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Fluorinated organic azides – their preparation and synthetic applications

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

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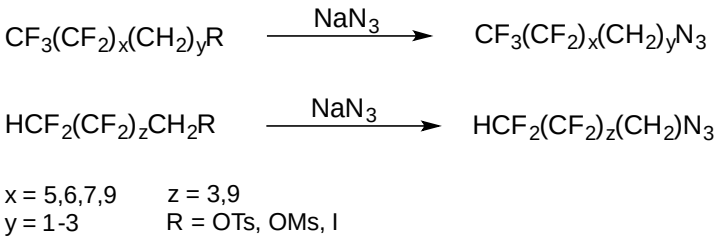
Abstract

Alkyl azides are widely used in many reactions. Although synthesis of such species is relatively well documented, fluorinated azides, especially with large perfluorinated or highly fluorinated groups, are sometimes tricky to make. The presence of fluorine in reacting molecules, sometimes causes significant changes in the reactivity of reacting species. In this paper we give a short overview of re-examination of currently available methods of synthesis of selected azides with highly fluorinated groups.



Keywords: Organic azides, fluorine in organic compounds, fluorinated azides, phase transfer catalysis, 'click' chemistry

Introduction

The use of organic azides has increased throughout the centuries. They are energy-rich molecules with many synthetic applications. The first organic azide – phenyl azide – was prepared in 1864 by *Peter Grieß*.[1,2] Many years later, in the 1950s and 1960s azides attracted significant interest as functional groups easily transformable into other functionalities. Not only aryl azides, but also alkyl and acyl azides have been prepared.[3] Synthetically, alkyl azides represent an important class of compounds which can be obtained by nucleophilic substitution reactions with heating,[4] phase transfer catalysis,[5] microwave irradiation[6,7] or some mixed procedures. Different azide group sources can be used e.g. trimethylsilyl azide (TMSA), tributyltin azide, (TBSnA), tetrabutylammonium azide (TBAA) and lithium azide (LiN_3). Sodium azide (NaN_3) is an easily accessible and cheap reagent and is most commonly used.[8–11] Nowadays the most common reaction where azides are utilised, is probably 1,3-dipolar cycloaddition, someties referred to as a 'click' reaction. Azides have also been involved in the preparation of new materials with unprecedented properties e.g. membranes, surfactants, liquid crystals and in biomedical applications.[12,13]

Within the series of different azides, fluorine-containing azides are of special interest. The reason is that having an azide functionality in a molecule it is relatively simple to introduce flurorinated motif to a parent molecule, changing its properties (e.g. increasing lipophilicity). This is an interesting and common approach in several 'drug delivery systems', employing a 'click' reaction as an efficient synthetic step for the introduction of a fluorinated chain. Fluorinated azides are an excellent tool for the synthesis of fluoroalkylated [1,2,3]-triazoles in typical Huisgen cycloadditions.[11,14,15]

It is well known that the presence of fluorine atoms in a molecule, can unexpectedly change the reactivity of the compound, and may lead to increased biological activity. This is due to the unique properties of the fluorine atom. Fluorine is the element with the highest electronegativity and forms a very strong carbon-fluorine bond.[16] Fluorine present in the molecule, in most cases causes increased stability. Comparing the steric effects of $-CF_2-$ and $-CH_2-$ groups, fluorination always increases the steric size of the fluorinated group. The size of a trifluoromethyl group is almost twice that of a methyl group. This effect can be explained by the van der Waals radius of fluorine (1.47 Å) even though it is only 20% larger than hydrogen (1.20 Å). Secondly, the C-F bond length is 1.38 Å compared with common C-H bonds at 1.09 Å. It is worth mentioning that microorganisms or enzymes often do not recognize the difference between analogues with C-F bonds instead of C-H, because the fluorine atom is similar in size to a hydrogen atom.[17,18] In fact, the fluorine atoms in fluorinated chains tightly screen a carbon chain, in contrast to hydrogen atoms. As a result, fluorinated compounds have a low surface energy, are more resistant to wetting or hydrolysis and are more slippery.[19] All these properties combined, are important factors influencing the application of fluorinated vs non-fluorinated systems.

