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Synthesis of Geminal Difluorides by Oxidative Desulfurization−Difluorination of Alkyl Aryl Thioethers with Halonium Electrophiles in the Presence of Fluorinating Reagents and Its Application for ^{18}F-Radiolabeling

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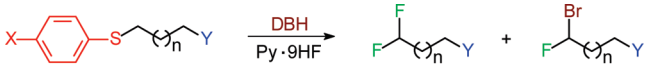
Received April 9, 2010



X = NO_2, Cl, F, Me; Y = Br, OMe, $OPhNO_2$, NPhth, CO_2Me; n = 3, 9, 10, 13

Various ω-substituted 1,1-difluoroalkanes are synthesized in good yields from alkyl aryl thioethers by a new oxidative desulfurization−difluorination protocol with the reagents combination of 1,3-dibromo-5,5-dimethylhydantoin (DBH) as an oxidizer and pyridine·9HF (Py·9HF) as a fluoride source. The reaction proceeds via a fluoro-Pummerer-type rearrangement followed by an oxidative desulfurization−fluorination step. Starting from α-fluorinated thioethers, this reaction is promising for ^{18}F-labeling ($\tau_{1/2}$ = 110 min) of ligands applicable for positron emission tomography (PET). Using the combination of DBH and carrier-added Py·9H[^{18}F]F, an ^{18}F-labeled difluoride was synthesized from the corresponding α-fluoro thioether with a radiochemical yield of 9%.

Introduction

The development of new methods for the introduction of one or several fluorine atoms into organic compounds is one of the most important tasks of current organofluorine chemistry considering the enormous impact of fluorinated molecules on medicinal and materials chemistry,[1] and many efficient and selective methods have been developed in recent years.[2] Among them, different oxidative fluorinations of sulfur compounds and oxidative desulfurization−fluorination methods have come into focus.[3] Originally electrophiles such as xenon difluoride,[4] *N*-fluoropyridinium salts,[5] or electrochemical oxidation in the presence of different fluorinating reagents[6] were applied for α-fluorination of sulfides. Later

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Published on Web 08/26/2010 DOI: 10.1021/jo100689v

other oxidants such as selectfluor[7] or difluoroiodoarenes[8] were shown to be useful. Recently, combinations of chemical oxidants such as 1,3-dibromo-5,5-dimethylhydantoin (DBH) combined with tetrabutylammonium dihydrogentrifluoride ($TBAH_2F_3$)[9] or iodine pentafluoride (IF_5) in the presence of triethylamine tris(hydrogenfluoride) ($Et_3N \cdot 3HF$)[10] have been applied. Treatment of alkyl aryl sulfides with IF_5 in an inert solvent at elevated temperature gave rise to aryl polyfluoroalkyl sulfides.[11] It has been shown that these reactions proceed similarly to the original fluoro-Pummerer rearrangement of sulfoxides with diethylaminosulfurtrifluoride (DAST).[12]

The oxidative desulfurization−fluorination reaction is another efficient protocol for the introduction of one or more fluorine atoms into organic molecules. The original hazardous reagents such as CF_3OF and/or HF/F_2[13] were replaced by more convenient ones such as *N*-bromosuccinimide (NBS)/Olah's reagent (Py·9HF) or DAST in due course.[14] Also the combinations of methyl fluorosulfonate and cesium fluoride[15] or nitrosonium tetrafluoroborate ($NOBF_4$) with Olah's reagent[16] or application of *p*-iodotoluene difluoride[17] resulted in a transformation of arylthioethers into the corresponding fluorides by substitution of the arylthio group.

Particularly the difluoromethyl group became interesting recently because of its biological properties. This group is isopolar and almost isosteric with a carbonyl group, and several compounds bearing this moiety are metabolically more stable than the original biologically active molecules and/or are potent enzyme inhibitors.[18] Consequently, a variety of methods for their preparation have been described.[19] Originally, Sondej and Katzenellenbogen transformed 1,3-dithiolanes or 1,3-dithianes to *gem*-difluorides by treatment with a halonium ion donor (DBH, NBS) and a fluoride source.[20] Moreover, it is known that aliphatic *gem*-difluoro compounds can be prepared by anodic fluorodesulfurization of aldehyde thioacetals in the presence of $Et_3N \cdot 3HF$.[21] Also several other oxidants such as SO_2ClF, SO_2Cl_2, or $NOBF_4$ in combination with Olah's reagent[16,22] or with $TBAH_2F_3$[23] or the hexafluoropropene-diethylamine reagent[24] as well as bromine trifluoride[25] are suitable for this transformation. Recently, difluoromethyl- and trifluorothioethers have been synthesized by reaction of alkyl aryl thioethers with IF_5.[11]

Here we report on a new oxidative desulfurization−difluorination protocol of alkyl aryl thioethers leading to *gem*-difluoroalkanes. Preliminary results have been communicated recently.[26a] This method might be useful for radiolabeling with [^{18}F]fluoride.

Results and Discussion

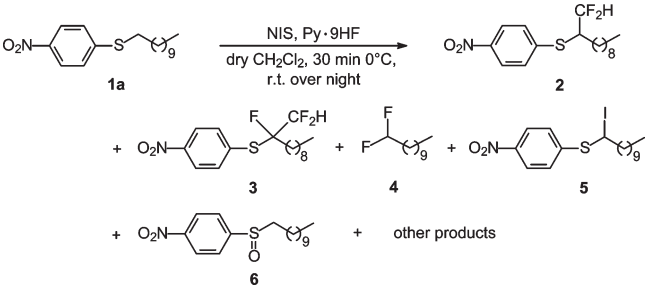
Chemistry. To develop a convenient method for the selective introduction of one or more fluorine atoms into the activated α-position, we reacted various types of alkyl aryl thioethers with several electrophiles in the presence of Olah's reagent as a fluoride source.

The initial reaction of *p*-nitrophenyl undecyl thioether (**1a**) as a sample molecule with *N*-iodosuccinimide (NIS) and Olah's reagent was not selective but gave mixtures of di- and trifluoro thioethers **2** and **3** and the *gem*-difluoroalkane **4** depending on the molar ratio of substrate and reagents (Table 1). In addition, the α-iodinated thioether **5** and the sulfoxide **6** were found in the crude product mixture among other unidentified trace products (Scheme 1).

TABLE 1. Reaction of 1a with NIS and Olah's Reagent under Various Conditions

		crude product mixture (GC %)						
NIS (equiv)	Py·9HF (equiv)	**1a**	**2**	**3**	**4**	**5**	**6**	others
1.1	2.2	55	12			2	28	3
2.2	4.4	33	42	1		2	19	3
4.4	4.4		41	23	6	7	11	12
6.0	6.0		3	43	14		12	28

SCHEME 1. Reaction of 1a with NIS and Olah's Reagent



The mechanism of formation of the di- and trifluoro thioethers is similar to the one proposed by Hara et al.[11] The introduction of the first fluorine atom proceeds according to the mechanism of the fluoro-Pummerer rearrangement (Scheme 2).[12]

The sulfur in **1a** is attacked by the electrophile NIS to form the sulfonium intermediate **I**, which gives the vinylic sulfide **7**

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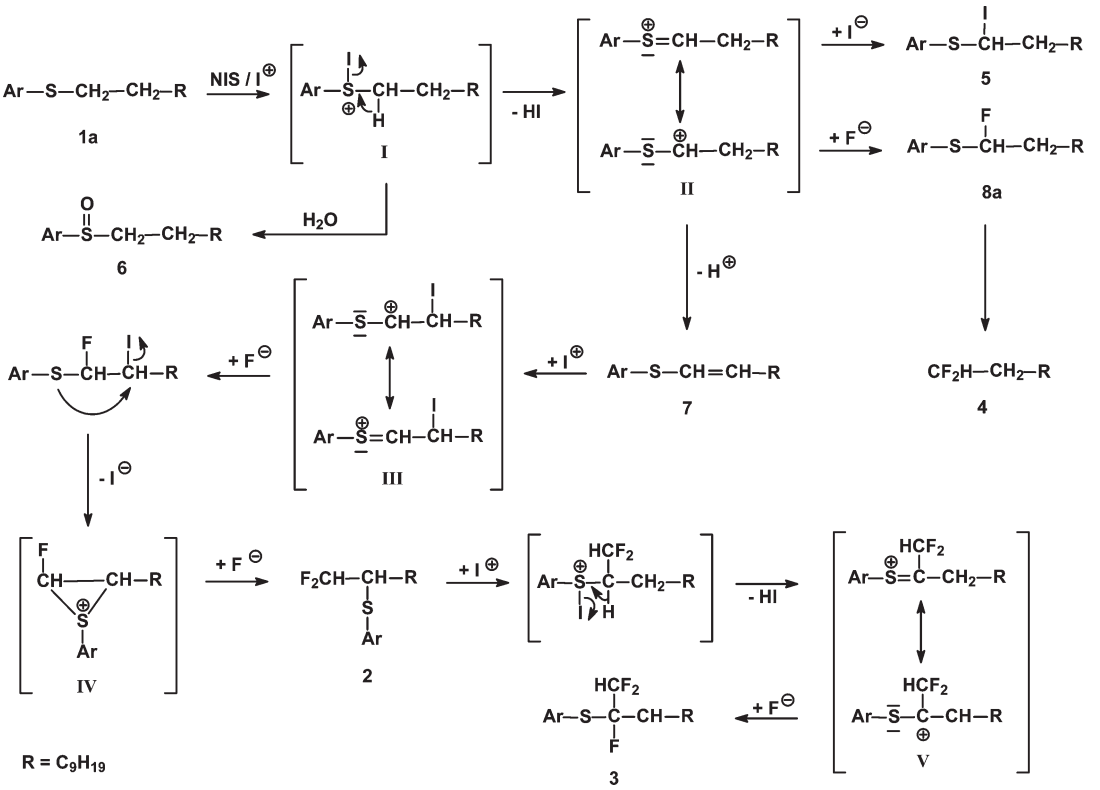
SCHEME 2. Reaction Mechanism of the Formation of Difluoro Thioether 2, Trifluoro Thioether 3, and Difluoride 4



