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Strain-Release Pentafluorosulfanylation

By

YANNICK KRAEMER
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:

Prof. Cody Ross Pitts, Chair

Prof. Jared T. Shaw

Prof. Dean J. Tantillo

Committee in Charge

2026

Abstract of Dissertation

This dissertation is comprised of five published bodies of work pertaining to strain-release pentafluorosulfanylation. Until recently, extant methods to introduce the pentafluorosulfanyl functional group to aliphatic organic molecules have solely focused on the addition of a pentafluorosulfanyl-centered radical to a non-aromatic π -bond. The major innovation that enabled the entirety of the work explored in this dissertation was the addition of the SF₅ radical intermediate to strained σ -bonds. Following the introductory chapter, Chapter 2 details the advent of strain-release pentafluorosulfanylation. That is, a method for the formal chloropentafluorosulfanylation with the canonical strain-release reagent – [1.1.1]propellane – was developed, creating access to a novel “hybrid bioisostere.” In Chapter 3, this synthetic logic is extended to the exploration of a curious polarity-mismatched case of formal chloropentafluorosulfanylation of sulfone- and carbonyl-substituted bicyclo[1.1.0]butanes. The operative mechanisms were of fundamental interest, paving the way for computational investigation and mechanistic experiments. In Chapter 4, the propensity of bicyclo[1.1.0]butanes (BCBs) to act as “spring-loaded” electrophiles is leveraged to create divergent access to complementary OCF₃- and OSF₅-containing cyclobutane building blocks. Chapter 5 reports a rare instance heteroatom–SF₅ bond formation employing 3-aryl azabicyclo[1.1.0]butanes as substrates. The resulting pentafluorosulfanylated azetidines were then evaluated as lipophilic bioisosteres for small sulfonamides through *in vitro* ADME assays. Finally, Chapter 6 chronicles the application of a tetrafluorosulfanyl(aryl)bicyclopentane in the context of materials design and thermosolient crystals. Upon cooling a single crystal of this compound, the sample violently shattered into small fragments. Extensive mechanistic studies revealed that the phase transition of a trace impurity concomitant with a phase transition at the interface with the bulk material leads to the observed destruction.

Für meine Großeltern

Epigraph

*Listen, hear he is inside
One who lives while others lie
I will close my eyes and walk a thousand years
A thousand years that aren't mine, hey
It seems he's near me as I walk
One who loved what love denied
He lives these years that I walk blind
All these years that cannot be mine*

-Kim A. Thayil

*See you all from time to time
Isn't it so strange how far away we all are now?
Am I the only one that remembers that summer?
Oh-Oh I remember
Every day, each time the place was saved
The music that we made
The wind has carried all of that away*

-Layne T. Staley & Mark W. Lanegan

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Publications Drawing Upon this Dissertation

- 1) **Kraemer, Y.**,[†] Ghiazza, C.;[†] Ragan, A. N.; Ni, S.; Lutz, S.; Neumann, E. K.; Fetting, J. C.; Nöthling, N.; Goddard, R.; Cornella, J.;^{*} Pitts, C. R.* "Strain-release Pentafluorosulfanylation and Tetrafluoro(aryl)sulfanylation of [1.1.1]Propellane: Reactivity and Structural Insight" *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892.
- 2) **Kraemer, Y.**; Buldt, J. A.; Kong, W.-Y.; Stephens, A. M.; Ragan, A. N.; Park, S.; Haidar, Z. C.; Patel, A. H.; Shey, R.; Dagan, R.; McLoughlin, C. P.; Fetting, J. C.; Tantillo, D. J.;^{*} Pitts, C. R.* "Overcoming a Radical Polarity Mismatch in Strain-Release Pentafluorosulfanylation of [1.1.0]Bicyclobutanes: An Entryway to Sulfone- and Carbonyl-Containing SF₅-Cyclobutanes" *Angew. Chem. Int. Ed.* **2024**, *63*, e202319930.
- 3) **Kraemer, Y.**; Stephens, A. M.; Buldt, J. A.; Young, A.; McLoughlin, C. P.; Fetting, J. C.; Holder, L. M.; Pitts, C. R.* "Strain-Release Trifluoromethoxylation and Pentafluorosulfanylation of [1.1.0]Bicyclobutanes: Expanded Access to Fluorinated Cyclobutane Hybrid Bioisosteres" *Chem. Commun.* **2025**, *61*, 3159-3162.
- 4) Ragan, A. N.;[†] **Kraemer, Y.**,[†] Chaudhary, S. K.; Fonoti, O. J.; Cook, C.; Liu, G.-y.;^{*} Trapp, N.;^{*} Koski, K. J.;^{*} Pitts, C. R.* "Tetrafluoro(aryl)sulfanylated Bicyclopentane Crystals that Self-Destruct upon Cooling" *J. Am. Chem. Soc.* **2025**, *147*, 1463-1473.

- 5) **Kraemer, Y.**[†] Park, S.;[†] Kong, W.-Y.; Chen, Y.; Witt, A. J.; Buldt, J. A.; Ragan, A. N.; Holder, L. M.; Tantillo, D. J.;^{*} Pitts, C. R.^{*} "Direct *N*-SF₅ and *N*-SF₄CF₃ Bond Formation through Strain-Release Functionalization of 3-Substituted [1.1.0]Azabicyclobutanes" *J. Am. Chem. Soc.* **2025**, *147*, 27892-27904.

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Publications Not Included in this Dissertation

- 1) **Kraemer, Y.**; Bergman, E. N.; Togni, A.;* Pitts, C. R.* "Oxidative Fluorination of Heteroatoms Enabled by Trichloroisocyanuric Acid and Potassium Fluoride" *Angew. Chem. Int. Ed.* **2022**, *61*, e202205088.
- 2) Ragan, A. N.;[†] **Kraemer, Y.**;[†] Kong, W.-K.;[†] Prasad, S.; Tantillo, D. J.;* Pitts, C. R.* "Evidence for C-F Bond Formation through Formal Reductive Elimination from Tellurium(VI)" *Angew. Chem. Int. Ed.* **2022**, *61*, e202208046.
- 3) Buldt, J. A.;[†] Kong, W.-Y.;[†] **Kraemer, Y.**; Belsuzarri, M.; Patel, A. H.; Fetting, J. C.; Tantillo, D. J.;* Pitts, C. R.* "Controlled Oligomerization of [1.1.1]Propellane through Radical Polarity Matching: Selective Synthesis of SF₅- and CF₃SF₄-Containing [2]Staffanes" *Beilstein J. Org. Chem.* **2024**, *20*, 3134-3143.
- 4) Stephens, A. M.; Olvera, J. A.; Kraemer, Y.; Vu, T.; Kong, W.-Y.; Chaturvedi, S.; Wang, J. M.; Tantillo, D. J.;* Pitts, C. R.* "Strain-Release Pentafluorosulfanylation of Carbonyl-Containing Disubstituted Bicyclobutanes: Insight on SF₅···C=O Interactions and a Fortuitous Path to SF₅-Containing Oxa[2.1.1]bicyclohexanes" *ChemRxiv* **2025**, DOI: 10.26434/chemrxiv-2025-xtbsz.

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Chapter 1: Introduction

1.1 Introduction.

The work presented in this dissertation is predicated upon the merger of two distinct subfields of organic chemistry: 1) the chemistry of the pentafluorosulfanyl (SF_5) functional group and its congeners, and 2) strain-release functionalization of σ -bonds. The simple, yet powerful idea of merging SF_5 radical chemistry with strain-release functionalization paved the way for method development, mechanistic studies, applications of hybrid bioisosteres in medicinal chemistry, materials chemistry, and beyond. To provide context for the advent of strain-release pentafluorosulfanylation, a brief background of the current state of the literature for both is presented below.

1.2 The Pentafluorosulfanyl Group.

First reported in 1950 by Silvey and Cady,¹ the pentafluorosulfanyl (SF_5) group is a highly fluorinated functional group that has attracted increased attention over the last several years due to its unique properties, including high lipophilicity, electronegativity, large van der Waals volume, and remarkable chemical stability (Figure 1.1).^{2a-c}

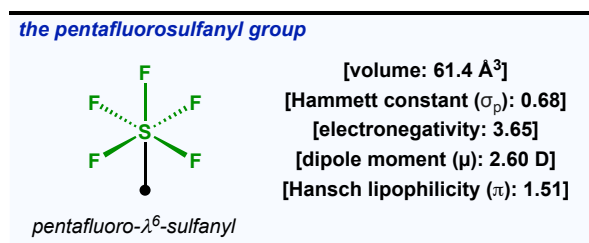


Figure 1.1 The pentafluorosulfanyl (SF_5) functional group.

The central sulfur atom of the SF₅ group exists in the 6+ oxidation state and typically adopts a distorted octahedral geometry. The S^{VI} atom also forms a three-center four-electron bond³ that localizes electron density on two equatorial fluorine atoms. Further, the SF₅ group has most often been compared to the trifluoromethyl (CF₃) and *tert*-butyl (*t*-Bu) groups due to similarities in electronegativity and size, respectively. For example, the electronegativity (χ) of the SF₅ group has been estimated to be 3.65 vs. 3.36 for CF₃. The Hammett constant (σ_p) of the pentafluorosulfanyl group in the *para* position of a benzene ring is slightly larger than that of the trifluoromethyl group (0.68 vs. 0.54), which provides additional context for its electron-withdrawing effect. Additionally, the van der Waals volume (V_{vdW}) of the SF₅ group is approximately 61.4 Å³, whereas the volume of the CF₃ group has been estimated to be 42.7 Å³. On the other hand, the V_{vdW} of the *tert*-butyl group (76.4 Å³) is closer to that of the SF₅ group and is predicted to have similar lipophilicity (π_p = 1.98 for *t*-Bu vs. 1.23 for SF₅).⁴ Ultimately, the combination of high lipophilicity and extreme electronegativity makes the SF₅ moiety an intriguing tool in the context of targeted molecular design. Indeed, productive incorporation of the SF₅ group into biologically active molecules,⁵ agrochemicals², and materials⁶ have been reported (Figure 1.2). Most notably, two anti-malarial drug candidates (DSM-265 and IWY357) bearing this motif have advanced to clinical trials, marking the first examples of small molecules containing the SF₅ group in the clinic.

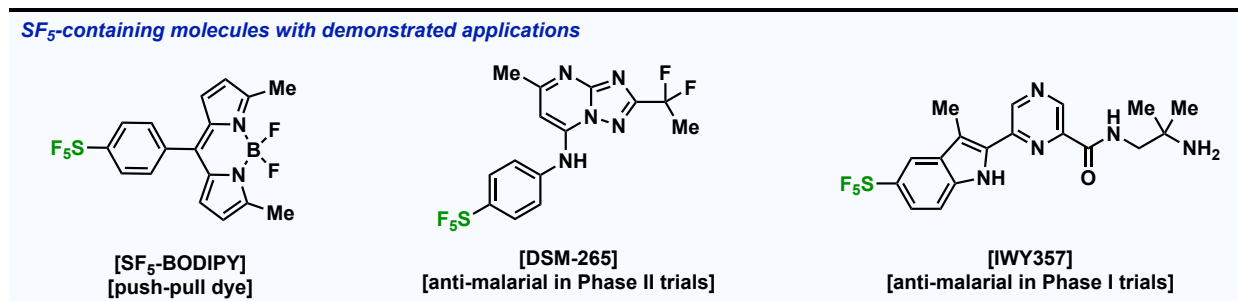


Figure 1.2 SF₅-containing molecules with demonstrated applications.

Despite these demonstrated applications, the SF₅ group remains underutilized in the broader chemical community. One reason for this incongruence lies with the scarcity of methods to synthesize SF₅-containing molecules. In brief, there exist two strategies for incorporating the SF₅ functional group: 1) synthesis of aryl-SF₅ compounds by a *bottom-up* oxidative fluorination approach, and 2) use of a transfer reagent to install the SF₅ group *via* SF₅ radical addition to π -bonds (or, as detailed in this thesis, strained σ -bonds).² A handful of protocols for aryl-SF₅ synthesis have been developed over the years, with innovation in the area being driven by increased safety and synthetic accessibility. Thus, the current state of the art has evolved to allow the practitioner to choose between free thiols or masked derivatives such as disulfides, sulfonyl phthalimides, phosphorothiolates, or trityl-protected thiolates as starting materials to subject to oxidative fluorination conditions (e.g., Cl₂/KF, AgF₂, F₂/N₂, or TCICA/KF, then [M]F).⁷ This strategy has enabled the establishment of a suite of Ar-SF₅ building blocks that account for a majority of known SF₅-containing compounds that are commercially available.

In contrast, access to aliphatic-SF₅-containing building blocks remains even more elusive, as most strategies to forge C(sp³)-SF₅ bonds require the use of pentafluorosulfanyl chloride (SF₅Cl) – a known source of the SF₅ radical. Pentafluorosulfanyl chloride is a toxic, corrosive gas that is rarely commercially available and has historically required the use of other harsh, toxic gas reagents to synthesize. Despite these drawbacks, SF₅Cl is the most reliable SF₅ transfer reagent to date and has been utilized in the addition of SF₅ to various π -bonds *via* radical chain propagation mechanisms.^{2a,b} A seminal report by Dolbier and co-workers in 2002, demonstrated that addition of SF₅Cl to olefins could be initiated at –45 °C using BEt₃/O₂.⁸ The method also smoothly

translated to SF₅Cl addition across alkynes, generating synthetically useful building blocks for the synthesis of SF₅-containing heterocycles.⁵

Given its demonstrated utility, the synthesis of SF₅Cl has been explored since 1959 when it was first synthesized from S₂F₁₀. Subsequent advancements from 1962–2009 still necessitated the use of difficult-to-handle toxic gases such as SF₄, Cl₂, and ClF; it was not until 2018 when Pitts, Santschi, and Togni disclosed the synthesis of SF₅Cl utilizing the innocuous trichloroisocyanuric acid (TCICA) in combination with KF and elemental sulfur that SF₅Cl became accessible without the use of specialized equipment (Figure 1.3).⁹ In 2021, a practical extraction protocol was reported by Qing and co-workers that enabled access to a stock solution of ~0.1 M SF₅Cl in a hydrocarbon solvent (hexanes), dismantling the economic and infrastructural barriers standing in the way of rapid innovation in this field.¹⁰ With access to SF₅Cl drastically improved, the stage was set for the development of new methodology to expand the accessible chemical space of SF₅-bearing molecules.

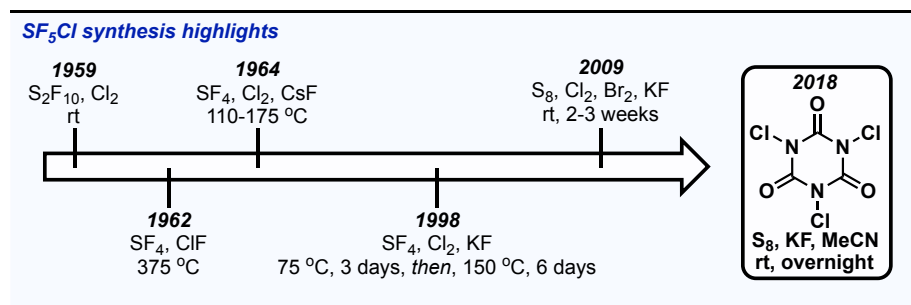


Figure 1.3. Timeline of major milestones in the synthesis of SF₅Cl since its discovery.

Contemporaneously to the work presented herein, the development of new, bench-stable SF₅ transfer reagents has begun to provide another avenue toward the democratization of SF₅ chemistry. For one, the Tlili group reported the development of imine-based SF₅ transfer reagents that liberate SF₅ radicals under energy transfer catalysis, as well as their applications in both imino- and hydro-pentafluorosulfanylation.¹¹ Simultaneously, Paquin and co-workers disclosed a

sulfonyl-based transfer reagent that generates SF₅ radicals following reduction and the release of SO₂ and ethylene gas. Later in the same year, Qin and co-workers developed a suite of bench-stable SF₅-transfer reagents (synthesized from SF₅Cl) that operate following a similar mechanism (in this case producing an equivalent of CO₂).¹² These advances will undoubtedly enable further innovation in the field pentafluorosulfanyl chemistry.

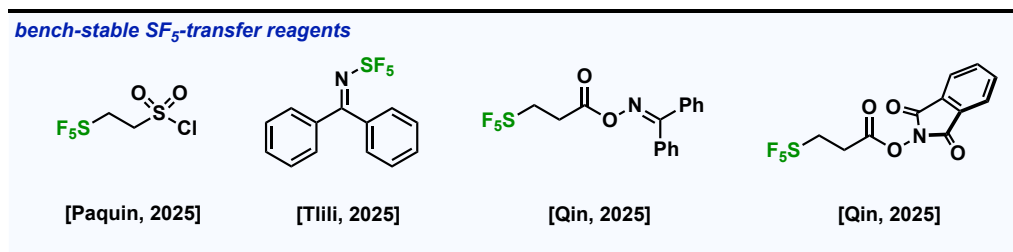


Figure 1.4. Emerging shelf-stable SF₅-transfer reagents.

Finally, it is worth noting that within the same timeline, the synthesis of SF₅Cl has been iteratively improved between our group, as well as by the Qing and Guo laboratories. In fact, the synthesis of SF₅Cl is now possible without the need for a glovebox or specialized pressure vessels. In all, pentafluorosulfanylation chemistry is gaining steady momentum, and future directions will likely focus on strategies for late-stage pentafluorosulfanylation on more complex substrates.

1.3 Strain-Release Reagents.

Strain-release functionalization is a reaction paradigm whereby a reaction is driven by the substantial release of ring-strain. This concept has led to the development of a suite of so-called strain-release reagents that are small carbocycles characterized by the presence of a highly strained σ -bond (Figure 1.5).¹³ The reagent with the highest strain energy is [1.1.1]propellane, which was theoretically predicted in 1971 by Newton and Schulman¹⁴ and first synthesized by Wiberg and Walker¹⁵ in 1982. It has a predicted ring strain of approximately 98 kcal mol⁻¹. Formal hydrogenation of the central bond results in the formation of a bicyclopentane (BCP), which itself

contains a substantial amount of ring strain energy (67 kcal mol^{-1}).¹⁶ An unsubstituted bicyclo[1.1.0]butane (BCB) exhibits a large ring strain energy of approximately $66.3 \text{ kcal mol}^{-1}$, which is $39.8 \text{ kcal mol}^{-1}$ greater than the ring-opened cyclobutane product. Similarly, substitution of one bridgehead carbon atom for a nitrogen atom gives aza-bicyclo[1.1.0]butanes (ABBs), which have ring strain energies of approximately 66 kcal mol^{-1} compared to $26.3 \text{ kcal mol}^{-1}$ for an azetidine.¹⁷ The final, least strained class of strain-release reagents are the bicyclo[2.1.0]pentanes (colloquially known as “housanes”), which have a calculated ring strain of $54.7 \text{ kcal mol}^{-1}$.¹⁶ It is also worth noting that several higher order propellanes (e.g., [3.1.1], [2.2.1], and [2.2.2]propellane) have also been synthesized but remain less explored than their [1.1.1] counterpart due to challenging syntheses and lower relative thermodynamic stability.¹⁸

<i>strain-release reagents</i>				
				
ring strain energy	[1.1.1]propellane	bicyclo[1.1.0]butane	aza-bicyclo[1.1.0]butane	bicyclo[2.1.0]pentane
kcal/mol	98.2	66.3	~66.3	54.7
	↓	↓	↓	↓
				
ring strain energy	bicyclopentane	cyclobutane	azetidine	cyclopentane
kcal/mol	67	26.5	26.3	7.4

Figure 1.5. Structures and ring strain energies associated with common strain-release reagents.¹³

Strain-release reagents are generally reactive towards nucleophiles, electrophiles, and radicals as a consequence of the high p-character the central bonds possess. In fact, the bent σ -bond of BCBs has been theorized to consist of 96% p-character. The central bond of housanes was predicted to be similar in nature to that of BCBs, while the transannular bond of ABBs is considered to contain pure p character. The central bond in [1.1.1]propellane is has been described as a charge-shift bond that experimentally behaves similarly to a π bond in atom transfer radical

addition (ATRA) reactions. For example, it can be opened to the bridgehead anion following nucleophilic attack. Conversely, activation with an electrophilic reaction partner may result in BCP ring opening to form an exocyclic cyclobutene. These structural features have inspired the development of diverse synthetic methods, some of which are briefly summarized in Figure 1.6 (*vide infra*).¹⁹

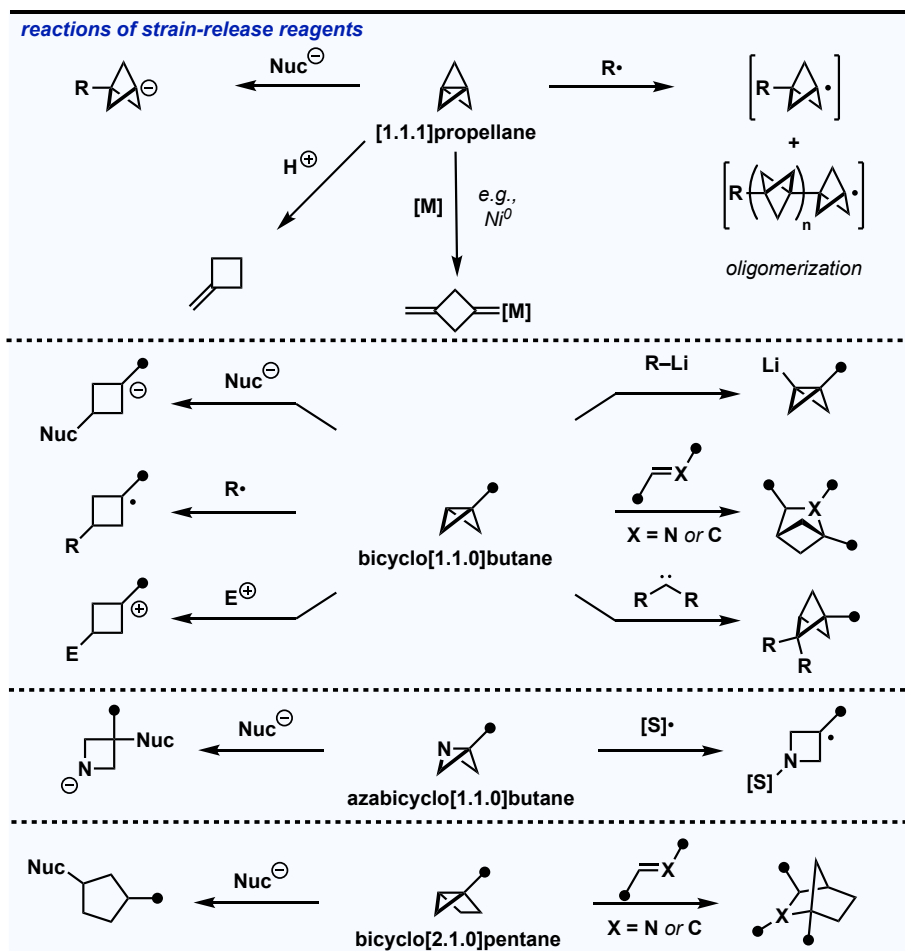


Figure 1.6. Summary of known reactions of strain-release reagents.

The observed rise in interest in these reagents can be largely attributed to the increasing demand for novel bioisosteric replacements for comparably more easily accessible benzene derivatives and aromatic heterocycles.²⁰ As outlined in Lovering, Bikker, and Humblet's "*Escape from Flatland*," increasing the fraction of Csp³ atoms in biologically active chemical matter can

improve drug-like properties, driving innovation in this area.²¹ Additionally, these small rings allow for additional control over molecular geometry and spatial orientation of functional groups.²² In summary, exploring the reactivity of these diverse molecules remains a vibrant area of research. A strong emphasis has been placed on those reactions that generate access to novel ring systems that may be of value in the pharmaceutical industry.

1.4 Organization of the Chapters.

Each chapter within this dissertation represents a previously *published* body of work with only minor alterations made to the text to fit the thesis format. The chapters are organized thematically to tell the story of the evolution of strain-release pentafluorosulfanylation within the laboratory.

1.5 Brief Overview.

Strain-release pentafluorosulfanylation began with a collaboration between our laboratory and the Cornella laboratory at the Max-Planck-Institut für Kohlenforschung. Recent advancements in oxidative fluorination chemistry had enabled access to the valuable SF₅ transfer reagent, pentafluorosulfanyl chloride (SF₅Cl), prompting us to explore the development of new methods to install this underutilized functional group. Ultimately, it was found that SF₅Cl reacted with [1.1.1]propellane under white LED irradiation to afford the chloropentafluorosulfanylated bicyclopentane (BCP) adduct SF₅–BCP–Cl, a molecule that contains two distinct elements of bioisosterism. This result laid the foundation of the work that was to follow and is described in detail in Chapter 2. Despite our best efforts, applications of this “hybrid bioisostere” remained elusive at the time, mostly due to the unexpected challenges in functionalizing the bridgehead C–Cl bond. However, characterization of SF₅–BCP–Cl in the solid state by single crystal X-ray diffraction (SC-XRD) revealed a curiously short C···C non-bonding distance, prompting a more

detailed analysis. Beyond the addition of SF₅Cl it was found that tetrafluoro(aryl)sulfanyl chlorides (ArSF₄Cl) could also undergo strain-release addition to [1.1.1]propellane. Following the development of a distinct set of reaction conditions, a small scope of Ar–SF₄–BCP–Cl compounds was synthesized. Ultimately, this venture into [1.1.1]propellane functionalization established critical proof-of-concept that SF₅ radicals could add across strained σ -bonds and defined the direction of research in the laboratory for the next several years.

In Chapter 3, extension of the strain-release pentafluorosulfanylation logic to bicyclo[1.1.0]butanes (BCBs) is described. Irradiation of a sulfone-containing BCB substrate with SF₅Cl led to a pentafluorosulfanylated cyclobutane (CB) with high regioselectivity for the less sterically hindered 3-position. Interestingly, this regioselectivity is observed despite a glaring radical polarity mismatch, which ostensibly is overcome with the additional driving force of strain release. This avenue prompted further method development, ultimately leading to the development of a copper-mediated *anti*-selective variant, a formal one-pot hydropentafluorosulfanylation, tetrafluoro(aryl)- and tetrafluoro(trifluoromethyl)sulfanylation, and 3-component reactions. Several mechanistic aspects were studied in collaboration with the Tantillo laboratory, shedding light on the observed regio- and diastereoselectivity.

Following the success of the atom transfer radical addition (ATRA) reactions that were developed with BCBs, we next wondered if we could expand the repertoire of fluorinated CBs using weak nucleophiles, such as AgOCF₃ or AgOSF₅. In Chapter 4, the additional driving force of strain-release afforded by BCBs was leveraged to synthesize trifluoromethoxy- and pentafluorosulfanoxy-containing CBs. This strategy enabled divergent access to a small suite of fluorinated CBs, which were evaluated as hybrid bioisosteres through *in vitro* absorption, distribution, metabolism, and excretion (ADME) profiling. The results of these preliminary assays

showed for the first time that these hybrid bioisostere motifs are viable for use in medicinal chemistry campaigns.

At this juncture, our experience with BCBs and the results of studies in the laboratory led by Jón Buldt and Alexander Stephens demonstrated that both the electrophilic nature of the SF₅-centered radical and substituent effects could have a large effect on reaction outcomes. With these themes in mind, 3-aryl-1-azabicyclo[1.1.0]butanes (ABBs) were employed as substrates under pentafluorosulfanylation conditions, resulting in a rare example of direct *N*-SF₅ bond formation (Chapter 5). The reaction was also found to proceed using CF₃SF₄Cl as a surrogate, enabling comparative studies throughout the project. We once again teamed up with the Tantillo laboratory to study mechanistic details and other properties of the newly accessible azetidines including inversion barriers, bond dissociation energies, p*K*_a, and more. Lastly, the application of the *N*-SF₅ moiety as a lipophilic replacement for a methyl sulfonamide was also explored with the help of Dr. Lauren Holder at Novartis, lending credence to the notion that these azetidines may be useful building blocks in the context of medicinal chemistry.

Finally, Chapter 6 details the serendipitous discovery of a tetrafluoro(aryl)bicyclopentane single crystal that violently self-destructs upon cooling below 193 K. During the structural survey of the products described in Chapter 2, we discovered this effect upon cooling a sample under the cryostream of the diffractometer. Such dramatic thermosalient responses upon cooling are relatively scarce in the literature, which motivated us to investigate the mechanism of this unexpected transformation. A multi-disciplinary study with support from the Liu and Koski groups at UC Davis and Dr. Nils Trapp at ETH Zürich ultimately revealed the role of a sulfone hydrolysis product as a catalyst in a destructive phase transition.

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Chapter 2: Strain-Release Pentafluorosulfanylation and Tetrafluoro(aryl)sulfanylation of

[1.1.1]Propellane: Reactivity and Structural Insight.

2.1 Introduction.

The pentafluorosulfanyl (SF_5) group is situated on an exclusive list of fluorinated functional groups with documented utility that remain underemployed.²³ The reason for this dissonance is attributed to limited pentafluorosulfanylation methods and reagents, particularly with respect to introducing the SF_5 group to aliphatic frameworks.²⁴ For instance, SF_5Cl gas – one of the few reliable sources of SF_5 radicals with applications in $\text{C}(\text{sp}^3)\text{--SF}_5$ synthesis²⁵ – has been historically difficult to synthesize and handle,²⁶ thus preventing widespread adoption of the chemistry and impeding further innovation. This contrasts with the relative accessibility of its $\text{Ar-SF}_4\text{Cl}$ congeners,²⁷ which are analogous sources of Ar-SF_4 radicals with applications in $\text{C}(\text{sp}^3)\text{--SF}_4\text{Ar}$ synthesis.²⁸

However, as part of a larger effort to make polyfluorinated groups more accessible in 2019,²⁹ the first user-friendly, gas-reagent free synthesis of SF_5Cl in the patent literature through oxidative fluorination of S_8 using inexpensive trichloroisocyanuric acid (TCICA) and potassium fluoride was disclosed.³⁰ In 2021, Qing and co-workers reported an optimized workup protocol for this TCICA/KF approach whereby SF_5Cl can be extracted directly into hexanes to produce a storable stock solution, *thus obviating the need to handle SF_5Cl as a gas*.³¹ Together, these recent advancements not only enable the broader chemical community to synthesize their own SF_5Cl solution more safely, but facilitates the invention of pentafluorosulfanylation reactions and the study of heretofore unknown SF_5 -containing motifs.³²

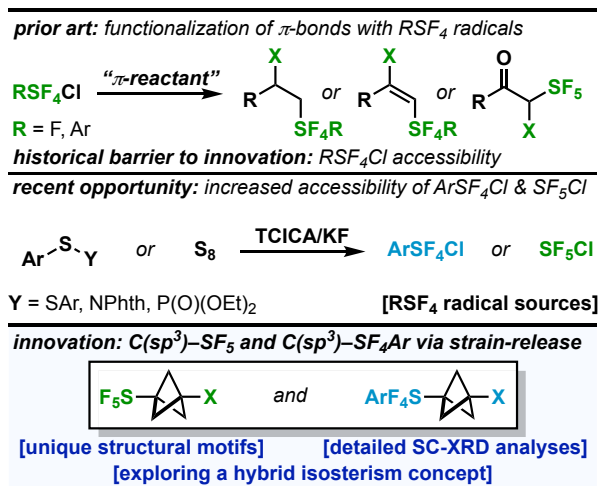


Figure 2.1. Strain-release pentafluoro- and tetrafluoro(aryl)sulfanylation in context. (*Top panel*) Known reactivity of SF_4R radicals and barrier to innovation. (*Middle panel*) Recent increased accessibility of key reagents. (*Bottom panel*) This work.

To date, the known methods of forming $C(sp^3)-SF_5$ and $C(sp^3)-SF_4Ar$ bonds from either SF_5 or $Ar-SF_4$ radicals involve formal addition to π -systems (Figure 2.1, *top*). Alternatively, with the key reagents more accessible (Figure 2.1, *middle*), we sought opportunities to add SF_5Cl and $Ar-SF_4Cl$ compounds across other types of bonds such as the central bond in [1.1.1]propellane.³³ Conceptually, the result of combining SF_5 radical chemistry with strain-release functionalization³⁴ would enable investigation of the structural consequences of merging a bioisosteric replacement for phenyl groups or alkynes (i.e., bicyclopentane, or “BCP”)³⁵ with a bioisosteric surrogate for trifluoromethyl or *tert*-butyl groups (i.e., SF_5).³⁶ Additionally, appending an $Ar-SF_4$ moiety with a BCP ring would provide access to another type of hybrid isostere that may be of interest in the design of materials, such as liquid crystals.³⁷

Herein, we report a mild, radical pentafluorosulfanylation and tetrafluoro(aryl)sulfanylation of [1.1.1]propellane (Figure 2.1, *bottom*). Based on a detailed structural analysis of this unusual SF_5 -BCP motif, we also found that the resulting transannular $C\cdots C$ distance in SF_5 -BCP-Cl is one of the shortest allegedly nonbonding $C\cdots C$ distances reported in the CSD (see Section 2.5 for search details). This prompted synthesis of a suite of

tetrafluoro(aryl)sulfanyl derivatives and extensive single-crystal X-ray diffraction (SC-XRD) and NMR comparative analyses. Furthermore, the nature of the dramatic impact of the SF₅ group on the BCP ring scaffold was studied further using density functional theory (DFT).

2.2 Results and Discussion.

We began our investigation by applying a well-established strategy to generate SF₅ radicals from SF₅Cl (i.e., using catalytic BEt₃/O₂) in the presence of [1.1.1]propellane (**1**).³⁸ The desired SF₅-BCP-Cl product (**2**) was observed by ¹⁹F NMR in a promising 48% yield.³⁹ This prompted an optimization campaign that led to the discovery that irradiating SF₅Cl and **1** with white LEDs for 4 h would ultimately allow isolation of volatile **2** in 86% yield (Figure 2.2, *top left*).

Based on previous literature on both SF₅Cl and **1**, a radical chain propagation mechanism is most likely at play following initial formation of SF₅ radicals (see Section 2.5 for calculated free energy profiles).⁴⁰ Control experiments indicate that SF₅Cl does not undergo decomposition under irradiation with white LEDs in the absence of **1**, suggesting **1** is involved in the initiation step.⁴¹ It is plausible that SF₅ radicals are formed initially through visible light-excitation of an electron donor-acceptor complex between SF₅Cl and **1** and then propagate a radical chain reaction, similar to the mechanism proposed by Paquin and co-workers.^{25b} Additionally, we isolated a minor byproduct (**3**) in 7% yield that incorporates two bicyclopentane motifs; similar types of dimerization products (i.e., “[2]staffanes”) have been observed previously in radical chain processes involving **1**.⁴² The difference in free energies calculated at ωB97XD/6-311++G** (using the default Et₂O solvent continuum) for the product determining steps are also consistent with our observed selectivity, as the path from putative INT-1 to **2** is 17 kcal/mol more exergonic than to INT-2 (Figure 2.2, *top right*).

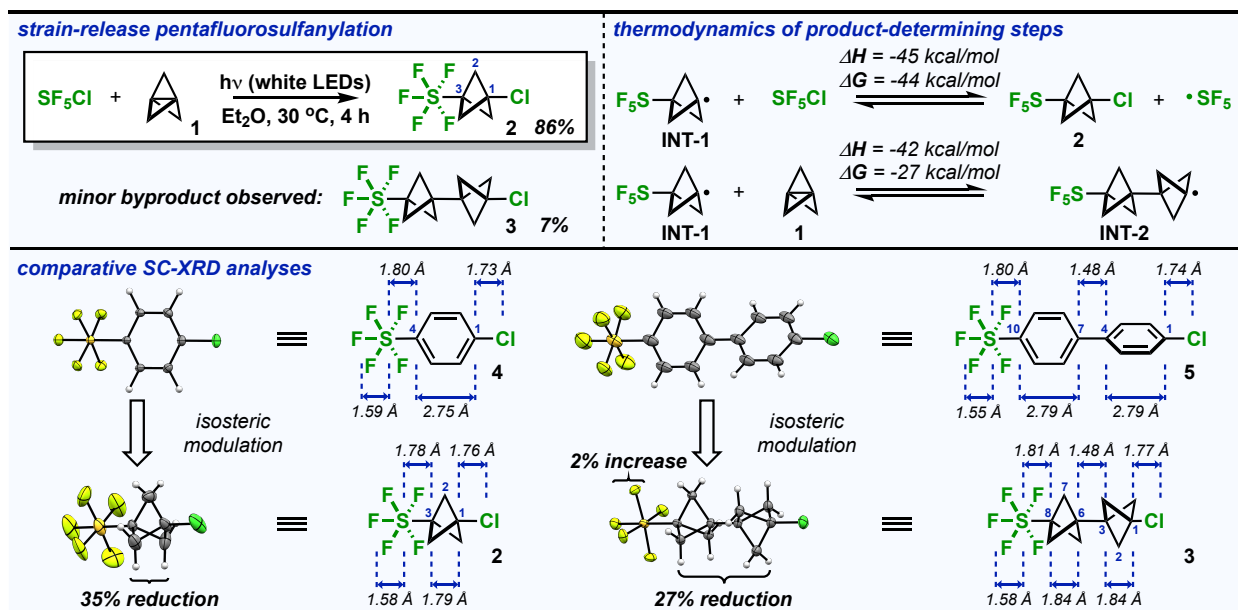


Figure 2.2 (Top left panel) Major product **2** (and minor byproduct **3**) observed under optimized pentafluorosulfanylation conditions, using 1.5 equiv. SF_5Cl and 1.0 equiv. **1**. Isolated yields reported. (Top right panel) Thermodynamic parameters associated with the product-determining steps, calculated at wB97XD/6-311++G** using the default Et_2O solvent continuum. (Bottom panel) Structural differences in the linear array of atoms upon net replacement of benzene rings in **4** and **5** with bicyclopentane (BCP) rings to make “hybrid” SF_5 -BCP isosteres **2** and **3**. Structures determined by single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability). Only non-disordered parts are shown for clarity.

After much effort, we also managed to grow single crystals of **2** suitable for X-ray diffraction to examine the SF_5 -BCP motif in the solid state at 100 K (Figure 2.2, bottom). The most striking feature is the exceptionally short transannular $\text{C}_1 \cdots \text{C}_3$ distance of 1.789(6) Å (libration corrected value: 1.800 Å).⁴³ It is notably within error of the transannular $\text{C}_1 \cdots \text{C}_3$ distance reported for Adcock and co-workers’ pyridinium-substituted bicyclopentane – 1.80(2) Å – which they claimed at the time was, “*not only the shortest nonbonding contact for bicyclo[1.1.1]pentanes but also for any known organic compound.*”⁴⁴ To put it in perspective, the transannular distance in **2** is significantly shorter than in an unsubstituted [1.1.1]bicyclopentane (with a transannular distance of ~1.85-1.87 Å)⁴⁵ and is approaching that of one of the longest C–C bonds reported (i.e., 1.780(7) Å).⁴⁶

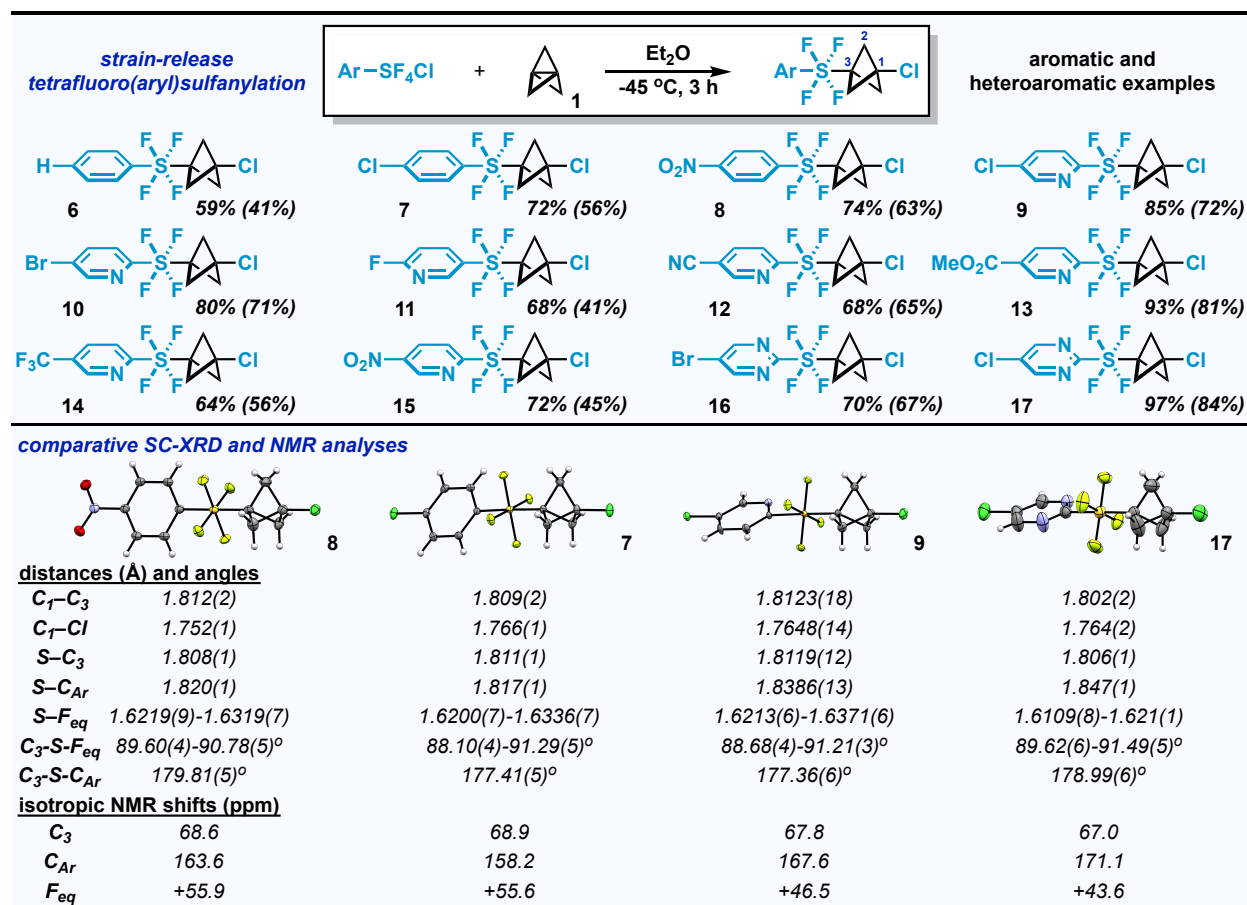


Figure 2.3. (Top panel) Reaction scope under optimized tetrafluoro(aryl)sulfanylation conditions, using 1.0 equiv. ArSF_4Cl and 1.2 equiv. **1**. ^{19}F NMR yields are reported; isolated yields are in parentheses. (Bottom panel) Structural differences and select ^{13}C and ^{19}F NMR data associated with the linear array of atoms upon systematic alteration of electronic properties of the (hetero)arene. Structures determined by single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability).

To put the structural features of the linear array of atoms about the $\text{C}_1\text{--C}_3$ axis of **2** into context, we obtained SC-XRD data for $\text{SF}_5\text{--Ph--Cl}$ (**4**). This allowed us to assess the consequences of $\text{Ph} \rightarrow \text{BCP}$ isosteric replacement in the presence of an SF_5 group (Figure 2.2, bottom). While maintaining a relatively linear central axis, the $\text{C}_1\cdots\text{C}_3$ transannular distance in **2** is attenuated by ~35% relative to the $\text{C}_1\cdots\text{C}_4$ distance in **4** (2.745(1) Å). The C–S bond in **2** is marginally shorter than in **4** (1.779(4) Å⁴³ vs. 1.7952(6) Å, respectively), while the C–Cl bond in **2** is slightly longer than in **4** (1.759(5) Å⁴³ vs. 1.7302(6) Å, respectively). The equatorial fluorine (F_{eq}) atoms of the

SF₅ group on both **2** and **4** sport average S–F_{eq} distances of ~1.57-1.59 Å, and $\theta_{C3-S-Feq}$ for both **2** and **4** deviates only slightly from perpendicularity on average (i.e., ~92.3° vs. ~92.6°). We also noted that the axial S–F_{ax} bond distance in **2** at 1.579(4) Å⁴³ is within range of **4** (1.5869(5) Å).

Additionally, we obtained SC-XRD data for the [2]staffane byproduct – SF₅-BCP-BCP-Cl (**3**) – to compare alongside **2** as well as the previously published structure of its SF₅-Ph-Ph-Cl congener, **5** (Figure 2.2, *bottom*).⁴⁷ In this case, both transannular C···C distances in the bicyclopentane rings of **3** (1.835(4) Å and 1.839(4) Å) are notably longer than that of **2**. Alternatively, the conduit C–C bonds connecting the ring structures in **3** and **5** are similar in length; this makes the composite effect of replacing both Ph rings in the biphenyl array with BCP rings a ~27% reduction in distance between the terminal carbon atoms. Also, similar to **2** vs. **4**, the C–Cl bond in **3** is longer than in **5**, and average S–F_{eq} distances are ~1.58-1.60 Å in each case. However, the S–F_{ax} bond in **3** is ~2% longer than in **5**.

At this juncture, we envisioned that incorporation of an Ar-SF₄ moiety on the BCP ring instead of SF₅ would allow us to explore another concept in “hybrid isosterism,” as the *trans*-substituted -SF₄- linear architecture has been entertained as a replacement for an alkyne (or even a BCP ring).⁴⁸ This would also prove advantageous for further crystallographic analyses, as modification of the aryl group allows us to examine effects of remote substitution on the BCP ring. Under identical conditions to the reaction of SF₅Cl with **1**, we discovered that Ar-SF₄Cl compounds can indeed be converted into the desired Ar-SF₄-BCP-Cl products, albeit in modest yields. Thus, the reaction conditions were re-optimized explicitly for Ar-SF₄Cl addition across **1**.³⁹ Note that, in this case, the reaction proceeds spontaneously in the dark at –45 °C. The propensity of Ar-SF₄Cl compounds to react more readily with **1** than SF₅Cl is consistent with the fact that the S–Cl bond has been determined to be weaker in Ar-SF₄Cl compounds (i.e., computed

BDEs are on the order of 6-7 kcal/mol lower than the S–Cl BDE in SF₅Cl).^{28a} It is also known that both **1**⁴⁹ and Ar-SF₄Cl compounds,⁵⁰ independently, can initiate radical chain propagations spontaneously in some cases in the absence of a designated radical initiator or other initiation source, such as light.

We then explored the scope of accessible arene- and heteroarene-containing compounds under optimized conditions (Figure 2.3, *top*). For one, Ar-SF₄Cl starting materials containing benzene rings – either unsubstituted or substituted with electron-withdrawing groups – provided the desired addition products **6-8** in good yields. Moreover, starting materials containing pyridine rings with various halogen (**9-11**), cyano (**12**), ester (**13**), trifluoromethyl (**14**), and nitro (**15**) substituents performed generally well under specified conditions. Additionally, the scope includes examples of pyrimidine-containing products, such as **16** and **17** - the latter formed in 97% yield by ¹⁹F NMR and isolated in 84%. During these studies, we noted that pyridine- and pyrimidine-based products of all substitution patterns were *generally* less prone to decomposition during attempted purification than benzene-based products without a strong electron withdrawing substituent present (e.g., a nitro group), though we noted some exceptions (**6** and **7**). This phenomenon is in accord with what has been observed previously in compounds containing the Ar-SF₄ moiety,²⁸ and we have indicated a few examples of compounds in our Supporting Information where decomposition on silica gel (or basic alumina) was problematic, in contrast to the entries shown in Figure 2.3.

In the process of examining the reaction scope, we managed to obtain SC-XRD data on compounds **7**, **8**, **9**, and **17** (Figure 2.3, *bottom*). In this suite, the C₁⋯C₃ transannular distances are still unusually short but all slightly longer than that of **2**,⁴³ decreasing in the order of: **8** (1.812(2) Å) ~ **9** (1.8123(18) Å) > **7** (1.809(2) Å) > **17** (1.802(2) Å). The C₃–S bonds (ranging

from 1.806(1) Å in **17** to 1.8119(12) Å in **9**) and the S–F_{eq} bonds (average distances of ~1.62–1.64 Å in the series) are also both notably longer in these Ar–SF₄–BCP–Cl compounds than in **2**. The C₁–Cl bond distance in these four compounds varies but is centered around that of **2**, ranging from 1.752(1) Å in **8** to 1.766(1) Å in **7**. Another noticeable difference is that the $\theta_{C3-S-F_{eq}}$ in these Ar–SF₄–BCP–Cl compounds, on average, is closer to 90° than in **2**, where the equatorial fluorine atoms of the SF₅ group seem to pucker away from the BCP ring. This could be attributed to an increased repulsive interaction between the equatorial fluorine atoms and the BCP ring in **2**, as **2** exhibits a shorter C₃–S bond than the Ar–SF₄–BCP–Cl compounds. A trend can be found in the linear array of atoms in the four Ar–SF₄–BCP–Cl compounds in Figure 2.3: the C_{Ar}–S bond lengths increase as the (hetero)arenes become increasingly electron deficient, i.e., in the order of **7** (1.817(1) Å) < **8** (1.820(1) Å) < **9** (1.8386(13) Å) < **17** (1.847(1) Å). This type of trend has been observed previously in other compounds containing an Ar–SF₄ motif and is associated with an increase in ionic character in the C_{Ar}–S bond.^{28,51} The dramatic “downfield” shift in ¹³C NMR shift of the *ipso* carbon atom (C_{Ar}) from **7** to **17** is also consistent with this idea (note that the cross-ring C₃ atom ¹³C shift is less impacted by remote arene functionalization but experiences the opposite trend).

Additionally, we managed to obtain and analyze SC-XRD data for meta-stable Ar–SF₄Cl compounds **18** and **19** – the starting materials for **8** and **15**, respectively (Figure 2.4). When compared alongside the only other two Ar–SF₄Cl compounds reported in the solid state,⁴⁷ they seem to also follow this trend of increasing S–C_{Ar} distance with electron-withdrawing effect of the arene (concomitant with a decrease in S–Cl distance).

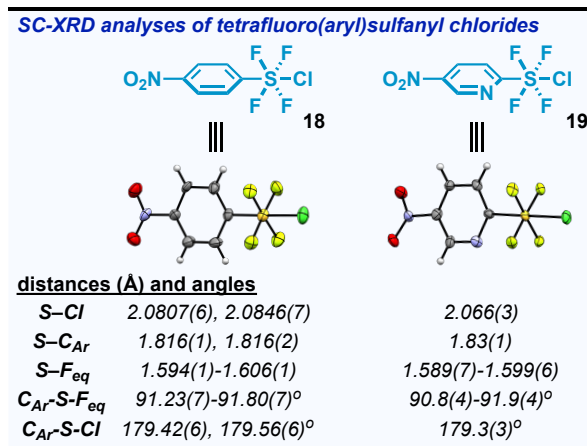


Figure 2.4. Structures of Ar-SF₄Cl starting materials determined by single-crystal X-ray diffraction (displacement ellipsoids depicted at 50% probability). The unit cell for **18** contains two symmetry-independent moieties (only one shown).

Finally, we sought more insight as to *why* the C₁⋯C₃ contact is so short in the structures included in this study, especially in the instance of **2**. Broadly, the tendency for σ-electron withdrawing groups to decrease the C₁⋯C₃ distance in BCP rings has been established in the literature and is often attributed to some type of through-space interaction involving the linear arrangement of atoms about the C₁–C₃ axis (e.g., both an attractive “percaudal” interaction⁵² and a decrease in e[−]–e[−] repulsion between rear orbital lobes contribute to this effect).^{33a,53} It has also come to light that a form of hyperconjugation involving the “wing” C–C bonds may contribute significantly to stabilization (e.g., in studies pertaining to the bicyclo[1.1.1]pent-1-yl cation, among others).^{54,55} To study this systematically, we performed geometry optimization and natural bond orbital (NBO) second-order perturbation analysis of SF₅–BCP–Cl (**2**) at ωB97XD/cc-pVQZ, as well as BCP (**20**), SF₅–BCP–H (**21**), and Cl–BCP–H (**22**) for comparisons (Figure 2.5, *top left*).⁵⁶ The trend in computed C₁⋯C₃ distances (as well as θ_{Cl–C2–C3} angles) is as expected, following the increase in electron-withdrawing effect: **2** > **22** ~ **21** > **20**. The Wiberg bond index between C₁ and C₃ also seems to follow a similar trend, increasing from 0.035 in **20** to 0.085 in **2**

(while this trend is noteworthy, these values are too small to argue incipient bond formation).⁵⁷ Additionally, by NBO analysis, *the wing C–C bonds contribute a far greater two-electron stabilization energy via a side-on interaction than donor-acceptor interactions in the linear array* (Figure 2.5, *top left*). While computed NBO energies should be carefully considered as only an “upper bound” for actual stabilization energies due to overestimation of electron delocalization effects,⁵⁵ the computed wing stabilization energies are over an order of magnitude larger than the percaudal interaction energies in each case. Moreover, the stabilization energies increase when wing C–C bonds are situated across the ring from electron-withdrawing substituents (**21**, **22**, and **2**), consistent with increased orbital overlap.⁵⁸ Representative depictions of these key donor-acceptor interactions in **2**, resembling an agostic-like donation from the wing C–C σ -bond to the $\sigma^*_{\text{C-EWG}}$ orbital, can be found in Figure 2.6.

Intuitively, a simplified resonance-like depiction of this type of wing interaction (Figure 2.5, *top right*) accounts for more “bonding character” between C₁ and C₃, and it also suggests there should be a lengthening in the C₃–C₂ bond opposite the EWG relative to the C₂–C₂ bond.⁵⁹ For experimental support, we turned to the X-ray structure of compound **3**. Here, we see a break in symmetry in both BCP rings and elongation of all wing bonds opposite the EWG’s versus the adjacent ones (i.e., $d(\text{C}_3\text{--C}_2)$ and $d(\text{C}_6\text{--C}_7) \sim 1.56 \text{ \AA}$ vs. $d(\text{C}_1\text{--C}_2)$ and $d(\text{C}_8\text{--C}_7) \sim 1.54 \text{ \AA}$). While the depiction also suggests elongation of the C–EWG bond, this is complicated for the C–Cl bond, as the stabilization energy derived from Cl lone-pair donation into wing $\sigma^*_{\text{C-C}}$ orbitals is not negligible, and this would conceptually manifest in shortening of the bond (i.e., effects may cancel each other out). However, in the case of the SF₅ group (devoid of a lone pair), the predicted structural manifestation of this interaction is clearer, as the C–S bond in **3** is longer than in **2** by $\sim 1.5\%$ (Figure 2.2, *bottom*).

It is also apparent that the C₁⋯C₃ distance in the X-ray structure of **3** is approximately equal to the C₆⋯C₈ distance (~1.84 Å), both of which are shorter than the C₁⋯C₃ distance in unsubstituted [1.1.1]bicyclopentane.⁴⁵ This indicates that a Cl atom and an SF₅ group have a similar composite effect on shortening the transannular distance in a BCP ring. One can attribute this in large part to the strong electron withdrawing effects of these substituents through the σ-framework.⁶⁰

Lastly, when the bicyclopentane ring is substituted with two σ-EWG's, a unifying depiction of dominant donor-acceptor interactions by NBO analysis (Figure 2.5, *bottom*) also accounts for the further decrease in C₁⋯C₃ distance and would suggest that there are competing forces dictating bond elongation/contraction and charge distribution on the wings.^{54b} Theoretically, these *push-pull* effects would not result in the same structural trends observed for compounds like **3**; in fact, this was found to be the case experimentally in structures **2**, **7**, **8**, **9**, and **17** (Figure 2.5, *bottom*).

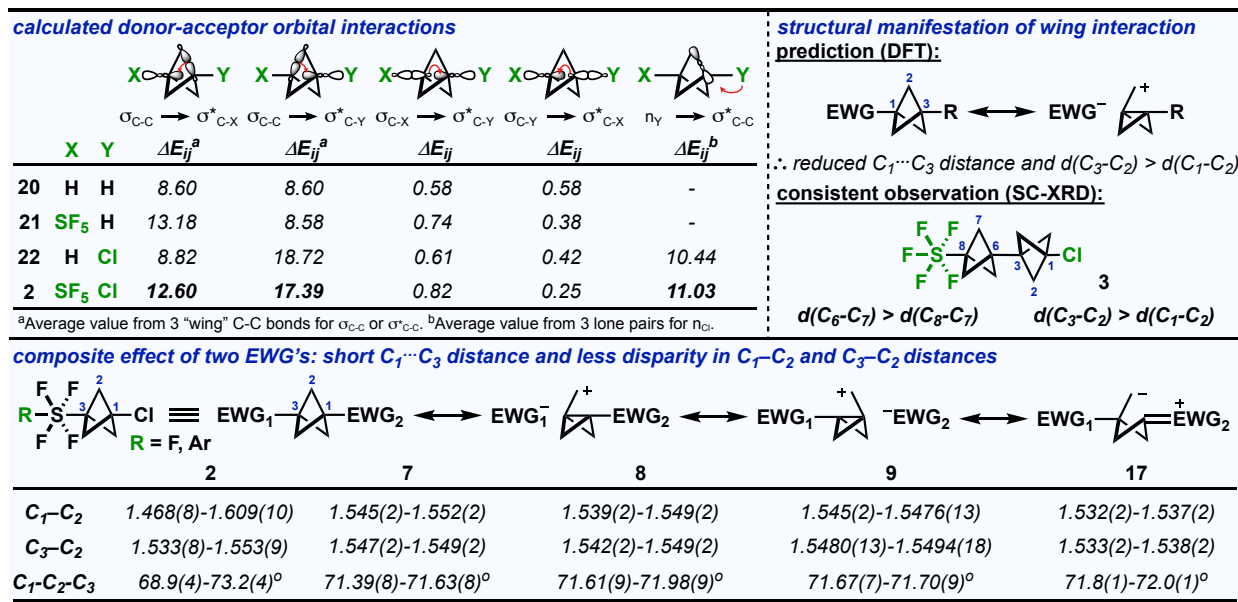


Figure 2.5. (Top left panel) Comparative analysis of significant donor-acceptor interactions. Geometry optimizations and NBO analyses conducted at wB97XD/cc-pVQZ. ΔE_{ij} (in kcal/mol) is the two-electron stabilization energy associated with delocalization between donor (i) and acceptor (j) NBOs. (Top right panel) Observations in SC-XRD data of **3** consistent with predicted structural effects. (Bottom panel) Depiction of composite effects from donor-acceptor interactions consistent with observed short $C_1 \cdots C_3$ contacts and less disparity in wing C-C distances in SC-XRD data for **2**,⁴³ **7-9**, and **17**. Distances reported in angstroms (Å).

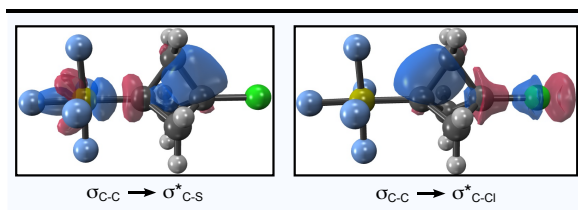


Figure 2.6. Molecular orbital depictions of donor-acceptor interactions involving wing C-C bonds in compound **2**. NBOs were generated at ω B97XD/cc-pVQZ.

2.3 Conclusion.

This work was originally motivated by the methodological advancement of forging novel, tertiary $C(sp^3)-SF_5$ and $C(sp^3)-SF_4Ar$ bonds through strain-release functionalization of [1.1.1]propellane. As SF_5-BCP and $-SF_4-BCP$ motifs were recognized in this study as types of hybrid isosteres (for $[CF_3/t-Bu + Ph]$ and $[alkyne/BCP + Ph]$, respectively; see Figure 2.7), this prompted detailed SC-XRD studies that led to the discovery and additional investigations of short

transannular C $\cdots$ C distances. Lastly, DFT calculations and previous literature support the notion that donor-acceptor interactions involving the wing C–C bonds in BCP rings play a significant role (alongside linear through-space interactions) in this shortening phenomenon. The theoretical model was corroborated by X-ray data,⁶¹ whereby manifestations of these “wing donation” effects were observed in solid-state structures.

We believe these “hybrid isosteres” afford an unusual and subtle type of flexibility in molecular design that may prove useful (Figure 2.7). Following this critical proof of concept and detailed structural study, future work will pertain to installing SF₅-BCP and ArSF₄-BCP motifs onto more complex molecules and evaluating applications.

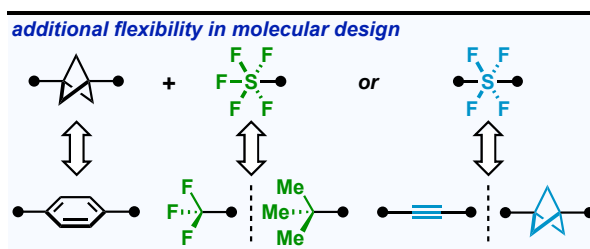


Figure 2.7. Highlighting the *mix-and-match* design potential associated with hybrid isosteres.

2.4 Author Contributions.

Y.K., C.G., A.N.R., S.N., and S.L. performed synthetic work and data analysis. Y.K. synthesized compounds **6–17**, **18**, **19**; Y.K. and A.N.R. synthesized the ArSF₄Cl precursors and optimized the tetrafluoro(aryl)sulfanylation reaction. C.G., S.N., and S.L. synthesized and isolated **2** and **3** and optimized the synthesis of **2**. C.R.P. conducted all computational analyses and provided initial proof-of-concept for formation of compound **2**. E.L.N. performed HRMS analyses. J.C.F., N.N., and R.G. collected SC-XRD data. J.C. and C.R.P. conceptualized and supervised the project and acquired funding. The manuscript was written and edited with contributions from all authors.

2.5 Experimental.

2.5.1 Procedure for the Synthesis of SF₅Cl.

Trichloroisocyanuric acid (9.60 g, 4.5 equiv.) was added to a flame-dried 100 mL pressure flask equipped with a stir bar under Ar. Then, spray-dried potassium fluoride (4.84 g, 9.0 equiv.) was added, followed by sulfur (297 mg, 1.0 equiv.). MeCN (46 mL) was added *via* syringe and the reaction vessel was tightly capped, wrapped in aluminum foil, and transported to the fume hood where it was allowed to stir behind a blast shield at room temperature for 48 h. After completion, the reaction vessel was submerged in a $-78\text{ }^{\circ}\text{C}$ dry ice acetone bath. When the solution reached $-78\text{ }^{\circ}\text{C}$, anhydrous hexanes (or *n*-pentane, 29 mL) was added quickly *via* syringe, while avoiding outgassing. The reaction vessel was then tightly sealed and allowed to warm to room temperature while stirring. Once the mixture reached room temperature, the solution was transferred to an oven-dried separatory funnel. The MeCN layer was discarded and the hexanes (or *n*-pentane) solution containing SF₅Cl was stored in a Schlenk flask under Ar and wrapped in aluminum foil.

2.5.2 General Procedure for (3-chlorobicyclo[1.1.1]pentan-1-yl)pentafluoro- λ^6 -sulfane.

A flame-dried 8 mL screw-capped tube was charged with [1.1.1]propellane in Et₂O (1.0 equiv.). A solution of SF₅Cl in *n*-pentane (1.5 equiv.) was added and the mixture was stirred under white LED irradiation at approx. $30\text{ }^{\circ}\text{C}$ (estimated temperature based on proximity to the light source, ca. 2 cm) for 4 h. Purification of the final product was achieved *via* distillation:



(3-Chlorobicyclo[1.1.1]pentan-1-yl)pentafluoro- λ^6 -sulfane (2). The reaction was run according to the general procedure. The final compound was isolated as a colorless liquid (86%). Crystals suitable for SC-XRD were obtained by progressive cooling of the neat liquid to $-60\text{ }^{\circ}\text{C}$ in a dry-ice acetone bath.

^1H NMR (600 MHz, CDCl_3): $\delta = 2.65$ (s, 6H); **^{19}F NMR (565 MHz, CDCl_3):** $\delta = 78.65$ – 77.60 (m, 1F), 54.54 (d, 4F, $^2J_{\text{F,F}} = 148.1$ Hz); **$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3):** $\delta = 63.58$ (m, C-SF_5), 60.52 (quint, $^2J_{\text{C,F}} = 2.4$ Hz, 3C-CH_2), 45.07 (bs, C-Cl); **HRMS:** (DIP-Cl) for $[\text{C}_5\text{H}_6\text{SClF}_5\text{-H}]^+$: calculated 226.971518, measured 226.971100.



(3'-Chloro-[1,1'-bi(bicyclo[1.1.1]pentan)]-3-yl)pentafluoro- λ^6 -sulfane (3). The final compound was isolated as a white solid (7%) as a byproduct of the synthesis of compound **2**. Crystals suitable for SC-XRD were obtained by slow solvent evaporation from the crude mixture. **^1H NMR (300 MHz, CDCl_3):** $\delta = 2.19$ (s, 6H), 2.05 (s, 6H); **^{19}F NMR (565 MHz, CDCl_3):** $\delta = 80.17$ – 78.10 (m, 1F), 48.49 (d, 4F, $^2J_{\text{F,F}} = 145.8$ Hz).

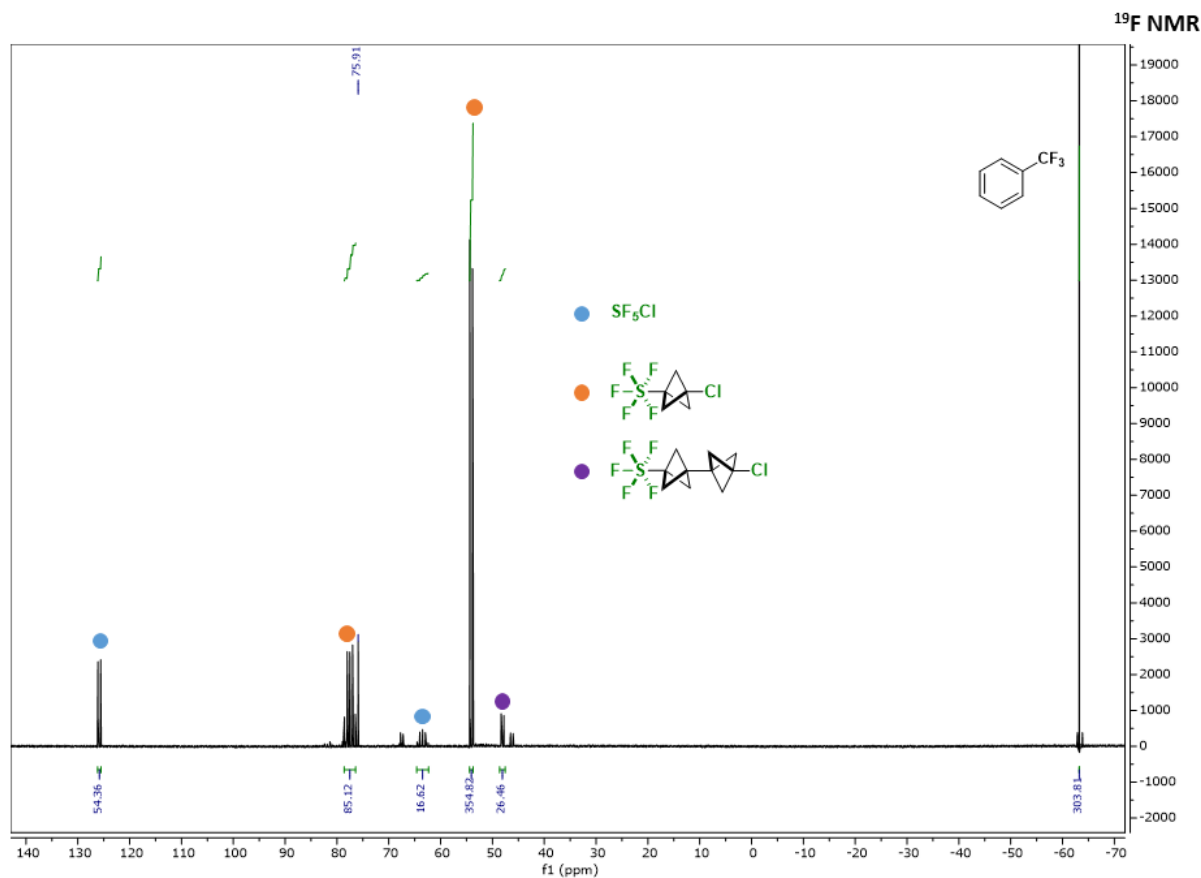


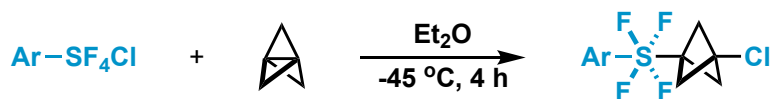
Figure 2.8: ^{19}F NMR spectrum of crude of synthesis of (3-chlorobicyclo[1.1.1]pentan-1-yl)pentafluoro- λ^6 -sulfane (compound **2**). Note: the ^{19}F shifts for (3'-chloro-[1,1'-bi(bicyclo[1.1.1]pentan)]-3-yl)pentafluoro- λ^6 -sulfane (compound **3**) are also given.

2.5.3 General procedure of Synthesis of Aryl Tetrafluoro- λ^6 -sulfanyl Chlorides.

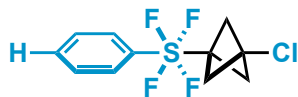
Trichloroisocyanuric acid (18.0 equiv.) was added to an oven-dried round bottom flask charged with a stir bar under glovebox atmosphere. Then, spray-dried potassium fluoride (32.0 equiv.) was added, followed by the disulfide starting material (1.0 equiv.). Acetonitrile was added to the reaction flask followed by a solution of trifluoroacetic acid (0.1 equiv.) in acetonitrile. The reaction was stirred under glovebox atmosphere at room temperature (ca. 23 °C) for 18 h. Upon completion of the reaction, TCICA and KF were removed by filtration of the solvent through a

PTFE syringe filter into a PFA vessel; the solvent was then removed *in vacuo*. The left-over white solids were extracted with *n*-pentane (or hexanes), filtered through a PTFE syringe filter into a PFA vessel and concentrated *in vacuo*.

2.5.4 General Procedure for Tetrafluoro(aryl)bicyclopentanes.

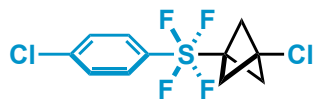


An oven-dried microwave vial equipped with a stir bar was introduced to the glovebox, and the (chlorotetrafluoro- λ^6 -sulfanyl)arene was added (0.1 mmol, 1.0 equiv.); the vial was sealed with a crimper. The reaction vessel was removed from the glovebox, wrapped in aluminum foil, and anhydrous Et₂O (0.76 mL) was added. The solution was cooled to $-45\text{ }^\circ\text{C}$ in an acetonitrile dry ice bath; a solution of [1.1.1]propellane (0.5 M in Et₂O, 0.24 mL, 1.2 equiv.) was added in one portion down the side of the reaction vessel. The reaction was then transferred to an ice bath and stirred for 3 h at $0\text{ }^\circ\text{C}$. The crude reaction mixture was then concentrated *in vacuo*. The final product was isolated by column chromatography with hexanes and ethyl acetate. (Solvent systems for individual compounds are given below). *Note: the concentration of the [1.1.1]propellane solution was variable between batches; the necessary volume of this solution was calculated and Et₂O was added to give a concentration of 0.1 M with respect to the limiting reagent.*



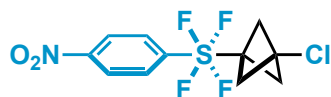
(3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro(phenyl)- λ^6 -sulfane (6). The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (41%) after elution with 9:1 to 8:1 hexanes:EtOAc. *Note: the compound is prone to hydrolysis and should be stored in a PFA vessel under Ar atmosphere.*

R_f: 0.26 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 7.84-7.57 (m, 5H), 2.38 (s, 6H); **¹⁹F (282 MHz, CDCl₃):** δ = 68.6 (s, 4F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 136.8, 134.3, 129.5, 128.5, 57.1, 49.7, 48.5; **ATR-IR:** 1586, 721, 687, 668 cm⁻¹; **MS:** Theoretical m/z 284.0, measured m/z 284.1 for molecular ion. Isotopic distribution consistent with a chlorinated species.



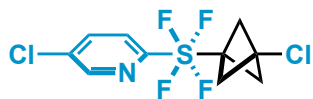
(3-Chlorobicyclo[1.1.1]pentan-1-yl)(4-chlorophenyl)tetrafluoro- λ^6 -sulfane (7). The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (56%) after elution with 9:1 hexanes:EtOAc. Crystals suitable for SC-XRD were grown by solvent evaporation from EtOAc.

R_f: 0.25 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 7.67-7.62 (2H, dt, J = 2.96, 9.1 Hz), 7.36-7.33 (2H, d, J = 8.72 Hz), 2.68 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +55.6 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 158.9-157.5 (quint, $^2J_{C-F}$ = 23.5 Hz), 136.4, 128.4, 127.8-127.5 (quint, $^3J_{C-F}$ = 5.3 Hz), 69.6-68.1 (quint, $^2J_{C-F}$ = 29.0 Hz), 61.3-61.2 (quint, $^4J_{C-F}$ = 2.7 Hz), 45.43-45.38 (quint, $^4J_{C-F}$ = 1.9 Hz); **ATR-IR:** 1574, 751, 736, 681 cm⁻¹; **MS:** Molecular ion not detected. Isotopic distribution of fragmented species consistent with a chlorinated molecular ion.



(3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro(4-nitrophenyl)- λ^6 -sulfane (8). The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (63%) after elution with 95:5 hexanes:EtOAc. Crystals suitable for SC-XRD were grown by solvent evaporation from EtOAc.

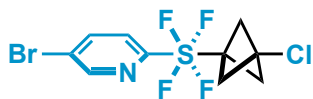
R_f: 0.21 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.24-8.22 (2H, d, J = 8.9 Hz), 7.90-7.88 (2H, dt, 2.3, 9.2 Hz), 2.70 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +55.9 (4F, s); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 163.9-163.2 (quint, $^2J_{C-F}$ = 26.6 Hz), 148.3, 127.7-127.5 (quint, $^2J_{C-F}$ = 5.5 Hz), 123.7, 69.0-68.2 (quint, $^2J_{C-F}$ = 27.6 Hz), 61.2, 45.2; **ATR-IR:** 1611, 1528, 1353, 756, 729, 669 cm⁻¹; **MS:** Theoretical m/z 375.0, measured m/z 375.1 for molecular species adducted to solvent. Isotopic distribution of fragmented species consistent with a chlorinated molecular ion.



5-Chloro-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)pyridine (9).

The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (72%) after elution with 9:1 hexanes:EtOAc. Crystals suitable for SC-XRD were grown by vapor diffusion. The isolated compound was dissolved in a minimum amount of EtOAc, and hexanes was added as the counter solvent.

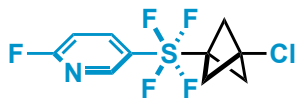
R_f: 0.31 (9:1, hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.44-8.43 (1H, d, J = 2.3 Hz), 7.81-7.76 (1H, d, J = 8.7 Hz), 7.66-7.63 (1H, d, J = 8.7 Hz), 2.70 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +46.5 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 168.0-167.2 (quint, $^2J_{C-F}$ = 31.6 Hz), 146.12-146.06 (m, $^3J_{C-F}$ = 2.1 Hz), 137.99, 134.1, 122.6-122.3 (quint, $^3J_{C-F}$ = 4.6 Hz), 68.1-67.4 (quint, $^2J_{C-F}$ = 27.0 Hz), 61.2-61.1 (quint, $^4J_{C-F}$ = 2.7 Hz), 45.4; **ATR-IR:** 1571, 1560, 751, 734, 692 cm⁻¹; **MS:** Theoretical m/z 337.0, measured m/z 337.1 for hydrated molecular species. Isotopic distribution consistent with a chlorinated species.



5-Bromo-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)pyridine (10).

The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (71%) after elution with 8:2 hexanes:EtOAc.

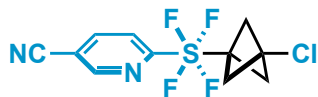
R_f: 0.15 (9:1, hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.54-8.53 (1H, d, J = 2.2 Hz), 7.95-7.92 (1H, d, J = 8.3 Hz), 7.59-7.56 (1H, d, J = 8.7 Hz), 2.69 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +47.1 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 151.8, 141.0, 126.0, 124.4, 61.1, 58.0, 48.6; **ATR-IR:** 1567, 1553, 779, 760, 628 cm⁻¹; **MS:** Molecular ion not detected. Isotopic distribution of fragmented species consistent with a chlorinated and brominated molecular ion.



5-((3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)-2-fluoropyridine (11).

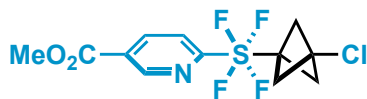
The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (41%) after elution with 95:5 to 8:2 hexanes:EtOAc.

R_f: 0.46 (9:1, hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.58-8.57 (1H, d, J = 1.6 Hz), δ = 8.13-8.06 (1H, m, J = 2.2, 7.9 Hz), 6.96-6.92 (1H, dd, J = 2.9, 8.9 Hz), 2.69 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +47.1 (4F, s), -64.5 (1F, s); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 145.9, 139.4, 109.4, 109.2, 68.8, 61.2, 45.1; **ATR-IR:** 1589, 1575, 749, 688 cm⁻¹; **MS:** Theoretical m/z 326.0, measured m/z 326.1 for molecular species. Isotopic distribution consistent with a chlorinated species.



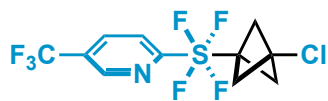
6-((3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)nicotinonitrile (12). The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (65%) after elution with 9:1 hexanes:EtOAc.

R_f: 0.31 (9:1, hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.79-8.78 (1H, d, J = 1.7 Hz), 8.13-8.11 (1H, d, J = 8.5 Hz), 7.84-7.82 (1H, d, J = 8.5 Hz), 2.71 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +46.5 (4F, s); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 171.5-171.0 (quint, $^2J_{C-F}$ = 32.9 Hz), 150.5, 141.8, 122.04-121.98 (quint, $^3J_{C-F}$ = 4.4 Hz), 115.3, 112.3, 67.8-67.4 (quint, $^2J_{C-F}$ = 26.0 Hz), 61.1, 45.1; **ATR-IR:** 2243, 1584, 1562, 759, 739, 707 cm⁻¹; **MS:** Theoretical m/z 312.0, measured m/z 312.0 for molecular species. Isotopic distribution consistent with a chlorinated species.



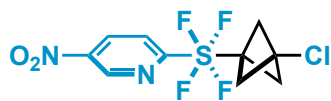
Methyl 6-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)nicotinate (13). The reaction was run according to the general procedure. The product was isolated as a white crystalline solid (81%) after elution with 5:1 hexanes:EtOAc.

R_f: 0.31 (5:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 9.08 (1H, d, J = 2.2 Hz), 8.43 (1H, d, J = 8.5 Hz), 7.78 (1H, d, J = 8.5 Hz), 3.98 (3H, s), 2.72 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +46.2 (4F, s); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 172.3-171.9 (quint, $^2J_{C-F}$ = 31.3 Hz), 164.4, 148.9, 139.8, 128.1, 121.4-121.3 (quint, $^3J_{C-F}$ = 4.6 Hz), 61.12-61.09 (quint, $^3J_{C-F}$ = 2.6 Hz), 52.9, 45.3. *Note: the quintet of the alkyl carbon atom adjacent to the -SF₄- unit could not be resolved;* **ATR-IR:** 1736, 1726, 1585 (br), 744, 683 cm⁻¹; **MS:** Theoretical m/z 377.0, measured m/z 376.9 for chlorinated molecular species. Isotopic distribution consistent with a chlorinated species.



2-((3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)-5-(trifluoromethyl)pyridine (*14*). The reaction was run according to the general procedure. The product was isolated as a white crystalline solid (56%) after elution with 9:1 hexanes:EtOAc.

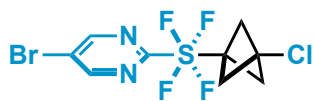
R_f: 0.21 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** 8.78 (1H, s), 8.10-8.08 (1H, d, J = 8.5 Hz), 7.85-7.83 (1H, d, J = 8.5 Hz), 2.73 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +46.5 (4F, s), -62.5 (3F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 172.1-171.2 (quint, $^2J_{C-F}$ = 32.3 Hz), 144.9-144.8 (quint, $^2J_{C-F}$ = 2.2 Hz), 135.99-135.95 (quint, $^2J_{C-F}$ = 3.3 Hz), 129.5-128.1 (quint, $^2J_{C-F}$ = 33.8 Hz), 124.5, 121.9-121.7 (quint, $^3J_{C-F}$ = 4.8 Hz), 68.3-66.9 (quint, $^2J_{C-F}$ = 26.7 Hz), 61.2-61.0 (quint, $^3J_{C-F}$ = 2.7 Hz), 45.3; **ATR-IR:** 1598, 1580, 750, 735, 692 cm⁻¹; **MS:** Theoretical m/z 353.0, measured m/z 353.0 for molecular species.



2-((3-Chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)-5-nitropyridine (15).

The reaction was run according to the general procedure. The final compound was isolated as a white crystalline solid (45%) after elution with 9:1 hexanes:EtOAc.

R_f: 0.3 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 9.54-9.53 (1H, d, J = 2.4 Hz), 8.78-8.75 (1H, dd, J = 2.4, 8.5 Hz), 8.32-8.29 (1H, d, J = 8.5 Hz), 2.60 (6H, s); **¹⁹F (282 MHz, CDCl₃):** δ = +47.36 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 160.97, 145.7, 133.9, 123.6, 58.2, 48.4. *Note: the quintets of aryl and alkyl carbon atoms adjacent to the -SF₄- unit could not be resolved;* **ATR-IR:** 1602, 1568, 1533, 1358, 752, 737, 694 cm⁻¹; **MS:** Theoretical m/z 376.97, measured m/z 376.99 for molecular species adducted to solvent. Isotopic distribution consistent with a chlorinated species.

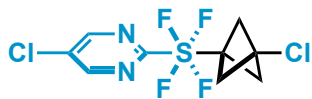


5-Bromo-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)pyrimidine

(16). The reaction was run according to the general procedure. The product was isolated as a white crystalline solid (67%) after elution with 9:1 hexanes:EtOAc.

R_f: 0.29 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃):** δ = 8.86 (2H, s), 2.71 (6H, s).

¹⁹F (282 MHz, CDCl₃): δ = +43.61 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 158.9, 121.84, 61.11-61.06 (quint, $^3J_{C-F}$ = 2.6 Hz), 31.1. *Note: the quintets of aryl and alkyl carbon atoms adjacent to the -SF₄- unit could not be resolved*; **ATR-IR:** 1541(br), 746, 694 cm⁻¹; **MS:** Molecular ion not detected. Isotopic distribution of fragmented species consistent with a chlorinated and brominated molecular ion.



5-Chloro-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)pyrimidine

(17). The reaction was run according to the general procedure. The product was isolated as a white crystalline solid (84%) after elution with 9:1 hexanes:EtOAc. Crystals suitable for SC-XRD were grown by vapor diffusion. The isolated compound was dissolved in a minimum amount of EtOAc, and hexanes was added as the counter solvent.

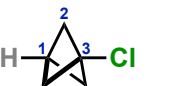
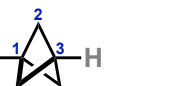
R_f: 0.29 (9:1 hexanes:EtOAc); **¹H NMR (300 MHz, CDCl₃)**: δ = 8.78 (2H, s), 2.73 (6H, s).

¹⁹F (282 MHz, CDCl₃): δ = +43.64 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 171.5-170.5 (quint, $^2J_{C-F}$ = 37.7 Hz), 156.51-156.47 (quint, $^3J_{C-F}$ = 1.6 Hz), 132.8, 67.2-66.5 (quint, $^2J_{C-F}$ = 26.1 Hz), 61.0-60.9 (quint, $^3J_{C-F}$ = 2.7 Hz), 45.3; **ATR-IR**: 1567, 1553, 753, 737, 690 cm⁻¹; **MS**: Theoretical m/z 380.98, measured m/z 381.05 for molecular species adducted to solvent. Isotopic distribution of fragmented species consistent with a chlorinated molecular ion.

2.5.5. Computational Methods.

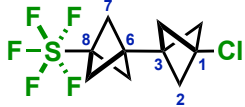
The Gaussian 09, Revision E.01^[62] and Gaussian 16, Revision A.03^[63a] suites were used for all calculations. Geometry optimizations and subsequent vibrational analyses were performed at either ω B97XD/6-311++G** or ω B97XD/cc-pVQZ.^[63b] The ω B97XD functional was used to account for long-range and dispersion interactions.⁶⁴ Polarization functions were applied to account for effects from ring strain. Minima were confirmed by means of vibrational analysis using the same functional/basis set combination: no imaginary frequencies were found. Natural bond orbital (NBO) second-order perturbation analyses and determination of Wiberg bond index (WBI) were performed at ω B97XD/cc-pVQZ on coordinates optimized using the same functional/basis set combination. Pictures of molecular orbitals were rendered using the IQmol program.^[65]

Table 2.1. Computed $C_1\cdots C_3$, C_1-C_2 , and C_2-C_3 distances, as well as $\theta_{C1-C2-C3}$ angles and Wiberg bond indexes for $C_1\cdots C_3$, for a series of substituted bicyclopentane rings and [1.1.1]propellane at ω B97XD/cc-pVQZ.

					
$d(C_1-C_3)$:	1.816 Å	1.835 Å	1.838 Å	1.873 Å	1.556 Å
$d(C_1-C_2)^a$:	1.543 Å	1.552 Å	1.552 Å	1.549 Å	1.511 Å
$d(C_2-C_3)^a$:	1.544 Å	1.539 Å	1.539 Å	1.549 Å	1.511 Å
$\theta_{C1-C2-C3}^a$:	72.1°	72.8°	73.0°	74.4°	62.0°
WBI (C_1-C_3):	0.085	0.063	0.071	0.035	0.79

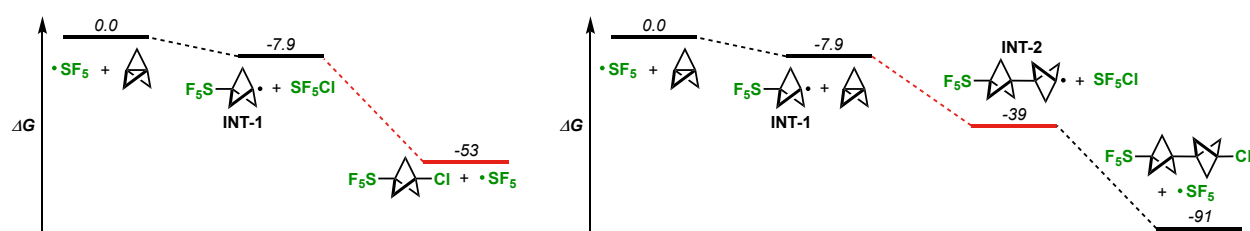
^aAverage values for all three wing C–C bond distances and angles.

Table 2.2. Computed transannular $C\cdots C$ and wing C–C distances, as well as $\theta_{C1-C2-C3}$ and $\theta_{C6-C7-C8}$ angles and Wiberg bond indexes for $C_1\cdots C_3$ and $C_6\cdots C_8$, for SF₅-BCP-BCP-Cl (**3**) at ω B97XD/cc-pVQZ.

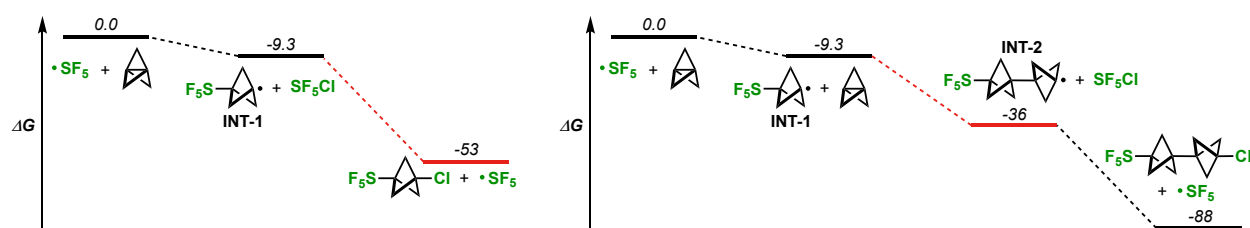
		
$d(C_8-C_6)$:	1.838 Å	$d(C_1-C_3)$: 1.842 Å
$d(C_8-C_7)^a$:	1.538 Å	$d(C_1-C_2)^a$: 1.539 Å
$d(C_7-C_6)^a$:	1.555 Å	$d(C_2-C_3)^a$: 1.554 Å
$\theta_{C8-C7-C6}^a$:	72.9°	$\theta_{C1-C2-C3}^a$: 73.1°
WBI (C_8-C_6):	0.068	WBI (C_1-C_3): 0.076

^aAverage values for all three wing C–C bond distances and angles.

free energy reaction profiles calculated at ω B97XD/6-311++G** (no solvent model applied)



free energy reaction profiles calculated at ω B97XD/6-311++G** (default Et_2O solvent model)



free energy reaction profiles calculated at ω B97XD/6-311++G** (default heptane solvent model)

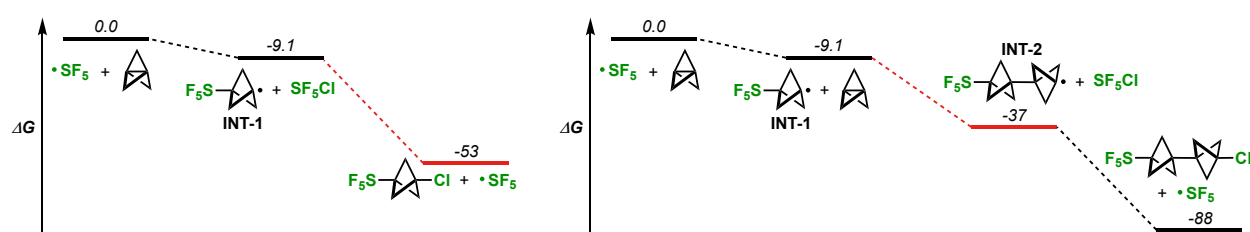


Figure 2.9. Gibbs free energy reaction profiles of proposed mechanisms to form $\text{SF}_5\text{-BCP-Cl}$ and $\text{SF}_5\text{-BCP-BCP-Cl}$ highlighting the computed differences in free energies of the product-determining steps (note: energy of the Cl radical not included in the 0.0). All structures were optimized at ω B97XD/6-311++G** and contain no imaginary frequencies; results from different solvent models (specified in the figure above) are compared.

2.5.6. SC-XRD Data.

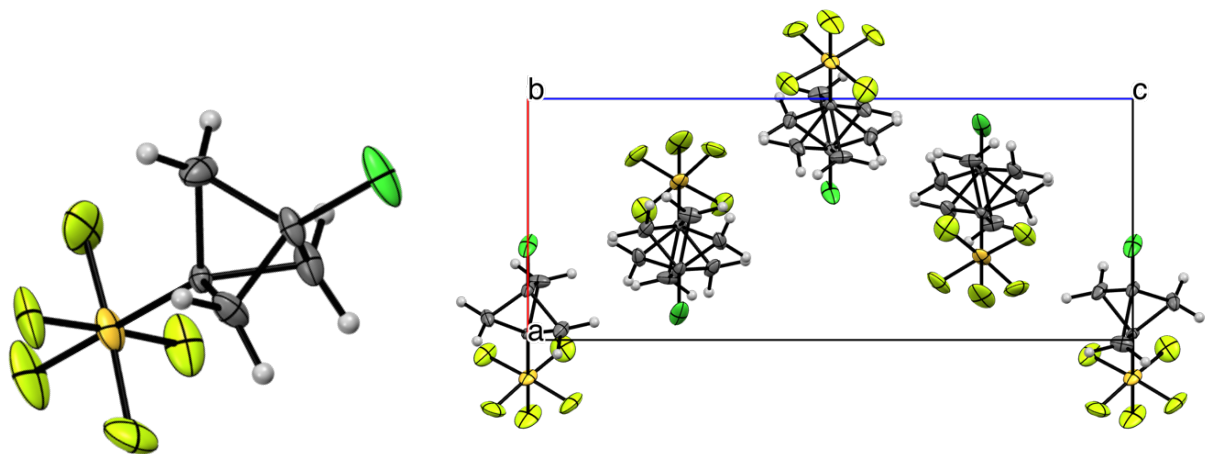


Figure 2.10. Molecular structure and packing of **2** ($P4_12_12$).

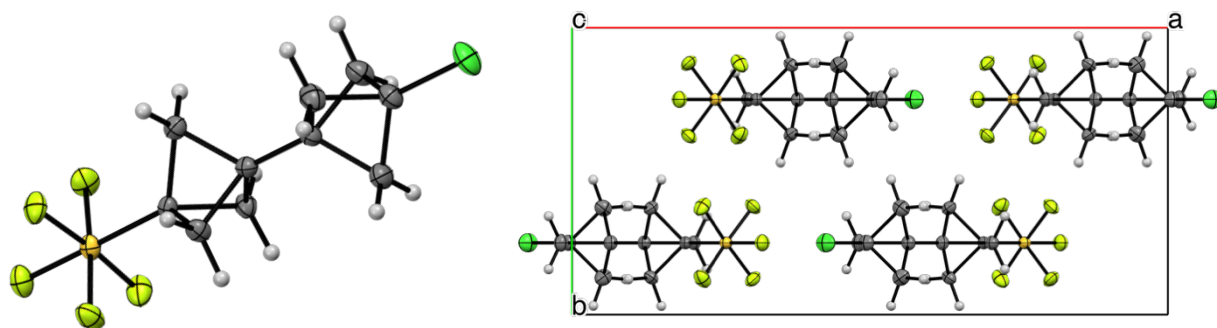


Figure 2.11. Molecular structure and packing of **3** ($Pnma$).

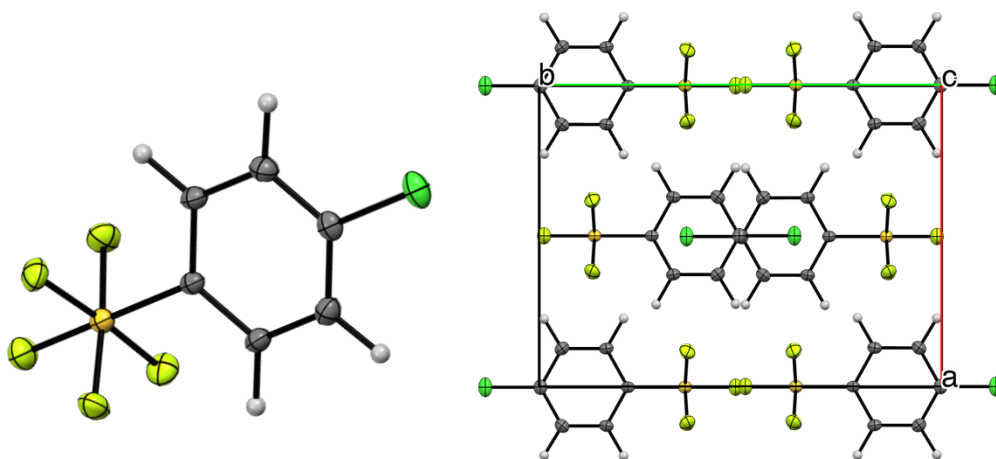


Figure 2.12. Molecular structure and packing of **4** (*Cmcm*).

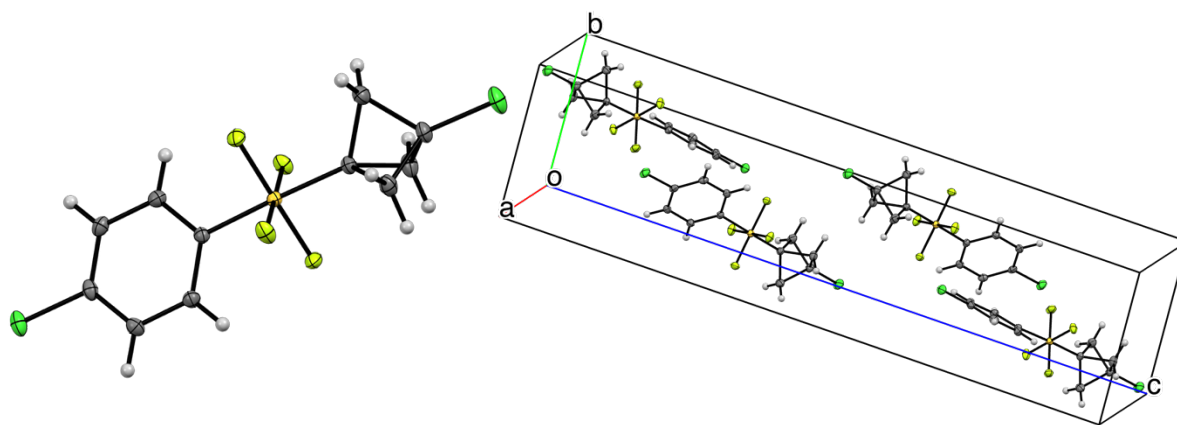


Figure 2.13. Molecular structure and packing of **7** (*P*₂₁/*c*).

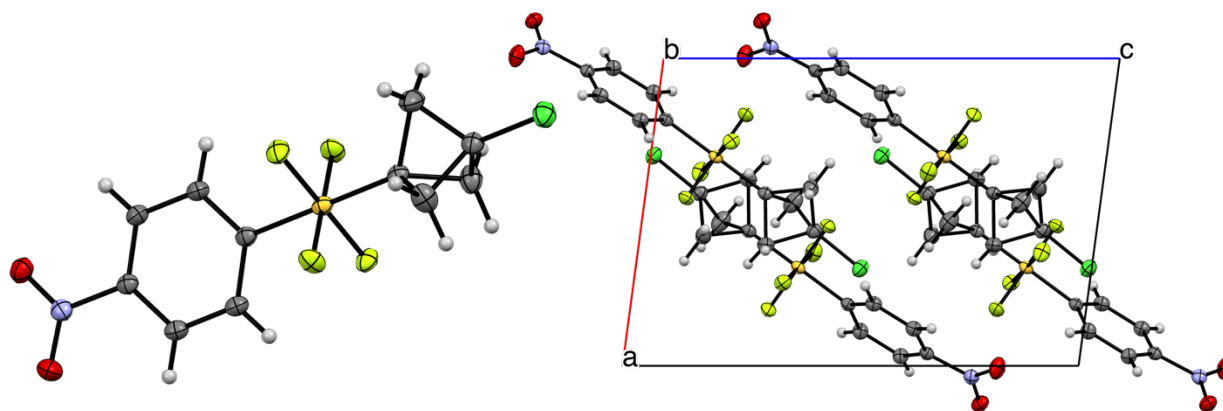


Figure 2.14. Molecular structure and packing of **8** (*P*₂₁/*c*).

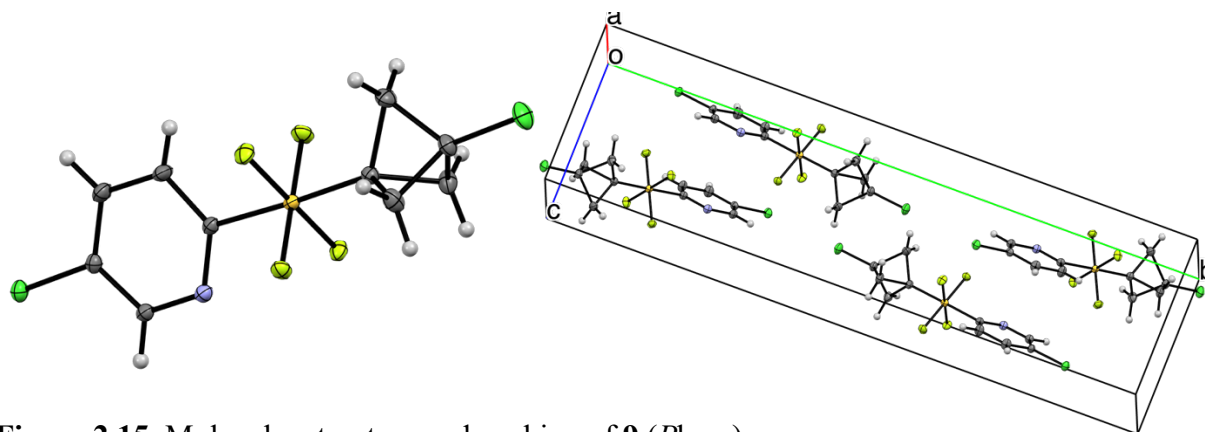


Figure 2.15. Molecular structure and packing of **9** (*Pbcm*).

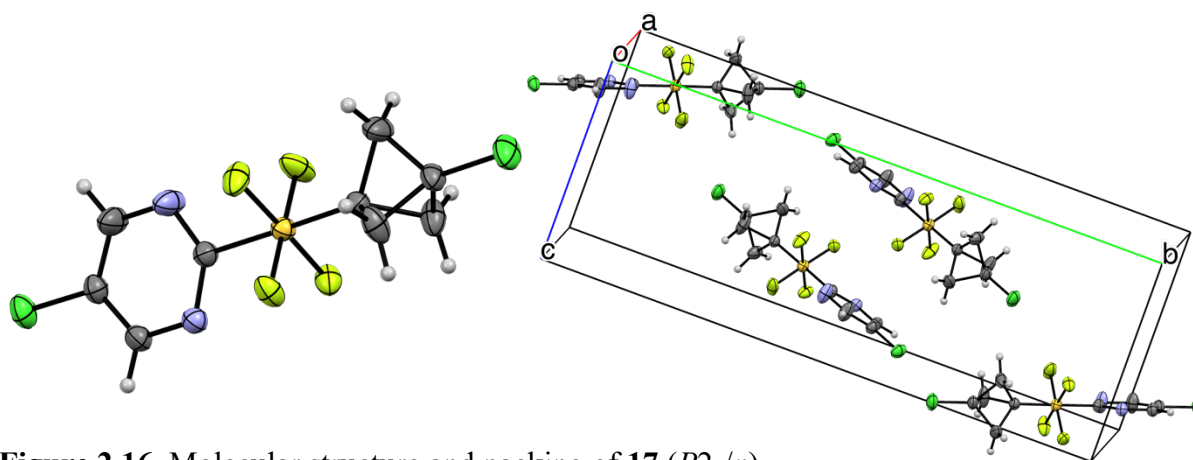


Figure 2.16. Molecular structure and packing of **17** (*P2₁/n*).

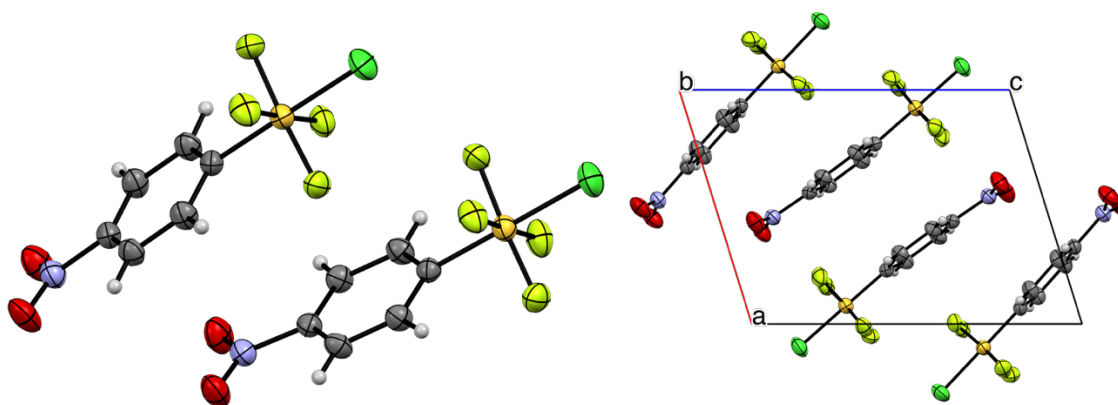


Figure 2.17. Molecular structure and packing of **18** (*P-1*); the unit cell contained two symmetry-independent moieties.

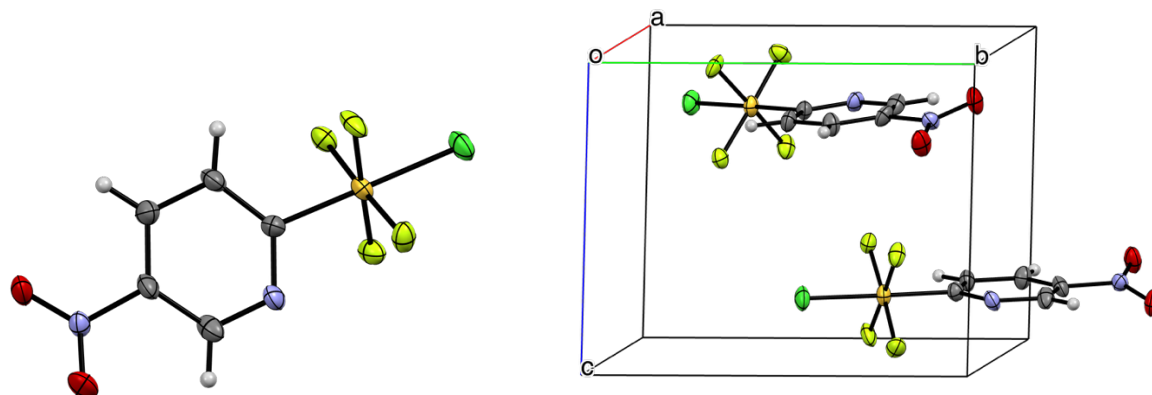


Figure 2.18. Molecular structure and packing of **19** ($P2_1$).

For additional experimental details and NMR spectra, please refer to the Supporting Information of the associated publication: Kraemer, Y.;[†] Ghiazza, C.;[†] Ragan, A. N.; Ni, S.; Lutz, S.; Neumann, E. K.; Fettingner, J. C.; Nöthling, N.; Goddard, R.; Cornella, J.;^{*} Pitts, C. R.^{*} *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892.

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Chapter 3: Overcoming a Radical Polarity Mismatch in Strain-Release

Pentafluorosulfanylation of [1.1.0]Bicyclobutanes: An Entryway to Sulfone- and Carbonyl-Containing SF₅-Cyclobutanes

3.1 Introduction.

The pursuit of new methods to install the pentafluorosulfanyl (SF₅) group on organic molecules is no longer reserved for connoisseurs. Traditionally, synthesizing or working with SF₅Cl – one of the few known SF₅-transfer reagents – has mandated handling toxic and corrosive gases (arguably stifling growth in this research area).^[66] However, using a contemporary mild oxidative fluorination strategy,^[67,68] a stock solution of SF₅Cl can now be prepared easily in house without the need to handle it as a gas.^[69] This timely advance in reagent accessibility empowers the broader chemical community to address a lag in the development of new tactics to make C–SF₅ bonds.

Notably distinct from *bottom-up* aryl-SF₅ synthesis,^[67,70] methods for *direct* C–SF₅ bond formation have been largely limited to SF₅ radical addition across π -bonds for decades (i.e., alkenes and alkynes,^[71] as well as α -diazo carbonyls^[69b]).^[66b] This topic remains a lively focus of several research programs and has served as a prominent strategy to access SF₅-containing building blocks.^[72] These efforts have, for instance, enabled the evaluation of the SF₅ group as a promising bioisosteric replacement for a CF₃ or *t*-Bu group in medicinal and agrochemistry settings.^[73]

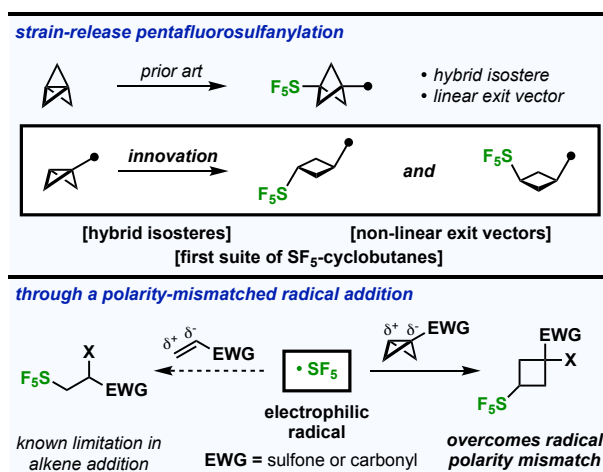


Figure 3.1. (Top) Strain-release pentafluorosulfanylation of [1.1.1]propellane (previous work) and [1.1.0]bicyclobutane (this work) to access hybrid isosteres. (Bottom) Strain-release SF₅-functionalization overrides a radical polarity mismatch that has hindered related transformations.

Recently, our group has begun to explore an alternative approach to C–SF₅ bond formation by merging SF₅ radical chemistry with strain-release functionalization of σ -bonds. In collaboration with the Cornella group in 2022, we reported the first strategy for pentafluorosulfanylation of [1.1.1]propellane (Figure 3.1, *top panel*).^[74] Remarkably, the resultant SF₅-bicyclopentane (SF₅-BCP) core structure comprises two distinct elements of bioisosterism, as BCPs are established bioisosteric replacements for arenes.^[75] We proposed that access to SF₅-BCP and similar "hybrid isosteres" could create new opportunities for mix-and-match molecular design strategies in drug discovery.^[74,76] Note that additional validation for the concept was provided recently in a study on the role of CF₂-BCPs in such a capacity.^[77]

Herein, we disclose synthetic methods that grant access to complementary types of SF₅-containing hybrid isosteres – SF₅-cyclobutanes (SF₅-CBs) – through SF₅ radical addition across [1.1.0]bicyclobutanes (BCBs).^[78] Similar to BCPs, cyclobutane (CB) rings are being employed more frequently in medicinal chemistry,^[79] e.g., as bioisosteric replacements for arenes or alkenes.^[80] In contrast to SF₅-BCPs, the non-linear exit vectors of SF₅-CBs afford an added degree of flexibility in the three-dimensional organization of the SF₅ group (Figure 3.1, *top panel*).

To our knowledge, no SF₅-containing cyclobutanes with 1,3-substitution patterns have been reported in the literature to date,^[81] prompting further investigation into structural features, chemical stability, and downstream functionalization of SF₅-CBs. This study also demonstrates that addition of "electrophilic" SF₅ radicals across BCBs substituted with electron-withdrawing groups (EWGs) such as sulfones, esters, or amides can overcome an apparent radical polarity mismatch^[82] that has notoriously inhibited analogous reactions with alkenes (Figure 3.1, *bottom panel*).^[71] Furthermore, we report rare instances (i.e., upon examining carbonyl-containing BCBs later in the study) whereby radical addition to the 1-position of a BCB becomes competitive, though interestingly remains a minor pathway relative to the polarity mismatch addition.

3.2 Results and Discussion.

We began screening for pentafluorosulfanylation conditions using 1-(phenylsulfonyl)bicyclo[1.1.0]butane, due to the relative synthetic accessibility of sulfone-substituted BCBs.^[83] During reaction optimization (see Section 3.5), we determined that overnight irradiation of the substrate and SF₅Cl with white LEDs in an *n*-pentane:EtOAc solvent mixture provided the anticipated chloropentafluorosulfanylated products (**1**) in 71% yield by ¹⁹F NMR analysis (Table 3.1). The *anti* and *syn* isomers of **1** formed in a 1.1:1 ratio and proved completely separable by chromatography on silica gel without need for HPLC purification. Isomers were assigned based on distinct shifts in the ¹H NMR spectra and confirmed by single-crystal X-ray diffraction (SC-XRD).

Using these conditions, we explored the scope of the reaction on a variety of sulfone-substituted BCBs (Method A, Table 3.1). For one, chloropentafluorosulfanylated CBs bearing arylsulfonyl substituents with a range of electron-withdrawing and electron-donating substituents in the *para* (**2-8**), *meta* (**9-10**), and *ortho* (**11-12**) positions are accessible in 52-85% yield by ¹⁹F

NMR. Products containing alkylsulfonyl substituents, such as *i*-Pr (**13**) or *t*-Bu (**14**), were also formed in good yields (92% and 63%, respectively). Additionally, we found that both unsaturated and saturated heterocycles may be tolerated to varying degrees. For instance, thiophene-containing **15** formed in 76% yield, while the piperidine-based sulfonamide **16** only formed in 25% yield (isolation also proved particularly challenging for **16**). Note that indole-containing substrates and sterically hindered substrates (e.g., with a 1-phenylsulfonyl-2,2-dimethyl or a 1-phenylsulfonyl-3-trimethylsilyl substitution pattern) were less compatible under these conditions.

The *anti:syn* ratios observed using Method A range from 1:1 to 2.5:1, which is typical for radical addition reactions to similarly-substituted BCBs.^[84] It is important to stress that the difference in retention factors (R_f values) of both isomers is enough to permit complete chromatographic separation in nearly all cases.

Table 3.1. Substrate scope for chloropentafluorosulfanylation (Method A) and hydropentafluorosulfanylation (Method B) of [1.1.0]bicyclobutanes. Method A: BCB (0.20 mmol, 1.0 equiv.), ~0.10 M solution of SF₅Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). Method B: *following method A conditions and solvent swap*, Co(acac)₂ (0.30 mmol, 1.5 equiv.), NaBH₄ (1.0 mmol, 5.0 equiv.). ¹⁹F NMR yields are reported with isolated yields in parentheses. ^aObserved *anti:syn* product ratio. ^bObserved *cis:trans* product ratio. ^cOnly the *syn* isomer was isolated.

 1	71% (51%) (1.1:1) ^a	 2	64% (49%) (1.2:1) ^a
 3	62% (42%) (1.2:1) ^a	 4	60% (45%) (1.1:1) ^a
 5	85% (59%) (1.1:1) ^a	 6	59% (48%) (1.4:1) ^a
 7	78% (54%) (1.1:1) ^a	 8	60% (51%) (1.1:1) ^a
 9	62% (37%) (1.1:1) ^a	 10	52% (47%) (1.1:1) ^a
 11	52% (45%) (2:1) ^a	 12	67% (61%) (1.3:1) ^a
 13	92% (58%) (1.1:1) ^a	 14	63% (60%) (2.5:1) ^a
 15	76% (54%) (1.1:1) ^a	 16	25% (1.4:1) ^{a,c}
 17	63% (54%) (1.1:1) ^b	 18	51% (44%) (1.2:1) ^b
 19	trace	 20	55% (53%) (1.1:1) ^b
 21	73% (57%) (1.1:1) ^b	 22	47% (41%) (1.1:1) ^b
 23	61% (47%) (1.1:1) ^b	 24	64% (53%) (1.1:1) ^b
 25	35% (32%) (1.1:1) ^b	 26	49% (43%) (1.1:1) ^b
 27	54% (54%) (1.2:1) ^b	 28	37% (31%) (1.3:1) ^b
 29	80% (62%) (1.2:1) ^b	 30	43% (41%) (1.6:1) ^b
 31	49% (39%) (1.1:1) ^b	 32	21% (1.4:1) ^b

Over the course of this study, we also discovered that hydropentafluorosulfanylated cyclobutanes often accounted for a portion of the material balance. Initial attempts to re-optimize reaction conditions for hydropentafluorosulfanylation (inspired by recent work from Paquin and co-workers^[85]) indicated that chloropentafluorosulfanylation often still competes. To circumvent this problem, we pursued an alternative approach to access hydropentafluorosulfanylated cyclobutanes from their chlorinated congeners via C–Cl bond reduction following Method A conditions.

Upon screening for C–Cl bond functionalization conditions, we found that **1** can be converted to **17** using inexpensive transition metal salts and NaBH₄, i.e., via a metal boride-type reduction.^[86] Originally, we observed that Co(acac)₂, NiCl₂, FeCl₂, and CuCl₂ were all competent in transforming purified **1** to **17** (see Section 3.5). We later discovered that Co(acac)₂ provided reliably higher conversions when telescoping the crude reaction mixture from Method A to reductive conditions without intermediate purification. This convenient one-pot formal hydropentafluorosulfanylation sequence is defined as Method B in Table 3.1.

The substrate scope and functional group tolerance of Method B to access compounds **17-32** largely reflect that of Method A, with some exceptions. For instance, upon submitting a crude reaction mixture containing **3** to reduction conditions, conversion to **17** in 52% yield by ¹⁹F NMR was observed in lieu of **19**. This is consistent with the known propensity of metal borides and aluminides to reduce aryl bromides to their corresponding benzene rings.^[87] The *cis:trans* ratios observed using Method B range from 1:1 to 1.6:1 and often differ from ratios observed using Method A, suggesting that epimerization occurs during C–Cl bond reduction. Similar to Method A, it is important to stress that the difference in retention factors (*R_f* values) of both isomers

resulting from Method B is also enough to permit complete chromatographic separation in nearly all cases.

Although a complete mechanistic study on the metal boride reduction step in Method B is beyond the scope of this work, we conducted a few experiments to provide insight regarding 1) stereochemical consequences of the reduction, 2) potential sources of the H atom and differences in mechanism vs. aryl halide reduction, and 3) selectivity for α -chloro-sulfone reduction in a broader context. First, upon performing independent experiments with pure **syn-1** and pure **anti-1**, we confirmed epimerization at the α -site – virtually a 1:1 *cis:trans* ratio of **17** was observed in each case (Figure 3.2, *top panel*). Next, we conducted a systematic isotopic labelling study of the hydride and proton sources using **anti-3**, which undergoes both α -chloro and aryl bromide reduction (Figure 3.2, *middle panel*). Our observations of % D incorporation under these reaction conditions are consistent with previous metal boride and aluminide literature on aryl halide reduction and also suggest that α -chloro reduction likely occurs via a different mechanism, possibly involving a radical or anionic intermediate.^[88] This also comports with the observed epimerization. Lastly, we examined the reductive dechlorination conditions on **syn-33**, which contains a second aliphatic C–Cl bond (Figure 3.2, *bottom panel*). In this case, C–Cl bond reduction still proceeds preferentially at the α -site (to form **34**); this is noteworthy beyond the context of SF₅-CB synthesis.

