Use and Applications of Sulfur Dioxide Surrogates in the Synthesis of Sulfonyl Derivatives

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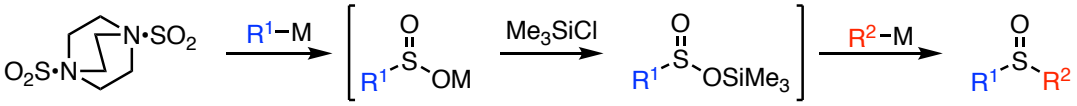
Abstract

This thesis presents the development of novel methodologies toward the synthesis of a range of sulfonyl derivative compounds. These processes employ easy-to-handle sulfur dioxide surrogate DABSO (*vide infra*) and exploit the ability of the sulfonyl functional group to react on both the sulfur atom and the oxygen atom to deliver compounds such as sulfoxides, sulfonate esters and sulfinate esters.

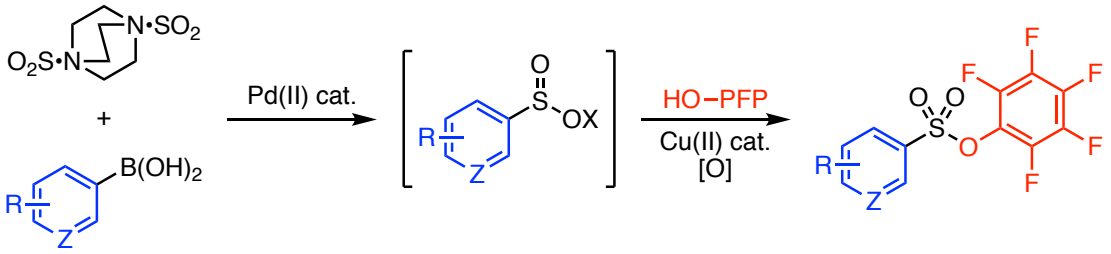
Chapter 1 is a literature review of the synthesis and applications of sulfonyl-containing compounds and the organic chemistry of sulfur dioxide. The discovery and established used of the various kind of sulfur dioxide surrogates with organometallic reagents, metal-catalysts, and metal-free conditions for the synthesis of sulfonyl-containing compounds is also described.

Chapter 2 describes the development of a one-pot process for the synthesis of unsymmetrical sulfoxides and sulfinamides using organometallic nucleophiles, DABSO, and trimethylsilyl chloride.[1] Reacting sulfur dioxide with an organometallic reagent provides a metal-sulfinate intermediate. *In situ* conversion of the sulfinate to a sulfinate silyl ester, using TMS-Cl, generates an electrophilic species, which enables the addition of a second nucleophile (an organometallic reagent or a metal-amide complex) for the synthesis of the desired sulfoxide or sulfinamide products.

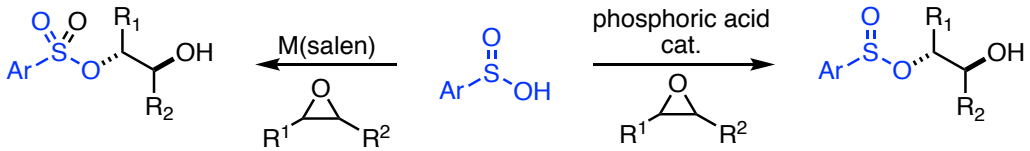


Chapter 3 details the synthesis of pentafluorophenyl sulfonate esters based on a novel copper-catalysed oxidative transformation of *in situ* generated aryl and heteroaryl

sulfinates to the corresponding sulfonate esters. The sulfinate intermediates are synthesised from boronic acids and DABSO, under the action of a palladium catalyst. The use of aryl bromides as suitable substrates for the synthesis of sulfinate ester was also established.[2]



Chapter 4 documents various catalysed processes employed to promote enantioselective ring-opening of epoxides with sulfinic acid as nucleophile. Firstly, the use of metal-salen complexes is reported and shows the formation of the corresponding β-hydroxy sulfonate ester products. Secondly, the unexpected reactivity of sulfinic acid with epoxides under the control of phosphoric acid provides a simple and attractive route to useful β-hydroxy sulfinate species.



Chapter 5 presents a summary of the research and the potential future work.

Chapter 6 provides experimental details and data.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Vincent Vedovato

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Abbreviations and Acronyms

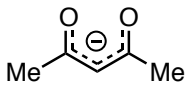
Å	Angström (10^{-10} meters)
Ac	acetyl
acac	acetylacetonate
app.	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BQ	benzoquinone
bpy	bipyridine
Bz	benzyl
cat	catalyst
Cbz	carboxybenzyl
CI	chemical ionisation
CRL	Chemistry Research Laboratory
Cy	cyclohexyl
d	doublet or deuterated
D	dimension
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane-*bis*(sulfur dioxide) adduct
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMA	dimethylamine
DMF	*N,N*-dimethylformamide
DMPS	dimethylphenylsilane
DMPU	*N,N*-dimethylpropylene urea
DMSO	dimethylsulfoxide
E	electrophile

EBX	ethynyl-benziodoxolone
EI	electron impact
EPSRC	Engineering and Physical Science Research Council
eq.	equation
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
eV	electron volt
FT	Fourier transform
g	gas or gram
GSK	GlaxoSmithKline
h	hour
HDA	hetero-Diels-Alder
hept.	heptet
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hetrz
i	iso
IR	infrared
J	coupling constant
L	ligand or litre
l	liquid
LDA	lithium diisopropylamide
LED	light-emitting diode
LHMDS	lithium hexamethyldisilylamide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	metal or molar or mega (10^{6})
m	meter or milli (10^{-3}) or multiplet
m	*meta*
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl

min	minute(s)
mol	mole
mp	melting point
MS	molecular sieves or mass spectrometry
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
m/z	mass to charge ratio
n	normal
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
[O]	oxidant
p	*para*
PEG	polyethylene glycol
PFP	pentafluorophenyl
Ph	phenyl
Pin	pinacol
ppm	parts per million
Pr	propyl
PVP	polyvinylpyridine
q	quartet
quin.	quintet
R	generic group/substituent
RM	organometallic
rt	room temperature
s	singlet or solid
s	secondary
sat.	saturated
sex.	sextet
S_N1	nucleophilic substitution (unimolecular)
S_N2	nucleophilic substitution (bimolecular)
S_Ni	nucleophilic substitution (internal)
t	triplet

t	tertiary
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS	tertbutyldimethylsilyl
TBME	*tert*-butyl methyl ether
TES	triethylsilane
Tf	triflyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl
Ts	tosyl
UV	ultraviolet
wt	weight
W	Watt
X	(pseudo)halide or generic counterion
Z	heteroatom
δ	chemical shift
μ	micro (10^{-6})
ν	frequency
Δ	heat

Ligands and Chemical Structures



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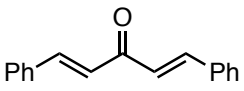

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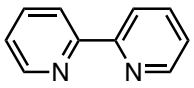

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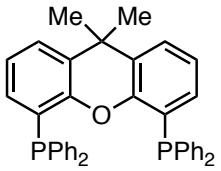
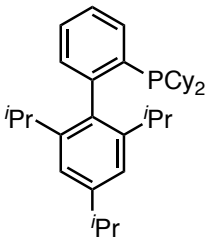


Xantphos



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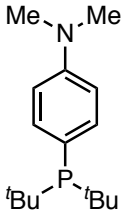

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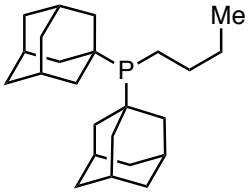

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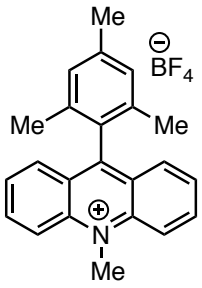

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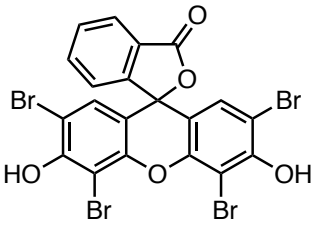

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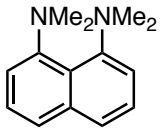

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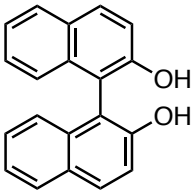

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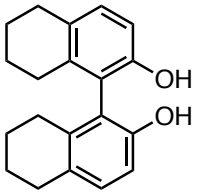


(H_8)-BINOL

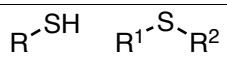
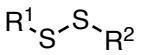
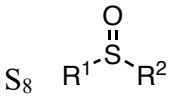
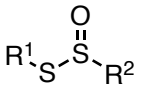
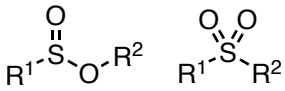
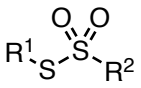
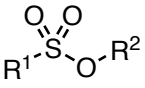
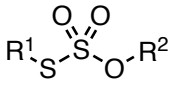
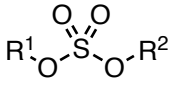
Chapter 1 - Introduction

1.1 Sulfur Oxides in Organic Chemistry

1.1.1 Biological and Synthetic Applications

The importance of organosulfur compounds has been extensively studied and documented.[3-5] Due to the availability of the sulfur *d*-orbital, there are a plethora of functional groups in sulfur chemistry. A wide range of oxidation states are therefore accessible for the sulfur atom. Sulfur oxidation states can vary from -2 to +6 (Table 1).

Table 1 Examples of organosulfur moieties depending on the sulfur oxidation state

Oxidation State of Sulfur	Example
-2	
-1	
0	
+1	
+2	
+3	
+4	
+5	
+6	

Sulfoxides, sulfones, sulfonamides, sulfonyl halides, and sulfonate esters are among the most ubiquitous sulfur containing moieties in modern organic chemistry. These

distinct functional groups are commonly found in many target molecules in the pharmaceutical,[6-9] agrochemical,[10,11] materials,[12,13] and food additives industry (Figure 1.1).[14] In fact, sulfonamides have found such a broad application within the pharmaceutical industry, mainly due to their antibacterial properties, that the term 'sulfa drug' was created to represent this class of compounds.[15]

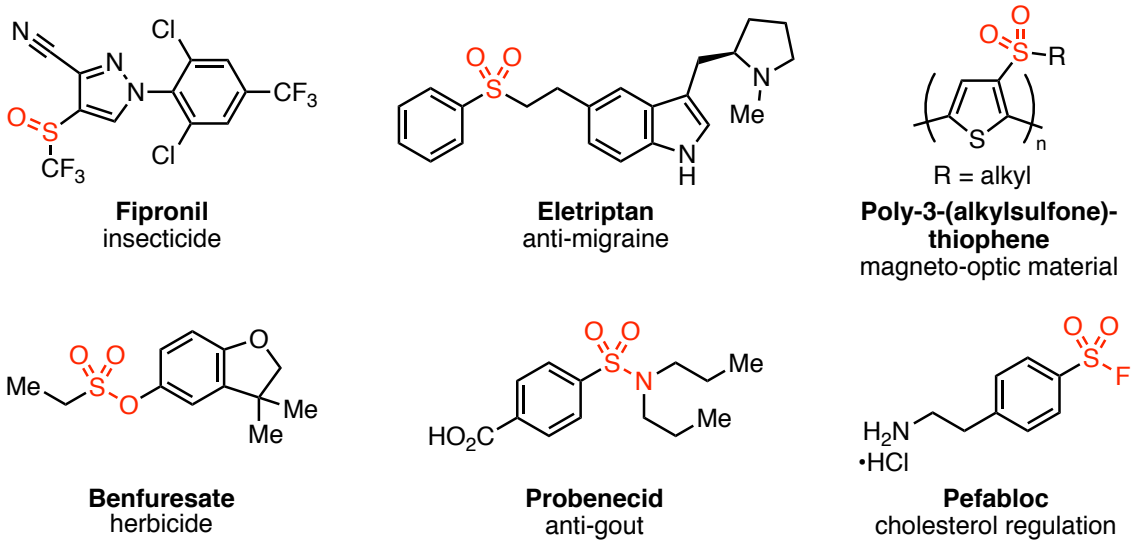
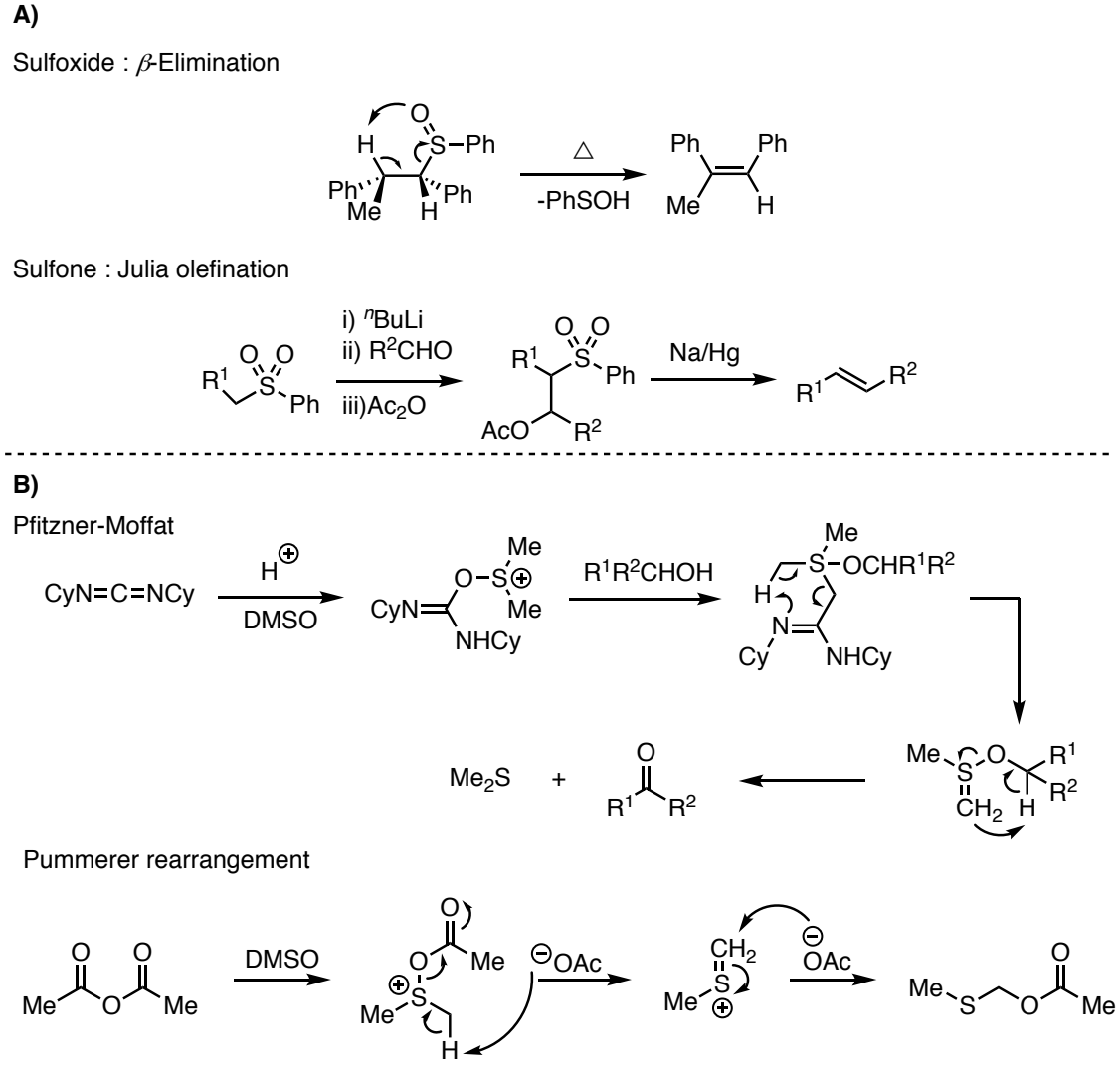


Figure 1.1 Examples of pharmaceutical, agrochemical, and material target molecules containing different sulfur oxide functional groups

Aside from their attractiveness as biologically active molecules, organosulfur compounds have been used extensively as synthetic intermediates.[16-18] While sulfonamides are commonly known to be used as protecting groups for amines,[19,20] sulfones and sulfoxides have also been employed in desulfonylative reactions, such as the *β*-elimination reactions,[21-23] or the Julia olefination,[24,25] allowing easy access to alkene products, through extrusion of the sulfinyl or sulfonyl motif (Scheme 1.1, A). Due to the ambidentate nature of sulfoxides, they can be both nucleophilic, with electron donation possible at both the oxygen and sulfur, and electrophilic, upon activation of the oxygen to give an electrophilic sulfur atom.[26] These remarkable properties have established sulfoxide containing compounds as an important class of reagents in organic chemistry.

As a result, sulfoxides have been use in a wide range of transformations,[27] such as the Pfitzner-Moffatt reaction,[28,29] for the oxidation of primary or secondary alcohols, or the Pummerer rearrangement,[30-32] for synthesis of α-acyloxy-thioether (Scheme 1.1, B). Furthermore, due to the coordinating abilities of the sulfoxide moiety, sulfoxides have been explored in catalysis either as directing groups for *ortho* C-H activation, or as ligands for asymmetric catalysis (Section 2.1.1).



Scheme 1.1 Examples of chemical transformations utilizing sulfones and sulfoxides

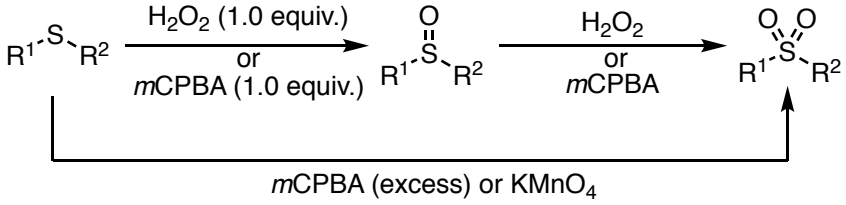
Other species such as sulfinate esters,[33] sulfonate esters,[34] as well as sulfonate halides,[35,36] can act as good electrophiles. Thus, they have been employed almost

exclusively as leaving groups, yielding the corresponding sulfoxides, sulfones, and sulfonamides.[37]

1.1.2 Synthesis of Organosulfur Oxide Compounds

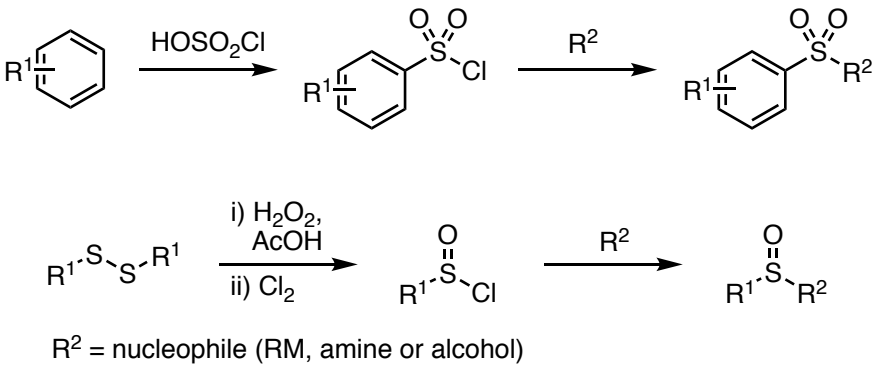
Organosulfur oxide compounds have found such a widespread utility in various industries that a great number of methodologies have been developed for their synthesis. Nevertheless, only three methodologies are utilised predominantly to incorporate the desired sulfur oxide moiety into target molecules.

Firstly, the oxidation of sulfenyls or sulfides to the corresponding sulfur oxide functional group is the most commonly employed method for the synthesis of sulfoxides and sulfones (Scheme 1.2).[38-41] However, this process requires strong oxidising agents such as hydrogen peroxide,[42] *m*CPBA,[43,44] or $KMnO_4$.[45] As only a restricted range of functional groups can tolerate such harsh conditions, the application of this method can be limited.



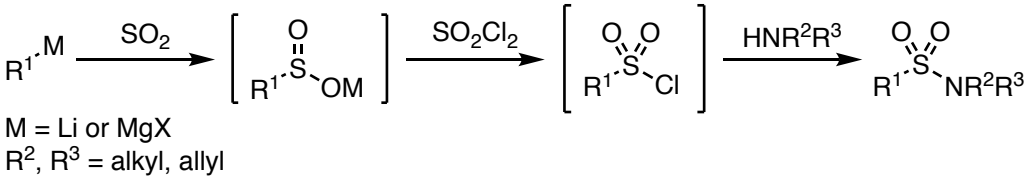
Scheme 1.2 Synthesis of sulfoxide and sulfone *via* oxidation

Secondly, sulfinyl halides and sulfonyl halides can deliver, in an efficient manner, different organosulfur oxide moieties (e.g. sulfoxides, sulfones, sulfonamides, sulfinate and sulfonate esters), through nucleophilic displacement of the halide.[37,46] Nonetheless, the syntheses of starting materials are often challenging and require harsh acidic conditions (Scheme 1.3),[47,48] which can pose a serious problem for functional group tolerance.



Scheme 1.3 Synthesis of sulfoxides and sulfonyl derivatives utilising sulfinyl and sulfonyl halides as intermediates

Finally, sulfur dioxide gas can be employed in combination with organometallics (e.g. organolithiums or Grignard reagents), to directly integrate the sulfonyl moiety (-SO_2-). This protocol allows the *in situ* formation of metal sulfinate intermediates, which upon reaction with sulfuryl chloride, produces sulfonyl chloride intermediates that allow easy access to sulfones, sulfonate esters, and sulfonamides (Scheme 1.4).[49] It has also been reported that a similar method has been used for a Sandmeyer reaction by employing diazonium reagents as starting materials.[50] However, the methodology presents an inconvenience in the use of sensitive starting materials and toxic, difficult to handle, sulfur dioxide gas.



Scheme 1.4 Synthesis of sulfonyl derivatives with *in situ* formation of the metal sulfinate intermediate

Given the extensive use of organosulfur oxide compounds in modern organic chemistry and the limitations of these protocols, there is a need for the development of novel methodologies that exhibit milder conditions, higher selectivity and versatility, for the incorporation of the sulfur oxide functional groups in organic molecules.

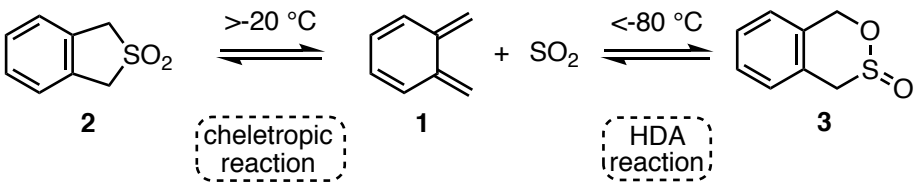
1.2 Sulfur Dioxide

1.2.1 General

Sulfur dioxide is a colourless gas with a pungent odour. It is a common air pollutant produced naturally by active volcanoes and forest fires. However, the majority of the sulfur dioxide present in the atmosphere is due to the burning of coal and oil at large industrial plants, such as oil refineries and power stations. Sulfur dioxide is produced on a vast scale of millions of tonnes per annum and is mainly used as a chemical intermediate in the production of sulfuric acid and other sulfonyl derivatives. Because of its antimicrobial properties, sulfur dioxide is also used in the food industry as a preservative (E220). It is frequently used in the winemaking process as an antioxidant.

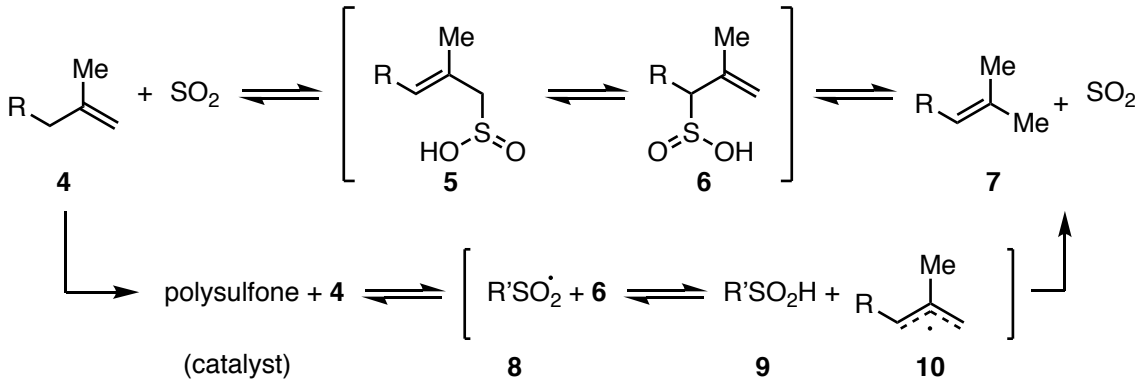
1.2.2 Sulfur Dioxide in Organic Chemistry

The most widely known type of organic reactions involving sulfur dioxide as a reagent are pericyclic reactions. Some of the pioneering work reported the homocheletropic and cheletropic addition of gaseous SO_2 to 1,4-dienes, delivering sulfolane products.[51] Further studies showed that hetero-Diels-Alder (HDA) addition of sulfur dioxide with highly reactive dienes **1** could readily deliver cyclic sulfinic acid esters **3** at low temperature (Scheme 1.5).[52,53] Other cycloadditions of sulfur dioxide to ketenes,[54] ketimines,[55] cyclic polyenes,[56,57] and quadricyclane have also been reported.[58]



Scheme 1.5 Examples of pericyclic reactions using SO_2 as a reagent

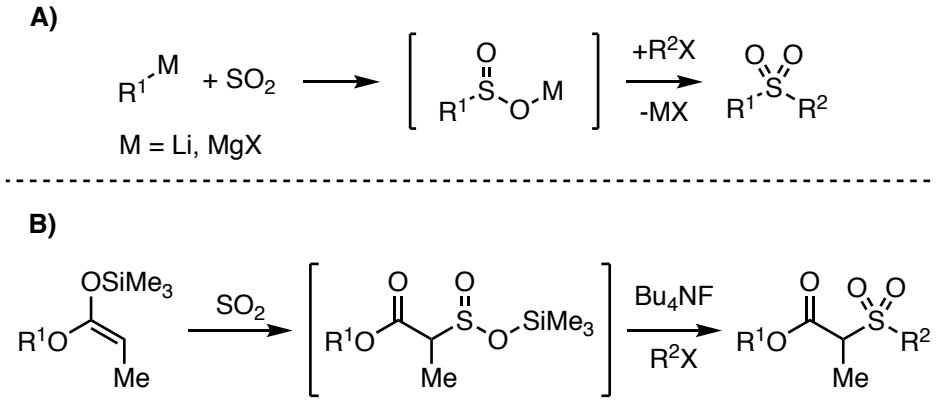
Employing sulfur dioxide to induce double bond migration in alkenes is also well documented (Scheme 1.6).[59] The proposed mechanism for this transformation is commonly accepted as an ene-reaction between SO_2 and alkene **4**, to give a β,γ-unsaturated sulfinic acid intermediate **5**. Intermediate **5** then undergoes a [1,3]-sigmatropic shift, delivering an isomeric β,γ-unsaturated sulfinic acid **6**, which upon a retro-ene reaction, eliminates sulfur dioxide to give isomeric alkyne **7**.[60] Vogel and co-workers' work on this reaction showed conclusive evidence of a radical-based mechanism with the *in situ* formation of a polysulfone, which acts as an organocatalyst that promotes the alkene isomerisation. The isomerisation of alkene **4** to alkene **7** can also be induced by heat (80 – 120 °C) or UV irradiation.[61]



Scheme 1.6 SO_2 induced alkene isomerisation

Gaseous sulfur dioxide has been extensively used as a reagent for the synthesis of sulfones. Indeed, one of the most documented and widely used method for utilising SO_2 is to first condense it before reducing into sulfur dioxide anion with organometallic reagents (most commonly Grignard reagents or organolithium reagents).[49,62] The anionic sulfinate intermediate could then further react with allyl halides or Michael acceptors to give the desired sulfones (Scheme 1.7, eq. A).[63] However, this method suffers from severe drawbacks due to the use of sensitive reagents and gaseous SO_2. Following on from his previous work, Vogel and co-workers also developed an ene-reaction of sulfur dioxide

with silyl enol ethers to generate stable silyl sulfinates, which upon activation can be trapped by a variety of electrophiles to deliver the desired sulfones in one pot (Scheme 1.7, eq. B).[64,65]



Scheme 1.7 Examples of SO_2 incorporation *via* reaction with organometallic species (A) and *via* ene-reaction with silyl enol ether (B)

1.2.3 Sulfur Dioxide in Inorganic Chemistry

Although the first sulfur dioxide-transition metal complex was reported by Gleu in 1938,[66,67] it was only in the 1960s that spectroscopic and structural studies revealed the versatility of sulfur dioxide as a ligand, made aware by extensive studies of platinum-sulfur dioxide complexes.[68-70] The small molecule of SO_2 displays a variety of bonding modes (Figure 1.2, A) and this phenomenon can be understood by looking at the frontier orbitals of sulfur dioxide (Figure 1.2, B).[71-73] Molecular orbital calculations indicated that the HOMO of SO_2 is concentrated primarily on the sulfur atom, with contributions from the oxygen 2*p* orbitals. This orbital possesses an a_1 symmetry and is often referred as the SO_2 "lone pair" orbital. Due to its weak antibonding character between S atom and O atom, and bonding character between O atoms, the HOMO is suitable for electron donation into an empty orbital with the appropriate symmetry. Theoretical studies also demonstrated that sulfur dioxide possesses a LUMO of b_1 symmetry. This orbital is suitable for back donation from a metal atom with filled *d* orbitals. Therefore, the HOMO

and LUMO are considered to be symmetrically equivalent to the frontier orbitals of a carbene, and complexes of type I are consequently closely related in structure to carbene complexes.[74,75]

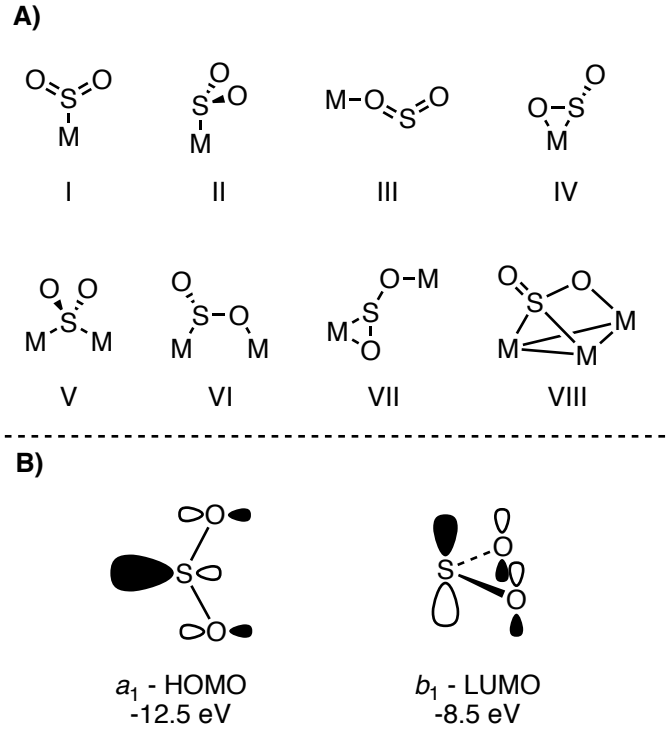
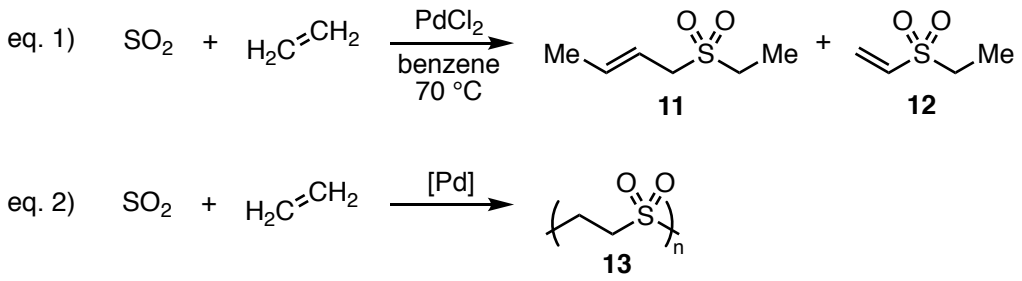


Figure 1.2 Different types of SO_2 complexes and the frontier orbitals of SO_2 and their energies

On the other hand, hard Lewis acids prefer to coordinate to the oxygen atoms (Figure 1.2, complex III), with the $SO_2.SbF_5$ adduct being a typical example of such systems.[76] Due to a non-negligible coefficient on the oxygen atoms in the LUMO, SO_2 can also coordinate to a transition metal side-on (Figure 1.2, complex IV), but this type of coordination is limited to electron rich complexes.[77,78] In polynuclear complexes, the SO_2 is almost exclusively bonding as a carbene-type 2-electron bridging ligand (Figure 1.2, complex V).[79] The SO_2 in complexes VI,[80] VII,[81] and VIII[82] (Figure 1.2) functions as a 4-electron donor and can be considered as products of an electrophilic attack on the oxygen atoms of complexes of type II, IV and V, respectively.

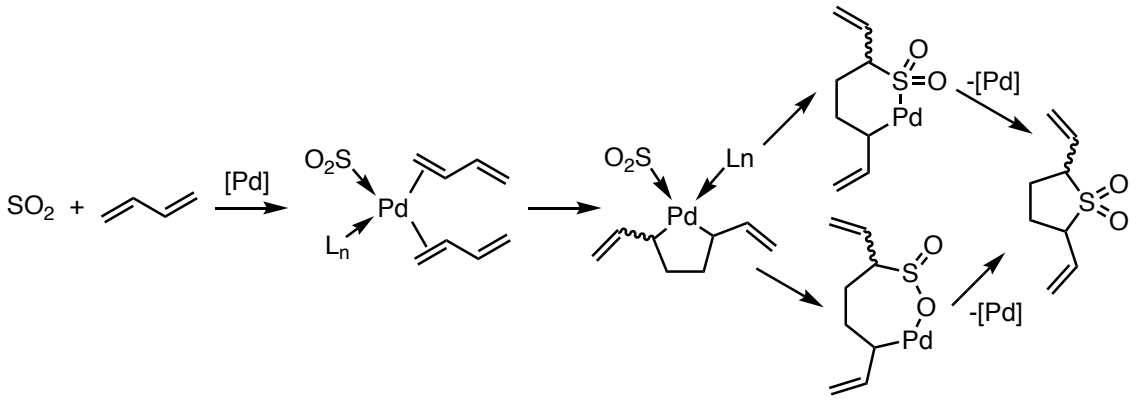
1.2.4 Sulfur Dioxide in Transition Metals Catalysis

Despite the importance and ubiquity of the sulfonyl moiety, examples of sulfonylative processes utilising transition metal catalysts and gaseous SO_2 for direct incorporation of sulfur dioxide into organic molecules are still relatively limited. The first example of a sulfinato complex formed from the metal-mediated incorporation of the sulfonyl moiety was reported in 1968.[83] It featured the reaction of ethylene with sulfur dioxide in the presence of $PdCl_2$ to deliver a mixture of ethyl trans-2-enyl sulfone **11** and ethyl vinyl sulfone **12** (Scheme 1.8, eq. 1). Later, by employing different sets of reaction conditions, an array of palladium catalysts was able to promote the formation of a perfectly alternating ethylene-sulfur dioxide copolymer **13** (Scheme 1.8, eq. 2).[84]



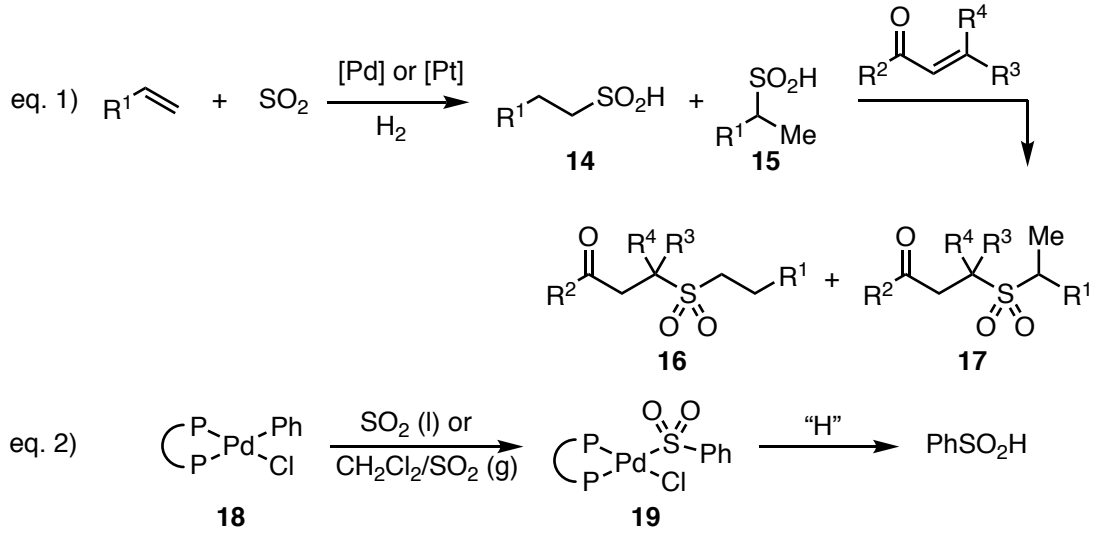
Scheme 1.8 Palladium-catalysed reactions between SO_2 and ethene

Following this work, Kunakova and co-workers reported the palladium-catalysed transformation of 1,3-dienes into divinylsulfolanes (Scheme 1.9).[85] In this study, a large excess of the triphenylphosphine ligand was required to keep the catalyst active in the presence of SO_2. A similar observation was previously made by Goldwhite and co-workers in their study on the reactions between sulfur dioxide and phosphines.[86] Kunakova *et al.* postulated that the insertion of SO_2 into the metal-carbon bond led to two types of complexes which are then able to deliver the desired products in good yields.



Scheme 1.9 Palladium-catalysed formation of sulfonlane from SO_2 and 1,3-diene

Another achievement in this field was the development of the hydrosulfination reaction using either palladium or platinum as catalysts (Scheme 1.10, eq. 1).[87] The utility of this process was further demonstrated by the reaction of the formed sulfinic acids **14** and **15** with Michael acceptors, readily delivering substituted sulfones **16** and **17**.[88] It is worth noting that, in order to prove the postulated mechanism for the hydrosulfination, Goddard and co-workers isolated the first Pd-SO_2 intermediate (**19**) formed *via* the insertion of SO_2 into the palladium-phenyl bond, which later gave the sulfinic acid (Scheme 1.10, eq. 2).[88]



Scheme 1.10 Palladium and platinum-catalysed hydrosulfination and isolation of the complex leading to sulfinic acid

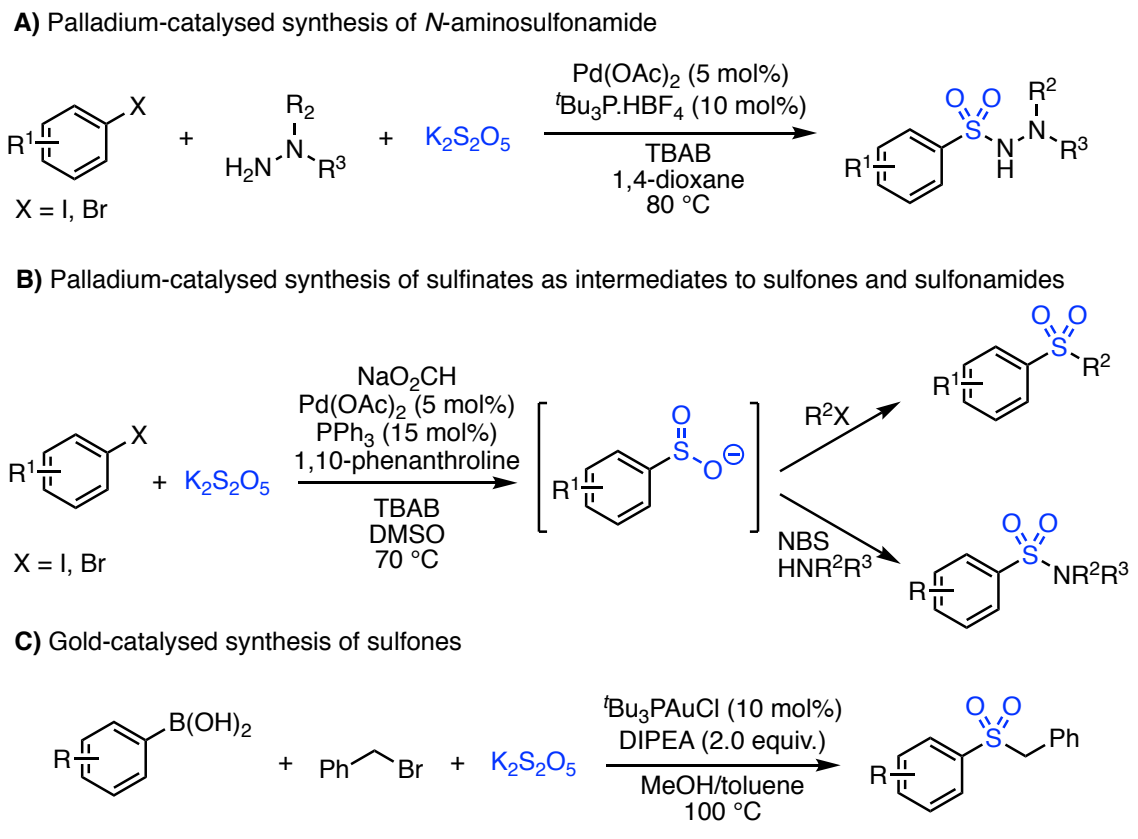
1.3 Sulfur Dioxide Surrogates

Although the direct use of sulfur dioxide for sulfonylative reactions presents advantages due to its versatility as a reagent that allows access to a wide range of compounds, the synthetic application of these processes is arguably still limited. The primary reason is due to the inconvenience that arises from the use of a toxic gaseous reagent, where a specialised pressurised equipment and additional safety precautions are necessary. Furthermore, there is difficulty in controlling the amount of sulfur dioxide incorporated into the reaction, causing sulfur dioxide to be used in large excess, whether as a gas or liquid. As such, the highly reactive sulfur dioxide can result in undesired side reactions and/or catalyst poisoning.

The recent and rapid development of the chemistry related to SO_2 incorporation into organic molecules arises from the development of innocuous and bench-stable sulfur dioxide surrogates. Sulfur dioxide surrogates are mostly solids, which under certain conditions will decompose and release sulfur dioxide *in situ*. The use of surrogates is a practical and convenient method because it removes the need for specialised equipment and reduces the safety risks associated with the toxicity of sulfur dioxide. Furthermore, using sulfur dioxide surrogates allows controlled loading of sulfur dioxide, thereby limiting possible metal catalyst sequestration. Due to the series of advantages sulfur dioxide surrogates present, paired together with the previously demonstrated ubiquity of organosulfur oxide compounds in the pharmaceutical and the agrochemical industry, it is unsurprising to see numerous methodologies exploiting the use of these surrogates to insert SO_2 into target molecules in a safer and Greener way. It is important to note that sulfur dioxide surrogates are not simply alternatives to sulfur dioxide gas, they also provide additional distinct reactivities.

1.3.1 Inorganic Salts

The ability of inorganic metal sulfite/metabisulfite salts (M_2SO_3, $M_2S_2O_5$) to release sulfur dioxide, upon treatment with protonic acid, has been known and well documented over the years. These metal sulfites are commercially available and easy-to-handle solids, and their applications to chemical transformations were pioneered by Beller and co-workers. Sodium sulfite (Na_2SO_3) was used to produce sulfur dioxide *ex situ*, and the gas produced was later transferred into the sulfur dioxide insertion reaction mixture *via* a two-chamber reaction vessel, in order to perform a palladium-catalysed aminosulfonylation.[89] On the other hand, *in situ* formation of sulfur dioxide can be achieved by using potassium metabisulfite ($K_2S_2O_5$). This method was exploited for several palladium-catalysed sulfonylative transformations (Scheme 1.11, eq. A and B).[90,91] The ability of $K_2S_2O_5$ to release SO_2 *in situ* was also applied to a gold-catalysed sulfone synthesis, in a one-step method (Scheme 1.11, eq. C).[92]



Scheme 1.11 $K_2S_2O_5$ based, transition metal-catalysed sulfonylative reactions

1.3.2 Amine-Sulfur Dioxide Complexes

The ability of sulfur dioxide and amines to form complexes have been reported since the mid-1800s, however, no real attention was given to these complexes. Later in the early 1900s, a wide range of amine-sulfur dioxide complexes such as anilines,[93] pyridines,[94] ammonia,[95] secondary and tertiary amines,[96,97] were isolated (Figure 1.3). These studies focused on investigating the structures and the bonding properties of the complexes rather than their applications. These charge transfer adducts were formed by a dative covalent bond between the Lewis basic nitrogen atom of the amine and the Lewis acidic sulfur of sulfur dioxide.

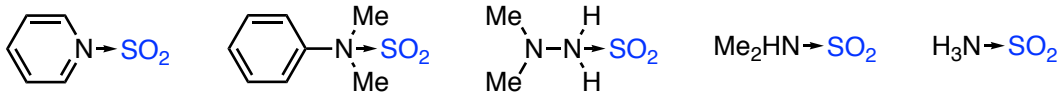
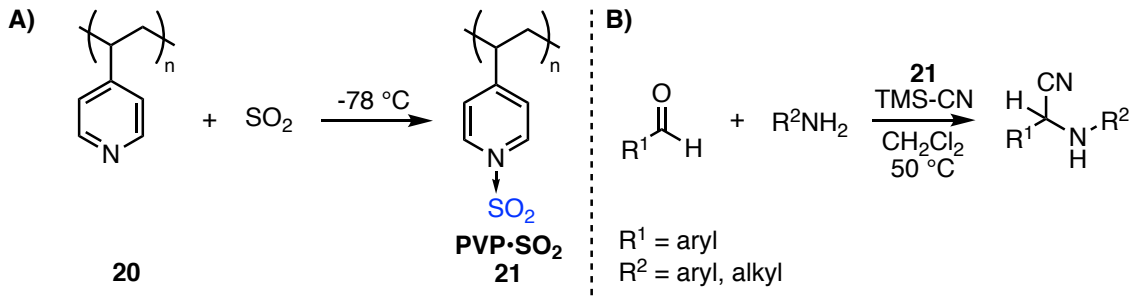


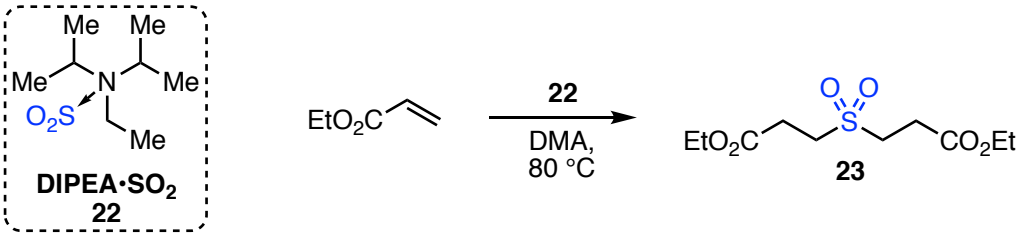
Figure 1.3 Examples of amine-sulfur dioxide charge transfer adducts

Olah and co-workers were the first to report the use of trimethylamine and triethylamine complexes as reagents for organic chemical transformation. With these complexes, they performed the dehalogenation of α-halo-ketones,[98] the reduction of sulfoxides,[99] and the reduction of pyridine *N*-oxides.[100] These reactions were previously performed with gaseous SO_2. Following on this work, the authors prepared a polyvinylpyridine-sulfur dioxide complex **21** (PVP·SO_2) and demonstrated its ability to act as a mild acid catalyst in a Strecker-type synthesis of α-aminonitriles (Scheme 1.12, eq. A and B).[101]



Scheme 1.12 Preparation of PVP·SO_2 and Strecker reaction catalysed by PVP·SO_2

The first example of amine-sulfur dioxide complex being used for the insertion of sulfur dioxide in organic synthesis was reported by Eugène *et al*. Diisopropylethylamine-SO_2 complex **22** (DIPEA·SO_2) was isolated and reacted with a ethyl acrylates to form symmetrical sulfone **23** (Scheme 1.13).[102]

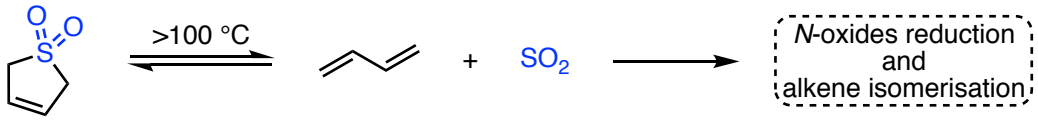


Scheme 1.13 DIPEA·SO_2 based, sulfonylation of Michael acceptor

More recently, 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) complex (DABCO·$(SO_2)_2$ or DABSO) was reported by the Willis group as a reliable sulfur dioxide surrogate for organic transformations.[103,104] They established that DABSO can not only be used as a direct replacement for gaseous sulfur dioxide, but have also developed novel processes with it (see Section 1.4).

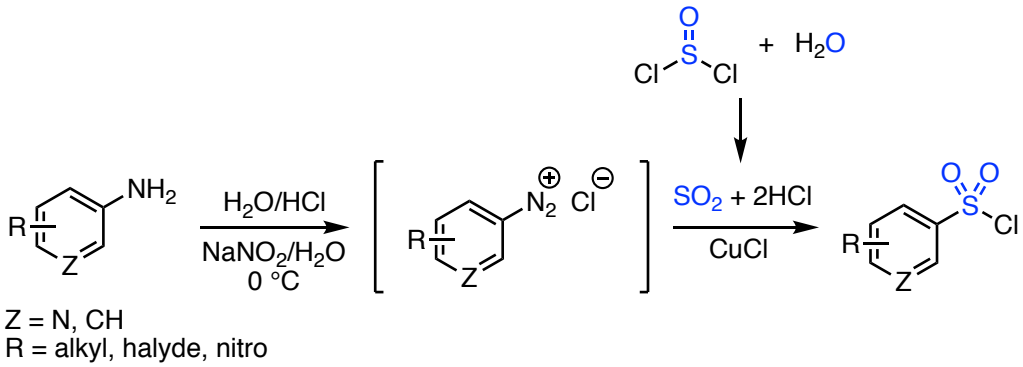
1.3.3 Miscellaneous Sulfur Dioxide Surrogates

Other procedures for generating sulfur dioxide *in situ* have also been documented. While 3-sulfolene is commonly used as a masked butadiene reagent,[105] it can also produce sulfur dioxide and butadiene through a thermal cheletropic extrusion reaction (Scheme 1.14). Yamamoto and co-workers used this protocol to perform two well-known reactions: the reduction of *N*-oxides and the isomerisation of steroidal alkenes.[106] Nonetheless, the harsh conditions required to release sulfur dioxide and the formation of the reactive molecule butadiene led to undesired side reactions.



Scheme 1.14 Use of sulfolene as a source of SO_2 for organic transformations

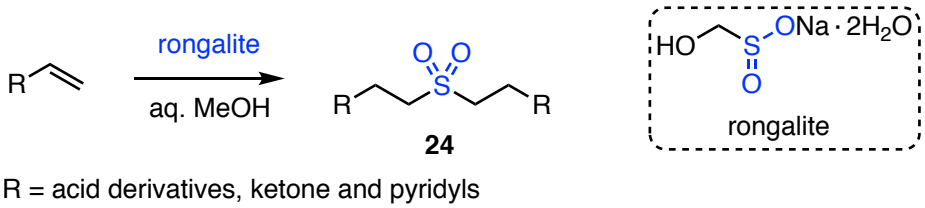
The production of sulfur dioxide *in situ* can also be achieved *via* the reaction of thionyl chloride with water. This method has been used in the Sandmeyer reaction for the production of sulfonyl chlorides (Scheme 1.15).[107] Although the approach is tolerated under harsh aqueous hydrochloride acid conditions necessary for the Sandmeyer reaction, there were still several drawbacks present. The process is very exothermic and produces hydrochloride acid as a by-product, which may limit the functional group tolerance.



Scheme 1.15 Thionyl chloride as a source of SO_2 in Sandmeyer chemistry

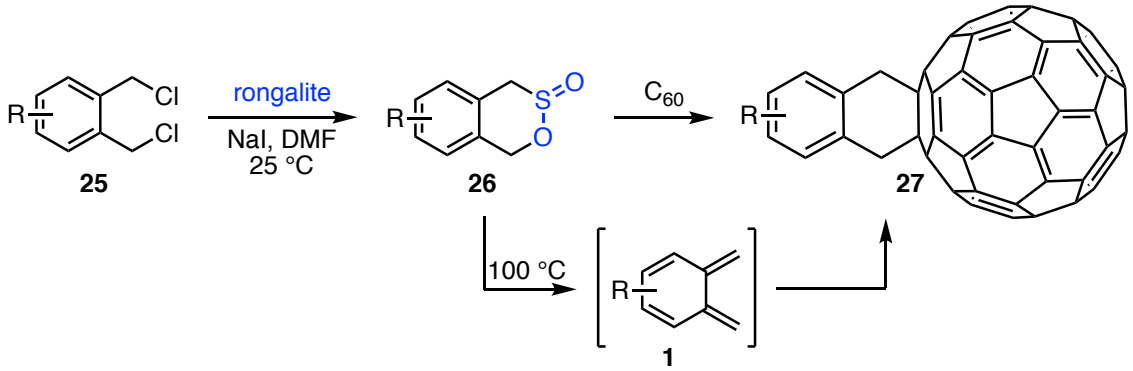
Rongalite (sodium formaldehyde sulfoxylate, with the chemical formula $HOCH_2SO_2Na{\bullet}2H_2O$), is a commercially available solid that has found applications in a wide range of synthetic transformations. Notably, this reagent introduces a -SO_2- unit, upon decomposition, as a radical anion $SO_2^{-\bullet}$ or an anion SO_2^{2-} rather than a direct source of SO_2. The utilisation of rongalite for sulfur dioxide incorporation has been documented since the early 1900s, when Fromm and co-workers first described the reaction between rongalite and benzyl chlorides in aqueous alcohols to deliver dibenzylsulfones.[108] Later,

Kerber and co-workers reported the rongalite-mediated synthesis of *β,β'*-disubstituted diethyl sulfones **24** in aqueous methanol (Scheme 1.16).[109]



Scheme 1.16 Rongalite based synthesis of diethyl sulfones

Dittmer and co-workers have also demonstrated the use of rongalite in the synthesis of sultines (Scheme 1.17).[110] Rongalite was first reacted with *α,α'*-dichloro-oxylenes **25** and sodium iodide to give the desired sultines **26**. Under thermal conditions, sultines **26** readily decompose to deliver diene **1** *in situ*. Sultines have been used extensively as precursors for Diels-Alder reactions with one of the most notable examples being their utilisation for the preparation of functionalised fullerene derivatives **27** under mild conditions.[111]



Scheme 1.17 Rongalite based synthesis of sultines and their use as diene precursor for Diels-Alder reactions

Rongalite has also been employed as a reagent for numerous other types of reactions that do not involve sulfur dioxide insertion into organic molecules. An excellent review

published by Sambasivarao *et al*. presents an overview of the applications of rongalite in modern organic chemistry.[112]

1.4 1,4-Diazabicyclo[2.2.2]octane *bis*(sulfur dioxide), DABSO

In 1988, Santos *et al.* documented the isolation and the Raman spectroscopy of the complex formed between tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO) and two molecules of sulfur dioxide.[113] However, no application of this complex in organic synthesis was reported until 2010, when the Willis group described the utilisation of the 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) complex (which they named DABSO, **28**) as a reliable sulfur dioxide surrogate (Figure 1.4). DABSO is a bench-stable and easy-to-handle white solid, with >50 wt% SO_2. As a result, the amount of waste generated is considerably reduced despite employing an amine carrier. DABSO can be readily prepared in bulk by condensing sulfur dioxide on solid DABCO. Allowing the reaction mixture to warm to room temperature followed by the evaporation of the remaining SO_2 gives DABSO as a pure solid that does not require any further purification. Bischoff *et al*. also documented the synthesis of DABSO using DABCO and the Karl-Fisher reagent.[114]

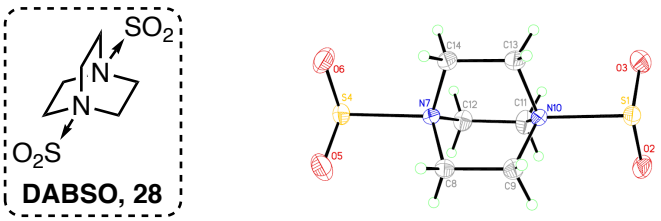
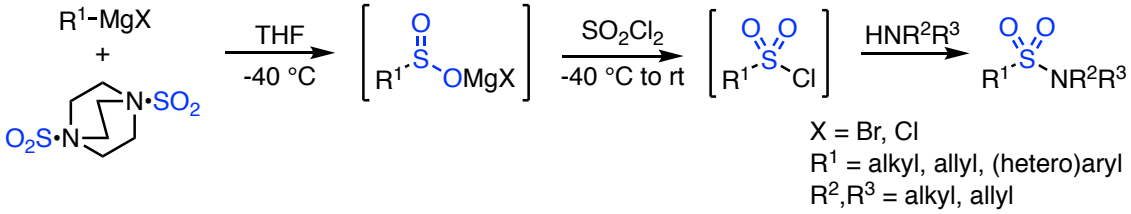


Figure 1.4 Structure of the charge transfer adduct DABSO

1.4.1 Application with Non-Transition Metals

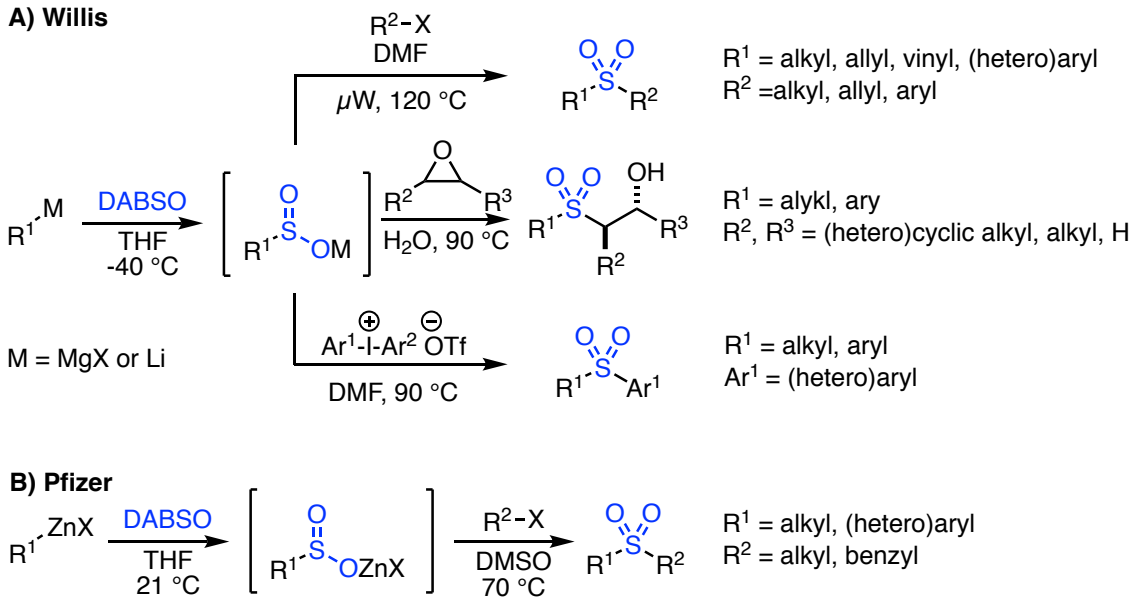
The use of sulfur dioxide gas in combination with organometallic reagents such as Grignard,[49,63] organolithium,[115] and organozinc[116] are well established processes for the

synthesis of sulfinate salts. These salts are privileged starting material for the synthesis of various sulfonyl containing functional groups (e.g. sulfones,[63,117,118] sulfonyl chlorides,[62] and sulfonamides[49]) due to their versatility. However, the scope of commercially available sulfinate salts is limited to a handful of sodium salts. Therefore, the *in situ* formation of metal sulfinates offers a significant improvement in the availability of starting materials for these transformations. In 2003, Barrett and co-workers documented the one-pot synthesis of sulfonamides using Grignard reagents and SO_2 gas to form the magnesium sulfinates, which were thereon oxidised *in situ* to the sulfonyl chlorides. The chloride can then be displaced by the appropriate amine, to afford the desired sulfonamides.[49] Willis and co-workers were able to demonstrate the ability of DABSO to act as an efficient sulfur dioxide surrogate by adapting the sequence reported by Barrett (Scheme 1.18).[119] Indeed, by combining a Grignard reagent with DABSO, the authors were able to generate the desired magnesium sulfinates, which after oxidation, reacted with the appropriate amines to deliver the desired sulfonamides in an efficient manner.



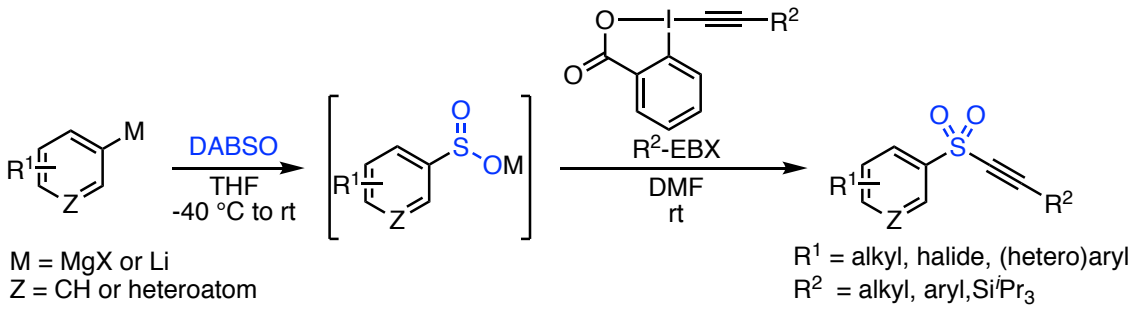
Scheme 1.18 DABSO based sulfonamide synthesis

More recently, the Willis group and a group from Pfizer, documented independently, a one-pot synthesis of sulfones, based on the reaction of organolithium, Grignard, or organozinc reagents with DABSO (Scheme 1.19).[120,121] The resulting metal sulfinate species was further transformed *in situ* upon reaction with a library of electrophiles.



Scheme 1.19 DABSO based synthesis of sulfones

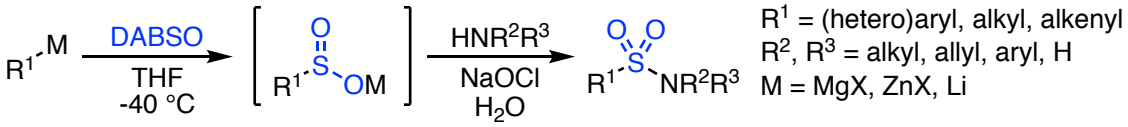
With the use of DABSO over sulfur dioxide gas, both methods provided a safe and straightforward sulfone synthesis, with access to a wild range of substrates. To further expand the scope of sulfones accessible through the reaction of DABSO with organometallic reagents, Waser and co-workers documented the *in situ* reaction of magnesium sulfinates with ethynyl-benziodoxolone (EBX) reagent (Scheme 1.20).[122] This unprecedented one-pot, three-component procedure delivered numerous arylalkynyl sulfones in an efficient manner.



Scheme 1.20 DABSO based synthesis of arylalkynyl sulfones

As a follow up, the Willis group further explored the opportunities offered by the reaction of DABSO with an organometallic reagent. In 2013, they established that the

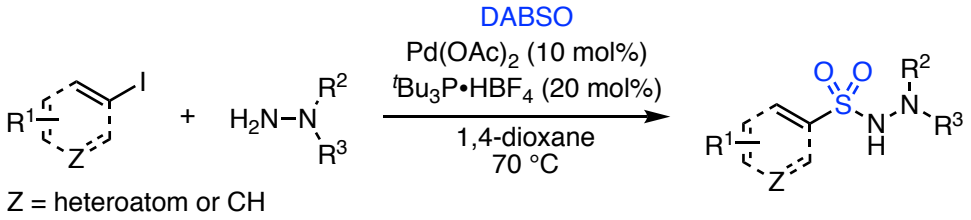
lithium sulfinate species, arising from the reaction of lithium aryls with DABSO, could be further transformed into diarylsulfones *via* a palladium(0)-catalysed reaction with aryl bromides.[123] In 2014, the same group reported a one-pot sulfonamide synthesis. This procedure was based on the reaction of metal sulfinates and *N*-chloroamines, both generated *in situ* under oxidative reaction conditions (Scheme 1.21).[124] With this robust protocol, the synthesis of a great number of sulfonamides bearing a wide range of functional groups was made possible.



Scheme 1.21 DABSO based synthesis of sulfonamides under oxidative reaction conditions

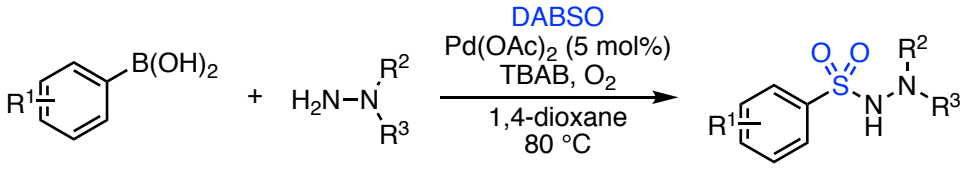
1.4.2 Applications with Transition Metals

The first example of a transition metal-catalysed sulfonylative reaction, using DABSO as a sulfur dioxide source, was reported in 2010 by Willis *et al.* in a palladium-catalysed aminosulfonylation reaction.[125] They initially documented a palladium(0) catalytic system which promoted the coupling of hydrazines and aryl iodides in the presence of DABSO as a SO_2 source (Scheme 1.22). A series of aryl, heteroaryl and alkenyl iodides, bearing diverse functional groups, were successfully coupled with a range of hydrazines under these reaction conditions. Only a very slight excess of DABSO (1.1 equiv.) was needed to enable an efficient catalytic turnover, thereby demonstrating the ability of this surrogate to release SO_2 molecules complexed to it without causing catalyst poisoning. However, no other nucleophilic coupling partner other than hydrazines could be tolerated in this protocol.



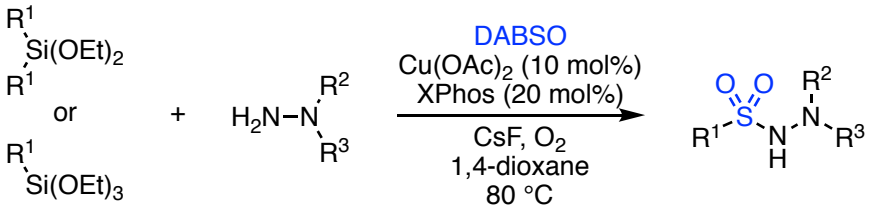
Scheme 1.22 DABSO and aryl iodides used in a palladium-catalysed aminosulfonylation reaction

The Wu group later demonstrated a similar aminosulfonylation employing arylboronic acids instead.[126] A palladium(II) catalyst was used under oxidative conditions (Scheme 1.23). This method proceeded well with arylboronic acids bearing various functional groups. However, they noted that similar to what the Willis group had observed, only hydrazines could be tolerated as the amine nucleophile in this process.



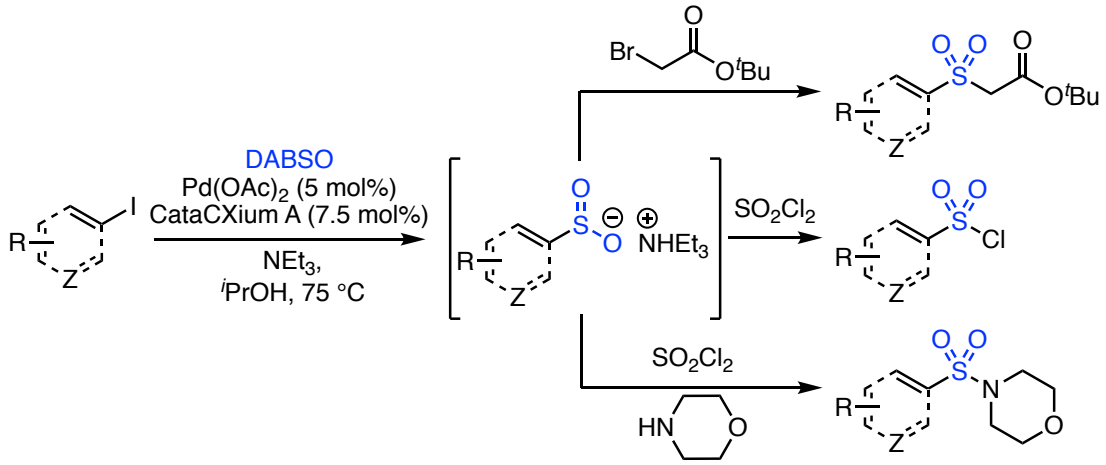
Scheme 1.23 DABSO and arylboronic acids used in a palladium-catalysed aminosulfonylation reaction

Additionally, Wang and co-workers documented a copper-catalysed three-component reaction of triethoxysilane, DABSO and hydrazines to generate *N*-aminosulfonamides under oxidative conditions (Scheme 1.24).[127] Several triethoxy(aryl)silanes, triethoxy(alkyl)silanes, and diethoxy(diaryl)silanes proved to be compatible in their protocol, but again, only hydrazines appeared to be effective nucleophiles for this coupling.



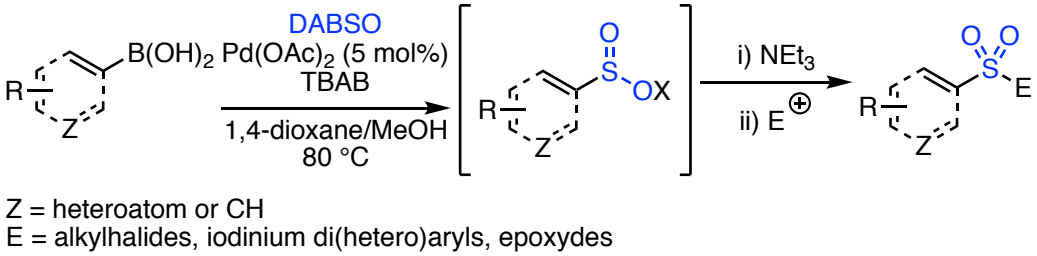
Scheme 1.24 DABSO and silanes used in a copper-catalysed aminosulfonylation reaction

In 2014, Willis and co-workers developed the first palladium-catalysed sulfonylative reaction using DABSO which is not exclusive to hydrazines as coupling partners (Scheme 1.25).[128] They were able to transform a wide range of aryl, heteroaryl, and alkenyl iodides into the corresponding ammonium sulfinates. In order to obtain a turnover in this palladium(0)/palladium(II) catalytic system, isopropanol was used as both the solvent and the essential reductant for the palladium catalysis. The ammonium sulfinate salts could then be transformed *in situ* into a variety of sulfonyl functional groups.



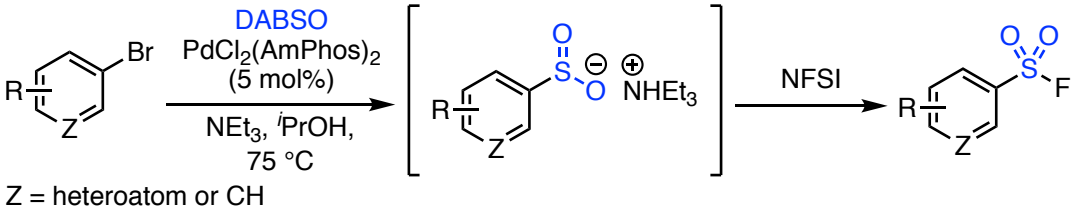
Scheme 1.25 Palladium(0)-catalysed ammonium sulfinate synthesis using DABSO and alkenyl and (hetero)aryl iodides

Later, the Willis group developed a sulfinate synthesis based on a redox-neutral palladium(II) system. By using arylboronic acids with DABSO and commercially available palladium(II) acetate, they generated various ammonium sulfinate species (Scheme 1.26).[129] This method not only extended the scope of the reaction reported previously, it also removed the necessity of employing an expensive phosphine ligand, and drastically decreased the reaction time needed for the sulfinate formation from 16 hours to 30 minutes. The sulfinates were then reacted *in situ* with a range of electrophiles, leading to the desired sulfones and sulfonamides.



Scheme 1.26 Palladium(II)-catalysed ammonium sulfinate synthesis using DABSO and arylboronic acids

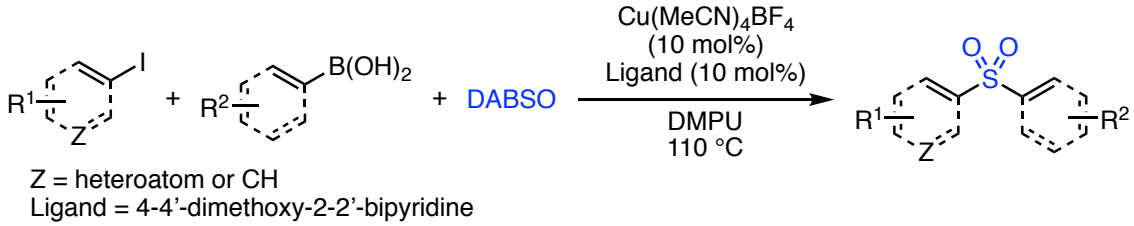
Then in 2017, the Willis group documented the first palladium-catalysed synthesis of sulfonyl fluorides starting from aryl bromides.[130] With the use of DABSO and readily available aryl bromides they were able to produce the corresponding ammonium sulfinates efficiently, these sulfinates could be easily fluorinated with the electrophilic fluorine source NFSI (Scheme 1.27). Numerous aryl and heteroaryl bromides, bearing various sensitive functional groups were well tolerated under the reaction conditions.



Scheme 1.27 Palladium(0)-catalysed sulfonyl fluorides synthesis using DABSO and (hetero)aryl bromides

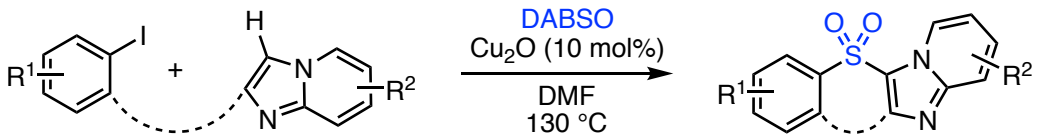
Willis and co-workers continued to explore the application of DABSO as a sulfur dioxide surrogate in association with transition metals. In 2017, they published a highly efficient copper(I)-catalysed sulfonylative Suzuki-Miyaura cross-coupling (Scheme 1.28).[131] This one-pot, one-step reaction was able to deliver a vast library of sulfone compounds by coupling arylboronic acids with aryl iodides, in the presence of DABSO and under the action of a simple copper(I) catalyst. They were also able to demonstrate that aryl iodides, in combination with DABSO and a copper(I) catalyst, could directly

give the corresponding aryl sulfinates, which are useful intermediates generated *in situ* for further transformations.



