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Practice of fluorous biphase chemistry: convenient synthesis of novel fluorophilic ethers via a Mitsunobu reaction

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Dedicated to Professor András Messmer on the occasion of his 80th birthday.

Abstract

The evolution of the term fluorous is addressed first, then a concise terminology is proposed, including fluorous partition coefficient, specific fluorophilicity and fluorousness. Some examples are shown for the design of higher generation fluorophilic molecules, involving Class I to Class III ponytails. Fluorophilic ethers of the structure of $ArC(CF_3)_2O(CH_2)_m(CF_2)_nF$ ($m = 1, n = 1, 7$; $m = 3, n = 8$) are obtained in high yields, when 2-aryl-1,1,1,3,3,3-hexafluoro-propanols are reacted either with trifluoroethyl- and 1*H*,1*H*-perfluorooctyl triflates (NaH/DMF, Williamson ether synthesis) or with 3-perfluorooctyl-propanol ($Ph_3P/EtO_2CN{=}NCO_2Et/PhCF_3$, Mitsunobu reaction), respectively. Fluorophilic phenol- and perfluoro-*tert*-butyl ethers can also be prepared effectively by the latter method. In case of higher homologues ($n = 7, 8$) product isolation can be facilitated using fluorous extraction (C_6F_{14}/CH_3OH). Specific fluorophilicity values of target molecules are estimated using a 2D method and compared with experimentally determined ones.

Keywords: Fluorine; Specific fluorophilicity; Mitsunobu reaction; Perfluoroalkylmethyl triflates

1. Introduction

The fluorous phase (i.e. the C–F bond rich part of a multiphase system [1,2]) has been involved in several innovative catalyst and reagent immobilization protocols, fluorous isolation techniques, and seems to alter the way of our thinking about synthetic chemistry [1–15]. In this respect not only chemical reactions, but product separations should also be considered at the design level of a chemical synthesis [1,3,7,12]. The native phasephilicity (e.g. hydrophilic, lipophilic, fluorophilic, etc.) of the components of a chemical reaction will determine their separation [16]. Thus, fluorous extraction can effectively be used for fluorophilic compounds [3,7,16], while chromatography over *F*-SiO_2 is the method of choice for the sequential isolation of untagged and *F*-tagged (i.e. perfluoroalkylated) molecules [13]. The popularity of these fluorous techniques is partly due to the unique physical and chemical properties associated with perfluorinated solvents, such as hydrophobicity and lipophobicity (amphiphobic [17]), inertness, non-toxicity, and easy separation [1–16].

The concept of fluorous biphase systems noticed by Vogt [18] in 1991, but first drafted by Horváth and Rábai [1] in 1994, served as a basis of several novel applications in homogeneous catalytic chemistry utilizing the temperature dependent miscibility of perfluorocarbon fluids with standard organic solvents [1,3,5,7,18]. Soon afterwards, Curran and coworkers introduced a series of synthetic and purification methods, called fluorous synthesis, in which organic target molecules are rendered selectively soluble in the fluorous phase by the temporary or permanent attachment of adequate fluorous labels [10–13]. Fluorous mixture synthesis, developed by Curran and coworkers [14] is the most recent application of the power of fluorous-tagging coupled with *F*-SiO_2 chromatography [13] to allow separation of a mixture of related compounds by their 'fluorine content' (or 'fluorousness' [16,19]).

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$\{F(CF_2)_n\text{-linker}\}_m(\text{parent molecule})$

Scheme 1. Structural pattern of a 'classic' fluorophile.

1.1. Terminology

The key issues of synthesis design besides choosing appropriate chemical reactions are solvent selection and the purposeful tuning of the phasephilicities of the involved molecules [1,3,5,7,12,16,20]. The term of phasephilicity [16] could be classified such as (1) *monophilic*: e.g. organophilic, hydrophilic, fluorophilic, and $scCO_2$-philic [21] (only one type of phase character is expressed in the molecules); (2) *amphiphilic* (two different types of domains are involved) [22]; or (3) *multiphilic* (more than two types of domains are involved in the complex structures) [23]. In certain cases, supercritical carbon dioxide ($scCO_2$) can be a substitute for fluorocarbon solvents [15,21].

A fluorous molecule, can be regarded as the union of fluorous (perfluorocarbon-like, rich in C–F bonds) and nonfluorous structural fragments and has a constitution as shown in Scheme 1.

If the above entity (Scheme 1) has a fluorous partition coefficient [20] value larger than one, $P_{FBS} > 1$, or fluorophilicity value larger than zero, $f = \ln P_{FBS} > 0$, [perfluoro(methylcyclohexane)-toluene solvent pair, $T = 25\ ^\circ C$], then it is called fluorophilic (or fluorophile) [16]. The synthesis of a fluorophile can be easily achieved by appending fluorous ponytails of appropriate number, length and shape (topology) as demonstrated by the early examples of the FBS concept [1–3]. At that time the word 'fluorous' was reserved for the identification of the C–F bond rich part of a multiphase system, which consisted of perfluorinated and other solvents, fluorous ligands, catalysts, and reagents. However, the meaning of the word fluorous expanded continuously and much of its original meaning has been lost if phase preference was considered. Thus, compounds having at least one perfluoroalkyl-group (R_{fn}) are called as 'light' (organophilic, $f = \ln P_{FBS} < 0$) or 'heavy' fluorous (fluorophilic, $f = \ln P_{FBS} > 0$) ones [16]. By now, both 'fluorophilicity' and 'fluorous phase affinity' are the used measures for phase preference, related to fluorous partition coefficient (P_{FBS}) [16,20]. Recently, specific fluorophilicity has been defined for compound '*i*', as the product of fluorophilicity and of the ratio of the van der Waals volumes of the expelled fluorous solvent and the entering solute molecules (Eq. (1), [16]).

$$f_{spec}(i) = \frac{V_{vdw}(CF_3C_6F_{11})}{V_{vdw}(i)} \quad (1)$$

While phase preferences can be easily predicted by Eq. (2), using calculated Hildebrand parameters (δ_{calcd}) [16], little is known about absolute solubilities in fluorous solvents.

$$f_{spec}(i) = a - b\delta_{calcd}(i) \quad (a, b \text{ are constants and } a, b > 0) \quad (2)$$

1.2. First and higher generation fluorophilic compounds

The question 'what makes a compound particularly soluble in the fluorous phase?' is still unanswered. However, the most important fact is that molecules rendered soluble in the fluorous phase usually do not have exposed functional groups capable for attractive intermolecular interactions via directional forces (e.g. dipole–dipole, hydrogen-bonding, π–π interaction, etc.); only weak interactions via universal attractive forces are appearing [24].

