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Sírné reagenty pro nukleofilní a radikálové zavedení tetrafluorethylových a tetrafluorethylénových skupin

Sulfur-based reagents for nucleophilic and radical introduction of tetrafluoroethyl and tetrafluoroethylene groups

Disertační práce

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Praha, 2014

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis

ABSTRAKT

Tento projekt byl zacílen na vývoj nových metodologií (syntetických postupů) pro selektivní zavedení tetrafluorethylových a tetrafluorethylénových skupin do organických molekul. Výzkum byl zaměřen na reaktivitu fluorovaných sulfonů a sulfidů jako tetrafluoralkylačních reagentů.

V části Úvod této disertační práce jsou nastíněny hlavní aspekty organofluorové chemie a je zde také ilustrován efekt fluoru na fyzikální, chemické a biologické vlastnosti organických sloučenin. Jsou popsány obecné syntetické metody pro selektivní zavedení atomů fluoru a fluoralkylových skupin do organických molekul. Zvláštní pozornost je věnována reaktivitě a použití látek s CF_2CF_2 skupinou v souvislosti s obtížemi v syntetických přístupech při tetrafluoralkylaci.

Část Výsledky a diskuze popisuje reaktivitu čtyřech nových fluorovaných organosírných reagentů jako tetrafluorethylových a tetrafluorethylénových stavebních kamenů. Použití těchto reagentů jako různých karbaniontových a radikálových syntonů se ukázalo být výhodné při zavádění CF_2CF_2 skupin. Je popsána úspěšná syntetická strategie založená na nukleofilní a radikálové adici těchto reagentů na různé druhy substrátů jako např. karbonylové sloučeniny, enaminy a alkeny.

Experimentální část obsahuje detailní postupy přípravy a kompletní charakterizaci produktů.

ABSTRACT

This project was aimed at developing new methodologies for selective introduction of tetrafluoroethyl and tetrafluoroethylene groups into organic molecules. The study was focused on reactivities of fluorinated sulfones and sulfides as tetrafluoroalkylation reagents.

In the Introduction part of the thesis, main aspects of organofluorine chemistry are outlined, illustrating beneficial effects of fluorine atoms on physical, chemical and biological properties of organic compounds. General synthetic methods for the selective introduction of fluorine atoms and fluoroalkyl groups to organic molecules are described. Particular attention is given to reactivity and applications of CF_2CF_2 -containing compounds, indicating challenges in synthetic approaches toward tetrafluoroalkylation.

The Results and discussion part describes reactivities of four new fluorinated organosulfur reagents as tetrafluoroethyl and tetrafluoroethylene building blocks. The application of these reagents as various carbanionic or radical synthons proved to be effective for the incorporation of CF_2CF_2 moieties. The successful synthetic strategy based on nucleophilic and radical additions of these reagents is reported for different kinds of substrates, such as carbonyl compounds, enamines and alkenes.

The Experimental section contains detailed synthetic procedures and full characterization of products.

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Abbreviations and symbols

Å	Ångström
Ac	acetyl
AIBN	azo-bis- <i>iso</i> -butyronitrile
Alk	alkyl
aq.	aqueous
Ar	argon
Bn	benzyl
br	broad
bp	boiling point
<i>n</i> -Bu	normal butyl
<i>t</i> -Bu	tertiary butyl
ca.	circa = approximately (from Latin)
calcd	calculated
cat.	catalytic
CCDC	the Cambridge Crystallographic Data Centre
D	deuterium
d	doublet
δ	chemical shift
DAST	dimethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
ddt	doublet of doublets of triplets
DFI	2,2-difluoro-1,3-dimethylimidazolidine
DFT	density functional theory
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	2,5-dimethylpyrrole
DMSO	dimethyl sulfoxide

dr	diastereomeric ratio
dt	doublet of triplets
<i>ee</i>	enantiomeric excess
equiv	equivalents
Et	ethyl
eV	electron volt
FIS	perfluoroalkylphenyliodonium hydrogen sulfates
FITS	perfluoroalkylphenyliodonium triflates
F-TEDA-BF ₄	Selectfluor
g	grams
GCMS	gas chromatography-mass spectroscopy
h	hour(s)
HOMO	highest occupied molecular orbital
kcal	kilocalorie
kJ	kilojoule
M	mol per litre (concentration units)
m	multiplet
Me	methyl
mg	milligram
min.	minute(s)
mL	milliliter
μL	microliter
mmol	millimole
MOST	morpholino sulfurtrifluoride
mp	melting point
MP2	Møller-Plesset perturbation theory of the second order
<i>m/z</i>	mass to charge ratio
NMP	<i>N</i> -methyl-2-pyrrolidone
Pd/C	palladium on activated carbon
PFC	perfluorocarbon
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature

s	singlet
sat.	saturated
SET	single electron transfer
S _N 2	bimolecular nucleophilic substitution reaction
SOMO	singly occupied molecular orbital
t	triplet
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBABF	tetrabutylammonium bifluoride
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
td	triplet of doublets
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMAF	tetramethylammonium fluoride
TMS	trimethylsilyl
TS	transition state
Ts	<i>p</i> -toluenesulfonyl
V	volt
ν _{max}	wave number corresponding to maximal absorption in infra red spectra

1. Introduction

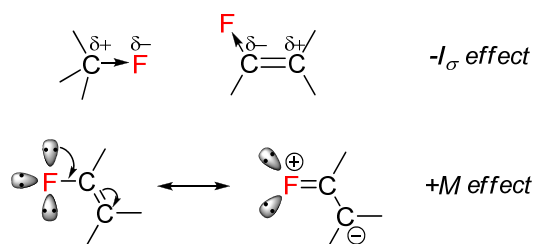
1.1 Introduction to fluoroorganic chemistry

Organofluorine chemistry has drawn an extensive scientific and commercial interest during the last few decades. Organic compounds containing fluorine atoms are widely used in various applications ranging from medicinal chemistry to material science. Nowadays, around 20% of all pharmaceuticals and 40% of all agrochemicals contain at least one fluorine atom.¹

Fluoroorganic compounds feature a set of unique and unusual chemical and physical properties which play an important role in designing new drugs and advanced materials. Most of the significant effects induced by the presence of fluorine atoms in a molecule arise from the structural and fundamental atomic properties of the fluorine: extreme electronegativity, small size, excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon, and very strong bond with carbon.

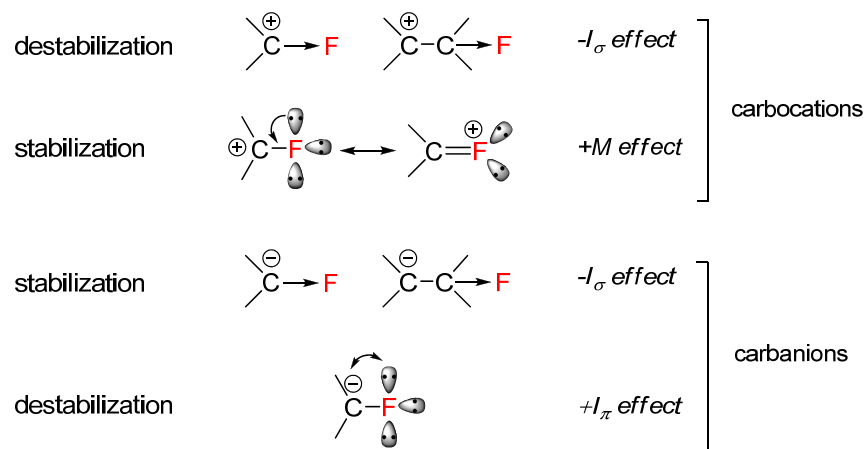
In highly fluorinated compounds such as perfluorocarbons, the presence of fluorine atoms has the strongest impact on their physical properties. Low electronic polarizability of PFCs leads to weak intermolecular interactions and consequently to low boiling points compared to hydrocarbon analogs.² Another interesting outcome of PFCs non-polar character and poor intermolecular interactions is their ability to dissolve gases, for instance oxygen. Thus, in combination with non-toxicity and physiological inertness, PFCs found their application as oxygen transfer liquids (blood substituents).³ Additionally, the great strength of the carbon-fluorine bond results in high thermal and chemical stability of perfluorinated compounds, which justifies their use as polymers and inert fluids.⁴

In contrast to highly fluorinated molecules, incorporation of few fluorine atoms (from a single F to a C₂F₅ group) significantly modifies chemical reactivity of a molecule and has only modest effect on physical properties. Fluorine, as an extremely electronegative atom, strongly influences electron distribution in a molecule. In saturated systems, carbon-fluorine bond is highly polarized due to the negative inductive ($-I_{\sigma}$) effect, which results in electron withdrawal to fluorine. However, in unsaturated systems, besides the expected $-I_{\sigma}$ effect, fluorine exerts an electron-donating effect (+M) by means of its lone-pair electrons (Scheme 1.1).



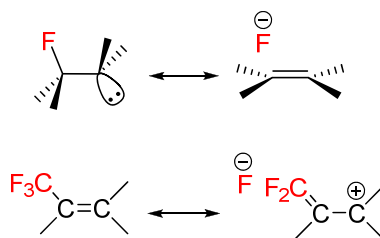
Scheme 1.1 Electronic effects of fluorine in saturated and unsaturated systems.

This versatile nature of fluorine electronic effects leads to an interesting behavior in stabilization of carbanions and carbocations. Despite the negative inductive effect, fluorine tends to stabilize α -carbocations by the overlap of its lone-pair electrons to the vacant p-orbital of the cation. Yet, it destabilizes β -carbocation because of its electron-withdrawing effect. In case of α -carbanion repulsion between adjacent electron pairs would be destabilizing while inductive effect on β -carbanion leads to its strong stabilization (Scheme 1.2).⁵



Scheme 1.2 Electronic effects of fluorine on charged species.

Moreover the concept of negative hyperconjugation can be used to explain stabilization of β -carbanion and strong activation of π double bond attached to the CF_3 -group. Here, the interaction of low-lying σ^* -orbitals of the C-F bond and filled p-orbitals on carbon induces so called “double bond-no bond resonance” (Scheme 1.3).⁶



Scheme 1.3 Fluorine hyperconjugation effect.

Because of the strong electronegativity, fluorine substitution also significantly affects acidity and basicity of organic molecules. For example, the acidity (dissociation constant) of trifluoroacetic acid ($pK_a = 0.52$) is four orders of magnitude higher than that of acetic acid ($pK_a = 4.76$).⁷

Other effects of fluorine introduction involve influence on lipophilicity and ability to interact with protons through hydrogen bonding. These factors have a large impact on the biological activity of fluoroorganic compounds. Lipophilicity, for example, controls many parameters such as absorption, biological barrier passage and interaction with the macromolecular target.⁸ Furthermore, fluorinated groups (e.g., F, CF_2) are isosteric or isopolar with various functional groups, and they can mimic them in the association processes with biological macromolecules.⁹ All these aspects together make “lightly fluorinated” molecules the focus of bioorganic and medicinal chemistry.

Despite the relatively high abundance of fluorine in earth’s crust, naturally occurring organofluorine compounds are rare.¹⁰ As a result, the field of organofluorine chemistry is obviously a synthetic field and new efficient methods for selective introduction of fluorinated species are sought after.

1.2 Synthesis of fluoroorganic compounds

The task of development new fluorination methods has presented a distinct challenge to chemists due to the specific reactivity of organofluorine compounds.

Because of the high reactivity and hazardous nature of elemental fluorine and hydrofluoric acid, chemists had to find more convenient synthetic methodologies and available starting materials for the preparation of fluorinated compounds. Over the past few decades, numerous reagents and building blocks have been discovered and great improvements have been achieved in this area.

The present chapter describes general methods for preparation of fluorinated compounds which include fluorinations and fluoroalkylations.

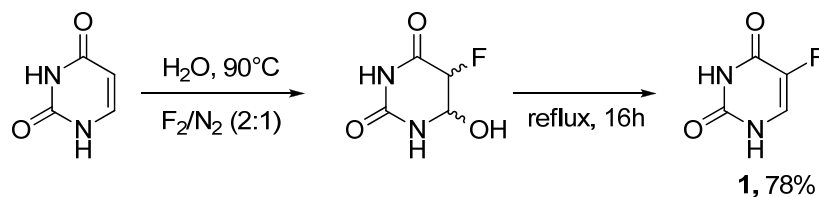
1.2.1 Fluorinations

One of the most important industrial processes for the production of perfluorinated organic compounds is the direct fluorination with fluorine gas. Reactions between hydrocarbons and elemental fluorine are extremely exothermic because of the formation of highly stable carbon-fluorine bonds (approximately $456 \text{ kJ}\cdot\text{mol}^{-1}$). Together with low homolytic dissociation energy of fluorine (ca. $157 \text{ kJ}\cdot\text{mol}^{-1}$) it leads to uncontrollable radical chain reaction, which can proceed even in the dark and at low temperature.¹¹ A number of methods were developed to control this process including dilution of fluorine with inert gases and ‘aerosol fluorination’ technique. In the latter method, an organic substrate is absorbed into fine particles of sodium fluoride which are then sprayed into a stream of dilute fluorine gas.¹² An alternative approach of improved fluorination reaction called the LaMar (Lagow-Margrave) process. It uses nickel reactor with different temperature zones and fluorine gas extensively diluted in nitrogen or helium.¹³ Using these methods, perfluorination of many hydrocarbon compounds has been accomplished.

For the production of functionalized perfluorinated compounds, such as carboxylic acids, ethers, sulfonic acids, and amines, the method of electrochemical fluorination is preferred. In this process, the organic substrate is dissolved in anhydrous hydrofluoric acid and a direct electric current is passed through the solution. Because of using low voltages (5-6 V), no fluorine gas is evolved. The reaction is supposed to proceed via the formation of high-valence nickel fluorides at the nickel anode, which act as fluorine atom carriers. During the reaction all hydrogens in an organic substrate are replaced by fluorine, but some functional groups are

retained. The industrial production of trifluoroacetic acid by electrochemical fluorination is one of the examples of commercial use of this method.¹⁴

Despite the generally unselective character of fluorination reaction it is also possible to carry out selective direct fluorination. When hydrogen is attached to carbon center of high electron density or to a heteroatom, it can be replaced with fluorine atom through electrophilic mechanism.¹⁵ Reactions are usually performed in polar solvent such as chloroform or acetonitrile.¹⁶ A regioselective introduction of fluorine by the direct reaction with the element has been demonstrated for many organic substrates, including carbanions, enolates, olefins, and certain aromatics. One of the most important industrial applications of selective direct fluorination is the synthesis of 5-fluorouracil (**1**), an anticancer drug (Scheme 1.4).¹⁷



Scheme 1.4 Synthesis of 5-fluorouracil by the direct fluorination.

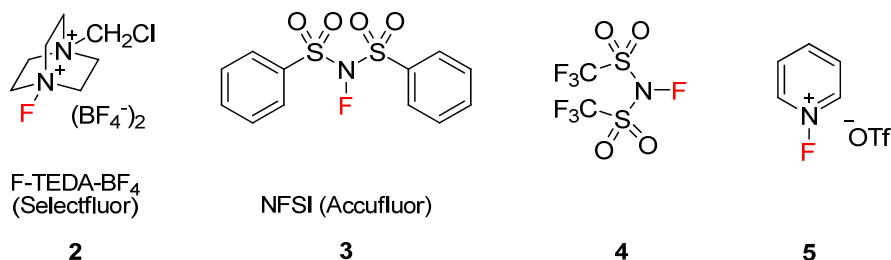
Other methods for selective introduction of a fluorine atom can be divided into two main synthetic strategies: electrophilic and nucleophilic fluorinations.

Reagents for electrophilic fluorination have been used for introducing fluorine at centers of high electron density. The ability of fluorine to act as an electrophile is achieved both by a withdrawal of the electron density from fluorine and an attachment of an excellent leaving group to fluorine.

Among the first reagent sources of positive fluorine were perchloryl fluoride (FClO_3), xenon difluoride (XeF_2), trifluoromethyl hypofluorite (CF_3OF), and various acyl and perfluoroacyl hypofluorites (RC(O)OF and $\text{R}_f\text{C(O)OF}$). These compounds show good reactivity in additions of the fluorine to carbanions and enolates and in electrophilic fluorinations of aromatics.¹⁸ While FClO_3 , XeF_2 , and the hypofluorites are generally more selective electrophilic fluorination reagents than F_2 , there are limitations that have precluded their widespread use. They are very powerful oxidizing as well as fluorinating agents. The hypofluorites are highly toxic liquids or gases. In addition, perchloryl fluoride and hypofluorites pose a constant risk of explosion.¹⁹

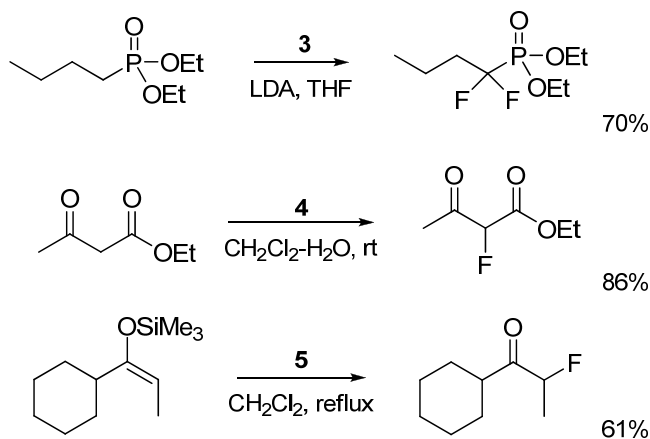
Considerable improvements have appeared in the field of electrophilic fluorination with the discovery of new so-called “NF”-reagents. These substrates have fluorine bound to

electronegative nitrogen, activated either by electron-withdrawing groups such as carbonyl or sulfonyl or by non-stabilized positive charge. Reagents of this class include, for example, Selectfluor or F-TEDA-BF₄ (**2**)²⁰, *N*-fluorosulfonimides **3**²¹ and **4**²², and 1-fluoropyridinium triflate **5**²³ (Scheme 1.5).



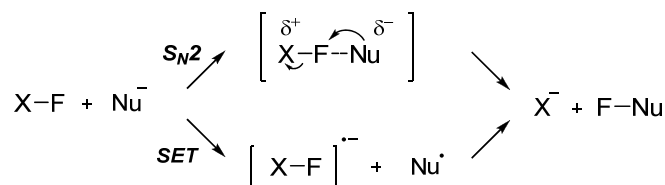
Scheme 1.5 Electrophilic fluorination reagents.

Most of these reagents are commercially available, they are stable, easy-to-handle and allow, under mild conditions, the fluorinations reaction of aromatic rings, heterocycles (nucleic bases and nucleosides), sulfoxides, sulfonamides, carbonyl derivatives, enol ethers^{20,24}, amino acids, phosphonates, alkenes, glycols^{20,21}, and allyl and aryl silanes²⁵. Some examples of selective fluorination with NF-reagents are shown in Scheme 1.6.²⁶



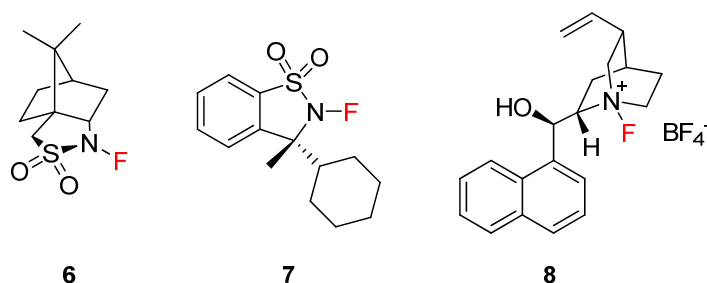
Scheme 1.6 Fluorinations using electrophilic NF-reagents.

There is a long-standing debate about the reaction mechanism for the electrophilic fluorination reaction. In particular, it is controversial, whether the reaction proceeds by a single-electron transfer (SET) or is a simple nucleophilic substitution (S_N2) at the fluorine atom (Scheme 1.7).²⁷



Scheme 1.7 Possible mechanisms for electrophilic fluorination.

Several approaches toward enantioselective electrophilic fluorination have been realized. It can be achieved by use of a variety of chiral NF-reagents, such as *N*-fluorocamphorsultam **6**, *N*-fluorosultam **7** or NF-derivatives of Cinchona alkaloids **8** (Scheme 1.8)²⁸ or by use of chiral auxiliary groups on the substrate²⁹. These reagents allow the enantioselective fluorination of different ketone enolates, although enantiomeric excesses are often moderate.

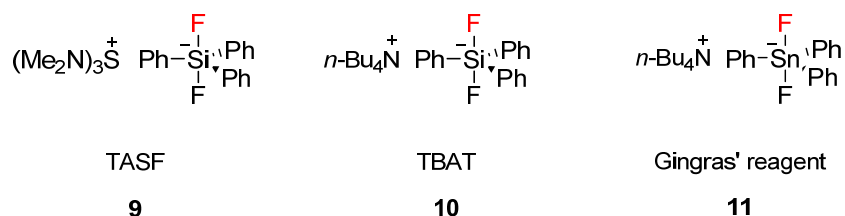


Scheme 1.8 Asymmetric electrophilic fluorination reagents.

Another synthetic strategy for the selective fluorination of organic compounds is nucleophilic fluorination. Nucleophilic reactions by means of a fluoride anion are not always straightforward. Small size (ionic radius 1.47 Å)³⁰, large negative charge density and low polarizability favor basic character of the fluoride anion and limit its nucleophilicity. Moreover, fluoride forms strong hydrogen bonds in protic solvents.³¹

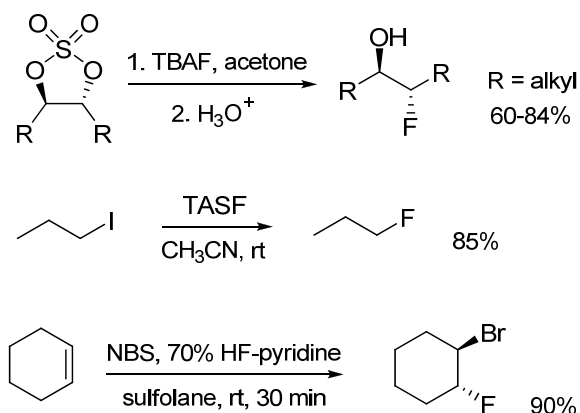
Main sources of so-called “naked fluoride” reagents are metal fluorides³² (K^+ , Cs^+ , Ag^+) and quaternary ammonium fluorides³³ $Bu_4N^+F^-$ (TBAF) and $Bu_4N^+HF_2^-$ (TBABF). These

reagents allow displacement of a sulfonate or a halide anions in polar aprotic solvents, such as acetonitrile, *N*-methylpyrrolidinone or glymes.³⁴ Such solvents dissolve sufficient metal fluoride, due to coordination of the oxygen or nitrogen donor groups with the metal cation, remaining the fluoride anion relatively unsolvated. However, low solubility, high hydroscopic nature and low reactivity of alkali metal fluorides limit their use in substitution reactions. The alternative sources of fluoride ions are difluorosilicates³⁵ (TASF **9**, TBAT **10**) and difluorostannates³⁶ (Gingras' reagent **11**) (Scheme 1.9), which are not hydroscopic, are soluble in organic solvents and show better reactivity.



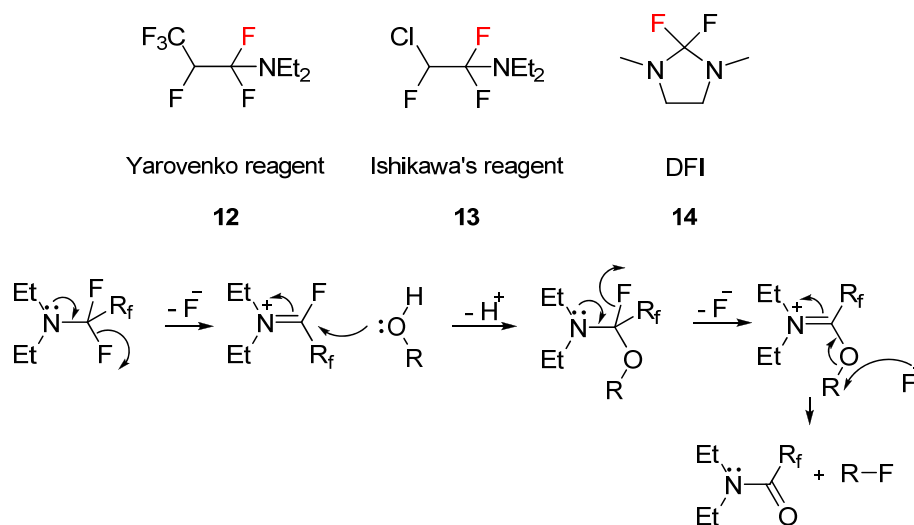
Scheme 1.9 Silicon and tin reagents as fluoride anion sources.

Various complexes of hydrogen fluoride with amines are often used as nucleophilic fluorination agents in ring opening of epoxides³⁷, hydrofluorination and halofluorination of multiple bonds³⁸. Pyridinium polyhydrogen fluoride (Olah's reagent)³⁹ and triethylamine tris(hydrogen fluoride)⁴⁰ are the most common base/HF systems. They act as more stabilized and less volatile forms of hydrofluoric acid. Some examples of nucleophilic fluorinations with fluorides and HF-amine complexes are shown in Scheme 1.10.^{35a,39,41}



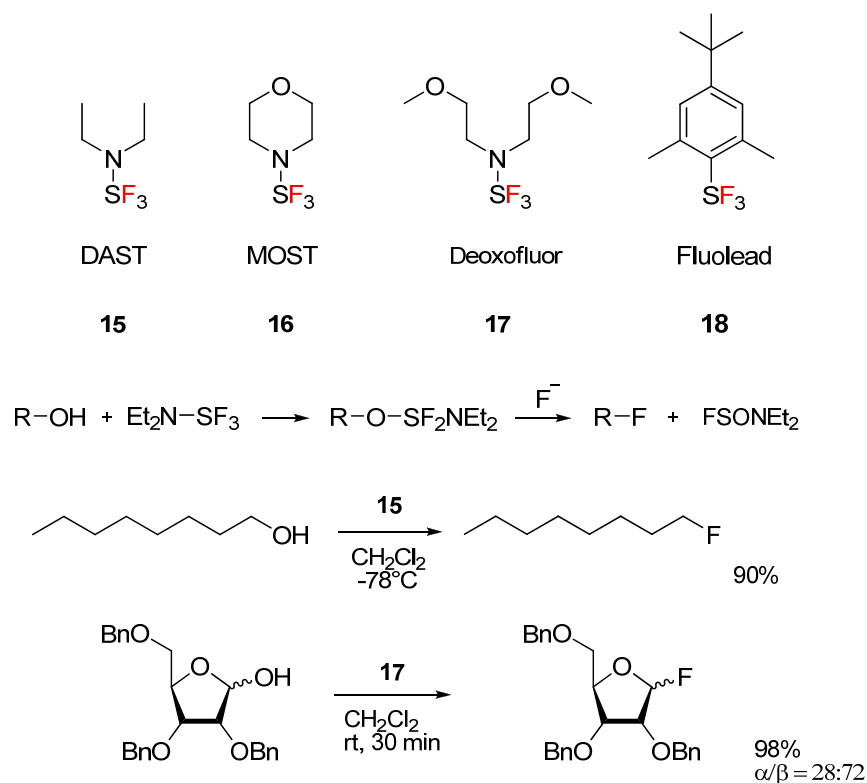
Scheme 1.10 Examples of nucleophilic fluorinations with fluorides and HF-amine complexes.

Fluoroalkylamine reagents represent another group of nucleophilic fluorination agents which are used for one-step exchange of hydroxy groups for fluorine. Examples of this kind are Yarovenko's reagent **12**⁴², Ishikawa's reagent **13**⁴³ and 2,2-difluoro-1,3-dimethylimidazolidine (DFI) **14**⁴⁴. The mechanism of their action is supposed to proceed through an activation-substitution pathway (Scheme 1.11).⁴⁵



Scheme 1.11 Examples of fluoroalkylamine reagents and possible mechanism of their action.

Replacement of the hydroxyl group can be also achieved by means of sulfur-based reagents, such as sulfur tetrafluoride (SF_4), diethylamino sulfurtrifluoride (DAST) **15**,⁴⁶ morpholino sulfurtrifluoride (MOST) **16**, Deoxofluor **17**⁴⁷ and Fluolead **18**⁴⁸ (Scheme 1.12). The most reactive sulfur tetrafluoride is used for the conversion alcohols into fluorides, fluorination of aldehydes and ketones to the corresponding difluorides, and carboxylic acids to trifluoromethyl derivatives.⁴⁹ The mechanism of the reaction is similar to that of fluoroalkylamine reagents: an alkoxy-sulfur trifluoride intermediate is attacked by a liberated fluoride anion (Scheme 1.12).⁵⁰ In spite of the versatility of SF_4 , it has some major disadvantage such as high toxicity and low boiling point (b.p. -38°C). Alkylamino derivatives of SF_4 **15-17** are less volatile and easier to handle, although the reactivity is slightly lower compared with SF_4 due to the less strong inductive effect of the dialkylamino substituents and their steric hindrance. With these reagents, primary and secondary hydroxyl groups are replaced by fluorine in excellent yields (Scheme 1.12).^{46,47,51}



Scheme 1.12 Sulfur-based fluorination reagents.

1.2.2 Fluoroalkylations

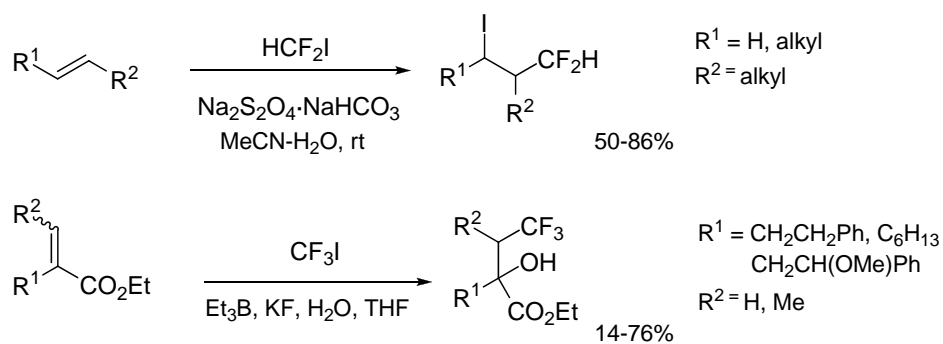
In contrast to fluorination methods described above, introduction of fluoroalkyl groups is a carbon-carbon bond forming reaction, where the transfer of fluorine atoms is performed using various building blocks, already containing carbon-fluorine fragment in their structure.

Selective fluoroalkylation is generally focused on the incorporation of perfluoroalkyl groups $-(\text{CF})_n-$, $-(\text{CF}_2)_n\text{CF}_3$, trifluoromethyl $-(\text{CF}_3)$, difluoromethyl and difluoromethylene $-(\text{CF}_2-$ and $-\text{CF}_2\text{H})$ and monofluoromethyl $-(\text{CH}_2\text{F})$. In this chapter, synthetic methods are organized by the type of fluoroalkylation: nucleophilic, electrophilic, and radical.

Fluoroalkyl radicals can be generated under oxidative, reductive, photochemical, thermal, and electrochemical conditions or by treatment with radical initiators.

Perfluoroalkyl halides serve as the most available source of perfluoroalkyl radicals. Trifluoromethyl iodide CF_3I , iododifluoromethane CHF_2I and dibromodifluoromethane CF_2Br_2 are used in the sulfinatodehalogenation reactions to transfer fluoroalkyl radical to a variety of target molecules, which have electron-rich centers such as alkenes, alkynes and

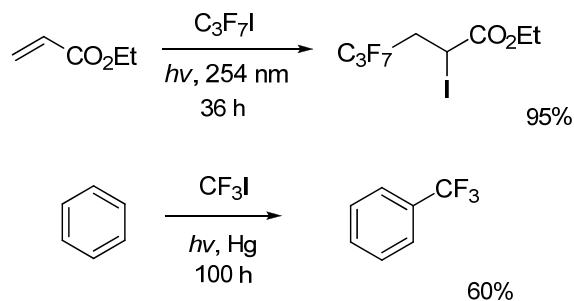
arenes.⁵² These reactions are promoted by sodium dithionite or related reagent systems, in which sulfenic radical anion generates the highly electrophilic fluoroalkyl radical. The production of fluoroalkyl radical can also be mediated by triethylborane. For example, silyl enol ethers and α,β -unsaturated ethers were reacted with CF_3 radical generated from CF_3I by means of triethylborane (Scheme 1.13).⁵³



Scheme 1.13 Radical addition of fluoroalkyl halides to unsaturated systems.

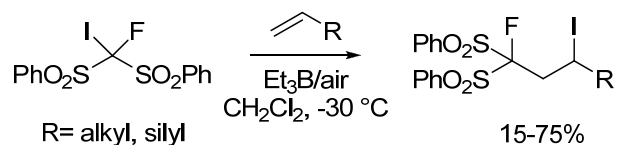
Other sources of fluoroalkyl radicals such as sodium trifluoromethanesulfinate $\text{CF}_3\text{SO}_2\text{Na}$ and trifluoromethanesulfonyl chloride $\text{CF}_3\text{SO}_2\text{Cl}$ have been developed for the introduction of CF_3 group to alkenes, enol acetates, silyl enol ethers and aromatics.⁵⁴

Photochemical and thermal activation of perfluoroalkyl halides, perfluorodiacyl peroxides and perfluoroalkyl sulfonyl halides is used for adding perfluoroalkyl radicals to olefins and aromatics (Scheme 1.14).⁵⁵



Scheme 1.14 Photochemical activation of perfluoroalkyl halides.

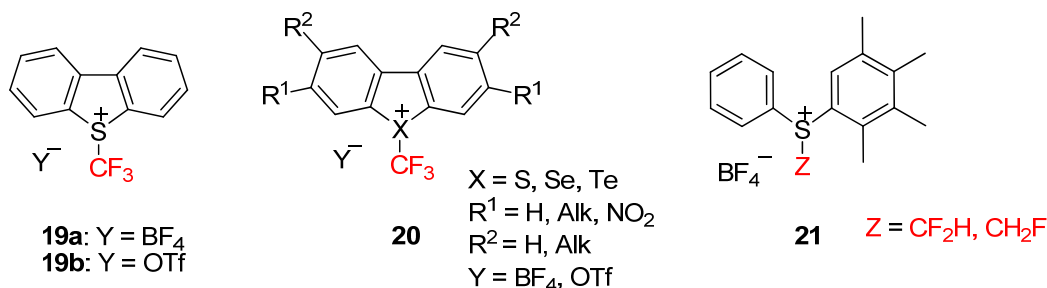
Unlike free radical trifluoromethylation and difluoromethylation, synthetic free radical monofluoromethylation is almost unknown. In 2008, Prakash presented a $\text{Et}_3\text{B}/\text{air}$ -initiated radical reaction of terminal alkenes with fluoriodobis(phenylsulfonyl)methane (Scheme 1.15).⁵⁶



Scheme 1.15 Radical fluorobis(phenylsulfonyl)methylation of alkenes.

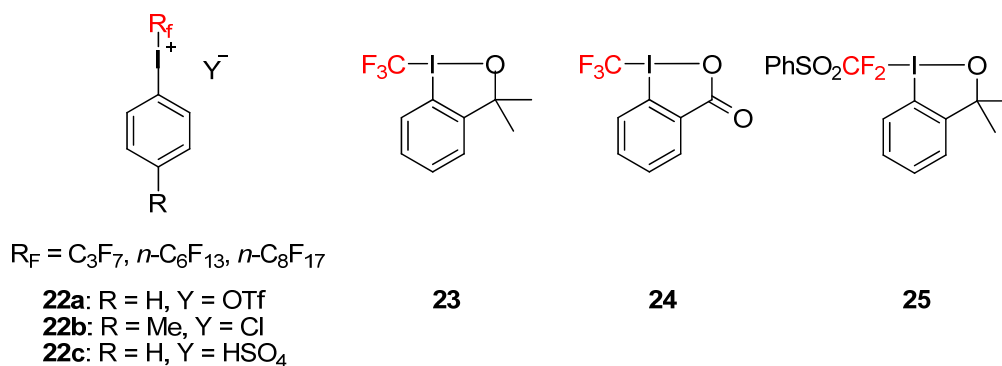
The strategy of electrophilic fluoroalkylation can be considered by analogy with electrophilic fluorination. The R_F group is expected to act as an electrophile when it is polarized in a positive sense by combination with a group containing electronegative elements. Several classes of electrophilic reagents have been developed: the chalcogen salts (sulfonium, selenonium, telluronium, and oxonium), the iodonium salts and Johnson-type reagents.

(Perfluoroalkyl)chalcogen salts **19-21** are the most widely used reagents for effective trifluoro-, difluoro- and monofluoromethylation of a wide range of nucleophiles. Typical reagents are the *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (**19a**) and triflate (**19b**), both of which are commercially available (Scheme 1.16). The reactivities of these compounds vary depending on heteroatoms and ring substituents which are present. By matching the power of the reagent with a proper nucleophilic substrate, it is possible to transfer fluoroalkyl group to C-nucleophiles (carbanions, silyl enol ethers, enamines) and to S-, O-, N-, P-nucleophiles.⁵⁷



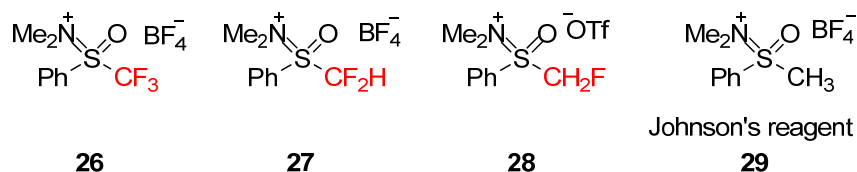
Scheme 1.16 (Perfluoroalkyl)chalcogen salts as electrophilic fluoroalkylation reagents.

Another class of electrophilic reagents is fluoroalkyliodonium salts. Perfluoroalkylphenyliodonium triflates (FITS) **22a**, *p*-tolylperfluoroalkyliodonium chlorides **22b** and perfluoroalkylphenyliodonium hydrogen sulfates (FIS) **22c** have been developed for fluoroalkylation of a variety of substrates. However, their use is limited to reagents with perfluoroalkyl groups ($R_F = (CF)_nCF_3$) only. More stable hypervalent iodine(III) reagents **23-25** were found to be efficient trifluoro- and difluoromethylating agents. They have demonstrated generality in functionalizing of β -keto esters, α -nitro esters, thiols, phosphines and aliphatic alcohols (Scheme 1.17).



Scheme 1.17 Perfluoroalkyliodonium salts as electrophilic fluoroalkylation reagents.

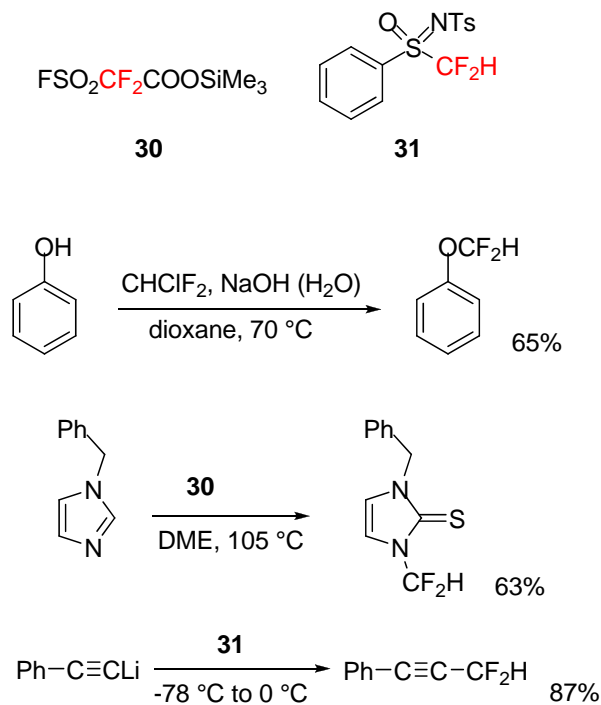
More recently fluoroalkyl analogs **26-28** of Johnson's methyl-transfer reagent **29** have been reported as efficient trifluoro-, difluoro- and monofluoromethylating agents for carbon and oxygen nucleophiles (Scheme 1.18).⁵⁸



Scheme 1.18 Fluoroalkylsulfoxinium salts as electrophilic fluoroalkylation reagents.

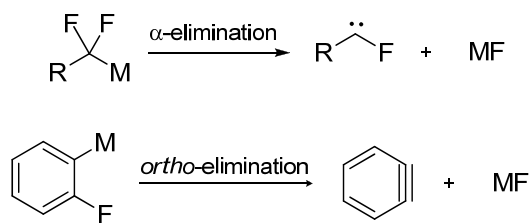
All above mentioned electrophilic fluoroalkylation methods represent a strategy where the reagent transfers an electrophilic species R_F^+ to a target molecule, by S_N2 type mechanism or single electron transfer mechanism. An alternative route to electrophilic fluoroalkylation is based on difluorocarbene reagents. Some important examples of difluorocarbene precursors

include halofluoromethanes⁵⁹ (CHClF_2 , CF_2Br_2), chlorodifluoroacetic acid derivatives⁶⁰, such as $\text{ClCF}_2\text{COONa}$ and $\text{ClCF}_2\text{COOMe}$, trimethylsilyl fluorosulfonyldifluoroacetate⁶¹ (TFDA) **30** and *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine⁶² (**31**) (Scheme 1.19).



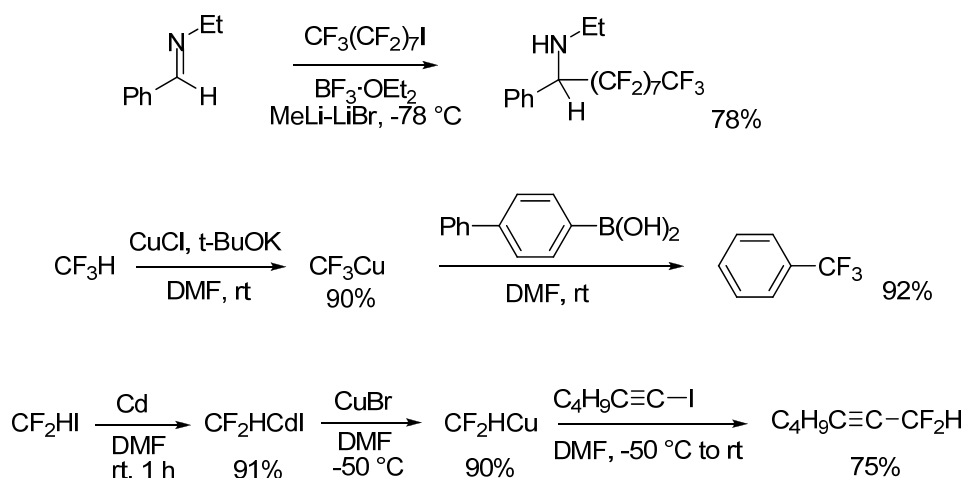
Scheme 1.19 Electrophilic difluoromethylation with difluorocarbene reagents.

For nucleophilic perfluoroalkylation, either α -fluoro carbanion or its equivalent (i.e., a pentacoordinate silicon species) or a fluoroalkyl metal species ($\text{R}_\text{F}\text{M}$), must be generated and reacted with a suitable electrophile. Generally, it can be done by the same methods as usual alkyl or aryl anions: deprotonation of C-H bonds with strong bases or by exchange of a halogen atom with a metal atom. However, specific features of perfluoroalkyl carbanions should be taken into account while working with them. One of the difficulties lies in low thermal stability of the fluoroalkyl anions. Despite a certain stabilization of carbanion through negative inductive effect of fluorine atom, the strong repulsion between lone pair of the carbanion and those on fluorine atom can result in α -elimination of a fluoride ion. Moreover, when the carbanion is bound to a metal of “hard” nature such as lithium, high lattice energy of LiF formation ($247 \text{ kcal mol}^{-1}$) favors the fragmentation of the fluoroalkyl metal compound (Scheme 1.20).⁶³



Scheme 1.20 Fragmentation pathways of fluorocarbon metal compounds.

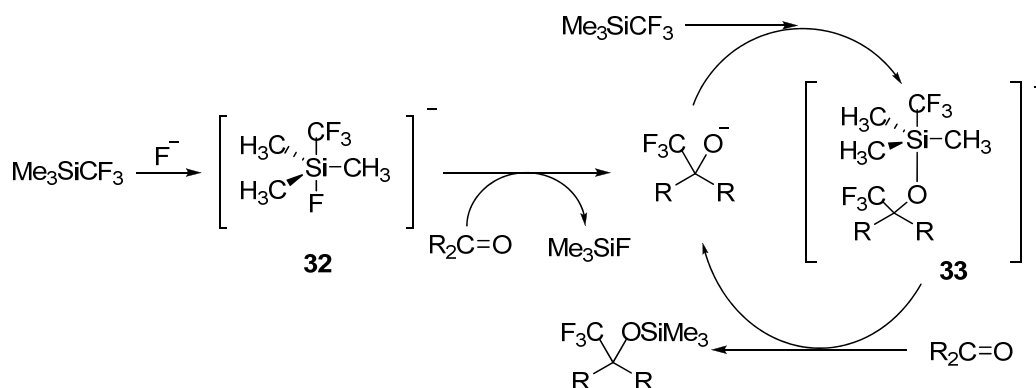
Some perfluoroalkyl lithium compounds can be generated *in situ* at very low temperatures and immediately reacted with an electrophile.⁶⁴ More stable perfluoroalkyl metal compounds can be achieved using “soft” Lewis acids, such as zinc, cadmium or copper. Such compounds are stabilized due to the more covalent character of the metal-carbon bond, and therefore can be readily isolated, handled and reacted over a broad temperature range. Perfluoroalkyl copper reagents are commonly used in cross-coupling reactions (Scheme 1.21).⁶⁵



Scheme 1.21 Nucleophilic fluoroalkylation with perfluoroalkyl metal compounds.

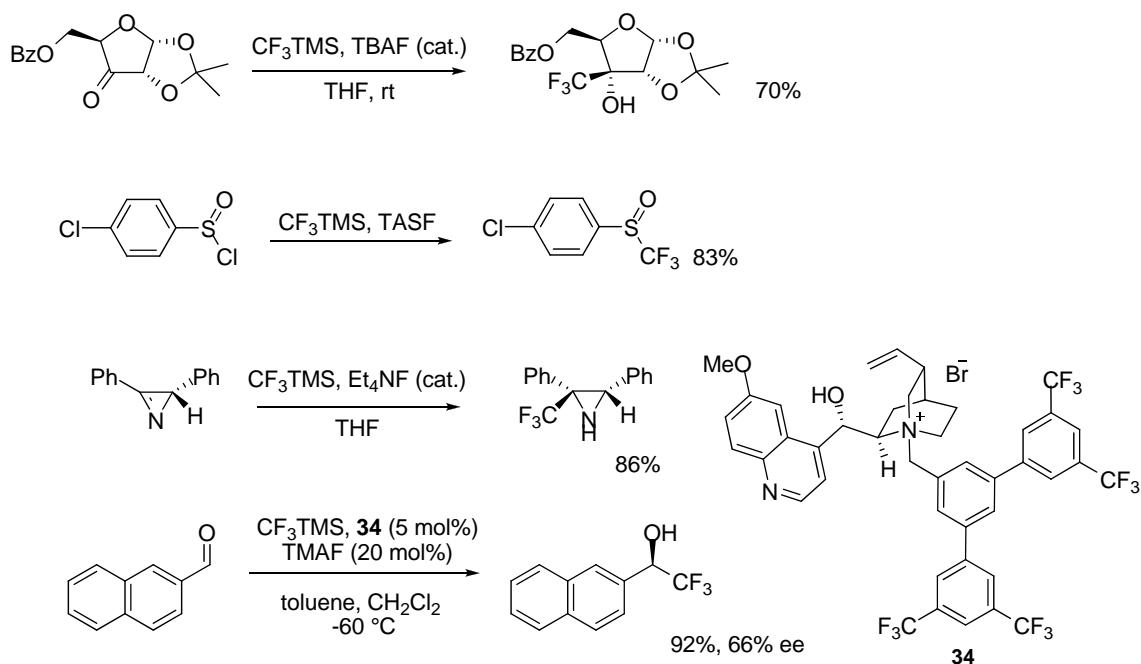
A major breakthrough in the field of nucleophilic fluoroalkylation was the discovery of trifluoromethyl(trimethyl)silane CF_3SiMe_3 (the Ruppert-Prakash reagent). The efficiency of this reagent is due to the fact that the reaction does not involve the formation of a free CF_3^- anion, but proceeds through a pentacoordinated siliconate intermediate, where negative charge brought by the CF_3 is involved in a labile σ -bond with the silicon atom. The chain reaction starts with catalysis by a suitable initiator forming siliconate species **32**, which adds

to an electrophile. The resulting alkoxy trimethyl trifluoromethyl siliconate intermediate **33** acts as a real agent (nucleophilic initiator) for the transfer of the CF₃ group (Scheme 1.22).⁶⁶



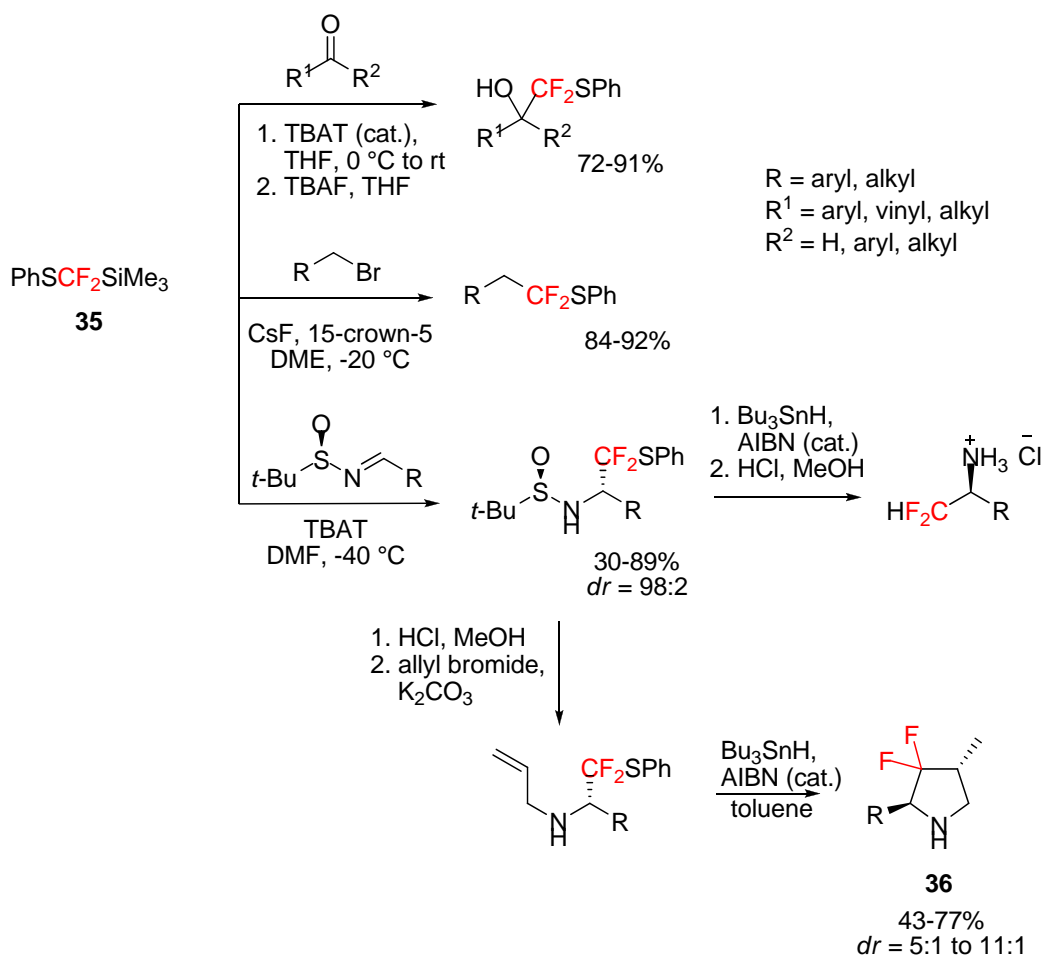
Scheme 1.22 Mechanism of nucleophilic trifluoromethylation of carbonyl compounds by Me₃SiCF₃.

The Ruppert-Prakash reagent has become popular in organic synthesis because of its stability, convenience of handling (the boiling point of Me₃SiCF₃ is 54-55 °C) and the remarkable properties as a nucleophilic trifluoromethylating agent. The nature of the initiator and the choice of the solvent have a major role in the success of the reaction. Most widely used initiators are various fluoride sources, such as cesium fluorides, TBAF, tetramethylammonium fluoride (TMAF) or TBAT. Other kinds of catalysts including metal alkoxides, amine N-oxides, acetates, phosphines and even Lewis acids are also suitable for the activation of trifluoromethyl(trimethyl)silane.⁶⁷ This reagent easily reacts with numerous types of carbonyl compounds, imines, thiocyanates, disulfides and other electrophiles.⁶⁸ Trifluoromethylated analogs of natural products, such as carbohydrates, nucleotides and steroids, have been prepared by this general approach.⁶⁹ The synthesis of enantiomerically enriched trifluoromethylated compounds has been achieved by means of Me₃SiCF₃ in the presence of chiral quaternary ammonium fluoride catalysts, such as Cinchona alkaloids, however, enantioselectivity is often relatively modest.⁷⁰ Some selected examples of the synthetic utility of the Ruppert-Prakash reagent are shown in Scheme 1.23.



Scheme 1.23 Nucleophilic trifluoromethylation with CF_3SiMe_3 reagent.

