

Synthetic Studies on Perfluorinated Compounds
by Direct Fluorination

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Abbreviations

5-FU	5-fluorouracil
Ac	acetyl
AK-225	ASAHI KLIN [®] 225
Ar	aryl
bp	boiling point
bs	broad singlet (in NMR)
calcd	calculated
CFC	chlorofluorocarbon
CI	chemical ionization
CTFE	chlorotrifluoroethylene
d	doublet (in NMR)
dd	double doublet (in NMR)
DMF	dimethylformamide
dt	double triplet (in NMR)
ECF	electrochemical fluorination
EI	electron ionization
eq	equivalent
eq.	equation
ETFE	ethylene/tetrafluoroethylene copolymer
FEP	tetrafluoroethylene/hexafluoropropylene copolymer
GC	gas chromatography

HALEX	aromatic halogen exchange
HCFC	hydrochlorofluorocarbon
HFA	hexafluoroacetone
HFC	hydrofluorocarbon
HFIP	1, 1, 1, 3, 3, 3-hexafluoro-2-propanol
HFP	hexafluoropropylene
HFPO	hexafluoropropylene oxide
HRMS	high resolution mass spectrum
Hz	hertz
IT	information technology
J	coupling constant (in NMR)
kPa	kilopascal
LC	liquid crystal
m	multiplet (in NMR)
MHz	megahertz
MPa	megapascal
MS	mass spectrometry
NMR	nuclear magnetic resonance
PCTFE	poly(chlorotrifluoroethylene)
PERFECT	perfluorination of an esterified compound followed by thermolysis
PFA	perfluoroalkoxy copolymer
PFPE	perfluoropolyether
Ph	phenyl
POF	plastic optical fiber

PPVE	perfluorinated propyl vinyl ether
PTFE	poly(tetrafluoroethylene)
PVdF	poly(vinylidene fluoride)
PVF	poly(vinyl fluoride)
q	quartet (in NMR)
R	alkyl
R113	1, 1, 2-trichlorotrifluoroethane
R225	dichloropentafluoropropane
R _F	perfluorinated alkyl
R _H	non-fluorinated alkyl
SDF	selective direct fluorination
t	triplet (in NMR)
Tf	trifluoromethanesulfonyl
TFE	tetrafluoroethylene
TFE-P	tetrafluoroethylene/propylene copolymer
TFT-LCD	thin film transistor-liquid crystal display
TM	trade mark
uv	ultra violet
vic	vicinal
WO	code of WIPO (World Intellectual Property Organization) patents
δ	scale (in NMR)

Chapter I

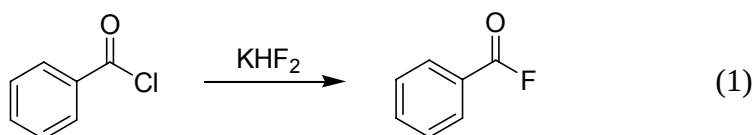
General Introduction

I-1. Historical Background of Organofluorine Chemistry

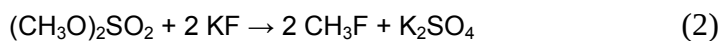
— Industrial Viewpoint —

I-1-1. Incunabula

Alexander Borodin (1833 – 1887), who is well-known as a composer in classical music, is said to have made the first organofluorine compound.¹ More precisely, he carried out the first nucleophilic replacement of a different halogen atom by fluoride (eq. 1) and reported the results in 1862.^{2, 3} This was the first example of synthesis of an organofluorine compound by halogen exchange, which is now broadly used in fluorine chemistry and especially in fluorochemical industry for the introduction of fluorine atoms into organic molecules. Borodin was a promising young chemist, and became a professor of chemistry in 1864.

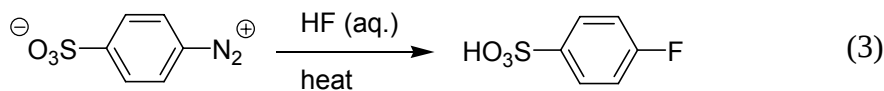


Actual first synthesis of an organofluorine compound was reported by Dumas *et al.* in 1835,³ who prepared methyl fluoride from dimethyl sulfate (eq. 2).



Formation of an aryl C-F bond was first carried out through diazofluorination by Schmitt *et al.* in 1870 (though the characterization was wrong), then by Lenz in 1877

(eq. 3).³



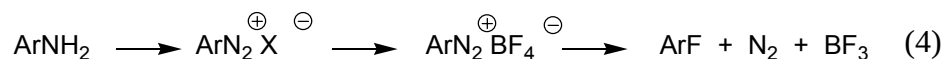
Mineral fluorides were recognized and used as early as 16th century. In 17th century, it was already known that glass was etched when it was exposed to a new acid generated from fluorspar and sulfuric acid.⁴ The generated acid was called hydrofluoric acid and was characterized by Scheele in 1771.^{4, 5} Then it was eventually realized that hydrofluoric acid contained a previously unknown element, fluorine. Although organofluorine compounds were prepared in mid 18th century, elemental fluorine itself was not isolated at that time.

After continuous efforts by a great number of chemists, elemental fluorine was finally isolated in 1886 by Moissan, who electrolyzed a melt mixture of potassium hydrogen difluoride and hydrogen fluoride.^{4, 6, 7}

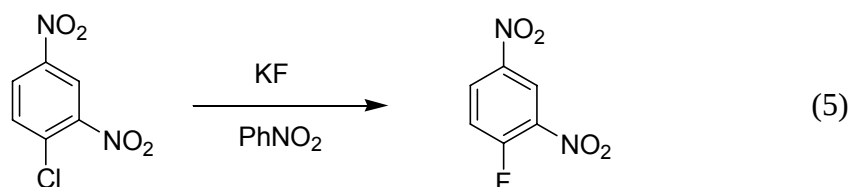
Because of hazards and difficulties in handling highly reactive and corrosive reagents, organofluorine chemistry remained relatively undeveloped until 1920's.

In 1926, carbon tetrafluoride was first isolated from the product of the reaction of fluorine with wood charcoal by French chemists, Lebeau and Damiens,⁸ and was fully characterized 4 years later by Ruff.⁹

In 1927, Schiemann found an aromatic fluorination methodology:¹⁰ diazonium salts of aromatic amines were first prepared, and then decomposed in the presence of hydrofluoric acid to give fluorinated aromatic compounds (eq. 4). This reaction was improved and is still used even now for the manufacture of fluoroaromatic compounds.



Another important synthesis of fluoroaromatic compounds, nucleophilic halogen exchange from Cl to F using KF (eq. 5), was reported by Gottlieb in 1936.^{3, 11} This was the first example of halogen exchange method used in the fluoroarene synthesis.



Aromatic compounds with fluorinated side chain was reported by Swarts in 1898 for the first time.^{3, 12} Benzotrichloride was found to react rapidly with SbF_3 (eq. 6).

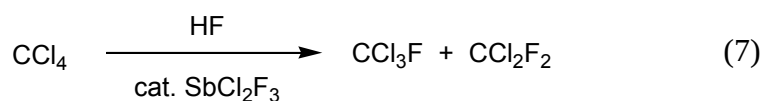


This conversion from aromatic $-\text{CCl}_3$ to $-\text{CF}_3$ was later achieved with HF and reported in 1930's.¹³

I-1-2. Development with material industry

In 1928, General Motors Corporation, manufacturers of refrigerators, appointed McNary, Midgley and Henne to the task of finding inert refrigerants. Until then, available conventional refrigerants had serious drawbacks: some were flammable, others like SO₂ were corrosive and toxic, and still others like NH₃ combined all three hazards.⁵ Midgley *et al.* studied on a fundamental basis, plotting trends of toxicity, flammability, and boiling point on a periodic chart of the element. He concluded that desired boiling range of 0 °C to – 40 °C might be achieved by fluoroaliphatic compounds. At first, carbon tetrafluoride (CF₄) seemed appropriate because its boiling point was reported by Moissan as – 15 °C¹⁴ (though this was incorrect)³. However, feeling that the synthesis of CF₄ would be difficult, they decided to select CCl₂F₂ as their first choice and prepared samples by the reaction of CCl₄ and SbF₃, a synthesis originally reported by Swarts.¹⁵ Midgley gave a dramatic introduction of the new refrigerant by filling his lungs and extinguishing a light candle at a meeting of American Chemical Society in 1930.^{3, 16}

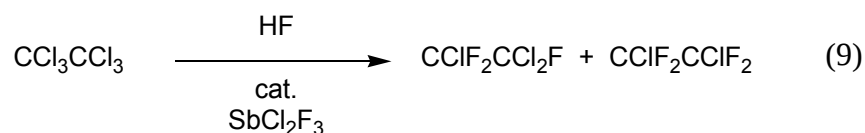
In the meantime, General Motors had approached E. I. du Pont de Nemours & Company (DuPont) with a proposal to manufacture this product.⁵ The original work was soon supplemented by development studies for the practical production on a commercial scale (eq. 7).^{3, 5, 17}



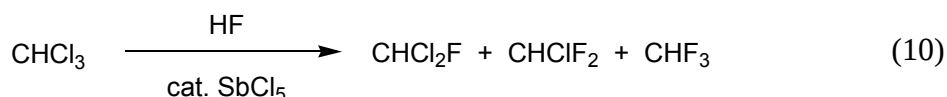
In 1930, a joint corporation, Kinetic Chemicals Inc., was formed by the two companies. By early 1931, the new product, trademarked Freon[®]-12, was being produced in commercial quantities. Application of the new compound was successful, and by the end of 1931, Kinetic Chemicals had expanded its facilities, and begun manufacture of anhydrous hydrofluoric acid, a basic raw material (eq. 8).⁵



Expansion during the next few years was continuous, and the product line was expanded as early as 1932 to include Freon[®]-11 (CCl_3F) as well as Freon[®]-113 ($\text{CClF}_2\text{CCl}_2\text{F}$) and Freon[®]-114 ($\text{CClF}_2\text{CClF}_2$), two of the polychlorofluoroethane derivatives (eq. 9).^{3, 5, 18, 19}

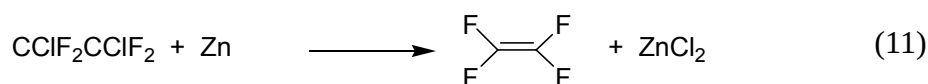


In 1935, this reaction was improved and employed for the synthesis of chlorofluoromethanes, the fluorinated derivatives of chloroform (eq. 10).⁵



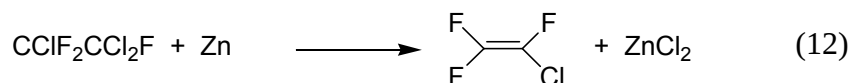
One of these, Freon[®]-22 (CHClF_2), soon gained wide acceptance. This compound later became very important as the precursor of tetrafluoroethylene (TFE). At that time, however, TFE was synthesized by dechlorination of Freon[®]-114 with zinc (eq.

11).^{3, 18}



In 1938, a DuPont chemist Plunkett, who was working with new chlorofluorocarbon gases relating to Freon[®] refrigerants, discovered polytetrafluoroethylene (PTFE).²⁰ When Plunkett was preparing for an experiment with tetrafluoroethylene (TFE) and attempted to pump the gaseous TFE into hydrochloric acid to chlorinate it, he observed that nothing was coming out. He weighed the cylinder and it was the same as before. Plunkett then cut the cylinder open and discovered a waxy substance formed inside.³ After studying the powder, he found the substance to be heat resistant and chemically inert, and to have very low surface friction so that most other substances would not adhere to it. Plunkett realized that the exact combination of pressure and cold temperature, along with the age of the gas in a cylinder, had allowed the TFE gas molecules to polymerize to give this product PTFE with such potentially useful characteristics. Chemists and engineers in the Central Research Department of DuPont investigated the substance further.

Although PTFE is the best known fluoropolymer nowadays, it was not the first of the fluoroplastics to be prepared. The first one was poly(chlorotrifluoroethylene), PCTFE, the polymer of chlorotrifluoroethylene (CTFE), which was obtained by the dechlorination of Freon[®]-113 (eq. 12)¹⁸ on an experimental scale as early as 1934.^{21, 22}



At that time, fluoropolymers were so expensive to produce that all believed they would never find a market. Their features were striking in fulfilling the requirements of the gaseous diffusion process of the Manhattan project at Columbia University in New York City during World War II and the fluoropolymers were first used as materials that could tolerate by fluorine or its derivative uranium hexafluoride (UF_6).²³

Even after the isolation of fluorine by Moissan in 1886, the difficulties in research using fluorine discouraged most chemists, and it was not until World War II when development was undertaken. The first large-scale production of fluorine was carried out for the atomic bomb Manhattan project which needed UF_6 as a gaseous carrier of uranium to separate the ^{235}U and ^{238}U isotopes of uranium. Uranium tetrafluoride (UF_4), which was prepared from uranium dioxide (UO_2) and hydrogen fluoride (HF), was converted to UF_6 by reaction with fluorine.^{5, 23, 24}

UF_6 was almost as reactive as elemental fluorine. In order to use it in a gas-diffusion plant, a wide range of materials which would not react with UF_6 remained to be developed. These would include relatively low molecular weight liquids for coolants; higher molecular weight materials for lubricants; and polymers that could be fabricated into gaskets, valve packings and tubing.^{5, 23} In 1937 and more extensively in 1939, preparative methods and properties of liquid fluorocarbons were disclosed by Simons and Block.²⁵ In 1940, the possibility of use of fluorocarbons as sealants and coolants and as materials that are directly exposed to UF_6 was suggested by Simons. A 2 mL sample of liquid fluorocarbon was sent from Simons to Urey at Columbia University and tested to show that it had the desired properties.²⁶ The problem was preparation of fluorocarbons on a large scale. Several methods were subsequently

The first major process was a catalytic fluorination process using fluorine. However, it was found extremely difficult to extend this process to large-scale production.²⁶

$$2 \text{CoF}_3 \xrightarrow{\text{RH}} \text{RF} + \text{HF} + 2 \text{CoF}_2$$


 F_2

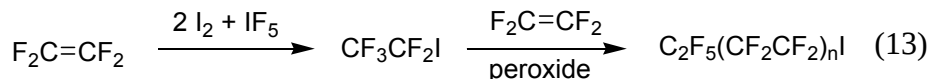
Treatment of a hydrocarbon with CoF_3 at 400 °C gives a product where all the hydrogen atoms are replaced by fluorine. Cobalt difluoride (CoF_2) is co-produced but is converted with elemental fluorine to cobalt trifluoride.

After World War II, Minnesota Mining and Manufacturing Company (3M)

acquired the technology of ECF and improved it to a pilot plant level as early as 1947.³² The first commercial plant for the production of fluorocarbons was put into operation in 1951.³²

Further study of ECF was carried out after the launch of fluorocarbons, and product line was extended to production of fluorocarbon derivatives possessing functional groups: perfluoroethers, perfluoroacyl fluorides, perfluoroalkanesulfonyl fluorides, and perfluorinated amines.^{32, 33} Among them, perfluoroacyl fluorides led to the development of 3M's Scotchgard[®], textile finishes.³² It works as an water and oil repellent agent.

Perfluoroalkyl iodides, which are synthesized by the telomerization method (eq. 13) reported by Haszeldine around 1950,^{34, 35} are utilized for the same purpose.

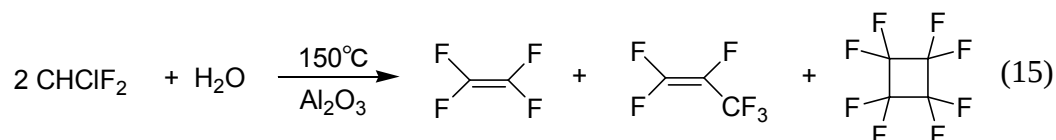
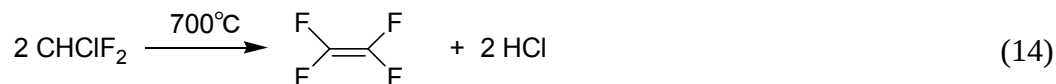


Further process development on CoF₃ fluorination after Manhattan project was carried out at ISC Chemicals Limited,³⁶ and led to production of low molecular weight fluorocarbon fluids (Flutec[®]) later.

The first commercial products of PTFE were sold under the 'Teflon' tradename by DuPont in 1948.³ Teflon[®] has become a familiar household name, recognized worldwide for the superior non-stick properties associated with its use as a coating on cookware and as a soil and stain repellent for fabrics and textile products.

The monomer TFE is manufactured by the method developed in Manhattan project,^{23,37} namely by the pyrolysis of Freon[®]-22 (eq. 14). Product TFE is accompanied by hexafluoropropylene (HFP) when pyrolysis was carried out with steam and alumina

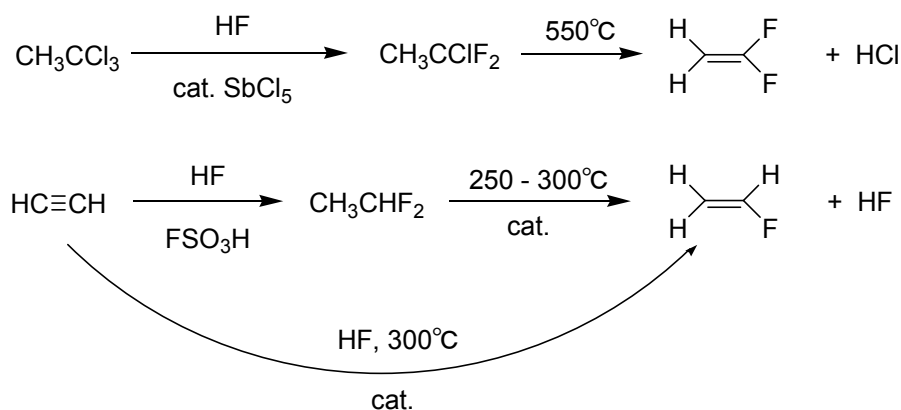
(eq. 15).^{38, 39} HFP is also obtained by pyrolysis of TFE at 850 °C.³⁸



After World War II, PCTFE, or Kel-F[®], was marketed by M. W. Kellogg. It became generally available in the early 1950's and was taken over by 3M in 1957.²²

In addition to perfluorinated homopolymer, TFE/HFP copolymer (fluorinated ethylene/propylene copolymer : FEP) was studied during the Manhattan project²² and commercialized in 1959 by DuPont.⁴⁰ PTFE is characterized by high melting point, high thermal stability, insolubility, and chemical inertness. However, it cannot be processed by conventional melt techniques. This difficulty was overcome by FEP.

Polymers with partially-fluorinated monomers, that is, PVdF (poly(vinylidene fluoride)) was developed in DuPont in 1948 and commercialized in 1950.⁴⁰ Poly(vinyl fluoride) (PVF) was also studied and launched in 1960's.²² The monomers are produced by a route shown in Scheme 2.



Scheme 2. Synthesis of partially-fluorinated ethylene monomers

The majority of commercial homopolymers nowadays are produced from only four monomers discussed above: tetrafluoroethylene (TFE), chlorotrifluoroethylene (CTFE), vinyl fluoride (VF), and vinylidene fluoride (VdF). Perfluorinated polymers are prepared by a free-radical polymerization reaction in water or in a fluorinated solvent.

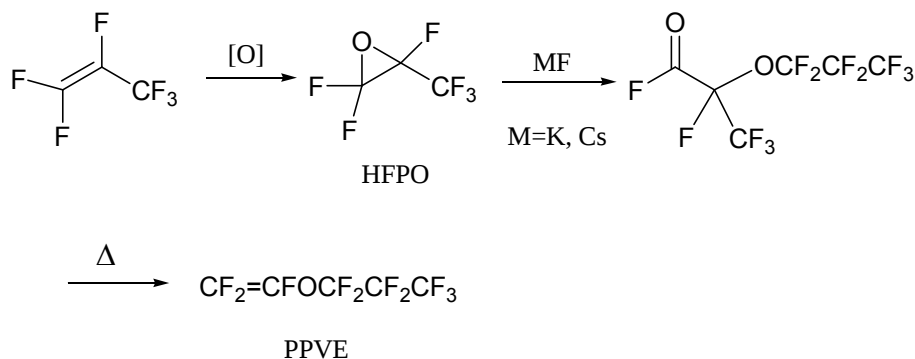
Copolymerization of these monomers with hydrocarbon monomers were studied world-wide and commercialized in 1970's.

Ethylene/TFE copolymer (ETFE): 1972 by DuPont and Asahi Glass independently.⁴⁰

Tetrafluoroethylene/propylene copolymer (TFE-P) Aflas[®]: 1975 by Asahi Glass.⁴⁰

On the other hand, it was difficult to copolymerize TFE with perfluorinated monomers other than HFP. However, perfluorinated vinyl ethers were found to react with TFE to give copolymers.⁴¹ Thus, perfluoroalkoxycopolymer (PFA) was synthesized and commercialized in 1972 by DuPont.⁴⁰ The monomer, perfluorinated propyl vinyl ether (PPVE) is synthesized from hexafluoropropylene oxide (HFPO)⁴² as

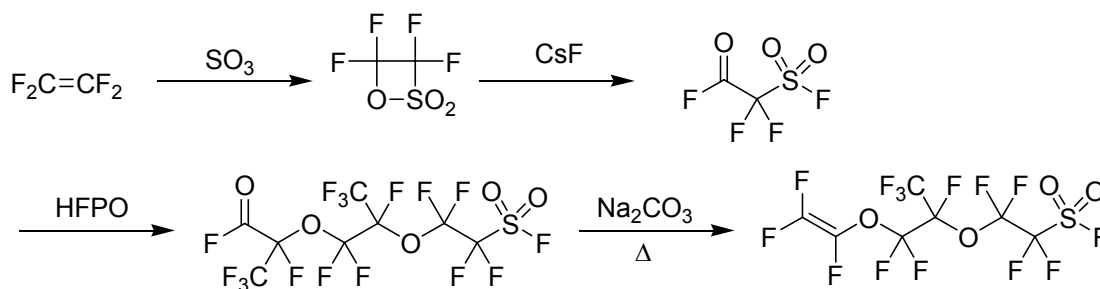
shown in Scheme 3.^{33, 43}



Scheme 3. Synthesis of PPVE

Before PFA was manufactured, HFPO was used as a monomer for anion polymerization in the preparation of perfluoropolyether (PFPE) fluids, which was developed by DuPont and commercialized as Krytox[®].^{44, 45, 46} Direct photo-oxidation of HFP or TFE was also developed for this purpose by Montedison (Fomblin[®]).^{45, 46, 47} The products PFPE fluids, which were commercialized in 1960's, have high chemical and thermal stability and excellent physical properties as lubricants which are highly reliable under very severe conditions.

In 1960's, NASA used fuel cell for space exploration project including Gemini and Apollo. Nafion[®], membranes made of a perfluorinated sulfonic acid ionomer, was first employed as a separator in the fuel cell. It is made of the polymer prepared by copolymerization of TFE and the functional perfluorovinyl ether, which is derived from HFPO as shown in Scheme 4.³⁹

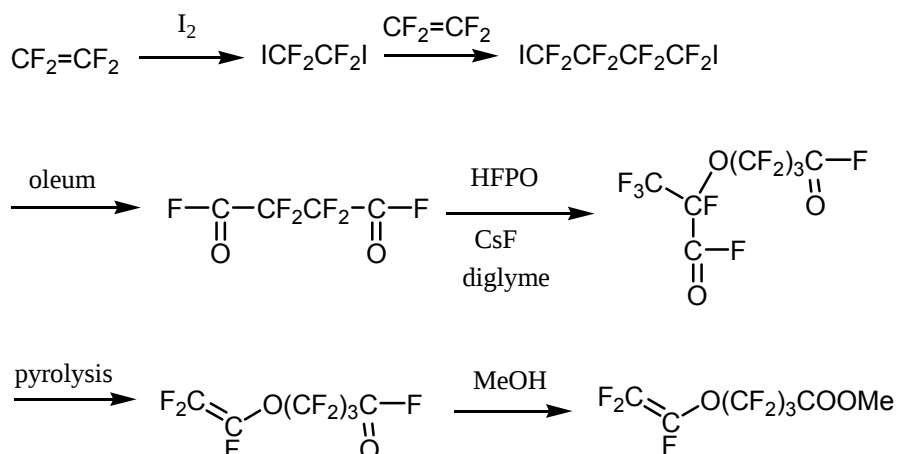


Scheme 4. Synthesis of a monomer for ion-exchange membrane

In the late 1960's, the chemical business came up against environmental issues. The sea around Kyushu, Japan, turned out to be the site of an outbreak of Minamata Disease, said to be one of the worst cases of mercury poisoning in history. This incident caused deep concern about chemical production processes. In 1968, Japanese government announced its consensus that "Minamata Disease was caused by industrial waste water containing organic mercury." Restrictions were later placed on the use of inorganic mercury as well for electrochemical production of caustic soda (NaOH). One of the candidates for new mercury-free approach was the "ion-exchange membrane electrolysis method". The key was a central membrane that only allowed specific ions to pass through. When sodium chloride (NaCl) is electrolyzed to produce sodium hydroxide (NaOH), a violent situation to the membrane with strong alkali occurs. Only a membrane made from fluoropolymer could withstand this reaction.

The ion-exchange membrane Nafion[®] for fuel cell was applied to this purpose.³⁹ Performance of Nafion[®] was not high enough, however, and a perfluorinated carboxylate polymer membrane was required to obtain an higher concentration of caustic soda. Flemion[®] (Asahi Glass) were developed as such an ion exchange membrane,⁴⁸ and commercially produced since 1978.^{39, 49}

The perfluorinated carboxylic acid membrane consists of a copolymer of TFE and perfluorinated vinyl ether, which has a carboxylic acid group in the side chain. The manufacturing process is shown in Scheme 5.⁵⁰



Scheme 5. Synthesis of perfluorinated carboxylic acid membrane monomer

The electrolysis process with ion-exchange membrane electrolysis method became common in commercial applications in 1984, and further improved to employ sulfonate-carboxylate laminated polymer membrane eventually achieving 100% proliferation in Japan and 51% worldwide (as of 2007). Moreover, the energy consumption of electrolysis processes was dramatically reduced by developing an advanced electrode.

Common plastics are made from a variety of organic materials, but the use of these materials should be minimized for reducing environmental burden. One way is to ensure products last longer. For example, for outdoor coating products that are exposed to outdoor environment, durable fluorinated materials are used. Lumiflon[®], the first solvent-soluble fluoropolymer for coatings, was developed by Asahi Glass,⁴⁰ which is

the material for anti-corrosive coating of various structures such as bridges. It is made of CTFE/non-fluorinated vinyl ether copolymer.^{39, 51} Although conventional coating materials without fluorine last a few more than 10 years at best, Lumiflon[®] lasts up to 30 or 40 years. The added fluorinated structure enabled to create surprisingly durable coating materials.

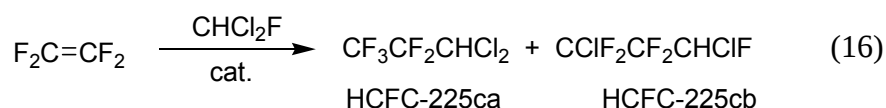
The outstanding resistance to violent chemicals in ion-exchange membranes and the excellent weatherability are derived from high stability of C-F bonds. Any oxidants or chemicals hardly attack the fluorine-substituted carbons.

However, this stability was backfired in chlorofluorocarbons (CFCs). Studies have shown that in the deep blue sky, CFCs and other substances released into the atmosphere are causing damage to the ozone layer.^{52, 53} In 1985, an ozone hole was discovered over the South Pole. CFCs are so stable substances that they moved far into the upper atmosphere, causing the destruction of the ozone layer. It was therefore necessary to find alternative CFCs that are decomposed before they reach the stratosphere.

CFCs had three main applications: Refrigerants for air conditioners and refrigerators, blowing agents for urethane foaming, and precision equipment cleaning agents. Refrigerant CFC-12 (the same compound as Freon[®]-12: CCl_2F_2) was replaced by HFC-134a ($\text{CF}_3\text{CH}_2\text{F}$), and blowing agent CFC-11 (CCl_3F) was substituted by HCFC-141b ($\text{CH}_3\text{CCl}_2\text{F}$) and then HFC-245fa ($\text{CF}_3\text{CH}_2\text{CHF}_2$).⁵⁴ However, there were no alternatives for cleaning agents CFC-113 ($\text{CCl}_2\text{FCClF}_2$).

The alternative material for CFC-113 was developed by Asahi Glass (HCFC-225ca and cb: ASAHIKLIN[®] AK-225). The innovative development was assisted by not only conventional experimental chemistry but computer chemistry

technologies and the most appropriate alternative to CFC-113 was selected from thousands of candidate materials, then actually synthesized by modified Prins reaction of TFE and CHCl_2F (HCFC-21) (eq. 16).^{55, 56}



Thus, organofluorine chemistry plays important roles in minimization of environmental impact and in production of various materials for industrial use such as thermoplastics, elastomers, membranes, textile finishes, coatings.

