



Fluorous Ethers

Journal:	<i>Green Chemistry</i>
Manuscript ID:	GC-CRV-06-2015-001345.R3
Article Type:	Critical Review
Date Submitted by the Author:	11-Aug-2015
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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Fluorous ethers having one or more fluoros ponytails containing longer and shorter $F(C_xF_{2x})$ -perfluoroalkyl substituent(s) where ($x \geq 6$) or ($x = 1 - 5$), respectively, were reviewed including some of their basic properties, synthesis and selected applications in chemical processes.

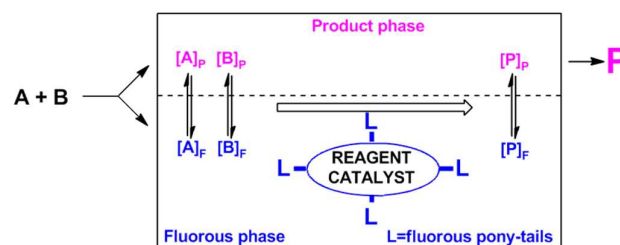
Introduction

Solvents have been playing an important role to perform chemical reactions and processes, isolate and purify chemical compounds by extraction, crystallization, or azeotrope distillation, clean surfaces, and assist the structural and analytical characterization of chemicals.¹ Traditionally, the right combination of physical and chemical properties of molecules were the only important criteria to select suitable solvents or design new ones. Well-known and publicized solvents related accidents² as well as the negative environmental and health effects of some of the commonly used solvents³ have changed the selection strategies⁴ and requirements: low vapour pressure, no or low flammability, no or low toxicity, low persistency, and high biodegradability have become additional features of today's preferred solvents.⁵ For example, chlorofluorocarbons (CFCs) were developed as a safe, non-toxic, and non-flammable replacement of toxic and dangerous refrigerants,⁶ such as ammonia and sulfur dioxide. In addition, they were widely used as cleaning solvents, agricultural propellants, and blowing agents. Their increasing popularity led to more and more releases to the atmosphere, which resulted in the ozone depletion.^{7a} The production of CFCs ceased globally by the middle of the nineties and the ozone layer is on track to recovery.^{7b} Hydrofluoroethers (HFEs) are emerging alternatives to replace perfluorocarbons (PFCs), CFCs, and hydrochloro-fluorocarbons (HCFCs).⁸ HFEs have shorter life-time in the atmosphere due to their facile decomposition by their reaction with hydroxy radicals.⁹ Consequently, HFEs have no ozone depletion and low global warming potentials. Since HFEs are less expensive and considerably less persistent and toxic in the environment, they have been used as refrigerants, cleaning solvents, blowing and degreasing agents.¹⁰

The most popular green solvents are water, alcohols, ionic liquids, and supercritical fluids.⁵ Although many of them exhibit very attractive solvent properties and have been used successfully, they are not necessarily free of environmental and/or health issues. The polar green solvents such as water, alcohols, and some of the ionic liquids could distribute low level polar contaminations including toxic chemicals. Ionic liquids have become very popular,¹¹ though their toxicity could be an issue, especially if their solubility in water could lead to contamination. Supercritical carbon dioxide and water have emerged as green solvents,¹² though the required higher pressures increase the risks for accidents. In all cases, the environmental benefits offered by the greener solvents must be a contributor to their favourable economic performance. While a broad range of greener polar solvents are available, only a few non-polar solvents have been developed. The most non-polar chemicals are the perfluorinated alkanes (C_xF_{2x+2}), dialkylethers ($[C_xF_{2x+1}]_2O$), and trialkyl amines ($[C_xF_{2x+1}]_3N$), which could be used as solvents as well.¹³

Fluorous Biphasic System (FBS)

Perfluorinated liquid compounds could easily form liquid-liquid biphasic systems with polar organics. The facile separation of the perfluorinated liquid reach phase was the basis of the fluorous biphasic concept, which was introduced together with the term fluorous, in 1994.¹⁴ Fluorous transformations should be controlled by carefully designed fluorous reagents or catalysts, which are preferentially soluble in the fluorous phase and has limited solubility in the product phase (Scheme 1).



Scheme 1 Fluorous biphasic system

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The temperature regulation of the fluororous biphasic systems leading to one phase at higher temperatures and two phases at lower temperatures, a simple approach to control mass transfers *via* thermoregulation, was also recognized.¹⁴

The introduction of the fluororous biphasic concept was followed by the rapid development of fluororous chemistry,¹⁵ which is closely connected to organofluorine chemistry.¹⁶ While the latter is dedicated to the fundamental aspects of making and breaking carbon-fluorine bond(s), fluororous chemistry is concerned with the design and attachment of perfluoro-alkyl group(s) containing substituents to the hydrocarbon domains of fluororous reagents and catalysts to ensure their efficient solubility and separation (Scheme 1). Originally,¹⁴ high fluororous partition ($P_F = C_{\text{fluorous phase}}/C_{\text{other phase}}$ in 50/50 vol.% $\text{C}_6\text{F}_{11}\text{CF}_3/\text{toluene}$)¹⁷ or fluorophilicity ($\ln P_F$)¹⁸ of the fluororous compounds was achieved by the attachment of $\text{C}_6\text{-C}_{12}$ -perfluoroalkyl ponytails to the hydrocarbon domains of fluororous reagents or catalysts in appropriate number.

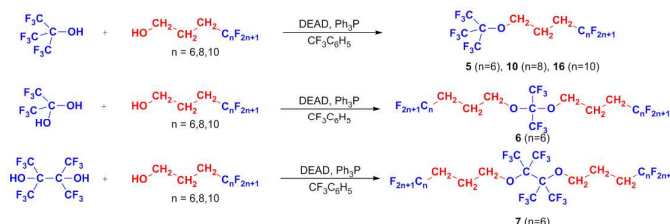
Commercially attractive fluororous systems should be designed to remain inside the laboratory or the production facility. However, low level leaching of a fluororous reagent or a catalyst to the product(s) or its accidental releases could result in long term environmental and health issues. If a fluororous compound with a long perfluoroalkyl group would enter the environment, its oxidative and/or hydrolytic fragmentation would lead to the formation of a long-chain perfluoroalkyl carboxylate (LCPFAC) (Scheme 2), among which perfluoro-octanoic acid ($\text{CF}_3(\text{CF}_2)_6\text{-COOH}$ or PFOA) is the best known.¹⁹



Scheme 2 Proposed formation of perfluoroalkyl carboxylate from fragmentation of long-chain fluororous compound in environment.