Scheme 1.28 Copper(I)-catalysed Suzuki-Miyaura cross-coupling for the synthesis of diarylsulfones

The most recent development is the transition metal-catalysed sulfonylation was reported by Wang and co-workers. They reported a copper-catalysed cross-coupling reaction of heteroaryls, DABSO and aryl halides (Scheme 1.29).[132] This process delivers sulfone products efficiently and does not require the use of a base or ligand. Under their optimised reaction conditions, a variety of imidazopyridines, bearing various functional groups, could be coupled to a series of substituted aryl iodides. Furthermore, the authors also described the intramolecular equivalent of their novel copper-catalysed sulfonylation reaction, by using commercially available 2-(2-halophenyl)imidazo[1,2-a]pyridines.

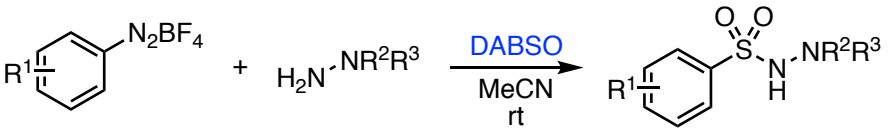


Scheme 1.29 Copper(I)-catalysed synthesis of diaryl sulfones using DABSO, aryl iodides, and heteroaryls

1.4.3 Application in Metal-Free Reactions

Inspired by the use of aryldiazonium salts as starting materials in the Sandmeyer reaction to produce sulfonyl chlorides,[133] the Wu group became the first to discover the reactivity of aryldiazonium salts in the presence of DABSO as a sulfur dioxide source, under metal-free reaction conditions. Their first breakthrough was made in 2014, when

they reported a novel route to *N*-aminosulfonamides by reacting a variety of aryldiazonium tetrafluoroborate salts, DABSO, and hydrazines together (Scheme 1.30).[134] Under their mild metal-free reaction conditions, a range of sensitive aryldiazonium tetrafluoroborate salts bearing various functional groups were well tolerated, and together with a series of hydrazines, the corresponding *N*-aminosulfonamides were delivered in good yields.

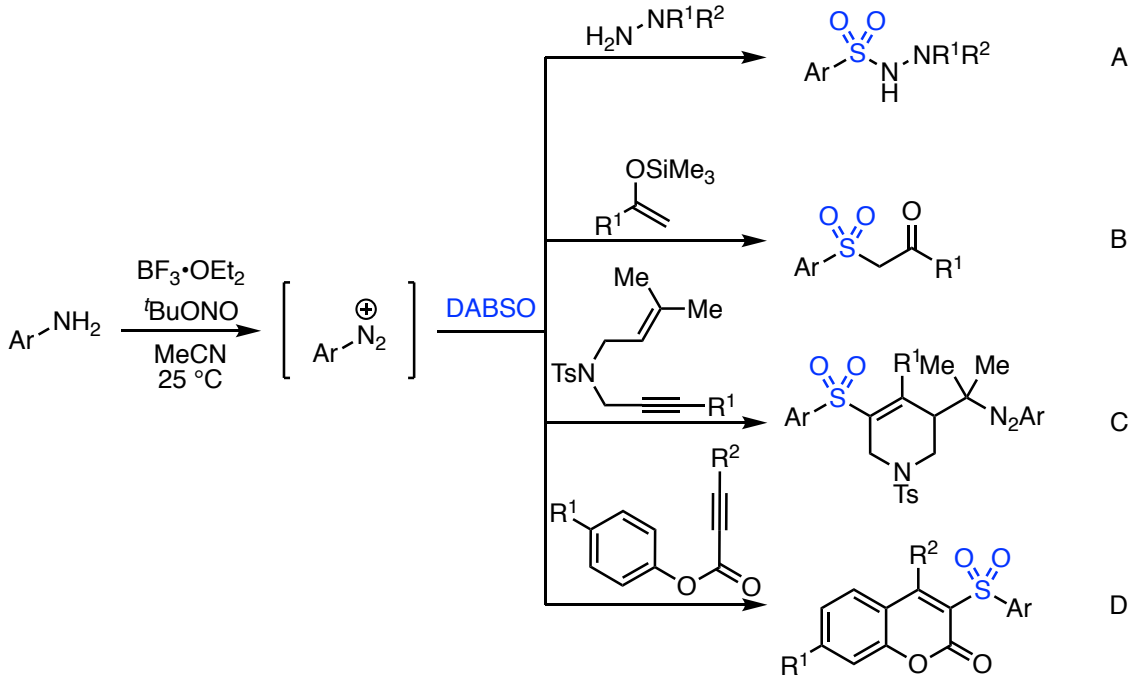


Scheme 1.30 *N*-aminosulfonamide synthesis utilising DABSO under metal-free condition

Based on both experimental and computational results, the authors proposed the mechanism to involve the initial formation of an aryl radical species, which could react with sulfur dioxide to generate a sulfonyl radical. The latter could then be trapped by the hydrazine radical to afford the desired *N*-aminosulfonamide.

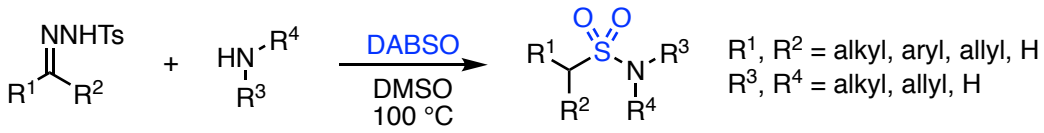
Encouraged by these results, the same group further expanded their methodology to include more substrates. Since the *in situ* generation of aryldiazonium tetrafluoroborate salts from aromatic amines is known, Wu and co-workers chose to work on using aromatic amines as starting materials for their metal-free sulfonylative reaction conditions. Initially, Wu *et al*. reported the synthesis of *N*-aminosulfonamides by using aromatic amines as aryl radical sources (Scheme 1.31, A).[135] Then, they extended the application of their process by employing other radical trapping agents, thereby leading to other types of sulfonyl containing functional groups. The reaction of aryldiazonium salts with silyl enol ethers, in the presence of DABSO, afforded a wide range of β-keto sulfones (Scheme 1.31, B).[136] While investigating the mechanism of the transformation, the authors found that the use of DABSO was indispensable for the reaction to proceed.

This observation led to the hypothesis that the carrier amine DABCO was involved in the desilylation step of this process. Later, Wu and co-workers developed a series of methods in which the sulfonyl radical species reacted with alkynes to afford alkenyl radical intermediates. These intermediates then underwent intramolecular cyclisation to afford various products such as tetrahydropyridine derivatives (Scheme 1.31, C)[137] and 3-sulfonated coumarins (Scheme 1.31, D).[138]



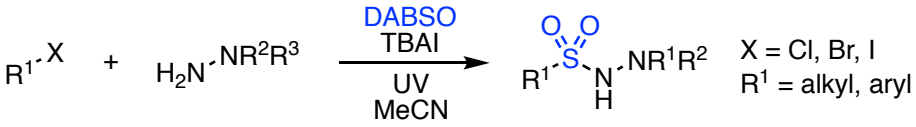
Scheme 1.31 *In situ* formation of aryldiazonium salts and their application in sulfonylative reactions under metal-free conditions

In addition, Tsai *et al*. also reported a metal-free, one-step sulfonamide synthesis in 2016.[139] The method was established by reacting *N*-tosylhydrazones and DABSO with primary or secondary amines (Scheme 1.32). Although the mechanism for this transformation remains unclear, a variety of sulfonamides could be made in moderate to good yields. It was also demonstrated that acetophenone could be converted into a sulfonamide in a two-step, one-pot process under their optimised reaction conditions.



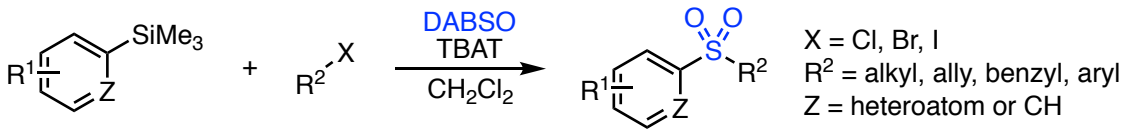
Scheme 1.32 Metal-free sulfonamide synthesis from hydrazones and DABSO

More recently, the Wu group documented various methods to generate sulfonyl radicals. In 2016, they reported the photoinduced, metal-free coupling of alkyl/aryl halides with DABSO and hydrazines, delivering a range of *N*-aminosulfonamides (Scheme 1.33).[140] The radical initiation resulted from the initial bond dissociation of alkyl/aryl halide under UV irradiation. Inspired by these preliminary results, they later trapped the sulfonyl radicals with silyl enol ethers. As a result, *β*-keto sulfones could be made from readily available aryl halides efficiently.



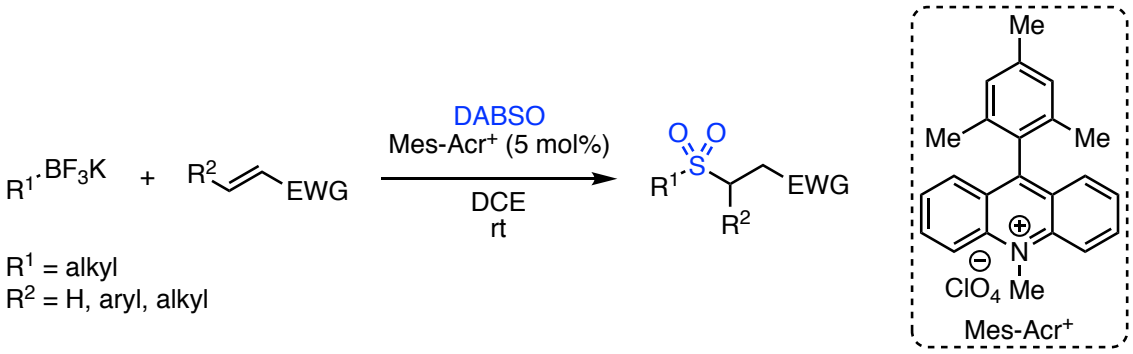
Scheme 1.33 Photoinduced *N*-aminosulfonamide synthesis using DABSO as a SO_2 source

Cantat and co-workers documented an alternative approach for the generation of sulfones under metal-free conditions. They demonstrated that the activation of organosilanes by a fluoride source, in the presence of DABSO, could generate a sulfinate ion which could subsequently be trapped by an electrophile (Scheme 1.33).[141] This method tolerates the use of heteroaryl and arylsilanes, and the sulfinate ion formed could be trapped with alkyl, allyl, benzyl, and aryl halides, illustrating a wide range of sulfones that could be formed under mild, metal-free reaction conditions. The authors not only showed that the presence of sulfur dioxide was crucial for the cleavage of the C-Si bond to occur, they also reported, both experimentally and computationally, the presence of a stable FSO_2^- ion, which can act as a fluoride transfer agent that promotes the scission the of C-Si bond.



Scheme 1.33 Metal-free synthesis of sulfones from (hetero)arylsilanes and DABSO

Finally, the latest advancement reported in the field of metal-free sulfonylative reaction was in 2018 by Wu and co-workers. They documented a one-pot photocatalysed sulfone synthesis from potassium alkyltrifluoroborates, DABSO and alkenes (Scheme 1.34).[142] With the help of visible light and the photocatalyst, the alkyltrifluoroborate species could give an alkyl radical species that will react with sulfur dioxide to form a sulfonyl radicals. This radical intermediate could then be trapped by alkenes to deliver the desired sulfone products. A broad range of alkenes bearing various sensitive functional groups and a broad series of alkyltrifluoroborates were well tolerated under the reaction conditions, thereby generating a wide range of substituted sulfones.



Scheme 1.34 Photocatalysed sulfone synthesis from alkyltrifluoroborates and DABSO

1.5 Research Aims

Organosulfur compounds have found a wide range of applications in many industries. However, the difficulty related to the use of toxic gaseous sulfur dioxide gas has caused great limitation to the field of sulfonylation chemistry. The Willis group (and now others), have set important precedents in term of sulfonylative methodologies by using sulfur dioxide surrogates, such as the bench stable DABSO, as a source of sulfur dioxide. The remaining of this thesis will present further explorations of the reactivity of DABSO through transition metal catalysis, organocatalysis, and reaction with organometallic reagents. Hence, the broadening of the scope of organosulfur oxide compounds accessible from DABSO can be expected.

Chapter 2 - A One-Pot Sulfoxide Synthesis Using DABSO and Organometallic Reagents

2.1 Sulfoxides

2.1.1 Traditional Synthesis and Applications

The sulfinyl functional group is present in a vast library of organic compounds and natural products, which have found a widespread application in the pharmaceutical and agrochemical industries, as well as in material science (Figure 2.1).[143-145] Sulfoxides, a class of sulfinyl containing compounds have been utilised in the pharmaceutical industry for several decades. The most famous example being the discovery of the anti-ulcer agent, Omeprazole in 1979,[6] which subsequently became the world's highest selling drug in 1997.

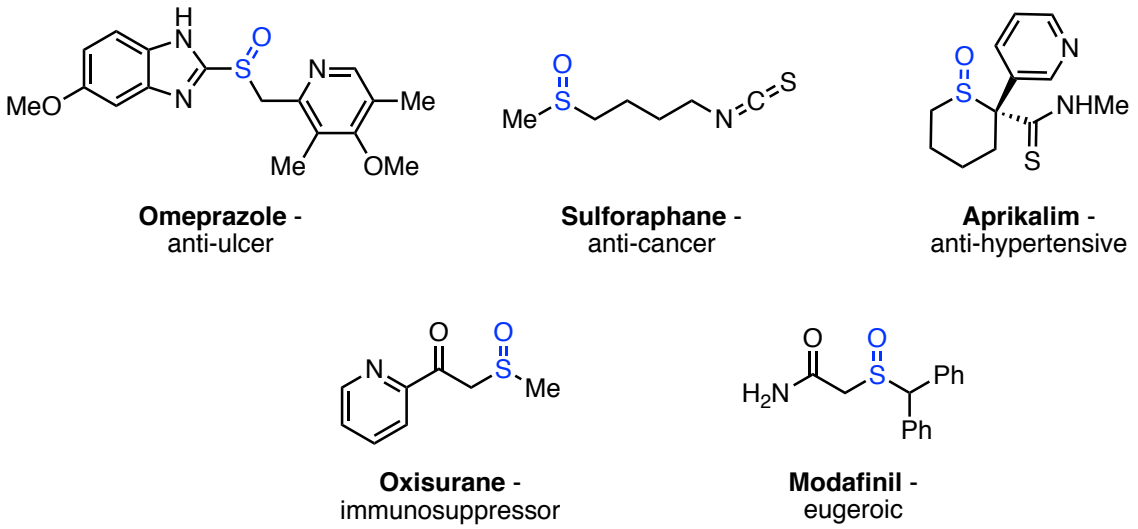
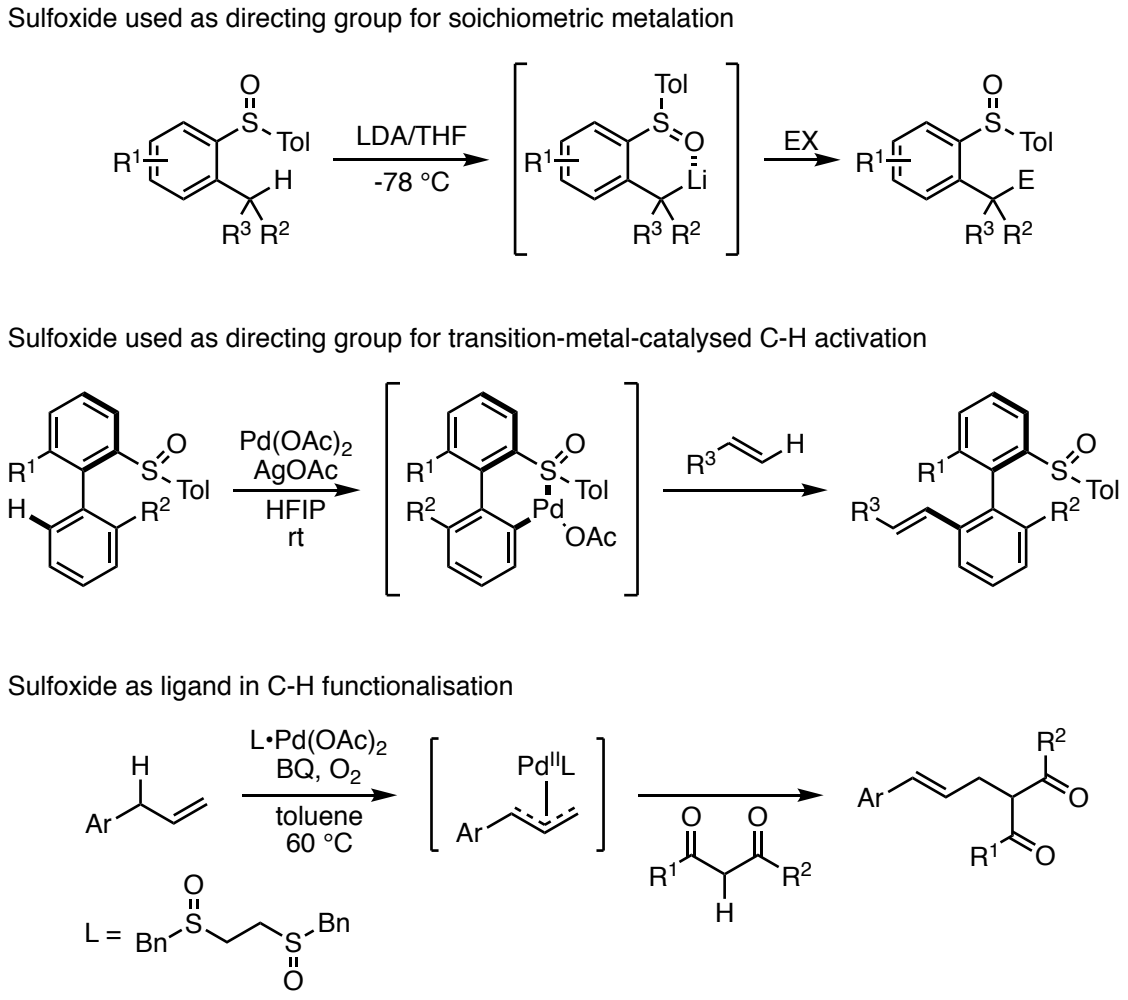


Figure 2.1 Examples of pharmaceutical agents containing the sulfoxide functional group

Moreover, sulfoxides have also found numerous applications in chemical synthesis.[28] Commonly, sulfoxides have been used as intermediates in transformations such as the Pummerer rearrangement (Section 1.1.1),[146] or used as a directing group for stoichiometric metalation and functionalisation of C-H bonds.[147] Recent reports disclosed

the ability of sulfoxides to be used as directing groups and as directing ligands, for transition-metal-catalysed C-H activation processes (Scheme 2.1).

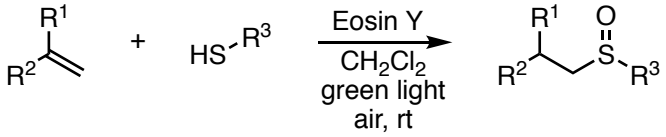


Scheme 2.1 Sulfoxides used as directing group for C-H functionalisation

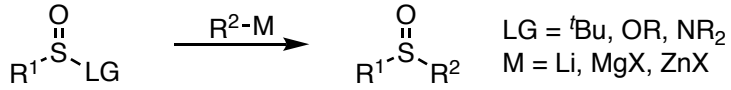
Given the significance of the sulfoxide moiety, it is not surprising that many methodologies documenting the synthesis of sulfoxides exist. The most conventional protocol for the synthesis of sulfoxide derivatives is through the oxidation of sulfides using strong oxidising agents (e.g. peroxides or peracids).[39] However, the necessity to use a stoichiometric amount of oxidant results in a low functional group tolerance, as well as a non-negligible amounts of sulfone side-product formed by over oxidation (Section 1.1.2). Additionally, the corresponding starting material sulfides are not always easy to make and often requires the use of odorous thiols, which are themselves not always

commonly available, thus requiring a long and linear synthesis to reach the desired product. In recent years, the radical mediated addition of thiols to alkenes, combined with a photo-oxidation process, using O_2 as an oxidant has been reported.[148] The much milder reaction conditions allowed for greater functional group compatibility, nevertheless, a substantial amount of sulfone product was still produced (Scheme 2.2, A). As an alternative route to sulfoxides, sulfinyl derivatives, such as sulfinamides,[149,150] sulfinic acids,[46] and sulfinyl halides,[151,152] have been used in combination with organometallic reagents (Scheme 2.2, B). However, these sulfinyl derivatives are highly reactive and sensitive, thus they have restricted commercial availability. The transition-metal-catalysed transformation of simple sulfoxides to more complex sulfoxide products has also been reported (Scheme 2.2, C).[153] However, the sulfoxide starting material often require to be synthesised, therefore leading to a long and linear synthetic sequence.

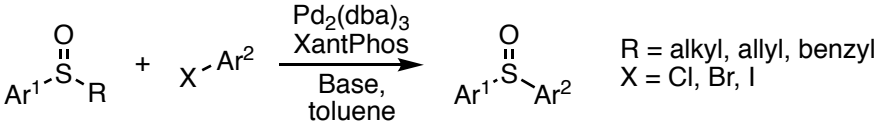
A) Sulfoxides synthesis *via* photo-oxidation



B) Sulfoxides synthesis *via* displacement of a leaving group



C) Palladium-catalysed diarylsulfoxide synthesis



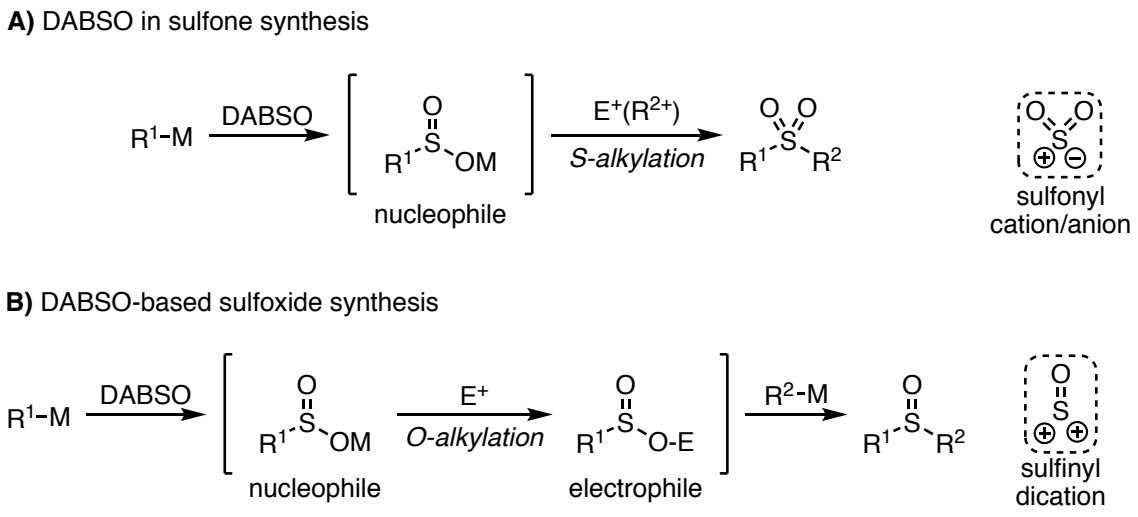
Scheme 2.2 Alternative pathways for the synthesis of sulfoxides

2.1.2 Origin of Project and Previous Work

With the conventional synthetic pathways to sulfoxides having limitations, mainly due to the requirement of harsh reaction conditions, a more robust and general approach for

accessing sulfoxides is highly desirable. Therefore, the development of a method for sulfoxide generation under mild conditions, using a readily-available and easy-to-handle starting material would be a significant improvement over the existing literature. It was the ambition of this project to develop a system employing the easy-to-handle sulfur dioxide surrogate DABSO, in combination with readily accessible reagents, to allow access to a variety of sulfoxide products, containing aryl, heteroaryl, alkenyl and alkyl groups.

Our group recently reported a two-step one-pot sulfone synthesis.[120] This process used the reaction between an organometallic reagent and DABSO, acting as a sulfur dioxide source, to form a metal-sulfinate intermediate *in situ*. This intermediate could then further react with an electrophile, through *S*-alkylation, to deliver the desired sulfones. This process exemplifies the ambidentate nature of the sulfur dioxide to act as a sulfonyl cation/anion synthon simultaneously (Scheme 2.3, A).

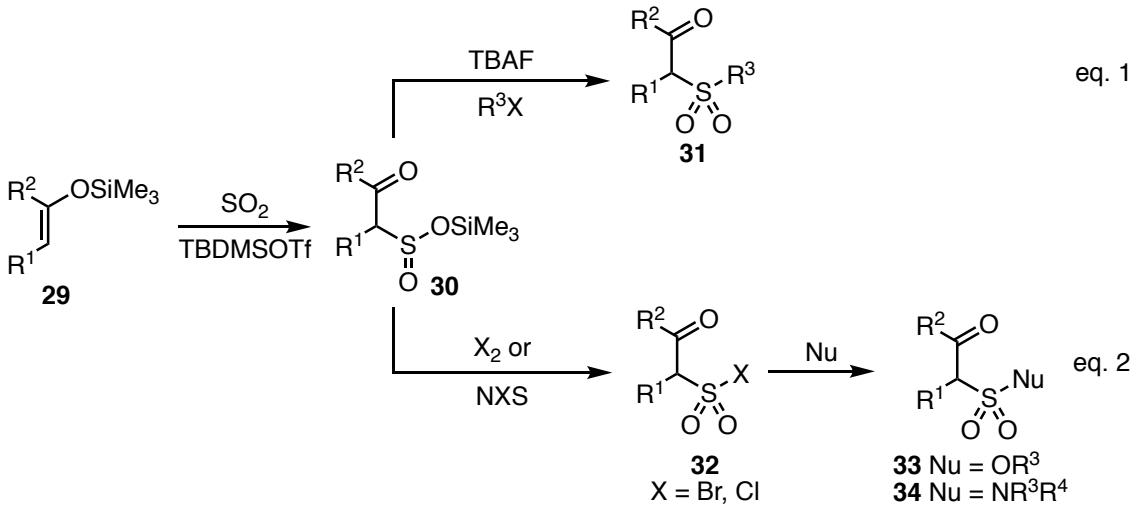


Scheme 2.3 Different reactivities of the same *in-situ* generated metal-sulfinate specie

From the observations made in the sulfone chemistry, we postulated that it should be possible to employ an electrophile that favours *O*-alkylation, instead of *S*-alkylation, of the *in situ* generated metal sulfinate. The so-formed sulfinate ester could then react with

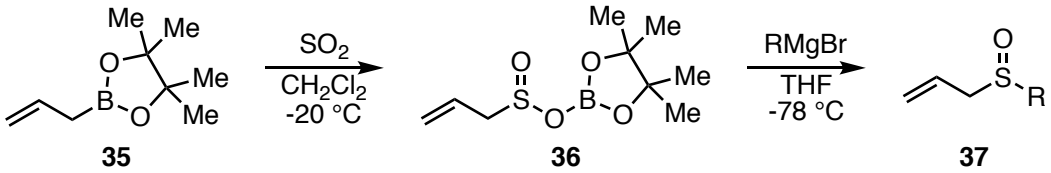
a nucleophile to afford the desired sulfoxide product. In this process, sulfur dioxide would effectively act as a sulfinyl dication synthon (Scheme 2.3, B).

The ability of sulfinates to react on an oxygen atom has been reported by Vogel and co-workers in the sila-ene reaction of gaseous sulfur dioxide and enoxysilanes **29**, to generate sulfinates **30**. Which after *in situ* desilylation, can be trapped with a variety of electrophiles, delivering the desired sulfones **31** (Scheme 2.4, eq. 1).[64]



Scheme 2.4 Sulfone synthesis and derivatives *via* the silyl sulfinate intermediate 32

Upon oxidative conditions, the silyl sulfinate can readily deliver the corresponding halide sulfinate **32**, which can be further reacted with alcohols and amines, delivering sulfinate esters **33** and sulfonamides **34**, respectively (Scheme 2.4, B).[65] Later, the same group also documented the reaction of prop-2-ene-1-boronate **35** with SO_2, forming the sulfinate intermediate **36**, which upon reaction with a Grignard reagent, delivered the desired sulfoxides **37** (Scheme 2.5).[61] This process demonstrates the application of an umpolung effect of the sulfinate species, which enables access to the desired sulfur oxidative state. However, this protocol suffers from several drawbacks due to the high reactivity of the formed intermediate, the restricted substrate scope, and the use of gaseous sulfur dioxide.



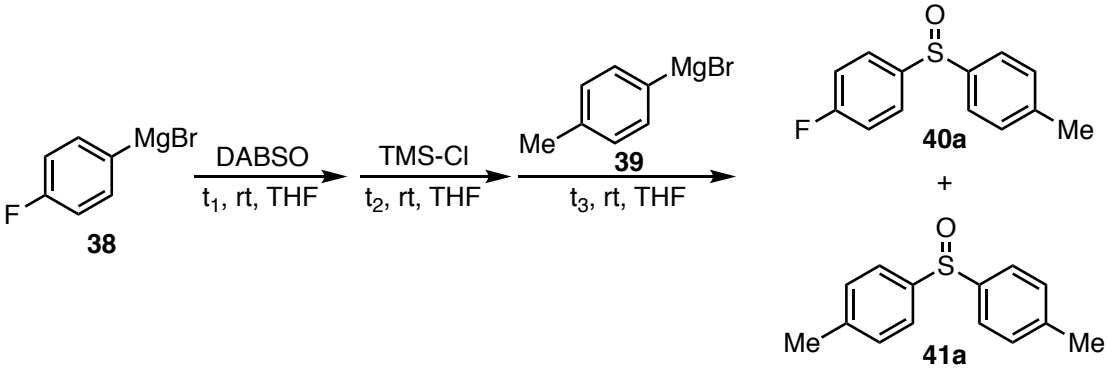
Scheme 2.5 Bora-ene reaction of SO_2 and prop-2-ene-1-boronic esters

2.1.3 Initial Investigation

This project targeting the synthesis of sulfoxides through the use of DABSO was developed in collaboration with Danny Lenstra, a visiting MSc student in the Willis Group. The starting point of our investigation was inspired for the first step from reaction conditions developed by our group for sulfones synthesis. The first objective was the synthesis of diaryl sulfoxide **40a**, from the association of the two-corresponding aryl Grignards **38** and **39**, DABSO as a source of sulfur dioxide, and an appropriate electrophile to favour *O*-alkylation.[154] Consequently, the identification of the appropriate electrophile was the first focus of this study. Encouraged by Vogel's work on the silyl-ene reactions, using silyl sulfinates as intermediates, we hypothesised that a silicon-based electrophile should be trapped by the oxygen atom, thus forming the desired sulfinate ester intermediate. A few Si-electrophiles were tested, and the simplest and most cost-effective silyl reagent, trimethylsilyl chloride (TMS-Cl), appeared to be the most effective to promote this transformation (Table 2.1, entry 1). However, this initial result revealed a selectivity issue, because of the co-contaminant formation of the symmetrical sulfoxide **41a**. The formation of this by-product can be explained by the reaction between sulfoxide **40a** and unreacted Grignard reagent **39**, which could displace the 4-fluorophenyl fragment of the sulfoxide **40a**, yielding the symmetrical sulfoxide **41a**. The generation of this by-product was controlled by varying the stoichiometries of the reagents. The selectivity toward **40a** started to improve when more DABSO was used (entries 1-3). Reducing the equivalents of the second Grignard reagent also had a positive impact on

the selectivity (entries 4-7), as did increasing the amount of TMS-Cl used in the reaction (entries 7-8). Finally, we reduced the time of each step of the reaction from 90 minutes to 45 minutes, which allowed us to increase the amount of Grignard reagent **39** employed without it being detrimental to the selectivity of the reaction (entries 9-10).

Table 2.1 Optimisation of conditions favouring the formation of sulfoxide 40a



Entry	DABSO (equiv.)	$t_1/t_2/t_3$ (min)	TMS-Cl (equiv.)	**39** (equiv.)	Yield (%)[a]/ (**40a**:**41a**)
1	0.40	90	1.30	1.20	91 (3:1)
2	0.50	90	1.30	1.20	83 (6:1)
3	0.60	90	1.30	1.20	89 (7:1)
4	0.50	90	1.30	1.00	75 (10:1)
5	0.50	90	1.30	0.95	87 (17:1)
6	0.50	90	1.30	0.75	98 (18:1)
7	0.50	90	1.30	0.5	96 (14:1)
8	0.50	90	1.50	0.5	96 (>25:1)
9	0.50	45	1.50	0.5	97 (>25:1)
10	**0.50**	**45**	**1.50**	**0.75**	**97 (>25:1)**

Reaction conditions: **38** (1.0 equiv.), and as in table. [a]Isolated yields, ratio (**40a**:**41a**) determined by ^{1}H NMR

The entire optimisation of the reaction conditions presented above, were carried out by Danny Lenstra.

2.1.4 Initial Reaction Scope

With the optimised conditions in hand, we then turned our attention to the exploration of the scope of the reaction (Figure 2.2). Commercially available Grignard reagents were used for the synthesis of sulfoxides, as well as some which required generation *in situ via* magnesium-halogen exchange (e.g. **40c**).[155] Pleasingly, the reaction proceeded smoothly with a wide range of aryl Grignard reagents, bearing electron-donating, neutral, and withdrawing functional groups, and delivered unsymmetrical diaryl sulfoxide products (**40a-d**) in good to excellent yields. The aryl silyl sulfinate intermediate also reacted efficiently with primary (**40e**), secondary (**40f-g**), and tertiary alkyl Grignard reagents (**40h**), to afford arylalkyl sulfoxides.

Reversing the order of the addition of the Grignard reagents had a small detrimental effect in the yield for the arylalkyl sulfoxide **40i/40j**. A variety of primary and secondary alkyl Grignard reagents performed well under our reaction conditions, when associated with an aryl Grignard reagent as the final nucleophile (**40k-m**). Several other combinations of different type of Grignard reagents were also tested, such as alkyl/alkyl (**40n**), allyl/aryl (**40o**), alkenyl/aryl (**40p**), and benzyl/aryl (**40q-r**), and afforded the corresponding sulfoxide products in good to excellent yields. Various heterocycle-derived sulfoxide products were also produced efficiently with our methodology (**40s-u**). To further display the utility and the robustness of this process, we applied our optimised reaction conditions to a larger scale synthesis of sulfoxide **40f**. Pleasingly, the desired product was generated in 92% yield (2.65 g) when using 2.0 g of DABSO (8.5 mmol).

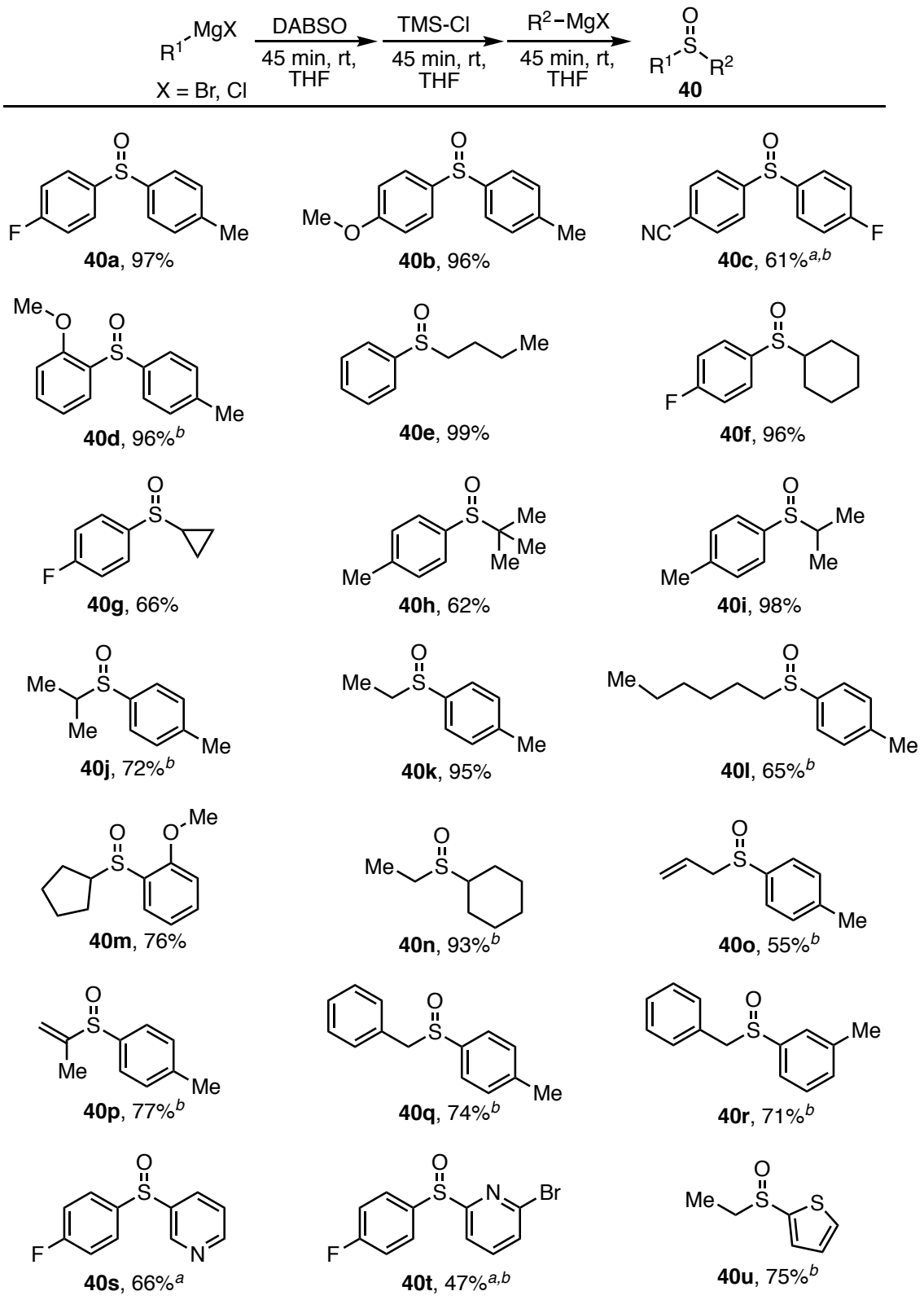


Figure 2.2 Grignard reagents scope for the synthesis of sulfoxides

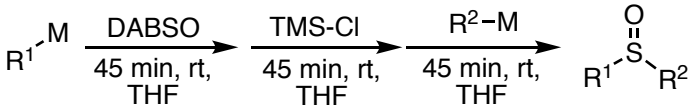
Reaction conditions: R^1–MgX (1.0 equiv.), DABSO (0.5 equiv.), TMS–Cl (1.5 equiv.), R^2–MgX (0.75 equiv.), THF [0.33 M]. Isolated yield. [a]RMgX generated from the corresponding bromide and ^{i}PrMgCl. [b]Compounds synthesised by Danny Lenstra.

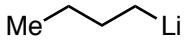
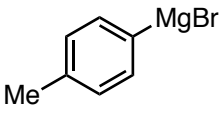
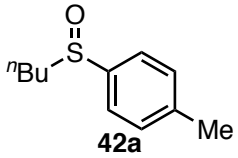
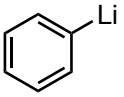
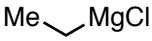
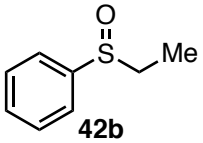
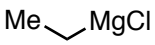
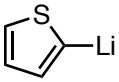
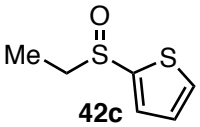
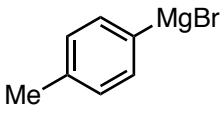
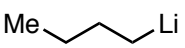
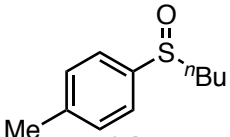
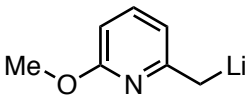
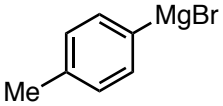
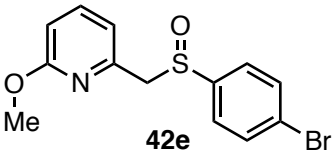
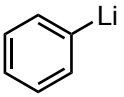
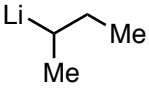
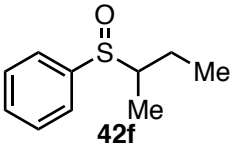
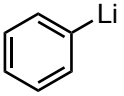
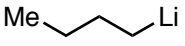
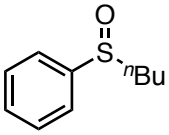
2.1.5 Use of Different Organometallic Reagents

To further diversify the scope of our reaction, as well as to probe its limitations, we turned our attention to other organometallic reagents that might be compatible with our transformation. Due to their ability to react as strong base and nucleophiles, and their wide commercial availability, organolithium reagents are among the most important compounds in modern organic chemistry. Furthermore, our group had previously reported the utilisation of organolithium reagents for sulfone synthesis, with DABSO to access metal sulfinates.[120,123,124]

Therefore, we started to investigate using an organolithium reagent as the first nucleophile. We were pleased to see that using either an aryl or alkyllithium reagents delivered the desired sulfoxide products in good yields, in combination with an alkyl or aryl Grignard reagent as the final nucleophile (Table 2.2, **42a-b**). Employing alkyl or aryl organolithium reagent as the final nucleophile also provided good yields, when combined with aryl or alkyl Grignard reagents as the first nucleophile (**42c-d**). When more challenging substrates were used, such as methyl lithium pyridines (**42e**), the yield dropped dramatically. A poor mass balance was recovered from this reaction, which could suggest that the lithium sulfinate species formed was unstable and decomposed rapidly. More surprisingly, when organolithium reagents were combined as both first, and final nucleophiles, the reaction did not proceed well, and the corresponding sulfoxide was therefore isolated in poor yield (**42f**). Here again, a poor mass balance was recovered from this reaction. When *n*-butyllithium was used in combination with phenyllithium, in either position in the sequence, no product was formed (Table 2.2, entry 7). This final result could suggest that the presence of magnesium in the reaction mixture is essential for the reaction to proceed smoothly.

Table 2.2 Sulfoxide synthesis employing varied organometallic reagent



Entry	R^1-M	R^2-M	Sulfoxide	Yield (%)
1			 **42a**	85
2			 **42b**	72[b]
3			 **42c**	71[b]
4			 **42d**	66
5			 **42e**	18[a]
6			 **42f**	29
7				No Product

Reaction conditions: R^1–MgX (1.0 equiv.), DABSO (0.5 equiv.), TMS–Cl (1.5 equiv.), R^2–MgX (0.75 equiv.), THF [0.33 M]. Isolated yield. [a]RLi generated from the corresponding bromide and ^{n}BuLi. [b]Compounds synthesised by Danny Lenstra.

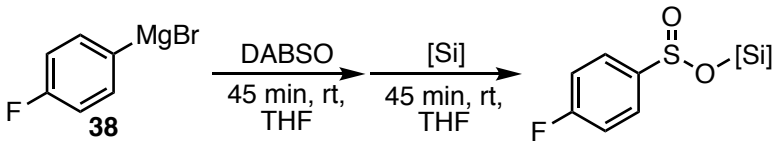
Organozinc reagents have been used in combination with DABSO in order to synthesise sulfones (Section 1.4.1).[121] Their milder reactivity, compared to Grignard and organolithium reagents, are ideal for a broader functional group tolerance, by decreasing the likelihood of side reactions. Therefore, organozinc reagents were explored under our

optimised reaction conditions. Both aryl and alkylzinc reagents were submitted to our reaction sequence, as the first or as the final nucleophile, however, no sulfoxide product was formed in all cases. When the organozinc reagent was used as a first nucleophile, the corresponding zinc sulfinate could be observed by HPLC, however, the latter did not react with TMS-Cl and decomposed over time. As a final nucleophile, the organozinc species did not react with the silyl sulfinate intermediate.

2.1.6 Mechanistic Evidence

In the design of this new methodology, we hypothesised that a silyl sulfinate ester intermediate would be generated *in situ*. In order to investigate if such a silyl sulfinate ester intermediate was indeed generated, we attempted to isolate it. Unfortunately, our efforts to isolate the intermediate from the reaction of the metal sulfinate and TMS-Cl were unsuccessful.

Table 2.3 Screening of silyl groups for the synthesis of silyl sulfinate ester



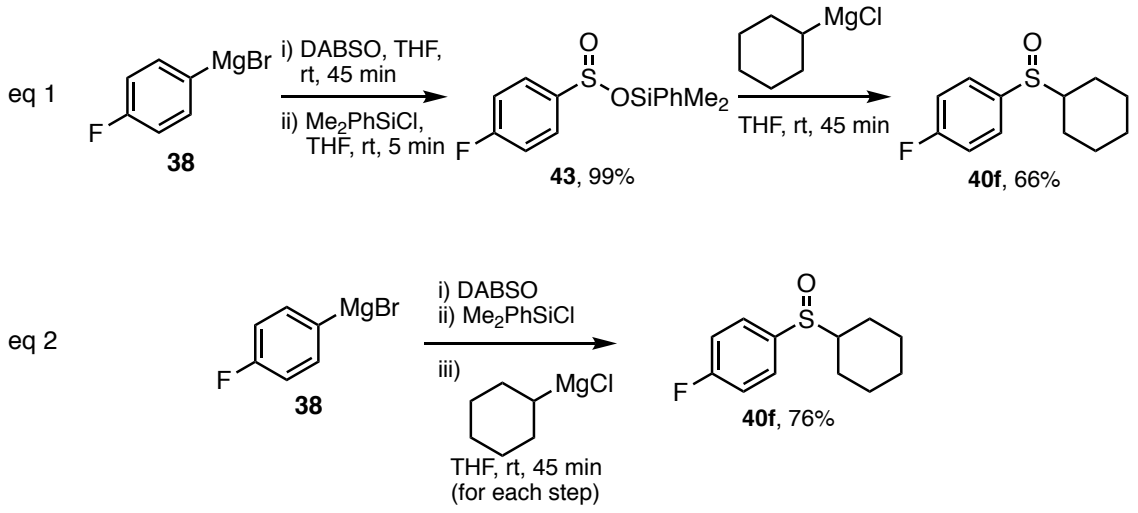
Entry	Silyl Reagent	Conversion (yield[a])
1	TMS-Cl	-
2	TIPS-OTf	-
3	TBDMS-Cl	58%
4	DMPS-Cl	100% (37%)
5	DMPS-Cl	100% (>99%)[b]

Reaction conditions: *p*-fluorophenylmagnesium bromide (1.0 equiv.), DABSO (0.5 equiv.), silyl group (1.0 equiv.), THF [0.33M]. [a]Isolated yield. [b]Second step quenched after 5 minutes at room temperature.

Various work-up conditions were tried, nonetheless, the crude material always decomposed (Table 2.3, entry 1). Different silyl group were investigated such as triisopropylsilyl trifluoromethanesulfonate (TIPS-OTf; entry 2), but no reaction was observed, possibly because of the increase steric bulk around the silicon atom, which can

inhibit the reaction. Therefore, the less sterically incumbered *tert*-butyldimethylsilyl chloride (TBDMS-Cl) was employed, and some conversion toward the silyl sulfinate ester could be observed (entry 3). However, changing the temperature, the time of the reaction, the number of equivalents, or the work-up conditions, showed no significant improvement. Motivated by this preliminary result, dimethylphenylsilyl chloride (DMPS-Cl) was submitted to our optimized reaction conditions (entry 4), and provided the desired intermediate in a promising 37% yield and showed full conversion of DMPS-Cl. Reducing progressively the reaction time after the addition of DMPS-Cl to 5 minutes allowed us to isolate the corresponding silyl sulfinate ester intermediate **43** in a quantitative yield (entry 5).

In order to confirm that the silyl sulfinate ester isolated was indeed the intermediate by which the reaction proceeds, we resubmitted sulfinate ester **43**, after isolation and characterisation, to the reaction conditions. Treatment of the silyl sulfinate with cyclohexyl magnesium chloride afforded the sulfoxide product **40f** in 66% yield (Scheme 2.6, eq. 1).



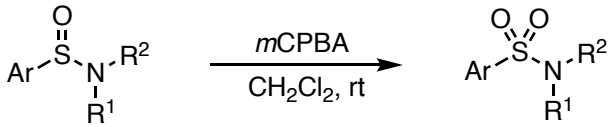
Scheme 2.6 Synthesis of sulfoxide **42f** *via* silyl sulfinate ester intermediate **43**

To further emphasise that our mechanistic model using DMPS-Cl correlates to our standard reaction conditions, we performed a one pot sequence for the synthesis of the

sulfoxide **40f**, using DMPS-Cl instead of TMS-Cl, which delivered the desired product in a satisfactory 76% yield (Scheme 2.6, eq. 2).

2.2 Sulfinamides

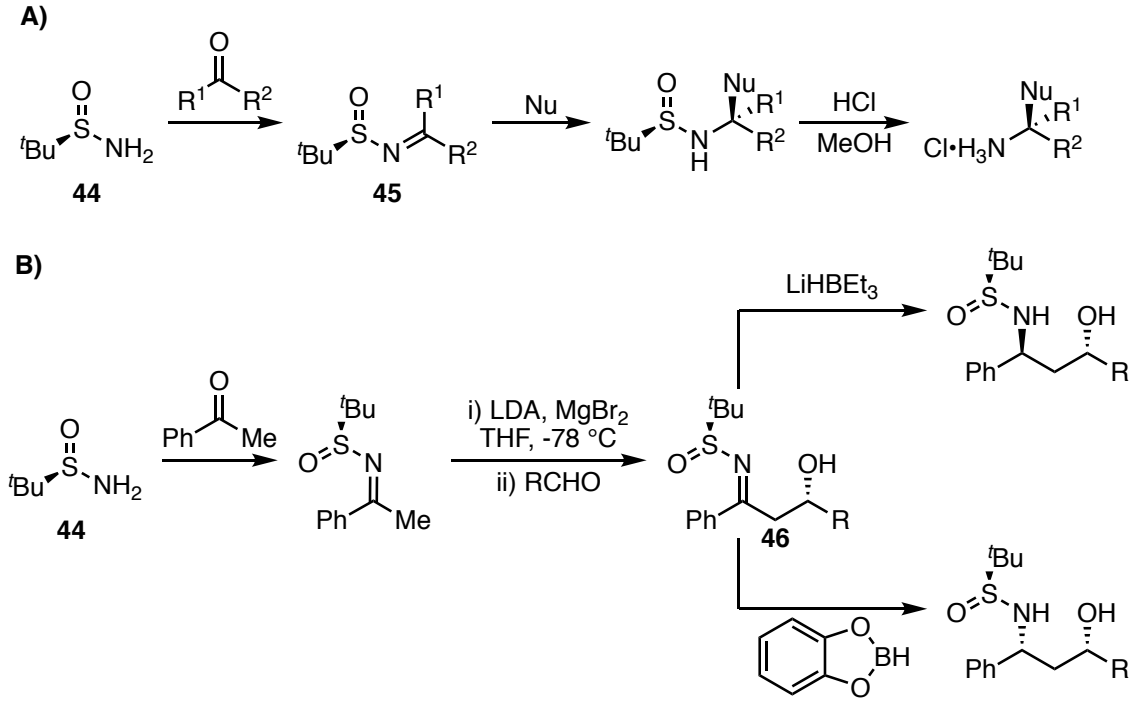
Sulfinamides are commonly used as key intermediates for the preparation of a range of sulfonamides, which are one of the most abundant moiety found in target molecules in the pharmaceutical and agrochemical industry.[156,157] Several drugs including anticonvulsants, HIV protease inhibitors, and anticancer, antibacterial, anti-inflammatory, and antiviral agents contain a sulfonamide unit. Generally, two methods are prevalent for the synthesis of sulfonamides; the oxidation of the corresponding sulfide to form *in situ* a sulfinate species which can further react with an amine,[48,158,159] and the amide coupling of sulfonyl chloride with amines.[160,161] However, both methods suffer from drawbacks, such as the use of odorous thiols for the preparation of sulfide precursors, or the use of sulfonyl chlorides, which limits the range of possible substrates accessible due to the harsh acidic conditions necessary for electrophilic aromatic substitution for the synthesis of starting materials. Therefore, due good stability of sulfinamide products to long term storage, they have been used as convenient precursors.[39,150] A simple oxidation, can convert a sulfinamide efficiently into the corresponding sulfonamide in one step (Scheme 2.7).[48]



Scheme 2.7 Use of sulfinamides as precursors for sulfonamides

Furthermore, sulfinamide products can be used as versatile intermediates for the synthesis of a variety of chiral amines, which are another very important motif in most

chemical industries. Since the introduction by Ellman in 1997 of the 2-methyl-2-propanesulfinamide as a chiral ammonia equivalent,[162] the utilisation of sulfinamides as chiral amine precursors have been documented for numerous amines, such as α-branched amines, α- and β-amino acids, aziridines, and amino phosphonic acids.[156] In most of these synthesis, *tert*-butanesulfinamide (**44**) was used as an extremely versatile and practical auxiliary for chiral amines. The direct condensation of sulfinamide **44** with ketones and aldehydes, provides *tert*-butanesulfinyl imines (**45**).[163] A vast library of nucleophiles, such as organometallic reagents and metal enolates, can be added to the sulfinyl imines with high diastereoselectivity and in high yields. Upon acid conditions, the sulfinyl group can be cleaved, therefore providing the desired chiral amine products (Scheme 2.8, A).[164]

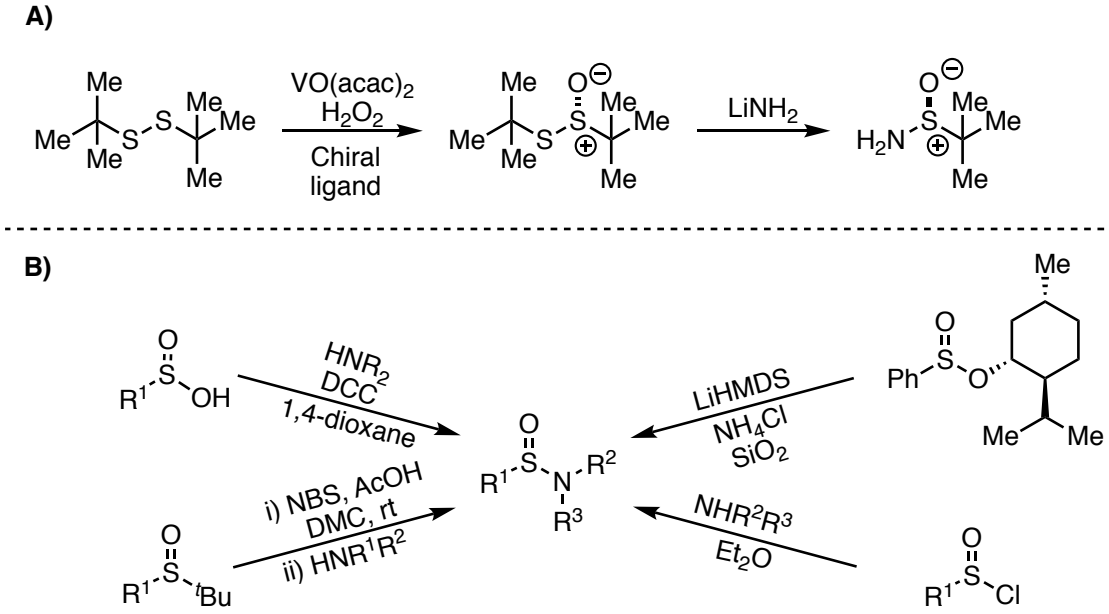


Scheme 2.8 Use of sulfinamides for the synthesis of various chiral amines

Other studies showed that *tert*-butanesulfinyl imines can also be employed in enolate type reactions. Upon treatment with LDA to promote α-deprotonation of the sulfinyl imine, subsequently trapping the metalloenamine with aldehydes, provides access to β-hydroxy *N*-sulfinyl ketimines (**46**) in good yield and with high diastereoselectivity. *Syn*-

or *anti*- 1,3 amino alcohols could be accessed by reduction with catecholborane or $LiBHEt_3$, respectively (Scheme 2.8, B).[165]

Given the large number of important motifs accessible through the use of sulfinamides, a variety of methodologies have been reported for their synthesis. The most commonly used route to sulfinamide products is the two-step process of catalytic asymmetric oxidation of *tert*-butyl disulfide, followed by reaction of the resulting *tert*-butanethiosulfinate intermediate with an amide anion, as described by Ellman and co-workers (Scheme 2.9, A).[166] Other methods documented the use of sulfinic acids,[167] sulfinate ester,[163] sulfinyl chlorides,[168] and sulfoxides,[169] in association with primary and secondary amines, as starting materials for the synthesis of sulfinamides (Scheme 2.9, B).

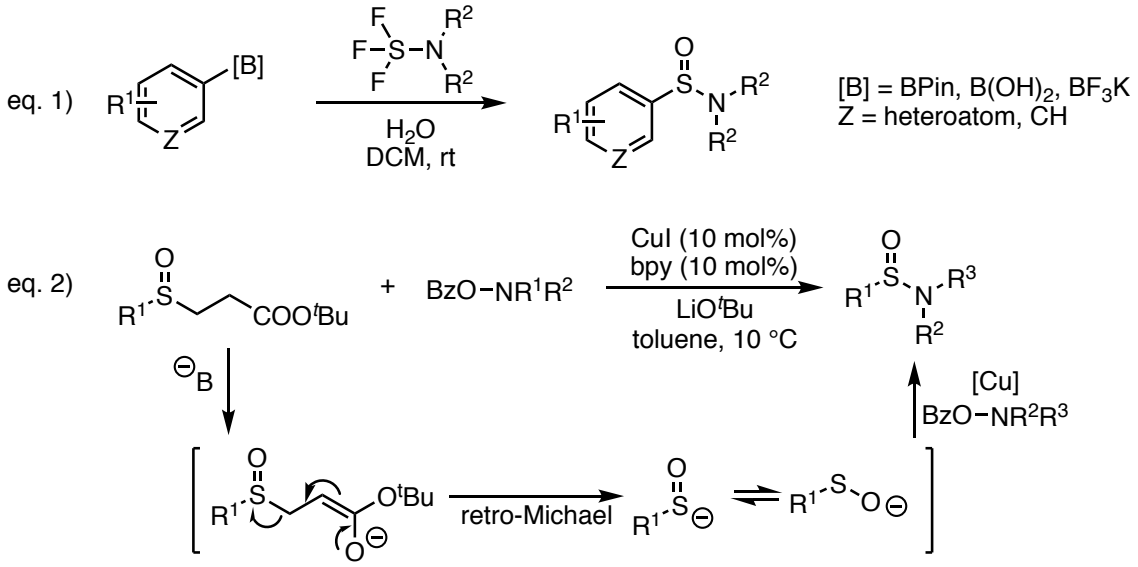


Scheme 2.9 Common routes to sulfinamide products

However, these methods for sulfinamides synthesis suffer from important drawbacks, such as harsh conditions, and a limited range of products being accessible due to the difficulty to synthesis starting materials or their instability. Therefore, some more general, milder, and Greener methodologies were reported. Wang *et al.* demonstrated the metal-

free cross-coupling between boronic acids and diethylaminosulfur trifluoride (DAST), allowing access to aryl and heteroaryl sulfinamides in moderate to good yields (Scheme 2.10, eq. 1).[170] Most recently, Zhang and co-workers published a copper-catalysed electrophilic amination of sulfenate anions, employing *N*-benzoyloxyamines as the animation reagents (Scheme 2.10, eq. 2).[171] The formation of the sulfenate anion stems from a retro-Michael reaction of *β*-sulfinyl esters in basic conditions. This process gives access to aryl and alkyl sulfinamides in moderate to good yield.

Despite significant advancements toward a more efficient, milder, and more practical synthesis of sulfinamides, these methods still have a limited scope and require the use of sensitive reagents or strong bases. Therefore, we felt that the development of a more general method for the synthesis of sulfinamides was still needed.

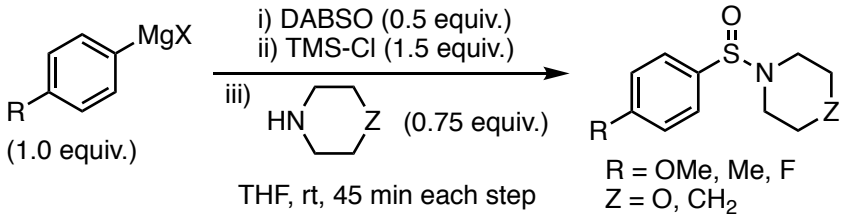


Scheme 2.10 Alternative synthesis of sulfinamides

2.2.1 Initial Optimisation of Conditions

Following on from our recent success for the synthesis of sulfoxide products,[1] employing DABSO, in association with organometallic reagents and TMS-Cl, we

postulated that a similar process could deliver a wide range of sulfinamides in an efficient manner. Therefore, we started our investigations by reacting a range of aryl Grignard reagents with DABSO, TMS-Cl and various nucleophilic amines (Scheme 2.11). However, none of these attempts produced the desired product, or showed any sign of reactivity between the *in situ* generated silyl sulfinate ester species and the morpholine.

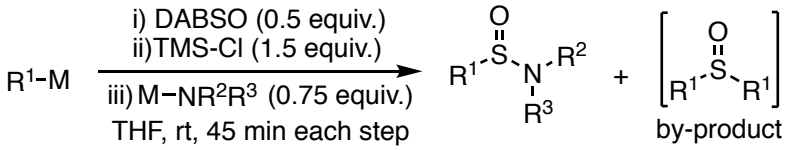


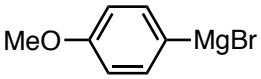
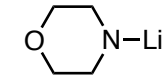
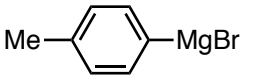
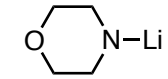
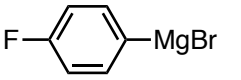
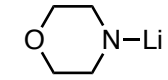
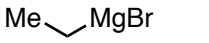
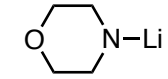
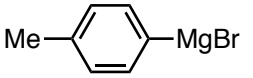
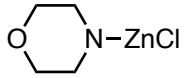
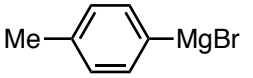
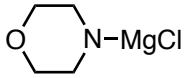
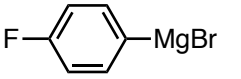
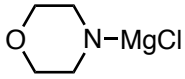
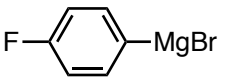
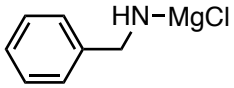
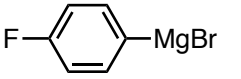
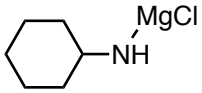
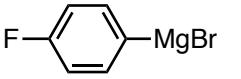
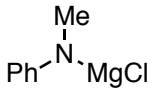
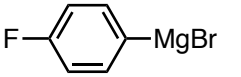
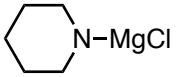
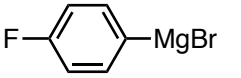
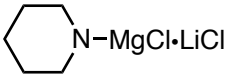
Scheme 2.11 Sulfinamide synthesis using

The nucleophilic potential of metal amides has been extensively used and studied in organic chemistry for numerous transformations such as reductions,[172] alkylations,[173] deprotonations,[174] desymmetrisations,[175] and kinetic resolutions.[176] Therefore, we hypothesised that, because of their enhanced nucleophilic character, metal amides could be more suitable partners for our reaction. Thus, we decided to test our hypothesis by treating a range of sulfinates with various metal amides (Table 2.4). Our first choice was to use an *in situ* generated lithiated morpholine and react it with electron-poor, neutral, and rich aryl silyl sulfinates (entries 1-3), and with an alkyl silyl sulfinate (entry 4). Although the desired sulfinamides could be isolated, the major product generated in most cases, was the corresponding symmetrical sulfoxide. The formation of this by-product could possibly stem from decomposition of the silyl sulfinate intermediate, or from poor chemoselectivity, with the metal amide reacting with the silicon atom rather than with the sulfur atom. It is known for organometallic compounds that the counter cation can greatly influence the chemoselectivity of the reaction.[177] To moderate the nucleophilicity of the amine, we decided to generate *in situ* a zinc chloride morpholine (entry 5), by direct deprotonation with methyl zinc chloride or by transmetalation from the lithium

morpholine. However, no product was generated, and only some traces of the by-product could be observed. Next, we generated *in situ* a magnesium morpholine, by deprotonation of morpholine with iso-propylmagnesium chloride, which was subsequently reacted with 4-tolylsilyl sulfinate (entry 6). Although the increase in yield compared to the reaction with lithium morpholine is marginal, the amount of by-product generated during the reaction was significantly reduced. When the magnesium morpholine species was combined with 4-fluorophenylsilyl sulfinate, the corresponding product could be isolated in an encouraging 26% yield (entry 7). A variety of *in situ* generated magnesium amides were then explored under our reaction conditions. Unfortunately, when primary amines, such as a benzylamine and cyclohexylamine were deprotonated with isopropyl magnesium chloride, only traces of the desired sulfinamide products were generated (entry 8 and 9 respectively). However, when magnesium *N*-methylaniline was employed, the desired product could be isolated in 42% yield (entry 10). Finally, to further explore the scope of magnesium amides, we submitted the *in situ* generated magnesium piperidine to our reaction conditions, which delivered the desired sulfinamide in a promising 49% yield (entry 11). Baran and co-workers reported the use of turbo-amides,[178] previously developed in the Knochel's group.[177,179] Therefore, we treated piperidine with turbo-Grignard isopropylmagnesium chloride - lithium chloride complex and subsequently submitted it to our reaction conditions (entry 12). Nonetheless, the reaction became more complex and the yield dropped significantly.

Table 2.4 Initial screening of conditions for the synthesis of sulfinamide products



Entry	Substrate	Metal amide complex	Yield (%)[a] Product (by-product)
1			22
2			7 (72)
3			13
4			11
5			No product
6			18 (52)
7			26
8			traces
9			6
10			42
11			49 (35)
12			25 (38)

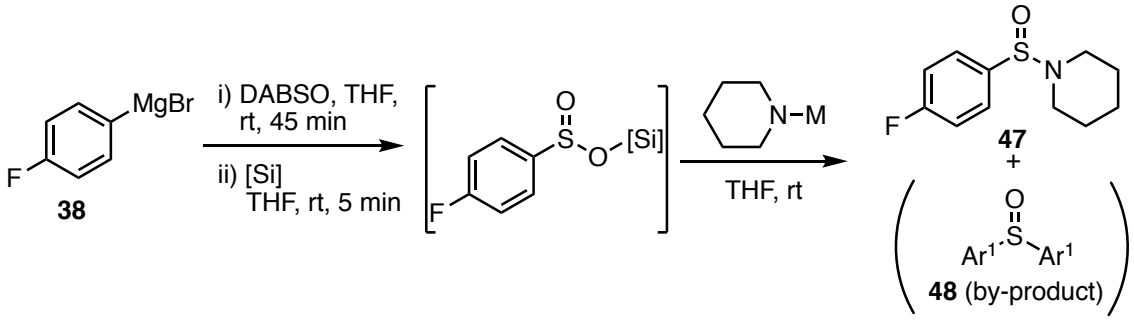
Reaction conditions: 1) R^2R^3NH (1.0 equiv.), R-M (1.1 equiv.), THF [0.3 M], at -20 °C, 1 hour under N_2 atmosphere; 2) R^1–MgX (1.0 equiv.), DABSO (0.5 equiv.), TMS–Cl (1.5 equiv.), R^2R^3N–M (0.75 equiv.), THF [0.33 M], under N_2 atmosphere. [a]Isolated yield.

Various experiments were performed using 4-fluorophenyl magnesium bromide, DABSO, TMS-Cl and magnesium chloride piperidine, in an attempt to improve the selectivity of the reaction, as well as the overall yield. First, we tried changing the number

of equivalents of the metal amide complex. However, increasing as well as decreasing the stoichiometry of the amide appeared to be detrimental to the reaction. Next, we tried decreasing the temperature for the final step of our reaction sequence, hoping that it would affect both the selectivity and the stability of the intermediate under our reaction conditions. We monitored the progress of the reaction by HPLC at 0 °C, -40 °C and at -78 °C. In the first two cases, when no more conversion to the product could be observed, the reaction was quenched and the sulfinamide product isolated. The yield of the reaction dropped to 40% and 23%, respectively, and some of the symmetrical sulfoxide by-product could still be observed. Leaving the reaction at -78 °C completely inhibited the reaction. Additionally, we tried to vary the concentration of the reaction, but it also proved to have a negative impact on the overall yield of the reaction.

Previously, we showed that the silicon group used for the formation of the silyl sulfinate intermediate had an influence on the outcome of the reaction (Section 2.1.6). Therefore, we tested various electrophilic groups which were susceptible to react with the oxygen atom of the sulfinate rather than with the sulfur atom to form the desired intermediate, starting from Grignard reagent **38**. We also subjected these silyl intermediates to various metal-piperidine complexes (Table 2.5). However, despite our best efforts, no improvement in the yield could be observed. The intermediates arising from the reaction of magnesium sulfinates with TMS-Cl and triethylsilyl chloride (TES-Cl) appeared to have similar reactivities and stability under our reaction conditions, while *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and DMPS-Cl showed lower reactivity. This could be explained from the increase in bulk around silicon atom, which could block the access to the sulfur atom for the metal piperidine complex.

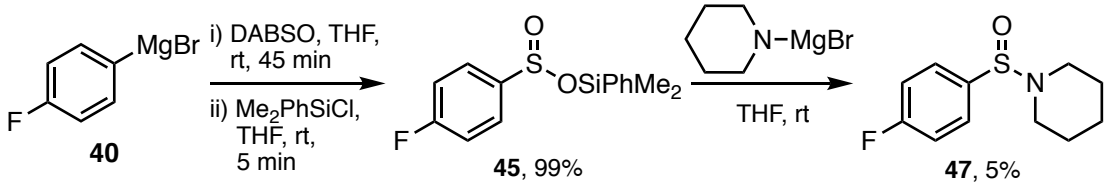
Table 2.5 Screening of silicon groups and metal amide complexes



Entry	Electrophile	Metal piperidine complex	Yield (%)[a] **47** (**48**)
1	TMS-Cl	Na	21 (68)
2	TMS-Cl	K	3 (10)
3	TES-Cl	Li	33 (42)
4	TES-Cl	MgCl	46 (29)
5	TES-Cl	MgCl.LiCl	27 (22)
6	TBDMS-Cl	Li	13 (33)
7	TBDMS-Cl	Na	13 (12)
8	TBDMS-Cl	K	11 (17)
9	TBDMS-Cl	MgCl	23 (43)
10	TBDMS-Cl	MgCl.LiCl	14 (40)
11	DMPS-Cl	Li	20 (43)
12	DMPS-Cl	Na	19 (54)
13	DMPS-Cl	K	11 (21)
14	DMPS-Cl	MgCl	31 (33)
15	DMPS-Cl	MgCl.LiCl	24 (56)

Reaction conditions: 1) R^2R^3NH (1.0 equiv.), R-M (1.1 equiv.), THF [0.3 M], at -20 °C, 1 hour under N_2 atmosphere; 2) i) **40** (1.0 equiv.), DABSO (0.5 equiv.), THF [0.33 M], under N_2 atmosphere; ii) [Si] (1.5 equiv.); iii) R^2R^3N–M (0.75 equiv.). [a]HPLC yield relative to benzophenone.

In our study for the synthesis of sulfoxides, we were able to isolate the silyl sulfinate intermediate **45** and to resubmit it successfully to our reaction conditions to deliver the desired product (Section 2.1.6). Therefore, we decided to isolate and subsequently submit the same intermediate **45** to our new reaction conditions (Scheme 2.12). This would have the effect of removing any unreacted Grignard reagent which could react with **45** and form the undesired by-product.



Scheme 2.12 Synthesis of sulfinamide 47 *via* silyl sulfinate ester intermediate 45

Despite various attempts with different sets of equivalents and temperatures, only traces of the desired sulfinamide product could be isolated, and the symmetrical sulfoxide by-product was still being generated. These results showed that the intermediate formed was not stable under our reaction conditions. It was then necessary to change our approach in order to gain access to the desired sulfinamide products in good yield.

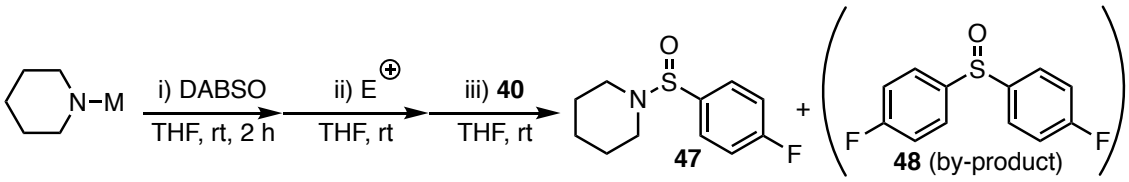
2.2.2 Second Optimisation of Conditions

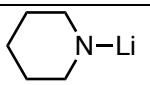
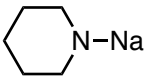
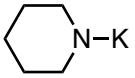
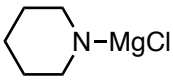
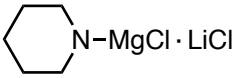
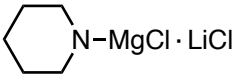
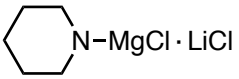
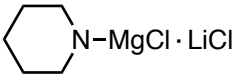
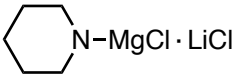
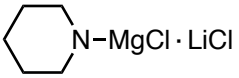
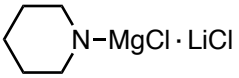
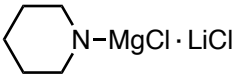
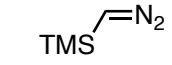
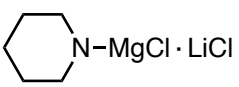
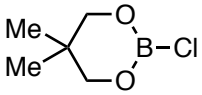
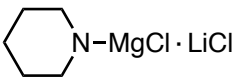
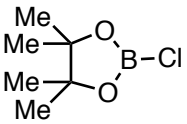
We considered inverting the order of addition of the different nucleophiles. Indeed, the formation of an amine sulfinate intermediate had been postulated previously by Tsai and co-worked, in one of the possible mechanisms for their one-step sulfonamides synthesis.[139] The first challenge was to ensure full conversion of the metal piperidine to the amide sulfinate intermediate. In order to monitor the sulfonylation step by HPLC, we used 4-phenylpiperidine, which we deprotonated with different metallic bases. Two hours were required for the metal piperidine to be fully converted in THF at room temperature, however, the full reaction sequence did not proceed well and afforded complex mixture of products and a poor mass balance. To further investigate the feasibility of this protocol, we submitted different metal piperidine complexes to DABSO for two hours at room temperature, before adding a variety of electrophiles, and finishing the reaction sequence with the addition of 4-fluorophenylmagnesium bromide **38**, in THF (Table 2.6). First, we focused on different metallic bases for the formation of the metal piperidine complex (entries 1-5), however, lithium, sodium, and potassium piperidine proved to be

inefficient, and only the Grignard and turbo-Grignard piperidine derivative successfully delivered the desired sulfinamide product in low yields of 18% and 14%, respectively (entries 4 and 5), however, the by-product **48** remained the major product formed. Next, we turned our attention to different silicon groups which could be used to form the corresponding silyl sulfinate intermediate. When TMS-Cl was substituted with TBDMS-Cl, the yield of the reaction dropped significantly (entries 6 and 7). However, when DMPS-Cl was used, **47** was isolated in a modest 35% yield (entries 8 and 9), but the by-product **48** was still formed in large amount. To ensure full conversion of the silicon group into the silyl sulfinate, we attempted to leave this step for longer, nevertheless, the yield of the overall procedure did not improve. Next, we tried to vary the amount of the final nucleophile (entries 10 and 11). Although these experiments did not succeed in improving the yield, we found that using an excess of Grignard reagent was favourable for the formation of the undesired symmetrical sulfoxide, which could indicate that any unreacted Grignard reagent left in the reaction mixture could react with the sulfinamide product and displace the piperidine.