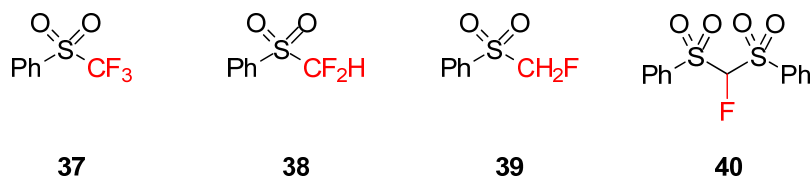
Difluoro- and monofluoromethylated analogs of the Ruppert-Prakash reagent have also been investigated. Such reagents as $\text{R}_3\text{SiCF}_2\text{H}$ and $\text{TMSCF}_2\text{CH}_3$ showed lower reactivity in nucleophilic addition to carbonyl compounds compared with Me_3SiCF_3 . This is probably due to the fact that $\text{Si}-\text{CF}_2$ bond is less polarized, which makes its cleavage more difficult.⁷¹ To solve this problem, several functionalized difluoromethylsilanes have been developed. Electron-withdrawing phenylthio group was used as an activating group to facilitate the reactivity of [difluoro(phenylthio)methyl]trimethylsilane ($\text{PhSCF}_2\text{SiMe}_3$, **35**). Under fluoride-induced conditions reagent **35** can efficiently transfer the “ PhSCF_2 ” group into electrophilic substrates. It was successfully applied in nucleophilic additions to carbonyl compounds, primary alkyl halides and imines. Moreover, its synthetic application as a difluoromethylene radical anion synthon ($^-\text{CF}_2$) has been demonstrated in the preparation of fluorinated pyrrolidines **36** (Scheme 1.24).⁷²



Scheme 1.24 Nucleophilic difluoromethylation with $\text{PhSCF}_2\text{SiMe}_3$ (**35**) and transformations of (phenylthio)difluoromethylated compounds.

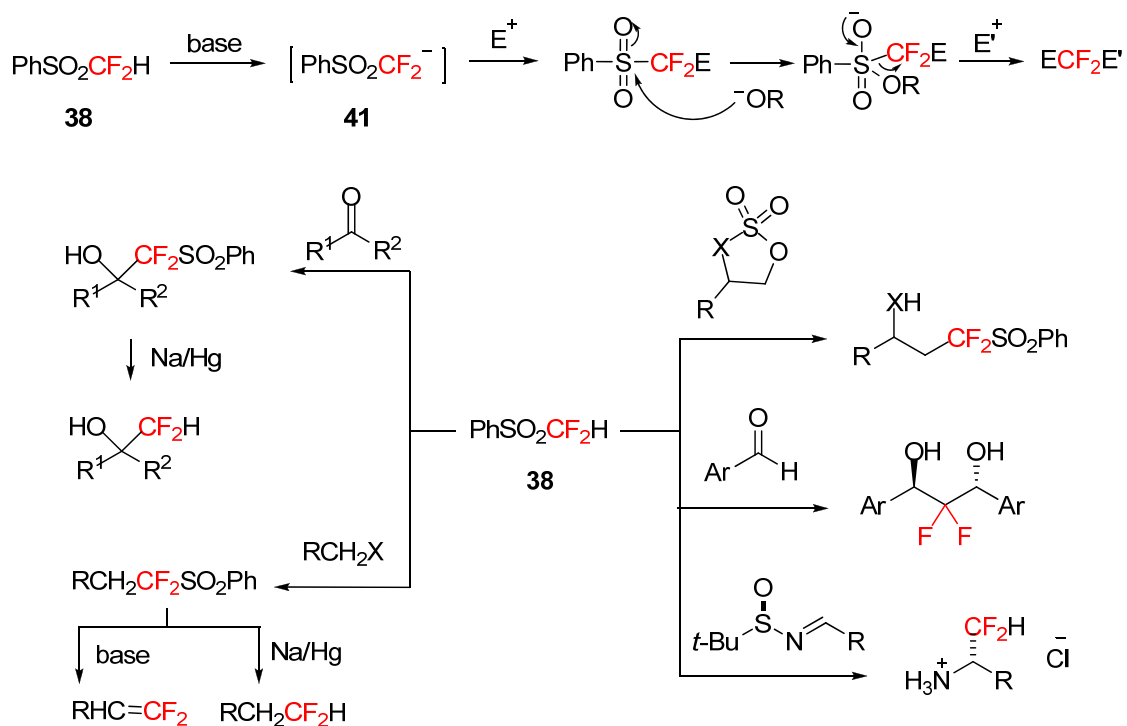
An alternative approach towards nucleophilic fluoroalkylation has been realized using functionalized fluoroalkyl derivatives. The presence of an electron-withdrawing group (such as sulfonyl, sulfinyl, sulfanyl, carbonyl, phosphonyl, ester, cyano or nitro) at fluoroalkyl center can significantly stabilize the fluorinated carbanions via electron delocalization.⁷³

The phenylsulfonyl group is one of the most frequently used functionalities due to its versatility: it possesses strong electron-withdrawing ability, stabilizing the fluorinated carbanion, and act as an auxiliary group that can be removed. Substrates **37-40** work as nucleophilic fluoroalkylation reagents for the transfer of either $-\text{CF}_3$, $-\text{CF}_2\text{H}$, or $-\text{CH}_2\text{F}$ moieties (Scheme 1.25).⁷⁴



Scheme 1.25 Sulfone-based nucleophilic fluoroalkylation reagents.

Using the appropriate base, deprotonation or S-C bond cleavage occurs, generating a fluorinated carbanion, which can be treated with a suitable electrophile. For example, substrate **38** has been extensively used as a nucleophilic difluoromethylation reagent. Under activation by *t*BuOK or LHMDS it forms PhSO₂CF₂⁻ anion **41**, which reacts with alkyl halides, aldehydes and ketones, imines, cyclic sulfates, and sulfamidates to give corresponding substitution or addition products. (Phenylsulfonyl)difluoromethyl group can be further transformed into difluoromethyl (CF₂H) and difluoromethylidene (=CF₂) functionalities via reductive desulfonation or base-mediated dehydrosulfonylation (Scheme 1.26).⁷⁵

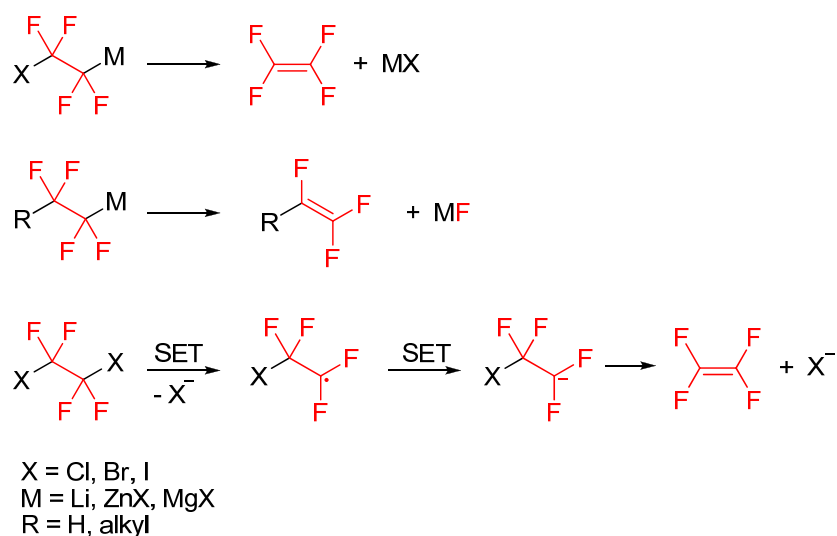


Scheme 1.26 Nucleophilic difluoromethylation reactions with PhSO₂CF₂H (**38**).

1.3 Incorporation of tetrafluoroethyl (–CF₂CF₂H) and tetrafluoroethylene (–CF₂CF₂–) groups

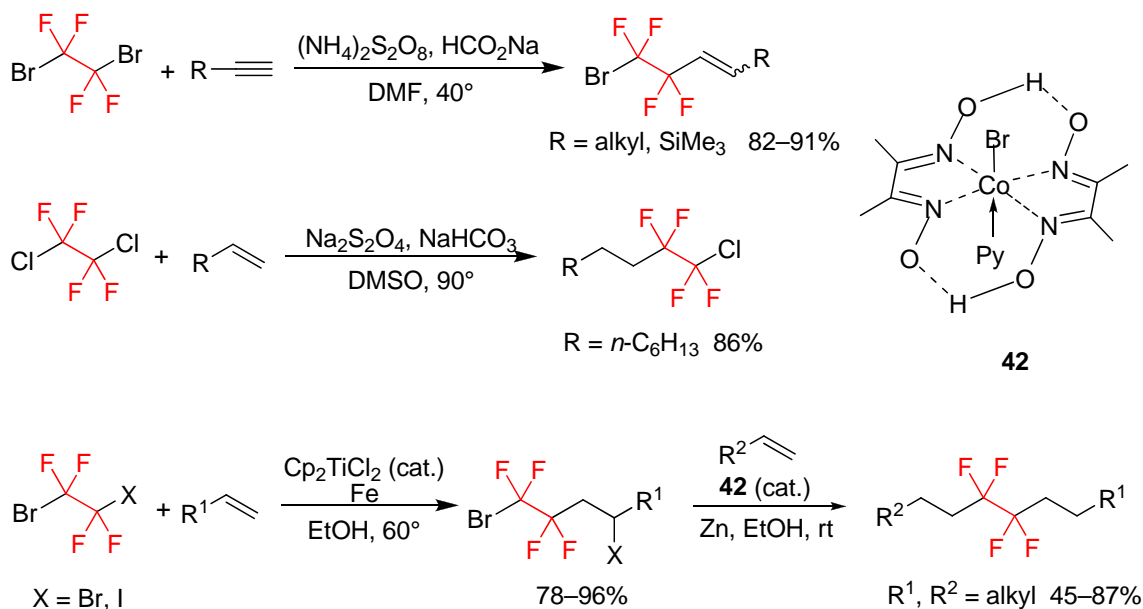
The present chapter gives a general overview of different aspects of tetrafluoroethylene (–CF₂CF₂–) motif, the synthesis of organic compounds containing –CF₂CF₂– group, their reactivity and applications.

Tetrafluoroethylene group, in comparison to other fluoroalkyl groups, has not been extensively studied and methods for selective introduction of tetrafluoroethyl or tetrafluoroethylene moieties are just emerging. A major challenge related to tetrafluoroethylene group transfer is decomposition of anionic or radical CF₂CF₂ species via a highly favourable β -elimination mechanism. Organometallic compounds suffer from facile β -halogen eliminations affording terminal perfluoroalkenes or tetrafluoroethylene. In the same manner, 2-halotetrafluoroethyl radicals undergo β -fragmentation in radical reactions of tetrafluoroethylhalides (Scheme 1.27).⁷⁶



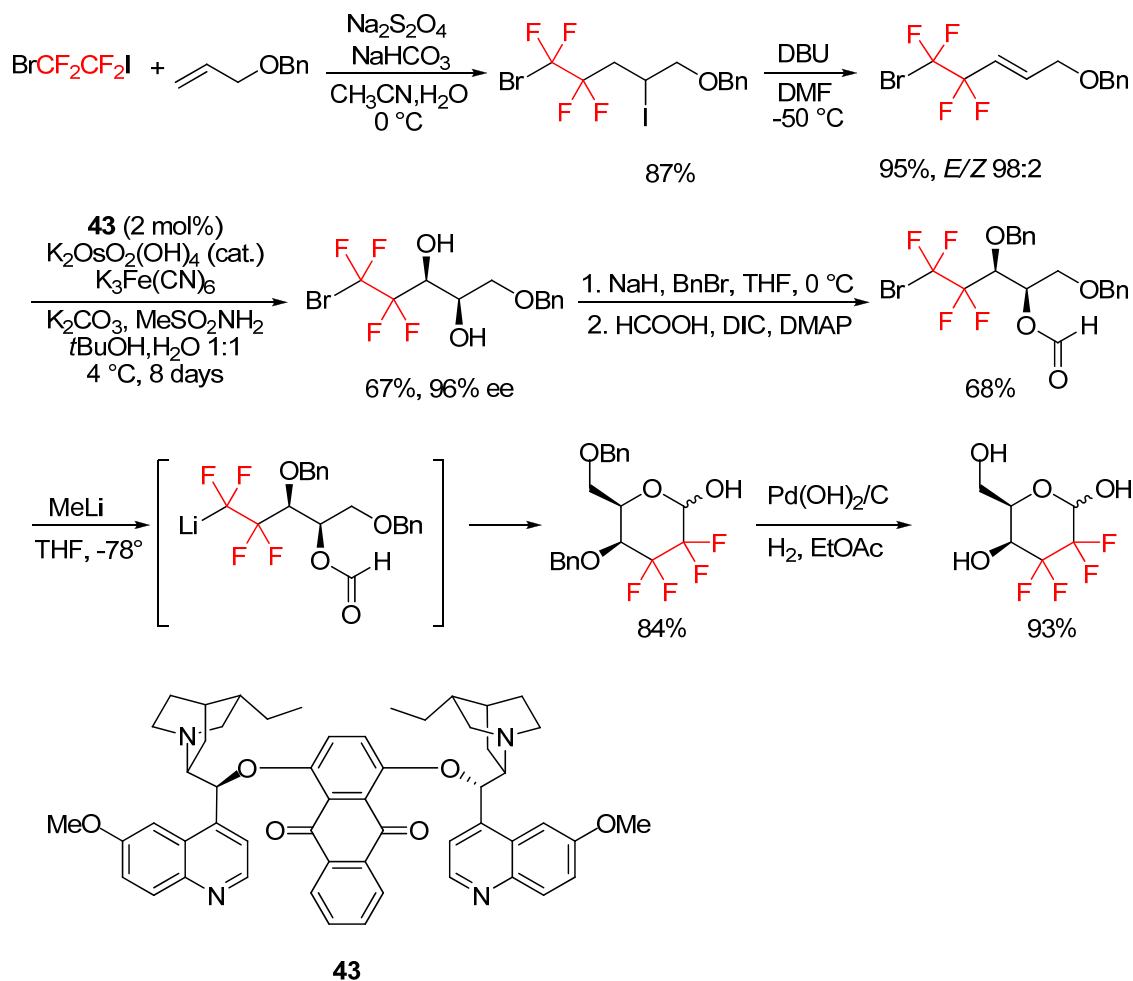
Scheme 1.27 β -fragmentation pathways of tetrafluoroethylene species.

Dihalotetrafluoroethanes XCF₂CF₂X (X = Cl, Br, I) are the most available precursors for the synthesis of tetrafluoroethylene containing compounds. Groups of Chen and Hu developed radical fluoralkylation of alkenes and alkynes promoted by ammonium peroxydisulfate/sodium formate redox system⁷⁷, sodium dithionite in basic media⁷⁸ or by means of cobaloxime/Zn redox couple and Fe/Cp₂TiCl₂⁷⁹ (Scheme 1.28).



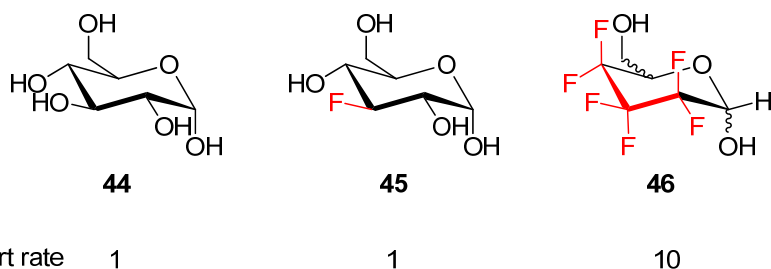
Scheme 1.28 Synthesis of tetrafluoroethylene-containing compounds by radical chain reactions.

This radical approach was used for the preparation of tetrafluoroethylene-containing sugars and C-nucleosides derivatives. Linclau and co-workers described the enantioselective synthesis of tetrafluorinated glucose and galactose derivatives. In the first step, the $\cdot\text{CF}_2\text{CF}_2\text{Br}$ radical is generated from $\text{BrCF}_2\text{CF}_2\text{I}$ using sodium dithionite and added to allyl benzyl ether. Later in the sequence, the fluorinated organolithium substrate is prepared by the reaction of $\text{RCF}_2\text{CF}_2\text{Br}$ with MeLi followed by the nucleophilic addition to a carbonyl group (Scheme 1.29).⁸⁰ This concept has been used and extended for the synthesis of a number of monosaccharides and C-nucleoside analogs with tetrafluoroethylene fragment.⁸¹



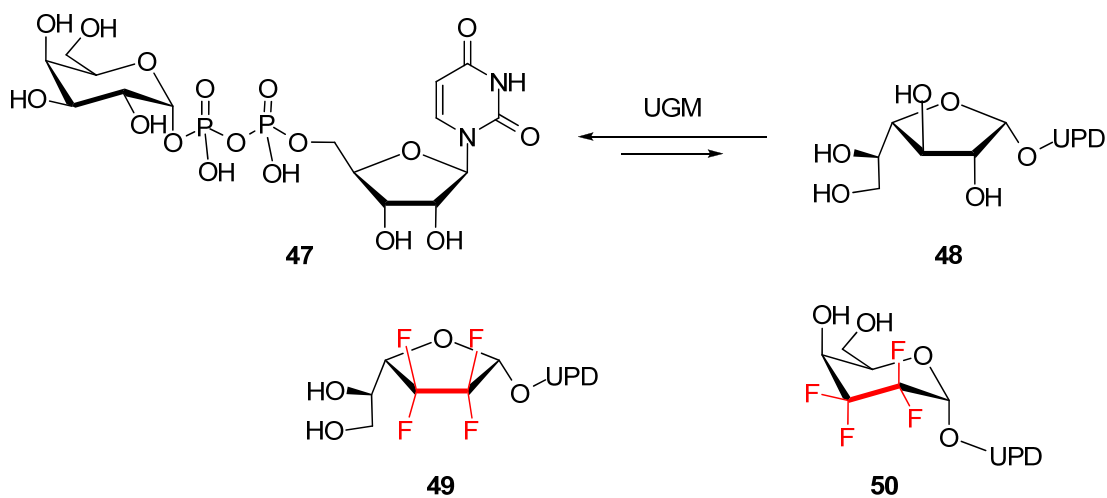
Scheme 1.29 Enantioselective synthesis of 2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactose.

The interest in the synthesis of heavily fluorinated carbohydrate analogues originated from the pioneering report of DiMugno and co-workers. It was shown that 1-hydroxy-5-hydroxymethyl-2,2,3,3,4,4-hexafluorooxane **46** crosses the red blood cell membrane at an approximately ten times higher rate than 3-deoxy-3-fluoro-D-glucose **45**, while the permeability of **45** is very similar to that of glucose **44** (Scheme 1.30). It was proven that the rate increase was the result of higher affinity of **46** to the transporter protein.⁸² A concept of “polar hydrophobicity” was proposed to explain the enhanced protein-binding affinity for fluorinated sugars in comparison to nonfluorinated ones. It was suggested that replacement of hydroxyl groups with fluorines in carbohydrates increases the free energy of binding due to two major factors: desolvation of hydrophobic fluoroalkyl surface and favourable dipolar interactions of the C-F bond and a receptor binding site. These effects together provided a more specific molecular recognition.⁸³



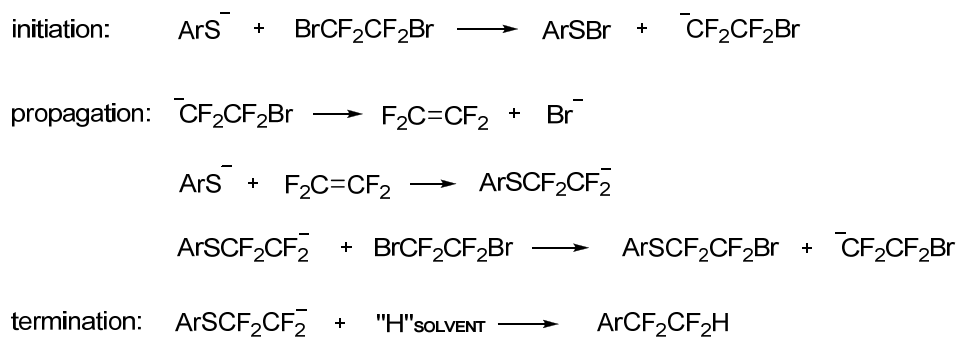
Scheme 1.30 Relative transport rate of carbohydrates across erythrocyte membrane.

A very recent study on tetrafluorinated analogs of UDP-galactopyranose **49** and UDP-galactofuranose **50** showed higher binding of the corresponding substrates to UDP-galactopyranose mutase (UGM) compared to the parent, natural 2,3-dihydroxylated substrate **47** (Scheme 1.31). UGM is a key enzyme in the biosynthesis of the mycobacterial cell wall, where it catalyzes isomerization of the substrate **47** to UDP-galactofuranose **48**. Tetrafluorinated sugar derivatives as better binders can inhibit enzyme action and therefore prevent mycobacterial proliferation.⁸⁴



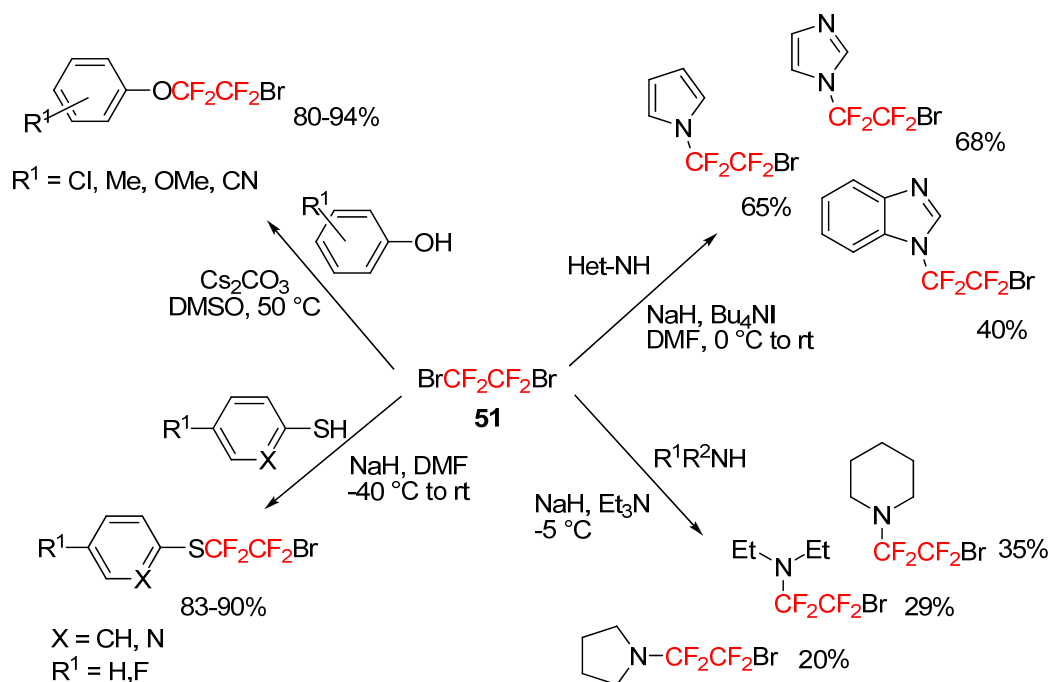
Scheme 1.31 Tetrafluorinated analogs of UDP-galactopyranose as inhibitors of UGM.

Dihalotetrafluoroethanes were reported to react with phenolates, thiophenolates and salts of heterocyclic amines and alkylamines. In these reaction systems, halophilic attacks of sulfur, oxygen or nitrogen nucleophiles on C-Br bond are involved. Reaction proceeds via an ionic chain mechanism passing through tetrafluoroethylene formation (Scheme 1.32).⁸⁵



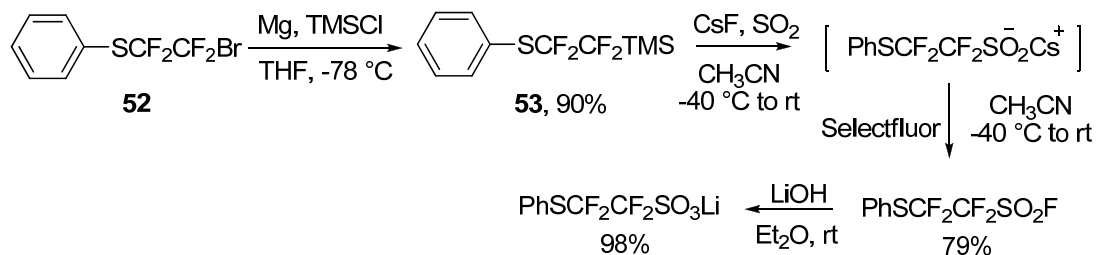
Scheme 1.32 An ionic chain mechanism for reactions of thiophenolates with $\text{BrCF}_2\text{CF}_2\text{Br}$.

1,2-Dibromo-1,1,2,2-tetrafluoroethane $\text{BrCF}_2\text{CF}_2\text{Br}$ (**51**) acts both as a brominating agent and a tetrafluoroethylene precursor. Thiophenols and phenols with different substituents in aromatic rings can be converted to O-, and S-tetrafluoroethylene derivatives (Scheme 1.33).⁸⁶ In the case of alkylamines N-(2-bromotetrafluoroethyl) products were found to hydrolyze easily, while N-fluoroalkylated nitrogen-containing heterocycles are more stable owing to the involvement of the nitrogen lone pair in the aromatic six-electron π -system (Scheme 1.33).⁸⁷



Scheme 1.33 Reactivity of $\text{BrCF}_2\text{CF}_2\text{Br}$ toward S-, O-, N-nucleophiles.

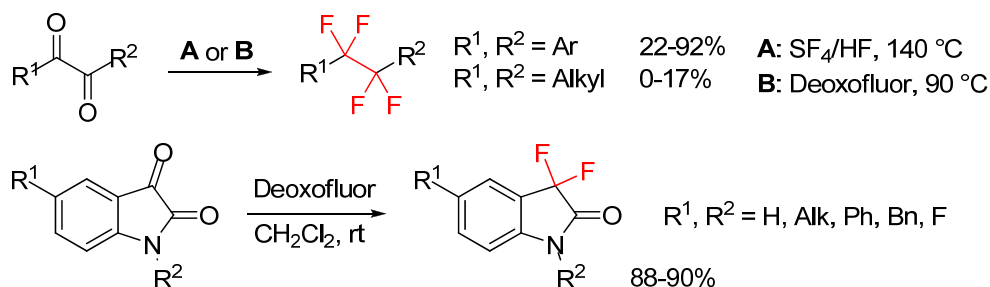
Some of the obtained bromotetrafluoro derivatives were further functionalized by the replacement of the remaining bromine atom. For example, silane **53** was prepared by the treatment of sulfonyl compounds **52** with magnesium and trimethylchlorosilane. It was further converted to sulfonyl fluoride and lithium sulfonate, which have potential application as electrolytes in lithium-polymer batteries (Scheme 1.34).^{86c,88}



Scheme 1.34 Preparation of tetrafluoroethanesulfonyl fluorides and lithium sulfonates from $\text{BrCF}_2\text{CF}_2\text{Br}$.

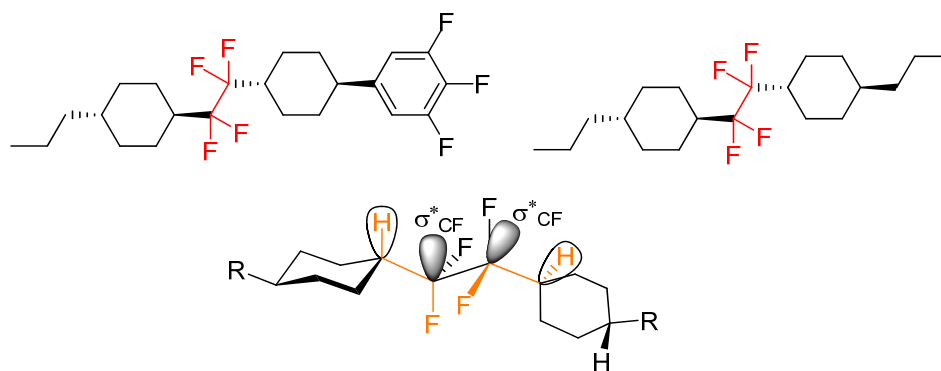
A number of compounds with aryl tetrafluoroethyl ether fragment were shown to have display activity as inhibitors of cholesteryl ester transfer protein for the treatment of atherosclerosis and coronary heart disease.⁸⁹

Another approach toward tetrafluoroethylene-containing compounds is based on the use of sulfur tetrafluoride (SF_4) and Deoxofluor. In a single-step reaction, α -diketones can be converted to tetrafluoro products (Scheme 1.35). This reaction is very much dependent on the nature of the substituents vicinal to the carbonyl group. Benzil derivatives were found to be the most reactive substrates, whereas compounds with alkyl substituents give very low yields.⁹⁰ With α -ketoamides only one carbonyl can be converted to the CF_2 -group, the carbonyl vicinal to the nitrogen atom is deactivated by the donation of the lone pair of electrons from the nitrogen to the carbonyl carbon, thus reducing its electrophilic character.⁹¹



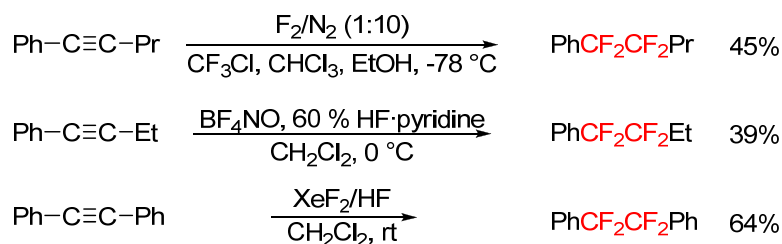
Scheme 1.35 Tetrafluorination of dicarbonyl compounds with sulfur-based reagents.

This method was used and extended to the synthesis of liquid crystals containing a tetrafluoroethylene bridge in their structure (Scheme 1.36). Such fluorinated liquid crystals displayed improved mesogenic and viscoelastic properties compared to non-fluorinated analogous materials. These properties depend to a great extent on molecular geometry. The effect of the fluorine bridge is in stabilization of a linear, minimum-energy conformation of the liquid crystal molecule. The $\text{CF}_2\text{-CF}_2$ fragment adopts a conformation where alkyl substituents in anti-periplanar positions, one C-F bond is anti-parallel to the axial bridgehead hydrogen and the other anti-parallel to the adjoining cyclohexane C-C bond (Scheme 1.36). This combination of steric and stereoelectronic effects favours rod-like conformers, which exhibit improved liquid crystals behavior.^{90c,92}



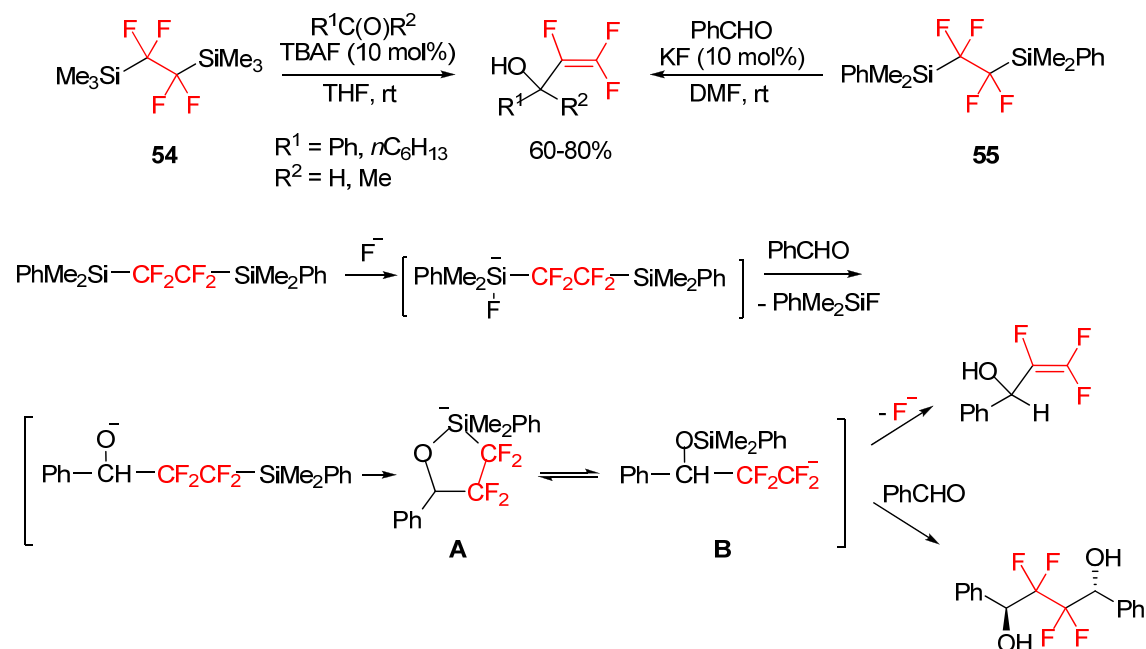
Scheme 1.36 Liquid crystals containing a $\text{CF}_2\text{-CF}_2$ bridge and their conformational structure.

Compounds with the internal $\text{CF}_2\text{-CF}_2$ group can be prepared by reactions of arylacetylenes with elemental fluorine, by the treatment with XeF_2/HF or with nitrosonium tetrafluoroborate (NO^+BF_4^-) and pyridinium polyhydrogen fluoride (PPHF) reagent which acts as a convenient *in situ* F_2 equivalent.⁹³ Fluorine addition proceeds selectively across the triple bond, giving good yields for diarylacetylenes and moderate yields for monoarylsubstituted acetylenes (Scheme 1.37).



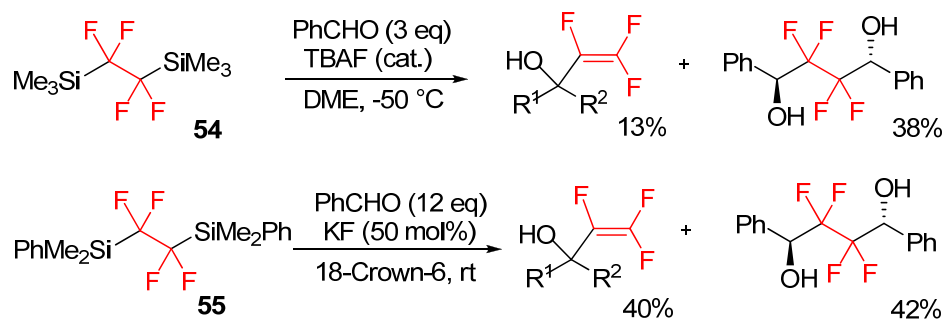
Scheme 1.37 Preparation of tetrafluoro derivatives by the fluorination of arylacetylenes.

Silylated tetrafluoroethanes **54-55** with two silyl groups attached to the adjacent carbon atoms seemingly represent the ${}^{-}\text{CF}_2\text{CF}_2{}^{-}$ dianion equivalent. However, when these reagents were subjected to nucleophilic addition to carbonyl compounds at room temperature, no formation of tetrafluoroethylene-containing products were observed. Due to the highly favored β -fluoride elimination, trifluorovinylated compounds were formed as sole products (Scheme 1.38). The mechanism is supposed to proceed via a cyclic pentacoordinate silicon intermediate **A**, producing a carbanion **B**, which easily eliminates fluoride ion.⁹⁴



Scheme 1.38 Formation of trifluorovinylated compounds.

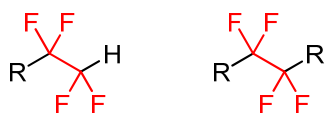
The elimination pathway can be suppressed at low temperature or by using large excess of carbonyl compounds at room temperature. Under such conditions mixtures of trifluorovinylalcohols and tetrafluoroethylene-containing diols are formed (Scheme 1.39).^{94,95}



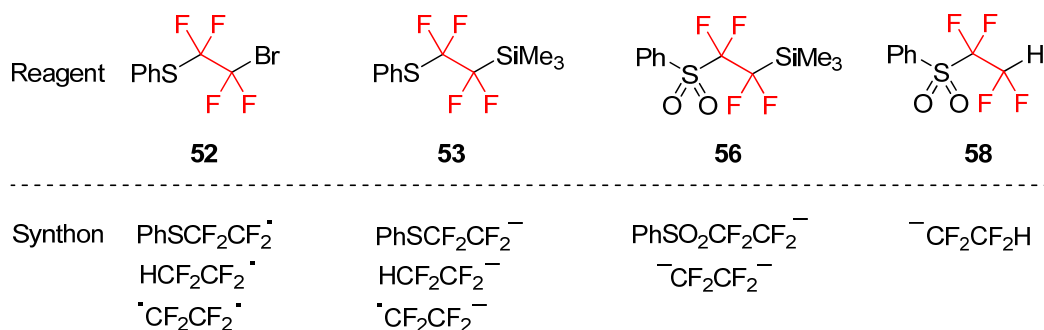
Scheme 1.39 Formation of tetrafluorinated diols.

2. Aims of the project

The primary aim of the project was to develop new synthetic methodologies for the introduction of tetrafluoroethyl and tetrafluoroethylene groups to organic molecules.



The main goal was to explore reactivity of sulfur containing reagents **52**, **53**, **56** and **58** as various carbanionic or radical synthons for the preparation of CF_2CF_2 -containing compounds.



Research objectives were to find optimal reaction conditions for the activation of radical and anionic centers of the reagents and study their reactivities in nucleophilic and radical reactions.

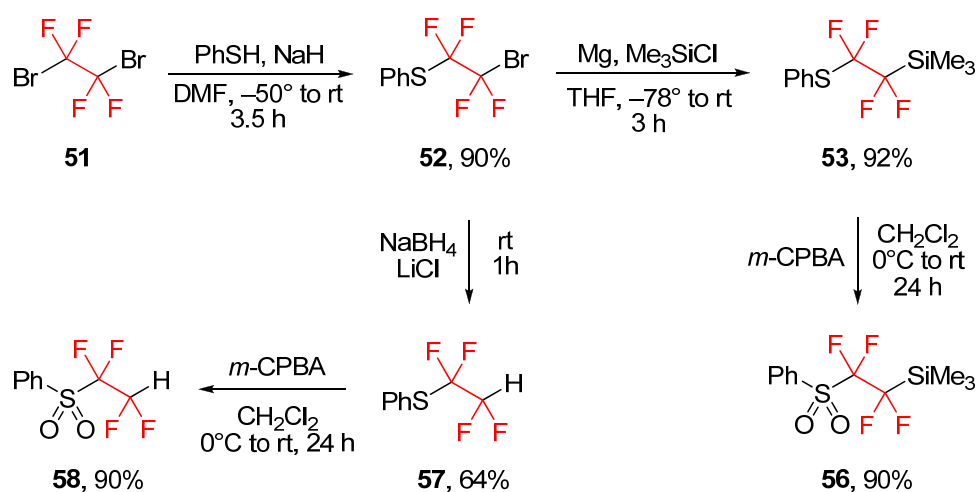
3. Results and discussion

3.1. Preparation of starting reagents.

The investigations in the development of new sulfur-based reagents for the transfer of tetrafluoroethylene and tetrafluoroethyl moieties were started by the preparation of sulfide and sulfoxide reagents as shown in Scheme 3.1.

1,2-Dibromotetrafluoroethane **51** was used as a starting material. This compound, also known as Freon 114B2 or Halon 2402, a colorless, inflammable, volatile liquid (b.p. 47 °C), which is used as refrigerant, fire extinguisher, leak detector, and in fire suppression systems, mainly in military land vehicles, naval vessels and aircrafts. Large scale production of Halon 2402 has been banned since 1994 under the Montreal Protocol on Substances that Deplete the Ozone Layer. However, the compound is still commercially available for research purposes and multikilogram quantities can be obtained at a low price from specialized storage facilities.⁹⁶

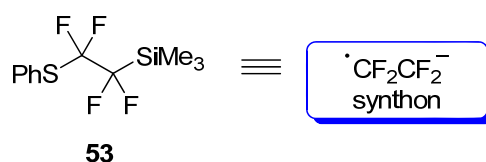
Starting from 1,2-dibromotetrafluoroethane **51** sulfide **52** was prepared by reaction with sodium benzenethiolate following a previously described procedure.^{86c} Barbier coupling reaction of **52** with magnesium metal and chlorotrimethylsilane gave the product **53** in excellent yield.^{86c, 97} Reagent **58** was prepared by the reduction of **52** with NaBH₄/LiCl and subsequent oxidation of **57** with *m*-CPBA. Oxidation of the compound **53** with *m*-CPBA provided sulfone **56** in high yield.



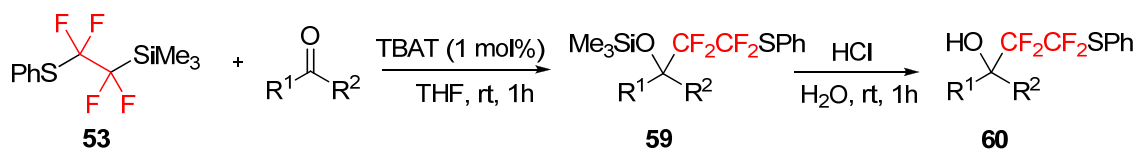
Scheme 3.1 Synthesis of starting reagents.

3.2. Reactivity of PhSCF₂CF₂TMS.

Reagent PhSCF₂CF₂SiMe₃ (**53**) features two types of difluoromethylene groups: a CF₂⁻ center, which can be obtained by nucleophilic activation of the trimethylsilyl group, and a CF₂[·] center, which can be formed by homolytic cleavage of the C–S bond under free radical conditions. This design should overcome β-fluoride elimination problem with dihalotetrafluoroethanes, enabling preparation of selectively substituted tetrafluoroethylene-containing compounds utilizing orthogonal reactivities of fluorinated carbanion and radical centers.



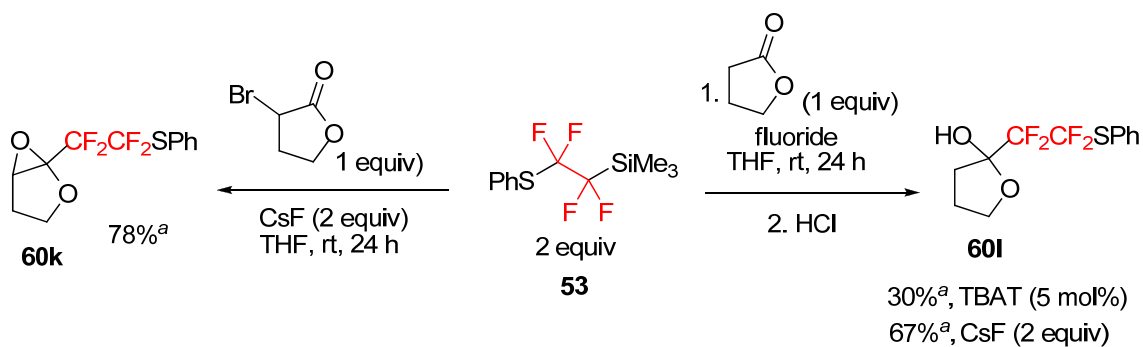
The study of the reactivity of PhSCF₂CF₂SiMe₃ (**53**) was started with nucleophilic addition to carbonyl compounds (Table 3.1). It was found that reaction with benzaldehyde proceeds smoothly in the presence of a twofold excess of **53** and catalytic amounts of fluoride initiator such as TBAT in THF or CsF in DMF at room temperature, giving adduct **59a** as a TMS-ether, which after silyl group removal using aqueous hydrochloric acid afforded **60a** in excellent yield (Table 3.1, entry 1). The TBAT/THF system was preferred for other substrates because of easier product isolation, while the use of excess **53** improved product conversion (PhSCF₂CF₂H (**57**) was identified as a by-product). Aromatic aldehydes with either electron withdrawing or electron donating groups worked equally well, and good yields of adducts **60** were also obtained starting from aliphatic aldehydes. In contrast, the reactivity of simple ketones was significantly reduced. For example, acetophenone gave only 36% of the corresponding **60h** (Table 3.1, entry 8). Efforts to increase the product yield, by employing other, less sterically demanding initiators (CsF, *n*-Bu₄NF, Me₄NF), were not successful. Furthermore, only traces of the product were formed from cyclohexanone (Table 3.1, entry 9). Interestingly, use of trifluoroacetophenone resulted in formation of a TMS-ether adduct which is resistant to HCl cleavage; however, aqueous HF gave **60j** in excellent yield (Table 3.1, entry 10).⁹⁸ This result suggests that the lack of reactivity of simple ketones is due to their low electrophilicity rather than for steric reasons.

Table 3.1 Preparation of adducts **60** by nucleophilic addition of **53** to carbonyl compounds.^a

Entry	R ¹	R ²	60 , Yield (%) ^b
1	Ph	H	60a , 91
2	4-ClC ₆ H ₄	H	60b , 93
3	4-MeOC ₆ H ₄	H	60c , 86
4	1-naphthyl	H	60d , 80
5	2-naphthyl	H	60e , 75
6	<i>n</i> -C ₆ H ₁₃	H	60f , 72
7	PhCH ₂ CH ₂	H	60g , 86
8	Ph	Me	60h , 36
9	-(CH ₂) ₅ -		60i , traces
10	Ph	CF ₃	60j , 91 ^c

^a Reactions were performed with carbonyl compound (2 mmol), **53** (4 mmol, 2.0 equiv) and TBAT (1 mol%) in THF (8 mL) at room temperature for 1 h, followed by addition of HCl (3 mL, 1 M) at room temperature for 1 h. ^b Isolated yields. ^c HF (4 mL, 1 M) was used instead of HCl.

When α -bromo- γ -butyrolactone was used as a substrate under similar reaction conditions (5 mol% TBAT in THF), no reaction proceeded. However, the use of excess CsF resulted in 78% yield of the epoxide product **60k** arising presumably from nucleophilic addition to the carbonyl group followed by epoxide formation rather than expected five-membered ring opening (Scheme 3.2). In contrast, simple γ -butyrolactone reacted with **53** giving product **60l** in 30% yield with catalytic TBAT and 67% yield with an excess of CsF (Scheme 3.2). Replacement of CsF with KF was uneventful.



^a Isolated yield

Scheme 3.2 Nucleophilic additions of **53** to lactones.

Proton decoupled fluorine NMR spectrum of compound **60a** shown on Figure 3.1 represents typical $^{19}\text{F}\{^1\text{H}\}$ NMR spectrum of fluorinated alcohols **60**. The presence of a chiral center on the carbon adjacent to the hydroxyl group makes all fluorine atoms diastereotopic. Therefore, the fluorine NMR spectrum exhibits four signals, with each fluorine atom appearing as a doublet of doublets of doublets with large geminal couplings of 270 Hz and 223 Hz.

In contrast, in the case of compound **53**, CF_2 groups appear as triplets with vicinal couplings of 5 Hz (Figure 3.2).

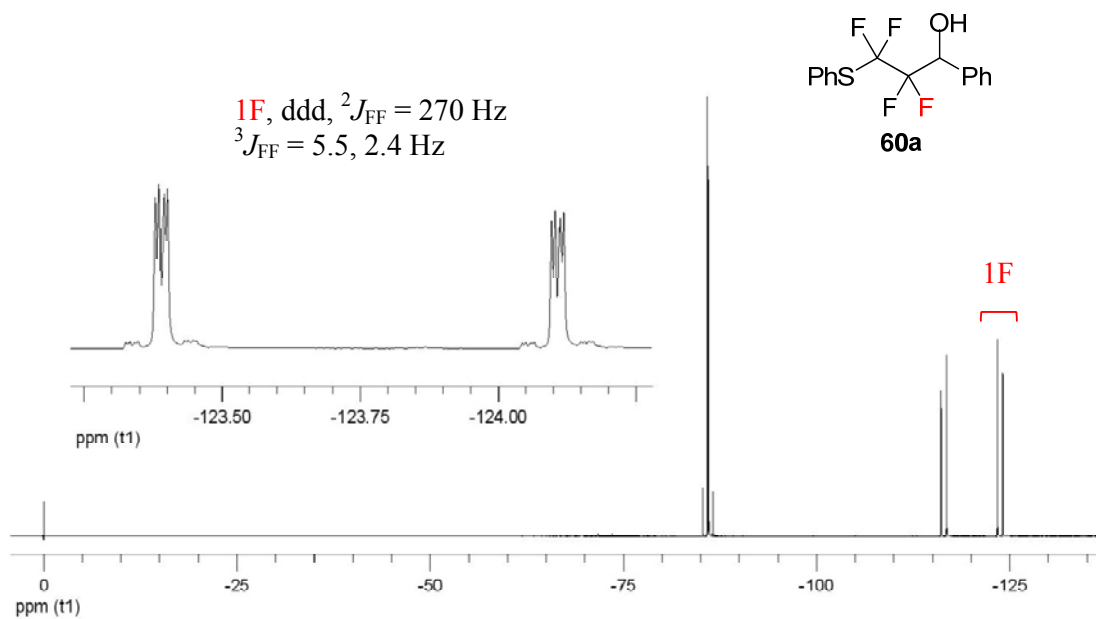


Figure 3.1 $^{19}\text{F}\{^1\text{H}\}$ NMR spectrum of compound **60a**.

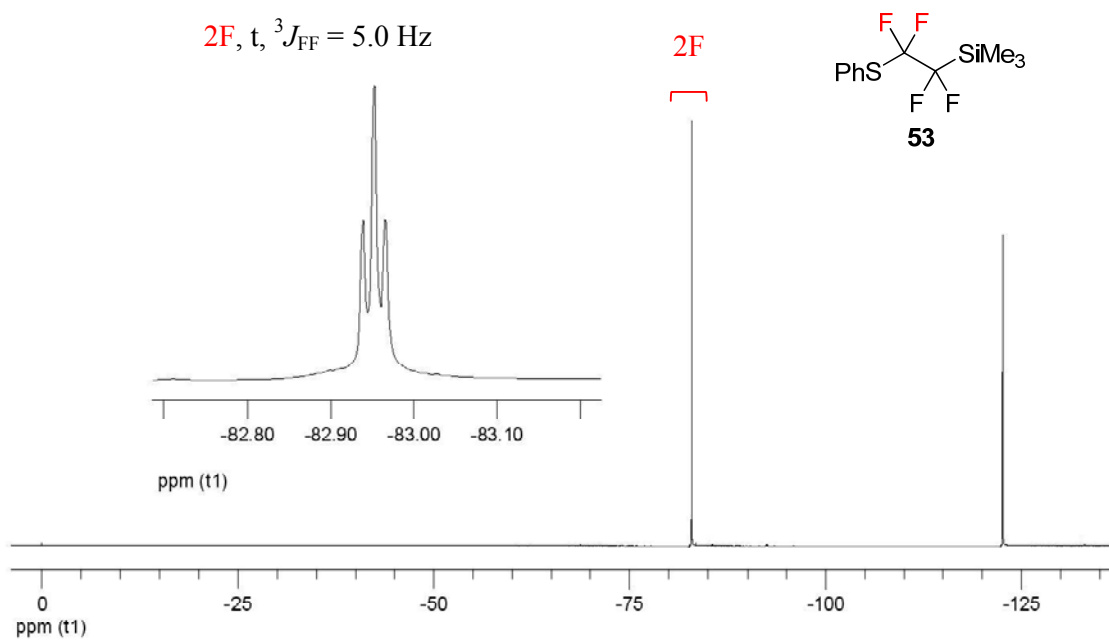


Figure 3.2 $^{19}\text{F}\{^1\text{H}\}$ NMR spectrum of compound **53**.

Following synthesis of adducts **60**, reductive cleavage of the phenylsulfanyl (PhS) group was investigated. The PhS group was readily substituted with hydrogen using an excess amount of *n*-Bu₃SnH and catalytic amount of an AIBN in refluxing toluene, giving the corresponding tetrafluoroethyl-containing secondary or tertiary alcohols **61** in good to high yields (Table 3.2).⁹⁸

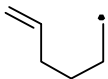
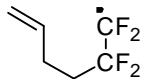
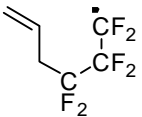
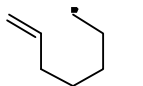
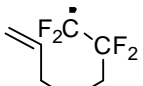
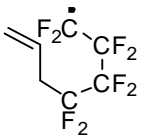
Table 3.2 Preparation of alcohols **61** by the reductive cleavage of adducts **60**.^a

Entry	60	R ¹	R ²	61 , Yield (%) ^b
1	60a	Ph	H	61a , 77
2	60b	4-ClC ₆ H ₄	H	61b , 98
3	60c	4-MeOC ₆ H ₄	H	61c , 80
4	60d	1-naphthyl	H	61d , 65 ^c
5	60e	2-naphthyl	H	61e , 84
6	60f	<i>n</i> -C ₆ H ₁₃	H	61f , 92
7	60g	PhCH ₂ CH ₂	H	61g , 92
8	60h	Ph	Me	61h , 89

^a Reactions were conducted using **60** (1 mmol), *n*-Bu₃SnH (1.75 mmol, 1.75 equiv) and AIBN (0.15 mol, 0.15 equiv) in toluene (8 mL) under reflux for 4 h. ^b Isolated yields. ^c Reaction time was 15 h.