PFOAs and some of their precursors are persistent, widely present in humans and the environment, have long half-lives in humans, can cause adverse effects in laboratory animals, and were linked to developmental and reproductive problems, liver toxicity and cancer.²⁰ Under the Toxic Substances Control Act, US Environmental Protection Agency (EPA) has recently proposed to amend a significant new use rule for LCPFACs,²¹ where $5 < n < 21$ or $6 < m < 21$:

1. $\text{CF}_3(\text{CF}_2)_n\text{-COO-M}$ where $\text{M} = \text{H}$ or any other group where a formal dissociation can be made;
2. $\text{CF}_3(\text{CF}_2)_n\text{-CH=CH}_2$;
3. $\text{CF}_3(\text{CF}_2)_n\text{-C(=O)-X}$ where X is any chemical moiety;



Scheme 5 Mitsunobu reaction of perfluoro- and fluororous alcohols

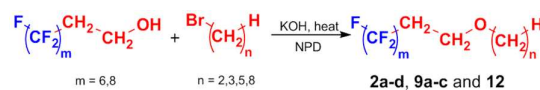
4. $\text{CF}_3(\text{CF}_2)_m\text{-CH}_2\text{-X}$ where X is any chemical moiety;
5. $\text{CF}_3(\text{CF}_2)_m\text{-Y-X}$ where $\text{Y} = \text{non-S, non-N heteroatom}$ and where X is any chemical moiety.

The bioaccumulation and toxicity of the homologues of perfluoroalkyl carboxylates is higher for longer compared to those with shorter perfluoroalkyl chain lengths.²⁰ Therefore, the combination of shorter C_{1-4} -perfluoroalkyl-groups was suggested to maintain high fluororous solubility and partition and minimize bioaccumulation.²²

Synthesis of C_{6-10} Perfluorinated Alkyl group(s) Containing Fluororous Ethers

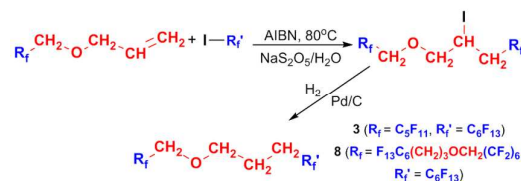
Examples of available long-chain perfluorinated alkyl ethers are listed in Table 1. Fluorination of dialkyl-ethers and polyethers has been the most used direct synthesis of perfluoroethers such as **1**, **4** and **13** with different molecular weights and boiling points (Table 1).²³

Fluororous ethers **2a-d**, **9a-c** and **12** (Table 1) have been prepared by reacting fluororous alcohols with alkyl bromides in the presence of KOH in N-methyl-2-pyrrolidone (Scheme 3).²⁴



Scheme 3 Synthesis of fluororous ethers involving nucleophilic substitution.

Long-chain containing fluororous ethers **3** and **8** (Table 1) were synthesised by preparing fluororous iodides from fluororous allyl ethers and perfluoroalkyl iodides in the presence of AIBN and aqueous $\text{Na}_2\text{S}_2\text{O}_5$, followed by the heterogeneous palladium catalysed hydrogenation (Scheme 4).²⁵



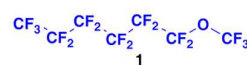
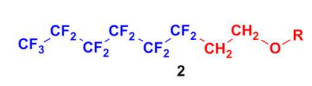
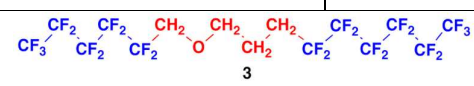
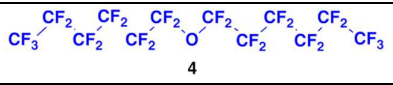
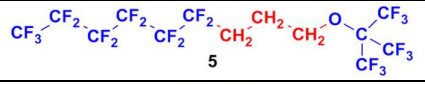
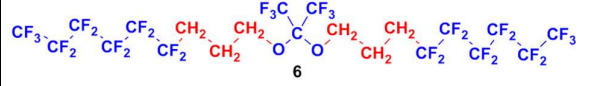
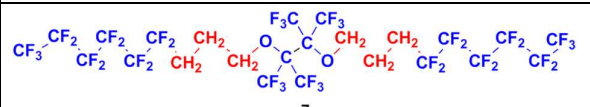
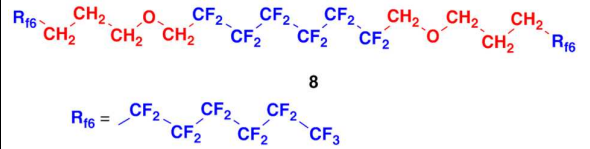
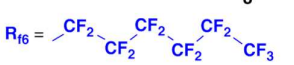
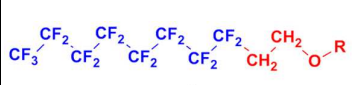
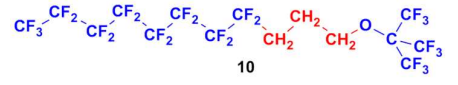
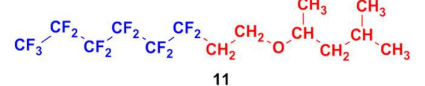
Scheme 4 Formation of fluororous ether by radical reaction of fluororous vinyl compound and fluororous iodide.

