Fluorinated hypervalent sulfur compounds in synthesis

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Fluorinated Hypervalent Sulfur Compounds in Synthesis

by

Cortney N. von Hahmann

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Abstract

The polar and steric effects of pentafluorosulfanyl (SF₅) substitution on selectivity and reactivity were investigated in the ketene imine [2+2] cycloaddition reaction. The kinetic resolution of racemic aldimines rely on the stereocontrol of cyclization by dipolar substituent effects. Functionalized SF₅-bearing β-lactams are used in the preparation of conformationally constrained SF₅-containing β-amino acids and peptides, in the study of novel antibacterial agents and in the design of new β-lactamase inhibitors.

Trifluoromethyl-λ⁶-tetrafluorosulfanes are prepared by chemically initiated radical addition processes that will enable exploration of the effect of the CF₃SF₄ group on reactivity and conformation. The diminished dipole and electron withdrawing effects as well as the hydrophobicity of the CF₃SF₄ group will be used to systematically investigate the influence of CF₃SF₄-substitution on the secondary structure of peptides.
Dedication

To my parents and sister..
Acknowledgements

I would like to express my deepest appreciation to my academic professor, research advisor, and mentor, Professor John T. Welch. I am forever grateful that he taught an extra class so that during my last semester as a master’s student at the University at Albany, I could benefit from such a relevant topic to my career before graduating. Additionally, I am extremely appreciative that he noticed my work as an undergraduate and for his confidence on my research contributions, so much that he was willing to present my results at an international conference within my first year after joining his group. Encouraging me to attend the fluorine conferences where he has introduced me to famous and renowned chemists has contributed a great deal to my achievements. Winning the Moissan Fellowship, working in a fluorine lab abroad for Professor David O’Hagan at the University of St. Andrews in Scotland, and being offered a position to work toward my PhD with Professor Thomas Braun at Humboldt University in Berlin, Germany are only the beginning of a successful career. Just as the simple things in the lab made me fall in love with chemistry, the littlest conversations are the most memorable to me. He has spent a countless number of hours giving me advice about the United Kingdom for my studies abroad in 2013 and he continues to bring up maps of Germany to this day to prepare for my trip this summer. He has been the single-most influential person in my academic career thus far. Thank you, Professor Welch, for acknowledging my “talents” and being such an exceptional mentor.

I would like to extend my gratitude to Professor Maksim Royzen, for his help in Advanced Organic Chemistry class and invaluable advice about choosing a PhD school.

I would like to express my sincere thanks to the members of Professor Welch’s research group for all of the assistance and support in the past 3 years. This group feels like family and the laboratory is my second home. Especially patient with me explaining techniques and theories were Dr. Alexander Penger, Mr. Kelly Boss, Mr. Paul Savie and Mr. Linbin Zhong.
Finally, all of the other faculty and staff in the chemistry department have been so encouraging and assisted me in a countless number of ways during my education.
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Chapter 1

1. Introduction:

1.1 Properties of fluorine:

Introduction of fluorine to potential drug targets has become a ubiquitous practice in drug discovery. The inclusion of fluorine in a molecule may not only change the physical properties dramatically, it can have a powerful effect on the pharmacology of the molecule.\(^1\) While the inductive effects of fluorine have been known for some time, fluorinated molecules are also more lipophilic and therefore readily cross cell membranes resulting in increased bioavailability.\(^1\) Fluorinated molecules also have enhanced metabolic stability, most notably due to the reduced susceptibility of nearby moieties to oxidation by cytochrome P450.\(^2\) Fluorine can effect binding, selectivity and ligand affinity at the molecular level.\(^3\) As a result of these effects, nearly 20% of current pharmaceuticals and 30% of agrochemicals include fluorine, a fraction that will likely continue to increase.\(^4\) Some notable examples include the antidepressant fluoxetine (Prozac),\(^5\) cholesterol lowering atorvastatin (Lipitor),\(^6\) and the antibacterial ciprofloxacin (Ciprobay)\(^7\) (Fig. 1).
Fluorine is most commonly employed in pharmaceutics either as an aromatic substituent, or by introduction of a trifluoromethyl moiety to the active agent. Fluorine is only slightly larger than hydrogen, yet the carbon-fluorine bond is longer than a typical carbon-hydrogen bond by about 0.4 Å, approximately the same length as a carbon-oxygen bond. As a consequence inclusion of fluorine in a molecule changes the overall steric demand insignificantly in most applications. Due to the high reactivity, poor selectivity, and safety concerns, the use of elemental fluorine is often impractical. Several reagents have been developed to enable nucleophilic fluorination, such as DAST, DFI, pyridinium poly(hydrogen fluoride), and Deoxofluor. Commercially available electrophilic fluorinating reagents have been developed including Selectfluor, and NFSI. Incorporation of trifluoromethyl groups may be obtained by the use of TMSCF₃, or a number of trifluoroacetamides (Fig. 2). Despite the number of fluorinating
reagents available, incorporation of fluorine is not trivial, and many of these reagents are too expensive for commercial applications.

Figure 2. Examples of fluorinating reagents.

1.3 Biological Applications:

The fluorination of biologically active molecules increases their membrane permeability and hydrophobic binding stability, all the while improving the overall pharmacological properties. β-Lactam antibiotics can be especially responsive to fluorination. The activity of the β-lactam antibiotics depends on the irreversible inhibition of bacterial cell wall synthesis. This inhibition is a consequence of the reactivity of the β-lactam ring, where the reactivity is derived from ring strain and strongly electron attracting ring substituents. The introduction of fluorine or a fluoroalkyl group to the β-lactam ring can be anticipated to influence not only the lipophilicity or metabolic stability of the ring but can also afford an entrée to the preparation of fluorinated β-amino acids.
1.4. Fluorinated hypervalent sulfur compounds:

The pentafluorosulfanyl (SF₅) group is one of the few truly new functional groups to be introduced to synthetic organic chemistry in the last 100 years. Although the chemistry of the pentafluorosulfanyl group is very much in its infancy, the unique electron withdrawing effects and lipophilicity of the SF₅ group may deliver the desired effects of fluorination while mitigating undesirable aspects such as antigenicity.

$\lambda^6$-Pentafluorosulfanes or $\lambda^6$-tetrafluorosulfanes present sulfur in a pseudo-octahedral geometry. With SF₅, a square pyramid of sulfur-bound fluorines occupy a volume slightly less than that of a tert-butyl group. The electron density of the fluorines, in addition to the large dipole moment of the carbon-SF₅ bond, may result in substituent effects, particularly in reactions sensitive to polar effects. Fluorinated sulfur substituents can influence the acidity and the steric accessibility of adjacent protons as well as the conformation of neighboring functional groups.

The paucity of hypervalent fluorinated sulfur-containing materials is a result of the inaccessibility of reagents for the introduction of SF₅, the absence of general methods for the preparation of either SF₅- or SF₄-containing molecules and the lack of functionalized SF₅- or SF₄-containing building blocks. As a result of these challenges, relatively little is known about how to control or utilize the reactivity of SF₅- or SF₄- containing aliphatic molecules.

The hypotheses that I’ve tested in my research are; 1) A combination of the steric effects and novel electrostatic interactions of the pentafluorosulfanyl unit can direct the stereochemistry of reactions and the conformation of products of interest to medicinal chemists and materials scientists 2) Comparison of the diminished dipole
and the greater occupied volume of trifluoromethyl-$\lambda^6$-tetrafluorosulfanyl group-containing amino acids and peptides with SF$_5$-substituted peptides and amino acids will enable discrimination between the steric and dipolar effects of substitution.
Chapter 2

Pentafluorosulfanyl-substitution

2. Introduction

2.1 Why SF$_5$ Research? The Importance of the Unique Properties of the SF$_5$ Group.

In Life Sciences Research. The key physical properties of the SF$_5$ substituent are only beginning to be elucidated. Since 2000, SF$_5$-substituted materials were described in 325 patents, in the preceding 38 years only 75 patents were reported. With a substantial occupied volume, a relatively even distribution of charge at the group surface as well as a large group dipole moment, SF$_5$ substitution can lead to an archetypal demonstration of polar hydrophobicity.[9] The profound influence of the SF$_5$ group on molecular conformation was demonstrated by heptapeptide coiling,[10] enabling even small molecules to present essential binding epitopes (Fig. 3).

![Diagram of heptapeptide sequence](image)

Figure 3. Heptapeptide sequence designed to test the propensity of SF$_5$-nordehydroleucine molecules to assume an $\alpha$-helix.
Even with poorly defined receptor geometries such as that associated with the 5-hydroxytryptamine (5-HT, serotonin) family of receptors, SF₅ substitution led to distinctive binding patterns.[¹¹]

The steric demand and square pyramidal array of fluorines of the SF₅ group can influence optimal ligand binding by constraining the geometry of adjacent polar functional groups and pendant alkyl chains, thereby diminishing the conformational freedom of the ligand.[¹²] Concurrently, immunogenicity resulting from antigen formation by metabolic, mechanism-based dehydrofluorination is not possible with an SF₅ group. Dehydrofluorination involving SF₅ groups most commonly leads to hydrolytic formation of relatively benign sulfonic acids.

*In Materials Science.* A major limitation of fluorinated organics is persistence in the environment and consequent bioaccumulation.[¹³] Environmental degradation studies of SF₅–substituted molecules indicate that degradative pathways lead to environmentally benign products such as sulfonyl fluorides compared to CF₃-substituted molecules which form difluoromethylene groups that might covalently inhibit an enzyme by Michael addition.[¹⁴] The profound dipole moment of fluorinated hypervalent sulfur compounds has been utilized in liquid crystal design.[¹⁵] The introduction of SF₅ in high-performance polymers lends lubricant and oil resistance properties, improves protective surface coatings, and enhances insulating properties.[¹⁶] A variety of polymeric systems prepared from SF₅-containing olefins,[¹⁷] SF₅-substituted acrylates[¹⁸] and silanes[¹⁹] are characterized by robust thermal and chemical stability as well as high hydrophobicity.