Organic azides arouse industrial interest as precursors for synthesis of amines or heterocycles such as tetrazoles and triazoles.[20,21] As mentioned already, azides are widely used as 'click' chemistry reactants, as scaffolds to introduce some other functions (e.g. in drug delivery systems, surface modification of reactants, etc). Although synthesis of such species is relatively well documented, fluorinated azides, especially with large perfluorinated or highly fluorinated groups, are sometimes tricky to prepare.

Results and Discussion

Transformation of alkyl alcohols or iodides to corresponding azides is widely described in the literature.[22–25] On the other hand, synthesis of analogous azides possessing a long fluorinated chain tends to be more challenging. Classical transformation of an alcoholic hydroxyl group into a better leaving group, such as tosylate, mesylate, or incorporation of iodide instead a hydroxyl group, provide the opportunity to obtain the desired products.[14,26–36]

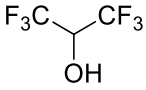
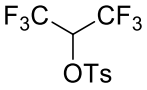
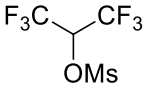
In our recent studies, we focused on the long chain compounds which possess a fluorinated alkyl chain and a different -CH_2- linkers attached directly to the azido group. Although the preparation of azides is very well documented, there are no much precedences to synthesize fluorinated analogues. By including a short spacer (-CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-) between the azido group and the perfluorinated chain we can reduce the inductive effect caused by the fluorine substituents in the alkyl chain and increase the reactivity of these compounds in further synthesis.[12,14]

In this study we have focused on the synthesis of novel compounds, as well as modifications of the experimental procedure to yield the desired fluorinated long chain azides with better efficiency. In some cases we have used different starting materials or modified methodologies to yield corresponding products with better yields.

In 1977 *Rondestvedt et al.*[28] presented a convenient synthesis of 1*H*,1*H*,2*H*,2*H*-perfluorooctyl azide **9** by simple reaction of the iodide with sodium azide in moist *tert*-butanol or isopropanol with satisfying conversions of around 90%. *Wu et al.*[37] described conversion of fluorinated alcohols into mesylates and their further transformation into corresponding azides by the use of sodium azide and 18-crown-6 ether as a catalyst. *Zhu et al*.[14] reported the transformation of tosylates in a mixture of DMF and benzene using sodium azide with good (70%) yields. In many cases the reaction between the iodide and sodium azide takes place by heating in MeCN or DMSO as a solvent.[32,38] This kind of reaction can be carried out also under microwave irradiation and the reaction time is significantly reduced (e.g. from 24 hours to 1 hour).[15]

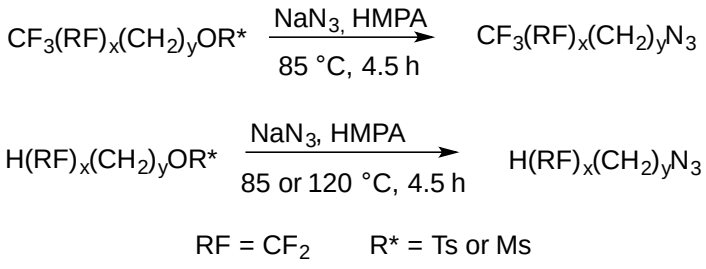
A transformation of an alcohol into its corresponding tosylate or mesylate and subsequent nucleophilic substitution with sodium azide to yield fluoroalkyl azides is one of the methodologies used in the literature. Starting materials, can be obtained from commercially available fluoroalkyl alcohols by reaction with *p*-toluenesulfonyl chloride or methanesulfonyl chloride, converting the hydroxyl group into a good leaving group. A procedure for preparation of fluoroalkyl tosylates is described by *Zhu et al.*,[14] and we have used an analogous procedure to prepare fluoroalkyl mesylates (Table 1).[24,29,32,34,36,39]

