloxiranyl], 49 (2), 43 (2) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (1) [$C_3H_3^+$]. **5f**: 189 (4) [M^+ +1], 188 (31) [M^+], 113 (8), 112 (100) [$C_6H_5FO^+$, fluorophenol], 111 (3), 95 (8) [M^+ –$C_3H_6FO_2$], 83 (7), 75 (4), 57 (6) [$C_3H_5O^+$, methyloxiranyl], 47 (2), 39 (2) [$C_3H_3^+$].

3.2.8. 2-(2-Chloro-phenoxymethyl)-oxirane (**3g**) with Py·9HF

^{19}F NMR δ: −194.19 to −194.33 (several multiplets) (Σ 21.5%), −194.66 (m), −195.07 (m) (Σ 8.0%), −196.83 (m) (20.0% **5g**), −231.70 to −231.89 (several multiplets) (Σ 18.5%), −233.09 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (32.0% **4g**). MS (GLC–MS, 70 eV) *m/z* (%) **4g**: 207 (2), 206 (8), 204 (24) [M^+], 171 (3) [M^+ –CH_2F], 160 (4) [M^+ –C_2H_4O], 141 (6) [M^+ –C_2H_4FO], 130 (33), 128 (100) [$C_6H_5ClO^+$, chlorophenol], 127 (4), 111 (10) [M^+ – $C_3H_6FO_2$], 99 (4), 92 (4), 84 (2), 77 (6) [$C_6H_5^+$], 75 (7), 65 (3) [$C_5H_5^+$], 64 (8), 63 (7), 49 (4), 43 (5) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (3) [$C_3H_3^+$]. **5g**: 206 (8), 204 (26) [M^+], 131 (3), 130, (33), 128 (100) [$C_6H_5ClO^+$, chlorphenol], 99 (4), 92 (4), 75 (5), 64 (8), 62 (2), 47 (2), 39 (3) [$C_3H_3^+$].

3.2.9. 2-(4-Chloro-phenoxymethyl)-oxirane (**3h**) with Py·9HF

^{19}F NMR δ: −193.99 (m), −194.05 (m) (Σ 19.2%), −194.43 to −194.78 (several multiplets) (Σ 6.1%), −196.42 (m) (23.0% **5h**), −231.04 to −231.32 (several multiplets) (Σ 15.1%), −232.82 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (36.6% **4h**). MS (GLC–MS, 70 eV) *m/z* (%) **4h**: 207 (1), 206 (10), 204 (30) [M^+], 184 (2) [M^+ –HF], 171 (2) [M^+ –CH_2F], 160 (3) [M^+ –C_2H_4O], 141 (7) [M^+ – C_2H_4FO], 130 (33), 128 (100) [$C_6H_5ClO^+$, chlorophenol], 113 (6), 111 (13) [M^+ –$C_3H_6FO_2$], 99 (4), 93 (1), 86 (2), 84 (2), 75 (8), 65 (7) [$C_5H_5^+$], 59 (2), 49 (5), 43 (6) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (3) [$C_3H_3^+$]. **5h**: 207 (2), 206 (13), 204 (40) [M^+], 141 (4) [M^+ –C_2H_4FO], 130 (42), 128 (100) [$C_6H_5ClO^+$, chlorophenol], 113 (4), 111 (8) [M^+ – $C_3H_6FO_2$], 99 (6), 77 (4) [$C_6H_5^+$], 75 (8), 65 (7) [$C_5H_5^+$], 49 (6), 39 (6) [$C_3H_3^+$].