I-1-3. Development of fine chemicals

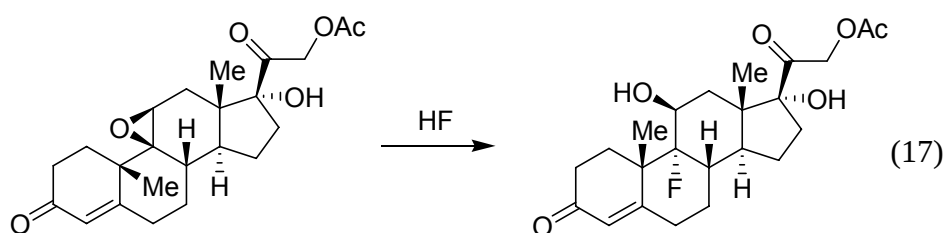
Fluorine is the most electronegative element in the periodic table. When bound to carbon, it forms the strongest bonds in organic chemistry. This makes introduction of fluorine attractive for the development of material science. Although highly polarized, the C-F bond gains stability from the resultant electrostatic attraction between C and F atoms.⁵⁷ Application to materials is mostly based on the properties derived from the fluorine-carbon bonds, which are hardly attacked by any oxidants or chemicals since C-F bonds tolerate various conditions. Therefore, normal metabolism in a living body is easily inhibited as well (block effect) by such strong bonds.

On the other hand, the van der Waals radius of fluorine is similar to that of hydrogen. Accordingly, organofluorine compounds are similar in steric size to

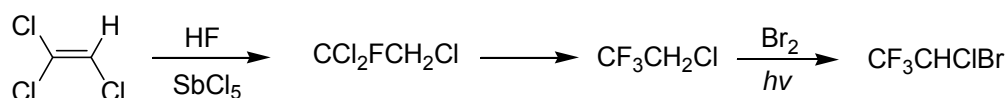
non-fluorinated ones but quite different in electronic nature. As a living body can not sterically distinguish fluorinated molecules from the corresponding non-fluorinated one, fluorinated molecules are incorporated into metabolic sequences in a manner similar to that of non-fluorinated one (mimic effect). However, since the C-F bond in the fluorinated molecule resists the metabolism common with the parent compound due to opposite polarization, the normal metabolism in a living body is inhibited to cause various biological effects. This makes fluorine substitution attractive for invention of pharmaceuticals and agrochemicals.^{58, 59}

The first example of biologically active organofluorine compounds was developed during World War II as a poison gas, methyl monofluoroacetate.⁶⁰ The toxicity of fluoroacetic acid against mammals is attributed to the “lethal synthesis” of (2R, 3R)-2-fluorocitric acid, which blocks the citric acid cycle, by citrate synthase.⁶¹ After World War II, sodium monofluoroacetate had been used as a rodenticide.⁶² It was originally synthesized from chloroacetamide through halogen exchange reaction with SbF₃.⁶³

In 1953, Fried and Sabo of Squibb found enhanced anti-inflammatory activity in 9 α -fluoro-hydrocortisone acetate.^{64, 65} It was prepared by ring-opening of epoxides with hydrogen fluoride (eq. 17), a reaction already established for the synthesis of β -fluorinated alcohols in 1949.⁶⁶ A wide variety of 9 α - and 6 α -fluoro-steroid were developed.^{58, 60}

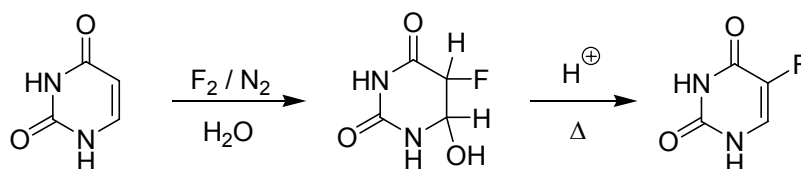


Inhalation anesthetic halothane was synthesized by addition of hydrogen fluoride to trichloroethylene and halogen exchange with a SbCl_5 catalyst by Suckling of ICI (Scheme 6), and introduced clinically in 1956.^{58, 67}



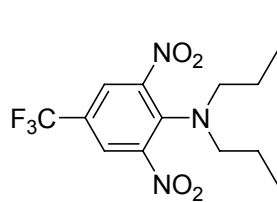
Scheme 6. Synthesis of halothane

In 1957, Heidelberger and his coworkers found that 5-fluorouracil (5-FU) exhibited significant tumor-inhibiting activity.^{58, 59, 68} The original synthesis was refined later by PCR as shown in Scheme 7.⁵⁸ It was probably the first example of selective fluorination with fluorine in industrial application.

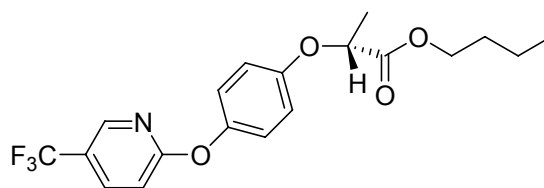


Scheme 7. Fluorination of uracil

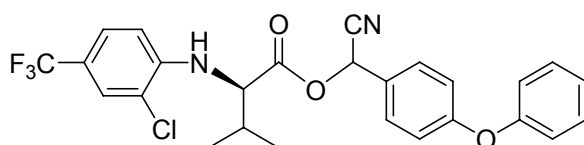
In 1960, trifluralin, an important herbicide, was introduced to market. Its manufacture includes the conversion of p-chlorobenzotrichloride to p-chlorobenzotrifluoride with $\text{HF}/\text{SbCl}_2\text{F}_3$,³³ a reaction originated in 1930's.¹³ Many herbicides, pesticides, and other agrochemicals were developed that use benzotrifluoride or trifluoromethylated heteroaromatic derivatives as a building block. Representative examples are shown in Scheme 8.^{59, 62, 69}



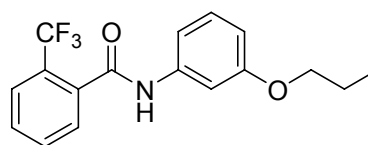
Trifluralin (herbicide)



Fluazifop-butyl (herbicide)



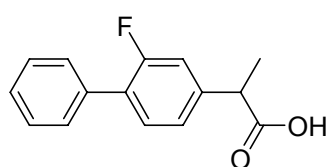
Fluvalinate (pesticide)



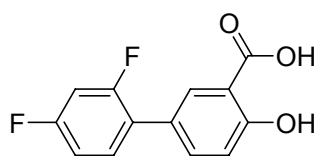
Flutolanil (bactericide)

Scheme 8. Ar- CF₃ containing agrochemicals

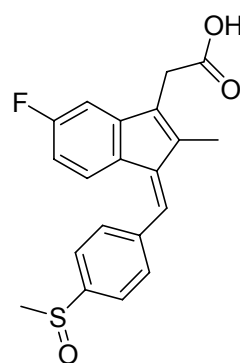
Non-steroidal anti-inflammatory drugs (NSAIDs) launched in 1960's. Among them, the most effective ones possess a fluorobenzene moiety (Scheme 9).^{58, 59}



Flurbiprofen



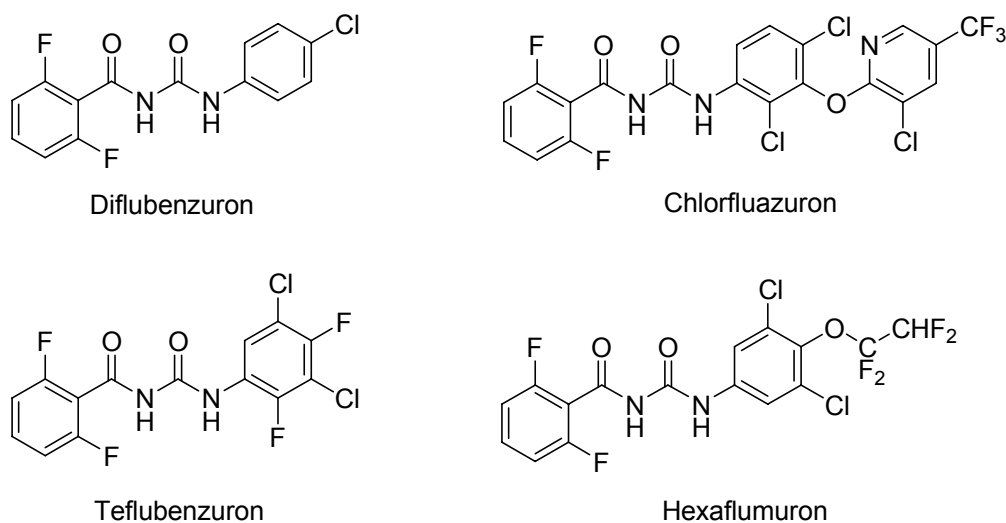
Diflunisal



Sulindac

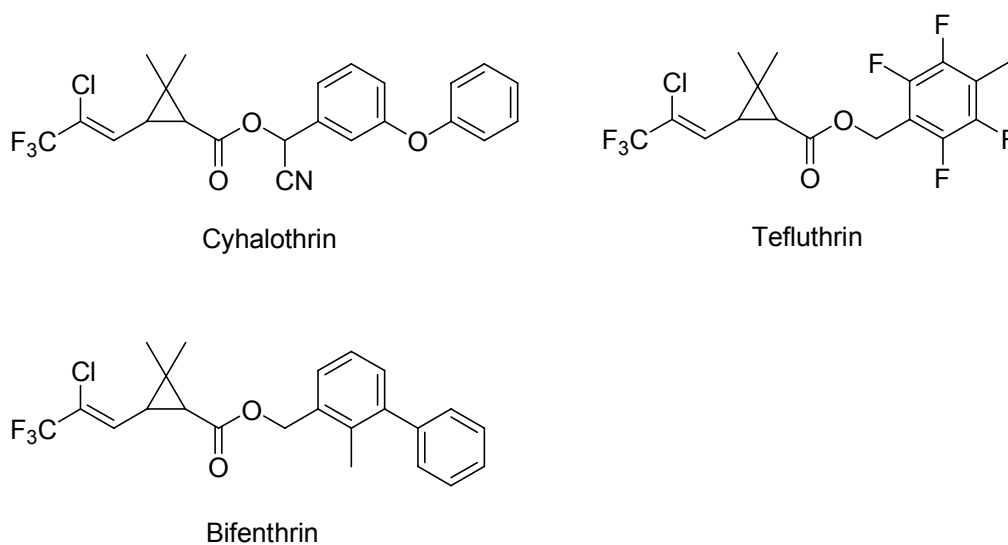
Scheme 9. NSAIDs

Fluoroaromatics were synthesized by Balz-Schiemann reaction or the HALEX (aromatic halogen exchange) reaction with potassium fluoride,⁷⁰ originally developed in 1930's.^{3, 11} The HALEX reaction, which exchanges chlorine atom(s) with fluorine atom(s) in aromatic substrates activated towards S_NAr reactions, and was used for the preparation of a variety of insecticides developed in 1970's and 80's (Scheme 10).⁶⁹

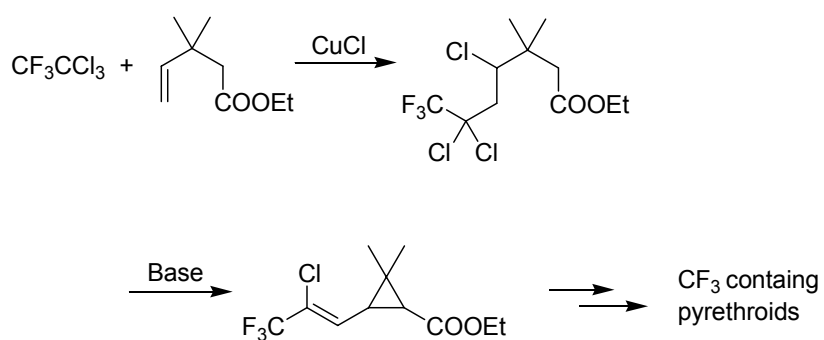


Scheme 10. Fluorinated benzoylurea insecticides

Fluorine-containing pyrethroids were also developed as another kind of insecticide in 1970's.^{59,62} Among them, cyclopropanecarboxylates with a trifluoromethyl-substituted olefinic group (Scheme 11) exhibit higher activity than the corresponding dichloro- or dimethyl derivatives. These are synthesized using CFC-113a (CF_3CCl_3) as the fluorinated building block (Scheme 12).^{59, 62, 69} Mixtures of stereo isomers result in general. However, stereoselective synthesis was later proposed.⁷¹

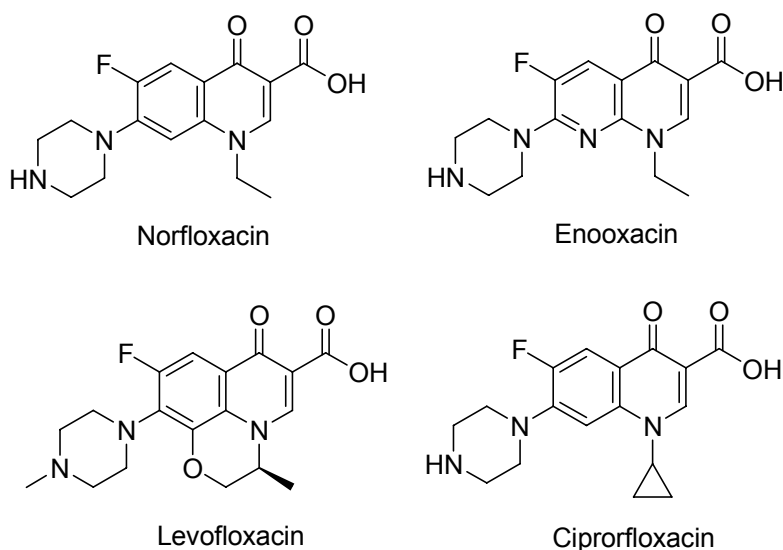


Scheme 11. Fluorine-containing pyrethroids



Scheme 12. Synthetic route to CF₃ containing pyrethroids

In 1980's, a series of fluorine-containing anti-bacterial agents were developed (Scheme 13).⁷² In order to introduce fluorine atom(s), the HALEX reaction is mainly used.



Scheme 13. Fluorine-containing anti-bacterial agents

The HALEX reaction is extensively performed on a commercial scale to produce aromatic intermediate building blocks of low fluorine content for pharmaceuticals, agrochemicals, and functional materials such as liquid crystals (LCs). Nowadays, more sophisticated syntheses are carried out for manufacturing LCs particularly for thin film transistor-liquid crystal display (TFT-LCD),⁷³ transparent fluorinated resin such as Cytop[®]⁷⁴ for plastic optical fiber (POF) and for semi-conductor manufacturing process,⁷⁵ and various fluorine-containing pharmaceuticals.⁷²

Organofluorine compounds are essential especially in recent IT, electronics, and medical applications in our society.⁷⁶

I-2. Methodology for Synthesis of Fluorochemicals

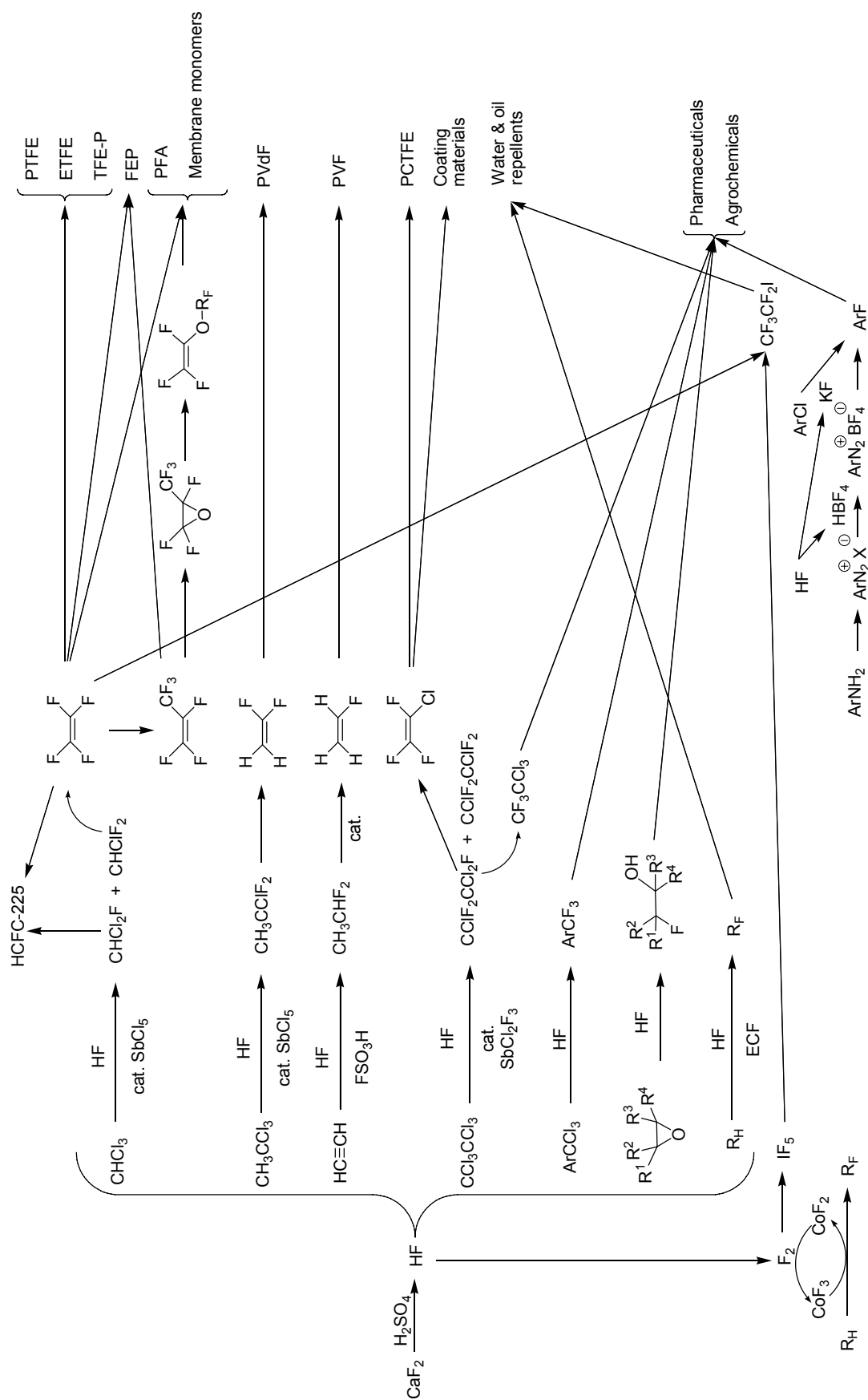
I-2-1. Methods used in organofluorine industry

As discussed before, organofluorine compounds play important roles in both materials and pharmaceuticals.⁷⁷ From the synthetic viewpoints, there are two approaches. The one is an introduction of fluorine to target molecules (fluorination method). The other utilizes fluorinated compounds of low molecular weights (building block method).

Fluorination methods are particularly important in industry, and summarized in Scheme 14.

For fluorination method, most of fluoropolymers in manufacturing process depend on halogen-exchange reaction, especially fluorine-substitution of chlorinated methanes and ethanes, a basic process developed by Swarts,¹⁵ for the introduction of fluorine atoms into organic molecules, as summarized in Scheme 14. An exception is PVF, which is produced by addition of hydrogen fluoride to carbon-carbon triple bonds followed by elimination. For products of low molecular weight, the perfluorination with CoF_3 , nucleophilic ring-opening reaction by hydrogen fluoride, the Balz-Schiemann reaction, and HALEX reaction are appropriately applied.

For the building-block or synthon approach, proper selection of polyfunctional fluorine-containing synthons is a key part in synthetic schemes.⁷⁸ However, reactivity of substrates and reagents drastically changes when fluorine atoms are introduced into the reacting sites.⁷⁹ This tendency becomes more obvious when number of fluorine



atoms increases.

A striking example is the reactivity of alkyl halides: although S_N1 and S_N2 mechanisms work when few fluorine atoms are incorporated in relatively remote positions of aliphatic chains, perfluoroalkyl halides are usually resistant to these classical processes. This makes it difficult to connect perfluorinated building blocks through carbon-carbon bond formation with perfluorinated substrates.

There are only a few C-C bond forming reactions which are applied to manufacturing perfluorinated compounds.

One is telomerization of perfluorinated olefins (see section I-1-2, eq. 13).^{34, 35} The resulting raw material is used for water and oil repellent agents. Hereby, only telomers of even carbon numbers are obtained; telomers with specific value of n are hardly accessible in a selective manner.

For the construction of branched structure, carbon-oxygen bond formation is important rather than carbon-carbon bond formation. For example, perfluoro alkoxides are allowed to add to perfluoro epoxides. This reaction is applied to synthesis of perfluorinated vinyl ethers as shown in Scheme 3 (Section I-1-2). The alkoxides, usually prepared from perfluoroacyl fluorides and a fluoride anion, react with hexafluoropropylene oxide (HFPO) to give C-O bond formation products. The reaction may look curious to conventional organic chemists, because perfluorinated alkoxides are not prepared from the corresponding alcohols and a base but from acyl fluorides and a fluoride anion. This means the alkoxides are equivalent to acyl fluorides. Moreover, the nucleophilic attack occurs at sterically hindered side due to a CF_3 substituent. In any events, it is used in an industrial scale. However, there is a problem that synthesis of starting acyl fluorides of complicated structures is difficult at moment.

Therefore, an entirely new synthetic methodology for multifunctional fluorinated chemicals has been required. Direct fluorination of substrates which are accessible by conventional organic synthesis has been considered promising, because many carbon-carbon bond forming transformations are available for common substrate.

Reactions using CoF_3 or ECF are formally direct fluorination. However, they have serious drawbacks of low productivity and poor yields.⁸⁰ Thus, improvement of direct fluorination with elemental fluorine has been the target of one present synthetic research.

I-2-2. Direct fluorination with elemental fluorine

Elemental fluorine was first prepared in small quantities by Henri Moissan in 1886 by electrolysis of anhydrous hydrogen fluoride (see section I-1-1). He was lucky to achieve the first synthesis because anhydrous hydrogen fluoride used in the experiment contained a small amount of potassium fluoride. This method is still used today for generation of fluorine by electrolysis of $\text{KF} \cdot 2\text{HF}$ not only in laboratory but in industry, particularly for production of IF_5 , a raw material of telogen for water and oil repellent agents, and for production of UF_6 from UF_4 in nuclear electricity generation (see Section I-1-2).

Moissan himself was the first to carry out the reactions between neat fluorine and several organic compounds. However, only decomposed products resulted and, occasionally, explosions occurred.⁸¹

In the early 20th century, it was very difficult to control the reactions with fluorine because of the violence in nature. For example, in 1929, Bancroft and Jones reported explosions during attempted fluorination of benzene and toluene with molecular fluorine.^{82,83} However, dilution of fluorine by inert gases such as nitrogen came to allow the reactions with fluorine to be carried out safely and efficiently.

In 1931, Bancroft and Wherty tried the fluorination of benzene again using fluorine diluted with nitrogen. The explosion was avoided, though they obtained only tarry products.^{81, 84} Boeckmuller attempted the fluorination of several aromatic compounds with fluorine, but also obtained only tars with high fluorine content.^{81,85}

During World War II, the first sample of fluorocarbons, found to be inert towards UF_6 , had been made by direct reaction between carbon and elemental fluorine catalyzed by mercury.²³ In 1941, Bigelow and Fukuhara reported that direct fluorination of benzene with elemental fluorine in the vapor phase over copper gauze catalyst gave perfluorocyclohexane with only moderate degradation.^{23, 86} This method looked promising for Manhattan project, and was investigated in detail. Although yields were improved up to 58% of perfluorocyclohexane from benzene, CoF_3 method was found more suitable to preparation of various fluorocarbons.²³

After World War II, in order to modify the high reactivity of fluorine, the vapor-phase fluorination (“Jet fluorination”) apparatus for direct fluorination was developed by Bigelow and coworkers.⁸⁷ Jet fluorination seems to be a method of choice for preparation of low-molecular-weight fluorocarbons. It was used on a semi-technical scale for production of perfluoropropane, which is used as a dry (plasma) etchant in microelectronics industry.³³

In 1970, the low temperature gradient fluorination (“LaMar fluorination”)

technique was developed by Lagow and Margrave.^{88,89} In the LaMar fluorination process, substrates are condensed at low temperature into a tube packed with copper turnings through which fluorine, initially highly diluted in either helium or nitrogen, is passed. The concentration of fluorine and the reaction temperature are slowly increased over a period of several days to permit perfluorination. This batch process requires relatively long reaction times to obtain perfluorinated material.

Some years later, Adcock invented a flow version, an aerosol fluorination process.⁹⁰ The principle is that substrates are absorbed onto the surface of fine sodium fluoride particles in a fluorination apparatus, into which fluorine is introduced and the apparatus is warmed and UV irradiated to complete perfluorination. This process has an advantage that it is a continuous flow method and the control of reaction parameters are easier.

Thermodynamics of fluorination reactions has been studied since late 1950's.^{91,92} Reactions between hydrocarbons and fluorine are highly exothermic, because very strong C-F and H-F bonds are formed whilst the dissociation energy of fluorine is very low. Therefore, the propensity of fluorine to react by radical chain reactions is extremely high.

Consequently, exhaustive fluorination is generally regarded as a free radical process (Table 1).⁸¹

Table 1. Thermodynamic data for direct fluorination

			ΔH_{25} (kJ/mol)
Overall reaction : $\text{R-H} + \text{F}_2 \rightarrow \text{RF} + \text{HF}$			- 431
Initiation :	$\text{F}_2 \rightarrow 2 \text{F}\cdot$		+ 158
	$\text{R-H} + \text{F}_2 \rightarrow \text{R}\cdot + \text{HF} + \text{F}\cdot$		+ 16
Propagation :	$\text{R}\cdot + \text{F}_2 \rightarrow \text{RF} + \text{F}\cdot$		- 289
	$\text{R-H} + \text{F}\cdot \rightarrow \text{R}\cdot + \text{HF}$		- 141
Termination :	$\text{R}\cdot + \text{F}\cdot \rightarrow \text{RF}$		- 446
	$\text{R}\cdot + \text{R}\cdot \rightarrow \text{R-R}$		- 351

The overall reaction in the replacement of hydrogen is highly exothermic (431 kJ/mol). On the other hand, the central carbon-carbon bond strength in butane, for example, is 364 kJ/mol. Therefore, the overall reaction is exothermic enough to break carbon-carbon bonds. This may be the main reason for explosions. However, what is the most important here is that no individual step in this reaction sequence is exothermic enough to break carbon-carbon bonds except this termination step of 446 kJ/mol. Therefore, in the early stages of the fluorination, reaction of F_2 rather than F radical is required to be involved. This means large excess of F_2 relative to H to be replaced in a molecule should be maintained. Thus, the propagation step is reasonably mild enough if heat is removed rapidly and properly. As the fluorination reaction proceeds, further fluorination of partly fluorinated substrates becomes increasingly difficult, because the carbon skeleton becomes increasingly protected by fluorine atoms, namely, the non-bonding electron pairs of fluorines inhibit further attack by incoming fluorine atoms. On the other hand, the introduction of F makes C-C bonding stronger. For example, C-C bond energy of perfluorobutane is as strong as 469 kJ/mol. This is more than 446 kJ/mol suggested for the termination step. Therefore for completion of

fluorination, powerful fluorination with F radicals is required. This means the presence of a radical generator is necessary through out fluorination.

Another basic problem of direct fluorination involves kinetics. The rate of the reaction must be slowed down so that the energy liberated from the reaction may be removed. The most crucial aspect in control of direct fluorination is a dilution technique.⁸⁸

Thus, use of a solvent inert to fluorine is preferable for reaction control. However, there is a contradictory that such an inert compound as an appropriate solvent becomes the target product itself. This problem was solved by other perfluorination methods such as ECF and indirect fluorination using CoF_3 .

In early 1980's, Scherer, Yamanouchi, and Ono disclosed a practical liquid-phase direct perfluorination method through study on artificial blood substitutes.^{83, 93} The method is quite characteristic in i) inverse addition of a substrate into an inert liquid saturated F_2 gas, ii) undiluted 100% fluorine gas is used, and iii) UV irradiation. In fact, in the liquid-phase direct fluorination process, the reactant is injected at a very slow constant rate into an inert fluorocarbon solvent saturated by fluorine. It is pointed out to be very important that a large excess of F_2 relative to hydrogen atoms to be replaced in a substrate should be maintained. This method is, however, only suitable for the perfluorination of substrates, such as partially fluorinated ethers and amines, both soluble in a perfluorocarbon solvent and can withstand such vigorous reaction conditions.