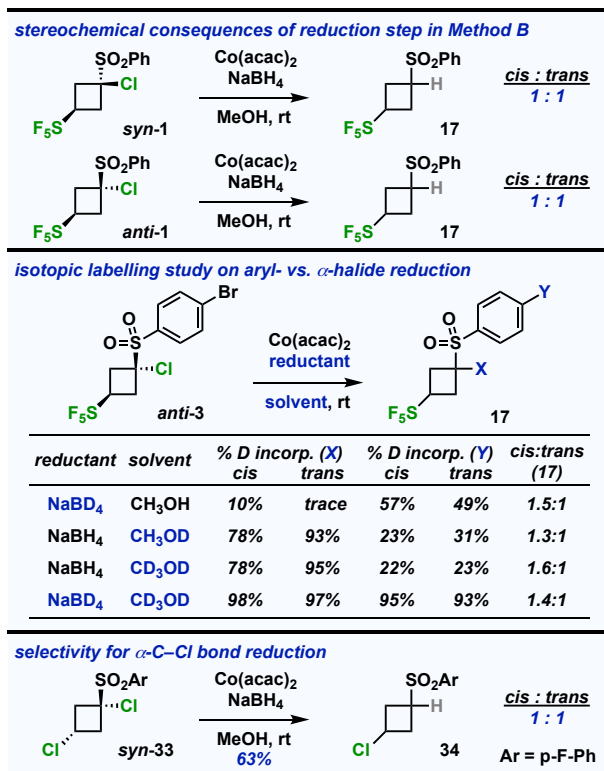


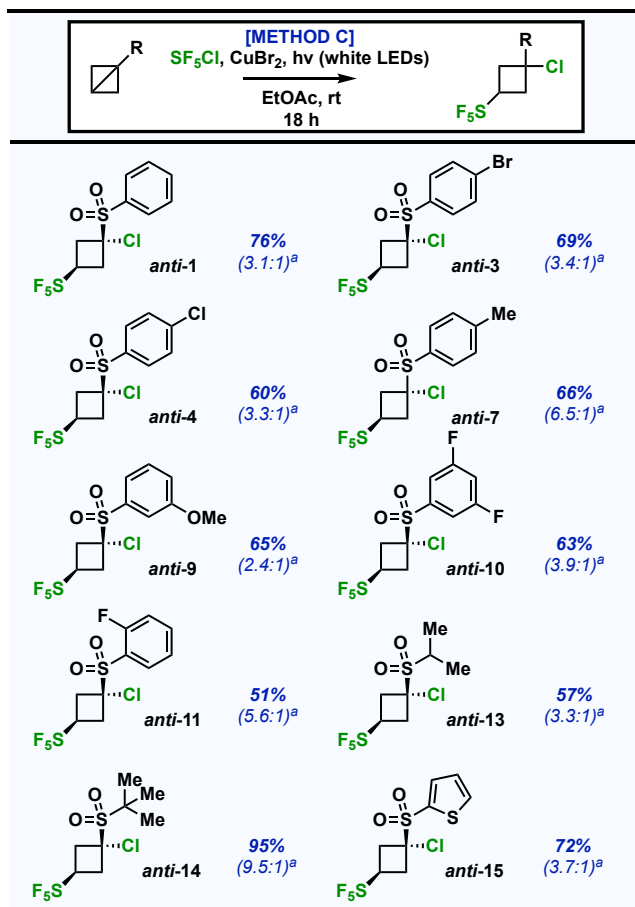
Figure 3.2. (Top) Reductive dechlorinations using pure *syn* and *pure anti* isomers of **1** result in epimerization. (Middle) Reduction of **anti-3** with deuterium-labelled reagents suggests difference in mechanisms in aryl- vs. α -halide reduction. (Bottom) Highlighting selectivity for reduction of α -chloro-sulfones. Isolated yield is reported.

While reductive dechlorination of some α -chloro-EWG-containing substrates using metal borides has been reported,^[86,89] to our knowledge, this approach was not investigated extensively on α -chloro-sulfones prior to this work. Moreover, it is remarkable that the SF₅ group remains unscathed under such conditions.

At this juncture, a stereoselective variation of Method B remains a lofty goal. However, during a later stage of our study, it was discovered that the innate selectivity of SF₅ radical addition in Method A can be overridden with the inclusion of a transition metal salt additive, i.e., an inexpensive copper salt. After additional reaction screening (see Section 3.5), we found that CuBr₂ can be employed in an *anti*-stereoselective variant of Method A (defined as Method C in Table 3.2). That is, the *anti:syn* ratio observed in the synthesis of **1** using Method A (1.1:1 – virtually

unselective) improves to 3.1:1 when using Method C, also improving the overall product yield. To examine generality, we briefly explored the scope of Method C on representative substrates for a side-by-side comparison with results using Method A. In all cases, we observed a clear preference for formation of the *anti* isomer in good yields, with *anti:syn* ratios now ranging from 2.4:1 to 9.5:1. While the origin of this *anti*-stereoselectivity and the precise role of the copper salt are not yet understood (to be investigated in future work), we provide proof-of-concept that stereochemical control over strain-release pentafluorosulfanylation is feasible. Beyond the context of pentafluorosulfanylation, Method C represents a rare instance whereby a transition metal additive evidently overrides (or perhaps exacerbates) substituent influence on selectivity in radical additions to BCBs.

Table 3.2. Substrate scope for *anti*-stereoselective chloropentafluorosulfanylation of [1.1.0]bicyclobutanes. Method C: BCB (0.10 mmol, 1.0 equiv.), CuBr₂ (0.10 mmol, 1.0 equiv.), ~0.10 M solution of SF₅Cl in *n*-pentane (0.12 mmol, 1.2 equiv.). ¹⁹F NMR yields are reported; the structure of major isomer is shown. ^aObserved *anti*:*syn* product ratio.



Subsequently, we examined whether the aforementioned methods translate to tetrafluoro(aryl)sulfanylation or tetrafluoro-(trifluoromethyl)sulfanylation of BCBs (Figure 3.3). Both aryl-SF₄Cl compounds and CF₃SF₄Cl are known to participate in radical chain propagation reactions a la SF₅Cl^[67a,74,90,91] and have recently become more accessible through corrosive gas reagent-free syntheses.^[67,69a,92] Yet, it cannot be *assumed* they will always react like SF₅Cl. For example, tetrafluoro(aryl)sulfanylation of **35** required additional optimization; however, we were able to access phenyl- and pyrimidyl-based compounds **36–39** in modest ¹⁹F NMR yields. Note that the –SF₄– moiety in each case was prone to hydrolysis during multiple attempts at

workup/isolation (see Section 3.5 for details); thus, we did not pursue this avenue any further. Conversely, tetrafluoro(trifluoromethyl)sulfanylation proceeded smoothly using Method A to provide **40** in 75% isolated yield, though we found that Method C conditions do not directly translate. Furthermore, the CF₃SF₄ group tolerated Method B conditions and afforded **41** in 56% isolated yield. To our knowledge, **40** and **41** are the first CF₃SF₄-CBs disclosed.

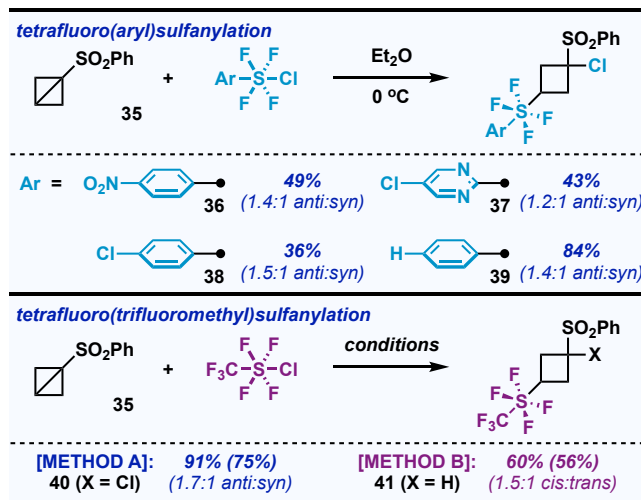


Figure 3.3. (*Top*) Extension of logic to tetrafluoro(aryl)sulfanylation. (*Bottom*) Extension of logic to tetrafluoro(trifluoromethyl)sulfanylation. ¹⁹F NMR yields are reported with isolated yields in parentheses.

Additionally, we were inspired by the recent work of Qing and co-workers^[93] to attempt iodopentafluorosulfanylation of BCBs. To our satisfaction, we were able to obtain proof-of-concept that **35** can be converted to **42** (1.5:1 *anti:syn*) using a similar type of three-component reaction (3CR) strategy (Figure 3.4, *top panel*). A complete optimization table is located in the Experimental Section. Note that **1** is still formed as a by-product under our specified conditions (in 15% yield), but **17** is not. Moreover, we were able to extend this 3CR logic to achieve formal pentafluorosulfanylation-allylation of a BCB (Figure 3.4, *bottom panel*).^[94] After another separate optimization campaign (see Section 3.5), we obtained proof-of-concept that strain-release pentafluorosulfanylation can be coupled with C–C bond formation in one pot to form **43** in 52%

yield by ^{19}F NMR. In this case, **1** and **17** were formed as by-products in <10% yield. We found that chromatographic separation of **43** from minor by-products **1** and **17** was permissible without need for HPLC purification.

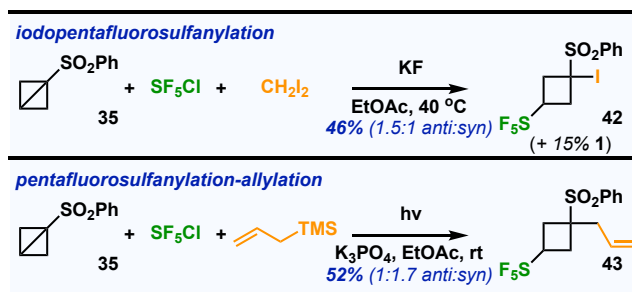


Figure 3.4. (Top) Proof-of-concept for a three-component reaction (3CR), i.e., iodopentafluorosulfanylation. (Bottom) Extension of 3CR logic to achieve formal pentafluorosulfanylation-allylation. ^{19}F NMR yields are reported.

Having generated access to a variety of SF_5 -CBs using the methods disclosed above, we proceeded to study and contextualize 1) structural aspects and 2) mechanistic features of SF_5 radical addition.

Considering cyclobutane rings have been employed as bioisosteric replacements for arenes,^[80a] we saw fit to compare structural features of SF_5 -CBs with a similarly-substituted SF_5 -arene using SC-XRD (Figure 3.5). Compound **44** was synthesized according to literature,^[95] and single crystals were grown that proved suitable for X-ray diffraction. This SF_5 -arene structure – already containing one element of bioisosterism (i.e., the SF_5 group^[73]) – was compared to "hybrid isostere" (SF_5 -CB) structures of *trans*-**17**, *syn*-**1**, and *cis*-**17**. The analogous SF_5 -BCP (**45**) was also synthesized/crystallized for another point of comparison.

Figure 3.5 provides a condensed view of key structural differences. In general, the replacement of the phenyl ring with a cyclobutane effectively results in a 21-24% reduction in distance between transannular carbon atoms. Replacement of the phenyl ring with a BCP ring results in ~34% reduction in distance. The virtue, however, of the $\text{Ph} \rightarrow \text{CB}$ replacement is the

added flexibility in spatial reorganization of the SF₅ group that SF₅-arenes (or SF₅-BCPs) cannot offer. In **44**, the S–C1–C4–S array, with the axis defined by C1 and C4, is virtually linear; this is also the case in **45**. In *trans*-**17**, the SF₅ group is situated well below the axis defined by C1 and C3 ($\theta \approx 42^\circ$), while the SO₂Ph substituent hovers above it ($\phi \approx 63^\circ$). Interestingly, the introduction of a Cl substituent in *syn*-**1** simultaneously decreases θ to 38° and increases ϕ to 70° . In *cis*-**17**, both the SF₅ and SO₂Ph groups float above the axis defined by C1 and C3 with $\omega \approx 31^\circ$ and $\phi \approx 37^\circ$, respectively. Additional crystallographic comparisons can be found in Section 3.5.^[96]

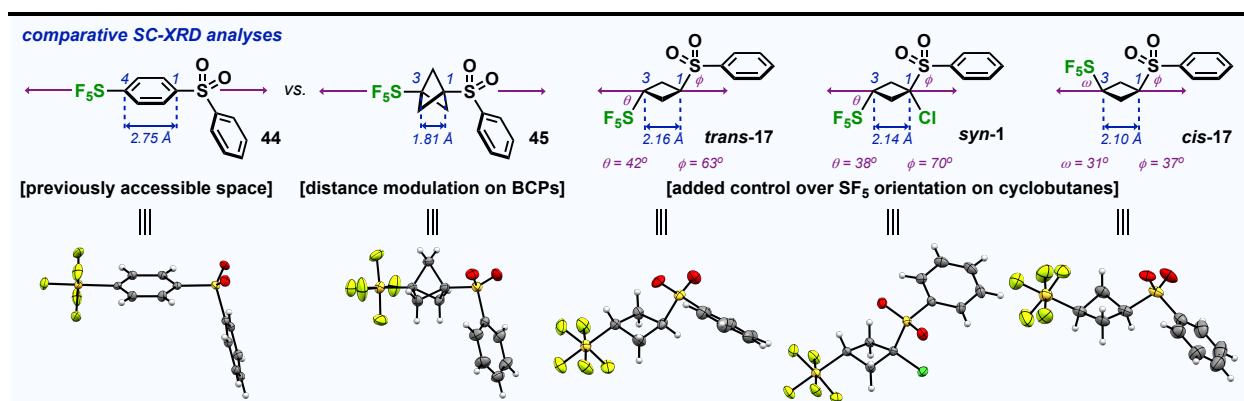


Figure 3.5. Select structural comparisons. Crystal structures for **44**, **45**, *trans*-**17**, *syn*-**1**, and *cis*-**17** determined by SC-XRD (displacement ellipsoids depicted at 50% probability level). The unit cell for **44** contains two symmetry-independent moieties (only one shown).

At this juncture, we proceeded to investigate the mechanism of chloropentafluorosulfanylation of BCBs (using **35** as a model substrate) under Method A conditions through a combined experimental and computational approach.

First, we considered possible initiation mechanisms for SF₅ radical formation under irradiation with white LEDs. Note that SF₅Cl does not absorb light in the visible region and homolytic S–Cl bond cleavage through direct photolysis seems unlikely.^[97] Direct excitation of **35** can similarly be ruled out.^[98] Thus, we propose one possible initiation mechanism that involves 1) initial complexation, e.g., of SF₅Cl and the strain-release reagent, 2) formal Cl atom transfer

concomitant with strained C–C bond homolysis, and 3) Cl atom abstraction from SF₅Cl by the resultant carbon-centered radical (e.g., to form **46**). This sequence would theoretically generate 2.0 equiv. of SF₅ radicals and an observable by-product. The proposed pathway for pentafluorosulfanylation of a BCB substrate is shown in Figure 3.6, *top panel*.

Although direct isolation of the proposed by-product from any of the reaction mixtures proved challenging, we managed to synthesize **syn-33** independently (confirmed by SC-XRD) as a fluorine-labelled external standard (Figure 3.6, *bottom panel*). Using this standard, we were able to confirm by both ¹⁹F NMR and GC/MS analyses that **syn-33** is formed in <3% yield by ¹⁹F NMR under pentafluorosulfanylation conditions, consistent with our proposed initiation mechanism. Density functional theory (DFT) calculations also indicate that formal Cl atom transfer from SF₅Cl to **35** in the ground state, e.g., through an inner-sphere single-electron transfer (SET) type of process, is prohibitively high in energy ($\Delta G^\ddagger = 30$ kcal/mol); an outer-sphere SET can similarly be ruled out ($\Delta G^\ddagger = 72$ kcal/mol to form the charge transferred species). Photochemical excitation of a complex involving SF₅Cl and **35** would effectively “lower” this barrier, offering a potential explanation for the reliance on light. At this time, we cannot rule out the possibility of alternative (synergistic) initiation pathways playing a role, but DFT calculations and observed formation of **syn-33** indicate the proposed pathway in Figure 3.6 could be operative.

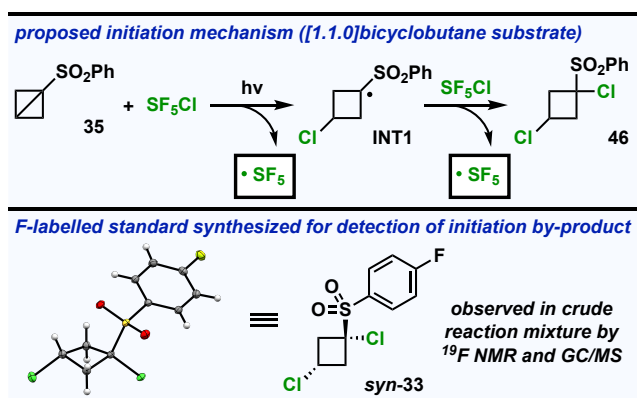


Figure 3.6. (Top) Proposed radical chain initiation mechanism for pentafluorosulfanylation of [1.1.0]bicyclobutane substrates. (Bottom) Fluorine-labelled standard independently synthesized and used to confirm by-product formation in reaction mixture.

Assuming prerequisite formation of SF_5 radicals, we examined the energetic feasibility of a radical chain propagation pathway using DFT calculations at the PWPB95-D4/def2-QZVPP//PCM(Et_2O)- $\omega\text{B97X-D/def2-SVP}$ level of theory.^[99] Several features of the energy profile located in Figure 3.7 (top panel) are worth highlighting that fully comport with experimental observations. For one, SF_5 radical addition to the less-hindered 3-position of **35** is predicted to have a significantly lower activation energy barrier than respective addition to the 1-position ($\Delta\Delta G^\ddagger = 7.3$ kcal/mol), despite the evident radical polarity mismatch.^[82] Under reaction conditions, pentafluorosulfanylation was observed exclusively at the 3-position. In addition, the reactive intermediate **INT2₃** can undergo Cl atom abstraction to form either *syn* or *anti* isomers of **1**. DFT calculations predict virtually no difference in activation energy barriers between **syn-1** and **anti-1** formation; our observed diastereoselectivity under Method A conditions was also consistently low (e.g., the **anti-1:syn-1** ratio is typically 1.1:1). Furthermore, calculations predict that Cl atom abstraction from SF_5Cl has a lower activation energy barrier in each case than, e.g., H atom abstraction from a solvent molecule (*n*-pentane), but only by a few kcal/mol. This ostensibly accounts for our observation of minor hydrogenated by-products (**17**) in addition to

chlorinated products (e.g., **1:17** product ratio under Method A conditions is typically 10:1). Lastly, it is also worth mentioning that we observed reaction inhibition in the presence of a variety of known radical scavengers (including BHT, TEMPO, dihydroanthracene, and O₂; see Section 3.5).^[100]

This computed radical chain propagation pathway is buttressed with isotope effect experiments. For example, we synthesized **35-*d*₁** with a deuterium atom selectively incorporated in the 3-position^[101] and carried out intermolecular competitive isotope effect experiments with **35** (Figure 3.7, *bottom-left panel*). The average [P_H]/[P_D] ratio observed was 0.94 – indicative of a small inverse secondary KIE.^[102] This is consistent, for instance, with rehybridization of the sp²-like carbon atom at the 3-position of **35** to ~sp³ in the first product-determining step. In fact, the computed KIE at PCM(Et₂O)-ωB97X-D/def2-TZVP also predicts a value of 0.94.

Subsequently, we designed an isotope effect experiment to probe the second product-determining step in our proposed mechanism, i.e., to examine chlorination vs. hydrogenation (Figure 3.7, *bottom-right panel*). We compared the **17:1** product ratio (1:7.7) resulting from the reaction of SF₅Cl and **35** in *n*-pentane/EtOAc with the **17-*d*₁:1** product ratio (1:41) observed when *n*-pentane-*d*₁₂ was employed instead. This “double competition” experiment both 1) confirms that off-cycle H atom abstraction (to form minor by-products) is occurring primarily from *n*-pentane and 2) allows us to indirectly probe the primary KIE for H atom abstraction by **INT2₃** (i.e., [Cl/D]/[Cl/H] ~ [H/D] ~ 5.3).^[103,104]

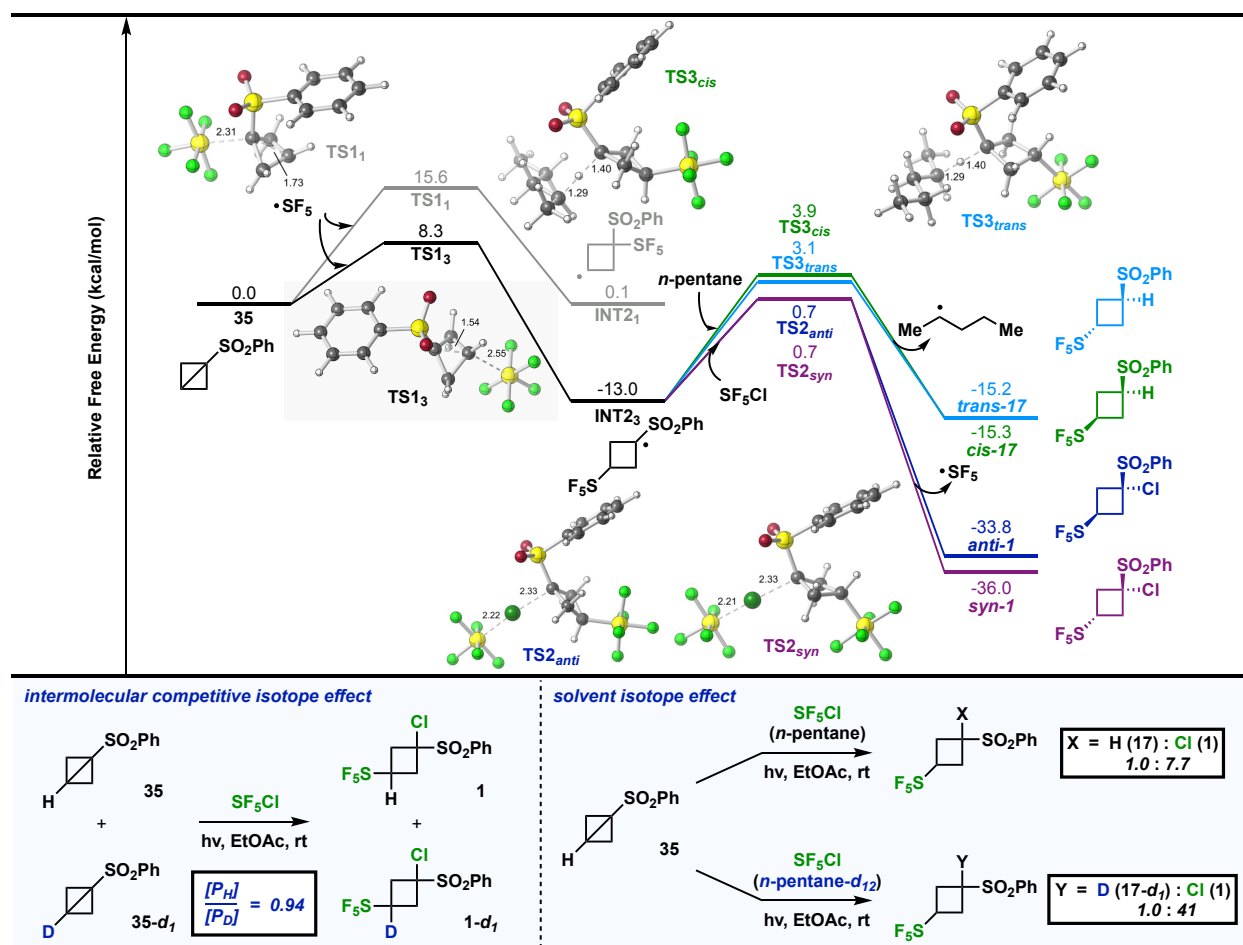


Figure 3.7. (Top) Computed free energy profile for SF₅ radical addition to a model BCB (**35**) computed at the PWPB95-D4/def2-QZVPP/PCM(Et₂O)- ω B97X-D/def2-SVP level of theory. (Bottom-Left) Intermolecular competitive isotope effect experiment probing the first product-determining step. (Bottom-Right) Solvent isotope effect experiment probing the second product-determining step.

While both SF₅Cl and BCBs are known to participate in radical chain propagations, the apparent addition of electrophilic SF₅ radicals to the 3-position of EWG-substituted BCBs is notable.

That is, nucleophilic radicals are typically employed in radical additions across BCBs substituted with EWGs^[105] (likewise, electrophilic radicals pair with more electron-rich BCBs^[106]). Also, SF₅ radical addition to analogous alkenes, such as **47** (Figure 3.8, top panel), is an established limitation due to the apparent radical polarity mismatch (**48** is formed in <10% yield

even when other established initiation conditions are employed). Another comparison between similarly substituted [1.1.0]bicyclobutane and [2.1.0]bicyclopentane, or “housane,” substrates (Figure 3.8, *bottom panel*) reveals that conversion of **50** to **51** does not proceed as efficiently as pentafluorosulfanylation of **49** to make **2**, despite a similar release in ring strain.^[78b]

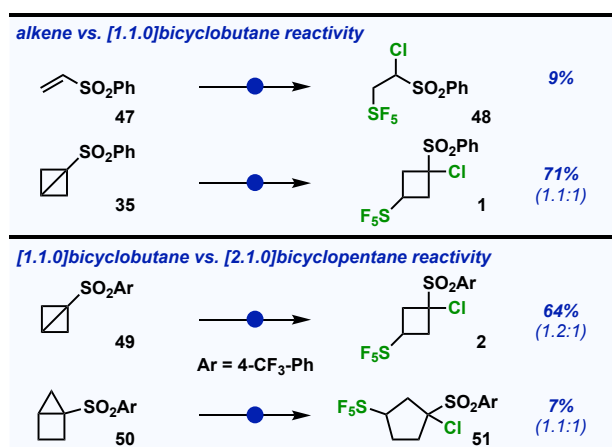


Figure 3.8. (*Top*) BCB reactivity vs. an analogously substituted alkene (Method A). (*Bottom*) BCB reactivity vs. an analogously substituted housane (Method A). ¹⁹F NMR yields are reported with isomeric ratios in parentheses.

DFT studies at the PWPB95-D4/def2-QZVPP//PCM(Et₂O)-ωB97X-D/def2-SVP level of theory (see SI of the associated publication for computational details)^[99] provide some insight into the observed differences in reactivity among analogously substituted BCBs, housanes, and alkenes (Figure 3.9). For one, SF₅ radical addition to **35** (to make **INT2**₃) and **52** (to make **INT3**) are both predicted to be exergonic by 13.0 and 22.6 kcal/mol, respectively. On the other hand, SF₅ radical addition to **47** (to make **INT4**) is endergonic ($\Delta G = +3.6$ kcal/mol). In addition, a significantly lower activation energy barrier was determined for pentafluorosulfanylation of **35** ($\Delta G^\ddagger = 8.3$ kcal/mol for **TS1**₃) vs. **52** ($\Delta G^\ddagger = 13.3$ kcal/mol for **TS4**), consistent with SF₅ radical addition being less likely to occur on housanes vs. BCBs, despite appearing more favorable from a thermodynamic standpoint. A similar barrier was computed for SF₅ radical addition to **47** ($\Delta G^\ddagger =$

13.4 kcal/mol for **TS5**). Thus, C(sp³)–SF₅ bond formation was determined to be more kinetically favorable for the BCB than either the housane or the alkene. It is important to note, however, that overall reaction barriers will also account for the generation of the SF₅ radical.

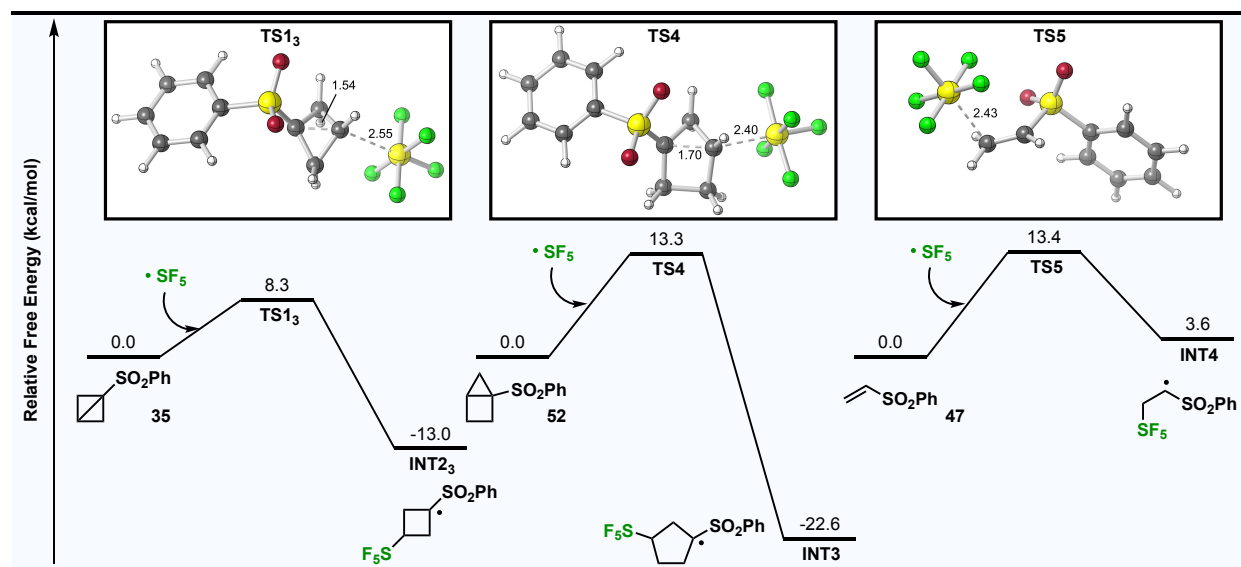


Figure 3.9. Free energy profiles at the PWPB95-D4/def2-QZVPP//PCM(Et₂O)-ωB97X-D/def2-SVP level of theory comparing SF₅ radical addition across an analogously substituted BCB (**35**), housane (**52**), and alkene (**47**).

Our relative predicted barriers for radical attack are consistent with Duarte's model based on bond delocalization in small rings,^[107] including the observation that BCB **35** is still determined to be less susceptible to radical attack than [1.1.1]propellane – the topic of our previous work.^[74] Finally, our observations are further corroborated by analysis of radical Fukui functions (Figure 3.10).^[108] Condensed Fukui functions computed for **35**, **47**, and **52** at the PCM(Et₂O)-ωB97X-D/def2-SVP level of theory indicate that the BCB has a stronger susceptibility toward radical attack compared to the alkene and housane.

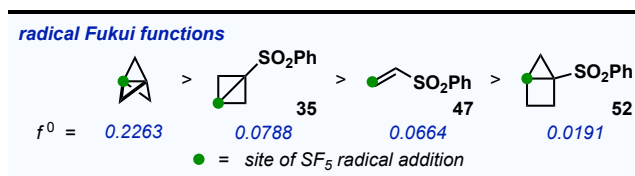
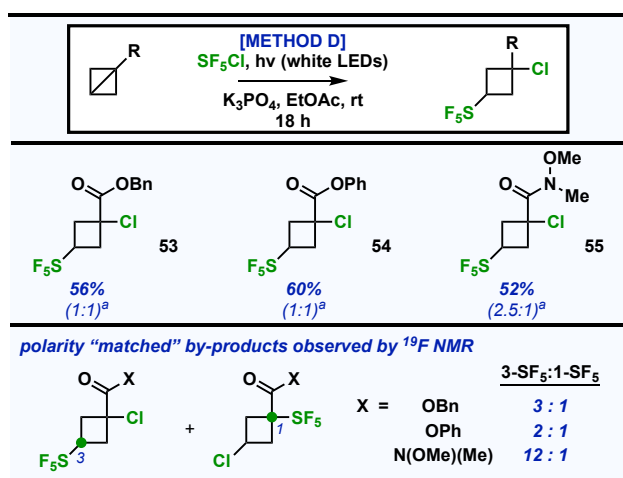


Figure 3.10. Fukui functions comparing site-susceptibilities to radical attack.

Nonetheless, the curious polarity mismatch addition of SF_5 radicals to sulfone-based BCBs poses another fundamental question: *is it possible to access the polarity “matched” products (i.e., with the SF_5 group in the 1-position)?* Conceptually, if the sulfone is replaced with another strong EWG that poses less steric hindrance to the approach of the SF_5 radical, this mechanistic pathway could become viable. Accordingly, we screened a variety of other EWG-substituted BCBs, including ketone, ester, amide, nitrile, halide, and boron-based groups. We obtained preliminary evidence that SF_5 radical addition to the 3-position proceeds in nearly all cases under Method A conditions, albeit in poor-to-modest yields (unoptimized; see Section 3.5). However, upon close inspection, the ^{19}F NMR spectra of the crude reaction mixtures using ester- and amide-based substrates also contained SF_5 signals of minor products that lack the distinct $^3J_{Feq-H}$ -coupling diagnostic of SF_5 in the 3-position. To investigate this further, we embarked on another focused optimization campaign specifically for SF_5Cl addition across ester- and amide-containing BCBs to access **53**, **54**, and **55** (defined as Method D in Table 3.3, *top panel*). Furthermore, we recognize that access to SF_5 -CBs with carbonyl functional group handles would also be particularly valuable from a synthetic standpoint.

Table 3.3. (Top) Optimized protocol for ester- and amide-based BCBs. Method D: BCB (0.10 mmol, 1.0 equiv.), ~0.10 M solution of SF₅Cl in *n*-pentane (0.30 mmol, 3.0 equiv.), K₃PO₄ (0.10 mmol, 1.0 equiv.). ¹⁹F NMR yields are reported for the major 3-SF₅ regioisomers (shown). ^aObserved *anti:syn* product ratio. (Bottom) Observation of polarity “matched” by-products (1-SF₅ regioisomers) in pentafluorosulfanylation of ester- and amide-based BCBs and regioisomeric ratios relative to 3-SF₅ formation.



Under Method D conditions, polarity mismatched products **53–55** were all still formed preferentially and in acceptable yields (Table 3.3, *top panel*); however, the polarity matched by-products (i.e., with the SF₅ group in the 1-position) are now clearly observed in the reaction mixtures. As anticipated, 3-SF₅:1-SF₅ regioisomeric ratios seem to correlate loosely with a steric effect within this series (Table 3.3, *bottom panel*). These findings are notable beyond the context of pentafluorosulfanylation, as radical addition directly to the 1-position of 1-substituted BCBs has seldom been reported, to our knowledge.^[78]

DFT studies shed additional light as to why 1-SF₅ product formation becomes competitive in pentafluorosulfanylation of carbonyl-substituted BCBs, where solely 3-SF₅ product formation was observed employing sulfone-substituted BCBs (Figure 3.11). Specifically, transition state analyses indicate that SF₅ radical addition to the 1-position of **56** has only a slightly higher activation barrier than addition to the 3-position ($\Delta\Delta G^\ddagger = 0.7$ kcal/mol), consistent with our observations. In contrast, the $\Delta\Delta G^\ddagger$ for SF₅ radical addition to the 1-position of **35** relative to the

3-position is 7.9 kcal/mol. While we have yet to optimize the reaction explicitly for 1-SF₅ product formation, this study has laid the groundwork for us to pursue this in future work.

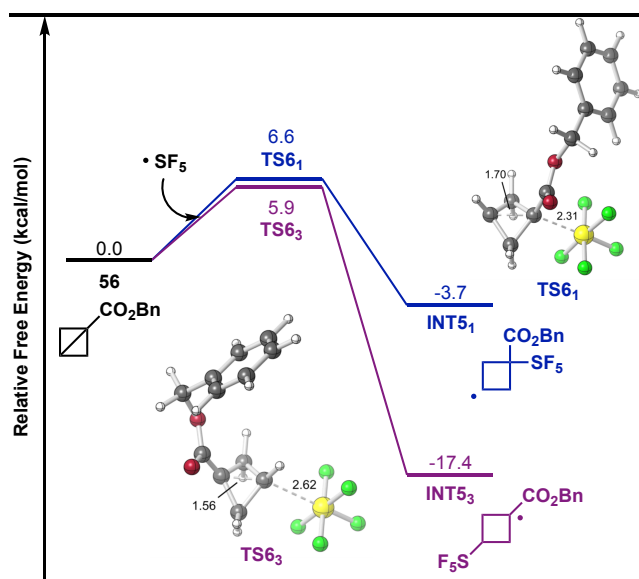


Figure 3.11. Free energy profiles showing comparison of SF₅ radical addition at 1-position and 3-position of **56** at PWPB95-D4/def2-QZVPP//PCM(Et₂O)- ω B97X-D/def2-TZVP level of theory.

Finally, we briefly examined downstream synthetic modifications of select sulfone- and carbonyl-containing SF₅-CBs reported herein to demonstrate compatibility with reactions commonly employed in a medicinal chemistry setting^[109] (Figure 3.12).^[110] First, we found that SF₅-CBs are compatible with palladium-catalyzed arylation (Suzuki) conditions;^[111] i.e., we converted **syn-3** to **57**. In a similar vein, we found that the SF₅-CB moiety is compatible with S_NAr conditions.^[112] That is, we converted **5** to **58** and in 70% isolated yield. In both cases, note that the SF₅-CB survived heating under basic conditions. We have also included data on preliminary attempts at C–Cl and C–H bond functionalization of **35** in the SI of the associated publication. We will explore these facets in greater detail in due course.

Lastly, we validated that the SF₅ group in the 3-position of carbonyl-containing SF₅-CBs is compatible with common carbonyl group manipulations (Figure 3.12, *bottom panel*). For

instance, we found that the SF₅-CB in **55** survived PhLi under Weinreb amide arylation conditions in the synthesis of **59**.^[113] Furthermore, we were able to carry **60** through a chloropentafluorosulfanylation, ester hydrolysis, and amide bond formation sequence to access **61** in 23% isolated yield over 3 steps without intermediate purification. While **54** is admittedly challenging to isolate without the aid of HPLC, we were able to demonstrate that the crude mixture can be telescoped through 2 additional steps, after which isomers of **61** proved separable. The ability to make these carbonyl derivatives, in principle, greatly expands the types of SF₅-CBs accessible using the strain-release approach we have outlined herein.

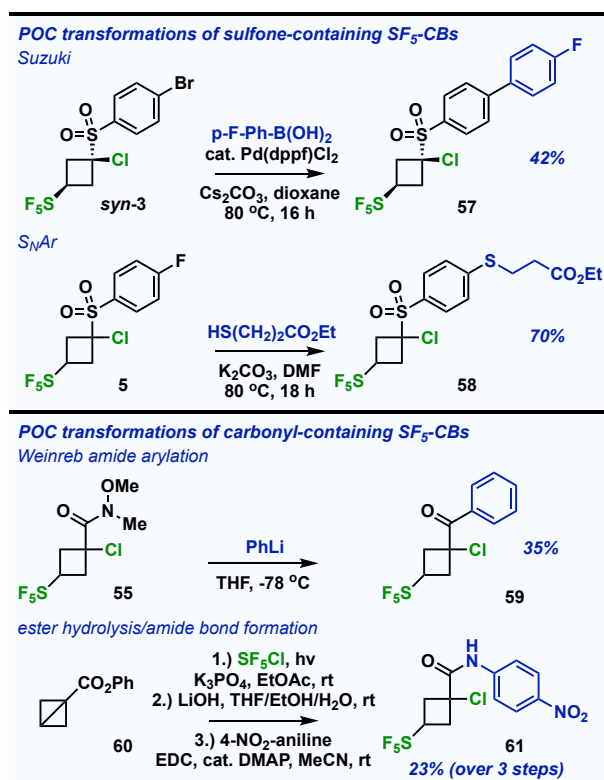


Figure 3.12. Proof-of-concept (POC) transformations of (*top*) sulfone- and (*bottom*) carbonyl-containing SF₅-CBs synthesized during this study. Isolated yields reported.

3.3 Conclusion.

We report on the synthesis, modification, and structure^[114] of pentafluorosulfanylated cyclobutanes (SF₅-CBs), as well as demonstrate proof-of-concept for synthesis of ArSF₄-CB and CF₃SF₄-CB congeners and assembly of SF₅-CBs through three-component reactions. In total, seven new methodologies were independently optimized and disclosed in this study. Furthermore, mechanistic studies provide some insight on the observed *polarity mismatch* radical addition and have led to the discovery that polarity matching, in some cases, can begin to guide radical addition to the unconventional site of a 1-substituted BCB. Future work will expand the scope of pentafluorosulfanylation of [1.1.0]bicyclobutanes, as well as explore applications of SF₅-CBs as "hybrid isostere" building blocks in complex molecule synthesis.

3.4 Author Contributions.

Y.K., J.A.B., A.M.S., A.N.R., S.P., and Z.C.H. performed synthetic work and data analysis. Y.K. optimized methods A, B, C, D, and F, synthesized compounds **1**, **5**, **7**, **10**, **12**, **14**, **16**, **17**, **21**, **23**, **26**, **28**, **30**, **32**, **40**, **41**, **42**, **43**, **44**, **57**, **58** and **61**, evaluated the scope of pentafluorosulfanylation in the presence of CuBr₂, and performed mechanistic experiments; J.A.B. optimized method E, synthesized compounds **2–4**, **6**, **8**, **9**, **15**, **18**, **19**, **20**, **22**, **24**, **25**, **31**, **36**, **37**, **38**, and **39**, and performed KIE/ deuterium labelling experiments; A.M.S. synthesized compounds **11**, **13**, **27**, **29**, **53**, **54**, **55**, **59**, and the sulfide precursor to **45**, performed mechanistic experiments, and explored the reactivity of 2- and 3-substituted sulfone BCBs; A.N.R. synthesized compounds **33** and **46**, collected UV-vis spectra, and performed GC/MS analyses; S.P. synthesized compound **45**; Z.C.H. explored the reactivity of phenyl vinyl sulfone. Y.K., J.A.B., A.M.S., A.N.R., S.P., Z.C.H., A.H.P., R.S., and R.D. synthesized starting materials. W.-Y.K. conducted all computational analyses. C.P.M. and J.C.F. collected SC-XRD data. D.J.T. and C.R.P. conceptualized and supervised the

project and acquired funding. The manuscript was written and edited with contributions from all authors.

3.5 Experimental.

3.5.1 General Information.

Unless otherwise stated, all reactions were carried out strictly under anhydrous conditions and under N₂ or Ar atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), diethyl ether (Et₂O) and toluene (PhMe) were obtained from a solvent purification system directly before use. Methanol (MeOH), acetonitrile (MeCN), *n*-pentane, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and ethyl acetate (EtOAc) were purchased in sealed bottles containing molecular sieves and were used as received. All other solvents were used as received unless otherwise stated. Spray-dried KF was always weighed out under glovebox atmosphere. All NMR data were collected on either a 300, 400, or 600 MHz spectrometer. For ¹⁹F NMR yield determination, α,α,α-trifluorotoluene (TFT) or fluorobenzene was introduced after each reaction as an internal standard, and the d1 relaxation delay was increased to 30 s during data collection. The ¹H, ¹³C, and ¹⁹F NMR chemical shifts are given in parts per million (δ) and calibrated to either residual solvent or TMS signal (¹H and ¹³C), α,α,α-trifluorotoluene (TFT) (δ = −62.61 ppm in CDCl₃), or fluorobenzene (δ = −112.96 in CDCl₃). NMR data are reported in the following fashion: chemical shift (multiplicity (s = singlet, d = doublet, q = quartet, p = pentet, sept = septet, dt = doublet of triplets, dd = doublet of doublets, tt = triplet of triplets, ttp = triplet of triplet of pentets, m = multiplet), integration, coupling constants (Hz)). Infrared spectroscopy (IR) data were collected on a Bruker Tensor 27 FT-IR spectrometer with ATR-IR attachment. IR signals are reported in reciprocal centimeters (cm^{−1}) and

are rounded to the nearest 1 cm^{-1} . High-resolution mass spectrometry (HRMS) data was collected on a Thermo Q-Exactive HF. Melting point data was collected on a Stanford Research Systems MPA120EZ-Melt automated melting point system.

3.5.2 Preparation of Bicyclo[1.1.0]butane Starting Materials.

Sulfone-containing BCBs were synthesized following a one-pot procedure reported by Jung and Lindsay,^[122] or by a stepwise route reported by Baran and co-workers.^[138] 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane was purchased from Millipore-Sigma (SKU: ALD00558). All other BCBs were prepared according to literature procedures. Ester, ketone, and amide-substituted BCBs were synthesized according to procedures reported by Procter, Studer, Glorius, and Malins.^[78] Sulfoxide, Bpin, and Br-substituted BCBs were synthesized according to procedures reported by Aggarwal and co-workers.^[70] The nitrile-substituted BCB was prepared according to a procedure from Gryko and co-workers.^[70] All spectral data were consistent with previously reported data.

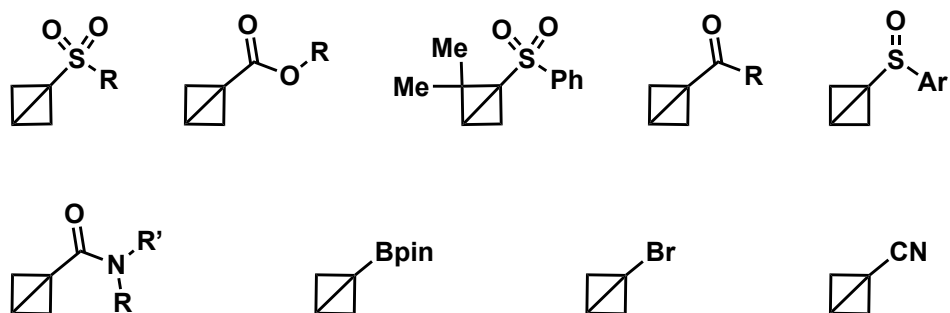
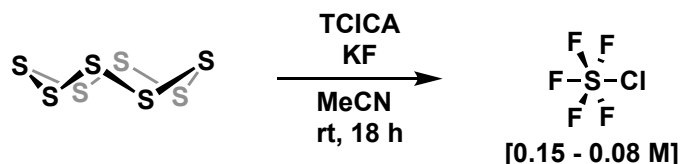


Figure 3.13. Bicyclobutane starting materials.

3.5.3 Synthesis of SF₅Cl.

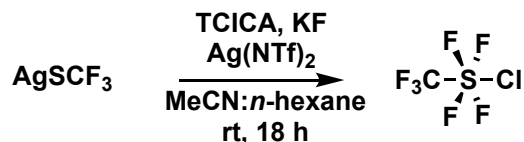


An oven-dried heavy-walled 350 mL pressure vessel equipped with a large stir bar was introduced to a nitrogen-filled glove box; trichloroisocyanuric acid (18.9 g, 4.5 equiv.) and spray-dried potassium fluoride (9.5 g, 9.0 equiv.) were added followed anhydrous MeCN (84 mL). The vessel was wrapped in aluminum foil and tightly sealed with a Teflon screwcap, and the mixture was vigorously stirred under glovebox atmosphere for 15 to 20 minutes. Sulfur (581 mg, 1.0 equiv.) was added, and the vessel was tightly sealed and quickly transported to a fume hood where it was submerged in a water bath to regulate the temperature. It was stirred vigorously at room temperature for 18 h (the reaction could also be run for 48 or 72 hours without lowering the yield). Upon reaction completion, the mixture was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice-acetone bath for approximately 30 min. Under a stream of Ar, anhydrous *n*-pentane (76 mL) was added slowly to avoid outgassing. The vessel was sealed, and the mixture was stirred vigorously until it reached room temperature. The MeCN and *n*-pentane layers were decanted into an oven-dried separatory funnel, the MeCN layer was discarded, and the SF₅Cl solution was transferred to a Schlenk flask under Ar atmosphere *via* syringe. Typically, 50-60 mL of the stock solution were obtained with concentrations ranging from 0.15 – 0.08 M. *Caution: SF₅Cl is highly toxic and should only be handled in a well-ventilated fume hood!*

Concentration determination:

An oven-dried 3mm NMR tube was fitted with a septum cap, evacuated, and backfilled with Ar. 5 μ L of α,α,α -trifluorotoluene (TFT) were added, followed by 0.4 mL anhydrous CDCl_3 , and a 0.2 mL aliquot of the SF_5Cl stock solution. During data collection the relaxation delay was set to 30 s and O1P to +30 ppm.

3.5.4 Synthesis of *trans*- $\text{CF}_3\text{SF}_4\text{Cl}$.

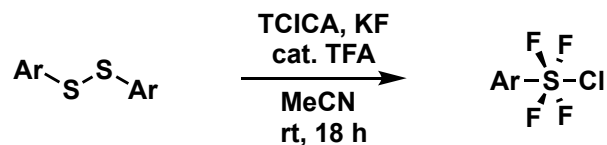


Following a literature procedure,^[92] an oven-dried 20 mL microwave vial equipped with a stir bar was charged with trichloroisocyanuric acid (2.78 g, 12 mmol, 12 equiv.); the vessel was then transported to a nitrogen-filled glovebox. Spray-dried potassium fluoride (348 mg, 4.0 mmol, 4.0 equiv.) was added, followed by AgNTf_2 (1.55 g, 4.0 mmol, 4.0 equiv.) and AgSCF_3 (209 mg, 1.0 mmol, 1.0 equiv.). Then, anhydrous MeCN (2.0 mL) and anhydrous *n*-hexane (2.0 mL) were added, and the vessel was sealed with a crimper. The vessel was transported to a fume hood where it was stirred vigorously at room temperature for 18 h. Upon reaction completion, the mixture was allowed to settle and cooled to -78°C in a dry ice/acetone bath. The *n*-hexane layer was removed *via* cannula into a sealed microwave vial under Ar. An additional 2.0 mL *n*-hexane were added at -78°C to extract the MeCN layer; the mixture was warmed to room temperature and stirred vigorously for approximately 20 minutes. After that time, the mixture was allowed to settle, and the *n*-hexane layer was collected *via* cannula transfer.

Concentration determination:

A 0.1 mL aliquot of the *trans*-CF₃SF₄Cl stock solution in *n*-hexane was added to an oven-dried 3 mm diameter NMR tube containing 5 μ L fluorobenzene and 0.4 mL CDCl₃. During data collection, the relaxation delay was set to 30 s and the O1P was set to 0 ppm.

3.5.5 Synthesis of Aryl Tetrafluoro- λ^6 -sulfanyl Chlorides.



Trichloroisocyanuric acid (18.0 equiv.) was added to an oven-dried round bottom flask equipped with a stir bar under glovebox atmosphere. Then, spray-dried potassium fluoride (32 equiv.) was added, followed by the disulfide starting material (1.0 equiv.). MeCN (1.5 M) was added to the reaction flask followed by a solution of trifluoroacetic acid (0.1 equiv.) in MeCN. The reaction was stirred under glovebox atmosphere at room temperature (ca. 23 °C) for 18 h. Upon completion of the reaction, TCICA and KF were removed by filtration of the solvent through a PTFE syringe filter into a PFA vessel; the solvent was then removed *in vacuo*. The left-over white solids were extracted with *n*-pentane (or hexanes), filtered through a PTFE syringe filter into a PFA vessel and concentrated *in vacuo*.

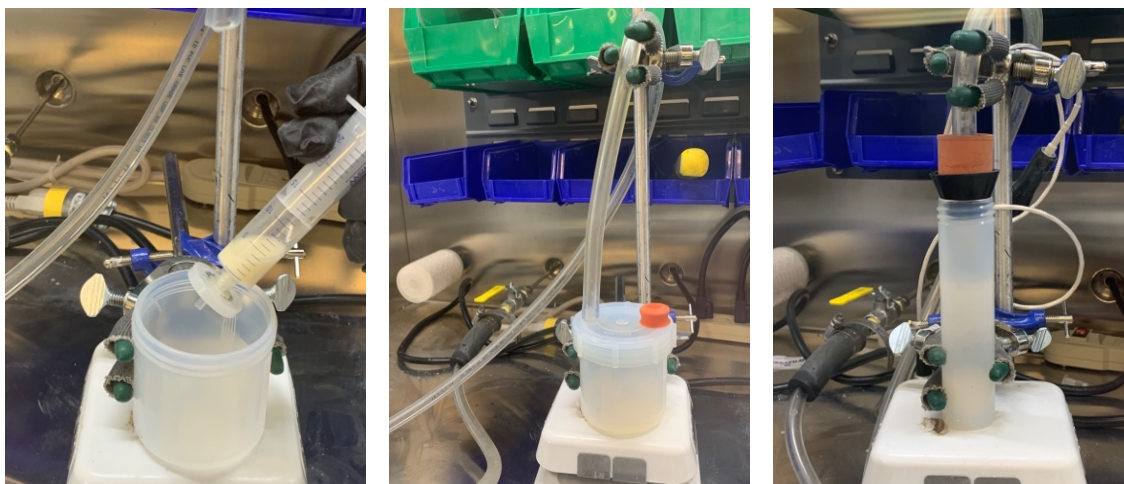
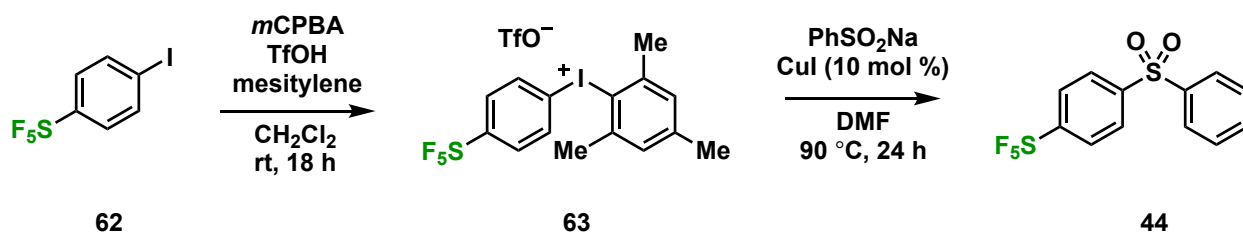


Figure 3.14. Left: Filtration of MeCN layer. Middle: Concentrating filtered MeCN. Right: Concentrating filtered *n*-pentane extract.

3.5.6 Synthesis of pentafluoro(4-(phenylsulfonyl)phenyl)- λ^6 -sulfane.



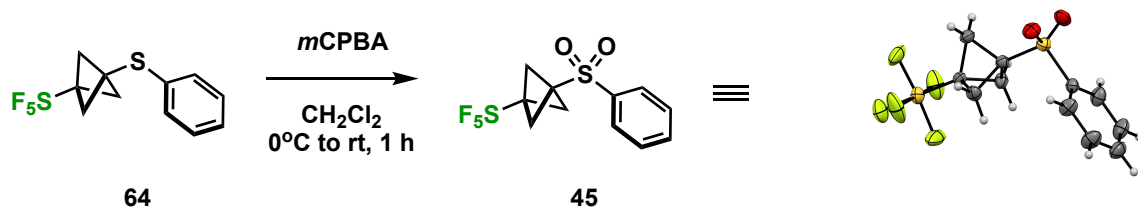
Following a literature procedure^[95], an oven-dried 25 mL flask equipped with a stir bar was charged with *m*CPBA (545 mg, 2.2 mmol, 1.1 equiv.). The flask was capped with a septum and placed under vacuum for 1 hour. Then, pentafluoro(4-iodophenyl)- λ^6 -sulfane (653 mg, 2.0 mmol, 1.0 equiv., **62**) and anhydrous CH_2Cl_2 (6.0 mL) were added, and the contents were placed under Ar atmosphere. The solution was cooled to 0 °C and TfOH (0.3 mL, 3.4 mmol, 1.7 equiv.) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. After 2 h, mesitylene (0.3 mL, 2.2 mmol, 1.1 equiv.) was added dropwise and the resulting solution was stirred at room temperature overnight. Upon completion, the solvent was removed *in vacuo* and crude product was precipitated by the addition of Et_2O (approx. 15 mL). The precipitate was filtered and dried *in vacuo* to afford mesityl(4-(pentafluoro- λ^6 -sulfanyl)phenyl)iodonium trifluoromethanesulfonate (**63**) as a fine white powder (973 mg, 81%).

¹H (300 MHz, (CD₃)₂CO): δ = 8.28-8.25 (d, 2H, *J* = 8.7 Hz), 8.08-8.05 (d, 2H, *J* = 9.2 Hz), 7.32 (s, 2H), 2.72 (s, 6H), 2.38 (s, 3H); **¹⁹F (282 MHz, (CD₃)₂CO):** δ = 82.63-80.52 (p, 1F, ²*J*_{F-F} = 146.6 Hz), 62.27-61.74 (d, 4F, ²*J*_{F-F} = 146.6 Hz), -78.93 (s, 3F).

To obtain pentafluoro(4-(phenylsulfonyl)phenyl)-λ⁶-sulfane, three identical reactions were set up in parallel. To an oven-dried culture tube equipped with a stir bar and Teflon-lined screw cap were added mesityl(4-(pentafluoro-λ⁶-sulfanyl)phenyl)iodonium trifluoromethanesulfonate (**63**, 132 mg, 0.22 mmol, 1.1 equiv.), sodium benzenesulfinate (33 mg, 0.2 mmol, 1.0 equiv.), and copper(I)iodide (3.8 mg, 0.02 mmol, 10 mol %). The vials were sealed and placed under Ar atmosphere. Then, anhydrous DMF (0.4 mL) was added, and the reactions were transferred to a pre-heated oil bath at 90 °C and stirred at that temperature for 24 h. Upon completion, the reactions were cooled to room temperature, quenched with sat. NH₄Cl (1.0 mL), and then all combined in a separatory funnel. The combined mixture was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and concentrated. The crude residue was purified by column chromatography on silica gel eluting with 95:5 hexanes:EtOAc to yield pentafluoro(4-(phenylsulfonyl)phenyl)-λ⁶-sulfane (**45**) as a white powder (74 mg, 36%). Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

R_f: 0.14 (95:5 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, (CDCl₃):** δ = 8.06-8.04 (d, 2H, *J* = 8.1 Hz), 7.98-7.95 (d, 2H, *J* = 7.8 Hz), 7.90-7.88 (d, 2H, *J* = 8.8 Hz), 7.65-7.61 (m, 1H), 7.57-7.53 (m, 2H).; **¹⁹F (282 MHz, (CDCl₃):** δ = 82.49-80.89 (p, 1F, ²*J*_{F-F} = 150.6 Hz), 62.67-62.27 (d, 4F, ²*J*_{F-F} = 150.6 Hz)

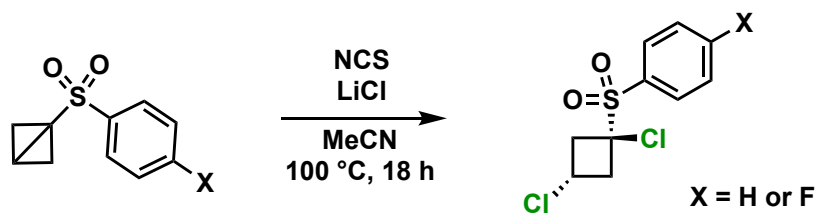
3.5.7 Synthesis of pentafluoro(3-(phenylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-λ⁶-sulfane.



To a solution of the sulfide^[93] **64** (25 mg, 0.08 mmol, 1.0 equiv) in CH₂Cl₂ (1.6 mL), *m*-CPBA (44 mg, 0.25 mmol, 3.0 equiv) was added in one portion at 0 °C. The ice-bath was removed, and the mixture was stirred at rt for 1 h. The resulting mixture was cooled to 0 °C and quenched with sat. Na₂SO₃ (2 mL) and sat. NaHCO₃ (2 mL). The mixture was extracted with CH₂Cl₂ three times (3 × 5 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:acetone = 5:1, v/v) to yield **45** (21 mg, 76 %) as white solid. Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

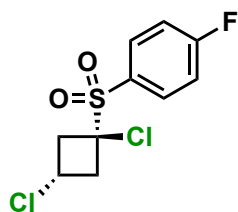
R_f: 0.27 (hexanes:acetone 5:1), vis: UV (254 nm); **m.p.**: 176–180 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 7.90–7.84 (m, 2H), 7.77–7.68 (m, 1H), 7.65 – 7.58 (m, 2H), 2.56 (s, 6H); **¹⁹F NMR (282 MHz, CDCl₃)**: δ = 77.72-75.64 (p, 1F, *J* = 147.1 Hz), 50.67-50.15 (d, 4F, *J* = 147.1 Hz); **¹³C NMR (150 MHz, CDCl₃)**: δ = 136.8, 135.0, 130.1, 129.0, 55.8-55.7 (p, *J* = 2.7 Hz), 1.5; **ATR-IR (ν_{max})**: 2161, 1979, 1449, 1311, 1196, 1157, 1089, 982, 903, 859, 821, 804, 792, 753, 721, 684, 651, 612 cm⁻¹.

3.5.8 Synthesis of 1-((-1,3-dichlorocyclobutyl)sulfonyl)-4-fluorobenzene (46) & ((1,3-dichlorocyclobutyl)sulfonyl)benzene (33).



An oven-dried round bottom flask was charged with the appropriate BCB substrate (0.52 mmol, 1.0 equiv.) under Ar atmosphere. The BCB was dissolved in anhydrous MeCN (7 mL). To the resulting mixture were added *n*-chlorosuccinimide (0.62 mmol, 1.2 equiv., 0.083 g) and lithium chloride (5.2 mmol, 10 equiv., 0.220 g) successively. The reaction was heated to reflux (100 °C) in an oil bath for 18 h. Upon completion, the reaction was diluted with water (5 mL) and extracted into CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over MgSO₄, filtered through a Celite plug, and then concentrated *in vacuo*. The crude material was purified by column chromatography, followed by preparative TLC 9:1 hexanes:EtOAc.

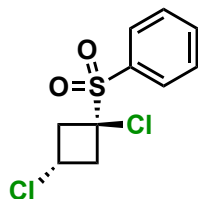
Compound **33** was prepared according to the procedure outlined above. The crude residue was purified first by column chromatography (9:1 hexanes:EtOAc) using silica gel, followed by preparative TLC (9:1 hexanes:EtOAc) to obtain a white solid (11 mg) in 8% yield. Crystals suitable for SC-XRD were grown by solvent evaporation from toluene.



Compound 33: 1-((1,3-dichlorocyclobutyl)sulfonyl)-4-fluorobenzene

R_f: 0.42 (9:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 112.5-115.1 °C; **¹H (300 MHz, CDCl₃):** δ = 7.95-7.91 (m, 2H), 7.24-7.19 (m, 2H), 4.55-4.45 (m, 1H), 3.66-3.58 (m, 2H), 2.93-2.85 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = -100.95 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 168.1-165.5 (d, 258.9 Hz), 133.9-133.8 (d, 9.8 Hz), 129.3-129.2 (d, 3.1 Hz), 116.8-116.6 (d, 22.6 Hz), 74.5, 46.9, 44.5; **ATR-IR (ν_{max}):** 2918, 1584, 1330, 1236, 1147, 842, 726 cm⁻¹; **HRMS (m/z):** Not found. ESI, APCI, MALDI all attempted in both positive and negative mode.

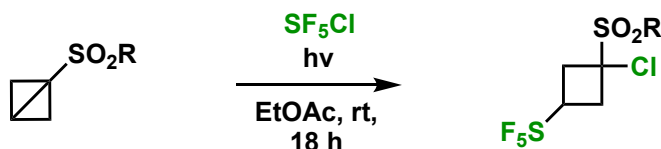
Compound **46** was prepared according to the procedure outlined above. The compound was purified by column chromatography (9:1 hexanes:EtOAc) using silica gel, followed by preparative TLC on silica (9:1 hexanes:EtOAc) to obtain a white solid (12 mg) in 9% yield.



Compound 46: ((1,3-dichlorocyclobutyl)sulfonyl)benzene

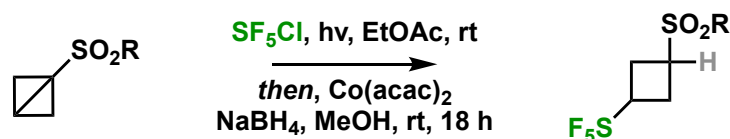
R_f: 0.27 (9:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 132.8-139.8 °C; **¹H (300 MHz, CDCl₃):** δ = 8.00-7.97 (m, 2H), 7.77-7.72 (m, 1H), 4.63-4.53 (m, 1H), 3.76-3.68 (m, 2H), 3.00-2.92 (m, 2H); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 135.0, 133.3, 131.0, 129.2, 74.5, 46.9, 44.6; **ATR-IR (ν_{max}):** 2918, 1585, 1312, 1147, 830, 729 cm⁻¹; **HRMS (m/z):** Not found. ESI, APCI, MALDI all attempted in both positive and negative mode.

3.5.9 General Procedure A: Strain Release Pentafluorosulfanylation of 1-sulfonyl bicyclo[1.1.0]butanes.



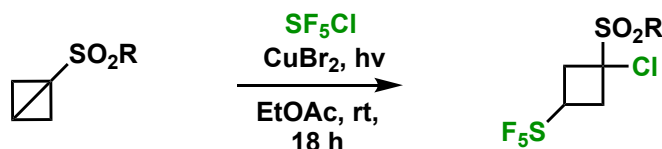
An oven-dried microwave vial equipped with a stir bar was charged with the bicyclobutane (0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. EtOAc (2.0 mL) was added followed by a solution of SF_5Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LED's (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Upon reaction completion, the solvent was removed *in vacuo*, and the crude residue was purified *via* silica gel chromatography or preparative thin-layer chromatography (TLC) (specific conditions for individual compounds are given below).

3.5.10 General Procedure B: One-pot Strain Release Pentafluorosulfanylation and C–Cl Reduction of 1-Sulfonylbicyclo[1.1.0]butanes.



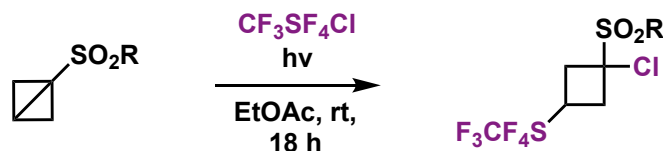
An oven-dried microwave vial equipped with a stir bar was charged with the bicyclobutane (0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added followed by a solution of SF_5Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LED's (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Then, the solvent was removed *in vacuo* and MeOH (1.3 mL, 0.15 M) was added followed by $\text{Co}(\text{acac})_2$ (77 mg, 0.3 mmol, 1.5 equiv.). NaBH_4 (38 mg, 1.0 mmol, 5.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 hours. Upon completion, the solution was diluted with CH_2Cl_2 (approx. 2.0 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5.0 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×5.0 mL). The combined organic fractions were washed with H_2O and brine (1×5.0 mL), dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified *via* silica gel chromatography or preparative TLC (specific conditions for individual compounds are given below).

3.5.11 General Procedure C: anti-Selective Strain Release Pentafluorosulfanylation of 1-sulfonylbicyclo[1.1.0]butanes.



An oven-dried microwave vial equipped with a stir bar was charged with the bicyclobutane (0.1 mmol, 1.0 equiv.) and CuBr₂ (22 mg, 0.1 mmol, 1.0 equiv.) . The vial was crimped, then evacuated and backfilled with Ar three times. EtOAc (1.0 mL) was added followed by a solution of SF₅Cl in *n*-pentane (0.12 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LED's (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Upon reaction completion, an aliquot was taken for ¹⁹F yield and diastereomeric ratio determination.

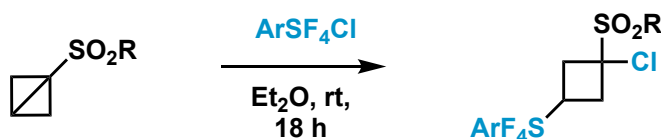
3.5.12 General Procedure D: Strain Release Tetrafluoro(trifluoromethyl)sulfanylation of 1-sulfonylbicyclo[1.1.0]butanes.



An oven-dried microwave vial equipped with a stir bar was charged with the bicyclobutane (0.1 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. EtOAc (1.0 mL) was added, followed by a solution of CF₃SF₄Cl in *n*-hexane (0.12 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LED's (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Upon reaction completion, the solvent was removed *in vacuo*, and the crude residue was purified *via* preparative thin-layer chromatography (TLC) (specific conditions for individual

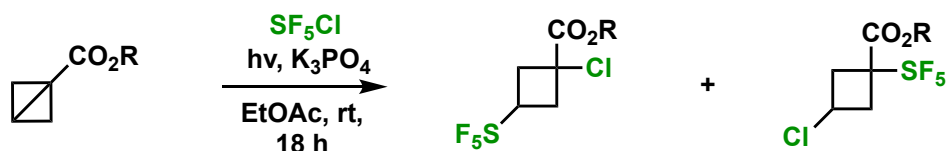
compounds are given below). The reduction method was performed as described in general procedure B, on a 0.1 mmol scale.

3.5.13 General Procedure E: Strain Release Tetrafluoro(aryl)sulfanylation of 1-sulfonylbicyclo[1.1.0]butanes.



An oven-dried microwave vial equipped with a stir bar was charged with **35** (0.05 mmol, 1 equiv.) and purged with Ar three times. Then, anhydrous Et_2O (0.3 mL) was added, and the resulting solution was cooled to 0°C . Separately, in a nitrogen-filled glovebox, an oven-dried microwave vial was charged with ArSF_4Cl (0.05 mmol, 1.1 equiv.), sealed with a crimper, and transported to a fume hood. The ArSF_4Cl compound was quickly dissolved using anhydrous Et_2O (0.3 mL). The resulting solution was added dropwise under Ar to the vial containing **35**. The ice-bath was removed, and the reaction mixture was stirred at room temperature (ca. 23°C) for 18 hours. Upon completion, the reaction was concentrated *in vacuo* and the crude residue was purified via preparative TLC using 4:1 hexanes:EtOAc.

3.5.14 General Procedure F: Strain Release Pentafluorosulfanylation of Ester-substituted and Amide-substituted Bicyclo[1.1.0]butanes.



To an oven-dried microwave vial equipped with a stir bar was added K_3PO_4 (21.1 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed and then evacuated and refilled with Ar three times. Then, the BCB (0.1 mmol, 1.0 equiv.) was added as a solution in EtOAc (1.0 mL), followed by SF_5Cl in pentane (0.3 mmol, 3.0 equiv.). The resulting mixture was stirred vigorously under white LED irradiation overnight (the temperature was kept at rt with a fan). Upon completion, the reaction was diluted with EtOAc and filtered through a small plug of Celite. The crude residue was either carried forward without purification or purified by preparative TLC.

3.5.15 Optimization Table.

The general procedure A was followed during optimization experiments with a few modifications. A stock solution of the BCB (**35**) in anhydrous EtOAc (or other solvent during solvent screens) was prepared to give a 0.1 M solution. If applicable, the additive (1.0 equiv.) was added to a sealed, oven-dried microwave vial equipped with a stir bar, and Ar atmosphere was established. Then, **35** (9.7 mg, 0.05 mmol, 0.5 mL stock solution) was added followed by a solution of SF₅Cl (0.06 mmol, 1.2 equiv.) in *n*-pentane. The mixture was irradiated with white LEDs for 18 h (typically the mixture reached approximately 35 °C). Upon reaction completion, a 0.2 mL aliquot was taken for ¹⁹F yield determination. 10 μL of α,α,α-trifluorotoluene was introduced as an internal standard, followed by 0.5 mL CDCl₃. During data collection, the relaxation delay was increased to 30 s, and the O1P was set to +30 ppm.

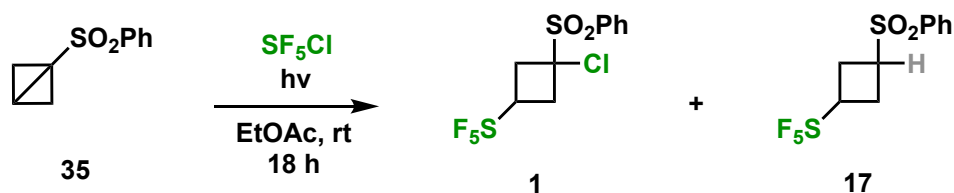


Table 3.4. Optimization of SF₅Cl addition across **35**.

Entry	Deviations from standard conditions	¹⁹ F Yield (%) 1 ^a	<i>anti:syn</i> ratio ^b	¹⁹ F Yield (%) 17 ^a
1 ^c	none	77	1.1:1	10
2 ^c	0.2 mmol scale	71	1.1:1	7
3	1.0 equiv. 35 and 1.0 equiv. SF ₅ Cl	25	1:1	3
4	1.0 equiv. 35 and 5.0 equiv. SF ₅ Cl	40	1:1.1	<1
5	1.2 equiv. 35 and 1.0 equiv. SF ₅ Cl	20	1:1	3
6	2.0 equiv. 35 and 1.0 equiv. SF ₅ Cl	11	1:1.1	<1
7	5.0 equiv. 35 and 1.0 equiv. SF ₅ Cl	<1	n.d.	n.d.
8	with CH ₂ Cl ₂ instead of EtOAc	54	1.6:1	10
9	with THF instead of EtOAc	13	n.d.	n.d.
10	with Et ₂ O instead of EtOAc	40	1:1.1	16
11	with toluene instead of EtOAc	49	1:1.1	32
12	with 1,2-DCE instead of EtOAc	67	1.1:1	10
13	dark at room temperature	4	1:1	<1
14	dark at 50 °C	9	1:1.1	0
15	ambient light at room temperature	12	1:1.1	0
16 ^b	task lamp as cool white LED source	39	1:1.1	4
17	Blue LED	40	1:1	0
18	with BEt ₃ /O ₂ as initiator (10 mol %)	<1	n.d.	<1
19	with Cy ₂ NH·BH ₃ as initiator (10 mol %)	5	1:1	<1
20	with K ₃ PO ₄ (1.0 equiv.)	<2	n.d.	n.d.
21	with Na ₂ CO ₃ (1.0 equiv.)	50	1:1.1	16
22	with CuCl (1.0 equiv.)	41	2.8:1	0
23 ^e	with DIPEA (1.0 equiv.)	0	n.d.	n.d.
24 ^e	with DBU (1.0 equiv.)	0	n.d.	n.d.

[a] Yields determined by ¹⁹F NMR. [b] Ratios determined by ¹⁹F NMR. [c] 40 W Kessil A160WE Tuna Blue LED light was used in the optimized conditions (on white setting). [d] 72 W Coleman LED Rechargeable Task Light (“cool white” LEDs) were used. [e] Complete decomposition of starting materials.

3.5.16 Product Distribution Table.

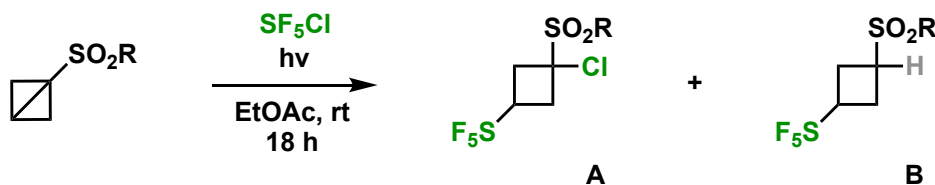


Table 3.5. Chloropentafluorosulfanylation (major pathway) vs. hydropentafluorosulfanylation (minor pathway) from Method A.

R ¹ =	% yield A ^a	<i>anti:syn</i> ratio A ^b	% yield B ^a	<i>cis:trans</i> ratio B ^b	A:B
Ph	71	1.1:1	7	1:1	10:1
4-CF ₃ -Ph	64	1.2:1	19	1:1	3.4:1
4-Br-Ph	62	1.2:1	15	1:1	4.1:1
4-Cl-Ph	60	1.1:1	10	1.1:1	6.0:1
4-F-Ph	85	1.1:1	9	1:1	9.4:1
4-OCF ₃ -Ph	59	1.4:1	18	1.1:1	3.3:1
4-Me-Ph	78	1.1:1	12	1:1	6.5:1
4-OMe-Ph	60	1:1	4	1:1	15:1
3-OMe-Ph	62	1:1	2	1:1	31:1
3,5-diF-Ph	52	1.1:1	22	1:1	2.4:1
2-F-Ph	52	2:1	9	1:1	5.8:1
2-OMe-Ph	67	1.3:1	3	n.d.	22:1
<i>i</i> -Pr	92	1:1.1	8	1:1.3	12:1
<i>t</i> -Bu	63	2.5:1	trace	n.d.	>63:1
Thiophene	76	1:1	14	1.1:1	5.4:1
Piperidine	25	1.4:1	0	n.d.	n.d.

[a] Yields determined by ¹⁹F NMR. [b] Ratios of stereoisomers determined by ¹⁹F NMR.

3.5.17 Effect of Cu additives on *anti:syn* ratios.

Given the modest selectivity observed for the *anti* isomer with CuCl (entry 22) as an additive, the effect of metal salts and ligands was briefly investigated.

The general procedure A was followed during optimization experiments with a few modifications. A stock solution of the BCB (**35**) in anhydrous EtOAc (or other solvent during solvent screens) was prepared to give a 0.1 M solution. Then, **35** (9.7 mg, 0.05 mmol, 0.5 mL stock solution) was added to a sealed, oven-dried microwave vial containing a stir bar under and the

designated additives under Ar atmosphere. A solution of SF₅Cl (0.06 mmol, 1.2 equiv.) in *n*-pentane was added *via* syringe. The mixture was irradiated with white LEDs for 18 h. Upon reaction completion, a 0.2 mL aliquot was taken for ¹⁹F yield determination. 10 μL of α,α,α-trifluorotoluene was introduced as an internal standard, followed by 0.3 mL CDCl₃. During data collection, the relaxation delay was increased to 30 s, and the O1P was set to +30 ppm.

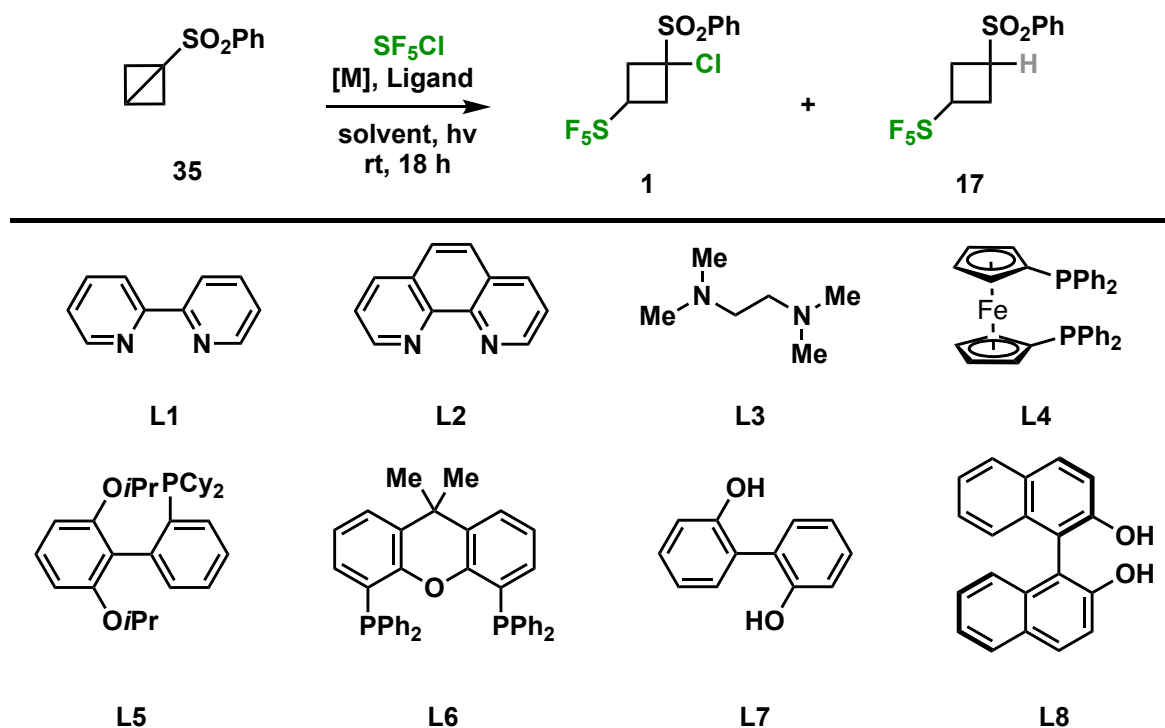


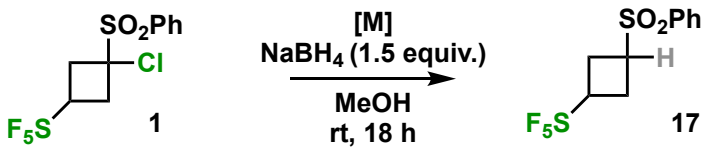
Table 3.6. Study of the effect of metal salts and ligand additives on diastereoselectivity.

Entry	[M] (equiv.)	Ligand (equiv.)	Solvent (0.1 M)	¹⁹ F Yield 1 (%) ^a	<i>anti:syn</i> ratio ^b	¹⁹ F Yield 17 (%) ^a
1	Cu(OTf) ₂ (1.0)	–	EtOAc	<2	n.d.	0
2	CuF ₂ (1.0)	–	EtOAc	51	2.7:1	<1
3	CuBr (1.0)	–	EtOAc	14	2.3:1	0
4	CuBr ₂ (1.0)	–	EtOAc	76	3.1:1	0
5	CuCl ₂ (1.0)	–	EtOAc	42	3.4:1	0
6	CuI (1.0)	–	EtOAc	12	3.1:1	<1
7	Cu(OAc) ₂ (1.0)	–	EtOAc	63	3.4:1	0
8	CuCN (1.0)	–	EtOAc	47	2.5:1	8
9	Cu(MeCN) ₄ PF ₆ (1.0)	–	EtOAc	60	2.9:1	0
10	Cu(MeCN) ₄ PF ₆ (1.0)	L1 (1.0)	EtOAc	33	1.1:1	0
11	Cu(MeCN) ₄ PF ₆ (1.0)	L2 (1.0)	EtOAc	22	1:1.1	0
12	Cu(OAc) ₂ (1.0)	L1 (1.0)	EtOAc	50	1:1.1	0
13	Cu(OAc) ₂ (1.0)	L2 (1.0)	EtOAc	20	1:1.1	0
14	Cu(OAc) ₂ (1.0)	L3 (1.0)	EtOAc	0	–	0
15	Cu(OAc) ₂ (1.0)	L4 (1.0)	EtOAc	6	n.d.	0
16	Cu(OAc) ₂ (1.0)	L5 (1.0)	EtOAc	0	–	0
17	Cu(OAc) ₂ (1.0)	L6 (1.0)	EtOAc	0	–	0
18	Cu(OAc) ₂ (1.0)	L7 (1.0)	EtOAc	26	2.7:1	0
19	Cu(OAc) ₂ (1.0)	L8 (1.0)	EtOAc	0	–	0
20 ^c	Cu(OAc) ₂ (1.0)	–	EtOAc	0	n.d.	0
21 ^c	Cu(OAc) ₂ (1.0)	–	acetone	<1	n.d.	0
22 ^d	Cu(OAc) ₂ (1.0)	–	EtOAc	<1	n.d.	0
23	NiCl ₂ (1.0)	–	EtOAc	21	1.1:1	15
24	FeCl ₂ (1.0)	–	EtOAc	70	3.6:1	7
25	Co(acac) ₂ (1.0)	–	EtOAc	0	–	0
26	MnBr ₂ (1.0)	–	EtOAc	0	n.d.	0
27	CuBr ₂ (1.0)	–	acetone	35	3.3:1	<1
28	Cu(OAc) ₂ (1.0)	–	acetone	23	1.2:1	13
29	CuCl ₂ (1.0)	–	acetone	60	3.9:1	0
30	CuCl ₂ (0.5)	–	acetone	13	4.9:1	0
31	CuCl ₂ (2.0)	–	acetone	10	4.8:1	0
32	CuCl ₂ (5.0)	–	acetone	22	4.8:1	0
33	(PPh ₃)AuCl (1.0)	–	acetone	25	2:1	0
34	AuCl ₃ (1.0)	–	acetone	0	n.d.	0
35	AgF ₂ (1.0)	–	acetone	29	1:1.1	24

[a] Yields determined by ¹⁹F NMR. [b] Ratios determined by ¹⁹F NMR. [c] Reaction was run under ambient conditions. [d] Reaction was run in the absence of light (wrapped in aluminum foil).

3.5.18 Optimization of C–Cl Bond Reduction.

Table 3.7. Screening conditions for reduction of C–Cl bond.



Reaction scheme: **1** (cyclobutane with SO₂Ph, CF₃, and Cl) $\xrightarrow[\text{MeOH, rt, 18 h}]{\text{NaBH}_4 (1.5 \text{ equiv.}), [M]}$ **17** (cyclobutane with SO₂Ph, CF₃, and H)

Entry	[M] (equiv.)	¹⁹ F yield 17 (%)
1	Co(acac) ₂ (1.0)	75
2	NiCl ₂ (1.0)	95
3	FeCl ₂ (1.0)	quant.
4	CuCl ₂ (1.0)	80

Discussion of the choice of Co(acac)₂: While iron (II) chloride was a suitable additive for the reduction of **1**, this system resulted in incomplete conversion of other substrates (e.g., **5** and **7**). It was found that increasing the equivalents of Co(acac)₂ and NaBH₄ yielded quantitative conversion in each case. Portionwise addition of NaBH₄ also proved beneficial to the reaction.

3.5.19 Optimization of Chloropentafluorosulfanylation of Carbonyl-BCBs.

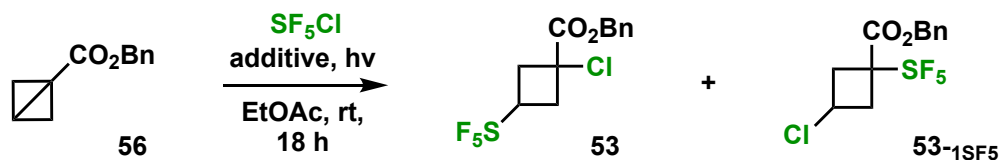


Table 3.8. Optimization of addition of SF₅Cl across **56**.

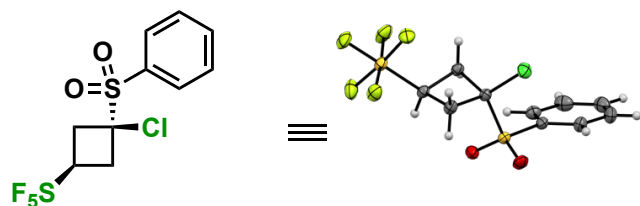
Entry	Equiv. SF ₅ Cl	Additive (equiv.)	% yield 53 ^a	d.r. ^b	% yield 53-1SF₅ ^a
1	1.2	—	15	1:1	13
2 ^c	1.2	—	10	1:1.1	20
3	2.0	—	32	1:1	12
4	3.0	—	45	1:1	18
5 ^d	3.0	—	35	1:1	14
6	3.0	K ₃ PO ₄ (1.0)	55	1:1	19
7	1.2	CuBr ₂ (1.0)	24	1:1.1	13

[a] Yields were determined by ¹⁹F NMR. [b] Diastereomeric ratios were determined by ¹⁹F NMR. [c] 40 W Kessil A160WE Tuna Blue LED light was used on the blue setting (blue LEDs). [d] Reaction was run on 0.5 mmol scale.

The optimization of compound **56** was then directly translated to **60** and the Weinreb amide containing BCB. The other carbonyl containing BCBs (ester and amide) performed similarly under the specified reaction conditions.

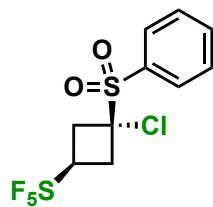
3.5.20 Characterization Data for Compounds 1–32.

Compound **1** was prepared according to the general procedure A; *anti*-**1** and *syn*-**1** formed in 71% yield by in a 1.1:1 ratio by ^{19}F NMR. Compound *syn*-**1** was isolated as a white solid (17.5 mg) and *anti*-**1** was isolated as a clear oil (18.9 mg); the total isolated yield was 51%. A mixture of diastereomers was obtained by column chromatography on silica gel and the isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc, followed by preparative thin-layer chromatography (TLC) using 4:1 hexanes:EtOAc.



Compound *syn*-1: 3-chloro-(3-(phenylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

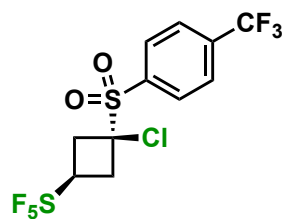
R_f: 0.57 (4:1 hexanes:EtOAc), 0.31 (9:1 hexanes:EtOAc), 0.59 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **m.p.:** 128.0 – 130.7 °C; **^1H (300 MHz, CDCl₃):** δ = 7.95-7.92 (m, 2H), 7.73-7.67 (m, 1H), 7.59-7.53 (m, 2H), 4.77-4.62 (tpp, 1H, J = 8.9, 8.8, 5.7 Hz), 3.52-3.44 (m, 2H), 3.29-3.21 (m, 2H); **^{19}F (282 MHz, CDCl₃):** δ = 82.91-80.85 (p, 1F, $^2J_{\text{F-F}}$ = 145.4 Hz), 52.00-51.46 (dd, 4F, $^2J_{\text{F-F}}$ = 145.4 Hz, $^3J_{\text{F-H}}$ = 5.7 Hz); **$^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl₃):** δ = 135.2, 132.8, 130.6, 129.4, 73.4, 68.1-67.7 (p, J = 17.6 Hz), 40.1-39.9 (p, J = 4.4 Hz); **ATR-IR (ν_{max}):** 1585, 1450, 1309, 1146, 832, 802 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁ClF₅O₂S₂⁺ [M+H]⁺ 356.9804, found 356.9805.



Compound anti-1: 3-chloro-(3-(phenylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

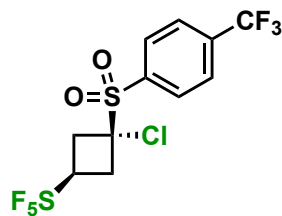
R_f: 0.51 (4:1 hexanes:EtOAc), 0.29 (9:1 hexanes:EtOAc), 0.53 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.97-7.94 (m, 2H), 7.78-7.72 (m, 1H), 7.65-7.59 (m, 2H), 4.82-4.64 (tt, 1H, J = 9.2, 8.9, 5.3 Hz), 3.88-3.73 (m, 2H), 2.79-2.70 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.23-80.16 (p, 1F, $^2J_{F-F}$ = 144.7), 53.78-53.24 (dd, 4F, $^2J_{F-F}$ = 144.7 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 135.3, 133.4, 131.1, 129.5, 74.4, 69.0-68.5 (p, J = 16.5 Hz), 41.4-41.2 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 1585, 1449, 1321, 1156, 829, 795, 686 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁ClF₅O₂S₂⁺ [M+H]⁺ 356.9804, found 356.9804.

Compound **2** was prepared according to the general procedure A; **anti-2** and **syn-2** formed in 64% yield in a 1.2:1 ratio by ¹⁹F NMR. Compound **syn-2** was isolated as a white solid (15.6 mg) and **anti-2** was isolated as a white solid (26.2 mg); the total isolated yield was 49%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, then 100% CH₂Cl₂. *Note: purification typically involved a first round of preparative TLC where the desired products were separated from other reaction byproducts. The second round of preparative TLC was then used to separate the isomers.*



Compound syn-2: (3-chloro-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

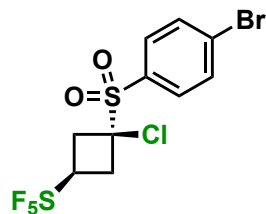
R_f: 0.74 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 125.9 – 132.6 °C; **¹H (400 MHz, CDCl₃):** δ = 8.09-8.06 (d, 2H, J = 8.2 Hz), 7.84-7.81 (d, 2H, J = 8.2 Hz), 4.77-4.61 (tt, 1H, J = 9.9, 8.9, 5.6 Hz), 3.52-3.44 (m, 2H), 3.32-3.24 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 82.62-80.55 (p, 1F, $^2J_{F-F}$ = 146.9 Hz), 52.02-51.48 (dd, 4F, $^2J_{F-F}$ = 146.9 Hz, $^3J_{F-H}$ = 5.6 Hz), -63.38 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 136.6, 131.8, 126.6-126.5 (q, $^2J_{C-F}$ = 3.6 Hz), 124.5, 121.7, 73.5, 68.9-68.2 (p, J = 16.7 Hz), 41.4-41.3 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 1586, 1325, 1168, 1150, 824, 799, 742, 655 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₀ClF₈O₂S₂⁺ [M+H]⁺ 424.9678, found 424.9678.



Compound anti-2: (3-chloro-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

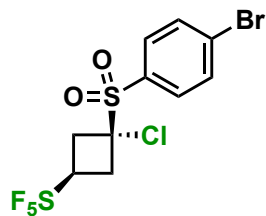
R_f: 0.64 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 84.8 – 87.0 °C; **¹H (400 MHz, CDCl₃):** δ = 8.04-8.01 (d, 2H, J = 8.3 Hz), 7.83-7.80 (d, 2H, J = 8.3 Hz), 4.75-4.59 (tpp, 1H, J = 9.8, 8.9, 5.5 Hz), 3.83-3.73 (m, 2H), 2.74-2.66 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 81.97-79.90 (p, 1F, $^2J_{F-F}$ = 144.6 Hz), 53.77-53.23 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.5 Hz), -63.35 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 137.2, 131.3, 126.7-126.6 (q, $^2J_{C-F}$ = 3.7 Hz), 124.5, 121.8, 74.2, 68.1-67.4 (p, J = 17.4 Hz), 40.1-39.9 (p, J = 4.1 Hz); **ATR-IR (v_{max}):** 2979, 1321, 1159, 1142, 830, 798, 621 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₀ClF₈O₂S₂⁺ [M+H]⁺ 424.9678, found 424.9674.

Compound **3** was prepared according to the general procedure A; **anti-3** and **syn-3** formed in 62% yield in a 1.2:1 ratio by ¹⁹F NMR. Compound **syn-3** was isolated as a white solid (19.9 mg) and **anti-3** was isolated as a white solid (19.5 mg); the total isolated yield was 42%. The isomers were separated *via* successive preparative TLC on silica gel using 8:2 hexanes:EtOAc, then 100% CH₂Cl₂.



Compound syn-3: (3-((4-bromophenyl)sulfonyl)-3-chlorocyclobutyl)pentafluoro- λ^6 -sulfane

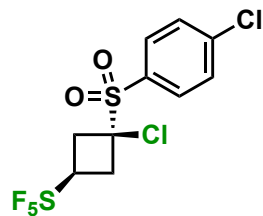
R_f: 0.68 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 150.9 – 154.0 °C; **¹H (300 MHz, CDCl₃):** δ = 7.87-7.83 (m, 2H), 7.79-7.75 (m, 2H), 4.82-4.66 (tpp, 1H, J = 9.9, 8.7, 5.6), 3.56-3.48 (m, 2H), 3.36-3.28 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.77-80.70 (p, 1F, $^2J_{F-F}$ = 144.6 Hz), 52.03-51.49 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.7 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 132.9, 132.5, 131.9, 131.3, 73.5, 68.9-68.3 (p, J = 16.8 Hz), 41.5-41.3 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2921, 1146, 812, 768 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀BrClF₅O₂S₂⁺ [M+H]⁺ 434.8909, found 434.8902.



Compound *anti*-3: (3-((4-bromophenyl)sulfonyl)-3-chlorocyclobutyl)pentafluoro- λ^6 -sulfane

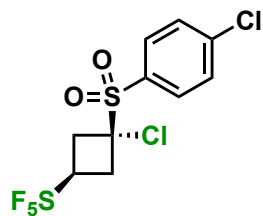
R_f: 0.64 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 116.5 – 119.7 °C; **¹H (300 MHz, CDCl₃):** δ = 7.75-7.72 (m, 4H), 4.73-4.58 (tpp, 1H, J = 9.7, 8.9, 5.3 Hz), 3.79-3.70 (m, 2H), 2.72-2.63 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.10-80.04 (p, 1F, $^2J_{F-F}$ = 144.6), 53.78-53.25 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 132.9, 132.4, 131.9, 131.0, 74.3, 68.1-67.4 (p, J = 17.2 Hz), 40.0-39.9 (p, J = 3.9 Hz); **ATR-IR ($\nu_{\max}$):** 2921, 1146, 812, 768 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀BrClF₅O₂S₂⁺ [M+H]⁺ 434.8909, found 434.8914.

Compound **4** was prepared according to the general procedure A; ***anti*-4** and ***syn*-4** formed in 60% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound ***syn*-4** was isolated as a white solid (17.6 mg) and ***anti*-4** was isolated as a white solid (17.9 mg); the total isolated yield was 45%. The isomers were separated *via* successive preparative TLC on silica gel using with 4:1 hexanes:EtOAc, then 100% CH₂Cl₂.



Compound syn-4: (3-chloro-3-((4-chlorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

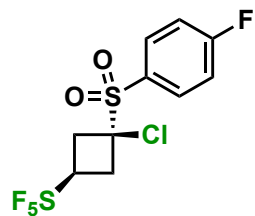
R_f: 0.74 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 140.6 – 143.6 °C; **¹H (300 MHz, CDCl₃):** δ = 7.88-7.84 (m, 2H), 7.55-7.51 (m, 2H), 4.75-4.59 (tt, 1H, J = 9.8, 8.8, 5.7 Hz), 3.49-3.41 (m, 2H), 3.29-3.21 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.77-80.71 (p, 1F, $^2J_{F-F}$ = 144.6), 52.03-51.49 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 4.5 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 142.5, 132.5, 129.9, 73.5, 69.1-68.2 (p, J = 16.8 Hz), 41.5-41.2 (p, J = 4.5 Hz); **ATR-IR ($\nu_{\max}$):** 2918, 1584, 1477, 1321, 1149, 820, 796, 653 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀Cl₂F₅O₂S₂⁺ [M+H]⁺ 390.9414, found 390.9421.



Compound *anti*-4: (3-chloro-3-((4-chlorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

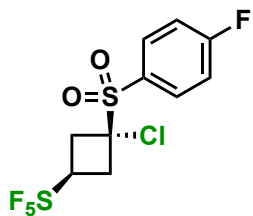
R_f: 0.67 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 112.1 – 113.6 °C; **¹H (300 MHz, CDCl₃):** δ = 7.84-7.79 (m, 2H), 7.55-7.50 (m, 2H), 4.75-4.56 (tt, 1H, J = 9.8, 8.8, 5.5 Hz), 3.79-3.70 (m, 2H), 2.72-2.64 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.11-80.04 (p, 1F, $^2J_{F-F}$ = 144.6), 53.78-53.25 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 4.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 142.4, 131.9, 129.9, 74.3, 68.2-67.3 (p, J = 17.3 Hz), 40.1-39.9 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2919, 1583, 1478, 1152, 828, 793, 629 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀Cl₂F₅O₂S₂⁺ [M+H]⁺ 390.9414, found 390.910.

Compound **5** was prepared according to the general procedure A; ***anti*-5** and ***syn*-5** formed in 85% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound ***syn*-5** was isolated as a white solid (21.3 mg) and ***anti*-5** was isolated as a clear oil (20.7 mg); the total isolated yield was 59%. The isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc, followed by preparative TLC using 100% CH₂Cl₂.



Compound syn-5: (3-chloro-3-((4-fluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

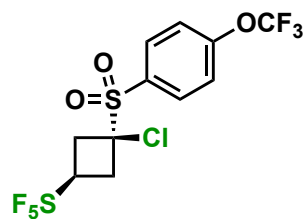
R_f: 0.69 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 118.0 – 120.7 °C; **¹H (300 MHz, CDCl₃):** δ = 7.99-7.92 (m, 2H), 7.27-7.20 (m, 2H), 4.76-4.60 (ttp, 1H, J = 9.8, 8.8, 5.7 Hz), 3.49-3.41 (m, 2H), 3.29-3.21 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.80-80.74 (p, 1F, $^2J_{F-F}$ = 144.2 Hz), 52.02-51.48 (dd, 4F, $^2J_{F-F}$ = 144.2 Hz, $^3J_{F-H}$ = 5.7 Hz), -100.44 (m 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 168.7-165.3 (d, J = 258.8 Hz), 134.1-133.9 (d, J = 9.7 Hz), 128.9-128.8 (d, J = 3.4 Hz), 117.1-116.8 (d, J = 22.6 Hz), 73.6, 69.1-68.3 (p, J = 16.6 Hz), 41.5-41.2 (p, J = 4.3 Hz); **ATR-IR (v_{max}):** 3033, 1587, 1492, 1322, 1143, 805, 732 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀ClF₆O₂S₂⁺ [M+H]⁺ 374.9709, found 374.9709.



Compound anti-5: (3-chloro-3-((4-fluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

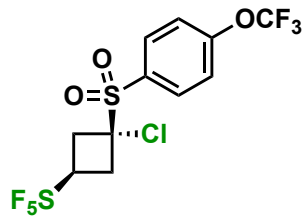
R_f: 0.60 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.93-7.87 (m, 2H), 7.27-7.19 (m, 2H), 4.73-4.58 (tt, 1H, J = 9.6, 8.9, 5.3 Hz), 3.79-3.70 (m, 2H), 2.72-2.63 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.13-80.07 (p, 1F, $^2J_{F-F}$ = 144.9 Hz), 53.77-53.23 (dd, 4F, $^2J_{F-F}$ = 144.9 Hz, $^3J_{F-H}$ = 5.3 Hz), -100.69 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 168.7-165.2 (d, J = 258.8 Hz), 133.6-133.5 (d, J = 9.8 Hz), 129.5-129.4 (d, J = 3.3 Hz), 117.2-116.9 (d, J = 22.7 Hz), 74.4, 68.2-67.3 (p, J = 16.8 Hz), 40.1-39.9 (p, J = 4.1 Hz); **ATR-IR ($\nu_{\max}$):** 3070, 1590, 1320, 1164, 801, 729 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀ClF₆O₂S₂⁺ [M+H]⁺ 374.9709, found 374,9709.

Compound **6** was prepared according to the general procedure A; **anti-6** and **syn-6** formed in 59% yield in a 1.4:1 ratio by ¹⁹F NMR. Compound **syn-6** was isolated as a white solid (22.1 mg). Compound **anti-6** was isolated as a white solid (20.2 mg); the total isolated yield was 48%. The isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc, followed by preparative TLC using 100% CH₂Cl₂. *Note: syn-6 and anti-6 were not very UV active on the prep plate, it is recommended to stain a small portion with KMnO₄ to better visualize the product bands.*



Compound syn-6: (3-chloro-3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

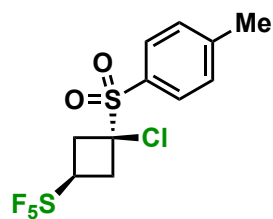
R_f: 0.75 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 105.1 – 107.9 °C; **¹H (300 MHz, CDCl₃):** δ = 8.07-8.04 (d, 2H, J = 8.9 Hz), 7.44-7.42 (d, 2H, J = 8.9 Hz), 4.83-4.67 (tpp, 1H, J = 9.8, 8.9, 5.7 Hz), 3.57-3.49 (m, 2H), 3.38-3.30 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.71-80.65 (p, 1F, $^2J_{F-F}$ = 144.1 Hz), 52.00-51.47 (dd, 4F, $^2J_{F-F}$ = 144.1 Hz, $^3J_{F-H}$ = 5.6 Hz), -57.54 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 154.7-154.4 (q, J = 1.7 Hz), 133.5, 130.9, 122.1, 120.9, 118.6, 73.6, 69.1-68.2 (p, J = 16.6 Hz), 41.5-41.2 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 3106, 1590, 1490, 1333, 1164, 1147, 822, 727, 654 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₀ClF₈O₃S₂⁺ [M+H]⁺ 440.9627, found 440.9621.



Compound anti-6: (3-chloro-3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

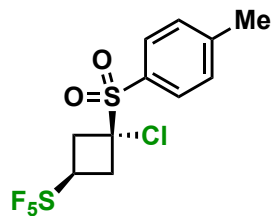
R_f: 0.67 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 95.8 – 98.8 °C; **¹H (300 MHz, CDCl₃):** δ = 8.02-7.99 (d, 2H, J = 8.9 Hz), 7.44-7.41 (d, 2H, J = 8.9 Hz), 4.81-4.66 (tpp, 1H, J = 9.7, 8.9, 5.3 Hz), 3.88-3.78 (m, 2H), 2.81-2.72 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.04-79.99 (p, 1F, $^2J_{F-F}$ = 146.6 Hz), 53.74-53.21 (dd, 4F, $^2J_{F-F}$ = 146.6 Hz, $^3J_{F-H}$ = 5.3 Hz), -57.65 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 154.33-154.27 (q, J = 1.6 Hz), 133.0, 131.5, 122.1, 121.0, 118.6, 74.4, 68.2-67.3 (p, J = 16.6 Hz), 40.1-39.9 (p, J = 4.2 Hz); **ATR-IR ($\nu_{\max}$):** 1590, 1492, 1332, 1159, 812, 799, 656 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₀ClF₈O₃S₂⁺ [M+H]⁺ 440.9627, found 440.9630.

Compound **7** was prepared according to the general procedure A; **anti-7** and **syn-7** formed in 78% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound **syn-7** was isolated as a white solid (20.0 mg) and **anti-7** was isolated as a white solid (20.1 mg); the total isolated yield was 54%. The isomers were separated *via* column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by preparative TLC using 100% CH₂Cl₂.



Compound syn-7: (3-chloro-3-tosylcyclobutyl)pentafluoro- λ^6 -sulfane

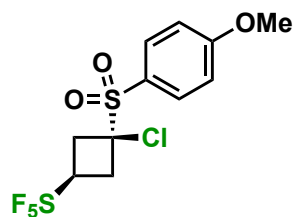
R_f: 0.60 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 139.5 – 140.1 °C; **¹H (300 MHz, CDCl₃):** δ = 7.81-7.78 (d, 2H, J = 8.3 Hz), 7.35-7.33 (d, 2H, J = 8.3 Hz), 4.75-4.61 (tpp, 1H, 9.9, 8.8, 5.7 Hz), 3.50-3.42 (m, 2H), 3.27-3.19 (m, 2H), 2.42 (s, 3H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.99-80.93 (p, 1F, $^2J_{F-F}$ = 146.9 Hz), 52.00-51.47 (dd, 4F, $^2J_{F-F}$ = 146.9 Hz, $^3J_{F-H}$ = 5.7 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 146.9, 131.2, 130.2, 129.9, 73.6, 69.5-68.8 (p, J = 16.8 Hz), 41.6-41.4 (p, J = 4.3 Hz), 22.1; **ATR-IR (v_{max}):** 2921, 1596, 1309, 1152, 820, 789, 727 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₂S₂⁺ [M+H]⁺ 370.9960, found 370.9962.



Compound anti-7: (3-chloro-3-tosylcyclobutyl)pentafluoro- λ^6 -sulfane

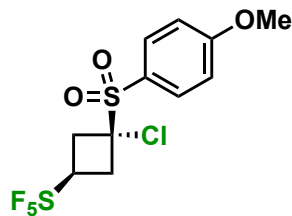
R_f: 0.54 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 118.8 – 119.5 °C; **¹H (300 MHz, CDCl₃):** δ = 7.77-7.74 (d, 2H, J = 8.4 Hz), 7.35-7.32 (d, 2H, J = 8.4 Hz), 4.72-4.57 (tpp, 1H, J = 9.7, 8.8, 5.4 Hz), 3.79-3.70 (m, 2H), 2.69-2.62 (m, 2H), 2.41 (s, 3H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.29-80.23 (p, 1F, $^2J_{F-F}$ = 144.5 Hz), 53.79-53.25 (dd, 4F, $^2J_{F-F}$ = 144.5 Hz, $^3J_{F-H}$ = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 146.6, 130.6, 130.4, 130.2, 74.4, 68.4-67.5 (p, J = 17.1 Hz), 40.2-39.9 (p, J = 4.1 Hz), 21.9; **ATR-IR ($\nu_{\max}$):** 3030, 2924, 1597, 1319, 1144, 831, 798, 727 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₂S₂⁺ [M+H]⁺ 370.9960, found 370.9969.

Compound **8** was prepared according to the general procedure A; **anti-8** and **syn-8** formed in 60% yield by in a 1:1 ratio by ¹⁹F NMR. Compound **syn-8** was isolated as a white solid (20.0 mg). Compound **anti-8** was isolated as a white solid (19.5 mg); the total isolated yield was 51%. The isomers were separated *via* successive preparative TLC on silica gel, eluting using 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound syn-8: (3-chloro-3-((4-methoxyphenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

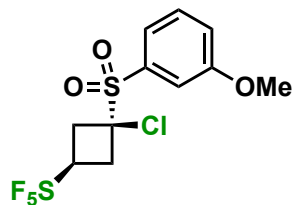
R_f: 0.47 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 72.7 – 75.8 °C; **¹H (300 MHz, CDCl₃):** δ = 7.86-7.83 (d, 2H, J = 8.9 Hz), 7.00-6.97 (d, 2H, J = 8.9 Hz), 4.76-4.60 (tt, 2H, J = 9.8, 8.7, 5.8 Hz), 3.84 (s, 3H), 3.48-3.40 (m, 2H), 3.27-3.19 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.05-80.98 (p, 1F, $^2J_{F-F}$ = 144.6 Hz), 52.02-51.48 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 6.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 165.0, 133.2, 123.8, 114.5, 73.5. 69.1-68.4 (p, J = 16.6 Hz), 55.8, 41.3-41.2 (p, J = 4.0 Hz); **ATR-IR (v_{max}):** 3034, 1593, 1498, 1321, 1144, 820, 798, 649 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₃S₂⁺ [M+H]⁺ 386.9909, found 386.9907.



Compound anti-8: (3-chloro-3-((4-methoxyphenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

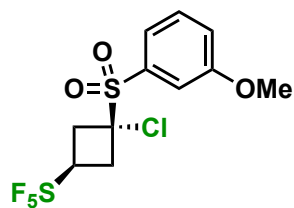
R_f: 0.39 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 120.7 – 124.1 °C; **¹H (300 MHz, CDCl₃):** δ = 7.81-7.78 (d, 2H, J = 8.9 Hz), 7.00-6.97 (d, 2H, J = 8.9 Hz), 4.72-4.56 (tt, 2H, J = 9.8, 8.8, 5.3 Hz), 3.84 (s, 3H), 3.78-3.69 (m, 2H), 2.70-2.61 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.34-80.28 (p, 1F, J = 144.6 Hz), 53.79-53.25 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 165.1, 132.9, 124.5, 74.6, 68.3-67.6 (p, J = 16.9 Hz), 56.0, 40.2-40.0 (p, J = 4.0 Hz); **ATR-IR ($\nu_{\max}$):** 2917, 1595, 1321, 1147, 827, 792, 655 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₃S₂⁺ [M+H]⁺ 386.9909, found 386.9906.

Compound **9** was prepared according to the general procedure A; **anti-9** and **syn-9** formed in 62% yield in a 1:1 ratio by ¹⁹F NMR. Compound **syn-9** and **anti-9** were first obtained as a mixture of isomers (28 mg, 37%, clear oil, estimated 95% purity) The isomers were separated via successive preparative TLC on silica gel with 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂, and finally 1:1 hexanes:CH₂Cl₂. *Note: syn-9 and anti-9 were not very UV active on the prep plate. It is recommended to stain a small portion of the plate with KMnO₄ to identify the product bands. Additionally, both isomers tended to coelute with a small portion of impurity, likely attributed to decomposition of the product.*



Compound syn-9: (3-chloro-3-((3-methoxyphenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

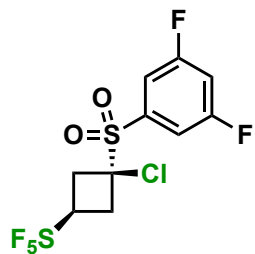
R_f: 0.60 (4:1 hexanes:EtOAc), 0.45 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.58-7.46 (m, 4H), 4.83-4.67 (ttp, 1H, J = 9.2, 8.8, 5.7 Hz), 3.89 (s, 3H), 3.59-3.51 (m, 2H), 3.36-3.28 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.67-81.12 (p, 1F, $^2J_{F-F}$ = 145.4 Hz), 51.95-51.55 (dd, 4F, $^2J_{F-F}$ = 145.4 Hz, $^3J_{F-H}$ = 5.7 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 160.1, 133.9, 130.4, 123.2, 121.6, 115.7, 68.9-68.6 (p, J = 17.1 Hz), 56.0, 41.5-41.3 (p, J = 4.2 Hz); **ATR-IR ($\nu_{\max}$):** 2971, 1598, 1371, 1317, 1188, 1151, 833, 795 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₃S₂⁺ [M+H]⁺ 386.9909, found 386.9911.



Compound anti-9: (3-chloro-3-((3-methoxyphenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

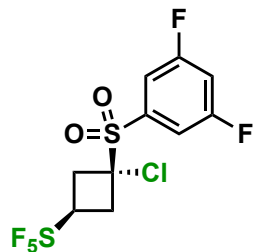
R_f: 0.51 (4:1 hexanes:EtOAc), 0.42 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.52-7.50 (m, 2H), 7.42 (m, 1H), 7.29-7.23 (m, 1H), 4.77-4.64 (m, 1H), 3.89-3.78 (m, 5H), 2.80-2.71 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.84-80.17 (p, 1F, ²J_{F-F} = 145.1 Hz), 53.80-53.26 (dd, 4F, ²J_{F-F} = 145.1 Hz, ³J_{F-H} = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 160.2, 134.5, 130.5, 122.6, 121.5, 115.1, 68.1-67.8 (p, *J* = 16.2 Hz), 56.0, 40.2-40.0 (p, *J* = 4.4 Hz); **ATR-IR (ν_{max}):** 2975, 1597, 1371, 1317, 1188, 1151, 833, 794 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₁₁H₁₃ClF₅O₃S₂⁺ [M+H]⁺ 386.9909, found 386.9911.

Compound **10** was prepared according to the general procedure A; **anti-10** and **syn-10** formed in 52% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound **syn-10** was isolated as a clear oil (16.5 mg) and **anti-10** was isolated as a clear oil (17.2 mg); the total isolated yield was 47%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 9:1 hexanes:EtOAc.



Compound syn-10: (3-chloro-3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

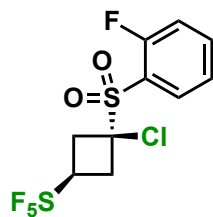
R_f: 0.67 (9:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (400 MHz, CDCl₃):** δ = 7.49-7.46 (m, 2H), 7.18-7.12 (tt, 1H, J = 8.3, 2.3 Hz), 4.74-4.59 (tpp, 1H, J = 9.7, 8.9, 5.6 Hz), 3.52-3.42 (m, 2H), 3.33-3.25 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 82.61-80.55 (p, 1F, $^2J_{F-F}$ = 144.6 Hz), 52.04-51.50 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.6 Hz), -104.40 - -104.45 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.3-161.6 (dd, J = 258.3, 10.9 Hz), 136.2-136.1 (t, J = 8.5 Hz), 114.9-114.6 (dd, J = 28.7, 8.7 Hz), 111.5-110.9 (t, J = 24.6 Hz), 73.6, 68.8-68.1 (p, J = 17.3 Hz), 41.5-41.3 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 3103, 1606, 1314, 1146, 1133, 818, 804, 718, 614 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₉ClF₇O₂S₂⁺ [M+H]⁺ 392.9709, found 392.9617.



Compound anti-10: 3-chloro-3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

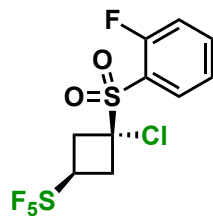
R_f: 0.53 (9:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (400 MHz, CDCl₃):** δ = 7.44-7.41 (m, 2H), 7.17-7.10 (tt, 1H, J = 8.3, 2.3 Hz), 4.75-4.59 (tt, 1H, J = 9.7, 8.9, 5.3 Hz), 3.80-3.71 (m, 2H), 2.77-2.68 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 81.91-79.84 (p, 1F, $^2J_{F-F}$ = 144.4 Hz), 53.79-53.26 (dd, 4F, $^2J_{F-F}$ = 144.4 Hz, $^3J_{F-H}$ = 5.3 Hz), -104.28 - -104.33 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.4-161.7 (dd, J = 258.2, 11.6 Hz), 136.8, 114.3-114.1 (dd, J = 28.1, 8.7 Hz), 111.3-110.8 (t, J = 24.8 Hz), 74.2, 68.0-67.3 (p, $^3J_{C-F}$ = 17.1 Hz), 40.1-39.9 (p, $^4J_{C-F}$ = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 3104, 1605, 1320, 1153, 1128, 829, 793, 623 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₉ClF₇O₂S₂⁺ [M+H]⁺ 392.9709, found 392.9620.

Compound **11** was prepared according to the general procedure A; **anti-11** and **syn-11** formed in 52% yield in a 2:1 ratio by ¹⁹F NMR. Compound **syn-11** was isolated as a white solid (10.0 mg) and **anti-11** was isolated as a white solid (15.1 mg); the total isolated yield was 45%. The isomers were separated *via* column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by preparatory TLC using 100% CH₂Cl₂.



Compound syn-11: (3-chloro-3-((2-fluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

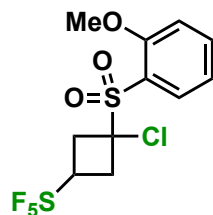
R_f: 0.50 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 95.1 – 98.6 °C; **¹H (400 MHz, CDCl₃):** δ = 7.94-7.90 (m, 1H), 7.70-7.65 (m, 1H), 7.34-7.30 (m, 1H), 7.26-7.21 (m, 1H), 4.74-4.62 (tpp, 1H, J = 9.8, 8.8, 5.7 Hz), 3.71-3.65 (m, 2H), 3.34-3.27 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 82.62-81.07 (p, 1F, $^2J_{F-F}$ = 145.1), 51.98-51.57 (dd, 4F, $^2J_{F-F}$ = 145.1 Hz, $^3J_{F-H}$ = 5.7 Hz), – 103.75 – 103.81 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 161.3-158.7 (d, J = 259.4 Hz), 137.9-137.8 (d, J = 8.8 Hz), 134.1, 125.00-124.96 (d, J = 3.7 Hz), 121.8-121.7 (d, J = 14.0 Hz), 118.0-117.8 (d, J = 22.8 Hz), 74.3, 68.9-68.3 (p, J = 17.3 Hz), 41.3-41.1 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2928, 1600, 1475, 1334, 1151, 826, 794, 707 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀ClF₆O₂S₂⁺ [M+H]⁺ 374.9709, found 374.9703.



Compound anti-11: (3-chloro-3-((2-fluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

R_f: 0.41 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 110.5 – 113.6 °C; **¹H (400 MHz, CDCl₃):** δ = 7.93-7.89 (m, 1H), 7.69-7.63 (m, 1H), 7.34-7.30 (m, 1H), 7.23-7.18 (m, 1H), 4.75-4.63 (tpp, 1H, J = 9.8, 8.8, 5.4 Hz), 3.91-3.64 (m, 2H), 2.84-2.78 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 81.93-80.38 (p, 1F, $^2J_{F-F}$ = 144.2), 53.72-53.32 (dd, 4F, $^2J_{F-F}$ = 144.2 Hz, $^3J_{F-H}$ = 5.4 Hz), – 105.62 – 105.68 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 161.0-158.5 (d, J = 257.7 Hz), 137.6-137.5 (d, J = 8.9 Hz), 133.1, 125.1-125.0 (d, J = 3.7 Hz), 122.5-122.3 (d, J = 15.1 Hz), 117.6-117.4 (d, J = 21.1 Hz), 74.8, 68.4-67.8 (p, J = 17.3 Hz), 40.4-40.2 (p, J = 4.1 Hz); **ATR-IR ($\nu_{\max}$):** 2922, 1599, 1331, 1152, 826, 795, 706 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀ClF₆O₂S₂⁺ [M+H]⁺ 374.9709, found 374.9617.