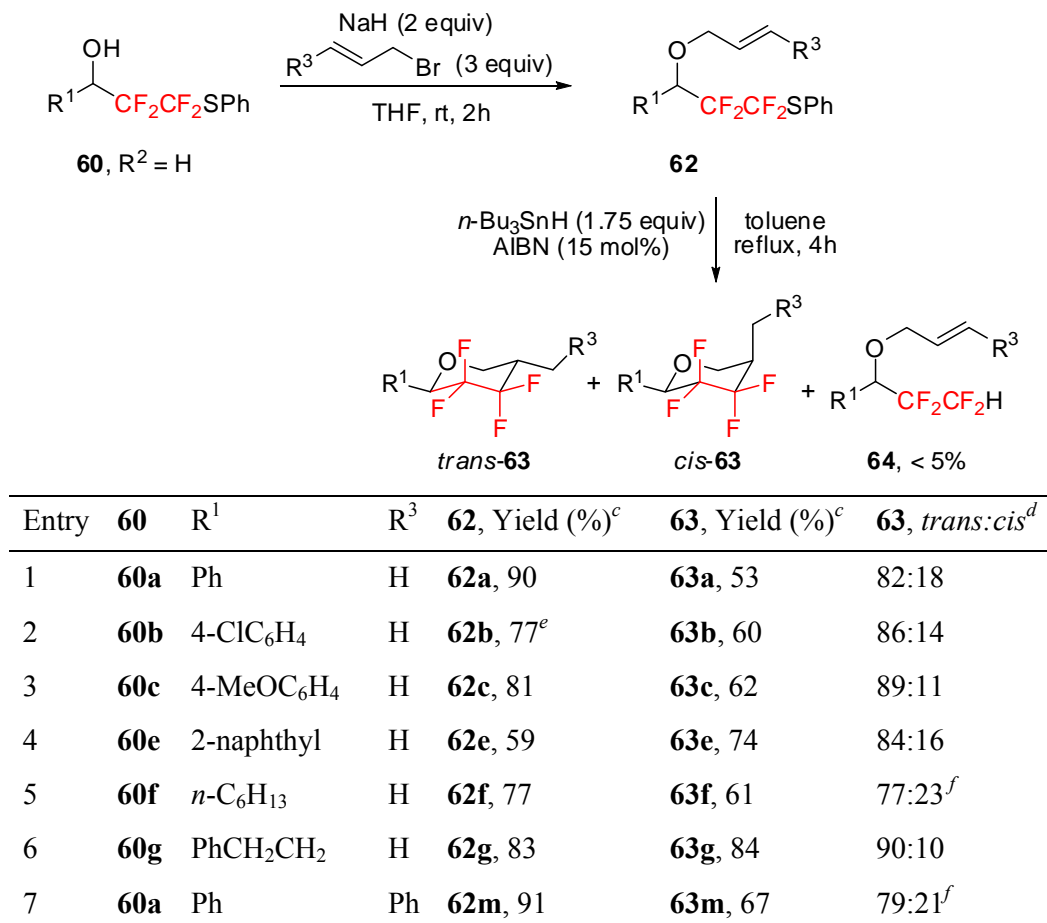
The possibility of radical addition of adducts **60** to alkenes was next considered. Of a particular interest was the intramolecular trapping of the tetrafluoroethyl radical intermediate, generated by carbon–sulfur bond cleavage, by an unsaturated functional moiety. For this purpose, the allyl ethers **62** were synthesized and subjected to 6-*exo* radical cyclization (Table 3.4). It was expected that 6-*exo* cyclizations of tetrafluoro-6-heptenyl ether radicals to tetrafluoro-tetrahydropyrans should be relatively fast. A systematic study by Dolbier Jr. and co-workers demonstrated that fluorine substitution on the radical center is associated with a remarkable rate enhancement effect in 5-*exo*, 6-*exo* and 6-*endo* cyclizations (Table 3.3).⁹⁹ For example, 6-*exo* cyclizations of tetra- and octafluoroheptenyl radicals occur with rate constants which are three orders of magnitude larger than those observed for their hydrocarbon analogues.

Table 3.3 Cyclization reactivities of hydrocarbon and hydrofluorocarbon radicals at 25 °C.⁹⁹

						
k_{5-exo} (s ⁻¹)	2.7·10 ⁵	1.2·10 ⁷	4.5·10 ⁷			
k_{6-exo} (s ⁻¹)				5.4·10 ³	1.4·10 ⁷	2.0·10 ⁷
k_{6-endo} (s ⁻¹)	5.0·10 ³		5.6·10 ⁶			

Using reaction conditions similar to those employed for the formation of compounds **61**, a series of tetrafluoro-tetrahydropyran derivatives **63** was synthesized in moderate to good yields (Table 3.4). Formation of side products **64** was suppressed by slow addition of *n*-Bu₃SnH and AIBN. Compounds **63** were formed as mixtures of *trans* and *cis* isomers. A single *trans*-**63a** was obtained by crystallization from *n*-hexane, and its relative stereochemistry was determined by X-ray crystallography (Figure 3.3, CCDC 824772). Based on X-ray structure analysis of the major *trans*-isomer of **63a** and a comparison of the ¹⁹F NMR spectra of *trans*-**63a** and *cis*-**63a**, it was established that the *trans*-isomers of **63b–k** were the major isomers, and that the *trans*:*cis* ratio ranged from 76:24 to 89:11.⁹⁸

Table 3.4 Formation of allyl ethers **62**^a and radical cyclizations to tetrafluoro-tetrahydropyrans **63**^b.



^a Reactions were induced using **60** (1 mmol), NaH (2 mmol) and R³CH=CHCH₂Br (3 mmol) in THF (5 mL) at room temperature for 2 h. ^b Reactions were performed by addition of *n*-Bu₃SnH (1.75 mmol) and AIBN (0.15 mmol) in toluene (5 mL) over 3 h (using a syringe pump) to a refluxing solution of **62** (1 mmol) in toluene (3 mL) followed by reflux for 1 h. ^c Isolated yields. ^d Determined by ¹⁹F NMR of the crude reaction mixture. ^e Reaction time was 4 h. ^f Determined by GCMS of the crude reaction mixture.

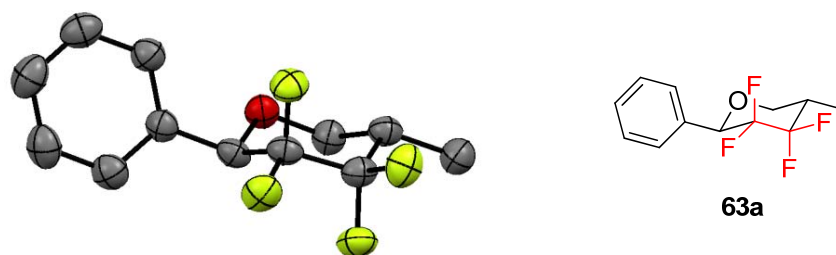
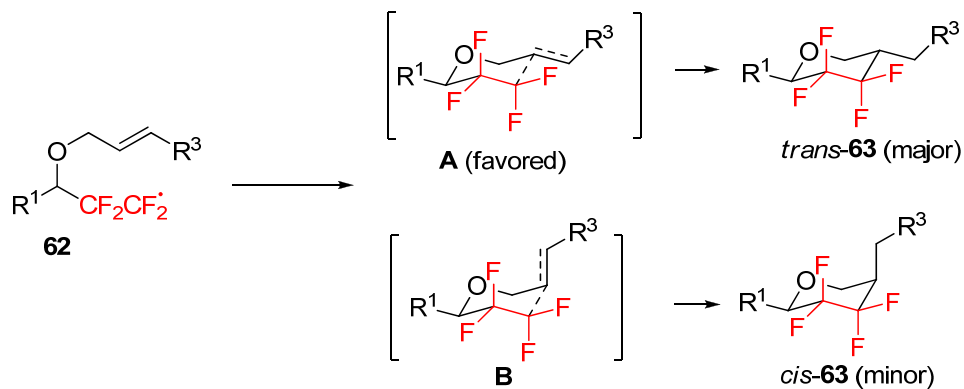


Figure 3.3 X-ray crystal structure of the major isomer of **63a**.

The stereochemistry assumed by compounds **63** can be rationalized as shown in Scheme 3.3, where radical mediated cyclization proceeds via a 6-*exo-trig* cyclization mode. The transition state **A** which leads to *trans*-**63** is energetically more favorable than the *cis*-**63** transition state **B** because it does not involve unfavorable 1,3-diaxial interactions between the fluorine atom and the CHR³ group.



Scheme 3.3 Proposed transition states for 6-*exo* radical cyclizations of **62** to **63**.

We were interested to perform a theoretical study of the stereochemical outcome of intramolecular cyclization reactions. Computational analysis was carried out for compound **63a** in the gas-phase and in toluene using density functional theory (DFT) level and the Møller-Plesset perturbation theory of the second order (MP2). The calculations of single-point energies were done both on the DFT and MP2 level, and the values of Gibbs free energy were calculated on DFT level. The cyclization pathways of compound **62a** are depicted in Figures 3.4 and 3.5. As shown in Figure 3.4, relative Gibbs energy values for the transition state TS-*trans*-**63a** are lower than for TS-*cis*-**63a**, thus favoring *trans* cyclization pathway. Interestingly, according to DFT calculations in the gas-phase, the final product *cis*-**63a** is more stabilized than *trans*-**63a** (Figure 3.4). Obtained result points out that the role of solvent should be considered, since it can have some prevalence on energies and geometries. In contrast to DFT study, MP2 calculation results were in full agreement with the experimental data (Figure 3.5). Stereoselectivity for **63a** was calculated from the free energy difference of corresponding transition states. The theoretical result (*trans*:*cis* = 89:11) for toluene and gas-phase corresponded to the experimental values (*trans*:*cis* = 82:12)

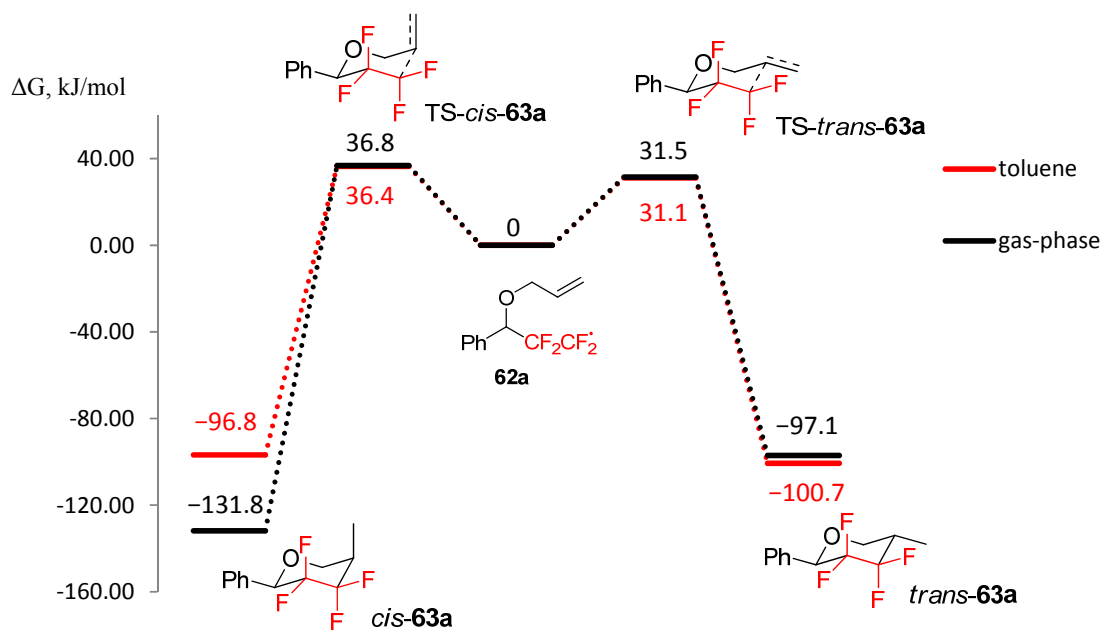


Figure 3.4 DFT-based cyclization pathway of **62a** in toluene and in the gas-phase.

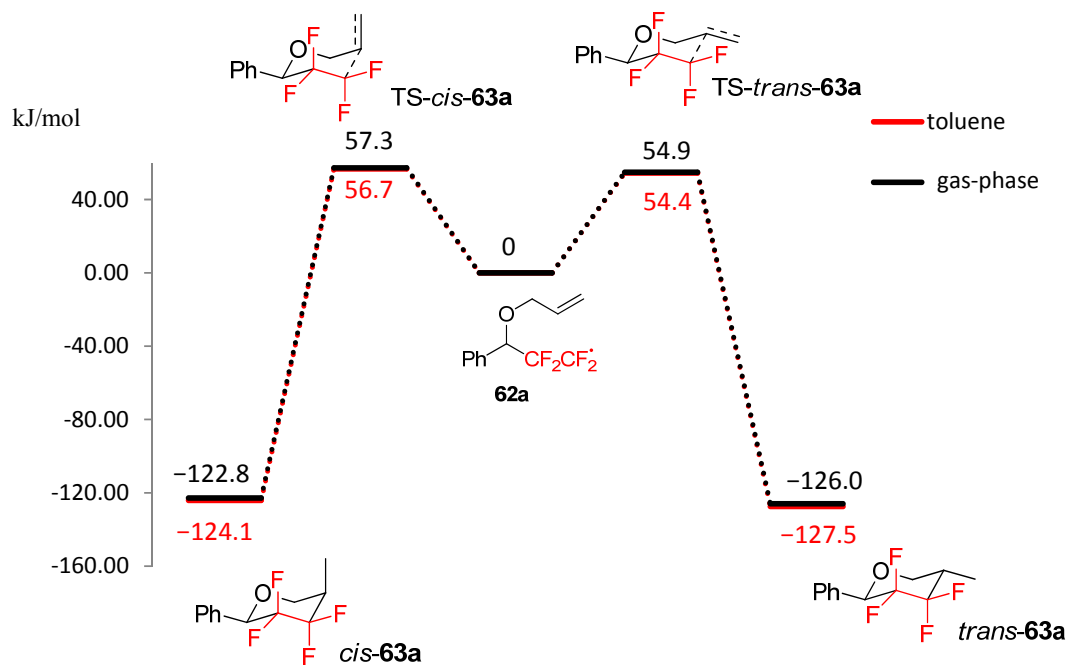
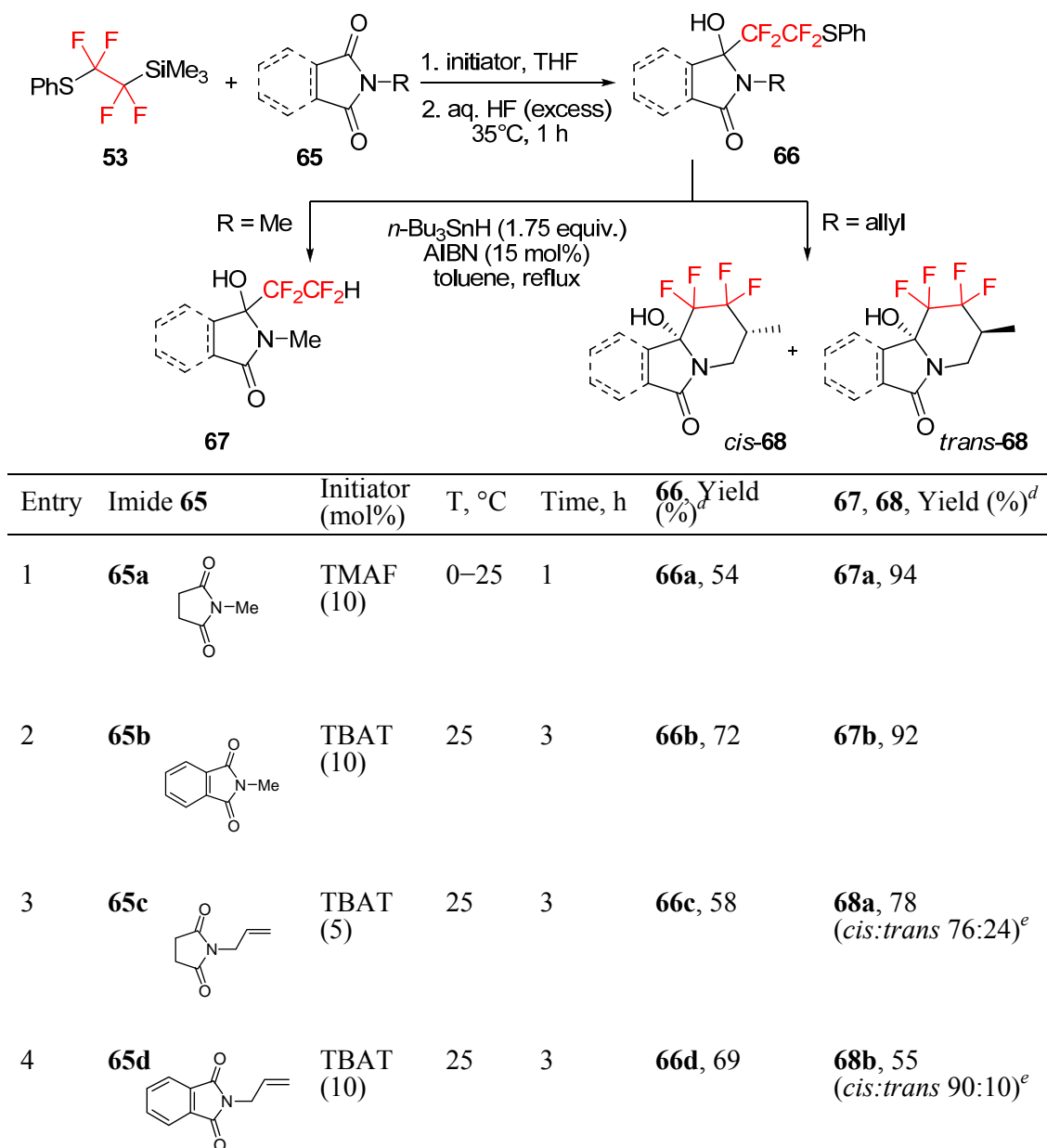


Figure 3.5 MP2-based cyclization pathway of **62a** in toluene and in the gas-phase.

Next, our attention was turned to the additions of PhSCF₂CF₂SiMe₃ (**53**) to cyclic imides. *N*-methyl- and *N*-allyl-substituted succinimides and phthalimides **65** were chosen as substrates (Table 3.5). Using 5-10 mol% of TBAT or TMAF initiator was found to be satisfactory for nucleophilic addition of **53** to imides **65**, while with TBAF no desired adduct was formed and the silyl reagent **53** transferred to PhSCF₂CF₂H (**57**). Reducing the amount of catalyst to 1 mol%, which is the amount of initiator sufficient for the reaction with aldehydes, did not provide good conversions of cyclic imides. Hydrolysis of TMS ether adducts to compounds **66** with HCl was not successful, therefore HF with slight heating had to be used. Cyclic imides were found to be less reactive than aldehydes, presumably, due to their lower electrophilicity and higher steric hindrance. The reductive desulfonylation of adducts **66a** and **66b** (R = Me) was achieved by treating with *n*-Bu₃SnH and catalytic amount of AIBN in refluxing toluene. The tetrafluoroethyl-containing hydroxyl lactams **67a** and **67b** were obtained in excellent yields (Table 3.5). For adducts **66c** and **66d** (R = allyl) similar free radical conditions gave products of 6-*exo* cyclization **68a** and **68b** in good yields (Table 3.5). Formation of the product of phenylsulfanyl group reduction was minimized to less than 10% conversion by a slow addition of *n*-Bu₃SnH and AIBN. Compound **68a** was formed as a mixture of *cis* and *trans* isomers in an 76:24 ratio. A single *cis*-**68a** was obtained by crystallization from methanol, and its relative stereochemistry was determined by X-ray crystallography (Figure 3.6, CCDC-860878). The phthalimide derived cyclized product **68b** was also formed as a mixture of *cis* and *trans* isomers in an 90:10 ratio. The major isomer of **68b** was assigned as *cis* by comparison of ¹H and ¹⁹F NMR data with *cis*-**68a**.¹⁰⁰

Table 3.5 Preparation of adducts **66^a**, lactams **67^b** and 1-azabicyclic compounds **68^c**.



^a Reactions were performed with **65** (2 mmol), **53** (4 mmol, 2.0 equiv) and an initiator (5–10 mol%) in THF (2 mL), followed by the addition of HF (4 mL, 1 M) at 35 °C for 1 h. ^b

Reactions were conducted using **66a–b** (1 mmol), *n*-Bu₃SnH (1.75 mmol, 1.75 eq) and AIBN (0.15 mol, 0.15 eq) in toluene (8 mL) under reflux for 4 h. ^c Reactions were performed by addition of *n*-Bu₃SnH (1.75 mmol) and AIBN (0.15 mmol) in toluene (5 mL) over 3 h (using a syringe pump) to a refluxing solution of **66c–d** (1 mmol) in toluene (3 mL) followed by reflux for 24 h. ^d Isolated yields. ^e Determined by ¹⁹F NMR of the crude reaction mixture.

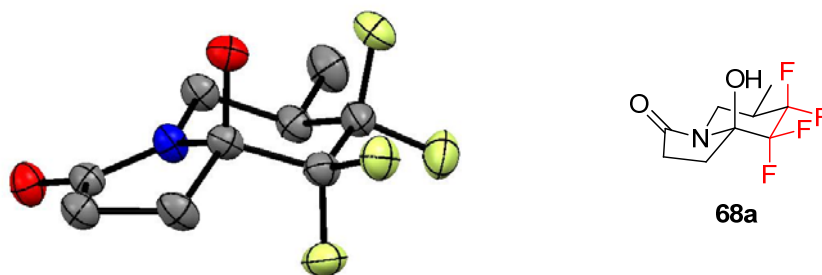
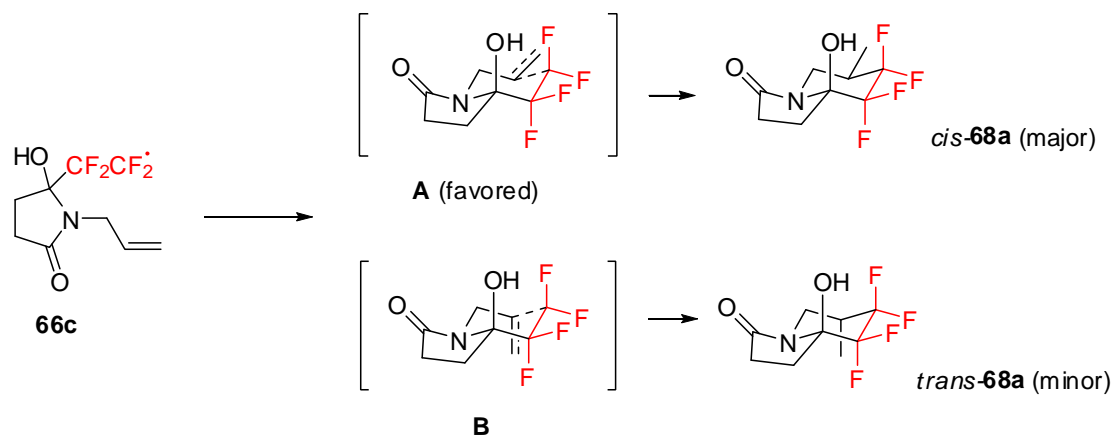


Figure 3.6 X-ray crystal structure of the major isomer of **68a**.

The stereochemical outcome of compound **68a** can be rationalized as shown in Scheme 3.4, where radical-mediated cyclization proceeds again through a 6-*exo-trig* cyclization mode. The forming fused bicyclic structure adopts a conformation with pseudoaxial hydroxyl group. Transition state **A**, which leads to *cis*-**68a**, should be energetically more favorable than transition state **B** because it does not involve unfavorable 1,3-diaxial interactions between the fluorine atom and the methyl group.



Scheme 3.4 Proposed transition states for 6-*exo* radical cyclizations of **66c** to **68a**.

We performed a computational study of the cyclization reaction of **66c** to **68a**. DFT and MP2 calculations of the transition states energies and products energies confirmed the experimental results. As shown in Figures 3.7 and 3.8, *cis* cyclization pathway is more favorable both in the gas-phase and in toluene. The calculated *trans:cis* ratio (76:24 in gas-phase and 67:33 in toluene) was in the agreement with experimental data (*trans:cis* = 76:24).

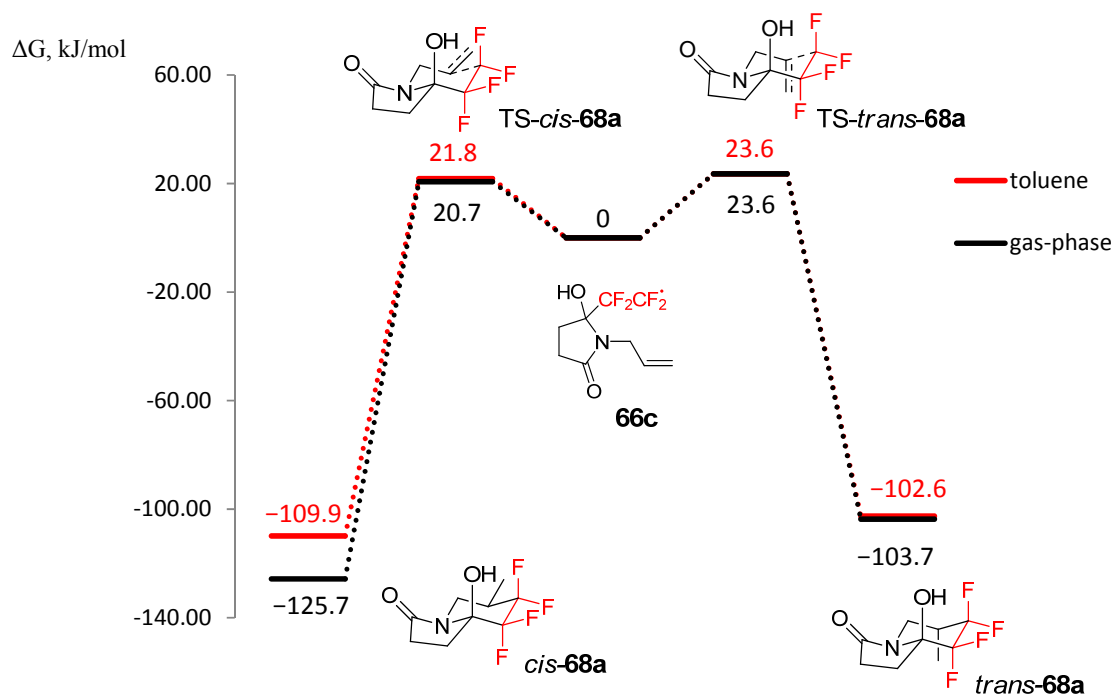


Figure 3.7 DFT-based cyclization pathway of **66c** in toluene and in the gas-phase.

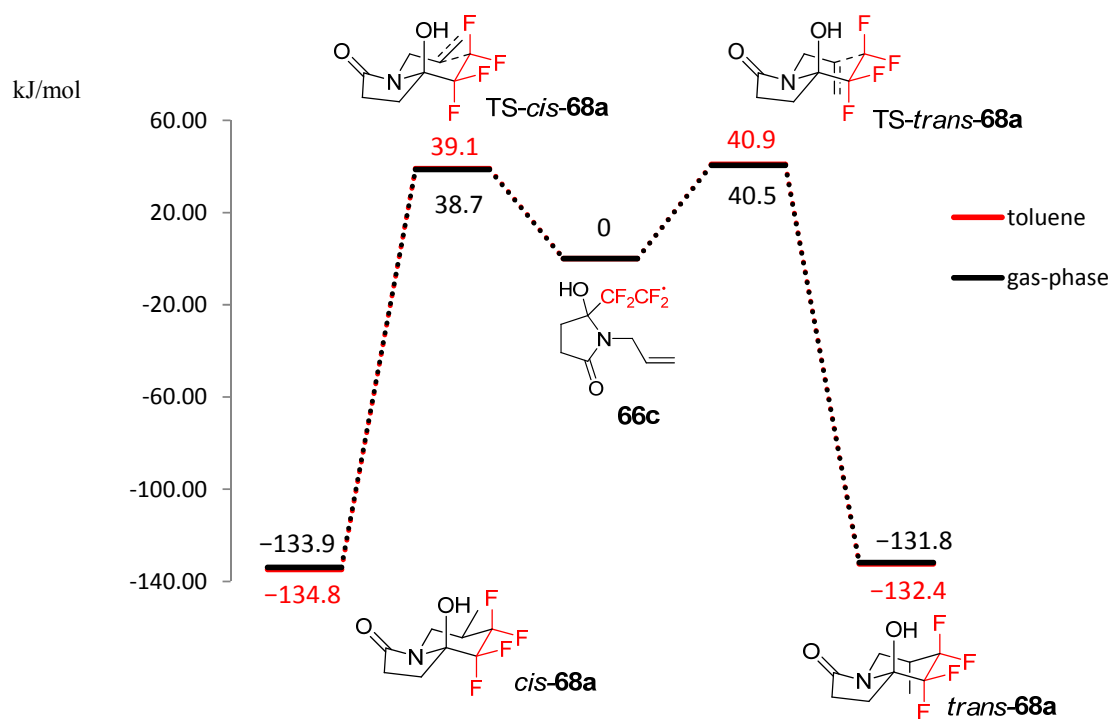
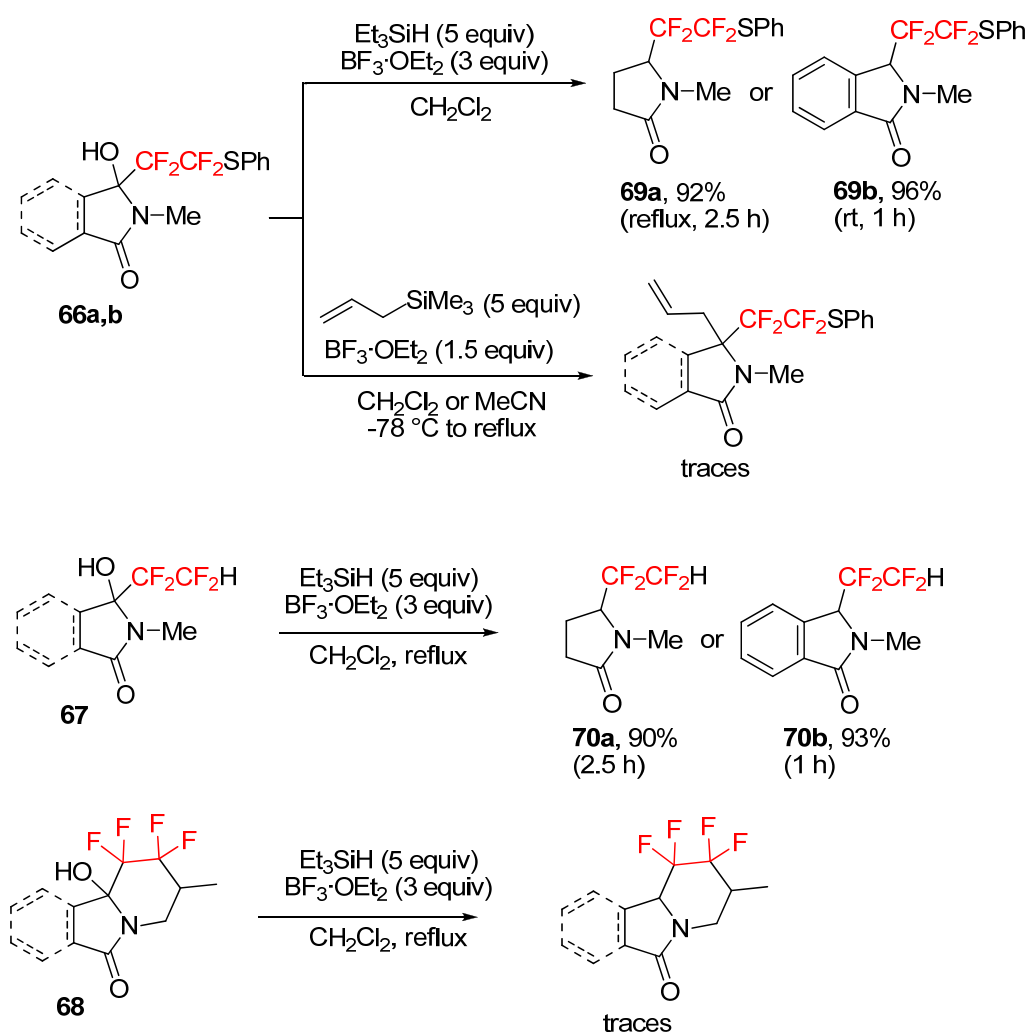


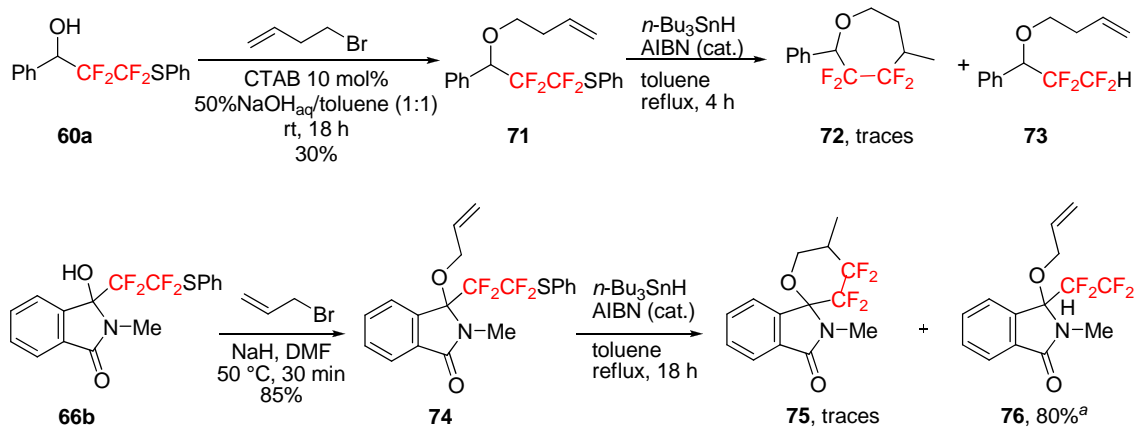
Figure 3.8 MP2-based cyclization pathway of **66c** in toluene and in the gas-phase.

It was expected that the presence of hydroxyl group in adducts **66**, **67** and **68** will provide a convenient access to an iminium intermediate, which can be trapped by an appropriate nucleophile. However, the compounds **66a** or **66b** could not be efficiently allylated with allyltrimethylsilane, and the cyclized compounds **68** did not undergo reduction with Et₃SiH in the presence of BF₃·OEt₂ (Scheme 3.5). This lack of reactivity is probably due to the presence of the electron-withdrawing tetrafluoroethyl group, which destabilize the iminium intermediates. In contrast, reduction of adducts **66a,b** and **67** with Et₃SiH in the presence of BF₃·OEt₂ to *N*-methyl pyrrolidinones and isoindolinones **69** and **70** proceeded in excellent yields (Scheme 3.5).¹⁰⁰



Scheme 3.5 Reduction of adducts **66a,b** and **67**, attempted reduction of **68**, and attempted allylation of **66a,b**.

After successful formation of six-membered rings with the internal CF₂CF₂ fragment, we tried to extend the methodology to the preparation of seven-membered rings. Cyclization was carried out under similar free radical conditions as for 6-*exo* cyclizations. Unfortunately, only traces of the desired product **72** were detected in the reaction mixture and compound **73** was the main product (Scheme 3.7). Clearly, 7-*exo-trig* cyclization is not a preferred process even for electrophilic fluorinated radicals. Furthermore, when similar conditions were applied for the synthesis of *spiro*-bicyclic compound **75**, the product of PhS- group reduction **76** was formed solely (Scheme 3.7). Presumably, the unsuccessful cyclization results can be attributed to the rigidity and limited conformation flexibility of tetrafluoroethylene segment.¹⁰¹



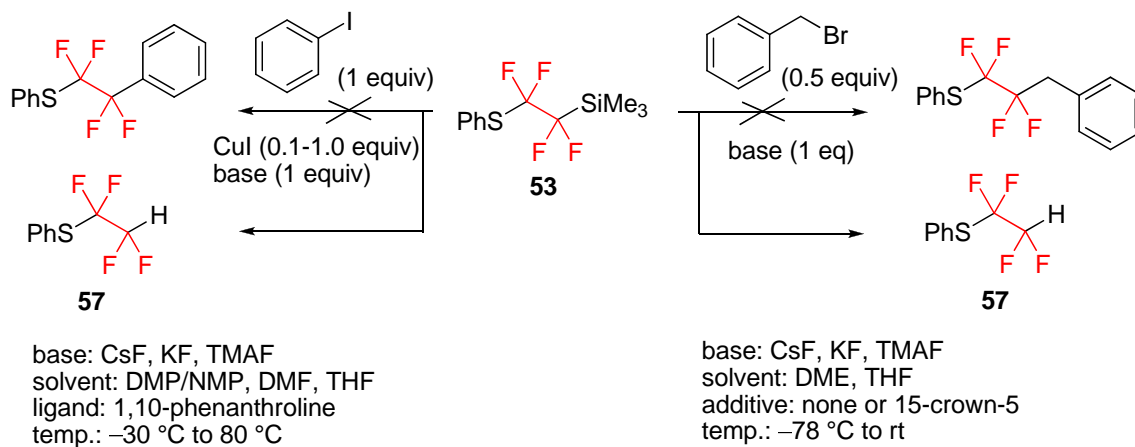
CTAB = *N*-cetyl-*N,N,N*-trimethylammonium bromide

^a Isolated yield

Scheme 3.6 Attempted cyclization reactions of adducts **71** and **74**.

Next, nucleophilic substitution reaction between PhSCF₂CF₂SiMe₃ (**53**) and organic halides was investigated. It was reported that cross-coupling of aliphatic halides RX (X = Br, I) and Me₃SiR_F (R_F = CF₃, C₂F₅) gives the perfluoroalkylated products R-R_F in the presence of stoichiometric amount of fluoride source.¹⁰² Using benzyl bromide as a substrate, we screened different conditions varying the fluoride source (CsF, KF, TMAF), the solvent (THF, DME), additives (15-crown-5), the temperature range (-78 to 25 °C) and the ratio of benzyl bromide to **53** (1:1 and 1:2). In all cases no desired products were observed and PhSCF₂CF₂H (**57**) was formed solely (Scheme 3.7). We have also studied the CuI-mediated cross-coupling of aryl halides¹⁰³ with **53**. A number of experiments were carried out using iodobenzene in the

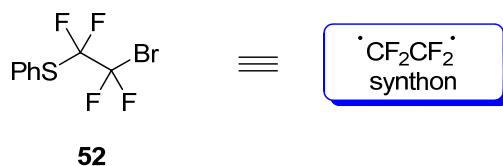
presence of fluoride sources under different conditions. Again, **57** was the only product observed (Scheme 3.7).



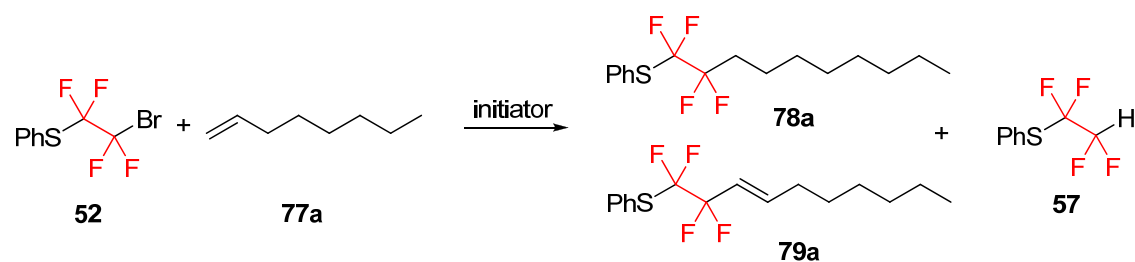
Scheme 3.7 Attempted reactions of organic halides with **53**.

3.3. Reactivity of PhSCF₂CF₂Br.

Reagent PhSCF₂CF₂Br (**52**) represents a 'CF₂CF₂' diradical synthon. It was expected that the carbon-bromine and carbon-sulfur bond can be selectively cleaved and trapped with hydrogen radicals or added to alkenes or alkynes.

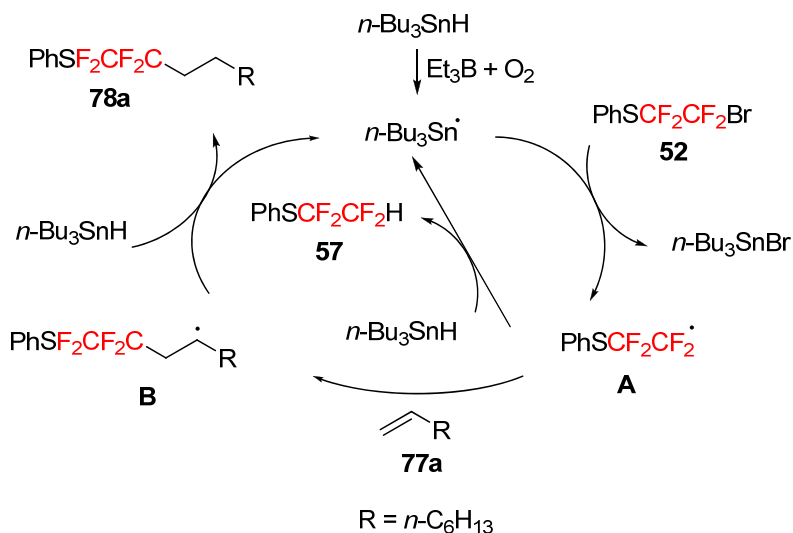


At the outset of the study, radical additions of **52** to 1-octene **77a** were investigated (Table 3.6). It was found that a combination of sodium dithionite and bicarbonate in DMSO under various reaction conditions gave only moderate yields of the bromine-free addition product **78a** (Table 3.6, entries 1-3). A better yield of **78a** was achieved with tributyltin hydride and catalytic AIBN in toluene under elevated temperature (Table 3.6, entry 4). Further experiments showed that a combination of tributyltin hydride with triethylborane in dichloromethane under ambient temperature was particularly effective in this radical addition reaction and that the amount of triethylborane could be reduced to half an equivalent. The best result was observed when a solution of tributyltin hydride in dichloromethane was slowly added to a mixture of **52** and **77a** and Et₃B (Table 3.6, entry 10). A plausible mechanism of the addition of **52** to 1-octene is shown in Scheme 3.8. Tributyltin radical produced from triethylborane and traces of oxygen abstracts bromine atom from **52** to provide tributyltin bromide and radical **A**, which reacts faster with alkene to form **B** than with tributyltin hydride to give PhSCF₂CF₂H (**57**). The formation of the side product **57** was suppressed by slow addition of *n*-Bu₃SnH to the reaction mixture. The radical adduct **B** abstracts hydrogen atom from tributyltin hydride providing product **78a**, regenerating tributyltin radical and thus closing the cycle. The reaction conducted under argon atmosphere gave better yields than in an open flask suggesting that traces of oxygen present in the solvent are sufficient to initiate the reaction with Et₃B.¹⁰⁴ Replacement of dichloromethane with diethyl ether or *n*-hexane led to significant decrease in chemical yields, resulting in phenylsulfanyl group cleavage (PhS-SnBu₃ was detected by GCMS). Reduction of PhS-group in dichloromethane is presumably suppressed by the competing elimination of chlorine atom from the solvent, since no PhS-SnBu₃ was observed in the reaction mixture, but tributyltin chloride was detected instead.¹⁰⁵

Table 3.6 Optimization of addition of **52** to 1-octene.^a

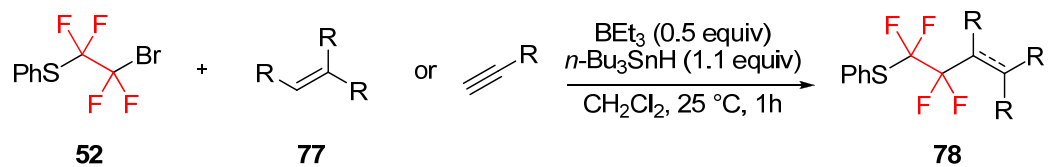
Entry	Initiator (equiv)	Solvent	T, °C	Time (h)	78a , Yield (%) ^b
1 ^c	Na ₂ S ₂ O ₄ (1.5)/NaHCO ₃ (1.5)	DMSO	75	2	29 ^d
2 ^c	Na ₂ S ₂ O ₄ (1.5)/NaHCO ₃ (1.5)	DMSO	40	5	32
3 ^c	Na ₂ S ₂ O ₄ (1.5)/NaHCO ₃ (1.5)	MeCN/H ₂ O (3:1)	60	24	31
4 ^c	AIBN (0.3), Bu ₃ SnH (1.7)	toluene	90	48	55
5	Et ₃ B (1)/air	CH ₂ Cl ₂	25	144	28
6	Et ₃ B (1)/O ₂	CH ₂ Cl ₂	25	26	3
7	Et ₃ B (1)/air, <i>n</i> -Bu ₃ SnH (1)	CH ₂ Cl ₂	25	3	35
8 ^c	Et ₃ B (1), <i>n</i> -Bu ₃ SnH (1)	CH ₂ Cl ₂	-40 to 25	1.5	40
9 ^c	Et ₃ B (1), <i>n</i> -Bu ₃ SnH ^e (1)	CH ₂ Cl ₂	25	1	70
10 ^c	Et ₃ B (0.5), <i>n</i> -Bu ₃ SnH ^e (1)	CH ₂ Cl ₂	25	1	70 (63)
11 ^c	Et ₃ B (0.3), <i>n</i> -Bu ₃ SnH ^e (1)	CH ₂ Cl ₂	25	1	55
12 ^c	Et ₃ B (1), <i>n</i> -Bu ₃ SnH ^e (1)	hexane	25	2	13
13 ^c	Et ₃ B (1), <i>n</i> -Bu ₃ SnH ^e (1)	Et ₂ O	25	1.5	13

^a Reactions were performed with **52** (0.5 mmol), **77a** (2 equiv) in solvent (1 mL). Et₃B (1M) solution in *n*-hexane was used. ^b ¹⁹F NMR yield using PhCF₃ as an internal standard. In brackets isolated yield. ^c Reaction was conducted under argon. ^d Products **78a** and **79a** were formed as a 3:1 mixture. After reduction with H₂/Raney Ni in EtOH (25 °C, 96 h) product **78a** was isolated in 29% yield. ^e Added during 1 h by a syringe pump.



Scheme 3.8 Mechanism for radical addition of **52** to 1-octene.

To evaluate the scope of this radical addition reaction, we next examined the effects of substituents on the substrates (Table 3.7). The radical formed from **52** by the abstraction of bromine atom should demonstrate electrophilic character; its addition onto electron-rich alkenes is efficient due to a favorable SOMO-HOMO interaction.¹⁰⁶ However, addition of fluoroalkyl radicals onto electron-deficient systems was reported for CF₃·, RCF₂·, RCOCF₂· radicals.¹⁰⁷ The ambiphilic character of RCF₂· radical may arise from the combination of electronic effects: the σ inductive effect of one fluorine atom and the π donating effect of the second fluorine atom.¹⁰⁸ It was observed that PhSCF₂CF₂Br (**52**) can add both to electron-rich and electron-poor alkenes with terminal double bond. Products **78** were formed along with reduced product PhSCF₂CF₂H (**57**) and oligomeric material ($\leq 5\%$ observed by ¹⁹F NMR). 1,2-Disubstituted alkenes gave reduced yield of **78** due to steric crowding (Table 3.7, entries 5,8). Addition to triple bond of ethyl propiolate or phenylacetylene was inefficient and PhSCF₂CF₂H (**57**) was observed as the main product (Table 3.7, entries 13,14).¹⁰⁵

Table 3.7 Et₃B-initiated addition of **52** to alkene or alkynes.^a

Entry	77	Alkene	78	Product	Yield (%) ^b
1	77a		78a		63
2	77b		78b		46
3	77c		78c		77
4	77d		78d		42
5	77e		78e		23
6	77f		78f		50
7	77g		78g		65
8	77h		78h		traces ^c
9	77i		78i		51
10	77j		78j		64
11	77k		78k		38 ^d
12	77l		78l		30

Table 3.7 (Continued)

Entry	77	Alkene	78	Product	Yield (%) ^b
13	77m	\equiv -CO ₂ Et	78m	PhSF ₂ CF ₂ C \equiv C _n CO ₂ Et	traces ^c
14	77n	\equiv -Ph	78n	PhSF ₂ CF ₂ C \equiv C _n Ph	30 ^d (6:1)

^a Reactions were performed by addition of *n*-Bu₃SnH (1.1 equiv), in CH₂Cl₂ (2 mL) at 25 °C during 1 h using a syringe pump to a solution of **52** (1-2 mmol), **77** (2 equiv), and Et₃B (1 M in *n*-hexane, 0.5 equiv) in CHCl₂ (1 mL). ^b Isolated yield. ^c Determined by GCMS analysis. ^d Determined by ¹⁹F NMR of the crude reaction mixture using PhCF₃ as an internal standard.

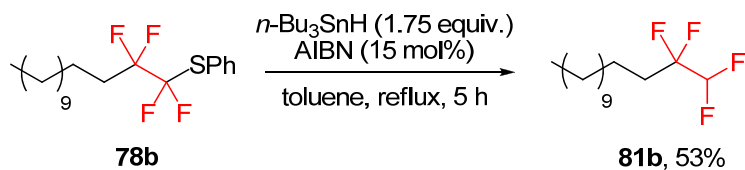
Next, radical addition reactions of compound **78a** to alkenes were attempted. Slow addition of a toluene solution of tributyltin hydride and catalytic AIBN to a refluxed toluene solution of compound **78a** and the excess 1-octene (**77a**), 1-dodecene (**77b**), or phenyl vinyl sulfone (**77j**) resulted in the formation of adducts **80**, featuring the CF₂CF₂ segment in the middle of the hydrocarbon chain (Table 3.8). However, addition of **78a** to styrene or addition of **78f** or **78g** to 1-octene gave conversions of 25% or less.¹⁰⁵

Table 3.8 Radical addition of **78a** to alkenes.^a

Entry	77	R	80a	Yield (%) ^b
1	77a	<i>n</i> -C ₆ H ₁₃	80aa	61
2	77b	<i>n</i> -C ₁₀ H ₂₁	80ab	41
3	77j	SO ₂ Ph	80aj	50

^a Reactions were performed by addition of *n*-Bu₃SnH (1.75 equiv), and AIBN (0.3 equiv) in toluene (2mL) over 3 h using a syringe pump to a refluxed solution of **78a** (1 mmol) and **77** (3 mmol) in toluene (5 mL) followed by reflux overnight. ^b Isolated yield.

Reductive cleavage of the phenylsulfanyl group of **78b** proceeded well and the corresponding 1,1,2,2-tetrafluorotetradecane **81b** was isolated in moderate yield (Scheme 3.9). Adducts **78a** and **78f** also showed high conversions in this reaction, but could not be isolated pure from tin side products.¹⁰⁵



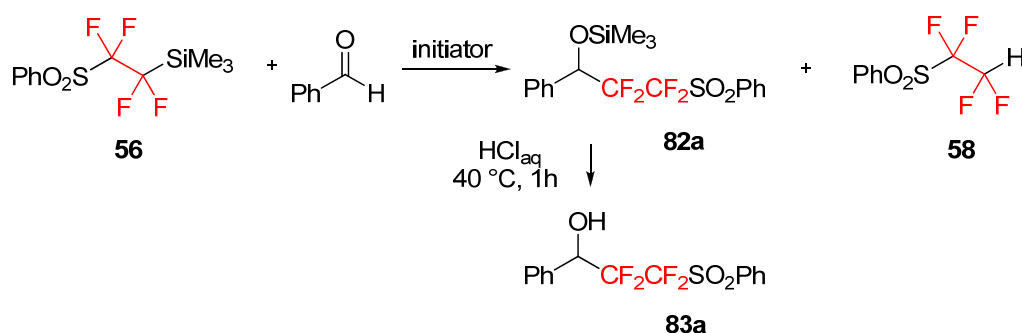
Scheme 3.9 Radical cleavage of phenylsulfanyl group in adduct **78b**.

3.4. Reactivities of PhSO₂CF₂CF₂TMS and PhSO₂CF₂CF₂H.

Sulfone PhSO₂CF₂CF₂SiMe₃ (**56**) is an alternative nucleophilic tetrafluoroalkylation reagent to PhSCF₂CF₂SiMe₃ (**53**). The aim was to study application of **56** as a carbanionic synthon and compare its reactivity with the reagent **53**.

Nucleophilic addition reaction of PhSO₂CF₂CF₂SiMe₃ (**56**) with carbonyl compounds was studied. Firstly, conditions optimized for the reaction of PhSCF₂CF₂SiMe₃ (**53**) with carbonyl compounds were applied (1 mol% TBAT in THF at rt), however, no reaction proceeded with benzaldehyde after 2 h (Table 3.9, entry 1). Increasing the amount of TBAT to 20 mol% led to slow decomposition of the starting silane **56** during 15 h, and protodesilylated product PhSO₂CF₂CF₂H (**58**) was the only fluorinated species detected by ¹⁹F NMR.

Table 3.9 Optimization of reaction conditions for the addition of **56** to benzaldehyde.^a



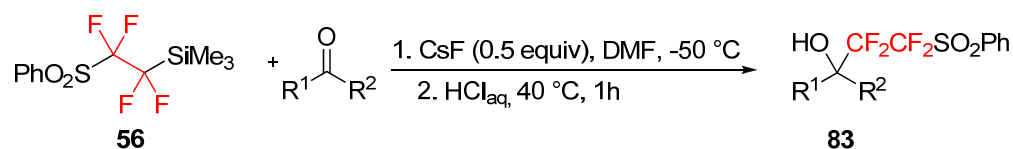
Entry	Initiator (equiv)	Solvent	T, °C	Time, h	Ratio 82a : 58 ^b
1	TBAT (0.01)	THF	rt	2	— ^c
2	TMAF (1)	DMF	rt	1.5	6:94
3	Cs ₂ CO ₃ (1)	DMF	rt	2.5	0:100
4	KF (1)	THF	rt	15	16:84
5	KF (0.5)	DMF	−50 to rt	20	38:62
6	CsF (1)	THF	rt	1	20:80
7	CsF (0.5)	THF	rt	26	32:68
8	CsF (0.5)	DMF	rt	2	35:65
9	CsF (0.5)	DMF	−50 to rt	2.5	88:12 (70 ^d)
10	CsF (0.1)	DMF	−50 to rt	15	66:34 (50 ^d)

^a Reactions were performed with **56** (0.5 mmol, 1 equiv) and benzaldehyde (2 equiv). ^b Ratio was determined by GCMS analysis. ^c No reaction proceeded. ^d Isolated yield of **83a**.

Similarly, the employment of TMAF and cesium carbonate as initiators did not provide the desired product. Considering, that the low reactivity of **56** can be due to the steric bulk both tetrabutylammonium counterion and phenylsulfonyl group, KF and CsF were chosen as reaction promoters. It was found that substoichiometric amount of CsF in DMF is able to activate silane **56** and provide the TMS-ether **82a** in good conversion, while the final product **83a** was isolated in 70% yield (Table 3.9, entry 9).