*In Basic Chemical Science.* The influence of the SF₅ group on conformation and reactivity is only beginning to be understood. Selective fluorination can effectively
control conformation;\textsuperscript{[20]} however the orbital interactions of perfluoroalkyl groups analogous to the SF\textsubscript{5} moiety have relatively limited impact. With the SF\textsubscript{5} group, control of the geometry of both neighboring polar groups such as alcohols\textsuperscript{[12b]} and alkyl chains\textsuperscript{[12a]} has been observed, with electronic effects important in the first case and steric effects in the second.

From our preliminary results there is evidence for the importance of polar and field effects on reactions involving SF\textsubscript{5}-containing reactants. Stereoselectivity is influenced by destabilizing interactions of the substituent dipole and developing charges in the transition state.\textsuperscript{[21]} In the Staudinger reaction, the SF\textsubscript{5} group has a profound influence on the diastereofacial selectivity of the imine on cyclization. While the origin of this effect is not yet clear, the electrostatic influence of the SF\textsubscript{5} group would be greatest in processes with asynchronous transition states and greater charge separation\textsuperscript{[22]} such as that found in the ketene-imine cycloaddition of fluoroketene.\textsuperscript{[23]}

2.2 SF\textsubscript{5} Background

2.2.1 SF\textsubscript{5} Electronic and Steric Effects

λ\textsuperscript{6}-Pentafluorosulfanes or λ\textsuperscript{6}-tetrafluorosulfanes present sulfur in a pseudoctahedral geometry. With SF\textsubscript{5}, a square pyramid of sulfur-bound fluorines occupies a volume somewhat less than that of a tert-butyl group. The electron density associated with the fluorines, in addition to the large dipole moment of the carbon-SF\textsubscript{5} bond, may result in long range substituent effects, particularly in reactions sensitive to polar effects. Fluorinated sulfur substituents can influence the acidity and the steric accessibility of adjacent protons as well as the conformation of neighboring functional groups.
The relative steric demand of the SF$_5$ group, slightly less than that of a t-butyl group,$^{[24]}$ can be compared and contrasted with the CH$_3$, CF$_3$ and CF$_3$SF$_4$ groups. (Fig. 4) The associated dipole moment of SF$_5$ group is the largest and the CF$_3$SF$_4$ group is the most sterically demanding.

<table>
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<th>Connolly volume:</th>
<th>Connolly surface:</th>
<th>Dipole:</th>
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<tr>
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<tr>
<td>CF$_3$SF$_4$-methane</td>
<td>138.93 Å$^3$</td>
<td>156.76 Å$^2$</td>
<td>2.301 Debye</td>
</tr>
</tbody>
</table>

Figure 4. Relative volumes, areas and dipoles C$_2$H$_6$, CF$_3$CH$_3$, SF$_5$CH$_3$ and CF$_3$SF$_4$CH$_3$

2.2.1.1 Influence of the SF$_5$ group on reactivity: Dipole moment and electron rich Connolly surface. The SF$_5$ electrostatic potential surface is greater than that of CF$_3$ and, in addition, the square pyramid defined by fluorine is inverted relative to the trigonal pyramid of CF$_3$. The electron-withdrawing effect of a SF$_5$ group is of similar magnitude to that of a CF$_3$ group as assessed by the carbon 1s photoelectron spectra.$^{[25]}$ $^{[26]}$ The electronegativity of the SF$_5$ group, 3.65, is slightly higher than that of the CF$_3$ group, 3.36.$^{[27]}$ The decreased resonance and increased inductive contributions to Hammett $\sigma_p$ with a $\sigma_I$ value for SF$_5$ of 0.55 and a $\sigma_R$ value of 0.11$^{[28]}$ in contrast to $\sigma_I$ value for CF$_3$ of 0.39 and a $\sigma_R$ value of 0.12.$^{[29]}$ The SF$_5$ group was also shown to dramatically increase the acidity of a proton on an adjacent carbon as would be consistent with the greater dipole.$^{[30]}$ The stability of the resulting anion toward loss of fluoride ion was, in part, dependent upon the counterion.$^{[30a]}$ Prior explorations of the
organic chemistry of the SF$_5$ group$^{[24, 31]}$ did not generally address the influence of the SF$_5$ group on reactivity and selectivity.

The paucity of hypervalent fluorinated sulfur-containing materials is a result of the inaccessibility of reagents for the introduction of SF$_5$, the absence of general methods for the preparation of either SF$_5$- or SF$_4$-containing molecules and the lack of functionalized SF$_5$- or SF$_4$-containing building blocks. As a result of these challenges, relatively little is known about how to control or utilize the reactivity of SF$_5$- or SF$_4$- containing aliphatic molecules.

2.2.1.2 Steric Influences on conformation.

Kirsch proposed the phenyl-SF$_5$ barrier to rotation is different with ortho protons in contrast to ortho fluorines. Computationally the $F_{eq}$-S-$F_{eq}$ angle would increase or decrease to allow the passage of the aryl fluorines or aryl protons (Fig. 5).

![Figure 5](image_url)  
Figure 5. Influence of ortho substituents on pentafluorosulfanyl group rotations. a.) ortho protons; b.) ortho fluorines.
Figure 6. Influence of SF\textsubscript{5} on alkyl groups.\textsuperscript{[12a]}

The Welch lab determined experimentally that the protons H\textsubscript{1} of \(\gamma\)-methylene group (See Fig. 6) are diastereotopic or magnetically nonequivalent.\textsuperscript{[12a]} The NMR resonance structures of compound 1 assigned to the geminal protons \(\gamma\) to the SF\textsubscript{5} group, were consistent with those protons being diastereotopic. One proton embeds itself between two equatorial fluorines. The \(\gamma\)-carbon to which the proton is bonded to is fixed so it cannot rotate as the conformation is locked since the SF\textsubscript{5} group is locked by interaction with the X or Y groups.

This hypothesis was tested first computationally at the B3LYP/6-31++G (d,p) level of theory and experimentally using rigorous coupling constant analyses. The barriers to rotation about the C-X bond were determined when as the X-C-C-OH torsional angle was varied (Fig. 7).\textsuperscript{[12b]} The energy barrier for bond rotation in compounds with SF\textsubscript{5} substitution is nearly double that of the CF\textsubscript{3}, CF\textsubscript{2}H, C(CH\textsubscript{3})\textsubscript{3} groups.
In the absence of interaction with a neighboring hydroxyl group, the barrier to rotation of the carbon-SF$_5$ bond is surprisingly small. When the hydroxyl group is replaced with a proton and the energy rotation barrier is recomputed to determine if there is hydrogen-bonding, the barrier dropped from 2 kcal to 1 kcal but didn’t disappear (Fig. 8). This phenomenon can be rationalized by considering that the shallow minimum is principally a consequence of the inability of rotation to lead to an un eclipsed state.
Hydrogen-bonding may guide the dihedral angle because the hydroxyl group is located close to the equatorial fluorines of the SF$_5$ group. It was determined that there is an interaction but not one derived from hydrogen bonding (Fig 9).

Figure 8. Interaction of the SF$_5$-goup with the hydroxyl group.$^{[12b]}$

Figure 9. Influence of SF$_5$ on OH interactions
The natural charges do not change much (0.2 electrons) as would be anticipated in a hydrogen bonding interaction. The conformational constraint appears to be derived from a stereoelectronic interaction. The homo of the SF$_5$-C bond, that has a significant coefficient on fluorine overlaps with the CH$_2$-O σ* orbital that is localized on a hydrogen of the CH$_2$ group. This interaction is not possible with a CF$_n$H$_{3-n}$ group.

Figure 10. Geometric constraint of the S-C-C-OH torsional angle by the pentafluorosulfanyl group.

2.2.2 Aliphatic SF$_5$ chemistry (alkyl pentafluoro-$\Lambda^6$-sulfanes)

As mentioned aliphatic SF$_5$ chemistry is much less well developed$^{[15i, 31a, 32]}$ than the study of aryl SF$_5$ compounds largely because of the paucity of reactions available for the introduction of the groups into aliphatic systems. SF$_5$X additions (X=, Cl, Br or SF$_5$) across multiple bonds are the principal route to the preparation of SF$_5$-containing aliphatics. Unfortunately the preparation of SF$_5$Cl, SF$_5$Br or S$_2$F$_{10}$ is challenging even to inorganic experts and therefore, with a few notable exceptions, the reagents have found little application in organic chemistry.
The vast majority of SF$_5$X addition reactions form simple acyclic halides, esters or salts that were used to prepare intermediates for the preparation of SF$_5$-containing polymers.$^{[31a]}$ In earlier work the addition reactions of SF$_5$Cl were initiated photochemically, however the relatively low boiling point of SF$_5$Cl necessitated the use of sealed vessels or an excess of valuable reagent.$^{[30a]}$ These difficulties were overcome using triethylborane to initiate reaction.$^{[33]}$ The greater reactivity of SF$_5$Br, coupled with a higher boiling point and the relatively greater reactivity of the bromide-containing addition product, led to the exploration of this difficulty accessible reagent. Thermal promotion of reaction$^{[34]}$ was supplanted by the triethylborane catalyzed addition previously described for the reactions of SF$_5$Cl.$^{[35]}$ To date there are few systematic studies of the influence of the SF$_5$ group on reactivity, stereoselectivity or conformation beyond those derived from work conducted in our lab.$^{[10, 12a, 36]}$

2.3 Results

2.3.1 SF$_5$-substitution and β-lactam synthesis

My research initially involved the incorporation of the pentafluorosulfanyl (SF$_5$) group into β-lactams. The pentafluorosulfanyl group adds synthetic challenges to the formation of β-lactams in contrast to the more commonly employed methyl or trifluoromethyl (CF$_3$) substitution. The SF$_5$ group is strongly electron withdrawing as well as especially sterically demanding. In addition introduction of a pentafluorosulfanyl group can dramatically increase the lipophilicity of the product lactam. The increase in steric demand may restrict the accessible conformations, but most interestingly the profound dipole of the pentafluorosulfanyl group at a chiral carbon can modulate the diastereofacial selectivity of β-lactam formation.
**Rationale.** The highly polar transition state of the Staudinger reaction is an ideal platform to refine our tentative understanding of the dipolar influence of the SF$_5$ group on the stereochemistry of reactions while preparing novel molecules with potential applications in medicinal chemistry.