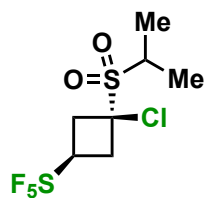
Compound **12** was prepared according to the general procedure A; **anti-12** and **syn-12** formed in 67% yield in a 1.3:1 ratio by ¹⁹F NMR. Compound **12** was isolated as mixture of isomers (47.5 mg, clear oil). The total isolated yield was 61%. The isomers were obtained *via* preparative TLC on silica gel, eluting with 4:1 hexanes:EtOAc. *Note: syn-12 and anti-12 were not very UV active on the prep plate. It is recommended to stain a small portion of the plate with KMnO₄ to identify the product bands.*



Compound 12: (3-chloro-3-((2-methoxyphenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

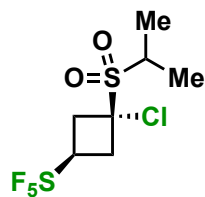
R_f: 0.34 (4:1 hexanes:EtOAc, *syn* isomer), 0.33 (4:1 hexanes:EtOAc, *anti* isomer), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 8.02-7.98 (m, 2H), 7.69-7.62 (m, 2H), 7.17-7.11 (m, 2H), 7.09-7.03 (m, 2H), 4.83-4.64 (m, 2H), 4.00-3.87 (m, 10H), 3.40-3.32 (m, 2H), 2.91-2.83 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.36-80.61 (m, 2F), 53.81-53.28 (dd, 4F, $^2J_{F-F}$ = 145.5 Hz, $^3J_{F-H}$ = 5.2 Hz), 52.14-51.60 (dd, 4F, $^2J_{F-F}$ = 145.2 Hz, $^3J_{F-H}$ = 5.7 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 157.6, 157.3, 136.8, 136.6, 133.5, 132.5, 123.03, 122.95, 120.99, 120.93, 112.6, 112.2, 75.1, 74.5, 69.1-68.2 (m, 2C), 56.2, 56.1, 41.6-40.9 (m, 2C); **ATR-IR ($\nu_{\max}$):** 2924, 1591, 1309, 1131, 816, 793, 733, 716 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₃ClF₅O₃S₂⁺ [M+H]⁺ 386.9909, found 386.9911.

Compound **13** was prepared according to the general procedure A; *anti*-**13** and *syn*-**13** formed in 92% yield in a 1:1 ratio by ¹⁹F NMR ratio. Compound *syn*-**13** was isolated as a white solid (17.2 mg) and *anti*-**13** was isolated as a white solid (17.0 mg); the total isolated yield was 58%. The isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc.



Compound syn-13: (3-chloro-3-(isopropylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

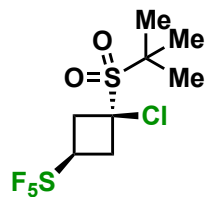
R_f: 0.53 (4:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **m.p.:** 112.7 – 114.3 °C; **¹H (300 MHz, CDCl₃):** δ = 4.67-4.56 (ttp, 1H, J = 9.6, 8.8, 5.7), 3.89-3.79 (sept, 1H, J = 6.9 Hz), 3.64-3.58 (m, 2H), 3.43-3.35 (m, 2H), 1.45-1.43 (d, 6H, J = 6.9 Hz); **¹⁹F (282 MHz, CDCl₃):** δ = 82.60-81.05 (p, 1F, $^2J_{F-F}$ = 145.9 Hz), 51.79-51.28 (dd, 4F, $^2J_{F-F}$ = 145.9 Hz, $^3J_{F-H}$ = 5.7 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 72.1, 69.1-68.4 (p, J = 16.9 Hz), 51.3, 42.2-42.1 (p, J = 4.3 Hz), 29.8, 16.0; **ATR-IR (v_{max}):** 2919, 1308, 1134, 869, 792 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₇H₁₃ClF₅O₂S₂⁺ [M+H]⁺ 322.9960, found 322.9960.



Compound anti-13: (3-chloro-3-(isopropylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

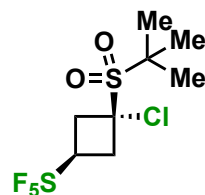
R_f: 0.41 (4:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **m.p.:** 109.6 – 111.0 °C; **¹H (300 MHz, CDCl₃):** δ = 4.79-4.67 (tpp, 1H, J = 9.3, 8.7, 5.2), 3.79-3.68 (m, 3H), 2.83-2.76 (m, 2H), 1.33-1.31 (d, 6H, J = 6.9 Hz); **¹⁹F (282 MHz, CDCl₃):** δ = 81.88-80.33 (p, 1F, $^2J_{F-F}$ = 147.1 Hz), 53.67-53.27 (dd, 4F, $^2J_{F-F}$ = 147.1 Hz, $^3J_{F-H}$ = 5.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 72.9, 68.9-68.3 (p, J = 17.2 Hz), 50.0, 41.0-40.9 (p, J = 4.1 Hz), 29.8, 15.2; **ATR-IR (v_{max}):** 2924, 1311, 1130, 869, 733 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₇H₁₃ClF₅O₂S₂⁺ [M+H]⁺ 322.9960, found 322.9960.

Compound **14** was prepared according to the general procedure A; **anti-14** and **syn-14** formed in 63% yield in a 2.5:1 ratio by ¹⁹F NMR. Compound **syn-14** and **anti-14** were isolated as a white solid (40.4 mg, 60%). The diastereomers were obtained as a mixture *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc. ¹H NMR shifts for **syn-14** and **anti-14** are assigned based on trends observed with other substrates. Separation of the isomers was attempted with preparative TLC on silica gel using 100% CH₂Cl₂ and *p*-anisaldehyde stain but resulted in inadequate separation.



Compound syn-14: (3-(*tert*-butylsulfonyl)-3-chlorocyclobutyl)pentafluoro- λ^6 -sulfane

R_f: 0.22 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (300 MHz, CDCl₃):** δ = 4.67-4.53 (ttp, 1H, *J* = 9.7, 8.8, 5.9), 3.69-3.36 (m, 2H), 2.85-2.76 (m, 2H), 1.52 (s, 9H).

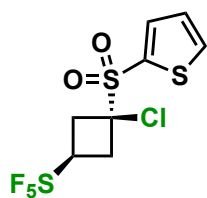


Compound anti-14: (3-(*tert*-butylsulfonyl)-3-chlorocyclobutyl)pentafluoro- λ^6 -sulfane

R_f: 0.20 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (300 MHz, CDCl₃):** δ = 4.79-4.64 (ttp, 1H, *J* = 9.7, 8.8, 5.1), 3.82-3.73 (m, 2H), 2.85-2.76 (m, 2H), 1.49 (s, 9H).

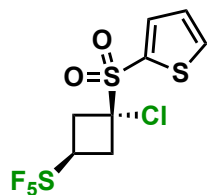
¹⁹F (282 MHz, CDCl₃) of mixture: δ = 83.08-80.19 (m, 2F), 53.85-55.32 (dd, 4F, ²*J*_{F-F} = 145.9 Hz, ³*J*_{F-H} = 5.5 Hz), 51.80-51.26 (dd, 4F, ²*J*_{F-F} = 146.1 Hz, ³*J*_{F-H} = 5.5 Hz); **¹³C{¹H} (101 MHz, CDCl₃) of mixture:** δ = 74.1, 73.8, 69.1-68.8 (p, *J* = 16.7 Hz), 66.0, 64.6, 43.6-43.4 (p, *J* = 4.7 Hz), 42.3-42.1 (p, *J* = 4.4 Hz), 25.8, 25.3; **ATR-IR of mixture (ν_{max}):** 1366, 1294, 1189, 1118, 833, 792, 689 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₈H₁₅ClF₅O₂S₂⁺ [M+H]⁺ 337.0117, found 337.0117.

Compound **15** was prepared according to the general procedure A; *anti*-**15** and *syn*-**15** formed in 76% yield in a 1:1 ratio by ^{19}F NMR. Compound *syn*-**15** was isolated as a white solid (19.0 mg) and *anti*-**15** was isolated as a white solid (20.0 mg); the total isolated yield was 54%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH_2Cl_2 .



Compound *syn*-15: 2-((1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)sulfonyl)thiophene

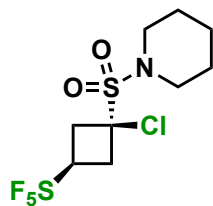
R_f: 0.48 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 138.0 – 147.0 °C; **^1H (300 MHz, CDCl_3):** δ = 7.83-7.77 (m, 2H), 7.20-7.17 (m, 1H), 4.74-4.59 (tpp, 1H, J = 9.2, 8.7, 5.7 Hz), 3.53-3.45 (m, 2H), 3.32-3.24 (m, 2H); **^{19}F (282 MHz, CDCl_3):** δ = 82.88-80.82 (p, 1F, $^2J_{\text{F-F}}$ = 144.4 Hz), 52.10-51.57 (dd, 4F, $^2J_{\text{F-F}}$ = 144.4 Hz, $^3J_{\text{F-H}}$ = 5.7 Hz); **$^{13}\text{C}\{^1\text{H}\}$ (151 MHz, CDCl_3):** δ = 138.3, 136.9, 132.3, 128.4, 73.9, 69.0-68.4 (p, J = 16.0 Hz), 41.3-41.2 (p, J = 4.3 Hz); **ATR-IR (ν_{max}):** 1502, 1323, 1144, 1021, 955, 802, 722, 653, 607 cm^{-1} ; **HRMS (m/z):** (ESI) calc'd for $\text{C}_8\text{H}_9\text{F}_5\text{ClO}_2\text{S}_3^+$ $[\text{M}+\text{H}]^+$ 362.9368, found 362.9362.



Compound anti-15: 2-((1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)sulfonyl)thiophene

R_f: 0.39 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 67.3 – 69.1 °C; **¹H (300 MHz, CDCl₃):** δ = 7.82-7.74 (m, 2H), 7.20-7.17 (m, 1H), 4.74-4.58 (ttp, 1H, J = 9.5, 8.6, 5.2 Hz), 3.80-3.70 (m, 2H), 2.75-2.68 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.16-80.10 (p, 1F, $^2J_{F-F}$ = 144.5 Hz), 53.82-53.28 (dd, 4F, $^2J_{F-F}$ = 144.5 Hz, $^3J_{F-H}$ = 5.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 137.9, 136.9, 132.8, 128.5, 74.8, 68.0-67.3 (p, J = 16.9 Hz), 40.1-40.0 (p, J = 4.0 Hz); **ATR-IR ($\nu_{\max}$):** 1501, 1398, 1154, 1075, 793, 740, 655, 609 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₈H₉F₅ClO₂S₃⁺ [M+H]⁺ 362.9368, found 362.9363.

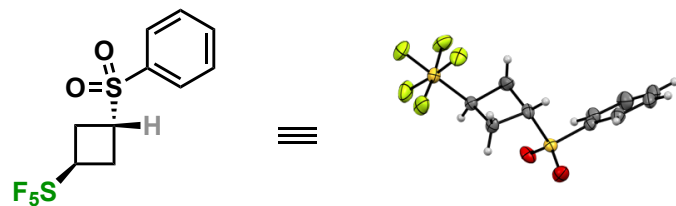
Compound **16** was prepared according to the general procedure A; **syn-16** and **anti-16** formed in 25% yield in a 1.4:1 ratio by ¹⁹F NMR. Compound **syn-16** was obtained with several impurities as a clear oil (3.2 mg) *via* successive preparative TLC using 4:1 hexanes:EtOAc, followed by 9:1 hexanes:EtOAc.



Compound syn-16: 1-((1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)sulfonyl)piperidine

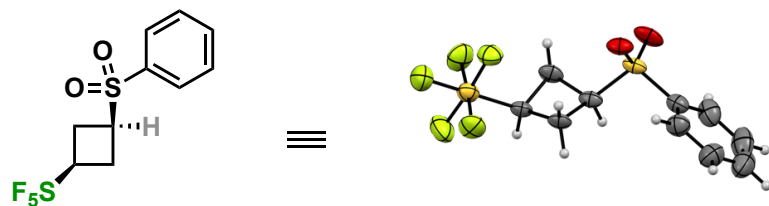
R_f: 0.45 (4:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (600 MHz, CDCl₃):** δ = 4.71-4.63 (ttp, 1H, J = 9.2, 8.8, 5.8 Hz), 3.49-3.43 (m, 6H), 3.36-3.32 (m, 2H), 1.67-1.64 (m, 6H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.45-81.18 (p, 1F, $^2J_{F-F}$ = 145.1 Hz), 52.13-51.60 (dd, 4F, $^2J_{F-F}$ = 145.1 Hz, $^3J_{F-H}$ = 5.8 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 74.3, 69.0-68.2 (p, J = 16.1 Hz), 49.2, 43.0-42.9 (p, J = 4.2 Hz), 26.3, 23.8; **ATR-IR ($\nu_{\max}$):** 2928, 1336, 1169, 1143, 833, 742 cm⁻¹.

Compound **17** was prepared according to the general procedure B; *cis*-**17** and *trans*-**17** formed in 63% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound *cis*-**17** was isolated as a white solid (18.1 mg) and *trans*-**17** was isolated as a white solid (16.9 mg); the total isolated yield was 54%. The diastereomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc. Crystals suitable for SC-XRD for *trans*-**17** were obtained by slow evaporation from EtOAc and crystals suitable for SC-XRD for *cis*-**17** were obtained by slow evaporation from 1,2-dichloroethane.



Compound *trans*-17: pentafluoro(3-(phenylsulfonyl)cyclobutyl)- λ^6 -sulfane

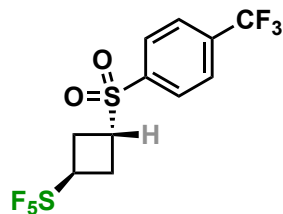
R_f: 0.32 (8:2 hexanes:EtOAc); 0.26 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **m.p.:** 114.4 – 116.2 °C; **¹H (600 MHz, CDCl₃):** δ = 7.91-7.89 (m, 2H), 7.71-7.68 (m, 1H), 7.61-7.58 (m, 2H), 4.95-4.85 (ttp, 1H, J = 8.8, 7.6, 6.1 Hz), 3.74-3.71 (m, 1H), 3.09-3.03 (m, 2H), 2.94-2.90 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.87-81.82 (p, 1F, $^2J_{F-F}$ = 145.2 Hz), 51.77-51.23 (dd, 4F, $^2J_{F-F}$ = 145.2 Hz, $^3J_{F-H}$ = 6.1 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 137.2, 134.5, 129.8, 128.6, 73.1-72.7 (p, J = 15.4), 53.1, 29.67-29.61 (p, J = 4.4 Hz); **ATR-IR ν_{max} :** 2254, 1225, 1111, 903, 724, 650 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₂F₅O₂S₂⁺ [M+H]⁺ 323.0193, found 323.0195.



Compound *cis*-17: pentafluoro(3-(phenylsulfonyl)cyclobutyl)- λ^6 -sulfane

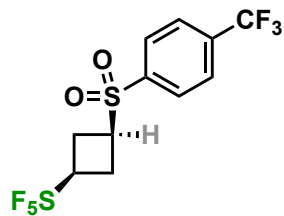
R_f: 0.26 (8:2 hexanes:EtOAc); 0.10 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **m.p.:** 150.5 – 151.6 °C; **¹H (400 MHz, CDCl₃):** δ = 7.90-7.87 (m, 2H), 7.73-7.65 (m, 1H), 7.62-7.57 (m, 2H), 4.36-4.20 (ttp, 1H, J = 9.4, 8.9, 5.3 Hz), 3.56-3.45 (tt, 1H, J = 9.5, 7.7 Hz), 3.22-3.11 (m, 2H), 2.68-2.58 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.64-80.58 (m, 1F, $^2J_{F-F}$ = 143.9 Hz), 52.14-51.60 (dd, 4F, $^2J_{F-F}$ = 143.9 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 137.4, 134.5, 129.8, 128.6, 69.7-68.9 (p, J = 15.5), 50.3, 30.51-30.45 (p, J = 4.1 Hz); **ATR-IR ν_{max} :** 2255, 1310, 1113, 903, 724, 650 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₂F₅O₂S₂⁺ [M+H]⁺ 323.0193, found 323.0199.

Compound **18** was prepared according to the general procedure B; ***cis*-18** and ***trans*-18** formed in 51% yield in a 1.2:1 ratio by ¹⁹F NMR. Compound ***cis*-18** was isolated as a white solid (21.5 mg) and ***trans*-18** was isolated as a white solid (12.5 mg); the total isolated yield was 44%. The isomers were separated *via* preparative TLC on silica gel with 9:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



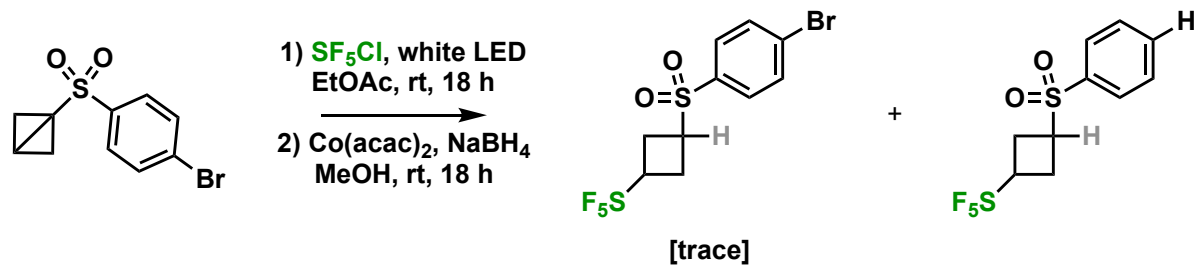
Compound trans-18: pentafluoro(3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

R_f: 0.53 (8:2 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 122.0 – 124.9 °C; **¹H (300 MHz, CDCl₃):** δ = 7.99-7.96 (d, 2H, J = 8.3 Hz), 7.82-7.79 (d, 2H, J = 8.3 Hz), 4.92-4.77 (ttp, 1H, J = 9.5, 8.8, 5.7 Hz), 3.72-3.65 (m, 1H), 3.08-2.97 (m, 2H), 2.91-2.81 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.57-81.42 (p, 1F, $^2J_{F-F}$ = 143.5 Hz), 51.78-51.25 (dd, 4F, $^2J_{F-F}$ = 143.5 Hz, $^3J_{F-H}$ = 5.7 Hz), – 63.32 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 140.7, 136.4-136.0 (d, J = 33.4 Hz), 129.2, 127.0-126.8 (q, J = 3.6 Hz), 124.9-121.2 (d, J = 273.5 Hz), 73.0-72.2 (p, J = 14.7 Hz), 53.1, 29.6-29.4 (p, J = 4.6 Hz); **ATR-IR ($\nu_{\max}$):** 1590, 1490, 1331, 1165, 1148, 805, 727, 655 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₈O₂S₂⁺ [M+H]⁺ 391.0067, found 391.0064.

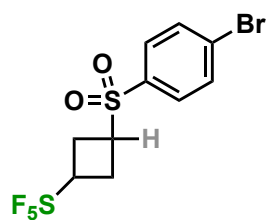


Compound cis-18: pentafluoro(3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

R_f: 0.30 (8:2 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 132.5 – 139.6 °C; **¹H (300 MHz, CDCl₃):** δ = 7.97-7.94 (d, 2H, J = 8.3 Hz), 7.81-7.78 (d, 2H, J = 8.3 Hz), 4.31-4.16 (tpp, 1H, J = 9.7, 8.9, 5.3 Hz), 3.52-3.40 (tt, 1H, J = 9.7, 7.6 Hz), 3.19-3.07 (m, 2H), 2.63-2.54 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.39-80.32 (p, 1F, $^2J_{F-F}$ = 143.9 Hz), 52.11-51.58 (dd, 4F, $^2J_{F-F}$ = 143.9 Hz, $^3J_{F-H}$ = 5.3 Hz), –63.30 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 141.0, 136.4-135.9 (d, J = 33.3 Hz), 129.2, 127.0-126.8 (q, J = 3.6 Hz), 124.9-121.3 (d, J = 273.8 Hz), 69.1-68.3 (p, J = 16.0 Hz), 50.3, 30.4-30.2 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 1590, 1491, 1333, 1164, 1148, 808, 728, 655 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₈O₂S₂⁺ [M+H]⁺ 391.0067, found 391.0065.



Upon subjecting the appropriate BCB to reductive conditions (general procedure B), we observed the major product by ^{19}F NMR was **17**. Only trace amounts of **19** were observed by ^{19}F NMR.

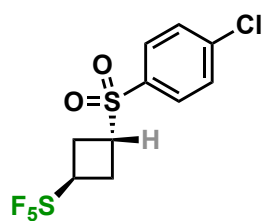


Compound 19: (3-((4-bromophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

^{19}F (282 MHz, CDCl_3): $\delta = 52.14\text{--}51.77$ (dd, 4F, $^2J_{\text{F-F}} = 145.2$ Hz), $51.62\text{--}51.26$ (dd, 4F, $^2J_{\text{F-F}} = 145.3$ Hz).

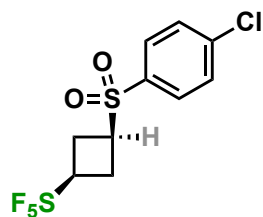
Note: The pentets corresponding to the axial F from the SF_5 group were overlapping and could not be unequivocally assigned.

Compound **20** was prepared according to the general procedure B; *cis*-**20** and *trans*-**20** formed in 55% yield in a 1.1:1 ratio by ^{19}F NMR. Compound *cis*-**20** was isolated as a white solid (16.9 mg) and *trans*-**20** was isolated as a white solid (20.9 mg); the total isolated yield was 53%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH_2Cl_2 .



Compound trans-20: 3-((4-chlorophenyl)sulfonyl)cyclobutyl pentafluoro- λ^6 -sulfane

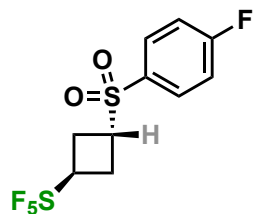
R_f: 0.42 (8:2 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 135.8 – 136.2 °C; **^1H (300 MHz, CDCl_3):** δ = 7.78-7.75 (m, 2H), 7.52-7.49 (m, 2H), 4.90-4.75 (tpp, 1H, J = 9.1, 8.7, 5.7), 3.67-3.61 (m, 1H), 3.06-2.96 (m, 2H), 2.89-2.79 (m, 2H); **^{19}F (282 MHz, CDCl_3):** δ = 83.72-81.67 (p, 1F, $^2J_{\text{F-F}}$ = 143.7 Hz), 51.79-51.26 (dd, 4F, $^2J_{\text{F-F}}$ = 143.7 Hz, $^3J_{\text{F-H}}$ = 5.7 Hz); **$^{13}\text{C}\{^1\text{H}\}$ (151 MHz, CDCl_3):** δ = 141.5, 135.6, 130.2, 130.0, 72.9-72.6 (p, J = 14.5 Hz), 53.3, 29.7-29.5 (p, J = 4.7 Hz); **ATR-IR (ν_{max}):** 2919, 1634, 1585, 1277, 1145, 811, 784 cm^{-1} ; **HRMS (m/z):** (ESI) calc'd for $\text{C}_{10}\text{H}_{11}\text{ClF}_5\text{O}_2\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 356.9804, found 356.9798.



Compound *cis*-20: 3-((4-chlorophenyl)sulfonyl)cyclobutyl pentafluoro- λ^6 -sulfane

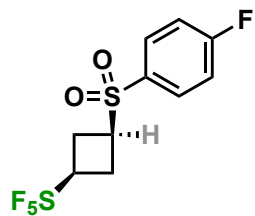
R_f: 0.17 (8:2 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 158.6 – 159.1 °C; **¹H (300 MHz, CDCl₃):** δ = 7.76-7.74 (m, 2H), 7.52-7.49 (m, 2H), 4.30-4.15 (tpp, 1H, J = 9.2, 8.1, 5.2), 3.48-3.37 (m, 1H), 3.14-3.03 (m, 2H), 2.62-2.52 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.54-80.48 (p, 1F, $^2J_{F-F}$ = 144.4 Hz), 52.13-51.60 (dd, 4F, $^2J_{F-F}$ = 144.4 Hz, $^3J_{F-H}$ = 5.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 141.4, 135.8, 130.1, 129.9, 69.0-68.6.6 (p, J = 15.5 Hz), 50.3, 30.4-30.3 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2921, 1318, 1146, 812, 768, 683 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁ClF₅O₂S₂⁺ [M+H]⁺ 356.9804, found 356.9799.

Compound **21** was prepared according to the general procedure B; ***cis*-21** and ***trans*-21** formed in 73% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound ***cis*-21** was isolated as a clear oil (20.3 mg) and ***trans*-21** was isolated as a white solid (18.5 mg); the total isolated yield was 57%. The isomers were separated via column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc, followed by preparative TLC using 100% CH₂Cl₂.



Compound trans-21: pentafluoro(-3-((4-fluorophenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

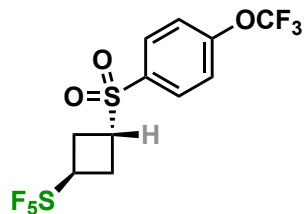
R_f: 0.43 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.93-7.89 (m, 2H), 7.29-7.23 (m, 2H), 4.96-4.80 (tpp, 1H, J = 9.1, 8.8, 5.8 Hz), 3.73-3.67 (m, 1H), 3.11-3.00 (m, 2H), 2.94-2.85 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.76-81.70 (p, 1F, $^2J_{F-F}$ = 143.6 Hz), 51.79-51.25 (dd, 4F, $^2J_{F-F}$ = 143.6 Hz, $^3J_{F-H}$, 5.8 Hz), -102.03 - -102.12 (m, 1F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 167.2-165.5 (d, J = 257.0 Hz), 133.20-133.17 (d, J = 3.1 Hz), 131.5-131.4 (d, J = 9.8 Hz), 117.2-117.1 (d, J = 22.4 Hz), 72.9-72.5 (p, J = 14.8 Hz), 53.3, 29.7-29.5 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2928, 1595, 1496, 1280, 1146, 825, 782 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁F₆O₂S₂⁺ [M+H]⁺ 341.0099, found 341.0100.



Compound cis-21: pentafluoro(-3-((4-fluorophenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

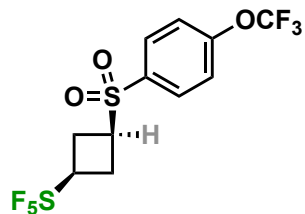
R_f: 0.29 (9:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 137.2 – 140.2 °C; **¹H (300 MHz, CDCl₃):** δ = 7.92-7.87 (m, 2H), 7.29-7.23 (m, 2H), 4.35-4.20 (tt, 1H, J = 9.8, 8.1, 5.1 Hz), 3.54-3.43 (tt, 1H, J = 9.3, 7.9 Hz), 3.19-3.09 (m, 2H), 2.67-2.58 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.56-80.51 (p, 1F, J = 146.7 Hz), 52.11-51.58 (dd, 4F, $^2J_{F-F}$ = 146.7 Hz, $^3J_{F-H}$ = 5.1 Hz), -102.11-102.02 (m, 1H); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 167.2-165.5 (d, J = 256.4 Hz), 133.37-133.36 (d, J = 3.3 Hz) 131.5-131.4 (d, J = 9.7 Hz), 117.2-117.1 (d, J = 23.2 Hz), 69.0-68.6 (p, J = 15.5 Hz), 50.4, 30.5-30.4 (p, J = 4.5 Hz); **ATR-IR (v_{max}):** 2929, 1592, 1494, 1324, 1146, 831, 726, cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁F₆O₂S₂⁺ [M+H]⁺ 341.0099, found 341.0102.

Compound **22** was prepared according to the general procedure B; **cis-22** and **trans-22** formed in 47% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound **cis-22** was isolated as a white solid (18.9 mg) and **trans-22** was isolated as a white solid (14.4 mg); the total isolated yield was 41%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound trans-22: pentafluoro(3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

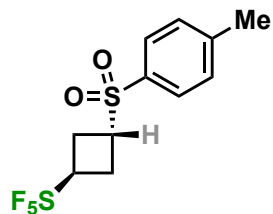
R_f: 0.51 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 87.3 – 89.6 °C; **¹H (300 MHz, CDCl₃):** δ = 7.99-7.94 (m, 2H), 7.43-7.41 (d, 2H, J = 8.9 Hz), 5.01-4.81 (ttp, 1H, J = 9.1, 8.9, 5.9 Hz), 3.77-3.70 (m, 1H), 3.15-3.04 (m, 2H), 2.97-2.88 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.57-81.52 (p, 1F, $^2J_{F-F}$ = 143.5), 51.78-51.25 (dd, 4F, $^2J_{F-F}$ = 143.5 Hz, $^3J_{F-H}$ = 5.9 Hz), -63.32 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 153.7-153.6 (q, J = 1.9 Hz), 135.6, 130.8, 122.0, 121.4, 118.6, 69.2-68.3 (p, J = 15.9 Hz), 50.3, 30.5-30.3 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2920, 1590, 1324, 1177, 1118, 813, 767, 674 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₈O₃S₂⁺ [M+H]⁺ 407.0016, found 407.0013.



Compound cis-22: pentafluoro(3-((4-(trifluoromethoxy)phenyl)sulfonyl)cyclobutyl) - λ^6 -sulfane

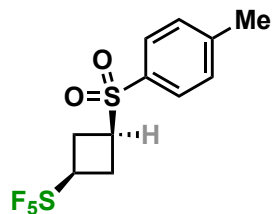
R_f: 0.32 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 109.4 – 112.2 °C; **¹H (300 MHz, CDCl₃):** δ = 7.97-7.92 (m, 2H), 7.43-7.40 (m, 2H), 4.40-4.21 (tt, 1H, J = 9.1, 8.9, 5.3 Hz), 3.58-3.46 (tt, 1H, J = 9.5, 7.7), 3.24-3.12 (m, 2H), 2.71-2.61 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.46-80.41 (p, 1F, $^2J_{F-F}$ = 144.0), 52.10-51.57 (dd, 4F, $^2J_{F-F}$ = 144.0 Hz, $^3J_{F-H}$ = 5.3 Hz), -57.70 (s, 3F); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 153.7-153.6 (q, J = 1.9 Hz), 135.6, 130.8, 122.0, 121.4, 118.6, 69.1-68.3 (p, J = 15.9 Hz), 50.3, 30.5-30.3 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2976, 1591, 1493, 1115, 816, 784, 714, 665 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₈O₃S₂⁺ [M+H]⁺ 407.0016, found 407.0011.

Compound **23** was prepared according to the general procedure B; **cis-23** and **trans-23** formed in 61% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound **cis-23** was isolated as a white solid (18.0 mg) and **trans-23** was isolated as a white solid (14.0 mg); the total isolated yield was 47%. The isomers were separated *via* preparative TLC on silica gel using with 9:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound trans-23: pentafluoro(-3-tosylcyclobutyl)- λ^6 -sulfane

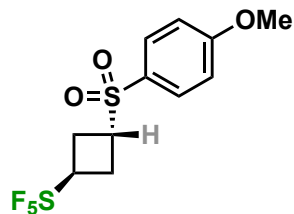
R_f: 0.68 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 136.0 – 136.7 °C; **¹H (300 MHz, CDCl₃):** δ = 7.72-7.69 (d, 2H, J = 8.2 Hz), 7.33-7.30 (d, 2H, J = 8.2 Hz), 4.90-4.74 (ttp, 1H, J = 9.0, 8.9, 6.0 Hz), 3.66-3.59 (m, 1H), 3.03-2.92 (m, 2H), 2.89-2.79 (m, 2H), 2.39 (s, 3H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.95-81.90 (p, 1F, $^2J_{F-F}$ = 144.0), 51.77-51.23 (dd, 4F, $^2J_{F-F}$ = 144.0 Hz, $^3J_{F-H}$ = 6.0 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 145.6, 134.1, 130.4, 128.6, 73.1-72.8 (p, J = 14.7), 53.2, 29.8, 29.7-29.6 (p, J = 4.3 Hz), 21.8; **ATR-IR (v_{max}):** 2927, 1596, 1323, 1188, 1146, 819, 799, 721, 662 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₄F₅O₂S₂⁺ [M+H]⁺ 337.0350, found 337.0350.



Compound cis-23: pentafluoro(-3-tosylcyclobutyl)- λ^6 -sulfane

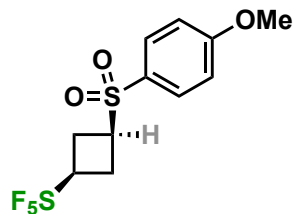
R_f: 0.56 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 144.6 – 145.4 °C; **¹H (300 MHz, CDCl₃):** δ = 7.70-7.67 (d, 2H, J = 8.2 Hz), 7.32-7.30 (d, 2H, J = 8.2 Hz), 4.28-4.12 (tpp, 1H, J = 9.5, 8.8, 5.2 Hz), 3.47-3.35 (tt, 1H, J = 9.3, 7.8 Hz), 3.13-3.02 (m, 2H), 2.59-2.50 (m, 2H), 2.39 (s, 3H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.72-80.66 (p, 1F, $^2J_{F-F}$ = 144.3 Hz), 52.14-51.61 (dd, 4F, $^2J_{F-F}$ = 144.3 Hz, $^3J_{F-H}$ = 5.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 145.6, 134.3, 130.3, 130.2, 128.5, 69.2-68.8 (p, J = 15.4 Hz), 50.3, 30.5-30.4 (p, J = 4.4 Hz), 29.8, 21.8; **ATR-IR ν_{max} :** 2930, 1596, 1323, 1188, 1146, 823, 799, 664 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₄F₅O₂S₂⁺ [M+H]⁺ 337.0350, found 337.0353.

Compound **24** was prepared according to the general procedure B; **cis-24** and **trans-24** formed in 64% yield in a 1:1 ratio by ¹⁹F NMR. Compound **cis-24** was isolated as a white solid (19.3 mg) and **trans-24** was isolated as a white solid (18.4 mg); the total isolated yield was 53%. The isomers were separated *via* preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound trans-24: pentafluoro(3-((4-methoxyphenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

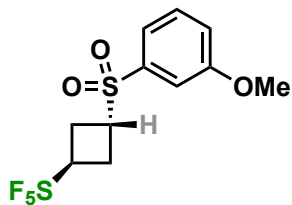
R_f: 0.25 (4:1 hexanes:EtOAc), **vis:** UV (254 nm); **m.p.:** 89.4 – 96.3 °C; **¹H{¹⁹F} (300 MHz, CDCl₃):** δ = 7.76-7.73 (d, 2H, J = 8.9 Hz), 6.98-6.95 (d, 2H, J = 8.9 Hz), 4.88-4.76 (tt, 1H, J = 9.6, 8.8 Hz), 3.82 (s, 3H), 3.66-3.57 (tt, 1H, J = 10.0, 7.1 Hz), 3.03-2.92 (m, 2H), 2.87-2.78 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 84.00-81.94 (p, 1F, $^2J_{F-F}$ = 143.6 Hz), 51.79-51.25 (dd, 4F, $^2J_{F-F}$ = 143.6 Hz, $^3J_{F-H}$ = 6.2 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.4, 130.7, 128.5, 114.9, 73.3-73.7 (p, J = 14.4 Hz), 55.9, 53.3, 29.8-29.6 (p, J = 4.7 Hz); **ATR-IR (v_{max}):** 2963, 1595, 1499, 1287, 1148, 803, 782 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₅O₃S₂⁺ [M+H]⁺ 353.0299, found 353.0295.



Compound cis-24: pentafluoro(3-((4-methoxyphenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

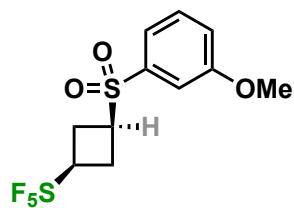
R_f: 0.10 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 121.8 – 126.5 °C; **¹H (300 MHz, CDCl₃):** δ = 7.75-7.72 (d, 2H, J = 9.0 Hz), 6.98-6.95 (d, 2H, 9.0 Hz), 4.28-4.12 (ttp, 1H, J = 9.4, 8.9, 5.1 Hz), 3.82 (s, 3H), 3.46-3.35 (tt, 1H, 9.5, 7.7 Hz), 3.35-3.11 (m, 2H), 2.60-2.50 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.77-80.71 (m, 1F, $^2J_{F-F}$ = 145.0 Hz), 52.14-51.61 (dd, 4F, $^2J_{F-F}$ = 145.0 Hz, $^3J_{F-H}$ = 5.1 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.3, 130.7, 128.6, 114.9, 69.3-68.7 (p, J = 15.4 Hz), 55.9, 50.4, 30.6-30.5 (p, J = 4.2 Hz); **ATR-IR ($\nu_{\max}$):** 2983, 1595, 1499, 1320, 1147, 803, 782 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₅O₃S₂⁺ [M+H]⁺ 353.0299, found 353.0295.

Compound **25** was prepared according to the general procedure B; *cis*-**25** and *trans*-**25** formed in 35% yield in a 1:1 ratio by ¹⁹F NMR. Compound *cis*-**25** was isolated as a clear oil (8.6 mg) and *trans*-**25** was isolated as a clear oil (14.2 mg); the total isolated yield was 32%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 1:1 hexanes:CH₂Cl₂.



Compound trans-25: pentafluoro(3-((3-methoxyphenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

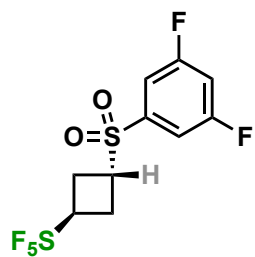
R_f: 0.34 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.45-7.35 (m, 2H), 7.30-7.28 (m, 1H), 7.15-7.11 (m, 1H), 4.29-4.14 (ttp, 1H, J = 9.3, 8.8, 5.3 Hz), 3.81 (s, 3H), 3.50-3.38 (tt, 1H, J = 9.4, 7.6 Hz), 3.16-3.04 (m, 2H), 2.61-2.51 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.69-80.63 (p, 1F, $^2J_{F-F}$ = 144.1 Hz), 52.16-51.62 (dd, 4F, $^2J_{F-F}$ = 144.1 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 160.4, 138.2, 130.8, 120.7, 120.6, 113.1, 73.1-72.7 (p, J = 15.1 Hz), 55.9, 53.1, 29.7-29.6 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2944, 2365, 1591, 1318, 1135, 806, 714 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₅O₃S₂⁺ [M+H]⁺ 353.0299, found 353.0301.



Compound *cis*-25: pentafluoro(3-((3-methoxyphenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

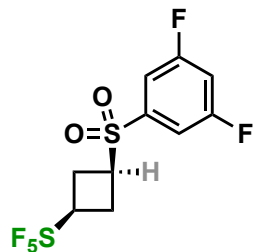
R_f: 0.24 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.45-7.35 (m, 2H), 7.30-7.28 (m, 1H), 7.15-7.11 (m, 1H), 4.29-4.14 (tt, 1H, J = 9.4, 8.9, 5.2 Hz), 3.81 (s, 3H), 3.50-3.38 (tt, 1H, J = 9.4, 7.7 Hz), 3.16-3.04 (m, 2H), 2.61-2.51 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.69-80.63 (m, 1F, $^2J_{F-F}$ = 144.0 Hz), 52.16-51.62 (dd, 4F, $^2J_{F-F}$ = 144.0 Hz, $^3J_{F-H}$ = 5.2 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 160.4, 138.5, 130.8, 120.7, 120.5, 112.9, 69.1-68.7 (p, J = 15.5 Hz), 55.9, 50.2, 30.5-30.4 (p, J = 3.8 Hz); **ATR-IR ($\nu_{\max}$):** 3027, 2365, 1598, 1317, 1152, 838, 726 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₅O₃S₂⁺ [M+H]⁺ 353.0299, found 353.0301.

Compound **26** was prepared according to the general procedure B; *cis*-**26** and *trans*-**26** formed in 49% yield in a 1.1:1 ratio by ¹⁹F NMR. Compound *cis*-**26** and *trans*-**26** were first obtained as a mixture as a clear oil (30.9 mg); the total isolated yield was 43%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound trans-26: (3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

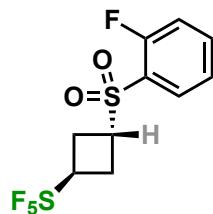
R_f: 0.56 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.46-7.43 (m, 2H), 7.18-7.11 (tt, 1H, J = 8.3, 2.3 Hz), 4.97-4.82 (ttp, 1H, J = 9.1, 8.8, 5.8 Hz), 3.79-3.72 (m, 1H), 3.16-3.05 (m, 2H), 2.97-2.88 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.52-81.46 (p, 1F, $^2J_{F-F}$ = 143.9 Hz), 51.80-51.27 (dd, 4F, $^2J_{F-F}$ = 143.9 Hz, $^3J_{F-H}$ = 5.8 Hz), -103.92 - -103.97 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.6-161.9 (dd, J = 256.8, 11.7 Hz), 140.5-140.4 (t, J = 8.1 Hz), 112.3-112.1 (dd, J = 19.7, 8.1 Hz), 110.5-110.0 (t, J = 24.9 Hz), 72.8-77.1 (p, J = 15.4 Hz), 53.1, 29.6-29.4 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2184, 1603, 1305, 1139, 1130, 811, 765, 698 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀F₇O₂S₂⁺ [M+H]⁺ 359.0005, found 358.9998.



Compound *cis*-26: (3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

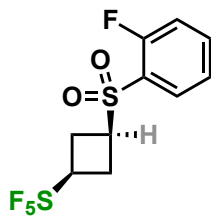
R_f: 0.34 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.44-7.41 (m, 2H), 7.18-7.11 (tt, 1H, J = 8.4, 2.3 Hz), 4.39-4.23 (ttp, 1H, J = 9.2, 8.8, 5.2 Hz), 3.59-3.47 (tt, 1H, J = 9.4, 7.8 Hz), 3.24-3.13 (m, 2H), 2.72-2.62 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.33-80.27 (p, 1F, $^2J_{F-F}$ = 147.0), 52.14-51.60 (dd, 4F, $^2J_{F-F}$ = 147.0 Hz, $^3J_{F-H}$ = 5.2 Hz), -103.91 - -103.96 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.57-161.90 (dd, J = 257.1, 11.0 Hz), 140.8-140.7 (t, J = 7.7 Hz), 112.2-112.0 (dd, J = 19.3, 8.5 Hz), 110.5-110.0 (t, J = 24.9 Hz), 69.0-69.3 (p, J = 16.4 Hz), 50.2, 30.4-30.2 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2157, 1604, 1306, 1140, 1130, 818, 805, 787, 611 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₀F₇O₂S₂⁺ [M+H]⁺ 359.0005, found 359.0000.

Compound **27** was prepared according to the general procedure B; *cis*-**27** and *trans*-**27** formed in 54% yield in a 1.2:1 ratio by ¹⁹F NMR. Compound *cis*-**27** was isolated as a white solid (10.4 mg) and *trans*-**27** was isolated as a white solid (8.1 mg); the total isolated yield was 54%. The isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc followed by preparative TLC using 100% CH₂Cl₂.



Compound trans-27: pentafluoro(3-((2-fluorophenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

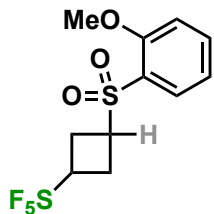
R_f: 0.38 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 148.6 – 150.5 °C; **¹H (400 MHz, CDCl₃):** δ = 8.00-7.96 (m, 1H), 7.73-7.67 (m, 1H), 7.40-7.36 (m, 1H), 7.29-7.25 (m, 1H), 4.98-4.87 (ttp, 1H, J = 9.3, 8.8, 6.0 Hz), 4.05-.00 (m, 1H), 3.17-3.08 (m, 2H), 2.96-2.89 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 83.52-81.98 (p, 1F, $^2J_{F-F}$ = 144.1 Hz), 51.69-51.28 (dd, 4F, $^2J_{F-F}$ = 144.1 Hz, $^3J_{F-H}$ = 6.0 Hz), -107.88 - -107.94 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 161.0-158.0 (d, J = 256.0 Hz), 137.0-136.9 (d, J = 8.1 Hz), 131.2, 125.15-125.11 (d, J = 3.7 Hz), 117.8-117.5 (d, J = 21.6 Hz), 73.3-72.7 (d, J = 14.8 Hz), 52.8, 29.4-29.2 (p, J = 4.7 Hz); **ATR-IR ($\nu_{\max}$):** 2922, 1599, 1378, 1326, 1177, 1147, 876, 817, 762, 729 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁F₆O₂S₂⁺ [M+H]⁺ 341.0099, found 341.0051.



Compound cis-27: pentafluoro(3-((2-fluorophenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

R_f: 0.26 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 134.5 – 135.1 °C; **¹H (400 MHz, CDCl₃):** δ = 7.98-7.94 (m, 1H), 7.71-7.65 (m, 1H), 7.39-7.35 (m, 1H), 7.28-7.23 (m, 1H), 4.40-4.28 (tt, 1H, J = 9.2, 8.9, 5.3 Hz), 3.83-3.75 (tt, 1H, J = 9.2, 7.8 Hz), 3.27-3.19 (m, 2H), 2.73-2.66 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 82.30-80.76 (p, 1F, $^2J_{F-F}$ = 144.4 Hz), 52.05-51.65 (dd, 4F, $^2J_{F-F}$ = 144.4 Hz, $^3J_{F-H}$ = 5.3 Hz), -108.25 - -108.31 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 161.1-158.5 (d, J = 256.6 Hz), 136.9-136.8 (d, J = 8.1 Hz), 131.4, 125.6-125.5 (d, J = 14.7 Hz), 125.22-125.18 (d, J = 3.6 Hz), 117.6-117.4 (d, J = 21.4 Hz), 69.3-68.7 (p, J = 16.0 Hz), 50.00, 30.3-30.1 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2927, 1600, 1136, 1149, 1125, 836, 814, 760, 729 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₀H₁₁F₆O₂S₂⁺ [M+H]⁺ 341.0099, found 341.0089.

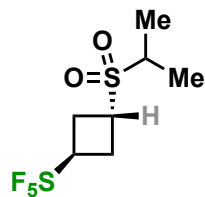
Compound **28** was prepared according to the general procedure B; *cis*-**28** and *trans*-**28** formed in 37% yield in a 1.3:1 ratio by ¹⁹F NMR. Compound **28** was obtained as a clear oil (21.8 mg) after successive preparative TLC using 4:1 hexanes:EtOAc, followed by 1:1 hexanes:EtOAc; the total isolated yield was 31%. *Note: The final products were prone to decomposition at ambient conditions.*



Compound 28: pentafluoro(3-((2-methoxyphenyl)sulfonyl)cyclobutyl)- λ^6 -sulfane

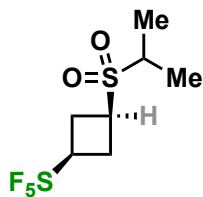
R_f: 0.14 and 0.08 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 8.00-7.94 (m, 2H), 7.65-7.55 (m, 2H), 7.15-7.08 (m, 2H), 7.06-7.02 (m, 2H), 5.00-4.84 (m, 2H), 4.24-4.17 (m, 1H), 4.40-4.27 (m, 1H), 4.24-4.17 (m, 1H), 3.96-3.95 (m, 7H), 3.26-3.15 (m, 2H), 3.12-3.00 (m, 2H), 2.90-2.81 (m, 2H), 2.68-2.58 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 84.20-80.87 (m, 2F), 52.15-51.62 (dd, 4F, $^2J_{F-F}$ = 144.9 Hz, $^3J_{F-H}$ = 5.3 Hz), 51.71-51.18 (dd, 4F, $^2J_{F-F}$ = 144.6 Hz, $^3J_{F-H}$ = 5.9 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 157.58, 157.55, 136.3, 136.2, 131.2, 131.1, 129.5, 127.8, 121.1, 121.0, 112.7, 112.5, 73.6-73.2 (p, J = 14.3 Hz), 69.5-69.1 (p, J = 15.3 Hz), 56.49, 56.47, 51.4, 49.0, 30.4-30.2 (p, J = 4.2 Hz), 29.5-29.2 (p, J = 4.4 Hz); **ATR-IR ($\nu_{\max}$):** 2923, 1592, 1314, 1188, 1145, 934, 856, 813, 761 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁F₅O₃S₂⁺ [M+H]⁺ 353.0299, found 353.0292.

Compound **29** was prepared according to the general procedure B; *cis*-**29** and *trans*-**29** formed in 80% yield in a 1.2:1 ratio by ¹⁹F NMR. Compound *cis*-**29** was isolated as a white solid (16.2 mg) and *trans*-**29** was isolated as a white solid (20.0 mg); the total isolated yield was 62%. The isomers were separated *via* column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc.



Compound trans-29: pentafluoro(3-(isopropylsulfonyl)cyclobutyl)- λ^6 -sulfane

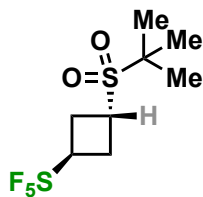
R_f: 0.15 (9:1 hexanes:EtOAc), vis: KMnO₄; **m.p.:** 105.8 – 111.2 °C; **¹H (300 MHz, CDCl₃):** δ = 4.91-4.79 (tpp, 1H, J = 9.3, 8.8, 5.9 Hz), 3.77-3.72 (m, 1H), 3.19-3.10 (m, 3H), 3.00-2.93 (m, 2H), 1.38-1.36 (d, 6H, J = 6.9 Hz); **¹⁹F (282 MHz, CDCl₃):** δ = 83.62-82.09 (p, 1F, $^2J_{F-F}$ = 143.1 Hz), 51.61-51.21 (dd, 4F, $^2J_{F-F}$ = 143.1 Hz, $^3J_{F-H}$ = 5.9 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 73.4-72.8 (p, J = 14.7), 52.0, 47.3, 29.5-29.3 (p, J = 4.4 Hz), 15.4; **ATR-IR (v_{max}):** 2947, 1391, 1307, 1167, 1132, 824, 792 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₇H₁₄F₅O₂S₂⁺ [M+H]⁺ 289.0350, found 289.0241.



Compound cis-29: pentafluoro(3-(isopropylsulfonyl)cyclobutyl)- λ^6 -sulfane

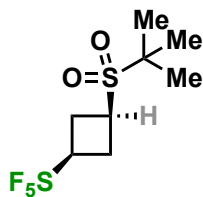
R_f: 0.10 (9:1 hexanes:EtOAc), vis: KMnO₄; **m.p.:** 103.9 – 110.5 °C; **¹H (300 MHz, CDCl₃):** δ = 4.45-4.34 (ttp, 1H, J = 9.3, 8.9, 5.3 Hz), 3.56-3.47 (tt, 1H, J = 9.4, 7.7 Hz), 3.27-3.18 (m, 2H), 3.10-3.00 (sept, 1H, J = 7.0 Hz), 2.76-2.69 (m, 2H), 1.37-1.35 (d, 6H, J = 7.0 Hz); **¹⁹F (282 MHz, CDCl₃):** δ = 82.32-80.78 (p, 1F, $^2J_{F-F}$ = 144.5 Hz), 52.01-51.61 (dd, 4F, $^2J_{F-F}$ = 144.5 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 69.9-69.3 (p, J = 15.6 Hz), 52.8, 44.8, 30.4-30.3 (p, J = 4.3 Hz), 15.4; **ATR-IR ($\nu_{\max}$):** 2165, 1307, 1167, 1134, 824, 786 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₇H₁₄F₅O₂S₂⁺ [M+H]⁺ 289.0350, found 289.0241.

Compound **30** were prepared according to the general procedure B; **cis-30** and **trans-30** formed in 43% yield in a 1.6:1 ratio by ¹⁹F NMR. Compound **cis-30** was isolated as a clear oil (13.2 mg) and **trans-30** was isolated as a clear oil (17.1 mg); the total isolated yield was 41%. The isomers were separated *via* column chromatography on silica gel eluting with 9:1 hexanes:EtOAc.



Compound trans-30: (3-(*tert*-butylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

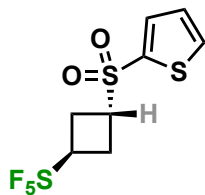
R_f: 0.15 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (300 MHz, CDCl₃):** δ = 4.89-4.74 (tpp, 1H, J = 9.3, 8.6, 5.8 Hz), 3.93-3.83 (m, 1H), 3.21-2.98 (m, 4H), 1.39 (2, 9H); **¹⁹F (282 MHz, CDCl₃):** δ = 84.09-82.04 (p, 1F, J = 143.6 Hz), 51.84-51.31 (dd, 4F, $^2J_{F-F}$ = 143.6 Hz, $^3J_{F-H}$ = 5.8 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 73.7-73.1 (p, J = 14.3 Hz), 60.2, 45.4, 30.2-30.0 (p, J = 4.5 Hz), 23.9; **ATR-IR ($\nu_{\max}$):** 2932, 1479, 1366, 1188, 1119, 834, 792, 660 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₈H₁₆F₅O₂S₂⁺ [M+H]⁺ 303.0506, found 303.0499 .



Compound cis-30: (3-(*tert*-butylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

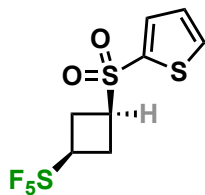
R_f: 0.10 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (300 MHz, CDCl₃):** δ = 4.46-4.31 (tpp, 1H, *J* = 9.2, 8.9, 5.1 Hz), 3.67-3.55 (tt, 1H, *J* = 9.4, 7.6 Hz), 3.30-3.19 (m, 2H), 2.77-2.67 (m, 2H), 1.38 (s, 9H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.66-80.61 (p, 1F, ²*J*_{F-F} = 144.0), 52.13-51.60 (dd, 4F, ²*J*_{F-F} = 144.0 Hz, ³*J*_{F-H} = 5.1 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 70.0-69.7 (p, *J* = 16.0 Hz), 59.5, 42.7, 31.3-31.1 (p, *J* = 4.5 Hz), 23.7; **ATR-IR (ν_{max}):** 2933, 1449, 1367, 1294, 1189, 1118, 833, 792, 660 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₈H₁₆F₅O₂S₂⁺ [M+H]⁺ 303.0506, found 303.0496.

Compound **31** was prepared according to the general procedure B; **cis-31** and **trans-31** formed in 49% yield in a 1:1 ratio by ¹⁹F NMR. Compound **cis-31** was isolated as a white solid (14.2 mg) and **trans-31** was isolated as a white solid (11.7 mg); the total isolated yield was 39%. The isomers were separated *via* successive preparative TLC on silica gel using 4:1 hexanes:EtOAc, followed by 100% CH₂Cl₂.



Compound trans-31: 2-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)thiophene

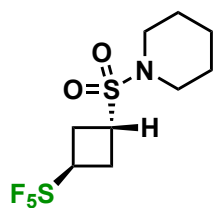
R_f: 0.34 (4:1 hexanes:EtOAc); **m.p.:** 99.0 – 102.5 °C; **¹H (400 MHz, CDCl₃):** δ = 7.79-7.78 (dd, 1H, J = 5.0, 1.3 Hz), 7.73-7.71 (dd, 1H, J = 3.8, 1.3 Hz), 7.22-7.19 (dd, 1H, J = 5.0, 3.8 Hz), 4.96-4.80 (tpp, 1H, J = 9.1, 8.9, 5.8 Hz), 3.84-3.77 (m 1H), 3.18-3.06 (m, 2H), 3.02-2.92 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.81-81.76 (p, 1F, $^2J_{F-F}$ = 144.4 Hz), 51.85-51.31 (dd, 4F, $^2J_{F-F}$ = 144.4 Hz, $^3J_{F-H}$ = 5.8 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 137.7, 135.1, 135.0, 128.4, 73.0-72.7 (p, J = 15.2 Hz), 54.6, 30.0-29.8 (p, J = 4.4 Hz); **ATR-IR (v_{max}):** 3098, 2920, 1433, 1399, 1323, 1166, 1138, 821, 738 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₈H₁₀F₅O₂S₃⁺ [M+H]⁺ 328.9758, found 328.9753.



Compound *cis*-31: 2-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)thiophene

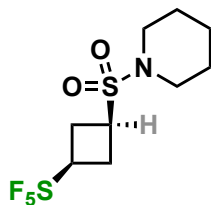
R_f: 0.17 (4:1 hexanes:EtOAc); **m.p.:** 134.4 – 137.5 °C; **¹H (300 MHz, CDCl₃):** δ = 7.79-7.77 (dd, 1H, J = 5.0, 1.3 Hz), 7.72-7.70 (dd, 1H, J = 3.8, 1.3 Hz), 7.22-7.19 (dd, 1H, J = 5.0 Hz, 3.8 Hz), 4.38-4.22 (tt, 1H, J = 9.3, 8.9, 5.3 Hz), 3.67-3.56 (tt, 1H, J = 9.5, 7.9 Hz), 3.24-3.13 (m, 2H), 2.75-2.65 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.60-80.54 (p, 1F, $^2J_{F-F}$ = 144.0 Hz), 52.18-51.65 (dd, 4F, $^2J_{F-F}$ = 144.0 Hz, $^3J_{F-H}$ = 5.3 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 137.7, 135.1, 128.5, 69.0-68.3 (p, J = 15.5 Hz), 51.4, 30.7-30.6 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2920, 1429, 1400, 1143, 1069, 817, 779, 733, 662, 638 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₈H₁₀F₅O₂S₃⁺ [M+H]⁺ 328.9758, found 328.9754.

Compound **32** was prepared according to the general procedure B; *cis*-**32** and *trans*-**32** formed in 21% yield a 1.4:1 ratio by ¹⁹F NMR. Compound *cis*-**32** was isolated as a clear oil (1.3 mg) *via* preparative TLC on silica gel, using 100% CH₂Cl₂.



Compound trans-32: 1-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)piperidine

R_f: 0.52 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (300 MHz, CDCl₃):** δ = 4.94-4.86 (tpp, 1H, J = 9.2, 8.6, 5.6 Hz), 3.69-3.66 (m, 1H), 3.35-3.25 (m, 4H), 3.17-3.10 (m, 2H), 2.92-2.87 (m, 2H), 1.67-1.62 (m, 5H); **¹⁹F (282 MHz, CDCl₃):** δ = 84.19-82.14 (p, 1F, $^2J_{F-F}$ = 143.2 Hz), 51.85-51.32 (dd, 4F, $^2J_{F-F}$ = 143.2 Hz, $^3J_{F-H}$ = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 69.8-69.6 (p, J = 14.9 Hz), 47.2, 45.8, 31.8-31.7 (p, J = 4.4 Hz), 26.0, 23.9; **ATR-IR ($\nu_{\max}$):** 1329, 1152, 833, 727 cm⁻¹.



Compound cis-32: 1-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)piperidine

R_f: 0.52 (9:1 hexanes:EtOAc), vis: KMnO₄ or *p*-anisaldehyde; **¹H (600 MHz, CDCl₃):** δ = 4.36-4.28 (tpp, 1H, J = 9.3, 8.9, 5.1 Hz), 3.45-3.39 (tt, 1H, J = 9.5, 7.4 Hz), 3.26-3.24 (m, 4H), 3.16-3.10 (m, 2H), 2.76-2.71 (m, 2H), 1.65-1.62 (m, 5H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.91-80.86 (p, 1F, J = 143.4 Hz), 52.12-51.59 (dd, 4F, $^2J_{\text{F-F}}$ = 143.4 Hz, $^3J_{\text{F-H}}$ = 5.1 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 73.5-73.3 (p, J = 15.1 Hz), 47.3, 37.9, 30.7-30.6 (p, J = 4.3 Hz), 26.0, 23.9; **ATR-IR (ν_{max}):** 1333, 1149, 831, 728 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₉H₁₇F₅NO₂S₂⁺ [M+H]⁺ 330.0615, found 330.0613.

3.5.21 Preliminary Data for Other BCB Substrates.

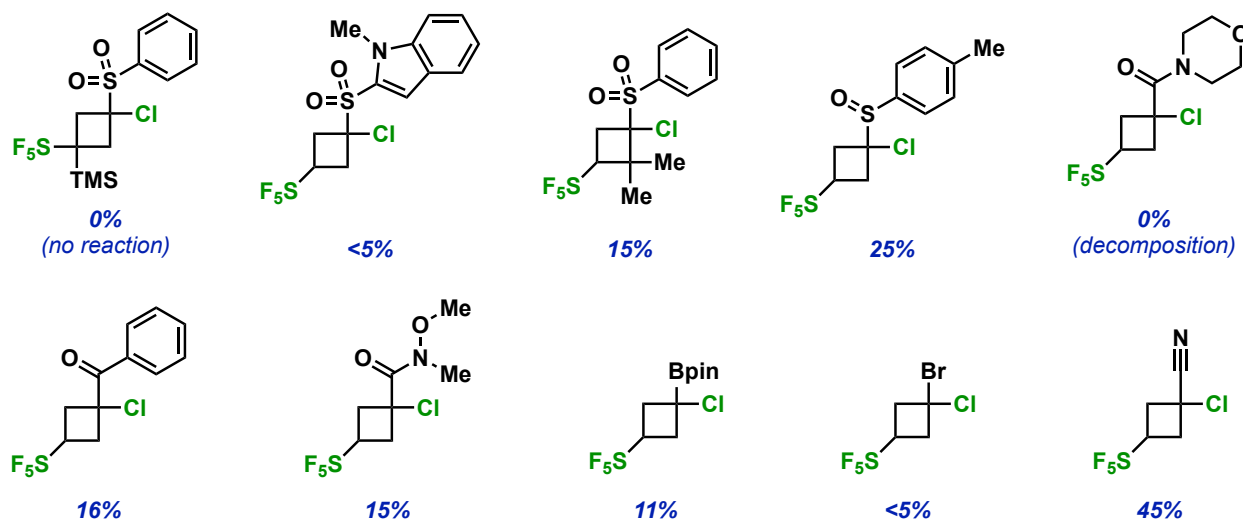


Figure 3.15. Preliminary data obtained for BCB substrates with various EWG substituents following general procedure A or C (see table below for more details).

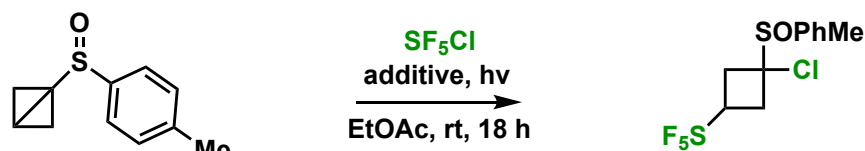


Table 3.9. Screening conditions for chloropentafluorosulfanylation of sulfoxide-BCB.

Entry	Equiv. SF ₅ Cl	Additive (1.0 equiv.)	¹⁹ F Yield (%) ^a	d.r. ^b
1	1.2	—	10	1:1
2	1.2	(PPh ₃)AuCl	24	1:1
3	1.2	CuBr ₂	25	1:1
4	3.0	CuBr ₂	19	1.1:1
5 ^c	3.0	CuBr ₂	>1	n.d.
6	3.0	K ₃ PO ₄	14	1:1

[a] Yields were determined by ¹⁹F NMR [b] *Anti*:*syn* ratio was determined by ¹⁹F NMR. [c] Reaction was run in acetone.

In addition to screening with boronic ester and sulfoxide BCBs separately, the addition of SF₅Cl across *in-situ* generated boronate BCBs as reported by Aggarwal and co-workers^[51d] was attempted.

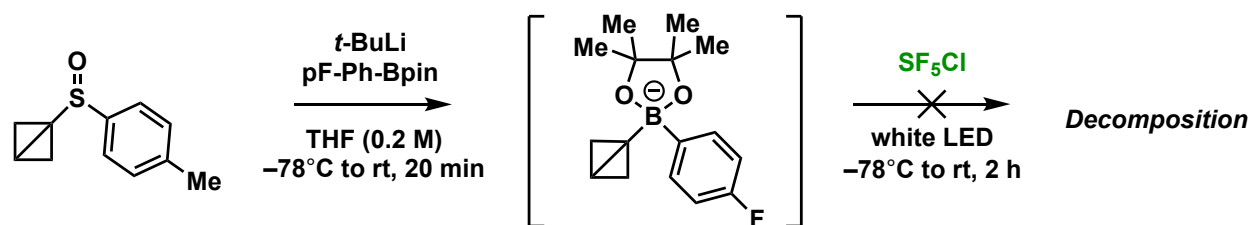
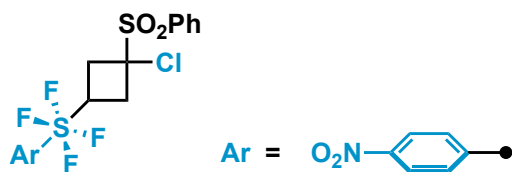


Table 3.10. NMR shifts of chloropentafluorosulfanylation of various EWG-BCBs. *Note: The shifts of the apical F were not assigned due to significant overlap. Additionally, putative syn and anti isomers are tentatively assigned based on trends observed in the literature and with other substrates.*

$\text{SF}_5\text{-CB}$	Yield & <i>anti:syn</i> ratio using method A	<i>Syn</i> isomer (equatorial F)	<i>Anti</i> Isomer (equatorial F)
	15% (2.7:1)	62.93-62.40 dd, $J = 145.4, 6.1$	61.64-61.11 dd, $J = 145.4, 6.9$
	10% (1:1)	53.95-53.55 dd, $J = 145.3, 5.4$ Hz	51.72-51.32 dd, $J = 145.3, 5.6$ Hz
	16% (1.2:1)	53.08-52.57 dd, $J = 144.3, 5.4$ Hz	52.56-52.03 dd, $J = 144.3, 5.6$ Hz
	17% (2.2:1)	53.34-52.81 dd, $J = 145.1, 5.8$ Hz	52.61-52.08 dd, $J = 145.1, 5.7$ Hz
	11% (1:1)	52.54-52.00 dd, $J = 143.8, 5.7$ Hz	52.00-51.47 dd, $J = 143.8, 6.3$ Hz
	trace (n.d.)	53.77-53.23 dd, $J = 146.6, 5.6$ Hz	53.09-52.55 dd, $J = 146.6, 5.6$ Hz
	45% (1.2:1)	53.33-52.92 dd, $J = 146.2, 5.4$ Hz	52.85-52.44 dd, $J = 146.2, 5.5$ Hz

3.5.22 Tetrafluoro(aryl)cyclobutane Characterization.

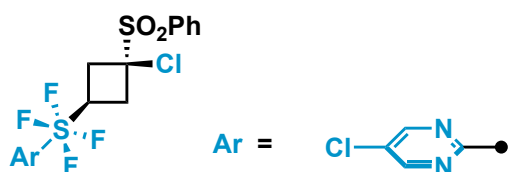
Compound **36** was prepared according to the general procedure E in 54% in a 1.4:1 ratio by ^{19}F NMR. *Note: ^{19}F NMR shifts were obtained from an aliquot of the crude reaction mixture. The resulting product hydrolyzed too quickly for ^1H and ^{13}C NMR to be collected.*



Compound 36: (3-chloro-3-(phenylsulfonyl)cyclobutyl)tetrafluoro(4-nitrophenyl)- λ^6 -sulfane

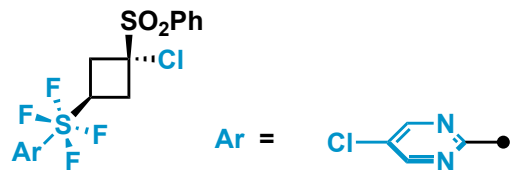
^{19}F (282 MHz, CDCl_3): δ = 54.47-54.46 (d, 4F, $^2J_{\text{F-H}} = 5.4$ Hz), 52.64 – 52.62 (d, 4F, $^2J_{\text{F-H}} = 5.4$ Hz).

Compound **37** was prepared according to the general procedure D. *syn-37* and *anti-37* were formed in 43% yield in a 1:1.2 ratio by ^{19}F NMR. The products were stable enough to obtain ^1H and ^{19}F NMR data, but ^{13}C data was not obtained.



Compound anti-37: 5-chloro-2-((3-chloro-3-(phenylsulfonyl)cyclobutyl)tetrafluoro- λ^6 -sulfanyl)pyrimidine

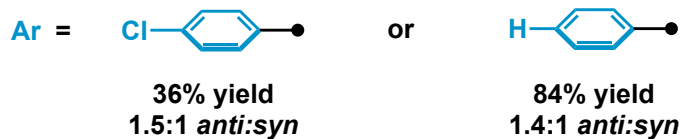
^1H (300 MHz, CDCl_3): δ = 8.79 (s, 2H), 8.05-8.01 (m, 2H), 7.79-7.72 (m, 1H), 7.65-7.60 (m, 2H), 5.13-4.99 (m, 1H), 3.66-3.50 (m, 4H); ^{19}F (282 MHz, CDCl_3): δ = 39.41-39.39 (d, 4F, $^3J_{\text{F-H}} = 5.2$ Hz).



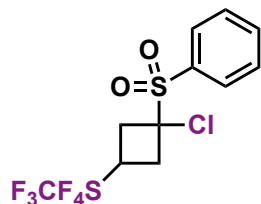
Compound *syn*-37: 5-chloro-2-((3-chloro-3-(phenylsulfonyl)cyclobutyl)tetrafluoro- λ^6 -sulfanyl)pyrimidine

^1H (300 MHz, CDCl_3): δ = 8.79 (s, 2H), 7.98-7.95 (m, 2H), 7.76-7.71 (m, 1H), 7.64-7.58 (m, 2H), 5.10-4.95 (m, 1H), 4.07-3.98 (m, 2H), 2.85-2.77 (m, 2H); ^{19}F (282 MHz, CDCl_3): δ = 41.26-41.25 (d, 4F, $^3J_{\text{F-H}} = 5.2$ Hz).

In addition to the deactivated arenes shown above, two other electron rich ArSF_4Cl compounds were also investigated.

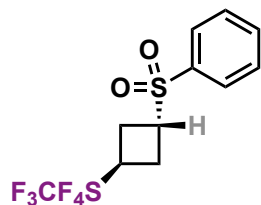


3.5.23 Tetrafluoro(trifluoromethyl)sulfanylcyclobutane Characterization.



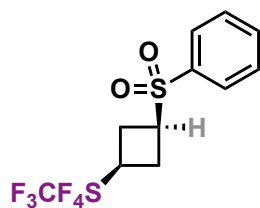
Compound 40: (3-chloro-3-(phenylsulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ^6 -sulfane

R_f: 0.51 (4:1 hexanes:EtOAc, *anti* isomer), 0.62 (4:1 hexanes:EtOAc, *syn* isomer), vis: UV (254 nm); **¹H (400 MHz, CDCl₃):** δ = 8.01-7.94 (m, 4H), 7.78-7.73 (m, 2H), 7.64-7.60 (m, 4H), 4.93-4.78 (m, 2H), 3.92-3.86 (m, 2H), 3.58-3.52 (m, 2H), 3.40-3.34 (m, 2H), 2.78-2.73 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 30.52-30.31 (qd, 4F, $^3J_{F-F}$ = 24.6 Hz, $^2J_{F-H}$ = 5.3 Hz), 28.7-28.5 (qd, 4F, $^3J_{F-F}$ = 25.4 Hz, $^2J_{F-H}$ = 5.4 Hz), -63.3 - -63.7 (p, 6F, $^3J_{F-F}$ = Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 135.3, 135.1, 133.5, 132.9, 131.1, 130.6, 129.5, 129.4, 74.3, 73.6, 71.3-70.6 (p, J = 18.1 Hz), 70.3-69.9 (p, J = 19.0 Hz), 41.6-41.4 (p, 4.3 Hz), 40.3-40.1 (p, J = 4.4 Hz); **ATR-IR (v_{max}):** 2923, 1327, 1313, 1148, 1096, 820, 765, 687 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₁ClF₇O₂S₂⁺ [M+H]⁺ 406.9772, found 406.9778.



Compound trans-41: Tetrafluoro(3-(phenylsulfonyl)cyclobutyl)(trifluoromethyl)- λ^6 -sulfane

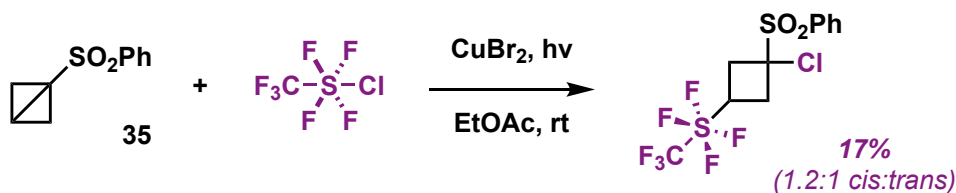
R_f: 0.40 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 120.7 – 123.4 °C; **¹H (400 MHz, CDCl₃):** δ = 7.92-7.89 (m, 2H), 7.73-7.67 (m, 1H), 7.62-7.56 (m, 2H), 5.09-4.94 (ttp, 1H, J = 9.2, 8.8, 6.1 Hz), 3.78-3.71 (m, 1H), 3.17-3.05 (m, 2H), 2.98-2.89 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 28.30-28.01 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), –63.33 - –63.69 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 137.2, 134.4, 129.7, 128.5, 75.6-74.8 (p, J = 17.3 Hz), 53.2, 30.0-29.7 (p, J = 4.7 Hz); **ATR-IR (v_{max}):** 2926, 1741, 1449, 1311, 1143, 1086, 773, 672 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₂F₇O₂S₂⁺ [M+H]⁺ 373.0162, found 373.0157.



Compound cis-41: Tetrafluoro(3-(phenylsulfonyl)cyclobutyl)(trifluoromethyl)- λ^6 -sulfane

R_f: 0.26 (4:1 hexanes:EtOAc), vis: UV (254 nm); **m.p.:** 155.3 – 156.8 °C; **¹H (400 MHz, CDCl₃):** δ = 7.90-7.87 (m, 2H), 7.72-7.67 (m, 1H), 7.62-7.57 (m, 2H), 4.48-4.32 (tpp, 1H, J = 9.4, 8.9, 5.4 Hz), 3.56-3.44 (tt, 1H, J = 9.4, 7.8 Hz), 3.27-.16 (m, 2H), 2.69-2.59 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 28.90-28.61 (qd, 4F, $^2J_{F-F}$ = 25.2 Hz), –68.38 - –63.74 (dd, 4F, $^2J_{F-F}$ = 25.2 Hz.); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 137.4, 134.4, 129.7, 128.5, 71.63-70.71 (p, J = 17.5 Hz), 50.32, 30.79-30.55 (p, J = 4.3 Hz); **ATR-IR ($\nu_{\max}$):** 2926, 1741, 1449, 1433, 1218, 1149, 1086, 763, 686 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₁₂F₇O₂S₂⁺ [M+H]⁺ 373.0162, found 373.0157.

The effect of 1.0 equiv. CuBr₂ as an additive in the tetrafluoro(trifluoromethyl)sulfanylation of **35** was investigated. Interestingly, we observed both a decrease in yield and lower selectivity for the *cis* isomer.



3.5.24 Proof-of-Concept for Pentafluoro(iodo)sulfanylation.

To an oven-dried microwave vial equipped with a stir bar was added **35** (19.4 mg, 0.1 mmol, 1.0 equiv.) and spray-dried KF (5.8 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed with a crimper and removed from the glovebox. Anhydrous EtOAc (0.5 mL) and CH₂I₂ (24 µL, 0.3 mmol, 3.0 equiv.) were added *via* syringe. Then SF₅Cl (1.35 mL, 0.12 mmol, 1.2 equiv.) was added and the mixture was stirred at 40 °C overnight. Upon completion, the crude reaction mixture was diluted with EtOAc (2.0 mL) and filtered through a Pasteur pipette containing a small cotton plug. The crude mixture was concentrated and loaded directly to a preparative TLC plate with CH₂Cl₂. **42** and **1** were obtained as a mixture as a clear oil. *Note: All other screens were performed on 0.1 mmol scale.*

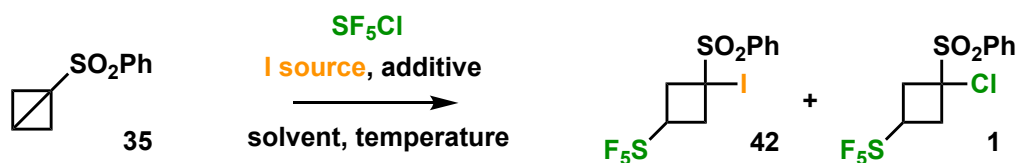


Table 3.11. Optimization table for pentafluoro(iodo)sulfanylation.

Entry	I source (equiv.)	Additive (equiv.)	Solvent (mL)	Temperature °C	¹⁹ F Yield (%) 38 ^a	¹⁹ F Yield (%) 1 ^a
1	CH ₂ I ₂ (0.5)	–	EtOAc (0.2)	23	0	0
2	CH ₂ I ₂ (0.5)	–	Et ₂ O (0.2)	23	0	trace
3 ^b	CH ₂ I ₂ (1.0)	–	EtOAc (1.0)	23	11	40
4	CH ₂ I ₂ (1.0)	KF (1.0)	EtOAc (1.0)	40	10	15
5	CH ₂ I ₂ (2.0)	KF (1.0)	EtOAc (1.0)	40	14	7
6	CH ₂ I ₂ (3.0)	KF (1.0)	CH ₂ Cl ₂ (1.0)	40	trace	trace
7 ^c	CH ₂ I ₂ (3.0)	KF (1.0)	EtOAc (1.0)	40	46	15
8 ^c	CH ₂ I ₂ (3.0)	LiF (1.0)	EtOAc (1.0)	40	0	0
9 ^c	CH ₂ I ₂ (3.0)	NaF (1.0)	EtOAc (1.0)	40	<1	0
10 ^c	CH ₂ I ₂ (3.0)	CsF (1.0)	EtOAc (1.0)	40	0	5
11 ^c	CH ₂ I ₂ (3.0)	KCl (1.0)	EtOAc (1.0)	40	<1	0
12 ^c	CH ₂ I ₂ (3.0)	KBr (1.0)	EtOAc (1.0)	40	0	0
13 ^c	CH ₂ I ₂ (3.0)	KI (1.0)	EtOAc (1.0)	40	0	0
14 ^c	CH ₂ I ₂ (3.0)	CuF ₂ (1.0)	EtOAc (1.0)	40	0	0
15 ^c	CH ₂ I ₂ (3.0)	AgF (1.0)	EtOAc (1.0)	40	<2	0
16 ^c	CH ₂ I ₂ (3.0)	K ₃ PO ₄ (1.0)	EtOAc (1.0)	40	11	25
17 ^c	CH ₂ I ₂ (3.0)	K ₂ CO ₃ (1.0)	EtOAc (1.0)	40	22	8
18 ^c	CH ₂ I ₂ (3.0)	KOAc (1.0)	EtOAc (1.0)	40	0	0
19 ^c	CH ₂ I ₂ (3.0)	CuCl (1.0)	EtOAc (1.0)	40	0	0
20 ^c	CHI ₃ (3.0)	KF (1.0)	EtOAc (1.0)	40	2	0
21 ^c	Cl ₄ (3.0)	KF (1.0)	EtOAc (1.0)	40	>1	0
22 ^c	I ₂ (3.0)	KF (1.0)	EtOAc (1.0)	40	0	0
23 ^d	KI (4.0)	18-crown-6 (1.0)	THF (0.6)	–78	12	0
24 ^d	KI (4.0)	18-crown-6 (1.0)	THF (0.6)	23	<2	0
25 ^d	KI (4.0)	18-crown-6 (1.0)	<i>n</i> -pentane (1.0)	23	<1	0
26 ^{d,e}	KI (4.0)	18-crown-6 (1.0)	THF (3.4)	–78	4	0

[a] Yields were determined by ¹⁹F NMR. [b] Reaction run under white LED irradiation using Kessil Tuna

Blue. [c] SF₅Cl (in *n*-pentane) was added in 3 portions over 6 hours. [d] 3.0 equiv. SF₅Cl were used. [e]

The reaction was run on 0.55 mmol scale.

Note: ^1H NMR signals could not be unequivocally assigned due to significant overlap with **1**.

^{19}F (282 MHz, CDCl_3): $\delta = 54.21\text{--}53.81$ (dd, 4F, $^3J_{\text{F-F}} = 146.0$ Hz, $^2J_{\text{F-H}} = 5.4$ Hz), $51.95\text{--}51.57$ (dd, 4F, $^2J_{\text{F-F}} = 146.0$ Hz, $^3J_{\text{F-H}} = 5.4$ Hz).

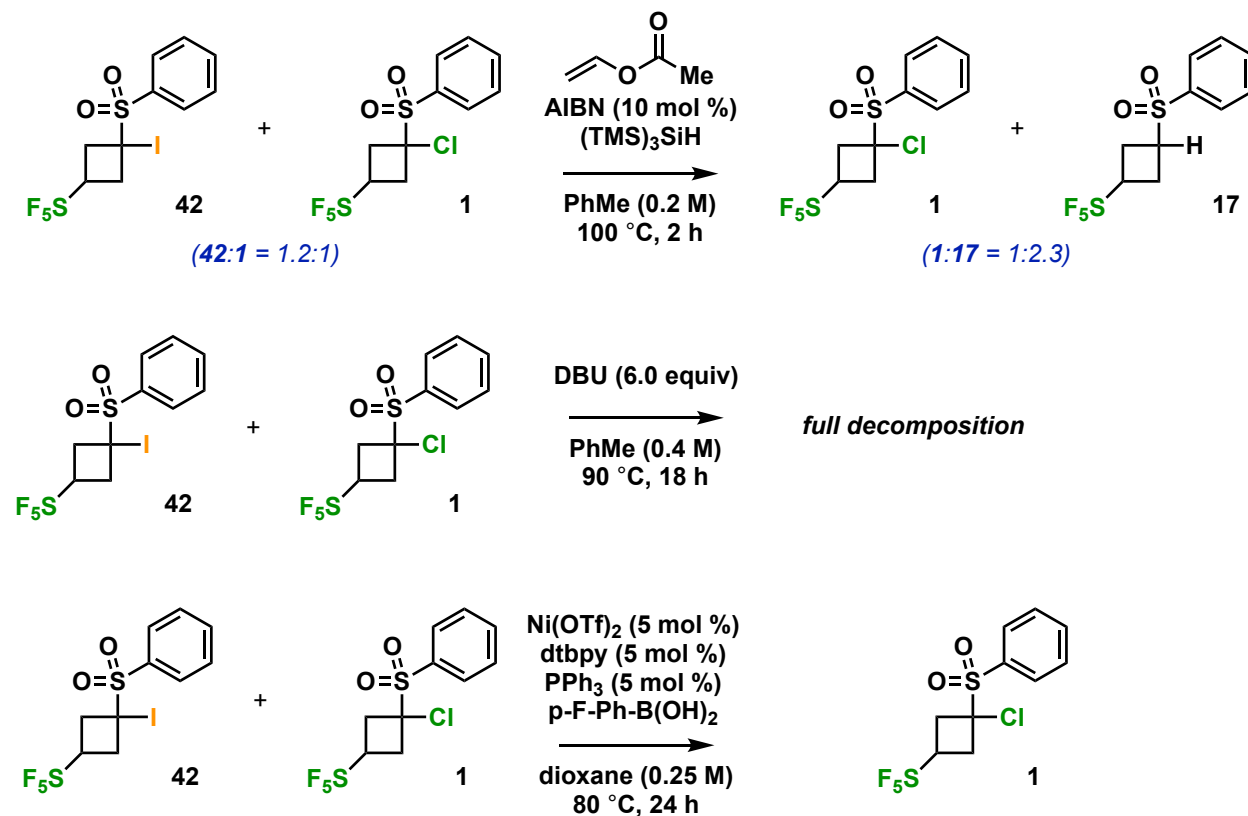


Figure 3.16. Initial attempts at C–I bond functionalization.

3.5.25 3-Component Pentafluorosulfanylation-Allylation.

To an oven-dried microwave vial equipped with a stir bar was added **35** (19.4 mg, 0.1 mmol, 1.0 equiv.) and K₃PO₄ (21 mg, 0.1 mmol, 1.0 equiv.). Anhydrous EtOAc (0.5 mL) and allyltrimethylsilane (24 μ L, 0.1 mmol, 1.0 equiv.) were added *via* syringe under Ar atmosphere. Then SF₅Cl (1.35 mL, 0.12 mmol, 1.2 equiv.) was added and the mixture was irradiated with white LEDs overnight. Upon completion, the crude reaction mixture was diluted with EtOAc (2.0 mL) and filtered through a Pasteur pipette containing a small cotton plug. The crude mixture was concentrated and loaded directly to a preparative TLC plate with CH₂Cl₂. The major (*syn*) isomer was isolated (using 9:1 hexanes:EtOAc) as a clear oil.

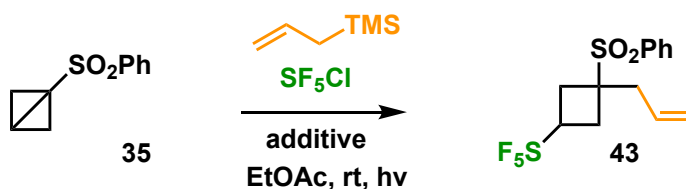
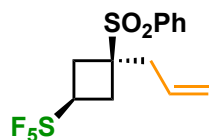


Table 3.12. Optimization table for pentafluorosulfanylation-allylation.

Entry	Equiv. Allyl-TMS	Additive (equiv.)	¹⁹ F Yield (%) 43 ^a
1	1.0	—	34
2^b	1.0	—	35
3^c	1.0	—	34
4	2.0	—	32
5	3.0	—	39
6	1.0	CuBr ₂ (1.0)	0
7	1.0	K ₃ PO ₄ (1.0)	52
8	2.0	K ₃ PO ₄ (1.0)	39
9	3.0	K ₃ PO ₄ (1.0)	44
10^c	1.0	K ₃ PO ₄ (1.0)	0

[a] Yields were determined by ¹⁹F NMR. [b] 2.0 equiv. **35** was used. [c] 2.0 equiv. of SF₅Cl was used. [d]

Reaction was run in the absence of light.

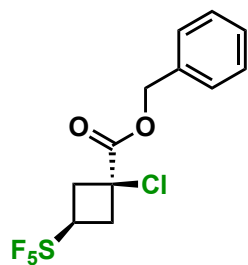


Compound syn-43: (3-allyl-3-(phenylsulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane

R_f: 0.54 (9:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.88-7.87 (m, 2H), 7.72-7.70 (m, 1H), 7.62-7.59 (m, 2H), 5.85-5.78 (m, 1H), 5.29-5.21 (m, 2H), 4.28-4.19 (m, 1H), 3.49-3.45 (m, 2H), 2.44-2.40 (m, 4H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.27-81.21 (p, 1F, J = 147.2 Hz), 52.95-52.42 (dd, 4F, J = 147.2, 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 135.1, 134.3, 130.5, 129.7, 129.4, 121.6, 68.5-68.3 (p, J = 14.8 Hz), 58.5, 38.2, 36.4, 32.7-32.6 (p, J = 3.9 Hz); **ATR-IR (ν_{max}):** 1307, 1154, 1091, 914, 872, 840, 744, 689, 630, 615 cm⁻¹; **HRMS (m/z):** (ESI) Not found.

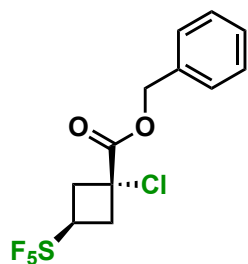
3.5.26 Characterization Data for Compounds **53** – **55**.

Compounds **53** and **53-_{1SF5}** were prepared according to the general procedure E; *syn*-**53** and *anti*-**53** formed in 56% yield a 1:1 ratio; *syn*-**53-_{1SF5}** and *anti*-**53-_{1SF5}** formed in 19% yield in a 1:1 ratio by ¹⁹F NMR. *Syn*-**53** and *anti*-**53** were initially isolated as a mixture of isomers from the crude reaction *via* preparative TLC on silica gel, using 5% EtOAc in hexanes. Note that all four products of the reaction eluted as a large band with multiple solvent systems, and the 3-SF₅ regioisomers could be obtained as a mixture by only collecting the bottom 1/3 of this band. Further purification of this mixture *via* preparative TLC using 3:1 hexanes:CH₂Cl₂ afforded *syn*-**53** as a clear oil. The *syn* and *anti* isomers are tentatively assigned based on trends observed in ¹H, ¹⁹F, and ¹³C NMR. We were not able to access pure *anti*-**53**; further attempts at purification always resulted in mixtures of isomers. Although challenging, compound **53-_{1SF5}** could be isolated as a mixture of isomers following further preparative TLC with 3:1 hexanes:CH₂Cl₂. Further purification also proved unsuccessful in our hands.



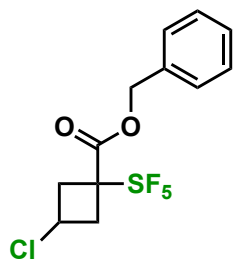
Compound syn-53: benzyl 1-chloro-3-(pentafluoro- λ^6 -sulfanyl)cyclobutane-1-carboxylate

R_f: 0.67 (3:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.40-7.36 (m, 5H), 5.25 (s, 2H), 4.46-4.30 (tt, 1H, J = 9.3, 7.4, 5.5 Hz), 3.35-3.20 (m, 4H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.28-81.22 (p, 1F, J = 144.4 Hz), 52.40-51.86 (dd, 4F, J = 144.4, 5.5 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 169.6, 134.6, 128.8, 128.2, 68.8-68.4 (p, J = 16.6 Hz), 56.6, 43.3-43.2 (p, J = 4.4 Hz).



Compound anti-53: benzyl 1-chloro-3-(pentafluoro- λ^6 -sulfanyl)cyclobutane-1-carboxylate

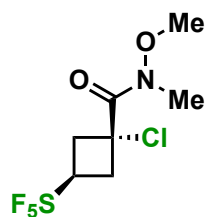
R_f: 0.67 (3:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.40-7.36 (m, 5H), 5.26 (s, 2H), 4.88-4.72 (tt, 1H, J = 8.7, 6.9, 5.6 Hz), 3.51-3.41 (m, 2H), 2.91-2.82 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.45-81.39 (p, 1F, J = 146.6 Hz), 53.35-52.81 (dd, 4F, J = 146.6, 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 168.5, 134.7, 128.8, 128.1, 69.9-69.3 (p, J = 15.9 Hz), 58.8, 42.1-41.9 (p, J = 3.9 Hz).



Compound *syn-53*-_{1SF5}: benzyl 3-chloro-1-(pentafluoro- λ^6 -sulfanyl)cyclobutane-1-carboxylate

R_f: 0.67 (3:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.41-7.35 (m, 4H), 5.30 (s, 2H), 5.25 (s, 2H), 4.45-4.42 (m, 1H), 3.99-3.94 (m, 1H), 3.62-3.58 (m, 2H), 3.43-3.40 (m, 2H), 3.26-3.21 (m, 2H), 3.15-3.11 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.30-80.26 (p, 1F, J = 146.3 Hz), 81.44-79.39 (p, 1F, J = 144.2 Hz), 52.67-52.67-52.16 (d, 4F, J = 146.3 Hz), 52.19-51.68 (d, 4F, J = 144.2 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 166.7, 134.4, 134.2, 128.9, 128.8, 128.72, 128.66, 128.5, 128.4, 82.4-82.1 (p, J = 13.5 Hz), 69.0, 68.9, 46.6, 44.5-44.4 (p, J = 2.3 Hz), 43.4-43.3 (p, J = 3.2 Hz), 43.2; *Note: the C-SF₅ ¹³C signal of the putative anti isomer was resolved due to low signal-to-noise.*

Compound **55** was obtained following the general procedure E; *syn-55* and *anti-55* formed in 52% yield a 1:2.5 ratio. The major isomer, *anti-55*, was isolated via preparative TLC (using 3:1 CH₂Cl₂:hexanes) as a clear oil. *Note: the final product was highly volatile.* Further attempts to isolate the minor *syn* isomer were unsuccessful.



Compound anti-55: 1-chloro-*N*-methoxy-*N*-methyl-3-(pentafluoro- λ^6 -sulfanyl)cyclobutane-1-carboxamide

R_f: 0.34 (3:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 4.81-4.73 (m, 1H), 3.78 (s, 3H), 3.38-3.34 (m, 2H), 3.24 (s, 3H), 2.88-2.84 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = 83.94-81.88 (p, 1F, J = 144.3 Hz), 53.60-53.06 (dd, 4F, J = 144.3, 5.7 Hz); **¹³C{¹H} (151 MHz, CDCl₃):** δ = 168.8, 70.4-70.0 (p, J = 15.9 Hz), 61.1, 58.9, 42.1-42.0 (p, J = 3.9 Hz), 32.6; **ATR-IR (ν_{max}):** 1732, 1578, 1321, 1156, 904, 833, 796, 722, 624 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₇H₁₂ClF₅NO₂S⁺ [M+H]⁺ 304.0192, found 304.0192.

3.5.27 Evidence for Epimerization.

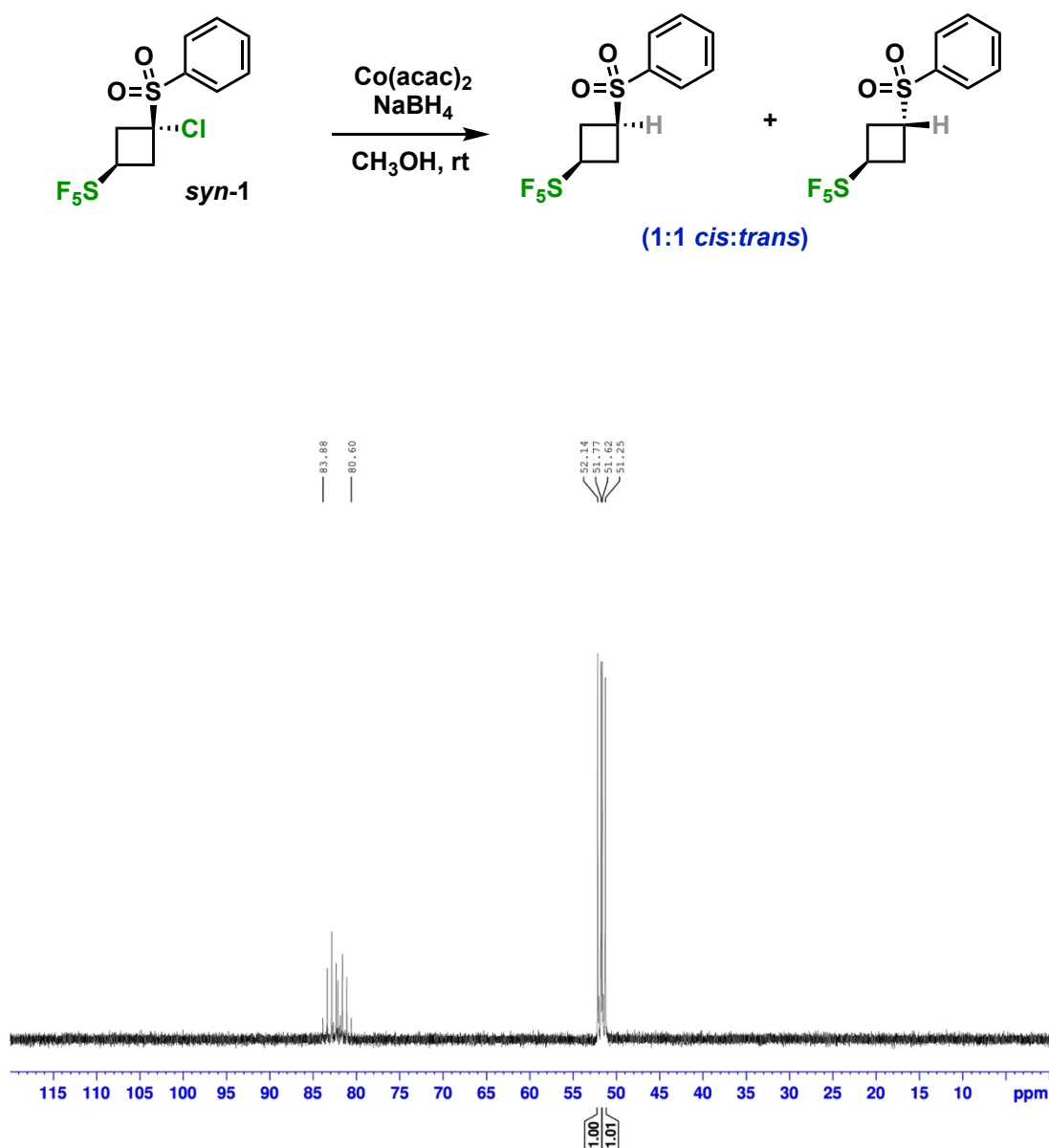


Figure 3.17. Crude ^{19}F NMR spectrum from the reaction of **syn-1** with $\text{Co}(\text{acac})_2$ and NaBH_4 in CH_3OH .

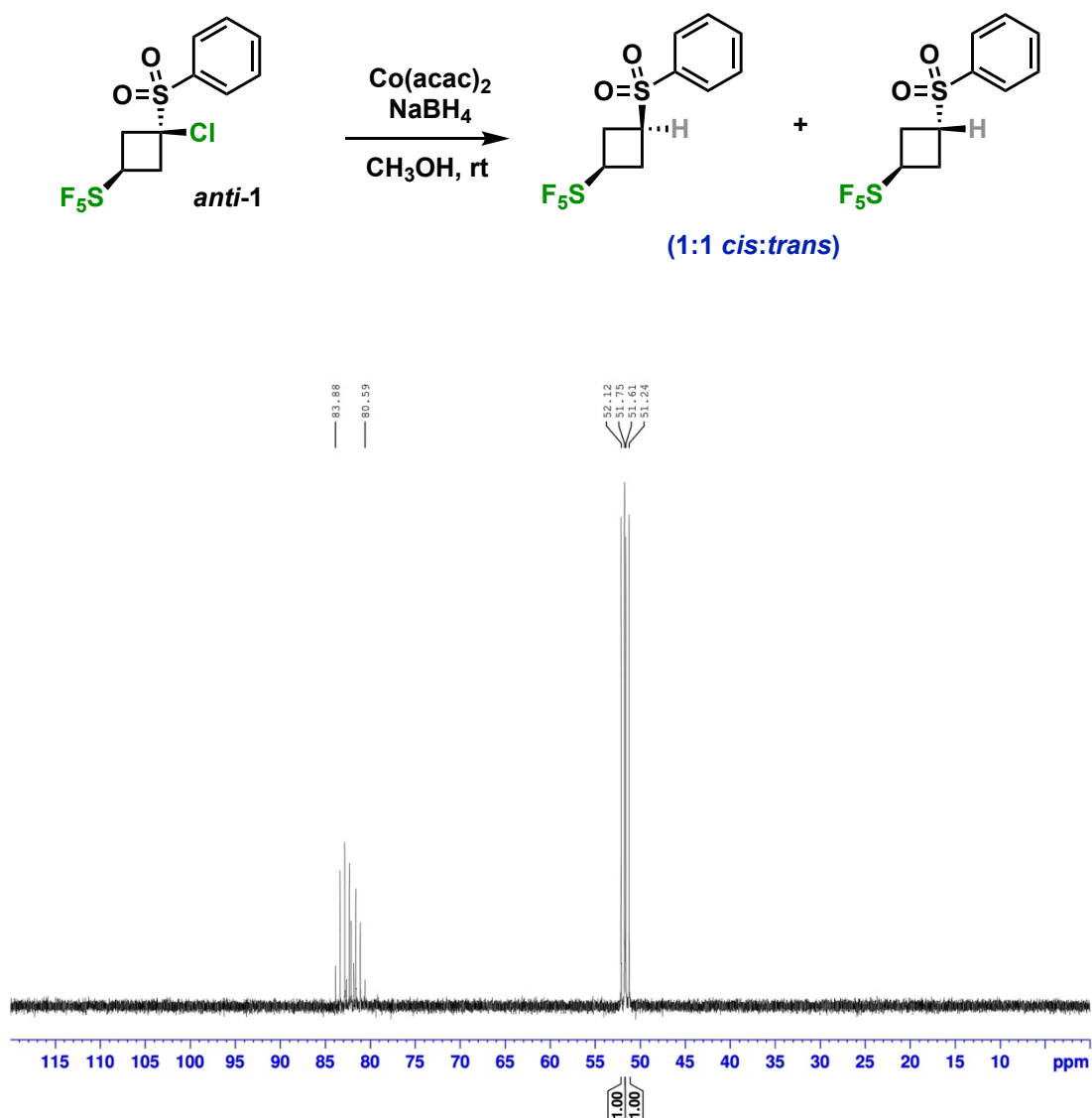
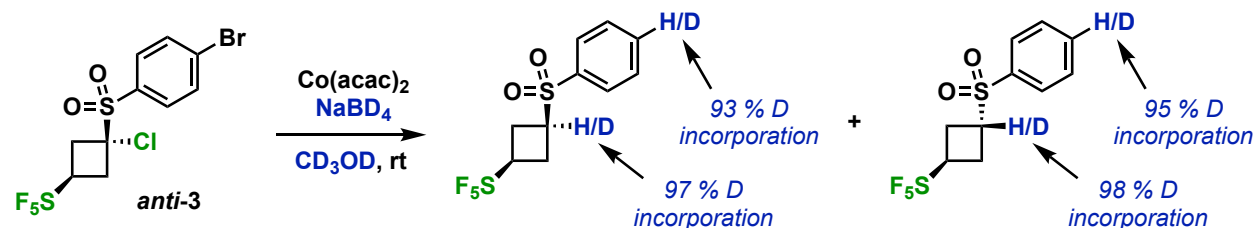
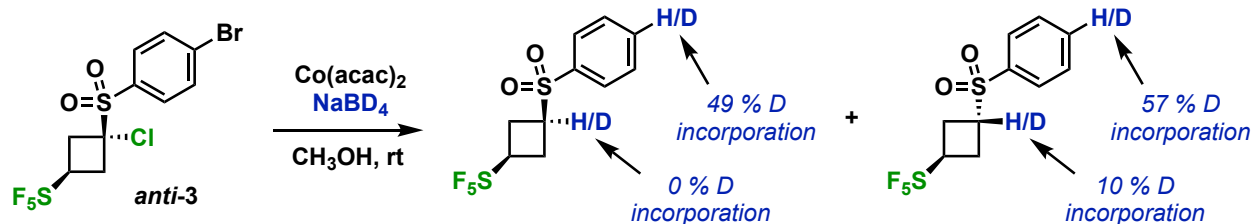


Figure 3.18. Crude ^{19}F NMR spectrum from the reaction of *anti*-1 with $\text{Co}(\text{acac})_2$ and NaBH_4 in CH_3OH .

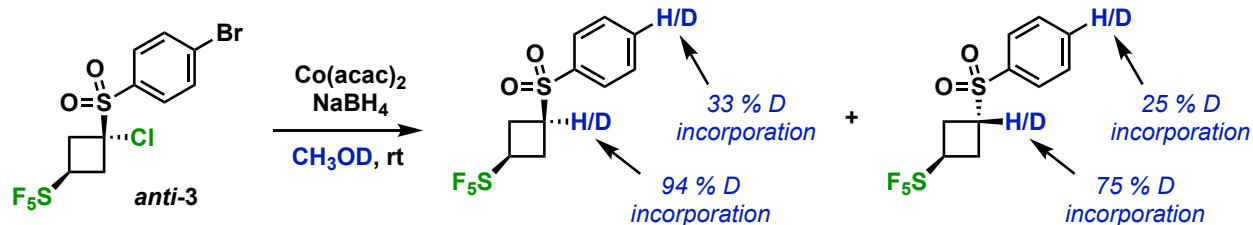
3.5.28 Deuterium-Labeling Experiments with Method B.



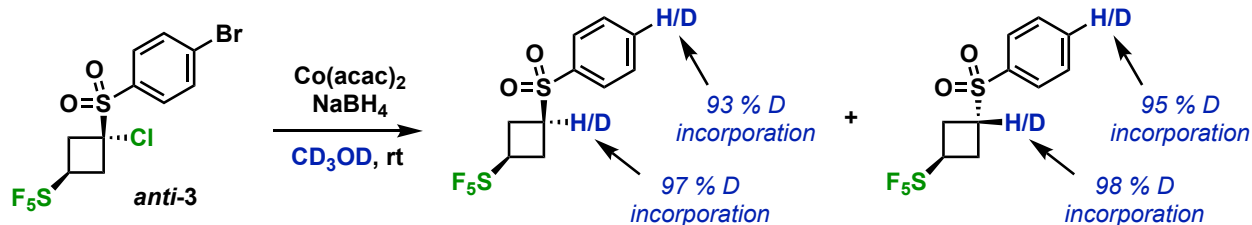
An oven-dried microwave vial equipped with a stir bar was charged with **anti-3** (40 mg, 0.092 mmol, 1.0 equiv.). CD_3OD (2.0 mL) was added followed by $\text{Co}(\text{acac})_2$ (71 mg, 0.276 mmol, 3.0 equiv.). NaBD_4 (39 mg, 0.92 mmol, 10.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 h. Upon completion, the solution was diluted with MeOH (approx. 2 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified *via* preparative TLC using 4:1 hexanes:EtOAc. Followed preparative TLC using 9:1 CH_2Cl_2 :hexanes. Note: Starting material had low solubility.



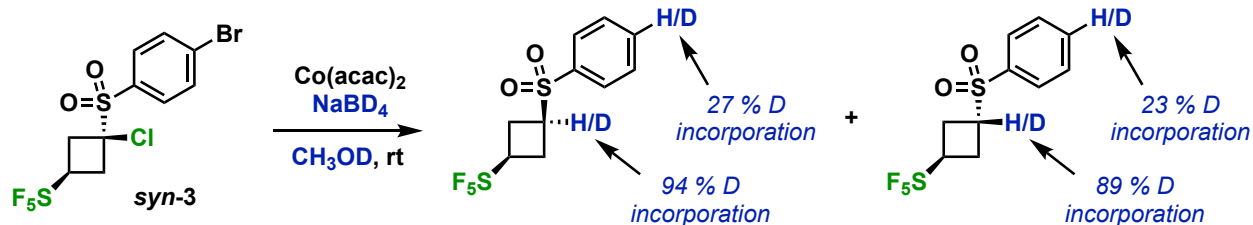
An oven-dried microwave vial equipped with a stir bar was charged with **anti-3** (33 mg, 0.073 mmol, 1.0 equiv.). CH_3OH (2.0 mL) was added followed by $\text{Co}(\text{acac})_2$ (56mg, 0.219 mmol, 3.0 equiv.). NaBD_4 (31 mg, 0.730 mmol, 10.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 h. Upon completion, the solution was diluted with MeOH (approx. 2 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified via preparative TLC using 4:1 hexanes:EtOAc, followed by preparative TLC using 9:1 CH_2Cl_2 :hexanes. Note: Starting material had low solubility.



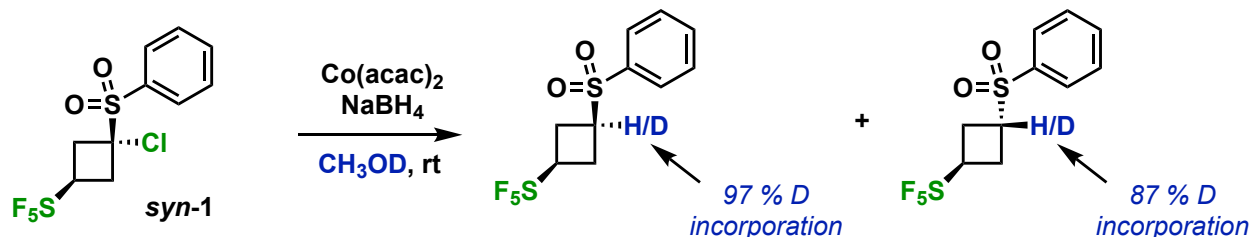
An oven-dried microwave vial equipped with a stir bar was charged with the **anti-3** (40 mg, 0.092 mmol, 1.0 equiv.). CH_3OD (2.0 mL) was added followed by $\text{Co}(\text{acac})_2$ (71 mg, 0.276 mmol, 3.0 equiv.). NaBH_4 (35 mg, 0.92 mmol, 10.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 h. Upon completion, the solution was diluted with MeOH (approx. 2 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified via preparative TLC using 4:1 hexanes:EtOAc, followed by a second prep. plate using 9:1 CH_2Cl_2 :hexanes. Note: Starting material had low solubility.



An oven-dried microwave vial equipped with a stir bar was charged with the **anti-3** (40 mg, 0.092 mmol, 1.0 equiv.). CD_3OD (2.0 mL) was added followed by $\text{Co}(\text{acac})_2$ (71 mg, 0.276 mmol, 3.0 equiv.). NaBH_4 (35 mg, 0.92 mmol, 10.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 h. Upon completion, the solution was diluted with MeOH (approx. 2 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified via preparative TLC using 4:1 hexanes:EtOAc, followed by a second prep. plate using 9:1 CH_2Cl_2 /hexanes. Note: Starting material had low solubility!



An oven-dried microwave vial equipped with a stir bar was charged with the **syn-3** (32 mg, 0.073 mmol, 1.0 equiv.). CH_3OD (3.5 mL) was added followed by $\text{Co}(\text{acac})_2$ (56 mg, 0.219 mmol, 3.0 equiv.). NaBH_4 (28 mg, 0.730 mmol, 10.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 18 h. Upon completion, the solution was diluted with MeOH (approx. 2 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH_4Cl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 or MgSO_4 , concentrated *in vacuo*, then purified via preparative TLC using 4:1 Hexanes:EtOAc, followed by preparative TLC using 9:1 CH_2Cl_2 :hexanes. Note: Starting material had low solubility.



The reaction was performed according to the general procedure B, using CH₃OD instead of CH₃OH. The crude residue was then purified via preparative TLC using 4:1 Hexanes/EtOAc, followed by preparative TLC using 100% CH₂Cl₂.

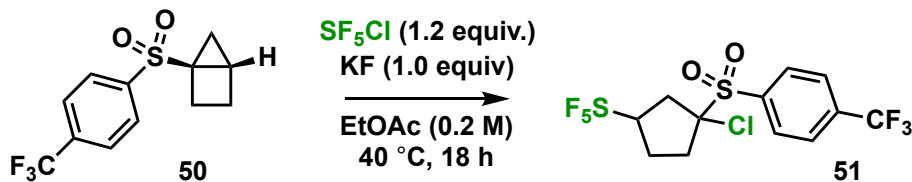
3.5.29 Reactivity of Phenyl Vinyl Sulfone and Housane Derivatives.



To an oven-dried 5 mL microwave vial equipped with a stir bar was added phenyl vinyl sulfone (**47**) (33.6 mg, 0.2 mmol, 1.0 equiv.). The vial was sealed, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added via syringe, followed by SF₅Cl in *n*-pentane (2.4 mL, 1.2 equiv.). The resulting solution was irradiated with white LEDs (Kessil A160WE Tuna Blue LED light, intensity set to maximum) at room temperature with vigorous stirring overnight. Upon reaction completion, 10 μL of α,α,α-trifluorotoluene was added as an internal standard and a 0.2 mL aliquot was taken for crude ¹⁹F NMR analysis.

Compound 43: (2-chloro-2-(phenylsulfonyl)ethyl)pentafluoro-λ⁶-sulfane

¹⁹F NMR (282 MHz, CDCl₃): 74.23-73.62 (m, 4F); *Note: the apical F was not resolved due to poor signal-to-noise.*

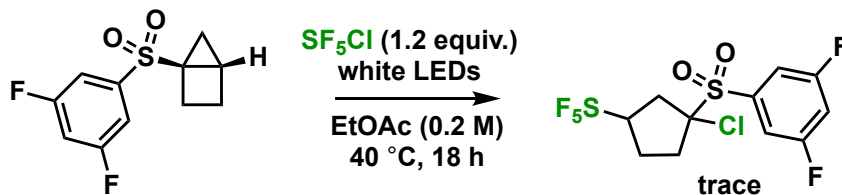


To an oven-dried 2 mL microwave vial equipped with a stir bar was added spray-dried KF (5.8 mg, 0.1 mmol, 1.0 equiv.) under glovebox atmosphere. The vial was sealed with a crimper, removed from the glovebox, and placed under Ar. Racemic 1-((4-trifluoromethylphenyl)sulfonyl)bicyclo[2.1.0]pentane (27.6 mg, 0.1 mmol, 0.1 equiv., purchased from Sigma-Aldrich) was added as a solution in anhydrous EtOAc (0.5 mL). Then SF₅Cl (0.12 mmol, 1.2 equiv.) was added as a solution in *n*-pentane and the reaction was stirred at 40 °C for 18 h. Upon completion, the reaction was diluted with EtOAc (2.0 mL) and filtered through a Pasteur pipette containing a cotton plug. The crude mixture was concentrated *in vacuo* and the crude residue was purified by preparative TLC using 9:1 hexanes:EtOAc. The resulting cyclopentane was obtained as a white solid. *Note: in all cases, the starting material could be recovered.*

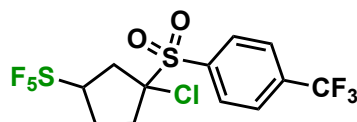
Table 3.13. Screening table for the addition of SF₅Cl across **50**.

Entry	Deviations from standard conditions	¹⁹ F Yield (%)
1	none	12
2	with K ₃ PO ₄ instead of KF	6
3^a	white LEDs and no KF	7
4	with DCM instead of EtOAc	11
5^a	white LEDs no KF for 72 h at rt	<1
6^a	blue LEDs and no KF at rt	<1
7	with BEt ₃ /O ₂ and no KF at rt	0
8^b	with 302 nm light source and no KF at rt	<1

[a] 40 W Kessil A160WE Tuna Blue LED light was used (reported in manuscript). [b] AnalytikJena 302 nm UV pen lamp was used (lamp was placed 2.0 cm away from the reaction vessel).



Note: Racemic 1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (purchased from Sigma-Aldrich) was also employed in initial screening for the addition of SF_5Cl across housanes. The same conditions as those provided in general procedure A resulted in a trace amount of product detected by ^{19}F NMR.



Compound 51: (3-chloro-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)pentafluoro- λ^6 -sulfane

R_f: 0.71 (4:1 hexanes:EtOAc); **^1H (600 MHz, CDCl_3):** δ = 8.16-8.15 (m, 4H), 7.90-7.89 (m, 4H), 4.60-4.44 (m, 2H), 3.39-3.35 (m, 1H), 3.27-3.23 (m, 2H), 3.07-3.02 (m, 1H), 2.81-2.72 (m, 2H), 2.64-2.51 (m, 4H), 2.27-2.23 (m, 1H), 2.19-2.14 (m, 1H); **^{19}F (282 MHz, CDCl_3):** δ = 84.75-82.71 (m, 2F), 59.72-59.18 (dd, 4F, $^2J_{\text{F-F}}$ = 145.0 Hz, $^2J_{\text{F-H}}$ = 5.2 Hz), 59.04-58.51 (dd, 4F, $^2J_{\text{F-F}}$ = 144.2 Hz, $^2J_{\text{F-H}}$ = 5.2 Hz), -63.35 (s, 6F); **$^{13}\text{C}\{^1\text{H}\}$ (151 MHz, CDCl_3):** δ = 137.9-137.6 (m), 137.0-136.3 (q, J = 33.1 Hz), 131.9, 131.7, 126.4-126.3 (q, J = 4.4 Hz), 125.8-120.4 (1, J = 273.6 Hz), 86.0, 85.3, 82.1-81.7 (p, J = 13.4 Hz), 81.5-81.1 (p, J = 13.6 Hz), 55.6, 48.7, 42.18-42.00 (p, J = 4.3 Hz), 41.99-41.87 (p, J = 4.4 Hz), 36.5, 35.4, 29.8-29.6 (p, J = 4.5 Hz), 28.5-28.3 (p, J = 4.5 Hz); **ATR-IR (ν_{max}):** 1405, 1308, 1176, 824, 789, 653 cm^{-1} ; **HRMS (m/z):** (ESI) calc'd for $\text{C}_{12}\text{H}_{12}\text{ClF}_8\text{O}_2\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 438.9834, found 438.9838.

3.5.30 Effect of Radical Scavengers and Photosensitizers.

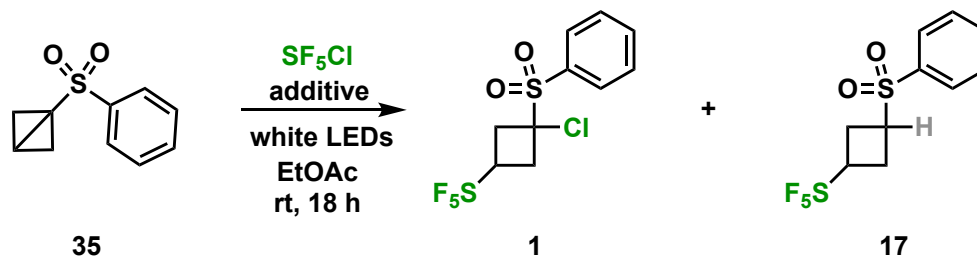


Table 3.14. Screening results from both radical scavenger and photosensitizer additives.

Entry	Additives (equiv.)	¹⁹ F Yield (%) 1 ^a	<i>anti:syn</i> ratio ^b	¹⁹ F Yield (%) 17 ^a	<i>cis:trans</i> ratio ^b
1	none	69	1:1	8	1:1
2	TEMPO (1.0)	-	-	-	-
3	BHT (1.0)	-	-	2	1.1:1
4	DHA (1.0)	16	1.1:1	35	1:1
5	O _{2(g)}	15	1:1	2	1.1:1
6	TEMPO (0.1)	3	1:1	0	-
7	BHT (0.1)	21	1:1	0	-
8	DHA (0.1)	32	1.1:1	18	1:1
9	Xanthone (0.1)	61	1:1	4	1.1:1
10	Benzophenone (0.1)	63	1:1	3	1.2:1
11	9-fluorenone (0.1)	54	1:1	8	1:1
12	Thioxanthene-9-one (0.1)	38	1.1:1	0	-

[a] Yields determined by ¹⁹F NMR. [b] Ratios determined by ¹⁹F NMR.

3.5.31 GC/MS Analysis of Crude Reaction Mixtures.

A reference standard for GC/MS experiments was prepared by dissolving approximately 1 mg in 1.0 mL HPLC grade MeOH. This solution was filtered through a syringe filter into a GC/MS vial and was then further diluted with an additional 0.5 mL MeOH. 0.2 μ L of the sample was injected at 60 $^{\circ}$ C.

Method: 60 $^{\circ}$ C to 300 $^{\circ}$ C over 23 min.

Column: Agilent DB-5ms, 30 m x 0.25 mm x 0.25 μ m (Capillary Tubing: Fused silica)

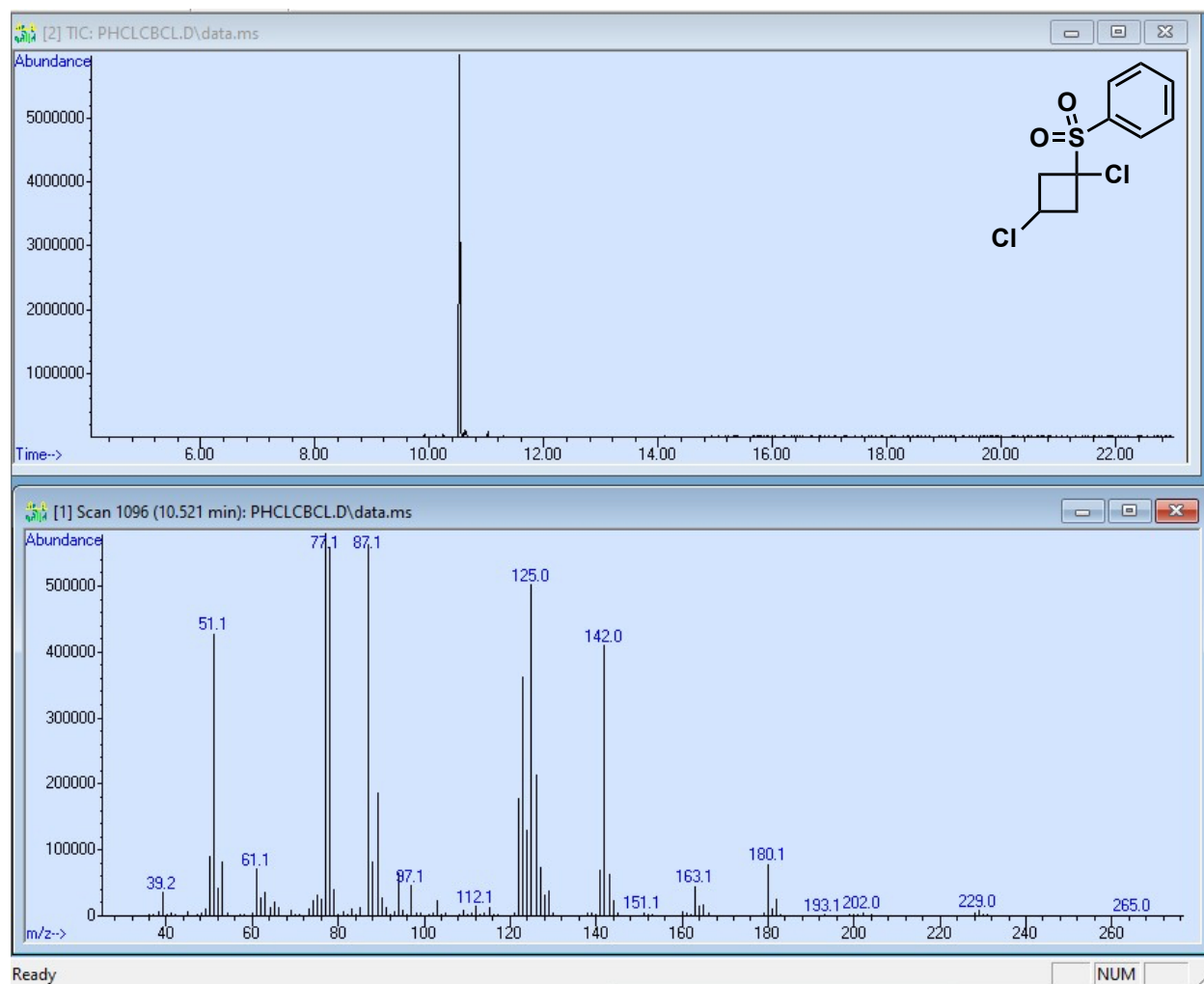


Figure 3.19. GC/MS spectrum of synthetic standard of compound 46.