Optimized reaction conditions were applied for nucleophilic addition of **56** to various carbonyl compounds (Table 3.10). Reactions of aliphatic aldehydes and aromatic aldehydes with either electron withdrawing or electron donating groups proceeded well and gave the hydroxyl compounds **83** in moderate yields. However, ketones, both cyclic and acyclic, were unreactive under these conditions (Table 3.10, entries 8 and 9). In contrast, highly electrophilic trifluoroacetophenone showed a good reactivity (Table 3.10, entry 10).

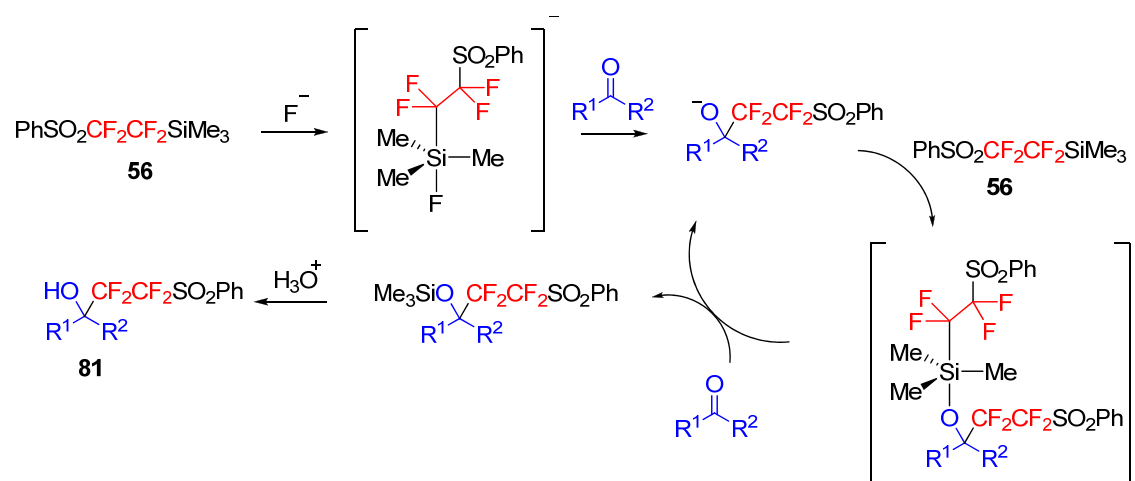
Table 3.10 Preparation of adducts **83** by the nucleophilic addition of **56** to carbonyl compounds.^a



Entry	R ¹	R ²	83 , Yield (%) ^b
1	Ph	H	83a , 70
2	4-ClC ₆ H ₄	H	83b , 56
3	4-MeOC ₆ H ₄	H	83c , 51
4	1-naphthyl	H	83d , 40
5	2-naphthyl	H	83e , 56
6	<i>n</i> -C ₆ H ₁₃	H	83f , 51
7	PhCH ₂ CH ₂	H	83g , 51
8	Ph	Me	83h , traces
9	-(CH ₂) ₅ -		83i , traces
10	Ph	CF ₃	83j , 48
11	4-BrC ₆ H ₄	H	83k , 71

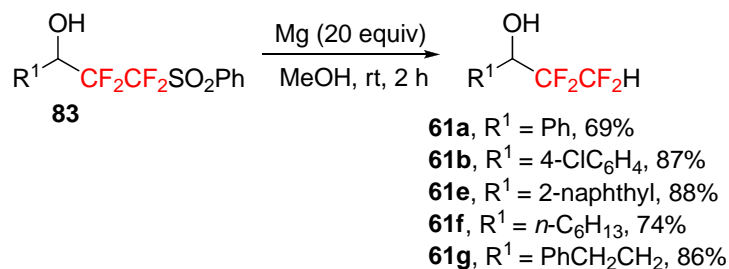
^a Reactions were performed with carbonyl compound (2 mmol), **56** (1 mmol, 1.0 equiv) and CsF (0.5 equiv) in DMF (8 mL) at -50 °C for 3 h, followed by addition of HCl (5 mL, 1 M) at 40 °C for 1 h. ^b Isolated yields.

The decreased reactivity of silane $\text{PhSO}_2\text{CF}_2\text{CF}_2\text{SiMe}_3$ (**56**) in comparison with $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**53**) can be explained by the lower nucleophilicity owing to the stronger electron-withdrawing effect of the phenylsulfonyl group compared to that of the phenylsulfide counterpart. The mechanism of nucleophilic addition of silanes **53** and **56** is shown in Scheme 3.10. In the first step, the silane **53** has a greater susceptibility to form a five-coordinate silicon intermediate due to the electron-withdrawing effect of PhSO_2 group. However, in the nucleophilic addition step, protodesilylation prevails over the addition to carbonyl group due to lower nucleophilicity of the resulting anionic silicon species.



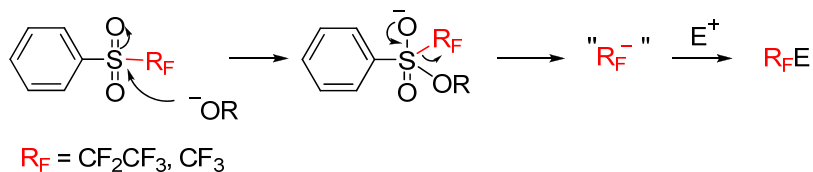
Scheme 3.10 Plausible mechanism of nucleophilic addition of **56** to carbonyl compounds.

To demonstrate the utility of products obtained after fluoroalkylation of aldehydes and ketones, we performed the desulfurization of sulfonyl group. Thus, the sulfone fragment was removed from products **83** by the treatment with magnesium in methanol¹⁰⁹, furnishing tetrafluoroethyl-containing secondary alcohols **61** in good yields (Scheme 3.11).



Scheme 3.11 Preparation of alcohols **61** by the reductive desulfonylation of adducts **83**.

Next, attention was turned to the generation of fluoroalkyl carbanion by the cleavage of carbon-sulfur bond. Prakash *et al.* reported the alkoxide and hydroxide-induced fluoroalkylation reaction using sulfones or sulfoxides (Scheme 3.12).¹¹⁰



Scheme 3.12 Alkoxide induced “R_F⁻” generation from perfluorosulfones.¹¹⁰

We were interested in a similar type of nucleophilic addition reaction with our products bearing sulfone functionality. It was expected that by using a suitable alkoxide, PhSO₂ group can be removed to release the RCF₂CF₂⁻ anion. Sodium methoxide, potassium hydroxide and potassium *tert*-butoxide were tested as nucleophiles to attack the sulfur center and benzaldehyde was used as an electrophile (Table 3.11). The expected products of nucleophilic addition to benzaldehyde were never observed. The reaction did not proceed at low temperatures, while increasing the temperature led to a slow decomposition of the starting sulfone substrates and the formation of benzyl alcohol by competing Cannizzaro reaction.

Table 3.11 Attempted reactions of sulfones with benzaldehyde induced by alkoxide or hydroxide.

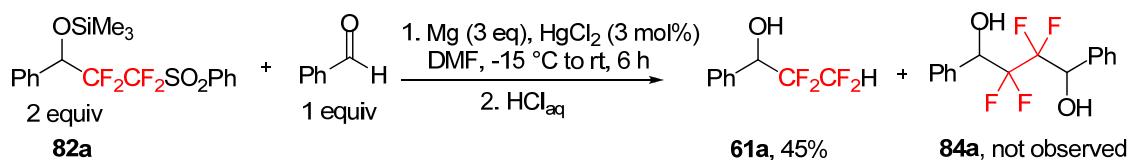
$$\text{R}^1\text{CF}_2\text{CF}_2\text{SO}_2\text{Ph} + \text{PhCHO} \xrightarrow[24\text{ h}]{\text{RO}^-} \text{R}^1\text{CF}_2\text{CF}_2\text{CH(OH)Ph}$$

1 equiv
2-3 equiv

Entry	Substrate	Alkoxide (equiv)	Solvent and T, °C
1	83a 	<i>t</i> -BuOK (2)	DMF -50 to rt
2	83a 	MeONa (6)	DMF -30 to rt
3	83a 	KOH (8)	DMF/H ₂ O(1:1) 50
4	82a 	<i>t</i> -BuOK (5)	DMF 25
5	58 HCF ₂ CF ₂ SO ₂ Ph	<i>t</i> -BuOK (2)	DMF -50 to rt

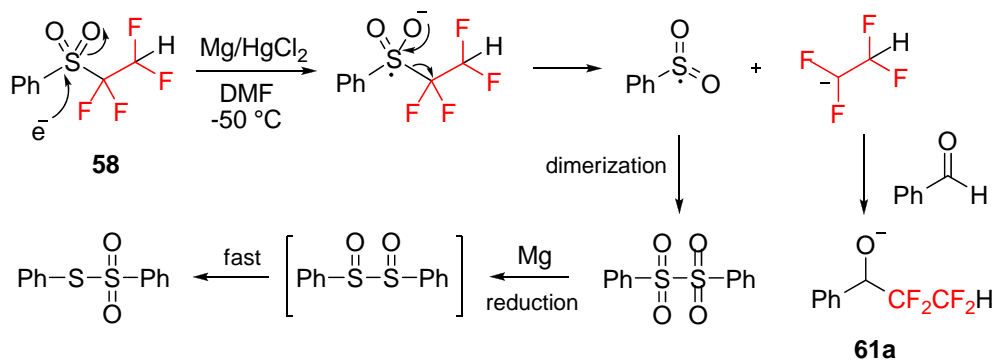
After the unsuccessful results in alkoxide activation of carbon-sulfur bond, the metal-mediated desulfonative reduction was considered. Chlorosilanes were reported to undergo a reductive fluoroalkylation via a magnesium-mediated C-S bond cleavage of fluoroalkyl sulfones and sulfoxides. For example, it was shown that PhSO₂-CF₃ readily reacts with trimethylsilyl chloride in the presence of magnesium to form CF₃-SiMe₃.¹¹¹ Moreover, other electrophiles, such as aldehydes were reported to react with PhSO₂-CF₃ giving products of nucleophilic addition using the Mg/HgCl₂(cat.) system.¹¹² This prompted us to investigate the reactivity of tetrafluoroethyl-containing sulfones in nucleophilic addition reactions through reductive desulfonylation.

First, the alcohol **82a** was tested in order to obtain the diol product **84a**. Treatment of **82a** with Mg/HgCl₂ in DMF resulted in 45% conversion of the starting material to the reduction product **61a** and no desired product **84a** was observed (Scheme 3.13).



Scheme 3.13 Attempted nucleophilic addition of **82a** to benzaldehyde.

Next, reagent PhSO₂CF₂CF₂H (**58**) was subjected to the reaction with benzaldehyde. It was found that magnesium in the presence of catalytic amount of HgCl₂ efficiently activates carbon-sulfur bond giving the product of nucleophilic addition **61a** in 57% yield (Scheme 3.14). Other additives such as CuBr₂ and FeCl₃ could not activate magnesium surfaces to induce the required desulfonylation reaction. Low temperature (-50 °C) was needed to prevent decomposition of highly unstable HCF₂CF₂⁻. By analogy with PhSO₂-CF₃ reagent¹¹⁰, the reaction mechanism is assumed to involve single-electron transfer and tetrafluoroethyl anion species (Scheme 3.14). The formation of sulfur radical species PhSO₂[•] was confirmed by the observation of the side product PhS-SO₂Ph, which can be formed by the dimerization of the radical and subsequent reduction of diphenyldisulfone.



Scheme 3.14 Plausible mechanism of nucleophilic addition of **58** to benzaldehyde via reductive desulfonylation.

These conditions were examined for different aldehydes and ketones (Table 3.12). Both aromatic and aliphatic aldehydes gave good yields in most cases. The decreased reactivity of 1-naphthaldehyde compared to 2-naphthaldehyde was probably due to the steric hindrance caused by the presence of *peri*-hydrogen atom in the former (Table 3.12, entries 4 and 5).

Aldehydes bearing electron-withdrawing groups showed lower reactivities in nucleophilic additions because of competing pinacol coupling under reductive conditions (Table 3.12, entry 2). In case of *p*-bromobenzaldehyde, the reduction of bromine occurred during the reaction and product **61a** was formed together with the desired product **61k** (Table 3.12, entry 10). Unfortunately, ketones, both activated and inactivated, did not provide the desired products at all. The reaction with acetophenone yielded only traces of product **61h**, while in case of trifluoroacetophenone, the product of pinacol coupling was formed solely (Table 3.12, entries 8 and 9). Under these conditions, electrophilic substrates display selective reactivity towards nucleophilic addition. However, the method allows one-step synthesis of tetrafluoroethyl-containing alcohols **61**, whereas reagents **53** and **56** required two steps for the preparation of **61**.

Table 3.12 Preparation of adducts **61** by nucleophilic addition of **58** to carbonyl compounds.^a



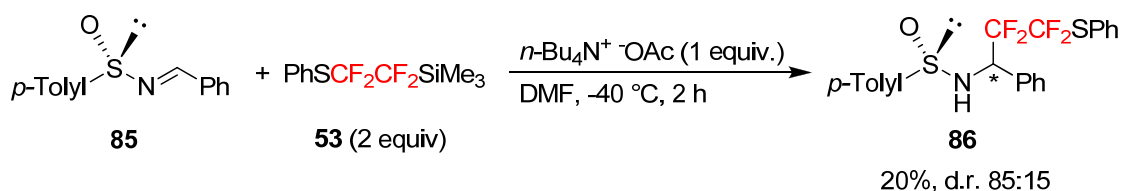
Entry	R ¹	R ²	61 , Yield (%) ^b
1	Ph	H	61a , 57
2	4-ClC ₆ H ₄	H	61b , 27
3	4-MeOC ₆ H ₄	H	61c , 77
4	1-naphthyl	H	61d , 24
5	2-naphthyl	H	61e , 80
6	<i>n</i> -C ₆ H ₁₃	H	61f , 91
7	PhCH ₂ CH ₂	H	61g , 74
8	Ph	Me	58h , 0
9	Ph	CF ₃	61j , 0 ^c
10	4-BrC ₆ H ₄	H	61k , 20 ^d

^a Reactions were performed with carbonyl compound (2 mmol), **58** (1 mmol, 0.5 equiv), Mg (3 mmol, 1.5 equiv) and HgCl₂ (0.06 equiv) in DMF (5 mL) at -50 °C for 4–8 h, followed by addition of HCl (3 mL, 1 M) at rt. ^b Isolated yields. ^c Pinacol coupling proceeded instead of expected formation of **61j**. ^d Product **61k** was formed together with **61a** (ratio **61k**:**61a** = 38:62 according to ¹⁹F NMR).

3.5. Nucleophilic addition of PhSCF₂CF₂TMS and PhSO₂CF₂CF₂TMS to enamines.

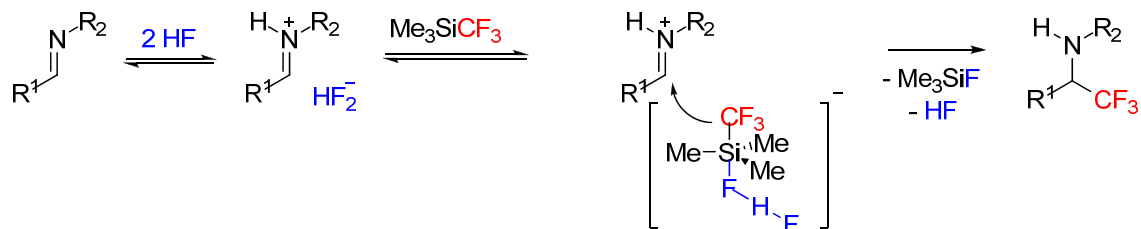
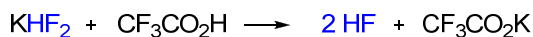
Fluorinated amines are important class of pharmaceutical compounds. The strong electron-withdrawing effect of fluorine lowers the basicity of amines. Changes in the p*K*_a can have effects on a number of different parameters, including physicochemical properties (solubility), binding affinities (potency, selectivity), and absorption, distribution, metabolism and safety issues.^{1,9,113}

One of the ways to synthesize fluorinated amines is the nucleophilic fluoroalkyl addition to C=N bonds of imines, iminium ions, nitrones or hydrazones.¹¹⁴ We were interested to study reactivities of silanes **53** and **56** towards nitrogen-containing electrophiles. Since the electrophilicity of imines depends on the character of substituents at nitrogen, imines bearing the sulfinyl group were considered as suitable substrates. Firstly, the diastereoselective nucleophilic addition of **53** to (*S*)-*N*-benzylidene-5-toluenesulfinamide (**85**) under various basic conditions was investigated. When TMAF, TBAF, TBAT and CsF (in THF or DMF, up to 1 equivalent of fluoride source) were used as initiators, the reactions proceeded in low yields (0-14%) of **86** leading to the product of protodesilylation **57** (PhSCF₂CF₂H). The best yield (20%) was obtained using tetrabutylammonium acetate in DMF (Scheme 3.15).



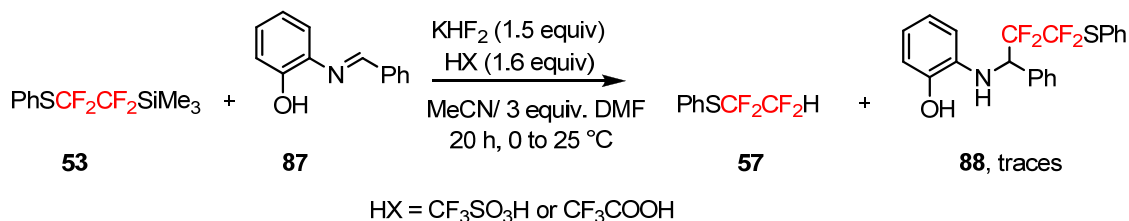
Scheme 3.15 Nucleophilic addition of **53** to (*S*)-*N*-benzylidene-4-toluenesulfinamide (**85**).

Imines bearing aryl or alkyl groups at nitrogen are less reactive towards nucleophilic additions compared to *N*-sulfinyl imines. Dilman *et al.* developed a general protocol for the trifluoromethylation of unactivated imines using acidic conditions.¹¹⁵ In this method, highly reactive iminium ion was generated from the imine under treatment with hydrofluoric acid and reacted with fluoroalkyl silicon species (Scheme 3.16). The use of hydrofluoric acid, which is formed *in situ* from potassium hydrogen difluoride and a strong acid (TfOH or TFA), is crucial, since it allows both activation of the imine and the silane. This methodology was successfully applied for reaction of imines and enamines with fluorinated silanes RCF₂SiMe₃ (R = F, CN, PhS, PhSO₂, P(O)(OEt)₂).¹¹⁶



Scheme 3.16 Mechanism of nucleophilic trifluoroalkyl group transfer to imines under acidic conditions.¹¹⁵

Imine **87** was chosen as a substrate and its reaction with $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**53**) under acidic conditions was studied. When the solution of imine **87**, KHF_2 and acid (trifluoroacetic or triflic) was treated with silane **53**, only traces of the expected product **88** were observed in the reaction mixture and slow conversion of **53** to the side product **57** proceeded (Scheme 3.17).

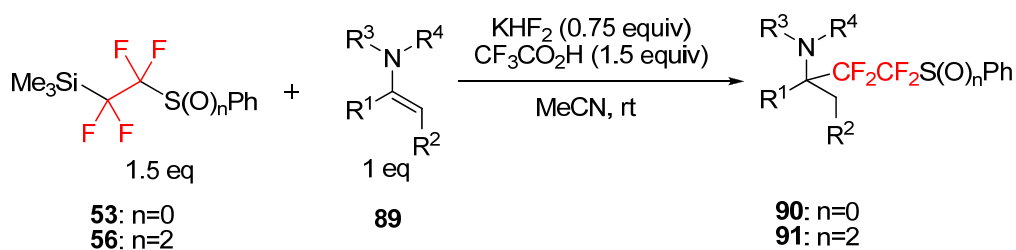


Scheme 3.17 Attempted nucleophilic addition of silane **53** to 2-(benzylideneamino)phenol **87**.

Since enamines more readily generate iminium cations under acidic conditions, they are expected to be more reactive than imines. Therefore, our attention was turned to reactions of highly electrophilic iminium salts formed from enamines. The reaction of enamine **89a** with the silane **53** was performed under similar conditions as for imine **87** (1.5 equiv. of silane and TFA, 0.75 equiv. of KHF_2 in MeCN) and the desired product **90a** was isolated in 68% yield (Table 3.13). These conditions were used in the reaction scope study. Enamines **89** derived from enolizable ketones such as cyclopentanone, cyclohexanone, acetophenone, 1-phenylpropan-2-one and 2,3-dihydro-1*H*-inden-1-one and secondary amines such as morpholine, pyrrolidine, *N*-methyl-1-phenylmethanamine and dibenzylamine react with both

silanes **53** and **56** to form addition products **90** and **91**, respectively, in modest to high yields (Table 3.13).¹¹⁷ The silane **56** was less reactive than silane **53** in most cases, which can be explained by a lower nucleophilicity of the fluorinated carbainion species derived from **56** because of stronger electron acceptor character of the phenylsulfonyl group compared to that of the phenylsulfide counterpart. Sterically hindered enamines **89f** and **89g** gave lower yields, while enamines derived from morpholine and enolizable aldehydes such as propionaldehyde **89h** or 2-phenylacetaldehyde **89i** did not lead to expected products at all. Due to the increased reactivity of sterically unhindered iminium cation it can interact with enamine and undergo fast self-condensation. In the reaction of **89h** with PhSO₂CF₂CF₂SiMe₃, the product **91h'**, formed from enamine dimerization and subsequent nucleophilic attack, was detected (Table 3.13, entry 16).

Table 3.13 Addition of silanes **53** and **56** to enamines under acidic conditions.^a



Entry	Silane	89	Enamine	Time (h)	Product	Yield ^b (%)
1	53	89a		1	90a	68
2	56	89a		2	91a	93

Table 3.13 (Continued)

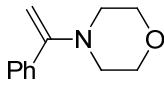
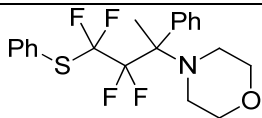
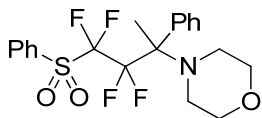
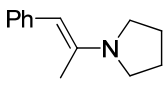
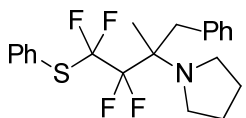
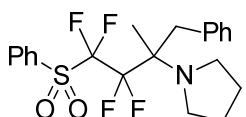
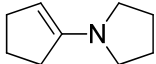
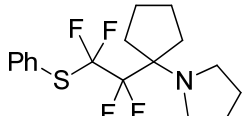
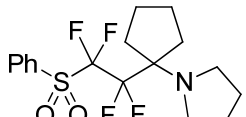
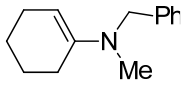
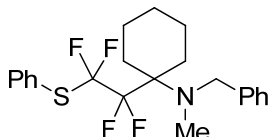
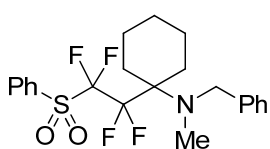
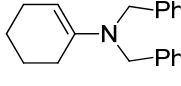
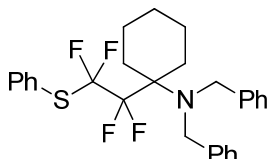
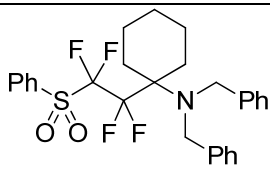
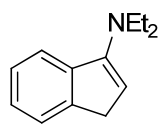
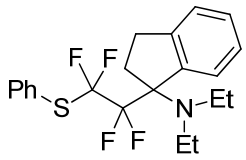
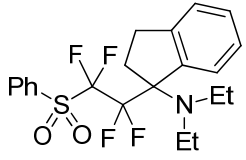
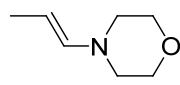
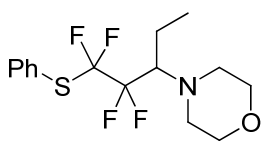
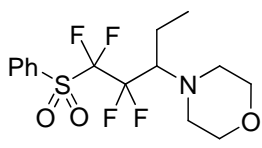
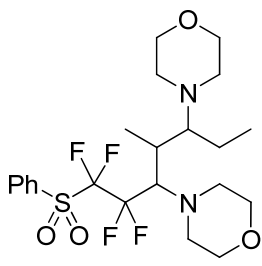
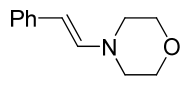
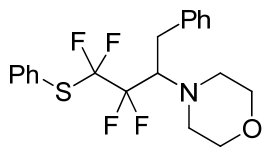
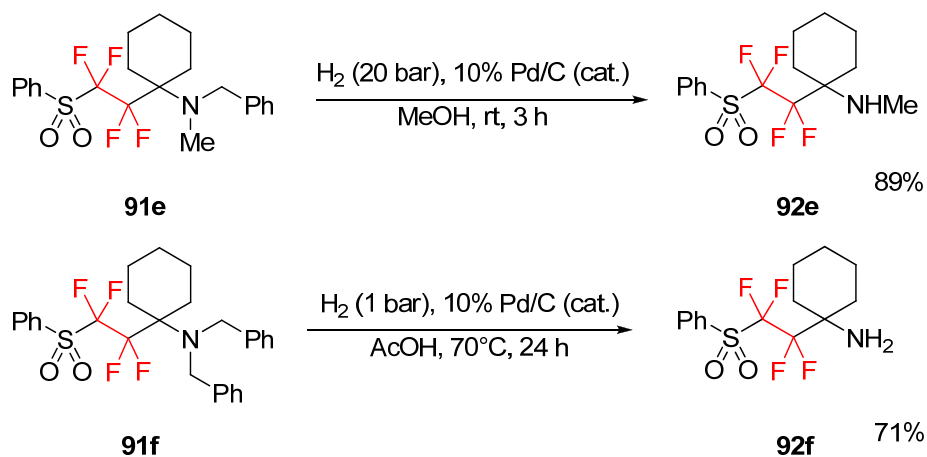
Entry	Silane	89	Enamine	Time (h)	Product	Yield ^b (%)
3	53	89b		2.5	90b 	43
4	56	89b		4	91b 	40
5	53	89c		2	90c 	91
6	56	89c		1	91c 	45
7	53	89d		4	90d 	68
8	56	89d		1.5	91d 	41
9	53	89e		2	90e 	70
10	56	89e		1	91e 	66
11	53	89f		4	90f 	28

Table 3.13 (Continued)

Entry	Silane	89	Enamine	Time (h)	Product	Yield ^b (%)
12	56	89f		1.5	91f 	20
13	53	89g		4	90g 	38
14	56	89g		1	91g 	20
15	53	89h			90h 	0
16	56	89h			91h 	0
					91h' 	15 ^c
17	53	89i			90i 	0

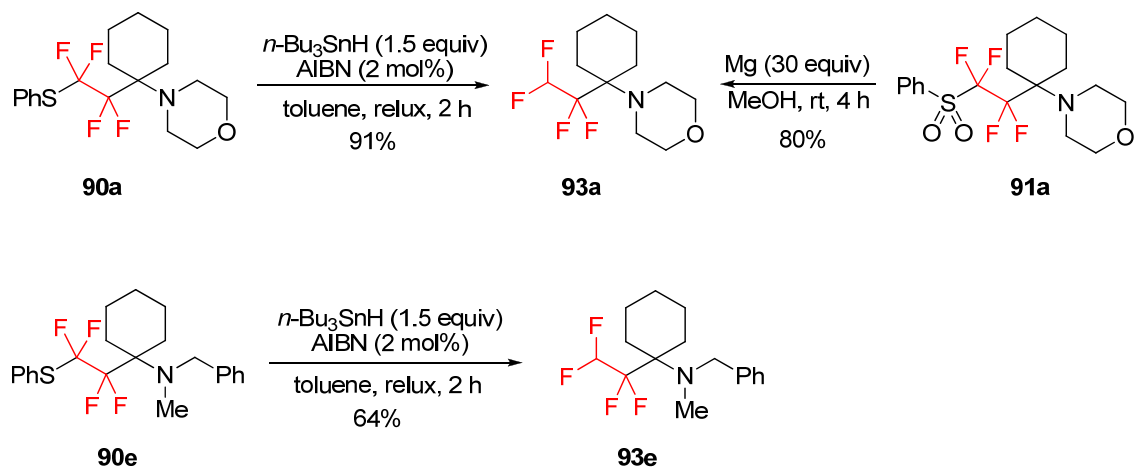
^a Reactions were performed with **53** or **56** (1.5 equiv), **89** (1 equiv), KHF₂ (0.75 equiv), TFA (1.5 equiv) in MeCN at rt. ^b Isolated yield. ^c ¹⁹F NMR yield using PhCF₃ as an internal standard.

The nucleophilic fluoroalkylation reactions gave access to fluorinated tertiary amines **90** and **91**. In order to prepare primary or secondary amines we envisioned a hydrogenolysis of the benzyl groups in adducts formed from *N*-benzyl enamines **89e** and **89f**. Debenzylation of **91e** with hydrogen and catalytic palladium on charcoal provided *N*-methylamines **92** in high yields (Scheme 3.18). Debenzylation of **91f** required the use of acidic medium and elevated temperature (Scheme 3.18). On the other hand, analogous reaction with sulfide **90e** was not successful presumably because of the catalyst poisoning with sulfur of the phenylsulfanyl moiety.



Scheme 3.18 Debenzylation of adducts **91**.

Next, we investigated substitutions of the phenylsulfanyl group in compounds **90** or phenylsulfonyl group in compounds **91** for hydrogen atom. Substitution of the phenylsulfanyl group of **90a** and **90e** was achieved under radical conditions giving tetrafluoroethyl-substituted amines **93** in good yields (Scheme 3.19). Reductive desulfonylation of **91a** provided **93a** also in good yield (Scheme 3.19).¹¹⁷



Scheme 3.19 Radical and reductive desulfurization to provide tetrafluoroethyl-substituted amines **93**.

4. Experimental section

4.1. General information

^1H and ^{19}F NMR spectra were recorded on a Bruker 400 MHz instrument at 400 and 376 MHz, respectively. ^{13}C NMR spectra were recorded on a Bruker 400 MHz, Bruker 500 MHz and Bruker 600 MHz at 100, 125 and 150 MHz, respectively. Spectra were recorded at ambient temperature in CDCl_3 (unless stated otherwise) using 5 mm diameter NMR tubes. The chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (0 ppm, for ^1H NMR), residual CHCl_3 (7.26 ppm for ^1H NMR), CDCl_3 (77.0 ppm for ^{13}C NMR) and internal CFCl_3 (0 ppm for ^{19}F NMR). Coupling constants (J) are given in Hertz. ^{13}C and ^{19}F NMR spectra were proton decoupled.

GCMS spectra were recorded on an Agilent 7890A gas chromatograph coupled with a 5975C quadrupole mass-selective electron impact (EI) detector (70 eV). Chromatographic separations were performed using an Agilent HP 19091S-433 5% methyl phenyl siloxane (30m \times 250 μm with a film thickness of 0.25 μm) column. All compounds were measured by using the following GCMS method: 1 μL injection volume (50:1 split ratio), 1 mL/min flow of helium as a carrier gas; temperature profile: 50 $^\circ\text{C}$, hold for 2.5 min, then at 20 $^\circ\text{C}/\text{min}$ to 300 $^\circ\text{C}$, hold for 5 min (total time 20 min); solvent delay 4 min; MS scan mode 30–600 amu, 2.58 scans/s.

High-resolution mass spectra (HRMS) were recorded on an Agilent 7890A gas chromatograph coupled with a Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) or chemical (CI) ionizations or on a LTQ Orbitrap XL instrument using electrospray (ESI) ionization.

Infrared spectra were measured on a NICOLET 6700 instrument in the range of 3800–400 cm^{-1} using film technique. The sample was first dissolved in CHCl_3 . A drop of this solution was deposited on surface of glass cell. The solution was then evaporated to dryness and the film formed on the cell was analyzed directly.

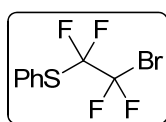
Melting points were determined in Pyrex capillaries using a Biocote (Cat No. SMP10) heater instrument.

Purifications of products were performed by flash column chromatography using silica gel 60. Thin layer chromatography (TLC) was performed using DC-Fertigfolien ALUGRAM® Xtra Sil G/UV254 plates and visualized with ultraviolet light (254 nm) and/or with KMnO_4 staining solution (3g KMnO_4 , 20 g K_2CO_3 , 0.25 g NaOH , 400 ml H_2O).

Solvents were dried either by distillation from Na/benzophenone immediately before the use (THF, toluene) or distilled and stored under argon with activated molecular sieves (3 Å) before the use (CH₂Cl₂, DMF, MeCN, MeOH). Hexane, ethyl acetate, diethyl ether were used without purification. 1,2-Dibromo-1,1,2,2-tetrafluoroethane (**51**) was purified by distillation (b.p. 46–47 °C, 760 torr). All other reagents were purchased from commercial sources and used without further purification, unless specifically stated.

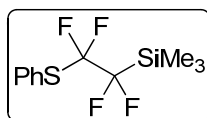
4.2. Synthesis and characterization of products

(2-Bromo-1,1,2,2-tetrafluoroethyl)(phenyl)sulfane^{86c} (**52**).



To a suspension of sodium hydride (1.76 g, 73 mmol) in anhydrous DMF (60 mL) was slowly added thiophenol (5 mL, 50 mmol) at 0 °C within 30 min and stirred at 0 °C under argon for another 30 min. The reaction mixture was then cooled to -50 °C for 15 min before 1,2-dibromo-1,1,2,2-tetrafluoroethane (**51**) (7.3 mL, 61 mmol) was added dropwise. The resulting mixture was maintained at -50 °C for 1.5 h then warmed to room temperature within 1 h. The crude mixture was cooled in an ice-water bath, and excess sodium hydride was quenched by dropwise addition of water (75 mL). The aqueous phase was extracted with Et₂O (3×50 mL), the combined organic layers were washed with water (3×50 mL) and brine (35 mL) and dried over MgSO₄. Filtration and solvent evaporation left a crude product that was purified by chromatography on silica gel (hexane). Product **52** was obtained as a colorless liquid (13.0 g, 90% yield). The physical and spectroscopic data were identical to those reported in the literature.^{86c} *R*_f 0.83 (hexane); ¹H NMR: δ 7.38–7.52 (m, 3*H*_{Ar}), 7.62–7.68 (m, 2*H*_{Ar}); ¹³C NMR (100 MHz): δ 116.7 (tt, ¹*J*_{CF} = 312.9, ²*J*_{CF} = 40.50, CF₂), 122.1 (tt, ¹*J*_{CF} = 290.6, ²*J*_{CF} = 34.0, CF₂), 123.5, 129.3, 130.9, 137.0; ¹⁹F NMR: δ -85.65 (t, ³*J*_{FF} = 8.2, 2F), -62.69 (t, ³*J*_{FF} = 8.2, 2F).

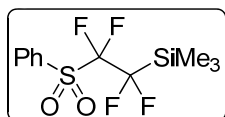
Trimethyl(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)silane^{86c} (**53**).



Reagent **52** (11.6 g, 40 mmol) was added dropwise, at -78 °C, to a mixture of Mg turnings (1.94 g, 80 mmol), TMSCl (20.3 mL, 160 mmol), and anhydrous THF (100 mL). The reaction mixture was stirred for 1 h at -78 °C under argon, then warmed to room temperature over 3 h. After the reaction was completed (monitored by TLC), most of the THF was evaporated, and hexane (150 mL) was added to the residue. The resulting salt was filtered and the filtrate concentrated to give crude product, which was purified by chromatography on silica gel (hexane) to give **53** as a

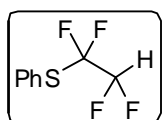
colorless liquid (10.4 g, 92% yield). The physical and spectroscopic data were identical to those reported in the literature.^{86c} R_f 0.63 (hexane); ^1H NMR: δ 0.27 (s, 9H, $3\times\text{CH}_3$), 7.34–7.48 (m, $3H_{\text{Ar}}$), 7.62–7.68 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ -4.11, 122.6 (tt, $^1J_{\text{CF}} = 272.3$, $^2J_{\text{CF}} = 45.2$, CF_2), 124.5, 127.1 (tt, $^1J_{\text{CF}} = 282.0$, $^2J_{\text{CF}} = 32.5$, CF_2), 129.0, 130.1, 137.1; ^{19}F NMR: δ -122.6 (t, $^3J_{\text{FF}} = 5.0$, 2F), -82.95 (t, $^3J_{\text{FF}} = 5.0$, 2F).

Trimethyl(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)silane (56).



3-Chloro-peroxybenzoic acid (4.32 g, 25 mmol) was added to a solution of silane 53 (2.82 g, 10 mmol) in CH_2Cl_2 (100 mL) at 0 °C and the mixture was stirred 2 h at 0 °C. Cooling bath was removed and the mixture was stirred for 24 h at room temperature. Saturated $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL) was added at 0°C, the mixture was filtered, extracted into CH_2Cl_2 and the organic extract was washed with aqueous NaHCO_3 . The combined organic phase was dried (MgSO_4), filtered and concentrated under vacuum. Resulting mixture was dissolved in hexane-EtOAc (90:10), filtered and concentrated under vacuum to give **56** as a white solid (2.83 g, 90% yield). Mp 37–39 °C; R_f 0.32 (hexane-EtOAc, 95:5); ^1H NMR: δ 0.28 (s, 9H, $3\times\text{CH}_3$), 7.58–7.71 (m, $3H_{\text{Ar}}$), 7.98–8.08 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 4.4, 117.3 (tt, $^1J_{\text{CF}} = 291.5$, $^2J_{\text{CF}} = 32.6$, CF_2), 123.5 (tt, $^1J_{\text{CF}} = 273.4$, $^2J_{\text{CF}} = 41.4$, CF_2), 129.3, 130.7, 135.6; ^{19}F NMR: δ -126.1 (s, 2F), -109.2 (s, 2F); MS (EI): m/z 299 (15%), 214 (14), 166 (50), 141 (14), 135 (100), 77 (65), 73 (93); HRMS (CI): m/z calcd for $\text{C}_{11}\text{H}_{15}\text{F}_4\text{O}_2\text{SSi}$ $[\text{M}+\text{H}]^+$ 315.0498, found 315.0496.

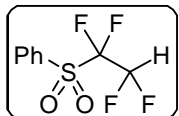
Phenyl(1,1,2,2-tetrafluoroethyl)sulfane (57).



NaBH_4 (2.26 g, 60.0 mmol) and LiCl (2.54 g, 60 mmol) were suspended in dry DMF (40 mL) in an oven-dried Schenk flask under argon. **52** (5.78 g, 20 mmol) was added dropwise at room temperature over a period of 30 min and the mixture was stirred for 30 min. Water (40 mL) was added slowly, the mixture was extracted with Et_2O (3×50 mL), washed with brine (3×25 mL) and water (2×30 mL). Solvent was removed under vacuum, affording **57** as colourless liquid (2.68 g, 64% yield). R_f 0.49 (hexane); ^1H NMR: δ 5.76 (tt, 1H, $^2J_{\text{HF}} = 53.7$, $^3J_{\text{HF}} = 3.4$, CF_2H), 7.40 (dd, 2H, $^3J_{\text{HH}} = 7.5$, 7.4, H_{Ar}), 7.47 (tt, 1H, $^3J_{\text{HH}} = 7.4$, $^4J_{\text{HH}} = 1.2$, H_{Ar}), 7.65 (dd, 2H, $^3J_{\text{HH}} = 7.5$, $^4J_{\text{HH}} = 1.2$, H_{Ar}); ^{13}C NMR (100 MHz): δ 109.4 (tt, $^1J_{\text{CF}} = 252.8$, $^2J_{\text{CF}} = 37.5$, CF_2H), 122.5 (tt, $^1J_{\text{CF}} = 284.1$, $^2J_{\text{CF}} = 29.5$, CF_2), 123.4 (t, $^3J_{\text{CF}} = 2.8$, C_{Ar}), 129.4, 130.7, 137.0; ^{19}F NMR: δ -133.1 (t, 2F, $^3J_{\text{FF}} = 9.4$), -92.0 (t, 2F, $^3J_{\text{FF}} = 9.4$); MS (EI): m/z 210 (100%) $[\text{M}]^+$, 191 (3), 171 (6), 159

(89), 109 (69), 101 (10), 77 (28), 51 (21); HRMS (CI): m/z calcd for $C_8H_7F_4S$ $[M+H]^+$ 211.0205, found 211.0201.

(1,1,2,2-Tetrafluoroethylsulfonyl)benzene (58).

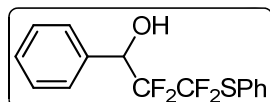


Reagent **57** (2.45 g, 11.7 mmol) was dissolved in CH_2Cl_2 (80 mL) and the solution was cooled down to 0 °C. 3-Chloro-peroxybenzoic acid (70%; 8.6 g, 35 mmol) was added and the mixture was stirred at room temperature for 26 h. The residual acid was quenched with saturated solution of $Na_2S_2O_3$ (100 mL) and the suspension was filtered. The product was extracted to CH_2Cl_2 (3×40 mL), washed with $NaHCO_3$ (5×70 mL) and brine (100 mL), dried over $MgSO_4$, then filtered and evaporated. The product was obtained as a pale yellow liquid (2.55 g, 90% yield). R_f 0.42 (hexane-EtOAc, 15:85); 1H NMR: δ 6.31 (tt, 1H, $^2J_{HF} = 52.2$, $^3J_{HF} = 5.7$, CF_2H), 7.69 (dd, 2H, $^3J_{HH} = 7.5$, 7.8, H_{Ar}), 7.85 (tt, 1H, $^3J_{HH} = 7.5$, $^4J_{HH} = 1.2$, H_{Ar}), 8.04 (dd, 2H, $^3J_{HH} = 7.8$, $^4J_{HH} = 1.2$, H_{Ar}); ^{13}C NMR (100 MHz): δ 107.5 (tt, $^1J_{CF} = 255.8$, $^2J_{CF} = 29.2$, CF_2H), 114.4 (tt, $^1J_{CF} = 295.9$, $^2J_{CF} = 26.8$, CF_2), 129.6, 130.9, 132.0 (t, $^3J_{CF} = 2.8$, C_{Ar}), 136.3; ^{19}F NMR: δ -135.4 (t, 2F, $^3J_{FF} = 8.5$), -120.2 (t, 2F, $^3J_{FF} = 8.5$); IR (film): ν_{max} (cm^{-1}) 3073, 1584, 1479, 1451, 1359, 1174, 1316, 1243, 1125, 1115, 1072, 721, 684, 601, 590, 528; MS (EI): m/z 242 (2%) $[M]^+$, 159 (1), 141 (54), 125 (8), 101 (12), 77 (100), 51 (42); HRMS (CI): m/z calcd for $C_8H_7O_2F_4S$ $[M+H]^+$ 243.0103, found 243.0097.

General procedure for the synthesis of compounds 60.

A solution of TBAT (11 mg, 1 mol%) in dry THF (2 mL) was added dropwise to a solution of **53** (1129 mg, 4 mmol) and a carbonyl compound (2 mmol) in dry THF (6 mL). The mixture was stirred at room temperature under argon for 1 h, followed by the addition of aqueous HCl (3 mL, 1 M), or HF (4 mL, 1 M) in case of **60j**, and stirred for another hour. The reaction product was extracted in Et_2O (3×25 mL), the combined organic phase was washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2 , hexane-EtOAc) to give the desired product **60**.

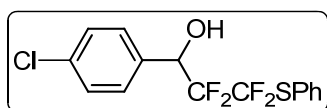
2,2,3,3-Tetrafluoro-1-phenyl-3-(phenylthio)propan-1-ol (60a): white solid (575 mg, 91%



yield); mp 62–64 °C; R_f 0.22 (hexane-EtOAc, 85:15); 1H NMR: δ 2.64 (br s, 1H, OH), 5.16–5.22 (m, 1H, CHOH), 7.35–7.39 (m,

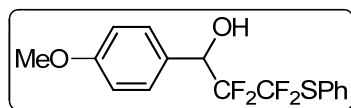
$5H_{Ar}$), 7.42–7.47 (m, $3H_{Ar}$), 7.61–7.63 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 72.3 (dd, $^2J_{CF} = 28.3, 22.9$, CH), 115.7 (ddt, $^1J_{CF} = 261.4, 256.7, ^2J_{CF} = 30.8$, CF_2), 124.6 (dddd, $^1J_{CF} = 290.0, 288.7, ^2J_{CF} = 36.0, 35.0$, CF_2), 127.9, 128.1, 128.4, 129.2, 129.3, 130.1, 130.5, 134.8, 135.0, 135.1, 137.1; ^{19}F NMR: δ -123.5 (ddd, 1F, $^2J_{FF} = 270.2, ^3J_{FF} = 5.5, 2.4$), -116.5 (ddd, 1F, $^2J_{FF} = 270.2, ^3J_{FF} = 6.5, 4.1$), -86.3 (ddd, 1F, $^2J_{FF} = 223.9, ^3J_{FF} = 6.5, 2.4$), -85.5 (ddd, 1F, $^2J_{FF} = 223.9, ^3J_{FF} = 5.5, 4.1$); IR (film): ν_{max} (cm^{-1}) 3456, 3089, 3064, 3037, 1601, 1585, 1575, 1495, 1475, 1455, 1441, 1087, 1061, 1046, 751, 734, 697, 690; MS (EI): m/z 316 (10%) $[M]^+$, 190 (15), 107 (100), 79 (45), 77 (35); HRMS (ESI): m/z calcd for $C_{15}H_{11}F_4OS$ $[M-H]^-$ 315.0472, found 315.0471.

2,2,3,3-Tetrafluoro-1-(4-chlorophenyl)-3-(phenylthio)propan-1-ol (60b): white solid (651



mg, 93% yield); mp 63–66 °C; R_f 0.13 (hexane-EtOAc, 95:5); 1H NMR: δ 2.60 (br d, 1H, $^3J_{HH} = 4.7$, OH), 5.16–5.23 (m, 1H, CHOH), 7.35–7.42 (m, $6H_{Ar}$), 7.45–7.49 (m, $1H_{Ar}$), 7.61–7.63 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 71.7 (dd, $^2J_{CF} = 28.1, 23.2$, CH), 115.5 (dddd, $^1J_{CF} = 261.4, 257.0, ^2J_{CF} = 31.0, 26.6$, CF_2), 123.8, 124.6 (tt, $^1J_{CF} = 288.8, ^2J_{CF} = 35.6$, CF_2), 128.6, 129.2, 130.6, 133.1, 135.3, 137.1; ^{19}F NMR: δ -123.6 (ddd, 1F, $^2J_{FF} = 270.7, ^3J_{FF} = 5.0, 2.4$), -116.5 (ddd, 1F, $^2J_{FF} = 270.7, ^3J_{FF} = 6.2, 4.2$), -86.2 (ddd, 1F, $^2J_{FF} = 224.4, ^3J_{FF} = 6.2, 2.4$), -85.5 (ddd, 1F, $^2J_{FF} = 224.4, ^3J_{FF} = 5.0, 4.2$); IR (film): ν_{max} (cm^{-1}) 3589, 3482, 3064, 3040, 3009, 1599, 1580, 1494, 1476, 1114, 1091, 1070, 769, 750, 690; MS (EI): m/z 352 (2%) $[M]^+$, 350 (7) $[M]^+$, 190 (13), 143 (42), 141 (100), 109 (25), 77 (41); HRMS (ESI): m/z calcd for $C_{15}H_{10}ClF_4OS$ $[M-H]^-$ 349.0082, found 349.0079.

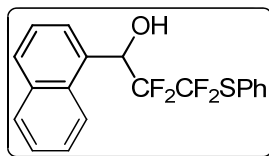
2,2,3,3-Tetrafluoro-1-(4-methoxyphenyl)-3-(phenylthio)propan-1-ol (60c): pale orange



solid (595 mg, 86% yield); mp 60–62 °C; R_f 0.20 (hexane-EtOAc, 85:15); 1H NMR: δ 2.30 (br s, 1H, OH), 3.81 (s, 3H, OCH_3), 5.12–5.18 (m, 1H, CHOH), 6.90–6.92 (m, $2H_{Ar}$), 7.37–7.41 (m, $4H_{Ar}$), 7.44–7.48 (m, $1H_{Ar}$), 7.62–7.64 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 55.3 (s, OCH_3), 72.0 (dd, $^2J_{CF} = 28.2, 22.8$, CH), 113.9, 115.8 (ddt, $^1J_{CF} = 260.9, 256.3, ^2J_{CF} = 30.4, 30.4$, CF_2), 124.1, 124.6 (tt, $^1J_{CF} = 289.3, ^2J_{CF} = 36.0$, CF_2), 126.9, 129.2, 129.4, 130.5, 137.1, 160.4; ^{19}F NMR: δ -123.8 (ddd, 1F, $^2J_{FF} = 269.3, ^3J_{FF} = 5.3, 2.6$), -116.9 (ddd, 1F, $^2J_{FF} = 269.3, ^3J_{FF} = 6.4, 4.3$), -86.4 (ddd, 1F, $^2J_{FF} = 223.6, ^3J_{FF} = 6.4, 2.6$), -85.6 (ddd, 1F, $^2J_{FF} = 223.6, ^3J_{FF} = 5.3, 4.3$); IR (film): ν_{max} (cm^{-1}) 3467, 3064, 3040, 3007, 2840, 1613, 1588, 1578, 1515, 1476, 1465, 1253, 1116, 1091, 1070, 843, 790, 751, 691; MS (EI): m/z 346 (3%) $[M]^+$,

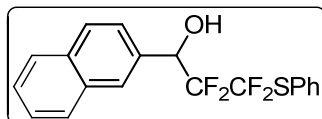
137 (100), 109 (20), 94 (9), 77 (12); HRMS (ESI): m/z calcd for $C_{16}H_{13}F_4O_2S$ $[M-H]^-$ 345.0578, found 345.0579.

2,2,3,3-Tetrafluoro-1-(naphthalen-1-yl)-3-(phenylthio)propan-1-ol (60d): pale yellow



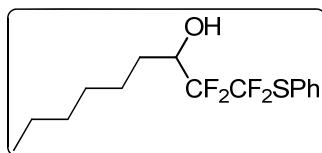
solid (585 mg, 80% yield); mp 70–72 °C; R_f 0.34 (hexane-EtOAc, 80:20); 1H NMR: δ 2.68 (br d, 1H, $^3J_{HH} = 4.8$, OH), 6.10–6.17 (m, 1H, CHOH), 7.36–7.40 (m, $2H_{Ar}$), 7.44–7.48 (m, $1H_{Ar}$), 7.49–7.56 (m, $3H_{Ar}$), 7.63–7.65 (m, $2H_{Ar}$), 7.83–7.90 (m, $3H_{Ar}$), 8.03 (d, 1H, $^3J_{HH} = 8.3$, H_{Ar}); ^{13}C NMR (100 MHz): δ 67.7 (dd, $^2J_{CF} = 29.3$, 22.0, CH), 116.0 (ddt, $^1J_{CF} = 263.5$, 256.1, $^2J_{CF} = 30.7$, CF_2), 123.0, 125.2, 125.7, 126.5, 126.6, 128.9, 129.2, 129.9, 130.5, 131.0, 131.5, 133.6, 137.1; ^{19}F NMR: δ -125.1 (d, 1F, $^2J_{FF} = 270.8$), -114.0 (ddd, 1F, $^2J_{FF} = 270.8$, $^3J_{FF} = 6.9$, 4.6), -86.8 (ddd, 1F, $^2J_{FF} = 223.7$, $^3J_{FF} = 6.9$, 2.3), -85.9 (ddd, 1F, $^2J_{FF} = 223.7$, $^3J_{FF} = 6.9$, 4.6); IR (film): ν_{max} (cm^{-1}) 3568, 3465, 3063, 3025, 1599, 1577, 1514, 1094, 1069, 789, 773, 750, 690; MS (EI): m/z 366 (21%) $[M]^+$, 157 (100), 129 (81), 109 (10); HRMS (ESI): m/z calcd for $C_{13}H_9OF_4$ $[M-H]^-$ 365.0629, found 365.0629.

2,2,3,3-Tetrafluoro-1-(naphthalen-2-yl)-3-(phenylthio)propan-1-ol (60e): white solid (549



mg, 75% yield); mp 73–75 °C; R_f 0.10 (hexane-EtOAc, 90:10); 1H NMR: δ 2.66 (br d, 1H, $^3J_{HH} = 5.05$, OH), 5.35–6.42 (m, 1H, CHOH), 7.36–7.40 (m, $2H_{Ar}$), 7.43–7.48 (m, $1H_{Ar}$), 7.49–7.53 (m, $2H_{Ar}$), 7.57–7.59 (m, $1H_{Ar}$), 7.62–7.65 (m, $2H_{Ar}$), 7.84–7.88 (m, $3H_{Ar}$), 7.94 (s, $1H_{Ar}$); ^{13}C NMR (100 MHz): δ 72.5 (dd, $^2J_{CF} = 27.7$, 22.0, CH), 125.1, 126.4, 126.7, 127.7, 127.9, 128, 129.2, 130.5, 132.1, 132.9, 133.7, 137.1; ^{19}F NMR: δ -123.3 (ddd, 1F, $^2J_{FF} = 269.6$, $^3J_{FF} = 5.7$, 2.3), -116.3 (ddd, 1F, $^2J_{FF} = 269.3$, $^3J_{FF} = 6.9$, 4.6), -86.3 (ddd, 1F, $^2J_{FF} = 223.7$, $^3J_{FF} = 6.9$, 2.3), -85.6 (ddd, 1F, $^2J_{FF} = 223.7$, $^3J_{FF} = 5.7$, 4.6); IR (film): ν_{max} (cm^{-1}) 3433, 3060, 3026, 1601, 1509, 1475, 1113, 1066, 862, 825, 748, 689, 479; MS (EI): m/z 366 (32%) $[M]^+$, 157 (100), 129 (64), 109 (13); HRMS (ESI): m/z calcd for $C_{19}H_{13}F_4OS$ $[M-H]^-$ 365.0629, found 365.0628.