Importantly, in preliminary disc diffusion assays,(M.H. Cynamon, VA Medical Center Syracuse, NY) 6 suppressed the growth of methicillin-resistant *Staphylococcus aureus* (MRSA) (ATCC 33591). Since 6 lacks the 3-amino group of monobactams, such as aztreonam 7, and in addition, the lactam nitrogen of 6 was protected, the synthesis of unprotected 3-amino azetidinones is highly desirable in an effort to increase antibacterial activity.

![Figure 11. SF$_5$-substituted β-lactam 6 and aztreonam 7.](image)

The product β-lactams can also be central building blocks in the β-lactam synthon method,[37] e.g., in the preparation of a β-amino acid such as 8. As an example, esterification of 8 with baccatin 9, suggests a SF$_5$ analog of the highly efficacious docetaxel.(Fig. 12) It is proposed that the increased lipophilicity of the pentafluorosulfanyl group can enhance binding in the hydrophobic pocket of β-tubulin,
the target of docetaxel, while the simultaneously constraining the conformation of the 2-hydroxyl residue involved in hydrogen bonding with His227 of β-tubulin.[38]

![Chemical structure](image)

Figure 12: Condensation of pentafluorosulfanyl acid 8 with baccatin 9.

### 2.3.2 Synthesis of SF₅Cl

Pentafluorosulfanyl chloride (SF₅Cl) that is central to our approach to β-lactam synthesis has only limited commercial availability and when it is available is quite expensive. To obviate these concerns, I prepared the SF₅Cl used in subsequent syntheses.

The first successful preparation of SF₅Cl in 1959 was based on the reaction of Cl₂ with S₂F₁₀, which is difficult to synthesize itself.

\[
S₂F₁₀ + Cl₂ \rightarrow 2SF₅Cl
\]

Another challenging approach was reported years later where S₂F₁₀ was reacted with SCl₂ at -10 °C. In my work SF₅Cl was prepared by reaction of potassium fluoride, sulfur tetrafluoride and chlorine in the presence of a catalytic amount of bromine at ambient temperature.[39]
The KF and Br₂ were added into a Monel pressure vessel under ambient conditions. After the reaction vessel was sealed with an applied torque of 15 inch-pounds per bolt, the reactor was cooled to -198 °C. A stoichiometric quantity of SF₄ was transferred from a metal ballast cylinder followed by a stoichiometric quantity of Cl₂. The sealed reaction vessel was then allowed to warm to room temperature. As the reaction is heterogeneous and magnetic stirring inside the vessel ineffective, mechanical agitation of the reaction contents was employed to facilitate mixing. Practically this process was effected by the addition of two one cm steel ball bearings to the reactor. The vessel was cautiously shaken twice a day so to assure contact of the gaseous reagents with a fresh KF surface. After a week, the autoclave was cooled to -80 °C and allowed to warm to -60 °C slowly to allow the product SF₅Cl to be condensed into an evacuated ballast at -196 °C. The ballast was warmed to -15 °C and the SF₅Cl was transferred by a trap to trap distillation into a Teflon bottle containing a known volume of pentane at -30 °C.

The product is characterized by transferring a low pressure of material to a short pathlength infrared gas cell equipped with ZnSe windows. Commonly seen are SOF₂ peaks appearing at 1340, 808, 750, 410 and 390 cm⁻¹ as observed in the IR spectrum of my initial attempt at SF₅Cl synthesis (Fig 13a). Reproduction of this effort subsequently yielded pure product (Fig. 13b). The improvement in outcome was likely influenced a result of the careful handling of the potassium fluoride. The KF was ground into a finer powder and left to oven dry for a week instead of 4 days to eliminate the
moisture held by clumps of KF. In the spectrum b, the SF₅Cl peaks are the most prominent at 909.65, 853.81 and 601.86 cm⁻¹. The reported values from literature are 909, 855 and 602 cm⁻¹. The starting materials, SF₄, Cl₂ and Br₂, are completely consumed. The starting SF₄ peaks are located at 876, 738 and 723 cm⁻¹, the Cl₂ peak is at 557 cm⁻¹ and the Br₂ peak can be found at 316.8 cm⁻¹.

Figure 13. Experimentally determined infrared spectra of SF₅Cl illustrating both the high purity of the product obtained (b) and also the IR signature of the principal contaminants resulting from either hydrolysis or incomplete reaction as in (a).

2.3.3. Radical Mechanism

Triethylborane is used as a catalytic initiator to promote the addition of SF₅Cl across double or triple bonds. Triethylborane in the presence of oxygen allows for a convenient, regiospecific and highly selective addition to unsaturated compounds. An ethyl radical is produced when Et₃B reacts with O₂ (Fig. 14). Ethyl radical abstracts chlorine from SF₅Cl to generate the electrophilic SF₅ radical.⁴⁰ Dolbier utilization of triethylborane in SF₅Cl addition reactions was a crucial advance in this chemistry.⁴¹
Figure 14. Putative mechanism for the role of triethylboron as a radical initiator.

This radical addition is regiospecific with the SF$_5$ group adding initially to the least substituted position of the double or triple bond and the halogen adding to the most substituted position.$^{[36]}$ The homolysis of SF$_5$Cl in the presence of triethylborane forms a SF$_5$ radical which donates its electron more readily to a π system with a low LUMO energy level.

2.3.4 Aldehyde Synthesis

It was Gard that first reported the successful addition of SF$_5$X to vinyl acetate albeit under pressure.$^{[42]}$ Previously we have reported the addition of SF$_5$Cl to enol acetates to form pentafluorosulfanylated aldehydes,$^{[36]}$ but the purity of the aldehydes prepared in this manner proved problematic. In contrast 2-pentafluorosulfanylalkanals were cleanly prepared by the addition of SF$_5$Cl to enol ethers. The pentafluorosulfanyl group had a profound influence on the diastereoselectivity of carbonyl addition reactions. This is most likely due to the remarkably large C-SF$_5$ bond dipole moment that as predicted by the Cornforth addition model would located the SF$_5$-group in an anticlinal relationship to the carbonyl oxygen.
Experimentally observed decomposition of the aldehyde \( \text{19} \) was obvious by transformation of the orange product to a dark brown color within 30 minutes of synthesis requiring the immediate further transformation of the product to the imine.

2.3.5 Imine Synthesis

To synthesize the SF\(_5\)-containing \( \beta \)-lactam, the pentafluorosulfanyl aldimines had to be utilized immediately. The imine was generated by the initial suspension of anhydrous magnesium sulfate in distilled dichloromethane. To the uniform suspension, the aldehyde \( \text{19} \) was slowly added dropwise, rendering the suspension a cloudy light brown color. Both dichloromethane solutions of benzyl amine and allyl amine were used. The reaction was allowed to stir for the weekend until the \( \beta \)-lactam reaction was attempted.

To begin the \( \beta \)-lactam reaction triethylamine, dichloromethane and acetyl chloride were added to an oven-dried round-bottom flask under argon at 0 °C. An inverse fritted filter funnel was used to separate the magnesium sulfate from the imine reaction. The \( ^{19}\text{F} \) NMR spectrum of the solution verified imine formation by the characteristic upfield shift at \( \delta \) 68.8 ppm from the aldehyde shift at \( \delta \) 72.4 ppm. The enamine was also formed where the equatorial fluorines were visible at \( \delta \) 65.5 ppm (Fig. 16). The dichloromethane solution of the imine was readily reacted with the ketene to afford the SF\(_5\)-containing \( \beta \)-lactam.
Hermann Staudinger introduced the ketene-imine cycloaddition to prepare substituted β-lactams in 1907.\textsuperscript{[43]} In this [2+2] cycloaddition of ketenes with imines, the imine acts as the nucleophile which attacks the Bose-Evans ketene formed \textit{in situ} from the reaction of benzyloxyacetyl chloride with trimethylamine (Fig. 17).\textsuperscript{[44]} The reaction occurs by the attack on the LUMO of the ketene carbonyl group by the imine nitrogen. While described as a cycloaddition process the addition proceeds stepwise forming a zwitterionic intermediate that is susceptible to undesirable isomerizations. Although the acetyl chloride yields the reactive ketene that can undergo the 1,2-\textit{lk} conrotatory ring closure with the imine. The chloride ion may also intercept the iminium ion hence functioning as a leaving group for the β-lactam ring-closure reaction.
In the cyclization of the SF$_5$-substituted imine, isomerization the intermediate iminium ion is potentially problematic. However, the SF$_5$ group has a strong electron withdrawing effect so the rate of ring closure will be accelerated. Therefore the addition of the polar SF$_5$ substituent to aldimines and ketimines forms in β-lactams with stereochemical control. Cyclization results in formation of the cis-β-lactam as a racemic mixture from the two-step mechanism of the ketene addition, via the zwitterionic intermediate (Fig. 18).
Figure 18. The Staudinger reaction can lead to a mixture of products but in F$^{19}$ NMR the only stereoisomeric pair observed with an SF$_5$ stereogenic center is the $l_k,l_k$ pair and neither of the $l_k,u_l$, $u_l,l_k$ or $u_l,u_l$ pairs.