LRMS: Found 51.1, 77.1, 87.1, 125.0 and 142.0 with $R_T = 10.503$ min.

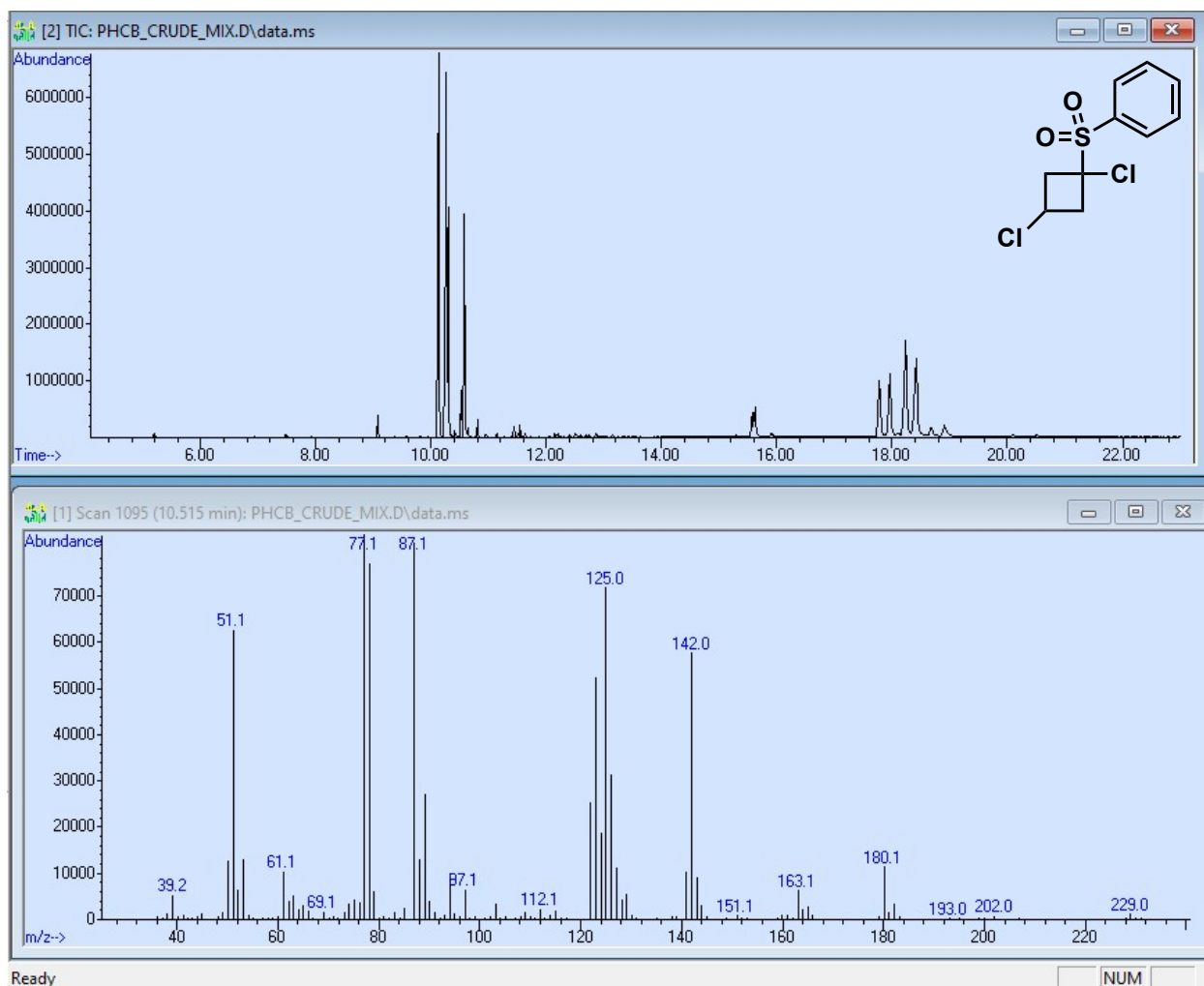


Figure 3.20. GC/MS spectrum of compound **46** detected in the crude reaction mixture.

LRMS: Found 51.1, 77.1, 87.1, 125.0 and 142.0 with $R_T = 10.515$ min.

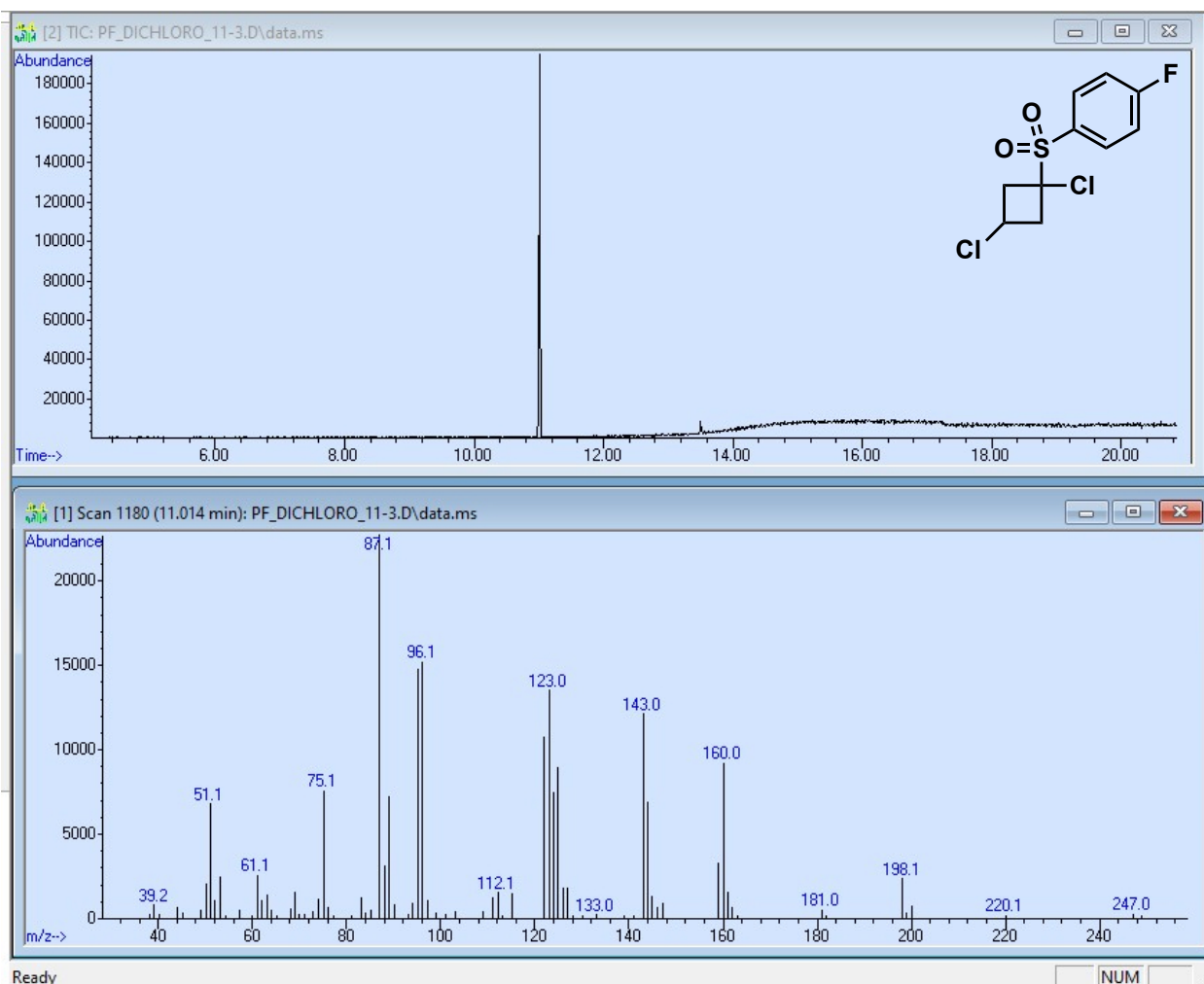


Figure 3.21. GC/MS spectrum of the synthetic standard compound **33**.

LRMS: Found 75.1, 87.1, 96.1, 123.0, 143.0, 160.0 and 247.0 with $R_T = 11.014$ min.

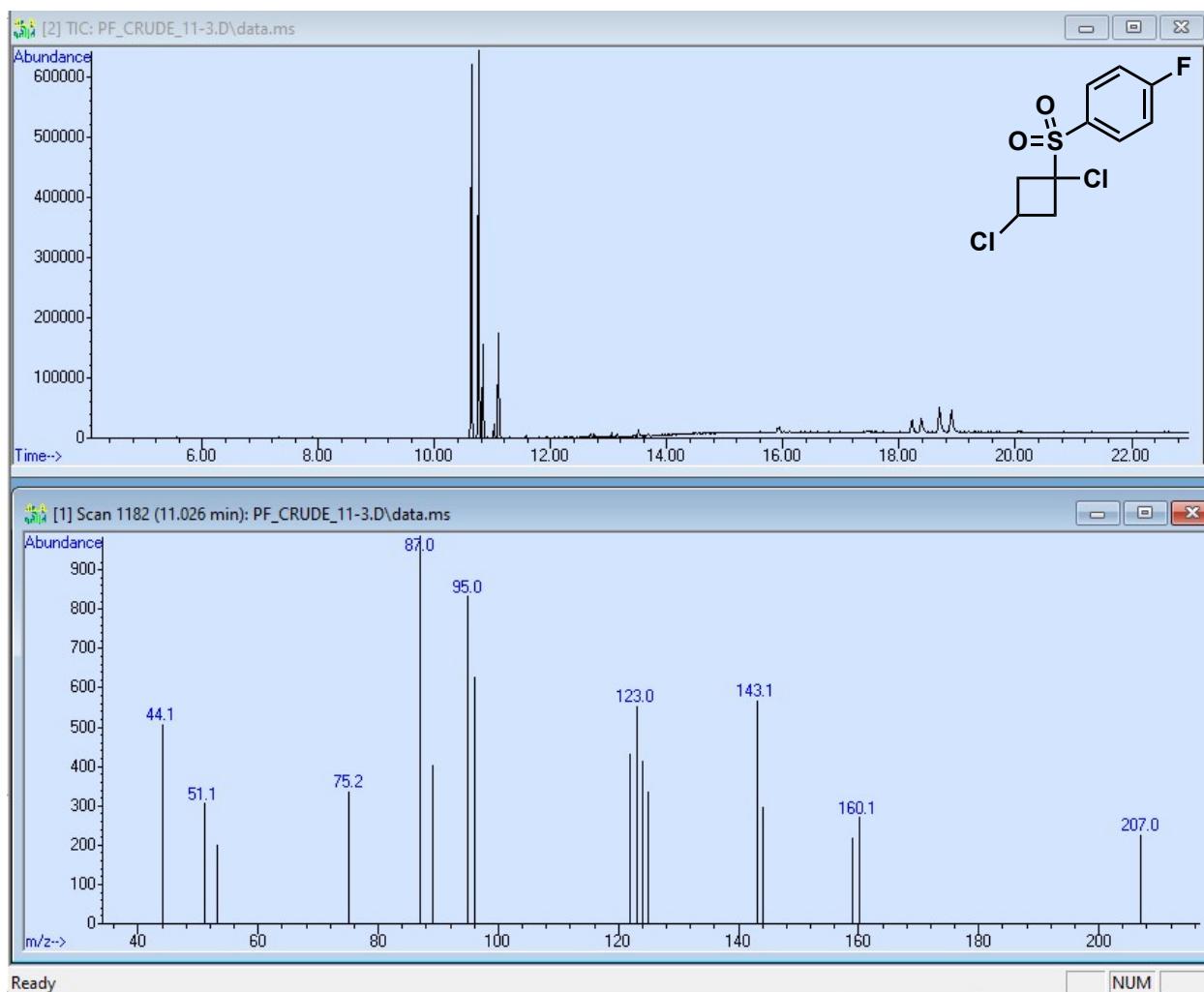
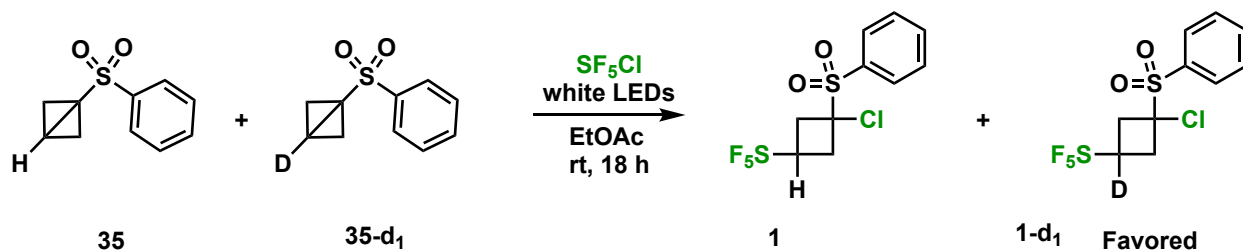


Figure 3.22. GC/MS spectrum of compound **33** detected in the crude reaction mixture.

LRMS: Found 75.2, 87.0, 96.1, 123.0, 143.1, and 160.0 with $R_T = 11.026$ min.

3.5.32 Competitive KIE Experiments.



A 20 mL oven-dried microwave vial equipped with a stir bar was charged with **35** (20 mmol, 10 equiv., 0.388 g) and **7-d₁** (20.0 mmol, 10 equiv., 0.390 g). The vial was crimped, then evacuated and backfilled with Ar three times. EtOAc (15 mL) was added followed by a solution of SF_5Cl in *n*-pentane (0.20 mmol, 1.0 equiv.). The Ar line was removed, and the resulting mixture was irradiated with a white LED Kessil lamp (Kessil A160WE Tuna Blue, maximum intensity) for 18 h at approx. 30 °C (estimated temperature based on proximity to the light source, ca. 2 cm). Upon completion, the solvent was removed *in vacuo*, and the crude residue was prepared for ^{19}F NMR analysis. The crude mixture was dissolved in 1.0 mL CDCl_3 . In an NMR tube was combined 0.1 mL crude reaction mixture, 10 μL internal standard (trifluorotoluene), and 0.4 mL CDCl_3 . During data collection, the relaxation delay was increased to 30 s, dummy scans were set to 0, and the O1P was set to +30 ppm. *The competitive KIE experiments were run in triplicate. See data below.*

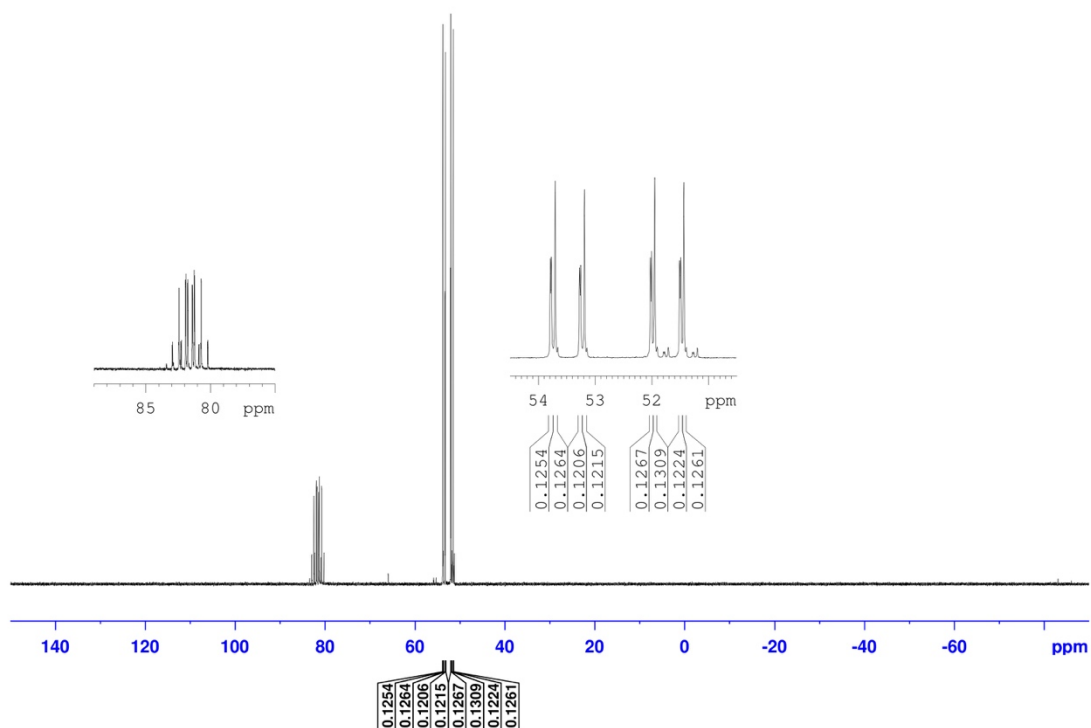
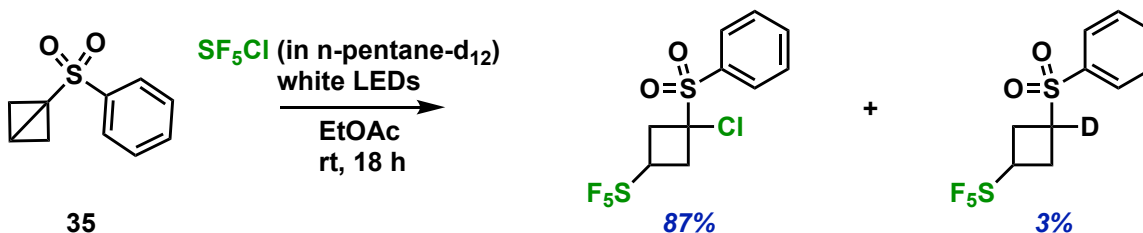


Figure 3.23. ^{19}F NMR spectrum of crude competitive KIE reaction mixture.

Table 3.15. Competitive KIE experimental results.

Entry	$[\text{P}_{\text{anti-H}} / \text{P}_{\text{anti-D}}]$	$[\text{P}_{\text{syn-H}} / \text{P}_{\text{syn-D}}]$
1	0.89	0.95
2	0.94	0.95
3	0.95	0.94
Average	0.93	0.95



SF_5Cl was synthesized on a 1.0 mmol scale and extracted into $n\text{-pentane-d}_{12}$ by the following procedure. To an oven dried 20 mL microwave vial equipped with a stir bar was added trichloroisocyanuric acid (1.05 g, 4.5 mmol, 4.5 equiv.), spray dried KF (532 mg, 9.0 mmol, 9.0 equiv.), sulfur (32.1 mg, 1.0 mmol, 1.0 equiv.), and MeCN (4.0 mL). The vial was wrapped with aluminum foil, sealed with a crimper, removed from the glovebox, and stirred vigorously at room temperature for 18 h. Upon completion, the mixture was cooled to $-78\text{ }^\circ\text{C}$, an Ar line was introduced, and $n\text{-pentane-d}_{12}$ (2.0 mL) was added *via* syringe. The mixture was allowed to warm to room temperature and stirred vigorously for 30 minutes. After that time, the mixture was allowed to settle and cooled to $-78\text{ }^\circ\text{C}$. The resulting SF_5Cl solution was collected by cannula transfer to a sealed microwave vial under Ar atmosphere; 1.6 mL of a 0.06 M SF_5Cl stock solution was obtained (10%). This solution was immediately used in the labelling experiment. *Note: in proof-of-concept experiments on this scale using $n\text{-pentane}$, higher concentration solutions of SF_5Cl could be obtained by multiple successive extractions.*

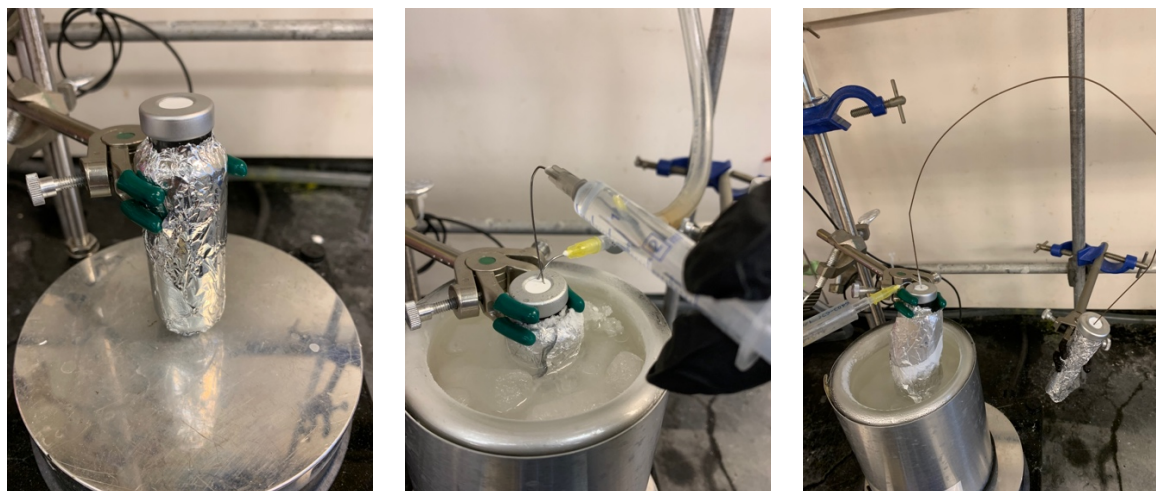


Figure 3.24. **Left.** Running the reaction overnight at room temperature. **Middle.** Addition of *n*-pentane- d_{12} to the reaction mixture at $-78\text{ }^{\circ}\text{C}$. **Right.** Cannula transfer of the stock SF_5Cl solution.

To an oven dried 2 mL microwave vial equipped with a stir bar was added **7** (14.6 mg, 0.075 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. EtOAc (0.75 mL) was added followed by a solution of SF_5Cl in *n*-pentane- d_{12} (1.5 mL, 0.09 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LED's (Kessil A160WE Tuna Blue, maximum intensity) for 16 hours (the vial was placed ca. 5 cm away from the light source). Upon reaction completion, the solvent was removed *in vacuo*, and the crude residue was prepared for NMR and GC-MS analysis. The crude mixture was taken up in 1.0 mL CHCl_3 . A 0.2 mL aliquot was taken for ^{19}F NMR analysis. Then, approximately 0.2 mL of the solution was transferred to a vial and concentrated *in vacuo*. The resulting oil was dissolved in 1.0 mL HPLC grade MeOH and filtered through a syringe filter into a GC/MS vial. This solution was further diluted with 0.5 mL MeOH, and the vial was sealed. 0.2 μL of the sample was injected into the instrument at $60\text{ }^{\circ}\text{C}$; the temperature was ramped to $300\text{ }^{\circ}\text{C}$ over 23 min.

LRMS: Found 54.2, 77.1, 125.1, 141.0, 196.1, and 323.0 with $R_T = 10.25$ min.

LRMS: Found 54.2, 77.1, 125.1, 141.0, 196.1, and 323.0 with $R_T = 10.58$ min.

3.5.33 UV-Vis Experiments.

A solution of 1:1 *n*-pentane and EtOAc was used as a blank. Then, 0.092 mmol of **35** (17.87 mg) was dissolved in 2.0 mL *n*-pentane and 2.0 mL EtOAc. This was then mixed thoroughly, and 2.0 mL of the solution was placed into a 1.0 cm pathlength cuvette for data collection (blue). 2 mL SF₅Cl solution in *n*-pentane (0.092 mmol, 0.046 M) was combined with 2 mL EtOAc in an air-free vessel (green). This solution was only open to air immediately prior to data collection to reduce any outgassing of SF₅Cl. Lastly, another solution of **35** was made with 0.092 mmol of **35** in 2 mL EtOAc and was combined with 2.0 mL of SF₅Cl solution in *n*-pentane (purple). These were combined immediately before data collection to reduce potential outgassing of SF₅Cl.

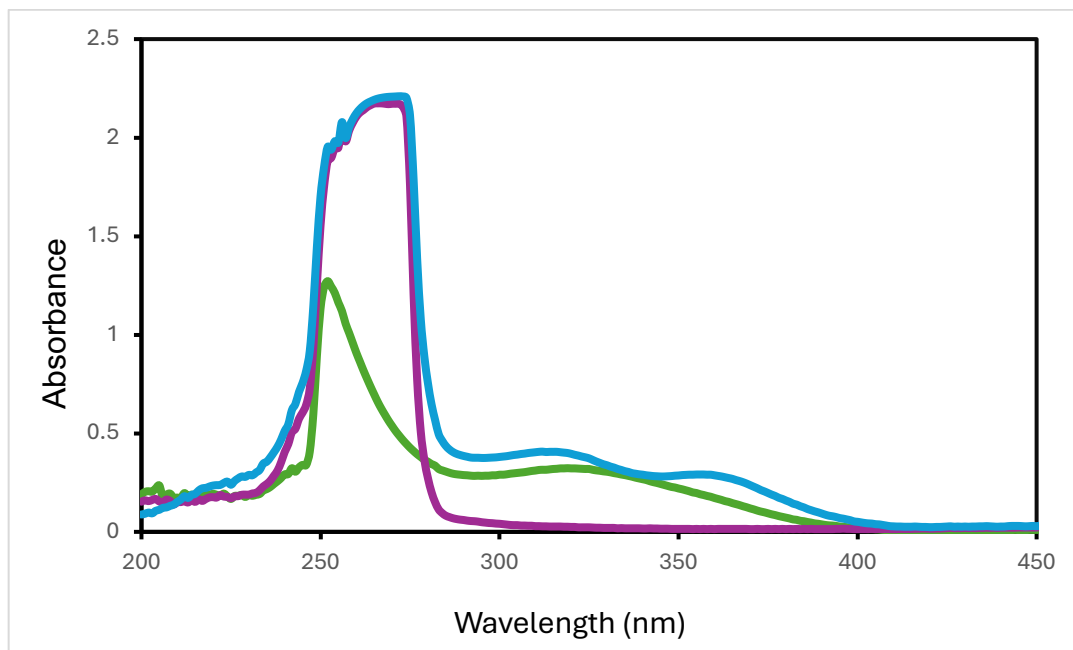
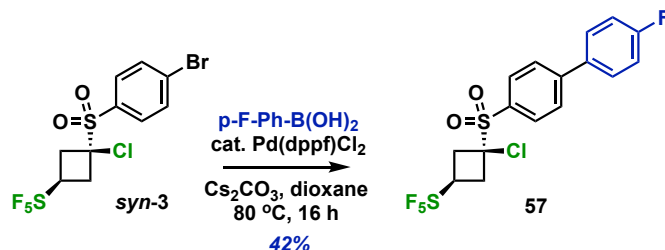


Figure 3.25. UV-vis absorption spectra. Green line: SF₅Cl stock solution in *n*-pentane. Blue line: Compound **35** in a 1:1 mixture of *n*-pentane:EtOAc. Purple line: SF₅Cl stock solution and compound **35** in *n*-pentane and EtOAc.

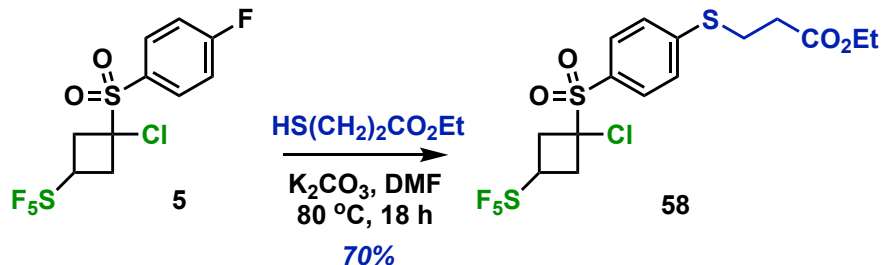
3.5.34 Post-Synthetic Transformations.



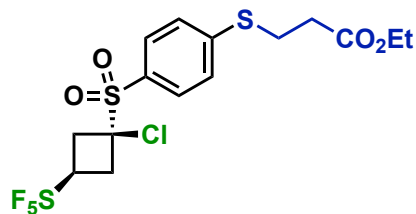
To an oven-dried microwave vial equipped with a stir bar was added **syn-3** (43.6 mg, 0.1 mmol, 1.0 equiv.), 4-fluorophenyl boronic acid (16.8 mg, 0.12 mmol, 1.2 equiv.), Pd(dppf)Cl₂ (7.3 mg, 0.01 mmol, 10 mol %), Cs₂CO₃ (97.7 mg, 0.3 mmol, 3.0 equiv.), and 1,4-dioxane (2.5 mL). The mixture was transferred to a pre-heated oil bath and stirred at 80 °C for 18 h. Upon completion, the reaction was cooled to room temperature, diluted with H₂O (3.0 mL) and EtOAc (2.0 mL). The aqueous layer was extracted with EtOAc (2 × 3.0 mL). The combined organic layers were washed with brine (3.0 mL), dried over MgSO₄, and concentrated. The crude residue was purified by preparative TLC using 9:1 hexanes:EtOAc to afford **57** as a white solid (18.9 mg, 42%).

Compound 57: (3-chloro-3-((4'-fluoro-[1,1'-biphenyl]-4-yl)sulfonyl)cyclobutyl)pentafluoro-λ⁶-sulfane

R_f: 0.76 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (400 MHz, CDCl₃):** δ = 8.05-8.03 (d, 2H, *J* = 8.5 Hz), 7.77-7.75 (d, 2H, *J* = 8.5 Hz), 7.62-7.59 (m, 2H), 7.22-7.18 (m, 2H), 4.84-4.73 (t, 1H, *J* = 9.4, 8.8, 5.7 Hz), 3.60-3.51 (m, 2H), 3.37-3.31 (m, 2H); **¹⁹F (376 MHz, CDCl₃):** δ = 82.66-81.11 (p, 1F, 2*J*_{F-F} = 145.5 Hz), 51.97-51.56 (dd, 4F, 2*J*_{F-F} = 145.5 Hz, 3*J*_{F-H} = 5.7 Hz), -112.43 - -112.51 (m, 1F); **¹³C (151 MHz, CDCl₃):** δ = 164.3-162.6 (d, *J* = 250.2 Hz), 147.1, 134.85-134.83 (d, *J* = 3.1 Hz), 131.5, 131.1, 129.3-129/2 (d, *J* = 8.9 Hz), 127.6, 116.3-116.2 (d, *J* = 21.0 Hz), 73.4, 68.8-68.4 (p, *J* = 16.7 Hz), 41.3-41.2 (p, *J* = 3.8 Hz); **HRMS (*m/z*):** (ESI) Not found.

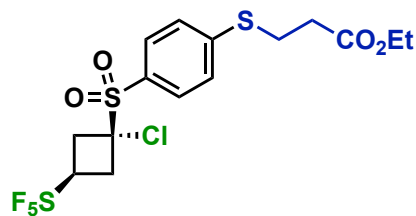


To an oven-dried culture tube equipped with a stir bar was added **5** (34 mg, 0.09 mmol, 1.0 equiv.) and K_2CO_3 (25 mg, 0.18 mmol, 2.0 equiv.). DMF (0.5 mL) was added *via* syringe followed by ethyl 3-mercaptopropanoate (23 μL , 0.18 mmol, 2.0 equiv.). The vial was sealed with a cap and mixture was stirred at 80 $^\circ\text{C}$ open to air for 18 h. Upon completion, the reaction was diluted with EtOAc (2.0 mL) and transferred to a separatory funnel. The organic layer was washed with water (3 $\times$ 3.0 mL), then brine (2.0 mL). The organic layer was dried over Na_2SO_4 and concentrated. The resulting crude oil was purified by column chromatography eluting with 4:1 Hexanes:EtOAc affording a mixture of isomers as a pale-yellow oil (31 mg, 70%). The *syn* and *anti*-isomers were separated by preparative TLC using 9:1 hexanes:EtOAc.



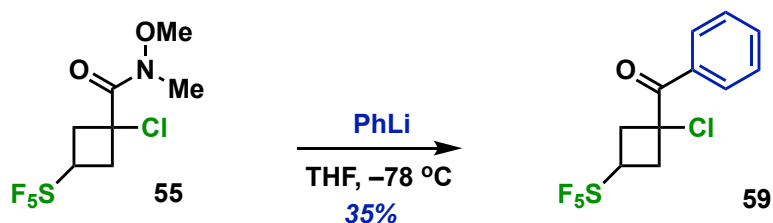
Compound syn-58: Ethyl 3-(((4-((-1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)sulfonyl)phenyl) thio) propanoate.

R_f: 0.3 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (400 MHz, CDCl₃):** δ = 7.86-7.84 (d, 2H, J = 8.6 Hz), 7.43-7.41 (d, 2H, J = 8.6 Hz), 4.78-4.71 (t, 1H, J = 9.6, 8.6, 5.3 Hz), 4.20-4.16 (q, 2H, J = 7.2 Hz), 3.53-3.49 (m, 2H), 3.33-3.29 (m, 4H), 2.73-2.70 (t, 2H, 7.2 Hz), 1.29-1.26 (t, 3H, J = 7.2 Hz); **¹⁹F (376 MHz, CDCl₃):** δ = 82.93-80.86 (p, 1F, J = 144.3 Hz), 52.02-51.49 (dd, 4F, J = 144.3, 5.3 Hz); **¹³C (151 MHz, CDCl₃):** δ = 171.1, 147.3, 131.2, 128.6, 126.4, 73.4, 68.8-68.4 (p, J = 16.9 Hz), 61.1, 41.3-41.2 (p, J = 4.2 Hz), 33.6, 26.7, 14.2; **ATR-IR (v_{max}):** 1756, 1700, 1528, 1350, 1279, 1256, 1148, 847, 832, 791 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₅H₁₉ClF₅O₄S₃⁺ [M+H]⁺ 489.0049, found 489.0052.

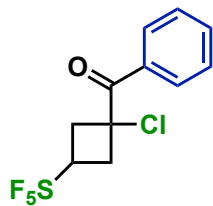


Compound *anti*-**58**: Ethyl 3-(((4-((-1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)sulfonyl)phenyl) thio) propanoate (*anti* isomer).

R_f: 0.25 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (400 MHz, CDCl₃)**: δ = 7.82-7.80 (d, 2H, J = 8.6 Hz), 7.43-7.41 (d, 2H, J = 8.6 Hz), 4.77-4.67 (tpp, 1H, J = 9.6, 7.8, 5.1 Hz), 4.20-4.16 (q, 2H, J = 7.1 Hz), 3.83-3.79 (m, 2H), 3.31-3.29 (t, 2H, J = 7.1 Hz), 2.76-2.70 (m, 4H), 1.28-1.26 (t, 3H, J = 7.1 Hz); **¹⁹F (376 MHz, CDCl₃)**: δ = 82.23-80.17 (p, 1F, J = 144.4 Hz), 53.79-53.26 (dd, 4F, J = 144.4, 5.1 Hz); **¹³C (151 MHz, CDCl₃)**: δ = 171.1, 147.3, 131.2, 128.6, 126.4, 73.4, 68.8-68.4 (p, J = 16.6 Hz), 61.1, 41.65-41.15 (p, J = 3.9 Hz), 33.6, 26.7, 14.2; **ATR-IR (v_{max})**: 1731, 1331, 1266, 1159, 1079, 841, 800 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₅H₁₉ClF₅O₄S₃⁺ [M+H]⁺ 489.0049, found 489.0052.

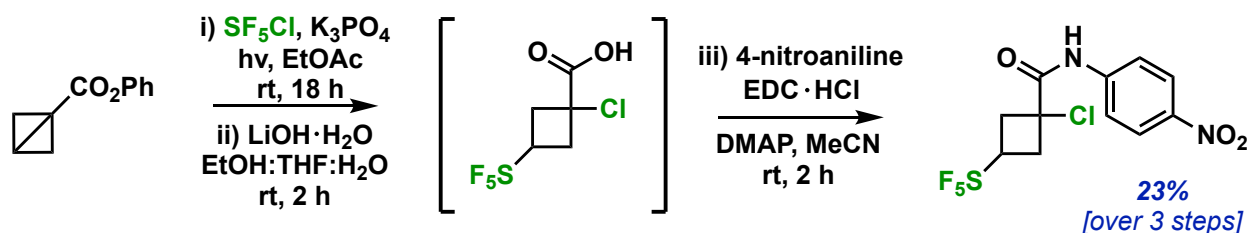


The arylation of Weinreb amide **55** was conducted by telescoping the crude mixture after SF_5Cl addition: Following Method D, the crude reaction mixture was passed through a silica plug and concentrated in a round bottom flask without further purification. A stir bar was added, and the flask was sealed with a septum. The crude mixture containing **55** (56 mg, approx. 85% estimated purity of starting material) was dissolved in anhydrous THF (2.0 mL, 0.1 M) and cooled to -78°C in a dry ice acetone bath. PhLi (0.45 mL, 0.9 mmol, 4.5 equiv.) was added dropwise at that temperature, and the reaction stirred overnight at rt. Upon completion, the reaction was quenched with sat. NH_4Cl , extracted with EtOAc (3×5 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude reaction mixture was purified using preparative TLC (using 6:1 hexanes:EtOAc) to give approx. 18 mg of the arylated product as a mixture of isomers (35%, clear oil).



Compound *anti*-58: (1-chloro-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutyl)(phenyl)methanone

R_f: 0.40 (6:1 hexanes:EtOAc), vis: UV (254 nm); **¹⁹F (376 MHz, CDCl₃):** δ = 83.53-81.47, 53.89-52.82; **ATR-IR (ν_{max}):** 1653, 1559, 901, 719 cm⁻¹.



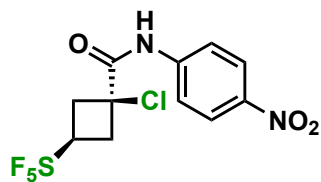
Following general procedure E, four identical pentafluorosulfanylation reactions were set up in parallel as follows. A 0.1 M stock solution of **60** in anhydrous EtOAc was prepared under Ar atmosphere. To an oven-dried 5 mL microwave vial equipped with a stir bar was added K₃PO₄ (21.2 mg, 0.1 mmol, 1.0 equiv.). The vial was crimped, and an Ar atmosphere was established. Then, 1.0 mL of the **60**-stock solution (0.1 mmol, 1.0 equiv.), and SF₅Cl in *n*-pentane (0.3 mmol, 3.0 equiv.) were added *via* syringe. The reactions were stirred vigorously under white LED irradiation for approximately 18 h. Upon completion, the four reaction mixtures were combined and filtered through a Celite/silica plug. The solvent was removed *in vacuo*, and the crude material was carried forward without further purification.

^{19}F (282 MHz, CDCl_3): δ = 53.44-52.90 (dd, 4F, J = 145.5, 5.6 Hz), 52.97-52.46 (d, 4F, J = 144.8 Hz), 52.61-52.09 (d, 4F, J = 145.0 Hz), 52.52-51.99 (dd, 4F, J = 145.7, 5.6 Hz). *Note: shifts of the apical F were not assigned due to significant overlap.*

To the crude yellow oil was added a stir bar and EtOH (1.3 mL), THF (1.3 mL), and DI H_2O (1.3 mL). $\text{LiOH}\cdot\text{H}_2\text{O}$ (18 mg, 0.44 mmol, 1.1 equiv.) was added in one portion, and the mixture was stirred open to air at rt for 2 h or until TLC indicated consumption of the starting material. Upon completion, 5.0 mL 1M HCl was added dropwise, and the contents of the flask were transferred to a separatory funnel. The acidified aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was taken up in 5.0 mL EtOAc and sat. NaHCO_3 was added until the pH 8 was reached. The EtOAc layer was discarded, then conc. HCl was added dropwise until the pH reached between 0–1. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford the crude carboxylic acid was a pale-yellow oil (68 mg), which was used in the next step without further purification.

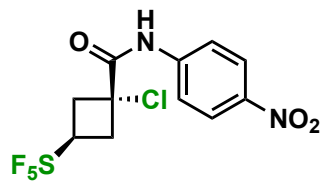
^1H (300 MHz, CDCl_3): δ = 8.19 (br s, 2H), 4.88-4.77 (ttp, 1H, J = 9.5, 8.7, 5.3 Hz), 4.53-4.42 (ttp, 1H, J = 9.5, 8.7, 5.4 Hz), 3.55-3.48 (m, 2H), 3.40-3.27 (m, 4H), 2.93-2.88 (m, 2H); **^{19}F (282 MHz, CDCl_3):** δ = 82.93-81.38 (p, 1F, 146.9 Hz), 82.76-81.21 (p, 1F, J = 145.7 Hz), 53.21-52.81 (dd, 4F, J = 146.9, 5.3 Hz), 52.22-51.81 (dd, 4F, J = 145.7, 5.4 Hz).

To the resulting crude carboxylic acid (assuming 0.26 mmol) were added 4-nitroaniline (36.0 mg, 0.26 mmol, 1.0 equiv.), EDC·HCl (54.8 mg, 0.29 mmol, 1.1 equiv.), and DMAP (3.6 mg, 0.03 mmol, 0.1 equiv.). The flask was sealed with a septum, and Ar atmosphere was established. Anhydrous MeCN (2.6 mL, 0.1M) was added via syringe and the mixture was stirred at rt for 2 h. Upon completion, the solvent was removed *in vacuo* and the resulting yellow oil was loaded directly onto a short column (SiO₂) equilibrated with 3:1 hexanes:EtOAc. The product was eluted using 3:1 hexanes:EtOAc and was obtained as a mixture of isomers (35.1 mg, off-white solid, 23 %). The resulting mixture of *anti* and *syn* isomers was further purified to afford pure **syn-61** and **anti-61** using preparative TLC eluting with 2:1 hexanes:EtOAc. *Note: The products are only sparingly soluble in CDCl₃, C₆D₆, and CD₃CN.*



Compound syn-61: 1-chloro-*N*-(4-nitrophenyl)-3-(pentafluoro-λ⁶-sulfaneyl)cyclobutane-1-carboxamide

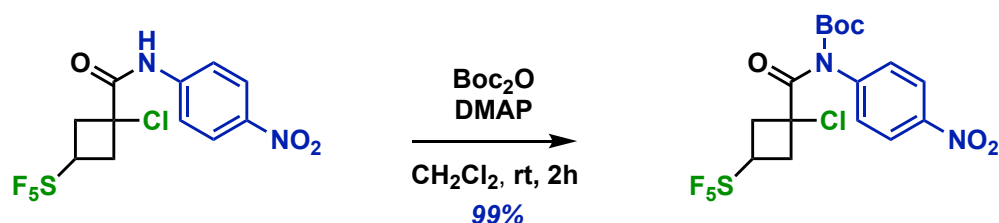
R_f: 0.40 (3:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CD₃CN):** δ = 9.10 (br s, 1H), 8.23-8.22 (d, 2H, *J* = 9.2 Hz), 7.85-7.84 (d, 2H, *J* = 9.2 Hz), 4.64-4.56 (tpp, 1H, *J* = 11.9, 7.7, 6.0 Hz), 3.55-3.51 (m, 2H), 3.30-3.26 (m, 2H); **¹⁹F (282 MHz, CD₃CN):** δ = 83.45-81.92 (p, 1F, *J* = 143.9 Hz), 51.56-51.57 (dd, 4F, *J* = 143.9, 5.5 Hz); **¹³C{¹H} (151 MHz, CD₃CN):** δ = 167.9, 143.97, 143.88, 120.0, 69.5-69.1 (p, *J* = 15.0 Hz), 58.5, 43.0-42.9 (p, *J* = 4.1 Hz); **ATR-IR (ν_{max}):** 3287, 2923, 1673, 1513, 1333, 822 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₁₁H₉ClF₅N₂O₃S⁻ [M-H]⁻ 378.9948, found 378.9964.



Compound anti-61: 1-chloro-*N*-(4-nitrophenyl)-3-(pentafluoro- λ^6 -sulfaneyl)cyclobutane-1-carboxamide

R_f: 0.27 (3:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CD₃CN):** δ = 8.98 (br s, 1H), 8.23-8.21 (d, 2H, J = 9.2 Hz), 7.86-7.85 (d, 2H, J = 9.2 Hz), 5.08-5.01 (tpp, 1H, J = 11.6, 8.2, 5.9 Hz), 3.61-3.56 (m, 2H), 3.00-2.95 (m, 2H); **¹⁹F (282 MHz, CD₃CN):** δ = 83.62-82.10 (p, 1F, J = 144.2 Hz), 52.61-52.21 (dd, 4F, J = 144.2, 5.6 Hz); **¹³C{¹H} (151 MHz, CD₃CN):** δ = 163.4, 144.0, 143.9, 124.7, 120.0, 70.2-70.0 (p, J = 14.7 Hz), 61.1, 41.43-41.37 (p, J = 4.1 Hz); **ATR-IR (v_{max}):** 3286, 2923, 1673, 1514, 1334, 823 cm⁻¹; **HRMS (m/z):** (ESI) calc'd for C₁₁H₉ClF₅N₂O₃S⁻ [M-H]⁻ 378.9948, found 378.9963.

The resulting amide (**61**) also smoothly underwent Boc protection under standard conditions.



To a 2.0 mL microwave vial equipped with a stir bar was added **61** (8 mg, 0.02 mmol, 1.0 equiv.), DMAP (0.4 mg, 20 mol%), and Boc₂O (9.6 μL, 0.04 mmol, 2.0 equiv.), followed by CH₂Cl₂ (0.2 M). The reaction was stirred open to air at rt for 2 h (until TLC indicated SM consumption). The mixture was concentrated *in vacuo*, and the crude residue was purified by preparative TLC (using 9:1 Hexanes:EtOAc) to yield the Boc-protected product as a clear oil (10 mg, 99%, mixture of isomers).

R_f: 0.52 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃, mixture of isomers)**: δ = 8.30-8.29 (m, 2H), 7.31-7.29 (m, 2H), 4.83-4.74 (m, 1H), 4.34-4.28 (m, 1H), 3.73-3.64 (m, 4H), 3.38-3.34 (m, 2H), 3.05-3.01 (m, 2H), 1.41 (s, 9H), 1.39 (s, 1H); **¹⁹F (282 MHz, CDCl₃, mixture of isomers)**: δ = 83.92-81.56 (m, 2F), 53.55-53.02 (dd, 4F, *J* = 145.8, 5.8 Hz), 52.68-52.14 (dd, 4F, *J* = 145.3, 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃, mixture of isomers)**: δ = 171.8, 170.7, 150.7, 150.6, 147.3, 144.3, 128.9, 124.6, 124.5, 85.5, 85.2, 70.0-69.8 (p, *J* = 15.4 Hz), 69.0-68.8 (p, *J* = 16.1 Hz), 62.9, 60.2, 43.5-43.4 (p, *J* = 3.7 Hz), 42.8-42.7 (p, *J* = 3.9 Hz), 27.63, 27.61; **ATR-IR (ν_{max})**: 1755, 1698, 1528, 1350, 1266, 1151, 832, 735, 704 cm⁻¹.

3.5.35 SC-XRD.

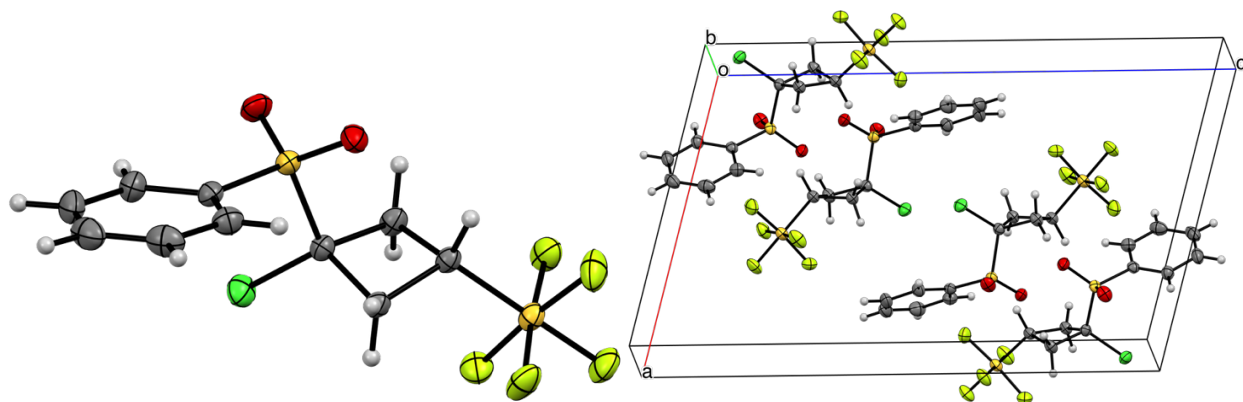


Figure 3.26. Molecular structure and packing of **1** ($P2_1/n$).

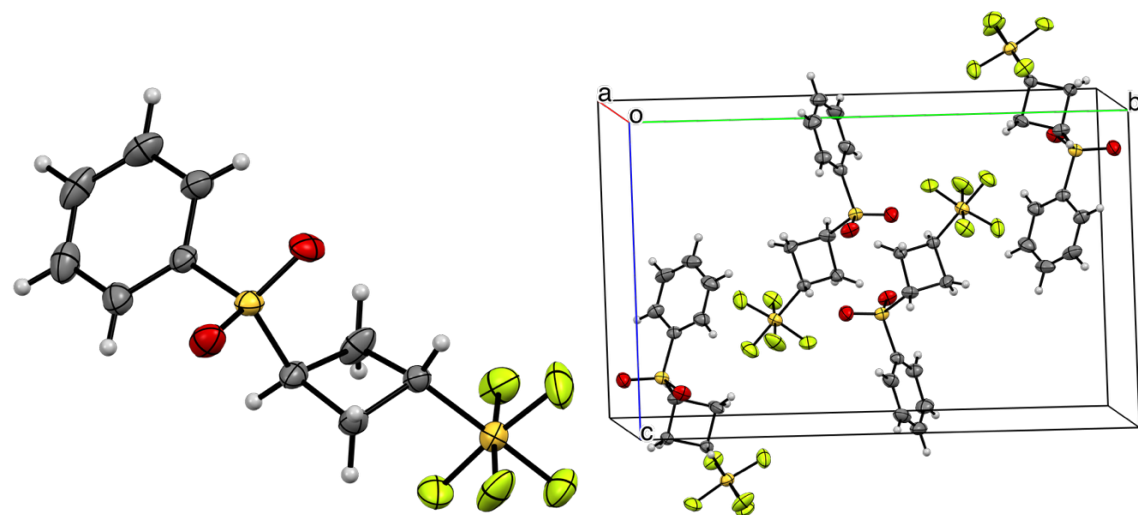


Figure 3.27. Molecular structure and packing of **trans-17** ($P2_1/c$).

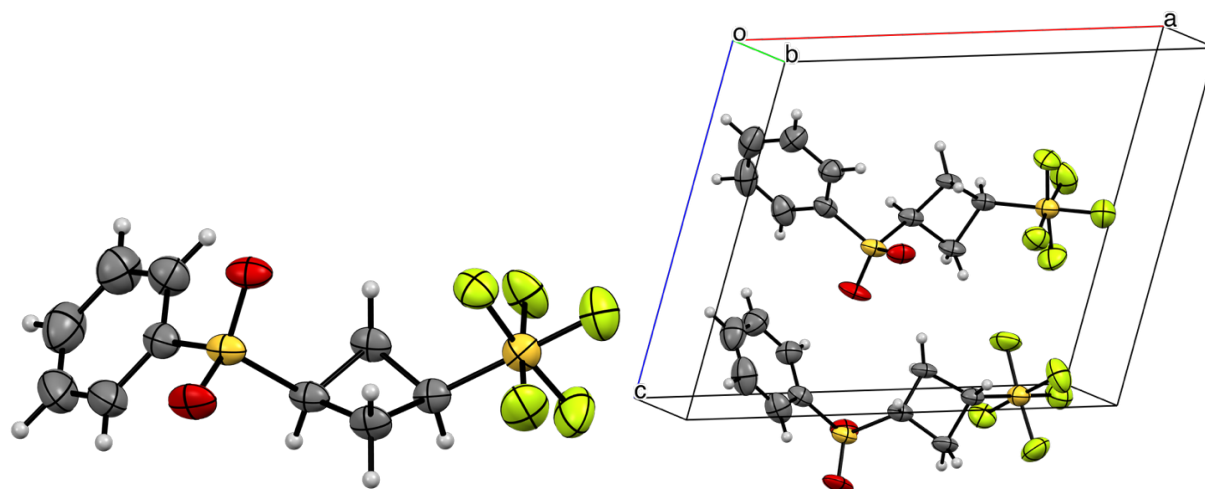


Figure 3.28. Molecular structure and packing of *cis*-17 (*Pc*).

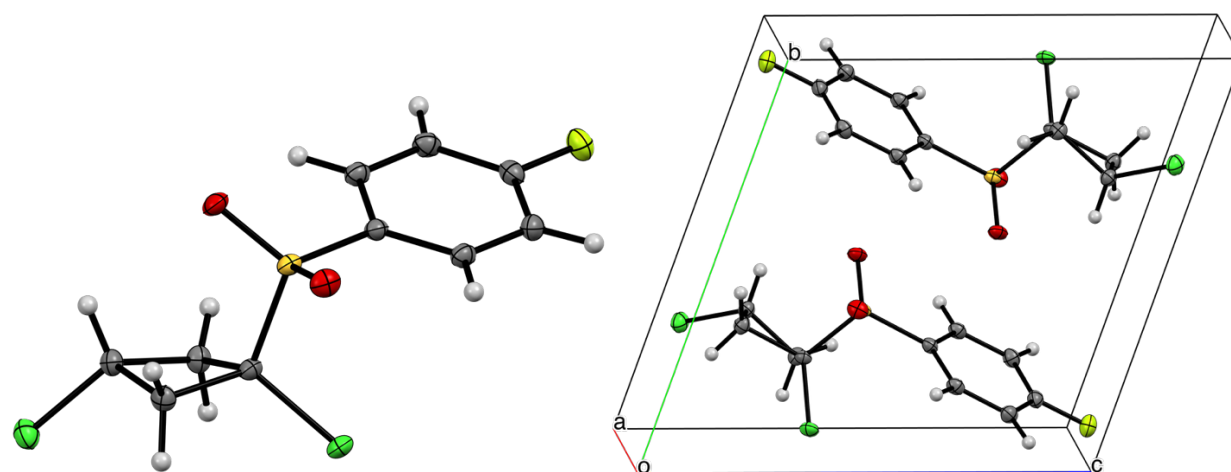


Figure 3.29. Molecular structure and packing of *syn*-33 (*P*-1).

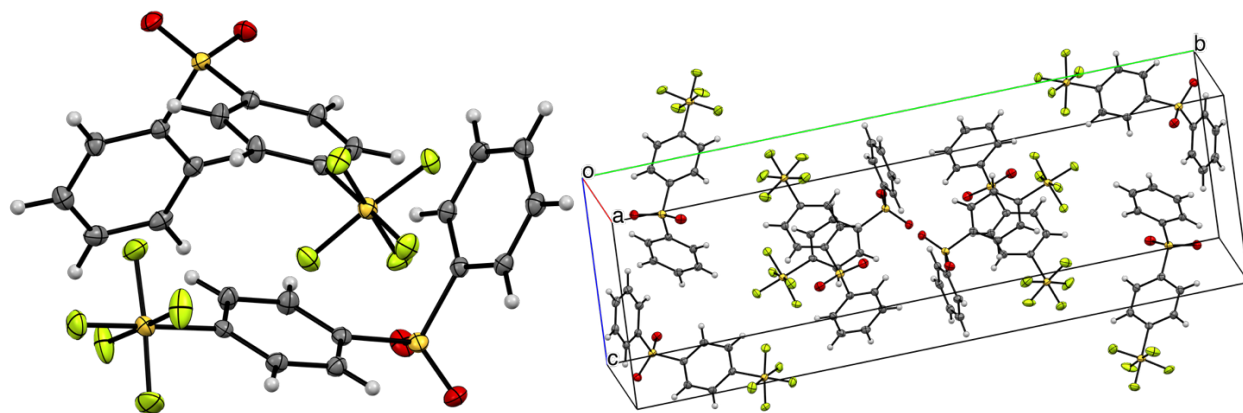


Figure 3.30. Molecular structure and packing of **44** ($P2_1/c$).

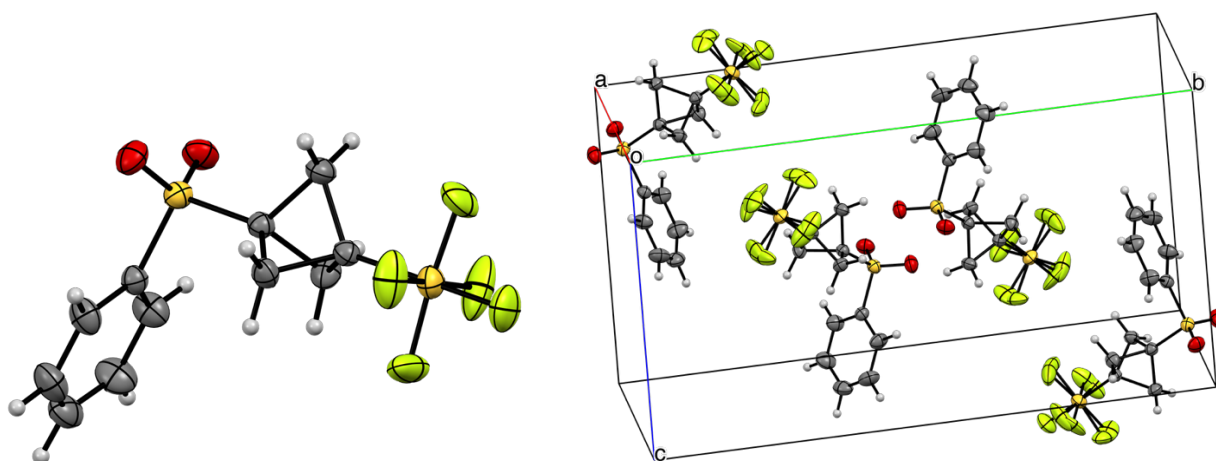


Figure 3.31. Molecular structure and packing of **45** ($P2_1/c$).

The molecular structure of compounds *cis*-**41** and *trans*-**41** were not disclosed in the associated publication but are included here for the sake of completion. The structure of *cis*-**41** was collected as a part of the Zürich School of Crystallography by Dr. Michael Wörle and is not of suitable quality for publication. The crystalline sample was determined to be twinned, causing the resulting model to be plagued by high intensity statistics and enlarged ellipsoids. Nonetheless, the model still establishes the relative stereochemistry and selectivity of the reduction step.

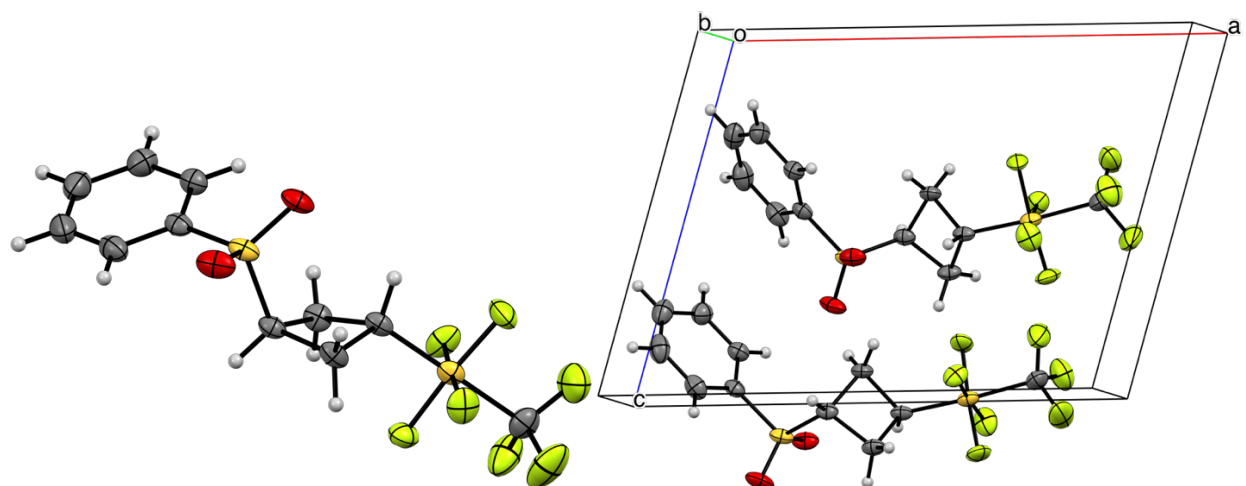


Figure 3.32. Molecular structure and packing of *trans*-**41** (*Pc*).

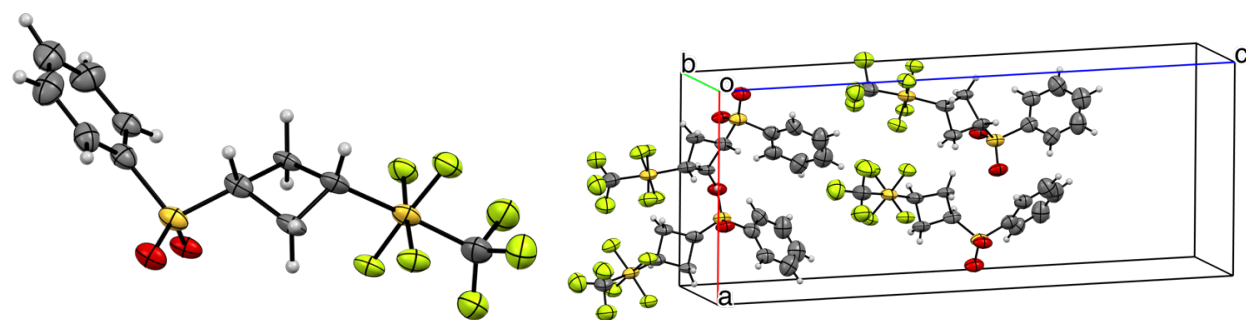


Figure 3.33. Molecular structure and packing of *cis*-**41** (*Pca*2₁). Note: Ellipsoids displayed at the 30% probability level for the molecular structure.

For additional experimental/computational details and NMR spectra, please refer to the Supporting Information of the associated publication: Kraemer, Y.; Buldt, J. A.; Kong, W.-Y.; Stephens, A. M.; Ragan, A. N.; Park, S.; Haidar, Z. C.; Patel, A. H.; Shey, R.; Dagan, R.; McLoughlin, C. P.; Fettingner, J. C.; Tantillo, D. J.;* Pitts, C. R.* *Angew. Chem. Int. Ed.* **2024**, 63, e202319930.

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Chapter 4: Strain-Release Trifluoromethoxylation and Pentafluorosulfanoylation of [1.1.0]Bicyclobutanes: Expanded Access to Fluorinated Cyclobutane Hybrid Bioisosteres

4.1 Introduction.

Recently, our group reported synthetic strategies for pentafluorosulfanylation and tetrafluoro(trifluoromethyl)-sulfanylation of [1.1.0]bicyclobutanes (BCBs) to access a collection of SF₅- and CF₃SF₄-containing cyclobutanes (CBs).¹¹⁵ In these specific instances we found that the added “strain release” associated with BCB ring opening aids in overcoming an apparent radical polarity mismatch that is a known limitation in functionalization of the corresponding alkenes.¹¹⁶ Considering BCBs also behave as spring-loaded electrophiles,¹¹⁷ we posited that these substrates may be suitable reaction partners to engage with weak or metastable fluorinated nucleophiles (e.g., OCF₃¹¹⁸ or OSF₅¹¹⁹ anions), which similarly can pose limitations in certain addition or substitution reactions.¹²⁰ This would enable use of BCBs as a rapid entryway to a larger variety of fluorinated CB building blocks to facilitate medicinal chemistry campaigns.

Herein, we describe a method for trifluoromethoxylation of BCBs to access OCF₃-containing CBs using AgOCF₃ and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH). The logic also extends to pentafluorosulfanoylation of BCBs using AgOSF₅ to access heretofore unknown OSF₅-containing CBs, albeit in lower yields. Accordingly, we underscore that BCBs are candidates for divergent syntheses of SF₅-, CF₃SF₄-, OCF₃-, and OSF₅-containing CBs, enabling structural comparisons, synthetic studies, and evaluation of such moieties as “hybrid bioisosteres” (Figure 4.1).¹²¹

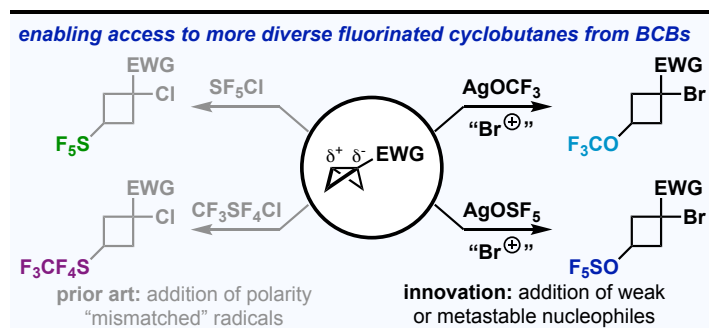


Figure 4.1. Trifluoromethoxylation and pentafluorosulfanoylation of BCBs enables more divergent access to fluorinated CBs.

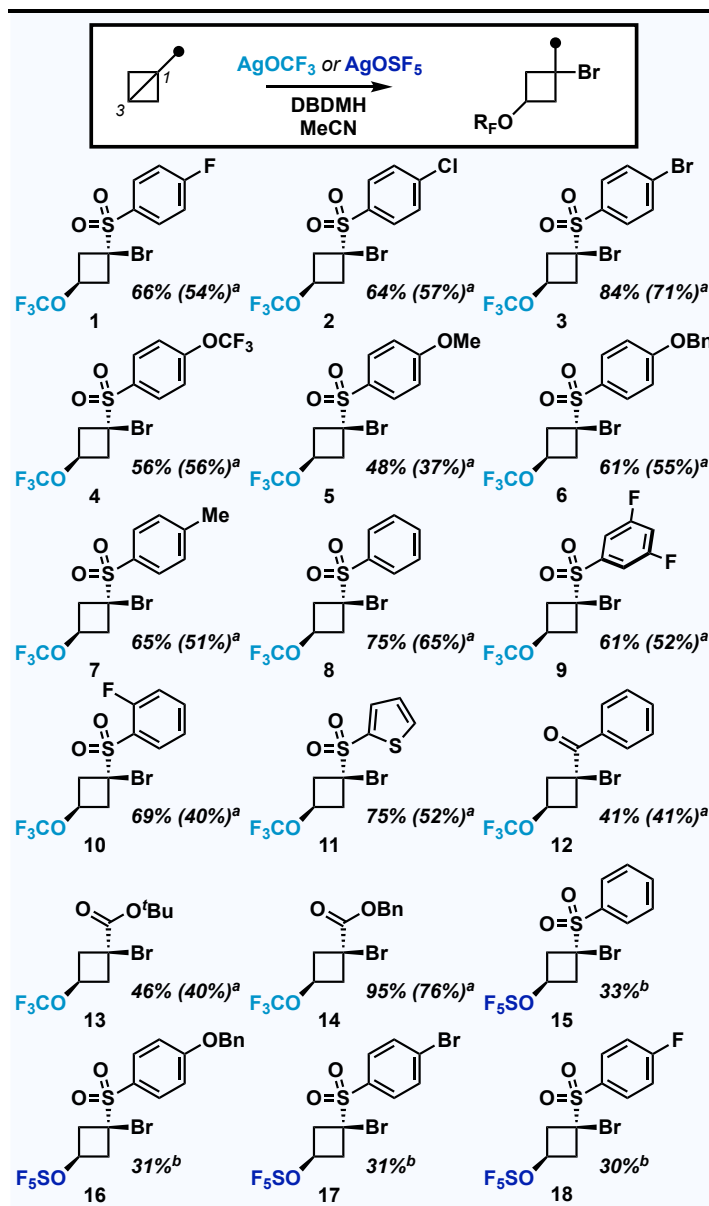
4.2 Results and Discussion.

We began screening for trifluoromethoxylation conditions using 1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane as a model substrate,¹²² AgOCF₃,¹²³ and various electrophilic halogenating reagents. We found that trifluoromethoxylation coupled with bromination (i.e., to trap the putative CB anion intermediate) proceeded smoothly, while iodination and chlorination attempts resulted in poor yields (see Section 4.5 for details). Upon further optimization, we found that stirring the model BCB substrate with 1.5 equiv. DBDMH and 3.0 equiv. AgOCF₃ at room temperature in MeCN overnight provided OCF₃-containing CB **1** in 66% yield as a single regioisomer and diastereomer by ¹⁹F NMR analysis (Table 4.1).

With optimized conditions in hand, we briefly explored the scope of the reaction. Strain-release trifluoromethoxylation proceeded smoothly to access a variety of arylsulfone-containing CBs with electron withdrawing (**1–4**), electron donating (**5–7**), or electron neutral (**8**) substituents in the *para* position, as well as products with fluorine atoms in the *meta* (**9**) or *ortho* (**10**) positions (Table 4.1). The reaction conditions also tolerate certain heteroaryl sulfones, e.g., providing access to thiophene-containing product **11**. However, we found that neither alkylsulfones nor indole-containing sulfones were

compatible; reactions with these substrates tended to result in complex mixtures. Overall, isolated yields for arylsulfone-containing OCF₃-CB products ranged from 37-71%.

Table 4.1. Substrate scope. ¹⁹F NMR yields reported with isolated yields in parentheses. ^aConditions: BCB (0.2 mmol), AgOCF₃ (0.6 mmol), and DBDMH (0.3 mmol) stirred in MeCN at rt for 16 h under Ar. ^bConditions: BCB (0.4 mmol), AgOSF₅ (0.2 mmol) and DBDMH (0.3 mmol) stirred in MeCN at 60 °C for 16 h under Ar.



Additionally, ketone- and ester-based BCBs proved to be suitable candidates for strain-release trifluoromethoxylation. Specifically, phenyl ketone **12** was accessible in 41% isolated yield, and both *tert*-butyl and benzyl esters **13** and **14** were isolated in 40% and 76% yield, respectively. On the other hand, amide-, sulfoxide-, and Bpin-containing BCBs were not tolerated under the specified reaction conditions.

Beyond varying the BCB substrate, we found that replacing AgOCF₃ with AgSCF₃ does not result in favorable trifluoromethylthiolation of BCBs, by analogy. Yet, AgOSF₅ – now accessible without needing to handle a hazardous gas reagent (i.e., SOF₄)¹²⁴ – could be used to install the more elusive OSF₅ group onto a CB using similar strain-release logic. After additional screening, we arrived at modified reaction conditions that afforded arylsulfone-containing OSF₅-CBs **15–18**, albeit in only 30-33% yield by ¹⁹F NMR analysis in our best cases (Table 4.1). Under these conditions, the BCB is completely consumed, indicating that other deleterious pathways compete with the desired pentafluorosulfanoylation (see Section 4.5 for details). We attribute reduction in yield and reaction efficacy with AgOSF₅ to the decrease in nucleophilicity and increase in steric hindrance of the OSF₅ anion relative to the OCF₃ anion.¹²⁵ Nonetheless, this approach provided access to the first OSF₅-CBs in sufficient quantities for initial synthetic and structural studies.

Also, note that the *syn* diastereoselectivity for both trifluoromethoxylation and pentafluorosulfanoylation of BCBs was confirmed through single-crystal X-ray diffraction (SC-XRD) and is consistent with what has been reported for other nucleophilic additions to BCBs (Figure 2).¹²⁶ To our knowledge, the only structure of an OSF₅-containing organic molecule characterized previously by SC-XRD is an aryl–OSF₅ compound, according to the CSD. In the OSF₅-CB compound **15**, we found that the C3–

O–S angle is 120.9(1)°, the C–O distance is 1.451(3) Å, and the O–S distance is 1.593(2) Å; these features are similar to what has been observed for the C(sp²)-bound OSF₅ group.¹²⁷

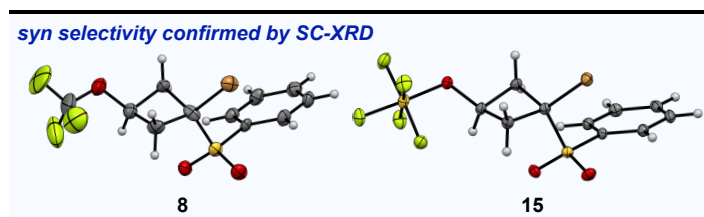


Figure 4.2. Crystal structures for **8** and **15** determined by SC-XRD (displacement ellipsoids depicted at 50 % probability level).

Subsequently, we examined the compatibility of select OCF₃- and OSF₅-CB products with metal boride reduction conditions,¹²⁸ i.e., to achieve a formal hydrofunctionalization of BCBs with OCF₃ and OSF₅ anions. Ultimately, we found that **6** and **16** could be converted to **19** and **20** in good yields upon stirring with 50 mol % NiCl₂ and 5.0 equiv. NaBH₄ in MeOH at room temperature overnight (Figure 4.3). In both cases, the stereochemistry at C1 was scrambled following C–Br bond reduction, with a slight preference for inversion of the sulfone substituent; that is, the observed *cis:trans* ratios for **19** and **20** under specified conditions were 2.5:1 and 2.3:1, respectively. We also found that separation of *cis* and *trans* isomers in both instances was possible using standard chromatographic techniques, without the need for HPLC purification.

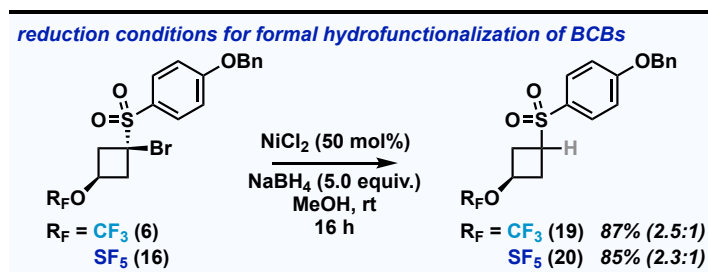


Figure 4.3. Metal boride reduction conditions. ¹⁹F NMR yields reported with observed *cis:trans* ratios in parentheses.

In previous studies, *cis*-substituted cyclobutane rings have been employed as viable bioisosteric replacements of *para*-substituted benzene rings with a higher fraction of C(sp³) atoms.^{129,130} With access to OCF₃-CBs and OSF₅-CBs, we then performed more detailed

structural analyses to provide context for potential applications. Single crystals suitable for SC-XRD were grown from the *cis* isomers of **19** and **20**; the analogous *p*-CF₃-Ph derivative **21** was also synthesized/crystallized as a reference compound (Figure 4.4).

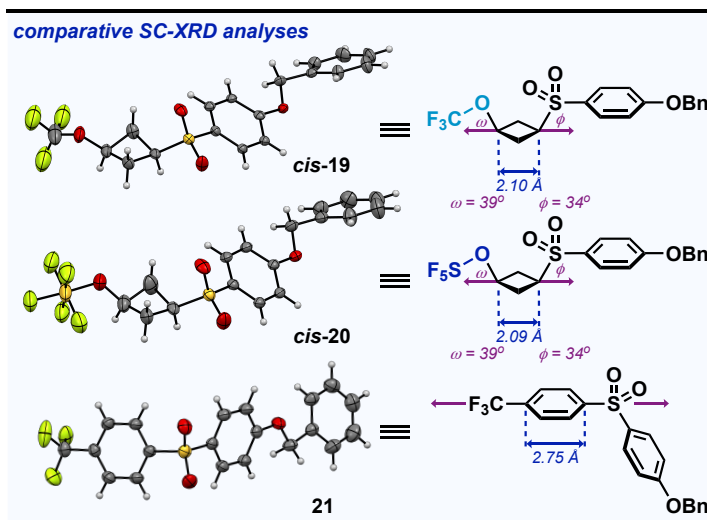


Figure 4.4. Crystal structures for **19**, **20**, and **21** determined by SC-XRD (displacement ellipsoids depicted at 50 % probability level). The minority occupancy positions of the OCF₃ group in *cis*-**19**, OSF₅ group in *cis*-**20**, and CF₃ group in **21** are omitted for clarity.

In *cis*-**19**, the OCF₃ and SO₂Ar groups are situated above the axis defined by C1 and C3 with $w \approx 39^\circ$ and $f \approx 34^\circ$, respectively. Similar angles were also observed for the orientation of the OSF₅ and SO₂Ar groups in *cis*-**20** (i.e., $w \approx 39^\circ$ and $f \approx 33^\circ$). Note that both the OCF₃ and OSF₅ groups are disordered, preventing accurate measurements of the C3–O–CF₃ and C3–O–SF₅ bond angles by SC-XRD. However, calculated structures at ω B97XD/6-311++G** using density functional theory (DFT) suggest that the C3–O–CF₃ angle ($\approx 117^\circ$) is slightly narrower than the C3–O–SF₅ angle ($\approx 122^\circ$) in pruned versions of *cis*-**19** and *cis*-**20** (OBn replaced with H; see Section 4.5 for details). In both cases, the O atom serves as a “kink” that can reorient the fluorinated group closer to the C1–C3 plane in space.

A single bioisosteric replacement of the Ph ring with a CB in a *p*-CF₃-Ph compound such as **21** would lead to an ~24% reduction in transannular C...C distance, more significant changes in exit vectors, and shortened overall distances between the sulfone and fluorinated substituents. Here, we find that the hybrid bioisosteric replacements that incorporate the O atom kink (i.e., Ph → CB concomitant with CF₃ → OCF₃ or OSF₅) in *cis*-**19** and *cis*-**20** relative to **21** enable changes to the three-dimensional structure while maintaining similar overall distances between the sulfone and the fluorinated substituent (~5.9–6.2 Å; measured from the S atom in SO₂Ar to either the C atom in CF₃ or S atom in SF₅).

Lastly, with divergent access to now SF₅-, CF₃SF₄-, OCF₃-, and OSF₅-containing CBs from sulfone-based BCBs using accessible reagents,¹³¹ we sought to obtain proof-of-concept that any of these motifs could indeed be viable hybrid bioisosteric replacements for the *p*-CF₃-Ph motif in a medicinal chemistry setting. We identified a sulfone-containing glycine reuptake inhibitor (GRI) in the patent literature (**22**) that proved to be a suitable candidate for preliminary comparative ADME studies (Figure 4.5, *top*).¹³² In addition to synthesizing **22** for control experiments, we managed to access milligram quantities of the *cis* isomers of each the OCF₃-CB (**23**), SF₅-CB (**24**), and CF₃SF₄-CB (**25**) derivatives using the same synthetic sequence shown in the *bottom* of Figure 4.5 (i.e., without additional optimization; see Section 4.5 for details). Note that our initial attempts to synthesize the OSF₅-CB derivative were unsuccessful. While the OSF₅ group tolerated the metal boride reduction, hydrogenation, and nucleophilic substitution sequence, it did not survive heating in the presence of amine base.

Compound **22** and its putative hybrid bioisosteres **23–25** were submitted for *in vitro* profiling, and the results are tabulated in Table 4.2. Interestingly, the measured LogD value of 2.1 for **25** was virtually identical to the value for the control compound (**22**), but the values measured for **23** and **24** were notably lower (1.1 and 1.3, respectively). These LogD measurements suggest the OCF₃-CB and SF₅-CB hybrid bioisosteric replacements can be employed to strategically *lower* lipophilicity relative to a parent *p*-CF₃-Ph-containing compound, in certain circumstances. This is particularly striking for **24**, since the SF₅ group has been employed as a single bioisosteric replacement for a CF₃ group to *increase* lipophilicity in many cases.¹³³

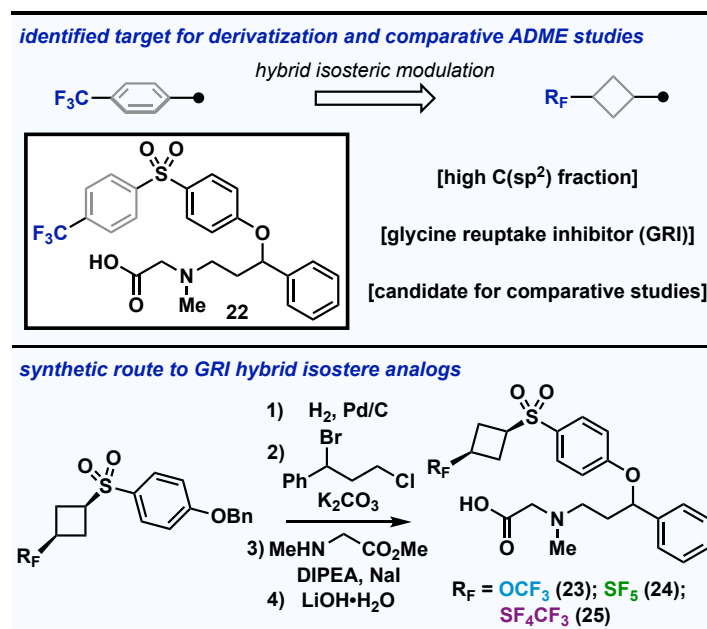


Figure 4.5. (top) Glycine reuptake inhibitor (GRI) target identified for derivatization and in vitro studies. (bottom) General synthesis route for fluorinated cyclobutane analogs.

Additionally, low intrinsic clearance was observed in both rat and human liver microsomes across all compounds, indicating that metabolic stability can be maintained in this context upon replacement of *p*-CF₃-Ph with the fluorinated CB motifs. High throughput solubility at pH = 6.8 was also generally high, with near identical values for the control compound **22** and the SF₅-CB derivative **24**, as well as for the OCF₃-CB and

CF₃SF₄-CB derivatives **23** and **25**. Cellular permeability was determined to be generally poor for all of the GRI analogs (including the control molecule **22**), which one might attribute to the high polarity and charged nature of the parent molecule in this context. Furthermore, given the novelty of the SF₄R groups, we pursued additional characterization for **24** and **25** and were pleased to find that analogs with both SF₅ and CF₃SF₄ substituents proved non-cytotoxic (HepG2 IC₅₀ >100 μ M) and did not inhibit CYP3A4 (IC₅₀ >25 μ M).

Table 4.2. Summary of ADME properties for compounds **22–25**.

compound	LogD _{7.4}	HT solubility pH = 6.8 (mM)	r / h LM CL _{int} (μ L/min/mg)	HepG2 CC ₅₀ (μ M)	CYP3A4 IC ₅₀ (μ M)
22	2.1	0.266	24 / <23	n.d.	n.d.
23	1.1	0.504	<23 / <23	n.d.	n.d.
24	1.3	0.259	26 / 27	>25	>100
25	2.1	0.498	14 / 24	>25	>100

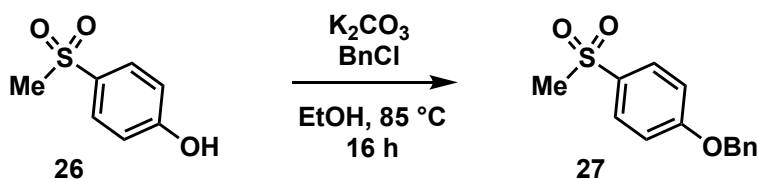
4.3 Conclusion.

In all, the methods reported herein for the installation of OCF₃ and OSF₅ groups on CBs via strain-release functionalization of BCBs are complementary to known strategies for installation of SF₅ and CF₃SF₄ groups,¹¹⁵ enabling rapid, divergent access to a variety of fluorinated cyclobutanes. Notably, comparative studies indicate that OCF₃-, SF₅-, or CF₃SF₄-containing CBs can be viable structural alternatives, or “hybrid bioisosteres,” for the *p*-CF₃-Ph motif that are capable of preserving good physiochemical and ADME properties in a medicinal chemistry context. Moreover, note that novel SF₅- or CF₃SF₄-containing compounds, in particular, may provide additional opportunities to establish unique intellectual property space.

4.4 Author Contributions.

Y.K., A.M.S., and J.A.B. performed synthetic work and data analysis. Y.K. optimized the AgOCF₃ and AgOSF₅ addition reaction conditions and synthesized compounds **1 – 9**, and **14– 22**. A.M.S. synthesized compounds **5**, **10 – 13**, and **23**. J.A.B. synthesized compounds **24** and **25**. Y.K., A.M.S., and J.A.B., and A.Y. synthesized starting materials. Y.K., C.M., and J.C.F. collected SC-XRD data. L.M.H. performed *in vitro* ADME studies and interpreted the results. C.R.P. performed DFT calculations and analysis, supervised the project, and acquired funding. Y.K. and C.R.P. conceptualized the project. The manuscript was written and edited with contributions from all authors.

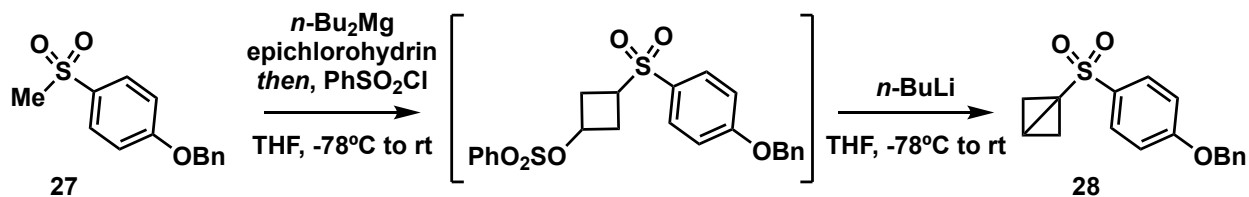
4.5 Experimental.



A 500 mL round bottom flask equipped with a stir bar was charged with 4-hydroxyphenyl methyl sulfone (5.00 g, 29.0 mmol, 1.0 equiv., *purchased from Synthonix*) and dissolved in EtOH (150 mL). To the resulting mixture were added benzyl chloride (5.02 mL, 43.6 mmol, 1.5 equiv.) and potassium carbonate (6.02 g, 43.6 mmol, 1.5 equiv.); the flask was placed into a pre-heated oil bath set to 85 °C and stirred for 16 h. Upon completion, 300 mL H₂O was added to the reaction vessel and transferred to a 1 L separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous Na₂SO₄, filtered through a pad of Celite, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography on silica gel, eluting with 20-

40% EtOAc in hexanes (elution gradient). 1-(Benzyloxy)-4-(methylsulfonyl)benzene (**27**) was obtained as a white, crystalline solid (6.9 g, 90%).

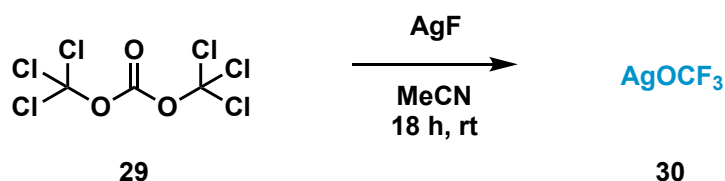
R_f: 0.40 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 134.3 – 139.0 °C; **¹H** (300 MHz, CDCl₃): δ = 7.89-7.85 (m, 2H), 7.43-7.33 (m, 5H), 7.11-7.08 (m, 2H), 5.15 (s, 2H), 3.03 (s, 3H); **¹³C**{**¹H} (201 MHz, CDCl₃): δ = 163.0, 135.9, 132.7, 129.7, 128.9, 128.6, 127.6, 115.5, 70.6, 45.0; **ATR-IR** (ν_{max}): 2951, 2921, 2852, 1591, 1574, 1497, 1391, 1310, 1293, 1249, 1138, 1092, 999, 965, 831, 770, 752, 701 cm⁻¹; **HRMS** (*m/z*): (ESI) calc'd for C₁₄H₁₅O₃S⁺ [M-H]⁺ 263.0737, found 262.0725.**



Synthesis of the [1.1.0]bicyclobutane **28** was adapted from a known literature procedure.^[Error! Bookmark not defined.] An oven-dried 250 mL round bottom flask equipped with a magnetic stir bar was charged with 1-(benzyloxy)-4-(methylsulfonyl)benzene (6.00 g, 22.9 mmol, 1.0 equiv.), capped and flushed with Ar, anhydrous THF (115 mL) was added and the resulting solution was cooled to -78 °C. A solution of *n*-Bu₂Mg (23 mL, 1.0 M in heptane, 22.9 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred for 30 min at -78 °C. To the resulting mixture was added (±)-epichlorohydrin (1.79 mL, 22.9 mmol, 1.0 equiv) *via* syringe and the solution was slowly warmed to room temperature and stirred for 18 h. Then, the reaction was cooled to 0 °C in an ice bath and benzenesulfonyl chloride (3.79 mL, 29.7 mmol, 1.3 equiv.) was added dropwise *via* syringe and the mixture was stirred for 16 h at room temperature. The resulting

solution was cooled to $-78\text{ }^{\circ}\text{C}$, a solution of *n*-BuLi (11 mL, 27.5 mmol, 1.2 equiv) was added, and the reaction was slowly warmed to room temperature and stirred at the specified temperature for 2 h. The reaction was quenched by sequential addition of H_2O (45 mL) and aq. sat. NH_4Cl (45 mL), extracted three times with EtOAc, the combined organic fractions were dried over Na_2SO_4 or MgSO_4 and concentrated under vacuum. The resulting crude 1-sulfonylbicyclo[1.1.0]butane was purified by flash column chromatography on silica gel, eluting with 10-20% EtOAc in hexanes (elution gradient). The final product **28** was obtained as a white, crystalline solid (3.7 g, 54%).

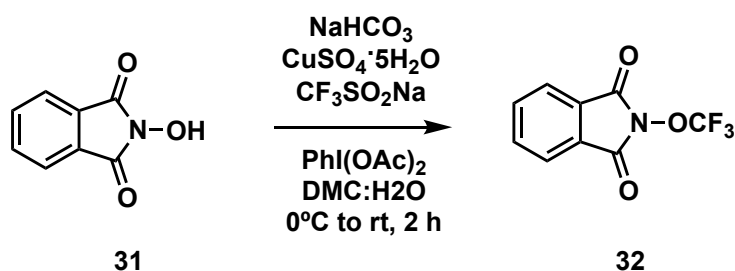
R_f: 0.20 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: $125.1 - 130.0\text{ }^{\circ}\text{C}$; **^1H (300 MHz, CDCl_3)**: $\delta = 7.88\text{--}7.84$ (m, 2H), $7.45\text{--}7.33$ (m, 5H), $7.11\text{--}7.07$ (m, 2H), 5.15 (s, 2H), 2.51-2.47 (m, 3H), 1.37-1.34 (m, 2H); **$^{13}\text{C}\{^1\text{H}\}$ (151 MHz, CDCl_3)**: $\delta = 162.5, 136.0, 133.9, 129.5, 128.9, 128.5, 127.6, 115.3, 70.5, 38.1, 23.6, 12.5$; **ATR-IR (ν_{max})**: 3095, 2964, 2927, 1591, 1575, 1497, 1392, 1308, 1290, 1252, 1134, 1113, 1083, 1071, 1004, 818, 810, 768, 751, 701, 687, 625 cm^{-1} ; **HRMS (m/z)**: (ESI) calc'd for $\text{C}_{17}\text{H}_{17}\text{O}_3\text{S}^+$ $[\text{M}-\text{H}]^+$ 301.0893, found 301.0878.



AgOCF_3 (**30**) was prepared according to a known literature procedure.^[134] To an oven-dried 20 mL microwave vial equipped with a stir bar were added triphosgene (594 mg, 2.0 mmol, 1.0 equiv.) and silver(I) fluoride (2.28 g, 18.0 mmol, 9.0 equiv.) under N_2 atmosphere in a glovebox. The vial was wrapped with aluminum foil, sealed with a Teflon-lined cap, and the MeCN (6.0 mL) was added via syringe. The suspension was stirred vigorously at room temperature

overnight (note that there is an initial strong exotherm). Upon completion, the solution was filtered through a syringe filter (45 microns) into an oven-dried microwave vial which was wrapped with aluminum foil and sealed with a Teflon-lined cap. The solution was stored at $-20\text{ }^{\circ}\text{C}$ in the dark until it was ready to use. *Note: typically, the AgOCF_3 solution appeared colorless or very pale yellow. Occasionally, the stock solution would appear a dark yellow color, which always led to greatly diminished yields (20-40% drop). We observed that the quality of AgF is an important factor regarding the quality of the final AgOCF_3 solution. It is recommended to use a fresh batch of AgF to prepare the reagent. Additionally, the rate of stirring was an important factor in the success of the reaction - vigorous stirring is recommended.*

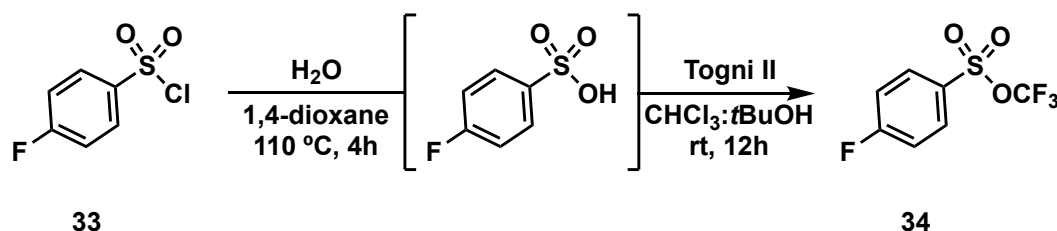
^{19}F (282 MHz, CD_3CN): $\delta = -27.11$ (s, 3F).



2-(Trifluoromethoxy)isoindoline-1,3-dione (**32**) was prepared according to a known literature procedure.¹³⁵ To a 100 mL round bottom flask were added NaHCO_3 (210 mg, 2.5 mmol, 0.5 equiv.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (62.5 mg, 5 mol %), and $\text{CF}_3\text{SO}_2\text{Na}$ (1.56 g, 10.0 mmol, 2.0 equiv.). Dimethylcarbonate (16 mL) and DI H_2O (4.0 mL) were added *via* syringe, and the mixture was stirred until the solids dissolved. Then, *N*-hydroxyphthalimide (816 mg, 2.5 mmol, 1.0 equiv.) and PhI(OAc)_2 (3.22 g, 10.0 mmol, 2.0 equiv.) were added in quick succession, open to air. The reaction became dark green over the course of 5-10 minutes and colorless upon completion after stirring at rt for 2 h. The reaction mixture was quenched by the addition of sat. NaHCO_3 (10 mL) and was then diluted with EtOAc (10 mL) and transferred to a separatory funnel. The aqueous

phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were washed with brine (1 × 5.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel, eluting with 9:1 hexanes:EtOAc. The desired product **32** was obtained as a white solid (0.386 g, 24%); all analyses matched previous literature reports. *Note that the product elutes closely above an impurity.*

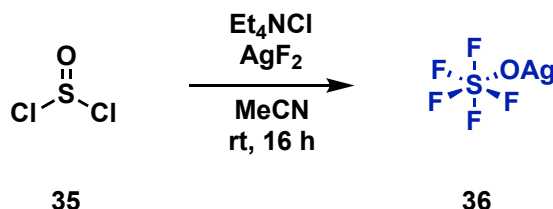
¹H (300 MHz, CDCl₃): δ = 7.97-7.93 (m, 2H), 7.89-7.85 (m, 2H); ¹⁹F (282 MHz, CDCl₃): δ = –65.14 (s, 3F).



Trifluoromethyl 4-fluorobenzenesulfonate (**34**) was prepared according to a known literature procedure.¹³⁶ To a 20 mL microwave vial equipped with a stir bar was added 4-fluorobenzenesulfonyl chloride (973 mg, 5.0 mmol, 1.0 equiv.) followed by 1,4-dioxane (2.5 mL) and DI H₂O (2.5 mL). The vial was tightly sealed with a crimper, and the mixture was stirred at 110 °C for 4 h. Upon completion, the stir bar was removed, and the solvents were removed *in vacuo* (rotary evaporator). The resulting solid was azeotroped once with PhMe to ensure removal of water. Then, the stir bar was returned to vessel, and Togni's Reagent II was added (1.6 g, 5.0 mmol, 1.0 equiv.); the vial was sealed with a crimper, evacuated, and backfilled with Ar. Then, CHCl₃ (5.5 mL) and *t*-BuOH (1.5 mL) were added *via* syringe, and the resulting mixture was stirred at rt for 12 h. Upon completion, the reaction was quenched by the addition of sat. NaHCO₃ (5.0 mL) and diluted with CH₂Cl₂ (5.0 mL). The aqueous phase was extracted with EtOAc (2 × 5.0 mL) and the combined organic phases were washed with brine (1 × 5.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography

on silica gel, eluting with 100:1 hexanes:EtOAc to give the desired product **34** as a clear oil (0.323 g, 15%). *Note: the final product is volatile!*

^1H (300 MHz, CDCl_3): δ = 8.08-8.04 (m, 2H), 7.35-7.29 (m, 2H); ^{19}F (282 MHz, CDCl_3): δ = –53.96 (s, 3F), –99.08 (m, 1F).

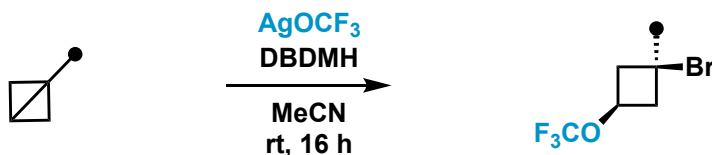


AgOSF_5 was synthesized according to a known literature procedure with some modifications.^[137] To an oven-dried 20 mL microwave vial (vial **A**) was added Et_4NCl (0.33 g, 2.0 mmol, 2.0 equiv.). The vial was sealed, heated with a heat gun under vacuum, and refilled with Ar. This was repeated two times to remove residual moisture, then the vial was transported to a glovebox. Under N_2 atmosphere, a separate oven-dried 20 mL microwave vial (vial **B**) equipped with a stir bar was charged with AgF_2 (2.3 g, 16 mmol, 16 equiv.). Then, to vial **A** was added anhydrous MeCN (6.0 mL, 0.2 M) followed by thionyl chloride (73 μL , 1.0 mmol, 1.0 equiv.). This solution was then added slowly to vial **B** *via* syringe, and the resulting suspension was vigorously stirred at rt for 16 h. Upon completion, the resulting brown suspension was filtered through a syringe filter (occasionally, the filtrate would take on a light-pink color which disappeared after about 10 minutes). To the remaining solids was added 2.0 mL MeCN, which was then filtered and combined with the previous filtrate. A 0.3 mL aliquot was taken for ^{19}F NMR concentration determination with α,α,α -trifluorotoluene as internal standard. During data collection, 8 scans and 0 dummy scans were taken, the O1P was set to +30, and the d1 relaxation delay was extended to 30 s. *Note: to screen the effect of concentration on the reactivity of AgOSF_5*

with BCBs, the stock solution could be concentrated *in vacuo* to about 1/5 the volume, typically yielding a 0.5 M solution.

^{19}F (282 MHz, CD_3CN): $\delta = 134.84$ (p, 1F, $J = 159.9$ Hz), 91.53 (d, 4F, $J = 159.9$ Hz).

4.5.1 General Procedure A: Bromotrifluoromethoxylation of [1.1.0]Bicyclobutanes:



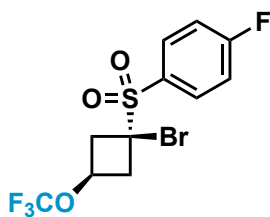
To an oven-dried microwave vial equipped with a stir bar was added the BCB substrate (0.2 mmol, 1.0 equiv.) and dibromodimethylhydantoin (DBDMH) (85 mg, 0.3 mmol, 1.5 equiv.). The vial was sealed with a crimper and then evacuated and backfilled with Ar three times. A solution of AgOCF_3 (0.6 mmol, 3.0 equiv.) was added *via* syringe and the mixture was allowed to stir at room temperature for 16 h. Upon completion, a 0.1 mL aliquot was taken for ^{19}F yield determination using a known amount of α,α,α -trifluorotoluene as an internal standard. The NMR sample was recombined with the crude reaction mixture and filtered through a pad of silica. The silica plug was rinsed with CH_2Cl_2 , and the organic layer was concentrated *in vacuo*. The crude residue was then purified by column chromatography or preparative TLC (pTLC); see specific conditions for each substrate below.

4.5.2 General Procedure B: Bromopentafluorosulfanoylation of [1.1.0]Bicyclobutanes:



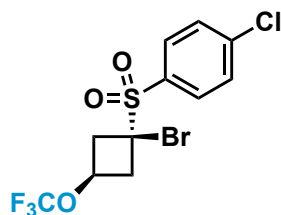
To an oven-dried microwave vial equipped with a stir bar was added the BCB substrate (0.4 mmol, 2.0 equiv.) and dibromodimethylhydantoin (DBDMH) (85 mg, 0.3 mmol, 1.5 equiv.). The vial was sealed with a crimper and then evacuated and backfilled with Ar three times. A solution of AgOSF_5 (0.2 mmol, 1.0 equiv.) in MeCN was added *via* syringe and the mixture was allowed to stir at 60 °C for 16 h. Upon completion, a 0.1 mL aliquot was taken for ^{19}F NMR yield determination using a known amount of α,α,α -trifluorotoluene as an internal standard. The NMR sample was recombined with the crude reaction mixture and filtered through a pad of silica. The silica plug was rinsed with CH_2Cl_2 , and the organic layer was concentrated *in vacuo*. The crude residue was then purified by column chromatography or preparative TLC (pTLC); see specific conditions for each substrate below.

4.5.3 Characterization Data for 1-Bromo-3-Trifluoromethoxycyclobutanes:



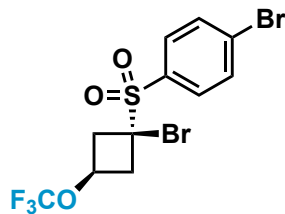
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-fluorobenzene (1) was synthesized from 1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by pTLC (preparative thin layer chromatography) eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white, crystalline solid (41 mg, 54%).

R_f: 0.46 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 82.0 – 84.5 °C; **¹H (300 MHz, CDCl₃)**: δ = 8.07-8.01 (m, 2H), 7.32-7.24 (m, 2H), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.65-3.58 (m, 2H), 3.10-3.02 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.94 (s, 3F), -100.99 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 168.6-165.1 (d, *J* = 258.7 Hz), 134.3-134.1 (d, *J* = 9.8 Hz), 129.52-129.48 (d, *J* = 3.3 Hz), 126.3-116.1 (q, *J* = 257.9 Hz), 116.9-116.6 (d, *J* = 22.5 Hz), 66.6-66.5 (q, *J* = 3.6 Hz), 62.3, 44.5; **ATR-IR (ν_{max})**: 3112, 1592, 1492, 1327, 1225, 1194, 1169, 1148, 1076, 847, 821, 723, 695 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₁H₈BrF₄O₃S- [M-H]⁻ 374.9319, found 374.9330.



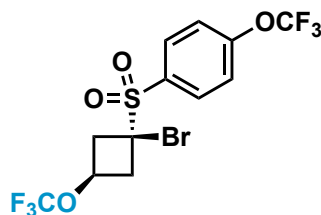
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-chlorobenzene (2) was synthesized from 1-((4-bromophenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (45 mg, 57%).

R_f: 0.44 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 69.8 – 72.7 °C; **¹H (300 MHz, CDCl₃):** δ = 7.97-7.93 (d, 2H, *J* = 8.7 Hz), 7.60-7.56 (d, 2H, *J* = 8.7 Hz), 5.05-4.96 (p, 1H, *J* = 6.8 Hz), 3.66-3.58 (m, 2H), 3.10-3.03 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = -59.93 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 142.2, 132.6, 131.9, 129.6, 126.2-116.0 (q, *J* = 257.2 Hz), 66.6-66.4 (q, *J* = 3.4 Hz), 62.1, 44.4; **ATR-IR (ν_{max}):** 3096, 1579, 1476, 1322, 1143, 1084, 827, 758, 714, 687 cm⁻¹; **HRMS (*m/z*):** (ESI) calc'd for C₁₁H₈BrClF₃O₃S⁻ [M-H]⁻ 392.8999, found 392.9003.



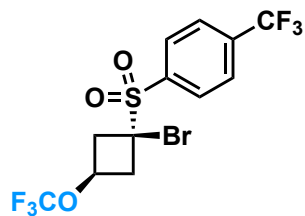
1-Bromo-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (3) was synthesized from 1-((4-bromophenyl)sulfonyl) bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (62 mg, 71%).

R_f: 0.43 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 65.3 – 66.6 °C; **¹H (300 MHz, CDCl₃):** δ = 7.88-7.85 (d, 2H, *J* = 8.6 Hz), 7.76-7.73 (d, 2H, *J* = 8.6 Hz), 5.04-4.95 (p, 1H, *J* = 6.8 Hz), 3.65-3.57 (m, 2H), 3.09-3.02 (m, 2H); **¹⁹F (282 MHz, CDCl₃):** δ = −59.90 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 132.51, 132.49, 132.38, 130.8, 126.1-115.9 (q, *J* = 256.9 Hz), 66.5-66.3 (q, *J* = 3.3 Hz), 62.0, 44.3; **ATR-IR (ν_{max}):** 3089, 1573, 1321, 1144, 1083, 842, 744, 710 cm^{−1}; **HRMS (*m/z*):** (ESI) calc'd for C₁₁H₈Br₂F₃O₃S[−] [M-H][−] 434.8518, found 434.8538.



1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethoxy) benzene (4) was synthesized from 1-((4-(trifluoromethoxy)phenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (50 mg, 56%).

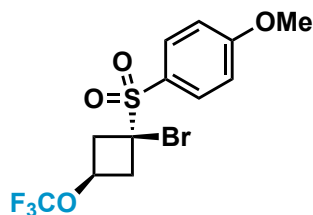
R_f: 0.59 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 57.1 – 57.4 °C; **¹H (300 MHz, CDCl₃)**: δ = 8.10-8.07 (d, 2H, *J* = 8.9 Hz), 7.44-7.42 (d, 2H, *J* = 8.9 Hz), 5.06-4.99 (p, 1H, *J* = 6.8 Hz), 3.67-3.61 (m, 2H), 3.11-3.06 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -57.66 (s, 3F), -59.99 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 154.2-154.1 (q, *J* = 1.9 Hz), 133.6, 131.6, 125.0-117.3 (q, *J* = 257.7 Hz), 124.2-116.4 (q, *J* = 260.2 Hz), 66.5-66.4 (q, *J* = 3.3 Hz), 62.1, 44.5; **ATR-IR (ν_{max})**: 3099, 2359, 1324, 1141, 839, 758, 715 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₂H₈BrF₆O₄S⁻ [M-H]⁻ 440.9236, found 440.9236.



1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-(trifluoromethyl)benzene

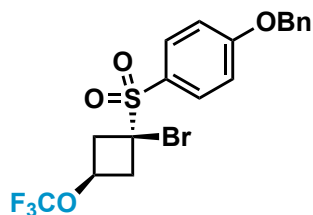
(4') was synthesized from 1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A to further investigate the influence of electron-withdrawing groups on the outcome of the reaction. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (57 mg, 59%).

R_f: 0.50 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.18-8.15 (d, 2H, *J* = 8.2 Hz), 7.90-7.87 (d, 2H, *J* = 8.2 Hz), 5.07-4.99 (p, 1H, *J* = 6.9 Hz), 3.69-3.61 (m, 2H), 3.13-3.06 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.96 (s, 3F), -63.35 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 137.2, 136.8-136.7 (q, *J* = 33.3 Hz), 131.8, 126.3-126.2 (q, *J* = 3.8 Hz), 66.4-66.3 (q, *J* = 3.3 Hz), 61.8, 44.4; **ATR-IR (ν_{max})**: 3098, 1323, 1264, 1154, 1062, 732, 704 cm⁻¹; **HRMS (*m/z*)**: (APCI) calc'd for C₁₁H₈F₈O₃S₂ [M-HBr] 404.98, not found.



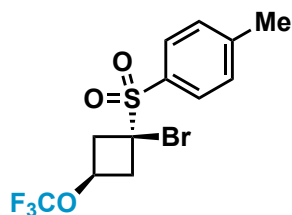
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methoxybenzene (5) was synthesized from 1-((4-methoxyphenyl)sulfonyl) bicyclo[1.1.0]butane following the general procedure A with an additional 0.4 mL MeCN. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (29 mg, 37%).

R_f: 0.17 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 73.4 – 76.1 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.96-7.91 (d, 2H, *J* = 9.0 Hz), 7.07-7.02 (d, 2H, *J* = 9.0 Hz), 5.04-4.95 (p, 1H, *J* = 6.8 Hz), 3.91 (s, 3H), 3.65-3.57 (m, 2H), 3.08-3.00 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.88 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.9, 133.5, 124.6, 122.9-116.1 (q, *J* = 257.4 Hz), 114.5, 66.8-66.6 (q, *J* = 3.3 Hz), 62.7, 55.9, 44.5; **ATR-IR (ν_{max})**: 2920, 1596, 1498, 1325, 1143, 1081, 844, 724 698 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₂H₁₃BrF₃O₃S⁺ [M+H]⁺ 388.9665, found 388.9640.



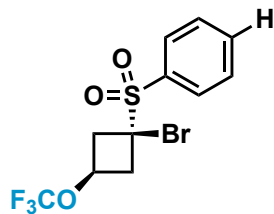
1-(Benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (6) was synthesized from 1-((4-(benzyloxy)phenyl) sulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil. The reaction was also repeated on 1.0 mmol scale to yield 309 mg of the desired product (55%).

R_f: 0.29 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.96-7.92 (d, 2H, *J* = 9.0 Hz), 7.44-7.34 (m, 5H), 7.14-7.11 (d, 2H, *J* = 9.0 Hz), 5.16 (s, 2H), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.65-3.58 (m, 2H), 3.09-3.01 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.85 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.0, 135.5, 133.4, 128.9, 128.6, 127.6, 126.2-115.7 (q, *J* = 257.4 Hz), 124.7, 115.2, 70.6, 66.7-66.6 (q, *J* = 3.4 Hz), 62.6, 44.5; **ATR-IR (ν_{max})**: 2931, 1592, 1259, 1230, 1143, 1080, 859, 741 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₈H₁₇BrF₃O₄S⁺ [M+H⁺] 464.9978, found 464.9960.



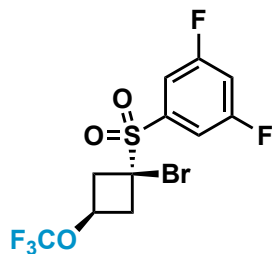
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-4-methylbenzene (7) was synthesized from 1-tosylbicyclo[1.1.0]butane following the general procedure A with an additional 0.4 mL MeCN. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (38 mg, 51%).

R_f: 0.33 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 77.4 – 79.9 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.90-7.88 (d, 2H, *J* = 8.2 Hz), 7.41-7.38 (d, 2H, *J* = 8.2 Hz), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.67-3.59 (m, 2H), 3.08-3.01 (m, 2H), 2.48 (s, 3H); **¹⁹F (282 MHz, CDCl₃)**: δ = −59.88 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 146.3, 131.1, 130.3, 129.7, 126.2-115.9 (q, *J* = 257.3 Hz), 66.6-66.5 (q, *J* = 3.4 Hz), 44.4, 21.8; **ATR-IR (ν_{max})**: 2963, 2927, 1598, 1326, 1266, 1144, 1080, 860, 757, 715, 692 cm^{−1}; **HRMS (*m/z*)**: (ESI) calc'd for C₁₂H₁₃BrF₃O₃S⁺ [M+H⁺] 372.9716, found 374.9692.



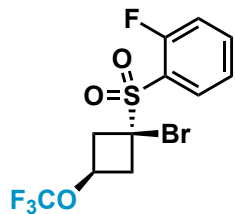
((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (8) was synthesized from 1-(phenylsulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (47 mg, 65%).

R_f: 0.41 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 85.7 – 90.1 °C; **¹H (300 MHz, CDCl₃)**: δ = 8.03-8.01 (m, 2H), 7.76-7.72 (m, 1H), 7.63-7.59 (m, 2H), 5.05-4.98 (p, 1H, *J* = 6.8 Hz), 3.67-3.62 (m, 2H), 3.09-3.03 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = –59.90 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 135.1, 133.5, 131.2, 129.2, 125.0-117.3 (q, *J* = 258.0 Hz), 66.62-66.59 (q, *J* = 3.4 Hz), 62.1, 44.5; **ATR-IR (ν_{max})**: 1591, 1492, 1329, 1274, 1228, 1142, 840, 719 cm^{–1}; **HRMS (*m/z*)**: (ESI) calc'd for C₁₁H₁₁BrF₃O₃S⁺ [M+H⁺] 360.9539, found 360.9548.



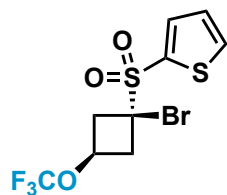
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-3,5-difluorobenzene (9) was synthesized from 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a white solid (41 mg, 52%).

R_f: 0.42 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.58-7.55 (m, 2H), 7.24-7.17(m, 1H), 5.05-4.96 (p, 1H, *J* = 6.9 Hz), 3.68-3.60 (m, 2H), 3.14-3.06 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.98 (s, 3F), -104.79 - -104.85 (m, 2F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.5-161.0 (m), 136.8-136.6 (t, *J* = 8.4 Hz), 126.2-116.0 (q, *J* = 258.1 Hz), 115.0-114.6 (m), 111.2-110.5 (t, *J* = 24.8 Hz), 66.4-66.2 (q, *J* = 3.5 Hz), 61.7, 44.5; **ATR-IR (ν_{max})**: 3089, 2362, 1591, 1443, 1334, 1257, 1148, 1034, 870, 697 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₁H₇BrF₃O₃S₂⁻ [M-H⁺] 392.9224, found 392.9216.



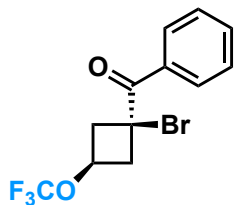
1-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)-2-fluorobenzene (10) was synthesized from 1-((2-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane following the general procedure A, but on a 0.1 mmol scale. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (15 mg, 40%).

R_f: 0.36 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.04-7.99 (m, 1H), 7.76-7.68 (m, 1H), 7.41-7.35 (m, 1H), 7.32-7.25 (m, 1H), 5.05-4.96 (p, 1H, *J* = 6.8 Hz), 3.89-3.82 (m, 2H), 3.14-3.07 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.87 (s, 3F), -103.61 - -103.70 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 161.5-158.0 (d, *J* = 258.0 Hz), 137.5-137.4 (d, *J* = 8.9 Hz), 134.1, 126.2-116.0 (d, *J* = 257.3 Hz), 124.75-124.70 (d, *J* = 3.8 Hz), 122.6-122.4 (d, *J* = 13.9 Hz), 117.9-117.6 (d, *J* = 22.3 Hz), 66.7-66.5 (q, 3.5 Hz), 63.0, 44.22-44.17 (d, *J* = 4.1 Hz); **ATR-IR (ν_{max})**: 3104, 2359, 1596, 1325, 1256, 1142, 1098, 828, 773, 721, 702, 664 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₁H₈BrF₄O₃S- [M-H⁺]⁻ 374.9319, found 374.9325.



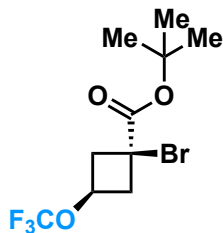
2-((1-Bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)thiophene (11) was synthesized from 2-(bicyclo[1.1.0]butan-1-ylsulfonyl)thiophene following the general procedure A. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (38 mg, 52%).

R_f: 0.47 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.61-7.59 (d, 1H, *J* = 4.1 Hz), 7.22-7.21 (d, 1H, *J* = 4.1 Hz), 5.02-4.93 (p, 1H, *J* = 6.9 Hz), 3.65-3.57 (m, 2H), 3.14-3.06 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.94 (m, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 138.5, 133.6, 131.2, 126.2-116.0 (q, *J* = 257.6 Hz), 125.0, 66.5-66.4 (q, *J* = 3.6 Hz), 62.6, 44.3; **ATR-IR (ν_{max})**: 3102, 1508, 1396, 1261, 1139, 1018, 805, 701, 663 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₉H₇BrF₃O₃S₂⁻ [M-H⁺] 362.8978, found 362.8975.



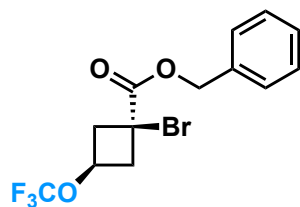
(1-Bromo-3-(trifluoromethoxy)cyclobutyl)(phenyl)methanone (12) was synthesized from bicyclo[1.1.0]butan-1-yl(phenyl)methanone following the general procedure A. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (33 mg, 41%).

R_f: 0.51 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.09-8.05 (m, 2H), 7.62-7.45 (m, 3H), 4.54-4.45 (p, 1H, *J* = 6.9 Hz), 3.75-3.66 (m, 2H), 3.20-3.12 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.72 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 192.9, 133.9, 131.6, 130.6, 128.6, 66.8-66.7 (*J* – 3.3 Hz), 48.1, 45.0; **ATR-IR (ν_{max})**: 3020, 1680, 1272, 1215, 1152, 748, 675 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for [M+H]⁺ 323.1092, not found; **HRMS (*m/z*)**: (APCI) calc'd for [M-HBr] 244.07, found 244.04.



***tert*-Butyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (13)** was synthesized from *tert*-butyl bicyclo[1.1.0]butane-1-carboxylate following the general procedure A. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (26 mg, 40%).

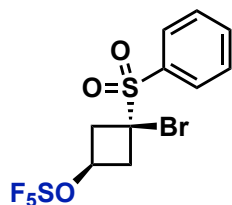
R_f: 0.59 (95:5 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 4.64-4.55 (p, 1H, *J* = 6.9 Hz), 3.39-3.32 (m, 2H), 2.97-2.90 (m, 2H), 1.51 (s, 9H); **¹⁹F (282 MHz, CDCl₃)**: δ = –59.90 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 169.5, 122.5-119.9 (q, *J* = 253.9 Hz), 83.4, 66.8-66.7 (q, *J* = 3.3 Hz), 45.8, 45.2, 27.7; **ATR-IR (ν_{max})**: 2924, 1725, 1300, 1232, 1145, 749, 681 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for [M+H]⁺ 318.0078, not found; **HRMS (*m/z*)**: (APCI) calc'd for [M-HBr] 240.09, found 240.14.



