SYNTHESIS OF A FLUOROUS BENZODITHIOL SUPPORT AND ITS UTILITY IN THE CONSTRUCTION OF DIVERSE RING SYSTEMS

by

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ABSTRACT

A method for the synthesis of a symmetrical fluorous tagged benzodithiol support has been developed through a seven-step synthetic pathway. The Wittig olefination and catalytic hydrogenation reactions were employed to attach two perfluoroalkyl chains in the *o*-positions of phthalaldehyde. These fluorous tags were used as soluble supports which facilitated the purification of the crude reaction mixtures using fluorous solid phase extraction (FSPE).

A selective and high yielding dibromination reaction was developed to synthesize a fluorous tagged 1,2-dibromo aryl compound. A thorough study was carried out to demonstrate the ease of an aryl-sulfur bond formation with the 1,2-dibromo compound varying palladium catalysts and ligands. A new palladium catalyzed dithiolation reaction is reported to synthesize a surrogated dithiol, which was exploited as a precursor for the synthesis of hitherto inaccessible symmetrical fluorous tagged benzodithiol support. The utility of the benzodithiol was explored by the synthesis of benzodithianes with two aldehydes. The lithiated dithiane generated was further used to form a C-C bond employing the umpolung reaction. The ring-closing metathesis reaction using Grubbs II catalyst was performed to construct 5-membered and 6-membered spiro-ring systems. Several approaches were made to form a C-C bond with lithiated dithianes using various nitrogen containing electrophiles leading to *N*-heterocycles.

ACKNOWLEDGEMENTS

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Last but not the least, I express my sincere thanks to my husband for his support and encouragement to my research work.

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LIST OF ABBREVIATIONS

Ac	Acetyl
aq	Aqueous
Ar	Aryl
Bu	*n*-butyl
t-Bu	*tert*-butyl
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
Bz	Benzoyl
c	concentration in g/100 mL
Cbz	Benzyloxycarbonyl
Cy	Cyclohexyl
δ	NMR chemical shift in ppm
de	diastereomeric excess
DDQ	dichlorodicyanoquinone
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DIPEA	diisopropylethylamine
ee	enantiomeric excess
Et	ethyl
EtOH	ethanol
F-HPLC	fluorous high-performance liquid chromatography
Fmoc	9-fluorenylmethoxycarbonyl
FMS	Fluorous mixture synthesis
FSPE	fluorous solid phase extraction
h	hour
HMDS	Hexamethyldisilazane
HMPA	hexamethylphosphoramide

J	coupling constant (in NMR)
LDA	lithium diisopropylamide
Me	methyl
MeOH	methanol
Mes	methanesulfonyl
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PTSA	toluene-*p*-sulfonic acid
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
Tf	trfluoromethanesulfonyl
TFA	trifluoroacetic acid
TEA	triethylamine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Ts	4-toluenesufonyl

CHAPTER 1: INTRODUCTION

1.1 General Introduction

This research is comprised of three parts: 1) synthesis of a symmetrical fluorous tagged protected benzodithiol employing a palladium catalyzed dithiolation reaction, 2) synthesis of benzodithianes and their use in C-C bond formation by the umpolung reaction, and 3) construction of diverse ring systems using the ring-closing metathesis reaction. This review will give a detailed discussion about the use of fluorous chemistry in different fields of organic chemistry. The evolution of the fluorous tagging technology and its application in various fields of organic chemistry starting from separation methods to library generation using fluorous mixture synthesis will be discussed. The use of fluorous tagged thiols in heterocyclic chemistry as a scavenger and as a traceless linker will be highlighted. Some features of the aryl-sulfur bond formation including catalyst poisoning will be introduced. A brief introduction on dithiane chemistry and recent progress on the ring-closing metathesis reaction using fluorous tagged Grubbs-Hoveyda catalysts will be included.

1.2 Fluorous Organic Synthesis

1.2.1 General Aspects of Fluorous Chemistry

Fluorous chemistry is a powerful technique in today's drug discovery effort for the synthesis of organic molecules in a high-throughput manner. Traditional solution phase chemistry stands in an awkward position for its time-consuming product purification steps. The term "fluorous" for highly fluorinated solvents was introduced as an analogue to the term "aqueous".[1] Gladysz and Curran defined the adjective "fluorous" to mean highly fluorinated saturated organic molecules which are based upon sp^3-

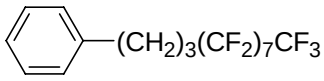
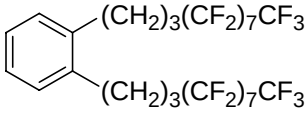
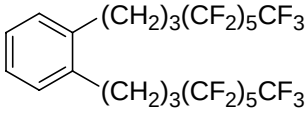
hybridized carbons.[2] The fluorous phase is defined as the fluorocarbon-rich or fluorohydrocarbon-rich phase. Fluorocarbons are also known as perfluorinated compounds where all H atoms are replaced with F atoms in the parent compound. Fluorohydrocarbons are partially fluorinated compounds in which at least one H atom is not replaced with F atoms in the parent compound. Perfluoroalkanes, perfluoroalkylethers and perfluoroalkylamines are examples of fluorocarbons.[1,3]

Fluorous separation methods are based on the restricted solubility and miscibility of partially or fully fluorinated compounds with nonfluorinated compounds and on the "like dissolves like" principle.[1,4] The partially or fully fluorinated substances preferably dissolve in the perfluorinated solvents and exhibit a significant partition coefficient towards the fluorous phase in liquid-liquid extractions. This selective miscibility arises from sufficiently different intermolecular forces between the two species.[1] To measure the extent of the fluorous phase preference for a compound "i", Rabai and coworkers[5] defined the term "fluorophilicity", f_i from the partition coefficient "P_i" between two particular solvents, perfluoro(methylcyclohexane) and toluene at 25 ^{o}C as represented by equation (1).

$$f_i = \ln P_i = \ln\left(\frac{c_{i,CF_3C_6F_{11}}}{c_{i,CH_3C_6H_5}}\right) \qquad T = 25\ ^{o}C \qquad (1)$$

For a fluorophilic compound, the value of f_i is positive. A widely used protocol to measure fluorophilicity of a compound is the 'fluorous partition coefficient'. Some examples are shown in Table 1.2.1.1 to reflect the phase affinity of hydrocarbon and fluorocarbon materials.

Table 1.2.1.1: Fluorous/hydrocarbon liquid/liquid partitioning [6,7]

Entry	Substrate	Solvent system	Partitioning % organic/fluorous
1	$CH_3(CH_2)_7CH{=}CH_2$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	95.2/4.8
2	$CF_3(CF_2)_7CH{=}CH_2$	$CH_3C_6H_5$:$CF_3C_6F_{11}$	6.5/93.5
3		$CH_3C_6H_5$:$CF_3C_6F_{11}$	50.5/49.5
4		$CH_3C_6H_5$:$CF_3C_6F_{11}$	8.8/91.2
5		$CH_3C_6H_5$:$CF_3C_6F_{11}$	26.3/73.7

1-Decene and 1*H*,1*H*,2*H*-heptadecafluoro-1-decene (Table 1.2.1.1, entry 1 cf. 2) have roughly equal but opposite phase affinity. One $CF_3(CF_2)_7CH_2CH_2CH_2$ substituent in a benzenoid compound gives approximately 50:50 partition coefficient (entry 3) while two *ortho* substituents (entry 4) give 8.8:91.2 partition coefficients. When the fluorous segment of the pony tail is shortened (entry 5), the fluorous phase affinity decreases.[7]

The fluorous phase concept was first described in an unpublished thesis of M. Vogt[4] who attempted to utilize the solvophobic properties of perfluorinated ethers of the Hostinert 216 type (Figure 1.2.1.1) for phase separation in homogeneous catalytic reactions. Hostinert is a trademark of Hoechst AG for various perfluoroalkylpolyether oils.

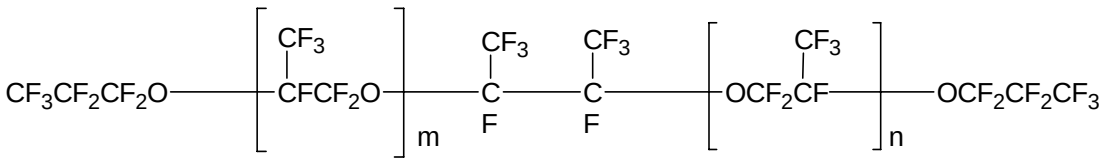
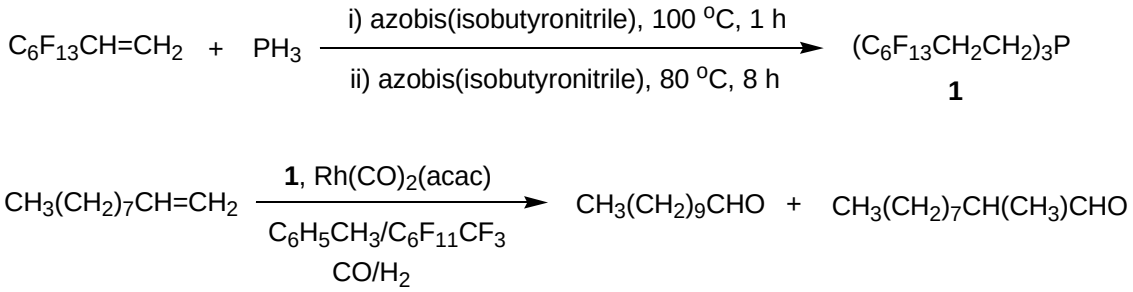


Figure 1.2.1.1: Hostinert 216 type perfluorinated ether.

Horvath and Rabai introduced the "fluorous biphase system" or FBS to perform chemical transformations in stoichiometric and catalytic synthesis.[1,8] A fluorous biphase system is a combination of fluorous and organic phases that display a temperature-dependent miscibility, allowing the formation of a homogeneous reaction environment at high temperature. This is an ingenious strategy for immobilizing reagents or catalysts in the fluorous phase. A phosphine ligand **1** was synthesized and used to generate a fluorous soluble phosphine-modified rhodium catalyst for a standard hydroformylation reaction (Scheme 1.2.1.1). Introduction of an ethylene spacer group was important to decrease the strong electron-withdrawing effects of the fluorous segment on the Lewis basicity of the phosphorus atom in **1**.



Scheme 1.2.1.1: Synthesis of fluorous phosphine ligand and hydroformylation reaction.

The hydroformylation was carried out in a biphasic mixture of perfluoro(methylcyclohexane) and toluene under a CO/H_2 atmosphere. Initially, the olefins and the rhodium catalyst formed a biphasic system. At higher temperature, the reaction occurred in a homogeneous monophasic environment. After cooling down, the

products and the catalyst again formed a biphasic system. The products were isolated from the catalyst by a simple liquid-liquid extraction. The advantage of this approach is the ease of separation. Also, the fluorous rhodium catalyst can be recovered and reused.

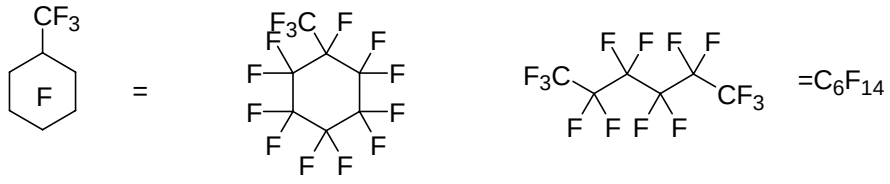
1.2.2 Heavy Fluorous Synthesis

Studer *et al.*[9,10] introduced fluorous synthetic methods as strategic alternatives to solid phase synthesis where the inherent efficiency of solution phase synthesis and the convenient separation feature of solid phase synthesis combine together. The original strategy ("heavy fluorous synthesis") entailed the tagging of a substrate or a library of substrates with a highly fluorinated tag. Heavy fluorous molecules usually have greater than 60% of fluorine content by molecular weight.[11] They contain multiple fluorous tags to ensure good partition coefficient between fluorous and organic solvents. Tagged products are then separated from the non-tagged ones by partitioning between an organic liquid and a fluorous liquid in a liquid-liquid extraction. Such highly fluorinated molecules can have little or no solubility in organic solvents making the separation stage very convenient, but this poor solubility has liabilities in the reaction stage. Thus, heavy fluorous synthesis resembles solid-phase synthesis. Multiple extractions are required to fully isolate fluorous molecules from non-fluorous molecules. This protocol is coupled with an intensive gain in molecular weight and cost, which could be a limiting factor for industrial fluorous biphasic system applications.

1.2.3 Light Fluorous Synthesis

Curran and Luo subsequently developed the light fluorous technology.[12] Light fluorous compounds typically contain fewer than 21 fluorine atoms, such as a single perfluorohexyl or a perfluorooctyl group. They have similar chemical and physical

properties to their non-fluorous counterparts. Thus, light-fluorous molecules exhibit poor solubility in fluorocarbon solvents and high solubility in many organic solvents affording homogeneity with standard reaction kinetics and reliable scalability.[13]



perfluoromethylcyclohexane immiscible with EtOAc, CH_2Cl_2, H_2O and CH_3CN

partially soluble in Et_2O, THF and CCl_4

Figure 1.2.3.1: Example of perfluorocarbon solvents.[13]

In this method, the reaction is carried out in an organic solvent, and the perfluoroalkyl-tagged compound is separated from the products by solid-phase extraction on fluorous silica gel (Section 1.3.2). One advantage of the light fluorous technique is that the tagged molecules require lower F-content than is normally needed for fluorous biphasic applications.

1.2.4 Characteristics of Fluorocarbons and Fluorous Substrates

Because of their large number of fluorine atoms, perfluorinated solvents exhibit unique physical properties. They have high densities, low polarity, low boiling points than the corresponding saturated hydrocarbons and the lowest dielectric constants because of the very high ionization potential, electronegativity and low polarizability of fluorine.[14] Additionally, perfluorinated compounds possess weak intermolecular forces such as van der Waals' interactions. As a consequence, perfluorinated solvents are immiscible with many organic solvents at room temperature.[3,4]

Perfluorinated solvents are chemically and thermally inert because of very strong carbon-fluorine bonds.[14] Due to the presence of the perfluorinated chain, the fluorous compounds also have low polarizabilities and are highly hydrophobic in nature.[5]

The Hildebrand solubility parameter (δ) scale locates a compound in the phasephilicity map.[5,15,16] The native phasephilicity (e.g. hydrophilic, lipophilic, fluorophilic, etc.) of the components of a chemical reaction determines their separation.[17] The term phasephilicity can be classified as (i) monophilic: e.g. organophilic, hydrophilic and fluorophilic (only one type of phase character is expressed in the molecules); (ii) amphiphilic (two different types of domains are involved); or (iii) multiphilic (more than two types of domains are involved in the complex structures).

Table 1.2.4.1: Phasephilicity map.[5]

δ (**Fluorous solvents)** **Fluorophilic** organophobic, hydrophobic	δ **(Organic solvents)** **Organophilic** hydrophobic, fluorophobic	δ **(Water/Brine)** **Hydrophilic** organophobic, fluorophobic
Perfluorohexane , 12.1	Acetonitrile, 24.3	Water, 48
Perfluoroheptane, 12.3	Dichloromethane, 19.8	Methanol, 29.7
Perfluoro(methylcyclohexane),12.5	Toluene, 18.2	

Using the phasephilicity map, homogeneous as well as biphasic systems can be selected from solvent-solvent and solvent-solute likeness, which can be estimated by the closeness of the empirical δ values. Perfluorinated solvents represent the lowest δ values,

while organic solvents span a wide polarity range and water has the highest δ value (Table 1.2.4.1).

1.3 Development of Fluorous Purification Technologies

1.3.1 Fluorous Liquid-Liquid Extractions (F-LLE)

This method is ideal for heavy fluorous molecules which have good partition coefficients between fluorous and organic solvents.[11] The separation can be carried out with an organic/fluorous biphasic extraction or an organic/aqueous/fluorous triphasic extraction if water-soluble materials are involved. In a triphasic system the fluorous phase is orthogonal to (i.e. immiscible with) both the organic and aqueous phases (Figure 1.3.1.1). Fluorous solvents are expensive, which is a disadvantage of this technique.

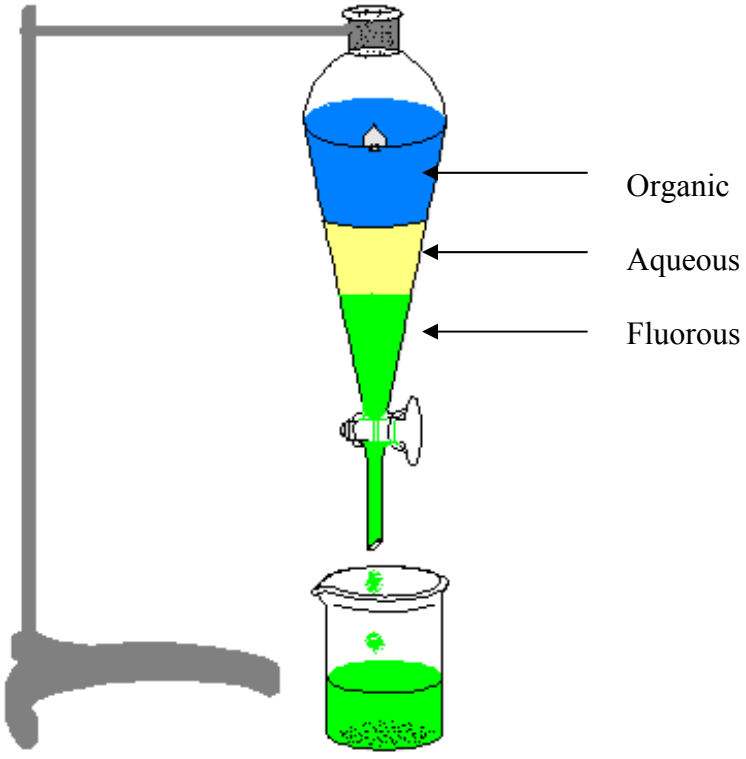


Figure 1.3.1.1: Fluorous liquid-liquid extraction.[11]

1.3.2 Fluorous Solid-Phase Extractions (F-SPE)

The separation of light fluorous molecules can be achieved by fluorous silica gel-based solid-phase extraction without the use of fluorous solvents. Remarkable progress in fluorous separation was achieved after the invention of fluorous silica gel (Fluoro*Flash*) which has a bonded phase of Si-$(CH_3)_2CH_2CH_2C_8F_{17}$).[18] F-SPE provides an easy separation of light fluorous molecules from non-fluorous molecules exploiting fluorophilicity. In an ideal F-SPE separation, a crude reaction mixture is loaded onto the SPE cartridge, where a fluorophobic solvent such as 70:30 MeOH/H_2O is used to elute the non-fluorous compounds and a fluorophilic solvent such as MeOH, acetone, acetonitrile, or THF is used to get the pure fluorous compound. Easy separation and recyclability of the cartridges make this separation technology a popular technique among synthetic chemists.

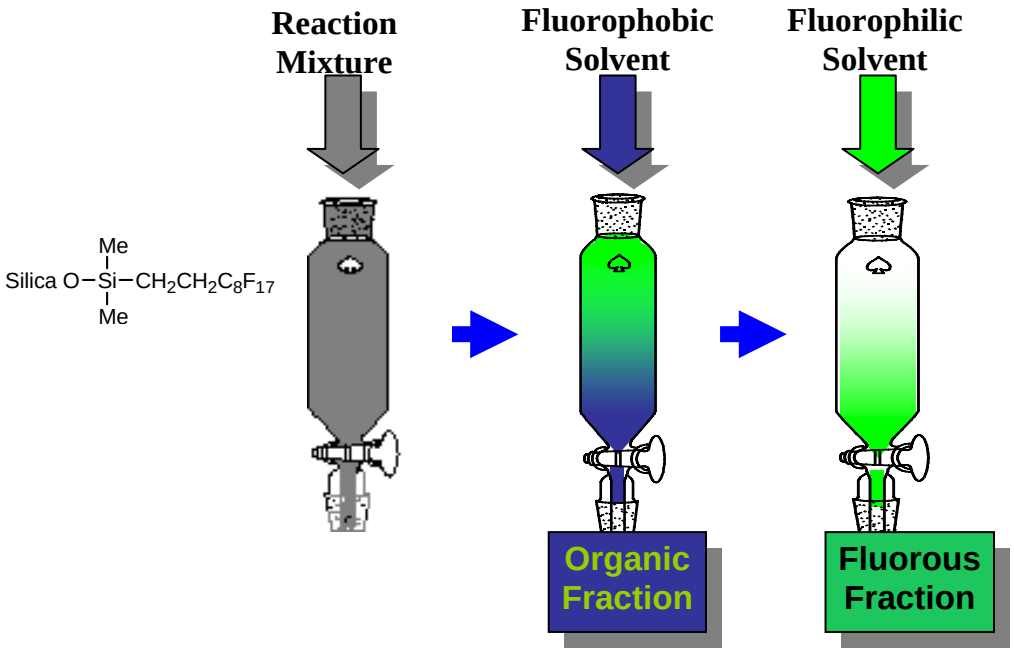


Figure 1.3.2.1: F-SPE separation technique.

1.3.3 Reverse FSPE

A new separation technique called "reverse fluorous solid-phase extraction (R-FSPE)" was developed by Curran *et al.*[19,20] where fluorous-tagged compounds can be separated from organic (non-tagged) compounds by eluting with fluorous solvents. However, the disadvantage associated with this method is the cost of fluorous solvents.

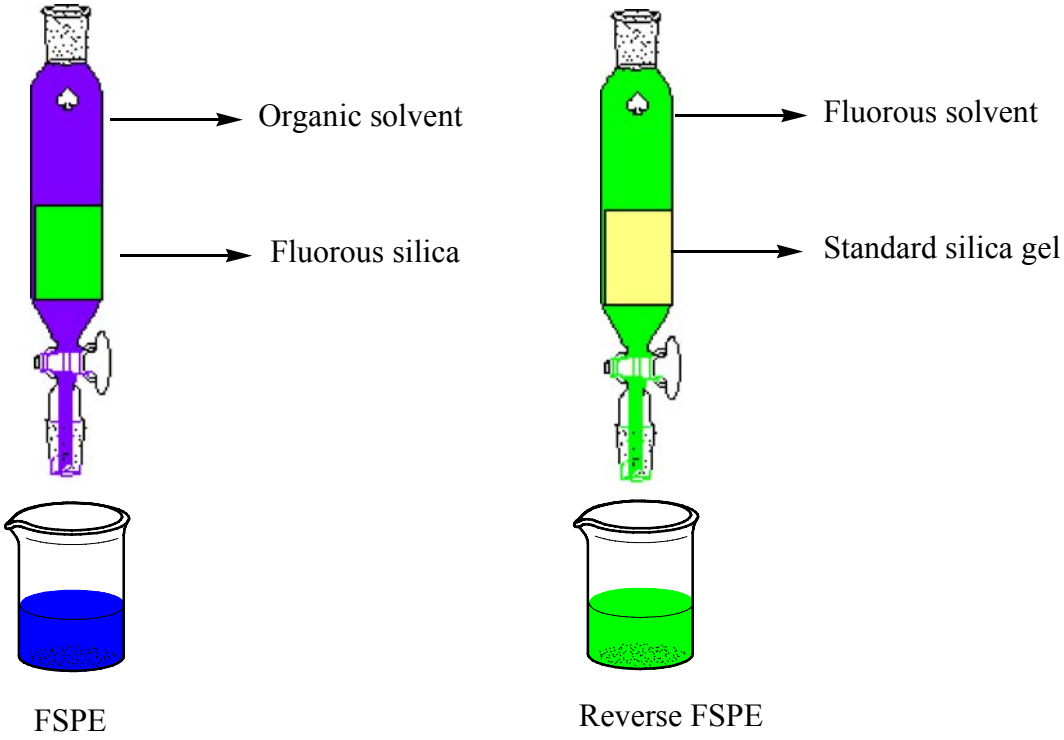


Figure 1.3.3.1: Comparison of FSPE and reverse FSPE.[21]

1.3.4 Fluorous HPLC (F-HPLC)

Another highly efficient fluorous separation technique is F-HPLC,[11] a hybrid of fluorous separation and modern HPLC technology using an F-HPLC column packed with Fluoro*Flash* silica gel. Here, the nonfluorous compounds have very weak retention and fluorous compounds can be retained and separated in an order of increasing fluorine content. The mobile phase used is usually a gradient of MeOH/H_2O, MeCN/H_2O or THF/H_2O.

1.3.5 Fluorous Flash Chromatography (F-FC)

New technologies have been developed for fluorous flash chromatography[11] with improved features. Instruments are available in the market from different suppliers such as Biotage (Horizon) and Isco (CombiFlash). Different size of cartridges and samplets are available.

1.4 Tagging Technology

1.4.1 Advantages of Fluorous Tags over Polymer Resin Beads

Fluorous synthesis is conceptually similar to solid-phase synthesis using functionalized polystyrene beads. Several advantages of fluorous synthesis distinguish it from polymer bound solid phase synthesis. The introduction of two phases in a polymer bound solid phase synthesis makes the product available through a simple filtration. On the other hand, the functionality of the polymer and its general insolubility creates unfavorable heterogeneous reaction kinetics.[22] Instead of resin, functionalized perfluoroalkyl groups are employed as phase tags in fluorous synthesis to facilitate the separation process. Fluorous labels are much more robust than polymers and linkers used in solid phase synthesis. Some resin based linkers such as silyl linker macrobead[23] and BromoWang polystyrene[24] are not compatible with strong acids like HF, trifluoroacetic acid and HCl whereas fluorous labels are highly inert.[13] In fluorous synthesis F-SPE or F-HPLC is employed to separate the byproducts whereas in solid phase synthesis byproducts are removed by washing and filtering. Unlike solid phase synthesis, fluorous reactions which involve discrete molecules can be easily monitored by conventional methods such as TLC, HPLC, and GC and can be analyzed by NMR, IR and mass spectrometry without cleaving from the fluorous linker.[25]

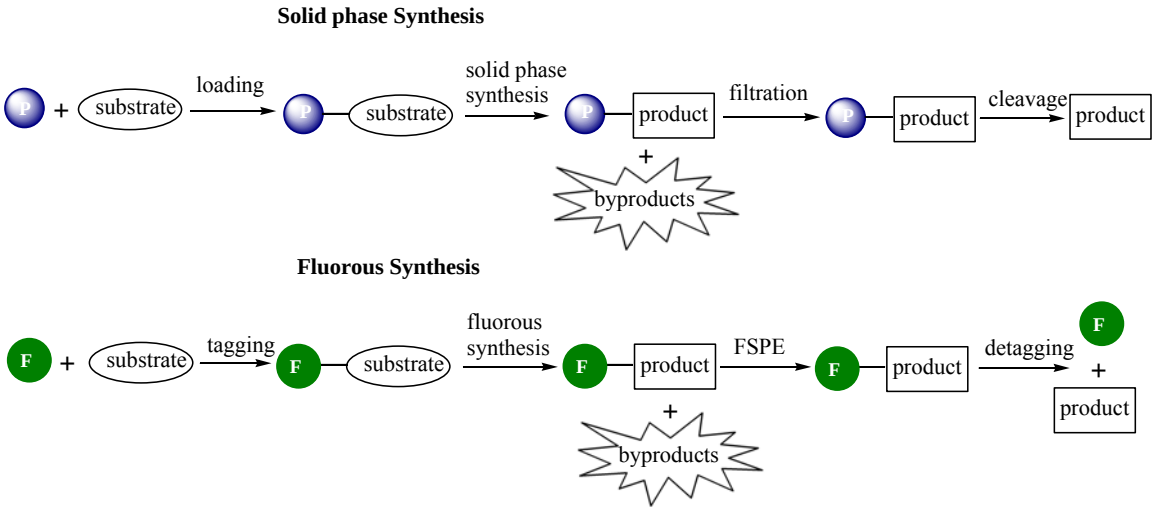
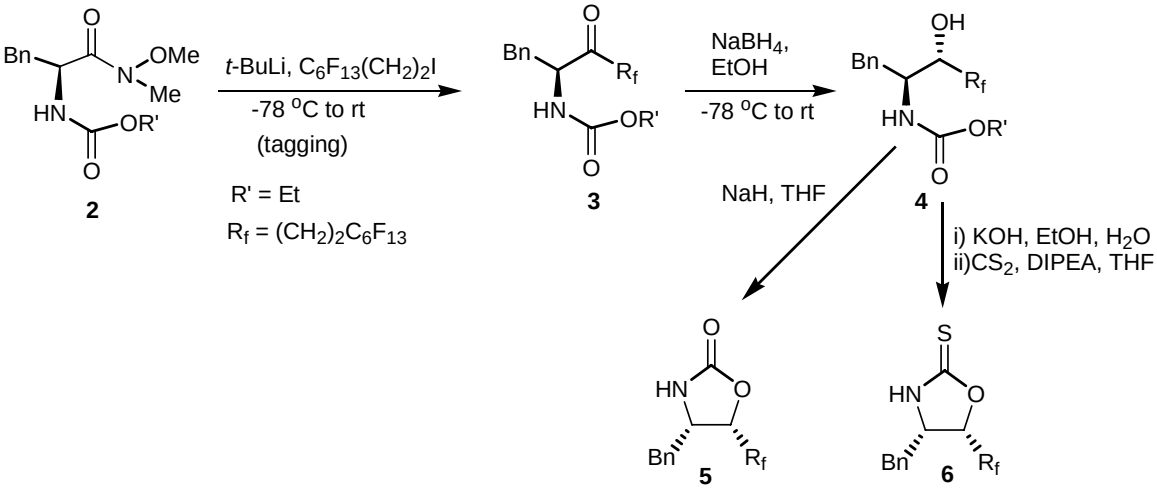


Figure 1.4.1.1: Schematic representation of solid phase and fluorous synthesis.[26]

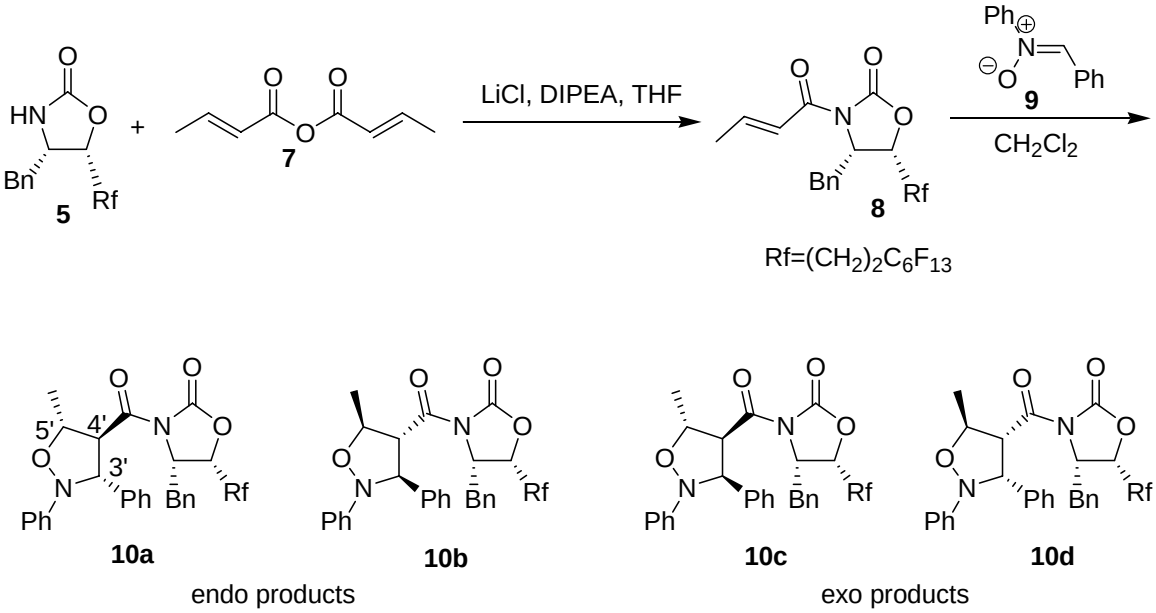
1.4.2 Fluorous Tagging Attached to Chiral Auxiliaries

A new series of fluorous tagged chiral auxiliaries, oxazolidinone and thiazolidinethione was synthesized by Hultin's group.[27] The Weinreb amide **2** was treated with a lithiated fluorous linker to yield ketone **3** (Scheme 1.4.2.1). Diastereoselective reduction of the ketone provided anti alcohol **4** which on cyclization gave chiral auxiliary **5**. Fluorous tagged thiazolidinethione **6** was prepared from **4** by hydrolysis followed by treatment with CS_2.



Scheme 1.4.2.1: Synthesis of fluorous chiral auxiliaries.[27]

The chiral auxiliary **5** was successfully used in the asymmetric 1,3-dipolar cycloaddition of diphenylnitrone with chiral conjugated alkene **8** under catalytic as well as noncatalytic conditions. The diastereomers **10a** and **10b** resulted from endo cycloaddition, while **10c** and **10d** resulted from exo cycloaddition (Scheme 1.4.2.2).

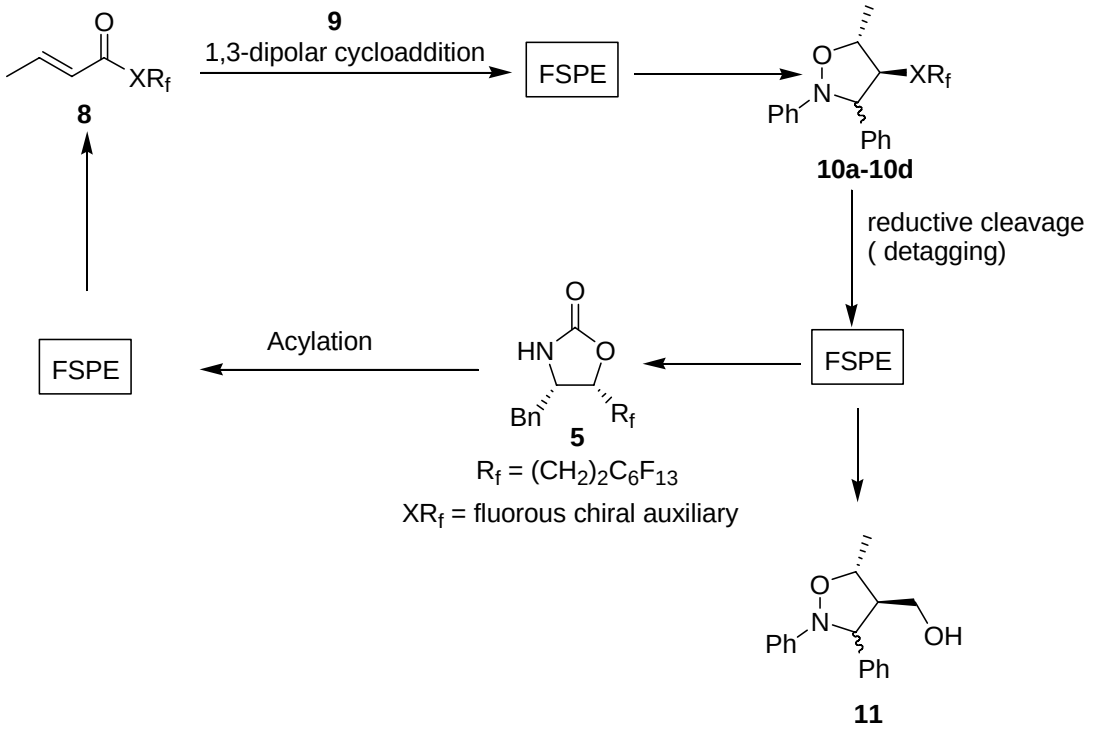


Scheme 1.4.2.2: 1,3-Dipolar cycloaddition of diphenylnitrone with compound **8**.[28]

There are two stereoselectivity issues involved in both noncatalytic and Lewis acid catalyzed 1,3 dipolar cycloaddition reactions. One is diastereofacial selectivity with respect to the dipolarophile (which controls the 4′,5′ stereochemistry of the product) and the other is *endo*/*exo* selectivity (which dictates the relative stereochemistry of the 3′ and 4′ centres). The facial selectivity of the cycloadditions (with attack on the *si* face of **8** gave 1**0a** and **10c** while *re* face addition gave **10b** and **10d**) is controlled by the coordination of the metal catalyst such as $Mg(ClO_4)_2$, $Sc(OTf)_3$ with carbonyls of the dipolarophile. An important finding of this experiment is that fluorous tagged reactions predominantly gave the (3′S,4′S,5′R) product in the presence of Mg^{2+}, but gave the

(3′R,4′R,5′S) product in the absence of the metal ion resembling solution phase 1,3-dipolar cycloaddition reactions.[29]

The beauty of this synthetic strategy is associated with the high recyclability (89%) of the fluorous tagged chiral oxazolidinone **5** making it an environmentally benign and cost-effective technology. Cycloadducts obtained from diphenylnitrone **9** and dipolarophile **8** were reductively cleaved from the auxiliary. The free auxiliary was acylated to reform the dipolarophile which was immediately used for further cycloadditions with no decrease in its efficiency (Scheme 1.4.2.3).[28] Similar reactions using polymeric supports were reported by Faita *et al.*[30,31,32] but attempts to re-use the supports in these cases led to declining yields and levels of stereoselectivity.



Scheme 1.4.2.3: Recyclability of fluorous tagged chiral auxiliary **5**.[28]

1.4.3 Cap and Tag Approach

For the synthesis of oligomers, two general fluorous methods are used.[11] In approach A, fluorous materials are used to cap the deletion sequences after each coupling reaction. At the end of the synthesis, all sequences are cleaved from the resin. The desired nonfluorous product is separated from the fluorous capped byproduct by F-HPLC. In approach B, nonfluorous materials are used to cap the deletion sequences, while the desired sequence is capped by a fluorous tag after the last coupling. The target oligomer is obtained by F-HPLC or F-SPE purification followed by detagging (Figure 1.4.3.1).

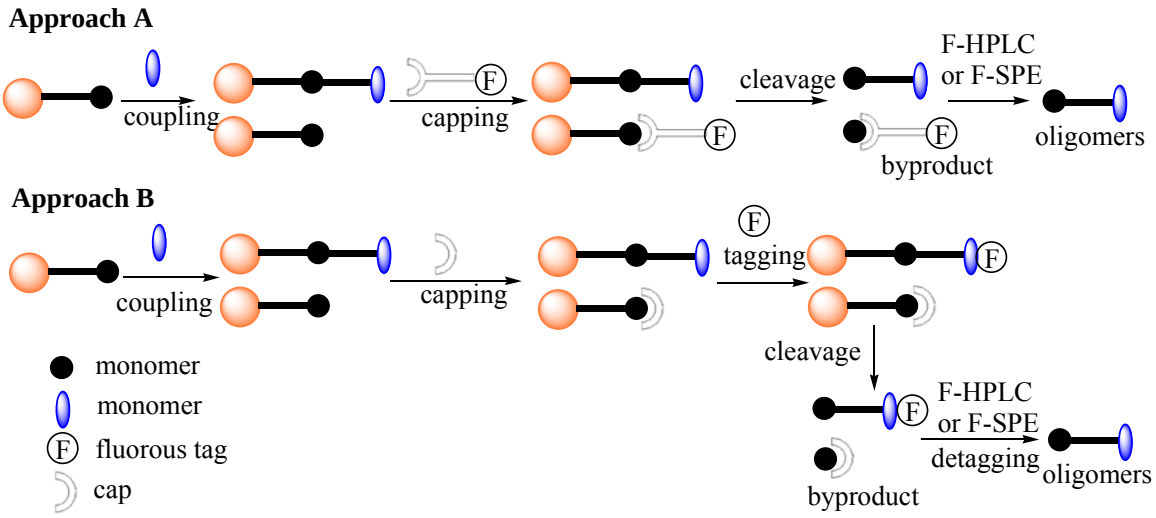
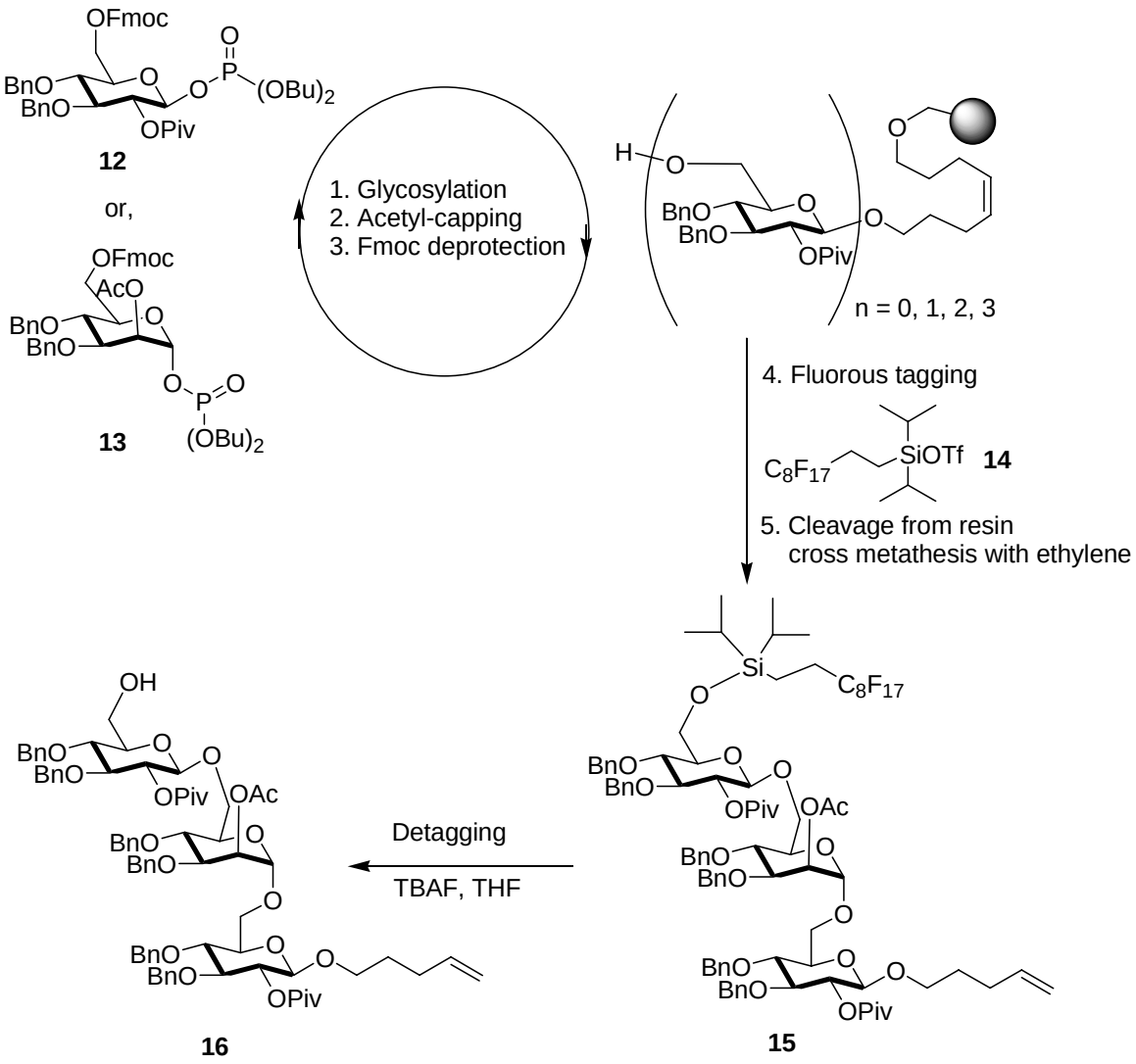


Figure 1.4.3.1: Schematic representation of cap-and-tag technology.[11, 33]

An example of "cap-and-tag" strategy applied to solid phase oligosaccharide synthesis is shown in Scheme 1.4.3.1. Acetyl-capping and fluorous-tagging allowed the facile separation of the desired F-tagged oligosaccharide from the acetyl-capped deletion sequences using fluorous solid phase extraction.[34]



Scheme 1.4.3.1: Cap and tag technology for oligosaccharide synthesis.[34]

1.4.4 Structure Elucidation through Fluorous Mixture Synthesis

Fluorous tagging technology has been burgeoning interest in recent years. Its utility has been extended to stereoisomer library generation of natural products through fluorous mixture synthesis (FMS), a highly efficient solution-phase technology for library synthesis. FMS is a technique where the stereocenters are introduced and tagged en route during the synthesis.[35] This approach employs a minimum number of steps and fewer fluorous tags than the number of stereoisomers in the library. In the traditional synthesis

of stereoisomer libraries, the reaction products are divided into two parts prior to the introduction of each new stereocenter and each portion is processed separately (Figure 1.4.4.1). On other hand, in FMS, the division and complementary reactions to introduce a new stereocenter in both possible configurations are followed by tagging and remixing. As a result, the synthesis is not divergent as long as there are sufficient tags to accommodate the isomers. A library of n molecules is uniquely encoded with 2/n+1 tags. The pairwise combination of tags T1–T3 generates four products with differing numbers of fluorine atoms.[35]

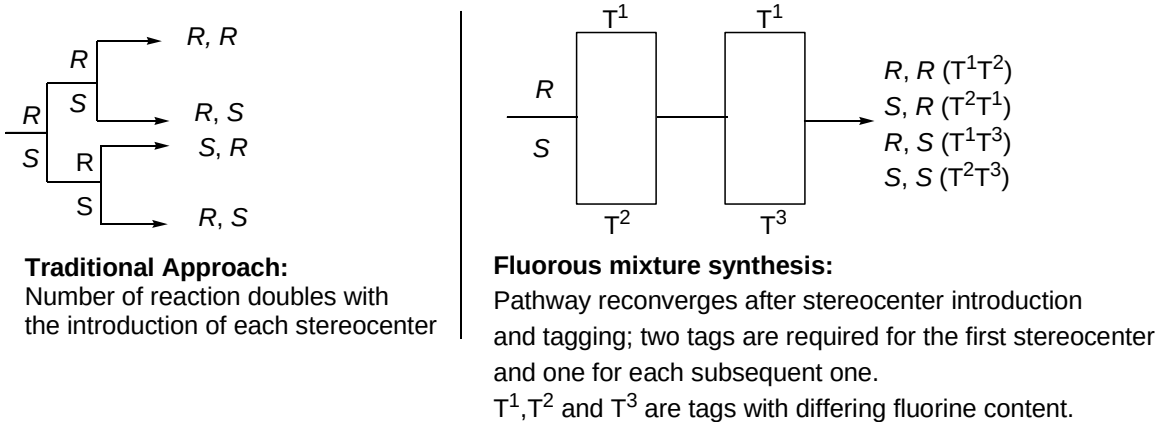


Figure 1.4.4.1: Strategies for the synthesis of stereoisomer libraries with the formation of stereocenters en route.[35]

Asymmetric synthesis and racemic synthesis/resolution are two general methods for the preparation of enantiopure or enantioenriched organic molecules. FMS provides a third option, known as quasiracemic synthesis. Quasienantiomers[36] are not enantiomers because they are not isomers. One quasienantiomer is approximately reflected into the other by a mirror, but the molecules differ in one part such that an atom or a group of one quasienantiomer is reflected into a chemically similar but not identical atom or group of the other (Figure 1.4.4.2). "Quasiracemic" follows as a mixture of equal parts of

quasienantiomers. In quasiracemic synthesis, both enantiomers are obtained through a single synthetic sequence.

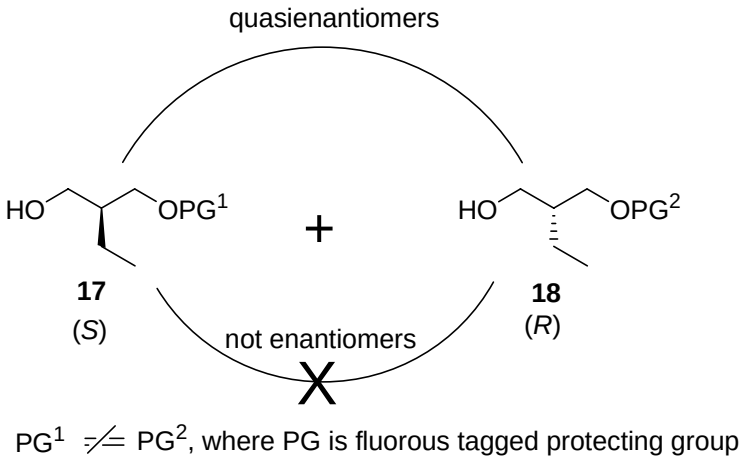


Figure 1.4.4.2: Example of quasienantiomers.[36]

Fluorous tagging dictates separation, analysis and identification of quasiracemic mixtures. Fluorous protecting groups differing in fluorine content permit the separation of the mixtures by F-HPLC. A simple deprotection condition for the corresponding protecting groups is used for final detagging. Mixing of the resulting quasienantiomers provides a quasiracemate, analogous to a true racemate in the successive steps of the synthesis. F-HPLC is used to separate ("demix") the final quasiracemate into its two components, which are then detagged to provide (true) enantiomeric products.

The availability of n tags in a single tagging strategy allows n compounds to be tagged. The addition of m new tags to a given class of n tags increases the maximum possible size of a mixture to (n + m) (Figure 1.4.4.3).