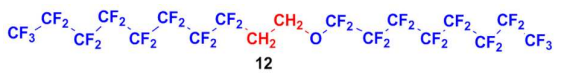
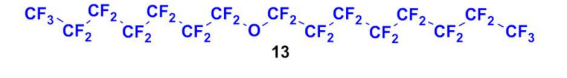
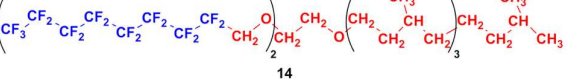
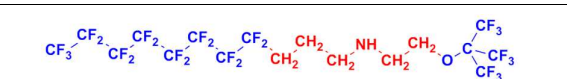
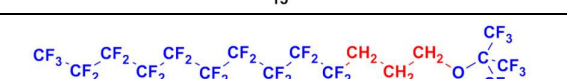
A series of fluororous dialkyl-ethers **5 – 7**, **10** and **16** (Table 1) were prepared by using the Mitsunobu reaction of perfluoro and perfluoroalkyl alcohols (Scheme 5).²⁶

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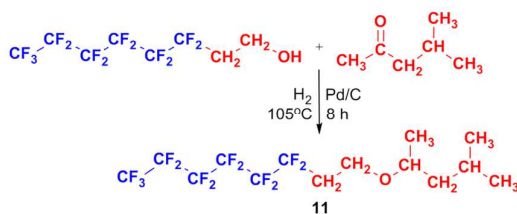
Table 1 – C₆₋₁₀ Perfluorinated alkyl group(s) containing fluororous ethers

Compound	Formula	MW [g/mol]	F [w%]	mp [°C]	bp [°C]	Yield [%]	Ref
	C ₇ F ₁₆ O	404	75.2	N/A	36	N/A	23
	R = C ₂ H ₅ (2a)	C ₁₀ H ₉ F ₁₃ O	392	63.0	< -80	65	24
	R = C ₃ H ₇ (2b)	C ₁₁ H ₁₁ F ₁₃ O	406	60.8	< -80	145	
	R = C ₅ H ₁₁ (2c)	C ₁₃ H ₁₃ F ₁₃ O	434	56.9	-46.8	110 ^a	
	R = C ₈ H ₁₇ (2d)	C ₁₆ H ₂₁ F ₁₃ O	476	51.9	-21.2	150 ^b	
	C ₁₅ H ₈ F ₂₄ O	660	69.1	N/A	210	82	25
	C ₁₂ F ₂₆ O	654	75.5	N/A	179	N/A	23
	C ₁₃ H ₆ F ₂₂ O	596	70.1	ca. -70	195-199	71	26
	C ₂₁ H ₁₂ F ₃₂ O ₂	904	67.3	-10 to -8	180-190 ^c	66	26
	C ₂₄ H ₁₂ F ₃₈ O ₂	1054	68.5	24 - 26	170-180 ^c	85	26
 	C ₂₅ H ₁₄ F ₃₈ O ₂	1068	67.6	Oil, N/A	>260	88	25
	R = C ₂ H ₅ (9a)	C ₁₂ H ₉ F ₁₇ O	492	65.7	< -80	72	24
	R = C ₃ H ₇ (9b)	C ₁₃ H ₁₁ F ₁₇ O	506	63.8	< -80	165	24
	R = C ₅ H ₁₁ (9c)	C ₁₅ H ₁₃ F ₁₇ O	534	60.5	-19.4	130 ^b	24
	C ₁₅ H ₆ F ₂₆ O	696	71	-37	224-227	91	26
	C ₁₄ H ₁₇ F ₁₃ O	448	13.7	Liquid, N/A	214	92	27

Compound	Formula	MW [g/mol]	F [w%]	mp [°C]	bp [°C]	Yield [%]	Ref
	C ₁₈ H ₂₁ F ₁₇ O ^d	576	56.1	-8.5	160 ^e	72	24
	C ₁₅ F ₃₂ O	804	75.6	N/A	215	N/A	23
	C ₄₁ H ₅₀ F ₃₄ O ₃	1236	52.3	<20	N/A	82	28
	C ₁₇ H ₁₁ F ₂₆ NO	739	66.8	Liquid, N/A	150-155 ^f	60	29
	C ₁₇ H ₆ F ₃₀ O	796	71.6	15	140 ^g	88	26

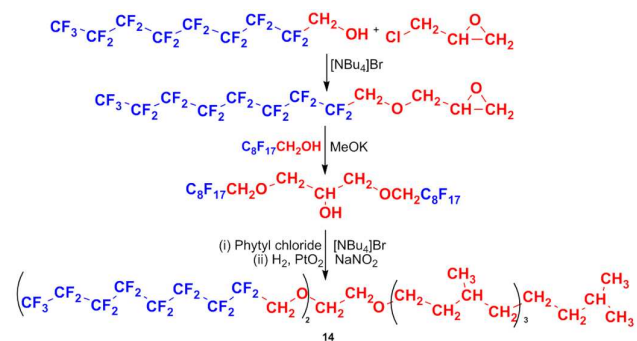
^a 4.5mmHg, ^b 5.25mmHg, ^c 16mmHg, ^d mixture of isomers (10:1, GC), ^e 0.75mmHg, ^f 20mmHg, ^g iso-octane

The palladium catalysed reaction of 1H,1H,2H,2H-perfluorooctanol with 4-methyl-2-pentanone under hydrogen has been used for the synthesis of fluoros ether **11** (F-626) (Scheme 6).²⁷



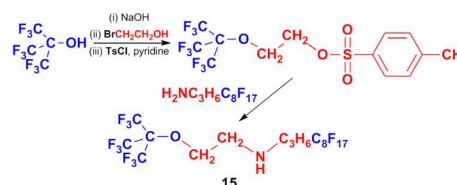
Scheme 6 Scheme of palladium catalysed reaction of perfluoroalcohol and ketone to form fluoros ether **11**.

The surfactant fluoros ether **14** (Table 1) was synthesized according to Scheme 7.²⁸



Scheme 7 Scheme of synthesising branched phytol chain fluoros surfactant.

15 was prepared by the reaction of perfluoro-*tert*-butanol, 1-bromo-ethanol and 4-toluenesulfonyl chloride, followed by the addition of 3-perfluorooctyl-1-propyl amine (Scheme 8).²⁹

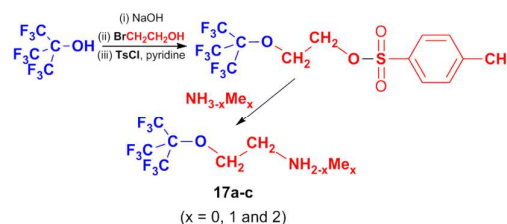


Scheme 8 Synthesis of fluoros ether from perfluoro-*tert*-butanol to fluoros amine, via platform fluoros tosylate compound.