Benzyl 1-bromo-3-(trifluoromethoxy)cyclobutane-1-carboxylate (14) was synthesized from benzyl bicyclo[1.1.0]butane-1-carboxylate following **the general procedure A**, on 0.5 mmol scale. The crude residue was purified by column chromatography eluting with 9:1 hexanes:EtOAc. The final product was obtained as a clear oil (134 mg, 76%). *Note: the desired product eluted very closely with a UV-active impurity, leading to mixed fractions and reduced isolated yield.*

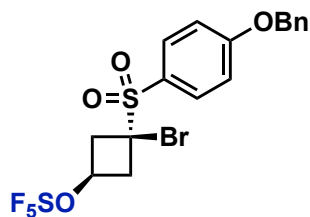
R_f: 0.67 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.41-7.39 (m, 5H), 5.25 (s, 2H), 4.68-4.59 (p, 1H, *J* = 7.0 Hz), 3.46-3.39 (m, 2H), 3.03-2.96 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.92 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 170.4, 134.9, 128.8, 128.7, 128.1, 126.2-116.0 (q, *J* = 255.9 Hz), 68.4, 66.6-66.5 (q, *J* = 3.3 Hz), 45.8, 43.6; **ATR-IR (ν_{max})**: 3036, 2961, 1733, 1456, 1377, 1263, 1141, 736, 696 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for [M+H]⁺ 353.1352, not found; **HRMS (*m/z*)**: (APCI) calc'd for [M-HBr] 274.08, found 274.07.

4.5.4 Characterization Data for 1-Bromo-3-Pentafluorosulfanoxycyclobutanes:



(3-Bromo-3-(phenylsulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane (**15**) was prepared from 1-(phenylsulfonyl)bicyclo[1.1.0]butane following the general procedure B. The crude residue was purified by pTLC eluting with 1:1 hexanes:CH₂Cl₂, followed by 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (11 mg, 13%)

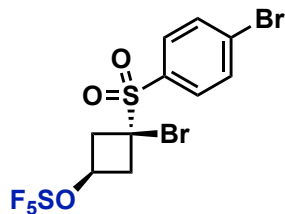
R_f: 0.43 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: not determined; decomposition observed above 100 °C; **¹H (300 MHz, CDCl₃)**: δ = 8.04-8.01 (m, 2H), 7.78-7.72 (m, 1H), 7.64-7.59 (m, 2H), 5.42-5.33 (p, 1H, J = 6.9 Hz), 3.71-3.63 (m, 2H), 3.11-3.04 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 76.61-74.38 (p, 1F, J = 153.8 Hz), 63.19-62.59 (m, 4F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 135.1, 133.4, 131.3, 129.2, 71.9-71.8 (p, J = 4.8 Hz), 61.5, 44.8; **ATR-IR (ν_{max})**: 2924, 2360, 2339, 1446, 1208, 1153, 1078, 859, 763, 691 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₀H₁₁BrF₅O₃S₂⁺ [M+H]⁺ 416.9248, not found; **HRMS (m/z)**: (APCI) calc'd for [M-HBr] 338.00, found 338.00; **LRMS (m/z)**: (GC) calc'd for C₁₀H₁₀F₅O₃S₂⁺ [M-Br]⁺ 336.9, found 337.0, calc'd for C₁₀H₁₀BrO₂S⁺ [M-OSF₅]⁺ 277.0, found 276.9.



3-((4-(Benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro- λ^6 -sulfane (16)

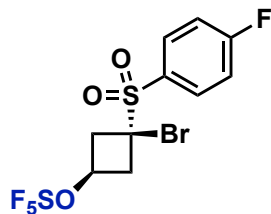
was prepared from 1-((4-(benzyloxy) phenyl) sulfonyl) bicyclo[1.1.0]butane following the general procedure B. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by pTLC eluting with 1:1 hexanes:CH₂Cl₂, followed by pTLC with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (17 mg, 11%)

R_f: 0.36 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: not determined; decomposition observed above 105 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.95-7.92 (d, H, J = 9.0 Hz), 7.43-7.37 (m, 5H), 7.14-7.11(d, 2H, J = 9.0 Hz), 5.40-5.31 (p, 1H, J = 6.9 Hz), 5.16 (s, 2H), 3.67-3.59 (m, 2H), 3.10-3.02 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 76.74-74.50 (p, 1F, J = 154.3 Hz), 63.21-62.61 (m, 4F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 164.1, 135.6, 133.5, 129.0, 128.7, 127.7, 124.7, 115.3, 72.0-71.9 (p, J = 4.8 Hz), 70.7, 62.0, 44.8; **ATR-IR ($\nu_{\max}$)**: 2923, 1445, 1210, 1150, 1079, 859, 761, 690 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₇H₁₇BrF₅O₄S₂⁺ [M+H]⁺ 522.9667, not found; **HRMS (m/z)**: (APCI) calc'd for [M-HBr] 444.05, found 443.99; **LRMS (m/z)**: (GC) calc'd for C₁₇H₁₇BrF₅O₄S₂⁺ [M+H]⁺ 523.0, not found.



(3-Bromo-3-((4-bromophenyl)sulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane (17) was prepared according to the general procedure B. The crude residue was purified by column chromatography on silica gel eluting with 9:1 hexanes:EtOAc, followed by pTLC eluting with 4:1 hexanes:EtOAc. The product was obtained as a clear oil (12 mg, 12%)

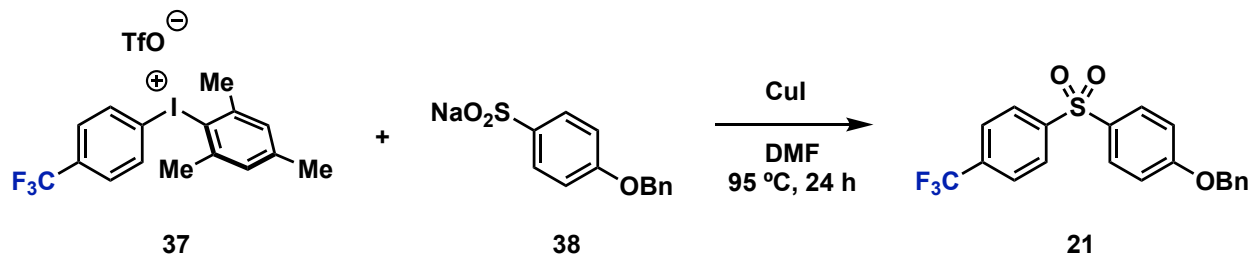
R_f: 0.45 (9:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.89-7.86 (d, 2H, J = 8.7 Hz), 7.77-7.74 (d, 2H, J = 8.7 Hz), 5.41-5.32 (p, 1H, J = 6.9 Hz), 3.68-3.60 (m, 2H), 3.12-3.04 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 76.48-74.24 (pent., 1F, J = 161.8 Hz), 63.18-62.59 (m, 4F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 132.58, 132.57, 132.4, 130.9, 71.7-71.5 (pent., 4.8 Hz), 61.4, 44.7; **ATR-IR (v_{max})**: 3102, 2360, 1574, 1471, 1388, 1152, 1073, 843, 777, 681 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₀H₁₀Br₂F₅O₃S₂⁺ [M+H]⁺ 494.8353, not found; **LRMS (m/z)**: (GC) calc'd C₁₀H₁₀Br₂F₅O₃S₂⁺ [M+H]⁺ 495.8, found 495.9.



(3-Bromo-3-((4-fluorophenyl)sulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane (18) was synthesized from 1-(phenylsulfonyl)bicyclo[1.1.0]butane, following the general procedure B. The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid (13 mg, 15%). Melting point data was not obtained due to the small amount of material obtained.

R_f: 0.41 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.08-8.01 (m, 2H), 7.32-7.27 (m, 2H), 5.42-5.32 (p, 1H, J = 6.8 Hz), 3.68-3.60 (m, 2H), 3.12-3.05 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 76.51-74.27 (p, 1F, J = 155.0 Hz), 63.18-62.58 (m, 4F), -100.74- -100.83 (m, 1F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 167.5-166.2 (d, J = 259.2 Hz), 134.21-134.17 (d, J = 9.9 Hz), 129.39-129.37 (d, J = 3.8 Hz), 116.8-116.7 (d, J = 22.7 Hz), 71.7-71.6 (p, J = 4.6 Hz), 61.6, 44.8; **ATR-IR (ν_{max})**: 3114, 2993, 1587, 1489, 1351, 1316, 1147, 1081, 840, 732, 694 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₀H₁₀BrF₆O₃S₂⁺ [M+H]⁺ 436.9154, not found; **LRMS (m/z)**: (GC) calc'd for C₁₀H₁₀BrF₆O₃S₂⁺ [M+H]⁺ 436.9, not found.

4.5.5 Glycine Reuptake Inhibitor Analogs.

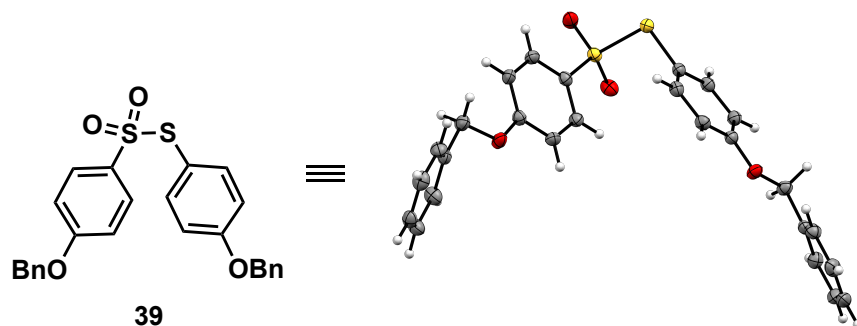


To an oven-dried 5 mL microwave vial equipped with a stir bar were added CuI (39 mg, 0.2 mmol, 0.2 equiv.), sodium 4-(benzyloxy)benzenesulfinate (270 mg, 1.0 mmol, 1.0 equiv.), and mesityl(4-(trifluoromethyl)phenyl) iodonium trifluoromethanesulfonate (594 mg, 1.1 mmol, 1.1 equiv.). The vial was sealed with a crimper and DMF (10 mL) was added *via* syringe. The vessel was transferred to a pre-heated oil bath (95 °C) and allowed to stir for 24 h, during which a color change from light yellow to amber was observed. Upon reaction completion, the mixture was diluted with H₂O (15 mL) and EtOAc (5.0 mL) and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (3 × 5.0 mL) and the combined organic layer was washed with H₂O (1 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with hexanes:EtOAc, followed by another flash column eluting with hexanes/CH₂Cl₂. 1-(Benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (**21**) was obtained as a white solid (106 mg, 27%).

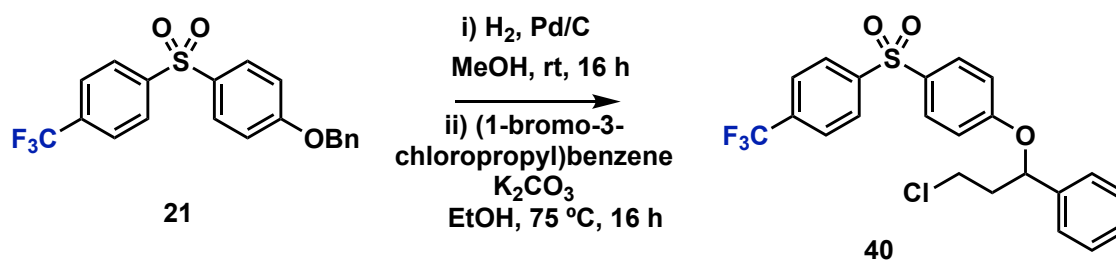
R_f: 0.20 (1:1 hexanes:CH₂Cl₂), vis: UV (254 nm); **m.p.**: 139.6-141.8 °C; **¹H (300 MHz, CDCl₃)**: δ = 8.06-8.03 (d, 2H, *J* = 8.3 Hz), 7.90-7.87 (d, 2H, *J* = 9.0 Hz), 7.76-7.73 (d, 2H, *J* = 8.3 Hz), 7.40-7.34 (m, 5H), 7.08-7.05 (d, 2H, *J* = 9.0 Hz), 5.11 (s, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -63.16 (s, 3F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 163.0, 146.0, 135.6, 135.2-133.9 (q, *J* = 32.8 Hz), 132.2,

130.3, 128.8, 128.5, 128.0, 127.5, 126.5-126.4 (q, $J = 3.5$ Hz), 115.7, 70.5; **ATR-IR** (ν_{max}): 3058, 1593, 1497, 1324, 1256, 1176, 1156, 1137, 1108, 1062, 721, 669 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 393.0767, not found.

The desired benzyl-protected sulfone starting material elutes very closely with a sulfonothioate side-product impurity. Using a 4:1 hexanes:EtOAc solvent system as the mobile phase results in this mixture appearing as a single spot by TLC. However, with 1:1 hexanes: CH_2Cl_2 mobile phase separation is achievable. The identity of the impurity was serendipitously confirmed by SC-XRD when a single crystal of the sulfonothionate was picked from bulk material. The crystal was grown by slow solvent evaporation from EtOAc.



R_f: 0.18 (1:1 hexanes: CH_2Cl_2), vis: UV (254 nm); **^1H** (300 MHz, CDCl_3): δ = 7.53-7.50 d, 2H, J = 9.0 Hz), 7.45-7.37 (m, 10H), 7.30-7.27 (m, 4H), 6.97-6.91 (m, 4H), 5.14 (s, 2H), 5.10 (s, 2H); **$^{13}\text{C}\{^1\text{H}\}$** (201 MHz, CDCl_3): δ = 162.8, 161.5, 138.6, 136.2, 135.8, 135.2, 130.3, 130.1, 128.91, 128.89, 128.6, 128.4, 127.6, 119.4, 115.9, 114.8, 70.5, 70.3; **ATR-IR** (ν_{max}): 3056, 1591, 1492, 1455, 1323, 1230, 1264, 1174, 1139, 732, 702 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $[\text{M}+\text{H}]^+$ 463.5855, not found.



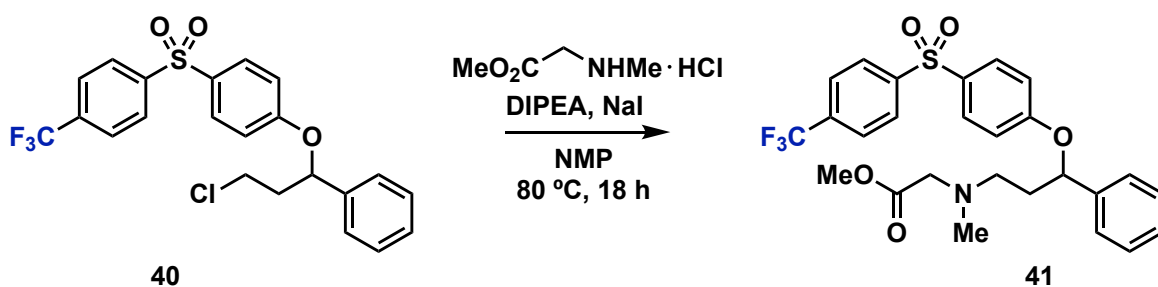
1-(benzyloxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (57 mg, 0.15 mmol, 1.0 equiv.) and Pd/C (10 mol %) were added to an oven-dried 2 mL microwave vial equipped with a stir bar. The vial was sealed, and MeOH (2.0 mL) was added. The vial was fitted with an H₂ balloon, and the reaction was vigorously stirred at rt for 16 h. After TLC indicated consumption of the starting material, the suspension was filtered over a pad of Celite and concentrated into a tared microwave vial. The resulting crude material was used without further purification.

R_f: 0.47 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.05-8.03 (d, 2H, *J* = 8.1 Hz), 7.87-7.85 (d, 2H, *J* = 8.8 Hz), 7.76-7.74 (d, 2H, *J* = 8.1 Hz), 6.95-6.92 (d, 2H, *J* = 8.8 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = -63.19 (s, 3F).

To the vessel containing the crude phenol and a stir bar were added K₂CO₃ (40 mg, 0.3 mmol, 2.0 equiv.) and (1-bromo-3-chloropropyl)benzene (54 mg, 0.23 mmol, 1.5 equiv.) as a solution in EtOH (1.0 mL). The mixture was vigorously stirred at 75 °C overnight (approx. 16 h) until TLC indicated consumption of the starting material. The mixture was diluted with H₂O (3.0 mL) and CH₂Cl₂ (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (2 × 2.0 mL), the combined organic layers were dried over Na₂SO₄ and concentrate *in vacuo*. The resulting crude oil was purified by pTLC eluting with 4:1 hexanes/EtOAc to afford

the desired 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene as a clear oil (35 mg, 51% over 2 steps).

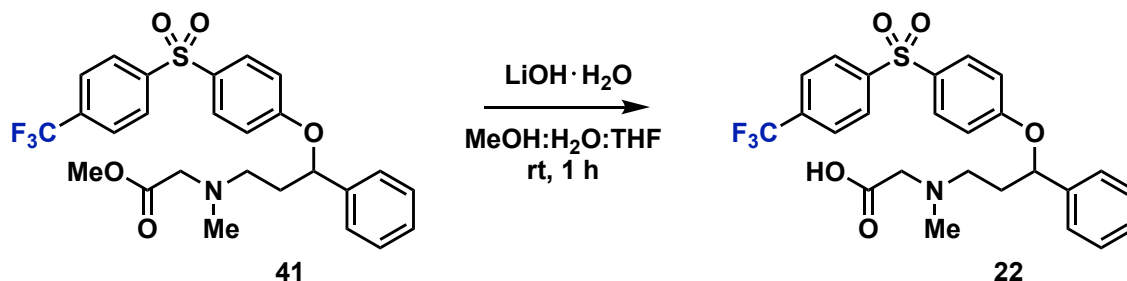
R_f: 0.45 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.01-7.98 (d, 2H, *J* = 8.2 Hz), 7.79-7.71 (m, 4H), 7.38-7.29 (m, 5H), 6.96-6.93 (d, 2H, *J* = 8.9 Hz), 5.46-5.42 (m, 1H), 3.79-3.71 (m, 1H), 3.60-3.53 (m, 1H), 2.56-2.42 (m, 1H), 2.27-2.16 (m, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = -63.18 (s, 3F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 162.3, 145.9, 139.5, 132.4, 130.2, 129.2, 128.9, 128.5, 128.0, 126.7, 126.5 (m), 125.9, 116.6, 77.4, 56.1, 41.2, 41.0, 24.6, 21.7, 13.6; **ATR-IR (ν_{max})**: 3064, 2925, 1592, 1494, 1403, 1321, 1253, 1153, 1106, 1062, 836, 721 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₂₂H₁₉ClF₃O₃S⁺ [M+H]⁺ 455.0691, found 455.0670.



An 8 mL vial equipped with a stir bar was charged with 1-(3-chloro-1-phenylpropoxy)-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene (16 mg, 35 μmol, 1.0 equiv.), sodium iodide (5.2 mg, 35 μmol, 1.0 equiv.), and sarcosine methyl ester hydrochloride (9.6 mg, 70 μmol, 2.0 equiv.). NMP (0.4 mL) was added via syringe, followed by DIPEA (24 μL, 140 μmol, 4.0 equiv.). The reaction was heated to 70 °C and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H₂O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na₂SO₄, and

concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes:EtOAc to afford the desired methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl)phenoxy)propyl)glycinate as a clear oil (10 mg, 55%).

R_f: 0.31 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.00-7.98 (d, 2H, *J* = 8.2 Hz), 7.77-7.71 (m, 4H), 7.35-7.28 (m, 5H), 6.95-6.93 (d, 2H, *J* = 8.9 Hz), 5.34-5.31 (m, 1H), 3.64 (s, 3H), 3.24 (s, 2H), 2.69-2.55 (m, 2H), 2.37 (s, 3H), 2.22-2.13 (m, 1H), 2.01-1.93 (m, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = − 63.18 (s, 3F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 171.4, 162.6, 146.0, 140.6, 131.9, 130.1, 128.9, 128.1, 128.0, 126.5-126.3 (q, *J* = 3.7 Hz), 125.9, 116.5, 78.7, 58.6, 53.0, 51.6, 42.4, 36.7; **ATR-IR (ν_{max})**: 2950, 2851, 1743, 1592, 1494, 1319, 1252, 1142, 1061, 702 cm^{−1}; **HRMS (*m/z*)**: (ESI) calc'd for C₂₆H₂₇F₃NO₅S⁺ [M+H]⁺ 522.1557, not found.



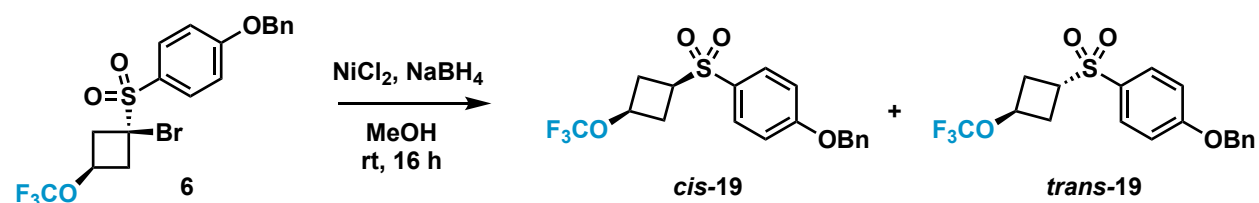
To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl)phenoxy)propyl)glycinate (17 mg, 32 μmol, 1.0 equiv.), followed by MeOH (0.5 mL), THF (0.5 mL), and H₂O (0.5 mL). While stirring, lithium hydroxide monohydrate (6.6 mg, 0.16 mmol, 5.0 equiv.) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to approx. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na₂SO₄ and

concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH₂Cl₂ to afford the desired *N*-methyl-*N*-(3-phenyl-3-(4-((4-(trifluoromethyl)phenyl)sulfonyl)phenoxy)propyl)glycine as a white solid (3 mg, 6%). All analytical data matched the previously reported literature. Due to the small amount of material obtained the ¹³C chemical shifts were not fully resolved. Additionally, the final product was not fully soluble in CDCl₃ leading to peak broadening and loss of resolution. As the material needed to be prepared for *in vitro* testing, the purity of the material was estimated by integration of the ¹H NMR spectrum with an increased d1 relaxation delay.

R_f: 0.11 (9:1 CH₂Cl₂:MeOH), vis: UV (254 nm); **¹⁹F (282 MHz, CDCl₃)**: δ = −63.15 (s, 3F);

HRMS (*m/z*): (ESI) calc'd for C₂₅H₂₄F₃NO₅S⁺ [M+H]⁺ 508.1406, found 508.1374; **HRMS (*m/z*)**: (APCI) calc'd for C₂₅H₂₃F₃NO₅S[−] [M-H][−] 506.13, found 506.12.

N-methyl-*N*-(3-phenyl-3-(4-((-3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycine

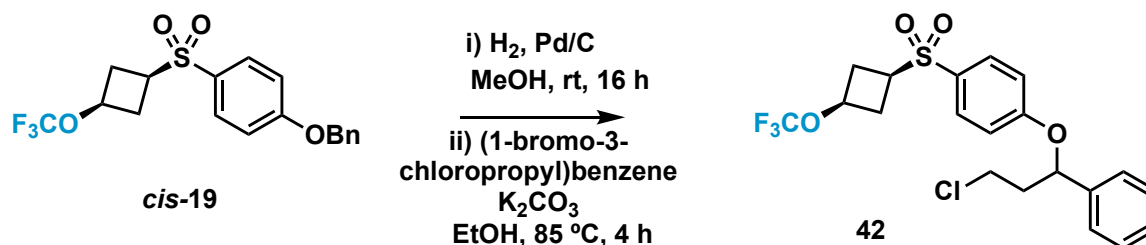


To an 8-mL vial equipped with a stir bar was added 1-(benzyloxy)-4-((1-bromo-3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (81 mg, 0.17 mmol, 1.0 equiv.), followed by MeOH (1.0 mL). The mixture was stirred until all the starting material had dissolved and NiCl₂ (11 mg, 90 μmol, 0.5 equiv.) was added in one portion and NaBH₄ (32 mg, 0.85 mmol, 5.0 equiv.) in three portions. Strong bubbling was observed alongside the formation of a black precipitate.

The reaction was allowed to stir for 16 h before 5.0 mL CH₂Cl₂ were added. The crude suspension was filtered through a Celite plug into a separatory funnel. The organic layer was washed with sat. NH₄Cl (2 × 2.0 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by pTLC, eluting with 7:3 hexanes:EtOAc. The *cis* and *trans* isomers were completely separable with careful loading. The desired 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene was obtained as a white solid (58 mg, 87%), only the *cis* isomer was carried forward.

R_f: 0.34 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.81-7.77 (m, 2H), 7.45-7.33 (m, 5H), 7.12-7.08 (m, 2H), 5.14 (s, 2H), 4.57-4.47 (p, 1H, *J* = 7.5 Hz), 3.42-3.30 (m, 1H), 2.80-2.55 (m, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.66 (s, 3F).

¹³C{¹H} (201 MHz, CDCl₃): δ = 163.3, 135.7, 130.6, 129.4, 128.9, 128.6, 127.6, 115.6, 70.6, 65.1-65.0 (q, *J* = 3.3 Hz), 49.0, 32.0; **ATR-IR (ν_{max})**: 3060, 2987, 1737, 1592, 1496, 1228, 1177, 1136, 997, 848, 807, 744, 693 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for [M+H]⁺ 387.0873, found 387.0873.



To an oven-dried 2 mL microwave vial equipped with a stir bar were added 1-(benzyloxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (32 mg, 83 μmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper and MeOH (4.0 mL) was added *via* syringe. The vessel was purged with an H₂ balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After

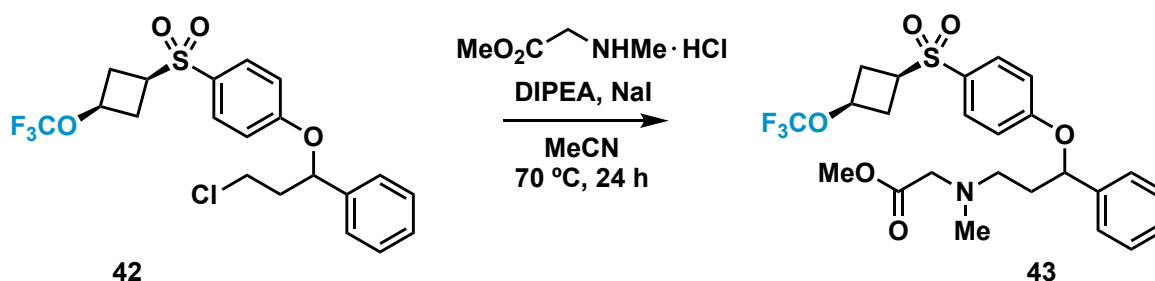
TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The crude material was used in the next step without further purification.

R_f: 0.5 (1:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.75-7.70 (m, 2H), 7.00-6.95 (m, 2H), 6.56 (s, 1H), 4.58-4.48 (p, 1H, *J* = 7.5 Hz), 3.44-3.33 (m, 1H), 2.79-2.56 (m, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.79 (s, 3F)

The crude 4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (0.5 mL), and (1-bromo-3-chloropropyl)benzene (42 mg, 0.18 mmol, 2.0 equiv.) was added as a solution in EtOH (0.5 mL). Potassium carbonate (23 mg, 0.18 mmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 85 °C overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H₂O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH₂Cl₂ and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. The desired 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (**42**) was obtained as a clear oil (20 mg, 54% over 2 steps).

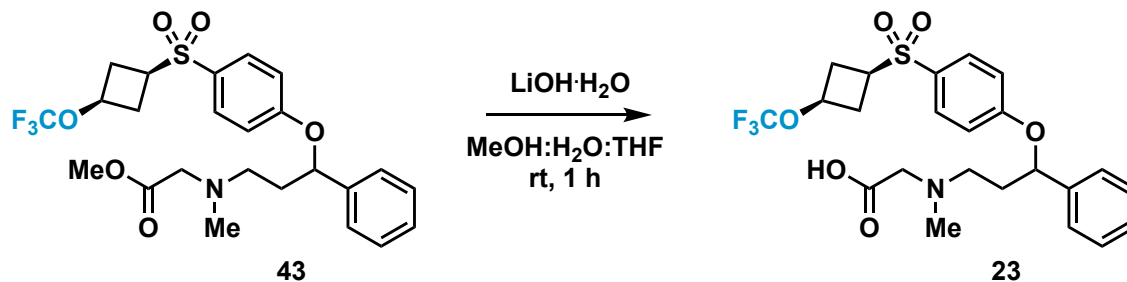
R_f: 0.42 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.70-7.67 (m, 2H), 7.40-7.28 (m, 5H), 6.99-6.96 (m, 2H), 5.50-5.45 (m, 1H), 4.54-4.45 (p, 1H, *J* = 7.5 Hz), 3.82-3.74

(m, 1H), 3.63-3.56 (m, 1H), 3.36-3.24 (m, 1H), 2.77-2.69 (m, 2H), 2.60-2.46 (m, 3H), 2.31-2.19 (m, 1H); ^{19}F (282 MHz, CDCl_3): δ = -59.78 (s, 3F); $^{13}\text{C}\{^1\text{H}\}$ (201 MHz, CDCl_3): δ = 162.5, 139.5, 130.5, 130.4, 129.6, 129.2, 128.6, 126.0, 123.7-118.6 (q, J = 256.5 Hz), 116.6, 77.5, 65.1-65.0 (q, J = 3.3 Hz), 49.0, 41.2-41.1 (d, J = 14.3 Hz), 32.0-31.9 (q, J = 7.7 Hz); ATR-IR (ν_{max}): 3020, 1593, 1494, 1215, 1145, 1089, 835, 746, 697 cm^{-1} ; HRMS (m/z): (ESI) calc'd for $[\text{M}+\text{H}]^+$ 449.0796, found 449.0790.



To an 8-mL vial equipped with a stir bar was added 1-(3-chloro-1-phenylpropoxy)-4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (20 mg, 40 μmol , 1.0 equiv.), sodium iodide (11.0 mg, 70 μmol , 1.5 equiv.), and sarcosine methyl ester hydrochloride (10 mg, 70 μmol , 1.5 equiv.). MeCN (0.5 mL) was added *via* syringe, followed by DIPEA (30 μL , 0.12 mmol, 3.0 equiv.). The reaction was heated to 70 $^{\circ}\text{C}$ and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H_2O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2×2.0 mL). The combined organic layers were washed with brine (1×2.0 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes:EtOAc. The desired methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (**43**) was obtained as a clear oil (8 mg, 40 %).

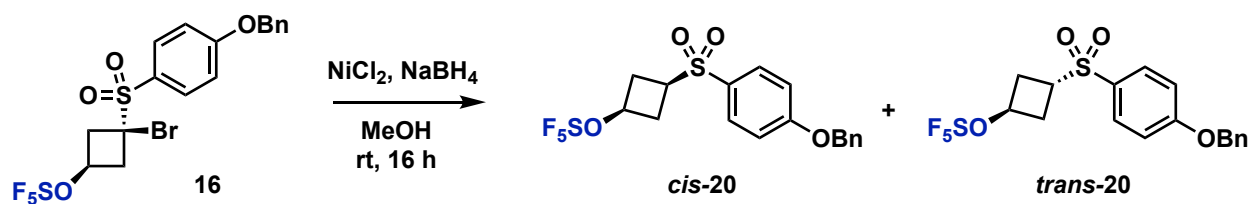
R_f: 0.35 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.67-7.64 (m, 2H), 7.38-7.25 (m, 5H), 6.99-6.96 (m, 2H), 5.39-5.34 (m, 1H), 4.54-4.44 (p, 1H, *J* = 7.5 Hz), 3.66 (s, 3H), 3.35-3.23 (m, 3H), 2.77-2.51 (m, 6H), 2.38 (s, 3H), 2.26-2.15 (m, 1H), 2.05-1.94 (m, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.78 (s, 3F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 171.4, 162.9, 140.7, 130.4, 129.1, 129.0, 128.2, 122.0-120.3 (m), 116.6, 78.7, 65.1-65.0 (q, *J* = 3.3 Hz), 58.6, 53.1, 51.7, 49.0, 42.4, 36.7, 32.0-31.9 (d, *J* = 6.9 Hz), 31.1; **ATR-IR (ν_{max})**: 3021, 1740, 1592, 1495, 1454, 1273, 1215, 1175, 1143, 835, 746, 682 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for [M+H]⁺ 516.1663, found 516.1623.



To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (40 mg, 78 μmol, 1.0 equiv.), followed by MeOH (1.0 mL), THF (1.0 mL), and H₂O (1.0 mL). While stirring, lithium hydroxide monohydrate (16 mg, 0.39 mmol, 5.0 equiv.) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1M HCl to approx. pH 4-5, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH₂Cl₂ to afford the desired *N*-methyl-*N*-(3-phenyl-3-((3-(trifluoromethoxy)cyclobutyl)sulfonyl)phenoxy)propyl)glycine (**23**) as a white solid (17 mg, 43 %).

R_f: 0.14 (99:1 CH₂Cl₂:MeOH), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.63-7.60 (d, 2H, *J* = 8.7 Hz), 7.36-7.27 (m, 5H), 6.96-6.93 (d, 2H, *J* = 8.7 Hz), 5.42 (br s, 1H), 4.54-4.44 (p, 1H, *J* = 7.4 Hz), 3.38-3.16 (m, 5H), 2.72-2.49 (m, 7H), 2.34-2.25 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -59.73 (s, 3F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 162.1, 139.4, 130.6, 129.7, 129.2, 128.6, 126.2-116.0 (q, *J* = 257.0 Hz), 125.9, 116.7, 78.2, 65.1-65.0 (q, *J* = 3.5 Hz), 48.8, 32.0, 31.9, 29.8; **ATR-IR (ν_{max})**: 2992, 2562, 1712, 1562, 1380, 1142, 1088, 865, 800, 758, 654 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₂₃H₂₅F₃NO₆S⁻ [M-H]⁻ 500.1360, not found; **HRMS (*m/z*)**: (APCI) calc'd for C₂₃H₂₅F₃NO₆S⁻ [M-H]⁻ 500.14, found 500.14; **LRMS (*m/z*)**: (GC) calc'd for C₂₃H₂₅F₃NO₆S⁻ [M-H]⁻ 500.1, not found.

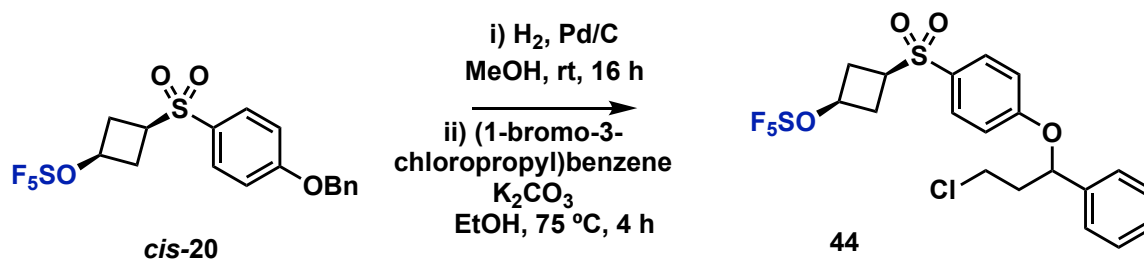
Attempts toward *N*-methyl-*N*-(3-(4-((-3-((pentafluoro-λ⁶-sulfonyl)oxy)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycine



To an 8 mL vial equipped with a stir bar was added (3-((4-(benzyloxy)phenyl)sulfonyl)-3-bromocyclobutoxy)pentafluoro-λ⁶-sulfane (31 mg, 60 μmol, 1.0 equiv.), followed by MeOH (1.0 mL). The mixture was stirred until all the starting material had dissolved and NiCl₂ (3.9 mg, 30 μmol, 0.5 equiv.) was added in one portion and NaBH₄ (11.3 mg, 0.3 mmol, 5.0 equiv.) in three portions. Strong bubbling was observed alongside the formation of a black precipitate. The

reaction was allowed to stir for 16 h before 5.0 mL CH₂Cl₂ were added. The crude suspension was filtered through a Celite plug into a separatory funnel. The organic layer was washed with sat. NH₄Cl (2 × 2.0 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by pTLC, eluting with 3:2 hexanes:EtOAc. The *cis* and *trans* isomers were completely separable with careful loading. The desired (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane was obtained as a white solid (20 mg, 70%), only the *cis* isomer was carried forward.

R_f: 0.18 (*cis* isomer, 4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.80-7.70 (d, 2H, *J* = 9.0 Hz), 7.42-7.36 (m, 5H), 7.12-7.07 (d, 2H, *J* = 9.0 Hz), 5.14 (s, 2H), 4.95-4.85 (p, 1H, *J* = 7.4 Hz), 3.39-3.27 (m, 1H), 2.83-2.73 (m, 2H), 2.67-2.58 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 77.41-75.17 (p, 1F, *J* = 154.8 Hz), 63.12-62.53 (m, 4F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 163.2, 135.6, 130.4, 129.3, 128.8, 128.5, 127.5, 115.6, 70.5, 70.4-70.2 (p, *J* = 4.7 Hz), 48.1, 32.4; **ATR-IR (v_{max})**: 2919, 1592, 1496, 1387, 1309, 1275, 1140, 1089, 995, 857, 747, 722 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₇H₁₈F₅O₄S₂⁺ [M+H]⁺ 445.0562, not found; **HRMS (*m/z*)**: (APCI) calc'd for C₁₇H₁₈F₅O₄S₂⁺ [M+H]⁺ 445.06, found 445.06.



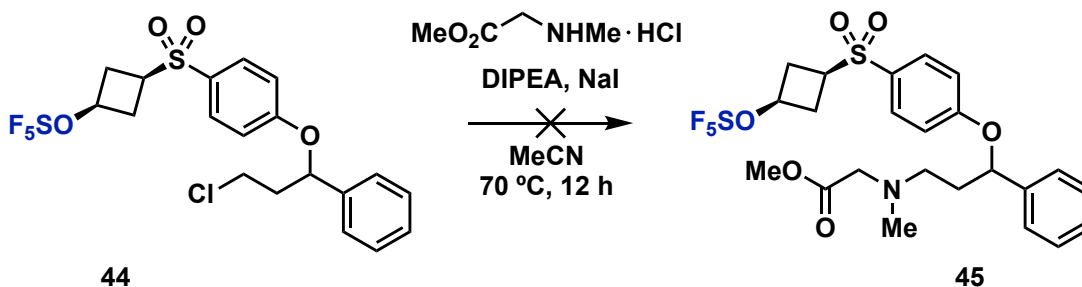
To an oven-dried 2-mL microwave vial equipped with a stir bar were added (3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane (20 mg, 45 μ mol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper and MeOH (0.5 mL) was added *via* syringe.

The vessel was purged with an H₂ balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.25 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.72-7.70 (d, 2H, J = 8.7 Hz), 6.99-6.98 (d, 2H, J = 8.7 Hz), 4.94-4.87 (p, 1H, J = 7.4 Hz), 3.39-3.30 (m, 1H), 2.80-2.72 (m, 2H), 2.67-2.60 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 77.00-75.30 (p, 1F, J = 155.6 Hz), 63.01-62.60 (m, 4F).

The crude 4-((3-((pentafluoro-λ⁶-sulfanyl)oxy)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (0.25 mL), and (1-bromo-3-chloropropyl)benzene (13 mg, 54 μmol, 1.2 equiv.) was added as a solution in EtOH (0.25 mL). Potassium carbonate (11 mg, 90 μmol, 2.0 equiv.) was added in one portion and the mixture was stirred at 85 °C overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H₂O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH₂Cl₂ and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. The desired (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro-λ⁶-sulfane (**44**) was obtained as a clear oil (12 mg, 53% over 2 steps).

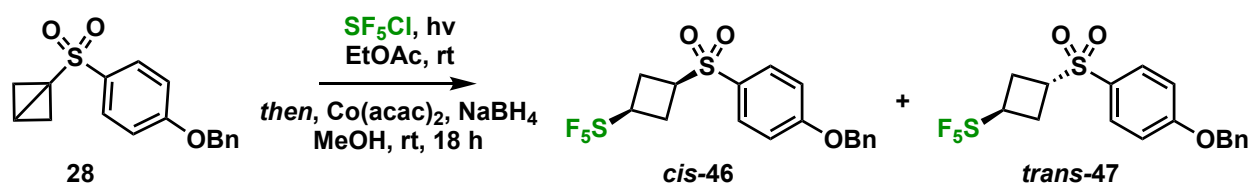
R_f: 0.41 (4:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.70-7.67 (d, 2H, *J* = 9.0 Hz), 7.37-7.30 (m, 5H), 7.00-6.97 (m, 2H, *J* = 9.0 Hz), 5.50-5.45 (m, 1H), 4.92-4.82 (p, 1H, *J* = 7.3 Hz), 3.82-3.74 (m, 1H), 3.62-3.55 (m, 1H), 3.33-3.22 (m, 1H), 2.80-2.69 (m, 2H), 2.64-2.45 (m, 3H), 2.30-2.19 (m, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = 77.41-75.16 (p, 1F, *J* = 161.5 Hz), 63.11-62.52 (m, 4F); **¹³C{¹H} (201 MHz, CDCl₃)**: δ = 162.5, 139.5, 130.4, 129.5, 129.2, 128.6, 125.9, 116.6, 77.5, 70.5-70.3 (p, *J* = 4.7 Hz), 48.4, 41.2, 41.1, 32.5, 32.4; **HRMS (*m/z*)**: (ESI) calc'd for C₂₀H₂₃ClF₅O₄S²⁺ [M+H]⁺ 521.0641, not found.



To an 8-mL vial equipped with a stir bar was added (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutoxy)pentafluoro- λ^6 -sulfane (20 mg, 39 μmol , 1.0 equiv.), sodium iodide (7.0 mg, 47 μmol , 1.2 equiv.), and sarcosine methyl ester hydrochloride (6.6 mg, 47 μmol , 1.2 equiv.). MeCN (0.2 mL) was added *via* syringe, followed by DIPEA (16 μL , 94 μmol , 2.4 equiv.). The reaction was heated to 70 $^\circ\text{C}$ and progress was monitored by TLC. Upon consumption of the starting material (ca. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H₂O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 $\times$ 2.0 mL). The combined organic layers were washed with brine (1 $\times$ 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Analysis by ¹H and ¹⁹F NMR indicated that a majority of the OSF₅-CB had decomposed under the designated reaction conditions (less than 5% OSF₅-CB could be accounted for by ¹⁹F). We postulated that either 1) the starting material is

sensitive to base, leading to OSF₅ elimination or 2) the OSF₅ group may act as a superior leaving group, and substitution occurred on the CB instead. Similar results were obtained when the reaction temperature was lowered to 50 °C and when NMP was used in place of MeCN.

***N*-methyl-*N*-(3-(4-((3-(pentafluoro-λ⁶-sulfanyl)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycine:**



An oven-dried microwave vial equipped with a stir bar was charged with 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (60 mg, 0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added followed by a solution of SF₅Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LEDs (Kessil A160WE Tuna Blue, maximum intensity) for 18 hours (the vial was placed ca. 5 cm away from the light source). Then, the solvent was removed *in vacuo* and MeOH (1.3 mL, 0.15 M) was added followed by Co(acac)₂ (77 mg, 0.3 mmol, 1.5 equiv.). NaBH₄ (38 mg, 1.0 mmol, 5.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 16 h. Upon completion, the solution was diluted with CH₂Cl₂ (approx. 2.0 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH₄Cl (5.0 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic fractions were washed with H₂O and brine (1 × 5 mL), dried over Na₂SO₄ or MgSO₄, concentrated *in vacuo*. The crude residue was purified by pTLC

(preparative thin-layer chromatography) eluting with 4:1 hexanes:EtOAc. Followed by 100% CH₂Cl₂. 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane was obtained as a white, crystalline solid (51 mg, 60%). Compound *trans*-**21** was isolated as a white solid (28 mg) and *cis*-**21** was isolated as a white solid (23 mg); the total isolated yield was 60%.

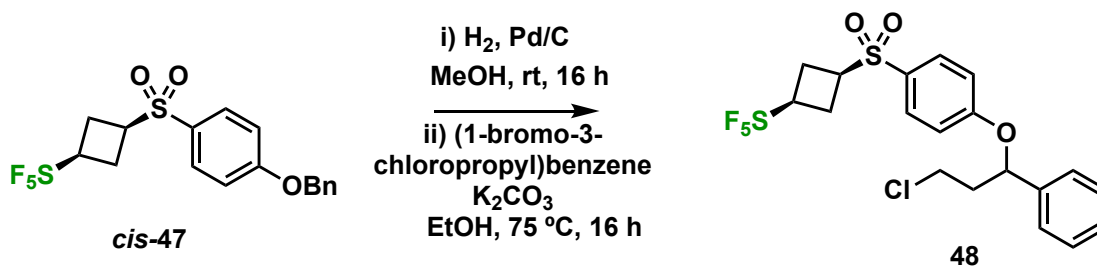
trans-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane:

R_f: 0.32 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 131.2 – 137.0 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.84-7.79 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.96-4.80 (m, 1H), 3.71-3.65 (m, 1H), 3.10-2.85 (m, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 84.00-81.95 (p, 1F, J = 143.2 Hz), 51.79-51.21 (dd, 4F, J = 143.2 Hz, J = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 163.5, 135.7, 130.8, 128.9, 128.7, 128.6, 127.6, 115.7, 73.5-72.6 (m), 53.3, 29.8-29.6 (m); **ATR-IR ($\nu_{\max}$)**: 2984, 2921, 2851, 1592, 1574, 1496, 1294, 1250, 1163, 1089, 848, 826, 794, 767, 748, 724, 696, 653 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₇H₁₈F₅O₃S₂+[M-H]⁺ 429.0613, found 429.0612

cis-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane:

R_f: 0.16 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 150.5 – 153.5 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.82-7.77 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.35-4.19 (m, 1H), 3.53-3.41 (m, 1H), 3.18-3.07 (m, 2H), 2.67-2.57 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.78-80.72 (p, 1F, J = 143.2 Hz), 52.16-51.62 (dd, 4F, J = 143.2 Hz, J = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 163.5, 135.7, 130.8, 128.9, 128.9, 128.6, 127.6, 115.8, 70.6, 69.4-68.6 (m), 50.4, 30.7-30.4 (m); **ATR-IR ($\nu_{\max}$)**: 2952, 2921, 2852, 1592, 1578, 1498, 1281, 1260, 1247, 1142, 1115, 872, 840,

818, 783, 751, 734, 722, 695, 662, 637 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $\text{C}_{17}\text{H}_{18}\text{F}_5\text{O}_3\text{S}_2 + [\text{M}-\text{H}]^+$ 429.0613, found 429.0595



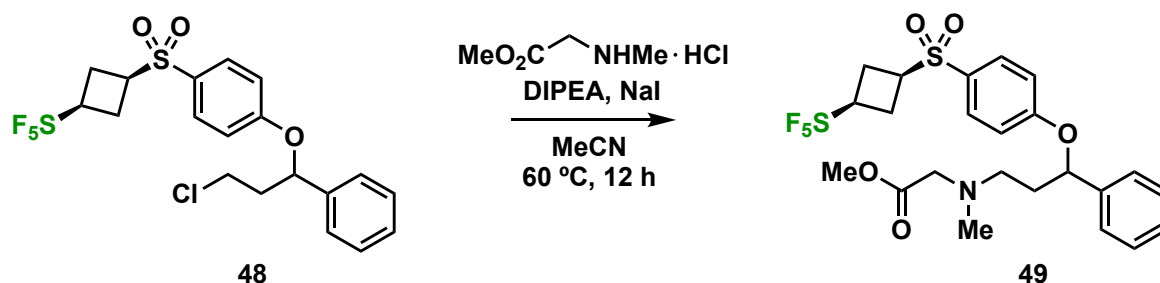
To an oven-dried 2-mL microwave vial equipped with a stir bar were added *cis*-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro- λ^6 -sulfane (130 mg, 0.30 mmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper, then MeOH (0.75 mL) and THF (0.75 mL) were added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (approx. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.21 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **^1H (300 MHz, CDCl_3)**: δ = 7.78-7.75 (m, 2H), 7.00-6.97 (m, 2H), 5.82 (s, 1H), 4.35-4.19 (m, 1H), 3.53-3.42 (m, 1H), 3.18-3.07 (m, 2H), 2.67-2.58 (m, 2H).

The crude 4-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenol was concentrated into an 8-mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (2 mL), and (1-bromo-3-chloropropyl)benzene (140 mg, 0.60 mmol, 2.0 equiv.) was added as a solution in EtOH (1 mL). Potassium carbonate (83 mg, 0.60 mmol, 2.0 equiv.) was added in

one portion and the mixture was stirred at 75 °C overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H₂O (3.0 mL) and EtOAc (2.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH₂Cl₂ and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. 3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ⁶-sulfane was obtained as a clear oil (93 mg, 63% over 2 steps).

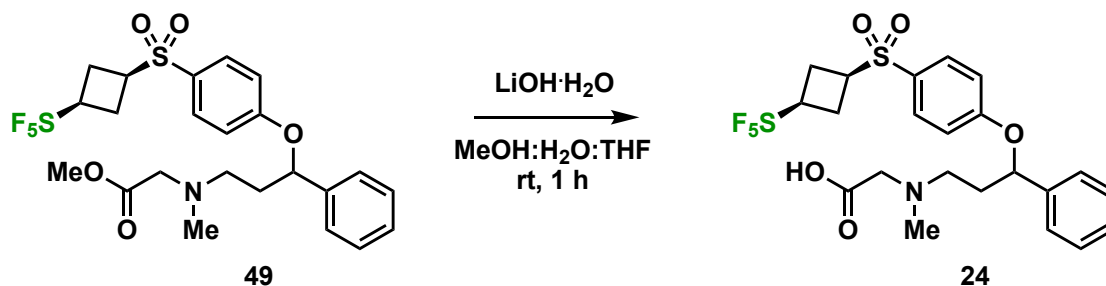
R_f: 0.14 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.71-7.66 (m, 2H), 7.40-7.27 (m, 5H), 7.01-6.97 (m, 2H), 5.50-5.46 (m, 1H), 4.32-4.16 (m, 1H), 3.82-3.74 (m, 1H), 3.63-3.55 (m, 1H), 3.47-3.36 (m, 1H), 3.15-3.03 (m, 2H), 2.63-2.45(m, 3H), 2.30-2.19 (m,1H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.78-80.73 (p, 1F, *J* = 143.2 Hz), 52.15-51.61 (dd, 4F, *J_F* = 143.2 Hz, *J* = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 162.6, 139.4, 130.6, 129.2, 129.0, 128.6, 125.9, 116.6, 69.3-68.5 (m), 50.34, 41.14-41.07 (m), 30.6-30.4 (m); **ATR-IR (ν_{max})**: 3066, 3032, 2966, 2928, 1592, 1494, 1320, 1300, 1280, 1251, 1167, 1142, 824, 785, 699, 635 cm⁻¹; **HRMS (*m/z*)**: (ESI) calc'd for C₁₉H₂₁ClF₅O₃S₂⁺ [M-H]⁺ 491.0536, found 491.0533.



To an 8-mL vial equipped with a stir bar was added (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ⁶-sulfane (21.5 mg, 44 μmol, 1.0 equiv.), sodium iodide

(7.9 mg, 53 μ mol, 1.2 equiv.), and sarcosine methyl ester hydrochloride (7.4 mg, 53 μ mol, 1.2 equiv.). MeCN (X mL) was added *via* syringe, followed by DIPEA (18.5 μ L, 106 μ mol, 2.4 equiv.). The reaction was heated to 70 °C and progress was monitored by TLC. Upon consumption of the starting material (ca. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H₂O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 $\times$ 2.0 mL). The combined organic layers were washed with brine (1 $\times$ 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes/EtOAc to afford methyl *N*-methyl-*N*-(3-(4-(3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl) sulfonyl)phenoxy)-3-phenylpropyl)glycinate as a clear oil (9.8 mg, 40%).

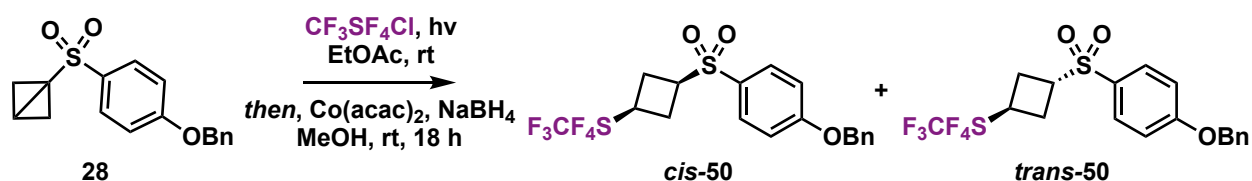
R_f: 0.10 (1:1 hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.70-7.65 (m, 2H), 7.37-7.27 (m, 5H), 7.01-6.97 (m, 2H), 5.40-5.35 (m, 1H), 4.31-4.15 (m, 1H), 3.67 (s, 3H), 3.46-3.35 (m, 1H), 3.27 (s, 2H), 3.13-3.02 (m, 2H), 2.74-2.53 (m, 4H), 2.39 (s, 3H), 2.26-1.94 (m, 3H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.78-80.72 (p, 1F, J = 143.2 Hz), 52.14-51.61 (dd, 4F, J = 143.2 Hz, J = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 171.4, 163.0, 140.6, 130.5, 129.0, 128.5, 128.2, 126.0, 116.7, 78.8, 69.2-68.8 (m), 58.6, 53.1, 51.7, 50.4, 42.4, 36.7, 30.6-30.5 (m); **ATR-IR (ν_{max})**: 3032, 2953, 2847, 2808, 1743, 1592, 1577, 1494, 1455, 1321, 1302, 1280, 1254, 1204, 1175, 1144, 1089, 830, 787 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₂₃H₂₉F₅NO₅S₂⁺ [M-H]⁺ 558.1402, found 558.1381.



To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-(4-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycinate (7.8 mg, 0.014 mmol, 1.0 equiv.), followed by MeOH (0.1 mL), THF (0.1 mL), and H₂O (0.1 mL). While stirring, lithium hydroxide monohydrate (1 mg) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to ca. pH 4-5, and the aqueous layer was extracted with EtOAc (3 $\times$ 2.0 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH₂Cl₂ to afford *N*-methyl-*N*-(3-(4-((3-(pentafluoro- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenoxy)-3-phenylpropyl)glycine as a white solid (7.2 mg, 95 %).

R_f: 0.51 (4:1 DCM:MeOH), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.73-7.70 (m, 2H), 7.43-7.26 (m, 5H), 7.14-7.11 (m, 2H), 5.61-5.56 (m, 1H), 4.78-4.69 (m, 1H), 3.85-3.74 (m, 2H), 3.27 (m, 2H), 2.86-2.73 (m, 4H), 2.66-2.56 (m, 2H), 2.48 (m, 2H), 2.26-1.99 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 86.87-84.81 (p, 1F, J = 143.2 Hz), 52.92-52.39 (dd, 4F, J = 143.2 Hz, J = 5.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 162.0, 140.3, 130.3, 128.7, 128.5, 128.0, 126.0, 116.5, 77.5, 69.8, 58.3, 52.5, 48.8, 41.5, 40.0, 34.5, 29.9; **ATR-IR (ν_{max})**: 3429, 3170, 2847, 1643, 1593, 1382, 1322, 1280, 1251, 1146, 870, 837, 790, 700, 663 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₂₂H₂₇F₅NO₅S₂⁺ [M-H]⁺ 544.1246, found 544.1257.

***N*-methyl-*N*-(3-phenyl-3-(4-(((1*s*,3*s*)-3-(tetrafluoro(trifluoromethyl)- λ⁶-sulfonyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine**



To an oven-dried microwave vial equipped with a stir bar was added 1-((4-(benzyloxy)phenyl)sulfonyl)bicyclo[1.1.0]butane (60 mg, 0.2 mmol, 1.0 equiv.). The vial was crimped, then evacuated and backfilled with Ar three times. Anhydrous EtOAc (2.0 mL) was added followed by a solution of CF₃SF₄Cl in *n*-pentane (0.24 mmol, 1.2 equiv.). The Ar line was removed, and the reaction was irradiated with white LEDs (Kessil A160WE Tuna Blue, maximum intensity) for 18 h (the vial was placed ca. 5 cm away from the light source). Then, the solvent was removed *in vacuo* and MeOH (1.3 mL, 0.15 M) was added followed by Co(acac)₂ (77 mg, 0.3 mmol, 1.5 equiv.). NaBH₄ (38 mg, 1.0 mmol, 5.0 equiv.) was added slowly in three portions (vigorous bubbling and formation of a black precipitate was observed). The reaction mixture was stirred at room temperature (ca. 23 °C) for 16 h. Upon completion, the solution was diluted with CH₂Cl₂ (approx. 2.0 mL) and filtered through a Celite plug. The filtrate was then transferred to a separatory funnel and sat. NH₄Cl (5.0 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic fractions were washed with H₂O and brine (1 × 5 mL), dried over Na₂SO₄ or MgSO₄, concentrated *in vacuo*. The crude residue was purified by pTLC (preparative thin layer chromatography) eluting with 4:1 hexanes:EtOAc. Followed by 100% CH₂Cl₂. 3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)pentafluoro-λ⁶-sulfane was obtained as a

white, crystalline solid (39 mg, 64%). The *trans* isomer was isolated as a white solid (18 mg) and *cis* isomer was isolated as a white solid (21 mg); the total isolated yield was 54%.

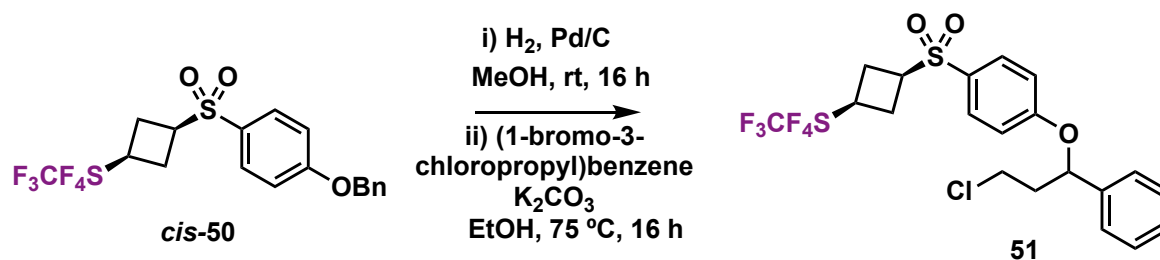
trans-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ^6 -sulfane:

R_f: 0.39 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 161.4-168.6 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.84-7.79 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 5.06-4.94 (m, 1H), 3.74-3.65 (m, 1H), 3.15-3.04 (m, 2H), 2.95-2.86 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 28.31-28.02 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), -63.34 - -63.70 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 163.46, 135.68, 130.98, 128.97, 128.77, 128.66, 127.65, 115.76, 75.75-75.01 (m), 70.64, 53.49, 30.12-29.83 (m); **ATR-IR (v_{max})**: 2960, 2920, 2851, 1592, 1574, 1494, 1273, 1236, 1219, 1138, 1088, 989, 802, 784, 774, 747, 724, 700, 664 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₁₈H₁₈F₇O₃S₂⁺ [M-H]⁺: calculated 479.0581, measured 479.0583

cis-3-((4-(benzyloxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ^6 -sulfane:

R_f: 0.15 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **m.p.**: 157.9-162.8 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.82-7.77 (m, 2H), 7.44-7.33 (m, 5H), 7.13-7.08 (m, 2H), 5.15 (s, 2H), 4.47-4.31 (m, 1H), 3.52-3.41 (m, 1H), 3.24-3.13 (m, 2H), 2.68-2.58 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 28.91-28.62 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), -63.37 - -63.73 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 163.44, 135.69, 130.73, 128.98, 128.94, 128.63, 127.63, 115.73, 71.47-70.63 (m), 50.49, 30.82-30.71 (m); **ATR-IR (v_{max})**: 3036, 2921, 1594, 1579, 1499, 1326, 1302, 1281, 1248,

1226, 1183, 1164, 1139, 1091, 1027, 993, 782, 768, 751, 724, 710, 690, 644, 627 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $\text{C}_{18}\text{H}_{18}\text{F}_7\text{O}_3\text{S}_2^+$ $[\text{M}-\text{H}]^+$: calculated 479.0581, measured 479.0693.



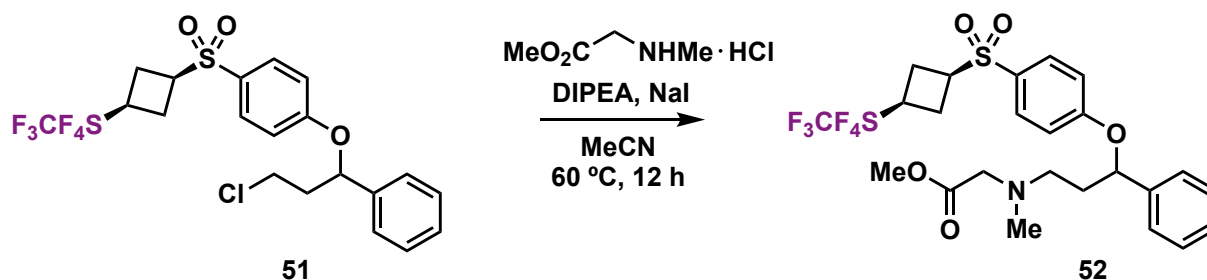
To an oven-dried 2 mL microwave vial equipped with a stir bar was added *cis*-3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ^6 -sulfane (95 mg, 0.20 mmol, 1.0 equiv.) and Pd/C (10 mol %). The vial was sealed with a crimper, then MeOH (0.55 mL) and THF (0.55 mL) were added *via* syringe. The vessel was purged with an H_2 balloon and allowed to stir vigorously overnight (ca. 16 h) at rt. After TLC indicated complete consumption of the starting material, the suspension was filtered over tightly packed Celite and the filtrate was concentrated *in vacuo*. The resulting crude material was used in the next step without further purification.

R_f: 0.30 (3:2 Hexanes:EtOAc), vis: UV (254 nm); **^1H (300 MHz, CDCl_3)**: δ = 7.79-7.74 (m, 2H), 7.01-6.96 (m, 2H), 5.73 (s, 1H), 4.47-4.32 (m, 1H), 3.52-3.41 (m, 1H), 3.24-3.13 (m, 2H), 2.68-2.60 (m, 2H).

The crude 4-((-3-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenol was concentrated into an 8 mL vial, dried under high vacuum, and stir bar was added. The crude oil was taken up in EtOH (1.5 mL), and (1-bromo-3-chloropropyl)benzene (93 mg, 0.40 mmol, 2.0 equiv.) was added as a solution in EtOH (0.5 mL). Potassium carbonate (55 mg, 0.40 mmol,

2.0 equiv.) was added in one portion and the mixture was stirred at 75 °C overnight (approx. 16 h). After TLC indicated consumption of the starting material, the mixture was diluted with H₂O (3.0 mL) and EtOAc (2.0 mL). The layers were separated and the aqueous was extracted with EtOAc (1 × 2.0 mL). The combined organic layers were washed with brine (1 × 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was taken up in 0.2 mL CH₂Cl₂ and loaded directly onto a pTLC plate, eluting with 4:1 hexanes:EtOAc. (3-((4-(3-chloro-1-phenylpropoxy)phenyl)sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)-λ⁶-sulfane was obtained as a clear oil (66 mg, 61% over 2 steps).

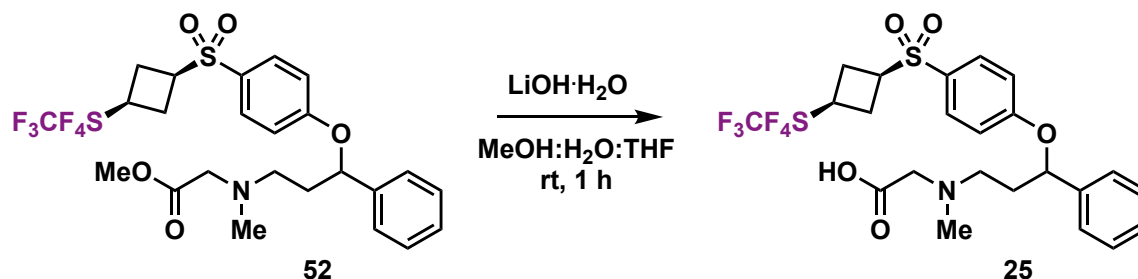
R_f: 0.16 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ= 7.72-7.66 (m, 2H), 7.40-7.27 (m, 5H), 7.01-6.95 (m, 2H), 5.50-5.46 (m, 1H), 4.44-4.28 (m, 1H), 3.82-3.74 (m, 1H), 3.63-3.55 (m, 1H), 3.47-3.35 (m, 1H), 3.20-3.09 (m, 2H), 2.64-2.45 (m, 3H), 2.30-2.17 (m, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = 28.89-28.60 (qd, 4F, ³J_{F-F} = 25.6, ³J_{F-H} = 5.8 Hz), -63.39 - -63.74 (dd, 4F, ²J_{F-F} = 25.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ= 162.6, 143.9, 139.5, 130.6, 129.2, 129.1, 128.8, 128.6, 128.1, 125.93, 125.90, 116.6, 71.5, 71.4-71.0 (m), 50.4, 41.9, 41.6, 41.2, 41.1, 30.8-30.7 (m); **ATR-IR (ν_{max})**: 2969, 1592, 1493, 1321, 1301, 1280, 1231, 1143, 1089, 783, 721, 706, 639 cm⁻¹; **HRMS (m/z)**: (ESI) calc'd for C₂₀H₂₁ClF₇O₃S₂⁺ [M-H]⁺ 541.0504, found 541.0539



To an 8-mL vial equipped with a stir bar was added ((3-((4-(3-chloro-1-phenylpropoxy) phenyl) sulfonyl)cyclobutyl)tetrafluoro(trifluoromethyl)- λ^6 -sulfane (33 mg, 61 μ mol, 1.0 equiv.), sodium iodide (11 mg, 73 μ mol, 1.2 equiv.), and sarcosine methyl ester hydrochloride (10 mg, 73 μ mol, 1.2 equiv.). MeCN (0.7 mL) was added *via* syringe, followed by DIPEA (25 μ L, 146 μ mol, 2.4 equiv.). The reaction was heated to 70 °C and progress was monitored by TLC. Upon consumption of the starting material (approx. 24 h), the mixture was diluted with EtOAc (2.0 mL) and H₂O (2.0 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (1 $\times$ 2.0 mL). The combined organic layers were washed with brine (1 $\times$ 2.0 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by pTLC eluting with 3:2 hexanes/EtOAc to afford methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate as a clear oil (12.7 mg, 34%).

R_f: 0.10 (1:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.70-7.65 (m, 2H), 7.37-7.27 (m, 5H), 7.01-6.96 (m, 2H), 5.39-5.35 (m, 1H), 4.43-4.27 (m, 1H), 3.67 (s, 3H), 3.46-3.34 (m, 1H), 3.26 (s, 2H), 3.19-3.08 (m, 2H), 2.74-2.53 (m, 4H), 2.39 (s, 3H), 2.26-1.94 (m, 3H); **¹⁹F (282 MHz, CDCl₃)**: δ = 28.89-28.60 (qd, 4F, $^3J_{F-F}$ = 25.6, $^3J_{F-H}$ = 5.8 Hz), -63.39 - -63.75 (dd, 4F, $^2J_{F-F}$ = 25.6 Hz); **¹³C{¹H} (151 MHz, CDCl₃)**: δ = 171.4, 163.0, 140.6, 131.1, 130.5, 129.0, 128.6, 128.2, 126.0, 116.6, 116.15, 78.8, 71.3-71.1 (m), 58.6, 53.1, 51.7, 50.4, 42.4, 36.7, 30.8-30.7 (m); **ATR-IR (v_{max})**: 2952, 2864, 1748, 1592, 1577, 1494, 1456, 1321, 1302, 1281, 1233,

1175, 1144, 1089, 1056, 1033, 784, 707 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $\text{C}_{24}\text{H}_{29}\text{F}_7\text{NO}_5\text{S}_2^+ [\text{M}-\text{H}]^+$ 608.1370, found 608.1343

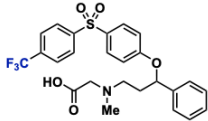
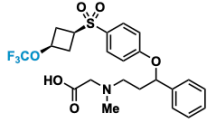
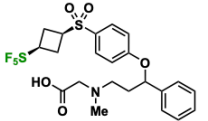
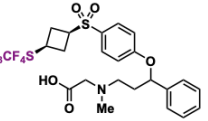


To an 8-mL vial equipped with a stir bar was added methyl *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycinate (12.7 mg, 0.021 mmol, 1.0 equiv.), followed by MeOH (0.15 mL), THF (0.15 mL), and H₂O (0.15 mL). While stirring, lithium hydroxide monohydrate (1 mg) was added in one portion. The reaction was stirred vigorously at room temperature until the starting material was consumed as indicated by TLC. The reaction was carefully acidified with 1 M HCl to ca. pH 4-5, and the aqueous layer was extracted with EtOAc (3 $\times$ 2.0 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude solid was purified by pTLC eluting with 10% MeOH in CH₂Cl₂ to afford the desired *N*-methyl-*N*-(3-phenyl-3-(4-((3-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)cyclobutyl)sulfonyl)phenoxy)propyl)glycine as a white solid (11 mg, 86%).

R_f: 0.28 (4:1 DCM:MeOH), vis: UV (254 nm); **¹H** (300 MHz, CDCl₃): δ = 7.73-7.70 (m, 2H), 7.42-7.25 (m, 5H), 7.14-7.11 (m, 2H), 5.60-5.56 (m, 1H), 4.92-4.77 (m, 1H), 3.84-3.73 (m, 1H), 3.27 (m, 1H), 2.88-2.78 (m, 4H), 2.67-2.57 (m, 2H), 2.47 (m, 2H), 2.26-1.98 (m, 2H); **¹⁹F** (282 MHz, CDCl₃): δ = 28.76-28.47 (qd, 4F, $^3J_{\text{F-F}} = 25.6$, $^3J_{\text{F-H}} = 5.8$ Hz), -63.20 - -63.55 (dd, 4F, $^2J_{\text{F-F}} = 25.6$ Hz); **¹³C**{¹H} (151 MHz, CDCl₃): δ = 162.0, 140.3, 130.3, 128.7, 128.6, 128.0, 126.0,

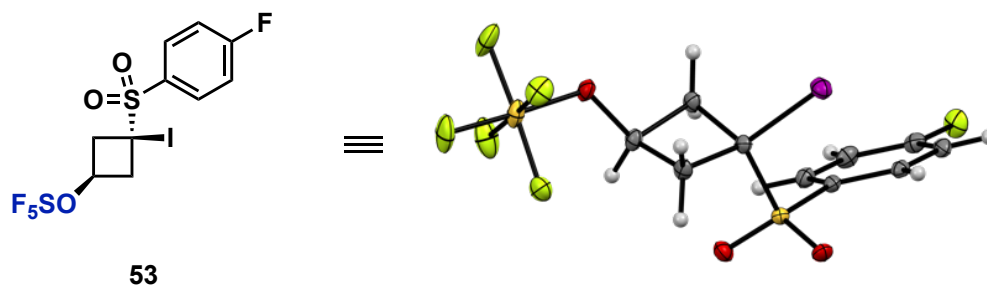
116.5, 77.5, 72.3, 58.3, 52.5, 48.9, 41.5, 40.0, 34.4, 30.2; **ATR-IR** ($\nu_{\max}$): 3428, 3170, 2846, 1641, 1593, 1548, 1235, 1146, 788, 722, 708 cm^{-1} ; **HRMS** (m/z): (ESI) calc'd for $\text{C}_{23}\text{H}_{27}\text{F}_7\text{NO}_5\text{S}_2^+$ $[\text{M}-\text{H}]^+$ 594.1214, found 594.1221.

Table 4.3. Summary of ADME properties for compounds **22-25**.

				
Compound	22	23	24	25
Measured LogD / calc'd	2.10 / 2.36	1.10 / 1.44	1.30 / 1.69	2.10 / 2.74
HT Solubility pH = 6.8 (mM) ^a	0.266	0.504	0.259	0.498
LM CL _{int} m / r / h ($\mu\text{L}/\text{min}/\text{mg}$) ^b	<23 / 24 / <23	- / <23 / <23	32 / 26 / 27	17 / 14 / 24
CYP3A4 inhibition IC ₅₀ (μM)	-	-	>25	>25
HepG2 Cytotoxicity CC ₅₀ (μM)	-	-	>100	>100
LE-MDCK _s P _{appAtoB} (cm^2/s) / Recovery	2.60 / 63%	0.30 / 66%	0.30 / 62%	1.00 / 75%

^a HT = high throughput. ^b LM CL_{int} = liver microsomal intrinsic clearance in mouse, rat, and human, respectively. ^c Low efflux Madin-Darby canine kidney permeability.

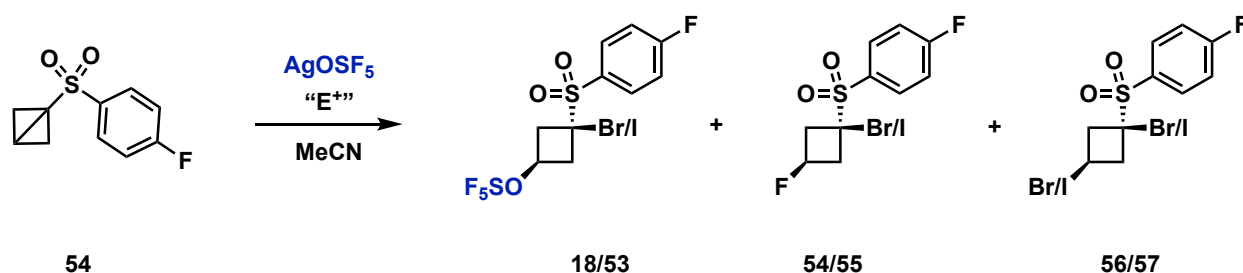
4.5.6 Iodo-Pentafluorosulfanoxylation Attempts.



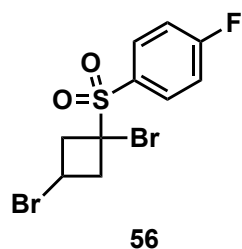
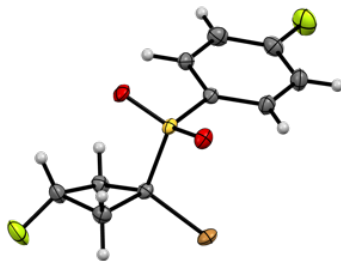
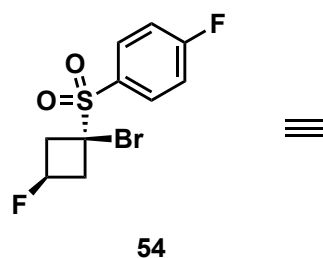
Pentafluoro(3-((4-fluorophenyl)sulfonyl)-3-iodocyclobutoxy)- λ^6 -sulfane (compound **53**) was prepared from 1-(phenylsulfonyl)bicyclo[1.1.0]butane using *N*-iodosuccinimide or I_2 . The crude residue was purified by pTLC eluting with 9:1 hexanes:EtOAc. The product was obtained as a white amorphous solid; several reaction mixtures were combined to obtain enough material for crystal growth. Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

R_f: 0.5 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.11-8.06 (m, 2H), 7.32-7.27 (m, 2H), 5.57-5.51 (app. t, 1H, *J* = 6.9 Hz), 3.75-3.69 (m, 2H), 3.17-3.12 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = 76.66-74.42 (p, 1F, *J* = 160.7 Hz), 63.20-62.60 (m, 4F), -100.91 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 167.9-165.3 (d, *J* = 258.7 Hz), 134.4-134.3 (d, *J* = 9.9 Hz), 129.79-129.76 (d, *J* = 3.3 Hz), 116.6-116.4 (d, *J* = 22.8 Hz), 73.6-73.5 (p, *J* = 4.9 Hz), 46.7, 34.2.

4.5.7 Side-Products Observed during Pentafluorosulfanoxylation Reactions.



We found two major unproductive pathways compete with OSF₅-cyclobutane formation. First, we observed the formation of **54** under nearly all conditions screened during reaction optimization. We managed to isolate and confirm the stereochemistry of this side product during the synthesis of **18** (see X-ray Crystallography section). Second, the formation of a dibrominated or diiodinated cyclobutane was observed when employing DBDMH or NIS/I₂, respectively. The formation of these side products is consistent with the known reactivity of molecular halogens in the presence of sulfonyl-containing BCBs.¹³⁸



R_f: 0.47 (4:1 Hexanes:EtOAc), vis: UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.05-8.00 (m, 2H), 7.31-7.25 (m, 2H), 4.75-4.64 (m, 1H), 3.89-3.81 (m, 2H), 3.28-3.20 (m, 2H); **¹⁹F (282 MHz, CDCl₃)**: δ = -101.06 (m, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 168.5-165.1 (d, *J* = 258.4 Hz), 134.2-134.1 (d, *J* = 9.8 Hz), 129.64-129.59 (d, *J* = 3.2 Hz), 116.8-116.5 (d, *J* = 22.6 Hz), 65.1, 48.1, 33.1; **ATR-IR (ν_{max})**: 3096, 1923, 1580, 1476, 1323, 1262, 1231, 1177, 1084, 827,

4.5.8 Preliminary Mechanistic Studies.

The control reaction between AgOCF_3 and DBDMH revealed that no reaction occurs. In contrast, treating AgSCF_3 with DBDMH leads to rapid and unselective decomposition of the reagent. These deleterious side reactions are likely the reason for the low yields observed in the bromo-trifluoromethylthiolation reaction described above.

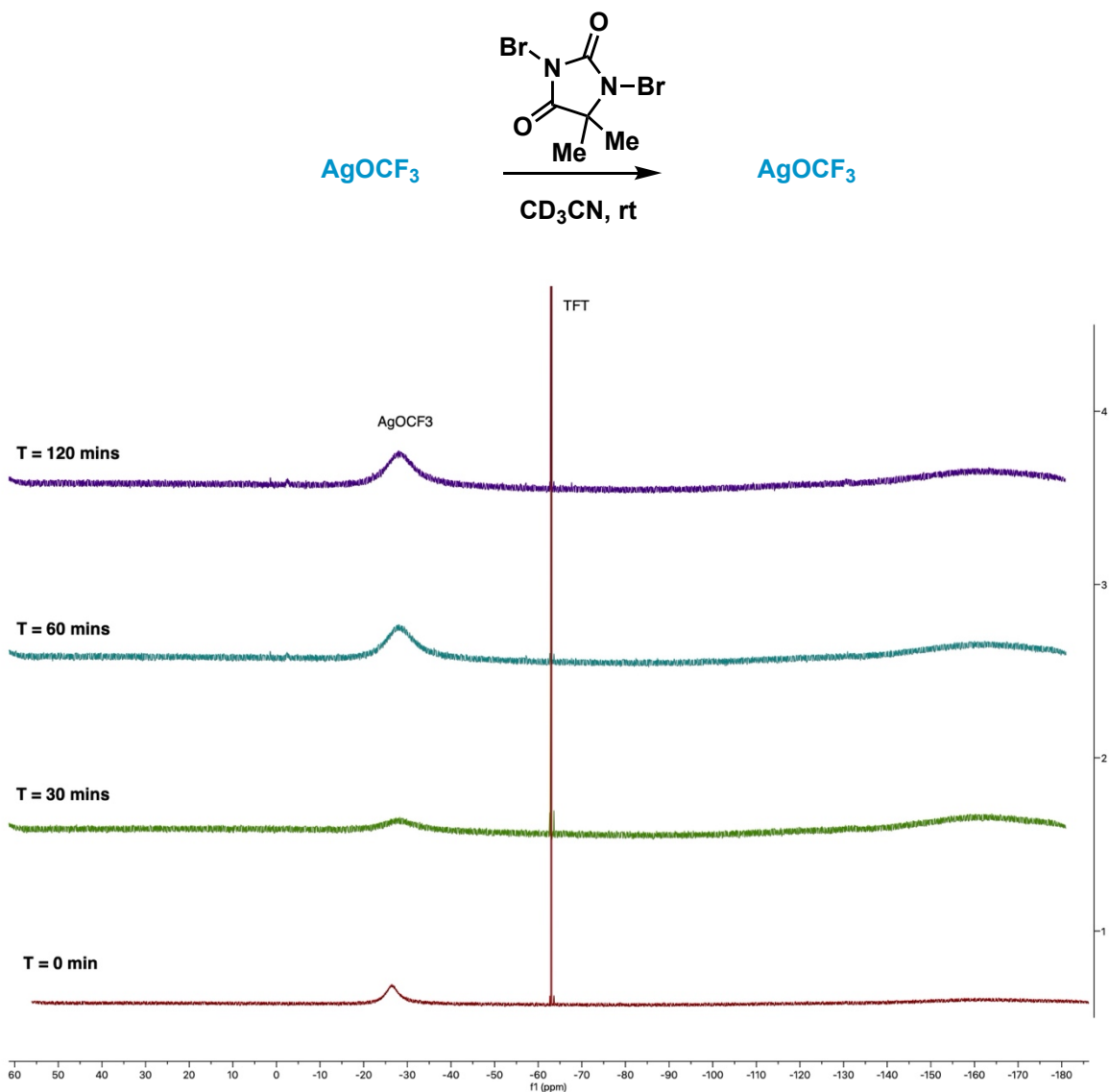


Figure 4.6. Tracking a mixture of AgOCF_3 and DBDMH (1:1) in CD_3CN over time.

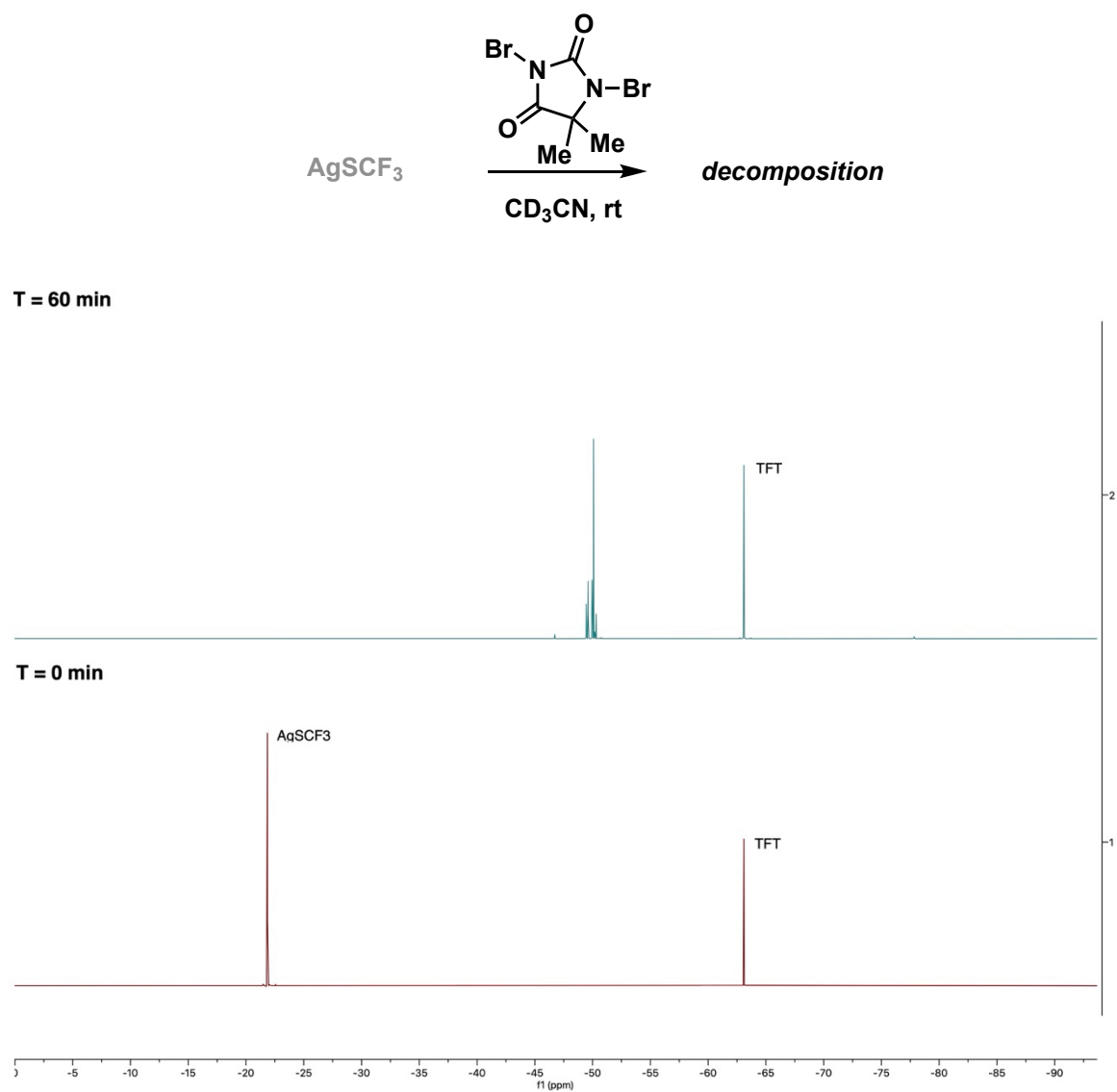


Figure 4.7. Decomposition of AgSCF_3 in the presence of DBDMH in CD_3CN .

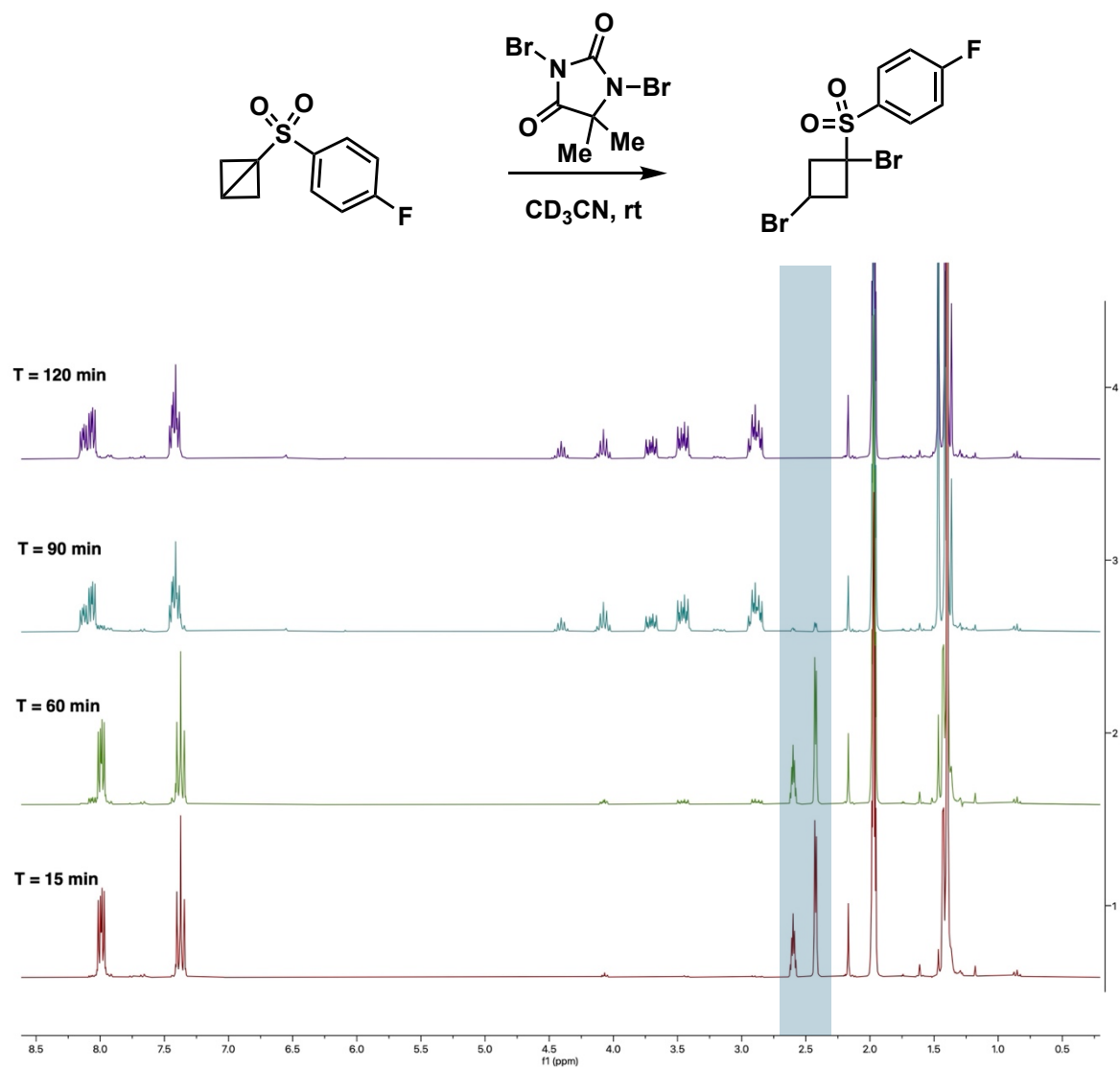
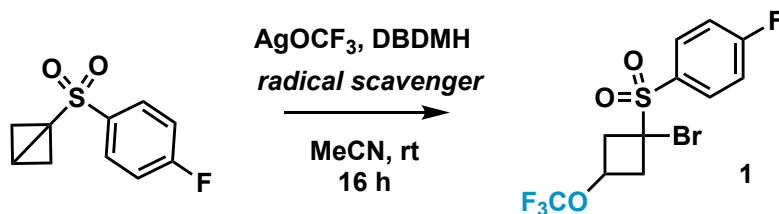


Figure 4.8. Tracking a mixture of BCB and DBDMH in CD_3CN over time. The blue bar indicates signals corresponding to the BCB.

4.5.9 Effect of Radical Scavengers.



The **general procedure A** was followed with the addition of 1.0 equiv. of the specified radical scavenger (or with the addition of an O₂ balloon instead of Ar). Upon reaction completion, an aliquot was taken for ¹⁹F NMR yield determination. Note that the product yield decreased in the presence of TEMPO, BHT, and hydroquinone, but this alone is not sufficient evidence to indicate a radical mechanism (i.e., these reagents could be inhibiting the reaction in other ways). On the other hand, flooding the reaction mixture with O₂ gas resulted in 56% product yield and seems to be more suggestive of a polar pathway than a radical pathway.

Table 4.4. Effect of radical scavengers on the bromo-trifluoromethoxylation.

Entry	Additive (1.0 equiv.)	% yield 1
1	TEMPO	11
2	BHT	16
3	hydroquinone	3
4	O ₂ (1 atm)	56

Additionally, the reaction was conducted open to air to investigate the tolerance of the reaction to the presence of O₂ and moisture. The yield determined by ¹⁹F NMR was 40%, indicating the exclusion of moisture is important.

4.5.10 SC-XRD.

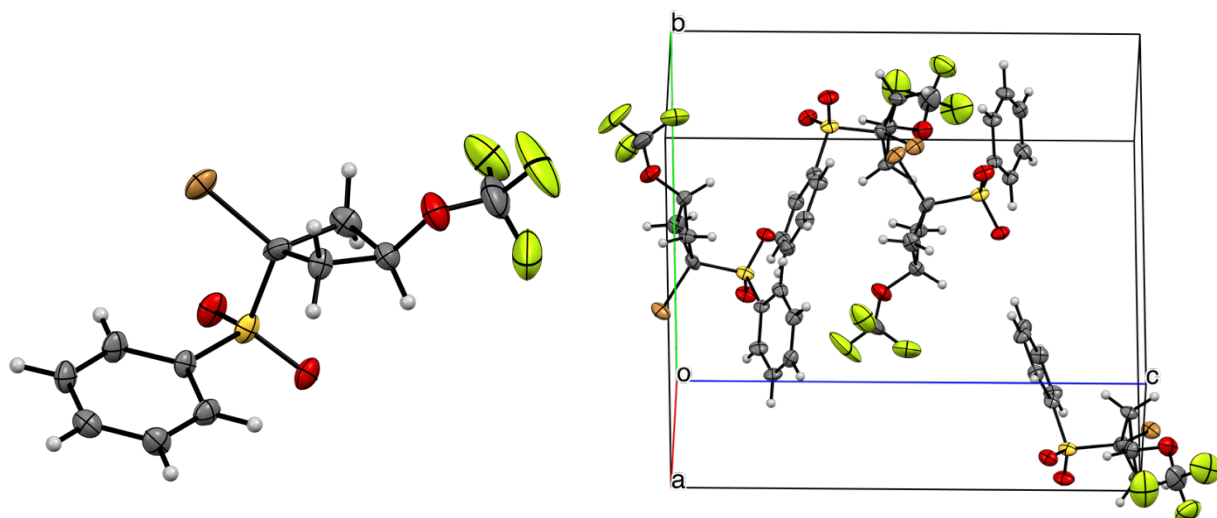


Figure 4.9. Molecular structure and packing of **8** ($P2_12_12_1$).

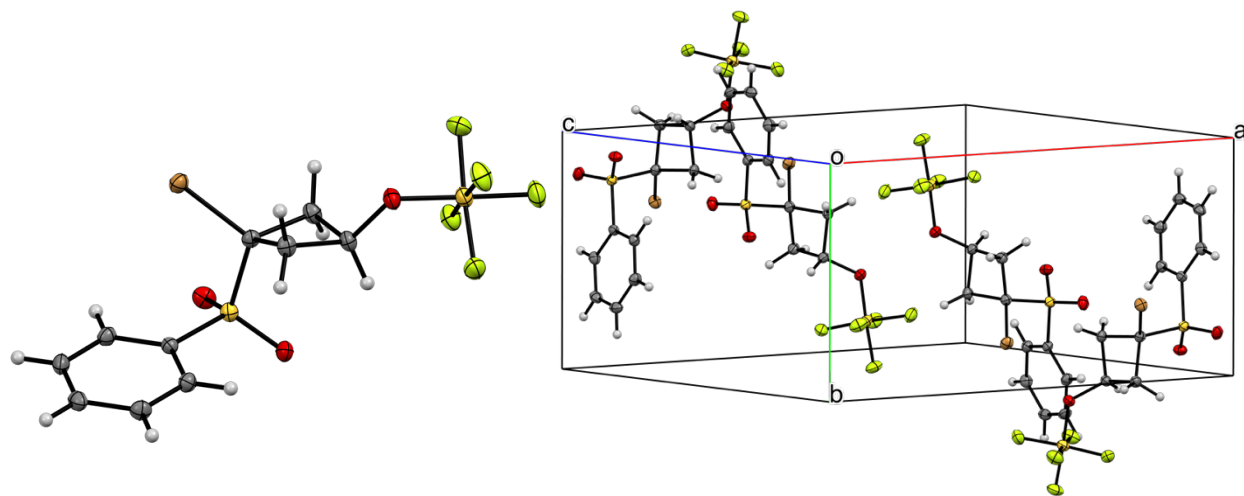


Figure 4.10. Molecular structure and packing of **15** ($P2_1/c$).

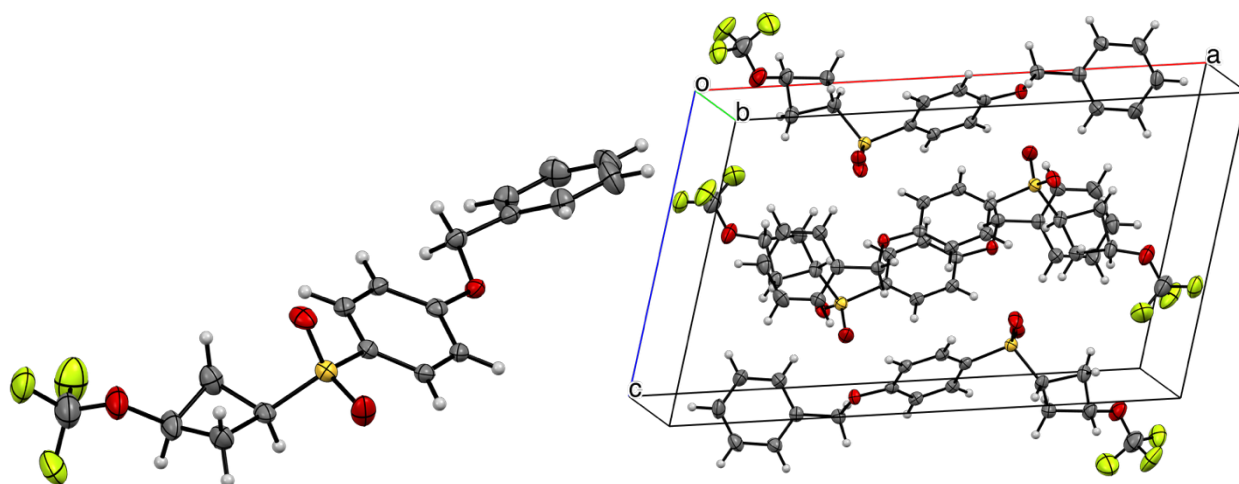


Figure 4.11. Molecular structure and packing of *cis*-19 ($P2_1/c$).

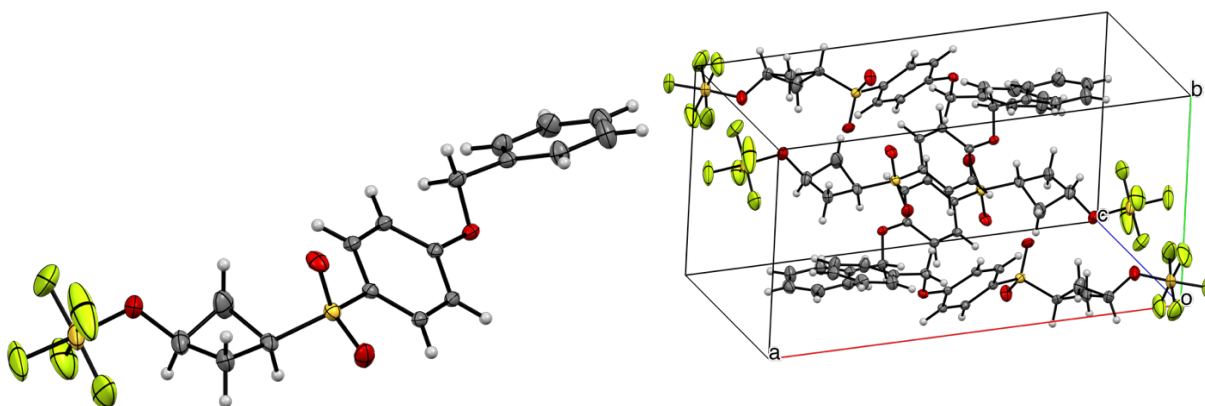


Figure 4.12. Molecular structure and packing of *cis*-20 ($P2_1/c$).

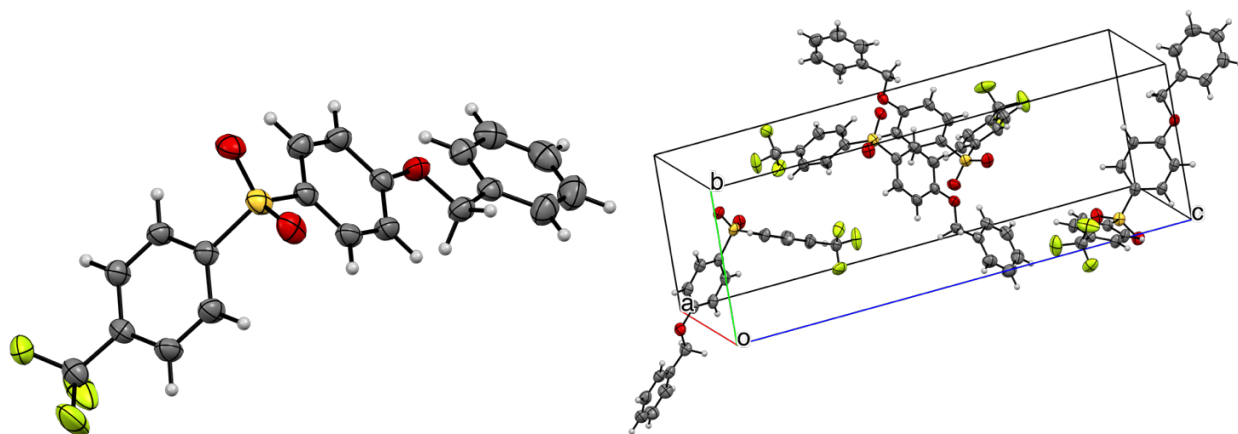


Figure 4.13. Molecular structure and packing of **21** ($P2_12_12_1$).

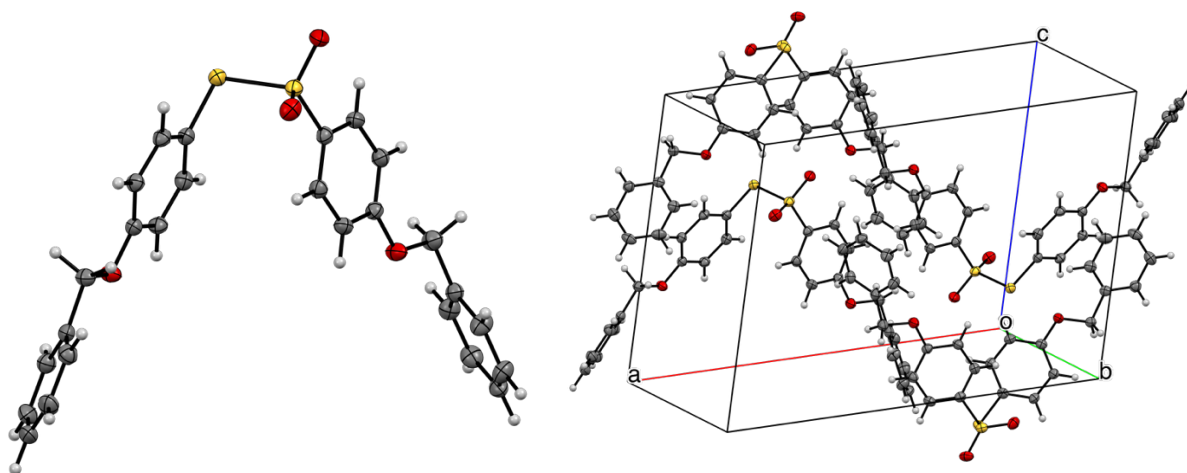


Figure 4.14. Molecular structure and packing of **39** ($P2_1/c$).

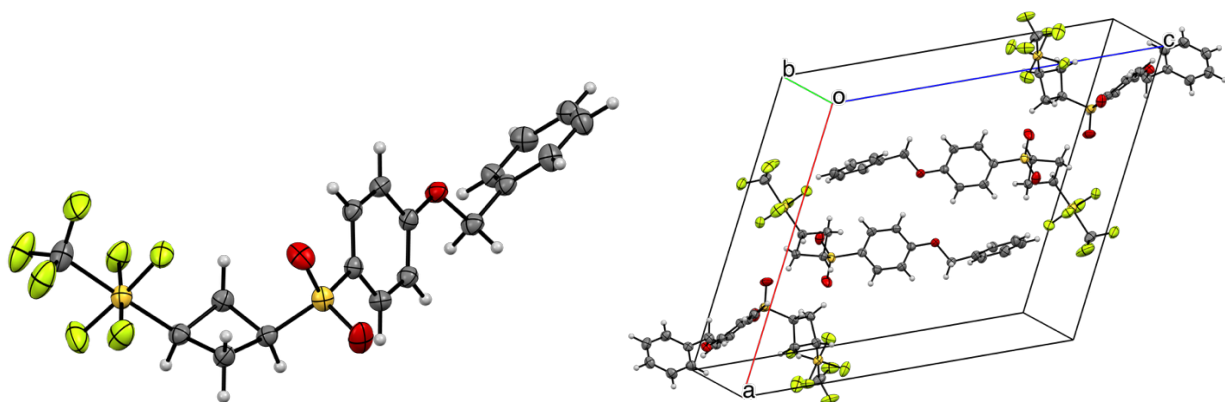


Figure 4.15. Molecular structure and packing of *cis*-**50** ($P2_1/n$).

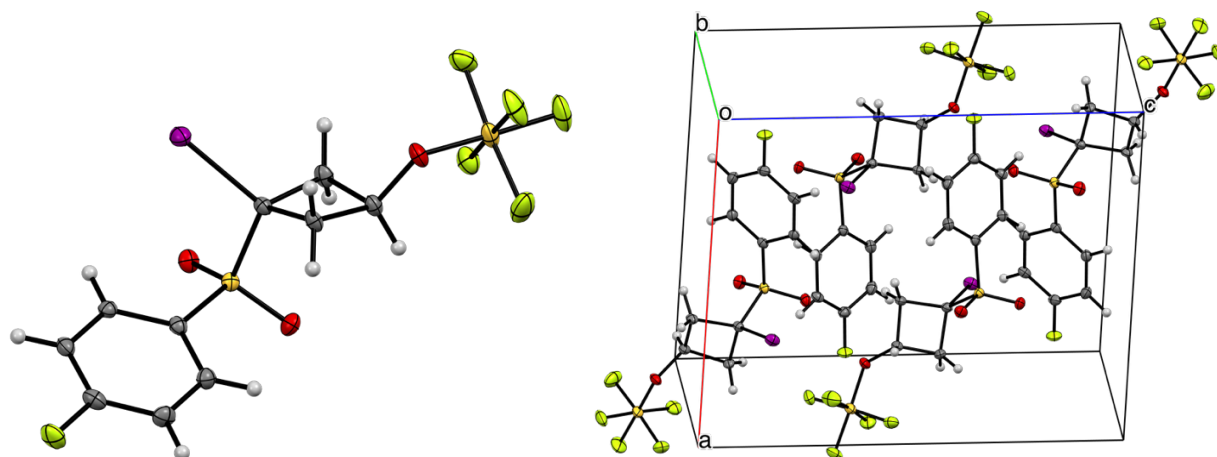


Figure 4.16. Molecular structure and packing of **53** ($P2_1/c$).

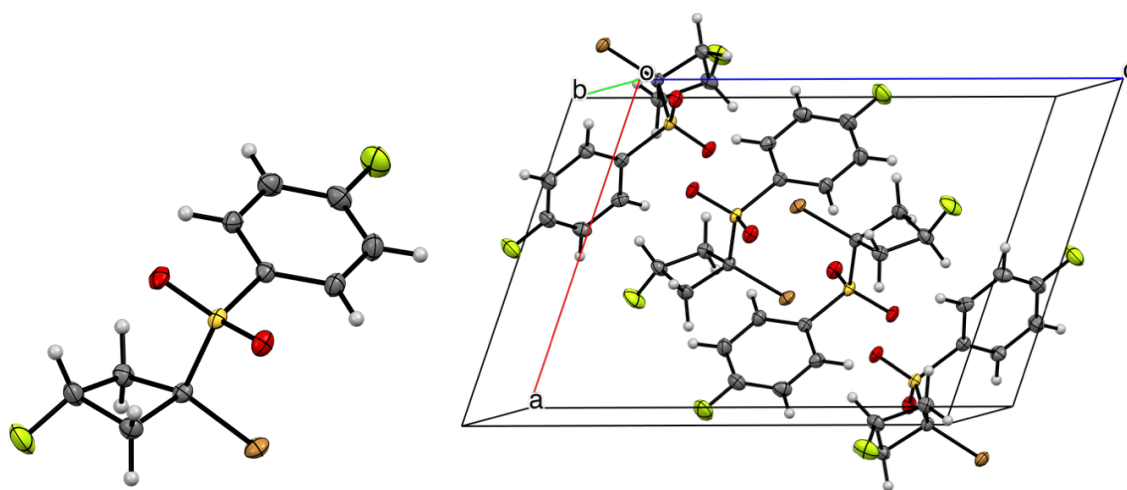
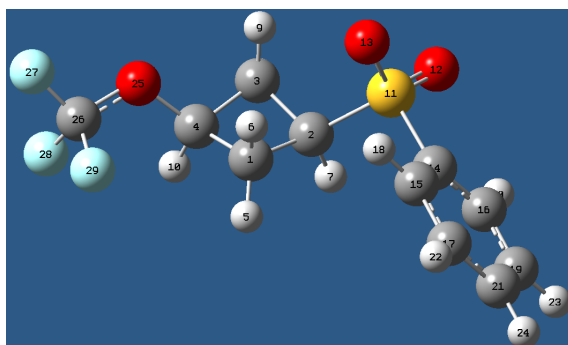


Figure 4.17. Molecular structure and packing of **54** ($P2_1/n$).

4.5.11 Computational Methods.

The Gaussian 09, Revision E.01^[139] and Gaussian 16, Revision A.03^[140] suites were used for all calculations. Geometry optimizations and subsequent vibrational analyses were performed at ω B97XD/6-311++G**. The ω B97XD functional was used to account for long-range and dispersion interactions.^[141] Polarization functions were applied to account for effects from ring strain. Minima were confirmed by means of vibrational analysis using the same functional/basis set combination: no imaginary frequencies were found.

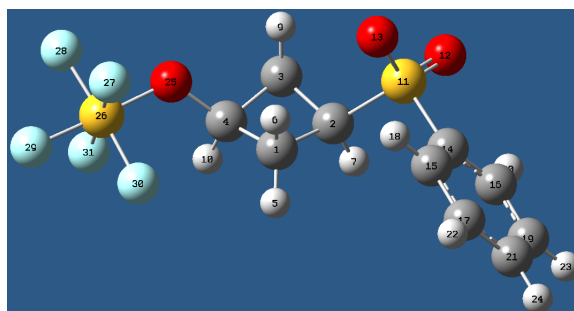
((3-(trifluoromethoxy)cyclobutyl)sulfonyl)benzene (*cis* isomer)



opt freq wb97xd/6-311++g(d,p) geom=connectivity

Center Number	Atomic Number	Forces (Hartrees/Bohr)		
		X	Y	Z
1	6	-0.000005890	-0.000012764	-0.000001056
2	6	-0.000015462	0.000021060	-0.000025313
3	6	-0.000006796	-0.000003360	0.000001406
4	6	-0.000012841	0.000012944	0.000002342
5	1	-0.000007485	0.000003938	0.000006268
6	1	0.000005471	0.000002826	0.000005166
7	1	-0.000005019	-0.000001932	-0.000003577
8	1	-0.000008707	0.000007388	-0.000018559
9	1	0.000003221	0.000001821	-0.000014294
10	1	-0.000015003	0.000003402	-0.000002933
11	16	0.000010279	-0.000004382	-0.000007374
12	8	0.000005375	0.000004823	-0.000013162
13	8	0.000010924	-0.000005198	-0.000007227
14	6	0.000007835	-0.000008882	-0.000002392
15	6	0.000012083	0.000001217	0.000008362
16	6	0.000001229	0.000000458	-0.000001369
17	6	0.000011828	-0.000011584	0.000011076
18	1	0.000015021	-0.000005150	0.000005928
19	6	0.000011702	-0.000002628	-0.000000232
20	1	0.000004907	-0.000001096	-0.000009623
21	6	0.000010360	-0.000001575	0.000011862
22	1	0.000013863	-0.000007634	0.000017638
23	1	0.000004592	-0.000003558	0.000002364
24	1	0.000010677	-0.000007196	0.000014350
25	8	-0.000007401	0.000003590	-0.000006142
26	6	-0.000030208	-0.000000503	0.000013888
27	9	-0.000006283	0.000009412	0.000007514
28	9	-0.000015138	0.000005598	-0.000008543
29	9	-0.000003133	-0.000001035	0.000013633

pentafluoro(3-(phenylsulfonyl)cyclobutoxy)- λ^6 -sulfane (*cis* isomer)



opt freq wb97xd/6-311++g(d,p) geom=connectivity

Center Number	Atomic Number	Forces (Hartrees/Bohr)		
		X	Y	Z
1	6	0.000002014	0.000005176	-0.000007346
2	6	-0.000008171	-0.000006516	0.000019131
3	6	0.000006802	0.000004879	-0.000010324
4	6	0.000018227	-0.000007416	0.000017533
5	1	-0.000003316	-0.000001504	-0.000003949
6	1	-0.000000669	0.000002448	-0.000000315
7	1	0.000002068	-0.000002534	0.000001869
8	1	0.000004486	-0.000002186	0.000012184
9	1	0.000007299	0.000008640	0.000010248
10	1	-0.000005298	-0.000001762	-0.000008227
11	16	0.000005165	-0.000006390	-0.000000250
12	8	0.000009532	0.000003770	0.000014679
13	8	0.000004836	0.000006489	0.000004048
14	6	0.000003608	0.000000968	0.000006522
15	6	-0.000002775	-0.000001578	0.000001078
16	6	-0.000001276	-0.000009162	0.000004794
17	6	-0.000004911	-0.000004145	-0.000005045
18	1	0.000002283	0.000002125	-0.000003362
19	6	-0.000001698	-0.000016232	0.000002328
20	1	0.000001278	-0.000011154	0.000009482
21	6	-0.000003584	-0.000007728	0.000001017
22	1	-0.000004377	-0.000001773	-0.000006080
23	1	-0.000003392	-0.000015676	0.000005426
24	1	-0.000006250	-0.000011858	-0.000002217
25	8	-0.000026253	-0.000001085	-0.000005528
26	16	0.000009911	0.000013626	-0.000038100
27	9	0.000000044	0.000022558	0.000001018
28	9	-0.000003125	0.000009384	-0.000000221
29	9	-0.000001431	0.000016764	-0.000008861
30	9	-0.000000977	0.000005600	-0.000004559
31	9	-0.000000050	0.000006270	-0.000006974

For additional experimental details and NMR spectra, please refer to the Supporting Information of the associated publication: Kraemer, Y.; Stephens, A. M.; Buldt, J. A.; Young, A.; McLoughlin, C. P.; Fettingner, J. C.; Holder, L. M.; Pitts, C. R. *Chem. Commun.* **2025**, 61, 3159-3162.

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Chapter 5: Direct N -SF₅ and N -SF₄CF₃ Bond Formation through Strain-Release

Functionalization of 3-Substituted [1.1.0]Azabicyclobutanes

5.1 Introduction.

The history surrounding the pentafluorosulfanyl (SF₅) group follows a tale often told in the field of organofluorine chemistry. While its utility in medicinal chemistry, agrochemistry, and materials arenas is well documented,^{142–144} the SF₅ group has yet to experience widespread adoption by the chemical community for a similar reason several promising fluorinated groups (e.g., the CF₃ group^{145,146}) were initially sidelined: synthetic accessibility.¹⁴⁷ Considering two SF₅-containing compounds have reached clinical candidacy to date, with the most recent one announced by Novartis in late 2024, demolition of the synthetic barriers that hinder innovation in pentafluorosulfanylation chemistry seems long overdue.^{148,149}

Our laboratory,¹⁵⁰ as well as the Qing¹⁵¹ and Guo¹⁵² laboratories, have begun to chisel away at these walls by making one of the most reliable SF₅ group transfer reagents – pentafluorosulfanyl chloride (SF₅Cl) – significantly safer to synthesize (using a mild oxidative fluorination strategy^{153–158}) and easier to handle. For instance, with access to SF₅Cl in solution, we recently established strain-release functionalization as a viable strategy for direct C–SF₅ bond formation,¹⁵⁹ inspired by extant methods on SF₅ radical addition across conventional π -bonds.^{160–162} This enabled the synthesis of SF₅-containing "hybrid bioisosteres" that are complementary to the aryl-SF₅ motif.^{163,164}

Although method development for C–SF₅ bond formation has been gaining momentum in recent years in our laboratory and several others,^{165–176} *direct heteroatom-SF₅ bond formation* remains somewhat stalled at the starting line. Traditionally, N -SF₅-containing compounds have

been synthesized *via* a bottom-up approach relying on hazardous gas reagents, such as SF₄,^{177,178} F₂,^{179,180} HF,¹⁸¹ ClF,¹⁸² and NSF₃.^{183–186} Typically, these studies were motivated by fundamental advances in inorganic fluorine chemistry and did not focus on the development of practical, user-friendly synthetic methodologies. To the best of our knowledge, only a few examples of *direct N*–SF₅ bond formation *via* SF₅Cl addition across perhalogenated nitriles have been reported by Tullock and Shreeve¹⁸⁸ (Figure 5.1, *top panel*). Additionally, in 1976, Shreeve and co-workers reported that SF₅Cl and SF₅Br react with Me₂NTMS to yield Me₂NSF₄X (X = Cl, Br), indicating that direct nucleophilic substitution is unlikely a viable strategy to access the *N*–SF₅ motif.¹⁸⁹ Beyond these scarce examples, this research area has lain dormant for decades. Even the relatively more accessible OSF₅ motif is installed on organic molecules through C–OSF₅ bond formation (e.g., using AgOSF₅^{190,191} or MeEt₃NOSF₅¹⁹² in nucleophilic substitution/addition reactions), as opposed to direct O–SF₅ bond formation.

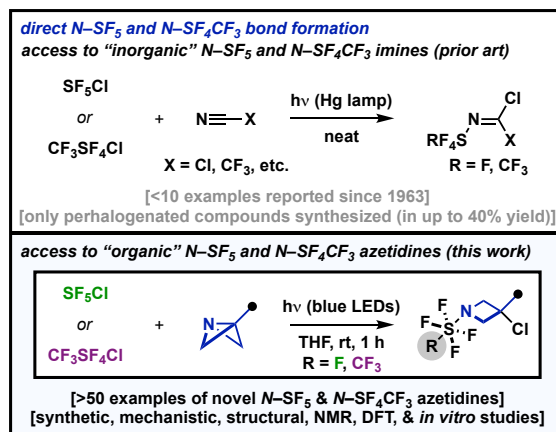


Figure 5.1. (*Top*) Precedent for RSF₄Cl (R = F, CF₃) addition across nitriles using condensed gas reagents. (*Bottom*) Synthetic strategy presented herein that provides access to and enables foundational studies on heretofore unknown *N*–SF₅ and *N*–SF₄CF₃ azetidines (the primary source of innovation for this work).

Considering previous reports provided proof-of-concept for direct *N*–SF₅ bond formation *via* addition of SF₅Cl across a conventional π -bond, we posited that, under the right circumstances, it should also be possible *via* addition of SF₅Cl across the strained central bond of a

[1.1.0]azabicyclobutane^{193,194} (akin to strain-release C–SF₅ bond formation) to provide access to heretofore unknown *N*–SF₅ azetidines. In fact, seminal work from Dell’Amico and co-workers demonstrated selectivity for sulfonyl radical addition to the *N*-site of 3-substituted ABBs, lending credence to this approach to *N*–SF₅ bond formation.¹⁹⁵

Herein, we report a synthetic strategy for direct *N*-pentafluorosulfanylation of 3-aryl [1.1.0]azabicyclo-butanes (ABBs) using SF₅Cl that generates access to the first suite of 3-aryl *N*–SF₅ azetidines (Figure 5.1, *bottom panel*). To our surprise, these *N*–SF₅ azetidines displayed remarkable chemical stability, indicating they can be incorporated into complex molecule synthesis. Interestingly, we also found that *trans*-CF₃SF₄Cl is a competent surrogate for SF₅Cl, providing more exotic *N*–SF₄CF₃ azetidines in similar yields. Throughout this study, divergent access to both *N*–SF₅ and *N*–SF₄CF₃ azetidines fueled comparative synthetic, mechanistic, selectivity, structural, spectroscopic, and physical property comparisons to provide foundational understanding of these heretofore unknown fluorinated motifs. Furthermore, we subjected an *N*–SF₅ azetidine derivative of a spleen tyrosine kinase inhibitor to *in vitro* profiling and comparative ADME studies; the results not only indicate that *N*–SF₅ azetidines are viable motifs to incorporate into SAR studies, but they suggest the *N*–SF₅ motif may qualify as a lipophilic bioisosteric replacement for a small sulfonamide (e.g., an *N*–SO₂Me azetidine).