3.2.10. 2-(4-Bromo-phenoxymethyl)-oxirane (**3i**) with Py·9HF

^{19}F NMR δ: −193.90 to −194.05 (several multiplets) (Σ 19.1%), −194.46 to −194.78 (several multiplets) (Σ 5.2%), −196.26 (m) (24.1% **5i**), −230.94 to −231.10 (several multiplets) (Σ 6.3%), −231.29 (m), −231.33 (m) (Σ 8.2%), −232.70 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (37.1% **4i**). MS (GLC–MS, 70 eV) *m/z* (%) **4i**: 251 (5) [M^+ +1], 250 (37) [M^+], 249 (5) [M^+ +1], 248 (40) [M^+], 230 (3) [M^+ –HF], 228 (3) [M^+ –HF], 217 (3) [M^+ – CH_2F], 215 (3) [M^+ –CH_2F], 206 (4) [M^+ –C_2H_4O], 204 (4) [M^+ –C_2H_4O], 197 (2), 188 (2), 187 (8) [M^+ –C_2H_4FO], 185 (8) [M^+ –C_2H_4FO], 175 (9), 174 (100) [$C_6H_5BrO^+$, bromophenol], 173 (12), 172 (100) [$C_6H_5BrO^+$, bromophenol], 171 (3), 157 (12), 155 (12), 136 (6), 106 (2), 94 (4), 93 (12) [$C_6H_5BrO^+$ –Br], 78 (4), 77 (10) [$C_6H_5^+$], 76 (11), 75 (10), 65 (16), 63 (8), 51 (4), 43 (8) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (7) [$C_3H_3^+$]. **5i**: 251 (5) [M^+ +1], 250 (44) [M^+], 249 (6) [M^+ +1], 248 (44) [M^+], 230 (1) [M^+ –HF], 228 (1) [M^+ –HF], 187 (3) [M^+ –C_2H_4FO], 185 (3) [M^+ – C_2H_4FO], 174 (96) [$C_6H_5BrO^+$, bromophenol], 172 (100) [$C_6H_5BrO^+$, bromophenol], 157 (6), 155 (6), 145 (5), 143 (5), 94 (3), 93 (12) [$C_6H_5BrO^+$ –Br], 92 (2), 76 (7), 75 (7), 74 (3), 65 (15), 63 (9), 62 (3), 50 (6), 39 (6) [$C_3H_3^+$].

3.2.11. 2-(2-Nitro-phenoxymethyl)-oxirane (**3j**) with Py·9HF

^{19}F NMR δ: −194.46 (m), 194.48 (m) (Σ 18.3%), −196.69 (m) (15.9% **5j**), −232.37 (m), −232.43 (m) (Σ 20.1%), −233.13 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (45.7% **4j**). MS (GLC–MS, 70 eV) *m/z* (%) **4j**: 216 (4) [M^+ +1], 215 (26) [M^+], 182 (6) [M^+ –CH_2F], 140 (8), 139 (100) [$C_6H_5NO_3^+$, nitrophenol], 124 (16), 123 (62) [$C_6H_5NO_2^+$], 122 (24) [$C_6H_4NO_2^+$], 109 (16), 106 (34) [123 – OH], 94 (8), 93 (12), 92 (9), 81 (12), 78 (17), 77 (9) [$C_6H_5^+$], 65 (21), 63 (14), 53 (6), 51 (12), 43 (9) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (11) [$C_3H_3^+$]. **5j**: 215 (22) [M^+], 140 (12), 139 (100) [$C_6H_5NO_3^+$, nitrophenol], 124 (4), 123 (13) [$C_6H_5NO_2^+$], 122 (7) [$C_6H_4NO_2^+$], 109 (17), 106 (8) [123 –OH], 92 (8), 84 (5), 81 (14), 76 (7), 65 (15), 64 (14), 59 (4), 51 (10), 50 (6), 39 (10) [$C_3H_3^+$].

3.2.12. 2-(4-Nitro-phenoxymethyl)-oxirane (**3k**) with Py·9HF

^{19}F NMR δ: −193.90 (m), 193.92 (m) (Σ 15.8%), −195.69 (m) (14.3% **5k**), −230.52 to −231.06 (several

multiplets) (Σ 19.3%), −231.56 (m), 231.60 (m) (Σ 6.8%), −232.36 (dt, CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (43.8% **4k**). MS (GLC–MS, 70 eV) *m/z* (%) **4k**: 216 (8) [M^+ +1], 215 (67) [M^+], 199 (2), 182 (4) [M^+ –CH_2F], 172 (10), 171 (5), 152 (24) [M^+ –C_2H_4FO], 140 (24), 139 (100) [$C_6H_5NO_3^+$, nitrophenol], 136 (16), 123 (22) [$C_6H_5NO_2^+$], 122 (15) [$C_6H_4NO_2^+$], 109 (34), 94 (8), 93 (18), 92 (11), 81 (7), 76 (22), 75 (15), 65 (25), 63 (22), 57 (5) [$C_3H_5O^+$, methyloxiranyl, C_3H_6FO –HF], 50 (14), 44 (14), 43 (12) [$C_2H_3O^+$, oxiranyl, C_2H_4FO –HF], 39 (14) [$C_3H_3^+$]. **5k**: 216 (8) [M^+ +1], 215 (79) [M^+], 211 (4), 199 (3), 152 (6) [M^+ –C_2H_4FO], 140 (11), 139 (100) [$C_6H_5NO_3^+$, nitrophenol], 122 (10) [$C_6H_4NO_2^+$], 109 (38), 94 (9), 93 (16), 92 (9), 81 (9), 77 (16) [$C_6H_5^+$], 76 (11), 65 (20), 64 (16), 57 (12), 50 (8), 47 (12), 39 (13) [$C_3H_3^+$].

