Preparation and Applications of Perfluoroalkoxides Bearing α-Fluorines

by

Benson Jacob Jelier

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Approval

Name: Benson Jacob Jelier
Degree: Doctor of Philosophy (Chemistry)
Title: Preparation and Applications of Perfluoroalkoxides Bearing α-Fluorines

Examiner Committee: Chair: Dr. Michael H. Eikerling
Professor

Dr. Daniel B. Leznoff
Senior Supervisor
Professor

Dr. Peter D. Wilson
Supervisor
Associate Professor

Dr. Steven Holdcroft
Supervisor
Professor

Dr. Chadron M. Friesen
Supervisor
Adjunct Faculty

Dr. Craig D. Montgomery
Supervisor
Adjunct Faculty

Dr. Tim Storr
Internal Examiner
Associate Professor

Dr. Jennifer A. Love
External Examiner
Associate Professor
Department of Chemistry
University of British Columbia

Date Defended: 27 April 2016
Abstract

Partially fluorinated ethers, known as hydrofluoroethers, have been introduced as *inert* replacements of chlorofluorocarbons and predominately find use as refrigerants and solvents. However, these materials are not inert as purported but readily methylate Group 15 nucleophiles. Not only are hydrofluoroethers reactive, when the reaction is performed under a moisture-free environment, the sole reaction products from the interaction of tertiary amines are quaternary ammonium perfluoroalkoxides bearing α-fluorines. This general route allows for the single-step synthesis of a highly under-represented organofluorine functional group from commercially available reagents negating the use of air-sensitive reagents, anhydrous fluorides, and often highly toxic, expensive precursors. Hence, 30 new perfluoroalkoxides have been prepared from a series of methoxy hydrofluoroethers from CH$_3$OCF$_3$ through to CH$_3$OCF$_4$F$_9$ including clinical inhalation anaesthetic methoxyflurane. The products were isolated in 9-99% yield with product conversions commensurate with increasing length of the fluorinated segment of the hydrofluoroether in the presence of sterically unhindered, nucleophilic tertiary amines. Thermal analysis of isolated tetramethylammonium perfluoro- propoxides and butoxides indicated stability to 150 °C before partially decomposing under vacuum at 180 °C to NMe$_3$ and CH$_3$F as evidenced by thermogravimetric analysis.

In two divergent studies, a series of experiments were devised to develop a functional group tolerant protocol for the trifluoromethoxylation of arenes, a current and largely unsolved synthetic problem. A wide range of strategies towards C$_\text{aryl}$–OCF$_3$ bond formation were attempted using the prepared tetraalkylammonium trifluoromethoxides including both metal and non-metal-mediated protocols. By considering traditional cross-coupling methods with state-of-the-art Ni$^{0}$-Ni$^{II}$, Pd$^{0}$-Pd$^{II}$, Cu$^{I}$-Cu$^{III}$, Ag$^{I}$-Ag$^{II}$, and Au$^{I}$-Au$^{III}$ manifolds, it was determined that β-fluorination of aryl precursors from the coordinated OCF$_3$ ligand outcompetes C–O bond formation at temperatures necessary for reductive elimination. The poor nucleophilicity, high moisture sensitivity, and propensity for β-fluoride elimination from $\text{OCF}_3$ precluded its use as a general synthetic building block for many metal-mediated cross-couplings.

In a second study, the efficacy of the ostensibly *fluoride-free* tetraalkylammonium perfluoroalkoxides were tested as initiators for the anionic ring-opening polymerization of
the perfluorooxirane monomer, hexafluoropropylene oxide (HFPO). While these perfluoroalkoxides did not outperform the industry optimized CsF/tetraglyme conditions, it was demonstrated that tetraalkylammonium perfluoroalkoxides can successfully ring-open HFPO, provide a direct study of the cation, and a means to measure chain transfer while providing oligomers with $DP_n = 1-3$. The inoperative chain transfer process is likely a multi-faceted problem involving physical properties of the polymerization process. For instance, the phase-transfer mechanism and solvent choice play a critical role in propagation of polymeric based perfluoroalkoxides. Initial synthetic efforts were undertaken to design oligio(HFPO) terminated ethylene glycol surfactants or soluble oligio(HPFO) hydrofluoroethers to overcome the need for polar organic solvents required to dissolve the ionic initiators.

Keywords: perfluoroalkoxides, trifluoromethoxylation, fluoropolymers, hexafluoropropylene oxide, organofluorine, refrigerants, anaesthetics
Dedication

To my family
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Benson Jacob Jelier
*Simon Fraser University*
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List of Abbreviations, Acronyms and Trivial Names

Å  angstrom (unit), 1x10^{-10} m
Ac  acetyl
Anhyd.  anhydrous
Ar  aryl
aq  aqueous
atm  atmosphere (unit of pressure, 1 atm = 760 mmHg)
ATR  attenuated total reflectance
b  broad
BAIB  bis(acetoxy)iodobenzene
B3LYP  Becke, three-parameter, Lee-Yang-Parr; hybrid functional
Bn  benzyl
Bu  butyl
bipy  2,2’-bipyridine
b.p.  boiling point
BPin  boron pinacol ester or *i.e.* 4,4,5,5-tetramethyl-1,3,2-dioxaborolane
BPO  benzoyl peroxide, or *i.e.* [C_6H_5C(O)]_2O_2
°C  degree Celsius
cal  calorie (unit), 1 cal = 4.184 J
calcd.  calculated
cat.  catalytic
CDCl_3  deuterated chloroform
CD_3CN  deuterated acetonitrile
CFC  chlorofluorocarbon
conc.  concentrated
Cy  cyclohexyl
δ  NMR chemical shift in ppm downfield of a standard
d  day, doublet
D  Debye, a unit of measurement for molecular dipoles (10^{-18} statC cm)
DABCO 1,4-diazabicyclo[2.2.2]octane
DAST diethylaminosulfur trifluoride
Demnum® PFPE polymers of 2,2,3,3-tetrafluoro-oxetane (Daikin Inc., Japan)
Deoxofluor® \( \text{bis}(2\text{-methoxyethyl})\text{aminosulfur trifluoride} \)
DCM dichloromethane, \( \text{CH}_2\text{Cl}_2 \)
DCE 1,2-dichloroethane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT density functional theory
DMF \( N,N\)-dimethylformamide
\( DP_n \) degree of polymerization
\( \overline{DP}_n \) average degree of polymerization
dppf \( 1,1'\text{-bis}(\text{diphenylphosphino})\text{ferrocene} \)
equiv equivalent
ESI electron spray ionization
et al. and others
EtOAc ethyl acetate
Fomblin® perfluoropolyether of TFE or HFP from Solvay Specialty Products (Milan, Italy)
Freon 113 1,1,2-Trichloro-1,2,2-trifluoroethane (CFC-113)
F−TEDA 1-(chloromethyl)-4-fluoro-1,4-diaziabicyclo[2.2.2]octane
g gram(s)
h hours(s)
HCFC hydrochlorofluorocarbon
HFE hydrofluoroether
HFE-7000 3M Co. tradename for \( \text{CH}_3\text{OC}_3\text{F}_7 \)
HFE-7100 3M Co. tradename for \( \text{CH}_3\text{OC}_4\text{F}_9 \)
HFP hexafluoropropylene, \( \text{CF}_2=\text{CFCF}_3 \)
HFPO hexafluoropropylene oxide
HFX 1,3-hexafluoroxylene \textit{i.e.} 1,3-\textit{bis} (trifluoromethyl)benzene
H\(_2\)O water
HOMO highest occupied molecular orbital
HRMS high resolution mass spectrometry
Hz Hertz
iPr isopropyl
IR infrared
\( J \) scalar coupling constant
\( J \) Joule (unit)
Krytox® tradename for poly(HFPO) (Chemours Company)
L liter

xxxi
LA Lewis acid
LCP ligand close-packing model
LiHMDS lithium bis(trimethylsilyl)amide
LUMO lowest unoccupied molecular orbital
3M Minnesota Mining and Manufacturing Company
m multiplet
mCPBA meta-chloroperoxybenzoic acid
MALDI-TOF MS matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
Me methyl
MeCN acetonitrile
MeOH methanol
Ms mesyl or i.e. methanesulfonyl, CH₃SO₂-
Me₃pyF 1-fluoro-2,4,6-trimethylpyridinium
Mₙ number-average molecular weight
Mₘ weight-average molecular weight
min minute(s)
mmHg millimetre of mercury, unit of pressure
mol mole (unit) or molecular
mol% mole percentage
m/z mass to charge ratio
n number of equivalents or normal i.e. straight-chain
NFSI N-fluorobenzenesulfonimide
NHC N-heterocyclic carbene
NMR nuclear magnetic resonance
NPT National Pipe Thread taper
n.r. no reaction (observed)
OAc acetate
OCF₃ trifluoromethoxide
O.N. oxidation number
oligomer a "few" monomer units
PDI polydispersity index: a measure of the distribution of molecular mass
Penthrane® methoxyflurane, an inhalation anaesthetic from Abbott Laboratories
PFPE perfluoropolyether
Ph phenyl
phen 1,10-phenanthroline
Phenofluor® a bench-stable deoxyfluorination reagent from Scifluor Life Sciences
pin pinacol
pm picometre, 1x10⁻¹² m
Chapter 1

Introduction

1.1 Importance of Modern Fluorine Chemistry

1.1.1 Introduction

Historically, few chemists specialized in the manipulation of fluorine and fluorinated molecules.\[^1^,^2^\] Those that did were carefully trained in handling extremely hazardous gases and often-explosive compounds\[^1^,^3^-^6^\] However, it was the extreme properties of $\text{F}_2$ that led to spectacular developments in the understanding of chemistry at a fundamental level including the nature of chemical bonds and how they form.\[^1^\] For example, the isolation of this reactive element alone, was sufficient for H. Moissan to win the 1906 Nobel Prize\[^7^-^9^\] while experiments by N. Bartlett in 1962 at University of British Columbia prove the revolutionary concept that noble gases are not inert.\[^10^\] The serendipitous polymerization of tetrafluoroethylene (Teflon\(^\circledR\)) by R. Plunkett while at DuPont not only expanded the polymer and material chemistry fields but enabled safe handling of uranium hexaflouride, a pivotal historical development in nuclear chemistry.\[^1^\] As a fluorine chemist, R. Gillespie (McMaster University) developed the Valence-Shell Electron Pair Repulsion model currently taught as an introductory explanation for the predictive geometry of molecules.\[^11^-^13^\] Through experimentation with fluorine and superacids at Dow Chemical (Sarnia, Ontario), G. Olah was awarded the 1994 Nobel Prize for his pioneering work on the reactivity of carbocations.\[^14^-^16^\] Furthermore, to the great interest of inorganic chemists, the highest and most unusual oxidation states of transition metal elements are typically generated by elemental fluorine.\[^17^,^18^\]

Due to the destructive and indiscriminate nature of fluorine on organic molecules by direct fluorination, an on-going effort to tame the activity of fluorine by means of simple, bench-stable reagents have made handling this element significantly safer, even for the non-fluorine minded chemist.\[^1^,^2^,^19^\] Consequently, fluorine chemistry has become a very important area of research. In the past decade, synthetic methodology for the \textit{tactical}

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\[^1^\]References begin on page 15
placement of fluorine into organic structures has become highly prominent, evidenced by
the sheer number of high impacting publications.\textsuperscript{[19–24]} Through new reagents, the special
effects of fluorine have been exploited extensively in drug design including \([^{18}\text{F}]\text{fluoride}
radionuclides while also advancing fundamental theories and mechanisms.\textsuperscript{[1,23–25]}

### 1.1.2 Properties of the Fluorine Atom

Fluorine is unique in that it is possible to substitute hydrogen for fluorine in organic
compounds to the extent of the original hydrocarbon being fully fluorinated (commonly re-
tered to as perfluorinated) while not substantially destabilizing the parent molecule.\textsuperscript{[1,2,19,26]} However, the introduction of one or more fluorine atoms into an organic molecule can significantly change molecular conformation and electronics in comparison to its non-fluorinated
parent compound.\textsuperscript{[2,6,26]} Firstly, fluorine is the most electronegative element in the periodic
table (3.98 on the Pauling electronegativity scale compared to 2.20 for H, 3.44 for O, and
2.55 for C) due to its high effective nuclear charge ($Z_{\text{eff}}$).\textsuperscript{[1]} As a result, the electrons of the
fluorine atom are pulled toward the centre of the atom resulting in one of the smallest atomic
radii (van der Waals radius of 147 pm; 120 pm for hydrogen)\textsuperscript{[1,19]} while presenting only minimal steric demands on the parent compound. Furthermore, the high electronegativity of fluorine results in a highly polarized C–F bond which provides a strong dipole moment ($\mu_{\text{C–F}} = 1.41$ D).\textsuperscript{[19]} The large positive charge of the nucleus and the absence of shielding also lowers the valence orbital energy levels (HOMO & LUMO) of a fluorocarbon compared
to an analogous hydrocarbon.\textsuperscript{[6]} Importantly, lowering the orbital’s energy results in higher
bond energy and hence C–F bonds (484 kJ mol$^{-1}$) are typically stronger than C–C (347 kJ
mol$^{-1}$) and C–H (410 kJ mol$^{-1}$) bonds.\textsuperscript{[19]}

### 1.2 Introduction of the Perfluoroalkoxy Moiety

Beyond replacing a single hydrogen atom for a fluorine atom,\textsuperscript{[26–28]} researchers in the past
decade have focused on the introduction of nearly every fluorinated functional group into
organic frameworks. However, the introduction of fully fluorinated alkoxides (perfluoro–) have
been in high demand but synthetic strategies toward this goal have been highly elusive. For
instance, the perfluoroalkoxy moiety can impart a range of desirable properties including high
metabolic stability, increased lipophilicity, and a degree of thermal and chemical stability that
is unprecedented with other functional groups.\textsuperscript{[6,19,25,29–34]} Furthermore, perfluoroalkoxides
have been demonstrated to act as inductively electron withdrawing ancillary ligands in the
design of olefin metathesis catalysts,\textsuperscript{[35–39]} have been proposed as a precursor to solvents for
metal/air batteries,\textsuperscript{[40–43]} and are the active, but not well studied, species in the anionic
ring-opening polymerization of commercially available perfluoropolyethers.\textsuperscript{[44–46]} While the
number of strategies for the late stage incorporation of fluorine,\textsuperscript{[29,47–50] perfluoroalkyl,\textsuperscript{[51–53]}
and perfluorothiolate\textsuperscript{[54–63]} moieties continues to increase, the perfluoroalkoxylation of
aliphatic and aryl substrates has been hindered in part by the lack of a convenient, fluoride-free preparation of thermally stable perfluoroalkoxides.

1.3 Preparation of Perfluoroalkoxides

Unlike their hydrocarbon analogues, perfluoroalkoxides with α-fluorines can not be derived from the corresponding perfluoroalcohols and therefore have been difficult to prepare and isolate.\[64,65\] Perfluoroalcohols are thermodynamically unstable since the elimination of HF affords the corresponding acyl fluoride even at very low temperatures (Scheme 1.1).\[66–69\]

**Scheme 1.1.** Elimination of Fluoride from α-Fluorinated Alcohols and Alkoxides

![Scheme 1.1](image)

Rather, perfluoroalkoxides have been accessed through the formation of adducts between alkali metal (K\(^+\), Rb\(^+\), Cs\(^+\)) fluorides and perfluorinated carbonyl derivatives as first reported by Willis and Redwood more than 50 years ago (Scheme 1.2).\[70–72\] However, these products can readily revert back to their starting point with elimination of an alkali metal fluoride and hence have limited synthetic utility beyond ring opening of perfluoro-epoxides.\[44–46\]

**Scheme 1.2.** Preparation of Perfluoroalkoxides by the Introduction of Anhydrous Fluoride to a Perfluoroacyl Precursor (top) or Trifluoromethyl Triflate (bottom) Although Limited to the Preparation of \(-\text{OCF}_3\)

![Scheme 1.2](image)

However, the presence of a non-metal cation tends to shift the equilibrium to the perfluoroalkoxide and improve the synthetic utility significantly.\[73–76\] The first structurally
characterized non-metal perfluoroalkoxide, \( \text{tris} \text{(dimethylamino)} \text{sulfonium} \ (\text{TAS}^+) \) trifluoromethoxide, was prepared by Farnham and Middleton.\(^{[75,76]} \) More recently, four additional examples were reported between the reaction of an anhydrous fluoride ion and the corresponding perfluorocarbonyl or trifluoromethyl trifluoromethanesulfonates (\text{SCHEME 1.3}).\(^{[31,66,73,74,77–79]} \) Particularly noteworthy is the preparation of the only two isolated transition metal complexes bearing a trifluoromethoxide moiety by Vicic \textit{et al.}\(^{[80,81]} \) However, the high cost, toxicity of low molecular weight carbonyl fluorides, air-sensitivity of the required reagents, the need for an anhydrous fluoride source, the difficulty of having a fluoride free perfluoroalkoxide, as well as the often \textit{in situ} preparation of the perfluoroalkoxides, had severely limited synthetic applications to date.

\textit{Scheme 1.3.} A Timeline for the Preparation of Perfluoroalkoxides Bearing \( \alpha \)-Fluorines

1.4 Research Objectives and Thesis Overview

The goal of the research presented in this thesis is to explore a \textit{new synthetic methodology} for the preparation of non-metal perfluoroalkoxides in order to address two current unsolved problems; namely, preparation of perfluoroalkyl aryl ethers and initiators for the ring-opening polymerization of perfluorooxiranes. Rather than pursue new perfluoroacyl fluoride (or perfluorotriﬂates) as precursors which are inhibited by the need for a source of competing, anhydrous fluoride, we envisioned an alternative pathway to thermally-stable perfluoroalkoxides \textit{via} commercially available hydrofluoroethers. It was initially observed at DuPont that commercially available and "inert" hydrofluoroether solvents such as methoxy heptafluoropropane (\( \text{CH}_3\text{OC}_3\text{F}_7 \), HFE-7000) 3 and methoxy nonafluorobutane (\( \text{CH}_3\text{OC}_4\text{F}_9 \), HFE-7100) 4 could afford white, air-sensitive solids in the presence of tertiary amines under mild conditions. Although the identity of the reaction products were unknown, we speculated that this may be a valuable new route to tetraalkylammonium perfluoroalkoxides.
Herein, we review the role, preparation, and reactivity of hydrofluoroethers. Subsequently, in Chapter 2 we explore the preparation and full characterization of these reaction products from CH$_3$OC$_2$F$_5$ 2, CH$_3$OC$_3$F$_7$ 3 and CH$_3$OC$_4$F$_9$ 4. In Chapter 3, we successfully extend this preparation to the simplest perfluoroalkoxide, OCF$_3$ from commercially available refrigerant CH$_3$OCF$_3$, and survey an array of organometallic and organic strategies to incorporate this motif into functionalized arenes. In Chapter 4, we focus on polymer chemistry to use tetraalkylammonium perfluoroalkoxides to ring open hexafluoropropylene oxide with the goal of limiting the inoperative fluoride-mediated chain transfer process in the current commercial process of perfluoropolyethers: Krytox® (Chemours, previously DuPont) and Demnum® (Daikin, Japan). Lastly, in the final chapter general conclusions are made about the research described herein with a focus on new directions.

1.5 Hydrofluoroethers

1.5.1 Evolution of Heat Transfer Fluids

The development of chlorofluorocarbons (CFCs) at General Motors Research Corporation in the late 1920s by Midgley and Henne was a wonder of science. Their discoveries established both safety and durability over existing hazardous refrigerants like propane, ether and ammonia. Chlorofluorocarbons were deemed effective, non-toxic, inflammable, chemically compatible refrigerants that made storing perishable foods a household feature. In addition, they were ubiquitous blowing agents and excellent aerosol propellants. However, research in the 1970s that culminated in the 1995 Nobel prize for Molina and Rowland recognized the concerns over anthropogenic ozone layer depletion specifically caused by chlorofluorocarbons.

Fig. 1.1. Evolution of Heat Transfer Fluids
Unfortunately, CFCs are persistent chemicals that do not readily decompose in the lower troposphere but rather absorb UV light in the stratosphere. The ensuing photodissociation initiates a long-lasting catalytic radical degradation of ozone. This global problem brought about a phasing-out of CFCs as mandated by the 1987 Montreal Protocol and as a result a third generation of refrigerants consisting of hydrochlorofluorocarbons (HCFCs) began to emerge (Fig 1.1). The introduction of hydrogen into halogenated compounds can reduce the atmospheric lifetime of the compound via highly reactive atmospheric hydroxy radicals. However, due to the overall stability of HCFCs and the continued presence of chlorine (not fluorine!), these compounds continued to deplete the ozone layer and therefore more recent versions of the Montreal Protocol also call for the phasing out of HCFCs. In turn, the industry made incremental changes for chlorine-free replacements that have included perfluorocarbons (PFCs) and hydrofluorocarbons (HFCs). Perfluorocarbons and hydrofluorocarbons were considered an acceptable class of alternative compounds since they do not deplete the ozone and have a high thermal stability.

Unfortunately the high oxidation stability of both perfluorocarbons and hydrofluorocarbons leads to slow atmospheric degradation where they continue to be highly radiatively-active and contribute to global climate change by the greenhouse effect. The United Nations Framework Convention on Climate Change held in Kyoto in 1997 called for the complete phasing out of these materials. For instance, the most important commercial hydrofluorocarbon refrigerant still in use today, HFC-134a (CF$_3$CFH$_2$), has a global warming potential 1300 times that of CO$_2$. As of July 2, 2015, the US EPA ruled that HFC-134a must be completely discontinued by 2021. Since all halogenated compounds absorb infrared energy, the most effective approach is to design refrigerants that have shorter atmospheric lifetimes.

By introducing an ether linkage into HFCs, the resulting hydrofluoroethers (HFEs) tend to have lower global warming potentials and do not cause ozone depletion since they of course do not contain chlorine or bromine. By definition, HFEs contain at least one C-H bond and hence have shorter atmospheric lifetimes through hydrogen abstraction by hydroxyl radicals, which is the predominant loss mechanism for most atmospheric releases of HFEs. Empirical results demonstrated that if HFEs have a segregated hydrocarbon and perfluorocarbon moieties, there is a minimum in reducing atmospheric lifetimes. However, HFEs are still considered greenhouse gases and are currently more expensive to produce than other HFC alternatives leading to less commercial interest as refrigerants except in high value sectors. In 2011, Honeywell and DuPont have since commercialized a superior class of refrigerants based upon hydrofluoroolefins (HFO) which may prove to be the next generation of low global warming potential refrigerants. Nonetheless, HFEs are estimated to have an annual production over 4.5 million kilograms.
1.5.2 Widespread Utility of Hydrofluoroethers

In addition to their significant role as refrigerants, hydrofluoroethers display a combination of physical properties such as low surface tension, low flammability and low toxicity, which allow this class of compounds to find application in a wide range of commercial uses: as solvents in precision cleaning, fingerprinting, fire extinguishing agents, manufacturing of cosmetics and fragrances, detergents and lithium battery co-solvents. Indeed many inhalation anesthetics are variants of hydrofluoroethers (Fig. 1.2).

![Chemical structures of hydrofluoroethers](image)

**Fig. 1.2.** Examples of the most commonly used hydrofluoroethers of which methoxyflurane and hydrofluoroethers 1 – 4 are investigated herein.

Every published patent, report and research articles listed on Scifinder® for HFEs 1-4 was thematically categorized. As presented in Fig. 1.3, the majority of publications concern the use of HFEs as a refrigerant, non-flammable solvent, or some attempt to understand a fundamental thermodynamic property of HFEs. Typically as the molecular weight of the HFE increases, there is a transition from its use as a heat transfer fluid to a general solvent. For instance, while only 4% of references for CF₃OCH₃, b.p. –24 °C, concern its use as a solvent, nearly half of the references for C₄F₉OCH₃, b.p. 61 °C, concern its use as a non-flammable solvent. Like others, we have found that commercially available HFEs such as 3M’s methoxy heptafluoropropane (HFE-7000) 3 and methoxy nonafluorobutane (HFE-7100) 4 to be particularly good laboratory co-solvents for the manipulation of organofluorine compounds. These solvents are fluorophilic, miscible with a variety of common organic solvents and are mildly polar solvents. Overall this utility is underpinned by the chemical inertness of HFEs.

1.5.3 Preparation of Hydrofluoroethers

Since the term hydrofluoroether can broadly describe any hydrocarbon ether incorporating fluorine, the synthetic preparation of HFEs can vary from unselective direct fluorination with F₂ of a parent hydrocarbon ether to more sophisticated and selective fluorinations with
modern fluorination reagents (Scheme 1.4). However, asymmetric HFEs in which one segment is fully fluorinated and segregated from the hydrocarbon portion can not be prepared by direct fluorination since F₂ is unselective. Rather, asymmetric HFEs are typically prepared by alkylation of perfluoroalkoxides with dimethylsulfate or alkyl triflates. The perfluoroalkoxide is prepared in situ from the respective perfluoroacyl fluoride, ketone, or epoxide in the presence of an anhydrous alkali metal fluoride in a polar aprotic solvent. For instance, the commercially available HFEs 1-4 used in this thesis have been prepared by either Synquest Labs or 3M Corporation using this method (see Fig. 1.4). Since 3 and 4 are prepared on an industrial scale as part of 3M’s Fluorinert® Electronic Liquids family, the starting acyl fluorides are prepared by the Simmons electrochemical fluorination (ECF) of the hydrocarbon propanoic and butanoic acids. As a result of fragmentation, coupling and rearrangement during the electrochemical (radical) fluorination process, 4 is composed of a nearly equal mixture of n- and iso- nonafluorobutane isomers that cannot be separated by distillation and have nearly indistinguishable properties.

Beyond the alkylation of perfluoroalkoxides, several alternative specialized methods exist for the preparation of hydrofluoroethers (Scheme 1.4). For instance, Sekiya utilized the highly reactive methyl hypofluorite (CH₃OF) to afford methoxy hydrofluoroethers in 63-94% yield. However, due to the high reactivity of CF₃OF, the reactions are hazardous to
**Scheme 1.4. General Synthetic Strategies for the Preparation of Hydrofluoroethers**

**Direct Fluorination** (F₂) of an Ether

\[ \text{R}_1\text{R}_2\text{O} + \text{F}_2\text{N}_{2(p)} \xrightarrow{\text{HF}} \text{R}_1\text{F}\text{R}_2\text{O} \]

**Hydroalkoxylation of Perfluoroalkenes**

\[ \text{R}_1\text{F\text{R}_2} + \text{RO-H} \xrightarrow{\text{Method A: 45% KOH/H}^+} \text{R}_1\text{O}\text{R}_2\text{F} \]

**Oxidation of Perfluoroalkenes by Methyl Hypofluorite**

\[ \text{R}_1\text{F\text{R}_2} + \text{CH}_3\text{OF} \xrightarrow{\text{Method B: Pd}0/\text{L, CH}_3\text{CN}} \text{R}_1\text{OF}\text{R}_2\text{F} \]

**Fluorination of Thionoesters**

\[ \text{R}\text{SOCH}_3 \xrightarrow{\text{Deoxo-Fluor® xylene}} \text{R}\text{OC}\text{F}_7 \]

**[2+2] Acid Catalyzed Cycloaddition of Formaldehyde and TFE**

\[ \text{H}\text{H} \xrightarrow{\text{cat. HF}} \text{H}\text{H} \]

**Alkylation of in situ Perfluoroalkoxide**

\[ \text{R}_1\text{O}\text{R}_2\text{F} + \text{CH}_3\text{C}^+\text{H}_2\text{O} \xrightarrow{\text{1) O}^+\text{F}^-, Q = K, Cs}} \text{R}_1\text{F}\text{R}_2\text{O} \]

**carry out. Rather, the electrophilic nature of perfluoroolefins enable a facile ether synthesis via the nucleophilic addition of hydrocarbon alkoxides followed by an acidic workup. Since the β-fluorinated carbanion intermediate in this process can lead to formation of unsaturated vinyl ethers by β-fluoride elimination, Sekiya developed an alternative process to afford the same product using palladium(0) catalysis under neutral conditions at ambient temperature.**[114]

The cyclic HFE, 2,2,3,3-tetrafluoro-1-oxetane, is a monomer for the production of Denum® fluids, an important class of fluoropolymers used *inter alia* for coatings of electronic touch screens (Scheme 1.4). It is commercially prepared by the acid-catalyzed [2+2] cycloaddition of formaldehyde and tetrafluoroethylene by Daikin Industries (Japan) but the synthesis requires the use of difficult to handle tetrafluoroethylene and the product can be difficult to isolate. Lastly, specialized reagents such as DAST or Deoxofluor® enable nucleophilic fluorodesulfurization of thionoesters or xanthates to afford α,α-difluoro ethers (Scheme 1.4).

### 1.5.4 Reactivity of Hydrofluoroethers

Hydrofluoroethers are marketed as thermally stable and chemically compatible *inert* fluids – desirable properties for a solvent, refrigerant, or blowing agent. These materials are considered inert due to their highly fluorinated nature and hence have significantly higher thermal stability than their hydrocarbon analogues.[94] For instance, \( \text{CH}_3\text{OC}_3\text{F}_7 \) is thermally stable to 275 °C, does not form peroxides or does not have a flash point.[94] However, the high temperature stability of HFEs decreases as the amount of fluorine substituents decrease.[94]

Not only are alkyl HFEs reported to be unreactive,[94] the \( \text{OCF}_3 \) of trifluoromethoxy aryl ethers have also been reported by Aldrich and Sheppard to be "thermally and chemically resistant to attack by acids, bases, organometallic reagents and oxidizing/reducing agents."
Although hydrofluoroethers have been prepared as early as 1935,\cite{115,116} to the best of our knowledge there are no reports of reactivity with hydrofluoroethers 1-4. As the historical development of refrigerants illustrate, understanding the environmental implications of any industrial chemical is imperative prior to their widespread use particularly if it is an abundantly produced volatile organic compound that can leak out of consumer products. As a result, a large volume of well-established literature exists on the proposed gas-phase photochemistry and calculated global warming potentials of hydrofluoroethers.\cite{84,117,118} For instance, the generally agreed upon atmospheric oxidation process for HFE-7100 4 initially involves hydrogen abstraction from the methyl C–H by atmospheric hydroxy radicals to afford the peroxy radical C\(_4\)F\(_9\)OCH\(_2\)O\(_2\) and eventually affording COF\(_2\) and CO\(_2\) amongst other species.\cite{89,119,120} These atmospheric reactions occur under extremely low concentration and pressure with intense atmospheric radiation, not typical of laboratory conditions.

### 1.5.5 Precedent for Hydrofluoroethers as Methylating Agents

The first documented reactivity of hydrofluoroethers was presented by Knunyants in 1972 reported in Russian that a series of five perfluorovinyl methyl ethers (such as 5) alkylate trimethylamine or triethylamine (Scheme 1.5).\cite{121} The resulting tetraalkylammonium perfluoroenolates could be prepared in reasonable yields (31-87%) although in each case the starting materials were both impure and contained a mixture of isomers and only the most rudimentary of analysis was performed on the products.\cite{121}

**Scheme 1.5.** Alkylation of Tertiary Amines by Perfluorovinyl Alkyl Ethers Such As Vinyl Ether 5 by Knunyants in 1972

![Scheme 1.5](image)

Two derivative experiments were also conducted with MeI or anhydrous HCl with perfluoroenolate 6 as shown in Scheme 1.5. Similar to Krespan and England,\cite{122} Knunyants et al. found that the identical perfluoroalkoxides could also be prepared by the deprotonation of fluorinated ketones containing a \(\alpha\)-hydrogen, for example, \((\text{CF}_3)_2\text{CHCOCH(CF}_3)_2\).

Although much of 3M Company literature highlights the inert properties of HFEs, 3M inventor R. Flynn’s book chapter, *Fluorinated Ethers and Amines* (2000)\cite{123} states that
hydrofluoroethers can be more susceptible to chemical reagents than fully fluorinated ethers including *strong amine bases such as piperidine* with which “some of them may be reactive”. However, no further details are disclosed. Around the time we first presented this work, 3M Company published a report in *Magn. Reson. Chem.* that the cleaning agent, Novec 7100DL which is an azo trope composed of HFE-7100 4 and 4.5% isopropyl alcohol are very stable mixtures but have been found to react very slowly to afford HF, isopropyl methyl ether, and perfluoro-esters of isopropanol at a rate of 1 ppm/year at ambient conditions (Scheme 1.6).[124]

**Scheme 1.6.** The 3M Company Investigated the Reaction between CH$_3$OC$_4$F$_9$ 4 and Isopropanol, the Two Major Components in Their Commercial Cleaner HFE-7100DL, and Concluded That This Reaction Occurs at a Rate of 1 ppm/year

In 2000, Ishikawa reported the one-pot preparation of 3,3,3-trifluoro-2-(trifluoromethyl) propanoyl fluoride, a small fluorinated precursor for the synthesis of trifluoromethylated heterocyclic compounds (Scheme 1.7).[125] Dehydrofluorination followed by nucleophilic substitution on the methyl group of hydrofluoroether 7, afforded tetraalkylammonium perfluoroalkoxide 8, a perfluoro-enolate. This *in situ* perfluoroalkoxide was subsequently treated with anhydrous HCl to afford the final product 9 in a high conversion (91% against an internal standard by $^{19}$F NMR analysis) but in moderate isolated yield.[125] Uniquely, the fluorinated moiety of 7 is not fully fluorinated but includes an acidic β-hydrogen on the backbone on C(2). Dehydrofluorination most likely generates an *in situ* perfluorovinyl ether almost identical to 10 and 11 reported by Knunyants in 1972.[121] The ether (not shown) subsequently alkylates the second equivalent of triethylamine in what would be an overall two-step process.

**Scheme 1.7.** Dehydrofluorination of Hydrofluoroether 7 Followed by Nucleophilic Substitution of the Methyl Group by Triethylamine Afforded the In Situ Perfluoroalkoxide 8
In 2002, Blazejewski attempted a Knoevenagel condensation of ester 12 with benzaldehyde as a means to prepare trifluoromethoxyacrylate monomers (Scheme 1.8). Although ester 12 is structurally different and substantially less fluorinated than HFEs 1-4, ester 12 underwent nucleophilic substitution of the OCF₃ substituent by piperidine, affording the alkylated tertiary amine 13 as the major product (Scheme 1.8). The authors speculated that the OCF₃ decomposed under the reaction conditions to afford the carbonyl fluoride and generate the observed bis(pentamethylene)urea 14 with concurrent formation of HF. Rather than pursue this unintentional reactivity further, the authors modified their approach by using LiHMDS to afford the lithium enolate to successfully prepare the desired acrylates.

Scheme 1.8. Anecdotal Evidence by Blazejewski et al. for the Alkylation of Piperidine by Trifluoromethoxy Ester 12 in an Attempted Knoevenagel Condensation

In 2006, M. Gagné sought new methods for the neutralization of chemical warfare agents including mustard gas which can be expunged by nucleophilic absorbants. The mustard gas analogue, 2-chloroethylphenyl sulfide (CEPS) was dissolved in HFE-7100 and eluted through specially prepared monolithic polystyrene supported dialkylamino columns (Scheme 1.9). The authors state that HFE-7100 was chosen as an eluting solvent since it had a low dielectric permeability, it can increase the rate of reaction via the fluorophobic effect, and most importantly, it is purported to be chemically inert! However, the columns failed at neutralizing the warfare analogues which was traced to an incompatibility between HFE-7100 and the polyamines used to derivatize the column. The authors state that they were unable to determine the exact nature of the many products formed between HFE-7100 and the amines (the white precipitate and some soluble compounds). However, NMR analysis suggested that a range of polar polyfluoroalkylated amine-containing products were afforded. Although the product mixtures were not successfully characterized, the presence of these by-products and rate of production clearly coincided an incompatibility of the solvent attenuating the column’s propensity for simulant sorption.

In 2011, Grubbs and Cooke published a spectroscopic study on the methyl group internal rotation in HFE-7100. Of particular interest, the authors noted that that methoxy-based...
**Scheme 1.9.** Derivatized Polymer Columns Containing Amino Substituents for the Decontamination of Mustard Gas Simulant, 2-chloroethylphenyl sulfide (CEPS), Eluted with HFE-7100 Failed Due to an Concomitant Reaction with HFE-7100

hydrofluoroethers have extremely short C\textsubscript{fluorinated}–O ether bond in comparison to the C\textsubscript{hydrocarbon}–O (see **Table 1.1**). Their results support previous work by Allen and Kirby\cite{128} that the variable nature of the C–O single bond in ethers can be related to the pK\textsubscript{a}s of the alcohols comprising the ether. Since fluorinated alcohols have a highly electron withdrawing R group and hence low pKa, a considerable contribution of an ionic valence bond tautomer is imbued to the structure of the ether. Alternatively, Grubbs and Cooke described this as a negative hyperconjugation effect involving orbital interaction between the lone pair on the oxygen and the antibonding, \(\sigma^*\), orbital of the C–F bond(s).\cite{127} This is important to the work undertaken here in which the electronegative perfluoralkyl chain causes a tautomeric contribution to the structure of CH\textsubscript{3}+–OC\textsubscript{4}F\textsubscript{9}, resulting in a relatively long C\textsubscript{methyl}–O bond length and a remarkably short C\textsubscript{fluorinated}–O bond length.\cite{127} It is worthwhile noting that the fluorinated C–O bond length of 1.337 Å in both isomers of C\textsubscript{4}F\textsubscript{9}OC\textsubscript{3} are equal in length but apparently also the shortest reported C–O bond length in any ether.\cite{127} Typically, C–O single bonds are about 1.43 Å.\cite{127}

**Table 1.1:** Selected Bond Lengths and Angles for Fluorinated Ethers Where C\textsubscript{H} is a Hydrocarbon Fragment and C\textsubscript{F} is a Fluorinated Fragment (Adapted from Grubbs and Cooke)

<table>
<thead>
<tr>
<th>Ether</th>
<th>r(C\textsubscript{H}-O) /Å</th>
<th>r(C\textsubscript{F}-O) /Å</th>
<th>(\angle\text{COC})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF\textsubscript{3}OCH\textsubscript{3}</td>
<td>1.427</td>
<td>1.348</td>
<td>115.5</td>
</tr>
<tr>
<td>CH\textsubscript{3}OCH\textsubscript{3}</td>
<td>1.415</td>
<td>1.415</td>
<td>111.8</td>
</tr>
<tr>
<td>n–C\textsubscript{4}F\textsubscript{9}OCH\textsubscript{3}</td>
<td>1.436</td>
<td>1.337</td>
<td>115</td>
</tr>
<tr>
<td>(CF\textsubscript{3})\textsubscript{2}CFCFC\textsubscript{2}OCH\textsubscript{3}</td>
<td>1.439</td>
<td>1.337</td>
<td>115</td>
</tr>
</tbody>
</table>

### 1.6 Summary and Research Scope

Only after an extensive search of the literature over several years, were we able to find examples that provide precedent for the reactivity of hydrofluoroethers. Often obscured by language or recorded as anecdotal observations, we detail these references to demonstrate the results described in the following chapters are a continuation of earlier reports, provide
credit to those that previously proposed such reactivity, while highlighting how our results (vide infra) provide insight to previously noted observations.

The work presented in this thesis can thus be considered a series of hypotheses based on the observation that triethylamine in the presence of commercially-available hydrofluoroether CH$_3$OC$_4$F$_9$ (HFE-7100) unexpectedly formed a white, air-sensitive precipitate that etched glass reactors in the presence of water:

1. Are a class of compounds replacing fluorinated refrigerants inert as purported by industry?

2. What are the reaction products due to the interaction of amines with methyl hydrofluoroethers?

3. Can a functional-group tolerant protocol be developed for the trifluoromethoxylation of arenes?

4. Can we improve a commercial polymerization process of high temperature lubricants?

The work reported herein addresses each of these hypotheses in the progression from Chapter 2 to Chapter 4 provided the initial assessment that the hydrofluoroethers are methylating agents. Thus, in Chapter 2, the reactivity of hydrofluoroethers CH$_3$OC$_2$F$_5$, CH$_3$OC$_3$F$_7$, and CH$_3$OC$_4$F$_9$ with tertiary amines will be established with a clear emphasis on the level of difficulty of characterizing these materials due to the air-sensitivity (on a similar scale to Grignards). The preparation of the simplest congener, CH$_3$OCF$_3$ is reserved for Chapter 3 as the emphasis in this survey was to establish a methodology for trifluoromethoxylation rather than full characterization of the NMe$_4$OCF$_3$ and related salts. In the following chapter, the source of the chain transfer process in the polymerization of HFPO is probed through the use of the newly tetraalkylammonium perfluoroalkoxides and whether ring opening-polymerization can be carried out in an more efficient fashion. Finally, a global perspective and future work is summarized in the final chapter.
1.7 References


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Chapter 2

A Convenient Route to Perfluoroalkoxides from Hydrofluoroethers

2.1 Introduction$^{1,2}$

In this chapter, we explore our pivotal discovery that a class of commercial refrigerants known as hydrofluoroethers are alkylating agents. In particular, HFEs are capable of methyllating Group 15 nucleophiles under mild conditions. This is the first reported reactivity for a class of compounds that were typically known to be inert. Not only are hydrofluoroethers reactive, when the reaction is performed under a moisture-free environment, the sole reaction products are quaternary ammonium perfluoroalkoxides bearing α-fluorines. This general route allows for the single-step synthesis of a highly under-represented organofluorine functional group from commercially available reagents. Hence, we have prepared, isolated, and characterized 28 new perfluoroalkoxides from a series of methoxy hydrofluoroethers from CH$_3$OCF$_2$CF$_3$ 2 through to CH$_3$OC$_4$F$_9$ 4 including the inhalation anaesthetic, methoxyflu-rane (Penthrane®) and briefly explore the trends in thermal stability and chemical reactivity using standard synthetic techniques.

2.2 Discovery that Hydrofluoroethers are Methylation Agents

2.2.1 Reactivity of Hydrofluoroethers with Tertiary Amines

Despite their reported chemical inertness, we observed a noteworthy but expected degradation pathway for C$_2$F$_5$OCH$_3$ 2, C$_3$F$_7$OCH$_3$ 3, and C$_4$F$_9$OCH$_3$ 4 (scheme 2.1). Thus,

---

$^{1}$Portions of this chapter have been adapted from: Jelier, B. J.; Howell, J. L.; Montgomery, C. D.; Leznoff, D. B.; Friesen, C. M. Angew Chem Int. Edit., 2015, 54, 10, 2945-2949.

$^{2}$References begin on page 99.
methoxy hydrofluoroethers alkylate tertiary amines under mild conditions in moderate to
good yields, affording tetraalkylammonium perfluoroalkoxides. Not only is this the first doc-
umented reactivity of CH$_3$OC$_2$F$_5$ 2 to CH$_3$OC$_4$F$_9$ 4. this method can be used in a profound
way to prepare a class of perfluoroalkoxides with α-fluorines. This underrepresented func-
tional group has otherwise been historically very difficult to prepare and isolate (CHAPTER
1). Furthermore, a range of hydrofluoroethers and tertiary amines are commercially available
which may establish this method as the most general route to perfluoroalkoxides bearing
non-metal cations. A notable difference reported herein is that this synthetic strategy does
not require a source of anhydrous, nucleophilic fluoride anion. Anhydrous fluoride salts are
formidable to prepare and are more nucleophilic than the desired perfluorinated alkoxide and
often form very stable metal-fluoride bonds either shifting the equilibrium or inhibiting any
metal-mediated cross-couplings.[2–4] From a synthetic organic perspective, methoxy-HFEs
could be considered a masked or protected perfluoroacyl fluoride. Deprotection of the
fluorinated moiety can then be carried out under ambient conditions with the addition of a
tertiary amine.

To probe the scope of this reaction, we investigated the reactivity of 14 tertiary amines,
including trialkylamines, diamines and aromatic amines with hydrofluoroethers CH$_3$OC$_2$F$_5$
2 to CH$_3$OC$_4$F$_9$ 4 (TABLE 2.1). In most cases, the perfluoroalkoxide which is the only
detectable product precipitates out of the reagent mixture, affording a clean workup by
filtration or, if the amine is volatile, both reagents can be simply removed under reduced
pressure to afford multi-gram quantities of the desired perfluoroalkoxide adduct. If the
reaction mixture is not agitated, the two reagents are often biphasic and over a course of a few
hours or days, the product will crystallize out of solution forming colorless, thin, plate-like
crystals. The products are inherently moisture sensitive and require rigorously anhydrous
reagents, solvents, and a thoroughly moisture-free atmosphere (< 5 ppm). However, in our
hands, the products can be stored in oven-dried borosilicate vials for an extended period of
time at ambient temperature under a moisture-free atmosphere without noticeable etching
of glass or decomposition by NMR analysis.

**Scheme 2.1.** Methylation of Group 15 Nucleophiles by Hydrofluoroethers is a General Route to
Perfluoroalkoxides Bearing α-Fluorines

![Scheme 2.1](image-url)

<table>
<thead>
<tr>
<th>2, 3 and 4</th>
<th>3a–l, 4a–k and 15</th>
</tr>
</thead>
</table>

*Prior to our recent report, Scifinder® had no recorded reactions for CH$_3$OC$_2$F$_5$ to CH$_3$OC$_4$F$_9$. [1]*
Reactions with gases such as trimethylamine b.p. (4°C, 1 bar) and CF$_3$CF$_2$OCH$_3$ 2, (b.p. 5°C, 1 bar) required the use of careful trap-to-trap transfer techniques using specifically constructed and calibrated stainless-steel, Swagelok® vacuum manifolds (1) to exclude moisture, (2) to measure appropriate equivalents of reagents for yield considerations, and (3) to minimize loss of gaseous reagents. Each reaction was carried out in magnetically stirred, pressure rated glassware from Ace® Company rated to 150 psig at 150°C sealed with a modified PTFE Ace threaded stopper equipped with a 1/4 in. NPT valve, pressure gauge and quick-connect valve. Although all gas manipulations were typically performed in a fumehood behind a safety shield, the pressure upon warming to 50°C never exceed 40 psig, and in most cases was below 15 psig. Once complete, the volatiles were trapped on the vacuum manifold and then subsequently worked up in a similar fashion described above.

To gain a better understanding of the reactivity of hydrofluoroethers 3 and 4, the conversion of amine to tetraalkylammonium were measured at 25°C and 50°C (Table 2.1). After 48 hours, volatiles were removed under reduced pressure affording the isolated
product. Once complete, excess reagents were removed in vacuo and the perfluoroalkoxide was collected in a fine fritted disk in a glovebox and triturated with anhydrous hexanes and further dried in vacuo. The filtrate was analyzed by $^1$H and $^{19}$F NMR spectroscopy to ensure no loss of product. In the case of high boiling point amines that are not readily removed by vacuum, an aliquot of the mixture was dissolved in CD$_3$CN and the percent conversion was easily calculated by $^1$H NMR spectroscopy.

### 2.2.2 Establishing the Identity of the Reaction Product between HFEs and Tertiary Amines

Each of the 28 new perfluoroalkoxides reported herein was characterized by $^1$H, $^{19}$F NMR and IR spectroscopy, as well as elemental analysis. The characterization of [N(CH$_3$)$_3$(CH$_2$Ph)] [OC$_3$F$_7$] 3f, is described here as an example (scheme 2.2).

**Scheme 2.2.** Methylation of $N,N$-Dimethylbenzylamine by CH$_3$OC$_3$F$_7$ 3 Affords the Sole Product, $N,N,N$-Trimethylbenzylammonium Perfluoropropoxide, 3f

![Scheme 2.2](image)

The $^1$H NMR spectrum of 3f shows no evidence of the signal at 3.74 ppm assigned to CH$_3$ of the HFE starting material CH$_3$OC$_3$F$_7$ (Fig. 2.3). Instead, three signals appear: at 3.07 ppm (s, 9H), assigned to the three methyl groups of the [NMe$_3$Bn]$^+$ cation; at 4.54 ppm (s, 2H) assigned to the methylene protons and at 7.07-7.73 (m, 5H) due to the aromatic protons consistent with the proposed trimethylbenzylammonium cation (Fig. 2.3). The $^{19}$F NMR spectrum likewise displays three signals at -125.77 ppm (s, 2F), -81.99 ppm (s, 3F) and -27.81 ppm (br s, 2F) (Fig. 2.3). These are assigned to the $^{19}$F nuclei of the $\beta$-CF$_2$, the CF$_3$ and the $\alpha$-CF$_2$ units respectively. The broadness and chemical shift of the $\alpha$-CF$_2$ is consistent with analogous perfluoroalkoxides (vide infra).

Gratifyingly, the X-ray crystal structure of 3f was determined and clearly depicts a methylated $N,N$-dimethylbenzylamine with a perfluoropropoxide anion (Fig. 2.4). Since the oxygen atom is isoelectronic with the adjacent fluorines in an otherwise symmetrical anion, it was not immediate obvious which atom should be assigned as the oxygen. Thus the identity was checked using the same method as Seppelt, namely exchanging the atom with one of the fluorine atoms bound to the same carbon atom.$^6$ The exchange resulted in higher R-values, less uniform vibrational parameters, and less realistic bond lengths in all other permutations. This structure is the seventh overall perfluoroalkoxide structure and the first structurally characterized $n$-perfluoropropoxide. The resulting bond lengths are
Table 2.1: Reactivity of Methoxy Hydrofluoroethers with Tertiary Amines.

<table>
<thead>
<tr>
<th>Cation</th>
<th>(-\text{OC}_2\text{F}_5) (%)</th>
<th>(-\text{OC}_3\text{F}_7) (%)</th>
<th>(-\text{OC}_4\text{F}_9) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(isol.)\textsuperscript{[a]}</td>
<td>25 °C</td>
<td>50 °C</td>
</tr>
<tr>
<td>2a</td>
<td>92 (96)</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>2b</td>
<td>–</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>2c</td>
<td>–</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>2d</td>
<td>–</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>2e</td>
<td>–</td>
<td>n.r.</td>
<td>39</td>
</tr>
<tr>
<td>2f</td>
<td>51 (95)</td>
<td>35</td>
<td>86</td>
</tr>
<tr>
<td>2g</td>
<td>–</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>2h</td>
<td>89 (99)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2i</td>
<td>92 (98)</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>2j</td>
<td>57 (93)</td>
<td>33</td>
<td>97</td>
</tr>
<tr>
<td>2k</td>
<td>85 (76)</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>2l</td>
<td>–</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>2m</td>
<td>–</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>2n</td>
<td>–</td>
<td>34</td>
<td>51</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Yields refer to the isolated material of > 98% purity after optimization. See Experimental for conditions.  
\textsuperscript{[b]} Yield determined either by gravimetric analysis or by \textsuperscript{1}H NMR spectroscopy after 48 h at the specified temperature.  
\textsuperscript{[c]} n.r. = no reaction.
consistent with the other six known perfluoroalkoxide structures, including a significantly short C–O bond (here 128.3 pm) and a elongated α-C–F bonds (Table 2.2 & 2.5).

2.2.3 Conversions and Reactivity of Tertiary Amines with Hydrofluoroethers

A number of trends are observed in the percentage conversion data given in Table 2.1. First, as expected, as the steric bulk of the amines increases, the reactivity decreases, as do the yields. For example in the case of trimethyl-, triethyl- and tripropylamines, the percentage yield decreases in accordance with the steric bulk of the amine substituents (N(CH₃)₃ > N(CH₂CH₃)₃ > N(CH₂CH₂CH₃)₃). The high steric bulk of N,N-diisopropylethylamine shut down the reaction completely no alkylation of the amine was observed. Under the conditions reported here, N,N-dimethylaniline is not methylated. In example 3n and 4n, the heterocyclic amine is methylated but not the dimethylaniline moiety. As a result, one would expect pyridine to be methylated; however we have been unable to cleanly isolate the methylated product as of yet.

Examining the effect of the perfluoroalkyl portion of the HFE upon the percent yield, the yields are greater in the case of the perfluorobutoxides than those of the perfluoro...
**Fig. 2.4.** X-ray structure of [Me₃NBn]OC₃F₇ 3f with thermal ellipsoids at the 30% probability level (P21/c, 150 K, R = 7.11%). A complete table of crystallographic data can be found in the Experimental description (Section 2.10).

**Table 2.2:** C–O and C–F Bond Lengths of All Structurally Characterized Perfluoroalkoxides Bearing α-Fluorines Using CCDC’s Conquest Database Search

<table>
<thead>
<tr>
<th>Cation</th>
<th>Anion</th>
<th>C–O (pm)</th>
<th>F (pm)</th>
<th>Database</th>
<th>Reference[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAS⁺</td>
<td>OCF₃</td>
<td>122.8</td>
<td>138.9</td>
<td>138.9</td>
<td>Farnham</td>
</tr>
<tr>
<td>Cs⁺</td>
<td>OCF₃</td>
<td>130.6</td>
<td>135.1</td>
<td>135.2</td>
<td>Jansen</td>
</tr>
<tr>
<td>Os</td>
<td>OCF₃</td>
<td>127.7</td>
<td>139.8</td>
<td>145.6</td>
<td>LAVKUP</td>
</tr>
<tr>
<td>pip⁺[b]</td>
<td>OCF₂CF₃</td>
<td>123.0</td>
<td>140.2</td>
<td>144.7</td>
<td>Seppelt</td>
</tr>
<tr>
<td>NMe₄⁺</td>
<td>OCF₂COF</td>
<td>122.0</td>
<td>141.3</td>
<td>148.0</td>
<td>Seppelt</td>
</tr>
<tr>
<td>pip⁺[b]</td>
<td>OCF(CF₃)₂</td>
<td>134.3</td>
<td>141.6</td>
<td></td>
<td>Seppelt</td>
</tr>
<tr>
<td>3f</td>
<td>OCF₂CF₂CF₃</td>
<td>128.3</td>
<td>134.2</td>
<td>141.9</td>
<td>Friesen</td>
</tr>
</tbody>
</table>

[a] Only structures with R-Factor less that 10% are listed. [b] pip⁺ = 1,1,3,3,5,5-hexamethylpiperidinium

Propoxides or ethoxides. Such a trend is consistent with the LUMO energies of these HFEs: in each case, DFT calculations (B3LYP/6-31G*) show the LUMO lies on the CH₃ carbon atom with the LUMO energy for CH₃OCF₂CF₂CF₃ (1.51 eV) being greater than that of the butyl HFEs, either CH₃OCF₂CF₂CF₂CF₃ (1.03 eV) or CH₃OCF₂CF(CF₃)₂ (0.79 eV) 4 (Fig. 2.6). The pattern of the LUMO being destabilized with decreasing length of the perfluoroalkyl chain continues with CH₃OCF₂CF₂CF₃ to CH₃OCF₃. Thus, the reaction is relatively more favourable in the case of the perfluorobutyl appended HFEs. It is likely that the low energy LUMO makes it relatively more susceptible to nucleophilic attack.

A comparison of the reactivity of mono- and diamines uncovers a third trend: diamines are more reactive. The yields obtained with TMEDA were higher than those of trimethylamine, with both HFEs and at both 25°C and 50°C. Again this may be explained in terms of
energies of the frontier orbitals by utilizing DFT calculations. These calculations show the energies of the diamine HOMOs to be relatively higher than those of the monoamines. In addition, the reactivity of the first nitrogen atom in a diamine may be compared with that of the second. The second amine functional group of a diamine was significantly less reactive and dimethylation was never observed. Again, a comparison of the HOMO energy of the methylated TMEDA cation [(CH$_3$)$_2$NCH$_2$CH$_2$N(CH$_3$)$_3$]$^+$ (-3.85 eV) with that of TMEDA (-5.41 eV) shows a significant destabilization of the HOMO upon methylation, resulting in the inability of the HFEs to effect a second methylation of the diamines, as expected with the proximity of the two cationic nitrogen centres.

Finally, it is clear that yields increased with temperature, in the case of both HFEs, thus suggesting the relative thermodynamic stability of the quaternary ammonium perfluoroalkoxide salts over the amine and HFE starting materials.

2.2.4 Structural and Spectroscopic Analysis of Tetraalkylammonium Perfluoroalkoxides

In order to better understand the fundamental features of the fluorinated alkoxide functional group, we sought to report all spectroscopic experiments available to us. Prior to this study, a total of ten perfluoroalkoxides have been prepared, mainly by Willis (1965),$^{[6–9]}$ Farnham (1985),$^{[10,11]}$ Seppelt (1997),$^{[5]}$ and Vicic (2012),$^{[12]}$ Through the course of this work, this number has now expanded to more than 40 in part due to the convenience of the methodology. We therefore reported the $^1$H, $^{13}$C, $^{19}$F NMR, IR, XRD (3f only), and elemental analysis for all perfluoroalkoxides in order to establish both chemical identity and purity of each product. Particular attention to the unusual aspects in the spectroscopic data will be discussed here. It should be noted that the irregularities are not specific to the tetraalkylammonium perfluoroalkoxides prepared herein but are also consistent with earlier results reported by Willis,$^{[6–9]}$ Farnham,$^{[10,11]}$ Seppelt,$^{[5]}$ and Lillquist.$^{[13]}$ Unfortunately,
the expected spectroscopic data for many of the previous alkoxides is incomplete or not reported with an appropriate NMR reference.

As expected, NMR spectroscopy was the most convenient method to characterize the reaction products as the products are composed of NMR active nuclei including $^1$H, $^{13}$C and $^{19}$F nuclei. All products were highly soluble in CD$_3$CN and in certain cases, cations with larger organic substituents were soluble in less polar solvents such as CH$_2$Cl$_2$. This is particularly noteworthy and represents an expected improvement in solubility over metallic based cations which are soluble only in glymes and acetonitrile.$^{[5,13]}$ While all previously characterized perfluoroalkoxides were only performed in CD$_3$CN and provides easy comparisons to past work, the effect of solvent can now in theory be more broadly studied.

Samples of the isolated products could be easily handled in a well operated dry box or Schlenkware. However, trace amounts of H$_2$O in the anhydrous NMR solvents often afforded residual signals that correlated with the respective perfluorocarboxylate in discernible (< 3%) amounts. Early on, pre-dried anhydrous CH$_3$CN and CH$_2$Cl$_2$ were stored over CaH$_2$ however it was found that moisture derived impurities were largely prevented by storing solvents over activated 3 Å or 4 Å molecular sieves for a minimum of 48 h in a glovebox.
**1H NMR Analysis**

The 1H NMR spectra were routine and indicated the presence of quaternary ammonium or phosphonium cations evident by a downfield shift of methyl signal from the hydrofluoroether starting material to a quaternary ammonium or phosphonium. Integration of this CH₃ signal gave initial evidence for the methylation of the tertiary amine and also provided a sense of purity of the crude reactions products. In addition, the isolated products were painstakingly confirmed by elemental analysis (as HRMS is not convenient for air-sensitive compounds).

**19F NMR Analysis**

Initially, we expected that the fluorinated anions would likewise be routine. On the contrary, the pertinent α-fluorines of CF₂O⁻ were very broad to the point of being indiscernible and exhibited no coupling to adjacent nuclei at room temperature. In addition, the neighbouring β- and γ-fluorines on C2 and C3 appeared as singlets. The broadness of the α-fluorines and lack of coupling seemed to qualitatively increase as the length of the fluorinated chain decreased from C₄F₉OCH₃ to C₂F₅OCH₃ but also varied within a sample to sample basis of perfluoroalkoxide. This made the assignment of the respective fluorines signals difficult.

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*Fig. 2.7.* Variable Temperature ¹⁹F NMR spectrum of perfluoropropoxide 3f in CH₂Cl₂ with emphasis of the OCF₂ region.
While the lack of coupling has not been previously reported, the broadness of the α-fluorines is well known. For instance, Lillquist noted that a solution of C₃F₇OH–NEt₃ heated from −45 °C to 100 °C exhibited no resolution of the broad OCF₂ signal while no acid fluoride was observed in either ¹H and ¹⁹F NMR experiments at any temperature.[¹³] Others simply report the ¹⁹F chemical shifts as 'broad.' However, at no point did we observe the corresponding acyl fluorides of 2-4 which is particularly evident in the +20 – +35 ppm region in the ¹⁹F NMR spectra or the corresponding free fluoride. In every example, the OCF₂ signal integrates to two fluorines. The presence of anhydrous F⁻ is highly solvent dependent but careful analytical work by Christe demonstrated that nearly anhydrous NMe₄F in anhydrous CD₃CN has a chemical shift at -73.2 ppm.[³,⁴] While not observed in perfluoroalkoxides of 3 and 4, a signal at -73.2 ppm is seen in perfluoroalkoxides derived from C₂F₅OCH₃ 2.

![Fig. 2.8. Variable Temperature ¹⁹F NMR spectra of perfluoropropoxide 3f in CH₂Cl₂. Coupling between adjacent signals is resolved below −28 °C.](image)

In attempt to slow and observe the purported equilibrium between the perfluoroalkoxide and acyl fluoride, solutions of Me₃NBn⁺ 3f and quinMe⁺ 3h in CH₂Cl₂ were cooled from 22 °C to −78 °C and spectra recorded in 10 degree intervals. As presented in Fig. 2.8, the ¹⁹F NMR signal gratifyingly sharpened below −28 °C at which point splitting was observed in all three signals. Below −68 °C, the alkoxides have limited solubility and begin to crash out of solution. Upon inspecting the coupling patterns at low temperature, three signals are
**Table 2.3:** Chemical Shift of the \( \alpha \)-Fluorines of Perfluoroalkoxides Derived from Hydrofluoroethers 2, 3 and 4.\(^{[a]}\)

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\(^{[a]}\) unless otherwise noted, all \(^{19}\)F NMR analyses were performed on purified samples at RT in CD\(_3\)CN at 376 MHz. \(^{[b]}\) Navarini et al. \(^{[c]}\) diglyme. Cheburkov et al. \(^{[13]}\) \(^{[d]}\) -40 °C, CD\(_3\)CN, Seppelt et al. \(^{[14]}\) in CDCl\(_3\) Roschenthaler et al. \(^{[15]}\) in CD\(_3\)CN it is -92.5 ppm, possibly solvent dependent. \(^{[15]}\)
expected: the α-fluorines of C(1) should be split into a triplet due to the adjacent CF₂, the central β-fluorines of C2 a multiplet (triplet of quartets) and the γ-fluorines of C3 a triplet.

Indeed in Fig. 2.8, three signals are seen: a multiplet at -28.11 ppm (integration = 2), a triplet at -81.2 ppm (integration = 3) and a triplet at -126.07 ppm (integration = 2). Based on all previous literature reports, the chemical shift of α-fluorines of perfluoroalkoxides should be evident in the -20 to -45 ppm range (see Table 2.3). There are therefore three inconsistencies with this spectrum:

1. the assigned OCF₂ fluorines are split into a multiplet
2. the fluorines on the middle CF₂ and CF₃ are both split as triplets
3. yet the coupling constants for β- and γ-fluorines are different

Clearly, these signals appear to be misassigned! Although this is the first reported synthesis of α-perfluoropropoxides and butoxides, the chemical shift of the α-fluorines of all perfluoroalkoxides including OCF₃ are reported within this chemical shift range. Since the SC-XRD structure of 3f indicates that the α-fluorines are of different length, also observed for other perfluoroalkoxides (Table 2.2), we surmised that maybe the two α-fluorines are chemically inequivalent. Thus, each α-fluorine would be a doublet of triplets and may account for a process that at higher temperature broadens and averages the two signals (Fig. 2.9).

![Fig. 2.9. A Possible Explanation for the Multiplet Assigned to the α-Fluorines of the –OCF₂ Signal](image)

Although the α-fluorines seem to be inequivalent in the solid state structure of many perfluoroalkoxides (Table 2.2), observing what amounts to a bond vibration (10⁻¹² s) on an NMR time-scale (10⁻¹ s) is preposterous. Furthermore, no reasonable simulation of such an
arrangement accounted for the observed splitting pattern. Rather, we could think of two possible explanations. Firstly, the assignment of the signal at -28.11 ppm is simply not the expected $\alpha$-fluorines of the OCF$_2$ signal but rather the $\beta$-fluorines of C2 (and vice versa) as explained above. This would be the most plausible explanation based on the splitting patterns and integration of each signal.

Alternatively, the signal at -28.11 ppm may be a first order triplet of quartets seen as a sextet. This can be easily simulated using the observed coupling constants of the two triplets ($^3J_{\text{FF}} = 10.03$ Hz and $^4J_{\text{FF}} = 8.09$ Hz) (Fig. 2.10) suggesting that the OCF$_2$ is coupling to both the fluorines of C2 and C3. These values are consistent with expected ranges of $^3J_{\text{FF}}$ and $^4J_{\text{FF}}$ coupling constants although the $^4J$ is on the upper limit.$^{[16,17]}$ It should be noted that the CH$_3$ is not coupled to the $\alpha$-fluorines. Typically, $^{19}$F experiments are $^1$H broad-band decoupled but even if the decoupling channel was turned off in an additional experiment, the $^4J_{\text{HF}}$ coupling is not observed. Furthermore, the methyl group in the $^1$H NMR spectrum appears as a singlet.

To determine if this unexpected coupling arrangement is unique to perfluoroalkoxides, we looked to the reported data of the hydrofluoroether CH$_3$OCF$_2$CF$_2$CF$_3$ 3. We were dismayed to find that although 3 is an industrially produced product, is easily handled, and has multiple published preparations, there was no agreement on the assignment of the fluorines in $^{19}$F NMR spectra. Of the only two reports identifying the $^{19}$F NMR signals,

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**Fig. 2.10.** Comparison of observed and simulated $^{19}$F NMR sextet (tq) splitting pattern of perfluoropropoxide 3f. Spin simulation at 376 MHz, 64K point resolution, line width 2.5 Hz with 10.03 and 8.09 Hz coupling constants in a 3 spin AMX system.
Sekiya in 2003 reported the $\alpha$-fluorines at -129.4 ppm$^{[15]}$ while Navarrini reported the same fluorines in 2005 at -90.0 ppm$^{[18]}$ (no coupling analysis performed in either case). All other references$^{[13,19–21]}$ did not report $^{19}$F NMR data. In addition, no experimental spectra were included in the supporting information of any article and to the best of our knowledge no $^{13}$C NMR data had been reported to date.