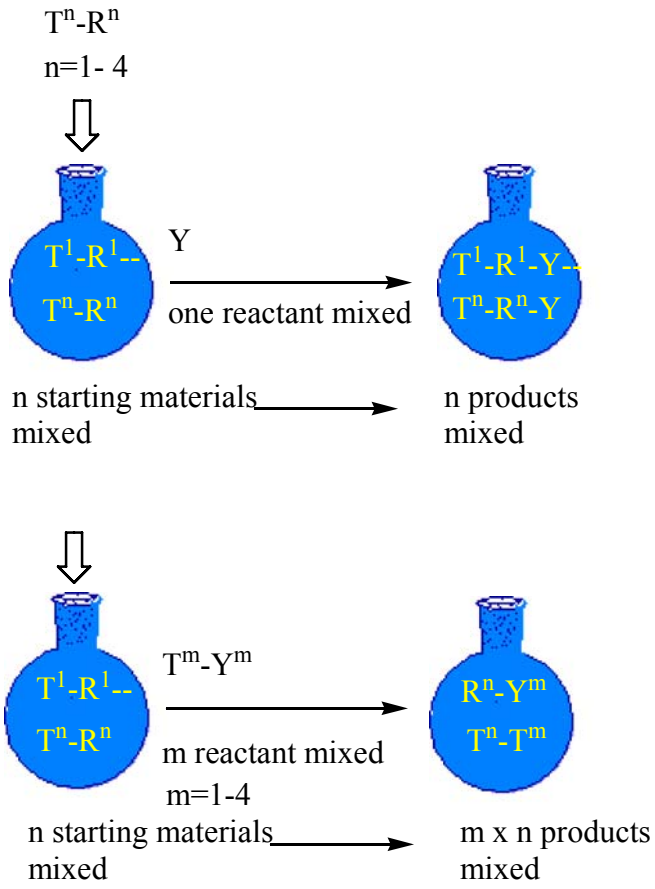
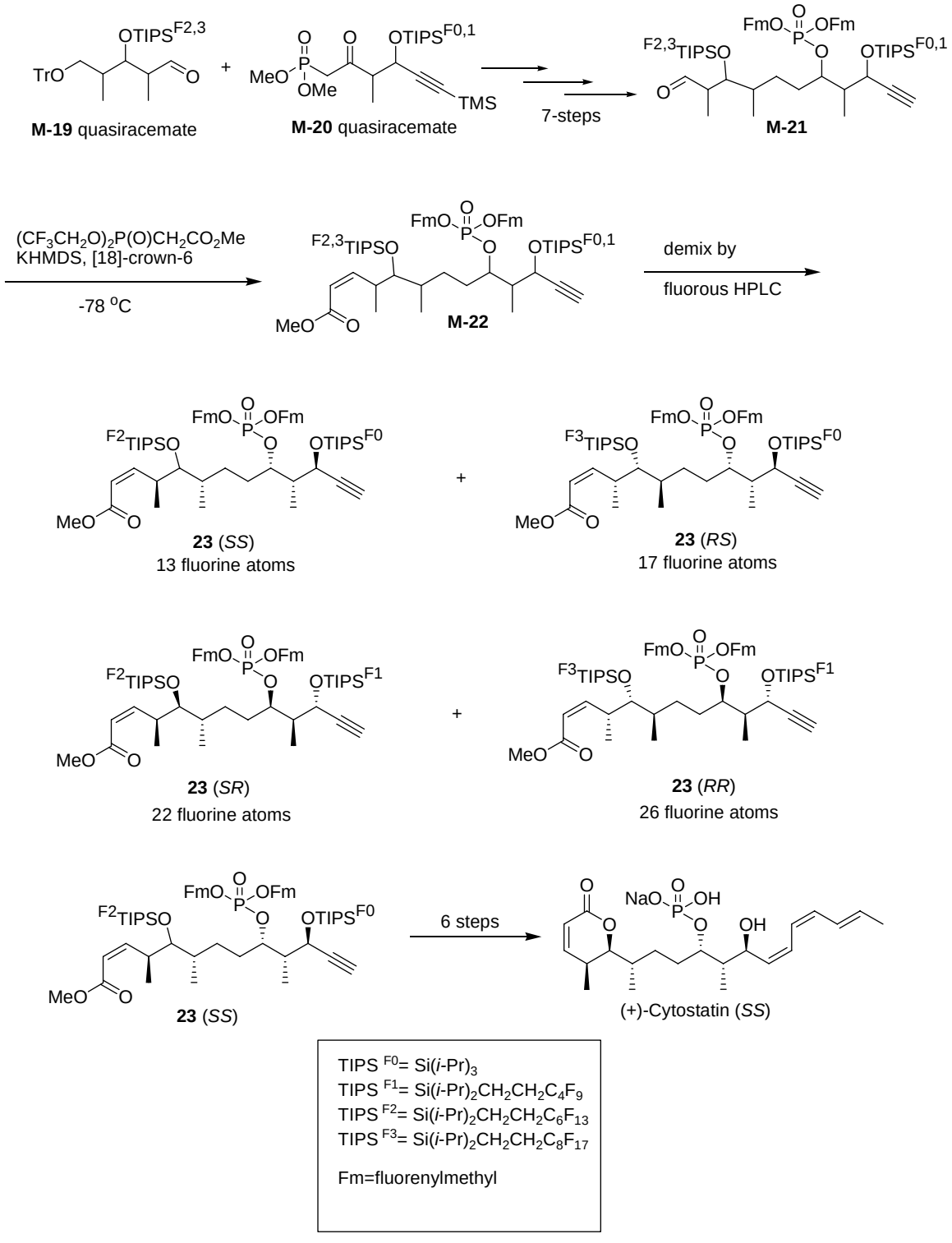


Figure 1.4.4.3: Single (top) and double (bottom) separation tagging.[37]

Curran and coworkers[38] confirmed the stereochemistry of (+)-cytostatin as (*SS*) by fluorous mixture synthesis out of its four stereoisomers (Scheme 1.4.4.1). The cytostatin stereoisomers were prepared from a mixture of (*Z*) α,β-unsaturated esters **M-22**. The mixture **M-22** was prepared from the aldehyde mixture **M-21** by treatment with KHMDS, 18-crown-6 and trifluoroethyl phosphonate ester employing Gennari olefination.[39,40] Gennari olefination is an analogue of Wittig reaction and gives *Z* olefins. The aldehyde mixture **M-21** was obtained from quasiracemates **M-19** and **M-20** through seven steps. The mixture **M-22** was demixed into four individual quasiisomers by preparative fluorous HPLC. Each quasiisomer was converted to the corresponding

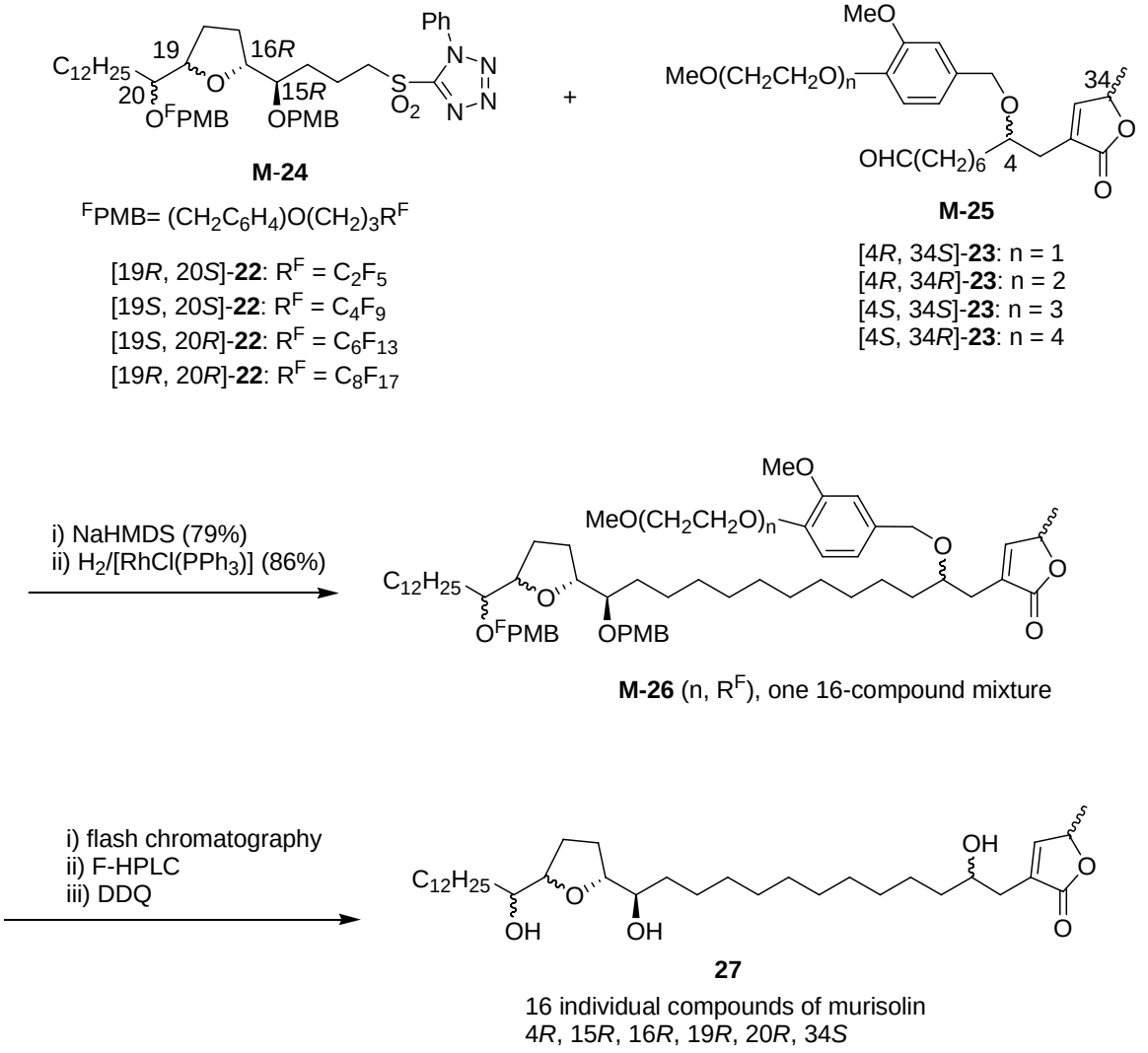
cytostatin stereoisomer and compared with the natural product. Only the *SS*-isomer matched natural (+)-cytostatin.



Scheme 1.4.4.1: Synthesis of (+)-cytostatin from quasiracemates.[38]

1.4.5 Library Generation by Fluorous Mixture Synthesis

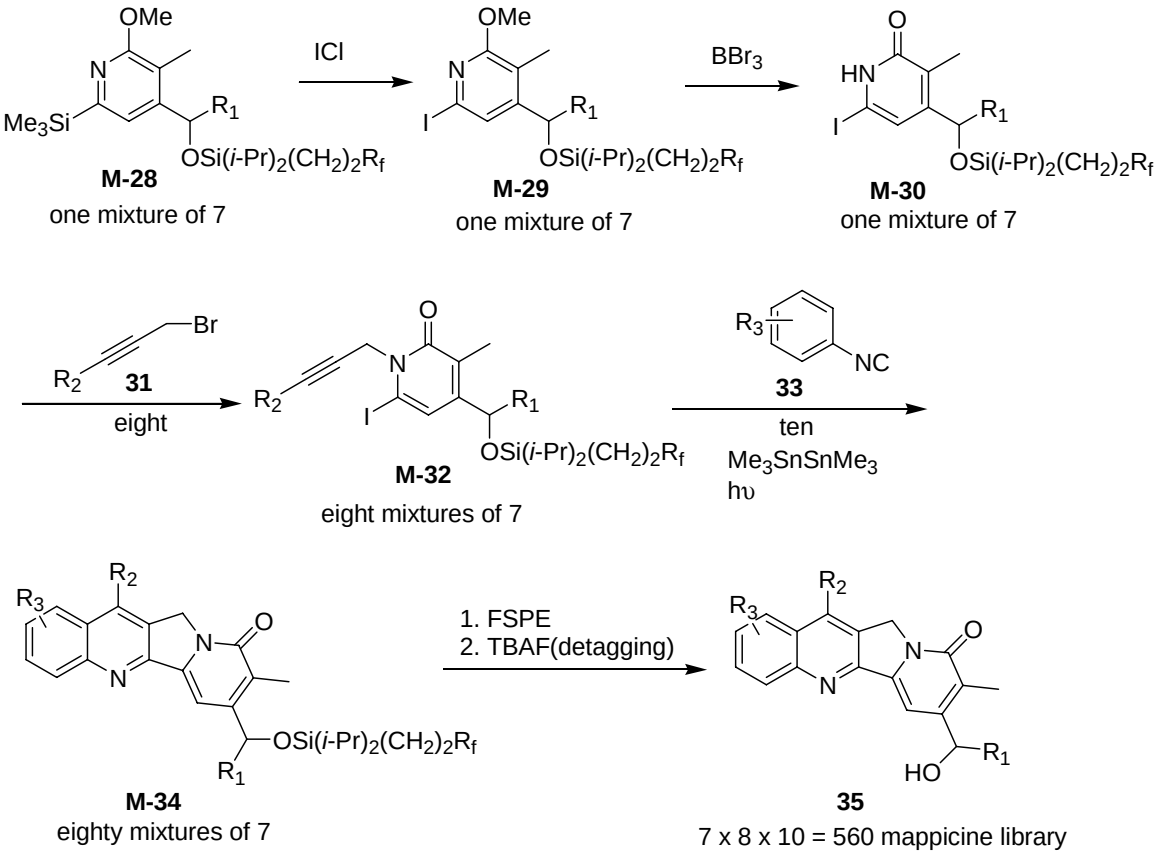
A stereoisomer library of 16 individual murisolins was prepared by Curran and his group[37,41] employing a fluorous double demixing technique. The Kocienski–Julia coupling[42] of the four-compound fluorous-tagged mixture **M-24** and the four-compound oligoethyleneglycol (OEG) tagged mixture **M-25** followed by direct hydrogenation gave rise to 16-compound mixture **M-26** (Scheme 1.4.5.1).



Scheme 1.4.5.1: Synthesis of 16-membered library of murisolin.[37]

Flash chromatography separated four fractions based on the OEG tag from OEG1 (least polar) to OEG4 (most polar). Demixing was conducted by F-HPLC. Simultaneous detagging of fluorous and OEG tags along with PMB deprotection was performed using DDQ.

The generation of a 560-membered library of the analogues of mappicine was demonstrated by Zhang *et al*.[43] employing fluorous mixture synthesis. A seven-component mixture of pyridinyl alcohols bearing different R_1 groups was carried through a four-step mixture synthesis to incorporate two additional points of diversity onto the tetracyclic core (Scheme 1.4.5.2).



Scheme 1.4.5.2: Generation of 560-membered mappicine library.[43]

1.5 Usefulness of Fluorous Tagged Thiols

The inherent chemical properties of thiols engendered a new field in fluorous technology. Thiols are good nucleophiles, and function as Michael donors towards conjugated electrophiles. Sulfides can be easily cleaved by oxidative or reductive methods. Due to these reasons, fluorous thiols have applications in diverse areas of chemistry and biology.

1.5.1 Fluorous Thiols for Tagging in Proteomics

Proteins in living organisms are Nature's exquisite paradigms of molecular engineering. Fluorous proteomics involves the use of perfluorinated compounds for the effective enrichment and subsequent characterization of various peptide subsets from highly complex mixtures of biological origin.The "fluorous proteomics" concept was introduced by Brittain *et al*.[44] in 2005.

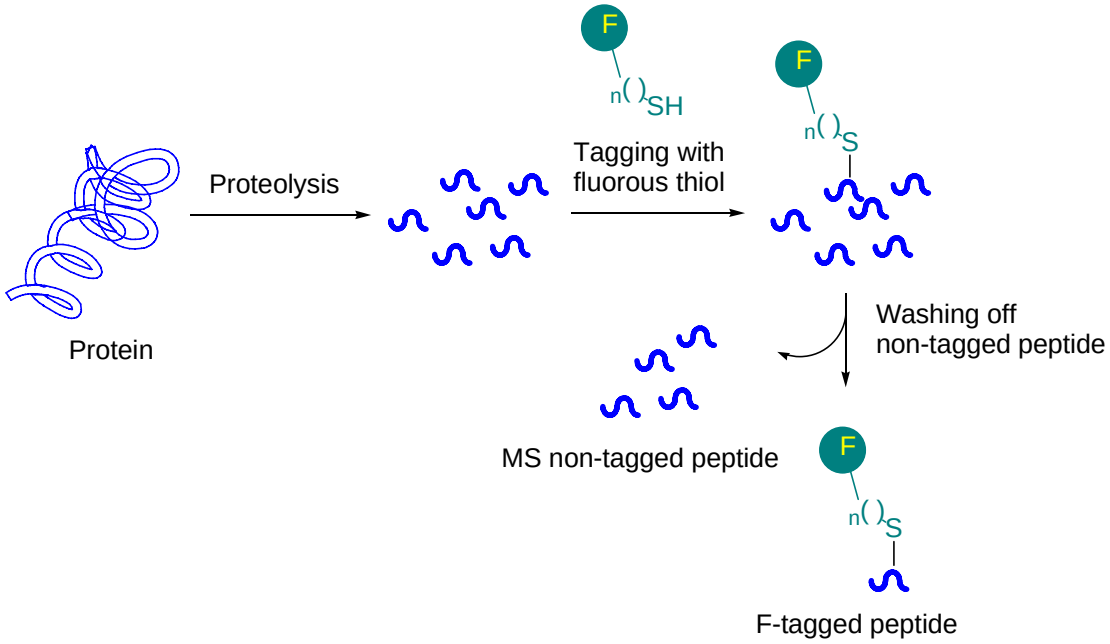
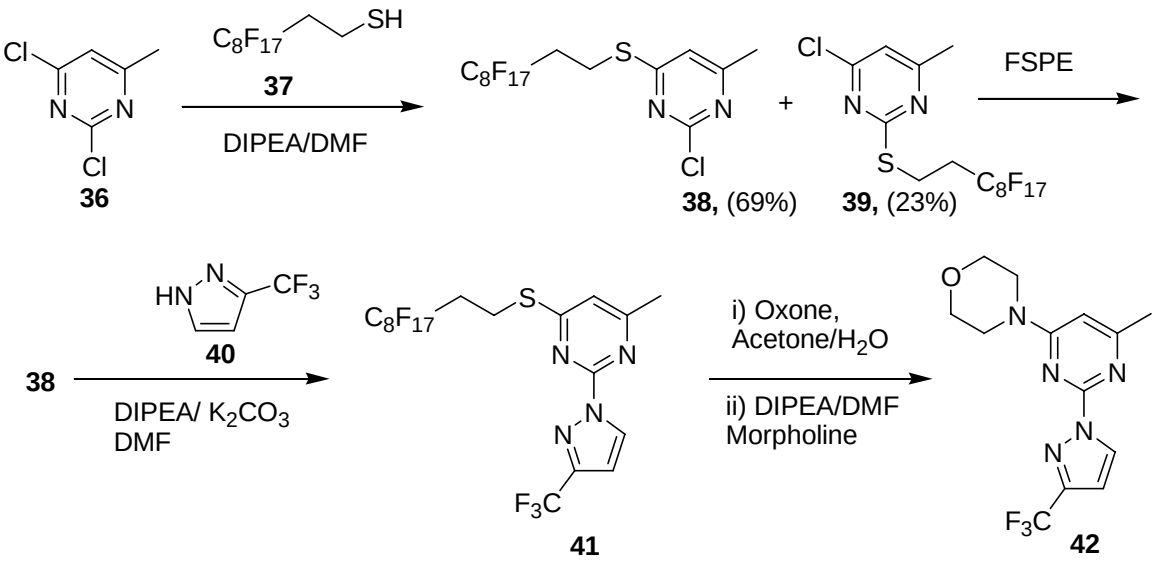


Figure 1.5.1.1: Tagging of peptides with fluorous thiols.[44]

Proteolysis of the protein content of a cell with trypsin results in peptides. The peptides were treated with performic acid to oxidize cysteine residues to cysteic acid. The oxidized peptides were subjected to β-elimination/Michael addition using $C_8F_{17}CH_2CH_2SH$ as a Michael donor, and subsequently oxidized with H_2O_2 to generate a specific MS/MS marker for identification. Simple FSPE separates the nonlabeled peptides from the labeled peptides which are characterized by a compatible MS/MS sequencing strategy. The facile and extremely selective enrichment of peptides bearing thiol, amino or other side-chain functionalities, or specific post-translational modifications makes this strategy versatile in contrast to classical bioaffinity-based enrichment strategies used in functional proteome characterization.

1.5.2 Tagging in Heterocyclic Chemistry

The utility of fluorous thiols has been explored in pyrimidine chemistry, where 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol **37** was used to tag disubstituted pyrimidines.[45] The tagged substrate was substituted with 3-(trifluoromethyl)pyrazole **40** followed by thioether oxidation and the tag was displaced with secondary amines (Scheme 1.5.2.1). Two regioisomers can be separated using this technique.



Scheme 1.5.2.1: Tagging of pyrimidines by a fluorous thiol.[45]

1.5.3 Fluorous Thiols as Scavengers

A brilliant use of fluorous thiols as scavengers was demonstrated by Curran and coworkers.[46] In *N*-alkylation reactions, excess α-bromoketone or benzyl bromide can be quenched with a fluorous thiol. The excess reagent tagged by the fluorous thiol can be removed by FSPE from the pure product (Scheme 1.5.3.1).

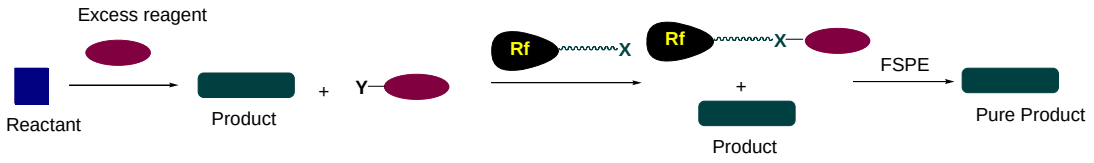
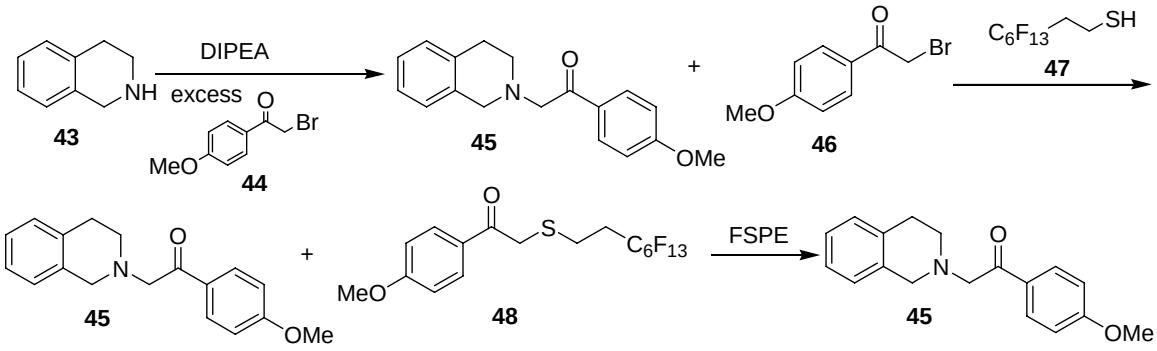


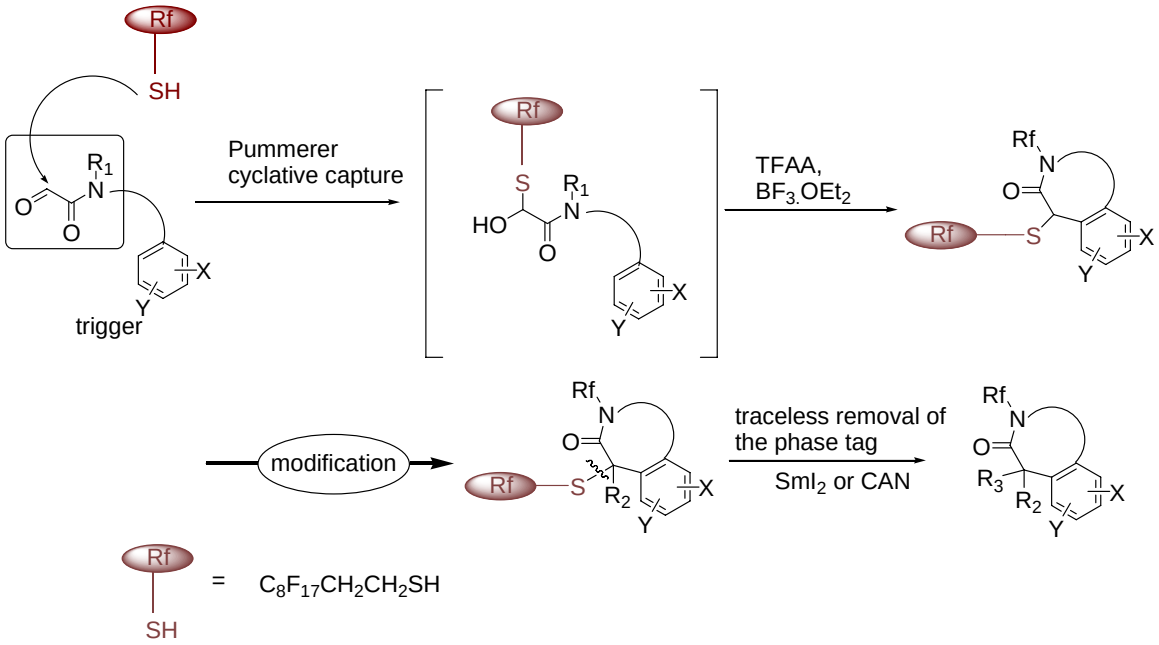
Figure 1.5.3.1: Schematic representation of a fluorous scavenger.[46]



Scheme 1.5.3.1: Quenching of excess reagent by a fluorous thiol.[46]

1.5.4 Fluorous Thiols as Traceless Linkers

A remarkable concept, "fluorous cyclative capture through Pummerer cyclization" and "traceless linker cleavage" was introduced and pioneered by Procter and coworkers.[47] Traceless reductive or oxidative cleavage of the fluorous-phase tag provides a method to synthesize a diverse range of heterocycles in a high-throughput manner. The treatment of readily accessible glyoxamides with fluorous thiol **37** captured the substrate through hemithioacetal formation. Activation of the intermediate with trifluoroacetic anhydride (TFAA) and treatment with $BF_3{\cdot}OEt_2$ gave the product heterocycles in good yield after rapid purification employing FSPE. The fluorous tag can be removed reductively or oxidatively from elaborated heterocyclic systems (Scheme 1.5.4.1).

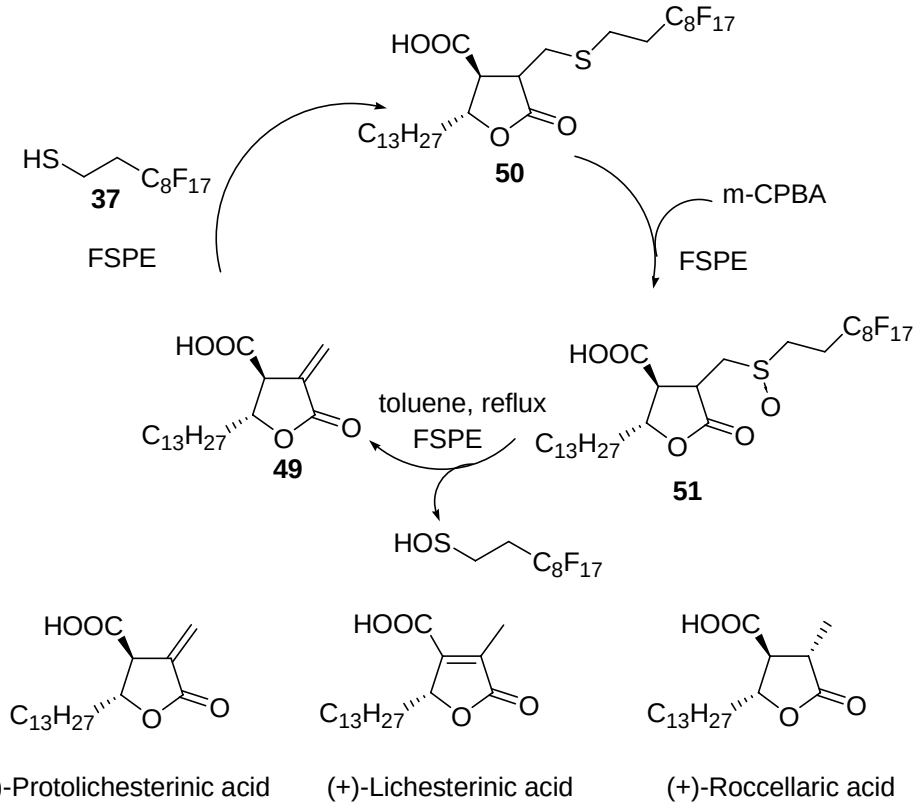


Scheme 1.5.4.1: Fluorous Pummerer cyclization and removal of traceless linker.[47]

1.5.5 Fluorous Thiols in Isolation of Natural Products

Needless to say, the isolation and purification of natural products are challenging, lengthy, and tedious processes. However, successful application of a fluorous thiol "catch

and release" approach to isolate (+)-protolichesterinic acid from a mixture of (+)-lichesterinic acid, (+)-roccellaric acid and (+)-protolichesterinic acid paved the way for a new natural product isolation technique.[48] These three paraconic acids are extracted from a well-known lichen *Cetraria islandica (L.)* Ach. The (+)-protolichesterinic acid **49** was captured with fluorous thiol **37** through a Michael addition reaction and released via a retro-Michael reaction (Scheme 1.5.5.1).

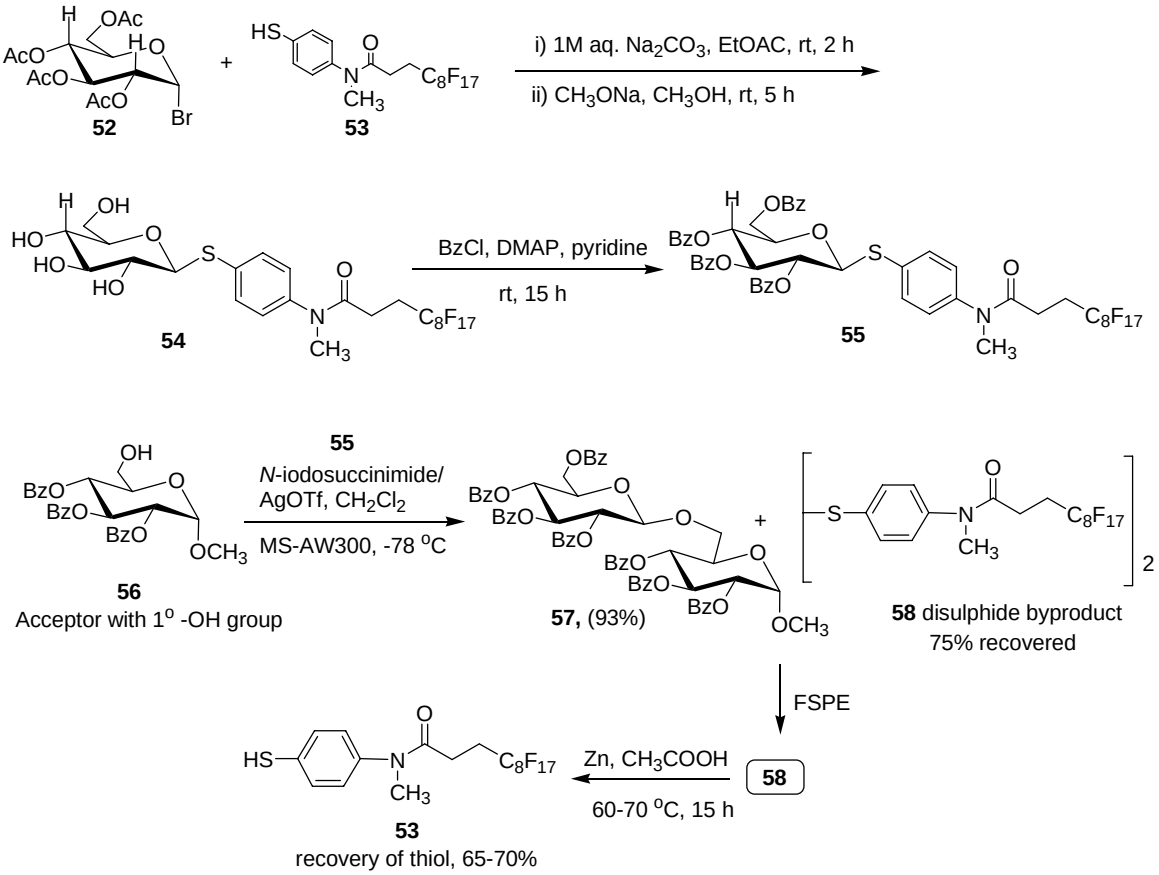


Scheme 1.5.5.1: Fluorous "catch and release" approach in natural product separation.[48]

1.5.6 Fluorous Thiols in Oligosaccharide Synthesis

An odorless fluorous thiol, *p*-methylamido thiophenol **53** was synthesized and it was further used to prepare a highly fluorinated thioglycosyl donor **55** (Scheme 1.5.6.1).[49] Fluorous tagged thioglycosides exhibit excellent reactivity in glycosylation reactions. They are stable under esterification, etherification, deacetylation, and

glycosylation conditions and are also readily separable by FSPE. The fluorous thiol can be recovered from the glycosylation mixture and recycled.



Scheme 1.5.6.1: Fluorous thiol as a glycosyl donor in oligosaccharide synthesis.[49]

1.6 Aryl-Sulfur Bond Formation

The prevalence of aryl-sulfur bonds in many important natural products and pharmaceutical compounds makes methods for the formation of these bonds as indispensable tools in synthetic chemistry. Anilino diaryl sulfide **59** is an elegant example of a pharmaceutically important compound because of its potential activity towards acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection, and reperfusion injury.[50] Another example of a bioactive compound containing

an aryl-sulfur core is 2-substituted aminobezothiazole sulfonamide **60,** a potent broad spectrum HIV protease inhibitor.[51]

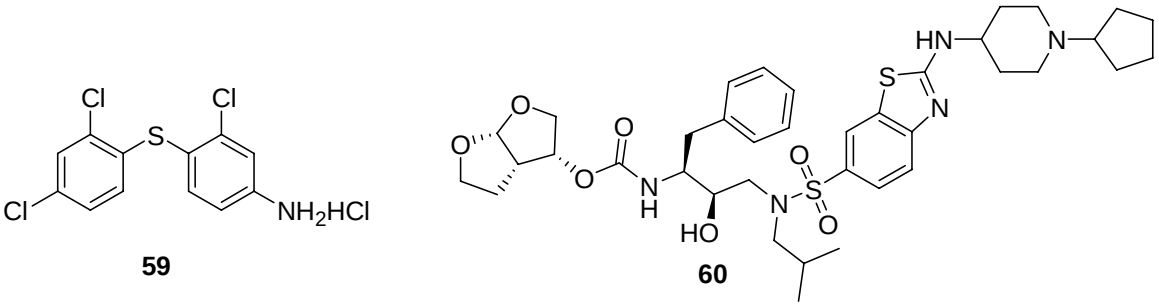
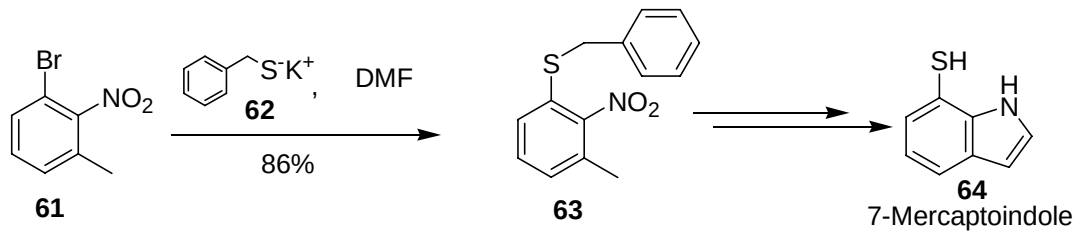


Figure 1.6.1: Bioactive compounds having aryl-sulfur bonds.

An aryl-sulfur bond can be formed by noncatalytic copper thiolate chemistry, and copper or palladium catalyzed reactions. Direct noncatalytic nucleophilic displacement of the bromo group in the electron deficient system of 3-bromo-2-nitrotoluene **61** with the potassium salt of benzylmercaptan **62** was employed by Brown and coworkers to synthesize 7-mercaptoindoles **64**.[52]

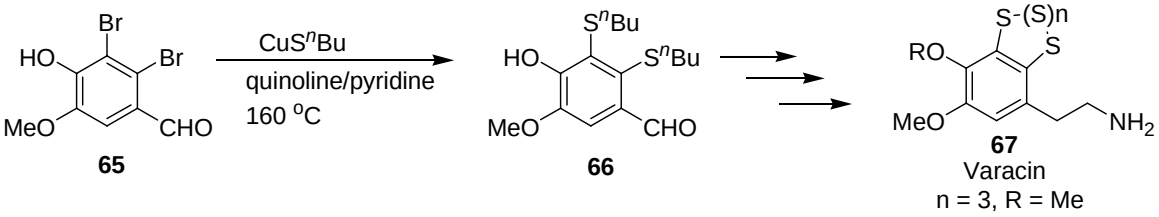


Scheme 1.6.1: Noncatalytic aryl-sulfur bond formation.[52]

1.6.1 Copper Thiolate Noncatalytic Reactions

Hitherto the most widely used protocol for thiolation reactions was discovered by Adams and coworkers in 1959.[53] Aryl and alkyl thioethers were synthesized by treatment of cuprous mercaptides with aryl bromides. The reaction was generalized with mono bromo-, dibromo- and tribromo- benzene systems. The disadvantages associated with this

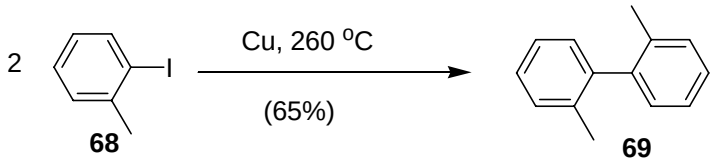
traditional method are harsh reaction conditions, long reaction times and poor yields. This method was utilized in the total synthesis of varacin **67**, an unusual dopamine-derived cyclic polysulfide. In addition to its unique structure, varacin exhibits significant antifungal and cytotoxic activities.[54,55]



Scheme 1.6.1.1: Total synthesis of varacin.[54]

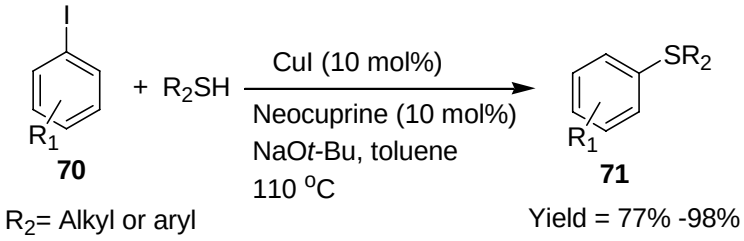
1.6.2 Copper Catalyzed C-S bond formation: The Ullmann reaction

The Ullmann reaction[56,57] is an important method to form C-C bonds. There are two types of Ullmann reactions. One involves biaryl formation by homocoupling of aryl halides. The reactivity of the aryl halide follows an order of I > Br > Cl. An electronegative group in the ortho position activates the reaction. The use of bromides and chlorides maximizes unsymmetrical coupling, while iodo compounds generally give the symmetrical coupling product. The other type of the Ullmann reaction is copper mediated coupling of aryl halides with phenols, thiophenols and anilines. Traditional Ullmann reactions suffer drawbacks from its harsh reaction conditions and stoichiometric use of copper reagents.



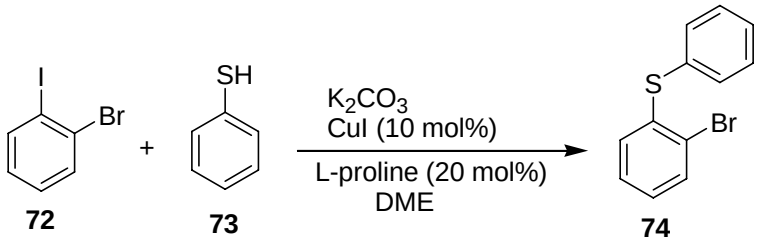
Scheme 1.6.2.1: Homocoupling of aryl iodides.

On the other hand, the advantages of copper mediated Ullmann type reactions are functional group tolerance, catalytic use of Cu catalyst, low temperature conditions and higher yields. A mild, palladium-free synthetic protocol for the cross-coupling reaction of aryl iodides and thiols using CuI and neocuproine was reported by Venkataraman (Scheme 1.6.2.2).[58]



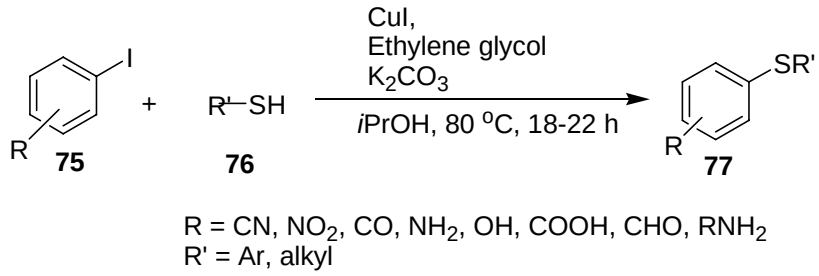
Scheme 1.6.2.2: Catalytic aryl-sulfur bond formation by the Ullmann reaction.

Another mild procedure for the CuI-catalyzed coupling reactions of aryl iodides with aliphatic and aromatic thiols involves *L*-proline as a ligand for copper. This method tolerates a wide range of other functional groups.[59] An iodide can be selectively substituted in the presence of a bromide (Scheme 1.6.2.3).



Scheme 1.6.2.3: Selective aryl-sulfur bond formation in the presence of a bromide.

Buchwald reported efficient C-S bond formation conditions for both aryl and alkyl thiols using CuI, potassium carbonate, and ethylene glycol. The process is extremely tolerant of a variety of common functional groups and of steric hindrance.[60]



Scheme 1.6.2.4: Cu catalyzed aryl-sulfur bond formation.[60]

1.6.3 Pd Catalyzed Aryl-Sulfur Bond Formation

The methods for Pd catalyzed aryl-sulfur bond formation are less common in the literature compared to routes to aryl ethers and aryl amines. The palladium catalyzed aryl-sulfur bond formation reaction is an emerging area of research in organosulfur chemistry.[61,62] The typical mechanism for a Pd (0) catalyzed aryl-sulfur bond formation reaction is based on the cycle shown below (Figure 1.6.3.1).

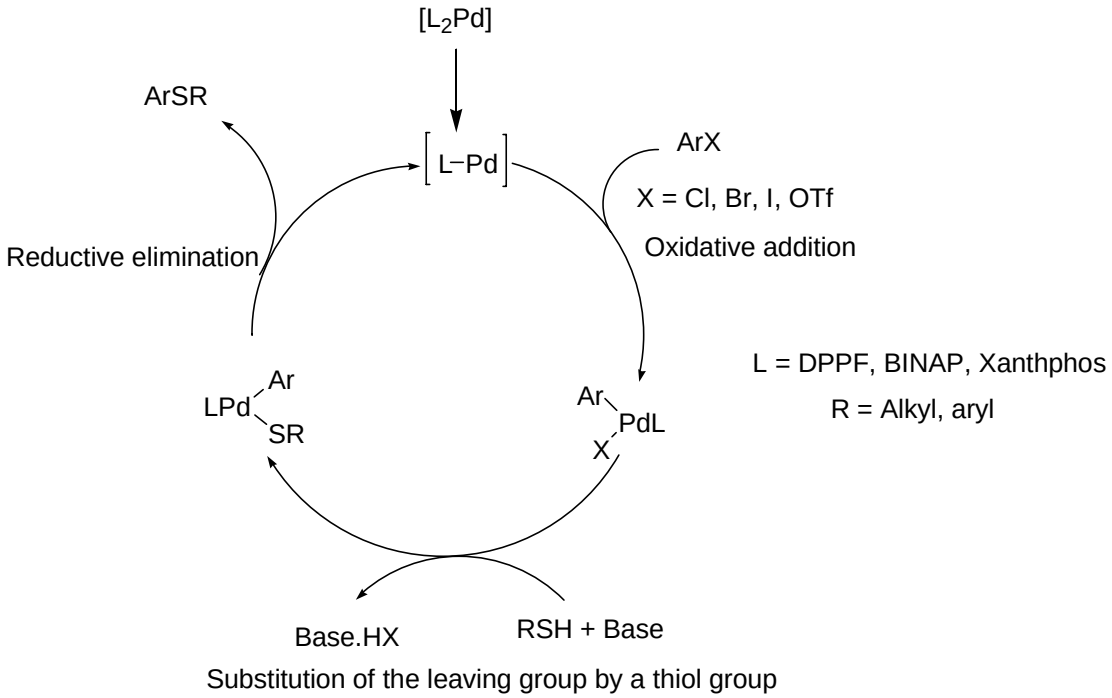
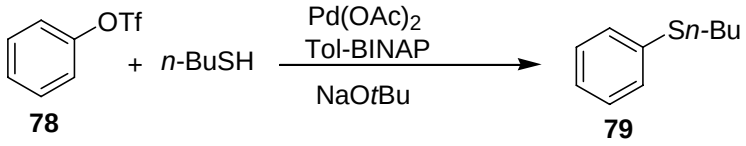


Figure 1.6.3.1: Catalytic cycle for Pd (0) catalyzed thiolation reaction.[63]

The key steps that recur throughout this course are oxidative addition of ArX group to Pd (0) converting it to Pd (II); substitution of the leaving group by a thiol group; and then reductive elimination of the coupled product (ArSR) to release the metal Pd (0).

An aryl-sulfur bond formation was achieved by treatment of aryl triflates with sodium alkanethiolates on catalytic treatment with $Pd(OAc)_2$ and Tol-BINAP, a bidentate phophine ligand.[61] Zheng observed that electronically neutral or electron deficient aryl triflates gave better yields than electron rich triflates.



78 **79**

Scheme 1.6.3.1: Thiolation reaction with triflate.[61]

1.6.4 Sulfur Poisoning in Pd Catalysis

Poisoning of palladium catalysts by sulfur compounds is a frequent problem in organic chemistry. The poisoning effect of sulfur on Pd and Rh catalysis was studied by Kulishkin *et al*.[64] It was reported that SO_2 and H_2S are strong poisons of rhodium and palladium catalysts for liquid-phase hydrogenation of 3-thiolene-1,1-dioxide and thiophene. For heterogeneous catalysis, sulfur-containing compounds act as catalyst poisons because of their strong coordinating and adsorptive properties and often render the catalysts totally ineffective.[65,66] Adsorbed poisons may dissolve in the bulk phase of the catalyst in addition to poisoning the surface. Sulfur poisoning of the catalyst may result in surface morphology change.[67]

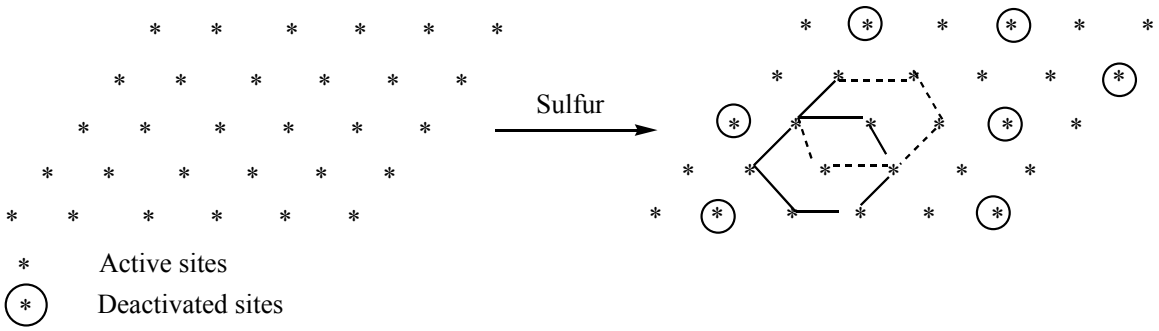


Figure 1.6.4.1: Sulfur poisoning.[67]

An extensive study was carried out to understand sulfur poisoning in heterogeneous Pd catalysis. Gao[65] analyzed the poisoning effects and mechanisms of sulfur on Pd-based metal membranes. Synchrotron-based high-resolution photoemission spectroscopy suggested that after chemisorption of sulfur on the Pd surface, there is a substantial decrease in the electron density belonging to the metal near the Fermi level and a simultaneous drop in the electron population of its 4d band. This phenomenon has a strong impact on the surface properties of Pd membranes.[68]

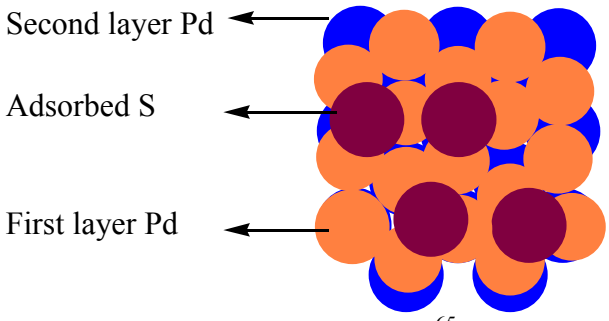


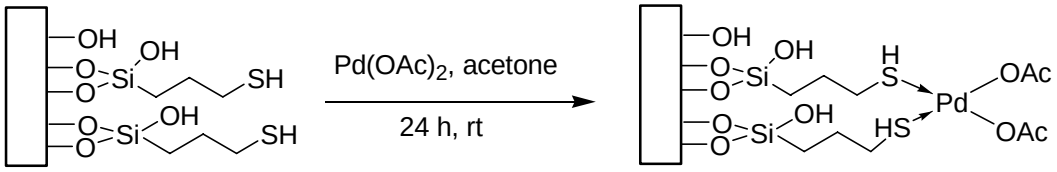
Figure 1.6.4.2: Chemisorption of sulfur on Pd surface.[65]

1.6.5 Thiol Poisoning in Homogeneous Pd Catalysis

Multiple deactivation pathways exist for soluble palladium, including redeposition on supports, formation of palladium black, and overcoordination by strongly

binding ligands such as thiols. Aryl iodides are more active than aryl bromides or aryl chlorides due to their rapid oxidative addition to Pd (0), forming a Pd (II) complex.[69] As the aryl iodide is consumed in the reaction, less of it is available to complex to Pd, and the distribution of Pd can shift to favor Pd (0). Unless stabilizing ligands are present, Pd (0) can aggregate to from palladium nanoparticles or palladium black, a typically inactive form of palladium that commonly precipitates out of solution.

In homogeneous catalytic reactions, usually 5-10 mol% Pd catalyst and a stoichiometric amount of thiol is used for thiolation reactions. The thiol can form a complex with Pd and hence, deactivates the catalyst. In 2004, Shimizu *et al.*[70] reported a detailed characterization of mesoporous silica, FSM-16, grafted with 3-mercaptopropylsiloxanes and metalated with palladium acetate to form Pd-SH-FSM. This was the first work to confirm that most of Pd atoms are bound to two sulfur atoms and are in a Pd (II) oxidation state on these types of mercaptopropyl modified silica supports. Recently, the poisoning of $Pd(OAc)_2$ catalyst in homogeneous Suzuki and Heck reactions by solid supported thiol 3-mercaptopropylsiloxanes SH-SBA-15 **80**, was investigated.[69] SH-SBA-15 is an effective and selective poison of homogeneous palladium species.

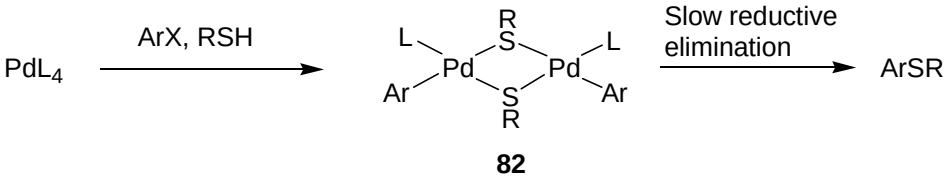


SH-SBA-15
80

Pd-SH-SBA-15
81

Figure 1.6.5.1: Poisioning of Pd catalyst in Heck and Suzuki reaction.[69]

Hartwig synthesized and isolated a bridging complex **82,**[71] which was responsible for slowing down the reductive elimination step. He proposed that the addition of thiols to PdL_4 can form an anionic thiolate complex or a bridging complex **82.**



82

Scheme 1.6.5.1: Formation of stable bridging complex.

In order to address this problem of bridging complex formation with thiols, bidentate phosphine ligands with restricted backbone conformation, steric hindrance, and strong electron donating group "R" are chosen. These form strong complexes with palladium as well as promote the oxidative addition and reductive elimination steps in the catalytic cycle. Oxidative addition of ArX to **83** gives complex **84** and displacement of the leaving group X by a thiol followed by *trans-cis* isomerization results in **86**. Finally, reductive elimination will give the thioether ArSR (Figure 1.6.5.2). The electron donating nature of the R group will increase the rate of oxidative addition, while a sterically crowded phosphine ligand will increase the rate of the reductive elimination step. The steric hindrance of the R group of bidentate ligands will prevent the formation of bridging complexes.[72] Thus, bridging complex formation and the poisoning effect of thiols in homogeneous Pd catalysis can be circumvented by switching to a rigid, electron donating bidentate phosphine ligand from a monodentate phosphine ligand.

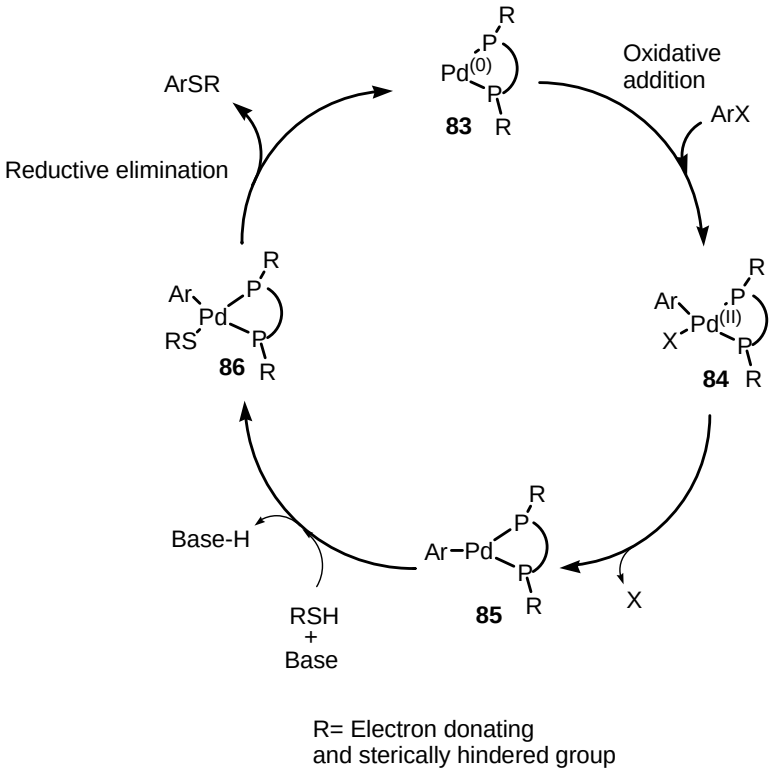
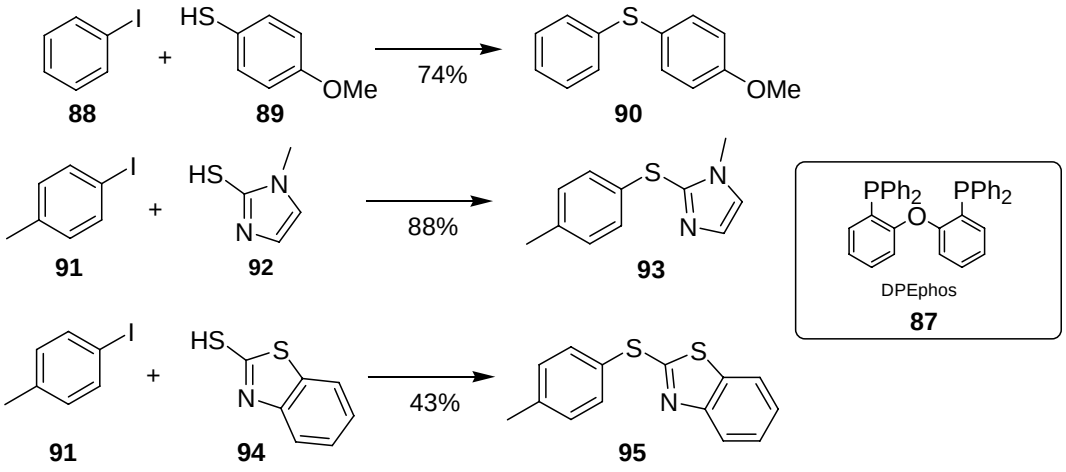


Figure 1.6.5.2: Effect of R group on catalytic cycle.[63,76]

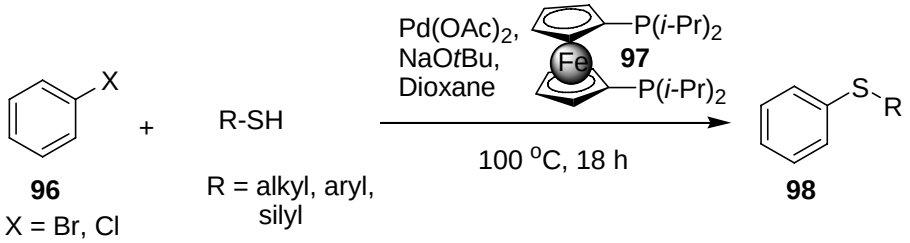
Ulrich Schopfer reported the synthesis of heterocyclic thioethers from heteroaromatic iodides as well as various heteroaromatic thiols using the bidentate ligand DPEphos **87** and Pd_2dba_3 (Scheme 1.6.5.2).[62]



Reaction condition: 1 mol% Pd_2dba_3, 2 mol% DPEphos, *t*-BuOK, Toluene, 100 ^oC, 2 h

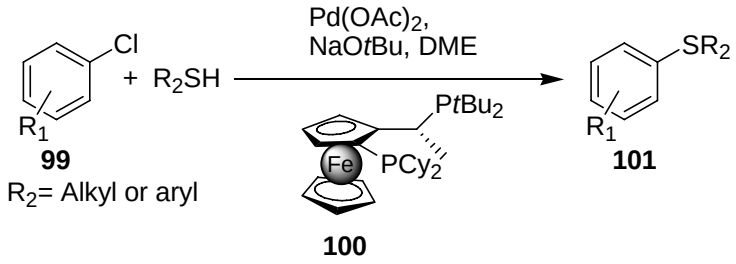
Scheme 1.6.5.2: Use of DPEphos and Pd_2dba_3 in aryl-sulfur bond formation reactions.[62]

In general, unactivated aryl chlorides are intransigent towards thiolation reactions. A general method for cross-coupling of thiols with aryl halides encompassing unactivated aryl chlorides using $Pd(OAc)_2$ and 1,10-bis(diisopropylphosphino)ferrocene (DiPPF) **97** was developed by Buchwald (Scheme 1.6.5.3).[73] The coupling is facile with electron-rich and sterically-hindered aryl halides as well as primary, secondary, tertiary and aromatic thiols.