A very simple method for the estimation of fluorophilicities using only 2D structural formulae of compounds is based on the following experimental observation: the lower the calculated Hildebrand parameter, the higher the specific fluorophilicity of the molecule [16].

A 'universal protocol' for designing fluorophilic molecules consists of assembling several structural fragments to a molecule in a way that allows the required chemistry, while keeping the calculated Hildebrand parameter (δ_{calcd}) of the final constitution at the lowest value possible.

Simple calculations suggest (Eq. (3), that this can be achieved by incorporating CF_3 groups and branching in the fluorous ponytails, along with the use of other building blocks with low cohesive increments, such as $Si(CH_3)_3$ or $C(CH_3)_3$, if non-fluorous groups are considered [25].

These values (δ_{calcd}) can be estimated by a group contribution method using Eq. (3) [25], assuming that a compound's phase behavior is a result of the sum of the independent interactions of their constituents with like and unlike molecules [24].

$$\delta_{calcd} = \left(\frac{\sum^z \Delta U}{\sum^z \Delta V}\right)^{1/2} \quad (3)$$

Thus, for example isomeric ethers, such as $C_6H_5CH_2O$–$C(CF_3)_3$ and $C_6H_5C(CF_3)_2O$–CH_2CF_3, should have equal δ_{calcd} values and consequently similar fluorophilicities.

Furthermore, the effect of the highly electronegative perfluoroalkyl-groups on reaction centers can be insulated by the insertion of appropriate spacer groups in-between the R_{fn} groups and the organic domains (Scheme 1) [1,26,27]. Presently, the $-(CH_2)_n-$ and $-Si(CH_3)_2CH_2CH_2-$ groups are the most preferred ones [28,29]. Since, the physical properties of hetero atoms connected to *F*-alkyl groups are rather different from those of connected to alkyl groups, we propose that these atoms be regarded as part of the fluorous ponytails (e.g. OCF_3, SCF_3, Table 1).

With the exception of some perfluoropolyether type substitutions [15,18,30], all relevant publications seem to rely on the use of Class I ponytails, mostly involving *n*-perfluoroalkyl groups. The effect of branching [31] of the ponytail on fluorous phase affinity has been addressed very recently by both theory [16] and experiment [32].

We propose that compounds with higher generation fluorous ponytails, i.e. others than listed in Class I of Table 1, be studied for both their phase behavior and effective syntheses (cf. Rule 5. 'The structure of the fluorous ponytail' of [16]).

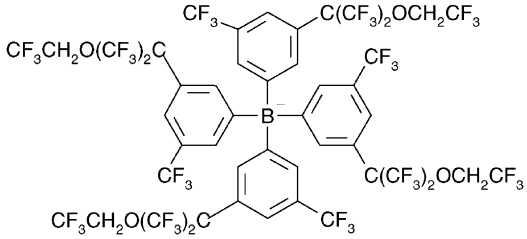
Table 1
Classification of selected fluorous ponytails

Entry	Group	Formula	M_w	F (%)	Used in FBC
Class I[a]					
1	CF_3	CF_3	69	82.6	No
2	$(CF_2)_3CF_3$	C_4F_9	219	78.1	Yes
3	$C(CF_3)_3$	C_4F_9	219	78.1	No
4	$(CF_2)_5CF_3$	C_6F_{13}	319	77.4	Yes
5	$(CF_2)_7CF_3$	C_8F_{17}	419	77.1	Yes
6	$(CF_2)_9CF_3$	$C_{10}F_{21}$	519	76.9	Yes
7	SF_5	SF_5	127	74.8	No
Class Ii[a]					
8–12	$(CF_2)_nX$, X = Cl, Br, I, SF_5, H				No
13	OCF_3	CF_3S	85	67.1	No
14	SCF_3	CF_3O	101	56.4	No
15	$N(CF_3)_2$	C_2F_6N	152	75.0	No
16	$P(CF_3)_2$	C_2F_6P	169	67.5	No
17	$CF_2CF_2OR_{fn}$				No
18	$CF_2CF_2N(R_{fn})_2$				No
19	$C(O)CF(CF_3)[OCF_2$-$CF(CF_3)]_mOCF_2CF_2CF_3$				Yes
Class III[a]					
20	$C(CF_3)_2OCH_2CF_3$	$C_5H_2F_9O$	249	68.7	No

[a] Class I–III groups contain one, two or three more atom type(s) than fluorine, respectively.

2. Results and discussion

In this study we aimed at identifying novel and effective fluorous solubilizing groups, which can be made from easily accessible precursors. Since the CF_3 group has been recognized as a superdense fluorophilic group [16], we preferred structures in which a number of CF_3 groups are incorporated. Although compounds with 'CF_3-rich' functional groups, such as $PhC(CF_3)_3$ [33], $CH_3OC(CF_3)_3$ [34], $HetOC(CF_3)_2CF_2CF_2OCF(CF_3)_2$ [35], $PhSC(CF_3)_3$ [36], $PhSeC(CF_3)_3$ [37], $PhN(CF_3)_2$ [38,39] and $HN(C(CF_3)_3)_2$ [40] are already known in the literature [41], none of these *F*-groups have been involved in fluorous studies.



Scheme 2. Constitution of a lipophilic 'CF_3-rich' anion.

However, highly lipophilic tetraarylborate ions substituted with many CF_3 groups, which are capable of incorporating various cations into hydrophobic solution phases in the form of ion pairs, have been prepared by Ichikawa and coworkers (Scheme 2) [42].