after hydrogen iodide elimination and deprotonation of the resonance stabilized carbenium-sulfonium ion **II**. This unsaturated thioether (unidentified, but might be among the side products) is then attacked again by an iodonium ion to give the stabilized intermediate **III**, which finally adds fluoride in α-position to sulfur. Anchimeric assistance of the arylthio group leads to elimination of iodide with formation of an episulfonium ion **IV**. Subsequent nucleophilic ring-opening by fluoride attack at the terminal position results in the migration of the arylthio group and formation of the difluorinated thioether **2**. With an increasing excess of the reagents compound **2** reacts further to give **3** as shown in Scheme 2 and Table 1. Moreover, with excess of NIS/Py·9HF also the *gem*-difluoroalkane **4** is formed. This compound is derived from intermediate **II** by α-fluorination to form **8a** and subsequent oxidative desulfurization−difluorination. From the intermediate **II** also the side product **5** (not isolated, but suggested by GC−MS of the crude product mixture) can arise by iodide addition. Analogous products were not found in the reactions of alkyl aryl thioethers with IF_5.[11] The formation of sulfoxide **6** can be explained by hydrolysis of intermediate **I** during aqueous workup. This means that the steps succeeding the initial electrophilic attack on **1** are slow. This assumption is supported by the fact that quenching of the reaction (ratio of **1a**: NIS:Olah's reagent = 1:4.4:4.4) with water after 1 h of reaction time at room temperature gave the sulfoxide **6** almost exclusively. The oxidation of alkyl aryl thioethers by halogens in the presence of water has already been described in the literature.[27]

Since we were unable to increase the selectivity of the reaction by variation of the reaction conditions (time, temperature, application of $Et_3N \cdot 3HF$ instead of Olah's reagent), we changed from iodonium to bromonium ions as electrophiles. However, reactions of **1a** with NBS or DBH and $Et_3N \cdot 3HF$ were unselective and incomplete after 16 h at room temperature and 5 h at 50 °C. Finally, the combination of DBH and Olah's reagent was found to be most selective to form the *gem*-difluoroalkane **4**. However, under these conditions another side product, the *gem*-bromofluoroalkane **9**, was identified. The reaction of the thioether **1a** with excess DBH/Olah's reagent was complete after 3 h, giving a 4:1 ratio of the products **4** and **9** (Table 2, entry 1).

Contrary to our expectation, addition of $Et_3N \cdot 3HF$ as additional more nucleophilic fluoride source[28] did not increase the portion of **4** but increased that of **9** leading to an approximate 1:1 mixture of **4** and **9** (entry 2). The same effect was observed when AgF or KHF_2 was added (entries 3 and 4). The ratio of **4**:**9** was not significantly changed. We do not have an explanation for this effect yet, since addition of tetrabutylammonium bromide (TBAB) or potassium bromide increased the ratio of **4**:**9** but simultaneously yielded a bigger amount of other side products (entries 5 and 6). The use of NBS as a source of the electrophile led to much slower reactions and increased amounts of byproduct and was less selective with regard to the formation of difluoride **4**.

Further optimization experiments (see Table S1 in Supporting Information) showed that the reaction of the thioether **1a** with excess DBH/Olah's reagent was complete after 1 h at room temperature (or 30 min at 45 °C), giving a 89:11 mixture of products **4** and **9** (Table 3, entry 1).[26a] Also other

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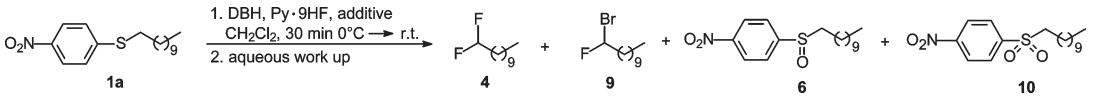
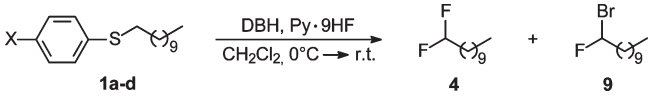
TABLE 2. Oxidative Desulfurization−Difluorination of the Thioether 1a in the Presence of Different Additives



						crude product mixture (GC %)				
entry	additive	additive (equiv)	DBH (equiv)	Py·9HF (equiv)	reaction conditions	**4**	**9**	**6**	**10**	others
1			3.0	6.0	30 min, 0 °C, 2.5 h, rt	67	19			14
2	$Et_3N·3HF$	1.0	3.0	6.0	1 h, rt	39	33	5	1	22
3	AgF	1.0	3.0	6.0	30 min, 0 °C, 4 h, rt	36	35		11	18
4	KHF_2	1.0	3.0	6.0	30 min, 0 °C, 1 h, rt	37	31	3	6	23
5	TBAB	1.0	3.0	6.0	30 min, 0 °C, 20 h, rt	54	18			28
6	KBr	1.0	3.0	4.0	30 min, 0 °C, 3 d, rt	61	19			26

TABLE 3. Oxidative Desulfurization−Difluorination of *p*-Substituted Alkyl Aryl Thioethers 1a−d with DBH and Olah's Reagent



						crude product (GC %)[a]		
entry	compd	X	DBH (equiv)	Py·9HF (equiv)	reaction conditions	**4**	**9**	yield (%)[b]
1	**1a**	NO_2	3.0	6.0	1 h, rt	89	11	80[26]
2	**1a**	NO_2	3.0	6.0	15 min, 40 W, 37 °C	88	12	*c*
3	**1a**	NO_2	3.0	2.2	15 min, 100 W, 45 °C	68	32	*c*
4	**1b**	Cl	3.0	6.0	4 h, 30 °C	86	14	77
5	**1b**	Cl	3.0	2.2	30 min, 100 W, 45 °C	94	6	*c*
6	**1c**	F	3.0	6.0	4 h, 30 °C	83	17	75
7	**1d**	CH_3	3.0	6.0	30 h, 29 °C	92	8	*c*

[a]The ratio (GC) calibrated to 100% (approximately 10% of unidentified byproduct was also found in the crude product mixture after aqueous workup). [b]Isolated yield of difluoride **4**. [c]Aliquots for reaction control were taken; yields were not determined.

alkyl aryl thioethers **1b−d** bearing different substituents in the *para* position did react similarly but needed longer reaction time and higher temperature to go to completion. Less electron-withdrawing or electron-donating *para* substituents slowed down the reaction rate but did not significantly affect the ratio of **4**:**9**. The reason for the slower reaction might be the stabilization of the intermediates of types **I** and **II** (Scheme 3) by substituents with positive inductive or resonance effects. Thus, elimination of hydrogen bromide from **I** or addition of fluoride or bromide to **II** becomes slower. Deprotonation of **II** to form **7** (cf. Scheme 2) or succeeding products seems not to occur under these conditions. Under microwave irradiation the reaction of thioether **1a** with 3.0 equiv of DBH and 6.0 equiv of Py·9HF was complete after 15 min (40 W, 37 °C), and even a minimum of 2.2 equiv of Olah's reagent led to full conversion of **1a** in 15 min at 45 °C and 100 W. The reaction time for the thioether **1b** with 3.0 equiv of DBH and 2.2 equiv of Olah's reagent could also be reduced to 30 min at 45 °C and 100 W.

The formation of the *gem*-bromofluoride **9** as a byproduct could not be suppressed completely in the reactions of the thioethers **1a−d**. However, the CHBrF group represents also an interesting unit for the synthesis of α-fluorinated thioethers or other monofluorinated compounds. Therefore, we also optimized the reaction conditions for the synthesis of *gem*-bromofluoroalkanes realizing that the product ratio significantly depends on the quality of Olah's reagent. Using Olah's reagent from a bottle opened several times already ("old") led to increased formation of bromofluoride **9** (Table 4, entries 1 and 2), whereas use of Olah's reagent from a freshly opened bottle ("fresh") showed the opposite selectivity (entry 3). The conversion of **1a** with DBH, triethylamine trishydrofluoride, and "old" Olah's reagent also resulted in preferred formation of *gem*-bromofluorides. With 3 equiv of DBH, 5 equiv of $Et_3N·3HF$, and 6 equiv of Py·9HF a ratio of difluoride to bromofluoride of 23:77 was obtained (entry 4). An additional byproduct of this reaction was the dibromofluoroundecane **11** (12%, for the mechanism of formation see ref 26b). The reaction with DBH and $Et_3N·3HF$ exclusively led to sulfoxide **6** as the sole product isolated after 17 h of reaction time and hydrolytic workup (entry 6).