Scheme 1.6.5.3: Pd catalyzed monothiolation reaction.[73]

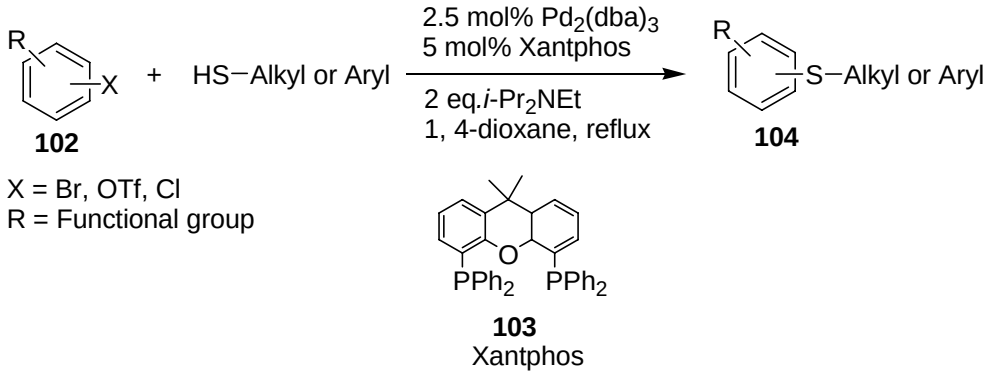
Hartwig[72] reported thiolation reactions of aromatic halides containing a wide range of other substituents using $Pd(OAc)_2$ and the Josiphos ligand [dicyclohexylphosphinoferrocenyl]ethyl di-*t*-butyl phophine, CyPF-*t*Bu **100**. The examples in this paper included some stubborn aryl chlorides. The restricted backbone conformation, high degree of steric hindrance, and strong electron donating ability of this ligand gave high turnover numbers.



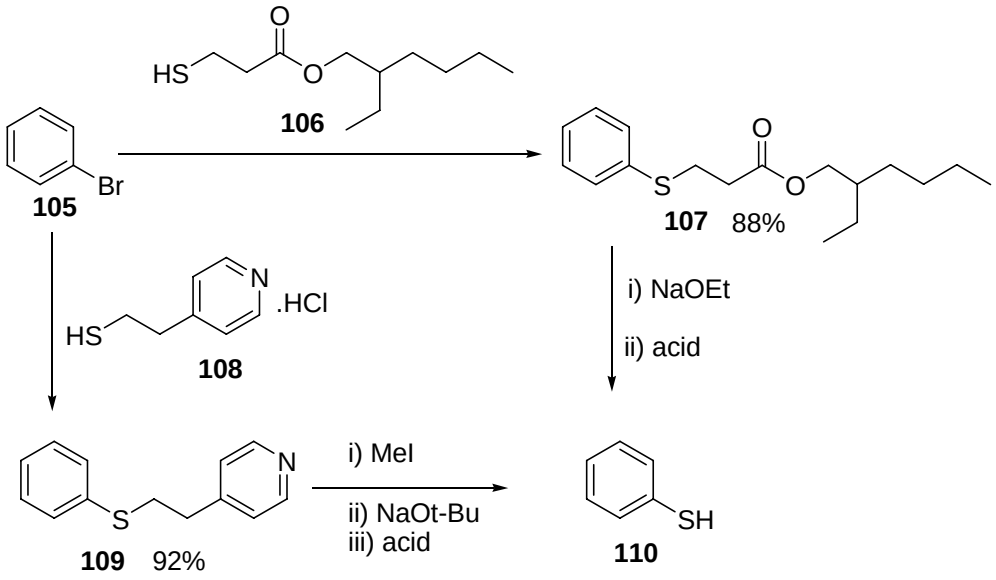
Scheme 1.6.5.4: Pd catalyzed thiolation reaction with chloro derivatives.[72]

Itoh and coworkers pioneered an efficient and robust Pd-catalyzed reaction to form aryl-sulfur bond between both aryl and alkyl thiols and aryl bromides, triflates and

active chlorides using $Pd_2(dba)_3$ and Xantphos **103** (Scheme 1.6.5.5).[74,75] The process involved a Pd catalyzed coupling reaction of aryl bromides with surrogate thiols or pyridine thiols. 2-(4-Pyridyl)ethanethiol hydrochloride salt **108** and 2-ethylhexyl-3-mercaptopropionate **106** are two odorless and inexpensive thiol surrogates. After installation of the aryl-sulfur bond, the ester or pyridine part was removed by treatment with a base via a β-elimination reaction (Scheme 1.6.5.6).

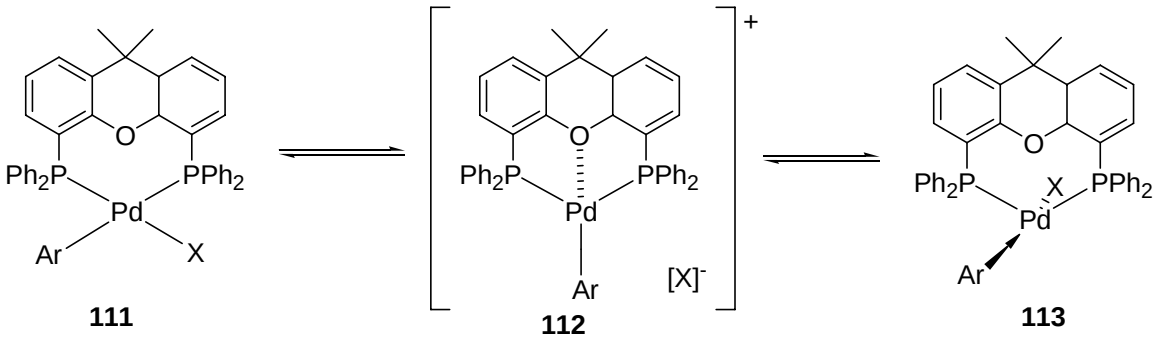


Scheme 1.6.5.5: Pd catalyzed thiolation reaction using Xantphos ligand.



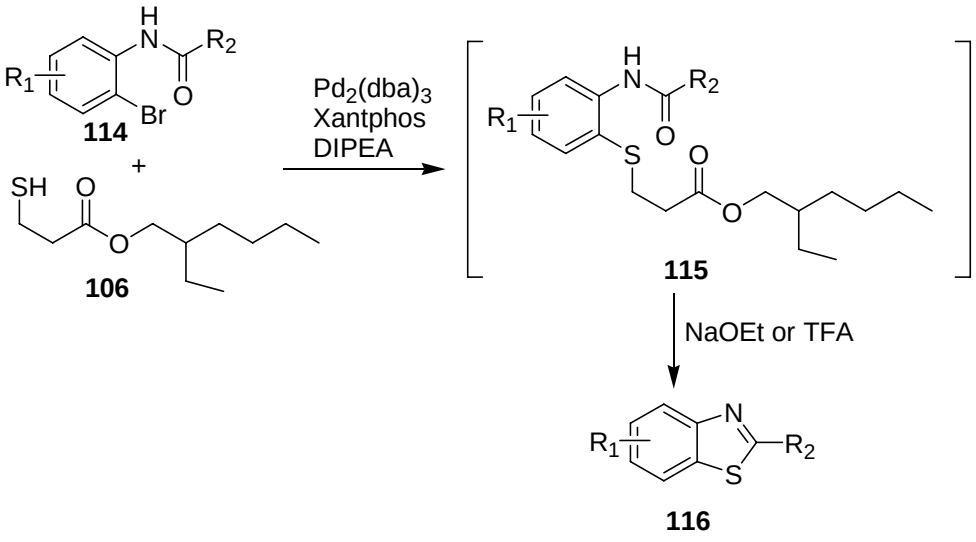
Scheme 1.6.5.6: Thiol surrogates in aryl-sulfur bond formation reactions.[75]

The Xantphos ligand plays an important role in this high yielding reaction. According to van Leeuwen's[76] proposal, the ionic intermediate **112** formed during the interchange from the *cis*- to *trans*-complex is stabilized by the oxygen atom on Xantphos.



Scheme 1.6.5.7: *Cis-trans* isomerization.[76]

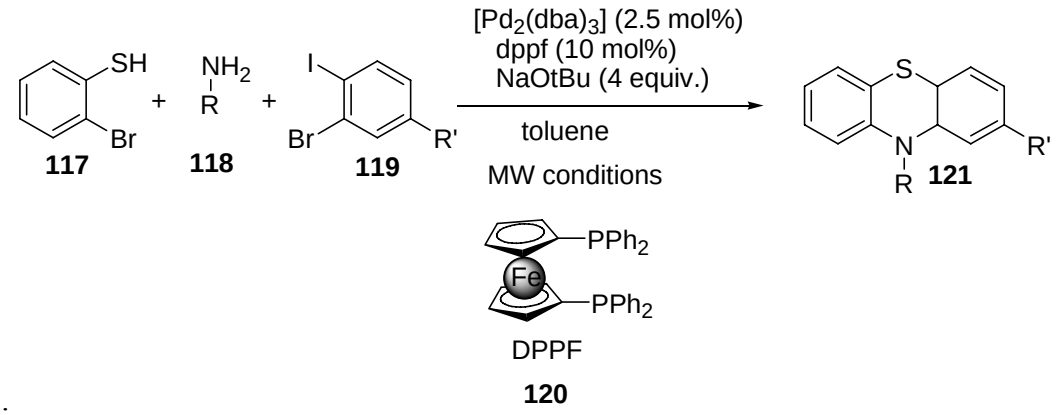
Itoh[77] employed this strategy in medicinal chemistry by synthesizing substituted benzothiazoles **116** from 2-bromoanilides **114** (Scheme 1.6.5.8). The resulting thiols **115** were converted to the corresponding benzothiazoles via a condensation reaction under basic or acidic conditions.



Scheme 1.6.5.8: Synthesis of benzothiazoles.[77]

Recently, a three-component tandem Buchwald thiolation and amination reaction of *o*-bromobenzenethiol **117**, a primary amine **118** and a substituted *o*-bromoiodobenzene

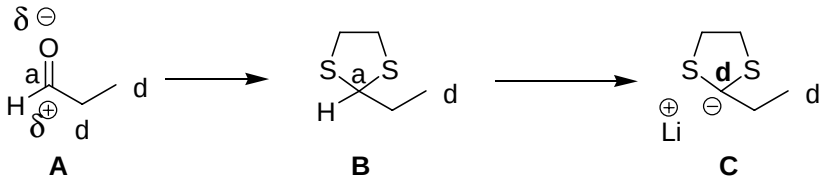
119 in the presence of Pd_2dba_3 and 1,1'-bis(diphenylphosphino)ferrocene, DPPF **120** was carried out under microwave irradiation to give promazine derivatives **121** in good yield.[78]



Scheme 1.6.5.9: Synthesis of a promazine derivative using a three-component reaction.[78]

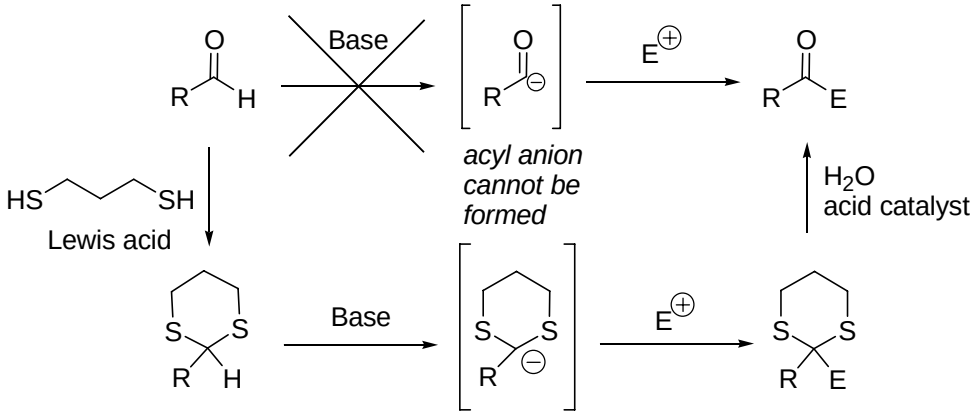
1.7 Dithianes and Umpolung Reactions

Seebach[79] classified the reaction sites in organic molecules used to make and break bonds into two categories: nucleophilic or donor **(d)** and electrophilic or acceptor **(a)** sites. He defined "umpolung" as a process by which donor and acceptor reactivity of a site within a molecule is interchanged. The carbonyl carbon of **A** is acceptor in nature. After the formation of the dithiane **B,** the central carbon will still have '**a**' or acceptor properties, although these properties will be significantly attenuated (Scheme 1.7.1). Treatment of **B** with *n*-BuLi will generate carbanion **C**; however, in this case the carbon will have donor character "**d**". This is a typical "umpolung" situation, because the dithiane can be regarded as a masked carbonyl and its conjugate base is thus synthetically equivalent to an "acyl anion".



Scheme 1.7.1: Example of umpolung in dithiane carbanion.

E. J. Corey demonstrated that the metalation of 1,3-dithianes leads to synthetic equivalents for acyl anions.[80] Dithianes are among the most important umpolung reagents. There are tremendous applications of this type of reagent for C-C bond formation in organic synthesis. These include the reactions between 2-lithio-1,3-dithianes with common electrophiles such as alkyl, allyl and benzyl halides, aldehydes, ketones, carboxylic acid derivatives, epoxides and aziridines.[81] After the formation of the desired C-C bond by reaction with a suitable electrophile, the dithiane can be hydrolyzed to reveal the masked carbonyl group[80] (Scheme 1.7.2).

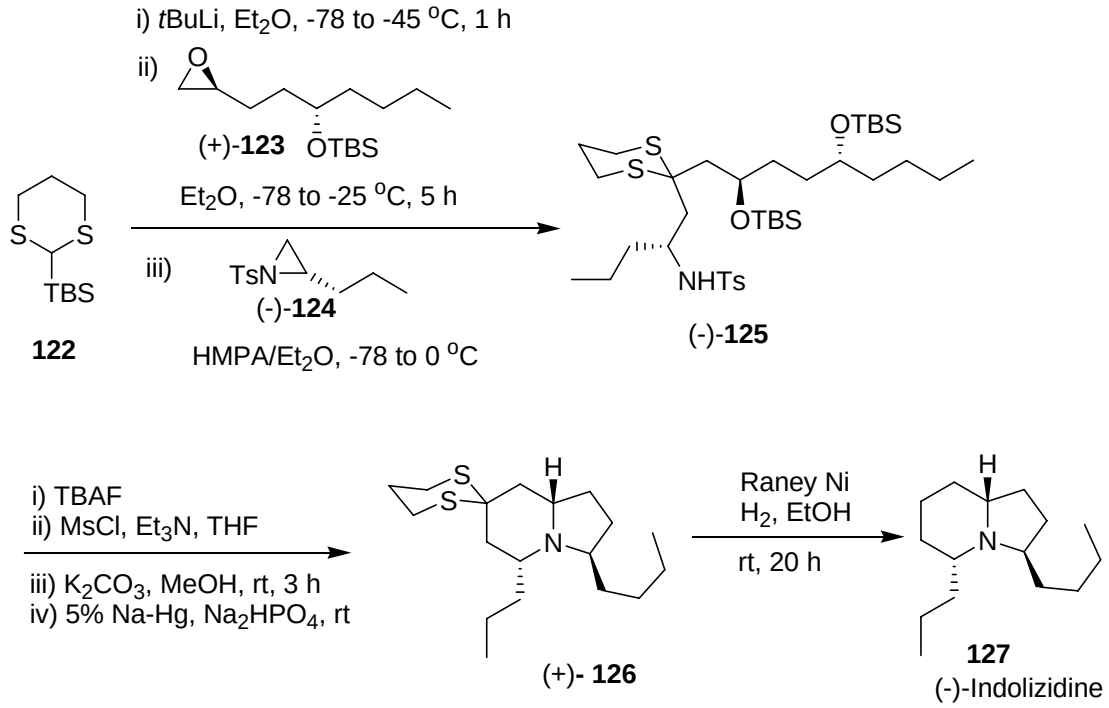


Scheme 1.7.2: Use of dithianes as acyl equivalents.

1.7.1 Applications of Umpolung Reaction in Natural Products Syntheses

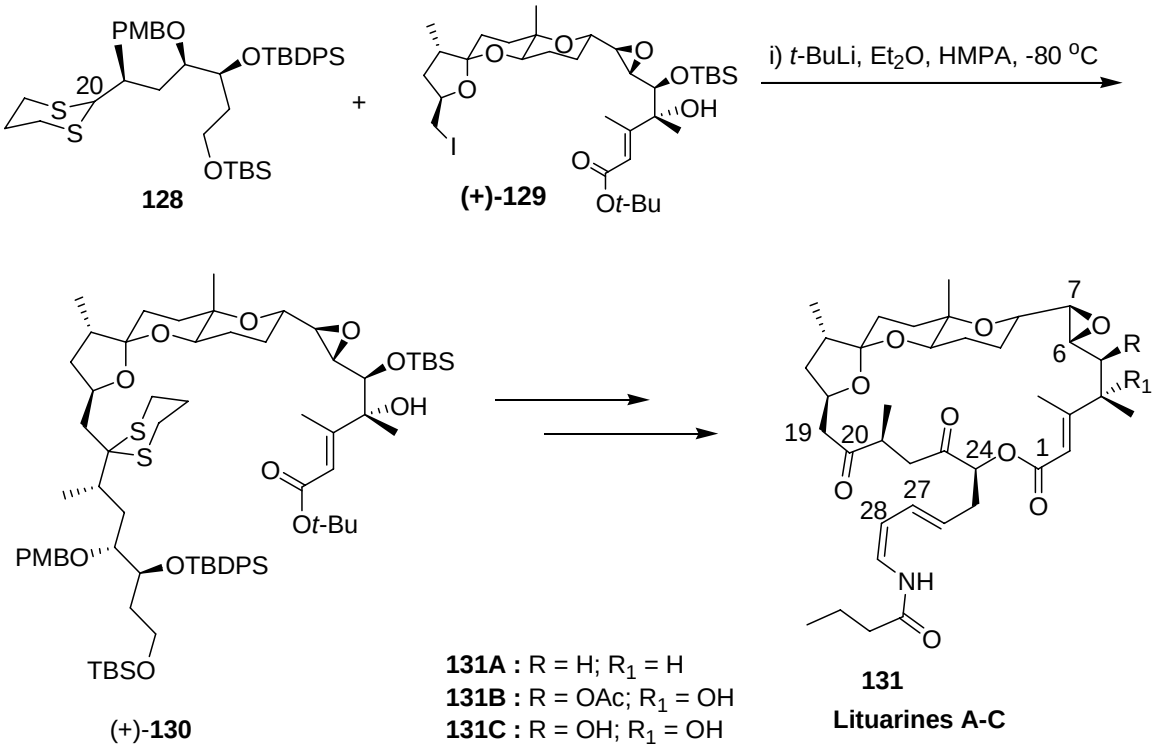
An efficient, stereocontrolled assembly of the indolizidine alkaloid, indolizidine was achieved using a three-component coupling reaction followed by a one-pot sequential construction of the indolizidine ring system.[82,83] The lithiated anion of silyl

dithiane **122** was quenched with epoxide (+)-**123**. The resulting alkoxide underwent the Brook rearrangement to reform a dithiane carbanion, which was counter quenched with aziridine (-)-**124** in the presence of HMPA to furnish (-)-**125** in 56% yield. Compound (-) **125** was converted to (-)-indolizidine **127** through 5 steps.



Scheme 1.7.1.1: Application of the umpolung reaction in indolizidine synthesis.[83]

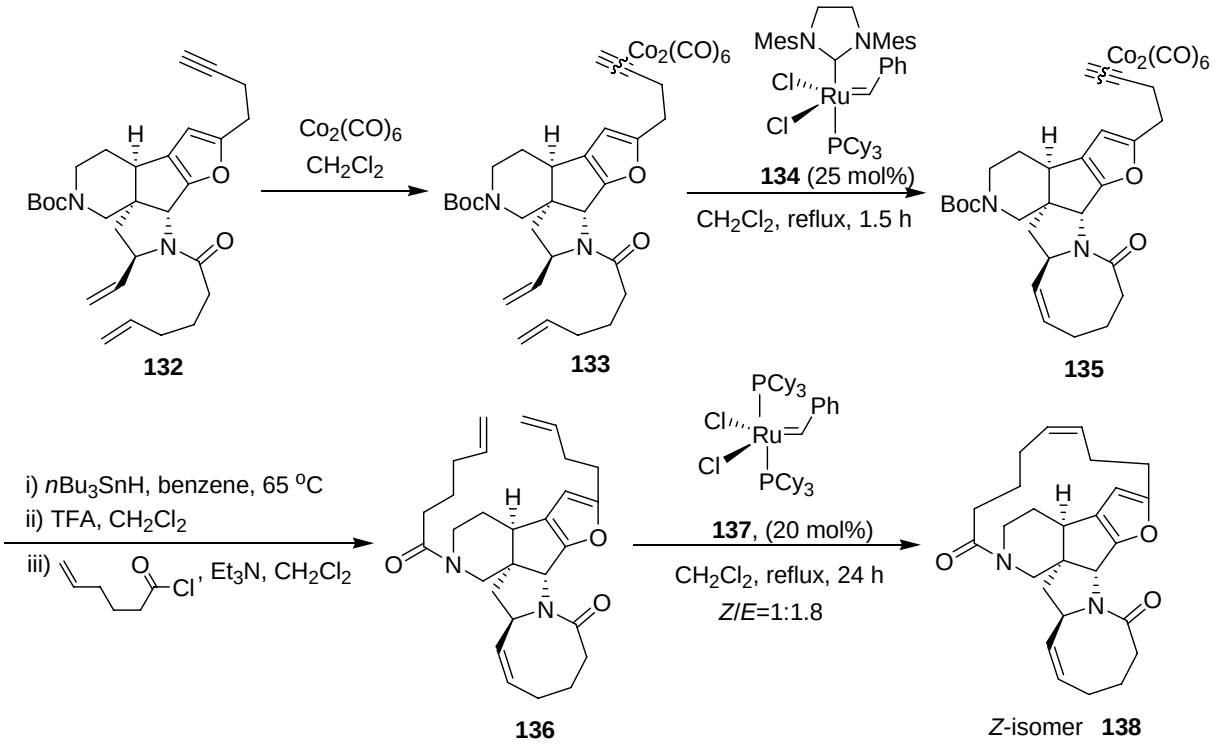
Another application of the umpolung reaction was found in the total synthesis of marine natural products lituarines A-C.[84] Here, C-C bond formation was achieved by lithiation of (-)-**128** in the presence of HMPA, followed by the addition of alkyl iodide (+)-**129** to furnish (+)-**130**, a key intermediate in the total synthesis (Scheme 1.7.1.2). In this case, the dithiane group was removed to reveal the C-20 carbonyl group of the target molecule.



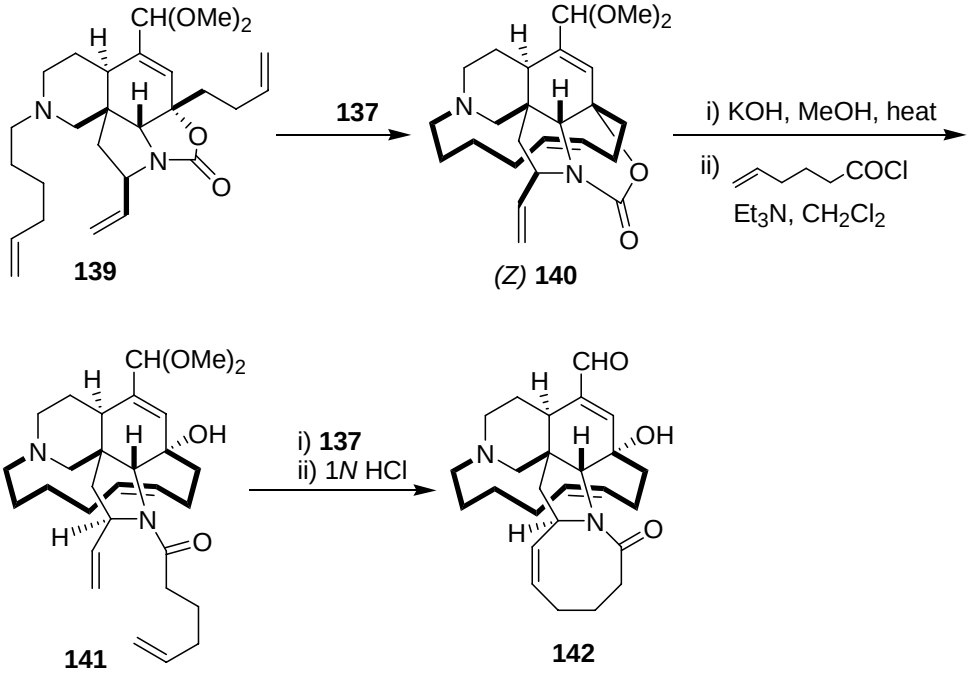
Scheme1.7.1.2: Application of umpolung in lituarines syntheses.[84]

1.8 Ring-Closing Metathesis Reactions in Fluorous Systems

The ring-closing metathesis reaction (RCM) facilitates a plethora of methods for forming rings of various sizes. Grubbs catalyst is widely used in different fields including total synthesis of natural products.[85,86] Dienyne **132** was protected as a dicobalt hexacarbonyl complex **133** which on treatment with Grubbs (II) catalyst **134** afforded azocine lactam **135**. Following three steps of reductive decomplexation, deprotection of the Boc group and *N*-acylation, compound **136** was obtained. This was further treated with Grubbs (I) catalyst **137** to get the RCM product **138**, a precursor to (-)-nakadomarin A. Similarly, 8 and 13 membered rings (intermediates **140** and **142**) are formed in the total synthesis of manzamine A using Grubbs (I) catalyst (Scheme 1.8.1).



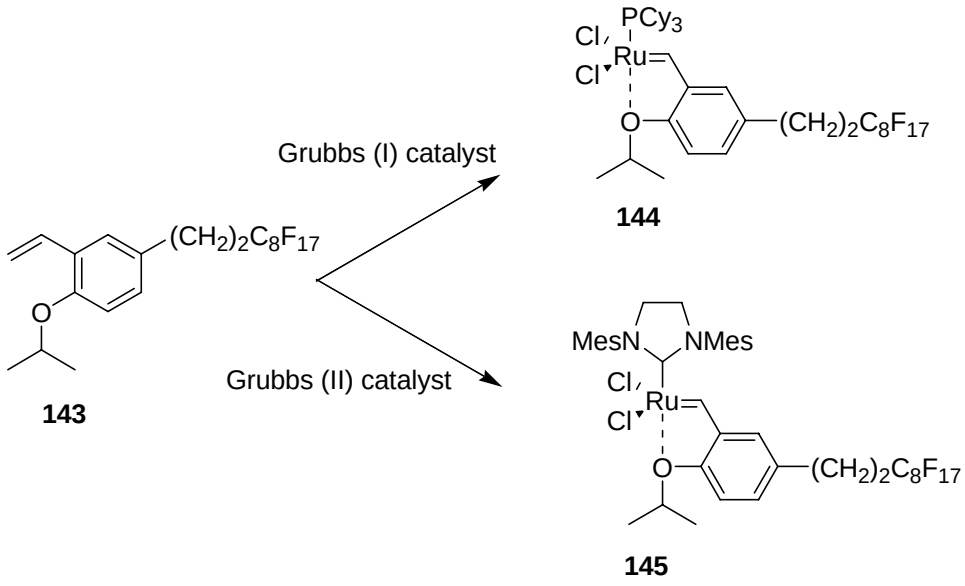
Ono, K. *et al. Angew. Chem. Int. Ed.* **2004**, 43, 2020-2023.



Humphrey, J. M. *et al. J. Am. Chem. Soc*. **2002**, *124*, 8584-8592.

Scheme 1.8.1: Use of Grubbs catalysts in total syntheses of natural products.

Palladium or ruthenium catalyzed reactions (both achiral and chiral) have provided access to more complex structures in fewer steps and with less waste. However, a major limitation of metathesis reactions with Grubbs catalysts is the high leaching of Ru into the product as those with palladium-catalyzed reactions. This is an especially significant problem for the pharmaceutical industry since medicinal molecules must meet government requirements of <5 ppm residual metal impurities in product streams.[87] The use of Hoveyda-type catalyst significantly decreases Ru leaching. Nitrogen containing heterocycles with different size were synthesized using this catalyst.[88] Additionally, the catalyst is precious, and its recovery from the reaction medium is worthwhile. In terms of fluorous chemistry, there are two ways by which the catalyst can be recovered. One choice is to use a perfluoroalkylated catalyst which can be recovered by FPSE.

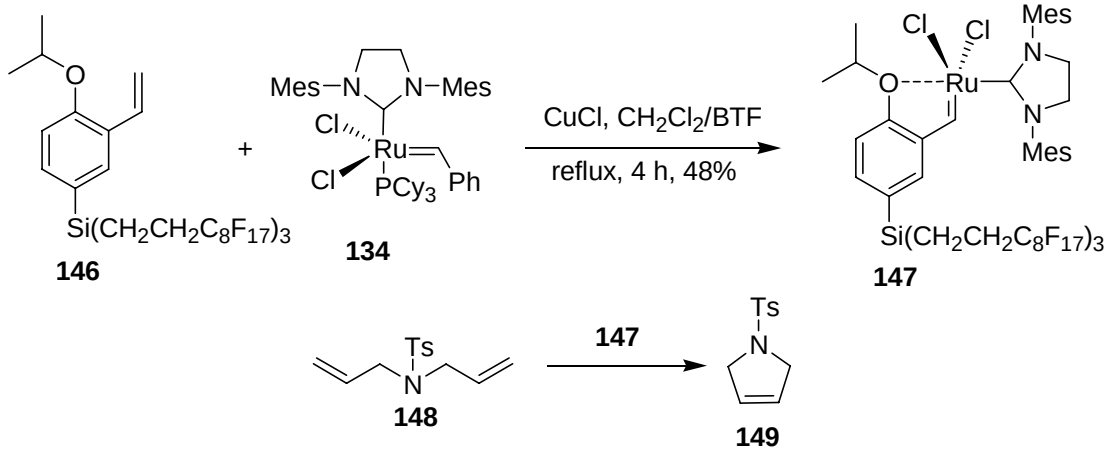


Scheme 1.8.2: Fluorous tagged Grubbs-Hoveyda catalysts.[89]

Light fluorous first- and second-generation Grubbs-Hoveyda catalysts were synthesized by Curran and his group (Scheme 1.8.2).[89] These induce alkene metathesis

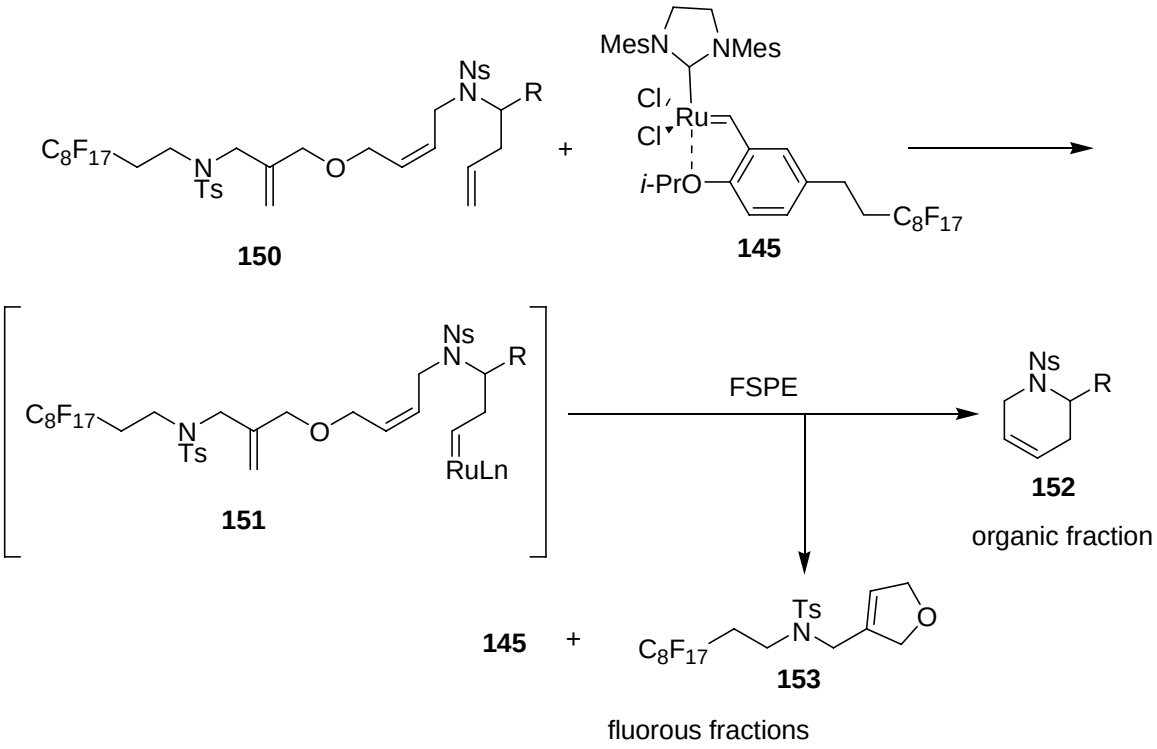
reactions under the same conditions as their nonfluorous parents. However, the catalysts can be recovered using FSPE and are reusable.

Michalak and Bannwarth[90] employed a fluorous Grubbs-Hoveyda catalyst in metathesis reactions. A Grubbs–Hoveyda metathesis catalyst **147** bearing a tris(perfluoroalkyl)silyl tag for efficient noncovalent attachment to fluorous silica gel was synthesized and employed in ring closing metathesis reactions in CH_2Cl_2 (Scheme 1.8.3). After the reaction, a solvent switch to a polar system allowed for recovery of the catalyst by filtration and its reuse. The approach was demonstrated for a number of different substrates. Furthermore, it was shown that the application of this catalytic system yielded products with low ruthenium content.



Scheme 1.8.3: Use of fluorous Grubbs-Hoveyda catalyst in metathesis reactions.[90]

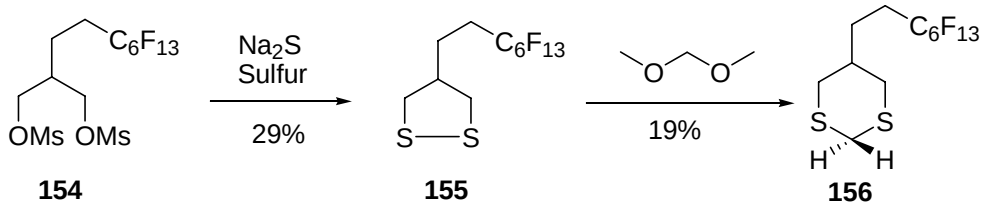
The second way is to choose a perfluoroalkyl-tagged substrate and a non-fluorous catalyst. In this method, the product can be separated from the catalyst by FSPE Recently, the Nelson group[91] used fluorous-tagged linkers for the parallel synthesis of small-ring, medium-ring and macrocyclic nitrogen heterocycles using ring-closing metathesis reactions (Scheme 1.8.4).



Scheme 1.8.4: Fluorous molecules in RCM.[91]

1.9 Fluorous Dithianes

Fluorous dithiane chemistry is still a young field and offers a great scope for the development of new technologies. The synthesis of a fluorous dithiane **156** was patented by Read.[92] The disadvantage associated with this synthesis are the poor yields of the key steps (Scheme 1.9.1).



Scheme 1.9.1: Fluorous dithiane synthesis.

Moreover, diastereomeric complexity will arise upon dithiane formation with aldehydes. The desired diastereomer will have low yield as well as its separation from the others will be difficult (Figure 1.9.1).

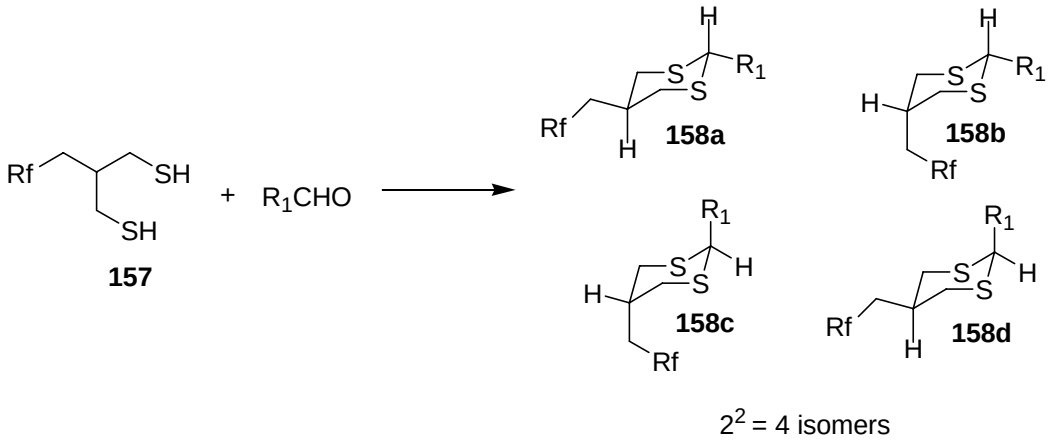


Figure 1.9.1: Possible diastereomers on dithiane formation.

In order to address this problem we planned to construct a symmetrical fluorous tagged benzodithiane and explore its applications to construct diverse size ring systems.

CHAPTER 2: THESIS OBJECTIVES

2.1 Design and Synthesis of a Symmetrical Fluorous Dithiol Support

It is evident from Section 1.5 that fluorous tagged thiols have a wide range of application and scope in proteomics as well as in synthetic organic chemistry. The goal of this thesis was to develop a method to obtain diverse ring systems using a symmetrical fluorous tagged benzodithiol linker. The diastereomeric problem associated with the dithiane formation of the unsymmetrical thiol **157** was discussed in Section 1.9. In order to circumvent this problem we wanted to synthesize a symmetrical fluorous tagged benzodithiol **159** which is free from diastereomeric complexity upon ring formation.

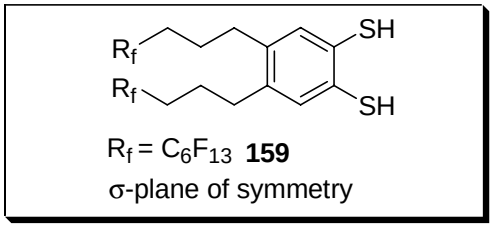
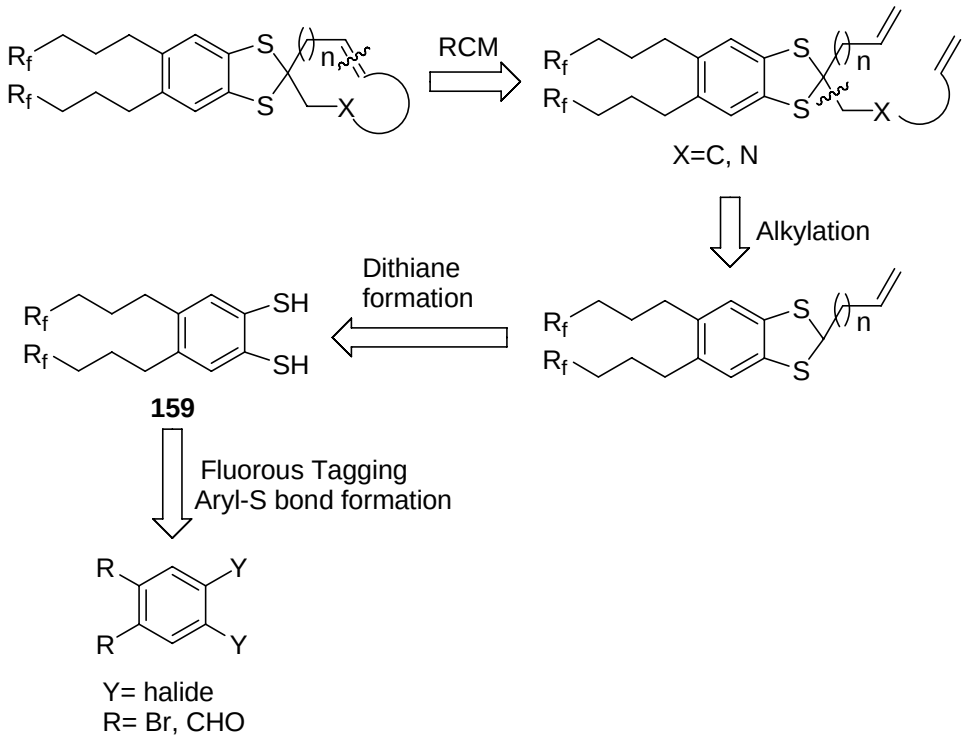


Figure 2.1.1: Designed fluorous tagged benzodithiol support.

A retrosynthetic disconnection for the synthesis of the fluorous dithiol **159** and and its utility in the construction of diverse ring systems is depicted in Scheme 2.1.2. The synthetic pathway involves several key processes: i) the incorporation of fluorous tags with a spacer, ii) formation of aryl-sulfur bonds, iii) dithiane formation, iv) alkylation by the umpolung reaction and v) construction of rings by the ring-closing metathesis reaction.



Scheme 2.1.2: Retrosynthetic disconnection.

The Ullmann reaction or the Wittig olefination can be used to attach the perfluoroalkyl chains to an appropriate benzene system. After the fluorous tagging, the next task is to form aryl-sulfur bonds. Aryl-sulfur bonds can be formed either by copper or palladium catalyzed reactions. However, Pd (0) catalyzed thiolation reactions have disadvantages because of sulfur poisoning and bridging complex formation (Section 1.6.4 and Section 1.6.5). Because a Pd (0) catalyzed *o*-dithiolation reaction in benzene system is not known in the literature, a thorough study was required in this field. Also, because our designed dithiol has two perfluoroalkyl chains, the system will be highly fluorinated. The products can be separated from non-fluorous compounds employing FSPE. A distinct advantage of a benzenedithiol based linker is that it can be easily recovered as a salt. Aromatic thiols are acidic in nature and can form water soluble salts with bases, which can be used as a second mode of separation after FSPE.

Following the synthesis of the fluorous dithiol, the focus of the research shifted to applying this to dithiane formation. A high yielding dithiane formation condition can exploit the system for new ring formation. Various benzodithianes can be prepared from the dithiol using different aldehydes.

The umpolung reaction is a useful approach to form C-C bonds by the alkylation of the lithiated dithianes. Two terminal olefins can be closed by the ring closing metathesis approach. Diverse ring systems can be constructed varying aldehydes with different number of carbon chain lengths while forming the benzodithianes. The scope of the method can be explored by a traceless reductive or oxidative cleavage, which will be a detagging step in terms of fluorous chemistry.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

The development of a new and efficient synthesis of the fluorous tagged benzodithiane is a successful outcome of our research. Early in our work, we had to overcome several challenges. The selection of an appropriate material where both the perfluoroalkyl groups and the *o*-dithiols had to incorporate symmetrically was a crucial stage for the project. This part of the thesis consists of the discussions of the approaches we made and outlines the findings of these studies in the entire synthesis.

Fluorine atoms due to their electronegative nature impart strong inductive electron withdrawing (-I) effects when two perfluorinated chains are attached to a system. Further, these fluorous chains may add steric hindrance. These factors may cause serious adverse effects on reactive sites in fluorous-tagged molecules. The introduction of a spacer can insulate the perfluoroalkyl chains from the system.

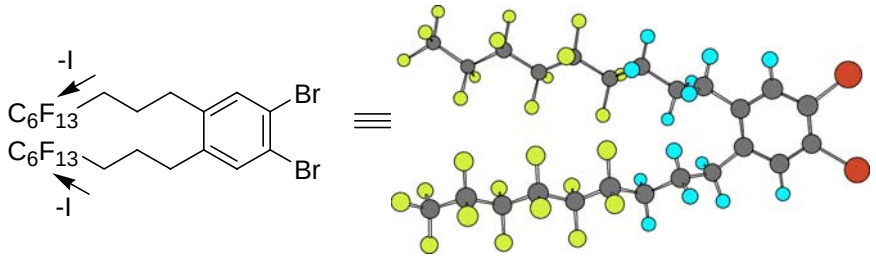
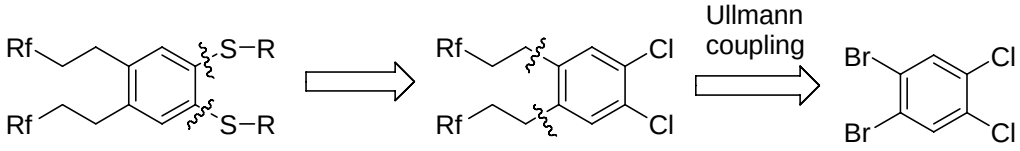


Figure 3.1.1: Steric and electronic environment of a fluorous tagged compound.

In order to install fluorous linkers to a benzene system, two methods can be used. As the Ullmann reaction is a useful tool for aryl C-C bond formation,[93,94] our first choice was to use this approach to attach the linkers.

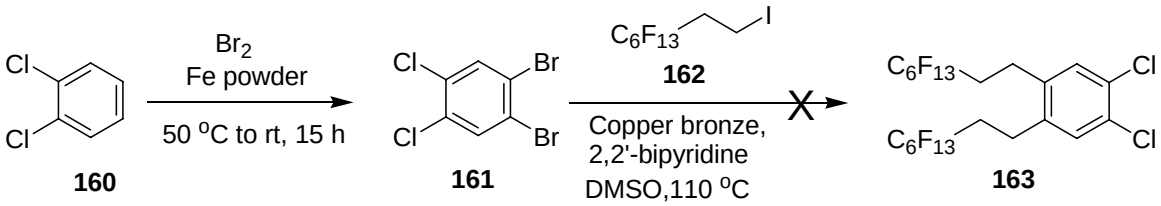
3.2 First Approach to Synthesize the Symmetrical Dithiol

For the Ullmann coupling, we started our synthesis with 1,2-dibromo-4,5-dichlorobenzene **161** and $C_6F_{13}(CH_2)_2I$ **162** (Scheme 3.2.2). After installation of the fluorous tags, we thought that the protected dithiol could be obtained using either copper thiolate or Pd-catalyzed aryl-sulfur bond formation from the corresponding dichloro derivatives.



Scheme 3.2.1: Retrosynthetic disconnection.

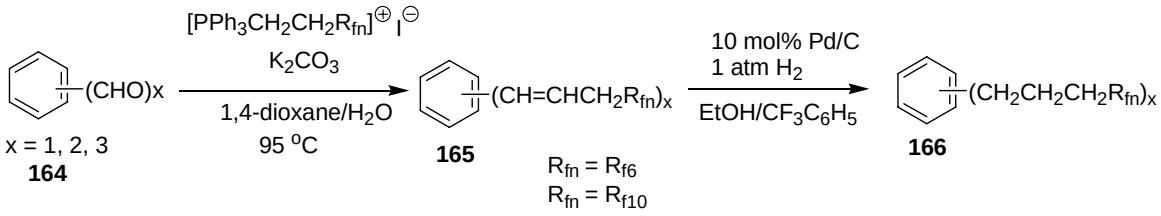
1,2-Dibromo-4,5-dichlorobenzene **161** was prepared in large scale from *o*-dichlorobenzene **160** using the reported conditions, in 26% yield.[95,96] In order to incorporate fluorous tags, various Ullmann coupling conditions were tried.[93,94,97] Treatment of **161** with **162** in the presence of copper bronze and 2,2'-bipyridine at 110 ^oC did not give the desired coupled product **163**. Prolonged heating at 140 ^oC led to decomposition of the iodide, but no product was observed in crude NMR and mass spectra. The reaction was tried using different solvents like DMF, DMSO, and DMF/DMSO mixtures. This study did not identify suitable reaction conditions for the perfluoroalkane linker attachment and the Ullmann coupling was deemed unsuitable for our purpose.



Scheme 3.2.2: Attempted Ullmann coupling.

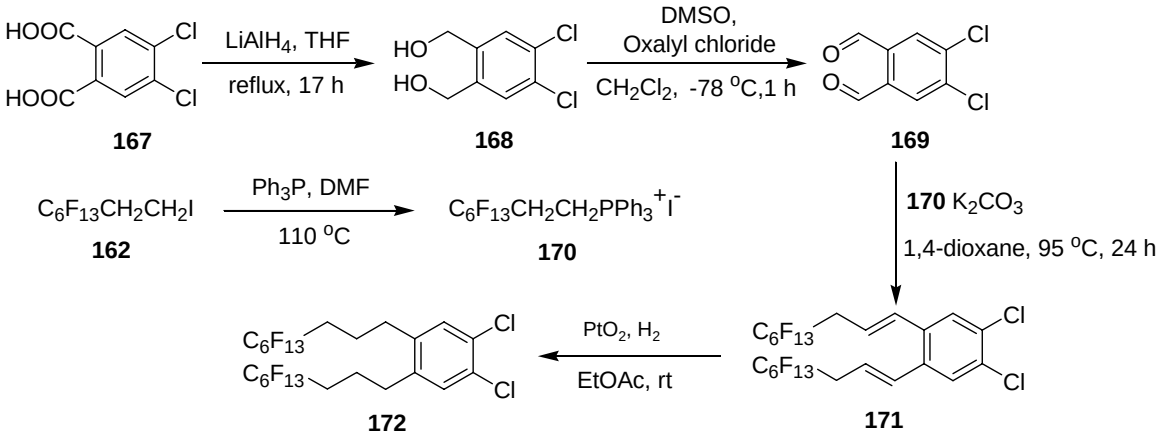
3.3 Second Approach for Installation of Fluorous Tags

After encountering problems with the Ullmann coupling, we tried a strategy reported by Rocaboy and coworkers.[98] They reported the high-yield conversion of benzaldehydes to fluoroalkyl benzenes with one to three fluorous pony tails, $(CH_2)_3(CF_2)_{n-1}CF_3$ (n = 6, 8, 10) via Wittig olefination and hydrogenation. The protocol itself is a combination of the advantages of one-phase chemistry (higher temperature) and biphasic product separation (lower temperature)



Scheme 3.3.1: Syntheses of fluorous benzenes.[98]

Following this approach we started our synthesis with the reduction of the cheap commercially available starting material 4,5-dichlorophthalic acid **167** using $LiAlH_4$ to give 4,5-dichloro-1,2-bis(hydroxymethyl)benzene[99] **168** in 75% yield (Scheme 3.3.2). Swern oxidation of **168** afforded 4,5-dichlorophthalaldehyde **169** in 91% yield. A Wittig salt $C_6F_{13}CH_2CH_2PPh_3^+I^-$ **170** was prepared from Ph_3P and iodide **162** in 93% yield. Treating a mixture of **169** and **170** with potassium carbonate in aqueous dioxane gave a 78:22 *ZZ/EZ* mixture of di-olefins **171** in 89% yield.



Scheme 3.3.2: Installation of fluorous tags.

In our system there is no electron withdrawing group to stabilize the ylide. So, our system can be considered as an unstabilized ylide. Unstabilized ylides give *Z*-stereoselectivity. In order to explain *Z*-stereoselectivity, Vedejs[100,101] proposed an asynchronous cycloaddition with a four-center puckered transition state, in which steric arguments and the hybridization states of the phosphorus atom are responsible for the *Z*-stereoselectivity. In case of unstabilized ylides and sterically hindered aromatic aldehydes, Ar-Ph steric interaction becomes dominant. In our case, the aryl (Ar) group of the aldehyde could interfere sterically with the phenyl groups on phosphorus in the oxaphosphetane if it adopted an axial orientation. As a result, the reaction favors locating the Ar group in an equatorial position to give *Z*-olefin predominantly (Figure 3.3.1).