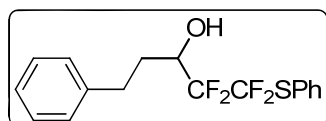
1,1,2,2-Tetrafluoro-1-(phenylthio)nonan-3-ol (60f): colorless oil (466 mg, 72% yield); R_f



0.19 (hexane-EtOAc, 85:15); 1H NMR: δ 0.87–0.91 (m, 3H, CH_3), 1.26–1.41 (m, 7H, $3 \times CH_2$, CH^aH^b), 1.57–1.66 (m, 2H, CH_2), 1.74–1.81 (m, 1H, CH^aH^b), 1.92 (br s, 1H, OH), 4.06–4.15

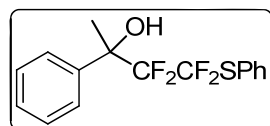
(m, 1H, CHOH), 7.38–7.43 (m, 2H_{Ar}), 7.45–7.50 (m, 1H_{Ar}), 7.64–7.67 (m, 2H_{Ar}); ¹³C NMR (100 MHz): δ 14.0 (s, CH₃), 22.6 (s, CH₂), 25.1 (s, CH₂), 28.9 (s, CH₂), 29.4 (s, CH₂), 31.6 (s, CH₂), 70.4 (dd, ²J_{CF} = 27.3, 23.8, CH), 116.5 (tt, ¹J_{CF} = 258.1, ²J_{CF} = 30.7, CF₂), 124.0, 124.6 (tt, ¹J_{CF} = 289.0, ²J_{CF} = 36.1, CF₂), 129.2, 130.5, 137.1; ¹⁹F NMR: δ -124.7 (ddd, 1F, ²J_{FF} = 269.7, ³J_{FF} = 5.5, 3.6), -119.4 (dt, 1F, ²J_{FF} = 269.7, ³J_{FF} = 4.5), -86.7 (ddd, 1F, ²J_{FF} = 223.5, ³J_{FF} = 5.5, 3.6), -86.0 (dt, 1F, ²J_{FF} = 223.5, ³J_{FF} = 4.5); IR (film): ν_{max} (cm⁻¹) 3603, 3414, 3080, 3065, 3027, 1579, 1476, 1468, 1113, 1090, 1070, 749, 690; MS (EI): *m/z* 324 (70%) [M]⁺, 190 (45), 159 (40), 127 (37), 110 (100), 55 (55); HRMS (ESI): *m/z* calcd for C₁₅H₁₉F₄OS [M-H]⁻ 323.1098, found 323.1098.

1,1,2,2-Tetrafluoro-5-phenyl-1-(phenylthio)pentan-3-ol (60g): pale yellow solid (591 mg,



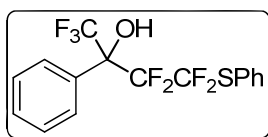
86% yield); mp 54–56 °C; *R_f* 0.20 (hexane-EtOAc, 80:20); ¹H NMR: δ 1.90–2.15 (m, 3H, CH₂, OH), 2.68–2.82 (m, 1H, CH^aH^b), 2.90–3.00 (m, 1H, CH^aH^b), 4.04–4.17 (m, 1H, CHOH), 7.18–7.24 (m, 3H_{Ar}), 7.27–7.33 (m, 2H_{Ar}), 7.36–7.42 (m, 2H_{Ar}), 7.44–7.49 (m, 1H_{Ar}), 7.60–7.66 (m, 2H_{Ar}); ¹³C NMR (100 MHz): δ 30.9 (s, CH₂), 31.1 (s, CH₂), 70.4 (dd, ²J_{CF} = 26.3, 23.4, CH), 126.2, 128.5, 128.6, 129.2, 130.5, 137.1, 140.7; ¹⁹F NMR: δ -124.2 (dt, 1F, ²J_{FF} = 269.6, ³J_{FF} = 4.6), -119.4 (dt, 1F, ²J_{FF} = 269.6, ³J_{FF} = 4.6), -86.4 to -86.3 (m, 2F, CF₂); IR (film): ν_{max} (cm⁻¹) 3580, 3433, 3084, 3063, 3028, 1603, 1597, 1584, 1105, 1071, 750, 700, 690; MS (EI): *m/z* 344 (25%) [M]⁺, 110 (43), 91 (100), 77 (22), 65 (18); HRMS (ESI): *m/z* calcd for C₁₇H₁₅OF₄S [M-H]⁻ 343.0785, found 343.0786.

3,3,4,4-Tetrafluoro-2-phenyl-4-(phenylthio)butan-2-ol (60h): pale yellow oil (237 mg,



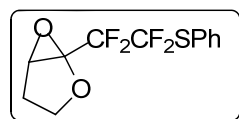
36% yield); *R_f* 0.25 (hexane-EtOAc, 95:5); ¹H NMR: δ 1.82 (s, 3H, CH₃), 2.57 (br s, 1H, OH), 7.31–7.44 (m, 6H_{Ar}), 7.54–7.59 (m, 4H_{Ar}); ¹³C NMR (100 MHz): δ 25.2 (s, CH₃), 76.0 (t, ²J_{CF} = 24.8, COH), 116.7 (tt, ¹J_{CF} = 262.7, ²J_{CF} = 29.7, CF₂), 124.5, 125.3 (tt, ¹J_{CF} = 290.8, ²J_{CF} = 36.6, CF₂), 126.4, 128.0, 128.2, 129.0, 130.3, 137.1, 139.4; ¹⁹F NMR: δ -116.7 (dt, 1F, ²J_{FF} = 272.6, ³J_{FF} = 4.9), -115.7 (dt, 1F, ²J_{FF} = 272.6, ³J_{FF} = 5.6), -82.5 (br t, 2F, ³J_{FF} = 5.3, CF₂); IR (film): ν_{max} (cm⁻¹) 3600, 3569, 3063, 3040, 3030, 3006, 1603, 1584, 1497, 1476, 1449, 1443, 1124, 1096, 1077, 751, 701, 691; MS (EI): *m/z* 330 (3%) [M]⁺, 121(100), 109 (22), 77 (20); HRMS (ESI): *m/z* calcd for C₁₆H₁₃F₄OS [M-H]⁻ 329.0629, found 329.0628;

1,1,1,3,3,4,4-Heptafluoro-2-phenyl-4-(phenylthio)butan-2-ol (60j): colorless oil (698 mg,



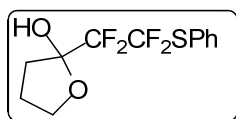
91% yield); R_f 0.41 (hexane-EtOAc, 90:10); ^1H NMR: δ 3.52 (br s, 1H, OH), 7.30–7.35 (m, $2H_{\text{Ar}}$), 7.39–7.44 (m, $4H_{\text{Ar}}$), 7.50–7.52 (m, $2H_{\text{Ar}}$), 7.73–7.75 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 115.2 (tt, $^1J_{\text{CF}} = 267.9$, $^2J_{\text{CF}} = 30.7$, CF_2), 121.9, 123.7 (m, CF_3), 124.1–124.8 (m, CF_2), 127.0, 128.2, 129.2, 129.7, 130.6, 137.2; ^{19}F NMR (CDCl_3): -114.7 to -114.5 (m, 2F, CF_2S), -83.7 to -82.4 (m, 2F, $\text{CF}_2\text{CF}_2\text{S}$), -74.3 (t, 3F, $^4J_{\text{FF}} = 12.6$, CF_3); IR (film): ν_{max} (cm^{-1}) 3597, 3551, 3080, 3067, 3039, 1606, 1501, 1476, 1197, 1180, 1160, 751, 708; MS (EI): m/z 384 (70%) [M] $^+$, 175 (100), 127 (19), 105 (86), 77 (30); HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{10}\text{F}_7\text{OS}$ [$\text{M}-\text{H}$] $^-$ 383.0346, found 383.0344.

1-(1,1,2-Tetrafluoro-2-(phenylthio)ethyl)-2,6-dioxabicyclo[3.1.0]hexane (60k).



Reagent **53** (600 mg, 2.12 mmol) was added dropwise to a solution of CsF (322 mg, 2.12 mmol) and α -bromo- γ -butyrolactone (88 μL , 1.06 mmol) in dry THF (5 mL). The mixture was stirred at room temperature under argon for 24 h. The reaction product was extracted in Et_2O (3 \times 25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO_4), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2 , hexane-EtOAc) to give the desired product **60k** as yellow oil (243 mg, 78% yield). R_f 0.67 (hexane-EtOAc, 80:20); ^1H NMR: δ 2.17–2.25 (m, 1H), 2.50 (ddt, 1H, $^3J_{\text{HH}} = 14.0$, 7.8, $^4J_{\text{HF}} = 2.0$), 4.04–4.11 (m, 2H), 4.30 (td, 1H, $^3J_{\text{HH}} = 9.1$, $^2J_{\text{HH}} = 2.2$), 7.50–7.63 (m, 3H), 7.74–7.84 (m, 2H); ^{13}C NMR (100 MHz): δ 26.9, 60.8 (d, $^3J_{\text{CF}} = 2.2$, CH-O), 68.4, 87.5 (dd, $^2J_{\text{CF}} = 35.4$, 31.3, O-C-O), 112.4 (tdd, $^1J_{\text{CF}} = 257.5$, 254.4, $^2J_{\text{CF}} = 32.7$, CF_2), 123.4 (tt, $^1J_{\text{CF}} = 290.1$, $^2J_{\text{CF}} = 34.0$, CF_2), 123.6 (t, $^3J_{\text{CF}} = 2.3$, C_{Ar}), 129.2, 130.6, 137.1; ^{19}F NMR: δ -119.95 (dt, 1F, $^2J_{\text{FF}} = 270.0$, $^3J_{\text{FF}} = 6.8$), -117.8 (dt, 1F, $^2J_{\text{FF}} = 270.0$, $^3J_{\text{FF}} = 6.8$), -87.5 (m, 2F); IR (film): ν_{max} (cm^{-1}) 3064, 2991, 2852, 1476, 1310, 1253, 1210, 1136, 1097, 933, 867, 751, 504; MS (EI): m/z 294 (44%) [M] $^+$, 274 (21), 218 (18), 198 (21), 165 (41), 159 (98), 127 (40), 121 (59), 109 (100), 77 (65), 65 (38); HRMS (CI): m/z calcd for $\text{C}_{12}\text{H}_{10}\text{F}_4\text{O}_2\text{S}$ [M] $^+$ 294.0338, found 294.0335.

2-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)tetrahydrofuran-2-ol (**60l**).



Reagent **53** (600 mg, 2.12 mmol) was added dropwise to a solution of CsF (322 mg, 2.12 mmol) and γ -butyrolactone (81 μ L, 1.06 mmol) in dry THF (5 mL). The mixture was stirred at room temperature under argon for 24 h, followed by the addition of aqueous HCl (3 mL, 1 M) and stirred for 6 h at 40 $^{\circ}$ C. The reaction product was extracted in Et₂O (3 \times 25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **60l** as yellow oil (396 mg, 67% yield). *R_f* 0.24 (hexane-EtOAc, 90:10); ¹H NMR: δ 1.95–2.36 (m, 4H), 3.97–4.03 (m, 1H), 4.17–4.22 (m, 1H), 7.37–7.48 (m, 3H), 7.64–7.67 (m, 2H); ¹³C NMR (100 MHz): δ 24.2, 33.7, 70.3, 104.2 (t, ²*J*_{CF} = 27.0, C-OH), 114.5 (tt, ¹*J*_{CF} = 261.1, ²*J*_{CF} = 30.1, CF₂), 124.3, 124.7 (tt, ¹*J*_{CF} = 289.1, ²*J*_{CF} = 34.8, CF₂), 129.1, 130.4, 137.2; ¹⁹F NMR: δ -121.6 (d, 1F, ²*J*_{FF} = 272.0), -119.9 (ddd, 1F, ²*J*_{FF} = 272.0, ³*J*_{FF} = 5.9, 4.8), -85.0 (ddd, 1F, ²*J*_{FF} = 224.6, ³*J*_{FF} = 5.6, 5.1), -83.9 (ddd, 1F, ²*J*_{FF} = 224.6, ³*J*_{FF} = 5.9, 4.8); IR (film): ν_{max} (cm⁻¹) 3412, 3086, 3064, 1476, 1133, 1202, 1097, 1067, 1042, 930, 504; MS (EI): *m/z* 296 (11%) [*M*⁺], 190 (9), 159 (12), 109 (22), 87 (100), 43 (19); HRMS (CI): *m/z* calcd for C₁₂H₁₂F₄O₂S [*M*]⁺ 296.0494, found 296.0484;

Synthesis of compounds **61** by radical cleavage of adducts **60** (*Method A*).

A solution of *n*-Bu₃SnH (471 μ L, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added dropwise to a solution of **60** (1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon for 4 h (15 h in case of **60d**), followed by concentration under reduced pressure and purification by flash column chromatography (SiO₂, hexane-EtOAc) to give product **61**.

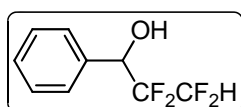
Synthesis of compounds **61** by desulfonylation of **83** with magnesium (*Method B*).

Magnesium metal (396 mg, 16.5 mmol) and I₂ (one ball) were stirred in an oven-dried Schlenk tube under Ar for 10 min. **83** (0.75 mmol) was added and the mixture was slightly heated with a heat gun. MeOH (20 mL) was added and the solution quickly turned yellow and then grey in 5 min. After stirring for 2 h, NH₄Cl (10 mL) and 1M HCl (30 mL) were added. The product was extracted to Et₂O (5 \times 20 mL), washed with brine (1 \times 20 mL), dried over MgSO₄, filtered, and ether was evaporated yielding crude **61**, which was purified by flash column chromatography (SiO₂, hexane-EtOAc).

Synthesis of compounds **61** by addition of **58** to carbonyl compounds (*Method C*).

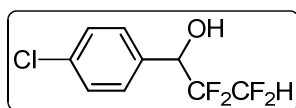
Magnesium metal (72 mg, 3 mmol), HgCl₂ (16 mg, 0.06 mmol) were suspended in dry DMF at -60 °C in an oven-dried Schlenk flask under Ar. **58** (242 mg, 1 mmol) was added, followed by the carbonyl-containing compound (2 mmol). The temperature was slowly increased while the reaction was monitored by GCMS. On full consumption of **58**, 1M HCl (10 mL) was added. The product was extracted to Et₂O (5×20 mL), washed with brine (1×20 mL), dried over MgSO₄, filtered, and ether was evaporated yielding crude **61**, which was purified by flash column chromatography (SiO₂, hexane-EtOAc).

2,2,3,3-Tetrafluoro-1-phenylpropan-1-ol (61a): colorless oil (*Method A*: 160 mg, 77%



yield; *Method B*: 108 mg, 69% yield; *Method C*: 119 mg, 57% yield); *R_f* 0.18 (hexane-EtOAc, 85:15); ¹H NMR: δ 2.72 (br d, 1H, ³*J*_{HH} = 4.4, OH), 4.99–5.06 (m, 1H, CHOH), 5.95 (dddd, 1H, ²*J*_{HF} = 53.7, 52.8, ³*J*_{HF} = 8.3, 2.9, CF₂H), 7.38–7.41 (m, 3*H*_{Ar}), 7.43–7.46 (m, 2*H*_{Ar}); ¹³C NMR (100 MHz): δ 72.1 (dd, ²*J*_{CF} = 28.4, 23.2, CH), 109.4 (dddd, ¹*J*_{CF} = 251.6, 248.9, ²*J*_{CF} = 37.3, 29.7, CF₂H), 114.8 (dddd, ¹*J*_{CF} = 254.1, 252.8, ²*J*_{CF} = 26.9, 23.2, CF₂), 127.8, 128.6, 129.4, 134.5; ¹⁹F NMR: δ -141.7 (ddd, 1F, ²*J*_{FF} = 300.8, ³*J*_{FF} = 10.3, 6.4), -137.6 (ddd, 1F, ²*J*_{FF} = 300.8, ³*J*_{FF} = 10.8, 2.1), -131.5 (ddd, 1F, ²*J*_{FF} = 269.8, ³*J*_{FF} = 10.3, 2.1), -129.2 (ddd, 1F, ²*J*_{FF} = 269.8, ³*J*_{FF} = 10.8, 6.4); IR (film): ν_{max} (cm⁻¹) 3594, 3458, 3094, 3069, 3038, 3014, 1606, 1588, 1496, 1457, 1239, 1182, 1109, 1064, 746, 732, 700; MS (EI): *m/z* 208 (3%) [M]⁺, 107 (100), 79 (80), 77 (65), 51 (30); HRMS (ESI): *m/z* calcd for C₉H₇F₄O [M-H]⁻ 207.0439, found 207.0440.

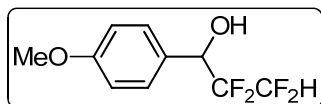
2,2,3,3-Tetrafluoro-1-(4-chlorophenyl)propan-1-ol (61b): colorless oil (*Method A*: 237 mg,



98% yield; *Method B*: 158 mg, 87% yield; *Method C*: 65 mg, 27% yield); *R_f* 0.33 (hexane-EtOAc, 85:15); ¹H NMR: δ 2.59 (br d, 1H, ³*J*_{HH} = 4.0, OH), 5.02–5.09 (m, 1H, CHOH), 5.99 (dddd, 1H, ²*J*_{HF} = 53.6, 52.7, ³*J*_{HF} = 8.4, 2.5, CF₂H), 7.40 (m, 4*H*_{Ar}); ¹³C NMR (100 MHz): δ 71.5 (dd, ²*J*_{CF} = 28.7, 23.2, CH), 109.5 (dddd, ¹*J*_{CF} = 252.0, 248.9, ²*J*_{CF} = 37.9, 29.9, CF₂H), 114.6 (dddd, ¹*J*_{CF} = 254.3, 252.7, ²*J*_{CF} = 27.3, 23.2, CF₂), 127.8, 129.1, 132.8, 135.5; ¹⁹F NMR: δ -141.5 (ddd, 1F, ²*J*_{FF} = 301.5, ³*J*_{FF} = 9.7, 6.7), -137.2 (ddd, 1F, ²*J*_{FF} = 301.5, ³*J*_{FF} = 10.3, 2.2), -131.3 (ddd, 1F, ²*J*_{FF} = 271.3, ³*J*_{FF} = 9.7, 2.2), -128.6 (ddd, 1F, ²*J*_{FF} = 271.3, ³*J*_{FF} = 10.3, 6.7); IR (film): ν_{max} (cm⁻¹) 3598, 3444, 3000, 1600, 1581, 1494, 1107, 819; MS (EI): *m/z* 244 (2%) [M]⁺, 242

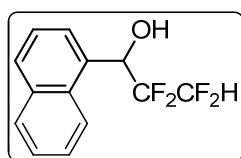
(6) $[M]^+$, 143 (35), 141 (100), 113 (19), 77 (73), 51 (15); HRMS (ESI): m/z calcd for $C_9H_6ClF_4O$ $[M-H]^-$ 241.0049, found 241.0053.

2,2,3,3-Tetrafluoro-1-(4-methoxyphenyl)propan-1-ol (61c): colorless oil (*Method A*: 190



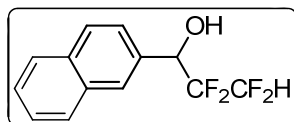
mg, 80% yield; *Method C*: 183 mg, 77% yield); R_f 0.26 (hexane-EtOAc, 80:20); 1H NMR: δ 2.40 (br d, 1H, $^3J_{HH} = 4.3$, OH), 3.82 (s, 3H, OCH₃), 4.95–5.03 (m, 1H, CHOH), 5.95 (dddd, 1H, $^2J_{HF} = 53.6$, 52.9, $^3J_{HF} = 8.3$, 2.9, CF₂H), 6.91–6.95 (m, 2H_{Ar}), 7.36–7.38 (m, 2H_{Ar}); ^{13}C NMR (100 MHz): δ 55.3 (s, OCH₃), 71.7 (dd, $^2J_{CF} = 28.5$, 23.0, CH), 109.4 (dddd, $^1J_{CF} = 251.7$, 249.0, $^2J_{CF} = 37.4$, 29.8, CF₂H), 114.1, 114.8 (tt, $^1J_{CF} = 254.3$, $^2J_{CF} = 23.3$, CF₂), 126.4, 129.1, 160.5; ^{19}F NMR: δ -141.7 (ddd, 1F, $^2J_{FF} = 300.8$, $^3J_{FF} = 10.4$, 6.6), -137.7 (ddd, 1F, $^2J_{FF} = 300.8$, $^3J_{FF} = 10.9$, 2.1), -131.8 (ddd, 1F, $^2J_{FF} = 269.0$, $^3J_{FF} = 10.4$, 2.1), -129.6 (ddd, 1F, $^2J_{FF} = 269.0$, $^3J_{FF} = 10.9$, 6.6); MS (EI): m/z 238 (16%) $[M]^+$, 137 (100), 109 (27), 94 (24), 77 (22); HRMS (ESI): m/z calcd for $C_{10}H_9F_4O_2$ $[M-H]^-$ 237.0544, found 237.0543.

2,2,3,3-Tetrafluoro-1-(naphthalene-1-yl)propan-1-ol (61d): pale yellow oil (*Method A*: 168



mg, 65% yield; *Method C*: 62 mg, 24% yield); R_f 0.38 (hexane-EtOAc, 85:15); 1H NMR: δ 2.75 (br s, 1H, OH), 5.94–6.01 (m, 1H, CHOH), 6.13 (dddd, 1H, $^2J_{HF} = 54.0$, 52.8, $^3J_{HF} = 9.2$, 1.8, CF₂H), 7.50–7.60 (m, 3H_{Ar}), 7.83 (d, 1H, $^3J_{HH} = 7.3$, H_{Ar}), 7.89–7.94 (m, 2H_{Ar}), 8.06 (d, 1H, $^3J_{HH} = 8.4$, H_{Ar}); ^{13}C NMR (100 MHz): δ 67.8 (dd, $^2J_{CF} = 30.7$, 23.4, CH), 109.4 (dddd, $^1J_{CF} = 251.8$, 247.4, $^2J_{CF} = 38.1$, 27.8, CF₂H), 112.6–118.1 (m, CF₂), 122.9, 125.1, 125.9, 126.3, 126.7, 128.9, 130.0, 130.6, 131.4, 133.7; ^{19}F NMR: δ -142.2 (ddd, 1F, $^2J_{FF} = 299.4$, $^3J_{FF} = 10.3$, 8.0), -137.1 (ddd, 1F, $^2J_{FF} = 299.4$, $^3J_{FF} = 11.5$, 3.4), -130.9 (ddd, 1F, $^2J_{FF} = 270.8$, $^3J_{FF} = 10.3$, 3.4), -128.0 (ddd, 1F, $^2J_{FF} = 270.8$, $^3J_{FF} = 11.5$, 8.0); IR (film): ν_{max} (cm⁻¹) 3547, 3442, 3056, 3014, 1599, 1580, 1514, 1105, 788, 774; MS (EI): m/z 258 (40%) $[M]^+$, 157 (89), 129 (100), 51 (8); HRMS (ESI): m/z calcd for $C_{13}H_9F_4O$ $[M-H]^-$ 257.0595, found 257.0585.

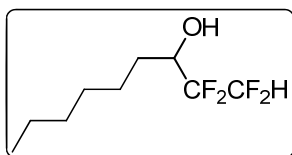
2,2,3,3-Tetrafluoro-1-(naphthalene-2-yl)propan-1-ol (61e): white solid (*Method A*: 217



mg, 84% yield; *Method B*: 170 mg, 88% yield; *Method C*: 206 mg, 80% yield); mp 38–40 °C; R_f 0.25 (hexane-EtOAc, 90:10); 1H NMR: δ 5.17–5.24 (m, 1H, CHOH), 5.99 (dddd, 1H, $^2J_{HF} = 53.69$, 52.80, $^3J_{HF} = 8.18$, 2.88, CF₂H), 7.46–7.58 (m, 3H_{Ar}), 7.79–7.96 (m, 4H_{Ar}); ^{13}C NMR (100 MHz): δ 72.3 (dd, $^2J_{CF} = 27.8$, 23.4, CH), 109.4 (dddd, $^1J_{CF} = 251.8$, 248.8, $^2J_{CF} = 36.6$, 29.3,

CF₂H), 115.0 (dddd, ¹J_{CF} = 257.6, 254.7, ²J_{CF} = 26.3, 23.4, CF₂), 124.7, 126.6, 126.9, 127.6, 127.7, 128.2, 128.5, 131.8, 133.0, 133.8; ¹⁹F NMR: δ -141.6 (ddd, 1F, ²J_{FF} = 300.6, ³J_{FF} = 10.3, 6.9), -137.5 (dd, 1F, ²J_{FF} = 300.6, ³J_{FF} = 10.3), -131.1 (dd, 1F, ²J_{FF} = 269.6, ³J_{FF} = 10.3), -128.9 (ddd, 1F, ²J_{FF} = 270.8, ³J_{FF} = 10.3, 6.9); IR (film): ν_{max} (cm⁻¹) 3550, 3448, 3062, 3027, 1603, 1501, 1107, 864, 823, 763, 479; MS (EI): *m/z* 258 (49%) [M]⁺, 157 (83), 129 (100); HRMS (ESI): *m/z* calcd for C₁₃H₉F₄O [M-H]⁻ 257.0595, found 257.0596.

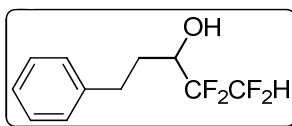
1,1,2,2-Tetrafluorononan-3-ol (61f): colorless oil (*Method A*: 199 mg, 92% yield; *Method B*:



120 mg, 74% yield; *Method C*: 197 mg, 91% yield); *R_f* 0.61 (hexane-EtOAc, 85:15); ¹H NMR: δ 0.88–0.91 (m, 3H, CH₃), 1.26–1.43 (m, 7H, 3×CH₂, CH^aH^b), 1.53–1.63 (m, 2H, CH₂), 1.72–1.84 (m, 2H, CH^aH^b, OH), 3.89–4.00 (m, 1H, CHOH), 6.01 (dddd,

1H, ²J_{HF} = 53.8, 52.8, ³J_{HF} = 8.4, 2.4, CF₂H); ¹³C NMR (100 MHz): δ 14.0 (s, CH₃), 22.5 (s, CH₂), 25.0 (s, CH₂), 28.9 (s, CH₂), 29.0 (s, CH₂), 31.6 (s, CH₂), 70.1 (dd, ²J_{CF} = 28.0, 24.3, CH), 109.5 (dddd, ¹J_{CF} = 251.3, 248.0, ²J_{CF} = 38.6, 30.3, CF₂H), 115.7 (dddd, ¹J_{CF} = 253.5, 251.4, ²J_{CF} = 27.5, 23.4, CF₂); ¹⁹F NMR: δ -142.1 (ddd, 1F, ²J_{FF} = 301.3, ³J_{FF} = 8.0, 5.8), -137.3 (ddd, 1F, ²J_{FF} = 301.3, ³J_{FF} = 9.2, 2.0), -133.6 (ddd, 1F, ²J_{FF} = 271.5, ³J_{FF} = 8.0, 2.0), -129.8 (ddd, 1F, ²J_{FF} = 271.5, ³J_{FF} = 9.2, 5.8); IR (film): ν_{max} (cm⁻¹) 3606, 3420, 2959, 2931, 2870, 2862, 1468, 1381, 1110; MS (EI): *m/z* 115 (38%), 97 (82), 70 (56), 55 (100), 43 (50), 41 (45); HRMS (ESI): *m/z* calcd for C₉H₁₅F₄O [M-H]⁻ 215.1065, found 215.1067.

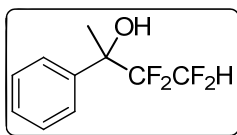
1,1,2,2-Tetrafluoro-5-phenylpentan-3-ol (61g): colorless oil (*Method A*: 217 mg, 92%



yield; *Method B*: 152 mg, 86% yield; *Method C*: 175 mg, 74% yield); *R_f* 0.41 (hexane-EtOAc, 85:15); ¹H NMR: δ 1.95 (d, 1H, ³J_{HH} = 7.5, OH), 1.89–2.00 (m, 1H, CH₂), 2.06–2.15 (m, 1H, CH₂),

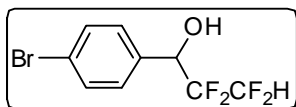
2.70–2.80 (m, 1H, CH^aH^b), 2.90–3.00 (m, 1H, CH^aH^b), 3.91–4.03 (m, 1H, CHOH), 6.05 (dddd, 1H, ²J_{HF} = 53.6, 52.9, ³J_{HF} = 8.1, 2.6, CF₂H), 7.19–7.25 (m, 3H_{Ar}), 7.29–7.34 (m, 2H_{Ar}); ¹³C NMR (100 MHz): δ 30.5 (s, CH₂), 31.1 (s, CH₂), 69.4 (dd, ²J_{CF} = 29.3, 24.9, CH), 109.4 (dddd, ¹J_{CF} = 250.3, 247.4, ²J_{CF} = 38.1, 30.7, CF₂H), 115.6 (ddt, ¹J_{CF} = 251.8, ²J_{CF} = 27.8, 23.4, CF₂), 126.4, 128.4, 128.6, 140.4; ¹⁹F NMR: δ -141.5 (ddd, 1F, ²J_{FF} = 301.7, ³J_{FF} = 8.0, 5.7), -137.3 (dd, 1F, ²J_{FF} = 301.7, ³J_{FF} = 8.0), -133.0 (dd, 1F, ²J_{FF} = 273.1, ³J_{FF} = 8.0), -129.1 (ddd, 1F, ²J_{FF} = 273.1, ³J_{FF} = 8.0, 5.7); IR (film): ν_{max} (cm⁻¹) 3430, 3088, 3065, 3030, 1604, 1497, 1456, 1100, 754, 701; MS (EI): *m/z* 236 (32%), 117 (42), 105 (21), 91 (100), 77 (12), 65 (12); HRMS (ESI): *m/z* calcd for C₁₁H₁₁F₄O [M-H]⁻ 235.0752, found 235.0747.

3,3,4,4-Tetrafluoro-2-phenylbutan-2-ol (61h): colorless oil (*Method A*: 198 mg, 89% yield);



R_f 0.11 (hexane-EtOAc, 90:10); ^1H NMR: δ 1.77 (s, 3H, CH_3), 2.39 (br s, 1H, OH), 5.79 (ddt, 1H, $^2J_{\text{HF}} = 53.0$, $^3J_{\text{HF}} = 6.9$, 5.5, CF_2H), 7.33–7.42 (m, 3 H_{Ar}), 7.53–7.55 (m, 2 H_{Ar}); ^{13}C NMR (100 MHz): δ 24.1 (s, CH_3), 75.1 (t, $^2J_{\text{CF}} = 24.9$, COH), 109.0 (tt, $^1J_{\text{CF}} = 251.6$, $^2J_{\text{CF}} = 30.7$, CF_2), 115.6 (tt, $^1J_{\text{CF}} = 259.1$, $^2J_{\text{CF}} = 22.0$, CF_2), 125.9, 128.3 (H_{Ar}), 128.4 (H_{Ar}), 139.1; ^{19}F NMR: δ -135.8 (m, 2F, CF_2H), -130.3 (dt, 1F, $^2J_{\text{FF}} = 268.5$, $^3J_{\text{FF}} = 8.0$), -126.3 (dt, 1F, $^2J_{\text{FF}} = 269.6$, $^3J_{\text{FF}} = 6.9$); IR (film): ν_{max} (cm^{-1}) 3614, 3564, 3481, 3095, 3065, 3032, 1605, 1586, 1497, 1115, 762, 702; MS (EI): m/z 121 (100%), 77 (21), 51 (17), 43 (82); HRMS (ESI): m/z calcd for $\text{C}_{10}\text{H}_9\text{F}_4\text{O}$ $[\text{M}-\text{H}]^-$ 221.0595, found 221.0598.

1-(4-Bromophenyl)-2,2,3,3-tetrafluoropropan-1-ol (61k): yellow oil (*Method C*: 57 mg,

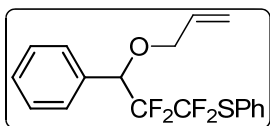


20% yield); R_f 0.40 (hexane- EtOAc, 85:15); ^1H NMR: δ 3.12 (d, 1H, $^3J_{\text{HH}} = 4.8$, OH), 4.98–5.07 (m, 1H, CHOH), 5.99 (m, 1H, CF_2H), 7.30–7.55 (m, 4 H_{Ar}); ^{13}C NMR (100 MHz): δ 71.5 (dd, $^2J_{\text{CF}} = 29.2$, 23.1, CH), 109.3 (dddd, $^1J_{\text{CF}} = 252.3$, 248.8, $^2J_{\text{CF}} = 37.9$, 30.1, CF_2H), 114.6 (dddd, $^1J_{\text{CF}} = 254.1$, 252.9, $^2J_{\text{CF}} = 27.4$, 23.3, CF_2), 123.7, 129.4, 131.8, 133.4; ^{19}F NMR: δ -141.9 (ddd, 1F, $^2J_{\text{FF}} = 301.1$, $^3J_{\text{FF}} = 10.0$, 6.8), -137.3 (ddd, 1F, $^2J_{\text{FF}} = 301.1$, $^2J_{\text{FF}} = 10.7$, 2.4), -131.5 (ddd, 1F, $^2J_{\text{FF}} = 271.0$, $^3J_{\text{FF}} = 10.0$, 2.4), -128.7 (ddd, 1F, $^2J_{\text{FF}} = 271.0$, $^2J_{\text{FF}} = 10.7$, 6.8); IR (film): ν_{max} (cm^{-1}) 3595, 3452, 3094, 3069, 1595, 1490, 1239, 1076, 1059, 1012, 789, 701; MS (EI): m/z 286 (10%), 185 (100), 156 (21), 101 (10), 77 (76), 51 (25); HRMS (CI): m/z calcd for $\text{C}_9\text{H}_8\text{OF}_4\text{Br}$ $[\text{M}+\text{H}]^+$ 286.9695, found 286.9705.

General procedure for the synthesis of compounds 62.

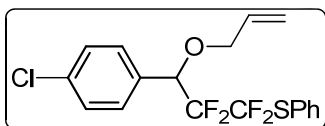
Sodium hydride (48 mg, 2 mmol) was added to a solution of **62** (1 mmol) in dry THF (5 mL). After 30 minutes of stirring under argon at room temperature, allyl or cinnamyl bromide (3 mmol) was added and the mixture was stirred for 2 h (4 h in case of **62b**). Aqueous NH_4Cl (15 mL) was added and the product was extracted into Et_2O (3×15 mL); the combined organic phase was then washed with brine (15 mL), dried (MgSO_4), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2 , hexane-EtOAc) to give the desired product **62**.

(3-(Allyloxy)-1,1,2,2-tetrafluoro-3-phenylpropyl)(phenyl)sulfane (62a): colorless oil (320



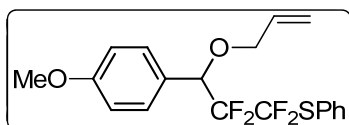
mg, 90% yield); R_f 0.50 (hexane-EtOAc, 95:5); $^1\text{H NMR}$: δ 3.89 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 6.4$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.06 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 5.0$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.85 (dd, 1H, $^3J_{\text{HF}} = 18.9$, $^4J_{\text{HF}} = 5.3$, CF_2CH), 5.20-5.29 (m, 2H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.88-5.94 (m, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 7.33-7.46 (m, $8H_{\text{Ar}}$), 7.59-7.70 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 70.6 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 77.9 (dd, $^2J_{\text{CF}} = 30.7$, 22.0, CH), 115.4 (dddd, $^1J_{\text{CF}} = 264.9$, 253.2, $^2J_{\text{CF}} = 42.4$, 30.7, CF_2), 118.2 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 124.6 (ddt, $^1J_{\text{CF}} = 289.8$, $^2J_{\text{CF}} = 36.6$, 33.7, CF_2), 128.3, 129.1, 129.3, 130.3, 132.9, 133.4 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 137.1; $^{19}\text{F NMR}$: δ -123.9 (ddd, 1F, $^2J_{\text{FF}} = 272.0$, $^3J_{\text{FF}} = 4.6$, 3.4), -114.5 (ddd, 1F, $^2J_{\text{FF}} = 272.0$, $^3J_{\text{FF}} = 6.9$, 4.6), -87.3 (ddd, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 6.9$, 3.4), -85.2 (dt, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 4.6$); IR (film): ν_{max} (cm^{-1}) 3080, 3066, 3034, 1649, 1603, 1585, 1578, 1495, 1125, 1094, 988, 910, 750, 736, 700, 691; MS (EI): m/z 221 (30%), 171 (23), 159 (27), 147 (100), 105 (83), 91 (39), 77 (38), 41 (58); HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{16}\text{F}_4\text{OSNa}$ $[\text{M}+\text{Na}]^+$ 379.0750, found 379.0749.

(3-(Allyloxy)-1,1,2,2-tetrafluoro-3-(4-chlorophenyl)propyl)(phenyl)sulfane (62b):



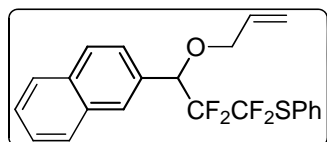
colorless oil (300 mg, 77% yield); R_f 0.62 (hexane-EtOAc, 95:5); $^1\text{H NMR}$: δ 3.89 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 6.3$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.06 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 5.3$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.82 (dd, 1H, $^3J_{\text{HF}} = 18.2$, $^3J_{\text{HF}} = 5.3$, CF_2CH), 5.20-5.29 (m, 2H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.83-5.93 (m, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 7.32-7.47 (m, $7H_{\text{Ar}}$), 7.58-7.70 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 70.8 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 77.4 (dd, $^2J_{\text{CF}} = 30.3$, 21.5, CH), 115.3 (dddd, $^1J_{\text{CF}} = 264.1$, 253.7, $^2J_{\text{CF}} = 40.9$, 30.6, CF_2), 118.5 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 124.4 (ddt, $^1J_{\text{CF}} = 289.9$, $^2J_{\text{CF}} = 35.9$, 33.6, CF_2), 128.7, 129.1, 130.2, 130.4, 131.5, 133.2 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 135.3, 137.1; $^{19}\text{F NMR}$: δ -123.7 (d, 1F, $^2J_{\text{FF}} = 273.1$), -114.5 (ddd, 1F, $^2J_{\text{FF}} = 273.1$, $^3J_{\text{FF}} = 6.9$, 4.6), -87.2 (ddd, 1F, $^2J_{\text{FF}} = 222.6$, $^3J_{\text{FF}} = 6.9$, 2.3), -85.2 (ddd, 1F, $^2J_{\text{FF}} = 222.6$, $^3J_{\text{FF}} = 5.7$, 4.6); IR (film): ν_{max} (cm^{-1}) 3081, 3066, 3025, 1649, 1597, 1581, 1492, 1125, 1092, 988, 910, 793, 751, 691; MS (EI): m/z 221 (19%), 181 (100), 159 (26), 139 (72), 109 (27), 77 (29), 41 (83), 28 (44); HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{15}\text{F}_4\text{OSCl}$ $[\text{M}]^+$ 390.0464, found 390.0461.

(3-(Allyloxy)-1,1,2,2-tetrafluoro-3-(4-methoxyphenyl)propyl)(phenyl)sulfane (62c): white



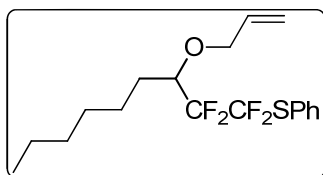
solid (312 mg, 81% yield); mp 64–66 °C; R_f 0.68 (hexane-EtOAc, 90:10); ^1H NMR: δ 3.81 (s, 3H, -OCH₃), 3.87 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 6.3$, CH₂=CH-CH₂-), 4.06 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 5.1$, CH₂=CH-CH₂-), 4.80 (dd, 1H, $^3J_{\text{HF}} = 18.4$, $^4J_{\text{HF}} = 5.6$, CF₂CH), 5.18–5.29 (m, 2H, CH₂=CH-CH₂-), 5.84–5.94 (m, 1H, CH₂=CH-CH₂-), 6.86–6.98 (m, 2H_{Ar}), 7.33–7.47 (m, 5H_{Ar}), 7.58–7.70 (m, 2H_{Ar}); ^{13}C NMR (100 MHz): δ 55.2 (s, OCH₃), 70.3 (s, CH₂=CH-CH₂-), 77.6 (dd, $^2J_{\text{CF}} = 30.3$, 21.3, CH), 113.8, 115.5 (dddd, $^1J_{\text{CF}} = 263.6$, 252.7, $^2J_{\text{CF}} = 40.8$, 29.9, CF₂), 118.1 (s, CH₂=CH-CH₂-), 124.6 (ddt, $^1J_{\text{CF}} = 289.9$, $^2J_{\text{CF}} = 36.0$, 33.7, CF₂), 124.7, 129.1, 130.2, 130.3, 133.5 (s, CH₂=CH-CH₂-), 137.1, 160.4; ^{19}F NMR: δ -124.1 (d, 1F, $^2J_{\text{FF}} = 271.9$), -114.6 (ddd, 1F, $^2J_{\text{FF}} = 271.9$, $^3J_{\text{FF}} = 6.9$, 5.7), -87.3 (ddd, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 6.9$, 3.4), -85.2 (ddd, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 5.7$, 4.6); IR (film): ν_{max} (cm⁻¹) 3079, 3065, 3039, 3007, 2840, 1648, 1612, 1587, 1514, 1253, 1120, 1092, 989, 910, 800, 751, 691; MS (EI): m/z 177 (100%), 135 (58), 121 (26), 77 (16), 41 (25); HRMS (ESI): m/z calcd for C₁₉H₁₈F₄O₂NaS [M+Na]⁺ 409.0856, found 409.0855.

(3-(Allyloxy)-1,1,2,2-tetrafluoro-3-(naphthalene-2-yl)propyl)(phenyl)sulfane (62e): white



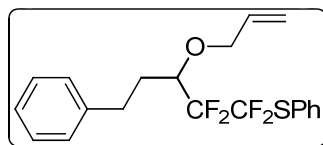
solid (239 mg, 59% yield); mp 62–64 °C; R_f 0.21 (hexane); ^1H NMR: δ 3.92 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 6.7$, CH₂=CH-CH₂-), 4.11 (dd, 1H, $^2J_{\text{HH}} = 12.6$, $^3J_{\text{HH}} = 5.1$, CH₂=CH-CH₂-), 5.02 (dd, 1H, $^3J_{\text{HF}} = 18.7$, 5.3, CF₂CH), 5.19–5.29 (m, 2H, CH₂=CH-CH₂-), 5.86–5.96 (m, 1H, CH₂=CH-CH₂-), 7.34–7.38 (m, 2H_{Ar}), 7.40–7.44 (m, 1H_{Ar}), 7.47–7.51 (m, 2H_{Ar}), 7.57–7.59 (m, 1H_{Ar}), 7.63–7.66 (m, 2H_{Ar}), 7.82–7.92 (m, 4H_{Ar}); ^{13}C NMR (100 MHz): δ 70.7 (s, CH₂=CH-CH₂-), 78.1 (dd, $^2J_{\text{CF}} = 30.3$, 21.4, CH), 115.6 (dddd, $^1J_{\text{CF}} = 263.9$, 253.5, $^2J_{\text{CF}} = 40.9$, 30.5, CF₂), 118.4 (s, CH₂=CH-CH₂-), 124.6 (ddt, $^1J_{\text{CF}} = 289.89$, $^2J_{\text{CF}} = 36.1$, 34.0, CF₂), 125.8, 126.3, 126.6, 127.7, 128.2, 128.9, 129.1, 130.3, 130.4, 132.9, 133.4 (s, CH₂=CH-CH₂-), 133.8, 137.1; ^{19}F NMR: δ -123.3 (d, 1F, $^2J_{\text{FF}} = 271.9$), -114.3 (ddd, 1F, $^2J_{\text{FF}} = 271.9$, $^3J_{\text{FF}} = 6.9$, 4.6), -87.2 (ddd, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 6.9$, 2.3), -85.2 (dt, 1F, $^2J_{\text{FF}} = 221.4$, $^3J_{\text{FF}} = 4.6$); IR (film): ν_{max} (cm⁻¹) 3062, 3025, 1719, 1648, 1602, 1578, 1510, 1125, 1105, 989, 910, 863, 808, 785, 749, 691, 479; MS (EI): m/z 406 (13%) [M]⁺, 350 (14), 197 (100), 169 (35), 155 (56), 141 (40), 127 (27), 41 (31); HRMS (ESI): m/z calcd for C₂₀H₁₈F₄ONaS [M+Na]⁺ 429.09067, found 429.09072.

(3-(Allyloxy)-1,1,2,2-tetrafluorononyl)(phenyl)sulfane (62f): colorless oil (280 mg, 77%



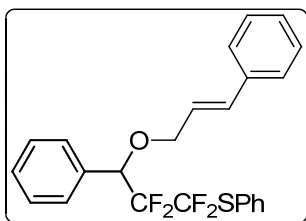
yield); R_f 0.32 (hexane-EtOAc, 97:3); $^1\text{H NMR}$: δ 0.87–0.91 (m, 3H, CH_3), 1.25–1.39 (m, 7H, $3\times\text{CH}_2$, CH^aH^b), 1.51–1.60 (m, 1H, CH^aH^b), 1.67–1.74 (m, 2H, CH_2), 3.75–3.84 (m, 1H, CF_2CH), 4.07 (dd, 1H, $^2J_{\text{HH}} = 12.1$, $^3J_{\text{HH}} = 6.3$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.23 (dd, 1H, $^2J_{\text{HH}} = 12.1$, $^3J_{\text{HH}} = 5.3$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.18–5.33 (m, 2H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.88–5.98 (m, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 7.34–7.50 (m, $3H_{\text{Ar}}$), 7.61–7.71 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 14.0 (s, CH_3), 22.6 (s, CH_2), 25.4 (s, CH_2), 29.0 (s, CH_2), 29.1 (s, CH_2), 31.6 (s, CH_2), 73.7 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 77.5 (dd, $^2J_{\text{CF}} = 25.6$, 22.8, CH), 117.1 (dddd, $^1J_{\text{CF}} = 260.1$, 258.0, $^2J_{\text{CF}} = 33.1$, 31.1, CF_2), 117.8 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 121.5–127.9 (m, CF_2), 129.1, 130.3, 134.0 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 137.1; $^{19}\text{F NMR}$: δ -119.7 (ddd, 1F, $^2J_{\text{FF}} = 271.9$, $^3J_{\text{FF}} = 5.7$, 4.6 Hz CF^aF^b), -116.7 (ddd, 1F, $^2J_{\text{FF}} = 271.9$, $^3J_{\text{FF}} = 5.7$, 4.6), -86.6 (ddd, 1F, $^2J_{\text{FF}} = 221.6$, $^3J_{\text{FF}} = 5.7$, 4.6), -85.9 (ddd, 1F, $^2J_{\text{FF}} = 221.6$, $^3J_{\text{FF}} = 5.7$, 4.6); IR (film): ν_{max} (cm^{-1}) 3082, 3066, 3040, 3019, 2958, 2930, 2870, 2860, 1649, 1584, 1578, 1476, 1111, 996, 750, 691; MS (EI): m/z 364 (5%) $[\text{M}]^+$, 335 (11), 307 (48), 159 (58), 110 (55), 95 (41), 77 (29), 57 (34), 41 (100); HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{24}\text{F}_4\text{OS}$ $[\text{M}]^+$ 364.1484, found 364.1478.

(3-(Allyloxy)-1,1,2,2-tetrafluoro-5-phenylpentyl)(phenyl)sulfane (62g): pale yellow oil



(318 mg, 83% yield); R_f 0.69 (hexane-EtOAc, 95:5); $^1\text{H NMR}$: δ 2.00–2.11 (m, 2H, CH_2), 2.64–2.72 (m, 1H, CH^aH^b), 2.86–2.95 (m, 1H, CH^aH^b), 3.78–3.87 (m, 1H, CF_2CH), 4.04 (dd, 1H, $^2J_{\text{HH}} = 12.1$, $^3J_{\text{HH}} = 6.1$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 4.28 (dd, 1H, $^2J_{\text{HH}} = 12.1$, $^3J_{\text{HH}} = 5.3$, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.19–5.33 (m, 2H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 5.89–5.99 (m, 1H, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 7.18–7.21 (m, $3H_{\text{Ar}}$), 7.26–7.30 (m, $2H_{\text{Ar}}$), 7.34–7.39 (m, $2H_{\text{Ar}}$), 7.41–7.46 (m, $1H_{\text{Ar}}$), 7.60–7.68 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 30.6 (s, CH_2), 31.4 (s, CH_2), 73.6 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 76.8 (dd, $^2J_{\text{CF}} = 25.6$, 23.1, CH), 114.3–120.1 (m, CF_2), 117.9 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 121.4–127.5 (m, CF_2), 126.1, 128.4, 128.5, 129.1, 130.4, 133.9 (s, $\text{CH}_2=\text{CH}-\text{CH}_2-$), 137.1, 141.0; $^{19}\text{F NMR}$: δ -118.9 (ddd, 1F, $^2J_{\text{FF}} = 273.1$, $^3J_{\text{FF}} = 5.7$, 4.6, CF^aF^b), -116.6 (ddd, 1F, $^2J_{\text{FF}} = 273.1$, $^3J_{\text{FF}} = 5.7$, 4.6), -86.6 (ddd, 1F, $^2J_{\text{FF}} = 222.6$, $^3J_{\text{FF}} = 5.7$, 4.6), -85.8 (ddd, 1F, $^2J_{\text{FF}} = 222.6$, $^3J_{\text{FF}} = 5.7$, 4.6); IR (film): ν_{max} (cm^{-1}) 3084, 3064, 3028, 1648, 1603, 1584, 1497, 1113, 1068, 999, 899, 750, 701, 691; MS (EI): m/z 384 (8%) $[\text{M}]^+$, 327 (15), 159 (89), 131 (48), 109 (25), 105 (27), 91 (100), 77 (26), 41 (30); HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{20}\text{F}_4\text{ONaS}$ $[\text{M}+\text{Na}]^+$ 407.10632, found 407.10636.

(E)-(3-(Cinnamyloxy)-1,1,2,2-tetrafluoro-3-phenylpropyl)(phenyl)sulfane (62m):

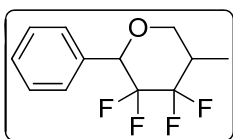


colorless oil (393 mg, 91% yield); R_f 0.40 (hexane); $^1\text{H NMR}$: δ 4.06 (dd, 1H, $^2J_{\text{HH}} = 12.5$, $^3J_{\text{HH}} = 6.8$, $\text{OCH}_2\text{-CH=CHPh}$), 4.25 (dd, 1H, $^2J_{\text{HH}} = 12.5$, $^3J_{\text{HH}} = 5.5$, $\text{OCH}_2\text{-CH=CHPh}$), 4.90 (dd, 1H, $^3J_{\text{HF}} = 18.8$, $^4J_{\text{HF}} = 5.2$, CF_2CH), 6.22–6.29 (m, 1H, $\text{OCH}_2\text{-CH-CHPh}$), 6.60 (d, 1H, $^3J_{\text{HH}} = 16.0$, $\text{OCH}_2\text{-CH-CHPh}$), 7.21–7.48 (m, 13 H_{Ar}), 7.62–7.67 (m, 2 H_{Ar}); $^{13}\text{C NMR}$ (100 MHz): δ 70.3 (s, $\text{CH}_2\text{=CH-CH}_2\text{-}$), 77.8 (dd, $^2J_{\text{CF}} = 30.4$, 21.4, CH), 124.6, 126.6, 127.9, 128.4, 128.5, 129.0, 129.1, 129.3, 130.3, 132.9, 133.6, 136.4, 137.1; $^{19}\text{F NMR}$: δ -123.7 (ddd, 1F, $^2J_{\text{FF}} = 272.0$, $^3J_{\text{FF}} = 5.8$, 3.6), -114.4 (ddd, 1F, $^2J_{\text{FF}} = 272.0$, $^3J_{\text{FF}} = 6.8$, 5.8), -87.2 (ddd, 1F, $^2J_{\text{FF}} = 221.6$, $^3J_{\text{FF}} = 6.8$, 3.6), -85.1 (dt, 1F, $^2J_{\text{FF}} = 221.6$, $^3J_{\text{FF}} = 5.8$); IR (film): ν_{max} (cm^{-1}) 3082, 3063, 3030, 1655, 1599, 1578, 1496, 1123, 1070; MS (EI): m/z 299 (18%), 221 (33), 159 (24), 133 (63), 117 (51), 105 (100), 91 (14), 77 (23); HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{F}_4\text{ONaS}$ $[\text{M}+\text{Na}]^+$ 455.10632, found 455.10668.

General procedure for the synthesis of compounds 63.

A solution of $n\text{-Bu}_3\text{SnH}$ (471 μL , 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 3 h using a syringe pump to a refluxing solution of **62** (1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon for additional hour, followed by concentration under reduced pressure and purification by flash column chromatography (SiO_2 , hexane-EtOAc) to give product **63**.