An explanation for the formation of bromide ions in reaction mixtures of NBS and fluorinating agents was given by Guerrero et al.[29] An analogous mechanism is possible with DBH and triethylamine trishydrofluoride, which is less acidic as compared to Py·9HF, so that the generation of bromide ions and consequently the formation of the bromofluoride **9** is favored (see also the discussion in ref 28b).

Repetition of the experiment (entry 4) with "fresh" Olah's reagent and excess triethylamine trishydrofluoride yielded the *gem*-difluoride **4** as the major product (Table 4, entry 5).

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SCHEME 3. Mechanism of Formation of Difluoride 4 and Bromofluoride 9[26]

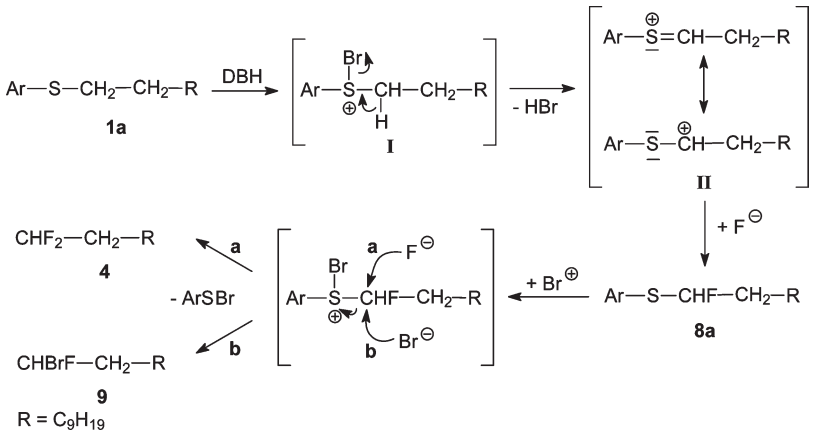


TABLE 4. Optimization of Reaction Conditions Towards *gem*-Bromofluoride 9

							crude product (GC %)				
entry	**1a** (mmol)	H_2O (equiv)	DBH (equiv)	$Et_3N \cdot 3HF$ (equiv)	Py·9HF (equiv)	reaction conditions	**4**	**9**	**6**	**10**	others
1	0.5		2.0		4.0 (old)[a]	30 min, 0 °C; 4.5 h, rt	18	58	10	7	7
2	0.5		2.0		5.0 (old)[a]	30 min, 0 °C; 4.5 h, rt	18	53	16	8	5
3	0.5		2.0		4.0 (fresh)	30 min, 0 °C; 4.5 h, rt	76	16		3	5
4	0.5		3.0	5.0	6.0 (old)[a]	30 min, 0 °C; 1 h, rt	20	68			12[b]
5	0.5		3.0	5.0	6.0 (fresh)	30 min, 0 °C; 1 h, rt	68	19	10		3
6	0.5		2.0	12.0		30 min, 0 °C; 17 h, rt			80		20
7	0.25	0.67	3.0	6.0	6.0 (fresh)	30 min, 0 °C; 20 h, rt	8	53	14	5	
8	0.5	0.55	3.0	6.0	6.0 (fresh)	30 min, 0 °C; 20 h, rt	19	53	13		15
9	1.0	0.44	3.0	6.0	6.0 (fresh)	30 min, 0 °C; 20 h, rt	32	52	9		7[b]

[a]Olah's reagent from a bottle already opened several times. [b]1,1-Dibromo-1-fluoroundecane (**11**).

From these results we suspected that traces of water in the reaction mixture might be responsible for the significant change of selectivity. Therefore, a small amount of water was added to the reaction mixture (Table 4). For a 0.25 mmol scale reaction with 3 equiv of DBH, 6 equiv of Py·9HF, and 6 equiv of $Et_3N \cdot 3HF$, the addition of 0.67 equiv of water showed the best results with regard to the selective formation of the bromofluoride **9**. Simple scale-up of this reaction was not possible, because more water prevented complete conversion of the thioether **1a** to the *gem*-difluoride **4** or *gem*-bromofluoride **9**, and the sulfone **10** became the major reaction product after hydrolysis. Stepwise increase of the reaction scale showed that addition of 0.55 equiv of water led to the best selectivity for **9** in a 0.5 mmol batch, whereas for a 1.0 mmol batch 0.44 equiv of water was shown to be optimal.

These optimization experiments showed that the addition of traces of water resulted in an increased chemoselectivity for bromofluoride **9**. Further addition of water resulted in incomplete reaction, formation of sulfoxide **6** or sulfone **10**, and a bigger amount of other byproduct depending on the amount of DBH. No increase in selectivity toward the *gem*-bromofluoride **9** was achieved by this way.

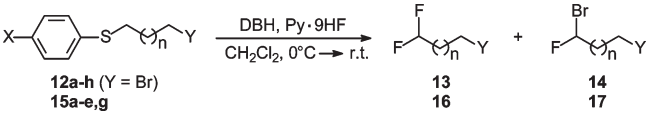
To make the new oxidative desulfurization−difluorination protocol suitable for the preparation of substituted compounds, which are useful as building blocks,[30] we prepared several ω-substituted starting materials such as **12a**−**h**, **15a**−**e**, and **15g**. For the reactions of thioethers **12**, which are terminally substituted with bromine in the alkyl chain, the difluoride **13** was generally favored over the formation of *gem*-bromofluoroalkane **14** (Table 5). Again higher temperature and longer reaction times were necessary to completely convert starting thioethers with a less electron-withdrawing or with an electron-releasing substituent in the *para* position of the phenyl ring (Table 5, entries 2−4). Elevation of the reaction temperature to 30 °C did not significantly influence the chemoselectivity of the reaction.

The reactions of thioethers substituted by other terminal functional groups on the alkyl chain such as ester, ether, and phthalimide (**15a**−**e** and **15g**) yielded also predominately difluorides (Table 5, entries 9−15). With terminal alcohol or acid functions (Y = OH, COOH), complex mixtures of unidentified products were formed. Deprotection of the phthalimido compounds **16e** and **17e** with hydrazine provided the terminal amines **16f** and **17f** in high yield. The oxidative desulfurization−difluorination of the thioether **15g** with a *p*-nitrophenylether at the terminal position of the alkyl chain was characterized by a high selectivity for *gem*-difluorides **16g1** and **16g2**, formed by additional mono- and dibromination of the phenyl ring with excess DBH.

Similarly to the mechanism shown in Scheme 2, the monofluoride **8a** should be formed from **1a** as an intermediate via cations **I** and **II** (Scheme 3) according to a Pummerer-like rearrangement with simultaneous oxidation of the α-carbon and fluoride introduction. This compound is subsequently oxidized at sulfur by another bromonium species giving, after a second fluoro-Pummerer rearrangement, the terminal difluorides **4** (pathway **a**). Addition of bromide to the same

(30) Podichetty, A. K.; Faust, A.; Kopka, K.; Wagner, S.; Schober, O.; Schäfers, M.; Haufe, G. *Bioorg. Med. Chem.* **2009**, *17*, 2680–2688.

TABLE 5. Oxidative Desulfurization−Fluorination of *p*-Substituted Alkyl Aryl Thioethers 12a−h, 15a−e, and 15g with Various Terminal Groups on the Alkyl Chain

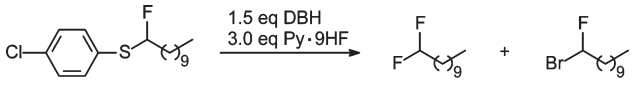


12a-h (Y = Br) **15a-e,g** | **13** **16** | **14** **17**

								crude product (GC %)[a]		
entry	compd	X	Y	*n*	DBH (equiv)	Py·9HF (equiv)	reaction conditions	**13/16**	**14/17**	yield (%)[b]
1	**12a**	NO_2	Br	10	5.0	6.0	2 h, rt	81	19	68
2	**12b**	Cl	Br	10	3.0	6.0	5 h, 30 °C	87	13	*c*
3	**12c**	F	Br	10	3.0	6.0	5 h, 30 °C	93	7	92[26]
4	**12d**	CH_3	Br	10	3.0	6.0	29 h, rt	86	14	*c*
5	**12e**	NO_2	Br	9	3.0	6.0	2 h, rt	86	14	86[26]
6	**12f**	NO_2	Br	3	3.0	6.0	20 h, rt	52	48	51
7	**12g**	F	Br	3	3.0	6.0	20 h, rt	75	25	42
8	**12h**	NO_2	Br	13	3.0	6.0	20 h, rt	48	52	23
9	**15a**	NO_2	COOMe	8	3.0	6.0	4.5 h, rt	60	40	54
10	**15b**	Cl	COOMe	8	3.0	6.0	18 h, rt	95	5	80[26]
11	**15c**	F	COOMe	8	3.0	6.0	18 h, rt	80	20	*c*
12	**15d**	Cl	OMe	9	3.0	6.0	18 h, rt	94	6	93
13	**15e**	Cl	PhthN	9	3.0	6.0	18 h, rt	88	12	88[26]
14	*d*	*d*	NH_2	9	*d*	*d*	*d*	66	34	56
15	**15g**	Cl	$OPhNO_2$	10	3.0	6.0	18 h, rt	96[e]	4	38[e]
								96[f]	4	57[f]

[a]The ratio is calibrated to 100%. Approximately 10% of unidentified byproduct was also found by GC of the crude product mixture after aqueous workup. [b]Isolated yield of difluoride **13** or **16**. [c]Aliquots for reaction control were taken; yields were not determined. [d]The mixture of phthalimido derivatives **16e** and **17e** was used as starting material to form **16f** and **17f** by hydrazinolysis (cf. Experimental Section). [e]Compound **16g1** with monobrominated phenyl ring (ratio by ^{19}F NMR). [f]Compound **16g2** with dibrominated phenyl ring (ratio by ^{19}F NMR).