Almost the same time, Exfluor Corporation claimed that various ethers and esters are perfluorinated without UV irradiation (Exfluor-Lagow method).^{89, 94, 95} Their methods are based on the essential idea of inverse addition of substrates into an inert

liquid dissolving fluorine gas. The Exfluor-Lagow method involves slow addition of both a hydrocarbon substrate and fluorine in excess into a vigorously stirred chlorofluorocarbon (CFC) or a perfluorinated inert solvent. If required, the reaction is accelerated by adding a small quantity of a highly reactive hydrocarbon such as benzene, which reacts spontaneously with fluorine to produce a very high concentration of fluorine radicals that ensure perfluorination of substrates.

The Exfluor-Lagow elemental fluorine process can give products of the liquid-phase fluorination process in high yields. However, reaction solvents are limited to now-regulated CFCs, particularly for direct fluorination of substrates which contain functional group(s) in the structure because of solubility problem.

Partially fluorinated substrates are more stable towards the fluorination process, since solubility increases, and presence of a polyfluoroalkyl group significantly lowers the oxidation potential of the substrates. Consequently, perfluorinated compounds are generally produced in higher yields than the corresponding non-fluorinated compounds. This method was applied to preparation of perfluoroethers.⁹⁶

Considering these results, it is suggested that direct fluorination method had almost reached an adequate standard level of monomer synthesis in industry.

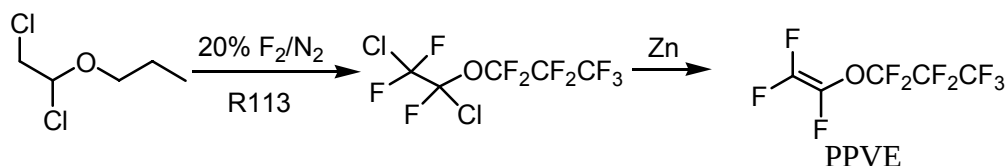
Direct fluorination with fluorine for perfluorination is quite different in nature from that for partial fluorination (selective direct fluorination: SDF),⁸¹ even though the reagent is the same. The former proceeds through a radical mechanism as discussed above. On the other hand, the latter is carried out in polar solvents so that the reaction proceeds principally through a polar mechanism.

In this Thesis, the Author focuses on direct fluorination as a tool for perfluorination.

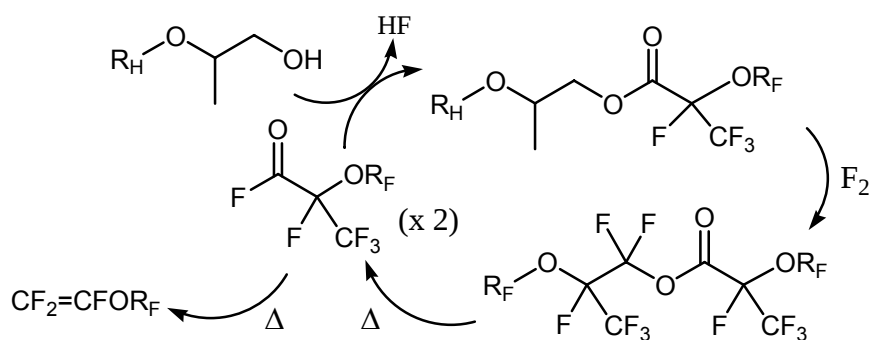
I-3. Summary of This Thesis

The Author created a new synthetic procedure for the preparation of various perfluoroalkanoyl fluorides and perfluoro ketones, which are precursors to perfluorinated monomers for industrial use, starting with non-fluorinated alcohols. In this Thesis, he describes synthetic studies on such perfluorinated compounds through a synthetic procedure, which utilizes direct fluorination with elemental fluorine.

In Chapter II, the Author describes i) an attempt at the direct application of Exfluor-Lagow method to the synthesis of the monomer PPVE for perfluoroalkoxy copolymer (PFA) (Scheme 15), and ii) invention of entirely new synthetic methodology. He describes first direct fluorination of *vic*-dichlorinated ether with fluorine gas diluted with nitrogen gas, basically applying the Exfluor-Lagow method, and has observed that it sometimes leads to an explosion. Then, the invention of an entirely new methodology, *pur*fluorination of esterified compounds followed by thermolysis, abbreviated as PERFECT, is demonstrated, where available perfluoro(alkoxyalkanoyl) fluorides such as perfluoro(2-propoxypropionyl) fluoride can be multiplied by use of the hydrocarbon counterpart alcohols and fluorine gas as raw materials (Scheme 16).

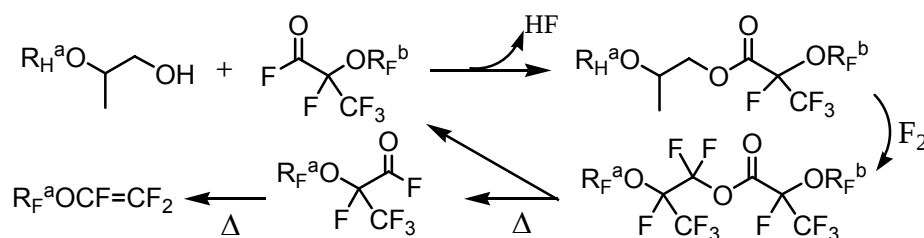


Scheme 15. Synthesis of PPVE from a non-fluorinated dichloroethyl ether



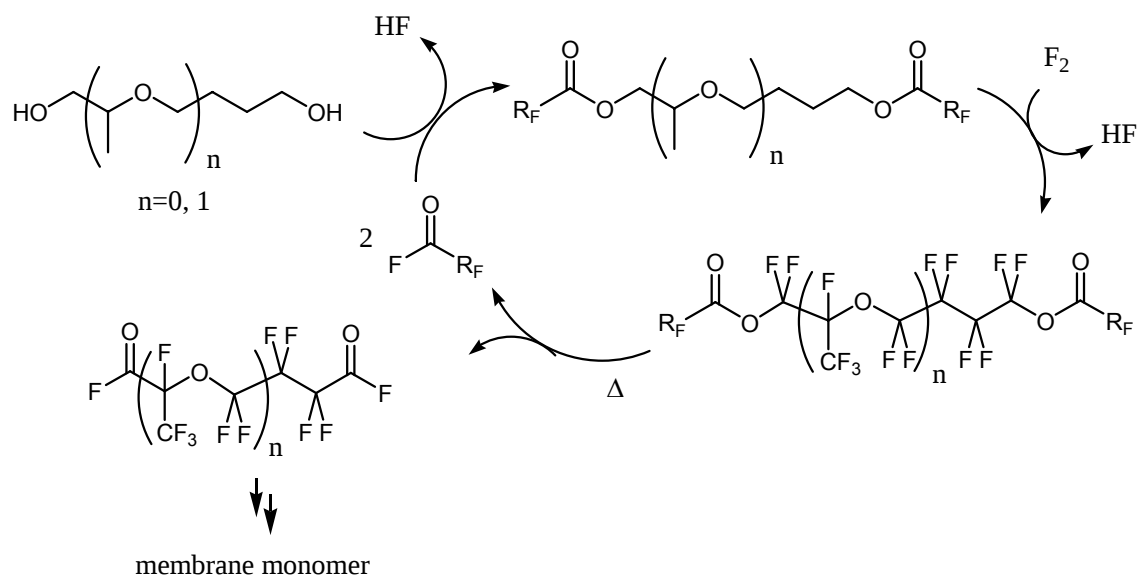
Scheme 16. The PERFECT method for synthesis of perfluorinated vinyl ethers

Subsequently, the Author extended the possibility of the PERFECT method to synthesis of more general perfluoroacyl fluorides, and describes in Chapter III the scope and limitation of the synthesis of perfluoroacyl fluorides by the PERFECT method. In the case that the desired perfluoro(alkoxyalkanoyl) fluoride is not readily available, it can be obtained from its hydrocarbon counterpart alcohol and an available perfluoroacyl fluoride (Scheme 17).



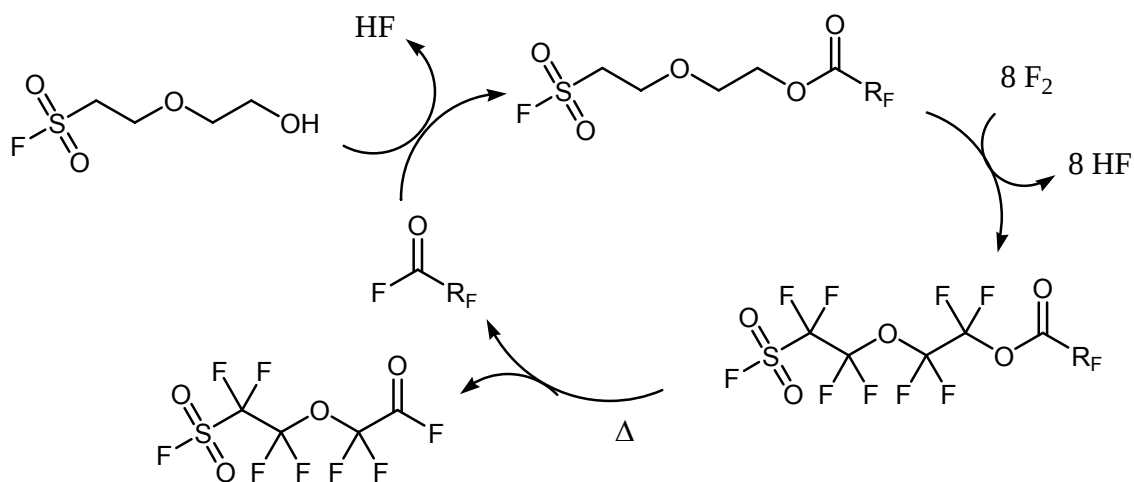
Scheme 17. The PERFECT method for synthesis of various perfluorinated acyl fluorides

In Chapter IV, the Author discusses application of the PERFECT method to the synthesis of perfluorinated diacyl fluorides, which are used for the carboxylic acid type ion exchange membrane (Scheme 18). Non-fluorinated diols are employed as the substrates.



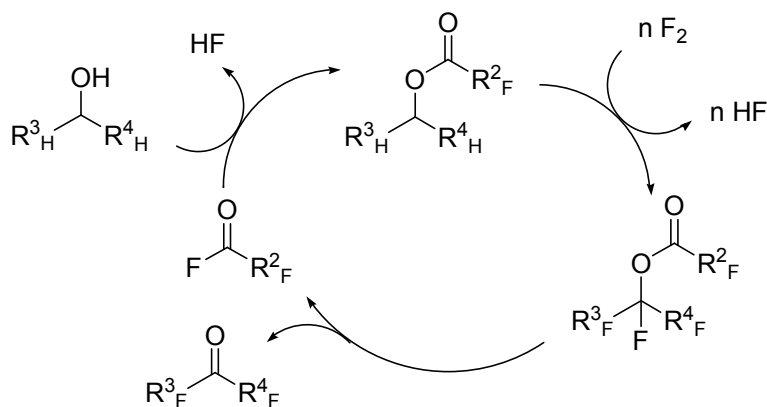
Scheme 18. The PERFECT method for synthesis of carboxylic acid membrane monomers

In Chapter V, the Author focuses on synthesis of perfluoroalkanesulfonic acid type membrane monomers. Also described is synthesis of the substrate for direct fluorination, which possesses a sulfonyl group in an end (Scheme 19).



Scheme 19. The PERFECT method for synthesis of perfluorosulfonic acid membrane monomers

Chapter VI describes an application of the PERFECT method to non-fluorinated secondary alcohols as a starting material (Scheme 20). The products hereby are perfluorinated ketones. Synthesis of a precursor polyfluoro ketone for fluoropolymer resists for 157nm microlithography is also discussed.



Scheme 20. The PERFECT method for synthesis of perfluoro ketones

In summary, the Author succeeded in synthesis of perfluorinated compounds which are versatile as industrial materials by an entirely new method PERFECT, applying modified liquid-phase direct fluorination with elemental fluorine.

Thus, the potential of the PERFECT methodology is demonstrated to be high enough to create novel perfluorinated building blocks.

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Chapter II

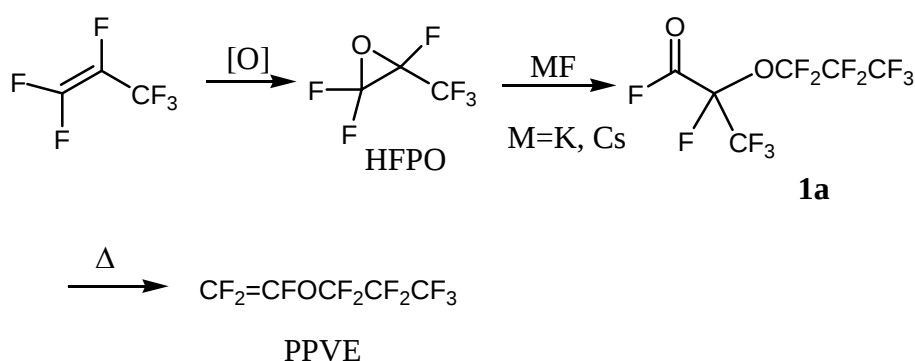
A New Route to Perfluoro(Propyl Vinyl Ether) Monomer: Synthesis of Perfluoro(2-propoxypropionyl) Fluoride from Non-fluorinated Compounds

Abstract

Perfluoro(2-propoxypropionyl) fluoride, an acid fluoride that is the precursor of perfluorinated propyl vinyl ether (PPVE) monomer of an industrially important perfluoroalkoxy copolymer (PFA), was synthesized by direct fluorination of a non-fluorinated counterpart for the first time. A partially-fluorinated ester was synthesized from the above acid fluoride and the non-fluorinated alcohol that has the same carbon skeleton corresponding to the acid fluoride and was perfluorinated through liquid-phase direct fluorination with elemental fluorine. Degradation of the resulting perfluorinated ester gave two molecules of the acid fluoride. Achieving self-multiplication of a perfluorinated acid fluoride from a non-fluorinated alcohol.

II-1. Introduction

Perfluoroalkoxy copolymer [PFA: copolymer of tetrafluoroethylene (TFE) and perfluoro(propyl vinyl ether) (PPVE)] is one of the most important perfluorinated polymers that is used as a both thermally and chemically resistant material in industrial use, and especially in recent medical, IT and electronics applications.^{1,2} However, it has been prepared from very costly hexafluoropropylene oxide (HFPO) (Scheme 1).³ Thus, its expensiveness has been a disadvantage so far.



Scheme 1. Conventional synthesis of PPVE

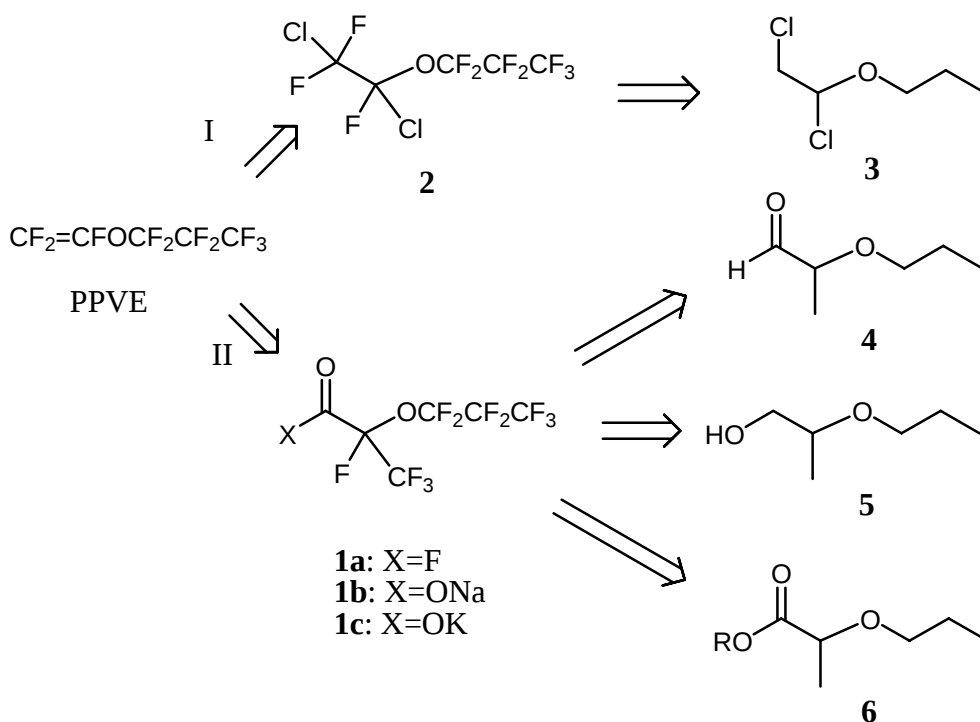
Recently, perfluorinated hypofluorite chemistry⁴ has been improved to some extent. Also, direct fluorination is applied to partially fluorinated 1,2-dichloroethyl ethers to synthesis of perfluoro(alkyl vinyl ethers).⁵ However, these syntheses still require expensive (per)fluorinated starting materials.

Presented herein is an essentially different approach. The Author invented a new synthetic route to PPVE, starting from a non-fluorinated counterpart and utilizing liquid-phase direct fluorination⁶ as a key step (Scheme 4). This approach is expected to solve the long-standing problem discussed above. The desired perfluorinated acyl

fluoride **1a**, a precursor of PPVE, can be multiplied by supplying non-fluorinated alcohol **5** with a carbon skeleton that corresponds to the desired product **1a**. The essential starting materials of this process are only the non-fluorinated alcohol **5** and fluorine gas, although it still requires equal amount of the perfluoroacyl fluoride **1a** for the first cycle.

II-2. Results and Discussion

In 1989, Lagow *et al.* reported liquid-phase direct fluorination of non-fluorinated compounds.⁶ Although they applied this process only to simple molecules such as octyl octanoate, the Author considered that it could also be applicable to the synthesis of industrially important compounds such as perfluorinated alkyl vinyl ethers, providing that he could make the corresponding hydrocarbon counterparts. From such viewpoint, he reexamined synthesis of PPVE retrosynthetically (Scheme 2).



Scheme 2. Retrosynthetic analysis of PPVE

PPVE would be made either by dechlorination of perfluorinated dichloroethyl ether **2** (Route I)⁴ or by thermal elimination of perfluorocarboxylic acid derivatives **1a-c** (Route II).³ Compound **2** may be obtained by direct fluorination of the corresponding dichloroethyl ether **3**. Perfluoroacyl fluoride **1a** may be derived from aldehyde **4**, whose all hydrogen atoms are to be substituted by fluorine atoms. Alcohol **5** would also be a precursor of acid fluoride **1a** because its perfluorinated derivative would lead to the desired compound **1a**. Alkali salts of perfluorocarboxylic acid **1b** and **1c** would be derived from acid fluoride **1a**.

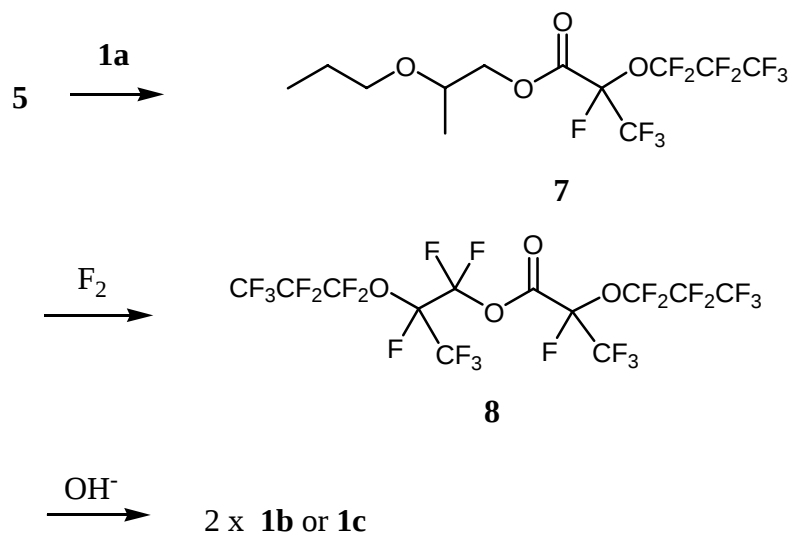
Among these candidates, compound **3** seemed the best at first sight, because it could be obtained from inexpensive propyl vinyl ether in only one step. Therefore, the Author chose Route I for his first trial.

Chlorination of propyl vinyl ether was conducted according to a literature⁷ to

give dichloroethyl ether **3** in 75 % yield. The chlorination turned out relatively problematic because of formation of a trichloro derivative. Besides, it was difficult to purify dichloroethyl ether **3** by distillation or by chromatography due to its instability. Accordingly, without purification of the substrate, direct fluorination was carried out, basically applying Lagow's method. The fluorination was conducted with 20% F₂/N₂ and proceeded as expected, but the yield was only 40% at best: migration of chlorine atoms made the reaction complex. Furthermore, considerable amounts of products arising from C-C and C-O bond cleavage formed during the fluorination, probably because of some reaction which took place in the vapor phase. This suggested that substrate **3** was too volatile to be fluorinated in a liquid phase.

The Author then returned back to the retrosynthesis shown in Scheme 2 and decided to examine Route II. There were three possible precursors as discussed above. Among them, compound **5** was chosen because of easy preparation. However, direct fluorination of **5** seemed dangerous in view of possible formation of an unstable hypofluorite at first.⁸ In addition, protection of the OH group was essential in this route.

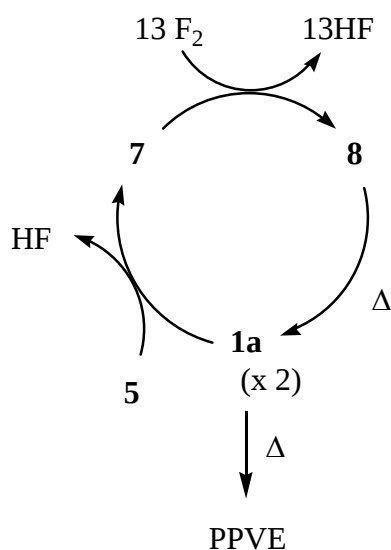
The protecting group in this case should be a perfluorinated group of large molecular weight in order to moderate the reactivity towards fluorination and to suppress volatility. Moreover, it should be removable after fluorination. Considering these requirements, -COCF(CF₃)OCF₂CF₂CF₃ seemed to be the most attractive, because it could be removed by alkaline hydrolysis after perfluorination to give the same component **1b** or **1c** as the one derived from the hydrocarbon moiety (Scheme 3). Besides, this protecting agent is available as acid fluoride **1a**, which is an intermediate for PPVE in the conventional manufacturing process.



Scheme 3. Use of **1a** as a protecting agent

At the time when the study of this method started, Lagow *et al.* reported that thermal decomposition of a perfluoroester gave double amount of perfluoroacyl fluorides.⁹ For example, thermal decomposition of perfluoro(octyl octanoate) gave perfluorooctanoyl fluoride in a double amount. Thus, it indicated that the acyl fluoride **1a** could be recyclable, by adopting it in the process.

Scheme 4 illustrates a mechanistic scheme. Non-fluorinated alcohol **5** is esterified with perfluoroacyl fluoride **1a**, before direct fluorination. Then, liquid-phase direct fluorination of the resulting partially-fluorinated ester **7** should give perfluorinated ester **8**. Thermal fragmentation of **8** gives 2 molar amounts of acyl fluoride **1a**. The obtained acyl fluoride can be used either for another production or for further thermal fragmentation to give PPVE. The Author named this process “PERFECT”, an abbreviation of PERFluorination of Esterified Compounds followed by Thermolysis.



Scheme 4. The PERFECT process for synthesis of **1a**

The actual synthesis was carried out as follows. The starting alcohol, 2-propoxy-1-propanol (**5**), was synthesized from inexpensive propylene oxide and 1-propanol in one step.¹⁰ Although the reaction gave a mixture of regio-isomers in ca. 1:1 ratio, it was possible to separate them by distillation, and the undesired isomer, 1-propoxy-2-propanol, could be used as a commercial detergent.

Esterification, direct fluorination, and thermal degradation were achieved to obtain **1a** in 99%, 93% and 94% yield, respectively. Further thermal degradation to PPVE from **1a** is a well known process.³

Esterification was carried out simply by mixing non-fluorinated alcohol **5** with perfluoroacyl fluoride **1a** and by removing the HF formed during the reaction, out of the reaction system, with a stream of nitrogen.

The liquid-phase direct fluorination was repeated with a higher-molecular weight partially-fluorinated ester **7** as the substrate without any dangerous vapor-phase reactions. Solubility of the substrate in the solvent used in the liquid-phase fluorination,

i.e. 1,1,2-trichlorotrifluoroethane or even compound **1a** itself, could be improved remarkably. This is in sharp contrast to that of a non-fluorinated compound.¹¹ As described in the literature,^{6, 11b} for successful perfluorination, appropriate dilution of fluorine, and a substrate in an inert solvent, and use of excess amount of fluorine to replace all of the hydrogen atoms in the substrate were essential. Continuous feed of both diluted fluorine gas and a substrate in a perfluorinated solvent at a controlled rate with a molar ratio $F_2/H = 2.8$ was carried out. Injection of a diluted solution of benzene after substrate addition was effective for complete perfluorination, because benzene reacts with elemental fluorine to generate many fresh fluorine radicals.⁶ Total reaction time was quite long in laboratory scale experiments, because it depends on the flow rate of fluorine gas. Manufacturing efficiency would be better on a larger scale, because a large amount of fluorine gas can be generated in a factory.

The following thermal fragmentation step was carried out either in a vapor-phase without catalyst, or in a liquid-phase with a catalytic amount of alkali fluoride, as described in the literature.^{9, 12} For example, liquid-phase reaction with 30 mol% of sodium fluoride gave the desired product **1a** in an excellent yield.

By repeating the synthetic cycle shown in Scheme 4, perfluoro-(2-propoxypropionyl) fluoride (**1a**) increases in geometric progression. For the case of perfluoro(propyl vinyl ether), overall yield of product **1a** was 170% for one cycle based on the amount of starting perfluoroacyl fluoride **1a** used. Thus, after repeating of the cycle n times, the amount of **1a** should increase 1.7^n times in theory. Accordingly, the cycle shown in Scheme 4 is a self-multiplication process.

Application to other perfluorinated compounds using the above synthetic method is expected to give many other perfluoro acid fluorides of the desired structure.

II-3. Conclusions

Liquid-phase direct fluorination with elemental fluorine was investigated for synthesis of the industrially important perfluoromonomer PPVE. Whereas direct fluorination of dichloroethyl ether **3** was shown to proceed in poor yields possibly because of high volatility and low solubility, direct fluorination of partially-fluorinated ester **7** derived from non-fluorinated alcohol **5** and perfluorinated acid fluoride **1a** itself was achieved in high yields. Thermal fragmentation of the resulting perfluoroester **8** gave desired acid fluoride **1a** in a double amounts (Scheme 4).

The substrate used in the liquid-phase direct fluorination is a partially-fluorinated ester, which is provided by conventional organic synthesis directly from a hydrocarbon precursor. Thus, characteristic features can be summarized as follows.

1. Vapor-phase reaction is suppressed by employing a substrate of low vapor pressure.
2. Solubility of substrate in a perfluorinated solvent used for fluorination significantly increases, as compared with non-fluorinated ester.
3. Partially-fluorinated substrate is easily prepared from readily available perfluorinated acyl fluoride **1a**, which is produced through self-multiplication.

In view that the starting materials are inexpensive propylene oxide, 1-propanol and fluorine gas and hydrogen fluoride evolved during the reactions is readily recycled back to fluorine gas and hydrogen, the present method is considered to reduce the manufacturing cost of PPVE.

II-4. Experimental

General Remarks: NMR spectra were obtained on a JEOL EX-400 or α -600 (tetramethylsilane as internal standard for ^1H , trichlorofluoromethane for ^{19}F , and CDCl_3 for ^{13}C). High resolution mass spectra were obtained on JEOL SX-102A coupled to HP-5890 with a 60 m capillary column J&W DB-1 or DB-1301. Elemental fluorine was generated by Fluoro Gas Fluorodec 30. Although the use of CFC-113 (R113: 1,1,2-trichlorotrifluoroethane) is regulated, experimental results with it are described for convenience, because it is still much more cheaply available (Aldrich) than compound **1a** for use as a solvent. Care must be taken in order to avoid discharge into the environment. Once enough amounts of compound **1a** is obtained in a synthetic cycle, it should be used in lieu of CFC-113. Other reagents were obtained from Kanto Chemicals and used without purification.