Inspired by this work, we decided to develop effective methods for the synthesis of novel fluorophilic compounds, including $ArC(CF_3)_2OR_{(f)}$, $ArOCH_2CH_2CH_2R_{fn}$ and $(CF_3)_3CO(CH_2)_mR_{fn}$ type ethers. Their potential for fluorous applications can be judged using predicted fluorophilicity values (Table 2). It is clearly seen, that both polarity (δ_{calcd}) and volume (V_m) affect phase preference. Thus, an unknown compound like phosphine **16** with six ponytails and a large

Table 2
Selected properties of partially fluorinated compounds

Entry	Compound (M_w)	F (%)	$V_{m,\ calcd}$[a]	δ_{calcd}[b]	$f_{spec,\ pred}$[c]	f_{pred}[d]	f_{exp}[e]
1	$CF_3SO_2OCH_2CF_3$, (232.1)	49.1	159	14.3	1.28	1.04	[f]
2	$CF_3SO_2OCH_2R_{f7}$, (532.1)	64.3	297	14.0	1.48	2.24	[f]
3	$C_6H_5C(CF_3)_2Cl$, (262.6)	43.4	191	16.7	−0.33	−0.32	−2.04
4	$C_6H_5C(CF_3)_2OCH_3$, (258.2)	44.2	205	15.6	0.41	0.92	−1.83
5	$C_6H_5C(CF_3)_2OCH_2CF_3$, (326.2)	52.4	245	14.9	0.88	1.10	−0.62
6	$C_6H_5C(CF_3)_2OCH_2R_{f7}$, (626.2)	63.7	383	14.5	1.15	2.25	1.90
7	$C_6H_5C(CF_3)_2O(CH_2)_2R_{f8}$, (690.2)	63.3	422	14.6	1.08	2.33	1.46
8	$C_6H_5C(CF_3)_2OCH(CH_3)R_{f8}$, (690.2)	63.3	422	14.4	1.21	2.60	1.39
9	$C_6H_5C(CF_3)_2O(CH_2)_3R_{f8}$, (704.2)	62.0	438	14.7	1.01	2.26	1.16
10	$1,3\text{-}C_6H_4[C(CF_3)_2OCH_3]_2$, (438.2)	52.0	319	14.6	1.08	1.76	−0.89
11	$1,3\text{-}C_6H_4[C(CF_3)_2OCH_2CF_3]_2$, (574.2)	58.5	399	13.9	1.55	3.16	1.19
12	$1,3\text{-}C_6H_4[C(CF_3)_2O(CH_2)_3R_{f8}]_2$, (1330.4)	65.7	785	14.1	1.41	5.64	4.67
13	$1,3,5\text{-}IC_6H_3[C(CF_3)_2O(CH_2)_3R_{f8}]_2$, (1456.3)	60.0	798	14.8	0.94	3.83	3.91
14	$1,3\text{-}CF_3C_6H_4O(CH_2)_3R_{f8}$, (622.2)	61.1	381	15.3	0.61	1.19	0.15
15	$(CF_3)_3CO(CH_2)_3R_{f8}$, (696.2)	71.0	424	12.5	2.49	5.39	4.04
16	$P\{C_6H_3[C(CF_3)_2O(CH_2)_3R_{f8}]_2\}_3$, (4019.2)	65.2	2104	14.1	1.41	15.1	–

[a] Calculated from group increments, see: Eq. (3), V_m ($cm^3\ mol^{-1}$).
[b] Calculated from group increments, see: Eq. (3); δ ($MPa^{1/2}$).
[c] Estimated by regression equation $f_{spec} = 10.86-0.67\delta$, obtained for compounds **1–59** [16].
[d] $f = \ln P_{FBS}\ (i) = [V_m(i)/V_m(CF_3C_6F_{11})]f_{spec}$, where $V_m(CF_3C_6F_{11}) = 196\ cm^3\ mol^{-1}$.
[e] Determined by GC; see Section 4.
[f] Not determined by GC; samples decomposed at injection (230 °C).

molar volume is expected to have a fluorous partion coefficient, $P_{FBS}(\mathbf{16}) > 10^6$, while its precursor arene **12** with only two ponytails and a smaller volume, would result in a much lower value, $P_{FBS}(\mathbf{12}) = 280$, in spite of that both compounds have the same calculated polarity ($\delta_{calcd} = 14.1$).

Furthermore, a knowledge of these partition values ahead of synthesis of target molecules could facilitate the selection of appropriate work up procedures. Their estimation involves the following steps:

(a) molar volume (V_m) and Hildebrand parameter (δ_{calcd}) values are calculated first from group increments based on 2D chemical structures (Eq. (3));
(b) then these data are substituted for the appropriate parameters of the regression equation (Eq. (2) to yield specific fluorophilicity ($f_{spec,pred}$) values;
(c) which are finally converted to fluorophilicities (Eq. (1)) and partition coefficients ($f = \ln P_{FBS}$) according to their definitions (Table 2).

The experimental fluorophilicity values (f_{exp}) of this set of compounds (Entries 3–15, Table 2) determined by a simple GC method were found to correlate well with the predicted ones. However, the latter numbers are somewhat overestimated ($R = 0.94$, S.D. = 0.78, Fig. 1).

Since 2-aryl-hexafluoro-propanols are accessible easily with the reaction of aromatic hydrocarbons and hexafluoroacetone [43,44], their use for fluorous solubilisation of aromatic reagents or catalyst precursors seems reasonable (Scheme 3).

In addition, these fluorinated ethers are expected to be very robust, such as their parent compounds, $PhC(CF_3)_2OR$, where the $PhC(CF_3)_2$-fragment has been introduced as a protecting group for alcohols using a Mitsunobu reaction [45]. Other β-CF_3-substituted alcohols are known as suitable acid components, if their coupling with nonfluorinated alcohols is considered [46,47].

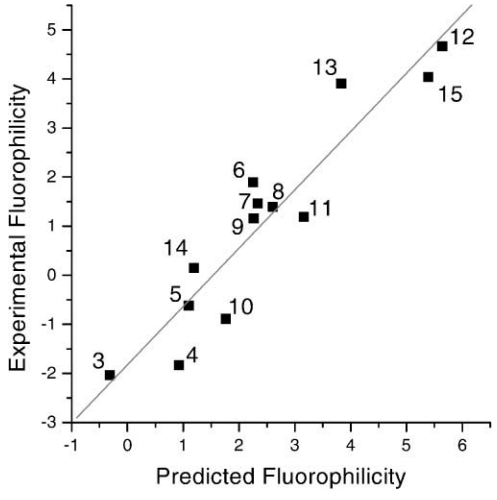
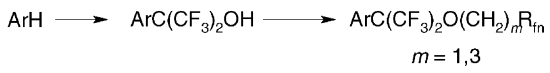


Fig. 1. Efficacy of the prediction of phase preference for compounds **3–15**.