TABLE 6. Oxidative Desulfurization Fluorination of 8b



8b | **4** | **9**

				crude product (GC %)[a]	
entry	DBH (equiv)	Py·9HF (equiv)	reaction conditions	**4**	**9**
1	1.5	3.0	20 h, rt	95	5
2	1.5	2.0	40 min, 45 °C, 100 W	90	10
3	1.5	1.1	40 min, 45 °C, 100 W	93	7

[a]The ratio is calibrated to 100%, < 5% impurities.

sulfonium ion formed in the first reaction step leads to the *gem*-bomofluorides **9** (pathway **b**).[26] An alternative route for the formation of the *gem*-bromofluoride **9** is the addition of bromide instead of fluoride to the intermediate **II** followed by a fluoro-Pummerer rearrangement. Compounds **13** or **16** and **14** or **17**, respectively, are formed analogously.

To prove this mechanism, reactions of the thioether **1a** were carried out with less DBH and Olah's reagent. With 1.0 and 2.0 equiv of DBH and 1.0 and 2.0 equiv of Py·9HF, the α-fluoro thioether **8a** was found as the main product after 1 h at room temperature. The isolation of **8a** failed because of HF elimination during column chromatography on silica gel. However, the synthesis of the α-fluoro thioethers **8b,d,e**, **18b**, and **19b,g** (see Supporting Information) was possible from thioethers **1b,d,e**, **12b**, and **15b,g** using DAST and $SbCl_3$ according to a method by Wnuk and Robins.[12b]

To prove that α-fluoro thioethers of type **8** are intermediates in the formation of the *gem*-difluorides, by way of example *p*-chlorophenyl-(1-fluoroundec-1-yl)thioether (**8b**) was reacted with 1.5 equiv of DBH and 3 equiv of Olah's reagent in dry dichloromethane at room temperature for 20 h (Table 6). 1,1-Difluoroundecane (**4**) and 1-bromo-1-fluoroundecane (**9**) were obtained in a ratio of 95:5. By mircowave irradiation the amount of fluorinating reagent and the reaction time could be reduced to 1.1 equiv and 40 min. Thus, α-fluoro thioethers **8** were verified as intermediates of the oxidative desulfurization−difluorination reaction of thioethers **1** to *gem*-difluoride **4** and *gem*-bromofluoride **9** and substituted analogues.

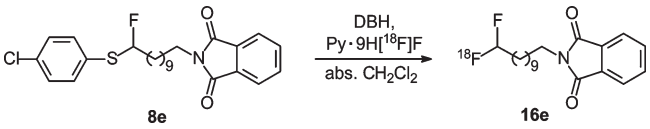
Moreover, these experiments proved the fast introduction of a second fluorine atom into α-fluoro thioethers by oxidative desulfurization−fluorination. This might be an interesting method for the introduction of the short living ^{18}F isotope ($\tau_{1/2}$ = 110 min) into biologically relevant compounds for positron emission tomography (PET) applications. Therefore this reaction was tested with compound **8e** in order to develop a new carrier-added radiofluorination method with [^{18}F]fluoride.[31]

Radiochemistry. In initial experiments reactions of the α-fluorinated thioether **8e** with X[^{18}F]F (X = Br, Cl) generated in situ from DBH or *N*-chlorosuccinimide (NCS), K[^{18}F]F, and sulfuric acid as described by Katzenellenbogen et al.[32]

(31) For reviews on radiofluorination methods, see: (a) Lasne, M.-C.; Perrio, C.; Rouden, J.; Barré, L.; Roeda, D.; Dollé, F.; Crouzel, C. *Top. Curr. Chem.* **2002**, *222*, 201–258. (b) Dollé, F.; Roeda, D.; Kuhnast, B.; Lasne, M.-C. In *Fluorine and Health. Molecular Imaging, Biomedical Material and Pharmaceuticals*; Tressaud, A., Haufe, G., Eds.; Elsevier: Amsterdam, 2008; pp 3−65.

(32) (a) Chi, D. Y.; Kiesewetter, D. O.; Katzenellenbogen, J. A. *J. Fluorine Chem.* **1986**, *31*, 99–113. (b) Chi, D. Y.; Lindström, P. J.; Choe, Y. S.; Bonasera, T. A.; Welch, M. J.; Katzenellenbogen, J. A. *J. Fluorine Chem.* **1995**, *71*, 143–147. (c) Choe, Y. S.; Lindström, P. J.; Chi, D. Y.; Bonasera, T. A.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1995**, *38*, 816–825.

TABLE 7. Results of Radiofluorination of 8e with DBH and Carrier-Added Py·9H[^{18}F]F



8e **16e**

entry	Py·9H[^{18}F]F (μL)	CH_2Cl_2 (μL)	product	rcy[a,c] (%)	rcp[b,c] (%)
1−3	2.5	150	[^{18}F]**8e**	6.9 ± 1.5	78 ± 3
4−6	5.0	300	[^{18}F]**16e**	9.0 ± 1.4[d]	65 ± 14
7−9	10.0	150	[^{18}F]**16e**	5.5 ± 0.4[d]	61 ± 24

[a]rcy = radiochemical yield (decay corrected). [b]rcp = radiochemical purity of the prepurified (C18 cartridge) reaction solution determined by HPLC. [c]Values are the mean ± standard deviation of three experiments. [d]Compound [^{18}F]**8e** was formed as a byproduct with 0.5% rcy.

for halofluorination of olefins were investigated. Unfortunately, the expected difluoro compound **16e** was not formed under these conditions. Therefore, DBH (3 equiv) and pyridinium [^{18}F]poly(hydrogen fluoride) (Py·9H[^{18}F]F) prepared as previously described[33] was utilized for the desulfurization−fluorination of **8e** (25 μmol batch) and [^{18}F]**16e** was obtained. The results of the radiochemical reactions (average of three identical experiments) with carrier-added Py·9H[^{18}F]F and **8e** are outlined in Table 7.

The product spectrum of the reactions depended on the amount of carrier-added Py·9H[^{18}F]F in the reaction mixture. Small excess (entries 1−3, 4 equiv of HF) resulted in a fluorine-18 for fluorine-19 exchange and formation of [^{18}F]**8e** as the radiochemical main product. Here, the difluoride [^{18}F]**16e** was not observed. On the other hand quadruplication of Py·9H[^{18}F]F (entries 7−9, 16 equiv of HF) provided the desulfurization−fluorination product [^{18}F]**16e** with a radiochemical yield (rcy) of 5.5% (decay corrected, dc). When a median amount of Py·9H[^{18}F]F (entries 4−6, 8 equiv of HF) was used and the solvent amount was doubled from 150 to 300 μL, rcy of [^{18}F]**16e** was increased to 9.0% (dc). Compared to the experiments with the small excess of fluorination reagent (entries 1−3), only traces (rcy ~0.5%) of the isotopic exchange product [^{18}F]**8e** were formed in experiments 4−9.

Conclusion

Different ω-substituted alkyl aryl thioethers can be directly transformed to terminal 1,1-difluoroalkanes by two succeeding oxidations of sulfur by an electrophile and fluoro-Pummerer-like rearrangements using the reagents combination of DBH and Olah's reagent. In contrast, both the anodic and other chemical desulfurization−fluorination reactions do need thioacetals as starting materials.[21−25] In general this desulfurization−fluorination reaction is also possible starting from intermediate α-fluorinated alkyl aryl thioethers. On the basis of the latter transformation, a new radiofluorination protocol was developed. The radiolabeled difluoride [^{18}F]**16e** was synthesized from α-fluorothioether **8e** by combination of DBH and carrier-added Py·9H[^{18}F]F. Maximal radiochemical yield of 9.0% [^{18}F]**16e** was achieved with 8-fold excess of Py·9H[^{18}F]F.

Experimental Section

Chemistry. General analytical methods and equipment as well as general procedure for oxidative desulfurization−difluorination with DBH/Olah's reagent are given in Supporting Information. For some long chain compounds ^{13}C NMR signals at $\delta \sim$ 29 ppm do have multiple intensity.

Radiochemistry. Radiosyntheses were carried out using an automated PET tracer synthesizer. The recorded data were processed by a commercial software. Identification of the radiosynthesized compounds [^{18}F]**8e** and [^{18}F]**16e** was performed by gradient radio-HPLC system with an UV detector, a γ-detector, and a Nucleosil 100-5 C18 column (250 mm × 4.6 mm). Detection was conducted at λ = 254 nm. The solvents used were A (water + 0.1% TFA) and B (CH_3CN + 0.1% TFA). The mobile phase was a gradient using 40:60 A/B to 1:99 A/B mixture over 20 min, holding for 18 min and back to 40:60 A/B mixture in 2 min at a common flow rate of 1.5 mL/min. Radiochemical yield and purity were determined by the analysis of the HPLC chromatograms of the γ-channel.