Finally, we tested different types of electrophiles such as TMS-diazomethane, and chloro dioxaborinanes, in the hope that they could bring better stability and selectivity to the reaction (entries 12-14). However, the formation of the corresponding electrophilic sulfinate intermediate could not be confirmed, and none of these attempts delivered the desired product **47**.

Table 2.6 Optimisation of the reaction conditions for the synthesis of **47** via an amide sulfinate intermediate

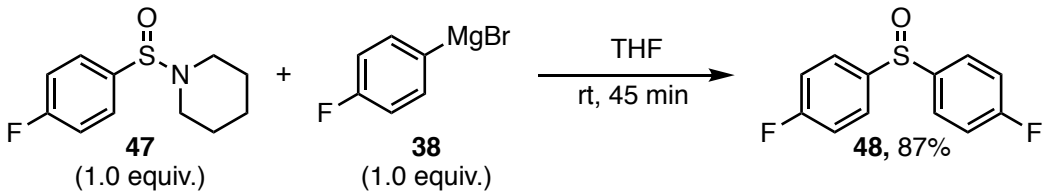


Entry	Metal-piperidine complex	Electrophile	Yield (%)[a] **47** (**48**)
1		TMS-Cl	No Product
2		TMS-Cl	No Product
3		TMS-Cl	No Product
4		TMS-Cl	18 (55)
5		TMS-Cl	24 (42)
6		TBDMS-Cl	5 (14)
7[b]		TBDMS-Cl	9 (17)
8		DMPS-Cl	35 (43)[e]
9[b]		DMPS-Cl	33 (48)[e]
10[c]		DMPS-Cl	8 (73)[e]
11[d]		DMPS-Cl	3 (21)
12			No product
13			No product
14			No product

Reaction conditions: 1) R^2R^3NH (1.0 equiv.), R-M (1.0 equiv.), THF [0.33 M], at -20 °C, 1 hour under N_2 atmosphere, 2) i) DABSO (0.5 equiv.) 2 hours at rt, ii) electrophile (1.5 equiv.), iii) **40** (0.75 equiv.). [a]HPLC yield relative to benzophenone. [b]Step 2 left at room temperature for 1.5 hour. [c]**40** (2.0 equiv.). [d]**40** (0.5 equiv.). [e]Isolated yield.

Next, we speculated that the isolation of the amide sulfinate intermediate could allow us to have a better control over the overall reaction sequence. This could potentially allow the reaction to proceed under milder reaction conditions and therefore improve the stability of the various intermediates. However, despite numerous attempts, the amide sulfinate intermediate could never be isolated from the reaction successfully. Sadly, this was also the case when we attempted to isolate the amide silyl sulfinate intermediate, which, we assume decomposed during the work up.

Finally, we decided to subject the pure sulfinamide **47** to 4-fluorophenylmagnesium bromide **38**, to confirm that a Grignard reagent could displace the piperidine fragment to form the symmetrical sulfoxide (Scheme 2.13). Performing this experiment affords the symmetrical sulfoxide product **48** in 87% isolate yield. This demonstrates that our latest reaction sequence for the synthesis of sulfinamide products is not viable, as any of the unreacted Grignard reagent would be able to attack the electrophilic sulfur atom and therefore displace the piperidine fragment of the sulfinamide.



Scheme 2.13 Synthesis of symmetrical sulfoxide 48 from sulfinamide 47 and Grignard reagent 38

Despite our best efforts, the reaction we envisioned did not proceed as well as we had hoped. At this point, we decided not to investigate any further the reaction conditions leading to sulfinamide products.

2.3 Project Summary

In summary, a general one-pot protocol for the generation of alkyl, aryl and heteroaryl sulfoxides has been developed based on the generation and coupling of magnesium and lithium sulfinates using DABSO, and trimethylsilyl chloride. This method serves as an attractive alternative to current methods of sulfoxide synthesis by employing readily accessible organometallic reagents, bench-stable and easy-to-handle SO_2 surrogate DABSO, at room temperature, and with short reaction times, in a one-pot process; avoiding the use of gaseous sulfur dioxide and of stoichiometric oxidant and thiols.

The synthesis of sulfinamide products using a similar approach was studied. However, despite a significant investigation of reaction conditions, only a few sulfinamide products were synthesised, in modest to low yield. Nevertheless, due to the high demand for new routes to sulfinamides, the attractiveness of this protocol still remains. Indeed, if successful, it would allow a rapid and easy access to sulfinamides by coupling readily accessible Grignard reagents, DABSO, dimethylphenylsilyl chloride, and a metal-amide complex, under mild reaction conditions.

Chapter 3 - Copper-Catalysed Oxidative Synthesis of Activated Sulfonate Esters

3.1 Traditional Synthesis and Applications

Sulfonyl (-SO_2-) containing functional groups such as sulfonamides, sulfones, and sulfonate esters, have proved to be of great importance for numerous industries. Indeed, the sulfonamide and the sulfone motifs are ubiquitous in pharmaceutical and agrochemical products.[9,180] The presence of the sulfonamide unit in antibiotics emerged in the 1930s, since then, their application in the pharmaceutical industry has vastly expanded. The sulfonamide and sulfone motifs can now be found in blockbuster medical agents such as anti-diabetics, anticancer drugs, thrombin inhibitors, and anticonvulsants (Figure 3.1).[37,181,182] Sulfonamides have also been used extensively in synthetic organic chemistry as useful amine protecting groups.

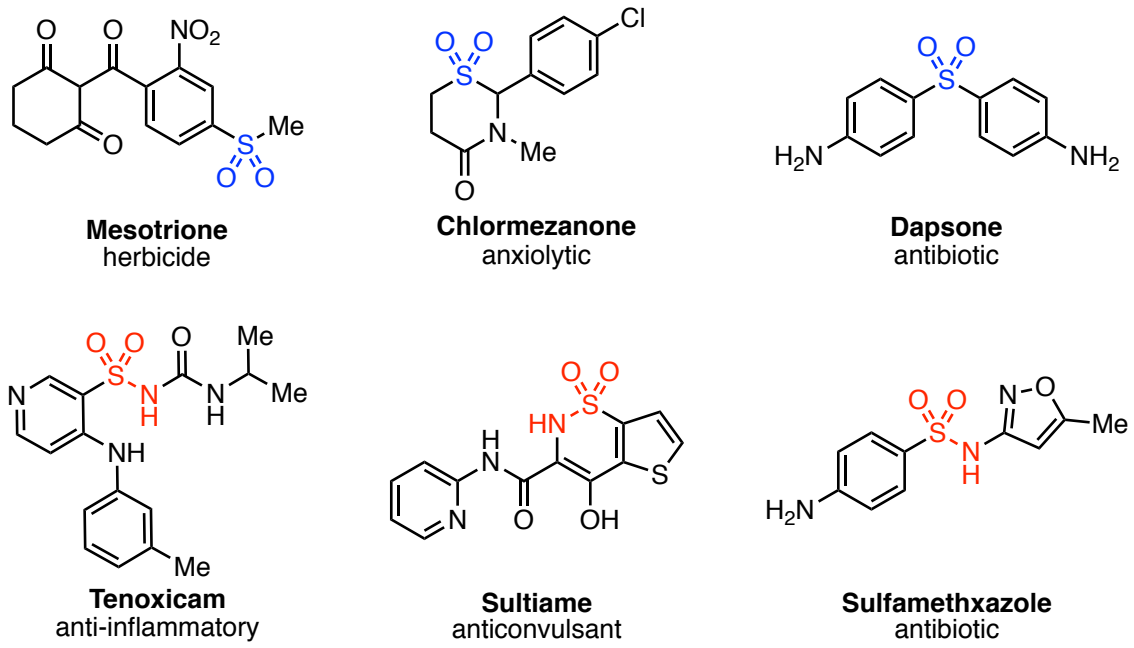
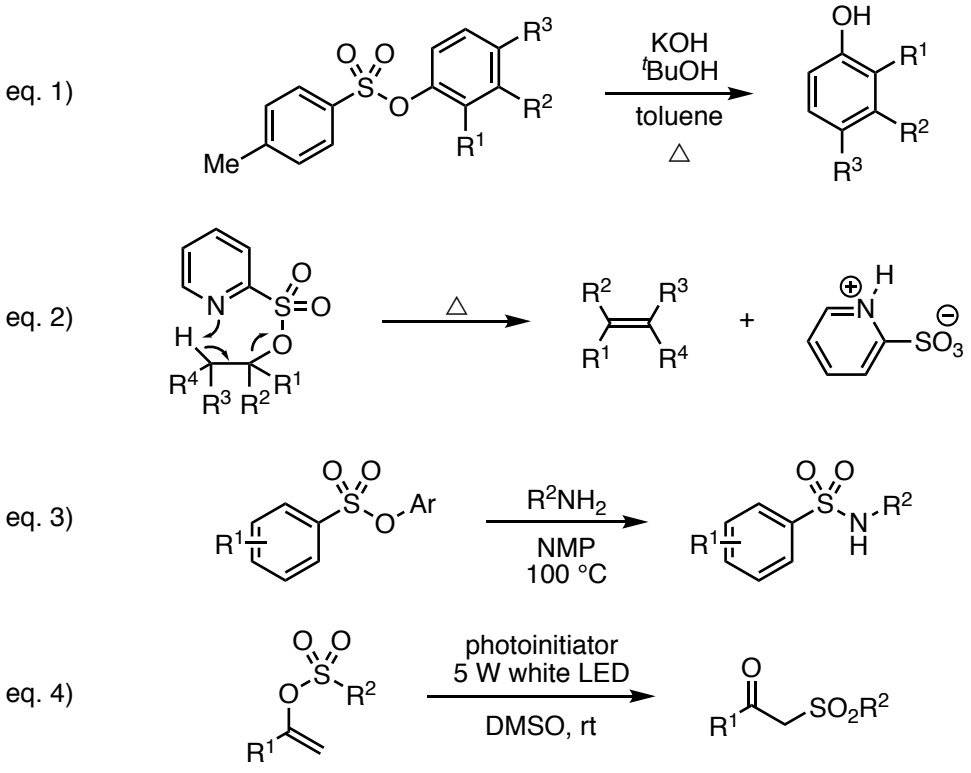


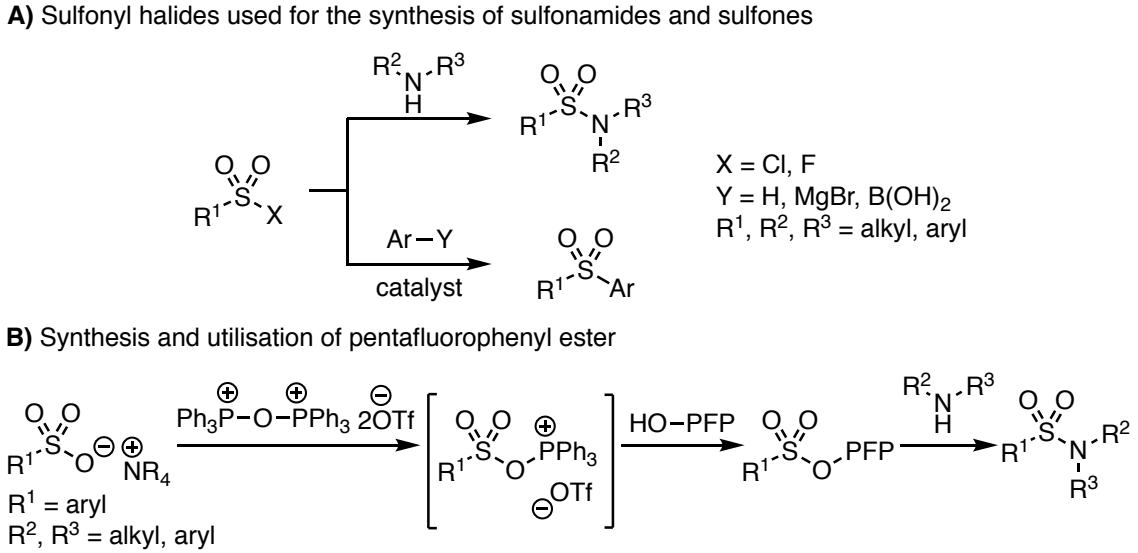
Figure 3.1 Examples of commercial sulfone/sulfonamide containing drug molecules

The presence of sulfonate esters in final products with industrial applications is arguably less common. However, their application as valuable intermediates is well documented. One of the most studied transformations, which proceeds by a sulfinate ester species is the activation of alcohols with a tosyl group.[183] The frequent use of this protecting group is explained by its ability to survive various harsh reaction conditions, and because it can be easily removed under basic conditions (Scheme 3.1, eq. 1). However, the utilisation of sulfonate esters is not limited to the protection of alcohols. Indeed, in 1988 Corey documented an olefin synthesis *via* pyrolysis of sulfonate esters (Scheme 3.1, eq. 2).[184] This publication exemplifies the ability of the sulfonate ester moiety (-SO_3-) to act as a leaving group. Another well-established application of sulfonate esters is for the formation of sulfonamides and sulfones (Scheme 3.1, eq. 3 and 4).[185-187] The feasibility of this reaction is based on the strong electrophilic character of the sulfur atom in the sulfonate ester moiety.



Scheme 3.1 Examples of applications of sulfonate esters as synthetic intermediates

Despite some examples reporting the utilisation of sulfonate esters as versatile precursors, the most common method to prepare sulfone and sulfonamide products remains through the reaction of sulfonyl halides with the appropriate nucleophiles (Scheme 3.2, A).[35,36,118,188,189] Sulfonyl chlorides' are often the electrophile of choice for these reactions. The prevalence of the utilisation of sulfonyl chlorides can be rationalised by their broad commercial availability, and their high reactivity.[160] However, some difficulties are also associated with the sulfonyl chlorides' high reactivity, as this may limit their stability to long term storage due to their moisture sensitivity, and make their synthesis and purification difficult.[36] In order to overcome these limitations, several strategies have been explored, such as the *in situ* generation of sulfonyl chlorides,[119,190,191] or by employing alternative forms of sulfonyl electrophiles.[36,185,192] Pentafluorophenyl (PFP) sulfonate esters have emerged as an efficient replacement for sulfonyl chlorides in the formation of sulfonamides.[186,192-196] These activated sulfonate esters are generally highly crystalline, and are bench-stable, whilst conserving their useful electrophilicity (Scheme 3.2, B).



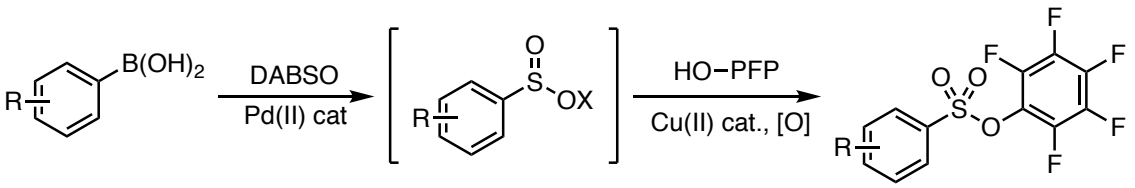
Scheme 3.2 (A) Sulfone and sulfonamide synthesis *via* sulfonyl halides; (B) sulfonamide synthesis *via* pentafluorophenyl sulfonate esters

However, a major disadvantage associated with aryl PFP sulfonate esters is that their synthesis usually starts from the corresponding sulfonic acid, or related salt, and these reagents suffer from a limited commercial availability.[194]

3.2 Origin of Project and Previous Work

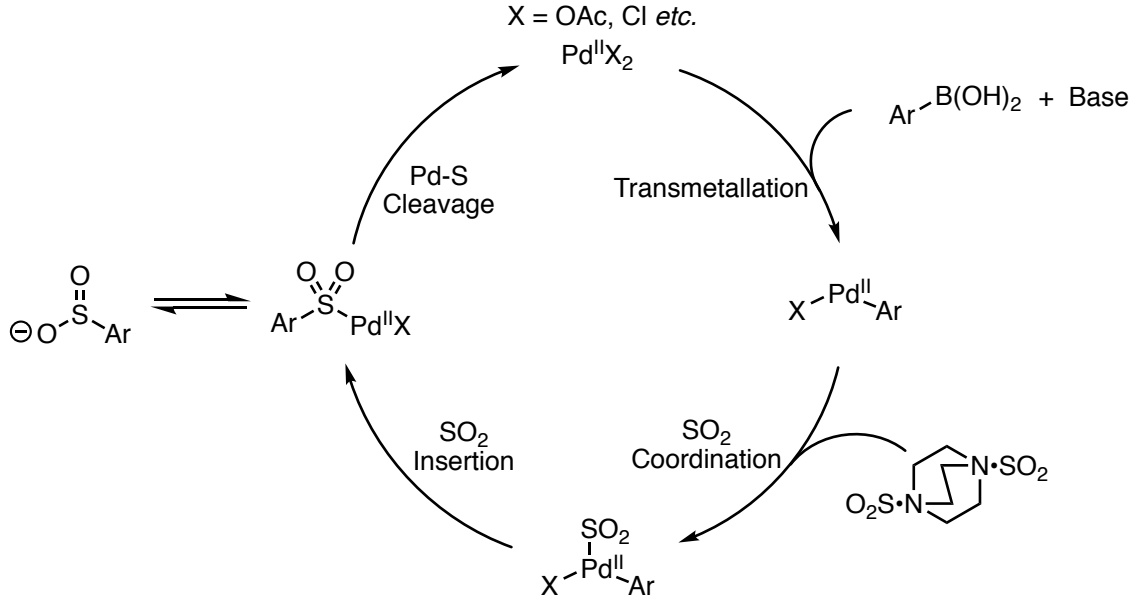
Given that the general route to sulfonamide and sulfone products can be restrictive due to the difficulty of synthesis and handling of the starting materials – often sulfonyl chloride species – a more general synthetic pathway leading to a more convenient to use, and yet effective, sulfonyl derivative is greatly sought. Pentafluorophenyl sulfonyl esters have been identified as viable alternatives to sulfonyl chlorides, however, their synthesis is limited by the poor availability of starting materials. Therefore, a new methodology for their synthesis, using easy-to-handle starting materials, with broad commercial availability, would facilitate the access to intermediate sulfonate esters, and consequently to sulfonamides and sulfones.

Our group, and others, previously reported the use of DABSO as a sulfur dioxide source, in combination with boronic acids – one of the most diverse set of monomers available – to generate *in situ* sulfinates under the action of a catalyst.[129,131,197,198] Therefore, we envisaged an alternative pathway to PFP sulfonate esters, starting from boronic acids, using our previously reported set of reaction conditions, with the challenge of identifying new reaction conditions which would allow the *in situ* transformation of the sulfinate intermediates into the desired sulfonate ester products (Scheme 3.3).



Scheme 3.3 Formation of PFP sulfinate ester from *in situ* generated sulfinate species

The formation of the sulfinate intermediates from boronic acids and DABSO is based on redox-neutral palladium catalysis (Scheme 3.4).[129] This process for the synthesis of sulfinate species does not requires the use of specialised, often expensive, phosphine ligands, or the presence of oxidants, therefore allowing a great functional group tolerance and mild reaction conditions.



Scheme 3.4 Proposed catalytic cycle for the sulfination of aryl boronic acids

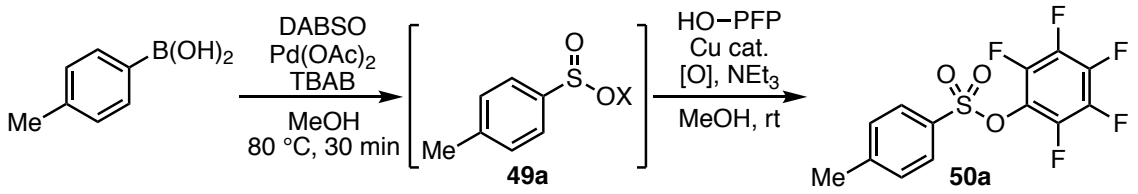
3.3 Initial Investigations

3.3.1 Optimisation of Conditions

To assess the feasibility of our proposed route for the synthesis of pentafluorophenyl sulfonate esters, we began by exploring the transformation of 4-tolylboronic acid into PFP sulfonate ester **50a** (Table 3.1). We used our reported conditions for sulfinate formation,[129] with DABSO as a sulfur dioxide source, boronic acid, and $Pd(OAc)_2$ as a catalyst, for the formation of the sulfinate intermediate **49a**, and then explored a variety of reaction conditions to transform the sulfinate species into the desired PFP sulfonate ester. Our initial screening focused on various oxidising agents subsequent to the

formation of the sulfinate intermediate. However, the use of I_2, NBS, and *tert*-butyl hydroperoxide in combination with pentafluorophenol provided only trace amounts of the PFP sulfonate ester (entries 1-3). However, the addition of $Cu(OAc)_2$ as a catalyst significantly increased the yield of the reaction (entries 4 and 5). By further studying the combination of copper (II) salts with various oxidising agents, we found that the use of $K_2S_2O_8$ as the oxidising agent, $CuBr_2$ as the catalyst, and the addition of molecular sieves afforded the desired PFP sulfonate ester **50a** in good yield (entries 6-11). Adding NaBr proved to have a favourable effect on the reaction and allowed the isolation of the desired PFP sulfonate ester in 86% yield (entry 12).

Table 3.1 Reaction optimisation for the formation of pentafluorophenyl sulfonate ester **50a**



Entry	Catalyst	[O]	Additive	Yield (%)[a]
1	-	I_2	-	Trace
2	-	NBS	-	0
3	-	^{t}BuOOH	-	0
4	$Cu(OAc)_2$	I_2	-	13
5	$Cu(OAc)_2$	NBS	-	37
6	$Cu(OAc)_2$	$K_2S_2O_8$	-	42
7	$Cu(OTf)_2$	$K_2S_2O_8$	-	30
8	$Cu(acac)_2$	$K_2S_2O_8$	-	34
9	$Cu(OAc)_2$	$Na_2S_2O_8$	-	65
10	$Cu(OAc)_2$	$Na_2S_2O_8$	3 Å MS	69
11	$CuBr_2$	$Na_2S_2O_8$	3 Å MS + NaBr	75
12	$CuBr_2$	$Na_2S_2O_8$	3 Å MS + NaBr	92 (86)

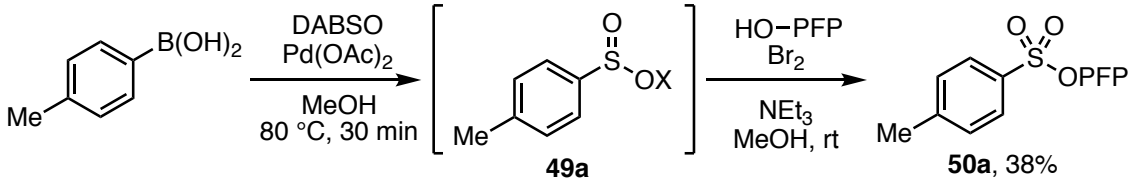
Reaction conditions: boronic acid (0.5 mmol), DABSO (0.5 mmol), TBAB (0.15 mmol), $Pd(OAc)_2$ (0.025 mmol), MeOH [0.17 M], 80 °C for 30 minutes; then pentafluorophenol (0.25 mmol), $Na_2S_2O_8$ (0.5 mmol), $CuBr_2$ (0.05 mmol), NaBr (0.15 mmol), NEt_3 (1.0 mmol), 3 Å MS (250 mg). [a]Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. Value in parentheses is isolated yield.

The second step occurs at room temperature and requires 18 hours to go to completion, in an attempt to increase the rate of the reaction, we increased the temperature used for this step. However, if the temperature was increased above 60 °C, the crude reaction became more complex, and a large amount of the pentafluorophenol could be recovered. With the same goal of reducing the time of reaction, we tried increasing the equivalents of pentafluorophenol used in the reaction, and the number of equivalents of triethylamine. Nevertheless, these variations were either detrimental to the reaction or did not show any improvement.

3.3.2 Mechanistic Considerations

In order to gain some insights on the role played by the copper catalyst in the reaction, we started by removing it from the reaction mixture. Doing so had the effect of suppressing any reactivity between the sulfinate species and pentafluorophenol. We postulated that the copper (II) salt could act as a Lewis acid by activating the *in situ* generated sulfinate species. Therefore, we tested this hypothesis by exchanging $CuBr_2$ with various Lewis acids ($Zn(OTf)_2$, $Sc(OTf)_3$, $AgNO_3$, AgOAc, Ag_2CO_3). However, none of the Lewis acids employed were able to promote the formation of the desired PFP sulfonate ester **50a**. In the reaction conditions reported previously by our group for the palladium-catalysed sulfonamide synthesis, some examples only proceeded in the absence of TBAB. Therefore, in order to simplify the reaction and thus have a better understanding of the possible interactions between the copper (II) salt and the rest of the reagents, we decided to perform our standard reaction without TBAB. The formation of the sulfinate proceeded almost as well, but to our surprise, the second step of the reaction was completely inhibited. This result suggests that the combination of TBAB and the copper catalyst was essential for the reaction to happened. Similar reaction conditions were previously described in the literature, where $CuBr_2$ and a high concentration of

bromide ion was reported to form *in situ* a novel $CuBr_4^{2-}$ species.[199] This copper species was then described as an efficient brominating agent on alkenyl glycosides.[200] Based on these previous reports, we postulated that once the sulfinate intermediate was formed, it could be brominated to form a sulfonyl bromide species. The bromide could then be displaced by pentafluorophenol, affording the desired sulfonate ester. However, when Br_2 was used in place of $CuBr_2$, NaBr, $Na_2S_2O_8$ and TBAB, the desired product could only be isolated in 38% yield (Scheme 3.5). This result and the possible presence of the $CuBr_4^{2-}$ species could suggest that the process by which the reaction occurs is not a conventional electrophilic addition.



Scheme 3.5 Synthesis of sulfinate ester **50a** using Br_2

Therefore, it is possible to hypothesise that TBAB plays multiple roles in our reaction sequence. In the first step, although its presence is not compulsory for the reaction to proceed, we believe that TBAB could promote a faster SO_2 coordination/insertion. It is also known in palladium-catalysed Suzuki-type cross-coupling, that the use of alkylammonium salts as additives can limit the hydro-deboronation side-reaction.[201-203] In our cases, it is possible that the ammonium salt may play a similar role in limiting the homocoupling of the boronic acid substrate. Finally, in our second step, the presence of TBAB was proved to be essential for the reaction to proceed. When TBAB was removed and only NaBr was added into the reaction for the second step, the desired PFP sulfonate ester could be isolated in slightly reduced yield. This result suggests that the bromine ion is involved in the transformation process, possibly to promote the formation of the $CuBr_4^{2-}$ catalyst species.

3.4 Scope of the Reaction

3.4.1 Scope of the Boronic Acids

With the optimised reaction conditions in hand, we examined the scope of this transformation with respect to the boronic acid substrates (Figure 3.2). Numerous boronic acids were found to be suitable substrates for this reaction. Boronic acids featuring a range of electron-donating substituents at all positions of the aryl ring afforded the desired pentafluorophenyl sulfonate esters in good yields (**50a-n**). It is worth noting that examples bearing sensitive functional groups such as free phenols (**50i**), amido (**50j-k**), and amino groups (**50l**) were tolerated under our reaction conditions. Methylenedioxyphenyl boronic acid (**50m**), and benzodioxane boronic acid (**50n**) delivered the desired sulfinate esters in high yield. Aryl boronic acids bearing electron-withdrawing substituents (**50o-r**) also proceeded smoothly under our optimised reaction conditions, although the isolated yields were slightly lower compared to the electron-donating examples. 4-Bromo-pentafluorophenyl sulfonate ester **50q** was synthesised on a multi-gram scale from a 10 mmol reaction. More complex substrates, such as tyrosine derived **50s**, and tri-substituted example **50t**, were generated in good yields. Next, we turned our attention to heteroaromatic boronic acid substrates. Heterocycles such as benzofuran (**50u**), indole (**50v**), and azaindole (**50w**) were subjected to our reaction conditions and delivered the corresponding PFP sulfonate ester products in good yields.

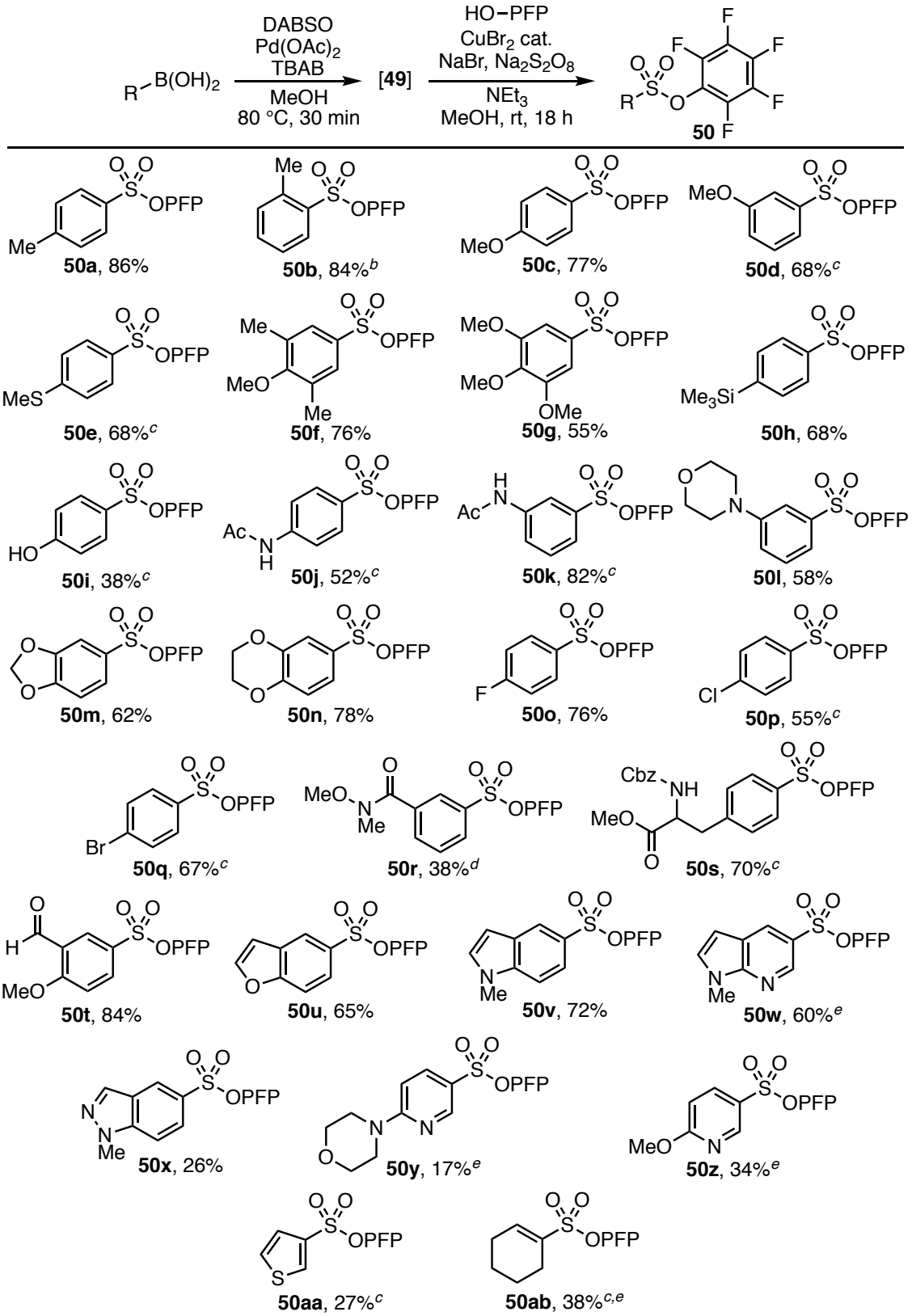


Figure 3.2 Evaluation of reaction scope with respect to boronic acid[a]

[a]Reaction conditions: boronic acid (0.5 mmol), DABSO (0.5 mmol), TBAB (0.15 mmol), $Pd(OAc)_2$ (0.025 mmol), MeOH [0.17 M], 80 °C for 30 minutes; then PFPOH (0.25 mmol), $Na_2S_2O_8$ (0.5 mmol), $CuBr_2$ (0.05 mmol), NaBr (0.15 mmol), NEt_3 (1.0 mmol), 3 Å MS, rt, 18 hours. [b]No TBAB used. [c]Sulfination step 1 hour. [d]Sulfination step 3 hours. [e]MeOH/1,4-dioxane (1:1) [0.16 mL] used as solvent.

However, when indazole boronic acid was submitted to our reaction sequence, the corresponding PFP sulfonate ester **50x** was isolated in low yield. Pleasingly, we were able to successfully transform pyridine boronic acid substrates (**50y, z**), as well as a thiophene substrate (**50aa**) in the corresponding pentafluorophenol sulfonate esters. Although the isolated yield of **50ab** was low, we were pleased to see that alkenyl boronic acids could also be tolerated, to an extent, under our reaction conditions.

3.4.2 Scope of the Phenol Coupling Partner

Having explored the transformation of a range of *in situ* generated sulfinate species with pentafluorophenol, we turned our attention to the different classes of sulfonate species accessible using our reaction sequence. Up to this point, sulfinate intermediates had been utilised in coupling reaction with strong nucleophiles such as amines or hydrazines to generate sulfonamide and aminosulfonamide products respectively.[124,125,190] However, pentafluorophenol can be considered as a relatively weak nucleophile compared to amine or hydrazine substrates. Thus, we focused our attention on the exploration of a range of coupling partners which were not suitable for the previously reported sulfinate intermediary transformations. Our first interest was to employ various phenol substrates in our transformation with varying pK_a values (Figure 3.3). Employing other phenols would allow us to generate a library of sulfonate esters with different properties in term of stability and reactivity. We anticipated a trend in term of reactivity of the phenols used, as the pK_a increased, we assumed that the reactivity would also increase. However, when different phenols bearing various substituents were submitted to our optimised reaction conditions, the majority showed no reactivity. Generally, only the phenols with the closest pK_a value of pentafluorophenol were converted into the desired sulfonate esters in low yields (**51a** and **b**). Numerous bases were tried in order to increase the reactivity of the phenols, unfortunately, no

improvement in the conversion of the sulfinates into the desired sulfonate esters was observed. These results could indicate that the reaction has a strong dependence on the pK_a value of the coupling partner.

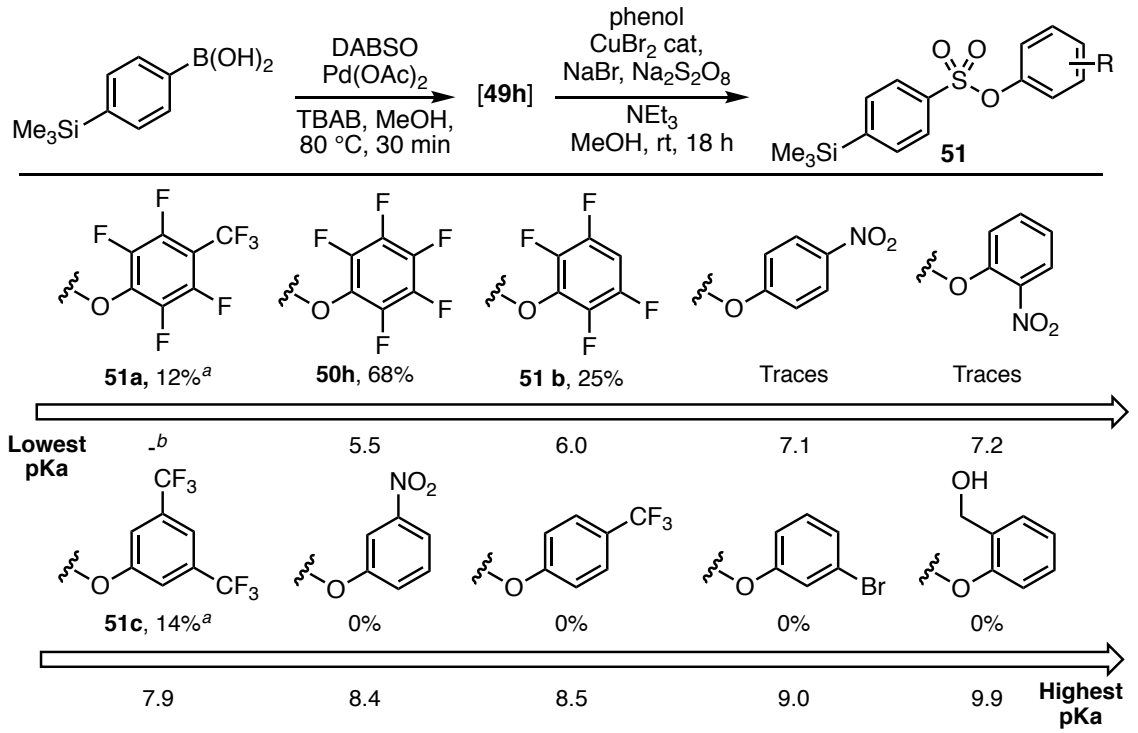
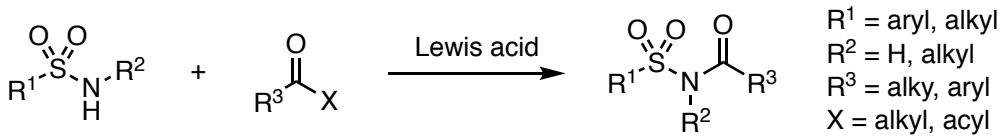


Figure 3.3 Scope of the phenol coupling partner and their pK_a value in water

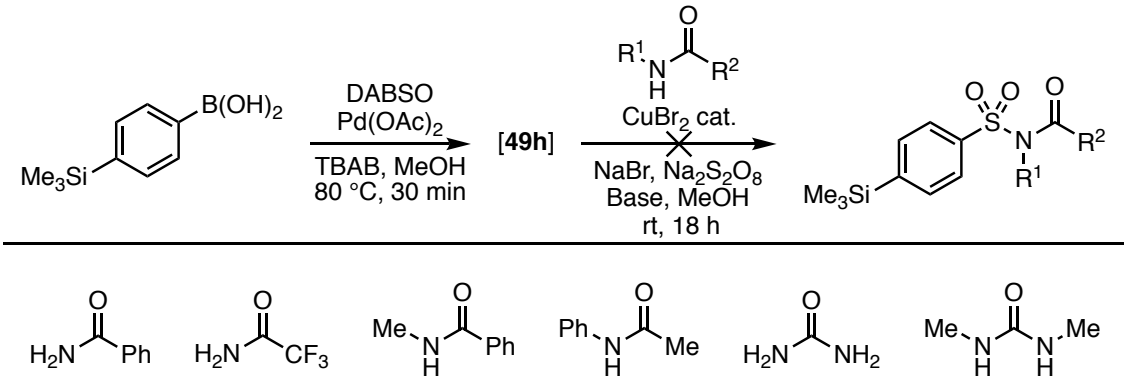
Reaction conditions: boronic acid (0.5 mmol), DABSO (0.5 mmol), TBAB (0.15 mmol), $Pd(OAc)_2$ (0.025 mmol), MeOH [0.17 M], 80 °C for 30 minutes; then phenol (0.25 mmol), $Na_2S_2O_8$ (0.5 mmol), $CuBr_2$ (0.05 mmol), NaBr (0.15 mmol), NEt_3 (1.0 mmol), 3 Å MS, rt, 18 hours. [a]Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [b]Assumed lower, no literature value.

Amide and urea moieties are of significant importance in the pharmaceutical industry.[204] However, because of their weak nucleophilic character, their direct coupling with sulfinate species was, to the best of our knowledge, never documented. These products are usually formed from Lewis acid promoted *N*-acylation of sulfonamides with various anhydrides or esters (Scheme 3.6).[205,206]



Scheme 3.6 Lewis-acid promoted *N*-acylation of sulfonamides

Motivated by the fact that pentafluorophenol proceeded well under our optimised reaction conditions, we hypothesised that primary or secondary amides and ureas might be potent coupling partners for our transformation (Scheme 3.7). A range of primary and secondary amides and ureas were submitted to our reaction sequence, unfortunately, the desired sulfonamide products could not be generated. In order to ensure full deprotonation of the amides/ureas, triethylamine was replaced in favour of various other amine bases such as DBU, TBD, MTBD, and proton sponge. However, the reaction did not proceed, both the sulfinate and the amide/urea coupling partners were fully recovered after 18 hours at room temperature.



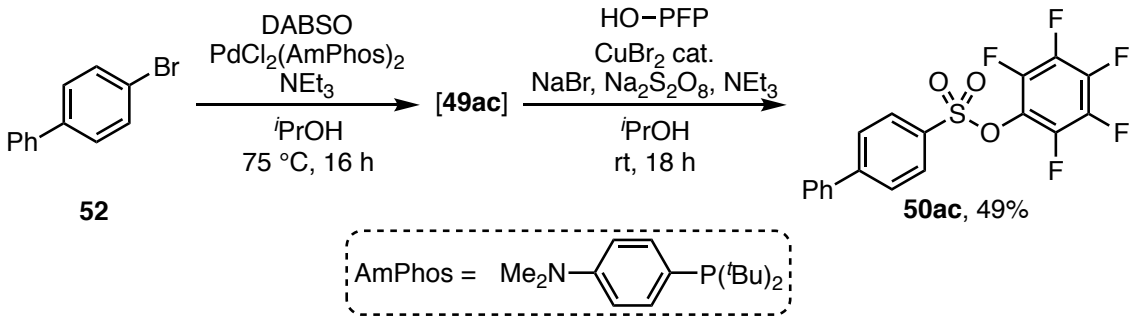
Scheme 3.7 Copper-catalysed sulfonamides synthesis using ureas and amides as coupling partners

Therefore, it was decided to increase the temperature of the reaction while using DBU as a base, in an attempt to force some reactivity. Unfortunately, this too proved to be ineffective. Thus, we decided not to investigate any further the copper-catalysed coupling of in situ generated sulfinate and amides/ureas.

3.5 Alternative Sulfinates

Although a broad range of boronic acids are commercially available, which gives access to a vast library of starting materials for the synthesis of pentafluorophenyl sulfonate esters, it was important to demonstrate that this protocol could also be applied to *in situ* generated sulfinate intermediates derived from the reactions of DABSO with other types of starting materials. Being able to combine our novel route for the transformation of sulfinates into sulfonate esters with previously reported methods describing complementary *in situ* synthesis of sulfinates, would therefore diversify the reaction conditions which could be employed for the formation of the pentafluorophenyl sulfonate ester species, which could be compatible with functional groups that were not tolerated under the previous reaction conditions.

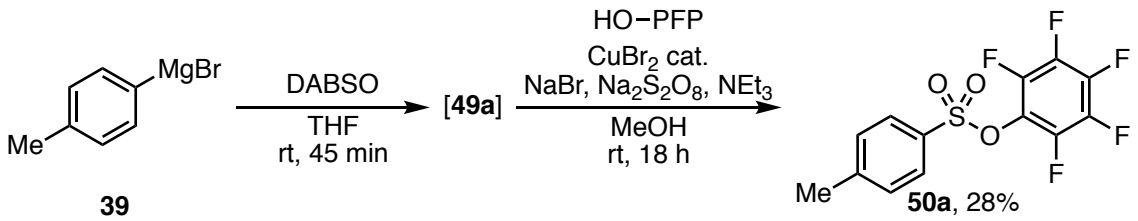
Our group had previously documented a palladium-catalysed synthesis of sulfonyl fluoride products from aryl bromides, which are arguably one of the most abundant commercially available starting materials.[130] Therefore, being able to merge these two processes would further emphasise the utility of our novel transformation and broaden its range of application. Aryl bromide **52** was first converted into the corresponding sulfinate **49ac** according to the reported palladium-catalysed procedure. The *in situ* generated sulfinate intermediate was then converted into the corresponding PFP sulfonate ester **50ac**, employing our reported copper-catalysed reaction conditions for the sulfinate ester formation (scheme 3.8).



Scheme 3.8 PFP sulfonate ester synthesis starting from aryl bromide

The extended reaction time necessary to achieve sulfinate formation, compared to the boronic acid examples, makes this method less attractive, although, this transformation also establishes an important proof of concept that aryl bromides are viable substrates for our reaction and can be used to deliver PFP sulfonate esters.

To explore even further the range of sulfinate intermediates capable of being employed into our copper-catalysed transformation, and given our previous demonstration of the efficient addition of Grignard reagents to DABSO to form magnesium halide sulfinate salts (Section 2.1),[1] we envisioned their coupling with pentafluorophenol under our reaction conditions. Therefore, 4-tolylmagnesium bromide **39** was reacted with DABSO, affording the corresponding sulfinate intermediate. After a solvent switch from THF to methanol, the sulfinate was submitted to our reaction conditions to afford the desired PFP sulfinate ester **50a** (Scheme 3.9).



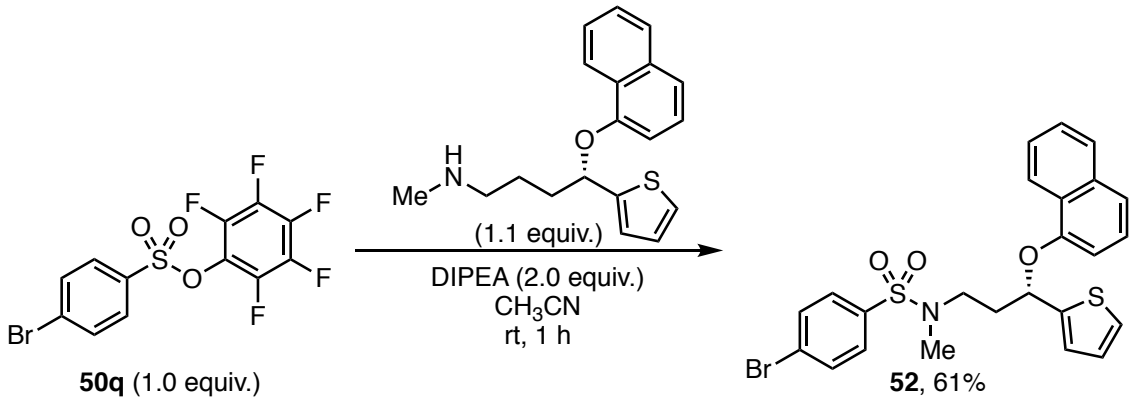
Scheme 3.9 PFP sulfonate ester synthesis starting from aryl Grignard reagent **39**

Although PFP sulfinate ester **50a** was synthesised in a relatively low yield using this reaction sequence, compared to that derived from 4-tolylboronic acid (86%), it is worth noting that no re-optimisation was performed. Therefore, it is reasonable to believe that, upon further optimisation, the efficiency of this process could be significantly improved. However, our interest in performing this transformation was only to further exemplify the wide range of applications possible by using our novel copper-catalysed transformation of sulfinate species into PFP sulfonate esters.

3.6 Derivatisation of the PFP Sulfonate Esters

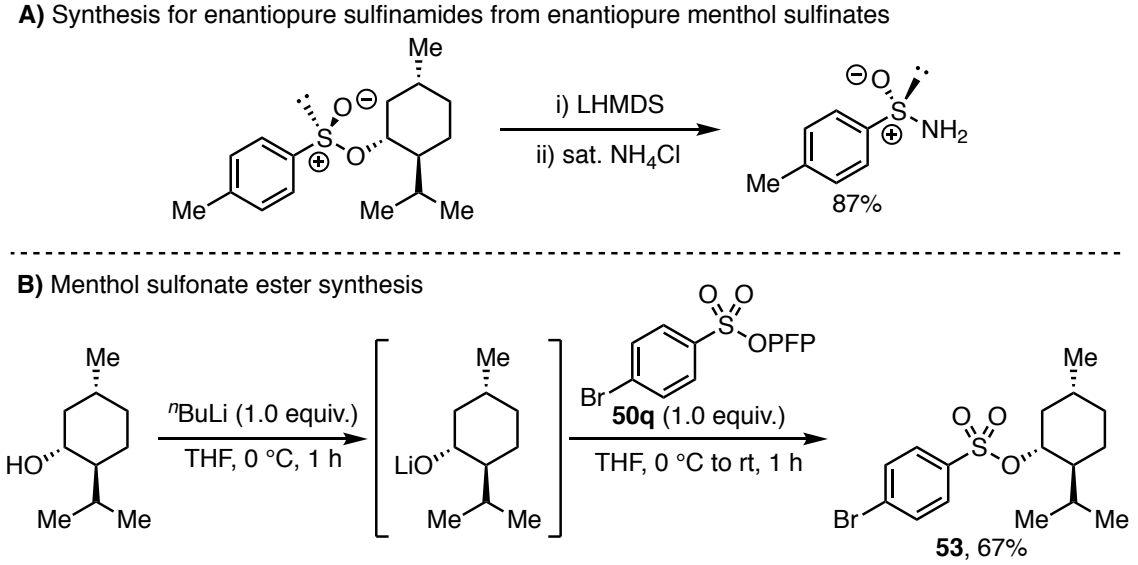
To demonstrate the utility of the pentafluorophenol sulfonate esters species, as a valuable intermediate for synthetic chemistry, we chose to further transform the 4-bromophenylsulfonate ester (**50q**) into a variety of products of interest.

As discussed previously, the importance of the sulfonamide moiety in numerous industries is now well established (Section 3.1). Therefore, the first transformation of **50q** which we chose to attempt was to synthesise a sulfonamide product (Scheme 3.10). Various reaction conditions have previously been reported for such a transformation, however, we decided to follow the conditions reported by Kristensen and co-workers,[186] which did not require any specific equipment such as microwave,[193] or any heating or cooling,[195] or the use of any additives.[196] Indeed, the simple treatment of the sulfonate ester **50q** with the appropriate secondary amine, in the presence of Hünigs base, at room temperature for one hour, provided the desired sulfonamide product **52** in good yield. The amine used in this transformation is the anti-anxiety compound Duloxetine, first commercialised by the pharmaceutical company Eli Lilly.



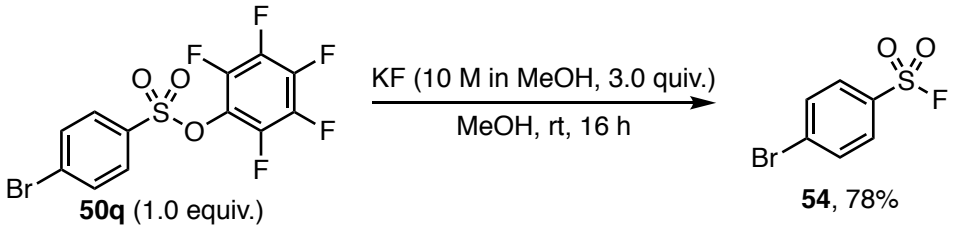
Scheme 3.10 Synthesis of a Duloxetine derivative from pentafluorophenol ester **50q**

In 1999, Davis and co-workers developed a method for the synthesis of enantiopure sulfinimines.[163] Their process was based on the reaction of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with LHMDS, to obtain the desired enantiopure sulfinamide (Scheme 3.11, A). Although sulfonate ester species do not have a chiral sulfur atom, a chiral substituent directly bound to the sulfur atom, such as a menthol substituent, could lead to interesting properties and reactivities. To synthesise this new menthol sulfonate ester (**53**), our PFP sulfonate ester **50q** was treated with an *in situ* generated lithium menthol species,[207] affording the desired sulfonate ester in good yield (Scheme 3.11, B).



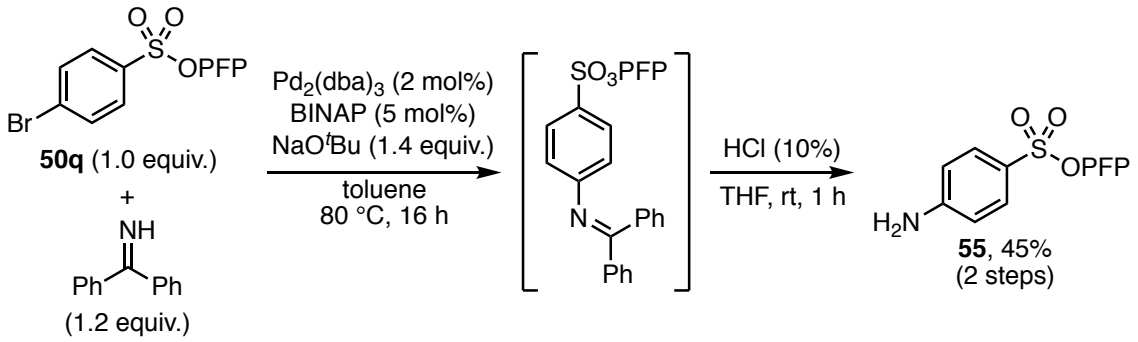
Scheme 3.11 A) Use of enantiopure menthol sulfinate, B) synthesis of menthol sulfonate ester **53** form PFP sulfonate ester **50q**

The importance of sulfonyl fluorides in chemical biology is now well documented,[208] they have also been used as more stable and less active sulfonyl chloride alternatives, for the incorporation of the sulfonamide moiety into molecules of interest for the pharmaceutical and agrochemical industries.[36] Thus, treating the PFP sulfonate ester **50q** with a solution of KF in methanol delivered the desired sulfonyl fluoride **54** in 78% yield (Scheme 3.12).



Scheme 3.12 Derivatisation of PFP sulfonate ester **50q** into sulfonyl fluoride **54**

Finally, one of the most interesting properties of the PFP sulfonate ester is its ability to tolerate reaction conditions in which other sulfonyl groups cannot survive. In 2005, Avitabile and co-workers reported the synthesis of biaryl and heteroaryl PFP sulfonate esters *via* a Suzuki-Miyaura reaction.[209] In order to further investigate the reaction conditions which are tolerated by the pentafluorophenol sulfonate ester products, the aryl bromide of sulfonate **50q** was used as starting material to perform a palladium-catalysed amination reaction, coupling with benzophenone imine, following by acid deprotection.



Scheme 3.13 Palladium-catalysed animation reaction on PFP sulfonate ester **50q** to introduce a primary amine

This reaction sequence delivered the desired primary amine **55** in 45% yield over two steps, with the pentafluorophenyl sulfonate ester group remaining intact (Scheme 3.13).

3.7 Project Summary

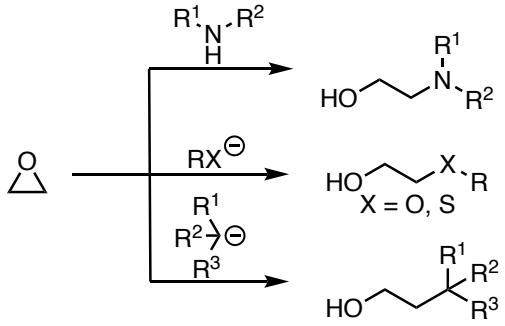
In summary, a robust one-pot two-step synthesis of pentafluorophenol sulfonate esters has been developed based on the coupling of *in situ* generated metal sulfinates and pentafluorophenol with the action of a copper salt, under oxidative conditions. The sulfinate intermediates were formed from the corresponding boronic acid and DABSO, under the action of a palladium catalyst. The attractiveness of this process comes from the possibility of using readily available starting materials and catalysts, as well as from the use of easy-to-handle sulfur dioxide surrogate DABSO, and from the fact that no addition of ligands is necessary for either step of the process. A broad range of aryl and heteroaryl boronic acids were successfully employed in the reaction sequence and provided the desired PFP sulfonate esters in generally good yields. Furthermore, we were able to show that aryl bromides are viable substrates for this chemistry. Finally, the utility of the PFP sulfonate ester products was demonstrated by performing various reactions, which efficiently delivered compounds of great value such as a sulfonamide species, a sulfonyl fluoride product, and a menthol sulfonate ester, showing that PFP sulfonate esters are viable alternatives to sulfonyl chlorides. It was also possible to perform a palladium-catalysed amination reaction, which showed that PFP sulfonate esters are not only alternatives to sulfonyl chlorides, but could also display complementary reactivities in cases where sulfonyl chlorides are no suitable to be used.

Chapter 4 - Enantioselective Sulfonative Epoxide Ring-Opening

4.1 Transition Metal-Catalysed Epoxide Ring-Opening

4.1.1 Traditional Methods and Applications

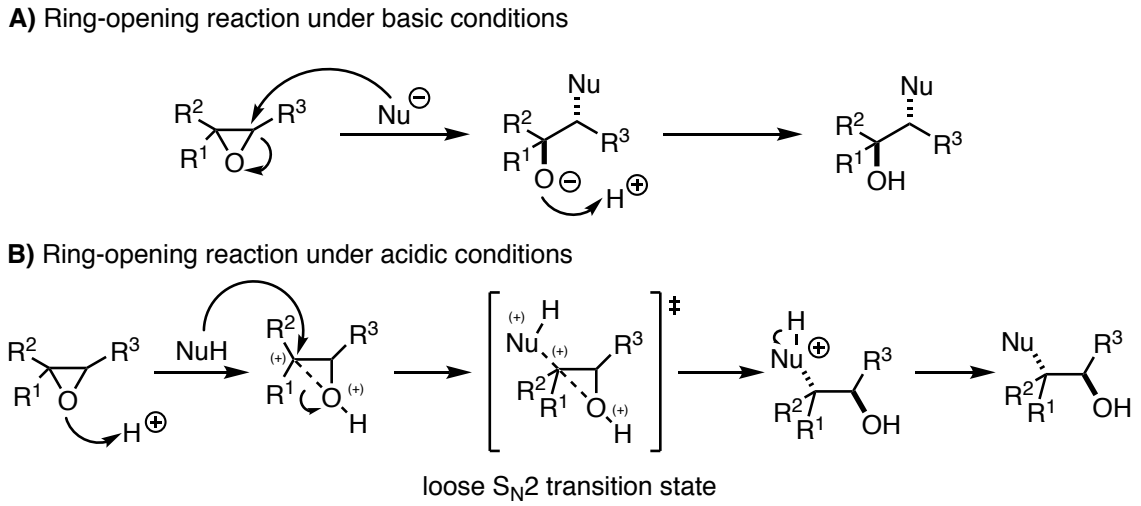
Epoxides have been extensively studied and utilised as versatile intermediates in organic synthesis, as they can be prepared without difficulty using well established procedures. These use readily available starting materials such as alkenes[210] and carbonyl compounds,[211] and are subsequently transformed into many other functional groups. An example of this is the ring opening of epoxides with various nucleophiles, which plays an essential role in the stereoselective preparation of 1,2-disubstituted products (Scheme 4.1). This has been one of the most studied reaction classes of epoxides, and a range of promoters and conditions have been developed.[212]



Scheme 4.1 Epoxide ring-opening with various nucleophiles

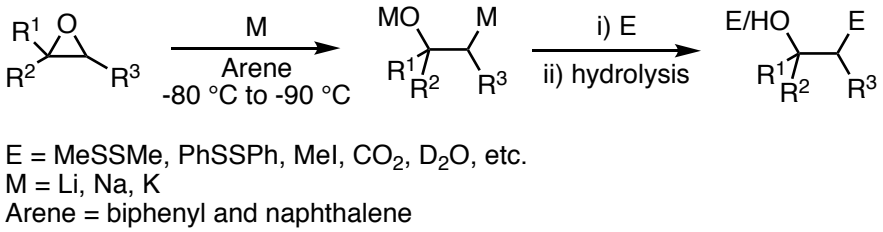
It is generally accepted that, under neutral or basic reaction conditions, the nucleophilic ring-opening reaction of epoxides proceeds *via* an S_N2 mechanism, with inversion at the attacked carbon atom, where attack is favoured at the least hindered carbon where no further electronic considerations are present. Under these conditions, ring-opening delivers 1,2-disubstited products with a *trans* relationship of the nucleophile

to the oxygen leaving group (Scheme 4.2, eq. 1). Under acidic conditions, a loose S_N2 transition state was mentioned to justify the electronic pull on the oxygen by an acid (Scheme 4.2, eq. 2). [213,214]



Scheme 4.2 Proposed mechanisms for nucleophilic epoxide ring-opening under (A) basic and (B) acidic conditions

The electrophilic ring-opening reaction of small heterocycles such as epoxides, using stoichiometric metals has also been reported. In 1986, Bartmann documented a different pathway to perform the ring-opening of epoxides by treating it with radical anion salts of aromatic hydrocarbons at low temperature. Under these reaction conditions, epoxides are transformed into β-metalated alkoxide species. These highly reactive organometallics can subsequently react with alkyl halides, disulfides, and carbon dioxide (Scheme 4.3).[215]



Scheme 4.3 Electrophilic ring-opening of epoxides using stoichiometric metals

4.1.2 Transition Metal-Catalysed Enantioselective Ring-Opening

The development of chiral salen-metal-based catalysts (H_2salen = bis(salicylidene)ethylenediamine) by Jacobsen and co-workers was a significant advancement in the asymmetric ring-opening of epoxides.[216,217] Jacobsen and co-workers hypothesised that chiral salen ligands which are known to be able to discriminate effectively between the enantiomeric faces of an approaching olefin (Figure 4.1, A),[218,219] might also be able to generate an asymmetric environment for nucleophilic attack on a coordinated epoxide (Figure 4.1, B). The salen-complex could also coordinate and deliver the nucleophile in an enantioselective manner (Figure 4.1, C). This transformation would proceed through a mechanism of ring-opening involving activation of epoxide by a chiral, Lewis acidic metal-salen complex.[216]

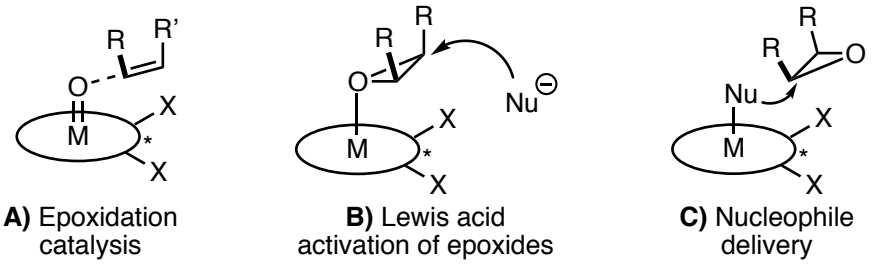
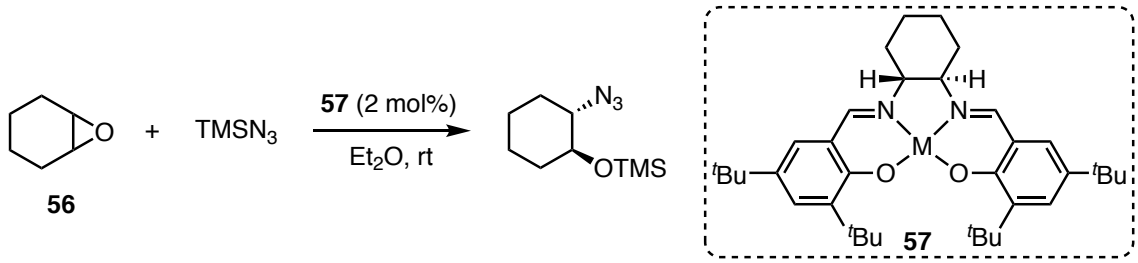


Figure 4.1 Schematic use of chiral metal salen complexes for A) olefin epoxidation; B) epoxide activation for asymmetric ring-opening; C) controlled delivery of the nucleophile for asymmetric ring-opening

In order to test their hypothesis, Jacobsen's group evaluated the ability of various metal salen complexes to induce an asymmetric ring-opening of the *meso* epoxide cyclohexene oxide **56**, by $TMSN_3$ (Scheme 4.4). During this screening study the (salen)$Cr^{III}Cl$ complex **57c** proved to be the most efficient in term of conversion and gave the best enantioselectivity. Other metals, such as titanium and aluminium showed similar levels of reactivity but displayed very low enantioselectivity.

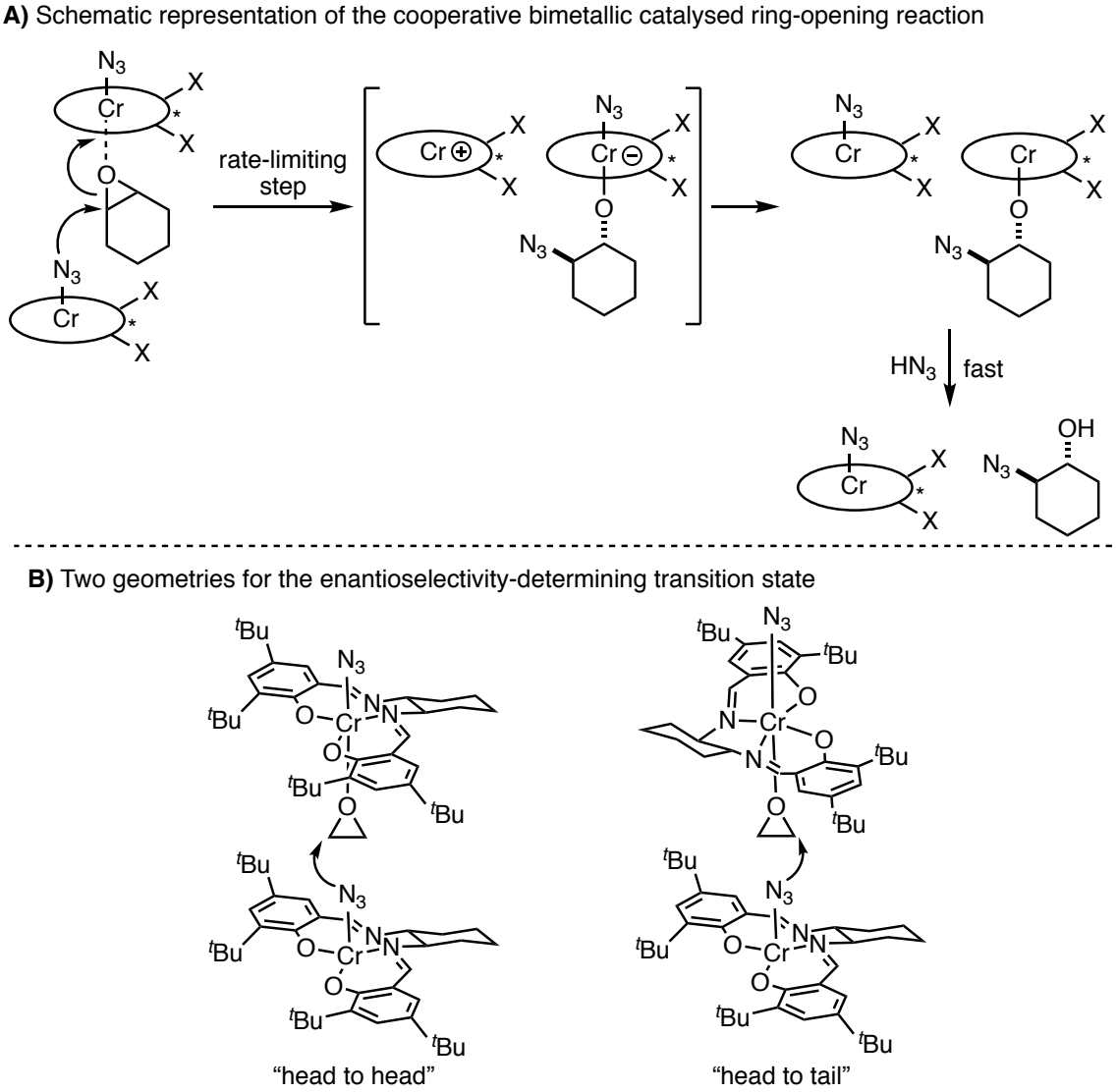


57a: M = Al-Cl, yield = 70%, ee = 5%
57b: M = Ti-Cl_2, yield = 72%, ee = 7%
57c: M = Cr-Cl, yield = 96%, ee = 85%
57d: M = Mn-Cl, yield = 14%, ee = 2%
57e: M = Fe-Cl, yield = 17%, ee = 0%
57f: M = Co-I, yield = 22%, ee = 50%

Scheme 4.4 Screen of metal salen complexes for the catalytic asymmetric ring-opening of cyclohexene oxide with $TMSN_3$

From the results gathered during the screening phase, Jacobsen and co-workers postulated that, due to the difference in reactivity and selectivity observed, the mechanism of catalytic activation of the epoxide by the chromium complex must be different than for the other complexes. The formation of trace amounts of chlorohydrins indicated that the (salen)$Cr^{III}Cl$ complex **57c** served only as a precatalyst which was transformed into a (salen)Cr^{III} azide complex after the first catalytic cycle. Subsequent kinetic studies suggested that the (salen)Cr^{III} azide complex fulfilled a double role by activating the epoxide as a Lewis acid, and delivering the azide nucleophile (Scheme 4.5, A).[220] The structure of the complex was proven by crystallographic analysis. The authors proposed that the epoxide ring-opening proceeds *via* a cooperative bimetallic mechanism, wherein both the epoxide and the nucleophile are activated by separated (salen)metal complexes in the rate-limiting ring-opening event. Two limiting geometries were postulated for the selectivity-determining step where the epoxide and the azide are "sandwiched" between two distinct catalyst units (Scheme 4.5, B).[216] This provided the inspiration for the preparation and study of a variety of linked multi(salen)metal complexes. In some cases, these studies demonstrated a catalyst system with a significant enhancement of the rate of the reaction relative to the monomeric catalyst. However, the synthesis of these

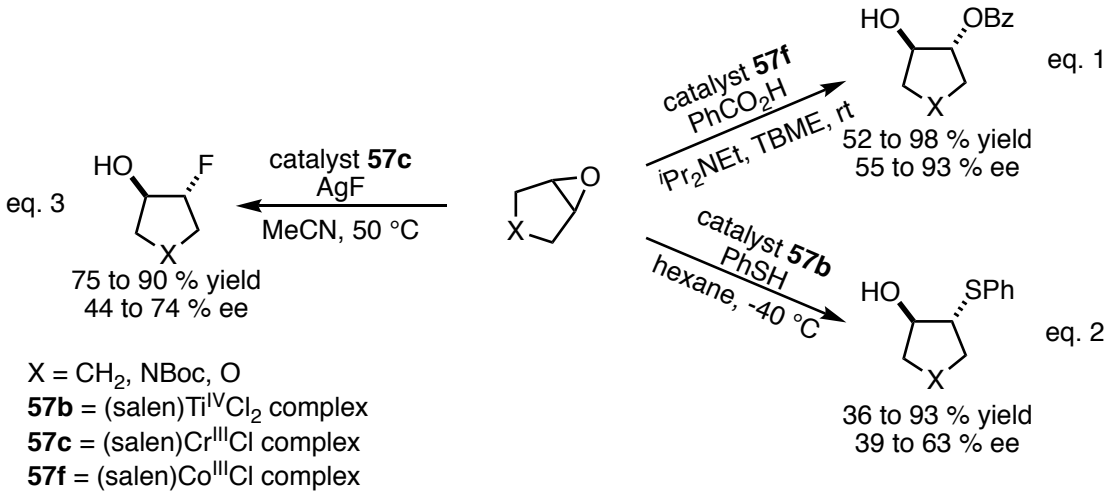
multi(salen)metal complexes was much more difficult and therefore less attractive from a practical standpoint.



Scheme 4.5 Mechanistic rationale for the Cr(salen)-catalysed asymmetric ring opening of epoxides

From the discovery of the ability of salen-metal complexes to catalyse the desymmetrisation of *meso* epoxides with azides, the Jacobsen group, and others, have reported their applications in asymmetric ring-opening reactions with a variety of nucleophiles. In 1997, Jacobsen and co-workers documented the first catalytic, enantioselective addition of an oxygen nucleophile to a *meso* epoxide.[221] Benzoic acid was added to a range of epoxides under the action of (salen)Co^{III} complex **57f** and

delivered 1,2-diol monoesters in excellent yield and good to excellent enantioselectivity (Scheme 4.6, eq. 1). The same group then looked at the addition of benzyl thiol to various epoxides. Unfortunately, the (salen)$Cr^{III}Cl$ complex **57c** only afforded moderate levels of enantioselectivity for this transformation.[222] However, Hou and co-workers employed chiral salen-titanium complex **57b**, which converted a range of epoxides into the corresponding *β*-hydroxy sulfides in excellent yield, but still with moderate to good enantioselectivity (Scheme 4.6, eq. 2).[223] Enantioselective addition of fluoride to *meso* epoxides was also made possible under the action of the (salen)$Cr^{III}Cl$ catalyst **57c** (Scheme 4.6, eq.3).[224] Although, in order to access good yields and enantioselectivities, the use of 50 to 100 mol% of the chiral catalyst was required.



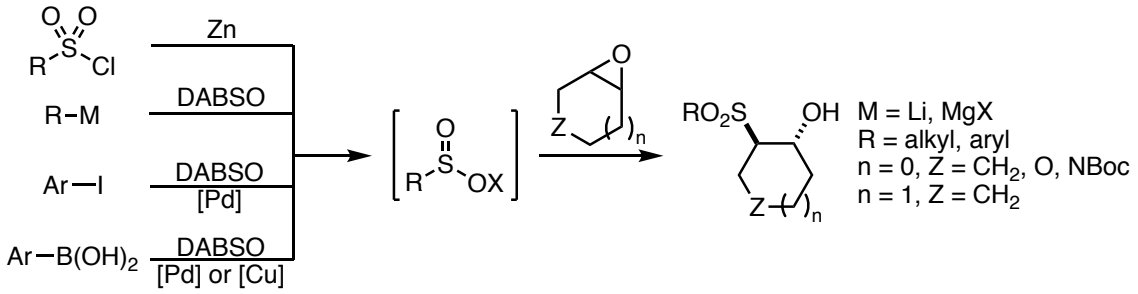
Scheme 4.6 Use of various nucleophiles for salen-metal complex catalysed asymmetric ring-opening of meso epoxides

4.2 Origin of Project

The sulfonyl moiety is well represented in active ingredients across the pharmaceutical and agrochemical industries (Section 3.1). Therefore, it is not surprising that a wide range of methodologies have been developed for the direct incorporation of sulfonyl motifs into molecules of interest. Arguably, fewer methods have been developed in order to deliver

asymmetric sulfone molecules, particularly where the asymmetry is adjacent to the sulfone functionality. Such products have previously been generated by transition metal-catalysed substitution,[225,226] cycloadditions,[227] and C-H insertion.[228] Diels-Alder reactions mediated by Lewis acids have also been reported to deliver chiral sulfone products in high enantioselectivity.[229] However, most of these methods focus on the transformation of the carbon adjacent to the sulfonyl functionality, not on the direct enantioselective incorporation of the sulfonyl motif.