Thus, the $^{19}$F spectra of 3 was acquired and expectedly, had the same coupling patterns as perfluoralkoxides 3f,h: two triplets (with integrations of 2F and 3F respectively) and a multiplet (2F) of the same shape as as perfluoroalkoxides 3f,h (Fig. 2.11). The multiplet (sextet) of interest was centred at -90.19 ppm rather than -28.12 ppm in the perfluoroalkoxide indicating that this is may be the OCF$_2$ signal which expectantly moves downfield in the perfluoroalkoxide. However, the $^{19}$F NMR COSY (through bond correlation) of 3 indicates that the CF$_2$ signal at -90.19 ppm is coupled to both other signals while the other CF$_2$ at -130.1 ppm is only coupled to the adjacent CF$_2$ and NOT the CF$_3$. As a result, the $^{19}$F COSY supports the claim by Sekiya, that the signal at -90.19 ppm is the $\beta$-fluorines of C2 and the signal at -130.1 ppm the $\alpha$-fluorines of the OCF$_2$ signal.$^{[15]}$ However, why would the $\beta$-fluorines move downfield 70 ppm in the perfluoroalkoxide yet the $\alpha$-fluorines remain relatively constant chemical shift in 3a–o?

Since we were able to unambiguously assign each of the $^{13}$C NMR signals due to the distinct $^1J_{CF}$ coupling constants (Fig. 2.13) an analysis we were unable to do with any perfluoroalkoxide ($vide infra$), we concluded that the only decisive evidence would be a
Fig. 2.12. Experimental $^{19}$F NMR COSY of $\text{CH}_3\text{OCF}_3\text{F}_7$ 3 in CDCl$_3$ referenced to CFCl$_3$ (0.00 ppm) at 376 MHz at $-18^\circ C$. The CF$_2$ signal at -90.1 ppm is coupled to both the CF$_3$ and a CF$_2$, circled in red, while the CF$_2$ at -130.1 ppm is only coupled to the other CF$_2$ at -90.1 ppm.

$^{13}$C-$^{19}$F HSQC one bond correlation experiment of 3. This type of experiment requires a three channel probe capable of having a $^{13}$C and $^{19}$F channels which many institutions do not have available. Fortunately, SFU has this capability and with the expertise of Dr. Andrew Lewis, we were able to acquire this correlation spectrum which clearly indicates the identify of each signal in the $^{19}$F NMR spectrum (Fig. 2.14). Thus, for the first time, the signals of 3 can be unambiguously identified as -82.1 ppm (CF$_3$), -90.1 ppm (OCF$_2$, $\alpha$-fluorines), and -130.1 ppm (CF$_2$, $\beta$-fluorines). Consequently, the signal at -28.11 ppm in the $^{19}$F spectra of perfluoroalkoxides must also be the $\alpha$-fluorines in the same fashion.

Although this second argument is satisfactory for the explanation for the splitting of the $\alpha$-fluorines on C(1) signal at -28.12 ppm, the corollary therefore suggests that $\beta$-fluorines on C(2) appears as a triplet and not an expected multiplet (i.e. a triplet of quartets) is due to a lack of coupling between C(2) and C(3) (Fig. 2.15). Likewise, the three $\gamma$-fluorines of C(3) are being split into a triplet due to a $^4J_{\text{FF}}$ interaction and not the predominate expected $^3J_{\text{FF}}$ interaction. Thus there are two principle observations for HFEs 2, 3 and 4 and perfluoroalkoxides that need to be explained here: why is there a lack of coupling between the $\beta,\gamma$-fluorines and why is there a strong $^{19}$F-$^{19}$F spin-spin $^4J$ coupling between $\alpha,\gamma$-fluorine nuclei?

Despite being a rare phenomenon, these same observations were first studied by Petrakis and Sederholm in 1961\[17\] and reviewed by Mallory in 2007.\[22\] They both methodically argue
**Fig. 2.13.** Experimental $^{13}$C NMR (101 MHz) Spectrum of CH$_3$OC$_3$F$_7$ 3 in CDCl$_3$ Assigned Based on Fluorine Coupling ($I = 1/2$) where t = triplet, q = quartet.

**Fig. 2.14.** Experimental 2D $^{13}$C-$^{19}$F HSQC spectrum of CH$_3$OC$_3$F$_7$ 3 in CDCl$_3$ indicating the multiplet at -90.1 ppm is the OCF$_2$ signal.
that one can qualitatively account for all F–F coupling constants in saturated fluorocarbons if one assumes that the major contribution to the coupling constants comes about as a result of direct through-space coupling rather than coupling through the bonds. This is an unverifiable assumption since there is a lack of a reliable means of resolving the coupling into its respective through-space and through-bond components. Nonetheless, this situation is in sharp contrast to analogous hydrocarbon ethers such as methoxypropane. The difference may be due to the contribution of the atomic p orbitals centred on F atoms which contribute greatly to bonding, while the "p character" of atomic orbitals centred on protons is considered small. Thus through-space coupling can be attributed to the overlap of a pair of lone-pair orbitals, one pair from each of the two coupled fluorine atoms. If the distance between these two fluorines are less than the van der Waals radius of fluorine (147 pm) than the lone pairs of the fluorine would be expected overlap to a small extent. Compelling evidence for the through-space coupling comes from the molecular structure (Fig. 2.4 or 2.17) or easily seen if one builds a molecular model of the perfluoropropoxide anion. It is then easy to see that the $\alpha$-fluorines of C(1) are in closer proximity to the $\gamma$-fluorines of C(3) than those of C(2) which face away due to restrictions in bond angles (Fig. 2.17). In 2015, Veige nicely demonstrated that in a series of organotitanium and hafnium complexes bearing fluoro-decorated pincer ligands that when confined to within 2.8 Å benchmark, two fluorine atoms will magnetically couple even if there is no direct bonding between the atoms. While there clearly is a correlation between internuclear distance and coupling constant, it would be naive to assume the coupling constant $J_{FF}$ is only dependent on the internuclear distance which would clearly ignore the contribution of other magnetic and structurally derived interactions on the coupling constants.

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3$J_{FF}$ = 10.44 Hz
2 $J_{FF}$ = 8.04 Hz

Fig. 2.15. Proposed explanation for the observation of C2 and C3 fluorines of –OCF$_2$CF$_2$CF$_3$ 3f,h each appearing as triplets with different coupling constants at 376 MHz.

4see Letters to the Editor in J. Chem. Phys for a published discourse between Musher and E.J. Corey (Harvard) and these authors regarding some differences in opinion.
**Fig. 2.16.** Observed $^{19}$F-$^{19}$F coupling between methoxy-hydrofluoroethers and respective tetraalkylammonium perfluoroalkoxides illustrating the importance of through-space F···F coupling contribution in perfluoroalkyls.

This small F···F overlap between α,γ-fluorines in 3 or 3f can be thought of as a two-centred molecular orbital comprising a weakly bonding orbital $\sigma_{\text{FF}}$ and a weakly anti-bonding orbital $\sigma^*_{\text{FF}}$ of which the pr-pF orbitals provide the only symmetry and spatial overlap (Fig. 2.17). While this combination of one filled bonding and anti-bonding orbital leads no net chemical bonding, Mallory has more recently argued that this model in similar systems provides a means of direct electron density that can transmit nuclear spin information between the two interacting fluorine nuclei between C(1)-C(2) and C(1)-C(3). It is of course interesting to note that this lone pair overlap theory is attributed to the same kind of interactions that are involved with through-bond coupling. The only distinction is that the electrons in the through-space interaction are occupied in weak "bonding" orbitals whereas through-bond is transmitted by electrons that occupy strongly bonding orbitals thus muddling the concept of what is exactly "through-space" vs "through-bond" interaction.
Nonetheless, the coupling constant seems to be a sensitive function of the internuclear distance between the magnetically interacting nuclei. Thus the coupling constants between α,β-fluorine atoms are not observed unless some shortening of the fluorine-fluorine distance occurs due to steric hindrance caused by neighbouring groups. This can be seen in the iso-butyl isomer of 4 in which all environments have measurable coupling due to steric compression of the perfluoroisobutyl group (the coupling in the n-perfluorobutoxy of 4 could not be determined with confidence due to poor resolution of the multiplets at 376 MHz). For instance, the $^3J_{FF}$ coupling between α,β-fluorines is 19.18 Hz while the $^4J_{FF}$ is still 10.92 Hz. Furthermore, through-space coupling explains the lack of observed coupling in CH$_3$OCF$_2$CF$_3$ 2 and OCF$_2$CF$_3$ 2f in which both fluorine environments appear as singlets, even if cooled to −68 °C in VT $^{19}$F NMR experiments (Fig. 2.18). Upon methylation, the observed coupling constants of the perfluoroalkoxide dramatically increase between the α,β-fluorines, while the β,γ-fluorines remain uncoupled and the α,β-fluorines increase by 1-2 Hz. These increases must be a consequence of an increase in F···F p-orbital overlap due to constraints of the short C–O bond length in the resulting perfluoroalkoxide.

Lastly, it should be noted that the products of HFE-7100 4 were a mixture of two isomers, consistent with the commercially-available reagent being a nearly equal mixture of iso-butyl and n-butyl perfluoroalkoxides. Separation of these two isomers was not undertaken due to the nearly identical physical properties of the two HFEs and the high reactivity of the corresponding products. If desired, the individual n-butoxy or iso-butoxy analogues could be prepared directly from the corresponding HFE. Characterization was not impeded by this mixture as each signal was well resolved.

In summary, the $^{19}$F NMR spectra of both hydrofluoroethers 2, 3 and 4 and perfluoroalkoxides provide examples of how fluorine can be useful spectroscopic handle to gain an understanding of structure. Through a rigorous analysis using all available resources, we argue for the first time that the signal at -90.1 ppm is conclusively that of the α-fluorines.

**Fig. 2.17.** The schematic representation of the dominant p$_F$···p$_F$ orbital overlap in perfluoroproxide 3f accounts for the strong through space coupling between αγ-FF. This is a result of spatial overlap and perfect energy match of the intramolecular F···F bond distance measured by X-ray crystallography. Adapted from Mallory.[22]
Fig. 2.18. The two $^{19}$F NMR signals of $[\text{NMMe}_3\text{Bn}][\text{OCF}_2\text{CF}_3]$ 2f in CH$_2$Cl$_2$ at $-28^\circ$C appear as singlets continuously from $32^\circ$C to $-58^\circ$C.

of the OCF$_2$ based on thorough 1D variable temperature and 2D NMR analysis and not the $\beta$-fluorines as Sekiya has (understandably) claimed.$^{[15]}$ Further, upon O-demethylation, the new signal between -20 and -35 ppm is due to the $\alpha$-fluorines of the perfluoroalkoxide. The fine splitting of this multiplet is due to $^3J_{FF}$ of $\beta$-fluorines and unexpected strong and anomalous $^4J_{FF}$ to the $\gamma$-fluorines predominately from a through-space interaction rather than through-bond as presented independently by Sederholm,$^{[17]}$ Rinaldi,$^{[25]}$ Snyder,$^{[26]}$ or Mallory.$^{[22]}$ The unexpected lack of coupling between the $\beta,\gamma$-fluorines can be best explained as a function of the sensitive internuclear distance in structural geometry of all studied hydrofluoroethers and perfluoroalkoxides. Furthermore, we argue for the first time that the exhibited near-zero coupling in CH$_3$OCF$_2$CF$_3$ and resulting perfluoroethoxides should be expected, while steric compression in iso-perfluorobutoxide leads to coupling between all fluorine environments.

$^{13}$C NMR Analysis

While the tetraalkylammonium cations are easily identified by $^{13}$C NMR analysis, we went through great difficulty to obtain $^{13}$C NMR spectra of the perfluoroalkoxides, the key structural motif. To address this issue, we, together with Dr. Andrew Lewis, repeatedly utilized SFU’s state-of-the-art, 600 MHz high-field Bruker NMR (operating at 151 MHz)
equipped with a liquid N₂-cooled cryoprobe and even after four hours, only the CF₃CF₂ portion of CF₃CF₂CF₂O⁻ began to emerge out of the baseline. The important α-carbons of the perfluoroalkoxide(s) were not detectable. To illustrate this, the full ¹³C{¹H} spectrum and zoomed in portion of the perfluoroalkoxide region (100-120 ppm) for 3f is shown in Fig. 2.19.

![Fig. 2.19. ¹³C NMR Spectrum of [Me₃NBn]OC₃F₇ 3f Acquired after 4 h on a 151 MHz Cooled Cryoprobe with Emphasis of the Perfluoroalkoxy Region](image)

However, upon a detailed search of the literature, we found no reported ¹³C spectra of the perfluoroalkoxide anion (of any carbon length). We highlight the following key references that do not include ¹³C data including the explicit statement by Kolomeitsev that the carbon atom from OCF₃ is not observed at 20°C.[27]

Other well-respected reports by Leroux, Pazenok, and Langlois utilize an *in situ* formation of perfluoroalkoxides from known precursors and only report $^{13}$C NMR spectra data of perfluoroalkoxy ether products.[28–34] The difficulty seems to be three-fold:

1. Perfluoroalkoxides are typically only soluble in CH$_3$CN or DMF. Acetonitrile has a strong resonance at 118 ppm in the middle of the expected region of perfluoroalkoxides.

2. Even with a saturated solution of the perfluoroalkoxide in CH$_3$CN (which is still low), the signal is split by $^{19}$F, which decreases the height of the peaks, and makes detection even more difficult.

3. Quite possibly, for the same reason that the $–$CF$_2$O signal in the $^{19}$F NMR spectrum is broad, it is likely that the environment around this $\alpha$-carbon is fluxional, a not well-understood phenomenon which may make detection more difficult.

Ideally, a high-field instrument with a probe capable of simultaneous broad-band $^1$H & $^{19}$F decoupling would be a key strategy to efficiently characterize perfluoroalkoxides by $^{13}$C NMR analysis however this is not typically available on most spectrometers. For this reason, only the tetraalkylammonium cation was detectable by $^{13}$C NMR analysis.

Lastly, for the cations with rigidity or high symmetry about the quaternary ammonium centre, the carbons exhibited spin-spin coupling between $^{14}$N and $^{13}$C nuclei (Fig. 2.20). This $^{14}$N-$^{13}$C type of coupling is seldom observed since the quadrupolar coupling constant of $^{14}$N is usually quite substantial. This typically leads to fast relaxation and the $^{13}$C nuclei observes the $^{14}$N nuclei in a single average state affording a singlet. However, in highly symmetric environments for example 1a–f, the high symmetry makes the $^{14}$N relaxation much slower due to the virtue of its lower quadrupolar coupling constants and hence coupling and well-resolved 1:1:1 triplets are observed in these spectra. The magnitude of the coupling constants were consistent with the reported $J_{NC}$ couplings by Taylor.[35]

**Infrared Studies**

Infrared (IR) spectroscopy is an extremely useful tool for the identification of functional groups in a molecular structure. In particular, it is a convenient way to study bond strength as it proportional to the frequency of the vibrational energy. A great effort was undertaken to simply measure the $\nu$C–O of nearly all $–$OC$_3$F$_7$ and $–$OC$_4$F$_9$ alkoxides prepared. Due to the high moisture sensitivity of the perfluoroalkoxides, the entire IR spectrophotometer had to be placed inside a glovebox since any number of glovebag-type enclosures built or bought for this purpose were insufficient. After spectrophotometer and glovebox equilibration, all samples were conveniently measured under a nitrogen atmosphere as powders using ATR accessory with a Ge and diamond crystal without influence of a matrix (such as KBr).

The results for the IR absorption frequency for the $\nu$C–O of each perfluoroalkoxide are listed in Table 2.4. While not all references have reported IR spectra, the data is in good
Fig. 2.20. Due to the high rigidity about the quaternary ammonium centre (for instance, NMe$_4^+$ of 2a), the α-carbons exhibited spin-spin coupling between $^{14}$N and $^{13}$C nuclei evidenced by a 1:1:1 triplet (101 MHz, CD$_3$CN).

agreement with key references such as Farnham (for instance, 1553 cm$^{-1}$ for TASOCF$_3$ in CH$_2$Cl$_2$)$^{[10,11]}$ and Willis’ assignment of the 1550 cm$^{-1}$ region in all spectra to the C−O bond of the metal perfluoroalkoxides.$^{[6,8,9]}$ In addition, the DFT calculated spectra of the $\text{OC}_3\text{F}_7$ anion is also consistent with this assignment, predicting a much higher $\nu$C−O frequency than typical for a C−O single bond (1000-1300 cm$^{-1}$) (Fig. 2.21). These 20 results demonstrate that the C−O bond of perfluoroalkoxy anion ranges from 1534 - 1550.85 cm$^{-1}$ (with the exception of 3k and 4k), the C−O bond must have much more double bond character than suggested by the drawn structure, that the tetraalkylammonium cation has little influence over the anion, and lastly, there is no discernible difference between the frequency and the length of the perfluoroalkoxide anion.
Table 2.4: Infrared Vibrational Absorption of the vC–O of the Prepared Perfluoro-Propoxides and Butoxides.\[a\]

<table>
<thead>
<tr>
<th>Cation</th>
<th>(^{-}\text{OC}_3\text{F}_7) (cm(^{-1}))</th>
<th>(^{-}\text{OC}_4\text{F}_9) (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>1546.58</td>
<td>4a 1544.38</td>
</tr>
<tr>
<td>3b</td>
<td>1550.85</td>
<td>4b 1546.09</td>
</tr>
<tr>
<td>3c</td>
<td>1550.35</td>
<td>4c 1544.68</td>
</tr>
<tr>
<td>3e</td>
<td>1534.15</td>
<td>4e 1542.65</td>
</tr>
<tr>
<td>3f</td>
<td>1550.46</td>
<td>4f 1519.11</td>
</tr>
<tr>
<td>3g</td>
<td>1543.31</td>
<td>4g 1536.99</td>
</tr>
<tr>
<td>3i</td>
<td>1540.46</td>
<td>4i 1543.78</td>
</tr>
<tr>
<td>3j</td>
<td>1539.10</td>
<td>4j 1538.67</td>
</tr>
<tr>
<td>3k</td>
<td>1514.91</td>
<td>4k 1524.22</td>
</tr>
<tr>
<td>3n</td>
<td>1539.07</td>
<td>4n 1541.32</td>
</tr>
</tbody>
</table>

\[a\] C–O stretch of select perfluoroalkoxides.
**Fig. 2.21.** Calculated IR Vibrational Frequencies of the Perfluoropropoxide Anion using Wavefunction Spartan at the B3LYP 6-31G* level. The circle absorption corresponds to the predicted $\nu_{C-O}$.

**Fig. 2.22.** Comparison of carbon oxidation number in structurally analogous $\text{OCH}_3$ and $\text{OCF}_3$ illustrates why the latter can rearrange to a perfluoroacyl fluoride.

### 2.3 Structural Considerations of Perfluoroalkoxides Bearing $\alpha$-Fluorines

#### 2.3.1 Bonding in Perfluoroalkoxides

**Oxidation States**

Perfluoroalkoxides are uniquely different than their hydrocarbon analogues. At first glance this may seem surprising as both are considered conjugate bases of their respective alcohol and would be expected to be similar in bonding and reactivity. Other than increased acidity due to the highly inductive effect of a perfluoroalkyl group, perfluoroalcohols could be considered uninteresting structural analogues. However, if one simply considers the formal oxidation number (O.N.) of the C(1) carbon atom, primary perfluoroalkoxides (O.N. = +3) would be expected to have less in common than their structural hydrocarbon analogues (O.N. -3). Likewise, $\text{OCF}_3$ anion having an oxidation state of +4 would not be expected to undergo any further oxidation being more similar to CO$_2$ and CF$_4$ (O.N. +4) than $\text{OCH}_3$ (O.N. -3). Thus, interconversion of a primary perfluoro-alkoxide RCF$_2$O$^-$ to RCOF and F$^-$ is a rearrangement or elimination without a change in oxidation state (Fig. 2.22). For example, it would be exceptional if a primary alkoxide RCH$_2$O$^-$ would spontaneously
undergo a similar transformation to an aldehyde (O.N. +1) without an oxidizing agent under normal conditions and then form an equilibrium process interconverting the two species.

**Perfluoroalkoxide Equilibria**

The spectral data in the preceding sections also highlight the following unusual but possibly related set of observations for perfluoroalkoxides:

1. no observable C(1) signal in the $^{13}$C NMR spectra
2. lack of observable $J$ coupling in the $^{19}$F NMR spectra above $−28$ °C
3. broadness of the $^{19}$F NMR signal for the $\alpha$-fluorines of $\text{OCF}_2\text{R}_F$
4. short length of the C–O bond in the crystal structure of trimethylbenzylammonium perfluoropropoxide $3f$
5. increased frequency of the C–O stretch in the IR for all measured perfluoroalkoxides

These observations are consistent with previously characterized perfluoroalkoxides and have been attributed to an equilibrium process between the perfluoroalkoxide and the acyl fluoride and fluoride, the reverse reaction for the standard preparation of perfluoroalkoxides. At ambient conditions the intermolecular fluxional process would be faster than the NMR time scale. As a result, the broadening of the $\alpha$-fluorine signal, the lack of C(1) signal in the $^{13}$C NMR spectra and lack of $^{19}$F-$^{19}$F coupling in the $^{19}$F NMR spectra about the same carbon is due a fluxional environment. This equilibrium process is expected in earlier synthetic strategies as the preparation of the perfluoroalkoxide was the shifting of this equilibrium towards the perfluoroalkoxide favoured at low temperatures with an excess of fluoride. It was postulated that larger organic cations would shift this equilibrium to the right as the crystal lattice energy for the resulting fluoride would be lower. To a large part this was demonstrated by Farnham and co-workers at DuPont through the use of tris(dimethylamino)sulfoninum ($\text{TAS}^+$) difluorotrimethylsilicate ($[\text{SiF}_2(\text{CH}_3)_3]^-$, a masked $\text{F}^−$ source.\cite{11} However, here we demonstrate for the first time that perfluoroalkoxides can be prepared without the use of fluorides or fluoride sources. Yet, the above NMR observations would suggest that perfluoroalkoxides made in this fashion are still subject to rearrangement to the perfluoroacyl fluoride and fluoride equilibria at ambient conditions even with a non-metal based anion. However, at no point have we observed by solution state NMR the distinct signals for free fluoride or perfluoroacyl fluoride for perfluoroalkoxides for $\text{OC}_3\text{F}_7$ $3$ or $\text{OC}_4\text{F}_9$ $4$. The perfluoroethoxide $2f$ however does indicate the presence of what may appear as a $\text{F}^−$ anion at -74 ppm at RT although no presence of trifluoroacetyl fluoride is observed in a sealed NMR tube. Furthermore, upon cooling a solution of $2f$ in CH$_2$Cl$_2$ in a VT NMR
experiment, the fluoride signal disappeared, the OCF$_2$ signal sharpens, and a new signal corresponding to the distinctive HF$_2^-$ anion appears at -145.4 ppm ($J_{HF} = 121$ Hz) at low temperatures.[4] Upon warming back to elevated temperatures (45$^\circ$C), the HF$_2^-$ signal disappeared and the formation of the F- signal is restored.

**Fig. 2.23.** VT$^{19}$F NMR spectra of [NMe$_3$Bn][OCF$_2$CF$_3$] 2f in CH$_2$Cl$_2$ from 32$^\circ$C to -58$^\circ$C

In general, the broadness of the OCF$_2$ signal seems to be dependent upon the cation, sample and the solvent (more broad in CH$_3$CN than in CH$_2$Cl$_2$) but not in a distinguishable trend. Each $^{19}$F signal integrates for the expected number of fluorines regardless of the temperature or broadness of the signal suggesting that there is not unaccounted signals. Therefore the signal between -25 to -35 ppm may represent the coalescence of the perfluoroalkoxide, perfluoroacyl fluoride and fluoride signals at some sub-second NMR time-scale. Alternatively, the broadness of the OCF$_2$ signal may be attributed to rotation about the C-C axis which gives rise to possible rotamers. This is well-known for hydrocarbons bearing fluorine substituents (such as 1,2-difluoroethane) in which the gauche rotamer is more stable by -0.8 kcal/mol than the anti-rotamer.[36] This phenomenon known as the *gauche effect* is quite sensitive to solvent effects due to polarity difference between rotamers.[37,38] It is worthwhile to note that in the SC-XRD structure of 3f, the C-O and C(2)-CF$_3$ is in a gauche conformation. Evidence of possible individual rotamers should be evident by spectroscopic means but this has not been established as of yet. Lastly, trace impurities such as H$^+$ could also account for broadness of the $\alpha$-fluorines as evidenced by the presence of HF$_2^-$ in Fig. 2.23 and variations in peak broadness from sample to sample analysis. Yet none
of the three scenarios full account for all observations. This broadness is only observed in perfluoroalkoxides, since upon metallic coordination or alkylation, the signal is sharp.\cite{12} Unfortunately without further investigation the broadness of the OCF$_2$ must be relegated to as others have as broadly pertaining to "a fluxional process" or "slow fluoride exchange" which is clearly unsatisfying.\cite{11,39}

**Negative Hyperconjugation**

The downfield shift of the OCF$_2$ signal in the $^{19}$F NMR spectrum, the increased IR C–O frequency, and short bond distance of the C–O bond with a concomitant lengthening of the $\alpha$-C–F bonds of the perfluoroalkoxide by XRD demonstrates the need to describe the C–O bond of a perfluoroalkoxide differently than a hydrocarbon based alkoxide which is how it is usually denoted. The C–O bond appears to be less representative of a single bond 16 and more representative of a double bond 17 based on observed bond length.

\[
\begin{array}{c}
\text{16} \\
\begin{array}{c}
\text{O} \\
\text{R} = \text{F or RF}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{17} \\
\begin{array}{c}
\text{O} \\
\text{R}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{18} \\
\begin{array}{c}
\text{O} \\
\text{R}
\end{array}
\end{array}
\]

**Fig. 2.24.** (above) Negative hyperconjugation in perfluoroalkoxides to explain both broad signals in the $^{19}$F NMR spectra and observed bond lengths and (below) frontier molecular orbital depiction of negative hyperconjugation from $n \rightarrow \sigma^*_{C-F}$.

The shortening of the C–O bond has been described by nearly every textbook and publication by either a resonance or frontier molecular orbital approach by utilizing *negative* hyperconjugation to explain perturbations in bond lengths and angles (19) (Fig. 2.24).\cite{5,11,12,40–45} The negative hyperconjugation model of perfluoroalkoxides was made widely known by Farnham’s seminal report in 1985 using the crystal structure of TAS$^+$–OCF$_3$] augmented with *in silico* work. Quite simply, negative hyperconjugation is the back donation of electron density from the oxygen lone pairs (HOMO) to the $\sigma^*$ orbitals of the $\alpha$-C–F bonds (LUMO). Thus the negative hyperconjugation explanation is solicited to explain the increased C–O double bond character and lengthening of the C–F bonds. In so doing, the perfluoroalkoxide can be represented by resonance structures 16 and 17.
Since the C–O bond length is nearly that of the C–O in COF$_2$, it seems that resonance structure 16 is not consistent with structural or spectroscopic data and should alternatively be drawn as 18. A carbon having five bonds is of course contrary to the octet rule thus structure 20 seems to be the most important resonance structure. This is also unsatisfactory since an increase in ionic character typically results in a stronger bond, not a weaker bond. Therefore, it is of utmost importance to recognize that these resonance structures do not provide an explanation for the bond lengths (the why) but simply a description. This is because the resonance structures and back-donation were invoked after the solid state structures were initially obtained to account for the unexpected bond lengths. Furthermore, Wiberg has pointed out that based on calculations and XRD data that both fluorinated and hydrocarbon alkoxides have shorter C–O$^-$ bond lengths and increased bond lengths for $\alpha$-substituents on C in comparisons to parent alcohols C–OH.$^{[46]}$ This is not consistent with negative hyperconjugation since the $\alpha$-substituents on the central carbon should have much higher energies for hydrocarbon CH and CCH$_3$ then CF $\sigma^*$ orbitals.$^{[46,47]}

**Ligand Close-Packing Model**

In 1997, Gillespie (McMaster) developed a complementary model to his very successful valence shell electron pair repulsion (VSEPR) theory called ligand close-packing (LCP) model.$^{[47,50–54]}$ Even though he developed this empirical model while studying fluorinated Period 2 compounds, the comprehensive LCP model is useful for explaining the exceptions in the VSEPR model but also as general treatment for other molecular effects, namely the anomeric effect, methyl tilt, and stereochemical inactive lone pairs in AX$_6$E molecules.$^{[51]}$ In so doing, he addresses the bonding description in perfluoroalkoxides in several papers devoted to this topic.$^{[47,53]}$ For reasons unknown, these reports have been overlooked by the fluorine community.$^6$ He very clearly provides an alternative opinion for the bonding in perfluoroalkoxides which does not require the negative hyperconjugation model.$^{[47]}

'We do not need to use the concept of negative hyperconjugation in describing the bonding in ONF$_3$ and OCF$_3$. It was introduced simply as means of deriving one unsatisfactory Lewis structure from another unsatisfactory Lewis structure, both of which unsuccessfully attempt to describe the polarity of the bonds. Negative hyperconjugation cannot be regarded as a physical phenomenon any more than can the concept of resonance. In the molecular orbital model the description of hyperconjugation as the donation of nonbonding electrons into anti-bonding $\sigma^*$ orbitals is simply an unnecessarily complicated way of describing the polarity of the bonds.' - R.J. Gillespie et al. *Inorg. Chem.*, 1998, 37, 6884

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$^5$Although derived independently, the Gillespie LCP model is an improvement on previous observations by Bartell$^{[48]}$ who published a skeletal version of this concept in 1960 based on the SC-XRD of isopropylene.$^{[59]}$ This idea was then developed further by Hargittai, Glidewell and Baird during the 1980s.$^{[50]}$

$^6$This article in *Inorg. Chem.* has only received 8 citations to date
While VSEPR is an electronic model for molecular geometry, the LCP model is a steric model. The basis for the LCP model is that attraction between the negatively charged substituents or ligands (X) of a positively charged central atom (A) in a molecule AX\(_n\) causes the X ligands to cluster as closely as possible around A in the equilibrium geometry so that the molecule is as compact as possible.\(^{[50–52]}\) According to this model, bond lengths and angles are determined by ligand-ligand interactions in which ligands can be viewed as spheres at their limit of compressibility which are drawn electrostatic fashion towards the central atom until they come in contact with each other, i.e. close-packing (Fig. 2.25). This leads to almost constant interligand X–X distances for any combination of ligands in a variety of molecules AX\(_n\). In mixed ligand systems, the interligand distance between two different ligands X and Y are give to a very good approximation by \(d_{X-Y} = r_x + r_y\) where \(r\) is the ligand radius. This effect is especially pronounced when the central atom A is one of the elements from Period 2, namely, Be, B, C, N, because of their small size due to \(Z_{\text{eff}}\) and for X ligands like O or F which are more electronegative than the central atom. These highly electronegative ligands have a large negative charge and are therefore much larger in size than positively charged central atom.

\[\text{Fig. 2.25. Visualizing Gillespie's ligand close-packing (LCP) model as it pertains to the simplest perfluoroalkoxide } \cdot\text{OCF}_3 \text{ in which the negatively charged ligands } X = O^2-, F^- \text{ are drawn close to the central atom } A = C^{4+}. \text{ The C–O bond distance is shorter than C–F bonds due to the increased electrostatic attraction.}\]

Thus, if one measures the crystallographic distance X–X between two homoleptic ligands X, known as the interligand (or contact) distance, the radius of X can be calculated by halving this distance. Of key importance, this ligand radius has been shown to be almost constant for molecules bearing the same central atom (Table 2.5). Herein, we found every relevant crystal structure of perfluoroalkoxides and summarized the interligand distances in Fig. 2.6. It is important to note that the ligand radius is (only) dependent upon the central atom because the size of the central atom is dependent upon the charge and electronegativity of the central atom, a topic typically explored in introductory chemistry. Thus the standard radius of the fluorine atom will be different in OBF\(_3\) than \(\cdot\text{OCF}_3\) or ONF\(_3\). The experimentally determined interligand distance between the two fluorines in the
three coordinate COF₂ is 216 pm while that of CF₄ and OCF₃ are nearly identical at 215 pm and 216 pm respectively! This distance can be calculated a priori by using the F ligand radius of 108 pm (2 x 108 pm = 216 pm). Ligand close-packing model therefore explains why the bond angle of OCl₂ is greater than the ideal geometrical angle of 109.5 degrees when VSEPR would predict it to be less than 109.5 degrees due to bond-lone pair repulsion. Thus the size of the chlorine ligands inhibits closer packing, causing longer bond lengths and greater bond angles than H₂O. VSEPR fails since it neglects ligand-ligand repulsions. For a full discussion of how LCP pertains to weakly electronegative elements, ligand-ligand interactions for period 3-6 elements and lone pairs, the reader is directed to a thorough treatment of a wide variety of examples in the references.[48,50–52,54]

**Fig. 2.26.** Experimentally derived crystallographic geometrical parameters related to ligand close-packing (LCP) model in perfluoroalkoxides. Note the consistency in intermolecular ligand (X) distances X···X around the central atom.
Table 2.5: Structural Bond Lengths and Internuclear Distances About C(1) for a Series of Related Fluorinated Compounds

<table>
<thead>
<tr>
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<tr>
<td>C–O</td>
<td>117.0</td>
<td>122.8</td>
<td>123</td>
<td>128.5</td>
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<td>136.2</td>
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<td>C–C(2)</td>
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<td>156.1</td>
<td>153.2</td>
<td>153.8</td>
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<td>O···F</td>
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<td>234.9</td>
<td>237.9</td>
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<td>239</td>
<td></td>
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<tr>
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<td>215</td>
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<tr>
<td>F···C(2)</td>
<td>229.3</td>
<td>233.8</td>
<td>232</td>
<td>234.5</td>
<td>234</td>
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<tr>
<td>C(2)···C(2)</td>
<td>257.5</td>
<td>253.1</td>
<td>246.7</td>
<td>239</td>
<td></td>
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</tbody>
</table>

[a] All values in picometers (pm) calculated from experimental crystal structure (.cif) file. [b] from Gillespie and Robinson[53]. [c] Calculated using Gillespie's Table of Ligand Radii with carbon as the centre atom (pm)[52].

Table 2.6: Ligand Close-Packing Model Ligand Radii (pm) for Selected Atoms Relevant to this Work

<table>
<thead>
<tr>
<th>Central Atom</th>
<th>( C_{Bartell} )</th>
<th>( C_{Gillespie} )</th>
<th>( C_{CF_3} )[b]</th>
<th>( O_{Bartell} )</th>
<th>( O_{Gillespie} )</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>125</td>
<td>126</td>
<td>128</td>
<td>114</td>
<td>113</td>
<td>108</td>
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</table>

[a] All values in picometers (pm) as reported by Gillespie[52] or Bartell[49].

[b] Calculated by dividing the average internuclear distance for \( CF_3···CF_3 \) distances from 28 and 29 by two.
Using LCP, we can then explain the bonding in perfluoroalkoxides such as \([\text{NMe}_3\text{Bn}][\text{OC}_3\text{F}_7]\) 3f. Satisfyingly, the O···F and the F···F were consistent with experimentally derived interligand distances of known compounds in Fig. 2.26, namely COF$_2$ 22 to OC(CH$_3$)$_3$ 30 or the calculated interligand radii (Table 2.6). We calculated the ligand radii for a carbon atom of a CF$_3$ (128 pm) from 28 and 29 which is only slightly larger than that of CH$_3$ (126 pm) reported by Gillespie or Bartell (see Table 2.5). Due to the higher negative charge on oxygen and high positive charge on the carbon, the C–O bond of the perfluoroalkoxide is expectedly and consistently short, nearly equal to a C=O double bond. The C-F bonds of 3f are longer due to closer packing of the strongly bonding oxygen atom increasing the length of the two fluorines by steric hindrance. However, the bond lengths for both C–O and C-F in 3f are longer than OCF$_3$ due to the substitution of one of the F in 31 with a CF$_2$CF$_3$ group. This effectively lowers the charge on the central carbon, slightly decreasing the electrostatic interaction of the O and F substituents. Likewise, if further substitution of the α-fluorines were to occur, this would continue to increase the bond lengths of the remaining C–F and C–O bond lengths which is what is observed in 29 and 30.

The treatment of perfluoroalkoxides using Lewis structures 16, 17 and 18 is difficult. Using LCP theory, the most suitable structure is the unconventional and controversial pentavalent 20. Gillespie argues that this is because bond lines in these types of molecules do not have a clear meaning as they typically are designed to illustrate nearly pure covalent bonds as is done with typical organic structures comprising of C–C and C–H bonds.\cite{47,50,55} The bonds within perfluoroalkoxides are not truly covalent 18 or ionic 21 and are inadequately represented in the Lewis structure.\cite{47,54} Rather, the C-O bond of perfluoroalkoxides can be considered 50% ionic and 50% covalent in which the C$^+$–O$^-$ bond has four bonding electrons between the C and O atoms.\cite{47,52,53} At first glance this looks like a single bond but there is no reason why it must be considered longer than a covalent double bond.\cite{54,56}

Part of the difficulty here in trying to explain bonding in traditional terms is that it is futile to denote bonds using the Lewis system for bonding molecules that are not almost entirely covalent in nature. So when molecules such as perfluoroalkoxides are considered in which the ligands are more electronegative than the central atom, the coordination number is primarily determined by the size of both the central atom and ligands.\cite{47,53,54} Thus Period 2 atoms have a coordination number of 4, not because of the octet rule, but because this is the maximum number of ligands that can be supported by the central atom due to size restrictions or close-packing. Group 3 and larger central atoms are larger and can thus support higher coordination numbers.\cite{47,53,54} No Group 2 molecule in its equilibrium geometry has to this point been assigned a coordination number greater than four.\cite{57} Thus it is reasonable to draw perfluoroalkoxides that are indeed at most four coordinate but

\footnote{The definition of organic will not be defined here as it is debatable whether molecules such as perfluoroalkoxides can be even considered classical organic compounds. It is worth noting that the preparation and discussion of such molecules has been explored almost entirely from an inorganic perspective and at the minimum should be classified as carbogens.}
appear as pentavalent in a Lewis diagram, if one assumes that the Lewis line drawings do not adequately represent ionic nature (polarity) within the bonds or view perfluoroalkoxides as a resonance between 20 and 21. Thus depiction 20 is then consistent with the experimental spectroscopic observations (IR, NMR, XRD) that perfluoroalkoxides have a strongly bonded C–O and longer, weaker bound α-fluorine atoms. Further, LCP predicts that with substitution of the α-fluorines both the C–O and C–F bonds consistently become longer which is what is observed (Table 2.5). The LCP model provides a simpler explanation that also can predict with high success the bond distances when the ligands (O, F) are considered anion-like ligands close packed around a positive central atom governed by interligand repulsions better described in an ionic model than a purely covalent model.

2.4 Thermal Stability of Tetraalkylammonium Perfluoroalkoxides

Upon preparing tetraalkylammonium perfluoroalkoxides with α-fluorines, a synthetically relevant question considered was whether these compounds can be considered "stable." Therefore we investigated two types of stability: moisture and thermal stability. Thermal stability can be viewed both as solution or solid-state stability. It is more difficult to determine solution stability since this must be done by spectroscopic methods in the presence of a solvent (Section 2.2.4) or by designing experiments where the perfluoroalkoxide is a reagent (Section 2.6). However, both of these strategies were inconclusive as we have yet to verify the presence of either free fluoride or the respective perfluoroacyl fluoride with reasonable certainty at the exclusion of other factors. Thus we consider solid state thermal stability and moisture sensitivity next.

2.4.1 Solid State Thermal Stability of Tetraalkylammonium Perfluoroalkoxides

Since perfluoroalkoxides tend to eliminate fluoride with concomitant formation of perfluoroacyl fluoride at elevated temperatures, we hypothesized that thermal decomposition of tetraalkylammonium perfluoroalkoxides could enable a facile route to truly anhydrous tetraalkylammonium fluorides while simultaneously providing an understanding of thermal stability (Scheme 2.3). Initially, the prepared tetramethylammonium perfluoropropoxides were subjected to thermal analysis utilizing a standard departmental thermogravimetric analysis (TGA) instrument.

However, even with quick transfer of the sample, decomposition due to moisture prevailed rendering further analysis unproductive. After searching extensively for a glovebox equipped with a TGA instrument, we were pleased that the Miller group at the University of Utah not only were willing to run our samples but also were equipped with a TGA-MS capable
Scheme 2.3. General Thermal Rearrangement of Perfluoroalkoxides Bearing α-Fluorines to the Perfluoroacyl Fluoride

\[
\begin{align*}
\text{anhydrous} \\
\text{R = C}_2\text{F}_5, \text{C}_3\text{F}_7 \\
\text{NR}_4 \text{F} + \text{RCF}_2\text{O} \xrightarrow{\Delta} \text{RF}_\text{F} + \text{NR}_4 \text{F} \\
\end{align*}
\]

of multiple ion detection (0-300 amu) in a < 5 ppm oxygen nitrogen filled glovebox. This added mass spectrometry feature can provide valuable evidence of decomposition products during thermally induced mass loss. Upon selecting a range of ions characteristic of the expected decomposition, the expected mass loss were volatile perfluoroacyl fluorides, residual unreacted starting materials (HFE and NR$_3$) and the decomposition products of quaternary ammonium fluorides (CH$_3$F and NR$_3$).[58]

Scheme 2.4. Thermal Decomposition of \([\text{NMe}_4]\text{OC}_3\text{F}_7\) 3a in the Solid State via TGA-MS, IR, $^{19}$F NMR, and GC/MS spectroscopy

As shown in Scheme 2.4, disappointingly adventitious amounts of moisture were sufficient enough to decompose the tetraalkylammonium perfluoroalkoxides to the carboxylic acid even though the analysis was carried out in a glovebox. The carboxylic acid thus underwent decarboxylation of the anion and concomitant Hofmann elimination of the cation between 185 - 200°C, affording a mixture of volatile products, including tetrafluoroethylene (Fig. 2.28 and 2.29). A portion of the 3a sample was intentionally exposed to atmospheric moisture briefly and also analyzed in the same fashion. As can be seen in Fig. 2.27, the decomposition was very similar to those treated in an anhydrous fashion. Alternative mechanisms such as the intermediate formation and decomposition of perfluoro-esters do not easily explain...
relative high abundance of HF, CF$_3$CF$_2$H and H$_2$O which are typically associated with moisture.

![Thermogravimetric analysis of tetramethylammonium perfluoroalkoxides of OC$_3$F$_7$ 3a and OC$_4$F$_9$ 4a acquired under a nitrogen atmosphere.](image)

**Fig. 2.27.** Thermogravimetric analysis of tetramethylammonium perfluoroalkoxides of OC$_3$F$_7$ 3a and OC$_4$F$_9$ 4a acquired under a nitrogen atmosphere.

However, with careful handling in the appropriate Schlenkware on a stainless steel vacuum line equipped with a gas cell IR, we were able to manually determine that the tetramethylammonium perfluoroalkoxide were surprisingly stable up to 150°C at 1 Torr for a period of 1 h and partial decomposition did not occur until 180°C. However, above this temperature, the tetramethylammonium perfluoropropoxide underwent immediate decomposition of the tetramethylammonium fluoride to fluoromethane (CH$_3$F) and trimethylamine based on gas phase IR (Fig. 2.31) and GC/MS (Fig. 2.33) analysis of the trapped off-gas and $^{19}$F NMR spectra analysis (Fig. 2.32) of the residue.
**Fig. 2.28.** Examples of Thermogravimetric Analysis of $\text{NMe}_4\text{OC}_3\text{F}_7$ 3a with Selective Ion Monitoring Illustrating Substantial Mass Loss of HF, CH$_3$F and NMe$_3$

**Fig. 2.29.** Examples of Thermogravimetric Analysis of $\text{NMe}_4\text{OC}_4\text{F}_9$ 4a with Selective Ion Monitoring Illustrating Substantial Mass Loss of HF, CH$_3$F and NMe$_3$
Fig. 2.30. Thermal stability of [NMe₄]OC₃F₇ 3a was determined both by TGA-MS and manual trap-to-trap gas transfer at 50 °C-180 °C at 1 Torr.

Fig. 2.31. Inline FTIR Gas-Phase Monitoring of Decomposition of NMe₄OC₃F₇ 3a at 180 °C with Significant Presence of Perfluoropropanoyl Fluoride and Trimethylamine
Fig. 2.32. $^{19}$F NMR (376 MHz) analysis in CD$_3$CN of NMe$_4$OC$_3$F$_7$ 3a residue after heating for 1 h in the solid state at the specified temperature illustrating the emergence of the decomposition products at 180°C.

Fig. 2.33. GC Chromatogram (top) and Mass Spectrum (bottom) of NMe$_4$OC$_3$F$_7$ 3a heating for 1 h at 180°C demonstrating the presence of trimethylamine ($M^+ = 59$ m/z) at a retention time of 1.52 min.

Thus we can conclude that tetramethylammonium propoxides and butoxides bearing $\alpha$-fluorines are thermally stable up to 180°C in the solid state but are required to be
handled under rigorously moisture free environments (scheme 2.30). Upon decomposition, the tetramethylammonium fluoride cannot be isolated due to immediate decomposition to trimethylamine and fluoromethane (CH₃F). As expected, the stability of non-metal perfluoroalkoxides are higher than those such as those reported earlier by Willis but similar to TAS⁺ and other ammonium based salts. However, tetraalkylammoniums bearing β-hydrogens would likely decompose at lower temperatures due to increased rate of Hofmann degradation therefore the results here would represent perfluoroalkoxides with the highest thermal stability in the series studied.

2.4.2 Select Group 15 N, P, As Nucleophiles

To further survey the methylating ability of 3, we targeted analogous group 15 substrates and observed that the yield unsurprisingly decreased with lower nucleophilicity of the heteroatom. The yield of the respective quaternary Group 15 -onium salt decreases from NMe₃ to AsMe₃ which was isolated in only trace amounts (Table 2.7).

**Table 2.7**: Methylation of Group 15 Substrates by CH₃OCF₂CF₂CF₃

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Yield[a] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe₃</td>
<td>77</td>
</tr>
<tr>
<td>PMe₃</td>
<td>12</td>
</tr>
<tr>
<td>PPh₃</td>
<td>n.r.</td>
</tr>
<tr>
<td>AsMe₃</td>
<td>trace</td>
</tr>
</tbody>
</table>

[a] Yields refer to the isolated material of > 98% purity unless otherwise noted. n.r. = no reaction after 48 h.

Of particular interest was the product of trimethylphosphine and 3. The spectroscopic details are entirely consistent with a tetramethylphosphonium perfluoropropoxide 3o rather than a pentacoordinate phosphorane with a fluoro 32 or perfluoroalkoxy 33 moiety (Scheme 2.5). Unstable perfluoroalkoxides bearing α-F substituents are capable of rearrangement liberating a highly active "naked" fluoride and corresponding acyl fluoride (vide infra). Kor- nath and Neumann observed that an anhydrous fluoride ion with the tetramethylammonium cation can form a five coordinate, Me₄PF phosphorane structure in non-polar solvents and in the gas phase, although the P-F₂ax is exceptionally weak.[59,60] This tendency for a semi-ionic bond due to the fluorine atom dynamically moving within a solvate sphere can result in suppression of the fluorine couplings in the associated NMR spectra.
Scheme 2.5. Reactivity of PMe$_3$ with HFE-7000 3

While final efforts to obtain a single crystal for structural analysis are still ongoing, all RT spectroscopic data seems to be highly consistent with a tetramethylphosphonium perfluoropropoxide. Conveniently, every nuclei is NMR active and provides an easy handle for structural assignment. By $^1$H NMR and $^{13}$C NMR analysis, all methyl groups are equivalent and are split into a doublet centred around 1.96 ppm ($^2J_{HP} = 14.9$ Hz) and 9.46 ppm ($P$–CH$_3$, $^1J_{CP} = 56.4$ Hz) respectively, which collapses into a singlet in a $^1$H$^{31}$P decoupling experiment. Likewise the $^{31}$P and $^{31}$P{$^1$H} NMR spectrum clearly depicts a signal species as a singlet at 24.36 ppm. The proposed tetramethylphosphonium cation is consistent with spectroscopic data for the tetramethylphosphonium cation, for example PMe$_4$Cl. Although both are highly solvent dependent, PMe$_4$F phosphorane has a $^{19}$F chemical shift in the +50 ppm region and the Me$_4$P$^+$F$^-$ salt has a chemical shift at -71 ppm. If there was a P–F bond, this coupling would have been evident by the corresponding doublet $^1J_{PF}$ of 600-800 Hz although fast exchange processes in Me$_4$PF can obfuscate this signal. However, no evidence for a free fluoride in the -70 to -75 ppm range, the presence of a broad signal at -25.67 ppm is consistent with a -CF$_2$O$^-$, and elemental analysis are consistent with [PMe$_4$][OC$_3$F$_7$].

2.4.3 Reactivity of HFE-7000 with $N,N$-Diethylamine

The reaction of CF$_3$CF$_2$CF$_2$OCH$_3$ 3 was extended to simple secondary amine $N,N$-diethylamine (Scheme 2.6). The methylation of this substrate afforded a mixture of products including the major product, $N,N$-diethyl-2,2,3,3,3-pentafluoropropanamide, a literature compound identified by GC/MS and NMR spectroscopy. While the preparation of perfluoro-amides via this method is simple to carry out, it is not particularly efficient since hydrofluoroethers are initially prepared from acyl fluorides. Typically perfluoroamides are prepared directly from the parent perfluoroacyl halide or perfluoro(thio)ester and the corresponding secondary amine.
Scheme 2.6. Reactivity of HFE-7000 3 with Secondary Amine, N,N-Diethylamine

In addition, the reaction reported herein requires excess amine since 1 equivalent undergoes initial methylation by the HFE. This methylated amine is deprotonated in situ by the perfluoroalkoxide, eliminating HF and undergoing condensation with another equivalent of N,N-diethylamine. Due to the presence of dimethylethylammonium bifluorides, the deprotonation of the newly formed diethylmethylamine can undergo methylation a second time affording the quaternary ammonium bifluoride, identified by $^1$H and $^{19}$F NMR spectroscopy (Scheme 2.6), resulting in an overall mixture of substituted ammonium salts and an inefficient process for perfluorinated amides and not pursued further.

Scheme 2.7. (a) Proposed Mechanisms Accounting for the Mixture of Ammonium Salts and (b) Reactivity of Perfluoropropoxide 3a with N,N,N-Triethylamine Hydrochloride

(A) Proposed Mechanism:

(B) Decomposition of NMe$_4$OC$_3$F$_7$
2.5 Reactivity of the Inhalation Anaesthetic Methoxyflurane

2.5.1 Incorporation of Fluorine into Inhalation Anaesthetics

The development of modern anaesthetics occurred during the same time period for much of the same reasons as refrigerants discussed in the previous chapter. Rather than diethyl ether (1846), chloroform (1847) and nitrous oxide (1840s), greater safety and reliability were afforded by low molecular weight, non-flammable, partially fluorinated ethers.\[61\] Predominantly these reagents all are hydrofluoroethers with the exception of halogenated alkane, Halothane \[34,8\]. The most widely used inhalation anaesthetics, especially Isoflurane, Desflurane and Sevoflurane are outlined in \textbf{Table 2.8}. One particular anaesthetic, methoxyflurane \[35\] produced by Abbott Laboratories (as Penthrane\textsuperscript{®}) was of direct interest to us. Hence, the motivation to study the interaction between tertiary amines and the commercially available inhalation anaesthetic \[35\] could be summarized as follows:

1. similarity in structure to \[2 - 4\].

2. paucity of information on the reactivity of methoxyflurane.

3. could provide a source for difunctional perfluoroalkoxides.

4. contribute to the much discussed source of renal toxicity of methoxyflurane and speculation on the mechanism for the formation of inorganic fluoride and dichloroacetic acid (DCAA) \[35a\]

\[8\]While fascinating, structure-activity relationship and the mechanism of action for the anaesthetics properties of fluorinated ethers will not be discussed here. Rather, readers are directed towards insightful reviews on this matter.\[61,62\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Common Name</th>
<th>Metabolic Products</th>
</tr>
</thead>
</table>
| 35    | \[ \text{Cl} \quad \text{F} \]
       | \[ \text{H} \rightarrow \text{C} \quad \text{C} \quad \text{O} \quad \text{C} \rightarrow \text{O} \quad \text{CH}_3 \]
       | methoxyflurane | 50% metabolized, high levels of $\text{F}^-$, dichloroacetic acid; high nephrotoxicity |
| 34    | \[ \text{F} \quad \text{Br} \]
       | \[ \text{F} \quad \text{C} \rightarrow \text{C} \quad \text{H} \]
       | \[ \text{CF}_3 \quad \text{H} \]
       | halothane | not significantly defluorinated |
| 36    | \[ \text{F} \quad \text{H} \]
       | \[ \text{F} \quad \text{C} \rightarrow \text{C} \quad \text{O} \quad \text{C} \rightarrow \text{O} \quad \text{H} \]
       | \[ \text{CF}_3 \quad \text{F} \]
       | sevoflurane | undergoes significant defluorination |
| 37    | \[ \text{F} \quad \text{H} \]
       | \[ \text{F} \quad \text{C} \rightarrow \text{C} \quad \text{O} \quad \text{C} \rightarrow \text{O} \quad \text{H} \]
       | \[ \text{Cl} \quad \text{F} \]
       | isoflurane | 2-5% metabolized, low defluorination |
| 38    | \[ \text{F} \quad \text{H} \]
       | \[ \text{F} \quad \text{C} \rightarrow \text{C} \quad \text{O} \quad \text{C} \rightarrow \text{O} \quad \text{H} \]
       | \[ \text{Cl} \quad \text{F} \]
       | enflurane | high serum $[\text{F}^-]$ levels\(^{[63]}\) |
| 39    | \[ \text{F} \quad \text{H} \]
       | \[ \text{F} \quad \text{C} \rightarrow \text{C} \quad \text{O} \quad \text{C} \rightarrow \text{O} \quad \text{H} \]
       | \[ \text{F} \quad \text{F} \]
       | desflurane | 2-5% metabolized, not significantly defluorinated |

Methoxyflurane \(^{35}\) is an extremely potent anaesthetic and can be self-administered as a rapid acting analgesic. As a non-flammable liquid, it is easier to use than gaseous nitrous oxide and an alternative to opiate based morphine.\(^{[64,65]}\) Methoxyflurane was one of the first introduced (1940s) inhalation anaesthetics and sought widespread clinical use in the 1960s.\(^{[65]}\) However, one of significant and well-established side-effects in the clinical use of methoxyflurane is renal tubular lesions leading to kidney failure.\(^{[65]}\) This acute nephrotoxicity led to its reduced use and was largely replaced in the late 1970s by its derivatives which were much less harmful.\(^{[63,64]}\) The United States and Canada discontinued the use of \(^{35}\) in 1999 and the US FDA determined in 2005 that \(^{35}\) should be withdrawn from the market for safety reasons. However, it is still widely available and used in Australia and New Zealand.\(^{[65]}\)
Scheme 2.8. Proposed O-demethylation Metabolic Pathway of Methoxyflurane with Proposed or Unstable Intermediates in Square Brackets. cP450 = cytochrome P450 enzyme. (Adapted from Kharasch et al.)

Scheme 2.8:

Methoxyflurane is rapidly metabolized in humans ostensibly by oxidative demethylation and defluorination. In humans, it is thought that 50-70% of absorbed methoxyflurane is metabolized either in the liver or kidneys via cytochrome P450 enzymes. The major metabolites formed are fluoride and dichloroacetate (DCAA) which are excreted in urine and can be quantified. Based on the association between dose related methoxyflurane exposure and renal failure, it was concluded that the nephrotoxicity was caused by the decomposition of 35 into inorganic fluoride. As a result, the classically accepted fluoride toxicity hypothesis was expanded to the metabolism of all inhalation anaesthetics and the notion that fluoride acts as a specific toxic agent to kidneys prevailed for many years. Research performed by Kharasch in 2006 however unambiguously elucidated that the presence of inorganic fluoride was not the source for nephrotoxicity. Rather, toxicity seems specific to methoxyflurane and to certain extent, sevofluorane. In systematic rat studies, the toxicity of known metabolites namely, inorganic fluoride (as NaF), methoxydifluoroacetic, DCAA, alone or injected together were not the cause of renal failure. Upon investigating possible metabolic pathways for the 35, the results of several well thought-out experiments by Waskell suggested that the most likely metabolic pathway is attributed to O-demethylation of 35 resulting in metabolites such as unstable perfluoroalcohol that in turn eliminate HF or F\(^{-}\) (Scheme 2.8). Although the authors concluded that the source of toxicity is still unknown the source was deemed to be in this initial process. In perspective of this chapter, the noted toxicity of methoxyflurane and the observed metabolic products are both expected and consistent with the alkylation ability of methoxy fluorinated ethers and gave us an impetus to study this particular relevant HFE further.
2.5.2 Reactivity of Methoxyflurane Towards Tertiary Amines

Having established that the series of hydrofluoroethers 2-4 can readily methyleate tertiary amines, we were interested in further diversifying the scope of this reaction. Although not fully fluorinated, we speculated if chloro-substitution would inductively weaken the CH$_3$–OR$_F$ bond sufficiently to enable O-demethylation with a tertiary amine. Alternatively, the presence of an active H on C(2) could result in a two-step process by an initial dehydrofluorination to afford the *in situ* enol ether. This then could undergo O-demethylation *via* a second equivalent of tertiary amine to afford the corresponding enolate. In either case, the resulting analogous perfluoroalkoxide (or enolate) could provide a route to a synthetically desirable difunctional fluorinated alkoxide for derivatization of organic scaffolds (Chapter 3) or as initiators for the polymerization of perfluoro-epoxides (Chapter 4).

Despite being commercially applicable and having a long history of being clinically utilized as an anaesthetic, we were surprised that there was only one report of reactivity for 35. Thus, Ramig reported in 1999 that refluxing methoxyflurane in the presence of potassium hydroxide undergoes dehydrofluorination to afford the corresponding enol ether 35d.\textsuperscript{[67]} Although characterized by $^1$H and $^{19}$F NMR spectroscopy, 35d was not isolated but carried forward without purification in subsequent steps (Scheme 2.9).\textsuperscript{[67]}

\textbf{Scheme 2.9.} Dehydrofluorination of Methoxyflurane 35 with KOH to Afford Enol Ether 35d as Reported by Ramig in 1999 is the Only Reported Reaction for This Anaesthetic in the Chemical Literature

\[ \text{Cl} \quad \text{F} \quad \text{F} \quad \text{O} \quad \text{CH}_3 \quad \text{KOH} \quad \text{Cl} \quad \text{F} \quad \text{O} \quad \text{CH}_3 \]

\text{N}_2, \text{reflux, 12 h}

\text{35} \quad \text{35d} \quad \text{(not isolated)}

2.5.3 Results

We carried out initial DFT calculations on methoxyflurane that suggested that a substantial contribution of the LUMO was located on the methyl of 35. Due to the lower basicity and higher nucleophilicity for unhindered tertiary amines compared to aqueous hydroxide, we hoped that under the appropriate conditions, we could directly prepare the fluorinated alkoxide. Since NMe$_3$ consistently gave isolated yields between 86-96% with 2-4 and is easily removed under a reduced pressure, an excess (3.1 equivalents) of anhydrous NMe$_3$ was vacuum transferred to a pressure vessel containing 35. Once warmed to RT, a white precipitate began to form over a 3 hours similar to previous results with HFEs (2-4). After 12 h, the contents of the reaction converted to a dark brown residue which in follow-up experiments quickened with heating or rapidly formed with the highly reactive quinuclidine or after a prolonged period with $N,N$-dimethylbenzylamine.
Scheme 2.10. Reaction between Inhalation Anaesthetic Methoxyflurane 35 and Trimethylamine at RT

![Reaction Scheme]

After removal of volatiles, preliminary analysis indicates that methoxyflurane 35 reacts readily with NMe$_3$ as evidenced by NMR and GC/MS analysis. The characteristic signals of methoxyflurane 35 in the $^1$H NMR spectrum are no longer present with complete loss of the CH$_3$ signal at 3.71 ppm and terminal CCl$_2$H. A new singlet with identical chemical shift as NMe$_4$OC$_2$F$_5$ 2a suggests the presence of a tetramethylammonium cation due to methylation of NMe$_3$. The dehydrofluorination product CH$_3$OCF=CCl$_2$ as reported by Ramig is not observed but broad singlet far downfield at 13.61 ppm indicates the presence of a highly electron deficient hydrogen environment. Dichloroacetyl fluoride CHCl$_2$COF (6.09 ppm, d, $J = 2.6$ Hz) or +HNMe$_3$ is also not observed. Further unexplained signals in the $^1$H NMR spectrum, particularly a singlet at 2.55 ppm indicate more complexity than hydrofluoroethers 2-4 and suggest the presence of unaccounted for competing by-products.

![NMR Spectra]

Fig. 2.34. An annotated comparison of $^{13}$C NMR spectra of methoxyflurane 35 (top), crude reaction between of methoxyflurane and NMe$_3$ (middle) and analogous NMe$_4$OC$_2$F$_5$ 2a (bottom) all in CD$_3$CN at 101 MHz with CFCl$_3$ (0.00 ppm).
However, every signal in the $^{13}$C NMR spectrum can be identified. Once again, the CH$_3$ relating to the methyl ether of methoxyflurane have been replaced by a 1:1:1 triplet characteristic of the predicted quaternary ammonium cation (NMe$_4^+$). By measuring the coupling constants, the signal at 68.33 ppm previously assigned to the CCl$_2$H has shifted upfield to 45.23 ppm. Similar to the other HFEs investigated, the C(1) signal bearing α-fluorines at 120.87 ppm is no longer observed after reaction with trimethylamine. While the $^{19}$F NMR spectrum further indicates that all methoxyflurane 35 was consumed during the reaction, the presence of the α-fluorines in RT NMR experiments is not easily confirmed unless VT NMR experiments have been carried out since there are no additional fluorinated environments within the proposed perfluoroalkoxide, OCF$_2$Cl$_2$H.

Although the reactivity of methoxyflurane is still under investigation, preliminary results suggest that methoxyflurane is highly reactive, alkylating the tertiary amines under ambient conditions. This is highly evident by the complete loss of spectroscopic signals relating to CH$_3$OCF$_2$Cl$_2$H and appearance of the tetramethylammonium cation NMe$_4^+$ in both $^1$H and $^{13}$C NMR analysis although the presence of minor products indicate potential competing pathways. The results here are consistent with the in vivo O-demethylation mechanism proposed by Kharasch and provide possible mechanistic explanation for the methylation of reactive sites (such as particularly nucleophilic enzyme) within hepatic or renal metabolic pathways by 35. Further work is required to address the optimization and purification of the desired tetraalkylammonium perfluoroalkoxides, [MeNR$_3$][OCF$_2$CCl$_2$H] for synthetic purposes. However, since methoxyflurane has become a case study in the design of inhalation anaesthetics, it is hoped the preliminary results elucidate a potential chemical interpretation of the nephrotoxicity of 35.

2.6 Perfluoroalkoxylation of Benzyl Bromides

2.6.1 Introduction

The incorporation of a perfluoroalkoxy moiety into organic frameworks is of current interest as the fluorinated ether can impart dramatic electronic, steric and hydrophobic properties. Often this is utilized for the modification of pharmaceutical, agrochemical and material based applications, but as discussed earlier in this chapter, also relevant for the preparation of new fluorinated solvents, refrigerants and anaesthetics. Recently Billard$^{[33,34,68]}$, Cheburkov$^{[13]}$, and Kolomeitsev$^{[27]}$, explored the preparation of trifluoromethoxy alkyl ethers (Alkyl-OCF$_3$) from corresponding aliphatic bromides, iodides and triflates in a two-step process: (1) generation of a in situ perfluoroalkoxide using an anhydrous fluoride with a perfluoroalkoxy reagent and (2) followed by the introduction of the aliphatic substrate. For instance, Billard stated in 2014 that "obviously, the best synthesis of trifluoromethyl ethers would be the direct introduction of the whole –OCF$_3$ moiety."$^{[68]}$ However as they noted, numerous attempts by others to carry this out with perfluoroalkoxide salts failed due
to the perfluoroalkoxide collapsing into the corresponding fluoride and acyl fluoride, even at low temperatures. Rather, they and others have successfully prepared perfluoroalkoxy ethers by an \textit{in situ} preparation of nucleophilic perfluoroalkoxides using acyl fluorides (like gaseous fluorophosgene, COF$_2$) or reagents that generate perfluoroalkoxides with a fluoride source with bulky cations (such as Cs$^+$, Ag$^+$, (Me$_2$N)$_3$S$^+$, NMe$_4$) to generate aliphatic perfluoroalkoxy ethers. The reagents used such as 2,4-dinitro(trifluoromethoxy) benzene 40, alkyl fluoroformates 41 or the low boiling point trifluoromethyl triflate 42 are either inconvenient to prepare, not commercially available, or simply have no established synthetic protocols (an improved synthesis of 42 is discussed in Chapter 3). Nonetheless, previous reports found that activated, sterically unhindered alkyl halides such as benzyl, \(\alpha\)-halocarbonyl, and allyl ("easy") substrates with good leaving groups are converted to the respective ether in moderate to good yields (4-100\%). The synthesis of aliphatic ethers beyond alkyl-OCF$_3$ are limited with only one report of benzyl perfluoropropoxy ethers by Cheburkov and Lillquist utilizing pentafluoropropionyl fluoride, liquid NEt$_3$–3HF and benzyl bromide. The best conversion of PhCH$_2$OCF$_3$ was 53\% which was not isolated in this case which is typically for many reports most often reporting conversions by GC/MS, often without even an internal standard.