Special Caution: *As elemental fluorine is a highly toxic and corrosive gas and may cause explosion when it meets organics in a vapor-phase, extreme care must be taken when handling it! Since both liquid and gas phase of hydrogen fluoride (bp. 19.5°C) evolved during the reaction are also highly corrosive and cause severe burns upon contact. Deep care must be taken! Prior to use, all hydrocarbon greases must be removed and all the apparatus must be gradually passivated with elemental fluorine.*

1,2-Dichloro-1,2,2-trifluoroethyl 1,1,2,2,3,3,3-heptafluoropropyl ether (2).⁵ In a 2 L autoclave made of hastelloy C, equipped with a condenser maintained at -10 °C at the gas outlet of the autoclave, a suspension of sodium fluoride (60.0g, 1.43mol) and

1,1,2-trichlorotrifluoroethane (1.29 kg) was stirred and maintained at -10 °C. Nitrogen gas was blown into the system for 1.5 h, and then, fluorine gas diluted to 20% with nitrogen gas, was blown into the mixture for 1 h at a flow rate of 12.5 L/h under an atmospheric pressure. While blowing the 20% fluorine / nitrogen at the same rate, a solution of 1,2-dichloroethyl propyl ether (**3**)⁷ (20.0 g, 0.127 mol) dissolved in 1,1,2-trichlorotrifluoroethane (394g) was injected over a period of 18 h. Then, while blowing the 20% fluorine / nitrogen at the same rate, a solution (12 mL) of benzene in 1,1,2-trichlorotrifluoroethane (0.01 g/mL) was injected, while raising the temperature from -10 °C to room temperature. Then, the inlet for benzene injection was closed, and the outlet valve of the autoclave was closed. When the pressure reached 0.12 MPa, the fluorine gas inlet valve of the autoclave was closed, and stirring was continued for 1 h. During this time, the pressure dropped slightly. The pressure was then adjusted to an atmospheric pressure. The internal temperature of the reactor being maintained at room temperature, another benzene solution (12mL) was injected, and the same operation was repeated five times. The total amount of benzene injected was 0.74 g. Further nitrogen gas was blown into the mixture for 4.5 h. Yield was determined to be 40% by NMR with perfluorobenzene as an internal standard.

2-Propoxypropyl perfluoro(2-propoxypropanoate) (7). In a 2 L autoclave made of hastelloy C, perfluoro(2-propoxypropanoyl) fluoride (**1a**) (1.80 kg, 5.43 mol) was added dropwise to distilled 2-propoxy-1-propanol (0.620 kg, 5.25 mol) over a period of 8 h, while bubbling nitrogen gas to strip off hydrogen fluoride evolved and maintaining the internal temperature at from 25 to 35 °C. After the addition was completed, stripping off remaining HF and excess acyl fluoride **1a** by bubbling nitrogen gas gave

partially-fluorinated ester **7** (2.25 kg, 99.2% yield); bp. 52 to 61°C/3.6 to 4.0 kPa; ^1H NMR (399.8 MHz, CDCl_3) δ : 0.90 (t, $J=7.5$ Hz, 3H), 1.20 (d, $J=5.4$ Hz, 3H), 1.50 to 1.60 (m, 2H), 3.33 to 3.50 (m, 2H), 3.64 to 3.74 (m, 1H), 4.23 to 4.29 (m, 1H), 4.34 to 4.41(m, 1H); ^{19}F NMR (376.2 MHz, CDCl_3) δ : -80.9 and -87.4 (2F, AB quartet, $J_{\text{FF}}=149$ Hz), -82.3 (3F), -83.1 (3F), -130.7 (2F), -132.7 (1F); HRMS (EI) m/z 431.0746 [M+H]. Calcd for $\text{C}_{12}\text{H}_{14}\text{F}_{11}\text{O}_4$: 431.0716.

Perfluoro(2-propoxypropyl 2-propoxypropanoate) (8). In a 3 L autoclave made of nickel, equipped with a condenser maintained at 20 °C, a NaF pellet packed layer and condenser maintained at -10 °C in series at the gas outlet of the autoclave, and a liquid returning line in order to return a condensed liquid from the condenser maintained at -10°C, 1,1,2-trichlorotrifluoroethane (1.89 kg) was stirred and maintained at 25 °C. Nitrogen gas was blown into the system for 1.5 h, and then, fluorine gas (20%) diluted with nitrogen gas, was blown into the mixture for 3 h at a flow rate of 8.91 L/h at an atmospheric pressure. While blowing the 20% fluorine / nitrogen at the same rate, a solution of partially-fluorinated ester **7** (60.0 g, 0.139 mol) dissolved in 1,1,2-trichlorotrifluoroethane (0.60 kg) was injected over a period of 63.7 h. Then, while blowing the 20% fluorine / nitrogen at the same rate, a solution (12 mL) of benzene in 1,1,2-trichlorotrifluoroethane (0.01 g/mL) was injected and then raised the temperature from 25°C to 40°C. The inlet for benzene injection was then closed, and the outlet valve of the autoclave was closed. When the pressure reached 0.20 MPa, the fluorine gas inlet valve of the autoclave was closed, and stirring was continued for additional 1 h. As the pressure dropped slightly, the pressure was adjusted to atmospheric pressure. While maintaining the internal temperature of the reactor at 40 °C,

another benzene solution (6 mL) was injected, and the same operation was repeated twice. Total amount of benzene injected was 0.309 g. Further nitrogen gas was blown into the mixture for 2 h. Distillation gave perfluorinated ester **8** (86 g, 93% yield); bp. 46 to 51 °C/5.2 kPa; ^{19}F NMR (564.6 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ : -80.6 (1F), -80.8 and -80.9 (3F), -81.6 to -83.1 (2F), -82.6 (6F), -82.8 (3F), -86.7 (1F), -87.4 (1F), -87.5 (1F), -130.6 (4F), -132.2 (1F), -145.7 and -145.9 (1F); ^{13}C NMR (150.8 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$) δ : 100.26 and 100.28, 102.8, 106.8, 107.0, 116.0, 116.2, 116.5 and 116.6, 117.4, 117.5, 117.9, 117.9, 152.2 and 152.3; HRMS (CI) m/z 664.9496 $[\text{M}+\text{H}]$. Calcd for $\text{C}_{12}\text{HF}_{24}\text{O}_4$: 664.9492.

Thermal fragmentation of perfluorinated ester 8. In a 100 mL flask with a reflux condenser adjusted at 70 °C, a suspension of perfluorinated ester **8** (55.3 g, 83.2 mmol) and a NaF powder (0.70 g, 17 mmol) was heated at 140 °C for 15 h in an oil bath under vigorous stirring. A liquid sample (52.1 g, 94.2% yield) was recovered through the condenser. It turned out to be identical with the authentic sample of **1a**¹³ both by GC and NMR.

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Chapter III

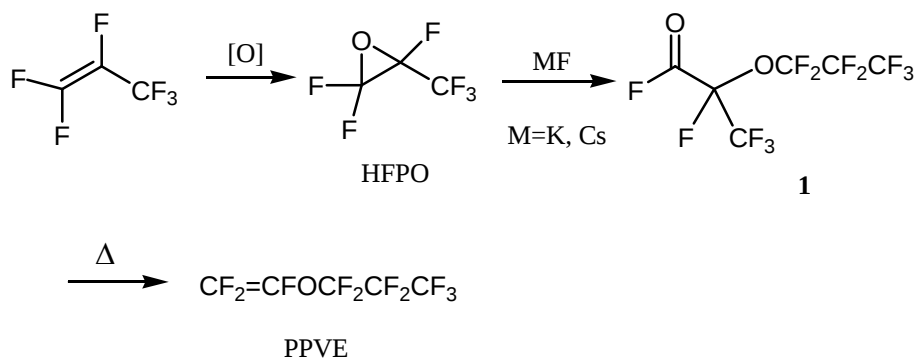
A New Route to Perfluorinated Vinyl Ether Monomers: Synthesis of Perfluoro(alkoxyalkanoyl) Fluorides from Non-fluorinated Substrates

Abstract

A new synthetic procedure has been developed for the preparation of various perfluoro(alkoxyalkanoyl) fluorides, precursors of perfluorinated vinyl ether monomers, from non-fluorinated alkoxyalcohols has been developed. Available perfluoro(alkoxyalkanoyl) fluorides such as perfluoro(2-propoxypropionyl) fluoride, so called HFPO dimer, can be multiplied by the use of the hydrocarbon counterpart alcohols and fluorine gas as raw materials. In the case that the desired perfluoro(alkoxyalkanoyl) fluoride is not readily available, it can be obtained from its hydrocarbon counterpart alcohol and an available perfluoroacyl fluoride.

III-1. Introduction

Perfluoro(2-alkoxyalkanoyl) fluorides are important intermediates of fluororesins such as PFA (perfluoroalkoxy copolymer). PFA is one of the most important perfluorinated polymers that are used as both thermally and chemically resistant material with melt processibility for industrial purpose.¹⁻⁶ One of its monomers, perfluoro(propyl vinyl ether) (PPVE), has been prepared via dimerization of hexafluoropropylene oxide (HFPO)⁷ (Scheme 1). Although the HFPO chemistry is well-established, it is specific to the propoxy side chain in PPVE, because HFPO itself is employed as a reactant for the reaction with perfluoroalkoxide. For perfluoro(alkyl vinyl ethers) other than PPVE, preparation of the precursor perfluoro(2-alkoxyalkanoyl) fluoride is essential but costly at present.⁸⁻¹⁰



Scheme 1. Conventional synthesis of PPVE

Recent progress in perfluorinated hypofluorite chemistry¹¹ and fluorination methodology for partially-fluorinated 1,2-dichloroethyl ethers¹² allows to prepare perfluoro(alkyl vinyl ethers) other than PPVE. However, these approaches are still costly, because they require expensive (per)fluorinated starting materials.

Although a process for converting perfluorinated esters to perfluorinated acyl fluorides with a nucleophile has been reported,¹³ application to synthesis of a precursor to perfluorinated polymers has remained yet to be studied.

Herein the Author presents an essentially different synthesis. His new synthetic route starts from non-fluorinated counterparts and utilizes liquid-phase direct fluorination¹⁴ as a key step. Although Lagow *et al.* reported liquid-phase direct fluorination of non-fluorinated compounds,¹⁴ they just adopted it to molecules with such simple structure as octyl octanoate. The Author considered that it could be applied to the synthesis of industrially important compounds, such as perfluorinated alkyl vinyl ethers, if he could make the corresponding hydrocarbon counterparts.

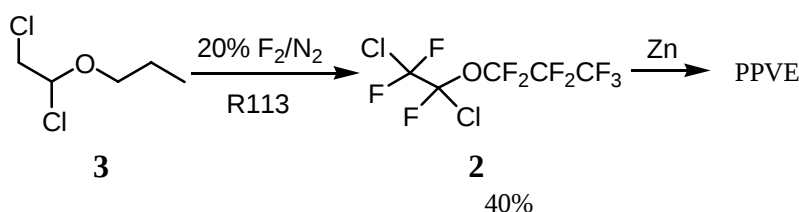
III-2. Results and Discussion

III-2-1. Synthesis of PPVE precursors

The Author chose PPVE as the first target molecule because of relatively simple structure. PPVE can be made either by thermal fragmentation of perfluoro(2-propoxypropionyl) fluoride (1) or by dechlorination of perfluoro(1,2-dichloroethyl propyl ether) (2). The dichloroethyl ether 2 could be obtained by direct fluorination of the corresponding hydrocarbon 1,2-dichloroethyl propyl ether (3), which is obtained from inexpensive propyl vinyl ether in only one step.^{15,16} Because it seemed relatively easy, this route was selected as the first trial.¹⁷

As dichloroethyl ether (3) is difficult to purify by distillation or even by

chromatography, the direct fluorination without purification of substrate was first carried out, basically applying the Lagow's method. Direct fluorination was conducted with 20% fluorine gas diluted in nitrogen gas and the reaction proceeded as expected (Scheme 2). However, migration of chlorine atoms accompanied to form considerable amounts of by-products arising from C-C and C-O bond cleavage. The complex results may be ascribed to vapor phase reaction due to high volatility of the substrate, and yield of **2** was only 40% at best. This suggested that substrates of low volatility are desirable for the liquid-phase reaction.

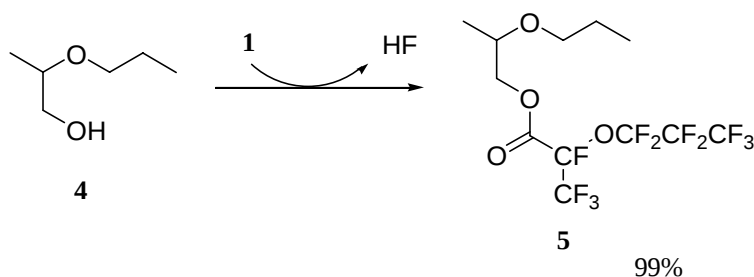
Scheme 2. Synthesis of PPVE from dichloroethyl ether **3**

The Author next examined the synthesis of perfluoroacyl fluoride **1**.¹⁷ This compound was considered to be derived from alkoxy alcohol **4** as the precursor. However, its direct fluorination seemed to be dangerous, because formation of unstable hypofluorite was expected to occur at first.¹⁸ Accordingly, protection of the OH group was considered to be essential. An appropriate protecting group in this case should be a perfluorinated group in view of inertness during fluorination, large molecular weight to gain low volatility, and easy deprotection after fluorination. Consequently, -CF(CF₃)OCF₂CF₂CF₃ turned out to be the group of choice, because the corresponding acyl fluoride was available as the intermediate to PPVE in the conventional manufacturing process, and, it was designed to give the same acyl fluoride from the

perfluorinated substrate after thermolysis in the presence of fluoride ion.

Synthesis was carried out as follows.

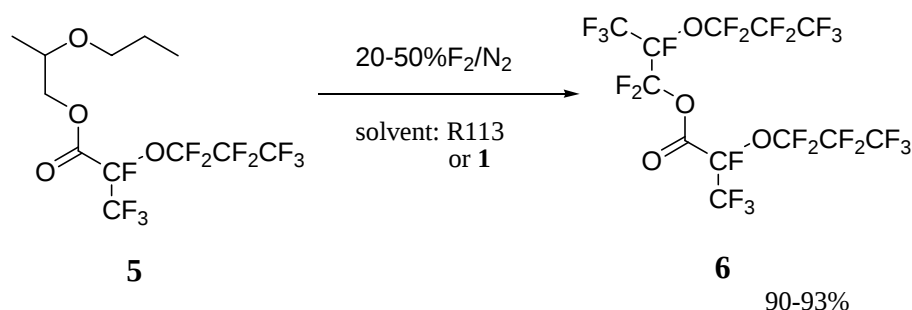
Starting alkoxy alcohol **4** was prepared from inexpensive propylene oxide and 1-propanol in the presence of an acid catalyst in one step.¹⁹⁻²¹ Esterification (Scheme 3) was carried out simply by mixing alkoxy alcohol **4** and perfluoroacyl fluoride **1** available from the conventional manufacturing route, removing HF formed during the reaction by blowing a stream of nitrogen, to give the partially-fluorinated ester **5** in 99% yield.



Scheme 3. Synthesis of partially-fluorinated ester **5**

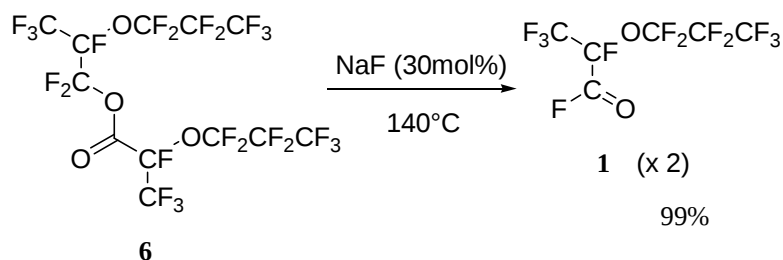
The next liquid-phase direct fluorination was carried out basically in a manner similar to the Lagow's method (Scheme 4). Cooling was essential in order to control the reaction temperature using an inert solvent, to appropriately dilute both fluorine and the substrate. An excess of fluorine to replace all of the hydrogen atoms in the substrate was always used as was the case of the non-fluorinated substrates described in the literature.^{14,22} In the present experiment, however, a potentially dangerous vapor-phase reaction could be avoided by employing a higher-molecular weight partially-fluorinated ester as the substrate. An additional benefit is that the solubility of the substrate in the perfluorinated solvent increased.²³ This contrasts sharply to the reaction with totally

non-fluorinated substrates. Moreover, the starting acyl fluoride itself turned out to be a good solvent for this fluorination. Thus, direct fluorination of partially-fluorinated ester **5** was carried out with 1.5-3.0 molar equivalents of fluorine (diluted to 20-50% in molecular nitrogen) to give the desired perfluoroester **6** in over 90% yield. In case of low conversion, addition of benzene was effective. Benzene perhaps reacts with fluorine to generate fluorine atoms which completes the fluorination process.



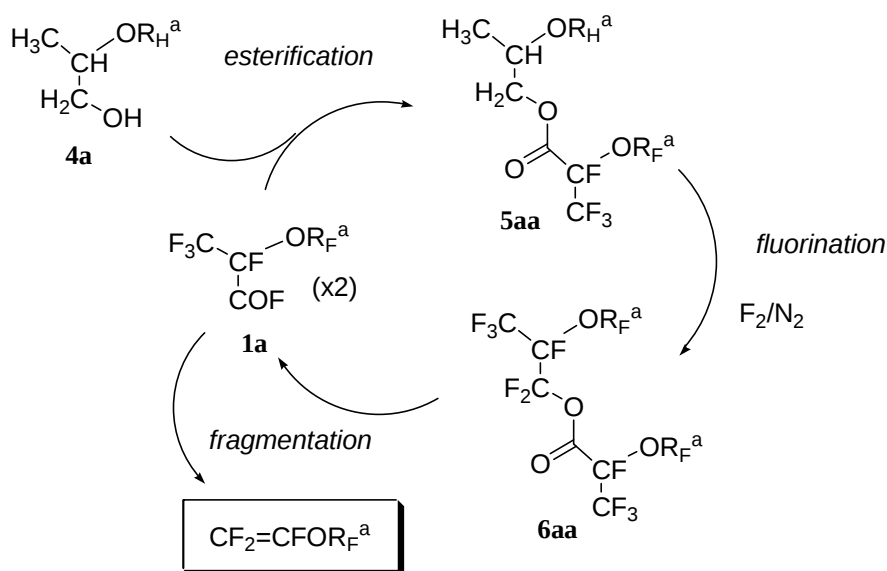
Scheme 4. Direct fluorination of partially-fluorinated ester **5**

Resulting perfluorinated ester **6** was converted to desired acyl fluoride **1** by thermolysis in the presence of 30 mol% of sodium fluoride as a catalyst (Scheme 5). This fluoride-mediated fragmentation reaction gave 2 moles of the desired acyl fluoride in 99% yield at lower temperature compared to the thermal reaction without catalyst.²⁴



Scheme 5. Fluoride-mediated fragmentation

The total process leading to a perfluorinated vinyl ether is summarized in Scheme 6. The Author has named this process PERFECT, an abbreviation of PERFluorination of Esterified Compounds followed by Thermolysis. For the case of synthesis of PPVE, the overall yield of acyl fluoride **1a** from starting substrates was 180% per cycle. By repeating the cycle, the amount of acyl fluoride **1a** increases in a geometric progression. In this sense, the synthetic cycle is a multiplication of the acyl fluoride.

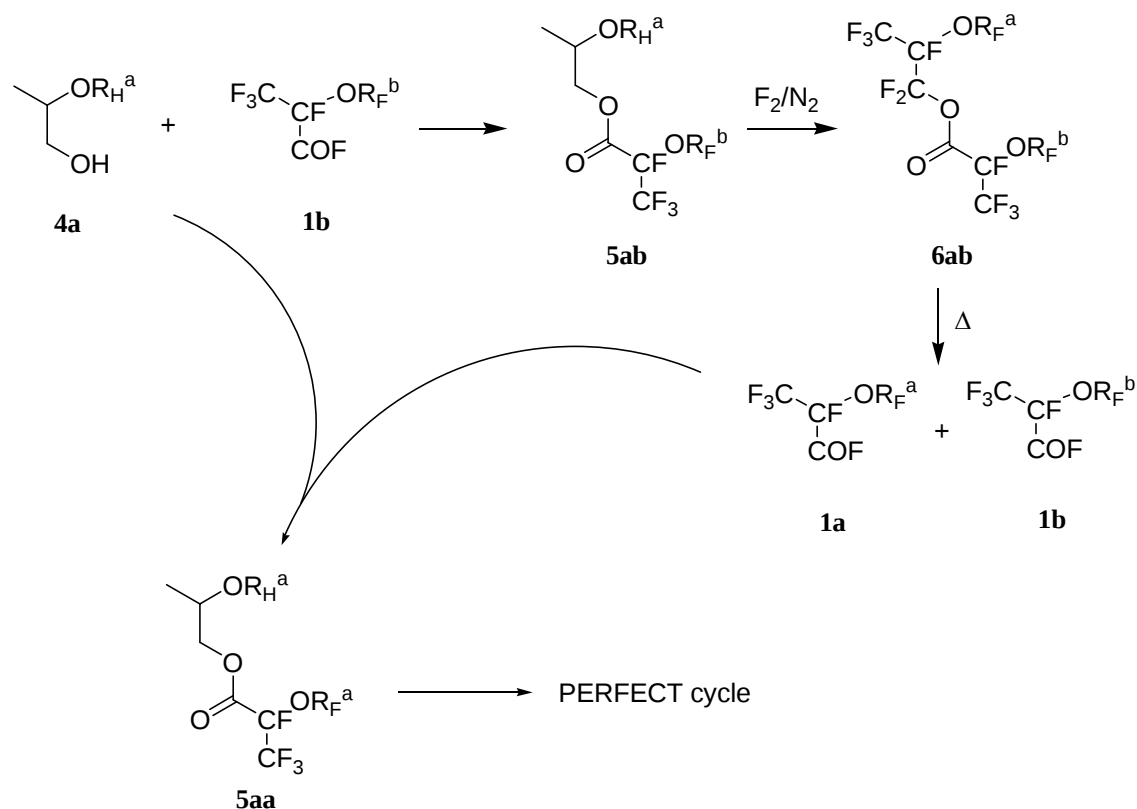


Scheme 6. The synthetic cycle of the PERFECT process

III-2-2. Synthesis of perfluoro(alkoxyalkanoyl) fluorides via perfluorinated mixed esters

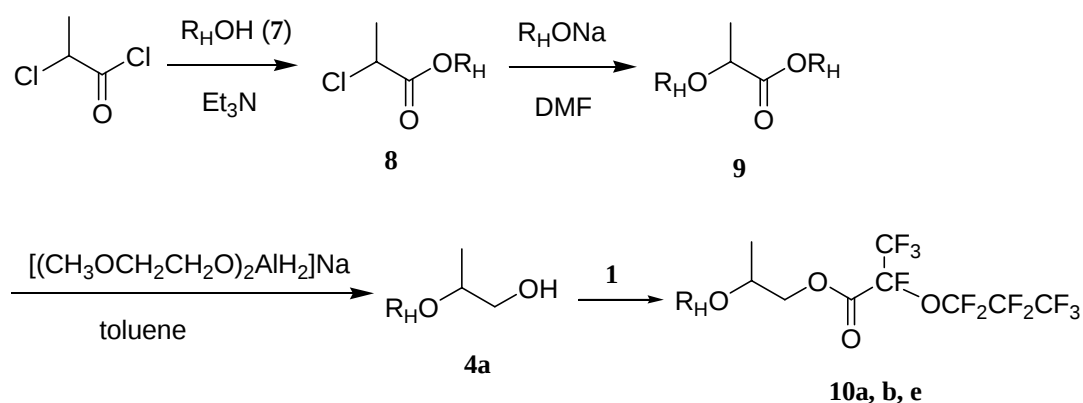
In cases where the desired perfluoroacyl fluoride is available, it can be multiplied by the method shown above. However, in many cases, the desired acyl

fluorides are not always readily available. In such situations, hydrocarbon counterpart alcohols **4a** whose structure corresponds to desired acyl fluoride **1a** is reacted with available acyl fluoride **1b** (Scheme 7). The resulting mixed ester **5ab** is fluorinated to give the perfluoroester **6ab**, and the following thermal fragmentation gives desired acyl fluoride **1a** and recovered starting fluoride **1b**. Once desired acyl fluoride **1a** is obtained, then it can be multiplied by synthesizing homo ester **5aa** and applying the PERFECT process. Thus, liquid-phase direct fluorination followed by thermal elimination gives 2 mols of desired acyl fluoride **1a**. According to this methodology, various perfluoroacyl fluorides were synthesized.



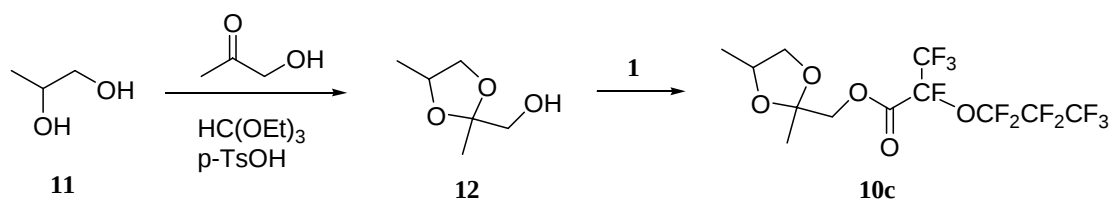
Scheme 7. The PERFECT method for the synthesis of various perfluoroacyl fluorides

When hydrocarbon counterpart alkoxy alcohol **4a** is not commercially available, it was prepared from inexpensive 2-chloropropionyl chloride in 3 steps as shown in Scheme 8. The reaction of alcohol **7**, which corresponds to the alkoxy moiety of **4a**, with 2-chloropropionyl chloride gave propionate ester **8**. Nucleophilic substitution with the alkoxide^{25,26} of alcohol **7** gave 2-alkoxypropionate **9**. Reduction with sodium bis(2-methoxyethoxy)aluminum hydride in toluene gave desired alkoxy alcohol **4a**. Esterification with readily available acyl fluoride **1**, a precursor of PPVE in the conventional manufacturing process, gave the substrate, partially-fluorinated ester **10**, for the liquid-phase direct fluorination.



Scheme 8. Preparation of partially-fluorinated esters

When the substrate for the direct fluorination has a dioxolane unit, the desired counterpart, alcohol **12**, was synthesized as shown in Scheme 9. Esterification with available acyl fluoride **1** gave partially-fluorinated ester substrate **10c**, which is now ready for liquid-phase direct fluorination.



Scheme 9. Preparation of partially-fluorinated ester **10c**

The partially-fluorinated esters were perfluorinated by liquid-phase direct fluorination. A general procedure is following. A 5.0 g of the substrate (5 % solution in 1,1,2-trichlorotrifluoroethane (R113)) was continuously introduced to R113 (200 mL) at 25 °C with blowing 20% F₂/N₂ at a flow rate controlled at a ratio of F₂/H = 3.0-4.5 (3.0-4.5 molar equivalents to replace all of the hydrogen atoms in the substrate). Then 0.01% benzene (0.010-0.036 eq) in R113 was portion-wise introduced under continuously blowing 20% F₂/N₂ and raising temperature up to 40 °C at 0-0.2 MPa. The results are summarized in Table 1. Both acyclic and cyclic partially-fluorinated esters were perfluorinated in good yields (runs 1 and 2). Yields of compounds with a longer alkyl chain were slightly lower, possibly because some C-C bond cleavage took place (run 1). Worthy to note is that dioxolane derivatives were also fluorinated in good yields (runs 3 and 4). Substrates with an aromatic moiety were also fluorinated to give a perfluorocyclohexane ring rather than a perfluorobenzene ring²⁷ but in quite low yields (runs 5 and 6). For example, although direct fluorination of an aromatic substrate (run 5) gave a product identical to that from a cyclohexyl derivative (run 2), yield was only 21%. Formation of many C-C bond dissociation products was observed, due probably to too much radicals generated from the reaction of F₂ and a phenyl moiety. On the other hand, fluorination with a simple vinyl substrate gave the corresponding saturated perfluoroalkyl product in a good yield (run 7).