3.3. Syntheses of N-substituted imides

3.3.1. 1-(2,3-Epoxypropyl)-succinimide (**6a**)

Potassium succinimide (4 g, 30 mmol) was suspended in acetonitrile (20 ml) and heated to 60°C. Then epichlorohydrin (3.4 ml, 44 mmol, 1.5 eq.) was added in portions and the reaction mixture was refluxed for 6 h. The resulting potassium chloride was filtered off and the solvent removed under reduced pressure. The viscous residue was treated with toluene (10 ml) and this mixture stored overnight in the refrigerator and the precipitated crystals were collected. Yield: 1.4 g (37%); m.p. 58–59°C (toluene), ([31], m.p. 52°C). ^{1}H NMR δ: 2.62 (dd, 1H, CH_2O, $^2J_{H_a,H_b} = 4.8$ Hz, $^3J_{H_a,H_x} = 2.6$ Hz, H_a), 2.70–2.80 (m, 5H, CH_2O, CH_2–CH_2), 3.13–3.18 (m, 1H, CHO), 3.63 (dd, 1H, NCH_2, $^2J_{H'_a,H'_b} = 14.1$ Hz, $^3J_{H'_b,H_x} = 4.8$ Hz, H'_b, 3.74 (dd, 1H, NCH_2, $^2J_{H'_a,H'_b} = 14.1$ Hz, $^3J_{H'_a,H_x} = 5.5$ Hz, H'_a). ^{13}C NMR δ: 28.1 (2t, CH_2–CH_2), 40.4 (t, CH_2O), 46.0 (t, NCH_2), 48.3 (d, CHO), 176.7 (s, C=O).

3.3.2. 1-(2,3-Epoxypropyl)-phthalimide (**6b**)

Potassium phthalimide (15 g, 80 mmol) was suspended in epichlorohydrin (30 ml, 0.4 mol) and the reaction mixture stirred for 15 h at 140–150°C (oil bath temperature). The surplus epichlorohydrin was removed and the residue taken up in 100 ml of hot ethanol. This suspension was refluxed for half an hour. The resulting potassium chloride was filtered off, the filtrate was stored overnight in the refrigerator and the crystalline product was isolated. Yield: 9.0 g (67%); m.p. 97–98°C ([32], m.p. 96–98°C). ^{1}H and ^{13}C NMR data agree with those given in [33].

3.4. Conversion of the N-substituted imides with Olah's reagent

3.4.1. 1-(2,3-Epoxypropyl)-succinimide (**6a**) with Py·9HF

Deviating from the already described general procedure for the hydrofluorination of epoxides, **6a** (0.77 g, 5 mmol) was dissolved in dichloromethane (10 ml) and Olah's reagent (3 ml, 100 mmol) was added. After one day the reaction mixture was worked up and the aqueous layer was extracted continuously with ethyl acetate (three days). After the solvent was removed the ^{19}F NMR spectrum of the crude product showed only the two signals of the regioisomeric main products. ^{19}F NMR δ: −152.10 (s), −194.84 (m) (16% **8a**), −232.69 (m) (84% **7a**).

3.4.2. 1-(2,3-Epoxypropyl)-phthalimide (**6b**) with Py·9HF

Deviating from the general procedure for the hydrofluorination of epoxides the reaction was performed without solvent. ^{19}F NMR δ: −193.78 (m) (15% **8b**), −230.04 (dt, –CH_2F, $^2J_{H,F} = 47.7$ Hz, $^3J_{H,F} = 19.1$ Hz) (85% **7b**).

The syntheses of β-(nitroimidazolyl)epoxides their ring opening with Olah's reagent, and the characterization of the main product have already been described [24].

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