Direct opening of symmetrical epoxides by sodium sulfinates in aqueous alcohol was reported by Culvenor *et al.* in 1949.[230] Inspired by this work, various methodologies have been documented using *in situ* generated sulfinates as nucleophiles for ring-opening reactions (Scheme 4.7). Sampson and co-workers showed in 2006 that reacting a sulfonyl chloride with zinc could form the corresponding sulfinate, which could be further reacted with symmetrical epoxides.[116] In 2014, the Willis group demonstrated that magnesium sulfinates, arising from the reaction of DABSO and a Grignard reagents, are efficient nucleophiles to open epoxides and deliver the desired sulfone products.[120] Later, the same group reported various methodologies to generate *in situ* sulfinate species under transition metal catalysis, which were then used as nucleophiles to open epoxides.[128,129,131]



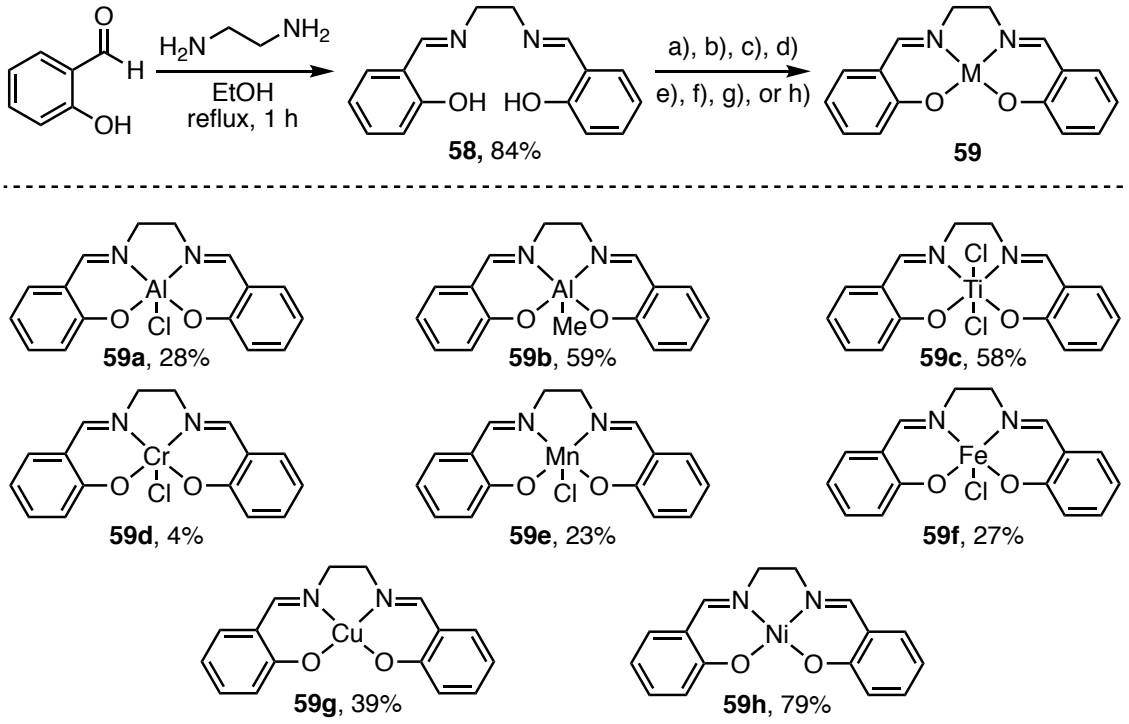
Scheme 4.7 Examples of using sulfinates as nucleophile for ring-opening reactions

Inspired by these previous reports, we envisaged that the ring-opening reaction of a symmetrical epoxide could be achieved in an enantioselective manner, employing sulfinate derivatives as the nucleophile and chiral salen-metal complexes as catalysts.

4.3 Metal-Salen Catalysed Sulfonylative Ring-Opening Reaction

4.3.1 Synthesis of Metal-Salen Complexes

Although some salen-metal complexes can be acquired from commercial sources, it was essential to be able to screen a wide range of metal complexes to maximise our chances to find the appropriate reactivity. Synthesising the complexes was therefore the best way to achieve this goal. In order to probe the reactivity of the salen-metal complexes, it was decided to first synthesise the achiral H_2salen ligand **58** (Scheme 4.8).



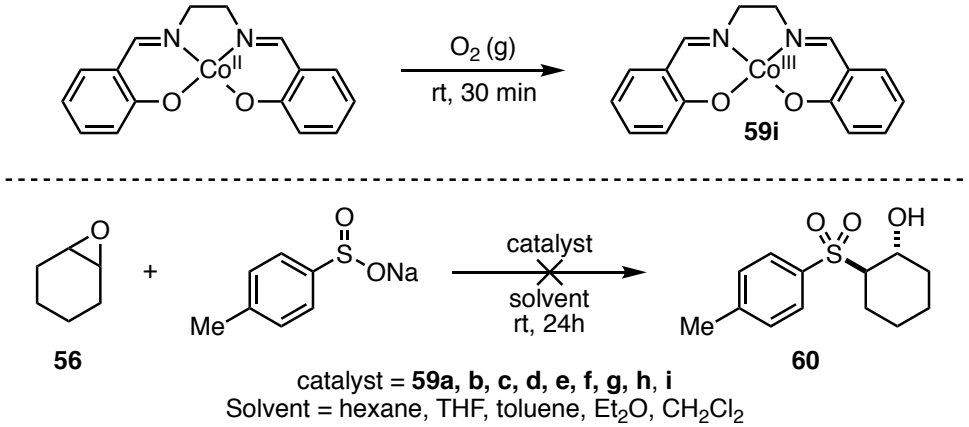
Scheme 4.8 Synthesis of a range for H_2salen-metal complexes

Reaction conditions: a) **58** (1.0 mmol), $AlEt_2Cl$ (1.0 M in hexane, 1.0 mmol), DCM [0.14 M], N_2 atmosphere at rt for 1 h; b) **58** (1.0 mmol), $AlMe_3$ (2.0 M in chlorobenzene, 1.0 mmol), toluene [0.05 M], N_2 atmosphere, reflux for 12 h; c) **58** (1.0 mmol), $TiCl_4$ (1.0 mmol), THF/toluene (4:1) [0.4 M], reflux for 30 min; d) **58** (1.0 mmol), $CrCl_2$ (1.0 mmol), THF [0.05 M], N_2 atmosphere for 3 h, then air for 3 h at rt; e) **58** (1.0 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (1.0 mmol), EtOH [0.1 M], reflux for 1 h, then LiCl (3.0 mmol), reflux for 30 min; f) **58** (1.0 mmol), $FeCl_3$ (1.0 mmol), EtOH [0.25 M], reflux for 2 h; g) **58** (1.0 mmol), $Cu(NO_3)_2 \cdot 2.5H_2O$ (1.0 mmol), EtOH [0.06 M], reflux for 1 h) **58** (1.0 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (1.0 mmol), EtOH [0.1 M], reflux for 2 h.

A condensation reaction of salicylaldehyde and ethylenediamine provided the desired Schiff base in excellent yield.[231] Then, following various procedures reported by the Jacobsen group,[232-234] a range of metal-salen complexes (**59a-f**) were prepared.

4.3.2 Initial Optimisation of Reaction Conditions

We began our investigation by using the commercially available sodium *p*-toluenesulfinate and the symmetrical epoxide cyclohexene oxide, in the presence of our various catalysts for 24 hours at room temperature. First, we decided to vary the solvent used for the reaction with the previously synthesised salen complexes as well as the (salen)Co^{III} **59i**, which was obtained from oxidation of the commercially available (salen)Co^{II} complex (Scheme 4.9).[221] Unfortunately, for reaction employing the salen manganese, iron, aluminium, titanium, and cobalt complexes, no reactivity could be observed in any of the solvents which the reaction was submitted to. The salen copper and nickel complexes only decomposed the sulfinate starting material in THF, diethyl ether, and dichloromethane, and did not succeed in providing the desired sulfone product **60**.



Scheme 4.9 Formation of Salen complex **59i** and salen-metal complex catalysed ring-opening with sodium sulfinate and cyclohexene oxide

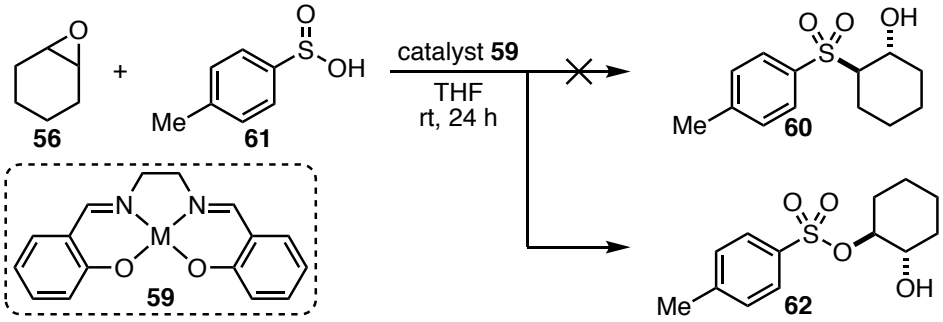
In order to improve reactivity, the temperature of the reaction was increased to 50 °C. Although the starting materials were consumed, it appeared that the catalyst was not involved in the transformation, as our control experiment which was set up in parallel without a catalyst gave similar conversion.

The poor solubility of the sodium sulfinate salt in organic solvents could be one of the factors detrimental to the reaction. The use of carboxylic acids as nucleophiles in metal-salen catalysed ring-opening reactions was previously reported by Jacobsen and co-workers.[221] We envisioned that using a sulfinic acid might be a better option than the corresponding salt.

Thus, we synthesised *p*-tolylsulfinic acid **61** simply by treatment of the corresponding the sodium sulfinate salt with a solution of hydrochloric acid. Most epoxide ring-opening reactions reported proceed in ethereal solvents, therefore, we first studied the reactivity of our catalysts with the sulfinic acid **61** and cyclohexene oxide in THF. $^{i}Pr_2NEt$ was also added to the reaction; this reaction showed good conversion, however, this was due to the background reaction and was not affected by the presence of the catalysts.

In order to supress this background reaction, the base was removed and the action of the various catalysts on the reaction studied (Table 4.1). Under these reaction conditions, the salen-metal complexes **59a**, **59b**, and **59f** showed no reactivity, and both starting materials could be fully recovered (entries 1 - 2, and 6). The complexes **59g** and **59h** delivered a very poor mass balance and a complex crude mixture, of which no distinct product could be isolated in sufficient quantities to be fully characterised (entries 7 - 8).

Table 4.1 Catalyst screen for the ring-opening reaction of cyclohexene oxide with sulfinic acid **61**

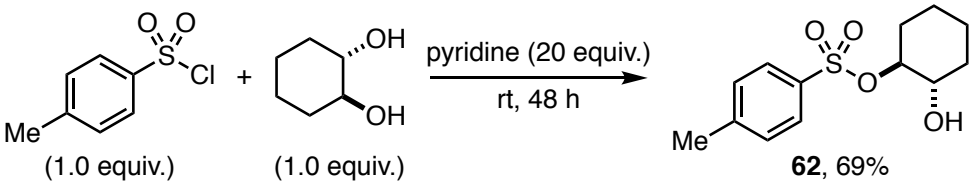


Entry	**59** (M)	Yield (%)[a] **60** / **62**
1	**59a** ($Al^{III}Cl$)	0 / 0
2	**59b** ($Al^{III}Me$)	0 / 0
3	**59c** ($Ti^{IV}Cl_2$)	0 / 11
4	**59d** ($Cr^{III}Cl$)	0 / 5
5	**59e** ($Mn^{III}Cl$)	0 / 30
6	**59f** ($Fe^{III}Cl$)	0 / 0
7	**59g** (Cu^{II})	0 / 0
8	**59h** (Ni^{II})	0 / 0
9	**59i** (Co^{III})	0 / 38

Reaction conditions: cyclohexene oxide (0.1 mmol), **61** (0.11 mmol), salen-metal complex (10 mol%), THF [0.017 M], opened to air at room temperature for 24 hours. [a]Isolated yields.

The (salen)$Ti^{IV}Cl_2$ **59c**, (salen)$Cr^{III}Cl$ **59d**, (salen)$Mn^{III}Cl$ **59e**, and (salen)Co^{III} **59i**, all showed conversion of the starting materials, however, the major product isolated from these reactions was not the expected sulfone product **60**, but the corresponding sulfonate ester **62** (entries 3-5, and 9).

In order to confirm the structure of the product formed, the sulfonate ester **62** was synthesised using a procedure previously reported in the literature (Scheme 4.10).[235] NMR spectroscopy and mass analysis were in accordance with the ones obtained from our product. Hence, confirming that the product formed under our reaction conditions was indeed the sulfonate ester **62**.

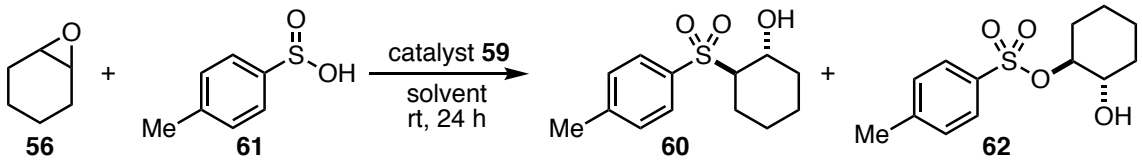


Scheme 4.10 Alternative synthesis of the sulfonate ester **62**

With regards to the origin of the oxidation of the sulfinic acid to the sulfonate ester, it can be rationalised by two ways. Firstly, the sulfinic acid could disproportionate under our reaction conditions. Thereby producing, among other products, the corresponding sulfonic acid species, which could then be used as a nucleophile to ring-open the epoxide partner. Secondly, the reaction being performed under air, the sulfinic acid could be oxidised under our reaction conditions by the oxygen present in the atmosphere. These hypotheses will be further examined in Section 4.3.3.

To continue the optimisation, a range of solvents were employed with each salen-metal complex that showed reactivity in the previous screening of reaction conditions (Table 4.2). When diethyl ether was used as a solvent for the reaction, it led to very similar results to those observed with THF (entries 1-4). Each catalyst submitted to the reaction provided the sulfonate ester **62** in lower yield than with THF and did not favour the sulfone product.

Table 4.2 Solvent effect on the ring-opening reaction of cyclohexene oxide with sulfinic acid[a]



Entry	Catalyst **59**	Solvent	Yield (%)[b] **60**/**62**
1	**59c** ($Ti^{IV}Cl_2$)	Et_2O	0/9
2	**59d** ($Cr^{III}Cl$)	Et_2O	0/5
3	**59e** ($Mn^{III}Cl$)	Et_2O	0/traces
4	**59i** (Co^{III})	Et_2O	0/traces
5[c]	**59c** ($Ti^{IV}Cl_2$)	CH_2Cl_2	0/traces
6[c]	**59d** ($Cr^{III}Cl$)	CH_2Cl_2	0/14
7[c]	**59e** ($Mn^{III}Cl$)	CH_2Cl_2	0/12
8[c]	**59i** (Co^{III})	CH_2Cl_2	0/11
9[c]	**59c** ($Ti^{IV}Cl_2$)	hexane	0/22
10[c]	**59d** ($Cr^{III}Cl$)	hexane	0/13
11[c]	**59e** ($Mn^{III}Cl$)	hexane	0/17
12[c]	**59i** (Co^{III})	hexane	0/13
13[c]	**59c** ($Ti^{IV}Cl_2$)	toluene	0/36
14[c]	**59d** ($Cr^{III}Cl$)	toluene	0/31
15[c]	**59e** ($Mn^{III}Cl$)	toluene	0/27
16[c]	**59i** (Co^{III})	toluene	0/25

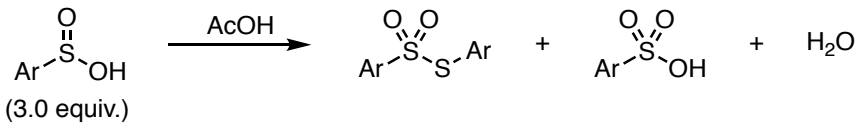
[a]Reaction conditions: cyclohexene oxide (0.1 mmol), **61** (0.11 mmol), salen-metal complex (10 mol%), THF [0.017 M], open to air at rt for 24 h. [b]Isolated yields. [c]Reaction run at -60 °C

Interestingly, when dichloromethane, hexane, or toluene were used as solvents, the reaction proceeded at a much greater rate and without the presence of the catalyst. In order to supress this background reaction, the temperature was dropped to -60 °C. However, at that temperature almost no reactivity was observed after 24 hours when dichloromethane was used as solvent (entries 5-8) and again the sulfone product **60** was not observed, and only the sulfonate ester **62** could be isolated. Hexane gave similar results as those observed with dichloromethane (entries 9-12). Toluene was able to

promote the reaction better with all of the catalysts, with the exception of when the (salen)Co^{III} complex **59i** was used in THF (Table 4.1, entry 9). Motivated by this result, the reaction was left to stir at -60 °C for 48 hours, but unfortunately no improvement in the yield of the sulfonate ester **62** could be observed.

4.3.3 Mechanistic Considerations

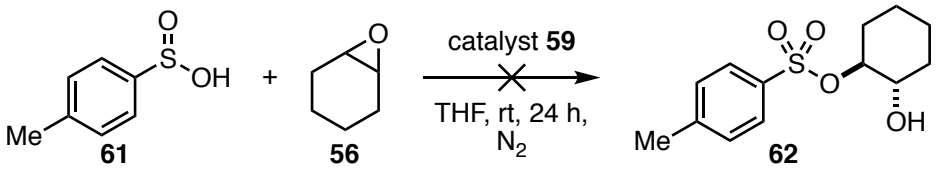
Although the desired sulfone product could not be synthesised using salen-metal complexes, it was important to us to understand the synthetic pathway through which the sulfonate ester **62** was produced. Our first hypothesis was that in the presence of the catalyst, the sulfonic acid could disproportionate, therefore providing the sulfonate species responsible for the ring-opening reaction of the epoxide. However, the disproportionation reaction of aromatic sulfinic acids has long been known,[236] and a thiolsulfonate species should also be produced as a side-product (Scheme 4.11).[237] Although the fact that the thiolsulfonate product was not observed does not completely diminish this hypothesis, as this species could be instable and decompose rapidly under our reaction conditions, leaving the sulfonic acid available to react with the epoxide substrates.



Scheme 4.11 Disproportionation of aromatic sulfinic acids

Our second hypothesis was that the sulfinic acid could be oxidised by the catalyst in combination with oxygen. In order to verify this hypothesis, we performed the reactions which produced sulfonate ester **62** under inert atmosphere (Scheme 4.12). No sulfonate

ester **62** was formed under these reaction conditions, and the starting materials were fully recovered. These results suggest that the presence of oxygen is required for the oxidation.

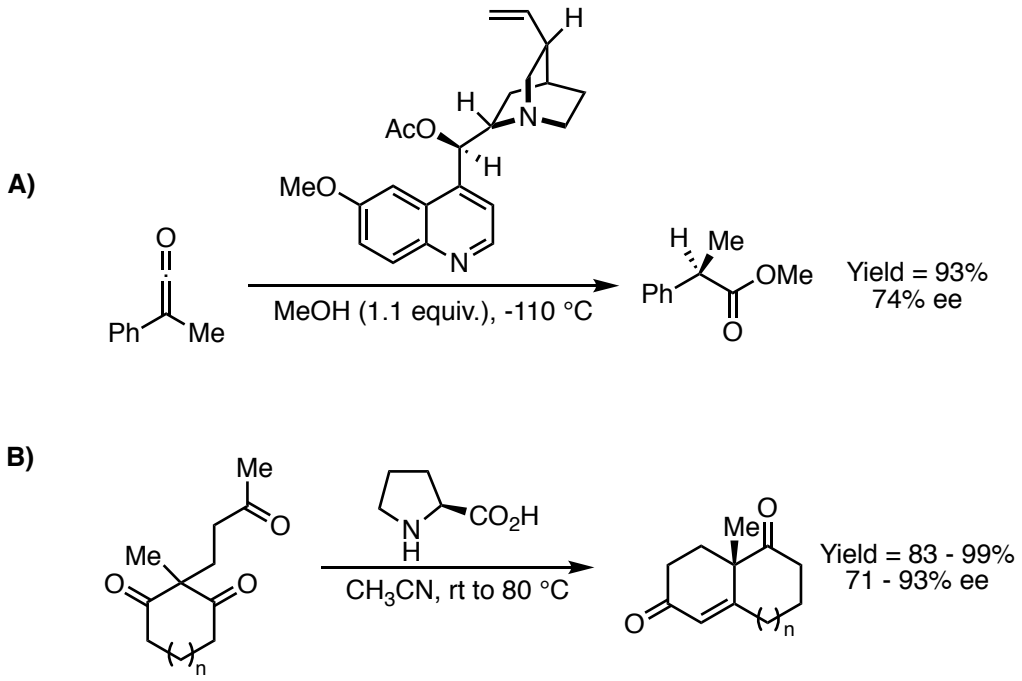


Scheme 4.12 Ring-opening reaction inhibited under inert atmosphere

This protocol could be an interesting pathway to deliver monoprotected diols in a single step. Although, due to the low yields obtained despite a broad screening of metal-salen catalysts, and the long reaction times necessary, compared to other existing methods,[238] it was decided not to investigate this reaction further.

4.4 Organocatalysed Epoxide Ring-Opening Reaction

In 2002, MacMillan defined the term organocatalysis as the use of low molecular weight organic molecule as catalysts for organic transformations,[239] which has now become the standard definition of organocatalysis. However, a large number of publications reported the use of small organic molecules as catalysts long before MacMillan popularised the concept. In 1960, Pracejus and co-workers reported an efficient process allowing the addition of methanol to ketenes promoted by cinchona alkaloids with high enantioselectivity (Scheme 4.13, A).[240,241] A significant advancement in the field of organocatalysis was reported independently by the pharmaceutical companies Hoffman-La Roche[242] and Schering AG[243] in the 1970's. They documented the use of proline to catalyse intramolecular aldol reaction in high yield and good enantioselectivity (Scheme 4.13, B). This reaction is now best known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, after its principal investigators.



Scheme 4.13 Pioneering examples of organocatalysis

More recently, asymmetric organocatalysis has proven to be an independent synthetic tool alongside asymmetric transition metal catalysis and enzymatic catalysis for the synthesis of chiral organic molecules. The rapid growth of the field can be explained by the fact that organocatalysts are generally non-toxic and robust compounds, and a large number of them are commercially available and/or easily synthesised. They are usually stable under aerobic conditions, and the reaction often does not require anhydrous conditions. The reactions are commonly conducted under mild conditions and in high concentration, avoiding the use of a large amount of solvent and minimising waste.

One of the ways to broadly classify most but not all organocatalysts is by means of the interaction with the substrate as covalent or non-covalent catalysts (Figure 4.2). With covalent catalysts, a covalent bond is formed with the substrate, increasing the interaction between the substrate and the reagent in the reaction. This category includes aminocatalysts[244] and carbene catalysis.[245] The non-covalent catalysts such as Brønsted acids activate the substrate *via* hydrogen bonding interactions[246] (*e.g.*, thioureas,[247]

squaramides,[248] and phosphoric acids[249]). Another mode of activation for non-covalent catalysts is *via* ionic interactions (*e.g.*, cinchona alkaloids[250] and phase-transfer catalysts[251]).

Only non-covalent catalysts were explored in the work presented in this chapter; the reactivity and applications of covalent organocatalysts will not be further presented in this thesis. However, there are numerous publications and reviews that document their use.[244,245,252-255]

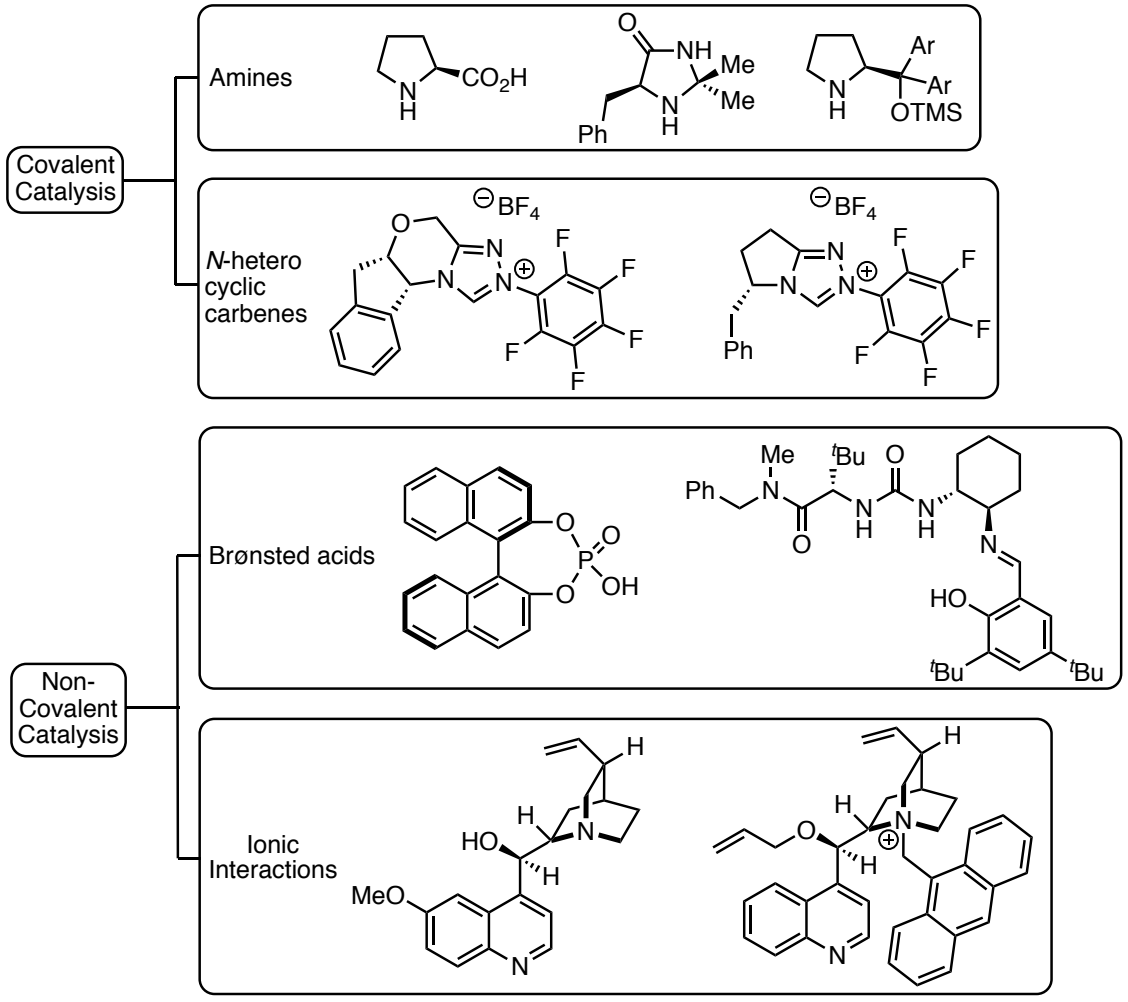


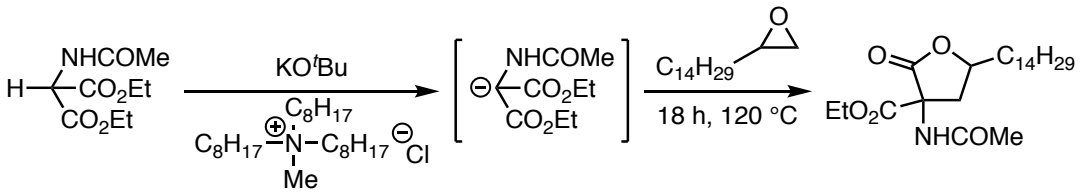
Figure 4.2 A classification of organocatalysts by their activation mode

4.4.1 Traditional Methods and Applications

4.4.1.1 Phase-Transfer Catalysed Ring-Opening

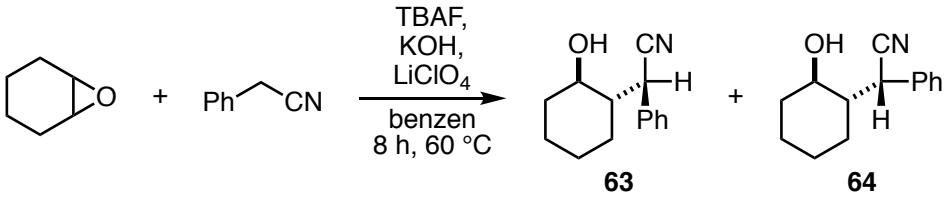
In the mid to late 1960's, Stark and Makosza laid the foundations of phase-transfer catalysis by reporting the catalytic activity of quaternary onium salts.[256-258] Since then, the field of phase-transfer catalysis as grown exponentially and found some industrial applications.[259] Phase-transfer catalysts enable the transfer of a molecule or ion from one reaction phase to another, and thereby, can increase drastically the rate of the reaction. The most widely used phase-transfer catalysts for this type of reactions are quaternary ammonium salts.

Due to the many advantages offered by phase-transfer catalysis, these processes have been applied to a wide range of reactions,[251,260] including the ring opening of small heterocycles with a variety of nucleophiles. In 1994, Loupy and co-workers reported the ring-opening reaction of tetradecyl-oxirane with diethyl acetamidomatonate with basic conditions, under solvent free, solid-liquid phase-transfer catalysis (Scheme 4.14). The major product is a lactone which is formed by ring-opening of the epoxide and subsequent cyclisation.[261]



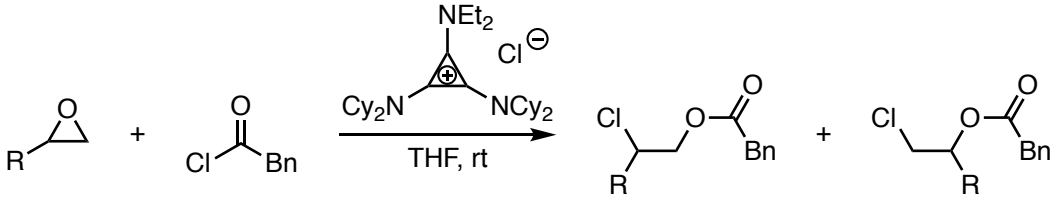
Scheme 4.14 Phase-transfer catalysed ring-opening reaction of epoxide under solvent free conditions

Later, Marković *et al.* demonstrated the phase transfer catalysed ring-opening of cyclohexene oxide by *in situ* generated potassium phenylacetonitrile, in a solid-liquid and liquid-liquid two phase system.[262] Under the action of TBAF as the phase-transfer catalyst, KOH as the base, and $LiClO_4$ as a Lewis acid to activate the epoxide, they were able to generate the diastereomers **63** and **64** in 76% yields with a 1:1 dr (Scheme 4.15).



Scheme 4.15 Ring-opening of cyclohexene oxide with TBAF as catalyst

In 2015, Lambert and co-workers studied the catalytic activity of cyclopropenium salts, for various reactions, including the ring-opening reaction of epoxides with acid chlorides.[263] This methodology provided a straightforward route to synthetically useful halohydrin esters (Scheme 4.16).

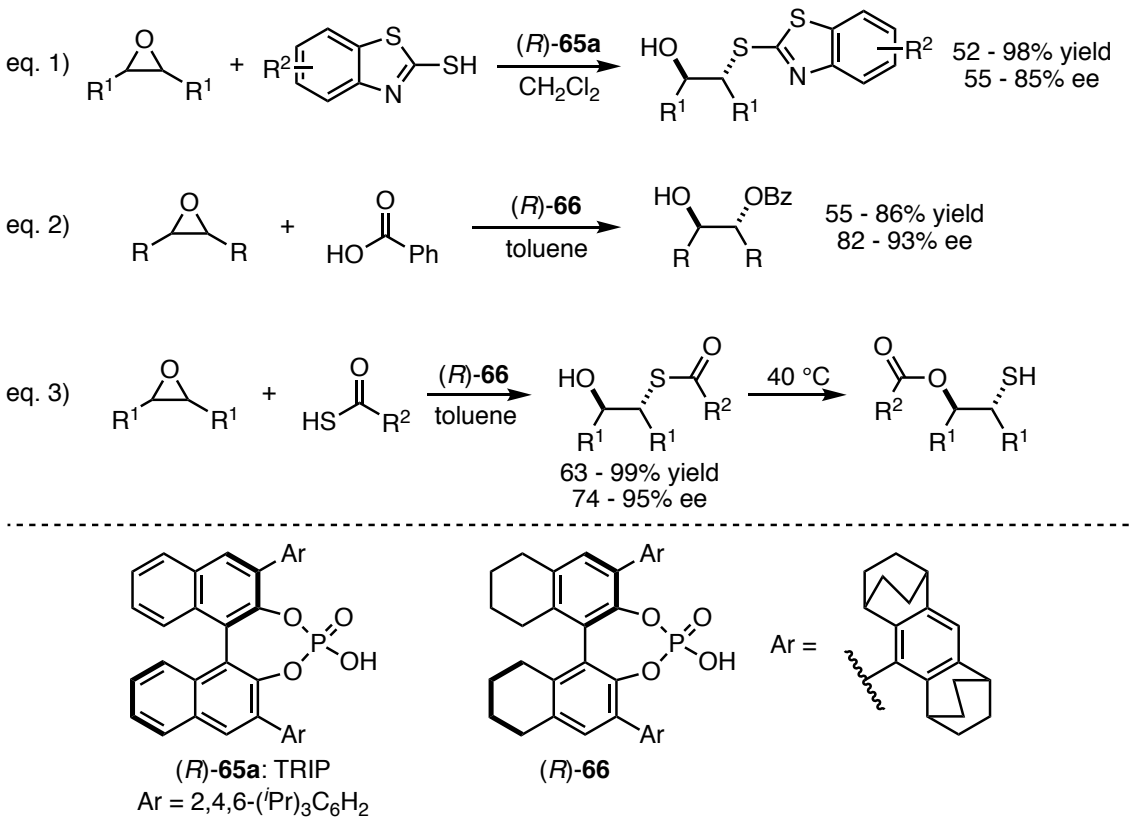


Scheme 4.16 Use of cyclopropenium salt as phase-transfer catalyst for epoxide ring-opening reactions

4.4.1.2 Phosphoric Acid-Catalysed Ring-Opening

The use of phosphoric acids to catalyse various reactions has gained in popularity since their introduction a decade ago.[264,265] Recently, chiral phosphoric acid catalysts have been employed in the enantioselective synthesis of 1,2-difunctionalised compounds through the desymmetrisation of *meso*-epoxides. Sun and co-workers documented the first chiral Brønsted-acid-catalysed, nonenzymatic nucleophilic meso-epoxide ring-opening in 2013.[266] They studied the catalytic activity of several phosphoric acid catalysts for the opening of various *meso*-epoxides with mercaptobenzothiazole as a nucleophile, and BINOL-derived catalyst TRIP **65a** provided the best enantiocontrol and reactivity (Scheme 4.17, eq. 1). The authors also showed that the aryl sulfides which are formed by this reaction can be cleaved to generate the corresponding β-hydroxythiols with no loss

of enantiomeric excess. Subsequently, List and co-workers reported a phosphoric acid catalysed synthesis of monoprotected *trans*-1,2-diols through asymmetric ring-opening of meso-epoxides with carboxylic acids (Scheme 4.17, eq. 2).[267] The authors suggest that the stereocontrol of their reaction is ensured by the novel design of their phosphoric acid catalyst **66**. Indeed, **66** being built on a (H_8)-BINOL scaffold and featuring a novel sterically demanding polycyclic ring system at the 3- and 3'-positions, provides a more tightly confined chiral reactive site. Shortly after this, the same group documented a ring-opening reaction of *meso*-epoxides with thiocarboxylic acids as the nucleophile, which delivered efficiently and selectively *O*-protected *β*-hydroxythiols through Brønsted acid catalysis and a thermal rearrangement (Scheme 4.17, eq. 3).[268]



Scheme 4.17 1) First report of a phosphoric acid catalysed ring-opening of *meso*-epoxides; 2) Phosphoric acid catalysed ring-opening with carboxylic acids; 3) Phosphoric acid catalysed ring-opening with thiocarboxylic acids

The design of the phosphoric acid catalyst used by Sun and co-workers relied on the conventional stereochemical models in which the preferred transition state is the one that minimises steric interactions with the chiral environment of the catalyst (Figure 4.3, A). In the system developed by List and co-workers they use a conceptually new approach for the activation of carboxylic acids in asymmetric-ring opening reactions. They showed that the phosphoric acid catalyst could activate a carboxylic acid in a supramolecular self-assembly (Figure 4.3, B). This would be responsible for the enhancement of the nucleophilicity of the carboxylic acid reagent, and an increase of the acidity of the heterodimer.[269] They postulate that the increase of acidity is an important factor for the activation of the electrophile in the Brønsted acid catalysed reaction.

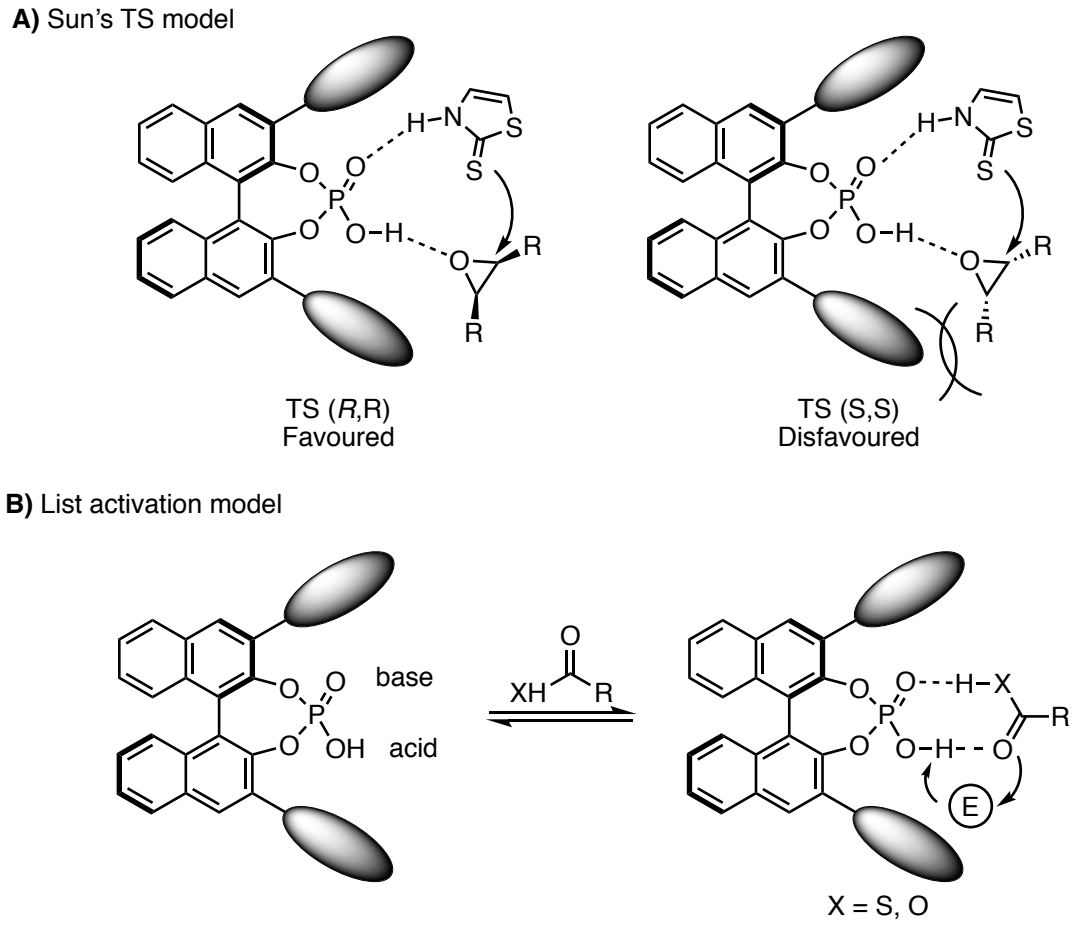
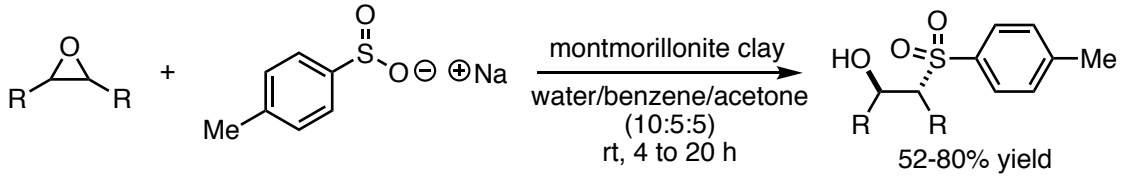


Figure 4.3 A) Transition state model of Sun and co-workers; B) Novel activation mode by formation of a heterodimer species reported by List and co-workers

4.5 Origin of Project

Despite the wide range of methodologies reporting organocatalysed ring-opening reactions with various nucleophiles, the number of examples documenting the organocatalysed synthesis of β-hydroxy sulfones *via* ring-opening of epoxides are scarce. The first example was published by Biswas *et al.* in 1991.[270] In this study the author described the ring-opening of various epoxides with sodium *p*-toluenesulfinate, under liquid-liquid phase transfer conditions using montmorillonite clay (Scheme 4.18). They postulated that montmorillonite clay facilitates the ring-opening reaction by acting as a Lewis acid and coordinating with the epoxide. Under these conditions, a variety of epoxides were successfully transformed to β-hydroxy sulfones under mild conditions.



Scheme 4.18 Montmorillonite clay catalysed synthesis of β-hydroxy sulfones under liquid-liquid phase-transfer reaction conditions

Inspired by these results, the same group published another ring-opening reaction using sodium *p*-toluenesulfinate as nucleophile and using polyethylene glycol 4000 (PEG 4000) as a phase-transfer catalyst.[271] The reaction proceeded in a liquid-liquid phase-transfer system (water/benzene 1:1) at reflux. Under these conditions, a range of symmetrical and non-symmetrical epoxides were successfully used to generate the corresponding β-hydroxy sulfones.

Motivated by these reports, we envisaged that it could be possible to synthesis a range of enantioenriched β-hydroxy sulfones through an organocatalysed ring-opening, using a variety of *in situ* generated sulfinates as nucleophile. Therefore, we set out to find

appropriate reaction conditions in which the sulfinate would be stable and yet reactive enough to open the epoxide under the action of the chiral organocatalysts.

4.6 Phase-Transfer Catalysed Synthesis of β-Hydroxy Sulfones

The ring-opening reactions of *meso*-epoxides using sodium *p*-toluenesulfinate as the nucleophile, under phase-transfer reaction conditions is known with catalysts such as PEG 4000[271] and montmorillonite clay.[270] Furthermore, the ability of quaternary ammonium salts to catalyse enantioselective ring-opening reactions with various nucleophiles, has also been documented.[251] Therefore, we postulated that sulfinates could react with epoxides, in an enantiocontrolled manner, under the action of a chiral phase-transfer catalyst, to deliver enantioenriched β-hydroxy sulfones under mild reaction conditions.

With regard to the quaternary ammonium salts derived from cinchona alkaloids, it is well known that the reactivity and selectivity of the catalysts can be greatly affected by the various substituents present on the *N*-arylmethyl unit and on the quinine motif.[272] It has been proposed that the enantioselectivity of this type of catalyst is mainly due to the steric bulkiness of the *N*-arylmethyl group.[273,274] Therefore, a variety of cinchona alkaloids derived catalysts bearing different substituents on the *N*-arylmethyl and on the quinine motifs were selected to perform our study (Figure 4.4).

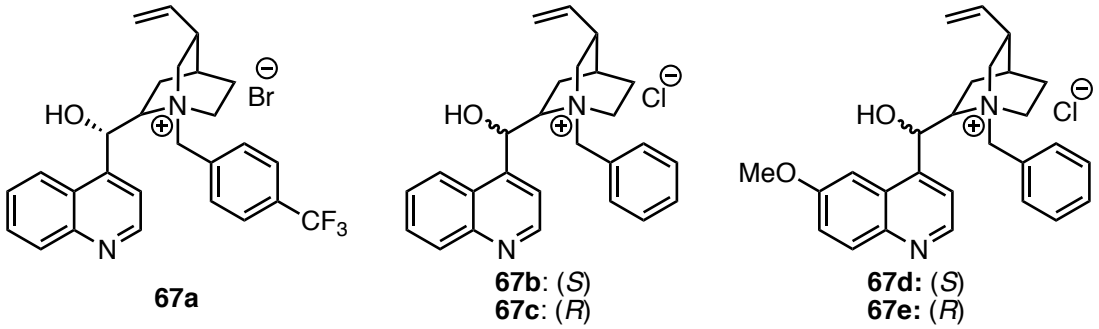
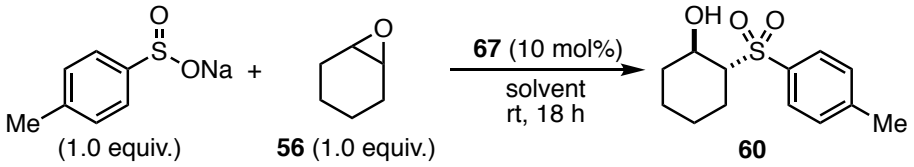


Figure 4.4 Range of quaternary ammonium salts used as phase-transfer catalysts

To study the feasibility of the reaction, commercially available sodium *p*-toluenesulfinate was selected as the nucleophile to perform the ring-opening reaction with cyclohexene oxide. In the initial optimisation of the reaction conditions, the range of cinchonidium phase-transfer catalysts **67** were submitted to various liquid-liquid phase-transfer systems (Table 4.3). Disappointingly, the desired *β*-hydroxy sulfone was isolated in very small amount and with no apparent enantiocontrol, regardless of the catalysts used or the liquid-liquid phase transfer system employed. The solvent system toluene/water seemed to be able to promote the reaction more effectively than $CHCl_3$/water, however, the yields were still not satisfactory. When the reaction was performed in the absence of catalyst, similar conversion to the desired sulfone was observed (entries 11 and 12). These results show that the background reaction was responsible for the formation of the sulfone product, explaining that no enantiomeric excess was observed.

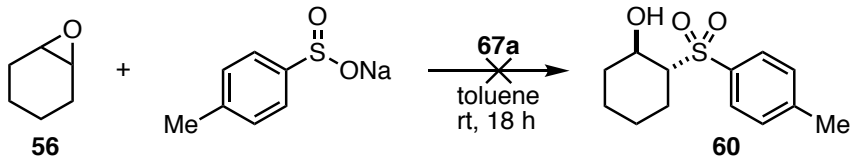
Table 4.3 Initial optimisation of reaction conditions for the phase-transfer catalysed synthesis of 60



Entry	Catalyst	Solvent (ratio)	Yield (%)[a]	ee (%)
1	**67a**	Toluene/H_2O (1:1)	8	0
2	**67a**	$CHCl_3$/H_2O (1:1)	3	0
3	**67b**	Toluene/H_2O (1:1)	9	0
4	**67b**	$CHCl_3$/H_2O (1:1)	5	0
5	**67c**	Toluene/H_2O (1:1)	6	0
6	**67c**	$CHCl_3$/H_2O (1:1)	trace	-
7	**67d**	Toluene/H_2O (1:1)	10	0
8	**67d**	$CHCl_3$/H_2O (1:1)	trace	-
9	**67e**	Toluene/H_2O (1:1)	9	0
10	**67e**	$CHCl_3$/H_2O (1:1)	trace	-
11	**-**	Toluene/H_2O (1:1)	7	-
12	**-**	$CHCl_3$/H_2O (1:1)	trace	-

Reaction conditions: cyclohexene oxide (0.1 mmol), sodium *p*-tolylsulfinate (0.1 mmol), **67** (10 mol%), toluene/water (1:1) [0.25 M]. [a]Isolated yield.

In order to inhibit the background reaction, a different phase-transfer method was studied (Scheme 4.19). Unfortunately, this solid-liquid phase-transfer system was not successful and did not produce any of the desired product, and the starting materials were fully recovered.

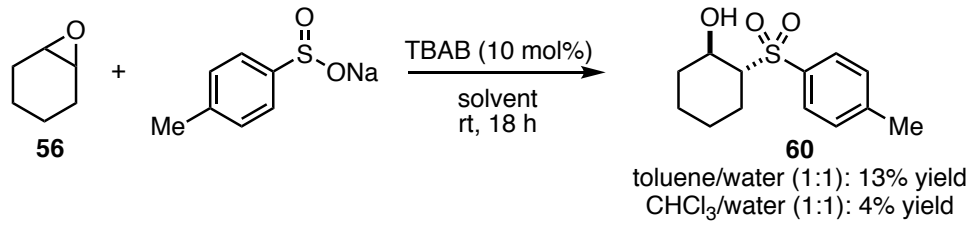


Scheme 4.19 Solid-liquid phase-transfer catalytic system for the ring-opening of cyclohexene oxide

In another attempt to diminish the background reaction, a different phase-transfer system was explored. In order to decrease the non-catalysed interactions between the

reagent, the volume of the aqueous phase was increased tenfold. By decreasing the concentration of the sulfinate salt, we hypothesised that the interactions between substrates at the interphase would be less likely, and therefore would increase the role played by the catalyst. It was decided not to increase the volume of the organic phase to keep a high concentration of substrate, which would allow a fast reaction. However, even under these more dilute reaction conditions, the background reaction still occurred, and no improvement in yield or enantiomeric excess was observed.

In order to assess the capability of quaternary ammonium salts to catalyse the desired ring-opening reaction, tetrabutylammonium bromide (TBAB) was employed in place of **67** (Scheme 4.20). Unfortunately, TBAB was not able to catalyse the reaction, and yield similar to the background reaction were observed.

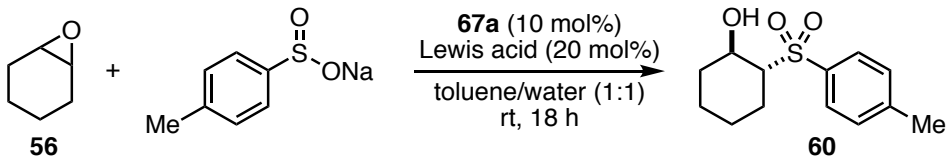


Scheme 4.20 TBAB promoted ring-opening reaction for the synthesis of *β*-hydroxy sulfone **60**

These results demonstrate that quaternary ammonium salts might not be able to catalyse the reaction under these reaction conditions. Nonetheless, combining a quaternary ammonium salt and a Lewis acid, could increase the reactivity of the epoxide and therefore, allow the phase-transfer catalyst to promote the reaction. Thus, a range of Lewis acids were screened with **67a** (Table 4.4). Unfortunately, the majority of Lewis acids showed no improvement in yield. However, when aluminium trichloride (entry 6) and trimethylsilyl triflate (entry 10) were combined with quaternary ammonium salt **67a**, the yields of the respective reactions increased significantly, although no improvement in the enantioselectivity of the reaction was observed. In order to confirm that the involvement of the phase-transfer catalyst, the reaction with aluminium trichloride and

trimethylsilyl triflate were studied without **67a** being present in the reaction mixture. These reactions produced similar yield as the ones with phase-transfer catalyst, confirming that **67a** was not catalysing the reaction and explaining why there was no enantiomeric excess. The enhancement of the yield observed for the reactions in present of $AlCl_3$ and TMS(OTf) can be rationalised by the reaction of these Lewis acids with water which produces hydrochloric acid and triflic acid respectively. These *in situ* generated acids could then activate the epoxide and promote the ring-opening reaction.

Table 4.4 Investigation of the effect of Lewis acid on phase-transfer catalysed ring-opening reaction



56 **60**

Entry	Lewis Acid	Yield (%)[a]	ee (%)
1	$AgNO_3$	9	-
2	AgOAc	7	-
3	Ag_2CO_3	9	-
4	$Zn(OTf)_2$	9	-
5	$ZnCl_2$	8	-
6	$AlCl_3$	38[b]	0
7	$FeCl_3$	10	-
8	$InCl_3$	8	-
9	$Sc(OTf)_3$	11	-
10	TMS(OTf)	35[b]	0
11	$BF_3.Et_2O$	7	-
12	CuBr	8	-
13	$Cu(OAc)_2$	6	-

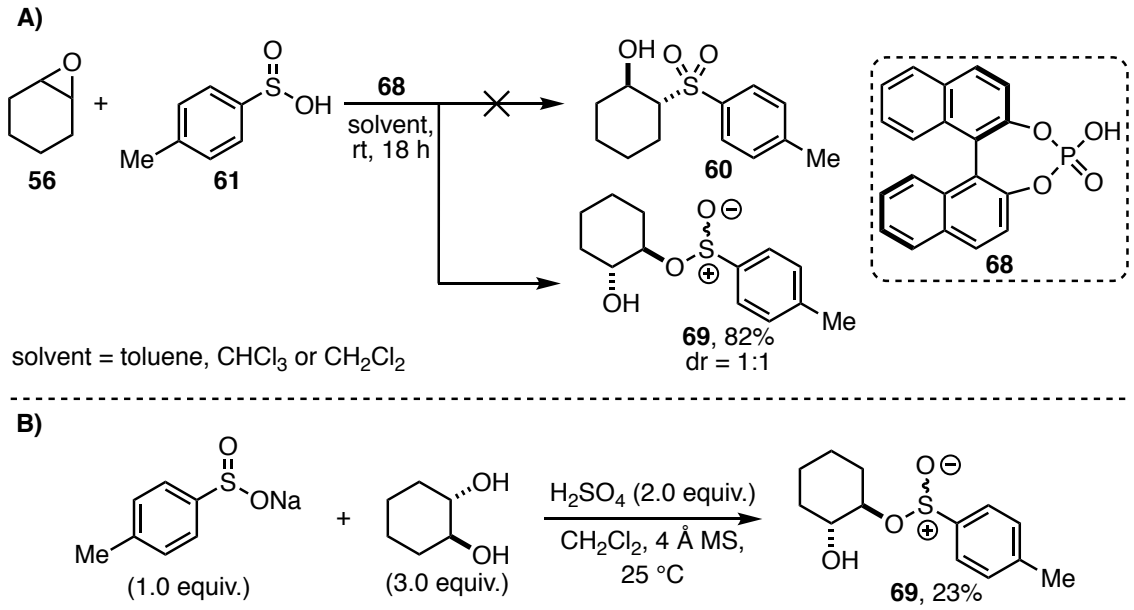
Reaction conditions: cyclohexene oxide (0.1 mmol), sodium *p*-tolylsulfinate (0.1 mmol), **67a** (10 mol%), toluene/water (1:1) [0.25 M]. [a]HPLC yield relative to 4,4-dimethylbiphenyl. [b]Isolated yield.

4.7 Brønsted Acid Catalysed Ring-Opening Reaction

4.7.1 Desymmetrisation of *Meso*-Epoxide Using Sulfinic Acid Nucleophiles

Motivated by our previous results (Section 4.6), we reasoned that, under the right reaction conditions, a chiral phosphoric acid could efficiently catalyse the ring-opening of an epoxides with the sulfinic acid as nucleophile.

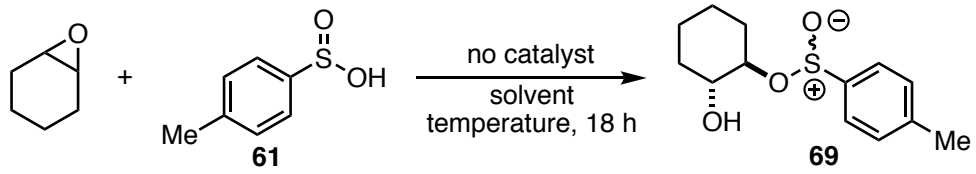
Our first objective was to investigate the Brønsted acid catalysed desymmetrisation of *meso*-epoxides with a sulfinic acid as the nucleophile. In order to study the viability of this route to β-hydroxy sulfones, sulfinic acid and cyclohexene oxide were submitted to various reaction condition in the presence of the (*R*)-BINOL derived phosphoric acid **68** as a catalyst (Scheme 4.21, A). Interestingly, both starting materials were fully consumed, regardless of the solvent employed. However, the desired product **60** was not observed and the major product was the sulfinate ester species **69** in a 1:1 diastereomeric ratio. In order to confirm the structure of the product formed, the sulfinate ester **69** was synthesised using a modified procedure reported in the literature (Scheme 4.21, B).[275] NMR spectroscopy and mass analysis were in accordance with the ones obtained from our product. Thus, confirming that the product formed under our reaction conditions was the sulfinate ester **69**.



Scheme 4.21 A) Phosphoric acid catalysed ring-opening with sulfinic acid as the nucleophile; B) Alternative synthesis of sulfinate ester **69**

In parallel, control experiments without the phosphoric acid catalyst were run (Table 4.5), and each control experiment provided the same sulfinate product in similar yield (entries 1-3). It was decided study the effect of the temperature on the background reaction. We hypothesised that decreasing the temperature of the reaction should diminish the background reaction. We were pleased to see that reducing the temperature to 0 °C seemed to have the desired effect on the conversion of the sulfinic acid **61** (entries 4-6), and this effect increased significantly as the temperature of the reaction decreased.

Table 4.5 Initial optimisation of reaction conditions for the synthesis of **60**



Entry	Solvent	Temperature (°C)	Conversion (%)[a]
1	Toluene	rt	100
2	$CHCl_3$	rt	100
3	CH_2Cl_2	rt	100
4	Toluene	0	93
5	$CHCl_3$	0	88
6	CH_2Cl_2	0	86
7	Toluene	-40	31
8	$CHCl_3$	-40	23
9	CH_2Cl_2	-40	19
10	Toluene	-60	14
11	$CHCl_3$	-60	12
12	CH_2Cl_2	-60	trace
13	Toluene	-78	trace
14	$CHCl_3$	-78	0
15	CH_2Cl_2	-78	0

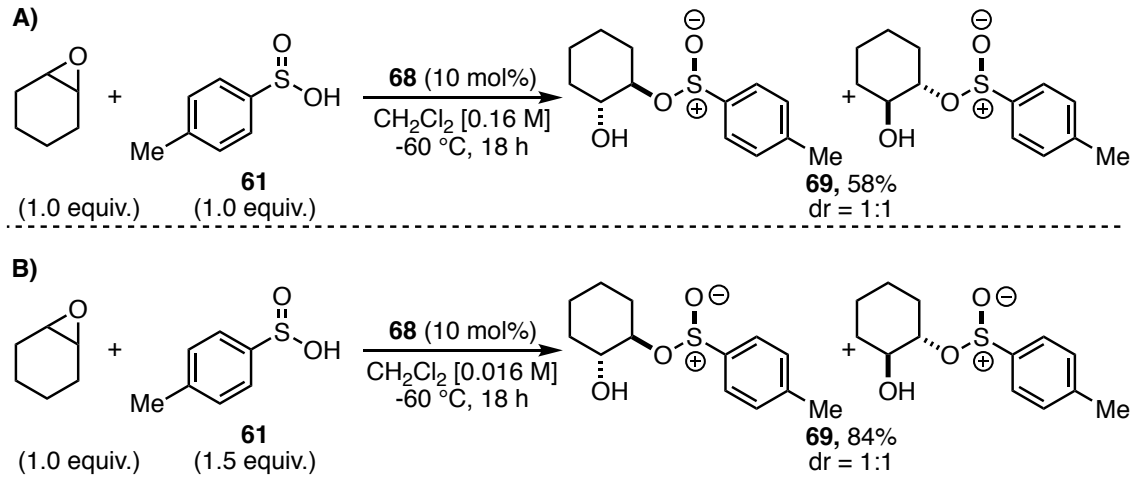
Reaction conditions: cyclohexene oxide (0.1 mmol), **61** (0.1 mmol), solvent [0.16 M]. [a]Conversion of **61** measured by HPLC relative to 4,4-dimethylbiphenyl

Indeed, only a trace amount of the sulfinic acid was consumed in dichloromethane at -60 °C (entry 12). Although the background reaction was fully inhibited at -78 °C (entries 13-15), the trace amount of **61** being consumed at -60 °C in CH_2Cl_2 appeared to us as the best option to explore the ability of the phosphoric acid to catalyse the reaction.

Although the major product synthesised is not the desired *β*-hydroxy sulfone, sulfinate species such as **69** are valuable intermediates in organic synthesis as they can act as electrophiles or nucleophiles depending on the reaction conditions (Section 2.1). The

synthesis of this intermediates can suffer from several drawbacks, such as the necessity to use highly reactive starting materials, long duration of reaction time and a limited functional group compatibility.[276] The development of a straightforward enantioselective synthesis is of great value.

With this new set of conditions in hand, the catalytic activity of phosphoric acid **68** was studied. Pleasingly, **68** was able to catalyse the reaction and the desired sulfinate ester was isolated as a pair of diastereomers in an encouraging 58% yield (Scheme 4.22, A). However, the crude reaction mixture appeared to be a complex mixture. Therefore, in order to improve the selectivity of the reaction, more dilute conditions were used (from 0.16 M to 0.016 M). This proved to be beneficial to the reaction and the isolated yield of the diastereomers increased to 63%. Finally, the number of equivalents of the sulfinic acid **61** was increased from 1.0 to 1.5, which improved the yield significantly and allowed the diastereomers **69** to be isolated in 84% yield but with zero diastereomeric excess (Scheme 4.22, B).



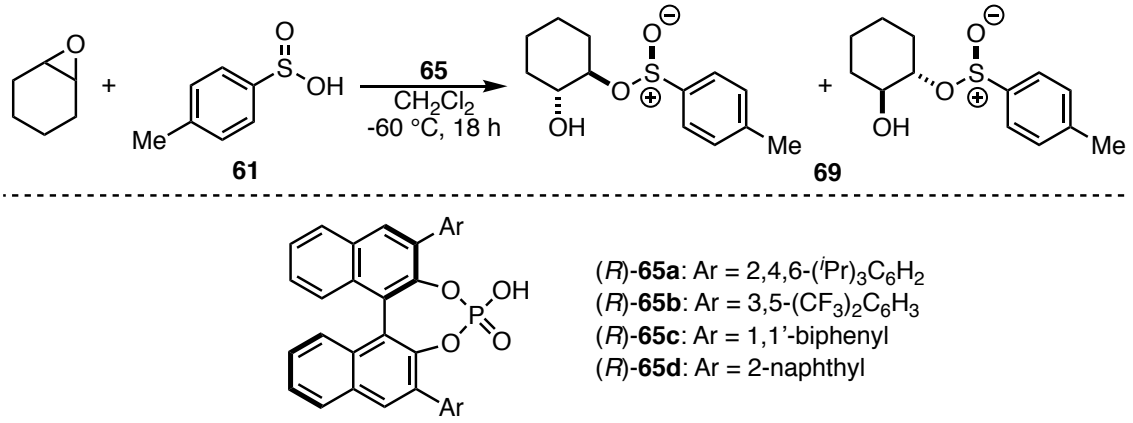
Scheme 4.22 (*R*)-BINOL derived phosphoric acid catalysed ring-opening reaction

By reacting on the oxygen of the sulfinic acid, the generated sulfinate ester species creates a stereocenter on the sulfur atom. Therefore, each diastereomer is itself composed

of a pair of enantiomers. However, when phosphoric acid **68** was used to catalyse the reaction, no enantiomeric excess could be observed for either of the diastereomers when submitted to chiral HPLC analysis. Nonetheless, motivated by this result, a range of 3-,3'-substituted BINOL derived phosphoric acid catalysts were screened under our optimised reaction conditions (Table 4.6). Despite the variation of the phosphoric acid catalyst, no significant improvement could be observed in terms of selectivity of the reaction, with both the diastereomeric ratio and the enantiomeric excess remaining low. Nevertheless, a small enhancement of the dr and ee could be observed when phosphoric acid (*R*)-**65d** was used to catalyse the ring-opening reaction. Furthermore, each phosphoric acid catalyst was able to provide high reactivity, therefore, it is within reason to assume that with a broader screening of phosphoric acids catalysts could have a significant effect on the selectivity of the reaction. Indeed, List and co-workers have shown that variating both the substituents at the 3-,3'-positions and the backbone has for effect to modify the size of the binding site of the catalyst, which can affect the selectivity of the reaction.[269,277]

However, due to a limited amount of time left to further investigate this reaction and a restricted amount of phosphoric acid catalysts available, we decided not to pursue the study of this reaction further. We turned our attention to another interesting aspect of ring-opening reaction; the catalysed ring-opening of unsymmetrical epoxides.

Table 4.6 Investigation of a range of phosphoric acid catalysts



Entry	Catalyst	Yield (%)[a]	dr[b]	ee1 (%)	ee2 (%)
1	(*R*)-**65a**	74	61:39	3	5
2	(*R*)-**65b**	71	57:43	2	6
3	(*R*)-**65c**	69	56:44	1	5
4	(*R*)-**65d**	81	59:41	7	8

Reaction conditions: cyclohexene oxide (0.1 mmol), **61** (0.15 mmol), CH_2Cl_2 [0.016 M]. [a]Isolated yield. [b]Diastereomeric ratio determined from ^{1}H NMR analysis of the crude material.

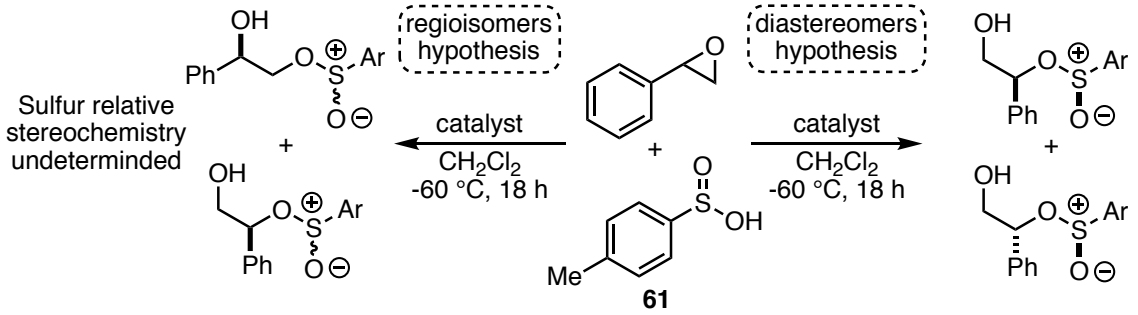
4.7.2 Ring-Opening Reaction of Unsymmetrical Epoxide Using Sulfinic Acid Nucleophiles

The ring-opening of unsymmetrical epoxides allows the formation of a stereocenter with high efficiently and selectivity, often under mild conditions. Therefore, a wide range of methodologies have been reported previously for such transformation with a number of substrates.[278] In order to investigate further the reactivity between sulfinic acids and epoxides in the presence of a phosphoric acid catalyst, we decided to submit styrene oxide to our optimised reaction conditions. Pleasingly, the control experiment did not produce any background reaction, therefore assuring that any reactivity detected during the reaction would be promoted by the catalyst. A range of BINOL-derived phosphoric acid catalysts were submitted to the reaction conditions (Table 4.7). Regardless of the catalyst used, each of the reactions afforded a complex crude mixture, from which two isomers

could be isolated in low yield and poor product ratio. In regards of the structure of the isomers, two hypotheses were envisaged.

The first possibility is that, the two isomers are regioisomers resulting from a regioselectivity issue, by which the epoxide is opened at either carbon of the epoxide. Such regioselectivity problems have been encountered by other groups in their study of ring-opening reactions of unsymmetrical epoxides.[117,279,280] However, this hypothesis could imply perfect diastereocontrol, as no diastereomer was observed for either of the products by NMR spectroscopy analysis (Scheme 4.23, A).

Table 4.7 Catalyst screening for the ring-opening reaction of cyclohexene oxide



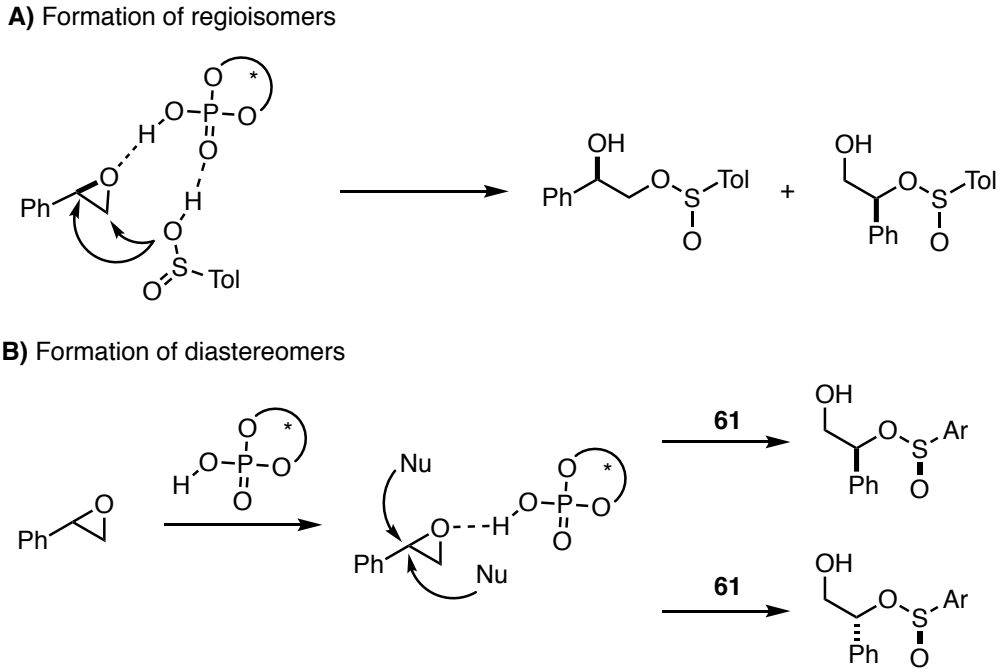
Entry	Catalyst	Overall yield (%)[a]	isomeric ratio[b]
1	(*R*)-**68**	10	1:1
2	(*R*)-**65a**	34	1:1
3	(*R*)-**65b**	28	1:1.6

Reaction conditions: styrene oxide (0.1 mmol), **61** (0.15 mmol), CH_2Cl_2 [0.016 M]. [a]Isolated yield. [b]Diastereomeric ratio determined from ^{1}H NMR analysis of the crude material. An arbitrary enantiomer has been drawn.

The second hypothesis is that the regioselectivity of the reaction is controlled and styrene oxide is only opened at the benzylic position, as described by List and co-workers in their ring-opening reaction with carboxylic acids.[281] This would suggest that the two isomers isolated are diastereomers (Scheme 4.23, B).

Unfortunately, the poor yields did not allow 2D NMR analysis to be executed. However, 2D NMR analysis could have helped in differentiating regioisomers and diastereomers, therefore allowing to confirm one of the two hypotheses. Indeed, an

experiment such as a HSQC would have help visualising properly the benzylic signal and therefore help to attribute the different NMR signals.



Scheme 4.23 A) Rationalisation for hypothesis 1; B) Rationalisation for hypothesis 2

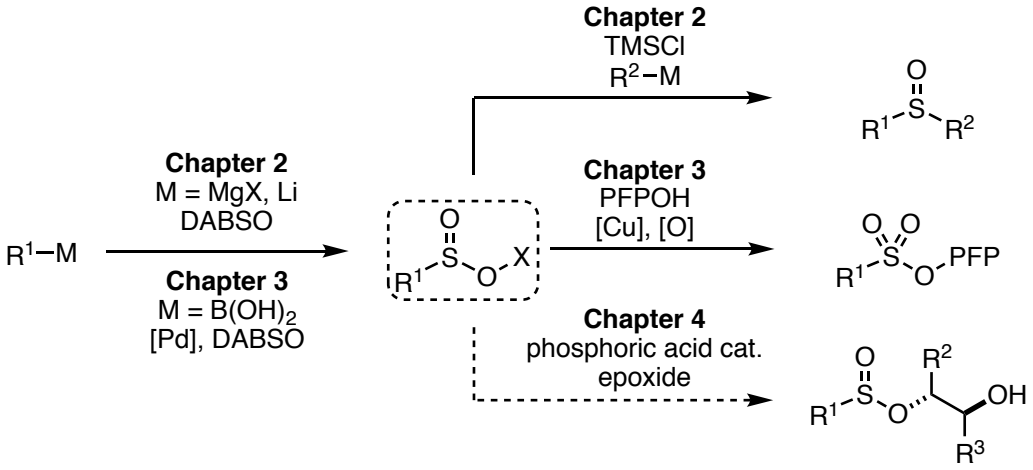
4.8 Project Summary

In summary, novel reactivities were discovered by studying the ring-opening of various epoxides with sulfinic acids, under the influence of different catalytic systems. Firstly, various metal-salen complexes have been utilised to catalyse epoxide ring-opening for the synthesis of sulfonate esters. However, the low yields and the long reaction times diminished the attractiveness of this method.

Chiral phosphoric acid catalysed ring-opening of epoxides with sulfinic acid delivered some exciting results. In the ring-opening of *meso*-epoxides, this method provided very good reactivity but low selectivity. In the ring-opening of unsymmetrical epoxides, this methodology showed some interesting results, but further investigated need to be conducted to confirm the structure of the products and understand the selectivity of the reaction.

Chapter 5 - Conclusion and Future Work

Since the first application of DABSO as an easy-to-handle sulfur dioxide surrogate in palladium-catalysed aminosulfonylation reaction,[125] our group and others have contributed to the development of numerous robust methodologies toward the synthesis of molecules of interest which incorporate sulfonyl functional groups. The Willis group has made important contributions to the field by determining that DABSO was an efficient sulfur dioxide source for catalytic and stochiometric sulfonylative processes, as well a safe alternative to sulfur dioxide gas for organic synthesis. This thesis presents work that has attempted to further exemplify the capability of DABSO to be used safely in organic synthetic protocols, as well as broadening its application by focusing on the functionalisation of sulfinic acid derivatives. Firstly, unsymmetrical sulfoxide species have been synthesised in a robust one-pot procedure from DABSO and organometallic reagents, proceeding through an electrophilic sulfinate ester intermediate.[1] In addition, we disclosed the discovery of a copper-catalysed oxidative synthesis of activated sulfonate esters from boronic acid, DABSO and pentafluorophenol. This protocol allows an easily accessible route to pentafluorophenyl sulfonate ester products, which are of great value as efficient alternatives to sulfonyl chlorides.



Finally, and of particular importance, a novel phosphoric acid catalysed ring-opening reaction employing a sulfinic acid as a nucleophile was disclosed. This method offers a straightforward route to highly valuable, enantioenriched, β-hydroxy sulfinate products. However, this methodology is at the very beginning of its optimisation and therefore will require further investigations of reaction conditions to make it a valuable and applicable synthetic method. This novel synthesis is also interesting on a mechanistic point of view, to determine how specifically the phosphoric acid catalyst interact with the epoxides and the sulfinic acid substrate, thus, important future work in regard to this chemistry is to investigate the mechanism of the reaction. By gaining insights into the key interactions of the different species would help to target the appropriate type of phosphoric acid scaffold in order to increase selectivity.

Future work investigating the application of sulfur dioxide surrogates in known reactions of sulfur dioxide gas would be of great interest. For example, studying the isomerisation of alkenes promoted by amine-sulfur dioxide complexes could be of significant importance. Developing alternative catalytic methods (such as organocatalysis) for sulfonylation reactions, employing DABSO, would also prove to be of great value, as it would broaden the range of starting materials that can be used, and reaction conditions which can be used to the incorporate sulfonyl functional groups in target molecules.