Table 1. Liquid-phase direct fluorination of partially-fluorinated esters

$ \begin{array}{ccc} \begin{array}{c} \text{CF}_3 \\ \\ \text{R}_\text{H}-\text{O}-\text{C}(=\text{O})-\text{CF}-\text{OCF}_2\text{CF}_2\text{CF}_3 \\ \\ \text{O} \end{array} & \xrightarrow[\text{R113}]{20\% \text{ F}_2/\text{N}_2} & \begin{array}{c} \text{CF}_3 \\ \\ \text{R}_\text{F}-\text{O}-\text{C}(=\text{O})-\text{CF}-\text{OCF}_2\text{CF}_2\text{CF}_3 \\ \\ \text{O} \end{array} \\ \mathbf{10} & & \mathbf{13} \end{array} $			
run	substrate	product	yield
1	$ \begin{array}{c} \text{CH}_3(\text{CH}_2)_9\text{O}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (10\text{a}) $	$ \begin{array}{c} \text{CF}_3 \\ \\ \text{CF}_3(\text{CF}_2)_9\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (13\text{a}) $	69
2	$ \begin{array}{c} \text{C}_6\text{H}_{11}-\text{CH}_2-\text{O}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (10\text{b}) $	$ \begin{array}{c} \text{CF}_3 \\ \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \quad \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2 \end{array} \quad (13\text{b}) $	75
3	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{O}-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \\ \text{O} \quad \text{O} \end{array} \quad (10\text{c}) $	$ \begin{array}{c} \text{CF}_3 \\ \\ \text{F}_3\text{C}-\text{C}(\text{F}_2)-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \\ \text{O} \quad \text{O} \end{array} \quad (13\text{c}) $	87
4	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{O}-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \\ \text{O} \quad \text{O} \end{array} \quad (10\text{d}) $	$ \begin{array}{c} \text{CF}_2 \\ \\ \text{F}_3\text{C}-\text{C}(\text{F}_2)-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \\ \text{O} \quad \text{O} \end{array} \quad (13\text{d}) $	78
5	$ \begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2-\text{O}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (10\text{e}) $	$ \begin{array}{c} \text{CF}_3 \\ \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \quad \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2 \end{array} \quad (13\text{b}) $	21
6	$ \begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (10\text{f}) $	$ \begin{array}{c} \text{F}_2 \\ \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \quad \quad \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2 \end{array} \quad (13\text{f}) $	25
7	$ \begin{array}{c} \text{CH}_2=\text{CH}-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \\ \text{O} \end{array} \quad (10\text{g}) $	$ \begin{array}{c} \text{F}_2 \\ \\ \text{F}_3\text{C}-\text{C}(\text{F}_2)-\text{O}-\text{C}(\text{F}_2)-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{Rf} \\ \quad \quad \\ \text{F}_2\text{C}-\text{C}(\text{F}_2)-\text{CF}_2 \end{array} \quad (13\text{g}) $	86

Rf: -CF(CF₃)OCF₂CF₂CF₃

In order to obtain an intermediate for transparent fluororesin, a compound containing a vicinal dichloro moiety was perfluorinated (Table 2). When fluorination was carried out as usual at temperature of 25-40 °C, chlorine migration^{28, 29} took place partially (run 1). The chlorine migration was found to depend on reaction temperature. When the fluorination was carried out mostly at -10 °C and the last stage of fluorination was carried out at 40 °C, the migration was suppressed below ca 3 % (run 2). This suggests that the chlorine migration does not take place even at 40 °C after most of hydrogen atoms in the substrate are substituted by fluorine atoms.

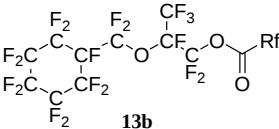
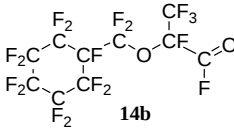
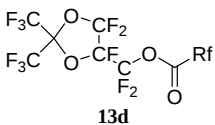
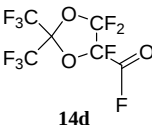
Table 2. Liquid-phase direct fluorination of a chlorine-containing partially-fluorinated ester

run	temperature(°C)	13h	13h'
1	25 → 40	63	32
2	-10 → 40	58	3

Rf: -CF(CF₃)OCF₂CF₂CF₃

Fluoride-mediated fragmentation of the obtained perfluoro esters with a catalytic amount of sodium fluoride gave the desired acyl fluorides with recovery of starting acyl fluoride **1**. The results are shown in Table 3.

Table 3. Fluoride-mediated fragmentation

substrate	product	amount of NaF (mol%)	temperature(°C)	yield(%)
 13b	 14b	18	120	66
 13d	 14d	20	120	73

Rf: -CF(CF₃)OCF₂CF₂CF₃

Perfluorinated acyl fluoride **1a** can be converted to the desired perfluoro(alkyl vinyl) ethers as described in the literature.³⁰

Thus, a synthetic cycle including conventional organic synthesis, liquid-phase direct fluorination, and fluoride-induced fragmentation is demonstrated to provide a new methodology for synthesis of various perfluoro(alkyl vinyl) ethers. Scaling-up of this process is being investigated at present.

III-3. Conclusions

Various perfluoro(alkoxyalkanoyl) fluorides were prepared utilizing liquid-phase direct fluorination with elemental fluorine. Direct fluorination of partially-fluorinated esters prepared from non-fluorinated alkoxy alcohols and perfluorinated acid fluorides **1** was achieved to give various perfluorinated esters in high

yields. Fluoride-mediated fragmentation of the resulting perfluoroesters is shown to give the desired acid fluoride. The advantages of the present method over known direct fluorination methods are as follows.

1. Nonselective vapor-phase reaction is suppressed by employing substrates with low vapor pressure.
2. Solubility of partially-fluorinated substrates in perfluorinated solvents used for fluorination is significantly enhanced, as compared with totally non-fluorinated esters.
3. Partially-fluorinated substrates are easily prepared using readily available perfluorinated acyl fluoride **1**.
4. Various perfluoroacyl fluorides are accessible, because conventional organic synthesis allows to construct readily the requisite hydrocarbon backbone.

The raw materials used in the present synthesis are inexpensive hydrocarbon substrates and fluorine gas. Therefore, this method is expected to provide useful perfluorinated acid fluorides at reasonable cost.

III-4. Experimental

Typical procedures

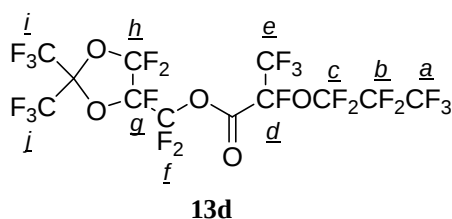
(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl perfluoro(2-propoxypropionate) (10d).

Perfluoro(2-propoxypropanoyl) fluoride (**1a**) (40.0 g, 0.120 mol) was added dropwise to solketal, 2,2-dimethyl-1,3-dioxolane-4-methanol, (15.0 g, 113 mmol) over a period of 30 min, while bubbling a nitrogen gas to strip off hydrogen fluoride evolved and maintaining the internal temperature at 25 to 30°C. After the addition was completed, stirring was continued at room temperature for 3 h, and an aqueous saturated sodium hydrogen carbonate solution (50 mL) was added at an internal temperature below 15 °C. The organic layer was washed twice with water (50 mL), dried over magnesium sulfate and then filtered. The filtrate was evaporated under reduced pressure to obtain a residue which turned out to be **10d** (11.3 g, 23% yield, 99% purity by GC); ¹H NMR (399.8 MHz, CDCl₃) δ: 1.36 and 1.42 (s, 6H), 3.78 and 4.10 (dt, ³J = 8.8 Hz, ⁴J = 5.2 Hz; dd, ³J = 8.8 Hz, ⁴J = 6.4 Hz, 2H), 4.31-4.51 (m, 3H); ¹⁹F NMR (376.2MHz, CDCl₃) δ: -80.3 (1F, OCF₂), -81.8 (3F, C(=O)CF(CF₃)O), -82.6 (3F, OCF₂CF₂CF₃), -87.0 (1F, OCF₂), -130.2 (2F, OCF₂CF₂CF₃), -132.2 (1F, C(=O)CF(CF₃)O); HRMS (CI⁺) *m/z* 445.0537 [M+H]⁺. Calcd for C₁₂H₁₂F₁₁O₅: 445.0509.

Perfluoro[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-propoxypropionate] (13d). A

500 mL autoclave made of nickel was equipped with a condenser maintained at 20 °C, an NaF pellet packed layer, and a condenser maintained at -10 °C in series at the gas outlet of the autoclave, as well as a liquid returning line in order to return the condensed

liquid from the condenser maintained at -10 °C, R113 (312 g) was put in the autoclave, stirred and maintained at 25 °C. Nitrogen gas was blown into the system for 1 h, and then, fluorine gas diluted to 20% with nitrogen gas was blown into the mixture for 1 h at a rate of 7.71 L/h at an atmospheric pressure. While blowing the 20% fluorine / nitrogen at the same rate, a solution of **10d** (5.01 g, 11.7 mmol) in R113 (100 g) was injected over a period of 5.6 h. Then, while blowing the 20% fluorine / nitrogen at the same rate, a solution (9 mL) of benzene in R113 (0.01 g/mL) was injected while raising the temperature from 25 °C to 40 °C. Then, the inlet for benzene injection was closed, and the outlet valve of the autoclave was closed. When the pressure reached 0.20 MPa, the fluorine gas inlet valve of the autoclave was closed, and stirring was continued for 0.9 h. During this time, the pressure dropped slightly. Then, the pressure was adjusted to an atmospheric pressure. While maintaining the internal temperature of the reactor at 40 °C, another portion of benzene solution (6 mL) was injected. The same operation was repeated four times. Total amount of injected benzene was 0.340 g (4.35 mmol), and the total amount of R113 injected was 33 mL. Further, nitrogen gas was blown into the mixture for 1.5 h. The desired product was quantitatively analyzed by ¹⁹F-NMR. Yield of **13d** was estimated to be 78%; ¹⁹F NMR (376.2MHz, CDCl₃) δ: -77.9 (1F, h), -79.6 to -80.8 (1F, c), -81.1 (3F, i), -81.2 (3F, j), -81.8 to -82.6 (3F of a, 3F of e and 1F of h), -85.9 to -88.0 (1F of c and 2F of f), -122.6 (1F, q), -130.4 (2F, b), -132.4 and -132.5 (1F, d); HRMS (EI⁺) *m/z* 622.9418 [M-F]⁺. Calcd for C₁₂F₂₁O₅: 622.9410.

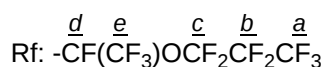
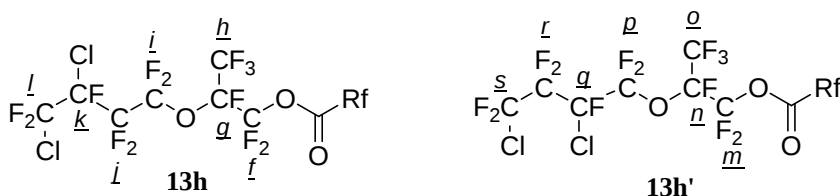


2,2-Bis(trifluoromethyl)-4,5,5-trifluoro-1,3-dioxolane-4-carbonyl fluoride (14d). In a 50 mL flask equipped with reflux condenser adjusted at 20 °C, a suspension of **13d** (1.8 g, 2.8 mmol) and NaF powder (0.021 g, 0.50 mmol) was heated at 120 °C for 12 h with vigorous stirring. After cooling, a liquid (1.6 g) resulted, which was confirmed to be the mixture of **1** and **14d**. The NMR spectrum of **14d** obtained corresponded with the literature.³¹ Yield of **14d** was estimated with an internal standard (C₆F₆) to be 73%.

2-(3,4-Dichlorobutoxy)propyl perfluoro(2-propoxypropionate) (11h). Under stirring in a 100 mL flask, a nitrogen gas was bubbled into 2-(3-butenyloxy)-1-propanol (19.2 g, 98% purity, 145 mmol). To this were added calcium chloride (2.2 g, 20 mmol) and water (3.6 g), and the resulting mixture was cooled to 10 °C. Chlorine gas was bubbled into the mixture for 2 h at a supply rate of about 4 g/h. After consumption of the starting material was confirmed by GC, the reaction mixture was diluted with diethyl ether (200 mL) and water (200 mL). The organic layer was separated and dried over magnesium sulfate. Concentration by distillation gave a crude product, which was put into a 300 mL flask and stirred while bubbling nitrogen gas. Acyl fluoride **1** (50 g, 150 mmol) was added dropwise over 1 h while maintaining the internal temperature at 25 to 30 °C. After completion of the dropwise addition, stirring was continued at room temperature for 3 h before saturated aqueous sodium hydrogen carbonate solution (80 mL) was added at an internal temperature below 15°C. The mixture was diluted with water (50 mL) and chloroform (100mL). The organic layer was separated and washed with water (100 mL) twice, dried over magnesium sulfate. Filtration and concentration gave a crude liquid, which was purified by a silica gel column chromatography (eluent: hexane / ethyl acetate = 4/1), and then by a silica gel column chromatography (eluent: AK-225)

to obtain **10h** (37 g, 50% yield, 99% purity by GC); ^1H NMR (399.8MHz, CDCl_3) δ : 1.21(dd, $^3J = 6.3\text{Hz}$, $^4J = 1.3\text{Hz}$, 3H), 1.81-1.93 (m, 1H), 2.19-2.26 (m, 1H), 3.59-3.65 (m, 1H), 3.68-3.80 (m, 4H), 4.20-4.46 (m, 3H) ; ^{19}F NMR (376.2MHz, CDCl_3) δ : -80.3 (1F, OCF_2), -81.6 (3F, $\text{C(=O)CF(CF}_3\text{)O}$), -82.4 (3F, $\text{OCF}_2\text{CF}_2\text{CF}_3$), -86.7 (1F, OCF_2), -130.0 (2F, $\text{OCF}_2\text{CF}_2\text{CF}_3$), -132.0 (1F, $\text{C(=O)CF(CF}_3\text{)O}$). HRMS (CI^+) m/z 513.0112 $[\text{M}+\text{H}]^+$. Calcd for $\text{C}_{13}\text{H}_{14}^{35}\text{Cl}_2\text{F}_{11}\text{O}_4$: 513.0094.

Perfluoro[2-(3,4-dichlorobutoxy)propyl 2-propoxypropionate] (13h) and perfluoro[2-(2,4-dichlorobutoxy)propyl 2-propoxypropionate] (13h'). Fluorination of **10h** was carried out in a manner similar to the synthesis of **13d**. The product was quantitatively analyzed by ^{19}F NMR (376.2 MHz, CDCl_3). **13h** (63% yield): δ : -64.7 (2F, $\underline{l}$), -76.5 to -80.0 (1F, $\underline{i}$), -80.0 to -81.0 (3F of $\underline{h}$ and 1F of $\underline{c}$), -82.2 (3F, $\underline{a}$), -82.5 (3F, $\underline{e}$), -82.0 to -82.9 (1F, $\underline{i}$), -86.4 to -88.1 (2F of $\underline{f}$ and 1F of $\underline{c}$), -117.0 to -119.7 (2F, $\underline{j}$), -130.4 (2F, $\underline{b}$), -131.9 (1F, $\underline{k}$), -132.3 (1F, $\underline{d}$), -145.9 (1F, $\underline{g}$); **13h'** (32% yield): δ : -65.7 to -67.2 (2F, $\underline{s}$), -76.5 to -80.0 (2F, $\underline{p}$), -81.0 to -81.3 (3F of $\underline{q}$ and 1F of $\underline{c}$), -82.0 to -83.0 (6F, $\underline{a}$ and $\underline{e}$), -86.5 to -88.5 (2F of $\underline{m}$ and 1F of $\underline{c}$), -112.5 to -116.0 (2F, $\underline{r}$), -130.5 (2F, $\underline{b}$), -131.9 to -132.4 (1F, $\underline{d}$), -136.5 (1F, $\underline{q}$), -145.9 (1F, $\underline{n}$). HRMS (EI^+) m/z 726.8797 $[\text{M}-\text{F}]$. Calcd for $\text{C}_{13}^{35}\text{Cl}_2\text{F}_{23}\text{O}_4$: 726.8806.



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Chapter IV

Synthesis of Perfluorinated Carboxylic Acid Membrane Monomers by Liquid-phase Direct Fluorination

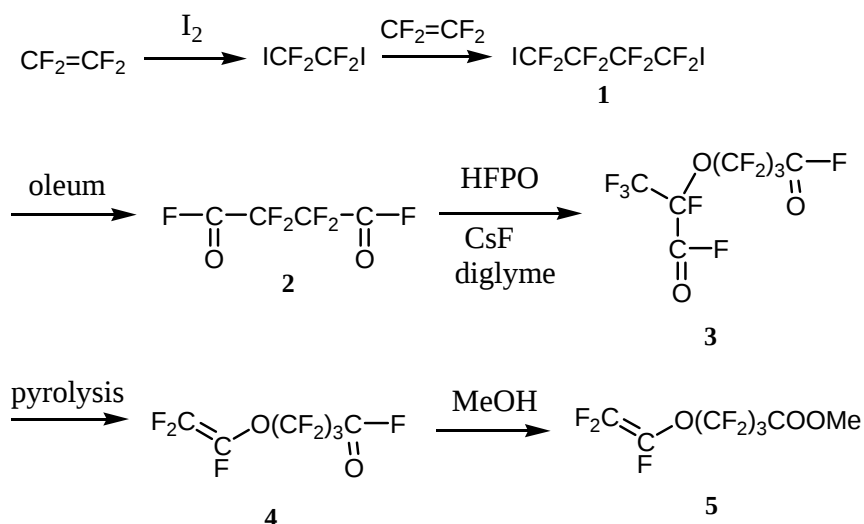
Abstract

A new synthetic procedure for the preparation of perfluorinated carboxylic acid membrane monomers has been developed starting from non-fluorinated substrates. The key step of the synthetic scheme is liquid-phase direct fluorination reaction with elemental fluorine. Direct fluorination of a partially-fluorinated diester, which was prepared from a hydrocarbon diol and a perfluorinated acyl fluoride, followed by thermal fragmentation, gave a perfluorinated diacyl fluoride, which is a precursor of a perfluorinated carboxylic acid membrane monomer.

IV-1. Introduction

The ion exchange membrane Flemion[®], which was developed by Asahi Glass, is used as a membrane in the energy-saving and pollution-free chlor-alkali production process. Nafion[®] (DuPont) is also used for the same purpose. They surpass the conventional mercury cell or diaphragm processes.^{1,2} Recently, a sulfonate-carboxylate laminated polymer membrane has been used to obtain an higher concentration of caustic soda. A perfluorinated carboxylic acid membrane is an important component thereof.³

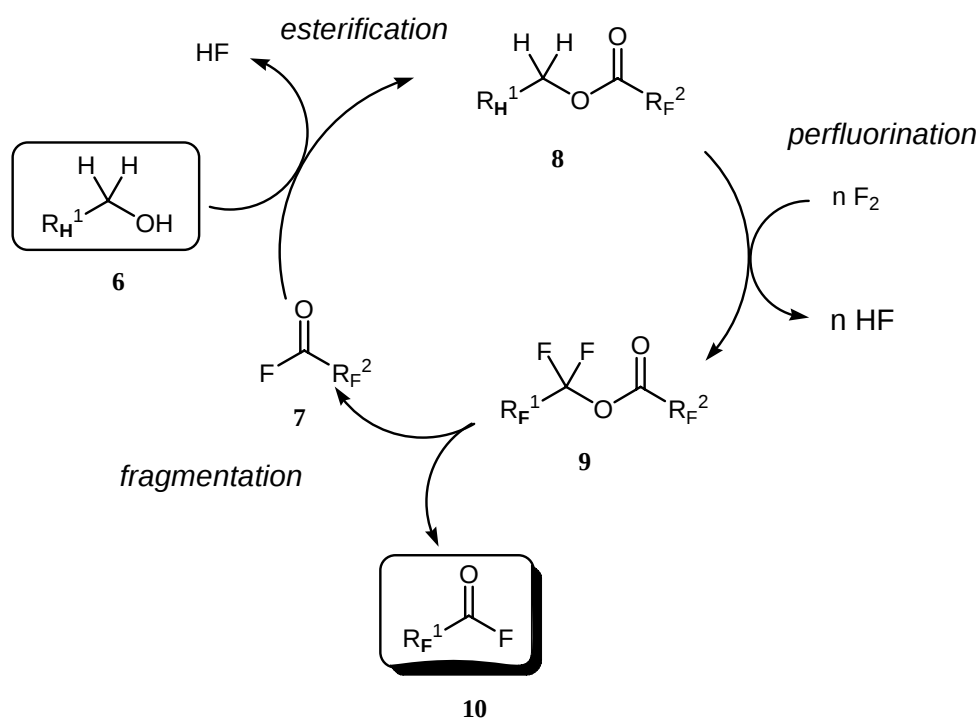
Flemion[®] carboxylic acid is a copolymer of tetrafluoroethylene (TFE) and perfluorinated vinyl ether, which has a carboxylic acid group in the side chain. The conventional manufacturing process of the Flemion[®] comonomer is shown in Scheme 1.⁴



Scheme 1. Conventional synthesis of Flemion[®] carboxylic acid monomer

Diiodide **1** obtained from TFE and iodine is reacted with oleum to give diacyl fluoride **2**, which upon treatment with cesium fluoride is assumed to generate cesium alkoxide. This then adds to hexafluoropropylene oxide (HFPO) to give diacyl fluoride **3**. Pyrolysis followed by methanolysis affords Flemion[®] comonomer **5**. Although this chemistry is well-established, it is still costly, uses hazardous reagents such as oleum, and has an iodine-containing waste problem. Moreover, there are restrictions in the monomer structure because of poor availability of raw materials.

The Exfluor-Lagow elemental fluorine process is effective under mild conditions.⁵⁻⁷ Lagow *et al.* reported liquid-phase direct fluorination of relatively simple non-fluorinated substrates, such as octyl octanoate, and the method was shown to be powerful for synthesis of perfluorinated compounds. The present synthetic method, the PERFECT process, utilizes liquid-phase direct fluorination as a key step (Scheme 2).^{8,9}



Scheme 2. The synthetic cycle of the PERFECT process

A hydrocarbon component having a backbone structure of target alcohol **6** is prepared by conventional organic synthesis. Then, **6** is esterified with a perfluorinated protecting group, like perfluoroacyl fluoride **7** in a typical case, to form a larger partially-fluorinated molecule **8**. Perfluorination is achieved by direct fluorination of the partially-fluorinated ester compound **8**, which allows to avoid a vapor-phase reaction since substrate **8** has low vaporizability. In addition, solubility of substrate **8** in a perfluorinated solvent is significantly higher than **6**. This is an advantage because various perfluorinated solvents other than CFCs can be employed. Finally, thermal elimination followed by separation of the mixture of acyl fluorides gives the desired perfluorinated compound **10** and recovered **7**.

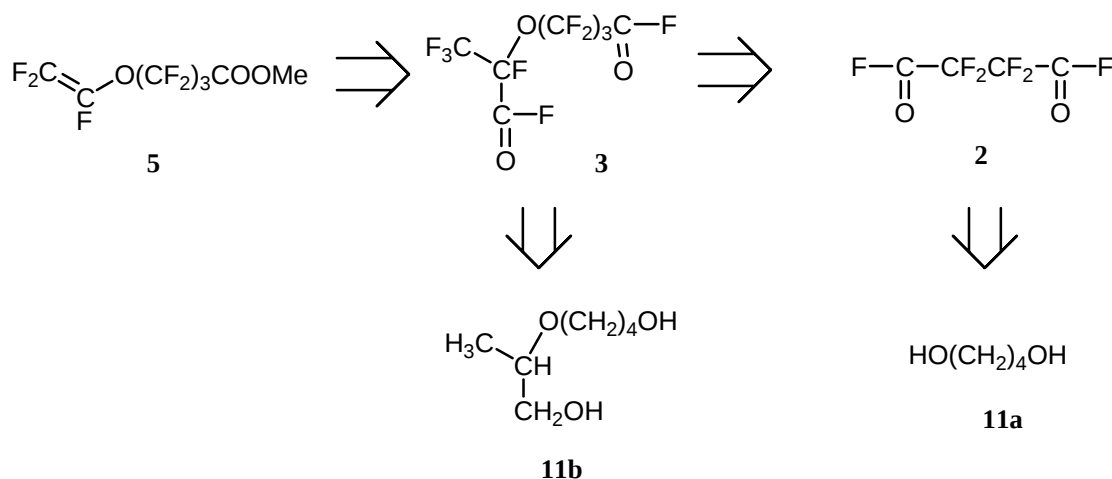
Examples are perfluoro(propyl vinyl ether), PPVE,^{8, 9} and perfluorinated butenyl vinyl ether BVE, which is a monomer of transparent perfluorinated cyclic polymer, CYTOP[®] as reported by the Author.¹⁰ He has also reported the synthesis of perfluoroalkanesulfonyl fluorides (see Chapter V),¹¹ and perfluoroketones (see Chapter VI).¹²

Presented in this Chapter is a new synthesis of a perfluorinated carboxylic acid membrane monomer using the PERFECT process. It also serves to provide novel monomer candidates.

IV-2. Results and Discussion

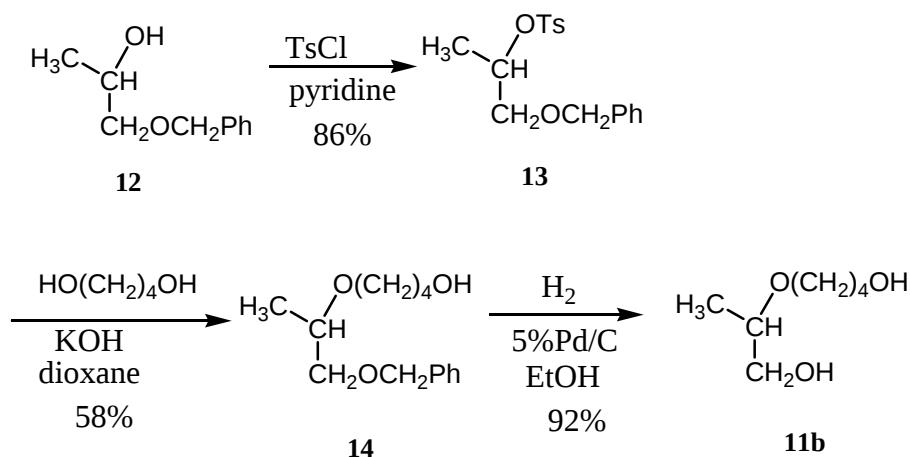
IV-2-1. Preparation of substrates for the PERFECT process

Flemion[®] monomer **5** is made from diacyl fluoride **2** through diacyl fluoride **3**. Therefore, it was postulated that these perfluorinated diacyl fluorides would be synthesized by the PERFECT method, wherein the hydrocarbon alcohol having the same carbon framework is esterified with a perfluoroacyl fluoride. Accordingly, diols **11a** and **11b** are selected as the candidates of starting materials for the PERFECT process (Scheme 3).



Scheme 3. Retrosynthetic analysis

One of the starting non-fluorinated diols, 1,4-butanediol (**11a**), is commercially available and inexpensive. On the other hand, diol **11b** is not readily available and thus was prepared by a synthetic route shown in Scheme 4.



Scheme 4. Synthesis of diol **11b**

The starting material was 1-benzyloxy-2-propanol (**12**) which was treated with tosyl chloride in pyridine to give tosylate **13** in 86% yield. Tosylate **13** was allowed to react with 1,4-butanediol to give mono-substituted alcohol **14** in 58% yield. Removal of the benzyl protecting group from **14** by hydrogenolysis gave desired diol **11b** in 92% yield.

IV-2-2. PERFECT process for synthesis of diacyl fluorides

Esterification was carried out simply by mixing non-fluorinated diol **11** and perfluoropropanoyl fluoride (**15**) under removal of HF formed during the reaction from the reaction system by a stream of nitrogen (Table 1). In the case of the esterification of **11b**, yield was not high due probably to C-O bond cleavage by HF in the reaction mixture.

Table 1. Esterification of **11** with perfluoropropanoyl fluorides **15**

$$\text{HOH}_2\text{C}-\text{R}^2_{\text{H}}-\text{CH}_2\text{OH} \quad \textbf{11} \quad + \quad 2 \quad \text{C}_2\text{F}_5\text{COF} \quad \textbf{15} \quad \xrightarrow{2 \text{ HF}} \quad \text{C}_2\text{F}_5-\text{C}(=\text{O})-\text{O}-\text{CH}_2-\text{R}^2_{\text{H}}-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{C}_2\text{F}_5 \quad \textbf{16}$$

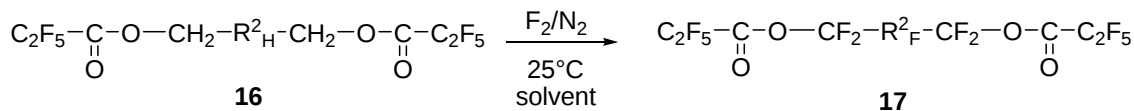
substrate	R ² _H	product	yield (%)
11a	-(CH ₂) ₂ -	16a	97*
11b	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CHO}(\text{CH}_2)_3 - \end{array} $	16b	46

* Crude yield

Liquid-phase direct fluorination of partially fluorinated esters **16** was carried out basically in a manner similar to the Exfluor-Lagow method. In order to control the reaction, heat removal, use of an inert solvent, appropriate dilution of both fluorine and a substrate, and presence of fluorine in excess at all times to replace all of the hydrogen atoms in a substrate were essential as in the case of totally non-fluorinated substrates.

The modified conditions allow to avoid dangerous vapor-phase reactions by employing a higher-molecular weight partially-fluorinated ester as the substrate. Thus, the reaction was carried out using 1.5-3.0 molar equivalents of fluorine diluted to 20-50% in nitrogen and the desired perfluoroester was isolated in high yields (Table 2).

Table 2. Direct fluorination



substrate	R ² _H	R ² _F	solvent	F ₂ /N ₂	yield (%)*
16a	-(CH ₂) ₂ -	-(CF ₂) ₂ -	R113	20%	92
			R113	50%	89
			perfluorohexane	20%	78
16b	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CHO}(\text{CH}_2)_3 - \end{array}$	$\begin{array}{c} \text{CF}_3 \\ \\ -\text{CFO}(\text{CF}_2)_3 - \end{array}$	R113	20%	94

*determined by ¹⁹F-NMR

To raise conversion, addition of benzene was effective: benzene is considered to generate fluorine radicals¹³ in high concentrations to induce further fluorination.