Table 1. Preparation of fluorinated tosylates and mesylates from corresponding fluorinated alcohols with *p*-toluenesulfonyl or methanesulfonyl chloride with triethylamine (Et_3N) in dichloromethane

Entry	Substrate	Product -OTs	Yield* (%)	Product -OMs	Yield* (%)
1	 **1**	 **1a**	87	 **1b**	72
2	$HCF_2(CF_2)_3CH_2OH$ **2**	$HCF_2(CF_2)_3CH_2OTs$ **2a**	90	$HCF_2(CF_2)_3CH_2OMs$ **2b**	77
3	$CF_3(CF_2)_6CH_2OH$ **3**	$CF_3(CF_2)_6CH_2OTs$ **3a**	77	$CF_3(CF_2)_6CH_2OMs$ **3b**	82
4	$CF_3(CF_2)_5CH_2CH_2OH$ **4**	$CF_3(CF_2)_5CH_2CH_2OTs$ **4a**	94	$CF_3(CF_2)_5CH_2CH_2OMs$ **4b**	90
5	$HCF_2(CF_2)_9CH_2OH$ **5**	$HCF_2(CF_2)_9CH_2OTs$ **5a**	91	$HCF_2(CF_2)_9CH_2OMs$ **5b**	39

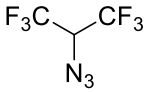
* Isolated yields.

Several different methodologies for the synthesis of fluorinated tosylates or mesylates have been described, where instead of triethylamine **1a**,[24] **1b**,[32,34] **2b**,[36] **3b**,[29] **4a**[40] other bases were used such as sodium or potassium hydroxide **2a**,[24,41] **3a**,[30,35] **5a**,[42,43] pyridine **1a**,[44] diisopropylamine **4b**,[39] DABCO **1a**.[45] For compound **1b** different conditions also used $SbCl_5$.[46] The products were obtained within a range of good to excellent yields e.g.: **1a** 88%,[45] **3a** 75% [35] and **3b** 51%.[37] To our best knowledge, fluorinated mesylate **5b** has not been reported. Typically, transformation of a tosylate or mesylate into the corresponding fluoroalkyl azide proceeds in toluene or DMSO as solvent, sometimes with addition of a catalyst such as 18-crown-6 ether.[31,37,47,48] Other reports use DMF/benzene as a solvent and simple nucleophilic substitution with sodium azide at elevated temperature.[14] We have changed the solvent to hexamethylphosphoramide (HMPA) and used a threefold excess of sodium azide without any extra additives. The reaction mixture was heated in an inert atmosphere in 85 °C or 120 °C for 4.5 hours (Scheme 1). The desired azides were obtained with moderate to good yields of 46-89% (Table 2).



Scheme 1. Nucleophilic substitution with sodium azide.

Table 2. Synthesis of fluorinated alkyl azides from fluorinated tosylates or mesylates with HMPA as solvent

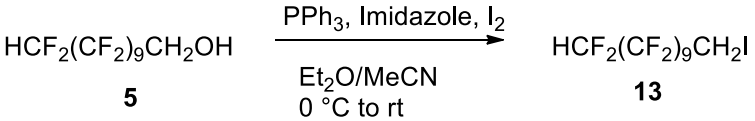
Entry	Substrate	T °C	Product	Yield (%)
1	**1a**	85		76[a]
2	**1b**	85	**6**	65[a]
3	**2a**	120	$HCF_2(CF_2)_3CH_2N_3$	61*
4	**2b**	120	**7**	50*
5	**3a**	85	$CF_3(CF_2)_6CH_2N_3$	76*
6	**3b**	85	**8**	64*
7	**4a**	85	$CF_3(CF_2)_5CH_2CH_2N_3$	70*
8	**4b**	85	**9**	46*
9	**5a**	120	$HCF_2(CF_2)_9CH_2N_3$	89*
10	**5b**	120	**10**	72*

* Isolated yields.