As the stereochemistry of the addition is determined primarily by the structure of the imines and the nature of the free or bound ketene, deprotonation is problematic leading to loss of stereocontrol and product selectivity. The initial approach of the ketene to the imine is orthogonal and subsequently upon rotation into a plane the ring closure is conrotatory in nature. This is a result of the dipole influence of the SF$_5$ group.

2.4 Discussion of Results

2.4.1 The role of $N$-protection on the yield of reaction.

The goal of this research is the investigation of the effects of an SF$_5$ substituent on the utility of $\beta$-lactams as antibiotics. The first attempt at the $\beta$-lactam synthesis employed
an SF$_5$ imine protected by a benzyl group. This reaction was successful, but required two purifications by flash column chromatography and the yield was less than 10%. The next attempt at the $\beta$-lactam synthesis utilized an SF$_5$ imine protected by the allyl group in hopes of a higher yield. The synthesis of this $\beta$-lactam was much less complex and required only one purification by flash column chromatography to provide a surprising increase in yield. The purity of the product was evident on TLC with a clear $R_f$ value of 0.2 allowing for an easier separation than previously with a benzyl group was employed. The most probable explanation is the steric hindrance of the benzyl group. There also could have been interactions between the benzyl group and SF$_5$ group causing additional steric constraints and ultimately a reduction in the yield.

2.4.2. Determination of the stereoselectivity of ring formation.

2.4.2.1 NMR methods. The $^{19}$F-$^1$H coupling constants facilitate determination of the structure of the fluoro-$\beta$-lactam product through $^{19}$F NMR spectroscopy. The $^{19}$F NMR spectra provides the first indication as to whether the desired product was obtained or if ionic addition occurred. The intermediate imine had a complex $^1$H NMR spectra but it was used immediately without purification, therefore only the $^{19}$F NMR was necessary. The SF$_5$ addition had fluorine signals appear as a pentet at $\delta$ 83 ppm and a doublet at $\delta$ 67 ppm shown in Figure 19. With the introduction of a methyl group alpha to SF$_5$ there is a characteristic upfield shift in $^{19}$F NMR due to the interactions with the protons located on the methyl and the four equatorial fluorines.

With a change in protecting group, there was no change observed in the spectra. The final $^1$H NMR spectra for the $\beta$-lactam included resonances for the protons of the carbon
alpha to the SF$_5$, or the lactam ring, the benzene ring, and the allyl chain, then the desired product was obtained (Fig. 19). To establish the formation of the product $^{13}$C NMR and mass spectrometry were used as well as the $^1$H NMR and $^{19}$F NMR.

Figure 19. Selectivity of ring formation as shown in the $^{19}$F NMR spectra of crude $\beta$-lactams.
Figure 20. Selectivity of ring formation as shown in the $^1$H NMR spectra of crude β-lactams. Spectrum labeled in accordance with above figure.

2.4.2.2 Single crystal X-ray diffraction studies. The β-lactam structure determined by single crystal X-ray diffraction demonstrates the asymmetric center and clear selectivity (Fig. 21).
2.4.3 Rationale for stereoselectivity of cyclization.

The crystal structure confirms that the SF$_5$ group, carbon of the β-lactam ring, and nitrogen of the β-lactam ring are aligned in a manner that is consistent with the reaction being under the control of the Cornforth hypothesis (Fig. 22).

![Cornforth model](image)

Figure 22. Cornforth model for addition to carbonyl groups where $X$ is an electron withdrawing group.

The Cornforth model is based on a combination of steric and electronic considerations including the polarization of the transition state. The energy of the transition state is...
lowest when the dipoles are antiparallel lowering the energy of the system. (Fig. 24) The symmetry of the carbon bearing the SF$_5$ group controls the ring closure and favors the observed 1,2 $\text{lk}$ ($\text{Si, Si-S}$) or ($\text{Re, Re-R}$) ring closure.

Figure 24. Newman projection of possible rotamers describing the position of the SF$_5$ group.

In the absence of a chiral center bearing the SF$_5$ group, SF$_5$-methylene and the benzyoxy substituent of the ketene are located in the same face of the $\beta$-lactam, indicating imine isomerization is negligible and that the conrotatory ring closure step is preserved.

Figure 25. The experimentally observed $\text{lk}$-ring closure process.

Ring closure of the pentafluorosulfanyl butanimine demonstrates clearly the power that the SF$_5$ group has on stereochemical control. The chiral center created on pentfluorosulfanylation controls the diastereoselectivity of the ring closure step.
diastereofacial reactivity of the imine is greatest when the carbon-sulfur bond is antiperiplanar to the forming carbon-nitrogen bond.

This ring closure cannot be under Felkin-Anh control as the C-S σ* orbital does not have a node that can interact with the C-N π bond.

![Chemical Structures](image)

Figure 26. Failure of the 1,2-\(\text{Ik,ul}\) ring closure to occur.

The SF\(_5\) group dictates 1,2-\(\text{Ik,ik}\) (Si,Si-S) or (Re,Re-R) stereochemistry is not as expected which is most likely due to the dipole influencing the diastereoselectivity (Fig. 27). The conrotatory ring closure to the 4-membered β-lactam requires bond formation between the iminium ion carbon and the enolate carbon which proves to be facile.
Figure 27. Dipole influence of the SF$_5$ group on the initial attack of the ketene on the imine nitrogen (A) and the direction of the conrotatory ring closure (B).

2.4.4. *N*-deprotection.

Stereoselective β-lactam formation can be converted to 3-amino-2-hydroxy-3-pentafluorosulfanylpropanoic acids then coupled to the protected baccatin nucleus of docetaxel in preparation of fluorinated amino acids. The introduction of fluorine into an amino acid paired with the ability to control the stereochemistry of the amino acid is crucial for its implementation into biologically relevant molecules or drugs. The transformation of SF$_5$-substituted β-lactams into SF$_5$-substituted amino acids has not yet been reported, however, independently synthesized SF$_5$-substituted amino acids have been incorporated into peptides with measurable changes in the peptide structure.

Next, it was necessary to isomerize the double bond of the allyl chain with Rh(P(Ph)$_3$)$_2$Cl to prepare the β-lactam for deprotection (Fig. 28).
Figure 28. \( N \)-allyl isomerization by rhodium.

Two strategies were used for \( N \)-deprotection but both appeared to be unsuccessful (Fig. 29). On \( \text{KMnO}_4 \) treatment it appeared that the benzyloxy group adjacent to the carbonyl group was lost when the nitrogen was deprotected. Ultimately the allyl group was isomerized to the vinyl group for storage until the ring opening.

Figure 29. Allyl deprotection strategies.

2.5 Conclusion and Future Directions

Conclusions drawn from the \( \beta \)-lactam formation translate to the diasteroselective preparation of a pentafluorosulfanylated 3-amino-2-hydroxy-3-propanoic acid. \( \text{SF}_5 \)-containing \( \beta \)-lactams can be formed from the corresponding aldimines and ketimines. The products are formed with high 1,2 diastereoselectivity consistent with a conrotatory ring closure step. Additionally, when the pentafluorosulfanyl group is substituted on a
secondary carbon the ring closure is remarkably diastereoselective favoring 1,2 \( \text{Ik,Ik} \) ring closure.

The anticancer drugs paclitaxel and docetaxel are first line drugs for the recovery of refractory ovarian cancer, metastatic breast cancer, melanoma, non-small-cell lung cancer and Kaposi's sarcoma. Although the taxoid antitumor compounds can be very effective, both drug resistance and side effects continue to be problematic. In third-generation derivatives it has been found that replacement of the phenyl group of the \(-\text{amino-2-hydroxy-3-phenylpropanoic acid side chain of docetaxel can reduce the development of drug resistance by 100-fold and also lead to the recovery of activity against docetaxel- and paclitaxel-resistant cell lines. From the conversion of pentafluorosulfanylated \( \beta \)-lactams to 3-amino-2-hydroxy-3-pentafluorosulfanylpropanoic acids, the protected baccatin nucleus of docetaxel will be coupled (Fig. 30). The increased lipophilicity of the SF\(_5\) group will enhance binding in the hydrophobic pocket of \( \alpha \)-tubulin, the target of docetaxel, while simultaneously increasing the acidity of the 2-hydroxyl residue which will strengthen the hydrogen bond formed between the 2-hydroxyl and His227 of \( \alpha \)-tubulin.
Figure 30: Condensation of pentafluorosulfanyl acid with baccatin.
3.1 Introduction.

The effects of pentafluorosulfanylation may be modulated by replacement of the apical fluorine by a trifluoromethyl group forming the trifluoromethyl-\(\lambda^6\)-tetrafluorosulfanyl group. The simplistic Rundle-Pimentel model\[^{[46]}\] captures an essential feature of the trifluoromethyl-tetrafluoro-\(\lambda^6\)-sulfanyl group (See Fig. 31) without the need for more complex molecular orbital descriptions.\[^{[47]}\] Substitution of fluorine by a trifluoromethyl group is predicted to influence the coefficient of charge density on the carbon bound at the opposite apex. Counter intuitively, electron withdrawing substituents may decrease acidity by increasing electron density at carbon thereby diminishing the acidity of an attached proton. It can be postulated that the CF\(_3\) group will have a smaller effect on the remote carbon than fluorine as the CF\(_3\)-S-C bond is less polarized,\[^{[9b, 15g]}\] however experimental observations on the influence of the CF\(_3\)SF\(_4\) group on reactivity are lacking.