Synthesis of C₁₋₅ Perfluorinated Alkyl Group(s) Containing Fluorous Ethers

Due to the toxicity and persistent characters of LCPFACs, the combination of shorter C₁₋₄-perfluoroalkyl-groups should be the preferred choice for commercial applications.²²

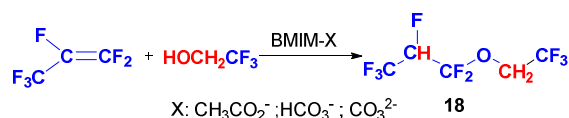
17a-c were prepared by the reaction of perfluoro-*t*-butanol, 1-bromo-ethanol and 4-toluenesulfonyl chloride, followed by the addition of NH_{3-x}Me_x (x=0-2) (Scheme 9, Table 2).²⁹



Scheme 9 Synthesis of fluoros ether from perfluoro-*tert*-butanol to fluoros amine, via platform fluoros tosylate compound.

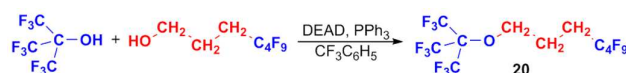
Fluorous ether **18** was prepared by the hydroalkylation of perfluoropropylene with CF₃CH₂OH in the presence of 1-butyl-3-methyl-imidazolium based ionic liquid with different anions

(Scheme 10).³⁰ The ionic liquids have served as both catalysts and solvents. It should be noted that the elimination of HF from **18** resulted in an olefinic side-product, which was hydroalkylated with $\text{CF}_3\text{CH}_2\text{OH}$ to yield **19** (Table 2).³⁰



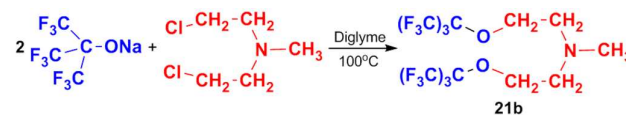
Scheme 10 Synthesis scheme of fluorinated ethers using ionic liquids BMIM-X, where X = $\text{CH}_3\text{CO}_2^-/\text{HCO}_3^-/\text{CO}_3^{2-}$.

The Mitsunobu reaction of perfluoro-*t*-butanol and $\text{C}_4\text{F}_9\text{C}_3\text{H}_6\text{OH}$ was used to prepare **20** (Scheme 11).²⁶



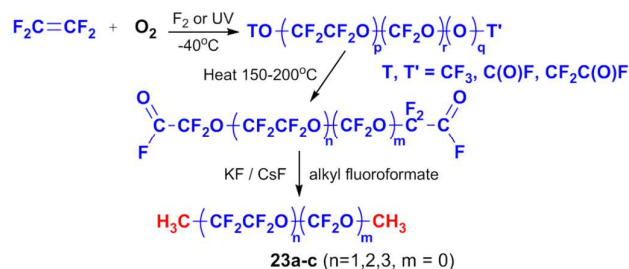
Scheme 11 Mitsunobu reaction of perfluoro- and fluorinated alcohols.

The reaction of perfluoro-*t*-butanol, 1-bromo-ethanol and 4-toluenesulfonyl chloride followed by the addition of **17a** resulted in **21a** (Table 2).²⁹ **21b** and **22** were synthesised by the reaction of the sodium salt of perfluoro-*t*-butanol with $(\text{ClCH}_2\text{CH}_2)_2\text{NCH}_3$ or $(\text{ClCH}_2\text{CH}_2)_3\text{N}$, respectively (Scheme 12).²⁹



Scheme 12. Synthesis of fluorinated amine ether by using sodium perfluoro-*tert*-butoxide.

The synthesis of **23a-c** was developed by Solvay-Solexis according to Scheme 13.³¹

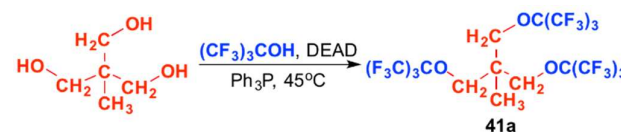


Scheme 13 General oxidative polymerisation scheme of producing fluorinated dialkyl polyethers.

Direct fluorination has been used for the synthesis of C_{1-5} perfluoro or fluorinated dialkyl-ethers (Table 2) including **24-31**, **34-40**, **43-47** and **52-53** with different molecular weights and boiling points.²³

Fluorinated ethers **32** and **33** are analogues of **23a-c** with different perfluoropolyether chain between the two methyl end-groups and were prepared according to Scheme 13.³¹

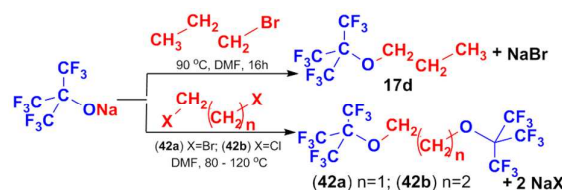
Fluorinated ether **41a** was prepared by the Mitsunobu reaction of $(\text{CF}_3)_3\text{C-OH}$ and $\text{CH}_3\text{C}(\text{CH}_2\text{OH})_3$ (Scheme 14).³²



Scheme 14 Another Mitsunobu reaction on synthesis of branched fluorinated ether.

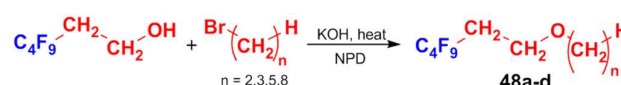
The reaction of $\text{PhCH}_2\text{OC}(\text{CH}_2\text{OC}(\text{CF}_3)_3)_3$ with aluminium chloride and anisole resulted in $\text{HOC}(\text{CH}_2\text{OC}(\text{CF}_3)_3)_3$ (**41b**), which could be methylated to give $\text{MeOC}(\text{CH}_2\text{OC}(\text{CF}_3)_3)_3$ (**41c**) (Table 2).

Perfluoro-*t*-butyl propyl ether (**17d**) or bis-perfluoro-*t*-butyl diethyl or dipropyl ethers, **42a** and **42b**, respectively, were prepared in good yields by reacting sodium perfluoro-*t*-butoxide with the appropriate alkyl halides (Scheme 15). The cytotoxicity of these fluorinated ethers were shown to be lower than PFOA.³³



Scheme 15 Synthetic scheme of using sodium perfluoro-*tert*-butoxide to yield bis-perfluoro-*tert*-butyl ethers.