Scheme 3. Making arene fluorophiles with Class III ponytails.

We noticed that the Mitsunobu reaction [48] can be applied for the effective synthesis of ethers if 3-perfluorooctyl-propanol (**2eb**) is used as the alcohol component (R^2OH), while the yield drops significantly with 2-perfluorooctyl-ethanol (**2d**) (cf. [49]), due to its facile dehydration reaction, and finally in case of perfluoroheptyl-methanol (**2cb**) no ether formation occurs (Table 3). These results can be interpreted with the effect of the strongly electron withdrawing perfluoroalkyl groups on reaction centers, which is only insulated properly in the first case.

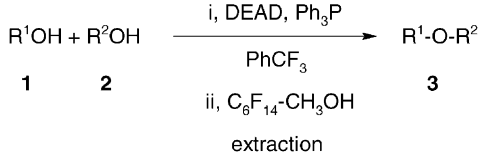
However, the above reactions were performed in a solvent (BTF) providing acceptable solubility for all reaction components (Scheme 4). It is worth to note, that the fluorophilic ethers formed can be separated effectively from all other organic compounds, if the solvent is removed first by distillation and then the residue is partitioned between a fluorous solvent, such as FC-72 (perfluorohexanes) or perfluoro(methylcyclohexane) and methanol (Method B, Table 2).

On the contrary, ethers with a $-(CF_3)_2COCH_2CF_2-$ structural fragment (**3ab**, **3ac** and **3bb**) can be obtained in acceptable yields if trifluoroethyl- (**2b**) or 1H,1H-perfluoroheptyl triflates (**2ca**) are reacted with in situ formed sodium alcoholates in DMF solution (Method A, Table 3).

The methylation reactions took place under milder conditions, where methyl methanesulfonate (**2a**) at room temperature affords the appropriate ethers (**3aa** and **3ba**) in good yields. Unlike to Mitsunobu synthesis, the reaction of 3-perfluorooctyl-propyl iodide (**2ea**) and $NaOC(CF_3)_2Ph$ in DMF gave the fluorophilic ether (**3ae**) only in low isolated yield, which can be ascribed to the heterogeneous nature of this alkylation process.

We found here, that phenols and perfluoro-*tert*-butyl alcohol can also be selected as the 'acidic component' (cf. [50]) of a fluorous Mitsunobu reaction (Table 3, runs 12 and 13).

Due to the access to $PhC(CF_3)_2OCH_3$ [51] and $PhC(CF_3)_2OCCl_3$ [52] ethers, we thought to apply them as precursors for the synthesis of a novel 'CF_3-rich' compound, $PhC(CF_3)_2OCF_3$, which is an isomer of the unknown perfluoro-*tert*-butyl phenyl ether, $PhOC(CF_3)_3$. However, the results of these efforts will be published later and elsewhere.



Scheme 4. Mitsunobu ether synthesis coupled with fluorous separation.

Table 3
Synthesis of fluorinated ethers: R^1–OH (or HO–R^1–OH)+R^2–X → R^1–O–R^2 (or R^2O–R^1–OR^2)

Run	R^1–OH (**1a–e**)	R^2–X (**2a–eb**)	Method[a]	R^1–O–R^2 R^2O–R^1–OR^2	Bp (°C/mmHg) mp (°C/solvent)	Yield (%)
1	$C_6H_5C(CF_3)_2OH$ (**1a**)	CH_3–OSO_2CH_3 (**2a**)	A	**3aa**	164	85
2	$C_6H_5C(CF_3)_2OH$ (**1a**)	CF_3CH_2–OSO_2CF_3 (**2b**)	A	**3ab**	<250[b]	75
3	$C_6H_5C(CF_3)_2OH$ (**1a**)	$C_7F_{15}CH_2$–OSO_2CF_3 (**2ca**)	A	**3ac**	120–129/20	33
4	$C_6H_5C(CF_3)_2OH$ (**1a**)	$C_7F_{15}CH_2$–OH (**2cb**)	B	**3ac**	[c]	0[c]
5	$C_6H_5C(CF_3)_2OH$ (**1a**)	$C_8F_{17}CH_2CH_2$–OH (**2d**)	B	**3ad**	[b]	11[d]
6	$C_6H_5C(CF_3)_2OH$ (**1a**)	$C_8F_{17}CH_2CH_2CH_2$–I (**2ea**)	A	**3ae**	130–131/1	35
7	$C_6H_5C(CF_3)_2OH$ (**1a**)	$C_8F_{17}CH_2CH_2CH_2$–OH (**2eb**)	B	**3ae**	160–168/20	88
8	1,3-$C_6H_4[C(CF_3)_2OH]_2$ (**1b**)	CH_3–OSO_2CH_3 (**2a**)	A	**3ba**	82–84/C_6H_{14}	81
9	1,3-$C_6H_4[C(CF_3)_2OH]_2$ (**1b**)	CF_3CH_2–OSO_2CF_3 (**2b**)	A	**3bb**	120–125/20	64
10	1,3-$C_6H_4[C(CF_3)_2OH]_2$ (**1b**)	$C_8F_{17}CH_2CH_2CH_2$–OH (**2eb**)	B	**3be**	39–41/*i*-octane	61
11	1,3,5-$IC_6H_3[C(CF_3)_2OH]_2$ (**1c**)	$C_8F_{17}CH_2CH_2CH_2$–OH (**2eb**)	B	**3ce**	180–184/1	86
12	1,3-$CF_3C_6H_4OH$ (**1d**)	$C_8F_{17}CH_2CH_2CH_2$–OH (**2eb**)	B	**3de**	165–170/20	76
13	$(CF_3)_3COH$ (**1e**)	$C_8F_{17}CH_2CH_2CH_2$–OH (**2eb**)	B	**3ee**	224–227	91

[a] Method A (Williamson): R^1OH + NaH/DMF, R^2X at RT then heating. Method B (Mitsunobu): R^1OH + R^2OH, Ph_3P/DEAD/$PhCF_3$ at RT, then C_6F_{14}/CH_3OH partition.
[b] Not determined.
[c] No formation of **3ac** detected (GC).
[d] Mixture of isomers: $R_{f8}CH_2CH_2OR^1$ to $R_{f8}CH(OR^1)CH_3$ ~ 10:1 (GC).