The CF\(_3\)SF\(_4\) group is also one of the most lipophilic groups known with a lipophilicity, \(\pi_p\) of 2.14.\[^{[15g]}\] Simultaneously the group has a \(\sigma_p\) nearly equivalent to that of the SF\(_5\)-group with an occupied volume greater than a \(t\)-butyl group (See Fig. 4). All of these properties contribute to the unique substituent effects of CF\(_3\)SF\(_4\) substitution of biologically active compounds.
The utility of the steric and stereoelectronic effects of the CF₃SF₄ group on the induction of secondary peptide structure as well as the influence of the profound polar hydrophobicity of the CF₃SF group on peptide tertiary structure can expand the architectural toolkit of peptide chemists. Systematic comparison of the effect of the SF₅ and CF₃SF₄ groups can enable dissection of the effect of the 35% greater occupied volume of the CF₃SF₄ group when combined with the 33% reduction in associated CF₃SF₄ group dipole moment.

**Rationale.** The systematic investigation of substitution of the apical fluorine of SF₅ by carbon has validated the hypothesis that substitution at this site can modulate not only reactivity but also structure and bonding of the product tetrafluorosulfanes.⁴⁸ We have previously described the limitations the SF₅ group imposes on the reactivity and conformation of aliphatic compounds. (Chapter 2) These shortcomings may be obviated by substitution of the apical fluorine by a trifluoromethyl group that depresses the equatorial plane of the fluorines, both reducing the molecular dipole⁹ and in principle, the importance of the ylidic contribution to anion stabilization. This outcome can enhance the reactivity of a CF₃SF₄-substituted enolate toward electrophiles. The simultaneous increase in steric demand that accompanies introduction of the CF₃ group enables systematic comparison of the steric influences of CF₃SF₄- and SF₅-substitution on reactivity. A strand-loop-strand oligopeptide motif bearing both CF₃SF₄- and SF₅-substituents will be prepared to demonstrate the utility of proposed polar hydrophobicity⁹ on controlling peptide conformation.

### 3.2 Background.

#### 3.2.1 Bonding in trifluoromethyl-λ⁶-tetrafluorosulfanyl group
Tetrafluoro- $\lambda^6$-sulfanes where the combination of the electronic effects of hypervalent fluorinated sulfur can be tuned by selective substitutions have been studied very little. Previously synthetic access to systematically substituted compounds was challenging. Substitution of the apical fluorine by a trifluoromethyl group increases the steric demand as well as diminishes the dipole of the substituent. The Connolly surface of the SF$_5$ group: 122.71 Å$^2$ increases to 138.93 Å$^2$ for the CF$_3$SF$_4$ group. Furthermore, the dipole moment of the SF$_5$ group is 3.310 Debye and decreases for CF$_3$SF$_4$ to 2.301 Debye. These properties may lead to decreased acidity of a proton on the attached carbon.

The calculated (B3LYP/cc-pVTZ) dipole moment of CF$_3$CH$_3$ of 2.267 D contrasts with the dipole moment of SF$_5$CH$_3$, 3.310 D, that is reduced by introduction the CF$_3$ in CF$_3$SF$_4$CH$_3$ to 2.301 D. Beyond the dipole moment computed for this application, and the experimental measurements from Kirsch$^{15g}$ on the reduced dipole of CF$_3$SF$_4$-substituted arenes, very little is known about the effect of the CF$_3$SF$_4$ group.

3.2.2 Preparation.

Previously synthetic access to systematically substituted tetrafluoro- $\lambda^6$-sulfanes was challenging. Diaryl tetrafluorosulfanes have been prepared by fluorination of the corresponding diaryl sulfides with trifluoromethylhypofluorite$^{49}$ or fluorine.$^{50}$ Aryl trifluoromethyl tetrafluorosulfanes were synthesized by direct fluorination of the corresponding trifluoromethyl sulfides.$^{15g}$ Several alkyl trifluoromethyl tetrafluorosulfanes were prepared by photochemically promoted addition of trifluoromethyl tetrafluorosulfanyl chloride to alkenes or alkynes,$^{51}$ the requisite trifluoromethyl tetrafluorosulfanyl chloride was prepared by oxidative fluorination of
trifluoromethyl chlorosulfides with chlorine fluoride.\textsuperscript{[52]} Systematic investigations of substituent effects are unknown.

3.3. Results

The effects of (trifluoromethyl)tetrafluorosulfanyl(CF$_3$SF$_4$)-substituted compounds have received far less attention than SF$_5$-substituted compounds. Substitution of the apical fluorine in an SF$_5$ group by a trifluoromethyl group increases the steric demand. The Connolly surface of the SF$_5$ group is 122.71 Å$^2$ whereas the Connolly surface of the CF$_3$SF$_4$ group is 138.93 Å$^2$. The group dipole of the CF$_3$SF$_4$ substituent is as well diminished to SF$_5$. The dipole moment of the SF$_5$ group is 3.310 Debye vs. the dipole moment of CF$_3$SF$_4$ is 2.301 Debye. These properties may lead to decreased acidity of a proton on the attached carbon. The electron density of the carbon is diminished relative to that of the alpha carbon of a SF$_5$ substituted alkyl group.

3.3.1 Preparation of trifluoromethylsulfenyl chloride (CF$_3$SCI)

A convenient and efficient method to produce the starting material for a reaction is essential for investigation of the reactivity of analogs. Previously, perfluoromethylsulfenyl chloride was synthesized by Scherer, Korinth and Starck\textsuperscript{[53]} using CCl$_3$SCI, HF and a Ni filled with Cr oxyfluoride tube. A safer process based upon an alkali fluoride-chloride exchange of perchloromethylsulfide was developed using carefully dried sodium fluoride in sulfolane (Fig. 32). This procedure was developed from a process described in the patent literature by Tullock.\textsuperscript{[54]}
3.3.2 Trifluoromethyl-λ⁶-tetrafluorosulfanyl chloride (CF₃SF₄Cl)

Published preparations of CF₃SF₄Cl require either the use of ClF to oxidatively fluorinate CF₃SCl or CF₃SSCF₃[52, 55] or the treatment of the more difficulty accessible CF₃SF₃[56] with Cl₂ in the presence of CsF.[51b, 57] We have developed a preparation of CF₃SF₄Cl from the common chemical intermediate perchloromethyl mercaptan (trichloromethanesulfenyl chloride) (Fig. 33). The synthesis is easily carried out in glassware without the need for special equipment. The convenient and efficient 2-step synthesis provides our starting material in less than 2 days. The product CF₃SF₄Cl may be stored in pentane solution at -22 °C for use in future reactions.

Unreacted chlorine was not completely separated by distillation. In preliminary experiments with solutions of partially purified CF₃SF₄Cl numerous side reactions occurred. There was evidence of SF₅ and CF₃ addition, as well as the desired CF₃SF₄ reaction with double and triple bonds. Much cleaner reactions were possible by
removing the excess chlorine. A chlorine-free solution was prepared by allowing the pale yellow solution to stir at 0 °C with elemental mercury for an hour under argon.

3.3.3 Addition reactions of CF₃SF₄Cl.

To establish the scope and generality of the addition process while minimizing the reaction scale, the progress of reactions was followed by ¹⁹F-NMR using benzotrifluoride (BTF) as an internal standard. BTF was added to the CF₃SF₄Cl solution in an amount that would yield a signal intensity appropriate for careful integration upon quenching of the reaction. The use of BTF as an internal standard provides reproducibly sharp and neat spectral signals for comparative integration. At around δ -65 ppm in the ¹⁹F-NMR, the resonance corresponding to BTF appears as a singlet that can be easily integrated. Comparison of this integral with those of the resonances can enable estimation of the product yields.

The CF₃SF₄Cl addition studies were performed in an oven-dried Schlenk flask in an ice bath under an argon atmosphere. The CF₃SF₄Cl-pentane solution was added slowly, dropwise against the cold side of the flask to preserve the concentration of the CF₃SF₄Cl-pentane solution. The argon flow was suspended then triethylborane was added dropwise against the cold wall of the flask as well. Over the course of the addition of triethylborane, intermittently, 10 mL volumes of air were introduced above the surface of the solution. Upon completion of the addition of triethylborane the reaction mixture was allowed to stir for 30-45 minutes in an ice bath only partially stoppered.
3.3.3.1 Terminal Alkenes:

In reactions with conjugated systems such as \( \rho \)-phenylstyrene 43 polymerization was much more rapid than CF\(_3\)SF\(_4\)Cl addition.

\[
\begin{align*}
\text{CF}_3\text{SF}_4\text{Cl} + \text{Et}_3\text{B}, \text{O}_2, \text{pentane} & \rightarrow \text{Cl} - F_4\text{SCF}_3 \\
0 \degree \text{C}, 30 \text{ minutes} & \rightarrow \\
\text{42} + \text{43} & \rightarrow \text{44}
\end{align*}
\]

There was evidence of CF\(_3\)SF\(_4\)Cl fragmentation to give -SF\(_4\)CF\(_3\) addition, -CF\(_3\) addition, and –SF\(_5\) addition (Fig. 34).

\[
\begin{align*}
\text{CF}_3\text{SF}_4\text{Cl} + \text{45} & \rightarrow \text{Cl} - F_4\text{SCF}_3 + \text{SF}_5 + \text{CF}_3 \\
0 \degree \text{C}, 45 \text{ minutes} & \rightarrow \\
\text{42} + \text{45} & \rightarrow \text{46} + \text{47} + \text{48}
\end{align*}
\]

Figure 34. Experimentally observed products when CF\(_3\)SF\(_4\)Cl was added to butyl vinyl ether 45.