Perfluoroethers **48a-d** were synthesised by the Williamson etherification of $\text{C}_4\text{F}_9\text{CH}_2\text{CH}_2\text{OH}$ and alkyl bromides with various length of alkyl groups (Scheme 16).²⁴



Scheme 16 General scheme of Williamson etherification for fluorinated ether formation.

49 was synthesised by preparing fluorinated iodides from perfluoropropyl allyl ether and perfluorobutyl iodide in the presence of AIBN and aqueous $\text{Na}_2\text{S}_2\text{O}_5$, followed by the heterogeneous palladium catalysed hydrogenation.²⁵

Fluorinated ethers **50** and **51** are analogues of **6** and **7**, and were prepared by Mitsunobu reaction of the appropriate perfluoro and fluorinated alcohols.²⁶

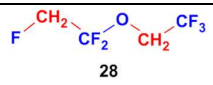
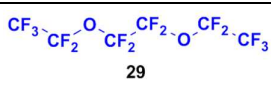
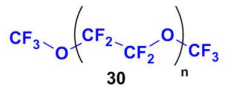
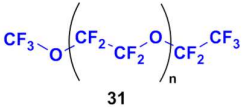
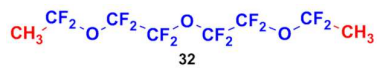
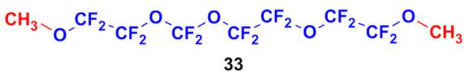
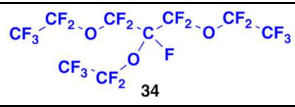
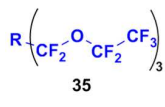
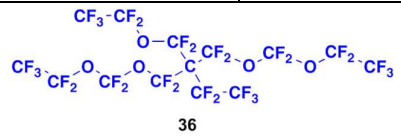
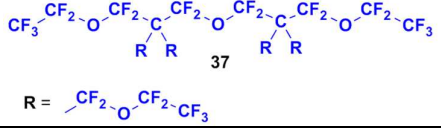
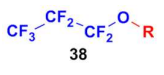
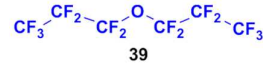
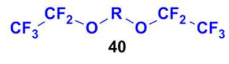
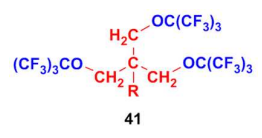


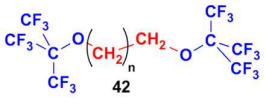
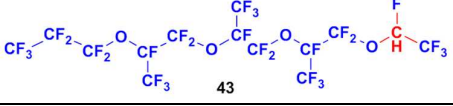
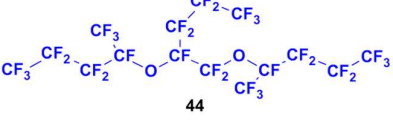
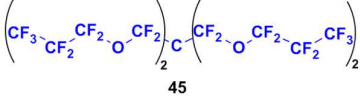
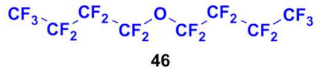
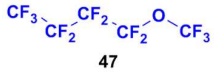
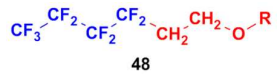
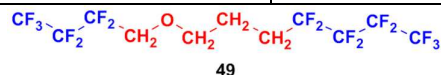
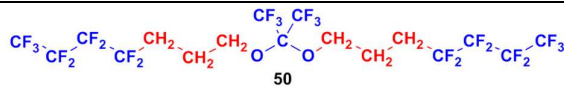
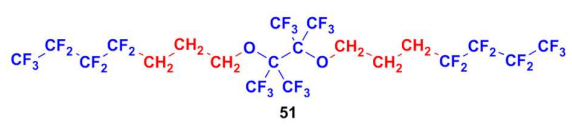
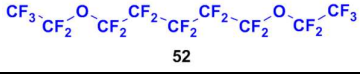
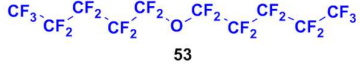
Green Chemistry

Review

Table 2 – C₁₋₅ Perfluorinated alkyl group(s) containing fluoruous ethers

Compound	Formula	F [w%]	MW [g/mol]	mp [°C]	bp [°C]	Yield [%]	Ref	
 17	R = NH ₂ (17a)	C ₆ H ₉ F ₉ NO	61.3	279	Oil, N/A	110	28	
	R = NHCH ₃ (17b)	C ₇ H ₈ F ₉ NO	58.4	293	Oil, N/A	140-160 ^a		69
	R = N(CH ₃) ₂ (17c)	C ₈ H ₁₀ F ₉ NO	55.7	307	Liquid, N/A	116		36
	R = CH ₃ (17d)	C ₇ H ₇ F ₉ O	61.5	278	Liquid, N/A	N/A	64	33
 18	C ₅ H ₃ F ₉ O	68.4	250	N/A	N/A	max. 96.5 ^b	30	
 19	C ₇ H ₃ F ₁₁ O ₂	63.3	330	N/A	N/A	max. 1.2 ^c	30	
 20	C ₁₁ H ₆ F ₁₈ O	69	496	-150 to 130	107-110	N/A	26	
 21	R = H (21a)	C ₁₂ H ₉ F ₁₈ NO ₂	63.2	541	Oil, N/A	120 ^{ad}	29	
	R = CH ₃ (21b)	C ₁₃ H ₁₁ F ₁₈ NO ₂	61.6	555	Liq., N/A	130-140 ^{ae}		53
 22	C ₁₈ H ₁₂ F ₂₇ NO ₃	63.9	803	Oil, N/A	140 ^d	33	29	
 23	n = 1 (23a)	C ₄ H ₆ F ₄ O ₂	46.9	162	-21.2	92	31	
	n = 2 (23b)	C ₆ H ₆ F ₈ O ₃	54.7	278	-64.2	135		N/A
	n = 3 (23c)	C ₈ H ₆ F ₁₂ O ₄	57.9	394	-34.2	161		N/A
 24	C ₄ F ₁₀ O	74.8	254	N/A	10	N/A	23	
 25	C ₄ H ₃ F ₇ O	66.5	200	N/A	N/A	N/A	8, 23	
 26	C ₄ H ₄ F ₆ O	62.6	182	N/A	54.3	N/A	8, 23	
 27	R = CH ₃ (27a)	C ₄ H ₄ F ₆ O	62.6	182	N/A	51	8, 23	
	R = CH ₂ CH ₂ F (27b)	C ₄ H ₃ F ₇ O	66.5	200	N/A	58.6		N/A