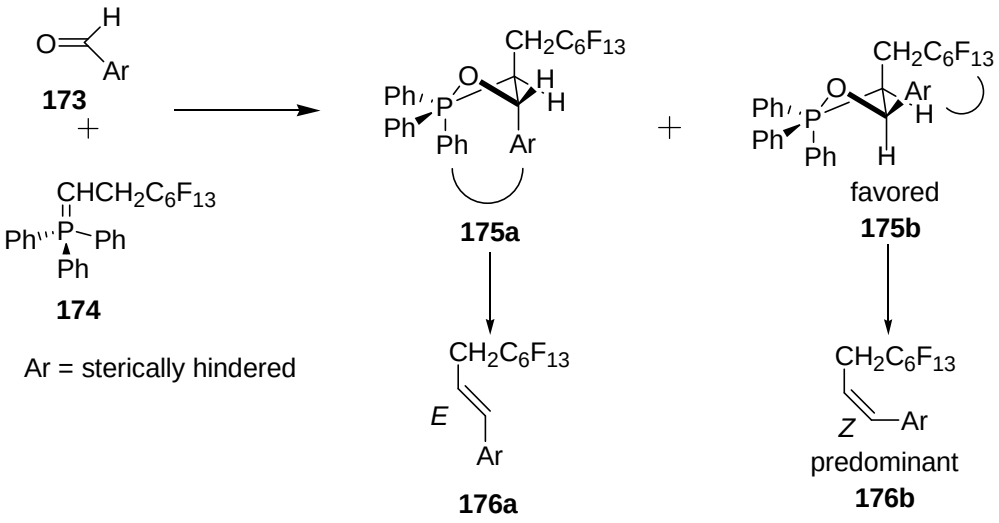


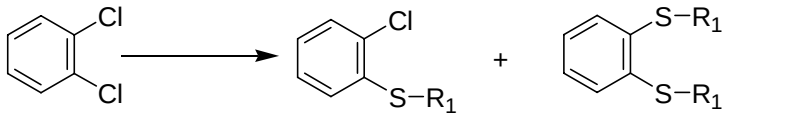
Figure 3.3.1 Steric interaction in oxaphosphetane ring.[100]

A general problem associated with Wittig olefination reactions is the separation of Ph_3PO from the olefin. Triphenylphosphine oxide was readily separated from our olefin mixtures using FSPE. After loading the crude product on fluorous silica, Ph_3PO was removed using 85:15 MeOH/H_2O and the product was eluted at 90:10 MeOH/H_2O. The minor *EZ* di-olefin was not chromatographically separable from the *ZZ* isomer. Since the next step was a hydrogenation reaction which would reduce both alkene isomers to the same hydrocarbon, we proceeded with the mixtures. Hydrogenation over a Pd/C catalyst also reduced the chloro groups in **171** (Scheme 3.3.2). The double bonds could be reduced selectively without affecting the chloro groups using a catalytic amount of PtO_2 and H_2 gas. The reaction was scaled up to multi-gram quantities with 81% yield.

Dichloro compound **172** was ready for the formation of the aryl-sulfur bonds. To understand the reactivity of the chloro groups towards thiolation reactions, a non-fluorous model system was selected. Different conditions for the dithiolation reaction were tried with 1,2-dichlorobenzene **177**. The results are summarized in Table 3.3.1.

Unactivated aryl halides undergo substitution by thiolate anions in polar solvents.[102-104] But, in this model study the desired dithiolated product **179** was obtained only in trace amount with sodium isopropyl thiolate under forcing conditions, although monothiolated product **178** was obtained in good yield (entries 1, 2).

Table 3.3.1 Attempted dithiolation reactions with 1,2-dichlorobenzene.

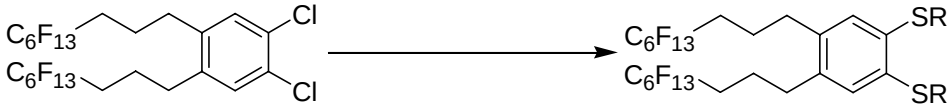


177 **178,** R_1=$CH(CH_3)_2$ **179,** R_1=$CH(CH_3)_2$

Entry	Thiol	Solvent	Catalyst	Ligand	Base	Temp/ time	Result
1[102]	$(CH_3)_2CHSNa$	DMA	-	-	-	18 h, 140°C	**178** (90%) + **179** (trace)
2[103]	$(CH_3)_2CHSNa$	DMF	-	-	-	36 h, 100°C	**178** (90%) + **179** (trace)
3[74]	$(CH_3)_2CHSH$	Dioxane	Pd_2dba_3	Xantphos	Cs_2CO_3	18 h, 100°C	SM
4[73]	$(CH_3)_2CHSH$	Dioxane	$Pd(OAc)_2$	DiPPF	NaO*t*Bu	72 h, 100°C	**178** (50%)
5[72]	$CH_3(CH_2)_7SH$	DME	$Pd(OAc)_2$	CyPF*t*-Bu	NaO*t*Bu	24 h, 110°C	SM
6[73]	$CH_3(CH_2)_7SH$	Dioxane	$Pd(OAc)_2$	DiPPF	NaO*t*Bu	24 h, 110°C	SM
7	$CH_3(CH_2)_7SNa$	DMA	-	-	-	24 h, 150°C	unidentified products
8[74]	$HS(CH_2)_2SH$	Dioxane	Pd_2dba_3	Xantphos	Cs_2CO_3	18 h, 110°C	unidentified products
9[104]	$NaS(CH_2)_2SNa$	DMA	-	-	-	18 h, 160°C	unidentified products

Only one Pd-catalyzed condition was successful to give monothiolated product with 2-propane thiol (entry 4). All the other conditions gave either no reaction or some unidentified products (entries 7, 8, 9). Despite this failure with the model system, we proceeded to do dithiolation with the fluorous compound **172** following some efficient methods including palladium catalyzed reactions for the coupling of thiols with unactivated aryl chlorides.[72,73,74] These attempts are illustrated in Table 3.3.2.

Table 3.3.2: Attempted dithiolation reactions with the fluorous dichloro compound **172**.



172

entry	Thiol	solvent	catalyst	ligand	base	temp./time	yield
1[73]	$(CH_3)_2CHSH$	dioxane	$Pd(OAc)_2$	DiPPF	NaO*t*Bu	110 ^oC/66 h	none
2[72]	$CH_3(CH_2)_3SH$	DME	$Pd(OAc)_2$	CyPF-*t*Bu	NaO*t*Bu	110 ^oC/36 h	none
3[74]	$HS(CH_2)_2SH$	dioxane	Pd_2dba_3	Xantphos	Cs_2CO_3	100 ^oC/24 h	none
4[73]	$HS(CH_2)_2SH$	dioxane	$Pd(OAc)_2$	DiPPF	NaO*t*Bu	100 ^oC/24 h	none
5[104]	$NaS(CH_2)_2SNa$	DMA	-			150 ^oC/24 h	none
6[102]	$CH_3(CH_2)_7SH$	Tetra-glyme	-		NaH	180 ^oC/48 h	none

From the data in Table 3.3.2, it appears that no dithiolation reaction was observed in either catalytic or stoichiometric conditions. Tetraglyme can effectively solvate the sodium cation to generate a highly nucleophilic unsolvated thiolate anion.[102] In our system, high reaction temperature and the use of tetraglyme as a solvent could not give the desired product. Also, use of additives like NaI[105] in entries 5 and 6 and CuI[106] in entry 3 in the above reactions remained futile.

These observations of stubborn dithiolation reactions are consistent with the idea that the first thiolation may deactivate the compound towards a second thiolation both electronically as well as sterically. The dichloro compound **177** is electron deficient, which is a driving force for faster rate of monothiolation. However, once monothiolation occurred, an electron withdrawing chloro group will be substituted with an alkyl thiol, which has a modest electron donating effect[107] as well as causes steric repulsion for the second Pd insertion into an Ar-Cl bond. Since no dechlorinated compound was observed even in trace amount after aqueous work up, we propose that the second palladium insertion did not take place.

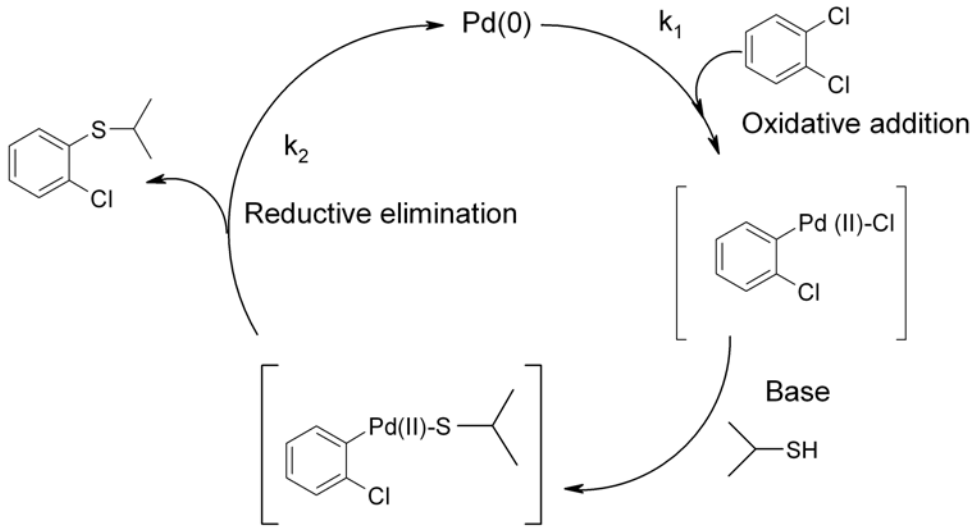
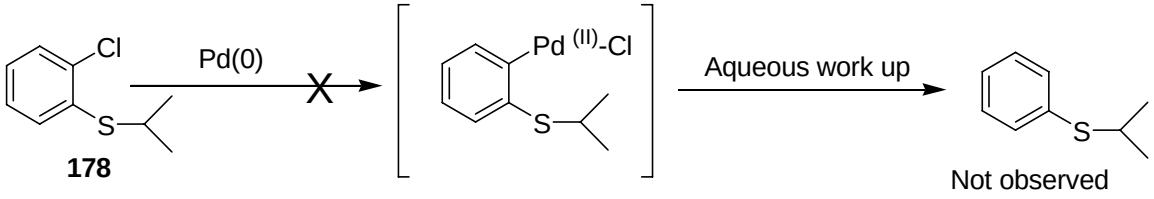


Figure 3.3.2: Possible catalytic pathway for monothiolation.[63]

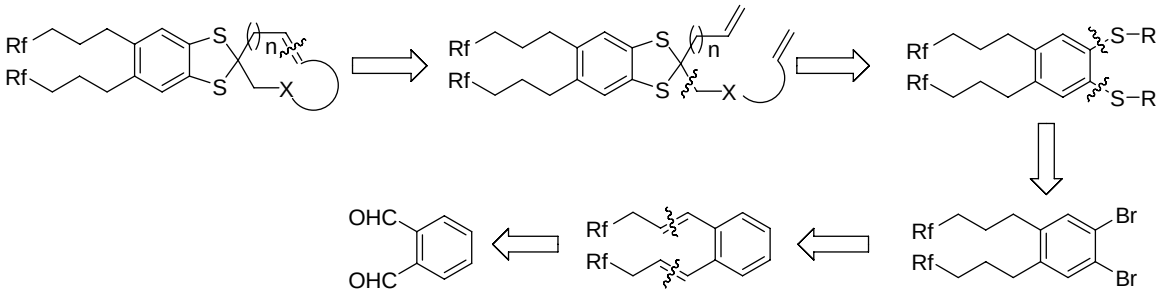


Scheme 3.3.3: Thiolation of non-fluorous system.

This failure gave us a clue to explore a new system which might be reactive for dithiolation reactions. Hence, we moved to more labile *o*-bromosubstituents.

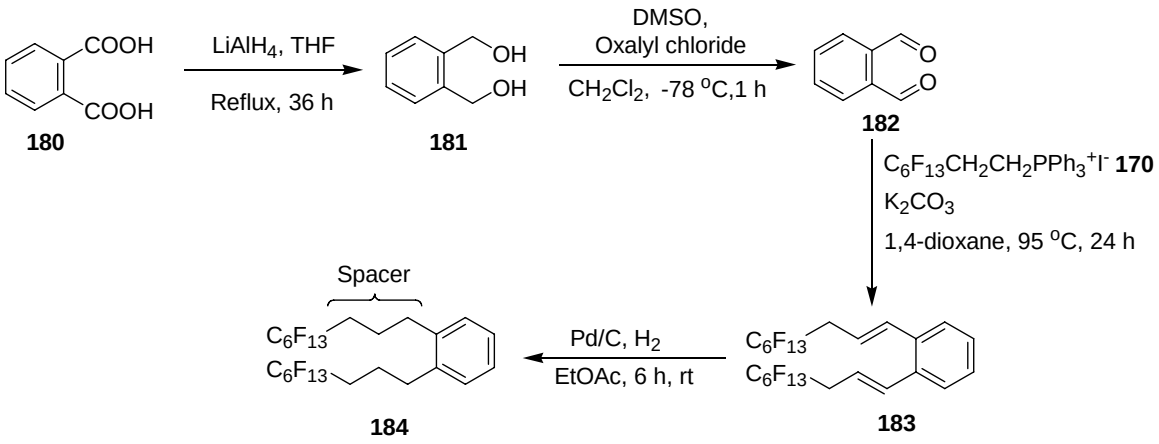
3.4 Third Approach Towards the Synthesis of Symmetrical dithiol

From Section 3.3, we found that Wittig olefination and hydrogenation reactions provide a high yielding, reproducible and scalable way of attaching fluorous chains to an aryl ring. In the previous section we found that aryl chlorides were not sufficiently reactive to permit bis-thiolation. In order to use a more-reactive aryl bromide in the thiolation, the key step was to develop a high yielding *o*-dibromination condition.



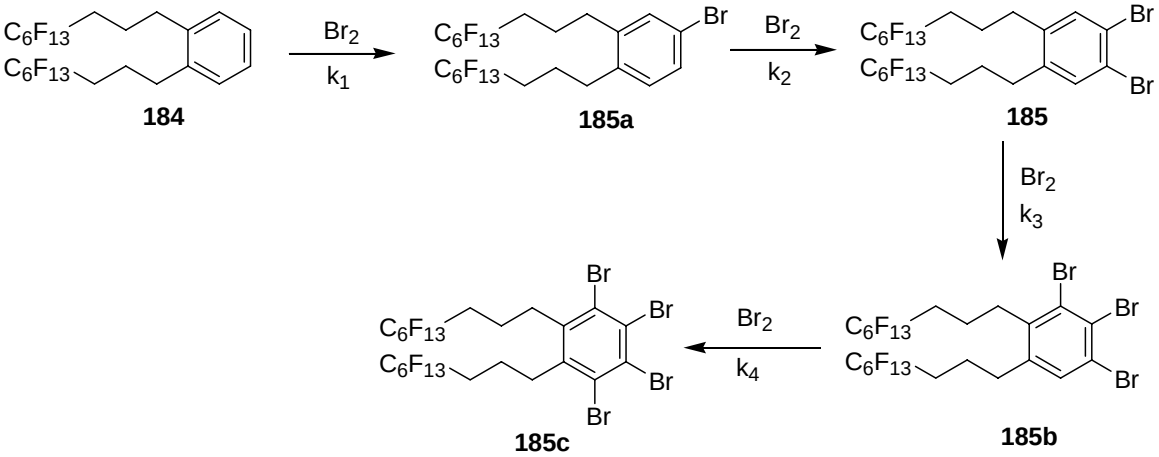
Scheme 3.4.1: Retrosynthetic disconnection for the third approach.

As shown in Scheme 3.4.2, phthalic acid **180** was reduced with $LiAlH_4$ to afford 1,2-bis(hydroxymethyl)benzene[108] **181**, which on Swern oxidation yielded phthalaldehyde **182**. The treatment of phthalaldehyde with the fluorous salt **170** in the presence of potassium carbonate at 95 ^oC gave 1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene **183** with 90:10 *ZZ*/*EZ* ratio. This ratio was measured from the integrated NMR signal intensity ratio. Triphenylphosphine oxide was separated by FSPE using 85:15 MeOH/H_2O to obtain the olefin mixtures in 92% yield. The di-olefin **183** was hydrogenated using Pd/C to give 1,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **184** with 92% yield. Compound **184** is highly fluorinated as it contains 61.9% fluorine content by molecular weight.



Scheme 3.4.2: Introduction of fluorous tags with spacer.

We wanted to do a selective dibromination reaction with compound **184** which can be used as a precursor for the symmetrical 1,2-dithiol. Numerous reported conditions were tried.[109-115] The bromination reaction in our fluorous tagged system was prone to give mixtures of mono, di, tri and tetra-bromo products.



Scheme 3.4.3: Nonselective bromination reaction.

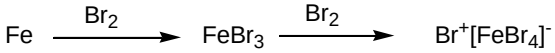
After trying different conditions varying solvent, temperature and the way of addition of Br_2 (Table 3.4.1), we noticed that the bromination reaction showed a strong dependence on reaction temperature There are two scenarios based on the temperature at which bromine was added to the reactant and the products observed:

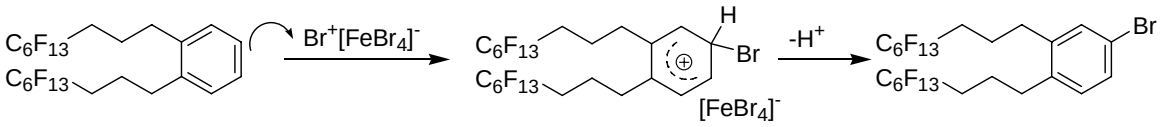
i) When the addition was done at 0 ^{o}C, we obtained dibromo (major), monobromo and tribromo (minor) and tetrabromo (trace amount) products. This is an example of sequential reaction. The introduction of the first electron withdrawing bromo group will make the system less active towards another electrophilic aromatic substitution reaction leading to k1 > k2. The formation of the monobromo product **185a** will reach maximum and the formation of the dibromo product **185** will follow a sigmoidal curve. After dibromination, the system will be eve less active for a third bromination reaction because of steric and inductive effects of two electron withdrawing bromo groups leading to k2 >> k3 and k3>>>k4. As a result, **185** will be the major product while **185a** and **185b** will be minor products of the reaction.

ii) In the second reaction condition, bromine was added at -10 ^{o}C. After the completion of the addition, the temperature was increased to -5 ^{o}C over 2 h as no reaction was observed at -10 ^{o}C. The bromination reaction was initiated at -5 ^{o}C, and the reaction was maintained at that temperature and monitored by NMR over time. It was observed that the dibromo compound was obtained predominantly when the reaction was left for 12 h at -5 ^{o}C. As the reaction rate is dependent on temperature so k1 > k2, and k3 and k4 are negligible at -5 ^{o}C. So, the sequential reaction will have only two steps.

Keeping the temperature at -5 ^{o}C for a long time is not very convenient. In order to speed up the reaction, the temperature was raised to 0 ^{o}C after maintaining the temperature at -5 ^{o}C for 2 h (where the maximum of monobromo product formation occured). The reaction was completed after 8 h at 0 ^{o}C and the desired dibromo compound **185** was obtained in 93% yield. The yield was incredibly high for the sequence.

The bromination reaction was carried out using iron powder and a catalytic amount of I_2 in dark condition. The mechanism of the reaction is an electrophilic aromatic substitution. The role of the Fe catalyst is to generate $FeBr_3$ in the reaction medium.

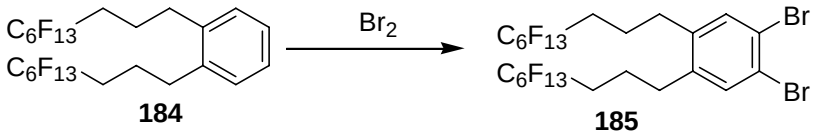




Scheme 3.4.4: Mechanism of the bromination reaction.

Compound **185** was characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectrum. In the mass spectrum, the characteristic isotope pattern for a dibromo compound was observed at m/z 953.9 (M^+, 54), 955.9 (M+2, 100) and 957.9 (M+4, 50).

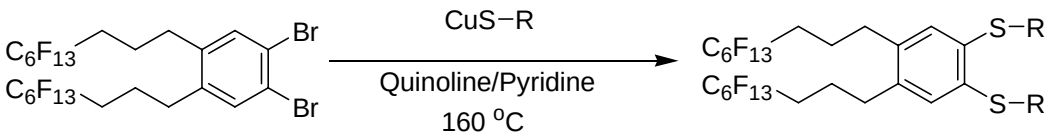
Table 3.4.1: The dibromination reaction under different conditions.



184 **185**

Entry	Solvents	Catalytic	Temperature	Result
1[110]	CH_2Cl_2	Fe/I_2	0 ^oC	Mixtures (**185a**, **185**, **185b**, **185c**)
2	CH_2Cl_2	Fe/I_2	0 ^{o} to -20 ^oC	Mixtures (**185a**, **185**, **185b**, **185c**)
3[114]	CH_2Cl_2	-----	0 ^oC	Mixtures (**185a**, **185**, **185b**, **185c**)
4	CCl_4	-----	0 ^oC - rt	Mixtures (**185a**, **185**, **185b**, **185c**)
5	CH_2Cl_2	Fe/I_2	-10^oC- 0 ^oC	93%

This positive result prompted us to go forward towards the formation of aryl-sulfur bonds. Ford *et al*.[54] had demonstrated that the electron deficient compound **65** underwent a dithiolation reaction with *n*-butylthiol in 63% yield (Scheme 1.6.1.1). As shown in Scheme 3.4.5, the reaction of copper *i*-propylthiolate with compound **185** in pyridine/quinoline afforded the bis-*i*-propylsulfide **186a**, while a similar reaction using copper *n*-butylthiolate gave the bis-*n*-butylsulfide **186b.** These reactions only gave poor yields (30-37%). So, a palladium catalyzed condition for aryl-sulfur bond formation appeared to be a better choice.



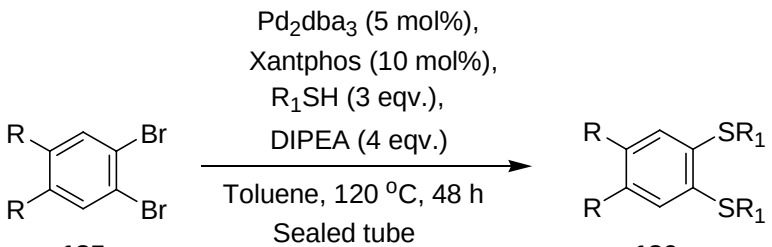
185

186a, R = *i*-Pr, 37%
186b, R = *n*-Bu, 30%

Scheme 3.4.5: Aryl-sulfur bond formation by traditional method.

When we tried the conditions reported by Itoh *et al*. (Scheme 1.6.5.5),[74,75] the dithiolated product **186b** was obtained in 80% yield using Pd_2dba_3 catalyst and Xantphos ligand. The separation of the catalyst and the ligand from the product is a common problem in these catalytic reactions. However, in our fluorous tagged molecule FSPE proved to be a very effective separation technique. The reaction was tested with two thiols, fluorous and non-fluorous dibromoaryl compounds and gave better yields than the traditional method (Table 3.4.2).

Table 3.4.2: Dithiolation using palladium catalyst.



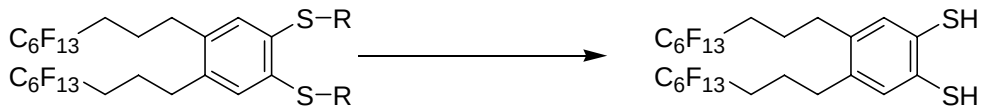
185
185
187
187

186a
186b
188a
188b

Entry	Compound	R	R_1	Product	Yield
1	**185**	$C_6F_{13}(CH_2)_3$	$(CH_3)_2CH$-	**186a**	75%
2	**185**	$C_6F_{13}(CH_2)_3$	$CH_3(CH_2)_3$-	**186b**	80%
3	**187**	CH_3	$(CH_3)_2CH$-	**188a**	48%
4	**187**	CH_3	$CH_3(CH_2)_3$-	**188b**	56%

While getting good yields in dithiolation reactions, we encountered problems in removing the *n*-butyl and *i*-propyl groups using harsh reaction conditions such as Li/NH_3,[55] Na/NH_3[54,103,116] and Na/napthalene[117] reductions (Table 3.4.3). Under these conditions, our fluorous tagged bis-thioethers did not give the desired dithiol.

Table 3.4.3: Deprotection conditions for alkyl dithiolated products.



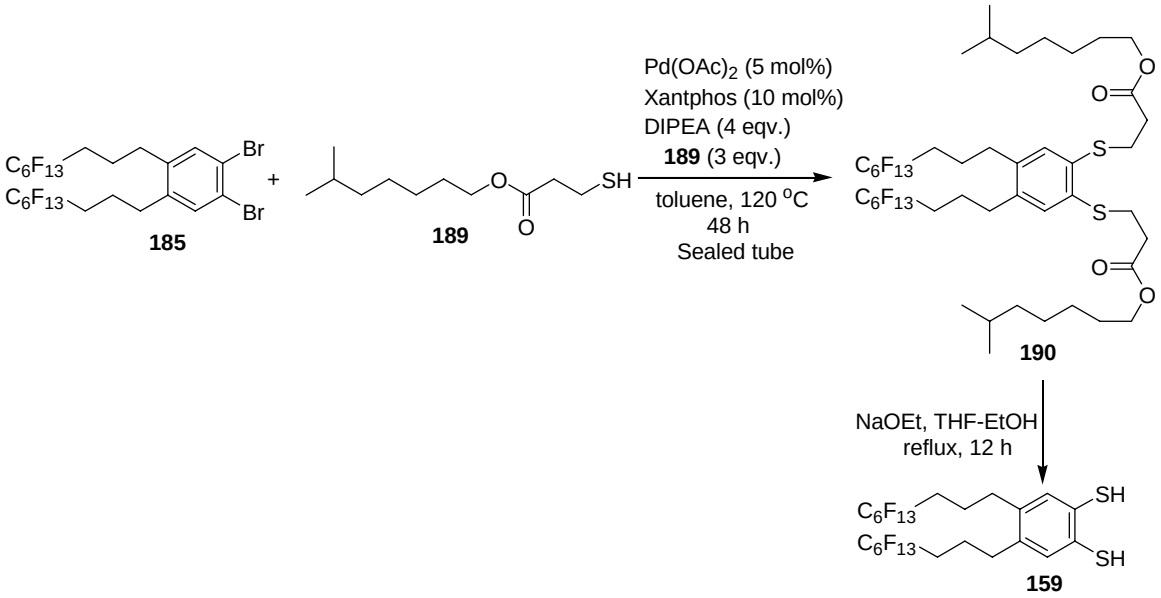
186a, R = *i*-Pr
186b, R = *n*-Bu

159

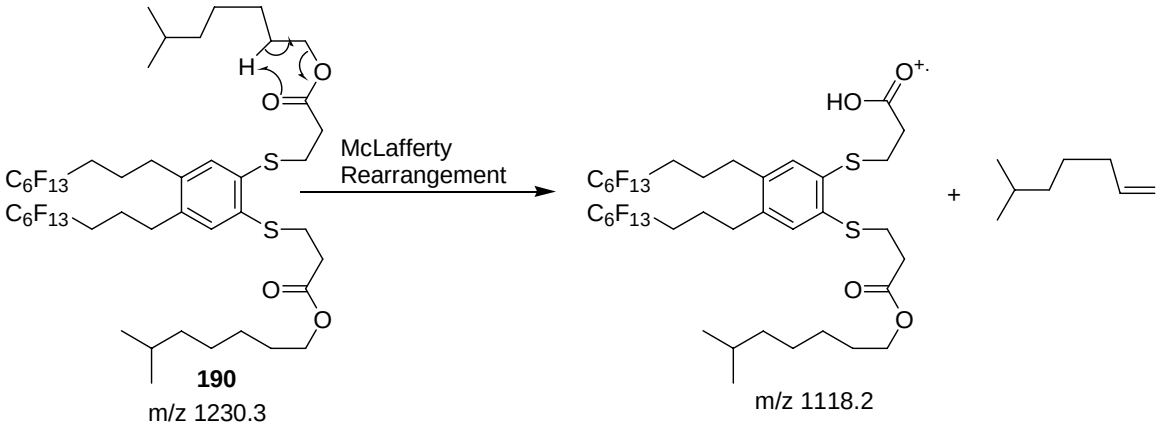
Entry	Compound	Base	Solvent	Temperature	Result
1	**186a**	Na/NH_3	Neat	-33°C/1 h	SM
2	**186a**	Li/NH_3	Neat	-33 °C/1 h	unidentified product
3	**186a**	Na/NH_3	Et_2O	-33 °C/1 h	SM
4	**186a**	Li/NH_3	THF	-33 °C/1 h	unidentified product
5	**186a**	Na/naphthalene	THF	rt/1 h	**159** (Trace amount)
6	**186b**	Na/NH_3	Neat	-33 °C/1 h	SM
7	**186b**	Li/NH_3	Neat	-33 °C/1 h	SM
8	**186b**	Na/NH_3	Et_2O	-33 °C/1 h	SM
9	**186b**	Li/NH_3	THF	-33 °C/1 h	SM
10	**186b**	Na/naphthalene	THF	rt/1 h	SM

From the data shown in Table 3.4.3 we observed that only *i*-propyl thioether gave a trace amount of the dithiol under Na/NH_3 reduction. As the alkyl thioethers **186a** and **186b** proved to be stubborn towards reductive dealkylation, we decided to employ a surrogate part which could be easily removed by a β-elimination reaction on treatment with a base. Thiol surrogates were used in aryl-sulfur bond formation reactions by Itoh *et al.* (Scheme 1.6.5.6).[74,75]

In our case, isooctyl-3-mercaptopropionate **189** proved to be an ideal candidate for the Pd catalyzed dithiolation reaction. The dithiolated product **190** was obtained in 80% yield using the literature procedure with Pd_2dba_3 catalyst (Scheme 3.4.6). We also obtained high yields with $Pd(OAc)_2$ catalyst and Xantphos ligand. As $Pd(OAc)_2$ is cheaper than Pd_2dba_3, we scaled up this reaction to afford the desired product **190**. The fluorine content of **190** is 40.14% by molecular weight, which is an example of light fluorous molecule and hence is ideal for FSPE. The removal of Pd catalyst and ligand from these catalytic reactions is a problematic task after the work up. In FSPE, Pd catalyst and ligands were removed using 70% MeOH/H_2O and the product was eluted with 90% MeOH/H_2O. The compound **190** was characterized by ^{1}H NMR, ^{19}FNMR and mass spectrum. In the mass spectrum, M^+ and M+1 peaks appeared at m/z 1230.3 (100) and 1231.3. The fragment observed at m/z 1118.2 (M-111) was due to a characteristic loss of the $(CH_3)_2CH(CH_2)_3CH{=}CH_2$ fragment because of McLafferty rearrangement.[118]

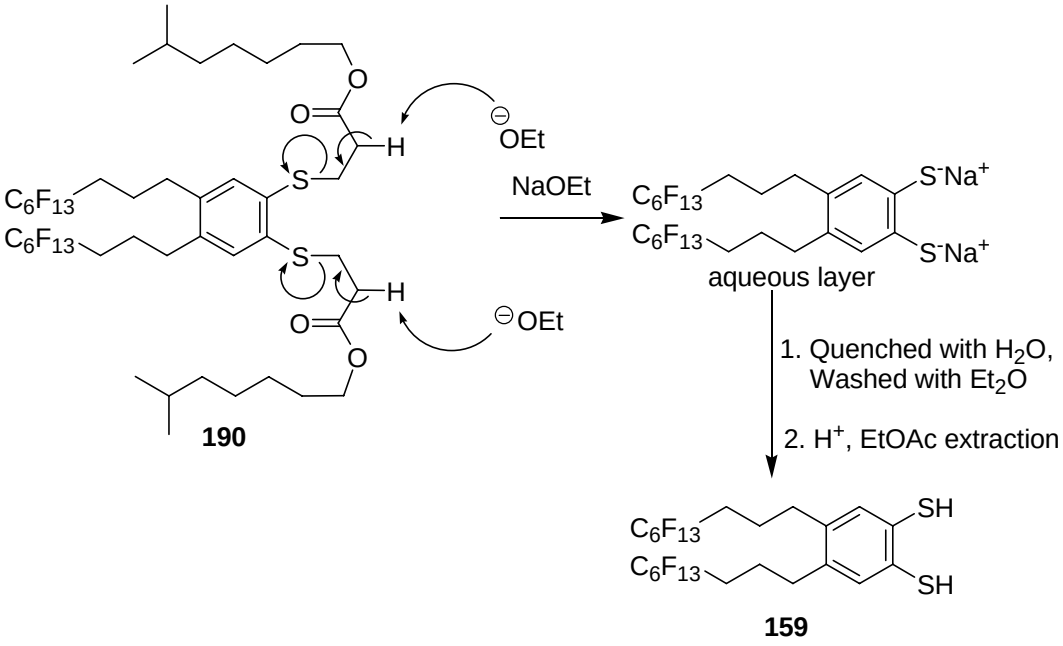


Scheme 3.4.6: Synthesis of the benzodithiol **159**.



Scheme 3.4.7: Fragmentation pattern of compound **190** via McLafferty rearrangement.

The treatment of the dithiolated compound **190** with NaOEt followed by an acidic work up provided the desired dithiol **159**. The mechanism of the reaction proceeds via E2 type β-elimination process. There is a simultaneous abstraction of the acidic proton (α to the carbonyl group) by $^{-}$OEt and departure of the leaving group (Scheme 3.4.8).



Scheme 3.4.8: β-elimination mechanism.

We observed that dithiols are not stable in oxygen atmosphere when we tried to purify the dithiol **159** by column chromatography using silica gel. So, we took an advantage of the acidic nature of benzothiols. After treatment with NaOEt, the reaction was quenched with water and extracted with Et_2O to remove nonpolar impurities while sodium thiolate remained in the aqueous layer. After acidification of the aqueous layer, extraction with ethyl acetate provided the dithiol which was directly used for the next step without further purification.

We wanted to generalize the dithiolation reaction with the surrogate thiol varying Pd catalysts and ligands. Some ligands used in the experiments were DPPF; 2-(di-*t*-butylphophino)biphenyl, DTBPBP and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, BINAP.

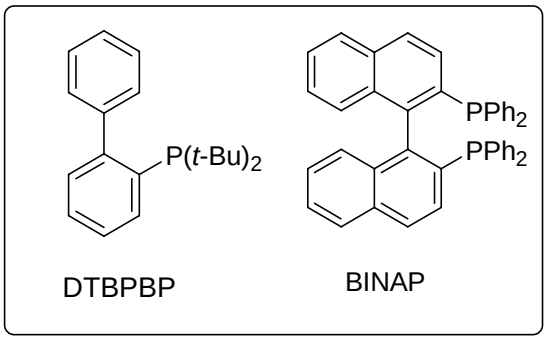
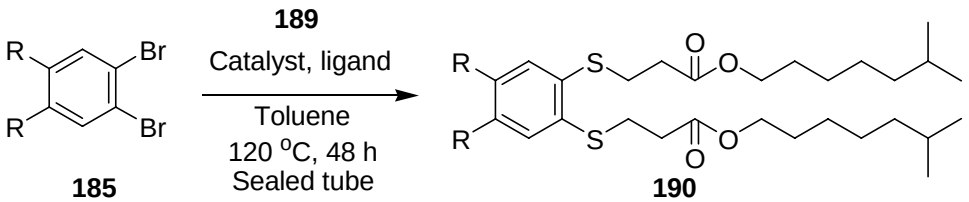


Figure 3.4.1: Ligands used in dithiolation reactions.

Table 3.4.4: Attempted aryl-sulfur bond formation reactions with surrogate thiol **189.**



185
187

190
191

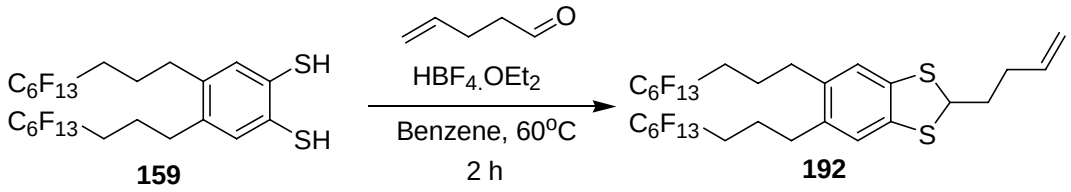
Entry	Compound	R	Catalyst (5 mol%)	Ligand (10 mol%)	Yield (%)
1	**185**	$C_6F_{13}(CH_2)_3$	$Pd_2(dba)_3$	Xantphos	79
2	**185**	$C_6F_{13}(CH_2)_3$	$Pd_2(dba)_3$	DPPF	70
3	**185**	$C_6F_{13}(CH_2)_3$	$Pd_2(dba)_3$	BINAP	No product
4	**185**	$C_6F_{13}(CH_2)_3$	$Pd_2(dba)_3$	DTBPBP	No product
5	**185**	$C_6F_{13}(CH_2)_3$	Pd $(OAc)_2$	Xantphos	80
6	**185**	$C_6F_{13}(CH_2)_3$	$Pd(OAc)_2$	DPPF	68
7	**185**	$C_6F_{13}(CH_2)_3$	$Pd(OAc)_2$	BINAP	No product
8	**185**	$C_6F_{13}(CH_2)_3$	$Pd(OAc)_2$	DTBPBP	No product
9	**187**	CH_3	$Pd_2(dba)_3$	Xantphos	45

From Table 3.4.4, we observed no thiolated product when monodentate biaryl ligand and BINAP were used (entries 3, 4, 7 and 8). Itoh *et al.*[74,75] also observed no thiolation reaction when $Pd(PPh_3)_4$ was used. He proposed that bidentate phosphine ligands promoted the reductive elimination through a *trans* to *cis* isomerization (Section 1.6.5, Scheme 1.6.5.7). Hartwig[72] also proposed that electron donating bidentate phosphine ligands with rigid structures prevented the formation of undesired complexes,

such as bridging or thiolate anionic complexes, which poisoned the smooth catalytic pathway.

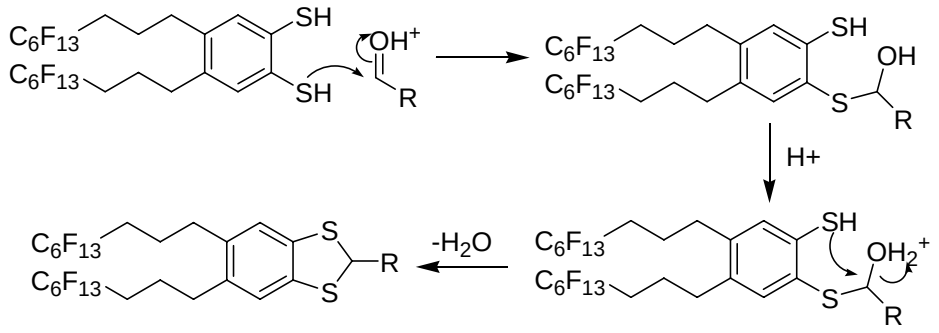
3.5 Synthesis of Diverse Ring Systems using Umpolung and Ring-Closing Metathesis Reactions

Diversity oriented synthesis of different size rings is known as skeletal diversity.[119] The synthesis of the symmetrical fluorous tagged surrogate dithiol gave a new direction in this project. Following our previous planning, our next step was to form benzodithianes from the dithiol. Different benzodithianes can be obtained by treating the dithiol with aldehydes of varying carbon chains. That will be the introduction of skeletal diversity to the system.



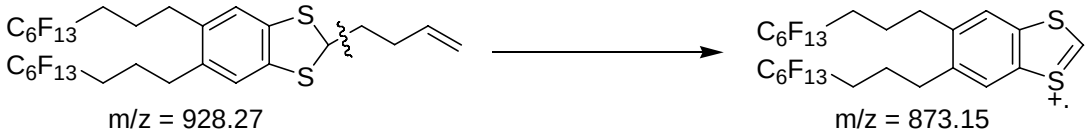
Scheme 3.5.1: Preparation of benzodithiane **192.**

Treatment of the crude dithiol with commercially available 4-pentenal in the presence of tetrafluoroboric acid[120] gave 2-but-3-enyl-5,6-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **192**. The purification of the product was done using FSPE starting from 70:30 MeOH/H_2O to 90:10 MeOH/H_2O to obtain a yellowish oil with 56% yield.



Scheme 3.5.2: Proposed mechanism of the dithiane formation.

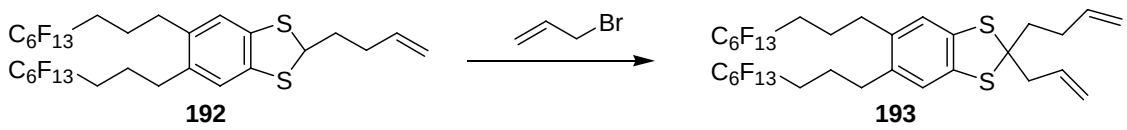
In the mass spectrum, the bezodithiane **192** has a characteristic fragmentation pattern and a metastable ion peak at m/z = 873.15, where a loss of $CH_2CH_2CH{=}CH_2$ m/z (55) fragment was observed.



Scheme 3.5.3: Fragmentation pattern of the dithiane **192** in the mass spectrum.

For the generation of the carbanion of benzodithiane **192**, *t*-BuLi and *n*-BuLi were tested using Et_2O and THF as solvents at different temperatures from -78 ^oC to -30 ^oC.[80,121] The results of these experiments are summarized in Table 3.5.1. We observed that the optimized temperature for the carbanion generation is -78 ^oC. When we tried to generate the anion at higher temperatures than -30 ^oC and quenched with the reactive electrophile allyl bromide, no alkylated product was obtained. This indicates that maintaining the temperature at -78 ^oC is crucial for the generation of the benzodithiane carbanion. Addition of *n*BuLi resulted in a red color in the solution, and the carbanion was stable at -78 ^oC for 40 min. Upon addition of allyl bromide, the reaction mixture turned to colorless.

Table: 3.5.1 Effect of solvents and bases on the lithiation of the benzodithiane **192**.

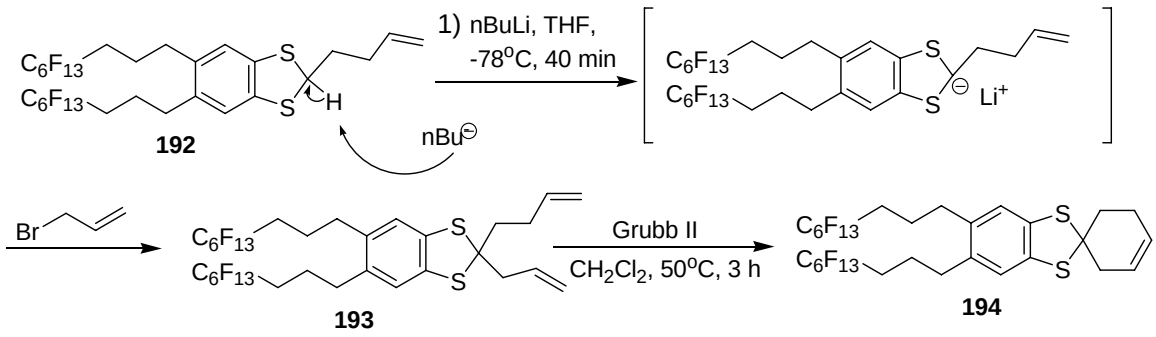


192 **193**

Entry	Base	Solvent	Temperature	Result
1	*n*-BuLi	THF	-78 ^{o}C/20 min	SM:**193** 1:1
2	*n*-BuLi	Et_2O	-78 ^{o}C/20 min	SM
3	*t*-BuLi	THF	-78 ^{o}C/20 min	unidentified Product
4	*t*-BuLi	Et_2O	-78 ^{o}C/20 min	unidentified Product
5	*n*-BuLi	THF	-78 ^{o}C/40 min	90%

In case of a benzodithiane system, the methine proton is very acidic and *n*-BuLi can easily abstract this proton to give the carbanion at -78 ^{o}C. When the reaction was quenched with allyl bromide after 20 min at -78 ^{o}C, we observed that lithiation was not completed; a half conversion of the reaction gave the starting material and the product in equal proportion (Table 3.5.1, entry 1). When the reaction time was increased to 40 min (entry 5), the allylated product was obtained with 90% conversion.

The diene **193** was treated with Grubbs (II) catalyst to undergo ring closing metathesis reaction to furnish 5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-spiro[benzo[d]1,3-dithiolene-2,4'-cyclohexane]-10-ene **194** with 58% yield over two steps. FSPE is found to be a useful tool to separate the non-fluorous Grubbs catalyst from the fluorous material. As Grubbs catalyst is expensive it is possible to recycle the catalyst employing FSPE.

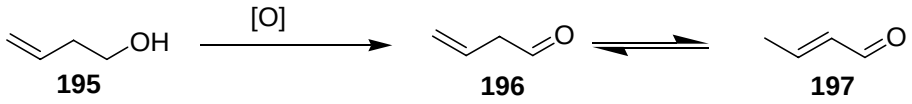


Scheme 3.5.4: Formation of the six membered ring **194**.

In the mass spectrum of compound **194**, the cyclohexene ring has a characteristic fragmentation pattern; a fragment at m/z = 885.9 was observed due to a loss of butadiene (m/z =54) via retro-Diels-Alder type cleavage.

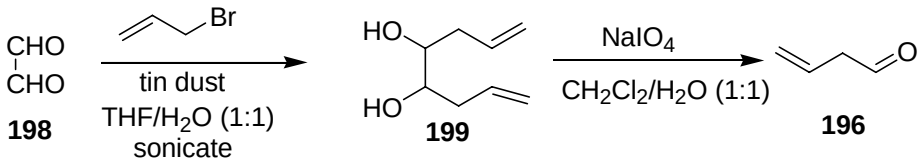
Scheme 3.5.5: Fragmentation pattern of compound **194**.

In order to explore 5-membered ring formation, the sequence was tried with 3-butenal. 3-Butenal is not commercially available, and direct oxidation of 3-butenol gave isomerized aldehyde **197** under Swern or PDC oxidation (Scheme 3.5.6). A similar observation was also reported in the literature.[122]



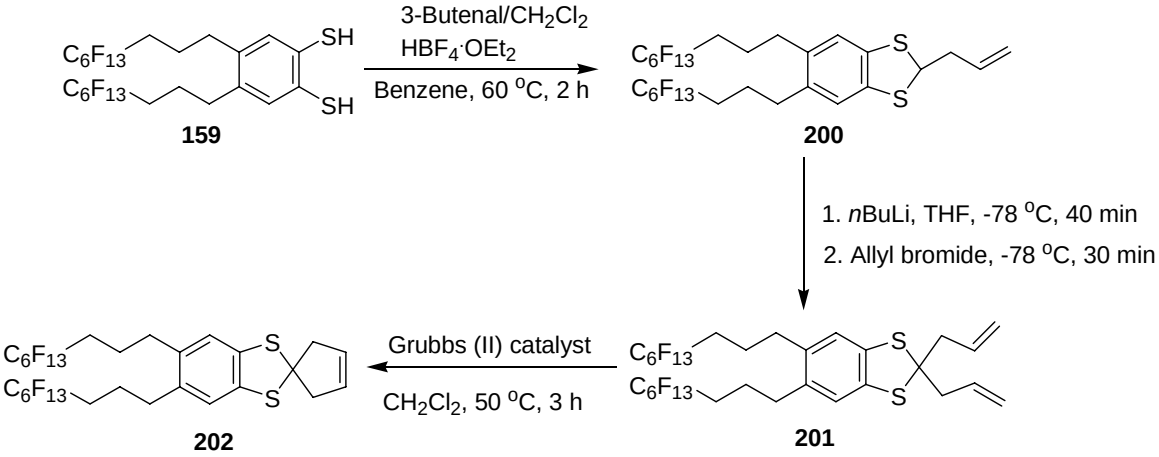
Scheme 3.5.6: Isomerization of 3-butenol.

3-Butenal was prepared as a solution in CH_2Cl_2 by treatment of glyoxal with allyl bromide in the presence of tin dust followed by oxidation with sodium periodate, according to a literature procedure (Scheme 3.5.7).[122]



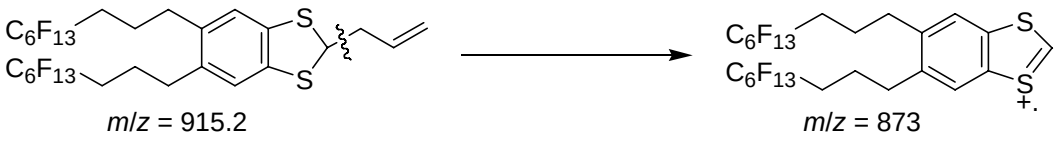
Scheme 3.5.7: Preparation of 3-butenal.

The dithiol **159** was treated with 3-butenal in the presence of HBF_4OEt_2 to afford 2-allyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **200** (Scheme 3.5.8).



Scheme 3.5.8: Formation of five membered ring **202**.

In the ^{1}H NMR spectrum, the characteristic CH methine proton was observed as a triplet at 4.89 ppm. In the ^{13}C spectrum, the methine carbon of the dithiane ring appeared at 54.1 ppm. In the mass spectrum, a peak at m/z 873 indicated the loss of the allyl group.

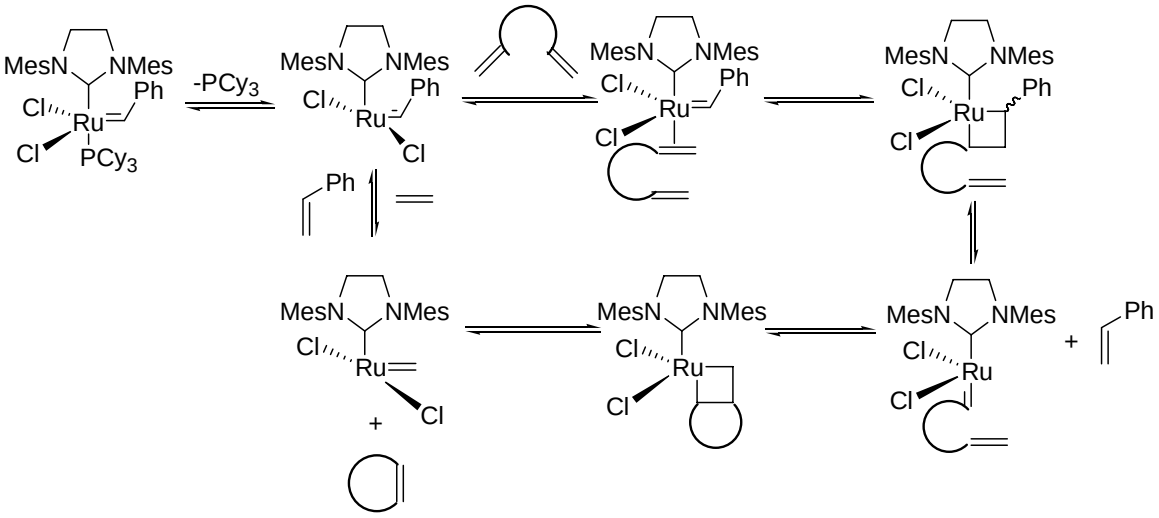


Scheme 3.5.9: Fragmentation pattern of benzodithiane **200** in the mass spectrum.

The allylation of the lithiated dithiane **200** gave the diene 2,2-diallyl-5,6-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **201**, which on treatment with Grubbs (II) catalyst gave 5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-

tridecafluorononyl)spiro[benzo[d]1,3-dithiolene-2,4'-cyclopentane]-10-ene **202** with 56% yield over two steps.