[a] crude product yields.

A difficulty occurred in the case of the secondary azide 2-azido-1,1,1,3,3,3-hexafluoropropane **6** since we were not able to visualize the product on TLC plate (stain solution desired for azides: 10% PPh_3 in DCM and 3% ninhydrin in *t*-BuOH and CH_3COOH did not give satisfying result). Nevertheless, ^1H NMR analysis of **6** showed signals due to protons typical for the -CH_2N_3 situation: δ: 4.38 ppm (septet).

Iodides are either commercially available as (4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl iodide **11**, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl iodide **12** and 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosafluorododecyl iodide **13**) or can be prepared from corresponding fluorinated alcohols (**2**, **5**) by the procedure described by *Seeberger et al.*[49] by reaction with triphenylphosphine, imidazole and iodine (Table 3) (Scheme 2).[50,51] There are also reports describing preparation of iodides with other methodologies e.g. with P_2O_5, H_3PO_4 and KI as a source of iodide anion in an elimination-addition reaction or microwave synthesis with polymer-bound triphenylphosphine and iodine.[22,52] A very interesting method has also been described by *Badache et al.*[23] The reaction of a fluorinated alcohol with diisopropylcarbodiimide yields fluorinated isoureas. Subsequently, the use of hydriodic acid in the next step, afforded fluorinated iodide. This procedure was also used in preparation of hydrogenated iodides with satisfactory yields.



Scheme 2. Synthesis of fluorinated iodide **13**.

Table 3. Preparation of fluorinated alkyl iodides from corresponding alcohols

Entry	Substrate	Product	Yield* (%)
1	$HCF_2(CF_2)_3CH_2OH$ **2**	$HCF_2(CF_2)_3CH_2I$ **14**	36
2	$HCF_2(CF_2)_9CH_2OH$ **5**	$HCF_2(CF_2)_9CH_2I$ **15**	72

* Isolated yields.

Although there are some reports of the preparation of 1-azido-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecane **16**,[53,54] the synthetic methodology and characterization of this product is not available in the literature. The synthesis and characterization of azide **16** prepared from iodide **11** is presented in this paper. On the other hand preparation of 1*H*,1*H*,2*H*,2*H*-perfluorooctyl azide **9** from the corresponding iodide **12** with sodium azide and Aliquat® 336,[55–57] in DMF,[14,58] in DMSO[45] or methyl-tridecylammonium chloride[59] has already been described.

Prepared or purchased iodides were submitted to nucleophilic substitution with sodium azide. The typical procedures used either moist *tert*-butanol, isopropanol or water as solvent, sometimes with the addition of Aliquat® 336. Reactions were typically performed at elevated temperatures. The synthesis of 1*H*,1*H*,2*H*,2*H*-perfluorododecyl azide **17** from 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosafluorododecyl iodide **13** proceeded in water at 90-110 °C with addition of Aliquat® 336.[56] Reaction time varied from 6 to 12 hours and the reaction yields were very good 87-93%. We decided to extend the reaction time to 17.5 hours but perform the reaction at lower temperature 80 °C. As an additive we used Aliquat® 336 and we changed solvent to a mixture of Et_2O and H_2O (1:1, v/v). As a result we obtained the desired product **17** in an excellent yield of 97%. The results are summarized in the Table 4.

Table 4. Preparation of fluorinated azides from iodides

Entry	Substrate	Product	Yield* (%)
1	$HCF_2(CF_2)_3CH_2I$ **14**	$HCF_2(CF_2)_3CH_2N_3$ **7**	43
2	$HCF_2(CF_2)_9CH_2I$ **15**	$HCF_2(CF_2)_9CH_2N_3$ **10**	72
3	$CF_3(CF_2)_7CH_2CH_2CH_2I$ **11**	$CF_3(CF_2)_7CH_2CH_2CH_2N_3$ **16**	91
4	$CF_3(CF_2)_5CH_2CH_2I$ **12**	$CF_3(CF_2)_5CH_2CH_2N_3$ **9**	58
5	$CF_3(CF_2)_9CH_2CH_2I$ **13**	$CF_3(CF_2)_9CH_2CH_2N_3$ **17**	97

*- Isolated Yields

The typical methodology of azide preparation from iodides, described by *Riess et al*.[60], using an anhydrous solvent like DMF, without any additives, also allowed us to obtain the desired azides (**9**, **16**, **17**), however with significantly lower yields (**16, 17**) (Table 5).