Fluorination of the Thioethers with NIS and Olah's Reagent. General Procedure. The reaction was carried out in a 100-mL Teflon flask. To a solution of thioether (0.5 mmol) in absolute CH_2Cl_2 (5 mL) was added Olah's reagent (for equivalents used, see Table 1) via a polypropylene/polyethylene syringe. The mixture was cooled to 0 °C, and NIS (for the amounts, see Table 1) was added. After 30 min at 0 °C the reaction mixture was allowed to warm to room temperature and was stirred at this temperature overnight. Then ice−water was added, and the reaction mixture was neutralized with concentrated aqueous NH_3. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with 0.1 N HCl (2 × 20 mL) and 5% aqueous $NaHCO_3$ (2 × 20 mL) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the products **2**, **3**, and **4** were separated by column chromatography (silica gel, cyclohexane/ethyl acetate, 40:1) or HPLC (cyclohexane).

1,1-Difluoroundec-2-yl-(4-nitrophenyl)thioether (2). Following the general procedure the reaction was carried out in a 0.5 mmol scale using Olah's reagent (0.23 mL, 1.00 mmol, 2.0 equiv) and NIS (0.55 mmol, 1.1 equiv). After HPLC purification (cyclohexane) the product was obtained as a colorless oil (20 mg, 12%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, 3 H, CH_3, $^3J_{H,H}$ = 6.9 Hz), 1.30 (br s, 12 H, CH_2), 1.40−1.97 (m, 4 H, CH_2), 3.45 (m, 1 H, CH), 5.85 (td, 1 H, CH, $^2J_{H,F}$ = 56 Hz, $^3J_{H,H}$ = 4 Hz), 7.50 (d, 2 H, CH, $^3J_{H,H}$ = 8.8 Hz), 8.15 (d, 2 H, CH, $^3J_{H,H}$ = 8.9 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 14.1 (q), 22.7 (t), 26.6, 26.9, 27.9 (t, $^3J_{C,F}$ = 3.2 Hz), 29.2, 29.3, 29.4 (t), 31.8 (t), 50.4 (t, $^2J_{C,F}$ = 21.3 Hz), 116.3 (t, $^1J_{C,F}$ = 246 Hz), 124.0 (d), 129.5 (d), 144.5 (s), 146.2 (s). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −119.6 (ddd, 1 F, $^2J_{F,F}$ = 277.4 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 12.6 Hz), −119.8 (ddd, 1 F, $^2J_{F,F}$ = 277.4 Hz, $^2J_{H,F}$ = 56.4 Hz, $^3J_{H,F}$ = 12.6 Hz). MS (EI-GC inlet): m/z (%) 345 (97) [M^+], 328 (18) [$M^+ - OH$], 315 (18) [$M^+ - NO$], 294 (64) [$M^+ - CHF_2$], 260 (11) [$C_{11}H_{12}F_2NO_2S^+$], 232 (3) [$C_9H_8F_2NO_2S^+$], 218 (4) [$C_8H_6F_2NO_2S^+$], 207 (12), 168 (13) [$C_7H_6NO_2S^+$], 155 (100) [$HSC_6H_5-NO_2^+$], 125 (39) [$C_9H_{17}^+$], 124 (34), 109 (12) [$C_6H_5S^+$], 97 (18) [$C_7H_{13}^+$], 83 (24) [$C_6H_{11}^+$], 69 (33) [$C_5H_9^+$], 57 (38) [$C_4H_9^+$], 55 (52) [$C_4H_7^+$], 51 (5) [HCF_2^+], 43 (53) [$C_3H_7^+$] 41 (53) [$C_3H_5^+$]. HRMS (ESI): [M + Na^+] calcd for $C_{17}H_{25}F_2NO_2SNa^+$ 368.1466, found 368.1466.

1,1,2-Trifluoroundec-2-yl-(4-nitrophenyl)thioether (3). The product was obtained (entry 4, Table 1) as a colorless oil. Yield: 137 mg (35%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (m, 3 H, CH_3), 1.19−1.38 (m, 12 H, CH_2), 1.54−1.70 (m, 2 H, CH_2), 1.82−2.18 (m, 2 H, CH_2), 5.55 (ddd, 1H, CH, $^2J_{H,F}$ = 55.8 Hz, $^2J_{H,F}$ = 54.4 Hz,

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$^3J_{H,F}$ = 2.8 Hz), 7.79 (d, 2 H, CH_2, $^3J_{H,H}$ = 8.8 Hz), 8.22 (d, 2 H, $^3J_{H,H}$ = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 14.1 (q), 22.7 (t), 22.9 (td, $^3J_{C,F}$ = 2.6 Hz), 29.2, 29.4, 29.5, 29.7 (t), 31.8 (t), 32.6 (tdd, $^2J_{C,F}$ = 20.9 Hz, $^3J_{C,F}$ = 1.6 Hz), 104.3 (sddd, $^1J_{C,F}$ = 228.6 Hz, $^2J_{C,F}$ = 25.9 Hz, $^2J_{C,F}$ = 23.9 Hz), 112.3 (dddd, $^1J_{C,F}$ = 253.1 Hz, $^1J_{C,F}$ = 248.9 Hz, $^2J_{C,F}$ = 40.3 Hz), 123.8 (d), 136.2 (d, $^4J_{C,F}$ = 2.0 Hz), 136.5 (s), 148.5 (s). ^{19}F NMR (d_6-Benzol, 470 MHz): δ −126.8 (ddd, 1 F, $^2J_{F,F}$ = 284.1 Hz, $^2J_{H,F}$ = 54.3 Hz, $^3J_{F,F}$ = 13.4 Hz), −133.3 (ddd, 1 F, $^2J_{F,F}$ = 284.3 Hz, $^2J_{H,F}$ = 55.7 Hz, $^3J_{F,F}$ = 14.4 Hz), −143.0 (m, 1 F). MS (EI-GC inlet): *m/z* (%) 363 (48) [M^+], 346 (8) [M^+−OH], 343 (4) [M^+-HF], 312 (12) [M^+-CHF_2], 292 (7) [M^+-HF-CH_2], 281 (12), 231 (7), 207 (36) [$C_{11}H_{18}F_3^+$], 181 (5) [$C_9H_{12}F_3^+$], 165 (9) [$C_8H_{12}F_3^+$], 155 (100) [$C_6H_5NO_2S^+$], 124 (41) [$C_6H_5NO_2S^+$-NO], 109 (15) [$C_6H_5S^+$], 81 (19), 71 (33) [$C_5H_{11}^+$], 67 (15) [$C_5H_7^+$], 55 (33) [$C_4H_7^+$], 43 (51) [$C_3H_7^+$], 41 (42) [$C_3H_5^+$]. HRMS (ESI): [M + Na^+] calcd for $C_{17}H_{24}F_3NO_2SNa^+$ 386.1372, found 386.1370.

1,1-Difluoroundecane (4). Yield: 21 mg (11%, from entry 4, Table 1). The analytical data agree with those described in our earlier work.[26a]

Oxidative Desulfurization−Difluorination. General Procedure. The general procedure of this reaction and compounds **4**, **13a−e**, **16a−c**, and **16e** was described in our earlier work.[26a]

1-Bromo-1-fluoroundecane (9). Isolated by column chromatography (silica gel, pentane) from the optimization reaction (Table 4, entry 9). Yield: 90 mg (36%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3 H, CH_3, $^3J_{H,H}$ = 6.9 Hz), 1.19−1.40 (m, 12 H, CH_2,), 1.42−1.61 (m, 2 H, CH_2), 1.94−2.36 (m, 4 H, CH_2), 6.45 (dt, 1 H, CH, $^2J_{H,F}$ = 50.5 Hz, $^3J_{H,H}$ = 5.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q), 22.7 (t), 25.0 (td, $^3J_{C,F}$ = 3.9 Hz), 28.7, 29.3, 29.4, 29.5 (t), 31.9 (t), 40.6 (td, $^2J_{C,F}$ = 18.6 Hz), 95.8 (dd, $^1J_{C,F}$ = 252.4 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −130.7 (ddd, 1 F, $^2J_{H,F}$ = 50.5 Hz, $^3J_{H,F}$ = 20.4 Hz, $^3J_{H,F}$ = 17.4 Hz). MS (EI-GC inlet): *m/z* (%) 254/252 (< 0.1/ < 0.1) [M^+], 183/181 (1/1) [$C_6H_{11}BrF^+$], 169/167 (2/2) [$C_5H_9BrF^+$], 155/153 (9/9) [$C_4H_7BrF^+$], 131 (24) [$C_8H_{13}F^+$], 117 (38) [$C_7H_{14}F^+$], 103 (22) [$C_6H_{12}F^+$], 97 (48) [$C_7H_{13}^+$], 85 (50) [$C_6H_{13}^+$], 71 (58) [$C_5H_{11}^+$], 57 (81) [$C_4H_9^+$], 55 (89) [$C_4H_7^+$], 43 (81) [$C_3H_7^+$], 41 (100) [$C_3H_5^+$].