A schematic presentation of ring-closing metathesis reactions involving Grubbs (II) catalyst is portrayed in Scheme 3.5.10. The reaction proceeds in a dissociative fashion by an initial loss of the neutral ligand PCy_3 to generate a 14-electron intermediate. Upon binding of the olefin to Ru, a 2+2 addition with the metallocarbene gives a 4-membered ring. The loss of styrene and another 2+2 addition with the second olefin results a second 4-membered ring, which will give the ring-closed product, regenerating the Ru carbene complex.[123]

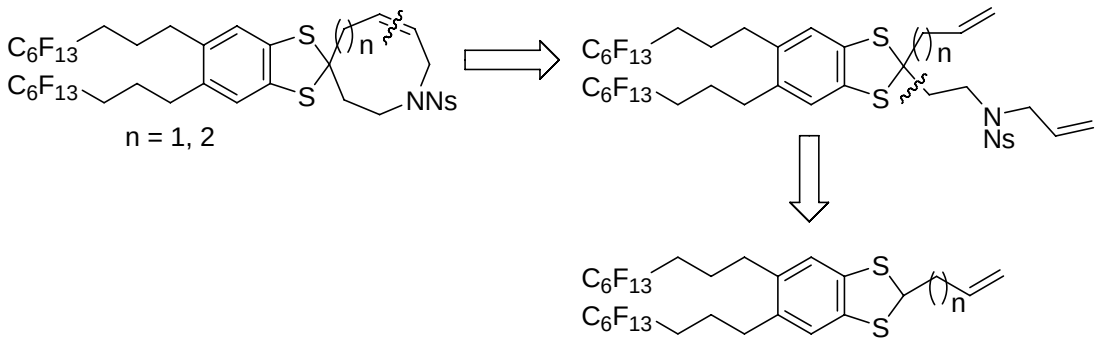


Scheme 3.5.10: Catalytic process in ring closing metathesis reaction.[123]

3.6 Approaches Towards the Synthesis of Heterocycles

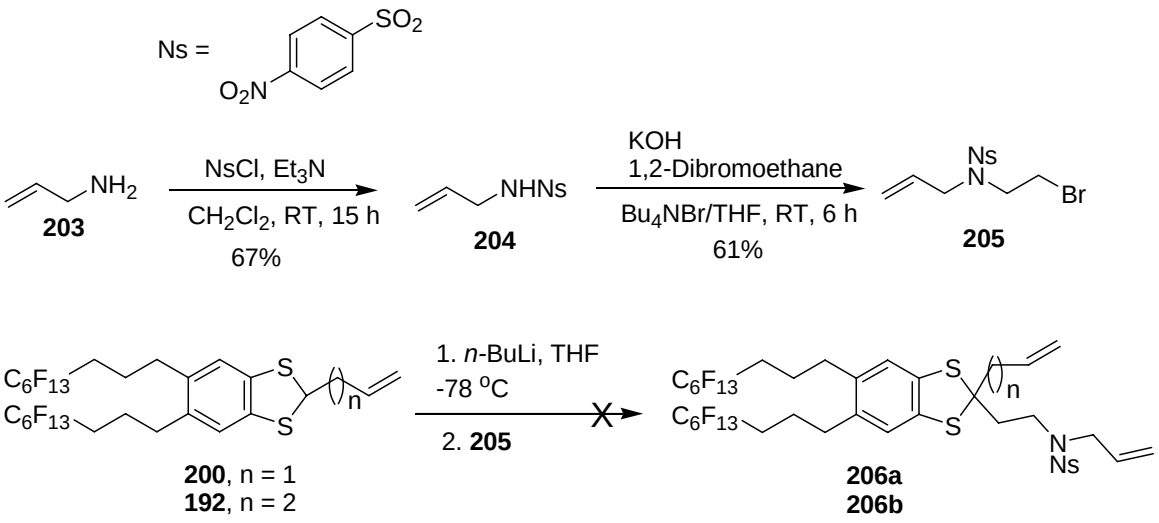
After synthesizing the spiro rings, the focus of this research turned to evaluating these benzodithianes in N-heterocycle synthesis. The major criteria remained that the fluorous support must assist in the purification of the desired products allowing the supported materials to be selectively and rapidly recovered using FSPE. As this method can be used to construct diverse ring systems, extension of this work to N-containing

systems can give different heterocycles. Later on the heterocycles can be separated from the fluorous support under traceless oxidative or reductive cleavage.[124] We tried to explore two approaches to construct heterocyclic systems. They are the ring-closing metathesis reaction and tandem Heck-Buchwald type reactions. But, the key challenge was to form the C-C bond by the alkylation reaction with the lithiated benzodithianes. Lithiated dithianes can be alkylated using alkyl halides.[84,125] We tried to form a C-C bond employing dithiane-alkylation approach with nitrogen containing electrophile, *N*-allyl-*N*-(2-bromoethyl)-4-nitrobenzenesulfonamide **205**.



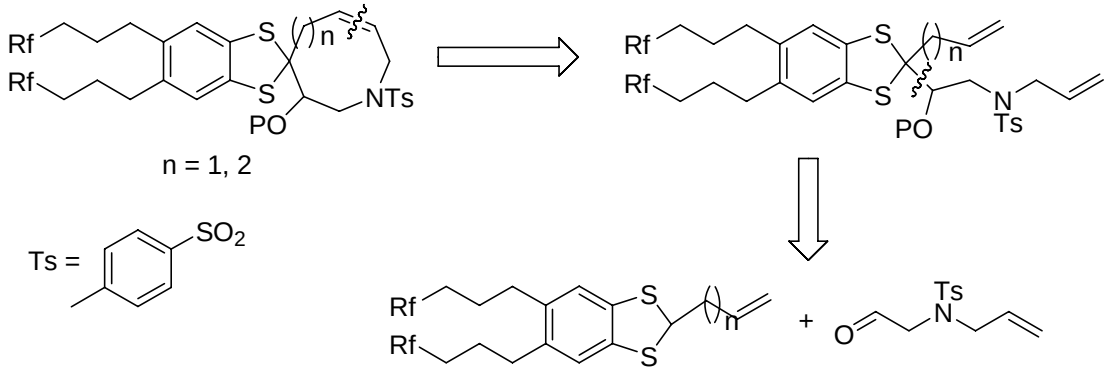
Scheme 3.6.1: Retrosynthetic disconnection.

In order to prepare nitrogen containing electrophiles, we protected allyl amine with an N-nosyl group to afford *N*-allyl-4-nitro-benzenesulfonamide **204** (Scheme 3.6.2). This was further treated with 1,2-dibromoethane under basic condition in the presence of tetrabutyl ammonium bromide to give *N*-allyl-*N*-(2-bromo-ethyl)-4-nitro-benzenesulfonamide **205**. Treatment of compound **205** with lithiated dithianes of **192 and 200** did not give the desired alkylated products **206a** and **206b**. The reaction was also performed using 10% HMPA as a cosolvent with THF[121] and NaI additive. However, no product was obtained and degradation of the electrophile **205** was observed after 15 min at -78 ^{o}C. Only the fluorous dithiane was recovered after the reaction.



Scheme 3.6.2: Attempted C-C bond formation with electrophile **205**.

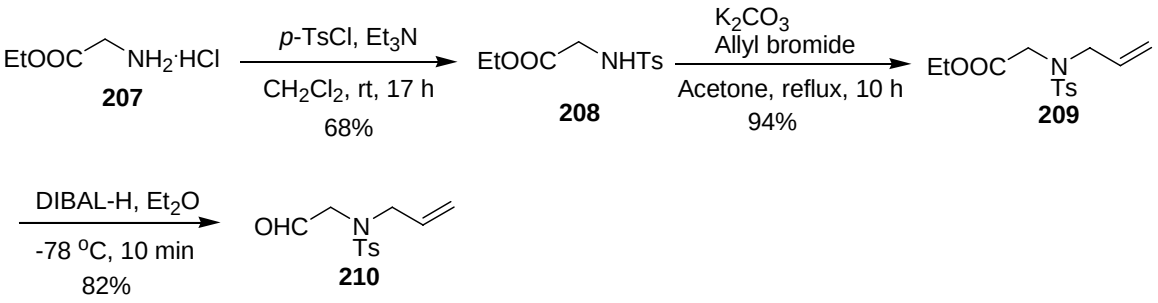
After facing problems to form the C-C bond with alkyl halide **205**, we moved to an electrophile with aldehyde functionality. The generated carbanion of a dithiane can be quenched with an aldehyde to form a C-C bond[121,126] Aditionally, moving to an aldehyde functionality will give a secondary alcohol group which can be protected with TMS group. This will add one diversity point and will be useful for funtionalization of heterocycle systems. The ring-closing metathesis reaction can be employed to close the two terminal olefins to form nitrogen heterocycles[127] (Scheme 3.6.3).



Scheme 3.6.3: Retrosynthetic disconnection.

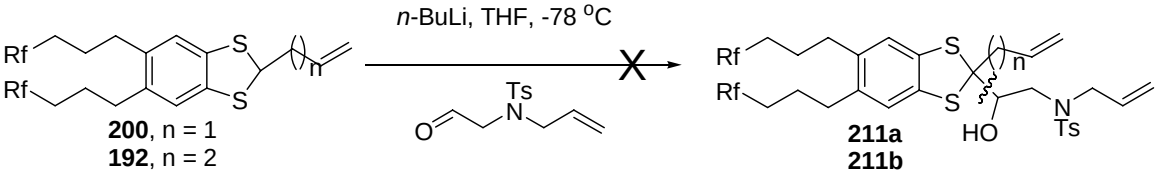
As shown in Scheme 3.6.4, glycine ethyl ester was protected with an *N*-tosyl group to give (toluene-4-sulfonylamino)-acetic acid ethyl ester **208** using a reported

method.[128,129] Allylation of the resulting ester afforded allyl-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester **209**. A controlled reduction with DIBAL-H converted the ester to *N*-allyl-4-methyl-*N*-(2-oxo-ethyl)-benzenesulfonamide **210** with 82% yield.



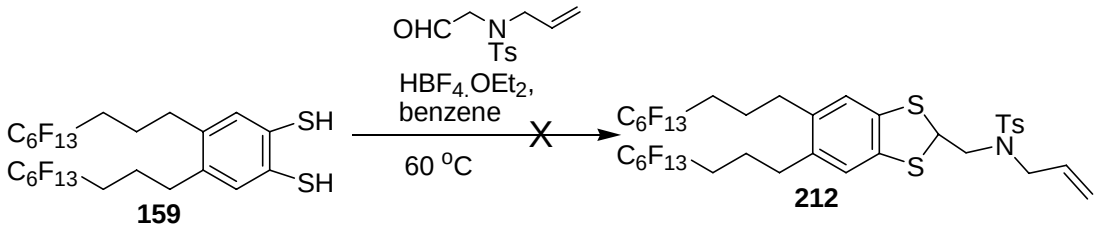
Scheme 3.6.4: Preparation of an electrophile with aldehyde functionality.

Treatment of the aldehyde **210** with the lithiated carbanions in different conditions varying solvents like Et_2O, THF and the use of cosolvent HMPA and temperatures from -78 ^oC to room temperature did not give the desired product. The reaction was tried with both the dithianes **192** and **200**, but no C-C bond formation was observed. In this case, mostly the starting material was recovered however, aldehydes could not be recovered.



Scheme 3.6.5: C-C bond formation with aldehyde.

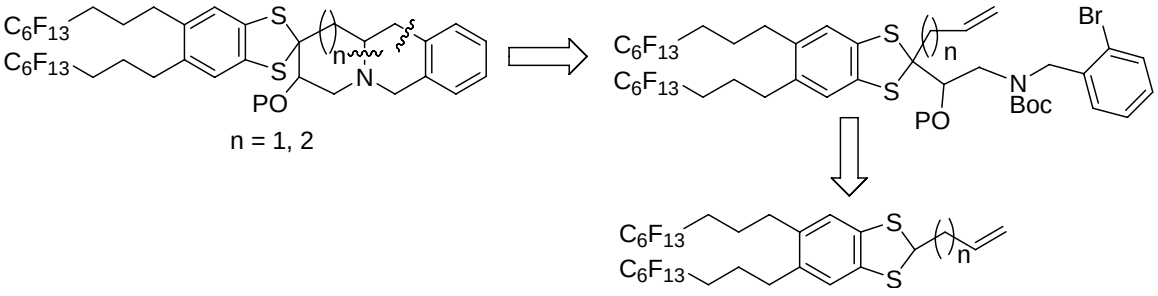
After this failure, we tried to prepare a dithiane of the aldehyde **210** from the dithiol **159** (Scheme 3.6.6). Under the typical condition for dithiane formation, mostly starting material was recovered. Prolonged heating led to decomposition of the aldehyde. The reason for this lack of reactivity is not clear, but we suspect the quality of the catalyst used in this experiment.



Scheme 3.6.6: Attempted reaction for dithiane formation.

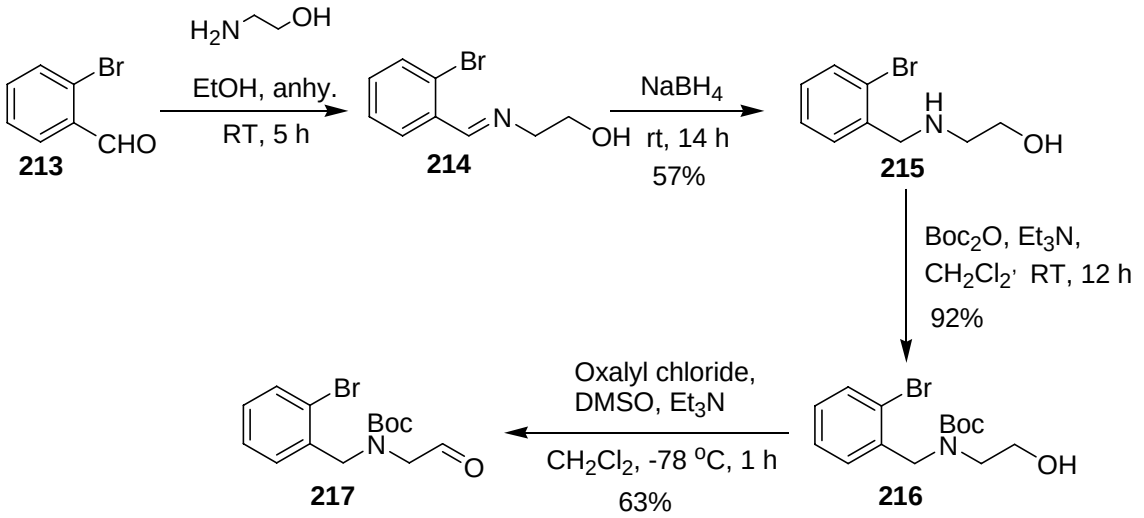
3.7 Heterocycle Synthesis using Tandem Heck and Buchwald type Reactions

The twofold Heck coupling is known in the literature to form bicyclic systems.[130] We wanted to explore Pd (0) catalyzed tandem Heck and Buchwald type reactions to synthesize a tetrahydroquinoline core in our fluorous system (Scheme 3.7.1). Our plan was to form a C-C bond with the lithiated dithiane of **192** and the aldehyde, (2-bromobenzyl)-(2-oxo-ethyl)carbamic acid *tert*-butyl ester **217**.



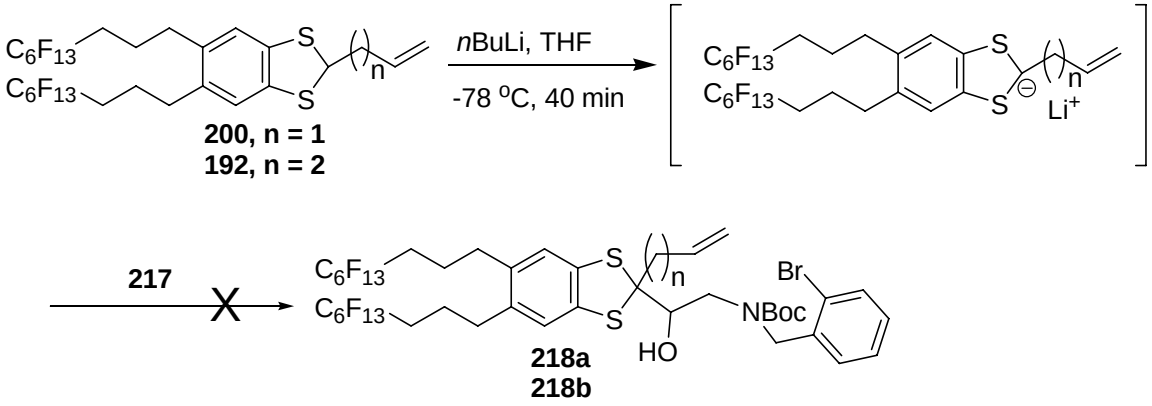
Scheme 3.7.1: Retrosynthetic disconnection.

2-(2-Bromobenzylamino)ethanol **215** was prepared from 2-bromobenzaldehyde and ethanolamine by the reductive amination reaction.[131] Treatment of Boc_2O with compound **215** gave (2-bromobenzyl)-(2-hydroxyethyl)carbamic acid *tert*-butyl ester **216**. Swern oxidation of this primary alcohol afforded (2-bromobenzyl)-(2-oxo-ethyl)carbamic acid *tert*-butyl ester **217**.



Scheme 3.7.2: Preparation of a N-containing electrophile.

Treatment of the lithiated carbanion of the dithianes **192** and **200** with compound **217** under several conditions using different solvents like THF, HMPA/THF and Et_2O and at different temperatures did not give the desired products (Scheme 3.7.3).

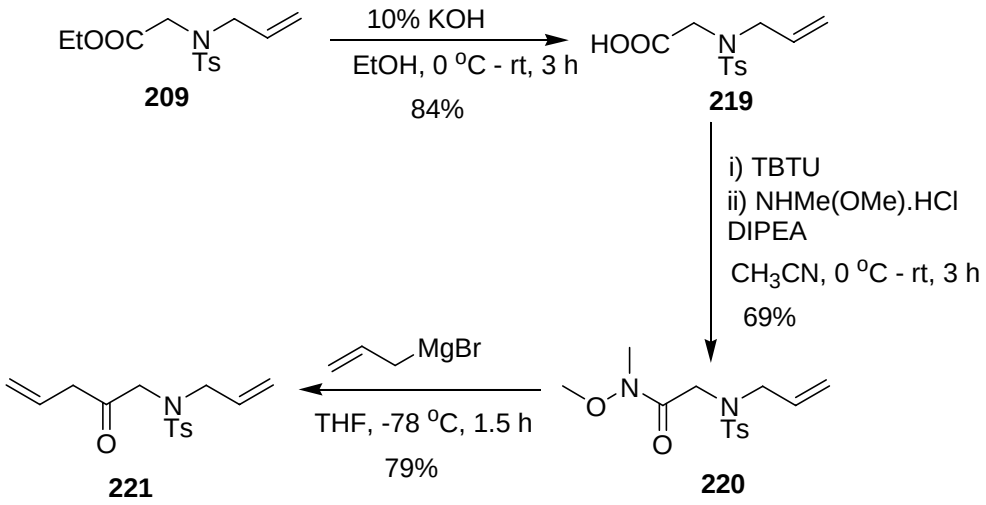


Scheme 3.7.3: Attempted C-C bond formation reaction with lithiated dithiane.

3.8 Formation of Dithianes from Ketones

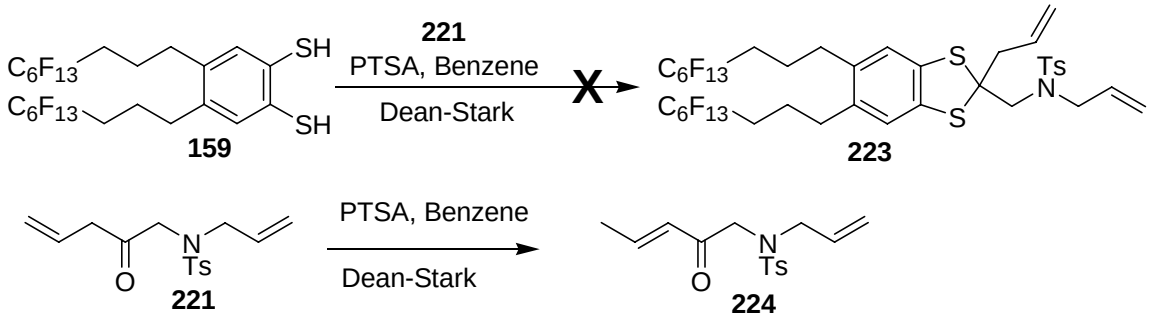
In order to explore the scope of dithiane formation directly from a dithiol and a ketone,[132] we tried to prepare a ketone having two terminal olefins. Allyl(toluene-4-sulfonyl)amino]acetic acid **219** was prepared by hydrolysis of the ester **209**. The Weinreb amide, 2-[allyl(toluene-4-sulfonyl)amino]*N*-methoxy-*N*-methyl acetamide **220** was

obtained from the acid **219** by treatment with *N,O*-dimethylhydroxyl amine hydrochloride in the presence of TBTU under basic conditions.[27] Addition of allyl magnesium bromide to this amide provided *N*-allyl-4-methyl-*N*-(2-oxo-pent-4-enyl)benzenesulfonamide **221**.



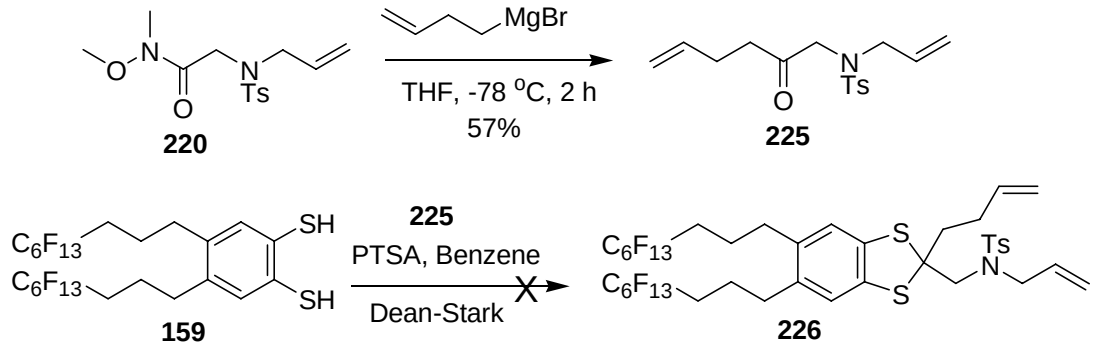
Scheme 3.8.1: Preparation of a *N*-Ts protected ketone.

The ketone **221** and the fluorous benzodithiol **159** were heated under reflux in the presence of a catalytic amount of PTSA using a Dean-Stark apparatus to get the corresponding dithiane compound **223**.[132,133] No product was obtained. Instead, the allylic double bond of the ketone **221** isomerized to give an α,β-unsaturated ketone **224** (Scheme 3.8.2).



Scheme 3.8.2: Isomerization of olefin.

Another ketone with terminal olefins, *N*-allyl-4-methyl-*N*-(2-oxo-hex-5-enyl)benzenesulfonamide **225** was obtained by treating the Weinreb amide **220** with freshly prepared 3-butene magnesium bromide (Scheme 3.8.3). This was further reacted with the fluorous dithiol under the PTSA condition using a Dean-Stark apparatus. No product was observed even after prolonged heating for 48 h.



Scheme 3.8.3: Attempted C-C bond formation reaction.

All the attempts we made to form nitrogen heterocycles remained unsuccessful. Hence, some modifications in the electrophiles are required to make them reactive towards the dithiane carbanions to form C-C bonds.

CHAPTER 4: CONCLUSIONS AND FUTURE WORK

4.1 Conclusions

This study has demonstrated the fulfillment of the primary goal of my thesis, synthesis of a symmetrical fluorous tagged benzodithiol support and its application in the synthesis of diverse ring systems. An efficient eight-step synthetic pathway has been developed to synthesize fluorous-tagged benzodithianes. A fluorous iodide containing an ethylene spacer was employed to render the system fluorous. The findings of this research are summarized below.

1. A very selective and a high yielding method for 1,2-dibromination in a fluorous tagged benzenoid system was developed.

2. A new condition for the palladium catalyzed dithiolation reaction using $Pd(OAc)_2$ and Xantphos is reported in this thesis. FSPE was successfully utilized to separate the catalyst and the ligand from the fluorous tagged dithiolated compounds. A symmetrical fluorous tagged benzodithiol **159** was obtained from a surrogated dithiol **190** and it was further used for the formation of two fluorous tagged benzodithianes, compounds **192** and **200**.

3. The application of these fluorous benzodithianes **192** and **200** was extended to construct two ring systems, compounds **194** and **202** employing the ring-closing metathesis reaction.

Nitrogen containing heterocycles with an eight-membered cyclic core are pharmaceutically and biologically important compounds.[85,86] So, the generation of a library of this kind of cyclic core has significant applications in medicinal chemistry. We synthesized three nitrogen containing electrophiles (compounds **205**, **210** and **217**) and

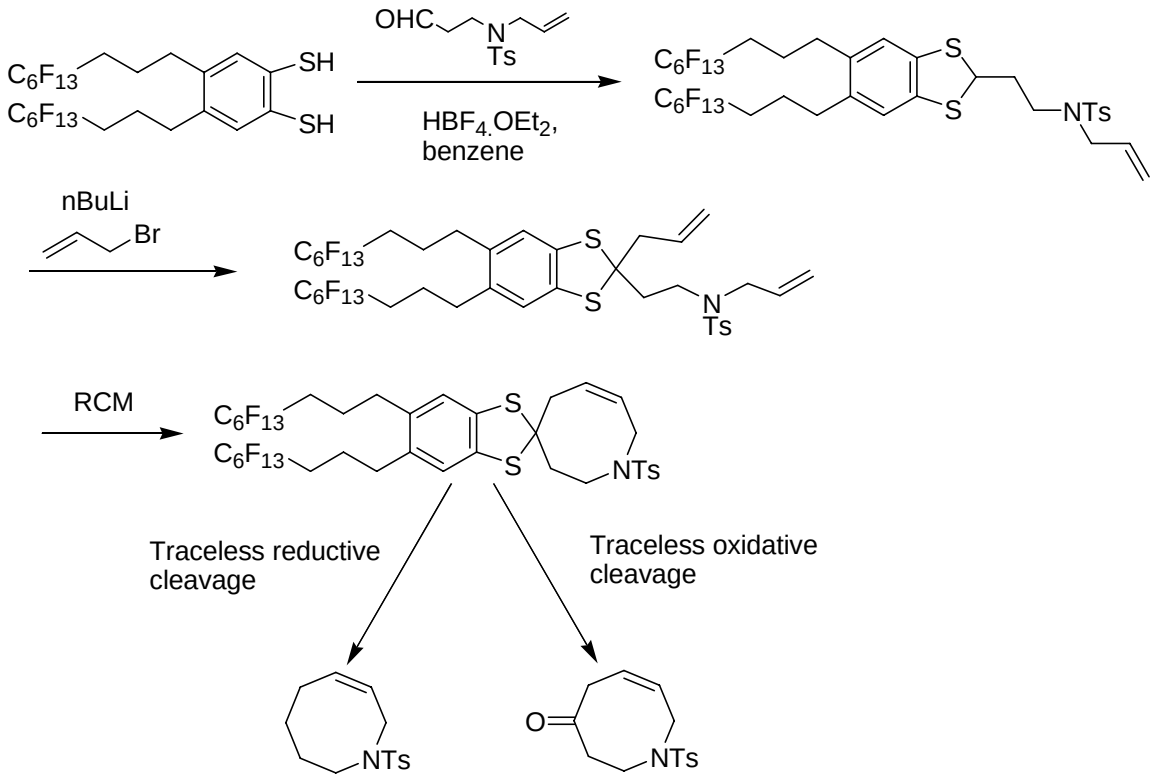
tried to form a C-C bond with lithiated fluorous benzodithianes. At the end of this study the attempts to form the C-C bond upon treatment of the lithiated dithianes with these electrophiles remained unsuccessful.

There may be few reasons for the failure of this key reaction. The problem associated with the generation of the benzodithiane anion is ruled out because the alkylation reaction worked smoothly with allyl bromide. Other factors might be the steric hindrance of our benzodithiane carbanion to the approaching sterically hindered electrophiles containing an *N*-Ts group (compound **210**) or an *N*-Ns group (compound **205**), and the stability of these electrophiles under strong basic condition, because the aldehydes were never recovered from the reaction mixtures. In case of the bromoderivative **205**, a competing reaction could be an elimination reaction.

4.2 Scope and FutureWork

There is a wide scope and prospect of the fluorous tagged dithianes in the formation of a diverse range of heterocycles, which could be important synthetic intermediates towards the drug discovery. The C-C bond formation was successful with the small and reactive electrophile, allyl bromide. So, we can take advantage of our success to design a better approach to move this project further. We also faced problems in dithiane formation with *N*-allyl-4-methyl-*N*-(2-oxo-ethyl)benzenesulfonamide **210**. However, the effect of steric hindrance and electron withdrawing effect of *N*-Ts group can be diluted by introducing an additional carbon atom between the aldehyde group and the *N*-Ts group.

After the formation of a medium size ring, the application and scope of traceless linker concept can be explored by oxidative or reductive cleavage[124] as shown in Scheme 4.2.1.



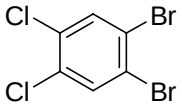
Scheme 4.2.1: Designed future synthesis of 8-membered heterocycles.

CHAPTER 5: EXPERIMENTAL PROCEDURES

5.1 General Materials and Methods

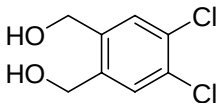
All experiments were performed in oven-dried glassware under nitrogen atmosphere, unless otherwise specified. Acetonitrile, dichloromethane, diethyl ether, THF and toluene were obtained from a solvent purifier (Innovative Technology Inc.) immediately before use. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone under nitrogen. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography with precoated (0.2 mm) Alugram® Sil G/UV gel plates. Unless otherwise noted, all organic layers from extractions were dried by standing over anhydrous $MgSO_4$ before being concentrated on a rotary evaporator. Flash chromatography was carried out with Silicycle Silica-P flash silica gel (230-400 mesh). Fluorous solid phase extraction was performed using bulk Fluoro*Flash*^{TM} silica gel obtained from Fluorous Technologies Inc. Melting points were measured on an Electrothermal® melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts are reported in parts per million (ppm) down field from TMS, relative to residual chloroform (δ_H = 7.27 or δ_C = 77.2 ppm) as an internal standard unless otherwise stated. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on a VG-7070E instrument of E-B geometry.

1,2-Dibromo-4,5-dichlorobenzene (161):



To a mixture of 1,2-dichlorobenzene (10.0 mL, 88.7 mmol) and iron powder (1.38 g, 24.7 mmol), Br_2 (11.4 mL, 222.4 mmol) was slowly added through an addition funnel at 50 ^oC. After cooling to room temperature, the mixture was stirred overnight. The brown solid formed was washed successively with hot water, 5% NaOH and again with hot water. The crude product was crystallized from toluene to give 1,2-dibromo-4,5-dichlorobenzene **161** as a white crystalline solid (7.09 g, 26% yield). Mp = 150 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H, -C_6H_2). These values matched literature values.[96]

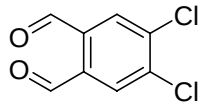
4,5-Dichloro-1,2-bis(hydroxymethyl)benzene (168):



To a slurry of $LiAlH_4$ (3.23 g, 85.1 mmol) in dry THF, a solution of 4,5-dichlorophthalic acid (10.00 g, 42.5 mmol) in THF (50 mL) was added dropwise at 0 ^oC. After the addition, the reaction mixture was allowed to warm to room temperature over 2 h and was then heated at reflux for 17 h. The reaction mixture was cooled to 0 ^oC, before being quenched with 15% NaOH solution (50 mL) followed by ice cold water (50 mL). The mixture was then diluted with THF (100 mL). The organic layer was washed with brine (2 × 50 mL) and the aqueous layer was extracted with Et_2O (3 × 100 mL). Both the organic layers were combined, dried and concentrated. The crude residue was recrystallized from MeOH to obtain the product **168** as colorless flakes (6.60 g, 75%

yield). Mp = 136 ^{o}C (lit.137-139 ^{o}C).[99] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 2H, -C_6H_2), 6.49 (s, 4H, 2×-CH_2OH).

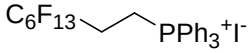
4,5-Dichlorobenzene-1,2-dicarbaldehyde (169):



To a stirred solution of oxalyl chloride (2.8 mL, 32.6 mmol) in CH_2Cl_2 (35 mL) at -78 ^{o}C, a solution of DMSO (5.0 mL, 70.4 mmol) in CH_2Cl_2 (10 mL) was slowly added. The resulting solution was then stirred for 15 min. To this solution, 4,5-dichloro-1,2-bis(hydroxymethyl)benzene (3.00 g, 14.4 mmol) in 5.0 mL of DMSO-CH_2Cl_2 solution (1:2) was added dropwise at -78 ^{o}C and the mixture was then stirred for 45 min at the same temperature. Then, Et_3N (16.0 mL, 114.8 mmol) was slowly added to the reaction mixture. After being stirred for 20 min, the reaction was warmed to room temperature and quenched with ice-cold water to give a milky white suspension. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Both the organic layers were combined, dried and concentrated. Purification by flash chromatography on silica gel (hexane-EtOAc, 4:1) gave 4,5-dichlorobenzene-1,2-dicarbaldehyde **169** as a yellowish white solid (2.68 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 2H, 2×-C*H*O), 8.05 (s, 2H, -C_6H_2).

Triphenyl(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phosphonium iodide (170):



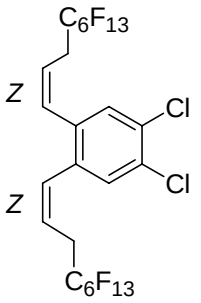
1*H*,1*H*,2*H*,2*H*-Perfluorooctyl iodide (12.40 g, 26.1 mmol) and triphenylphosphine (7.64 g, 29.1 mmol) were combined and DMF (15.0 mL) was added. The mixture was

heated for 24 h at 110 ^{o}C before cooling and removing the solvent under reduced pressure. The crude residue was triturated with Et_2O (100 mL) and filtered through a Buchner funnel. The residue was washed with Et_2O (2 × 30 mL) and dried in vacuo to give a yellowish white solid (18.03 g, 93%). Mp = 191 ^{o}C (lit. 191-195 ^{o}C).[98]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.71 (m , 15H), 4.22-4.13 (apparent quintet, 2H, $^{2}J_{PH}$ = 14.1 Hz, $^{3}J_{HH}$ = 7.6 Hz, PCH_2), 2.70-2.51 (m, 2H, -$CH_2CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 135.8 (d, 3C, $^{4}J_{CP}$ = 3 Hz), 135.7(d, 6C, $^{3}J_{CP}$ =10 Hz), 130.9 (d, 6C, $^{2}J_{CP}$ = 13 Hz), 117.0 (d, 3C, $^{1}J_{CP}$ = 87 Hz), 24.7 (t, 1C, $^{2}J_{CF}$ = 23 Hz, PCH_2CH_2), 16.4 (t, 1C, $^{1}J_{CP}$ = 56 Hz, PCH_2-); ^{19}F (282 MHz, $CDCl_3$) δ -82.1 (t, $^{3}J_{FF}$ = 9.8 Hz, CF_3), -113.62 (m, CF_2), -122.82 (br s, CF_2), 123.85 (br s, CF_2), 123.99 (br s, CF_2), 127.15 (br s, CF_2).

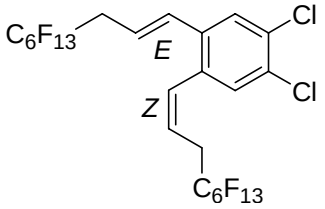
4,5-Dichloro-1,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene (171):

4,5-Dichlorobenzene-1,2-dicarbaldehyde (1.08 g, 5.32 mmol), triphenyl-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phosphonium iodide (9.79 g, 13.29 mmol) and potassium carbonate (2.20 g, 15.9 mmol) were combined. 1, 4-Dioxane (40 mL) was added and the yellow mixture was stirred vigorously at room temperature. After 5 min, water (0.5 mL) was added and the mixture was heated for 24 h at 95 ^{o}C. The solvent was removed using a rotary evaporator. The crude residue was suspended with ice cold water and extracted with CH_2Cl_2. The extract was dried and evaporated to dryness. The residual oil was purified by FSPE from 85% MeOH/H_2O wash to obtain a colorless gummy liquid (4.08 g, 89%, 78:22 *ZZ*/*EZ*).



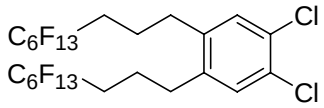
R_f = 0.4 (9:1-hexanes/ethyl acetate).

(*ZZ*) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 2H, -C_6H_2), 6.67 (d, 2H, $^3J_{HH}$ = 11.4 Hz, 2×ArC*H*=), 6.01-5.84 (dt, 2H, $^3J_{HH}$ = 11.7 Hz, $^3J_{HH}$ = 7.4 Hz, 2×=C*H*CH_2-), 3.00-2.85 (dt, 4H, $^3J_{HF}$ = 18.0 Hz, $^3J_{HH}$ = 7.6 Hz, 2×-C$H_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -82.1 (t, $^3J_{FF}$ = 9.8 Hz, $2CF_3$), -113.62 (m, $2CF_2$), -122.82 (br s, $2CF_2$), 123.85 (m, $2CF_2$), 123.99 (s, $2CF_2$), 127.15 (m, $2CF_2$).



(*EZ*) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 2H, -C_6H_2), 6.67 (d, 1H, $^3J_{HH}$ = 11.9 Hz, ArC*H*=), 6.65 (d, 1H, $^3J_{HH}$ = 15.4 Hz, ArC*H*=), 6.18-6.08 (dt, 1H, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.2 Hz, =C*H*CH_2-), 6.06 (m, 1H, =C*H*CH_2-), 3.00-2.85 (m, 4H, 2×-C$H_2C_6F_{13}$).

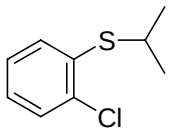
4,5-Dichloro-1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (172):



To a stirred solution of 4,5-dichloro-1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene (2.41 g, 2.79 mmol) in EtOAc (30 mL), was added PtO_2 (63.4 mg, 0.279 mmol) under N_2. The black reaction mixture was stirred at room temperature for 5 h under a thick-walled hydrogen gas balloon. The crude mixture was filtered through a Celite pad. After removal of the solvent by a rotary evaporator, the residue was purified by column chromatography (EtOAc/hexane, 1:4) to afford 4,5-dichloro-1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **172** as a colorless oil (1.96 g, 81% yield).

R_f = 0.4 (9:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.18 (s, 2H, -C_6H_2), 2.59 (t, 4H, $^3J_{HH}$ = 7.8 Hz, 2×ArCH_2-), 2.17-1.99 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.84-1.76 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 139.5 (2C), 13.1.2 (2C), 130.4 (2C), (due to low intensity $2C_6F_{13}$ carbons are obscured), 31.4 (2C), (due to low intensity triplet for $2CH_2C_6F_{13}$ carbons are obscured), 21.8 (2C).

1-Chloro-2-isopropylsulfanylbenzene (178):

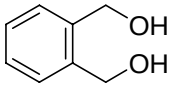


To a degassed solution of 1,2-dichlorobenzene (0.4 mL, 3.5 mmol) in 1,4-dioxane (10 mL) in a Schlenk tube were added $Pd(OAc)_2$ (16 mg, 0.071 mmol), diisopropylphosphinoferrocene DiPPF (35.6 mg, 0.085 mmol), NaO*t*-Bu (1.5 g, 15.60

mmol) and 2-propane thiol (1.3 mL, 13.92 mmol). The mixture was stirred for 3 days at 100 ^{o}C. After cooling to room temperature, the reaction mixture was filtered, washed with Et_2O and the filtrate was evaporated in a rotary evaporator. The residue was purified by column chromatography using hexane-EtOAc, 10:1 to obtain a gummy liquid (400 mg, 50% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 2H, -C_6H_2), 7.19-7.04 (m, 2H, -C_6H_2), 3.52 (septet, 1H, *J* = 6.6 Hz, -C*H*$(CH_3)_2$), 1.31 (d, 6H, *J* = 6.7 Hz, -CH(C*H*$_3)_2$). MS (EI mode): *m*/*z* (% relative intensity): 186 (M^+, 100), 187 (M+1, 11), 188 (M+2, 38).

1,2-Bis(hydroxymethyl)benzene (181):

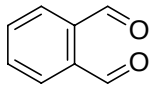


CAS = 612-14-6

To a stirred suspension of $LiAlH_4$ (4.11 g, 108.30 mmol) in 200 mL of THF at 0 ^{o}C, phthalic acid (10.00 g, 60.19 mmol) dissolved in THF (100 mL) was added dropwise via a cannula over a period of 1 h. The reaction was allowed to warm to room temperature in a period of 2 h and was then heated at reflux for 36 h. The reaction mixture was cooled to 0 ^{o}C and quenched with 50 mL of 15% NaOH solution. Then, 50 mL of ice cold water was added and diluted with 100 mL of THF and the layers were separated. The organic layer was washed with brine (2 × 30 mL) and the aqueous layer was extracted with Et_2O (2 × 100 mL). Both the organic layers were combined, dried, filtered and concentrated. The crude material was recrystallized from MeOH to obtain white flakes (7.0 g, 83%). Mp = 67 ^{o}C (lit. 68-69 ^{o}C).[108]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 4H, -C_6H_4), 4.45 (s, 4H, 2×-CH_2OH), 4.41 (br s, 2H, 2×-CH_2O*H*).

Phthalaldehyde (182):



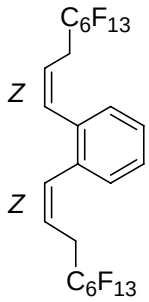
CAS = 643-79-8

Prepared from 1,2-bis(hydroxymethyl)benzene employing the same procedure as compound **169**. Isolated as a white solid, mp = 56 ^{o}C. This compound is commercially available.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (s, 2H, 2×-C*H*O), 7.99 (m, 2H, -C_6H_2), 7.79 (m, 2H, -C_6H_2); ^{13}C (75 MHz, $CDCl_3$) δ 192.2 (s, 2C, C_6H_4(*C*HO)$_2$), 134.4 (s, 2C),133.7 (s, 2C), 131.0 (s, 2C).

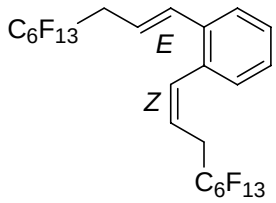
1,2-Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene (183):

The reaction/workup given for compound **171** was repeated with phthalaldehyde (1.4 g, 10.43 mmol), triphenyl-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phosphonium iodide (19.2 g, 26.07 mmol), potassium carbonate (5.04 g, 36.46 mmol), 1,4-dioxane (129 mL) and water (4.2 mL). This gave 1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene **183** as a colorless gummy liquid (8.2 g, 92%, 90:10 *ZZ*/*EZ*).



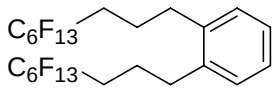
R_f = 0.57 (19:1-hexanes/ethyl acetate).

(*ZZ*) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 4H, -C_6H_4), 6.85 (d, 2H, 2×ArC*H*=, J = 11.4 Hz), 5.93 (dt, 2H, $^{3}J_{HH}$ = 11.5 Hz, $^{3}J_{HH}$ = 7.2 Hz, 2×=C*H*CH_2-), 3.08 (dt, 4H, $^{3}J_{HF}$ = 18.0 Hz, $^{3}J_{HH}$ = 7.0 Hz, 2×-C*H*$_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 134.9 (s, 2C, C_6H_4(*C*H=)$_2$), 134.3 (s, 2C), 128.7 (s, 2C), 127.6 (s, 2C), 123.4-104.2 (m, 12C, 2×-*C*$_6F_{13}$), 119.0 (t, 2C, $^{3}J_{CF}$ = 4.4 Hz, 2×=*C*HCH_2-), 30.7 (t, 2C, $^{2}J_{CF}$ = 22.3 Hz, 2×-*C*$H_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -82.21 (t, $^{3}J_{FF}$ = 10 Hz, $2CF_3$), -113.86 (m, $2CF_2$), -122.84 (br s, $2CF_2$), 123.87 (br s, $2CF_2$), 124.12 (br s, $^{2}J_{FF}$ = 13.7 Hz, $2CF_2$), 127.22 (m, $2CF_2$); MS (EI mode): *m*/*z* (% relative intensity): 793 (M^+,100) , 795 (M+1, 24).



(*EZ*) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 4H, -C_6H_4), 6.96 (d, 1H, J = 11.5 Hz, ArC*H*=), 6.85 (d, 1H, J = 11.4 Hz, ArC*H*=), 6.22 (dt, 2H, $^{3}J_{HH}$ = 15 Hz, $^{3}J_{HH}$ = 7.2 Hz, 2×=C*H*CH_2-), 3.08-2.94 (m, 4H, 2×-C*H*$_2C_6F_{13}$).

1,2-Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (184):

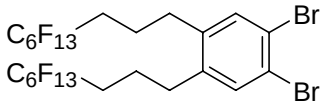


To a stirred solution of 1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-enyl)benzene (7.58 g, 9.54 mmol) in 40 mL of EtOAc (anhydrous), 10% Pd/C (500 mg, 5 mol%, 0.46 mmol) was added under N_2. The reaction was stirred vigorously for 24 h under hydrogen gas balloon. Pd/C was removed by filtration through a Celite pad by washing with EtOAc (2 × 50 mL) and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel

(hexane-EtOAc, 4:1) to afford 1,2-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **184** as a clear gummy liquid (6.96 g, 92%).

R_f = 0.5 (19:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.20 (m, 4H, -C_6H_4), 2.80 (t, 4H, $^3J_{HH}$ = 7.8 Hz, 2×ArCH_2-), 2.23 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 2.02 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ138.4 (s, 2C), 129.2 (s, 2C), 126.7 (s, 2C), 123.4-104.7 (m, 12C, 2×-C_6F_{13}), 31.7 (s, 2C, ArCH_2-), 30.9 (t, 2C, $^2J_{CF}$ = 22.4 Hz, 2×-$CH_2CH_2C_6F_{13}$), 21.7 (t, 2C, $^3J_{CF}$ = 3 Hz, 2×-$CH_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.89 (t, $^3J_{FF}$ = 10 Hz, $2CF_3$), -114.81 (m, $2CF_2$), -112.66 (br s, $2CF_2$), -123.66 (br s, $2CF_2$), -124.22 (br s, $2CF_2$), 126.9 (m, $2CF_2$); MS (EI mode): *m*/*z* (% relative intensity): 798 (M^+, 100), 799 (M+1, 30).

1,2-Dibromo-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (185):

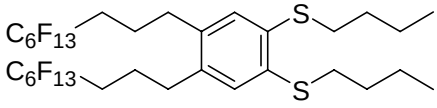


To a stirred solution of compound **184** (3.67 g, 4.59 mmol) in CH_2Cl_2 (35 mL), Fe powder (120 mg, 2.14 mmol) and I_2 catalyst (58 mg, 0.457 mmol) were added. The mixture was cooled to -10 ^{o}C. In another flask, a Br_2 stock solution in CH_2Cl_2 (10 mL, 1:9) was made. The Br_2 stock solution (5.4 mL, 10.53 mmol) was added to the reaction mixture dropwise over a period of 40 min maintaining the temperature of the ice bath at -10 ^{o}C. Following the completion of the addition, the reaction was allowed to warm to -5 ^{o}C and stirring was continued at that temperature for 2 h. Then, the temperature was increased to 0 ^{o}C and the reaction was stirred for an additional 8 h. The reaction was quenched with saturated $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The

extract was further washed with saturated $Na_2S_2O_3$ solution (30 mL), dried and concentrated. The crude oil was purified by flash chromatography (hexane-EtOAc, 9:1) to furnish 1,2-dibromo-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **185** as a colorless gummy liquid (4.08 g, 93%).

R_f = 0.3 (19:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2H, -C_6H_2), 2.66 (t, 4H, $^3J_{HH}$ = 7.95 Hz, 2×ArCH_2-), 2.21-2.06 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.93-1.82 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ139.6 (s, 2C), 134.1 (s, 2C), 122.6 (s, 2C), 122.9-107.0 (m, 12C, 2×-C_6F_{13}), 31.2 (s, 2C, 2×ArCH_2-), 30.7 (t, 2C, $^2J_{CF}$ = 22.4 Hz, 2×-$CH_2CH_2C_6F_{13}$), 21.5 (t, 2C, $^3J_{CF}$ = 3 Hz, 2×-$CH_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.50 (t, $^3J_{FF}$ = 10 Hz, $2CF_3$), -114.51 (m, $2CF_2$), -112.52 (br s, $2CF_2$), -123.49 (br s, $2CF_2$), -123.98 (br s, $2CF_2$), -126.73 (tt, J_{FF} = 15 Hz, J_{HF} = 3 Hz, 2-$CF_2CF_2CH_2$-); MS (EI mode): m/z (% relative intensity): 953 (M^+, 54), 955 (M+2, 100), 957 (M+4, 50).

1,2-Bis-butylsulfanyl-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-benzene (186b):



Copper Thiolate Method:

A brownish-red mixture of cuprous oxide (4.29 g, 29.98 mmol), 1-butane thiol (4.3 mL, 68.77 mmol) and anhydrous EtOH (75 mL) were heated at reflux until the reaction turned to white color. The white precipitate was filtered through a Buchner funnel and washed with EtOH and dried in a rotavapor to obtain cuprous *n*-butyl mercaptide as a foul-smelling white powder (6.9 g, 69%).

To a solution of 1,2-dibromo-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (682 mg, 0.713 mmol) in a mixture of pyridine (3 mL) and quinoline (10 mL) was added cuprous *n*-butyl mercaptide (1.1 g, 7.20 mmol). The mixture was heated at 160 ^{o}C for 6 h. The reaction mixture was filtered through a Celite pad and washed with CH_2Cl_2. A solution of 50% HCl (30 mL) was added to the filtrate at 0 ^{o}C. The organic layer was washed with 1M HCl (2 × 30 mL), brine (3 × 50 mL) and $NaHCO_3$ solution (3 × 30 mL). After removal of the solvent by a rotary evaporator, the residue was purified in column chromatography using 1:19 EtOAc/hexane to afford 1,2-bis-butylsulfanyl-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **186b** (255 mg, 37%) as a yellow needle shaped solid.

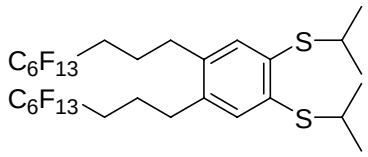
Pd Catalyzed Thiolation Condition:

To a degassed solution of 1,2-dibromo-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (1.00 g, 1.04 mmol) in dry toluene (30 mL) in a sealed vessel, Pd_2dba_3 (48 mg, 0.052 mmol), Xantphos (60 mg, 0.103 mmol) and DIPEA (0.7 mL, 4.01 mmol) were added with vigorous stirring under N_2. To this reaction mixture, 1-butanethiol (0.2 mL, 3.19 mmol) was added and the reaction was heated for 48 h at 120 ^{o}C. After cooling to room temperature, the reaction was filtered and concentrated using a rotary evaporator. The crude product was purified by chromatography (1:9 EtOAc/hexane) as well as by FSPE (80% MeOH/H_2O-90% MeOH/H_2O) to give compound **186b** (808 mg, 80% yield).

R_f = 0.4 (9:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 2H, -C_6H_2), 2.92 (t, 4H, *J* = 7.2 Hz, 2×-$SCH_2CH_2CH_2CH_3$), 2.69 (t, 4H, *J* = 7.7 Hz, 2×ArCH_2-), 2.23 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$,), 1.94 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.70 (m, 4H, 2×-SCH_2CH_2

CH_2CH_3), 1.54 (m, 4H, 2×-$SCH_2CH_2CH_2CH_2CH_3$), 0.95 (t, 6H, J = 7.3 Hz, 2×-$SCH_2CH_2CH_2CH_2CH_3$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 136.6 (s, 2C), 135.5 (s, 2C), 129.9 (s, 2C), 122.1-107.2 (m, 12C, 2×-C_6F_{13}), 33.1 (s, 2C, 2×-$SCH_2CH_2CH_2CH_3$), 31.4 (s, 2C, 2×-$SCH_2CH_2CH_2CH_3$), 30.9 (s, 2C, $ArCH_2$-), 30.7 (t, 2C, $^2J_{CF}$ = 22.3 Hz, 2×-$CH_2CH_2C_6F_{13}$), 22.0 (s, 2C, 2×-$SCH_2CH_2CH_2CH_3$), 21.7 (br s, 2C, 2×-$CH_2CH_2C_6F_{13}$), 13.4 (s, 2C, 2×- $SCH_2CH_2CH_2CH_3$); ^{19}F (282 MHz, $CDCl_3$) δ -81.57 (m, $2CF_3$), -114.63 (m, $2CF_2$), -122.52 (br s, $2CF_2$), -123.52 (br s, $2CF_2$), -124.01 (br s, $2CF_2$), -126.78 (m, $2CF_2$); MS (EI mode): m/z (% relative intensity): 974 (M^+, 100), 975 (M+1, 37), 976 (M+2, 14), 977 (M+3, 3).

1,2-Bis-isopropylsulfanyl-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (186a):

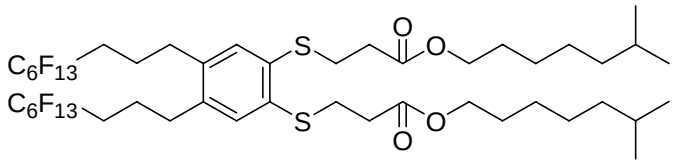


The same reaction procedure as in the preparation of compound **186b** was followed with compound **185** (655 mg, 0.68 mmol) in toluene (20 mL), Pd_2dba_3 (31 mg, 0.033 mmol), Xantphos (39 mg, 0.067 mmol), DIPEA (0.6 mL, 3.44 mmol) and 2-propanethiol (0.2 mL, 2.14 mmol). This gave 1,2-bis-isopropylsulfanyl-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene **186a** as a colorless gummy liquid (486 mg, 75%).

R_f = 0.68 (19:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 2H, -C_6H_2), 3.53 (septet, 2H, J = 6.6 Hz, 2×-$CH(CH_3)_2$), 2.70 (t, 4H, J = 7.6 Hz, 2×$ArCH_2$-), 2.16 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.92 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.32 (d, 12H, J = 6.6 Hz, 2×-

$CH(CH_3)_2$,); ^{13}C (partial) (75 MHz, $CDCl_3$) δ137.0 (s, 2C), 135.8 (s, 2C), 132.1 (s, 2C), 122.9-107 (m, 12C), 37.1 (s, 2C, 2×-$CH(CH_3)_2$), 31.3 (s, 2C, 2×ArCH_2-), 30.7 (t, 2C, $^2J_{CF}$ = 22.4 Hz, 2×-$CH_2CH_2C_6F_{13}$), 22.8 (s, 4C, 2×-$CH(CH_3)_2$), 21.6 (t, 2C, $^3J_{CF}$ = 3 Hz, 2×-$CH_2CH_2C_6F_{13}$,); ^{19}F (282 MHz, $CDCl_3$) δ -81.57 (m, $2CF_3$), -114.69 (m, $2CF_2$), -122.56 (br s, $2CF_2$), -123.55 (br s, $2CF_2$), -124.07 (br s, $2CF_2$), 126.79 (m, $2CF_2$); MS (EI mode): *m*/*z* (% relative intensity): 946 (M^+, 81).