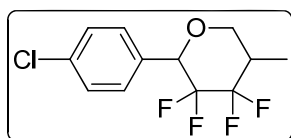
3,3,4,4-Tetrafluoro-5-methyl-2-phenyltetrahydro-2H-pyran (63a): column



chromatography gave product as white solid (131 mg, 53% yield, $\text{trans}:\text{cis} = 80:20$); crystallization from $n\text{-hexane}$ gave 30 mg of **63a** as a colorless crystall; mp 55–57 $^\circ\text{C}$ (trans); R_f 0.42 (hexane-EtOAc, 95:5); $^1\text{H NMR}$: δ 1.10 (d, 3H, $^3J_{\text{HH}} = 6.8$, CH_3 , trans), 1.35 (dd, 3H, $^3J_{\text{HH}} = 7.3$, $^4J_{\text{HF}} = 3.5$, CH_3 , cis), 2.40–2.50 (m, 1H, cis), 2.54–2.71 (m, 1H, trans), 3.47–3.57 (m, 1H, trans), 3.91–3.98 (m, 2H, cis), 3.99–4.05 (m, 1H, trans), 4.59–4.67 (m, 2H, $\text{trans}+\text{cis}$), 7.37–7.46 (m, 10 H_{Ar} , $\text{trans}+\text{cis}$); $^{13}\text{C NMR}$ (100 MHz): δ 6.2–6.4 (m, trans), 11.3 (dt, $^3J_{\text{CF}} = 7.5$, $^4J_{\text{CF}} = 2.9$, CH_3 , cis), 36.8–37.3 (m, trans), 38.6–39.0 (m, cis), 69.4 (d, $^3J_{\text{CF}} = 8.1$, CH_2 , trans), 69.8 (d, $^3J_{\text{CF}} = 7.3$, CH_2 , cis), 78.7 (ddd, $^2J_{\text{CF}} = 24.0$, 21.7, $^3J_{\text{CF}} = 2.8$, CH-O, trans), 79.0–79.5 (m, cis), 111.6–119.4 (m, $2\times\text{CF}_2$ $\text{trans} + 2\times\text{CF}_2$ cis), 128.0 (cis), 128.1 (trans), 128.2 (trans), 129.1 (cis), 129.2 (trans), 131.9 (trans); $^{19}\text{F NMR}$: δ (trans) –

135.0 (ddd, 1F, $^2J_{\text{FF}} = 259.0$, $^3J_{\text{FF}} = 16.0$, 10.7), -131.9 (ddd, 1F, $^2J_{\text{FF}} = 251.5$, $^3J_{\text{FF}} = 16.0$, 14.2), -131.3 (ddd, 1F, $^2J_{\text{FF}} = 259.0$, $^3J_{\text{FF}} = 17.9$, 14.2), -129.5 (ddd, 1F, $^2J_{\text{FF}} = 251.5$, $^3J_{\text{FF}} = 17.9$, 10.7); ^{19}F NMR: δ (*cis*) -130.4 (ddd, 1F, $^2J_{\text{FF}} = 262.6$, $^3J_{\text{FF}} = 14.7$, 10.1), -127.6 (ddd, 1F, $^2J_{\text{FF}} = 254.9$, $^3J_{\text{FF}} = 17.1$, 10.1), -126.4 (ddd, 1F, $^2J_{\text{FF}} = 262.6$, $^3J_{\text{FF}} = 17.1$, 12.6), -112.5 (ddd, 1F, $^2J_{\text{FF}} = 254.9$, $^3J_{\text{FF}} = 14.7$, 12.6); IR (film): ν_{max} (cm^{-1}) 3095, 3069, 3038, 1603, 1589, 1496, 1467, 1152, 1126, 1099, 1023, 739, 699; MS (EI): m/z 248 (100%) $[\text{M}]^+$, 153 (15), 140 (16), 105 (56), 91 (16), 77 (33); HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{12}\text{F}_4\text{O}$ $[\text{M}]^+$ 248.0824, found 248.0821.

3,3,4,4-Tetrafluoro-2-(4-chlorophenyl)-5-methyltetrahydro-2H-pyran (63b): column

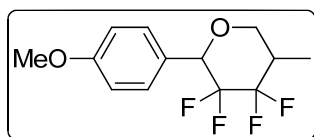


chromatography gave product as colorless oil (169 mg, 60% yield,

trans:cis = 82:18); R_f 0.46 (hexane-EtOAc, 95:5); ^1H NMR: δ 1.09 (d, 3H, $^3J_{\text{HH}} = 6.9$, CH_3 , *trans*), 1.33 (dd, 3H, $^3J_{\text{HH}} = 7.4$, $^4J_{\text{HF}} = 3.5$, CH_3 , *cis*), 2.42–2.52 (m, 1H, *cis*), 2.52–2.62 (m, 1H, *trans*), 3.47–

3.57 (m, 1H, *trans*), 3.90–3.96 (m, 2H, *cis*), 3.98–4.03 (m, 1H, *trans*), 4.57–4.65 (m, 2H, *cis+trans*), 7.32–7.42 (m, 8 H_{Ar} , *cis+trans*); ^{13}C NMR (100 MHz): δ 6.2–6.4 (m, *trans*), 11.3 (dt, $^3J_{\text{CF}} = 7.2$, $^4J_{\text{CF}} = 2.6$, CH_3 , *cis*), 36.8–37.3 (m, *trans*), 38.6–39.0 (m, *cis*), 69.4 (d, $^3J_{\text{CF}} = 8.1$, CH_2 , *trans*), 69.7 (d, $^3J_{\text{CF}} = 7.3$, CH_2 , *cis*), 78.0 (ddd, $^2J_{\text{CF}} = 26.8$, 21.8, $^3J_{\text{CF}} = 2.8$, CH-O , *trans*), 78.6 (ddd, $^2J_{\text{CF}} = 27.2$, 22.2, $^3J_{\text{CF}} = 2.8$, CH-O , *cis*), 109.8–119.0 (m, $2 \times \text{CF}_2$ *trans* + $2 \times \text{CF}_2$ *cis*), 128.5, 129.3, 129.4, 130.4, 135.2; ^{19}F NMR: δ (*trans*) -135.0 (ddd, 1F, $^2J_{\text{FF}} = 259.2$, $^3J_{\text{FF}} = 15.8$, 10.7), -131.9 (ddd, 1F, $^2J_{\text{FF}} = 251.9$, $^3J_{\text{FF}} = 15.8$, 14.3), -131.4 (ddd, 1F, $^2J_{\text{FF}} = 259.2$, $^3J_{\text{FF}} = 17.8$, 14.3), -129.5 (ddd, 1F, $^2J_{\text{FF}} = 251.9$, $^3J_{\text{FF}} = 17.8$, 10.7); ^{19}F NMR: δ (*cis*) -130.2 (ddd, 1F, $^2J_{\text{FF}} = 263.0$, $^3J_{\text{FF}} = 14.6$, 10.2), -127.4 (ddd, 1F, $^2J_{\text{FF}} = 255.5$, $^3J_{\text{FF}} = 17.2$, 10.2), -126.1 (ddd, 1F, $^2J_{\text{FF}} = 263.0$, $^3J_{\text{FF}} = 17.2$, 12.6), -112.3 (ddd, 1F, $^2J_{\text{FF}} = 255.5$, $^3J_{\text{FF}} = 14.6$, 12.6); IR (film): ν_{max} (cm^{-1}) 3040, 1601, 1580, 1495, 1154, 1141, 1127, 786; MS (EI): m/z 282 (58%) $[\text{M}]^+$, 247 (100), 174 (11), 139 (43), 113 (14), 105 (27), 77 (27); HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{15}\text{F}_4\text{OCl}$ $[\text{M}]^+$ 282.0435, found 282.0438.

3,3,4,4-Tetrafluoro-2-(4-methoxyphenyl)-5-methyltetrahydro-2H-pyran (63c): column



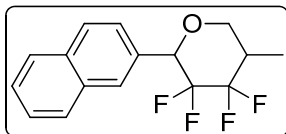
chromatography gave product as colorless oil (172 mg, 62%

yield, *trans:cis* = 82:18); R_f 0.50 (hexane-EtOAc, 95:5); ^1H NMR: δ 1.06 (d, 3H, $^3J_{\text{HH}} = 6.9$, CH_3 , *trans*), 1.33 (dd, 3H, $^3J_{\text{HH}} = 7.4$, $^4J_{\text{HF}} = 3.5$, CH_3 , *cis*), 2.38–2.49 (m, 1H, *cis*), 2.50–2.67 (m,

1H, *trans*), 3.43–3.53 (m, 1H, *trans*), 3.79 (s, 6H, *cis+trans*), 3.86–3.93 (m, 2H, *cis*), 3.94–

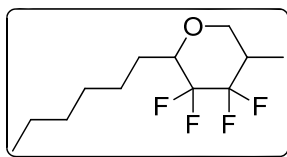
4.00 (m, 1H, *trans*), 4.53–4.60 (m, 2H, *cis+trans*), 6.85–6.97 (m, 4H_{Ar}, *cis+trans*), 7.29–7.41 (m, 4H_{Ar}, *cis+trans*); ¹³C NMR (100 MHz): δ 6.2–6.3 (m, *trans*), 11.3 (dt, ³J_{CF} = 7.5, ⁴J_{CF} = 2.8, CH₃, *cis*), 36.8–37.3 (m, *trans*), 38.6–39.1 (m, *cis*), 55.2 (*cis+trans*), 69.4 (d, ³J_{CF} = 8.2, CH₂, *trans*), 69.6 (d, ³J_{CF} = 7.3, CH₂, *cis*), 78.4 (ddd, ²J_{CF} = 27.1, 21.7, ³J_{CF} = 2.6, CH-O, *trans*), 79.0 (ddd, ²J_{CF} = 27.6, 21.9, ³J_{CF} = 2.5, CH-O, *cis*), 109.8–119.1 (m, 2×CF₂ *trans* + 2×CF₂ *cis*), 113.7, 124.0, 129.3, 129.4, 160.3; ¹⁹F NMR: δ (*trans*) –134.9 (ddd, 1F, ²J_{FF} = 259.2, ³J_{FF} = 15.5, 11.0), –131.9 (ddd, 1F, ²J_{FF} = 250.9, ³J_{FF} = 15.5, 14.3), –131.6 (ddd, 1F, ²J_{FF} = 259.2, ³J_{FF} = 17.7, 14.3), –129.4 (ddd, 1F, ²J_{FF} = 250.9, ³J_{FF} = 17.7, 11.0); ¹⁹F NMR: δ (*cis*) –130.1 (ddd, 1F, ²J_{FF} = 262.0, ³J_{FF} = 14.8, 10.3), –127.3 (ddd, 1F, ²J_{FF} = 254.7, ³J_{FF} = 17.3, 10.3), –126.3 (ddd, 1F, ²J_{FF} = 262.0, ³J_{FF} = 17.3, 12.5), –112.3 (ddd, 1F, ²J_{FF} = 254.7, ³J_{FF} = 14.8, 12.5); IR (film): ν_{max} (cm⁻¹) 3072, 3045, 2841, 1615, 1587, 1518, 1252, 1152, 1139, 1125, 795; MS (EI): *m/z* 278 (100%) [M]⁺, 247 (19), 170 (16), 135 (69), 121 (14), 77 (19); HRMS (EI): *m/z* calcd for C₁₃H₁₄F₄O₂ [M]⁺ 278.0943, found 278.0938.

3,3,4,4-Tetrafluoro-5-methyl-2-(naphthalen-2-yl)tetrahydro-2H-pyran (63e): column



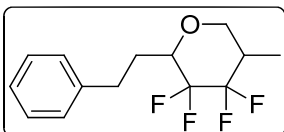
chromatography gave product as white solid (220 mg, 74% yield, *trans:cis* = 86:14); *R_f* 0.48 (hexane-EtOAc, 95:5); ¹H NMR: δ 1.06 (d, 3H, ³J_{HH} = 6.9, CH₃, *trans*), 1.36 (dd, 3H, ³J_{HH} = 7.4, ⁴J_{HF} = 3.4, CH₃, *cis*), 2.39–2.52 (m, 1H, *cis*), 2.54–2.70 (m, 1H, *trans*), 3.49–3.59 (m, 1H, *trans*), 3.89–3.96 (m, 2H, *cis*), 3.98–4.03 (m, 1H, *trans*), 4.74–4.82 (m, 2H, *trans+cis*), 7.42–7.60 (m, 6H_{Ar}, *trans+cis*), 7.78–7.96 (m, 8H_{Ar}, *trans+cis*); ¹³C NMR (100 MHz): δ 6.2–6.4 (m, *trans*), 11.3 (dt, ³J_{CF} = 7.5, ⁴J_{CF} = 2.8, CH₃, *cis*), 36.8–37.3 (m, *trans*), 38.6–39.1 (m, *cis*), 69.5 (d, ³J_{CF} = 8.1, CH₂, *trans*), 69.7 (d, ³J_{CF} = 7.3, CH₂, *cis*), 78.8 (ddd, ²J_{CF} = 26.7, 21.9, ³J_{CF} = 2.5, CH-O, *trans*), 79.4 (ddd, ²J_{CF} = 27.2, 22.0, ³J_{CF} = 2.2, CH-O, *cis*), 109.8–119.1 (m, 2×CF₂ *trans* + 2×CF₂ *cis*), 125.1, 125.2, 126.3, 126.6, 127.7, 127.8, 127.9, 128.2, 129.4, 132.9, 133.7; ¹⁹F NMR: δ (*trans*) –134.8 (ddd, 1F, ²J_{FF} = 258.9, ³J_{FF} = 14.6, 10.9), –131.9 (ddd, 1F, ²J_{FF} = 250.4, ³J_{FF} = 14.6, 14.4), –131.0 (ddd, 1F, ²J_{FF} = 258.9, ³J_{FF} = 16.8, 14.4), –129.4 (ddd, 1F, ²J_{FF} = 250.4, ³J_{FF} = 16.8, 10.9); ¹⁹F NMR: δ (*cis*) –129.9 (ddd, 1F, ²J_{FF} = 262.5, ³J_{FF} = 14.8, 10.2), –127.3 (ddd, 1F, ²J_{FF} = 254.8, ³J_{FF} = 17.2, 10.2), –125.8 (ddd, 1F, ²J_{FF} = 262.5, ³J_{FF} = 17.2, 12.7), –112.2 (ddd, 1F, ²J_{FF} = 254.8, ³J_{FF} = 14.8, 12.7); IR (film): ν_{max} (cm⁻¹) 3061, 3027, 2947, 2935, 2885, 2872, 1603, 1579, 1511, 1390, 1151, 1130, 1097, 863, 743, 688, 479; MS (EI): *m/z* 298 (100%) [M]⁺, 190 (10), 155 (35), 141 (28), 127 (21); HRMS (EI): *m/z* calcd for C₁₆H₁₄F₄O [M]⁺ 298.0981, found 298.0979.

3,3,4,4-Tetrafluoro-2-hexyl-5-methyltetrahydro-2H-pyran (63f): column chromatography



gave product as colorless oil (156 mg, 61% yield, *trans:cis* = 78:22); R_f 0.14 (hexane-EtOAc, 95:5); ^1H NMR: δ 0.87–0.93 (m, 6H, *trans+cis*), 1.01 (d, 3H, $^3J_{\text{HH}} = 6.9$, CH_3 , *trans*), 1.19 (d, 3H, $^3J_{\text{HH}} = 7.4$, CH_3 , *cis*), 1.23–1.38 (m, 14H, *trans+cis*), 1.47–1.57 (m, 2H, *trans+cis*), 1.60–1.73 (m, 4H, *trans+cis*), 2.31–2.51 (m, 2H, *trans+cis*), 3.26–3.36 (m, 1H, *trans*), 3.48–3.61 (m, 2H, *trans+cis*), 3.68–3.77 (m, 2H, *cis*), 3.79–4.85 (m, 1H, *trans*); ^{13}C NMR (100 MHz): δ 6.2–6.3 (m, *trans*), 10.6–10.8 (m, *cis*), 14.0 (*trans+cis*), 22.5 (*trans+cis*), 25.3 (*trans*), 25.4 (*cis*), 26.0 (*cis*), 26.3 (*trans*), 29.0 (*trans+cis*), 31.6 (*trans+cis*), 36.9–37.4 (m, *trans*), 38.4–38.8 (m, *cis*), 68.7 (d, $^3J_{\text{CF}} = 6.2$, CH_2 , *cis*), 69.3 (d, $^3J_{\text{CF}} = 7.8$, CH_2 , *trans*), 76.7–77.2 (m, *trans*), 77.3–77.9 (m, *cis*), 110.6–118.9 (m, $2\times\text{CF}_2$ *trans* + $2\times\text{CF}_2$ *cis*); ^{19}F NMR: (*trans* and *cis* isomers displayed identical ^{19}F NMR spectra) δ –137.8 (ddd, 1F, $^2J_{\text{FF}} = 256.8$, $^3J_{\text{FF}} = 14.3$, 9.8), –133.8 (ddd, 1F, $^2J_{\text{FF}} = 256.8$, $^3J_{\text{FF}} = 15.8$, 13.1), –132.6 (ddd, 1F, $^2J_{\text{FF}} = 250.6$, $^3J_{\text{FF}} = 14.3$, 13.1), –130.6 (ddd, 1F, $^2J_{\text{FF}} = 250.6$, $^3J_{\text{FF}} = 15.8$, 9.8); IR (film): ν_{max} (cm^{-1}) 2958, 2932, 2870, 2863, 1468, 1391, 1137, 1103, 1019; MS (EI): m/z 127 (14%), 107 (19), 91 (19), 70 (100), 55 (57), 41 (38); HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{20}\text{F}_4\text{O}$ $[\text{M}]^+$ 256.1450, found 256.1456.

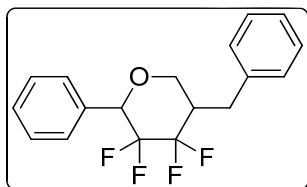
3,3,4,4-Tetrafluoro-5-methyl-2-phenethyltetrahydro-2H-pyran (63g): column



chromatography gave *trans*-**63g** product as colorless oil (231 mg, 84% yield); R_f 0.13 (hexane-EtOAc, 99:1); ^1H NMR: δ 0.99 (d, 3H, $^3J_{\text{HH}} = 6.9$, CH_3 , *trans*), 1.20 (d, 3H, $^3J_{\text{HH}} = 7.4$, CH_3 , *cis*), 1.92–2.07 (m, 4H, *trans+cis*), 2.29–2.52 (m, $2H_{\text{Ar}}$, *trans+cis*), 2.61–2.73 (m, $2H_{\text{Ar}}$, *trans+cis*), 2.80–2.95 (m, 2H, *trans+cis*), 3.23–3.33 (m, 1H, *trans*), 3.43–3.60 (m, 2H, *trans+cis*), 3.68–3.77 (m, 2H, *cis*), 3.80–4.90 (m, 1H, *trans*), 7.14–7.23 (m, $6H_{\text{Ar}}$, *trans+cis*), 7.26–7.32 (m, $4H_{\text{Ar}}$, *trans+cis*); ^{13}C NMR (100 MHz): δ 6.1–6.3 (m, *trans+cis*), 10.6–10.8 (m, *cis*), 27.6 (*cis*), 27.9 (*trans*), 31.0 (*trans*), 31.1 (*cis*), 36.9–37.3 (m, *trans*), 38.4–38.8 (m, *cis*), 68.7 (d, $^3J_{\text{CF}} = 6.3$, CH_2 , *cis*), 69.2 (d, $^3J_{\text{CF}} = 7.8$, CH_2 , *trans*), 75.8 (ddd, $^2J_{\text{CF}} = 26.9$, 22.9, $^3J_{\text{CF}} = 2.1$, CH-O, *trans*), 76.2–76.5 (m, *cis*), 110.8–118.9 (m, $2\times\text{CF}_2$ *trans* + $2\times\text{CF}_2$ *cis*), 126.2, 128.4, 128.5, 140.9; ^{19}F NMR: δ (*trans*) –137.8 (ddd, 1F, $^2J_{\text{FF}} = 256.3$, $^3J_{\text{FF}} = 13.9$, 9.3), –133.4 (ddd, 1F, $^2J_{\text{FF}} = 256.3$, $^3J_{\text{FF}} = 15.2$, 12.9), –132.4 (ddd, 1F, $^2J_{\text{FF}} = 250.7$, $^3J_{\text{FF}} = 13.9$, 12.9), –130.6 (ddd, 1F, $^2J_{\text{FF}} = 250.7$, $^3J_{\text{FF}} = 15.2$, 9.3); ^{19}F NMR: δ (*cis*) –132.5 (dt, 1F, $^2J_{\text{FF}} = 261.4$, $^3J_{\text{FF}} = 12.9$), –126.0 (dt, 1F, $^2J_{\text{FF}} = 261.4$, $^3J_{\text{FF}} = 11.6$), –115.8 (dt, 1F, $^2J_{\text{FF}} = 260.4$, $^3J_{\text{FF}} = 12.9$), –113.3 (ddd, 1F, $^2J_{\text{FF}} = 260.4$, $^3J_{\text{FF}} = 14.0$, 11.6); IR (film): ν_{max} (cm^{-1}) 3088, 3065, 3029, 1604,

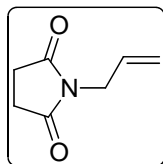
1586, 1497, 1150, 1131, 1108, 751, 700; MS (EI): m/z 276 (54%) $[M]^+$, 117 (22), 105 (23), 92 (100), 77 (15); HRMS (EI): m/z calcd for $C_{14}H_{16}F_4O$ $[M]^+$ 276.1137, found 276.1138.

5-Benzyl-3,3,4,4-tetrafluoro-2-phenyltetrahydro-2H-pyran (63m): column



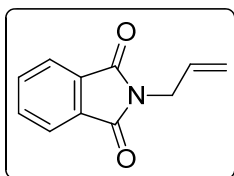
chromatography gave product as white solid (217 mg, 67% yield, *trans*:*cis* = 82:18); crystallization from *n*-hexane gave *trans*-**63m** as a colorless crystall; mp 132–134 °C (*trans*); R_f 0.67 (hexane-EtOAc, 90:10); 1H NMR: δ 2.47–2.59 (m, 1H, *cis*), 2.54 (dd, 1H, $^2J_{HH} = 14.1$, $^3J_{HH} = 10.7$, PhCH₂, *trans*), 2.68–2.86 (m, 1H, *trans*), 2.98–3.14 (m, 2H, *cis*), 3.19 (dd, 1H, $^2J_{HH} = 14.1$, $^3J_{HH} = 3.5$, PhCH₂, *trans*), 3.54–3.60 (m, 1H, *trans*), 3.73–3.81 (m, 1H, *cis*), 3.89–3.94 (m, 2H, *cis*+*trans*), 4.65 (dd, 1H, $^3J_{HF} = 25.5$, 22.8, *trans*), 4.66 (dd, 1H, $^3J_{HF} = 27.1$, 23.5, *cis*), 7.16–7.53 (m, 20H_{Ar}, *trans*+*cis*); ^{13}C NMR (100 MHz): δ (*trans*) 28.6–28.7 (m), 43.6–44.0 (m), 67.8–67.9 (m), 78.7 (ddd, $^2J_{CF} = 26.6$, 21.8, $^3J_{CF} = 1.8$, CH-O), 126.9, 128.0, 128.2, 128.7, 128.8, 129.2, 131.8, 137.3; ^{19}F NMR: δ (*trans*) –134.9 (ddd, 1F, $^2J_{FF} = 259.1$, $^3J_{FF} = 14.0$, 11.9), –131.1 (ddd, 1F, $^2J_{FF} = 259.1$, $^3J_{FF} = 10.1$, 7.4), –129.5 (ddd, 1F, $^2J_{FF} = 250.6$, $^3J_{FF} = 14.0$, 7.4), –128.7 (ddd, 1F, $^2J_{FF} = 250.6$, $^3J_{FF} = 11.9$, 10.1); ^{19}F NMR: δ (*cis*) –130.7 (ddd, 1F, $^2J_{FF} = 264.0$, $^3J_{FF} = 14.6$, 10.0), –127.0 (ddd, 1F, $^2J_{FF} = 256.0$, $^3J_{FF} = 17.0$, 10.0), –126.6 (ddd, 1F, $^2J_{FF} = 264.0$, $^3J_{FF} = 17.0$, 12.5), –111.1 (ddd, 1F, $^2J_{FF} = 256.0$, $^3J_{FF} = 14.6$, 12.5); IR (film): ν_{max} (cm⁻¹) 3089, 3066, 3032, 1604, 1578, 1497, 1146, 1101; MS (EI): m/z 324 (31%) $[M]^+$, 183 (14), 140 (16), 117 (24), 105 (19), 91 (100), 77 (12); HRMS (EI): m/z calcd for $C_{18}H_{16}F_4O$ $[M]^+$ 324.1137, found 324.1132.

1-Allylpyrrolidine-2,5-dione (65c).



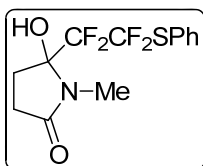
Prepared according to literature procedure.¹¹⁸ A mixture of pyrrolidine-2,5-dione (1.00 g, 10.1 mmol), allyl bromide (1.1 mL, 12.1 mmol), and anhydrous potassium carbonate (1.67 g, 12.1 mmol) was heated at reflux in anhydrous acetone (15 mL) for 1 h. After cooling, the mixture was filtered and the acetone evaporated to give **65c** as clear oil (1.25 g, 88% yield). Spectroscopic data were identical to those reported in the literature.¹¹⁹ 1H NMR: δ 2.65 (s, 4H), 4.12 (d, 2H, $^3J_{HH} = 5.8$), 5.15–5.28 (m, 2H), 5.69 (ddt, 1H, $^3J_{HH} = 17.4$, 9.0, 5.8). ^{13}C NMR: δ 28.1 (2C), 40.8, 118.1, 130.7, 176.8 (2C).

2-Allylisindoline-1,3-dione (**65d**).



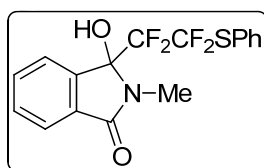
Prepared according to literature procedure.¹¹⁸ A mixture of isoindoline-1,3-dione (1.00 g, 6.8 mmol), allyl bromide (742 μ L, 8.2 mmol), and anhydrous potassium carbonate (1.1 g, 8.1 mmol) was heated at reflux in anhydrous acetone (15 mL) for 1 h. After cooling, the mixture was filtered and the acetone evaporated to give **65d** as white solid (1.02 g, 80% yield). Spectroscopic data were identical to those reported in the literature.¹²⁰ ^1H NMR: δ 4.30 (dt, 2H, $^3J_{\text{HH}} = 5.7$, $^4J_{\text{HH}} = 1.3$), 5.20 (ddd, 1H, $^3J_{\text{HH}} = 10.3$, $^2J_{\text{HH}} = 2.5$, $^4J_{\text{HH}} = 1.3$), 5.25 (ddd, 1H, $^3J_{\text{HH}} = 17.1$, $^2J_{\text{HH}} = 2.5$, $^4J_{\text{HH}} = 1.3$), 5.89 (1H, ddt, $^3J_{\text{HH}} = 17.1$, 10.3, 5.7), 7.71-7.75 (m, 2H_{Ar}), 7.84-7.88 (m, 2H_{Ar}). ^{13}C NMR: δ 39.9, 117.6, 123.2, 131.4, 132.0, 133.9, 167.8.

5-Hydroxy-1-methyl-5-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)pyrrolidin-2-one (**66a**).



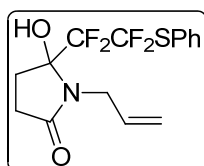
A solution of PhSCF₂CF₂SiMe₃ (**53**) (1.13 g, 4 mmol) in dry THF (2 mL) was added dropwise to a solution of TMAF (19 mg, 10 mol%) and *N*-methylsuccinimide (**65a**) (226 mg, 2 mmol) in dry THF (10 mL) at 0 °C under argon. The mixture was allowed to warm up to room temperature and stirred for 1 h, followed by the addition of aqueous HF (4 mL, 1M) and stirred at 35 °C for 2 h. The reaction product was extracted in Et₂O (3 \times 25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **66a** as a white solid (348 mg, 54% yield); mp 116–118 °C; *R*_f 0.26 (hexane-EtOAc, 50:50); ^1H NMR: δ 2.10–2.18 (m, 1H, CH₂), 2.39–2.45 (m, 2H, CH₂), 2.67–2.74 (m, 1H, CH₂), 2.87 (s, 3H, CH₃), 5.34 (br s, 1H, OH), 7.38–7.43 (m, 2H_{Ar}), 7.46–7.50 (m, 1H_{Ar}), 7.62–7.65 (m, 2H_{Ar}); ^{13}C NMR (100 MHz): δ 26.3 (s, CH₃), 28.8 (s, CH₂), 29.5 (s, CH₂), 90.7–91.2 (m, C-OH), 116.0 (tt, $^1J_{\text{CF}} = 262.2$, $^2J_{\text{CF}} = 30.9$, CF₂), 123.8, 124.8 (tt, $^1J_{\text{CF}} = 289.0$, $^2J_{\text{CF}} = 35.1$, CF₂), 129.2, 130.6, 137.2, 175.7 (s, C=O); ^{19}F NMR: δ -118.7 (dd, 1F, $^2J_{\text{FF}} = 273.2$, $^3J_{\text{FF}} = 8.0$), -117.5 (dd, 1F, $^2J_{\text{FF}} = 273.2$, $^3J_{\text{FF}} = 3.4$), -85.4 (dd, 1F, $^2J_{\text{FF}} = 224.5$, $^3J_{\text{FF}} = 8.0$), -83.6 (dd, 1F, $^2J_{\text{FF}} = 224.5$, $^3J_{\text{FF}} = 3.4$); IR (film): ν_{max} (cm⁻¹) 3191, 1680, 1578, 1105, 753, 691; MS (EI): *m/z* 190 (5%), 114 (100), 109 (11), 86 (9), 58 (13); HRMS (ESI): *m/z* calcd for C₁₃H₁₄F₄NO₂S [M+H]⁺ 324.06759, found 324.06760.

3-Hydroxy-2-methyl-3-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)isoindolin-1-one (**66b**).



A solution of TBAT (54 mg, 10 mol%) in dry THF (2 mL) was added dropwise to a solution of PhSCF₂CF₂SiMe₃ (**53**) (1.13 g, 4 mmol) and *N*-methylphthalimide (**65b**) (322 mg, 2 mmol) in dry THF (10 mL) at room temperature under argon. The mixture was 3 h, followed by the addition of aqueous HF (4 mL, 1M) and stirred at 35 °C for another hour. The reaction product was extracted in Et₂O (3×25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **66b** as pale yellow solid (534 mg, 72% yield); pale yellow solid; mp 124–126 °C; *R*_f 0.17 (hexane-EtOAc, 80:20); ¹H NMR: δ 2.87 (s, 3H, CH₃), 4.98 (br s, 1H, OH), 7.29–7.33 (m, 2H_{Ar}), 7.38–7.48 (m, 4H_{Ar}), 7.53–7.57 (m, 2H_{Ar}), 7.70–7.73 (m, 1H_{Ar}); ¹³C NMR (100 MHz): δ 25.5 (s, CH₃), 87.6–88.0 (m, C-OH), 114.0–123.0 (m, 2×CF₂), 123.3, 124.3, 129.1, 130.5, 130.9, 131.2, 132.5, 137.1, 141.4, 168.1 (s, C=O); ¹⁹F NMR: δ -117.4 (ddd, 1F, ²*J*_{FF} = 278.1, ³*J*_{FF} = 8.6, 2.6), -112.6 (ddd, 1F, ²*J*_{FF} = 278.1, ³*J*_{FF} = 6.4, 2.9), -85.3 (ddd, 1F, ²*J*_{FF} = 222.9, ³*J*_{FF} = 8.6, 2.9), -84.2 (ddd, 1F, ²*J*_{FF} = 222.9, ³*J*_{FF} = 6.4, 2.6); IR (film): ν_{max} (cm⁻¹) 3228, 3085, 3065, 1688, 1617, 1604, 1590, 1137, 751, 692; MS (EI): *m/z* 162 (100%), 133 (7), 109 (7), 77 (7); HRMS (ESI): *m/z* calcd for C₁₇H₁₄F₄NO₂ [M+H]⁺ 372.06759, found 372.06754.

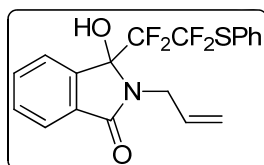
5-Hydroxy-1-allyl-5-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)pyrrolidin-2-one (**66c**).



A solution of TBAT (108 mg, 5 mol%) in dry THF (2 mL) was added dropwise to a solution of PhSCF₂CF₂SiMe₃ (**53**) (1.13 g, 4 mmol) and *N*-allylsuccinimide (**65c**) (278 mg, 2 mmol) in dry THF (10 mL). The mixture was stirred at room temperature under argon for 3 h, followed by the addition of aqueous HF (4 mL, 1M) and stirred at 35 °C for another hour. The reaction product was extracted in Et₂O (3×25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **66c** as a pale yellow solid (404 mg, 58% yield); mp 69–71 °C; *R*_f 0.09 (hexane-EtOAc, 80:20); ¹H NMR: δ 2.12–2.20 (m, 1H, CH₂), 2.38–2.52 (m, 2H, CH₂), 2.65–2.72 (m, 1H, CH₂), 3.84 (dd, 1H, ²*J*_{HH} = 15.7, ³*J*_{HH} = 6.4, CH₂=CH-CH₂-), 4.17 (dd, 1H, ²*J*_{HH} = 15.7, ³*J*_{HH} = 5.6, CH₂=CH-CH₂-), 5.12–5.15 (m, 1H, CH₂=CH-CH₂-), 5.20–5.25 (m, 1H, CH₂=CH-CH₂-), 5.33 (br s, 1H, OH), 5.79–5.89 (m, 1H, CH₂=CH-CH₂-), 7.37–7.42 (m, 2H_{Ar}), 7.45–7.49 (m, 1H_{Ar}), 7.62–7.65 (m, 2H_{Ar}); ¹³C NMR (100 MHz): δ 28.7, 29.6, 43.5 (d, *J*_{CF} = 2.4), 91.1–91.5

(m, C-OH), 115.9 (tt, $^1J_{CF} = 263.3$, $^2J_{CF} = 30.7$, CF₂), 117.6, 123.9, 124.7 (tt, $^1J_{CF} = 289.5$, $^2J_{CF} = 35.2$, CF₂), 129.2, 130.6, 133.5, 137.2, 175.5 (C=O); ^{19}F NMR: δ -118.6 (d, 1F, $^2J_{FF} = 272.2$), -117.7 (dd, 1F, $^2J_{FF} = 272.2$, $^3J_{FF} = 7.6$), -85.1 (dd, 1F, $^2J_{FF} = 224.1$, $^3J_{FF} = 7.6$), -83.1 (d, 1F, $^2J_{FF} = 224.1$); IR (film): ν_{max} (cm⁻¹) 3235, 3084, 1679, 1583, 1131, 1106, 994, 927, 752, 690; MS (EI): m/z 349 (3%) [M]⁺, 140 (100), 109 (18), 77 (8), 55 (15), 41 (26); HRMS (ESI): m/z calcd for C₁₅H₁₆F₄NO₂S [M+H]⁺ 350.08324, found 350.08318.

3-Hydroxy-2-allyl-3-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)isoindolin-1-one (66d).



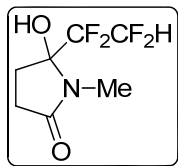
A solution of TBAT (108 mg, 10 mol%) in dry THF (2 mL) was added dropwise to a solution of PhSCF₂CF₂SiMe₃ (**53**) (1.13 g, 4 mmol) and *N*-allylphthalimide (**65d**) (374 mg, 2 mmol) in dry THF (10 mL). The mixture was stirred at room temperature under argon for 3 h, followed by the addition of aqueous HF (4 mL, 1M) and stirred at 35 °C for another hour. The reaction product was extracted in Et₂O (3×25 mL), the combined organic phase was washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **66d** as a white solid (547 mg, 69% yield); mp 96–98 °C; R_f 0.25 (hexane-EtOAc, 80:20); 1H NMR: δ 3.91 (dd, 1H, $^2J_{HH} = 15.7$, $^3J_{HH} = 6.7$, CH₂=CH-CH₂-), 4.37 (dd, 1H, $^2J_{HH} = 15.7$, $^3J_{HH} = 5.8$, CH₂=CH-CH₂-), 5.09–5.12 (m, 2H, CH₂=CH-CH₂-, OH), 5.23–5.28 (m, 1H, CH₂=CH-CH₂-), 5.83–5.93 (m, 1H, CH₂=CH-CH₂-), 7.29–7.34 (m, 2H_{Ar}), 7.39–7.52 (m, 5H_{Ar}), 7.63–7.70 (m, 2H_{Ar}); ^{13}C NMR (100 MHz): δ 43.0 (d, $J_{CF} = 4.2$), 88.2–88.7 (m, C-OH), 113.1–121.1 (m, 2×CF₂), 117.9, 123.4, 124.2, 129.1, 130.5, 130.9, 131.4, 132.5, 133.6, 137.1, 141.3, 167.5 (s, C=O); ^{19}F NMR: δ -116.7 (ddd, 1F, $^2J_{FF} = 277.7$, $^3J_{FF} = 8.3$, 3.7), -111.7 (ddd, 1F, $^2J_{FF} = 277.7$, $^3J_{FF} = 5.8$, 3.7), -84.5 (ddd, 1F, $^2J_{FF} = 222.9$, $^3J_{FF} = 8.3$, 3.7), -83.8 (ddd, 1F, $^2J_{FF} = 222.9$, $^3J_{FF} = 5.8$, 3.7); IR (film): ν_{max} (cm⁻¹) 3279, 3083, 1695, 1644, 1616, 1605, 1575, 1133, 992, 927, 752, 695; MS (EI): m/z 397 (3%) [M]⁺, 188 (100), 160 (19), 130 (20), 109 (9), 77 (8), 41 (13); HRMS (ESI): m/z calcd for C₁₉H₁₆F₄NO₂S [M+H]⁺ 398.08324, found 398.08324.

General procedure for the synthesis of compounds 67.

A solution of *n*-Bu₃SnH (470 μ L, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 1 h using a syringe pump to a refluxing solution of **66a** or **66b** (1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon for 3 h,

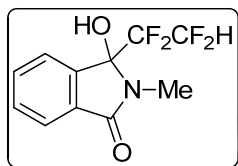
followed by concentration under reduced pressure and purification by flash column chromatography (SiO₂, hexane-EtOAc) to give product **67a** or **67b**.

5-Hydroxy-1-methyl-5-(1,1,2,2-tetrafluoroethyl)pyrrolidin-2-one (67a): colorless oil (202



mg, 94% yield); *R_f* 0.23 (hexane-EtOAc, 60:40); ¹H NMR: δ 1.90–2.00 (m, 1H, CH₂), 2.26–2.38 (m, 2H, CH₂), 2.41–2.50 (m, 1H, CH₂), 2.73 (d, 3H, ⁵*J*_{HF} = 2.5, CH₃), 6.59 (tdd, 1H, ²*J*_{HF} = 51.5, ³*J*_{HF} = 9.6, 3.5, CF₂H), 7.36 (br d, 1H, ⁴*J*_{HF} = 2.8, OH); ¹³C NMR (100 MHz): δ 25.8, 28.4, 28.8, 88.7–90.2 (m, C-OH), 173.8 (C=O); ¹⁹F NMR: δ –138.3 (ddd, 1F, ²*J*_{FF} = 301.0, ³*J*_{FF} = 10.7, 7.1), –134.3 (ddd, 1F, ²*J*_{FF} = 301.0, ³*J*_{FF} = 12.5, 1.3), –130.6 (ddd, 1F, ²*J*_{FF} = 265.8, ³*J*_{FF} = 12.5, 7.1), –126.8 (ddd, 1F, ²*J*_{FF} = 265.8, ³*J*_{FF} = 10.7, 1.3); IR (film): ν_{max} (cm⁻¹) 3204, 1687, 1110; MS (EI): *m/z* 198 (6%), 114 (100), 101 (8), 86 (20), 58 (45); HRMS (ESI): *m/z* calcd for C₇H₁₀F₄NO₂ [M+H]⁺ 216.06422, found 216.06417.

3-Hydroxy-2-methyl-3-(1,1,2,2-tetrafluoroethyl)isoindolin-1-one (67b): white solid (241

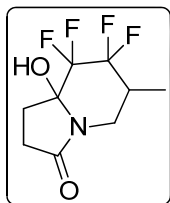


mg, 92% yield); mp 124–126 °C; *R_f* 0.54 (hexane-EtOAc, 50:50); ¹H NMR (DMSO-*d*₆): δ 2.96 (s, 3H, CH₃), 6.42 (tdd, 1H, ²*J*_{HF} = 51.0 Hz, ³*J*_{HF} = 6.6, 5.6 Hz, CF₂H), 7.63–7.68 (m, 1H_{Ar}), 7.70–7.72 (m, 2H_{Ar}), 7.74–7.77 (m, 1H_{Ar}), 7.91 (s, 1H, OH); ¹³C NMR (DMSO-*d*₆): δ 25.0, 86.9–87.2 (m, C-OH), 122.8, 124.4, 130.9, 131.4, 132.6, 141.7, 166.9 (C=O); ¹⁹F NMR (DMSO-*d*₆): δ –137.2 (ddd, 1F, ²*J*_{FF} = 301.9, ³*J*_{FF} = 10.1, 6.3), –135.3 (ddd, 1F, ²*J*_{FF} = 301.9, ³*J*_{FF} = 10.1, 4.1), –125.8 (ddd, 1F, ²*J*_{FF} = 271.2, ³*J*_{FF} = 10.1, 4.1), –124.6 (ddd, 1F, ²*J*_{FF} = 271.2, ³*J*_{FF} = 10.1, 6.3); IR (film): ν_{max} (cm⁻¹) 3228, 1693, 1616, 1477, 1116, 765; MS (EI): *m/z* 162 (100%), 133 (14), 105 (5), 77 (8); HRMS (ESI): *m/z* calcd for C₁₁H₁₀F₄NO₂ [M+H]⁺ 264.06422, found 264.06416.

General procedure for the synthesis of compounds 68.

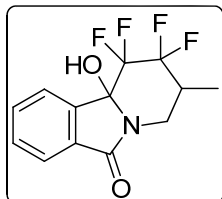
A solution of *n*-Bu₃SnH (470 μL, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 3 h using a syringe pump to a refluxing solution of **66c** or **66d** (1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon overnight, followed by concentration under reduced pressure and purification by flash column chromatography (SiO₂, hexane-EtOAc) to give product **68a** or **68b**.

7,7,8,8-Tetrafluoro-8a-hydroxy-6-methylhexahydroindolizin-3(2H)-one (68a): white solid



(188 mg, 78% yield, *cis:trans* = 76:24); crystallization from methanol gave *cis*-**68a** as colorless crystall; mp (*cis*) 160–162 °C; R_f 0.42 (hexane-EtOAc, 25:75); ^1H NMR: δ 0.91 (dd, 3H, $^3J_{\text{HH}} = 7.3$, $^4J_{\text{HF}} = 3.8$, CH_3 , *trans*), 1.02 (d, 3H, $^3J_{\text{HH}} = 6.7$, CH_3 , *cis*), 1.88–1.97 (m, 2H, *cis+trans*), 2.10–2.25 (m, 2H, *cis+trans*), 2.28–2.35 (m, 1H, *cis*), 2.37–2.40 (m, 1H, *trans*), 2.42–2.53 (m, 2H, *cis+trans*), 2.69–2.79 (m, 1H, *cis*), 3.16–3.23 (m, 1H, *trans*), 3.61–3.69 (m, 1H, *trans*), 3.77–3.88 (m, 1H, *cis*), 7.08 (s, 1H, OH, *trans*), 7.11 (s, 1H, OH, *cis*); ^{13}C NMR (100 MHz): δ *cis* 8.0 (d, $^3J_{\text{CF}} = 5.6$, CH_3), 25.9, 28.6, 35.3 (t, $^2J_{\text{CF}} = 21.4$, CH), 36.1 (d, $^3J_{\text{CF}} = 8.3$, CH_2), 88.1–88.7 (m, C-OH), 171.8 (C=O); ^{19}F NMR: δ -140.9 (ddd, 1F, $^2J_{\text{FF}} = 252.4$, $^3J_{\text{FF}} = 16.1$, 10.4, *cis*), -135.8 (ddd, 1F, $^2J_{\text{FF}} = 257.8$, $^3J_{\text{FF}} = 16.3$, 12.1, *trans*), -124.7 (ddd, 1F, $^2J_{\text{FF}} = 255.1$, $^3J_{\text{FF}} = 16.1$, 14.6, *cis*), -121.2 (ddd, 1F, $^2J_{\text{FF}} = 255.1$, $^3J_{\text{FF}} = 18.1$, 10.4, *cis*), -121.1 (ddd, 1F, $^2J_{\text{FF}} = 252.4$, $^3J_{\text{FF}} = 18.1$, 14.6, *cis*), -120.4 (ddd, 1F, $^2J_{\text{FF}} = 257.4$, $^3J_{\text{FF}} = 17.9$, 12.1, *trans*), -117.2 (ddd, 1F, $^2J_{\text{FF}} = 257.8$, $^3J_{\text{FF}} = 17.9$, 12.4, *trans*), -106.1 (ddd, 1F, $^2J_{\text{FF}} = 257.4$, $^3J_{\text{FF}} = 16.3$, 12.4, *trans*); IR (film): ν_{max} (cm^{-1}) 3252, 1699, 116; MS (EI): m/z 241 (2%) $[\text{M}]^+$, 221 (58), 201 (22), 173 (12), 112 (100), 84 (77), 55 (35); HRMS (EI): m/z calcd for $\text{C}_9\text{H}_{11}\text{F}_4\text{NO}_2$ $[\text{M}]^+$ 241.0726, found 241.0731.

1,1,2,2-Tetrafluoro-10b-hydroxy-3-methyl-1,3,4,10b-tetrahydropyrido-[2,1-a]isoindol-

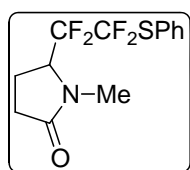


6(2H)-one (68b): white solid (159 mg, 55% yield, *cis:trans* = 90:10); crystallization from *n*-hexane gave *cis*-**68b** as colorless crystal; mp (*cis*) 224–226 °C; R_f 0.46 (*cis*) & 0.51 (*trans*) (hexane-EtOAc, 60:40); ^1H NMR: δ 0.96 (dd, 3H, $^3J_{\text{HH}} = 7.2$, $^4J_{\text{HF}} = 4.0$, CH_3 , *trans*), 1.12 (d, 3H, $^3J_{\text{HH}} = 6.7$, CH_3 , *cis*), 2.29–2.44 (m, 1H, *cis*), 2.68–2.81 (m, 1H, *trans*), 3.00–3.08 (m, 1H, *cis*), 3.46–3.53 (m, 1H, *trans*), 3.95–4.00 (m, 1H, *trans*), 4.16–4.22 (m, 1H, *cis*), 7.65–7.85 (m, $8H_{\text{Ar}}$, $2 \times \text{OH}$, *cis+trans*); ^{13}C NMR (100 MHz): δ *cis* 8.1 (d, $^3J_{\text{CF}} = 5.2$, CH_3), 35.9 (t, $^2J_{\text{CF}} = 21.1$, CH), 36.7 (d, $^3J_{\text{CF}} = 8.3$, CH_2), 86.8–87.4 (m, C-OH), 123.2, 123.4, 130.8, 132.9, 131.4, 140.9, 164.2 (C=O); ^{19}F NMR: δ -138.1 (ddd, 1F, $^2J_{\text{FF}} = 253.9$, $^3J_{\text{FF}} = 15.4$, 12.3, *cis*), -133.1 (ddd, 1F, $^2J_{\text{FF}} = 257.6$, $^3J_{\text{FF}} = 15.7$, 12.2, *trans*), -125.3 (ddd, 1F, $^2J_{\text{FF}} = 253.9$, $^3J_{\text{FF}} = 15.4$, 13.5, *cis*), -122.9 (ddd, 1F, $^2J_{\text{FF}} = 253.9$, $^3J_{\text{FF}} = 18.5$, 12.3, *cis*), -122.4 (ddd, 1F, $^2J_{\text{FF}} = 259.3$, $^3J_{\text{FF}} = 18.7$, 12.2, *trans*), -120.3 (ddd, 1F, $^2J_{\text{FF}} = 253.9$, $^3J_{\text{FF}} = 18.5$, 13.5, *cis*), -116.2 (ddd, 1F, $^2J_{\text{FF}} = 257.6$, $^3J_{\text{FF}} = 18.7$, 12.6, *trans*), -106.7 (ddd, 1F, $^2J_{\text{FF}} = 259.3$, $^3J_{\text{FF}} = 15.7$, 12.6, *trans*); IR (film): ν_{max} (cm^{-1}) 3246, 1690, 1615, 1117; MS (EI): m/z

289 (8%) [M]⁺, 269 (17), 160 (100), 105 (7), 77 (8); HRMS (EI): *m/z* calcd for C₁₃H₁₁F₄NO₂ [M]⁺ 289.0726, found 289.0732.

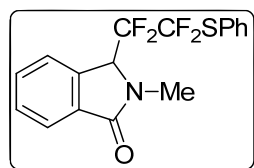
General procedure for the synthesis of compounds 69 and 70. To a solution of **66** or **67** (1 mmol) in CH₂Cl₂ (5 mL) was added dropwise triethylsilane (0.8 mL, 5 mmol) and BF₃·OEt₂ (377 μL, 3 mmol) under argon atmosphere. The mixture was refluxed for 2.5 h, followed by the addition of saturated NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (3×25 mL). The combined extracts were washed with brine and dried over anhydrous MgSO₄. Filtration followed by evaporation gave a crude product, which was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **69** or **70**.

1-Methyl-5-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)pyrrolidin-2-one (69a): colorless oil



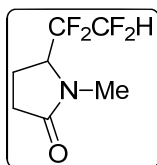
(282 mg, 92% yield); *R_f* 0.26 (hexane-EtOAc, 80:20); ¹H NMR: δ 2.15–2.34 (m, 3H, CH₂), 2.44–2.59 (m, 1H, CH₂), 2.95 (d, 3H, ⁵*J*_{HF} = 2.0, CH₃), 4.04–4.13 (m, 1H, CH), 7.37–7.43 (m, 2*H*_{Ar}), 7.44–7.51 (m, 1*H*_{Ar}), 7.56–7.68 (m, 2*H*_{Ar}); ¹³C NMR (100 MHz): δ 19.6–19.8 (m, CH₂), 29.0, 30.9–31.0 (m, CH₃), 60.8–61.4 (m, CH), 129.3, 130.7, 137.2; ¹⁹F NMR: δ -120.7 (dd, 1F, ²*J*_{FF} = 270.9, ²*J*_{FF} = 20.1), -111.0 (d, 1F, ²*J*_{FF} = 270.9), -86.3 (s, 2F); IR (film): *v*_{max} (cm⁻¹) 3063, 1707, 1577, 1108; MS (EI): *m/z* 109 (6%), 98 (100), 42 (5); HRMS (ESI): *m/z* calcd for C₁₃H₁₃F₄NNaOS [M+Na]⁺ 330.05453, found 330.05462.

2-Methyl-3-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)isoindolin-1-one (69b): pale yellow



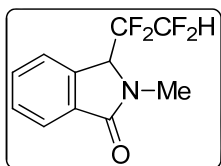
solid (340 mg, 96% yield); mp 112–114 °C; *R_f* 0.20 (hexane-EtOAc, 80:20); ¹H NMR: δ 3.23 (d, 3H, ⁵*J*_{HF} = 1.6, CH₃), 4.93 (dd, 1H, ³*J*_{HF} = 10.12, ⁴*J*_{HF} = 5.74, CH), 7.28–7.34 (m, 2*H*_{Ar}), 7.37–7.43 (m, 1*H*_{Ar}), 7.44–7.48 (m, 2*H*_{Ar}), 7.51–7.58 (m, 2*H*_{Ar}), 7.60–7.63 (m, 1 *H*_{Ar}), 7.82–7.87 (m, 1 *H*_{Ar}); ¹³C NMR (100 MHz): δ 29.9, 63.8 (dd, ²*J*_{CF} = 31.4, ³*J*_{CF} = 25.0, CH), 123.8, 124.3, 129.1, 129.7, 130.6, 131.8, 132.5, 137.1; ¹⁹F NMR: δ -108.4 (ddd, 1F, ²*J*_{FF} = 284.6, ³*J*_{FF} = 6.3, 5.0), -104.8 (ddd, 1F, ²*J*_{FF} = 284.6, ³*J*_{FF} = 5.8, 4.6), -84.5–84.4 (m, 2F); IR (film): *v*_{max} (cm⁻¹) 3061, 1710, 1617, 1598, 1578, 1076; MS (EI): *m/z* 355 (3%) [M]⁺, 146 (100), 109 (6), 91 (9); HRMS (ESI): *m/z* calcd for C₁₇H₁₃F₄NNaOS [M+Na]⁺ 378.05447, found 378.05462.

1-Methyl-5-(1,1,2,2-tetrafluoroethyl)pyrrolidin-2-one (70a): colorless oil (179 mg, 90%



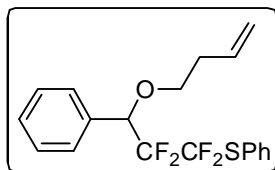
yield); R_f 0.11 (hexane-EtOAc, 80:20); $^1\text{H NMR}$: δ 2.18–2.40 (m, 3H, CH_2), 2.46–2.62 (m, 1H, CH_2), 2.97 (s, 3H, CH_3), 3.94–4.07 (m, 1H, CH), 5.88 (tdd, 1H, $^2J_{\text{HF}} = 53.35$, $^3J_{\text{HF}} = 4.84$, 2.44, CF_2H); $^{13}\text{C NMR}$ (100 MHz): δ 18.9–19.1 (m, CH_2), 28.9, 30.5 (d, $^4J_{\text{CF}} = 3.5$, CH_3), 60.0 (t, $^2J_{\text{CF}} = 23.0$, CH), 110.1 (tt, $^1J_{\text{CF}} = 251.0$, $^2J_{\text{CF}} = 39.1$, CF_2), 116.8 (tt, $^1J_{\text{CF}} = 252.7$, $^2J_{\text{CF}} = 27.5$, CF_2), 175.7 ($\text{C}=\text{O}$); $^{19}\text{F NMR}$: δ -136.9 (dd, 1F, $^2J_{\text{FF}} = 305.9$, $^3J_{\text{FF}} = 3.3$), -134.4 (dd, 1F, $^2J_{\text{FF}} = 305.9$, $^3J_{\text{FF}} = 3.5$), -124.5 (dd, 1F, $^2J_{\text{FF}} = 279.3$, $^3J_{\text{FF}} = 3.5$), -119.4 (dd, 1F, $^2J_{\text{FF}} = 279.3$, $^3J_{\text{FF}} = 3.3$); IR (film): ν_{max} (cm^{-1}) 1701, 1103; MS (EI): m/z 199 (1%) [M] $^+$, 98 (100), 70 (7), 42 (14); HRMS (ESI): m/z calcd for $\text{C}_7\text{H}_{10}\text{F}_4\text{NO}$ [$\text{M}+\text{H}$] $^+$ 200.06930, found 200.06930.