R113 was useful as a typical solvent for the laboratory scale synthesis. However, other perfluorinated solvents such as perfluorohexane can also be used. Ideally, this reaction may be carried out without any solvent: the product itself can be used as the solvent. When a sufficient quantity of the product is not formed, any perfluorinated solvents available can be employed.

Thermal fragmentation was carried out with sodium fluoride as the catalyst at 100 °C to give the desired perfluorinated diacyl fluorides after separation of the starting perfluoropropanoyl fluoride by distillation (Table 3).

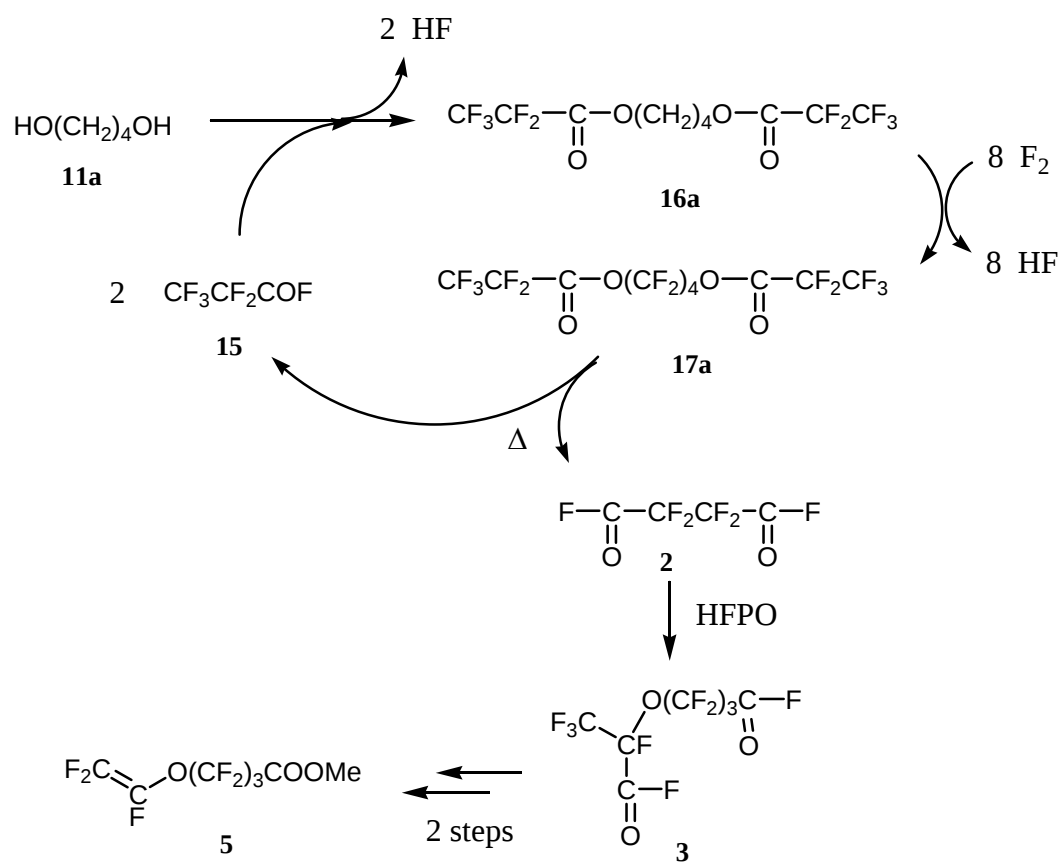
Table 3. Fluoride-induced fragmentation

$$\begin{array}{c}
 \text{C}_2\text{F}_5-\text{C}(=\text{O})-\text{O}-\text{CF}_2-\text{R}^2_{\text{F}}-\text{CF}_2-\text{O}-\text{C}(=\text{O})-\text{C}_2\text{F}_5 \\
 \text{17}
 \end{array}
 \xrightarrow[100^\circ\text{C}]{\text{NaF}}
 \begin{array}{c}
 \text{F}-\text{C}(=\text{O})-\text{R}^2_{\text{F}}-\text{C}(=\text{O})-\text{F} \\
 \left(+ 2 \text{ C}_2\text{F}_5-\text{C}(=\text{O})-\text{F} \right)
 \end{array}$$

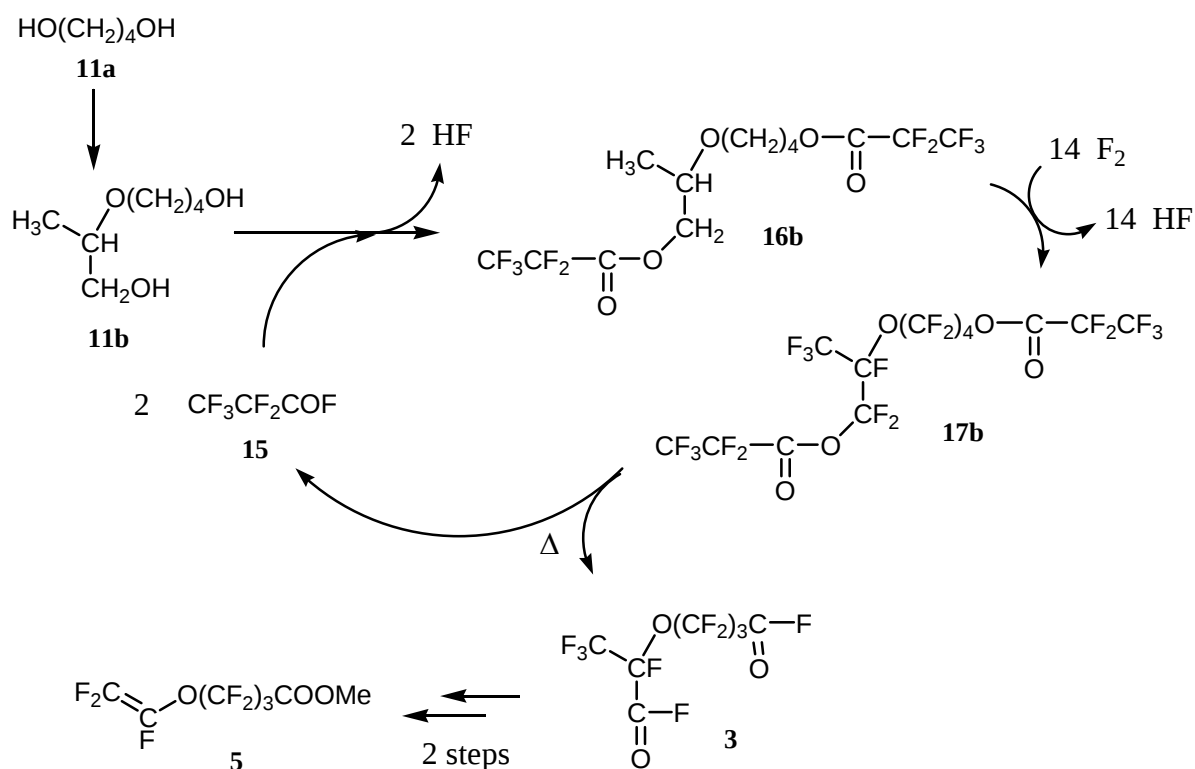
substrate	R ² _F	amount of NaF (eq)	product	yield (%)
17a	-(CF ₂) ₂ -	1	2	52
17b	$ \begin{array}{c} \text{CF}_3 \\ \\ -\text{CFO}(\text{CF}_2)_3^- \end{array} $	0.22	3	77

IV-2-3.Synthesis of the Flemion[®] monomer by the PERFECT process

Two different synthetic processes for preparation of the monomer of Flemion[®] are summarized in Schemes 5 and 6.



Scheme 5. Synthesis of **5** via **17a**



Scheme 6. Synthesis of **5** via **17b**

As for diacyl fluoride **2** production, 1,4-butanediol (**11a**) was employed as the starting material (Scheme 5). It was esterified with 2 mol of perfluoropropanoyl fluoride (**15**) to obtain partially-fluorinated ester **16a**. It was then perfluorinated with elemental fluorine in the liquid-phase to give perfluorinated ester **17a**. Thermal fragmentation afforded desired perfluorodiacyl fluoride **2** and perfluoropropanoyl fluoride **15** was recovered. This can be recycled.

By repeating the cycle, the quantity of perfluorodiacyl fluoride **2** will increase. Perfluorodiacyl fluoride **2** once obtained is reacted with HFPO to give perfluoroacyl fluoride **3**, and the following reactions gives Flemion[®] monomer **5** by a well-documented process.⁴

In the synthesis of perfluorodiacyl fluoride **3** by the PERFECT process, HFPO is not required (Scheme 6), because hydrocarbon backbone structure was synthesized before fluorination. Thus, diol **11b** was esterified with 2 mol of perfluoropropanoyl fluoride (**15**), perfluorinated with elemental fluorine, and fragmented to give desired perfluorodiacyl fluoride **3**. It is converted to Flemion[®] monomer **5** in further 2 steps.

This methodology is applicable to synthesis of other diacyl fluorides than Flemion[®] precursor **5** and is expected to be useful for various types of perfluorinated diacyl fluorides.

IV-3. Conclusions

Diacyl fluorides, precursors of Flemion[®] carboxylic acid membrane monomer, were synthesized by the PERFECT process from non-fluorinated diols by direct fluorination with elemental fluorine as a key step.

The PERFECT methodology has advantages that it does not require oleum and has no iodine-containing waste problem.

In addition, an additional solvent is not necessary when the product itself is used for the solvent for direct fluorination, and HF is the only by-product in the PERFECT cycle.

By using the PERFECT process, various new perfluorodiacyl fluorides, which are transformed into new Flemion[®] -type monomer, can be created.

IV-4. Experimental

Typical procedures

Preparation of butane-1,4-diyl perfluorodipropionate (16a). While bubbling nitrogen gas, perfluoropropanoyl fluoride **15** (0.800 kg, 4.82 mol) was introduced to 1,4-butanediol (**11a**, 0.200 kg, 2.22 mol) under stirring at 25 to 30 °C over a period of 2.5 h. After completion of the addition, stirring was continued at room temperature for 15 h. The resulting crude liquid was washed twice with saturated NaHCO₃ aqueous solution (500 ml) at 20 °C. The organic phase was washed three times with water (1 L), and dried over magnesium sulfate. After filtration, the crude liquid (825 g) was purified by silica gel column chromatography with R225 (mixture of CF₃CF₂CHCl₂ and CClF₂CF₂CHClF) as an eluent and following distillation at 91 to 93 °C /1.0 to 1.3 kPa afforded partially-fluorinated ester **16a** (255 g, 30.0%), which was shown to be 99% pure by GC. ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.85-1.89 (m, 4H, CH₂), 4.41-4.45 (m, 4H, OCH₂); ¹⁹F-NMR (282.65 MHz, CDCl₃) δ: -83.0 (6F, CF₃), -121.4 (4F, CF₂). HRMS (CI⁺) *m/z* 383.0367 [M+H]⁺. Calcd for C₁₀H₉F₁₀O₄: 383.0341.

Synthesis of perfluoro(butane-1,4-diyl dipropionate) (17a). Into a 3.0 L autoclave made of nickel, R113 (3.23 kg) was charged, stirred and maintained at 25 °C. At the gas outlet of the autoclave, a cooler maintained at -10 °C was installed. After supplying nitrogen gas for 1 h, 20% F₂/N₂ was supplied at a flow rate of 8.49 L/h for 2.3 h. While supplying 20% fluorine gas at the same flow rate, a solution of **16a** (80.0 g, 0.209 mol) in R113 (0.80 kg), was injected over a period of 45.7 h. Further, 20% fluorine gas was

supplied at the same flow rate for 0.5 h, and then nitrogen gas was supplied for 3.0 h to remove all the volatile material.

Yield of resulting perfluorinated ester **17a** was estimated by ^{19}F -NMR spectroscopy to be 92%. ^{19}F -NMR (376.0 MHz, CDCl_3) δ : -83.8 (6F, CF_3), -87.3 (4F, OCF_2), -122.6 (4F, CF_3CF_2), -126.6 (4F, OCF_2CF_2). HRMS (EI^+) m/z 506.9536 $[\text{M-F}]^+$. Calcd for $\text{C}_{10}\text{F}_{17}\text{O}_4$: 506.9525.

Synthesis of perfluorosuccinyl difluoride (2). Perfluorinated diester **17a** (5.00 g, 9.51 mmol) was charged together with 0.4 g of NaF powder into a flask and heated at 100 °C for 0.25 h in an oil bath while vigorously stirring. A gaseous sample (3.46 g) was recovered, which was identified to be a mixture of mainly acyl fluoride **15** and diacyl fluoride **2** by NMR.⁴ Yield of **2** was assayed as 52%.

Preparation of 2-(4-(perfluoropropionyloxy)butoxy)propyl perfluoropropionate (16b). p-Toluenesulfonyl chloride (63.1 g, 0.331 mol) was added gradually to $\text{HOCH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{Ph}$ (**12**, 50.0 g, 0.301 mol) in pyridine (150 ml) under stirring at 5 °C over a period of 1 h. The resulting mixture was poured into water (165 ml), and extracted with dichloromethane (165 ml). The organic layer was separated, washed with NaHCO_3 (165 ml), further washed three times with water (130 ml), dried over magnesium sulfate, and filtered. The filtrate was concentrated with an evaporator. The precipitated colorless crystals were collected by filtration and washed with hexane to obtain tosylate **13** (83.2 g, 86% yield); ^1H -NMR (300.4 MHz, CDCl_3) δ : 1.31 (d, $^3J = 6.3$ Hz, 3H, CH_3), 2.40 (s, 3H, $\text{CH}_3\text{C}_6\text{H}_4$), 3.46 (m, 2H, OCH_2CH), 4.41 (m, 2H, OCH_2Ph), 4.73 (m, 1H, CH), 7.19-7.34 (m, 7H, C_6H_5 and 2H of C_6H_4), 7.75-7.89 (m,

2H of C₆H₄).

Diol **11a** (37 g, 0.41 mol), potassium hydroxide (23 g, 0.41 mol) and dioxane (200 ml) were placed in a 500 mL flask, which was heated at an internal temperature of 102 °C to dissolve potassium hydroxide. To the base solution, a solution of tosylate **13** (63.7 g, 0.199 mol) in dioxane (65 ml) was added dropwise over a period of 1 h, and the reaction mixture was stirred for 4 h before quenching with water (350 ml). The mixture was extracted three times with dichloromethane (100 ml). The organic layer was washed with water (20 ml), dried over magnesium sulfate, and filtered. Concentration and purification of the residue by silica gel column chromatography gave 4-(1-(benzyloxy)propan-2-yloxy)butan-1-ol **14** (27.6 g, 58% yield); ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.15 (d, ³J = 6.2 Hz, 3H, CH₃), 1.64 (m, 4H, CH₂), 2.98 (bs, 1H, OH), 3.62-3.68 (m, 7H, OCH₂ and CH), 4.53 (m, 2H, OCH₂Ph), 7.23-7.29 (m, 5H, C₆H₅).

Under an argon atmosphere, benzyloxy alcohol **14** (15.2 g, 63.8 mmol) in ethanol (100 ml) was added to 5% palladium-carbon powder (1.5 g). The resulting mixture was stirred at room temperature for 17 h and then filtered through Celite®. The filtrate was concentrated to give diol **11b** (8.65 g, 92%); ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.11 (q, ³J = 6.2 Hz, 3H, CH₃), 1.68 (m, 4H, CH₂), 2.48 (bs, 2H, OH), 3.41-3.68 (m, 7H, OCH₂ and CH).

Perfluoropropanoyl fluoride (**15**, 276 g, 1.66 mol) was added over 6 h to diol **11b** (18.8 g, 0.127 mol) at 30 °C with nitrogen being swept, while maintaining the internal temperature at 30 °C. After completion of the addition, stirring was continued for 2 h at 30 °C while supplying nitrogen gas. A 5% NaHCO₃ aqueous solution (300 ml) was added at 15 °C. The organic layer was separated, washed twice with water (100 ml), dried over anhydrous magnesium sulfate and then filtered to obtain a crude liquid,

which was purified by silica gel column chromatography (eluent: R225) to give **16b** (25.9 g, 46% yield); $^1\text{H-NMR}$ (300.4 MHz, CDCl_3) δ : 1.20 (d, $^3J = 6.3$ Hz, 3H, CH_3), 1.56-1.68 (m, 2H, CH_2), 1.78 - 1.87 (m, 2H, $\text{CH}_2\text{CH}_2\text{OCO}$), 3.42 - 3.60 (m, 2H, OCH_2), 3.66 - 3.76 (m, 1H, OCH), 4.26 - 4.42 (m, 4H, COOCH_2); $^{19}\text{F-NMR}$ (282.7 MHz, CDCl_3) δ : -83.0 (6F, CF_3), -121.4 (2F, CF_2), -121.5 (2F, CF_2). HRMS (CI^+) m/z 441.0768 $[\text{M}+\text{H}]^+$. Calcd for $\text{C}_{13}\text{H}_{15}\text{F}_{10}\text{O}_5$: 441.0760.

Synthesis of perfluoro[2-(4-propionyloxybutoxy)propyl perfluoropropionate] (**17b**).

Direct fluorination of **16b** was carried out in a manner similar to the procedure for the synthesis of **16a**. Flow rate of 20% F_2/N_2 was adjusted to 10.1 L/hr, and a solution of **16b** (4.95 g, 11.2 mmol) in R113 (100 g) was supplied over a period of 5.5 h. Additionally, a solution of benzene in R113 (0.01 g/mL, 9 mL) was supplied intermittently at 0.20 MPa, and this operation was repeated four times. Nitrogen gas was supplied to remove solvent and all volatile materials to give a crude perfluorinated product, whose structure and yield were assayed by $^{19}\text{F-NMR}$ to be desired product **17b** and 94% yield: $^{19}\text{F-NMR}$ (376.0 MHz, CDCl_3) δ : -80.4 (3F, $\text{CF}(\text{CF}_3)$), -81.0 (2F, $\text{CF}(\text{CF}_3)\text{OCF}_2$), -83.3 (3F, CF_2CF_3), -83.4 (3F, CF_2CF_3), -86.8 (2F, COOCF_2), -86.9 (2F, COOCF_2), -122.1 (4F, CF_2CF_3), -125.9 (2F, OCF_2CF_2), -126.2 (2F, OCF_2CF_2), -145.6 (1F, CF). HRMS (EI^+) m/z 672.9378 $[\text{M}-\text{F}]^+$. Calcd for $\text{C}_{13}\text{F}_{23}\text{O}_5$: 672.9378.

Synthesis of perfluoro[4-(1-fluorocarbonylethoxy)butanoyl] fluoride (3). The thermal fragmentation of **17b** was carried out in a manner similar to the procedure for the thermal fragmentation of **17a**. Yield of desired product **3**⁴ was estimated to be 77% by $^{19}\text{F-NMR}$.

IV-5. References

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Chapter V

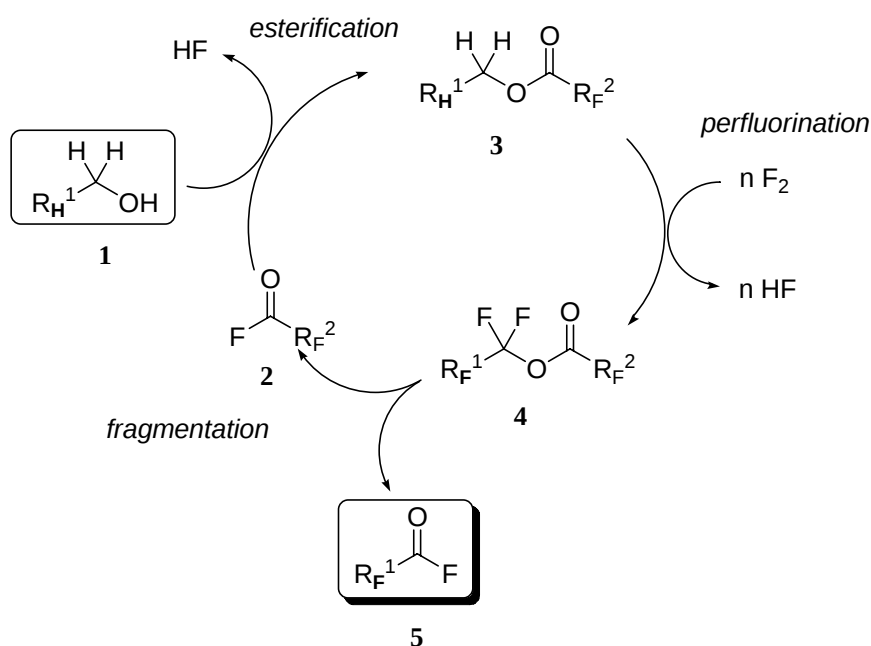
New Method for Synthesis of Perfluoroalkanesulfonyl Fluorides from Non-fluorinated Substrates

Abstract

A new synthetic procedure for perfluoroalkanesulfonyl fluorides has been developed through liquid-phase direct fluorination with elemental fluorine. A partially-fluorinated ester, which has an alkanesulfonyl fluoride functional group in an end, was synthesized from non-fluorinated counterparts and a perfluorinated acid fluoride according to the PERFECT process. Direct fluorination of the carboxylate ester gave the desired perfluorinated product in moderate yields as well as by-products arising from C-S bond cleavage. The results of the direct fluorination of some other model substrates suggest that the C-S bond cleavage occurred due to radical formation at the α -position rather than the β -position.

V-1. Introduction

Liquid-phase direct fluorination is a powerful tool to prepare perfluorinated compounds.¹⁻⁵ Especially, the Exfluor-Lagow elemental fluorine process is effective under mild conditions.⁶ Lagow *et al.* reported direct fluorination of non-fluorinated compounds with relatively simple structure.⁶ The Author has actually examined the reaction with octyl octanoate in order to establish whether it could be applied to the synthesis of useful perfluorinated monomers, and found that indeed it worked well. He has also examined the direct fluorination of such small molecules as monomer precursors. Unfortunately, he found that it was not easy. In some cases, a vapor phase reaction partly took place due to high volatility of the substrate and led to an explosion. In order to solve this problem, he has developed the PERFECT method as summarized in Scheme 1.^{7,8}



Scheme 1. The synthetic cycle of the PERFECT process

In the PERFECT method, perfluorination is achieved by direct fluorination of a partially-fluorinated compound.

First, a small hydrocarbon counterpart with a backbone structure identical to the desired compound but as primary alcohol form **1** is prepared by conventional organic synthesis. Then, it is coupled with a perfluorinated moiety, perfluoroacyl fluoride **2** in a typical case, to make a larger molecule, partially-fluorinated ester **3**. Perfluorination is achieved by liquid-phase direct fluorination with elemental fluorine to give perfluorinated ester **4**. In the direct fluorination process, a vapor-phase reaction is suppressed because substrates have low vapor pressure and are significantly soluble in perfluorinated solvents. An advantage is that perfluorinated solvents like CFCs may be replaced by perfluoroacyl fluoride itself. Final thermal fragmentation gives starting perfluoroacyl fluoride **2** and target perfluoroacyl fluoride **5**. When acyl fluoride **2** is not identical to desired acyl fluoride **5**, a mixture of acyl fluorides results, but each is readily separated by distillation. Then, desired perfluoroacyl fluoride **5** itself can be employed as starting perfluoroacyl fluoride **2** for the next PERFECT cycle. Thus, the desired perfluoroacyl fluoride can be multiplied by the synthetic cycle.

Such an example is shown by synthesis of perfluorinated butenyl vinyl ether, BVE, which is the monomer of transparent perfluorinated cyclic polymer, CYTOP[®].⁹ The Author has also reported synthesis of the carboxylic acid monomer for ion exchange membrane, Flemion[®], using a hydrocarbon diol as the starting material (see Chapter IV),¹⁰ and the synthesis of perfluoro ketones using a secondary alcohol as the starting material (see Chapter VI).¹¹

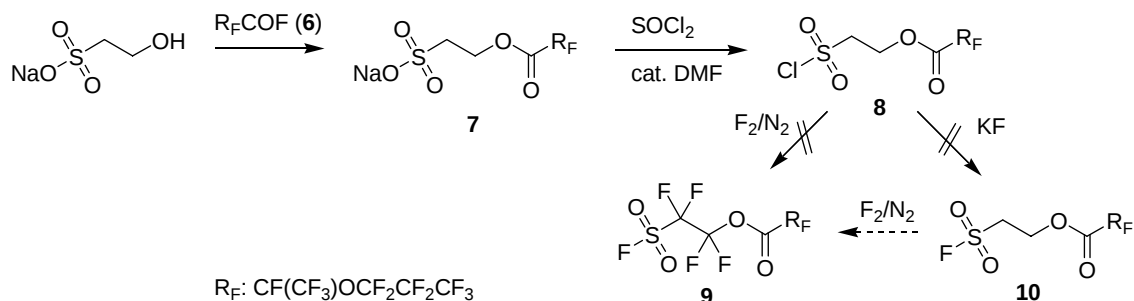
Herein presented is a new application of the PERFECT process to the preparation of perfluoroalkanesulfonyl fluoride.

V-2. Results and discussion

V-2-1. Synthesis of $\text{FSO}_2\text{CF}_2\text{CF}_2\text{OCF}_2\text{COF}$ (**16**)

Flemion[®], which has been developed by Asahi Glass, is used as the ion exchange membrane for chlor-alkali production process. Nafion[®] (DuPont) is also used for the same purpose.^{12, 13} The Author focused on the synthesis of a precursor of perfluorinated alkanesulfonic acid for the ion exchange membrane.

First, direct fluorination of alkanesulfonyl chloride **8** derived from isethionic acid sodium salt and perfluoroacyl fluoride **6** was attempted according to the PERFECT process. The synthetic route of the substrate is illustrated in Scheme 2.



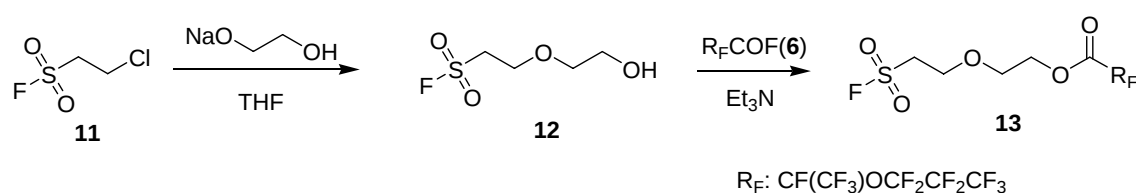
Scheme 2. Attempted synthesis from alkanesulfonyl chloride

Liquid-phase direct fluorination of partially-fluorinated alkanesulfonyl chloride **8**, which was prepared from the reaction of sodium isethionate and perfluorinated acid fluoride **6** followed by chlorination with thionyl chloride, did not afford the desired perfluoroalkanesulfonyl fluoride **9** at all under the typical conditions. Formation of compounds derived from C-S bond cleavage was observed.

The Author planned direct fluorination of the corresponding partially-fluorinated alkanesulfonyl fluoride **10**, which could be derived from chloride **8**, and attempted nucleophilic fluoride substitution of **8** with potassium fluoride. However, ester bond cleavage occurred instead of the desired substitution reaction. Thus, desired substrate for the next direct fluorination was not obtained at all.

Accordingly, the Author decided to adopt another synthetic strategy, which entails formation of the fluorosulfonyl group before the formation of the backbone structure.

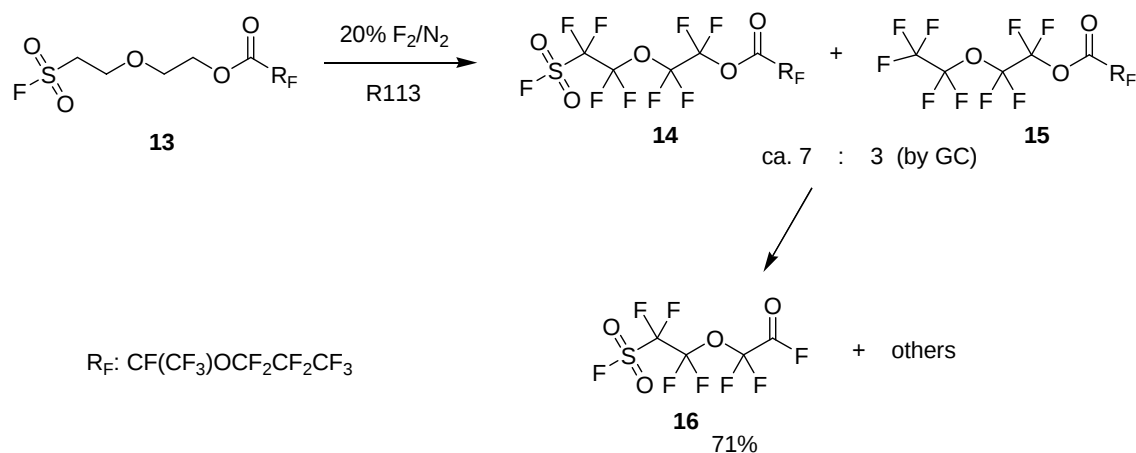
Reaction of 2-chloroethanesulfonyl fluoride **11**,¹⁴ a derivative of isethionic acid, with the sodium salt of ethylene glycol gave alcohol **12**, which was esterified was carried out as before to give partially-fluorinated ester **13** (Scheme 3). Although yield was not high (see experimental) possibly because the sulfonyl fluoride group in **12** competed the reaction with the hydroxyl group, **13** was obtained in an amount enough for subsequent fluorination reaction.