1,1-Dibromo-1-fluoroundecane (11). Found as a byproduct of the optimization reaction (Table 4, entry 9) for the synthesis of 1-bromo-1-fluoroundecane (**9**). Isolated by column chromatography (silica gel, pentane) as a colorless oil. Yield: 17 mg (5%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, 3 H, CH_3, $^3J_{H,H}$ = 7.0 Hz), 1.21−1.35 (m, 12 H, CH_2), 1.36−1.43 (m, 2 H, CH_2), 1.64−1.72 (m, 2 H, CH_2), 2.60−2.73 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 14.1 (q), 22.7 (t), 26.6 (td, $^3J_{C,F}$ = 2.3 Hz), 28.2, 29.3, 29.4, 29.5 (t), 31.9 (t), 53.1 (td, $^2J_{C,F}$ = 18.6 Hz), 97.2 (sd, $^1J_{C,F}$ = 320.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −43.4 (t, 1 F, $^3J_{H,F}$ = 15.5 Hz). MS (EI-GC inlet): *m/z* (%) 334/332/330 (< 0.1/ < 0.1/ < 0.1) [M^+], 253/251 (10/11) [M^+-Br], 211/209 (7/7) [$C_8H_{15}BrF^+$], 197/195 (10/10) [$C_7H_{13}BrF^+$], 183/181 (7/7) [$C_7H_{11}BrF^+$], 177/175 (8/8) [$C_7H_4Br^+$], 139/137 (6/7) [$C_3H_3BrF^+$], 109 (30), 95 (54) [$C_7H_{11}^+$], 85 (78) [$C_6H_{13}^+$], 71 (100) [$C_5H_{11}^+$], 57 (90) [$C_4H_9^+$], 41 (57) [$C_3H_5^+$].

5-Bromo-1,1-difluoropentane (13f). The reaction was carried out in a 0.5 mmol scale with 4-nitrophenyl-(5-bromopent-1-yl)-thioether (**12f**) in 20 h at room temperature. In addition to the title compound **13f**, 1,5-dibromo-1-fluoropentane **14f** was found as the major byproduct; **13f** was isolated as a colorless oil by column chromatography (silica gel, pentane). Yield: 48 mg (51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18−1.34 (m, 2 H, CH_2), 1.60−1.72 (m, 2 H, CH_2) 1.77−1.99 (m, 2 H, CH_2), 3.41 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.6 Hz), 5.80 (tt, 1 H, CH, $^2J_{H,F}$ = 56.7 Hz, $^3J_{H,H}$ = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9 (tt, $^3J_{C,F}$ = 5.6 Hz), 32.1 (t), 32.7 (t), 33.3 (tt, $^2J_{C,F}$ = 21.1 Hz), 117.0 (dt, $^1J_{C,F}$ = 239.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −116.4 (dt, 2 F, $^2J_{H,F}$ = 56.7 Hz, $^3J_{H,F}$ = 17.4 Hz). MS (EI-GC inlet): *m/z* (%) 188/186 (3/3) [M^+], 168/166 (2/2) [M^+-HF], 107 (100) [$C_5H_9F_2^+$], 93 (5)[$C_4H_7F_2^+$], 87 (79) [$C_5H_8F^+$], 67 (52) [$C_5H_7^+$], 59 (79) [$C_3H_4F^+$], 55 (79) [$C_4H_7^+$], 51 (39) [CHF_2^+], 41 (88) [$C_3H_5^+$].

1,5-Dibromo-1-fluoropentane (14f). Yield: 57 (46%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18−1.34 (m, 2 H, CH_2), 1.60−1.72 (m, 2 H, CH_2) 1.77−1.99 (m, 2 H, CH_2), 3.41 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.6 Hz), 6.46 (dt, 1 H, CH, $^2J_{H,F}$ = 50.2 Hz, $^3J_{H,H}$ = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9 (td, $^3J_{C,F}$ = 5.6 Hz), 32.1 (t), 32.7 (t), 33.3 (td, $^2J_{C,F}$ = 21.1 Hz), 94.75 (dd, $^1J_{C,F}$ = 252.4 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −131.7 (m, 1 F, $^2J_{H,F}$ = 50.3 Hz, $^3J_{H,F}$ = 18.9 Hz). MS (EI-GC inlet): *m/z* (%) 250/248/246 (< 0.1/ < 0.1/ < 0.1) [M^+], 169/167 (16/16) [M^+-Br˙], 149/147 (13/13) [$C_5H_8Br^+$], 109/107 (9/9) [$C_2H_4Br^+$], 95/93 (5/5) [CH_2Br^+], 87 (100) [$C_5H_8F^+$], 67 (47) [$C_5H_7^+$], 59 (63) [$C_3H_4F^+$], 41 (75) [$C_3H_5^+$].

15-Bromo-1,1-difluoropentadecane (13h). The reaction was carried out in a 0.135 mmol scale with 4-nitrophenyl-(15-bromopentadec-1-yl)thioether (**12h**) in 24 h at room temperature. After column chromatography (silica gel, pentane) a colorless oil of **13h** was isolated. Yield: 10.2 mg (23%). As the major product the bromofluoride 1,15-dibromo-1-fluorododecane (**14h**) was formed in this reaction. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18−1.38 (m, 16 H, CH_2), 1.38−1.63 (m, 4 H, CH_2), 1.71−1.93 (m, 4 H, CH_2), 2.03−2.40 (m, 2 H, CH_2), 3.41 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.9 Hz), 5.79 (tt, 1 H, CH, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,H}$ = 4.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (tt, $^3J_{C,F}$ = 5.5 Hz), 28.2, 28.7, 28.8, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7 (t), 32.8 (t), 34.0 (t), 34.1 (tt, $^2J_{C,F}$ = 20.5 Hz), 117.5 (dt, $^1J_{C,F}$ = 238.8 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −116.2 (dt, 2 F, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,F}$ = 17.6 Hz). MS (EI-GC inlet): *m/z* (%) 328/326 (< 0.1/ < 0.1) [M^+], 247 (< 0.1) [$C_{15}H_{29}F_2^+$], 205 (< 0.1) [$C_{12}H_{23}F_2^+$], 191 (1), [$C_{11}H_{21}F_2^+$], 177 (1) [$C_{10}H_{19}F_2^+$], 163 (3) [$C_9H_{17}F_2^+$], 149 (13) [$C_8H_{15}F_2^+$], 137/135 (83/100) [$C_4H_8Br^+$], 121 (17) [$C_6H_{11}F_2^+$], 107 (9) [$C_5H_9F_2^+$], 69 (25) [$C_5H_9^+$], 57 (33) [$C_4H_9^+$], 55 (39) [$C_4H_7^+$], 41 (23) [$C_3H_5^+$].

1,15-Dibromo-1-fluoropentadecane (14h). Yield: 23.3 mg (45%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18−1.38 (m, 16 H, CH_2), 1.38−1.63 (m, 4 H, CH_2), 1.71−1.93 (m, 4 H, CH_2), 2.03−2.40 (m, 2 H, CH_2), 3.41 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.9 Hz), 6.45 (dt, 1 H, CH, $^2J_{H,F}$ = 50.4 Hz, $^3J_{H,H}$ = 5.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.0 (td, $^3J_{C,F}$ = 3.9 Hz), 28.2, 28.7, 28.8, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7 (t), 32.8 (t), 34.0 (t), 40.6 (td, $^2J_{C,F}$ = 18.9 Hz), 95.8 (dd, $^1J_{C,F}$ = 252.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −130.7 (ddd, 1 F, $^2J_{H,F}$ = 50.5 Hz, $^3J_{H,F}$ = 20.4 Hz, $^3J_{H,F}$ = 17.5 Hz). MS (EI-GC inlet): *m/z* (%) 388/386 (< 0.1/ < 0.1) [M^+], 309/308 (2/2) [M^+ − Br•], 367/265 (2/2) [$C_{12}H_{23}BrF^+$], 253/251 (3/3) [$C_{11}H_{22}$-BrF^+], 239/237 (3/3) [$C_{10}H_{19}BrF^+$], 223/221 (3/3) [$C_9H_{17}BrF^+$], 207/205 (5/5) [$C_8H_{15}BrF^+$], 193/191 (5/5) [$C_8H_{16}Br^+$], 179/175 (6/5) [$C_7H_{14}Br^+$], 149/147 (12/12) [$C_5H_{10}Br^+$], 137/135 (41/41) [$C_4H_8Br^+$], 69 (68) [$C_5H_9^+$], 57 (65) [$C_4H_9^+$], 55 (100) [$C_4H_7^+$], 41 (56) [$C_3H_5^+$].

Methyl 11-Bromo-11-fluoroundecanoate (17a). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29−1.48 (m, 12 H, CH_2), 1.57−1.66 (m, 2 H, CH_2), 1.74−1.89 (m, 2 H, CH_2), 2.30 (t, 2 H, CH_2, $^3J_{H,H}$ = 7.5 Hz), 3.67 (s, 3 H, CH_3), 6.45 (dt, 1 H, CH, $^2J_{H,F}$ = 50.5 Hz, $^3J_{H,H}$ = 5.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.0 (td, $^3J_{C,F}$ = 4.0 Hz), 24.9 (t), 29.0, 29.1, 29.2 (t), 34.0 (t), 40.6 (td, $^2J_{C,F}$ = 18.7 Hz), 51.4 (s), 95.7 (dd, $^1J_{C,F}$ = 252.4 Hz), 174.3 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −130.8 (ddd, 1 F, $^2J_{H,F}$ = 50.5 Hz, $^3J_{H,F}$ = 20.4 Hz, $^3J_{H,F}$ = 17.5 Hz). MS (EI-GC inlet): *m/z* (%) 298/296 (< 0.1/ < 0.1) [M^+], 267/265 (2/2) [$C_{11}H_{19}BrFO^+$], 217 (4) [$C_{12}H_{22}FO^+$], 185 (3) [$C_{11}H_{21}O_2^+$], 101 (4) [$C_5H_9O_2^+$], 87 (34) [$C_4H_7O_2^+$], 74 (100) [$C_3H_6O_2^+$], 69 (11) [$C_5H_9^+$], 59 (12) [$C_2H_3O_2^+$], 55 (15) [$C_4H_7^+$], 43 (11) [$C_3H_7^+$], 41 (14) [$C_3H_5^+$]. HRMS (ESI): [M + Na^+] calcd for $C_{12}H_{22}BrFO_2Na^+$ 321.0660/319.0679, found 321.0655/319.0669.