Chapter 6 - Experimental Data and Procedures

6.1 General Considerations

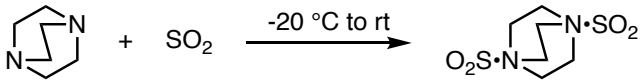
Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros and Fluorochem and were used as supplied unless otherwise stated. DABSO was prepared from DABCO and SO_2 gas as previously reported by our group. Tetra-*n*-butylammonuim bromide (TBAB) was recrystallised from ethyl acetate and dried *in vacuo* at 60 °C for two days. Sodium bromide was recrystallised from water and dried *in vacuo* at 140 °C overnight. Morpholine, piperidine, and triethylamine were purified by stirring over CaH_2 for 24 hours before distilling. Solvents were purchased from commercial suppliers and used without further purification unless otherwise stated. 1,4-Dioxane was dried over 4 Å molecular sieves and through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. 'Pet. ether' refers to low boiling point (40-60 °C) petroleum ether. Grignard reagents were titrated against iodine in a 0.5 M lithium chloride solution in THF. Organolithium reagents were titrated against *N*-benzylbenzamide in anhydrous THF.

Reactions were carried out with constant magnetic stirring unless otherwise stated. All glassware was dried in an oven (>200 °C, overnight) and allowed to cool down under positive flow of nitrogen prior to use. Standard Schlenk techniques were applied for the transfer of dry solvents and air sensitive reagents. Flash chromatography was carried out using silica gel (Merck silicagel 60, particle size 40-63 μm) with the indicated solvent. Thin layer chromatography (TLC) analysis was performed on aluminum-backed silica sheets (Merck TLC Silica 60 F_{254}) and visualized by UV fluorescence (254 nm) and/or by staining with potassium permanganate ($KMnO_4$).

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were obtained on Bruker AVIII400 or a Bruker AVII500 NMR spectrometer using the residual solvent as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants *J* are quoted in the unit of Hertz (Hz). Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, and comparison with spectra of related compounds. Multiplicity are given as following: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), hept (heptet), m (multiplet), app (apparent). Low-resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High-resolution mass spectra were measured by internal service at the University of Oxford using a Bruker Daltronics microTOF (ESI) spectrometer or a Micromass LCT spectrometer using filed ionization method (FI) or electron ionisation (EI). Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

6.2 Amine Sulfur Dioxide Complex

6.2.1 General Procedure for the Formation of DABSO



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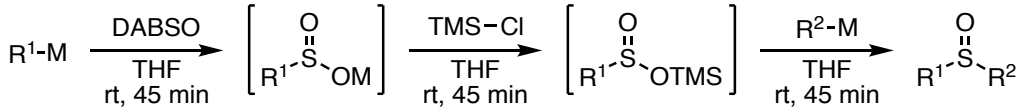
Method adapted from procedure documented by Santos and Mello.[113] A 250 mL round-bottom flask fitted with a cold-finger condenser and connected to a Dreschel bottle oil bubbler system was cooled under a flow of nitrogen. Sublimed 1,4-diazabicyclo[2.2.2]octane (DABCO) (12 g, 107 mmol) was added to the flask followed by flushing with nitrogen for 2 minutes. The nitrogen atmosphere was replaced with sulfur dioxide gas (~2 bubbles/sec) and the system flushed for 3 mins. The flask was then cooled to -30 °C by which point sulfur dioxide began to condense dropwise and this was aided further by cooling of the condenser to -78 °C. This was continued until the DABCO was fully submerged in liquid SO_2 and a free flowing slurry was obtained. The gas flow was then stopped and the flask warmed to -10 °C and left stirring at "reflux" for 1 hour. The flask was warmed to room temp. and the reaction left to stir under a flow of nitrogen for 16 hr. After this time, the excess of sulfur dioxide had evaporated through the bubbler system to afford DABSO as a white powder (26 g, 99%); ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 3.22 (12 H, s); ^{13}C NMR (100 MHz, MeOD- *d*$_4$) δ 45.4; IR ν_{max} (neat)/cm^{-1} 1476, 1459, 1354 (SO_2), 1100 (SO_2), 1088.

6.3 Data Chapter 2

6.3.1 General Procedure A for the synthesis of sulfoxides

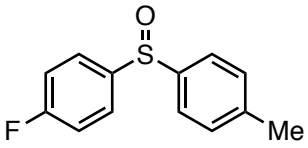


To a 25 mL two-neck round bottom flask was added DABSO (240 mg, 1.0 mmol, 0.5 equiv.) and anhydrous THF (4.0 mL), and the resulting suspension was flushed with nitrogen gas for 3 minutes. Under a constant flow of nitrogen gas, organometallic reagent 1 (R^1M, 2.0 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was left to stir for 45 minutes (t_1) at room temperature. Subsequently, chlorotrimethylsilane (381 μL, 3.0 mmol, 1.5 equiv.) was added and the reaction mixture was left to stir for 45 minutes (t_2) at room temperature before adding organometallic reagent 2 (R^2M, 1.5 mmol, 0.75 equiv.). After stirring at room temperature for another 45 minutes (t_3), the reaction mixture was quenched with saturated NH_4Cl aq. solution (10 mL). The organic material was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient.

Notes:

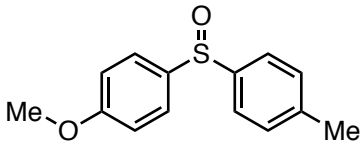
- Reaction times for each individual step (t_1, t_2, and t_3) were 45 minutes unless otherwise stated.
- Reactions were performed at room temperature unless otherwise stated.

p-Tolyl *p*-fluorophenyl sulfoxide (**40a**)



Prepared according to general procedure A using *p*-fluorophenylmagnesium bromide (2.3 mL, 0.89 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.85 M in THF, 1.5 mmol). Flash column chromatography (25% EtOAc in pet. ether) afforded the desired sulfoxide mixed with bis(*p*-tolyl) sulfoxide in a 25:1 ratio (ratio determined by ^{1}H NMR) as a white solid (341 mg, 97%). R_f = 0.30 (25% EtOAc in pet. ether); mp (pet. ether) 40-41 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (dd, *J* =8.9, 5.1 Hz, 2H, Ar-*H*), 7.51 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.27 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.14 (app. t, *J* = 8.9 Hz, 2H, Ar-*H*), 2.38 (s, 3H, ArCH_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.2 (d, $^{1}J_{CF}$ = 251.4 Hz), 142.3, 141.8, 141.4 130.1, 127.1 (d, $^{3}J_{CF}$ = 8.9 Hz), 124.8, 116.5 (d, $^{2}J_{CF}$ = 22.5 Hz), 21.4; ^{19}F NMR ($CDCl_3$, 377 MHz): δ -108.7; MS (ESI) *m/z* 235.1 $[M+H]^+$. Data are in accordance to that previously reported.[282]

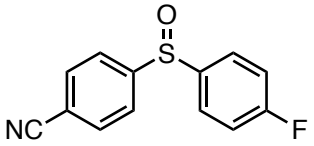
p-Methoxyphenyl *p*-tolyl sulfoxide (**40b**)



Prepared according to general procedure A using *p*-methoxyphenylmagnesium bromide (5.1 mL, 0.39 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.89 M in THF, 1.5 mmol). Flash column chromatography (30% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (353 mg, 96%). R_f = 0.30 (50% EtOAc in pet. ether); mp (pet. ether) 58-59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.57 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.52 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.28 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 6.97 (d, *J* = 8.6 Hz, 2H,

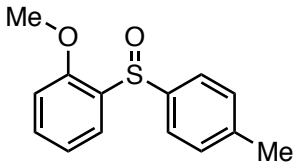
Ar-*H*), 3.84 (s, 3H, OC*H*$_3$), 2.39 (s, 3H, ArC*H*$_3$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.9, 142.7, 141.2, 137.1, 129.9, 127.1, 124.8, 114.8, 55.5, 21.4; MS (ESI) *m/z* 247.1 $[M+H]^+$. Data are in accordance to that previously reported. [283]

p-Cyanophenyl *p*-fluorophenyl sulfoxide (**40c**)



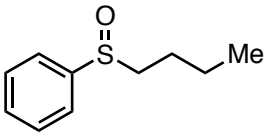
Prepared according to general procedure A from *p*-cyanophenylmagnesium chloride (2.0 mmol) and *p*-fluorophenylmagnesium bromide (1.7 mL, 0.89 M in THF, 1.5 mmol). *p*-cyanophenylmagnesium chloride was generated *in situ* from the corresponding bromide (364 mg, 2.0 mmol) using *iso*-propylmagnesium chloride lithium chloride complex (2.0 mL, 1.03 M, 2.1 mmol).[6] Flash column chromatography (25% to 50% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (209 mg, 61%). R_f = 0.25 (50% EtOAc in pet. ether); mp (pet. ether) 115-116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 – 7.70 (m, 4H, Ar-*H*), 7.65 (dd, *J* = 8.9, 5.0 Hz, 2H, Ar-*H*), 7.22 – 7.12 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7 (d, $^1J_{CF}$ = 253.6 Hz), 151.0, 140.2, 133.0, 127.4 (d, $^3J_{CF}$ = 9.2 Hz), 124.9, 117.7, 117.2 (d, $^2J_{CF}$ = 22.6 Hz), 114.8; ^{19}F NMR ($CDCl_3$, 377 MHz): δ -106.3; IR ν_{max} (neat)/cm^{-1} 2232 (CN), 1589, 1491, 1228, 1088, 1050 (SO), 832; MS (ESI) *m/z* 246.1 $[M+H]^+$; HRMS (ESI) found *m/z* 246.0383 $[M+H]^+$, $C_{13}H_9FNO^{32}S$ requires *m/z* 246.0389.

o-Methoxyphenyl *p*-tolyl sulfoxide (**40d**)



Prepared according to general procedure A using *o*-methoxyphenylmagnesium bromide (2.8 mL, 0.70 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.89 M in THF, 1.5 mmol). Flash column chromatography (25% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (355 mg, 96%). R_f = 0.21 (25% EtOAc in pet. ether); mp (pet. ether) 98-99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.39 (ddd, *J* = 8.2, 7.6, 1.7 Hz, 1H, Ar-*H*), 7.27 – 7.11 (m, 3H, Ar-*H*), 6.85 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 3.79 (s, 3H, OC*H*$_3$), 2.35 (s, 3H, ArC*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 142.3, 141.2, 133.2, 132.0, 129.6, 125.3, 124.4, 121.5, 110.9, 55.6, 21.3; MS (ESI) *m/z* 247.1 $[M+H]^+$. Data are in accordance to that previously reported. [284]

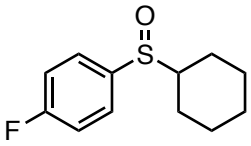
n-Butyl phenyl sulfoxide (**40e**)



Prepared according to general procedure A using phenylmagnesium bromide (2.4 mL, 0.84 M in THF, 2.0 mmol) and butylmagnesium chloride (1.2 mL, 1.23 M, 1.5 mmol). Flash column chromatography (30% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (272 mg, 99%). R_f = 0.40 (50% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 – 7.58 (m, 2H, Ar-*H*), 7.54 – 7.45 (m, 3H, Ar-*H*), 2.78 (t, *J* = 7.7 Hz, 2H, SC*H*$_2$CH$_2$), 1.80 – 1.66 (m, 1H, -C*H*$_2$-), 1.65 – 1.51 (m, 1H, -C*H*$_2$-), 1.52 – 1.32 (m, 2H, C*H*$_2$CH$_3$), 0.91 (t, *J* = 7.3 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 130.9,

129.1, 124.0, 57.1, 24.1, 21.9, 13.6; MS (ESI) *m/z* 205.1 $[M+Na]^+$. Data are in accordance to that previously reported. [285]

1-(Cyclohexylsulfinyl)-4-fluorobenzene (**40f**)



Procedure 1: Prepared according to general procedure A using *p*-fluoromagnesium bromide (3.1 mL, 0.64 M in THF, 2.0 mmol) and cyclohexylmagnesium chloride (1.1 mL, 1.32 M in THF, 1.5 mmol). Flash column chromatography (20% to 50% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (326 mg, 96%). mp (pet. ether) 99-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (m, 2H, Ar-*H*), 7.23-7.18 (m, 2H, Ar-*H*), 2.52 (tt, *J* = 11.6, 3.4 Hz, 1H, SC*H*), 1.84-1.81 (m, 4H, (C*H*$_2$)$_2$), 1.65 (m, *J* = 9.2 Hz, 1H, CH_aH$_b$), 1.43-1.15 (m, 5H, CH$_a$$H_b$ and (C*H*$_2$)$_2$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.6 (d, $^1J_{CF}$ = 254.3 Hz), 137.3, 127.2 (d, $^3J_{CF}$ = 8.6 Hz), 116.4 (d, $^2J_{CF}$ = 22.5 Hz), 63.3, 26.1, 25.54, 25.43, 25.28, 24.1; ^{19}F NMR ($CDCl_3$, 377 MHz): δ -108.8; IR ν_{max} (neat)/cm^{-1} 2931, 2855, 1491, 1221, 1038 (SO), 835; MS (ESI) *m/z* 249.0 $[M+Na]^+$; HRMS (ESI) found *m/z* 227.0871 $[M+H]^+$, $C_{12}H_{16}FO^{32}S$ requires *m/*z 227.0861.

Procedure 2: Prepared according to general procedure A using *p*-fluorophenylmagnesium bromide (18.5 mL, 0.92 M in THF, 17.0 mmol), DABSO (2.0 g, 8.5 mmol), TMS-Cl (3.2 mL, 25.5 mmol), and cyclohexylmagnesium chloride (9.7 mL, 1.32 M in THF, 12.8 mmol). Flash column chromatography (20% to 50% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (2.7 g, 92%).

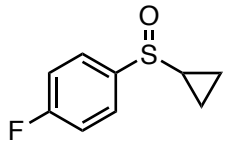
Procedure 3: To a flame dried 25 mL two-neck round bottom flask was added DABSO (240.3 mg, 1.0 mmol, 0.5 equiv.) and anhydrous THF (4.0 mL), and the resulting

suspension was flushed with nitrogen gas for 3 minutes. Under a constant flow of nitrogen gas, *p*-fluorophenylmagnesium bromide (3.1 mL, 0.64 M in THF, 2.0 mmol) was added dropwise and the reaction mixture was left to stir for 45 minutes at room temperature. Subsequently, chloro(dimethyl)phenylsilane (0.5 mL, 3.0 mmol, 1.5 equiv.) was added and the reaction mixture was left to stir for 5 minutes at room temperature. The reaction mixture was then quenched with (20%) Na_2CO_3 aq. solution (15.0 mL). The product was extracted from the aqueous layer with ethyl acetate (3 × 50.0 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The structure of the intermediate (43) was confirmed by ^1H NMR analysis and resubmitted to inert conditions. The crude material was diluted into anhydrous THF (4.0 mL). Under a constant flow of nitrogen gas, cyclohexylmagnesium chloride (0.8 mL,1.32 M in THF, 1.0 mmol) was added dropwise and the reaction mixture was left to stir for 45 minutes at room temperature. The reaction mixture was quenched with saturated NH_4Cl aq. solution (10.0 mL). The product was extracted from the aqueous layer with ethyl acetate (3 × 10.0 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (20% to 50% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (150 mg, 66%).

Procedure 4: To a flame dried 25 mL two-neck round bottom flask was added DABSO (240.3 mg, 1.0 mmol, 0.5 equiv.) and anhydrous THF (4.0 mL), and the resulting suspension was flushed with nitrogen gas for 3 minutes. Under a constant flow of nitrogen gas, *p*-fluorophenylmagnesium bromide (3.1 mL, 0.64 M in THF, 2.0 mmol) was added dropwise and the reaction mixture was left to stir for 45 minutes at room temperature. Subsequently, chloro(dimethyl)phenylsilane (0.5 mL, 3.0 mmol, 1.5 equiv.) was added and the reaction mixture was left to stir for 5 minutes at room temperature. Then, cyclohexylmagnesium chloride (1.1 mL, 1.32 M in THF, 1.5 mmol) was added dropwise

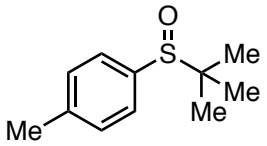
and the reaction mixture was left to stir for 45 minutes at room temperature. The reaction mixture was quenched with saturated NH_4Cl aq. solution (10.0 mL). The product was extracted from the aqueous layer with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (20% to 50% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (258 mg, 76%).

1-(Cyclopropylsulfinyl)-4-fluorobenzene (**40g**)



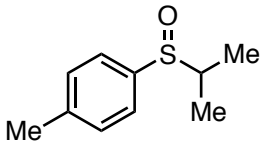
Prepared according to general procedure A using *p*-fluorophenylmagnesium bromide (1.2 mL, 1.63 M in THF, 2.0 mmol) and cyclopropylmagnesium bromide (2.0 mL, 0.76 M in THF, 1.50 mmol). Flash column chromatography (50% EtOAc in pet. ether) afforded the desired sulfoxide as a yellow oil (183 mg, 66%). R_f = 0.43 (70% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.64 (m, 2H, Ar-*H*), 7.24-7.18 (m, 2H, Ar-*H*), 2.23 (tt, *J* = 7.9, 4.9 Hz, 1H, SC*H*), 1.27-1.21 (m, 1H, CH_aH$_b$), 1.05-0.92 (m, 3H, CH_2CH$_a$CH_b); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.4 (d, $^1J_{CF}$ = 252.5 Hz), 140.5 (d, $^4J_{CF}$ = 3.1 Hz), 126.4 (d, $^3J_{CF}$ = 8.3 Hz), 116.6 (d, $^2J_{CF}$ = 22.9 Hz), 34.1, 3.6, 2.9; ^{19}F NMR ($CDCl_3$, 377 MHz): δ -108.9; IR ν_{max} (neat)/cm^{-1} 2933, 2836, 1589, 1222, 1045 (SO), 1023, 831; MS (ESI) *m/z* 185.1 $[M+H]^+$; HRMS (ESI) found *m/z* 185.0432 $[M+H]^+$, $C_9H_{10}OF^{32}S$ requires *m/z* 185.0431.

1-(tert-butylsulfinyl)-4-methylbenzene (**40h**)



Prepared according to general procedure A using *p*-tolylmagnesium bromide (2.1 mL, 0.94 M in THF, 2.0 mmol) and *tert*-butylmagnesium bromide (1.0 mL, 1.53 M in THF, 1.5 mmol). Flash column chromatography (30% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (184 mg, 62%). R_f = 0.26 (25% EtOAc in pet. ether); mp (pet. ether) 68-70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.22 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 2.34 (s, 3H, ArC*H*$_3$), 1.09 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.5, 136.7, 129.1, 126.2, 55.6, 22.7, 21.4; HRMS (ESI) found *m/z* 197.0999 $[M+H]^+$, $C_{11}H_{17}O^{32}S$ requires *m/z* 197.0995. Data are in accordance to that previously reported. [286]

Isopropyl *p*-tolyl sulfoxide (**40i** and **40j**)

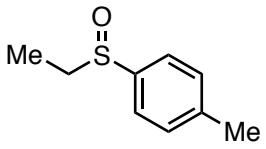


40i: Prepared according to general procedure A using 4-methylphenylmagnesium bromide (2.3 mL, 0.89 M, 2.0 mmol) and isopropylmagnesium chloride (1.0 mL, 1.44 M in THF, 1.5 mmol). Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (267 mg, 98%). R_f = 0.14 (25% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.32 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 2.82 (app hept, *J* = 6.8 Hz, 1H, $(CH_3)_2CHS$), 2.43 (s, 3H, ArC*H*$_3$), 1.19 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_a$(CH_3)$_b$), 1.14 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_a$(C*H*$_3$)$_b$);

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.4, 138.5, 129.6, 125.1, 54.5, 21.4, 15.7, 14.1; MS (ESI) *m/z* 183.1 $[M+H]^+$. Data are in accordance to that previously reported. [287]

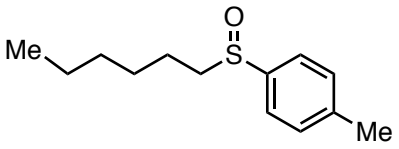
40j: Prepared according to general procedure A using isopropylmagnesium chloride (1.4 mL, 1.44 M in THF, 2.0 mmol) as the first nucleophile, and *p*-tolylmagnesium bromide (0.89 M, 1.7 mL, 1.5 mmol). Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (198 mg, 72%)

Ethyl *p*-tolyl sulfoxide (**40k**)



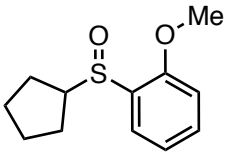
Prepared according to general procedure A using ethylmagnesium chloride (1.2 mL, 1.72 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.89 M, 1.5 mmol). Flash column chromatography (50% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (238 mg, 95%). R_f = 0.25 (25% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.33 (d, *J* = 8.2 Hz, 2H, Ar-*H*), δ 2.86 (dq, *J* = 13.2, 7.4 Hz, 1H, CH_3CH_aHbS), 2.75 (dq, *J* = 13.2, 7.4 Hz, 1H, $CH_3CH_aH_b$S), 2.42 (s, 3H, ArCH_3), 1.19 (t, *J* = 7.4 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4, 140.2, 129.8, 124.2, 50.4, 21.4, 6.0; MS (ESI) *m/z* 169.1 $[M+H]^+$. Data are in accordance to that previously reported. [288]

n-Hexyl p-tolyl sulfoxide (**40l**)



Prepared according to general procedure A using *n*-hexylmagnesium bromide (1.7 mL, 1.19 M in diethyl ether, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.85 M, 1.5 mmol). Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the desired sulfoxide mixed with bis(*p*-tolyl) sulfoxide in a 25:1 ratio as a colourless oil (219 mg, 65%). R_f = 0.25 (25% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.31 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 2.83 – 2.68 (m, 2H, CH_2CH_2S), 2.41 (s, 3H, $ArCH_3$), 1.80 – 1.52 (m, 2H, CH_2CH_2S), 1.48 – 1.32 (m, 2H, CH_2), 1.33 – 1.19 (m, 4H, $CH_3CH_2CH_2$), 0.86 (t, *J* = 7.0 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 140.8, 129.9, 124.1, 57.4, 31.3, 28.3, 22.4, 22.2, 21.4, 13.9; MS (ESI) *m/z* 225.1 $[M+H]^+$. Data are in accordance to that previously reported. [289]

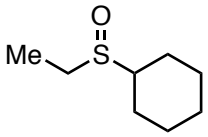
o-Methoxyphenyl cyclopentyl sulfoxide (**40m**)



Prepared according to general procedure A using cyclopentylmagnesium bromide (1.2 mL, 1.69 M in THF, 2.0 mmol) and *o*-methoxyphenylmagnesium bromide (2.1 mL, 0.70 M in diethyl ether, 1.5 mmol). Flash column chromatography (20% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (255 mg, 76%). R_f = 0.30 (50% EtOAc in pet. ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (dd, J = 7.7, 1.7 Hz, 1H, Ar-*H*), 7.41 (ddd, J = 8.2, 7.5, 1.7 Hz, 1H, Ar-*H*), 7.14 (app td, J = 7.5, 0.9 Hz, 1H, Ar-*H*), 6.88 (d, J = 8.2 Hz, 1H, Ar-*H*), 3.87 (s, 3H, OCH_3), 3.45 – 3.35 (m, 1H, C*H*S), 2.13 – 1.86 (m, 3H),

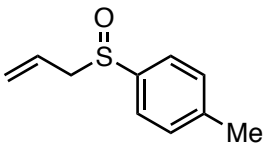
1.78 – 1.44 (m, 4H), 1.39 – 1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.1, 131.7, 131.2, 125.9, 121.3, 110.4, 59.5, 55.7, 28.4, 26.5, 25.9, 22.9; IR ν_{max} (neat)/cm^{-1} 2955, 1585, 1476, 1435, 1271, 1236, 1033 (SO), 755; MS (ESI) *m/z* 225.1 $[M+H]^+$; HRMS (ESI) found *m/z* 225.0944 $[M+H]^+$, $C_{12}H_{17}O_2{}^{32}S$ requires *m/z* 225.0944.

Ethyl cyclohexyl sulfoxide (**40n**)



Prepared according to general procedure A using ethylmagnesium chloride (1.2 mL, 1.72 M in THF, 2.0 mmol) and cyclohexylmagnesium bromide (1.3 mL, 1.16 M in diethyl ether, 1.5 mmol). Flash column chromatography (5% MeOH in DCM) afforded the desired sulfoxide as a colourless oil (224 mg, 93%). R_f = 0.50 (10% MeOH in DCM); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.75 – 2.58 (m, 2H, C*H*$_2$S), 2.59 – 2.47 (m, 1H, SC*H*), 2.15 – 2.05 (m, 1H), 1.97 – 1.78 (m, 3H, SCH$_2$C*H*$_3$), 1.74 – 1.65 (m, 1H), 1.53 – 1.17 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.1, 42.1, 26.4, 25.5, 25.4, 25.1, 24.8, 7.0; MS (ESI) *m/z* 161.1 $[M+H]^+$. Data are in accordance to that previously reported. [290]

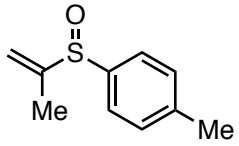
Allyl *p*-tolyl sulfoxide (**40o**)



Prepared according to general procedure A using allylmagnesium chloride (1.7 mL, 1.20 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.85 M in THF, 1.5 mmol). Flash column chromatography (30% to 40% EtOAc in pet. ether) afforded the

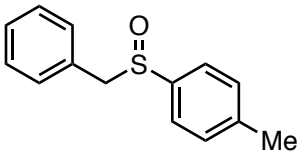
desired sulfoxide as a pale-yellow oil (149 mg, 55%). R_f = 0.2 (50% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.30 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 5.63 (ddt, *J* = 17.6, 10.1, 7.5 Hz, 1H, CH_2CHCH_2), 5.31 (dd, *J* = 10.1, 1.3 Hz, 1H, $CH_aH_bCHCH_2S$), 5.18 (dd, *J* = 17.6, 1.3 Hz, 1H, $CH_aH_bCHCH_2S$), 3.57 – 3.45 (m, 2H, $CHCH_2S$), 2.41 (s, 3H, $ArCH_3$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.6, 139.7, 129.8, 125.4, 124.4, 123.7, 61.0, 21.4; MS (ESI) *m/z* 181.1 $[M+H]^+$. Data are in accordance to that previously reported. [291]

Isopropene *p*-tolyl sulfoxide (**40p**)



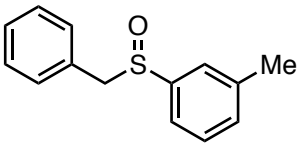
Prepared according to general procedure A using isopropenylmagnesium chloride (6.2 mL, 0.32 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.85 M in THF, 1.50 mmol). Flash column chromatography (20% to 40% EtOAc in pet. ether) afforded the desired sulfoxide mixed with bis(*p*-tolyl) sulfoxide in a 24:1 ratio (ratio determined by ^{1}H NMR) as a pale-yellow oil (207 mg, 77%). R_f = 0.30 (25% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.29 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 5.98 (d, *J* = 0.8 Hz, 1H, $CH_{cis}CMe$), 5.58 (d, *J* = 1.5 Hz, 1H, $CH_{trans}CMe$), 2.40 (s, 3H, $ArCH_3$), 1.71 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.2, 141.5, 139.1, 129.7, 125.1, 117.6, 21.3, 13.4; IR ν_{max} (neat)/cm^{-1} 1492, 1444, 1082, 1047 (SO), 921, 842; MS (ESI) *m/z* 181.0 $[M+H]^+$; HRMS (ESI) found *m/z* 181.0682 $[M+H]^+$, $C_{10}H_{13}O^{32}S$ requires *m/z* 181.0682.

Benzyl *p*-tolyl sulfoxide (**40q**)



Prepared according to general procedure A using benzylmagnesium chloride (1.2 mL, 1.65 M in THF, 2.0 mmol) and *p*-tolylmagnesium bromide (1.7 mL, 0.89 M in THF, 1.5 mmol). Flash column chromatography (30% to 40% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (257 mg, 74%). R_f = 0.25 (50% EtOAc in pet. ether); mp (pet. ether) 144-145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 – 7.24 (m, 7H, Ar-*H*), 7.03 (dd, *J* = 7.6, 1.5 Hz, 2H, Ar-*H*), 4.12 (d, *J* = 12.5 Hz, 1H, Ar-CH_aH$_b$S), 4.01 (d, *J* = 12.5 Hz, 1H, Ar-CH$_a$$H_b$S), 2.42 (s, 3H, ArC$H_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.6, 139.6, 130.4, 129.6, 129.4, 128.5, 128.2, 124.5, 63.7, 21.5; MS (ESI) *m/z* 231.1 $[M+H]^+$. Data are in accordance to that previously reported. [292]

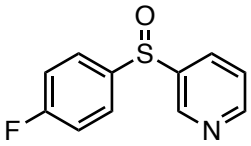
Benzyl *m*-tolyl sulfoxide (**40r**)



Prepared according to general procedure A using benzylmagnesium chloride (1.2 mL, 1.65 M in THF, 2.0 mmol) and *m*-tolylmagnesium bromide (5.7 mL, 0.26 M in THF, 1.5 mmol). Flash column chromatography (30% to 40% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (242 mg, 71%). R_f = 0.25 (50% EtOAc in pet. ether); mp (pet. ether) 61-62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.30 (m, 5H, Ar-*H*), 7.27 (s, 1H, Ar-*H*), 7.22 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 7.07 (dd, *J* = 7.8, 1.6 Hz, 2H, Ar-*H*), 4.15 (d, *J* = 12.5 Hz, 1H, SCH_aH$_b$), 4.06 (d, *J* = 12.5 Hz, 1H, SCH$_a$$H_b$), 2.41 (s, 3H, ArC$H_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7, 139.1, 132.0, 130.4, 129.3, 128.6, 128.4, 128.2,

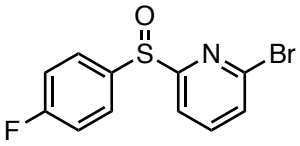
124.7, 121.5, 63.7, 21.3; MS (ESI) *m/z* 231.1 $[M+H]^+$. Data are in accordance to that previously reported. [293]

p-Fluorophenyl 3-pyridine sulfoxide (**40s**)



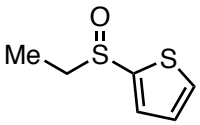
Prepared according to general procedure A from *p*-fluorophenylmagnesium bromide (2.3 mL, 0.89 M in THF, 2.0 mmol) and pyridin-3-ylmagnesium chloride (1.5 mmol). Pyridin-3-ylmagnesium chloride was generated *in situ* from 3-bromopyridine (143.0 μL, 1.5 mmol) using *iso*-propylmagnesium chloride lithium chloride complex (1.5 mL, 1.03 M in THF, 1.6 mmol).[6] Flash column chromatography (40% to 60% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (217 mg, 66%). R_f = 0.30 (85% EtOAc in pet. ether); mp (pet. ether) 64-65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (s, 1H, Ar-*H*), 8.68 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.66 (dd, *J* = 8.8, 5.0 Hz, 2H, Ar-*H*), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar-*H*), 7.18 (app t, *J* = 8.8 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6 (d, $^1J_{CF}$ = 253.0 Hz), 152.1, 146.3, 142.2, 140.2 (d, $^4J_{CF}$ = 3.2 Hz), 132.2, 127.1 (d, $^3J_{CF}$ = 9.1 Hz), 124.3, 117.0 (d, $^2J_{CF}$ = 22.7 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -107.0; IR ν_{max} (neat)/cm^{-1} 1574, 1491, 1413, 1225, 1048 (SO), 836, 705; MS (ESI) *m/z* 222.1 $[M+H]^+$; HRMS (ESI) found *m/z* 222.0384 $[M+H]^+$, $C_{11}H_9FNO^{32}S$ requires *m/z* 222.0383.

p-Fluorophenyl 2-(6-bromopyridine) sulfoxide (**40t**)



Prepared according to general procedure A from *p*-fluorophenylmagnesium bromide (2.3 mL, 0.89 M in THF, 2.0 mmol) and (6-bromopyridin-2-yl)magnesium chloride (1.5 mmol). (6-Bromopyridin-2-yl)magnesium chloride was generated *in situ* from 2,6-dibromopyridine (356.0 μL, 1.5 mmol) using *iso*-propylmagnesium chloride lithium chloride complex (1.5 mL, 1.03 M in THF, 1.6 mmol). Flash column chromatography (40% to 60% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (211 mg, 47%). R_f = 0.45 (50% EtOAc in pet. ether); mp (pet. ether) 93-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.80 (dd, *J* = 8.6, 5.1 Hz, 2H, Ar-*H*), 7.73 (app t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.48 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.17 (app t, *J* = 8.6 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8, 164.6 (d, $^1J_{CF}$ = 252.1 Hz), 142.1, 140.1, 138.8 (d, $^4J_{CF}$ = 3.0 Hz), 129.2, 127.1 (d, $^3J_{CF}$ = 8.9 Hz), 117.0, 116.6 (d, $^2J_{CF}$ = 22.6 Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -108.6; IR ν_{max} (neat)/cm^{-1} 1547, 1489, 1412, 1229, 1117, 1052 (SO), 834; MS (ESI) *m/z* 299.9 (^{79}Br) $[M+H]^+$, 302.0 (^{81}Br) $[M+H]^+$; HRMS (ESI) found *m/z* 321.9309, $C_{11}H_7{}^{79}BrFNO^{32}S^{23}Na$ requires *m/z* 321.9314.

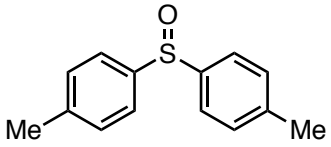
Ethyl 2-thiophene sulfoxide (**40u**)



Prepared according to general procedure A using ethylmagnesium chloride (1.2 mL, 1.72 M in THF, 2.0 mmol) and thienylmagnesium bromide (1.6 mL, 0.94 M in THF, 1.5

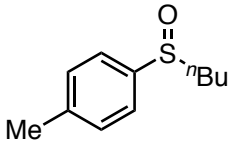
mmol). Flash column chromatography (50% to 80% EtOAc in pet. ether) afforded the desired sulfoxide as a pale-yellow oil (179.1 mg, 75%). R_f = 0.15 (50% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 7.45 (d, *J* = 3.7 Hz, 1H, Ar-*H*), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1H, Ar-*H*), 3.14 – 2.92 (m, 2H, CH_3CH_2S), 1.25 (t, *J* = 7.5 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.4, 131.0, 129.9, 127.5, 51.8, 6.9; IR ν_{max} (neat)/cm^{-1} 1405, 1042, 1019 (SO), 851, 715; MS (ESI) *m/z* 161.0 $[M+H]^+$, 183.0 $[M+Na]^+$; HRMS (ESI) found *m/z* 161.0091 $[M+H]^+$, $C_6H_9O^{32}S_2$ requires *m/z* 161.0089.

4,4'-sulfinylbis(methylbenzene) (**41a**)



This was isolated as a by-product from the synthesis of **40a**. mp (pet. ether) 91-92 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.55-7.52 (m, 4H, Ar-*H*), 7.29-7.26 (m, 4H, Ar-*H*), 2.38 (s, 6H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.7, 141.4, 130.0, 124.8, 21.4; MS (ESI) *m/z* 231.3 $[M+H]^+$. Data are in accordance to that previously reported. [287]

n-Butyl *p*-tolyl sulfoxide (**42a** and **42d**)

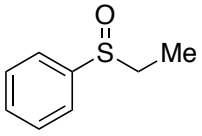


42a: Prepared according to general procedure A using *p*-tolylmagnesium bromide (2.8 mL, 0.72 M in THF, 2.0 mmol) and *n*-butyllithium (0.8 mL, 1.98 M in hexanes, 1.5 mmol). Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the

desired sulfoxide as a colourless oil (190 mg, 64%). R_f = 0.25 (50% EtOAc in pet. ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.32 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 2.85 – 2.69 (m, 2H, CH_2), 2.41 (s, 3H, ArCH_3), 1.77 – 1.33 (m, 4H, CH_2CH_2), 0.91 (t, *J* = 7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.5, 141.0, 130.0, 124.2, 57.3, 24.3, 22.1, 21.6, 13.8; MS (ESI) *m/z* 197.1 $[M+H]^+$, 219.1. Data are in accordance to that previously reported. [294]

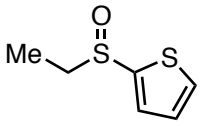
42d: Prepared according to general procedure A using *n*-butyllithium (1.0 mL, 1.98 M in hexanes, 2.0 mmol) and *p*-tolylmagnesium bromide (2.1 mL, 0.72 M in THF, 1.5 mmol). The time for SO_2 insertion (t_1) was adjusted from 45 minutes to 90 minutes. Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (251 mg, 85%).

Phenyl ethyl sulfoxide (**42b**)



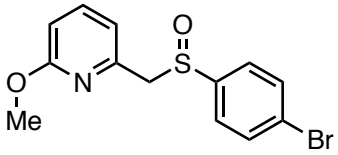
Prepared according to general procedure A using phenyllithium (1.4 mL, 1.39 M in dibutyl ether, 2.0 mmol) and ethylmagnesium chloride (0.9 mL, 1.65 M in THF, 1.5 mmol). Flash column chromatography (10% to 30% EtOAc in pet. ether) afforded the desired sulfoxide as a white solid (199 mg, 61%). R_f = 0.20 (50% EtOAc in pet. ether); mp (pet. ether) 119-120 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.62-7.58 (m, 2H, Ar-*H*), 7.54-7.48 (m, 3H, Ar-*H*), 2.90 (dq, *J* = 13.3, 7.4 Hz, 1H, SCH_aH$_b$), 2.76 (dq, *J* = 13.3, 7.4 Hz, 1H, SCH$_a$$H_b$), 1.19 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 131.0, 129.3, 124.3, 50.4, 6.1; MS (ESI) *m/z* 155.1 $[M+H]^+$. Data are in accordance to that previously reported. [295]

Ethyl 2-thiophene sulfoxide (**42c**)



Prepared according to general procedure A using ethylmagnesium chloride (1.2 mL, 1.72 M in THF, 2.0 mmol) and thienyllithium (1.0 mL, 1.50 M in hexane, 1.5 mmol). Flash column chromatography (50% to 80% EtOAc in pet. ether) afforded the desired sulfoxide as a colourless oil (170 mg, 71%). Data are in accordance to that previously reported under compound **40u**.

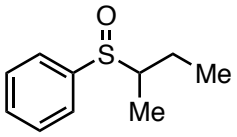
2-methoxy-6-((*p*-tolylsulfinyl)methyl)pyridine (**42e**)



A flame dried Schlenk flask, backfilled with nitrogen, was charged with freshly distilled 2-methoxy-6-methylpyridine (266 μL, 2.0 mmol) in THF (5.0 mL) to obtain a 0.4 M solution. After cooling at 0 °C, *n*-butyllithium (1.0 mL, 2.26 M, 2.2 mmol) was added dropwise and the solution was stirred for 1 hour. Next, the lithiated methylpyridine was transferred by cannula on a suspension of DABSO (240 mg, 1.0 mmol) in THF (4.0 mL) under inert atmosphere and stirred for 45 minutes at room temperature. To the solution, freshly distilled chlorotrimethylsilane (380 μL, 3.0 mmol) was added dropwise, and the cloudy mixture was stirred at room temperature for 45 minutes. Finally, *p*-tolylmagnesium bromide (1.8 mL, 0.82 M, 1.5 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 45 minutes. The reaction mixture was quenched with saturated NH_4Cl aq. solution and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried on $MgSO_4$, filtered and the solvent

was removed *in vacuo*. The crude residue was then purified by flash column chromatography over silica gel (25% EtOAc in pet. ether) to afford the desired sulfoxide as a brown solid (69 mg, 18%). R_f = 0.3 (50% EtOAc in pet. ether); mp (hexane) 43 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.47 (dd, *J* = 8.3, 7.2 Hz, 1H, Ar-*H*), 7.37 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.25 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 6.72 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.63 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 4.16 (d, *J* = 12.2 Hz, 1H, SC*H*$_a$H$_b$), 4.03 (d, *J* = 12.2 Hz, 1H, SCH$_a$*H*$_b$), 3.76 (s, 3H, OC*H*$_3$), 2.39 (s, 3H, ArC*H*$_3$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 163.9, 147.9, 141.6, 140.2, 138.9, 129.7, 124.5, 118.2, 110.2, 65.7, 53.4, 21.5; IR ν_{max} (neat)/cm^{-1} 2979, 2926, 1578, 1466, 1310, 1264, 1034 (SO), 807, 750; LRMS (ESI) *m/z* 262 $[M+H]^+$; HRMS (ESI) found *m/z* 262.0896, $C_{14}H_{16}O_2N^{32}S$ requires *m/z* 262.0896.

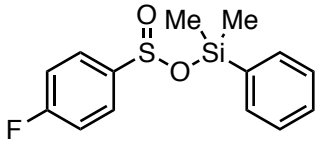
(*s*-Butylsulfinyl)benzene (**42f**)



Prepared according to general procedure A using phenyllithium (3.0 mL, 1.51 M in THF, 2.0 mmol) and *sec*-butyllithium (1.7 mL, 0.88 M in cyclohexanes, 1.5 mmol); d.r.=1:1 determined by ^{1}H NMR of the crude material. Flash column chromatography (20% to 60% EtOAc in pet. ether) afforded the desired sulfoxide as a yellow oil (78 mg, 29%). R_f = 0.25 (50% EtOAc in pet. ether). Diastereomer 1: ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56-7.54 (m, 2H, Ar-*H*), 7.51-7.46 (m, 3H, Ar-*H*), 2.56-2.48 (m, 1H, SC*H*), 1.98-1.87 (m, 1H, SOCHC*H*$_a$H$_b$), 1.49-1.42 (m, 1H, SOCHCH$_a$*H*$_b$), 1.07 (t, *J* = 7.4 Hz, 3H, CHC*H*$_3$), 1.03 (d, *J* = 6.8 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 142.0, 130.6, 128.9, 124.7, 61.2, 23.8, 11.6, 10.2. Diastereomer 2: ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60-7.58 (m, 2H, Ar-*H*), 7.48 (dt, *J* = 4.3, 2.7 Hz, 3H, Ar-*H*), 2.73-2.65 (m, 1H, SC*H*), 1.83-1.73 (m, 1H, SOCHC*H*$_a$H$_b$), 1.47-1.40 (m, 1H, SOCHCH$_a$*H*$_b$), 1.06 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.98

(t, J = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz; $CDCl_3$): δ 141.5, 131.1, 128.8, 125.4, 61.0, 22.1, 11.9, 11.0; IR ν_{max} (neat)/cm^{-1} 2966, 2930, 1443, 1087, 1041 (SO), 843, 747, 692; MS (ESI) *m/z* 183.0 $[M+H]^+$; HRMS (GCMS) found *m/z* 183.0877 $[M+H]^+$, $C_{10}H_{15}O^{32}S$ requires *m/z* 183.0844.

Dimethyl(phenyl)silyl 4-fluorobenzenesulfinate (**43**)

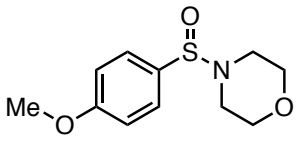


To a flame dried 25 mL two-neck round bottom flask was added DABSO (240 mg, 1.0 mmol) and anhydrous THF (4.0 mL), and the resulting suspension was flushed with nitrogen gas for 3 minutes. Under a constant flow of nitrogen gas, *p*-fluorophenylmagnesium bromide (0.89 M in THF, 2.3 mL, 2.0 mmol) was added dropwise and the reaction mixture was left to stir for 45 minutes at room temperature. Subsequently, chloro(dimethyl)phenylsilane (0.51 mL, 3.0 mmol) was added and the reaction mixture was left to stir for 5 minutes at room temperature. The reaction mixture was then quenched with (20%) Na_2CO_3 aq. solution (15 mL). The product was extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude material did not require any further purification and afforded the desired intermediate **43** as a yellow oil (588 mg, >99%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.59 (m, 4H, Ar-H), 7.40 (d, J = 6.5 Hz, 4H, Ar-H), 7.16 (t, J = 8.0 Hz, 1H, Ar-H), 0.40 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 164.4 (d, $^1J_{CF}$ = 252.4 Hz), 140.5, 139.7 (d, $^4J_{CF}$ = 30.2 Hz), 133.2, 129.5, 127.9, 127.2 (d, $^3J_{CF}$ = 9.2 Hz), 116.8 (d, $^2J_{CF}$ = 22.5 Hz), 0.1; ^{19}F NMR (376 MHz; $CDCl_3$): δ -107.6; IR ν_{max} (neat)/cm^{-1} 2954, 1491, 1252, 1230, 1118, 1065 (SO), 866, 728; HRMS (GCMS) found *m/z* 295.0618 $[M+H]^+$, $C_{14}H_{16}FO_2{}^{32}SSi$ requires *m/z* 295.0546.

6.3.2 General Procedure B for the synthesis of sulfinamides

A flame dried two necks round bottom flask, equipped with a magnetic stirrer bar, a rubber septum and under a nitrogen flow, was charged with DABSO (240 mg, 1.0 mmol,) and THF (4.0 mL). The corresponding Grignard reagent (2.0 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 45 minutes. To the transparent solution, freshly distilled chlorotrimethylsilane (381 μL, 3.0 mmol) was added dropwise, and the cloudy mixture was stirred at room temperature for 45 minutes. A flame dried Schlenk flask, backfilled with nitrogen, was charged with the corresponding amine (1.5 mmol, 0.75 equiv.) in THF (5.0 mL) to obtain a 0.3 M solution. After cooling at 0 °C, isopropylmagnesium chloride (1.5 mmol, 2.75 M, 0.75 equiv.) was added dropwise and the solution was stirred at this temperature for 30 minutes. The resulting solution was transferred by cannula to the reaction mixture and stirred for 45 minutes at room temperature. The reaction mixture was quenched with saturated aq. NH_4OH and extracted with ethyl acetate (3 × 15 mL). Combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography over silica gel to afford the desired sulfinamide.

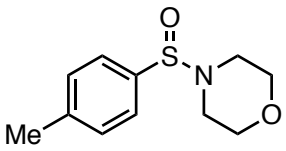
4-((4-Methoxyphenyl)sulfinyl)morpholine (**Table 2.4, Entry 1**)



Prepared according to general procedure B using 4-methoxyphenylmagnesium bromide (5.1 mL, 0.4 M), freshly distilled morpholine (0.26 mL, 1.5 mmol). Flash column chromatography (70% EtOAc in pet. ether) afforded the desired sulfinamide as a yellow solid (82 mg, 22%); mp 58 °C (pet. ether); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60-7.56 (m,

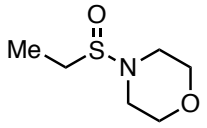
2H, Ar-*H*), 7.03-6.99 (m, 2H, Ar-*H*), 3.86 (s, 3H, OC*H*$_3$), 3.76-3.66 (m, 4H, O(C*H*$_2$)$_2$), 3.14 (dddd, *J* = 12.1, 6.1, 3.5, 0.7 Hz, 2H, N(C*H*$_2$)$_a$(CH$_2$)$_b$), 2.95 (dddd, *J* = 12.1, 6.1, 3.5, 0.7 Hz, 2H, N(CH$_2$)$_a$(C*H*$_2$)$_b$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 133.4, 127.8, 114.4, 66.9, 55.5, 45.6; IR ν_{max} (neat)/cm^{-1} 2915, 2852, 1593, 1453, 1251, 1089, 1067 (SO); MS (ESI) *m/z* 242.2 $[M+H]^+$; HRMS (ESI) found *m/z* 242.0847, $C_{11}H_{16}NSO_3$ requires *m/z* 242.0845.

4-(*P*-tolylsulfinyl)morpholine (**Table 2.4, Entry 2**)



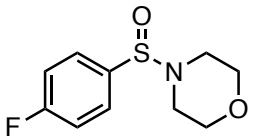
Prepared according to general procedure B using 4-methylphenylmagnesium bromide (3.2 mL, 0.62 M), freshly distilled morpholine (0.26 mL, 1.5 mmol). Flash column chromatography (70% Et_2O in pet. ether) afforded the desired sulfinamide as a white solid (23 mg, 7%); mp 110 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.55 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.32 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 3.76-3.67 (m, 4H, O(C*H*$_2$)$_2$), 3.15 (dddd, *J* = 12.1, 6.1, 3.5, 0.7 Hz, 2H, N(C*H*$_2$)$_a$(CH$_2$)$_b$), 2.96 (dddd, *J* = 12.1, 6.1, 3.5, 0.7 Hz, 2H, N(CH$_2$)$_a$(C*H*$_2$)$_b$), 2.42 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 139.3, 129.8, 126.3, 67.1, 45.9, 21.5; MS (ESI) *m/z* 226.1 $[M+H]^+$. Data in accordance with that previously reported.[296]

4-(Ethylsulfinyl)morpholine (**Table 2.4, Entry 4**)



Prepared according to general procedure B using ethylmagnesium chloride (1.2 mL, 1.72 M), freshly distilled morpholine (0.26 mL, 1.5 mmol). Flash column chromatography (5% MeOH in DCM) afforded the desired sulinamide as an orange oil (27 mg, 11%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82-3.74 (m, 4H, O(C*H*$_2$)$_2$), 3.21-3.10 (m, 4H, N(C*H*$_2$)$_2$), 2.79 (dq, *J* = 7.6 Hz, *J* = 1.8 Hz, 2H, SOC*H*$_2$CH$_3$), 1.20 (t, *J* = 7.6 Hz, 3H, SOCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.0, 45.80, 45.77, 8.1; MS (ESI) *m/z* 164.1 $[M+H]^+$; HRMS (ESI) found *m/z* 164.0738, $C_6H_{15}NSO_2$ requires *m/z* 164.0740.

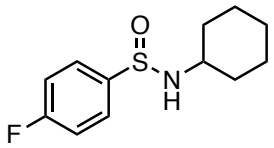
4-((4-fluorophenyl)sulfinyl)morpholine (**Table 2.4, Entry 7**)



Prepared according to general procedure B using of 4-fluorophenylmagnesium bromide (2.3 mL, 0.88 M), freshly distilled morpholine (0.26 mL, 1.5 mmol). Flash column chromatography (50% Et_2O in pet. ether) afforded the desired sulfonamide as a pale-yellow solid (89 mg, 26%); mp 104 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.68-7.65 (m, 2H, Ar-*H*), 7.24-7.18 (m, 2H, Ar-*H*), 3.77-3.67 (m, 4H, O(C*H*$_2$)$_2$), 3.16 (dddd, *J* = 12.1, 6.2, 3.5, 0.8 Hz, 2H, N(C*H*$_2$)$_a$(CH$_2$)$_b$), 2.95 (dddd, *J* = 12.1, 6.2, 3.5, 0.8 Hz, 2H, N(CH$_2$)$_a$(C*H*$_2$)$_b$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, $^{1}J_{CF}$ = 255.0 Hz), 138.1 (d, $^{4}J_{CF}$ = 2.7 Hz), 128.6 (d, $^{3}J_{CF}$ = 11.7 Hz), 116.3 (d, $^{2}J_{CF}$ = 22.5 Hz), 67.0, 45.9; ^{19}F NMR (377 MHz; $CDCl_3$) δ -108.9 ;IR ν_{max} (neat)/cm^{-1} 2918, 2853, 1587, 1487, 1086, 1067

(SO); MS (ESI) *m/z* 230.1 $[M+H]^+$; HRMS (ESI) found *m/z* 230.0645, $C_{10}H_{13}FNO_2{}^{32}S$ requires *m/z* 230.0646.

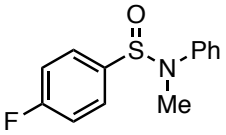
N-cyclohexyl-4-fluorophenylsulfinamide (**Table 2.4, Entry 9**)



A flame dried 25 mL two necks round bottom flask, equipped with a magnetic stirrer bar, rubber septums and under a nitrogen flow, was charged with DABSO (240 mg, 1.0 mmol) and THF (4.0 mL). 4-fluorophenylmagnesium bromide (2.3 mL, 0.86 M) was added dropwise and the reaction mixture was stirred at room temperature for 45 minutes. To the transparent solution, freshly distilled chlorotrimethylsilane (380 μL, 3.0 mmol) was added dropwise, and the cloudy mixture was stirred at room temperature for 45 minutes. A flame dried Schlenk flask, backfilled with nitrogen, was charged with freshly distilled cyclohexylamine (174 μL, 1.5 mmol) in THF (5.0 mL) to obtain a 0.3 M solution. After cooling at 0 °C, isopropylmagnesium chloride (1.0 mL, 1.72 M, 1.7 mmol) was added dropwise and the solution was stirred for 30 minutes. Next, the magnesium amide was transferred by cannula to the reaction mixture and stirred for 45 minutes at room temperature. Finally, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude residue was finally purified by flash column chromatography over silica gel (35% EtOAc in pet. ether) to afford the desired sulfinamide as a yellow oil (19 mg, 6%). R_f = 0.3 (40% EtOAc in pet. ether); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60-7.55 (m, 2H, Ar-*H*), 7.23-7.17 (m, 2H, Ar-*H*), 2.80 (dt, *J* = 13.7, 6.9 Hz, 1H, NC*H*), 2.03 (s, 1H, N*H*), 1.26-1.22 (m, 3H, $CH_2CH_aH_b$), 1.19 (d, *J* = 6.9 Hz, 4H, $(CH_2)_2$), 1.13 (d, *J* = 6.9 Hz, 3H, CH_2CH_aHb); ^{13}C NMR (101 MHz;

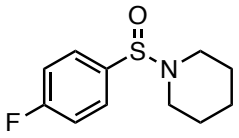
$CDCl_3$): δ 164.5 (d, $^1J_{CF}$ = 251.7 Hz), 137.2 (d, $^4J_{CF}$ = 3.0 Hz), 127.3 (d, $^3J_{CF}$ = 7.9 Hz), 116.4 (d, $^2J_{CF}$ = 22.3 Hz) , 54.8, 29.8, 15.7, 14.1; ^{19}F NMR (377 MHz; $CDCl_3$): δ -108.8; IR ν_{max} (neat)/cm^{-1}=2912, 2792, 1603, 1458, 1249, 1089, 1072 (SO); MS (ESI) *m/z* = 242 $[M+H]^+$; HRMS (ESI) found *m/z* = 242.1003, $C_{11}H_{16}NSO_3$ requires *m/z* = 242.1009;

4-Fluoro-*N*-methyl-*N*-phenylbenzenesulfinamide (**Table 2.4, Entry 10**)



Prepared according to general procedure B using 4-fluorophenylmagnesium bromide (2.3 mL, 0.88 M), freshly distilled *N*-methylaniline (163 μL, 1.5 mmol). Flash column chromatography (35% to 50% Et_2O in pet. ether) afforded the desired sulfinamide as brown oil (157 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H, Ar-*H*), 7.41-7.37 (m, 2H, Ar-*H*), 7.29-7.27 (m, 2H, Ar-*H*), 7.26-7.22 (m, 2H, Ar-*H*), 7.18 (app. t, *J* = 7.3 Hz, 1H, Ar-*H*), 2.87 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, $^1J_{CF}$ = 252.0 Hz), 145.7, 139.1 (d, $^4J_{CF}$ = 3.1 Hz) 129.5, 128.3 (d, $^3J_{CF}$ = 8.9 Hz), 124.5, 121.0, 116.4 (d, $^2J_{CF}$ = 22.5 Hz), 30.8; ^{19}F NMR (377 MHz; CDCl3) δ -109.6; IR ν_{max} (neat)/cm^{-1} 2711, 1591, 1223, 1027 (SO), 1007; MS (ESI) *m/z* 250.1 $[M+H]^+$; HRMS (ESI) found *m/z* 250.0693, $C_{13}H_{13}FON^{32}S$ requires *m/z* 250.0696.

1-((4-Fluorophenyl)sulfinyl)piperidine (**47**)

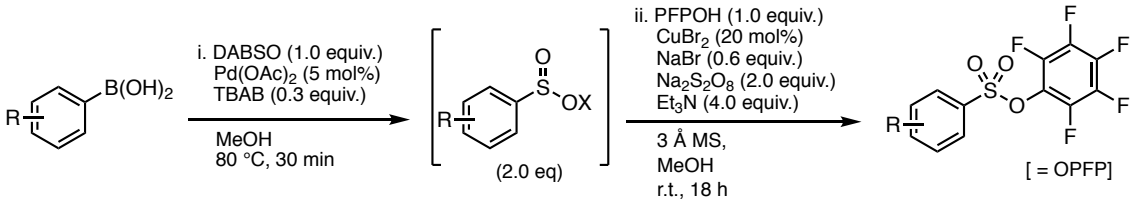


Prepared according to general procedure B using 4-fluorophenylmagnesium bromide (2.3 mL, 0.88 M, 2.0 mmol), freshly distilled piperidine (148 µL, 1.5 mmol). Flash column chromatography (50% Et_2O in pet. ether) afforded the desired sulfinamide as a beige solid (166.7 mg, 49%); mp 113 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.62 (m, 2H, Ar-*H*), 7.21-7.15 (m, 2H, Ar-*H*), 3.13-3.08 (m, 4H, N(CH_2)$_2$), 1.67-14.9 (m, 6H, (CH_2)$_3$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 164.4 (d, $^{1}J_{CF}$ = 251.2 Hz), 139.1, 128.6 (d, $^{3}J_{CF}$ = 9.6 Hz), 116.1 (d, $^{2}J_{CF}$ = 22.3 Hz), 47.0, 26.3, 24.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -109.9; IR ν_{max} (neat)/cm^{-1}= 2938, 2852, 1588, 1488, 1085, 1064; MS (ESI) *m/z* 228.0 $[M+H]^+$; HRMS (ESI) found *m/z* 228.0854, $C_{11}H_{15}FON^{32}S$ requires *m/z* 228.0853.

6.4 Chapter 3 Data

6.4.1 General Procedures for the synthesis of pentafluorophenyl sulfonate esters

General Procedure C



To a 10 mL round bottom flask was added DABSO (120 mg, 0.5 mmol), boronic acid (0.5 mmol), TBAB (48 mg, 0.15 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol). After the addition of methanol (3 mL), the reaction vessel was sealed using a rubber septum, and the reaction mixture was heated to 80 °C and stirred at this temperature for 30 minutes (t_1). After allowing the reaction mixture to cool to room temperature, pentafluorophenol (46 mg, 0.25 mmol), $Na_2S_2O_8$ (119 mg, 0.5 mmol), $CuBr_2$ (11.2 mg, 0.05 mmol), NaBr (16 mg, 0.15 mmol), powdered activated 3 Å molecular sieves (250 mg) and triethylamine (140 μL, 1.0 mmol) were added. The reaction vessel was resealed, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then diluted with EtOAc (5 mL), filtered through a plug of silica and washed with EtOAc (15 mL) before removing the solvent *in vacuo*. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient.

Note:

- Reaction time for the first step (t_1) was 30 minutes unless otherwise stated.

General procedure D – Solvent MeOH/1,4-dioxane (1:1)

To a 10 mL round bottom flask was added DABSO (120 mg, 0.5 mmol), boronic acid (0.5 mmol), TBAB (48 mg, 0.15 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol). After the addition of methanol (1.5 mL) and 1,4-dioxane (1.5 mL), the reaction vessel was sealed using a rubber septum, and the reaction mixture was heated to 80 °C and stirred at this temperature for 30 minutes (t_1). After allowing the reaction mixture to cool to room temperature, pentafluorophenol (46 mg, 0.25 mmol), $Na_2S_2O_8$ (119 mg, 0.5 mmol), $CuBr_2$ (11.2 mg, 0.05 mmol), NaBr (16 mg, 0.15 mmol), powdered activated 3 Å molecular sieves (250 mg) and triethylamine (140 μL, 1.0 mmol) were added. The reaction vessel was resealed, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then diluted with EtOAc (5 mL), filtered through a plug of silica and washed with EtOAc (15 mL) before removing the solvent *in vacuo*. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient.

Note:

- Reaction time for the first step (t_1) was 30 minutes unless otherwise stated.

General procedure E – No TBAB

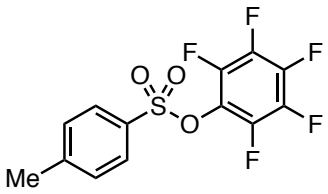
To a 10 mL round bottom flask was added DABSO (120 mg, 0.5 mmol), boronic acid (0.5 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol). After the addition of methanol (3 mL), the reaction vessel was sealed using a rubber septum, the reaction mixture was heated to 80 °C and stirred at this temperature for 30 minutes (t_1). After allowing the reaction mixture to cool to room temperature, pentafluorophenol (46 mg, 0.25 mmol), $Na_2S_2O_8$ (119 mg, 0.5 mmol), $CuBr_2$ (11.2 mg, 0.05 mmol), NaBr (16 mg, 0.15 mmol), powdered activated 3 Å molecular sieves (250 mg) and triethylamine (140 μL, 1.0 mmol) were

added. The reaction vessel was resealed, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then diluted with EtOAc (5 mL), filtered through a plug of silica and washed with EtOAc (15 mL) before removing the solvent *in vacuo*. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient.

Note:

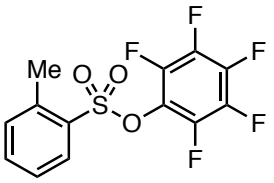
- Reaction time for the first step (t_1) was 30 minutes unless otherwise stated.

Pentafluorophenyl 4-methylphenylsulfonate ester (**50a**)



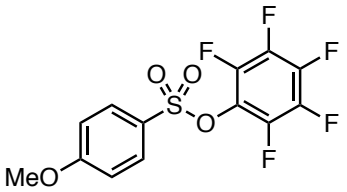
Prepared according to general procedure C using *p*-tolylboronic acid (68 mg, 0.5 mmol). Flash column chromatography (10% Et_2O in pet. ether) afforded the sulfonate as a white solid (73 mg, 86%). R_f = 0.59 (15% Et_2O in pet. ether); mp 61 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.85 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.41 (dd, *J* = 8.4, 0.6 Hz, 2H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 146.9, 142.4 (app. ddq, *J* = 255.7, 12.2, 3.8 Hz), 140.3 (app. dtt, *J* = 255.6, 13.7, 3.9 Hz), 138.0 (app. dtdd, *J* = 253.8, 13.5, 5.7, 3.1 Hz), 131.8, 130.3, 128.7, 124.3 (app. tdd, *J* = 14.3, 5.0, 2.5 Hz), 22.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 18.2 Hz, 2F), -155.5 (t, *J* = 22.0 Hz, 1F), -161.2 (dd, *J* = 21.6, 17.3 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1516, 1396 (SO_2), 1187 (SO_2), 994, 721 (C-O-S); HRMS (CI) found *m/z* 336.9959 [M-H]$^-$, $C_{13}H_6O_3F_5{}^{32}S$ requires *m/z* 336.9963.

Pentafluorophenyl 2-methylphenylsulfonate ester (**50b**)



Prepared according to general procedure E using 2-methylphenylboronic acid (68 mg, 0.5 mmol). Flash column chromatography (10% Et_2O in pet. ether) afforded the sulfonate as a white solid (71 mg, 84%). R_f = 0.53 (15% Et_2O in pet. ether); mp 100 °C (hexane); ^1H NMR (400 MHz; $CDCl_3$): δ 7.89 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar-*H*), 7.62 (td, *J* = 7.8, 1.3 Hz, 1H, Ar-*H*), 7.46 (ddt, *J* = 7.7, 1.2, 0.6 Hz, 1H, Ar-*H*), 7.35 (dddd, *J* = 8.0, 7.7, 1.2, 0.6 Hz, 1H, Ar-*H*), 2.81 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 142.4 (app. ddq, *J* = 255.7, 12.4, 4.2 Hz), 140.4 (app. dtt, *J* = 254.0, 13.5, 3.8 Hz), 139.8, 137.9 (app. dtdd, *J* = 253.3, 13.8, 5.8, 3.0 Hz), 135.3, 133.7, 133.1, 130.3, 126.5, 124.3 (app. tdd, *J* = 14.5, 4.9, 2.3 Hz), 20.7; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.4 Hz, 2F), -155.3 (t, *J* = 21.8 Hz, 1F), -161.1 (dd, *J* = 21.7, 17.6 Hz, 2F); IR νmax (neat)/cm^{-1} 1519, 1378 (SO_2), 1193 (SO_2), 995, 751, 718 (C-O-S); HRMS (CI) found *m/z* 336.9959 $[M-H]^-$, $C_{13}H_6O_3F_5{}^{32}S$ requires *m/z* 336.9963.

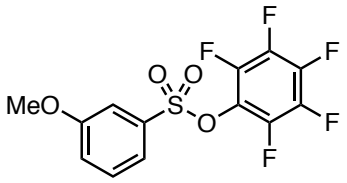
Pentafluorophenyl 4-methoxyphenylsulfonate ester (**50c**)



Prepared according to general procedure C using 4-methoxyphenylboronic acid (76 mg, 0.5 mmol). Flash column chromatography (10% Et_2O in pet. ether) afforded the sulfonate as a white solid (68 mg, 77%). R_f = 0.46 (10% Et_2O in pet. ether); mp 45 °C (hexane); ^1H NMR (500 MHz; $CDCl_3$): δ 7.91-7.88 (m, 2H, Ar-*H*), 7.07-7.04 (m, 2H, Ar-*H*), 3.93 (s,

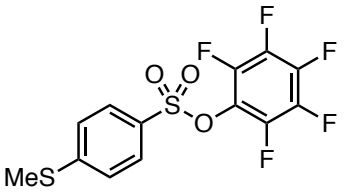
3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 143.5 (app. ddq, *J* = 255.5, 12.0, 3.7 Hz), 139.3 (app. dtt, *J* = 256.1, 13.6, 3.8 Hz), 137.0 (app. dtdd, *J* = 252.8, 14.7, 5.5, 3.1 Hz), 131.1, 125.9, 124.4 (app. tdt, *J* = 14.8, 5.1, 2.1 Hz), 114.9, 56.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.8 (d, *J* = 13.5 Hz, 2F), -155.5 (t, *J* = 21.9 Hz, 1F), -161.2 (dd, *J* = 21.7, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1518, 1390 (SO_2), 1172 (SO_2), 996, 722 (C-O-S); HRMS (CI) found *m/z* 352.9908 $[M-H]^-$, $C_{13}H_6O_4F_5{}^{32}S$ requires *m/z* 352.9912.

Pentafluorophenyl 3-methoxyphenylsulfonate ester (**50d**)



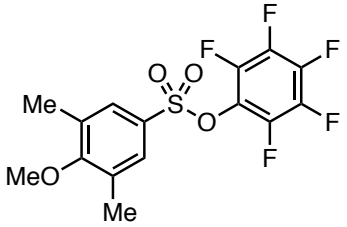
Prepared according to general procedure C using 3-methoxyphenylboronic acid (76 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. After flash column chromatography (30% CH_2Cl_2 in pet. ether), the material was further purified by trituration in hexane at 0 °C to afford the sulfonate as a pale yellow oil (60 mg, 68%). R_f = 0.28 (30% CH_2Cl_2 in pet. ether); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.55 (dt, *J* = 7.8, 1.5 Hz, 1H, Ar-*H*), 7.51 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.47 (t, *J* = 2.1 Hz, 1H, Ar-*H*), 7.28 (ddd, *J* = 8.1, 2.1, 1.3 Hz, 1H, Ar-*H*), 3.89 (s, 3H, OC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 160.3, 142.4 (app. ddq, *J* = 255.6, 12.3, 4.1 Hz), 140.4 (app. dtt, *J* = 255.6, 13.5, 3.8 Hz), 138.0 (app. dtdd, *J* = 253.6, 13.8, 5.4, 3.0 Hz), 135.8, 130.7, 124.2 (app. tdd, *J* = 14.4, 4.8, 2.2 Hz), 122.0, 120.9, 113.0, 56.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.6 Hz, 2F), -155.2 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.6, 17.9 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1398 (SO_2), 1183 (SO_2), 995, 879, 722 (C-O-S); HRMS (ESI) found *m/z* 387.0319 $[M+MeOH+H]^+$, $C_{14}H_{12}O_5F_5{}^{32}S$ requires *m/z* 387.0320.

Pentafluorophenyl 4-(methylthio)phenylsulfonate ester (**50e**)



Prepared according to general procedure C using 4-(methylthio)phenylboronic acid (84 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (20% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (63 mg, 68%). R_f = 0.41 (30% CH_2Cl_2 in pet. ether); mp 90 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.84-7.82 (m, 2H, Ar-*H*), 7.38-7.35 (m, 2H, Ar-*H*), 2.56 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 141.4 (app. ddq, *J* = 255.7, 12.3, 4.5 Hz), 139.4 (app. dtt, *J* = 256.7, 13.6, 3.9 Hz), 137.0 (app. tdd, *J* = 253.9, 13.7, 5.7, 3.1 Hz), 129.9, 128.8, 125.4, 124.3 (app. dddd, *J* = 16.9, 14.2, 4.8, 2.1 Hz), 14.8; ^{19}F NMR (377 MHz; $CDCl_3$): -150.5 (d, *J* = 17.7 Hz, 2F), -155.4 (t, *J* = 21.9 Hz, 1F), -161.0 (dd, *J* = 21.9, 17.2 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1393 (SO_2), 1184 (SO_2), 1079, 996, 766 (C-O-S), 716; HRMS (CI) found *m/z* 368.9679 [M-H]$^-$, $C_{13}H_7O_3F_5{}^{32}S_2$ requires *m/z* 368.9640.

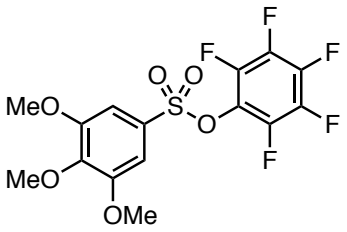
Pentafluorophenyl 3,5-dimethyl-4-methoxyphenylsulfonate ester (**50f**)



Prepared according to general procedure C using 3,5-dimethyl-4-methoxyphenylboronic acid (90 mg, 0.5 mmol). Flash column chromatography (30% CH_2Cl_2 in pet. ether), afford the sulfonate as a yellow oil (73 mg, 76%). R_f = 0.52 (30% CH_2Cl_2 in pet. ether); ^{1}H NMR

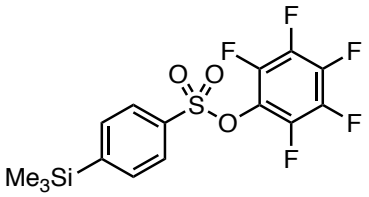
(400 MHz; $CDCl_3$): δ 7.65 (s, 2H, Ar-*H*), 3.81 (s, 3H, OC*H*$_3$), 2.36 (s, 6H, Ar-C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.1, 142.4 (app. ddq, *J* = 255.2, 12.2, 4.0 Hz), 140.3 (app. dtt, *J* = 255.2, 13.5, 3.8 Hz), 138.0 (app. dtdd, *J* = 253.4, 13.7, 5.6, 3.0 Hz), 133.1, 129.4, 129.2, 124.2 (app. tdd, *J* = 14.4, 4.6, 2.0 Hz), 60.0, 16.4; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.8 Hz, 2F), -155.6 (t, *J* = 21.8 Hz, 1F), -161.3 (dd, *J* = 21.6, 18.1 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2937, 1518, 1390 (SO_2), 1281, 1184 (SO_2), 996, 719 (C-O-S); HRMS (CI) found *m/z* 381.0221 $[M-H]^-$, $C_{15}H_{10}O_4F_5{}^{32}S$ requires *m/z* 381.0225.

Pentafluorophenyl 3,4,5-trimethoxyphenylsulfonate ester (**50g**)



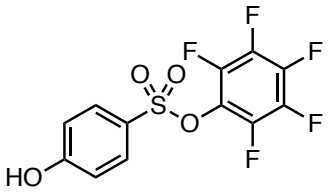
Prepared according to general procedure C using 3,4,5-trimethoxyphenylboronic acid (106 mg, 0.5 mmol). Flash column chromatography (70% CH_2Cl_2 in pet. ether), afford the sulfonate as a white solid (57 mg, 55%). R_f = 0.51 (70% CH_2Cl_2 in pet. ether); mp 102 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.19 (s, 2H, Ar-*H*), 3.97 (s, 3H, OC*H*$_3$), 3.92 (s, 6H, 2 × OC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 153.6, 144.1, 142.5 (app. ddq, *J* = 255.0, 12.4, 4.1 Hz), 140.4 (app. dtt, *J* = 255.6, 13.5, 3.8 Hz), 138.0 (app. dtdd, *J* = 252.3, 13.7, 5.6, 3.0 Hz), 128.9, 124.2 (app. tdd, *J* = 14.5, 4.8, 2.3 Hz), 106.1, 61.3, 56.8; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.7 Hz, 2F), -155.2 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.6, 18.0 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1516, 1413, 1375 (SO_2), 1313, 1178 (SO_2), 1125, 989, 746, 719 (C-O-S); HRMS (CI) found *m/z* 413.0118 $[M-H]^-$, $C_{15}H_{10}O_6F_5{}^{32}S$ requires *m/z* 413.0124.

Pentafluorophenyl 4-(trimethylsilyl)phenylsulfonate ester (**50h**)



Prepared according to general procedure C using 4-(trimethylsilyl)phenylboronic acid (97 mg, 0.5 mmol). Flash column chromatography (20% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (67 mg, 68%). R_f = 0.44 (20% CH_2Cl_2 in pet. ether); mp 77 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.94-7.91 (m, 2H, Ar-*H*), 7.76-7.74 (m, 2H, Ar-*H*), 0.33 (s, 9H, Si(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 150.9, 142.4 (app. ddq, *J* = 255.4, 12.3, 4.1 Hz), 140.4 (app. dtt, *J* = 256.2, 13.6, 3.7 Hz), 138.0 (app. dtdd, *J* = 253.2, 13.7, 5.5, 3.0 Hz), 134.9, 134.4, 127.3, 124.3 (app. tdd, *J* = 14.3, 4.7, 2.1 Hz), -1.3; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.6 Hz, 2F), -155.4 (t, *J* = 21.8 Hz, 1F), -161.1 (dd, *J* = 21.6, 17.9 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1394 (SO_2), 1190 (SO_2), 997, 845, 762, 714 (C-O-S); HRMS (CI) found *m/z* 395.0200 [M-H]$^-$, $C_{15}H_{12}O_3F_5{}^{32}S^{28}Si$ requires *m/z* 395.0202.

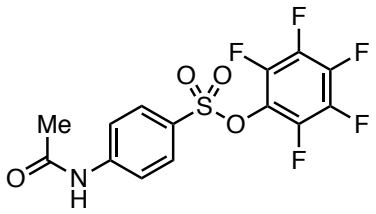
Pentafluorophenyl 4-hydroxyphenylsulfonate ester (**50i**)



Prepared according to general procedure C using 4-hydroxyphenylboronic acid (69 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (30% Et_2O in pet. ether) afforded the sulfonate as colourless crystals (32 mg, 38%). Rf = 0.26 (30% Et_2O in pet. ether); mp 98 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.87 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.01 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 5.92

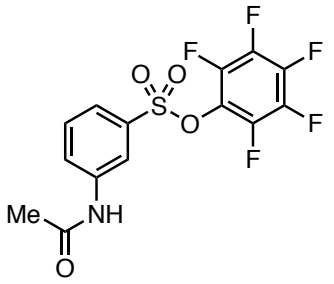
(s, 1H, O*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.0, 142.4 (app. ddq, *J* = 255.2, 12.4, 4.2 Hz), 140.3 (app. dtt, *J* = 256.3, 13.6, 3.8 Hz), 138.0 (app. dtdd, *J* = 253.2, 13.8, 5.7, 2.8 Hz), 131.4, 126.0, 124.3 (app. tdd, *J* = 14.3, 4.7, 2.2 Hz), 116.5; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.5 Hz, 2F), -155.4 (t, *J* = 21.8 Hz, 1F), -161.1 (dd, *J* = 21.6, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 3461, 1519, 1382 (SO_2), 1193, 1168 (SO_2), 996, 879, 726 (C-O-S); HRMS (ESI) found *m/z* 338.9754 $[M-H]^-$, $C_{12}H_4O_4NF_5{}^{32}S$ requires *m/z* 338.9756.