### 2.6.2 Optimization, Reactivity, Isolation and Characterization

With a convenient route to perfluoroalkoxides with improved thermal stability in the solid state, we then explored the reactivity of 3a with benzyl bromide substrates. Rather than design new perfluoroalkoxy ethers, the motivation was to develop an understanding of the nucleophilicity of tetraalkylammonium perfluoroalkoxides and to indirectly explore their solution state stability with respect to previously reported methods. Perfluoroalkoxides prepared from hydrofluoroethers do not require a source of fluoride which is a notable improvement over any previous methods.

\textit{Scheme 2.11.} Optimization of Benzyl Perfluoropropoxy Ether

Since anhydrous fluoride in aprotic solvents can act as an effective, highly competitive nucleophile (or base), any fluorination product observed we surmised would be the result of an elimination of F$^-$ from the perfluoroalkoxide. After optimizing the solvent and temperature, we found that acetonitrile at 45°C gave the highest conversion of perfluoroalkoxy benzyl ether 44. Surprisingly, even at 45°C, with 2.0 equivalents of tetramethylammonium perfluoropropoxide, only 1\% of 4-bromobenzyl fluoride 44a was obtained. However, at 75°C
the same conversion of ether was obtained but an increase in 4-bromobenzyl fluoride 44a. We hypothesized that the newly formed ether was in a reversible reaction with the Br⁻ nucleophuge increasing the likelihood of the irreversible fluorination. With the addition of 1 equivalent of AgBF₄, the conversion reached 94% with less than 1% benzyl fluoride after a standard 8 hours (Table 2.9). If, AgNO₃ is used, the corresponding benzyl nitrate ester is afforded.

**Table 2.9: Optimization of Reaction Parameters between [NMe₄]OC₃F₇ 3a and 4-Bromobenzyl Bromide**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>44 (%)[^a]</th>
<th>44a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>none</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>none</td>
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<td>1.0 eq AgBF₄</td>
<td>45</td>
<td>94</td>
<td>3</td>
</tr>
</tbody>
</table>

[^a] All yields were determined by GC/MS against a calibrated internal standard (4-bromotoluene).

Using tetramethylammonium perfluoropropoxide 3a, three benzyl perfluoropropoxy ethers were prepared in nearly quantitative conversion demonstrating that these reagents can be successfully utilized to generate new hydrofluoroethers. To demonstrate viability as a synthetic method, the perfluoroalkoxy benzyl ethers were isolated and characterized by standard methods. The AgBr and NMe₄BF₄ by-products can be easily filtered off, and resulting residue can be purified by standard flash chromatography using 100% pentane as the eluant. The volatility of the resulting ethers contributed to a lower isolated yield (62-70%) compared to observed GC/MS conversion, especially noted during roto-evaporation of the pentane from the product fractions.

Even though the benzyl substrates reported herein are simple in scope with no competing β-hydrogen elimination pathway, the perfluoroalkoxides are able to tolerate higher temperatures than previously reported with high conversion of the ether and only minor amounts of fluoride substitution. Whether the benzyl fluoride formed (up to 8% at 75 °C after 48 h) is a result of thermal instability of the perfluoroalkoxide or due to trace H₂O in the reaction solvent affording fluoride is not entirely clear. Arguably, benzyl fluorides are often difficult to form by direct nucleophilic substitution and even if fluoride was present, in a closed system, the benzyl perfluoropropoxy ether may be the thermodynamically preferred product. However, even if the perfluoroalkoxide is not in equilibrium with free fluoride, the newly formed ethers could still be susceptible to β-fluoride elimination. For instance, no product was observed with 2-bromoacetophenone derivative 46 but substantial amounts of
Fig. 2.35. Perfluoroalkoxylation of alkyl bromides with NMe₄OC₃F₇ 3a at 45°C in CH₃CN for 8 h. Conversions were determined by GC/MS analysis and yields of the pure isolated compound are reported in parentheses.

benzoyl fluoride derivatives while complex mixtures were observed with 47 and 48. The observation that bromide, nitrate, and perfluoropropionic acid can all displace the benzyl bromide or possibly the newly formed perfluoropropoxy substituent, highlights the very low nucleophilicity of -OC₃F₇ and tendency for it to act as a nucleophuge rather than a nucleophile.

2.7 Summary and Outlook

2.7.1 Conclusions

Commercially available methoxy based hydrofluoroethers are being used widely as a solvent, blowing agent and most importantly as a refrigerant and are considered to be inert. However, we report here that these chlorofluorocarbon replacements are not inert but are alkylating agents reacting readily with tertiary amines and phosphines. We have observed that three commercially available methyl hydrofluoroethers act as electrophilic methylating agents of tertiary amines affording quaternary ammonium perfluoroalkoxide. In our opinion, this work represents the largest and most complete spectroscopic analysis of perfluoroalkoxides to date since Willis’ seminal report on metal perfluoroalkoxides in 1965. We have utilized the full range of ¹H, ¹³C, ¹⁹F NMR, IR, TGA-MS, and elemental analysis to characterize the highly-moisture sensitive reaction products between hydrofluoroethers and tertiary amines. At first glance, perfluoroalkoxides may seem mundane but upon close inspection, the realization that these materials challenge both spectroscopic and bonding models provides a much deeper discussion. As such, perfluoroalkoxides have an unaccounted for fluxional process which initially obscures fine splitting in the NMR spectra until solutions are subject to low temperatures (below −28°C). Thus we note that through-space ¹⁹F-¹⁹F spin spin coupling has a greater effect than the expected through-bond coupling.
consistent with other small rigid fluorinated molecules. Furthermore, we discuss competing theories for the spectroscopic conundrum for the bonding in the C–O and α-C–F bond of perfluoroalkoxides. We highlight the value in Gillespie’s overlooked ligand close-packing model to understand and to predict geometric parameters to come to understanding that perfluoroalkoxides can be surprisingly considered pentavalent, four-coordinate species. These species can be alternatively viewed as resonance between ionic and covalent resonance structures.

Hydrofluoroethers provide access to new tetraalkylammonium perfluoroalkoxides in a synthetically pleasing, fluoride-free protocol that does not require specialized skill in fluorine chemistry. This general methodology thus opens up a new frontier for a fluorinated functional group that has not been easily accessible. These materials are isolable, thermally stable (to 180°C in the absence of moisture), and react with benzyl bromides to form perfluoropropoxy benzyl ethers. Alternatively, hydrofluoroethers can be considered a fairly robust protecting group for the otherwise highly moisture sensitive and valuable perfluoroacetyl moiety that can be simply deprotected under facile conditions (less than 50°C) with an unhindered tertiary amine in high conversion. In addition, the reactivity of hydrofluoroethers was briefly extended to secondary amines and other Group 15 nucleophiles. In a similar manner to hydrofluoroethers 2 - 4, the demonstrated reactivity can bring further understanding to the in vivo demethylation pathway of inhalation anaesthetic, methoxyflurane.

2.7.2 Future Work

This chapter leaves unanswered questions concerning the cause of the broadening of spectroscopic signals in the 13C and 19F NMR analyses. While this has been attributed to an unproven solution-state fluxional process, a more thorough investigation is needed to fully develop and a basis for this phenomenon. This is particularly critical for synthetic applications for its use as a perfluoroalkoxy moiety rather than its use as an unwanted source of fluoride, a topic discussed in subsequent chapters. While ongoing, obtaining further spectroscopic structural information through SC-XRD and VT-NMR spectroscopy would enhance the bonding model within α-fluorinated alkoxides. The extreme moisture-sensitivity of perfluoroalkoxides necessitates developing practical methods to carry out full characterization of novel compounds. This includes designing a mass spectroscopy protocol as an alternative to elemental analysis, constructing experiments for thermal stability (m.p. or decomposition temperatures), and complete characterization of all compounds by IR, data not typically reported for this class of intriguing fluorinated compounds.

While the general methodology presented in this chapter could be extended in many directions, industrially relevant precursors including fluorinated cyclic hydrofluoroethers such as oxiranes and oxetanes or more complex hydrofluoroethers with those bearing further functional groups seems highly appealing. Furthermore, with the appropriately designed protocol in mind, new methods for the preparation of highly valuable anhydrous
tetramethylammonium fluorides by intentional decomposition of perfluoroalkoxides can be realized. Such a procedure would render these materials not only truly anhydrous but also in a more convenient fashion than current methodologies. While only a few examples were demonstrated in this chapter, the perfluoroalkoxylation of a larger scope of alkyl (pseudo-) halides substrates can also be envisioned.

Lastly, the preliminary results within this chapters indicate that methoxyflurane could potentially methylate tertiary amines. This reaction has significant biological implications as amines are prevalent in the body from nucleotides to neurotransmitters and further studies between methoxyflurane and biological amines could be devised. As of now, very little has been communicated about the chemical reactivity of this anaesthetic. Beyond expanding the use as a precursor to fluorinated alkoxides, further studies would corroborate the proposed O-demethylation pathway.
2.8 Experimental

2.8.1 General Remarks

All manipulations were performed under the exclusion of moisture and oxygen using a Vacuum Atmospheres HE-493 glovebox with pre-purified nitrogen or with appropriate Schlenk techniques with oven dried glassware. All starting materials were commercially available and were purchased from Sigma Aldrich, unless otherwise noted. Pentafluoroethyl methyl ether 2, 98% was purchased as a compressed gas from SynQuest Labs Inc. (Alachua, Florida, USA) and was used as received. Hydrofluoroethers, methoxy heptafluoropropane (HFE-7000 3, Novec® -7000) and methoxy nonafluorobutane (HFE-7100 4, Novec® -7100) and were purchased from 3M Company, dried over P2O5 for a minimum of 48 h, distilled under nitrogen and subsequently stored over CaH2 and/or 3Å mol sieves under an inert environment. Methoxy nonafluorobutane consists of two isomers. These are (CF3)2CFCF2OCH3 (CAS No. 163702-08-7) and CF3CF2CF2CF2OCH3 (CAS No. 163702-07-6) and are inseparable by distillation. It is essential that the liquid tertiary amines were distilled under an inert atmosphere or reduced pressure and stored over CaH2. Hexanes were distilled over Na/benzophenone and stored over Na wire. Acetonitrile was distilled over CaH2 under nitrogen and stored over pre-conditioned 3Å mol sieves. Flash chromatography was performed on silica gel 60 (40-60μm) using a forced flow of eluant.

A Varian Mercury 400, Unity/Inova 500, Bruker ASCEND III 400 MHz, Bruker AVANCE III 500 MHz and Bruker AVANCE II 600 MHz 'QNP 600' running TopSpin 3.1.6 were employed for obtaining solution-state NMR data and processed with Mestrenova Software. Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz. 13C NMR spectra are recorded 1H decoupled and 19F NMR spectra are recorded 1H coupled unless otherwise noted. Chemical shifts are reported in ppm with the solvent resonance as the internal standard for 1H and 13C spectra whereas 19F NMR experiments was internally referenced to CFCl3 (0.00 ppm). Thermogravimetric analyses (TGA) with mass spectroscopic (MS) analysis of the gaseous products were performed at University of Utah with a TA Model Q500 TGA equipped with a Pfeiffer Thermostat GSD301T3 quadrupole mass spectrometer to identify gaseous products with masses less than 300 amu. Experiments were performed in a Vacuum Atmospheres DriLab under nitrogen to protect air- and moisture-sensitive samples. Samples were placed in an aluminum pan and heated at 10°C min⁻¹ under a continuous 10 mL min⁻¹ nitrogen flow. Infrared Analysis (IR) were performed on a ThermoFisher Nicolet 380 spectrophotometer housed inside a Vacuum Atmospheres HE-493 glovebox with a DLaTGS Detector with a Ge SmartIR ATR sampling assembly at 2 cm⁻¹ resolution. Elemental analyses (C,H,N) were performed by Canadian Microanalytical Services Ltd. (Delta, BC,
Canada). Computational analyses were carried out using the Spartan’10 package, at the B3LYP hybrid density functional level of theory employing the B3LYP/6-311+G** basis set with geometry optimization in the gas phase.

2.8.2 Preparation and Experimental Data

Note: All accompanying experimental spectra for this chapter if not presented here can be located in Appendix B, C, D, and E.

Experimental Procedures for Tetralkylammonium Perfluoroethoxides

Fig. 2.36. Vacuum transfer of CH$_3$OCF$_2$CF$_3$ for each of the following examples was carried out on a stainless steel transfer line to enable a known amount of reagent to be carefully added to each reaction

Tetramethylammonium perfluoroethoxide (2a)

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and anhydrous 1,4-dioxane (3.304 g). The tube was sealed and connected to a stainless steel vacuum line to
which anhydrous \text{NMe}_3 (1.464 \text{ g}, 24.7 \text{ mmol}, 1.0 \text{ equiv}) and pentafluoroethyl methyl ether 2 (7.704 \text{ g}, 51.3 \text{ mmol}, 2.1 \text{ equiv}) was transferred at $-196^\circ\text{C}$. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 69 h (max pressure <1 bar). The volatiles were removed under reduced pressure (0.5 Torr) to afford 2a as a fine white powder (4.781 g, 92%). $^1\text{H} \text{ NMR}$ (400 MHz, CD$_3$CN) δ 3.12 (s, 3H). $^{13}\text{C} \text{ NMR}$ (100.62 MHz, CD$_3$CN) δ 55.81, (fluorinated carbons not detectable). $^{19}\text{F} \text{ NMR}$ (376 MHz, CD$_3$CN) δ -32.02 (-CF$_2$O$^-$, broad s), -73.94 (F$^-$), -82.85 (CF$_3$, s).

$\text{N,N,N}$-trimethyl-1-phenylmethanaminium perfluoropropoxide (2f)

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and quinuclidine (1.148 g, 8.49 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (3 mL). The tube was sealed and connected to a stainless steel vacuum line to which pentafluoroethyl methyl ether 2 (2.74 g, 18.28 mmol, 2.15 equiv) was transferred at $-196^\circ\text{C}$. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 24 h (max pressure <1 bar). The volatiles were removed under reduced pressure (0.5 Torr) and the residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 2h as a fine white crystalline powder (2.394 g, 89%). $^1\text{H} \text{ NMR}$ (400 MHz, CD$_3$CN) δ 3.04 (s, 9H), 4.49 (s, 2H), 7.12-7.76 (m, 5H). $^{13}\text{C} \text{ NMR}$ (100.62 MHz, CD$_3$CN) δ 1.20 (CD$_3$CN) 53.01, 69.76, 118.26 (CD$_3$CN), 128.82, 129.98, 131.51, 133.78, (fluorinated carbons not detectable). $^{19}\text{F} \text{ NMR}$ (376 MHz, CD$_3$CN) δ -31.90 (-CF$_2$O$^-$, broad s), -73.91 (F$^-$), -82.84 (CF$_3$, s, 3F).

1-methylquinuclidinium perfluoroethoxide (2h)

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and quinuclidine
(1.148 g, 8.49 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (3 mL). The tube was sealed and connected to a stainless steel vacuum line to which pentafluoroethyl methyl ether 2 (2.74 g, 18.28 mmol, 2.15 equiv) was transferred at −196 °C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 24 h (max pressure < 1 bar). The volatiles were removed under reduced pressure (0.5 Torr) and the residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 2h as a fine white crystalline powder (2.394 g, 89%).

$$\delta$$ 1.95 (broad m (overlapping with CD$_3$CN), 6H), 2.15 (septet, $^3$$J_{HH}$ = 3.3 Hz, 1H), 2.91 (s, 3H), 3.41 (t, $^3$$J_{HH}$ = 8.06, 6H). $^{13}$C NMR (100.62 MHz, CD$_3$CN) $\delta$ 1.20 (CD$_3$CN), 19.84 (t, $J_{CN}$ = 4.88 Hz), 24.37, 52.62 (t, $J_{CN}$ = 4.72 Hz), 57.56 (t, $J_{CN}$ = 3.13 Hz) 118.26 (CD$_3$CN), (fluorinated carbons not detectable). $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -28.23 (-CF$_2$O$^-$, broad s.), -80.63 CF$_3$, s).

2-(dimethylamino)-N,N,N,N-trimethylethan-1-aminium perfluoroethoxide ($\text{2i}$)

$$\begin{array}{c}
\text{H}_3\text{C} \quad \text{OCF}_2\text{CF}_3 \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{H}_3\text{C} \\
\text{OCF}_2\text{CF}_3
\end{array}$$

dioxane
RT, 216 h

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and N,N,N,N-tetramethylethylenediamine (1.950 g, 16.78 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (5 mL). The tube was sealed and connected to a stainless steel vacuum line to which pentafluoroethyl methyl ether 2 (6.159 g, 41.05 mmol, 2.45 equiv) was transferred at −196 °C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 216 h (max pressure < 1 bar). The volatiles were removed under reduced pressure (0.5 Torr) and the slightly yellow crystalline residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 2i as a fine white powder (4.10 g, 92%). $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 2.21 (s, 6H), 2.64-2.68 (m, 2H), 3.13 (s, 9H), 3.40 (t, $J$ = 5.89 Hz, 2H). $^{13}$C NMR (100.62 MHz, CD$_3$CN) $\delta$ 1.16 (CD$_3$CN), 45.20, 54.14, 63.36 (t, $J_{CN}$ = 2.97 Hz), 118.26 (CD$_3$CN), (fluorinated carbons not detectable). $^{19}$F NMR (376 MHz, CD$_3$CN) -31.87 (-CF$_2$O$^-$, broad s.), -73.90 (F$^-$), -82.83 (CF$_3$, s, 3F).

1,1,4-trimethylpiperazin-1-ium perfluoroethoxide ($\text{2j}$)
A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and 1,4-dimethylpiperazine (1.692 g, 14.82 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (3.089 g). The tube was sealed and connected to a stainless steel vacuum line to which pentafluoroethyl methyl ether 2 (6.116 g, 40.76 mmol, 2.75 equiv) was transferred at −196 °C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at 40 °C for 68 h (max pressure < 1 bar). The volatiles were removed under reduced pressure (0.5 Torr) and the slightly yellow residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 2j as a white fine powder (2.234 g, 57%).

1H NMR (400 MHz, CD3CN) δ 2.31 (s, 3H), 2.66 (broad s, 4H), 3.09 (s, 6H), 3.28 (t, 3JHH = 5.12 Hz, 4H). 13C NMR (100.62 MHz, CD3CN) δ 1.20 (CD3CN), 45.04, 48.88, 62.49 (broad s), 118.26 (CD3CN) (fluorinated carbons not detectable). 19F NMR (376 MHz, CD3CN) -31.80 (-CF2O–, broad s), -73.90 (F–), -82.82 (CF3, s, 3F).

1-methyl-1,4-diazabicyclo[2.2.2]-octan-1-ium perfluoroethoxide (2k)

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and 1,4-diazabicyclo[2.2.2]-octane (1.770 g, 15.8 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (5.80g). The tube was sealed and connected to a stainless steel vacuum line to which pentafluoroethyl methyl ether 2 (6.142 g, 40.92 mmol, 2.59 equiv) was transferred at −196 °C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 48 h (max pressure < 1 bar). The volatiles were removed under reduced pressure (0.5 Torr) and the residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 2k as a fine white powder (4.133 g, 99%).

1H NMR (400 MHz, CD3CN) δ 2.95 (s, 3H), 3.08 (t, 3JHH = 7.12 Hz, 6H), 3.26 (t, 3JHH = 7.95 Hz, 6H). 13C NMR (100.62 MHz, CD3CN) δ 1.11 (CD3CN), 45.64, 52.01 (t, JCN = 4.56 Hz), 54.68 (t,
$J_{CN} = 3.62$ Hz), 118.26 (CD$_3$CN) (fluorinated carbons not detectable). $^{19}$F NMR (376 MHz, CD$_3$CN) -31.79 (-CF$_2$O –, broad s), -73.86 (F$^-$), -82.83 (CF$_3$, s, 3F).

Experimental Procedures for Tetralkylammonium Perfluoropropoxides

Methoxy heptafluoropropane (3)

\[ \text{H}_3\text{C} - \text{OCF}_2\text{CF}_2\text{CF}_3 \]

Colourless liquid. $^1$H NMR (400 MHz, CDCl$_3$) 3.808 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) 49.34 (t, $^1J_{CF} = 6.8$ Hz, 1C), 106.71 (CF$_2$, t hex, $^1J_{CF} = 264.5$, $^2J_{CF} = 38.9$ Hz, 1C), 116.04 (CF$_2$O, tt, $^1J_{CF} = 270.9$, $^2J_{CF} = 29.6$ Hz, 1C), 117.11 (CF$_3$, q, $^1J_{CF} = 284.9$, $^2J_{CF} = 33.5$ Hz, 1C). $^{19}$F NMR (376 MHz, CDCl$_3$) -82.97 (CF$_3$, t, $^3J_{FF} = 7$ Hz, 3F), -90.19 (CF$_2$), t, $^3J_{FF} = 7.2$ Hz, 2F), -130.73 (CF$_2$, t, $^3J_{FF} = 3.8$ Hz, 2F). Literature compound not previously fully characterized.

Tetramethylammonium perfluoropropoxide (3a)

A 60mL Ace® Glass Pressure tube with a #25 Teflon stopper, Swagelok® quick-connect, and pressure gauge was charged in a glovebox with a stir bar and anhydrous CH$_3$OC$_3$F$_7$ (16.910 g, 80.9 mmol) 3. The tube was sealed and connected to a vacuum line to which NMe$_3$ (1.91 g, 32.3 mmol) was transferred. The vessel was heated behind a blast shield at 50 °C for 22 h. The reaction vessel was then cooled, the volatiles removed under reduced pressure, and then the residue washed with 3x 10 mLs of anhydrous hexane in a fritted filter in a glovebox to afford 3a as a fine white solid (7.21 g, 86%). $^1$H NMR (400 MHz, CD$_3$CN) δ 3.160 (s, 3H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -125.84 (CF$_2$, s, 2F), -81.89 (CF$_3$, s, 3F), -27.67 (CF$_2$O, broad, s, 2F). Anal. Calcd. for C$_7$H$_{12}$F$_7$NO: C, 32.44; H 4.67, N 5.40; Found: C, 32.68; H, 5.21; N, 5.77.

$N,N$-diethyl-$N$-methylethanaminium perfluoropropoxide (3b)
A 20 mL vial in a glovebox was charged with excess CH₃OC₃F₇ 3 (10.270 g, 51.3 mmol) and anhydrous triethylamine (2.122 g, 21.0 mmol) and sealed for 48 h at 50 °C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3b as a fine crystalline white powder (3.692 g, 58%). ¹H NMR (400 MHz, CD₃CN) δ 1.27 (tt, 3 J₉H = 7.3 Hz, 2.0, 9H), 2.890 (s, 3H), 3.28 (q, 3 J₉H = 7.3 Hz, 6H). ¹⁹F NMR (376 MHz, CD₃CN) δ -125.75 (CF₂, s, 2F), -81.91 (CF₃, s, 3F), -27.92 (CF₂O, broad, s, 2F). Anal. Calcd. for C₁₀H₁₈F₇NO: C, 39.87; H, 6.02; N, 4.65. Found: C, 39.96; H, 5.48; N, 4.74.

N,N-dibutyl-N,N-dimethylpropan-1-aminium perfluoropropoxide (3c)

A 20 mL vial in a glovebox was charged with excess CH₃OC₃F₇ 3 (10.039 g, 50.2 mmol) and anhydrous tri-n-propylamine (2.887 g, 20.2 mmol) and sealed for 48 h at 50 °C. The precipitate was collected and washed with a minimum amount of cold, anhydrous hexanes in a glovebox to afford 3c as a white powder (0.757 g, 11%). ¹H NMR (400 MHz, CD₃CN) δ 1.07 (t, 3 J₉H = 7.3 Hz, 9H), 1.64-1.94 (m, 6H), 3.03 (s, 3H), 3.11-3.40 (m, 6H). ¹⁹F NMR (376 MHz, CD₃CN) δ -125.75 (CF₂, s, 2F), -81.89 (CF₃, s, 3F), -27.64 (CF₂O, broad, s, 2F). Anal. Calcd. for C₁₃H₂₄F₇NO: C, 45.48; H, 7.05; N, 4.08. Found: C, 45.67; H, 6.86; N, 4.12.

N,N-dibutyl-N-methylbutan-1-aminium perfluoropropoxide (3e)

A 20 mL vial in a glovebox was charged with excess CH₃OC₃F₇ 3 (10.085 g, 50.4 mmol) and tri-n-butylamine (3.633 g, 19.6 mmol) and sealed for 72 h at 50 °C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford
3e as a white powder (0.943 g, 13%). $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 0.99 (t, $^3$$J_{HH} = 7.4$ Hz, 9H), 1.37 (m, $^3$$J_{HH} = 7.4$ Hz, 6H), 1.56-1.82 (m, 6H), 2.94 (s, 3H), 3.06-3.32 (m, 6H). $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -125.74 (CF$_2$O, s, 2F), -81.89 (CF$_3$, s, 3F), -27.64 (CF$_2$O, broad, s, 2F). Anal. Calc. for C$_{16}$H$_{30}$F$_7$NO: C, 49.86; H, 7.85; N, 3.63. Found: C, 49.67; H, 7.86; N, 3.83.

$N,N,N$-trimethyl-1-phenylmethanaminium perfluoropropoxide (3f)

\[
\begin{align*}
\text{H}_3\text{C} & \text{OCF}_2\text{CF}_2\text{CF}_3 \\
\xrightarrow{50^\circ\text{C}, 48\text{ h}} & \\
\text{3} & \text{3f}
\end{align*}
\]

A 20 mL vial in a glovebox was charged with excess CH$_3$OCF$_3$F$_7$ (10.140 g, 50.7 mmol) and $N,N$-dimethylbenzylamine (2.794 g, 20.7 mmol) and sealed for 48 h at 50°C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3f as a white crystalline solid (5.921 g, 85%). $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 3.07 (s, 9H), 4.54 (s, 2H), 7.07-7.73 (m, 5H). $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -125.292 (CF$_2$, s, 2F), -81.081 (CF$_3$, s, 3F), -27.071 (CF$_2$O, broad, s, 2F). Anal. Calc. for C$_{13}$H$_{16}$F$_7$NO: C, 46.57; H, 4.81; N, 4.18. Found: C, 46.87; H, 4.99; N, 4.32.

![Isolated $N,N,N$-trimethyl-1-phenylmethanaminium perfluoropropoxide as a white crystalline, solid](image)

**Fig. 2.37.** Isolated $N,N,N$-trimethyl-1-phenylmethanaminium perfluoropropoxide as a white crystalline, solid

4,4-dimethylmorpholin-4-ium perfluoropropoxide (3g)
A 20 mL vial in a glovebox was charged with excess CH$_3$OC$_3$F$_7$ (10.308 g, 51.5 mmol) and 4-methylmorpholine (2.028 g, 20.0 mmol) and sealed for 48 h at 50 °C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3g as a white powder (1.356 g, 23%). $^1$H NMR (400 MHz, CD$_3$CN) δ 3.19 (s, 6H), 3.41 (m, 4H), 3.94 (m, 4H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -125.834 (CF$_2$, s, 2F), -81.920 (CF$_3$, s, 3F), -27.873 (CF$_2$O, broad, s, 2F). Anal. Calcd. for C$_9$H$_{14}$F$_7$NO$_2$: C, 35.89; H, 4.69; N, 4.65. Found: C 36.30; H, 4.19; N 4.73.

1-methylquinuclidinium perfluoropropoxide (3h)

A 20 mL vial in a glovebox was charged with excess CH$_3$OC$_3$F$_7$ (12.395 g, 62.0 mmol, 4.0 equiv) and quinuclidine (1.723 g, 15.50 mmol, 1.0 equiv) and sealed for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3h as a fine white powder (4.419 g, 92%). $^1$H NMR (400 MHz, CD$_3$CN) δ 1.97 (broad m (overlapping with CD$_3$CN), 6H), 2.16 (septet, $^3$J$_{HH} = 3.3$ Hz, 1H), 2.90 (s, 3H), 3.39 (t, $^3$J$_{HH} = 8.15$, 6H). $^{13}$C NMR (100.62 MHz, CD$_3$CN) δ 1.15 (CD$_3$CN), 19.83 (t, $J = 4.94$ Hz), 24.35, 52.55 (t, $J = 4.30$ Hz), 57.56 (t, $J = 3.06$ Hz) 118.26 (CD$_3$CN), (fluorinated carbons not identified). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -28.23 (CF$_2$O, broad, s, 2F), -80.63 (CF$_3$, s, 3F), -124.58 (CF$_2$, s, 2F).

2-(dimethylamino)-N,N,N-trimethylethan-1-aminium perfluoropropoxide (3i)
A 50 mL round bottom flask under nitrogen was charged with excess CH$_3$OCF$_3$F$_7$ 3 (13.190 g, 66.0 mmol) and N,N,N,N-tetramethylethylenediamine (3.825 g, 33.0 mmol) and stirred for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3i as a white, crystalline powder (9.917 g, 95%). $^1$H NMR (400 MHz, CD$_3$CN) δ 2.24 (s, 6H), 2.64-2.73 (m, 2H), 3.16 (s, 9H), 3.39-3.47 (m, 2H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -125.772 (CF$_2$, s, 2F), -81.847 (CF$_3$, s, 3F), -27.688 (CF$_2$O, broad, s, 2F). Anal. Calcd. for C$_{10}$H$_{19}$F$_7$N$_2$O: C, 37.98; H, 6.06; N, 8.86. Found: C, 37.68; H, 6.57; N, 8.96.

1,1,4-trimethylpiperazin-1-ium perfluoropropoxide (3j)

A 50 mL round bottom flask under nitrogen was charged with excess CH$_3$OCF$_3$F$_7$ 3 (13.283 g, 66.4 mmol) and 1,4-dimethylpiperazine (3.923 g, 34.4 mmol) and stirred for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3j as an off-white powder (8.143 g, 75%). $^1$H NMR (400 MHz, CD$_3$CN) δ 2.335 (s, 3H), 2.688 (broad s, 4H), 3.125 (s, 6H), 3.409 (t, $^3$J$_{HH}$ = 5.182 Hz, 4H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -125.782 (CF$_2$, s, 2F), -81.860 (CF$_3$, s, 3F), -27.686 (CF$_2$O, broad, s, 2F). Anal. Calcd. for C$_{10}$H$_{17}$F$_7$N$_2$O: C, 38.22; H, 5.45; N, 8.91. Found: C 38.57; H, 5.25; N, 9.11.

1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium perfluoropropoxide (3k)

A 50 mL round bottom flask under nitrogen was charged with excess CH$_3$OCF$_3$F$_7$ 3 (13.293 g, 66.4 mmol) and 1,4-diazabicyclo-[2.2.2]-octane (3.718 g, 33.1 mmol) and the suspension was stirred for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3k as a white, crystalline powder (10.348 g, 98 %). $^1$H NMR (400 MHz, CD$_3$CN) δ 2.97 (s, 3H), 3.11 (t, $^3$J$_{HH}$ = 7.54 Hz, 6H), 3.27 (t, $^3$J$_{HH}$ = 7.543 Hz, 6H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -125.786 (CF$_2$, s, 2F), -81.860 (CF$_3$, s, 3F), -27.686 (CF$_2$O, broad, s, 2F). Anal. Calcd. for C$_{10}$H$_{17}$F$_7$N$_2$O: C, 38.22; H, 5.45; N, 8.91. Found: C 38.57; H, 5.25; N, 9.11.
2F), -81.886 (CF₃, s, 3F), -27.846 (CF₂O, broad, s, 2F). Anal. Calcd. for C₁₀H₁₅F₇N₂O: C, 38.47; H, 4.84; N, 8.97. Found: C, 38.53; H, 4.40; N, 9.10.

4-(dimethylamino)-1-methylpyridin-1-ium perfluoropropoxide (3n)

A 20 mL vial in a glovebox was charged with excess CH₃OCF₃ (6.430 g, 32.1 mmol) and 4-(dimethylamino)pyridine (0.105 g, 0.86 mmol) and sealed for 48 h at 50°C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3n as a white powder (0.1410 g, 51%). ¹H NMR (400 MHz, CD₃CN) δ 3.181 (s, 6H), 3.905 (s, 3H), 6.88 (d, ²J_HH = 7.7 Hz, 2H), 8.03 (d, ²J_HH = 7.5 Hz, 2H). ¹⁹F NMR (376 MHz, CD₃CN) δ -125.725 (CF₂, s, 2F), -81.842 (CF₃, s, 3F), -27.760 (CF₂O, broad, s, 2F). Anal. Calcd. for C₁₁H₁₃F₇N₂O: C, 41.00; H, 4.07; N, 8.69. Found: C, 41.40; H, 4.09; N, 8.83.

Tetramethylphosphonium perfluoropropoxide (3o)

A 20 mL vial in a glovebox was charged with excess CH₃OCF₃ (12.0 g, 60.0 mmol) and trimethylphosphine (0.623 g, 8.2 mmol) and sealed for 51 h at 50°C. The vial was cooled and the volume of the solution was reduced 50% under reduced pressure in a glovebox. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 3o as a white crystalline powder (0.205 g, 9%). ¹H NMR (400 MHz, CD₃CN) δ 1.96 (d, ²J_HP = 14.9 Hz, 12H). ¹H{³¹P} NMR (400 MHz, CD₃CN) δ 1.96 (s, 12 H). ¹⁹F NMR (376 MHz, CD₃CN) δ -125.792 (CF₂, s, 2F), -81.895 (CF₃, s, 3F), -27.625 (CF₂O, broad, s, 2F). ³¹P{¹H} NMR (162 MHz, CD₃CN) δ 24.361 (s, 1P). ³¹P NMR (162 MHz, CD₃CN) δ 24.372 (m, ²J_PH = 14.894). ¹³C NMR (101 MHz, CD₃CN) δ 9.46 (P–CH₃, d, ¹J_CP = 56.4 Hz, 1C) (fluorinated carbons not detectable). Anal. Calcd. for C₇H₁₂F₇OP: C, 30.45; H, 4.38; N, 0.00 Found: C, 30.35; H, 3.89; N, <0.3.
Experimental Procedures for Tetralkylammonium Perfluorobutoxides

Methoxy -n and -iso nonafluorobutane (4)

\[
\begin{align*}
H_3C-OCF_2CF_2CF_2CF_3 & \quad H_3C-OCF_2(CF_3)_2 \\
\text{4} & \\
\end{align*}
\]

Colourless liquid. \(^1\)H NMR (400 MHz, CD\(_3\)CN) 3.808 (s, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -81.65 (CF\(_3\), tt, \(^3\)J\(_{FF}\) = 9.1 Hz, \(^4\)J\(_{FF}\) = 2.0 Hz, 3F), -88.98 (OCF\(_2\), m, 2F), -126.77 (CF\(_3\)CF\(_2\), m, 2F), -127.17 (CF\(_2\)CF\(_3\)CF\(_2\), m, 2F), and iso-butyl -73.69 (CF\(_3\), td, \(^3\)J\(_{FF}\) = 6.07 Hz, \(^4\)J\(_{FF}\) = 9.6 Hz, 6F), -82.5 (OCF\(_2\), \(^3\)J\(_{FF}\) = 9.43 Hz, \(^4\)J\(_{FF}\) = 9.6 Hz, 2F), -180.40 (CF, m, 1F).

Tetramethylammonium n- and iso- nonafluorobutoxide (4a)

\[
\begin{align*}
\text{H}_3\text{C}-\text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \quad \text{NMe}_3 \\
\text{H}_3\text{C}-\text{OCF}_2\text{CF}(\text{CF}_3)_2 & \quad \text{50}\text{°C, 48 h} \\
\text{4} & \quad \text{CH}_3 \\
& \quad \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 \\
& \quad \text{OCF}_2\text{CF}(\text{CF}_3)_2 \\
\text{4a} & \\
\end{align*}
\]

A 60mL Ace© Glass Pressure tube with a #25 Teflon stopper, Swagelok® quick-connect, and pressure gauge was charged in a glovebox with a stirbar and anhydrous CH\(_3\)OC\(_4\)F\(_9\) 4 (7.3639 g, 29.4 mmol). The tube was sealed and connected to a vacuum line to which NMe\(_3\) (0.316 g, 5.35 mmol) was transferred. The vessel was heated behind a blast shield at 50°C for 48 h. The reaction vessel was then cooled, the volatiles removed under reduced pressure, and then washed with 10 mL of anhydrous hexanes in a glovebox to afford 4a as a fine white solid (1.602 g, 96%) . \(^1\)H NMR (400 MHz, CD\(_3\)CN) 3.137 (s, 3H). \(^{19}\)F NMR (376 MHz, CD\(_3\)CN) \(\delta\) -26.99 (OCF\(_2\), broad s, 2F), -81.64 (CF\(_3\), t, \(^3\)J\(_{FF}\) = 9.1 Hz, 3F), -122.55 (CF\(_3\)CF\(_2\), q, \(^3\)J\(_{FF}\) = 8.8 Hz, 2F), -126.60 (CF\(_2\)CF\(_3\)CF\(_2\), s, 2F) and -18.54 (OCF\(_2\), broad s, 2F), -73.69 (CF\(_3\), d, \(^3\)J\(_{FF}\) = 5.8 Hz, 6F), -180.40 (CF, s, 1F). Anal. Calcd. for C\(_8\)H\(_{12}\)F\(_9\)NO: C, 31.08; H, 3.91; N, 4.53. Found: C, 31.40; H, 4.14; N, 4.94.

\(N,N\)-diethyl-\(N\)-methylethanaminium n- and iso- nonafluorobutoxide (4b)

\[
\begin{align*}
\text{H}_3\text{C}-\text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \quad \text{NEt}_3 \\
\text{H}_3\text{C}-\text{OCF}_2\text{CF}(\text{CF}_3)_2 & \quad \text{RT, 140 h} \\
\text{4} & \quad \text{CH}_3 \\
& \quad \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 \\
& \quad \text{OCF}_2\text{CF}(\text{CF}_3)_2 \\
\text{4b} & \\
\end{align*}
\]
A 50 mL round bottom flask under nitrogen was charged with excess CH₃OC₄F₉ 4 (20 mL, 30.4 g, 122 mmol) and triethylamine (10.164 g, 100 mmol) and stirred for 140 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4b as a white crystalline powder (11.914 g, 34%). ¹H NMR (400 MHz, CD₃CN) δ 1.41 (tt, 3J_HH = 7.3, 2.0 Hz, 9H), 3.02 (s, 3H), 3.41 (q, 3J_HH = 7.3 Hz, 6H). ¹⁹F NMR (376 MHz, CD₃CN) δ -26.88 (OCF₂, broad s, 2F), -81.62 (CF₃, t, 3J_FF = 9.2 Hz, 3F), -122.49 (CF₃CF₂, q, 3J_FF = 9.0 Hz, 2F), -126.61 (CF₂-CF₂-CF₂, s, 2F) and -18.46 (OCF₂, broad s, 2F), -73.73 (CF₃, d, 3J_FF = 6.1 Hz, 6F), -180.33 (CF, s, 1F). Anal. Calcd. for C₁₁H₁₈F₉NO: C, 37.61; H, 5.17; N, 3.99. Found: C, 37.97; H, 5.51; N, 4.19.

N,N-dimethyl-N,N-dipropylpropan-1-aminium n- and iso- nonafluorobutoxide (4c)

A 20 mL vial in a glovebox was charged with excess anhydrous CH₃OC₄F₉ 4 (20 mL, 30.4 g, 122 mmol) and anhydrous tri-n-propylamine (14.397 g, 101 mmol). The vial was sealed for 144 h at RT and stirred. The ensuing precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4c as a fine white, crystalline powder (3.459 g, 9%). ¹H NMR (400 MHz, CD₃CN) δ 1.11 (t, 3J_HH = 7.3 Hz, 9H), 1.86 (m, 6H), 3.08 (s, 3H), 3.39 (m, 6H). ¹⁹F NMR (376 MHz, CD₃CN) δ -26.81 (OCF₂, broad s, 2F), -81.62 (CF₃, t, 3J_FF = 9.0 Hz, 3F), -122.48 (CF₃CF₂, m, 3J_FF = 9.5 Hz, 2F), -126.60 (CF₂-CF₂-CF₂, t, 3J_FF = 8.3 Hz, 2F) and -18.46 (OCF₂, broad s, 2F), -73.73 (CF₃, d, 3J_FF = 10.7 Hz, 2F), -73.71 (CF₃, dt, 3J_FF = 10.9, 4J_FF = 6.2 Hz, 6F), -180.31 (CF, m, 1F). Anal. Calcd. for C₁₄H₂₄F₉NO: C, 42.75; H, 6.15; N, 3.56. Found: C, 42.93; H, 6.02; N, 3.72.

N,N-dibutyl-N-methylbutan-1-aminium n- or iso- nonafluorobutoxide (4e)

A 20 mL vial in a glovebox was charged with excess CH₃OC₄F₉ 4 (10.221 g, 40.9 mmol) and tri-n-butylamine (2.493 g, 13.4 mmol). The vial was sealed for 140 h at RT and stirred. The ensuing precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4e as a white powder (0.932 g, 16%). ¹H NMR (400 MHz,
CD₃CN) δ 0.99 (m, 3JHH = 7.4 Hz, 9H), 1.38 (m, 3JHH = 7.4 Hz, 6H), 1.66 (m, 6H), 2.93 (s, 3H), 3.17 (m, 6H). ¹⁹F NMR (376 MHz, CD₃CN) δ -26.81 (OCF₂, m, 2F), -81.61 (CF₃, t, 3JFF = 9.1 Hz, 2F), -122.47 (CF₂CF₂CF₂, broad s, 2F) and -18.30 (-OCF₂, broad s, 2F), -73.71 (CF₃, d, 3JFF = 5.9, 6F), -180.31 (CF, m, 1F). Anal. Calcd. for C₁₇H₃₀F₉NO: C, 46.89; H, 6.95; N, 3.22. Found: C, 47.24; H, 7.19; N, 3.31.

N,N,N-trimethyl-1-phenylmethanaminium n- and iso- nonafluorobutoxide (4f)

A 50 mL round bottom flask under nitrogen was charged with excess CH₃OC₄F₉ 4 (20 mL, 30.4 g, 122 mmol) and N,N-dimethylaniline (6.761 g, 50.0 mmol) and stirred for 140 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4f as a white, crystalline powder (18.373 g, 95%). ¹H NMR (400 MHz, CD₃CN) δ 3.086 (s, 9H), 4.564 (s, 2H), 7.559 (m, 4.5H). ¹⁹F NMR (376 MHz, CD₃CN) δ -26.93 (OCF₂, m, 2F), -81.59 (CF₃, t, 3JFF = 13.6, 4JFF = 2.8 Hz, 3F), -122.51 (CF₃CF₂, m, 3JFF = 9.5 Hz, 2F), -126.55 (CF₂CF₂CF₂, t, 3JFF = 8.4 Hz, 2F) and -18.44 (OCF₂, dm, 3JFF = 20.6, 4JFF =10.9 Hz, 2F), -73.69 (CF₃, dt, 3JFF = 11.0, 4JFF = 6.1 Hz, 6F) -180.36 (CF, m, 1F). Anal. Calcd. for C₁₄H₁₆F₉N: C, 43.65; H, 4.19; N, 3.64; Found: C, 44.04; H, 3.73; N, 3.79.

4,4-dimethylmorpholin-4-ium n- and iso- nonafluorobutoxide (4g)

A 20 mL vial in a glovebox was charged with excess CH₃OC₄F₉ 4 (10.169 g, 40.7 mmol) and 4-methylmorpholine (1.612 g, 16.0 mmol) and sealed for 140 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4g as a white powder (1.423 g, 25%). ¹H NMR (400 MHz, CD₃CN) δ 3.196 (s, 6H), 3.41 (t, 3JHH = 5.0 Hz, 4H), 3.939 (m, 4H). ¹⁹F NMR (376 MHz, CD₃CN) δ -27.08 (OCF₂, broad s, 2F), -81.63 (CF₃, t, 3JFF = 9.1 Hz, 3F), -122.55 (CF₂CF₂, q, 3JFF = 7.8
Hz, 2F), -126.59 (CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>, t, <sup>3</sup>JI = 7.8 Hz, 2F) and -18.61 (OCF<sub>2</sub>, m, <sup>3</sup>JI = 10.3 Hz, 2F), -73.73 (CF<sub>3</sub>, broad d, <sup>3</sup>JI = 5.9 Hz, 6F), -180.40 (CF, m, 1F). Anal. Calcd. for C<sub>10</sub>H<sub>14</sub>F<sub>9</sub>NO<sub>2</sub>: C, 34.20; H, 4.02; N, 3.99. Found: C, 34.42; H, 3.55; N, 4.15.

1-methylquinuclidinium <i>n</i>- and <i>iso</i>- nonafluorobutoxide (4h)

\[
\begin{align*}
\text{H}_3\text{C} \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \quad \begin{array}{c} \text{N} \end{array} \quad \text{H}_3\text{C} \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 \\
\text{H}_3\text{C} \text{OCF}_2\text{CF}(\text{CF}_3)_2 & \quad \begin{array}{c} \text{N} \end{array} \quad \text{H}_3\text{C} \text{OCF}_2\text{CF}(\text{CF}_3)_2
\end{align*}
\]

A 20 mL vial in a glovebox was charged with excess CH<sub>3</sub>OC<sub>4</sub>F<sub>9</sub> 4 (11.155 g, 44.61 mmol, 5.9 equiv) and quinuclidine (0.839 g, 7.55 mmol, 1.0 equiv) and sealed for 6 h at RT. The precipitate was collected and volatiles removed under reduced pressure without any further purification to afford 4h as a white powder (3.180 g, 99%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ 1.97 (broad m (overlapping with CD<sub>3</sub>CN), 6H), 2.16 (septet, <sup>3</sup>JI = 3.28 Hz), 1H), 2.94 (s, 3H), 3.37 (t, <sup>3</sup>JI = 8.15, 6H).<sup>13</sup>C NMR (100.62 MHz, CD<sub>3</sub>CN) δ 1.22 (CD<sub>3</sub>CN), 19.86 (t, <sup>1</sup>JI = 4.87 Hz), 24.35, 52.69 (t, <sup>1</sup>JI = 4.45 Hz), 57.63 (t, <sup>1</sup>JI = 3.04 Hz) 118.26 (CD<sub>3</sub>CN), (fluorinated carbons not identified). <sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>CN) δ -25.76 (OCF<sub>2</sub>, broad s, 2F), -80.32 (CF<sub>3</sub>, t, <sup>3</sup>JI = 9.29 Hz, 3F), -121.22 (CF<sub>3</sub>CF<sub>2</sub>, q, <sup>3</sup>JI = 8.86 Hz, 2F), -125.31 (CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>, s, 2F) and -17.30 (OCF<sub>2</sub>–, broad s, 2F), -72.44 (CF<sub>3</sub>, broad d, <sup>3</sup>JI = 6.32 Hz, 6F), -180.37 (CF, septet, <sup>3</sup>JI = 6.13 Hz, 1F).

2-(dimethylamino)-<i>N</i>,<i>N</i>,<i>N</i>,<i>N</i>-trimethylethan-1-aminium <i>n</i>- and <i>iso</i>-nonafluorobutoxide (4i)

\[
\begin{align*}
\text{H}_3\text{C} \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \quad \begin{array}{c} \text{N} \end{array} \quad \text{H}_3\text{C} \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 \\
\text{H}_3\text{C} \text{OCF}_2\text{CF}(\text{CF}_3)_2 & \quad \begin{array}{c} \text{N} \end{array} \quad \text{H}_3\text{C} \text{OCF}_2\text{CF}(\text{CF}_3)_2
\end{align*}
\]

A 50 mL round bottom flask under nitrogen was charged with excess CH<sub>3</sub>OC<sub>4</sub>F<sub>9</sub> 4 (20 mL, 30.4 g, 122 mmol) and <i>N</i>,<i>N</i>,<i>N</i>,<i>N</i>-tetramethylethylenediamine (5.826 g, 50.1 mmol) and stirred for 96 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4i as a white powder (17.998 g, 98%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ 2.246 (s, 6H), 2.689 (m, 2H), 3.149 (s, 9H), 3.397 (t, <sup>3</sup>JI = 11.96 Hz 2H). <sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>CN) δ -25.76 (OCF<sub>2</sub>, broad s, 2F), -80.32 (CF<sub>3</sub>, t, <sup>3</sup>JI = 9.29 Hz, 3F), -121.22 (CF<sub>3</sub>CF<sub>2</sub>, q, <sup>3</sup>JI = 8.86 Hz, 2F), -125.31 (CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>, s, 2F) and -17.30 (OCF<sub>2</sub>–, broad s, 2F), -72.44 (CF<sub>3</sub>, broad d, <sup>3</sup>JI = 6.32 Hz, 6F), -180.37 (CF, septet, <sup>3</sup>JI = 6.13 Hz, 1F).
m, 1F). Anal. Calcd. for C$_{11}$H$_{19}$F$_9$N$_2$O: C, 36.07; H 5.23; N, 7.65. Found: C, 36.41, H, 5.58; N, 7.94.

1,1,4-trimethylpiperazin-1-i-um n- and iso- nonafluorobutoxide (4j)

\[
\begin{align*}
\text{H}_3\text{C}-\text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \rightarrow \begin{array}{c}
\text{N} \\
\text{N} \\
\text{CH}_3
\end{array} \rightarrow \text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 \\
\text{RT, 72 h}
\end{align*}
\]

A 20 mL vial in a glovebox was charged with excess anhydrous CH$_3$OC$_4$F$_9$ 4 (11.097 g, 44.4 mmol) and anhydrous 1,4-dimethylpiperazine (1.764 g, 15.4 mmol) and sealed for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4j as a white powder (5.218 g, 93%). $^1$H NMR (400 MHz, CD$_3$CN) δ 2.337 (s, 3H), 2.688 (broad s, 4H), 3.124 (s, 6H), 3.41 (t, $^3$J$_{HH}$ = 5.2 Hz, 4H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -26.89 (OCF$_2$, broad s, 2F), -81.61 (CF$_3$, t, $^3$J$_{FF}$ = 9.1 Hz, 3F), -122.50 (CF$_3$CF$_2$, q, $^3$J$_{FF}$ = 9.0 Hz, 2F), -126.57 (CF$_2$CF$_2$CF$_2$, broad s, 2F) and -18.44 (OCF$_2$, m, $^3$J$_{FF}$ = 10.2 Hz, 2F), -73.69 (CF$_3$, broad d, $^3$J$_{FF}$ = 5.9 Hz, 6F), -180.35 (CF, broad m, 1F). Anal. Calcd. for C$_{11}$H$_{17}$F$_9$N$_2$O: C, 36.27; H, 4.70; N, 7.69. Found: C, 36.68; H, 4.90; N, 7.78.

1-methyl-1,4-diazabicyclo[2.2.2]-octan-1-ium n- and iso- nonafluorobutoxide (4k)

\[
\begin{align*}
\text{H}_3\text{C}-\text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3 & \rightarrow \begin{array}{c}
\text{N} \\
\text{N} \\
\text{OCF}_2\text{CF}_2\text{CF}_2\text{CF}_3
\end{array} \rightarrow \text{H}_3\text{C} \\
\text{RT, 72 h}
\end{align*}
\]

A 50 mL round bottom flask under nitrogen was charged with excess CH$_3$OC$_4$F$_9$ 4 (20 mL, 30.4 g, 122 mmol) and 1,4-diazabicyclo[2.2.2]octane (6.761 g, 60.3 mmol). The suspension was stirred for 72 h at RT. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4k as a white powder (16.688 g, 76%). $^1$H NMR (400 MHz, CD$_3$CN) δ 2.973 (s, 3H), 3.11 (t, $^3$J$_{HH}$ = 7.5 Hz, 6H), 3.27 (t, $^3$J$_{HH}$ = 7.5 Hz, 6H). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -26.90 (OCF$_2$, broad s, 2F), -81.62 (CF$_3$, t, $^3$J$_{FF}$ = 9.1 Hz, 3F), -122.50 (CF$_3$CF$_2$, q, $^3$J$_{FF}$ = 9.0 Hz, 2F), -126.57 (CF$_2$CF$_2$CF$_2$, broad s, 2F) and -18.44 (OCF$_2$, m, $^3$J$_{FF}$ = 10.2 Hz, 2F), -73.69 (CF$_3$, broad d, $^3$J$_{FF}$ = 5.9 Hz, 6F), -180.36 (CF, broad m, 1F). Anal. Calcd. for C$_{11}$H$_{15}$F$_9$N$_2$O: C, 36.27; H, 4.70; N, 7.73. Found: C, 36.90; H, 4.26; N, 8.14.
$N,N,N$-trimethylpyridin-4-aminium n- and iso- nonafluorobutoxide (4n)

\[
\begin{align*}
H_3C-OCF_2CF_2CF_2CF_3 & \quad \text{N} \quad H_3C-OCF_2CF(CF_3)_2 \\
\text{N} & \quad \text{H} \quad \text{N} \\
50^\circ \text{C}, 48 \text{ h} & \quad \text{O} \quad \text{N}
\end{align*}
\]

A 20 mL vial in a glovebox was charged with excess CH$_3$OC$_4$F$_9$ 4 (7.499 g, 30 mmol) and 4-(dimethylamino)pyridine (0.684 g, 5.6 mmol) and sealed for 48 h at 50°C. The precipitate was collected and washed with a minimum amount of anhydrous hexanes in a glovebox to afford 4n as a white powder (0.604 g, 29%). $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 3.312 (s, 6H), 4.026 (s, 3H), 7.00 (d, $^3J_{HH} = 7.7$ Hz, 2H), 8.12 (d, $^3J_{HH} = 7.6$ Hz, 2H). $^{19}$F NMR (376 MHz, CD$_3$CN) $\delta$ -26.95 (OCF$_2$, broad s, 2F), -81.62 (CF$_3$, t, $^3J_{FF} = 9.0$ Hz, 3F), -122.47 (CF$_3$CF$_2$, broad s, 2F), -126.57 (CF$_2$CF$_2$CF$_2$, s, 2F) and -180.31 (CF, broad m, 1F). Anal. Calcd. for C$_{12}$H$_{13}$F$_9$N$_2$O: C, 38.72; H, 3.52; N, 7.53. Found: C, 38.54; H, 3.93; N, 7.86.

**Experimental Procedure for Isolated Benzyl Ethers**

1-bromo-4-((perfluoropropoxy)methylene)benzene (44)

\[
\begin{align*}
\text{CH}_3\text{CN, 45}^\circ \text{C, 8 h} & \quad \text{Br} \quad \text{Br} \\
& \quad \text{O} \quad \text{F} \quad \text{F} \\
& \quad \text{O} \quad \text{F} \quad \text{F} \\
& \quad \text{Br} \\
\text{44} & \quad \text{3a}
\end{align*}
\]

In a nitrogen filled glovebox, a 1 mL CH$_3$CN solution of silver tetrafluoroborate (0.1740 g, 0.894 mmol, 1.0 equiv) was added drop-wise to a 5 mL CH$_3$CN solution of tetramethylammonium perfluoropropoxide 3 (0.3507 g, 2.203 mmol, 2.7 equiv) and 4-bromobenzyl bromide (0.1919 g, 0.803 mmol, 1.00 equiv) in a glass scintillation vial with stirring at 23°C. A white precipitate began forming immediately and the vial was sealed. The contents were stirred and heated at 45°C for 8 h in the dark. Upon cooling to RT, the mixture was filtered through a pad of Celite to remove AgBr(s) and the solvent gently removed in vacuo. The yellow residue was taken up in CH$_2$Cl$_2$, filtered through a pad of Celite a second time to remove NMe$_4$BF$_4$ and the solvent gently removed under reduced pressure. The residue was then purified by chromatography on silica gel eluting with hexanes to afford the product 44 as a colorless, volatile liquid (0.198 g, 70%). Trace hexanes were removed from the final product.
by sparging the flask with nitrogen. $^1$H NMR (600 MHz, CDCl$_3$) $\delta =$ 5.02 (CH$_2$, s, 2H), 7.23 (d, $^3$J$_{HH} =$8.4 Hz, 2H), 7.54 (d, $^3$J$_{HH} =$ 8.4 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 66.52 (CH$_2$, t, $^3$J$_{CF} =$ 5.8 Hz, 1C), 107.07 (CF$_3$CF$_2$, tm, $^1$J$_{CF} =$ 266.05 Hz, $^2$J$_{CF} =$ 38.69 Hz, 1C), 116.73 (CF$_2$O, $^1$J$_{CF} =$ 273.86, $^2$J$_{CF} =$ 29.72 Hz, 1C), 117.87 (CF$_3$, qt, $^1$J$_{CF} =$ 286.26 Hz, $^2$J$_{CF} =$ 33.3 Hz, 1C), 123.21 (Br-Ar$_{ipso}$, s, 129.59, 1C), 129.59 (Ar, s, 2C), 132.13 (s, Ar, 2C), 133.02 (ArCH$_2$ipso, s, 1C). $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta =$ -132.50 (CF$_2$O, t, $^3$J$_{FF} =$ 3.8 Hz, 2F), -89.30 (CF$_3$CF$_2$, qt, $^3$J$_{FF} =$ 7.4 Hz, $^3$J$_{FF} =$ 3.6, 2F), -84.49 (CF$_3$, t, $^3$J$_{FF} =$ 7.1 Hz, 3F). MS (70 eV): m/z (%): 356 (57) [M$^+$], 355 (8.6) [M$^+$], 354 (59) [M$^+$], 275 (100) [M-Br], 171 (66.2) [ +CH$_2$C$_6$H$_4$Br], 169 (82.5) [C$_3$F$_7^+$], and [CH$_2$C$_6$H$_4$Br$^+$], 119 (8.3) [C$_2$F$_5^+$] 69 (24.7) [CF$_3^+$].

The $^1$H and $^{19}$F NMR spectroscopic data for the non-isolated compound has been previously reported by Cheburkov and Lillquist.\cite{13}

4-((perfluoropropoxy)methylene)benzene (43)

![Chemical structure image]

In a nitrogen filled glovebox, a 1 mL CH$_3$CN solution of silver tetrafluoroborate (0.1727 g, 0.887 mmol, 1.1 equiv) was added drop-wise to a 5 mL CH$_3$CN solution of tetramethylammonium perfluoropropoxide 3a (0.3367 g, 2.115 mmol, 2.6 equiv) and benzyl bromide (0.1919 g, 0.803 mmol, 1.00 equiv) in a glass scintillation vial with stirring at 23°C. A white precipitate began forming immediately and the vial was sealed. The contents were stirred and heated at 45°C for 8 h in the dark. Upon cooling to RT, the mixture was filtered through a pad of Celite to remove AgBr(s) and the solvent gently removed in vacuo. The yellow residue was taken up in CH$_2$Cl$_2$, filtered through a pad of Celite a second time to remove NMe$_4$BF$_4$ and the solvent gently removed under reduced pressure. The residue was then purified by chromatography on silica gel eluting with pure pentane to afford the product 43 as a colorless, volatile liquid (0.139 g, 62%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta =$ 5.10 (CH$_2$, s, 2H), 7.04-7.88 (C$_6$H$_5$, m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 67.30 (C$_6$H$_5$CH$_2$, t, $^3$J$_{CF} =$5.8 Hz, 1C), 107.28 (CF$_3$CF$_2$, tm, $^1$J$_{CF} =$ 266.17 Hz, $^2$J$_{CF} =$ 38.58 Hz, 1C), 116.84 (CF$_3$O, $^1$J$_{CF} =$ 273.98, $^2$J$_{CF} =$ 29.21, 1C), 117.718 (qt, $^1$J$_{CF} =$ 286.29 Hz, $^2$J$_{CF} =$ 22.16 Hz, 1C), 128.00 (BrAr$_{ipso}$, 1C), 128.91 (Ar, 2C), 129.03 (Ar, 2C), 134.08 (ArCH$_2$ipso, 1C). $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta =$ -132.45 (CF$_2$O, t, $^3$J$_{FF} =$ 4.0 Hz, 2F), -89.15 (CF$_3$CF$_2$, qt, $^3$J$_{FF} =$ 7.3 Hz, $^3$J$_{FF} =$ 3.9 Hz, 2F), -84.45 (CF$_3$, t, $^3$J$_{FF} =$ 7.2 Hz, 3F). MS (70 eV): m/z (%): 277 (6.2) [M$_1^+$], 276 (56.6) [M$^+$],169 (6.9) [C$_3$F$_7^+$], 91.1(100) [C$_7$H$_6^+$], 119 (4.7) [C$_2$F$_5^+$], 69 (15.9) [CF$_3^+$].
1-((perfluoropropoxy)methylene)-4-(trifluoromethyl)benzene (45)

In a nitrogen filled glovebox, a 1 mL CH₃CN solution of silver tetrafluoroborate (0.1841 g, 0.946 mmol, 1.1 equiv) was added dropwise to a 5 mL CH₃CN solution of tetramethylammonium perfluoropropoxide 3a (0.3303 g, 2.113 mmol, 2.7 equiv) and 4-(trifluoromethyl)benzyl bromide (0.1805 g, 0.755 mmol, 1.00 equiv) in a glass scintillation vial with stirring at 23 °C. A white precipitate began forming immediately and the vial was sealed. The contents were stirred and heated at 45 °C for 8 h in the dark. Upon cooling to RT, the mixture was filtered through a pad of Celite to remove AgBr(s) and the solvent gently removed in vacuo. The yellow residue was taken up in CH₂Cl₂, filtered through a pad of Celite a second time to remove NMe₄BF₄ and the solvent gently removed under reduced pressure. The residue was then purified by chromatography on silica gel eluting with pure pentane to afford the product 45 as a colorless, volatile liquid (0.170 g, 65%).

**1H NMR (600 MHz, CDCl₃)** δ = 5.13 (CH₂, s, 2H), 7.47 (d, 3J Интер = 8.0 Hz, 2H), 7.67 (d, 3J Интер = 8.1 Hz, 2H).

**13C NMR (126 MHz, CDCl₃)** δ = 66.00 (C₆H₅CH₂, t, 3J CF = 5.9 Hz, 1C), 106.98 (CF₃CF₂, tm, 1J CF = 266.3 Hz, 2J CF = 38.7 Hz, 1C), 116.57 (CF₂O, tt, 1J CF = 273.56 Hz, 2J CF = 29.9 Hz, 1C), 117.43 (CF₃CF₂, qt, 1J CF = 286.40, 2J CF = 33.45, 1C) 123.85 (CF₃CF₂, qt, 1J CF = 286.40, 2J CF = 33.45, 1C) 125.69 (C₆H₄, q, 3J CF = 3.8 Hz, 2C), 127.63 (s, C₆H₄, 2C), 131.08 (CF₃Ar, s, 3F), 137.76 (ipso-C₆H₄CH₂-, s, 1C).

**19F NMR (471 MHz, CDCl₃)** δ = -132.50 (CF₂O, t, 3J FF = 4.0 Hz, 2F), -89.53 (CF₃CF₂, qt, 3J CF = 7.4 Hz, 3J FF = 3.9 Hz, 2F), -84.48 (CF₃CF₂, t, 3J FF = 7.1, 3F), -65.95 (CF₃Ar, s, 3F). MS (70 eV): m/z (%): 345 (4.1) [M⁺], 344 (28.6) [M⁺-1], 343 (2.9) [M-1], 325 (12.7) [M-F], 275 (100.0) [M-CF₃], 169 (16.3) [C₃F₇⁺], 159 (94.5) [(CF₃)C₆H₄CH₂⁺], 119 (12.2) [C₂F₅⁺], 69 (30.8) [CF₃⁺].

Methoxyflurane (Penthrane ®) 35

Colourless liquid. **1H NMR (400 MHz, CDCl₃)** 3.71 (s, 3H), 5.73 (t, 3J HF = 4.41 Hz, 1H). **13C NMR (101 MHz, CDCl₃)** 51.80 (t, 3J CF = 6.69 Hz, 1C), 67.79 (CCl₂, t, 2J CF = 94
42.71, 1C), 120.87 (CF₂, t, \( J_{CF} = 266.8 \) Hz, 1C). \(^{19}\)F NMR (376 MHz, CD₃CN) -85.62 (CF₂, s (splitting not observed), 3F). Literature compound not fully reported.

**Single Crystal X-Ray Diffraction Data for [Me₃NBn]OC₃F₇ 3f**

Crystals of 3f were obtained by crystallization of \( N,N \)-dimethylbenzylamine layered on HFE-7000 in a sealed glass vial over a period of 3 days at RT. A crystal suitable for data collection was selected on the bench and rapidly mounted using Paratone oil on a MiTeGen head and immediately placed in the cold stream (150 K) of the diffractometer. The temperature was regulated using an Oxford Cryosystems Cryostream.

All diffraction data was collected using a Bruker SMART APEX II CCD area detector diffractometer positioned 6.0 cm from the crystal. The X-ray source was a monochromated Mo K\( \alpha \) radiation (\( \lambda = 0.71073 \) Å). The frames were collected with a scan width of 0.5 in \( \omega \) and were integrated with the Bruker SAINT software. The structure was solved by direct methods using Bruker APEX II Suite. Subsequent refinements were performed in ShelXle and diagrams were made using Olex2. A summary of crystal, data and refinement parameters is provided in Table 2.10. Selected interatomic distances and angles appear in Table 2.12 and 2.11. Other tabulated data have been deposited (CCDC Deposition # 971479) which can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/products/csd/request/ or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
Table 2.10: Crystallographic Data for [Me$_3$NBn]OC$_3$F$_7$ 3f

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<td>μ (mm$^{-1}$)</td>
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Table 2.11: Bond Angles for Structure [Me₃NBn]OC₃F₇ 3f

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<td>N(1)-C(7)-C(8)</td>
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<td>C(6)-N(1)-C(7)</td>
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<td>H(7A)-C(7)-H(7B)</td>
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<td>F(1)-C(1)-C(2)</td>
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<td>N(1)-C(4)-H(4A)</td>
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**Table 2.12**: Bond Lengths for Structure [Me₃NBn]OC₃F₇ 3f

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2.9 References


Chapter 3

Towards Practical Methods for Trifluoromethoxylation of Hetero(arenes)

3.1 Introduction\textsuperscript{1,2}

In this chapter, we extend the preparation of tetraalkylammonium perfluoroalkoxides from Chapter 2 to the highly desirable tetraalkylammonium trifluoromethoxides \([\text{NR}_4][\text{OCF}_3]\). While select examples were easily prepared on a multi-gram scale in an operationally simple method, the main goal of this study was to develop a functional group tolerant protocol for the trifluoromethoxylation of arenes utilizing the \(\text{OCF}_3\) anion. Hence, a wide range of strategies towards \(\text{C}_{\text{aryl}} - \text{OCF}_3\) bond formation were attempted using these materials including both metal and non-metal-mediated protocols. The poor nucleophilicity, high moisture sensitivity, and propensity for \(\beta\)-fluoride elimination from \(\text{OCF}_3\) preclude its use as a general synthetic building block for many metal-mediated cross-couplings. Nevertheless, the work herein assists in the design of future synthetic reagents capable of general trifluoromethoxylation.