Table 5. Synthesis of fluorinated azides from iodides with DMF as solvent

Entry	Substrate	Solvent	Time h	T °C	Product	Yield* (%)
1	$CF_3(CF_2)_7CH_2CH_2CH_2I$ **1**	DMF	3	65	$CF_3(CF_2)_7CH_2CH_2CH_2N_3$ **16**	72
2	$CF_3(CF_2)_5CH_2CH_2I$ **12**	DMF	3.5	65	$CF_3(CF_2)_5CH_2CH_2N_3$ **9**	69
3	$CF_3(CF_2)_9CH_2CH_2I$ **13**	DMF	3.5	65	$CF_3(CF_2)_9CH_2CH_2N_3$ **17**	61

* Isolated yields.

Conclusion

A short overview of a re-examination of the synthetic methods for azides preparation with different linkers -CH_2- and a fluorinated chain has been provided. In summary, a series of highly fluoroalkyl azides were synthesized. The methodologies used were based on the reports available in the literature, however optimized and/or modified by us. All compounds were obtained with good to excellent yields. Further studies and use of prepared compounds as synthetic reagents, e.g. in Husigen cycloaddition reaction, will be reported in due course. All modified procedures for the synthesis of fluorinated compounds (**1a**-**17**) and new spectroscopic data are described in Experimental Section.

Experimental Section

General. All chemicals were reagent grade and used as purchased without further purification. Thin-layer chromatography (TLC) was carried out on silica gel plates (Silica gel 60, F254, Merck) with detection by UV light or with a stain solution (10% PPh_3 in DCM and 3% ninhydrin in *t*-BuOH and CH_3COOH). Purification was performed with preparative chromatography using normal-phase silica gel (Silica gel 60, 230-400 mesh, Merck). NMR spectra were calibrated using an internal reference: TMS (^1H), and $CFCl_3$ (^{19}F). Spectra were recorded in deuterated solvents $CDCl_3$ (7.26 ppm (^1H)) and $(CD_3)_2SO$ (2.49 ppm (^1H)) with a Varian VNMR-S 400 MHz or VARIAN Mercury 300 MHz. Chemical shifts are reported as δ values (ppm). Coupling constants (*J*) are given in hertz (Hz). Melting points were measured on a MEL-TEMP apparatus.

General procedure for the synthesis fluorinated tosylates and mesylates (1a-5b). A solution of TsCl (8.24 mmol, 1 equiv) or MsCl (8.24 mmol, 1 equiv) in DCM (24 mL) was added dropwise to a stirred solution of fluorinated alcohol 1-5 (8.24 mmol, 1 equiv) and Et_3N (1.78 mL, 1.55 equiv) at 0 °C. After complete addition

(10 min) the reaction mixture was allowed to reach rt and stirring was continued overnight. Then, the reaction mixture was washed with H_2O (34 mL) and brine (34 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The resulting crude product was crystallized from MeOH to afford **1a**-**5b**.

1,1,1,3,3,3-hexafluoroisopropyl *p*-toluenesulfonate (1a). White solid, yield 2.67 g (87%), mp 41-42 °C

1,1,1,3,3,3-hexafluoroisopropyl methanesulfonate (1b). Pale yellow liquid, yield 1.68 g (72%), ^{19}F NMR (379 MHz, $CDCl_3$): δ_F -73.39.