Scheme 3. Preparation of **13**

Direct fluorination of this partially-fluorinated sulfonyl fluoride **13** was carried out with elemental fluorine under the typical PERFECT conditions. Desired perfluorinated ester **14** was obtained in a moderate yield, although by-product **15** arising from C-S bond cleavage was still detected also in the PERFECT method. The ratio of

14 and **15** was ca. 7:3 as determined by GC. Thermal fragmentation led to desired product **16**, a precursor of a sulfonyl monomer for the ion exchange membrane (Scheme 4).

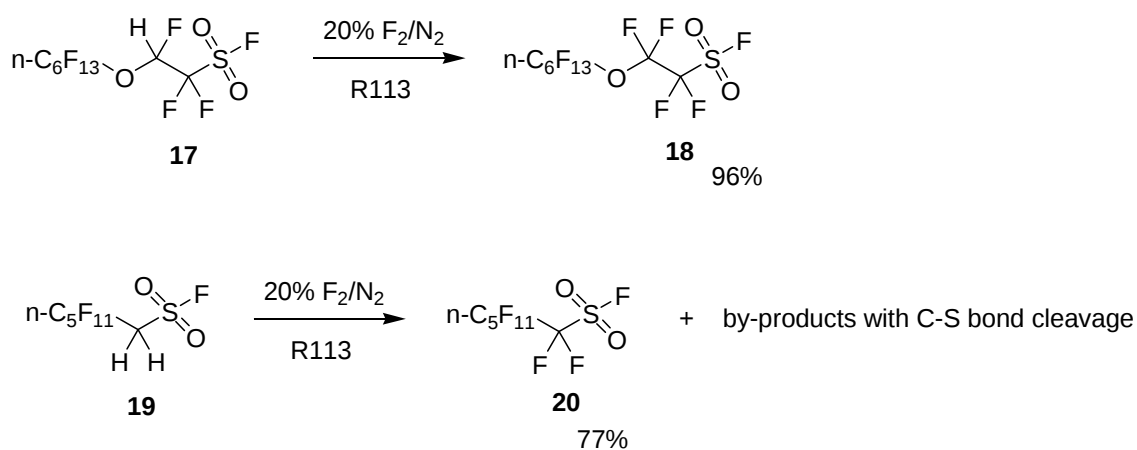


Scheme 4. Synthesis of **16** through direct fluorination

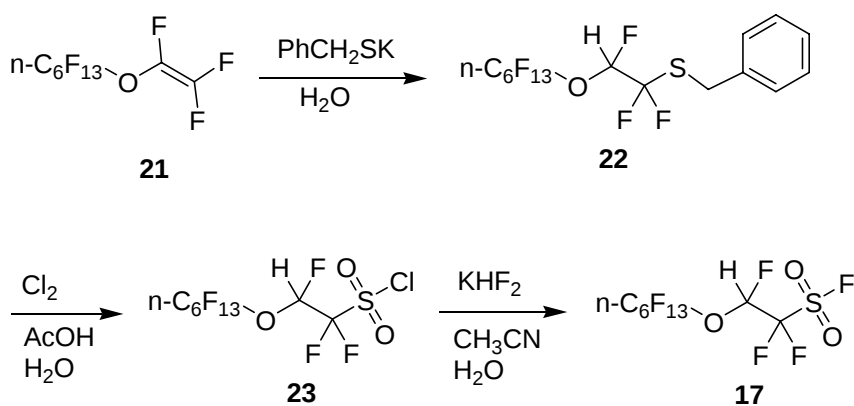
V-2-2. Fluorination at α - and β -position of fluorosulfonyl group

Cleavage of C-S bonds during liquid-phase direct fluorination has been reported previously.^{15,16} For example, octanesulfonyl fluoride was perfluorinated to give the corresponding perfluorooctanesulfonyl fluoride as well as by-product perfluorooctane arising from C-S bond cleavage, but yields are not described.¹⁵ Kobayashi *et al.* reported direct fluorination of methanesulfonyl fluoride,¹⁷ but also reported that direct fluorination of ethanesulfonyl fluoride led mainly to C-S bond cleavage and gave perfluoroethane and sulfonyl difluoride.¹⁶ This suggests that the C-S bond cleavage may be the result of β -elimination of the intermediate radical species. In the case shown above, the desired perfluorinated alkanesulfonyl fluoride was obtained in moderate

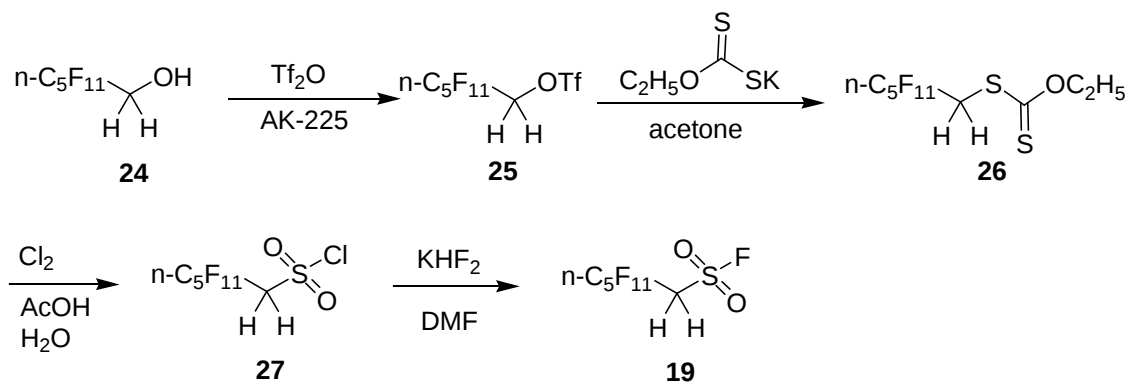
yield. However, C-S bond cleavage was also observed. In order to clarify the cause of the C-S bond cleavage, liquid-phase direct fluorination reactions of substrates **17** and **19** respectively were carried out (Scheme 5). Preparation of **17** and **19** are summarized in Schemes 6 and 7 respectively.



Scheme 5. Direct fluorination of model substrates



Scheme 6. Preparation of **17**



Scheme 7. Preparation of **19**

If a radical at the β -position which is formed during direct fluorination of substrate **17** promotes C-S bond cleavage, it should give by-products arising from the C-S bond cleavage: radical generation during the direct fluorination is possible only at the β -position. However, no C-S bond cleavage was observed and desired perfluorinated product **18** was obtained almost quantitatively.

If a radical at the α -position causes the C-S bond cleavage, then direct fluorination of the substrate **19** should give by-products arising from the C-S bond cleavage: radical generation is possible only at the α -position. Actually, direct fluorination of **19** gave desired perfluorinated product **20** in 77% yield along with the formation of products with the C-S bond cleavage in around 20% yield.

Based on the above results, the Author has concluded that the C-S bond cleavage occurs through an α -radical rather than β -radical, although it cannot explain the results of direct fluorination of methanesulfonyl fluoride.¹⁷

V-3. Conclusions

A synthetic method for perfluoro(alkanesulfonyl) fluorides utilizing liquid-phase direct fluorination with elemental fluorine was investigated. Whereas direct fluorination of a partially-fluorinated ester **8** with an alkanesulfonyl chloride group at an end according to the PERFECT process did not give the desired perfluorinated alkanesulfonyl fluoride **9**, substrate **13** with an alkanesulfonyl fluoride gave the desired perfluorinated products in a moderate yield as well as by-products arising from C-S bond cleavage. The results of the direct fluorination of substrate **17** and **19** suggest that C-S bond cleavage occurs due to the radical formation at the α - position rather than the β -position.

V-4. Experimental

Typical procedures

Synthesis of perfluoro[2-(fluorosulfonyl)ethoxyacetyl] fluoride (16). Ethylene glycol (141 g) and a methanol solution of sodium methoxide (28 wt%, 96.4 g, 0.500 mol) were charged in a 1 L flask, and the mixture was stirred and heated under reduced pressure to distill off methanol to give a solution of sodium salt of ethylene glycol. To a well-stirred solution of **11**¹⁴ (50 g, 0.341 mol) in THF (100 mL) was added dropwise under cooling with ice bath solution of sodium salt of ethyleneglycol over a period of 2.5 h, while maintaining the internal temperature at 10 °C. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for additional 2 h. The reaction mixture was poured to water (400 mL) and extracted with dichloromethane. Combined organic extracts were dried over magnesium sulfate. Filtration and evaporation gave a crude product **12** (47.1 g), which was used for the next step without purification. ¹H-NMR (300.4 MHz, CDCl₃) δ: 3.63 to 3.71 (m, 4H), 3.74 to 3.79 (m, 2H), 3.99 to 4.05 (m, 2H); ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: 58.4 (1F).

Crude oil **12** (47.1 g) and triethylamine (19.5 g, 0.193 mol) were put into a flask and cooled in an ice bath. To the mixture, perfluoro(2-propoxypropanoyl) fluoride **6** (64.1 g, 0.193 mol) was dropwise added over a period of 40 min under stirring and maintaining the internal temperature at or below 10 °C. After being stirred for 2 h at room temperature, the reaction mixture was poured to ice water (100 mL). The organic layer was separated, washed twice with water (100 mL), dried over magnesium sulfate, and filtered to give a crude oil, which was purified by silica gel column chromatography

(dichloropentafluoropropane (AK-225) as an eluent) to obtain product **13** (21.2 g, 43.8 mmol, 13% yield from **11**). $^1\text{H-NMR}$ (300.4 MHz, CDCl_3) δ : 3.57 to 3.63 (m, 2H), 3.81 (t, $^3J = 4.5$ Hz, 2H), 3.95 to 4.00 (m, 2H), 4.48 to 4.60 (m, 2H). $^{19}\text{F-NMR}$ (282.7 MHz, CDCl_3) δ : 58.2 (1F, *j*), -79.8 (1F of *c*), -81.3 (3F, *a*), -82.1 (3F, *e*), -86.6 (1F of *c*), -129.4 (2F, *b*), -131.5 (1F, *d*). (For assignment, see Fig. 1)

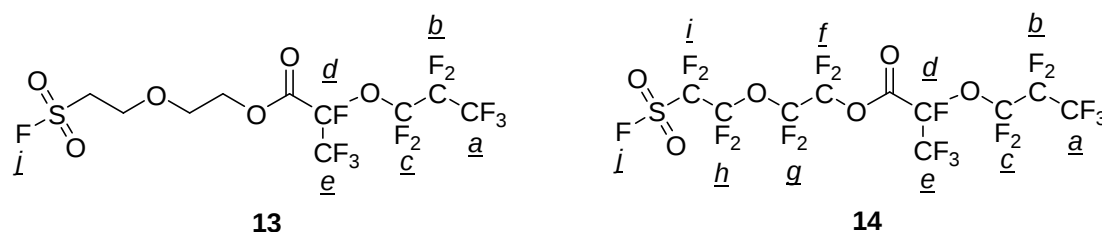


Fig. 1

Into a 500 mL autoclave made of nickel, R113 (313 g) was charged. At the gas outlet of the autoclave, a cooler maintained at 20 °C, a packed layer of NaF pellets and a cooler maintained at -10 °C, were installed in series. Further, a liquid-returning line was installed to return any condensed liquid from the cooler maintained at -10 °C to the autoclave. After supplying nitrogen gas for 1 h at 25 °C, 20% F_2/N_2 was supplied for 1 h at a flow rate of 7.78 L/h. Then, while supplying 20% F_2/N_2 at the same flow rate, a solution of **13** (7.01 g, 14.5 mmol) dissolved in R113 (140 g), was supplied over a period of 5.5 h. Then, a solution of benzene in R113 (0.01 g/mL, 6 mL) was supplied intermittently at 0.15 MPa, and this operation was repeated four times. Nitrogen gas was supplied to remove the solvent and all volatile materials to give the crude perfluorinated product. The ratio of the desired perfluorinated ester **14** and by-products arising from C-S bond cleavage was ca. 7:3, as determined by GC. The structure of desired perfluorinated ester **14** was confirmed by $^{19}\text{F-NMR}$ (376.0 MHz, CDCl_3) δ : 45.2

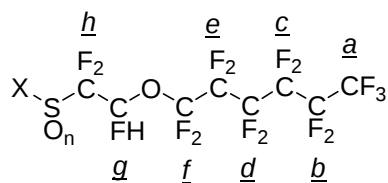
(1F, *j*), -79.9 (1F of *c*), -82.0 (3F, *a*), -82.2 (3F, *e*), -82.6 (2F, *h*), -87.0 (1F of *c*), -88.5 (2F, *g*), -92.3 (2F, *f*), -112.9 (2F, *i*), -130.2 (2F, *b*), -132.1 (1F, *d*). (Fig. 1)

Crude perfluorinated ester **14** (3.1 g) obtained as described above, was charged into a flask together with NaF powder (0.02 g) and heated at 140 °C for 10 h in an oil bath with vigorous stirring. At the upper portion of the flask, a reflux condenser adjusted at 20 °C was installed. After cooling, an oil (3.0 g) was recovered. GC-MS analysis suggested the presence of starting perfluoroacyl fluoride **6** and desired product **16** as the main components. The structure of desired product **16** was confirmed by ^{19}F -NMR¹⁸ and yield of **16** was estimated by ^{19}F -NMR to be 71%.

Synthesis of 2*H*-perfluoro[2-(hexyloxy)ethanesulfonyl] fluoride (17).

Addition of benzyl mercaptan to perfluorovinyl ether **21** was carried out in a manner similar to the procedure described in literature.¹⁹

Into a solution of 48% aqueous potassium hydroxide (3.1g, 26 mmol) and dioxane (8.0g), perfluoro(hexyl vinyl ether) (**21**) (7.1g, 17 mmol) was added, then benzyl mercaptan (2.4g, 19 mmol) was added dropwise at 10°C, and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with AK-225, washed 3 times with water, and dried over MgSO_4 . Evaporation gave a crude thioether (7.1g, 13 mmol, 77%), whose structure was confirmed to be benzyl thioether **22**. Yield was assayed by ^{19}F NMR. The purity was 99%. ^1H -NMR(300.4 MHz, CDCl_3) δ : 4.1 (s, 2H, SCH_2), 5.78 ~ 5.99 (dt, $^2J_{\text{HF}} = 54.4\text{Hz}$, $^3J_{\text{HF}} = 3.9\text{Hz}$, 1H, CHF), 7.27 (m, 5H, C_6H_5). ^{19}F -NMR(282.7MHz, CDCl_3) δ : -81.2(3F, *a*), -83.6 ~ -86.2(2F, *f*), -89.6 ~ -91.5(2F, *h*), -122.7 ~ -126.7(8F, *b,c,d,e*), -139.6(1F, *g*). (Fig. 2)



22 (X = Ph₂CH₂, n = 0), **23** (X = Cl, n = 2) and **17** (X = F, n = 2)

Fig. 2

Chlorination of benzyl thioether **22** was carried out in a manner similar to the literature procedure.²⁰

Into a mixture of crude thioether **22** (7.1g, 13 mmol), acetic acid (20g), and water (1.6g), nitrogen gas was passed through and then chlorine gas (2.7g, 38 mmol) was gradually supplied while maintaining the internal temperature at around 10°C. Nitrogen gas was supplied in order to remove chlorine. The reaction mixture was diluted with AK-225, washed 3 times with water, washed with brine, and dried over MgSO₄. Evaporation of the solvents gave crude sulfonyl chloride **23** (6.3g). The product was analyzed by ¹⁹F NMR. Yield was estimated to be 60%. ¹H-NMR (300.4 MHz, CDCl₃) δ: 6.45 (dt, ²J_{HF} = 52.7Hz, ³J_{HF} = 5.0Hz, 1H, CHF). ¹⁹F-NMR (282.7 MHz, CDCl₃): -81.0 (3F, *a*), -83.5 ~ -86.2 (2F, *f*), -109.6 ~ -110.1 (2F, *h*), -122.5~-126.4 (8F, *b*, *c*, *d*, *e*), -140.8 (1F, *g*). (Fig. 2)

Crude sulfonyl chloride **23** (6.3g, 7.3 mmol) was added dropwise to a mixture of KHF₂ (2g, 26 mmol), acetonitrile (10g), and water (8.5g) at room temperature. The mixture was stirred for 2 days, diluted with AK-225, and washed successively with water, sat. NaHCO₃, and with brine. The organic layer was dried over MgSO₄ and concentrated to give a crude product (5.0g), which was distilled (bp. 83°C/ 3.2KPa) to give desired product **17** (2.5g, 5.0 mmol, 68%). ¹H-NMR (300.4 MHz, CDCl₃) δ: 6.38

(dt, $^2J_{HF} = 52.9\text{Hz}$, $^3J_{HF} = 5.1\text{Hz}$, 1H, CHF). ^{19}F -NMR (282.7 MHz, CDCl_3) δ : 44.4 (1F, SO_2F), -81.2 (3F, *a*), -83.7~-86.7 (2F, *f*), -113.0 (2F, *h*), -122.7~-126.7 (8F, *b*, *c*, *d*, *e*), -142.5 (1F, *g*). (Fig. 2) HRMS (CI^+) m/z 500.9444 $[\text{M}+\text{H}]^+$. Calcd for $\text{C}_8\text{H}_2\text{F}_{17}\text{O}_3\text{S}$: 500.9453

Direct fluorination of 17. Direct fluorination of **17** was carried out in a manner similar to the procedure for direct fluorination of **13** with flow rate of 20% F_2/N_2 of 2.97 L/h and a solution of **17** (2.5 g) in R113 (15.4 g) being supplied over a period of 0.65 h. The structure of desired product **18** was confirmed by ^{19}F -NMR²¹ and yield was estimated to be 96%.

Synthesis of 1H,1H-perfluorohexanesulfonyl fluoride (19). Conversion from polyfluorinated alcohol **24** to triflate **25** was carried out in a manner similar to the procedure described in literature.²²

To a solution of $\text{C}_5\text{F}_{11}\text{CH}_2\text{OH}$ (**24**, 13 g, 43 mmol) in AK-225 (12 g), trifluoromethanesulfonic anhydride (13 g, 46 mmol) was added, and the mixture was stirred at 60°C for 1 day and further stirred at 80°C for another day. The reaction mixture was poured into water and extracted with AK-225. The organic layer was washed with water, saturated aqueous NaHCO_3 , and brine, respectively. Evaporation gave crude triflate **25** (15 g, purity = 96%, 35 mmol, 78% yield). ^1H -NMR (300.4 MHz, CDCl_3) δ : 4.8 (t, $^3J_{HF} = 12.3\text{Hz}$, 2H). ^{19}F -NMR (282.7MHz, CDCl_3) δ : -74.4 (3F, *g*), -81.3 (3F, *a*), -120.2 (2F, *e*), -122.5 ~ -124.2 (4F, *c,d*), -126.7 (2F, *b*). (Fig. 3)

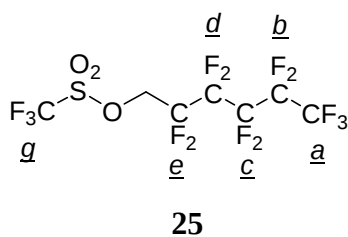


Fig. 3

Crude triflate **25** (15 g, 35mmol) was added dropwise to a stirred mixture of potassium ethyl xanthate (6.1 g, 38 mmol) in acetone (30 g) at 0 °C. After the mixture was stirred at room temperature for 12 h, AK-225 was added. The resulting mixture was washed 5 times with water. The organic layer was dried over MgSO₄ and evaporated to give crude xanthate **26** (10 g), which was used without further purification for the next reaction. ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.4 (t, ³J_{HH} = 7.2Hz, CH₃), 4.0 (t, ³J_{HF} = 17.4Hz, 2H, SCH₂), 4.7 (d, ³J_{HH} = 7.2Hz, 2H, OCH₂). ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: -81.3 (3F, *a*), -112.5 (2F, *e*), -122.9~ -123.5 (4F, *c,d*), -126.9 (2F, *b*). (Fig. 4)

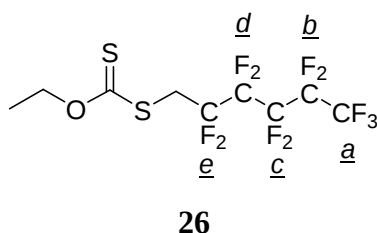


Fig. 4

Into a mixture of crude xanthate **26** (10 g, 23 mmol), acetic acid (20 g), and water (1.5 g), nitrogen gas was passed through and then chlorine gas (4.2 g, 59 mmol) was gradually supplied while maintaining the internal temperature around 10 °C. Then, nitrogen gas was supplied in order to remove excess chlorine. The reaction mixture was

diluted by AK-225, washed 3 times with water, washed with brine, and dried over MgSO₄. Evaporation gave crude sulfonyl chloride **27** (9.3 g, purity = 96%, 23 mmol, 67% yield for 2 steps). ¹H-NMR (300.4 MHz, CDCl₃) δ: 4.4 (t, ³J_{HF} = 15.0Hz, 2H). ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: -81.1 (3F, *a*), -113.1 (2F, *e*), -122.8 ~ -123.2 (4F, *c,d*), -126.6 (2F, *b*). (Fig. 5)

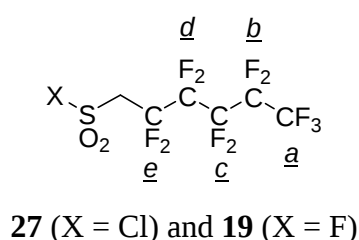


Fig. 5

Crude sulfonyl chloride **27** (9.3 g, 23 mmol) was added dropwise to a mixture of KHF₂ (5.0 g, 64 mmol) and DMF (8 g) at 0 °C. The mixture was stirred for 2 h, diluted with AK-225, and washed 3 times with water, sat. NaHCO₃, and brine, respectively, dried over MgSO₄, and concentrated. The residue was distilled (bp. 41~46°C/ 2.4 KPa) to give a mixture of DMF and desired product **19**. DMF was removed by washing 3 times with water to give **19** of 90% purity (0.91g, 2.5 mmol, 10% yield), which was used without further purification for the next reaction. ¹H-NMR (300.4 MHz, CDCl₃) δ: 4.2 (t, ³J_{HF} = 15.1Hz, 2H). ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: 66.7 (1F, SO₂F), -81.2 (3F, *a*), -113.0 (2F, *e*), -122.8 (4F, *c,d*), -126.6 (2F, *b*). (Fig. 5)

Direct fluorination of **19**.

Direct fluorination of **19** was carried out in a manner similar to the procedure

for direct fluorination of **13**, with a 3.04 L/h flow rate of 20% F₂/N₂, and a 0.6 h feed time of solution of **19** (0.91 g, 2.5 mmol) in R113 (13.7 g). Perfluorohexanesulfonyl fluoride (**20**) was obtained, and yield was estimated to be 77% as determined by ¹⁹F-NMR.

V-5. References

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Chapter VI

Synthesis of Perfluorinated Ketones by Liquid-Phase Direct Fluorination

Abstract

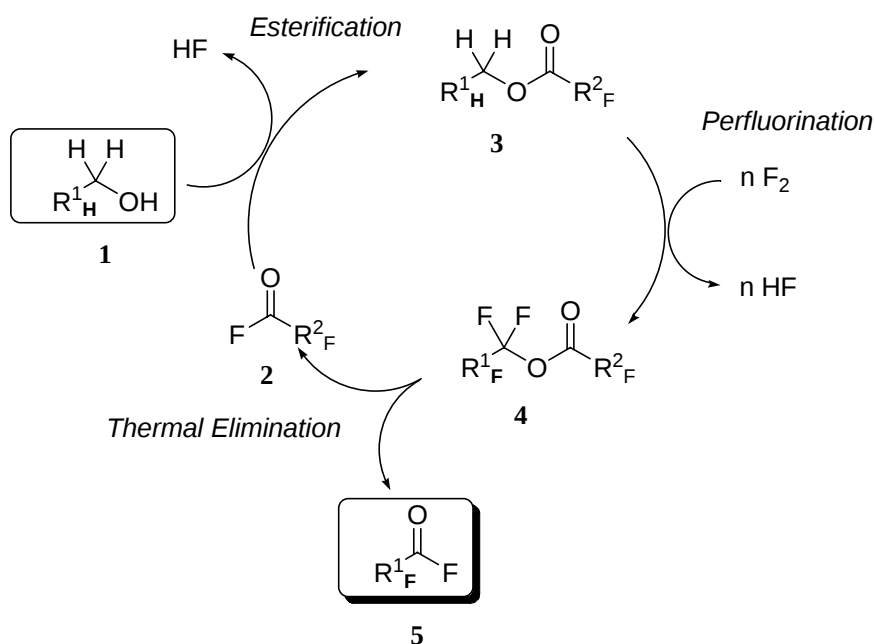
A new synthetic procedure for the preparation of perfluorinated ketones from nonfluorinated sec-alcohols has been developed. A key step in the synthetic route is liquid-phase direct fluorination reaction of partially-fluorinated esters with elemental fluorine. The substrate esters were prepared from non-fluorinated sec-alcohols and a perfluorinated acyl fluoride. Thermal fragmentation gave perfluorinated ketones and the starting perfluorinated acyl fluoride, which was reused for another synthesis. Application to synthesis of a polyfluoro ketone precursor for fluoropolymer resists for 157 nm microlithography was also successfully performed.

VI-1. Introduction

Perfluorinated unsaturated compounds are important precursors for industrial materials like both thermally and chemically resistant materials which are especially used for recent medical, IT and electronics fields.^{1,2} However, these fluorinated materials have disadvantages in cost, because they are prepared usually from fluorinated methane derivatives via multi-step reactions. Moreover, it has been difficult to synthesize novel perfluorinated monomers and perfluorinated building blocks, mainly because fluorinated compounds have restricted reactivity.

Liquid-phase direct fluorination is a powerful tool to make perfluorinated compounds.^{3,4} Especially, the Exfluor-Lagow elemental fluorine process is effective under mild conditions.^{5,6}

Lagow *et al.* reported direct fluorination of nonfluorinated compounds of relatively simple structure.⁶ In Chapter II, direct fluorination of small molecules such as monomer precursors was examined. However, it was found hard to reproduce the results.⁷ In some cases, vapor phase reaction partly took place due to high volatility of substrate and led to an explosion. In order to solve this problem, the Author has developed the PERFECT process (Scheme 1).⁷ By employing partially-fluorinated ester **3** of high-molecular weight, the dangerous vapor-phase reactions can be suppressed and solubility of substrates in a solvent used in the liquid-phase fluorination can be much improved. This contrasts sharply to that of non-fluorinated compounds.



Scheme 1. The synthetic cycle of the PERFECT process

Through the PERFECT process, various perfluoroacyl fluorides can be synthesized. Examples are synthesis of perfluorinated propyl vinyl ether (PPVE),⁷ the monomer of perfluoroalkoxy copolymer (PFA) (see Chapter II), various perfluoroacyl fluorides (see Chapter III),⁸ perfluoroalkanesulfonyl fluorides (see Chapter V),⁹ and the carboxylic acid monomers for ion exchange membrane (Flemion®) (see Chapter IV).¹⁰ Primary alcohols have been employed as the starting hydrocarbon components in all cases.