Pentafluorophenyl 4-acetamidophenylsulfonate ester (**50j**)



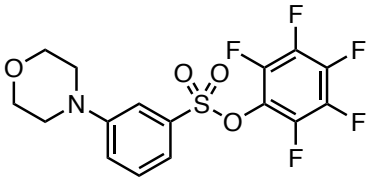
Prepared according to general procedure C using 4-acetamidophenylboronic acid (90 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (50% EtOAc in pet. ether) afforded the sulfonate as a beige solid (50 mg, 52%). R_f = 0.36 (50% EtOAc in pet. ether); mp 156-158 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.91 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.78 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.63 (s, 1H, N*H*), 2.26 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 168.9, 144.4, 142.4 (app. ddq, *J* = 255.4, 12.4, 4.1 Hz), 140.5 (app. dtt, *J* = 256.0, 13.5, 3.8 Hz), 138.0 (app. dtdd, *J* = 254.3, 13.7, 5.3, 3.0 Hz), 130.3, 128.9, 124.4 (app. tdd, *J* = 15.1, 5.1, 2.3 Hz), 119.4, 25.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.7 Hz, 2F), -155.3 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.7, 17.7 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 3318, 1676, 1590, 1513, 1382 (SO_2), 1259, 1178 (SO_2), 992, 740, 710 (C-O-S); HRMS (ESI) found *m/z* 380.0020 $[M-H]^-$, $C_{14}H_7O_4NF_5{}^{32}S$ requires *m/z* 380.0021.

Pentafluorophenyl 3-acetamidophenylsulfonate ester (**50k**)



Prepared according to general procedure C using 3-acetamidophenylboronic acid (90 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (50% EtOAc in pet. ether) afforded the sulfonate as a beige solid (78 mg, 81%). R_f = 0.49 (50% EtOAc in pet. ether); mp 163 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.11 (t, *J* = 1.7 Hz, 1H, Ar-*H*), 8.00 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.69 (ddd, *J* = 8.0, 1.7, 1.0 Hz, 1H, Ar-*H*), 7.57 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.47 (br. s, 1H, N*H*), 2.23 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 168.6, 142.4 (app. ddq, *J* = 255.2, 12.4, 4.1 Hz), 140.5 (app. dtt, *J* = 256.0, 17.9, 4.4 Hz), 139.3, 138.0 (app. dtdd, *J* = 254.3, 13.7, 5.2, 2.8 Hz), 135.5, 130.4, 126.1, 124.2 (app. tdd, *J* = 15.1, 5.1, 2.3 Hz), 123.9, 119.1, 24.8; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.4 Hz, 2F), -155.1 (t, *J* = 21.9 Hz, 1F), -161.2 (dd, *J* = 21.7, 18.1 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 3259, 1673, 1595, 1516, 1419 (SO_2), 1188 (SO_2), 995, 798, 748, 723 (C-O-S), 701; HRMS (ESI) found *m/z* 403.9986 $[M+Na]^+$, $C_{14}H_8O_4NF_5{}^{23}Na^{32}S$ requires *m/z* 403.9986.

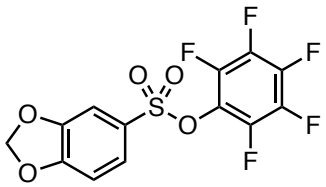
Pentafluorophenyl 3-morpholinophenylsulfonate ester (**50l**)



Prepared according to general procedure C using 3-(morpholino)phenylboronic acid (104 mg, 0.5 mmol). Flash column chromatography (90% CH_2Cl_2 in pet. ether) afforded the

sulfonate as a yellow oil (60 mg, 58%). R_f = 0.49 (95% CH_2Cl_2 in pet. ether); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.47 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.42 (t, *J* = 2.4 Hz, 1H, Ar-*H*), 7.41-7.38 (m, 1H, Ar-*H*), 7.23 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H, Ar-*H*), 3.90-3.87 (m, 4H, O(C*H*$_2$)$_2$), 3.25-3.23 (m, 4H, N(C*H*$_2$)$_2$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 152.0, 142.4 (app. ddq, *J* = 255.1, 12.1, 4.3Hz), 140.4 (app. dtt, *J* = 255.5, 13.4, 3.8 Hz), 138.0 (app. dtdd, *J* = 256.2, 13.7, 3.0 Hz), 135.7, 130.4, 124.3 (app. tdd, *J* = 14.3, 4.8, 2.2 Hz), 121.6, 119.0, 114.2, 66.6, 48.5; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.4 (d, *J* = 17.3 Hz, 2F) , -155.4 (t, *J* = 21.9Hz, 1F), -161.1 (dd, *J* = 21.7, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2973, 2854, 1519, 1387 (SO_2), 1267, 1192 (SO_2), 997, 719 (C-O-S); HRMS (CI) found *m/z* 410.0476 $[M+H]^+$, $C_{16}H_{13}O_4NF_5{}^{32}S$ requires *m/z* 410.0480.

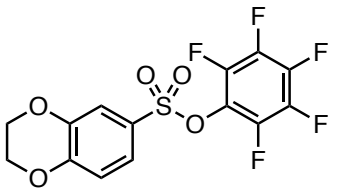
Pentafluorophenyl 3,4-(methylenedioxy)phenylsulfonate ester (**50m**)



Prepared according to general procedure C using 3,4-(methylenedioxy)phenylboronic acid (83 mg, 0.5 mmol). Flash column chromatography (50% CH_2Cl_2 in pet. ether) afforded the sulfonate as an off white solid (57 mg, 62%). R_f = 0.60 (50% CH_2Cl_2 in pet. ether); mp 64°C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.53 (dd, *J* = 8.3, 1.9 Hz, 1H, Ar-*H*), 7.36 (d, *J* = 1.9 Hz, 1H, Ar-*H*), 6.95 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 6.17 (s, 2H, OC*H*$_2$O); ^{13}C NMR (126 MHz; $CDCl_3$): δ 153.9, 148.8, 142.4 (app. ddq, *J* = 245.8, 12.3, 4.2 Hz), 140.4 (app. dtt, *J* = 250.9, 13.4, 3.8 Hz), 138.0 (app. dtdd, *J* = 253.6, 13.8, 5.2, 3.0 Hz), 127.4, 125.4, 124.2 (app. tdd, *J* = 14.4, 4.8, 2.2 Hz), 108.7, 108.5, 103.1; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.4 Hz, 2F), -155.4 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.7, 17.9 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1482, 1394 (SO_2), 1250, 1195

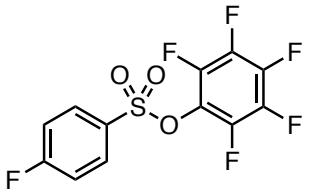
(SO_2), 996, 746, 724 (C-O-S); HRMS (ESI) found *m/z* 366.9701 $[M-H]^-$, $C_{13}H_4O_5F_5{}^{32}S$ requires *m/z* 366.9705.

Pentafluorophenyl 1,4-benzodioxane-6-sulfonate ester (**50n**)



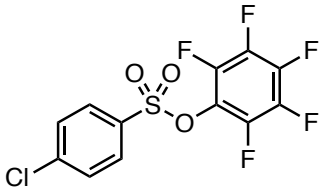
Prepared according to general procedure C using 1,4-benzodioxane-6-boronic acid (90 mg, 0.5 mmol). Flash column chromatography (40% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (75 mg, 78%). R_f = 0.48 (50% CH_2Cl_2 in pet. ether); mp 88 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.49 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 7.45 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar-*H*), 7.03 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 4.39-4.37 (m, 2H, OC*H*$_2$), 4.34-4.32 (m, 2H, OC*H*$_2$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.9, 144.0, 142.4 (app. ddq, *J* = 255.4, 12.4, 4.2 Hz), 140.3 (app. dtt, *J* = 255.4, 13.4, 3.8), 138.0 (app. dtdd, *J* = 255.7, 13.7, 5.5, 3.1 Hz), 126.6, 124.3 (app. tdd, *J* = 14.3, 4.5, 2.0), 122.7, 118.4, 64.9, 64.2; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.3 Hz, 2F), -155.6 (t, *J* = 21.9 Hz, 1F), -161.2 (dd, *J* = 21.8, 17.83 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1497, 1391 (SO_2), 1290, 1183 (SO_2), 995, 879, 722 (C-O-S); HRMS (ESI) found *m/z* 404.9827 $[M+Na]^+$, $C_{14}H_7O_5F_5{}^{23}Na^{32}S$ requires *m/z* 404.9827.

Pentafluorophenyl 4-fluorophenylsulfonate ester (**50o**)



Prepared according to general procedure C using 4-fluorophenylboronic acid (70 mg, 0.5 mmol). Flash column chromatography (5% CH_2Cl_2 and 5% Et_2O in pet. ether) afforded the sulfonate as a pale yellow oil (65 mg, 76%). R_f = 0.42 (5% CH_2Cl_2 and 5% Et_2O in pet. ether) ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.04-8.00 (m, 2H, Ar-*H*), 7.33-7.28 (m, 2H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8 (d, *J* = 259.5 Hz), 141.3 (app. ddq, *J* = 255.4, 12.1, 3.7 Hz), 139.5 (app. dtt, *J* = 256.3, 13.5, 3.8 Hz), 137.0 (app. dtdd, *J* = 253.7, 13.6, 5.7, 3.0 Hz), 131.7 (d, *J* = 10.0 Hz), 130.9 (d, *J* = 3.3 Hz), 124.1 (app. tdd, *J* = 12.5, 4.8, 2.6 Hz), 117.2 (d, *J* = 23.0 Hz); ^{19}F NMR (377 MHz; $CDCl_3$): δ -99.8(s ,1F), -150.6 (d, *J* = 17.2 Hz, 2F), -154.9 (t, *J* = 21.9 Hz, 1F), -160.8 (dd, *J* = 21.9, 17.2 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1518, 1394 (SO_2), 1195 (SO_2), 996, 751 (C-O-S), 725; HRMS (CI) found *m/z* 340.9708 [M-H]$^-$, $C_{12}H_3O_3F_6{}^{32}S$ requires *m/z* 340.9713.

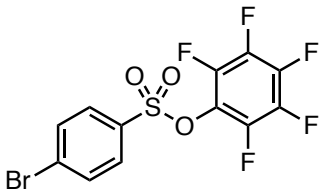
Pentafluorophenyl 4-chlorophenylsulfonate ester (**50p**)



Prepared according to general procedure C using 4-chlorophenylboronic acid (78 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (5% Et_2O in pet. ether) afforded the sulfonate as an off-white solid (49 mg, 55%). Rf = 0.38 (5% Et_2O in pet. ether); mp 46 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.77 (dd, *J* = 128.0, 8.4 Hz, 2H, Ar-H), 7.44 (dd, *J* = 37.3, 8.4 Hz, 2H, Ar-H);

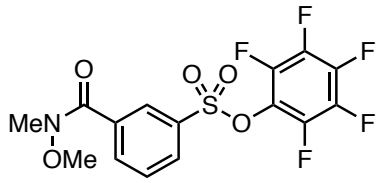
^{13}C NMR (126 MHz; $CDCl_3$): δ 142.5, 142.3 (app. ddq, *J* = 255.4, 12.5, 4.1 Hz), 140.6 (app. dtt, *J* = 256.4, 13.6, 3.9 Hz), 138.6, 138.0 (app. dtdd, *J* = 251.5, 13.7, 5.7, 3.0 Hz), 133.9, 133.3, 130.13, 130.05, 129.2 128.4, 123.9 (app. tdd, *J* = 15.1, 5.4, 2.0 Hz); ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.3 Hz, 2F), -155.1 (t, *J* = 21.9 Hz, 1F), -160.6 (dd, *J* = 21.7, 17.8 Hz, 2F); IR ν_{max} (neat)/cm-1 1514, 1395 (SO_2), 1193 (SO_2), 1089, 991, 825, 718 (C-O-S), 623; HRMS (CI) found *m/z* 356.9411 [M-H]-, $C_{12}H_3O_4{}^{35}ClF_5{}^{32}S$ requires *m/z* 356.9417.

Pentafluorophenyl 4-bromophenylsulfonate ester (**50q**)



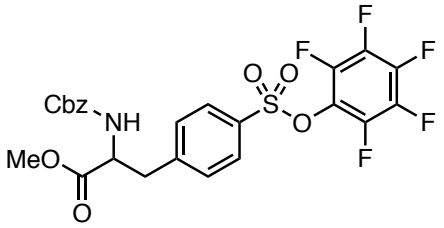
Prepared according to general procedure C using 4-bromophenylboronic acid (100 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (20% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (68 mg, 67%). R_f = 0.53 (30% CH_2Cl_2 in pet. ether); mp 62 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.86-7.83 (m, 2H, Ar-*H*), 7.79-7.76 (m, 2H, Ar-*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 141.3 (app. ddq, *J* = 255.6, 12.8, 4.0 Hz), 139.6 (app. dtt, *J* = 256.4, 13.4, 3.9 Hz), 137.0 (app. dtdd, *J* = 253.7, 13.5, 5.6, 3.0 Hz),133.9, 133.1, 131.1, 130.0, 124.1 (app. dddd, *J* = 14.4, 12.6, 4.9, 2.5 Hz); ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.3 Hz, 2F), -154.7 (t, *J* = 21.9 Hz, 1F), -160.6 (dd, *J* = 21.7, 17.3 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1519, 1398 (SO_2), 1197 (SO_2), 996, 761 (C-O-S), 716; HRMS (CI) found *m/z* 400.8908 $[M-H]^-$, $C_{12}H_3O_3{}^{79}BrF_5{}^{32}S$ requires *m/z* 400.8912.

Pentafluorophenyl 3-(N,O-dimethylhydroxylaminocarbonyl)phenylsulfonate ester (**50r**)



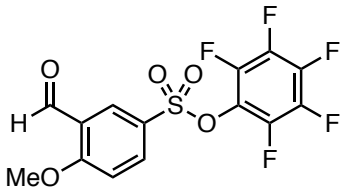
Prepared according to general procedure C using 3-(N,O-dimethylhydroxylaminocarbonyl)benzeneboronic acid (105 mg, 0.5 mmol). Time for SO_2 insertion (t1) was adjusted from 30 minutes to 3 hours. Flash column chromatography (70% Et_2O in pet. ether) afforded the sulfonate as a colourless oil (39 mg, 38%). R_f = 0.36 (70% Et_2O in pet. ether); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.33 (s, 1H, Ar-*H*), 8.09 (dd, *J* = 15.6, 7.9 Hz, 2H, Ar-*H*), 7.7 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 3.54 (s, 3H, OC*H*$_3$), 3.40 (s, 3H, NC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 167.0, 142.3 (app. ddq, *J* = 255.1, 12.6, 4.1 Hz), 140.5 (app. dtt, *J* = 256.4, 13.6, 4.0 Hz), 138.0 (app. dtdd, *J* = 253.8, 13.6, 5.3, 3.0 Hz), 135.8, 135.3, 134.9, 130.3, 129.6, 128.7, 124.1 (app. tdd, *J* = 14.4, 4.6, 2.3 Hz), 61.5, 33.3; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.7 Hz, 2F), -154.8 (t, *J* = 21.8 Hz, 1F), -160.7 (dd, *J* = 21.6, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1647, 1518, 1392 (SO_2), 1189 (SO_2), 995, 794, 719 (C-O-S); HRMS (ESI) found *m/z* 412.0268 $[M+H]^+$, $C_{15}H_{11}O_5NF_5{}^{32}S$ requires *m/z* 412.0273.

Methyl-2-(((benzyloxy)carbonyl)amino)-3-(4-((pentafluorophenoxy)sulfonyl ester)phenyl)propanoate (**50s**)



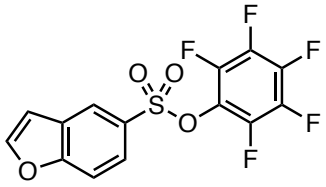
Prepared according to general procedure C using (4-(2-(((benzyloxy)carbonyl)amino)-3-methoxy-3- oxopropyl)phenyl)boronic acid (179 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (60% Et_2O in pet. ether) afforded the sulfonate as a pale-yellow oil (98 mg, 70%). R_f = 0.42 (65% Et_2O in pet. ether); ^1H NMR (500 MHz; $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.36-7.32 (m, 7H, Ar-*H*), 5.37 (d, *J* = 7.7 Hz, 1H, Ar(CH_aH$_b$)O), 5.10 (app. q, *J* = 10.6 Hz, 2H, N*H* and NHC*H*CH_2), 4.72 (d, *J* = 7.3 Hz, 1H, Ar(CH_a*H$_b$*)O), 3.73 (s, 3H, OC*H$_3$*), 3.24 (ddd, *J* = 65.7, 13.8, 6.1 Hz, 2H, C*H$_2$*CH); ^{13}C NMR (126 MHz; $CDCl_3$): δ 171.3, 155.6, 144.7, 142.3 (app. ddq, *J* = 255.5, 12.3, 4.0 Hz), 140.4 (app. dtt, *J* = 255.7, 13.6, 3.7 Hz), 138.0 (app. dtdd, *J* = 253.9, 13.7, 5.5, 3.0 Hz), 136.1, 133.5, 130.6, 128.82, 128.69, 128.5, 128.3, 124.2 (app. tdd, *J* = 15.3, 4.9, 2.3 Hz), 67.3, 54.6, 52.7, 38.5; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.8 Hz, 2F), -155.1 (t, *J* = 22.0 Hz, 1F), -160.9 (dd, *J* = 21.7, 18.1 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1734, 1722, 1518, 1391 (SO_2), 1200 (SO_2), 996, 747, 718 (C-O-S); HRMS (ESI) found *m/z* 560.0795 $[M+H]^+$, $C_{24}H_{19}O_7NF_5{}^{32}S$ requires *m/z* 560.0797.

Pentafluorophenyl 3-formyl-4-methoxyphenylsulfonate ester (**50t**)



Prepared according to general procedure C using 3-formyl-4-methoxyphenylboronic acid (90.0 mg, 0.5 mmol). Flash column chromatography (60 to 70% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (80.6 mg, 84%). R_f = 0.51 (75% CH_2Cl_2 in pet. ether); mp 144 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.46 (s, 1H, C*H*O), 8.41 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.14 (dd, *J* = 8.9, 2.5 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 4.10 (s, 3H, OC*H*$_3$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 187.4, 166.0, 142.3 (app. ddq, *J* = 255.2, 12.3, 4.2 Hz), 140.5 (app. dtt, *J* = 256.3, 12.5, 4.1 Hz), 138.0 (app. dtdd, *J* = 254.2, 13.8, 5.6, 3.0 Hz), 135.7, 130.1, 127.2, 125.2, 124.2 (app. tdd, *J* = 13.8, 5.3, 1.8 Hz), 113.0, 56.8; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.4 Hz, 2F), -154.9 (t, *J* = 21.9 Hz, 1F), -160.8 (dd, *J* = 21.6, 17.7 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1681, 1592, 1518, 1395 (SO_2), 1289, 1257, 1192 (SO_2), 990, 912, 745, 711 (C-O-S); HRMS (ESI) found *m/z* 383.0008 $[M+H]^+$, $C_{14}H_8O_5F_5{}^{32}S$ requires *m/z* 383.0007.

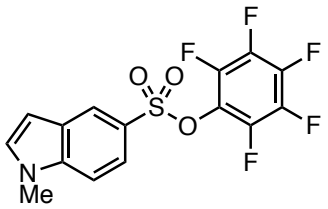
Pentafluorophenyl benzofuran-5-sulfonate ester (**50u**)



Prepared according to general procedure C using benzofuran-5-ylboronic acid (81 mg, 0.5 mmol). Flash column chromatography (20% Et_2O in pet. ether) afforded the sulfonate as a yellow solid (59 mg, 65%). R_f = 0.44 (20% Et_2O in pet. ether); mp 74 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.30 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.93 (dd, *J* = 8.8, 2.0 Hz,

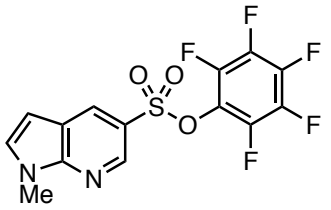
1H, Ar-*H*), 7.83 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 7.71 (ddd, *J* = 8.8, 0.9, 0.6 Hz, 1H, OC*H*), 6.95 (dd, *J* = 2.3, 0.9 Hz, 1H, OCHC*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.1, 148.1, 142.4 (app. ddq, *J* = 255.7, 12.4, 4.1 Hz), 140.4 (app. dtt, *J* = 255.8, 13.6, 3.9 Hz), 138.0 (app. dtdd, *J* = 255.8, 13.8, 5.5, 3.1 Hz), 129.4, 128.3, 124.7, 124.5-124.2 (m), 123.5, 112.9, 107.4; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.5 Hz, 2F), -155.4 (t, *J* = 21.9 Hz, 1F), -161.1 (dd, *J* = 21.7, 17.9 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1515, 1396 (SO_2), 1259, 1196 (SO_2), 1170, 990, 845, 746, 718 (C-O-S), 625; HRMS (CI) found *m/z* 363.9834 $[M]^-$, $C_{14}H_5O_4F_5{}^{32}S$ requires *m/z* 363.9834.

Pentafluorophenyl 1-methyl-1H-indole-5-sulfonate ester (**50v**)



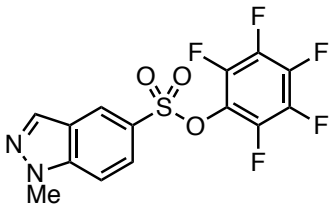
Prepared according to general procedure C using *N*-methylindole-5-boronic acid (88 mg, 0.5 mmol). Flash column chromatography (10% CH_2Cl_2 and 10% Et_2O in pet. ether) afforded the sulfonate as a white solid (68 mg, 72%). R_f = 0.31 (10% CH_2Cl_2 and 10% Et_2O in pet. ether); mp 108-110 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.28 (dd, *J* = 1.9, 0.7 Hz, 1H, Ar-*H*), 7.78 (dd, *J* = 8.8, 1.9 Hz, 1H, Ar-*H*), 7.48 (dt, *J* = 8.8, 0.7 Hz, 1H, Ar-*H*), 7.25 (d, *J* = 3.3 Hz, 1H, NC*H*), 6.68 (dd, *J* = 3.3, 0.7 Hz, 1H, NCHC*H*), 3.90 (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 142.5 (app. ddq, *J* = 255.3, 12.2, 3.8 Hz), 140.2 (app. dtt, *J* = 254.8, 13.9, 3.8 Hz), 139.7, 137.9 (app. dtdd, *J* = 254.8, 13.5, 5.7, 2.9 Hz), 132.1, 128.0, 124.74-124.47 (m), 124.66, 123.7, 121.2, 110.2, 103.5, 33.4; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J*= 17.3 Hz, 2F), -156.1 (t, *J* = 22.0 Hz, 1F), -161.5 (dd, *J* = 21.9, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1518, 1382 (SO_2), 1249, 1175 (SO_2), 1153, 995, 763 (C-O-S), 629; HRMS (ESI) found *m/z* 400.0037 $[M+Na]^+$, $C_{15}H_8O_3NF_5{}^{23}Na^{32}S$ requires *m/z* 400.0037.

Pentafluorophenyl 1-methyl-1H-pyrrolo[2,3-b]pyridine-5-sulfonate ester (**50w**)



Prepared according to general procedure D using 1-methyl-1H-pyrrolo[2,3-b]pyridine-5-boronic acid (88 mg, 0.5 mmol). Flash column chromatography (30-60% Et_2O in pet. ether), afforded the sulfonate as a yellow solid (57 mg, 60%). R_f = 0.50 (60% Et_2O in pet. ether); mp 99 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.84 (d, *J* = 0.5 Hz, 1H, Ar-*H*), 8.49 (d, *J* = 0.5 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 6.67 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 3.98 (s, 3H, NC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 149.8, 142.7, 142.4 (app. ddq, *J* = 255.6, 12.3, 4.1 Hz), 140.4 (app. dtt, *J* = 254.6, 13.4, 3.8), 138.0 (app. dtdd, *J* = 256.3, 13.8, 5.3, 2.9 Hz), 132.7, 130.0, 124.3 (app. tdd, *J* = 14.2, 4.7, 2.0), 122.9, 119.7, 101.9, 31.9; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.6 (d, *J* = 17.8 Hz, 2F), -155.4 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.6, 18.1 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2922, 1591, 1515, 1381 (SO_2), 1206, 1174 (SO_2), 991, 879, 738, 715 (C-O-S), 640; HRMS (ESI) found *m/z* 379.0166 $[M+H]^+$, $C_{14}H_8O_3N_2F_5{}^{32}S$ requires *m/z* 379.0170.

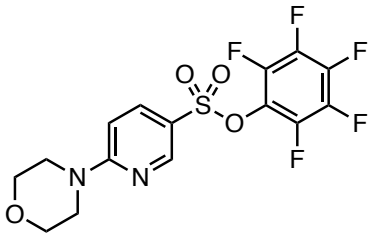
Pentafluorophenyl 1-methyl-1*H*-indazole-5-sulfonate ester (**50x**)



Prepared according to general procedure C using 1-methyl-1*H*-indazole-5-boronic acid (88 mg, 0.5 mmol). After flash column chromatography (20 - 40% EtOAc in pet. ether), the material was further purified by dissolving in EtOAc (10 mL) and washed with

saturated aq. $NaHCO_3$ (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated to afford the sulfonate as a yellow solid (25 mg, 26%). R_f = 0.28 (20% EtOAc in pet. ether); mp 114 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.44 (s, 1H, Ar-*H*), 8.19 (s, 1H, Ar-*H*), 7.94 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 7.59 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 4.18 (s, 3H, NC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 142.4 (app. ddq, *J* = 256.9, 12.2, 4.1 Hz), 141.8, 140.4 (app. dtt, *J* = 253.8, 13.6, 3.8 Hz), 138.0 (app. dtdd, *J* = 253.6, 13.7, 5.7, 3.0 Hz), 135.2, 126.6, 125.05, 125.01, 123.3, 124.5-124.2 (app. m), 110.4, 36.2; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 18.0 Hz, 2F), -155.4 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.5, 18.4 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2922, 2853, 1607, 1515, 1467, 1399 (SO_2), 1290, 1176 (SO_2), 1061, 987, 926, 800, 703 (C-O-S), 640; HRMS (ESI) found *m/z* 379.0170 $[M+H]^+$, $C_{14}H_8O_3N_2F_5{}^{32}S$ requires *m/z* 379.0173.

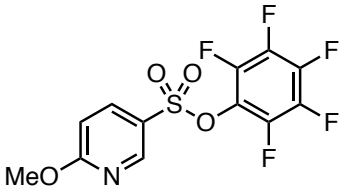
Pentafluorophenyl 2-morpholino-5-pyridinesulfonate ester (**50y**)



Prepared according to general procedure D using 2-morpholino-5-pyridineboronic acid (104 mg, 0.5 mmol). Flash column chromatography (50% CH_2Cl_2 in pet. ether) afforded the sulfonate as a white solid (17 mg, 17%). R_f = 0.68 (60% CH_2Cl_2 in pet. ether); mp 125 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.61 (s, 1H, Ar-*H*), 7.90 (d, *J* = 9.7 Hz, 1H, Ar-*H*), 6.65 (d, *J* = 9.7 Hz, 1H, Ar-*H*), 3.83 (t, *J* = 4.2 Hz, 4H, N(C*H*$_2$)$_2$), 3.75 (t, *J* = 4.2 Hz, 4H, O(C*H*$_2$)$_2$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 161.0, 150.3, 142.3 (app. ddq, *J* = 255.1, 12.4, 4.3 Hz), 140.2 (app. dtt, *J* = 258.6, 13.4, 3.9 Hz), 137.9 (app. dtdd, *J* = 253.3, 13.5, 5.2, 2.8 Hz), 137.2, 124.2 (app. tdd, *J* = 13.6, 4.9, 2.3 Hz), 117.9, 105.4, 66.6,

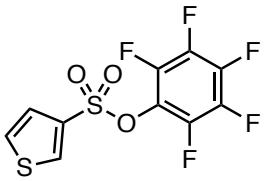
45.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.9 Hz, 2F), -155.6 (t, *J* = 21.8 Hz, 1F), -161.1 (dd, *J* = 21.7, 18.5 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1590, 1518, 1389 (SO_2), 1191 (SO_2), 996, 747, 711 (C-O-S); HRMS (ESI) found *m/z* 411.0428 $[M+H]^+$, $C_{15}H_{12}O_4N_2F_5{}^{32}S$ requires *m/z* 411.0432.

Pentafluorophenyl 2-methoxypyridine-5-sulfonate ester (**50z**)



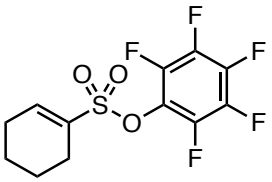
Prepared according to general procedure D using 2-methoxy-5-pyridineboronic acid (77 mg, 0.5 mmol). Flash column chromatography (10% EtOAc in pet. ether) afforded the sulfonate as a brown oil (30 mg, 34%). R_f = 0.57 (15% EtOAc in pet. ether); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.72 (dd, *J* = 2.6, 0.5 Hz, 1H, Ar-*H*), 8.07 (dd, *J* = 8.9, 2.6 Hz, 1H, Ar-*H*), 6.92 (dd, *J* = 8.9, 0.5 Hz, 1H, Ar-*H*), 4.06 (s, 3H, OC*H*$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 168.2, 149.4, 142.4 (app. ddq, *J* = 255.7, 12.4, 4.1 Hz), 140.4 (app. dtt, *J* = 255.8, 13.6, 3.9 Hz) 138.2, 138.0 (app. dtdd, *J* = 255.8, 13.8, 5.5, 3.1 Hz), 124.3, 123.9 (app. tdd, J = 13.3, 5.0, 2.3 Hz), 112.3, 54.9; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.4 Hz, 2F), -154.9 (t, *J* = 21.8 Hz, 1F), -160.7 (dd, *J* = 21.7, 17.6 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1591, 1519, 1487, 1384 (SO_2), 1196 (SO_2), 997, 726 (C-O-S); HRMS (ESI) found *m/z* 356.0010 $[M+H]^+$, $C_{12}H_7O_4NF_5{}^{32}S$ requires *m/z* 356.0011.

Pentafluorophenyl 3-thienylsulfonate ester (**50aa**)



Prepared according to general procedure C using 3-thienylboronic acid (64 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (10% Et_2O in pet. ether) afforded the sulfonate as an off-white solid (22 mg, 27%). Rf = 0.34 (15% Et_2O in pet. ether); mp 88 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.20 (dd, *J* = 3.1, 1.3 Hz, 1H, Ar-*H*), 7.56 (dd, *J* = 5.2, 3.1 Hz, 1H, Ar-*H*), 7.51 (dd, *J* = 5.2, 1.3z Hz, 1H, Ar-*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 142.6 (app. ddq, *J* = 255.6, 12.4, 4.2 Hz), 140.5 (app. dtt, *J* = 255.7, 13.6, 3.7 Hz), 138.0 (app. dtdd, *J* = 254.0, 13.8, 5.6, 3.0 Hz), 134.9, 133.8, 129.0, 126.3, 124.2 (app. tdd, *J* = 14.4, 4.7, 2.2 Hz); ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.8 (d, *J* = 17.5 Hz, 2F), -155.1 (t, *J* = 21.8 Hz, 1F), -160.9 (dd, *J* = 21.6, 17.7 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2975, 2922, 1515, 1381 (SO_2), 1178 (SO_2), 992, 807, 754, 719 (C-O-S), 622; HRMS (CI) found *m/z* 328.9367 $[M-H]^-$, $C_{10}H_2O_3NF_5{}^{32}S_2$ requires *m/z* 328.9371.

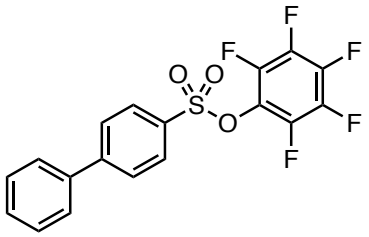
Pentafluorophenyl cyclohex-1-ene-1-sulfonate ester (**50ab**)



Prepared according to general procedure D using 1-cyclohexene-1-ylboronic acid (63 mg, 0.5 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (20% Et_2O in pet. ether) afforded the sulfonate as a yellow oil (32 mg, 38%). R_f = 0.58 (20% Et_2O in pet. ether); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.01

(tt, *J* = 3.5, 2.1 Hz, 1H, CH_2CHCS), 2.60 (tq, *J* = 6.2, 2.1 Hz, 2H,$SCCHCH_2$), 2.35 (tq, *J* = 6.2, 3.5 Hz, 2H, $SCCH_2$), 1.89-1.84 (m, 2H, CH_2), 1.75-1.70 (m, 2H, CH_2); ^{13}C NMR (101 MHz; $CDCl_3$): δ 143.9, 142.5 (app. ddq, *J* = 254.6, 12.4, 4.2 Hz), 140.3 (app. dtt, *J* = 255.4, 12.8, 4.2 Hz), 138.0 (app. dtdd, *J* = 255.8, 13.9, 5.6, 3.1 Hz), 135.4, 124.1 (app. tdd, *J* = 14.3, 4.7, 2.0 Hz), 26.0, 23.7, 21.8, 20.6; ^{19}F NMR (377 MHz; $CDCl_3$): δ -151.0 (d, *J* = 17.9 Hz, 2F), -155.8 (t, *J* = 21.8 Hz, 1F), -161.2 (dd, *J* = 21.6,3 18.2 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 2921, 1518, 1389 (SO_2), 1188 (SO_2), 997, 754, 707 (C-O-S), 619; HRMS (CI) found *m/z* 328.0195 $[M]^-$, $C_{12}H_9O_3F_5{}^{32}S$ requires *m/z* 328.0198.

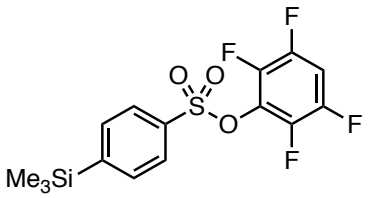
Pentafluorophenyl [1,1'-biphenyl]-4-sulfonate ester (**50ac**)



A glass reaction tube was charged with DABSO (72 mg, 0.3 mmol), $PdCl_2(AmPhos)_2$ (18 mg, 0.03 mmol) and 4-bromobiphenyl (117 mg, 0.5 mmol), sealed with a rubber septum and evacuated and filled with N_2 four times. Anhydrous isopropanol (1.9 mL) and anhydrous triethylamine (209 μL, 1.5 mmol), were added sequentially through the septum and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminium heating block at 75 °C for 16 hours. After allowing the reaction mixture to cool to room temperature, pentafluorophenol (46 mg, 0.25 mmol), $Na_2S_2O_8$ (119 mg, 0.5 mmol), $CuBr_2$ (11 mg, 0.05 mmol), NaBr (16 mg, 0.15 mmol), powdered activated 3 Å molecular sieves (250 mg) and triethylamine (140 μL, 1.0 mmol) were added. The reaction vessel was resealed, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then diluted with EtOAc (5 mL), filtered through a plug of silica and washed

with EtOAc (15 mL) before removing the solvent *in vacuo*. Flash column chromatography (2 to 5% Et_2O in pet. ether) afforded the sulfonate as a white solid (49 mg, 49%). R_f = 0.41 (30% Et_2O in pet. ether); mp 73 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.66-7.64 (m, 2H, Ar-*H*), 7.54-7.45 (m, 3H, Ar-*H*); ^{13}C NMR (126 MHz; $CDCl_3$): δ 148.5, 142.4 (app. ddq, *J* = 255.1, 12.3, 4.0 Hz), 140.5 (app. dtt, *J* = 255.7, 13.4, 3.8 Hz), 138.7, 137.0 (app. dtdd, *J* = 253.7, 13.5, 5.6, 3.0 Hz), 133.3, 129.4, 129.26, 129.13, 128.2, 127.6, 124.3 (app. tdd, *J* = 14.3, 4.5, 2.1 Hz); ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.5 (d, *J* = 17.8 Hz, 2F), -155.3 (t, *J* = 21.8 Hz, 1F), -161.0 (dd, *J* = 21.6, 17.8 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 1516, 1389 (SO_2), 1196 (SO_2), 990, 844, 767 (C-O-S), 711; HRMS (CI) found *m/z* 400.0195 $[M]^+$, $C_{18}H_9O_3F_5{}^{32}S$ requires *m/z* 400.400.0187.

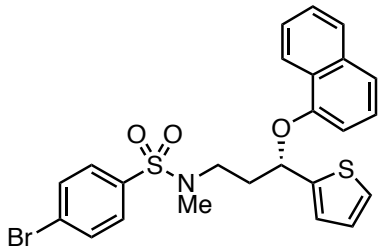
2,3,5,6-Tetrafluorophenyl 4-(trimethylsilyl)phenylsulfonate ester (**51b**)



Prepared according to general procedure C using 4-(trimethylsilyl)phenylboronic acid (97 mg, 0.5 mmol) and 2,3,5,6-tetrafluorophenol (42 mg, 0.25 mmol). Time for SO_2 insertion (t_1) was adjusted from 30 minutes to 1 hour. Flash column chromatography (5% Et_2O in pet. ether) afforded the sulfonate as a white solid (36 mg, 38%). Rf = 0.58 (10% Et_2O in pet. ether); mp 72 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.94 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.75 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.04 (tt, *J* = 9.8, 7.0 Hz, 1H, Ar-*H*), 0.33 (s, 9H, Si(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz; CDCl3): δ 150.7, 146.2 (app. dtd, *J* = 254.2, 11.8, 4.5 Hz), 141.8 (app. ddd, *J* = 254.2, 11.9, 4.6 Hz), 135.2, 134.3, 128.6 (app. tt, *J* = 14.2, 3.9 Hz), 127.3, 104.6 (t, *J* = 22.8 Hz), -1.3; ^{19}F NMR (377 MHz; $CDCl_3$): δ -137.8 (dd, *J* =

11.7, 9.9 Hz, 2F), -150.8 (dd, *J* = 12.2, 7.2 Hz, 2F); IR νmax (neat)/cm^{-1} 1524, 1486, 1380 (SO_2), 1250, 1184 (SO_2), 1050, 943, 841, 760, 726 (C-O-S); HRMS (ESI) found *m/z* 401.0262 $[M+Na]^+$, $C_{15}H_{14}O_3F_4{}^{23}Na^{32}S^{28}Si$ requires *m/z* 401.0261.

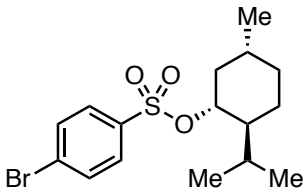
(*S*)-4-bromo-N-methyl-N-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)phenyl sulfonamide ester (**52**)



To a glass reaction tube was added pentafluoro 4-bromophenylsulfonate ester **50q** (202 mg, 0.5 mmol). Acetonitrile (1.5 mL) and (*S*)-Duloxetine (164 mg, 0.55 mmol) were added sequentially, and stirred 16 hours at room temperature. The reaction mixture was diluted with solution of 10% aq. KH_2PO_4 (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*. Flash column chromatography (20% Et_2O in pet. ether) afforded the sulfonamide as a brown solid (158 mg, 61%). $[\alpha]_D^{25}$ = +42.6 (c = 1.0, $CHCl_3$); R_f = 0.33 (30% Et_2O in pet. ether); mp 118 °C; ^1H NMR (400 MHz; $CDCl_3$): δ 8.30-8.28 (m, 1H, Ar-*H*), 7.79 (dd, *J* = 5.3, 3.3 Hz, 1H, Ar-*H*), 7.62-7.60 (m, 4H, 4 × Ar-*H*), 7.50-7.48 (m, 2H, Ar-*H*), 7.41 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 7.29 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 5.3 Hz, 1H, Ar-*H*), 7.11 (d, *J* = 3.3 Hz, 1H, Ar-*H*), 6.95 (t, *J* = 4.2 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.79-5.75 (m, 1H, OC*H*), 3.32-3.20 (m, 2H, NCH_2), 2.77 (s, 3H, CH_3), 2.53-2.46 (m, 1H, OCHCH_aH$_b$), 2.37-2.30 (m, 1H, OCHCH$_a$$H_b$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 153.1, 144.4, 136.4, 134.7, 132.5, 129.0, 127.81, 127.73, 126.9, 126.5,

126.1, 125.9, 125.46, 125.27, 125.17, 122.0, 121.1, 107.3, 73.7, 47.3, 37.7, 35.8; IR ν_{max} (neat)/cm^{-1} 2977, 2921, 1576, 1462, 1391 (SO_2), 1265, 1239, 1161 (SO_2), 1092, 937, 768, 641; HRMS (ESI) found *m/z* 538.0116 $[M+Na]^+$, $C_{24}H_{22}O_3N^{79}Br^{23}Na^{32}S_2$ requires *m/z* 538.0117.

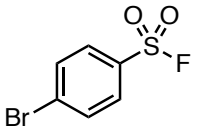
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-bromobenzenesulfonate ester (**53**)



A glass reaction tube was charged with (1*R*,2*S*,5*S*)-(−)-menthol (78 mg, 0.5 mmol), sealed with a rubber septum and evacuated and filled with N_2 four times. Anhydrous THF (0.5 mL) was added through the septum, and the reaction mixture was cooled down at 0 °C before *n*-BuLi (0.22 mL, 2.24 M in hexane, 0.5 mmol) was added dropwise. The reaction mixture for stirred at 0 °C for 1 hour. A 10 mL round bottom flask was charged with pentafluoro 4-bromophenylsulfonate ester **50q** (202 mg, 0.5 mmol), sealed with a rubber septum and evacuated and filled with N_2 four times, before anhydrous THF (1.5 mL) was added. The lithiated menthol solution was cannulated on the sulfonate ester solution at 0 °C. The reaction mixture was then warmed to room temperature and stirred 1 hour at this temperature. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed *in vac*uo. Flash column chromatography (5% Et_2O in pet.) afforded the desired sulfonate ester as a beige solid (126 mg, 67%). $[\alpha]_D^{25}$ = -51.9 (c = 1.0, $CHCl_3$); R_f = 0.56 (5% Et_2O in pet. ether); mp 89 °C (hexane/CH_2Cl_2); ^1H NMR (400 MHz; $CDCl_3$): δ 7.78 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.68 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.45 (td,

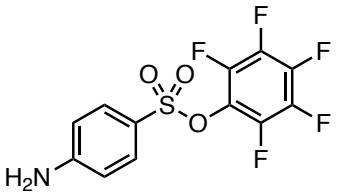
J = 10.8, 4.5 Hz, 1H, SOC*H*), 2.13 (dt, *J* = 12.3, 4.5 Hz, 1H, SOCHC$H_a$$H_b$), 1.86 (dtd, *J* = 13.9, 6.9, 2.0 Hz, 1H, C*H*$(CH_3)_2$), 1.69-1.63 (m, 2H, $CH_3CHCH_aH_b$ and $(CH_3)_2CHCHCH_aCH_b$), 1.48-1.34 (m, 2H, CH_3CH and $(CH_3)_2CHCH$), 1.19 (q, *J* = 11.7 Hz, 1H, $SOCHCH_aH_b$), 0.98 (qd, *J* = 13.0, 3.1 Hz, 1H, $(CH_3)_2CHCHCH_aCH_b$), 0.89 (d, *J* = 6.5 Hz, 3H, CH_2CHCH_3), 0.85-0.78 (m, 4H, $CHCHCH_{3a}$ and $CH_3CHCH_aH_b$), 0.56 (d, *J* = 6.9 Hz, 3H, $CHCHCH_{3b}$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 137.0, 132.5, 129.3, 128.6, 84.7, 47.7, 42.1, 33.8, 31.8, 25.7, 23.1, 22.0, 20.9, 15.4; IR ν_{max} (neat)/cm^{-1} 2955, 2867, 1577, 1454, 1357 (SO_2), 1180 (SO_2), 1068, 941, 907, 818, 739 (C-O-S); HRMS (ESI) found *m/z* 397.0443 $[M+Na]^+$, $C_{16}H_{23}O_3{}^{79}Br^{23}Na^{32}S$ requires *m/z* 397.0444.

4-Bromophenylsulfonyl fluoride (**54**)



In a 5 mL round bottom flask was charged perfluoro 4-bromophenylsulfonate ester **50q** (101 mg, 0.25 mmol) and methanol (2.0 mL). To the resulting mixture was added dropwise a solution of KF (75 μL,10 M in methanol, 0.75 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solution was dissolved in water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried on $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash column chromatography (10% CH_2Cl_2 in pet. ether) afforded the desired sulfonyl fluoride as colourless crystals (47 mg, 78%). R_f = 0.40 (10% CH_2Cl_2 in pet. ether); mp 58 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.88 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.79 (d, *J* = 8.2 Hz, 2H, Ar-*H*); ^{13}C NMR (101 MHz; $CDCl_3$): δ 133.3, 132.2, 131.5, 130.0; ^{19}F NMR (377 MHz; $CDCl_3$): δ 66.4; HRMS (CI) found *m/z* 237.9101 $[M]^+$, $C_6H_4BrO_2F^{32}S$ requires *m/z* 237.9094. Data in accordance with that previously reported.[297]

Pentafluorophenyl 4-aminophenylsulfonate ester (**55**)



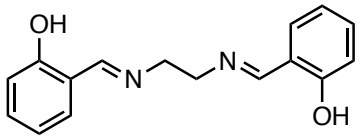
A 150 mL Schlenk flask was charged with perfluoro 4-bromophenylsulfonate ester **50q** (100.8 mg, 0.25 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), BINAP (7.8 mg, 0.013 mmol), and sodium tertbutoxide (33.7 mg, 0.35 mmol), sealed with a rubber septum and was evacuated and filled with N_2 four times. Anhydrous toluene (1.6 mL), and benzophenone imine (50 μL, 0.3 mmol) were added sequentially through the rubber septum. The reaction mixture was stirred under positive pressure of N_2 and heated at 80 °C for 18 hours. The reaction mixture was cooled to ambient temperature, filtered through celite and rinsed several times with CH_2Cl_2. After concentrating the solution under reduced pressure, the residue was diluted with THF (1.6 mL). To the reaction mixture was added a solution of 10% aq. HCl (1.6 mL). The resulting mixture was stirred vigorously at room temperature for 1 hour. The reaction mixture was neutralised by adding a solution of saturated aq. $NaHCO_3$. The resulting solution was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Flash column chromatography (5 to 50% Et_2O in pet. ether) afforded the desired product as an off white solid (38 mg, 45%). R_f = 0.46 (50% Et_2O in pet. ether); mp 147 °C (hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.71 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.71 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.38 (s, 2H, N*H*$_2$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 152.9, 142.5 (app. ddq, *J* = 254.9, 12.5, 4.1 Hz), 140.2 (app. dtt, *J* = 255.0, 17.9, 4.5 Hz), 138.0 (app. dtdd, *J* = 257.4, 14.0, 5.7, 2.9 Hz), 131.2, 124.5 (app. tdd, *J* = 14.1, 4.9, 2.0 Hz), 121.7, 114.1; ^{19}F NMR (377 MHz; $CDCl_3$): δ -150.7 (d, *J* = 17.8 Hz, 2F), -156.1 (t, *J* = 21.8 Hz, 1F), -161.5 (dd, *J* = 21.8, 17.6 Hz, 2F); IR ν_{max} (neat)/cm^{-1} 3489, 3390, 1636, 1598, 1365 (SO_2),

1201, 1168 (SO_2), 1091, 993, 830, 759 (C-O-S); HRMS (ESI) found *m/z* 361.9883 $[M+Na]^+$, $C_{12}H_6O_3NF_5{}^{23}Na^{32}S$ requires *m/z* 361.9881.

6.5 Chapter 4 Data

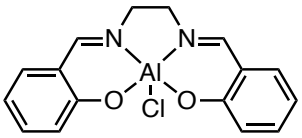
6.5.1 Starting Materials and Other Reactions

N,N'-Bis(2-hydroxybenzyl)-1,2-diaminoethane (**58**)



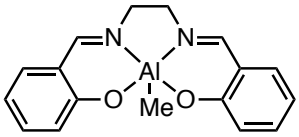
A 250 mL round bottom flask was charged with ethylenediamine (2.7 mL, 25 mmol) and ethanol (75 mL). Salicylaldehyde (5.3 mL, 50 mmol) was added to the solution. Immediately the solution turned yellow and within a minute a yellow precipitate was formed. The mixture was reflux for 1 hour during which the yellow compound redissolved. The solution was then cooled down to 0 °C. The precipitate was filtered off and washed with small amounts of ice-cold ethanol and dried *in vacuo* to give the desired product as yellow flakes (5.7 g, 85%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 13.19 (s, 2H, (O*H*)$_2$), 8.36 (s, 2H, (C*H*N)$_2$), 7.29 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 2H, Ar-*H*), 7.23 (dd, *J* = 7.6, 1.7 Hz, 2H, Ar-*H*), 6.94 (ddt, *J* = 8.3, 1.1, 0.5 Hz, 2H, Ar-*H*), 6.86 (ddd, *J* = 7.6, 7.3, 1.1 Hz, 2H, Ar-*H*), 3.94 (s, 4H (C*H*$_2$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 161.1, 132.5, 131.6, 118.82, 118.77, 117.1, 59.9; MS (ESI) *m/z* 269.1 $[M+H]^+$. Data are in accordance to that previously reported.[298]

Aluminium (III) chloride salendiamine complex (**59a**)



This complex was prepared by a modification of the method described in the literature.[299] A 50 mL round bottom flask was charged with *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268 mg, 1.0 mmol). The flask was sealed and evacuated and filled with N_2 four times before the addition of degassed dichloromethane (7.2 mL). To the vigorously stirred mixture, a solution of diethylaluminium chloride was slowely added (1.0 mL, 1.0 M in hexane, 1.0 mmol). The reaction mixture stirred for 2 hours at ambient temperature. The residual solvent was removed *in vacuo* and the resulting yellow sold was rinsed with hexane (25 mL) and dried *in vacuo* to afford the desired Al[Cl(Salen)] complex as a yellow solid (91 mg, 28%). IR ν_{max} (neat)/cm^{-1} 1620, 1611, 1491, 1438, 1453, 1402, 1337, 1314, 1208, 1130, 799, 739, 648; MS (ESI) *m/z* 293.3 $[M\text{-}Cl]^+$; HRMS (ESI) found *m/z* 293.0868 $[M\text{-}Cl]^+$, $C_{16}H_{14}O_2N_2{}^{27}Al$ requires *m/z* 293.0865.

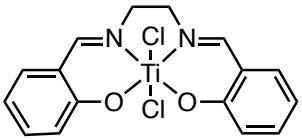
Aluminium (III) methyl salendiamine complex (**59b**)



This complex was prepared by a modification of the method described in the literature.[300] A 50 mL round bottom flask was charged with *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol). The flask was sealed and evacuated and filled with N_2 four times before the addition of degassed toluene (20.0 mL). To the vigorously stirred mixture, a solution of trimethylaluminium was slowely added (0.5 mL, 2.0 M in heptane, 1.0 mmol). The reaction mixture was refluxed for 12 hours, cooled to ambient

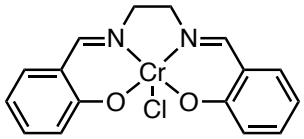
temperature and filtered to recover the precipitate. The solid was washed with pet. ether and dried *in vacuo* to afford the desired Al[Me(Salen)] complex as a white solid (182 mg, 59%). IR ν_{max} (neat)/cm^{-1} 1631, 1605, 1547, 1476, 1453, 1395, 1337, 1314, 1206, 1128, 908, 808, 758, 648, 603; MS (ESI) *m/z* 293.1 $[M\text{-}CH_3]^+$; HRMS (ESI) found *m/z* 293.0864 $[M\text{-}CH_3]^+$, $C_{16}H_{14}O_2N_2{}^{27}Al$ requires *m/z* 293.0865.

Titanium (IV) dichloride salendiamine complex (**59c**)



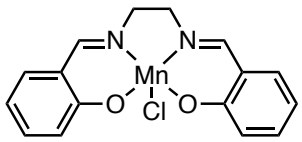
This complex was prepared by a modification of the method described in the literature.[301] A 10 mL round bottom flask was charged with *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol) and THF (2.0 mL). To the suspension was added a solution of $TiCl_4$ (110.0 μL, 1.0 mmol) in toluene (0.5 mL). The red-orange solution was refluxed for 30 minutes, the solvent was evaporated, and the red solid washed with cold acetone and dried *in vacuo*, affording the desired Ti(IV)[(Cl_2(Salen)] complex as a dark red powder (226 mg, 59%). IR ν_{max} (neat)/cm^{-1} 1612, 1594, 1553, 1440, 1392, 1268, 1246, 1124, 909, 812, 761, 655; MS (ESI) *m/z* 345.1 $[M\text{-}Cl_2\text{+}OCH_3]^+$; HRMS (ESI) found *m/z* 345.0711 $[M\text{-}Cl_2\text{+}OCH_3]^+$, $C_{17}H_{17}O_3N_2{}^{48}Ti$ requires *m/z* 345.0713.

Chromium (III) chloride salendiamine complex(**59d**)



This complex was prepared by a modification of the method described in the literature.[232] A 50 mL round bottom flask under inert atmosphere was charge with chromium(II) chloride (130 mg, 1.1 mmol), *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (283 mg, 1.1 mmol), and dry, degassed THF (21 mL). The resulting dark brown solution was stirred under N_2 for 3 hours and then in air for an additional 3 hours. The solution was then diluted with 100 mL of Et_2O and washed with saturated aq. NH_4Cl (3 × 80 mL) and brine (3 × 80 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*, affording the desired Cr(III)[Cl(Salen)] complex as a dark brown solid (16 mg, 4%). IR ν_{max} (neat)/cm^{-1} 3613, 3444, 2943, 2839, 1624, 1537, 1433, 1391, 1328, 1255, 1185, 1034, 834, 769, 769; MS (ESI) *m/z* 318.0 $[M\text{-}Cl]^+$; HRMS (ESI) found *m/z* 318.0455 $[M\text{-}Cl]^+$, $C_{16}H_{14}O_2N_2{}^{52}Cr$ requires *m/z* 318.0460.

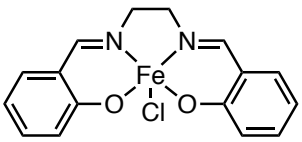
Manganese (III) chloride salendiamine complex (**59e)**



This complex was prepared by a modification of the method described in the literature.[302] A 25 mL round bottom flask was charged with *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol) and ethanol (10.0 mL). The slurry solution was heated until the solution was homogenous. Solid $Mn(OAc)_2 \cdot 4H_2O$ (245.1 mg, 1.0 mmol) was added in one portion and the reaction mixture was refluxed for 1 hour. The solution was then cooled down to room temperature and LiCl (63.6 mg, 1.5 mmol) was added in

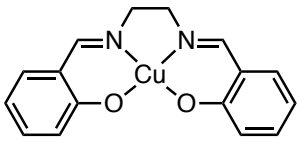
one portion. The reaction mixture was subsequently further refluxed for 1 hour. After cooling the mixture at 0 °C, the precipitate was filtered off and washed with water (2.5 mL), methanol (2.5 ml), ether (5.0 mL) and dried *in vacuo*. The resulting solid was recrystallised for dichloromethane, affording the desired Mn(III)[Cl(Salen)] complex as a brown solid (82 mg, 23%). mp 190-195 °C (dec.); IR ν_{max} (neat)/cm^{-1} 1624, 1597, 1540, 1466, 1387, 1330, 1266, 1203, 1037, 978, 900, 864, 799, 769, 630; MS (ESI) *m/z* 321.0 [M-Cl]$^{+}$; HRMS (ESI) found *m/z* 321.0428 [M-Cl]$^{+}$, $C_{16}H_{14}O_2N_2{}^{55}Mn$ requires *m/z* 321.0430.

Iron (III) chloride salendiamine complex (**59f**)



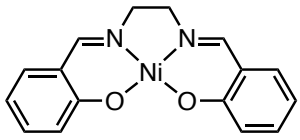
This complex was prepared by a modification of the method described in the literature.[303] A 10 mL round bottom flask was charged with *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol) and ethanol (4.0 mL). Solid Fe(III)Cl_3 (162.8 mg, 1.0 mmol) was added in one portion. The reaction mixture was refluxed for 2 hours. The precipitate was then separated by filtration. The brown solid was washed with ice-cold ethanol-water (15.0 mL, 1:1) and then dried *in vacuo*. The solid was recrystallised from acetone, affording the desired Fe(III)[Cl(Salen)] complex as a dark brown solid (98 mg, 27%). IR ν_{max} (neat)/cm^{-1} 1628, 1597, 1544, 1468, 1444, 1327, 1269, 1124, 905, 770, 759, 616; MS (ESI) *m/z* 322.0 [M-Cl]$^{+}$; HRMS (ESI) found *m/z* 322.0399 [M-Cl]$^{+}$, $C_{16}H_{14}O_2N_2{}^{56}Fe$ requires *m/z* 322.0398.

Copper (II) salendiamine complex (**59g**)



This complex was prepared by a modification of the method described in the literature.[304] In a 25 mL two neck round bottom flask was dissolved *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol) in ethanol (5.0 mL). The solution was heated to boiling temperature. A solution of $Cu(II)(NO_3)_2.2.5H_2O$ (232.6 mg, 1.0 mmol) in ethanol (12.5 mL) was added dropwise to the reaction mixture. The resulting solution was stirred and refluxed for 1 hour. After the solution was cooled to room temperature, the product was separated by filtration and recrystallised from $CHCl_3$/pet. ether, to afford the desired Cu(II)[Salen] complex as a dark green solid (127 mg, 39%). IR ν_{max} (neat)/cm^{-1} 1627, 1600, 1533, 1445, 1388, 1304, 1193, 1124, 902, 752, 646, 615; MS (ESI) *m/z* 330.1 $[M+H]^+$; HRMS (ESI) found *m/z* 330.0425 $[M+H]^+$, $C_{16}H_{15}O_2N_2{}^{63}Cu$ requires *m/z* 330.0424.

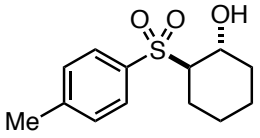
Ni (II) salendiamine complex (**59h**)



This complex was prepared by a modification of the method described in the literature. [305] A 25 mL round bottom flask was charged with Ni(II) $(OAc)_2 \cdot 4H_2O$ (248.8 mg, 1.0 mmol), *N,N'*-Bis(2-hydroxybenzyl)-1,2-diaminoethane (268.3 mg, 1.0 mmol) and ethanol (10.0 mL). The reaction mixture was refluxed for 2 hours and the pink solution turned red. The reaction mixture was cooled to room temperature and the precipitate was separated by filtration, washed with distilled water and dried *in vacuo* overnight. The

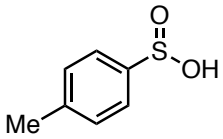
product was recrystallised from ethanol, affording the desired Ni(II)[Salen] complex as a dark orange solid (258, 79%). IR ν_{max} (neat)/cm^{-1} 1618, 1594, 1531, 1440, 1346, 1312, 1199, 1145, 1122, 1023, 899, 851, 735, 665, 630; MS (ESI) *m/z* 325.1 $[M+H]^+$; HRMS (ESI) found *m/z* 325.0478 $[M+H]^+$, $C_{16}H_{15}O_2N_2{}^{58}Ni$ requires *m/z* 325.0482.

2-tosylcyclohexan-1-ol (**60**)



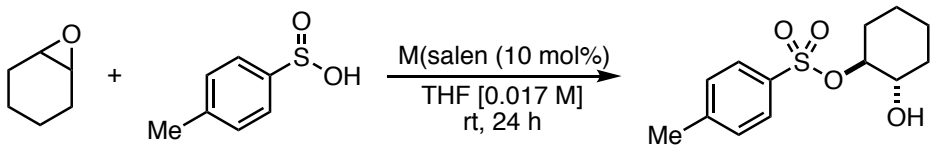
A 10 mL round bottom flask was charged with sodium *p*-tolylsulfinate (18 mg, 0.1 mmol), TBAB (3.2 mg, 10 mol%), distilled water (0.2 mL), and toluene (0.2 mL). The reaction mixture was stirred vigorously and cyclohexene oxide (10 μL, 0.1 mmol) was added. The reaction mixture was left to stir at room temperature for 18 hours. The crude material was quenched with saturated aq. $NaHCO_3$ (1.0 mL), and subsequently Et_2O (1.0 mL) was added, the two phases separated, and the aqueous layer extracted with Et_2O (3 × 3.0 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (50% Et_2O in pet. ether) afforded the desired sulfone product as an off-white solid (3.3 mg, 13 %); mp 125 °C (CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.77 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.38 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 4.37 (s, 1H, O*H*), 3.88 (td, *J* = 10.1, 4.9 Hz, 1H, C*H*OH), 2.95 (td, *J* = 10.8, 3.2 Hz, 1H, SC*H*CH_2), 2.47 (s, 3H, ArCH_3), 2.12 (d, *J* = 13.6 Hz, 1H, CH(OH)C$H_a$$H_b$), 1.90 (d, *J* = 13.6 Hz, 1H, SCHC$H_a$$H_b$), 1.71 (d, *J* = 6.9 Hz, 2H, CH_2), 1.35-1.17 (m, 4H, CH(OH)C$H_a$$H_b$, and SCHC$H_a$$H_b$, and C$H_2$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 145.3, 133.7, 129.9, 129.1, 68.9, 68.2, 34.1, 25.7, 24.6, 23.6, 21.7; MS (ESI) *m/z* 277 .3 $[M+Na]^+$. Data in accordance with previously reported.[129]

p-tolylsulfinic acid (**61**)



A 25 mL round bottom flask was charged with sodium *p*-tolylsulfinate (891 mg, 5.0 mmol), distilled water (4.0 mL) and ethanol (4.0 mL). The solution was vigorously stirred and conc. HCl (0.3 mL, 7.5 mL) was slowly added. The reaction mixture was left to stir at room temperature for 1 hour. The crude material was extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, and the residual solvent was evaporated *in vacuo*, affording the desired sulfinic acid as a white power (619 mg, 79%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.62-7.56 (m, 2H, Ar-*H*), 7.31 (dd, *J* = 8.6, 0.6 Hz, 2H, Ar-*H*), 6.80 (s, 1H, SO_2H), 2.42 (s, 3H, CH_3); ^{13}C NMR (101 MHz; $CDCl_3$): δ 143.2, 142.9, 130.0, 125.2, 21.7; MS (ESI) *m/z* 155.1 $[M-H]^-$. Data are in accordance to that previously reported.[306]

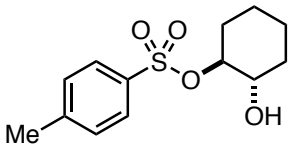
6.5.2 **General Procedure F** for the metal-salen complex catalysed epoxide opening with sulfinic acid nucleophile



A 10 mL round bottom flask was charged with *p*-tolylsulfinic acid **61** (17 mg, 0.11 mmol), metal-salen complex (10 mol%), THF (6.0 mL), and cyclohexene oxide (10 μL, 0.1 mmol), and the solution was stirred under air at room temperature for 24 hours. The reaction mixture was diluted with Et_2O (10.0 mL), washed with 1 M aq. HCl solution (5 × 10 mL), and saturated aq. $NaHCO_3$ solution (2 × 15 mL), dried over $MgSO_4$, filtered, and the residual solvent was concentrated *in vacuo*. The desired products were isolated

from the obtained crude material by flash column chromatography using the indicated solvents and gradient.

Trans-2-hydroxycyclohexyl 4-methylbenzenesulfonate ester (**62**)

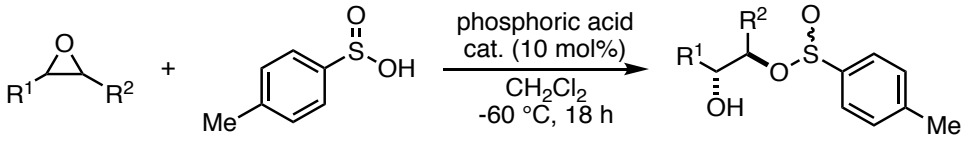


Procedure 1: Prepared according to procedure F using Co(III)salendiamine **59i** (3.3 mg, 10 mol%). The catalyst **59i** was in situ generated from stirring Co(II) salendiamine (3.3 mg, 10 mol%) in THF (0.2 mL) under an oxygen atmosphere for 30 minutes at room temperature. Flash column chromatography (40% Et_2O in pet. ether) afforded the sulfonate as a white solid (11 mg, 38%). R_f = 0.22 (50% Et_2O in pet. ether); mp 98 °C (hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.35 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 4.29 (ddd, *J* = 11.1, 8.6, 4.9 Hz, 1H, SOC*H*), 3.57 (dddd, *J* = 11.5, 7.8, 4.9, 2.5 Hz, 1H, C*H*OH), 2.45 (s, 3H, CH_3), 2.36 (d, *J* = 2.5 Hz, 1H, O*H*), 2.06-1.96 (m, 2H, SOCHCH_aH$_b$ and HOCHCH_aH$_b$), 1.68 (dd, *J* = 6.1, 2.5 Hz, 2H, CH_2CH$_2$CHOH), 1.49-1.39 (m, 1H, SOCHCH$_a$$H_b$), 1.30-1.21 (m, 3H, CH$_a$$H_b$CHOH and SOCHCH$_2CH_2$); ^{13}C NMR (101 MHz; $CDCl_3$): δ 145.0, 134.1, 130.0, 127.9, 86.9, 72.2, 32.5, 31.0, 24.1, 23.4, 21.8; MS (ESI) *m/z* 271.1 $[M+H]^+$. Data are in accordance to that previously reported.[235]

Procedure 2: A 10 mL round bottom flask was charged with p-tosylchloride (190 mg, 1.0 mmol), *trans*-1,2-cyclohexane diol (117 mg, 1.01 mmol), pyridine (1.8 mL, 20 mmol), and stirred at room temperature for 2 days. The reaction mixture was then poured on ice/H_2O (5 mL) and extracted CH_2Cl_2 (3 × 5 mL). The combined organic layers were

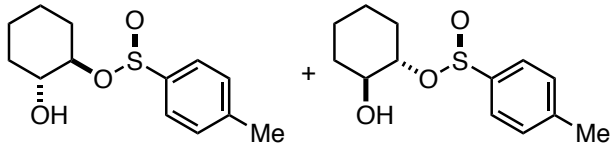
washed with aq. HCl (1M, 2 × 10 mL), then water (10 mL). The organic layer was dried over $MgSO_4$, filtered and the residual solvent removed *in vacuo*. Crystallisation of the crude material in hexane delivered the desired sulfonate ester product as a white solid (185 mg, 69%). Data in accordance with the ones reported in procedure 1.

6.5.3 **General Procedure G** for the phosphoric acid catalysed epoxide opening with sulfinic acid nucleophile

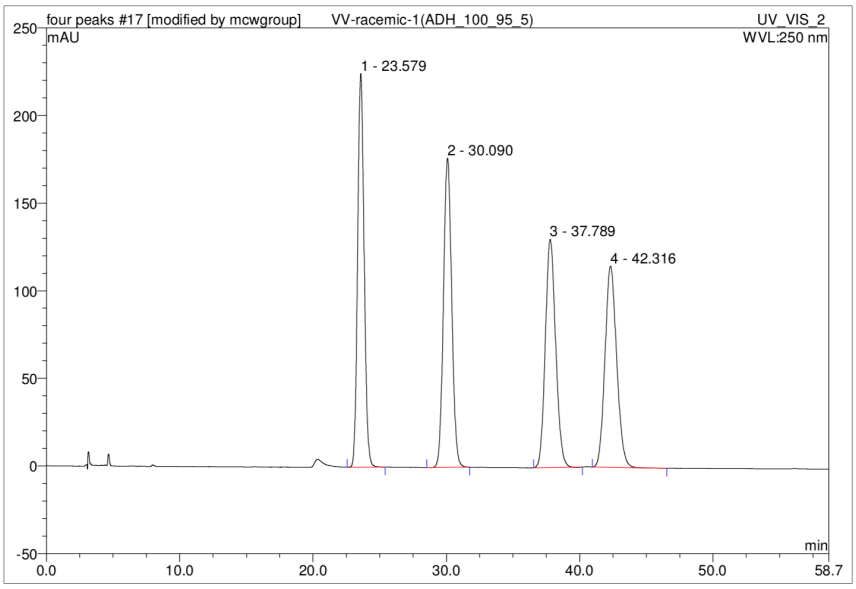


A 10 mL round bottom flask was charged with 4-methylbenzenesulfinic acid (23 mg, 0.15 mmol), phosphoric acid catalyst (10 mol%), and dichloromethane (6 mL). The solution was cooled to -60 °C and stirred for 10 minutes. The corresponding epoxide (0.1 mmol) was cooled and then added to the solution and the reaction mixture was stirred at -60 °C for 18 hours. The reaction mixture was poured in an ice-cold solution of saturated $NaHCO_3$ aq. (15 mL). The organic materials were extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient. The diastereomeric ratio of the product was determined by ^1H NMR analysis of the crude material. The enantiomeric excess of the product was determined by chiral HPLC analysis. The racemic sample of the product was prepared by performing the reaction with racemic binaphthyl-2,2′-diyl hydrogenphosphate at room temperature.

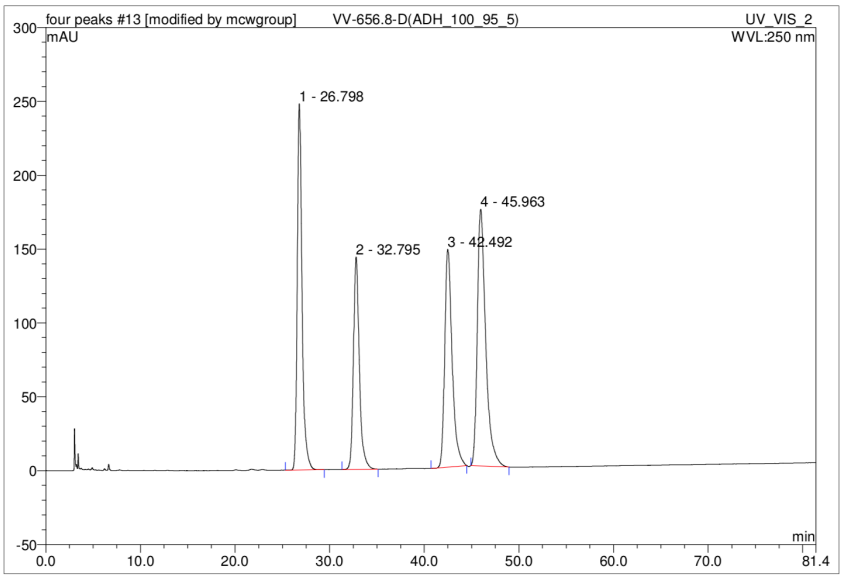
Trans-2-hydroxycyclohexyl 4-methylbenzenesulfinate ester (**69**)



Procedure 1: Prepared according to the general procedure G using phosphoric acid catalyst (*R*)-**56d** (6.6 mg, 10 mol%) and cyclohexene oxide (10 μL, 0.1 mmol). Flash column chromatography (50% Et_2O in pet. ether) afforded the sulfinate as a mixture of both diastereomers (21 mg, 81%), as a colourless oil. R_f = 0.47 (70% Et_2O in pet. ether); d.r. 59:41; 8% ee; HPLC analysis: Chiralpak AD-H, (hexane/2-propanol, 95:5); flow rate 1.0 mL/min; retention time: major diastereomer, 26.8 min (major), 32.8 min (minor); minor diastereomer, 42.5 min, 46.0 min. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.62 (dd, *J* = 7.9, 6.0 Hz, 4H, Ar-*H*), 7.34 (d, *J* = 7.9 Hz, 4H, Ar-*H*), 4.08 (ddd, *J* = 11.3, 8.4, 4.8 Hz, 1H, C*H*OH diastereomer 1), 3.78 (ddd, *J* = 11.3, 8.4, 4.8 Hz, 1H, C*H*OH diastereomer 2), 3.51-3.40 (m, 2H, C*H*OS diastereomer 1 and 2), 2.43 (d, *J* = 4.1 Hz, 6H, ArCH_3 diastereomer 1 and 2), 2.14-2.05 (m, 3H, CH_2 and CH_aH$_b$), 1.78-1.58 (m, 6H, CH_2), 1.52-1.39 (m, 2H, CH_2), 1.34-1.24 (m, 3H, CH_2 and CH$_a$$H_b$), 1.20-1.16 (m, 2H, C$H_2$); 13-C NMR (101 MHz; CDCl3): δ 143.22, 143.15, 142.5, 140.5, 129.92, 129.87, 125.6, 125.0, 87.4, 84.1, 72.7, 71.8, 32.8, 32.2, 32.03, 32.00, 24.43, 24.34, 23.69, 23.59, 21.7; IR ν_{max} (neat)/cm^{-1} 3057, 3030, 2932, 2861, 1600, 1490, 1451, 1291, 1180, 1022, 981, 901, 845, 767, 733, 644; MS (ESI) *m/z* 255.1 $[M+H]^+$; HRMS (ESI) found *m/z* 255.1050 $[M+H]^+$, $C_{13}H_{19}O_3{}^{32}S$ requires *m/z* 255.1049.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.58	n.a.	224.558	126.565	25.97	n.a.	BMB*
2	30.09	n.a.	176.509	126.654	25.99	n.a.	BMB*
3	37.79	n.a.	130.337	117.119	24.03	n.a.	BMB*
4	42.32	n.a.	114.869	117.006	24.01	n.a.	BMB*
Total:			646.273	487.343	100.00	0.000	

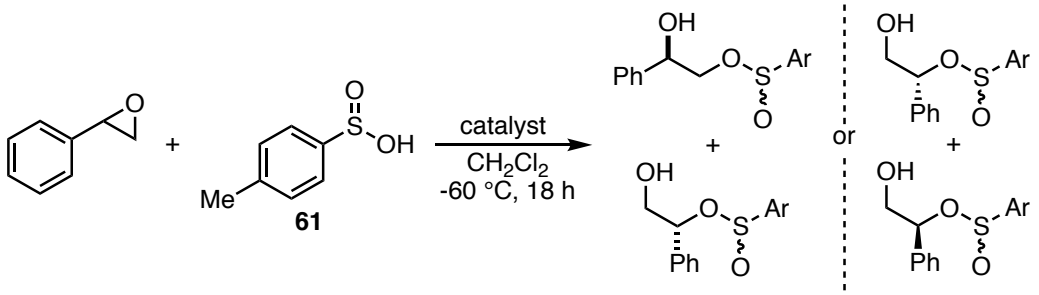


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.80	n.a.	247.980	145.388	25.87	n.a.	BMB*
2	32.80	n.a.	143.882	104.164	18.53	n.a.	BMB*
3	42.49	n.a.	147.535	134.092	23.86	n.a.	BMB*
4	45.96	n.a.	173.907	178.380	31.74	n.a.	BMB*
Total:			713.305	562.024	100.00	0.000	

Procedure 2: A 10 mL round bottom flask was charged with sodium *p*-tolylsulfinate (90 mg, 0.5 mmol), *trans*-1,2-cyclohexane diol (174 mg, 1.5 mmol), and CH_2Cl_2 (2.0 mL). The mixture was stirred vigorously and sulfuric acid (53.0 mL) was added slowly. After 30 minutes, powdered 4 Å molecular sieves (100 mg) were added. The reaction was

stirred at room temperature for 6 hours. The mixture was then diluted with CH_2Cl_2 (5 mL), and washed with water (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the residual solvent was removed *in vacuo*. Flash column chromatography (30% Et_2O in pet. ether) afforded the sulfinate as a mixture of both diastereomers (29 mg, 23%), as a colourless oil. R_f = 0.47 (70% Et_2O in pet. ether); dr 50:50. Data in accordance with the ones reported in procedure 1

Ring-Opening of unsymmetrical epoxides



Prepared according to the general procedure G using phosphoric acid catalyst (*R*)-**56a** (7.7 mg, 10 mol%) and styrene oxide (11.5 μL, 0.1 mmol). Flash column chromatography (40% Et_2O in pet. ether) afforded the sulfnate as a white solid. mp 106 °C; d.r. 50:50.