A typical \(^{19}\text{F}\) NMR spectrum illustrating the formation of the SF\(_5\), CF\(_3\) and CF\(_3\)SF\(_4\) addition products is shown in in Fig. 35. A pentet that can be attributed to the axial fluorine is present at \( \delta \) 81.0 ppm and the equatorial fluorines appear as a doublet of triplets is seen at \( \delta \) 65.7 ppm in the \(^{19}\text{F}\) NMR, consistent with reported chemical shifts in literature.\(^{[45]}\)
Figure 35. Experimentally observed SF$_5$ addition to butyl vinyl ether in $^{19}$F NMR.

The formation of pentafluorosulfanyl precursor to addition is likely the result of the complex fragmentation and reaction pathways accessible to CF$_3$SF$_4$Cl. The lability of both the parent compound and the CF$_3$SF$_4$ radical can afford an explanation for the formation of both the CF$_3$ and SF$_5$ addition products as shown below.
Figure 36. Plausible mechanism rationalizing a. CF$_3$SF$_4$, b. CF$_3$ or c. SF$_5$ addition to alkenes.

Under the correct conditions, pathway a. in figure 36 did produce the CF$_3$SF$_4$ addition which is shown in the spectral data.

3.3.3.1.1 1-(Vinyloxy)butane. Careful control of the reaction temperature enabled the successful addition of CF$_3$SF$_4$Cl to butyl vinyl ether 49. Under these conditions the $^{19}$F spectrum exhibited the expected pentet for the trifluoromethyl group at $\delta$ -65 ppm and doublet of quartets of the tetrafluorosulfanyl group at $\delta$ 40 ppm. Unfortunately however the crude product 50 underwent decomposition overnight precluding further purification.
3.3.3.1.2 Allyltrimethylsilane. The product of addition of CF$_3$SF$_4$Cl to allyl silane 51 is of considerable interest in light of the lability of the trimethylsilyl group, cleavage of which can generate a substituted allylic anion. Both allyltrimethylsilane 51 and the CF$_3$SF$_4$Cl addition product 52 were very volatile and were especially challenging to separate.

3.3.3.1.3 Vinyl acetate. Another CF$_3$SF$_4$Cl adduct that can be transformed readily is the chloro acetate adduct of vinyl acetate 53 and CF$_3$SF$_4$Cl. The general addition reaction conditions were optimized for this reaction because it proceeds smoothly and produced the desired $^{19}$F NMR signals. This reaction gave 54 in 52% yield.

3.3.3.2 Internal Alkenes:

3.3.3.2.1 Crotonaldehyde. The reaction of crotonaldehyde 55 with only partially purified CF$_3$SF$_4$Cl produced a complex mixture of products that did not contain fluorine illustrating the importance of utilizing the purest CF$_3$SF$_4$Cl solution possible. The product 56 was a black oil.
3.3.3.2.2 Bicyclo[2.2.1]hept-2-ene. In one of the few examples of CF$_3$SF$_4$Cl addition to internal alkenes, norbornene 57 produced the product 58 in 2.3% yield. This is the first time that a successful reaction of an internal alkene has been made.

3.3.3.2.3 3,4-dihydro-2H-pyran. When dihydropyran 59 was added to CF$_3$SF$_4$Cl the results were consistent with the ionic addition product 60 as assessed by $^{19}$F NMR spectroscopy. Ionic addition can be easily rationalized by considering the electron withdrawing character of the CF$_3$SF$_4$ group.

As can be seen in Fig. 37, sulfur chlorine bond heterolysis will lead to reduction of sulfur VI to sulfur IV and the trifluoromethide anion. The chloronium ion addition to the enol ether forms an oxonium ion that abstracts fluoride ion from the trifluoromethide anion. The difluoromethylene dimerizes readily to form TFE.
Figure 37. Decomposition to form trifluoromethylation product.

Future plans include attempting the reaction in trichlorofluoromethane or at lower temperatures to suppress the ionic process and form compound 61.

3.3.3.2.4 1H-indene. The reaction with indene was tried with different stoichiometries of indene. The first attempt at reacting indene 62 with CF₃SF₄Cl produced mostly starting material. The second attempt at the reaction used more indene and Et₃B to yield the desired product 63.

\[
\begin{align*}
\text{CF}_3\text{SF}_4\text{Cl} & + \text{Indene} \rightarrow \text{Et}_3\text{B}, \text{O}_2, \text{pentane} \\
0 \degree \text{C}, 30 \text{ minutes} & \rightarrow \text{Product 63}
\end{align*}
\]

3.3.3.3 Alkynes:

3.3.3.3.1 1-Ethynyl-4-methoxybenzene. Reacting CF₃SF₄Cl with 4´-methoxyphenyl acetylene 64 followed by purification by column chromatography resulted in pure 65. There is 0.06 g of analytically pure sample.

\[
\begin{align*}
\text{CF}_3\text{SF}_4\text{Cl} & + \text{Acetylene} \rightarrow \text{Et}_3\text{B, O}_2, \text{pentane} \\
30 \text{ minutes, } 0 \degree \text{C} & \rightarrow \text{Product 65}
\end{align*}
\]

3.3.3.3.2 2-Ethynyl-6-methoxynapthalene. 66 did not dissolve in pentane so was dissolved in distilled benzene before addition to CF₃SF₄Cl because the reagent is
insoluble in pentane. A successful addition to produce 67 was made on the second attempt of this reaction once it was known that benzene dissolved the reagent and didn’t interfere with the reaction.

![Chemical Reaction](image1)

3.3.3.3 1,3-Diethynylbenzene. Addition of 1,3-diethynyl benzene 68 to CF$_3$SF$_4$ produced the correct $^{19}$F signals for compound 69 after stirring for 30 minutes. This reaction mixture has been worked-up is in the freezer awaiting purification.

![Chemical Reaction](image2)

3.3.3.4 1,4-Diethynyl benzene. This reaction of CF$_3$SF$_4$Cl with 70 produced many products in the $^{19}$F NMR. This may be due to the purity of the starting material, CF$_3$SF$_4$Cl.

![Chemical Reaction](image3)

3.3.3.5 1-Ethynyl-2,4,5-trimethyl benzene. One of the first addition reactions was 1-ethynyl-2,4,5-trimethyl benzene 72 with CF$_3$SF$_4$Cl. The reaction went as desired and crystals formed when it was concentrated *in vacuo*. Many attempts were made to
crystallize the substrate 73. A few examples are: dissolving it in 0.25 mL of hexanes and 0.25 mL of dichloromethane and putting a piece of Parafilm over the beaker with a few holes. After a week crystal growth was visible but too fast. Next, the only solvent used was hexanes, but still crystal growth was too quick. Attempts were made in the -90 °C freezer, 0 °C freezer and refrigerator. Other solvents used were 1-chlorobutane, hexanes and acetone, heptane and many more. Clusters of crystals grew readily, however none were single crystals.

3.3.3.3.6 Methyl propiolate. Reaction with CF₃SF₄Cl with 74 provided compound 75 after purification by flash chromatography.
**Future Directions:**

1. The convenient preparation of CF$_3$SF$_4$Cl enabled the investigation of the addition reactions of CF$_3$SF$_4$ radicals to alkenes and alkynes. While many attempts at the addition of CF$_3$SF$_4$ and Cl across double and triple bonds were successful, the propensity of the intermediate radical to fragment led to degradation of the CF$_3$SF$_4$ moiety. This decomposition path resulted in the formation of trifluoromethylated side products. Additionally, while the trend for electron withdrawing substituents such as CF$_3$ to induce and upfield shift of vinylic carbon resonances was observed, the effect was less clear in the case of the acids and acetophenone structures. The role of the electron density on $^{13}$C NMR chemical shifts of the carbon bearing sulfur was not consistent in those cases. Thus, the charge shift bonding model and Rundel-Pimentel models may both be inadequate to describe the electronic properties of the products. Computations on the energies of bond homolysis and the radical decomposition of CF$_3$SF$_4$ and CF$_3$SF$_4$Cl confirm the hypothesis that variation of the substituents at the apical position modulates reactivity. Investigation of the bond lengths and angles of the crystal structures obtained further confirms the variability of the effect of substitution on the geometry about sulfur. Both CF$_3$SF$_4$ and SF$_5$ groups can be used in the synthesis of “Fluorinated Zipper” polypeptides. Selective positioning of both groups allows for presentation of a “hot loop” sequence$^6$. A C-terminal hexapeptide (C-G-A-G-PfsAbu-G) can be prepared using convergent fluorenlymethyloxycarbonyl (FMOC) solution synthesis while the N-terminal heptapeptide (TtsAbu-G-TtsAbu-G-SESL) contains two CF$_3$SF$_4$ groups synthesized using FMOC solid phase synthesis. The use of both groups “docked” like a zipper allows for potentially stronger interactions in the loop while
minimizing the dipolar repulsions associated with the previous helix formation that uses SF₅ alone⁷ (Fig.38). A challenge in this work will be to incorporate the hydrophobic CF₃SF₄ and SF₅ groups without inducing peptide aggregation or precipitation.