3. Conclusions

1. The use of calculated Hildebrand parameters of 'target molecules' and a regression equation fitted to a sizable database of experimentally determined fluorophilicity values is a powerful tool for estimation of their phase preference.
2. Mitsunobu and Williamson syntheses were found as complementary methods for the preparation of novel generation fluorophilic ethers involving Class III pony-tails.
3. Effective synthetic methods and separation procedures can be developed or selected, respectively, if the reaction components' phasephilicity is understood and purposefully tuned.

4. Experimental details

Most of the compounds (**1a**, **1b**, **1d**, **1e**, **2cb** [Apollo]; **2d** [Fluka]) used in this study are either commercially available or can be prepared according to literature examples {$PhC(CF_3)_2Cl$ [53], **3aa** [51], **2b** [54], **2ca** [55], **2ea** [56], **2eb** [57]}. The structures of all new compounds were confirmed by ^{1}H-, ^{13}C- and ^{19}F NMR spectroscopy (Varian INOVA 400, 400 MHz for ^{1}H) using TMS and $CFCl_3$ as internal standards in a solvent mixture of 1:1 (v/v) $CDCl_3$ and Freon-113 ($CF_2ClCFCl_2$). Mass spectra were determined on a VG ZAB2-SEQ tandem mass spectrometer using electron impact (70 eV) for ionization and direct probe for sample introduction at a source temperature of 180–250 °C. Mass range (*m/z*) from 25–1500 was considered. Fluorophilicities were determined by GC analysis as reported [27]; (Hewlett-Packard 5890 Series II, PONA [crosslinked methylsilicone gum] 50 m × 0.2 mm × 0.5 μm column, H_2 carrier gas, FID detection).

4.1. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (2b)

Yield: 5.34 g (46%) at a scale of 50 mmol, colourless oil, bp 89–91 °C, prepared as reported [54]. GC: 96.2%. ^{19}F NMR (δ, ppm): (SO_2)–C**F**$_3$: −74.90 (3F); –CH_2–C**F**$_3$: −75.19 (3F), t, $^3J_{F-H}$ = 7.6 Hz. ^{1}H NMR (δ, ppm): 4.63 qa, (7.3 Hz) ^{13}C NMR (δ, ppm): $\underline{C}F_3CH_2$ 121.3 qa (278.3 Hz), $CF_3\underline{C}H_2$ 68.9 (39.3 Hz), CF_3SO_2 118.9 qa (319.6 Hz) MS (EI) (*m/z*, I, *M*−X): 200(0.2%)$(M-32)^+$, 163(8.0%)$(M-69)^+$, 147(6.4%)$(M-85)^+$, 133(18%), 99(22%), 83(34%), 69(100%); MS (*CI, isobutane*) $(M+H)^+ = 233$.

4.2. 2,2,3,3,4,4,5,5,6,6,7,7,8,8-Pentadecafluorooctyl trifluoromethanesulfonate (2ca)

To an ice-cooled and stirred solution of alcohol **2cb** (12.0 g, 30 mmol) and pyridine (2.91 ml, 36 mmol) in absolute CH_2Cl_2 (60 ml) trifluoromethanesulfonic anhydride (6.0 ml, 36 mmol) was added during 1 h. The mixture was stirred for 1 h at 0 °C, then at room temperature overnight. After evaporation the residue was partitioned between ether (150 ml) and ice-water (40 ml). The ether phase was dried ($MgSO_4$) and evaporated to give pink oil, which on fractionation yielded 14.6 g (91.5%) colourless liquid of bp :< 100 °C/16 mmHg (cf. [55]). GC: 99.3%. ^{19}F NMR (δ, ppm): (SO_2)–C**F**$_3$:−74.81 (3F); –CF_2–C**F**$_3$: −81.44 (3F); –CH_2–C**F**$_2$: −120.22 (2F); others: −122.15 (2F); −122.30 (2F); −123.08 (2F); −123.32 (2F); −126.59 (2F). ^{1}H NMR (δ, ppm): 4.82 t, ($^3J_{F-H}$ = 12.3 Hz) ^{13}C NMR (δ, ppm): CH_2 68.4 t ($^2J_{C-F}$ = 28.8 Hz), $CH_2\underline{C}F_2$ 113.3 tt ($^1J_{C-F}$ = 262.0 Hz and $^2J_{C-F}$ = 32.6 Hz) $CF_2\underline{C}F_3$ 117.5 qa t

($^1J_{C-F} = 288.0$ Hz and $^2J_{C-F} = 32.6$ Hz), $(CF_2)_5$ 14–106 overlapping signals MS(EI) (*m/z*, I, $M - X$): 532(0.01%)-$(M)^+$, 513(0.2%)$(M - F)^+$, 463(0.7%)$(M - CF_3)^+$, 361-(1.1%)$(M–171)^+$, 313 (3.5%), 231(0.6%)$(C_5F_9)^+$, 219-(0.8%)$(C_4F_9)^+$, 169(2.6%)$(C_3F_7)^+$, 163(9.7%), 131(12%) $(C_3F_5)^+$, 99(22%), 69(100%)$(CF3)^+$. HR-MS *(CI, isobutane)* $(M + H)^+ = 532.9544$ thus $M = 531.9466$, calculated for $C_9H_3F_{18}SO_3$ $M = 531.9437$.

4.3. [2,2,2-Trifluoro-1-chloro-1-(trifluoromethyl)ethyl]benzene (Table 4, Entry 3)

Yield: 76%, colourless oil, bp 154 °C, prepared as reported [53]. GC: 92%. ^{19}F NMR (δ, ppm): C**F**$_3$:−70.44 (s). ^{1}H NMR Ar-2H and Ar-6H 7.91 br d (7.5 Hz; 2H), Ar-3H and Ar-4H and Ar-5H 7.51–7.55 br m (3H), ^{13}C NMR $\underline{C}(CF_3)_2$ 72.9 sept ($^2J_{C-F} = 30.7$ Hz), C($\underline{C}F_3)_2$Cl 123.7 qa (286.0 Hz), Ar-1C 129.6, Ar-2C and Ar-6C 129.8 br, Ar-3C and Ar-5C 130.1, Ar-4C 132.1.