Isomer 1: 5 mg, 19%; R_f = 0.62 (70% Et_2O in pet. ether); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.51 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.26-7.24 (m, 5H, Ar-*H*), 7.05-7.03 (m, 2H, Ar-*H*), 5.02 (dd, *J* = 8.6, 2.5 Hz, 1H, SOC*H*), 3.83 (dd, *J* = 12.4, 8.6 Hz, 1H, CH_aH$_b$OH), 3.62 (d, *J* = 12.4 Hz, 1H, CH$_a$$H_b$OH), 3.37 (s, 1H, O*H*), 2.40 (d, *J* = 5.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz; $CDCl_3$): δ 143.4, 139.9, 136.7, 129.9, 128.6, 126.7, 126.0, 82.3, 66.2, 21.7; IR ν_{max} (neat)/cm^{-1} 3426, 2923, 1494, 1453, 1132, 1108, 1079, 1042, 1017, 885, 812, 764, 699; MS (ESI) *m/z* 277.3 [M+H]$^+$; HRMS (ESI) found *m/z* 277.0893 [M+H]$^+$, $C_{15}H_{17}O_3{}^{32}S$ requires *m/z* 277.0893.

Isomer 2: 4 mg, 15%; R_f = 0.54 (70% Et_2O in pet. ether); ^1H NMR (400 MHz; $CDCl_3$): δ 7.60-7.57 (m, 2H, Ar-*H*), 7.42-7.32 (m, 7H, Ar-*H*), 5.43 (dd, *J* = 8.2, 3.3 Hz, 1H, SOC*H*), 3.85-3.73 (m, 2H, CH_2), 2.87 (dd, *J* = 9.6, 2.5 Hz, 1H, O*H*), 2.43 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 138.2, 129.9, 128.9, 128.6, 126.7, 126.0, 125.1, 88.2, 67.1, 21.7; MS (ESI) *m/z* 277.3 $[M+H]^+$; HRMS (ESI) found *m/z* 277.0890 $[M+H]^+$, $C_{15}H_{17}O_3{}^{32}S$ requires *m/z* 277.0893.

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Spectra

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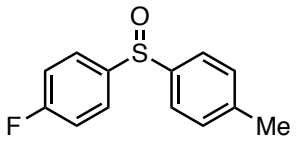

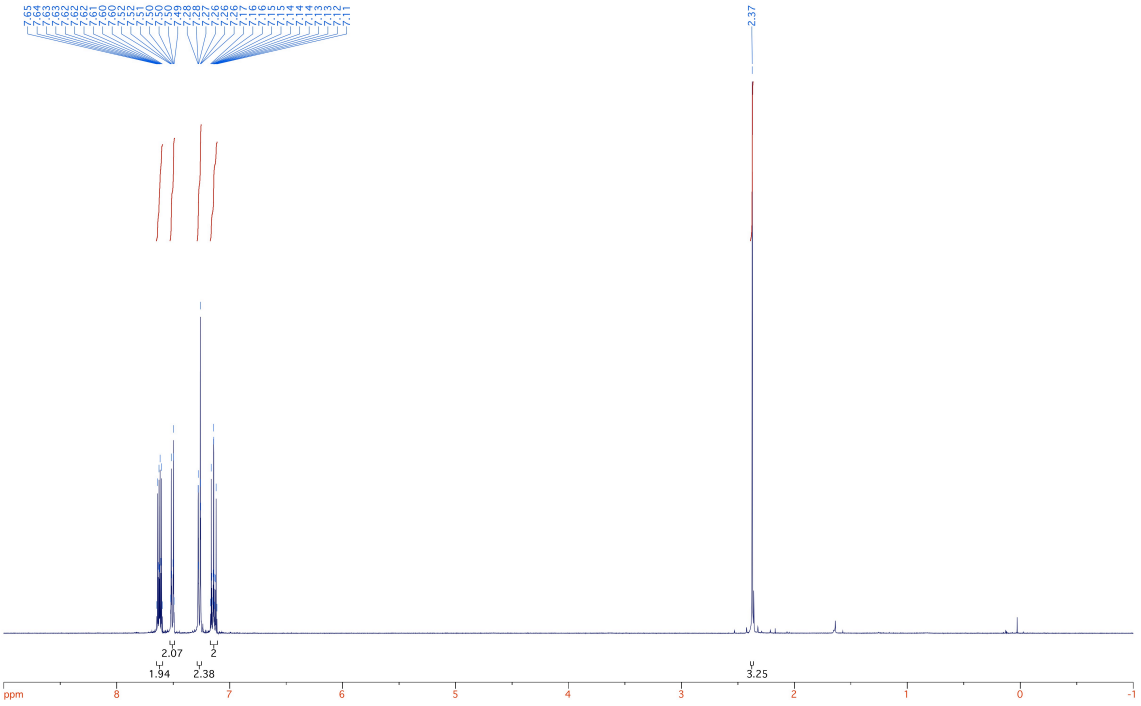

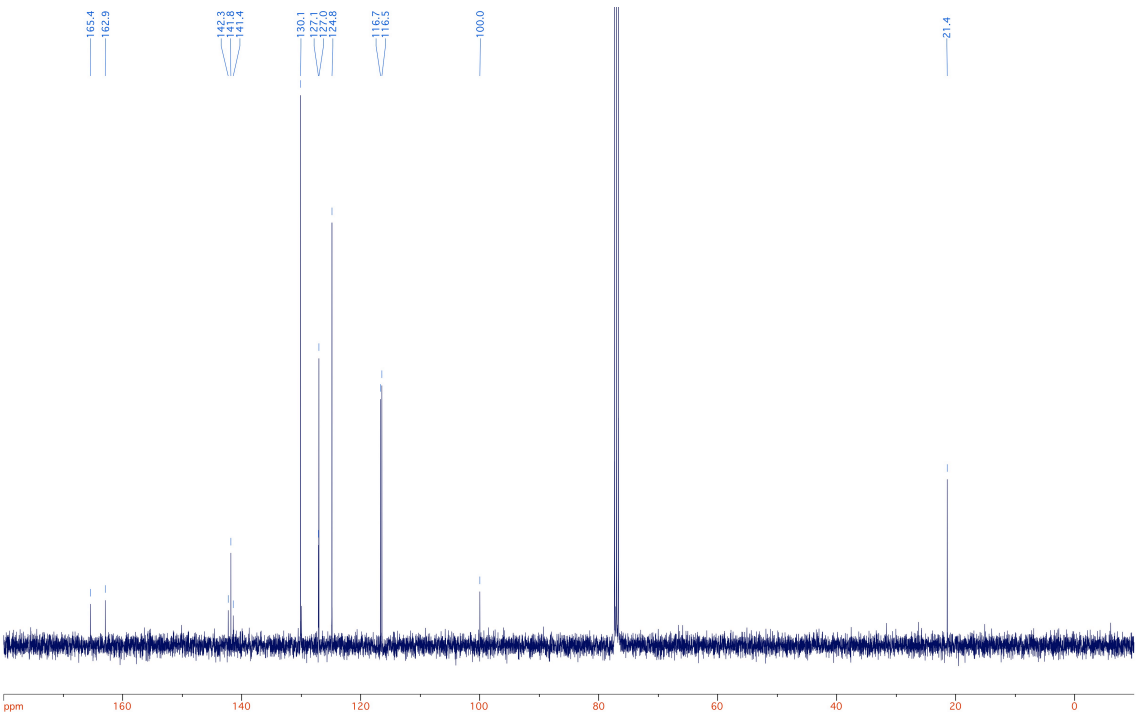

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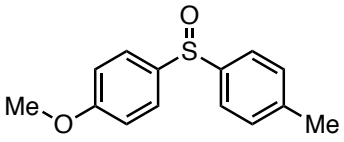

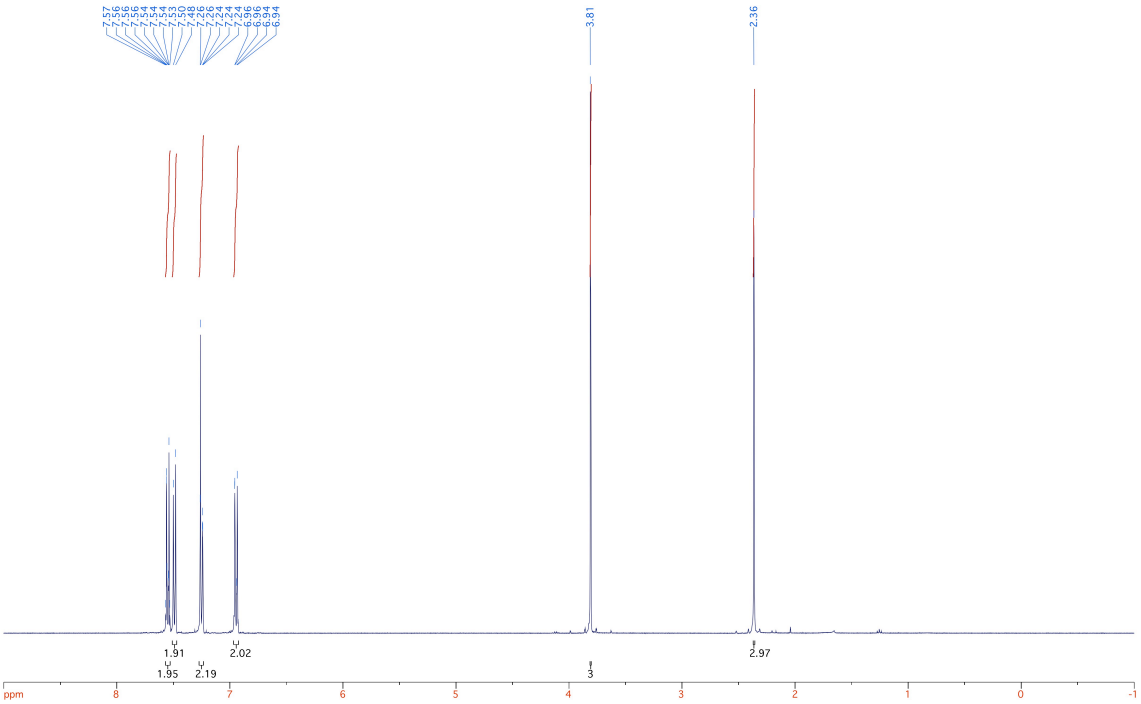

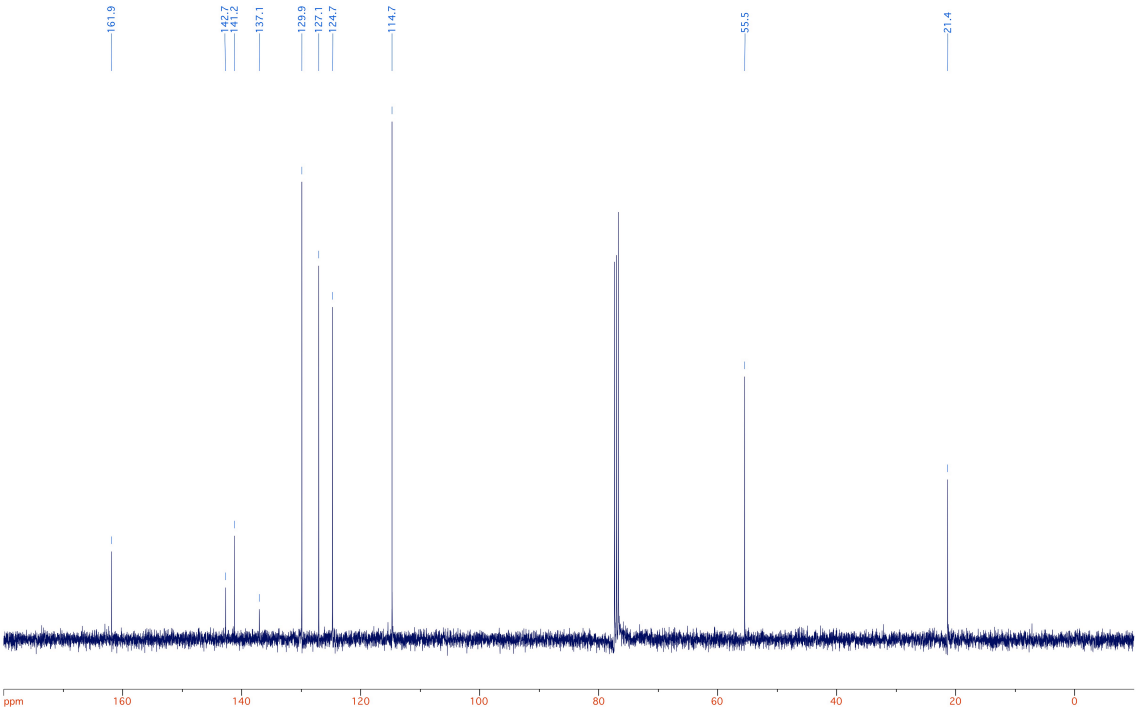

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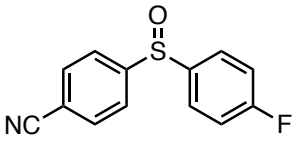

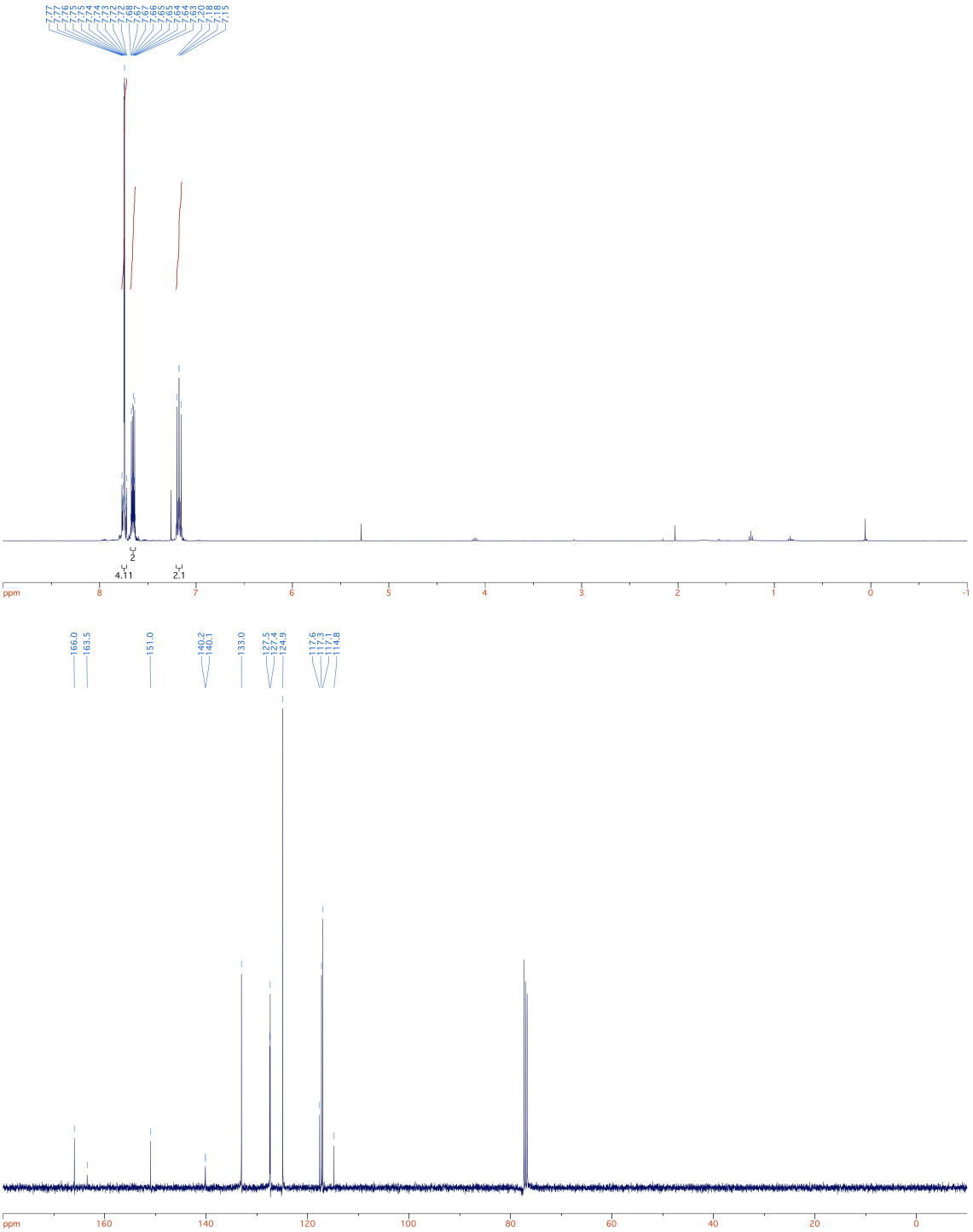

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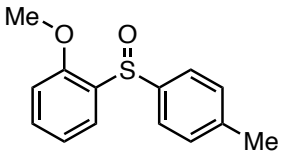

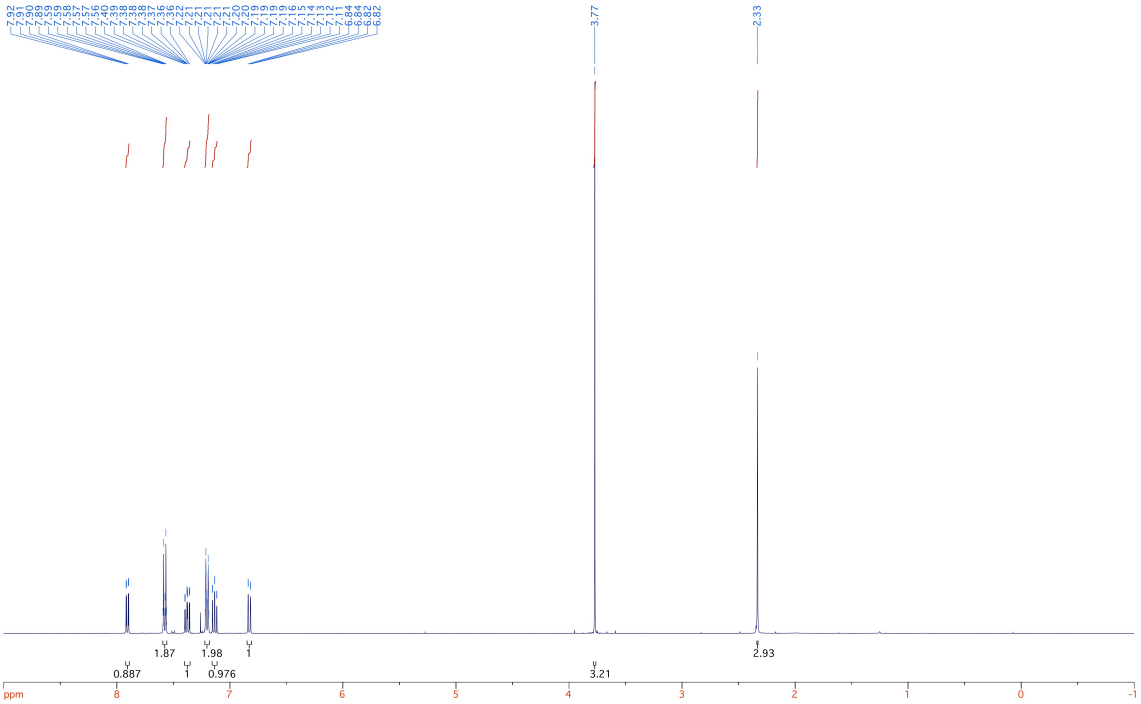

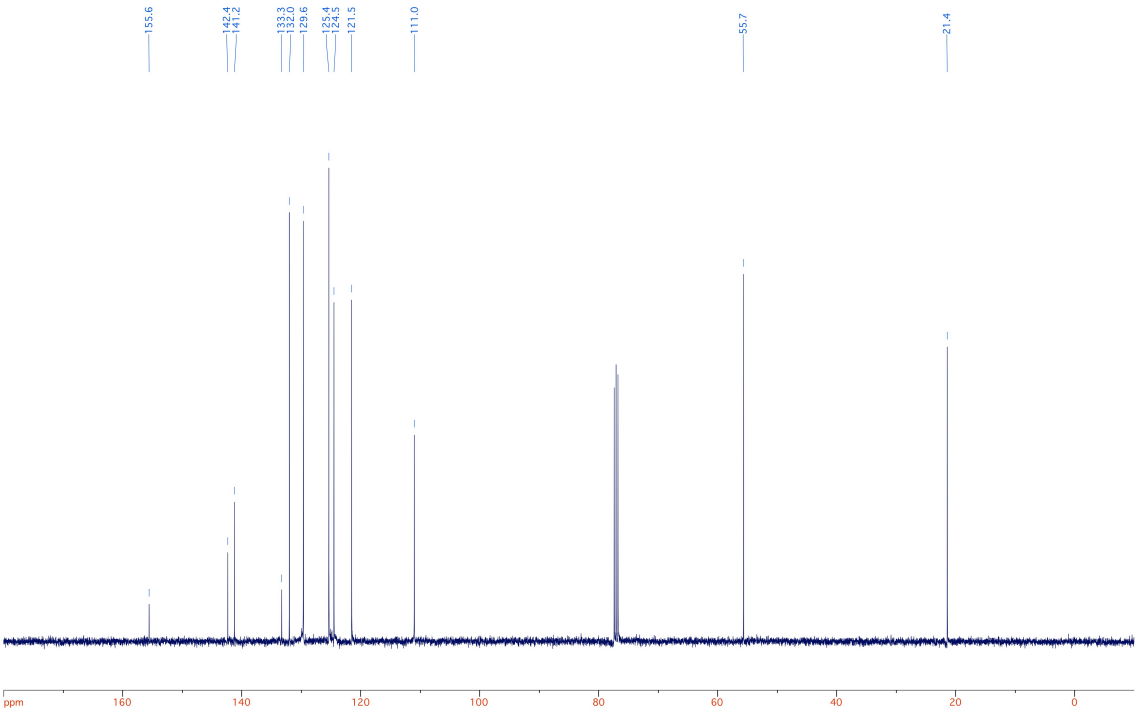

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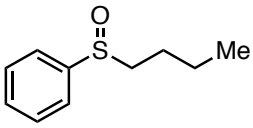

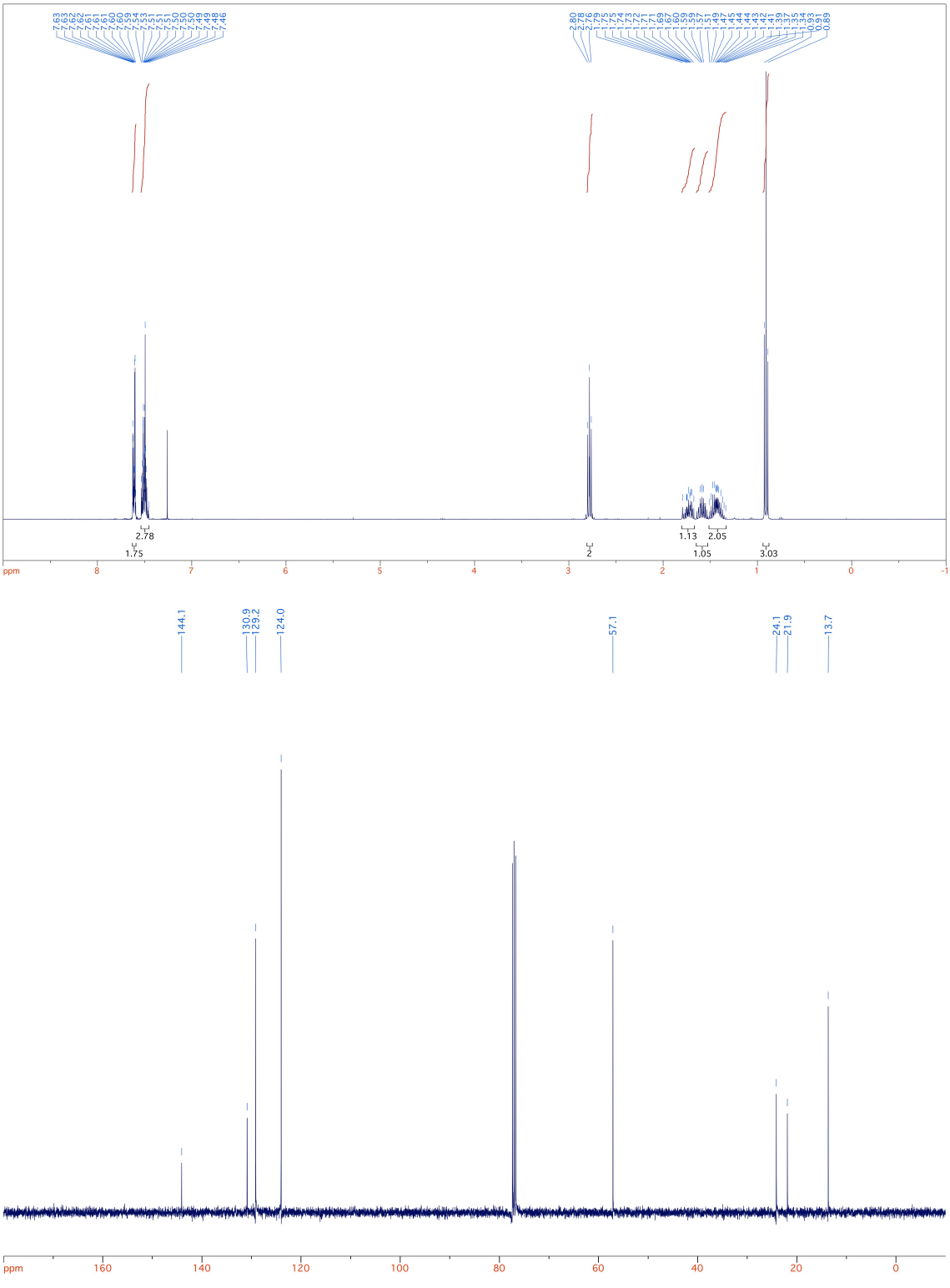

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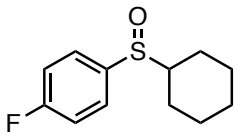
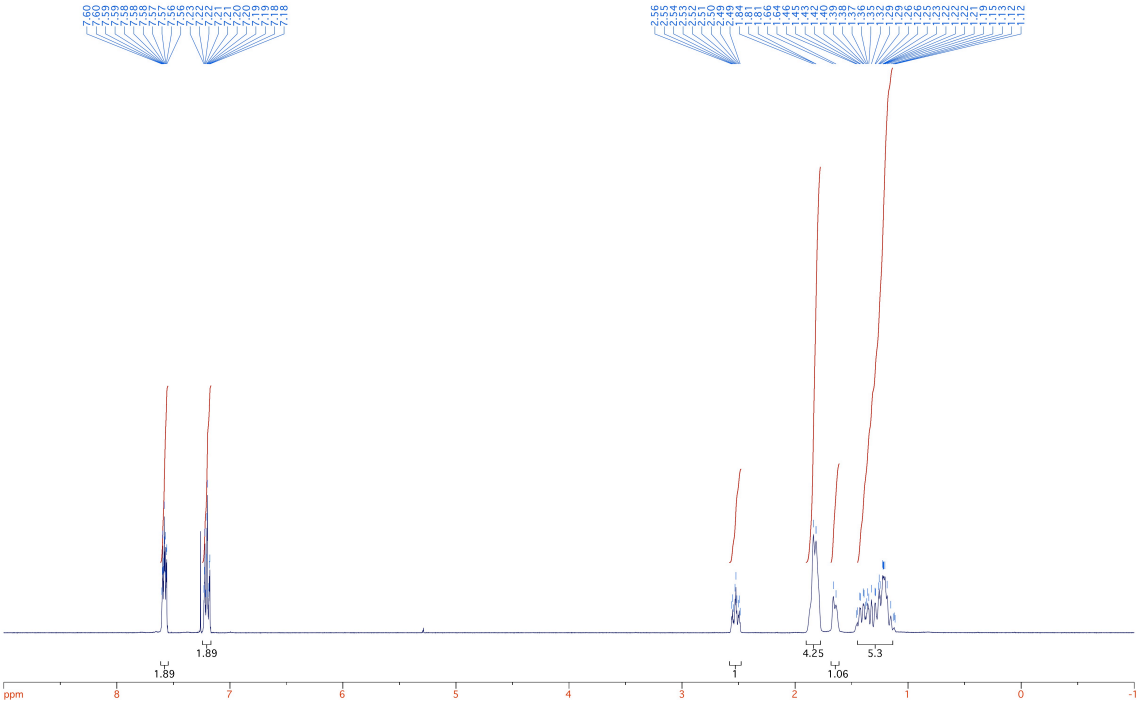
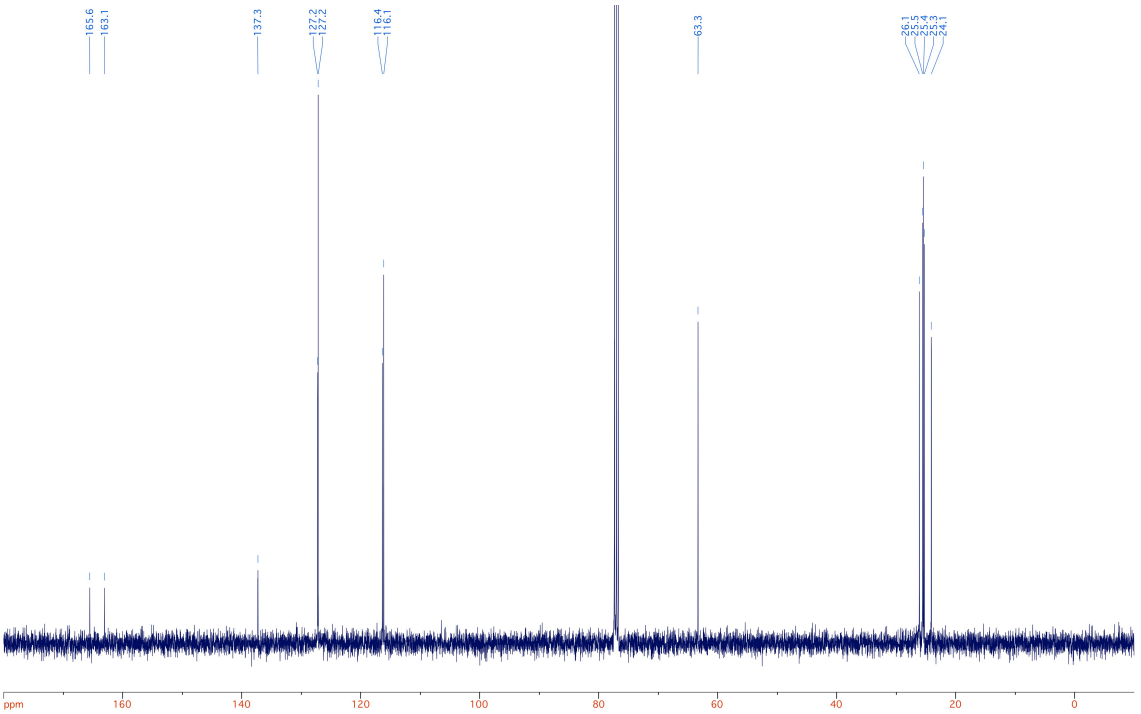
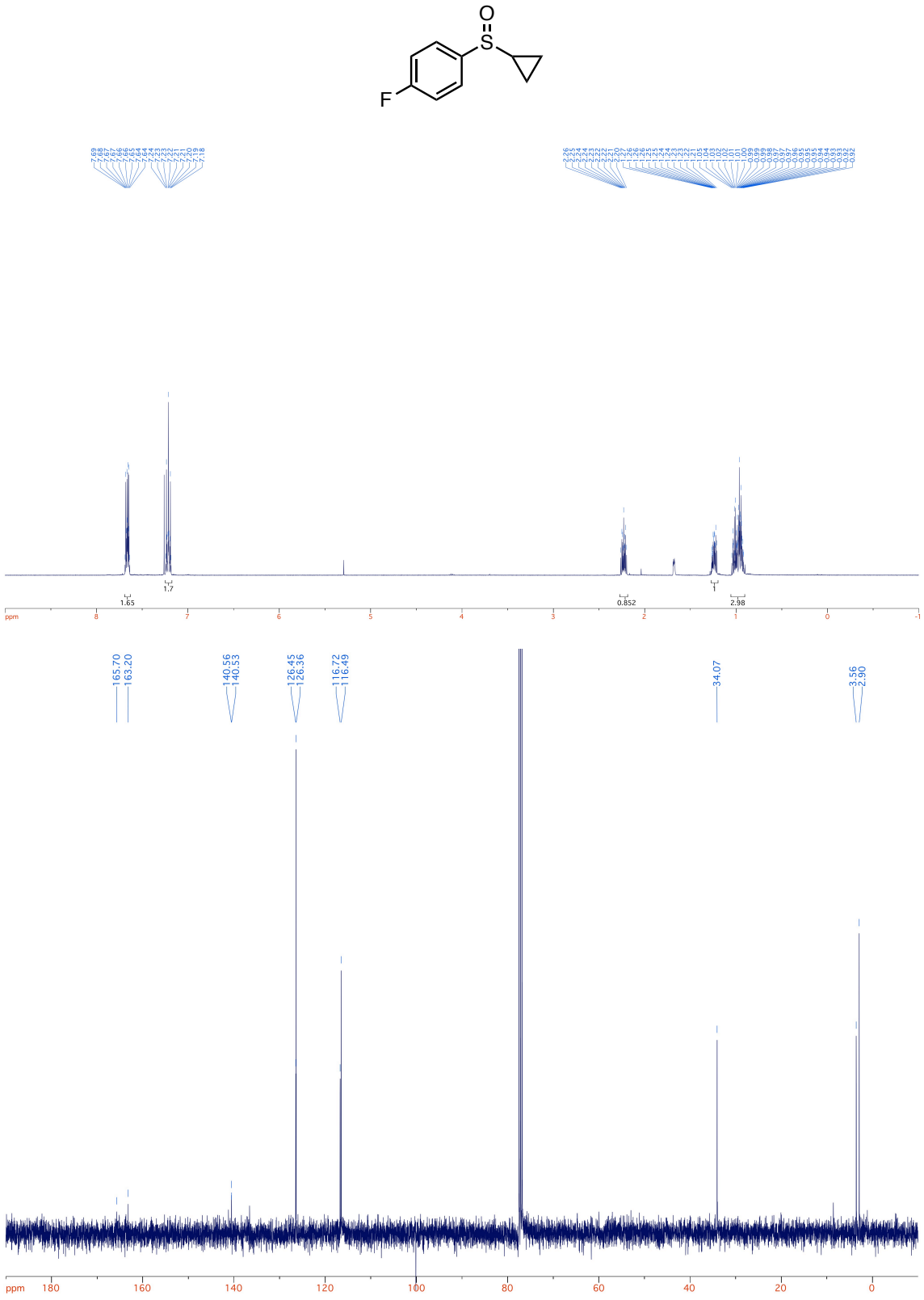






Compound 40**g**



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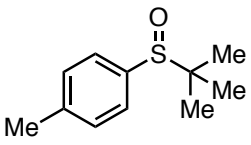
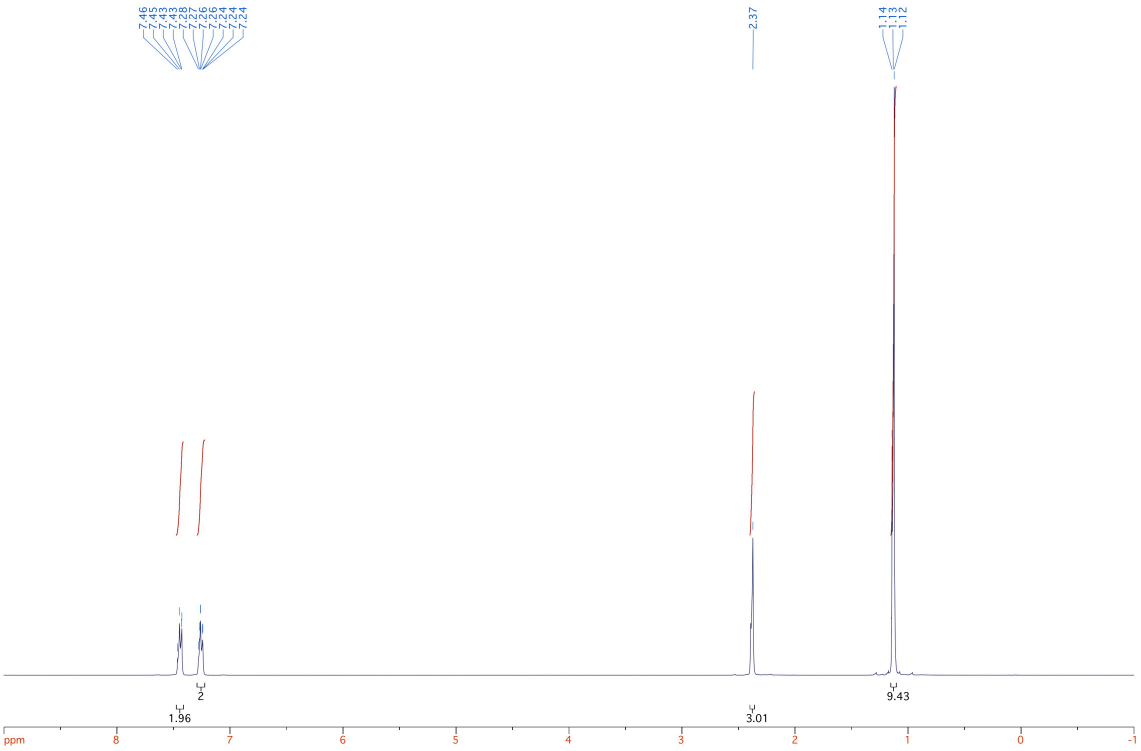
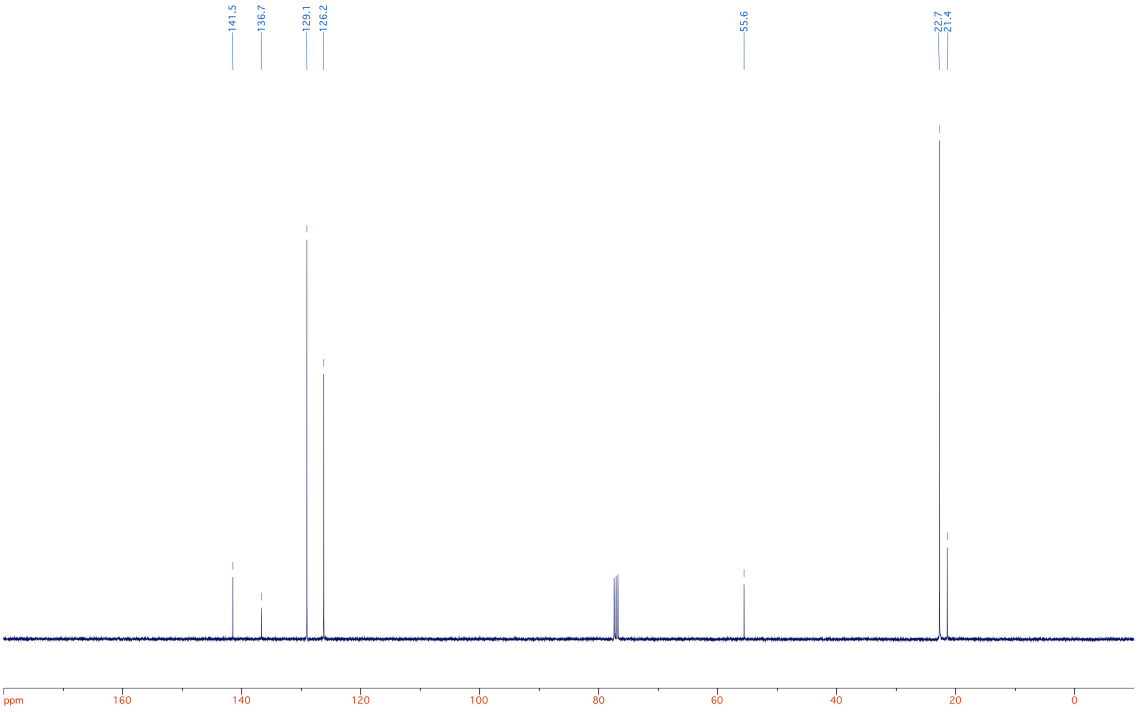
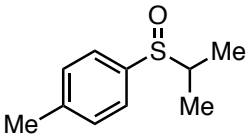
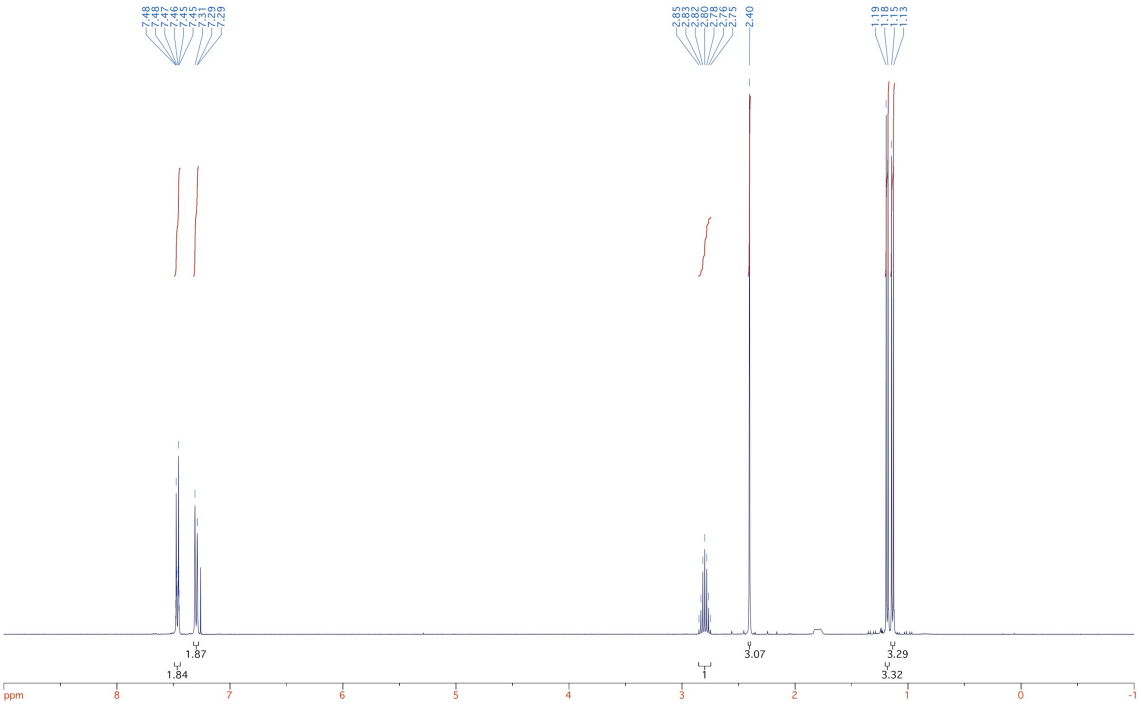


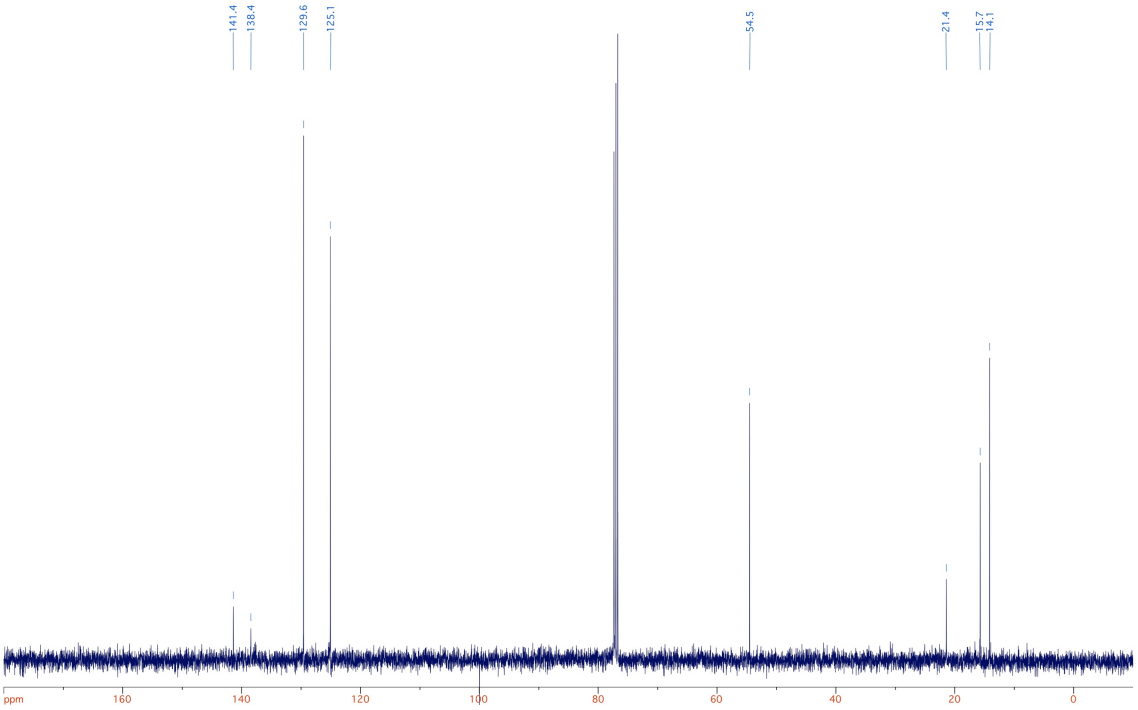




Compound **40i** and **40j**







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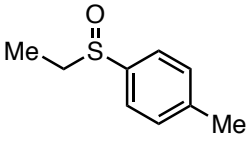
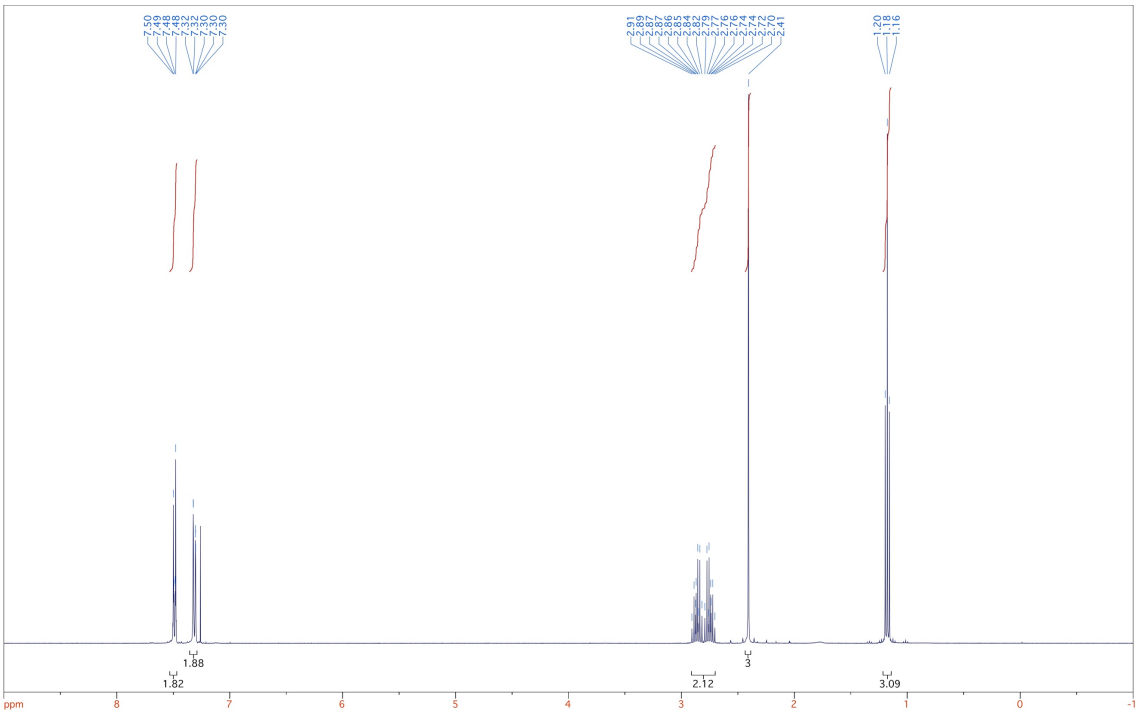
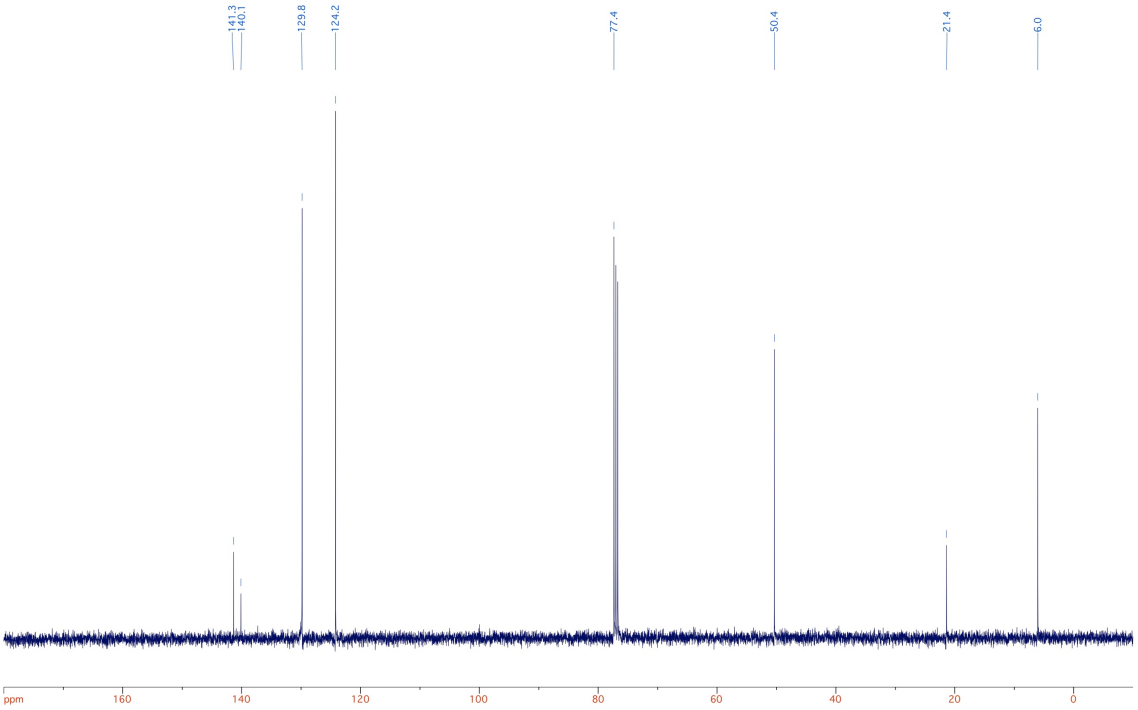
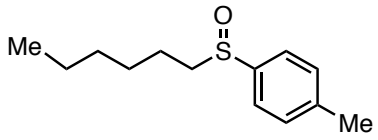
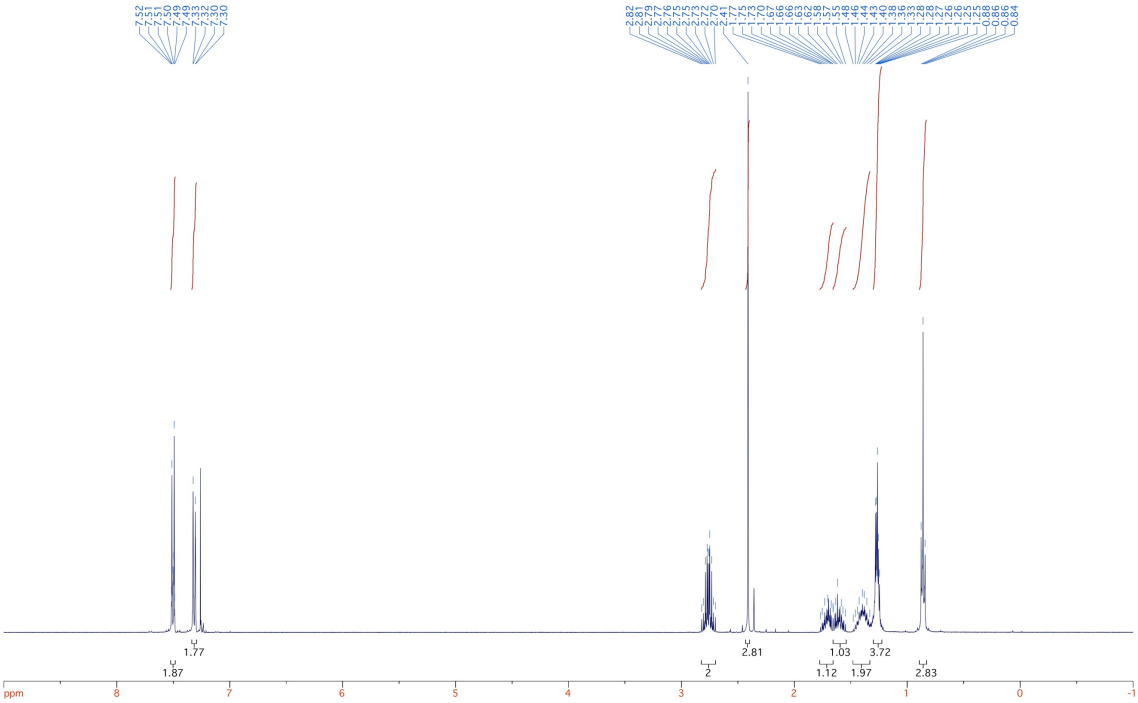