5.2 Results and Discussion.

5.2.1 Simplified Protocol for SF₅Cl Synthesis and Extraction.

At the outset of this study, we sought to establish a safer and more straightforward synthesis/extraction protocol to obtain stock solutions of SF₅Cl in larger quantities than previously reported. In 2019, the first gas reagent-free synthesis of SF₅Cl from S₈, trichloroisocyanuric acid (TCICA), and KF in MeCN was reported in the patent literature by Pitts, Santschi, and Togni.¹⁵⁰

In 2021, Shou, Xu, and Qing subsequently adapted this synthetic strategy and developed a valuable extraction protocol whereby SF₅Cl was synthesized in a pressure vessel, the vessel was cooled to −78 °C, *n*-hexane was introduced, the vessel was warmed to rt, and an ~0.10–0.15 M solution of SF₅Cl in *n*-hexane was obtained after partitioning the solvent layers in a separatory funnel.¹⁵¹ In 2024, Guo and co-workers amended their procedure by incorporating a custom separatory funnel designed for extraction at −35 °C; this enabled access to ≥0.30 M solutions of SF₅Cl in *n*-hexane.¹⁵² In early 2025, Charette and co-workers also demonstrated that SF₅Cl synthesis using TCICA/KF and *in-line* extraction/purification to obtain a solution in *n*-hexane is possible under continuous flow conditions with a tailor-made solid stirring reactor.¹⁹⁶

Under all the above batch conditions, as well as the *ex situ* conditions for SF₅Cl synthesis independently developed by Tlili¹⁹⁷ and De Borggraeve,¹⁹⁸ the reaction vessels invariably become pressurized, as SF₅Cl (b.p. −19 °C) accumulates in the head space. This also mandates cooling the reaction mixture well below the b.p. of SF₅Cl (typically, to −78 °C) to ensure safe introduction of the hydrocarbon solvent prior to warming back to room temperature (rt) and extraction. Instead, we envisioned that running this reaction in the presence of a hydrocarbon *co-solvent* – i.e., to dissolve SF₅Cl as it is formed – would not only mitigate the buildup of pressure in the reaction vessel (ostensibly rendering the protocol safer and more scalable), but both simplify and expedite extraction by avoiding the cooling/warming cycle altogether.

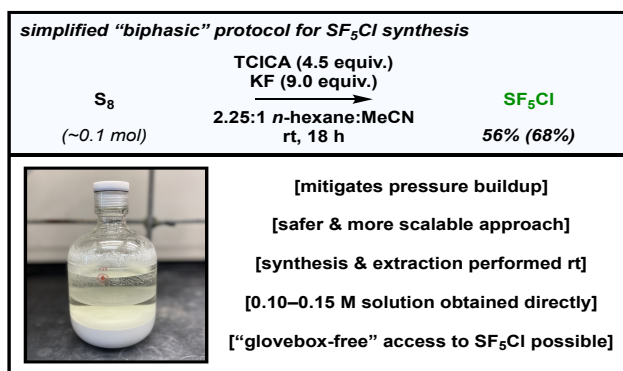


Figure 5.2. Simplified and scalable synthesis to obtain a stock solution of pentafluorosulfanyl chloride (SF₅Cl) in *n*-hexane, developed to facilitate method development. Isolated yield reported with ¹⁹F NMR yield in parentheses. Picture of biphasic reaction mixture prior to extraction shown.

After examining various solvent quantities and ratios (see SI for details), we found that stirring sulfur (32 mmol, 1.0 equiv.), TCICA (4.5 equiv.), and KF (9.0 equiv.) in a 2.25:1 mixture of *n*-hexane:MeCN in a sealed vessel under inert atmosphere at rt provides a 0.10 M solution of SF₅Cl in *n*-hexane in 54% yield (69% by ¹⁹F NMR, prior to extraction). Under these conditions, the reaction vessel can be opened to air at *room temperature* upon reaction completion, after which the contents can be transferred directly to a separatory funnel for collection of the *n*-hexane phase. In addition, we found that the yields obtained using this “biphasic” protocol are slightly higher than previously reported conditions at the same scale. For instance, in our hands, using the procedure reported by Qing and co-workers,¹⁵¹ we obtained a 0.15 M solution of SF₅Cl in 42% yield (48% by ¹⁹F NMR, prior to extraction). Furthermore, we performed the reaction on a 96 mmol scale (three times the largest scale reported in the literature to date) without incident and without detriment to the isolated yield (Figure 5.2, *top and bottom panels*).

Significantly, under these biphasic conditions, we also discovered that the pressure buildup in the vessel is limited to such an extent that *the reaction can be performed in a round-bottom flask using polyethylene stoppers, obviating the need to use either a pressure vessel or a glovebox*. Complete details of both reaction setups and extraction protocols are provided in the SI of the associated publication, as well as additional details regarding reaction optimization. We believe this modification to existing extraction protocols is an important step toward the democratization of pentafluorosulfanylation chemistry.

Lastly, we found that similar results can be obtained when substituting *n*-hexane with either *n*-heptane or *n*-pentane. Note that *n*-heptane tends to be preferred in a process chemistry setting

over either *n*-hexane or *n*-pentane.¹⁹⁹ From another perspective, *n*-pentane may be the hydrocarbon solvent of choice to facilitate isolation of potentially volatile products; for the purposes of the remainder of this study, we used primarily solutions of SF₅Cl in *n*-pentane in anticipation that certain products could be volatile.

5.2.2 Direct *N*-SF₅ and *N*-SF₄CF₃ Bond Formation through Strain-Release Functionalization.

With more straightforward access to stock solutions of SF₅Cl, we proceeded to examine the feasibility of SF₅Cl addition across ABBs.^{200,201} One conceptual obstacle is to favor *N*-SF₅ over C-SF₅ bond formation with this substrate class. Nonetheless, we envisioned that the regioselectivity of SF₅ radical addition could be heavily influenced by a substituent in the 3-position of an ABB. For instance, SF₅ radical addition to the *N*-site of a 3-aryl ABB would lead to a resonance-stabilized tertiary benzylic radical intermediate, which we would anticipate being kinetically and thermodynamically favored over SF₅ radical addition to the *C*-site (leading to formation of an *N*-centered radical).¹⁹⁵

Accordingly, we began screening for *N*-pentafluorosulfanylation reaction conditions using 3-phenyl-1-azabicyclo[1.1.0]butane as our model ABB substrate. Under optimized conditions (see SI for details), we ultimately found that irradiating a solution of the ABB substrate and 1.2 equiv. SF₅Cl (~0.1 M in *n*-pentane) in THF with blue LEDs for 1 h provided the desired *N*-SF₅ azetidine (**1**) in 85% yield by ¹⁹F NMR (Figure 5.3, *top panel*). The product proved stable toward purification *via* column chromatography on silica gel, enabling us to obtain **1** in 74% isolated yield. The regioselectivity of the transformation was initially assigned based on the magnitude of distinct ¹³C-¹⁹F coupling constants in the ¹³C{¹H} NMR spectrum and later confirmed by single crystal X-ray diffraction (SC-XRD). Interestingly, we found that these conditions translate to *N*-

tetrafluoro(trifluoromethyl)sulfanylation, simply by using a solution of *trans*-CF₃SF₄Cl in *n*-pentane in place of SF₅Cl.²⁰² Without additional optimization, we were able to obtain the analogous *N*-SF₄CF₃ azetidine (**2**) as a single regioisomer in 75% yield by ¹⁹F NMR. This product also proved stable toward purification *via* chromatography on silica gel, enabling access to **2** in 59% isolated yield.

We then proceeded to explore the scope of both *N*-SF₅ and *N*-SF₄CF₃ bond formation reactions in tandem (Figure 5.3, *top panel*). Note that, to the best of our knowledge, only a small number of 3-aryl ABB compounds have been previously reported in the literature. In order to provide a more substantial survey of functional group compatibility in the study at hand, we successfully synthesized >16 novel ABB substrates, effectively tripling the scope of symmetrical 3-aryl ABBs reported in the literature to date (see Section 5.5 for details).

First, we found that 3-aryl ABB starting materials bearing halogen substituents (F, Cl, Br, or I) in the *para* position provided the corresponding SF₅Cl and CF₃SF₄Cl addition products **3–10** in isolated yields ranging from 49–74%. Under standard conditions, the aryl iodide substrates did not perform well initially (likely due to light sensitivity); however, **9** and **10** were ultimately obtained in acceptable isolated yields (50% and 64%) upon decreasing the reaction time to 15 min. and increasing the quantity of SF₅Cl to 3.0 equiv. Beyond halogen substituents, we found that 3-aryl ABBs with stronger electron-withdrawing groups, such as OCF₃, CF₃, and CN, in the *para* position also tolerated the reaction conditions, providing products **11–16** in generally good yields (52–71% by ¹⁹F NMR). Note that the isolated yields of compounds **13–14** deviated from the ¹⁹F NMR yields to a greater extent due to volatility. Next, we examined 3-aryl ABB substrates containing mild electron-donating groups in the *para* position and found that we could access *N*-SF₅ and *N*-SF₄CF₃ azetidines containing alkyl (Me, Et, *t*-Bu; **17–22**), aryl (Ph; **23–24**), silyl (TMS;

25–26), and protected benzylic alcohol (CH₂OTBS; **27–28**) substituents on the arene under standard conditions.

Subsequently, we investigated 3-aryl ABBs bearing halogen substituents in the *meta* (F, Cl, Br) and *ortho* (Br) positions, which provided access to azetidines **29–36** in isolated yields ranging from 38-54% (compounds **29–32** proved to be volatile to varying extents). Finally, we found that *N*-SF₅ and *N*-SF₄CF₃ azetidines containing polycyclic substituents, such as naphthalene (**37–38**), and heterocyclic substituents, such as pyridine (**39–40**), were also accessible. Conversely, *meta*-OMe, *para*-NO₂, and thiophene-containing ABBs proved less compatible with the optimized reaction conditions, forming the desired products in <5% yield by ¹⁹F NMR analysis in each case.

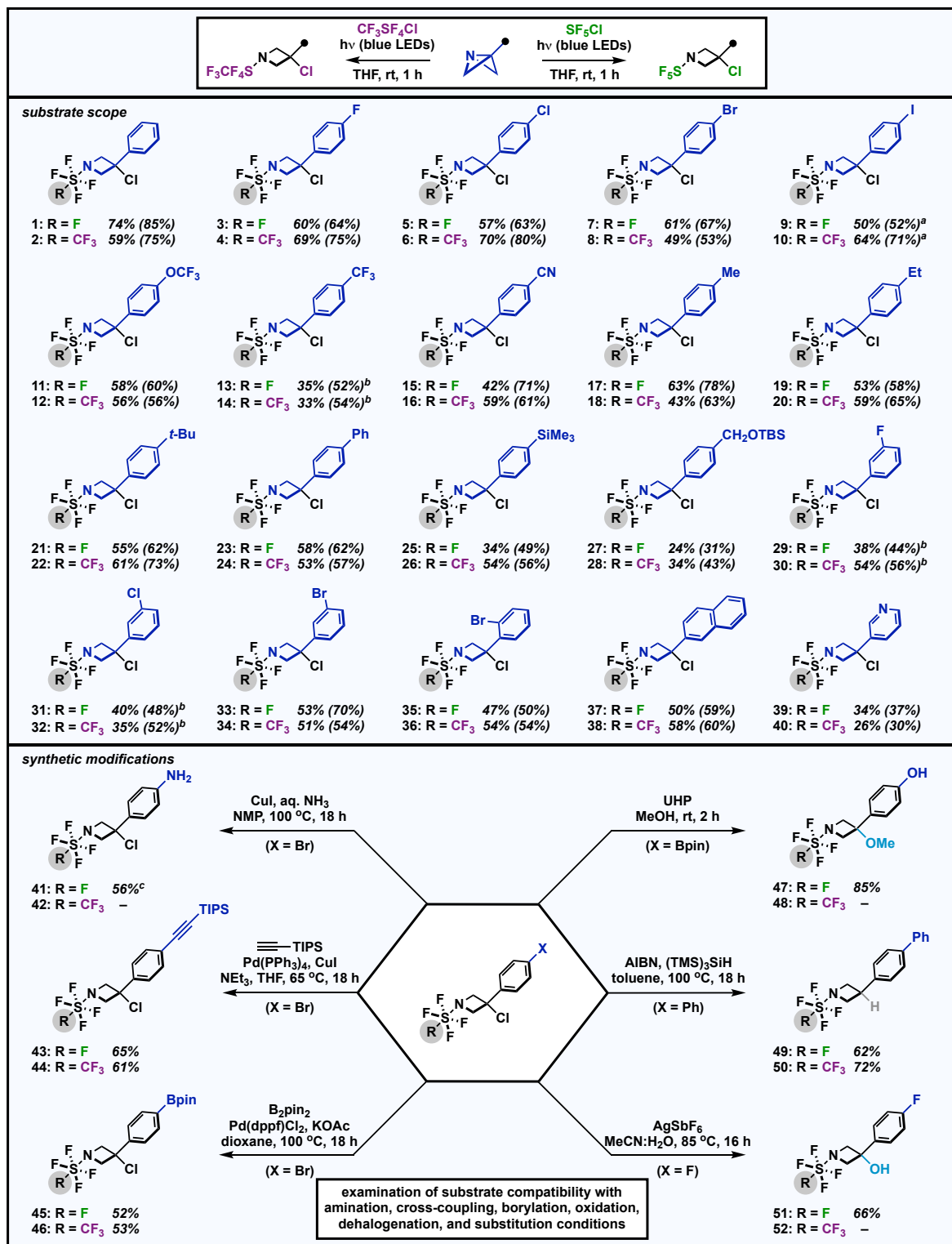


Figure 5.3. (Top) Substrate scope for synthesis of *N*-SF₅ and *N*-SF₄CF₃ azetidines from 3-aryl ABBs (1.0 equiv.) and solutions of either SF₅Cl or CF₃SF₄Cl in *n*-pentane (1.2 equiv.). Isolated yields are reported with ¹⁹F NMR yields in parentheses. ^aReaction time decreased to 15 min and 3.0 equiv. RSF₄Cl reagent used. ^bVolatile compound. (Bottom) Peripheral synthetic modifications and evaluation of chemical stability of the *N*-SF₅ and *N*-SF₄CF₃ motifs under various conditions. Isolated yields reported. ^cYield brsm.

Note that, throughout the course of this study, we found that the purity of the 3-aryl ABB starting material was imperative to the success of the reaction. Accordingly, we provide additional details and commentary in the experimental section regarding acceptable purification practices for each starting material.

Our exploration of substrate scope was, in part, limited by the state of the art in 3-aryl ABB synthesis.²⁰⁰ Thus, we proceeded to outline strategies to access additional *N*-SF₅ and *N*-SF₄CF₃ azetidine building blocks through product modifications. Simultaneously, these efforts also enabled us to examine the compatibility of the *N*-SF₅ and *N*-SF₄CF₃ motifs under a variety of reaction conditions (Figure 5.3, *bottom panel*). First, we subjected compounds **7** and **8** to Ullmann-type amination conditions in an effort to access the corresponding aniline derivatives **41** and **42**.²⁰³ Notably, upon heating **7** in the presence of aqueous NH₃ and copper(I) iodide in *N*-methyl-2-pyrrolidone at 100 °C, the desired aniline **41** was obtained in 56% yield based on recovered starting material. On the other hand, after **8** was subjected to the same conditions, we observed complete disappearance of the *N*-SF₄CF₃ signal in the ¹⁹F NMR spectrum of the crude reaction mixture.

Next, we examined the compatibility of *N*-SF₅ and *N*-SF₄CF₃ azetidines with Pd-catalyzed cross-coupling reactions. We found that subjecting **7** and **8** to Sonogashira cross-coupling conditions afforded TIPS-protected alkyne-substituted compounds **43** and **44** in 65% and 61% isolated yields.²⁰⁴ Additionally, when the same substrates were subjected to Miyaura borylation conditions, the corresponding Bpin-containing products **45** and **46** were obtained in 52% and 53% isolated yields.²⁰⁵ After subjecting boronic ester **45** to oxidation conditions (using UHP in MeOH),²⁰⁶ phenol **47** was obtained in 85% isolated yield. Interestingly, in addition to BPin oxidation, the substrate had also undergone an S_N1 reaction, effectively substituting the tertiary

chloride with a methoxy group. However, upon subjecting **46** to identical conditions, the corresponding phenol (**48**) was not observed; rather, ^{19}F NMR analysis of the crude reaction mixture indicated formation of a major trifluoromethanesulfonamide product instead. Thus, the equatorial S–F bonds in $N\text{--SF}_4\text{CF}_3$ azetidines appear to be substantially more prone to hydrolysis of than those in $N\text{--SF}_5$ azetidines.

Beyond arene substituent modifications, we also demonstrated that radical dechlorination using AIBN and $(\text{TMS})_3\text{SiH}$ proceeded smoothly on substrates **23** and **24** to provide formal hydropentafluorosulfanylated products **49** and **50** in 62% and 72% isolated yields.²⁰⁷ Furthermore, heating **3** to 85 °C in the presence of AgSbF_6 in 10:1 MeCN:H₂O provided 3-hydroxy $N\text{--SF}_5$ azetidine **51** in 66% isolated yield, whereas hydrolysis of the $N\text{--SF}_4\text{CF}_3$ motif to a trifluoromethanesulfonamide was observed by ^{19}F NMR analysis of the crude reaction mixture in lieu of **52** under identical conditions.

Overall, we found that the $N\text{--SF}_4\text{CF}_3$ motif was prone to decomposition in the presence of protic solvents, though it survived Pd-catalyzed cross-coupling and radical dehalogenation conditions. On the other hand, the $N\text{--SF}_5$ motif proved to be remarkably chemically stable under Ullman amination, Sonogashira cross-coupling, Miyaura borylation, oxidation, radical dehalogenation, and $\text{S}_{\text{N}}1$ -like conditions, thus providing access to a more diverse array of $N\text{--SF}_5$ azetidine building blocks and demonstrating a higher potential for applications in complex molecule synthesis.

5.2.3 Mechanistic Studies.

At this stage, we began to investigate the mechanisms of $N\text{--SF}_5$ and $N\text{--SF}_4\text{CF}_3$ bond formation. For one, it has been established in the chemical literature that SF_5Cl acts as a source of SF_5 radicals under irradiation with blue or white LEDs (and, by proxy, $\text{CF}_3\text{SF}_4\text{Cl}$ is a source of

CF₃SF₄ radicals).²⁰⁸ The radical initiation process may occur through, e.g., formation of a transient electron donor-acceptor (EDA) complex^{159,163,209} and/or autooxidation of an ethereal solvent.²¹⁰ In any case, with precedent for putative SF₅ and CF₃SF₄ radical formation under similar reaction conditions, we posited that formal SF₅Cl and CF₃SF₄Cl addition across 3-aryl ABBs likely occurs through a radical chain propagation mechanism. This would also be consistent with the reported mechanisms for other strain-release pentafluorosulfanylation and tetrafluoro(trifluoromethyl) sulfanylation reactions.^{159,163,208}

Accordingly, we examined the energetic feasibility of the radical chain propagation pathways using density functional theory (DFT) calculations at the PWPB95-D4/def2-QZVPP//PCM(Et₂O)- ω B97X-D/def2-SVP level of theory.^{211–222} First, we computed the free energy landscape for the *N*-pentafluorosulfanylation reaction (Figure 5.4, *top panel*). Theoretically, the SF₅ radical may add to either the *N*-site or the *C*-site (C3) of the strained central bond in the model ABB substrate (3-phenyl-1-azabicyclo[1.1.0]butane). The results of our calculations indicated that addition to the *N*-site through **TS1_N** is indeed favored over addition to the *C*-site through **TS1_C** ($\Delta\Delta G^\ddagger = 4.1$ kcal/mol), consistent with our observed regioselectivity. The relatively lower activation barrier for *N*-pentafluorosulfanylation is likely associated with 1) less steric hindrance at the *N*-site and 2) incipient formation of a thermodynamically stable tertiary benzylic radical. Note that while both C–SF₅ and *N*–SF₅ bond formation pathways were computed to be exergonic, **IM1_N** was predicted to be 7.6 kcal/mol lower in free energy than **IM1_C**.

Following formation of **IM1_N**, radical chlorination could conceivably occur through approach of SF₅Cl to the same face as the *N*–SF₅ substituent (i.e., to access “*syn*” invertomer **1_{N,syn}**) or to the opposite face (i.e., to access “*anti*” invertomer **1_{N,anti}**). The energy differences between **TS2_{N,syn}** and **TS2_{N,anti}** and overall free energies of the reactions to convert **IM1_N** to either **1_{N,syn}** or

1_{N,anti} are very small (≤ 1 kcal/mol), indicating there is not a significant preference for initial formation of one invertomer over another. Nonetheless, the computed lowest energy pathway exhibits a free energy of activation ($\Delta G^\ddagger$) of 11.9 kcal/mol and free energy of reaction (ΔG°) of -13.6 kcal/mol. Overall, the radical chain process for *N*-pentafluorosulfanylation is also thermodynamically favored by >23 kcal/mol over the antithetic C–SF₅ bond formation, which was not observed experimentally.

As anticipated, the free energy landscape for the analogous CF₃SF₄Cl addition reaction is similar in nature and accounts for our observed regioselectivity (Figure 5.4, middle panel). That is, *N*–SF₄CF₃ bond formation to make **IM2_N** through **TS3_N** is both kinetically ($\Delta\Delta G^\ddagger = 3.6$ kcal/mol) and thermodynamically ($\Delta\Delta G^\circ = 7.2$ kcal/mol) favored over C–SF₄CF₃ bond formation to make **IM2_C** through **TS3_C** in the first step of the propagation mechanism. In the second step, we also found that the lowest energy pathway (via **TS4**) has a free energy of activation ($\Delta G^\ddagger$) of 12.5 kcal/mol and free energy of reaction (ΔG°) of -15.7 kcal/mol, and that the overall process is exergonic and favored by >23 kcal/mol over corresponding C–SF₅ bond formation.

Beyond DFT calculations, we sought to substantiate our mechanistic hypothesis with additional experimental data. Conveniently, the use of 3-aryl ABB substrates enabled us to conduct linear free energy relationship (LFER) studies to examine *para* and *meta* substituent effects on relative rates of reactions.^{223,224} We assembled Hammett plots from the results of intermolecular competition experiments conducted under pseudo-first order conditions that were designed to investigate the selectivity-determining step (Figure 5.4, *bottom left panel*). Upon plotting $\log([P_X]/[P_H])$ against the corresponding Hammett substituent constants (s_p or s_m) for each substrate, we determined ρ values of -1.3 for SF₅Cl addition reactions and -0.7 for CF₃SF₄Cl addition reactions, with good coefficients of determination ($R^2 = 0.96$ in each case). These values

suggest a slight buildup of positive charge during the transition state of the rate-determining step being investigated (i.e., the *N*-SF₄R bond forming steps), since the rate of the reaction is relatively faster for ABBs with electron-donating substituents.^{225,226} The direction and magnitude of each slope is also more consistent with a radical pathway^{225,227} than a polar addition mechanism.²²⁸

Lastly, additional support for a radical chain propagation pathway was found during radical-trapping experiments (Figure 5.4, *bottom right panel*). Specifically, bromotrichloromethane (CCl₃Br) was added to the reaction mixtures of 3-(4-bromophenyl)-1-azabicyclo[1.1.0]butane and SF₅Cl or CF₃SF₄Cl in various equivalents as a source of atomic bromine.²²⁹ Analyses of the crude reaction mixtures by ¹⁹F NMR and HRMS revealed that the bromine-trapped product had indeed formed in addition to the anticipated chlorinated product, albeit in low yields. When 1.0 equiv. of CCl₃Br was added to the reaction mixture, the Br:Cl product ratio was 1:1.2 for SF₅Cl and 1:2 for CF₃SF₄Cl. Upon increasing to 5.0 equiv. of CCl₃Br, the reaction began to favor the 3-Br when SF₅Cl was employed (Br:Cl = 3.8:1), and the Br:Cl ratio was ~1:1 when CF₃SF₄Cl was used. While these conditions did not prove amenable to, e.g., practical three-component radical coupling, the results comport with our proposed radical chain mechanism.

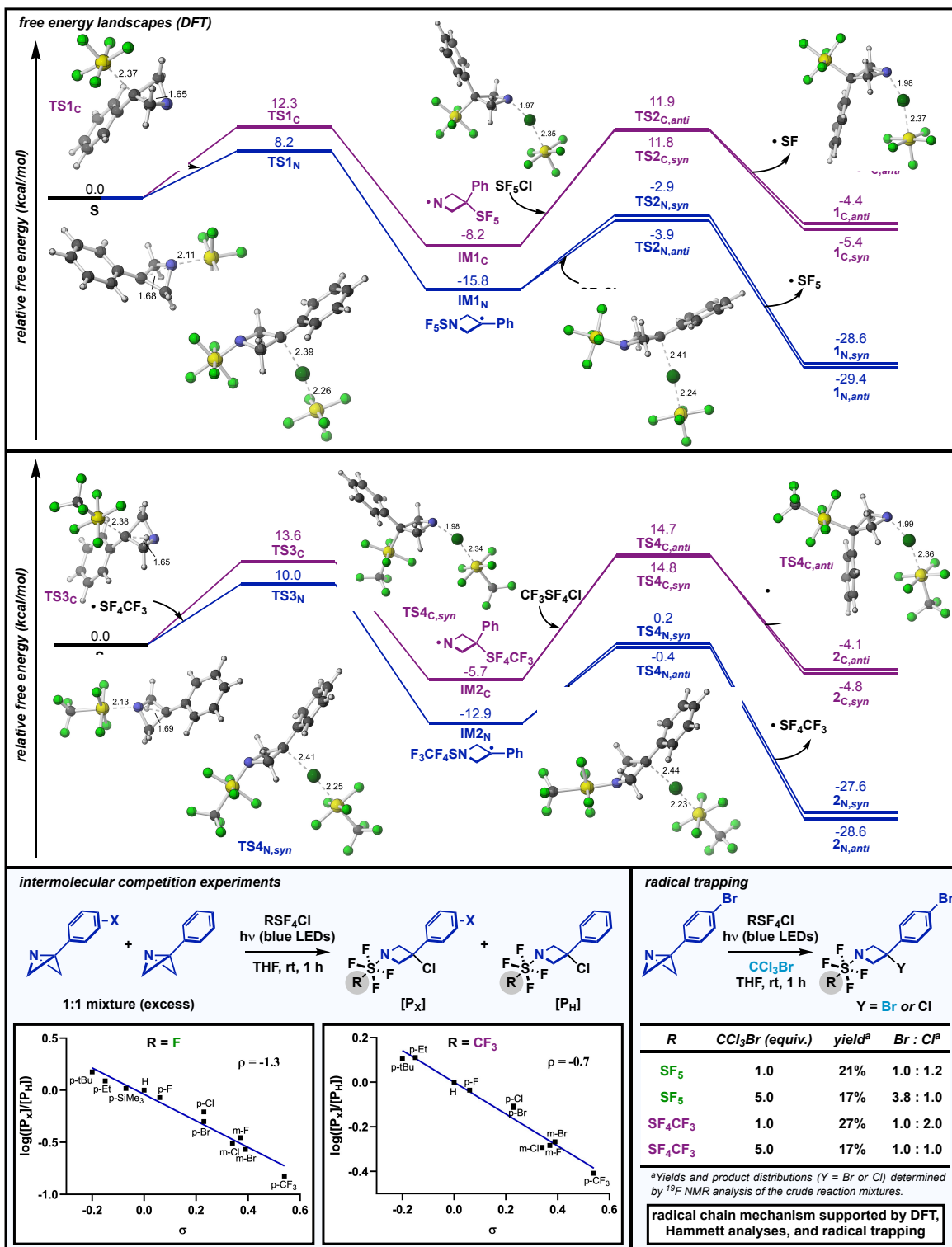
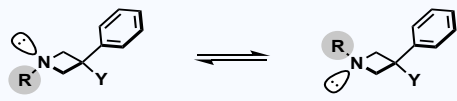


Figure 5.4. Free energy profiles for SF_5 (top) and CF_3SF_4 (middle) radical additions to 3-phenyl-[1.1.0]azabicyclobutane computed at the PWPB95-D4/def2-QZVPP//PCM(Et_2O)- $\omega\text{B97X-D}/\text{def2-SVP}$ level of theory. (Bottom left) Intermolecular competition experiments and associated Hammett plots for SF_5Cl ($\rho = -1.3$; $R^2 = 0.96$) and $\text{CF}_3\text{SF}_4\text{Cl}$ ($\rho = -0.7$; $R^2 = 0.96$) addition reactions. (Bottom right) Select results from radical trapping experiments using bromotrichloromethane.

5.2.3 On Nitrogen Inversion.

One question prompted during our mechanistic investigation was: what are the *N*-inversion barriers of such compounds? We first attempted to determine the *N*-inversion barriers experimentally through variable-temperature NMR spectroscopy (VT-NMR). However, after collecting VT-NMR data for a small variety of *N*-SF₅ and *N*-SF₄CF₃ azetidines, we observed only temperature-dependent ¹H and ¹⁹F chemical shifts in lieu of a coalescence point in each case.²³⁰ A reasonable explanation is that the *N*-inversion barriers are exceptionally low, resulting in dynamic processes that are too fast to observe by VT-NMR.²³¹ We turned to DFT calculations and quickly confirmed this hypothesis (Table 5.1). The computed *N*-inversion barrier ($\Delta G^\ddagger_{calc}$) at the PCM(Et₂O)-*w*B97X-D/def2-SVP level of theory was only 2.8 kcal/mol for *N*-SF₅ azetidine **1** and 3.7 kcal/mol for *N*-SF₄CF₃ azetidine **2**. We found that the computed barriers also do not change significantly for the dechlorinated derivatives **53** and **54**. For context, the experimentally determined barrier for nitrogen inversion of 1-methylazetidine was reported to be 10.0 kcal/mol,²³² and the *N*-inversion barrier of an *N*-aryl aziridine determined by DFT was reported to be 11.1 kcal/mol.²³³ For another point of comparison, the barrier for nitrogen inversion in acyclic amines is on the order of 6-7 kcal/mol.²³⁴

Table 5.1. Low *N*-inversion barriers for model *N*-SF₅ and *N*-SF₄CF₃ azetidines computed at the PCM(Et₂O)- ω B97X-D/def2-SVP level of theory.

<i>N</i> -inversion barriers (DFT)				
				
compound	R	Y	ΔG_{calc}^a	$\Delta G_{calc}^\ddagger^a$
1	SF ₅	Cl	-0.83	2.84
53	SF ₅	H	-1.32	3.08
2	SF ₄ CF ₃	Cl	-1.11	3.71
54	SF ₄ CF ₃	H	-1.19	3.31

All values reported in kcal/mol. ^aCalculated at the PCM(Et₂O)- ω B97X-D/def2-SVP level of theory. Barrier referenced to the lowest energy invertomer

Although such low *N*-inversion barriers preclude “freezing out” the invertomers in solution by VT-NMR, we managed to observe them in the solid state using single-crystal X-ray diffraction (SC-XRD). After growing single crystals of **23** and **24** using a vapor diffusion technique, the diffraction pattern for each structure was recorded at 90 K using Mo K α radiation. After structure solution and refinement,²³⁵ careful analysis of the Fourier difference map revealed electron density that could only be accounted for when modelling *N*-inversion disorder (see SI for details). For both **23** and **24**, the “*syn*” invertomer was preferred in the solid state, with the minor disordered part consisting of the “*anti*” invertomer (Figure 5.5). The refined occupancy of the *syn:anti* invertomers of **23** was 90:10, whereas the ratio was refined to 89:11 for **24**. Interestingly, when the diffraction data was collected near room temperature (296 K), the refined occupancies of the *syn:anti* invertomers shifted to 71:29 for both **23** and **24**, consistent with the temperature dependence of the Boltzmann distribution. It is also worth noting that this effect was reproducible,

with the same distribution of disordered parts occurring in single crystals obtained from different crystallization batches.

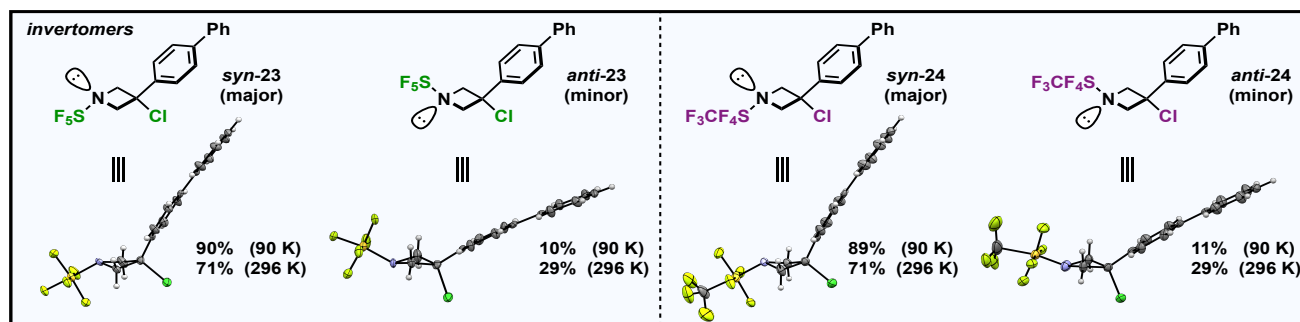


Figure 5.5. Invertomers and temperature dependence of refined occupancies observed from single crystal X-ray diffraction (SC-XRD) data on compounds **23** and **24** (ellipsoids depicted at 50% probability)

5.2.4 Spectroscopic and Crystallographic Features.

For additional context, it is also worth highlighting some of the spectroscopic and crystallographic features of *N*-SF₅ and *N*-SF₄CF₃ azetidines (Table 5.2).

The isotropic chemical shifts of the protons at the C2 position on azetidines **1** and **2** range from 4.60 to 4.71 ppm and manifest as AB quartets (ABq) with ²*J*_{HH} coupling constants of 8.7 Hz. The ¹⁹F NMR spectrum of **1** displays the typical AB₄ splitting pattern for an SF₅ group, whereby the four equatorial fluorine atoms (F_{eq}) appear as a doublet centered at +52.71 ppm and the axial fluorine atom (F_{ax}) appears as a pentet centered at +82.02 ppm (²*J*_{FF} = 155 Hz). On the other hand, the ¹⁹F NMR spectrum of **2** features a quartet centered at +29.61 ppm that corresponds to the four F_{eq} atoms and a pentet at −63.37 ppm that corresponds to the fluorine atoms on the CF₃ group (³*J*_{FF} = 25 Hz). The ¹³C{¹H} NMR spectra of **1** and **2** are very similar, with the benzylic carbon (C3) signals appearing at 60.5 and 60.7 ppm, respectively. The carbon atoms at the C2 position resolve as pentets (at 69.6 ppm for **1** and 69.7 ppm for **2**) due to coupling with the F_{eq} atoms (³*J*_{CF} = 3.7 Hz). Additionally, we managed to obtain ¹⁴N NMR chemical shifts of **1** and **2**, using a solution of

formamide as an external reference. The broad ^{14}N NMR signal for **1** is centered at +52 ppm, with a full width at half maximum (FWHM) of 54 ppm. Similarly, the ^{14}N NMR spectrum of **2** displays a broad singlet centered at +54 ppm, with a FWHM of 67 ppm. In both cases, the ^{14}N resonances are more shielded than that of HCONH_2 .²³⁶ Note that the larger FWHM for **2** likely stems from additional, unresolved, long-range splitting of the nitrogen nucleus by the fluorine nuclei of the CF_3 group. Finally, we noted that the IR spectra of **1** and **2** are dominated by strong S–F stretching modes, e.g., with $\nu_{\text{max}} = 800\text{ cm}^{-1}$ and 780 cm^{-1} , respectively.

Table 5.2. Select ^{14}N , ^{19}F , and $^{13}\text{C}\{^1\text{H}\}$ NMR and IR data for compounds **1** and **2**.

<i>NMR & IR</i>							
<i>compound</i>	<i>R</i>	$^{14}\text{N } \delta \text{ (ppm)}$	$^{19}\text{F}_{\text{eq}} \delta \text{ (ppm)}$	$^{19}\text{F}_{\text{ax}} \delta \text{ (ppm)}$	$^{19}\text{F}_{\text{CF}_3} \delta \text{ (ppm)}$	$^{13}\text{C}\{^1\text{H}\}_{\text{CF}_3} \delta \text{ (ppm)}$	$\nu_{\text{max}} \text{ (S–F)}$
1	SF_5	+52 (br s, FWHM = 54)	+52.71 (d, $^2J_{\text{FF}} = 155\text{ Hz}$)	+82.02 (p, $^2J_{\text{FF}} = 155\text{ Hz}$)	–	–	800 cm^{-1}
2	SF_4CF_3	+54 (br s, FWHM = 67)	+29.61 (q, $^2J_{\text{FF}} = 25\text{ Hz}$)	–	–63.37 (p, $^2J_{\text{FF}} = 25\text{ Hz}$)	+123.3 (qp, $J_{\text{CF}} = 329, 50\text{ Hz}$)	780 cm^{-1}

Next, we analyzed the molecular structures of **49** and **50** by SC-XRD (Figure 5.6). In juxtaposition with our SC-XRD data for **23** and **24**, the electron difference maps of the refined structures indicated that no disorder was present, permitting a more detailed analysis of bond distances and angles. Similar N–S bond distances were measured for the $N\text{--SF}_5$ motif (1.664(1) Å) and the $N\text{--SF}_4\text{CF}_3$ motif (1.673(1) Å). However, a notable difference in S–F_{eq} bond distances was observed between **49** and **50**. That is, the measured S–F_{eq} distances for **49** range from 1.573(1)–1.613(1) Å, while the S–F_{eq} distances for **50** were longer on average, ranging from 1.587(1)–1.673(1) Å. This discrepancy is consistent with the observed higher susceptibility of the $N\text{--SF}_4\text{CF}_3$ motif towards hydrolysis (note that the lower S–F_{eq} stretching frequency observed in the IR spectrum is also suggestive of weaker S–F_{eq} bonds in $N\text{--SF}_4\text{CF}_3$ relative to $N\text{--SF}_5$). Additionally, the C3–N–S angles deviate from the ideal trigonal pyramidal geometry significantly in both cases (typical for an azetidine),²³⁷ with 152.05(5)° observed for **49** and 151.21(8)° observed

for **50**. Lastly, it is also worth noting that in this case, the “*syn*” invertomer is preferred in the solid state for **49**, while **50** crystallized as the “*anti*” invertomer, ostensibly due to crystal packing effects.²³⁸

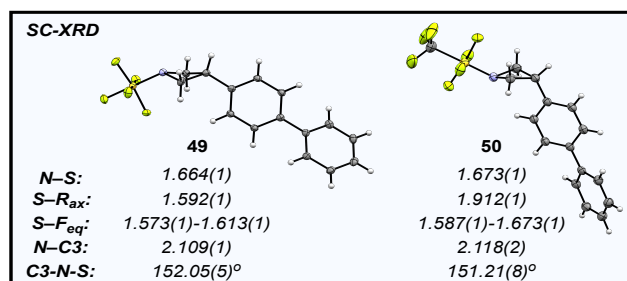


Figure 5.6. Select single crystal X-ray diffraction (SC-XRD) data on compounds **49** and **50** (ellipsoids depicted at 50% probability).

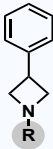
5.2.5 Bond Strength, Basicity, and Context for Bioisosterism.

In previous literature, the carbon-bound SF₅ group is most frequently employed as a bioisosteric replacement for a CF₃ group.¹⁴² It is plausible that the nitrogen-bound SF₅ group could be used in a similar manner as a replacement for the N-CF₃ motif.^{239–245} This may be of interest in light of the fact that the SF₅ group has been shown to degrade more easily than the CF₃ group under environmentally relevant conditions on other substrate classes.²⁴⁶ Alternatively, we envisioned that the N-SF₅ motif may also serve as a lipophilic substitute for a small sulfonamide (e.g., N-SO₂Me), while similarly attenuating nitrogen basicity.²⁴⁷ This facet has yet to be entertained and explored in the context of bioisosterism.

In order to provide additional context for downstream applications of N-SF₅ (and N-SF₄CF₃) azetidines, we compared relative azetidine N-R bond dissociation energies (BDE), N-R bond distances, and nitrogen basicity (pK_b values) using DFT for R = SF₅ (**53**), SF₄CF₃ (**54**), CF₃ (**55**), and SO₂Me (**56**) in Table 5.3. Calculations performed at the PCM(Et₂O)-wB97X-D/def2-SVP level of theory predict that the N-S BDEs in **53**, **54**, and **56** fall between 62 and 67 kcal/mol (with N-SF₅ and N-SF₄CF₃ both representing slightly stronger bonds than N-SO₂Me), while the

N -CF₃ BDE of **55** is 100 kcal/mol. Additionally, the predicted N -SF₅ and N -SF₄CF₃ bond distances (1.67-1.68 Å) are in reasonable accord with our SC-XRD data, similar in length to (or only marginally longer than) the N -SO₂Me bond distance in **56**, and significantly longer than the N -CF₃ bond distance in **55** (1.39 Å). Lastly, we found that the nitrogen atoms in **53** and **54** are substantially *less basic* than the nitrogen atoms in **55** and **56**. While the basicities of the N -SO₂Me and N -CF₃ motifs are quite similar (pK_b = 22.0 and 22.3), the pK_b of the N -SF₄CF₃ motif was notably higher (24.7); moreover, the pK_b of the N -SF₅ motif was the highest within this series (26.6). This underscores the significant electron-withdrawing effects that both the SF₅ and CF₃SF₄ groups exhibit on the nitrogen lone pair.

Table 5.3. Select computed bond dissociation energies (BDE), bond lengths, and basicities to contextualize N -SF₅ and N -SF₄CF₃ motifs.

	compound	R	BDE (N-R) ^a	d(N-R) (Å)	pK_b
	53	SF ₅	67	1.674	26.6
	54	SF ₄ CF ₃	64	1.682	24.7
	55	CF ₃	100	1.388	22.3
	56	SO ₂ Me	62	1.665	22.0

Calculated at the PCM(Et₂O)-ωB97X-D/def2-SVP level of theory.
^aValues reported in kcal/mol.

5.2.6 Complex Molecule Synthesis and Comparative in vitro ADME Profiling.

Although N -SF₄CF₃ azetidines may display interesting properties, they are unlikely reasonable candidates for incorporation into drug-like molecules in light of their hydrolytic instability (discussed above). On the other hand, the observed chemical stability of N -SF₅ azetidines indicates that they could be viable fluorinated motifs to consider during drug discovery campaigns.^{248–251}

We were particularly interested in the notion that the N -SF₅ motif could act as a lipophilic alternative to the N -SO₂Me (or N -SO₂Et) motif. Accordingly, we identified a spleen tyrosine

kinase inhibitor (**57**) developed by Portola Pharmaceuticals in the patent literature as a synthetically accessible target for comparative absorption, distribution, metabolism, and excretion (ADME) studies (Figure 5.7).²⁵² We first synthesized the control compound **57** in 4 steps from **58** according to the procedure outlined in the patent literature. Next, we intercepted the last step of the synthesis using building block **59** to access *N*-SF₅ derivative **60**. Both **57** and **60** were then submitted for *in vitro* profiling.

Preliminary results in Figure 5.7 indicate that, unsurprisingly, introduction of the *N*-SF₅ group dramatically increases lipophilicity (i.e., logD_{7.4} was determined to be 2.10 for **57** and >5.0 for **60**). Notwithstanding the substantial rise in logD, only a modest increase in intrinsic clearance was observed in **60** compared to **57** in both rodent and human liver microsomes.²⁵³ The *N*-SF₅ derivative (**60**) exhibits lower permeability (MDCK A-B P_{app} = 3.5 × 10⁻⁶ cm/s), relative to *N*-SO₂Me **57**. Both compounds proved to be non-cytotoxic (HepG2 CC₅₀ ≥ 40 μM) and did not inhibit hERG (IC₅₀ >30 μM), CYP3A4, 2D6, or 2C9 (IC₅₀ values >25 μM). Complete *in vitro* profiling details are included in the SI.

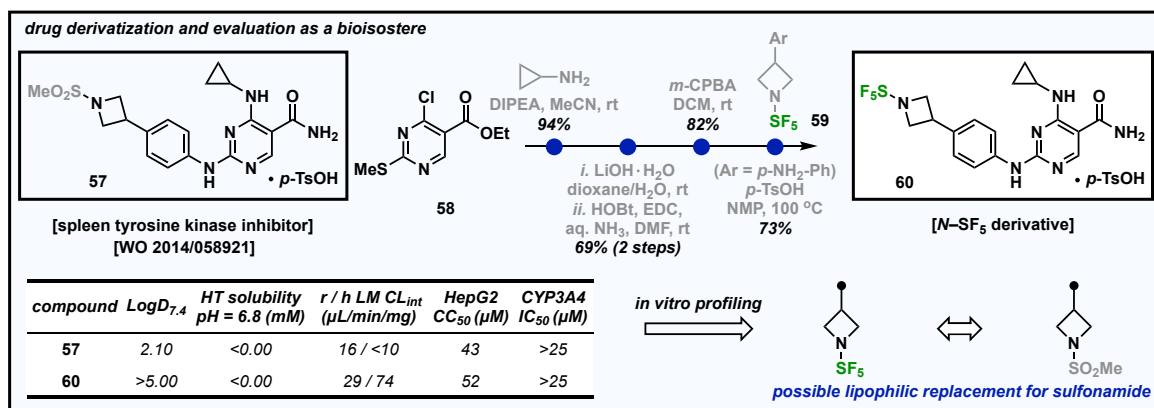


Figure 5.7. Synthesis of an *N*-SF₅ derivative (**60**) of a spleen tyrosine kinase inhibitor (**57**) reported in the patent literature and summary of *in vitro* ADME properties that evaluate the *N*-SF₅ motif as a possible lipophilic replacement for an *N*-SO₂Me motif.

In this specific instance, we found that replacement of the *N*-SO₂Me motif with the *N*-SF₅ motif did not necessarily improve the overall drug-like qualities of the parent molecule, though generally acceptable ADME properties were maintained (even despite the large increase in logD). This case study indicates that *N*-SF₅ azetidines are certainly viable candidates for structure-activity relationship (SAR) studies, and that they may serve as potential bioisosteres for *N*-SO₂Me azetidines on more polar molecules, where a lipophilic replacement for a small sulfonamide may be desired.²⁵⁴

5.3 Conclusion.

In summary, we developed complementary synthetic methods for the direct formation of heretofore unknown *N*-SF₅ and *N*-SF₄CF₃ azetidines *via* strain-release functionalization of 3-aryl azabicyclo[1.1.0]butanes. The *N*-SF₅ azetidines, in particular, displayed remarkable chemical stability under a variety of reaction conditions, enabling us to access additional building blocks and incorporate them into complex molecule synthesis. The mechanisms of the transformations were investigated using DFT calculations and corroborated experimentally by, e.g., Hammett analyses and radical trapping experiments. In addition, properties of the *N*-SF₅ and *N*-SF₄CF₃ azetidines were characterized and contextualized through NMR, IR, SC-XRD, and DFT analyses. These data support the notion that the *N*-SF₅ motif could serve as a potential bioisosteric replacement for a small sulfonamide within the context of medicinal chemistry. Lastly, we conducted comparative *in vitro* ADME profiling that indicate the *N*-SF₅ motif could indeed serve as a replacement for *N*-SO₂Me, in instances where increased lipophilicity is desirable.

5.4 Author Contributions.

Y.K., S.P., Y.C., A.J.W., J.A.B., and A.N.R. performed synthetic work and data analysis. Y.K. optimized the pentafluorosulfanylation reaction, synthesized compounds **1–4**, **6–16**, **18**, **21–23**, **25–28**, **30–36**, **41**, **43–51**, and **57–60**, performed radical trapping experiments, obtained VT-NMR spectra, and collected all SC-XRD data. S.P. synthesized the compounds **5**, **17**, **19**, **20**, **24**, **29**, **31**, **37**, **38** and completed the Hammett analyses. W.-Y.K. conducted all DFT investigations and analyses. Y.K., S.P., Y.C., and A.J.W. synthesized ABB starting materials. J.A.B. and A.N.R. conducted the SF₅Cl synthesis scale-up and optimization experiments. L.M.H. completed and interpreted the *in vitro* ADME profiling. C.R.P. and D.J.T. conceptualized and supervised the project and acquired funding. The manuscript was written and edited with contributions from all authors.

5.5 Experimental.

5.5.1 General Information.

Unless otherwise stated, all reactions were carried out under strictly anhydrous conditions, under N₂ or Ar atmosphere, and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred *via* syringe using standard Schlenk techniques. Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), diethyl ether (Et₂O) and toluene were obtained from a solvent purification system directly before use. Methanol (MeOH), acetonitrile (MeCN), *n*-pentane, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and ethyl acetate (EtOAc) were purchased in sealed bottles containing molecular sieves and were used as received. All other solvents were used as received unless otherwise stated. Spray-dried KF was always weighed out under glovebox (N₂) atmosphere. All NMR data were collected on either a 300, 400, or 600 MHz Bruker NMR spectrometer. For ¹⁹F NMR yield determination, α,α,α-trifluorotoluene (or

fluorobenzene) in CDCl_3 was introduced after each reaction as an internal standard, and the relaxation delay (d1) was increased to at least 30 s during data collection. The ^1H , ^{13}C , and ^{19}F NMR chemical shifts are given in parts per million (δ) and calibrated to either residual solvent signal (^1H and ^{13}C), α,α,α -trifluorotoluene (TFT) ($\delta = -62.61$ ppm in CDCl_3), or fluorobenzene ($\delta = -112.96$ in CDCl_3).²⁵⁵ NMR data are reported in the following fashion: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, dt = doublet of triplets, dd = doublet of doublets, tt = triplet of triplets, ttp = triplet of triplet of pentets, m = multiplet, br = broad), integration, coupling constants (Hz)). Infrared spectroscopy (IR) data were collected on a Bruker Tensor 27 FT-IR spectrometer with ATR-IR attachment. IR signals are reported in reciprocal centimeters (cm^{-1}) and are rounded to the nearest 1 cm^{-1} . High-resolution mass spectrometry (HRMS) data was collected on a Thermo Q-Exactive HF. Melting points were collected on a Stanford Research Systems MPA120EZ-Melt automated melting point system. X-ray diffraction data were collected on either a Bruker APEX-II Dual Source or Bruker D8 Venture Kappa Dual Source diffractometer.

Note on the ^1H NMR spectra of the $N\text{-SF}_5$ and $N\text{-SF}_4\text{CF}_3$ azetidines obtained in this study: the azetidine ring protons display an AB quartet splitting pattern and are reported in the following fashion: #.## (ABq, 2H, $\Delta\delta_{\text{AB}} = \#.##$, $J_{\text{AB}} = \#. \#$ Hz). In cases where the quartet has fully collapsed with no separation between peaks, the signal is reported as a singlet.

5.5.2 Synthesis of ABB Starting Materials.

The 3-aryl-1-azabicyclo[1.1.0]butane (ABB) starting materials were synthesized according to known literature procedures. **61**, **68** and **69** were reported previously by Dell'Amico and co-workers.²⁵⁶ Additionally, **61** and **67** were reported by Hortmann and Robertson.²⁵⁷ All analytical data were consistent with the reported literature, and ¹H and ¹³C{¹H} data are included for convenience. Compounds **62**, **63-6**, **70-80** were synthesized for the purposes of this study and also represent an expansion of scope for 3-aryl ABB synthesis.

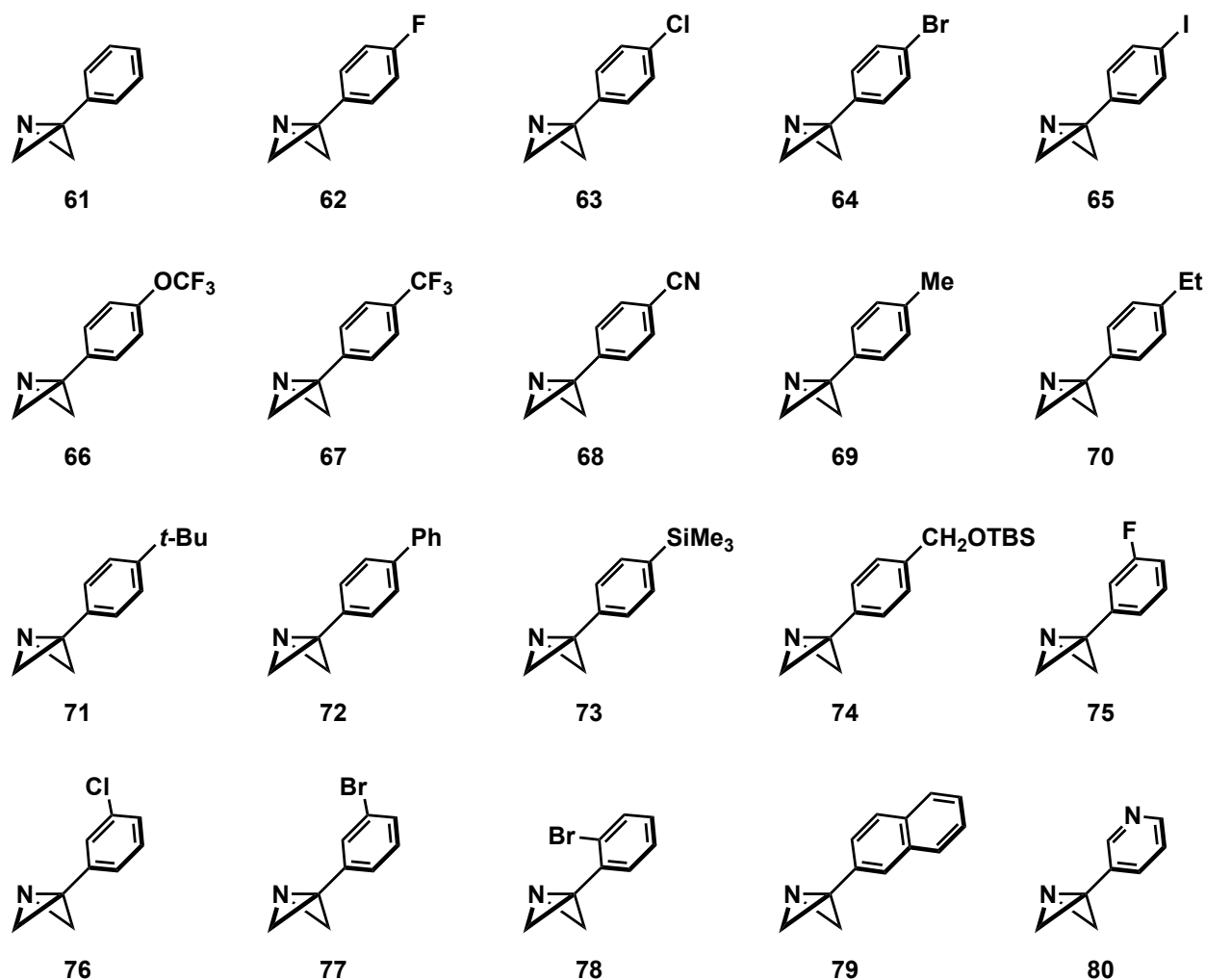


Figure 5.8. Azabicyclo[1.1.0]butanes (ABBs) synthesized for this study.

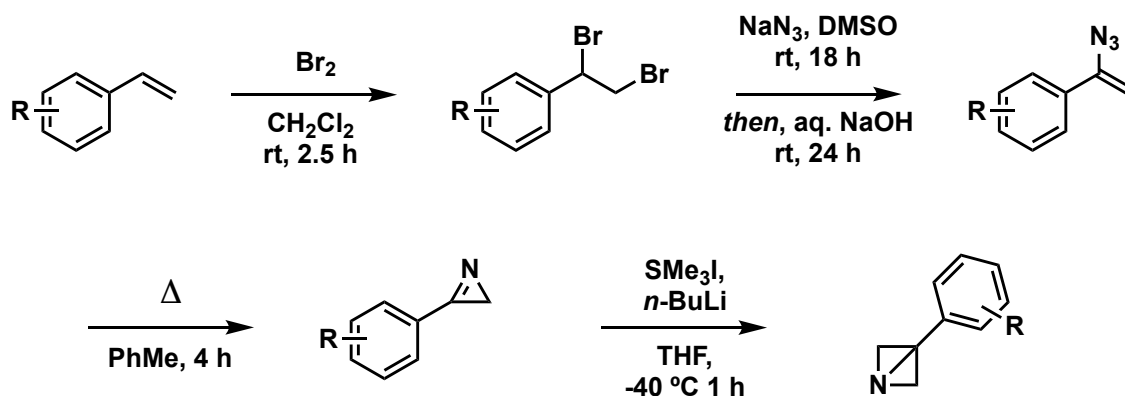
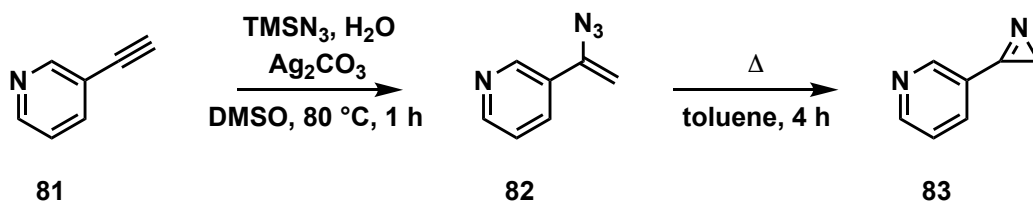


Figure 5.9. General synthetic route for the synthesis of ABB starting materials.

Adapted from the previously reported procedure, the styrene derivative (20 mmol) was dissolved in CH_2Cl_2 (40 mL), and Br_2 (1.0 equiv.) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 2.5 h, quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL), and then transferred to a separatory funnel. The combined mixture was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 , and concentrated to obtain the dibrominated intermediate. The crude reaction mixture was then dissolved in DMSO (28 mL), and NaN_3 (1.95 g, 30 mmol) was added portionwise. The resulting solution was stirred at room temperature for 18 h. Subsequently, NaOH (0.8 g, 20 mmol) in water (3 mL) was added to the reaction mixture, which was then stirred at room temperature for 24 h. The mixture was diluted with brine (40 mL) and extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were washed with brine (3×40 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to yield a crude residue containing the 1-azidostyrene derivative. The crude reaction mixture was then dissolved in toluene (40 mL) and heated to reflux for 4 h. After the reaction was complete (as indicated by TLC analysis), toluene was removed under reduced pressure to yield a crude residue containing the azirine derivative.^a

To a stirred solution of trimethylsulfonium iodide (4.84 g, 22 mmol) in THF (75 mL) at –40 °C under Ar atmosphere, 2.5 M *n*-BuLi in hexane (8.8 mL, 22 mmol) was added dropwise. After addition was completed, the reaction mixture was stirred for 30 min at –40 °C. The crude residue containing the azirine intermediate was dissolved in THF (5 mL) and then added dropwise; the reaction mixture stirred for 30 min. at –40 °C. The reaction mixture was then quenched with water (40 mL), transferred to a separatory funnel, and extracted with CH₂Cl₂ three times (3 × 80 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by either high-vacuum distillation or flash chromatography on silica gel to yield aza-bicyclo[1.1.0]butanes.

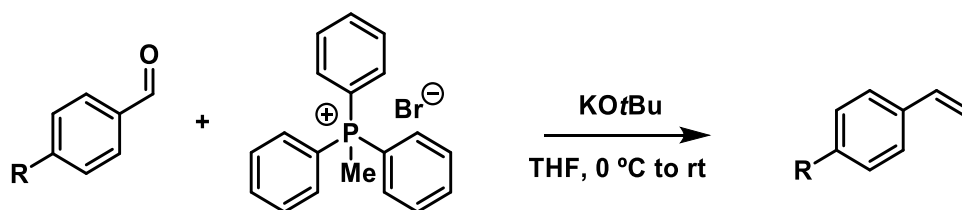
^aCaution! Organic azides are known to pose significant safety risks upon heating to elevated temperatures.²⁵⁸ The conversion of the 1-azidostyrene derivatives to the corresponding azirines must be conducted behind adequate shielding (e.g., the use of a blast shield is recommended). Recent strategies for the synthesis of aryl azirines under flow conditions have been developed that allow safer access to these intermediates on scale.^{259,260}



To a solution of 3-ethynylpyridine (**81**) (2.1 g, 20 mmol, 1.0 equiv.), TMS-N₃ (5.3 mL, 40 mmol, 2.0 equiv.), and H₂O (0.72 mL, 40 mmol, 2.0 equiv.) in DMSO (40 mL) at 80 °C was added Ag₂CO₃ (550 mg, 2 mmol, 0.1 equiv.). The mixture was stirred for 1 h until complete consumption of 3-ethynylpyridine, as indicated by TLC analysis. The reaction mixture was then diluted with brine (40 mL) and extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were washed

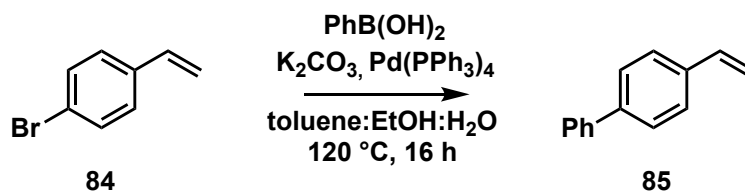
with brine (3×40 mL), dried over MgSO_4 , and concentrated under reduced pressure to afford a crude residue containing 3-(1-azidovinyl)pyridine (**82**). The crude reaction mixture was then dissolved in toluene (40 mL) and heated to reflux for 4 h. After completion of the reaction, toluene was removed under reduced pressure, yielding a crude residue containing 3-(2H-azirin-3-yl)pyridine (**83**). The product was purified by column chromatography on silica gel eluting with 3:1 hexanes/EtOAc. *Note: a thick emulsion formed after the addition of brine to the crude reaction mixture. It is recommended to filter the mixture prior to extraction with CH_2Cl_2 .*

Styrenes which were not commercially available were synthesized via Wittig reaction with the corresponding aldehyde:



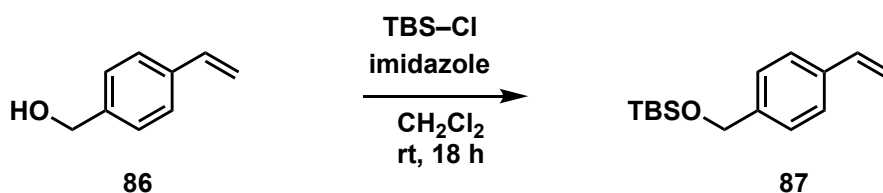
A suspension of methyltriphenylphosphonium bromide (33 mmol, 1.1 equiv., 11.8 g) in anhydrous THF (60 mL) at 0 °C was treated with KOt-Bu (33 mmol, 1.1 equiv., 3.7 g) and stirred for 30 min. A solution of commercially available 4-substituted benzaldehyde (30 mmol, 1.0 equiv.) in THF (15 mL) was then added dropwise to the reaction mixture over the course of 15 min. The suspension was allowed to warm to room temperature and stirred for 8 h before the reaction was quenched with H_2O (20 mL). The reaction mixture was then diluted with brine (60 mL), transferred to a separatory funnel, and extracted with ethyl acetate (3×60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford the 4-substituted styrene.

Preparation of biphenyl styrene:



To a solution of 1-bromo-4-vinylbenzene (**84**, 2.6 mL, 20 mmol, 1.0 equiv.) in toluene (80 mL) and EtOH (20 mL) was added a solution of K_2CO_3 (8.3 g, 60 mmol, 3.0 equiv.) in H_2O (20 mL) at room temperature. Phenylboronic acid (2.4 g, 20 mmol, 1.0 equiv.) and $\text{Pd(PPh}_3)_4$ (230 mg, 0.2 mmol, 0.01 equiv.) were then added sequentially. The mixture was refluxed at 120 °C for 16 h and then allowed to cool to room temperature. The reaction mixture was diluted with brine (60 mL) and extracted with EtOAc (3×80 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100% hexanes) to afford 4-vinyl-1,1'-biphenyl (**85**, 2.9 g, 81%) as a white solid. The spectroscopic data were consistent with the values reported in the literature.²⁶¹

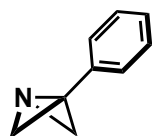
Preparation of para-CH₂OTBS styrene:



To a solution of (4-vinylphenyl)methanol (**86**, 3.7 g, 30 mmol, 1.0 equiv.) in CH_2Cl_2 (60 mL) was added imidazole (6.1 g, 90 mmol, 3.0 equiv.) and *tert*-butylchlorodimethylsilane (5.4 g, 36 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for 16 h. Subsequently, the reaction mixture was diluted with brine (60 mL), transferred to a separatory funnel, and extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated

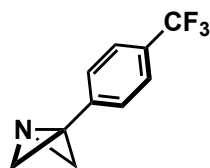
under reduced pressure. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to yield a *tert*-butyldimethyl((4-vinylbenzyl)oxy)silane (**87**, 6.3 g, 84%) as a colorless oil. The spectroscopic data were consistent with the values reported in the literature.²⁶²

5.5.3 Characterization Data for ABB Starting Materials.



3-(phenyl)-1-azabicyclo[1.1.0]butane (61) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–120 °C to afford the ABB as a clear oil which solidified upon storage at 4 °C (1.2 g, 40 % over 5 steps). Analytical data were consistent with the reported literature.

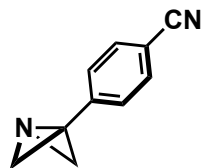
¹H (300 MHz, CDCl₃): δ = 7.42-7.32 (m, 5H), 2.80-2.79 (t, 2H, J = 1.2 Hz), 1.55-1.54 (t, 2H, J = 1.2 Hz); **¹³C{¹H} (76 MHz, CDCl₃):** δ = 134.8, 128.4, 127.9, 127.4, 53.9, 31.8.



3-(4-(Trifluoromethyl)phenyl)-1-azabicyclo[1.1.0]butane (67) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 110–140 °C to afford the ABB as a clear oil (420 mg, 11% over 5 steps).

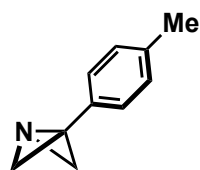
¹H (300 MHz, CDCl₃): δ = 7.63-7.57 (d, 2H, J = 8.2 Hz), 7.55-7.48 (d, 2H, J = 8.1 Hz), 2.85-2.80 (t, 2H, J = 1.0 Hz), 1.63-1.59 (t, 2H, J = 1.0 Hz); **¹⁹F{¹H} (282 MHz, CDCl₃):** δ = –62.74 (s, 3F);

$^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl_3): δ = 139.7, 130.3 (q, J = 32.6 Hz), 125.6 (q, J = 3.8 Hz), 124.2 (q, J = 272.1 Hz), 54.4, 31.4.



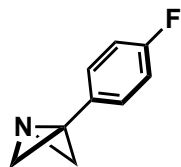
4-(1-Azabicyclo[1.1.0]butan-3-yl)benzonitrile (68) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 140–150 °C to afford the ABB as a white solid (67 mg, 1.4 % over 5 steps). Analytical data were consistent with the reported literature. *Note: previously, this was reported as a red solid; however, upon distillation we obtained a colorless solid. The low overall yield is most likely due to the propensity of this ABB to polymerize upon heating.*

^1H (300 MHz, CDCl_3): δ = 7.66-7.63 (d, 2H, J = 8.5 Hz), 7.51-7.49 (d, 2H, J = 8.5 Hz), 2.84-2.83 (t, 2H, J = 1.0 Hz), 1.65-1.64 (t, 2H, J = 1.0 Hz); $^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl_3): δ = 141.2, 132.2, 128.3, 118.6, 111.8, 54.4, 31.2



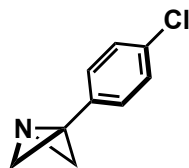
3-(*p*-Tolyl)-1-azabicyclo[1.1.0]butane (69) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–120 °C to afford the ABB as a clear oil which solidified upon storage at 4 °C (890 mg, 30% over 5 steps). Analytical data were consistent with the reported literature.

¹H (300 MHz, CDCl₃): δ = 7.33-7.27 (d, 2H, J = 8.1 Hz), 7.19-7.13 (d, 2H, J = 7.9 Hz), 2.78-2.76 (t, 2H, J = 1.1 Hz), 2.35 (s, 3H), 1.53-1.52 (t, 2H, J = 1.1 Hz); **¹³C{¹H} (76 MHz, CDCl₃):** δ = 137.9, 131.8, 129.3, 127.5, 54.0, 31.9, 21.3.



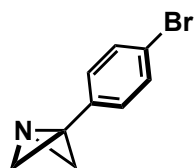
3-(4-Fluorophenyl)-1-azabicyclo[1.1.0]butane (62) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–120 °C to afford the ABB as a clear oil (500 mg, 17% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.37-7.30 (m, 2H), 7.04-6.97 (m, 2H), 2.72 (s, 2H), 1.51 (s, 2H); **¹⁹F{¹H} (282 MHz, CDCl₃):** δ = -113.72 (s, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.3-161.0 (d, J = 245.9 Hz), 130.71-130.67 (d, J = 3.1 Hz), 129.3-129.2 (d, J = 8.4 Hz), 115.7-115.4 (d, J = 21.7 Hz), 54.1, 31.4; **ATR-IR (ν_{max}):** 3051, 2944, 1607, 1529, 1509, 1407, 1221, 1158, 1143, 1087, 1014, 835, 793, 714 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₉H₉FN⁺ 150.0174, Found 150.0174.



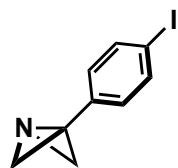
3-(4-Chlorophenyl)-1-azabicyclo[1.1.0]butane (63) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 120–140 °C to afford the ABB as a white solid (1.4 g, 43% over 5 steps).

m.p.: 34.7-37.2 °C; **¹H (300 MHz, CDCl₃):** δ = 7.31 (br s, 4H), 2.75-2.74 (t, 2H, *J* = 1.0 Hz), 1.54-1.53 (t, 2H, *J* = 1.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 133.9, 133.6, 128.9, 128.7, 54.1, 31.3; **ATR-IR (ν_{max}):** 3047, 2937, 1670, 1517, 1451, 1241, 1088, 1012, 811, 772, 705 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₉H₉ClN⁺ 166.0418, Found 166.0410.



3-(4-Bromophenyl)-1-azabicyclo[1.1.0]butane (64) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 120–140 °C to afford the ABB as a white solid (2.4 g, 57% over 5 steps).

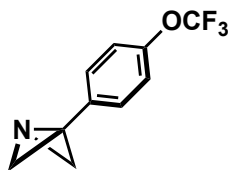
m.p.: 58.5-63.3 °C; **¹H (300 MHz, CDCl₃):** δ = 7.51-7.48 (d, 2H, *J* = 8.6 Hz), 7.31-7.28 (d, 2H, *J* = 8.6 Hz), 2.79-2.78 (t, 2H, *J* = 1.1 Hz), 1.58-1.57 (t, 2H, *J* = 1.1 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 134.2, 131.7, 129.2, 122.1, 54.2, 31.5; **ATR-IR (ν_{max}):** 3057, 2931, 1513, 1477, 1397, 1120, 1091, 1007, 804, 772, 709 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₉H₉BrN⁺ 209.9913, Found 209.9902.



3-(4-Iodophenyl)-1-azabicyclo[1.1.0]butane (65) was prepared according to the general procedure. The final product was purified *via* column chromatography on silica gel eluting with 100% EtOAc to afford the ABB as an orange solid (710 mg, 67%). Attempts to distill the ABB at low pressure were unsuccessful, but after multiple rounds of purification by column

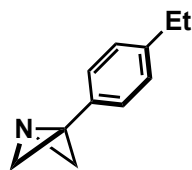
chromatography the starting material was of sufficient purity to undergo the SF₅Cl addition reaction.

R_f: 0.1 (100% EtOAc); vis. UV (254 nm); **m.p.**: 76.9-86.1 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.69-7.66 (d, 2H, *J* = 8.5 Hz), 7.15-7.12 (d, 2H, *J* = 8.5 Hz), 2.76-2.75 (t, 2H, *J* = 1.0 Hz), 1.56-1.55 (t, 2H, *J* = 1.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 137.5, 134.8, 129.4, 93.4, 54.1, 31.5; **ATR-IR (ν_{max})**: 3055, 2932, 2874, 1151, 1475, 1393, 1274, 1217, 1146, 1119, 1096, 1075, 1003, 800, 766 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₉H₉IN⁺ 257.9775, Found 257.9757.



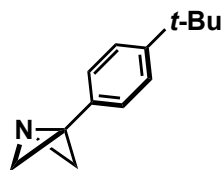
3-(4-(Trifluoromethoxy)phenyl)-1-azabicyclo[1.1.0]butane (66) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 84–108 °C to afford the ABB as a clear oil (451 mg, 25% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.44-7.41 (d, 2H, *J* = 8.8 Hz), 7.22-7.19 (d, 2H, *J* = 8.8 Hz), 2.77-2.78 (t, 2H, *J* = 1.0 Hz), 1.58-1.57 (t, 2H, *J* = 1.0 Hz); **¹⁹F{¹H} (282 MHz, CDCl₃)**: δ = -58.91 (s, 3F). **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 149.0-148.9 (q, *J* = 1.9 Hz), 133.8, 129.0, 121.1, 54.2, 31.2; **ATR-IR (ν_{max})**: 2949, 1527, 1494, 1253, 1202, 1156, 1073, 1018, 980, 922, 854, 820, 793, 759, 730 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₀H₉F₃ON⁺ 216.0631, Found 216.0616.



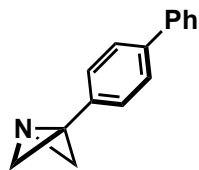
3-(4-Ethylphenyl)-1-azabicyclo[1.1.0]butane (70) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–140 °C to afford the ABB as a clear oil (490 mg, 15% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.36-7.29 (d, 2H, J = 8.0 Hz), 7.23-7.15 (d, 2H, J = 8.0 Hz), 2.78 (s, 2H), 2.70-2.61 (q, 2H, J = 7.6 Hz), 1.53 (s, 2H), 1.28-1.20 (t, 3H, J = 7.6 Hz); **¹³C{¹H} (76 MHz, CDCl₃):** δ = 144.3, 132.0, 128.1, 127.6, 54.1, 31.9, 28.7, 15.7; **ATR-IR ($\nu_{\max}$):** 2963, 2931, 2874, 1534, 1494, 1457, 1413, 1141, 1098, 979, 824, 809, 781 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₁₁H₁₄N⁺ 160.2395, Found 160.2389.



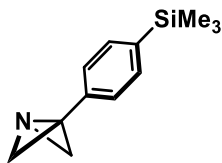
3-(4-(*tert*-Butyl)phenyl)-1-azabicyclo[1.1.0]butane (71) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 120–160 °C to afford the ABB as a clear oil (770 mg, 21% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.41-7.31 (m, 4H), 2.79-2.77 (t, 2H, J = 1.1 Hz), 1.57-1.51 (t, 2H, J = 1.1 Hz), 1.32 (s, 9H); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 151.3, 131.9, 127.3, 125.6, 54.1, 34.8, 31.8, 31.4; **ATR-IR ($\nu_{\max}$):** 2961, 2869, 1532, 1493, 1477, 1394, 1146, 1115, 1015, 837, 815, 772, 740, 708 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₁₃H₁₈N⁺ 181.1434, Found 188.1423.



3-([1,1'-Biphenyl]-4-yl)-1-azabicyclo[1.1.0]butane (72) was prepared according to the general procedure. The final product was purified *via* column chromatography eluting with 100% ethyl acetate to give the product as a light-orange fluffy solid (161 mg, 4% over 5 steps).

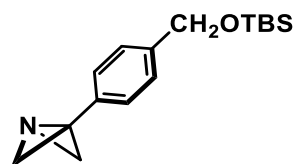
R_f: 0.31 (10% MeOH in CH₂Cl₂); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.61-7.58 (m, 4H), 7.50-7.47 (d, 2H, *J* = 8.1 Hz), 7.45-7.42 (d, 2H, *J* = 7.3 Hz), 7.38-7.33 (m, 1H), 2.85-2.84 (t, 2H, *J* = 1.1 Hz), 1.60-1.59 (t, 2H, *J* = 1.1 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 141.1, 140.8, 134.1, 129.0, 128.1, 127.6, 127.4, 127.2, 54.2, 31.9; **ATR-IR (ν_{max})**: 3036, 2154, 1483, 1449, 1408, 1145, 843, 759, 721, 691, 641; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₅H₁₄N⁺ 208.1121, Found 208.1121.



3-(4-(trimethylsilyl)phenyl)-1-azabicyclo[1.1.0]butane (73) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 120–150 °C to afford the ABB as a colorless oil (670 mg, 16% over 5 steps).

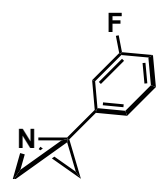
¹H (300 MHz, CDCl₃): δ = 7.54-7.36 (m, 4H), 2.80 (br s, 2H), 1.55 (br s, 2H), 0.26 (s, 9H); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = -3.87 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.5, 135.6, 133.6, 126.9, 54.2, 31.9, -1.0; **ATR-IR (ν_{max})**: 3051, 2954, 1603, 1486, 1386, 1248, 1146, 1116, 1086,

1069, 1011, 837, 811, 755, 719 cm^{-1} ; **HRMS (ESI) m/z :** $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_{12}\text{H}_{18}\text{NSi}^+$ 204.1204, Found 204.1191.



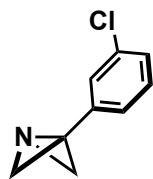
3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-1-azabicyclo[1.1.0]butane (74) was prepared according to the general procedure. The final product was purified *via* column chromatography eluting with 100% ethyl acetate to give the product as a clear liquid (420 mg, 8% over 5 steps).

R_f: 0.41 (10% MeOH in CH_2Cl_2); vis. UV (254 nm); **^1H (300 MHz, CDCl_3):** δ = 7.40-7.28 (m, 4H), 4.74 (s, 2H), 2.81-2.77 (br s, 2H), 1.56-1.53 (br s, 2H), 0.94 (s, 9H), 0.09 (s, 6H); **^{29}Si DEPT (80 MHz, CDCl_3):** δ = 20.69 (s); **$^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl_3):** δ = 141.6, 133.5, 127.5, 126.3, 64.8, 54.1, 31.9, 26.1, 18.6, -5.1; **ATR-IR (ν_{max}):** 2955, 1462, 1141, 1375, 1257, 1029, 1083, 1017, 835, 814, 776, 712 cm^{-1} ; **HRMS (ESI) m/z :** $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_{16}\text{H}_{26}\text{NOSi}^+$ 276.1778, Found 276.1775.



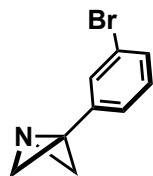
3-(3-Fluorophenyl)-1-azabicyclo[1.1.0]butane (75) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 110–140 °C to afford the ABB as a clear oil (1.8 g, 60% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.36-7.25 (m, 1H), 7.21-6.96 (m, 4H), 2.78 (br s, 2H), 1.57 (br s, 2H); **¹⁹F{¹H} (282 MHz, CDCl₃):** δ = -112.91-113.0 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 164.6-161.3 (d, *J* = 246.4 Hz), 137.9-167.8 (d, *J* = 7.8 Hz), 130.3-130.2 (d, *J* = 8.4 Hz), 123.4-123.3 (d, *J* = 2.9 Hz), 115.3-115.0 (d, *J* = 21.2 Hz), 114.8-114.5 (d, *J* = 22.4 Hz), 54.28, 31.54-31.51 (d, *J* = 2.4 Hz); **ATR-IR (ν_{max}):** 3052, 2943, 1616, 1588, 1486, 1447, 1273, 1135, 911, 870, 779, 751 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₉H₉FN⁺ 150.0714, Found 150.0714.



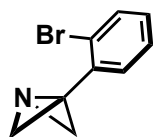
3-(3-Chlorophenyl)-1-azabicyclo[1.1.0]butane (76) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–120 °C to afford the ABB as a clear oil (1.4 g, 42% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.37 (br s, 1H), 7.26 (m, 3H), 2.76 (br s, 2H), 1.54 (br s, 2H); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 137.3, 134.5, 129.8, 128.2, 127.7, 125.7, 54.2, 31.4; **ATR-IR (ν_{max}):** 3052, 2937, 1601, 1572, 1477, 1427, 1223, 1147, 1112, 1043, 998, 879, 774, 713 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₉H₉ClN⁺ 166.0418, Found 166.0419.



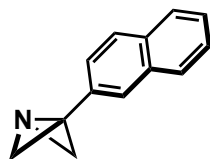
3-(3-Bromophenyl)-1-azabicyclo[1.1.0]butane (77) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 130–140 °C to afford the ABB as a clear oil (1.1 g, 26% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.56-7.53 (t, 1H, J = 1.7 Hz), 7.47-7.42 (ddd, 1H, J = 7.9, 1.9, 1.2 Hz), 7.35-7.31 (dt, 1H, J = 7.7, 1.3 Hz), 7.21 (t, 1H, J = 7.8 Hz), 2.79-2.77 (t, 2H, J = 1.0 Hz), 1.57-1.56 (t, 2H, J = 1.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 137.7, 131.2, 130.7, 130.1, 126.3, 122.7, 54.3, 31.4; **ATR-IR (ν_{max}):** 3049, 2942, 1599, 1566, 1476, 1391, 1223, 1144, 1066, 879, 772, 737 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₉H₉BrN⁺ 209.9913, Found 209.9902.



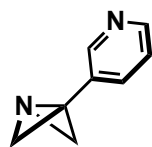
3-(2-Bromophenyl)-1-azabicyclo[1.1.0]butane (78) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 100–120 °C to afford the ABB as a clear oil (510 mg, 12% over 5 steps).

¹H (300 MHz, CDCl₃): δ = 7.61-7.55 (m, 1H), 7.33-7.26 (m, 2H), 7.23-7.15 (m, 1H), 2.56-2.53 (dd, 2H, J = 1.6, 1.0 Hz), 1.68 (dd, 2H, J = 1.7, 1.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 134.5, 132.7, 129.7, 129.4, 127.6, 126.1, 57.4, 32.4; **ATR-IR (ν_{max}):** 3053, 2937, 1565, 1472, 1439, 1391, 1144, 1121, 1034, 976, 824, 750, 718 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₉H₉BrN⁺ 209.9913, Found 209.9903.



3-(Naphthalen-2-yl)-1-azabicyclo[1.1.0]butane (79) was prepared according to the general procedure. The final product was purified *via* column chromatography eluting with 100% ethyl acetate to give the product as a light-yellow solid (290 mg, 8% over 5 steps).

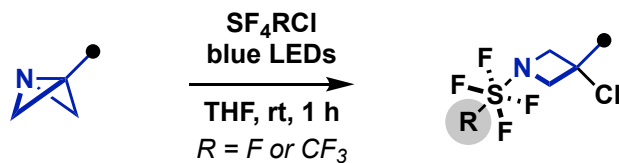
R_f: 0.38 (10% MeOH in CH₂Cl₂); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.91 (br s, 1H), 7.84-7.80 (m, 3H), 7.52-7.46 (m, 3H), 2.92-2.91 (t, 2H, *J* = 1.1 Hz), 1.65-1.64 (t, 2H, *J* = 1.1 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 133.3, 133.1, 132.5, 128.4, 127.9, 127.7, 127.3, 126.5, 126.2, 124.6, 54.3, 32.3; **ATR-IR (ν_{max})**: 3030, 2890, 1520, 1442, 1399, 1145, 982, 842, 752, 721, 696 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₃H₁₂N⁺ 182.0964, Found 182.0955.



3-(Pyridin-3-yl)-1-azabicyclo[1.1.0]butane (80) was prepared according to the general procedure. The final product was purified *via* distillation at 5 mbar between 120–160 °C to afford the ABB as a yellow oil (160 mg, 6% over 5 steps).

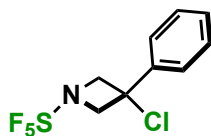
¹H (300 MHz, CDCl₃): δ = 8.68-8.66 (m, 1H), 8.58-8.54 (dd, 1H, *J* = 4.8, 1.6 Hz), 7.71-7.65 (ddd, 1H, *J* = 7.9, 2.3, 1.7 Hz), 7.30-7.24 (m, 1H), 2.83-2.78 (m, 2H), 1.63-1.59 (m, 2H); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 149.30, 149.26, 134.9, 131.1, 123.2, 54.2, 29.8; **ATR-IR (ν_{max})**: 2990, 2912, 2874, 1589, 1568, 1450, 1434, 1180, 993, 968, 824, 820, 768 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₈H₉N₂⁺ 133.0760, Found 133.0753.

5.5.4 General Procedure.



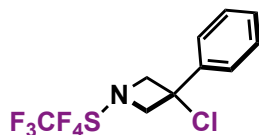
To an oven-dried 20 mL microwave vial equipped with a stir bar was added the ABB substrate (0.2 mmol, 1.0 equiv.) open to air. The vessel was sealed with a Teflon-lined cap using a crimper, and the vial was evacuated and backfilled with Ar three times. Then, anhydrous THF or Et₂O (6.0 mL) was added *via* syringe, and the vial was transported to the Kessil Photo rig. A solution of SF₅Cl or CF₃SF₄Cl in *n*-pentane (0.24 mmol, 1.2 equiv.) was slowly added down the sides of the vessel *via* syringe. The resulting mixture was irradiated with 2 Kessil blue LEDs at maximum intensity for 1 h with a fan maintaining the temperature around 25 °C. After the reaction was complete, the crude mixture was typically light-yellow and was carefully concentrated *in vacuo* (300 mbar, 40 °C). The resulting crude brown oil was purified by column chromatography or preparative TLC (pTLC) on silica gel. Specific conditions for each individual substrate are given below.

5.5.5 Characterization Data for *N*-SF₄R Azetidines.



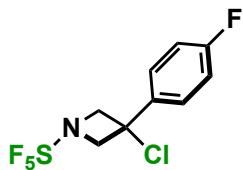
3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)-3-phenylazetidine (1) was prepared according to the general procedure. Depending on the scale, the product was purified by either preparative TLC (pTLC) or by column chromatography on silica gel. On a 0.1–0.2 mmol scale, the crude reaction mixture was concentrated under reduced pressure, taken up in 0.1 mL CH₂Cl₂, and loaded directly on a 50 × 100 mm pTLC plate (approx. 1 cm from the bottom). For pTLC, 100% hexanes was used as the eluent, and **1** was obtained as a colorless oil (44 mg, 75%). On larger scales – or with multiple 0.2 mmol scale reactions combined – the material could easily be purified by flash column chromatography, eluting with 0% → 10% EtOAc in hexanes.

R_f: 0.50 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.45–7.34 (m, 5H), 4.64 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.38–81.19 (p, 1F, J = 155 Hz), 52.99–52.44 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.9, 129.1, 128.9, 125.5, 69.7–69.5 (p, J = 3.7 Hz), 60.5; **ATR-IR (ν_{max})**: 2961, 1497, 1450, 1094, 800, 694 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₁₀ClF₅NS 294.0137, Found 294.0142.



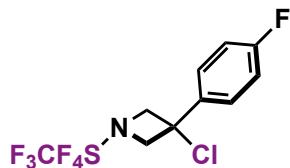
3-Chloro-3-phenyl-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (2) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (41 mg, 59%).

R_f: 0.43 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.47-7.35 (m, 5H), 4.66 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.74-29.45 (q, 4F, J = 25.0 Hz), -63.19-63.54 (p, 3F, J = 25.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.9, 129.1, 128.9, 125.5, 69.8-69.6 (p, J = 3.7 Hz), 60.7. *Note: F₃CSF₄⁻ was not fully resolved*; **ATR-IR (v_{max})**: 2965, 1610, 1515, 1226, 1150, 1089, 1016, 983, 825, 781, 690 cm⁻¹; **HRMS (ESI) m/z**: [M+H]⁺ Calc'd for C₁₀H₁₀ClF₇NS 344.0105, Found 344.0125.



3-Chloro-3-(4-fluorophenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (3) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (37 mg, 60%).

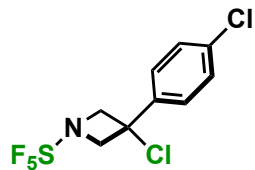
R_f: 0.63 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.43-7.38 (m, 2H), 7.13-7.08 (m, 2H), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.4 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.12-80.93 (p, 1F, J = 157 Hz), 52.91-52.36 (d, 4F, J = 157 Hz), -112.27-112.36 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.4-161.1 (d, J = 249.7 Hz), 136.93-136.88 (d, J = 3.4 Hz), 127.7-127.6 (d, J = 8.5 Hz), 126.4-120.8 (dq, J = 328.3, 49.7 Hz), 116.2-116.0 (d, J = 21.9 Hz), 69.9-69.7 (p, J = 4.0 Hz), 60.0; **ATR-IR (v_{max})**: 2963, 2927, 1606, 1513, 1336, 1236, 1163, 1108, 1015, 876, 799, 676, 610 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₉H₉ClF₆NS 312.0043, Found 312.0053.



3-Chloro-3-(4-fluorophenyl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (4)

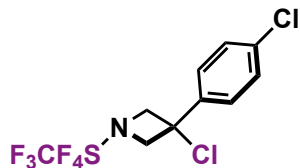
was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (50 mg, 69%).

R_f: 0.63 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.44-7.39 (m, 2H), 7.13-7.08 (m, 2H), 4.62 (ABq, 4H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.68-29.41 (q, 4F, J = 24.7 Hz), -63.20-63.55 (p, 3F, J = 24.7 Hz), -112.38-112.48 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.4-161.1 (d, J = 249.3 Hz), 136.9-136.8 (d, J = 3.4 Hz), 127.6-127.5 (d, J = 8.5 Hz), 116.3-116.0 (d, J = 21.9 Hz), 69.8-69.6 (p, J = 3.8 Hz), 59.8. *Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved*; **ATR-IR (ν_{max})**: 2962, 2888, 1610, 1514, 1226, 1149, 1088, 1016, 983, 827, 781, 691 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉ClF₈NS 362.0011, Found 362.0022.



3-Chloro-3-(4-chlorophenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (5) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless oil (37 mg, 57%).

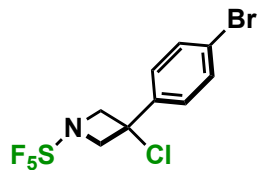
R_f: 0.60 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.43-7.34 (m, 4H), 4.60 (ABq, 4H, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.9 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.28-80.62 (p, 1F, J = 157 Hz), 52.90-52.35 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.3, 135.0, 129.3, 127.0, 69.8-69.5 (p, J = 3.7 Hz), 59.6; **ATR-IR (ν_{max})**: 2961, 1600, 1497, 1403, 1336, 1097, 1014, 875, 840, 801, 752, 719 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉Cl₂F₅NS 327.9747, Found 327.9754.



3-Chloro-3-(4-chlorophenyl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (6)

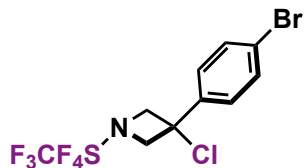
was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (53 mg, 70%).

R_f: 0.60 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.42-7.36 (m, 4H), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 9.9 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.68-29.42 (q, 4F, J = 25.0 Hz), -63.19-63.54 (p, 3F, J = 25.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.4, 135.0, 129.3, 127.1, 69.8-69.6 (p, J = 4.0 Hz), 59.88. *Note: F₃C $\overline{\text{S}}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 2961, 1600, 1497, 1403, 1334, 1227, 1150, 1096, 1014, 983, 823, 783, 753, 716 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉Cl₂F₇NS⁺ 377.9715, Found 377.9734.



3-(4-Bromophenyl)-3-chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidine (7) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (45 mg, 61%).

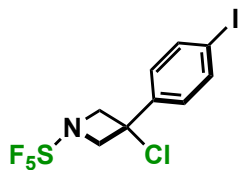
R_f: 0.51 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.57-7.54 (d, 2H, J = 8.7 Hz), 7.33-7.29 (d, 2H, J = 8.7 Hz), 4.59 (ABq, 4H, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 8.5 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.01-80.81 (p, 1F, J = 155 Hz), 53.90-52.35 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.6, 132.0, 127.1, 122.8, 69.5-69.2 (p, J = 4.0 Hz), 59.6; **ATR-IR (ν_{max})**: 2963, 1593, 1493, 1398, 1195, 1010, 984, 875, 840, 800, 741, 715 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉BrClF₅NS⁺ 371.9242, Found 371.9257.



3-(4-Bromophenyl)-3-chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (8)

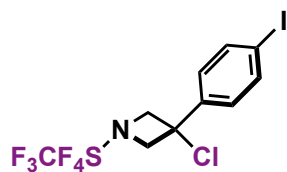
was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (41 mg, 49%).

R_f: 0.66 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.57-7.54 (d, 2H, J = 8.7 Hz), 7.33-7.30 (d, 2H, J = 8.7 Hz), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 8.5 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.69-29.43 (q, 4F, J = 24.9 Hz), -63.15-63.51 (p, 3F, J = 24.9 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.7, 132.1, 127.2, 123.0, 69.6-69.4 (p, J = 4.0 Hz), 59.7. *Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved*; **ATR-IR (v_{max})**: 2924, 1594, 1493, 1226, 1148, 1084, 1010, 982, 820, 783, 744 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉BrClF₇NS⁺ 421.9210, Found 421.9237.



3-Chloro-3-(4-iodophenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (9) was prepared with a modification to the general procedure; 3.0 equiv. SF_5Cl were used, and the total reaction time was reduced to 15 min. (due to potential light sensitivity of the aryl iodide). The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (42 mg, 50%).

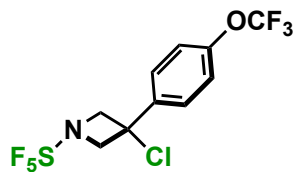
R_f: 0.50 (100% hexanes); vis. UV (254 nm); **1H (300 MHz, $CDCl_3$)**: δ = 7.78-7.75 (d, 2H, J = 8.0 Hz), 7.19-7.16 (d, 2H, J = 8.0 Hz), 4.59 (br s, 4H); **^{19}F (282 MHz, $CDCl_3$)**: δ = 83.04-80.84 (p, 1F, J = 155 Hz), 52.91-52.36 (d, 4F, J = 155 Hz); **$^{13}C\{^1H\}$ (101 MHz, $CDCl_3$)**: δ = 140.3, 138.1, 127.3, 94.7, 69.4-69.2 (p, J = 3.8 Hz), 59.6; **ATR-IR (ν_{max})**: 2962, 1589, 1489, 1450, 1394, 1335, 1194, 1090, 1026, 1007, 984, 874, 839, 800, 737, 711 cm^{-1} ; **HRMS (ESI) m/z** : $[M+H]^+$ Calc'd for $C_9H_9ClF_5INS^+$ 419.9105, Found 419.9109.



3-Chloro-3-(4-iodophenyl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (10)

was prepared with a *modification to the general procedure*; 3.0 equiv. CF_3SF_4Cl were used, and the total reaction time was reduced to 15 min. (due to potential light sensitivity of the aryl iodide). The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (60 mg, 64%).

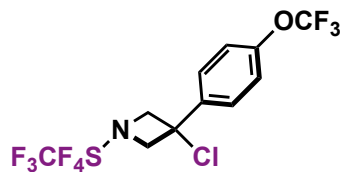
R_f: 0.54 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.77-7.75 (d, 2H, J = 8.7 Hz), 7.20-7.17 (d, J = 8.7 Hz), 4.64-4.57 (br s, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.70-29.44 (q, 4F, J = 24.8 Hz), - 63.16-63.51 (p, 3F, J = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.4, 138.1, 127.3, 94.6, 69.5-69.3 (p, J = 4.0 Hz), 59.8. *Note: $F_3CSF_4^-$ was not fully resolved*; **ATR-IR ($\nu_{\max}$)**: 2963, 1589, 1489, 1395, 1226, 1150, 1088, 1006, 981, 908, 891, 831, 782, 738, 711 cm^{-1} ; **HRMS (ESI) m/z** : $[M+H]^+$ Calc'd for C₁₀H₉ClF₇INS⁺ 469.9072, Found 469.9084.



3-Chloro-1-(pentafluoro- λ^6 -sulfaneyl)-3-(4-(trifluoromethoxy)phenyl)azetidine (11)

was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless oil (44 mg, 58%).

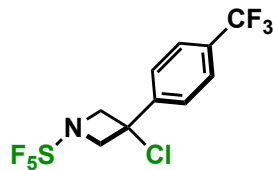
R_f: 0.55 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.49-7.46 (d, 2H, J = 8.8 Hz), 7.28-7.2 (d, 2H, J = 8.8 Hz), 4.61 (br s, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.84-80.65 (p, 1F, J = 155 Hz), 52.80-52.25 (d, 4F, J = 155 Hz), -57.96 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 149.30-149.27 (q, J = 1.8 Hz), 139.3, 127.2, 125.5-115.3 (q, J = 258.0 Hz), 121.3, 69.6-69.4 (p, J = 3.8 Hz), 59.3; **ATR-IR (ν_{max})**: 2959, 1513, 1255, 1210, 1164, 1093, 1019, 986, 878, 840, 802 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉ClF₈NOS⁺ 377.9960, Found 377.9976.



3-Chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)-3-(4-(trifluoromethoxy)

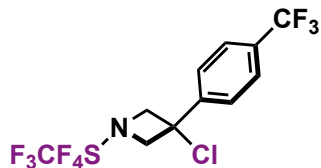
phenyl)azetidine (12) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100 % hexanes, affording the desired product as a colorless oil (48 mg, 56%).

R_f: 0.59 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.50-7.47 (d, 2H, J = 8.8 Hz), 7.28-7.25 (d, 2H, J = 8.8 Hz), 4.63 (br s, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.66-29.39 (q, 4F, J = 24.7 Hz), -57.92 (s, 3F), -63.20-63.55 (p, 3F, J = 24.7 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 149.3-149.2 (q, J = 1.9 Hz), 139.3, 125.5-115.3 (q, J = 257.8 Hz), 121.3, 69.8-69.5 (p, J = 4.0 Hz), 59.6. *Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved*; **ATR-IR (v_{max})**: 2965, 1513, 1210, 1166, 1149, 1116, 1093, 1020, 984, 892, 830, 783, 728, 715 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₁H₉ClF₁₀NOS⁺ 427.9928, Found 427.9944.



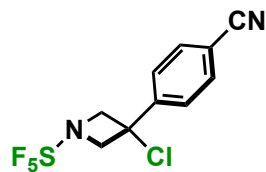
3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)-3-(4-(trifluoromethyl)phenyl)azetidine (13) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (25 mg, 35%). *Caution: the material is volatile.*

R_f: 0.43 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.71-7.68 (d, 2H, J = 8.4 Hz), 7.60-7.57 (d, 2H, J = 8.4 Hz), 4.64 (br s, 4H); **¹⁹F (282 MHz, CDCl₃):** δ = 82.75-80.55 (p, 1F, J = 155 Hz), 52.83-52.28 (d, 4F, J = 155 Hz), -62.87 (s, 3F); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 144.3, 131.7-130.4 (q, J = 32.9 Hz), 129.1-118.2 (q, J = 272.2 Hz), 126.1-126.0 (q, J = 3.8 Hz), 125.96, 69.4-69.2 (p, J = 3.8 Hz), 59.2; **ATR-IR (ν_{max}):** 2964, 1465, 1365, 1270, 1091, 1019, 984, 876, 804 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₁₀H₉ClF₈NS⁺ 362.0011, not found .



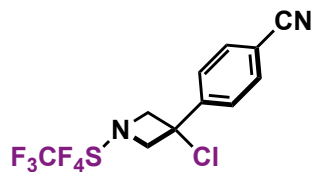
3-Chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)-3-(4-(trifluoromethyl)phenyl)azetidine (14) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a clear oil (27 mg, 33%).
Caution: the material is volatile.

R_f: 0.55 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃):** δ = 7.71-7.69 (d, 2H, J = 8.2 Hz), 7.61-7.58 (d, 2H, J = 8.2 Hz), 4.65 (br s, 4H); **¹⁹F (282 MHz, CDCl₃):** δ = 29.64-29.37 (q, 4F, J = 24.8 Hz), -62.90 (s, 3F), -63.19-63.54 (p, 3F, J = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 144.5, 131.9-130.5 (q, J = 32.8 Hz), 129.2-118.4 (q, J = 272.2 Hz), 126.3-126.1 (q, J = 3.8 Hz), 126.2, 69.7-69.5 (p, J = 4.0 Hz), 59.6. *Note: F₃C $\underline{\text{S}}$ F₄- was not fully resolved; ATR-IR (ν_{max}):* 2965, 1622, 1412, 1323, 1230, 1170, 1068, 1017, 829, 783, 725 cm⁻¹; **HRMS (ESI) m/z :** [M+H]⁺ Calc'd for C₁₁H₉ClF₁₀NS⁺ 411.9979, Found 411.9989.



4-(3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidin-3-yl)benzonitrile (15) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (26 mg, 42%).

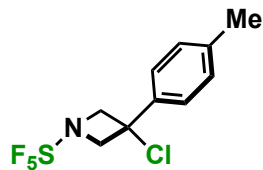
R_f: 0.21 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.75-7.72 (d, 2H, J = 8.6 Hz), 7.61-7.58 (d, 2H, J = 8.6 Hz), 4.62 (ABq, 4H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.53-80.33 (p, 1F, J = 155 Hz), 58.82-52.28 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 145.2, 132.8, 126.3, 117.9, 112.9, 69.4-69.2 (p, J = 3.9 Hz), 58.9; **ATR-IR (ν_{max})**: 2964, 2231, 1610, 1507, 1450, 1410, 1337, 1267, 1091, 1020, 985, 877, 832, 802, 735 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉ClF₅N₂S⁺ 319.0090, Found 319.0071.



4-(3-Chloro-1-(tetrafluoro(trifluoromethyl)-λ⁶-sulfanyl)azetidin-3-yl)benzonitrile

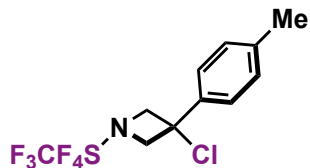
(16) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (44 mg, 59%).

R_f: 0.36 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.74-7.72 (d, 2H, *J* = 8.6 Hz), 7.62-7.59 (d, 2H, *J* = 8.6 Hz), 4.63 (ABq, 4H, Δδ_{AB} = 0.05, *J*_{AB} = 8.8 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.65-29.39 (q, 4F, *J* = 24.7 Hz), -63.17-63.52 (p, 3F, *J* = 24.7 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 145.3, 132.8, 126.4, 118.0, 112.9, 69.5-69.3 (p, *J* = 4.0 Hz), 59.2. *Note*: *F*₃C*SF*₄– was not fully resolved; **ATR-IR (ν_{max})**: 2960, 2232, 1612, 1228, 1150, 1091, 983, 910, 828, 783, 735 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₁H₉ClF₇N₂S⁺ 369.0058, Found 369.0065.



3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)-3-(*p*-tolyl)azetidine (17) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (39 mg, 63%).

R_f: 0.58 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.32-7.18 (m, 3H), 4.69-4.63 (d, 2H, J = 8.6 Hz), 4.64 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.5 Hz) 2.37 (s, 3H); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.62-81.15 (m, 1F, J = 157 Hz), 53.16-52.10 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.0, 138.0, 129.8, 125.4, 69.8-69.4 (p, J = 3.8 Hz), 60.5, 21.3; **ATR-IR (v_{max})**: 2927, 1652, 1517, 1456, 1336, 1262, 1092, 1021, 986, 876, 842, 809, 722 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₀H₁₂ClF₅NS⁺ 308.0294, Found 308.0292.



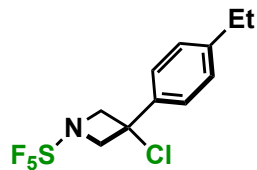
3-Chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)-3-(*p*-tolyl)azetidine (18) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a clear oil (31 mg, 43%).

R_f: 0.54 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.32-7.29 (d, 2H, J = 8.1 Hz), 7.24-7.22 (d, 2H, J = 8.1 Hz), 4.64 (ABq, 4H, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 8.4 Hz), 2.38 (s, 3H).

¹⁹F (282 MHz, CDCl₃): δ = 29.75-29.49 (q, 4F, J = 24.6 Hz), -63.20-63.55 (p, 3F, J = 24.6 Hz);

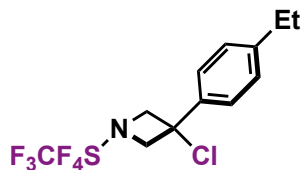
¹³C{¹H} (101 MHz, CDCl₃): δ = 138.9, 138.1, 129.8, 125.5, 69.9-69.7 (p, J = 4.0 Hz), 60.8, 21.2.

Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved; ATR-IR (v_{max}): 2965, 1615, 1517, 1336, 1225, 1186, 1150, 983, 780, 722, 708 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₁H₁₂ClF₇NS⁺ 358.0262, Found 358.0273.



3-Chloro-3-(4-ethylphenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (19) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless oil (34 mg, 53%).

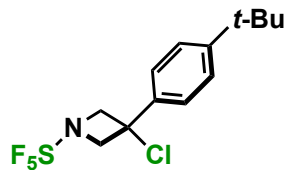
R_f: 0.54 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.33-7.22 (m, 4H), 4.62 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.5 Hz), 2.71-2.63 (q, 2H, J = 7.6 Hz), 1.28-1.22 (t, 3H, J = 7.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.49-81.30 (p, 1F, J = 157 Hz), 53.02-52.47 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 145.3, 138.2, 128.6, 125.5, 69.7-69.5 (p, J = 3.6 Hz), 60.6, 28.7, 15.5; **ATR-IR (ν_{max})**: 2960, 1648, 1534, 1472, 1410, 1350, 1270, 1098, 980, 823, 809, 722 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₁H₁₄ClF₅NS⁺ 322.0450, Found 322.0460.



3-chloro-3-(4-ethylphenyl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine (20)

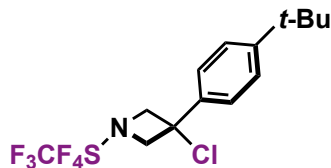
was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless oil (44 mg, 59%).

R_f: 0.51 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.35-7.22 (m, 4H), 4.63 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.6 Hz), 2.72-2.62 (q, 2H, J = 7.6 Hz), 1.29-1.21 (t, 3H, J = 7.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.77-29.51 (q, 4F, J = 24.8 Hz), – 63.17-63.52 (p, 3F, J = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 145.2, 138.3, 128.6, 125.5, 69.8-69.7 (p, J = 3.9 Hz), 60.8, 28.7, 15.5. *Note*: $F_3\text{CSF}_4^-$ was not fully resolved; **ATR-IR (ν_{max})**: cm^{-1} 2965, 1631, 1530, 1460, 1420, 1241, 1190, 983, 835, 780, 722 cm^{-1} ; **HRMS (ESI) m/z** : $[M+H]^+$ Calc'd for C₁₂H₁₃ClF₇NS⁺ 371.0340, Found 372.0427.



3-(4-(*tert*-Butyl)phenyl)-3-chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidine (21) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (38 mg, 55%).

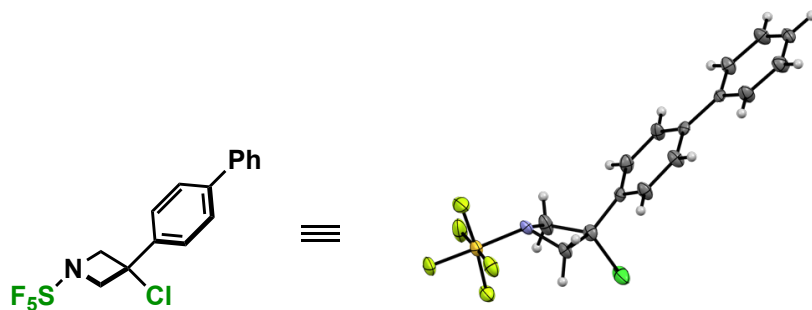
R_f: 0.50 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.47-7.44 (d, 2H, J = 8.6 Hz), 7.36-7.33 (d, 2H, J = 8.6 Hz), 4.65 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.6 Hz), 1.35 (s, 9H); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.53-81.34 (p, 1F, J = 155 Hz), 53.07-52.51 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 152.0, 137.7, 125.9, 125.1, 69.6-69.4 (p, J = 3.8 Hz), 60.3, 34.7, 31.2; **ATR-IR (ν_{max})**: 2965, 1465, 1397, 1336, 1269, 1190, 1115, 1091, 1019, 985, 876, 841, 804, 741, 705 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₃H₁₈ClF₅NS⁺ 350.0763, Found 350.0765.



3-(4-(*tert*-Butyl)phenyl)-3-chloro-1-(tetrafluoro(trifluoromethyl)-λ⁶-sulfanyl)

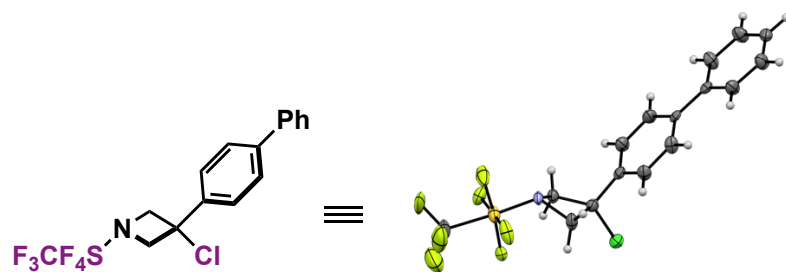
azetidine (22) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as an off-white, amorphous solid (49 mg, 61%).

R_f: 0.65 (100% hexanes); vis. UV (254 nm); **m.p.**: 60.9-62.3 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.47-7.44 (d, 2H, *J* = 8.6 Hz), 7.38-7.35 (d, 2H, *J* = 8.6 Hz), 4.66 (ABq, 4H, Δδ_{AB} = 0.11, *J*_{AB} = 8.5 Hz), 1.35 (s, 9H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.81-29.55 (p, 4F, *J* = 24.8 Hz), -63.19-63.54 (q, 3F, *J* = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 152.1, 137.9, 126.1, 125.3, 69.9-69.7 (p, *J* = 3.9 Hz), 60.7, 34.8, 31.3. *Note: F₃C₄SF₄ was not fully resolved*; **ATR-IR (ν_{max})**: 2969, 1465, 1394, 1364, 1226, 1152, 1114, 1015, 975, 893, 794, 782, 756, 743 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₄H₁₈ClF₇NS⁺ 400.0731, Found 400.0737.



3-([1,1'-Biphenyl]-4-yl)-3-chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidine (23) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless, amorphous solid (43 mg, 58%). Crystals suitable for SC-XRD were grown by vapor diffusion with minimal EtOAc and *n*-pentane as the anti-solvent.

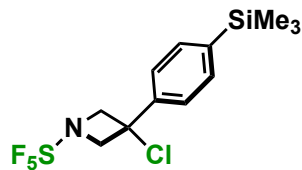
R_f: 0.31 (100% hexanes); vis. UV (254 nm); **m.p.**: 98.7 – 100.2 °C; **¹H (300 MHz, CDCl₃)**: δ = 7.66-7.37 (m, 9H), 4.68 (ABq, 4H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 8.5 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.36-81.17 (p, 1F, J = 157 Hz), 53.04-52.49 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 141.8, 140.1, 139.6, 128.9, 127.8, 127.7, 127.2, 125.9, 69.6-69.4 (p, J = 3.7 Hz), 60.2; **ATR-IR (ν_{max})**: 2953, 2923, 2874, 1488, 1103, 1079, 1020, 982, 872, 833, 810, 725, 673, 607 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₅H₁₄ClF₅NS⁺ 370.0450, Found 370.0459.



3-([1,1'-Biphenyl]-4-yl)-3-chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)

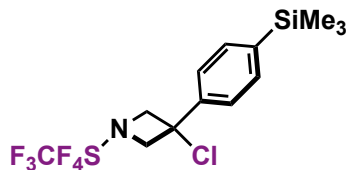
azetidine (24) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a white, amorphous solid (44 mg, 53%). Crystals suitable for SC-XRD were grown by vapor diffusion with minimal EtOAc and *n*-pentane as the anti-solvent.

R_f: 0.26 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.68-7.32 (m, 9H), 4.68 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.79-29.53 (q, 4F, J = 24.8 Hz), – 63.13-63.49 (p, 3F, J = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 141.8, 140.1, 139.6, 128.9, 127.8, 127.7, 127.2, 125.9, 76.6, 69.7-69.5 (p, J = 3.4 Hz), 60.4. *Note: F₃C $\overline{\text{S}}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 3055, 1490, 1265, 1234, 1149, 1091, 980, 835, 787, 705 cm^{–1}; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₆H₁₄ClF₇NS⁺ 420.0418, Found 420.0429.



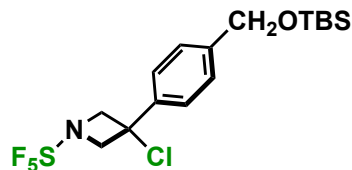
3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)-3-(4-(trimethylsilyl)phenyl)azetidine (25) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (25 mg, 34%).

R_f: 0.54 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.60-7.59 (d, 2H, J = 7.9 Hz), 7.41-7.39 (d, 2H, J = 7.9 Hz), 4.65 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.6 Hz), 0.30 (s, 9H); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.13-81.48 (p, 1F, J = 155 Hz), 52.95-52.54 (d, 4F, J = 155 Hz); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = -3.58 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 141.8, 141.0, 134.0, 124.6, 69.4-69.3 (p, J = 3.7 Hz), 60.3, -1.2; **ATR-IR (ν_{max})**: 2958, 1451, 1395, 1334, 1250, 1190, 1091, 1022, 984, 878, 834, 803, 756, 722 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₂H₁₈ClF₅NSSi⁺ 366.0532, Found 366.0532.



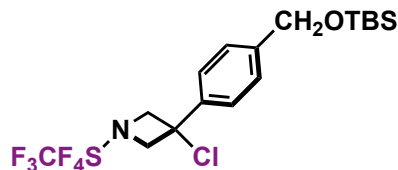
3-Chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)-3-(4-(trimethylsilyl)phenyl)azetidine (26) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (45 mg, 54%).

R_f: 0.57 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.60-7.57 (d, 2H, J = 8.3 Hz), 7.41-7.39 (d, 2H, J = 8.3 Hz), 4.65 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.8 Hz), 0.29 (s, 9H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.78-29.51 (q, 4F, J = 24.6 Hz), -63.17-63.52 (p, 3F, J = 24.6 Hz); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = -3.60 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 141.7, 141.1, 134.0, 124.6, 69.6-69.4 (p, J = 3.9 Hz), 60.5, -1.3. *Note: F₃CSF₄- was not fully resolved*; **ATR-IR (ν_{max})**: 2960, 1228, 1150, 1090, 1021, 982, 830, 817, 784, 751, 722 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₃H₁₈ClF₇NSSi⁺ 416.0500, Found 416.0509.



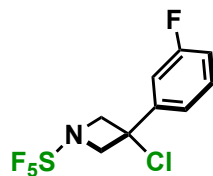
3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-3-chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidine (27) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (21 mg, 24%).

R_f: 0.39 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.38 (br s, 4H), 4.76 (s, 2H), 4.63 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.5 Hz), 0.96 (s, 9H), 0.12 (s, 6H); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.44-81.25 (p, 1F, J = 155 Hz), 52.99-52.45 (d, 4F, J = 155 Hz); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = 21.07 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 142.4, 139.4, 126.5, 125.4, 69.7-69.5 (p, J = 3.8 Hz), 64.5, 60.4, 26.0, 18.5, -5.2; **ATR-IR (ν_{max})**: 2956, 1736, 1471, 1414, 1376, 1335, 1256, 1191, 1092, 1018, 985, 940, 977, 877, 834, 803 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₆H₂₆ClF₅NOSSi⁺ 438.1108, Found 438.1106.



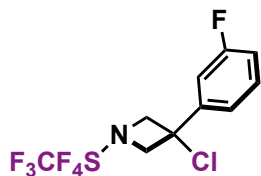
3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-3-chloro-1-(tetrafluoro (trifluoromethyl)- λ^6 -sulfanyl) azetidine (28) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (33 mg, 34%).

R_f: 0.41 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.38 (br s, 4H), 4.76 (s, 2H), 4.64 (ABq, 4H, $\Delta\delta_{AB}$ = 0.10, J_{AB} = 8.7 Hz), 0.96 (s, 9H), 0.12 (s, 6H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.75-29.49 (q, 4F, J = 24.9 Hz), -63.17-63.52 (p, 3F, J = 24.9 Hz); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = 21.03 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 142.3, 139.3, 126.4, 125.3, 69.7-69.5 (p, J = 3.9 Hz), 64.4, 60.5, 25.9, 18.4, -5.3. *Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved*; **ATR-IR (v_{max})**: 2954, 1472, 1416, 1362, 1228, 1151, 1091, 1019, 1006, 983, 940, 830, 794, 709 cm⁻¹; **HRMS (ESI) m/z**: [M+H]⁺ Calc'd for C₁₇H₂₆ClF₇NOSSi⁺ 488.1076, Found 488.1053.



3-Chloro-3-(3-fluorophenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (29) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (24 mg, 38%).

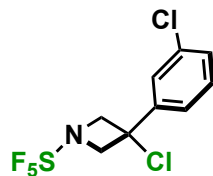
R_f: 0.50 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.46-7.35 (m, 1H), 7.25-7.02 (m, 3H), 4.65 (ABq, 4H, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.9 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.03-80.79 (p, 1F, J = 157 Hz), 52.91-52.36 (d, 4F, J = 157 Hz), - 111.11-111.23 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.5-161.2 (d, J = 247.9 Hz), 143.0-142.9 (d, J = 7.2 Hz), 130.8-130.7 (d, J = 8.3 Hz), 121.1-121.0 (d, J = 3.1 Hz), 116.0-115.7 (d, J = 21.1 Hz), 113.2-112.8 (d, J = 23.3 Hz), 69.6-69.4 (p, J = 3.7 Hz), 59.4; **ATR-IR (ν_{max})**: 2924, 2849, 1653, 1492, 1445, 1271, 1074, 987, 838, 803, 785, 716 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉ClF₆NS⁺ 312.0043, Found 312.0045.



3-Chloro-3-(3-fluorophenyl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine

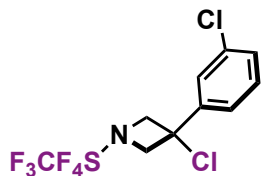
(30) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (39 mg, 54%).