2,2,3,3,4,4,5,5-octafluoropentyl *p*-toluenesulfonate (2a). Pale yellow liquid, yield 2.51 g (90%), ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.81 (m, 2H, Ar-H), 7.39 (m, 2H, Ar-H), 5.99 (1H, tt, *J* 51.7 Hz, 5.0 Hz, CF_2H), 4.46 (2H, brt, *J* 12.8 Hz, CH_2OTs), 2.48 (3H, s, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -120.19, -125.53, -130.35, -137.70.

2,2,3,3,4,4,5,5-octafluoropentyl methanesulfonate (2b). Pale yellow liquid, yield 1.72 g (77%), ^{19}F NMR (379 MHz, $CDCl_3$): δ_F -119.79, -125.03, -129.64, -137.15.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl *p*-toluenesulfonate (3a). White solid, yield 1.33 g (77%), mp 51-55 °C. ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -81.26, -119.89, -122.53, -123.39, -126.65.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl methanesulfonate (3b). White solid, yield 0.266 g (88%), mp 46-48 °C. ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -81.23, -119.97, -122.41, -123.36, -126.61.

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl *p*-toluenesulfonate (4a). White solid, yield 4.0 g (94%), mp 52-54 °C. ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -81.28, -114.07, -122.43, -123.40, -124.09, -126.67.

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methanesulfonate (4b). White solid, yield 0.90 g (90%), mp 37-39 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.52 (2H, t, *J* 6.5 Hz, CH_2OMs), 3.07 (3H, s, CH_3), 2.71-2.53 (2H, m, $CF_3(CF_2)_5CH_2$). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -81.29, -114.06, -122.38, -123.38, -124.02, -126.66.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-eicosafluoroundecan *p*-toluenesulfonate (5a). White solid, yield 1.17 g (91%), mp 77-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.82 (2H, m, Ar-H), 7.39 (2H, dd, *J* 8.6 Hz, 0.7 Hz, Ar-H), 6.06 (1H, tt, *J* 51.7 Hz, 4.9 Hz, HCF_2), 4.46 (2H, brt, *J* 12.9 Hz, CH_2OTs), 2.48 (3H, s, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -119.91, -122.33, -123.65, -129.76, -137.48.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-eicosafluoroundecan methanesulfonate (5b). Light yellow solid, yield 0.45 g (39%), mp 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.06 (1H, tt, *J* 51.8 Hz, 5.0 Hz, CF_2H), 4.66 (2H, tt, *J* 13.2 Hz, 1.2Hz, CH_2OMs), 3.16 (3H, s, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -119.97, -122.27, -123.64, -129.74, -137.46.

General procedure for the synthesis of fluorinated alkyl azides (6-10) from fluorinated tosylates or mesylates with HMPA as a solvent. Under an argon atmosphere the fluorinated tosylates **1a**-**5a** (1.78 mmol, 1 equiv) or mesylates **1b**-**5b** (1.78 mmol, 1 equiv) were added to NaN_3 (5.34 mmol, 3 equiv) and HMPA (3 mL) was added. The mixture was heated to 85 °C or 120 °C and stirred for 4.5 h. Subsequently, reaction mixture was poured into H_2O (8 mL) and extracted with Et_2O (3 x 8 mL). The combined organic layers were washed with brine (2 x 8 mL) and dried over Na_2SO_4. Solvent was evaporated under reduce pressure. Column chromatography (hexane/EtOAc 3:1 v/v) gave pure products **7**-**10**.

1-azido-2,2,3,3,4,4,5,5-octafluoropentane (7). Yellowish liquid, from **2a**: yield 61%, 0.120 g from **2b**: yield 50%, 0.104 g. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.08 (1H, tt, *J* 51.7 Hz, 4.9 Hz, HCF_2), 3.78 (2H, t, *J* 14.8 Hz, CH_2N_3). ^{19}F NMR (379 MHz, $CDCl_3$): δ_F -118.02, -125.51, -130.12, -137.54.

1-azido-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctane (8). Colorless liquid, from **3a**: yield 0.536 g (75%), from **3b**: yield 0.012 g (64%), ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.78 (2H, t, *J* 14.6 Hz, CH_2N_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -81.24, -117.93, -122.35, -123.42, -126.61.