2-Methyl-3-(1,1,2,2-tetrafluoroethyl)isoindolin-1-one (70b): white solid (229 mg, 93%



yield); mp 57–59 °C; R_f 0.52 (hexane-EtOAc, 85:15); $^1\text{H NMR}$: δ 3.29 (d, 3H, $^5J_{\text{HF}} = 2.03$, CH_3), 4.90–4.95 (m, 1H, CH), 5.60 (tdd, 1H, $^2J_{\text{HF}} = 52.5$, $^3J_{\text{HF}} = 5.6$, 5.1, CF_2H), 7.59–7.68 (m, 3 H_{Ar}), 7.90–7.93 (m, 1 H_{Ar}); $^{13}\text{C NMR}$ (100 MHz): δ 29.7, 62.9 (dd, $^2J_{\text{CF}} = 29.6$, 24.5, CH), 108.6 (tt, $^1J_{\text{CF}} = 252.3$, $^2J_{\text{CF}} = 33.2$, CF_2), 109.9, 115.4 (tt, $^1J_{\text{CF}} = 254.9$, $^2J_{\text{CF}} = 25.2$, CF_2), 123.7–124.2 (m, $C_{\text{Ar}}\text{H}$), 129.9, 130.9, 132.1, 132.3, 133.6, 168.8; $^{19}\text{F NMR}$: δ -136.8 (ddd, 1F, $^2J_{\text{FF}} = 305.4$, $^3J_{\text{FF}} = 7.5$, 4.2), -135.6 (ddd, 1F, $^2J_{\text{FF}} = 305.4$, $^3J_{\text{FF}} = 7.5$, 4.5), -117.6 (ddd, 1F, $^2J_{\text{FF}} = 284.5$, $^3J_{\text{FF}} = 7.5$, 4.2), -115.8 (ddd, 1F, $^2J_{\text{FF}} = 284.5$, $^3J_{\text{FF}} = 7.5$, 4.5); IR (film): ν_{max} (cm^{-1}) 3085, 3055, 1709, 1617, 1599, 1109; MS (EI): m/z 247 (1%) [M] $^+$, 146 (100), 91 (12); HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{10}\text{F}_4\text{NO}$ [$\text{M}+\text{H}$] $^+$ 248.06931, found 248.06930.

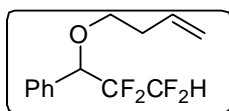
(3-(But-3-enyloxy)-1,1,2,2-tetrafluoro-3-phenylpropyl)(phenyl)sulfane (71).



4-Bromobut-1-ene (509 μL , 5 mmol) was added to a solution of **60a** (181 mg, 0.5 mmol) and N-cetyl-N,N,N-trimethylammonium bromide (18 mg, 0.05 mmol) in 50% NaOH_{aq} /toluene (2.5 mL/2.5 mL). The mixture was stirred for 18 h at room temperature. Aqueous NH_4Cl (5 mL) was added and the product was extracted into Et_2O (3 \times 15 mL); the combined organic phase was then washed with brine (15 mL), dried (MgSO_4), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2 , hexane-EtOAc) to give the desired product **71** as orange solid (56 mg, 30 % yield). R_f 0.73 (hexane-EtOAc, 90:10); $^1\text{H NMR}$: δ 2.33–2.41 (m, 2H), 3.45–3.53 (m, 2H), 4.75 (dd, 1H, $^3J_{\text{HF}} = 19.1$, $^3J_{\text{HF}} = 4.9$, CH-O), 5.00–5.10 (m, 2H), 5.75–5.82 (m, 1H), 7.34–7.51 (m, 8 H_{Ar}),

7.58–7.70 (m, 2H_{Ar}); ¹⁹F NMR: δ -123.7 (ddd, 1F, ²J_{FF} = 270.0, ³J_{FF} = 5.5, 3.0), -116.0 (ddd, 1F, ²J_{FF} = 270.0, ³J_{FF} = 6.4, 4.2), -87.5 (ddd, 1F, ²J_{FF} = 222.7, ³J_{FF} = 6.4, 3.0), -85.1 (ddd, 1F, ²J_{FF} = 222.7, ³J_{FF} = 5.5, 4.2); MS (EI): *m/z* 370 (1%) [M]⁺, 316 (14), 221 (46), 161 (100), 159 (51), 131 (74), 109 (25), 77 (40), 55 (80).

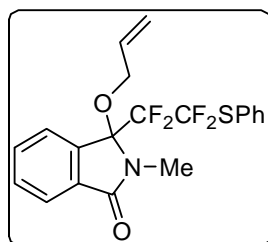
(1-(But-3-enyloxy)-2,2,3,3-tetrafluoropropyl)benzene (73). A solution of *n*-Bu₃SnH (87 μL,



0.3 mmol) and AIBN (4 mg, 0.03 mmol) in dry toluene (1 mL) was added over 4 h using a syringe pump to a refluxing solution of **71** (56 mg, 0.15 mmol) in dry toluene (2 mL). The resulting mixture was

refluxed under argon overnight, GCMS (EI) analysis of the crude reaction mixture showed the formation of **73** as a main product. ¹H NMR: δ 2.32–2.41 (m, 2H), 3.45–3.55 (m, 2H), 4.64 (dd, 1H, ³J_{HF} = 22.6, ³J_{HF} = 4.5, CH-O), 5.01–5.10 (m, 2H), 5.73–5.83 (m, 1H), 6.08 (dddd, ²J_{HF} = 54.2, 52.6, ³J_{HF} = 10.3, 1.3, CF₂H), 7.35–7.48 (m, 5H_{Ar}); ¹⁹F NMR: δ -144.0 (ddd, 1F, ²J_{FF} = 298.1, ³J_{FF} = 12.1, 9.0), -137.4 (ddd, 1F, ²J_{FF} = 298.1, ³J_{FF} = 12.4, 5.7), -130.6 (ddd, 1F, ²J_{FF} = 271.5, ³J_{FF} = 12.1, 5.7), -129.0 (ddd, 1F, ²J_{FF} = 271.5, ³J_{FF} = 12.4, 9.0); MS (EI): *m/z* 262 (0.2%) [M]⁺, 191 (100), 171 (36), 161 (78), 151 (25), 140 (33), 131 (38), 101 (5), 77 (21), 55 (62).

3-(Allyloxy)-2-methyl-3-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)isoindolin-1-one (74).

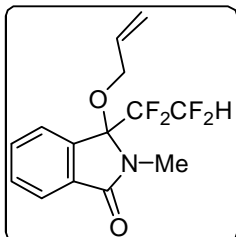


Sodium hydride (48 mg, 2 mmol) was added to a solution of **66b** (371 mg, 1 mmol) in dry DMF (5 mL). After 10 minutes of stirring under argon at room temperature, allyl bromide (87 μL, 3 mmol) was added and the mixture was stirred at 50 °C for 30 min. Aqueous NH₄Cl (15 mL) was added and the product was extracted into Et₂O

(3×15 mL); the combined organic phase was then washed with brine (15 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, hexane-EtOAc) to give the desired product **74** as white solid (349 mg, 85% yield). *R_f* 0.43 (hexane-EtOAc, 80:20); ¹H NMR: δ 3.02–3.12 (m, 3H, CH₃), 3.44–3.54 (m, 2H), 5.14–5.28 (m, 2H), 5.77–5.87 (m, 1H), 7.29–7.36 (m, 2H_{Ar}), 7.38–7.44 (m, 1H_{Ar}), 7.45–7.52 (m, 2H_{Ar}), 7.55–7.65 (m, 2H_{Ar}), 7.66–7.72 (m, 1H_{Ar}), 7.81–7.90 (m, 1H_{Ar}); ¹³C NMR (100 MHz): δ 25.7, 63.7, 117.6, 123.6, 124.9, 129.1, 130.5, 131.2, 132.2, 132.4, 133.0, 137.1, 167.9; ¹⁹F NMR: δ -117.0 (ddd, 1F, ²J_{FF} = 276.8, ³J_{FF} = 8.4, 3.2), -113.0 (ddd, 1F, ²J_{FF} = 276.8, ³J_{FF} = 6.8, 3.5), -85.0 (ddd, 1F, ²J_{FF} = 222.1, ³J_{FF} = 8.4, 3.5), -84.2 (ddd, 1F, ²J_{FF} =

222.1, $^3J_{\text{FF}} = 6.8, 3.2$); MS (EI): m/z 411 (0.2%) $[\text{M}]^+$, 354 (7), 202 (100), 160 (26), 159 (18), 145 (16), 109 (11), 77 (13), 41 (42); HRMS (CI): m/z calcd for $\text{C}_{20}\text{H}_{18}\text{F}_4\text{SNO}_2$ $[\text{M}+\text{H}]^+$ 412.0994, found 412.0993

3-(Allyloxy)-2-methyl-3-(1,1,2,2-tetrafluoroethyl)isoindolin-1-one (76). A solution of *n*-



Bu_3SnH (235 μL , 0.88 mmol) and AIBN (13 mg, 0.08 mmol) in dry toluene (3 mL) was added over 3 h using a syringe pump to a refluxing solution of **74** (206 mg, 0.5 mmol) in dry toluene (2 mL). The resulting mixture was refluxed under argon for 10 h, followed by concentration under reduced pressure and purification by flash column

chromatography (SiO_2 , hexane-EtOAc) to give product **76** as colorless oil (121 mg, 80% yield). R_f 0.18 (hexane-EtOAc, 90:10); ^1H NMR: δ 3.02-3.12 (m, 3H, CH_3), 3.45-3.55 (m, 2H), 5.14-5.28 (m, 2H), 5.68 (ddd, 1H, $^2J_{\text{HF}} = 52.6$, $^3J_{\text{HF}} = 6.5$, 4.7, CF_2H), 5.76-5.86 (m, 1H), 7.58-7.70 (m, $3H_{\text{Ar}}$), 7.83-7.94 (m, $1H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 25.8 (s, CH_3), 64.0 (s, $\text{CH}_2\text{-CH}=\text{CH}_2$), 91.9 (t, $^2J_{\text{CF}} = 23.7$, N-C-O), 108.4 (tt, $^1J_{\text{CF}} = 252.9$, $^2J_{\text{CF}} = 32.5$, CF_2H), 114.4 (tt, $^1J_{\text{CF}} = 263.0$, $^2J_{\text{CF}} = 24.4$, CF_2), 117.7 (s, $\text{CH}_2\text{-CH}=\text{CH}_2$), 123.9, 124.5 (s, $\text{CH}_2\text{-CH}=\text{CH}_2$), 131.4, 132.2, 132.5, 132.7, 137.5 (d, $^2J_{\text{CF}} = 2.0$, C_{Ar}), 167.7 (C=O); ^{19}F NMR: δ -136.3 (tt, 1F, $^2J_{\text{FF}} = 303.0$, $^3J_{\text{FF}} = 7.1$), -135.4 (ddd, 1F, $^2J_{\text{FF}} = 303.0$, $^3J_{\text{FF}} = 8.7$, 5.0), -126.6 (ddd, 1F, $^2J_{\text{FF}} = 276.1$, $^3J_{\text{FF}} = 7.6$, 7.1), -123.1 (ddd, 1F, $^2J_{\text{FF}} = 276.1$, $^3J_{\text{FF}} = 7.6$, 5.0); MS (EI): m/z 303 (0.1%) $[\text{M}]^+$, 246 (75), 202 (100), 160 (29), 145 (27), 177 (18), 76 (12), 41 (54); HRMS (CI): m/z calcd for $\text{C}_{14}\text{H}_{14}\text{F}_4\text{S}$ $[\text{M}+\text{H}]^+$ 304.0961, found 304.0957.

General procedure for the synthesis of compounds **78**

Et_3B (500 μL , 0.5 mmol, 1M solution in hexane) was added dropwise into a solution of **52** (289 mg, 1 mmol) and alkene (or alkyne) **77** (2 mmol) in CH_2Cl_2 (1mL). After 15 minutes of stirring at room temperature under argon atmosphere, a solution of *n*- Bu_3SnH (320 μL , 1.1 mmol) in DCM (0.5 mL) was added over 1 h period by syringe pump. When the addition was finished, the reaction mixture was concentrated under reduced pressure to give crude product. The resulting residue was purified by flash column chromatography (SiO_2 , hexane-EtOAc) to give the desired product **78**.

Phenyl(1,1,2,2-tetrafluorodecyl)sulfane (78a): colorless oil (202 mg, 63% yield); R_f 0.61 (hexane); $^1\text{H NMR}$: δ 0.85-0.92 (m, 3H, CH_3), 1.18-1.44 (m, 10H, CH_2), 1.53-1.62 (m, 2H, CH_2), 1.94-2.14 (m, 2H, CH_2), 7.35-7.50 (m, 3 H_{Ar}), 7.61-7.68 (m, 2 H_{Ar}); $^{13}\text{C NMR}$ (100 MHz): δ 14.1, 20.6 (t, $^3J_{\text{CF}} = 3.3$), 22.6, 29.1, 29.3, 31.1 (t, $^2J_{\text{CF}} = 22.9$), 31.8, 119.0 (tt, $^1J_{\text{CF}} = 252.1$, $^2J_{\text{CF}} = 32.2$, CF_2), 124.3, 124.8 (tt, $^1J_{\text{CF}} = 287.6$, $^2J_{\text{CF}} = 36.5$, CF_2), 129.1, 130.3, 137.1; $^{19}\text{F NMR}$: δ -112.7 (t, 2F, $^3J_{\text{FF}} = 4.0$), -88.8 (t, 2F, $^3J_{\text{FF}} = 4.0$); IR (film): ν_{max} (cm^{-1}) 1068, 1094, 1158, 1308, 1380, 1442, 1476, 1578, 1584, 2857, 2927, 3065, 3081; MS (EI): m/z 322 (100%) [M] $^+$, 159 (70), 109 (13), 77 (8); HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{F}_4\text{S}$ [M] $^+$ 322.1378, found 322.1377.

Phenyl(1,1,2,2-tetrafluorotetradecyl)sulfane (78b): colorless liquid (173 mg, 46% yield); R_f 0.75 (hexane); $^1\text{H NMR}$: δ : 0.85-0.91 (m, 3H, CH_3), 1.20-1.40 (m, 18H, CH_2), 1.52-1.67 (m, 2H, CH_2), 1.96-2.12 (m, 2H, CH_2), 7.36-7.41 (m, 2 H_{Ar}), 7.43-7.48 (m, 1 H_{Ar}), 7.62-7.67 (m, 2 H_{Ar}); $^{13}\text{C NMR}$ (100 MHz): δ 14.1, 20.6 (t, $^3J_{\text{CF}} = 3.3$), 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.1 (t, $^2J_{\text{CF}} = 22.9$), 31.9, 119.1 (tt, $^1J_{\text{CF}} = 252.3$, $^2J_{\text{CF}} = 32.2$, CF_2), 124.3, 124.6 (tt, $^1J_{\text{CF}} = 287.5$, $^2J_{\text{CF}} = 36.5$, CF_2), 129.1, 130.3, 137.1; $^{19}\text{F NMR}$: δ -112.7 (t, 2F, $^3J_{\text{FF}} = 4.0$), -88.8 (t, 2F, $^3J_{\text{FF}} = 4.0$); IR (film): ν_{max} (cm^{-1}) 749, 1025, 1068, 1094, 1442, 1475, 1584, 2855, 2955, 3080; MS (EI): m/z 378 (100%) [M] $^+$, 159 (41), 109 (9); HRMS (EI): m/z calcd for $\text{C}_{20}\text{H}_{30}\text{F}_4\text{S}$ [M] $^+$ 378.2004, found 378.2003;

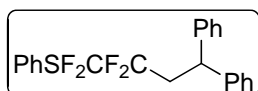
Trimethyl(4,4,5,5-tetrafluoro-5-(phenylthio)pentyl)silane (78c): colorless liquid (249 mg, 77% yield); R_f 0.68 (hexane); $^1\text{H NMR}$: δ : 0.02 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.52-0.60 (m, 2H, CH_2TMS), 1.56-1.66 (m, 2H, CH_2), 2.02-2.16 (m, 2H, CH_2), 7.38-7.52 (m, 3 H_{Ar}), 7.63-7.69 (m, 2 H_{Ar}); $^{13}\text{C NMR}$ (100 MHz): δ -1.8, 15.4 (t, $^3J_{\text{CF}} = 3.7$), 16.6, 34.8 (t, $^2J_{\text{CF}} = 22.6$), 118.9 (tt, $^1J_{\text{CF}} = 252.1$, $^2J_{\text{CF}} = 32.3$, CF_2), 124.3, 124.6 (tt, $^1J_{\text{CF}} = 287.5$, $^2J_{\text{CF}} = 36.5$, CF_2), 129.1, 130.3, 137.1; $^{19}\text{F NMR}$: δ -112.7 (t, 2F, $^3J_{\text{FF}} = 4.0$), -88.8 (t, 2F, $^3J_{\text{FF}} = 4.0$); IR (film): ν_{max} (cm^{-1}) 690, 749, 839, 861, 1025, 1052, 1068, 1094, 1273, 1308, 1328, 1413, 1476, 1584, 2883, 2954, 3065, 3081; MS (EI): m/z 324 (11%) [M] $^+$, 204 (100), 77 (90), 73 (85), 110 (74), 171 (44); HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{F}_4\text{SSi}$ [M] $^+$ 324.0991, found 324.0992;

(4-Ethoxy-1,1,2,2-tetrafluorobutyl)(phenyl)sulfane (78d): colorless oil (118 mg, 42% yield); R_f 0.23 (hexane-EtOAc, 99:1); $^1\text{H NMR}$: δ 1.20 (t, 3H, $^3J_{\text{HH}} = 7.0$, CH_2CH_3), 2.32–2.50 (m, 2H, CH_2CF_2), 3.50 (q, 2H, $^3J_{\text{HH}} = 7.0$, CH_2CH_3), 3.70 (t, 2H, $^3J_{\text{HH}} = 7.2$, CH_2OEt), 7.35–7.50 (m, $3H_{\text{Ar}}$), 7.60–7.67 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 15.1, 31.7 (t, $^2J_{\text{CF}} = 22.2$), 62.8 (t, $^3J_{\text{CF}} = 4.4$), 66.5, 118.3 (tt, $^1J_{\text{CF}} = 253.0$, $^2J_{\text{CF}} = 33.0$, CF_2), 124.0, 124.4 (tt, $^1J_{\text{CF}} = 287.5$, $^2J_{\text{CF}} = 36.0$, CF_2), 129.1, 130.4, 137.1; $^{19}\text{F NMR}$: δ -111.7 (t, 2F, $^3J_{\text{FF}} = 3.9$), -89.1 (t, 2F, $^3J_{\text{FF}} = 3.9$); IR (film): ν_{max} (cm^{-1}) 690, 1024, 1069, 1094, 1120, 1299, 1385, 1443, 1457, 1443, 1490, 1584, 2933, 2979, 3065; MS (EI): m/z 282 (100%) $[\text{M}]^+$, 237 (30), 159 (53), 125 (22), 109 (37), 77 (55); HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{14}\text{F}_4\text{OS}$ $[\text{M}]^+$ 282.0702, found 282.0706.

3-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)tetrahydrofuran (78e): colorless oil (64 mg, 23% yield); $^1\text{H NMR}$: δ 2.00–2.20 (m, 2H), 2.93–3.11 (m, 1H), 3.74–3.89 (m, 3H), 3.93–4.04 (m, 1H), 7.36–7.50 (m, $3H_{\text{Ar}}$), 7.62–7.68 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 41.2 (t, $^2J_{\text{CF}} = 22.1$), 66.8–67.1 (m), 68.1, 118.5 (tt, $^1J_{\text{CF}} = 253.5$, $^2J_{\text{CF}} = 32.7$, CF_2), 123.8, 124.7 (tt, $^1J_{\text{CF}} = 287.5$, $^2J_{\text{CF}} = 37.2$, CF_2), 129.2, 130.5, 137.1; $^{19}\text{F NMR}$: δ -116.0 (dd, 1F, $^2J_{\text{FF}} = 266.1$, $^3J_{\text{FF}} = 6.1$), -113.8 (dd, 1F, $^2J_{\text{FF}} = 266.1$, $^3J_{\text{FF}} = 6.4$), -87.6 (dd, 1F, $^2J_{\text{FF}} = 224.3$, $^3J_{\text{FF}} = 6.1$), -86.8 (dd, 1F, $^2J_{\text{FF}} = 224.3$, $^3J_{\text{FF}} = 6.4$); MS (EI): m/z 280 (70%) $[\text{M}]^+$, 70 (100), 159 (52), 77 (38), 109 (35), 91 (20); HRMS (CI): m/z calcd for $\text{C}_{12}\text{H}_{13}\text{F}_4\text{OS}$ $[\text{M}+\text{H}]^+$ 281.0623, found 281.0633.

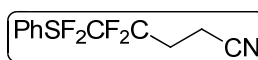
Phenyl(1,1,2,2-tetrafluoro-4-phenylbutyl)sulfane (78f): colorless oil (157 mg, 50% yield); R_f 0.46 (hexane); $^1\text{H NMR}$: δ 2.24–2.42 (m, 2H), 2.80–2.90 (m, 2H), 7.14–7.46 (m, $8H_{\text{Ar}}$), 7.55–7.65 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 27.0 (t, $^3J_{\text{CF}} = 4.6$), 33.2 (t, $^2J_{\text{CF}} = 22.7$), 118.7 (tt, $^1J_{\text{CF}} = 253.0$, $^2J_{\text{CF}} = 32.5$, CF_2), 124.1, 124.6 (tt, $^1J_{\text{CF}} = 287.9$, $^2J_{\text{CF}} = 35.9$, CF_2), 126.5, 128.3, 128.7, 129.2, 130.4, 137.1, 133.8; $^{19}\text{F NMR}$: δ -112.9 (t, 2F, $^3J_{\text{FF}} = 4.0$), -88.7 (t, 2F, $^3J_{\text{FF}} = 4.0$); IR (film): ν_{max} (cm^{-1}) 699, 749, 1065, 1094, 1442, 1455, 1498, 1584, 2855, 2929, 3035, 3087; MS (EI): m/z 314 (100%) $[\text{M}]^+$, 140 (63), 91 (40), 104 (30), 159 (32), 109 (20); HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{15}\text{F}_4\text{S}$ $[\text{M}+\text{H}]^+$ 315.0831, found 315.0823;

Phenyl(1,1,2,2-tetrafluoro-4,4-diphenylbutyl)sulfane (78g): colorless oil (253 mg, 65%



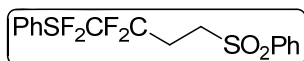
yield); R_f 0.09 (hexane); $^1\text{H NMR}$: δ 2.84–2.98 (m, 2H), 4.46 (t, 1H, $^3J_{\text{HH}} = 7.1$, CH), 7.14–7.46 (m, $13H_{\text{Ar}}$), 7.55–7.65 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 36.5 (t, $^2J_{\text{CF}} = 21.5$), 44.1 (t, $^3J_{\text{CF}} = 2.0$), 118.6 (tt, $^1J_{\text{CF}} = 254.7$, $^2J_{\text{CF}} = 32.3$, CF_2), 124.0, 124.4 (tt, $^1J_{\text{CF}} = 287.9$, $^2J_{\text{CF}} = 36.0$, CF_2), 126.6, 127.5, 128.6, 129.1, 130.4, 137.0, 143.6; $^{19}\text{F NMR}$: δ -110.9 (t, 2F, $^3J_{\text{FF}} = 3.9$), -88.9 (t, 2F, $^3J_{\text{FF}} = 3.9$); IR (film): ν_{max} (cm^{-1}) 733, 858, 1024, 1093, 1067, 1207, 1494, 1585, 1600, 1476, 3063; MS (EI) m/z 390 (40%) $[\text{M}]^+$, 167 (100), 280 (30), 152 (17), 109 (9); HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_4\text{O}_2\text{S}_2$ $[\text{M}]^+$ 390.1065, found 390.1073.

4,4,5,5-Tetrafluoro-5-(phenylthio)pentanenitrile (78i): colorless oil (134 mg, 51% yield);



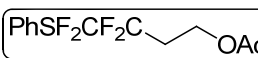
R_f 0.12 (hexane-EtOAc, 99:1); $^1\text{H NMR}$: δ 2.42–2.56 (m, 2H), 2.60–2.66 (m, 2H), 7.38–7.52 (m, $3H_{\text{Ar}}$), 7.61–7.66 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 10.0 (t, $^3J_{\text{CF}} = 5.5$), 27.7 (t, $^2J_{\text{CF}} = 23.4$), 117.3 (tt, $^1J_{\text{CF}} = 254.4$, $^2J_{\text{CF}} = 33.7$, CF_2), 117.4, 123.3, 123.8 (tt, $^1J_{\text{CF}} = 287.3$, $^2J_{\text{CF}} = 35.3$, CF_2), 129.3, 130.7, 137.1; $^{19}\text{F NMR}$: δ -113.5 (t, 2F, $^3J_{\text{FF}} = 3.7$), -88.9 (t, 2F, $^3J_{\text{FF}} = 3.7$); IR (film): ν_{max} (cm^{-1}) 691, 1024, 1069, 1095, 1300, 1476, 1577, 2256, 3065; MS (EI): m/z 263 (72%) $[\text{M}]^+$, 159 (100), 109 (47), 77 (28); HRMS (EI): m/z calcd for $\text{C}_{11}\text{H}_9\text{NF}_4\text{S}$ $[\text{M}]^+$ 263.0392, found 263.0396.

Phenyl(1,1,2,2-tetrafluoro-4-(phenylsulfonyl)butyl)sulfane (78j): white solid (242 mg,



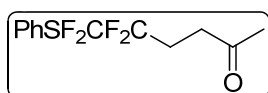
64% yield); R_f 0.20 (hexane-EtOAc, 90:10); $^1\text{H NMR}$: δ 2.50–2.67 (m, 2H), 3.32–3.38 (m, 2H), 7.38–7.45 (m, $2H_{\text{Ar}}$), 7.48–7.51 (m, $1H_{\text{Ar}}$), 7.58–7.69 (m, $4H_{\text{Ar}}$), 7.70–7.77 (m, $1H_{\text{Ar}}$), 7.93–8.00 (m, $2H_{\text{Ar}}$); $^{13}\text{C NMR}$ (100 MHz): δ 25.3 (t, $^2J_{\text{CF}} = 23.5$), 48.6, 117.6 (tt, $^1J_{\text{CF}} = 254.4$, $^2J_{\text{CF}} = 33.3$, CF_2), 123.4, 124.1 (tt, $^1J_{\text{CF}} = 287.8$, $^2J_{\text{CF}} = 35.7$, CF_2), 128.0, 129.3, 129.6, 130.6, 134.2, 137.1, 138.3; $^{19}\text{F NMR}$: δ -111.8 (t, 2F, $^3J_{\text{FF}} = 4.0$), -88.7 (t, 2F, $^3J_{\text{FF}} = 4.0$); IR (film): ν_{max} (cm^{-1}) 688, 1025, 1150, 1179, 1298, 1325, 1476, 3065; MS (EI): m/z 378 (45%) $[\text{M}]^+$, 237 (100), 77 (75), 159 (33), 109 (30); HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_4\text{O}_2\text{S}_2$ $[\text{M}]^+$ 378.0371, found 378.0377;

3,3,4,4-Tetrafluoro-4-(phenylthio)butyl acetate (78k): not isolated. $^{19}\text{F NMR}$: δ -112.0 to



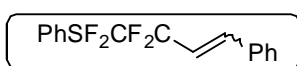
-111.4 (m, 2F), -89.4 to -89.0 (m, 2F); MS (EI): m/z 296 (82%) $[\text{M}]^+$, 159 (100), 43 (71), 109 (34), 77 (30);

5,5,6,6-Tetrafluoro-6-(phenylthio)hexan-2-one (78l): colorless oil (84 mg, 30% yield); R_f



0.28 (hexane-EtOAc, 90:10); ^1H NMR: δ 2.21 (s, 3H, CH_3), 2.32-2.52 (m, 2H), 2.68-2.80 (m, 2H), 7.35-7.52 (m, 3 H_{Ar}), 7.60-7.68 (m, 2 H_{Ar}); ^{13}C NMR (100 MHz): δ 24.5 (t, $^2J_{\text{CF}} = 22.8$), 29.9, 34.8 (t, $^3J_{\text{CF}} = 2.8$), 118.8 (tt, $^1J_{\text{CF}} = 252.6$, $^2J_{\text{CF}} = 32.6$, CF_2), 123.9, 124.2 (tt, $^1J_{\text{CF}} = 287.5$, $^2J_{\text{CF}} = 35.7$, CF_2), 130.5, 137.1, 205.3; ^{19}F NMR: δ -112.6 (t, 2F, $^3J_{\text{FF}} = 4.2$), -88.9 (t, 2F, $^3J_{\text{FF}} = 4.2$); IR (film): ν_{max} (cm^{-1}) 965, 1069, 1077, 1093, 1361, 1476, 1584, 1725, 3010, 3065; MS (EI): m/z 280 (30%) $[\text{M}]^+$, 43 (100), 109 (25), 77 (21), 159 (13), 171 (12); HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{12}\text{F}_4\text{O}_2\text{S}$ $[\text{M}]^+$ 280.0545, found 280.0537;

Phenyl(1,1,2,2-tetrafluoro-4-phenylbut-3-enyl)sulfane (78n): not isolated. ^{19}F NMR: δ

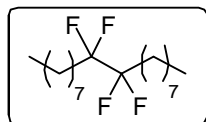


-109.7 (t, 2F, $^3J_{\text{FF}} = 7.5$, minor), -103.8 (t, 2F, $^3J_{\text{FF}} = 7.5$, major), -89.2 (t, 2F, $^3J_{\text{FF}} = 7.5$, major), -88.8 (t, 2F, $^3J_{\text{FF}} = 7.5$, minor); MS (EI): m/z 312 (18%) $[\text{M}]^+$, 153 (100), 133 (49), 159 (39), 77 (20), 109 (8).

General procedure for the synthesis of compounds 80a.

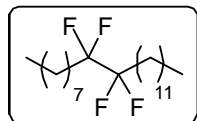
A solution of $n\text{-Bu}_3\text{SnH}$ (470 μL , 1.75 mmol) and AIBN (50 mg, 0.30 mmol) in dry toluene (2 mL) was added over 3 h using a syringe pump to a refluxing solution of **80a** (1 mmol) and alkene **77a**, **77b** or **77J** (3 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon overnight, followed by concentration under reduced pressure and purification by flash column chromatography (SiO_2 , hexane-EtOAc) to give product **80a**.

9,9,10,10-Tetrafluorooctadecane (80aa): colorless solid (198 mg, 61% yield); R_f 0.93



(hexane); mp 34-36 $^\circ\text{C}$; ^1H NMR: δ 0.94-1.08 (m, 6H, $2\times\text{CH}_3$), 1.25-1.54 (m, 14H), 1.61-1.80 (m, 2H), 1.95-2.16 (m, 2H), 2.22-2.34 (m, 10H); ^{13}C NMR (100 MHz): δ 14.0, 20.5, 22.6, 29.1, 29.3, 29.4, 31.8, 119.3 (tt, $^1J_{\text{CF}} = 250.2$, $^2J_{\text{CF}} = 37.7$, CF_2); ^{19}F NMR: δ -116.3 to -116.0 (m, 4F); MS (EI): m/z 43 (100%), 57 (87), 71 (48), 85 (29), 123 (18); HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{34}\text{F}_4$ $[\text{M}-\text{H}]^-$ 325.2512, found 325.2518.

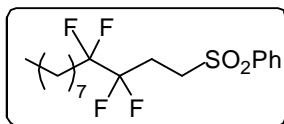
9,9,10,10-Tetrafluorodocosane (80ab): colorless solid (156 mg, 41% yield); recrystallized



from n -pentane; mp 32-34 $^\circ\text{C}$; ^1H NMR: δ 0.78-0.92 (m, 6H, $2\times\text{CH}_3$), 1.11-1.44 (32H), 1.46-1.60 (2H), 1.82-2.03 (2H); ^{13}C NMR (100 MHz): δ

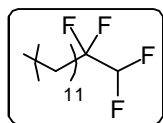
14.1, 20.5, 22.7, 29.0-29.6 (m), 31.8, 31.9, 33.8; ^{19}F NMR: δ -116.1 (s, 4F); MS (EI): m/z 382 (1%) $[\text{M}]^+$, 57 (100), 43 (69), 71 (54), 85 (32), 98 (10), 297 (6); HRMS (EI): m/z calcd for $\text{C}_{22}\text{H}_{42}\text{F}_4$ $[\text{M}-\text{H}]^-$ 381.3144, found 381.3152;

(3,3,4,4-Tetrafluorododecylsulfonyl)benzene (80aj): colorless oil (191 mg, 50% yield); R_f



0.62 (hexane); ^1H NMR: δ 0.84–0.92 (m, 3H, CH_3), 1.18–1.44 (m, 10H), 1.47–1.58 (m, 2H), 1.90–2.10 (m, 2H), 2.40–2.56 (m, 2H), 3.28–3.36 (m, 2H), 7.58–7.64 (m, $2H_{\text{Ar}}$), 7.68–7.74 (m, $1H_{\text{Ar}}$), 7.92–7.96 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 14.0, 17.5, 20.3, 24.4 (t, $^2J_{\text{CF}} = 23.6$), 29.0, 29.7 (t, $^2J_{\text{CF}} = 22.7$), 31.7, 128.0, 129.5, 134.2, 138.5; ^{19}F NMR: δ -115.4 to -115.3 (m, 2F), -115.0 to -114.9 (m, 2F); MS (EI): m/z 382 (4%) $[\text{M}]^+$, 142 (100), 200 (85), 77 (79), 116 (27), 125 (19), 43 (19), 158 (12), 169 (12); HRMS (CI): m/z calcd for $\text{C}_{18}\text{H}_{27}\text{F}_4\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 383.1668, found 383.1672

1,1,2,2-Tetrafluorotetradecane (81b).



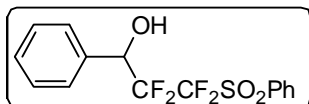
A solution of $n\text{-Bu}_3\text{SnH}$ (470 μL , 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 1 h using a syringe pump to a refluxing solution of **78b** (338mg, 1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon for 4 h, followed by concentration under reduced pressure and purification by flash column chromatography (SiO_2 , hexane-EtOAc) to give product **81b** as a colorless liquid (135 mg, 53% yield); ^1H NMR: δ 0.75–0.95 (m, 3H, CH_3), 1.06–1.43 (m, 20H), 1.46–1.60 (m, 2H), 5.69 (tt, $^2J_{\text{HF}} = 54.0$, $^3J_{\text{HF}} = 2.90$, CF_2H); ^{13}C NMR (100 MHz): δ 14.1, 20.3, 22.7, 29.3, 29.5, 31.9, 110.2 (tt, $^1J_{\text{CF}} = 249.0$, $^2J_{\text{CF}} = 41.5$, CF_2H); ^{19}F NMR: δ -116.7 (s, 2F), -136.6 (s, 2F); MS (EI): m/z 270 (3%) $[\text{M}]^+$, 57 (100), 43 (87), 71 (48), 85 (29), 171 (18), 185 (16); HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{26}\text{F}_4$ $[\text{M}-\text{H}]^-$ 269.1892, found 269.1895.

General procedure for the synthesis of compounds 83.

CsF (190 mg, 1.25 mmol) was suspended in dry DMF (15 mL) under argon in an oven-dried Schlenk flask. The reaction mixture was cooled down to -60 $^\circ\text{C}$ and the carbonyl-containing compound (5 mmol) was added, followed by addition of **56** (1 mmol) in DMF (7 mL). The mixture was stirred at -50 $^\circ\text{C}$ and monitored by GCMS until **56** was fully consumed (1–4 h). In case the silylated adduct **82** was present, 1M HCl (8 mL) was added. The mixture was warmed up to room temperature, quenched with aqueous NH_4Cl (10 mL), extracted to Et_2O

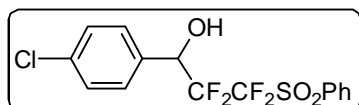
(3×15 mL), dried over MgSO₄ and evaporated to dryness. Product **83** was purified by flash column chromatography (SiO₂, hexane-EtOAc).

2,2,3,3-Tetrafluoro-1-phenyl-3-(phenylsulfonyl)propan-1-ol (83a): white solid (243 mg,



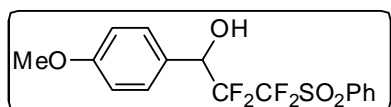
70% yield); mp 82–84 °C; *R_f* 0.07 (hexane-EtOAc, 95:5); ¹H NMR: δ 3.15–3.25 (br s, 1H, OH), 5.38 (dt, ³*J*_{HF} = 19.8, ⁴*J*_{HF} = 4.6, 1H, CH), 7.35–7.44 (m, 3*H*_A), 7.45–7.53 (m, 2*H*_{Ar}), 7.61–7.71 (m, 2*H*_{Ar}), 7.78–7.86 (m, 1*H*_{Ar}), 8.00–8.08 (m, 2*H*_{Ar}); ¹³C NMR (100 MHz): δ 72.2 (dd, ²*J*_{CF} = 28.6, 22.1, CH), 115.2 (ddt, ¹*J*_{CF} = 266.6, 257.9, ²*J*_{CF} = 25.6, CF₂), 116.2 (tt, ¹*J*_{CF} = 300.9, ²*J*_{CF} = 34.8, CF₂), 128.1, 128.4, 129.4, 129.5, 131.0, 132.4, 133.8, 136.2; ¹⁹F NMR: δ –124.5 (dd, 1F, ²*J*_{FF} = 280.3, ³*J*_{FF} = 6.3), –113.1 (dd, 1F, ²*J*_{FF} = 280.3, ³*J*_{FF} = 10.0), –111.6 (dd, 1F, ²*J*_{FF} = 254.3, ³*J*_{FF} = 6.3), –110.6 (d, 1F, ²*J*_{FF} = 254.3); IR (film): *v*_{max} (cm^{–1}) 3534, 3068, 1602, 1584, 1450, 1357, 1315, 1165, 1075, 1066, 1028, 999, 756, 597, 542; MS (EI): *m/z* 348 (0.2%) [*M*]⁺, 248 (9), 187 (14), 107 (100), 77 (48), 51 (14); HRMS (ESI): *m/z* calcd for C₁₅H₁₂F₄O₃SNa [*M*+Na]⁺ 371.03355, found 371.03354.

1-(4-Chlorophenyl)-2,2,3,3-tetrafluoro-3-(phenylsulfonyl)propan-1-ol (83b): white solid



(214 mg, 56% yield); m.p. 118–120 °C; *R_f* 0.10 (hexane-EtOAc, 85:15); ¹H NMR: δ 3.35 (br s, 1H, OH), 5.38 (dd, ³*J*_{HF} = 19.6, ⁴*J*_{HF} = 4.8, 1H, CH), 7.31–7.47 (m, 4*H*_{Ar}), 7.59–7.71 (m, 2*H*_{Ar}), 7.74–7.85 (m, 1*H*_{Ar}), 7.97–8.09 (m, 2*H*_{Ar}); ¹³C NMR (100 MHz): δ 71.5 (dd, ²*J*_{CF} = 28.4, 22.2, CH), 115.1 (tt, ¹*J*_{CF} = 268.4, ²*J*_{CF} = 25.3, CF₂), 116.1 (tt, ¹*J*_{CF} = 301.1, ²*J*_{CF} = 34.0, CF₂), 128.6, 129.5, 129.6, 131.0, 132.1, 132.2, 135.4, 136.3; ¹⁹F NMR: δ –124.7 (dd, 1F, ²*J*_{FF} = 280.4, ³*J*_{FF} = 5.5), –112.8 (d, 1F, ²*J*_{FF} = 280.4), –119.6 (dd, 1F, ²*J*_{FF} = 254.3, ³*J*_{FF} = 5.5), –110.6 (d, 1F, ²*J*_{FF} = 254.3); IR (film): *v*_{max} (cm^{–1}) 3569, 3523, 3034, 1598, 1582, 1493, 1450, 1416, 1357, 1315, 1288, 1160, 1112, 1091, 1075, 999, 847, 756, 598, 534; MS (EI): *m/z* 382 (0.15%) [*M*]⁺, 282 (6), 221 (10), 141 (100), 77 (62), 51 (14); HRMS (CI): *m/z* calcd for C₁₅H₁₂ClF₄O₃S [*M*–OH] 365.0026, found 365.0038.

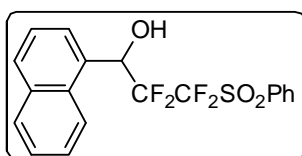
2,2,3,3-Tetrafluoro-1-(4-methoxyphenyl)-3-(phenylsulfonyl)propan-1-ol (83c): white



solid (193 mg, 51% yield); mp 154–156 °C; *R_f* 0.04 (hexane-EtOAc, 90:10); ¹H NMR: δ 3.50 (br s, 1H, OH), 3.82 (s, 3H, OCH₃), 5.32 (dd, ³*J*_{HF} = 19.2, ⁴*J*_{HF} = 5.2, 1H, CH), 6.85–6.98 (m, 2*H*_{Ar}), 7.35–7.47 (m, 2*H*_{Ar}), 7.59–7.71 (m, 2*H*_{Ar}), 7.76–7.86 (m, 1*H*_{Ar}),

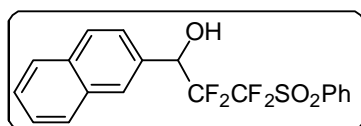
7.96–8.10 (m, 2 H_{Ar}); ^{13}C NMR (100 MHz): δ 55.2 (s, OCH₃), 71.8 (dd, $^2J_{CF}$ = 28.5, 22.0, CH), 113.7, 126.3, 129.4, 130.9, 136.0, 160.3; ^{19}F NMR: δ –124.6 (d, 1F, $^2J_{FF}$ = 280.0), –113.4 (d, 1F, $^2J_{FF}$ = 280.0), –111.5 (d, 1F, $^2J_{FF}$ = 255.5), –110.7 (d, 1F, $^2J_{FF}$ = 255.5); IR (film): ν_{max} (cm⁻¹) 3527, 3451, 2841, 1613, 1584, 1515, 1450, 1358, 1315, 1255, 1169, 1076, 1068, 1031, 999, 846, 758, 685, 634, 597, 534; MS (EI): m/z 378 (2%) [M]⁺, 207 (11), 149 (23), 137 (100), 77 (29); HRMS (ESI): m/z calcd for C₁₆H₁₃F₄O₃S [M–OH] 361.0522, found 361.0532.

2,2,3,3-Tetrafluoro-1-(naphthalene-1-yl)-3-(phenylsulfonyl)propan-1-ol (83d): yellow oil



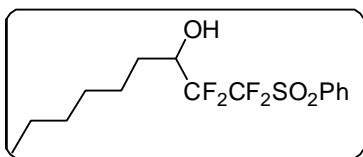
(159 mg, 40% yield); R_f 0.1 (hexane-EtOAc, 90:10); 1H NMR: δ 3.46 (br s, 1H, OH), 6.32 (d, 1H, $^3J_{HF}$ = 20.8, CH), 7.42–7.65 (m, 5 H_{Ar}), 7.69–7.77 (m, 1 H_{Ar}), 7.82–7.91 (m, 3 H_{Ar}), 7.98–8.10 (m, 3 H_{Ar}); ^{13}C NMR (100 MHz): δ 67.7 (dd, $^2J_{CF}$ = 30.0, 21.7, CH), 115.8 (ddt, $^1J_{CF}$ = 259.0, $^2J_{CF}$ = 26.5, $^2J_{CF}$ = 25.4, CF₂), 116.7 (ddt, $^1J_{CF}$ = 301.5, $^2J_{FF}$ = 32.2, $^2J_{FF}$ = 35.0, CF₂), 123.1, 125.1, 125.7, 126.7, 126.8, 129.5, 129.9, 129.9, 130.1, 130.9, 131.4, 132.2, 133.5, 136.2; ^{19}F NMR: δ –125.3 (dd, 1F, $^2J_{FF}$ = 280.8, $^3J_{FF}$ = 7.6), –112.0 (ddd, 1F, $^2J_{FF}$ = 253.0, $^3J_{FF}$ = 7.6, 2.7), –110.8 (dd, 1F, $^2J_{FF}$ = 280.8, $^3J_{FF}$ = 2.7), –110.6 (dd, 1F, $^2J_{FF}$ = 253.0, $^3J_{FF}$ = 2.7); IR (film): ν_{max} (cm⁻¹) 3536, 3066, 1624, 1598, 1583, 1514, 1450, 1356, 1315, 1163, 1122, 1075, 1061, 999, 816, 757, 596, 537; MS (EI): m/z 398 (8%) [M]⁺, 281 (23), 207 (100), 157 (85), 129 (40), 77 (21); HRMS (CI): m/z calcd for C₁₉H₁₅O₃F₄S [M+H]⁺ 399.0678, found 399.0670.

2,2,3,3-Tetrafluoro-1-(naphthalen-2-yl)-3-(phenylsulfonyl)propan-1-ol (83e): white solid



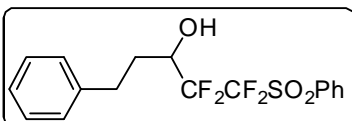
(223 mg, 56% yield); mp 106–110 °C; R_f 0.12 (hexane-EtOAc, 85:15); 1H NMR: δ 3.18 (br s, 1H, OH), 5.58 (dd, 1H, $^3J_{HF}$ = 19.8, $^4J_{HF}$ = 6.0, CH), 7.47–8.13 (m, 12 H_{Ar}); ^{13}C NMR (100 MHz): δ 72.4 (dd, $^2J_{CF}$ = 28.5, 22.1, CH), 112.5–119.5 (m, CF₂CF₂), 125.1, 126.4, 126.7, 127.7, 128.0, 128.2, 128.3, 129.6, 131, 131.2, 132.3, 132.9, 133.7, 136.2; ^{19}F NMR: δ –124.4 (dd, 1F, $^2J_{FF}$ = 279.6, $^3J_{FF}$ = 6.6), –112.4 (d, 1F, $^2J_{FF}$ = 279.6), –111.9 (ddd, 1F, $^2J_{FF}$ = 254.0, $^3J_{FF}$ = 6.6, 2.3), –110.5 (dd, 1F, $^2J_{FF}$ = 254.0, $^3J_{FF}$ = 2.3); IR (film): ν_{max} (cm⁻¹) 3612, 3560, 3067, 1604, 1585, 1577, 1512, 1479, 1450, 1376, 1355, 1314, 1270, 1186, 1168, 1154, 1130, 1126, 1095, 1063, 1024, 999, 964, 952, 881, 861, 625, 596, 557, 520, 478; MS (EI): m/z 398 (18%) [M]⁺, 157 (100), 129 (58), 77 (18); HRMS (CI): m/z calcd for C₁₉H₁₄O₃SF₄ [M]⁺ 398.0600, found 398.0596.

1,1,2,2-Tetrafluoro-1-(phenylsulfonyl)nonan-3-ol (83f): colorless oil (182 mg, 51% yield);



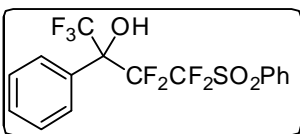
R_f 0.18 (hexane-EtOAc, 85:15); ^1H NMR: δ 0.76–0.98 (m, 3H, CH_3), 1.22–1.43 (m, 7H, $3\times\text{CH}_2$, CH^aH^b), 1.57–1.68 (m, 2H, CH_2), 1.71–1.83 (m, 1H, CH^aH^b), 2.17 (br s, 1H, OH), 4.19–4.34 (m, 1H, CHOH), 7.62–7.72 (m, $2H_{\text{Ar}}$), 7.79–7.89 (m, $1H_{\text{Ar}}$), 8.01–8.09 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 14.0 (s, CH_3), 22.6 (s, CH_2), 25.1 (s, CH_2), 28.6 (s, CH_2), 31.6 (s, CH_2), 70.4 (dd, $^2J_{\text{CF}} = 27.5$, 23.2, CH), 129.5, 131.0, 132.3, 136.2; ^{19}F NMR: δ -125.9 (dd, 1F, $^2J_{\text{FF}} = 278.5$, $^3J_{\text{FF}} = 6.0$), -115.9 (dd, 1F, $^2J_{\text{FF}} = 278.5$, $^3J_{\text{FF}} = 2.8$), -112.5 (dd, 1F, $^2J_{\text{FF}} = 254.2$, $^3J_{\text{FF}} = 6.0$), -110.6 (d, 1F, $^2J_{\text{FF}} = 254.2$, $^3J_{\text{FF}} = 2.8$); IR (film): ν_{max} (cm^{-1}) 3536, 3070, 2958, 2931, 1860, 1584, 1468, 1359, 1315, 1176, 1095, 1076, 1024, 757, 685, 597, 538; MS (EI): m/z 256 (19), 195 (18), 141 (100), 115 (37), 97 (41), 77 (96), 55 (37); HRMS (CI): m/z calcd for $\text{C}_{15}\text{H}_{21}\text{F}_4\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 357.1148, found 357.1156.

1,1,2,2-Tetrafluoro-5-phenyl-1-(phenylsulfonyl)pentan-3-ol (83g): yellow oil (192 mg,



51% yield); R_f 0.24 (hexane-EtOAc, 85:15); ^1H NMR: δ 1.93–2.13 (m, 2H, CH_2), 2.74 (m, $2H_r$, CH_2), 2.98 (m, 1H, OH), 4.27 (m, 1H, CHOH), 7.20–7.34 (m, $5H_{\text{Ar}}$), 7.64–7.81 (m, $3H_{\text{Ar}}$), 8.00 (d, 2H, $^3J_{\text{HH}} = 7.7$, H_{Ar}); ^{13}C NMR (100 MHz): δ 30.2 (CH_2), 31.1 (CH_2), 69.5 (dd, $^2J_{\text{CF}} = 27.6$, 23.3, CH), 112.9–119.5 (m, CF_2CF_2), 126.2, 128.5, 128.6, 129.6, 131.0, 132.1, 136.2, 140.7; ^{19}F NMR: δ -125.6 (ddd, 1F, $^2J_{\text{FF}} = 278.9$, $^3J_{\text{FF}} = 6.6$, 3.3), -115.8 (ddd, 1F, $^2J_{\text{FF}} = 278.9$), -112.6 (ddd, 1F, $^2J_{\text{FF}} = 254.5$, $^3J_{\text{FF}} = 6.6$, 2.8), -110.8 (dd, 1F, $^2J_{\text{FF}} = 254.6$, $^3J_{\text{FF}} = 3.3$); MS (EI): m/z 376 (9%) $[\text{M}]^+$, 215 (23), 197 (100), 91 (69), 77 (43); HRMS (CI): m/z calcd for $\text{C}_{17}\text{H}_{17}\text{O}_3\text{SF}_4$ $[\text{M}+\text{H}]^+$ 377.0835, found 377.0838.

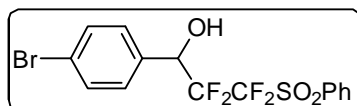
1,1,1,3,3,4,4-Heptafluoro-2-phenyl-4-(phenylsulfonyl)butan-2-ol (83j): white solid (200



mg, 48% yield); mp 107–109 °C; R_f 0.12 (hexane-EtOAc, 90:10); ^1H NMR: δ 4.50 (br s, 1H, OH), 7.50–7.58 (m, $3H_{\text{Ar}}$), 7.67–7.76 (m, $2H_{\text{Ar}}$), 7.80–7.93 (m, $3H_{\text{Ar}}$), 8.02–8.12 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 115.5–116.0 (m, CF_2), 116.1 (tt, $^1J_{\text{CF}} = 300.0$, $^2J_{\text{CF}} = 27.6$, CF_2), 118.8 (m, CF_3), 121.6, 126.8, 128.3, 129.5, 129.9, 131.0, 132.6, 136.1; ^{19}F NMR: δ -114.5 to -113.5 (m, 1F), -112.8 to -111.8 (m, 1F), -108.9 to -107.9 (m, 1F), -107.0 to -106.1 (m, 1F), -74.3 to -74.1 (m, 3F, CF_3); IR (film): ν_{max} (cm^{-1}) 3471, 1584, 1501, 1451, 1361, 1350, 1315, 1188, 1156, 1078, 997, 757, 705, 683, 589, 529; MS (EI): m/z 416 (1%) $[\text{M}]^+$, 347 (16), 175 (100),

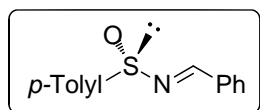
141 (44), 105 (62), 77 (96), 51 (23); HRMS (CI): m/z calcd for $C_{16}H_{12}F_7O_3S$ $[M+H]^+$ 417.0395, found 417.0392.

1-(4-Bromophenyl)-2,2,3,3-tetrafluoro-3-(phenylsulfonyl)propan-1-ol (83k): white solid



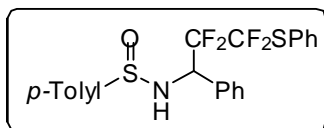
(303 mg, 71% yield); mp 112–114 °C; R_f 0.21 (hexane-EtOAc, 85:15); 1H NMR: δ 5.29 (s, 1H, OH), 5.37 (dd, $^3J_{HF} = 19.5$, $^3J_{HF} = 4.9$, 1H, CHOH), 7.35–7.40 (m, $2H_{Ar}$), 7.45–7.57 (m, $2H_{Ar}$), 7.61–7.67 (m, $2H_{Ar}$), 7.78–7.86 (m, $1H_{Ar}$), 7.98–8.06 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 71.5 (dd, $^2J_{CF} = 28.5$, 22.3, CH), 115.0 (ddt, $^1J_{CF} = 267.3$, 258.4, $^2J_{CF} = 25.0$, CF_2), 116.0 (tt, $^1J_{CF} = 301.0$, $^2J_{CF} = 32.8$, CF_2), 123.5, 129.6, 129.7, 131.0, 131.5, 132.1, 132.8, 136.3; ^{19}F NMR: δ -124.7 (dd, 1F, $^2J_{FF} = 280.4$, $^3J_{FF} = 6.3$), -112.8 (d, 1F, $^2J_{FF} = 280.4$), -111.9 (dd, 1F, $^2J_{FF} = 254.2$, $^3J_{FF} = 6.3$), -110.6 (d, 1F, $^2J_{FF} = 254.2$); IR (film): ν_{max} (cm^{-1}) 3530, 1595, 1584, 1489, 1450, 1357, 1315, 1165, 1075, 1024, 1013, 999, 958, 684, 597, 542; MS (EI): m/z 427 $[M]^+$, 326 (7), 185 (100), 77 (77), 51 (20); HRMS (CI): m/z calcd for $C_{15}H_{10}F_4O_2SBr$ $[M-OH]$ 408.9521, found 408.9557.