*4.4. General procedure for the synthesis of compounds **3aa**, **3ab**, **3ac**, **3ae**, **3ba**, **3bb** (Method A)*

To a stirred solution of alcohol **1a** (10 mmol) or **1b** (5.0 mmol) in absolute DMF (10 ml) pentane washed sodium hydride (∼0.3 g, ∼13 mmol) was added under an argon atmosphere during 30 min at about −10 to −20 °C temperature (*caution*!). After addition of **2a**, **2b**, **2ca** or **2ea** (12 mmol) to the reaction mixture, it was allowed to warm to room temperature, then stirred at this temperature for 12 h (**2a**) or heated at 60 °C for 6 h (**2b**, **2ca**) and for 12 h (**2ea**). Then, the mixture was added to ice (50 g) and extracted with ether (3× 30 ml). The organic phases were combined, washed with water (2× 20 ml) and dried ($MgSO_4$). After the solvent had been removed by atmospheric distillation, the crude product obtained was fractionated in a short path distillation apparatus. For boiling point and pressure data, see: Scheme B.

*4.5. [2,2,2-Trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]benzene (**3aa**)*

Yield: 2.20 g (85%) colourless oil, bp: 164 °C as of [51]. GC: 98.2%. ^{19}F NMR (δ, ppm): C**F**$_3$:−71.37 (s). ^{1}H NMR O–CH_3 3.53 s (3H), Ar-2H and Ar-6H 7.67 br (2H), Ar-3H and Ar-4H and Ar-5H 7.5 m (3H), ^{13}C NMR O–CH_3 55.5, $\underline{C}(CF_3)_2$ 84.6 sept ($^2J_{C-F} = 27.8$ Hz), C($\underline{C}F_3)_2$O 124.0 qa (290.8 Hz), Ar-1C 129.4, Ar-2C and Ar-6C 19.6, Ar-3C and Ar-5C 130.1, Ar-4C 131.7.

*4.6. [2,2,2-Trifluoro-1-(2,2,2-trifluoroethoxy)-1-(trifluoromethyl)ethyl]benzene (**3ab**)*

Yield: 2.45 g (75%) colourless oil, bp :< 250 °C (bath temperature). GC: 93%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.39 (6F); –CH_2–C**F**$_3$: −74.92 (3F), t, $^3J_{F-H} = 7.7$ Hz. ^{1}H NMR O–CH_2 3.89 qa (7.7 Hz), Ar-2H and Ar-6H 7.55 br d (7.3 Hz; 2H), Ar-3H and Ar-4H and Ar-5H 7.43-7.47 m(3H), ^{13}C NMR O–CH_2 64.2 qa (37.4 Hz), CH_2CF_3 123.1 qa (277.3 Hz), $\underline{C}(CF_3)_2O$ 83.3 sept (28.8 Hz), C($\underline{C}F_3)_2$O 122.4 qa (290.8 Hz), Ar-1C 126.9, Ar-2C and Ar-6C 128.4, Ar-3C and Ar-5C 129.5, Ar-4C 131.3. MS (EI) (*m/z*, I, $M - X$): 326(37%)$(M)^+$, 307(6.1%)$(M-F)^+$, 257(100%)$(M - CF_3)^+$, 227(7.1%) (M–151, PhC$(CF_3)_2)^+$, 207(17%), 177(18%), 175(9.2%), 127(29%), 105(42%), 83(32%), 77(20%), 69(25). HR-MS (EI)*:* $M = 326.0380$, calculated for $C_{11}H_7F_9O$ $M = 326.0353$.

*4.7. [2,2,2-Trifluoro-1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-1-(trifluoromethyl) ethyl]benzene (**3ac**)*

Yield: 2.08 g (33%) colourless oil, bp: 120–129 °C/20 mmHg. GC: 93%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.31 (6F); –CF_2–C**F**$_3$: −81.40 (3F), t, $^3J_{F-F} = 10.1$ Hz; CH_2–C**F**$_2$: −120.16 (2F); others: −122.38 (4F); −122.41 (2F); −122.44 (2F); −126.63 (2F). ^{1}H NMR (δ, ppm): O–CH_2 4.13 qa ($^3J_{F-H} = 12.5$ Hz), Ar-2H and Ar-6H 77.68 br d (7.3 Hz; 2H) 7.5–77.6 overlapping m's (3H). ^{13}C NMR (δ, ppm): O–CH_2 63.5 t (28.8 Hz), $\underline{C}(CF_3)_2O$ 83.1 sept (29.7 Hz), Ar-1C 126.8, Ar-2C and Ar-6C 128.3 br, Ar-3C and Ar-5C 129.3, Ar-4C 131.1. HR-MS (EI)*:* $M = 626.0178$, calculated for $C_{17}H_7F_{21}O$ $M = 626.0162$.

*4.8. [2,2,2-Trifluoro-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,-11,11-heptadecafluoroundecyloxy)-1-(trifluoro-methyl)ethyl]benzene (**3ae**)*

Yields: 2.46 g (35%) colourless oil, bp: 130–131 °C/ 1 mmHg. GC: 99.8%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.84 (6F); –CF_2–C**F**$_3$: −81.48 (3F), t, $^3J_{F-F} = 10.4$ Hz; –CH_2–C**F**$_2$: −114.90 (2F); others: −122.04 (2F); −122.24 (4F); −123.08 (2F); −123.80 (2F); −126.60 (2F). ^{1}H NMR (δ, ppm): O–CH_2 3.74 t (6.1 Hz), O–$CH_2\underline{C}H_2$ 2.08 tt (8.5 Hz and 6.1 Hz), CH_2CF_2 2.35 tt (18 and 8.5 Hz), Ar-2H and Ar-6H 7.63 br d (2H) (7.3 Hz), 7.5–7.6 overlapping multiplets m's (3H) ^{13}C NMR (δ, ppm):, O–CH_2 65.1, O–CH_2CH_2 21.3, $\underline{C}H_2CF_2$ 27.9 t ($^2J_{C-F} = 23.0$ Hz), $\underline{C}(CF_3)_2O$ 83.2 sept (27.8 Hz), Ar-1C 128.5, Ar-2C and Ar-6C 128.3 br, Ar-3C and Ar-5C 129.0, Ar-4C 130.5 MS (EI) (*m/z*, I, $M-X$): 704(0.2%)$(M)^+$, 635(2.0%) $(M-CF_3)^+$, 477(8.8%)$(M-227)^+$, 461(3.6%), 441(7.3%), 395(3.9%), 228(34%), 227(60) (PhC$(CF_3)_2)^+$, 208(32%), 207(18%), 175(100%), 159(40%), 105(37%), 77(10%), 69(16%), 47(28%). HR-MS (EI)*:* $M = 704.0413$, calculated for $C_{20}H_{11}F_{23}O$ $M = 704.0443$.