Compound	Formula	F [w%]	MW [g/mol]	mp [°C]	bp [°C]	Yield [%]	Ref
	C ₄ H ₄ F ₆ O	62.6	182	N/A	65	N/A	8, 23
	C ₆ F ₁₄ O ₂	71.9	370	N/A	N/A	100	23
	n = 2 (30a)	C ₆ F ₁₄ O ₃	68.9	386	N/A	61	N/A
	n = 3 (30b)	C ₈ F ₁₈ O ₄	68.1	502	N/A	105	N/A
	n = 2 (31a)	C ₇ F ₁₆ O ₃	69.7	436	N/A	85	N/A
	n = 3 (31b)	C ₉ F ₂₀ O ₄	68.8	552	N/A	118	N/A
	C ₈ H ₆ F ₁₂ O ₃	60.3	378	-78	N/A	N/A	31
	C ₉ H ₆ F ₁₄ O ₅	57.8	460	N/A	179	N/A	31
	C ₉ F ₂₀ O ₃	70.9	536	N/A	114	86	23
	R = CF ₃ C- (35a)	C ₁₁ F ₂₄ O ₃	71.7	636	N/A	153	71
	R = CF ₃ CF ₂ C- (35b)	C ₁₂ F ₂₆ O ₃	72	686	N/A	163	78
	R = CF ₃ CF ₂ O-CF ₂ C- (35c)	C ₁₃ F ₂₈ O ₄	70.7	752	N/A	169	99 ^f
	C ₁₄ F ₃₀ O ₅	69.7	818	N/A	218-220	49	23
	C ₂₂ F ₄₆ O ₇	69.9	1250	N/A	256	67	23
	R = CH ₃ (38a)	C ₄ H ₃ F ₇ O	66.5	200	N/A	67.9	N/A
	R = CH ₂ CH ₂ F (38b)	C ₄ H ₂ F ₈ O	69.7	218	N/A	43.3	N/A
	C ₆ F ₁₄ O	75.1	354	N/A	56	N/A	23
	R = (CF ₂) ₃ (40a)	C ₇ F ₁₆ O ₂	72.4	420	N/A	91	100
	R = CF ₂ (CF ₃) ₂ CF ₂ (40b)	C ₉ F ₂₀ O ₂	73.1	520	N/A	108	N/A
	R = (CF ₂) ₄ (40c)	C ₈ F ₁₈ O ₂	72.8	470	N/A	96	89
	R = CH ₃ (41a)	C ₁₇ H ₉ F ₂₇ O ₃	66.0	774	N/A	Oil, N/A	78
	R = OH (41b)	C ₁₆ H ₇ F ₂₇ O ₄	66.0	776	N/A	Oil, N/A	99
	R = OCH ₃ (41c)	C ₁₇ H ₉ F ₂₇ O ₄	65.0	790	N/A	Liquid, N/A	93

Compound	Formula	F [w%]	MW [g/mol]	m.p [°C]	b.p [°C]	Yield [%]	Ref	
	n = 1 (42a)	C ₁₀ H ₄ F ₁₈ O ₂	69.0	498	N/A	N/A	53	33
	n = 2 (42b)	C ₁₁ H ₆ F ₁₈ O ₂	67.0	512	N/A	N/A	43	33
	C ₁₄ HF ₂₉ O ₄	70.3	784	-115	192-195	N/A	23	
	C ₁₅ F ₃₂ O ₂	74.1	820	N/A	N/A	N/A	23	
	C ₁₇ F ₃₆ O ₄	71.8	952	N/A	219	49	23	
	C ₈ F ₁₈ O	75.3	454	N/A	100.4	N/A	23	
	C ₅ F ₁₂ O	75	304	N/A	35.4	N/A	23	
	R = C ₂ H ₅ (48a)	C ₈ H ₉ F ₉ O	58.6	292	< -80	56	95	26
	R = C ₃ H ₇ (48b)	C ₉ H ₁₁ F ₉ O	55.9	306	< -80	120	84	
	C ₁₁ H ₈ F ₁₆ O	66.1	460	N/A	155	82	25	
	C ₁₇ H ₁₂ F ₂₄ O ₂	64.8	704	-30	135-137	47	26	
	C ₂₀ H ₁₂ F ₃₀ O ₂	66.7	854	3 - 5	150-157 ^e	72	26	
	C ₉ F ₂₀ O ₂	73.1	520	N/A	85	75	23	
	C ₁₀ F ₂₂ O	75.5	554	N/A	139	N/A	23	

^a oil bath temperature, ^b Anion AcO⁻, ^c Anion CO₃²⁻, ^d 20mmHg, ^e 16mmHg

Commercial Fluorous Solvents

The major types of commercial fluorous solvents are perfluoroalkanes, perfluorodialkyl ethers and polyethers, perfluorotrialkyl amines, and hydrofluoroethers (Table 3).

Perfluorohexane (FC-72),^{34, 35} perfluoromethylcyclohexane (PFMC)³⁵ and perfluoro-decalin³⁵ are frequently used perfluoroalkanes, which are immiscible with most organic solvents at room temperature.