2. Another interesting project would be the synthesis of CF₃SF₄-substituted β-lactams to compare and contrast the differences between the already synthesized SF₅-substituent and the new CF₃SF₄-substituent. Furthermore the CF₃SF₄-substituted β-lactams could be converted into CF₃SF₄-substituted β-amino acids by opening the β-lactam ring to probe the effects of this more lipophilic, less polar substituent in various peptides.

Since the SF₅ group has a molecular dipole that controls the β-lactam formation it is unknown if the diminished dipole of the CF₃SF₄ group would lower the polarization of the charged intermediate slowing the reaction and lowering the yield. It is unclear as to whether the same degree of diastereoselective control would be achieved. However, in the cyclization of the SF₅-substituted imine, the acidity of the protons promoted

![Figure 38. Presentation of the SESLCG loop of TIMP-3, the TNFα converting enzyme inhibitor, in a short peptide conformationally constrained by SF₅–CF₃SF₄ hydrophobic interactions as modeled computationally.](image)
isomerization of the intermediate. Therefore, it is more obvious that the acidity of the protons of the attached carbon in CF₃SF₄ substituted compounds would be decreased. Theoretically, by decreasing the acidity of those protons the selectivity should be higher resulting in higher yields.

Finally, the CF₃SF₄-substituted β-lactam products may be transformed into CF₃SF₄-substituted β-amino acids. Opening the SF₅-substituted β-lactam proved to be incredibly challenging. However, it is possible and given the methods and techniques I’ve learned since, it would be interesting to see if the methanolysis reaction would yield a successful ring opening.

![Chemical diagram](image)

Figure 37. β-lactam methanolysis
Chapter 4

Materials and Methods:

General methods:

A Bruker- 400 MHz Nuclear Magnetic Resonance spectrometer was used to collect all spectra for $^1$H, $^{13}$C, and $^{19}$F. All $^1$H and $^{13}$C signals are $\delta$ 7.26 and $\delta$ 77.37, respectively in deuterated chloroform. The $^{13}$C spectra were gathered in proton-decoupled mode. Thin layer chromatography was carried out with silica gel $F_{254}$ (Sigma-Aldrich) as the adsorbent on 0.2 mm thick, polyethylene teraphthalate backed plates. The plates were visualized with short wave ultraviolet irradiation (254 nm) or by staining. Stains utilized include potassium permanganate and phosphomolybdic acid followed by heating. Column chromatography was performed with silica gel 60 (230-400 Sorbent Technologies).
SF₅ Experimental Methods:

**Pentafluoro-λ⁶-sulfanyl chloride**

\[
\text{SF}_4 + \text{KF} + \text{Br}_2 + \text{Cl}_2 \rightarrow \text{SF}_5\text{Cl} + \text{KCl} + \text{Br}_2
\]

Oven dried KF (9.9 g, 1.8 eq) and 2 steel ball bearings were added to an autoclave to dry overnight at 270 °C under vacuum (10 torr). Twelve hours later, the vessel was opened, Br₂ (14 g, 0.92 eq) was added to the KF, and the autoclave was sealed at 15 torque. At -198 °C, SF₄ (11 g, 1.0 eq) was condensed in followed by Cl₂ (7.2 g, 1.1 eq). The reaction mixture was allowed to warm to room temperature, and shaken manually twice a day. After 7 days the autoclave was cooled to -80 °C and allowed to warm to -60 °C while SF₅Cl condensed into an evacuated ballast at -196 °C. The ballast was warmed to -15 °C and the SF₅Cl was distilled into a Teflon bottle of pentane at -30 °C.

**2-Pentafluorosulfanyl-1-chloroethyl acetate**

\[
\text{OAc} + \text{SF}_5\text{Cl} + \text{BEt}_3 \rightarrow \text{F}_5\text{S} + \text{Cl} + \text{OAc}
\]

SF₅Cl (7 mL, 10 mmol) was added to a solution of vinyl acetate (0.85 g, 10 mmol) in a flame-dried flask under argon at 40 °C. After 5 minutes of stirring, BEt₃ (1 mL, 1 M) was added and the color changed from orange to clear. After half an hour the reaction was allowed to warm up to room temperature. The reaction mixture was quenched with six disposable Pasteur pipette volumes of sodium bicarbonate. The organic phase (hexanes and pentane) was separated. The aqueous phase was extracted with
dichloromethane. The color changed from slight yellow to colorless and gas evolved. The organic phase was extracted with dichloromethane (3 times). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo.

2-Pentafluorosulfanylacetaldehyde

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

A reflux condenser was attached to the reaction 24 hours after the previous reaction. An oil bath kept it at a constant temperature of 50 °C. Acetic acid (1.6 g) followed by HCl (1.6 g) was added changing the color to brown and the reaction stirred overnight. Sodium bicarbonate was then added through the reflux condenser until no gas was produced. Saturated sodium bicarbonate was also added to cease the gas production. A solid was produced and filtered with dichloromethane then extracted with dichloromethane (25 mL).

(E)-N-(2-Pentafluorosulfanyl)prop-2-en-1-imine

![Chemical structure](attachment:chemical_structure2.png)

To a warm round-bottom flask was added MgSO₄ (4 g) under argon. Distilled dichloromethane (7 mL) was then added and was allowed to stir. The SF₅-acetaldehyde (3.6 mL, 2.5 mmol) was added dropwise turning the cloudy white reaction
to a light brown. The allyl amine (285 mg, 0.5 mmol) was measured in a vial with dichloromethane (3 mL) and added to the solution. The reaction stirred overnight.

**1- Allyl-3-(benzyloxy)-4-(pentafluorosulfanylmethyl)azetidin-2-one**

![Chemical structure of 1-Allyl-3-(benzyloxy)-4-(pentafluorosulfanylmethyl)azetidin-2-one]

The imine along with MgSO$_4$ was attached to a flame-dried inverse frit filter with a round-bottom flask connected to the other end with a vacuum adapter. While it cooled, a separate warm round bottom flask was put under vacuum then argon. NEt$_3$ (1 g, 10 mmol) was added to the warm round bottom flask under argon mixed from dichloromethane (2 mL) in a vial. The reaction was then put under ice and kept at 0 °C. The inverse frit was inverted and vacuum was applied over short periods. Simultaneously, benzyloxyacetyl chloride (1.9 g, 10 mmol) was added dropwise. While still under argon the imine was transferred to the reaction dropwise. Two days later, six Pasteur pipette volumes of NaHCO$_3$ were added. Quenching with water and extraction with dichloromethane (3 times) was followed by washing with water. The reaction was dried over MgSO$_4$ and filtered with a frit filter. Silica gel (1 g) was added and
concentrated *in vacuo* to dryness. A column was packed with silica gel (60 g) and the solvent used was 20% ethyl acetate and 80% hexanes. The product was visible under both UV light and potassium permanganate with an *R*<sub>f</sub> value of 0.2.

(E)-3-(Benzyloxy)-4-(pentafluorosulfanylmethyl)-1-(prop-1-enyl)azetidin-2-one

![Chemical structure of 31 and 32](image)

To the β-lactam was added toluene (5 mL) at room temperature. The Rh complex, Rh(P(Ph₃)₃Cl was then added and stirred. The reaction was attached to a reflux condenser under argon. An oil bath kept the temperature at 110 °C while the reaction stirred for a day. To purify, column chromatography was performed in 10% ethyl acetate and 90% hexanes.
CF₃SF₄ Experimental Methods:

Trifluoromethylsulfenyl chloride

\[
\begin{align*}
\text{Cl}_3\text{CSCl} & \xrightarrow{\text{NaF}} \text{CF}_3\text{SCl} + \text{CF}_3\text{SSCF}_3 \\
39 & \quad 40 \quad 41
\end{align*}
\]

To a 2-neck, 100 mL round bottom flask was added NaF (10. g, 240 mmol) to dry overnight. Eight hours later, a Schlenk tube was attached to the side arm of the 2-neck flask under argon. Warm sulfolane (15 mL, 160 mmol) was then added to the NaF and stirred followed by the addition of perchloromethyl mercaptan (5.0 mL, 54 mmol). The Schlenk tube was emerged into a dry ice/acetone bath while the reaction was heated at 270 °C for 5 hours.

Trifluoromethyl-λ⁶-tetrafluorosulfanyl chloride

\[
\begin{align*}
\text{CF}_3\text{SCl} & \xrightarrow{\text{MeCN, KF}} \text{CF}_3\text{SF}_4\text{Cl} \\
40 & \quad 42
\end{align*}
\]

To a 2-neck, 100 mL round bottom Schlenk flask was added KF (15. g) to dry overnight. Eight hours later the Schlenk tube with CF₃SCl and CF₃SSCF₃ was assembled onto the side arm of the KF flask under argon. The reaction mixture was poured on to the KF at -80 °C followed by the addition of acetonitrile (25 mL). The reaction mixture was allowed to warm to 0 °C and stirred while Cl₂ (15 g) bubbled into the reaction. The reaction mixture stirred for a total of 5 hours. Once the reaction was complete a “U” shaped distillation head was attached to the reaction and a Schlenk flask. The reaction mixture was allowed to warm to room temperature while the product distilled into the
Schlenk flask at -80 °C. Cold pentane (30 mL) was added and the product was stored in a Teflon bottle at -80 °C.