(S)-(+)-N-Benzylidene-p-toluenesulfinamide (85).¹²¹



In a 100 mL two-necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and argon inlet was placed (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (1.0 g, 3.4 mmol) dissolved in freshly distilled THF (15 mL) and the mixture cooled to -78 °C. A solution of LiHMDS (4.4 mmol, 1.0 M solution in 3.5 mL of THF) was added dropwise via syringe, and the reaction mixture was allowed to warm to rt. After 22 h the reaction mixture was cooled to -78 °C, and benzaldehyde (386 μ L, 3.8 mmol) was added via syringe. After being stirred for 2 h at -78 °C, the reaction mixture was quenched with water (4 mL), diluted with ethyl ether (35 mL), and warmed to rt. The organic layer was washed with water (2 \times 30 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated to give oil that was crystallized from *n*-pentane to give a light yellow solid (200 mg) of **85**. The mother liquor was concentrated, and a second crop of crystals was obtained. This process was repeated three times to give a total yield of 630 mg (76% yield) of **85**. Spectroscopic data were identical to those reported in the literature.¹²² 1H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.32 (d, $2H_{Ar}$, $^3J_{HH} = 8.0$), 7.41–7.51 (m, 3H), 7.64 (d, $2H_{Ar}$, $^3J_{HH} = 8.0$), 7.83–7.86 (m, $2H_{Ar}$), 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 124.7, 128.8, 129.5, 129.7, 132.5, 133.7, 141.6, 160.5.

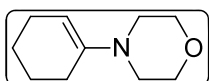
4-Methyl-*N*-(2,2,3,3-tetrafluoro-1-phenyl-3-(phenylthio)propyl)benzenesulfonamide



(86).

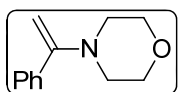
A solution of AcONBu₄ (302 mg, 1 mmol) in dry DMF (2 mL) was added to (*S*)-(+)-*N*-Benzyldene-*p*-toluenesulfonamide (**85**) (243 mg, 1 mmol) and **53** (565 mg, 2 mmol) in dry DMF (8 mL) at -40 °C. The reaction mixture was stirred at this temperature for 2 h, and then allowed to warm up to room temperature within 1 h. Aqueous saturated NH₄Cl solution (10 mL) was added and the mixture was extracted with Et₂O, the combined organic phase was washed with brine, water, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with hexane–EtOAc (95:5) to give 90 mg (20% yield, dr 83:17) of **86**. Pale yellow solid, *R_f* 0.04 (hexane–EtOAc, 95:5); ¹H NMR: δ 2.37 (s, 3H, CH₃, major), 2.43 (s, 3H, CH₃, minor), 4.58–4.72 (m, 1H, major), 4.72–4.78 (m, 1H, minor), 4.98–5.12 (m, 2H, major + minor), 7.10–7.70 (m, 28H_{Ar}, major + minor); ¹³C NMR (100 MHz): δ (major) 21.3, 58.6 (dd, ²*J*_{CF} = 24.4, 22.5, CH), 125.6, 128.4, 128.6, 128.9, 129.2, 129.4, 130.5, 134.6, 137.2, 141.3, 141.7; ¹⁹F NMR: δ -117.5 (dt, ²*J*_{FF} = 266.0, ³*J*_{FF} = 4.5, 1F, minor), -115.5 (dt, ²*J*_{FF} = 268.4, ³*J*_{FF} = 4.5, 1F, major), -114.5 (dt, ²*J*_{FF} = 268.4, ³*J*_{FF} = 4.5, 1F, major), -113.8 (dt, ²*J*_{FF} = 266.0, ²*J*_{FF} = 4.5, 1F, minor), -85.3 (t, ³*J*_{FF} = 4.5, 2F, minor), -84.8 (t, ³*J*_{FF} = 4.5, 2F, major); MS (EI): *m/z* 436 (15), 416 (11), 294 (12), 153 (11), 139 (12), 125 (100), 111 (50), 104 (30); HRMS (EI): *m/z* calcd for C₂₂H₁₉F₄NaOS₂ [M+Na]⁺ 476.07364, found 476.07365.

4-(Cyclohex-1-en-1-yl)morpholine (**89a**).¹²³



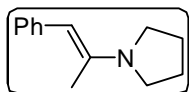
A solution of freshly distilled cyclohexanone (3.9 mL, 37.5 mmol), morpholine (6.6 mL, 75 mmol) and dry *p*-toluenesulfonic acid (71 mg, 0.4 mmol) in toluene (25 mL) was heated to boiling in a 100 mL round-bottomed flask to which was attached a water separator (a Dean-Stark trap) under a reflux condenser. The reaction mixture was stirred for 5 h at reflux under argon, then cooled down to room temperature. Distillation of the crude product gave **89a** (4.66 g, 74% yield) as a colorless liquid at 118–120°/10 Torr. ¹H NMR data were identical to those reported in the literature¹²⁴. ¹H NMR: δ 1.53–1.73 (m, 4H), 2.00–2.10 (m, 4H), 2.78 (t, 4H, ³*J*_{HH} = 4.8), 3.74 (t, 4H, ³*J*_{HH} = 4.8), 4.68 (t, 1H, ³*J*_{HH} = 3.8).

4-(1-Phenylvinyl)morpholine (**89b**).¹²⁵



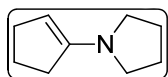
Solution of titanium chloride (660 μL , 6.0 mmol) in hexane (5 mL) was added dropwise to the cold (0 $^{\circ}\text{C}$) solution of morpholine (3.37 mL, 38.7 mmol) in hexane (10 mL). After the addition was complete, acetophenone (1 mL, 8.6 mmol) was added in one portion. The reaction mixture was stirred for 20 h at room temperature under argon. The reaction mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure. Distillation of the crude product gave **89b** (1.1 g, 69% yield) as a light yellow oil at 110–112 $^{\circ}$ /3 Torr. ^1H NMR data were identical to those reported in the literature.¹²⁶ ^1H NMR: 2.80 (t, 4H, $^3J_{\text{HH}} = 4.8$), 3.74 (t, 4H, $^3J_{\text{HH}} = 4.8$), 4.21 (s, 1H), 4.35 (s, 1H), 7.30–7.34 (m, 3H), 7.46–7.48 (m, 2H).

1-(1-Phenylprop-1-en-2-yl)pyrrolidine (**89c**).



Prepared according to the general procedure.¹²⁵ Solution of titanium chloride (1.64 mL, 15 mmol) in hexane (10 mL) was added dropwise to the cold (0 $^{\circ}\text{C}$) solution of pyrrolidine (4.7 mL, 50 mmol) in hexane (20 mL). After the addition was complete, phenylacetone (1.5 mL, 10 mmol) was added in one portion. The reaction mixture was stirred for 2 h at room temperature under argon. The reaction mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure. Distillation of the crude product gave **89c** (1.2 g, 64% yield) as yellow oil at 108–110 $^{\circ}$ /3 Torr. ^1H NMR: δ 1.89–1.96 (m, 4H), 2.10 (s, 3H, CH_3), 3.22–3.33 (m, 4H), 5.12 (s, 1H), 6.98–7.02 (m, 1 H_{Ar}), 7.12–7.16 (m, 2 H_{Ar}), 7.20–7.26 (m, 2 H_{Ar}). ^{13}C NMR (100 MHz): δ 16.8, 25.2, 47.8, 96.8, 123.0, 127.9, 128.3, 140.7; MS data were identical to those reported in the literature.¹²⁷ MS (EI): m/z 187 (100%) [M] $^+$, 115 (34), 91 (20), 68 (87).

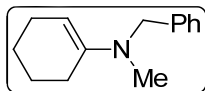
1-(Cyclopent-1-en-1-yl)pyrrolidine (**89d**).



Prepared according to the general procedure.¹²⁵ Solution of titanium chloride (2.8 mL, 25.5 mmol) in hexane (10 mL) was added dropwise to the cold (0 $^{\circ}\text{C}$) solution of pyrrolidine (7.07 mL, 85 mmol) in hexane (30 mL). After the addition was complete, cyclopentanone (1.5 mL, 17 mmol) was added in one portion. The reaction mixture was stirred for 5 h at room temperature under argon. The reaction mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure. Distillation of the crude product gave **89d** (1.86 g, 80% yield) as colorless oil at 70–72 $^{\circ}$ /3 Torr. Spectroscopic data were identical to those reported in the literature.¹²⁸ ^1H NMR: δ 1.78–1.85

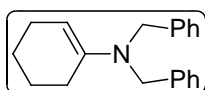
(m, 6H), 2.29–2.32 (m, 2H), 2.37–2.41 (m, 2H), 3.00–3.03 (m, 4H), 4.00 (s, 1H). ^{13}C NMR (100 MHz): δ 23.2, 25.3, 30.8, 33.0, 48.9, 92.2, 149.4.

***N*-Benzyl-*N*-methylcyclohex-1-enamine (89e).**



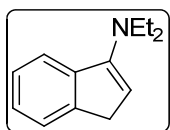
Prepared according to the general procedure.¹²⁵ Solution of titanium chloride (2.3 mL, 21 mmol) in hexane (10 mL) was added dropwise to the cold (0 °C) solution of benzylmethyl amine (7.47 mL, 56 mmol) in hexane (30 mL). After the addition was complete, cyclohexanone (1.5 mL, 14 mmol) was added in one portion. The reaction mixture was stirred for 26 h at room temperature under argon. The reaction mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure. Distillation of the crude product gave **89e** (1.24 g, 44% yield) as colorless oil at 126–128°/3 Torr. Spectroscopic data were identical to those reported in the literature.¹²⁹ ^1H NMR: δ 1.54–1.61 (m, 2H), 1.68–1.75 (m, 2H), 2.09–2.16 (m, 2H), 2.20–2.25 (m, 2H), 2.52 (s, 3H), 4.1 (s, 2H), 4.5 (t, 1H, $^3J_{\text{HH}} = 3.9$), 7.27–7.34 (m, 5H).

***N,N*-Dibenzylcyclohex-1-enamine (89f).**



Prepared according to the general procedure.¹²³ A solution of 3.9 mL (37.5 mmol) of cyclohexanone (freshly distilled), 7.2 mL (37.5 mmol) of dibenzyl amine, and 71 mg (0.4 mmol) of dry *p*-toluenesulfonic acid in 25 mL of toluene was heated to boiling in a 100 mL round-bottomed flask to which was attached a water separator (a Dean-Stark trap) under a reflux condenser. The reaction mixture was stirred for 3 h at reflux under argon, then cooled down to room temperature. Compound **89f** could not be distilled without decomposition. Solvent was removed under reduced pressure and unreacted cyclohexanone and dibenzyl amine were removed at 46–48°C/3 Torr 145–147°C/3 Torr, respectively. Product **89f** was obtained as yellow oil (2.9 g, 28% yield). ^1H NMR: δ 1.50–1.60 (m, 2H), 1.65–1.77 (m, 2H), 1.81–1.93 (m, 2H), 2.23–2.30 (m, 2H), 3.62 (s, 4H), 4.20 (t, 1H, $^3J_{\text{HH}} = 3.7$); ^{13}C NMR (100 MHz): δ 26.2, 26.5, 28.6, 53.8, 57.7, 126.4, 128.0, 128.4, 141.2; MS (EI): m/z 277 (12%) $[\text{M}]^+$, 186 (100), 91 (69), 81 (5), 65 (12).

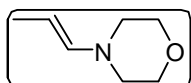
***N,N*-Diethyl-1*H*-inden-3-amine (89g).**



Prepared according to the general procedure.¹²⁵ Solution of titanium chloride (1.2 mL, 11.2 mmol) in hexane (7 mL) was added dropwise to the cold (0 °C) solution of diethyl amine (3.1 mL, 30 mmol) in hexane (20 mL). After the addition was complete, 1-indanone (1.0 g, 7.5 mmol) was added in one portion. The reaction

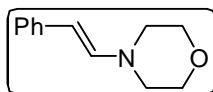
mixture was stirred for 26 h at room temperature under argon. The reaction mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure. Distillation of the crude product gave **89g** (490 mg, 35% yield) as yellow oil at 110–112°/3 Torr. ¹H NMR: δ 1.06 (t, 6H, ³J_{HH} = 7.08, N-CH₂), 3.14 (q, 4H, ³J_{HH} = 7.08, CH₃), 3.26 (d, 2H, ³J_{HH} = 2.4, CH₂), 5.4 (t, 1H, ³J_{HH} = 2.4, CH), 7.31-7.45 (m, 4H_{Ar}). MS (EI): *m/z* 187 (56%) [M]⁺, 172 (19), 158 (60), 144 (70), 130 (24), 115 (100), 103 (11).

4-(Prop-1-en-1-yl)morpholine (**89h**).¹³⁰



In a 100 mL flask was placed 4 mL (44 mmol) of morpholine and potassium carbonate (2.7 g, 20 mmol) and the mixture cooled to 0 °C. Propionaldehyde (1.5 mL, 20 mmol) was added dropwise via syringe over 1h period, and the reaction mixture was allowed to warm to rt. After being stirred for 40 h at rt under argon, the reaction mixture was filtered and the filter cake was washed with toluene. Morpholine was removed at reduced pressure to give **89h** as colorless liquid (2.3 g, 92% yield). Spectroscopic data were identical to those reported in the literature.¹³⁰ ¹H NMR: δ 5.78 (dq, ³J_{HH} = 14.0, ⁴J_{HH} = 1.4, 1H), 4.46 (dq, ³J_{HH} = 14, ³J_{HH} = 6.4, 1H), 3.71 (br m, 4H), 2.82 (t, ³J_{HH} = 4.8, 2H), 2.71 (t, ³J_{HH} = 4.8, 2H), 1.58 (dd, ³J_{HH} = 6.4, ⁴J_{HH} = 1.4, 3H).

4-Styrylmorpholine (**89i**).¹³¹



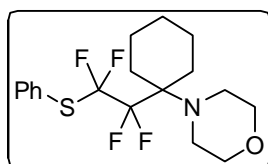
Molecular sieves (4 Å, 10 g) were added to a solution of phenylacetaldehyde (1 mL, 8.5 mmol) in CHCl₃ (40 mL) at rt. The solution was cooled to 0°C, then morpholine (897 μ L, 10.2 mmol) was added and the reaction mixture was stirred for 1h at 0 °C and 26 h at rt. The reaction mixture was then filtered and concentrated under reduced pressure. Morpholine was removed at reduced pressure to give **89i** as white solid (1.53 g, 95% yield). The physical and spectroscopic data were identical to those reported in the literature.¹³¹ Mp 58-60 °C; ¹H NMR: δ 3.02 (t, ³J_{HH} = 4.9, 2H), 3.80 (t, ³J_{HH} = 4.9, 2H), 5.44 (d, ³J_{HH} = 14.1, 1H), 6.61 (d, ³J_{HH} = 14.4, 1H), 7.02 (m, 1H), 7.28–7.04 (m, 4H).

General procedure for the synthesis of compounds **90** and **91**.

TFA (93 mL, 1.25 mmol) was added to a Schlenk flask containing a solution of **89** (1 mmol) and KHF₂ (59 mg, 0.75 mmol) in dry MeCN (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 5 min, and then **53** or **56** (1.5 mmol) was added to the reaction mixture. Ice bath was removed and the reaction mixture was stirred for appropriate time. Aqueous

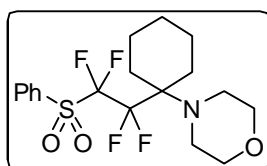
saturated Na₂CO₃ solution (5 mL) was added and the reaction mixture was extracted with Et₂O. The combined organic phase was washed with brine and water, dried (MgSO₄), and concentrated under vacuum. The crude product was purified by flash or column chromatography eluting with hexane–EtOAc to give pure product **90** or **91**

4-(1-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)cyclohexyl)morpholine (90a): white solid



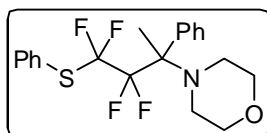
(208 mg, 68% yield); *R_f* 0.28 (hexane–EtOAc, 98:2); mp 82–84 °C; ¹H NMR: δ 1.11–1.31 (m, 1H), 1.36–1.65 (m, 6H), 1.65–1.75 (m, 1H), 1.96–2.12 (m, 2H), 2.77–2.98 (m, 4H), 3.28–3.96 (m, 4H), 7.32–7.51 (m, 3*H_{Ar}*), 7.57–7.69 (m, 2*H_{Ar}*); ¹³C NMR (100 MHz): δ 20.5 (CH₂), 25.9 (CH₂), 28.1 (t, ³*J_{CF}* = 3.3, CH₂), 46.7 (t, ³*J_{CF}* = 2.7, N-CH₂), 63.8 (t, ²*J_{CF}* = 19.7, N-C-CF₂), 68.4 (O-CH₂), 124.7, 129.0, 130.3, 137.3; ¹⁹F NMR: δ -110.3 (s, 2F), -82.4 (s, 2F); MS (EI): *m/z* 168 (100), 109 (4); HRMS (EI): *m/z* calcd for C₁₈H₂₄F₄S [M+H]⁺ 378.1515, found 378.1515.

4-(1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexyl)morpholine (91a): white



solid (341 mg, 93% yield); *R_f* 0.07 (hexane–EtOAc, 98:2); mp 98–100 °C; ¹H NMR: δ 1.11–1.28 (m, 1H), 1.38–1.63 (m, 6H), 1.65–1.75 (m, 1H), 1.94–2.10 (m, 2H), 2.77–2.98 (m, 4H), 3.17–4.00 (m, 4H), 7.56–7.66 (m, 2*H_{Ar}*), 7.71–7.81 (m, 1*H_{Ar}*), 7.93–8.05 (m, 2*H_{Ar}*); ¹³C NMR (100 MHz): δ 20.3, 25.6, 27.7 (t, ³*J_{CF}* = 3.2, CH₂), 46.6 (t, ³*J_{CF}* = 2.5, N-CH₂), 64.7 (tt, ²*J_{CF}* = 19.4, ³*J_{CF}* = 2.6, N-C-CF₂), 68.4, 117.0 (tt, ¹*J_{CF}* = 300.0, ²*J_{CF}* = 43.0, CF₂), 122.2 (tt, ¹*J_{CF}* = 264.0, ²*J_{CF}* = 31.8, CF₂), 129.3, 130.9, 134.8, 135.6; ¹⁹F NMR: δ -112.2 to -111.9 (m, 2F), -107.9 to -107.7 (m, 2F); MS (EI): *m/z* 168 (100), 77 (7); HRMS (EI): *m/z* calcd for C₁₈H₂₃F₄NO₃S [M+H]⁺ 410.1413, found 410.1404.

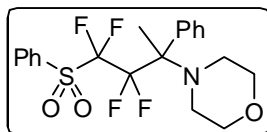
4-(3,3,4,4-Tetrafluoro-2-phenyl-4-(phenylthio)butan-2-yl)morpholine (90b): colorless oil



(138 mg, 43% yield); *R_f* 0.24 (hexane–EtOAc, 98:2); ¹H NMR: δ 1.74 (s, 3H, CH₃), 2.52–2.78 (m, 4H), 3.71–3.79 (m, 4H), 7.28–7.48 (m, 6*H_{Ar}*), 7.53–7.61 (m, 2*H_{Ar}*), 7.64–7.74 (m, 2*H_{Ar}*); ¹³C NMR (100 MHz): δ 13.8, 48.2, 67.4, 68.1 (t, ²*J_{CF}* = 19.8, N-C-CF₂), 119.2 (tt, ¹*J_{CF}* = 270.4, ²*J_{CF}* = 30.0, CF₂), 124.8, 126.0 (tt, ¹*J_{CF}* = 292.5, ²*J_{CF}* = 40.0, CF₂), 127.8, 128.0, 128.9, 129.0, 130.1, 137.1, 138.5; ¹⁹F NMR: δ -102.3 (d, ²*J_{FF}* = 268.1, 1F), -81.6 to -80.4 (m, 3F); MS (EI): *m/z*

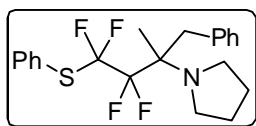
190 (100), 159 (6), 109 (3), 105 (4), 77 (6); HRMS (EI): m/z calcd for $C_{20}H_{22}F_4NOS$ $[M+H]^+$ 400.1358, found 400.1356.

4-(3,3,4,4-Tetrafluoro-2-phenyl-4-(phenylsulfonyl)butan-2-yl)morpholine (91b): pale



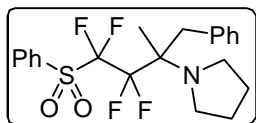
yellow solid (135 mg, 40% yield); R_f 0.29 (hexane–EtOAc, 98:2); mp 88–90 °C; 1H NMR: δ 1.61 (s, 3H, CH_3), 2.38–2.68 (m, 4H), 3.56–3.66 (m, 4H), 7.18–7.28 (m, $3H_{Ar}$), 7.45–7.58 (m, $4H_{Ar}$), 7.63–7.72 (m, $1H_{Ar}$), 7.82–7.92 (m, $2H_{Ar}$); ^{13}C NMR (125 MHz): δ 13.2, 47.9, 67.4, 68.9 (t, $^2J_{CF} = 18.7$, N-C- CF_2), 116.8 (tdd, $^1J_{CF} = 303.5$, $^2J_{CF} = 44.2$, 40.0, CF_2), 119.7 (tt, $^1J_{CF} = 262.7$, $^2J_{CF} = 27.6$, CF_2), 128.0, 128.2, 129.3, 130.9, 133.5, 137.6; ^{19}F NMR: δ -112.0 to -110.0 (m, 1F), -108.3 to -104.4 (m, 2F), -102.4 (d, $^2J_{FF} = 281.6$, 1F); MS (EI): m/z 190 (100), 105 (5), 77 (8); HRMS (CI): m/z calcd for $C_{20}H_{22}F_4NO_3S$ $[M+H]^+$ 432.1257, found 432.1255.

1-(3,3,4,4-Tetrafluoro-2-methyl-1-phenyl-4-(phenylthio)butan-2-yl)pyrrolidine (90c):



pale yellow oil (174 mg, 91% yield); R_f 0.71 (hexane–EtOAc, 95:5); 1H NMR: δ 1.29 (d, 3H, $^4J_{HF} = 3.6$, CH_3), 1.59–1.84 (m, 4H), 2.70–2.92 (m, 3H), 3.03–3.18 (m, 2H), 3.24–3.37 (m, 1H), 7.13–7.29 (m, $5H_{Ar}$), 7.34–7.48 (m, $3H_{Ar}$), 7.57–7.70 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 19.7, 24.9, 35.6, 46.6, 62.8 (t, $^2J_{CF} = 20.6$, N-C- CF_2), 120.0 (tt, $^1J_{CF} = 271.2$, $^2J_{CF} = 26.7$, CF_2), 125.5 (tt, $^1J_{CF} = 295.5$, $^2J_{CF} = 37.0$, CF_2), 126.3, 127.8, 128.9, 129.9, 131.2, 136.9; ^{19}F NMR: δ -112.6 (dd, $^2J_{FF} = 266.7$, $^3J_{FF} = 7.5$, 1F), -111.5 (ddd, $^2J_{FF} = 266.7$, $^3J_{FF} = 10.7$, 6.1, 1F), -85.8, (ddd, $^2J_{FF} = 219.9$, $^3J_{FF} = 10.7$, 7.5, 1F), -78.1 (dd, $^2J_{FF} = 219.9$, $^3J_{FF} = 6.1$, 1F); MS (EI): m/z 306 (100), 188 (35), 159 (4), 116 (15), 109 (3), 91 (6), 77 (3); HRMS (EI): m/z calcd for $C_{21}H_{24}F_4NS$ $[M+H]^+$ 398.1566, found 398.1552.

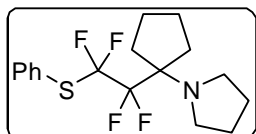
1-(3,3,4,4-Tetrafluoro-2-methyl-1-phenyl-4-(phenylsulfonyl)butan-2-yl)pyrrolidine



(91c): white solid (110 mg, 45% yield); R_f 0.8 (hexane–EtOAc, 80:20); mp 71–73 °C; 1H NMR: δ 1.19 (d, 3H, $^4J_{HF} = 1.1$, CH_3), 1.62–1.80 (m, 4H), 2.70–2.78 (m, 1H), 2.78–2.88 (m, 2H), 3.00–3.10 (m, 2H), 3.22–3.32 (m, 1H), 7.09–7.30 (m, $5H_{Ar}$), 7.58–7.68 (m, $2H_{Ar}$), 7.73–7.82 (m, $1H_{Ar}$), 7.98–8.10 (m, $2H_{Ar}$); ^{13}C NMR (150 MHz): δ 19.3, 24.4, 36.4, 46.6, 64.3 (t, $^2J_{CF} = 20.0$, N-C- CF_2), 117.3 (tt, $^1J_{CF} = 302.0$, $^2J_{CF} = 40.3$, CF_2), 121.4 (tdd, $^1J_{CF} = 267.0$, $^2J_{CF} = 30.9$, 26.9,

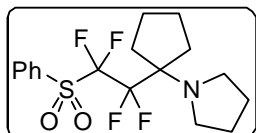
CF₂), 126.4, 127.9, 129.3, 130.9, 131.0, 133.9, 136.4, 135.5; ¹⁹F NMR: δ -111.2 (ddd, ²J_{FF} = 286.0, ³J_{FF} = 14.9, 7.2, 1F), -109.0 (ddd, ²J_{FF} = 251.3, ³J_{FF} = 14.9, 6.2, 1F), -107.3, (ddd, ²J_{FF} = 286.0, ³J_{FF} = 11.0, 6.2, 1F), -106.3 (ddd, ²J_{FF} = 251.3, ³J_{FF} = 11.0, 7.2, 1F); MS (EI): *m/z* 338 (100), 281 (13), 207 (40), 188 (45), 146 (23), 91 (12), 77 (18), 68 (17); HRMS (ESI): *m/z* calcd for C₂₁H₂₄F₄NO₂S [M+H]⁺ 430.1458, found 430.1458.

1-(1-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)cyclopentyl)pyrrolidine (90d): colorless oil



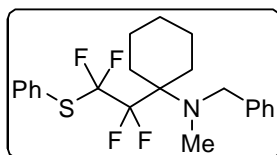
(304 mg, 68% yield); *R_f* 0.22 (hexane); ¹H NMR: δ 1.54–1.79 (m, 8H), 1.85–2.10 (m, 4H), 2.80–2.95 (m, 4H), 7.34–7.46 (m, 2*H_{Ar}*), 7.60–7.68 (m, 3*H_{Ar}*); ¹³C NMR (100 MHz): δ 24.4, 24.6, 31.0 (t, ³J_{CF} = 1.8, CH₂), 46.7 (t, ⁴J_{CF} = 1.7, N-CH₂), 70.2 (t, ²J_{CF} = 22.1, N-C-CF₂), 119.5 (tt, ¹J_{CF} = 263.6, ²J_{CF} = 29.4, CF₂), 125.7 (tt, ¹J_{CF} = 288.7, ²J_{CF} = 34.8, CF₂), 126.6, 128.8, 129.8, 136.8; ¹⁹F NMR: δ -111.3 (t, ³J_{FF} = 7.01, 2F), -83.8 (t, ³J_{FF} = 7.01, 2F); MS (EI): *m/z* 159 (1), 138 (100), 109 (5), 77 (3); HRMS (CI): *m/z* calcd for C₁₇H₂₂F₄NS [M+H]⁺ 348.1409, found 348.1411.

1-(1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclopentyl)pyrrolidine (91d): white



solid (222 mg, 41% yield); *R_f* 0.82 (hexane–EtOAc, 80:20); mp 118–120 °C; ¹H NMR: δ 1.51–1.75 (m, 8H), 1.82–2.03 (m, 4H), 2.64–2.83 (m, 4H), 7.61–7.72 (m, 2*H_{Ar}*), 8.00–8.08 (m, 3*H_{Ar}*); ¹³C NMR (100 MHz): δ 24.3, 24.7, 30.8, 46.4, 129.2, 129.6, 130.9, 135.4, 136.4; ¹⁹F NMR: δ -108.5 to -108.3 (m, 2F), -108.0 to -107.8 (m, 2F); MS (EI): *m/z* 138 (100), 77 (9); HRMS (CI): *m/z* calcd for C₁₇H₂₂F₄NO₂S [M+H]⁺ 380.1307, found 380.1306.

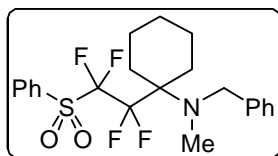
***N*-Benzyl-*N*-methyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)cyclohexanamine (90e):**



colorless oil (1.20 g, 70% yield); *R_f* 0.68 (hexane–EtOAc, 95:5); ¹H NMR: δ 1.16–1.33 (m, 1H), 1.43–1.57 (m, 2H), 1.60–2.84 (m, 5H), 2.16–2.29 (m, 2H), 2.38 (s, 3H, CH₃), 3.66–4.36 (br m, 2H, CH₂Ph), 7.16–7.26 (m, 1*H_{Ar}*), 7.28–7.52 (m, 7*H_{Ar}*), 7.59–7.73 (m, 2*H_{Ar}*); ¹³C NMR (100 MHz): δ 20.7, 25.8, 29.1 (t, ³J_{CF} = 2.6, CH₂), 34.4 (t, ⁴J_{CF} = 2.9, CH₃-N), 53.8 (t, ⁴J_{CF} = 3.0, CH₂Ph), 64.9 (tt, ²J_{CF} = 19.3, ³J_{CF} = 2.3, N-C-CF₂), 126.3, 127.6, 128.2, 129.1, 130.3, 137.4, 141.2; ¹⁹F NMR: δ -109.0 to -108.9 (m, 2F), -82.8 to -82.7 (m, 2F); MS (EI):

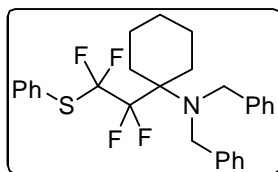
m/z 202 (100), 109 (5), 91 (40), 65 (3); HRMS (CI): m/z calcd for $C_{22}H_{26}F_4NS$ $[M+H]^+$ 412.1722, found 412.1730.

***N*-Benzyl-*N*-methyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine**



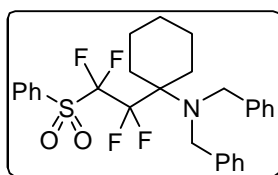
(91e): white solid (1.121 g, 66% yield); R_f 0.8 (hexane–EtOAc, 80:20); mp 116–118 °C; 1H NMR: δ 1.10–1.34 (m, 1H), 1.39–1.64 (m, 4H), 1.65–1.87 (m, 3H), 2.13–2.28 (m, 2H), 2.38 (s, 3H, CH_3), 3.67–4.34 (br m, 2H, CH_2Ph), 7.16–7.27 (m, $1H_{Ar}$), 7.28–7.39 (m, $4H_{Ar}$), 7.57–7.71 (m, $2H_{Ar}$), 7.73–7.85 (m, $1H_{Ar}$), 8.00–8.10 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 20.5, 25.6, 28.7 (t, $^3J_{CF} = 2.7$, CH_2), 34.2 (t, $^4J_{CF} = 2.8$, CH_3-N), 53.7 (t, $^4J_{CF} = 3.0$, CH_2Ph), 65.7 (tt, $^2J_{CF} = 19.1$, $^3J_{CF} = 2.3$, N-C- CF_2), 126.4, 127.5, 128.3, 129.3, 130.9, 133.9, 135.6, 140.7; ^{19}F NMR: δ -111.5 to -111.2 (m, 2F), -108.2 to -107.5 (m, 2F); MS (EI): m/z 202 (100), 91 (52); HRMS (CI): m/z calcd for $C_{22}H_{26}F_4NO_2S$ $[M+H]^+$ 444.1620, found 444.1628.

***N,N*-Dibenzyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)cyclohexanamine (90f):** colorless



oil (263 mg, 28% yield); R_f 0.18 (hexane); 1H NMR: δ 1.16–1.28 (m, 1H), 1.34–1.42 (m, 2H), 1.57–1.79 (m, 5H), 2.23–2.35 (m, 2H), 3.87 (s, 2H, CH_2Ph), 4.40 (s, 2H, CH_2Ph), 6.91–7.14 (m, $10H_{Ar}$), 7.34–7.51 (m, $3H_{Ar}$), 7.62–7.77 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 20.8, 25.6, 30.1 (t, $^3J_{CF} = 2.9$, CH_2), 54.5 (t, $^4J_{CF} = 2.8$, CH_2Ph), 67.1 (tt, $^2J_{CF} = 18.9$, $^3J_{CF} = 2.2$, N-C- CF_2), 121.7 (tt, $^1J_{CF} = 265.3$, $^2J_{CF} = 34.8$, CF_2), 124.7, 126.1, 126.7 (tt, $^1J_{CF} = 290.3$, $^2J_{CF} = 41.3$, CF_2), 127.6, 128.9, 129.1, 130.3, 137.4, 141.0; ^{19}F NMR: δ -82.5 (s, 2F), -107.1 (s, 2F); MS (EI): m/z 280 (3), 278 (100), 186 (6), 181 (7), 109 (6), 91 (40), 77 (2), 65 (4); HRMS (ESI): m/z calcd for $C_{28}H_{30}F_4NS$ $[M+H]^+$ 398.1566, found 488.2022.

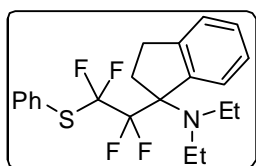
***N,N*-Dibenzyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (91f):**



white solid (200 mg, 20% yield); R_f 0.47 (hexane–EtOAc, 95:5); mp 138–140 °C; 1H NMR: δ 1.12–1.30 (m, 1H), 1.33–1.47 (m, 2H), 1.53–1.79 (m, 5H), 2.15–2.33 (m, 2H), 3.90 (s, 2H, CH_2Ph), 4.36 (s, 2H, CH_2Ph), 6.90–7.16 (m, $10H_{Ar}$), 7.58–7.70 (m, $2H_{Ar}$), 7.75–7.86 (m, $1H_{Ar}$), 7.97–8.12 (m, $2H_{Ar}$); ^{13}C NMR (100 MHz): δ 20.6, 25.5, 29.7 (t, $^3J_{CF} = 2.9$, CH_2), 54.2 (t, $^4J_{CF} = 3.1$, CH_2Ph), 67.8 (tt, $^2J_{CF} = 18.9$, $^3J_{CF} = 2.2$, N-C- CF_2), 117.5 (tt, $^1J_{CF} = 300.9$, $^2J_{CF} = 43.4$, CF_2), 122.8 (tt, $^1J_{CF} = 265.6$, $^2J_{CF} = 32.4$, CF_2), 126.2, 127.7, 128.9, 129.3, 130.9,

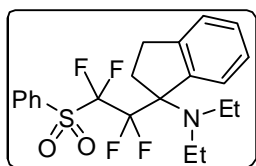
133.9, 135.6, 140.5; ^{19}F NMR: δ -82.5 to -109.6 (m, 2F), -107.7 to -107.5 (m, 2F); MS (EI): m/z 277 (11), 244 (8), 207 (12), 186 (94), 140 (34), 106 (11), 105 (3), 91 (100), 77 (58), 65 (17), 51 (19); HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{29}\text{F}_4\text{NNaO}_2\text{S}$ $[\text{M}+\text{Na}]^+$ 542.1747, found 542.1748.

***N,N*-Diethyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)-2,3-dihydro-1*H*-inden-1-amine**



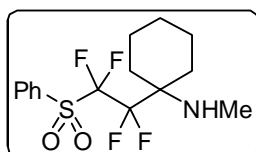
(90g): yellow oil (122 mg, 38% yield); R_f 0.36 (hexane-EtOAc, 95:5); ^1H NMR: δ 0.80 (t, $^3J_{\text{HH}} = 7.0$, 6H, $2\times\text{CH}_3$), 2.23–2.41 (m, 2H), 2.63–3.07 (m, 6H), 7.03–7.20 (m, $3H_{\text{Ar}}$), 7.22–7.37 (m, $3H_{\text{Ar}}$), 7.44–7.59 (m, $3H_{\text{Ar}}$); ^{13}C NMR (150 MHz): δ 15.2, 30.5, 32.0 (t, $^3J_{\text{CF}} = 2.2$, CH_2), 44.0 (t, $^4J_{\text{CF}} = 1.7$, N- CH_2), 119.2 (tt, $^1J_{\text{CF}} = 261.7$, $^2J_{\text{CF}} = 29.0$, CF_2), 120.2 (tt, $^1J_{\text{CF}} = 264.0$, $^2J_{\text{CF}} = 30.9$, CF_2), 124.6, 125.4, 127.7, 128.3, 129.0, 130.1, 137.2, 140.7, 145.0; ^{19}F NMR: δ -108.6 (dd, $^2J_{\text{FF}} = 273.6$, $^3J_{\text{FF}} = 7.4$, 1F), -106.5 (dd, $^2J_{\text{FF}} = 273.6$, $^3J_{\text{FF}} = 6.3$, 1F), -82.3, (dd, $^2J_{\text{FF}} = 217.4$, $^3J_{\text{FF}} = 7.4$, 1F), -80.6 (dd, $^2J_{\text{FF}} = 217.4$, $^3J_{\text{FF}} = 6.3$, 1F); MS (EI): m/z 188 (100), 159 (9), 115 (5), 109 (3), 77 (4); HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{24}\text{F}_4\text{NS}$ $[\text{M}+\text{H}]^+$ 398.1566, found 398.1557.

***N,N*-Diethyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)-2,3-dihydro-1*H*-inden-1-amine (91g):**



amine (91g): yellow oil (74 mg, 20% yield); R_f 0.8 (hexane-EtOAc, 80:20); ^1H NMR: δ 0.82 (t, $^3J_{\text{HH}} = 7.1$, 6H, $2\times\text{CH}_3$), 2.30–2.47 (m, 2H), 2.68–2.93 (m, 5H), 2.96–3.10 (m, 1H), 7.07–7.30 (m, $3H_{\text{Ar}}$), 7.38–7.47 (m, $1H_{\text{Ar}}$), 7.54–7.64 (m, $2H_{\text{Ar}}$), 7.68–7.80 (m, $1H_{\text{Ar}}$), 7.92–8.04 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 15.7, 30.3, 31.6 (t, $^3J_{\text{CF}} = 2.5$, CH_2), 44.3 (t, $^4J_{\text{CF}} = 2.1$, N- CH_2), 78.2 (tt, $^2J_{\text{CF}} = 20.3$, $^3J_{\text{CF}} = 2.2$, N-C- CF_2), 116.9 (tt, $^1J_{\text{CF}} = 301.9$, $^2J_{\text{CF}} = 43.6$, CF_2), 120.7 (tt, $^1J_{\text{CF}} = 263.2$, $^2J_{\text{CF}} = 33.8$, CF_2), 124.6, 125.6, 127.1, 128.5, 129.2, 130.8, 133.7, 135.4, 139.7, 145.0; ^{19}F NMR: δ -107.1 (dt, $^2J_{\text{FF}} = 249.7$, $^3J_{\text{FF}} = 3.5$, 1F), -106.9 (t, $^2J_{\text{FF}} = 249.7$, $^3J_{\text{FF}} = 3.5$, 2F), -105.2, (dt, $^2J_{\text{FF}} = 249.7$, $^3J_{\text{FF}} = 3.5$, 1F); MS (EI): m/z 188 (100), 77 (11); HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{F}_4\text{NNaO}_2\text{S}$ $[\text{M}+\text{Na}]^+$ 452.1278, found 452.1278.

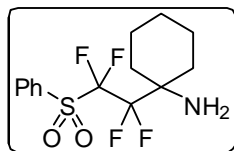
***N*-Methyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (92e).**



A mixture of 10% Pd/C (10 mg) and **91e** (444 mg, 1 mmol) in MeOH (10 mL) was stirred for 3 h in an autoclave (H_2 , 20 bar) at room temperature. The solution was then filtered through celite, the filtrate

was concentrated under reduced pressure and purified by column chromatography to give 314 mg of **92e** (89% yield). Colorless oil, R_f 0.8 (hexane–EtOAc, 80:20); ^1H NMR: δ 1.42–1.58 (m, 7H), 1.60–1.70 (m, 2H), 1.75–1.86 (m, 2H), 2.41 (t, 3H, $^5J_{\text{HF}} = 1.8$, CH_3), 7.58–7.76 (m, $2H_{\text{Ar}}$), 7.72–7.80 (m, $1H_{\text{Ar}}$), 7.98–8.06 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 20.4, 25.2, 27.7 (t, $^3J_{\text{CF}} = 2.5$, CH_2), 28.9 (t, $^4J_{\text{CF}} = 2.2$, $\text{CH}_3\text{-N}$), 60.8 (tt, $^2J_{\text{CF}} = 20.1$, $^3J_{\text{CF}} = 1.4$, N-C-CF₂), 118.0 (tt, $^1J_{\text{CF}} = 300.7$, $^2J_{\text{CF}} = 40.5$, CF₂), 120.4 (tt, $^1J_{\text{CF}} = 265.8$, $^2J_{\text{CF}} = 27.9$, CF₂), 129.2, 130.9, 133.9, 135.4; ^{19}F NMR: δ -112.8 (m, 2F), -107.9 (m, 2F); IR (film): ν_{max} (cm⁻¹) 536, 591, 603, 1105, 1160, 1360, 2817 (N-CH₃), 2859, 2935, 3103 (NH), 3412 (NH); MS (EI): m/z 310 (4), 168 (3), 112 (100), 77 (10); HRMS (ESI): m/z calcd for C₁₅H₂₀F₄NO₂S [M+H]⁺ 354.1145, found 354.1145

1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (**92f**).



A mixture of 10% Pd/C (50 mg) and **91f** (519 mg, 1 mmol) in AcOH (30 mL) was stirred at 70 °C for 24 h in a flask under atmospheric hydrogen pressure. The solution was then filtered through celite, the filtrate was concentrated under reduced pressure and purified by column chromatography to give 241 mg of **92f** (71% yield). Colorless oil; R_f 0.14 (hexane–EtOAc, 90:10); ^1H NMR: δ 1.51–1.76 (m, 10H), 2.08 (s, 2H, NH₂), 7.60–7.67 (m, $2H_{\text{Ar}}$), 7.74–7.82 (m, $1H_{\text{Ar}}$), 7.98–8.08 (m, $2H_{\text{Ar}}$); ^{13}C NMR (100 MHz): δ 20.2, 25.4, 29.9 (t, $^3J_{\text{CF}} = 2.4$, CH₂), 58.1 (tt, $^2J_{\text{CF}} = 21.5$, $^3J_{\text{CF}} = 2.2$, N-C-CF₂), 117.7 (tt, $^1J_{\text{CF}} = 300.5$, $^2J_{\text{CF}} = 40.7$, CF₂), 119.2 (tt, $^1J_{\text{CF}} = 260.6$, $^2J_{\text{CF}} = 27.4$, CF₂), 129.3, 130.9, 133.5, 135.6; ^{19}F NMR: δ -107.2 (m, 2F), -119.2 (m, 2F); IR (film): ν_{max} (cm⁻¹) 535, 602, 1104, 1159, 1359, 1450, 2863, 2937, 3068, 3354 (NH₂), 3426 (NH₂); MS (EI): m/z 296 (14), 98 (100), 77 (13); HRMS (CI): m/z calcd for C₁₄H₁₈F₄NO₂S [M+H]⁺ 340.0994, found 340.1001

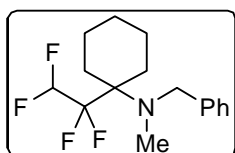
General procedure for the synthesis of compounds **93**.

Method A. A solution of *n*-Bu₃SnH (403 μL , 1.5 mmol) and AIBN (3 mg, 0.02 mmol) in dry toluene (2 mL) was added to a refluxing solution of **90a** or **90e** (1 mmol) in dry toluene (3 mL). The resulting mixture was refluxed for 3 h, followed by concentration under reduced pressure and purification by flash column chromatography (hexane–EtOAc) to give **93a** (91% yield) and **93e** (64% yield), respectively.

Method B. I₂ (40 mg, cat.) was added to Mg turnings (240 mg, 10 mmol), the mixture was heated up with a heat gun and stirred for 10 minutes. Then, a solution of **91a** (409 mg, 1

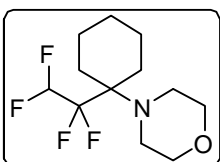
mmol) in MeOH (10 mL) was added, and the mixture was stirred for 1.5 h at room temperature. A second portion of Mg (480 mg, 20 mmol) was added, and the reaction mixture was stirred for 2.5 h at room temperature. Aqueous saturated NH₄Cl (15 mL) was added and the reaction mixture was extracted with Et₂O. The combined organic phase was washed with brine and water, dried (MgSO₄), and concentrated under vacuum. The crude product was purified by column chromatography eluting with hexane–EtOAc to give **93a** (80% yield).

N-Benzyl-N-methyl-1-(1,1,2,2-tetrafluoroethyl)cyclohexanamine (93e): colorless oil (194



mg, 64% yield); *R_f* 0.64 (hexane); ¹H NMR: δ 1.23–1.35 (m, 2H), 1.45–1.62 (m, 4H), 1.67–1.86 (m, 2H), 2.09–2.28 (m, 2H), 2.37 (s, 3H, CH₃), 4.0 (s, 2H, CH₂Ph), 5.82 (tt, ²*J*_{HF} = 52.9, ³*J*_{HF} = 5.9, CF₂H), 7.13–7.52 (m, 5H); ¹³C NMR (100 MHz): δ 20.5, 25.8, 28.5, 34.4 (t, ⁴*J*_{CF} = 2.2, CH₃-N), 54.0 (t, ⁴*J*_{CF} = 2.5, CH₂Ph), 62.4 (t, ²*J*_{CF} = 18.7, N-C-CF₂), 110.6 (tt, ¹*J*_{CF} = 251.9, ²*J*_{CF} = 36.1, CF₂H), 120.9 (tt, ¹*J*_{CF} = 261.7, ²*J*_{CF} = 25.0, CF₂), 126.5, 127.6, 128.3, 140.7; ¹⁹F NMR δ -134.0 (t, ³*J*_{FF} = 4.8, 2F), -120.8 to -119.6 (m, 2F); MS (EI): *m/z* 202 (100), 91 (64); HRMS (ESI): *m/z* calcd for C₁₆H₂₂F₄N [M+H]⁺ 304.16829, found 304.1683

4-(1-(1,1,2,2-Tetrafluoroethyl)cyclohexyl)morpholine (93a): white solid (245 mg, 91%



yield from **90a** or 215 mg, 80% yield from **91a**; *R_f* 0.30 (hexane–EtOAc, 95:5); mp 56–58°C; ¹H NMR: δ 1.12–1.37 (m, 1H), 1.40–1.67 (m, 6H), 1.69–1.80 (m, 1H), 2.05 (m, 2H), 2.75–2.98 (m, 4H), 3.52–3.78 (m, 4H), 5.79 (tt, 1H, ²*J*_{HF} = 53.0, ³*J*_{HF} = 5.8, CF₂H); ¹³C NMR (100 MHz): δ 20.3, 25.7, 27.4 (t, ³*J*_{CF} = 2.3, CH₂), 46.8 (t, ⁴*J*_{CF} = 2.0, CH₂-N), 61.7 (t, ³*J*_{CF} = 18.9, N-C-CF₂), 68.4, 110.5 (tt, ¹*J*_{CF} = 252.0, ²*J*_{CF} = 36.3, CF₂H), 120.5 (tt, ¹*J*_{CF} = 260.6, ²*J*_{CF} = 24.9, CF₂); ¹⁹F NMR δ -134.1 (t, ³*J*_{FF} = 4.7, 2F), -121.0 (s, 2F); MS (EI): *m/z* 182 (1), 168 (100), 101 (1); HRMS (CI): *m/z* calcd for C₁₂H₂₀F₄NO [M+H]⁺ 270.1481, found 270.1486

4.3. Computational methods

The geometries were optimized on the density functional theory (DFT) level employing the *Gaussian 09* suite.¹³² The unrestricted ωB97XD¹³³ functional was used with the Def2-TZVP basis set for all atoms.¹³⁴ All structures were confirmed by frequency analyses to be either true energy minima (no imaginary vibrations found) or transition states

(one imaginary vibration). The calculations of single-point energies were done both on the DFT and MP2 (Møller-Plesset perturbation theory of the second order) level (the ω B97XD// ω B97XD and MP2// ω B97XD approach, respectively). The values of enthalpy and Gibbs free energy were calculated at 298.150 K and 1 atm. The IEFPCM solvation model was applied using toluene with default parameters. The theoretical selectivity was calculated according to the following equation adapted from ref. ¹³⁵ employing the free energy difference of corresponding transition states:

$$\frac{n_{\text{major isomer}}}{n_{\text{minor isomer}}} = e^{-\Delta G^{\text{TS}}}$$

and then converted to the format comparable with the experiment using the following formula:

$$\frac{100e^{-\Delta G^{\text{TS}}}}{e^{-\Delta G^{\text{TS}}} + 1} : \frac{100}{e^{-\Delta G^{\text{TS}}} + 1}$$

(e.g. selectivity *trans/cis* 82:12)

5. Conclusions

We have developed four new reagents for the introduction of $-\text{CF}_2\text{CF}_2\text{H}$ and $-\text{CF}_2\text{CF}_2-$ groups. $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**52**) was successfully used as a tandem anion and radical tetrafluoroethylene equivalent. Sulfide **52** underwent fluoride-initiated nucleophilic addition to carbonyl compounds, such as aldehydes and ketones. Reactions proceeded very smoothly at room temperature with catalytic amount of fluoride anion providing substituted 2,2,3,3,3-phenylsulfanyl-tetrafluoropropan-1-ols (**60**) in high yields. Reduction of compounds **60** furnished tetrafluoroethyl-substituted alcohols **61** in good yields demonstrating the application of $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**52**) as a $[\text{CF}_2\text{CF}_2\text{H}]^-$ carbanion equivalent. Compounds **60** were converted into allyl ethers **62** and cyclized under free radical conditions to give substituted tetrafluorotetrahydropyrans **63** in moderate to good yields and *trans* selectivities.⁹⁸ $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**52**) was also reactive in nucleophilic addition to cyclic imides to give either the corresponding tetrafluoroethyl-containing adducts **67** (after reductive phenyl sulfanyl group removal) or the corresponding tetrafluorinated 1-azabicyclic compounds **68** (after radical 6-*exo* cyclization).¹⁰⁰ 1-Azabicyclic ring systems having angular substituents adjacent to nitrogen are structural motifs found in a variety of alkaloid natural products and biologically active agents.¹³⁶ Unfortunately, nucleophilic substitution of alkyl halides with **52** was not successful.

$\text{PhSO}_2\text{CF}_2\text{CF}_2\text{SiMe}_3$ (**56**) displayed decreased reactivity in nucleophilic additions to carbonyl compounds in comparison with $\text{PhSCF}_2\text{CF}_2\text{SiMe}_3$ (**53**) due to the stronger electron-withdrawing effect of the phenylsulfonyl group. Substoichiometric amount of cesium fluoride was needed for the activation of the silane **56** to provide alcohol adducts **83**, which were desulfonylated by the use of magnesium in methanol.

Tetrafluoroethyl-substituted alcohols **61** were prepared using $\text{PhSO}_2\text{CF}_2\text{CF}_2\text{H}$ (**58**) in nucleophilic addition reactions to aldehydes through magnesium-mediated desulfonylation. The method is limited to halogen-free substrates. With trifluoroacetophenone and chlorinated aldehydes, pinacol coupling was observed and with brominated aldehydes, competing reduction took place. However, the methodology provides an alternative one-step approach for efficient tetrafluoroethylation of both non-enolizable and enolizable aldehydes with a readily available reagent.

Sulfur reagents **53** and **56** were found to be effective in HF-mediated nucleophilic fluoroalkylations of iminium ions. In contrast to imines, which were unreactive under acidic conditions, enamines derived from ketones led to $\alpha\text{-CF}_2\text{CF}_2$ -substituted amines in moderate to

high yields. This strategy allowed the preparation of tertiary amines, while hydrogenolysis of benzyl groups in adducts formed from *N*-benzyl enamines afforded the corresponding primary or secondary amines.¹¹⁷ Fluoroalkyl amines continue to receive a remarkable attention in bioorganic and medical chemistry research due to the profound change of the basicity of the amine functionality imposed by the fluoroalkyl group.¹¹³

Sulfide PhSCF₂CF₂Br (**52**) underwent homolytic cleavage of the S–CF₂ and CF₂–Br bonds effectively creating [PhSCF₂CF₂•], [HCF₂CF₂•], and [•CF₂CF₂] synthons. In the presence of tributyltin hydride and catalytic triethylborane, **52** underwent addition of the 1,1,2,2-tetrafluoro-2-phenylsulfanyl moiety to a variety of alkenes to provide the corresponding bromine-free adducts **78**. Subsequent substitution of the phenylsulfanyl group for hydrogen under standard free-radical conditions gave a tetrafluoroethyl-containing alkane. Under the same conditions, in the presence of alkenes, radical addition takes place to yield compounds **80a** with tetrafluoroethylene moiety. This process represents a useful approach to both symmetrical and non-symmetrical alkanes with the tetrafluoroethylene segment within the carbon chain.¹⁰⁵

In summary, these newly reported reagents extend the synthetic toolkit for selective introduction of tetrafluoroethyl and tetrafluoroethylene groups by nucleophilic and radical additions and provide new ways to the synthesis of selectively fluorinated compounds.

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