Perfluoro and fluorous ethers and polyethers were introduced to the market for different industrial applications. Perfluoro-2-butyltetrahydrofuran (FC-75) has been available from Sigma-Aldrich.³⁵ The well-known engineering fluids, under the brand name Novec™ (for example Novec 7100: C₄F₉OCH₃ and Novec 7200: C₄F₉OC₂H₅) were developed by 3M, which have high boiling points, high thermal stability, low toxicity and can be used as a non-flammable solvents.³⁶ Solvay Chemicals has been producing perfluoropolyethers, called Galden™, with different boiling points from 55 to 270 °C. These were designed as chemically and thermally stable high

performance fluorinated heat transfer fluids.³⁷ Fluorinated Krytox™ oil from DuPont are chemically inert oils, which could provide lubrication in wide range of conditions, resisting to common organic solvents.³⁸

Perfluorotributylamin has been used under different names: FC 43, Flurosol 43, Flurinert FC 43, Mediflor FC 43) and has similar properties to FC-72.³⁵

Although benzotrifluoride (BTF)³⁵ contains only 39 w% fluorine, it is a very useful solvent for synthesis as it could dissolve both fluorine and non-fluorine compounds.³⁹ Consequently, it is called a “hybrid” or an “amphiphilic” substance, which is a stable and useful medium for organic reactions, which are beyond the scope of this review.

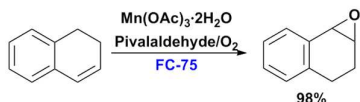
Table 3. Some commercially available fluorine solvents

Solvent	Formula	Average M.W	mp [°C]	bp [°C]	Density [g/cm ³]	Refractive index	Ref.
FC-72	C ₆ F ₁₄	338	-82	58-60	1.670	1.25 ^a	34, 35
PFMC	CF ₃ C ₆ F ₁₁	350	-37	76	1.787	1.29 ^a	35
Perfluorodecalin	C ₁₀ F ₁₈	468	-10	142	1.908	1.31 ^b	
FC-75	C ₈ F ₁₆ O	420	-88	99-107	1.770	1.77	36
Novoc™7100 ¹²	<i>n</i> -C ₄ F ₉ OCH ₃	250	-135	61	1.520	1.27	
Novoc™7200 ¹²	<i>n</i> -C ₄ F ₉ OCH ₂ CH ₃	264	-138	76	1.430	1.28	
Novoc™7500 ¹²	(<i>i</i> -C ₃ F ₇)(<i>n</i> -C ₃ F ₇)CFOC ₂ H ₅	414	N/A	128	1.614	1.29	
Gladen HT-110	CF ₃ (OC ₂ F ₄) _{<i>m</i>} (OCF ₂) _{<i>n</i>} OCF ₃	~580	N/A	110	1.71	1.28	
Gladen HT-135	CF ₃ (OC ₂ F ₄) _{<i>m</i>} (OCF ₂) _{<i>n</i>} OCF ₃	~610	N/A	135	1.72	1.28	
Gladen HT-170	CF ₃ (OC ₂ F ₄) _{<i>m</i>} (OCF ₂) _{<i>n</i>} OCF ₃	~760	N/A	170	1.77	1.28	
Gladen HT-200	CF ₃ (OC ₂ F ₄) _{<i>m</i>} (OCF ₂) _{<i>n</i>} OCF ₃	~870	N/A	200	1.79	1.28	
Krytox™ GPL 102	F-(C(CF ₃)-CF ₂ -O) _{<i>n</i>} -CF ₂ CF ₃ (n=10-60)	N/A	Oil, N/A	-63 to 132	1.91 ^c	N/A	
Krytox™ GPL 103	F-(C(CF ₃)-CF ₂ -O) _{<i>n</i>} -CF ₂ CF ₃ (n=10-60)	N/A	Oil, N/A	-60 to 154	1.92 ^c	N/A	
Krytox™ GPL 104	F-(C(CF ₃)-CF ₂ -O) _{<i>n</i>} -CF ₂ CF ₃ (n=10-60)	N/A	Oil, N/A	-51 to 179	1.93 ^c	N/A	
Krytox™ GPL 105	F-(C(CF ₃)-CF ₂ -O) _{<i>n</i>} -CF ₂ CF ₃ (n=10-60)	N/A	Oil, N/A	-36 to 204	1.94 ^c	N/A	
FC43	N(C ₄ F ₉) ₃	671	-50	178	1.884	1.29	35
BTF	C ₆ H ₅ CF ₃	146	-29	103	1.181	1.41	

^aat 20°C ^bat 17°C ^cat 0°C

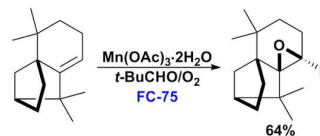
Examples for the Application of Fluorine Ethers as Solvents

Due to the high solubility of oxygen in perfluorocarbons, perfluoro-2-butyltetrahydrofuran (FC-75) was used as the medium in the epoxidation of 1,2-dihydronaphthalene (Scheme 17).⁴⁰ The reaction was completed in one hour, 3 times faster than in dichloromethane or benzotrifluoride, as expected. The product was easily separated and the fluorine solvent was recycled.



Scheme 17 Mn-catalysed epoxidation of 1,2-dihydronaphthalene in FC-75.

The acid-sensitive aerobic epoxidation of isolongifolene was performed in FC-75 to provide a neutral environment and lead to the formation of corresponding epoxide in good yield (Scheme 18).⁴¹



Scheme 18 Aerobic epoxidation of isolongifolene in FC-75.

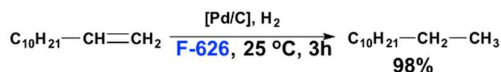
1*H*, 1*H*, 2*H*, 2*H*-perfluorooctyl-1,3-dimethyl-butyl-ether or (F-626) has been a very useful amphiphilic ether, which was introduced as an excellent solvent for fluorine and non-fluorine reactions and several well-known reactions have been tested.²⁷

The highly flammable diethyl ether was replaced successfully with F-626 in the reduction of benzoic acid ethyl ester with LiAlH₄ (Scheme 19).²⁷



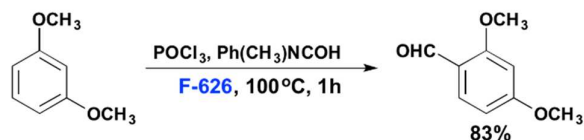
Scheme 19 Reduction of benzoic acid ethyl ester with LiAlH₄ in F-626.

The palladium-catalysed hydrogenation of 1-dodecene resulted in 98% 1-dodecane (Scheme 20).²⁷ It is important to note that reaction conducted in F-626 achieved better yield compared to diethyl ether (95%), and more than 90% of F-626 could be recovered after fluorine/organic work up.