\textsuperscript{1}A portion of the transition metal-mediated experiments in this chapter was carried out in equal contributions by Korwin Schelke (Heidelberg U.), Simon Roëssler (S.R.) (ETH-Zürich), and Benson Jelier. S.R. submitted his contribution as a M.Sc. thesis to ETH-Zürich, 2015.

\textsuperscript{2}References begin on page 186
3.2 Interest in Trifluoromethyl Aryl Ethers

A large effort towards the incorporation of small, fluorinated substituents CF₃,[1–8] SCF₃[9–20] and OCF₃[17,21–30] into organic frameworks has been undertaken over the past five years. The merits of these privileged and ubiquitous functional groups are well known and their use has been highlighted repeatedly in pharmaceutical, agrochemical and material science applications. (FIG. 3.1).[5,30–36]

Since the incorporation of fluorine into organic compounds can dramatically alter their chemical properties: the electronic, lipophilic and steric parameters can be fine tuned in bioactive compounds to appropriately influence desired pharmaceutical attributes.[30,31,35,37,38] Aryl trifluoromethyl ethers (ArOCF₃) are particularly intriguing in this way since the OCF₃ moiety imparts enhanced lipophilicity while improving metabolic stability.[31,37,38] Lipophilicity, a measure of the affinity of a chemical for a lipophilic environment, is often one of the most influential properties for a bioactive drug,[39,40] since it enhances its bioavailability by improving solubility, increasing its ability to cross cell membranes and enhancing target binding interactions.[39–41] One well-known method for quantifying this biological partition co-efficient is the Hansch-Leo parameters (π)[42] – a measure of hydrophobicity from standard octanol/water measurements.[42] Hence, the OCF₃ (π = +1.04) substituent is one of the

Fig. 3.1. Selected Examples of Biologically Active Agents (above) and Liquid Crystal Additives (below) Bearing an Aryl OCF₃ Substituent

Since the incorporation of fluorine into organic compounds can dramatically alter their chemical properties: the electronic, lipophilic and steric parameters can be fine tuned in bioactive compounds to appropriately influence desired pharmaceutical attributes.[30,31,35,37,38] Aryl trifluoromethyl ethers (ArOCF₃) are particularly intriguing in this way since the OCF₃ moiety imparts enhanced lipophilicity while improving metabolic stability.[31,37,38] Lipophilicity, a measure of the affinity of a chemical for a lipophilic environment, is often one of the most influential properties for a bioactive drug,[39,40] since it enhances its bioavailability by improving solubility, increasing its ability to cross cell membranes and enhancing target binding interactions.[39–41] One well-known method for quantifying this biological partition co-efficient is the Hansch-Leo parameters (π)[42] – a measure of hydrophobicity from standard octanol/water measurements.[42] Hence, the OCF₃ (π = +1.04) substituent is one of the
most lipophilic functional groups, second only to an analogous SCF$_3$ moiety ($\pi = +1.44$) and more than either F ($\pi = +0.14$) or CF$_3$ ($\pi = +0.88$).$^{[31,42,43]}$

Furthermore, the electronic properties of OCF$_3$ are unique and have often been characterized as a "super-halogen"—as it is in many ways similar to a chloro substituent.$^{[31,44]}$ For instance, Sheppard calculated the Hammet substituent constant for the inductive effect ($\sigma_I$) for OCF$_3$ to be $\sigma_I = +0.51$ indicating that it is more electron withdrawing than chlorine ($\sigma_I = +0.47$), while electron-donating by resonance ($\sigma_R = -0.13$), but less than that of Cl and OCH$_3$ ($\sigma_R = -0.25$, -0.47 respectively).$^{[45–47]}$

![Diagram](image)

**Fig. 3.2.** Different Geometries Associated with the Conformations of ArOCH$_3$ 49 vs ArOCF$_3$ 50

The trifluoromethoxy group 50 can adopt a much different conformational arrangement than the OCH$_3$ isostere 49.$^{[48]}$ Researchers at Roche observed that if sterically unhindered, the OCF$_3$ group tends to adopt an orthogonal position with respect to the plane of the aryl ring.$^{[31,37,41]}$ This is in direct contrast to the analogous methoxy group of anisole which tends to line in the plane (FIG. 3.2)$^{[31,37,48]}$ Furthermore, it is thought that the oxygen non-bonding electrons have minimal conjugation with the aromatic $\pi$ electrons due to the presence of the highly electron withdrawing CF$_3$.$^{[38,49]}$ This allows the OCF$_3$ to freely rotate out of the nucleus plane, thus minimizing electronic repulsions (calculated to be favoured by approximately 0.5 kcal/mol) and affording higher conformational flexibility.$^{[37,49]}$ As a direct effect of the reduced electron density of the etheral oxygen, the trifluoromethoxy group exhibits high thermal stability, is not easily cleaved by strong acids, nor readily undergoes cytochrome-P450 in vivo dealkylation.$^{[30,37,50,51]}$ Although the OCF$_3$ moiety does not look particularly exotic, its incorporation into sp$^2$ frameworks provides a diverse set of properties compared to other small fluorinated groups and as expected, much different than hydrocarbon analogues.$^{[52]}$ Despite such research, it has been recently reported that the trifluoromethoxy group is perhaps still the least well understood fluorine substituent.$^{[38]}$
3.3 Synthesis of Trifluoromethyl Aryl Ethers

3.3.1 Traditional Synthetic Routes for Building Blocks

Although the trifluoromethoxy group is prevalent in a wide range of pharmaceuticals, agrochemicals and materials, methods to introduce this motif into aryl scaffolds are highly underdeveloped and limited.\[5,30–32,38,43,52,53\] The synthesis of complex aryl trifluoromethyl ethers typically require building blocks prepared in multiple step syntheses with difficult to handle and often harsh reagents and conditions (\textbf{Scheme 3.1}).\[4,30,31\] Furthermore, many of these approaches either suffer from poor substrate scope or require the use of highly reactive, toxic or thermally unstable reagents.\[30–32,52\] Hence, there is a high cost for simple building blocks exacerbated by the need for early introduction in a synthetic sequence due to low functional group tolerance (\textbf{Fig. 3.3}).\[54\]

\textbf{Scheme 3.1.} Currently, Preparation of Trifluoromethyl Aryl Ether Building Blocks Typically Require Harsh Conditions That Have Limited Functional Group Tolerance

1. Side-Chain Chlorination/Halex Process:

2. Nucleophilic Substitution and In Situ Halex:

3. Fluorination of Aryl chlorothionoformates:

4. Electrophilic Trifluoromethylation of Phenols:

5. Oxidative Fluorodesulfurization of dithiocarbonates:

6. Addition of Trifluoromethyl Hypofluorite:

7. Radical Trifluoromethoxylation:

8. Radical Trifluoromethylation of Phenols:
Fig. 3.3. Due to the difficulty in preparation, even relatively simple building blocks are often cost prohibitive. (Adapted from Ngai et al, 2014)

3.3.2 Current Strategies for Late-Stage Synthesis of Trifluoromethyl Aryl Ethers

Due to the aforementioned difficulties, there continues to be a need for new methodologies that are both convenient and functional group tolerant, amenable to late-stage modification of complex frameworks. To meet this longstanding demand, two C–O retro-synthetic approaches have been demonstrated in recent years: constructing the aryl-OCF₃ bond (SCHEME 3.2, 51, 52, 53 and 54) or trifluoromethylation of an aryl alcohol (SCHEME 3.2, 55, 56, 57 and 58). More recently, a third route was presented by Gouverneur by fluorination of benzyl bromide precursors (SCHEME 3.2 59). Each of the envisioned disconnections can lead to various one electron or two electron approaches, summarized in Scheme 3.2.

Scheme 3.2. Retrosynthetic Analysis of Aryl Trifluoromethyl Ethers by Three Disconnections
Trifluoromethoxylation of Arenes by C–OCF$_3$ Bond Formation

In their pioneering work of 2011, the Ritter group demonstrated the first accessible late-stage approach to trifluoromethoxylation by a Ag-mediated cross-coupling of a trifluoromethoxide anion (–OCF$_3$) with aryl boronic acid or stannane substrates (Scheme 3.3).$^{[27,28]}$

**Scheme 3.3.** Ritter’s Seminal Report in 2011 on the Ag-Mediated Trifluoromethoxylation of Aryl Stannanes and Boronic Acids with [TAS]OCF$_3$

Subsequently, Ngai (2014) reported an alternative strategy by means of a thermal rearrangement of trifluoromethylated N-aryl-N-hydroxylamines 62 requiring Togni reagent I or II (Scheme).$^{[21,54,56]}$ In a followup mechanistic study,$^{[21]}$ it was shown that while the trifluromethylation is a radical process, the thermal rearrangement follows the migration of an in situ generated –OCF$_3$ anion in a C–OCF$_3$ bond formation. While both the Ritter and Ngai protocols are successful, the first requires the use of a challenging two-step procedure with the [TAS][OCF$_3$] 60 and less desirable toxic aryl stannanes and the latter example is only relevant for a narrow substrate scope involving ortho-substitution of specialized substrates.

**Scheme 3.4.** Thermal Rearrangement of Trifluoromethylated N-aryl-N-hydroxylamines via a Proposed in situ Trifluoromethoxy Species
Trifluoromethylation of Phenols by O−CF₃ Bond Formation

The second main approach to preparing ArOCF₃ is the O-trifluoromethylation of aryl alcohols (Scheme 3.2, 55-58). Unfortunately, simple trifluoromethylation by nucleophilic substitution of CF₃I via an S_N2 type mechanism does not lead to O-trifluoromethylation due to (1) the strong repulsion of the CF₃I fluorines and the phenoxide nucleophile and (2) the reverse polarity of the CF₃I.²¹,36,57 Rather, O-trifluoromethylation was first demonstrated with thermally unstable CF₃ oxonium reagents [CF₃⁺ synthon] but requires impractical temperatures (−90°C and irradiation) with in situ generated reagents.⁵⁸

Alternatively, bench-stable hypervalent iodine species such as 64 have received widespread acclaim over the past ten years for their simple two-step preparation and unique ability to trifluoromethylate a wide range of substrates (C, S, O, N, P centres).¹,⁵⁹ These reagents can trifluoromethylate readily under mild conditions with high functional group tolerance including most thiols and alkanols.¹,⁶⁰,⁶¹

Scheme 3.5. O-Trifluoromethylation of Phenols Predominately Leads to C-trifluoromethylation, Ostensibly by a Radical Trifluoromethylation of a Stabilized Phenoxy Radical Using a Hypervalent Iodine Such as the Noted Togni Reagent

While these trifluoromethyl bearing iodinane reagents are believed to undergo electrophilic trifluoromethylation, different mechanisms can possibly occur depending on the exact conditions.¹,⁶²-⁶⁵ Unfortunately, in an attempt to prepare trifluoromethyl aryl ethers with these reagents, the Togni group observed a product distribution composed mainly of C-trifluoromethylation with little O-trifluoromethylation.⁶⁴,⁶⁶,⁶⁷ This product distribution seems consistent with a fluorinated radical, single electron transfer process ostensibly due to the oxidizing ability of hypervalent iodine reagents and the high stability of the phenoxy radical. While Umemoto found that having both sterically bulky perfluoroisopropyl Rᵥ
groups and phenol substituents at higher temperatures improved the O/C-perfluoroalkylation ratio for similar iodinane reagents, current attempts by the Togni group to improve O-trifluoromethylation by reducing the electronic properties of the phenol were either, largely unsuccessful or limited the substrate scope dramatically, not amenable to substrates exhibiting greater molecular complexity.

However in 2015, Qing reported a Ag\textsuperscript{I}-mediated trifluoromethylation of phenols using the \([\text{CF}_3\text{–}]\) synthon and is noteworthy for being amenable for a range of functional groups and phenols under relatively mild conditions. Presumably this cross-coupling involves the transmetallation of a \([\text{F–Ag}^{\text{III}}–\text{CF}_3]\) to afford a closed shell Ag\textsuperscript{III}-phenoxide complex that undergoes reductive elimination. In many ways this is similar to Ritter’s Ag-mediated fluorination and trifluoromethoxylation work. However, it is unclear why the protocol requires 23 equivalents of fluorinated reagents including multiple oxidants, fluorinated solvents, and stoichiometric use of Ag (Scheme 3.6). To be a truly general and convenient method, the complexity of Qing’s conditions requires further optimization, a process they are surely undertaking.

**Scheme 3.6.** Recent Results by Qing for the Functional Group Tolerant Ag-Mediated Trifluoromethylation of Phenols Using the Ruppert-Prakash Reagent, TMS–CF\textsubscript{3}

![Reaction scheme](image)

**Nucleophilic Fluorination of ArOCF\textsubscript{2}Br Precursors**

In a quest to access all \([^{18}\text{F}]\) functional groups, the Gouverneur group (2015) approached the preparation of trifluoromethyl ethers for \([^{18}\text{F}]\) positron emitting therapy (PET) tracers through a different approach. By improving the traditional halogen exchange process of Ar–OCF\textsubscript{2}Br precursors, Gouverneur and co-workers were successful in preparing trifluoromethyl aryl ethers under mild conditions. To avoid the demanding thermal conditions required for halogen exchange, the introduction of silver (I) salts such as AgOTf in combination with a source of F\textsuperscript{–} or \([^{18}\text{F}]\) fluoride anions afforded the desired ArOCF\textsubscript{3} or ArOCF\textsubscript{2}\textsuperscript{[18F]} (Scheme 3.7). In reality, the halex approach of converting ArOCF\textsubscript{2}Br to ArOCF\textsubscript{3} products had been utilized previously in the patent literature by using harsh reagents such as HF, HF-pyridine, SbF\textsubscript{5}/SbCl\textsubscript{5} but also the silver salt, AgBF\textsubscript{4} in the presence of fluoride. Thus Gouverneur seeks to improve or popularize this method.
as an alternative to the previous disconnections especially suitable for $^{18}$F PET tracer labelling studies. However, while some substrates could be prepared simply under mild conditions by transforming the phenol precursor to ArOFCF$_3$Br by nucleophilic substitution of CF$_2$Br$_2$, most substrates required multi-step syntheses with harsh conditions to convert the phenol to the desired ArOFCF$_2$Br precursor, hampering the functional group tolerance, efficiency and simplicity of the overall reaction.[55]

**Scheme 3.7.** Recent Results by Gouverneur for the Ag-mediated Halogen Exchange (halex) of aryl–OCF$_2$Br Precursors for Radio-labelled $^{18}$F-PET Targets

While several notable strategies have been reported in recent years, there continues to be a compelling need to develop novel, highly efficient, and more convenient methods for the synthesis of trifluoromethyl aryl ethers to aid the discovery and development of new functional molecules.

### 3.4 Objective

The main goal of the research presented in this chapter was to develop a convenient, functional group tolerant methodology for the incorporation of the trifluoromethoxy (OCF$_3$) group into arenes, a particularly desirable but difficult approach as reported by several recent communications by key investigators in the field:


- "While the [TAS][OCF$_3$] 60 reagent allows for efficient trifluoromethoxylation of a variety of functionalized arenes, the need for *in situ* preparation renders the reaction less practical, and development of a stable trifluoromethoxide source that is readily stored and handled would be an important development." - Ritter et al., *Org. Process Res. Dev.* 2014, 18, 474.

- "Clearly, direct trifluoromethoxylation reactions which avoid the use of highly toxic and thermally labile reagents are greatly desired for direct introduction of the OCF$_3$ group into various organic molecules..." - Ngai et al., *Angew Chem Int Ed Engl.* 2014, 53, 1.


**Scheme 3.8.** The Principle Goal for This Project Was the Development of a Convenient, Efficient and Functional Group Tolerant Protocol for the Trifluoromethoxylation of Arenes

![Scheme 3.8](image)

Ultimately, a functional group tolerant protocol would enable the incorporation of typically expensive OCF$_3$ moieties in the final step, rather than telescoping a currently fluorinated substituent through a multi-step synthesis, as is the case in the preparation of Triflumuron (Scheme 3.9).\cite{75} Furthermore, late-stage incorporation allows the preparation of a range of structural analogues otherwise not available. For example, the inclusion of the nearly exclusively para-directing OCF$_3$ substituent\cite{38} early in a synthetic sequence limits preparation of structural analogues in drug candidates of higher molecular complexity. While the only late-stage trifluoromethoxylation method reported exhibits functional group tolerance,\cite{28} we hoped to improve the protocol by utilizing our new methodology for the preparation of NR$_4$OCF$_3$ and improving the substrate scope such that it would not require either aryl boronic acids or stannanes so as to provide a more broadly applicable strategy.

Thus, we set out to design a protocol that centred around the following three requirements: (1) Aryl-O disconnect (2) amenable to late-stage, functional group tolerant conditions, and (3) an experimentally practical designed protocol.

### 3.4.1 Logic of Synthesis

Faced with the very broad problem of arene cross-coupling with a poor nucleophiles such as OCF$_3$, we envisioned two general approaches: either transition metal-mediated or metal-free methodologies for the formation of a C–OCF$_3$ bond. In the first case, we were inspired by related strategies for catalytic cross-coupling of similar poor nucleophiles such as fluoride (F$^-$) and trifluoromethylthiolate (\textbf`SCF$_3$). Aryl fluorination (Ar-F) and
Scheme 3.9. Synthetic Preparation of Insecticide Triflumuron 69 from fluorinated aniline precursor 66. Alternatively, Late-Stage Trifluoromethoxylation Enables the Incorporation of the OCF₃ Moiety in the Final Step from Ar-X Precursor 67 or 68.

aryl trifluoromethylthiolations (Ar–SCF₃) protocols likewise face challenging reductive eliminations in metal-mediated processes (Section 3.6). However, we suspected that the OCF₃ nucleophile would be even more formidable due to its thermal instability and tendency to undergo β-fluoride elimination during high-valent intermediates necessary in traditional processes, problems not encountered with either F⁻[4,5,59,70,76,77] or -SCF₃.[10–12,14,16–18]

Thus the second approach of this chapter (Section 3.7) investigates a range of modern transition-metal free and de novo methods.

3.5 Preparation of Trifluoromethoxides

3.5.1 Tetraalkylammonium Trifluoromethoxides from CF₃OCF₃

Similar to the synthesis of the higher analogous of tetraalkylammonium perfluoroalkoxydes from Chapter 2,[78] we speculated that the commercially available hydrofluoroether CH₃OCF₃ would methylate tertiary amines, albeit in lower conversions than the higher and more reactive analogues CH₃OC₂F₅ 2 – CH₃OC₄F₉ 4. Pleasently, NMe₃ was methylated by CH₃OCF₃ affording a free-flowing, white powder in 20% isolated yield.

The spectroscopic data of 1a is consistent with previously prepared perfluoroalkoxydes both from Chapter 2 and the existing literature. Thus, only one signal was observed at 3.12 ppm in the ¹H NMR spectrum as expected for the NMe₄⁺ cation.[79] Likewise, an expected
**Scheme 3.10.** Methylation of Select Tertiary Amines by CH$_3$OCF$_3$ 1 Affording Highly Desirable Trifluoromethoxide Salts, 1a,g,h

\[
\begin{align*}
\text{H}_3\text{C}^{-}\text{O}^{-}\text{CF}_3 + \text{R}_1\text{N}^{-}\text{R}_2\text{R}_3 & \rightarrow \text{R}_1\text{N}^{+}\text{R}_2\text{R}_3\text{O}^{-}\text{CF}_3 \\
1 & \rightarrow \text{1a.g.h}
\end{align*}
\]

Downfield shift in the $^{19}$F NMR spectrum from a sharp singlet at -61.91 ppm$^{[79,80]}$ (CF$_3$OCH$_3$) to a new, broad singlet at -19.78 to -20.5 ppm. This downfield shift is consistent with that of other known trifluoromethoxides including [TAS][OCF$_3$] $^{[80]}$ 60 (-21.3 ppm, broad, in CD$_2$Cl$_2$)$^{[81]}$ and $N,N$-dimethylbenzylamine 1g and quinuclidine 1h also reported herein. While metal (M= K$^+$, Rb$^+$) trifluoromethoxides decompose readily above RT,$^{[82]}$ the expected thermal decomposition products, carbonyl fluoride COF$_2$ or free F$^-$ were not observed in any of our preparations. Even though [NMe$_4$][OCF$_3$] has been allegedly prepared by Minkwitz through the reaction of CF$_3$OCl and NMe$_4$Cl, the product 1a decomposed at RT under dynamic vacuum and no NMR data was included in the report.$^{[80,83,84]}$ Likewise, it has been reported that Kolomeitsev prepared 1a by the reaction of anhydrous NMe$_4$F and trifluoromethyl triflate CF$_3$SO$_3$CF$_3$ 70 but again no spectroscopic data was reported.$^{[85]}$ Thus, this may be the first report detailing the spectroscopic details of [NMe$_4$][OCF$_3$].

**Table 3.1:** Preparation of Tetraalkylammonium Trifluoromethoxides from CH$_3$OCF$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cation</th>
<th>Yield$^{[a]}$ (%)</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>N$^+$</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53$^{[b]}$</td>
</tr>
<tr>
<td>1g</td>
<td>N$^+$</td>
<td>24$^{[b]}$</td>
</tr>
<tr>
<td>1h</td>
<td>N$^+$</td>
<td>90$^{[b]}$</td>
</tr>
</tbody>
</table>

$^{[a]}$ Yields refer to the isolated material of $> 98\%$ purity.  
$^{[b]}$ Solvent: 1,4-dioxane

Since both reagents in the preparation of [NMe$_4$][OCF$_3$] are gases and there no detected side-products, the reaction is convenient to carry out and requires no workup other than removing volatiles under reduced pressure ($< 100$ mTorr, 1 h). Even after extended
periods of high vacuum, sample prepared in this way gave no evidence of $F^-$ (or COF$_2$). However, due to the lower conversion, it was found that the addition of 1,4-dioxane as a solvent considerably increased the conversion resulting in isolated yields up to 53% at 50°C after 48 h (Table 3.1). While further optimization and a larger substrate scope could be envisioned, we were able to prepare tetraalkylammoniums on a sufficiently large scale with the three examples to proceed with subsequent trifluoromethoxylation strategies. Furthermore, compounds 1a,g,h gave a desired range of solubility in common organic solvents including CH$_2$Cl$_2$ and CH$_3$CN.

If the required CF$_3$OCH$_3$ 1 is not commercially available or required on a large scale, it can be prepared inexpensively by the nucleophilic fluorination of triphosgene,[88] a measurable solid followed by O-methylation to afford the desired product in 80% yield (Scheme 3.11).[79,89] This is not without risk as COF$_2$ and dimethyl sulfate are highly toxic reagents.

**Scheme 3.11. A Potentially Inexpensive Preparation of CH$_3$OCF$_3$ 1 from Triphosgene 71**

![Diagram of the reaction](image)

3.5.2 Preparation of Silver Trifluoromethoxide 72 from Trifluoromethyl Triflate 70

In a comparative example, a large sample of [AgOCF$_3$] 72 was prepared by the literature procedure using trifluoromethyl triflate CF$_3$SO$_3$CF$_3$ 70 and AgF (Scheme 3.12). While trifluoromethylate triflate 70 has been advertised to be a convenient precursor to the trifluoromethoxide anion,[34,85] the synthesis of this precursor is unfortunately tedious and highly time-consuming.[28]

**Scheme 3.12. Preparation of [AgOCF$_3$] 72 from Trifluoromethyl Triflate 70 by the Improved Ritter Procedure**

![Diagram of the reaction](image)

---

$^{319}$F NMR data for NMe$_4$F in anhydrous CD$_3$CN has been reported by Christe and Wilson, $\delta_F = -73.2$ ppm.[86] The signal for COF$_2$ is found as a sharp singlet at $\delta_F = -22.75$ ppm[87]
Even with the optimized procedure (dehydration of triflic acid 73 with \( \text{P}_2\text{O}_5 \)) trifluoromethyl triflate (b.p. 20°C) had to be triple-distilled to obtain a relatively pure sample to remove triflic anhydride. In the subsequent displacement reaction, the highly sensitive solution of \([\text{AgOCF}_3]\) was difficult to obtain cleanly, in particular the removal of by-product \(\text{CF}_3\text{SO}_2\text{F}\) without decomposing the delicate \([\text{AgOCF}_3]\).\(^{[90]}\)

![Fig. 3.4.](image)

**Fig. 3.4.** The optimized preparation of the \([\text{AgOCF}_3]\) precursor trifluoromethyl triflate by the dehydration of \(\text{CF}_3\text{SO}_3\text{H}\) remains a tedious process.

In comparison, the preparation of tetraalkylammonium perfluoroalkoxides by the methylation of tertiary amines with \(\text{CF}_3\text{OCH}_3\) 1 is a much simpler preparation to carry out. Not only does it require non-moisture sensitive reagents but it also has several practical advantages (Table 3.2). As Yagupolskii observed, the thermal instability of analogous \([\text{NMe}_4][\text{SCF}_3]\) may be related to methods of preparation.\(^{[91]}\) While Clark reported that \([\text{NMe}_4][\text{SCF}_3]\) decomposed at 0°C,\(^{[92]}\) Vicic was able to prepare this same fluorinated salt which persisted up to 60°C in solutions of THF, sufficient to enable smooth Ni-catalyzed cross-coupling reactions.\(^{[93]}\) Thus we were hopeful that our novel preparation of \([\text{NMe}_4][\text{OCF}_3]\) could have further synthetic advantages beyond a convenient, fluoride-free preparation.

### 3.6 Transition Metal-Mediated Approach to Trifluoromethoxylation

Transition metals have been widely used in the cross-coupling reactions for the introduction of functional groups into unsaturated systems. In these reactions, the C–C or C-Nu bond can be formed by the combination of a suitable aryl substrate with a second reactant...
Table 3.2: Comparison of the synthetic protocols between AgOCF$_3$ and NR$_4$OCF$_3$

<table>
<thead>
<tr>
<th>[AgOCF$_3$] from Trifluoromethyl Triflate</th>
<th>NR$_4$OCF$_3$ from CF$_3$OCH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light-sensitive</td>
<td>Facile workup, no detectable side products</td>
</tr>
<tr>
<td>Non-isolable</td>
<td>Free-flowing solid easily handled in a glovebox</td>
</tr>
<tr>
<td>Only available in CH$_3$CN</td>
<td>Light and thermally stable</td>
</tr>
<tr>
<td>Estimated concentration</td>
<td>Soluble in a range of solvents</td>
</tr>
<tr>
<td>Thermally unstable above 25°C</td>
<td>Not easily oxidized</td>
</tr>
<tr>
<td>Must be stored in freezer</td>
<td>Multi-gram scale</td>
</tr>
<tr>
<td>Equilibrium with AgF</td>
<td>Does not require anhydrous fluoride to prepare</td>
</tr>
</tbody>
</table>

while the same transformation cannot be done with classical synthetic reactions without the presence of a metal catalysts.$^{[94,95]}$ Beyond the well-known, named C–C cross-couplings, the transition-metal-catalyzed introduction of functional groups containing heteroatoms (N,O,S)$^{[96–98]}$ or halides (especially F)$^{[4,99–101]}$ continue to expand as valuable tools for the synthetic chemist. However, for these reactions to take place, both the aryl substrate and heteroatom bearing group must be bound to the metal in a higher oxidation state and in close proximity to afford the key bond-forming step, reductive elimination.$^{[100,101]}$

For the transition metal-mediated trifluoromethoxylation of arenes, we envisioned the need for a thermally-stable intermediate complex [Ar–M–OCF$_3$]. As discussed in Chapter 2, the α-C–F bonds of the OCF$_3$ ligand are highly ionic and undesirably, can eliminate a highly nucleophilic fluoride anion in solution. Furthermore, [M]–OCF$_3$ species can undergo β-fluoride elimination upon coordination to a metal, a process that can occur with coordinately unsaturated metals (SCHEME 3.13).$^{[3,90]}$ The increased tendency towards β-fluoride elimination would be expected with both more electropositive metals, such as early transition metals or metals in high oxidations states.$^{[3,90]}$ Thus having a poor nucleophilic ligand such as OCF$_3$ in conjunction with two avenues for the formation of highly stable metal-fluoride bonds, which can shut down the active catalyst or provide unwanted fluorination, poses a formidable challenge.

**Scheme 3.13.** Decomposition of the Trifluoromethoxide Anion in the Presence of Metals to Afford Undesired Metal-Fluorides via a) an inter-molecular Lewis Acidic Metal or b) an intra-molecular β-Fluoride Elimination of a Metal Coordinated Trifluoromethoxide

![Scheme 3.13](image)

The bond dissociation energies (BDEs) for M-F bonds have been reported and when tabulated, we speculated that a plausible catalyst must have a low M-F BDE and be
preferentially more oxophilic than fluorophilic (Fig. 3.5).\textsuperscript{[102]} These demanding requirements suggest that the best candidates for a metal-mediated or -catalyzed trifluoromethoxylation process would be late transition metals as they have lowest M–F BDE (Pearson’s Hard-Soft Acid Base Theory).\textsuperscript{[102]}

![Fig. 3.5. Periodic trend of bond dissociation energies for M–F bond. The x-axis represents the Group number and the y-axis the BDE of the M–F bond (Used with Permission from Wiley).][102]

While partly fluorinated alkoxides such as early generation Schrock\textsuperscript{[103,104]} and Grubbs\textsuperscript{[105]} metathesis catalysts are valuable ligands, metals bearing \textit{perfluoro}-alkoxides are rare. So rare in fact that it was only in 2012 that Vicic reported the first two Cu and Au complexes having coordinated perfluoroalkoxide ligands (Fig. 3.6).\textsuperscript{[90]} These complexes mark a significant advance suggesting that with the appropriate ligand, stable transition metal complexes are viable.\textsuperscript{[90]} Furthermore, although not isolable, Ritter’s (and now Qing’s\textsuperscript{[24,25]}) silver-mediated methodology also indicate that late-transition metals can allow for ligand free environments by purported bimetallic Ag\textsuperscript{II}–Ag\textsuperscript{II} stabilization.\textsuperscript{[28,70]} Furthermore, reductive elimination can then importantly proceed at low temperatures.\textsuperscript{[27,28]} In late 2015, Li and Weng reported a third example, an (Aryl–BIAN)Ag(O\textsubscript{CF\textsubscript{3}}) • THF complex that is notable for being isolable in good yield and "only slightly air-sensitive."\textsuperscript{[106]} All three examples involving late transition metals: Cu, Ag, and Au consistent with the metals bearing the lowest M–F BDEs with the exception of the unique OsO\textsubscript{4} dihydroxylation complex.\textsuperscript{[107]}
**3.6.1 Preparation of Metal Complexes Bearing Fluorinated Alkoxides**

Initially, tetraalkylammonium perfluoroalkoxides were added to a series of transition and main group metals both at RT and at −78 °C to determine the full extent of β-fluoride elimination. Since the physical properties of perfluoropropionyl fluoride allow for better analysis than the COF₂, [NR₄][OC₃F₇] was chosen over OCF₃. Unsurprisingly, the immediate bubbling, formation of insoluble metal fluorides, and clearly detectable acyl fluorides by ¹⁹F NMR analysis gave a clear indication of immediate decomposition. Disappointingly, even main group chlorides PCl₃, PhPCl₂, OPCl₃, and SbCl₃ all readily formed the respective fluorides. As of yet, even simple perfluorophosphites such as P(OCF₃)₃ have not been reported and continue to be interesting target compounds.

\[
\text{L₃M—Cl} + x \text{[NMe₄][OCF₂CF₂CF₃]} \xrightarrow{\text{solvent temperature}} \text{L₃M—F} + \text{OCF₂CF₂CF₃}
\]

_Solvent: THF, CH₃CN, CH₂Cl₂, Toluene, Toluene/pyridine
Temperature: -78°C, 25°C_

**Fig. 3.7.** Metathesis of select early transition metal chlorides and main group chlorides with NMe₄OC₃F₇ 3a resulted in the corresponding metal fluoride.

The metathesis of NiCl₂(PMe₃)₂, a late-transition metal, with [NMe₄][OC₃F₇] 3a or [NMe₄][OC₄F₉] 4a did not afford the expected perfluoroalkoxy complex. Rather, under a variety of conditions (solvent and temperature), the NiCl₂(PMe₃)₂ was surprisingly rapidly
and fully consumed and gave clean formation of the known difluorophosphorane, PF$_2$(CH$_3$)$_3$, as evidenced by $^{19}$F and $^{31}$P NMR analysis (Fig. 3.8).\textsuperscript{[108]}

![Fig. 3.8. $^{31}$P-$^{1}$H NMR (162 MHz) spectrum of the reaction between [NMe$_4$]OC$_4$F$_9$ 4a and NiCl$_2$(PMe$_3$)$_2$ in CD$_3$CN at RT to afford known difluorophosphorane, PMe$_3$F$_2$.](image)

We surmised that this process could take place by a Ni-mediated fluorination of the phosphine ligand affording Ni$^0$ species and the difluorophosphorane. While HgF$_2$ is known to readily fluorinate a range of phosphines including PMe$_3$ forming Hg$^0$ and PF$_2$(CH$_3$)$_3$,\textsuperscript{[108]} or electrochemically with ammonium fluorides,\textsuperscript{[109]} the exact details of this redox reaction were not investigated further. However, the use of appropriate ligands with high steric bulk could be a possible avenue to mitigate unwanted fluorination by both changing the geometry about the Ni (from square planar to tetrahedral) or through the use of bidentate amino or N-heterocyclic ligands which maybe less-susceptible to unwanted fluorination.

A similar fluorination of ancillary phosphine ligands has been reported by Grushin in numerous attempts to prepare an aryl-fluoride bond from a Pd$^{II}$ reactive centre. However, it was found that the fluoride ligand preferentially binds to the P atom of the stabilizing phosphine, a process that since has been identified with several platinum group metals...
although this is the first report for NiII. This unwanted fluorination was overcome by Buchwald in the Pd-catalyzed fluorination of aryl triflates and bromides by the use of select bulky biarylphosphine ligands that coordinate tightly to the Pd metal centre, preventing attack of the fluoride ion on the ligated phosphorus.\textsuperscript{[111]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig39}
\caption{Experimental $^{19}$F NMR Spectra of coordinated and free $\text{OCF}_3$ to select late transition metals. The presence of ligands, especially N-Heterocyclic Carbene (SIr) on Cu, Au allows for a covalent structure rather than solvent-separated ion pairs.}
\end{figure}

Due to these preliminary results, the focus of our metal-mediated trifluoromethoxylation was with late-transition metals (Cu, Ag, Au, Ni and Pd) due to the known (1) existing cross-coupling manifolds and the (2) lower fluorophilicity of late-transition metals and (3) the easy access to low-valent metal trifluoromethoxides prepared herein (the $^{19}$F NMR spectra of each is shown in Fig. 3.9).

### 3.6.2 Silver-Mediated Approaches for Trifluoromethoxylation

#### Towards an Improved Ritter Methodology

Initially, we re-visited the successful Ag-mediated trifluoromethoxylation reported by the Ritter group in 2011 (Scheme 3.14).\textsuperscript{[28]} Aside from some concerns regarding the toxicity of aryl stannane precursors, the \textit{in situ} preparation of [TAS][OCF$_3$] and multi-step
procedure makes for a complicated protocol preventing widespread adoption by the synthetic community.\(^\text{[69]}\) We hoped that the reported procedure could be improved at the very least by (1) using a new source of \(\text{OCF}_3\) that can be easily manipulated rather than the \textit{in situ} generated \([\text{TAS}][\text{OCF}_3]\) in the original protocol\(^\text{[28]}\) and (2) carry out the reaction at ambient temperatures rather than \(-30^\circ\text{C}\).

**Scheme 3.14.** Silver-Mediated Trifluoromethoxylation of Aryl Stannanes with \textit{In Situ} Generated \([\text{TAS}][\text{OCF}_3]\) Using the 2011 Ritter Procedure

Thus, for the trifluoromethoxylation of 4-biphenylyltributylstannane \(74\), we screened different silver(I) salts, solvents, solvent mixtures, oxidants, temperatures and modes of addition with \([\text{NMe}_4][\text{OCF}_3]\) \(1\text{a}\) (\textit{Table 3.3}). We initially screened two F-oxidants in a variety of solvents (\(\text{CH}_2\text{Cl}_2\), DCE, THF, \(\text{CH}_3\text{CN}\), DMF; Entries 1-4). Although higher conversion was observed with Selectfluor-\(\text{PF}_6\)\(^4\) in \(\text{CH}_3\text{CN}\) and DMF, fluorination and proto-destannylation outcompeted the desired product \(76\) with substantially higher conversions of \(\text{ArF}\) \(75\) and biphenyl as indicated by \(^{19}\text{F}\) NMR and GC/MS analysis.

**Scheme 3.15.** To Suppress Aryl Fluorination by Reductive Elimination from Putative Intermediate \(78\), One Equivalent of TMS-additive Was Added After a 30 min Induction Period to Generate Silver Triflate \(79\)

We suspected that this reductive elimination from putative intermediate \(78\) at RT was faster than \(\text{OCF}_3\) ligand exchange leading to the competing fluorination. To suppress fluorination of biphenyl stannane \(74\), we altered the mode of addition by adding one equivalent of fluoride scavenger additives TMS–OTf or TMS-imidazole to abstract the fluoride from the \(\text{Ag}^{\text{II}}\) species followed by \(\text{OCF}_3\) after an induction period of 30 minutes. However this approach led to no substantial effect for TMS-OTf while production formation was completely inhibited by TMS-imidazole. We postulate that this occurs due to the liberated imidazole coordinating to the \(\text{Ag}^{\text{II}}\) species as TMS-OTf seemed to have minimal

\(^4\)Selectfluor is 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane derived from the fluorination of DABCO in \(\text{CH}_2\text{Cl}_2\) and is available with \(\text{BF}_4^-\) or \(\text{PF}_6^-\) counterions. It is a bench stable and most widely used source of \(\text{F}^+\) oxidant.
effect on the conversion of 76. In this study, the fluoride in silver intermediate 78 results in
the oxidation of the transmetallated AgI-Ar with Selectfluor, as such we investigated other
oxidants including TBA-Oxone®, BAIB, and DDQ\textsuperscript{5} to generate Ag\textsuperscript{II} intermediates and
avoid the formation of 78. Unfortunately, none of these attempts proved to be successful
and only lead to decomposition of \textsuperscript{1}OCF\textsubscript{3}.

Since [NMe\textsubscript{4}][OCF\textsubscript{3}] 1a displayed greater solubility in DMF, we screened a selection of
DMF co-solvents (Entries 5-8) with and without the fluoride scavenger TMS-OTf. While
some solvent combinations improved the yield, other solvent systems seemed to perform
equally well without the need for an additive. Since the presence of acidic protons can lead
to formation of HF and consequently, decomposition of \textsuperscript{1}OCF\textsubscript{3}, we investigated whether
a variety of typically Brønsted bases could lead to improved trifluoromethoxylation over
fluorination. Disappointingly, none of the additives led to improved yields and often were
counter-productive. Thus the best conversions of 22% to ArOCF\textsubscript{3} 81 were obtained with
DMF and either CH\textsubscript{3}CN or 1,4-dioxane without the presence of additives or acid scavengers.

\textsuperscript{5}TBA-oxone tetrabutylammonium hydrogen monopersulfate, BAIB = \textit{bis}(acetoxy)iodobenzene, and
DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Table 3.3: Selected Screening Conditions for the Silver-Mediated Trifluoromethoxylation of Biphenyl Stannane 74.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Acid scavenger</th>
<th>Additives</th>
<th>Solvent</th>
<th>ArOCF₃ 76 [%][b]</th>
<th>ArF 75 [%][b]</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Selectfluor-PF₆</td>
<td>–</td>
<td>–</td>
<td>THF</td>
<td>2</td>
<td>4</td>
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<tr>
<td>2</td>
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<td>–</td>
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<td>34</td>
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<tr>
<td>3</td>
<td>Selectfluor-PF₆</td>
<td>–</td>
<td>–</td>
<td>DMF</td>
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<td>15</td>
</tr>
<tr>
<td>4</td>
<td>[Me₃pyF]PF₆</td>
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<td>–</td>
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<td>–</td>
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<td>53</td>
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<tr>
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<td>–</td>
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<td>49</td>
</tr>
<tr>
<td>7</td>
<td>Selectfluor-PF₆</td>
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<td>–</td>
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<td>29</td>
</tr>
<tr>
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<td>Selectfluor-PF₆</td>
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<td>–</td>
<td>dioxane/DMF 3:1</td>
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<td>49</td>
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<td>22</td>
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<td>11</td>
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<td>TMS–imidazole</td>
<td>DMF</td>
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<td>0</td>
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<tr>
<td>12</td>
<td>Selectfluor-PF₆</td>
<td>–</td>
<td>TMS–imidazole</td>
<td>CH₃CN</td>
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<td>0</td>
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<tr>
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<td>CH₃CN/DMF 3:1</td>
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<tr>
<td>15</td>
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<tr>
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<td>–</td>
<td>TMS–OTf</td>
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<td>22</td>
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<td>31</td>
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<td>Selectfluor-PF₆</td>
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<td>–</td>
<td>THF/DMF 3:1</td>
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<td>35</td>
</tr>
<tr>
<td>19</td>
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<td>–</td>
<td>THF/DMF 3:1</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>

[a] Screening reactions were performed on a 0.025 mmol scale of substrate. See Experimental for conditions.

[b] Yields reported as percentages by $^{19}$F NMR analysis by integration against internal standard 3-nitrofluorobenzene (-112.0 ppm). 76 has chemical shift of $\delta_F = -58.2$ ppm (CDCl₃) [28] and 75 has chemical shift of $\delta_F = -117.2$ ppm (CDCl₃) [112].
In every case, fluorination seemed to highly outcompete trifluoromethoxylation of aryl stannanes at RT. We surmised that rapid reductive elimination of the [Ar-AgII-F] intermediate occurs faster than ligand exchange with OCF3 at higher temperatures irrespective of the OCF3 source, solvents and additives. Lowering the temperature to −30 °C may very well decrease the competing fluorination rate however, this is no different than the original procedure and thus improving the procedure only by the use of a new source of OCF3 is hardly justifiable.[28]

3.6.3 Copper-Mediated Approaches for Trifluoromethoxylation

Introduction

Copper-mediated reactions are an attractive strategy for the preparation of trifluoromethoxy ethers. Hence we were inspired by classic copper-mediated coupling reactions such as Ullman Ether Synthesis, Chan-Lam Coupling, and Rosenmund-von Braun[113] reaction which all enable carbon-heteroatom bond formation via oxidative-coupling.[114–116] For instance, the original Ullman copper-mediated reactions has since evolved from their original harsh conditions by choice in suitable solvents, bases, and ligands; enabling facile bond formation at much lower temperatures.[114,116,117] Thus these approaches often provide an attractive alternative to expensive palladium-mediated conditions when multi-equivalents of metal are required (explored in SECTION 3.6.5).

Scheme 3.16. Three Mechanistic Pathways to Acquire a High-Valent [Ar–CuIII] Intermediate Complex Which Could Possibly Undergo Reductive Elimination

Furthermore, based on the recently demonstrated stability of Vicic’s [NHC]CuI OCF3 complex[90] and the numerous copper-mediated fluorinations reactions by Hartwig[118–120] and Sanford,[99,121,122] we hypothesized that a high oxidation state CuIII intermediate bearing both an aryl species and trifluoromethoxy moiety would enable aryl–OCF3 bond formation.
It is quite well-known that Ar–Cu\textsuperscript{III} complexes undergo facile aryl-fluoride bond-forming reductive eliminations.\textsuperscript{[115,121]} To this end, three mechanistic approaches were envisioned to afford the desired, high-valent [Ar–Cu\textsuperscript{III}] intermediate 83 (Scheme 3.16).

Thus, we propose to attain this intermediate by one of three routes: (1) disproportionation of a Cu(II) precursor 82,\textsuperscript{[121,123]} (2) direct oxidative addition of aryl halide (or pseudo-halide) of a Cu\textsuperscript{I} species,\textsuperscript{[120]} or (3) a two-electron oxidation of a Cu\textsuperscript{I} species 85 with an external agent followed by transmetallation.\textsuperscript{[119]} We reasoned that if a [Ar–Cu\textsuperscript{III}] was attainable, the OCF\textsubscript{3} anion should then readily coordinate via ligand exchange to afford [Ar–Cu\textsuperscript{III}–OCF\textsubscript{3}] 86. Facile reductive elimination should then yield the desired Ar–OCF\textsubscript{3} (Scheme 3.16).\textsuperscript{[115]}

**Approach 1: Disproportionation of Cu\textsuperscript{II} Complexes**

In 2013, Sanford reported a Cu\textsuperscript{II}-mediated fluorination of aryltrifluoroborates with potassium fluoride (KF) under mild conditions (Scheme 3.17).\textsuperscript{[121]} Although yields generally varied between 45-70\%, this protocol exhibited a broad substrate scope and functional group tolerance. In so doing, Sanford proposed that Cu(OTf)\textsubscript{2}, a strongly oxidizing Cu source,\textsuperscript{6} readily underwent disproportionation to generate both a Cu\textsuperscript{I} species and an Ar–Cu\textsuperscript{III}–F (Scheme 3.17).\textsuperscript{[121]} Consistent with this postulate, the yield would drop if less than two equivalents of Cu(OTf)\textsubscript{2} were used in the reaction.\textsuperscript{[121]}

We proposed that if we could substitute our tetraalkylammonium trifluoromethoxides 1a.g.h for KF, this could provide access to a Cu\textsuperscript{II}(OTf)(OCF\textsubscript{3}) species that could undergo disproportionation in a similar manner. Aryl trifluoroborate precursors are popular as they can be efficiently prepared in two-steps by nickel\textsuperscript{[124]} or palladium-catalyzed borylation\textsuperscript{[125]} of (hetero)aryl halides or directly by Ir C-H functionalization with B\textsubscript{2}Pin\textsubscript{2}\textsuperscript{[126,127]} followed by fluorination with KHF\textsubscript{2}.\textsuperscript{[128]} Importantly, the substrate can be readily monitored by \textsuperscript{11}B and \textsuperscript{19}F NMR analysis.\textsuperscript{7}

A screening of different Cu\textsuperscript{II} sources in different solvents gave no yield of trifluoromethoxyolated products 87 and 76 respectively (Scheme 3.18). The Cu\textsuperscript{II} sources and solvents were chosen due to their ability to facilitate disproportionation.\textsuperscript{[121]} Although no trifluoromethoxylation was detected in any \textsuperscript{19}F NMR screening, Cu(OTf)\textsubscript{2} in CH\textsubscript{3}CN gave a moderate yield of fluorination with [NMe\textsubscript{4}][OCF\textsubscript{3}]. The nucleophilic fluoride necessary for the formation most likely is a result of the decomposition of the OCF\textsubscript{3} anion under the present reaction.

\textsuperscript{6}In a cyclic voltammetry (CV) experiment of 1a, we were unable to observe any oxidation of the OCF\textsubscript{3} anion 1a within the electrochemical window of anhydrous CH\textsubscript{3}CN. Conditions: 0.01 M 1a, 0.1 M NBu\textsubscript{4}PF\textsubscript{6} with a scan rate of 100 mV s\textsuperscript{-1}, Ag\textsuperscript{+}$/\text{Ag. Ref.}

\textsuperscript{7}Aryl trifluoroborates can be found between \textdelta F = -136.5 to -144 ppm.\textsuperscript{[128]} and aryl trifluoromethyl ethers in a range of \textdelta F = -55 to -65 ppm.\textsuperscript{[28]} Relevant boron species: BF\textsubscript{4} at \textdelta F = -151ppm. FBPin at \textdelta F = -151.9 ppm while \textdelta B = 20.6 (br s, CD\textsubscript{2}Cl\textsubscript{2}).\textsuperscript{[129]}

a) Sanford’s fluorination of aryltrifluoroborates:

\[
\text{BF}_3\text{K} \rightarrow \text{BF}_3\text{K} + \text{KF} + \text{Cu}^{II}(\text{OTf})_2 + \text{KF}
\]

\[
\text{CH}_3\text{CN, 60°C, 20 h}
\]

b) Sanford’s proposed disproportionation mechanism:

\[
\text{Cu}^{II}(\text{OTf})_2 + \text{KF} + \text{KOTf} \rightarrow \text{Cu}^{II}(\text{OTf})(\text{F}) + \text{KBF}_3 \text{OTf}
\]

conditions. This decomposition produces carbonyl fluoride which can also be observed by

\[^{19}\text{F} \text{NMR spectroscopy.}\]

The desired aryl-Cu\(^{III}\) species as well as trifluoroborate salts are Lewis acids and can facilitate this decomposition. While an incompatibility of cationic aryl-Cu\(^{III}\) with trifluoromethoxide would negate the use of copper-mediated reactions, an incompatibility with trifluoroborates would just exclude a certain substrate type. Investigation by \(^{11}\text{B} \text{NMR spectroscopy generated a signal at -1.5 ppm which likely corresponds to the anionic}[\text{BF}_4^-] \text{species: a compound formed as one equivalent of fluoride is abstracted by the Lewis acidic trifluoroborate. We suspected that alternative borylated substrates such as pinacol boronic esters (Ar-Bpin) would also suffer from this problem and thus were not pursued (vide infra). Furthermore, the presence of potassium salts from aryltrifluoroborates could also facilitate decomposition as suggested by Willis in his report that KOCF}_4 \text{ decomposes readily above -20°C to KF and COF}_2. [82]
**Scheme 3.18.** A Mild and Functional Group Tolerant Cu-Mediated Fluorination of Aryltrifluoroborates with Potassium Fluoride.

![Scheme 3.18](image)

**Scheme 3.19.** Hartwig’s Fluorination of Aryl Iodides with (tBuCN)\(_2\)CuOTf and AgF

![Scheme 3.19](image)

**Approach 2: Oxidative Addition to Cu\(^{1}\)**

**Aryl Iodides**

In a second approach, we investigated the direct oxidative addition of aryl halides such as biphenyl iodide to Cu\(^{1}\) sources. While there are many examples for oxidative addition of aryl halides to copper (I) salts, we started with a more recent procedure outlined by Hartwig and co-workers for the fluorination of aryl iodides (SCHEME 3.19).\(^{[120]}\) To prevent rapid disproportionation of unligated Cu\(^{1}\) fluorides to Cu\(^0\) and CuF\(_2\) and to improve the rate of oxidative addition, appropriate ligands are required. Thus, Hartwig found success with tBuCN ancillary ligands as they have a higher propensity for electron donation compared to other ligated nitriles.\(^{[120]}\) For the same rationale, we followed Hartwig’s suggestion with the use of (tBuCN)\(_2\)CuOTf as a Cu(I) source.\(^{[120]}\)
Since the NHC ligand, SIPr, allows for the formation of stable CuI–OCF3 complexes,[90] we added one equivalent to a solution of (tBuCN)2CuOTf and then screened the effect of solvent and temperatures. We quickly came to the conclusion that after screening a small variety of conditions and observing no trifluoromethoxylation that decomposition of OCF3 would most likely occur at the temperatures required for the initial oxidative addition of the aryl iodide. For the Hartwig system, this was at minimally 140 °C.[120] We suspected that the presence of cationic-Cu(I) at this temperature would lead to immediate decomposition of OCF3, affording anhydrous tetraalkylammonium fluorides. Hartwig and co-workers also found that the presence of tetrabutylammonium fluorides immediately facilitated decomposition of the CuI (whereas AgF provided a much lower rate of decomposition, possibly because of lower solubility).[120] With the insurmountable high energy barrier for direct oxidative addition of aryl halides, we considered oxidative addition of diaryliodonium salts to directly access aryl-CuIII intermediates under more mild conditions.

Diaryliodonium Salts

As a result of their highly electrophilic nature, diaryliodonium salts (Ar2I+) undergo fast oxidative addition to CuI thus enabling much milder reaction conditions than the previously Hartwig ArI conditions.[130] Effectively Ar2I+ reagents combine oxidant and aryl-substrate, directly generating the desired aryl-CuIII intermediates.[131] We hoped that thermal stability concerns with OCF3 could thus be mitigated provided electrophilic Ar2I+ are compatible with the OCF3 anion. Upon screening a selection of commercially-available Ar2I+ at RT, no decomposition was observed for OCF3 and gave us further impetus to study this CuI-CuIII manifold (vide infra).
**Scheme 3.21.** a) An Example of a Cu-Catalyzed Nucleophilic Fluorination Protocol of Asymmetric Diaryliodonium Suitable for a Broad Substrate Scope with High Chemoselectivity. b) Sanford’s Proposed Cu\(^{I}/Cu^{III}\)-Catalytic Cycle Illustrating the Desired Ar-Cu\(^{III}\)-Nu Intermediate.

**a) Sanford’s Cu-catalyzed fluorination of diaryliodoniums (2013):**

\[
\begin{align*}
\text{Ph} & \quad \text{F} \\
\text{Ph} & \quad \text{Cu} \text{(OTf)}_2 \\
0.2 \text{ equiv} & \quad [\text{Cu(OTf)}_2] \\
1.1 \text{ equiv} & \quad \text{KF} \\
0.4 \text{ eq} & \quad 18\text{-crown-6} \\
0.1 \text{ M DMF}, 60^\circ \text{C}, 18 \text{ h} & \quad \text{Ph} \\
\end{align*}
\]

86% (95:5)

**b) Sanford’s Proposed Cu\(^{I}/Cu^{III}\) Mechanism (2014):**

Sanford discovered that Cu-catalyzed fluorination of diaryliodonium salts proceeded smoothly with potassium fluoride and asymmetric diaryliodoniums.\[^{123}\] The sterically encumbered iodoniums containing the judicious choice of the mesityl (Mes) fragment undergo sterically controlled oxidative addition at Cu\(^{I}\) with selective transfer of the smaller aryl group.\[^{77,123,132,133}\] This improves the accessibility of electron rich arenes which are typically disfavoured.\[^{132}\] Although not as desirable as aryl halides and pseudo-halides due to their high reactivity (and the need for each substrate to be prepared prior to cross-coupling), many simpler diaryliodoniums are commercially available from Aldrich. Obviously, substrates with higher molecular complexity must be prepared; for instance, example preparations have been demonstrated by Sanford including those with more sensitive functional group such as aldehydes, ketones and thiophenes.\[^{77}\] Diaryliodoniums are readily accessed from aryl iodides,\[^{77}\] aryl trifluoroborates\[^{134}\] or directly by C-H activation\[^{135}\] which is more amenable to carrying through a multi-step synthesis. To gain mechanistic insights and determine potential side products involved in the trifluoromethoxylation of diaryliodonium...
salts, we synthesized a new asymmetric iodonium salt 93 under literature conditions in 84\% isolated yield >99\% purity.\textsuperscript{136} Thus the 4-fluoro substituent on the aryl ring was to serve as a convenient spectroscopic handle in $^{19}$F NMR mechanistic investigations.

\textbf{Scheme 3.22.} Three-step, One-Pot, Preparation of the Asymmetric Diaryliodonium Substrate 93 for Screening Reactions

\begin{equation*}
\begin{aligned}
\text{I} & \text{F}  \\
\text{1) mCPBA, CH}_2\text{Cl}_2, 0^\circ\text{C}  \\
\text{2) TfOH, 0^\circ\text{C} \rightarrow \text{RT, 2 h}}  \\
\text{3) mesitylene, 0^\circ\text{C} \rightarrow \text{RT, 12 h}}
\end{aligned}
\end{equation*}

\text{I} \text{F} \text{OTf} \quad 84 \%

Even though Cu-mediated fluorinations of IAr$_2^+$ reactions were determined to be a Cu$^\text{I}$-Cu$^\text{III}$ manifold in rigorous mechanistic studies (see Scheme 3.21), Sanford found that fluorination reactions proceeded smoothly with a Cu$^\text{II}$ catalyst: (tBuCN)$_2$CuOTf.\textsuperscript{123} In the proposed mechanism, the Cu$^\text{II}$ source undergoes a low barrier pre-catalytic disproportionation to afford the catalytic Cu$^\text{I}$ complex.\textsuperscript{123} This process is also consistent with the Hartwig Cu-mediated fluorination reactions outlined in the previous section. Owing to the success of this aforementioned Cu$^\text{I}$ catalyst, we started with the optimized Sanford conditions by investigating our three trifluoromethoxides 1a, g, h in different solvent systems at 60$^\circ$C (Table 3.4, Entries 1-6). Pleasingly, we found an initial hits of the desired Ar–OCF$_3$ 94 in up to 7\% conversion ($^{19}$F NMR analysis) with methylated quinuclidine (quinMe) salt in THF or dioxane. However, the major product was surprisingly, not the competing fluorination product 95, but the oxidative homocoupled product: 4,4'$\text{'}$difluorobiphenyl 96.

Next, we screened other common Cu$^\text{I}$ and Cu$^\text{II}$ sources which indicated that (tBuCN)$_2$CuOTf was indeed the most suitable copper source. THF and dioxane gave similar results regarding trifluoromethoxylation but homocoupling was the more dominant side reaction in dioxane as compared to THF. Cu(OTf)$_2$ gave no trifluoromethoxylation or homo-coupling but exclusively fluorination.
We reasoned that the unwanted oxidative homocoupling product 96 may be due to the 
in situ  generated Cu^{III} species in a process akin to Glaser-Hay coupling when conducted 
in the presence of O_{2}.\textsuperscript{[137]} If so, we surmised that this side reaction may be suppressed by 
the addition of the appropriate choice of ligands to prevent bis-oxo-bridged dimerization 
of higher-valent copper intermediates.\textsuperscript{[117,137]} Thus a variety of pyridyl ligands including 
tripodal ligand L4 known to be effective with in copper-mediated reactions were investigated. 
Unfortunately, the introduction of a 1.0 equivalent of ligand shut down all reactivity and 
neither trifluoromethoxylation or homocoupling was observed. Since, changing the order of 
the procedure seem to have no net effect on the product distribution, we investigated the 
reaction step-wise by $^{19}$F NMR experiments.
Table 3.4: Selected Screening Conditions for the Cu-Mediated Trifluoromethoxylation of Diaryliodonium-OTf 93.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cation</th>
<th>Solvent</th>
<th>[Cu]</th>
<th>Ligand</th>
<th>94 [%][a]</th>
<th>95 [%]</th>
<th>96 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMe₄</td>
<td>CH₂Cl₂</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>3</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>NMe₄</td>
<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>4</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>quinMe</td>
<td>CH₂Cl₂</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>3</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>quinMe</td>
<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>7</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>NMe₃CH₂Ph</td>
<td>Toluene</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>3</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>NMe₃CH₂Ph</td>
<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>7</td>
<td>0</td>
<td>inconcl.</td>
</tr>
<tr>
<td>7</td>
<td>quinMe</td>
<td>THF</td>
<td>[CuOTf]₂·benzene</td>
<td>–</td>
<td>7</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>quinMe</td>
<td>THF</td>
<td>(MeCN)₄CuPF₆</td>
<td>–</td>
<td>3</td>
<td>3</td>
<td>12</td>
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<tr>
<td>9</td>
<td>quinMe</td>
<td>THF</td>
<td>CuCl</td>
<td>–</td>
<td>7</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>quinMe</td>
<td>THF</td>
<td>Cu(OTf)₂</td>
<td>–</td>
<td>0</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>11</td>
<td>quinMe</td>
<td>1,4-dioxane</td>
<td>(tBuCN)₂CuOTf</td>
<td>–</td>
<td>5</td>
<td>inconcl.</td>
<td>35</td>
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<tr>
<td>12</td>
<td>quinMe</td>
<td>1,4-dioxane</td>
<td>[CuOTf]₂·benzene</td>
<td>–</td>
<td>6</td>
<td>inconcl.</td>
<td>31</td>
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<tr>
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<td>14</td>
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<td>0</td>
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<td>L3</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>quinMe</td>
<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
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<td>0</td>
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<tr>
<td>18</td>
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<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>L5</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>L6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>quinMe</td>
<td>THF</td>
<td>(tBuCN)₂CuOTf</td>
<td>L7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] The yield of product(s) was determined by comparing the integration of the ¹⁹F NMR signals: 1-fluoro-4-(trifluoromethoxy)benzene 94 (-117.0 ppm, -59.9 ppm), 1,4-difluorobenzene 95 (-121.7 ppm), 4,4'-difluorobiphenyl 96 (-118.0 ppm) and iodonium salt 93 (-107 ppm) with that of 3-nitrofluorobenzene (-112.0 ppm).
When iodonium 93 and \((\text{tBuCN})_2\text{CuOTf}\) were combined in THF at RT, there was an immediate loss of the \(^{19}\text{F}\) NMR signal corresponding to the [Mes-I-ArF] at -107 ppm and the emergence of a new signal in equal proportion at -110 ppm. To the best of our knowledge, this species has not been reported before but we speculated that this is the formation of the Ar-Cu\(^{\text{III}}\) species due to oxidative addition of the aryl fluoride across Cu\(^{\text{I}}\). This complex was relatively stable in THF solutions and did not degrade until the addition of \(-\text{OCF}_3\) anion which then resulted in exclusively the homocoupled side product 96. Thus, it appears that the presence of the trifluoromethoxide anion promotes homocoupling when added to the active Cu\(^{\text{III}}\) species. This is consistent with Maseras recent mechanistic investigation (2014) into the Glaser-Hay coupling of phenylacetylene with \(\text{O}_2\) as the external oxidant in which high-valent bis(\(\mu\)-oxo)-dicopper complexes lead to C-C homocoupling reactions.\(^{[116,137]}\)

Although we did not structurally characterize such intermediates, such a process is plausible since alkoxides are known to have an affinity for forming \(\mu\)-oxo bridges.\(^{[138]}\) Disappointingly, changing the order to first generate the Cu\(^{\text{I}}\)–\(-\text{OCF}_3\) complex before addition the iodonium salt did not lead to improved yields.

**Scheme 3.23.** Upon the Introduction of Diaryliodonium Salt 93 to \((\text{tBuCN})_2\text{CuOTf}\), We Observed a Novel \(^{19}\text{F}\) NMR Signal that Was Postulated to be the Intermediate High-valent Cu\(^{\text{III}}\) Intermediate Ar–[Cu\(^{\text{III}}\)].

Approach 3: Oxidation of Cu\(^{\text{I}}\) by F\(^+\) Oxidants

In a final approach, we investigated the copper-mediated fluorination of arylboronate esters that Hartwig and co-workers described the year prior (Scheme 3.24).\(^{[119]}\) Most importantly, they report mild conditions (50°C) and a good substrate scope in an operationally simple fashion.\(^{[119]}\) What particularly intrigued us was there reported mechanistic considerations of the Cu-mediated process (Scheme 3.25). Due to both the fluorinated nature of the F\(^+\) oxidant, substrates, and nucleophile, \(^{19}\text{F}\) NMR analysis proved to be a valuable spectroscopic tool, sufficient for them to elucidate and propose an entire mechanistic pathway.

Mechanistic studies carried out by Hartwig suggest that this fluorination reaction occurs readily by oxidation of Cu\(^{\text{I}}\) source to Cu\(^{\text{III}}\) by an electrophilic F\(^+\) source, 1-fluoro-2,4,6-
Scheme 3.24. Hartwig’s Copper-Mediated Fluorination of Boronate Ester Substrates under Mild Conditions by Means of an $F^+$ Oxidant

$$
\begin{align*}
\text{Ph} & \quad \text{BPin} \\
\text{Ph} & \quad \text{F} \\
97 & \quad \text{92}
\end{align*}
$$

2 equiv (tBuCN)$_2$CuOTf
3 equiv [Me$_3$pyF]PF$_6$
2 equiv AgF
THF, 50°C, 18 h
74% (isolated)

trimethylpyridinium ([Me$_3$pyF]$^+ = F^+$) triflate to generate a Cu$^{III}$-fluoride complex 98 (Scheme 3.25).[119] The solvent, THF, is not innocent in these reactions since the α-hydrogen atoms stabilize the neighbouring fluoride ligand in 98.[119] It is important to note that the initial Cu$^{III}$-fluoride 98 is not the fluoride that is disposed to form the aryl C-fluoride bond but in a subsequent, rate determining step, an arylboronate ester undergoes transmetallation by abstracting the Cu$^{III}$-F 99, liberating a fluoropinacol ester (F-BPin) and the desired Ar-Cu$^{III}$-OTf 100. Ligand exchange with −OTf and an equivalent of AgF generates the Ar−[Cu$^{III}$−F] 101 which then undergoes fast C−F reductive elimination yielding the desired aryl fluoride.

Scheme 3.25. Cu$^I$/Cu$^{III}$ Mechanistic Considerations for Hartwig’s Fluorination of Aryl-BPin substrates

Under the reaction conditions, we speculated that fluorination should at no point occur because the initial Cu$^{III}$-fluoride 98 is abstracted as it undergoes transmetallation with the Aryl-BPin to generate the aryl-Cu$^{III}$ 100. Thus, the F$^−$ is consumed as F-BPin and no
further species is capable of reductive elimination and in theory, should be able to react with a variety of nucleophiles such as OCF₃ provided there is no exogenous F⁻ present.

Hopeful, we then screened a variety of conditions including solvent, F⁺-oxidants, temperatures, and Cu sources (Scheme 3.26). Under all conditions that demonstrated reactivity, the aryl-BPin 97 underwent exclusive fluorination 92, not trifluoromethoxylation. Since [NMe₄][OCF₃] had limited solubility in THF, we preferentially utilized CD₃CN and 1,4-dioxane in further studies. We postulate that the fluorination was generated by decomposition of the –OCF₃ anion, possibly due to the electrophilic nature of the Cu³⁺. Thus, a variety of N-based ligands that are known to stabilize high-valent Cu were also introduced but all inhibited the reaction.