3-[2-[2-(6-Methylheptyloxycarbonyl)ethylsulfanyl]-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)phenylsulfanyl]propionic acid 6-methylheptyl ester (190):

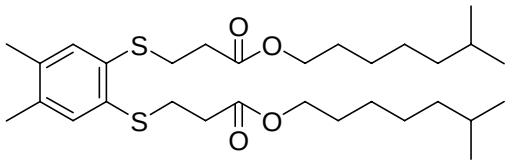


To a degassed solution of 1,2-dibromo-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene (2.00 g, 2.09 mmol) in dry toluene (35 mL) in a sealed tube (75 mL) were added $Pd(OAc)_2$ (23 mg, 0.102 mmol), Xantphos (121 mg, 0.209 mmol) and DIPEA (1.4 mL, 8.03 mmol) under N_2. The resulting reaction mixture was stirred for 5 min at room temperature and then isooctyl-3-mercapto propionate (1.4 mL, 6.09 mmol) was added. The reaction was heated at 120 ^oC for 72 h. After cooling to room temperature, the reaction was filtered, washed with Et_2O (2 × 30 mL) and concentrated. The crude product was purified by FSPE (90% MeOH/H_2O) to give the ester **190** as a colorless gummy liquid (2.02 g, 80%).

R_f = 0.7 (9:1-hexanes/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 2H, -C_6H_2), 4.14-4.05 (m, 4H, 2×-$SCH_2CH_2COOCH_2$-), 3.66 (t, 4H, *J* = 7.5 Hz, 2×-SCH_2-), 2.69 (p,

8H, J = 7.8 Hz, 2×-SCH$_2$CH_2COO-, 2×ArCH_2-), 2.24-2.06 (m, 4H, 2×-CH$_2$CH_2C$_6$F$_{13}$), 1.93-1.82 (m, 4H, 2×-CH_2CH$_2$C$_6$F$_{13}$), 1.74-1.22 (m, 12H, 2×-COOCH$_2$CH_2CH_2CH_2-), 1.19-1.02 (m, 2H, 2×-CH(CH$_3$)$_2$), 0.92-0.77 (m, 16H, 2×-CH(CH_3)$_2$, 2×-CH_2CH(CH$_3$)$_2$); ^{19}F (282 MHz, CDCl$_3$) δ -81.60 (t, $^3J_{FF}$ = 10 Hz, 2CF$_3$), -114.61 (m, 2CF$_2$), -122.57 (br. s, 2CF$_2$), -123.56 (br s, 2CF$_2$), -124.02 (br s, 2CF$_2$), -126.81 (m, 2CF$_2$); MS (EI mode): m/z (% relative intensity): 1230 (M^+, 100), 1231 (M+1, 50), 1232 (M+2, 28), 1233 (M+3, 8.7), 1118 (M-(CH$_3$)$_2$CH(CH$_2$)$_3$CH=CH$_2$).

3-{4,5-Dimethyl-2-[2-(6-methyl-heptyloxycarbonyl)ethylsulfanyl]phenylsulfanyl}-propionic acid 6-methyl-heptyl ester (191):

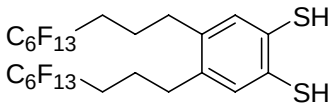


The reaction procedure for compound **186b** was repeated with 1,2-dibromo-4,5-dimethyl benzene (2.10 g, 7.95 mmol) in toluene (25 mL), Pd$_2$dba$_3$ (291 mg, 0.317 mmol), Xantphos (368 mg, 0.630 mmol), DIPEA (5.6 mL, 32.14 mmol) and isooctyl-3-mercaptopropionate (5.4 mL, 23.49 mmol). Purification by column chromatography (1:9 EtOAc/hexane afforded 3-{4,5-dimethyl-2-[2-(6-methyl-heptyloxycarbonyl)ethylsulfanyl]phenylsulfanyl}propionic acid 6-methyl-heptyl ester **191** as a white oil (1.94 g, 45%).

R_f = 0.7 (9:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.11 (s, 2H, -C$_6H_2$), 4.13-4.04 (m, 4H, 2×-OCH_2-), 3.14 (t, 4H, J = 7.5 Hz, 2×-SCH_2-), 2.63 (t, 4H, J = 7.02 Hz, 2×-SCH$_2$CH_2-), 2.21 (s, 6H, -C$_6$H$_2$(CH_3)$_2$), 1.65-1.25 (m, 12H, 2×-

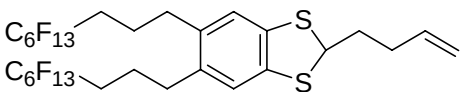
C(O)OCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$-), 1.14-1.10 (m, 2H, 2×-C*H*(CH$_3$)$_2$), 0.87-0.84 (m, 16H, 2×-CH(C*H*$_3$)$_2$, 2×-C*H*$_2$CH(CH$_3$)$_2$).

4,5-Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene-1,2-dithiol (159):



To a stirred solution of 3-[2-[2-(6-methylheptyloxycarbonyl)ethylsulfanyl]-4,5-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)phenylsulfanyl]propionic acid 6-methyl heptyl ester **190** (1.6 g, 1.29 mmol) in 21 mL of anhydrous EtOH/ THF (6:1), NaOEt (880 mg, 12.93 mmol) was added. The yellowish suspension was heated at 60 ^{o}C for 18 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was suspended in ice cold water (100 mL) and extracted with Et$_2$O (30 mL). The aqueous layer was acidified with 1M HCl, and then extracted with EtOAc (3 × 50 mL). The EtOAc extract was dried and concentrated under reduced pressure. After drying the crude material under high vacuum, it was carried through without further purification. MS (EI mode): m/z (% relative intensity): 861 (M^+, 100).

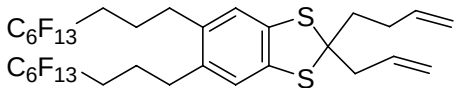
2-But-3-enyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-benzo[1,3]dithiole (192):



To a stirred solution of 4,5-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzene-1,2-dithiol (550 mg, 0.637 mmol) in anhydrous benzene (15 mL), 4-pentenal (63 μL, 0.638 mmol) was added. The light yellow mixture was stirred

for 5 min. Then, $HBF_4.OEt_2$ (60 µL, 0.440 mmol) was added dropwise. The reaction turned to a reddish brown color. The stirred mixture was heated for 2 h at 60 ^oC. After cooling to room temperature, water was added to the reaction mixture and it was extracted with Et_2O. The extract was washed with $NaHCO_3$ and water; dried and evaporated to dryness. The purification of the product was done by FSPE from 90% MeOH/H_2O wash to get 2-but-3-enyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-benzo[1,3]dithiole **192** as a light yellowish oil (308 mg, 56% yield). R_f = 0.75 (9:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2H, -C_6H_2), 5.82-5.68 (m, 1H, -C*H*=CH_2), 5.08-4.99 (m, 2H, -CH=CH_2), 4.86 (t, 1H, *J* = 7.1 Hz, -C*H*$CH_2CH_2CH=CH_2$), 2.63 (t, 4H, *J* = 7.9 Hz, 2×ArCH_2-), 2.24-1.98 (m, 8H, -CHCH_2CH_2CH=CH_2, 2×-CH_2C$H_2C_6F_{13}$), 1.90-1.82 (m, 4H, 2×-C$H_2CH_2C_6F_{13}$); ^{13}C (75 MHz, $CDCl_3$) δ136.6 (s, 1C, -*C*H=CH_2), 136.1 (s, 2C), 135.7 (s, 2C), 123.1 (s, 2C), 120-105 (m, 12C), 116.0 (s, 1C, -CH=*C*H_2), 54.1 (s, 1C, -*C*H$CH_2CH_2CH=CH_2$), 38.1 (s, 1C, -CH*C*$H_2CH_2CH=CH_2$), 31.6 (s, 1C, -$CHCH_2$*C*$H_2CH=CH_2$,), 31.0 (s, 2C, 2×Ar*C*H_2-), 30.9 (t, 2C, $^2J_{CF}$ = 22.3 Hz, 2×-CH_2*C*$H_2C_6F_{13}$), 21.8 (m, 2C, 2×-*C*$H_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.25 (m, $2CF_3$), -114.40 (m, $2CF_2$), -122.37 (br s, $2CF_2$), -123.32 (br s, $2CF_2$), -123.86 (br s, $2CF_2$), -126.54 (m, $2CF_2$); MS (EI mode): m/z (% relative intensity): 927 (M^+), 872 (M-C_4H_7).

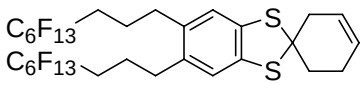
2-Allyl-2-but-3-enyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro nonyl)benzo[1,3]dithiole (193):



A solution of 2-but-3-enyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **192** (33.4 mg, 0.035 mmol) in THF (6 mL) was cooled to -78 ^{o}C. To this solution, *n*-BuLi (2 M in cyclohexane, 34.8 µL, 0.069 mmol) was added dropwise. After 1 min, the colorless reaction mixture developed a reddish color and it was stirred for 40 min at the same temperature. Then, allyl bromide (6 µL, 0.070 mmol) was introduced. The reddish color of the reaction mixture diminished and became colorless after 10 min. After stirring for 30 min at -78 ^{o}C, the reaction was slowly warmed to room temperature and stirred for 1 h. Then, it was quenched with saturated NH_4Cl solution and extracted with EtOAc. The extract was dried and concentrated under reduced pressure to give the crude material (44.5 mg). The crude product was carried on for the next reaction without purification.

R_f = 0.82 (9:1-hexanes/ethyl acetate).

5,6-Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)spiro[benzo[d]1,3-dithiolene-2,4'-cyclohexane]-10-ene (194):

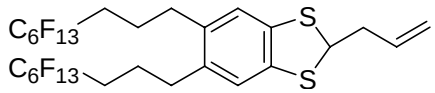


To a stirred solution of 2-allyl-2-but-3-enyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole (22 mg, 0.023 mmol) dissolved in 12 mL of degassed CH_2Cl_2, Grubbs (II) catalyst (2 mg, 0.002 mmol) was added by which the

reaction turned from light yellow to a green color. The reaction mixture was heated at reflux for 5 h. After cooling to room temperature, it was filtered and evaporated using a rotary evaporator. The crude mixture was purified using FSPE (90% MeOH/H_2O wash) to afford the product as clear oily compound over two steps (12.5 mg, 58% yield).

R_f = 0.88 (9:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 2H, -C_6H_2), 5.76-5.72 (m, 1H, -CCH_2CH=), 5.66-5.61 (m, 1H, -CCH_2CH=C*H*-), 2.84 (br s, 2H, -CH_2CH=CH-), 2.63 (t, 4H, *J* = 7.8 Hz, 2×ArCH_2-), 2.34-2.26 (m, 4H, -CCH_2CH_2CH=CH-), 2.25-2.04 (m, 4H, 2×-CH_2C$H_2$$C_6F_{13}$), 1.90-1.80 (m, 4H, 2×-C$H_2$$CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 136.0 (s, 2C), 126.5 (s, 2C), 124.3 (s, 2C), 123.2 (s, 2C), (due to low intensity 2C_6F_{13} carbons are obscured), 67.8 (s, 1C, quaternary carbon), 39.2 (s, 1C, -C*C*H_2CH_2CH=CH-), 36.0 (s, 1C, -C*C*H_2CH=CH-), 31.6 (s, 2C, 2×Ar*C*H_2-), 29.6 (2C), 24.1 (s, 1C, -CCH_2*C*H_2CH=CH-), 21.7 (s, 2C, 2×-*C*$H_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.23 (m, 2CF_3), -114.39 (m, 2CF_2), -122.32 (br s, 2CF_2), -123.38 (br s, 2CF_2), 123.81 (br s, 2CF_2), -126.53 (m, 2CF_2); MS (EI mode): *m*/*z* (% relative intensity): 940 (M^+), 941 (M+1), 942 (M+2).

2-Allyl-5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole (200):



3-Butenal was prepared adopting the literature procedure used by Crimmins.[122] To a solution of 40% aqueous glyoxal (18.8 mL, 129.7 mmol) in 65 mL of THF were added allyl bromide (27.7 mL, 309.6 mmol), tin metal (36.00 g, 303 mmol) and water (65 mL). The mixture was exposed to ultrasonic agitation for 1.5 h by which time the mixture

turned to orange color from white color. The resulting emulsion was concentrated in vacuo to half of its original volume. A 10% HCl solution was added until the two phases separated from each other. The aqueous layer was washed with EtOAc (3 × 50 mL). The collected organic layers were washed with brine and evaporated to dryness. The crude material was purified using column chromatography (MeOH/CH_2Cl_2, 1:9) to afford 1,7-octadiene-4,5-diol (4.0 g, 22% yield).

To a solution of 1,7-octadiene-4,5-diol (2.96 g, 20.81 mmol) in CH_2Cl_2 (25 mL) and water (25 mL) at 0 ^oC, sodium periodate (4.90 g, 22.90 mmol) was added in three portions. After stirring at room temperature for 3 h, the phases were separated. The organic layer was washed with water and brine, and dried. The solvent was removed at atmospheric pressure with a short path distillation head until when ^1H NMR indicated the presence of 3-butenal in the collected dichloromethane fractions. As 3-butenal was co-distilled with CH_2Cl_2, a solution of 3-butenal in CH_2Cl_2 was used for the next step.

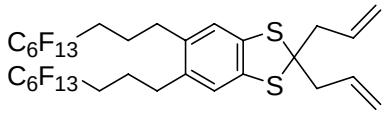
^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, 1H, *J* = 1.5 Hz, -C*H*O), 5.98-5.85 (m, 1H, -C*H*=CH_2), 5.26-5.18 (m, 2H, -CH=C*H*$_2$), 3.2- 3.17 (m, 2H,-C*H*$_2$CHO).

To a stirred solution of benzodithiol **159** (335 mg, 0.388 mmol) in anhydrous benzene (10 mL), 3-butenal in CH_2Cl_2 (1: 22 ratio, 9.4 mL, 0.57 mmol) followed by $HBF_4.OEt_2$ (37 μL, 0.271 mmol) were added. The light yellow mixture turned to reddish brown color. The stirred mixture was heated at 60 ^oC for 2 h. After cooling to room temperature, the reaction was quenched with water and extracted with Et_2O. The extract was successively washed with $NaHCO_3$ and water, dried and evaporated to dryness. The purification of the product by flash chromatography (where silica was neutralized with 5% triethylamine in hexane) using 1:19 EtOAc/hexane as eluent, afforded 2-allyl-5,6-

bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **200** as a light yellowish oil (308 mg, 56% yield).

R_f = 0.7 (9:1-hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2H, -C_6H_2), 5.87-5.74 (m, 1H, -C*H*=CH_2), 5.18-5.16 (m, 2H, -CH=CH_2), 4.89 (t, 1H, *J* = 7.1 Hz, -C*H*CH_2CH=CH_2), 2.70 (t, 2H, *J* = 6.9 Hz, -CHCH_2CH=CH_2), 2.63 (t, 4H, *J* = 7.9 Hz, 2×ArCH_2-), 2.22-2.04 (m, 4H, 2×-CH_2C$H_2$$C_6F_{13}$), 1.90-1.80 (m, 4H, 2×-C$H_2$$CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 136.2 (s, 2C), 135.7 (s, 1C), 133.6 (s, 1C), 123.3 (s, 2C), 123.1-104.6 (m, 12C), 118.6 (s, 2C), 54.1 (s, 1C, - *C*HCH_2CH=CH_2), 43.1 (s, 1C, -CH*C*H_2CH=CH_2), 31.6 (s, 2C, 2×Ar*C*H_2-), 30.8 (t, 2C, *J* = 22 Hz, 2×-CH_2*C*$H_2C_6F_{13}$), 21.8 (m, 2C, 2×-*C*$H_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.29 (m, $2CF_3$), -114.44 (m, $2CF_2$), -122.38 (br s, $2CF_2$), -123.36 (br s, $2CF_2$), -123.86 (br s, $2CF_2$), -126.58 (m, $2CF_2$); MS (EI mode): *m*/*z* (% relative intensity): 913 (M^+, 100) 915 (M+1, 32), 873 (M^+-C_3H_5).

2,2-Diallyl-5,6-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole (201):

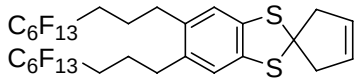


To a stirred solution of benzodithiane **200** (33.4 mg, 0.036 mmol) in 6 mL of THF was added *n*-BuLi (2.5 M solution in hexane, 22 µL, 0.055 mmol) at -78 ^{o}C. After being stirred for 5 min, the colorless reaction mixture developed a reddish color and it was left for 40 min at that temperature. Allyl bromide (6 µL, 0.071 mmol) was added and the reaction mixture immediately became colorless. After stirring for 30 min at -78 ^{o}C, the reaction was slowly warmed to room temperature and stirred for 1 h. The reaction was

quenched with saturated NH_4Cl solution and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The resulting 2,2-diallyl-5,6-bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)benzo[1,3]dithiole **201** was obtained as a colorless oil (20 mg) after drying under high vacuum and the product was carried on for the next reaction without any purification.

R_f = 0.78 (9:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 2H, -C_6H_2), 5.98-5.84 (m, 2H, 2×CH_2=C*H*-), 5.20 (d, 2H, *J* = 7 Hz, 2×-CH*H*=CH-), 5.15 (s, 2H, 2×-CH*H*=CH-), 2.84 (d, 4H, *J* = 7 Hz, 2×-CCH_2CH=CH_2), 2.62 (t, 4H, *J* = 7.7 Hz, 2×ArCH_2-), 2.21-2.04 (m, 4H, 2×-CH_2C$H_2$$C_6F_{13}$), 1.89-1.79 (m, 4H, 2×-C$H_2$$CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.28 (m, $2CF_3$), -114.37 (m, $2CF_2$), -122.41 (br s, $2CF_2$), -123.37 (br s, $2CF_2$), -123.85 (br s, $2CF_2$), -126.57 (m, $2CF_2$); MS (EI mode): m/z (% relative intensity): 954 (M^+, 100) 955 (M+1, 44), 956 (M+2, 34), 913 (M^+-C_3H_5).

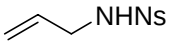
5,6-Bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)spiro[benzo[d]1,3-dithiolene-2,4'-cyclopentane]-10-ene (202):



To a stirred solution of compound **201** (20 mg, 0.021 mmol) dissolved in 12 mL of degassed CH_2Cl_2, Grubbs (II) catalyst (2 mg, 0.002 mmol) was added. The reaction mixture was heated at reflux for 5 h at 50 ^oC. After cooling to room temperature, it was filtered through a filter paper and evaporated using a rotary evaporator. The crude mixture was purified in flash chromatography using 2% EtOAc/hexane to get the ring-closing product 5,6-bis(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)spiro[benzo[d]1,3-dithiolene-2,4'-cyclopentane]-10-ene **202** as a clear oil (10.8 mg, 56% yield over two steps).

R_f = 0.87 (9:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 2H, -C_6H_2), 5.78 (s, 2H, -C*H*=C*H*-), 3.14 (s, 4H, -CH_2CH=CHCH_2-), 2.63 (t, 4H, *J* = 7.8 Hz, 2×ArCH_2-), 2.22-2.05 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$), 1.91-1.80 (m, 4H, 2×-$CH_2CH_2C_6F_{13}$); ^{13}C (partial) (75 MHz, $CDCl_3$) δ 136.6 (s, 2C), 136.1 (s, 2C), 129.4 (s, 2C), 123.0 (s, 2C), (due to low intensity 2×-C_6F_{13} carbons are obscured), 70.7 (s, 1C, quaternary carbon), 49.9 (s, 2C, -CH_2CH=CHCH_2-), 31.6 (s, 2C, 2×ArCH_2-), 30.0 (t, 2C, $^2J_{CF}$ = 25.4 Hz, 2×-$CH_2CH_2C_6F_{13}$), 29.6 (s, 2C, 2×-$CH_2CH_2C_6F_{13}$); ^{19}F (282 MHz, $CDCl_3$) δ -81.24 (m, $2CF_3$), -114.39 (m, $2CF_2$), -112.36 (m, $2CF_2$), -123.32 (br s, $2CF_2$), 123.82 (br s, $2CF_2$), -126.54 (m, $2CF_2$); MS (EI mode): m/z (% relative intensity): 926 (M^+, 100), 927 (M+1, 34), 928 (M+2, 13.7), 929 (M+3, 3.6).

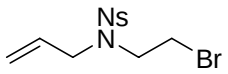
N-Allyl-4-nitrobenzenesulfonamide (204):



To a solution of allyl amine (3.2 mL, 42.7 mmol) in anhydrous CH_2Cl_2 (100 mL), Et_3N (7.2 mL, 51.6 mmol) followed by 4-nitrobenzene sulfonyl chloride (9.47 g, 42.7 mmol) were added at 0 ^{o}C. The reaction mixture turned to yellow color and was stirred at room temperature for 15 h. The solvent was evaporated and the reaction was quenched with $NaHCO_3$ solution and then extracted with EtOAc. The extract was further washed with $NaHCO_3$ solution, dried and concentrated. The crude product was purified by column chromatography using 1:4 EtOAc/hexane to afford *N*-allyl-4-nitrobenzenesulfonamide **204** as light yellow flakes (7.03 g, 67%).

R_f = 0.6 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 2H, *J* = 8.8 Hz), 8.01 (d, 2H, *J* = 8.8 Hz), 5.77-5.64 (m, 1H, CH_2=C*H*-), 5.21-5.11 (m, 2H, CH_2=CH), 4.77 (t, 1H, *J* = 5.5 Hz, -N*H*-), 3. 71 (tt, 2H, J_1 = 6 Hz, J_2 = 1.4 Hz, CH_2=CHCH_2N-).

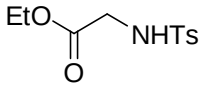
N-Allyl-*N*-(2-bromoethyl)-4-nitrobenzenesulfonamide (205):



To a solution of *N*-allyl-4-nitrobenzenesulfonamide (3.25 g, 13.45 mmol) in THF (40 mL), was added KOH (752 mg, 13.40 mmol) at 0 ^{o}C. After being stirred for 10 min, 1,2-dibromoethane (1.2 mL, 13.92 mmol) and tetrabutylammonium bromide (865 mg, 2.68 mmol) were added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water and then a 0.1 M HCl solution was applied to bring pH to 3-4. The acidic mixture was extracted with EtOAc. The extract was dried and concentrated using a rotary evaporator. The crude product was purified by flash chromatography (1:4 EtOAc/hexane) to obtain *N*-allyl-*N*-(2-bromoethyl)-4-nitrobenzenesulfonamide **205** as a light yellow solid (2.85 g, 61% yield).

R_f = 0.7 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 2H, *J* = 8.8 Hz, -C_6H_2), 8.01 (d, 2H, *J* = 8.8 Hz, -C_6H_2), 5.70- 5.56 (m, 1H, CH_2=C*H*-), 5.22-5.16 (m, 2H, CH_2=CH-), 3.89 (d, 2H, *J* = 6.4 Hz, -NCH_2CH=CH_2), 3.52-3.40 (m, 4H, -NC$H_2$$CH_2$Br, -$NCH_2CH_2$Br); ^{13}C (75 MHz, $CDCl_3$) δ 150.1 (s, 1C, C(SO_2-)C_4H_4*C*(NO_2), 145.2 (s, 1C, *C*(SO_2-)C_4H_4C(NO_2), 131.9 (s, 1C, CH_2=*C*H-), 128.4 (s, 2C), 124.5 (s, 2C), 120.3 (s, 1C, *C*H_2=CH-), 51.7 (s, 1C, -N(Ns)*C*$H_2$$CH_2$Br), 48.8 (s, 1C, CH_2=CH*C*H_2N-), 28.8 (s, 1C, -N(Ns)CH_2*C*H_2Br).

(Toluene-4-sulfonylamino)acetic acid ethyl ester (208):

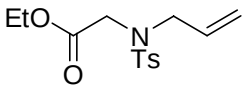


CAS = 5465-67-8

To a solution of glycine ethyl ester hydrochloride (5.00 g, 35.8 mmol) in anhydrous CH_2Cl_2 (60 mL), was added Et_3N (10.9 mL, 78.2 mmol) at 0 ^oC. 4-Toluenesulfonyl chloride (8.19 g, 43 mmol) was added in three portions to the reaction mixture while maintaining the temperature at 0 ^oC. After addition was complete, the reaction was stirred for 15 h at room temperature. The solvent was evaporated and the reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The extract was further washed with $NaHCO_3$ solution, dried and concentrated under reduced pressure. The crude material was filtered through a pad of silica gel using 1:4 EtOAc/hexane to give (toluene-4-sulfonylamino)acetic acid ethyl ester **208** as a white crystal (6.26 g, 68% yield). Mp = 62-64 ^oC and this value matched with that reported by Xu *et al*.[134]

^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.2 Hz, -C_6H_2), 7.12 (d, 2H, *J* = 8.1 Hz, -C_6H_2), 5.78 (s, 1H, -N*H*), 3.90 (q, 2H, *J* = 7.14 Hz, -COOC$H_2$$CH_3$), 3.60 (s, 2H, -OCOC$H_2$NH-), 2.20 (s, 3H, ArC$H_3$), 0.98 (t, 3H, *J* = 7.14 Hz, -CH_2CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 168.9 (s, 1C, -*C*O), 143.4 (s, 1C, C_5H_4(SO_2-)*C*(CH_3)-), 136.5 (s, 1C, C_4H_4*C*(SO_2-)C(CH_3), 129.5 (s, 2C), 127.0 (s, 2C), 61.5 (s, 1C, -COO*C*$H_2$$CH_3$), 44.2 (s, 1C, -OCO*C*$H_2$NH-), 21.2 (s, 1C, Ar*C*$H_3$), 13.7 (s, 1C, -$CH_2$*C*$H_3$).

[Allyl-(toluene-4-sulfonyl)amino]acetic acid ethyl ester (209):

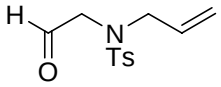


CAS = 869275-28-5

To a solution of (toluene-4-sulfonylamino)acetic acid ethyl ester (3.17 g, 12.3 mmol) in acetone (40 mL), potassium carbonate (1.87 g, 13.5 mmol) followed by allyl bromide (1.2 mL, 14.1 mmol) were added. The reaction was heated at reflux for 15 h. After cooling to room temperature, the white reaction mixture was diluted with water and acetone was evaporated using a rotary evaporator. The remained aqueous layer was extracted with Et_2O. The extract was dried and concentrated in vacuo. The crude material was chromatographed using 1:4 EtOAc/hexane to obtain [allyl-(toluene-4-sulfonyl)amino]acetic acid ethyl ester **209** as a colorless oil (3.47 g, 94% yield).

R_f = 0.73 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.2 Hz), 7.02 (d, 2H, *J* = 8.1 Hz), 5.43-5.32 (m, 1H, CH_2=C*H*-), 4.90-4.82 (m, 2H, CH_2=CH-), 3.80 (q, 2H, *J* = 7.4 Hz, -COOCH_2CH$_3$) 3.69 (s, 2H, -OCOCH_2N-), 3.62 (d, 2H, *J* = 6.45 Hz, CH_2=CHCH_2N-), 2.07 (s, 3H, ArCH_3), 0.86 (t, 3H, *J* = 7.14 Hz, -COOCH$_2$CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 168.3 (s, 1C, -*C*O), 143.1 (s, 1C, C_5H_4(SO_2) *C*(CH$_3$), 136.8 (s, 1C, C_4H_4*C*(SO_2)C(CH$_3$)), 132.2 (s, 1C, CH_2=*C*H-), 129.4 (s, 2C), 127.0 (s, 2C), 119.1 (s, 1C, *C*H_2=CH-), 60.7 (s, 1C, -COO*C*H$_2$CH$_3$), 50.5 (s, 1C, -OCO*C*H$_2$N-), 46.9 (s, 1C, CH_2=CHCH_2N-), 20.9 (s, 1C, Ar*C*H$_3$), 13.6 (s, 1C, -COOCH$_2$*C*H$_3$).

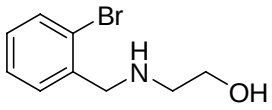
N-Allyl-4-methyl-*N*-(2-oxo-ethyl)benzenesulfonamide (210):



A solution of DIBAL-H in hexane (1M, 3.2 mL, 3.2 mmol) was slowly added to a solution of allyl(toluene-4-sulfonyl)amino]acetic acid ethyl ester (638 mg, 2.14 mmol) in anhydrous Et_2O (35 mL) at -78 ^oC. After being stirred at -78 ^oC for 15 min, the reaction mixture was quenched by the addition of MeOH: H_2O (1:2), and the resulting suspension was stirred for 1 h at room temperature. The crude reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was dried and concentrated using a rotary evaporator. Flash column chromatography on silica gel (1:4 EtOAc/hexane) provided *N*-allyl-4-methyl-*N*-(2-oxo-ethyl)benzenesulfonamide **210** as oily colorless liquid (445 mg, 82% yield). Different synthetic procedures for this compound are available in the literature.[128,129]

R_f = 0.55 (4:1-hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (br s, 1H, -C*H*O), 7.65 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.3 Hz), 5.68-5.55 (m, 1H, CH_2=C*H*-), 5.17-5.09 (m, 2H, CH_2=CH-), 3.77 (d, 2H, *J* = 6.7 Hz, CH_2=CHCH_2NTs-), 3.74 (br s, 2H, -NCH_2CHO), 2.38 (s, 3H, ArCH_3).

2-(2-Bromobenzylamino)ethanol (215):

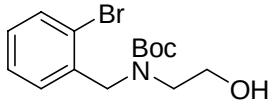


Ethanol amine (2.0 mL, 33.13 mmol) was added to a solution of 2-bromobenzaldehyde (3.0 mL, 25.6 mmol) in anhydrous ethanol (30 mL) at 0 ^oC. The colorless reaction mixture was stirred at room temperature for 6 h. The reaction was cooled to 0 ^oC and sodium borohydride (4.84 g, 127.90 mmol) was added in three

portions. The reaction turned to white color and was stirred for a further 10 h at room temperature. The reaction was then quenched by slow addition of saturated NH_4Cl solution and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. Purification by column chromatography using 5% MeOH in CH_2Cl_2 gave 2-(2-bromobenzylamino)ethanol **215** (3.41 g, 57% yield).

R_f = 0.22 (1:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 1H, J = 7.8 Hz), 7.29 (dd, 1H, J = 7.6 Hz, J = 1.4 Hz), 7.20 (t, 1H, J = 6.9 Hz), 7.04 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 3.76 (s, 2H, C_6H_4(Br)CH_2N-), 3.56 (m, 2H, -NCH$_2$CH_2OH), 3.31 (s, 2H, -O*H*, -N*H*-), 2.65 (t, 2H, -NCH_2CH$_2$OH, J = 5.2 Hz).

(2-Bromobenzyl)-(2-hydroxyethyl)carbamic acid *tert*-butyl ester (216):

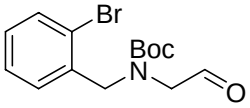


To a solution of 2-(2-bromobenzylamino)ethanol (2.64 g, 11.47 mmol) in CH_2Cl_2 (50 mL), Et_3N (2.1 mL, 15.06 mmol) followed by Boc_2O (2.75 g, 12.60 mmol) were added. After being stirred at room temperature for 12 h, the reaction was quenched with saturated $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine and concentrated. Flash chromatography on silica gel (5% MeOH in CH_2Cl_2) afforded the alcohol **216** as a colorless gummy liquid (3.47 g, 92% yield).

R_f = 0.4 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J_1 = 0.78 Hz, J_2 = 0.81 Hz, -C$_6H_1$,), 7.27-7.15 (m, 2H, -C$_6H_2$), 7.10 (t, 1H, J = 7.83 Hz, -C$_6H_1$), 4.51 (s, 2H, C_6H_4(Br)CH_2N-), 3.69 (t, 2H, J = 5.1 Hz, -NCH$_2$CH_2OH), 3.38 (s, 2H, -NCH_2CH$_2$OH), 1.37 (s, 9H, -N(CO)OC(CH_3)$_3$); ^{13}C (75 MHz, $CDCl_3$) δ 170.6 (s, 1C, -

N(*C*O)O-), 132.4 (s, 2C), 128.2 (s, 2C), 127.2 (s, 2C), 79.7 (s, 1C, -N(CO)O*C*$(CH_3)_3$), 60.0 (s, 1C, -NCH$_2$*C*H$_2$OH), 27.9 (s, 1C, -N*C*H$_2$CH$_2$OH), 20.6 (s, 1C, C_6H_4(Br)*C*H$_2$N), 13.9 (s, 3C, -N(CO)OC(*C*H$_3$)$_3$).

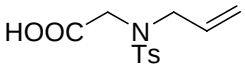
(2-Bromobenzyl)-(2-oxo-ethyl)carbamic acid *tert*-butyl ester (217):



To a solution of oxalyl chloride (0.18 mL, 2.096 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC, a solution of DMSO (0.31 mL, 4.368 mmol) in CH_2Cl_2 (4 mL) was added dropwise. After stirring for 10 min, a solution of alcohol **216** (661 mg, 2.001 mmol) in 3 mL of DMSO-CH_2Cl_2 mixture (1:17 ratio) was added. The reaction was stirred for 1 h at -78 ^oC. After that triethylamine (1.2 mL, 8.60 mmol) was slowly added and stirred for 20 min. The reaction was gradually warmed to room temperature and quenched with ice cold water. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried and concentrated. The resulting crude product was applied to a 10 cm pad of silica gel and eluted with 1:4 EtOAc/hexane to provide the aldehyde **217** as a colorless oil (413 mg, 63% yield).

R_f = 0.76 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (d, 1H, *J* = 10.5 Hz, -C*H*O), 7.47(d, 1H, *J* = 7.6 Hz, -C_6H_1), 7.26-7.21(m, 2H, -C_6H_2), 7.09-7.07 (m, 1H, -C_6H_1), 4.59 (s, 1H, C_6H_4(Br)CH*H*N-), 4.52 (s, 1H, C_6H_4(Br)CH*H*N-), 3.92 (s, 1H, -NCH*H*CHO), 3.81 (s, 1H, -NCH*H*CHO), 1.39 (s, 9H, -N(CO)OC(C*H*$_3$)$_3$).

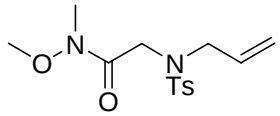
[Allyl(toluene-4-sulfonyl)amino]acetic acid (219):



To a solution of ester **209** (224 mg, 0.75 mmol) in ethanol (20 mL), was added a freshly prepared 10% KOH solution (5 mL) at 0 ^{o}C. The reaction was warmed to room temperature and stirred for 1 h. The solvent was evaporated by a rotary evaporator. The residue was diluted with water and extracted with ethyl acetate. The extract was dried and concentrated to give the acid **219** as a white solid (170 mg, 84% yield).

R_f = 0.35 (3:2-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.02 (br s, 1H, -COO*H*), 7.73 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 7.30 (d, 2H, *J* = 8.3 Hz, -C_6H_2) 5.71-5.14 (m, 1H, CH_2=C*H*-), 5.20-5.14 (m, 2H, CH_2=CH-), 4.01(s, 2H, -CH_2COOH), 3.88 (d, 2H, *J* = 6.5 Hz, CH_2=CHCH_2NTs-), 2.41 (s, 3H, ArCH_3).

2-[Allyl(toluene-4-sulfonyl)amino]-*N*-methoxy-*N*-methyl acetamide (220):

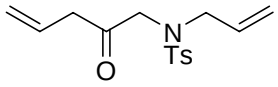


To a solution of [allyl(toluene-4-sulfonyl)amino]acetic acid **219** (623 mg, 2.31 mmol) in acetonitrile (20 mL) were added TBTU (1.11 g, 3.45 mmol) and *N*,*O*-dimethyhydroxylamine hydrochloride (338 mg, 3.47 mmol). The colorless reaction mixture was stirred at 0 ^{o}C for 10 min and then DIPEA (1.2 mL, 6.89 mmol) was added dropwise. The reaction was warmed to room temperature over 2 h. After stirring for 2 h at room temperature, the reaction was concentrated under vacuum and the residue was dissolved in Et_2O. The mixture in Et_2O was washed successively with 1 M HCl, 1 M $NaHCO_3$, and NaCl solution. The organic fraction was dried and concentrated.

Purification by column chromatography (1:4 EtOAc/hexane) afforded the Weinreb amide[27] **220** as a clear solid (500 mg, 69% yield).

R_f = 0.4 (3:2-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 7.27 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 5.75-5.62 (m, 1H, CH_2=C*H*-), 5.18-5.12 (m, 2H, C*H*$_2$=CH-), 4.21 (s, 2H, -COC*H*$_2$NTs-), 3.90 (d, 2H, *J* = 6.5 Hz, CH_2=CHC*H*$_2$NTs-), 3.66 (s, 3H, -CON(CH_3)OC*H*$_3$), 3.09 (s, 3H, -CON(C*H*$_3$)OCH_3), 2.38 (s, 3H, ArC*H*$_3$).

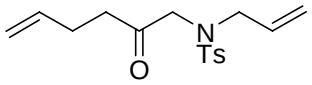
N-Allyl-4-methyl-*N*-(2-oxo-pent-4-enyl)benzenesulfonamide (221):



A 1.5 M solution of allyl magnesium bromide in THF (0.11 mL, 0.16 mmol) was added to a solution of Weinreb amide **220** (50 mg, 0.160 mmol) in dry THF (8 mL) at -78 ^oC. After stirring for 1.5 h at -78 ^oC, the reaction was quenched with NH_4Cl and extracted with EtOAc. The organic extract was dried and concentrated under reduced pressure. The crude product was filtered through a pad of Celite using 1:4 EtOAc/hexane to obtain the ketone **221** as a clear solid (37 mg, 79% yield).

R_f = 0.48 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 7.31 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 5.92 (m, 1H, CH_2=C*H*CH_2CO-), 5.70 (m, 1H, CH_2=C*H*CH_2NTs-), 5.20-5.08 (m, 4H, C*H*$_2$=CH-, C*H*$_2$=CH-), 3.96 (s, 2H, -COC*H*$_2$NTs-), 3.80 (d, 2H, *J* = 6.7 Hz, CH_2=CHC*H*$_2$NTs-), 3.24 (dt, 2H, J_1 = 6.9 Hz, J_2 = 1.1 Hz, -COC*H*$_2$CH=CH_2), 2.41 (s, 3H, ArC*H*$_3$).

N-Allyl-4-methyl-*N*-(2-oxo-hex-5-enyl)benzenesulfonamide (225):



The reaction procedure and workup used for compound **221** was followed with freshly prepared but-1-ene magnesium bromide (1.5 M in THF, 0.68 mL, 1.02 mmol) and a solution of Weinreb amide **220** (214 mg, 0.685 mmol) in dry THF (8 mL). The residue was purified by column chromatography using 1:9 EtOAc/hexane to afford *N*-allyl-4-methyl-*N*-(2-oxo-hex-5-enyl)benzenesulfonamide **225** (120 mg, 57% yield).

R_f = 0.52 (4:1-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 7.31 (d, 2H, *J* = 8.3 Hz, -C_6H_2), 5.82-5.57 (m, 2H, CH_2=C*H*-, CH_2=C*H*-), 5.17-4.95 (m, 4H, CH_2=CH-, CH_2=CH-), 3.92 (s, 2H, -COCH_2NTs-), 3.80 (d, 2H, *J* = 6.7 Hz, CH_2=CHCH_2NTs), 2.56 (t, 2H, *J* = 7.1 Hz, -COC$H_2$$CH_2$CH=$CH_2$) 2.41 (s, 3H, Ar$CH_3$), 2.32 (q, 2H, *J* = 6.6 Hz, -$COCH_2$CH_2CH=CH_2).

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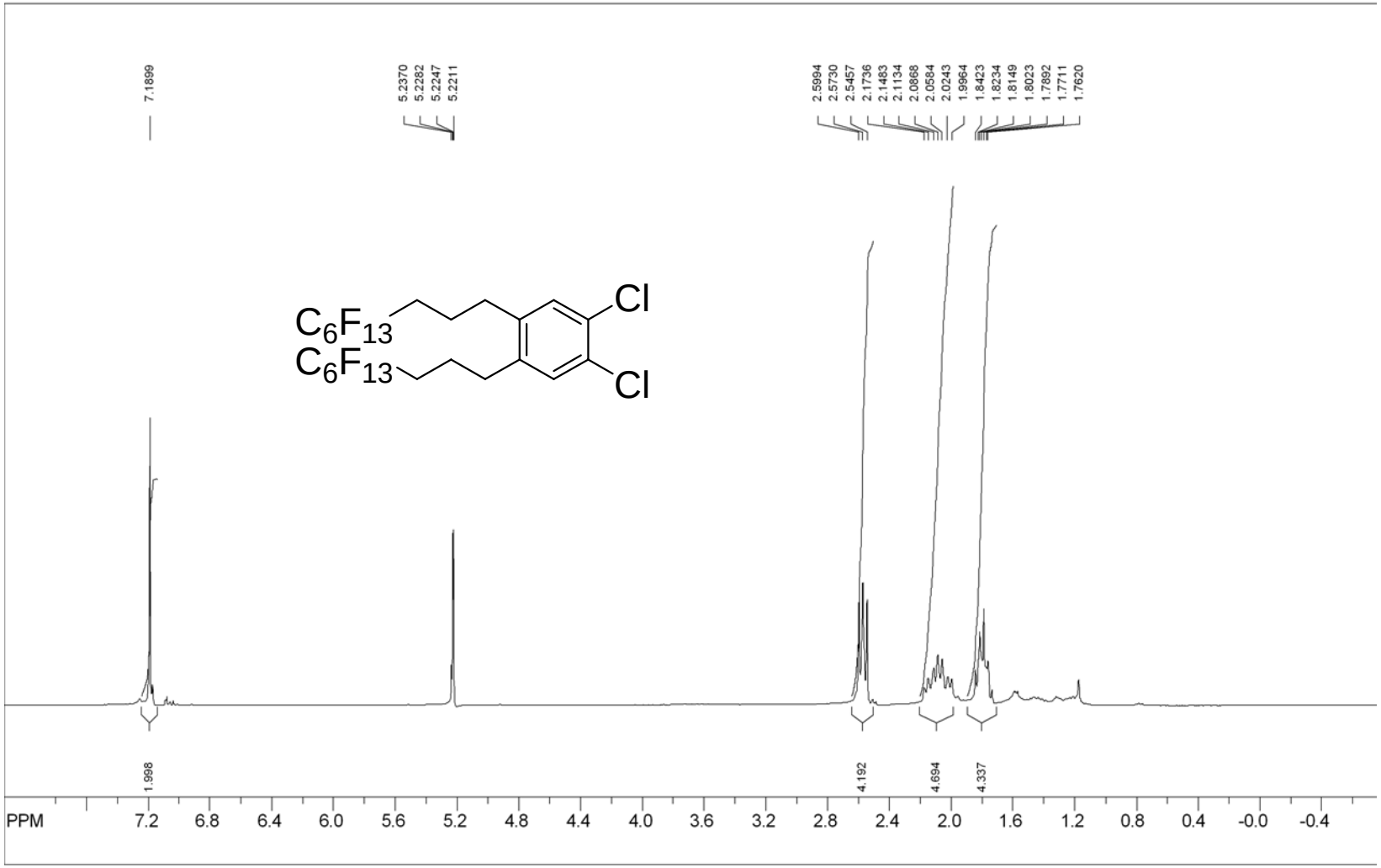
NMR SECTION

SpinWorks 2.5: pto2 reduction



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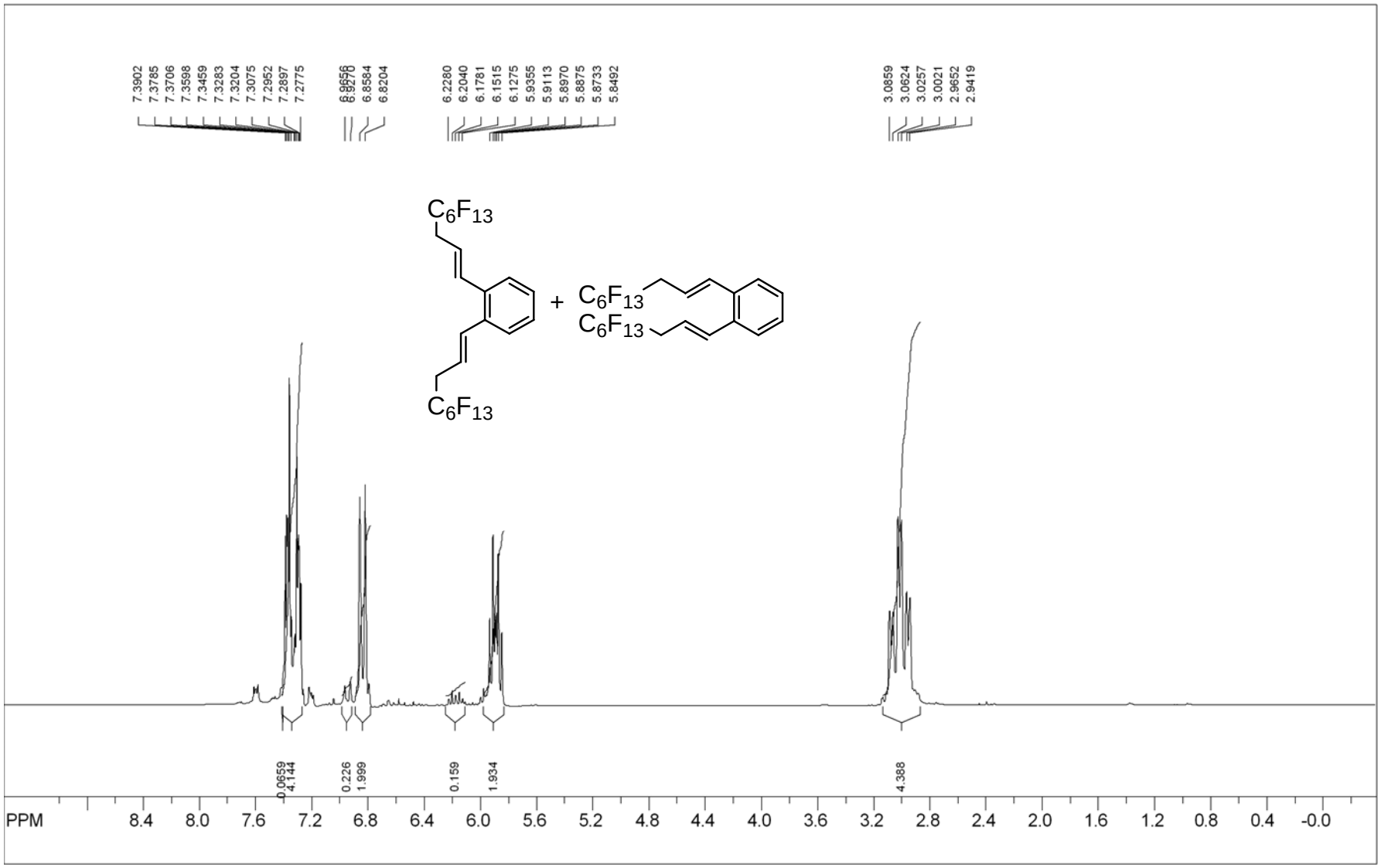
SpinWorks 2.5: wittig olefination



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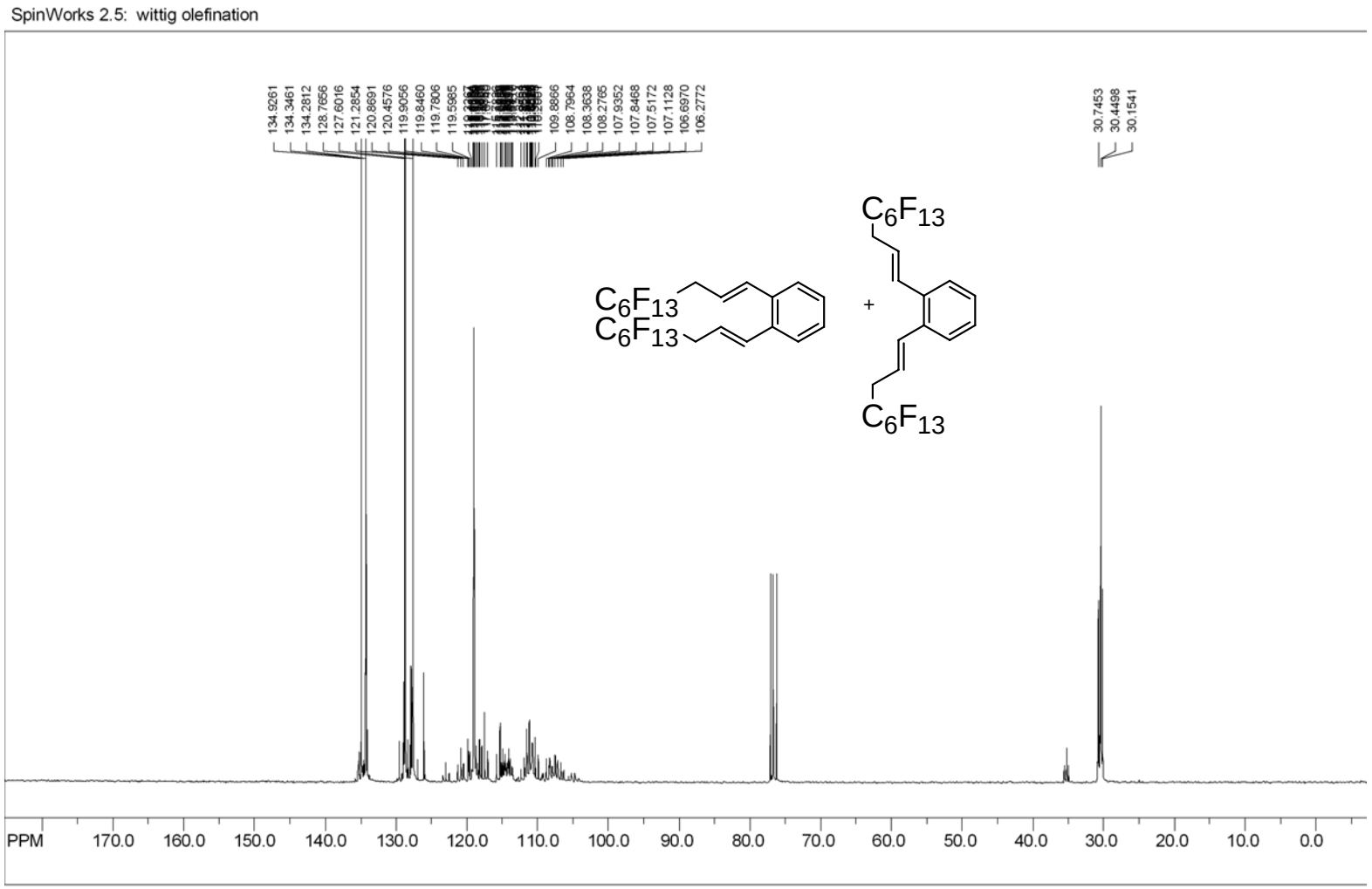
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120.4576
119.9056
119.8460
119.7806
119.5985
109.8866
108.7964
108.3638
108.2765
107.9352
107.8468
107.5172
107.1128
106.6970
106.2772
30.7453
30.4498
30.1541
C6F13
C6F13
C6F13
+
C6F13
PPM
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160.0
150.0
140.0
130.0
120.0
110.0
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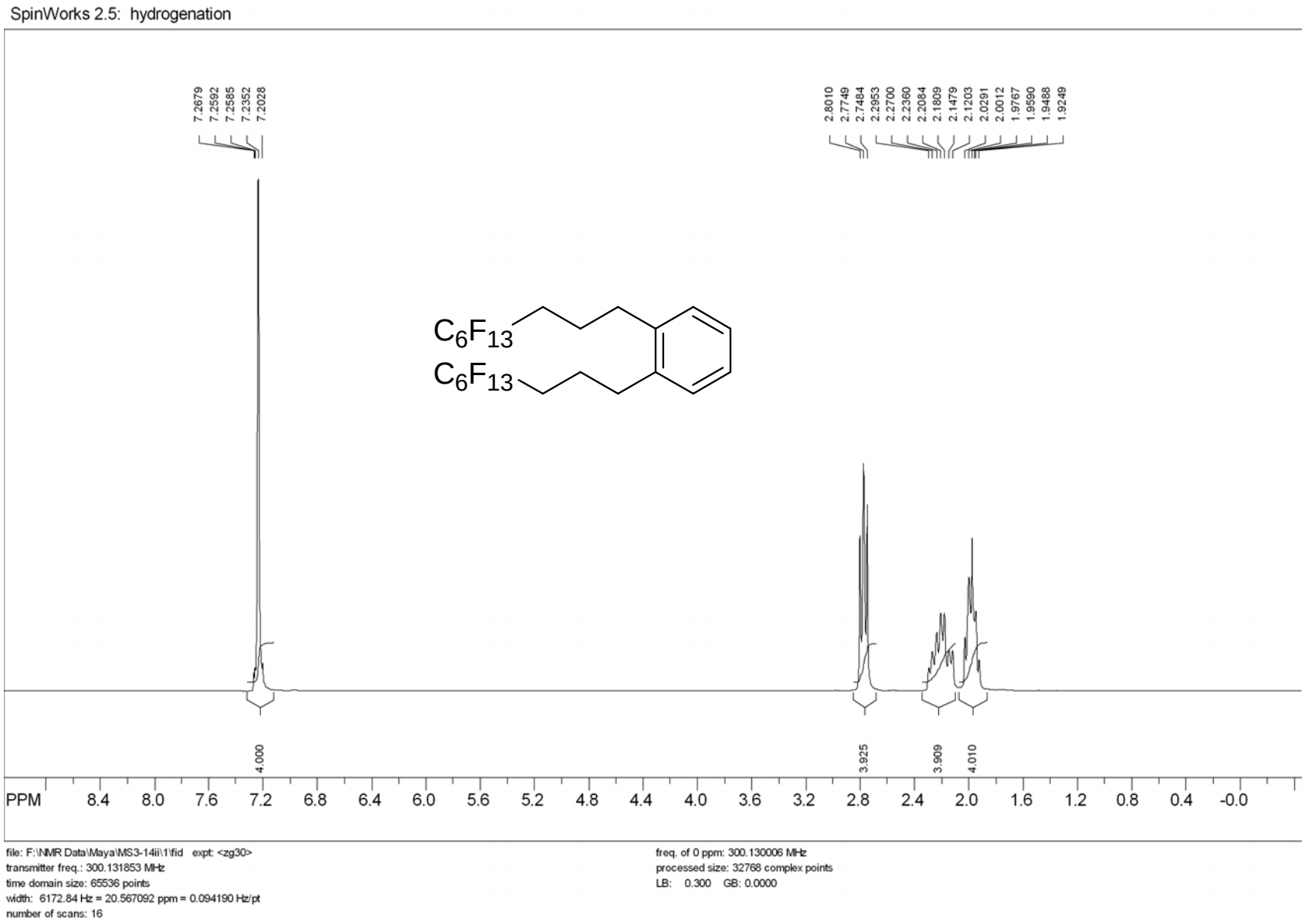
number of scans: 10000
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000