1,1-Difluoro-11-methoxyundecane (16d). The reaction was carried out in a 2.00 mmol scale with 4-chorophenyl-(11-methoxyundec-1-yl)thioether (**15d**) in 17 h at room temperature. Besides **16d**,

1-bromo-1-fluoro-11-methoxyundecane (**17d**, 6%) was formed as the major byproduct. After column chromatography (silica gel, pentane/diethylether 90:1) the product was isolated as a colorless oil. Yield: 413 mg (93%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24−1.38 (m, 12 H, CH_2), 1.38−1.62 (m, 4 H, CH_2), 1.71−1.91 (m, 2 H, CH_2), 3.33 (s, 3 H, CH_3), 3.36 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.6 Hz), 5.79 (tt, 1 H, CH, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,H}$ = 4.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (tt, $^3J_{C,F}$ = 5.4 Hz), 26.1 (t), 29.0, 29.3, 29.4, 29.5, 29.6 (t), 34.1 (tt, $^2J_{C,F}$ = 20.6 Hz), 58.5 (q), 72.9 (t), 117.4 (dt, $^1J_{C,F}$ = 238.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −116.2 (dt, 2 F, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,F}$ = 17.6 Hz). MS (EI-GC inlet): *m/z* (%) 222 (2) [M^+], 205 (6) [M^+−OH], 190 (6) [M^+-CH_4O], 162 (9) [$C_9H_{16}F_2^+$], 134 (7) [$C_7H_{12}F_2^+$], 120 (12) [$C_6H_{10}F_2^+$], 83 (29) [$C_6H_{11}^+$], 69 (30) [$C_6H_9^+$], 55 (38) [$C_4H_7^+$], 45 (100) [$C_2H_5O^+$], 41 (37) [$C_3H_5^+$]. HRMS (ESI): [M+Na^+] calcd for $C_{12}H_{24}F_2ONa^+$ 245.1687, found 245.1686.

1,1-Difluoro-11-aminoundecane (16f). A mixture of 1,1-difluoro-11-*N*-phthalimidylundecane and 1-bromo-1-fluoro-11-*N*-phthalimidylundecane[26a] (**16e/17e**, 60 mg, 0.175 mmol) and hydrazine hydrate (11 μL, 11.2 mg, 0.175 mmol) was dissolved in ethanol (2 mL) and stirred at room temperature overnight. Then water (5 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with water (2 × 5 mL) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the product was obtained as a colorless liquid (difluoride/bromofluoride, 66:34). Yield: 20 mg (56%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 1.25−1.37 (m, 14 H, CH_2), 1.37−1.56 (m, 2 H, CH_2), 1.62−1.95 (m, 2 H, CH_2), 2.67 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.8 Hz), 5.78 (tt, 1 H, CH, $^2J_{H,F}$ = 57.1 Hz, $^3J_{H,H}$ = 4.6 Hz). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 21.9 (tt, $^3J_{C,F}$ = 5.5 Hz), 26.6 (t), 28.8, 29.1, 29.2, 29.3 (t), 33.4 (t), 33.8 (tt, $^2J_{C,F}$ = 20.5 Hz), 41.9 (t), 117.4 (dt, $^1J_{C,F}$ = 238.4 Hz). ^{19}F NMR (CD_2Cl_2, 282 MHz): δ −116.1 (dt, 2 F, $^2J_{H,F}$ = 57.1 Hz, $^3J_{H,F}$ = 17.8 Hz). MS (EI-GC inlet): *m/z* (%) 207 (7) [M^+], 187 (2) [$C_{11}H_{22}FN^+$], 162 (1) [$C_9H_{16}F_2^+$], 148 (2) [$C_8H_{15}F_2^+$], 142 (6) [$C_9H_{15}F^+$], 128 (6) [$C_8H_{14}F^+$], 114 (11) [$C_7H_{16}N^+$], 100 (25) [$C_6H_{14}N^+$], 86 (57) [$C_5H_{12}N^+$], 55 (100) [$C_4H_7^+$], 43 (13) [$C_3H_7^+$], 41 (13) [$C_3H_5^+$]. HRMS (ESI): [M+H^+] calcd for $C_{11}H_{23}F_2NH^+$ 208.1858, found 208.1871.

12-(2-Bromo-4-nitrophenoxy)-1,1-difluorododecane (16g1) and 12-(2,6-Dibromo-4-nitrophenoxy)-1,1-difluordodecane (16g2). The reaction was carried out in a 0.5 mmol scale with 4-chlorophenyl-[12-(4-nitrophenoxy)dodec-1-yl]thioether (**15g**) in 20 h at room temperature. After column chromatography (silica gel, pentane/diethylether, 30:1) two ring-brominated difluorides were isolated. Bromofluorides brominated additionally in the ring were obtained as byproducts (4%).

12-(2-Bromo-4-nitrophenoxy)-1,1-difluorododecane (16g1). The product was obtained as an orange solid. Yield: 81 mg (38%). Mp 65 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (br s, 12 H, CH_2), 1.40−1.64 (m, 4 H, CH), 1.68−1.98 (m, 4 H, CH_2), 4.13 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.4 Hz), 5.79 (tt, 1 H, CH, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,H}$ = 4.5 Hz), 6.93 (d, 1 H, CH, $^3J_{H,H}$ = 9.1 Hz), 8.18 (dd, 1 H, CH, $^3J_{H,H}$ = 9.1 Hz, $^4J_{H,H}$ = 2.7 Hz), 8.45 (d, 1 H, CH, $^4J_{H,H}$ = 2.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (tt, $^3J_{C,F}$ = 5.4 Hz), 25.8 (t), 28.8, 29.0, 29.2, 29.3, 29.4 (t), 34.1 (tt, $^2J_{C,F}$ = 20.6 Hz), 70.1 (t), 111.4 (d), 112.1 (d), 117.5 (dt, $^1J_{C,F}$ = 238.6 Hz), 124.6 (d), 129.1 (s), 141.3 (s), 164.6 (s). ^{19}F NMR (CD_2Cl_2, 282 MHz): δ −116.3 (dt, 2 F, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,F}$ = 17.7 Hz). MS (EI-GC inlet): *m/z* (%) 423/421 (14/14) [M^+], 219/217 (17/14) [$C_6H_4BrNO_3^+$], 204 (17) [$C_{12}H_{22}F_2^+$], 161 (11) [$C_9H_{15}F_2^+$], 147 (25) [$C_8H_{13}F_2^+$], 121 (44) [$C_6H_{11}F_2^+$], 83 (33) [$C_6H_{13}^+$], 69 (50) [$C_5H_9^+$], 55 (100) [$C_4H_7^+$], 41 (72) [$C_3H_5^+$]. HRMS (ESI): [M + Na^+] calcd for $C_{18}H_{26}BrF_2NO_3Na^+$ 446.0937/444.0956, found 446.0942/444.0960.

12-(2,6-Dibromo-4-nitrophenoxy)-1,1-difluorododecane (16g2). The product was obtained as an orange oil. Yield: 144 mg (57%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (m, 12 H, CH_2), 1.47−1.66 (m, 4 H, CH_2), 1.67−2.00 (m, 4 H, CH_2), 4.09 (t, 2 H, CH_2, $^3J_{H,H}$ = 6.5 Hz), 5.79 (tt, 1 H, CH, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,H}$ = 4.5 Hz), 8.41 (s, 2 H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (tt, $^3J_{C,F}$ = 5.4 Hz), 25.7 (t), 29.0, 29.3, 29.4, 29.5, 29.7, 30.0 (t), 34.0 (tt, $^2J_{C,F}$ = 20.6 Hz), 74.4 (t), 117.4 (dt, $^1J_{C,F}$ = 238.7 Hz), 118.7 (d), 128.1 (s), 144.0 (s), 159.2 (s). ^{19}F NMR (CD_2Cl_2, 282 MHz): δ −116.2 (dt, 2 F, $^2J_{H,F}$ = 57.0 Hz, $^3J_{H,F}$ = 17.6 Hz). HRMS (ESI): [M + Na^+] calcd for $C_{18}H_{25}Br_2F_2NO_3Na^+$ 526.0021/524.0042/522.0061, found 526.0029/524.0046/522.0070.