**Scheme 3.26.** Reaction Conditions Screened Using the Hartwig F⁺ Protocol with [NMe₄]OCF₃ 1a and the Substrate Biphenyl-4-boronic Acid Pinacol Ester 97

Since none of the screening reactions provided any desired product, we undertook step-wise ¹⁹F NMR mechanistic studies in order to ascertain the fluorination process resulting from OCF₃ to better manipulate the reaction conditions (Scheme 3.27). Thus, in a step-wise fashion, we added [Me₃PyF]⁺ to (tBuCN)₂CuOTf and observed the immediate formation of a Cu³⁺ species by ¹⁹F NMR analysis. This is consistent with Hartwig’s observations where they proposed the structure to be [(Me₃pyF)(solvent)Cu(F)OTf]⁺. When we treated this Cu³⁺-F species with TMS-OTf, the formation of TMS-F was observed with depletion of the signal at -110 ppm by ¹⁹F NMR analysis. Upon addition of the BPin substrate, the signal associated with the Cu³⁺-fluoride disappeared, indicating that transmetallation occurred, an observation that Hartwig and co-workers were unable to observe under similar reaction conditions.

The introduction of [NMe₄][OCF₃] at this point did not lead to trifluoromethoxylation. Rather, by ¹¹B NMR analysis we observed a signal not correlating to proposed F–BPin
in the original report which should be observed at + 15.2 ppm but a signal at + 0.5 ppm which is more likely the anionic \([\text{F}_2\text{BPin}]^-\) species (Scheme 3.27). Although not previously explained by Hartwig, this does provide rationale why they required two equivalents of AgF necessary for fluorination: one equivalent may react with the liberated Lewis acid, F-BPin, and an additional equivalent for transmetallation. However, in our case, the Lewis acidity of F-BPin would be expected to degrade the \(-\text{OCF}_3\) anion, forming \([\text{F}_2\text{BPin}]^-\) and possibly serve as a \(F^-\) source for competing fluorination. For instance, it is known the normally unreactive BF\(_4^-\) anion can serve as a \(F^-\) source in the presence of high-valent Cu species.\(^{[119]}\)

**Scheme 3.27.** Alternatively, Oxidation of Cu\(^1\) 102 by [Me\(_3\)PyF]OTf Followed by Transmetallation of the Aryl Boronate Ester Substrate Affords the Desired \([\text{Ar}–\text{Cu}^{\text{III}}]\) 83 Intermediate but Only Leads to Aryl Fluorination Product 76.

In the reverse order, we quantitatively prepared the NHC-stabilized Cu\(^1\)–\(\text{OCF}_3\) complex, noted by the upfield shift in the \(^{19}\text{F}\) NMR spectrum at -33.5 ppm and complete loss of signal at -21 ppm (free \(-\text{OCF}_3\)), consistent with Vicic’s (NHC)Cu–\(\text{OCF}_3\) complexes (Scheme 3.28).\(^{[90]}\) Upon addition of either [Me\(_3\)PyF]\(^+\) or Selectfluor-PF\(_6\) \(F^+\)-oxidants, the signal at -110 ppm associated with Cu\(^{\text{III}}\)-F signal was observed but very surprisingly, the \(-\text{OCF}_3\) anion was displaced from the complex affording a free \(-\text{OCF\)} (evidenced at \(\delta_F = -21\) ppm).

It is unclear whether the \(-\text{OTf}\) anion is a stronger nucleophile than \(-\text{OCF}_3\). The addition of aryl BPin substrate 97 (or alternatively, 4-biphenylstannane) at this point, led to the disappearance of the proposed Cu\(^{\text{III}}\)–F, the appearance of \([\text{F}_2\text{BPin}]^-\) by \(^{11}\text{B}\) NMR spectroscopy, and exclusively the fluorination product.

In summary, we attempted three approaches towards Cu-mediated/catalyzed trifluoromethoxylation of aryl substrates, by adapting existing protocols from Sanford and Hartwig. However, in each case, the \(-\text{OCF}_3\) anion decomposed due to high temperatures, Lewis acidity of high-valent Cu complexes, or an incompatibility with the substrate (such as aryl-BPin). Nevertheless, through mechanistic determinations, we were able to determine that even if stable low-valent \([\text{M}]–\text{OCF}_3\) complexes can be prepared, this does not directly translate to guaranteed stability with the necessary high-valent state required for reductive elimination.

For Cu-mediated (or catalytic) transformations, a separate study needs to be performed to investigate ligands that could stabilize organometallic Cu\(^{III}\)–OCF\(_3\) complexes and to enforce the required square planar geometry required for reductive elimination modelled according to Ribas’ aza-macrocyclic stabilized Cu\(^{III}\) ligands.\(^{[115]}\) This study would be essential to acquiring a broader understanding whether Cu\(^{III}\) complexes are stable towards β-fluoride elimination and whether the Cu\(^{I}\)-Cu\(^{III}\) manifold is generally suitable for C–OCF\(_3\) bond formation.

3.6.4 Nickel-Mediated Approaches for Trifluoromethoxylation

In 2012, Vicic reported that nickel-bipyridine complexes were found to be active for the trifluoromethylthiolation of electron rich aryl-iodides and aryl-bromides at room temperature using the analogous [NMe\(_4\)][SCF\(_3\)] to afford Ar–SCF\(_3\) in good yields (37-92\%).\(^{[93]}\) Drawn to the congruency in our reagents including similar thermal stability concerns with [NMe\(_4\)][OCF\(_3\)] 1a and hence the requirement for mild conditions, we screened 42 reactions including Vicic’s optimized ligand choice (dmbpy, 4,4-dimethoxybipyridine, L3).

We selected a representative aryl-iodide 106 as aryl iodides were found to be more reactive than aryl-bromides or chlorides (0 % conversion).\(^{[93]}\) We supplemented the screen with an aryl-triflate 106 since these substrates have a simple preparation, tend to undergo facile oxidative addition, and provide a \(^{19}\)F NMR spectroscopic handle.
Scheme 3.29. Vicic Reported the Ni\(^{0}\)-catalyzed Trifluoromethylthiolation of Aryl Bromides and Iodides with dmbpy as a Ligand While Schoenebeck Reported Nearly Equivalent Conditions with the Wider Bite-Angle Ligand dppf to Access Aryl Chlorides.

Interestingly, Schoenebeck has since reported nearly the identical Ni-catalyzed conditions for the trifluoromethylthiolation of aryl chlorides with using \([\text{NMe}_4][\text{SCF}_3]\).\(^{139,140}\) The key difference to access aryl chlorides was the rational use of 1,1’-bis-(diphenylphosphino)ferrocene (dppf) (L5), a ligand we had chosen to screen as well.\(^{140}\) Meanwhile, Love and co-workers have found equal success with Ni(COD)$_2$ catalysis for trifluoromethylation accessing both (hetero)aryl bromides and chlorides with [AgSCF$_3$] in a ligand-free environment.\(^{141}\) While the need for ortho-directing groups for C-X activation may hinder a broader substrate scope, the conditions are conveniently both ligand and additive free and operate under ambient temperatures in THF for just 6-8 h.\(^{141}\)

Scheme 3.30. Following Vicic’s Catalytic Trifluoromethylthiolation in a Ni\(^{0}\)-Ni\(^{II}\) Manifold Using Ni(COD)$_2$, We Screened a Variety of N- and P- Ligands for Ni-Catalyzed Trifluoromethoxylation of an Aryl Trflate 106 and an Aryl Iodide 90

Similar to our previous results, \([\text{NMe}_4][\text{OCF}_3]\) was not soluble in THF and no reactivity was observed for either substrate, highlighting the importance for homogenous reaction...
conditions. While \([\text{NMe}_4][\text{OCF}_3]\) 1a, ligands, and substrate are highly soluble in CH\(_3\)CN, no trifluoromethoxylation was observed by \(^{19}\text{F}\) NMR analysis. Rather, aryl triflates underwent oxidative addition 107 to varying extents indicated by the presence of free \(^{-}\text{OTf}\) from Ar–OTf. However, the use of either mono- or bidentate ancillary phosphine ligands used in this screen resulted in the fluorination of the phosphorus ligand 108 (Scheme 3.31). This is consistent with our previous results with the attempted metathesis of Ni(PMe\(_3\))\(_2\)Cl\(_2\) with \(\text{NMe}_4\text{OCF}_3\text{F}_7\). With N-based ligands, uncoordinated \(^{-}\text{OCF}_3\) remained in solution and no decomposition products were observed (\(\text{F}^{-}\), HF\(_2^{-}\), or COF\(_2\)). Due to the limited success of perfluoroalkoxides with Ni\(^{\text{II}}\), further work with Ni related transformations were postponed. In our hands, substituting \([\text{NMe}_4][\text{OCF}_3]\) for \([\text{NMe}_4\text{SCF}_3]\) highlights the key difference a substitution of a single atom. While the Ni\(^{\text{II}}\)-Ni\(^{\text{IV}}\) redox couple exemplified in Ritter fluorinations provides an alternative Ni-mediated strategy for cross-coupling, it is to be questioned whether high-valent Ni\(^{\text{III}},\text{IV}\) complexes are compatible with \(^{-}\text{OCF}_3\).[142,143]

**Scheme 3.31.** No Trifluoromethoxylation Was Observed with Vicic’s Ni Conditions Although Oxidative Addition of the Aryl Triflate 106 Was Successful. The Presence of N- Ligands Led to No Trifluoromethoxylation Whereas Fluorination Occurred with P-Ligands.

3.6.5 Palladium-Mediated Approaches for Trifluoromethoxylation

The Buchwald group has developed highly active Pd\(^0\)-catalysts for the formation of not only C–C and C–N bond formation but for challenging C–O, C–F, C–CF\(_3\) and C–S bonds.[97] The pre-catalysts are air, moisture and thermally stable, making their preparation facile but more importantly, allow for the formation of the active Pd\(^0\) species without unnecessary reducing agents.[144] In particular, their 3rd generation pre-catalysts containing a cyclo-palladated 2-aminobiphenylmesylate backbone demonstrate high solution stability and accommodate bulky ligands necessary to prevent oxidation of fluorination of the phosphorus centre.[97] Furthermore, the active Pd\(^0\) catalysts exhibit excellent catalytic activity not possible with other Pd catalysts, for instance the common Pd precursor Pd(OAc)\(_2\).
The mesylate anion is a critical aspect to the design of Buchwald’s G3 Pre-catalysts since it not only dissociates more readily than \( \text{Cl}^- \) to accommodate bulkier ligands but we reasoned that the lower nucleophilicity of the mesylate anion would be less likely to interfere with the poor nucleophilicity and cross-coupling of \( \text{OCF}_3 \). Furthermore, the activation of the in situ \( \text{Pd}^{II} \) pre-catalyst in solution can occur through the action of a suitable, non-nucleophilic base to induce reductive elimination of the carbazole (which is retained in low %) and afford the highly active, 12-electron LPd^0 species.\[^{[144]}\] This is in contrast to the typical need of an exogenous reducing agent which may also interfere with \( \text{OCF}_3 \) anion, circumvented in the Buchwald protocol.

**Scheme 3.32.** The Buchwald Group Has Designed Highly Active Pd^0 Catalysts for Challenging Carbon-Carbon and Carbon-Heteroatom Cross-Couplings of Poor Nucleophiles

\[ \text{Pd}^0 \text{NH}_2 \text{Cl} \text{L} \]

\[ \text{Buchwald 1st Generation} \]

\[ \text{Buchwald 2nd Generation} \]

\[ \text{Buchwald 3rd Generation Pd} \]

\[ a) \text{Evolution of Buchwald Pd-Precatalysts} \]

\[ b) \text{In situ generation of active catalyst by reductive elimination of carbazole from pre-catalyst:} \]

\[ \text{Deprotonation} \]

\[ \text{Base: K}_3\text{PO}_4 \]

\[ \text{Reductive Elimination} \]

\[ \text{L}_1\text{Pd}^0 \text{Active Catalyst} \]

\[ c) \text{High activity is afforded in the Suzuki-Miyaura Coupling by Buchwald’s G3 Pd Catalyst} \]

\[ \text{OMe} \]

\[ \text{Cl} \]

\[ \text{B(OH)}_2 \]

\[ 2\% \text{Pd/L = XPhos} \]

\[ \text{K}_3\text{PO}_4/\text{THF} \]

\[ \text{RT, 30 min} \]

Thus, we prepared the required palladacyle dimer of the Buchwald 3\textsuperscript{rd} generation pre-catalyst on a multi-gram scale from 2-aminobiphenyl 109 and Pd(OAc)\textsubscript{2} according to established Buchwald procedures.\[^{[97]}\] The spectroscopic analysis of this complex was
in accordance with their reported spectral data. For efficiency reasons in large screening situations and in similarity to others, we prepared the actual Pd pre-catalyst in solution by measuring a known concentration (50 µL solution in THF) of ligand and adding it to the Pd-precursor in the presence of K$_3$PO$_4$. After an induction period of 30 min to generate the LPd$^0$ precursor, solutions of the substrate and [NMe$_4$]OCF$_3$ were pipetted into each sample vial, hermetically sealed, and heated for a period of 13.5 h. Typically for even activated catalysts such as these, slightly higher temperatures are required for difficult heteroatom couplings including C–O bond formation.$^{[144]}$

**Scheme 3.33.** Buchwald’s 3$^{rd}$ Generation Palladium Pre-Catalyst 112 Can Be Prepared in Three-Steps from 2-Aminobiphenyl 109

We chose to screen two substrates (106 and 113) on the basis that aryl triflates and aryl iodides are well-known to be suitable substrates that readily undergo oxidative addition to Pd$^0$ catalysts (Scheme 3.34). In particular, aryl triflates are easily accessed from phenols and provide a convenient $^{19}$F NMR spectroscopic handle.$^8$

As presented in Fig. 3.11, choosing the correct ligand from a large series of known (Buchwald-type) ligands can be a challenging endeavour. While the substituent effects are generally known to contribute to valuable reactivity aspects of the active Pd-catalyst (such as stability, increased ability to undergo oxidative addition, etc.), the correct ligand choice is less-elegantly elucidated through screening of all available ligands.$^{[101,145]}$ Thus we screened 12 Buchwald ligands that were on hand including 8 other sterically-encumbered phosphine and amine mono- and bidentate ligands. We hypothesized that these ligands tend to be used successfully with other cross-coupling scenarios but the steric bulk of the ligands may provide some protection of ligand to unwanted fluorination, an unfortunate problem we experience with the [Ni]-mediated protocols.

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$^8$ $^{19}$F NMR analysis indicated the presence of unreacted aryl triflate 106 at -75.8 ppm and free –OTf at -79.8 ppm
Structural Impacts on Buchwald Ligands

- **R**^1^: Promotes reductive elimination
- **R**^2^: Increases stability, prevents cyclometallation, improves formation of Pd^0^.
- **R**^3^: Ease of Synthesis

![Diagram of various Buchwald ligands](image)

**Fig. 3.11.** Buchwald ancillary ligands L1-L12 and other sterically-encumbered P- and N- centred ligands screened in Pd^0^-Pd^II^-catalyzed trifluoromethoxylation of aryl triflate 106 and Aryl bromide 113 substrates.
Upon screening a total of 84 entries with either aryl triflate 106 or aryl bromide 113, we disappointingly did not observe trifluoromethoxylation of either substrate. Rather we were able to ascertain the presence of varying amounts of free triflate anion suggesting that oxidative addition of the substrate 106 was not the concern. While, no fluorination of any of the phosphorus based ligands was observed and possibly indicates the need for protecting the phosphorus centre with appropriate designed ligand framework, we also did not observe fluorination of the substrates but nonetheless, disappearance of $\text{OCF}_3$. The results thus suggest that the key step, reductive elimination and C–OCF$_3$ bond formation did not occur but may have been possibly inhibited by formation of insoluble Pd$^{II}$ species, via $\beta$-fluorination.

In the event that the presence of K$_3$PO$_4$ facilitated decomposition by means of K$^+$ cation or deprotonation of the carbazole by-product by either $\text{OCF}_3$, an alternative, Buchwald Pd$^0$ catalyst was prepared in a two-step process.$^{[96]}$ This Pd catalyst 115 was designed in 2013 out of the need for a pre-catalyst that does not require an exogenous additive to generate the active the Pd pre-catalyst, have non-innocent anions, nor generate reactive byproduct anions, HF, or carbazole.$^{[96]}$ Hence, using 1-3% of complex 115, aryl triflates

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**Scheme 3.34.** Screening of Aryl Triflate 106 and Aryl Bromide 113 at 75 °C with the Highly-Active 3rd Generation Buchwald Pre-catalysts and Ligands (FIG. 3.11)
could be cleanly converted in the presence of CsF to the respective aryl fluoride in high yields at 80 °C without the presence of inhibitory species (for example, Cl– from [(cinnamyl)PdCl]$_2$ or formation of HF from Buchwald’s 3rd Gen. catalyst, [112]).

However, upon screening the same aryl triflate and aryl iodide substrates with 10 mol % Pd$^0$ pre-catalyst 115 loading, no trifluoromethoxylation of 106 and 113 was observed by $^{19}$F NMR analysis after 12 h at 70 °C.

**Scheme 3.35.** Preparation and Screening of Buchwald’s Stable Pd$^0$ Catalyst for the Trifluoromethoxylation of Aryl Iodide and Triflate

In retrospect, our results are consistent with a very recent publication by Guosheng Liu concerning a Pd-catalyzed intramolecular aminotrifluoromethoxylation of alkenes (SCHEME 3.36).[22] They rationalized that to achieve trifluoromethoxylation, reductive elimination of the metal complex should obviously proceed much faster than β-fluoride elimination (or $^-OCF_3$ decomposition).[22] So rather than electing to keep the electrophilicity of the metal centre as minimal as possible as we did, Liu approached this problem by procuring a high-valent metal approach.[22] Based on comparable hydrocarbon systems in which reductive elimination proceeds much faster than β-hydride elimination from high-valent Pd$^{IV}$, owing to the lack of open coordination site,[99] they chose similar conditions likewise to prevent undesired β-fluoride elimination.

Through comprehensive mechanistic studies and with a large substrate scope, they demonstrated that a high-valent Pd$^{IV}$–OCF$_3$ exhibited better stability than Pd$^{II}$–OCF$_3$, led to facile reductive elimination (even at −20 °C), and minimizing β-fluoride elimination, leading to successful C–OCF$_3$ bond formation in alkene sulfonamides. Liu and co-workers were able to access the key Pd$^{IV}$ species in a similar strategy as we approached with high-valent Cu in the previous section, namely, by means of an F$^+$ oxidant (Selectfluor-PF$_6$) followed by ligand exchange about the Pd$^{IV}$ centre. Although they attempted using [NMe$_4$][OCF$_3$], they inexplicably found better efficiency with [Ag]OCF$_3$. Although not
Scheme 3.36. Aminotrifluoromethoxylation of Alkenes by Facile Reductive Elimination of a PdIV–OCF₃ Complex to Form sp³ C–OCF₃

discussed, it is unclear whether the Ag⁺ cation plays a non-innocent role in the presence of high-valent Pd–F and F⁺ oxidants. Likewise, they were able to exclude ineffective CuCl₂, PtCl₂, and MnF₂ leading to fluorination as the major product.⁹² Consistent with out observations, the −OCF₃ anion in the presence of PdII leads exclusively to β-fluoride elimination.⁹²

While they have yet to apply this reactivity to the trifluoromethoxylation of arenes, their results importantly suggest that β-fluoride elimination and subsequent fluorination occurs from β-fluorination from a coordinated [M]−OCF₃ (as depicted in Scheme 3.13). This is stark contrast from an alternative, and less easily solved intermolecular fluoride abstraction from an uncoordinated −OCF₃ anion.

3.6.6 Gold-Mediated Approaches for Trifluoromethoxylation

In addition to (NHC)Cu–OCF₃ complex 104, Vicic had also reported that N-heterocyclic carbenes could stabilize Au⁺ complexes, allowing for the isolation of the analogous (SIPr)AuOCF₃ complex at −30 °C.⁹⁰ Consistent with mismatched electronics, Au⁺ does not readily form gold (I) fluorides and was originally, thought to be impossible to prepare.¹⁴⁶ Nevertheless, in 2005 Gray and Sadigh isolated and structurally characterized the first stable Au–F complex.¹⁴⁶ Similar to Vicic’s (SIPr)AuOCF₃ complex, the preparation of this species likewise required an NHC ligand (L = SIPr), thus allowing us to determine the identity of the β-fluoride elimination Au⁺ product (¹⁹F NMR = -247 ppm) if formed.⁹⁰,¹⁴⁶,¹⁴⁷

Au⁺/Au⁺-catalyzed organic transformations have become more prominent in the last decade including oxidative heteroarylation.¹⁴⁸–¹⁵² We were successfully able to prepare
**Scheme 3.37.** Direct Oxidative Arylation of Au\(^+\) Complex, (SIPr)Au–OCF\(_3\) \(\text{Au}^{19}\) Predominately Leads to Fluorinated Product PhF \(\text{Ph}^{121}\) with Trace Amounts of PhOCF\(_3\) \(\text{Ph}^{120}\)

A solution of the NHC stabilized Au\(^+\) complex, (SIPr)–Au–OCF\(_3\) \(\text{Au}^{19}\) readily at RT in a matter of minutes from the commercially available [(SIPr)Au\(^+\)][BF\(_4\)]– with [quinMe][OCF\(_3\)]. Consistent with Vicic’s spectroscopic data, the broad \(^{19}\text{F}\) NMR signal corresponding to the free \(\text{OCF}_3\) moved upfield upon coordination to a sharp singlet at -36 ppm although we found \(\text{Au}^{19}\) to be solution stable at RT.\(^{[90]}\) This upfield shift and sharpening of the signal is commensurate with a more covalent structure than a solvent separated ionic pair (Fig. 3.9).\(^{[90]}\) Alternatively, we found that \(\text{OCF}_3\) was not sufficiently nucleophilic to substitute the chloride ligand from (SIPr)AuCl but required one equivalent of a silver salt such as AgBF\(_4\) to abstract the chloride and generate the *in situ* cationic Au complex \(\text{Au}^{19}\). This species then underwent metathesis readily to afford the same complex.

We then investigated the direct oxidative arylation of diphenyliodonium in three different solvents, both at RT and 50°C (SCHEME 3.37). While no reaction occurred between [Au]–OCF\(_3\) in any solvent at ambient temperature, the major product in both THF and dioxane at 50°C was fluorobenzene with trace amounts of the desired trifluoromethoxylated product \(\text{PhF}^{120}\) (SCHEME 3.37). Solutions of [Au]–OCF\(_3\) in CH\(_2\)Cl\(_2\) underwent decomposition possibly suggesting the need for a coordinating solvent for this transformation. Since Au\(^+\)–F bonds tend to be labile and highly reactive\(^{[146]}\) we surmised that \(\beta\)-fluorination of an aryl-Au\(^{11}\) complex as a result of oxidative addition could lead to reductive elimination and the observed aryl fluoride, similar to results by Gouverneur and others.\(^{[153]}\) With no strategy to overcome the predominate fluorination, we briefly investigated an alternative Au strategy.

At the time, Bourissou reported for the first time that Au\(^+\) can undergo oxidative addition with aryl iodides with judicious choice of ligand.\(^{[154]}\) Linear Au\(^+\) complexes are historically highly stable and are reluctant to achieve higher coordination numbers without forcing conditions and/or the presence of a strong oxidant – conditions not typically amenable for late-stage modification of aryl frameworks. However, Bourissou was able to achieve oxidative addition of Au\(^+\) under mild conditions for a series of aryl iodides through the use of a rationally designed bidentate, 1,2-*bis*(diphenylphosphino)-1,2-dicarba-closo-dodecaborane
Scheme 3.38. Although Bourissou’s Gold(I) Carborane Complex 124 Readily Undergoes Oxidative Addition of Aryl Iodides such as 1-Fluoro-4-iodobenzene, Addition of [quinMe]OCF₃ 1h to Lₖ[Au]NTf₂ 124 Did Not Yield the Desired Trifluoromethyl Aryl Ether 94.
When the chloro anion is abstracted by AgNTf₂, the ensuing cationic Au⁺ triflamide salt can be handled at ambient temperature in a glovebox and in the presence of an aryl iodide, generates the stable, oxidative product 126.[154]

Since the respective gold chloro precursor 123 was conveniently made available to us, we prepared the corresponding [Aryl-Au⁺] species 125 (Scheme 3.38). Unfortunately, although the aryl iodide or aryl triflate substrates underwent oxidative addition under conditions reported by Bourrissou, the use of nucleophilic °OCF₃ did not provided access to the either trifluoromethyl ethers or aryl fluorides by ¹⁹F NMR analysis. Since quantities of these valuable precursors were limited, the transformation requires stoichiometric quantities of expensive Au and Ag precursors, and the possibility of forming unwanted high-valent gold fluorides, this Au-mediated route to trifluoromethoxylation became more of an intellectual curiosity rather than a means for an operationally simple, functional group tolerant methodology. As of yet, reductive eliminations with either traditional carbon or heteroatom nucleophiles has yet to be demonstrated with Bourrissou’s stable [aryl-Au] complexes. Provided it can be extended to a catalytic process, then the possibility of a Au-catalyzed trifluoromethoxylation of aryl halides becomes a more attractive methodology to consider.

3.7 Transition Metal-Free Approaches

While transition-metal-catalyzed reactions have evolved to be one of the most efficient and direct ways to construct carbon-heteroatom bonds, in this section we explored three alternative, non-transition metal coupling strategies for a functional-group tolerant trifluoromethoxylation protocol.⁹ While those that advertise non-metal pathways as preferable due to the expense of transition metals and ligands, tendency for air and moisture sensitivity, and the difficulty in removing their trace residues in pharmaceutical products, our main incentive to search for a transition-metal free protocol was to simply avoid persistent and competing fluorination, ostensibly via a metal-mediated β-fluorination elimination pathway. Since transition-metal free reactions undergo completely different mechanistic pathways than those afforded by traditional metal cross-coupling reactions, we hoped to exploit these alternative process for the installation of OCF₃ other small fluorinated moieties. Moreover, we were inspired by bench stable organic reagents for the incorporation of F and SCF₃ moieties.

⁹ For sake of clarity, transition-metal-free can be defined as either "without adding any external transition metal catalyst" or more precisely, exploiting a non-metal-mediated mechanistic pathway. This is out of concern for the possibility of highly active adventitious transition-metal residues in starting materials and solvents which often go undetected but in the end turn out to be a highly active catalytic species.[155–157]
3.7.1 Aryl–OCF₃ Bond Formation by Imidazolium Reagents

In 2011, the Ritter group developed a highly effective, easy-to-use, deoxfluorination reagent, Phenofluor® 127 (Scheme 3.39).[112] This fluorinated compound marked a significant improvement over existing commercially available reagents such as DAST, Deoxyfluor, and Xtalfluor reagents and is capable of fluorinating the ipso carbon of a diverse series of complex aryl and heteroaryl alcohols.[112] More recently, 127 has been extended to alkyl aryl ether bond formation by coupling primary or secondary alcohols with phenols.[158] They claim that the preliminary mechanistic studies including ¹⁸O labelled substrates are distinct from that of the similar Mitsunobu reaction which is typical utilized for the etherification of secondary alcohols (Scheme 3.39).[158] Although both methods rely on the formation of a strong driving force in deoxygenation by-products, notably 127 is also relevant for diaryl ether bond formation, a process that cannot be accessed through conventional Mitsunobu reactions. Critical to both fluorination and ether bond formation is the proposed presence of tight ion pairs which may be partly responsible for the efficient C–O bond formation. Both fluorination and ether formation with 127 are thought to follow a nucleophilic displacement mechanism (Scheme 3.39).[158]

**Scheme 3.39.** Functional Group Tolerant Deoxfluorination and Alkyl Ether Formation of Phenols Using Commercially Available Imidazolium Reagent, 127, Phenofluor®

2011, 2013: Fluorination of Phenols:

2015: Alkyl Aryl Ether Bond Formation:

24 examples, 50–92% (isolated)
Converting phenols to trifluoromethyl aryl ethers is a highly desirable transformation. Inspired by the ability of 127 to incorporate fluoride from the active but low nucleophilic species HF$_2^-$, we hoped to prepare a trifluoromethoxy reagent 128 capable for the conversion of phenols to trifluoromethyl aryl ethers (Scheme 3.40). Rather than begin directly by preparing 128, we rationalized that the key intermediate phenoxyimidazoliums 129a–c should be initially accessed. If introduction of the ‘OCF$_3$ nucleophile under anhydrous conditions could afford the trifluoromethyl ether presumably by nucleophilic aromatic substitution, then reagent 128 could be tested as a bench-stable reagent. We envisioned that the higher nucleophilicity of phenoxides would initially displace the –OCF$_3$ nucleophuge from the proposed imidazolium-OCF$_3$ reagent 128 but would form the desired tight ion pair which should then proceed under the same mechanistic process.

**Scheme 3.40.** Main Goal in Developing a Non-Metal OCF$_3$ Transfer Agents for the Conversion of Functionalized Phenols to Trifluoromethyl Aryl Ethers

Following procedures developed by the group,$^{[112]}$ phenoxyimidazolium intermediates were successful prepared by a silver activated nucleophilic substitution of chloro-imidazolium chloride 130 by the phenol substrate, a reaction that proceeds smoothly at 60 °C in CHCl$_3$. Upon isolation of phenoxyimidazolium 129a–c and recrystallization hot chloroform to remove minor amounts of imidazol-2-one, the phenoxyimidazolium were isolated as hygroscopic crystalline needles or blocks which were dried and pumped on at ultra low-vacuum overnight to remove volatiles. Introduction of either [AgOCF$_3$] or [NMe$_4$][OCF$_3$] under anhydrous conditions to generate trifluoromethoxy phenoxyimidazolium and hopefully trifluoromethyl aryl ethers lead to decomposition products COF$_2$ and HF$_2^-$ even at ambient temperatures as detected by $^{19}$F NMR spectroscopy.

Following the same procedure with phenols under anhydrous conditions in the glovebox to prevent acquiescence of atmospheric H$_2$O continued to furnish an equivalent of H$_2$O which is detectable in $^1$H NMR experiments by a down-shifted H$_2$O signal at 1.77 ppm.
Scheme 3.41. Trifluoromethoxylation of Phenoxy-Imidazolium 129a–c Led to Immediate Decomposition Due to a Proposed Strongly Bound H₂O to Acidic Backbone Hydrogen Substituents Consistent with a Known Phenoxyimidazolium Structure (Ritter, 2011)

No amount of heating under reduced pressure removed this bound equivalent of H₂O. We quickly reasoned that H₂O generated by using Ag₂CO₃ generated ½ equivalent of H₂O which is strongly hydrogen bound to the acidic 4,5-hydrogens on the imidazolium backbone. This is consistent with structure of phenoxyimidazolium 132 reported in 2011 in which a bifluoride anion is bound to a hydrogen on the backbone affording a dimer between two imidazoliums in the solid state.¹¹² The C···F bond distance of 3.0203 Å between C(4) and F⁻ indicates that the H···F is estimated to be 2.075 Å which is generally considered a strong H bond.¹¹²

The presence of bifluoride under fluorination conditions arising from the phenol substrate probably accounts for the three equivalents of CsF needed and >90 °C for fluorination.¹⁵⁹,¹⁶⁰ While acceptable for fluorination protocol as HF₂⁻ leads to the desired fluorination under more forcing conditions, the tightly bound equivalent of H₂O decomposes the OCF₃ anion. Thus we prepared the phenoxyimidazolium 128 by adding the isolated sodium phenoxide generated by NaH/THF under anhydrous conditions in the glovebox. The isolated phenoxyimidazoliums 129a–c generated by this route were water free but we suspected that an equivalent of solvent was coordinated in it’s place indicated by a solvent shifted signal when either CH₂Cl₂ or CH₃CN were used, but gratifyingly no H₂O was present. However, the introduction of OCF₃ still led to decomposition.

By replacing the chloroimidazolium chloride 130 used to prepare Phenofluor 127 with 2,4,5-dichloroimidazolium chloride 134, effectively removing the strong H-bonding sites, adding [NMe₄][OCF₃] in CD₃CN under anhydrous conditions cleanly and finally afforded the desired trifluoromethoxy-imidazolium 128 as indicated in an expected upfield shift in
**Fig. 3.13.** A deoxyfluorination intermediate, phenoxy-imidazolium intermediate 132, was structurally characterized by Tang et al. illustrating two strongly hydrogen bound HF$_2^-$ anions [112] (*diisopropyl* substituents and and aryl C-H removed for clarity in crystal structure).

**Scheme 3.42.** Substitution of 4,5-Dichloro-Phenoxyimidazolium by [NMe$_4$][OCF$_3$] Affords Trifluoromethoxy-Imidazolium 128. Introduction of 4-fluoro-phenoxide Leads to Expected Displacement of −OCF$_3$ but Decomposes at Temperatures Required for Displacement [28].
the $^{19}$F NMR at -33 ppm. Introduction of the sodium phenoxide $^{131a}$ to this solution expectantly displaced the bound OCF$_3$, consistent with its properties as a good nucleophile. Reversing the order and adding the OCF$^\cdot$ to a solution of the phenoxy-imidazolium $^{129a}$, also generated $^{19}$F NMR signals corresponding to the previously made trifluoromethoxy intermediate and free OCF$_3$ thus we suspected an equilibrium between OCF$_3$ and OPh imidazoliums. However, upon heating either solution for extended periods of time, no trifluoromethoxylation was detected at 60°C. Higher temperatures led to decomposition of OCF$_3$.

Although an attractive strategy that extends this valuable reagent, our initial results suggest that the strongly electrophilic H-bonds on the core of the imidazolium gives rise to the hygroscopic nature which leads to strongly bound H$_2$O and may also facilitate decomposition of the $^\cdot$OCF$_3$ anion. Re-designing the backbone framework afforded the desired reagent but disappointingly the poor nucleophilicity of OCF$_3$ requires thermal conditions that lead to decomposition of the nucleophile before SN$_2$Ar affords the desired class of compounds.

**Trifluoromethoxy Hypervalent Iodine Reagents**

Hypervalent iodine species $^{136a,b}$ have received widespread acclaim for their simple two-step preparation and unique ability to trifluoromethylate a wide range of substrates (C, S, O, N, P centres) readily under mild conditions with high functional group tolerance.$^{[1,161]}$ Beyond the CF$_3$ group, iodinane reagents are known to transfer difunctional fluorinated fragments$^{[162]}$ and the trifluoromethylthiolate anion $^\cdot$SCF$_3$ to aryl precursors.$^{[14,163]}$ Thus, we were inspired by the publication by Shen in 2013 that demonstrated a high degree of functional group tolerance for the trifluoromethylthiolation of $\beta$-ketoesters with $^{137a}$.$^{[163]}

**Scheme 3.43.** Preparation of Highly Valuable Electrophilic Trifluoromethylation Agents $^{139a,b}$ from Chloro-Iodinane 138, Are Capable of Trifluoromethylation an Extensive Array of C, N, O, P, S Nucleophiles

Shortly after their communication, Buchwald and co-workers used sophisticated analytical methods (including $^{13}$C NMR and Fujita’s crystalline sponge method for X-ray analysis) to demonstrate structurally that $^{137a}$ is structurally a trifluoromethanesulfenate $^{137b}$.$^{[164]}$
Although the mechanism for the preparation of the revised thioperoxide is unknown, Buchwald speculated that a plausible mechanism involves the reductive elimination from the hypervalent iodine centre facilitated by the strongly electron withdrawing substituents on the sulfur.[164]

**Scheme 3.44.** Preparation of an Electrophilic Hypervalent Iodine Reagent 137a for Efficient Trifluoromethylation of β-Ketoesters Has Been Demonstrated to Be Structurally Thioperoxide 140a by Buchwald in 2014

Since reagents 139a,b and 140a are prepared by the reaction of nucleophiles with chlorobenziodoxoles 138, we reasoned that an analogous trifluoromethoxy reagent may be an effective reagent to transfer the OCF₃ group. Thus we prepared four chloro and bromobenziodoxale precursors in high purity according to the revised literature protocol in two or three steps from the corresponding aryl precursor.[1,61,62,165,166]

**Scheme 3.45.** The Four Chloro- or Bromo-Benzodioxazoles Synthesized by the Togni Protocol from the Corresponding Alcohol or Acid Precursor in the Hopes of Preparing a Hypervalent Iodine Reagents 141a–d Bearing a Transferable OCF₃ Moiety

Introduction of [NMe₄][OCF₃] to 138b under rigorously anhydrous conditions at ambient temperatures, with or without AgOAc, predominately afforded the 1-fluoro-λ³-iodane 142a by ¹⁹F NMR (δ_F = -142.4 ppm)[165,167] instead of the desired trifluoromethoxy reagents 141a–
d. In a similar experiment, both AgF or [NMe₄][OCF₃] introduced to a solution of 138a afforded ¹⁹F NMR (δ_F = -169.17 ppm) ostensibly fluoro-iodinane 142b. While an undesired outcome, the moisture stable fluoroiodinane 142a had recently been prepared by Stuart in 2013 in 94% under acidic or basic conditions by nucleophilic substitution with a fluoride source and is a useful reagent for the fluorination of 1,3-ketoesters and 1,3-diketones. Our results are also consistent with an attempt by K. Niedermann (ETH-Zürich) documented in her PhD thesis in which [Ag]OCF₃ with 141d generated the corresponding fluoroiodinane as well.

**Scheme 3.46.** Introduction of [NMe₄]OCF₃ 1a to Chloro and Bromo-Iodinanes Affords the Corresponding 1-Fluoro-λ³-Iodanes

Since Shen’s structurally revised trifluoromethylthiolation reagent 137b comprises an open structure, thioperoxide O–SCF₃ bond, we wondered if it was possible to prepare a similar reagent by reversal of the O-S bond 143. Furthermore, in a follow-up structure-reactivity relationship study, Shen reported that 137a/137b without the aryl iodine substituent was found to render the reagent only slightly less efficient but simplified the preparation of the electrophilic trifluoromethylthiolating reagent significantly. Since our initial attempts in the preparation of thioester or thionoester precursors were futile, we envisioned a nucleophilic displacement of the easily accessible trityl hypochloride by OCF₃ could afford the desired reagent 144 that could undergo copper-catalyzed radical trifluoromethoxylation similar to Shen’s protocol.

**Scheme 3.47.** If Shen’s Reagent is a Stable Thioperoxide, Is the Reverse Thioperoxide a Reagent Capable of Being an Electrophilic OCF₃ Transfer Reagent?
Thus, trityl hypochlorothioite was prepared from triphenylmethanethiol and sulfuryl chloride by the procedure of Hiemstra and co-workers in 54% isolated yield as a fine yellow solid and recrystallized from CH$_3$CN (Scheme 3.48). In a subsequent step, the proposed reagent was prepared in situ by nucleophilic substitution with [NMe$_4$][OCF$_3$]. After 12 h, the $^{19}$F NMR signal corresponding to free $^\cdot$OCF$_3$ was fully and cleanly converted to a new signal at $\delta_F = -127.60$ ppm tentatively identified as 143 by HRMS (M$^+$ = 360.5275).

Scheme 3.48. In Situ Preparation of Trifluoromethoxytrityl Sulfane 144 from Trityl Hypochlorite 144 Did Not Afford the Corresponding Trifluoromethyl Aryl Ether under Identical Conditions from Shen’s Trifluoromethylthiolation of Aryl Boronic Acids.

We speculate that unlike Shen’s reagent which readily undergoes homolytic cleavage and often generates the disulfide CF$_3$SSCF$_3$, generating the highly reactive $^\cdot$OCF$_3$ radical would less likely form the trifluoromethoxy peroxide (CF$_3$OOCF$_3$). This should then preferentially react with Cu$^+$ catalyst and possibly allowing aryl$_{C-O}$ bond formation or by direct radical trifluoromethoxylation. Following Shen’s 2013 protocol for the copper-catalyzed trifluoromethylation of aryl boronic acids, we did not observe any reactivity of 144 as the signal remained unchanged by $^{19}$F NMR analysis at 45 $^\circ$C. We speculate that further structure-activity studies needed to be performed to acquire conditions for the homolytic cleavage of the desired thioperoxy of 144. However, due to time limitations, this continues to be a of future interest as a bench and thermally stable OCF$_3$ reagent such as trifluoromethoxytrityl sulfane 144 would be highly advantageous over highly moisture sensitive $^\cdot$OCF$_3$ salts.
3.7.2 Exploring Aryl Diazonium Salts

While aryl diazoniums are not an ideal class of substrates due to their limited thermal stability, light-sensitivity, and often aqueous preparations, diazonium salts provide access to a pseudo-aryl cation which can undergo ipso substitution of a wide array of nucleophiles (including \(\text{CF}_3\))\textsuperscript{[169]} While the reaction does not proceed well with \(\text{F}^-\) anions to generate aryl fluorides unless under Balz-Shiemann conditions with \(\text{BF}_4^-\), we briefly investigated several high-purity, anhydrous diazonium salts that were commercially available from Aldrich. Thus we attempted both direct nucleophilic substitution and Cu-mediated Sandmeyer conditions: (1) by the addition of Cu additives or (2) the pre-formation of CuOCF\(_3\) from CuBr. However, under none of the conditions studied were detectable amounts of the corresponding ArOCF\(_3\) by \(^{19}\text{F}\) NMR spectroscopy. However, upon warming all solutions were observed to undergo decomposition of the \(\text{OCF}_3\) anion and concomitant formation of dark red solutions often associated with competing diazo coupling.

**Scheme 3.49.** Several Conditions Were Unsuccessfully Screened for the Conversion of Aryl Diazoniums 148a–c to ArOCF\(_3\) 149a–c Including Copper-Mediated Sandmeyer Reactions

\[
\begin{align*}
148a–c & \quad \overset{\overset{\text{N}_2}{2.0 \text{ equiv}, \text{NR}_4\text{OCF}_3}}{\xrightarrow{\text{Solvent, Temperature, Cu-source, 8 h}}} \quad 149a–c
\end{align*}
\]
\(\text{R} = \text{Ph, F, Br, NO}_2\)
\(\text{NR}_4: \text{NMe}_4, \text{QuinMe}, \text{PhCH}_2\text{NMe}_3\)
\(\text{Temperature: } -45^\circ\text{C} \to \text{RT}, \text{RT}, 45^\circ\text{C}\)
\(\text{Solvent: } \text{CD}_3\text{CN, DMF, CH}_2\text{Cl}_2, \text{MeNO}_2\)
\(\text{Cu-sources: none, Cu}^0, \text{Cu(CH}_3\text{CN})_4\text{PF}_6, \text{CuBr}\)

3.7.3 Exploring Diaryliodonium Salts

Diaryliodoniums are versatile, stable reagents for direct electrophilic arylation of poor nucleophiles under metal-free conditions aided by the "hyperleaving" group ability of the ArI which has been estimated to be about a million times greater than that of the triflate group.\textsuperscript{[133]} While more complex diaryliodonium substrates have been prepared, several simpler diaryliodoniums are commercially available and have been demonstrated to arylate poor nucleophiles such as carboxylates, sulfonic acids, and the fluoride anion.\textsuperscript{[132,170]} To evaluate the ability of diaryliodoniums to arylate the \(\text{OCF}_3\) anion, the symmetrical diaryliodonium was heated at 60 °C for 4 hours in the presence of 1.5 equivalents of NMe\(_4\)OC\(_3\)F\(_7\). Pleasingly, up to 9% of the desired perfluoroalkyl aryl ether 150 was observed by GC/MS analysis of the
mixture including competing fluorination 151 resulting in fluorobenzene (77%) and arylation of the perfluorocarboxylate (14%) 152 most likely due to the presence of adventitious amounts of moisture in the diaryliodonium precursor.

Scheme 3.50. Product Distribution Between Diaryliodonium Salt 153 and NMe₄OC₃F₇ 3a in Toluene at 60 °C by GC/MS Analysis

Mechanistically, it is generally understood that diaryliodoniums react with nucleophiles under metal-free conditions to form a T-shaped intermediate with the nucleophile and one aryl group in a three-centre-four-electron bond.¹³¹ While alternative mechanisms such as SET and direct S_N Ar pathways have been suggested, the predominately held view is that the reaction proceeds by reductive elimination between the nucleophile and the adjacent, equatorial aryl group.¹³¹ To gain insight into the reaction between diphenyliodonium hexafluorophosphate and NMe₄OC₃F₇ 3a in CH₂Cl₂ was analyzed by VT ¹⁹F NMR analysis. The signal associated with the α-fluorines of 3a at -28 ppm was fully consumed and a new broad signal at -34.66 was present. This upfield shift is consistent with a more covalent bond and as the temperature was dropped in 10 °C intervals, the signal sharpened below -28 °C with concomitant appearance of a signal corresponding to the corresponding acyl fluoride, CF₃CF₂COF. Since the fluorodiphenyliodinane has been previously characterized (δ_F = -43.4ppm) and is not observed, the VT NMR experiments suggests that an equilibrium process between the two could be present. Upon heating, this may lead to competing aryl fluorination by β-fluorination of the perfluoroalkoxy iodinane.
**Scheme 3.51.** VT $^{19}$F NMR of Diphenyliodonium and $\text{NMe}_4\text{OC}_3\text{F}_7$ in $\text{CH}_2\text{Cl}_2$ with $\text{CFC}_3$ as an Internal Standard

$\text{OCF}_2\text{RF} + \text{[quinMe]PF}_6^- \rightarrow 1.5 \text{ eq } \text{NMe}_4\text{OC}_3\text{F}_7 \rightarrow \text{CH}_2\text{Cl}_2, \text{RT}$

$^{19}$F NMR
-43.4 ppm
*Org. Lett.*, 1999, 1, 673

$^{19}$F NMR
+18 ppm
Scifinder
3.8 Conclusion and Outlook

A new method for the preparation of non-metallic trifluoromethoxides is presented in this chapter. Rather than require the use of anhydrous fluoride sources, this unique method uses the commercially available refrigerant, CF\textsubscript{3}OCH\textsubscript{3} for the first time as an alkylating agent capable of methylating tertiary amines. The resulting tetraalkylammonium perfluoroalkoxides are thus prepared in a much more efficient (up to 90% isolated yield) and economic manner than previous methods while the products in our hands are most importantly easy to handle and are stable under an anhydrous atmosphere.

The late-stage preparation of trifluoromethyl aryl ethers in an efficient and functional-group tolerant protocol has been noted as a longstanding problem. This privileged motif is currently prepared as building blocks in multi-step procedures although new methods have been communicated recently. We have thus approached the problem in this chapter by limiting approaches to the aryl–OCF\textsubscript{3} disconnect with direct incorporation of the ¨OCF\textsubscript{3} anion.

A variety of transition-metal-mediated approaches were investigated through this chapter. Disappointingly, no suitable method was found for the trifluoromethoxylation of (hetero)arenes with Ag, Cu, Au, Ni or Pd methodologies. The extremely poor nucleophilicity, high moisture sensitivity, and propensity for α-fluoride elimination for metal coordinated ¨OCF\textsubscript{3} preclude its use as a general precursor for many metal-mediated cross-couplings. However, the results communicated herein allowed us to gain further insight towards trifluoromethoxylation.

While we found low-valent [M]–OCF\textsubscript{3} M = Ag\textsuperscript{I}, Cu\textsuperscript{I}, Au\textsuperscript{I} complexes to be "stable" intermediates, upon oxidation, these complexes readily undergo β-fluoride elimination and subsequent reductive elimination to generate the respective aryl fluoride. Thus rather than using, for example the Pd\textsuperscript{0}-Pd\textsuperscript{II} manifold as we have done, better success may be acquired as Liu found in 2015 with Pd\textsuperscript{II}-Pd\textsuperscript{IV} manifold even though this metal is highly electrophilic.\textsuperscript{[24]} Provided the metal is coordinately saturated and does not abstract a fluoride from ¨OCF\textsubscript{3}, reductive elimination may occur faster than β-fluoride elimination. Furthermore, the ancillary ligands (such as phosphines) for such metal complexes need to be stable towards oxidation and the substrates must not be Lewis acidic as was the case for aryl boronate esters and trifluoroborates.

To prevent β-fluoride elimination from electrophilic metals and secondly to prepare a convenient bench-stable reagent bearing a transferable-OCF\textsubscript{3} group that are not moisture sensitive, we pursued non-metal-mediated synthetic strategies and precursors. While low conversions of perfluoroalkoxylation was obtained with pseudo-cationic aryls such as di-
aryliodoniums, these substrates are not particularly amenable to a broad substrate scope and are furthermore not operationally simple procedures, both principle goals for this chapter. Despite designing protocols based on successful $F^-$ and $F_3CS^-$ transfer reagents including the imidazolium core of PhenoFluor® (fluorination) and hypervalent iodine reagents (trifluoromethylation, trifluoromethylthiolation, fluorination) we found little success due to either poor nucleophilicity of $\text{-OCF}_3$ or $\beta$-elimination to generate the fluoroiodinane.

However, reagents such as the revised thioperoxide do hold promise in generating a bench stable reagent that may enable radical trifluoromethoxylation similar to Shen\cite{14} and Buchwald.\cite{164} Furthermore, preparing $R_3N$–$\text{OCF}_3$ reagents by substitution of $R_3N$–$X$ precursors as Rueping has successfully done with $N$-(trifluoromethylthio)phthalimides\cite{16,23} are better accessed by the O-trifluoromethylation of $R_2NOH$ precursors,\cite{60} methodology that is outside the scope of this dissertation but remain an attractive approach toward this goal.

In conclusion, the stability of the trifluoromethoxide anion appears to constitute a major challenge to developing a novel and more general method for the synthesis of trifluoromethyl aryl ethers. However, knowing the limitations of the trifluoromethoxide anion will help better design novel synthetic protocols tailored towards trifluoromethoxylation of (hetero)arenes that utilize readily accessible precursors to gain greater levels of molecular complexity.
3.9 Experimental

3.9.1 General Remarks

All reactions were carried out under an inert nitrogen atmosphere unless otherwise indicated. Anhydrous solvents purchased from Aldrich were dried by passage through alumina (mBraun Solvent Purification System) unless otherwise stated, stored over 3 Å molecular sieves, and degassed prior to use.\textsuperscript{171} Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Flash chromatography was performed on Dynamic Adsorbents Silica Gel 40-63 μm particle size using a forced flow of eluent at 0.3-0.5 bar pressure.\textsuperscript{172} Concentration under reduced pressure was performed by rotary evaporation at 35-40°C (and at 5°C when specified) at appropriate pressure. Purified compounds were further dried under vacuum (0.01-0.2 Torr depending on volatility of compound). NMR spectra were recorded on a Varian Mercury 400 (400 MHz for $^1$H, 100 MHz for $^{13}$C, and 375 MHz for $^{19}$F acquisitions) or Unity/Inova 500 (500 MHz for $^1$H, 125 MHz for $^{13}$C, and 470 MHz for $^{19}$F acquisitions). $^{13}$C NMR spectra are recorded $^1$H decoupled. $^{19}$F NMR spectra are recorded $^1$H coupled. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl$_3$, 23°C, $^1$H NMR: 7.26 ppm, $^{13}$C NMR: 77.16 ppm). Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz; integration. High-resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers at the Harvard University Mass Spectrometry Facilities.

Dry acetone was was obtained by distillation over B$_2$O$_3$ and CF$_3$CF$_2$CF$_2$OCH$_3$ 3a was distilled over CaH$_2$ into a Straus flask and stored over 3 Å molecular sieves. Trifluoromethyl methyl ether 1, 98% was purchased as a compressed gas from SynQuest Labs Inc. (Alachua, Florida, USA) and was used as received. Triethylamine, $N,N$-dimethylbenzylamine, $N,N,N,N$-tetraethylenediamine, and $N,N$-diisopropylethylamine (Hünig’s base) were distilled over calcium hydride under a nitrogen atmosphere. All ligands, metal complexes and substrates are commercially available from Aldrich, VWR, TCI-America, Oakwood Products or Matrix Scientific unless otherwise noted. The following are not commercially available but have been prepared by (or adapted from) available literature protocols: AgOCF$_3$, \textsuperscript{72} chloro-and bromoiodinanes, \textsuperscript{138}a,b,d,e chloro- and phenoxy-imidazoliums, \textsuperscript{129}a-c and N,N'-1,3-bis(2,6-diisopropylphenyl)-4,5-dichloro-2-dicholoimidazolium chloride, \textsuperscript{128} Buchwald precatalysts, \textsuperscript{112} and \textsuperscript{115} and diaryliodonium salt, \textsuperscript{93} and Au-carborane complexes \textsuperscript{124}.\textsuperscript{173} High purity CF$_3$OCH$_3$ 1 is commercially available from Synquest Laboratories.
(Alachua, Florida, USA). NMR spectroscopic data of known compounds correspond to the data given in the appropriate references. NMR spectra of new or highly relevant compounds are attached.

3.10 Preparation and Experimental Data

Note: All accompanying experimental spectra for this chapter if not presented here can be located in Appendix A and F.

3.10.1 Experimental Procedures for Isolated Tetraalkylammonium Trifluoromethoxides

Tetramethylammonium Trifluoromethoxide (1a)

\[
\begin{align*}
\text{H}_2\text{C} & \text{O} \text{CF}_3 \\
\text{NMe}_3 \quad \text{dioxane, RT, 48 h} & \rightarrow \\
1 & \rightarrow 1\text{a} \\
\end{align*}
\]

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and 5 mL of anhydrous 1,4-dioxane. The tube was sealed and connected to a stainless steel vacuum line to which anhydrous NMe₃ (1.49 g, 25.2 mmol, 1.0 equiv) and trifluoromethyl methyl ether 1 (3.18 g, 31.8 mmol, 1.26 equiv) was transferred at −196°C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 48 h (max pressure 3.1 bar). The volatiles were removed under reduced pressure (0.5 torr) and the residue washed in the glovebox with 3x 5 mLs of anhydrous hexane on a glass-fritted filter to afford 1a as a fine white powder (2.129 g, 53%). \(^1\text{H} \text{NMR (500 MHz, CD}_3\text{CN)} \delta 3.12 (s, 3\text{H}). \(^{19}\text{F} \text{NMR (471 MHz, CD}_3\text{CN)} \delta -19.78 (\text{CF}_3, s, 3\text{F}).
Fig. 3.14. Preparation of [NMe₄][OCF₃] from CF₃OCH₃ and NMe₃

**N,N,N-Trimethylbenzylammonium Trifluoromethoxide (1g)**

A 60-mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and anhydrous N,N-dimethylbenzylamine (dried and distilled over CaH₂, 5.383 g, 39.8 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (1 mL). The tube was sealed and connected to a stainless steel vacuum line to which trifluoromethyl methyl ether 1 (8.33 g, 83.3 mmol, 2.1 equiv) was transferred at −196°C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 96 h (max pressure 2.8 bar). The reaction vessel was brought into the glovebox to which 20 mL of anhydrous pentane was added. The fine white precipitate was collected on a glass-fritted filter and washed with additional 3x 5-mL aliquots of anhydrous pentane to afford 1g as a fine white powder after removing trace volatiles under reduced pressure (1.320 g, 23%). ¹H NMR (600 MHz, CD₂Cl₂) δ 3.20 (-N(CH₃)₃, s, 9H), 4.67 (-CH₂-, s, 2H), 7.50-7.57 (Ar-, m, 4H). ¹⁹F NMR (471 MHz, CD₃CN) δ -20.23 (CF₃, s, 3F).
1-Methylquinuclidinium Trifluoromethoxide (1h)

A 60 mL Ace® Glass Pressure tube fitted with a #25 Teflon stopper housing a Swagelok® needle valve and pressure gauge was charged in a glovebox with a stir bar and quinuclidine (2.392 g, 21.5 mmol, 1.0 equiv) and anhydrous 1,4-dioxane (3 mL). The tube was sealed and connected to a stainless steel vacuum line to which trifluoromethyl methyl ether 1 (4.45 g, 44.5 mmol, 2.1 equiv) was transferred at $-196^\circ$C. The sealed vessel was then disconnected from the vacuum line and magnetically stirred behind a blast shield at RT for 26 h (max pressure 2.5 bar). The volatiles were removed under reduced pressure (0.5 torr) and the residue washed in the glovebox with 10 mLs of anhydrous diethyl ether on a glass-fritted filter to afford a 1h as a fine, slightly off-white powder (4.079 g, 90%). $^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 1.93-1.976 (-CH$_2$-, broad m, 6H), 2.15 (-CH, septet, 1H), 2.90 (-CH$_3$, s, 3H), 3.38 3.41 (-CH$_2$-, m, 6H). $^{13}$C NMR (126 MHz, CD$_3$CN) $\delta$ 19.85, 24.38, 52.67, 57.60 (fluorinated carbons not detectable). $^{19}$F NMR (471 MHz, CD$_3$CN) $\delta$ -21.09 (CF$_3$, s, 3F).

3.10.2 Preparation of Trifluoromethyl Triflate (70)$^{[28]}$


A 2 neck, 250-mL round-bottomed flask charged with a large magnetic stir bar, a 100-mL graduated addition funnel, 30-cm Vigreux column and condenser, and a 2 neck 100-mL round-bottomed receiving flask were dried in an oven for 12 h at 150°C. The system was assembled while the glass was hot and cooled under vacuum to 25°C and then backfilled with
N₂ and kept under a N₂ atmosphere. To the dry 250-mL round-bottomed flask charged with a magnetic stir bar was added sequentially dried, reagent grade sand (14.65 g) and anhydrous P₂O₅ (Acrors, 31.514 g, 111 mmol). To the addition funnel, trifluoromethanesulfonic acid (Oakwood Chemical, 100.0 g, 66.6 mmol, 1.00 eq) was added under N₂ and the contents added dropwise over the course of 5 min. The receiving flask was cooled to −78 °C in an acetone/dry ice bath. The reaction mixture was stirred at 26 °C for 3.25 h, then heated incrementally until reaching 111 °C for a total of 6.25 h. The distillate collected in the 100-mL round-bottomed Schlenk flask was then sealed. To the 100-mL round-bottomed flask at 0 °C was added a pre-cooled solution of 3 M KOH (45-mL) at 0 °C.

To the 100-mL round-bottomed flask containing the crude product was attached a short-path distillation apparatus with a 100-mL, round-bottomed Schlenk receiving flask containing 3 g of P₂O₅. The receiving flask was cooled to −78 °C in an acetone dry ice bath. The 100-mL round-bottomed flask was warmed with a water bath to 25 °C and the distillate collected via short-path distillation. The 100-mL round-bottomed Schlenk flask was then sealed after all the distillate was collected, warmed to 25 °C, and attached to a vacuum transfer apparatus with a 50-mL Schlenk flask. The vacuum transfer apparatus was flame-dried under vacuum and allowed to cool to 25 °C.

The distillate was then transferred via vacuum transfer at 0 °C (frozen solid with liquid nitrogen first, then during vacuum transfer allowed to warm to RT) over 15 min and the liquid collected in the 50-mL long-bodied Schlenk flask, cooled with liquid nitrogen, to afford 34.29 g of 70 as a colorless liquid (47.2%) which was stored in a 50-mL Schlenk flask at −30 °C in the glovebox. ¹⁹F NMR (471 MHz, CDCl₃) δ -53.08 (t, J = 3.65 Hz, 3F, OCF₃), -73.70 (t, J = 3.60 Hz, 3F, CF₃SO₂). (spectral data conforms to previously reported values by Ritter et al.)[27,28]

3.10.3 Preparation of Silver Trifluoromethoxide (72)[28,90]

Following the procedure from Vicic:[90] To a flame-dried 25-mL long-body schlenk with a PTFE stopper and a PTFE stirbar at −46 °C in the cold-well of a glovebox was subsequently added AgF (Aldrich, 2.5467g, 20.1 mmol, 1.00 equiv) and anhydrous CH₃CN (42.68-mL, 33.1605 g). The solution was stirred in the dark for 45 min. To the stirring solution was introduced cold trifluoromethyl triflate 70 (5-mL, 7.51 g, 34.4 mmol, 1.66 equiv) at −45 °C
and stirred for 2.25 h and then warmed slowly to RT at which point all the AgF dissolved to afford a slightly yellow solution. The solution was again cooled to −45°C upon which the solution was gently degassed by pumping on the solution in a controlled fashion to remove the by-product, CF$_3$SO$_2$F. In this way, 42.6-mL of AgOCF$_3$ in CH$_3$CN (approx. 0.470 mol L$^{-1}$) was obtained. This stock solution was stored in a Schlenk at −30°C in the dark; however, over a period of 2 months, trace amounts of dark solid began to precipitate. $^{19}$F NMR (471 MHz, CH$_3$CN) $\delta$ -25.10 ppm ([AgOCF$_3$], 3F); residue signals: Tf$_2$O = -72.2 ppm, CF$_3$SO$_2$OCF$_3$ 70 = -73.7 and -53.1 ppm; CF$_3$SO$_2$F = 38.28 (q, J = 18.52 Hz). (spectral data conforms to previously reported values by Vicic et al. Note: decomposition to AgF occurs if this stock solution is pumped dry according to Vicic et al.$^{[90]}$)

3.10.4 Preparation of Buchwald’s 3rd Generation Palladacycle Pre-catalyst, 111

![Scheme 111](image)

2-ammoniumbiphenyl mesylate, 110: Following the procedure from Buchwald$^{[97]}$ in a 250-mL 2 neck flame-dried round bottom flask equipped with a a 50-mL addition funnel, magnetic stir bar and fitted with a rubber septum under a nitrogen purge was charged with 2-aminobiphenyl 109 (Aldrich, 97%, 4.941 g, 29.20 mmol) and anhydrous diethyl ether (125-mL). A solution of methanesulfonic acid (1.94-mL in 30-mL diethyl ether) was added drop-wise and the mixture was stirred for 55 min. The reaction mixture was then filtered, washed with diethyl ether and dried under vacuum to provide 110 as a fine white powder in 94.7% yield, used without further purification. Yield: 7.335 g.

$\mu$-OMs palladacycle pre-catalyst, 111: Following the procedure from Buchwald$^{[97]}$ in a 250-mL 2 neck flame-dried round bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was introduced 2-ammoniumbiphenyl mesylate 110 (5.2844 g, 19.9 mmol) and Pd(OAc)$_2$ (4.4117 g, 19.7 mmol). The contents of the flask were evacuated and back filled with N$_2$ three times after and charged with 100-mL of anhydrous toluene
(from the SPS). The red suspension was heated to 50°C for 1 h upon which the colour of the solution turned from red to milky, off-white suspension after 30 min. Upon cooling to room temperature, the suspension was filtered and washed with toluene and diethyl ether and dried under vacuum for 20 h to afford 8.3122 g of 111 a fine white powder in 57.4% yield. \(^{1}\)H NMR (600 MHz, CD\(_3\)CN) \(\delta\) 1.96 (s, 1H), 2.33 (s, 2H), 2.56 (s, 7H), 6.25 (s, 5H), 7.16 (d, \(J = 1.2\) Hz, 1H), 7.19 (dd, \(J = 7.8, 1.2\) Hz, 3H), 7.22 – 7.31 (m, 4H), 7.36 (d, \(J = 1.8\) Hz, 1H), 7.46 (dd, \(J = 7.6, 1.6\) Hz, 3H), 7.60 (d, \(J = 7.3\) Hz, 2H). (spectral data conforms to previously reported values by Buchwald et al.\(^{[97]}\))

### 3.10.5 Phenoxyimidazoliums

**Preparation of 2-chloro-1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride, 130:** If the required chloro-imidazolium chloride 130 is not commercially available or if required on a large scale, it can be prepared inexpensively starting from 2,6-diisopropyline and glyoxal in three steps following the procedure by Ritter et al.\(^{[112]}\) Conveniently, since significant quantities of 130 were available to us, the synthesis of 130 was not required. Prior to use, 130 was heated at 40°C at < 0.1 torr for 12 h to remove any volatiles. \(^{1}\)H NMR (600 MHz, CD\(_3\)CN) \(\delta\) 1.31 (d, \(J = 6.85\) Hz, 6H), 1.35 (d, \(J = 6.85\) Hz, 6H), 2.42 (sept, 7.08 Hz, 2H), 7.615 (d, \(J = 7.78\) Hz, 2H), 7.80 (t, \(J = 7.71\) Hz, 1H), 8.23 (s, 1H). (spectral data conforms to previously reported values by Ritter et al.\(^{[112]}\))
Scheme 3.52. Preparation of 2-chloro-1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride, 130

Preparation of 1,3-bis(2,6-diisopropylphenyl)-2-(4-fluorophenoxy)-1H-imidazol-3-ium chloride, 129a:

To a 20-mL vial equipped with a PTFE stirbar was charged with chloro-imidazolium chloride 130 (505.8 mg, 1.10 mmol, 1.00 equiv), 4-fluorophenol (127.0 mg, 1.13 mmol, 1.03 equiv), and Ag$_2$CO$_3$ (163.9 mg, 0.594 mmol, 1.08 equiv). To this mixture was added degassed CHCl$_3$ (ACS grade, untreated, 10-mL) and heated at 60°C for 16 h in the dark. The hot suspension was filtered through Celite and the volatiles removed in vacuo an off-white residue. This crude product was re-dissolved in a minimum of hot 80% CHCl$_3$: 20% hexanes, then slowly cooled to RT and stored at −5°C overnight in a freezer affording colourless needles of 129a which were collected under vacuum filtration and washed with ice-cold 80% CHCl$_3$: 20% hexanes. Yield: 522 mg, 89%. $^1$H NMR (500 MHz, CDCl$_3$) δ 1.18 (d, 6.70 Hz, 6 H), 1.29 (d, 6.75 Hz, 6 H), 1.77 (s, bound H$_2$O), 2.46 (sept, J = 6.69 Hz, 2 H), 6.34-6.36 (mult.,
1H), 6.77 - 6.81 (m, 1H), 7.31 (d, J = 7.90 Hz, 2H), 7.56 (t, J = 7.83 Hz, 1H), 8.40 (s, 1H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 22.82, 25.65, 29.53, 117.11, 117.31, 119.86, 119.93, 123.61, 125.13, 127.40, 132.55, 145.37. $^{19}$F NMR (471 MHz, CDCl$_3$) δ 112.47 (ArF, s, 1F).