R_f: 0.53 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.44-7.37 (m, 1H), 7.25-7.22 (m, 1H), 7.19-7.14 (m, 1H), 7.10-7.04 (m, 1H), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.69-29.42 (q, 4F, J = 24.6 Hz), -63.18-63.53 (p, 3F, J = 24.6 Hz), -111.20-111.28 (m, 1F); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.5-161.2 (d, J = 247.8 Hz), 143.1-143.0 (d, J = 7.1 Hz), 130.7-130.6 (d, J = 8.3 Hz), 121.1-121.0 (d, J = 3.1 Hz), 116.0-115.7 (d, J = 21.3 Hz), 113.2-112.8 (d, J = 23.3 Hz), 69.7-69.5 (p, J = 3.7 Hz), 59.6. *Note: F₃C $\overline{\text{S}}$ F₄ was not fully resolved*; **ATR-IR (v_{max})**: 2921, 1614, 1594, 1492, 1445, 1337, 1272, 1199, 1162, 1098, 1002, 841, 806, 786, 716 cm⁻¹; **HRMS (ESI) m/z**: [M+H]⁺ Calc'd for C₁₀H₉ClF₈NS⁺ 362.0011, Found 362.0022.



3-Chloro-3-(3-chlorophenyl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (31) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a colorless oil (26 mg, 40%).

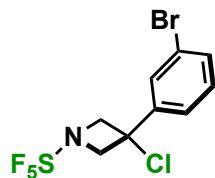
R_f: 0.50 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.44-7.29 (m, 4H), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.96-80.76 (p, 1F, J = 157 Hz), 52.91-53.39 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 142.7, 135.1, 130.5, 129.2, 126.1, 123.7, 69.6-69.4 (p, J = 3.9 Hz), 59.5; **ATR-IR (ν_{max})**: 2917, 2849, 1653, 1599, 1456, 1334, 1335, 1092, 999, 875, 843, 812, 788 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉Cl₂F₅NS⁺ 327.9747, Found 327.9759.



3-Chloro-3-(3-chlorophenyl)-1-(tetrafluoro(trifluoromethyl)-λ⁶-sulfanyl)azetidine

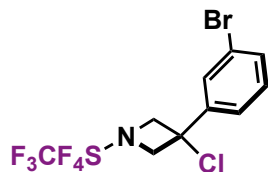
(32) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (26 mg, 35%).

R_f: 0.53 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.43-7.30 (m, 4H), 4.62 (ABq, 4H, Δδ_{AB} = 0.06, *J*_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.70-29.44 (q, 4F, *J* = 25.0 Hz), -63.17-63.51 (p, 3F, *J* = 25.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 142.6, 135.0, 130.3, 129.0, 125.9, 123.6, 69.5-69.3 (p, *J* = 4.0 Hz), 59.6. *Note: F₃C $\overline{\text{S}}$ F₄— was not fully resolved*; **ATR-IR (ν_{max})**: 2917, 1651, 1597, 1457, 1334, 1095, 1001, 874, 843, 810, 786, 718 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₀H₉Cl₂F₇NS⁺ 377.9715, Found 377.9735.



3-(3-Bromophenyl)-3-chloro-1-(pentafluoro- λ^6 -sulfaneyl)azetidine (33) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (39 mg, 53%).

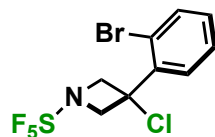
R_f: 0.50 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.59-7.57 (t, 1H, J = 1.8 Hz), 7.52-7.49 (dt, 1H, J = 7.6, 1.4 Hz), 7.38-7.35 (dt, 1H, J = 8.0, 1.4 Hz), 7.35-7.27 (dd, 1H, J = 8.0, 7.6 Hz), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.97-80.77 (p, 1F, J = 155 Hz), 52.92-52.37 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 142.7, 132.0, 130.5, 128.8, 124.0, 123.0, 69.4-69.2 (p, J = 3.7 Hz), 59.2; **ATR-IR (ν_{max})**: 2963, 1569, 1478, 1420, 1334, 1257, 1170, 1086, 973, 837, 798, 782 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉BrClF₅NS⁺ 371.9242, Found 371.9252.



3-(3-Bromophenyl)-3-chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine

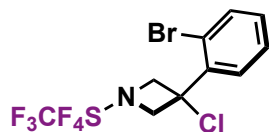
(**34**) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (43 mg, 51%).

R_f: 0.54 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.59-7.58 (t, 1H, J = 1.7 Hz), 7.52-7.49 (dt, 1H, J = 7.8, 1.4 Hz), 7.39-7.36 (dt, 1H, J = 8.0, 1.4 Hz), 7.35-.27 (dd, 1H, J = 8.0, 7.8 Hz), 4.62 (ABq, 4H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.71-29.44 (q, 4F, J = 25.0 Hz), -63.17-63.52 (p, 3F, J = 25.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 143.0, 132.1, 130.7, 129.0, 124.2, 123.1, 69.7-69.5 (p, J = 3.8 Hz), 59.6. *Note: F₃C $\overline{\text{S}}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 2966, 1596, 1479, 1332, 1226, 1149, 1085, 991, 829, 779, 759 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉BrClF₇NS⁺ 421.9210, Found 421.9233.



3-(2-Bromophenyl)-3-chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidine (35) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (35 mg, 47%).

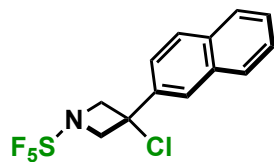
R_f: 0.49 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.66-7.64 (d, 1H, J = 7.9 Hz), 7.42-7.37 (t, 1H, J = 7.5 Hz), 7.28-7.19 (m, 2H), 4.72 (ABq, 4H, $\Delta\delta_{AB}$ = 0.20, J_{AB} = 9.1 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.48-81.28 (p, 1F, J = 155 Hz), 52.98-52.42 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.8, 134.4, 130.6, 127.9, 127.3, 121.7, 68.5-68.3 (p, J = 3.9 Hz), 61.8; **ATR-IR (ν_{max})**: 2956, 1590, 1475, 1440, 1331, 1245, 1091, 1034, 1017, 875, 836, 802, 760, 719 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₉H₉BrClF₅NS⁺ 371.9242, Found 371.9249.



3-(2-Bromophenyl)-3-chloro-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine

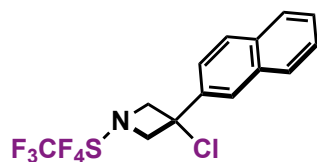
(36) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (46 mg, 54%).

R_f: 0.53 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.64-7.61 (d, 1H, J = 8.0 Hz), 7.40-7.35 (t, 1H, J = 7.5 Hz), 7.26-7.20 (m, 2H), 4.72 (ABq, 4H, $\Delta\delta_{AB}$ = 0.20, J_{AB} = 9.1 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.61-29.25 (q, 4F, J = 24.8 Hz), -63.19-63.54 (p, 3F, J = 24.8 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 139.9, 134.4, 130.5, 127.9, 127.3, 121.8, 68.6-68.4 (p, J = 4.1 Hz), 62.0. *Note: F₃C $\overline{\text{S}}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 2955, 1569, 1474, 1330, 1225, 1151, 1094, 828, 783, 738, 721 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₀H₉BrClF₇NS⁺ 421.9210, Found 421.9231.



3-Chloro-3-(naphthalen-2-yl)-1-(pentafluoro- λ^6 -sulfanyl)azetidine (37) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (34 mg, 50%).

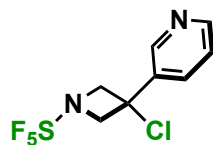
R_f: 0.41 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.96-7.79 (m, 2H), 7.59-7.45 (m, 2H), 4.74 (ABq, 4H, $\Delta\delta_{AB}$ = 0.13, J_{AB} = 8.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 83.64-80.67 (p, 1F, J = 157 Hz), 53.04-52.50 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 137.8, 133.0, 132.8, 129.3, 128.3, 127.7, 127.1, 127.0, 124.4, 123.1, 69.6–69.1 (p, J = 3.7 Hz), 60.6; **ATR-IR (ν_{max})**: 2971, 1600, 1507, 1457, 1096, 983, 861, 845, 826, 769, 713 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₃H₁₂ClF₅NS⁺ 344.0294, Found 344.0351.



3-Chloro-3-(naphthalen-2-yl)-1-(tetrafluoro(trifluoromethyl)- λ^6 -sulfanyl)azetidine

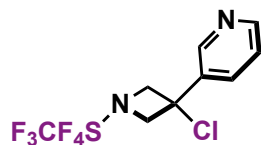
(**38**) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (46 mg, 58%).

R_f: 0.51 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.92-7.83 (m, 4H), 7.57-7.48 (m, 3H), 4.75 (ABq, 4H, $\Delta\delta_{AB}$ = 0.13, J_{AB} = 8.7 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.75-29.49 (q, J = 24.7 Hz), - 63.19-63.54 (p, J = 24.7 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 138.0, 133.1, 132.9, 129.4, 128.4, 127.9, 127.2, 127.1, 124.5, 123.2, 69.7-69.5 (p, J = 3.9 Hz), 61.0. *Note: F₃C $\overline{S}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 2923, 2856, 1363, 1227, 1199, 1069, 999, 898, 818, 770, 720 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₁₄H₁₂ClF₇NS⁺ 394.0262, Not Found.



3-(3-Chloro-1-(pentafluoro- λ^6 -sulfanyl)azetidin-3-yl)pyridine (39) was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 3:1 hexanes:EtOAc, affording the desired product as an orange oil (20 mg, 34%).

R_f: 0.21 (5:1 hexanes:EtOAc); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.80-8.76 (d, 1H, J = 2.5 Hz), 8.67-8.61 (dd, 1H, J = 4.8, 1.6 Hz), 7.83-7.77 (ddd, 1H, J = 8.1, 2.6, 1.6 Hz), 7.42-7.33 (ddd, 1H, J = 8.1, 4.8, 0.9 Hz), 4.65 (br s, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.61-80.41 (p, 1F, J = 157 Hz), 52.84-52.29 (d, 4F, J = 157 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 149.9, 146.9, 136.4, 133.3, 123.6, 69.6-69.3 (p, J = 3.6 Hz), 58.0; **ATR-IR (ν_{max})**: 2924, 2849, 1653, 1598, 1479, 1424, 1334, 1260, 1091, 999, 876, 842, 811, 788 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₈H₉ClF₅N₂S⁺ 295.0090, Found 295.0073.

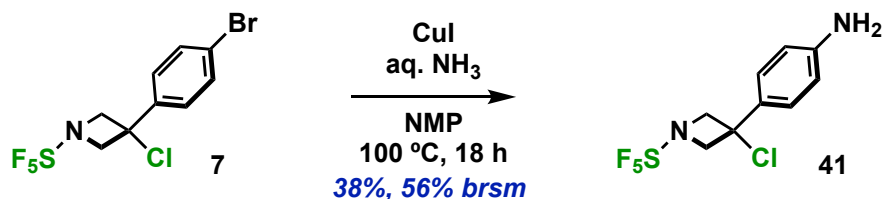


3-(3-Chloro-1-(tetrafluoro(trifluoromethyl)-λ⁶-sulfanyl)azetidin-3-yl)pyridine (40)

was prepared according to the general procedure. The crude residue was purified by pTLC, eluting with 100% hexanes, affording the desired product as a pale-yellow oil (18 mg, 26%).

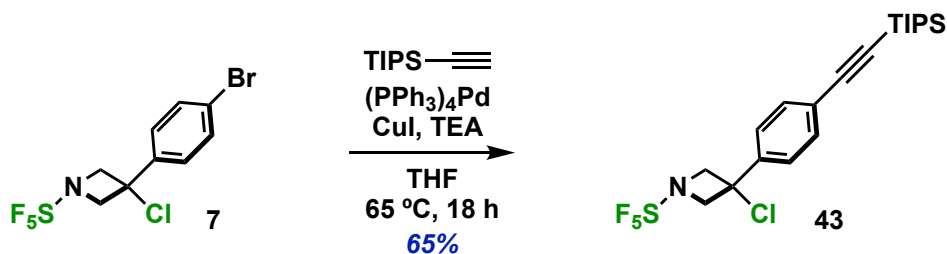
R_f: 0.24 (5:1 hexanes:EtOAc); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 8.79-8.78 (d, 1H, *J* = 2.2 Hz), 8.64-8.61 (dd, 1H, *J* = 4.9, 1.3 Hz), 7.83-7.78 (ddd, 1H, *J* = 8.1, 2.6, 0.8 Hz), 7.40-7.36 (ddd, 1H, *J* = 8.1, 4.9, 0.8 Hz), 4.65 (br s, 4H); **¹⁹F (282 MHz, CDCl₃)**: δ = 29.68-29.41 (q, 4F, *J* = 24.5 Hz), -63.15-63.50 (p, 3F, *J* = 24.5 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 150.0, 147.0, 136.4, 133.3, 123.7, 69.6-69.4 (p, *J* = 3.9 Hz), 58.1. *Note: F₃C $\overline{\text{S}}$ F₄– was not fully resolved*; **ATR-IR (ν_{max})**: 2955, 1472, 1261, 1092, 1017, 985, 876, 838, 809, 777, 739 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₉H₉ClF₇N₂S⁺ 345.0058, Found 345.0060.

5.5.6 Post-Synthetic Transformations.



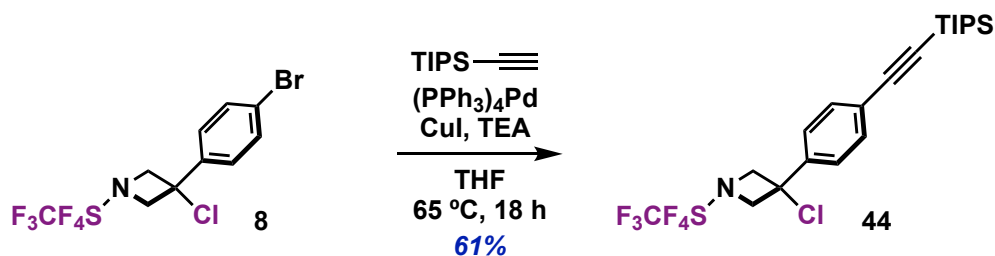
The procedure was adapted from the literature. To an oven-dried 5 mL microwave vial equipped with a stir bar were added **7** (49 mg, 0.13 mmol, 1.0 equiv.) and NMP (0.2 mL). Then, copper(I) iodide (2.5 mg, 0.013 mmol, 0.1 equiv.) was added, followed by aq. NH_3 (0.17 mL, 20.0 equiv.). Vigorous bubbling was observed concomitant with a color change of the solution from yellow to blue. The resulting mixture was stirred at $100\text{ }^\circ\text{C}$ in an oil bath for 18 h. Upon reaction completion, the mixture was diluted with EtOAc (2.0 mL) and sat. NH_4Cl (2.0 mL). The resulting mixture was transferred to a separatory funnel, the aqueous layer was extracted once with EtOAc (2.0 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude oil was loaded directly onto a pTLC plate and separated using 9:1 hexanes:EtOAc as the eluent, to afford the aniline **41** as a brown oil (16 mg, 38%). Additionally, 14 mg of **7** were recovered, making the yield based on recovered starting material 56%.

R_f: 0.21 (100% hexanes); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.54-7.51 (d, 2H, J = 8.6 Hz), 7.48-7.45 (d, 2H, J = 8.6 Hz), 4.30 (ABq, 4H, $\Delta\delta_{\text{AB}}$ = 0.13, J_{AB} = 8.0 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 84.42-82.22 (p, 1F, J = 155 Hz), 53.27-52.72 (d, 4F, J = 155 Hz); **ATR-IR (ν_{max})**: 3498, 2890, 1622, 1475, 1288, 1088, 961, 870, 782 cm^{-1} ; **HRMS (ESI) m/z** : $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_9\text{H}_{11}\text{ClF}_5\text{NS}^+$ 309.0246, not found.



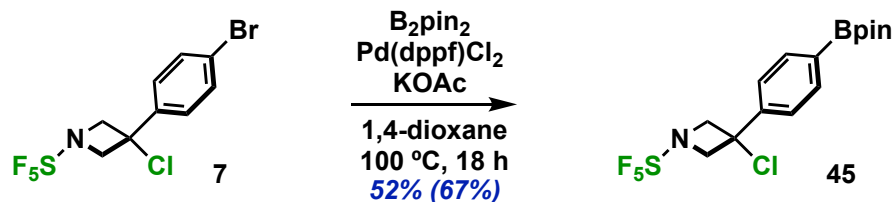
To an oven-dried 5 mL microwave vial equipped with a stir bar were added **7** (37 mg, 0.1 mmol, 1.0 equiv.), CuI (1 mg, 5 mol%), and (PPh₃)₄Pd (5.7 mg, 5 mol%). Then, THF (0.5 mL), TEA (0.15 mL) and ethynyltriisopropylsilane (25 μ L, 0.11 mmol, 1.1 equiv.), were added *via* syringe. The mixture was degassed by bubbling Ar through the solution for 10 mins. The degassed mixture was transferred to a pre-heated aluminum block and stirred at 65 $^\circ$ C for 16 h. Upon reaction completion, the mixture was diluted with CH₂Cl₂ (2.0 mL), quenched by addition of sat. NH₄Cl (2.0 mL), and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 2.0 mL) and the combined organic layers were washed with brine (1 $\times$ 2.0 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude oil was loaded directly onto a pTLC plate, using 100% hexanes as the eluent, to afford the alkyne **43** as a pale-yellow oil (31 mg, 65%).

R_f: 0.61 (100% hexanes); vis. UV (254 nm) or KMnO₄; **¹H (300 MHz, CDCl₃)**: δ = 7.53-7.51 (d, 2H, J = 8.4 Hz), 7.36-7.34 (d, 2H, J = 8.4 Hz), 4.61 (ABq, 4H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.5 Hz), 1.14 (s, 24H); **¹⁹F (282 MHz, CDCl₃)**: δ = 82.87-81.22 (p, 1F, J = 155 Hz), 52.85-52.43 (d, 4F, J = 155 Hz); **²⁹Si DEPT (80 MHz, CDCl₃)**: δ = -1.52 (s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.5, 132.5, 125.3, 124.3, 105.9, 92.5, 69.4-69.3 (p, J = 3.6 Hz), 59.9, 18.6, 11.3; **ATR-IR (v_{max})**: 2943, 2866, 2157, 1715, 1463, 1335, 1222, 1092, 878, 831, 807, 755 cm⁻¹; **HRMS (ESI) m/z** : [M+H]⁺ Calc'd for C₂₀H₃₀ClF₅NSSi⁺ 474.1471, found 474.1487.



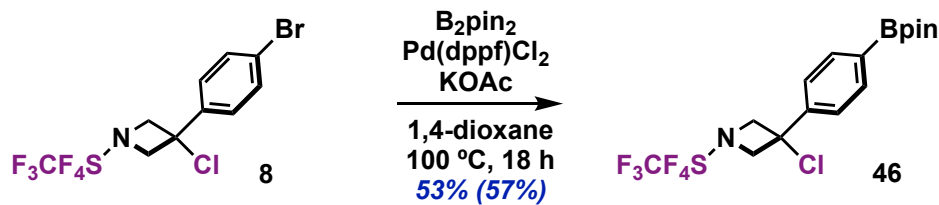
To an oven-dried 5 mL microwave vial equipped with a stir bar were added **8** (42 mg, 0.1 mmol, 1.0 equiv.), CuI (1 mg, 5 mol%), and $(\text{PPh}_3)_4\text{Pd}$ (5.7 mg, 5 mol%). Then, THF (0.5 mL), TEA (0.15 mL) and ethynyltriisopropylsilane (25 μL , 0.11 mmol, 1.1 equiv.), were added *via* syringe. The mixture was degassed by bubbling Ar through the solution for 10 mins. The degassed mixture was transferred to a pre-heated aluminum block and stirred at 65 $^\circ\text{C}$ for 16 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 (2.0 mL), quenched by addition of sat. NH_4Cl (2.0 mL), and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 2.0 mL) and the combined organic layers were washed with brine (1 $\times$ 2.0 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting crude oil was loaded directly onto a pTLC plate, using 100% hexanes as the eluent, to afford the alkyne **43** as a pale-yellow oil (32 mg, 61%).

R_f: 0.63 (100% hexanes); vis. UV (254 nm); **^1H (300 MHz, CDCl_3)**: δ = 7.53-7.50 (d, 2H, J = 8.6 Hz), 7.37-7.34 (d, 2H, J = 8.6 Hz), 4.61 (ABq, 4H, $\Delta\delta_{\text{AB}}$ = 0.06, J_{AB} = 8.7 Hz), 1.13 (s, 24H); **^{19}F (282 MHz, CDCl_3)**: δ = 29.70-29.43 (q, 4F, J = 24.9 Hz), -63.17-63.52 (p, 3F, J = 24.9 Hz); **$^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl_3)**: δ = 140.5, 132.5, 125.3, 124.2, 105.9, 92.4, 69.6-69.3 (p, J = 4.0 Hz), 60.4, 18.6, 11.3; **ATR-IR (ν_{max})**: 2945, 2867, 2157, 1716, 1461, 1333, 1224, 1091, 880, 791, 753 cm^{-1} ; **HRMS (ESI) m/z** : $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_{21}\text{H}_{30}\text{ClF}_7\text{NSSi}^+$ 524.1439, found 524.1411.



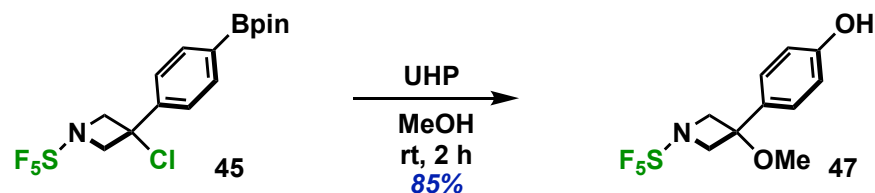
To an oven-dried 5 mL microwave vial equipped with a stir bar were added **7** (37 mg, 0.1 mmol, 1.0 equiv.), B_2pin_2 (30 mg, 0.12 mmol, 1.2 equiv.), Pd(dppf)Cl_2 (3.7 mg, 5 mol%), and potassium acetate (29 mg, 0.3 mmol, 3.0 equiv.). Anhydrous 1,4-dioxane (1.0 mL) was added *via* syringe, and Ar was bubbled through the solution for 10 min. The degassed solution was transferred to a pre-heated aluminum block and stirred at 100 °C for 16 h. Upon completion, the mixture was diluted with EtOAc, filtered through Celite, and the filtrate was transferred to a separatory funnel. The organic layer was washed with DI H_2O and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by pTLC, using 9:1 hexanes:EtOAc as the eluent, to afford the desired boronic ester **45** as a white solid (22 mg, 52%). Note: ^{19}F NMR yield is reported in parentheses.

R_f: 0.45 (9:1 hexanes:EtOAc); vis. UV (254 nm); ^1H (300 MHz, CDCl_3): δ = 7.90-7.88 (d, 2H, J = 8.1 Hz), 7.43-7.40 (d, 2H, J = 8.1 Hz), 4.65 (ABq, 4H, $\Delta\delta_{\text{AB}}$ = 0.10, J_{AB} = 8.4 Hz), 1.38 (s, 12H); ^{19}F (282 MHz, CDCl_3): δ = 83.32-81.13 (p, 1F, J = 155 Hz), 52.95-52.41 (d, 4F, J = 155 Hz); $^{13}\text{C}\{^1\text{H}\}$ (101 MHz, CDCl_3): δ = 143.4, 135.4, 124.6, 84.1, 69.3-69.1 (p, J = 3.8 Hz), 60.2, 24.8. Note: $\underline{\text{C}}$ -Bpin not observed due to quadrupolar broadening; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_{15}\text{H}_{21}\text{BClF}_5\text{NO}_2\text{S}^+$ 420.0968, found 420.0968.



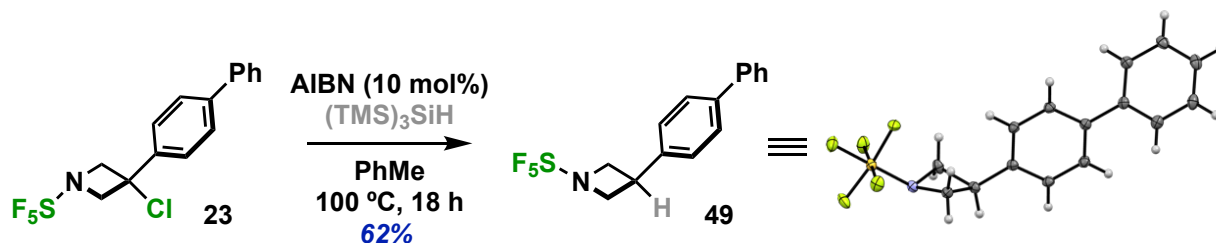
To an oven-dried 5 mL microwave vial equipped with a stir bar were added **8** (42 mg, 0.1 mmol, 1.0 equiv.), B_2pin_2 (30 mg, 0.12 mmol, 1.2 equiv.), $Pd(dppf)Cl_2$ (3.7 mg, 5 mol%), and potassium acetate (29 mg, 0.3 mmol, 3.0 equiv.). Anhydrous 1,4-dioxane (1.0 mL) was added *via* syringe, and Ar was bubbled through the solution for 10 min. The degassed solution was transferred to a pre-heated aluminum block and stirred at 100 °C for 16 h. Upon completion, the mixture was diluted with EtOAc, filtered through Celite, and the filtrate was transferred to a separatory funnel. The organic layer was washed with DI H_2O and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by pTLC, using 9:1 hexanes:EtOAc as the eluent, to afford the desired boronic ester **46** as a clear oil (25 mg, 53%). Note: ^{19}F NMR yield is reported in parentheses.

R_f: 0.49 (9:1 hexanes:EtOAc); vis. UV (254 nm); 1H (300 MHz, $CDCl_3$): δ = 7.87-7.84 (d, 2H, J = 7.8 Hz), 7.41-7.38 (d, 2H, J = 7.8 Hz), 4.64 (ABq, 4H, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 8.6 Hz), 1.35 (s, 12H); ^{19}F (282 MHz, $CDCl_3$): δ = 29.71-29.47 (q, 4F, J = 24.8 Hz), -63.17-63.52 (p, 3F, J = 24.8 Hz); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$): δ = 143.5, 135.5, 124.7, 84.2, 69.6-69.4 (p, J = 3.9 Hz), 60.5, 24.9
Note: $\underline{C}$ -Bpin not observed due to quadrupolar broadening, $F_3\underline{C}SF_4^-$ was not fully resolved;
HRMS (ESI) m/z : $[M+H]^+$ Calc'd for $C_{16}H_{21}BClF_7NO_2S^+$ 470.0957, found 470.0936.



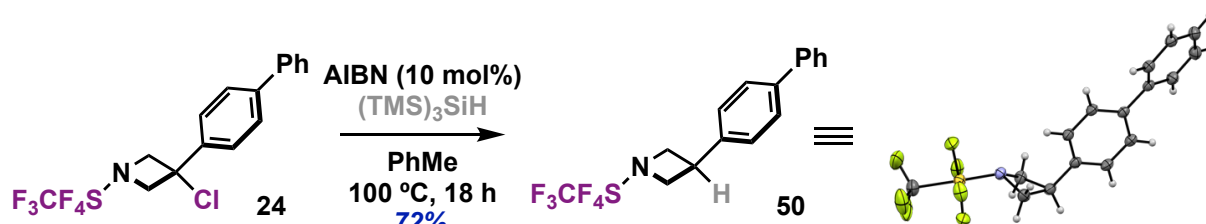
To an oven-dried 5 mL microwave vial equipped with a stir bar were added **45** (42 mg, 0.1 mmol, 1.0 equiv.) and urea hydrogen peroxide (24 mg, 0.25 mmol, 2.5 equiv.), followed by MeOH (0.1 mL). The mixture was stirred at room temperature for 2 h until complete consumption of **45** by TLC analysis. The reaction mixture was diluted with CH₂Cl₂ (2.0 mL), quenched by addition of DI H₂O (2.0 mL), and transferred to a separatory funnel. The organic layer was washed with DI H₂O (2.0 mL) and brine (2.0 mL), then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by pTLC, using 9:1 hexanes:EtOAc as the eluent, to afford **47** as a clear oil (26 mg, 85%).

R_f: 0.14 (9:1 hexanes:EtOAc); vis. UV (254 nm) or *p*-anisaldehyde (brown); **¹H (300 MHz, CDCl₃)**: δ = 7.30-7.27 (d, 2H, *J* = 8.8 Hz), 6.89-6.86 (d, 2H, *J* = 8.8 Hz), 5.18 (br s, 1H), 4.27 (ABq, 4H, Δδ_{AB} = 0.11, *J*_{AB} = 8.0 Hz), 3.06 (s, 3H); **¹⁹F (282 MHz, CDCl₃)**: δ = 84.56-82.36 (p, 1F, *J* = 155 Hz), 53.06-52.51 (d, 4F, *J* = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 155.6, 130.8, 127.6, 115.6, 74.6, 65.1-64.9 (p, *J* = 3.2 Hz), 51.6; **ATR-IR (ν_{max})**: 3362 (br), 2957, 1614, 1597, 1517, 1450, 1224, 1176, 1062, 1002, 873, 825, 777, 739 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₀H₁₃F₅NO₂S⁺ 306.0582, Found 306.0563.



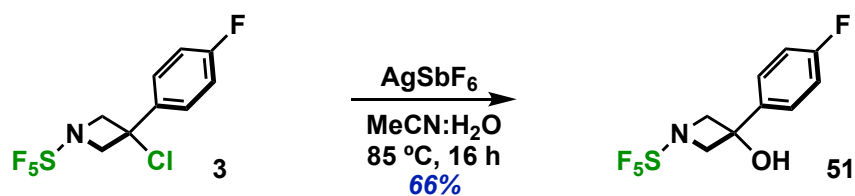
To an oven-dried microwave vial equipped with a stir bar was added **23** (25.0 mg, 1.0 equiv., 67 μmol). The vial was sealed with a septum, then evacuated and backfilled with Ar three times. Anhydrous toluene (0.3 mL) was added followed by (SiMe₃)₃SiH (25 μL, 1.2 equiv., 80 μmol) *via* syringe. Then, AIBN (2.2 mg, 10 mol%) was added, and the solution was purged with Ar for 5 min. The degassed solution was transferred to a pre-heated oil bath and stirred overnight at 100 °C. Upon reaction completion, the solvent was removed *in vacuo* and the resulting crude oil was purified *via* pTLC, using 100% hexanes as the eluent, to afford 3-([1,1'-biphenyl]-4-yl)-1-(pentafluoro-λ⁶-sulfanyl)azetidine (**49**) as a white solid (14 mg, 62%). Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

R_f: 0.21 (100% hexanes:); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.61-7.58 (m, 4H), 7.48-7.34 (m, 5H), 4.41-4.35 (t, 2H), 4.25-4.20 (t, 2H), 3.73-3.63 (p, 1H, *J* = 7.6 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 84.89-82.70 (p, 1F, *J* = 155 Hz), 51.73-51.18 (d, 4F, *J* = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.6, 140.5, 139.1, 128.9, 127.6, 127.52, 127.49, 127.1, 62.5-62.3 (p, *J* = 3.7 Hz), 33.1; **ATR-IR (ν_{max})**: 3026, 1484, 1084, 1066, 1007, 948, 875, 828, 789, 761, 729 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₁₅H₁₅F₅NS⁺ 336.0840, Found 336.0822.



To an oven-dried microwave vial equipped with a stir bar was added **24** (21 mg, 1.0 equiv., 50 μmol). The vial was sealed with a septum, then evacuated and backfilled with Ar three times. Anhydrous toluene (0.5 mL) was added, followed by $(\text{SiMe}_3)_3\text{SiH}$ (19 μL , 1.2 equiv., 60 μmol) *via* syringe. Then, AIBN (1.6 mg, 10 mol%) was added, and the solution was purged with Ar for 5 min. The degassed solution was transferred to a pre-heated oil bath and stirred overnight at 100 °C. Upon reaction completion, the solvent was removed *in vacuo* and the resulting crude oil was purified *via* pTLC, using 100% hexanes as the eluent, to afford **50** as a white solid (13 mg, 72%). Crystals suitable for SC-XRD were grown by slow solvent evaporation from toluene.

R_f: 0.69 (99:1 hexanes:EtOAc); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.63-7.55 (m, 4H), 7.48-7.34 (m, 5H), 4.41-4.36 (t, 2H, J = 7.8 Hz), 4.28-4.23 (t, 2H, J = 7.3 Hz), 3.73-3.63 (p, 1H, J = 7.8 Hz); **¹⁹F (282 MHz, CDCl₃)**: δ = 28.30-28.03 (q, 4F, J = 25.0 Hz), -63.08-63.43 (p, 3F, J = 25.0 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 140.5, 140.4, 139.0, 128.8, 127.51, 127.45, 127.4, 127.0, 127.69, 62.6-62.4 9 (p, J = 3.9 Hz), 33.2; **ATR-IR (ν_{max})**: 2952, 1485, 1226, 1147, 1081, 1059, 960, 825, 781, 765, 730 cm^{-1} ; **HRMS (ESI) m/z** : $[\text{M}+\text{H}]^+$ Calc'd for $\text{C}_{16}\text{H}_{15}\text{F}_7\text{NS}^+$ 386.0808, Found 386.0805.

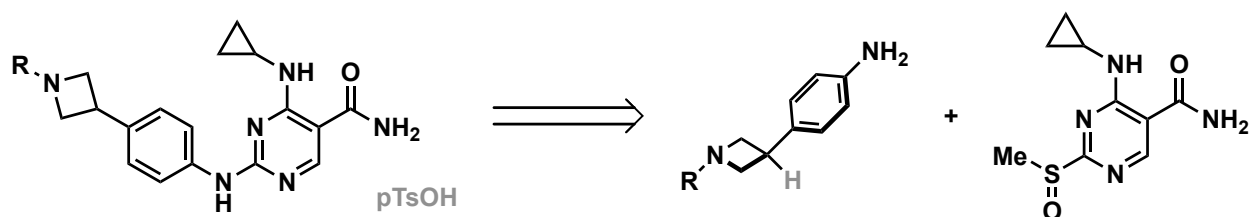


To a 7 mL scintillation vial equipped with a stir bar were added **3** (31 mg, 0.1 mmol, 1.0 equiv.) and silver(I) hexafluoroantimonate (38 mg, 0.11 mmol, 1.1 equiv.), followed by MeCN (1.0 mL) and DI H₂O (0.1 mL). The vial was sealed with a cap, transferred to a pre-heated oil bath, and stirred at 85 °C for 16 h. Upon reaction completion, the mixture was diluted with CH₂Cl₂ (2.0 mL) and quenched with sat. NaHCO₃ (2.0 mL). The reaction mixture was transferred to a separatory funnel, and the aqueous layer was extracted once with CH₂Cl₂ (1.0 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude oil was purified by pTLC, using 4:1 hexanes:EtOAc as the eluent, to afford **51** as a clear oil (20 mg, 66%)

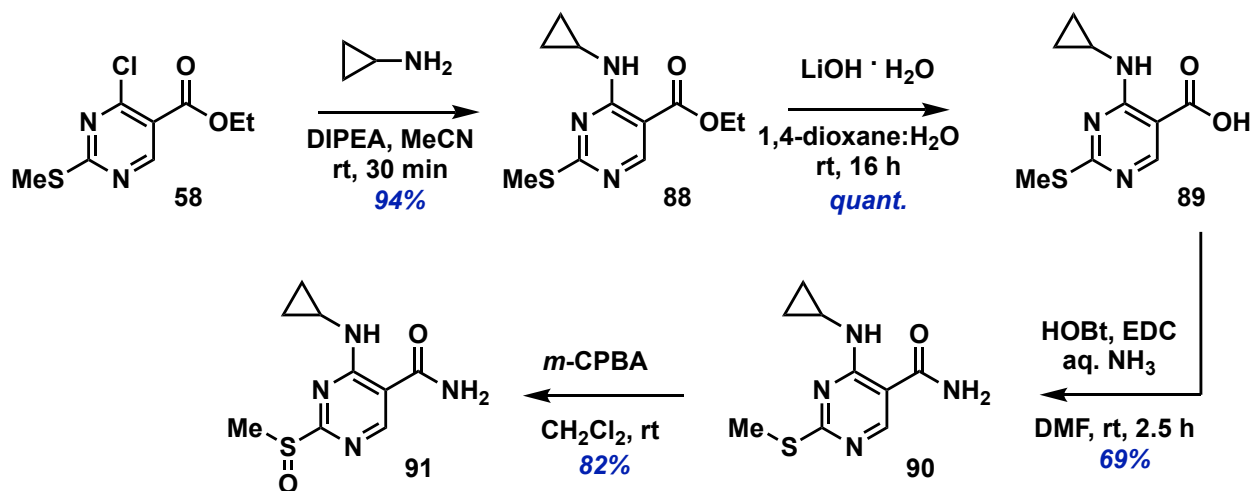
R_f: 0.54 (4:1 hexanes:EtOAc); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.55-7.51 (m, 2H), 7.13-7.08 (m, 2H), 4.32 (ABq, 4H, Δδ_{AB} = 0.01, J_{AB} = 8.2 Hz), 2.43 (br s, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = 84.15-81.96 (p, 1F, J = 155 Hz), 53.12-52.58 (d, 4F, J = 155 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 164.2-160.9 (d, J = 247.8 Hz), 137.43-137.39 (d, J = 3.2 Hz), 126.6-126.5 (d, J = 8.2 Hz), 115.8-115.6 (d, J = 21.8 Hz), 69.8, 69.2-69.1 (p, J = 3.0 Hz); **ATR-IR (ν_{max})**: 3362, 2956, 1595, 1451, 1223, 1176, 1001, 873, 825, 778, 739 cm⁻¹; **HRMS (ESI) m/z**: [M+H]⁺ Calc'd for C₉H₁₀F₆NOS⁺ 294.0382, Found 294.0384.

5.5.7 Synthesis of Drug Derivatives for *in vitro* ADME Profiling.

To facilitate comparative ADME studies, the following pyrimidine-based scaffold was identified in the patent literature.²⁶³ The analogs could be synthesized with a common sulfoxide precursor and the requisite aniline building block.



The synthesis of the sulfoxide-precursor **91** from **58** was detailed in the patent literature and is provided here for convenience.



To an oven-dried 50 mL round-bottom flask equipped with a stir bar were added ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (2.32 g, 10.0 mmol, 1.0 equiv., MilliporeSigma, CAS No: 5909-24-0, **58**) and MeCN (5.0 mL). Diisopropylethylamine (2.6 mL, 15.0 mmol, 1.5 equiv.) was added in one portion, and then cyclopropylamine was added dropwise (0.76 mL, 11.0 mmol, 1.1 equiv.), resulting in the onset of an exotherm. The reaction mixture was stirred for 15

min.; after returning to room temperature, the reaction mixture was quenched with sat. NH_4Cl (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×5.0 mL). The combined organic layers were washed with brine (3×10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified on silical gel, eluting with 9:1 hexanes:EtOAc, affording **88** as a clear oil (2.34 g, 94%).

$R_f = 0.29$ (9:1 hexanes:EtOAc); vis. UV (254 nm); ^1H (300 MHz, DMSO-d_6): $\delta = 8.50$ (s, 1H), 8.12 (br s, 1H), 4.28-4.21 (q, 2H, $J = 7.1$ Hz), 2.98-2.89 (m, 1H), 1.31-1.26 (t, 3H, $J = 7.1$ Hz), 0.82-0.76 (m, 2H), 0.61-0.56 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ (101 MHz, DMSO-d_6): $\delta = 175.1, 165.9, 160.6, 157.6, 100.6, 60.6, 23.5, 13.9, 13.6, 6.5$.

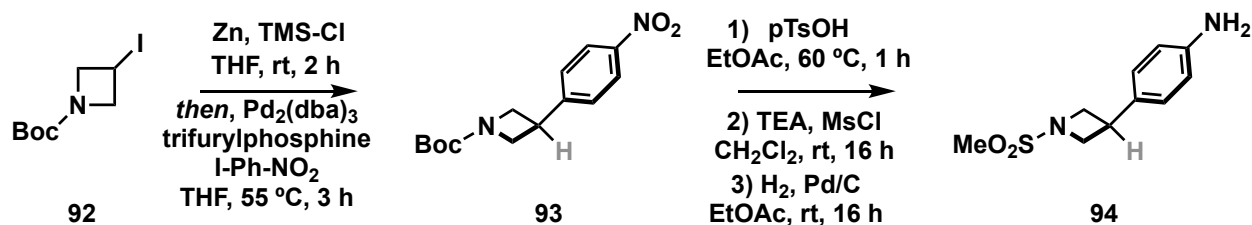
To an oven-dried 25 mL round-bottom flask equipped with a stir bar were added ethyl 4-(cyclopropylamino)-2-(methylthio)pyrimidine-5-carboxylate (633 mg, 2.5 mmol, 1.0 equiv.), 1,4-dioxane (2.5 mL) and DI H_2O (2.5 mL). Lithium hydroxide monohydrate (157 mg, 3.8 mmol, 1.5 equiv.) was added in one portion, and the reaction was stirred at room temperature for 16 h. Upon reaction completion, conc. HCl was added and a precipitate formed. The crude solid was collected by vacuum filtration, washed with cold Et_2O , and dried *in vacuo* before it was carried forward to the next step without further purification. The crude carboxylic acid (**89**) was added to a 25 mL round-bottom flask equipped with a stir bar. Then, HOBT (429 mg, 2.8 mmol, 1.1 equiv.) and EDC (466 mg, 3.0 mmol, 1.2 equiv.) were added successively, and the flask was evacuated and backfilled with Ar three times. Then, DMF (3.6 mL) and aq. NH_3 (0.34 mL, 5.0 mmol, 2.0 equiv.) were added *via* syringe and the resulting mixture was stirred at rt for 2.5 h. Upon completion, the reaction mixture was diluted with excess DI H_2O , which caused the a precipitate to form. The

precipitate was collected by vacuum filtration and dried *in vacuo* overnight to afford the desired amide **90** as a fluffy white solid (388 mg, 69% *over two steps*).

¹H (300 MHz, DMSO-*d*₆): δ = 9.07 (s, 1H), 8.52 (br s, 1H), 8.04 (br s, 1H), 7.45 (br s, 1H), 2.95-2.86 (m, 2H), 0.81-0.75 (m, 2H), 0.55-0.50 (m, 2H); **¹³C{¹H} (101 MHz, DMSO-*d*₆):** δ = 173.1, 168.6, 161.1, 155.0, 103.5, 23.2, 13.5, 6.5.

To a microwave vial equipped with a stir bar were added **90** (112 mg, 0.5 mmol, 1.0 equiv.) and CH₂Cl₂ (2.5 mL). Then, *m*-CPBA (135 mg, 0.6 mmol, 1.1 equiv.) was added in three portions and the resulting mixture was stirred at rt for 2 h over which time a precipitate had formed. The precipitate was collected by vacuum filtration, washed with cold CH₂Cl₂, and *dried in vacuo* overnight to afford sulfoxide **91** as a white solid (99 mg, 82%)

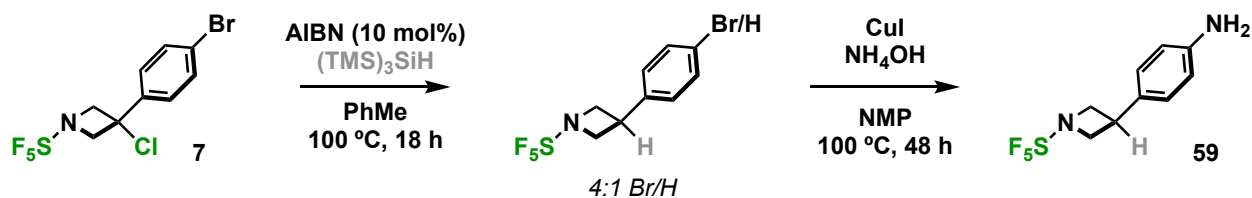
¹H (300 MHz, DMSO-*d*₆): δ = 9.22 (br s, 1H), 8.79 (s, 1H), 8.32 (br s, 1H), 7.77 (br s, 1H), 3.05-2.96 (m, 1H), 2.88 (s, 3H), 0.86-0.80 (dt, 2H, *J* = 7.1, 5.9 Hz), 0.63-0.58 (dt, 2H, *J* = 7.1, 4.3 Hz); **¹³C{¹H} (101 MHz, DMSO-*d*₆):** δ = 175.0, 168.3, 162.4, 155.8, 108.4, 24.0, 7.0; **ATR-IR (ν_{max}):** 3340, 3208, 3013, 1667, 1617, 1582, 1501, 1382, 1229, 1081, 1037, 968, 806 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₉H₁₃N₄O₂S⁺ 241.0754, Found 241.0737.



The first intermediate – *tert*-butyl 3-(4-nitrophenyl)azetidine-1-carboxylate (**93**) – was synthesized according to a modified procedure identified in the patent literature. To a 100 mL two-neck round-bottom flask were added Zn powder (901 mg, 13.8 mmol, 1.3 equiv.), THF (3.5 mL), and dibromoethane (0.15 mL, 1.69 mmol, 0.16 equiv.). The mixture was heated to 80 °C for 5 min. and then cooled to room temperature, at which point TMSCl (0.2 mL, 1.59 mmol, 0.15 equiv.) was added in one portion, and the mixture was stirred at room temperature for 5 min. Then, *tert*-butyl 3-iodoazetidine-1-carboxylate (**92**, 3.0 g, 10.6 mmol, 1.0 equiv.) was added as a solution in THF (4.0 mL), and the resulting suspension was stirred vigorously at room temperature for 2 h. Subsequently, $\text{Pd}_2(\text{dba})_3$ (155 mg, 0.17 mmol, 0.02 equiv.), trifurylphosphine (143 mg, 0.62 mmol, 0.06 equiv.), and 1-iodo-nitrobenzene (2.90 g, 11.7 mmol, 1.1 equiv.) were added as a solution in THF (18.0 mL), and the resulting mixture was stirred at 55 °C for 3 h. Upon reaction completion, the mixture was quenched with brine (15 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting orange oil was purified by column chromatography on silica gel eluting with 4:1 hexanes:EtOAc to afford *tert*-butyl 3-(4-nitrophenyl)azetidine-1-carboxylate as an orange oil (**93**, 2.11 g, 71%). All analytical data was consistent with the reported literature. Subsequent Boc-deprotection was achieved by treatment of with *para*-toluenesulfonic acid monohydrate in EtOAc. To a 25 mL round-bottom flask equipped with a stir bar were added *tert*-butyl 3-(4-nitrophenyl)azetidine-1-carboxylate (557 mg, 2.0 mmol, 1.0 equiv.), *para*-toluenesulfonic acid monohydrate (1.9 g, 10.0 mmol, 5.0 equiv.), and EtOAc

(10.0); the resulting mixture was stirred at 60 °C for 1 h. Upon reaction completion, the resulting mixture was filtered to afford 3-(4-nitrophenyl)azetidine (*p*-TsOH salt) as a white solid, which was telescoped to mesylation reaction conditions. To an oven-dried microwave vial equipped with a stir bar were added (350 mg, 1.0 mmol, 1.0 equiv.) and CH₂Cl₂ (5.0 mL). Then, triethylamine (0.18 mL, 1.3 mmol, 1.3 equiv.), methanesulfonyl chloride (0.11 mL, 1.3 mmol, 1.3 equiv.) were added sequentially *via* syringe at 0 °C, and the solution was stirred for 16 h while warming to room temperature. The resulting yellow solution was filtered through a plug of silica gel to afford the desired 1-(methanesulfonyl)-3-(4-nitrophenyl)azetidine as a clear oil (106 mg, 41%). To an oven-dried microwave vial equipped with a stir bar were added 1-(methanesulfonyl)-3-(4-nitrophenyl)azetidine (106 mg, 0.41 mmol, 1.0 equiv.) and Pd/C (30 mol%). The vial was sealed, evacuated, and backfilled with Ar, then EtOAc (2.0 mL) was added via syringe. An H₂ balloon was attached, and the suspension was vigorously stirred at rt overnight. Upon completion, the reaction was filtered over Celite and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica gel, eluting with 1:2 hexanes:EtOAc, to afford 4-(1-(methanesulfonyl)azetidin-3-yl)aniline (**94**) as a clear oil (87 mg, 93%).

¹H (300 MHz, CDCl₃): δ = 7.13-7.11 (d, 2H, *J* = 8.4 Hz), 6.68-6.65 (d, 2H, *J* = 8.4 Hz), 4.22-4.17 (t, 2H, *J* = 8.2 Hz), 4.01-3.96 (t, 2H, *J* = 8.2 Hz), 3.75-3.65 (m, 1H), 2.90 (s, 3H); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 145.8, 130.1, 127.8, 115.2, 57.4, 36.1, 32.4; **ATR-IR (ν_{max}):** 3078, 2957, 1602, 1516, 1412, 1344, 1144, 1101, 1063, 1014, 878, 850, 766, 734 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₁₀H₁₅N₂O₂S⁺ 227.0849, not found.



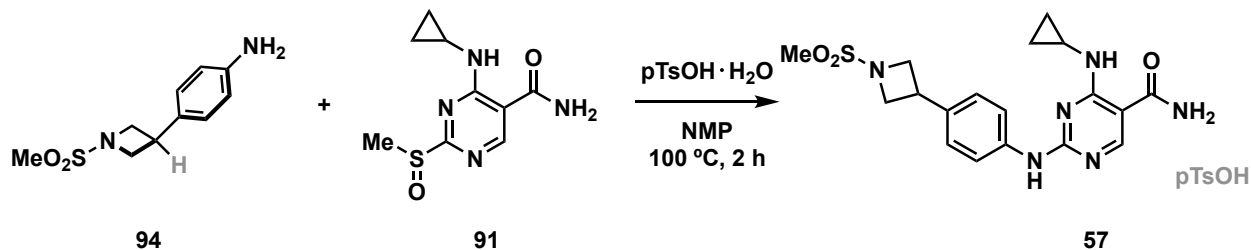
To an oven-dried 5 mL microwave vial equipped with a stir bar was added **7** (245 mg, 0.66 mmol, 1.0 equiv.). The vial was sealed with a septum, then evacuated and backfilled with Ar three times. Anhydrous toluene (1.3 mL) was added, followed by (SiMe₃)₃SiH (0.31 mL, 0.99 mmol, 1.5 equiv.). Then, AIBN (22 mg, 0.13 mmol, 20 mol%) was quickly added, and Ar was bubbled through the solution for 10 min. The degassed solution was transferred to a pre-heated oil bath and stirred at 100 °C for 18 h. The crude reaction mixture was concentrated under reduced pressure and purified directly by column chromatography on silica gel, eluting with 100% hexanes. The desired product was obtained as a 4:1 mixture of 3-(4-bromophenyl)-1-(pentafluoro-λ⁶-sulfanyl)azetidine:1-(pentafluoro-λ⁶-sulfanyl)-3-phenylazetidine. Based on the ratio of the inseparable products (determined by ¹⁹F NMR) approximately 115 mg of the desired bromide was obtained as a clear oil (~56%).

¹H (300 MHz, CDCl₃): δ = 7.51-7.48 (d, 2H, *J* = 8.5 Hz), 7.23-7.20 (d, 2H, *J* = 8.5 Hz), 4.39-4.34 (t, 2H, *J* = 7.8 Hz), 4.15-4.10 (t, 2H, *J* = 7.2 Hz), 3.64-3.53 (p, 1H, *J* = 7.8 Hz); **¹⁹F (282 MHz, CDCl₃):** δ = 84.61-82.42 (p, 1F, *J* = 154 Hz), 51.62-51.08 (d, 4F, *J* = 154 Hz); **¹³C{¹H} (101 MHz, CDCl₃):** δ = 139.0, 131.9, 128.7, 121.2, 62.1-61.9 (p, *J* = 3.8 Hz), 32.8.

To an oven-dried 5 mL microwave vial equipped with a stir bar was added 3-(4-bromophenyl)-1-(pentafluoro-λ⁶-sulfanyl)azetidine (assuming 115 mg, 0.34 mmol, 1.0 equiv.), followed by NMP (0.6 mL), copper(I) iodide (32 mg, 0.17 mmol, 0.5 equiv.), and aq. NH₃ (0.45

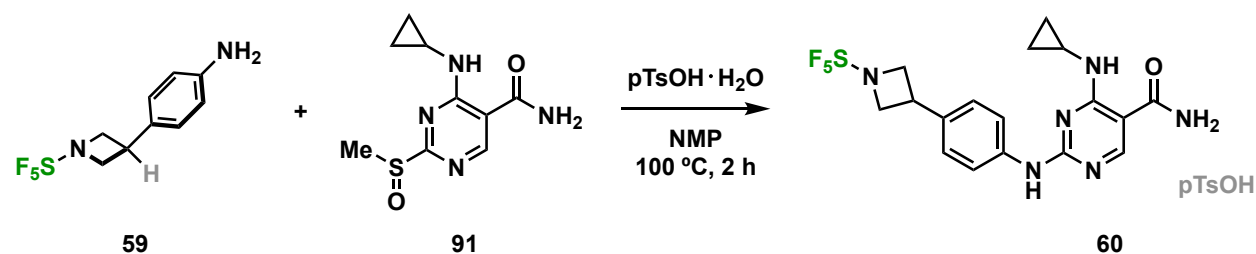
mL, 6.8 mmol, 20.0 equiv.). The resulting mixture was transferred to a pre-heated oil bath and stirred at 100 °C for 24 h. Upon completion, the mixture was diluted with CH₂Cl₂ (5.0 mL) and quenched by addition of sat. NH₄Cl (5.0 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 3.0 mL), and the combined organic layers were washed with brine (1 × 5.0 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography on silica gel, eluting with 4:1 hexanes:EtOAc, to afford **59** as a pale-yellow oil (30 mg, 32%); additionally, 83 mg of the mixture of Br/H starting material was collected.

R_f: 0.26 (4:1 hexanes:EtOAc); vis. UV (254 nm); **¹H (300 MHz, CDCl₃)**: δ = 7.13-7.10 (d, 2H, *J* = 8.2 Hz), 6.69-6.67 (d, 2H, *J* = 8.2 Hz), 4.31-4.26 (t, 2H), 4.16-4.11 (t, 2H), 3.68 (br s, 2H), 3.57-3.47 (p, 1H); **¹⁹F (282 MHz, CDCl₃)**: δ = 85.33-83.14 (p, 1F, *J* = 154 Hz), 51.86-51.31 (d, 4F, *J* = 154 Hz); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 145.8, 129.7, 128.0, 115.3, 62.9-62.7 (p, *J* = 3.6 Hz), 32.9; **ATR-IR (ν_{max})**: 3496, 3395, 2980, 2889. 1623, 1519, 1480, 1287, 1082, 962, 870, 780 cm⁻¹; **HRMS (ESI) *m/z***: [M+H]⁺ Calc'd for C₉H₁₂F₂N₂S⁺ 275.0636, found 275.0641.



To a 7 mL scintillation vial equipped with a stir bar were added **94** (36 mg, 0.16 mmol, 1.2 equiv.) and **91** (32 mg, 0.15 mmol, 1.0 equiv.), followed by NMP (0.4 mL) and *para*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol, 1.2 equiv.). The resulting suspension was transferred to a pre-heated oil bath and stirred vigorously at 100 °C for 2 h. After 2 h, the crude reaction mixture was diluted with DI H₂O, and the formation of a beige precipitate was observed. The solid was collected *via* filtration and dried *in vacuo* overnight, providing **57** as a beige solid (40 mg, 76%).

¹H (300 MHz, DMSO-*d*₆): δ = 10.21 (br s, 1H), 9.73 (br s, 1H), 8.46 (s, 1H), 8.09 (br s, 1H), 7.80-7.78 (d, 2H, *J* = 7.6 Hz), 7.49-7.47 (d, 2H, *J* = 8.0 Hz), 7.41-.37 (d, 2H, *J* = 7.6 Hz) 7.13-7.10 (d, 2H, *J* = 8.0 Hz), 4.22-4.17 (t, 2H, *J* = 7.6 Hz), 3.94-3.82 (m, 3H), 3.07 (s, 3H), 2.97-2.90 (m, 1H), 2.29 (s, 3H), 0.91-0.85 (m, 2H), 0.67-0.62 (m, 2H); **¹³C{¹H} (101 MHz, DMSO-*d*₆):** δ = 167.7, 133.3, 132.7, 130.7, 126.3, 62.1, 38.2, 37.0, 29.3, 26.0, 11.8; **ATR-IR (ν_{max}):** 3342, 3188, 2879, 1692, 1635, 1610, 1591, 1557, 1512, 1404, 1357, 1334, 1309, 1209, 1189, 1169, 1145, 1106, 1037, 1011, 966, 815, 798, 771, 735cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₁₈H₂₃N₆O₃S⁺ 403.1547, found 403.1523.

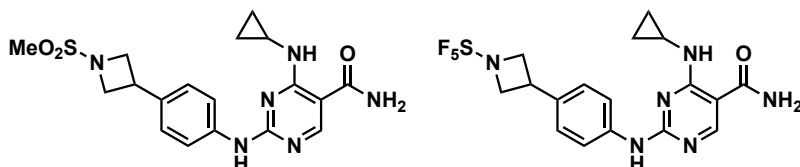


To a 7 mL scintillation vial equipped with a stir bar were added **59** (18 mg, 0.067 mmol, 1.2 equiv.) and **91** (13 mg, 0.055 mmol, 1.0 equiv.), followed by NMP (0.2 mL) and *para*-toluenesulfonic acid monohydrate (13 mg, 0.066 mmol, 1.2 equiv.). The resulting suspension was transferred to a pre-heated oil bath and stirred vigorously at 100 °C for 2 h. After 2 h, the crude reaction mixture was diluted with DI H₂O, and the formation of a beige precipitate was observed. The solid was collected *via* filtration and dried *in vacuo* overnight, providing **60** as a beige solid (18 mg, 73%).

¹H (300 MHz, DMSO-*d*₆): δ = 10.09 (br s, 1H), 9.62 (br s, 1H), 8.46 (s, 1H), 8.05 (br s, 1H), 7.82-7.79 (d, 2H, *J* = 8.3 Hz), 7.49-7.46 (d, 2H, *J* = 8.1 Hz), 7.36-7.33 (d, 2H, *J* = 8.3 Hz), 7.13-7.10 (d, 2H, *J* = 8.1 Hz), 4.40-4.35 (t, 2H, *J* = 7.6 Hz), 4.14-4.10 (t, 2H, *J* = 7.3 Hz), 3.77-3.66 (p, 1H, *J* = 7.6 Hz), 2.96-2.88 (m, 1H), 2.29 (s, 3H), 0.91-0.84 (m, 2H), 0.65-0.60 (m, 2H); **¹⁹F (282 MHz, DMSO-*d*₆):** δ = 88.51-86.30 (p, 1F, *J* = 156 Hz), 53.64-53.09 (d, 4F, *J* = 156 Hz); **¹³C{¹H} (101 MHz, DMSO-*d*₆):** δ = 163.0, 146.2, 138.1, 128.5, 127.8, 126.0, 62.6, 32.3, 24.4, 21.3, 7.1; **ATR-IR (ν_{max}):** 3305, 3185, 1696, 1685, 1577, 1406, 1209, 1171, 1125, 1063, 1038, 1012, 873, 828, 806, 735 cm⁻¹; **HRMS (ESI) *m/z*:** [M+H]⁺ Calc'd for C₁₇H₂₀F₅N₆OS⁺ 451.1334, found 451.1351.

5.5.8 Summary of *in vitro* ADME Profiling.

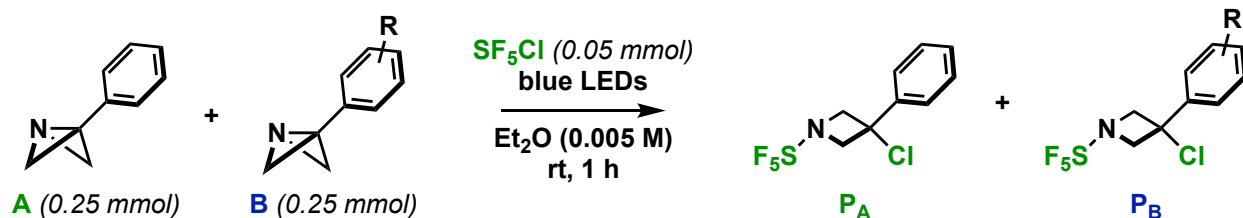
Table 5.3. Summary of *in vitro* ADME profiling of compounds **57** and **60**.



Compound	57	60
Measured LogD _{7.4} / calc'd	2.10 / 2.47	>5.00 / 4.85
HT Solubility pH = 6.8 (mM) ^a	<0.004	<0.004
LM CL _{int} m / r / h (μL/min/mg) ^b	19 / 16 / <10	42 / 29 / 74
HepG2 Cytotoxicity CC ₅₀ (μM)	43	52
MDCK-LE ^c P _{app} A–B (10 cm ² /s) / % Recovery	11.20 / 35	3.50 / 40
hERG inhibition Qube IC ₅₀ (μM)	>30.00 ^d	>30.00 ^d
CYP3A4 TDI k _{obs} (min ⁻¹)	0.01	0.01
CYP3A4 / 2D6 / 2C9 IC ₅₀ (μM)	>25 / >25 / >25	>25 / >25 / >25

^a HT = high throughput. ^b LM CL_{int} = liver microsomal intrinsic clearance in mouse, rat, and human, respectively. ^c Low efflux Madin–Darby canine kidney permeability. ^d Measured in triplicate. Note that one experimental replicate of hERG IC₅₀ values (8.91 μM for **57**, and 18.0 μM for **60**) was excluded from the statistical analysis as the results from this single experiment were revealed to be outliers. The remaining three experiments showed IC₅₀ values consistently >30 μM for both compounds.

5.5.9 Hammett Plot Experiments.



To an oven-dried 20 mL microwave vial equipped with a stir bar, compound **A** (**S1**, 33 mg, 0.25 mmol, 5.0 equiv.) and compound **B** (0.25 mmol, 5.0 equiv.) were added. The vial was sealed with a crimper, then evacuated and backfilled with Ar three times. Anhydrous Et_2O (10 mL, 0.005 M) was added *via* syringe, followed by SF_5Cl (0.05 mmol, 1.0 equiv., 0.05-0.10 M in *n*-pentane). The vial was irradiated with blue LEDs (Kessil Tuna Blue A160WE, maximum intensity) for 1 h using a fan to maintain the temperature around 25 °C. Upon completion, the solvent was removed under reduced pressure, and the remaining crude oil was dissolved in 1.0 mL of CDCl_3 . Trifluorotoluene (TFT) was added as an internal standard, and the ratio (**P_A**/**P_B**) was determined by ^{19}F NMR.

Table 5.5. Raw Hammett data from competition experiments (determined by ^{19}F NMR).

R =	σ value²⁶⁴	P_B/P_A	$\log (P_B/P_A)$
p- <i>t</i> Bu	-0.2	1.5	0.176091
H	0	1	0
p-Br	0.23	0.5	-0.30103
p-CF ₃	0.54	0.15	-0.82391
p-Cl	0.23	0.62	-0.20761
p-F	0.06	0.85	-0.07058
m-Br	0.39	0.27	-0.56864
p-Et	-0.15	1.23	0.089905
m-F	0.37	0.35	-0.45593
m-Cl	0.34	0.31	-0.50864
p-SiMe ₃	-0.07	1.04	0.017033

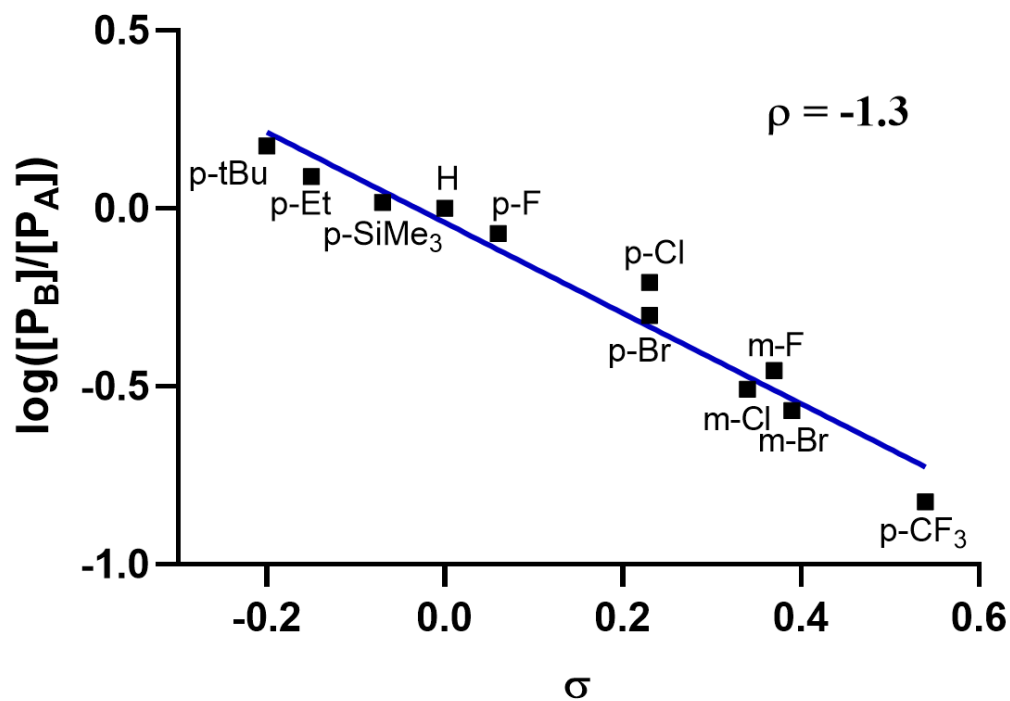
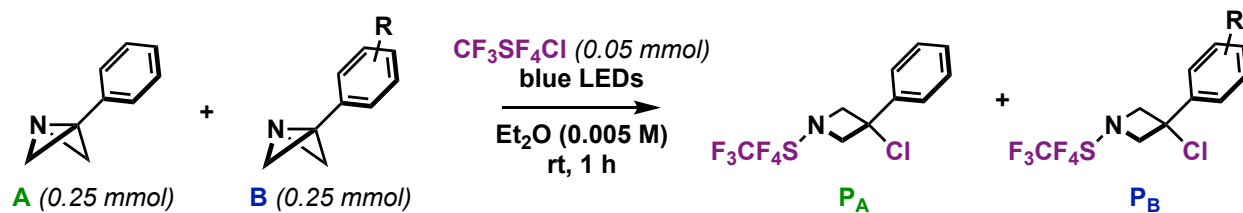


Figure 5.10. Plot of the $\log([P_B]/[P_A])$ versus Hammett constants ($R^2 = 0.9590$).



In an oven-dried 20 mL microwave vial equipped with a stir bar, compound **A** (**S1**, 33 mg, 0.25 mmol, 5.0 equiv.) and compound **B** (0.25 mmol, 5.0 equiv.) were added. The vial was sealed with a crimper, then evacuated and backfilled with Ar three times. Anhydrous THF (10 mL, 0.005 M) was added *via* syringe, followed by $\text{CF}_3\text{SF}_4\text{Cl}$ (0.05 mmol, 1.0 equiv., 0.09-0.10 M in *n*-pentane). The vial was irradiated with blue LEDs (Kessil Tuna Blue A160WE, maximum intensity) for 1 h using a fan to maintain the temperature around 25 °C. Upon completion, the solvent was removed under reduced pressure, and the remaining crude oil was dissolved in 1.0 mL of CDCl_3 . Trifluorotoluene (TFT) was added as an internal standard, and the ratio (**P_A** / **P_B**) was determined by ^{19}F NMR.

Table 5.6. Raw Hammett data from competition experiments (determined by ^{19}F NMR).

R =	σ value²⁶⁴	$\text{P}_\text{B}/\text{P}_\text{A}$	$\log (\text{P}_\text{B}/\text{P}_\text{A})$
p- <i>t</i> Bu	-0.2	1.27	0.103804
H	0	1	0
p-Br	0.23	0.77	-0.11351
p- CF_3	0.54	0.39	-0.40894
p-Cl	0.23	0.78	-0.10791
p-F	0.06	0.92	-0.03621
m-Br	0.39	0.54	-0.26761
p-Et	-0.15	1.29	0.11059
m-F	0.37	0.52	-0.284
m-Cl	0.34	0.51	-0.29243

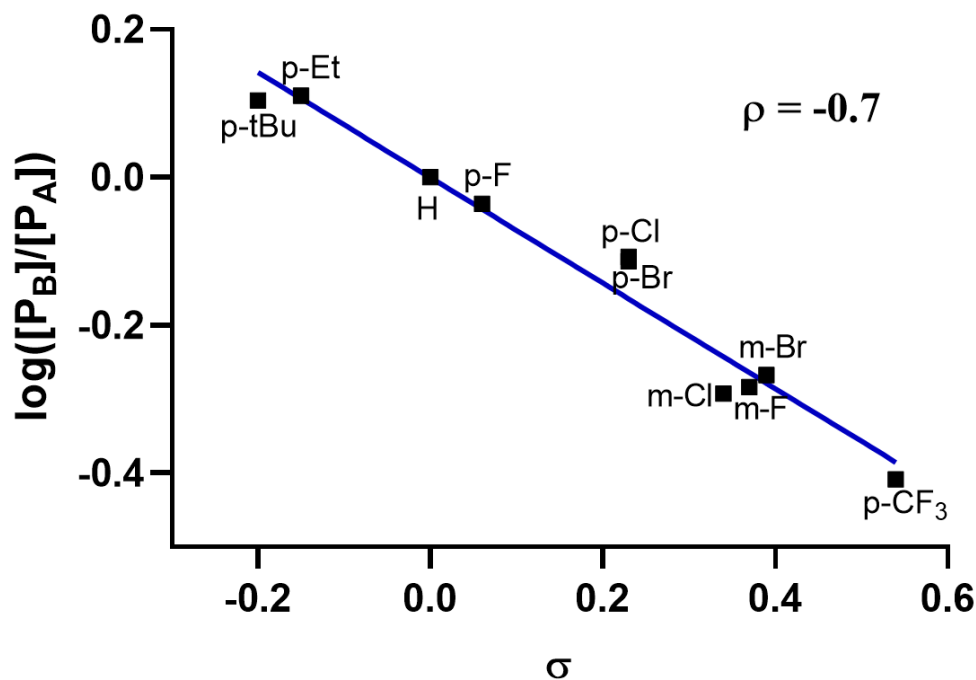


Figure 5.11. Plot of the $\log([P_B]/[P_A])$ versus Hammett constants ($R^2 = 0.9621$).

5.5.10 Radical Trapping Experiments.

Radical trapping experiments with bromotrichloromethane (CCl_3Br) were conducted following the general procedure. To an oven-dried 20 mL microwave vial equipped with a stir bar was added the ABB substrate (0.1 mmol, 1.0 equiv.) open to air. The vessel was sealed with a Teflon-lined cap using a crimper, and the vial was evacuated and backfilled with Ar three times. Then, anhydrous Et_2O (3.0 mL) and CCl_3Br were added *via* syringe. A solution of SF_5Cl or $\text{CF}_3\text{SF}_4\text{Cl}$ in *n*-pentane (0.12 mmol, 1.2 equiv.) was slowly added down the sides of the vessel *via* syringe, and the resulting mixture was irradiated with 2 Kessil blue LEDs at maximum intensity for 1 h using a fan to maintain the temperature around 25 °C. After the reaction was complete the crude mixture was typically light-yellow and was carefully concentrated *in vacuo* (300 mbar, 40

°C), redissolved in CDCl₃, and subjected to ¹⁹F NMR analysis. The crude reaction mixtures were combined and purified by pTLC to afford a mixture of the 3-bromo- and 3-chloro- products **92** and **7**.

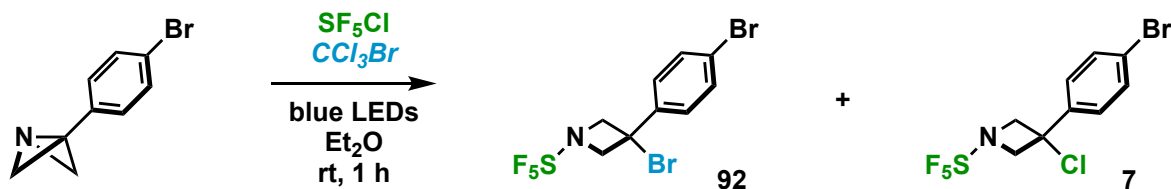


Table 5.7. Br:Cl ratios with increasing equiv. of CCl_3Br under standard reaction conditions using SF_5Cl .

<i>R</i>	CCl_3Br (equiv.)	yield ^a	Br : Cl
SF_5	1.0	21%	1.0 : 1.2
SF_5	2.0	14%	1.2 : 1.0
SF_5	3.0	20%	2.1 : 1.0
SF_5	5.0	17%	3.8 : 1.0

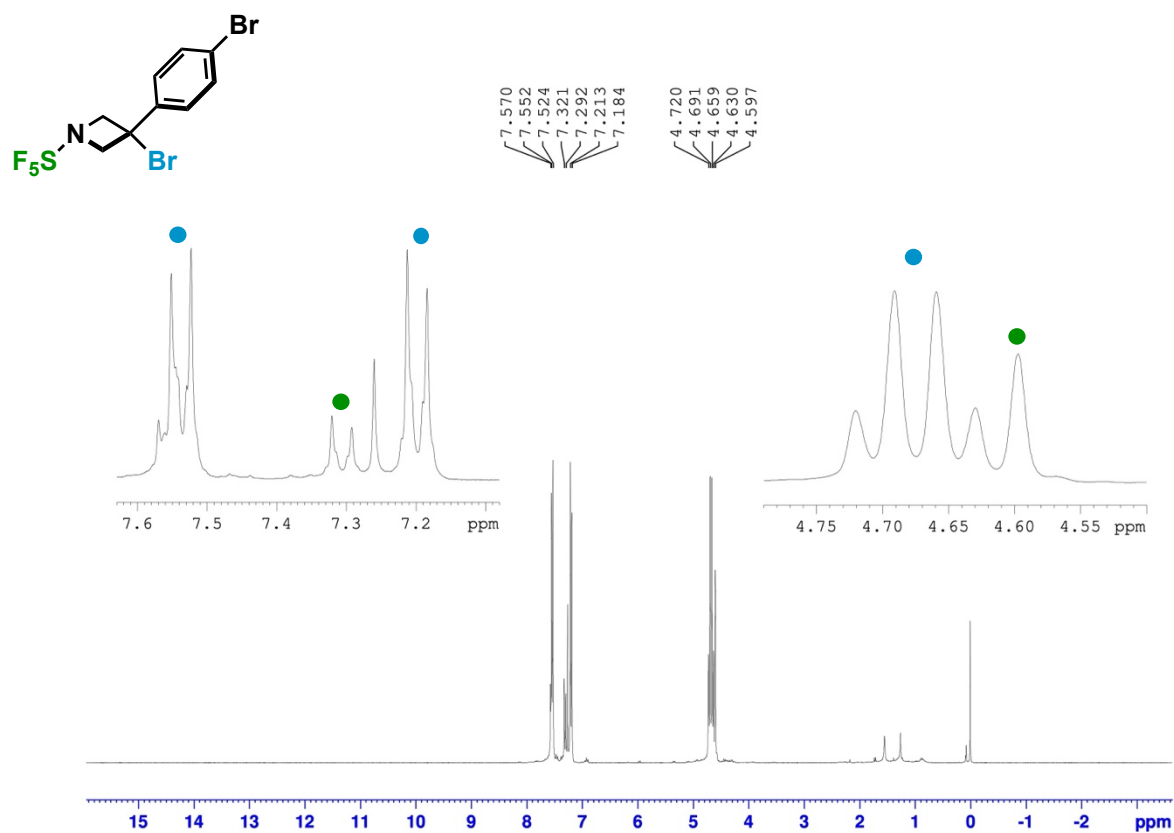


Figure 5.12. ¹H NMR of a 4.3:1 mixture of **92** to **7**. Distinct signals belonging to **7** are identified with a green sphere and distinct signals belonging to **92** are denoted with a blue sphere.

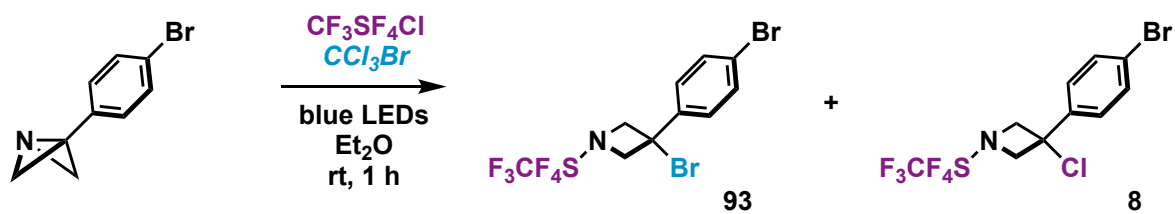


Table 5.8. Br:Cl ratios with increasing equiv. of CCl_3Br under standard reaction conditions using $\text{CF}_3\text{SF}_4\text{Cl}$.

<i>R</i>	<i>CCl₃Br</i> (equiv.)	yield ^a	<i>Br</i> : <i>Cl</i>
SF_4CF_3	1.0	21%	1.0 : 2.0
SF_4CF_3	5.0	17%	1.0 : 1.4
SF_4CF_3	1.0	27%	1.0 : 1.3
SF_4CF_3	5.0	17%	1.0 : 1.0

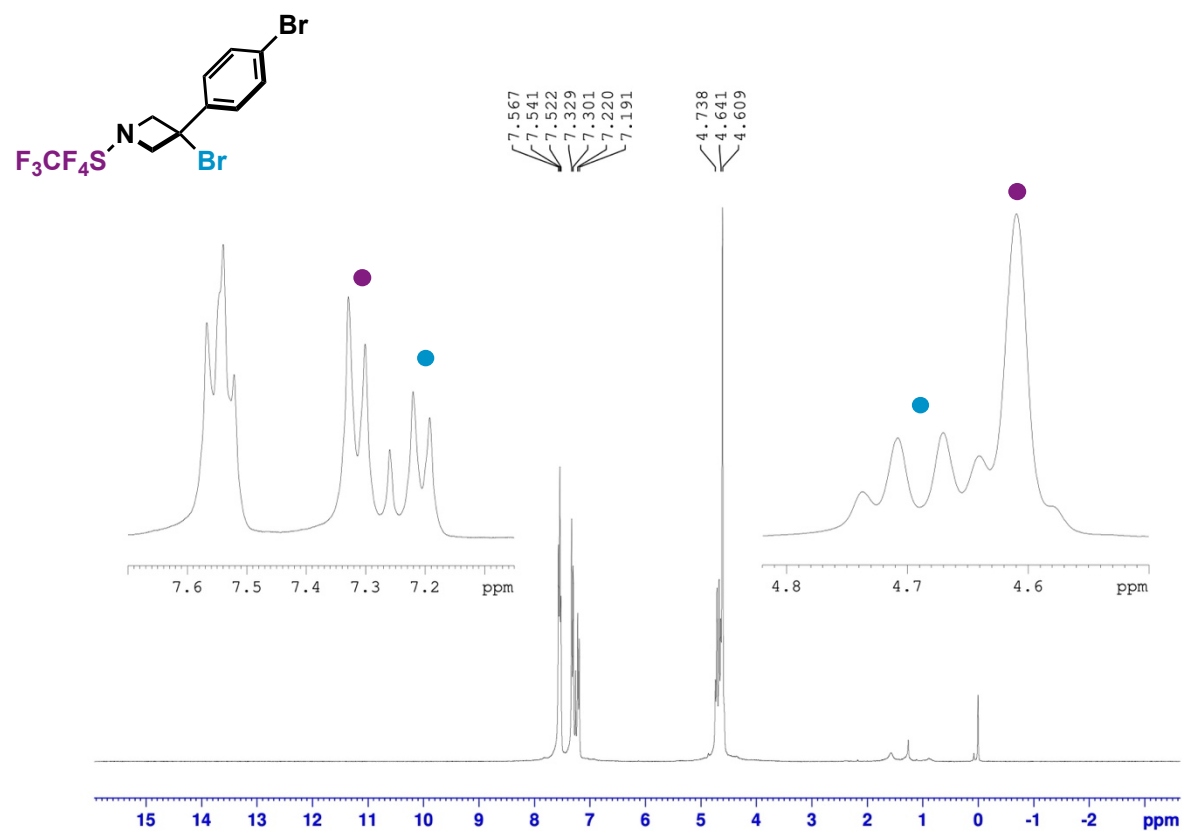


Figure 5.13. ¹H NMR of a ~0.95:1 mixture of **93** to **8**. Distinct signals belonging to **8** are identified with a purple sphere and distinct signals belonging to **93** are denoted with a blue sphere.

5.5.11 SC-XRD.

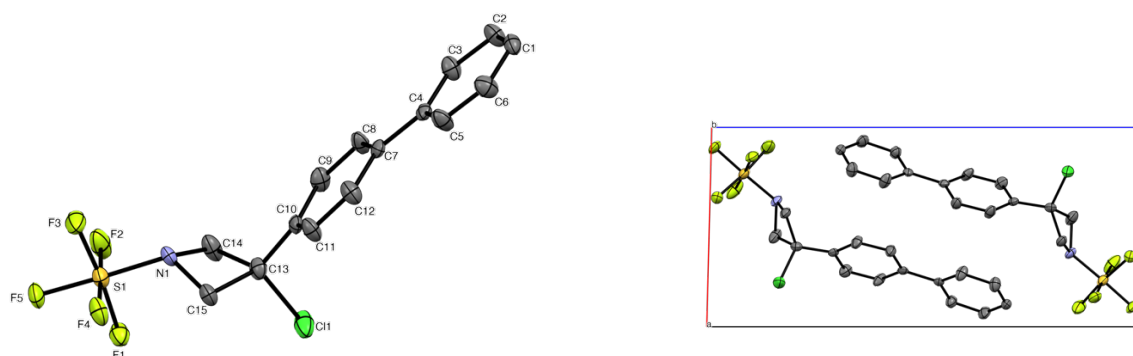


Figure 5.14. Crystal structure (H atoms omitted for clarity) and packing of compound **23** (ellipsoids displayed at 50% probability level, only the major disordered part is shown). The crystals were obtained by vapor diffusion using ethyl acetate and *n*-pentane as the anti-solvent at 4 °C. Color code: C, gray; H, white; N, blue; F, neon green; S, yellow.

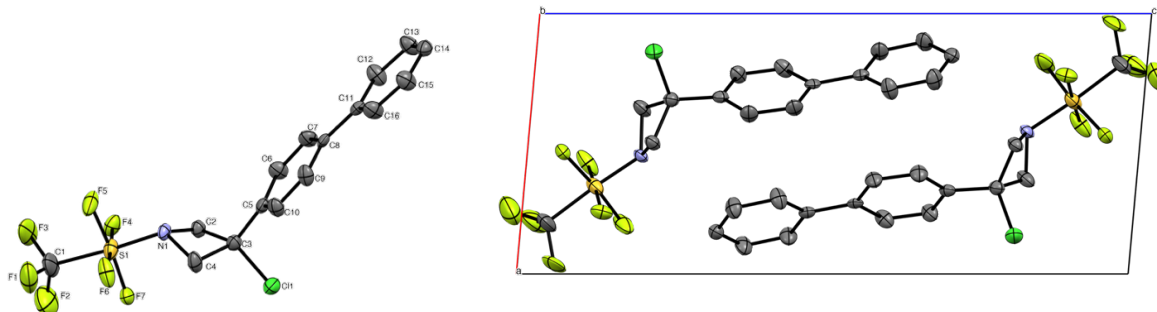


Figure 5.15. Crystal structure (H atoms omitted for clarity) and packing of compound **24** (ellipsoids displayed at 50% probability level, only the major disordered part is shown). The crystals were obtained by vapor diffusion using ethyl acetate and *n*-pentane as the anti-solvent at 4 °C. Color code: C, gray; H, white; N, blue; F, neon green; S, yellow.

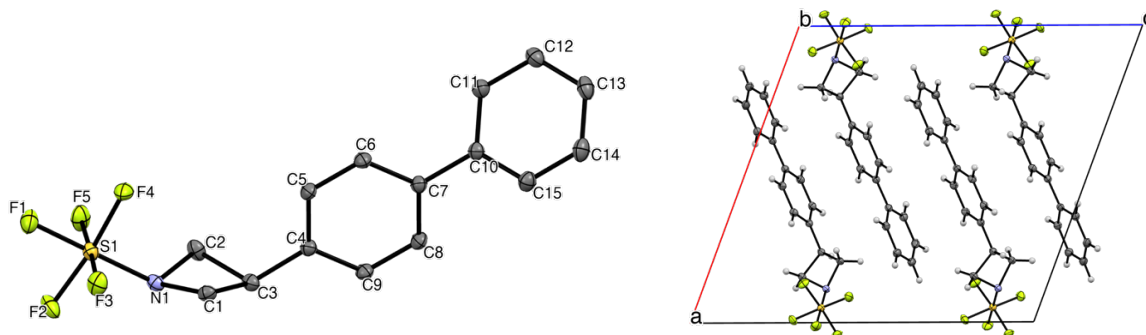


Figure 5.16. Crystal structure (H atoms omitted for clarity) and packing of compound **49** (ellipsoids displayed at 50% probability level). The crystals were obtained by slow evaporation from toluene. Color code: C, gray; H, white; N, blue; F, neon green; S, yellow.

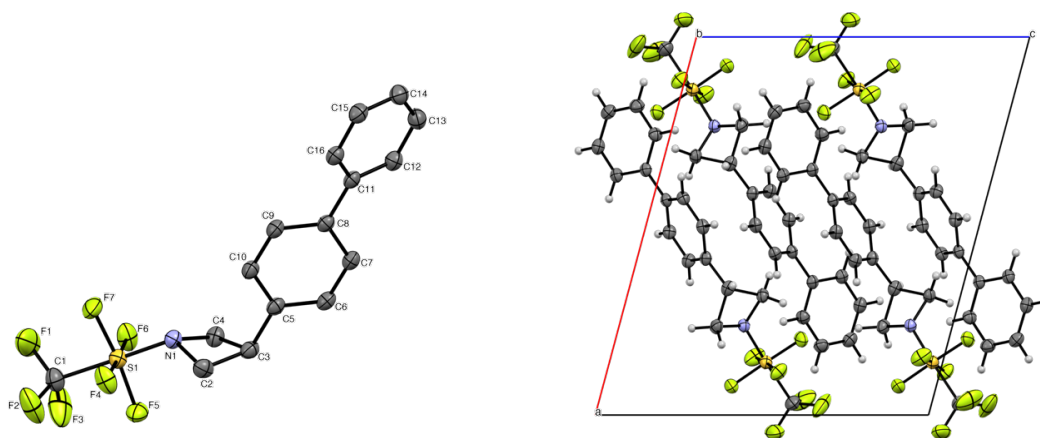


Figure 5.17. Crystal structure (H atoms omitted for clarity) and packing of compound **50** (ellipsoids displayed at 50% probability level). The crystals were obtained by slow evaporation from toluene. Color code: C, gray; H, white; N, blue; F, neon green; S, yellow.

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Chapter 6: Tetrafluoro(aryl)sulfanylated Bicyclopentane Crystals that Self-Destruct upon Cooling

6.1 Introduction.

Mechanically responsive single crystals of organic and organometallic compounds have historically eluded focused attention from synthetic and physical organic chemists.^{265,266} This is in stark contrast to the realized potential of mechanically responsive organic polymers,²⁶⁷ elastomers,²⁶⁸ liquid-crystal-like materials,²⁶⁹ and single molecular machines, as well as inorganic materials.²⁷⁰

While sporadic visual descriptions and investigations of mechanically responsive single crystals trace back to at least 1960, this area of research first became active for a period during the 1980's.²⁷¹ More recently, the field has experienced a noticeable resurgence in interest, which can be attributed primarily to 1) the prospect of employing mechanically responsive single crystals, e.g., as actuators²⁷² or in energy storage²⁷³ and 2) instrumental technological advancements that facilitate mechanistic studies. Organic/organometallic single crystals that demonstrate the ability to convert energy into motion from changes in temperature (thermoreponsive or “thermosalient”) and under photochemical conditions (photoresponsive or “photosalient”) have been the focus of several studies over the last decade or so.²⁷⁴ By comparison, organic crystals that are mechanically responsive at *very low* temperatures remain scarce in the chemical literature (Figure 6.1, *top panel*).

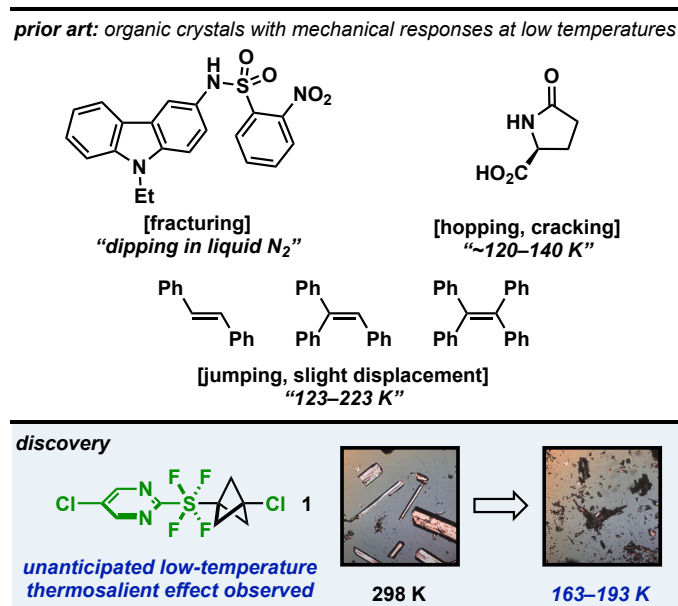


Figure 6.1. (top) Rare examples of organic compounds with reported single-crystal mechanical responses at cold temperatures in the chemical literature. (bottom) Focus of this work: discovery and detailed study of a new class of organic material with a low-temperature thermosalient effect.

One of the early examples of an organometallic crystalline compound eliciting a low-temperature thermosalient effect was reported by Edwards and Kington²⁷⁵ and later studied, e.g., by Bodenheimer²⁷⁶ and Naruse.²⁷⁷ It was found that ferrocene crystals "violently disintegrate" upon cooling to the temperature range of 108–125 K, which was attributed to latent strain accumulated following a phase transition at 164 K. A similar observation was made for nickelocene. In 2013, Lusi and Bernstein reported that crystals of $[\text{ZnBr}_2(2,2'\text{-bpy})]$ undergo a crystalline-crystalline phase transition that causes the crystals to break or jump when cooled below 215 K.²⁷⁸ In 2019, Seki, Mashimo, and Ito reported a gold isocyanide complex that exhibited jumping, bending, or splitting motion upon cooling to the range of 123–193 K.²⁷⁹ This was associated with a phase transition, and the response was found to be reversible upon warming from 123 K. There have also been reports of crystals of other organometallic compounds known to exhibit mechanical responses at both high and low temperatures, e.g., (phenylazophenyl)palladium

hexafluoroacetylacetonate (PHA), though effects at higher temperatures tend to be the major focus of study.^{280,281}

In contrast to organometallic compounds, examples of organic crystalline compounds that elicit a low-temperature thermosalient effect have been reported less frequently and were not necessarily studied in great detail (Figure 6.1, *top panel*).²⁸² For instance, Kumar, Rana, and Nangia noted that one of the Cardiosulfa analogues they studied "fractured" upon dipping in liquid N₂, forming a new polymorph.²⁸³ This was not the primary focus of their work, thus limited mechanistic insight was provided. It is also known that pyroglutamic acid (PGA) exhibits a mechanical response upon cooling, but it is weaker than its demonstrated thermosalient effect upon heating, which has accordingly received more attention.^{284,285,286} Additionally, Seki, Mashimo, and Ito found that di-, tri-, and tetraphenylethylene crystals "jump" or experience a "slight displacement" upon cooling in the range of 123–223 K.²⁸⁷ This response occurred in only ~5% of crystals and was not accompanied by a phase transition. Note that only a couple examples of organic crystalline compounds have been studied with mechanical responses that are not associated with crystalline phase transitions.²⁸⁸ However, little is known about the phenomena from a mechanistic viewpoint.

6.1.2 Discovery of an Organic Material with a Thermosalient Effect at Low Temperature.

In 2022, our laboratory reported synthetic methodologies for pentafluorosulfanylation and tetrafluoro(aryl)sulfanylation of [1.1.1]propellane²⁸⁹ (sparking our broader interest in strain-release functionalization as a tactic for SF₅- and aryl-SF₄ group installation on organic molecules²⁹⁰). At the time, we were interested in the structural consequences of SF₅ and aryl-SF₄ groups on transannular bicyclopentane (BCP) C···C distances; thus, there was a significant X-ray crystallography component to the study. Upon attempting to obtain single-crystal X-ray

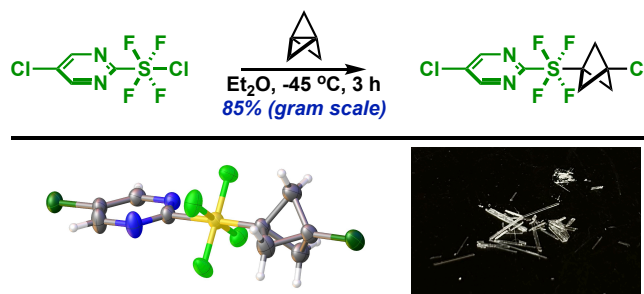
diffraction (SC-XRD) data on compound **1**, to our surprise, *we observed the crystal shatter into pieces and fly off the cryo-loop when cooling below 193 K*. This result was not disclosed at the time. While both -SF₄- and BCP moieties, independently, have appeared in liquid crystals,^{291,292} to our knowledge, this is the first observation of single crystals of an organic compound with these structural features (and arguably more generally) undergoing such an extreme mechanical response upon cooling.

Herein, we disclose the details of this peculiar finding and report an extensive study that sheds light on the origin of the observed low-temperature thermosalient effect of compound **1** (Figure 6.1, *bottom panel*).

6.2 Results and Discussion.

6.2.1 Synthesis & Initial Optical Cooling Investigations.

Previously, we developed a method to synthesize compound **1** in centigram quantities through formal addition of the corresponding tetrafluoro(aryl)-λ⁶-sulfanyl chloride (accessed *via* mild oxidative fluorination of a diaryl disulfide^{293,294}) across [1.1.1]propellane in Et₂O at 228 K. To facilitate the study at hand, we determined that the reaction can also be performed on a gram scale without detriment to the isolated yield (Scheme 6.1, *top panel*). Following synthesis and isolation *via* column chromatography, colorless rod-like crystals of varying length and width were obtained by diffusing *n*-pentane into a solution of purified **1** in EtOAc (Scheme 6.1, *bottom panel*). In contrast to its precursor, compound **1** can be crystallized/handled without inert atmosphere.



Scheme 6.1. (*top*) Scaled up synthesis of **1**. (*bottom left*) Structure of **1** determined by SC-XRD at 200 K (displacement ellipsoids depicted at 50% probability). (*bottom right*) Image of crystals of **1**.

Upon dipping individual crystals of **1** in liquid N₂, we found that the crystals forcefully disintegrated, effectively turning to dust. Subsequently, the phenomenon was more clearly captured through high-speed video recording *in situ* and in real time (see Movie S1 in the SI of the associated publication). The recording was acquired at a frame rate of 500 fps, while the crystals in an NMR tube were cooled rapidly by a stream of cold N₂ gas from liquid N₂ evaporation. During these experiments, we observed the crystals shatter and jump upon cooling, often releasing sufficient energy to propel a significant amount of material upward (Figure 6.2). The crystals continue to shatter upon cooling into progressively smaller pieces until the mechanical response ultimately ceases.

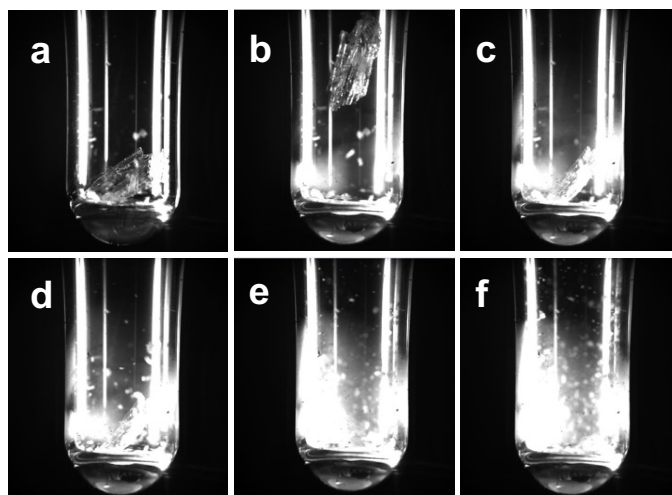


Figure 6.2. Snapshots from Movie S1, generated by recording images of a crystal of **1** during cooling (*temperature decreasing with time from a–f*). Six characteristic moments are displayed: (a) $t = 0.00$ s, the crystal at room temperature; (b) $t = 2.95$ s, part of the crystal was propelled upward upon cooling; (c) $t = 3.56$ s, after that part of the crystal had landed and before the next detonation event; (d) $t = 3.58$ s, the remaining crystal started cracking and smaller crystal pieces were propelled upward; (e) $t = 5.51$ s, further detonation and propelling of fragments; and (f) $t = 6.37$ s, further disintegration, after which only minor detonation events were observed. Note that the real experiment time was 15 s and recorded at 500 fps; Movie S1 is played at 30 fps.

Subsequently, using an Instec optical cooling stage, crystals were cooled to destruction with the entire process recorded at 15 fps; Figure 6.3 shows some illustrative snapshots. This approach also enabled more careful monitoring of temperature throughout the process. Here, the crystals displayed some noticeable changes, such as darkening in discrete areas that may be associated with optical density changes²⁹⁵ (blue arrow) or deposition of material from nearby destroyed crystals (Figure 6.3). The crystal shown in Figure 3 exhibits cracking and disintegration at a grain boundary upon cooling to 192 K (red arrow), followed by complete destruction of the crystal at 182 K. A video of the cooling process followed by rapid destruction of the crystal is found in the SI (Movie S2 of the associated publication).

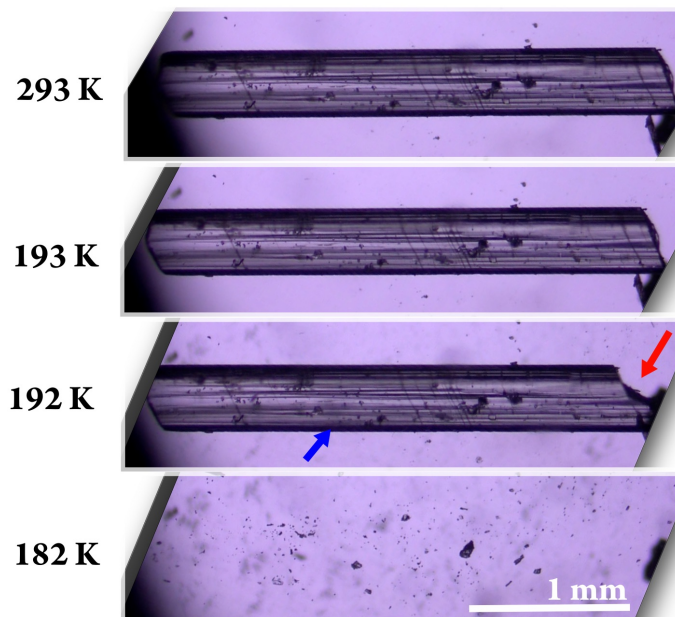


Figure 6.3. Optical microscopy image of a single crystal of **1** cooled to destruction. The blue arrow indicates slight darkening of the crystal. The red arrow indicates crystal break at a grain boundary.

Throughout the initial stages of this study, several experiments were performed on a cold stage to assess potential relationships between cooling rate, crystal length, thickness, or quality and the temperature at which the response first occurs. At this juncture, we have not observed any clear or direct correlations. However, we have found that initial shattering of **1** tends to occur within the range of 163–193 K; we have also observed the response down to at least 110 K, in some cases. Additionally, we found that some crystals of **1** did not elicit a response at all during thermocycles. These can tentatively be distinguished under the microscope by a lack of the appearance of a large domain microstructure and larger crystal grains. Preliminary SEM images and associated discussion are provided in Section 6.5.19.

Note that we also briefly examined the behavior of the crystals at higher temperatures. Upon heating the crystals in a melting point apparatus, we observed a melting point of 491 K. Immediately after melting, the resulting liquid began to bubble, and the compound underwent rapid decomposition. No mechanical response was observed.

6.2.2 Differential Scanning Calorimetry (DSC) and Single-Crystal X-ray Diffraction (SC-XRD) Studies.

In other instances, the most common reasons why crystals tend to exhibit a mechanical response when exposed to heat or light are either 1) a chemical transformation occurs or 2) more frequently, a crystalline-crystalline or crystalline-amorphous phase transition occurs.²⁹⁶ Regarding the origin of the low-temperature thermosalient effect in **1**, a bulk chemical transformation can be quickly ruled out, as there is no evident change in the ¹⁹F and ¹H NMR spectra before and after exposure of the sample to liquid N₂. The shattered crystals can also be recrystallized and will exhibit the response again upon cooling. Next, we analyzed the crystalline sample using differential scanning calorimetry (DSC) to probe for possible phase transitions. Interestingly, upon cycling the crystals between room temperature and 123 K at a rate of 5 K per minute, we found no discernible evidence that the response in **1** can be attributed solely to a crystalline-crystalline phase transition (see section 6.5 for details). This prompted us to investigate the phenomenon in more detail through SC-XRD experiments. Note that we obtained SC-XRD data for several samples that did exhibit a low-temperature thermosalient effect, as well as some that did not. For clarity, the data are summarized in detail in Section 6.5.13.

First, we analyzed an X-ray crystal structure of **1** obtained at 200 K – well above the temperature at which the response for this sample occurred. The compound crystallizes with the centrosymmetric monoclinic space group $P2_1/n$, and the bicyclopentane ring is rotationally disordered over two positions. Additionally, there are several notable short contacts in the packing diagram involving the fluorine atoms of the -SF₄- moiety. For instance, S–F $\cdots$ C distances (Σr_{vdW} = 3.17 Å) involving the pyrimidyl ring were observed that range from approximately 3.12–3.16

Å; S–F $\cdots$ H contacts ($\Sigma r_{vdW} = 2.67$ Å) were also observed involving one C–H bond of the pyrimidyl ring (approximately 2.6 Å) and two C–H bonds of the bicyclopentane ring (approximately 2.6 Å; hydrogen atoms were refined with idealized X–H distances using a riding model²⁹⁷). Consistent with trends in compounds bearing -SF₄- groups (distinct from trends associated with SF₅ groups), no close F $\cdots$ F contacts were observed.²⁹⁸ It is also important to note that no solvent molecule is present in the unit cell as determined by SC-XRD.

After a significant effort, we then managed to obtain X-ray data on a remaining crystal shard *after detonation and below the temperature at which the thermosalient effect occurred*. The structures of **1** at 200 K (above the initial response temperature range) and 100 K (below the initial response temperature range) display only subtle differences. Using a series of SC-XRD data collected from 200–100 K, we observed that the lengths of the short contacts mentioned above decreased slightly upon cooling (see Supporting Information for more details). For instance, the average S–F $\cdots$ C distances decreased from 3.15 Å at 200 K to 3.12 Å at 100 K. All other contacts also decreased in length upon cooling, albeit to a lesser extent.

For a meaningful comparison, we managed to obtain variable-temperature SC-XRD data for a crystal of **1** *that did not exhibit a thermosalient effect*. While recording camera footage to capture the detonation (Movies S3 and S4), we identified a crystalline sample that remained intact after two thermocycles. This sample did not display any changes (apart from general reduction of anisotropic displacement parameters) by SC-XRD after being cooled from room temperature to 200 K, 170 K, 120 K, or 100 K, suggesting that the mechanical response may be associated with a crystal microstructure property as opposed to a bulk material property. Similar observations have been made, e.g., in context of crystal thermal history and phase transitions.²⁹⁹ Additional support for this hypothesis is provided by our observation that responsive crystals of **1** displayed

very weak ring-shaped diffuse scattering, while the non-responsive crystal did not, even though both show the same rotational disorder in the bicyclopentane. This indicates the presence of an additional longer-range disorder not accounted for in the model.³⁰⁰

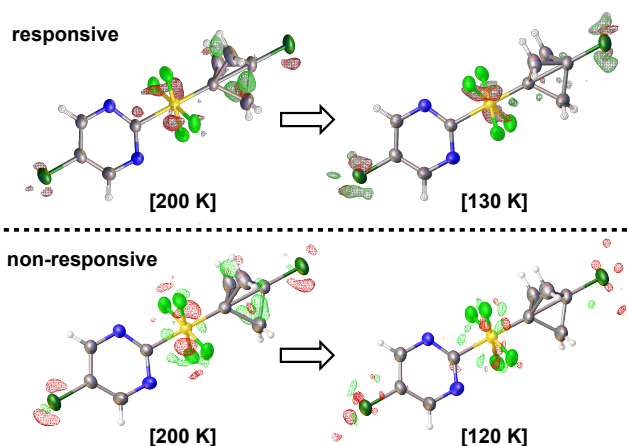


Figure 6.4. Bicyclopentane rotational disorder decreases upon cooling for both mechanically responsive and non-responsive crystals of **1** (difference electron density maps before modeling of the disorder shown, green = positive, red = negative; responsive sample (*top*), max./min. peak (200 K) = 0.2/-0.4 e⁻/Å³, max./min. peak (130 K, post-detonation) = 0.5/-0.6 e⁻/Å³, and non-responsive sample (*bottom*); max./min. peak (200 K) = 0.3/-0.5 e⁻/Å³, max./min. peak (120 K) = 0.6/-0.8 e⁻/Å³).

We then performed thermal expansion coefficient analyses for both a non-responsive and a responsive crystal of **1** over a similar temperature range using PASCAL software.³⁰¹ For the latter case, crystal remains were trapped directly on the mounting pin after detonation, and data pre- and post-detonation from the same specimen was used. We found that **1** exhibits significant anisotropic lattice dimension changes in both responsive and non-responsive crystals, with the *a* and *c* axes contracting and the *b* axis expanding marginally. The full analyses can be found in Section 6.5. This type of anisotropic behavior is characteristic of other reported mechanically responsive crystals^{287,302} and does not necessarily delineate the root cause of the mechanical response, but it may be associated with increasing strain in the crystal.

Another noteworthy observation in the variable-temperature SC-XRD data is that the rotational disorder about the bicyclopentane unit gradually disappears upon cooling. This effect

was observed for both responsive and non-responsive samples. For illustration, we generated representative electron difference maps for both samples in Figure 6.4. For the responsive sample, the relative refined occupancy of the minor rotamer is 11% at 200 K and is reduced to 9% at 170 K, 3% at 120 K, and 1% at 100 K. For the non-responsive sample, the relative refined occupancy is 10% at 200 K, 7% at 170 K, 4% at 120 K, and 4% at 100 K. Upon warming back to 170 K, a higher occupancy of the rotamer is once again observed in both cases, indicating some degree of reversibility. Moreover, upon careful inspection, it seems that the main orientation of the bicyclopentane (BCP) unit rotates slightly (approximately 3°) to account for the loss of the minor rotamer, and the -SF₄- unit follows.

6.2.3 Powder X-ray Diffraction (PXRD) Studies.

At this juncture, SC-XRD data alone could not fully account for the extreme mechanical response observed in **1**. Accordingly, we turned our attention to PXRD to investigate whether other microcrystalline components are present before or after cooling **1** past the point of detonation. Crystals of **1** were ground into a powder and transferred to a capillary tube, and a powder diffractogram was collected at 300 K on a single-crystal diffractometer with a rotating Cu anode. At 300 K, the produced diffractogram matched the simulated pattern very well with the notable absence of any observable microcrystalline components. Then, diffractograms were recorded at 200 K, 150 K, and 100 K using the maximum achievable cooling rate.

To our surprise, at 150 K, a new set of reflections emerged (Figure 6.5a), indicating partial transition to another phase. This transformation appears to be reversible, as evidenced by the first reflection of the new phase, which gained relative intensity again after heating back from 100 K to 300 K. Note that especially the first peaks of both species appear to be correlated, i.e., the new species grows while the known species shrinks and *vice versa*. The cooling/heating cycle was

repeated three more times, until no further change in the diffractograms could be detected. As already suspected by the results from other methods and visual observation, the process seems to occur in a wide temperature range and, notably, only part of the bulk is converted in the first cool-down cycle.

We surmised the known structure of **1** in space group $P2_1/n$ and this newly found transitioned structure must be closely related due to the strong similarity of their powder patterns. For further investigation, the capillary was cracked open, and crystals were extracted to attempt single-crystal structure determination. Throughout these attempts, all specimen that appeared remotely crystalline at first glance were identified as the $P2_1/n$ structure. Ultimately, a tiny, opaque, and very weakly diffracting fragment was found in a cracked capillary after cycling to 100 K that proved sufficient for structure determination. The structure, although of relatively low quality due to the growth conditions (i.e., twinned, $R1 = 8.6\%$, enlarged ellipsoids), solves and refines, and is sufficient to unambiguously describe this new phase. The structure crystallizes in space group $C2/c$ (Figure 6.5b). Its metrics are closely related to the previously known phase, with $a' \approx 2 \cdot c$, $b' \approx a$ and $c' \approx b$ (a, b, c : $P2_1/n$ phase and a', b', c' : $C2/c$ phase, respectively). No disorder was found in contrast to the $P2_1/n$ phase, but this could be due to the low structure quality. The structure was later reproduced independently (and an untwinned specimen could be measured) with crystals grown from a melt (see Section 6.5 for more details).

Note that all tested crystals of the $C2/c$ phase were only *metastable* and decayed relatively quickly during measurement (interestingly, both at 100 K and 300 K). We also observed that, over time, a large fraction of $C2/c$ phase crystals convert back to the $P2_1/n$ phase. The wide temperature window, the fact that only a small fraction of bulk material undergoes the phase transition under the applied cooling rates, and the reversibility explain why we never observed this crystalline-

crystalline phase transition during our SC-XRD and DSC studies, as discussed in the previous section.

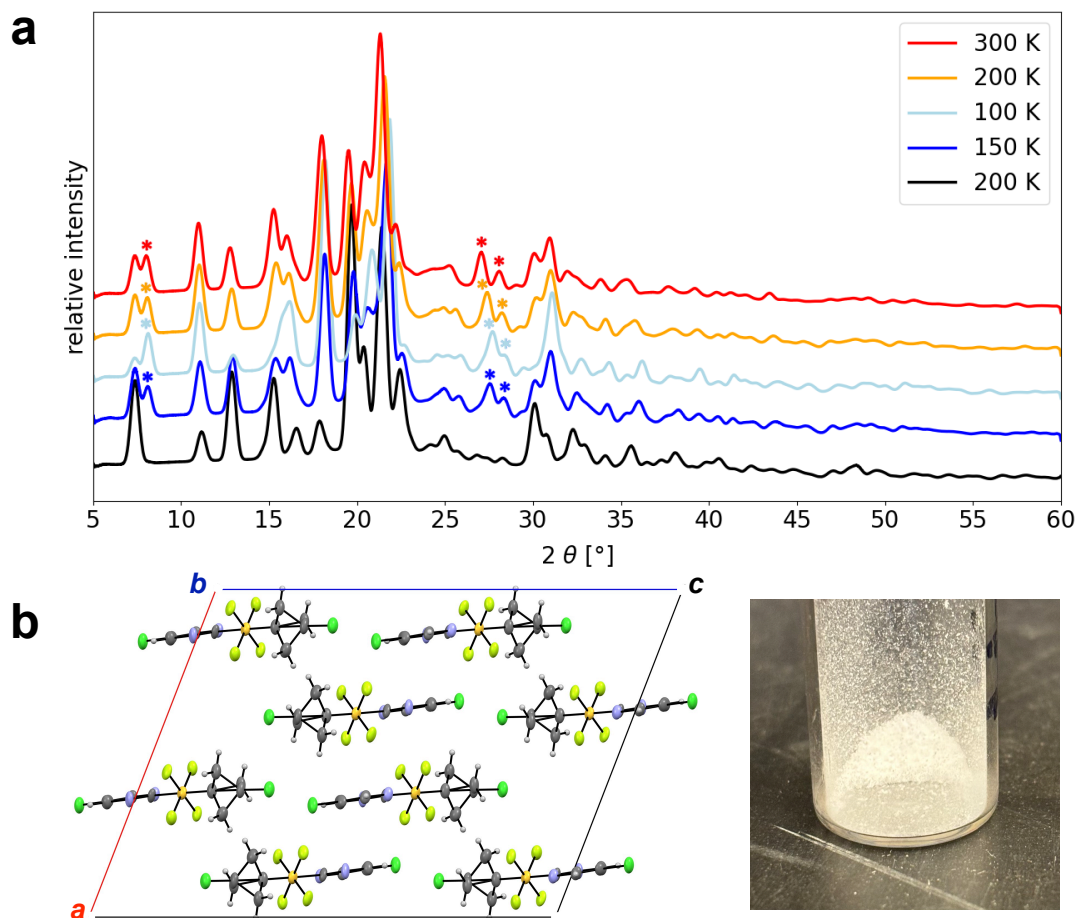


Figure 6.5. (a) Phase transition of **1** observed by PXRD. Patterns are presented in ascending order of the thermal history of **1**. The first pattern (pre-detonation; black) shows only the $P2_1/n$ phase, while the rest (post-detonation) indicate the presence of both the $P2_1/n$ phase and a new $C2/c$ phase (asterisks mark peaks that are unique to the new phase). (b) Cell packing and physical appearance of the $C2/c$ polymorph of **1** in a 7-mL scintillation vial.

Despite the discovery of this $C2/c$ phase that can be observed following the detonation of **1**, it was still not clear to us whether this phase transition alone was the root cause of the mechanical response. For instance, why would the $C2/c$ phase form only to convert back to the preferred $P2_1/n$ phase at both low and high temperatures? Is it possible this phase transition is an *effect* rather than a *cause*, or else coupled to another event?

We then examined **1** using additional spectroscopic methods, i.e., Raman and Brillouin scattering to obtain more insight. Raman is generally sensitive to molecular features (e.g., bond strength and molecular motion),³⁰³ whereas Brillouin is sensitive to, e.g., long-range/lattice effects and elasticity.³⁰⁴

6.2.4 Variable-Temperature Raman Spectroscopy.

Accordingly, a crystal of **1** was mounted on a cooling stage to facilitate variable-temperature Raman experiments. Raman scattering collected from room temperature (rt) to temperatures above the point at which the response occurred showed virtually no change (Figure 6.6a). However, just after the crystal shattered at ~193 K, several new sharp peaks appeared (Figure 6.6a; asterisks) in both low and high frequency ranges, in addition to those observed at higher temperatures. While the low frequency modes could not be definitively assigned, the new peaks between 300-450 cm⁻¹ observed at 192 K fall within the expected range for bending, wagging, and twisting modes associated with the –SF₄– and C–S–C moieties.³⁰⁵ In the higher frequency region, new peaks also show up at 192 K in the 2850-3100 cm⁻¹ range that correspond to bicyclopentane and chloropyrimidine C–H stretching frequencies (Figure 6.6a; inset).³⁰⁶ Changes in C–H stretching frequencies associated with the bicyclopentane ring, in particular, are likely also associated with the observed decrease in disorder by SC-XRD upon cooling (Figure 6.4).

During a separate set of experiments, we serendipitously managed to collect Raman scattering on a crystal that detonated *during the measurement*, allowing us to examine a spectrum extremely close to the point of detonation. We provide snapshots of measurements that were captured at room temperature (Figure 6.6b; black), during the destruction of the crystal – which occurred mid-measurement at 123 K while collecting spectra in the 2500-4000 cm⁻¹ range (Figure

6b; blue), from shards after the crystal shattered (Figure 6.6b; red), and finally after the crystal shard was returned to room temperature (Figure 6.6b; black). Both spectra at 123 K – before and after crystal detonation – are distinct from each other, as well as the rt data sets. For instance, broad Raman peaks become sharp during crystal transformation (Figure 6.6b; blue), which suggest that part of the sample undergoes some type of phase change or else may be associated with a release of strain as the crystal is destroyed.³⁰⁷ After crystal destruction, the same sharp Raman peaks generally resolve to broad shoulders with more asymmetry (Figure 6b; red); however, there remain subtle differences in the spectrum at 123 K relative to either of the rt spectra. Upon warming the crystal shard back to rt, the spectral features once again resemble those of the rt data set prior to cooling.

Over several different VT-Raman experiments (Figure 6.6c), we noted that the wavenumber shifts of the majority of vibrational stretches – beyond the new peaks mentioned above – remain unaffected by temperature. Additionally, low temperature measurements show there is not one discrete temperature for the thermosalient effect, nor does the response occur immediately once a certain temperature is reached. It can take a few seconds to minutes at temperature before the crystal responds.

Overall, the Raman data 1) support NMR data that indicate the bulk material does not undergo a chemical transformation and 2) suggest that either a phase transition occurs (consistent with our PXRD data) and/or that crystal strain is altered. However, if there is a minor component embedded within the crystals of **1** that was not detectable by X-ray diffraction,³⁰⁸ it is either structurally similar to **1** or else present in too small of an amount to clearly identify in the Raman spectra. Thus, we turned to Brillouin spectroscopy to measure crystal stiffness and response more definitively and whether it has anything to do with the observed thermosalient effect.

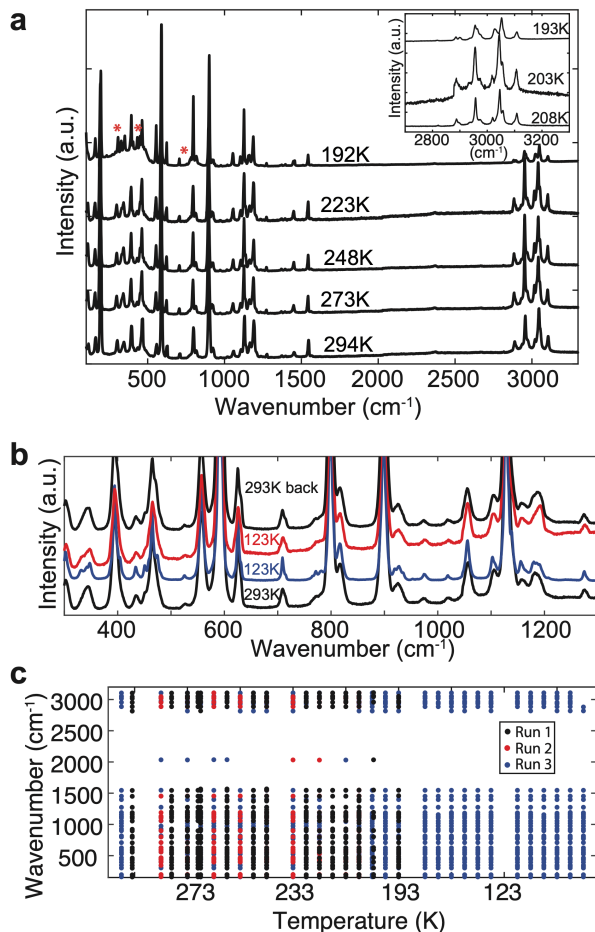


Figure 6.6. (a) Raman spectra with decreasing temperature; asterisks identify new sharp peaks. (b) Raman spectra were acquired at room temperature, at the moment of disintegration (123 K; blue), after disintegration (123 K; red), and with a return to room temperature, showing sharpening of Raman modes and thus a possible transition or release of strain at/below the response temperature. (c) Raman spectra across three runs show almost no increase or decrease in primary Raman mode frequencies with temperature.