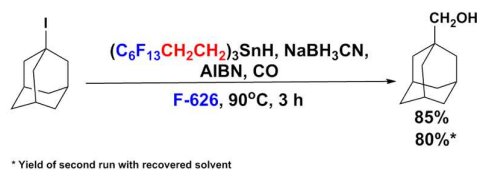
Scheme 20 Palladium-catalysed hydrogenation of 1-dodecene in F-626.

The Vilsmeier formylation of 1,3-dimethoxy-benzene was performed in F-626 in better yield (83%) than in the toxic *o*-dichlorobenzene (60%) and 97% of F-626 was recovered from the reaction mixture by extraction with FC-72 (Scheme 21).²⁷



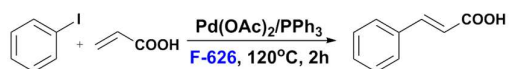
Scheme 21 Vilsmeier formulation in F-626.

The reductive radical carbonylation of 1-iodo-adamantane with tris(1*H*, 1*H*, 2*H*, 2*H*-perfluorooctyl) tin hydride proceeded in 85% yield (Scheme 22).²⁷ While the 1-adamantylmethanol was isolated from the organic phase of a triphasic solvent extraction system (H₂O/CH₂Cl₂/FC-72), the fluoros tin-catalyst was recovered in the F-626 reach phase. The product yield of 80% was achieved conveniently in the second run.



Scheme 22 Fluorous reductive radical carbonylation in F-626.

The Mizoroi-Heck arylation of acrylic acid was performed in F-626 in high yield (Scheme 23)⁴². After a fluoros/organic workup, the recovery of F-626 was higher than 94%. The product yields obtained from the second or further runs of reactions in recovered F-626 were similar.



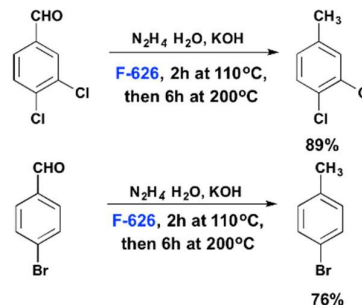
Run	Yield (%)	Recovery of F-626 (%)
1	88	96
2	85	94
3	86	97
4	85	95

Scheme 23 Mizoroi-Heck arylation of iodobenzene in F-626.

Novec™7500 [(CF₃CF₂CF₂)₂CF—O—CH₂CH₃] was successfully used as the primary reaction solvent in the Corey-Bakshi-Shibata reduction of ketones with light fluoros chiral prolinol precatalyst, which can be readily recycled.⁴³

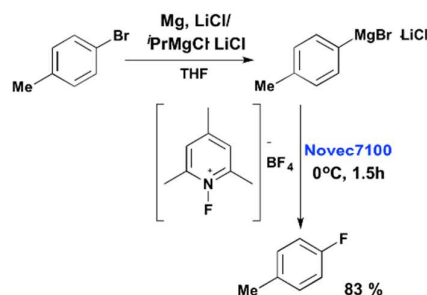
Addition of the high boiling solvent F-626 was shown to work well in a high temperature reaction such as the Wolff-Kishner reduction (Scheme 24).²⁷ Compared to diethylene glycol as the common solvent in such reaction, good yield was

obtained in F-626, followed by fluoros/organic biphasic workup, the separation and solvent recovery were performed in ease.



Scheme 24 Examples of Wolff-Kishner reduction in F-626.

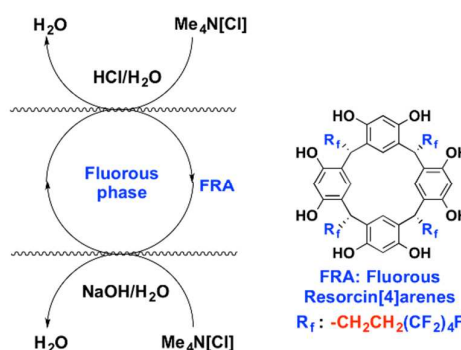
Novec™-7100 has been reported as effective co-solvent for the electrophilic fluorination of aryl Grignard reagents with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (Scheme 25).⁴⁴ The reaction worked well in both heptane and Novec™-7100 and have shown even better yields than in diethyl ether, dioxane, and benzofluoride.



Scheme 25 Fluorination of 4-bromoanisole in hydrofluorocarbon ether Novec™-7100.

Similar uses with Novec™-7200 were also reported for peptides and oligosaccharides synthesis.⁴⁵

Novec™-7100 has played an important role as a medium of the triphasic system with bulky fluoros membrane transport host. The triphasic transport experiment was demonstrated with TMA[Cl] in NaOH as source phase and HCl as the receiving phase (Scheme 26).⁴⁶



Scheme 26 Example of Novec™-7100 as medium of bulky fluoros membrane transport host.

Novec™-7100 was useful for fluoros solid-phase extraction and chromatography for fluoros cabodiimide coupling reaction, due to slightly higher polarity than perfluorocarbon and improved immiscibility with ethyl acetate to provide more suitable solvent system.⁴⁷ Moreover, its application was extended to enzymatic studies, the horse liver alcohol dehydrogenase (HLADH) in catalyzing oxidation/reduction reactions using fluoros coenzyme nicotinamide adenine dinucleotide (NAD) in Novec™-7100 gives better extraction and immisibility.⁴⁸

Conclusion

The basic properties and the typical synthesis of around fifty fluoros ethers with one or more perfluoroalkyl substituents [$F(C_xF_{2x})-$; ($x = 1-10$)] were reviewed. The selected applications of fluoros ethers with shorter perfluoroalkyl substituent(s) [$F(C_xF_{2x})-$; ($x = 1 - 5$)] were demonstrated. The advantages of the fluoros ethers containing more than one shorter fluoros ponytails include good to excellent recyclability, good thermal stability, lower persistency and ozone depletion potential. In addition, their oxidative and/or hydrolytic fragmentation in the environment would lead to the formation of shorter perfluoroalkyl caboxylates, which have lower bioaccumulation and toxicity with respect to the higher homologues. Fluoros ethers containing more than one shorter fluoros ponytails therefore could be attractive solvents for synthesis and other applications.

Acknowledgements

This work was funded by the City University of Hong Kong, project numbers 7002604 (2010) and 9667113 (2015).

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