1-azido-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctane (9). Yellowish oil, from **4a**: yield 0.28 g (70%), from **4b**: yield 0.047 g (46%).

1-azido-2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-eicosafluoroundecane (10). White solid, from **5a**: yield 0.147 g (89%), from **5b**: yield 0.035 g (72%), mp 54-56 °C. ^{1}H NMR **(**300 MHz, $CDCl_3$): δ_H 6.06 (1H, tt, J_{HF} 51.8 Hz, 5.0 Hz, CF_2H), 3.78 (2H, t, J_{HF} 14.6 Hz, CH_2N_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ_F -119.98, -122.28, -123.64, -129.75, -137.45.

General procedure for the synthesis of fluorinated iodides (14, 15) from fluorinated alcohols (2,5). To a solution of the alcohol **2**, **5** (1.48 mmol, 1 equiv) in Et_2O/MeCN (3.7:1.23 mL, 3:1 v/v) in 0 °C successively imidazole (4.43 g, 3 equiv) and triphenylphosphine (2.22 g, 1.5 equiv) were added. Iodine (2.22 g, 1.5 equiv) was added portionwise over 10-15 min. The solution was kept for a further 20 min at 0 °C and then was allowed to warm up to rt overnight. The reaction mixture was diluted with Et_2O (12 mLl) and washed with saturated aq $Na_2S_2O_3$ (10 mL) and brine (2 x 10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under vacuum. Column chromatography hexane/EtOAc (1:1 v/v) gave pure product **14**, **15**.

1-iodo-2,2,3,3,4,4,5,5-octafluoropentane (14). Colorless liquid, yield 0.150 g (36%).

1-iodo-2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-eicosafluoroundecane (15). White solid, yield 0.683 g (72%), mp 82-86 °C. ^{19}F NMR (282 MHz, $CDCl_3$): δ_H -119.98, -122.28, -123.64, -129.75, -137.45.

General procedure for the synthesis of fluorinated azides (7, 9, 10, 16, 17) from iodides (11-15). The fluorinated iodide **11**-**15** (2.44 mmol, 1 equiv) was added to a solution of ç (4.88 mmol, 3 equiv) in H_2O (1 mL), Et_2O (1 mL) and Aliquat® 336 (0.12 mmol, 0.05 equiv). The reaction mixture was heated overnight at 90-100 °C in a sealed tube. Then, the reaction mixture was poured into H_2O (8 ml) and extracted with Et_2O (3 x 8 mL), and dried over Na_2SO_4. Solvent was removed under reduced pressure to afford pure product **7**, **9**, **10**, **16**, **17**.

1-azido-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecane (16). Colorless liquid, yield 0.078 g (91%), yield 0.432 g (72%), ^{1}H NMR (403 MHz, $CDCl_3$): δ_H 3.43 (2H, t, J_{HF} 6.5Hz, CH_2N_3), 2.26-2.10 (2H, m, $CH_2CH_2N_3$), 1.95-1.86 (2H, m, J_{HF} 14.1 Hz, 6.5Hz, CF_2CH_2). ^{19}F NMR (379 MHz, DMSO-d_6): δ_F -81.24, -114.82, -122.32, -123.29, -124.13, -126.65.

1-azido-3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosafluorododododecane (17). White solid, yield 0.519 g (97%), yield 0.053 g (61%), mp 55-56 °C.

General procedure for the synthesis of fluorinated azides (9, 16, 17) from iodides (11-13) with DMF as solvent. Under an argon atmosphere, fluorinated iodide (**11**-**13**) (1.19 mmol, 1 equiv) and NaN_3 (3.57 mmol, 3 equiv) were dissolved in DMF (7.2 mL). Stirring was continued for 3-3.5h at 65 °C. Then, solvent was evaporated under reduced pressure and reaction mixture was poured into H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to afford **9**, **16**, **17**.

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