*4.9. 1,3-Bis[1-(methoxy)-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzene (**3ba**)*

Yield: 1.78 g (81%) white crystals, mp: 82–84 °C/C_6H_{14} same as reported [42]. GC: 98.1%. ^{19}F NMR (δ, ppm):

C**F**$_3$:−71.42 (s). ^{1}H NMR (δ, ppm): O–CH$_3$ 3.54 s (3H), Ar-2H 7.93 br s (1H), Ar-4H and Ar-6H 7.78 br d (7.9 Hz) (2H), Ar-5H 7.63 t (8.2 Hz) (1H), ^{13}C NMR (δ, ppm): O–CH$_3$ 54.2, CF$_3$ 122.6 q (288.9 Hz), C(CF$_3$)$_2$OCH$_3$ 83.3 sept (28.8 Hz), Ar-2C 128.8 br, Ar-1C and Ar-3C 129.5, Ar-4C and Ar-6C 130.4 br, Ar-5C 129.4.

*4.10. 1,3-Bis[1-(2.2.2-trifluoroethoxy)-2.2.2-trifluoro-1-(trifluoromethyl)ethyl]benzene (**3bb**)*

Yield: 1.84 g (64%) colourless oil, bp: 120–125 °C/20 mmHg. GC: 96.4%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.40 (12F); –CH$_2$–C**F**$_3$: −75.09 (6F), t, $^3J_{F-H}$ = 7.1 Hz. ^{1}H NMR (δ, ppm): O–CH$_2$ 4.03 qa ($^3J_{F-H}$ = 7.6 Hz), Ar-2H 8.04 br s, Ar-4H and Ar-6H 7.87 br d (7.3 Hz), Ar-4H 7.71 t (7.33 Hz), ^{13}C NMR (δ, ppm): O–CH$_2$ 64.4 qa ($^2J_{C-F}$ = 36.5 Hz), CH$_2$CF$_3$ 122.7 qa (277.3 Hz), C(CF$_3$)$_2$O 82.9 sept ($^2J_{C-F}$ = 29.7 Hz), C(CF$_3$)$_2$O 122.1 qa (289.8 Hz), Ar-1C and Ar-3C 128.9 s, Ar-2C 128.1 br s, Ar-4C and Ar-6C 130.7 br s, Ar-5C 130.1 s. HR-MS (EI): M = 574.0260, calculated for C$_{16}$H$_8$F$_{18}$O$_2$ M = 574.0237.

*4.11. General procedure for the synthesis of compounds **3ad**, **3ae**, **3be**, **3ce**, **3de**, **3ee** (Method B)*

The appropriate acidic component **1a**, **1d** and **1e** (10 mmol) or **1b** and **1c** (5.0 mmol), triphenyl-phosphine (4.10 g, 15.6 mmol) and the perfluoroalkyl-alkanol **2d** or **2e**, respectively, were dissolved in benzotrifluoride (90 ml) with stirring. Then, the solution was cooled in an ice-bath and diethyl azodicarboxylate (2.61 g, 15 mmol) dissolved in benzotrifluoride (10 ml) was added during 30 min. The mixture was allowed to warm to room temperature and stirred for 1 h. Then, the solvent was distilled off (bath temperature < 130 °C) and the residue was partitioned between perfluoro(2-butyltetrahydrofuran) or perfluorohexanes (50 ml) and methanol (50 ml). The fluorous phase was washed with methanol (2× 50 ml) and the fluorocarbon solvent was distilled off at a bath temperature less than 130 °C to afford the 'crude products' almost free from any organic impurities (GC purity > 90%). Further purification was effected by short path distillation (Raschig rings prevented foaming) or by recrystallization (Scheme B).

*4.12. [2,2,2-Trifluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,-10,10-pentadecafluorodecyloxy)-1-(trifluoromethyl)-ethyl]benzene and [2,2,2-trifluoro-2-(3,3,4,4,5,5,6,6,7,7,-8,8,9,9,10,10,10-pentadecafluorodecyloxy)-1-(trifluoromethyl)ethyl]benzene (**3ad**)*

Yield: 0.76 g (11%) colourless oil. GC: 95% mixture of isomers (10:1). ^{1}H NMR (δ, ppm): O–CH$_2$ 3.96 t (6.7 Hz), CH$_2$CF$_2$ 2.61 tt (17.7 Hz; 6.7 Hz), Ar-2H and Ar-6H 7.63 br d (2H; 77.3 Hz), Ar-3H and Ar-4H and Ar-5H 7.50–7.60 overlapping multiplets. The rearrangement is reflected from the presence of a CHCH$_3$ unit detected as an AX$_3$ signal set (1.33 d, CH3; 5.08 qa, CH). The coupling pattern is evidenced by 2D COSY. ^{13}C NMR (δ, ppm) O–CH$_2$ 59.0 br, CH$_2$CF$_2$ 32.0 t (23.0 Hz), C(CF$_3$)$_2$O 83.0 sept (27.9 Hz), Ar-1C 128.0, Ar-2C and Ar-6C 128.2 br, Ar-3C and Ar-5C 129.1, Ar-4C 130.7. HR-MS (EI): M = 690.0299, calculated for C$_{19}$H$_9$F$_{23}$O M = 690.0286.

*4.13. [2,2,2-Trifluoro-1-(4,4,5,5,6,6,7,7,8,8,9,9,-10,10,11,11,11-heptadecafluoroundecyloxy)-1-(trifluoromethyl)ethyl]benzene (**3ae**)*

Yield: 6.20 g (88%) colourless oil, bp: 160–168 °C/20 mmHg. GC: 99.8%. (see: Method A).