6.2.5 Variable-Temperature Brillouin Spectroscopy.

Brillouin scattering spectra of **1** were collected in a 180° backscattering geometry down a zone axis (Figure 6.7a). At room temperature, the spectrum shows two distinct longitudinal (L) acoustic modes – at 6.3 and 15.3 GHz. Typically, Brillouin scattering spectra display two transverse and one longitudinal mode. In a backscattering geometry, Brillouin scattering spectra display only longitudinal acoustic modes, as transverse modes are forbidden by symmetry.³⁰⁹ To

verify our mode assignments, we placed the crystal under crossed or same polarization with H polarization from the raised laser beam on the input and V or H on the output.

Under crossed polarizers, longitudinal modes should vanish. Indeed, both modes in **1** showed longitudinal character. Contextually, this indicates that there are two separate material compositions or two separate phases within the crystal, as spectra were collected down a crystallographic direction (Figure 6.7b). That is, the crystal has a possible impurity phase.

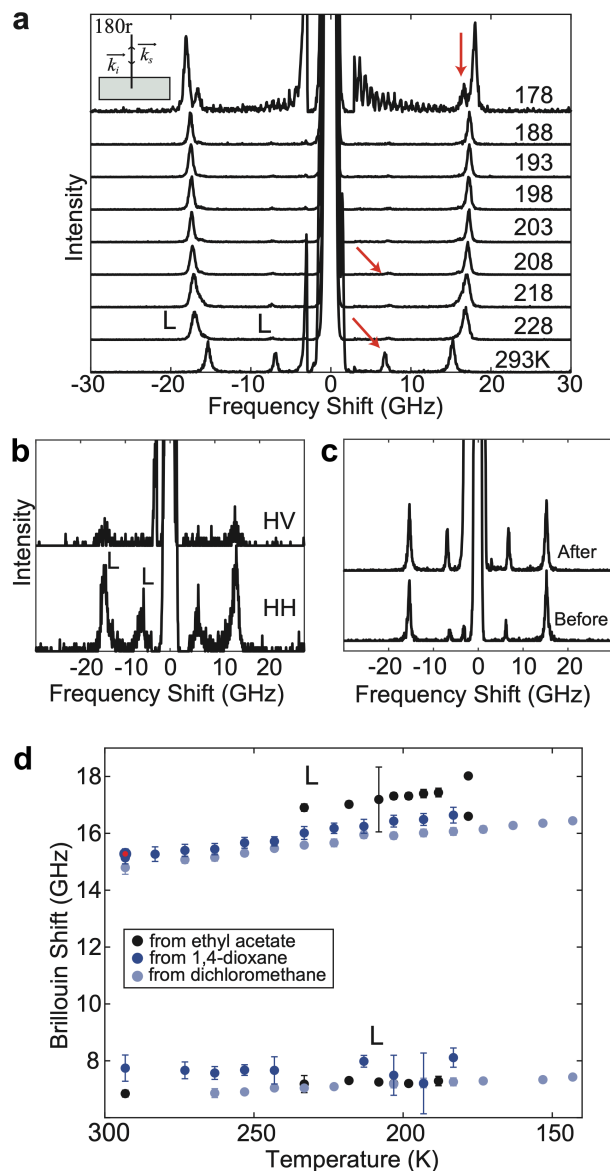


Figure 6.7. (a) Brillouin spectra with decreasing temperature show two longitudinal acoustic modes with one that vanishes after the explosion of the crystal or shifts to higher frequencies. The shutter cutoff edge is seen around -3 GHz. (b) Modes were identified as longitudinal (L) using polarization analysis. (c) The Brillouin lower frequency shift returns after crystallization. (d) VT Brillouin frequency shifts of crystals grown from different solvents.

The frequency shift at 15.3 GHz falls within an expected range for an organic crystalline material, whereas the frequency shift at 6.3 GHz would be more typical of a liquid, amorphous, or gel material (i.e., more disordered).³¹⁰ Interestingly, upon cooling below the point of the response

(for this sample, initial crystal detonation occurred somewhere in the range of 178–188 K), we observed the higher frequency mode shift slightly to 18.1 GHz and the lower frequency mode shift dramatically to 16.6 GHz. The latter instance is consistent with the notion of a disorder-order phase transition. Upon warming back up to room temperature, the lower frequency mode returns once more, indicating this putative phase transition or large change in strain state has some degree of reversibility (Figure 6.7c).

Beyond the low frequency mode being inconsistent with a crystalline material, its presence prior to the first cool-down cycle and mechanical response also militates against the notion that this is associated with the metastable $C2/c$ phase observed *via* PXRD. This was later confirmed by measuring Brillouin scattering on a sample that was subjected to multiple cool-down cycles, which displayed a new high frequency mode we can likely attribute to the $C2/c$ phase, in addition to the two modes discussed above (see Section 6.5 for details).

It is plausible that an amorphous (or strongly disordered) phase of **1** or a minor impurity is interspersed throughout the crystal or on its surface (which would not be observed by X-ray diffraction), and that the transition observed Brillouin scattering is somehow connected to the $P2_1/n$ to $C2/c$ phase transition discovered *via* PXRD. To ascertain whether the disordered component is not, e.g., layers of trapped crystallization solvent, we compared VT Brillouin data of 1) crystals grown by vapor diffusion of *n*-pentane into ethyl acetate (EtOAc; m.p. ~190 K), 2) crystals grown by slow evaporation of dichloromethane (DCM; m.p. ~177 K), and 3) crystals grown by slow evaporation of 1,4-dioxane (m.p. ~285 K).

We found that the higher frequency mode shifts slightly if **1** is crystallized using a different solvent and technique, but the lower frequency mode remains virtually the same in all three cases. That is, the frequencies of the two longitudinal acoustic modes at rt of **1** crystallized from EtOAc/*n*-

pentane are 15.3 ± 0.1 GHz and 6.3 ± 0.1 GHz, compared to 14.8 ± 0.1 GHz and 6.3 ± 0.1 GHz when **1** is crystallized from dichloromethane and 15.1 ± 0.2 GHz and 7.7 ± 0.5 GHz when **1** is crystallized from 1,4-dioxane (Figure 6.7d). The frequency shift in the higher longitudinal modes suggest that the stiffness of the crystalline phase is affected by crystallization solvent/technique; however, the same low-frequency response appears to be present in all three cases, and the thermosalient effect occurs near the same temperature range regardless of crystallization technique and solvent melting points. This definitively rules out “freezing solvent” trapped within the crystal as the root cause for crystal detonation.

6.2.6 Discovery of a Relevant “Sulfone” Impurity.

An important clue as to a possible identity for the impurity phase was discovered serendipitously during an attempt to crystallize the *C2/c* phase from melted crystals of **1**. That is, we managed to obtain an X-ray crystal structure of the corresponding sulfone (**2**), which represents a hydrolysis product of **1** that is anticipated to form in minor amounts, often during synthesis or isolation (Figure 6.8).

Subsequently, we independently synthesized and characterized compound **2**. This impurity was not identified in crystals of **1** until the late stages of our study for several reasons. For one, both ^1H NMR signals and Raman peaks of **1** and **2** exhibit significant overlap. Moreover, as we previously reported, this compound class poses challenges with obtaining reliable mass spectrometry data.²⁸⁹ Additionally, a comparison of the simulated powder patterns of all three structures shows that the sulfone would be almost impossible to detect by PXRD due to overlap with either of the other species, especially if it occurs in very small quantities (see Section 6.5 for more details).

The difference between **1** and **2** is that four S–F bonds have been effectively replaced with two S–O bonds. SEM-Energy Dispersive X-ray spectroscopy (EDX) shows that, while oxygen atoms are detected on a crystal of **1**, they appear to be confined to the surface (see Section 6.5 for details). Thus, if **2** is indeed present in crystals of **1**, it is predominantly located on the surface. This would be consistent with the notion that minor amount of **2** can form over time *via* chemical decomposition (formal hydrolysis) of **1**.

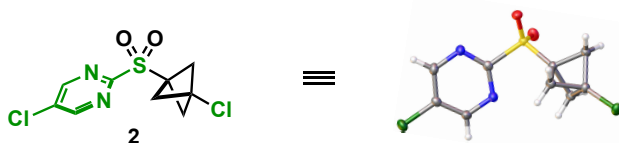


Figure 6.8. (*left*) An arylsulfonyl bicyclopentane impurity (**2**) that can form during synthesis/isolation of **1**. (*right*) Structure of **2** determined by SC-XRD (displacement ellipsoids depicted at 50% probability).

The next question is whether the presence of **2** as a minor impurity in crystals of **1** has any relevance in relation to the thermosalient effect. Brillouin scattering measurements on a single crystal of **2** showed no behavior akin to that observed for crystals of **1**. However, Brillouin scattering on an amorphous sample of **2** showed the presence of two longitudinal modes with one at a high frequency and one at a low frequency, similar to what was observed in crystals of **1**. Interestingly, the low frequency mode in the amorphous sample of **2** also disappeared at low temperature (193 K), but no mechanical response was observed. While not necessarily conclusive, this could suggest that if a minor impurity of **2** in crystals of **1** is in some way associated with crystal detonation, its behavior at low temperature would have to be coupled to another event to account for the mechanical response.

6.2.7 Proposed Mechanism.

The unit cell of **2** (*I2/a*) is strikingly similar to the *C2/c* polymorph of **1** (Table 6.1). The overall similarities of the patterns despite the big differences in metrics between *P2₁/n* and *C2/c*

suggests that an alternate description must exist that makes the structures similar. It also seems very unlikely at this stage that the similarity between **2** and the $C2/c$ polymorph of **1** is strictly coincidence (note that C vs. I centering is a choice, usually based on closeness of the resulting β angle to 90°).

Table 6.1. Comparison of unit cell parameters.

Structure	$a/\text{\AA}$	$b/\text{\AA}$	$c/\text{\AA}$	$\beta/^\circ$
$P2_1/n$ (1)	6.095	24.024	8.484	101.61
$C2/c$ (1)	17.400	6.253	23.301	110.54
$I2/a$ (2)	22.762	6.053	17.086	105.26

At first glance, the $P2_1/n$ and $C2/c$ phases of **1** appear unrelated, but closer examination reveals that they can be overlaid when taking into account the apparent metrics relationship. As mentioned above, the metrics (but not the cell orientations) are similar with $a' \approx 2^*c$, $b' \approx a$ and $c' \approx b$ (a, b, c : $P2_1/n$ and a', b', c' : $C2/c$ phase, respectively). However, the $P2_1/n$ structure can also be transformed into a more similar setting in space group $P2_1$ ($Z' = 4$) after applying the resulting matrix (0 0 2 1 0 0 0 1 0) derived from the apparent metrics relationship. In this setting, the angle relevant for the comparison would be $\alpha = 90^\circ$ instead of β , leading to an angular difference of about 20° between the phases (cf. $C2/c$: $\beta = 110.5^\circ$, $P2_1/n$: $\beta = 101.6^\circ$), which would result in significant local strain buildup (and thus, crystal detonation). The transformed structure solves and refines, albeit suffering from strong correlation, unsurprisingly.

The significant distortions between the metrics and drastic molecular motion must be associated with a steep kinetic barrier; this would explain the observed large temperature range over which the mechanical response occurs, the fact that only a small fraction of **1** converts at any given point in a cool-down cycle, why a phase transition was undetectable within the limits of our DSC instrument, and why the response (crystal “detonation”) appears so extreme.

Notably, the sulfone β angle of 105.3° falls between the relevant angles of the $P2_1/n$ (converted to a comparable setting) and $C2/c$ structures of **1**, and in the packing overlay the centers of gravity of the sulfone molecules are located between the corresponding positions of the interchanging phases. This suggests that *the sulfone may be an impurity in 1 that acts as a catalyst for a local crystalline-crystalline phase transition, and that crystals which do not detonate contain no or too little sulfone impurity.*

Finally, a slip plane search was carried out (using the CCDC Mercury program).³¹¹ This analysis can identify planes exhibiting very weak interplanar interactions. Several such planes were identified in the original $P2_1/n$ structure, but notably one plane appears in all three structures (i.e., including the sulfone). This plane is parallel to a and b in the $P2_1/n$ structure. Remarkably, its orientation matches with the first and major fault line visually observed when a crystal of **1** was recorded *pre* and *post* detonation. Additionally, this plane would be severely affected by the angle changes discussed above. It passes between the molecules such that a tear along this plane would impact any $\text{H}\cdots\text{F}$, $\text{Cl}\cdots\text{F}$, $\text{Cl}\cdots\text{O}$, or $\text{F}\cdots\text{F}$ contacts, as well as any rotational disorder in the bicyclopentane group.

6.3 Conclusion.

The origin of a surprising low-temperature thermosalient effect of an organic material, i.e., “shattering” or “self-destruction” of crystals of **1** upon cooling below ~ 193 K, was studied in detail *via* NMR, DSC, SC-XRD, PXRD, microscopy, Raman, and Brillouin. The effect cannot be attributed to a crystalline-crystalline phase transition of the entire material, distinguishing the mechanism from that of other mechanically responsive crystals reported in the literature. Our data led us to propose a plausible mechanism whereby 1) an impurity phase undergoes a disorder-order phase transition at low temperature, 2) the behavior of the impurity phase catalyzes a local

crystalline-crystalline ($P2_1/n$ to $C2/c$) phase transition in **1**, 3) the partial $P2_1/n$ to $C2/c$ phase transition results in significant strain buildup between the two phases (i.e., with an angular difference of about 20° between the unit cells), and 4) to ultimately relieve this strain, the crystal shatters and blows apart. The fact that the $C2/c$ phase of **1** converts back to the $P2_1/n$ phase over time at both low and high temperatures after crystal detonation indicates that the $C2/c$ phase is not a thermodynamic preference; it also suggests that the crystalline-crystalline phase transition may need to be coupled to another phenomenon (e.g., the observed disorder-order phase transition of another material phase) to overcome a kinetic barrier. Brillouin, XRD, and SEM-EDX experiments suggest that sulfone **2** – an anticipated hydrolysis product of **1** – is likely the identity of the material that undergoes the disorder-order phase transition; the striking similarity between the unit cells of a crystalline sample of **2** ($I2/a$) and the $C2/c$ phase of **1** also support the notion that a disorder-order transition in **2** could indeed catalyze the $P2_1/n$ to $C2/c$ phase transition in **1**. Additional investigations on this phenomenon are ongoing in our laboratory.

6.4 Author Contributions.

A.N.R. and Y.K. performed synthetic work and data analysis. A.N.R. and Y.K. synthesized compound **1** and grew the single crystals used in the study. Y.K. synthesized compound **2**. S.K.C. collected high-speed camera footage and obtained preliminary SEM images. O.F. synthesized the corresponding disulfide starting materials. C.C. collected XPS data. N.T. collected SC-XRD and PXRD data; Y.K. collected SC-XRD data for an independently synthesized compound **2**. K.J.K. collected Raman, Brillouin, and SEM-EDX data. G.-y.L., N.T., K.J.K. and C.R.P. conceptualized and supervised the project and acquired funding. The manuscript was written and edited with contributions from all authors.

6.5 Experimental.

6.5.1 General Experimental Information.

6.5.2 Synthesis.

Unless otherwise stated, all reactions were carried out strictly under anhydrous conditions and under N₂ or Ar atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred *via* syringe using standard Schlenk techniques. Reaction solvents were obtained from a solvent purification system or else were dried over molecular sieves directly before use. Spray-dried KF was always weighed out under glovebox atmosphere. All NMR data were collected on either 300, 400, or 600 MHz Bruker spectrometer. For ¹⁹F NMR yield determination, α,α,α -trifluorotoluene (or fluorobenzene) in CDCl₃ was introduced after each reaction as an internal standard, and the d1 relaxation delay was increased to 30 s during data collection. The ¹H, ¹³C, and ¹⁹F NMR chemical shifts are given in parts per million (δ) and calibrated to either residual solvent signal (¹H and ¹³C), α,α,α -trifluorotoluene (δ = -62.61 ppm in CDCl₃).³¹² NMR data are reported in the following fashion: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dt = doublet of triplets, dd = doublet of doublets, m = multiplet), coupling constants (Hz)). Melting points were collected on a Stanford Research Systems MPA120EZ-Melt automated melting point system, starting at 100 °C with a ramp rate of 1 °C/minute. PFA vessels for the isolation of the ArSF₄Cl intermediate were purchased from Savillex. Mass spectrometry experiments were performed on a Bruker timsTOF flex matrix-assisted laser desorption/ionization system. Isotopic distributions were modeled using

Bruker Compass Isotope Pattern software. Data was acquired in negative ion mode using 1,5-diaminonaphthalene. GC-MS and ESI-MS were unsuccessful for compound **1**.

6.5.3 High-Speed Camera Experiments.

Movie S₁ is a time-dependent optical microscopy video captured through a 0.5X objective in conjunction with a 4X eyepiece. The crystal **1** was located at the bottom of the NMR tube undergoing cooling by a stream of cold N₂ gas generated by boiling over liquid N₂. The video recorded the crystal during 15 seconds of cooling (see time stamp in each frame). This video was captured using a high-speed camera (Fastcam Mini AX, Photron Limited, Tokyo, Japan) at a frame rate of 500 fps, and Movie S₁ is rendered at a frame rate of 30 fps to allow clear visualization of the process.

6.5.4 Crystallography.

Single crystal diffraction data were collected on a Rigaku Oxford Diffraction XtaLAB Synergy-S Dualflex kappa diffractometer, equipped with a Dectris Pilatus 300 HPAD detector, using microfocus sealed tube Cu-K α radiation with mirror optics ($\lambda = 1.54178 \text{ \AA}$) and an Oxford Cryosystems Cryostream 800+ sample cryostat *or* a Rigaku Oxford Diffraction XtaLAB Synergy-R kappa diffractometer, equipped with a Rigaku HyPix Arc150 HPAD detector, using microfocus rotating anode Cu-K α radiation with mirror optics ($\lambda = 1.54178 \text{ \AA}$) and an Oxford Cryosystems Cryostream 1000+ sample cryostat. Variable temperature (VT) powder X-ray diffraction (PXRD) experiments were also carried out on the rotating anode instrument. Room temperature PXRD data were collected on a Stoe Stadi P transmission geometry powder diffractometer, equipped with a Dectris Mythen 1K HPAD detector, using monochromated Cu-K α 1 radiation (curved Ge monochromator, $1.54060 \text{ \AA}$). Powder samples were carefully & very lightly ground and flame-sealed in Hilgenberg Mark tubes (Lindemann glass, 0.2 or 0.3 mm).

Single crystal structure data were integrated using CrysAlisPro and corrected for absorption effects using a combination of empirical (ABSPACK) and numerical corrections.^[313] The structures were solved using SHELXT^[314] and refined by full-matrix least-squares analysis (SHELXL),^[315] using the program package OLEX2.^[316] Unless otherwise indicated below, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters (in terms of a riding model). Powder data were processed using CrysAlisPro or WinXPow (Stoe), intentionally not applying any baseline corrections.

CCDC 2365493-2365502 and 2381899-2381905 contain the supplementary crystallographic data for this paper, including structure factors and refinement instructions. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or *via* <https://www.ccdc.cam.ac.uk/structures>.

6.5.5 Raman, Brillouin, and XPS Spectroscopy.

Raman scattering was performed using a homebuilt Raman microscope with a Leica DMI8, 532 nm narrow linewidth, single frequency Coherent Sapphire SF laser, Princeton Instruments SCT320 with an 1800 groove/mm grating, and Princeton Instrument Pixis back-illuminated, back thinned CCD.

Brillouin scattering was collected in a backscattering (180) geometry using a scanning tandem Fabry-Perot Interferometer (TFP-1) with an incident laser of 532 nm from a Coherent Verdi V6. The mirror spacing was 4.5 mm with a 500 nm scan rate to achieve a Free Spectra Range (FSR) of 40 GHz. The focusing objective was provided by a 20 X SLWD Mitutoyo M Plan APO with a NA = 0.28 and f = 200mm. Temperature measurements were performed using an Instec

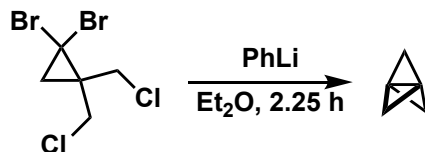
HCS612GXY stage cooled with liquid nitrogen. Videos were recorded on an Amscope T670 series fluorescence microscope with a 4x 0.1 N/A objective and HD1080A camera.

XPS was performed on a Kratos Axis Supra with an Al anode.

6.5.6 Scanning Electron Microscopy (SEM).

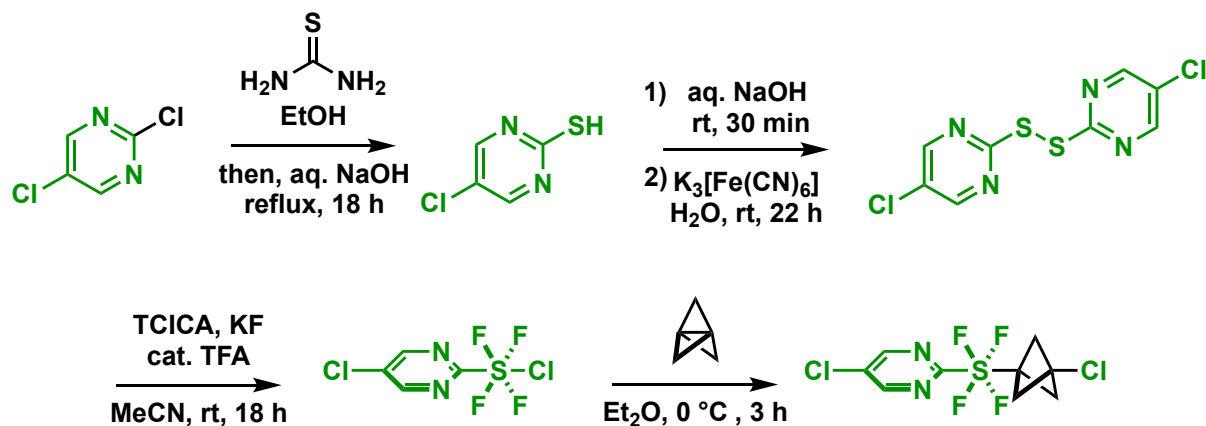
Each crystalline sample was mounted onto an Al-stub using a double-sided carbon conductive tape (Nisshin EM Co., Ltd, 23-9 Araki-cho, Shinjuku-ku, Tokyo, Japan), by picking up the materials using a plastic spatula (VWR International, LLC Radnor, PA, USA) then placed a top of the tape. Gentle force was applied afterwards to assure steady immobilization. Each sample was imaged before and after the cooling process described using a field emission scanning electron microscopy (FE-SEM) (S-4100T, Hitachi High Technologies America, Inc., Pleasanton, CA, USA). The pre-mounted sample was transported to the vacuum chamber of SEM. For imaging, the typical acceleration voltage and emission current were 3 kV and 8-10 μ A, respectively. To test the effect of cooling, the same sample was covered by a cap, then positioned with the bottom of Al-stub in touch with the surface of liquid nitrogen. Typically, the dramatic changes would occur within 1 minute. The sample was then re-imaged by SEM. Samples were coated with 10 nm gold before SEM imaging to remove the charging effect.

6.5.7 Procedure for the Synthesis of [1.1.1]propellane



[1.1.1]Propellane was synthesized according to an adapted literature procedure.³¹⁷ A two-neck 100 mL round bottom flask equipped with a stir bar was dried via heat gun under vacuum and subsequently backfilled with Ar. 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.94 g, 20 mmol, 1.0 equiv.) was added under positive Ar flow, followed by anhydrous Et₂O (20 mL). The solution was cooled to −45 °C in an MeCN/dry ice bath. Phenyllithium (PhLi) (1.8 M in *n*-Bu₂O, 22 mL, 40 mmol, 2.0 equiv.) was added dropwise *via* syringe. Upon addition of PhLi, the reaction mixture turned brown, and a precipitate formed. The reaction was stirred at −45 °C for 2 h and then was transferred to an ice-bath and stirred at 0 °C for an additional two hours. Upon completion of the reaction, a short path condenser connected to a 100 mL two-neck round bottom flask was introduced. The receiving flask was submerged in an acetone/dry-ice bath and kept at −78 °C for the duration of the distillation. A high vacuum was applied for 2 minutes, then static vacuum was maintained until the distillation was completed. A suspension of *n*-Bu₂O (approx. 20 mL) and salts remained in the reaction flask.

6.5.8 Synthesis of 5-chloro-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)tetrafluoro- λ^6 -sulfanyl)-pyrimidine (1).



To an oven-dried 250 mL two-neck round bottom flask equipped with a stir bar and reflux condenser was added 2,5-dichloropyrimidine (10.0 g, 68 mmol, 1.0 equiv) followed by 200 proof EtOH (135 mL). Then, thiourea (10.4 g, 136 mmol, 2.0 equiv.) was added under positive Ar flow and the reaction was stirred at reflux (oil bath temperature was set to 80 °C) for 18 h. Sodium hydroxide (7.3 g, 184 mmol, 2.7 equiv.) was dissolved in H_2O (20 mL) and added to the reaction mixture all at once. The solution was allowed to reflux for an additional 2 h (oil bath temperature was set to 110 °C). Upon reaction completion, EtOH was removed under a stream of air and approximately 40 mL of 1.0 M aqueous HCl was added dropwise until precipitation of the product ceased. The crude mixture was filtered, and the resulting yellow solid was washed with H_2O (50 mL). The desired thiol product was dried *in vacuo* and used without further purification.

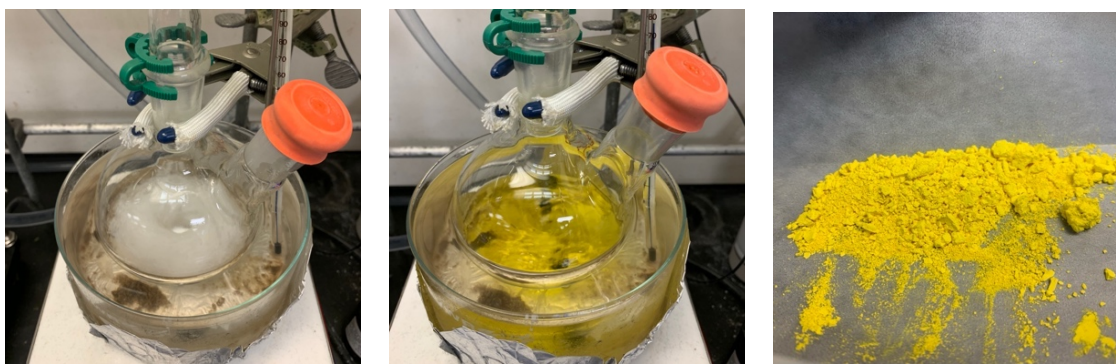


Figure 6.9. **Left:** Reaction mixture after thiourea addition and before heating. **Middle:** Reaction mixture after heating to 80 °C for 15 min. **Right:** Isolated intermediate thiol.

To a 100 mL round bottom flask equipped with a stir bar was added 5-chloropyrimidine-2-thiol (2.7 g, 18.2 mmol, 1.0 equiv.), H₂O (60 mL), NaOH (728 mg, 18.2 mmol, 1.0 equiv.). The reaction mixture was stirred open to air at room temperature (ca. 23 °C) for 30 min. K₃[Fe(CN)₆] (7.2 g, 21.8 mmol, 1.2 equiv.) was added and the solution instantly turned yellow, and a precipitate was formed. The reaction was stirred for a further 18 h at rt (ca. 23 °C) and upon completion was filtered. The resulting off-white solid was washed with H₂O and was then dissolved in CH₂Cl₂, dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was loaded onto a pre-equilibrated column with minimal CH₂Cl₂ and eluted with 3:1 hexanes/EtOAc. The desired disulfide was obtained as a white crystalline powder.



Figure 6.10. **Left:** Crude filtered disulfide. **Right:** Appearance of purified disulfide starting material.

5-Chloro-2-(chlorotetrafluoro- λ^6 -sulfanyl)pyrimidine was prepared several times to procure enough material for a gram-scale synthesis of **1**. In a typical run, an oven-dried 250 mL round bottom flask under glovebox atmosphere was equipped with a large stir bar and charged with TCICA (18.0 equiv.), spray-dried potassium fluoride (32 equiv.), and the disulfide (1.0 equiv.). Anhydrous MeCN (0.15 M) was added followed by TFA (10 mol %) and the reaction was allowed to stir overnight. Upon return, the MeCN layer was filtered into a PFA vessel through a syringe filter and concentrated. The resulting crude material was further extracted with *n*-pentane and concentrated in a PFA vessel to obtain the ArSF₄Cl as a fluffy white solid (typically >95% pure by ¹⁹F and ¹H NMR). Note that the ArSF₄Cl intermediate is metastable and must be synthesized and stored under inert atmosphere. Additionally, the material must be stored in PFA vessels and contact with glass must be avoided to prevent decomposition.

A gram-scale synthesis of 5-chloro-2-(chlorotetrafluoro- λ^6 -sulfanyl)pyrimidine was conducted. To an oven-dried 100 mL round bottom flask equipped with a stir bar was added the corresponding ArSF₄Cl compound (1.2 g, 4.7 mmol) under glovebox atmosphere. The flask was sealed with a Suba-Seal septum and transferred to the bench-top, where it was immediately placed under Ar atmosphere. Then, Et₂O (28 mL) was added, and the solution was cooled to 0 °C in an ice-water bath. [1.1.1]Propellane (12.2 mL, 5.6 mmol) was added *via* syringe and the reaction was stirred at 0 °C for 3 hours. Upon reaction completion, a white precipitate had formed – the solvent was removed *in vacuo* and the desired compound was isolated as a white crystalline solid after column chromatography on silica gel eluting with 9:1 hexanes:EtOAc (1.26 g, 85%). Crystals suitable for SC-XRD were grown by vapor diffusion. The isolated compound was dissolved in a minimum amount of EtOAc, and *n*-pentane was added to outer vessel as the *anti*-solvent.

Additionally, crystals grown *via* solvent evaporation from CH₂Cl₂ displayed a similar destructive phase-transition upon cooling. The final product **1** can be handled outside of the glovebox without special precaution for excluding air or moisture.

R_f: 0.29 (9:1 hexanes:EtOAc), vis: UV (254 nm) ; **m.p.**: 218.0-218.6 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 8.78 (2H, s), 2.73 (6H, s); **¹⁹F (282 MHz, CDCl₃)**: δ = +43.64 (4F, s); **¹³C{¹H} (101 MHz, CDCl₃)**: δ = 171.5-170.5 (quint, ²J_{C-F} = 37.7 Hz), 156.51-156.47 (quint, ³J_{C-F} = 1.6 Hz), 132.8, 67.2-66.5 (quint, ²J_{C-F} = 26.1 Hz), 61.0-60.9 (quint, ³J_{C-F} = 2.7 Hz), 45.3; **ATR-IR**: 753, 737, 690 cm⁻¹; **MS**: Theoretical *m/z* 380.98, measured *m/z* 381.05 for molecular species adducted to solvent. Isotopic distribution of fragmented species consistent with a chlorinated molecular ion.

6.5.9 ^1H NMR Spectra of **1** Before and After Mechanical Response.

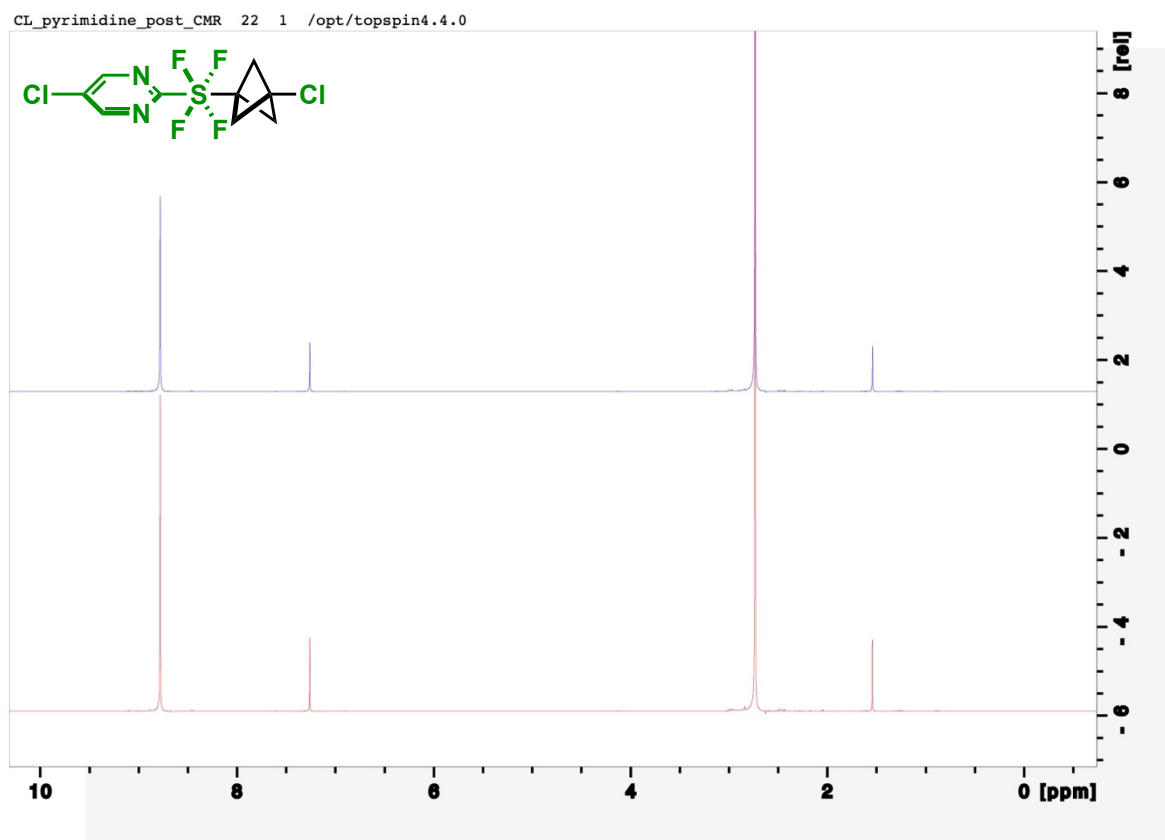
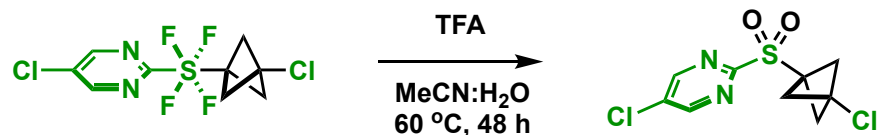


Figure 6.11. Stacked ^1H NMR spectra of crystals of **1** (from the same batch) that were either directly dissolved in CDCl_3 (*top*, blue) or treated with liquid N_2 until thermosaliency was observed and then dissolved in CDCl_3 (*bottom*, red). Both spectra are calibrated to residual CDCl_3 (7.26 ppm) and contain a small amount of water from the deuterated solvent (1.56 ppm).

6.5.10 Synthesis of 5-chloro-2-((3-chlorobicyclo[1.1.1]pentan-1-yl)sulfonyl)pyrimidine (2).



To an 8 mL dram vial equipped with a stir bar was added **1** (0.1 mmol) followed by MeCN and H₂O under an atmosphere of air. Trifluorotoluene (0.2 mmol) was added via syringe and the resulting mixture was stirred vigorously at 60 °C for 48 h. Upon consumption of the starting material, the reaction was quenched with the slow, dropwise addition of sat. NaHCO₃ (until the pH reached 8). The aqueous layer was extracted with EtOAc (3 × 2 mL) and the combined organic layers were washed with brine (1 × 2 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography eluting with 9:1 hexanes:EtOAc to yield the desired sulfone (0.18 mmol, 90%). Crystals suitable for SC-XRD and VT-Brillouin were grown by vapor diffusion with minimal EtOAc and *n*-pentane as the anti-solvent. Note that the evolution of HF results in the etching of the glassware, introducing a potential source of inorganic salt contamination.

R_f: 0.15 (9:1 hexanes:EtOAc), vis: UV (254 nm) ; **m.p.**: 220 °C; **¹H NMR (600 MHz, CDCl₃)**: δ = 8.90 (2H, s), 2.67 (6H, s); **¹³C{¹H} (150 MHz, CDCl₃)**: δ = 162.8, 157.3, 135.0, 58.4, 48.6, 48.3; **ATR-IR**: 3054, 1547, 1422, 1372, 1265, 1188, 1131, 1023 895, 731 cm⁻¹; **MS**: (ESI) *m/z* calc'd for C₉H₉Cl₂N₂O₂S⁺ [M+H]⁺ = 278.9756, found = 278.9747.

6.5.11 DSC (Differential Scanning Calorimetry) Experiments.

Low temperature DSC data were recorded using a Linkam optical DSC600 calorimetry cell equipped with an LNP96 liquid nitrogen pump. The cell was installed in a Linkam Imaging Station microscopy setup fitted with an Olympus PlanC 10X lens, condenser optics, polarizer (transmission) and a Point Grey IMX250 high speed camera with a field of view covering the whole DSC crucible.

The microscopy setup was used in combination with an optically transparent sapphire crucible to discriminate crystals undergoing a mechanical response from regular crystals. No noteworthy polarization effects were observed during cooling. Roughly 100 specimen were examined this way, and no correlation between crystal morphology and thermosaliency was found. Samples were thermocycled between room temperature and -160 °C up to three times (20 °C/min) to test if crystals remaining intact would detonate in subsequent cooling cycles, which was never the case. Also, crystal shards remaining after a thermosalient sample did not seem to react to further cooling cycles (this observation should be considered anecdotal, since most shards were usually propelled out of frame). This method was used to identify sample **sm181122_1**, described in the crystallography section.

Samples of the original primitive ($P2_1/n$) phase were cycled once with sampling rates of 2 °C/min, 5 °C/min and 20 °C/min in a range from room temperature to -160 °C. A fresh sample was employed in each attempt to exclude any thermal history effects associated with a mechanical response. The experiments were conducted both with the compound in crystalline form as received, and finely ground, with no significant difference in DSC profiles. Some deviations when compared to empty crucible profiles were observed in the relevant temperature range for the

thermosalient effect, but no sharp signal associated with a phase transition was detected in any experiment. Figure 6.12 shows a typical profile.

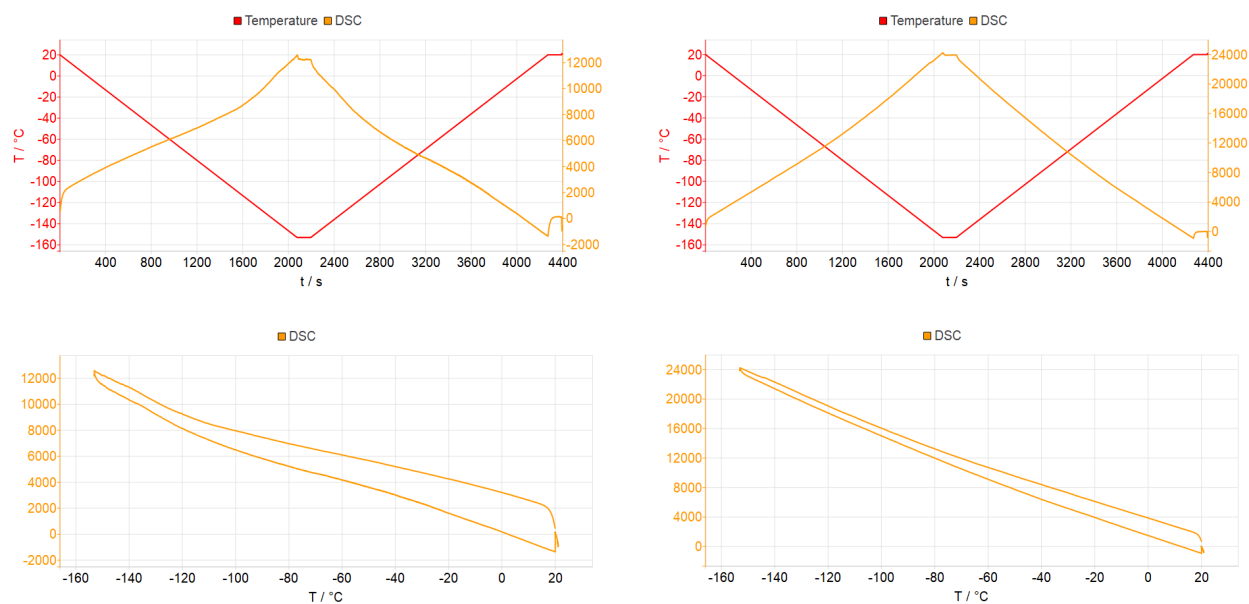


Figure 6.12. Left: Representative DSC profile of a crystalline sample of **1** (ground sample, 5 °C/min cooling/heating rate). No sharp signal corresponding to a phase transition was detected. **Right:** Profile of a sealed empty crucible recorded under the same conditions for comparison. DSC signal shown in arbitrary units.

6.5.12 Decomposition during Melting Point Determination.

The melting point of a single-crystalline sample of **1** ($P2_1/n$ phase) was obtained to investigate the response upon heating the material. Immediately after melting, the resulting clear liquid began to bubble and rapidly decomposed.

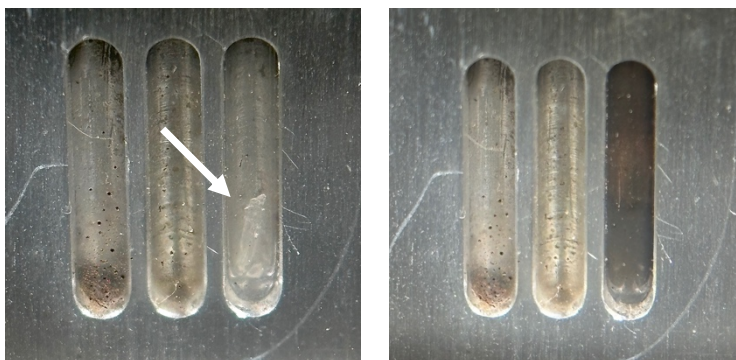


Figure 6.13. Left: Crystalline sample of **1** in melting point capillary prior to heating. Right: Decomposition of **1** upon heating to approx. 220 °C.

Additionally, the melting point of a sample of the $C2/c$ phase microcrystals (after 20 thermocycles) was determined. The sample melted at 211 °C and immediately thereafter rapidly decomposed.

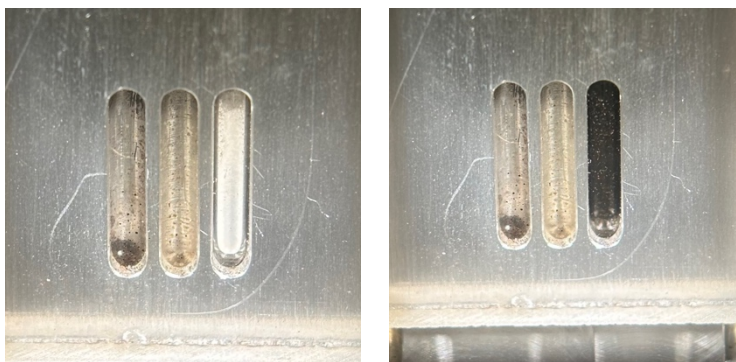


Figure 6.14. Left: Microcrystalline sample of **1** ($C2/c$ phase) in melting point capillary prior to heating. Right: Decomposition of microcrystalline **1** ($C2/c$ phase) upon heating to approx. 211 °C.

6.5.13 Variable Temperature SC-XRD.

sm181122_1 structures are a temperature series of a $P2_1/n$ crystal not undergoing a mechanical response. Data were obtained in 2 °C intervals between 200 K and 100 K (only cooling). Only selected temperatures are represented here. The crystal was identified by video microscopy under cooling in the DSC cell and remained intact and visually unchanged after two full thermocycles (see above).

sm091122 structures were determined from a shard remaining of a detonating crystal, which was identified by video microscopy under cooling in the DSC cell (see above). The structures were recorded in the following order: 200 K, 120 K, 100 K, 170 K.

sm210323 data were recorded on a $P2_1/n$ crystal that underwent a mechanical response on the diffractometer. The crystal was covered in high viscosity perfluoropolyalkylether oil, intended to prevent shards from being propelled away. Data were obtained in 2° C intervals between 200 K and 130 K (only cooling), with a final structure recorded of the remaining shards after the detonation. Only the starting and final structure are represented here because the cracking induced crystal motion and splitting, making the structures around the thermosalience temperature not entirely comparable. The diffraction pattern of the final measurement at 130 K shows contributions from at least 4 crystal shards, with the most significant domain accounting for approximately 60 % of the reflections. Twin integration was tested but showed little overlap and no improvement to the structure, so the main domain was processed as a single crystal. Before mechanical reponse, the crystal dimensions were 0.092 x 0.255 x 0.331 mm. No crystal dimensions are listed for the 130 K measurement, and only empirical absorption corrections were carried out, since it is not clear which of the visible shards actually corresponds to the integrated data. This is the data set used for generating the difference maps in **Figure 6.7**. It is not discussed further since the data

quality after shattering was slightly subpar but represents further evidence that the structure stays unchanged after mechanical response, with data recorded on the exact same crystal.

sm190824_1_1 data ($P2_1/n$) were recorded at 300 K solely to calculate a diffractogram to compare with room temperature PXRD data.

sm260724_2_1 data were recorded on a $C2/c$ crystal picked directly from the capillary in which the occurrence of this new phase was spotted for the first time after fast cooling (see description of PXRD experiments below). The same unit cell was identified multiple times, and the reported data set represents the best of several attempts. Overall, the data quality is poor, but sufficient to unambiguously identify the phase. All tested $C2/c$ crystals were twinned and visually appeared amorphous. Many tested crystals and microcrystals in this capillary could be clearly identified (by unit cell metric) as the $P2_1/n$ structure.

sm200824_1_1 data were recorded on a $C2/c$ crystal grown from the melt. Crystalline material ($P2_1/n$) was very lightly ground and flame-sealed in a 0.2 mm capillary, which was then dipped in liquid nitrogen and re-heated to room temperature 20 times (see description of PXRD experiments below). Microscope images showed extensive destruction of the crystals, with only microcrystalline or amorphous material remaining. The capillary was then heated to 480 K using the diffractometer sample thermostat until completely melted. The capillary was then cooled to 460 K (360 K/h) and observed until crystal growth stopped. The capillary was then cooled to room temperature, cracked and crystals were extracted. Tiny crystals of the $P2_1/n$ phase were still found and unambiguously identified (by unit cell metric) in the capillary, indicating the $C2/c$ structure grows even in the presence of seeding crystals of the original phase. While visually beautiful, $C2/c$ crystals grown from the melt exhibit low quality (high mosaicity, low diffraction limit, elongated

reflections, some specimen were also twinned). Nevertheless, this structure represents an independent crystallization attempt of the $C2/c$ phase.

sm170824_1_1 data ($C2/c$) were recorded at 300 K solely to calculate a diffractogram to compare with room temperature PXRD data. Crystals were obtained directly from a flame-sealed 0.2 mm capillary filled with $P2_1/n$ crystals, which was dipped in liquid nitrogen and re-heated to room temperature 20 times (see description of PXRD experiments below). The structure is of low quality, but proved sufficient to calculate a PXRD pattern in the relevant resolution range.

sm160824_1_1 (sulfone decomposition product) crystals were found after heating a flame-sealed capillary containing $P2_1/n$ crystals to 495 K (slightly above the melting point of the material), in an attempt to determine which compound crystallizes from the melt. The melt turned slightly brownish immediately, and after quick cooling a mixture of $P2_1/n$ crystals and the sulfone ($I2/a$) had crystallized.

sm160824_1_2 is a repeat measurement of **sm160824_1_1** at 300 K, to calculate a diffractogram to compare with room temperature PXRD data.

YK31_210824 is the independently synthesized sulfone (**2**) grown by vapor diffusion with ethyl acetate and *n*-pentane as the anti-solvent. The structure was collected on a Bruker APEX II Duo using Mo radiation. These crystals were thin needles and were found to display birefringence.

6.5.14 Short Contacts Analysis.

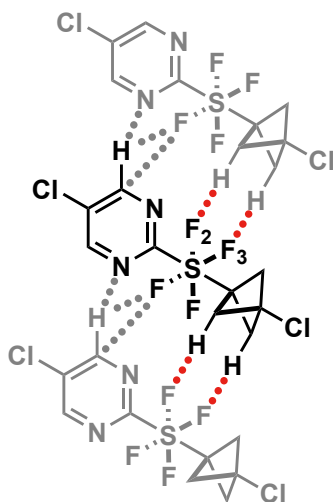


Table 6.2. Approximate change in BCP and -SF₄- contacts over 100K temperature range (SM181122).

Temp. (K)	Distance H2–F2 (Å)	Distance- vdW	Distance H4–F3 (Å)	Distance-vdW
200	2.64	-0.03	2.57	-0.10
170	2.63	-0.05	2.57	-0.10
120	2.60	-0.07	2.58	-0.10
100	2.60	-0.07	2.57	-0.11

Table 6.3. Approximate change in BCP and -SF₄- contacts (SM210323).

Temp. (K)	Distance H2–F2 (Å)	Distance- vdW	Distance H4–F3 (Å)	Distance-vdW
200	2.64	-0.03	2.58	-0.09
130	2.60	-0.07	2.56	-0.11

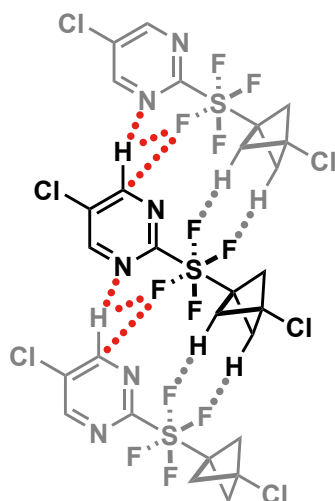


Table 6.4. Approximate change in BCP and -SF4- contacts over 100K temperature range (SM181122).

Temp. (K)	Distance F4–H9 (Å)	Length- vdW	Distance F4–C9 (Å)	Distance- vdW	Distance N1–H9 (Å)	Distance- vdW
200	2.52	-0.15	3.150(3)	-0.02	2.53	-0.22
170	2.52	-0.15	3.141(3)	-0.03	2.52	-0.23
120	2.50	-0.17	3.121(6)	-0.05	2.50	-0.25
100	2.50	-0.17	3.117(4)	-0.05	2.49	-0.26

Table 6.5. Approximate change in BCP and -SF4- contacts (SM210323).

Temp. (K)	Distance F4–H9 (Å)	Length- vdW	Distance F4–C9 (Å)	Distance- vdW	Distance N1–H9 (Å)	Distance- vdW
200	2.53	-0.14	3.157(3)	-0.04	2.53	-0.22
130	2.50	-0.17	3.124(3)	-0.05	2.51	-0.25

Table 6.6. Approximate changes in torsion Angles over 100 K Temperature Range: (SM181122)

Temp. (K)	Torsion C6-S1-C5-C2 (°)	Torsion C6-S1-C5-C3 (°)	Torsion C6-S1-C5-C4 (°)
200	94(5)	-27(5)	-147(5)
170	97(6)	-23(6)	-144(6)
120	92(12)	-27(12)	-148(11)
100	98(7)	-23(7)	-143(7)

6.5.15 Powder X-Ray Diffraction (PXRD) Experiments.

In an attempt to detect microcrystalline or amorphous material in crystalline bulk of **1**, crystals were lightly ground and transferred to a 0.2 mm capillary (Mark tube), which was then flame-sealed. A powder diffractogram was recorded at 300 K using a Cu rotating anode single crystal diffractometer, which is not ideal for PXRD but gave us access to more intensity/sensitivity and the cryostat installed on this system. The initial pattern matched very well with the pattern calculated from the known single crystal structure, apart from small temperature effects. Notably, the background was very low, indicating an absence of microcrystalline or amorphous components (background contributions by the capillary were later evaluated using a powder diffractometer, see below and Figure 6.16).

In a next step, the capillary was cooled at the highest possible cooling rate accessible on the cryostat (~12 K/min, "Turbo" mode), and powder diffractograms were recorded at 200 K, 150 K and 100 K. The cooling process was tracked visually to confirm detonation of the crystals (Figure 6.15), which could be observed between 180 K and 110 K. As expected, a large fraction of the material detonated, while the rest still appeared visually crystalline.

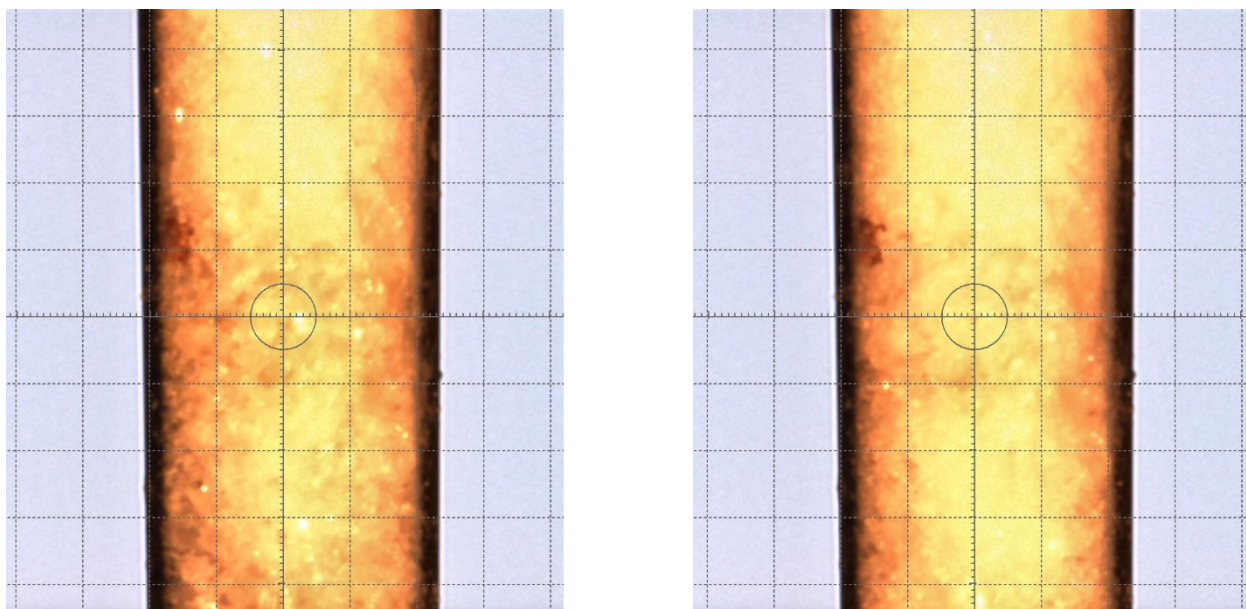


Figure 6.15. Capillary filled with crystallites of **1** before further cooling (200 K, **left**) and after cooling to 100 K and reheating (300 K, **right**). Clearly a part of the material detonated, but most of the bulk retained crystallinity.

At 150 K, a new set of reflections emerges (Figure 6.16), indicating a transition to another phase. This transformation appears to be at least partially reversible, as evidenced, e.g., by the first reflection of the original phase, which gains relative intensity again after heating back from 100 K to 300 K. Note that especially the first peaks of both species appear correlated, i.e. the new species grows while the known species shrinks and *vice versa*. The cooling / heating cycle was repeated three more times, until no further change in the diffractograms could be detected (Figure 6.17). As already suspected by the results from other methods and visual observation, the process seems to occur in a wide temperature range and notably, only part of the bulk is converted in the first cooldown cycle. Reflections of the new phase grow in tandem with the corresponding reflections of the $P2_1/n$ phase vanishing, and the background does not increase, which rules out crystal growth from some hypothetical undetected amorphous or microcrystalline material in the bulk.

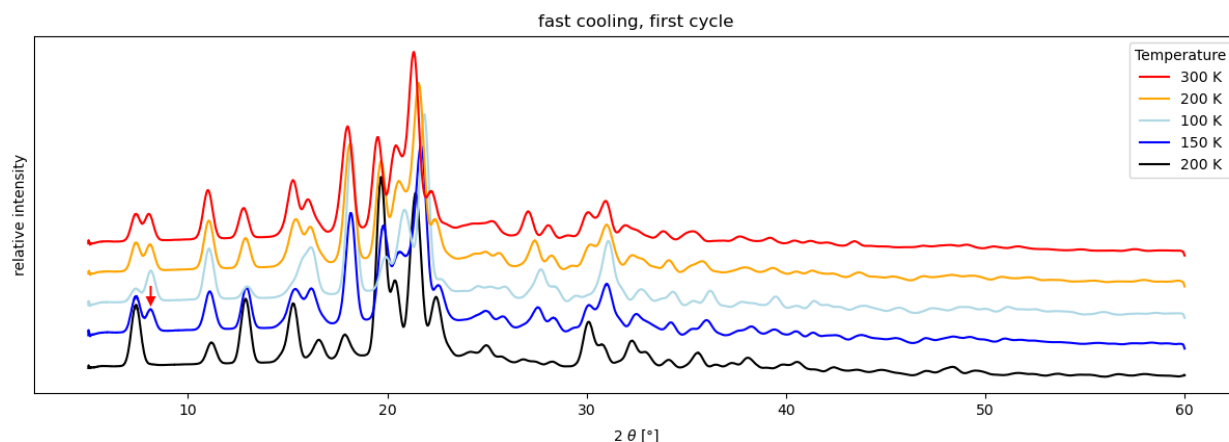


Figure 6.16. Variable temperature PXRD experiments of crystallites of **1** in a sealed capillary (recorded using Cu radiation on a rotating anode single crystal diffractometer). Patterns shown in ascending order (the black pattern was collected first). Emergence of the new phase at 150 K, easily spotted by its first reflection, is marked with a red arrow. Note the overall similarity of the patterns, indicating closely related unit cells. The first three reflections from the left are 0 2 0, 0 1 1 and 0 2 1 (in the known $P2_1/n$ phase) or 0 0 2, 2 0 -2 and 2 0 2 (in the later identified $C2/c$ phase), respectively. No baseline corrections were carried out.

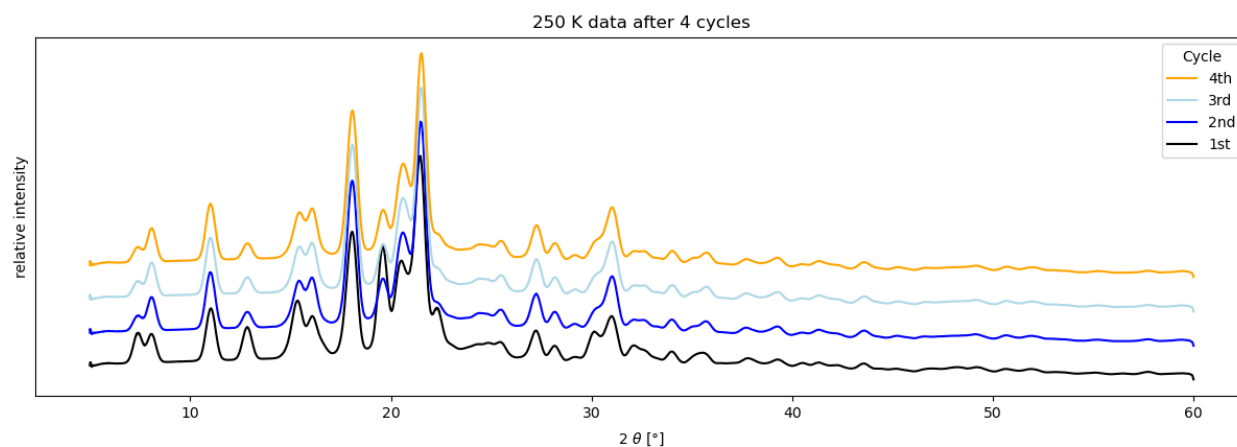


Figure 6.17. PXRD patterns of crystallites of **1** in a sealed capillary, recorded at 250 K following cooling/heating cycles between 250 K and 100 K. The data were collected using Cu radiation on a rotating anode single crystal diffractometer. No change was observed after the 2nd full cycle and a significant amount of the bulk material retains the known $P2_1/n$ structure. No baseline corrections were carried out. The sample had been equilibrated slightly longer before recording the first pattern (black), which might explain the higher fraction of the known species indicated by the first peak. This experiment indicates full reversibility.

From these results it became clear that the known structure of **1** in space group $P2_1/n$ and newly found transitioned structure must be closely related, due to the strong similarity of their powder patterns. The capillary was cracked open, and crystals could be extracted for single crystal structure determination. In these attempts, all material that appeared even vaguely crystalline at first glance could be clearly identified as the $P2_1/n$ structure (by unit cell metrics). Ultimately, a tiny opaque and very weakly diffracting fragment sufficient for structure determination was found in a cracked capillary after cycling to 100 K (**sm260724_2_1**, Figure 6.18). The structure, although of relatively low quality due to the growth conditions (i.e. twinned, $R1 = 8.6\%$, enlarged ellipsoids), solves and refines, and is sufficient to unambiguously describe this new phase. The structure crystallizes in space group $C2/c$. Its metrics are closely related to the previously known phase, with $a' = 2 \cdot c$, $b' = a$ and $c' = b$ ($a, b, c = P2_1/n$ and $a', b', c' = C2/c$ phase, respectively). No disorder as in the $P2_1/n$ structure was found, but this could be due to the low structure quality. The structure was later reproduced independently (and an untwinned specimen could be measured) with crystals grown from a melt (see below). It should be stated that all tested crystals of the $C2/c$ phase decayed relatively quickly during measurement (both at 100 K and 300 K), making it impossible to obtain better data.

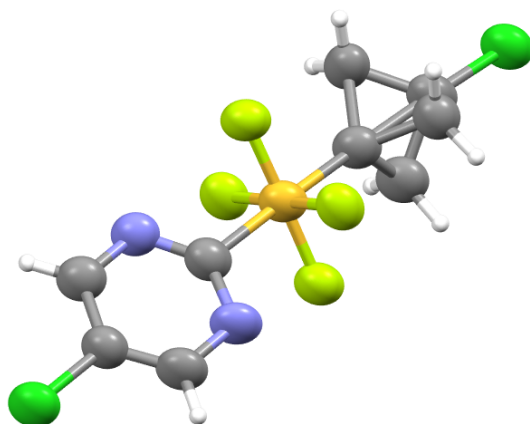


Figure 6.18. Asymmetric unit of the $C2/c$ crystal structure found after cooling (100 K data). Ellipsoids depicted at 50% probability.

For all further experiments, PXRD samples were prepared as follows: $P2_1/n$ material was carefully and not too finely ground and transferred to a 0.2 or 0.3 mm Hilgenberg Mark tube (capillary), which was then flame-sealed. The capillary was dipped 15 to 20 times in liquid nitrogen (LN_2), each dip followed by reheating to room temperature with a hot air gun. This never led to observed full conversion, but further dipping did not lead to any changes. Note that more material was converted this way than in the much slower linear cooling cycle in which the $C2/c$ phase was observed for the first time. It was later found that the new phase is metastable (see below) and a part of it possibly even converts back during more controlled cooling, especially at temperatures between 150 K and 200 K (cf. Figure 6.17). Metastability would also explain why we never observed full conversion, because the material must pass a few minutes at room temperature before measurements can be recorded.

A first sample prepared in this way was compared by PXRD before and after the dipping process. Room temperature data were collected on a dedicated powder diffractometer calibrated for accurate unit cell determination and small peak FWHM, in order to get a reliable comparison with powder data simulated from single crystal structures. All relevant single crystal structures were re-collected at 300 K for the simulation, to eliminate temperature shifts when comparing with powder data. No baseline correction was applied in order not to hide any possible amorphous component. Data were also compared to the pattern of an empty capillary.

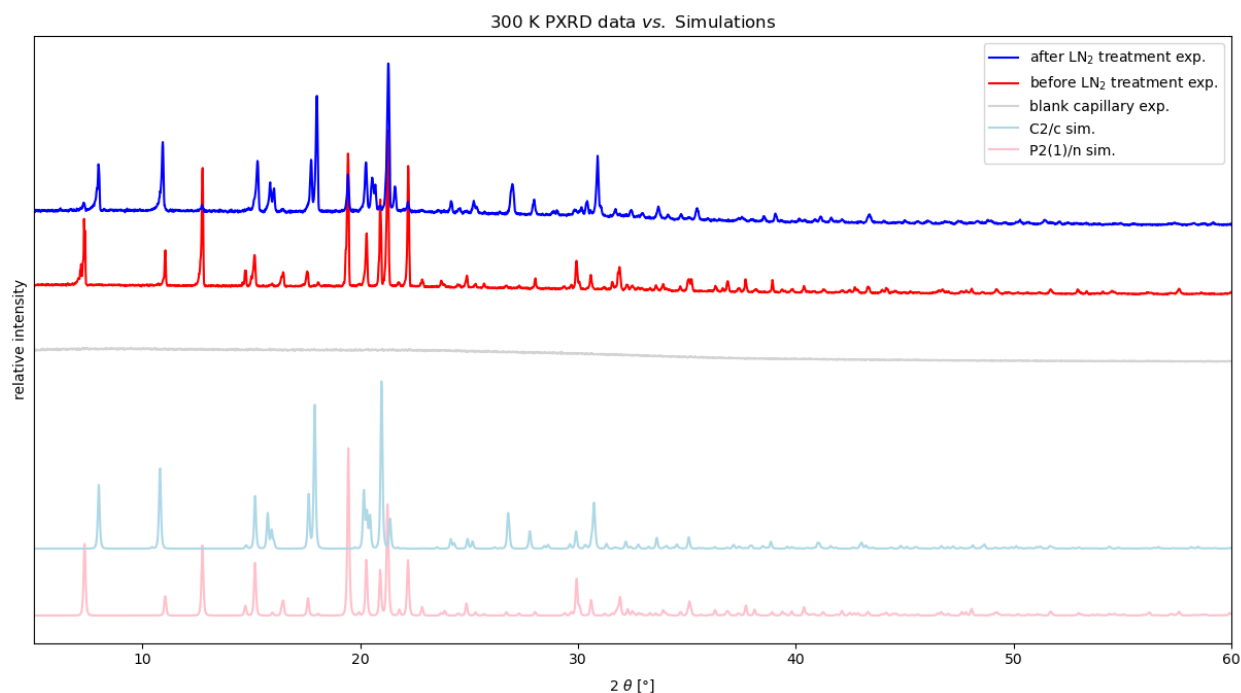


Figure 6.19. Room temperature experimental (**top**) and simulated powder patterns (**bottom**). The simulations are based on single crystal structures recorded at 300 K, to minimize temperature effects. Simulations were performed with WinXPow (Stoe). Data were recorded on a Stoe Stadi P powder diffractometer (sealed tube Cu radiation). This specific sample was dipped in liquid N₂ and re-heated 15 times and shows almost full conversion.

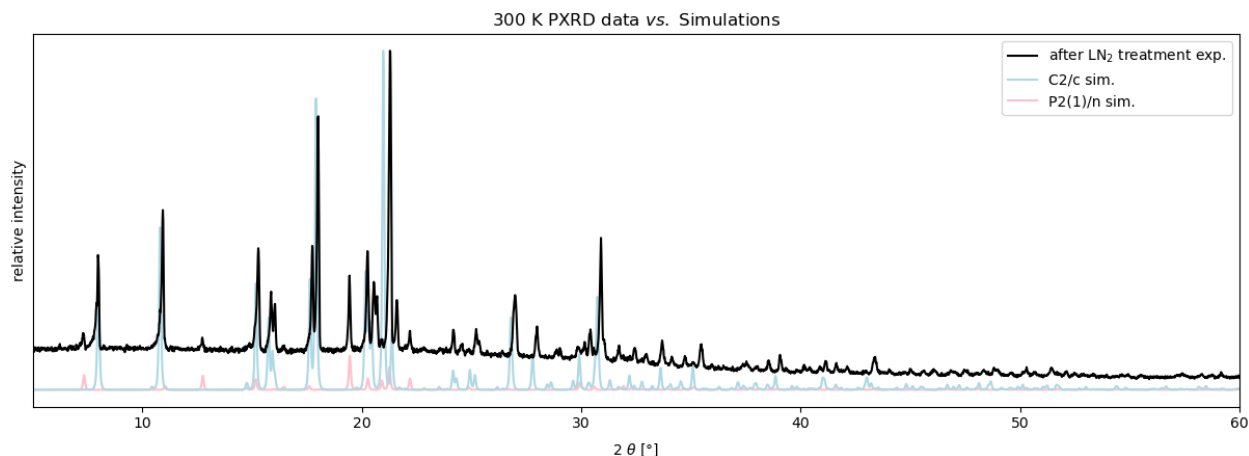
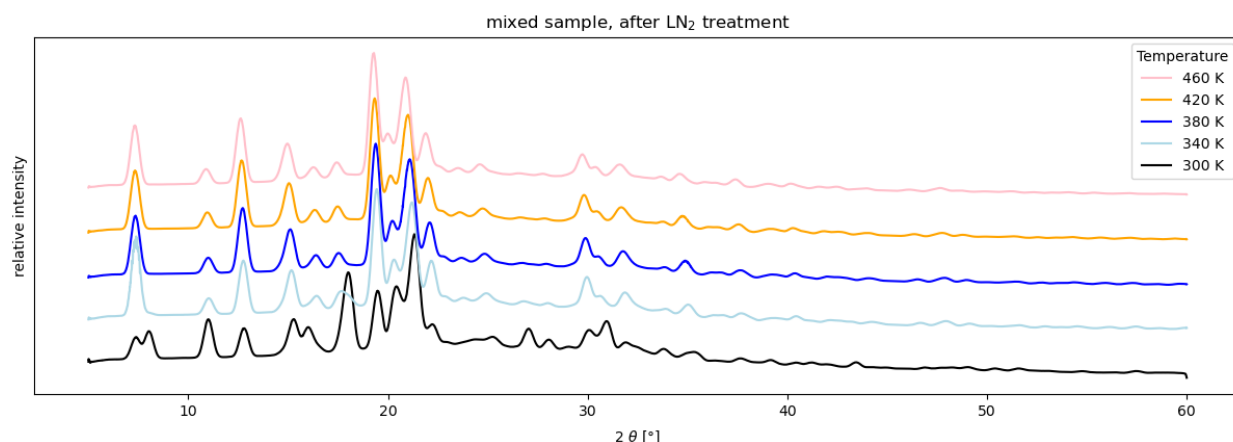


Figure 6.20. Overlay of room temperature experimental data after 15x liquid N₂ dipping and simulated powder patterns (condensed view demonstrating excellent match). The intensities of the $P2_1/n$ simulation were downscaled to 10% to roughly describe the contribution of the remaining fraction of this phase. Simulations were performed with WinXPow (Stoe).

Multiple observations suggested that the $C2/c$ phase is only metastable: 1) all measured single crystals decayed during the measurement, even at 100 K, 2) we could never observe a 100 % converted sample, 3) when crystals were picked from cracked capillaries, initially most of the specimen were identified as the $C2/c$ structure, but after a while all tested crystals were the $P2_1/n$ structure and 4) the patterns shown in Figures 6.16 & 6.17 indicate reversibility. Metastability is hard to confirm on the type of classic diffractometer we used for Figure 6.19, because it scans from low to high resolution and any peak changes at low resolution would not be recorded once the detector moved to higher angles. To test the stability of the $C2/c$ phase, a freshly converted sample was heated up and new data recorded on our single crystal diffractometer, which can collect the



whole pattern in a single detector setting (Figure 6.21). Already at 340 K the material is fully converted back to $P2_1/n$.

Figure 6.21. Variable temperature PXRD experiments of a liquid N_2 -treated sample in a sealed capillary (recorded using Cu radiation on a rotating anode single crystal diffractometer). No baseline corrections were carried out. The $C2/c$ phase appears to completely vanish at 340 K, while the peaks of the $P2_1/n$ phase are increasing.

To also test the stability of the $C2/c$ phase at room temperature, a fully converted sample was repeatedly measured at intervals. Indeed, the back-transformation can be observed within several days (Figure 6.22).

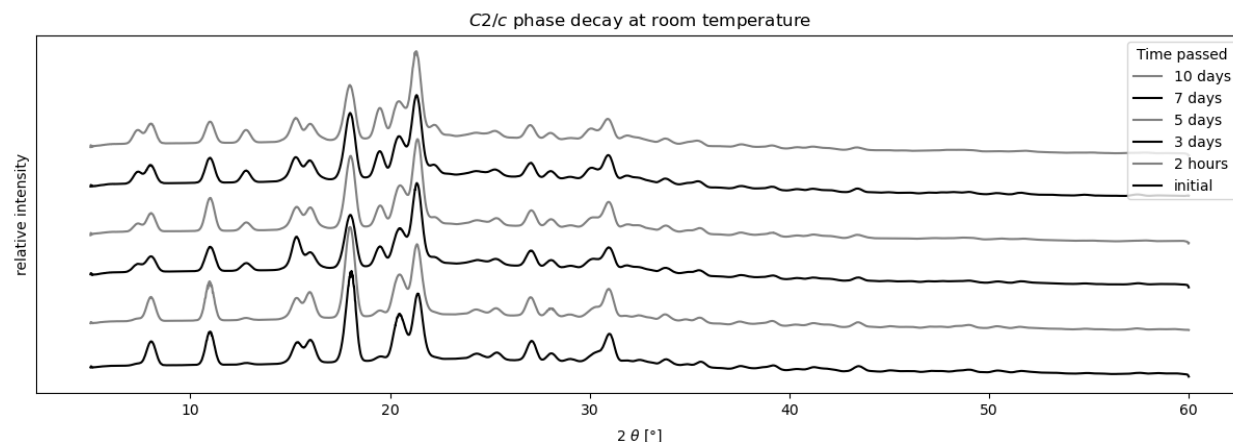


Figure 6.22. Room temperature PXRD experiments of a liquid N_2 -treated sample in a sealed capillary (recorded using Cu radiation on a rotating anode single crystal diffractometer). No baseline corrections were carried out. The first experiment was started a few seconds after converting the sample and almost full conversion was observed (e.g. the $0\ 2\ 0$ reflection of the $P2_1/n$ phase is only detected as a small

shoulder). The sample was then stored at room temperature and the measurement repeated at the specified intervals.

In later attempts to obtain a better crystal structure of the $C2/c$ phase by re-crystallizing from a melt, an interesting observation was made: Upon cooling the melt, spontaneous crystal formation occurred. We were not able to measure a powder diffraction pattern of this specific sample, but visually it still contained unmolten crystals of the $P2_1/n$ phase (which was also confirmed by testing the unit cell metrics of a crystal that could be recognized after cracking the capillary). However, even in the presence of these crystals of the $P2_1/n$ phase, the $C2/c$ polymorph crystallized initially, and the crystal structure could be re-confirmed by quickly extracting and measuring one of these specimen before they all converted (**sm200824_1_1**). This behavior is actually in accordance with Ostwald's rule, which states that often the less stable polymorph crystallizes first from a melt.

The $P2_1/n$ material was then also measured at increasing temperatures up to its melting point, to rule out any further phase transitions (Figure 6.23):

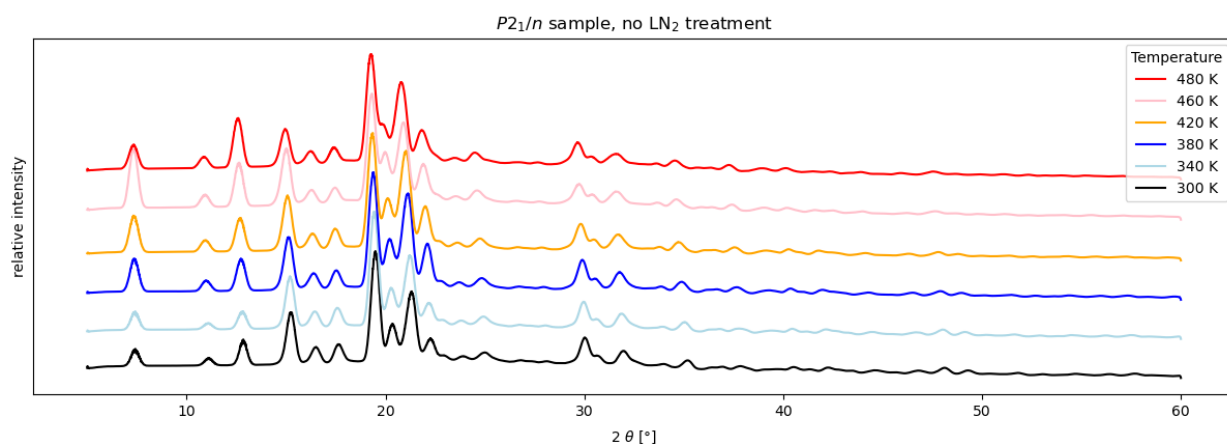


Figure 6.23. Variable temperature PXRD experiments of crystallites of the $P2_1/n$ phase in a sealed capillary (recorded using Cu radiation on a rotating anode single crystal diffractometer). The sample was heated to just above its melting point. No baseline corrections were carried out. Bubbling and discoloration occurred at ~490 K and the melt was cooled down quickly.

This sample was then briefly held in melted form and cycled around the melting point (in a failed attempt to get better $C2/c$), when suddenly bubbling and discoloration were observed. The sample was then quickly cooled to 450 K. Spontaneous crystal formation was observed. Surprisingly, a new cell in space group $I2/a$ was found. The structure turned out to be a known sulfone decomposition product, which had not been isolated before in crystalline form and had not previously been detected in neat **1** samples by other methods (Figure 6.24).

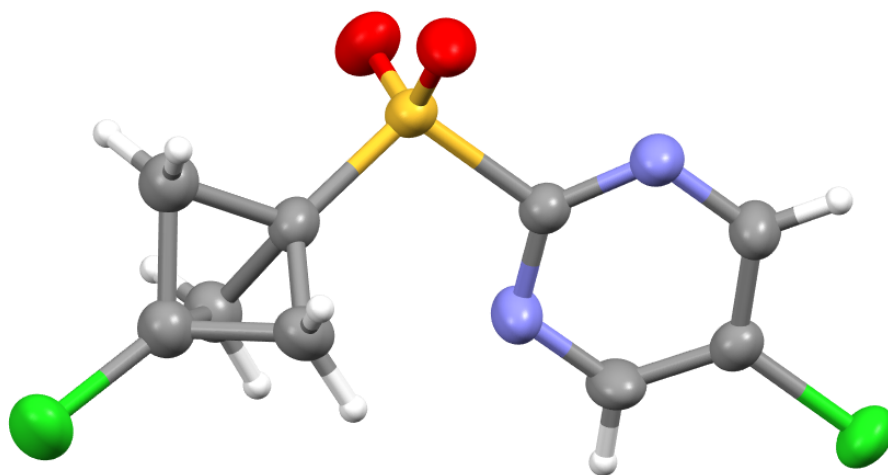


Figure 6.24. Asymmetric unit of the sulfone crystal structure ($I2/a$) grown from the melt (100 K data). Ellipsoids depicted at 50% probability.

The unit cell of this structure is stunningly similar to the $C2/c$ polymorph of **1** (see structure summary tables above for estimated standard errors).

Table 6.7. Comparison of unit cell metrics between two polymorphs of **1** and **2**.

Structure (100 K)	<i>a</i> /Å	<i>b</i> /Å	<i>c</i> /Å	β /°
<i>P</i> 2 ₁ / <i>n</i> (1)	6.095	24.024	8.484	101.61
<i>C</i> 2/ <i>c</i> (1)	17.400	6.253	23.301	110.54
<i>I</i> 2/ <i>a</i> (2)	22.762	6.053	17.086	105.26

A comparison of the simulated powder patterns of all three structures shows that the sulfone would be almost impossible to detect by PXRD, especially if it occurs in very small quantities, due to overlap with either of the other species (Figure S26). The overall similarities of the patterns despite the big differences in metrics between *P*2₁/*n* and *C*2/*c* suggests that an alternate description must exist that makes the structures similar. It also seems very unlikely that the similarity between the sulfone and *C*2/*c* polymorph is coincidence (*C* vs. *I* centering is a choice, usually based on closeness of the resulting β angle to 90°).

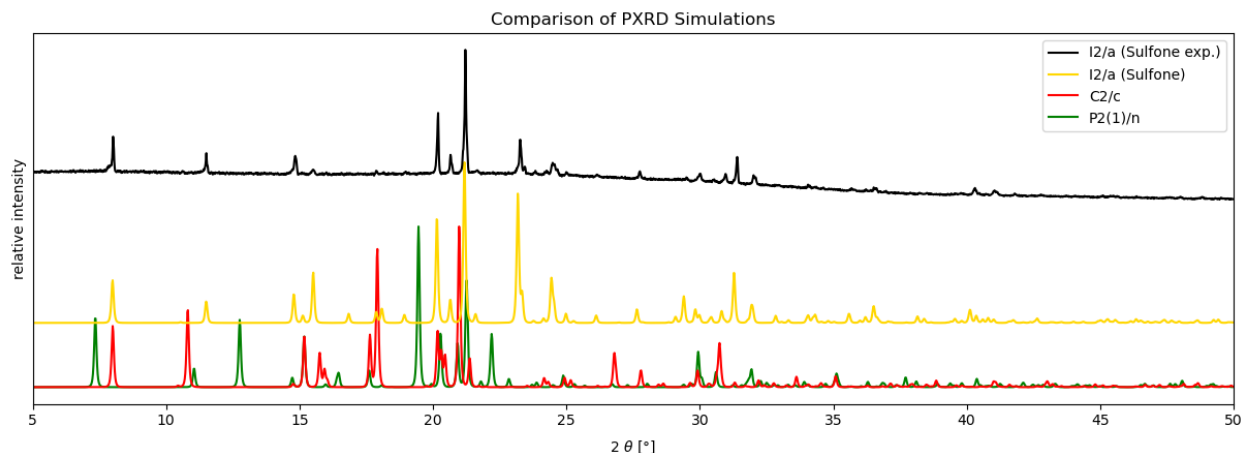


Figure 6.25. A comparison of simulated powder patterns and experimental data of the sulfone. Simulations are based on single crystal structures recorded at 300 K (to minimize temperature effects) and were performed with WinXPow (Stoe). The experimental data were measured at rt, using a capillary filled with finely ground isolated sulfone crystals (to reduce background from amorphous material). Note the close overlap of the sulfone structure (**2**) with either polymorph of **1**.

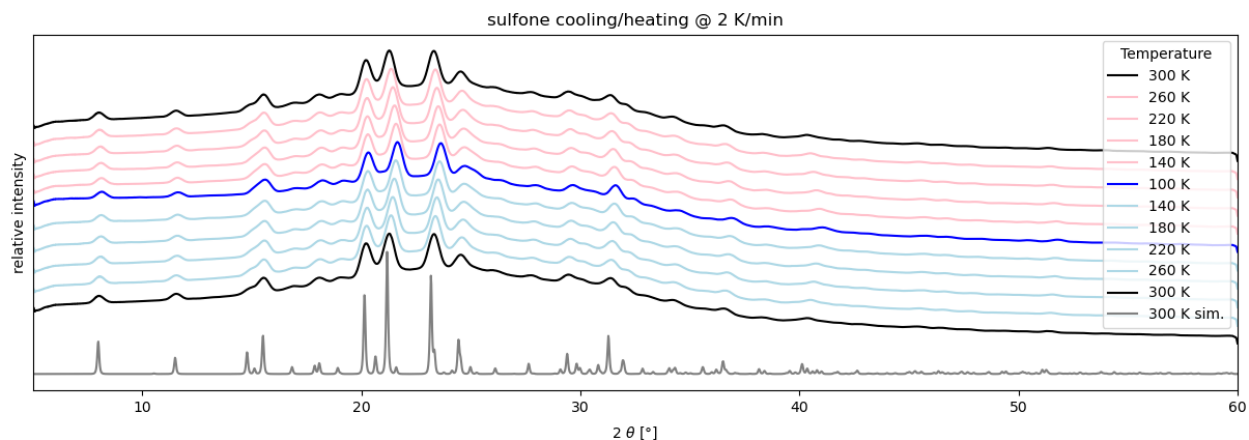


Figure 6.26. Variable temperature PXRD of a dominantly amorphous sample of **2** recorded with a cooling rate of 2 K/min (order measured = bottom to top). No background reduction and peak increase is observed, indicating that the amorphous component does not undergo a phase transition under these conditions.

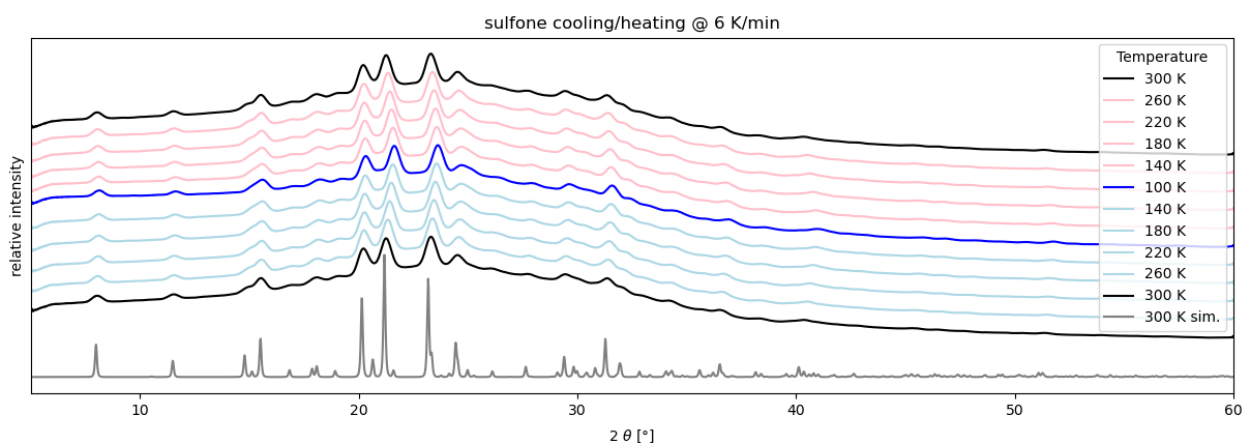
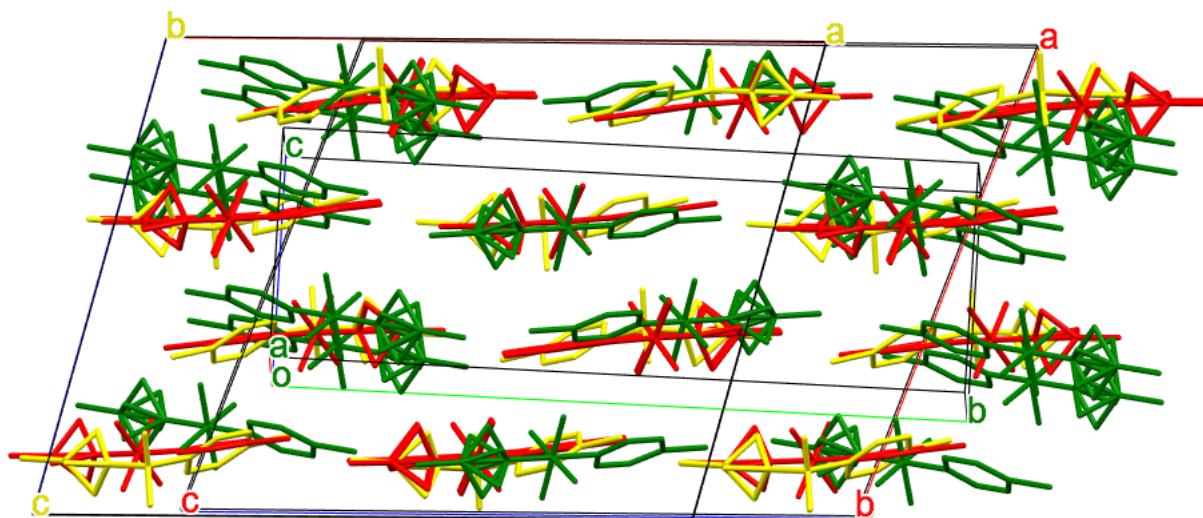


Figure 6.27. Variable temperature PXRD of a dominantly amorphous sample of **2** recorded with a cooling rate of 6 K/min (order measured = bottom to top). No background reduction and peak increase is observed, indicating that the amorphous component does not undergo a phase transition under these conditions.

6.5.16 Comparison of Structures.

At first glance, the $P2_1/n$ and $C2/c$ phases appear unrelated, but closer examination reveals that they can be overlaid when taking into account the apparent metrics relationship. As mentioned before, the metrics (but not the cell orientations) are similar with $a' = 2 \cdot c$, $b' = a$ and $c' = b$ ($a, b, c = P2_1/n$ and $a', b', c' = C2/c$ phase, respectively). However, the $P2_1/n$ structure can also be transformed into a more similar setting in space group $P2_1$ ($Z' = 4$) after applying the resulting

matrix $(0\ 0\ 2\ 1\ 0\ 0\ 1\ 0)$ derived from the apparent metrics relationship. Note that in this setting the angle relevant for the comparison would be $\alpha = 90^\circ$ instead of β , leading to an angular difference of about 20° between the phases (cf. $C2/c$: $\beta = 110.5^\circ$, $P2_1/n$: $\beta = 101.6^\circ$), which would result in huge local strain buildup. The transformed structure solves and refines, albeit suffering from strong correlation. Figure 6.28 shows an overlay of the different structures and the sulfone decomposition product.



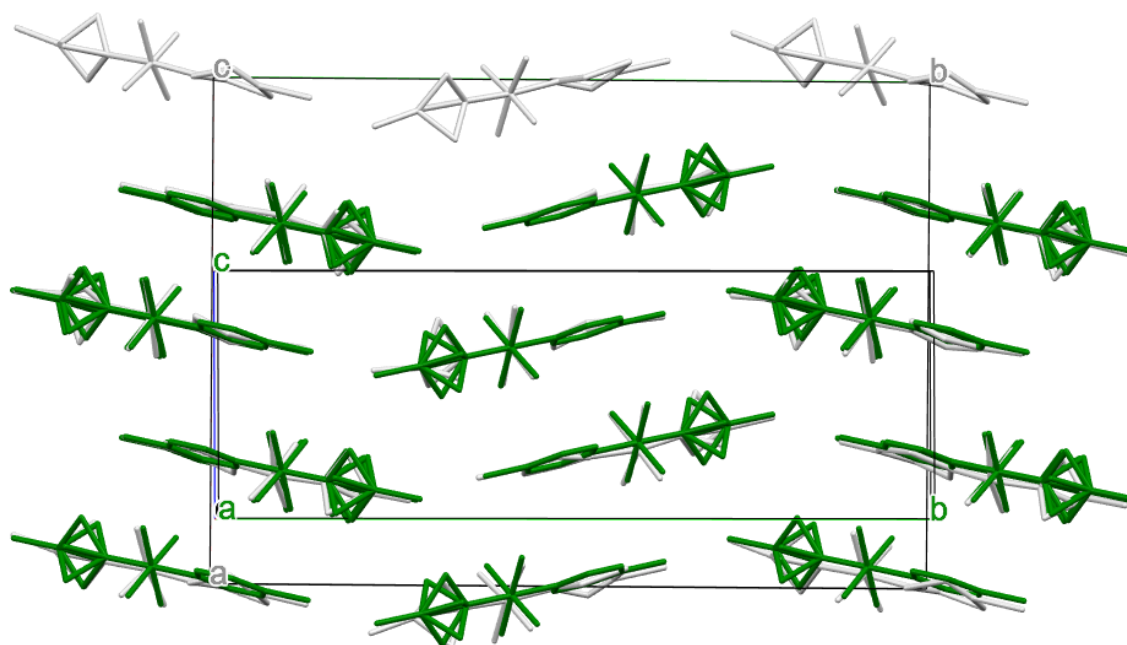


Figure 6.28. Top: Overlay of the unit cells and structures of the $P2_1/n$ phase (green), the $C2/c$ phase (red) and the sulfone decomposition product ($I2/a$, yellow), showing the deviations in molecule positions and metrics. The sulfone structure falls between the $P2_1/n$ and $C2/c$ phase. **Bottom:** Overlay of $P2_1/n$ phase (green) and a hypothetical structure of the same material ($P2_1$) generated by applying the transformation matrix relating the $P2_1/n$ and $C2/c$ phases. This hypothetical structure is visually a closer match to the $C2/c$ phase, and it becomes apparent that the relevant angle to compare in this projection is $\alpha = 90^\circ$. These images were created using the Mercury structure viewer program provided by the CCDC.³¹⁸

Notably, the sulfone β angle of 105.3° falls between the relevant angles of the $P2_1/n$ (converted to a comparable setting) and $C2/c$ structures of **1**, and in the packing overlay the centers of gravity of the sulfone molecules are located between the corresponding positions of the interchanging phases. This suggests that the sulfone is an impurity in the crystals that acts as a catalyst for the transition, and that crystals which do not detonate contain no or too little sulfone impurity.

Additionally, a slip plane search was carried out (using the CCDC Mercury program¹³). This analysis can identify planes exhibiting very weak interplanar interactions. Several such planes were identified in the original $P2_1/n$ structure, but notably one plane appears in all three structures (i.e., including the sulfone). This plane is parallel to a and b in the $P2_1/n$ structure. Remarkably, its orientation matches with the first and major fault line visually observed when a crystal of **1** could be recorded *pre* and *post* detonation (**sm210323_1_2**). Additionally, this plane would be severely affected by the angle changes discussed above. Also, it passes between the molecules such that a tear along this plane would impact any $\text{H}\cdots\text{F}$, $\text{Cl}\cdots\text{F}$, $\text{Cl}\cdots\text{O}$ or $\text{F}\cdots\text{F}$ contacts, as well as any rotational disorder in the bicyclopentane group. It could thus be speculated that the crystals contain layers of sulfone impurity parallel to this plane (see Figure 6.29).

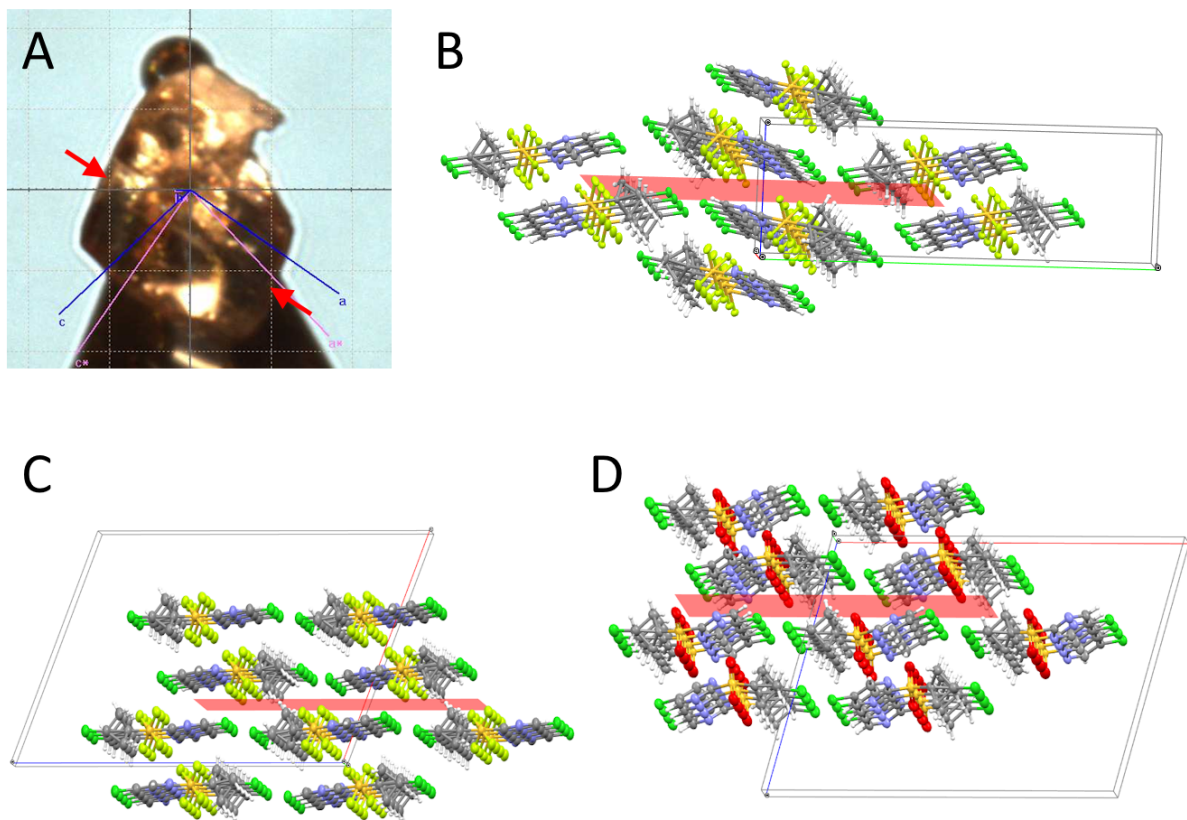


Figure 6.29. **A:** Video still image of a crystal (**sm210323_1_2**, 120 K) measured *pre* and *post* detonation. Real space and reciprocal axes are indicated in blue and pink, respectively. Red arrows indicate the first fault line observed when the crystal cracked spontaneously and violently. Further visible crystal damage in the top right corner developed much more slowly and with significant delay. The fault line is parallel to *a* and *b* (plane index (0 0 2) in the $P2_1/n$ description). **B:** The same plane was identified in the $P2_1/n$ structure (120 K) by slip plane analysis (CCDC Mercury). It is also detected in the $C2/c$ phase (100 K, **C**) and the sulfone structure (100 K, **D**). All ellipsoids depicted at 50% probability.

6.5.17 Experiments with $C2/c$ Phase Material.

To accumulate sample of the $C2/c$ phase, approximately 54 mg of crystalline $P2_1/n$ -phase material (grown by vapor diffusion with EtOAc and n -pentane at ambient temperatures) was placed into an 8 mL vial. The vial was submerged in liquid N_2 for 30 seconds, then allowed to warm to rt over the course of 3-4 minutes. This procedure was repeated 20 times to ensure full conversion.

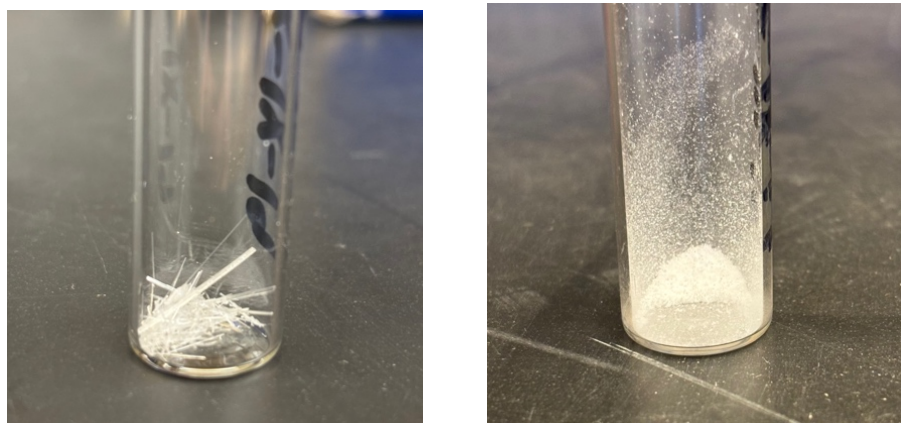


Figure 6.30. Left: Appearance of bulk $P2_1/n$ crystalline material before liquid N_2 thermocycles. **Right:** Appearance of mostly $C2/c$ phase microcrystalline material after 20× liquid N_2 to rt thermocycles after approximately 15 minutes.

6.5.18 Raman, Brillouin, and XPS Spectra.

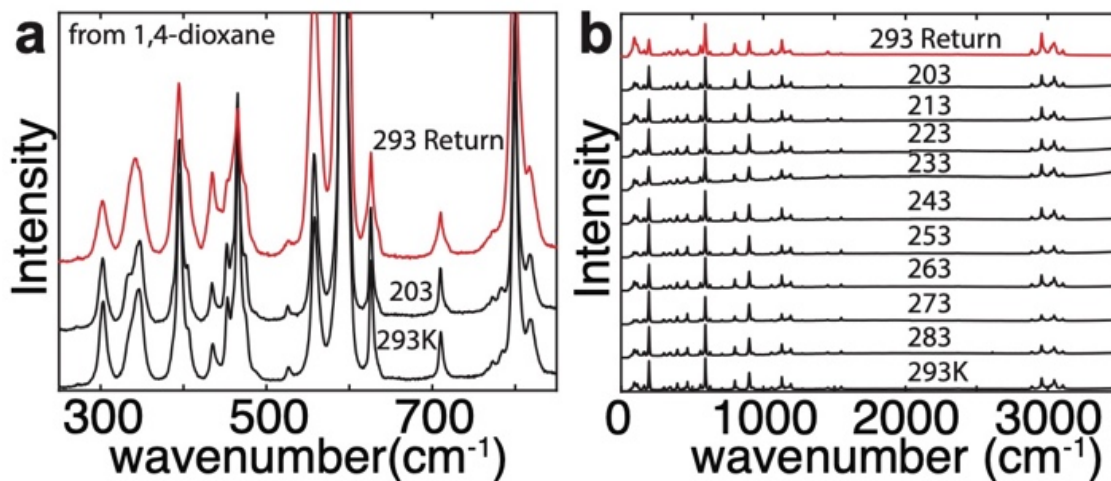


Figure 6.31. (a) Raman scattering of crystals grown using 1,4-dioxane (m.p.: 285 K) as solvent. Crystals decompose at around 185-205 K. Region between 250-800 cm^{-1} shows sharpening of peaks at the transition and return to a broad Raman mode. (b) Raman scattering of crystals grown using 1,4-dioxane (m.p.: 285 K) as solvent.

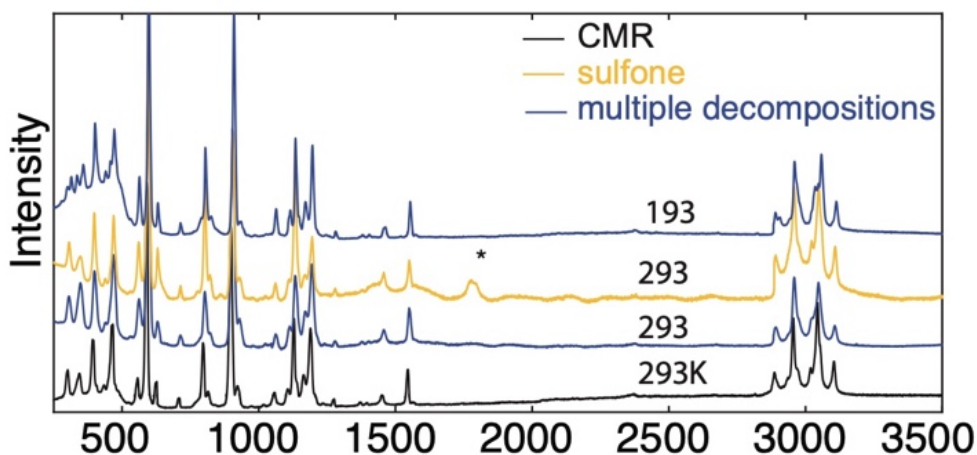


Figure 6.32. (a) Stacked plot of Raman scattering of thermosalient crystals, sulfone crystals, crystals from multiple decompositions of the thermosalient crystals. Low temperature Raman of crystals from multiple decompositions show doublets at low temperature. Sulfone crystals show two additional Raman modes not resolved in mechanically responsive crystals or multiply decomposed crystals (asterisks; *).

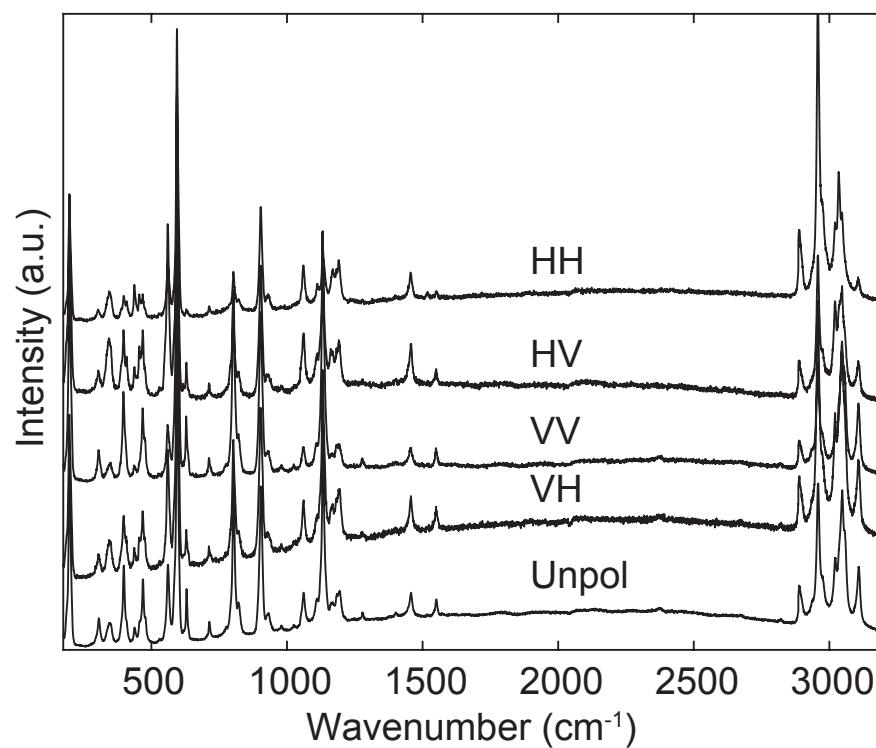


Figure 6.33. Raman polarization studies with thermosolient crystals. No obvious mode reduction or shift is observed. Any reduction in modes can be attributed to reduction in laser intensity with polarization optics.

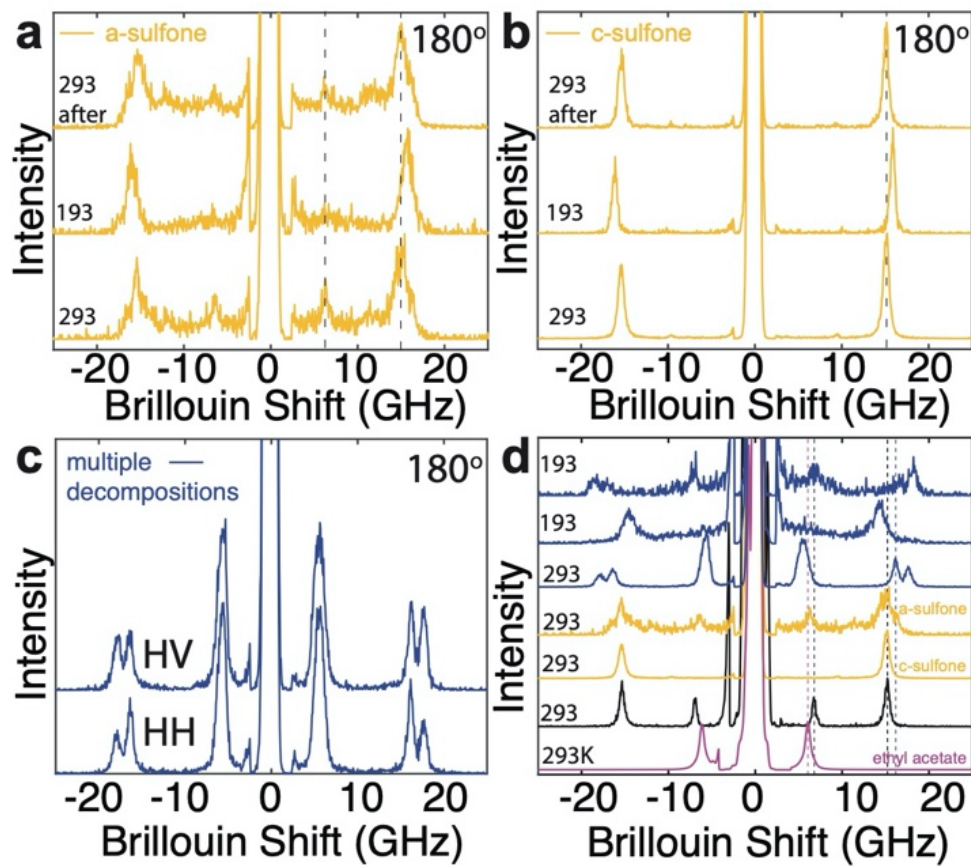


Figure 6.34. (a) Brillouin scattering of amorphous-sulfone (a-sulfone) shows a low frequency and high frequency mode like thermosolient crystals in this investigation. At low temperatures, the amorphous sulfone does not decompose but the low frequency mode vanishes like in thermosolient crystals. The low frequency mode does not completely return with the return to room temperature. The high frequency mode is too broad to note if a doublet is formed in amorphous sulfone like the thermosolient crystals. (b) Crystallized sulfone (c-sulfone) does not show much if any low frequency modes. No change is seen at low temperatures. (c) Mechanically responsive crystals that have been subjected to multiple decompositions have three Brillouin modes. Under parallel polarizers (HH), transverse modes should vanish and under cross-polarizers (HV), longitudinal modes should vanish. No peaks vanish in the multiply decomposed thermosolient crystals suggesting they have a mix of quasi-transverse and quasi-longitudinal nature. This is unusual in Brillouin scattering. (d) Brillouin scattering of ethyl acetate shows no peaks in common with thermosolient crystals (black) frown from ethyl acetate. High frequency modes in a-sulfone and c-sulfone are similar to thermosolient crystals. Multiply decomposed crystals show two types of behavior at low temperature: either a single mode or the same three modes seen at ambient temperature.

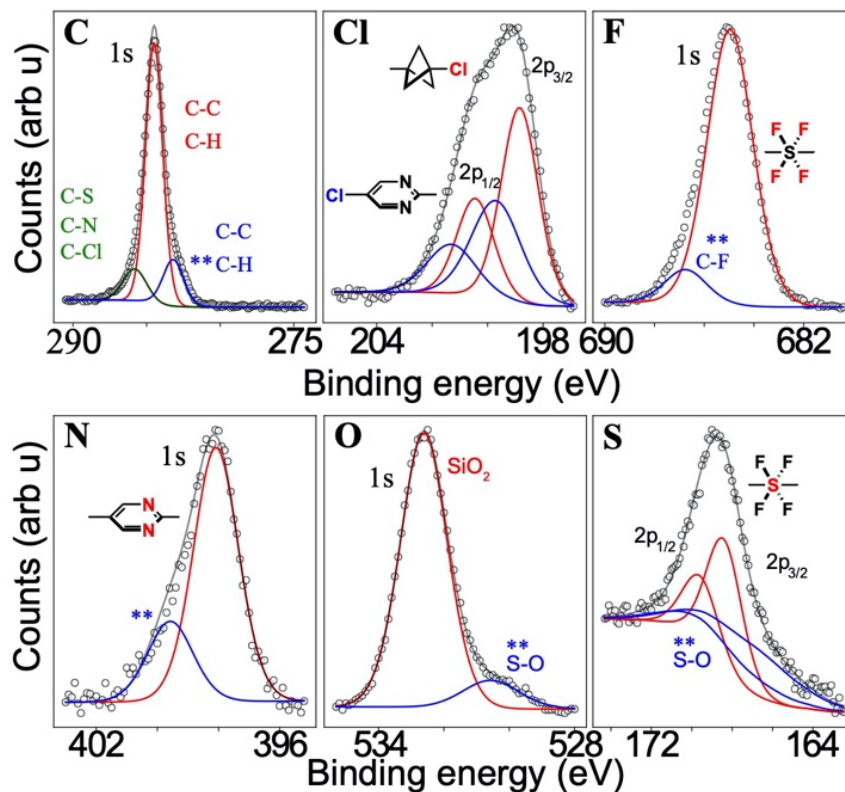


Figure 6.35. X-ray photoelectron spectroscopy characterization of thermosolient crystals of (**1**) on a silicon substrate. Spectra were calibrated to adventitious carbon (284.5 eV). Two Cl environments are found and identified. Fluorine shows two environments in the crystal with the additional peak matching well to literature values for C-F.¹³ De-fluorination is a known issue in XPS, and X-ray does damage these crystals, thus it is possible that this ** peak may be due to S bound to less fluorine exhibiting a higher binding energy. Nitrogen shows two environments with one unidentified. Sulfur shows two sulfur environments with possibly an S-O contamination on the surface.

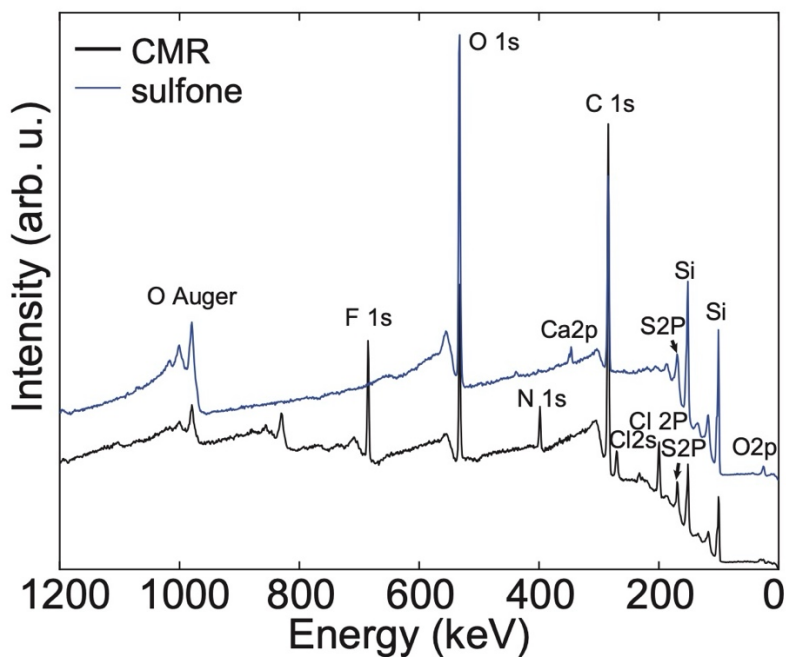


Figure 6.36. X-ray photoelectron spectroscopy (XPS) survey spectra of amorphous sulfone (**2**) and thermosolient crystals (**1**) on a silicon substrate. Note that the sulfone sample measured also contains inorganic impurities (likely resulting from the synthesis of **2**) by XPS.

6.5.19 Preliminary SEM.

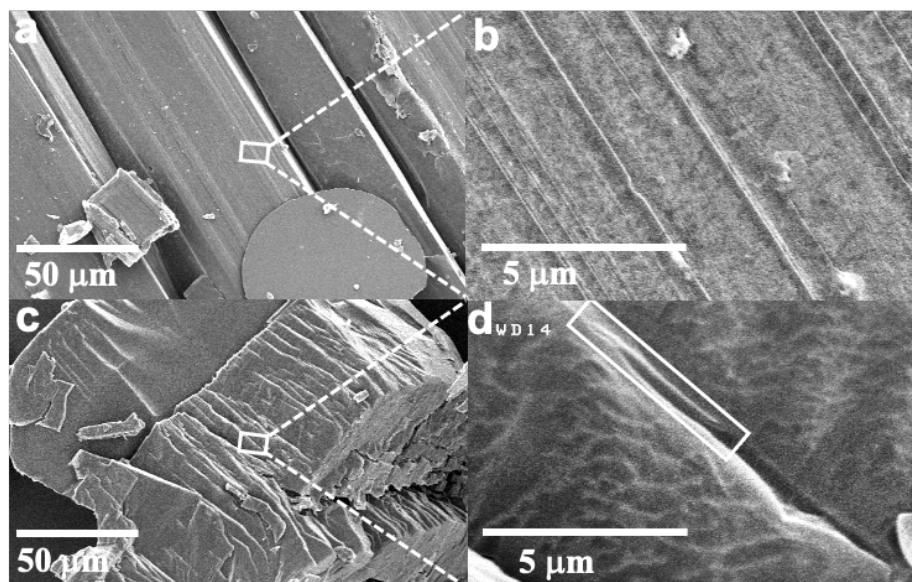


Figure 6.37. SEM images of **1** before (*top*) and after (*bottom*) cryo-treatment. (a) A 193 μm x 117 μm area of the outer surface of **1** before liquid nitrogen treatment; (b) An 11 μm x 7 μm zoomed-in view of the materials as indicated in the white frame in (a); (c) A 193 μm x 117 μm SEM image acquired on a fragment of **1** after liquid N_2 treatment; (d) An 11 μm x 7 μm zoomed-in view of the materials as indicated in the white frame in (c).

Before cooling, the crystals were characterized using SEM imaging. As shown in Figure 6.37a and b, a wide variety of microstructure including terraces, crystal flakes, and micro cliffs. In the crystal measured in Figure 6.37b, representative of one that undergoes a mechanical response, a zoomed-in view reveals that the terrace consists of flat crystalline domains shaping like stripes separated by boundary lines. Crystal regions are typically 0.2-2 μm wide and >10 μm long, separated by linear domain boundaries.

After cooling, the crystals disintegrated into small fragments, one of which was closely examined under SEM imaging and shown in Figure 6.37c. The size of crystalline domains is significantly smaller, as major cracks and fragmentations are now present even within the single piece. This observation is consistent with pronounced cracking along the crystalline domain

boundaries. A higher resolution image of one of the terraces is shown in Figure 6.37d. The crack is still present within that terrace, which likely happened along a linear boundary, leading to the splitting line features in Figure S39d (as indicated in the white rectangular frame).

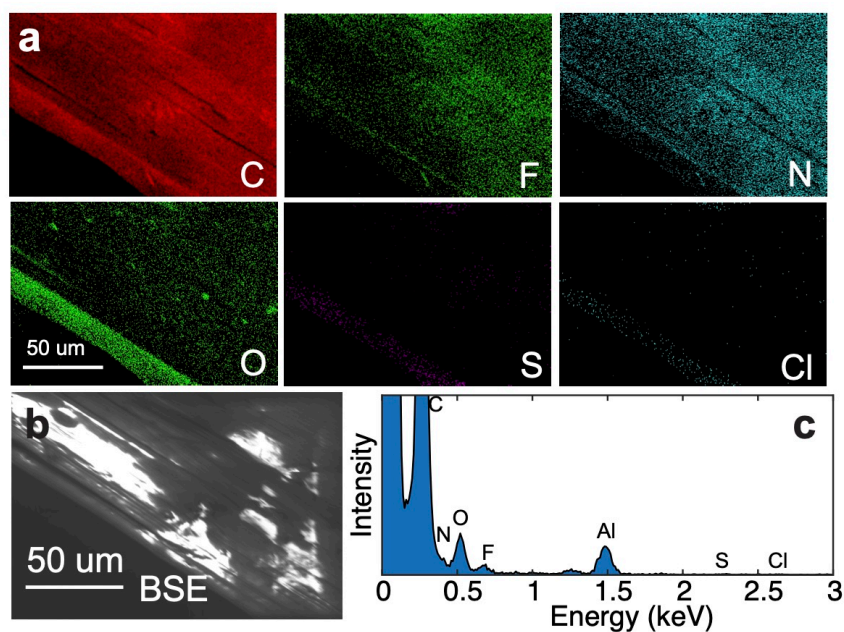


Figure 6.38. (a) SEM-EDX at 3 keV shows that the surface layer is very different from the bulk. At 3 keV, Cl Ka and S Ka are difficult to detect but are found in the crystal. (b) BSE SEM image, which is sensitive to surface defects, shows that the crystal has raised ridges defects rather than layers on the surface. (c) EDX spectrum of thermosalient crystal (1).

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