Preparation of 1,3-*bis*(2,6-diisopropylphenyl)-2-(4-(trifluoromethyl)phenoxy)-1H-imidazol-3-ium chloride, 129b:

To a 20-mL vial equipped with a PTFE stirbar was charged with chloro-imidazolium chloride 130 (249.8 mg, 0.544 mmol), 4-(trifluoromethyl)phenol (88.8 mg, 0.547 mmol, 1.01 equiv), and Ag$_2$CO$_3$ (79.9 mg, 0.290 mol, 1.07 equiv). To this mixture was added degassed CHCl$_3$ (ACS grade, untreated, 9-mL) and heated at 60°C for 16 h in the dark. The hot suspension was filtered through Celite and the volatiles removed in vacuo an off-white residue. This crude product was re-dissolved in a minimum of hot 80% CHCl$_3$: 20% hexanes, then slowly cooled to RT and stored at −5°C overnight in a freezer affording colourless needles of 129b which were collected under vacuum filtration and washed with ice-cold 80% CHCl$_3$: 20% hexanes. Yield: 305.3 mg, 96%. $^1$H NMR (500 MHz, CDCl$_3$) δ 1.19 (d, J = 6.87 Hz, 6H, CH$_3$), 1.32 (d, J = 6.79 Hz, 6H, CH$_3$), 1.77 (s, bound H$_2$O), 2.49 (sept, J = 6.84 Hz, 2H, CH), 6.59 (d, J = 8.51 Hz, 1H, ArH), 7.31 (d, J = 7.89 Hz, ArH), 7.42 (d, J = 8.78 Hz, 1H, ArH), 7.56 (t, J = 7.75 Hz, 1H), 8.56 (s, 1H, CH$_{\text{imidazolium}}$). $^{19}$F NMR (471 MHz, CDCl$_3$) δ 62.77 (ArCF$_3$, s, 3F).

Preparation of 1,3-*bis*(2,6-diisopropylphenyl)-2-(4-nitrophenoxy)-1H-imidazol-3-ium chloride, 129c:

To a 20-mL vial equipped with a PTFE stirbar was charged with chloro-imidazolium chloride 130 (498.0 mg, 1.084 mmol, 1.00 equiv), 4-nitrophenol (152.1 mg, 1.093 mmol, 1.01 equiv), and Ag$_2$CO$_3$ (154.1 mg, 0.559 mol, 1.03 equiv). To this mixture was added degassed CHCl$_3$ (ACS grade, untreated, 10-mL) and heated at 60°C for 16 h in the dark. The hot suspension was filtered through Celite and the volatiles removed in vacuo an off-white residue.
This crude product was re-dissolved in a minimum of hot CHCl₃, then slowly cooled to RT and stored at −5 °C overnight in a freezer affording colourless needles of 129c which were collected under vacuum filtration and washed with ice-cold 80% CHCl₃ : 20% hexanes. Yield: 226.1 mg, 37%. ¹H NMR (500 MHz, CDCl₃) δ 1.22 (d, J = 6.78 Hz, 6H), 1.33 (d, J = 6.78 Hz), 1.68 (s, bound H₂O), 2.55 (sept, J = 6.79 Hz, 2H), 6.735 (m, J = 9.21 Hz, 1H), 7.32 (d, J = 7.86 Hz), 7.57 (t, J = 7.8 Hz, 1H), 8.50 (s, 1H).

Preparation of 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)-2-(trifluoromethoxy)-1H-imidazol-3-ium chloride, 128:

To a 4-mL vial equipped with a PTFE stirbar was charged with 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)-2-chloro-1H-imidazol-3-ium chloride 134 (42.3 mg, 0.08 mmol, 1.00 equiv) and [NMe₄][OCF₃] 1a (33.6 mg, 0.21 mmol, 2.6 equiv) and anhydrous CH₃CN (1.5-mL). The vial was sealed and placed in a pie-block and heated with constant stirring at 65 °C for 8 h to afford the OCF₃ substituted product, 128. ¹⁹F NMR (471 MHz, none) δ -33.00 (s, 3F). To this solution was added sodium 4-fluorophenoxy (12.8 mg, mmol, equiv) in a glovebox and heated for 2 h. The resulting solution was analyzed by ¹⁹F NMR indicating the presence of unreacted 128, the 4-fluorophenoxy imidazolium 129a, COF₂, and HF₂⁻. ¹⁹F NMR (471 MHz, none) δ -17.01 (COF₂), -32.99 (128), -115.13 (NaOC₆H₄F), -116.50 (129a), and -150.17 (HF₂⁻).
3.10.6 Preparation of Chloro- and Bromoiodinanes 138a,b,d,e

Preparation of 1-chloro-1,2-benziodoxol-3(1H)-one, 138a

![Chemical structure of 1-chloro-1,2-benziodoxol-3(1H)-one, 138a]

A flame-dried and nitrogen filled 500-mL three-necked, round-bottom flask equipped with a Dimroth condenser, a nitrogen inlet, a 50-mL addition funnel with a rubber septum, a PTFE-coated stir bar and a rubber septum was charged with 2-iodobenzoic acid, (Alfa Aesar 98%, 20.00 g, 32.2 mmol, 1.00 equiv) and anhydrous CH₃CN (150-mL). The resulting solution was heated to 75°C. To the addition funnel was cannulated anhydrous CH₃CN (40-mL) and solid trichloroisocyanuric acid (TCICA, 6.3922g, 27.5 mmol, 3.5 equiv Cl⁺) which dissolved in approximately 10 min. The solution of TCICA was added drop-wise to a well agitated solution of 2-iodobenzoic acid over a period of 5 minutes upon which a visible white precipitate immediately formed. The resulting solution was maintained at 75°C for a period of 3 min. The hot solution was then easily filtered directly, while hot, through a tightly pressed pad of Celite and washed with boiling CH₃CN. The yellow solution was taken to dryness by means of a rotary evaporator and the crude product washed a second time with cold CH₃CN. The fine, light yellow, free-flowing solid was dried under high vacuum to afford 138a in 37.0% yield. A second crop of crystals was not collected as purity was more significant than isolated yield. Yield: 8.425 g. ¹H NMR (500 MHz, CDCl₃) δ 7.79 (td, J = 7.35, 0.82 Hz, 1H, ArH), 7.92 - 8.07 (m, 1H, ArH), 8.21 (dd, J = 8.47, 0.82 Hz, 1H, ArH), 8.26 (dd, J = 7.50, 1.63 Hz, 1H, ArH). ¹³C NMR (126 MHz, CDCl₃) δ 117.08, 126.85, 128.66, 131.85, 133.38, 136.61, 167.18. (spectral data conforms to previously reported values by Togni et al.)[165]
Preparation of 2-(2-iodophenyl)propan-2-ol, 156\textsuperscript{[165,166]}

Following the procedure from Togni:\textsuperscript{[165,166]} To a flame-dried and nitrogen filled 250-mL three-necked, round-bottom flask equipped with a Dimroth condenser, a nitrogen inlet, a 50-mL addition funnel with a rubber septum, a PTFE-coated stir bar and a rubber septum was charged with freshly ground Mg turnings (10.6422 g, 0.4328 mol, 3.47 equiv. Activated by heating with I\textsubscript{2}, washing with 3x 25-mL anhydrous ether followed by stirring overnight in 25-mL anhydrous ether). Additional anhydrous diethyl ether (50 ml) was introduced into the 500-mL round bottom flask and addition funnel. Subsequently, methyl iodide (17.3-mL, 278 mmol, 2.20 equiv) was added to the addition funnel and then after 2 minutes, dropwise added to the magnesium turnings with vigorous stirring. The ensuing vigorous bubbling indicated that the reaction had been initiated upon which additional diethyl ether (25 mL) was added to the 500-mL RBF. The remainder of the MeI solution was added at approx. 0.75-mL/min while maintaining an autonomous reflux. After addition of the MeI, the solution was kept stirring for a period of 45 minutes at which time the temperature re-assumed the ambient temperature and stirring was stopped to allow the Mg-turnings to settle to the bottom of the reaction flask.

The brown coloured solution containing MeMgBr was transferred via a large bore cannula into an adjacent (previously) flame-dried and nitrogen filled 500-mL three-necked, round-bottom flask equipped with the same attachments. To the additional funnel of the 500-mL round bottom flask was charged methyl 2-iodobenzene (19.1 mL, 126 mmol, 1.00 equiv) in diethyl ether (25-mL) by syringe. The methyl 2-iodobenzene solution in the addition funnel was subsequently added drop-wise to the MeMgBr at 0\textordmasculine}C with consistent stirring over a period of 8 minutes. The addition funnel was then rinsed with additional diethyl ether and the reaction solution was stirred at RT for 5.25 h. The solution was refluxed for a period of 1.25 h and the reaction mixture monitored by TLC.
Upon completion, the reaction was cooled on an ice bath. The reaction mixture was slowly and cautiously quenched with a solution of saturated aqueous NH₄Cl which formed a yellow precipitate. An additional 300-mL of deionized water and 50-mL of diethyl ether was added to the flask and the contents of the flask transferred to a 2 L separatory funnel and extracted twice with 200-mL of diethyl ether. The combined ether extracts were filtered through a fritted filter packed with Celite and then dried over anhydrous K₂CO₃. The solvent was removed under reduced pressure by means of a rotary evaporator and the residue dried under high vacuum to afford a red-brown oil. Yield: 26.0 g containing 84.9% mass of 156 and 15.1% 2-phenylpropan-2-ol (starting material) by ¹H NMR by comparing σH = 7.6 ppm (product) to H = 7.5 ppm (side-product) consistent with: Eisenberger, P.; Kieltsch, I.; Koller, R.; Stanek, K.; Togni, A. *Organic Syntheses* **2011**, 88, 168-180.

*Fig. 3.15.* Preparation of 2-(2-iodophenyl)propan-2-ol by addition of MeMgBr to methyl 2-iodobenzene
Preparation of 1-chloro-3,3-dimethyl-1,2-benziodoxole, 138b[^165]

A flame-dried 500-mL three-necked, round-bottom flask equipped with a Dimroth condenser, a nitrogen inlet, a 50-mL addition funnel with a rubber septum, a PTFE-coated stir bar and a rubber septum was charged with crude 2-(2-iodophenyl)propan-2-ol, 156 (9.9326 g at 84.9% purity, 32.2 mmol, 1.00 equiv) and anhydrous CH$_3$CN (100-mL) under a N$_2$ atmosphere. The resulting solution was heated to 75°C. To the addition funnel was cannulated anhydrous CH$_3$CN (28-mL) and solid trichloroisocyanuric acid (TCICA, 3.1051g, 40.1 mmol, 1.25 equiv Cl$^+$) which dissolved in approximately 4 min. The solution of TCICA was added drop-wise to a well agitated solution of 2-(2-Iodophenyl)propan-2-ol over a period of 3 min. The resulting solution was maintained at 75°C for a period of 5 min during which a visible white precipitate formed. The hot solution was then easily filtered directly, while hot, through a tightly pressed pad of Celite and washed with boiling CH$_3$CN. The yellow solution was concentrated to 15% of its original volume upon which the formation of a yellow precipitate began to form. The solution was cooled in a freezer at −8°C overnight and the resulting yellow solid was collected, washed with minimal amounts of cold CH$_3$CN. The fine, yellow solid was dried under high vacuum to afford 138b. Yield: 4.198 g, 44.0%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.55 (s, 1H, 6H, CH$_3$), 7.16 (dd, $J = 7.38$ Hz, 1.75 Hz, 1H, ArH), 7.52 (td, $J = 7.27$, 1.23 Hz, 1H, ArH), 7.56 (ddd, $J = 8.21$, 7.21, 1.67 Hz, 1H, ArH), 8.01 (dd, $J = 8.11$ Hz, 1.23 Hz; 1H, ArH). (spectral data conforms to previously reported values by Togni et al.)[^165]
Preparation of 1-bromo-3,3-dimethyl-1,2-benziodoxole, 138c

Following the procedure from Stuart: a flame-dried and nitrogen filled 250-mL three-necked, round-bottom flask equipped with a Dimroth condenser, a nitrogen inlet, a 50-mL addition funnel with a rubber septum, a PTFE-coated stir bar and a rubber septum was charged with 2-(2-iodophenyl)propan-2-ol (10.0 g, 38.2 mmol) \(156\) and \(N\)-bromosuccinimide (8.15 g, 45.8 mmol, crystalline white) was added to a solution of in \(\text{CHCl}_3\) (EMD, with stabilizer, 100-mL). The orange suspension was stirred at room temperature overnight. After this time, the yellow solution containing solid particulates filtered and then transferred to a 500-mL separatory funnel. The organic layer was washed with water (2 x 50-mL) and brine (50-mL). The organic layer was then dried (MgSO\(_4\), 2 h) and concentrated on a rotary evaporator to give a yellow solid which was recrystallized from hot ethyl acetate and hexanes to give 1-bromo-3,3-dimethyl-1,2-benziodoxole, \(138c\) as bright yellow crystals (4.326 g, 33%). The characterization data was in agreement with the literature. \(^{[167]}\) \(^1\)H NMR (500 MHz, \(\text{CDCl}_3\)) \(\delta\) 1.55 (s, 6H), 7.13-7.15 (m, 1H, ArH), 7.51-7.56 (m, 2H, ArH), 7.96-8.00 (m, 1H, ArH).

Preparation of 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol, 157

Following the procedure from Togni: to a 100-mL long-body schlenk in a glovebox was added a solution of \(n\)-BuLi (45.1 mL, 0.0721 mol, 2.2 equiv, 1.6 M in hexanes; Aldrich)
and anhydrous TMEDA (N,N,N',N'-tetramethylenediamine) (0.79-mL, 0.613g, 5.28 mmol, 0.16 equiv) at room temperature for 15 min and then cooled to 0 °C. To this solution was introduced in a drop-wise fashion a pre-cooled (0 °C) solution of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (8.00 g, 0.0328 mol, 1.00 equiv) in THF (5-mL) which upon full addition, was stirred for 30 min at 0 °C and then 18 h at ambient temperatures. Solid I₂ (8.227 g, 32.41 mmol, 1.01 eq.) was added in one portion with ice-cooling with a concomitant exotherm and stirring became difficult. The cooling bath was removed after 1 h and the reaction mixture was stirred at ambient temperature for 8 h. After hydrolysis with saturated aqueous NH₄Cl solution (30-mL) the aqueous phase was extracted with 75-mL Et₂O three times. The combined organic phases were washed with a solution of Na₂S₂O₃, dried over MgSO₄, filtered through a tightly pressed pad of Celite, the solvent was removed on a rotary evaporator and the residue was dried in vacuo to give 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol as a thick, orange oil used without further purification. Yield: 11.694 g, 96.4% isolated yield with 82.6% purity by ¹⁹F NMR, balance 17.4% starting material. ¹⁹F NMR (471 MHz, CDCl₃) δ -75.44 (CF₃, s, 0.21 integration, starting material), -73.36 (CF₃, 157, 1.00 integration). Spectral data conforms to previously reported values by Togni et al., 2006 [⁶⁵]

Preparation of 1-chloro-3,3-bis(trifluoromethyl)-1,2-benziodoxole, 138d

A flame-dried 500-mL three-necked, round-bottom flask equipped with a Dimroth condenser, a nitrogen inlet, a 50-mL addition funnel with a rubber septum, a PTFE-coated stir bar and a rubber septum was charged with crude 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol, 157 (11.34 g at 82.6% purity, 25.32 mmol, 1.00 equiv) and anhydrous CH₃CN (80-mL) under a N₂ atmosphere. The resulting solution was heated to 75 °C. To the addition funnel was cannulated anhydrous CH₃CN (20-mL) and solid trichloroisocyanuric acid (Aldrich, 97%, 2.5095 g, 10.8 mmol, 1.28 equiv Cl⁺) which dissolved in approximately 6 min. The solution of TCICA was added drop-wise to a well agitated solution of 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol, 157 over a period of 2 minutes forming a white precipitate within 5 sec of addition. The resulting solution was maintained at 75 °C for a period of 9 min during which a visible white precipitate continued to formed. The hot
solution was then easily filtered directly, while hot, through a tightly pressed pad of Celite and washed with boiling CH$_3$CN. The yellow solution was concentrated until the formation of a yellow crystalline precipitate began to precipitate. The resulting yellow crystals were collected, washed with minimal amounts of cold CH$_3$CN. The fine, yellow crystals was dried under high vacuum to afford 138d. Yield: 5.457 g, 53.3% isolated. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.71-7.77 (m, 2H), 7.79-7.92 (m, 1H), 8.09 (d, J = 8.45 Hz, 1H). $^{19}$F NMR (564 MHz, CDCl$_3$) δ -75.74 (CF$_3$, s, 6F). (spectral data conforms to previously reported values by Togni et al.)$^{[165]}$

**Preparation of 1-chloro-1,2-benziodoxol-3(1H)-one, 142b$^{[165,167]}$**

![Chemical structure 138a](image1.png)  
1.25 equiv AgF  
CH$_3$CN, RT, 72 h  
![Chemical structure 142b](image2.png)  
$^{19}$F NMR = -169.17 ppm

To an oven-dried 4-mL vial equipped with a PTFE micro-stir bar was add 1-chloro-1,2-benziodoxol-3(1H)-one, 138a (57.3 mg, 0.202 mmol, 1.00 equiv) and silver (I) fluoride (32.0 mg, 0.252 mmol, 1.24 equiv) and anhydrous CH$_3$CN at room temperature. As the silver (I) fluoride begins to dissolve, a visible white precipitate begins to form. After a period of 24 h, $^{19}$F NMR analysis indicated a new signal at ($\delta$$_F$ = -169.17 ppm). The same result was afforded when [NMe$_4$][OCF$_3$] 1a (35.5 mg, 0.223 mmol, 1.25 equiv) and 1-chloro-1,2-benziodoxol-3(1H)-one, 138a (50.4 mg, 17.8 mmol, 1.00 equiv) were combined in 2-mL anhydrous CH$_3$CN after a period of 12 h with constant stirring. $^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.69 - 7.84 (m, 1H), 7.95 (d, J = 8.27 Hz, 1H), 8.03 (ddd, J = 8.38, 7.24, 1.43 Hz, 1H), 8.21 (dd, J = 7.68, 1.57 Hz, 1H).

In a similar experiment, to an oven-dried 4-mL vial equipped with a PTFE micro-stir bar was add 138b (49.4 mg, 0.167 mmol, 1.00 equiv) and [NMe$_4$][OCF$_3$] 1a (37.2 mg, 0.234 mmol, 1.40 equiv) and anhydrous CH$_2$Cl$_2$ (2-mL). The vial was sealed and stirred at RT for 12 h. $^{19}$F NMR analysis indicated full conversion to a new species. $^{19}$F NMR (471 MHz, CD$_2$Cl$_2$) δ -142.00. This is nearly the identical chemical shift as Stuart’s previously reported 1-fluoro-3,3-dimethyl-1,2-benziodoxole ($^{19}$F, CDCl$_3$, 376.46 MHz, $\delta_F$ = -142.4 ppm).
The same $^{19}$F NMR is obtained by AgF or [NMe$_4$][OCF$_3$] 1a at RT in CD$_3$CN in the presence of 1-chloro-1,2-benziodoxol-3(1H)-one, 138a

### 3.10.7 Preparation of (Trifluoromethoxy)(trityl)sulfane

**Preparation of trityl hypochlorothioite, 147**

Following a modified procedure from Hiemstra$^{[168]}$ and Miller,$^{[174]}$ A flame-dried 250-mL 2-neck round bottom flask equipped with a N$_2$ adapter and a septa, cycled through a vacuum/N$_2$ backfill process three times. Using a syringe, the flask was charged anhydrous diethyl ether (50-mL) and anhydrous benzene (5-mL) and then triphenylmethanethiol (Aldrich, 97%, 5.193 g, 18.8 mmol, 1.00 equiv). The solution was cooled by an ice bath to
0°C upon which sulfuryl chloride (Aldrich, 97%, 1.82 mL, 3.030 g, 22.5 mmol, 1.20 equiv) was drop-wise added over a period of 4 min. The solution turned yellow with appearance of a white precipitate shortly after. The suspension was filtered through a fritted glass-filter and the slightly off-white solid was washed with cold diethyl ether and further dried under vacuum (< 200 mtorr) for 6 h to afford 147 in 54.2% yield (2.3904 g) which was stored at −30°C in a glovebox freezer. $^1$H NMR (600 MHz, CD$_2$Cl$_2$) δ 7.00 - 7.67 (m, 18H, ArH). (spectral data conforms to previously reported values by Miller et al.$^{[174]}$)

**Preparation of (Trifluoromethoxy)(trityl)sulfane, 144**

\[
\begin{align*}
\text{Ph} & \quad \text{S} & \quad \text{Cl} & \quad \text{Ph} \\
1.75 \text{equiv } & \text{NMe}_4\text{OCF}_3 & \rightarrow & \text{CH}_3\text{CN}, 45^\circ \text{C}, 12 \text{ h} & \quad \text{Ph} & \quad \text{S} & \quad \text{OCF}_3
\end{align*}
\]

147 144

To a 20-mL oven-dried borosilicate scintillation vial in a glovebox, trityl hypochlorothioite 147 (171.3 mg, 0.552 mmol, 1.00 equiv) and [NMe$_4$][OCF$_3$] 1a (154.3 mg, 0.970 mmol, 1.75 equiv) were combined with anhydrous CH$_3$CN (5-mL). The vial was sealed, and the white suspension was heated at 45°C for 12 h. The reaction vessel was brought back in to the glovebox and the solution was filtered through a tightly pressed pad of Celite and the solvent removed in vacuo, re-dissolved in CH$_3$CN, stored at −30°C in the glovebox. The solution was used without further purification. $^{19}$F NMR (471 MHz, C$_6$D$_6$) δ -127.63 (s, 3F). HRMS (ESI-TOF) m/z: [M]$^+$ Calcd for C$_{20}$H$_{15}$F$_3$OS 360.0796; Found 360.5275.

3.10.8 Screening of Oxidants and Solvents for the Silver-Mediated Trifluoromethoxylation of Stannane 74.

To a 4-mL vial containing [quinMe]OCF$_3$ 1h (21.1 mg, 0.10 mmol, 2.00 equiv), oxidant (0.06 mmol, 1.2 equiv) and AgPF$_6$ (25.3 mg, 0.10 mmol, 2.00 equiv) was added 1-mL solvent followed by 74 (25 µL, 0.05 mmol, 1.00 equiv). The reactions were stirred at room temperature for 4 h. To the reaction mixture was added 3-nitrofluorobenzene (5.3 µL, 0.05 mmol, 1.00 equiv). The yield was determined by comparing the integration of the $^{19}$F NMR (375 MHz, solvent, 23°C) resonance in appropriate regions with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages ($^{19}$F NMR).
3.10.9 Screening of Additives for the Silver-Mediated Trifluoromethoxylation of Stannane (74).

To a 4-mL vial containing F–TEDA–PF₆ (10.3 mg, 0.022 mmol, 1.10 equiv), additive (0.022 mmol, 1.10 equiv) and AgPF₆ (10.1 mg, 0.04 mmol, 2.00 equiv) was added 0.3-mL acetone. The reaction mixture was stirred for 30 min. 74 (8 µl, 0.02 mmol, 1.00 equiv) and 0.1 mL solvent containing [quinMe]OCF₃ (6.37 mg, 0.04 mmol, 2.00 equiv) were added in that order. The reactions were stirred at room temperature for 4 h. To the reaction mixture was added 3-nitrofluorobenzene (2.1 µl, 0.02 mmol, 1.00 equiv). The yield was determined by comparing the integration of the $^{19}$F NMR (375 MHz, solvent, 23°C) resonance in appropriate regions with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages (by $^{19}$F NMR) in Table 3.3.

3.10.10 Reaction Condition Screening for the Copper-Mediated Trifluoromethoxylation with Trifluoroborates (88) and (89).

To a 4-mL vial containing substrate (0.025 mmol, 1.00 equiv), copper(II) salt (0.10 mmol, 4.00 equiv) and [Me₄N]OCF₃ (0.10 mmol, 4.00 equiv) was added 0.3-mL of solvent. The
reactions were stirred at room temperature for 20 h. To the reaction mixture was added 3-nitrofluorobenzene (10.6 µl, 0.100 mmol, 1 equiv). The yield was determined by comparing the integration of the $^{19}$F NMR (375 MHz, solvent, 23°C) resonance in appropriate regions with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages ($^{19}$F NMR).

$$
\text{entry} \quad \text{substrate} \quad \text{solvent} \quad \text{copper(II) salt} \quad \text{ArOCF}_3 \quad \% \\
1 \quad 88 \quad \text{MeCN} \quad \text{Cu(OTf)}_2 \quad 0 \\
2 \quad 88 \quad \text{MeCN} \quad \text{Cu(OAc)}_2 \quad 0 \\
3 \quad 88 \quad \text{DCE} \quad \text{Cu(OTf)}_2 \quad 0 \\
4 \quad 88 \quad \text{DCE} \quad \text{Cu(OAc)}_2 \quad 0 \\
5 \quad 89 \quad \text{MeCN} \quad \text{Cu(OTf)}_2 \quad 0 \\
6 \quad 89 \quad \text{MeCN} \quad \text{Cu(OAc)}_2 \quad 0 \\
7 \quad 89 \quad \text{DCE} \quad \text{Cu(OTf)}_2 \quad 0 \\
8 \quad 89 \quad \text{DCE} \quad \text{Cu(OAc)}_2 \quad 0
$$

3.10.11 Preparation of Iodonium Salt (93$^{[136]}$)

$$
\text{entry} \quad \text{substrate} \quad \text{solvent} \quad \text{copper(II) salt} \quad \text{ArOTf} \quad \% \\
1 \quad 88 \quad \text{MeCN} \quad \text{Cu(OTf)}_2 \quad 84 \\
2 \quad 88 \quad \text{MeCN} \quad \text{Cu(OAc)}_2 \quad 84 \\
3 \quad 88 \quad \text{DCE} \quad \text{Cu(OTf)}_2 \quad 84 \\
4 \quad 88 \quad \text{DCE} \quad \text{Cu(OAc)}_2 \quad 84 \\
5 \quad 89 \quad \text{MeCN} \quad \text{Cu(OTf)}_2 \quad 84 \\
6 \quad 89 \quad \text{MeCN} \quad \text{Cu(OAc)}_2 \quad 84 \\
7 \quad 89 \quad \text{DCE} \quad \text{Cu(OTf)}_2 \quad 84 \\
8 \quad 89 \quad \text{DCE} \quad \text{Cu(OAc)}_2 \quad 84
$$
To a 250-mL round-bottom flask equipped with a stir bar containing 4-fluoroiodobenzene (9.99 g, 45.0 mmol, 1.0 equiv) was added 120-mL DCM. The resulting solution was cooled to 0 °C and mCPBA (60 wt%, 14.3 g, 50.0 mmol, 1.1 equiv) was added followed by dropwise addition of TfOH (6.6-mL, 75 mmol, 1.66 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and mesitylene (7.0-mL, 50.0 mmol, 1.1 equiv) was added. The ice bath was removed and the solution stirred for 12 h. The solvent was removed under reduced pressure and the resulting slurry suspended in 100-mL Et₂O and filtered. The precipitate was washed with Et₂O (3 x 50-mL) and dried under reduced pressure to yield 93 (18.6 g, 84% yield). ¹H NMR (500 MHz, CD₃CN) δ 7.91 (dd, J = 9.2, 4.8 Hz, 2H), 7.28 (dd, J = 9.2, 8.5 Hz, 2H), 7.25 (s, 2H), 2.63 (s, 6H), 2.37 (s, 3H). ¹⁹F NMR (471 MHz, CD₃CN) δ -79.36, -107.03.

3.10.12 Tetralkylammonium Trifluoromethoxide Salt and Solvent Screening for the Copper-Catalyzed Trifluoromethoxylation of Diaryliodonium (93).

To a 4-mL vial containing iodonium salt 93 (24.5 mg, 0.05 mmol, 1.00 equiv), (tBuCN)₂CuOTf (0.01 mmol, 0.20 equiv) and [R₄N]OCF₃ (0.06 mmol, 1.20 equiv) was added 1-mL of solvent. The reactions were stirred at 60 °C for 20 h. To the reaction mixture was added 3-nitrofluorobenzene (5.3 µl, 0.05 mmol, 1.00 equiv). The yield was determined by comparing the integration of the ¹⁹F NMR (375 MHz, solvent, 23 °C) resonance in appropriate regions with that of 3-nitrofluorobenzene (-112.0 ppm). Yields are reported as percentages (¹⁹F NMR).

<table>
<thead>
<tr>
<th>Entry</th>
<th>[R₄N]OCF₃</th>
<th>solvent</th>
<th>94 [%]</th>
<th>95 [%]</th>
<th>96 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Me₄N]OCF₃</td>
<td>MeCN</td>
<td>0</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>[Me₄N]OCF₃</td>
<td>DMF</td>
<td>0</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>[Me₄N]OCF₃</td>
<td>DCM</td>
<td>2</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>[Me₄N]OCF₃</td>
<td>toluene</td>
<td>&lt;1</td>
<td>inconcl.</td>
<td>inconcl.</td>
</tr>
<tr>
<td>5</td>
<td>[Me₄N]OCF₃</td>
<td>acetone</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
3.10.13 Screening of Ligands and Solvents for the Pd-Mediated Trifluoromethoxylation of Aryl triflate and Aryl Bromide (106 and 114).

To a 4-mL vial containing Buchwald’s 3rd Generation Pd pre-catalyst was measured out 112 (4 mol%), K$_3$PO$_4$ (1.05 equiv) and stock solution of each ligand in THF pipetted (50 µL, 5 mol% equiv); except ligands L$_{10,14,15,19,20}$ which were insoluble and measured out as solids) and selected solvent mixture (0.5-mL). The catalyst mixture was incubated for 30 min for formation of the active catalyst to which was subsequently added to the reaction mixture a solution of the substrate (50 µL, 1.00 equiv, 106 and 114 in CH$_2$Cl$_2$ with a calibrated pipette and [NMe$_4$][OCF$_3$] (1.50 equiv). The 4-mL vials were sealed and placed in a pieblock at 75°C for 13.5 h. To each sample was added 3-nitrofluorobenzene (2.1 µL, 0.02 mmol, 1.00 equiv). The yield was determined by comparing the integration of the $^{19}$F NMR (375 MHz, solvent, 23°C) resonance in appropriate regions with that of 3-nitrofluorobenzene (-112.0 ppm). No evidence of trifluoromethoxylation, aryl fluorination or HF$_2^-$ was observed.
3.11 References


Chapter 4

Perfluoroalkoxides as Initiators for the Polymerization of Hexafluoropropylene Oxide

4.1 Introduction\textsuperscript{1,2}

The main goal of this chapter was to utilize tetraalkylammonium perfluoroalkoxides as initiators to gain an understanding of the competing chain transfer process in the industrial ring-opening polymerization of hexafluoropropylene oxide (HFPO). The polymerization process currently suffers from a competing chain transfer process that limits the degree of polymerization, increases polydispersity and drives the overall efficiency of the polymerization process down. Rather than using anhydrous alkali metal fluorides to initiate the reaction, it was hoped that the unprecedented introduction of perfluoroalkoxides as initiators could enable control of the polymerization process to attain a truly living polymerization of HFPO, thus increasing the efficiency of the industrial process. More importantly, controlling chain transfer would further enable the development of difunctional polymeric materials, not easily obtained with current polymerization technology.

\textsuperscript{1} Portions of this chapter have been adapted from: Howell, J. L.; Friesen, C. M.; Jelier, B. J.; Quaternary ammonium perfluoroalkoxy salts for preparation of perfluoropolyethers. PCT Appl. WO 2014110329 A1, 2014 and Mountain, G. A.; Jelier, B. J.; Bagia, C.; Friesen, C. M.; Janjic, J. M. J. Fluorine Chem. 2014, 162, 38-44

\textsuperscript{2} References begin on page 263
4.2 Perfluorooxiranes

4.2.1 Tetrafluoroethylene Oxide, 159

An alternative method for the in situ preparation of perfluorinated alkoxides bearing α-fluorines is the nucleophilic ring-opening of perfluorooxiranes. Highly fluorinated epoxides do not particularly offer synthetic advantages over perfluorocarbonyl precursors from a synthetic perspective since a source of anhydrous fluoride is still required, the perfluorooxirane can be unstable, and the product is often difficult to isolate from the perfluoroolefin precursor (both are often gases).

**Scheme 4.1.** Tetrafluoroethylene Oxide, 159 Readily Undergoes Nucleophilic Addition at Low Temperatures and Can Be a Means to Prepare Perfluoroethoxides

For example, the simplest perfluorooxirane, tetrafluoroethylene oxide (TFEO) 159 requires extensive equipment and experience to handle the epoxidation of tetrafluoroethylene in a safe manner. Furthermore, TFEO must be handled below its b.p. of −65 °C to prevent spontaneous rearrangement to CF₃COF. Thus, the ring-opening of perfluorooxiranes is typically limited to three or more carbon systems preventing access to simpler perfluoroalkoxides. Nonetheless, TFEO 159 can readily undergo nucleophilic ring-opening to afford an in situ fluorinated ethoxide with nearly any nucleophile including solvents such as CH₃CN, acetone, and dimethyl ether furnishing a range of small molecule fluorinated adducts and acyl fluorides. In the special case of a fluoride anion nucleophile, 159 gives equilibrium mixtures of perfluoroalkoxides and acyl fluorides.
**Scheme 4.2.** Due to the Electrophilic Nature of Perfluorinated Olefins, HFP 160 Undergoes Nucleophilic Addition of a Hypochlorite Anion to Afford Epoxide, 161.

![Scheme 4.2 Diagram](image)

4.2.2 Hexafluoropropylene Oxide, 161

**Preparation of Hexafluoropropylene Oxide**

In marked contrast to TFEO, the higher analogue, hexafluoropropylene oxide (HFPO) 161 is thermally stable up to 150 °C, is not affected by free-radicals and is hydrolyzed only after extended periods of water exposure.[2] Although the numerous ways to prepare 161 have been reviewed, all preparations are based on the reaction of hexafluoropropylene 160 with an oxygen donor (Scheme 4.2).[1,2] For instance, the epoxidation of hexafluoropropene undergoes nucleophilic addition of a NaOCl or the hydrogen peroxide anion (‘OOH) rather than a concerted, electrophilic epoxidation one would expect in hydrocarbon counterparts.[1,2,4,11,12] When prepared industrially, the epoxidation with high pressure O₂ is thought to undergo a radical process.[13,14]

**Reactivity of Hexafluoropropylene Oxide**

In the presence of nucleophiles, it has been well established that 161 undergoes nucleophilic addition nearly exclusively at the more electrophilic C3 and rarely at C2 (only with nBuLi) yielding the fluorinated n-propoxide rather than the fluorinated iso-propoxide.[1,2,12,15–17] The reactivity of perfluorooxiranes is thus opposite that of hydrocarbon epoxides.[18–20] For example, under basic conditions, propylene oxide undergoes nucleophile attack at the less substituted carbon because of greater accessibility.[21]

As of yet, there are no examples of enantioselective epoxidation of hexafluoropropylene and all commercially available sources of HFPO are used as racemic mixtures.[15,22] As a result, the product distribution of nucleophilic addition is likewise a racemic mixture. Under low temperatures, the ring-open nucleophilic addition of an anhydrous fluoride anion to 161 can generate the perfluoropropoxide in equilibrium with the corresponding acyl fluoride.[1,2,6–9,11–13,23–27] As the title of this chapter suggests, under only particular conditions,
Scheme 4.3. General Reactivity of Hexafluoropropylene Oxide; Most Notably, Nucleophilic Addition Preferentially Occurs at Sterically Hindered but More Electrophilic C3.

The in situ generated perfluoropropoxide can lead to homopolymerization of 161, an industrially important polymer (vide infra).[28]

4.3 Development of Perfluoropolyethers (PFPEs)

4.3.1 Introduction

The outstanding properties of fluoropolymers are well known and have recently been reviewed.[14] The integration of fluoropolymers into modern life is often overlooked but fill an imperative role from coatings from fast food packaging, coatings on nearly all touchscreens, and surfaces of cooking pans to textiles. In particular, the ongoing demand for fluoropolymers to address current global issues such as water purification, renewable energy, electronics, and biomedical applications has led to an estimated global revenue for fluoropolymers of $5.58 billion in 2010 (and 4000 article citations) with an annual growth rate of 6.5% through 2016.[14]

Fully fluorinated fluoropolymers (perfluoropolymers) can be divided into two categories based on the backbone composition: perfluoroalkyl are only comprised of C–C bonds such as poly(tetrafluoroethylene) (PTFE, known as Teflon®) whereas those that include C–O bonds in the backbone are known as perfluoropolyethers (PFPEs).[28,29] Within in perfluoropolyethers, there are three commercially available, related polymers: Fomblin® (Solvay Specialty Polymers, Italy), Demnum® (Daikin, Japan), and Krytox® (Chemours, USA). Fomblin® is prepared by the radical copolymerization of tetrafluoroethylene 158 (or hex...
**Scheme 4.4.** Comparison of the Two Classes of Perfluropolymer Based on Polymeric Backbone Structure

<table>
<thead>
<tr>
<th>Perfluropolyalkyl</th>
<th>Perfluropolyether</th>
</tr>
</thead>
<tbody>
<tr>
<td>F - C - C - C - F</td>
<td>F - C - C - O - C - C - O -</td>
</tr>
</tbody>
</table>

rigid, high $T_g$  flexible, low $T_g$

afluoropropylene 160) in the presence of oxygen under UV while Demnum® is synthesized by anionic ring-opening polymerization of 2,2,3,3-tetrafluorooxetane 162 followed by direct fluorination.[28] In a similar fashion, Krytox® is obtained via anionic ring-opening polymerization of HFPO, 161.[6,16,28] The synthetic preparations of each are summarized in Scheme 4.5.

**Scheme 4.5.** The Three Commercially Produced PFPEs are Prepared by Solvay, Daikin and DuPont (now Chemours).

**Fomblin® Z (Solvay)**

$$\text{F} \quad \text{F} \quad \text{F} \quad \text{O}_2$$

radical process

$$\text{OCF}_2\text{CF}_2\text{OF}_2\text{CF}_2\text{O} \quad \text{m}$$

158

**Demnum® (Daikin)**

$$\text{H}_2\text{C} - \text{O}$$

1) cat. $\text{F}^-$

$$\text{F}_2\text{C} - \text{CF}_2$$

2) $\text{F}_2$

$$\text{CF}_2\text{CF}_2\text{OF}_2\text{CF}_2\text{O} \quad \text{n}$$

162

**Krytox® (DuPont)**

$$\text{FC} \quad \text{CF}_2$$

cat. $\text{F}^-$

$$\text{conditions}$$

$$\text{CF}_2\text{CF}_2\text{OF}_2\text{CF}_2\text{OF}_2\text{CF}_3 \quad \text{n}$$

161

### 4.3.2 Utility of Poly(HFPO)

Polymers of hexafluoropropylene oxide are exceptionally robust lubricants that service aerospace, oil and gas, cosmetic, and automotive industries.[6,20,30–32] Having the ability to withstand extreme conditions while being non-flammable, non-toxic and chemically inert, poly(HFPO) has found extensive commercial applications over the past sixty years as lubricants and coatings. For instance, both in aeronautical systems and space applications there
is a need for wide liquid range, high-viscosity index fluids stable thermally and oxidatively above 300 °C while maintaining low viscosity at sub-zero temperatures as hydraulic fluids and lubrication greases.\cite{33,34} In addition, oligomerization of HFPO is critical to the preparation of Nafion® membranes critical for fuel cell development since the 1960s. Only within the past decade has the value of poly(HFPO) begun to diversify beyond traditional lubricants and coatings applications\cite{32–36} and more recently recognized as a valuable component to fluorous biphasic systems,\cite{37–39} surfactants,\cite{30} and 19F MRI theranostic applications.\cite{40,41}

In part, PFPEs such as poly(HFPO) could be interesting substitutes for PTFE polymers. In contrast to PTFE which degrades into bioaccumulative and persistent perfluorooctanoic acid (PFOAs), the oxygen present in PFPEs allows for environmental degradation to purported benign products.\cite{30,42–46}

### 4.3.3 Rationale for the Industrial Development of poly(HFPO)

Since the development of PFPEs was spearheaded by industrial corporations, ensuing proprietary restrictions has resulted in a paucity of accessible information concerning the preparation of all polymers beyond the patent literature. For poly(HFPO), the work by Eleuterio (DuPont, 1972),\cite{2} Hill (DuPont, 1974),\cite{16} Millauer (Hoescht, 1985)\cite{1} and Ameduri (CNRS, Montpellier, 2009)\cite{47} have been the only references to provide insight into the polymerization mechanism; the latter being the only one from an academic laboratory.

The need for fluoropolymers with a combination of physical properties useful over a temperature range from −60 °C to 300 °C was first explored by DuPont in the mid-1950s. Since Teflon® is a rigid polymer and predictions were completely wrong with poly(hexafluoropropylene) (polyHFP), workers at DuPont speculated that perfluorinated polyethers with a flexible backbone imbued by the C–O bond might give the desired combination of physical properties without sacrificing the chemical properties.\cite{2,27} Thus, when 159 was condensed on activated carbon at −196 °C and then warmed to −60 °C, vigorous ring-opening polymerization occurred but polymers with a DP\textsubscript{n} of greater than 40 could not be acquired.\cite{2} To achieve higher levels, it was found that TFEO must be polymerized at −196 °C with 3 MeV X-rays which then quantitatively furnishes polyTFEO, a crystalline polymer with excellent thermal stability up to 440 °C with no weight loss (550 °C with only 2% weight loss).\cite{2}

Due to the sensitivity required in handling TFEO and relative ease of epoxidation of HFPO, polymerization of HFPO was studied as an alternative monomer.\cite{2} After screening several hundred conditions at DuPont, the best condition to polymerize HFPO was determined to be a 1:1 anhydrous CsF to tetruglyme (abbreviation of tetra(ethylene glycol) dimethyl ether, TG) between −30 °C to −50 °C under strictly anhydrous conditions.\cite{1,2,11,26}
This gives access to molecular weights up to 4000 g mol$^{-1}$ and an average degree of polymerization ($\overline{DP_n}$) of 24. Higher molecular weights of up to 12,000 g mol$^{-1}$ ($\overline{DP_n} = 72$) could be achieved with the introduction of hexafluoropropylene as a solvent in a two-step process.$^2,5$3

4.4 Anionic Ring-Opening Polymerization of HFPO

In the presence of a catalytic amount of fluoride ion (initiator), hexafluoropropylene oxide can undergo chain growth, ring-opening polymerization. Traditionally metal fluorides (MF where M = K$^+$ or Cs$^+$) are primarily utilized in the presence of an aprotic solvent such as diglyme or tetruglyme.$^{1,2,16}$ The resulting in situ perfluoropropoxide 163 becomes the active species which attacks another equivalent of HFPO 164 generating a structurally different perfluorinated alkoxide (Scheme 4.6). The process repeats itself to afford oligomers terminating as acyl fluorides 165.

The resulting perfluoroalkoxide becomes the active species in what could be considered a "living polymer." Polymerization should theoretically only cease upon full consumption of the monomer and thus the number-average degree of polymerization ($\overline{DP_n}$) is controlled by the stoichiometric ratio of initiator to monomer. However, chain growth is easily impeded by rapid chain transfer mechanism to the corresponding acyl fluoride, thus regenerating a fluoride ion from the $\alpha$-fluoride of the perfluoroalkoxide intermediate (Scheme 4.6).$^{2,6,13}$ The F$^-$ anion initiates a new polymer chain 166, the result of which corresponds to a "chain transfer reaction."

This chain transfer process is thought to occur by one of three postulated mechanisms (Scheme 4.7).$^{2,6,13}$ The basis for Mechanism A is the propensity for perfluoroalkoxides to rearrange to a perfluoroacyl fluoride, liberating a highly nucleophilic fluoride. As was seen in Scheme 4.6, there are actually two important perfluoroalkoxides generated in the polymerization: the initial fluoride induced ring-opened HFPO resulting in a linear 3 carbon perfluoropropoxide $^\cdot$OC$_3$F, effectively the in situ initiator and equivalent perfluoropropoxides of HFE-7000 prepared in Chapter 2. The second perfluoroalkoxide is the propoxide of the propagating polymeric chain solely dependent upon the structure of the monomer, HFPO. These two perfluoroalkoxides are structurally different and thus would be expected to have different stabilities towards elimination of a fluoride ion. In the subsequent two mechanisms

---

$^3$Although dependent upon the nature of the polymer, IUPAC has defined oligomers (or prefix oligo) to be typically less than $DP_{30}$ in which the removal of one or a few monomers significantly varies the physical properties of the material. The term polymer (or poly) is generally reserved for materials with "many" repeat units while a difference of a few monomers does not affect the bulk properties of the material. The term threshold molecular weight is defined to be the minimum molecular weight which an oligomer will display properties for a particular application which affects the terminology of oligo- vs poly-. Source: 'Glossary of basic terms in polymer science.' Pure Appl. Chem., 1996, 68, 12, 2287-2311
Scheme 4.6. The Anionic Ring-Opening Polymerization of Hexafluoropropylene Oxide, 161 in the Presence of CsF/Tetraglyme (TG) Catalytic System

Solvation:

\[
\text{CsF}(s) \xrightarrow{\text{tetraglyme (TG)}} -30^\circ C \quad \text{Cs}\cdot\text{TG} + F^\ominus \quad \text{TG} = H_3CO\left\{CH_2CH_2O\right\}_4CH_3
\]

Initiation:

\[
\begin{array}{ccc}
\text{161} & \xrightarrow{k_1} & \text{163}
\end{array}
\]

Propagation:

\[
\begin{array}{ccc}
\text{163} & \xrightarrow{k_2} & \text{164}
\end{array}
\]

\[
\begin{array}{ccc}
\text{164} & \xrightarrow{k_3} & \text{165}
\end{array}
\]

Chain Transfer:

\[
\begin{array}{ccc}
\text{163} & \xrightarrow{k_1} & \text{166}
\end{array}
\]
Scheme 4.7. Three Mechanisms Have Been Proposed by Eleuterio (1972) for the Impeding
Chain Transfer During the Polymerization of HFPO 161: in Mechanism A, the Elimination
Could Occur from Two Different Active Perfluoroalkoxides in the Polymerization, Namely the
Perfluoropropoxide \( \cdot \text{OC}_3\text{F}_7 \) or the Propagating Oligomer Perfluoroalkoxide. Mechanisms B and
C Involve a Concerted \( \alpha \)-Fluoride Transfer Directly between Oligomer Active Species.

A. Transfer of F- by Elimination from perfluoroalkoxide:

\[
\text{CF}_3\text{CF}_2\text{CF}_2\text{O}^- \xrightarrow{\text{F}} \text{F}_3\text{CF}_2\text{C}^\text{O} + \text{F} \quad \text{161} \\
\text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 \xrightarrow{\text{F}} \text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 + \text{F} \quad \text{161} \quad (\text{or})
\]

B. Transfer of F- directly from perfluoroalkoxide:

\[
\text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 \xrightarrow{\text{F}} \text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 + \text{F} \quad \text{161}
\]

C. Transfer of F- between perfluoroalkoxide and acyl fluoride of two oligomers:

\[
\text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 \xrightarrow{\text{F}} \text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 + \text{F} \quad \text{OC}_3\text{F}_7
\]

\[
\text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 \xrightarrow{\text{F}} \text{C}_3\text{F}_7\text{O} \left\{ \text{CFCF}_2\text{O} \right\}_n \text{CF}_3\text{F}_3 + \text{F} \quad \text{OC}_3\text{F}_7
\]
(B and C), chain transfer could possibly proceed directly from either perfluoroalkoxide to monomer (Mechanism B) or between an acyl fluoride/perfluoroalkoxide (Mechanism C) proceed without the liberation of a F$^{-}$ ion.\textsuperscript{[2]} In each case, chain transfer competes with propagation if the rate constant for ring-opening of HFPO $k_1$ is faster by nucleophilic attack by fluoride nucleophilic attack by the propagating alkoxide ($k_2$). Rate of F$^{-}$ attack $k_1$ has been empirically found to be higher at greater than $-30^\circ$C.\textsuperscript{[2,6,13]}

![Chemical reaction](image)

\textit{Fig. 4.1.} To obtain poly(HFPO), the reported two-step process involves the preparation of tetraglyme-soluble, low molecular weight oligomer perfluoroalkoxides (DP$_n$ = 0-3) of HFPO at 25°C which is used as an in situ initiator (liquid catalyst) in a second reactor at $-30^\circ$C to routinely provide poly(HFPO) up to 5500 g mol$^{-1}$.

As a result of this chain transfer process, it is difficult to achieve a high DP$_n$ and the process generally affords oligomers of (DP$_n$ = 1-7). Industrial methods found to partially circumvent the chain transfer process is by the incorporation of hexafluoropropylene 160 as a non-innocent solvent.\textsuperscript{[2,6,7,10,48]} According to early studies, Eleuterio\textsuperscript{[2]} and Hill\textsuperscript{[16]} have reported that hexafluoropropylene (HFP, 160, b.p. $-28^\circ$C) substantially improves DP$_n$ by improving heat transfer and decreasing the viscosity of the polymerization solution, both which can restrict molecular weight build up. Beyond acting as a diluent, HFP has been additionally reported to scavenge free F$^{-}$, generating dimers and trimers of HFP.\textsuperscript{[2]} While effective at improving the degree of polymerization, the exact nature the role HFP participates in the polymerization has not been disclosed in great detail.\textsuperscript{[49]} It would be expected that shifting an equilibrium by scavenging free fluoride should lead to an increase in chain transfer. Nonetheless, the addition of fluorinated solvents play an important role in the polymerization process.

The second method to improve the molecular weight of the polymer (up to a threshold molecular weight of 12,000 g mol$^{-1}$, DP$_n$ = 72) is a two-step process in which a stock "liquid...
initiator* is prepared comprising equimolar CsF/tetraglyme mixture with 2.5 equivalents of HFPO at 25 °C.\[6,16,26\] The resulting mixture generates a highly moisture and thermally sensitive, oligomeric mixture of poly(HFPO) perfluoroalkoxides (\(DP_n < 5, \text{Mn} < 830 \text{ g mol}^{-1}\)). This mixture of liquid catalyst is then used to polymerize 161 to desirable molecular weights.

### 4.5 Research Objective

The goal of this chapter was to determine for the first time, the efficacy of tetraalkylammonium perfluoroalkoxides as initiators for the ring-opening polymerization of HFPO and secondly develop a greater understanding of the chain transfer mechanism in the polymerization of HFPO to:

1. create a more efficient polymerization process (living polymerization conditions)
2. eliminate the need for a "liquid catalyst" to obtain high molecular weight poly(HFPO) (\(DP_n = 100\))
3. provide conditions for possible preparation of difunctional poly(HFPO)

This goal is particularly suited to the context of this thesis as the underlying basis for the proposed chain transfer mechanism illustrated in Scheme 4.7 is the propensity for the elimination of α-fluorine from oligo(HFPO) alkali metal perfluoroalkoxides. Until now, the current polymerization of HFPO is performed with potassium or cesium fluorides, which are known to readily eliminate a reactive fluoride ion.

**Scheme 4.8.** Determining the Efficacy of Tetraalkylammonium Perfluoroalkoxides as Initiators for the Ring-Opening Polymerization of HFPO 161

With the development of an effective methodology for the preparation of novel perfluoroalkoxides, the impact of tetraalkylammoniums prepared without the need for exogenous fluoride can properly be evaluated. Depending on the success of these new perfluoroalkoxide initiators, a much more efficient and convenient two-step, one-pot polymerization of HFPO could be envisioned than the current "liquid catalyst" process and the manipulation of large scale amounts of air-sensitive precursors.
4.6 Experimental Design

4.6.1 Standard Equipment for the Polymerization of HFPO

Initially, polymerizations were carried out in standard oven-dried glassware equipped with a $-78 \degree C$ dry-ice condenser equipped with an industrial pressurized HFPO cylinder. Although oligomerization of HFPO was successfully prepared in this fashion (vide infra), the difficulties in loading the perfluoroalkoxides with the exclusion of moisture, the inconsistency in controlling the temperature of the reaction vessel, variation in the rate of HFPO addition over long periods of time, and the lack of precision in metering amount of gaseous monomer, proved difficult to obtain consistent and reliable data. Thus a glovebox equipped with a high-pressure reactor was designed and constructed to control the many parameters involved including necessary purification of the monomer feedstock to scrub impurities$^4$ known to inhibit polymerization of HFPO.$^{161}$

4.6.2 High Pressure Glovebox Reactor

A reactor system was fabricated out of stainless steel (SS-316) with Swagelok® fittings and fluorinated ethylene propylene (FEP) tubing in a dedicated glovebox to allow for the manipulation of solid tetraalkylammonium perfluoroalkoxide initiators to be carefully weighed out with the exclusion of moisture. In a typical reaction, 25 g of HFPO monomer was transferred from a stock industrial cylinder to a pre-weighed 100-mL Hoke® transfer cylinder with a Swagelok® quick-connect fitting on a specifically constructed metal vacuum manifold in a fumehood (Table 4.1). Once measured, the Hoke® cylinder was connected externally.

$^4$Typical impurities in commercially available HFPO contain 1% hexafluoropropylene, 0.01-0.05% CO$_2$, 0-0.1% hexfluoroacetone and up to 0.2% perfluoroacetyl fluoride, COF$_2$, and perfluoropropionyl fluoride. The presence of HF in HFPO has been determined by Darling (DuPont, 1982) to be between 11-28 ppm. The use of molecular sieves has been reported to rearrange 161 to perfluoropropionyl fluoride and thus should not be used.
Polymerizations Were First Carried Out in a Stainless-Steel Parr Reactor or Slowly Fed into a Glass Reactor to the glovebox and metered by a two-stage diaphragm regulator to maintain a pressure of 25 psig during the course of the reaction. An inline electronic variable timer connected to a solenoid allowed for a continuous but slow addition of monomer to a mechanically stirred but hermetically sealed, commercially available Ace glass reactor tubes, capable of withstanding 150 psig at 200 °C (only tested to 80 psig at ambient temperature) (Scheme 4.3). Once the initiator and solvent were added to the reactor, the vessel was sealed and placed into a custom cold-well with minimal tolerances and externally cooled by circulating Neslab Ultra-cold circulator capable of −80 °C to 50 °C (Figure 4.4). The polymerization could proceed for extended periods of time without the need for any external adjustment.

4.6.3 Oligo(HFPO) Characterization

The molecular mass distribution of the resulting polymer is a critical factor to understanding the physical properties of the material and to evaluate the effect of chain transfer. Due to the moisture-sensitivity of the resulting acyl fluoride end group, the polymer is typically treated with anhydrous MeOH, readily and quantitatively affording the methyl ester derivative of oligo(HFPO). While industry has reported end group analysis (via 19F NMR spectroscopy) which does not establish PDI,[2,10,16] others have utilized GC/MS and MALDI-TOF spectroscopy.[6] but there is no study that compares all three methods, considering varying response factors of each instrument. Herein we utilize and evaluate a CsF/TG polymerization sample (Entry 1, Table 4.3) to demonstrate characterization of oligo(HFPO) by GC/MS, 19F NMR and MALDI-TOF spectroscopy to establish molecular mass and PDI of oligo(HFPO).
**Table 4.1:** Key Variables Relevant to the Polymerization of HFPO and Incorporated into the Design of the Glovebox-Enclosed Reactor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variable</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Temperature</td>
<td>Neslab Ultra-cold circulator (−80°C to 50°C) through a custom chiller apparatus with 0.1°C monitored by a computer.</td>
</tr>
<tr>
<td>2</td>
<td>Agitation Rate</td>
<td>Controlled by electronic mechanical stirrer (0 - 600 rpm) with tachometer (Parr Co.)</td>
</tr>
<tr>
<td>3</td>
<td>Monomer Purity</td>
<td>Pre-dried and scrubbed by 12&quot; x 0.5&quot; ∅ SS-316 anhydrous KOH column followed by a 12&quot; x 0.5&quot; ∅ column of CaH₂</td>
</tr>
<tr>
<td>4</td>
<td>Monomer Addition Rate</td>
<td>Controlled by a 555 electronic timer connected to inline solenoid</td>
</tr>
<tr>
<td>5</td>
<td>Amount of Monomer</td>
<td>Pre-weighted amount of monomer in a SS-316 Hoke® cylinder controlled by inline regulator (set at 25 psig)</td>
</tr>
<tr>
<td>6</td>
<td>Solvent Purity</td>
<td>dried and distilled by standard procedures</td>
</tr>
<tr>
<td>7</td>
<td>Solvent Choice</td>
<td>as required</td>
</tr>
<tr>
<td>8</td>
<td>Initiator Cation</td>
<td>[M]⁺, NR₄⁺ etc.</td>
</tr>
<tr>
<td>9</td>
<td>Initiator</td>
<td>−F, −OCF₃, −OC₂F₅, −OC₃F₇, −OC₄F₉</td>
</tr>
</tbody>
</table>

**Fig. 4.3.** Schematic for a Glovebox-Equipped Pressure Reactor Constructed Specifically for the Ring-Opening Polymerization of HFPO 161
19F NMR End Group Analysis

Full 19F NMR characterization of poly(HFPO) has been carried out initially by Hill\cite{16} and a more detailed study recently by Thrasher\cite{50} and Rinaldi\cite{22}. Thus, the $M_n$ was determined by the DuPont method by setting the integration of the signal corresponding to the (-CF$_2$-)$_2$ (-131.90 ppm) to 2.00 with respect to the signal corresponding to the -CF-$_4$ (-145.0) of the repeat unit; therefore $\bar{DP}_n = 3.73$ (see Fig. 4.5). The repeat unit $n$ is defined to be the number of repeat units of the polymer as depicted in Fig. 4.5.

In the F$^-$ initiated ring-opening polymerization of 161, there are $n+2$ equivalents of monomer required: one equivalent is consumed in the formation of the in situ perfluoropropoxide initiator ($\alpha$-group), and one equivalent in the terminal acyl fluoride/methyl ester end ($\omega$) group. Declaring the structure with an OC$_3$F$_7$ $\alpha$-end group simplifies the end-group analysis when comparing F$^-$ and R$_F$O$^-$ initiated poly(HFPO).

GC/MS Analysis

After quenching the polymerization reaction with MeOH, Gas Chromatography-Mass Spectrometry (GC/MS) analysis was conducted by direct manual injection of 1 µL of crude reaction residue. The GC method was developed with a carefully designed temperature program that allowed for resolution of each homologue ($n = 0,1,2...$) and characterization of each peak by its corresponding mass fragmentation pattern. (Fig. 4.6). The determination of $n = 0$ homologue was evidenced by 344 m/z fragment (seen as M$^+$-19 = 325 m/z) and 159
Fig. 4.5. $^{19}$F NMR Spectrum (376.46MHz, δ ppm from CFCl$_3$, NEAT) for oligo(HFPO) methyl ester sample obtained on a Bruker Ascend at 300K with optimized T1 relaxation. As determined by end-group analysis, $DP_n = 3.73$. 
m/z fragment (+CF(CF3)COOMe) at t = 1.60 min. The same method was used for each analysis, run without a solvent delay by direct manual inject of 1-µL of reaction residue.

**Fig. 4.6.** Method designed for the identification of constituent homologues by GC/MS (time (min) vs abundance) Agilent 6890N with a 5975 MSD, 70 eV EI). Thermal Ramp 15 °C/min.

**Fig. 4.7.** Mass spectral characterization of n = 0 depicts an M+−19 = 325 m/z peak whereas all other have an additional peak at 491 m/z peak [M+166] indicative of a repeat unit; 70 eV EI MS.

---

5see Experimental section for full analysis and GC/MS methodology.
The GC data was analyzed by conventional equations to determine the number-average degree of polymerization ($DP_n$, Eq. 4.1), number-average (Mn, Eq. 4.2) and weight-average ($M_w$, Eq. 4.3) molar masses as well the poly-dispersity index (PDI, Eq. 4.4):

\[
DP_n = \frac{\sum n_i i}{\sum i}
\]

\[
M_n = \frac{\sum n_i M_i}{\sum n_i}
\]

\[
M_w = \frac{\sum n_i M_i^2}{\sum n_i M_i}
\]

\[
PDI = \frac{M_w}{M_n}
\]

where $n_i$ and $M_i$ represent the percentage and molar mass of the $i$ oligomer, respectively.[6] Thus, $M_n = 981$ g mol\(^{-1}\) and $M_w = 1021$ g mol\(^{-1}\) for the same representative sample (Entry 1, Table 4.3). Although a common technique for the analysis of polymers, Gel Permeation Chromatography (GPC) is not a typical characterization tool for fluoropolymers as it can require high volumes of cost-prohibitive fluorinated solvents (see Handbook Of Size Exclusion Chromatography And Related Techniques, p. 261).[51]

MALDI-TOF Mass Spectrometry Analysis\(^6\)

Since the 1990s, matrix-assisted laser desorption time-of-flight (MALDI-TOF) mass spectroscopy (MS) provides an alternative technique to NMR and GC/MS spectroscopy.[52,53] As such, MALDI-TOF MS is a suitable soft-ionization (M+\(^+\)) technique for a wide range of polymeric samples, capable of detecting low concentration of analytes with molecular masses of 0 - 550,000 g mol\(^{-1}\) (Da) with high precision.[52,53] Generally, a sample is prepared and diluted in a solution of matrix material and applied to a metal plate. Under high vacuum, a pulsed laser irradiates the dried-droplet sample target, causing ablation and desorption of the matrix. Through this process, the polymeric analyte is ionized, and the hot gaseous cloud is accelerated towards a time of flight detector. When, the analyte is less than 10 kDa, the length of path to the detector can be extended by reflection (an ion mirror) towards a secondary detector to increase resolution.

\(^6\)for simplicity, MALDI-TOF Mass Spectrometry Analysis is abbreviated to "MALDI-TOF" in this thesis
After extensive experimentation, a range of post-polymerization poly(HFPO) derivatives were successfully analyzed with a Bruker Autoflex spectrometer equipped with a 1 kHz Smartbeam-II laser and reflector in positive ionization mode (Fig. 4.8). Samples were prepared in a matrix of perfluorocinnamic acid with LiCl as a cationizing agent generated [M+Li]+ molecular ions demonstrating a distribution of n = 8 to n = 17 with difference of mass between peaks of 166 g mol⁻¹, corresponding to one hexafluoropropylene oxide unit. Furthermore, the corresponding mass of each signal indicates the expected perfluropropoxy and methyl ester end groups. However, since the MALDI-TOF MS operates under a vacuum at 1x10⁻⁷ mtorr, samples of volatile oligo(HFPO) methyl esters with less than DP₈ were not detected, skewing the calculation of molar masses and $\overline{DP}_n$ calculation. We attempted to bypass this by preparing alternative derivatives such as quenching the reaction with diethylamine which only marginally decreased the volatility (see Experimental Section).

**Fig. 4.8.** Loss of Homologs of Oligo(HFPO) Methyl Ester with a $DP_n < 8$ under MALDI-TOF MS Conditions with Bruker Autoflex III

**Summary of Oligo(HFPO) Spectroscopic Techniques**

As presented in Table 4.2, a sample of oligo(HFPO) methyl ester was analyzed by three conventional spectroscopic methods. There are shortcomings in each of these analysis methods. In the first method, $^{19}$F NMR analysis cannot measure polydispersity, is incom-
compatible with overlapping fluorinated co-solvents, can be dependent upon the type of initiator, and fails to account for varying end groups within a sample. Secondly, GC/MS requires various constituents to be volatile with equal response factor, is limited to a maximum fragment of 600 m/z, and is difficult to resolve when there is more than one homologue distribution. Lastly, while identification of each homologue can be identified by MALDI-TOF MS including average molar mass and molar mass distribution, the quantification suffers from volatility of low molecular weight oligomers. Thus, for the experiments based on volatile oligo(HFPO) samples with DP\textsubscript{n} from 0 – 12, GC/MS proved to be the most useful to calculate the necessary polymerization parameters with a confirmation of \( M_n \) by GC/MS and verified by \(^{19}\text{F} \) NMR experiments.

**Table 4.2: Summary of Analytical Tools to Determine Relevant Polymerization Variables**

<table>
<thead>
<tr>
<th>Analytical Method[^{[a]}]</th>
<th>DP\textsubscript{n}</th>
<th>( M_n )</th>
<th>( M_w )</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{19}\text{F} ) NMR</td>
<td>3.73</td>
<td>963</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GC/MS</td>
<td>3.85</td>
<td>981</td>
<td>1028</td>
<td>1.049</td>
</tr>
<tr>
<td>MALDI-TOF MS</td>
<td>6.10</td>
<td>1364</td>
<td>1384</td>
<td>1.015</td>
</tr>
</tbody>
</table>

\[^{[a]}\] See Experimental for conditions.

### 4.7 Polymerization of HFPO in the Presence of Tetraalkylammonium Perfluoroalkoxides

#### 4.7.1 General Procedure with Alkali Metal Fluorides

Initially, preliminary tests with CsF/tetraglyme were carried out under standard conditions reported by DuPont to establish a benchmark and verify the reactor setup (TABLE 4.3).\[^{[2,16]}\] The presence of a catalytic amount of CsF ( \([\text{HFPO}] / [\text{CsF}] = 81\) ) under slow and continuous addition of HFPO over 5.25 h led to oligo(HFPO) with an average \( DP_n \) of 3.85 corresponding to \( M_n = 981 \text{ g mol}^{-1} \) and a product distribution of \( n = 0 \) to \( n = 10 \) by GC analysis (Entry 1). The obtained oligomeric distribution is slightly higher than those reported by Ameduri in 2009 with a reported average \( DP_n \) between 1.9 - 2.2 with oligomers \( DP_n \) ranging from \( n = 0 \) to \( n = 5 \) under similar conditions.\[^{[6]}\] Theoretically, the conditions reported in Entry 2 should lead to a targeted \( DP_n \) of 40 based on the \([\text{HFPO}] / [\text{CsF}] \) ratio. The assumption is that if one CsF molecule generates one polymer chain then intensive
chain transfer must occur under these conditions to provide a high conversion of HFPO (Entry 2 = 82%) with low $D_P_n$ oligomers.