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processed size: 32768 complex points
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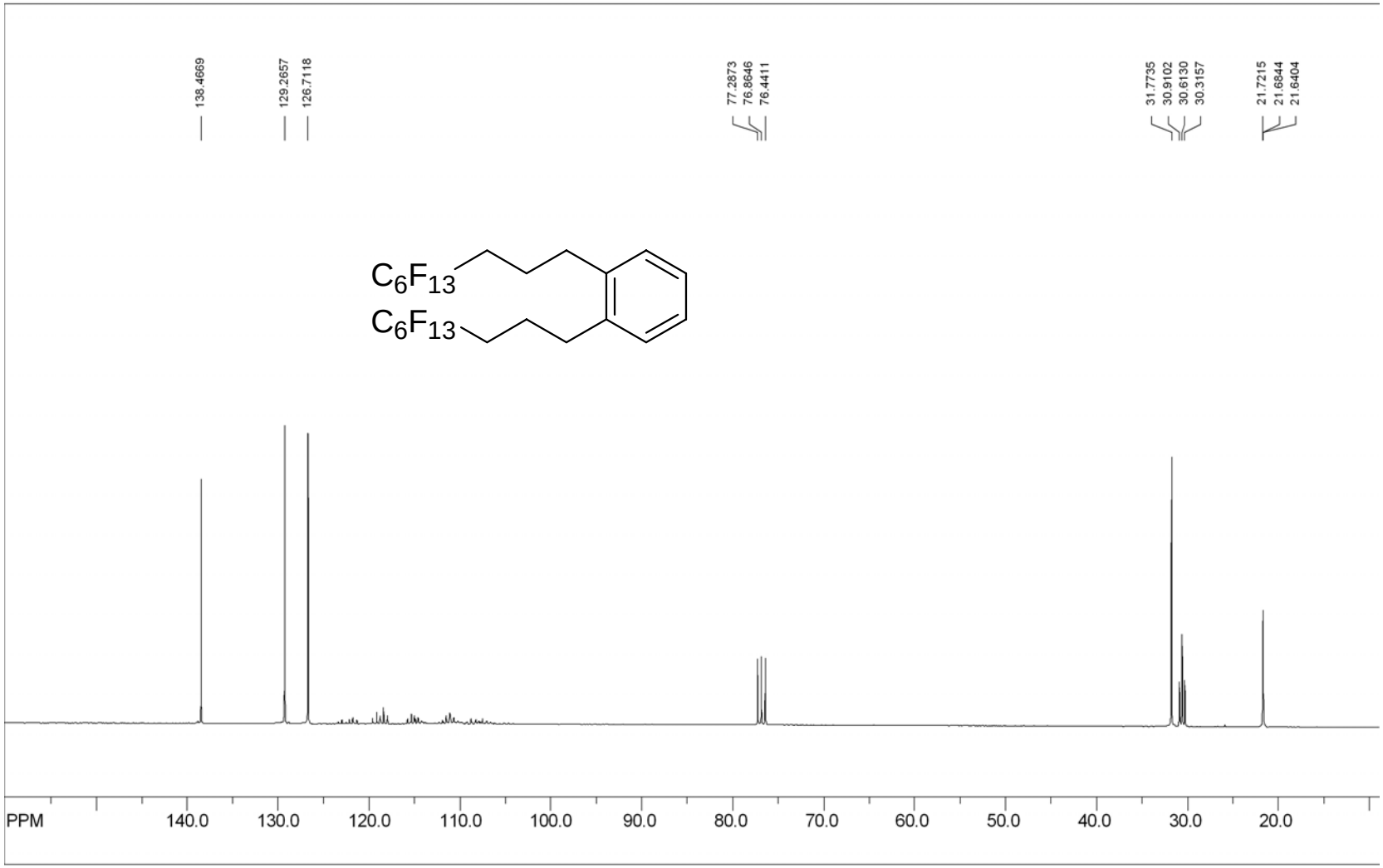

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freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
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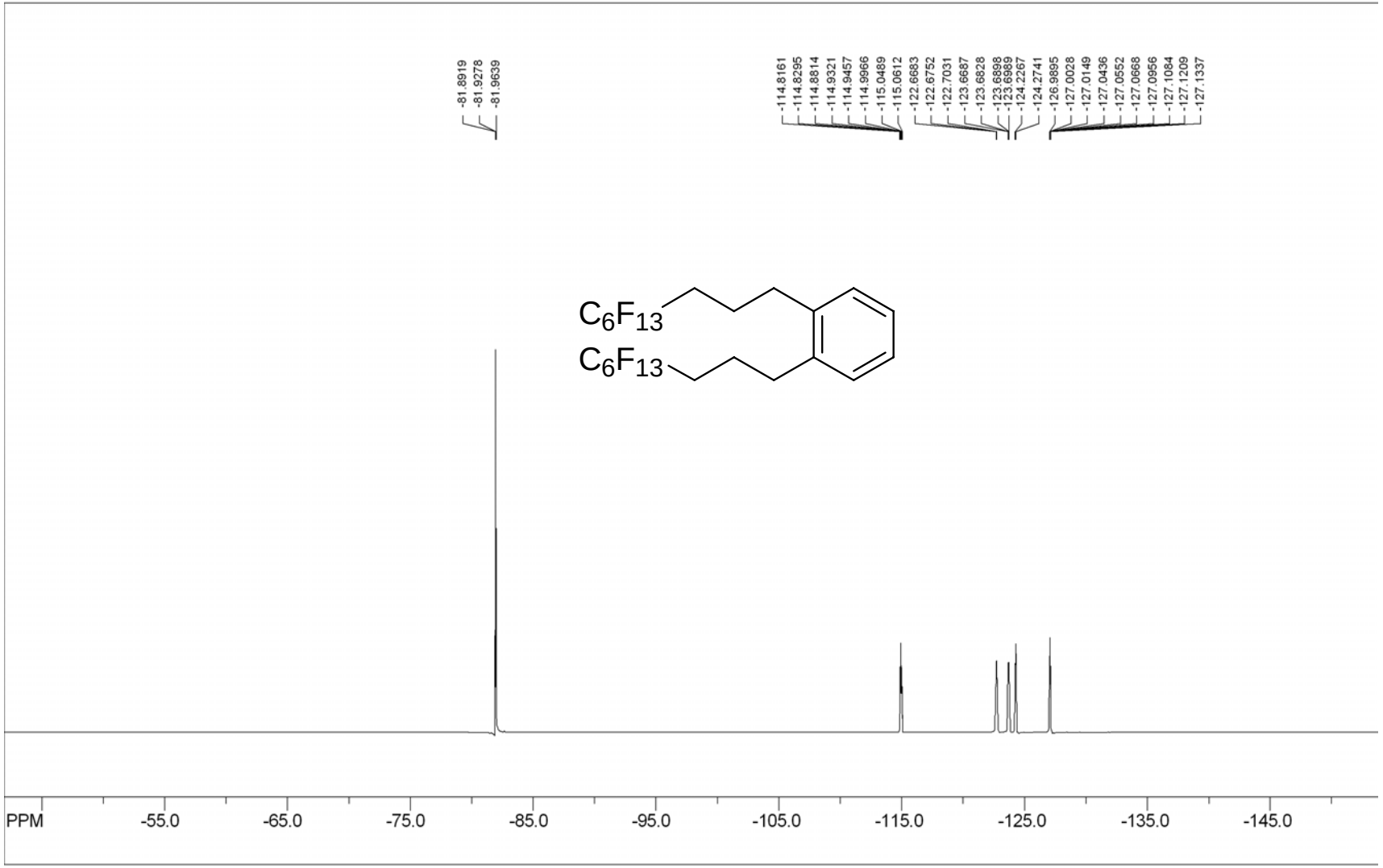
SpinWorks 2.5: hydrogenation



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number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
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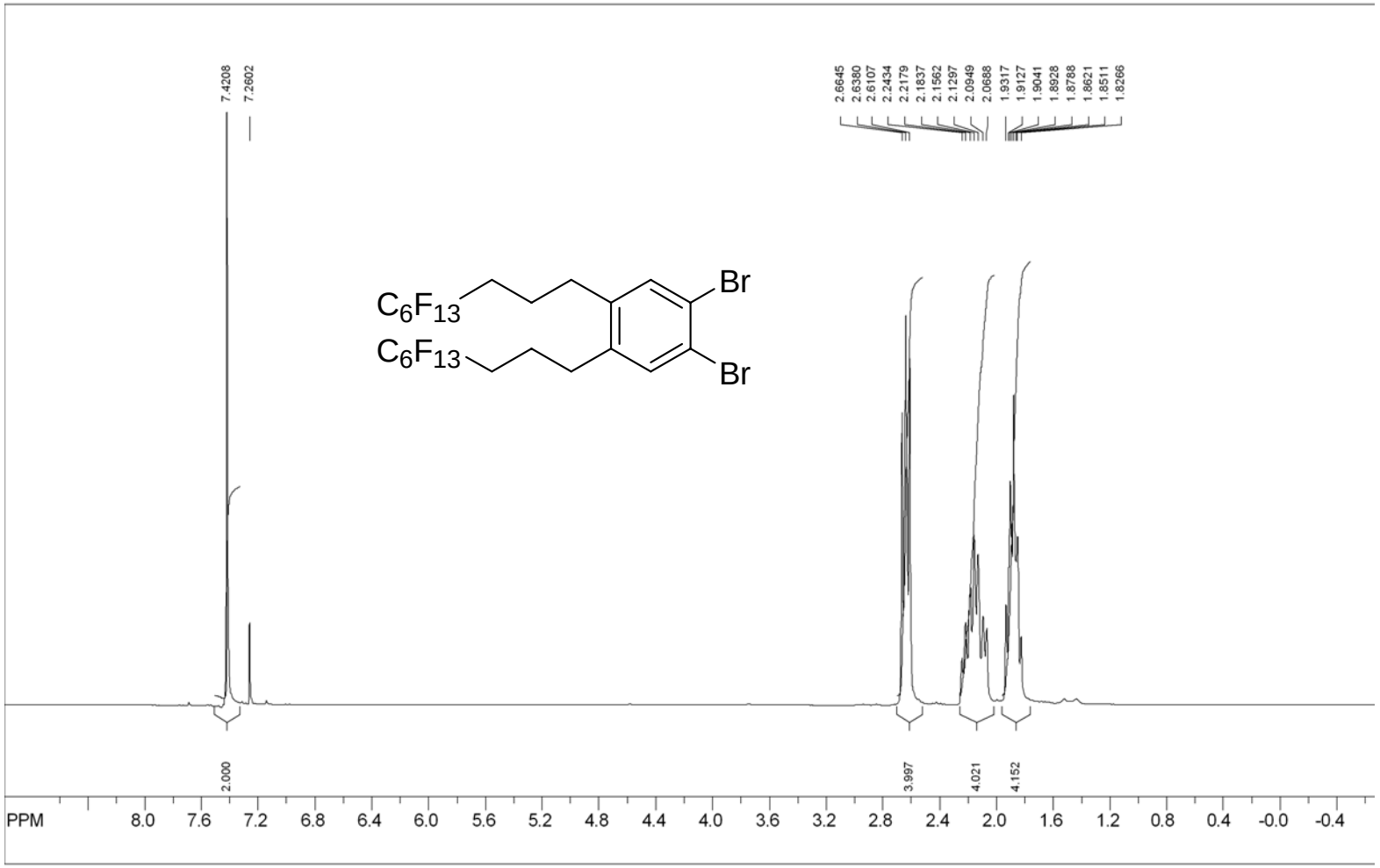
SpinWorks 2.5: 1,2-dibromo-4,5-(bisperfluoroalkyl)benzene



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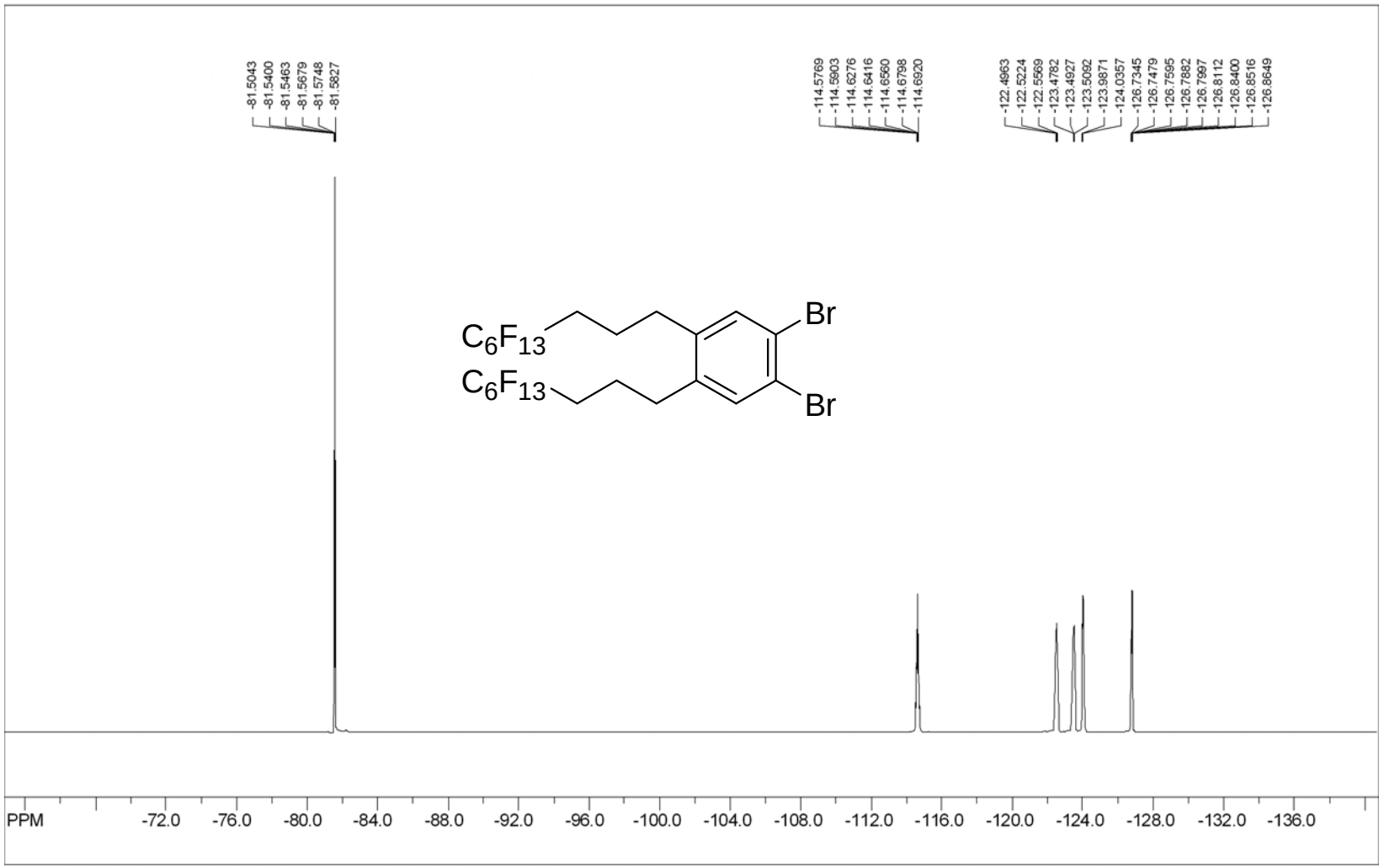
number of scans: 128

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: 1,2-dibromo-4,5-(bisperfluoroalkyl)benzene



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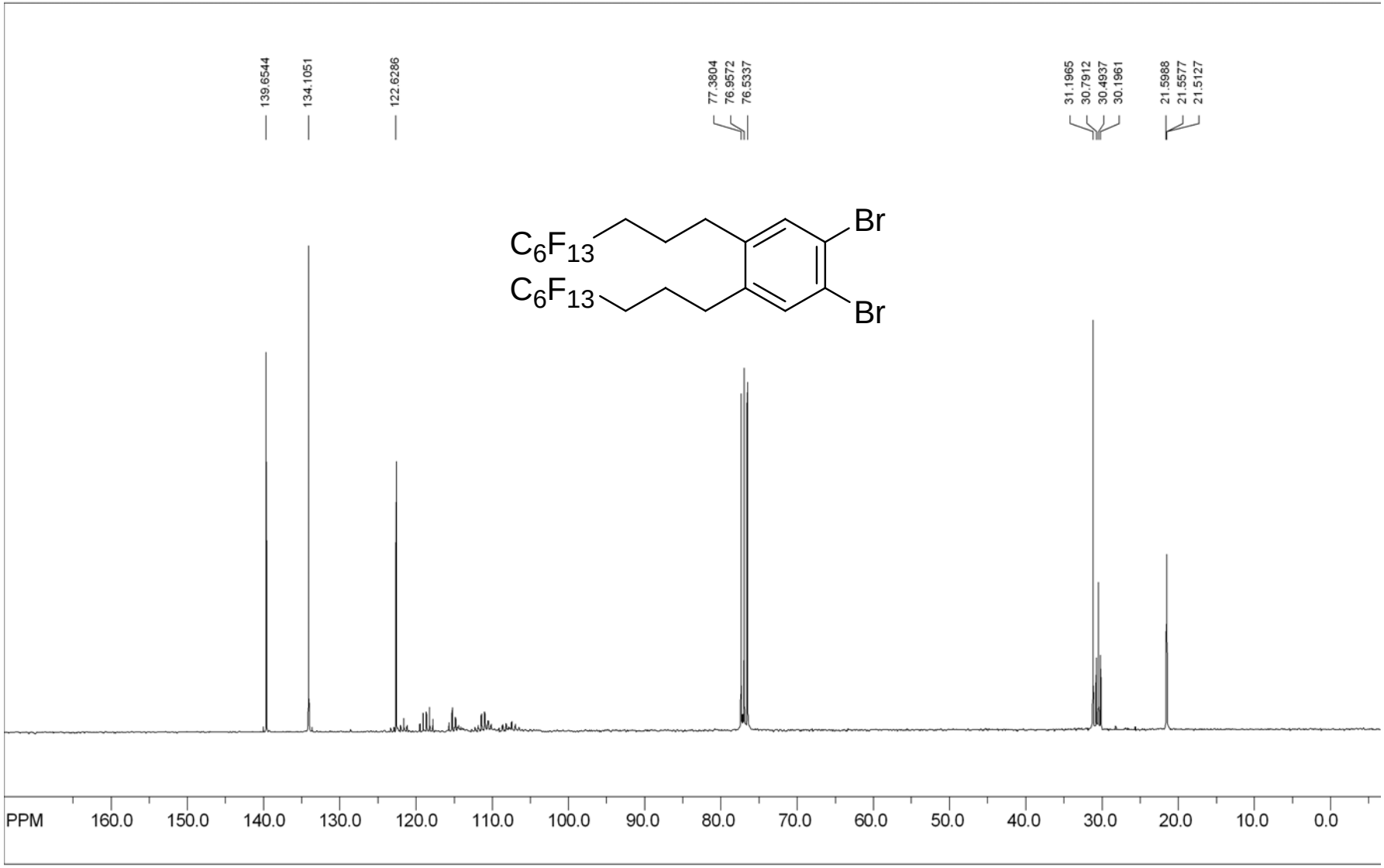
width: 67567.57 Hz = 239.282056 ppm = 0.515500 Hz/pt
number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: 1,2-dibromo-4,5-(bisperfluoroalkyl)benzene



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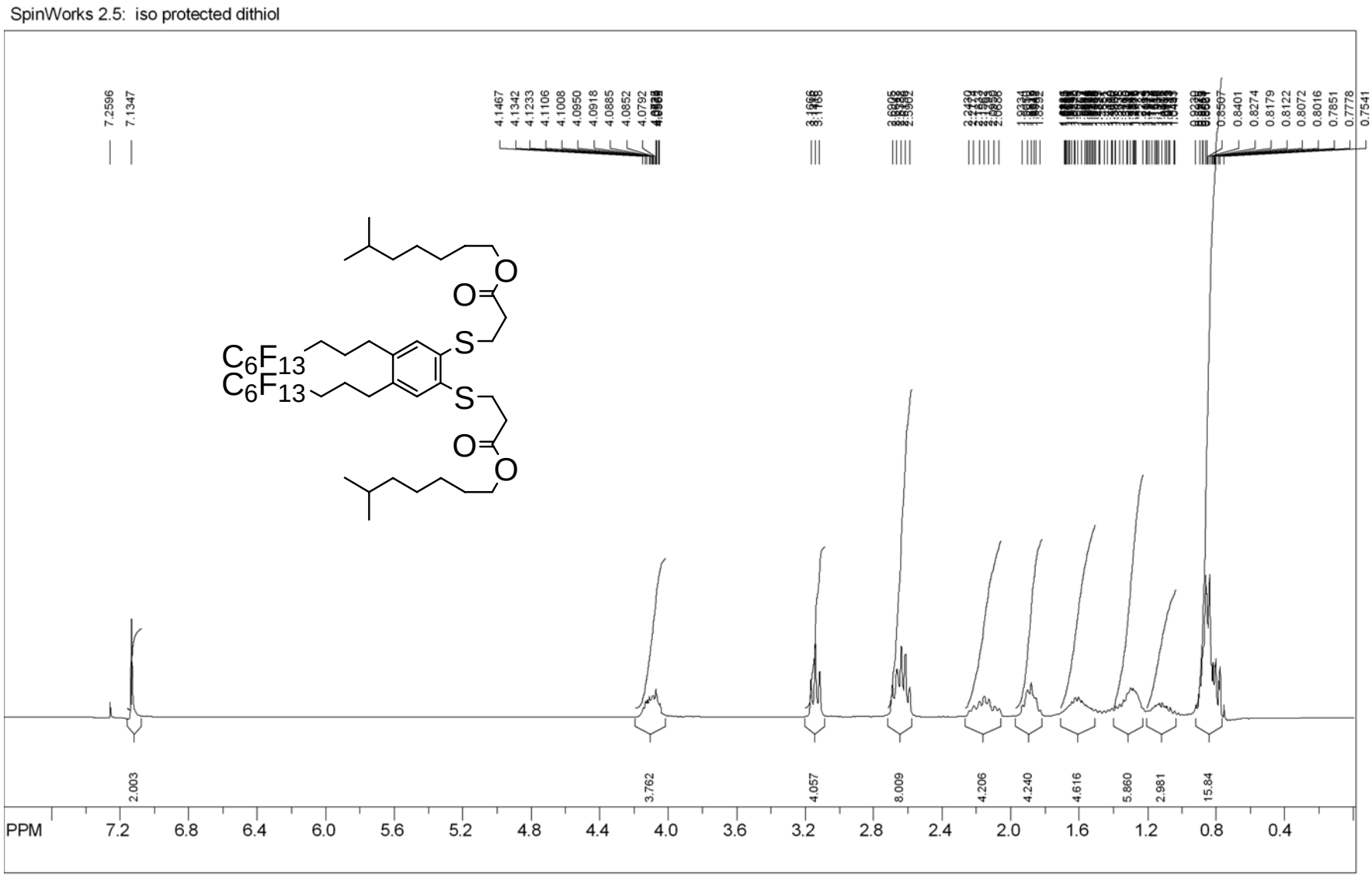
number of scans: 10000

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000



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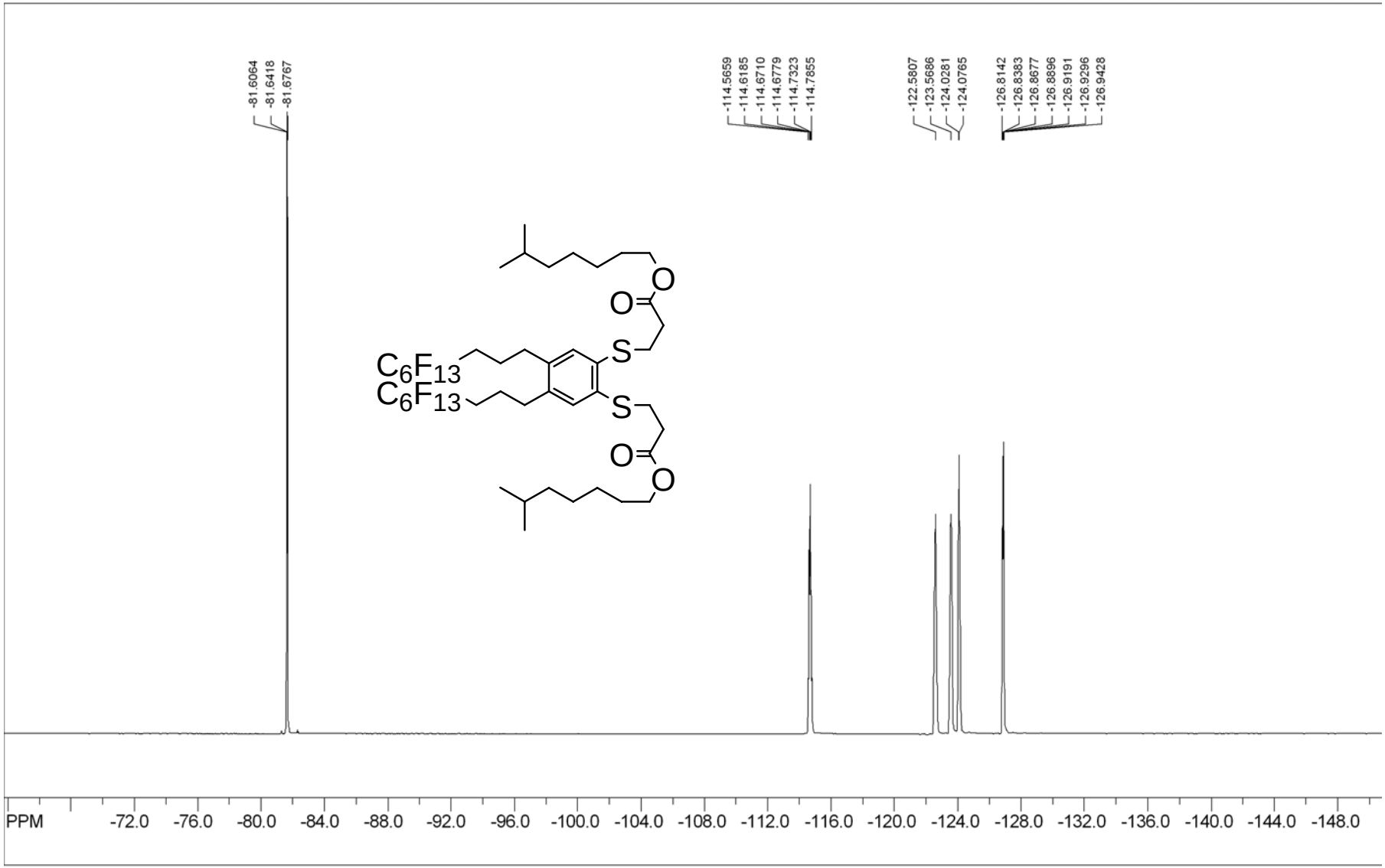

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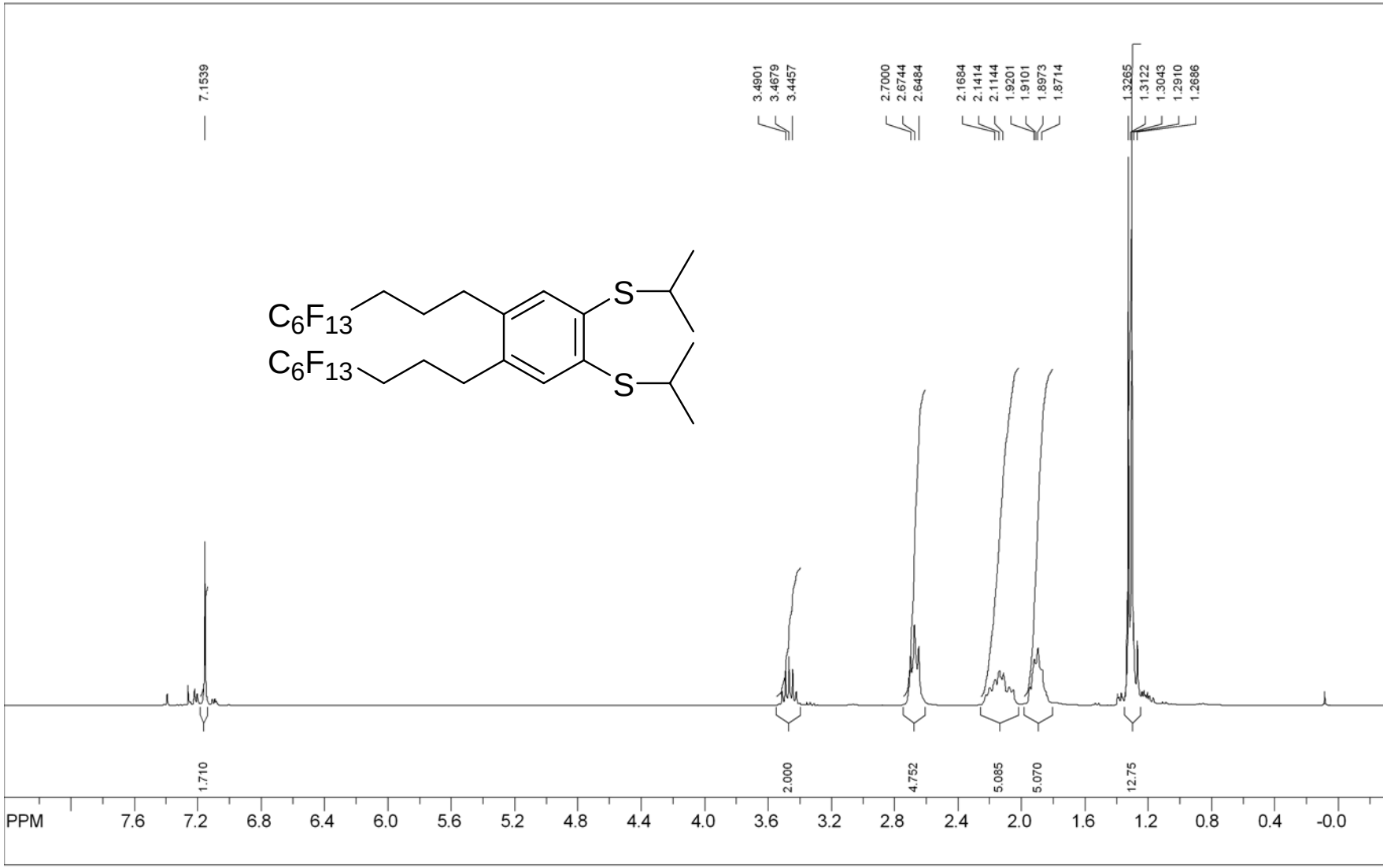
freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: isopropyl protected thiol



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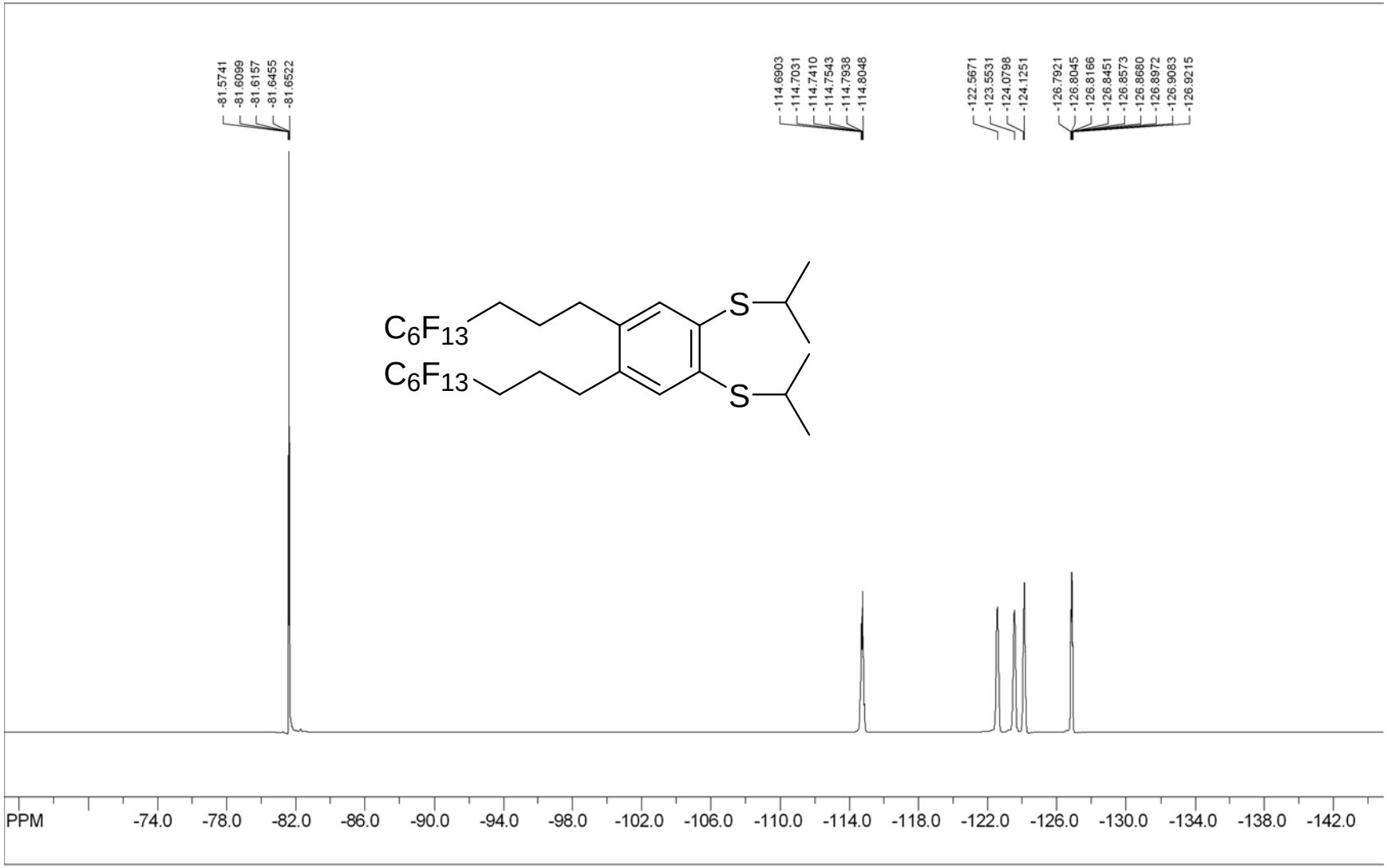
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: isopropyl protected thiol



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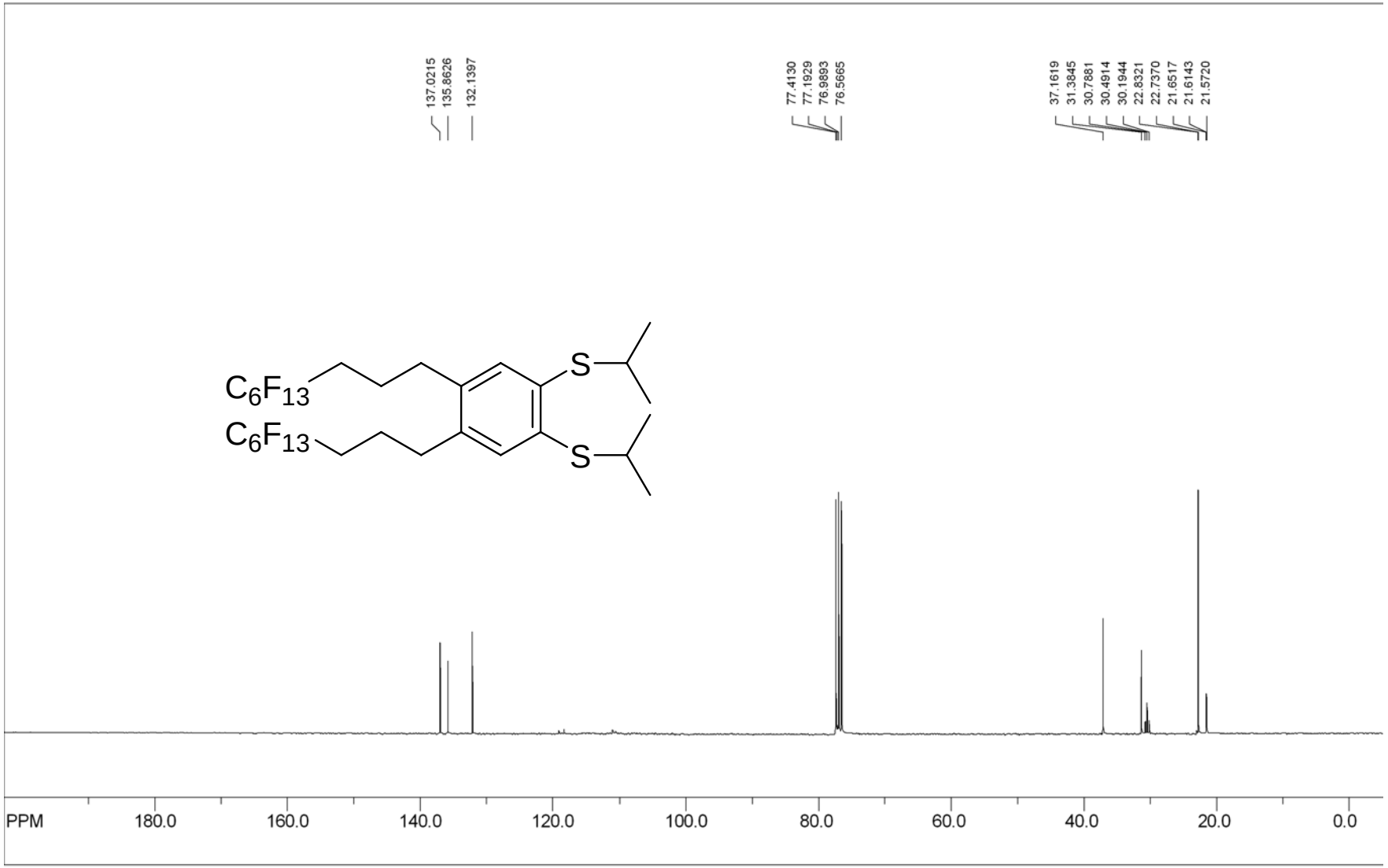
freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: isopropyl protected dithiol



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number of scans: 14000

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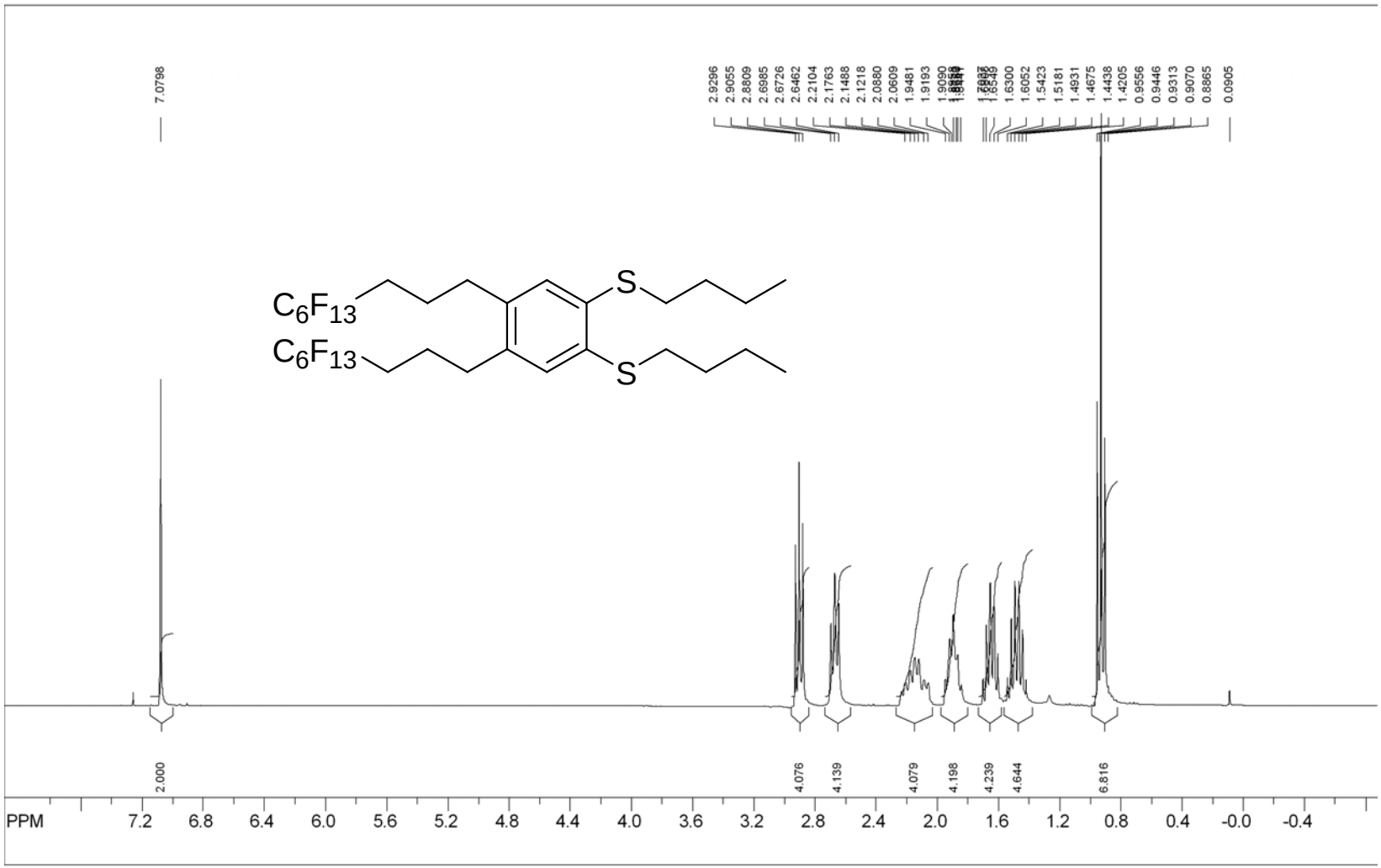
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

SpinWorks 2.5: PROTON CDCl3 u hultin 2



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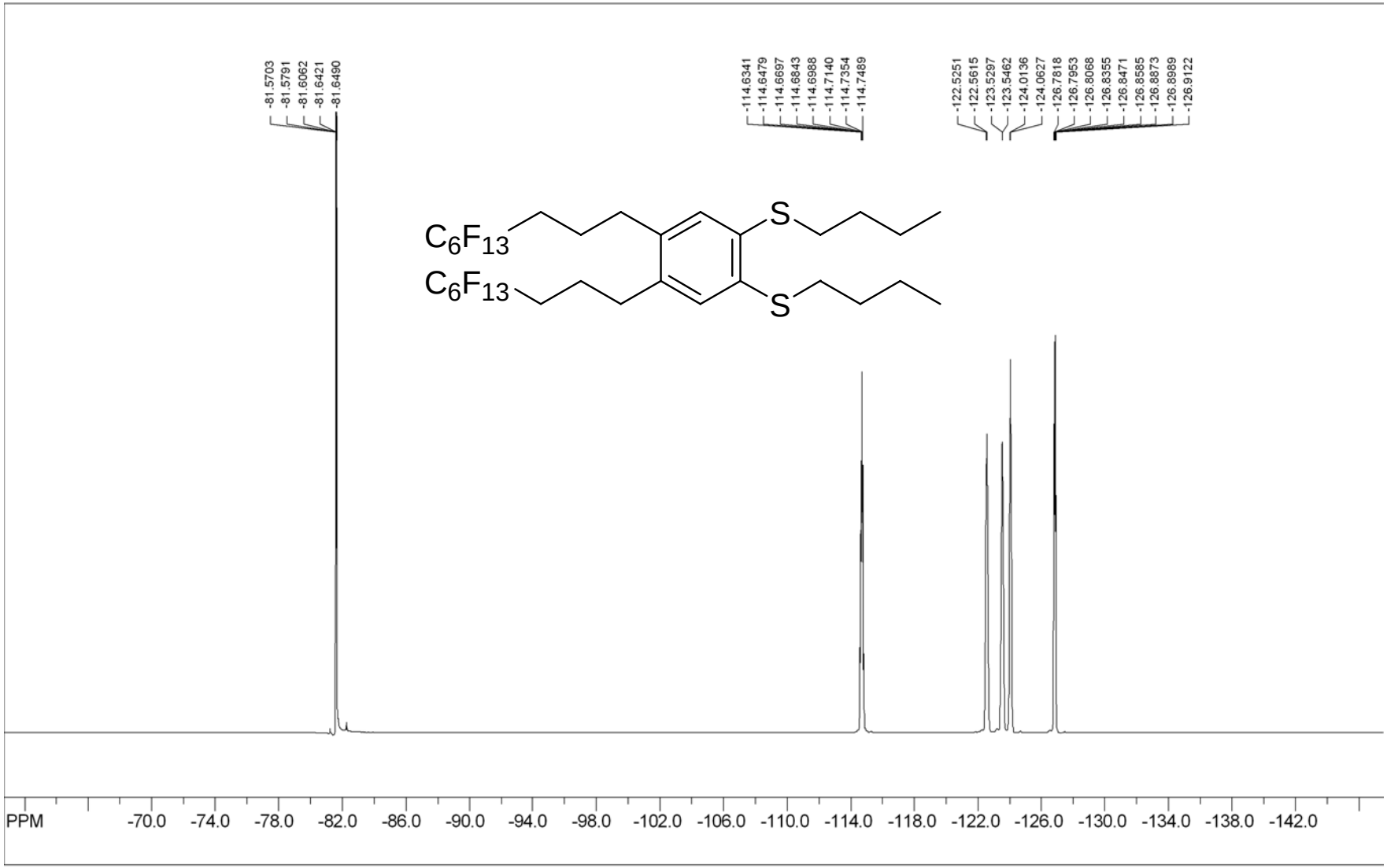
LB: 0.300 GB: 0.0000

SpinWorks 2.5: n-butyl protected dithiol



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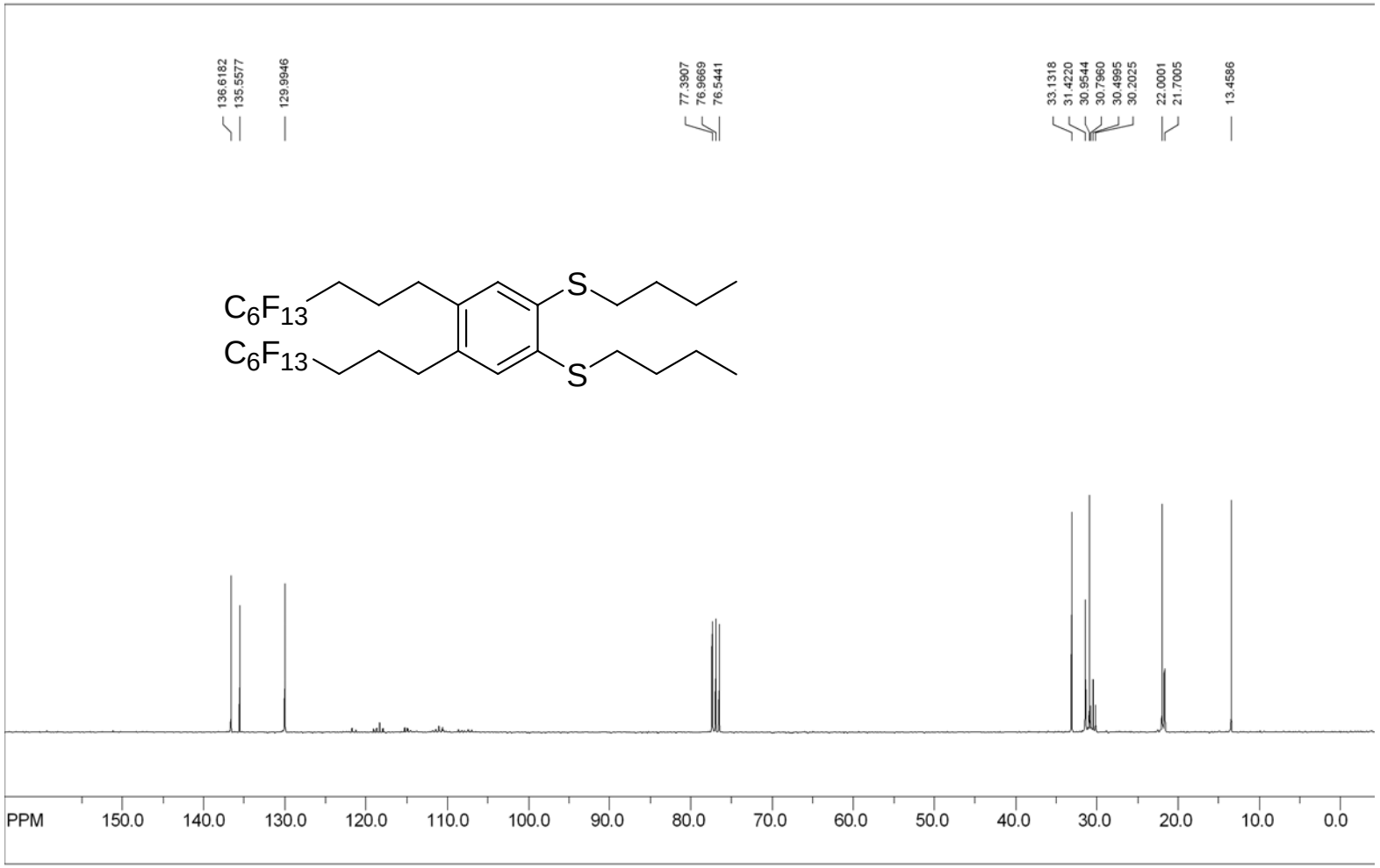
freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: n-butyl protected dithiol



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number of scans: 1000

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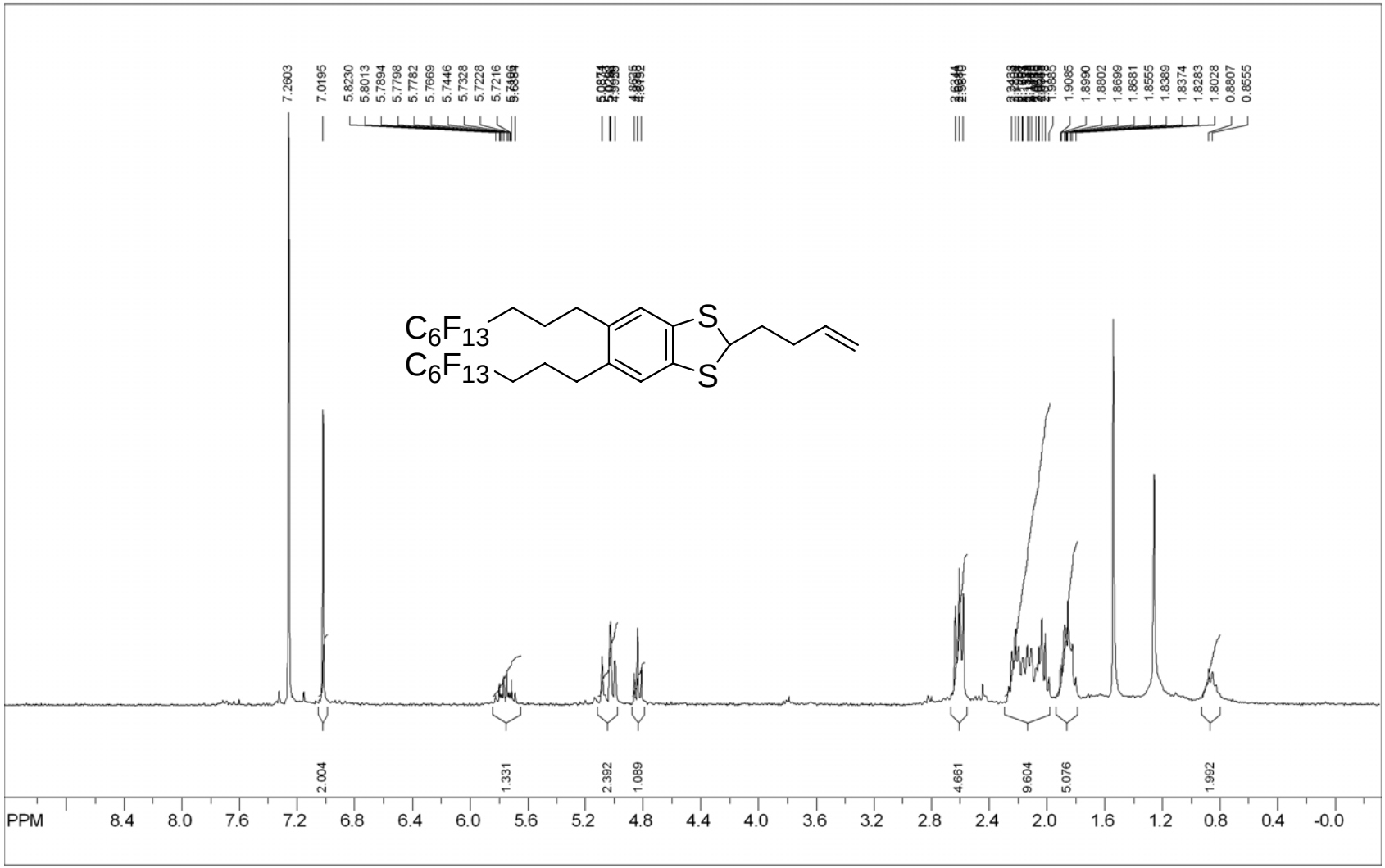
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