*4.14. 1,3-Bis[1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,-12,12,13,13,13-heptadecafluoroundecyloxy)-2,2,2-trifluoro-1-(trifluromethyl)ethyl]benzene (**3be**)*

Yield: 4.06 g (61%) white crystals, mp: 39–41 °C/*i*-octane. GC: 98.9%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.45 (6F);); –CF$_2$–C**F**$_3$: −81.49 (3F), t, $^3J_{F-F}$ = 9.9 Hz; –CH$_2$–C**F**$_2$: −115.50 (2F); others: −122.20 (2F); 122.39 (4F); −123.21 (2F); −123.91 (2F); −126.67 (2F). ^{1}H NMR (δ, ppm): O–CH$_2$ 3.73 t (6.1 Hz), O–CH$_2$CH$_2$ 2.09 tt (8.8 Hz; 6.1 Hz), CH$_2$CF$_2$ 2.32 tt (17.4 Hz; 8.8 Hz), Ar-2H 7.90 br s, Ar-4H and Ar-6H 7.77 br d (7.9 Hz), Ar-5H 7.63 t (7.9 Hz). ^{13}C NMR (δ, ppm): O–CH$_2$ 65.5, O–CH$_2$CH$_2$ 21.3 br, CH$_2$CF$_2$ 27.8 (23.0 Hz), CF$_3$ 122.5 qa (288.9 Hz), C(CF$_3$)$_2$OCH$_2$– 83.0 sept (28.8 Hz), Ar-1C and Ar-5C 129.6 coalesced lines, Ar-2C 128.1 br, Ar-4C and Ar-6C 130.3 br.

*4.15. 3,5-Bis[1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,-13,13,13-heptadecafluoroundecyloxy)-2,2,2-trifluoro-1-(trifluromethyl)ethyl]iodobenzene (**3ce**)*

Yield: 5.90 g (81%) colourless oil, bp: 180–184 °C/1 mmHg. GC: 97.6%. ^{19}F NMR (δ, ppm): (C)–C**F**$_3$: −71.28 (6F);); –CF$_2$–C**F**$_3$: −81.49 (3F), t, $^3J_{F-F}$ = 10.1 Hz; –CH$_2$–C**F**$_2$: −115.02 (2F); others: −122.11 (2F); −122.33 (4F); −123.15 (2F); −123.84 (2F); −126.68 (2F). ^{1}H NMR O–CH$_2$ 3.75 t (6.1 Hz), O–CH$_2$CH$_2$ 2.09 tt (8.3 Hz and 6.1 Hz), CH$_2$CF$_2$ 2.31 tt (17.1 Hz and 8.3 Hz), Ar-4H 7.86 br s (1H), Ar-2H and AR-6H 8.09 br s (2H). ^{13}C NMR O–CH$_2$ 65.9, O–CH$_2$CH$_2$ 21.3 br, CH$_2$CF$_2$ 27.8 t (21.1 Hz), C(CF$_3$)$_2$O 82.4 sept (29.7 Hz), CF$_3$ 122.3 qa (288.9 Hz), Ar-1C 94.3, Ar-2C and Ar-6C 139.3, Ar-3C and Ar-5C 131.5, Ar-4C 127.3.

*4.16. 1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)-3-(trifluoromethyl)benzene (**3de**)*

Yield: 4.73 g (76%) colourless oil, bp: 165–170 °C/20 mmHg. GC: 94.6%. ^{19}F NMR (δ, ppm): (Ph)–C**F**$_3$: −63.51 (3F);); –CF$_2$–C**F**$_3$: −81.46 (3F), t, $^3J_{F-F}$ =

9.9 Hz; –CH_2–$C\mathbf{F}_2$: −114.86 (2F); others: −122.03 (2F); −122.28 (4F); −123.11 (2F); −123.82 (2F); −126.60 (2F). ^{1}H NMR (δ, ppm): O–CH_2 4.12 t (5.8 Hz), O–$CH_2C\underline{H}_2$ 2.19 tt (8.0 and 5.8 Hz), CH_2CF_2 2.38 tt ($^3J_{H-F} = 18.3$ and 8.0 Hz), Ar-2H 7.19 br s, Ar-4H 7.27 br d (7.9 Hz), Ar-5H 7.42 t (8.0 Hz), Ar-6H 7.10 dd (8.2 Hz and 2.2 Hz). ^{13}C NMR (δ, ppm): O–CH_2 66.8, O–$CH_2\underline{C}H_2$ 20.9 br, $\underline{C}H_2CF_2$ 28.3 t (23.0 Hz), Ar-1C 159.1, Ar-2C 111.5 qa (3.8 Hz), Ar-3C 132.7 qa (32.6 Hz), Ar-4C and Ar-6C 118.0 two coalesced lines, Ar-5C 130.2, Ar-$\underline{C}F_3$ 124.2 qa (271.6 Hz). HR-MS (EI): $M = 622.0420$, calculated for $C_{18}H_{10}F_{20}O$ $M = 622.0412$.

*4.17. 1-[1,1-Bis(trifluoromethyl)-2,2,2-trifluoroethoxy]-3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecane (**3ee**)*

Yield: 6.33 g (91%) colourless oil, bp: 224–227 °C. GC: 99.8%. ^{19}F NMR (δ, ppm): (C)–$C\mathbf{F}_3$: −70.97 (9F);); –CF_2–$C\mathbf{F}_3$: −81.47 (3F), t, $^3J_{F-F} = 11.1$ Hz; –CH_2–$C\mathbf{F}_2$: −114.96 (2F); others: −122.15 (2F); −122.33 (4F); −123.16 (2F); −123.98 (2F); −126.64 (2F). ^{19}H NMR O–CH_2 4.17 t (5.8 Hz), O–$CH_2C\underline{H}_2$ 2.07 tt (8.0 and 5.8 Hz), CH_2CF_2 2.27 tt (18.3 and 8.0 Hz; $^3J_{H-F} = 18.3$ Hz), ^{13}C NMR: $(CF_3)_3CO$ 120.7 qa (292.7 Hz), $(CF_3)_3\underline{C}O$ 80.2 decett (29.7 Hz),O–CH_2 68.4 br, O–$CH_2\underline{C}H_2$ 21.3 br, $\underline{C}H_2CF_2$ 27.5 t (23.0 Hz), $CH_2\underline{C}F_2$ 118.5 tt (255.3 and 31.7 Hz), MS (EI) (*m/z*, I, $M - X$): 696(0.6%)$(M)^+$, 695(1.8%) $(M-1)^+$, 677(2.4%)$(M-F)^+$, 461(15%) $(M-235, M - OC(CF_3)_3)^+$, 441(38)$(M-255)^+$, 249(84%) $(CH_2OC(CF_3)_3)^+$, 91(61%), 69(27%)$(CF_3)^+$, 47(100%).

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