General Addition Reaction Procedure:

\[
\text{Starting Material} + \text{CF}_3\text{SF}_4\text{Cl} \rightarrow \text{Product}
\]

\[
\text{Et}_3\text{B, dried pentane} \quad 30\text{ minutes, 0 }^\circ\text{C}
\]

CF$_3$SF$_4$Cl and pentane solution that was stored in the -80 °C freezer with Mercury and BTF was added to an oven dried Schlenk flask in an ice bath under argon. The starting material was added slowly against the cold side of the flask. The argon was turned off and triethylborane was added dropwise against the cold side of the flask. Halfway through the addition of triethylborane 3 syringes of oxygen (10 mL) were slowly added throughout the remainder of the addition. The reaction mixture stirred for 30-45 minutes in an ice bath with the septa half off. It was then extracted with ether (50 mL x 3), dried over MgSO$_4$, and concentrated \textit{in vacuo}. A column was packed with silica gel (60 g) and the solvent used was hexanes for most products.
SF₅ Analytical Data:

\[
\text{SF}_5
\]

\[
\text{H}_2\text{O}
\]

\[
\begin{align*}
\text{H} & \quad \text{CHO} \\
\text{F} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{F}_5\text{S} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (CDCl}_3\text{)} & \delta/\text{ppm}: 9.79-9.77 (m, 1H, \text{CHO}), 4.37 (\text{pd}, 2H, J(\text{H-F}) = 8.0 \text{ Hz}, J(\text{H-H}) = 2.5 \text{ Hz, CH}_2). \\
\text{\textsuperscript{19}F-NMR (CDCl}_3\text{)} & \delta/\text{ppm}: 80.4 (9 \text{ signals, 1F}), 72.4 (\text{dm}, 4\text{F}, J(\text{F-F}) = 147.9 \text{ Hz}).
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (CDCl}_3\text{)} & \delta/\text{ppm}: 8.00-7.95 (m, 1H), 7.15 (\text{d}, 2\text{H}, J = 8.9 \text{ Hz}), 6.91 (\text{d}, 2\text{H}, J = 8.9 \text{ Hz}), 4.67-4.57 (m, 2\text{H, CH}_2), 3.82 (\text{s}, 3\text{H, CH}_3). \\
\text{\textsuperscript{19}F-NMR (CDCl}_3\text{)} & \delta/\text{ppm}: 81.3 (9 \text{ signals, 1F}), 68.8 (\text{dt}, 4\text{F}, F-F = 146.1 \text{ Hz}, J(F-F) = 7.3 \text{ Hz}).
\end{align*}
\]
$21b$

$^1$H-NMR (CDCl$_3$) $\delta$/ppm: 7.89-7.83 (m, 1H), 7.24 (d, 2H, $^3J = 8.6$ Hz), 6.92 (d, 2H, $^3J = 8.8$ Hz), 4.63 (s, 2H), 4.52-4.42 (m, 2H, $H_\alpha$), 3.84 (s, 3H).

$^{19}$F-NMR (CDCl$_3$) $\delta$/ppm: 92.6 (9 signals, 1F, enamine), 81.6 (9 signals, 1F), 73.2 (dd, 4F, $^2J(F-F) = 151.1$ Hz, $^3J(F-H) = 4.8$ Hz, enamine), 68.6 (dt, 4F, $^2J(F-F) = 145.9$ Hz, $^3J(F-H) = 7.1$ Hz).

$25b$

$^1$H-NMR (CDCl$_3$) $\delta$/ppm: 7.40-7.30 (m, 5H, $H_{Bn}$), 7.15 (d, 2H, $^3J = 8.5$ Hz, $H_{PMB}$), 6.87 (d, 2H, $^3J = 8.5$ Hz, $H_{PMB}$), 4.81 (AB, 2H, $^2J = 11.7$ Hz, $H_{Bn}$), 4.73 (d, 1H, $^3J = 4.9$ Hz, $H_\gamma$), 4.58 (d, 1H, $^2J = 15.1$ Hz, $CH_2_{PMB}$), 4.18 (ddd, 1H, $^2J = 10.4-11.2$ Hz, $^3J = 5.0$ Hz, $^3J = ??$ Hz, $H_\beta$), 4.11 (d, 1H, $^2J = 15.1$ Hz, $CH_2_{PMB}$), 4.07-3.93 (m, 1H, $H_\alpha$), 3.81 (s, 3H, OCH$_3$), 3.73-3.59 (m, 1H, $H_\alpha$).

$^{13}$C-$^1$H-NMR (CDCl$_3$) $\delta$/ppm: 167.0 (C=O), 159.4, 136.5, 129.5, 128.6, 128.3, 128.0, 127.0, 114.4, 81.8, 73.5, 68.6 ($^2J(C-F) = 13.0-13.4$ Hz, $C_\alpha$), 55.3, 54.2 ($^3J(C-F) = 4.9$ Hz $C_\beta$), 43.9.

$^{19}$F-NMR (CDCl$_3$) $\delta$/ppm: 83.3 (9 signals, 1F, $^2J(F-F) = 146.7$ Hz), 67.0 (dt, 4F, $^2J(F-F) = 146.7$ Hz, $^3J(F-H) = 8.3$ Hz).

HRMS (ESI, positive): Exact mass calcd. $C_{19}H_{20}F_5NO_3S [M]^+$ requires $m/z$: 437.1079, found $m/z$: 437.1092.
1H-NMR (CDCl3) δ/ppm: 7.41-7.30 (m, 5H, H_Bn), 5.73 (dddd, 1H, J_trans = 16.0 Hz, J_cis = 10.5 Hz, J = 6.7 Hz, J = 5.7 Hz, CH=CH2), 5.25 (dm, J = 10.5 Hz, CH=CH_cis), 5.24 (dm, J = 16.0 Hz, CH=CH_trans), 4.82 (AB, 2H, J = 11.7 Hz, H_Bn), 4.78 (d, 1H, J = 4.9 Hz, H), 4.37-4.32 (m, 1H, H), 4.09-4.02 (m, 1H, CH2N), 3.68 (dd, 1H, J(H-H) = 15.7 Hz, J(H-H) = 6.8 Hz, CH3N).

13C-1H-NMR (CDCl3) δ/ppm: 166.9 (C=O), 136.4, 131.0, 128.6, 128.3, 128.0, 119.4, 81.8, 73.4, 69.0 (p, J(C-F) = 13.0-13.2 Hz, Cα), 54.5 (p, J(C-F) = 4.8-5.0 Hz, Cβ), 43.0.

19F-NMR (CDCl3) δ/ppm: 83.3 (9 signals, 1F), 67.0 (dt, 4F, J(F-F) = 146.1 Hz, J(F-H) = 8.2 Hz).

HRMS (ESI, positive): Exact mass calcd. C14H16F5NO2S [M]+ requires m/z: 357.0822, found m/z: 357.0808.

1H-NMR (CDCl3) δ/ppm: 7.41-7.29 (m, 5H, H_Bn), 6.30 (dq, 1H, J_trans = 14.5 Hz, J = 1.7 Hz, NCH), 5.25 (dq, 1H, J_trans = 13.7 Hz, J = 6.7 Hz, NCHCH), 4.82 (AB, 2H, J = 11.7 Hz, H_Bn), 4.78 (d, 1H, J = 4.8 Hz, H), 4.53 (ddd, 1H, J = 8.4 Hz, J = 4.8 Hz, J = 2.1 Hz, H), 4.30-4.16 (m, 1H, H), 4.00-3.86 (m, 1H, H), 1.71 (dd, 3H, J = 6.8 Hz, J = 1.5 Hz, CH3).

13C-1H-NMR (CDCl3) δ/ppm: 163.1 (C=O), 136.4, 128.5, 128.2, 127.9, 120.3, 110.7, 80.9, 73.5, 65.4 (m, Cα), 54.2 (m, Cβ), 15.1.

19F-NMR (CDCl3) δ/ppm: 83.2 (9 signals, 1F), 66.8 (dt, 4F, J(F-F) = 146.7 Hz, J(F-H) = 8.0 Hz).
CF$_3$SF$_4$ Analytical Data:

![Chemical Structure](image)

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -43.07 (s), -46.17 (s).

![Chemical Structure](image)

$^{19}$F NMR (376 MHz, CDCl$_3$) δ 103.77 (q, $J_{F-F} = 22.0$ Hz), -65.79 (p, $J_{F-F} = 22.7$ Hz).

![Chemical Structure](image)

$^{19}$F NMR (376 MHz, CDCl$_3$) δ 36.50 (qd, $J = 25.3$, 6.0 Hz), -64.09 – -64.43 (m).

![Chemical Structure](image)

$^{19}$F NMR (376 MHz, CDCl$_3$) δ 34.13 (qd, $J = 25.5$, 7.0 Hz), -64.07 (p, $J = 25.4$ Hz).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 100.25 (p, $J = 11.6$ Hz), 63.46 (p, $J = 4.5$ Hz).

![Chemical Structure](image)

$^{19}$F NMR (376 MHz, CDCl$_3$) δ 44.08 (qd, $J =16.20$, 7.91 Hz), -64.36 (p, $J = 24.4$ Hz).
$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ 65.72 (dt, $J = 15.8$, 7.7 Hz), $\delta$ 81.03 (p, $J = 146.34$ Hz).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ 42.98 (qt, $J = 25.02$, 8.34 Hz), -64.43 (p, $J = 25.02$ Hz).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ 43.11 (qd, $J = 24.39$, 8.95 Hz), -64.25 (p, $J = 24.3$ Hz).
References:


SF₅ Spectra:

CvH-F SF₅ acid aldehyde 27

F₅S

Cl

18a
CvH-F 32 pure again

Ph

SF₅

25c
C-NH-H pure again
Proton
CF$_3$SF$_4$Cl Spectra:

 CvH-F_2 22

F
F
F
F
F
S
S
F

F
F
S
Cl

F
F
S
Cl
SF₄CF₃
Cl
58
ClSF₄CF₃

CvH+F 2,4,5 substituent concentrated

73