**Table 4.3: Oligomerization of Hexafluoropropylene Oxide 161 with Metal Fluorides (MX)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (h)</th>
<th>[HFPO]/[initiator]</th>
<th>$D_P_n$</th>
<th>$M_n$</th>
<th>$M_w$</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsF</td>
<td>TG, HFP</td>
<td>-30</td>
<td>5.3</td>
<td>81.0</td>
<td>3.85</td>
<td>981.0</td>
<td>1028.0</td>
<td>1.05</td>
</tr>
<tr>
<td>2</td>
<td>CsF</td>
<td>TG</td>
<td>-32</td>
<td>17</td>
<td>40.2</td>
<td>2.84</td>
<td>814.8</td>
<td>848.2</td>
<td>1.041</td>
</tr>
<tr>
<td>3</td>
<td>AgF</td>
<td>TG</td>
<td>-32</td>
<td>24</td>
<td>200.6</td>
<td>n.r.</td>
<td>713.3</td>
<td>782.2</td>
<td>1.097</td>
</tr>
<tr>
<td>4</td>
<td>CsF</td>
<td>HFX, TG</td>
<td>20</td>
<td>6</td>
<td>544.0</td>
<td>2.22</td>
<td>994.7</td>
<td>1038.3</td>
<td>1.044</td>
</tr>
<tr>
<td>5</td>
<td>CsF</td>
<td>HFX, TG</td>
<td>-32</td>
<td>15</td>
<td>402.6</td>
<td>3.92</td>
<td>981.0</td>
<td>1028.0</td>
<td>1.05</td>
</tr>
</tbody>
</table>

[a] $D_P_n$, $M_n$, $M_w$ and PDI were calculated according to Eq. 4.1 - 4.4 based on GC/MS data; see Experimental Section for details.

[b] HFP = hexafluoropropylene, HFX = 1,3-bis(trifluoromethyl)benzene, TG = tetraglyme.

[c] conducted in flame dried, 250-mL round-bottom flask.

[d] n.r. = no reaction.

Under the reaction conditions, CsF is only partially soluble in tetraglyme at $-30^\circ$C, is slow to form a Cs-tetraglyme complex, and as a buildup of oligomers ensued, phase separation occurs between an upper tetraglyme layer and higher density oligo(HFPO). Since the solubility of CsF is substantially higher in tetraglyme than in oligomeric HFPO, ring-opening of HFPO proceeds rapidly even at $-30^\circ$C in the tetraglyme phase. This generates very short oligomeric HFPO ($D_P_n < 3$) with decreasing solubility of oligomer chain as $D_P_n$ increases which in turns leads to phase separation of the oligo(HFPO) acyl fluoride, concomitant fluoride elimination with ensuing chain transfer, an inoperative process.

Cesium perfluoroalkoxides form the most stable alkali metal alkoxides corresponding to the lower lattice energy of CsF than its earlier congeners (**Table 4.4**). As evidenced in **Chapter 3**, silver perfluoroalkoxides tend to have even higher stability than its alkali counterions. For this reason, the attempted polymerization with AgF was undertaken (Entry 3) with the expectation of generating the in situ perfluoroalkoxide [Ag]OCF3F7. Although the presence of the corresponding methyl ester (CF3CF2COOMe) of this species was detected by GC analysis, AgF was ineffective in catalyzing the oligomerization of HFPO ($n \geq 0$) consistent with the high lattice energy of AgF (**Table 4.4**).

The addition of fluorinated solvent(s) *miscible with tetraglyme* can improve the degree of polymerization. In particular, Ameduri reported that the use of co-solvents 1,3-hexafluoroxylene (HFX) or 1,1,1,3,3-pentafluorobutane (C4F3H5) increased the degree of polymerization to an average $D_P_n$ up to 6.3 at 20°C or 15-18 at 0°C. In our hands, the
use of HFX at $-32^\circ\text{C}$ improved the $DP_n$ slightly from 3.85 to 3.92 (Entry 5) while at low temperatures may have hampered the polymerization at elevated temperatures by interfering in the solubility of CsF in tetraglyme. Nonetheless, since the preparation of oligomers were comparable to established protocols, the use of tetraalkylammoniums were investigated next.

### 4.7.2 Influence of Organic Solvents with Tetraalkylammonium Perfluoroalkoxides Initiators

Since the ring-opening polymerization of HFPO proceeds via an anionic process, the nature of the counterion should influence both propagation and transfer reactions. Early studies found that as the lattice energy decreased among alkali metal fluorides, there is a improvement in the $DP_n$ of the resulting polymer (consistent with Willis’ seminal report on the stability of perfluoroalkoxides).\textsuperscript{[54,55]} Being 200 kJ mol$^{-1}$ lower in energy than CsF, tetraalkylammonium fluorides would be expected to be on this basis superior catalysis for the polymerization of HFPO (Table 4.4).

**Table 4.4: Crystal Lattice Energies for a Series of Fluorides**

<table>
<thead>
<tr>
<th>Fluoride</th>
<th>Crystal Lattice Energy (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium Fluoride (LiF)</td>
<td>1021$^{[56]}$</td>
</tr>
<tr>
<td>Silver Fluoride (AgF)</td>
<td>912$^{[57]}$</td>
</tr>
<tr>
<td>Sodium Fluoride (NaF)</td>
<td>900$^{[56]}$</td>
</tr>
<tr>
<td>Potassium Fluoride (KF)</td>
<td>799$^{[56]}$</td>
</tr>
<tr>
<td>Rubidium Fluoride (RbF)</td>
<td>766$^{[56]}$</td>
</tr>
<tr>
<td>Cesium Fluoride (CsF)</td>
<td>715$^{[56]}$</td>
</tr>
<tr>
<td>Tetramethylammonium Fluoride (NMe$_4$F)</td>
<td>549$^{[58]}$</td>
</tr>
</tbody>
</table>

Although claimed in a patent, to the contrary there is no actual evidence indicating that tetraalkylammonium perfluoroalkoxides have been used as initiators.$^{[59]}$ Furthermore, tetraalkylammonium fluorides have been claimed but success is often limited, presumably due to the difficulty of rendering these materials anhydrous.$^{[11]}$ As established in Chapter 2 of this thesis, tetraalkylammonium perfluoroalkoxides prepared from methoxy hydrofluoroethers are advantageous in that they are prepared both completely anhydrous and fluoride free. Furthermore, rather than the in situ generated [Cs]OCF$_2$CF$_2$CF$_3$ from one equivalent HFPO and CsF, the effect of the analogous, and tetraglyme soluble tetramethylammonium perfluoroalkoxide [MeNR$_3^+$][OCF$_2$CF$_2$CF$_3$ can be directly measured. Thus we reasoned that any chain transfer is a result of instability of the propagating perfluoropropoxide or direct fluoride transfer (Mechanism B).

$^7$Only more recently have protocols been established for the preparation of anhydrous tetraalkylammonium fluorides but these salts readily degrade upon storing at $>-30^\circ\text{C}$.\textsuperscript{[60]}
Fig. 4.9. A representative GC Chromatogram of oligo(HFPO) initiated by [Me3NBn]OC4F9 highlighted in blue are outnumbered by polymer chains initiated by chain transfer product -OC3F7 highlighted in red (Entry 13, Table 4.5).

Results

As presented in Table 4.5, a range of tetraalkylammonium perfluoro-propoxides and -butoxides were tested as initiators in tetruglyme with a [HFPO]/[initiator] > 200 at −35°C under the similar conditions to CsF/tetruglyme experiments (Entries 6-9). While it was established that tetraalkylammonium perfluoroalkoxides can ring-open HFPO (Entry 6-14), the degree of polymerization in each case was significantly less than the representative CsF example. For the first time, the extent of chain transfer could be quantified by end group analysis when OC4F9 salts were utilized as initiators. Polymers initiated by -OC4F9 were resolved by GC and had a homologue distribution bearing the unique and characteristic 219 m/z fragment corresponding to +OC4F9 (see Fig 4.9). In all examples, GC analysis indicated that the majority (> 94%) of oligo(HFPO) was the result of chain transfer (Table 4.5).
Table 4.5: Oligomerization of Hexafluoropropylene Oxide 161 in the Presence of Organic Solvents

![Diagram of oligomerization process]

1) \( n \) \( \text{CF}_2\text{CF}_2 \) 161
2) \( \text{MeOH} \)

\( \text{solvent, temperature} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Temp (^\circ)C</th>
<th>Composition (%)</th>
<th>(DPP_n) Range (\text{(n)})</th>
<th>(M_n) (\text{(g mol}^{-1}))</th>
<th>(M_w) (\text{(g mol}^{-1}))</th>
<th>PDI</th>
<th>Composition (%)</th>
<th>(DPP_n) Range (\text{(n)})</th>
<th>(M_n) (\text{(g mol}^{-1}))</th>
<th>(M_w) (\text{(g mol}^{-1}))</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>[quinMe]OC(_4)F(_9) [\text{a}]</td>
<td>TG</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>0.961</td>
<td>0-3</td>
<td>503.5</td>
<td>540.0</td>
</tr>
<tr>
<td>7</td>
<td>[Me(_3)NBn]OC(_3)F(_7)</td>
<td>TG</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>1.640</td>
<td>0-4</td>
<td>616.7</td>
<td>639.5</td>
</tr>
<tr>
<td>8</td>
<td>[NMe(_4)]OC(_4)F(_9)</td>
<td>TG</td>
<td>-35</td>
<td>1.72</td>
<td>0.02</td>
<td>0-2</td>
<td>567.0</td>
<td>586.9</td>
<td>1.036</td>
<td>98.30</td>
<td>1.970</td>
<td>0-4</td>
<td>671.8</td>
</tr>
<tr>
<td>9</td>
<td>[NMe(_4)]OC(_4)F(_9)</td>
<td>CH(_3)CN</td>
<td>-35</td>
<td>1.59</td>
<td>0.82</td>
<td>0-2</td>
<td>530.2</td>
<td>550.7</td>
<td>1.039</td>
<td>98.41</td>
<td>1.668</td>
<td>0-5</td>
<td>621.0</td>
</tr>
<tr>
<td>10</td>
<td>[TMEDA-Me]OC(_4)F(_9) [\text{a}]</td>
<td>CH(_3)CN</td>
<td>-35</td>
<td>1.65</td>
<td>1.02</td>
<td>0-2</td>
<td>563.3</td>
<td>580.7</td>
<td>1.031</td>
<td>98.35</td>
<td>1.778</td>
<td>0-6</td>
<td>639.1</td>
</tr>
<tr>
<td>11</td>
<td>[NMe(_4)]OC(_4)F(_9) [\text{a}]</td>
<td>CH(_3)CN</td>
<td>-35</td>
<td>1.58</td>
<td>0.77</td>
<td>0-4</td>
<td>522.2</td>
<td>537.6</td>
<td>1.030</td>
<td>98.42</td>
<td>1.663</td>
<td>0-4</td>
<td>620.1</td>
</tr>
<tr>
<td>12</td>
<td>[NMe(_4)]OC(_4)F(_9)</td>
<td>CH(_3)CN</td>
<td>-45</td>
<td>1.97</td>
<td>0.41</td>
<td>0-1</td>
<td>461.7</td>
<td>476.1</td>
<td>1.031</td>
<td>98.03</td>
<td>1.487</td>
<td>1-4</td>
<td>590.9</td>
</tr>
<tr>
<td>13</td>
<td>[Me(_3)NBn]OC(_3)F(_7)</td>
<td>CH(_3)CN</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>0.711</td>
<td>0-2</td>
<td>462.0</td>
</tr>
<tr>
<td>14</td>
<td>[PMe(_4)]OC(_3)F(_7)</td>
<td>CH(_3)CN</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>1.302</td>
<td>0-4</td>
<td>560.2</td>
</tr>
<tr>
<td>15</td>
<td>Entry 9</td>
<td>–</td>
<td>-35</td>
<td>1.19</td>
<td>0.795</td>
<td>0-1</td>
<td>526</td>
<td>534.5</td>
<td>1.0162</td>
<td>98.81</td>
<td>0.991</td>
<td>0-3</td>
<td>508.5</td>
</tr>
<tr>
<td>16</td>
<td>Entry 2 + ex. CsF</td>
<td>–</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>2.87</td>
<td>1-6</td>
<td>820.7</td>
</tr>
</tbody>
</table>

[a] \(DPP_n\), \(M_n\), \(M_w\) and PDI were calculated according to Eq. 4.1 - 4.4 based on GC/MS data: see Experimental Section for details. Each reaction was carried out with [HFPO]/[initiator] \(> 200\). [b] HFX = 1,3-bis(trifluoromethyl)benzene, TG = tetraglyme, HFP = hexafluoropropylene 160, HFE-7100 = CH\(_3\)OC\(_4\)F\(_9\). [c] n.r. = no reaction. [d] [quinMe] = 1-methylquinuclidin-1-ium, [TMEDA-Me] = 2-(dimethylamino)-N,N,N-trimethylethylammonium. [e] with CaH\(_2\) as an acid scavenger.
While CsF is nearly insoluble in all aprotic solvents with the exception of being partially soluble in tetracycline, tetraalkylammonium perfluoroalkoxides are highly soluble in CH3CN. In Entries 9-14, a series of perfluoroalkoxides were tested with CH3CN and no noticeable improvement in chain transfer was observed with > 98% of oligomers resulting from chain transfer and low average degree of polymerizations between 1.4 to 1.7 (590 - 630 g mol⁻¹) with a distribution between $DP_0$ to $DP_6$. When the reaction was carried out in the presence of CaH₂ to scavenge any possible HF, no improvement was observed (Entry 11). Lowering the temperature to $-45^\circ C$ only reduced chain transfer a negligible amount but decreased uptake of HFPO 161. When perfluoropropoxides were introduced as initiators (Entry 13, 14) which probe the difference between Cs⁺ and NR₄⁺, both molecular weights and distributions were nearly the same as with -OC₄F₉.

4.7.3 Effect of Phase Separation on Ring-Opening Polymerization

In entry 14 of Table 4.5, initiator [PMe₄][OC₃F₇] afforded oligo(HFPO) between $DP_0$ to $DP_4$ with an average $DP_n = 1.3$. The use of PMe₄⁺ provided added insight into the polymerization conditions since the cation can be observed by ³¹P NMR analysis. Rather than quenching with MeOH at the completion of the reaction, both the upper and lower phases were sampled at $-35^\circ C$ which by ³¹P{¹H} NMR analysis indicated the presence of the PMe₄⁺ cation exclusively in the organic phase (Figure 4.10). Furthermore, ¹⁹F NMR analysis indicated the broad signal centred at $\delta_F = -29.1$ ppm associated with the presence of α-fluorinated alkoxide active species in the organic phase and acyl fluoride ($\delta_F = +23.0$ ppm) motif in the lower, fluorous phase (Figure 4.11).

In a second experiment, the activity of the lower fluorous phase towards HFPO 161 was tested (Entry 16, Table 4.5). Thus the same amount (27 g) of monomer was introduced to 1.952 g of the lower phase from Entry 8 (Table 4.5) at the same temperature. Unsurprisingly, no increase in the average $DP_n$ or distribution was observed by GC analysis and the ratio of beginning groups was left unchanged suggesting that no further propagation occurred. However, in a third experiment when the fluorous phase was exposed to additional, excess CsF at $-32^\circ C$ in the absence of added solvents, a slight increase in both the molecular weight (from $M_n$ 815 g mol⁻¹ to 821 g mol⁻¹) and conversion of all $DP_0$ was observed even though CsF was poorly soluble under the reaction conditions (Table 4.5).

Discussion

When the perfluoroalkoxide initiator is introduced, the first productive reaction is the nucleophilic ring-opening of HFPO. Thus if one equivalent of perfluoroalkoxide reacts
Fig. 4.10. $^{31}$P NMR (376 MHz) spectrum of the upper and lower phases of the reaction between [PMe$_4$]OC$_3$F$_7$ and HFPO at $-35^\circ$C demonstrating the presence of PMe$_4^+$ cation exclusively in the organic phase.

Fig. 4.11. $^{19}$F NMR (162 MHz) spectrum of the upper and lower phases of the reaction between [PMe$_4$]OC$_3$F$_7$ and HFPO at $-35^\circ$C indicate presence of $\alpha$-fluorinated alkoxide active species in the organic phase and acyl fluoride motif in the lower, fluorous phase.
completely with one equivalent of HFPO, a new common oligo(alkoxide) is generated that will have a different stability than the introduced initiator. With propagation, the resulting fluorinated oligomers in either tetraglyme or CH$_3$CN solvent reaches a maximum $D_P_n$, which induces phase separation due to the immiscibility of the oligomers with the highly polar solvents necessary to dissolve the initiator.$^{[6,61]}$ After phase separation, chain transfer is the key reaction mechanism with an increase in mass of oligomeric HFPO with low $D_P_n$.

The system after phase separation and with agitation is an emulsion of the organic solvent in bulk oligomeric HFPO acyl fluorides. Within the tetruglyme (or CH$_3$CN) emulsion, a concentration of highly reactive, free F$^-$ and $D_P_1$ alkoxides reacts more efficiently with monomer 161 than in the fluorinated phase as evidenced in the preceding experiment with PMe$_4^+$. In this case, the reactive ion pair is dissolved in the upper, organic phase and the lower, fluorinated phase is unreactive towards further monomer in followup experiments. Although the lattice energy of the initiator is a critical aspect of the initiator, we rationalized that if the reaction could proceed under monophasic conditions, the propensity for chain transfer may be diminished.

4.7.4 Influence of Fluorous Co-Solvents on the Tetraalkylammonium Perfluoroalkoxide Initiators

To improve solubility of the perfluoroalkoxide initiators with the fluorinated oligomers, the effect of a variety of fluorinated co-solvents on the polymerization of HFPO were investigated. In earlier studies, hexafluoropropylene (CF=CFCF$_3$) below its boiling point of $-28$ °C had improved propagation by suppressing chain transfer.$^{[2,7,10,16,23,61]}$ As presented in Table 4.6, the incorporation of HFP into the reaction system slightly improved the amount of oligomers bearing the $\text{OC}_4\text{F}_9$ initiator group suggesting that chain transfer was marginally suppressed (Entry 17-20). Encouraged by the modest improvement, amphiphilic-like fluorinated solvents that had improved the KF/tetraglyme system reported by Ameduri were also explored. In particular, hexafluoroxyylene (HFX or 1,3-$\text{bis}$($\text{trifluoromethyl}$)benzene) did not display an improvement over HFP, either alone or as binary co-solvent with tetraglyme or CH$_3$CN. However, hydrofluoroether HFE-7100 which is known to be a highly polar fluorinated solvent capable of dissolving poly(HFPO) but also organic solvents, improved the incorporation of $\text{OC}_4\text{F}_9$ initiator to the best result of 19 % at $-28$ °C although $D_P_n$ and $M_n$ were comparable to previous runs (Entry 21).
Table 4.6: Oligomerization of Hexafluoropropylene Oxide 161 in the Presence of Fluorinated Solvents

![Chemical structure](attachment:image.png)

**Experimental Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Composition (%)</th>
<th>$\text{DP}_n$ Range (n)</th>
<th>$M_n$ (g mol$^{-1}$)</th>
<th>$M_w$ (g mol$^{-1}$)</th>
<th>PDI</th>
<th>Composition (%)</th>
<th>$\text{DP}_n$ Range (n)</th>
<th>$M_n$ (g mol$^{-1}$)</th>
<th>$M_w$ (g mol$^{-1}$)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>[NMes]OCF$_3$</td>
<td>TG HFP</td>
<td>-30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>100.00</td>
<td>1.980</td>
<td>0-5</td>
<td>672.6</td>
<td>701.4</td>
</tr>
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<td>18</td>
<td>[NMes]OCF$_3$</td>
<td>TG HFP</td>
<td>-30</td>
<td>5.79</td>
<td>1.26</td>
<td>0-3</td>
<td>602.8</td>
<td>618.9</td>
<td>1.027</td>
<td>94.21</td>
<td>2.070</td>
<td>687.7</td>
<td>721.9</td>
</tr>
<tr>
<td>19</td>
<td>[NMes]OCF$_3$</td>
<td>TG HFP</td>
<td>-30</td>
<td>5.92</td>
<td>1.06</td>
<td>0-2</td>
<td>561.0</td>
<td>576.9</td>
<td>1.028</td>
<td>94.08</td>
<td>1.988</td>
<td>674.0</td>
<td>706.2</td>
</tr>
<tr>
<td>20</td>
<td>[Me$_3$NBn]OCF$_3$</td>
<td>TG HFP</td>
<td>-30</td>
<td>8.18</td>
<td>1.08</td>
<td>0-3</td>
<td>577.1</td>
<td>587.5</td>
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<td>91.82</td>
<td>1.719</td>
<td>641.3</td>
<td>670.9</td>
</tr>
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<td>21</td>
<td>[NMes]OCF$_3$</td>
<td>THF$^{[e]}$</td>
<td>HFE-7100</td>
<td>-28</td>
<td>19.16</td>
<td>1.16</td>
<td>0-4</td>
<td>585.9</td>
<td>627.1</td>
<td>80.84</td>
<td>1.997</td>
<td>675.6</td>
<td>711.8</td>
</tr>
<tr>
<td>22</td>
<td>[NMes]OCF$_3$</td>
<td>TG HFP, HFE-7100</td>
<td>-22</td>
<td>11.80</td>
<td>0.08</td>
<td>0-2</td>
<td>499.2</td>
<td>517.0</td>
<td>1.039</td>
<td>88.00</td>
<td>0.130</td>
<td>366.2</td>
<td>375.6</td>
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<td>23</td>
<td>[NMes]OCF$_3$</td>
<td>CH$_2$CN HFX, HFE-7100</td>
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<td>1.71</td>
<td>0-3</td>
<td>678.4</td>
<td>717.5</td>
<td>1.058</td>
<td>98.25</td>
<td>1.802</td>
<td>643.1</td>
<td>687.0</td>
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<td>24</td>
<td>[NMes]OCF$_3$</td>
<td>TG HFX</td>
<td>-35</td>
<td>2.39</td>
<td>1.42</td>
<td>0-4</td>
<td>629.9</td>
<td>674.7</td>
<td>1.071</td>
<td>97.61</td>
<td>1.992</td>
<td>674.7</td>
<td>708.4</td>
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<tr>
<td>25</td>
<td>[quinMe]OCF$_3$</td>
<td>TG HFP, HFE-7100</td>
<td>-35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>&gt;99%</td>
<td>0.612</td>
<td>445.5</td>
<td>481.4</td>
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<td>26</td>
<td>[MeNBu]OCF$_3$</td>
<td>– HFX</td>
<td>20</td>
<td>0.43</td>
<td>0.3</td>
<td>0-1</td>
<td>443.7</td>
<td>456.8</td>
<td>1.0294</td>
<td>99.57</td>
<td>0.575</td>
<td>439.5</td>
<td>470.1</td>
</tr>
<tr>
<td>27</td>
<td>[MeNBu]OCF$_3$</td>
<td>– HFX</td>
<td>20</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.432</td>
<td>581.7</td>
<td>626.9</td>
</tr>
</tbody>
</table>

$^{[a]}$ $M_n$, $M_w$, and PDI were calculated according to Eq. 4.1 - 4.4 based on GC/MS data; see Experimental Section for details. $^{[b]}$ HFX = 1,3-bis(trifluoromethyl)benzene, TG = tetraglyme, HFP = hexafluoropropylene 160, HFE-7100 = CH$_2$OCF$_3$ 4. $^{[c]}$ n.r. = no reaction. $^{[d]}$ [quinMe] = 1-methylquinuclidin-1-ium, [TMEDA] = 2-(dimethylamino)-N,N,N-trimethylethan-1-aminium. $^{[e]}$ also CH$_2$CN.
4.8 Polymerization with oligo(HFPO) Surfactants

4.8.1 Preparation of oligo(HFPO) Surfactants

Since no currently available fluorinated solvents are capable of simultaneously dissolving both highly ionic perfluoroalkoxides and non-polar oligomeric HFPO, novel surfactants were designed to mitigate phase separation during polymerization of HFPO. We reasoned that if alkali metal fluorides and tetraalkylammonium perfluoroalkoxides are highly soluble in tetraglyme, a surfactant comprising a polar organic domain of poly(ethylene oxide) units connected by a fluorous domain prepared from oligo(HFPO) may act as a superior solvent or a surfactant (Fig 4.12).

If phase separation could be prevented, then the propagation could continue unimpeded by the propensity for chain transfer by either $F^-$ or low molecular weight perfluoroalkoxides to an organic phase. In many ways, the industrial route inefficiently but successfully mirrors this approach by beginning with a prepared "liquid catalyst" comprising of oligomeric HFPO without organic solvent.

![Figure 4.12](image-url)

**Fig. 4.12.** A well-designed surfactant composing both a polar organic and fluorous domains may enable solvation of the initiators to mitigate phase separation during polymerization of HFPO (where $Q^+$ denotes cation).

Based on the simplicity of the reaction, esterification of oligo(HFPO) acyl fluoride product of $DP_{3.85}$ (Entry 1) and a sample of $DP_{5.53}$ (DuPont) with triethylene glycol monomethyl ether furnished oligo(HFPO)-poly(ethylene)glycol esters 172 and 173 after purification by chromatography in high yields (Scheme 4.12). The structure and purity of 172 and 173 was carried out by standard spectroscopic techniques including $^1$H, $^{13}$C, $^{19}$F NMR, and GC/MS analysis.8

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8 see Experimental section at the end of this chapter for conditions and spectroscopic data
**Scheme 4.10.** Preparation of Two Oligo(HFPO)-Poly(ethylene)glycol Ester Surfactants 172 and 173 by Condensation of Oligo(HFPO) Acyl Fluorides and Triethylene Glycol Monomethyl Ether.

Although the preparation of oligo(HFPO)-poly(ethylene)glycol esters 172 and 173 are relatively simple to carry out, we suspected that in the presence of anhydrous fluoride or perfluoroalkoxide anions, these fluorinated esters may be susceptible to nucleophilic attack. As part of an effort to functionalize poly(HFPO) by functional group interconversion, poly(HFPO) terminated iodides such as 176, readily undergo copper-catalyzed radical addition to alkene and aryl substrates. For example, after optimization, poly(HFPO) primary iodide can be cleanly converted in full conversion to the corresponding phenyl terminated poly(HFPO) 177 in high, isolated yield (Scheme 4.11).

**Scheme 4.11.** Copper-Catalyzed Radical Addition of Poly(HFPO) Primary Iodide to Benzene

Extending the reaction of oligo(HFPO) iodide 176 to atom transfer radical addition (ATRA) of alkenes, we envisioned the preparation of a more robust surfactant linked by a n-propyl segment by the appropriate poly(ethylene glycol) allyl ether precursor.\[62,63\] It is well-known that perfluoro iodides generate perfluoro radicals (R\(_F^\bullet\)) in the presence of a radical initiator such as benzoyl peroxide (BPO) and a catalytic amount of Cu.\[64\] The ensuing radical readily form adducts in high yields with electron rich alkenes\[62\] and we

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9 see Experimental section at the end of this chapter for conditions and spectroscopic data
reasoned that reduction by a suitable H· source can afford the desired oligo(HFPO)-b-PEG diblock surfactant.\cite{30}

**Scheme 4.12.** Synthesis of Oligo(HFPO)-b-PEG Diblock Surfactant 180 by Atom Transfer Radical Addition (ATRA) of PEG Allyl Ether 179 Followed by In Situ Reduction by HSnBu₃

Allylation of commercially available triethylene glycol monomethyl ether 178 was carried out under standard conditions affording the corresponding PEG allyl ether 179 in high, isolated yields (Scheme 4.12). After optimization from our established procedures,\cite{30,40} 179 readily underwent 100% conversion by GC/MS analysis to the desired intermediate iodide in the presence of 10 mol% (CuOAc)$_2$ at 95 °C in trifluorotoluene within 90 min. Although this intermediate can be isolated and characterized (see Experimental Section), it was expedient to telescope the crude reaction product forward in a one pot, two-step strategy by conducting the reduction with HSnBu₃ to afford the desired 180 in high conversion and *most importantly* purity but with low isolated yields after necessary column chromatography.\cite{10} Due to the difficulty in removing the highly toxic and persistent tributylstannyl iodide by-product even by an extended KF/EtOAc procedure, the reduction was found to proceed smoothly with the less toxic, but more expensive tris(trimethylsilyl)silane as an alternative reducing agent. The structure and purity of 180 was carried out by standard spectroscopic techniques including $^1$H, $^{13}$C, $^{19}$F NMR, and GC/MS but was too volatile for MALDI-TOF MS analysis.

### 4.8.2 Polymerization in the Presence of Oligo(HFPO) Surfactants

Upon cooling surfactants to the required −30 °C to conduct polymerizations, propyl linked 180 and ester bridged 173 surfactants disappointingly solidified and were insoluble in a variety of co-solvents. Thus, preliminary tests were carried out with the lowest molecular

\footnote{10 see Experimental section at the end of this chapter for conditions and spectroscopic data}
weight ester congener, 172 which did not suffer from this problem. To determine the effect of surfactant 172 on the polymerization of HFPO 161 with CsF or [Me₃NBn]OC₃F₇, the reaction was tested with and without solvents. No reaction was observed without solvent (Entry 28) or with CH₂Cl₂ (Entry 29). However, in the presence of tetraglyme and CsF, 161 oligomers with with an average $D_P_n$ of 3.5 spanning 0 - 10 were obtained as a milky white emulsion suggesting that although not exceeding the average $D_P_{3.85}$ obtained without surfactant, two distinct phases were not observed (Entry 1, Table 4.3). Increasing the temperature of the reaction, did not improve the degree of polymerization with CsF (Entry 31) as chain transfer is expected to increase due to instability of cesium perfluoroalkoxides in solution. Although no evidence of surfactant degradation was observed by GC/MS, future work could improve this preliminary results by designing alternative linkages of low molecular weight surfactants of oligo(HFPO).

### Table 4.7: Oligomerization of Hexafluoropropylene Oxide 161 with Surfactant 172

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>Surfactant</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Composition[a]</th>
<th>$D_P_n$ Range (n)</th>
<th>$M_n$ (g mol⁻¹)</th>
<th>$M_w$ (g mol⁻¹)</th>
<th>PDI[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>CsF</td>
<td>172</td>
<td>-</td>
<td>-35</td>
<td>n.r.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>[Me₃NBn]OC₃F₇</td>
<td>172</td>
<td>CH₂Cl₂</td>
<td>-35</td>
<td>n.r.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30</td>
<td>CsF</td>
<td>172</td>
<td>tetraglyme</td>
<td>-35</td>
<td>100</td>
<td>3.525 0-10</td>
<td>929.2</td>
<td>979.5</td>
<td>1.054</td>
</tr>
<tr>
<td>31</td>
<td>CsF</td>
<td>172</td>
<td>tetraglyme</td>
<td>-25</td>
<td>100</td>
<td>2.762 0-9</td>
<td>802.5</td>
<td>893.2</td>
<td>1.113</td>
</tr>
</tbody>
</table>

[a] n.r. = no reaction.  [b] $D_P_n$, $M_n$, $M_w$ and PDI were calculated according to Eq. 4.1 - 4.4 based on GC/MS data; see Experimental Section for details.

### 4.9 Preparation and Polymerization of Oligo(HFPO) Perfluoroalkoxides

#### 4.9.1 Introduction

Rather than preparing surfactants in multi-step syntheses with unpredictable results and potentially difficult process to remove the surfactant in a post-polymerization process, oligo(HFPO) hydrofluoroethers such as 181 provide an attractive approach both to probe the nature of the effect of phase separation and provide a potentially industrially feasible methodology (Scheme 4.13). We reasoned that if a tetraalkylammonium oligo(HFPO) perfluoroalkoxide could be prepared, then this species would enable direct polymerization without the need for an organic solvent and thus presumably avoid phase separation providing direct insight into the effect of a polar organic solvent on the reaction. If the oligo(HFPO)
perfluoroalkoxide could be isolated, this would give unprecedented spectroscopic information on the structure of the propagating species in the polymerization of HFPO (Scheme 4.13). Lastly, since the oligo(HFPO) methyl ether would be an easy to handle, non-air-sensitive or hygroscopic liquid, it could be an ideal initiator for a one-pot polymerization of HFPO by first introducing the amine for a period of time, followed by gas transfer of the monomer 161 avoiding the need to have additional anhydrous co-solvents and anhydrous fluorides required for the current industrial process.

4.9.2 Results

Following the protocol from Prakash,\textsuperscript{[65]} low molecular weight oligo(HFPO) acyl fluorides prepared in Entry 11 were treated with anhydrous KF in diglyme at 40 \degree C and the methylated with dimethyl sulfate in 91\% conversion (balance as the methyl ester due to hydrolysis). After workup, the crude oligo(HFPO) methyl ether 181 was distilled obtaining a colourless liquid in 58\% isolated yield (> 99\% purity) with a boiling point range of 115 \degree C-160 \degree C at 1 bar (see EXPERIMENTAL SECTION and APPENDIX G for all annotated spectra).

Scheme 4.13. Preparation and Isolation of Tetraalkylammonium Oligo(HFPO) Perfluoroalkoxides from Oligo(HFPO) Methoxy Ethers

The presence of a singlet in the $^1$H NMR spectra at 3.28 ppm was assigned to the Me resonance of ether 181. The signal at +26.10 ppm in the $^{19}$F NMR spectrum with an integration of 1F assigned to the perfluoroacyl fluoride starting material shifted to a new signal integrating to 2F at -90.8 ppm indicative of a new perfluoromethylene signal adjacent to the methoxy moiety. In addition to $^1$H and $^{19}$F NMR spectra, the identity and purity of
the ether 181 was fully confirmed by $^{13}$C NMR, and GC/MS spectroscopy consistent with the proposed structure.

Fig. 4.13. $^{19}$F NMR (376 MHz) spectra illustrating the conversion of the oligo(HFPO) acyl fluoride 182 (top) to the oligo(HFPO) methyl ether 181 by methylation (middle) and subsequent O-demethylation by NMe$_3$ to afford the desired oligoHFPO tetramethylammonium perfluoroalkoxide 184 (bottom).

Upon storing over pre-conditioned 4 Å mol sieves for 24 h, excitingly ether 181 was fully converted to the corresponding tetraalkylammonium perfluoroalkoxide at 50 °C in the presence of NMe$_3$ 184 or DABCO 183. These two amines had displayed high reactivity in previous studies and NMe$_3$ as a volatile amine (b.p. 3 °C) is simple to remove under extended period of high vacuum. The identity of each moisture-sensitive perfluoroalkoxide was once again confirmed by NMR spectroscopy with the $^{19}$F NMR spectrum clearly indicating the loss of the CF$_2$ signal at -90.8 ppm and a new signal at -25.47 ppm (2F) 183 and -25.64 ppm (2F) 184 consistent with α-fluorines of perfluoroalkoxides prepared in Chapter 2. In addition, the methylated amine in the $^1$H NMR spectrum is evidenced by a shift to a new singlet at 3.15 ppm and a 1:1:1 triplet in the $^{13}$C NMR spectrum assigned to the symmetrical MeNR$_3^+$ cation (see Experimental Section). In the case of oligo(HFPO) methyl ether 183, both starting materials are non-volatile and difficult to remove from the resulting
perfluoroalkoxide so a slight excess of the 181 was used as an excess of tertiary amine could result in an undesired reactivity with HFPO. Due to the high reactivity of DABCO, no unreacted starting material remained in the reaction by NMR analysis.

\[
\begin{align*}
\text{C}_3\text{F}_7\text{O} & \begin{array}{c} \text{CFCF}_2\text{O} \end{array} \begin{array}{c} \text{CF}_3 \end{array} \begin{array}{c} \text{CFCF}_2\text{O} \text{MeNR}_3 \end{array} \text{n HFPO} \\
\text{temperature, solvent} & \rightarrow \\
\text{C}_3\text{F}_7\text{O} & \begin{array}{c} \text{CFCF}_2\text{O} \end{array} \begin{array}{c} \text{CF}_3 \end{array} \begin{array}{c} \text{CFCF}_2\text{O} \text{MeNR}_3 \end{array} \begin{array}{c} \text{n-1} \end{array}
\end{align*}
\]

183 and 184 temperature: -28°C, +15°C solvent: none, diglyme 185 and 186

**Fig. 4.14.** Polymerization with tetraalkylammonium oligo(HFPO) perfluoroalkoxides 183 and 184 did not lead to further polymerization in the presence of HFPO 161.

Tetramethylammonium perfluoroalkoxide 184 was isolated as a soft, white solid which ostensibly is a result of the low molecular weight acyl fluoride \( \text{DP}_n = 1.46 \). Since tetraalkylammonium perfluoroalkoxides from \( \text{CH}_3\text{OC}_3\text{F}_7 \) 3 and \( \text{CH}_3\text{OC}_4\text{F}_9 \) 4 from **CHAPTER 2 did not ring-open HFPO in the solid state but required a solvent, this presented an unforeseen problem. The catalytic activity of perfluoroalkoxide 183 was initially tested to undergo polymerization with HFPO as it was prepared in a solution of oligo(HFPO) methyl ether. However, at both −25°C and at 15°C no ring-opening of HFPO was observed both by GC/MS analysis (**SCHEME 4.14**). Likewise, no polymerization with the \( \text{NMe}_4^+ \) cation at both −25°C and at 15°C in diglyme was observed with an unexplained formation of a white solid upon exposure to HFPO. Upon quenching with MeOH at the end of the reaction period, no additional increase in \( \text{DP}_n \) was observed (**SCHEME 4.14**).

**4.9.3 Discussion**

While the preliminary results did not achieve an increased degree of polymerization with the four examples presented in **FIGURE 4.14**, the ability to directly prepare oligo(HFPO) alkoxides provides an unprecedented strategy towards exploring the fundamentals of the polymerization of HFPO 161. Furthermore, the methylation ability of oligo(HFPO) methyl ether 181 extends the previous examples in **CHAPTER 2 and 3** for 1 – 4 as the most general methodology for preparing isolable, bench-stable perfluoroalkoxides bearing α-fluorines. It is expected that by starting with oligo(HFPO) acyl fluorides with a \( \text{DP}_n \) greater than 1.46 and through the possible use of larger organic cations as a substrate (ie. \( \text{MeNBu}_3^+ \)), oligo(HFPO) perfluoroalkoxides that remain as liquids maybe the most suitable initiators for the polymerization of HFPO. Once achieved, the impact of the polymerization without the need for an organic solvent can be explored with the goal of limiting phase separation to measure the effect of the chain transfer mechanism.
Towards Difunctional PFPAEs

Polymerization of Difunctional Materials

Currently there is a high need for difunctional poly(HFPO) to enable cross-linking of oligo(HFPO) and for specialized applications (confidential). Although polymerization of HFPO continues to suffer from chain transfer mechanism, mixtures of difunctional poly(HFPO) have been prepared through the use of a difunctional initiator. For instance, it is well known that in the presence of fuming sulfuric acid, 187 can be converted to methyl 3,3,3-trifluoropyruvate 188 in up to 83% yield (Scheme 4.14). Resnick (DuPont) demonstrated that 188 in the presence of KF/tetraglyme affords the corresponding perfluoroalkoxide and with the introduction of HFPO a nearly equal mixture of difunctional oligo(HFPO) \((n = 0 – 2)\) 190 and mono-functional oligo(HFPO) \((n = 0 – 3)\) can be prepared.

Scheme 4.14. Synthetic Pathways to Difunctional poly(HFPO) Initiators by O-Demethylation of Methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187 under Acidic Conditions as Done by Resnick (left) or More Efficiently under Basic Conditions with Tertiary Amines (right)

We envisioned that a more concise preparation of a difunctional oligo(HFPO) could be accessed directly from methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187. Since 187 is a hydrofluoroether, the introduction of a tertiary amine may afford a tetraalkylammonium perfluoroalkoxide bearing an ester moiety (Scheme 4.14). The isolated salt 191 could then be used as an initiator for the polymerization of HFPO.

Methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate as a difunctional initiator precursor

Following a modified procedure from Paleta, methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187 was readily prepared from HFPO under basic conditions (so as to avoid copious amounts...
of HF) and purified by distillation in 50% yield. After drying over CaH$_2$ to render the colourless liquid anhydrous, 187 was reacted with a series of tertiary amines at 25°C and 50°C for 48 h. In each case, a colourless crystalline product precipitated out of each reaction.

**Scheme 4.15.** Preparation of Methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187 from HFPO.

As evidenced by NMR spectroscopy, 187 did not afford the desired perfluoroalkoxide 192 but rather O-demethylation of the ester moiety of 187 which occurred more efficiently at 50°C than at RT (Table 4.8). The isolated products were furnished in 37 - 94% yield and fully characterized by $^1$H, $^{13}$C, $^{19}$F NMR and IR spectroscopies (see Experimental Section). Unfortunately, carboxylates are not suitable initiators for polymerization of HFPO which was confirmed by one attempted polymerization with 187a with no detectable ring-opening of HFPO at −25°C in tetruglyme.

While oligomerization of HFPO with Resnick’s difunctional perfluoroalkoxide 189 does provide a route to difunctional oligi(HFPO), his protocol is limited towards higher molecular weight oligo(HFPO) with a nearly 50:50 mixture of $DP_n < 1$ of mono- and difunctional materials. Rather, a series of di- or multi-methoxy hydrofluoroethers as precursors in the presence of tertiary amines would enable access to a wider range of conditions amenable to optimization as established in this work.

### 4.11 Summary and Outlook

#### 4.11.1 Conclusions

Herein, we investigated for the first time the use of fluoride-free, tetraalkylammonium perfluoroalkoxides on the ring-opening polymerization of HFPO 161. Based on the expected low lattice energy of tetraalkylammonium fluorides compared to CsF, these initiators were expected to decrease the competing chain transfer mechanism plauging current polymerization protocols. By using tetraalkylammonium perfluoroalkoxides from **Chapter 2** in a specifically designed reactor system, the effect of the tetraalkylammonium cation was specifically
Table 4.8: Reactivity of Hydrofluoroether 187 with Tertiary Amines

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Cation</th>
<th>Entry</th>
<th>25°C (%)[^a]</th>
<th>50°C (%)[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Cation 187a" /></td>
<td>187a</td>
<td>20</td>
<td>81</td>
</tr>
<tr>
<td><img src="image2.png" alt="Cation 187b" /></td>
<td>187b</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td><img src="image3.png" alt="Cation 187d" /></td>
<td>187d</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td><img src="image4.png" alt="Cation 187e" /></td>
<td>187e</td>
<td>41</td>
<td>67</td>
</tr>
<tr>
<td><img src="image5.png" alt="Cation 187f" /></td>
<td>187f</td>
<td>91</td>
<td>90</td>
</tr>
</tbody>
</table>

[^a]: Yields refer to the isolated material of > 98% purity. See Experimental Section for conditions.
targeted in a preliminary screen of 27 examples but did not demonstrate improvement for the polymerization of HFPO under comparable conditions to the traditional CsF/tetraglyme conditions. At best, tetraalkylammonium perfluoroalkoxides in polar organic solvents afforded average $DP_n = 2-3$ with slight improvements with the incorporation of fluorinated co-solvents but otherwise does not solve the problem at hand. However, the competing chain transfer product has been quantified by utilizing a series of novel tetraalkylammonium perfluorobutoxides by GC/MS analysis, providing direct evidence for chain transfer rather than till now indirect speculation.

An alternative explanation for the lower efficiency for tetraalkylammonium perfluoroalkoxides is the hydrogen-bond ability of $\alpha$-hydrogen atoms on tetraalkylammonium salts. The positive charge of the ammonium salt is typically delocalized over the $\alpha$-hydrogen atoms enabling interactions to anionic counterions, an effect most recently used by Maruoka to enable hydrogen-bond catalysis 193 in Mannich-type reactions. Although demonstrated only with weaker anions, the effect of an ionic fluoride ion or perfluoroalkoxide 194 in this capacity has not been studied but cannot be understated due to its highly ionic nature, especially upon the ring-opening polymerization of HFPO. Acquiring further solid state data (via SC-XRD) and DFT calculations on perfluoroalkoxides could be instrumental in determine the extent of this effects.

![Fig. 4.15.](image)

**Fig. 4.15.** The positive charge of ammonium salts are delocalized over the $\alpha$-hydrogens and are known to interact with anions as most recently demonstrated by Marouka (middle) – and quite possibly affecting the solution stability of $\alpha$-fluorines of perfluoroalkoxides (right).

While changing to a larger, more diffuse cation would be a notable development, there are no reports on improving the spontaneous phase separation on the polymerization process. Based on a study with $[\text{PMe}_4]\text{OC}_3\text{F}_7$, it can be shown that the active species in the polymerization is in the organic phase and migration of $\text{F}^-$ to the fluorous phase is limited at polymerization conditions, generating a lower fluorous phase that is chain terminated as perfluoro acyl fluorides. Clearly, chain transfer is a multi-faceted problem that minimally
encompasses both the nature of the cation and maybe more importantly, the solvent which has not been investigated to the same extent.

For the past 50 years, optimization of the polymerization of HFPO has been nearly limited to improving conditions for alkali metal fluorides including the most recent report by Ameduri in 2009 by changing temperature and solvent.\(^6\) Industrial workarounds of developing a liquid initiator by isolating this lower phase, and re-introducing alkali metal fluorides to gain access to high molecular weight poly(HFPO) skirts around the issue and is not a viable solution for the development of difunctional poly(HFPO) in an efficient manner. Thus rather than simply mimicking this workaround to simply claim higher \(M_n\) poly(HFPO), attempts at understanding and limiting phase transfer were undertaken by developing new hydrocarbon-fluorocarbon surfactants. Based on the success of tetraglyme, surfactants comprising both ethylene glycol and hexafluoropropylene oxide segments were successfully prepared but require further optimization by screening a wider array of co-solvents and temperatures to maintain viability of the surfactant. In the process of developing new surfactants, new methodology for the cross-coupling of oligo(HFPO) iodides and hydrocarbon unsaturated systems were developed and proved valuable for the incorporation into theranostic drug delivery nanoemulsion prototypes.\(^{40}\)

A second potentially more powerful strategy was explored by converting the phase transferred oligo(HFPO) acyl fluorides into methyl hydrofluoroethers which are readily accessed in high conversions with dimethyl sulfate. Using the methylating ability of HFEs, new oligo(HFPO) perfluoroalkoxides have been prepared under similar conditions reported in Chapter 2. For the first time, the actual active species in the polymerization of HFPO can be prepared and isolated in an operationally simple fashion, demonstrated to be thermally stable under ambient conditions, and characterized by standard techniques. Based on the results herein, it has been proposed that higher \(DP_n\) oligomers may offer the best opportunity for liquid oligo(HFPO) perfluoroalkoxides which may act as their own solvent negating the use polar organic so-solvents which cause phase separation. Alternatively, O-methylation/demethylation can be considered a successful way to protect/deprotect oligo(HFPO) in living polymerizations and may prove to useful methodology for preparing more diverse polymers.

### 4.11.2 Future Work

To further investigate the effect of phase separation on the ring-opening of HFPO, low molecular weight surfactants that are miscible with both poly(HFPO) \(195\) and tetraalkylammonium mono- and difunctional perfluoroalkoxides initiators with a non-ester linking group and a oligo(HFPO)s less than \(DP_3\) may provide the most robust alternatives to
those prepared within this chapter. Furthermore, higher molecular weight oligomeric HFPO methyl ethers (such as \( DP_n 4-10 \)) could be prepared in the identical fashion may be liquids rather solids and act as their own solvents (\text{SCH.EM 4.16}).


Rather than the difunctional HFE methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187, simpler methoxy hydrofluoroethers could be prepared from perfluoroacyl fluorides or perfluoroalkyl dibromides, a strategy that makes use of the O-demethylation of HFEs (\text{SCH.EM 4.17}). These methoxy functionalized initiators 197 - 198 may provide interesting architectures provided that the chain transfer process can be exquisitely controlled or preferentially eliminated (otherwise difficult to separate mixtures of the two will prevail).
Scheme 4.17. Proposed Difunctional and Trifunctional Hydrofluoroethers as Initiators for the Polymerization of HFPO Although Polymerization Could be Polymerized Selectively from a Single Direction and then Functionalized Post-Polymerization.

The ring-opening polymerization of other fluorinated monomers by perfluoroalkoxides can be extended to the commercially relevant 2,2,3,3-tetrafluorooxetane 162 currently used by Daikin in the preparation of Demnum 200 (Scheme 4.18). Since 2,2,3,3-tetrafluorooxetane 162 is a cyclic hydrofluoroether, a polymerization devoid of both anhydrous fluorides (required in the current Daikin process) or without tetraalkylammonium perfluoroalkoxides 200 (like this chapter) can be envisioned that simply requires a tertiary amine to generate the in situ perfluoroalkoxide initiator 201 and 202. This would be a remarkable advancement potentially harnessing both the utility of the tetraalkylammonium cation while improving the efficiency and ease of the reaction (Scheme 4.18).
Scheme 4.18. Extending Beyond HFPO 161 to Address Similar Issues in Chain Transfer with Polymerization of Daikin’s Monomer, 2,2,3,3-Tetrafluorooxetane 162 Either with Tetraalkylammonium Perfluoroalkoxides 200 or with Tertiary Amines as Initiators 201

Lastly, while the synthesis of a difunctional initiator from methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate 187 was not successful, the ease in preparing tetraalkylammonium salts of 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate in an efficient manner may in fact provide a highly valuable route to 1,1,2-trifluoro-2-methoxyethene, 203 (Scheme 4.19). This highly reactive monomer has been polymerized in the early 1960s by DuPont but has been seldom used due to its highly reactive nature, more formidable than the monomer tetrafluoroethylene from which it is prepared.[71] However, it is well known that tetrafluoroethylene can be safely handled and manipulated under an equivalent of CO₂ by decarboxylation of perfluoropropionic carboxylates.[72] Thus, it can be envisioned that monomer 203 can be prepared by decarboxylation of 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olates affording an equivalent of CO₂ in the process. If successful, 203 could be safely polymerized affording a new perfluoropolymer with pendent OCH₃ moieties, providing a valuable polymeric hydrofluoroether precursor akin to Nafion® like membranes in a more efficient manner.

Scheme 4.19. Decarboxylation of Tetraalkylammonium Salts of 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate 187a–e May Afford a Safer Synthesis of a Valuable Hydrofluoroether Monomer,1,1,2-Trifluoro-2-methoxyethene, 203
4.12 Experimental

4.12.1 General Remarks

All manipulations were performed under the exclusion of moisture and oxygen using a Vacuum Atmospheres HE-493 glovebox with pre-purified nitrogen or with appropriate Schlenk techniques with oven or flame dried glassware. All starting materials were commercially available and were purchased from Sigma Aldrich, unless otherwise noted. Hexafluoropropylene 160 and hexafluoropropylen oxide 161 were kindly received from DuPont in stainless steel cylinders and analyzed by GC/MS, $^1$H, $^{19}$F NMR and IR prior to use. Flash chromatography was performed on Aldrich Silica Gel 70-230 mesh with particles having a 60 Å pore volume (0.75 cm$^3$ g$^{-1}$) using a forced flow of eluent at 0.3-0.5 bar pressure.$^{[73]}$ Concentration under reduced pressure was performed by rotary evaporation at an appropriate pressure. Purified compounds were further dried under vacuum (< 1 Torr depending on volatility of compound).

As described within this Chapter, HFPO 161 was dried by the method of Moore et al. in which HFPO was passed successively through 30 cm columns of potassium hydroxide (ACS grade) followed by granular CaH$_2$ prior to use. Poly(hexafluoropropylene oxide) primary iodide ($M_n = 2094$ g mol$^{-1}$ based on MALDI-TOF-MS analysis) was provided by DuPont (Experimental Station, Wilmington, DE) and used as received. All other starting materials are commercially available and were purchased from Sigma Aldrich. Benzene was distilled over Na/benzophenone and stored over 4 Å mol sieves in a glove box whereas hexafluoroxylene, HFE-7000, HFE-7100 and acetonitrile were distilled over CaH$_2$ under a nitrogen atmosphere, collected in a Straus flask, and stored over 4 Å mol sieves in a glovebox. Potassium fluoride (KF) and cesium fluoride (CsF) was rendered anhydrous by the method of Prakash: heating under full vacuum (< 1 torr) at 250 °C for a minimum of 30 h, sealed under vacuum and stored in a glovebox.$^{[65]}$ Tetraalkylammonium perfluoroalkoxides were prepared according to the protocol listed in Chapter 2 and were handled under the exclusion of moisture in a nitrogen filled glovebox.$^{[74]}$

Solution state $^1$H, $^{13}$C, $^{19}$F NMR spectra were recorded on a Bruker Ascend spectrometer running TopSpin 3.1.6 operating at 400.13 ($^1$H), 100.62 ($^{13}$C), 376.46 ($^{19}$F) MHz and processed with Mestrenova Software. Data is reported as follows: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz. Chemical shifts are reported in ppm with the solvent resonance as the internal standard for $^1$H and $^{13}$C spectra whereas $^{19}$F NMR was internally referenced to CFCl$_3$ (0.00 ppm). For gas chromatography/mass spectrometry (GC/MS) analyses, an Agilent Technologies 6890N GC was coupled with an Agilent Technologies 7638B series injector and Agilent Technologies 5975B inert mass spectrometer detector (MSD) was employed.
with electron impact (EI) as the mode of ionization. Infrared Analysis (IR) were performed on a ThermoFisher Nicolet 380 spectrophotometer equipped with a gas IR cell (NaCl windows) or with a Ge SmartIR ATR sampling assembly at 2 cm\(^{-1}\) resolution. Matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) experiments were determined with a Bruker Autoflex III spectrometer equipped with a 1 kHz smartbeam-II laser and reflector in positive ionization. For sample preparation, a 2mg sample of 1-phenyl-poly(HFPO) was added to a 1-mL solution of 50:50 1% LiCl (m/v) in MeOH and 20% (m/v) 2,3,4,5,6-pentafluorocinnamic acid (CAS # 719-60-8) dissolved in 50:50 MeOH/Methoxynonafluorobutane (3M HFE-7100). A 2 µL solution was then pipette on to a ground steel plate, dried, and irradiated for a minimum of 5000 shots.

### 4.12.2 Preparation and Experimental Data

Note: All accompanying experimental spectra for this chapter if not presented here can be located in APPENDIX G.

**Synthetic Route to Hexafluoropropylene Oxide, 161**

If not commercially available, hexafluoropropylene oxide can theoretically be prepared by acid digestion of fluorospar 204 in a series of difficult synthetic steps or more conveniently from hexafluoropropylene via prolonged pyrolysis of poly(TFE) and subsequent oxidation. The general synthesis is outlined in Scheme 4.20.

**Scheme 4.20.** General Industrial Synthetic Scheme for the Preparation of Hexafluoropropylene Oxide 161 from the Mineral, Fluorite (CaF\(_2\)) 204.
**Fig. 4.16.** $^{19}$F NMR (376 MHz, CDCl$_3$) Annotated Spectrum of Commercial-Grade Hexafluoropropylene Oxide, 161

$^{19}$F NMR: (376 MHz, sparged through CDCl$_3$) δ -155.66 (m, 1F), -112.65 (dd, $^3J_{FF} = 40.2$ Hz, $^2J_{FF} = 17.2$ Hz, 1F), -109.84 (dd, $^3J_{FF} = 40.4$ Hz, $^3J_{FF} = 18.9$ Hz, $^3J_{FF} = 8.2$ Hz, 1F), -77.32 (dd, $^3J_{FF} = 8.2$, $^4J_{FF} = 2.7$ Hz, 3F).

Assignment of each signal indicated in Figure 4.16. **EIMS**, 70 eV, m/z (rel. int.): 31 (19.91)(CF$^+$), 50 (26.77)(CF$_2^+$), 69 (100.00)(CF$_3^+$), 81 (28.76)(CFCF$_2^+$), 97 (8.95)(CF$_2$COF$^+$), 100 (26.81)(CF$_2$CF$_2^+$), 119 (25.76)(CF$_3$CF$_2^+$), 131 (1.00)(CF$_3$CF=CF$^+$), 147 (2.13)(M$^+$$-19$). **IR** (gas cell, wavenumbers cm$^{-1}$): 1021.31 (s), 1234.01 (s), 1365.03 (s), 1150.81 (s), 1604.37 (s).
Polymerization of HFPO

The following are experimental conditions for the polymerization of HFPO 161 listed in this chapter:
Entry 1, Table 4.3: A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with anhydrous CsF (7.609 g, 0.0501 mol) and anhydrous tetraglyme (13 mL) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fumehood and connected to a source of N₂, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to −30 °C by means of an external bath of CH₃CN/CO₂ and hexafluoropropene (HFP) (10 g, 66.7, mmol) was transferred to the system. Hexafluoropropylene oxide (HFPO) (674 ± 1 g, 4.1 mol, 82.0 equiv) was then slowly introduced into the reactor with vigorous stirring over a 5.25 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 218.9 g. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.2 and 4.3.

Entry 2, Table 4.3: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with anhydrous CsF (0.764 g, 0.0050 mol) and anhydrous tetraglyme (0.764 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (34 ± 1 g, 0.205 mol, 40 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −32 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 17 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 27.8 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.3.

Entry 3, Table 4.3: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with anhydrous AgF (0.104 g, 0.82 mmol) and anhydrous tetraglyme (0.226 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (29 ± 1 g, 0.17 mol, 210 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −32 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 24 h, the vessel was warmed to ambient temperature in which only a trace residue was observed and no oligo(HFPO) was detected by GC/MS analysis.

Entry 4, Table 4.3: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with anhydrous CsF (0.037 g, 0.22 mmol), anhydrous tetraglyme (0.3 mL), and anhydrous hexafluoroxylene (4 mL). The vessel was sealed by attaching to a modified #25 Ace® Glass
PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (22.0 ± 1 g, 0.13 mol, 544 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and maintained at 20 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 6 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 22.0 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.3.

**Entry 5, Table 4.3:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with anhydrous CsF (0.075 g, 0.49 mmol), anhydrous tetraglyme (1.069 g), and anhydrous hexafluoroxyylene (1.017 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (33 ± 1 g, 0.199 mol, 403 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −32 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 15 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 36.5 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.3.

**Entry 6, Table 4.5:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [quinMe]OC₃F₇ (0.265 g, 1.00 mmol) and anhydrous tetruglyme (0.600 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.16 mol, 160 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 16 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 22.2 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.3.

**Entry 7, Table 4.5:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [Me₃NBn]OC₃F₇ (0.074 g, 22.1 mmol) and anhydrous tetraglyme (0.659 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (25 ± 1 g, 0.15 mol, 627 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled
to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 20 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 18.5 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

**Entry 8, Table 4.5:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [NMe₄]OC₄F₉ (0.075 g, 0.24 mmol) and anhydrous tetragnyle (1.159 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.16 mol, 670 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 12 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 12.0 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

**Entry 9, Table 4.5:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [NMe₄]OC₄F₉ (0.077 g, 0.25 mmol) and anhydrous CH₃CN (1.969 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (25 ± 1 g, 0.15 mol, 605 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 16 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 14.5 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

**Entry 10, Table 4.5:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [TMEDA–Me]OC₄F₉ (0.090 g, 0.25 mmol) and anhydrous CH₃CN (1.985 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (26 ± 1 g, 0.16 mol, 637 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 12 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene)
Entry 11, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [NMe₄]OC₄F₉ (0.083 g, 0.27 mmol), anhydrous CH₃CN (2.450 g), and CaH₂ (chunks, 0.204 g, 4.8 mmol). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (16 ± 1 g, 0.10 mol, 359 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 12 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 9.2 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

Entry 12, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [NMe₄]OC₄F₉ (0.070 g, 0.23 mmol) and anhydrous CH₃CN (1.453 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (23 ± 1 g, 0.14 mol, 611 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −45 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 41 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

Entry 13, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [Me₃NBn]OC₃F₇ (0.083 g, 0.25 mmol) and anhydrous CH₃CN (0.936 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.16 mol, 655 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 18 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 23.8 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.
Entry 14, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [PMe₄]OC₃F₇ (0.054 g, 0.20 mmol) and anhydrous CH₃CN (1.561 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.16 mol, 831 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 21 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 27.8 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.5.

Entry 15, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with an aliquot of the fluorous layer from Entry 9 (1.952 g, Mₙ (¹⁹F NMR) = 863.8 g mol⁻¹, 2.26 mmol, clear liquid) with no additional solvent. The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.16 mol, 72 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 32 h, the vessel was warmed to ambient temperature in which only a trace residue was observed with no additional oligo(HFPO) or increase in the DPₙ by GC/MS analysis.

Entry 16, Table 4.5: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with an aliquot of the fluorous layer from Entry 2 (0.628 g, Mₙ (GC) 815 g mol⁻¹, 0.77 mmol, clear liquid) and anhydrous CsF (0.038 g, 0.25 mmol). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and stirred at RT for 3 h after which was connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (27 ± 1 g, 0.163 mol, 211 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35 °C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 20 h, the vessel was warmed to ambient temperature affording a residue nearly equal in mass (146.036 - 145.977 = 0.059 g) to the mass of the charged flask prior to polymerization and only a minute increase in the DPₙ by GC/MS analysis.

Entry 17, Table 4.6: A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [NMe₄]OC₃F₇ (0.617 g, 2.38m mol) and anhydrous tetruglyme (13 mL) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed
in a fume hood and connected to a source of N\textsubscript{2}, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to $-30^\circ$C by means of an external bath of CH\textsubscript{3}CN/CO\textsubscript{2} and hexafluoropropene (HFP) (20 g, 0.13 mol) was transferred to the system. Hexafluoropropylene oxide (HFPO) \((104 \pm 1\text{ g}, 0.63\text{ mol}, 263\text{ equiv})\) was then slowly introduced into the reactor with vigorous stirring over a 6.5 h period. The reactor was then warmed to room temperature and the lower fluororous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 77.9 g. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.6.

**Entry 18, Table 4.6:** A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [(NMe\textsubscript{3}Et)]OC\textsubscript{4}F\textsubscript{9} \((1.730\text{ g}, 2.85\text{ mmol})\) and anhydrous tetruglyme \((13.528\text{ g})\) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fume hood and connected to a source of N\textsubscript{2}, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to $-30^\circ$C by means of an external bath of CH\textsubscript{3}CN/CO\textsubscript{2} and hexafluoropropene (HFP) \(10\text{ g, 0.06, mol}\) was transferred to the system. Hexafluoropropylene oxide (HFPO) \((166 \pm 1\text{ g}, 1.0\text{ mol}, 203\text{ equiv})\) was then slowly introduced into the reactor with vigorous stirring over a 5 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 140.8 g. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.6.

**Entry 19, Table 4.6:** A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [(NMePr\textsubscript{3})]OC\textsubscript{4}F\textsubscript{9} \((1.061\text{ g}, 2.70\text{ mmol})\) and anhydrous tetruglyme \((12\text{ mL})\) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fume hood and connected to a source of N\textsubscript{2}, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to $-30^\circ$C by means of an external bath of CH\textsubscript{3}CN/CO\textsubscript{2} and hexafluoropropene (HFP) \(10\text{ g, 0.06, mol}\) was transferred to the system. Hexafluoropropylene oxide (HFPO) \((102 \pm 1\text{ g}, 0.61\text{ mol}, 228\text{ equiv})\) was then slowly introduced into the reactor with vigorous stirring over a 5 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 109.5 g. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.6.
Entry 20, Table 4.6: A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [Me$_3$NBn]OC$_4$F$_9$ (0.924 g, 2.40 mmol) and anhydrous tetraglyme (15 mL) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fumehood and connected to a source of N$_2$, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to $-30^\circ$C by means of an external bath of CH$_3$CN/CO$_2$ and hexafluoropropene (HFP) (11 g, 0.07 mol) was transferred to the system. Hexafluoropropylene oxide (HFPO) (82 ± 1 g, 0.49 mol, 206 equiv) was then slowly introduced into the reactor with vigorous stirring over a 5 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 65.5 g. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.6.

Entry 21, Table 4.6: A oven-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [NMe$_4$]OC$_4$F$_9$ (0.306 g, 0.99 mmol), anhydrous HFE-7100 (20 mL), anhydrous THF (6 mL), and anhydrous CH$_3$CN (6 mL) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fumehood and connected to a source of N$_2$ and HFPO. With mechanical agitation, the reaction vessel was cooled to $-28^\circ$C by means of an external bath of 1,3-dichlorobenzene/CO$_2$. Hexafluoropropylene oxide (HFPO) (41 ± 1 g, 0.25 mol, 250 equiv) was then slowly introduced into the reactor with vigorous stirring over a 5 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.6.