SpinWorks 2.5: fraction 1



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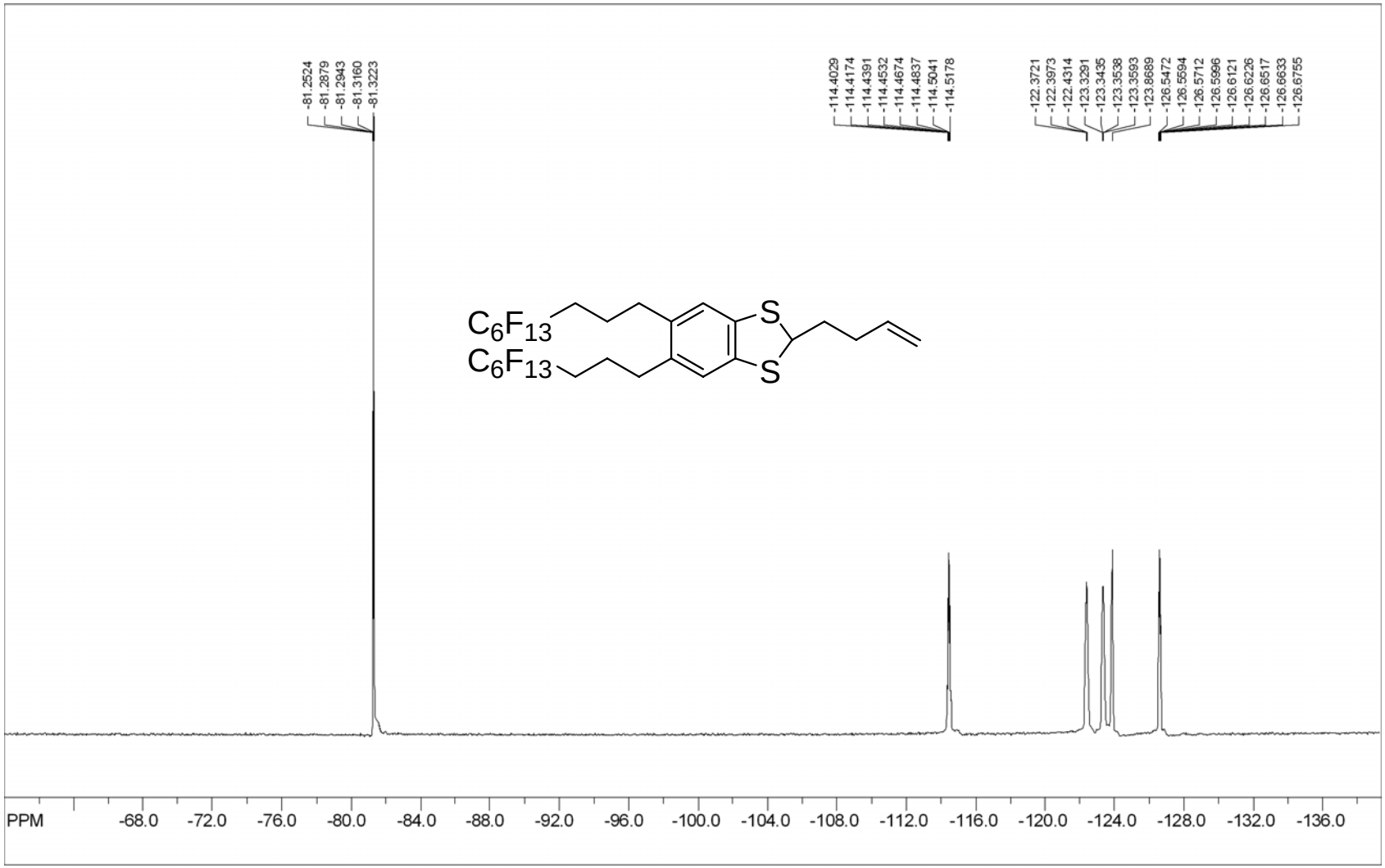

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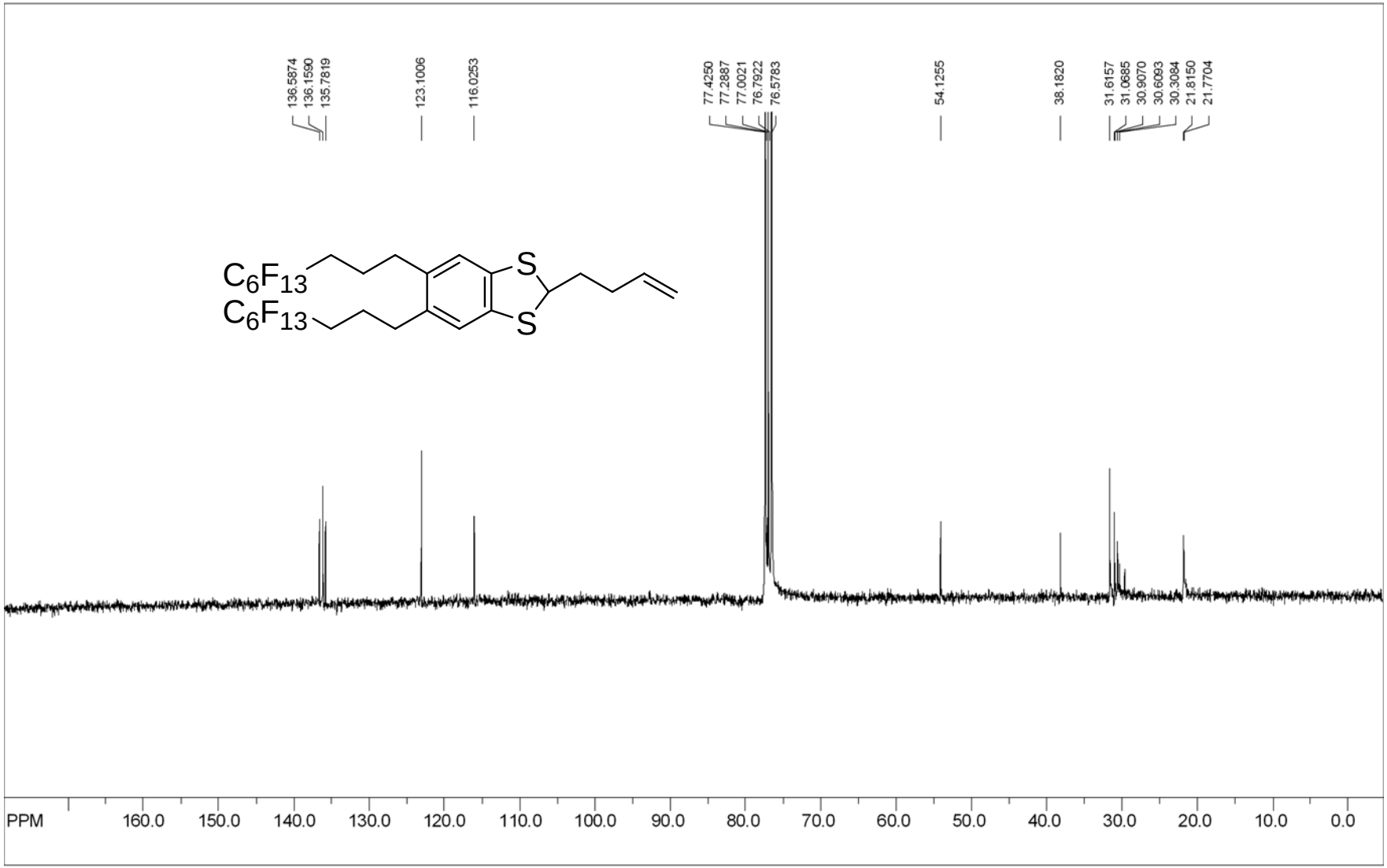
SpinWorks 2.5: thioacetal



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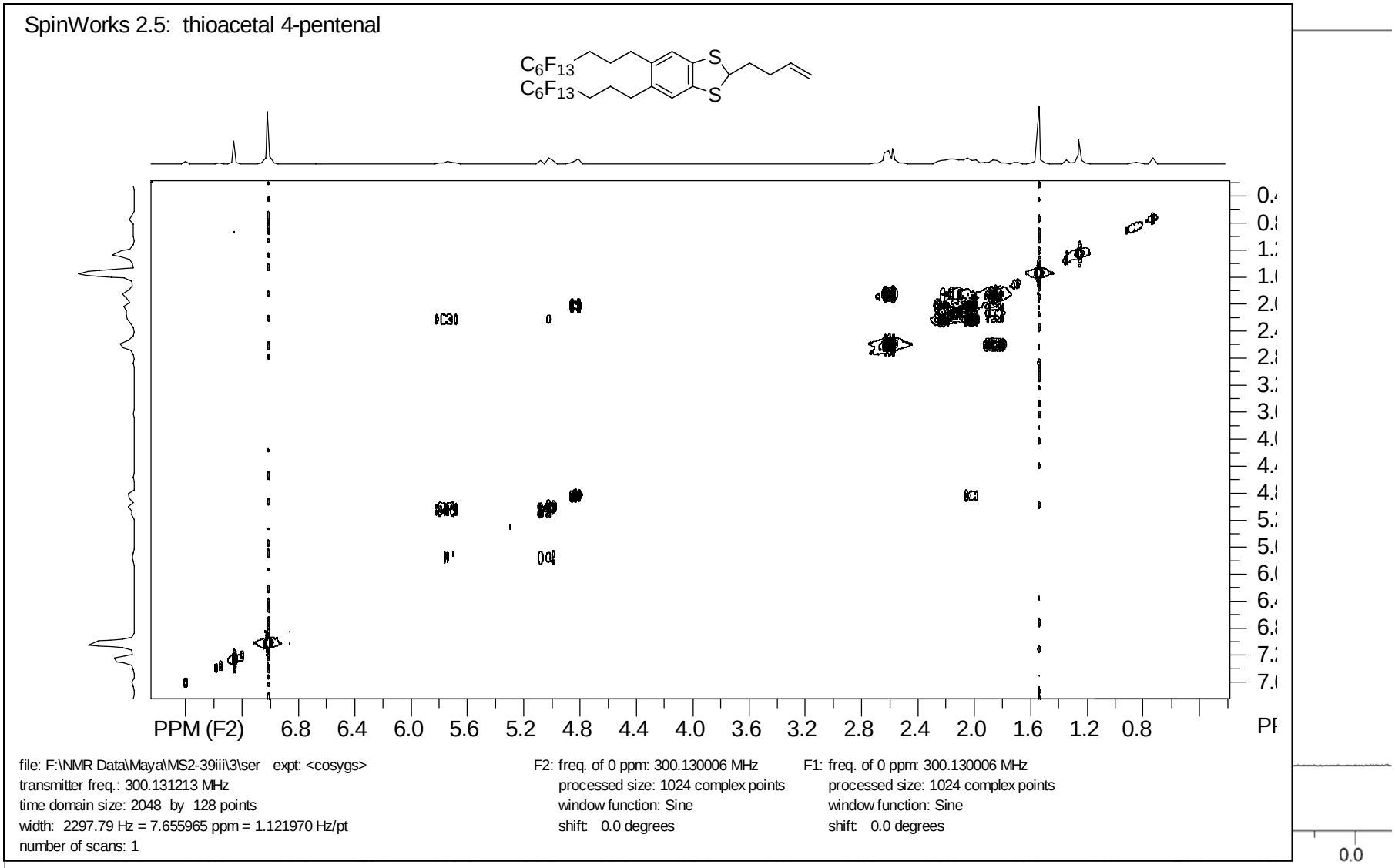
SpinWorks 2.5: thioacetal 4-pentenal
C_6F_{13}
C_6F_{13}
S
S
PPM (F2)
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
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F2: freq. of 0 ppm: 300.130006 MHz
processed size: 1024 complex points
window function: Sine
shift: 0.0 degrees
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processed size: 1024 complex points
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time domain size: 65536 points
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processed size: 32768 complex points
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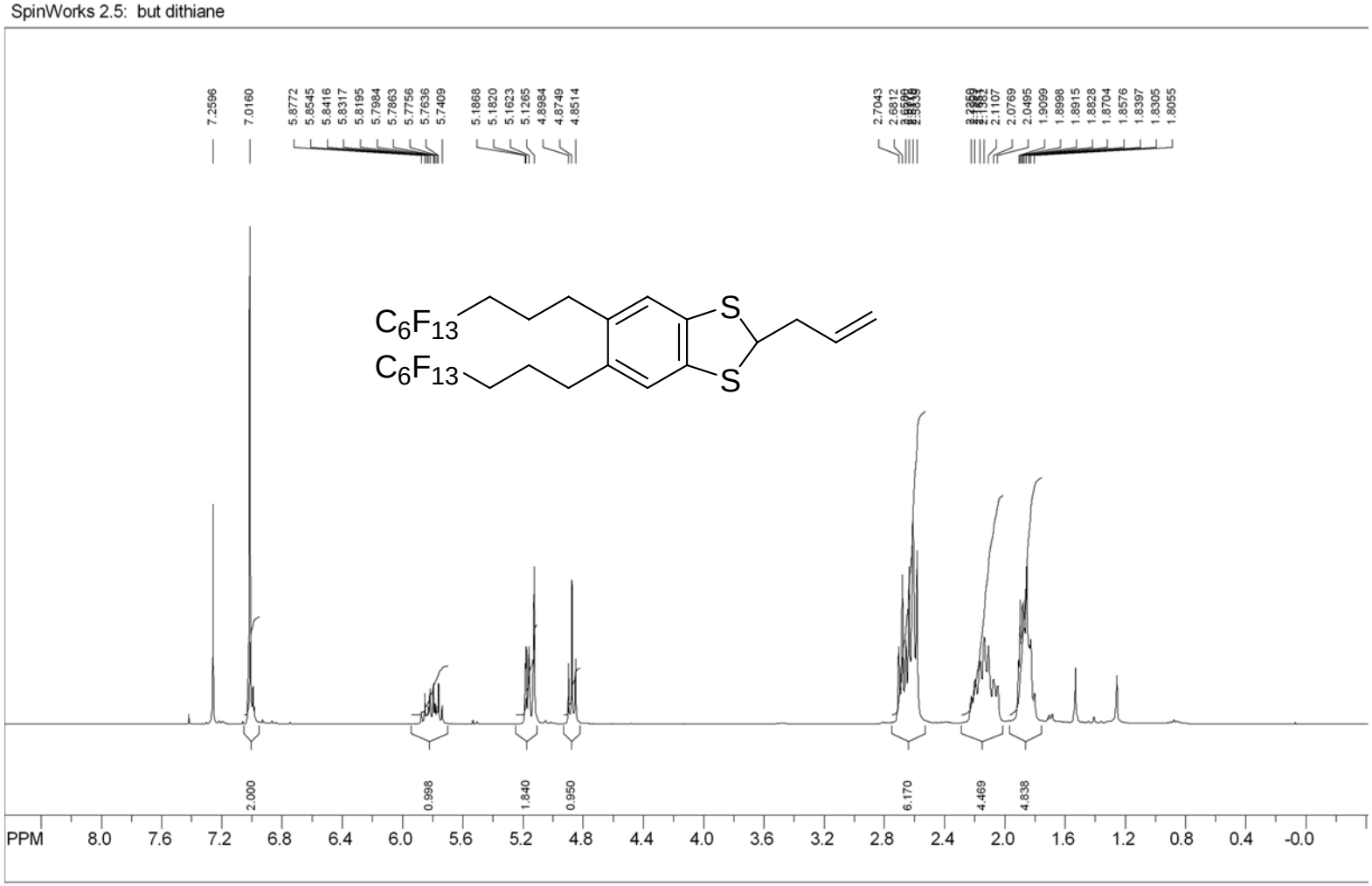

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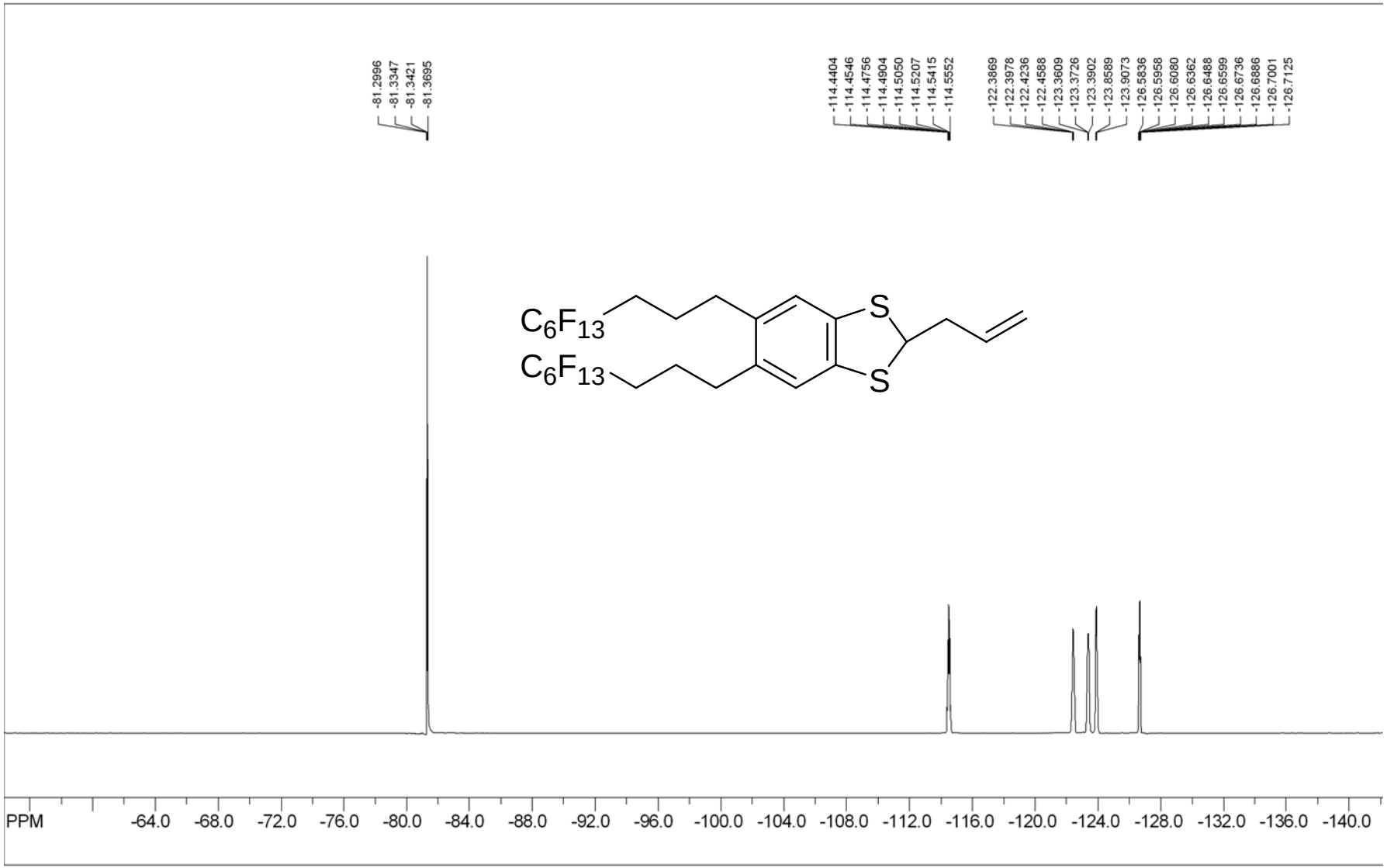

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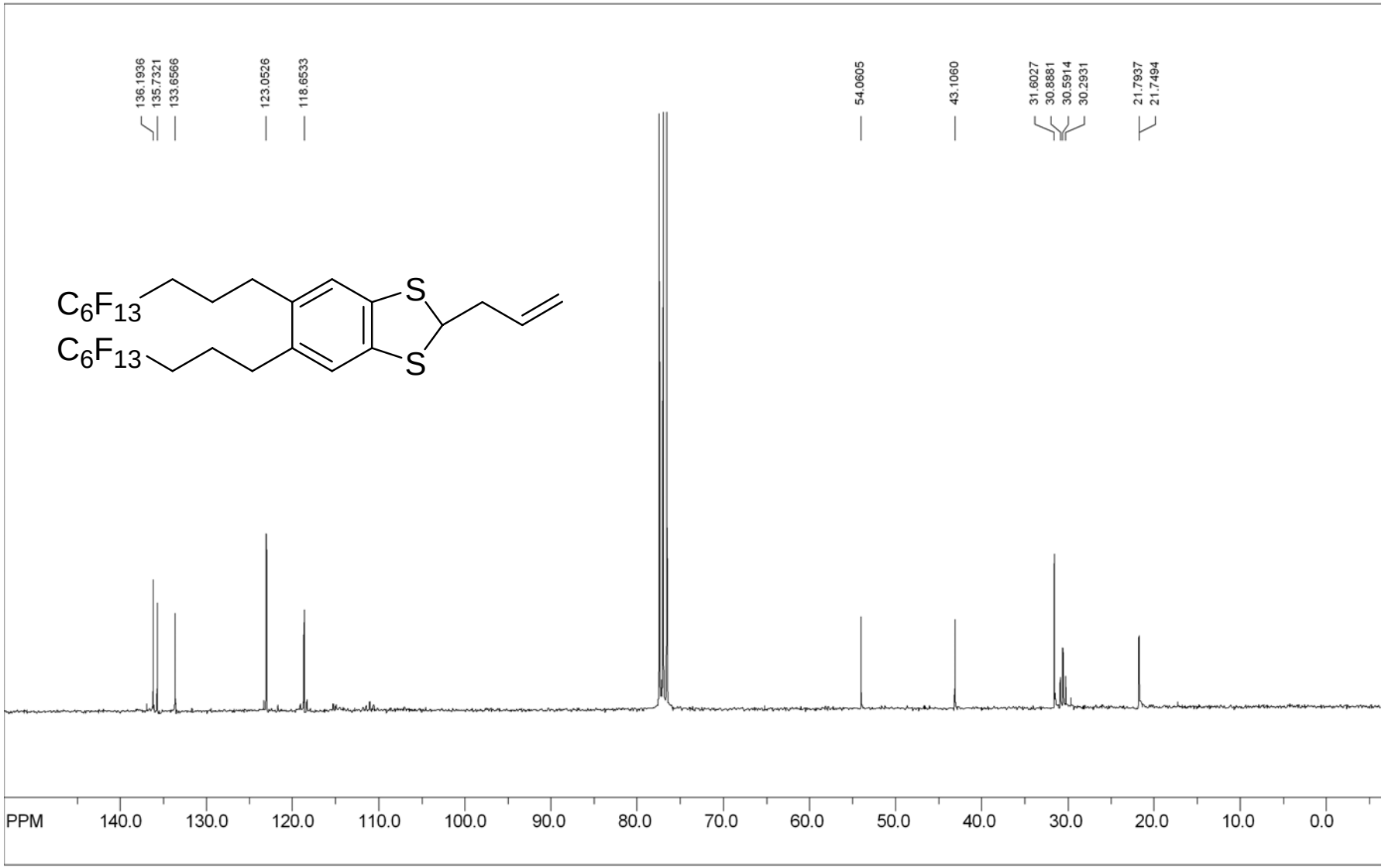
number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: C13CPD32 CDCl3 u hultin 3



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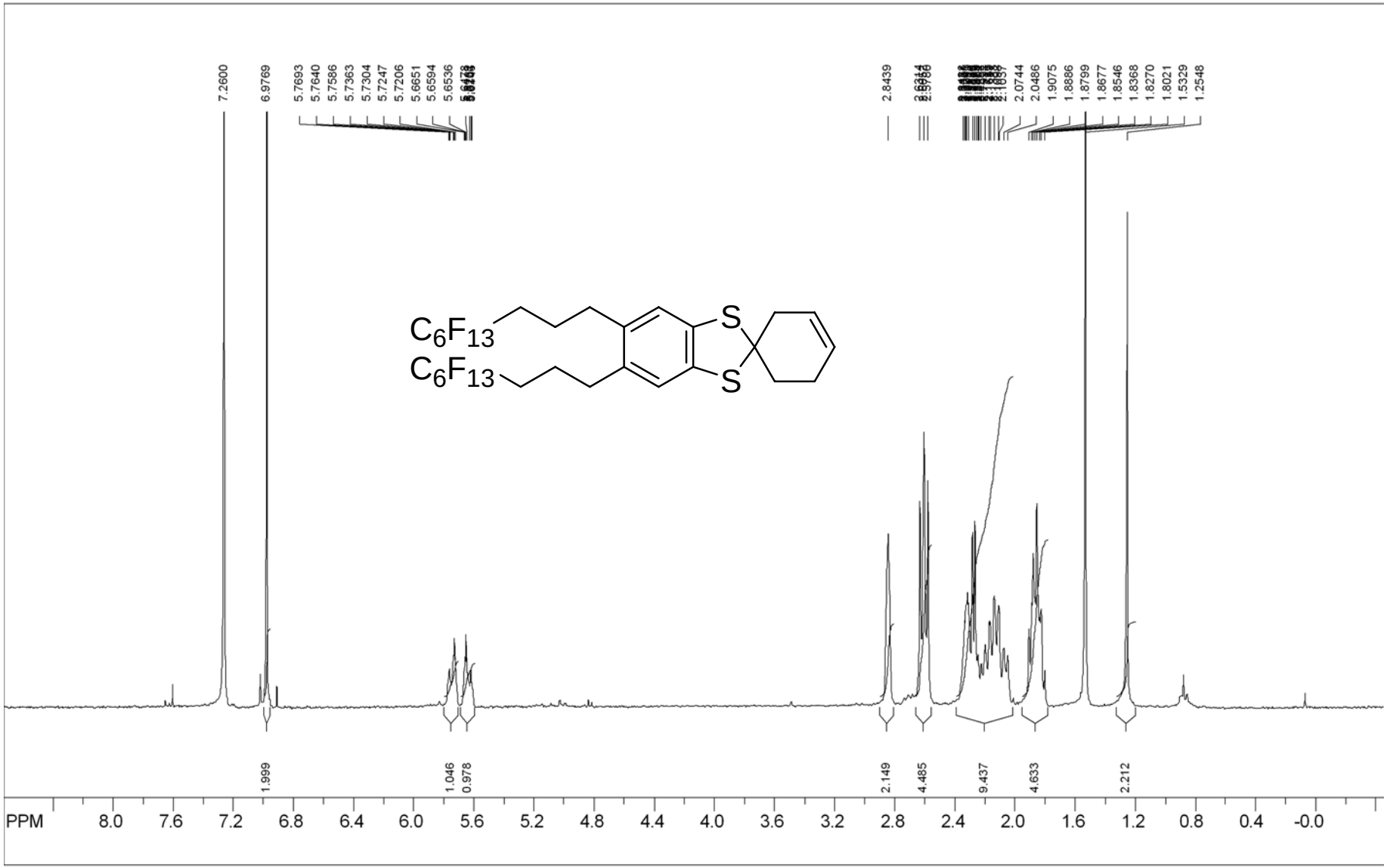
number of scans: 10000

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

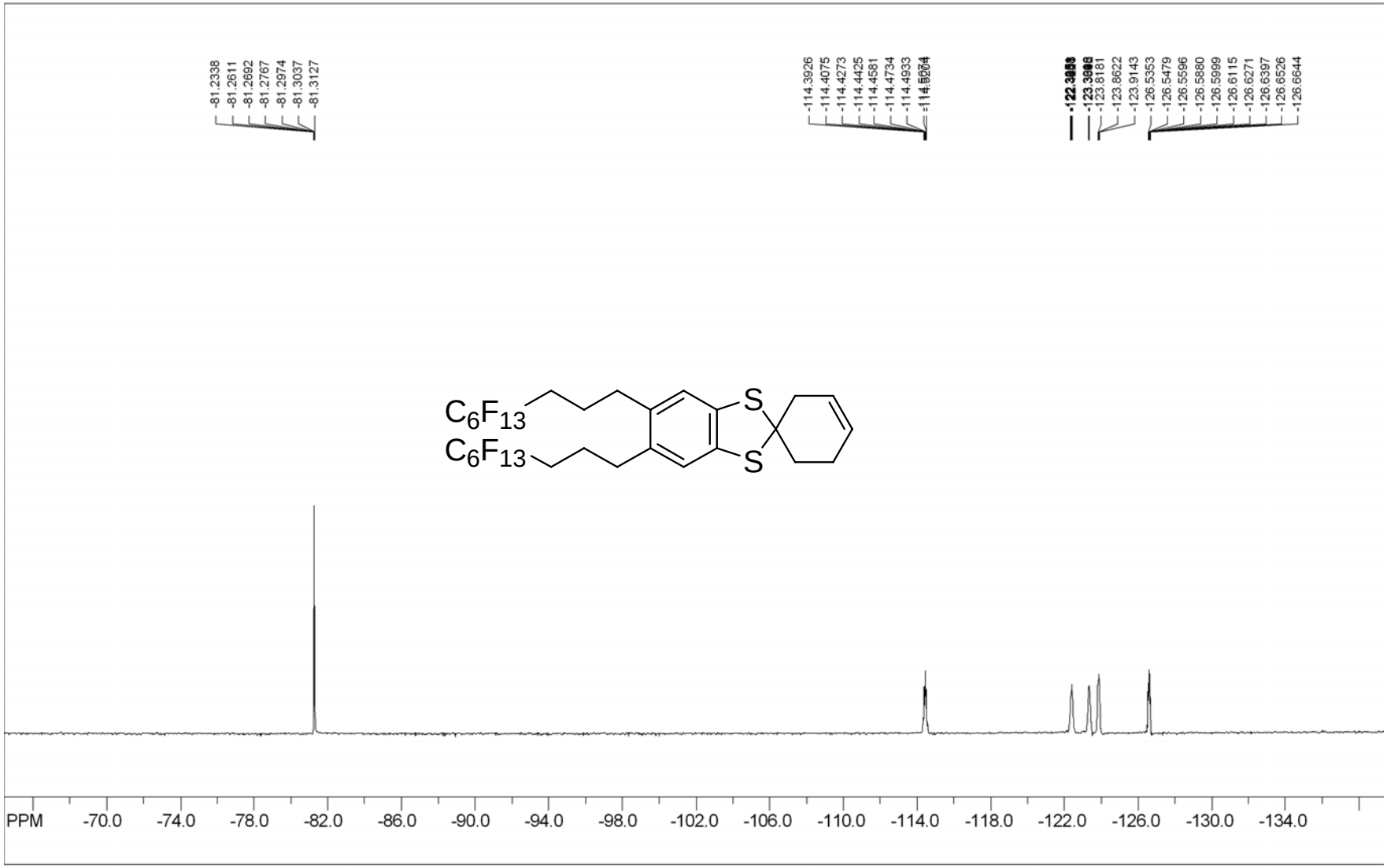
SpinWorks 2.5: PROTON128 CDCl3 u hultin 1



file: F:\NMR Data\Maya\MS2-58ii\2\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 128

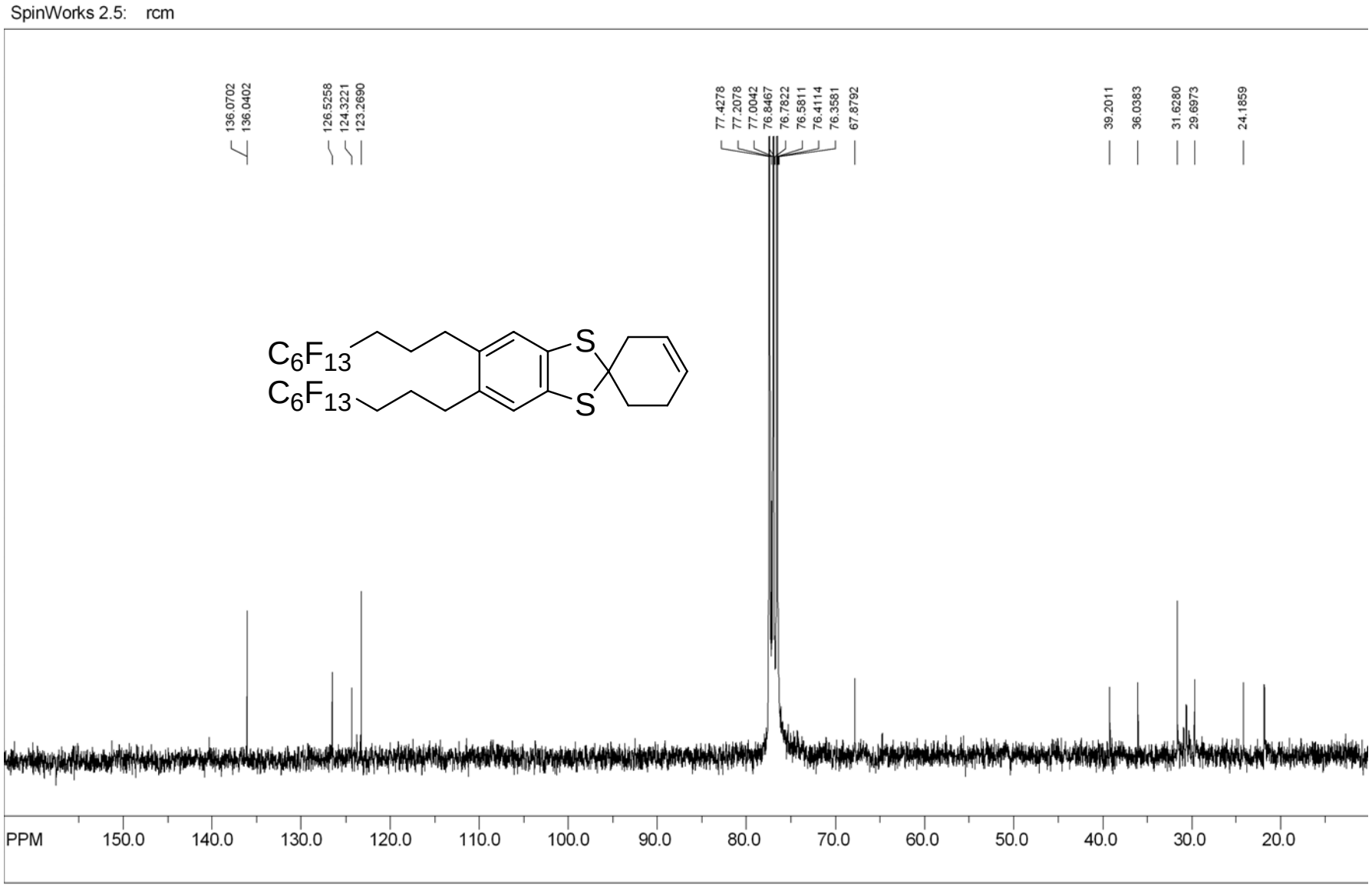
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: F19 CDCl3 u hultin 1

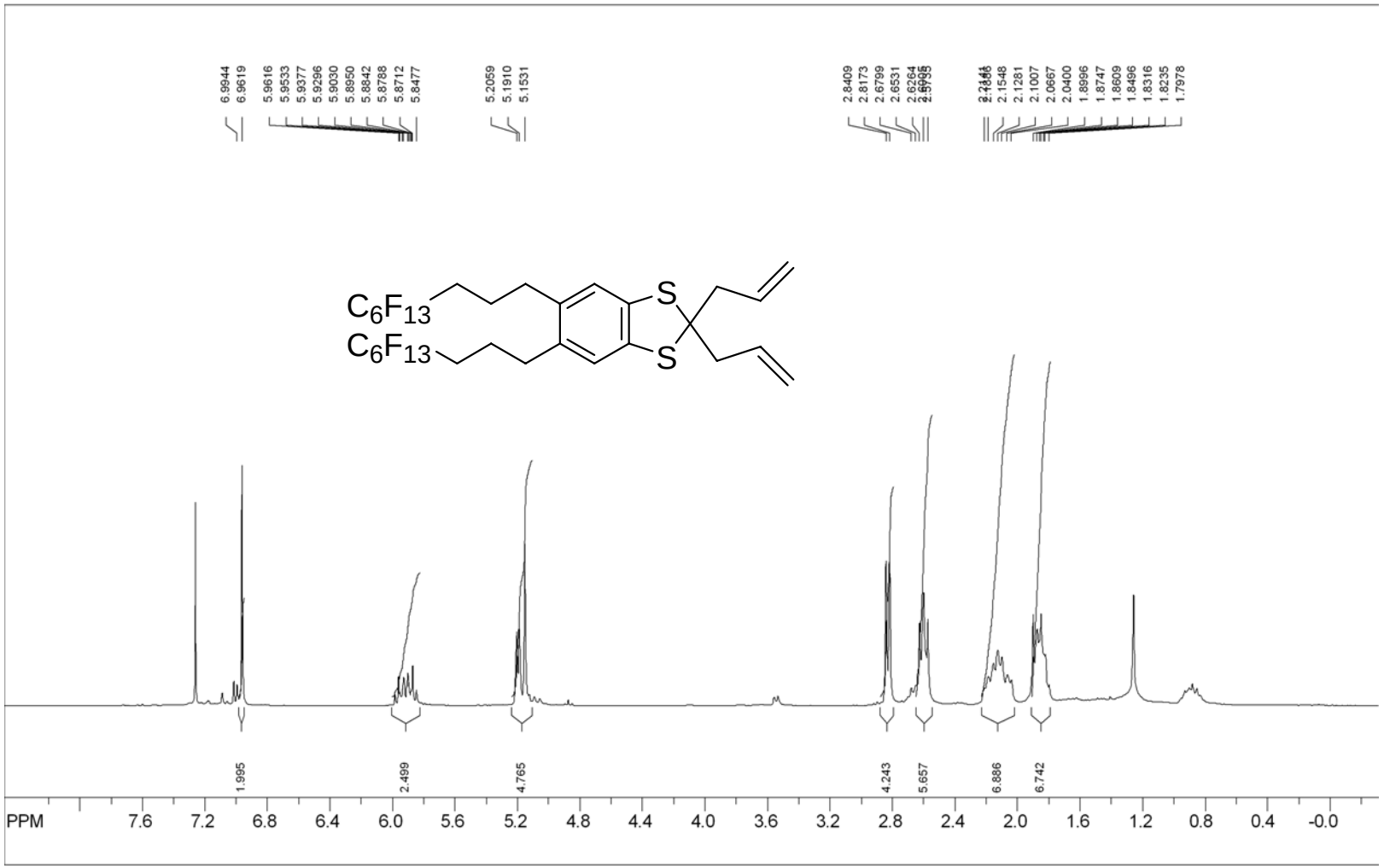


file: F:\NMR Data\Maya\MS2-58ii\3\fid expt: <zgflqn>
transmitter freq.: 282.376241 MHz
time domain size: 131072 points
width: 67567.57 Hz = 239.282056 ppm = 0.515500 Hz/pt
number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000


SpinWorks 2.5: rcm
136.0702
136.0402
126.5258
124.3221
123.2690
77.4278
77.2078
77.0042
76.8467
76.7822
76.5811
76.4114
76.3581
67.8792
39.2011
36.0383
31.6280
29.6973
24.1859
C6F13
C6F13
S
S
PPM
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
file: F:\NMR Data\Maya\MS2-58\3\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 14000
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000

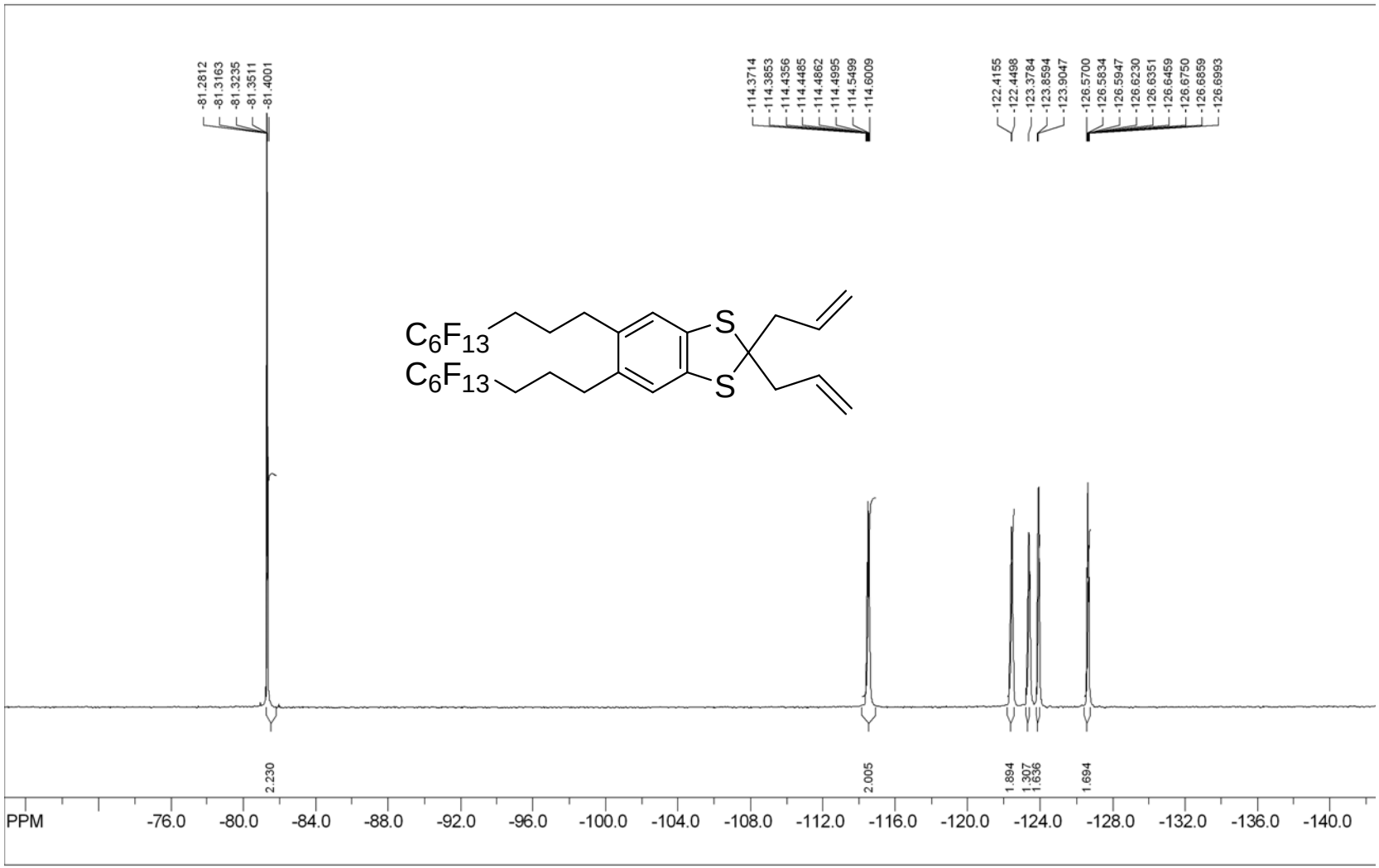
SpinWorks 2.5: PROTON128 CDCl3 u hultin 1



file: F:\NMR Data\Maya\MS2-138i\2\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 128

freq. of 0 ppm: 300.130006 MHz
processed size: 32768 complex points
LB: 0.000 GB: 0.0000

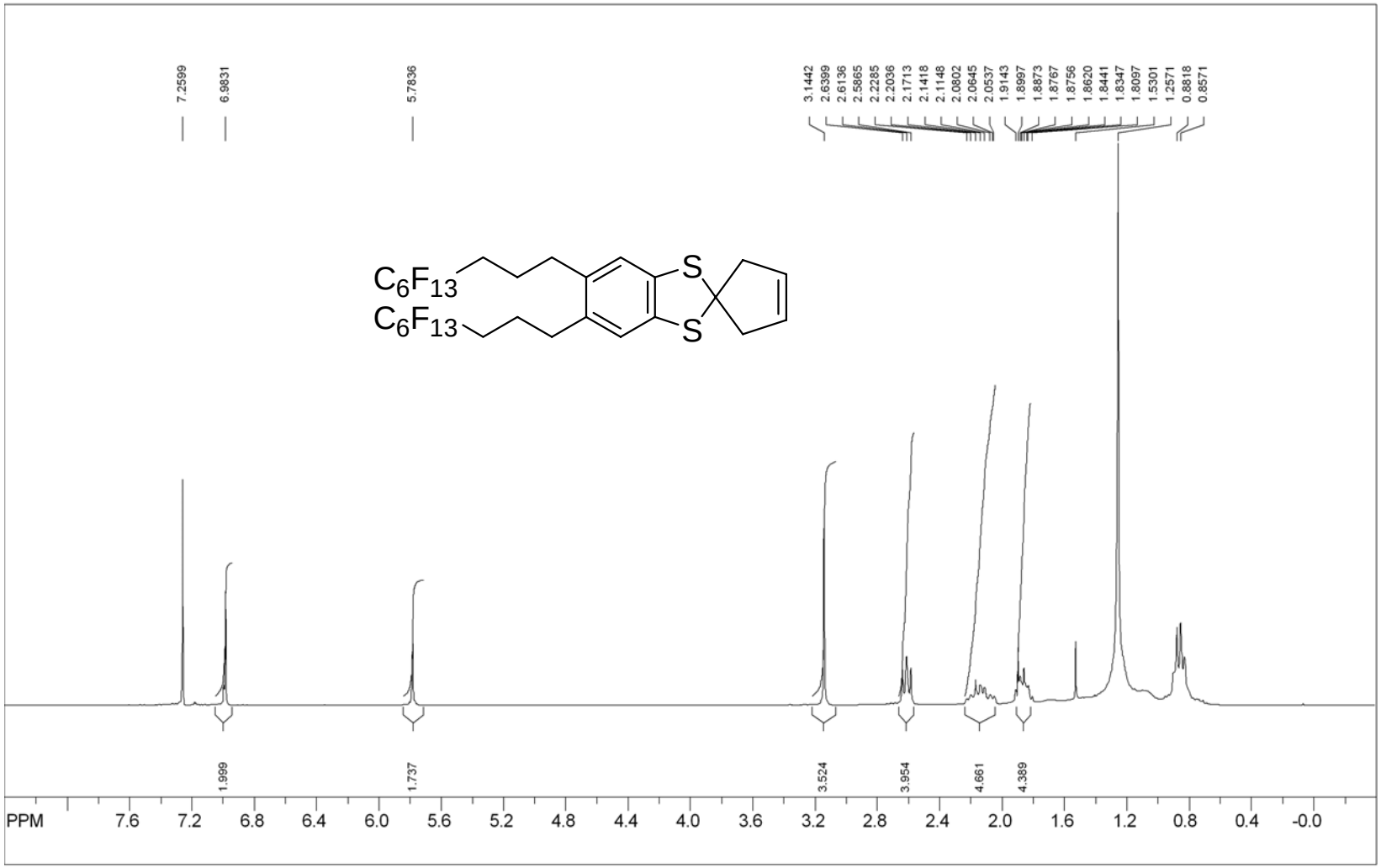
SpinWorks 2.5: F19 CDCl3 u hultin 1



file: F:\NMR Data\Maya\MS2-138i\3\fid expt: <zgflqn>
transmitter freq.: 282.376241 MHz
time domain size: 131072 points
width: 67567.57 Hz = 239.282056 ppm = 0.515500 Hz/pt
number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: rcm 5 membered



file: F:\NMR Data\Maya\MS2-140iii\1\fid expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 128

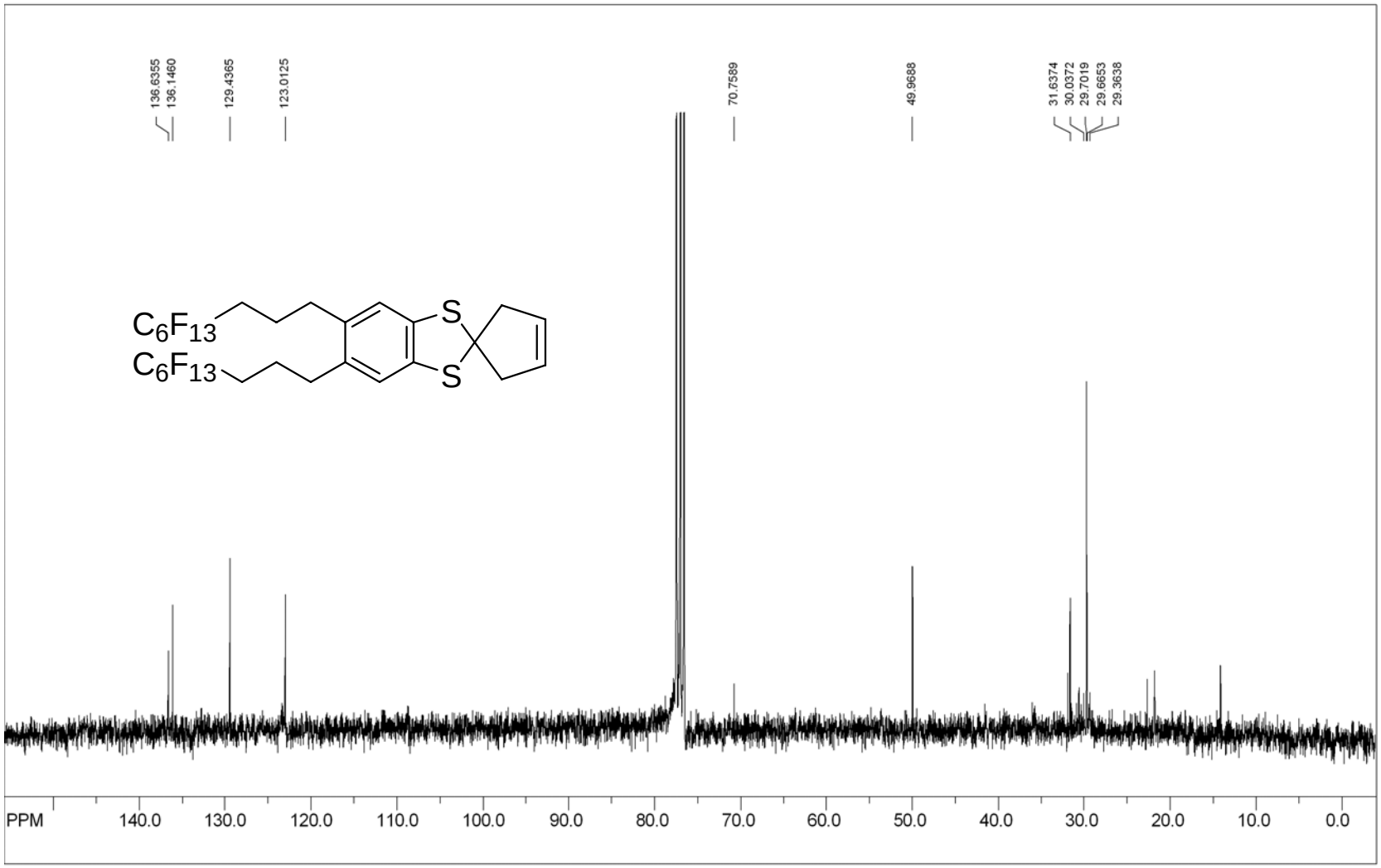
freq. of 0 ppm: 300.130006 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: rcm 5 membered

file: F:\NMR Data\Maya\MS2-140iii\2\fid expt: <zgflqn>
transmitter freq.: 282.376241 MHz
time domain size: 131072 points
width: 67567.57 Hz = 239.282056 ppm = 0.515500 Hz/pt
number of scans: 16

freq. of 0 ppm: 282.404481 MHz
processed size: 65536 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: C13CPD32 CDCl3 u hultin 3



file: F:\NMR Data\Maya\MS2-140iv\1\fid expt: <zgpg30>
transmitter freq.: 75.476020 MHz
time domain size: 65536 points
width: 18832.39 Hz = 249.514902 ppm = 0.287359 Hz/pt
number of scans: 1300

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 0.000 GB: 0.0000