On the other hand, the synthesis of perfluoro ketones by direct fluorination^{6,11} has remained yet to be studied, because it has not been appropriate for large-scale synthesis especially of small molecular weight ketones. Lagow *et al.* reported that all hydrocarbon secondary alkyl esters were perfluorinated and the following transesterification in the presence of sodium fluoride gave perfluoro ketones.⁶ Adcock *et*

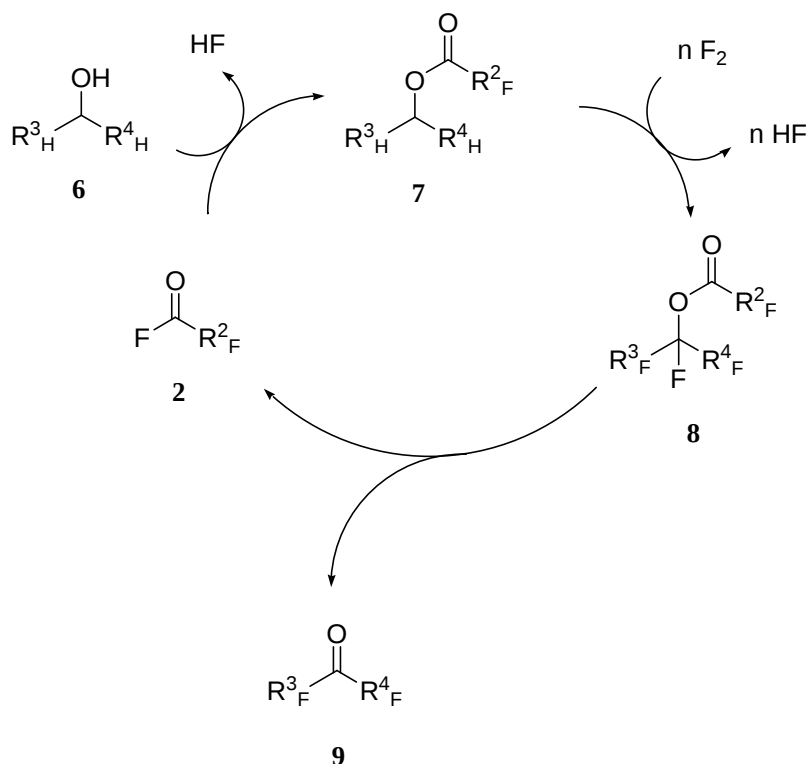
al. reported that ketones with adamantane structure were perfluorinated using aerosol to give perfluorinated ketones.¹¹

In this Chapter, the Author presents a new application of the PERFECT process to the preparation of perfluoro ketones starting with the corresponding secondary alcohols. The present method is shown to be applicable to a large scale synthesis.

VI-2. Results and Discussion

VI-2-1. PERFECT process for synthesis of hexafluoroacetone

In the PERFECT process, perfluorination is achieved by direct fluorination of a partially-fluorinated compound which later is fragmented into a perfluorinated product and a perfluoro agent used to construct the substrate. In application of the PERFECT process for perfluoro ketone synthesis, a nonfluorinated secondary alcohol is employed as the starting material (Scheme 2).

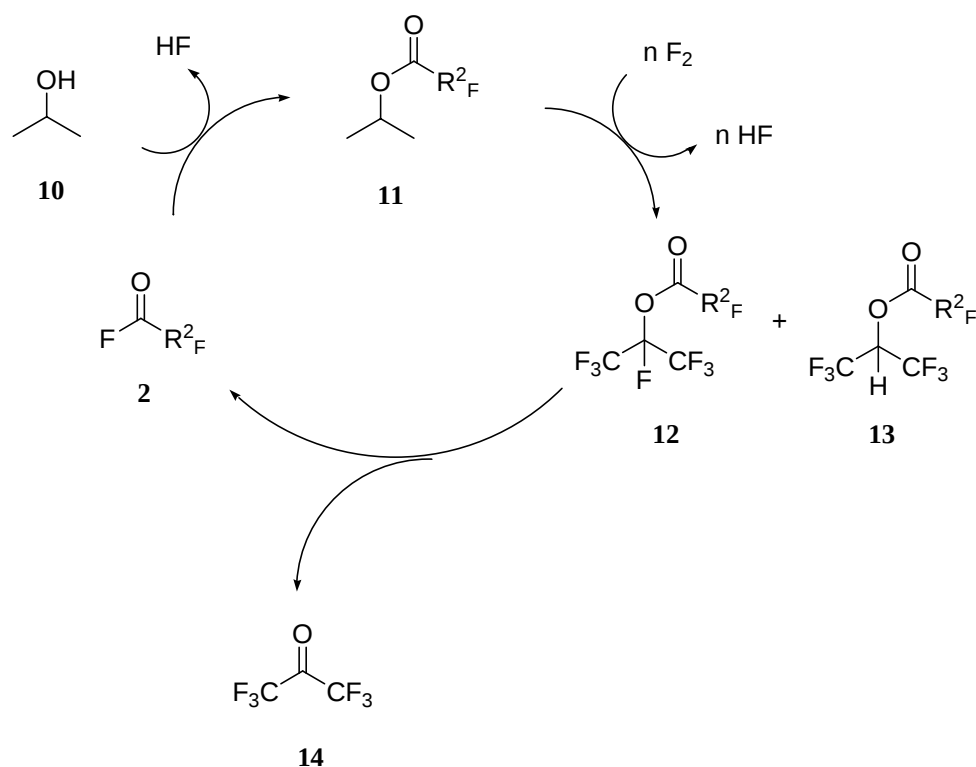


Scheme 2. The PERFECT process for synthesis of perfluoro ketones

At first, for a small hydrocarbon component with the backbone structure of the desired ketone, secondary alcohol **6** is selected and prepared by conventional organic synthesis when it is not commercially available. Then, it is coupled with a perfluorinated moiety, typically perfluoroacyl fluoride **2**, to make large molecular weight substrate in a form of partially-fluorinated ester **7**. Perfluorination is achieved by liquid-phase direct fluorination with elemental fluorine to give perfluorinated ester **8**. In the direct fluorination reaction of **7**, vapor-phase reaction is suppressed since substrate **7** has low vapor pressure and good solubility in a perfluorinated solvent. It has an advantage that various perfluorinated compounds other than CFCs can be used as the solvent. Typically, perfluoroacyl fluoride **2** itself is employed. Final thermal

fragmentation regenerates starting perfluoroacyl fluoride **2** and provides with desired perfluorinated ketone **9**. Separation of them is readily achieved by distillation.

The Author has first applied this methodology to synthesis of hexafluoroacetone (HFA) (Scheme 3).



Scheme 3. The PERFECT process for synthesis of HFA

Esterification was carried out simply by mixing 2-propanol (**10**) and perfluoroacyl fluoride **2** and by removing HF formed during the reaction out of the reaction system with a nitrogen stream. Both perfluoroacyl fluorides, so-called HFPO dimer **2a** and trimer **2b**, gave the desired partially-fluorinated esters **11**.

Subsequent liquid-phase direct fluorination was carried out in a manner basically similar to the Exfluor-Lagow method,⁶ which has a drawback that vapor phase reaction due to high volatility of non-fluorinated substrates partly takes place and leads to an explosion in some cases.

In the PERFECT process, dangerous vapor-phase reaction is favorably suppressed by employing higher-molecular weight partially-fluorinated esters as the substrate. Thus, the reaction of **11** was carried out with 1.5-3.0 molar amounts of fluorine diluted to 20-50% in nitrogen to give the desired perfluorinated esters (Table 1).

Table 1. Liquid-phase direct fluorination of partially-fluorinated ester **11**

11		12		13	11a: $R^2_F = -CF(CF_3)OCF_2CF_2CF_3$ 11b: $R^2_F = -CF(CF_3)OCF_2CF(CF_3)OCF_2CF_2CF_3$
Run	Solvent	F_2/N_2	Temp (°C)	Yield(%)	
				12	13
1	R113	20%	25	48	19
2	R113	20%	25	52	42
3	2b	50%	25	94	0

In particular, partially-fluorinated ester **11a** derived from **2a** was perfluorinated with 20% F_2/N_2 in 1,1,2-trichloro-1,2,2-trifluoroethane (R113) as the solvent at room temperature (run 1). Desired perfluorinated ester **12a** was obtained in 48% yield, but **13a** with a sterically hindered methine bond remaining unchanged was also obtained in

19% yield. The rest 30% was lost due possibly to the volatility of substrate **11a**. In the case of larger partially-fluorinated ester **11b** derived from **2b** as the substrate, material balance was improved, but still 42% of **13** remained unreacted (run 2). Longer reaction time was not effective at all. Addition of benzene to generate many fresh fluorine radicals¹² was effective to some extent, but the reaction did not complete yet. Higher concentration of fluorine was indeed effective, and 50% F₂/N₂ gave the desired perfluorinated ester **12b** in 94% yield (run 3). In this case, R113 was not an appropriate solvent, because it partly reacts with 50% F₂/N₂. Therefore, **2b** itself was used as the solvent.

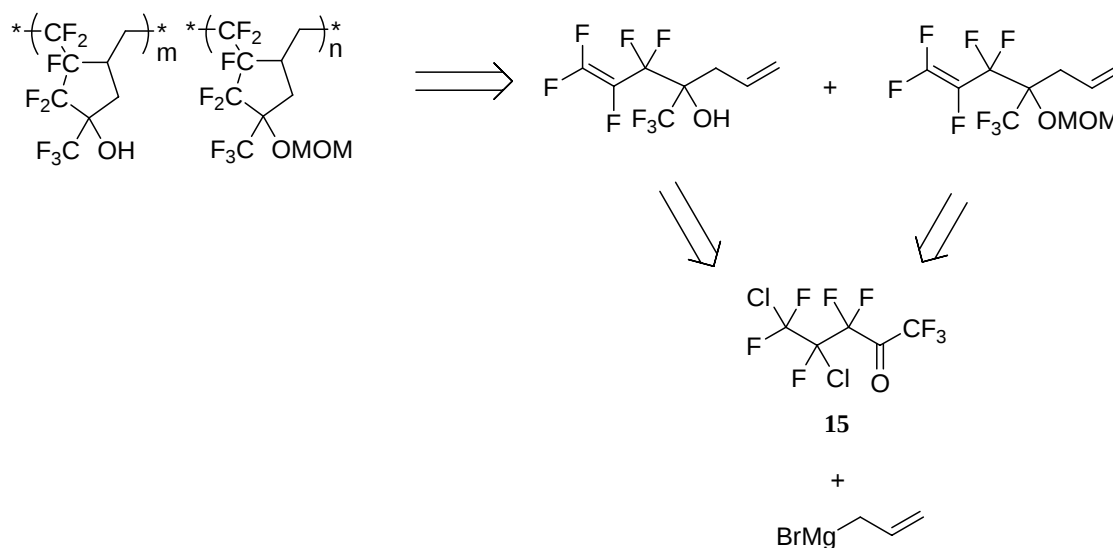
The next thermal fragmentation was carried out in the presence of potassium fluoride to give HFA (**14**) in an excellent yield. Potassium fluoride works as the catalyst of the reaction.

Thus obtained HFA (**14**) is reduced to give 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), an important material as a pharmaceutical intermediates¹³ and a special solvent.¹⁴

VI-2-2. PERFECT process for synthesis of polyfluoroketones for fluoropolymer resists

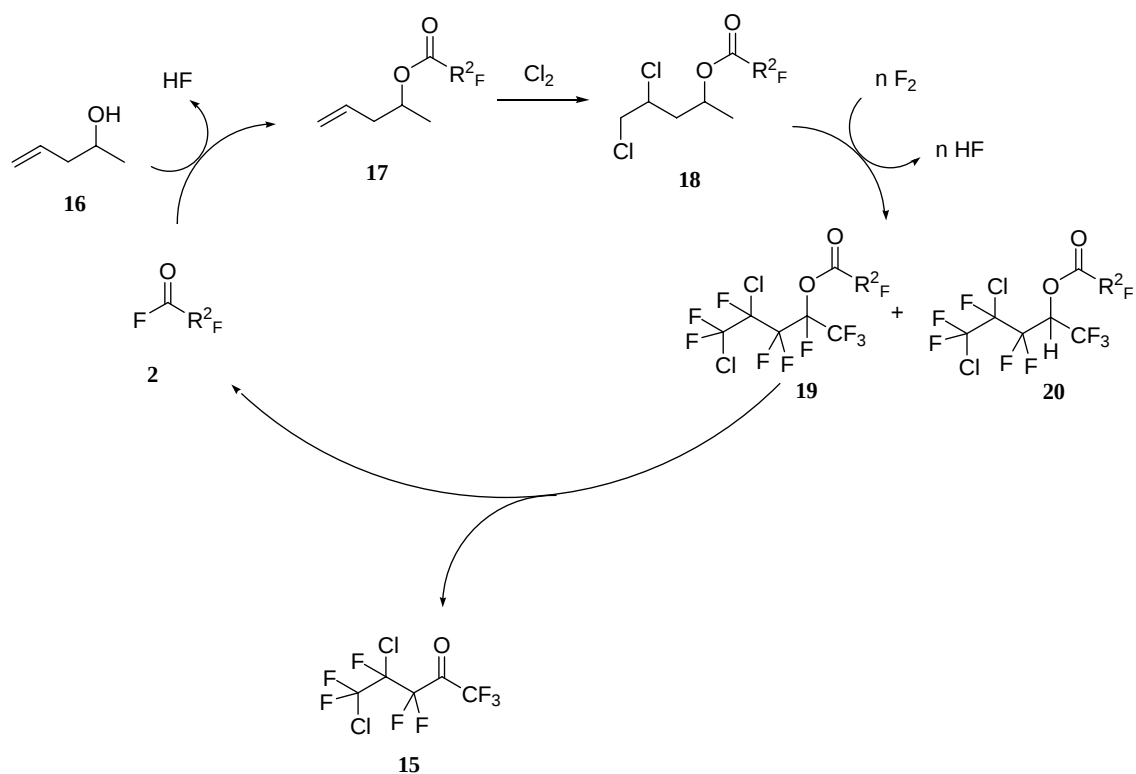
The PERFECT process was applied to synthesis of a ketone, component of a fluoropolymer resist for 157 nm microlithography.¹⁵

A key material is dichloropolyfluoropentanone **15**. Reaction of **15** with allyl Grignard reagent followed by dechlorination with zinc was considered to give the requisite monomer, as shown in the retrosynthetic analysis (Scheme 4).



Scheme 4. Retrosynthetic analysis of fluoropolymer resists

The structure of target ketone **15** has vicinal dichlorinated structure. Thus, 4-penten-2-ol (**16**), was chosen as the starting material. **16** was esterified with perfluoroacyl fluoride **2a**, and the resulting ester was chlorinated with chlorine before fluorination (Scheme 5).



Scheme 5. The PERFECT process for synthesis of fluoropolymer resists

Direct fluorination of **18** was carried out at first with 20% F₂/N₂ in R113 to afford **19** in 44% yield. Partially unreacted compound **20** remained again, and considerable amounts of by-products arising from Cl-atom migration formed.

As was the case of HFA synthesis, the reaction with 50% F₂/N₂ in perfluoroacyl fluoride **2b** as the solvent was carried out. Although C-H remaining compound **20** almost disappeared and yield was improved, the Cl-migrated products still existed. By-product **20** was removed after dechlorination in monomer synthesis.

The final thermal fragmentation was carried out as usual in the presence of potassium fluoride to give desired ketone **15** in 85% yield.

VI-3. Conclusions

Perfluoro ketones were synthesized by the PERFECT process from the corresponding nonfluorinated secondary alcohols through direct fluorination with elemental fluorine as a key step. Industrially useful HFA and perfluoro ketone **15** for a fluoropolymer resist were synthesized.

The PERFECT methodology is characterized by the following features: (1) It does not require iodine, oleum or other hazardous reagents. (2) It does not require solvent other than the starting perfluoroacyl fluoride. (3) HF, which can be electrolyzed to F_2 and H_2 , is essentially the only by-product in the PERFECT cycle. Therefore, the PERFECT process is considered to be an industrially suitable process.

VI-4. Experimental

Typical Procedures

Preparation of isopropyl perfluoro(2-propoxypropanoate) (11a). While bubbling nitrogen gas to a stirred 2-propanol (7.00 g, 116 mmol) was added perfluoroacyl fluoride **2a** (45.5 g, 137 mmol) dropwise at 25 to 30 °C over a period of 0.5 h. The mixture was stirred for 1 h at room temperature and quenched with a saturated aqueous solution of sodium hydrogencarbonate (50 mL) below 15 °C. The mixture was washed twice with water (50 mL), dried over magnesium sulfate and then filtered to give a crude oil. Distillation at 67 – 68 °C/10.7 kPa gave partially-fluorinated ester **11a** (24.9 g, GC purity: 99%, 58% yield). ¹H-NMR (399.0 MHz, CDCl₃) δ: 1.33 (d, *J* = 6.0 Hz, 6H), 5.17 to 5.29 (m, 1H). ¹⁹F-NMR (376.0 MHz, CDCl₃) δ: -79.6 (1F), -81.4 (3F), -82.3 (3F), -86.5 (1F), -129.6 (2F), -131.6 (1F). HRMS (CI⁺) *m/z* 373.0290 [M+H]⁺. Calcd for C₉H₈F₁₁O₃: 373.0298.

Preparation of isopropyl perfluoro[2-(2-propoxypropoxy)propanoate] (11b). A reaction was carried out in the same manner as the preparation of **11a** except that **2a** was changed to **2b** (61.0 g, 122 mmol). The reaction mixture was washed twice with water (50 mL), dried over magnesium sulfate and then filtered to obtain **11b** (64.0 g, GC purity: 98%, 100 % yield). ¹H-NMR (399.0 MHz, CDCl₃) δ: 1.23 to 1.29 (m, 6H), 5.15 to 5.27 (m, 1H). ¹⁹F-NMR (376.0 MHz, CDCl₃) δ: -79.1 to -80.5 (4F), -81.8 (3F), -82.1 (2F), -82.7 (3F), -84.8 to -85.6 (1F), -130.1 (2F), -132.0 (1F), -145.6 (1F). HRMS (CI⁺) *m/z* 539.0156 [M+H]⁺. Calculated for C₁₂H₈F₁₇O₄: 539.0156.

Synthesis of perfluoro(isopropyl 2-propoxypropanoate) (12a). In a 500 mL autoclave made of nickel, R113 (312 g) was placed and stirred at 25 °C. At the gas outlet of the autoclave, a cooler maintained at -15 °C was installed. After supplying nitrogen gas for 1 h, 20% F₂/N₂ was supplied for 1 h at a flow rate of 6.17 L/h, and the internal pressure of the reactor was maintained at 0.15 MPa. While maintaining the internal pressure of the reactor at 0.15 MPa and supplying 20% F₂/N₂ at the same flow rate, a solution of compound **11a** (4.99 g, 13.4 mmol) in R113 (100 g) was injected over a period of 5.3 h and then a solution of benzene in R113 (0.01 g/mL, 9 mL) was injected while raising the temperature from 25 to 40 °C, and 20% F₂/N₂ was supplied at the same flow rate for 0.5 h. Then the above benzene solution (6 mL) was injected, and 20% F₂/N₂ was supplied at the same flow rate for 0.5 h. The same operation was repeated again, and then nitrogen gas was supplied for 3 h to remove all volatile materials.

Yield of perfluorinated ester **12a** determined by ¹⁹F-NMR was 48%, and partially unreacted compound **13a** was 19%. Product **12a** decomposed on attempted silica gel column chromatography and partly decomposed even during distillation.

12a: ¹⁹F-NMR(376.0 MHz, CDCl₃) δ: -79.4 (3F), -79.6 (3F), -79.9 (1F), -82.1 (3F), -82.2 (3F), -87.7 (1F), -130.4 (2F), -132.1 (1F), -143.4 (1F). HRMS (EI⁺) *m/z* 478.9582 [M-F]⁺. Calcd for C₉F₁₇O₃: 478.9576.

13a: ¹H-NMR(399.0 MHz, CDCl₃) δ: 5.80 (m, 1H) ¹⁹F-NMR(376.0 MHz, CDCl₃) δ: -74.0 (3F), -74.1 (3F), -79.9 (1F), -82.3 (3F), -82.5 (3F), -87.7 (1F), -130.4 (2F), -132.6 (1F).

Synthesis of perfluoro[isopropyl 2-(2-propoxypropoxy)propanoate] (12b). The direct fluorination was carried out in a manner similar to the procedure for the direct

fluorination of **12a**, with a 42.0 L/h flow rate of 50% F₂/N₂, and a 24h feed time of solution of **11b** (2.88 kg, 5.36 mol) in **2b** (2.53 kg). The crude perfluoroester **12b** was obtained (4.19 kg) and the desired product was assayed by ¹⁹F-NMR (internal standard: C₆F₆). Yield of **12b** was estimated to be 94%. Product **12b** was found to decompose on silica gel column and partly decompose even in a distillation process. Thus, the crude product was directly used for the next step. ¹⁹F-NMR (376.0 MHz, CDCl₃) δ: -78.5 to -80.0 (7F), -80.7 (3F), -81.9 to -82.8 (8F), -84.8 to -86.3 (1F), -130.2 (2F), -132.2 (1F), -143.1 (1F), -145.4 (1F). HRMS (EI⁺) *m/z* 644.9422 [M-F]⁺. Calculated for C₁₂F₂₃O₄: 644.9429.

Synthesis of hexafluoroacetone (HFA) (14). An Inconel column (inner diameter: 14 mm, length 1 m) was packed with potassium fluoride (10-20 mesh, 50 g) and placed in a salt bath, and the internal temperature of the salt bath was adjusted to 200 °C. To this reactor, an 8:2 mixture of **12b** and **13b** obtained above was fed over 2 h at a rate of 60 g/h by means of a metering pump. At the outlet of the reactor, a reflux condenser adjusted at -20 °C was installed, and the mixture was separated into a gaseous sample and a liquid sample. The gaseous sample (23.2 g) was collected in a collecting container made of a fluorocarbon resin, and the liquid sample (95.8 g) was recovered in a glass trap. The gaseous sample was analyzed by GC-MS, and found to be HFA (yield from **12b** was 97%). From the liquid sample, **2b** (69.5 g) was recovered by distillation.

Preparation of 4,5-dichloropentan-2-yl perfluoro(2-propoxypropanoate) (18). To 4-penten-2-ol (**16**, 13.1 kg, 152 mol), to which nitrogen gas was bubbled, **2a** (54.3 kg, 164 mol) was added over 5 h, while maintaining the internal temperature at from 25 to

30 °C. After the addition was completed, the reaction mixture was stirred for 70 h at 30 to 50 °C under nitrogen gas bubbling. The obtained crude oil (58.3 kg) was confirmed to be **17**, which was used for the next step without purification. The purity by GC was 97%. ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.32 (d, *J* = 6.0 Hz, 3H), 2.30 to 2.50 (m, 2H), 5.07 to 5.21 (m, 3H), 5.61 to 5.76 (m, 1H). ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: -79.6 (1F), -81.3 (3F), -82.0 (3F), -86.3 (1F), -129.4 (2F), -131.5 (1F).

Into a 5 L flask equipped with a reflux condenser adjusted at 20°C, **17** (5.00 kg, 12.6 mol) obtained above was charged, and the reactor was cooled to -30 °C. Then, chlorine gas was continuously bubbled into **17** while maintaining the internal temperature at below 10 °C. When no more heat generation was observed, the reactor was warmed to room temperature and nitrogen gas bubbling was continued for 24 h to obtain a crude oil (5.90 kg). The compound **18** was found to have formed in 95% yield by GC analysis. ¹H-NMR (300.4 MHz, CDCl₃) δ: 1.42 (d, *J* = 6.3 Hz, 3H), 1.86 to 2.51 (m, 2H), 3.52 to 3.84 (m, 2H), 3.97 to 4.09 (m, 1H), 5.34 to 5.59 (m, 1H). ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: -80.4 (1F), -81.9 (3F), -82.5 (3F), -86.7 (1F), -130.2 (2F), -132.3 (1F). HRMS (Cl⁺) *m/z* 448.9772 [M-F]⁺. Calcd for C₁₁H₉³⁵Cl₂F₁₀O₃: 448.9769.

Synthesis of 4,5-dichloro-1,1,1,2,3,3,4,5,5-nonafluoropentan-2-yl perfluoro(2-propoxypropanoate) (19). Into a 3 L autoclave made of nickel and having an external circulation tubular type reactor, **2b** (2.51 kg) was circulated and stirred at 25 °C. At the gas outlet of the autoclave, a cooler maintained at -10 °C was installed. After supplying nitrogen gas for 2 h, 50% F₂/N₂ was supplied for 2 h at a flow rate of 64.4 L/h. While supplying 50% F₂/N₂ at the same flow rate, **18** (1.20 kg, 2.56 mol) was injected over 24 h. The resulting crude oil (1.40 kg) was extracted from the reactor. The same operation

was repeated 9 times, then nitrogen gas was supplied for 2 h. The combined reaction mixture was concentrated to give a crude oil. The crude liquid (totally 2.09 kg) was put into an autoclave, circulated and stirred again at 40 °C. After supplying nitrogen gas for 2 h, 50% F₂/N₂ was supplied for 2 h at a flow rate of 142 L/h. Then, while supplying 50% F₂/N₂ at the same flow rate, **18** (1.20 kg, 2.56 mol) was injected over a period of 24 h, and then nitrogen gas was supplied for 2 h to give an oil (3.65 kg), which was shown to be **19** by NMR. Yield of **19** was estimated by GC and NMR analysis to be 83%. ¹⁹F-NMR (282.7 MHz, CDCl₃) δ: -63.1 to -65.0 (2F), -75.5 to -76.5 (3F), -79.0 to -80.5 (1F), -81.9 (3F), -82.1 (3F), -86.0 to -88.0 (1F), -110.0 to -115.5 (2F), -130.0 (2F), -130.5 to -133.5 (2F), -135.0 to -138.0 (1F). HRMS (CI⁺) *m/z* 610.8915 [M-F]⁺. Calcd for C₁₁³⁵Cl₂F₁₉O₃: 610.8921.

Synthesis of 4,5-dichloro-1,1,1,3,3,4,5,5-octafluoropentan-2-one (15).¹⁶ A mixture of crude dichloropolyfluoro ester **19** (24.8 g, 32.7 mmol) obtained above and potassium fluoride powder (1.2 g, 2.0 mmol) was heated at 130 °C for 2 h and at 140 °C for 1.5 h while stirring vigorously. After cooling and filtration, a liquid sample (21.7 g) was obtained and analyzed by GC-MS. Yield of **15** from **19** was 85% as assayed by GC.

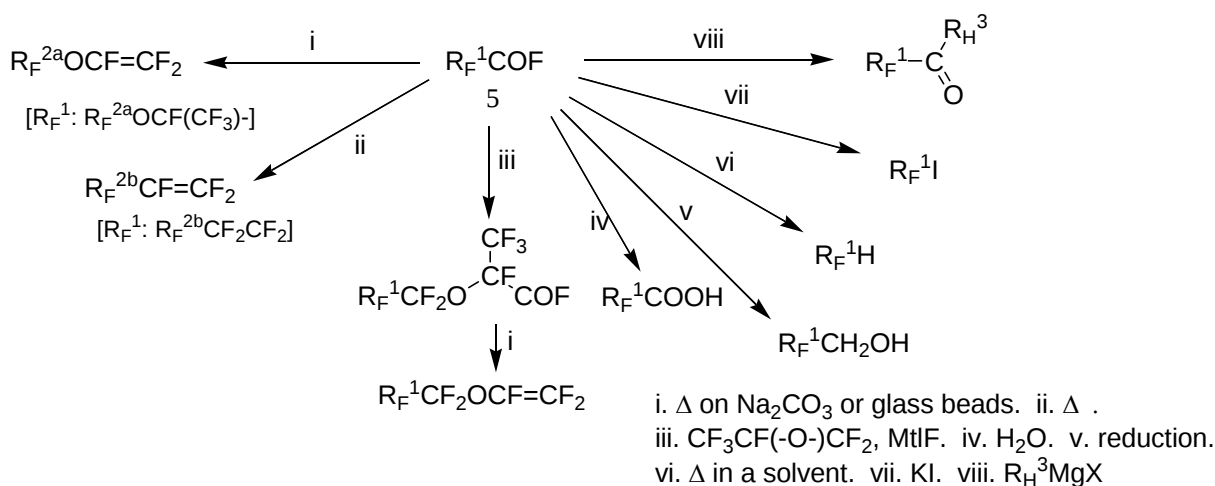
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Conclusions

In concluding this Thesis, the Author summarizes his contribution to organofluorine chemistry as follows: he has invented a new perfluorination method, the PERFECT process, for synthesis of various organofluorine compounds that serve as precursors of industrial materials and new fluorinated building blocks as summarized below.



The PERFECT process can provide with materials for leading-edge industries such as electronics, IT and energy industries with tailor-made functionalized materials. Because raw materials are inexpensive hydrocarbons, and the synthesis from hydrocarbon components makes it possible to create entirely new fluorinated compounds at will. Theoretically, by-product of the process is hydrogen only, because HF , which is formed in the process, can be converted electrochemically back to hydrogen and fluorine; fluorine can be used again in the process. Moreover, the

PERFECT process dose not use any solvent other than products or intermediates of the process. In that sense, it contributes to reduce environmental burden.

The PERFECT process has been further extended to synthesis of many other functionalized perfluoro materials by researchers in Research Center of Asahi Glass Co., Ltd. Some results are reported in literatures below:

Functional group transformation of perfluoroadamantane derivatives, K. Murata, S-Z. Wang, Y. Morizawa, K. Oharu, *J. Fluorine Chem.*, **127**, 1125-1129 (2006).

Synthesis and polymerization of a novel perfluorinated monomer, E. Murotani, S. Saito, M. Sawaguchi, H. Yamamoto, Y. Nakajima, T. Miyajima, T. Okazoe, *J. Fluorine Chem.*, **128**, 1131-1136 (2007).

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