Entry 22 Table 4.6: A oven-dried 100-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [NMe$_4$]OC$_4$F$_9$ (0.397 g, 1.28 mmol) and anhydrous tetraglyme (2.403 g) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fumehood and connected to a source of N$_2$, HFPO, and HFP. With mechanical agitation, the reaction vessel was cooled to $-30^\circ$C by means of an external bath of acetone/CO$_2$ and hexafluoropropene (HFP) (5 g, 0.033 mol) was transferred to the system. Hexafluoropropylene oxide (HFPO) (35 ± 1 g, 0.21 mol, 164 equiv) was then slowly introduced into the reactor with vigorous stirring over a 7 h period. The reactor was then warmed to room temperature and the lower fluorous product was isolated under a nitrogen atmosphere and placed in a dry
Entry 23, Table 4.6: A flame-dried 250-mL glass round-bottom flask equipped with inlet and outlet valves, dry ice condenser, and a mechanical stirrer paddle was charged in a glovebox with [NMe₄]OC₄F₉ (0.365 g, 1.18 mmol), anhydrous HFE-7100 (10 mL), anhydrous hexafluoroxylene (10 mL), and anhydrous CH₃CN (10 mL) in a glovebox. After being securely sealed with appropriate clips, the reaction vessel was placed in a fumehood and connected to a source of N₂ and HFPO. With mechanical agitation, the reaction vessel was cooled to 0°C by means of an external ice bath. Hexafluoropropylene oxide (HFPO) (103 ± 1 g, 0.62 mol, 524 equiv) was then slowly introduced into the reactor with vigorous stirring over a 4 h period. The reactor was then warmed to room temperature and the lower fluororous product was isolated under a nitrogen atmosphere and placed in a dry plastic poly(ethylene) bottle. Yield = 100.8 A small aliquot was treated with methanol to convert the acid fluoride end group to a methyl ester end group for analysis which is reported in Table 4.5.

Entry 24, Table 4.6: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [NMe₄]OC₄F₉ (0.082 g, 0.27 mmol), anhydrous CH₃CN (1.082 g) and anhydrous hexafluoroxylene (1.163 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (30 ± 1 g, 0.18 mol, 681 equiv) and HFP (20.8 g, 0.139 mol) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 3 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 13.0 g. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.6.

Entry 25, Table 4.6: In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [quinMe]OC₄F₉ (0.073 g, 0.23 mmol), anhydrous tetraglyme (0.220 g) and anhydrous HFE-7100 (2.501 g). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (21 ± 1 g, 0.13 mol, 539 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and cooled to −35°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 16.5 h, the vessel was warmed to ambient temperature and the lower phase was isolated under a nitrogen atmosphere and placed in a dry poly(ethylene) bottle. Yield = 37.0 g. A
sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.6.

**Entry 26, Table 4.6:** In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [MeNBu₃]OC₄F₉ (0.113 g, 0.26 mmol) and anhydrous hexafluoroxylene (4 mL). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (28 ± 1 g, 0.170 mol, 650 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and maintained at 20°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes. After 20 h, the pressure in the vessel was released. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.6.

**Entry 27, Table 4.6** : In a glovebox, a 60 mL Ace® Glass Pressure tube was charged with [Me₃NBn]OC₃F₇ (0.084 g, 0.251 mmol) and anhydrous hexafluoroxylene (4 mL). The vessel was sealed by attaching to a modified #25 Ace® Glass PTFE threaded stopper and connected to a mechanical stirrer and a Hoke® cylinder charged with HFPO 161 (11 ± 1 g, 0.066 mol, 268 equiv) as illustrated in Scheme 4.3. The vessel was lowered into a cold-well and maintained at 20°C by an external circulator and HFPO 161 was introduced for 1 second at 25 psig every 15 minutes (exotherm). After 20 h, the pressure in the vessel was released. A sample was treated with methanol to convert the acid fluoride end group to a methyl ester end group for GC/MS analysis which is reported in Table 4.6.

**Spectroscopic Data for Non-Commercially Available, Batch Specific poly(HFPO) Primary Iodide Used in the Preparation of Surfactants 177 and 180**

![Chemical Structure](image)

**19F NMR** (376 MHz, neat) δ -146.4 (m, repeat unit CF, 8.15 F), -135.19 (m, ω-CF, 1F), -131.84 (d, α-CF₂, 3JFF = 7.2 Hz, 2F), -81.43 (m, 49.67 F), -59.68 (m, CF₂I, 3JFF = 213.44 Hz, 2F). Mₙ (19F NMR) = 1765 g mol⁻¹. **13C NMR** (101 MHz, neat) δ 91.22 (tdd, CF₂I 1JCF = 320.6 Hz, 2JCF = 35.3 Hz, 3JCF = 11.6 Hz, 1C), 100.245 (m, J = 35.19 Hz, repeat unit CF), 106.16 (tdd, repeat unit CF₂, 1JFF = 268.0 Hz, 2JFF = 40.2 Hz, 1JFF = 36.9 Hz), 116.07 (qd, repeat unit CF₃, 1JFF = 288.52 Hz, 2JFF = 33.85 Hz). **EIMS**, 250
70 eV, m/z (rel. int.): 69 (48.58) (CF$_3^+$), 119 (32.83) (CF$_3$CF$_2^+$), 177 (7.57) (CF$_2$I$^+$), 169 (100.00) (CF$_3$CF$_2$CF$_2^+$), 277 (69.26) (CF(CF$_3$)CF$_2$I$^+$), 335 (7.88) (CF(CF$_3$)CF$_2$OCF(CF$_3$)CF$_2^+$), 443 (0.84) (CF(CF$_3$)CF$_2$OCF(CF$_3$)CF$_2$CF$_2$I$^+$). Assignment of each signal indicated in the associated spectra: Appendix G

Preparation of 1-Phenyl-poly(HFPO), 177

A dry 250-mL three necked round-bottomed flask was equipped with a magnetic stirrer and a reflux condenser adapted for a nitrogen blanket. Poly(hexafluoropropylene oxide) primary iodide (34.519 g, 16.48 mmol, $M_n = 2094$ g mol$^{-1}$) was added to the reaction flask followed by 50-mL glacial acetic. The contents were degassed by refluxing under nitrogen for 1 h. After cooling to 80°C, the vessel was charged with anhydrous benzene (74.2 g, 0.95 mol) and copper (II) acetate (0.208 g, 1.15 mmol). The reaction was heated in an oil bath at 95°C under a flow of nitrogen and upon continued stirring, benzoyl peroxide was added every 45-60 min in 2 g portions. After a period of 4 hours (total 10.33 g, 0.0426 mol), the reaction was complete by GC/MS analysis and the poly(HFPO) iodide was completely converted to the desired product. The reaction was cooled to room temperature, the upper organic layer removed, and the fluorinated product was washed 3x with 25-mL glacial acetic acid, followed by 3x 25-mL of ice-cold diethyl ether. The product was heated under reduced pressure at 90°C to remove any volatile materials for a period of 45 min to afford 28.327 g of 177 as colorless oil (84.1%). $^1$H NMR (400 MHz, none) $\delta$ 7.18 (t, $^3J = 7.4$ Hz, 2H), 7.24 (t, $^3J = 5.1$ Hz, 2H), 7.38 (d, $^3J = 7.2$ Hz, 1H). $^{13}$C NMR (101 MHz, none) $\delta$ 102.51 (qd, $^1J_{CF} = 270.7$, $^2J_{CF} = 36.7$ Hz, OCF(CF$_3$)CF$_2$), 117.22 (qd, $^1J_{CF} = 290.9$ Hz, $^2J_{CF} = 28.2$ Hz -OCF(CF$_3$)CF$_2$), 126.150 (s, C$_{ortho}$, 2C), 127.329 (s, C$_{meta}$, 2C), 128.81 (td, $^2J_{CF} = 24.2$, $^3J_{CF} = 3.7$ Hz C$_{ipso}$), 130.75 (s, C$_{para}$, 1C). $^{19}$F NMR (376 MHz, CDCl$_3$), $\delta$ -81.461 (s, -CF(CF$_3$)CF$_2$O-, 89.789 (s, CF$_3$CF$_2$CF$_2$O-, 3F), 81.611 (s, -CF(CF$_3$)CF$_2$O-, 2F), -145.976 (m, -CF(CF$_3$)CF$_2$O-, 9.69 F). EIMS, 70 eV, m/z (rel. int.): 69 (17) (CF$_3^+$), 77 (3) (C$_9$H$_5^+$), 119 (5) (CF$_3$CF$_2^+$) 127 (100) (PhCF$_2^+$), 169 (30) (CF$_3$CF$_2$CF$_2^+$), 227 (23) (PhCF$_2$CF(CF$_3$)$^+$), 393 (3) (PhCF$_2$CF(CF$_3$)OCF(CF$_3$)CF$_2^+$). MALDI-TOF-MS [412 + 166n + Li$^+$] = 1415.388 (n = 6), 1581.440 (n = 7), 1747.493 (n = 8), 1913.549 (n = 9), 2079.603 (n = 10), 2245.654 (n = 11), 2411.700 (n = 12), 2577.740 (n = 13), 2743.785 (n = 14). Assignment of each signal indicated in the associated spectra: Appendix G
Preparation of triethylene glycol allyl methyl ether, 179: Following a general procedure from Friesen et al.;[30] A flame-dried 250-mL three-necked round-bottom flask equipped with an addition funnel and a magnetic stirrer was evacuated 3x and backfilled with \( \text{N}_2 \). Under a \( \text{N}_2 \) atmosphere, the flask was charged with inhibitor-free, anhydrous THF (Aldrich, 75-mL) and NaH (60% dispersion in mineral oil (white powder), 5.237 g, 0.131 mol, 1.35 equiv). To the addition funnel was added 25-mL anhydrous THF and triethylene glycol monomethyl ether 178 (Aldrich, 97%, 15.938 g, 0.0971 mol, 1.00 equiv). The solution of 178 was added dropwise over a period of 45 min to the white suspension of NaH while cooling with an ice bath to maintain near 0\(^\circ\) C. After 1 h, the addition funnel was charged a second time with anhydrous THF (15-mL) and allyl bromide (13.568 g, 0.112 mol, 1.15 equiv). The resulting solution was added dropwise to the round-bottom flask, stirred for 2 h at RT at which point 100% conversion to the desired 179 was observed by GC/MS and the reaction flask carefully quenched with water. The resulting suspension was filtered through a firmly pressed filter pad of Celite® under vacuum and the volatiles were subsequently removed with a rotovap to afford a near colourless liquid as 99% 179 by GC analysis. The crude product was distilled, collecting the fraction with a b.p. of 85\(^\circ\)C-95\(^\circ\)C at 760 mmHg to afford 179 as a colourless liquid in 84.6% isolated yield (16.778 g).

\(^1\text{H} \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 3.38 (s, OCH\(_3\), 3H), 3.55 (m, CH\(_2\)O, 2H), 3.61 (dt, \( J =7.1, 2.8 \text{ Hz}, \) CH\(_2\)O, 2H), 3.66 (m, CH\(_2\)CH\(_2\)O, 8H), 4.03 (dt, \( 3J_{HH} = 5.7, 1.4 \text{ Hz}, \) CH\(_2\)CH=CH\(_2\), 2H), 5.18 (dq, \( 3J_{HH} = 10.3, 1.4 \text{ Hz}, \) =CH, 1H), 5.27 (dq, \( 3J_{HH} = 17.3, 1.7 \text{ Hz}, \) =CH 1H), 5.92 (ddt, \( 3J_{HH} = 17.3, 10.5, 5.7 \text{ Hz}, \) =CH, 1H). \(^{13}\text{C} \text{ NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 58.88, 70.42, 70.53, 71.84, 72.08, 116.84, 116.87, 134.71. EIMS, 70 eV, m/z (rel. int.): 41 (56.44) (CH\(_2\)=CHCH\(_2\)^+), 45 (27.17) (CH\(_3\)OCH\(_2\)CH\(_2\)^+), 59 (100) (CH\(_3\)OCH\(_2\)CH\(_2\)^+), 71 (8.57) (CH\(_2\)=CHCH\(_3\)OCH\(_2\)^+), 73 (28.66) (CH\(_3\)OCH\(_2\)CH\(_2\)CH\(_2\)^+), 85 (12.32) (CH\(_2\)=CHCH\(_2\)OCH\(_2\)CH\(_2\)^+), 101 (3.52) (CH\(_2\)=CHCH\(_2\)OCH\(_2\)CH\(_2\)^+), 103 (2.09) (CH\(_3\)O(CH\(_2\)CH\(_2\)OCH\(_2\)CH\(_2\)^+), 133 (2.09) (CH\(_3\)O(CH\(_2\)CH\(_2\)O)\(_2\)CH\(_2\)^+), 147 (1.17) (CH\(_3\)O(CH\(_2\)CH\(_2\)O)\(_2\)CH\(_2\)^+). Assignment of each signal indicated in the associated spectra: Appendix G
Preparation of Surfactant 180 by ATRA of triethylene glycol allyl methyl ether and oligo(HFPO) primary iodide, 176: In a procedure adapted from Friesen,[30] A flame dried 250-mL three-neck round-bottom flask equipped with a nitrogen supply, condenser and magnetic stir bar was charged with poly(HFPO) primary iodide 176 (29.477 g, 16.7 mmol, 1.0 equiv) and triethylene glycol allyl methyl ether 179 (4.931 g, 24.1 mmol, 1.44 equiv). The contents of the flask was degassed and backfilled with N₂ three times after which α,α,α-trifluorotoluene (Aldrich, > 99%, 80-mL) was added as a solvent. The colourless, stirred solution was heated to 95 °C and benzoyl peroxide (0.500 g, 2.1 mmol) was added followed by a second addition after 60 min (0.450 g, 1.9 mol). After 90 min, an aliquot was analyzed by GC/MS which indicated full conversion of poly(HFPO) primary iodide (complete loss 277 m/z fragment, CF₂I⁺) was detected and a new homologue distribution with an increased retention time and spectroscopic data consistent with the intermediate iodide adduct 208. The solvent can be removed in vacuo and the reaction residue can be purified by column chromatography on silica gel, eluting with hexane/EtOAc 4:1 (v/v), to afford a colourless liquid with spectroscopic data consistent with that previously reported for 208.[30]

¹⁹F NMR (376 MHz, neat) δ -145.66 (m, repeat unit CF, 6.54F), -130.81 (m, α-CF₂ 2F), -113.61 (m, CF₂CH₂ 2F), -81.34 (m, 28F). EIMS, 70 eV, m/z (rel. int.) 45 (18.10) (CH₃OCH₂⁺), 59 (100.00) (CH₃OCH₂CH₂⁺), 69 (41.30) (CF₃⁺), 73 (17.75) (CH₃OCH₂CH₂CH₂⁺), 103 (46.27) (CH₃O(CH₂CH₂OCH₂CH₂⁺), 119 (16.24) (CF₃CF₂⁺), 147 (43.14) (CH₃O (CH₂CH₂O)₂CH₂CH₂⁺), 150 (12.75) (CF₃CF₂CF₂⁺), 169 (80.80) (CF₃CF₂CF₂⁺), 335 (6.04) (C₃F₇OCF(CF₃)CF₂⁺), 177 (0.98) (CH₃O(CH₂CH₂O)₂OCH₂⁺), 501 (0.60) (C₃F₇O[CF(CF₃)CF₂]₂⁺). Assignment of each signal indicated in the associated spectra: Appendix G.
Preferentially, it was found that upon maintaining the reaction mixture at 95 °C, the reduction of the intermediate iodide 208 adduct could be efficiently afforded in a one-pot procedure by the addition of HSnBu₃ (5.421 g, 18.6 mmol, 1.11 equiv) and an additional equivalent of benzoyl peroxide (0.245 g, 1.0 mmol). Full conversion to 180 was confirmed by GC/MS analysis after 4.25 h and the transparent, slightly yellow reaction monophasic reaction mixture was cooled to RT and the solvent removed in vacuo. To the reaction residue was treated with EtOAc (70-mL) and anhydrous KF (1.71 g, 29.4 mol, 1.76 equiv) for a period of 24 h following a procedure from E.J. Corey et al to remove ISnBu₃. The solution was filtered through a pad of and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting initially with 100% hexane to remove trace poly(HFPO) primary hydrogen end-cap followed by a gradient to hexane/EtOAc 4:1 (v/v), to afford 17.25 g of the title compound 180 as a light yellow oil (56% yield). The spectroscopic data is similar with that previously reported. 

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 1.60 \text{ (b, CH}_2\text{CH}_2\text{CH}_2\text{CF}_2, 2\text{H}), 1.85 \text{ (b, CH}_2\text{CH}_2\text{CH}_2\text{CF}_2, 2\text{H}), 2.07 \text{ (b, CH}_2\text{CH}_2\text{CH}_2\text{CF}_2, 2\text{H}), 3.36 \text{ (m, CH}_3\text{O, 3H), 3.41-3.85 \text{ (b, CH}_2\text{O, 14 x H).}} \]

\[ ^19F \text{NMR} \ (376 \text{ MHz, CDCl}_3) \delta -145.59 \text{ (m, repeat unit CF 11.15F)} -130.68 \text{ (m, } \alpha\text{-CF}_2, 2\text{F), -114.65 \text{ (m, CF}_2\text{CH}_2, 2\text{F), -80 to -84 (} \alpha\text{-CF}_3, \text{ repeat unit CF}_3 & \text{CF}_2). EIMS, 70 eV, m/z (rel. int.) 45 (47.55) (CH}_3\text{OCH}_2^+, 59 (100.00) (CH}_3\text{OCH}_2\text{CH}_2^+, 69 (54.52) (CF}_3^+, 73 (7.98) (CH}_3\text{OCH}_2\text{CH}_2\text{CH}_2^+, 103 (52.90) (CH}_3\text{O(CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2^+, 119 (22.95) (CF}_3\text{CF}_2^+, 147 (33.09) (CH}_3\text{O(CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2^+, 150 (19.52) (CF}_3\text{CF}_2\text{CF}_2, 169 (86.29) (CF}_3\text{CF}_2\text{CF}_2^+, 191 (1.29) (CH}_3\text{O(CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2^+, 335 (10.17) (C}_3\text{F}_7\text{O}[\text{CF(CG}_3\text{CF}_2\text{CF}_2]_2^+.} \]

Preparation of Oligo(HFPO)-Triethylene Glycol Ester Surfactant, 172

A flame dried 250-mL three-neck round-bottom flask equipped with a nitrogen supply, addition funnel, and magnetic stir bar was charged with oligo(HFPO) acyl fluoride (DPₙ = 3.73, Mₙ = 951 g mol⁻¹, 49,886 g, 52.5 mmol, 1.28 equiv) under a nitrogen atmosphere. To the 50-mL addition funnel was added α,α,α-trifluorotoluene (Aldrich, > 99%, 35-mL) and triethylene glycol monomethyl ether (6.736 g, 41.0 mmol, 1.0 equiv) which was added dropwise at RT with steady agitation. After 4 h, NaHCO₃ (10 g, 0.12 mmol) was added to the reaction mixture and stirred for 2 h. The solution was filtered through a pad of Celite® and the
filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting initially with 100% hexane to remove trace trifluorotoluene and hydrogen terminated oligo(HFPO) followed by a gradient to hexane/EtOAc 2:1 (v/v), to afford 37.43 g of the title compound 173 as a colourless oil 172 (83.4% yield).

\[ \text{1}^\text{H} \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 3.38 \text{ (s, CH}_3\text{O, 3H), 3.54 \text{ (m, CH}_3\text{OCH}_2\text{H, 2H), 3.63 \text{ (m, 6H), 3.76 \text{ (t, CH}_2\text{CH}_2\text{O}_2\text{C, J =4.8 Hz, 2H), 4.52 \text{ (m, -CH}_2\text{O}_2\text{C, 2H). \text{1}^\text{3C} \text{ NMR (101 MHz, None) } \delta 57.41 \text{ (CH}_3\text{, 1C), 66.88 \text{ (CH}_2\text{O}_2\text{C, 1C), 67.55 \text{ (CH}_2\text{CH}_2\text{O}_2\text{C, 1C), 69.79 - 71 \text{ (CH}_2\text{O \times 3C), 71.34 \text{ (CH}_3\text{OCH}_2\text{H, 1C), 102.04 \text{ (m, OCF(CF}_3\text{)CF}_2\text{, 116.99 \text{ (m, repeat unit CF}_3\text{), 157.94 \text{ (d, -CO}_2\text{-, } \text{2J}_{CF} = 31.5 \text{ Hz, 1C). \text{1}^\text{9F} \text{ NMR (376 MHz, None) } \delta -145.16 \text{ (m, repeat unit CF, 4.93F), -132.94 \text{ (m, } \omega\text{-CF, 1F), -131.58 } \text{ (m, } \alpha\text{-CF}_2, \text{ 2F), -84.83 - -78.57 \text{ (m, CF}_3\text{, CF}_2\text{, 22F). \text{EIMS, 70 eV, m/z (rel. int.): 31 (6.18) (CH}_3\text{O}^+, \text{45.100 (14.37) (CH}_3\text{OCH}_2\text{H}^+, \text{59 (100.00) (CH}_3\text{OCH}_2\text{H}_2^+, \text{69 (22.78) (CF}_3\text{O}^+, \text{73 (2.11) (CH}_3\text{OCH}_2\text{CH}_2\text{H}_2^+, \text{103 (22.98) (CH}_3\text{O(CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2^+, \text{119 (7.00) (CF}_3\text{CF}_2^+, \text{147 (6.27) (CH}_3\text{O(CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{H}_2^+, \text{169 (36.71) (CF}_3\text{CF}_2\text{CF}_2^+, \text{335 (1.91) (C}_3\text{F}_7\text{OCF(CF}_3\text{)CF}_2^+.} \] 

Preparation of Oligo(HFPO)-Triethylene Glycol Ester Surfactant, 173

A flame dried 250-mL three-neck round-bottom flask equipped with a nitrogen supply, addition funnel, and magnetic stir bar was charged with oligo(HFPO) acyl fluoride \( \overline{DP}_n = 5.53 \), \( M_n = 1250 \text{ g mol}^{-1}, 36.409 \text{ g, 29.1 mmol, 1.21 equiv) under a nitrogen atmosphere. To the 50-mL addition funnel was added \( \alpha\alpha\alpha\alpha\alpha\)-trifluorotoluene (Aldrich, > 99%, 35-mL) and triethylene glycol monomethyl ether (3.943 g, 24.0 mmol, 1.00 equiv) which was added drop-wise at 0°C with steady agitation and stirred for 8 h at RT. The solution was filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting initially with 100% hexane to remove trace trifluorotoluene and oligo followed by a gradient to hexane/EtOAc 2:1 (v/v), to afford 29.11 g of the title compound 173 as a colourless oil 172 (87.1 % yield). \[ \text{1}^\text{H} \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 3.31 \text{ (s, CH}_3\text{O, 3H), 3.50 \text{ (m, CH}_3\text{OCH}_2\text{H, 2H), 3.59 \text{ (b, 6H), 3.76 \text{ (b, CH}_2\text{CH}_2\text{O}_2\text{C, 2H), 4.54 \text{ (m, -CH}_2\text{O}_2\text{C, 2H). \text{1}^\text{3C} \text{ NMR (101 MHz, None) } \delta 57.09 \text{ (CH}_3\text{, 1C), 67.04 \text{ (CH}_2\text{O}_2\text{C, 1C), 67.77 \text{ (CH}_2\text{CH}_2\text{O}_2\text{C, 1C), 69.84 - 70.18 \text{ (CH}_2\text{O \times 3C), 71.44 \text{ (CH}_3\text{OCH}_2\text{H, 1C), 102.65 \text{ (m, OCF(CF}_3\text{)CF}_2\text{, 117.35 \text{ (m, repeat unit CF}_3\text{), 158.18 \text{ (d, -CO}_2\text{-, } \text{2J}_{CF} = 31.5 \text{ Hz, 1C). \text{1}^\text{9F} \text{ NMR (376 MHz, None) } \delta -145.16 \text{ (m, repeat unit CF, 4.93F), -132.94 \text{ (m, } \omega\text{-CF, 1F), -131.58 } \text{ (m, } \alpha\text{-CF}_2, \text{ 2F), -84.83 - -78.57 \text{ (m, CF}_3\text{, CF}_2\text{, 22F). \text{EIMS, 70 eV, m/z (rel. int.): 31 (6.18) (CH}_3\text{O}^+, \text{45.100 (14.37) (CH}_3\text{OCH}_2\text{H}^+, \text{59 (100.00) (CH}_3\text{OCH}_2\text{H}_2^+, \text{69 (22.78) (CF}_3\text{O}^+, \text{73 (2.11) (CH}_3\text{OCH}_2\text{CH}_2\text{H}_2^+, \text{103 (22.98) (CH}_3\text{O(CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2^+, \text{119 (7.00) (CF}_3\text{CF}_2^+, \text{147 (6.27) (CH}_3\text{O(CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{H}_2^+, \text{169 (36.71) (CF}_3\text{CF}_2\text{CF}_2^+, \text{335 (1.91) (C}_3\text{F}_7\text{OCF(CF}_3\text{)CF}_2^+.} \]
Solubility of Surfactants 180, 172, and 173

The solubility of each of the surfactants were qualitatively determined at 19°C by measuring 0.10 mL of surfactant into 1 mL solvent as specified in Table 4.9:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>180</th>
<th>172</th>
<th>173</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dioxane</td>
<td>insoluble</td>
<td>insoluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>soluble</td>
<td>soluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>3</td>
<td>acetonitrile</td>
<td>insoluble</td>
<td>insoluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>4</td>
<td>tetracyline</td>
<td>cloudy</td>
<td>cloudy</td>
<td>insoluble and cloudy</td>
</tr>
<tr>
<td>5</td>
<td>HFE-7000</td>
<td>soluble</td>
<td>soluble</td>
<td>soluble</td>
</tr>
<tr>
<td>6</td>
<td>HFE-7100</td>
<td>soluble</td>
<td>soluble</td>
<td>soluble</td>
</tr>
<tr>
<td>7</td>
<td>CF₃Ph</td>
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<td>soluble</td>
<td>cloudy</td>
</tr>
<tr>
<td>8</td>
<td>Freon 113</td>
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<td>soluble</td>
<td>soluble</td>
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<td>soluble</td>
<td>soluble</td>
</tr>
<tr>
<td>10</td>
<td>Freon E2</td>
<td>cloudy</td>
<td>soluble</td>
<td>soluble</td>
</tr>
</tbody>
</table>

3M HFE-7000 = CH₃OCF₃, HFE-7100 = CH₃OCF₂F₉, 4, Freon 113 = 1,1,2-Trichloro-1,2,2-trifluoroethane (CFCl₂CF₂Cl), DuPont Freon E1 = C₃F₇OCFHF CF₃, DuPont Freon E₂ = C₃F₇OCF(CF₃)CF₂OCFHF CF₃

Preparation of oligo(HFPO) Perfluoroalkoxides, 183 and 184

\[
\text{CF}_3\text{CF}_2\text{CF}_2\text{O} \begin{array}{c} \text{CF} \newline \text{CF}_3 \\ \text{O} \newline \text{CF}_3 \end{array} \text{CF} \begin{array}{c} \text{C} \newline \text{O} \newline \text{F} \newline \text{CF}_3 \end{array} \]

oligo(HFPO) acyl fluoride pre-cursor, \(M_n = 577.7\ g\ mol^{-1}\): \(^{13}\text{C}\) NMR (101 MHz, neat) \(\delta = 102.68\ (m,\ \text{OCF(CF}_3\text{)CF}_2),\ 117.48\ (m,\ \text{repeat\ unit\ CF}_3),\ 148.50\ (dd,\ ^1J_{\text{CF}} = 373.4, ^2J_{\text{CF}} = 38.0\ Hz,\ 1C)\). \(^{19}\text{F}\) NMR (376 MHz, neat) \(\delta = -144.51\ (m,\ \text{repeat\ unit\ CF},\)

256
1.48F), -130.28 (m, ω-CF), -129.63 (m, α-CF, 2F), -90.45 – -71.85 (m, CF3, CF2, 16.22 F), 26.07 (d, COF, 3JFF = 35.5 Hz).

C3F7O CFCF2O CF CF3 F 1.48CF3 CF3 O

1) 4.15 equiv KF, diglyme 50°C, sonnication, 3 h
2) 2.95 equiv (CH3)2SO4, 40°C, 40 h

C3F7O CFCF2O CF CF3 F CH3

182 181

Synthesis of methyl oligo(HFPO) ether, 181: In a procedure adapted from Prakash [65]:

In a 500-mL flame-dried three-necked round-bottom flask equipped with a magnetic stir bar, addition funnel and a condenser was charged in a glovebox with rigorously dried KF (24.135 g, 0.415 mol, 4.15 equiv, see General Remarks for drying procedure), oligo(HFPO) acyl fluoride 182 (58.017 g, 0.100 mol, 1.00 equiv) and anhydrous diglyme (15-mL). The vessel was sealed and placed under a nitrogen atmosphere with an exclusion of moisture in a fumehood. The suspension was heated and sonicated at 50°C for 3 h. To the addition funnel was added dimethyl sulfate (37.20 g, 0.295 mol, 2.95 equiv - Caution: highly mutagenic substance, appropriate personal protective equipment mandatory!) and dropwise added to the reaction mixture with constant stirring at 40°C. The reaction was periodically monitored by GC/MS analysis by quenching an aliquot with anhydrous EtOH. After 40 h, the reaction reached full conversion by GC analysis (90.6% 181 and balance corresponding methyl ester) and the reaction mixture was subsequently and carefully quenched with concentrated KOHaq, and the lower layer washed three times with KOHaq, one time with 6M HCl, and lastly, three times with deionized H2O. The crude reaction mixture was dried over anhydrous MgSO4 and filtered to furnish 53.084 g of crude 181 as a colourless liquid (Mn = 611.7 g mol⁻¹, 86.4% yield). The product 181 was purified by distillation at 760 mmHg collecting the fraction with b.p. 115°C – 168°C as a colourless liquid having a homologue distribution (35.895 g, 58.6%).

1H NMR (400 MHz, neat) δ 3.28 (s, CH3O, 3H). 13C NMR (101 MHz, ) δ 49.19 (t, CH3O 3JCF = 6.9 Hz), 102.64 (dq, repeat unit CF, 1JCF = 266.7 Hz, 2JCF = 37.9 Hz), 106.02 (tsext, α-CF2, 1JCF = 296.06 Hz, 2JCF = 36.82 Hz, 1C), 116.59 (td, repeat unit CF2, 1JCF = 273.05, 2JCF = 28.0 Hz), 117.0 (qd, repeat unit CF3, 1JCF = 286 Hz, 2JCF = 30.97 Hz). 19F NMR (376 MHz, neat) δ -144.36 (m, repeat unit CF, 1.48F), -129.81 (m, α-CF2, 2F), -88.41 (m, ω-CF2OCH3, 2F), -83.68 – -78.10 (m, CF3, CF2, 12.59F). EIMS, 70 eV, m/z (rel. int.): 47 (2.11) (COF⁺), 69 (43.10) (CF3⁺), 81 (71.96) (CH3OCF2⁺), 119 (35.54) (CF3CF2⁺), 131 (71.53) (CH3OCF2CF2⁺), 147 (30.34) (CFCF3OCOF⁺), 169 (100.00) (C3F7⁺), 181 (88.48) (CH3OCF2CFCF3⁺), 347 (13.54) (CH3(OCF2CF(CF3))2⁺).
In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with DABCO (Aldrich, 1.812 g, 0.0160 mol, 1.00 equiv) and pre-dried (4 Å mol sieves, 24 h) methyl oligo(HFPO) ether, 181 (10.062 g, 0.0164 mol, 1.03 equiv). The heterogeneous mixture began to turn cloudy white after 5 min and the sealed vial was heated at 50°C with vigorous stirring in a pieblock. After 4 h at 50°C, the solution became transparent and homogenous with increasing viscosity. The reaction mixture was cooled to ambient temperature and placed in a glovebox. Spectroscopic analysis of the highly viscous liquid soluble in CH$_2$Cl$_2$ indicated full conversion of DABCO to 183 and 91.6% conversion of 181. Due to the inherent moisture sensitivity of perfluoroalkoxides, the reaction mixture could not be purified and was used as a solution 91.6% solution in 181.

$^1$H NMR (400 MHz, CD$_3$CN) δ 2.98 (s, CH$_3$, 3H), 3.12 (m, CH$_2$, 6H), 3.28 (m, CH$_2$, 6H). $^{13}$C NMR (101 MHz, CD$_3$CN) δ 45.50 (NCH$_2$, 3C), 51.88 (t, CH$_3$, $^1$J$_{CN}$ = 4.8 Hz, 3C), 45.58 (t, CH$_2$N$^+$, $^1$J$_{CN}$ = 3.34 Hz, 3C), (fluorinated carbons not observed). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -144.37 (m, repeat unit CF, 1.90 F), -136.68 (m, ω-CF, 1F), -129.08 (m, α-CF$_2$, 2F), -90.04 – -71.07 (m, CF$_3$, CF$_2$, 18.67F), -25.45 (s, CF$_2$O, 2F).

Synthesis of 1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium oligo(HFPO) perfluoroalkoxide, 183

In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with DABCO (Aldrich, 1.812 g, 0.0160 mol, 1.00 equiv) and pre-dried (4 Å mol sieves, 24 h) methyl oligo(HFPO) ether, 181 (10.062 g, 0.0164 mol, 1.03 equiv). The heterogeneous mixture began to turn cloudy white after 5 min and the sealed vial was heated at 50°C with vigorous stirring in a pieblock. After 4 h at 50°C, the solution became transparent and homogenous with increasing viscosity. The reaction mixture was cooled to ambient temperature and placed in a glovebox. Spectroscopic analysis of the highly viscous liquid soluble in CH$_2$Cl$_2$ indicated full conversion of DABCO to 183 and 91.6% conversion of 181. Due to the inherent moisture sensitivity of perfluoroalkoxides, the reaction mixture could not be purified and was used as a solution 91.6% solution in 181.

$^1$H NMR (400 MHz, CD$_3$CN) δ 2.98 (s, CH$_3$, 3H), 3.12 (m, CH$_2$, 6H), 3.28 (m, CH$_2$, 6H). $^{13}$C NMR (101 MHz, CD$_3$CN) δ 45.50 (NCH$_2$, 3C), 51.88 (t, CH$_3$, $^1$J$_{CN}$ = 4.8 Hz, 3C), 45.58 (t, CH$_2$N$^+$, $^1$J$_{CN}$ = 3.34 Hz, 3C), (fluorinated carbons not observed). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -144.37 (m, repeat unit CF, 1.90 F), -136.68 (m, ω-CF, 1F), -129.08 (m, α-CF$_2$, 2F), -90.04 – -71.07 (m, CF$_3$, CF$_2$, 18.67F), -25.45 (s, CF$_2$O, 2F).

Synthesis of tetramethylammonium oligo(HFPO) perfluoroalkoxide, 184

In a glovebox, a flame-dried 60 mL Ace® Glass Pressure tube equipped with a PTFE magnetic stir bar and PTFE stopper with a pressure gauge was charged with pre-dried (4 Å mol sieves, 24 h) methyl oligo(HFPO) ether, 181 (10.023 g, 16.4 mmol, 1.00 equiv). The vessel was sealed and attached a stainless-steel metal vacuum line and charged with NMe$_3$ (1.927 g, 32.6 mol, 2.00 equiv). Upon warming to RT, the vessel was heated and sonicated in an oil bath at 50°C for 3.75 h at which point the reaction mixture was homogenous and viscous. The reaction mixture was cooled to RT and re-attached under the absolute exclusion of moisture via a Swagelok® quick connect back to the stainless-steel vacuum line and all of
the volatiles were removed in vacuo to afford 10.652 g of 184 as a off-white soft, solid (\(M_n = 670.11\) g mol\(^{-1}\), 97 % yield) with full conversion of 181.

\(^1\)H NMR (400 MHz, CD\(_3\)CN) \(\delta\) 3.15 (s, CH\(_3\), 12H). \(^{13}\)C NMR (101 MHz, CD\(_3\)CN) \(\delta\) 55.57 (t, CH\(_3\), \(J_{CH} = 4.08\) Hz, 4C) (fluorinated carbons not observed). \(^{19}\)F NMR (376 MHz, CD\(_3\)CN) \(\delta\) -144.40 (m, repeat unit CF, 1.78 F), -136.74 (m, \(\omega\)-CF, 1F), -129.06 (m, \(\alpha\)-CF\(_2\), 2F), -83.30 - -77.04 (m, CF\(_3\), CF\(_2\), 18.67F), -25.66 (s, CF\(_2\)O, 2F).

Preparation of Methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, 187

In a flame-dried 250-mL three-necked round-bottom flask equipped with an addition funnel, dry ice condenser, HFPO cylinder connected to a N\(_2\) sparging assembly was added a commercially available 25% (m/v) NaOMe solution in MeOH (Aldrich #13525LA, 220-mL, 55 g NaOMe, 1.02 mol, 1.50 equiv). To the stirring solution of NaOMe at \(-10^\circ\)C was added HFPO 161 (113 g, 0.681 mol, 1.00 equiv) over a period of 4 h affording two-phases. The reaction was quenched by adding 1 L ice-cold deionized H\(_2\)O and separated the organic layer which was subsequently extracted three times with 75-mL CH\(_2\)Cl\(_2\) and the fractions dried over MgSO\(_4\) for 1 h. The solution was concentrated to half the volume by means of a rotary evaporator followed by a simple distillation at 760 mmHg, collecting the fraction with b.p. range of 119\(^\circ\)C to 120.5\(^\circ\)C under a N\(_2\) atmosphere to furnish 64.484 g of 187 as a colourless liquid (49.8% isolated yield and >99% by GC/MS).

Spectroscopic data and assignment consistent with that previously reported:\(^{[75]}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.58 (d, CFOX\(_3\), \(J_{HF} = 1.25\) Hz, 3H), 3.92 (s, COOCH\(_3\), 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 53.33 (bs, COOCH\(_3\) and OCH\(_3\), 2C), 104.43 (dq, CF, \(J_{CF} = 244.4\) Hz, \(J_{CF} = 36.2\) Hz, 1C), 119.16 (qd, CF\(_3\), \(J_{CF} = 285.2\), \(J_{CF} = 34.2\) Hz, 1C), 161.70 (d, CO\(_2\), \(J_{CF} = 37.5\) Hz, 1C) \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -135.22 (bs, CF, 1F), -80.99 (bs, CF\(_3\), 3F). EIMS, 70 eV, m/z (rel. int.): 59.10 (54.55) (COOCH\(_3^+\)), 69 (43.20) (CF\(_3^+\)), 131 (100.00) (CH\(_3\)OCFCF\(_3^+\)), 171 (0.77) (M\(^+\)-19), 190 (<1) (M\(^+\)).
Preparation of Tetraalkylammonium 1,1,1,2-Tetrafluoro-3-methoxy-3-oxopropan-2-olates, 187a–e

![187b](image1.png)

**Preparation of N,N-diethyl-N-methylethanaminium 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate, 187b:** In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with anhydrous triethylamine (0.963 g, 9.52 mmol, 1.00 equiv) and pre-dried methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, 187 (2.243 g, 11.8 mmol, 1.24 equiv). The reaction vessel was sealed and heated at 50°C with stirring for 48 h and then cooled to RT. The resulting precipitate was collected under vacuum in a glovebox and washed three times with anhydrous hexanes on a fritted-filter and the volatiles removed under vacuum (1 torr for 1 h) to afford the title compound 187b as white crystalline solid (1.019 g, 36.8% yield) as reported in Table 4.8.

**1H NMR** (400 MHz, CD$_3$CN) δ 1.26 (tt, $^3J_{HH} = 7.28$ Hz, $^2J_{HN} = 1.93$ Hz, 9H), 2.93 (s, N–CH$_3$, 3H), 3.32 (q, CH$_2$, $^3J_{HH} = 7.3$ Hz, 6H), 3.48 (d, OCH$_3$, $^4J_{HF} = 1.4$ Hz, 3H).

**13C NMR** (101 MHz, CD$_3$CN) δ 7.66 (s, CH$_3$, 3C, 44.30 – 50.25 (t, CH$_2$, $^1J_{CN} = 4.33$ Hz, 3C), 53.31 (s, CH$_3$O, 1C), 56.15 (t, NCH$_3$, $^2J_{CN} = 2.88$ Hz, 3C), 107.04 (dq, CF, $^1J_{CF} = 245.7$ Hz, $^2J_{CF} = 32.3$ Hz, 1C), 121.88 (qd, CF$_3$, $^1J_{CF} = 284.1$, $^2J_{CF} = 37.2$ Hz, 1C), 161.35 (d, COO$^-$, $^2J_{CF} = 28.4$ Hz, 1C).

**19F NMR** (376 MHz, CD$_3$CN) δ -81.35 (d, CF$_3$, $^3J_{FF} = 3.7$ Hz, 3F) -127.51 (m, CF, 1F).

![187a](image2.png)

**Preparation of N,N,N-trimethyl-1-phenylmethanaminium 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate, 187a:** In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with anhydrous N,N-dimethylbenzylamine (1.370 g, 10.1 mmol, 1.0 equiv) and pre-dried methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, 187 (2.180 g, 11.5 mmol, 1.14 equiv). The reaction vessel was sealed and heated at 50°C with stirring for 48 h and then cooled to RT. The resulting precipitate was collected under vacuum in a glovebox and washed three times with anhydrous hexanes on a fritted-filter
and the volatiles removed under vacuum (1 torr for 1 h) to afford the title compound \(187a\) as white crystalline solid (2.656 g, 80.6% yield) as reported in Table 4.8.

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN)} \delta 3.13 (s, CH}_3, 9H), 3.52 (d, OCH}_3 \text{; } \text{J}_{HF} = 1.4 \text{ Hz, 3H), 4.66 (s, CH}_2, 2H), 7.36 - 7.82 (m, C}_6\text{H}_5, - 5H). \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN)} \delta 52.68 (t, CH}_3, \text{J}_{CN} = 3.94 \text{ Hz, 3C), 53.33 (s, CH}_3\text{O, 1C), 69.35 (t, CH}_2, \text{J}_{CN} = 2.47 \text{ Hz, 1C), 107.03 (dd, \text{J}_{CF} = 245.8 \text{ Hz, 2J}_{CF} = 32.3 \text{ Hz, 1C), 121.85 (dq, CF, \text{J}_{CF} = 284.1 \text{ Hz, 2J}_{CF} = 37.2 \text{ Hz, 1C), 128.65 (s, Ar}_\text{para, 1C), 129.62 (s, Ar}_\text{meta, 2C), 131.14 (s, Ar}_\text{ipso, 1C), 133.53 (s, Ar}_\text{ortho, 1C), 161.64 (d, COO}^-, \text{J}_{CF} = 28.6 \text{ Hz, 1C). \}

\[ ^19F \text{NMR (376 MHz, CH}_3\text{CN)} \delta -127.30 (bs, CF, 1F), -80.92 (bs, CF}_3, 3F). \]

Preparation of 2-(dimethylamino)-\(N,N,N,N\)-trimethylethan-1-aminium 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate, \(187c\): In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with anhydrous \(N,N,N,N\)-tetramethylethlenediamine (1.012 g, 8.71 mmol, 1.00 equiv) and pre-dried methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, \(187\) (2.092 g, 11.0 mmol, 1.26 equiv). The reaction vessel was sealed and heated at 50°C with stirring for 48 h and then cooled to RT. The resulting precipitate was collected under vacuum in a glovebox and washed three times with anhydrous hexanes on a fritted-filter and the volatiles removed under vacuum (1 torr for 1 h) to afford the title compound \(187c\) as white crystalline solid (2.507 g, 94.0% yield) as reported in Table 4.8.

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN)} \delta 2.23 (s, NCH}_3, 6H), 2.68 (tt, CH}_2\text{N, 3J}_{HH} = 8.1 \text{ Hz, 3J}_{HN} = 2.2 \text{ Hz, 2H), 3.21 (s, CH}_3, 9H), 3.49 (d, OCH}_3 \text{; } \text{J}_{HF} = 1.5 \text{ Hz, 3H), 3.52 (t, CH}_2\text{N, 3J}_{HH} = 6.0 \text{ Hz, 2H). \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN)} \delta 44.98 (s, CH}_3, 2C), 53.36 (s, CH}_3\text{O, 1C), 53.75 (t, CH}_3, \text{J}_{CN} = 4.04 \text{ Hz, 3C), 53.98 (s, CH}_2, 1C), 62.94 (t, \text{J}_{CN} = 2.90 \text{ Hz, 1C), 107.01 (dq, CF, \text{J}_{CF} = 245.6 \text{ Hz, 2J}_{CF} = 32.4 \text{ Hz, 1C), 121.83 (qd, \text{J}_{CF} = 284.2 \text{ Hz, 2J}_{CF} = 37.2 \text{ Hz, 1C), 161.63 (d, COO}^-, \text{J}_{CF} = 28.6 \text{ Hz). \}

\[ ^19F \text{NMR (376 MHz, CH}_3\text{CN)} \delta -127.30 (bs, CF, 1F), -80.92 (bs, CF}_3, 3F). \]
Preparation of 1,1,4-trimethylpiperazin-1-ium 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate, 187d: In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with anhydrous 1,4-dimethylpiperazine (1.088 g, 9.53 mmol, 1.00 equiv) and pre-dried methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, 187 (2.139 g, 11.3 mol, 1.19 equiv). The reaction vessel was sealed and heated at 50 °C with stirring for 48 h and then cooled to RT. The resulting precipitate was collected under vacuum in a glovebox and washed three times with anhydrous hexanes on a fritted-filter and the volatiles removed under vacuum (1 torr for 1 h) to afford the title compound 187d as an off-white crystalline solid (1.945 g, 67.1% yield) as reported in Table 4.8.

$^1$H NMR (400 MHz, CD$_3$CN) δ 2.33 (s, CH$_3$, 3H), 2.69 (m, CH$_2$N, 4H), 3.49 (d, OCH$_3$, $^4$J$_{HF}$ = 1.5 Hz, 3H). $^{13}$C NMR (101 MHz, CD$_3$CN) δ 44.76 (s, NCH$_3$, 1C), 48.63 (s, NCH$_2$-, 2C), 53.33 (s, CH$_3$O, 1C), 62.04 (t, N(CH$_3$)$_2$, $^1$J$_{CN}$ = 2.71 Hz, 2C), 107.00 (dq, CF, $^1$J$_{CF}$ = 245.8, $^2$J$_{CF}$ = 32.4 Hz, 1C), 121.82 (qd, $^1$J$_{CF}$ = 284.1 Hz, $^2$J$_{CF}$ = 37.3 Hz, 1C), 161.51 (d, COO$^-$, $^2$J$_{CF}$ = 28.5 Hz, 1C). $^{19}$F NMR (376 MHz, CH$_3$CN) δ -127.26 (bs, CF, 1F), -80.94 (bs, CF$_3$, 3F).

Preparation of 1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium 1,1,1,2-tetrafluoro-3-methoxy-3-oxopropan-2-olate, 187e: In a glovebox, an oven-dried 20 mL scintillation vial equipped with a stir bar was charged with anhydrous DABCO (0.959 g, 8.55 mmol, 1.00 equiv) and pre-dried methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate, 187 (2.405 g, 12.7 mol, 1.49 equiv). The reaction vessel was sealed and heated at 50 °C with stirring for 48 h and then cooled to RT. The resulting precipitate was collected under vacuum in a glovebox and washed three times with anhydrous hexanes on a fritted-filter and the volatiles removed under vacuum (1 torr for 1 h) to afford the title compound 187e as white crystalline solid (2.331 g, 90.2% yield) as reported in Table 4.8.

$^1$H NMR (400 MHz, CD$_3$CN) δ 3.03 (s, CH$_3$, 3H), 3.10 (t, $^3$J$_{HH}$ = 7.42 Hz, 6H), 3.38 (t, $^3$J$_{HH}$ = 7.6 Hz, 6H), 3.48 (d, OCH$_3$, $^4$J$_{HF}$ = 1.5 Hz, 3H). $^{13}$C NMR (101 MHz, CD$_3$CN) δ 45.54 (s, CH$_2$N, 3C), 51.63 (t, CH$_2$N$^+$, $^1$J$_{CN}$ = 4.60 Hz, 3C), 53.41 (d, OCH$_3$, $^3$J$_{CF}$ = 1.1 Hz, 1C), 54.33 (t, CH$_3$, $^1$J$_{CN}$ = 3.62 Hz, 1C), 107.04 (dq, CF, $^1$J$_{CF}$ = 245.6 Hz, $^2$J$_{CF}$ = 32.4 Hz, 1C), 121.84 (qd, CF$_3$, $^1$J$_{CF}$ = 284.3, $^1$J$_{CF}$ = 37.2 Hz), 161.76 (d, COO$^-$, $^2$J$_{CF}$ = 28.6 Hz, 1C). $^{19}$F NMR (376 MHz, CD$_3$CN) δ -127.26 (bs, CF, 1F), -80.94 (bs, CF$_3$, 3F).
4.13 References


Chapter 5

Global Conclusions and Prospects

5.0.1 Discovery that Hydrofluoroethers are Methylating Agents

Hydrofluoroethers (HFEs) are highly fluorinated versions of hydrocarbon ethers. These materials were touted as being non-flammable, non-toxic, and unreactive and therefore find use in a wide range of applications including refrigeration fluids, inhalation anesthetics, cosmetics, and lithium battery co-solvents. Despite their reported chemical inertness, we have reported for the first time a noteworthy degradation pathway for HFEs. Thus, rather than being inert, methyl HFEs (including the anaesthetic methoxyflurane) can be quite reactive, capable of methylating amines and phosphines under mild conditions in yields up to 99%. In addition, if the reaction products are exposed to water, hydrofluoric acid and toxic, volatile acyl fluorides are generated.


\[
\begin{align*}
\text{RCF}_2\cdot\text{O} & \quad \rightarrow \quad \text{CH}_3 \\
\text{R}^1\cdot\text{N}^\cdot\text{R}^2 & \quad \rightarrow \quad \text{RCF}_2\cdot\text{O}^\oplus \\
\text{R}^3 & \quad \rightarrow \quad \text{CH}_3 \\
\text{R}^2 & \\
\end{align*}
\]

When the above reaction is carried out under a nitrogen atmosphere, the sole reaction products are tetraalkylammonium perfluoroalkoxides bearing α-fluorines. In this fashion, 31 examples were isolated in 9 -99% yield in an operationally simple method with yields

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1References begin on page 273
commensurate with the nucleophilicity of the amine and the number of fluorinated carbons in the hydrofluoroether. In each case, characterization of the isolated products was carried out by a range of spectroscopic techniques including SC-XRD constituting the largest number of examples for this underrepresented class of compounds. This was significant since the only prior way to prepare perfluoroalkoxides was shifting the equilibrium between a reaction of anhydrous fluoride and corresponding acyl fluoride or ketones. This requires working with very hazardous and volatile fluorinated gases, and often the products are only prepared in situ and revert back to their starting materials.

The general methodology presented in Chapter 2 thus opens up a new frontier for a fluorinated functional group which previously had few examples and was very difficult to synthesize. These materials are isolable, the NMe₄⁺ salts are thermally stable (to 180°C in the absence of moisture), and react with benzyl bromides to form perfluoropropoxy benzyl ethers. Alternatively, hydrofluoroethers can be considered a fairly robust protecting group for the otherwise highly moisture sensitive and valuable perfluoroacyl moiety that can be simply deprotected under facile conditions (less than 50°C) with an unhindered tertiary amine in high conversion. In addition, the reactivity of hydrofluoroethers was briefly extended to secondary amines and other Group 15 nucleophiles. In a similar manner to hydrofluoroethers CH₃OCF₃ 1 to CH₃OC₄F₉ 4, the preliminary studies of methoxyfluorane is consistent with the work of Kharasch in 2006 for the in vivo O-demethylation pathway of the inhalation anaesthetic, methoxyfluorane.

At first glance, perfluoroalkoxides may seem mundane but upon close inspection, the realization that these materials challenge both spectroscopic and bonding models provides a much deeper discussion. As such, perfluoroalkoxides have an unaccounted for fluxional process which initially obscures fine splitting in the NMR spectra until solutions are subject to low temperatures (below −28°C). Thus we note that through-space ¹⁹F-¹⁹F spin spin coupling has a greater effect than the expected through-bond coupling consistent with other small rigid fluorinated molecules. Furthermore, we discuss competing theories for the spectroscopic conundrum for the bonding in the C–O and α-C–F bond of perfluoroalkoxides. We highlight the value in Gillespie’s ligand close-packing model to understand and to predict geometric parameters consistent with the claim that perfluoroalkoxides can be surprisingly considered pentavalent, four-coordinate species. These species can be alternatively viewed as resonance between ionic and covalent resonance structures.

5.0.2 Towards Trifluoromethoxylation of Arenes

Having developed a method for the preparation of tetraalkylammonium perfluoroalkoxides, two highly-relevant applications were surveyed in subsequent chapters. In the first
case, there is a high demand for new methodology for incorporating OCF$_3$ moiety into organic frameworks which has been demonstrated to immensely benefit the development of liquid crystal displays, improves stability and uptake of biologically-active drugs, and furthers the design of agriculture crop protection agents. One of the biggest challenges was thought to be ease of accessing thermally stable perfluoroalkoxides. While working with tetraalkylammonium perfluoroalkoxides such as NMe$_4$OCF$_3$ is much improved over existing perfluoroalkoxides and as such can be readily prepared, easily handled, and safely stored in a glovebox without any special techniques, an extensive survey of both metal and non-metal-mediated pathways trifluoromethoxylation of arenes was largely found to be unsuccessful.

Early transition metals with high M-F bond dissociation energy immediately undergo $\beta$-fluoride elimination while late transition metals bearing sterically unhindered ancillary phosphines can be susceptible to unproductive fluorination of the ligand centre. Furthermore, by considering traditional cross-coupling methods with state-of-the-art Ni$^{0}$-Ni$^{II}$, Pd$^{0}$-Pd$^{II}$, Cu$^{1}$-Cu$^{III}$, Ag$^{I}$-Ag$^{II}$, and Au$^{I}$-Au$^{III}$ manifolds with various aryl substrates led predominately to fluorination over trifluoromethoxylation. While these metal systems are known to be highly active towards poor nucleophiles and in certain cases the low-valent [M]–OCF$_3$ are readily prepared, $\beta$-fluorination from the coordinated OCF$_3$ outcompetes C–O bond formation in higher valent oxidation states at temperatures necessary for reductive elimination. Rather, an alternative approach not yet applied to aryl trifluoromethoxylation has been recently communicated by Liu.$^{[1]}$ Hence, C–OCF$_3$ bond formation can be carried out with a Pd$^{II}$-Pd$^{IV}$ by preventing $\beta$-fluoride elimination from a coordinatively saturated metal centre. While the lower redox manifold was addressed here, in retrospect, transition metal-mediated protocols should address pathways involving [Ar–M–OCF$_3$] whereby the metal intermediate is coordinately saturated in it’s highest oxidation state regardless of the high electropositive nature of the metal centre.

At the time, to prevent $\beta$-fluoride elimination from electrophilic metals and secondly to prepare a convenient bench-stable reagent bearing a transferable-OCF$_3$ group that are not moisture sensitive, we pursued non-metal-mediated synthetic strategies and precursors. While low conversions of perfluoroalkoxylation was obtained with pseudo-cationic aryls such as diaryliodoniums, these substrates are not particularly amenable to a broad substrate scope and are furthermore not operationally simple procedures, both principles goal for Chapter 3. Despite designing protocols based on successful F$^-$ and F$_3$CS$^-$ transfer reagents including the imidazolium core of PhenoFluor® and hypervalent iodine reagents, we found little success due to either poor nucleophilicity of $\cdot$OCF$_3$ or $\beta$-elimination to generate the fluoroiodinane. However, reagents such as the revised thioperoxide do hold promise in generating a bench-stable reagent that may enable radical trifluoromethoxylation similar to Shen$^{[2]}$ and Buchwald.$^{[3]}$ Furthermore, preparing R$_3$N–OCF$_3$ reagents by substitution of R$_3$N–X
precursors as Rueping has successfully done with \( N \)-(trifluoromethylthio)phthalimides\[^{[4,5]} \]
are better accessed by the O-trifluoromethylation of \( R_2\text{NOH} \) precursors,\[^{[6]} \] methodology that is outside the scope of this dissertation but remain an attractive approach toward this goal.

### 5.0.3 Polymerization of Hexafluoropropylene Oxide

Lastly, DuPont had been preparing a range of high-temperature lubricants since the early 1960’s under the trade name Krytox®. These polymers are prepared from the anionic ring-opening polymerization of a fluorinated epoxide and are important lubricants for extreme applications including jet engines, space technology and wind turbines. Since the polymerization process generates an \textit{in situ} perfluoroalkoxide, it was hoped that tetraalkylammonium perfluoroalkoxides would reduce the \( \text{F}^- \) initiated chain transfer mechanism through increased solubility of the cation and a lower lattice energy of a resulting fluoride. This would both improve the efficiency in polymerization process and provide new opportunities in the functionalization of polymeric products.

While these perfluoroalkoxides did not outperform the industry optimized CsF/tetraglyme conditions, it was demonstrated that tetraalkylammonium perfluoroalkoxides \textit{prepared in a fluoride-free fashion} can ring-open HFPO, provide a direct study of the cation, and a means to measure chain transfer. The lower efficiency of tetraalkylammonium fluorides over alkali metals may be related the hydrogen bonding abilities of the \( \alpha \)-hydrogens of tetraalkylammonium salts which would require designing cations with a limited number of available sites. Furthermore, the chain transfer process is likely a multi-faceted problem and unto now, methods to prevent phase separation during oligomerization have not been attempted. While only initial synthetic efforts were undertaken to design oligio(HFPO) terminated ethylene glycol surfactants or soluble oligio(HPFO) hydrofluoroethers, the latter method extends the methylation ability of HFEs. Based on the results herein, it has been proposed that higher \( D\overline{F}_n \) oligomers may offer the best opportunity for liquid oligio(HFPO) perfluoroalkoxides which may act as their own solvent negating the use polar organic so-solvents which cause phase separation.

### 5.1 Conclusion

This thesis presents a survey for the preparation and reactivity of the perfluorinated alkoxide functional group, \( \cdot\text{RCF}_2\text{O}^- \), which is dissimilar to its non-fluorinated hydrocarbon analogue in both preparation and stability. Prior to our efforts, but yet recently, the trifluoromethoxy group (and by extension all perfluoroalkoxides bearing \( \alpha \)-fluorines) was
stated to be perhaps the least well understood fluorine substituent. While much work remains to address the full scope in both regards, the work disclosed herein presents new advances in the preparation and utility of perfluoroalkoxides towards both aryl trifluoromethoxylation and polymerization of perfluorooxiranes.
5.2 References


Appendix A

Spectra of Trifluoromethoxides

Fig. A.1. $^1$H NMR (500 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoromethoxide, 1a
Fig. A.2. $^{19}$F NMR (471 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoromethoxide, 1a

Fig. A.3. $^1$H NMR (600 MHz, CD$_2$Cl$_2$) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoromethoxide, 1g
Fig. A.4. $^{19}F$ NMR (471 MHz, CD$_2$Cl$_2$) spectrum of N,N,N-trimethyl-1-phenylmethanaminium perfluoromethoxide, 1g

Fig. A.5. $^1$H NMR (500 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoromethoxide, 1h
Fig. A.6. $^{13}$C NMR (126 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoromethoxide, 1h

Fig. A.7. $^{19}$F NMR (471 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoromethoxide, 1h
Appendix B

Spectra of Perfluoroethoxides
Fig. B.1. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoroethoxide, 2a

Fig. B.2. $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoroethoxide, 2a
**Fig. B.3.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoroethoxide, 2a
Fig. B.4. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoroethoxide, 2f

Fig. B.7. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoroethoxide, 2h
**Fig. B.5.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoroethoxide, 2f

**Fig. B.8.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoroethoxide, 2h
**Fig. B.6.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoroethoxide, 2f

**Fig. B.9.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoroethoxide, 2h
Fig. B.10. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 2-(dimethylamino)-$N,N,N$-trimethylethan-1-aminium perfluoroethoxide, 2i
**Fig. B.11.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 2-(dimethylamino)-$N,N,N$-trimethylethane-1-aminium perfluoroethoxide, $2i$

**Fig. B.12.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 2-(dimethylamino)-$N,N,N$-trimethylethane-1-aminium perfluoroethoxide, $2i$
Fig. B.13. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1,1,4-trimethylpiperazin-1-ium perfluoroethoxide, 2j

Fig. B.14. $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 1,1,4-trimethylpiperazin-1-ium perfluoroethoxide, 2j
**Fig. B.15.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1,1,4-trimethylpiperazin-1-ium perfluoroethoxide, $2j$

**Fig. B.16.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1-methyl-1,4-diazabicyclo[2.2.2]-octan-1-ium perfluoroethoxide, $2k$
**Fig. B.17.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium perfluoroethoxide, 2k

**Fig. B.18.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium perfluoroethoxide, 2k
Fig. B.19. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of methoxyflurane (Penthrane ®), 35
Fig. B.20. $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of methoxyflurane (Penthrane®), 35

Fig. B.21. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of methoxyflurane (Penthrane®), 35
Appendix C

Spectra of Perfluoropropoxides

Fig. C.1. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of methoxy heptafluoropropane, HFE-7000, 3
**Fig. C.2.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of methoxy heptafluoropropane, HFE-7000, 3

**Fig. C.3.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of methoxy heptafluoropropane, HFE-7000, 3
Fig. C.4. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoropropoxide, 3a

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Fig. C.5. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of tetramethylammonium perfluoropropoxide, 3a
Fig. C.6. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N$-diethyl-$N$-methylethanaminium perfluoroproxide, 3b
Fig. C.7. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N,N$-diethyl-$N$-methylethanaminium perfluoropropoxide, 3b

Fig. C.8. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N$-methyl-$N,N$-dipropylpropan-1-aminium perfluoropropoxide, 3c
**Fig. C.9.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N$-methyl-$N,dipropylpropan-1-aminium perfluoropropoxide, **3c**

**Fig. C.10.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N$-dibutyl-$N$-methylbutan-1-aminium perfluoropropoxide, **3e**
Fig. C.11. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of N,N-dibutyl-N-methylbutan-1-aminium perfluoropropoxide, 3e
**Fig. C.12.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoropropoxide, 3f

**Fig. C.13.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoropropoxide, 3f
Fig. C.14. $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of the perfluoroalkoxide region of $N,N,N$-trimethyl-1-phenylmethanaminium perfluoroproxide, 3f
Fig. C.15. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of N,N,N-trimethyl-1-phenylmethanaminium perfluoropropoxide, 3f

Fig. C.16. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 4,4-dimethylmorpholin-4-ium perfluoropropoxide, 3g
**Fig. C.17.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 4,4-dimethylmorpholin-4-ium perfluoropropoxide, 3g

**Fig. C.18.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoropropoxide, 3h
**Fig. C.19.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoropropoxide, 3h

**Fig. C.20.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium perfluoropropoxide, 3h
Fig. C.21. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 2-(dimethylamino)-N,N,N-trimethylethan-1-aminium perfluoropropoxide, 3i

Fig. C.22. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 2-(dimethylamino)-N,N,N-trimethylethan-1-aminium perfluoropropoxide, 3i
Fig. C.23. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1,1,4-trimethylpiperazin-1-ium perfluoropropoxide, 3j

Fig. C.24. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1,1,4-trimethylpiperazin-1-ium perfluoropropoxide, 3j
**Fig. C.25.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium perfluoropropoxide, 3k

**Fig. C.26.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1-methyl-1,4-diazabicyclo-[2.2.2]-octan-1-ium perfluoropropoxide, 3k
**Fig. C.27.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 4-(dimethylamino)-1-methylpyridin-1-ium perfluoropropoxide, 3n

**Fig. C.28.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 4-(dimethylamino)-1-methylpyridin-1-ium perfluoropropoxide, 3n
Fig. C.29. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of tetramethylphosphonium perfluoropropoxide, 3o

Fig. C.30. $^1$H{$^{31}$P} NMR spectrum of tetramethylphosphonium perfluoropropoxide, 3o
**Fig. C.31.** $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of tetramethylphosphonium perfluoropropoxide, 3o

**Fig. C.32.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of tetramethylphosphonium perfluoropropoxide, 3o
Fig. C.33. $^{31}\text{P}$ NMR spectrum of tetramethylphosphonium perfluoropropoxide, 3o

Fig. C.34. $^{31}\text{P}^{\{1\text{H}\}}$ spectrum of tetramethylphosphonium perfluoropropoxide, 3o
Appendix D

Spectra of Perfluorobutoxides

Fig. D.1. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of methoxy nonafluoropropane, HFE-7100, 4
Fig. D.2. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of methoxy nonafluorobutane, HFE-7100, 4

Fig. D.3. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of tetramethylammonium $n$- and iso-perfluorobutoxide, 4a
Fig. D.4. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of tetramethylammonium $n$- and iso-perfluorobutoxide, 4a

Fig. D.5. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of N,N-diethyl-N-methylethanaminium $n$- and iso-perfluorobutoxide, 4b
**Fig. D.6.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N,N$-diethyl-$N$-methylethanolaminium $n$- and iso-perfluorobutoxide, 4b

**Fig. D.7.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N$-methyl-$N,N$-dipropylpropan-1-aminium $n$- and iso-perfluorobutoxide, 4c
**Fig. D.8.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of N-methyl-$N,N$-dipropylpropan-1-aminium $n$- and iso-perfluorobutoxide, 4c

**Fig. D.9.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N$-dibutyl-$N$-methylbutan-1-aminium $n$- and iso-perfluorobutoxide, 4e
Fig. D.10. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N,N$-dibutyl-$N$-methylbutan-1-aminium $n$- and iso-perfluorobutoxide, 4e

Fig. D.12. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium $n$- and iso-perfluorobutoxide, 4f
Fig. D.11. $^1$H NMR (400 MHz, CD$_3$CN) spectrum of $N,N,N$-trimethyl-1-phenylmethanaminium $n$- and iso-perfluorobutoxide, 4f

Fig. D.13. $^1$H NMR (400 MHz, CD$_3$CN) of 4,4-dimethylmorpholin-4-ium $n$- and iso-perfluorobutoxide, 4g
**Fig. D.14.** $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 4,4-dimethylmorpholin-4-ium $n$- and iso-perfluorobutoxide, $4g$.

**Fig. D.15.** $^1$H NMR (400 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium $n$- and iso-perfluorobutoxide, $4h$. 
Fig. D.16. $^{13}$C NMR (101 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium $n$- and iso-perfluorobutoxide, 4h

Fig. D.17. $^{19}$F NMR (376 MHz, CD$_3$CN) spectrum of 1-methylquinuclidinium $n$- and iso-perfluorobutoxide, 4h
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* NMe$_4^+$

* CH$_2$Cl$_2$
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