4-Chlorophenyl-(1-fluoroundec-1-yl)thioether (8b). According to the method described by Wnuk and Robins[12b] a flame-dried Schlenk flask was purged with argon and charged with anhydrous CH_2Cl_2 (1 mL), 4-chlorophenylundec-1-ylthioether (0.25 mmol), and $SbCl_3$ (4 mg, 0.02 mmol, 0.07 equiv). DAST (0.46 mL, 57 mg, 0.35 mmol, 1.40 equiv) was injected via a polypropylene/polyethylene syringe, and the reaction mixture was stirred at ambient temperature for 24 h. Then ice-cold saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2C1_2 (2 × 20 mL), and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and evaporated to give a brown oil. Because of HF elimination the purification by column chromatography was not possible. Yield (crude product): 79 mg (100%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3 H, CH_3, $^3J_{H,H}$ = 6.9 Hz), 1.04−1.28 (m, 14 H, CH_2), 1.36−1.56 (m, 2 H, CH_2) 1.74−2.09 (m, 2 H, CH_2), 5.75 (ddd, 1 H, CH, $^2J_{H,F}$ = 55.6 Hz, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 7.30 (d, 2 H, CH, $^3J_{H,H}$ = 8.6 Hz), 7.44 (d, 2 H, CH, $^3J_{H,H}$ = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q), 22.6 (t), 25.3 (td, $^3J_{C,F}$ = 3.2 Hz), 29.0, 29.3, 29.4, 29.5 (t), 31.8 (t), 35.2 (td, $^2J_{C,F}$ = 21.8 Hz), 101.7 (dd, $^1J_{C,F}$ = 218.3 Hz), 129.1 (d), 131.5 (dd, $^4J_{C,F}$ = 2.2 Hz), 133.4 (sd, $^3J_{C,F}$ = 2.1 Hz), 134.1 (s, C-1). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −145.7 (ddd, 1 F, $^2J_{H,F}$ = 55.6 Hz, $^3J_{H,F}$ = 19.6 Hz, $^3J_{H,F}$ = 15.3 Hz). MS (EI-GC inlet): *m/z* (%) 316 (17) [M^+], 296 (71) [M^+−HF], 183 (58) [$C_9H_8ClS^+$], 157 (17) [$C_7H_6ClS^+$], 144 (100) [$C_6H_5ClS^+$], 108 (13) [$C_6H_4S^+$], 97 (42) [$C_7H_{13}^+$], 83 (33) [$C_6H_{13}^+$], 69 (25) [$C_5H_9^+$], 55 (25) [$C_4H_7^+$], 41 (33) [$C_3H_5^+$].

4-Tolyl-(1-fluoro-11-methoxyundec-1-yl)thioether (8d), 4-Chlorophenyl-(11-bromo-1-fluorododec-1-yl)thioether (18b), Methyl 11-(4-chlorophenylthio)-11-fluoroundecanoate (19b), and 4-Chlorophenyl-[12-(4-nitrophenoxy)-1-fluorododec-1-yl]thioether (19g). For spectroscopic data, see Supporting Information.

4-Chlorophenyl-(1-fluoro-11-*N*-phthalimidylundec-1-yl)thioether (8e). According to the method described by Wnuk and Robins,[12b] compound **8e** was synthesized from 2-[11-(4-chlorophenylthio)-undecyl]isoindoline-1,3-dione (**15e**) in a 0.25 mmol scale. Because of HF elimination the purification by column chromatography was not possible. Yield (crude product): 115 mg (100%). Mp 70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07−1.40 (m, 12 H, CH_2), 1.40−1.54 (m, 2 H, CH_2), 1.58−1.74 (m, 2 H, CH_2) 1.91 (m, 1H, CH_2), 2.97 (m, 1 H, CH_2), 3.67 (t, 2 H, CH_2, $^3J_{H,H}$ = 7.3 Hz), 5.73 (ddd, 1 H, CH, $^2J_{H,F}$ = 55.6 Hz, $^3J_{H,F}$ = 6.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 7.29 (d, 2 H, CH, $^3J_{H,H}$ = 8.5 Hz), 7.43 (d, 2 H, CH, $^3J_{H,H}$ = 8.5 Hz), 7.70 (dd, 2 H, CH, $^3J_{H,H}$ = 5.4 Hz, $^4J_{H,H}$ = 3.1 Hz), 7.83 (dd, 2 H, CH, $^3J_{H,H}$ = 5.4 Hz, $^4J_{H,H}$ = 3.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2 (td, $^3J_{C,F}$ = 3.2 Hz), 26.7 (t), 28.5 (t), 28.9, 29.0, 29.2, 29.3 (t), 35.1 (td, $^2J_{C,F}$ = 21.9 Hz), 38.0 (t), 101.6 (dd, $^1J_{C,F}$ = 218.3 Hz), 123.0 (s), 129.1 (d), 131.5 (sd $^3J_{C,F}$ = 2.1 Hz), 132.2 (s), 133.4 (dd, $^4J_{C,F}$ = 2.0 Hz), 133.8 (d), 134.1 (s), 168.4 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −145.9 (ddd, 1 F, $^2J_{H,F}$ = 55.6 Hz, $^3J_{H,F}$ = 19.6 Hz, $^3J_{H,F}$ = 15.3 Hz). MS (EI-GC-inlet): *m/z* (%) 461 (< 0.1) [M^+], 443 (25) [M^+−HF], 298 (4) [$C_{17}H_{26}ClS^+$], 230 (1) [$C_{14}H_{16}NO_2^+$], 216 (2) [$C_{13}H_{14}NO_2^+$], 202 (3) [$C_{12}H_{12}NO_2^+$], 160 (100) [$C_9H_6NO_2^+$], 148 (32) [$C_8H_6NO_2^+$], 144 (27) [$C_6H_5ClS^+$], 77 (4) [$C_6H_5^+$], 55 (5) [$C_4H_7^+$]. HRMS (ESI): [M+Na^+] calcd for $C_{25}H_{29}ClFNO_2SNa^+$: 484.1484; found: 484.1479.

Oxidative Desulfurization−Fluorination of 4-Chlorophenyl-(1-fluorundec-1-yl)-thioether (8b). Olah's reagent (0.09 mL,

0.375 mmol, 3 equiv) was added to a solution of 4-chlorophenyl-(1-fluorundec-1-yl)thioether (**8b**, 40 mg, 0.125 mmol) in dry CH_2Cl_2 (2.5 mL) in a Telfon flask via a polypropylene/polyethylene syringe. DBH (54 mg, 0.188 mol, 1.5 equiv) was added, and the mixture was stirred at room temperature overnight. Then ice−water was added, and the reaction mixture was neutralized with concentrated NH_3 solution. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with 0.1 N HCl (2 × 20 mL) and 5% aqueous $NaHCO_3$ (2 × 20 mL) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the product, 1,1-difluoroundecane (**4**), was obtained as a colorless oil. 1-Bromo-1-fluoroundecane (**9**, 5%, ^{19}F NMR) was formed as a byproduct.

Under microwave irradiation at 45 °C, the reaction time and the equivalents of Olah's reagent could be reduced to 40 min and 1.1 equiv (see Table 6).

Radiosynthesis of Py·9H[^{18}F]F. To prepare Py·9H[^{18}F]F, no-carrier-added aqueous [^{18}F]fluoride ions were produced by irradiation of a 1.2 mL water target using 10 MeV proton beams on 97.0% enriched [^{18}O]water by the ^{18}O(p,n)^{18}F nuclear reaction. After discharging the cyclotron target an aliquot of aqueous [^{18}F]fluoride ions (194−491 MBq) was used for the preparation of Py·9H[^{18}F]F. It was transferred in a polypropylene, tube and the water was carefully distilled off in vacuo at 120 °C. Then Py·9HF (2.5−10.0 μL, 2.8−11.0 mg, 96−385 μmol HF, 4−16 equiv) and 50−100 μL of CH_2Cl_2 were added, and the mixture was heated to 35 °C for 30 min in an ultrasound bath. The solution was used for the next step without further purification.

Radiosynthesis of 1,1-[^{18}F]Difluoro-11-*N*-phthalimidylundecane (16e). The Py·9H[^{18}F]F solution was transferred to a tube containing 4-chlorophenyl-(1-fluoro-11-*N*-phthalimidylundec-1-yl)thioether (**8e**) (11.5 mg, 25 μmol), and CH_2Cl_2 (50−100 μL) was added. After the addition of DBH (21.5 mg, 75 μmol, 3 equiv) and CH_2Cl_2 (50−100 μL) the tube was sealed, and the mixture was left in an ultrasound bath for 30 min at 35 °C. The reaction was quenched and diluted by injection of acetonitrile (1 mL) and water (10 mL). The mixture was passed through a Waters Sep-Pak Plus C18 cartridge. The cartridge was washed with a mixture of acetonitrile (1 mL) and water for injection (10 mL) and eluted with acetonitrile (3.0 mL). The eluate was evaporated to dryness in vacuo and redissolved in acetonitrile (300 μL). The preparation was completed within approximately 71 min. The solution was assayed concerning radiochemical yields and purities of the products [^{18}F]**8e** (t_R ([^{18}F]**8e**) = 30.0 min) and [^{18}F]**16e** (t_R ([^{18}F]**16e**) = 21.5 min) with a radio-RP-HPLC system (see General Methods, Radiochemistry). Results are listed in Table 7. The chemical identities of [^{18}F]**8e** and [^{18}F]**16e** were proven by HPLC on the above-mentioned gradient system providing coelution of [^{18}F]**8e** and [^{18}F]**16e** and their non-radioactive counterparts **8e** and **16e**, respectively, which were added to the injection solutions beforehand.

Acknowledgment. These investigations were supported by the Deutsche Forschungsgemeinschaft (DFG), Collaborative Research Center (Sonderforschungsbereich) 656 "Molecular Cardiovascular Imaging" Projects A3, B1), University of Münster, Germany and by Siemens Medical Solutions to the European Institute for Molecular Imaging (EIMI) at the University of Münster, Germany.

Supporting Information Available: General experimental conditions, spectroscopic data of compounds **5**, **6**, **8d**, **18b**, **19b, g**, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.