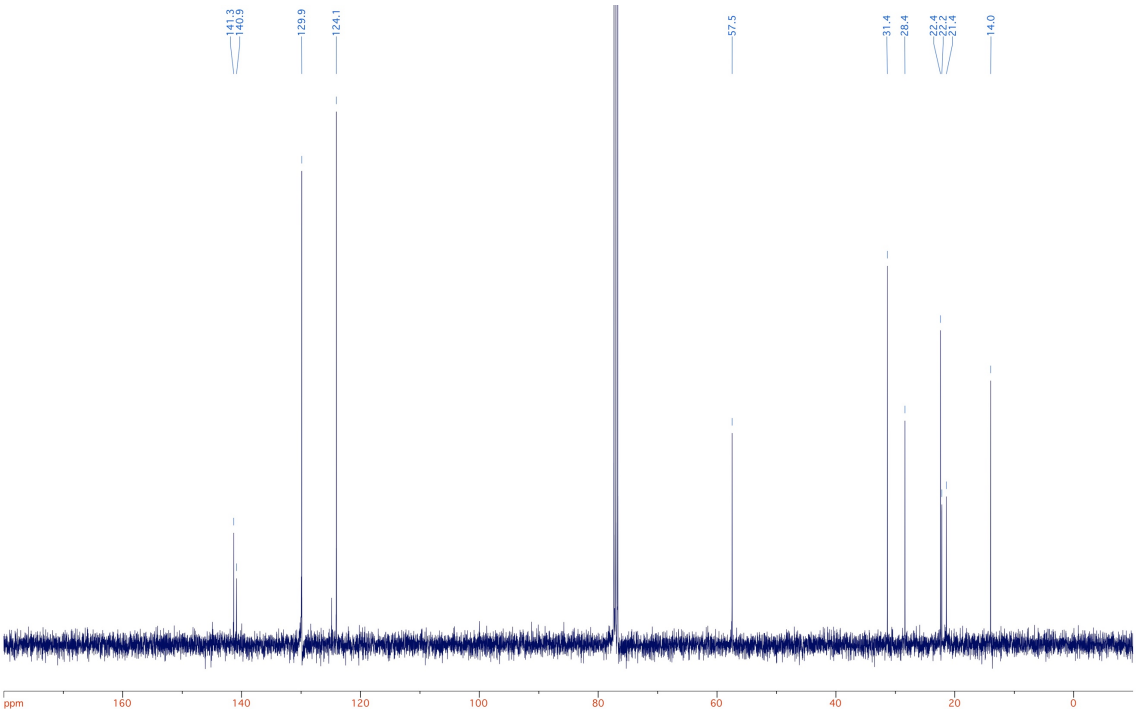




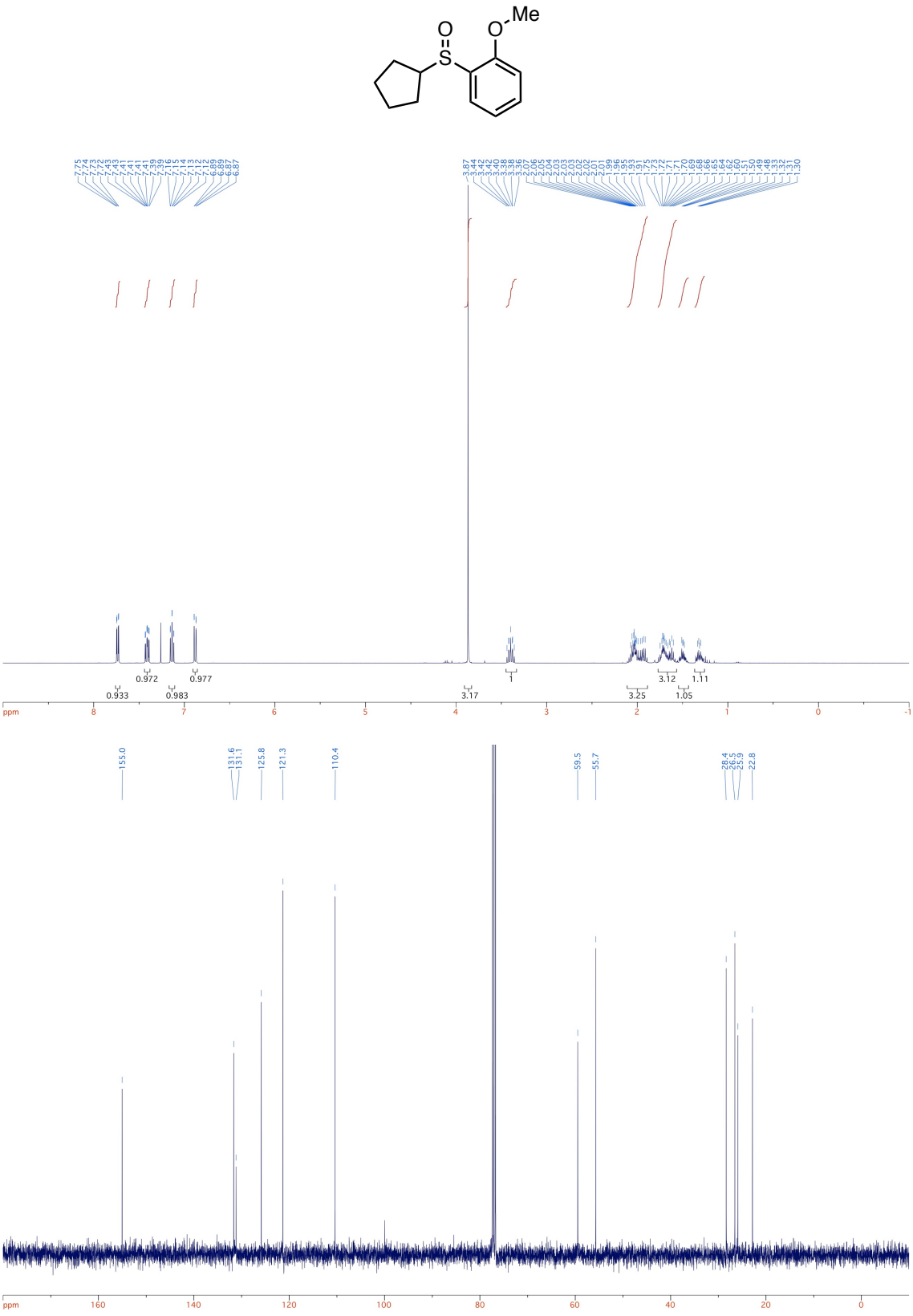
Compound **40l**



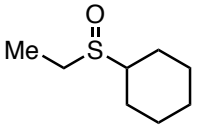


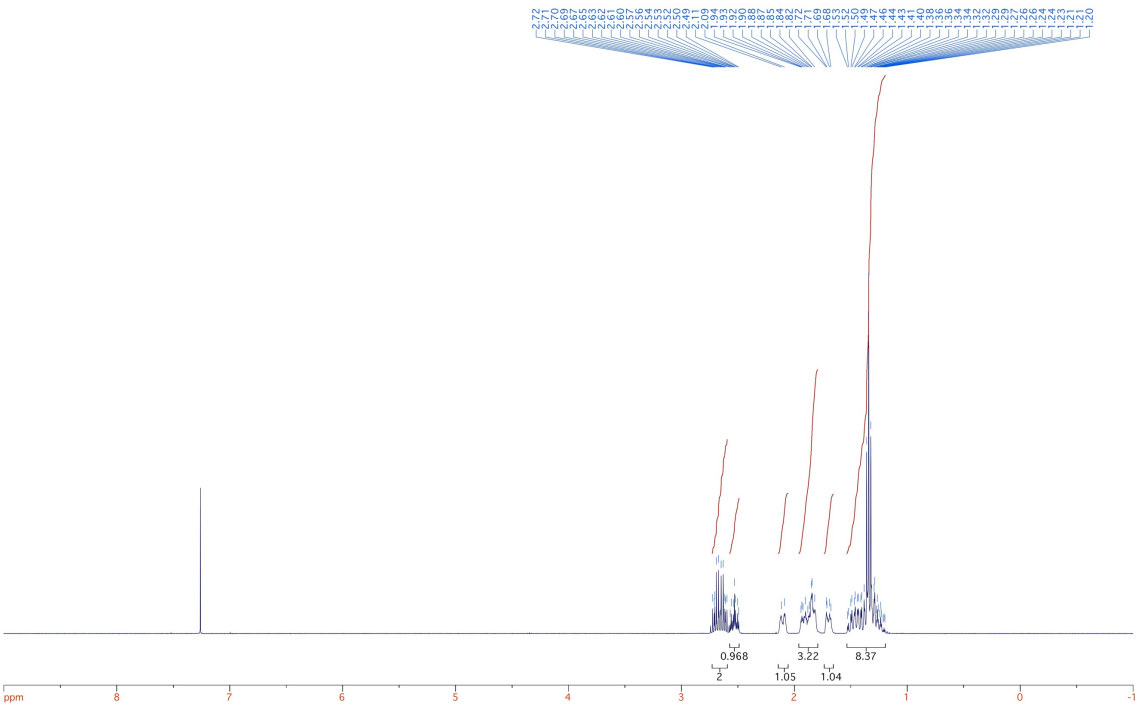


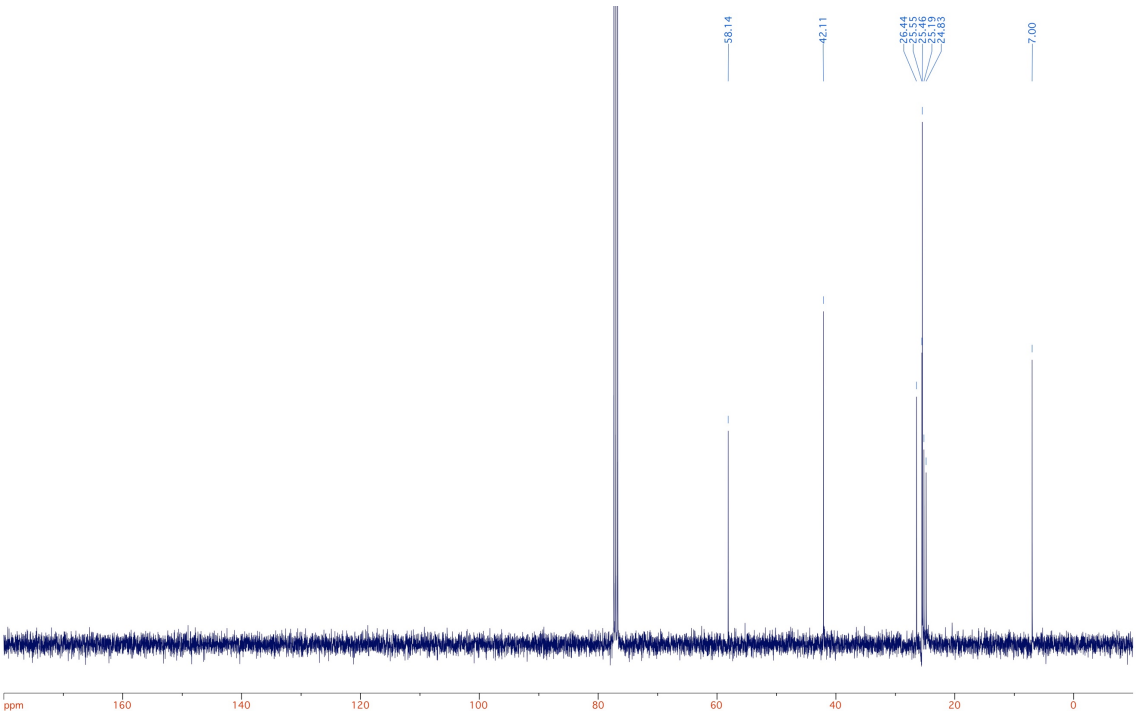
Compound **40m**



Compound **40n**

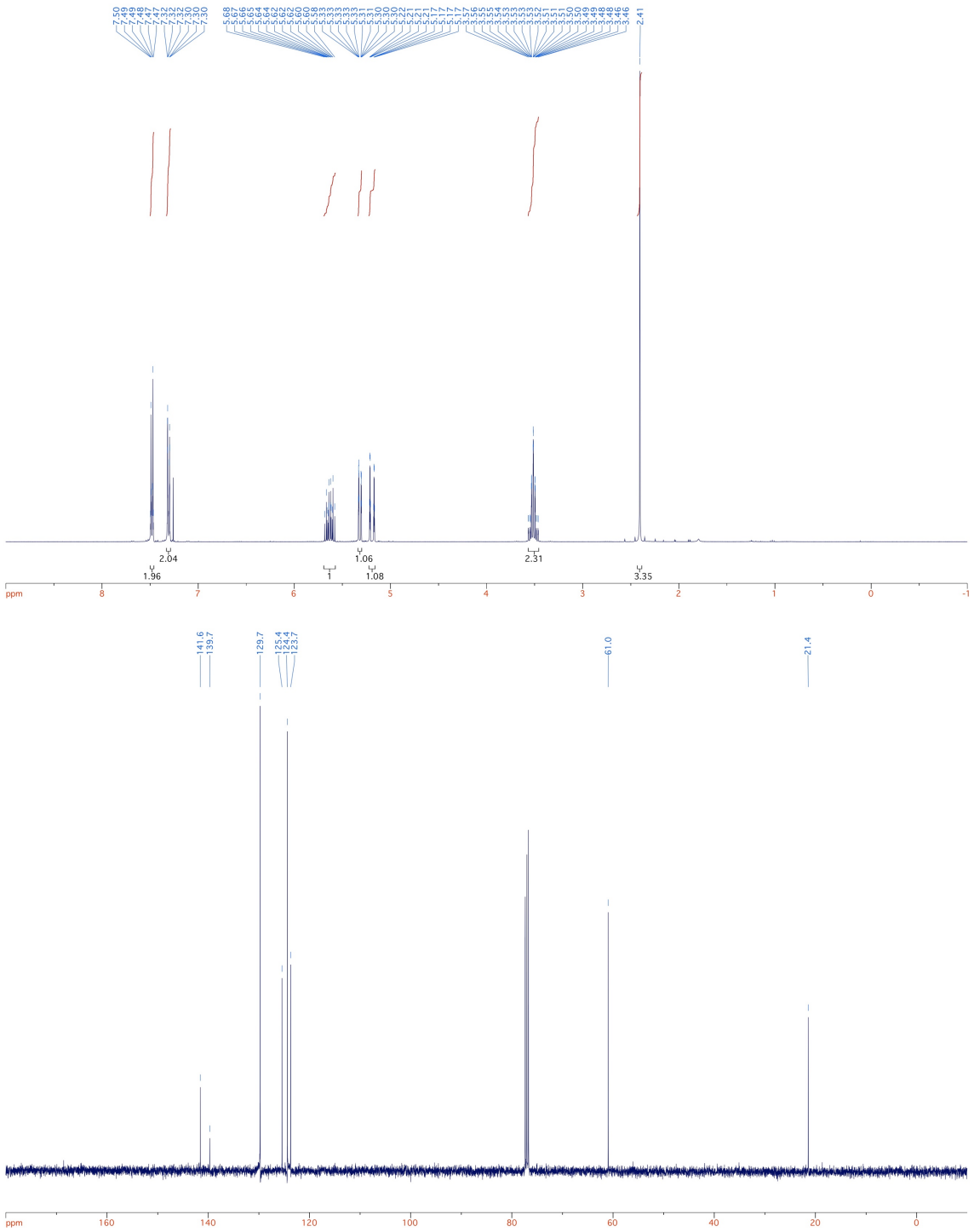






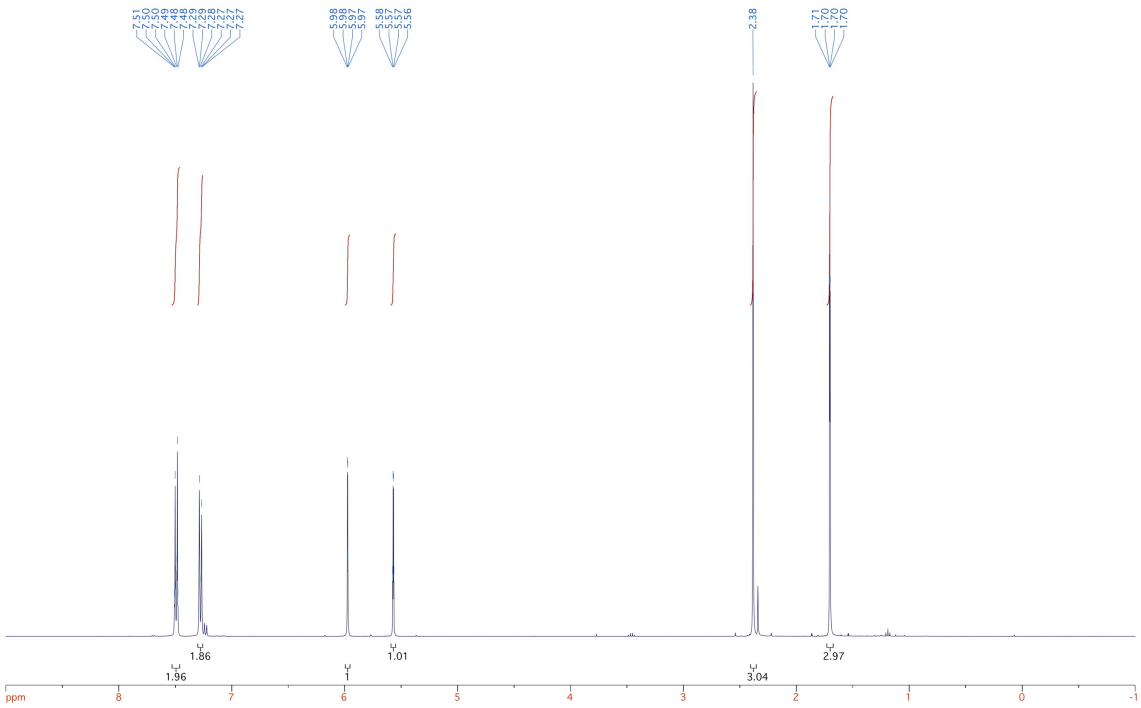
Compound **40o**

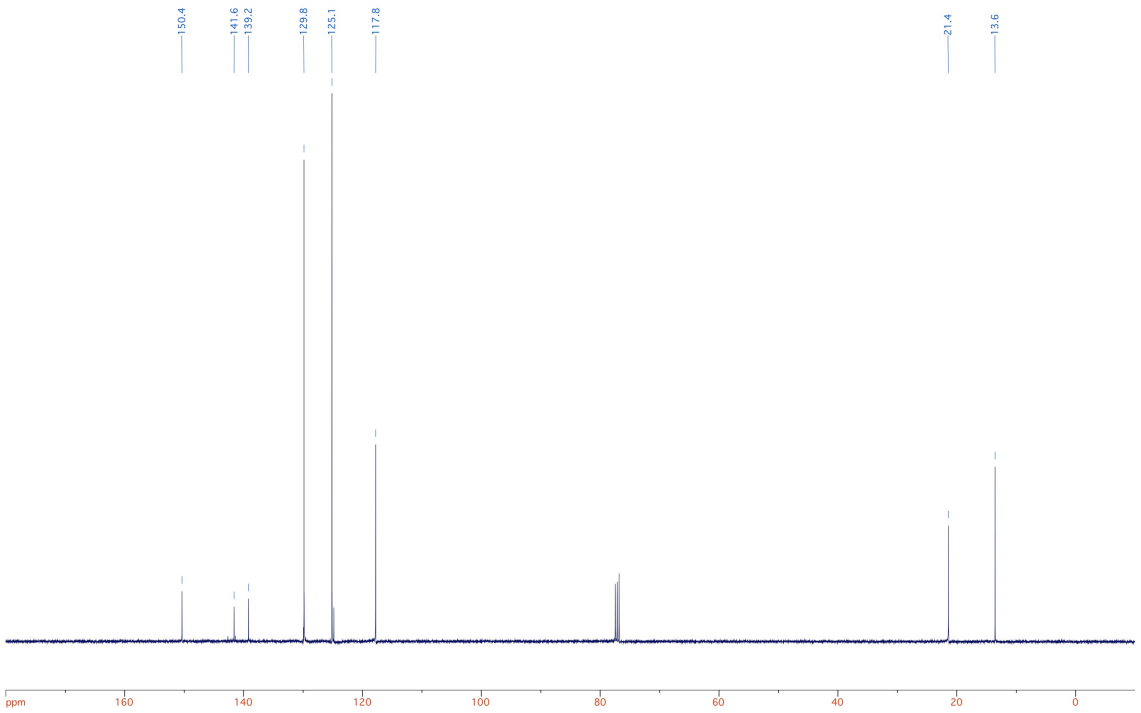




Compound **40p**

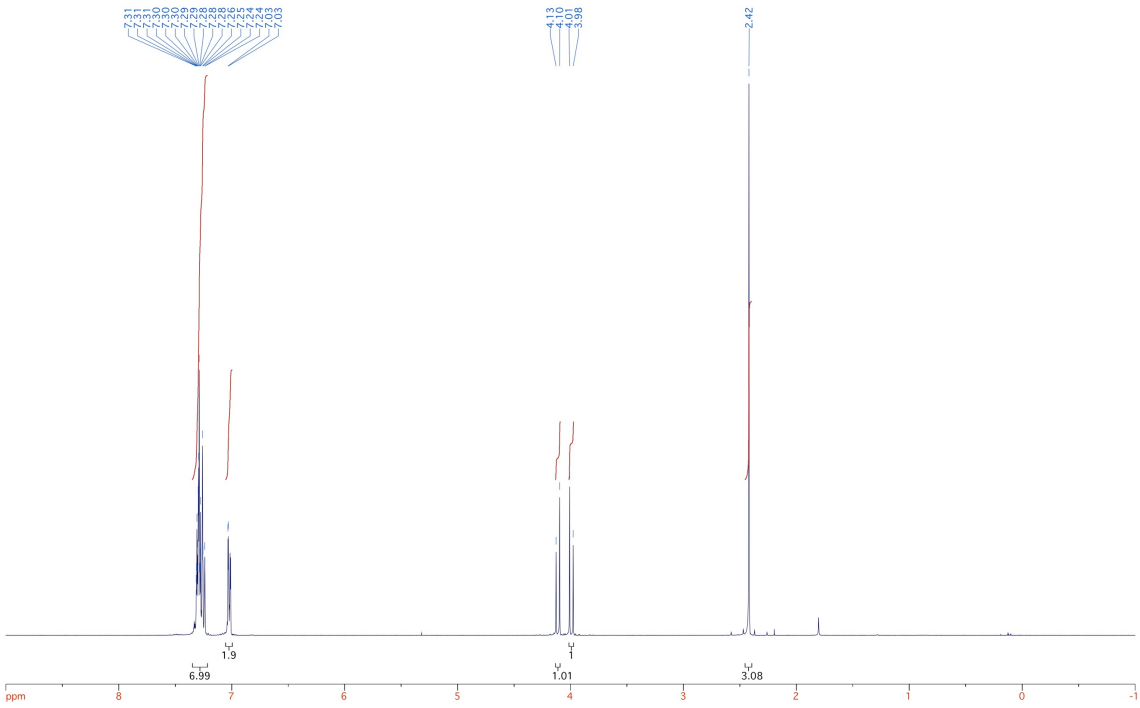


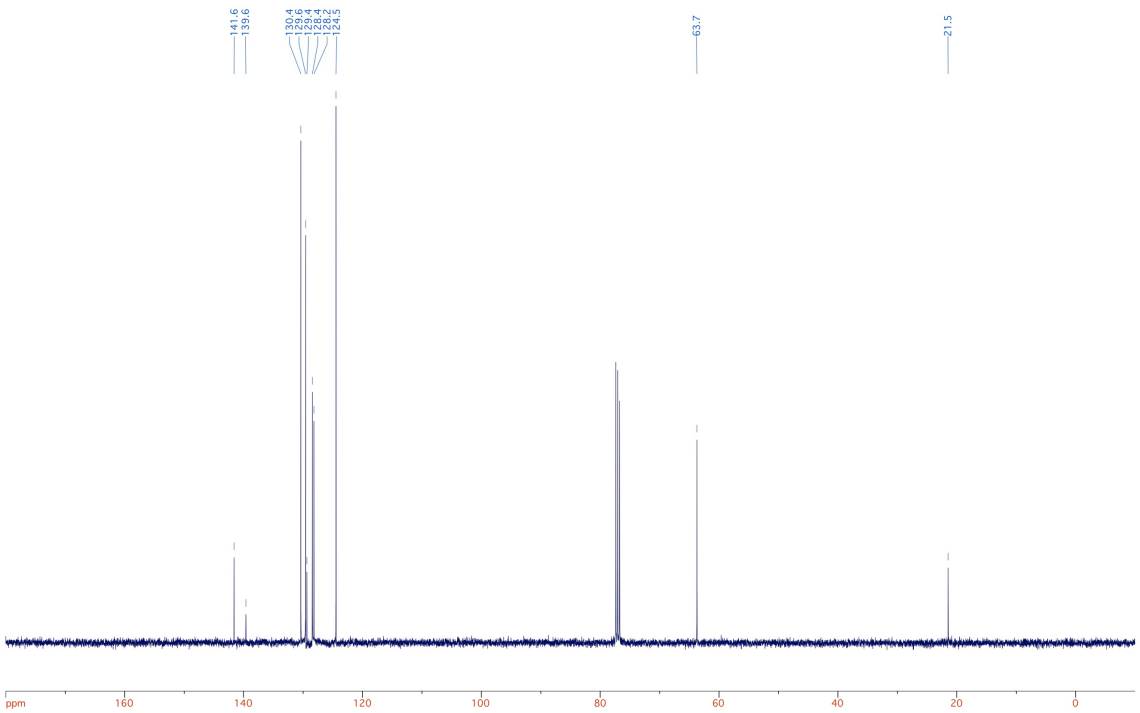




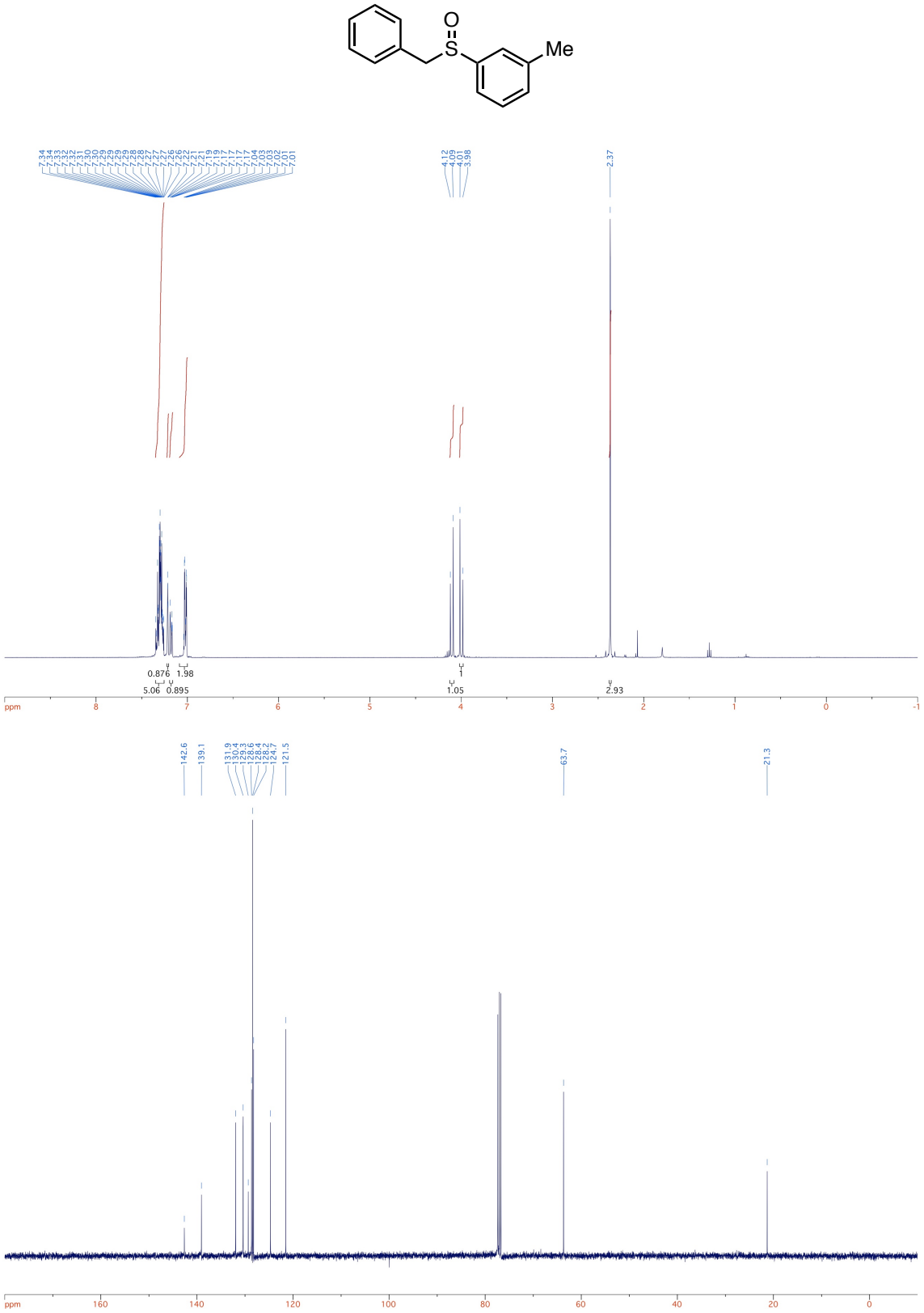
Compound **40q**



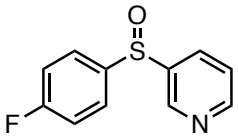


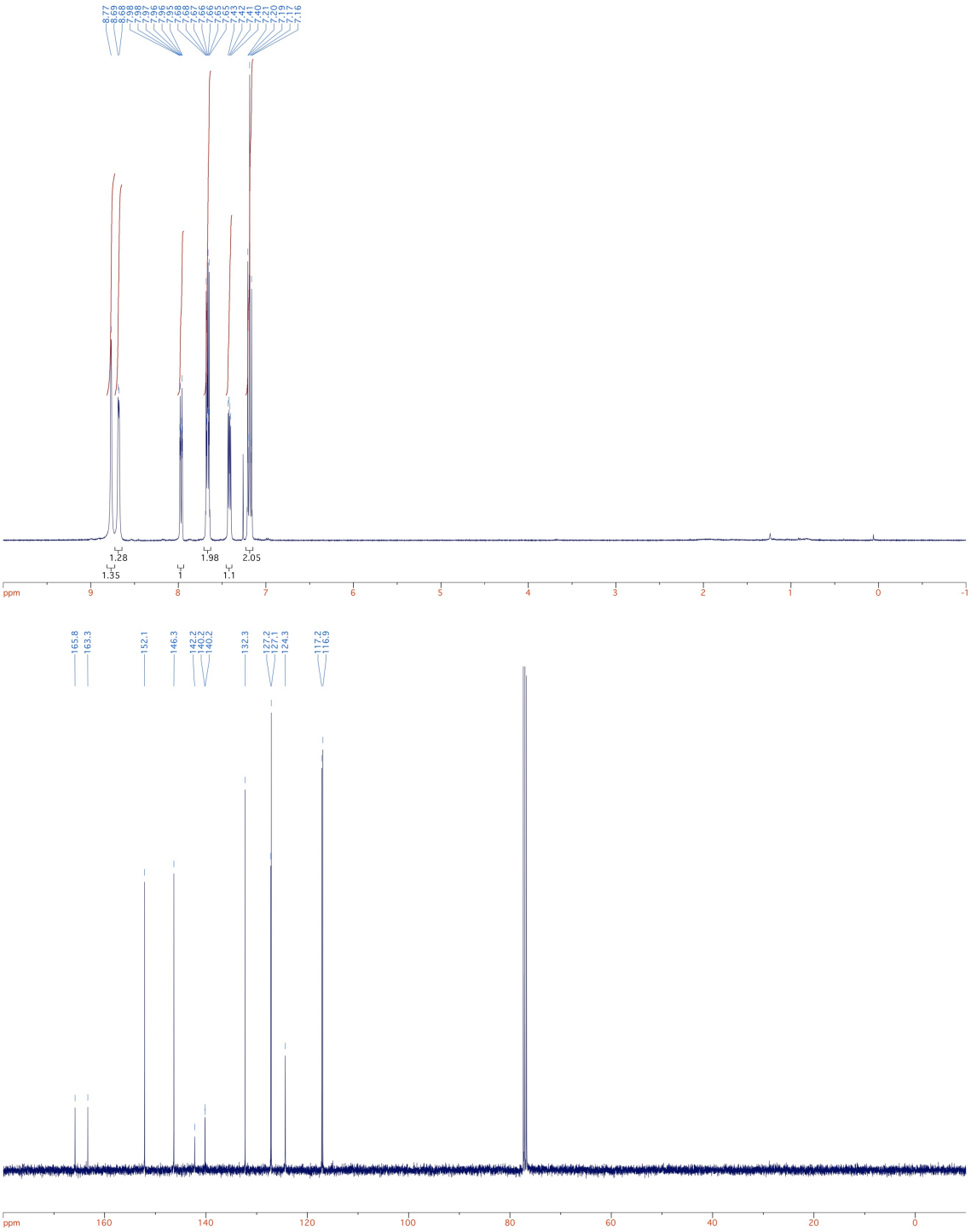


Compound **40r**

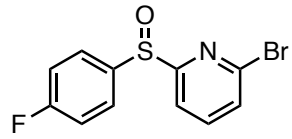


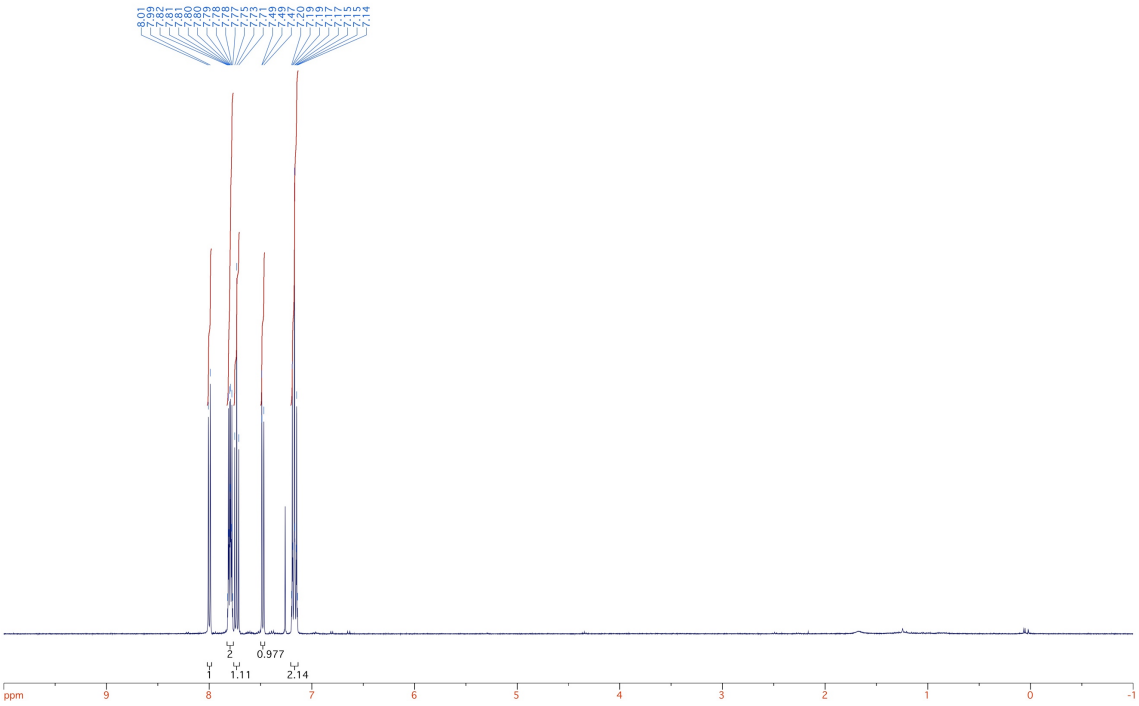
Compound **40s**

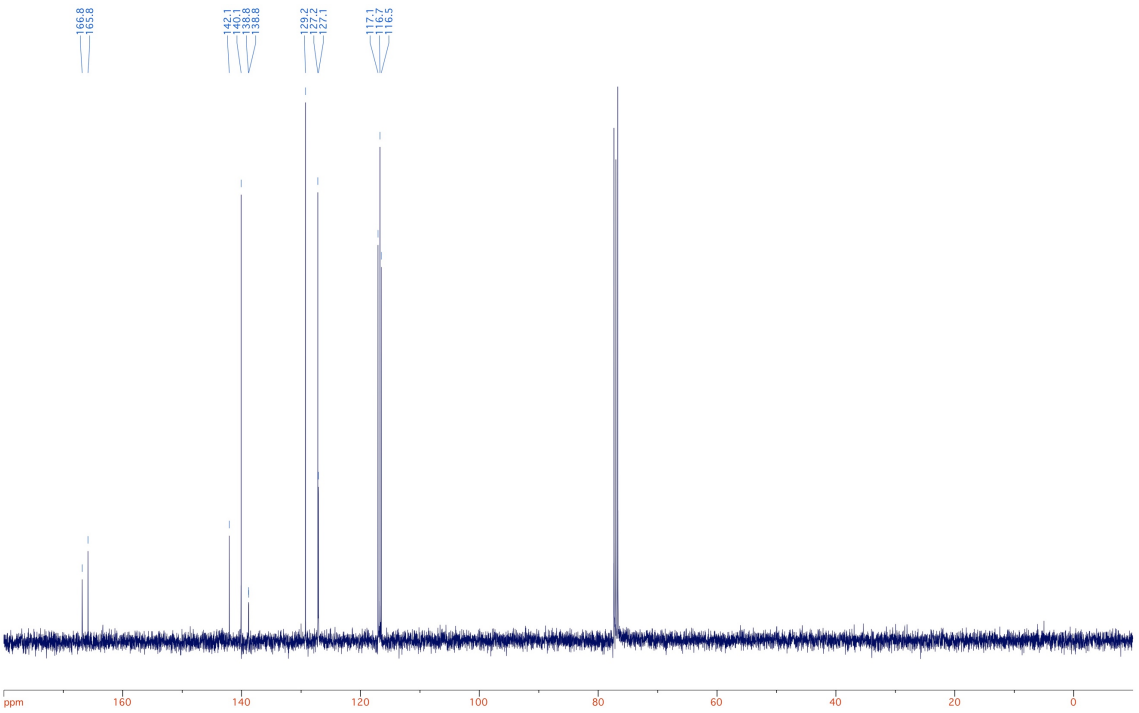




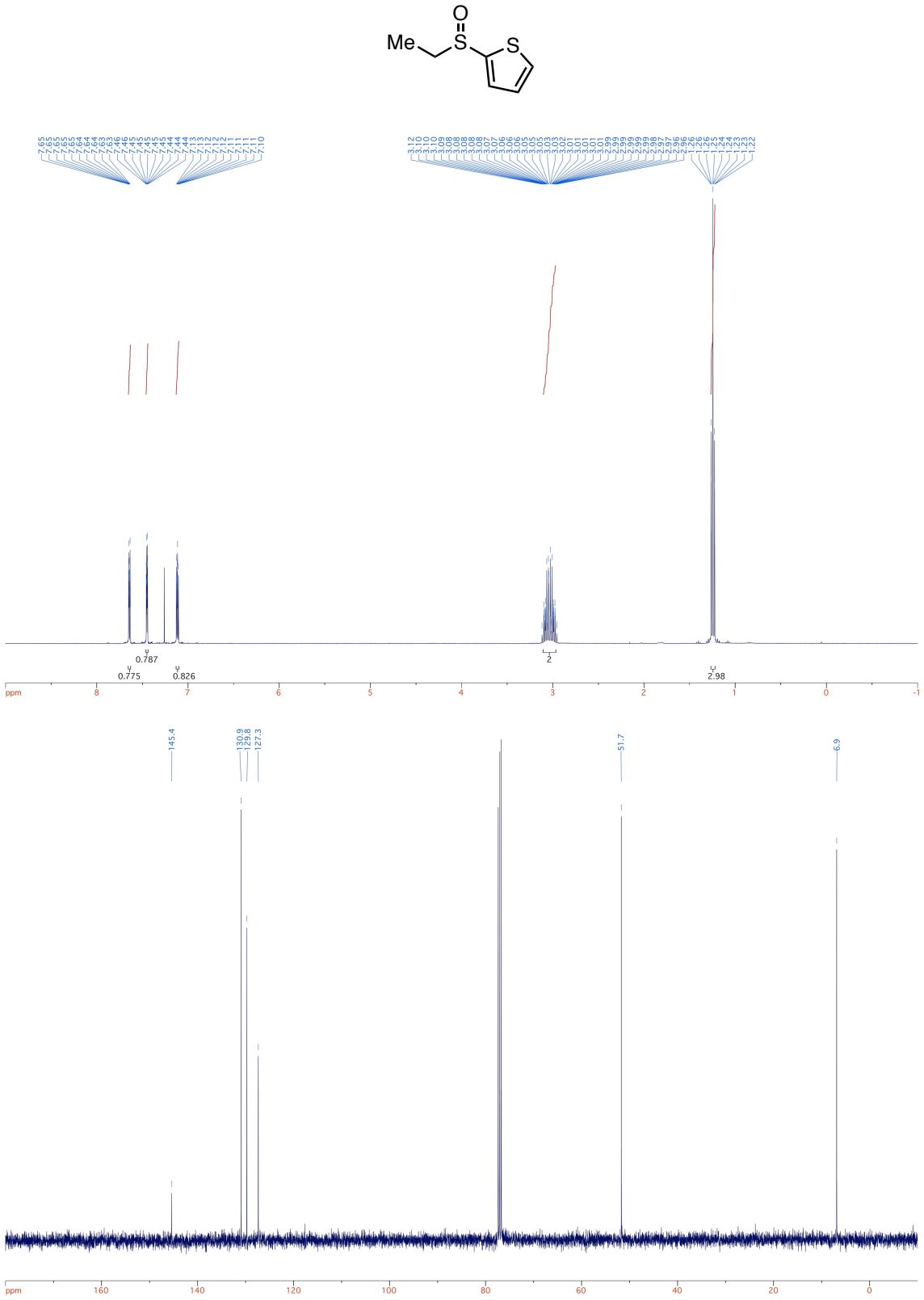
Compound **40t**



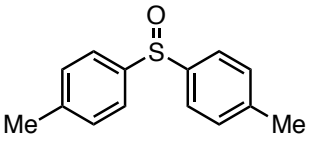


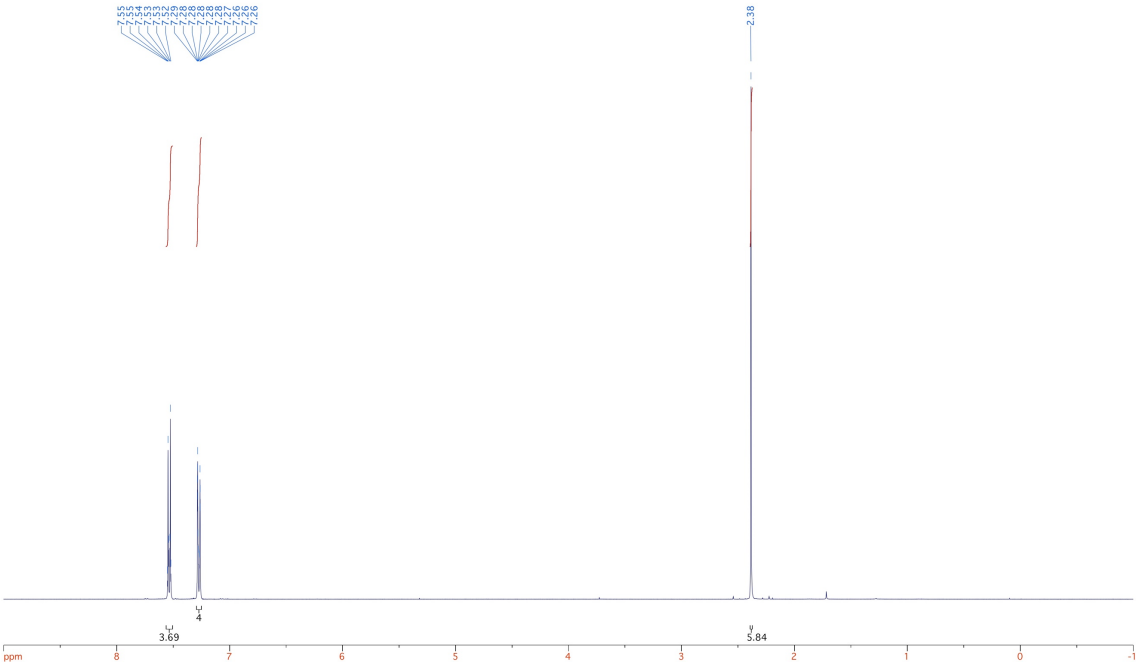


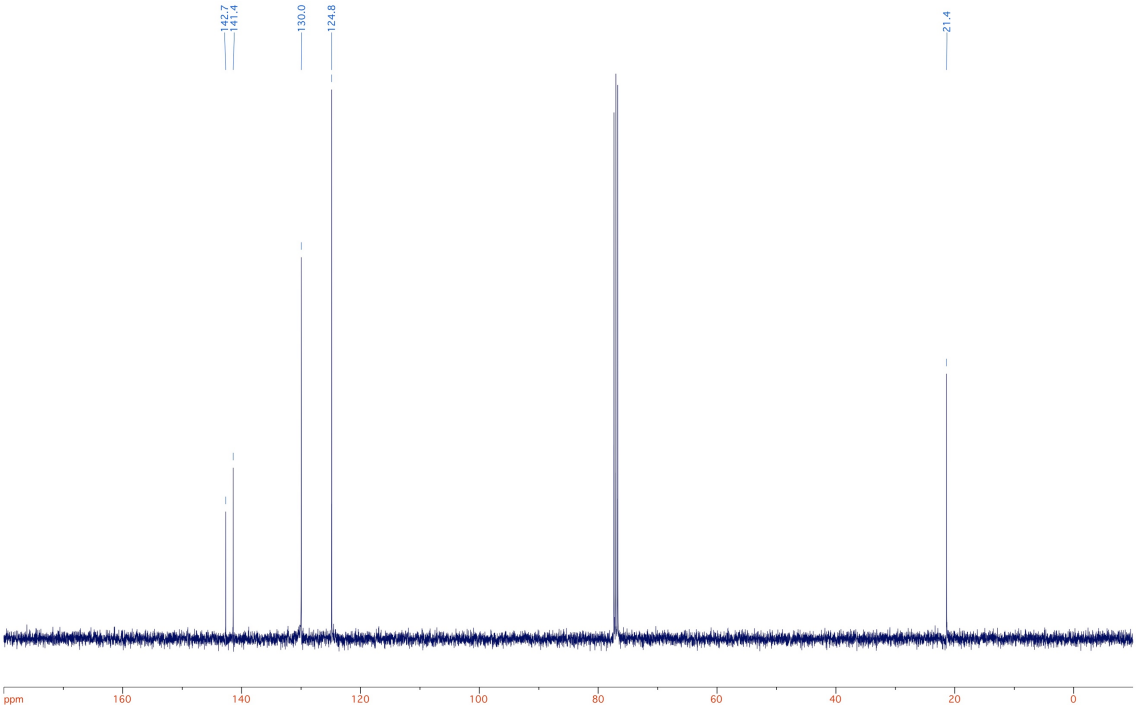
Compound **40u** and compound **42c**



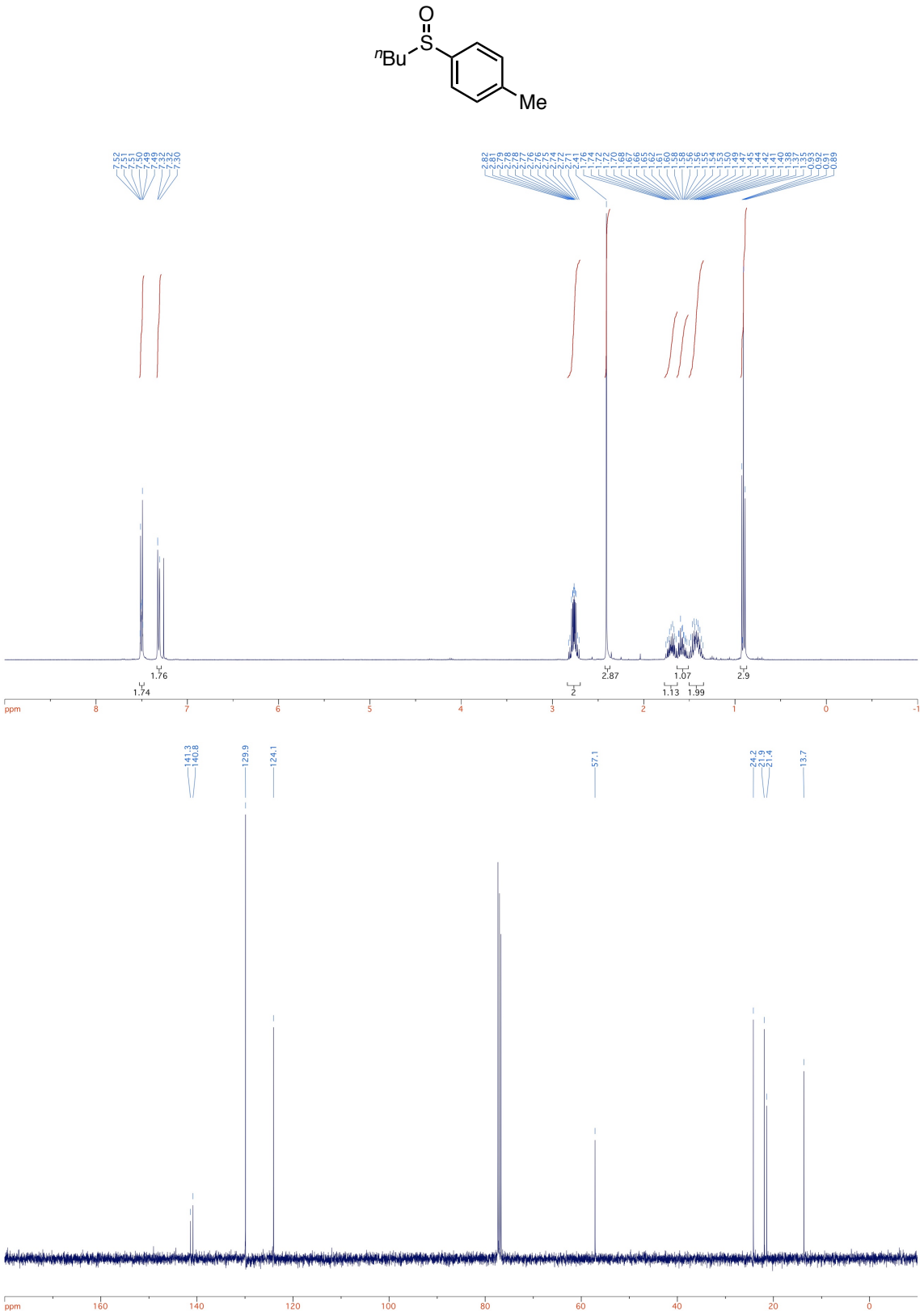
Compound **41a**



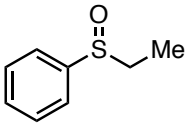


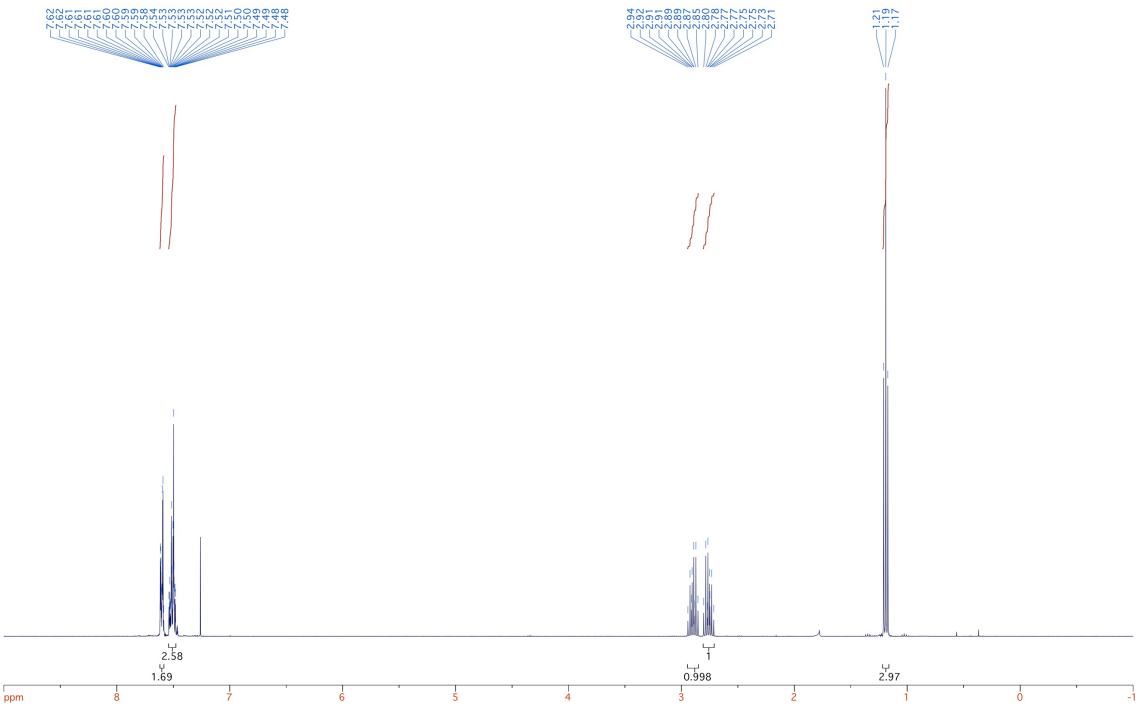


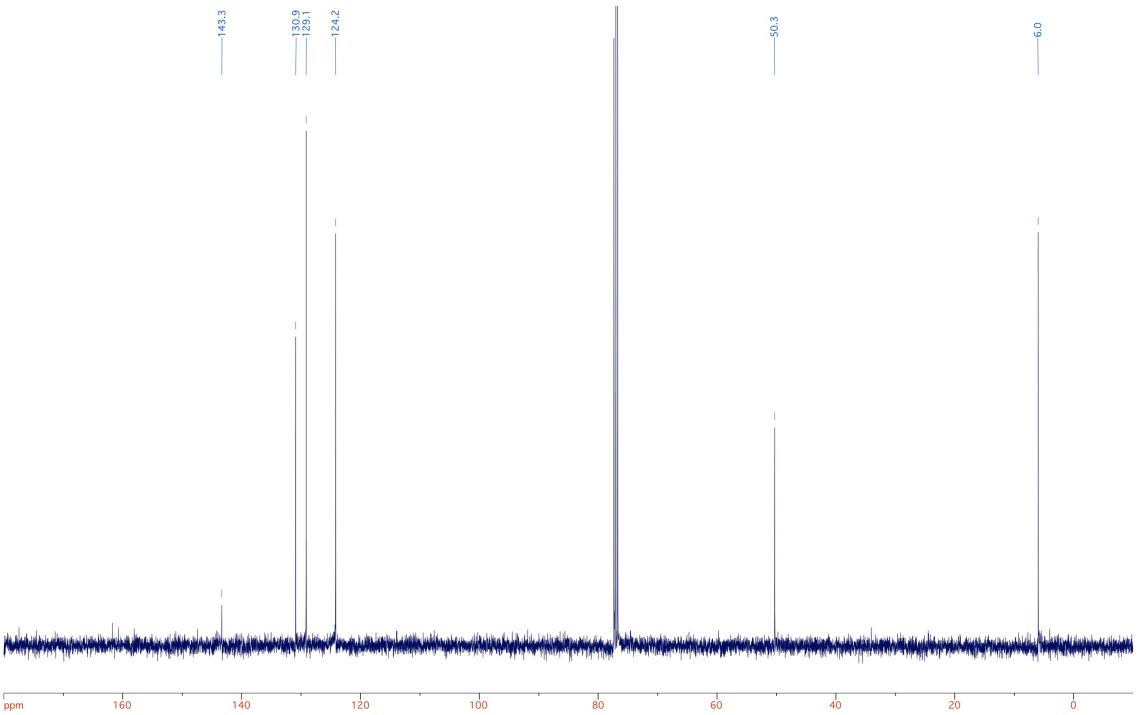
Compound **42a** and **42d**



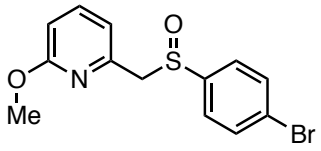
Compound **42b**

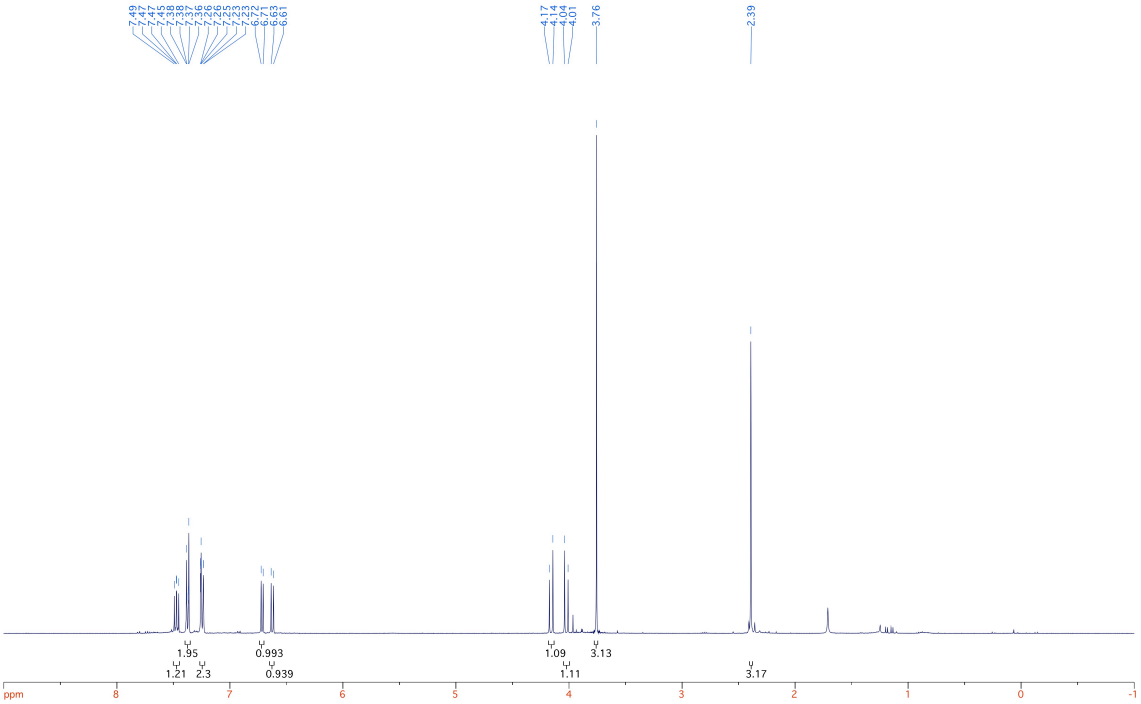


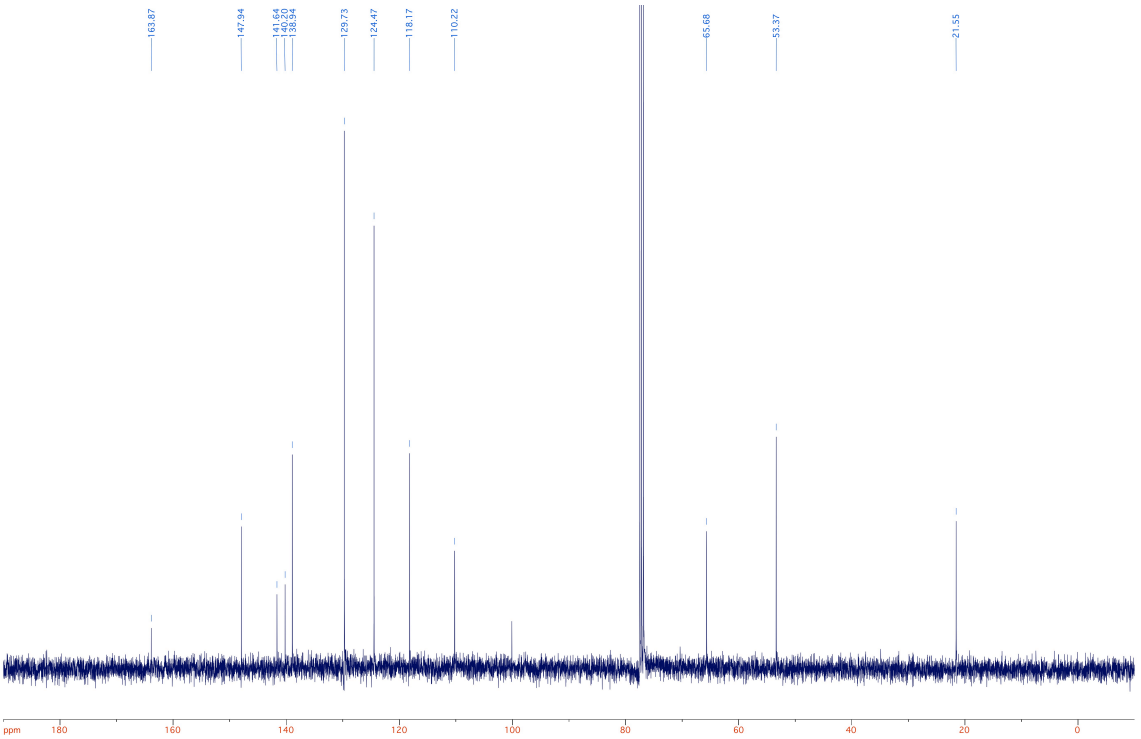




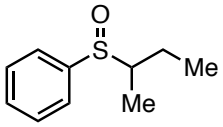
Compound **42e**

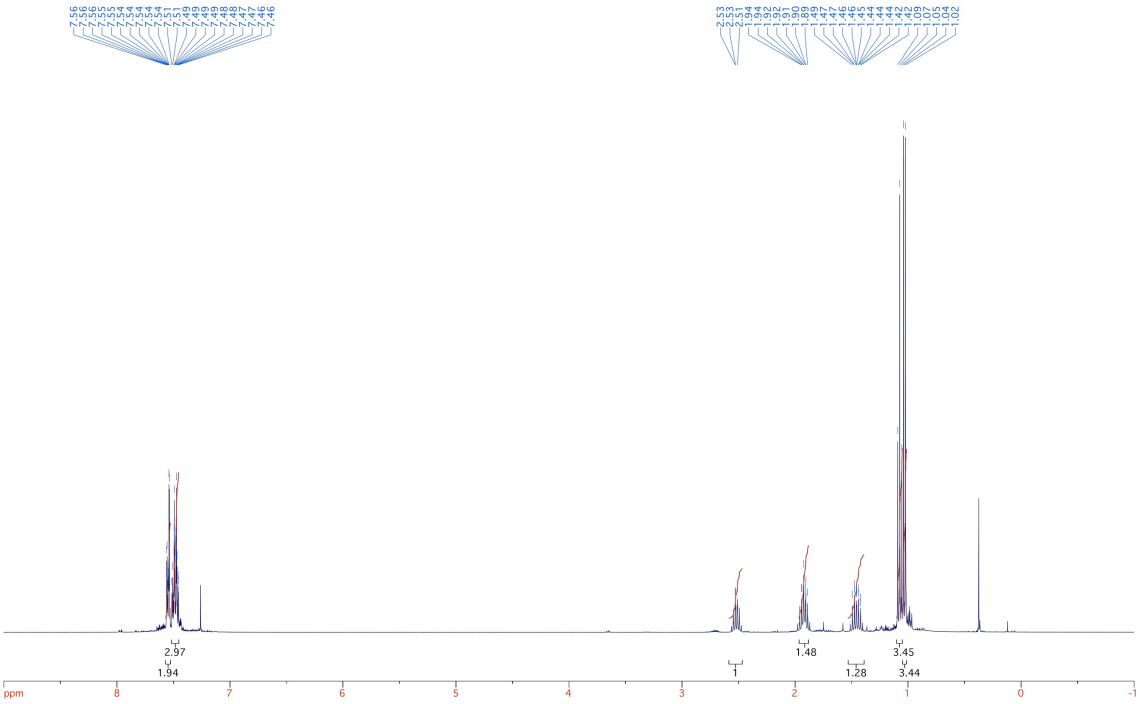


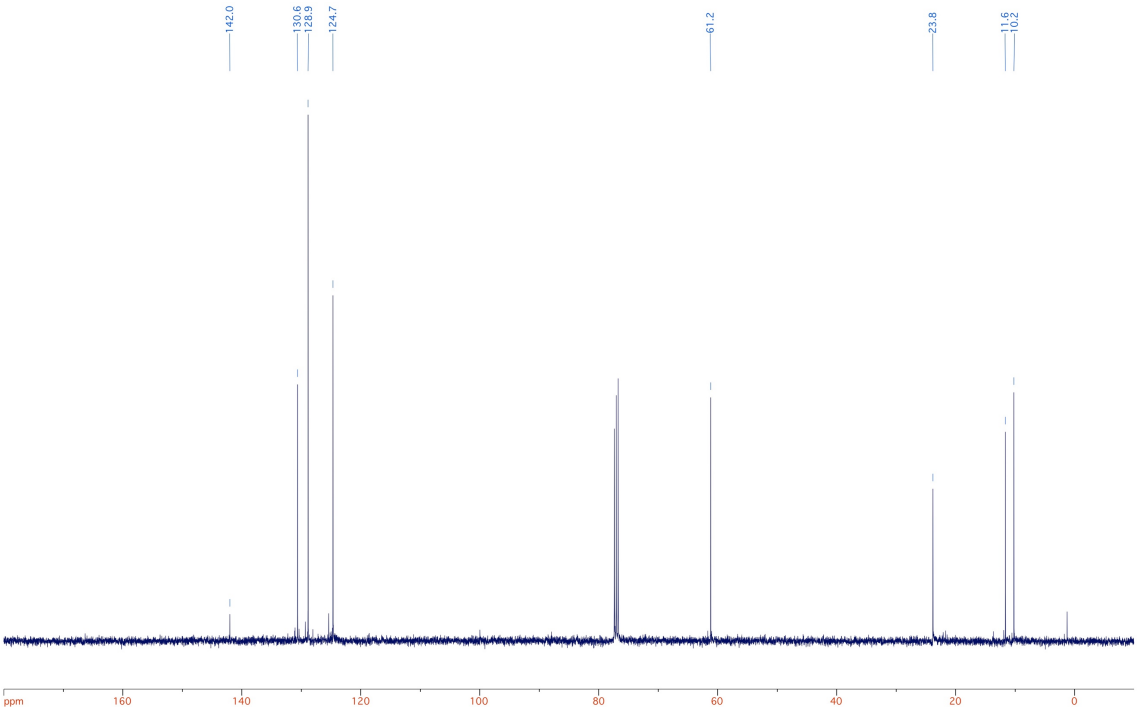




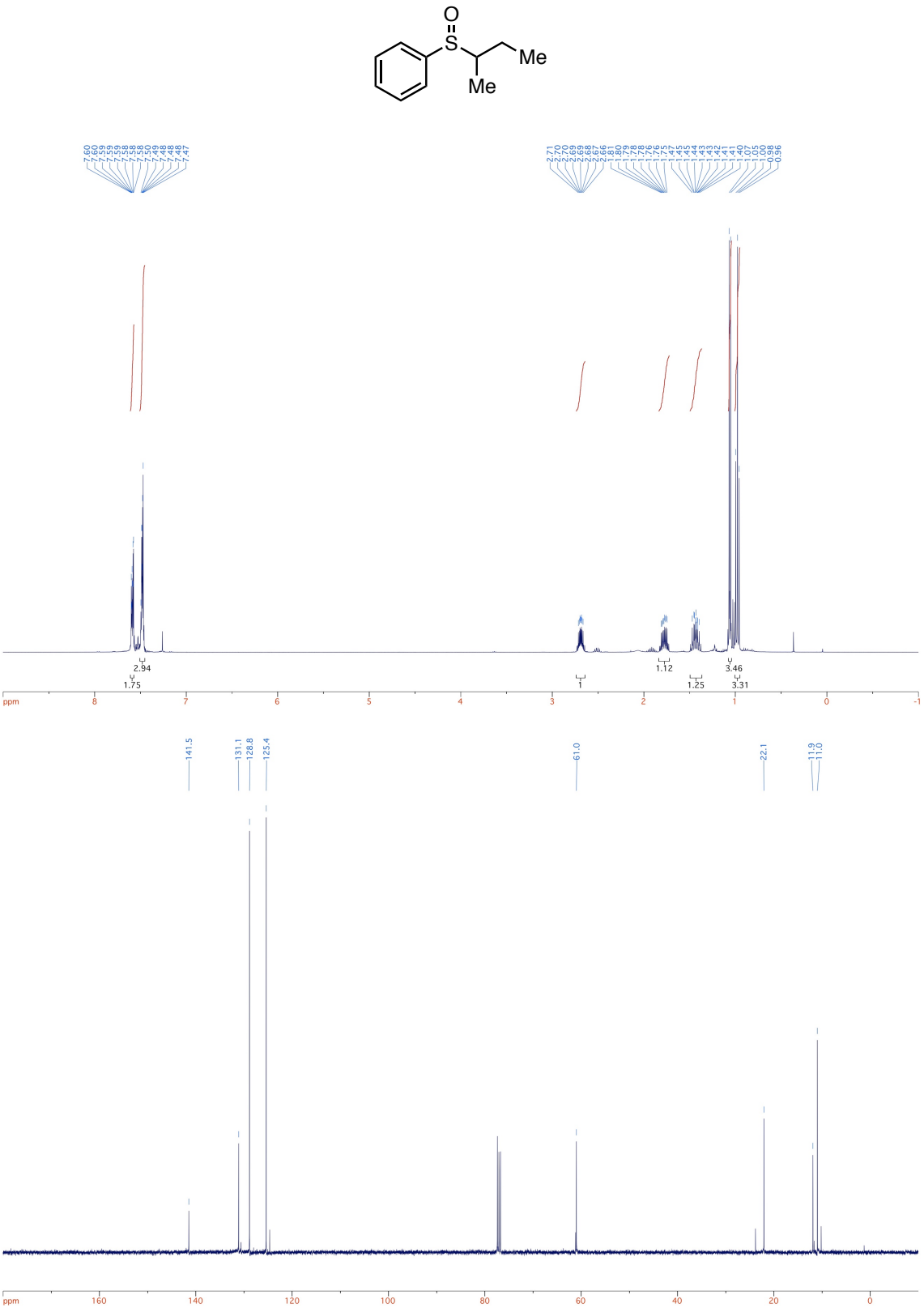
Compound **42f, Diastereomer 1**



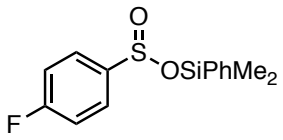


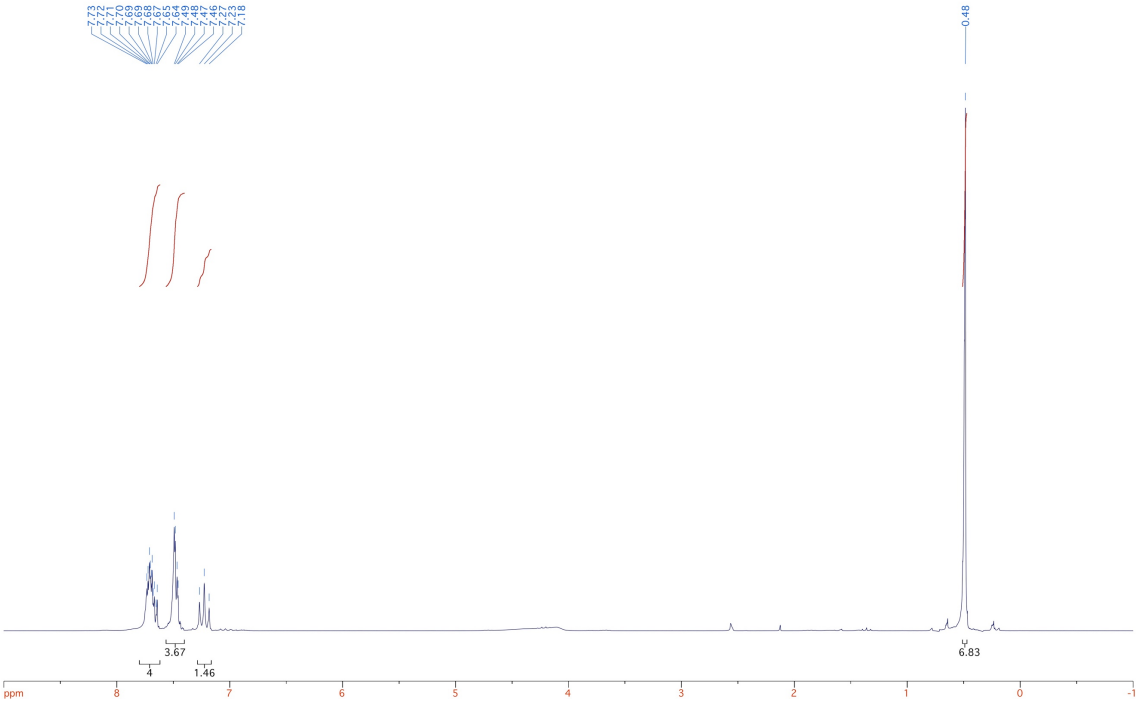


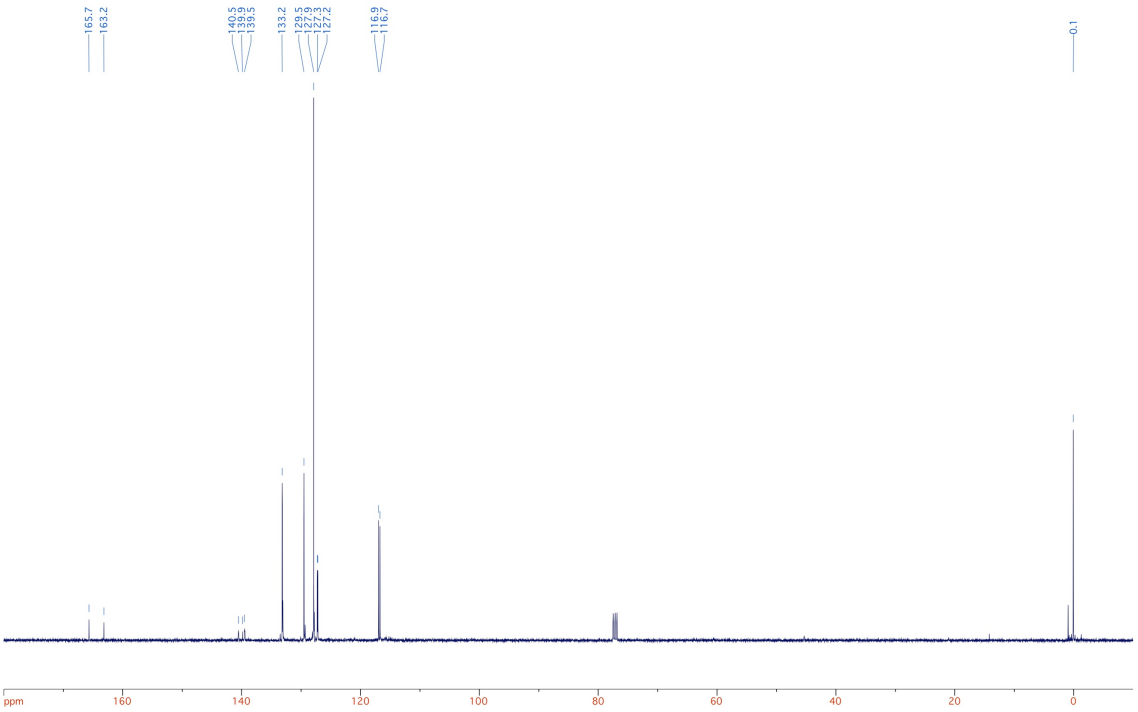
Compound **42f, Diastereomer 2**



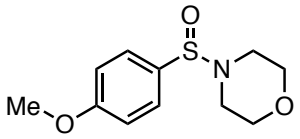
Compound **43**

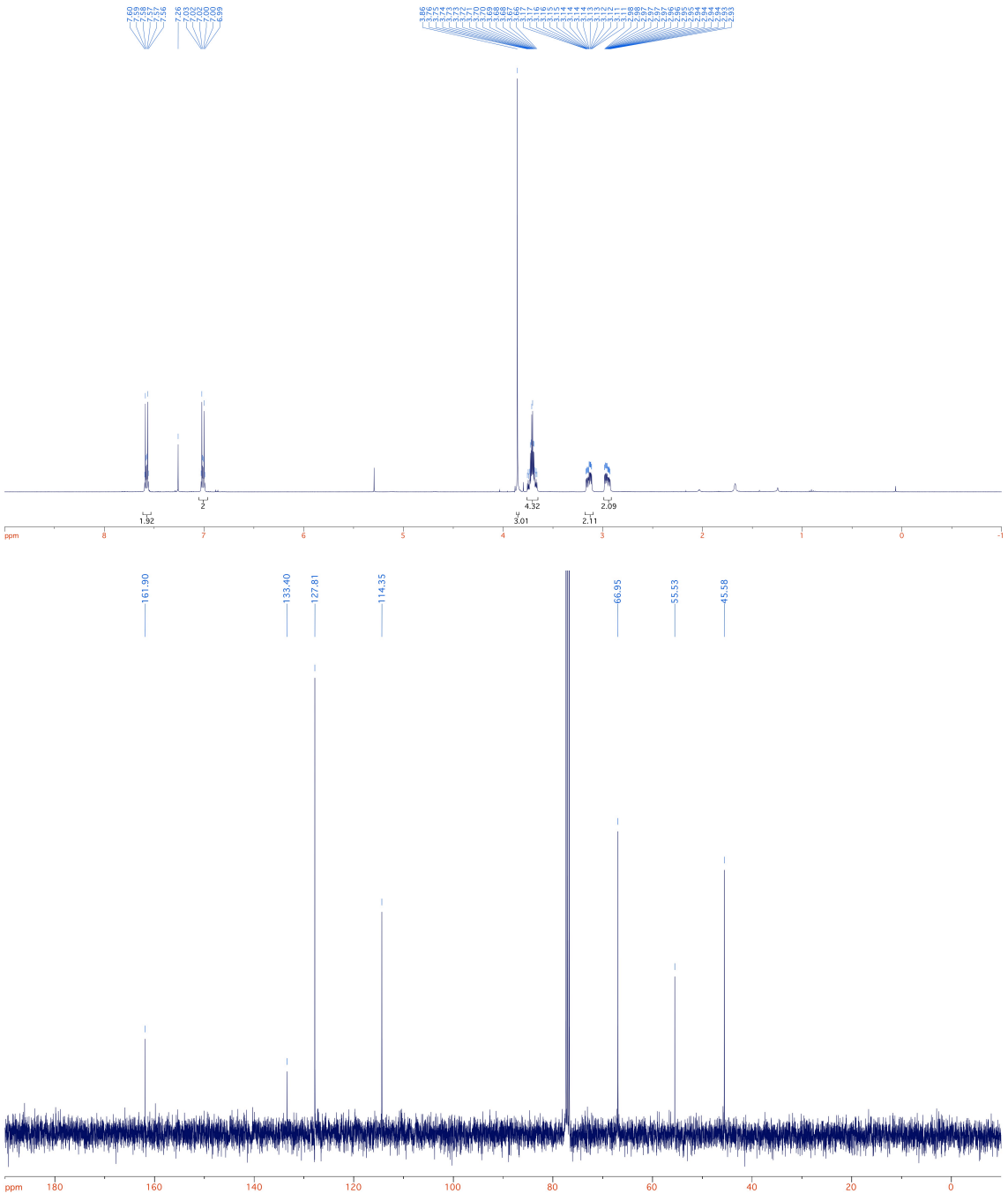

O
S
OSiPhMe2
F


7.73
7.72
7.71
7.70
7.69
7.68
7.67
7.65
7.64
7.49
7.48
7.47
7.46
7.23
7.18
0.48
3.67
4
1.46
6.83
ppm
8
7
6
5
4
3
2
1
0
-1

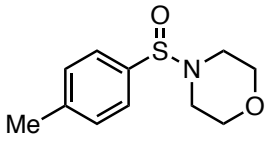

165.7
163.2
140.5
139.9
139.5
133.2
129.5
127.9
127.3
127.2
116.9
116.7
0.1
ppm
160
140
120
100
80
60
40
20
0

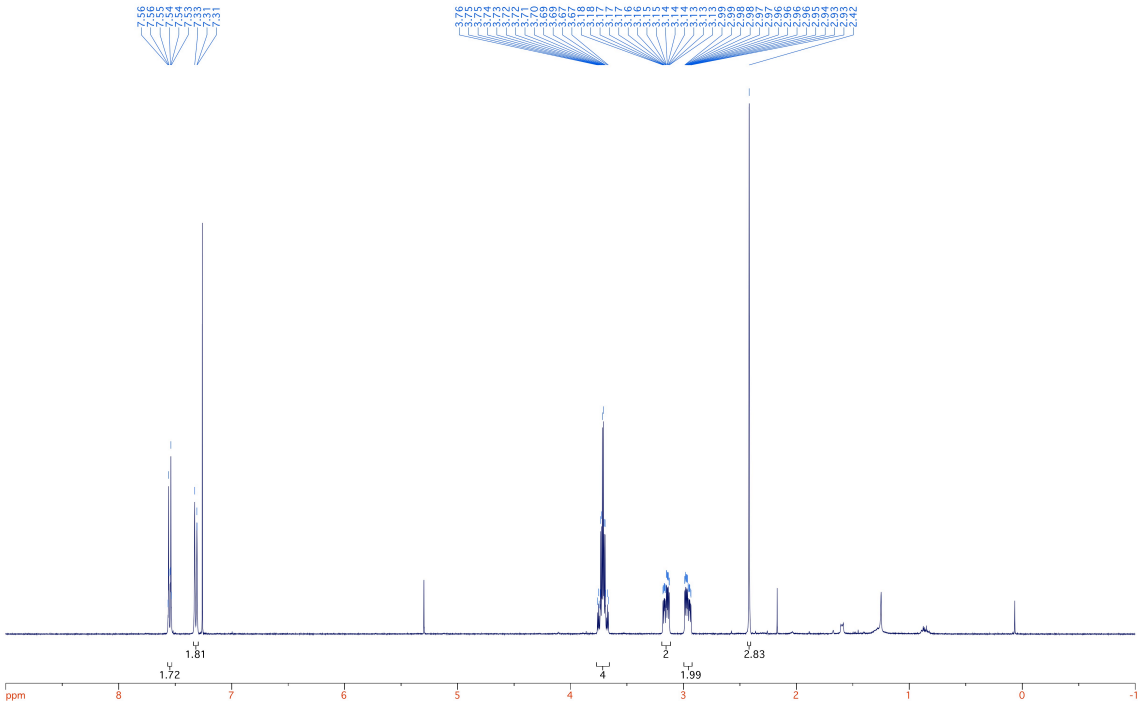
Compound **Table 2.4, Entry 1**

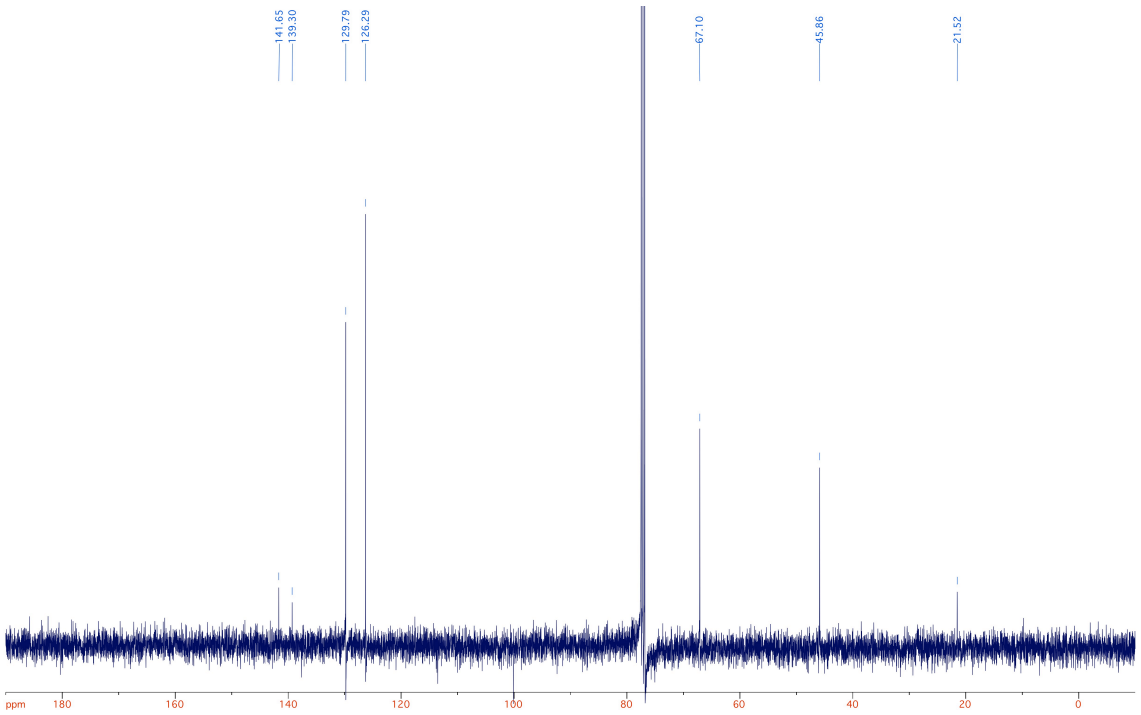




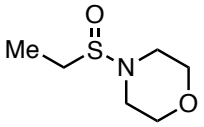
Compound **Table 2.4, entry 2**

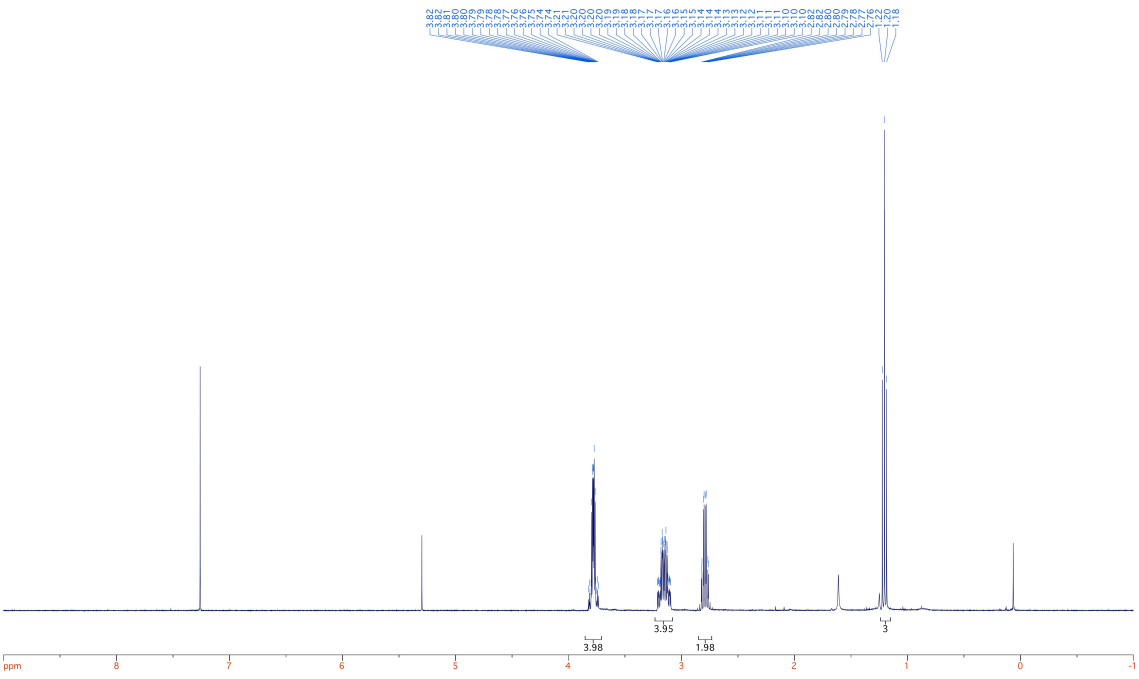


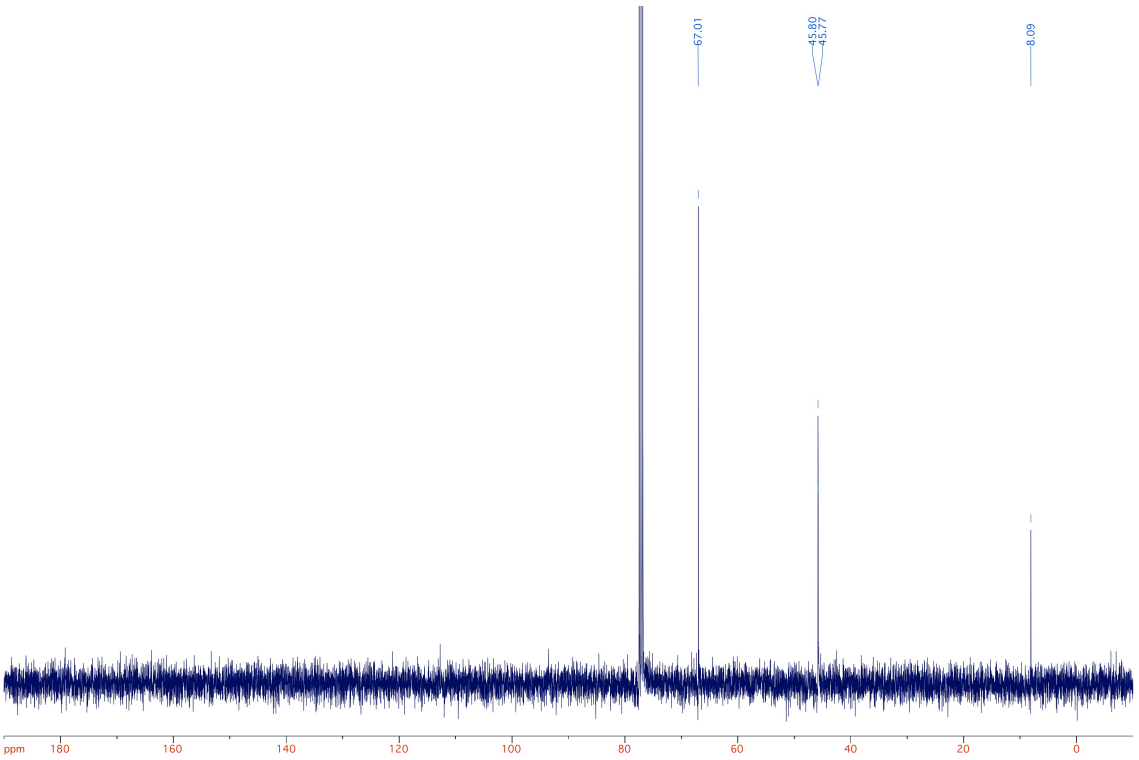




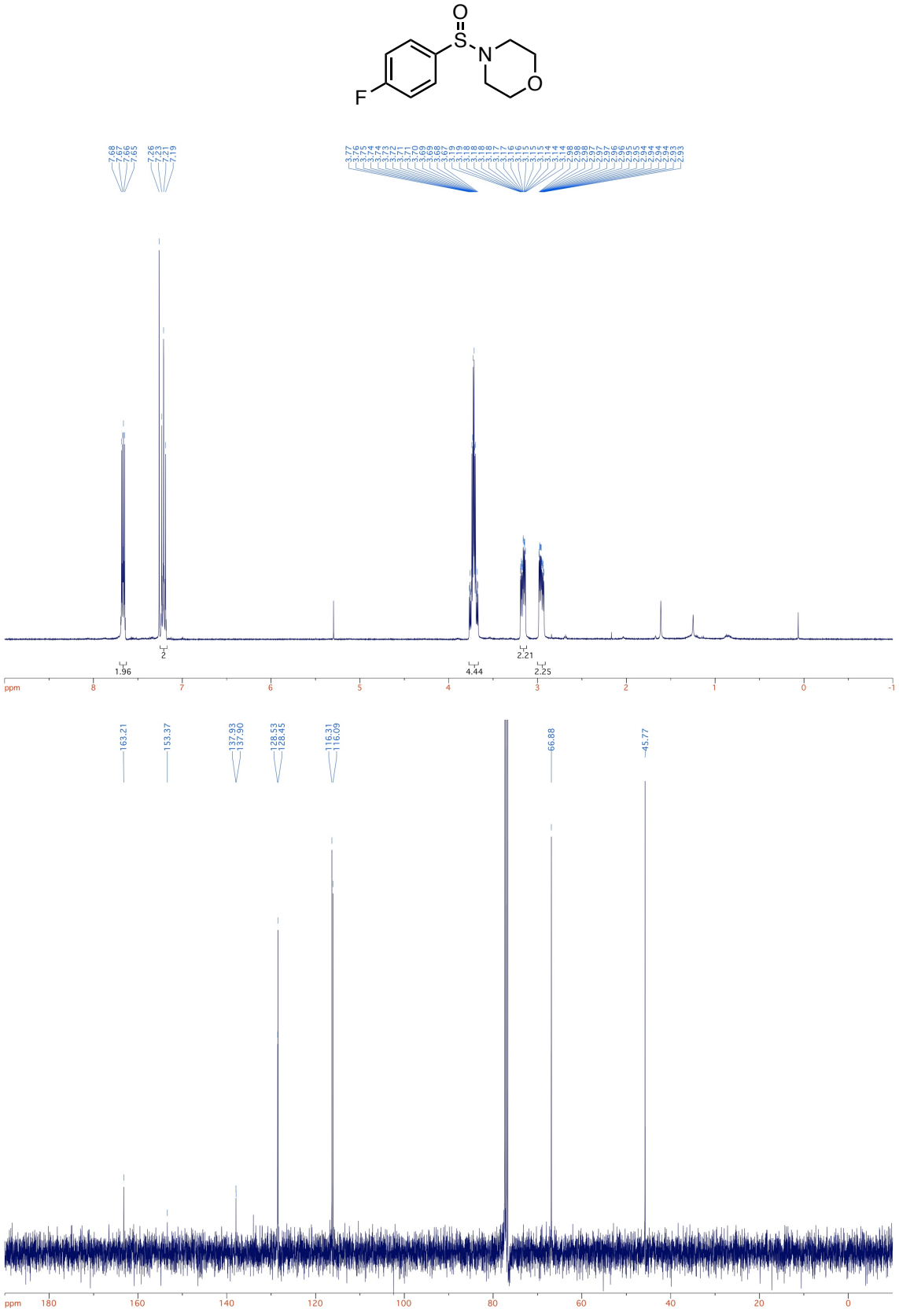
Compound **Table 2.4, entry 4**



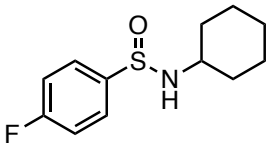


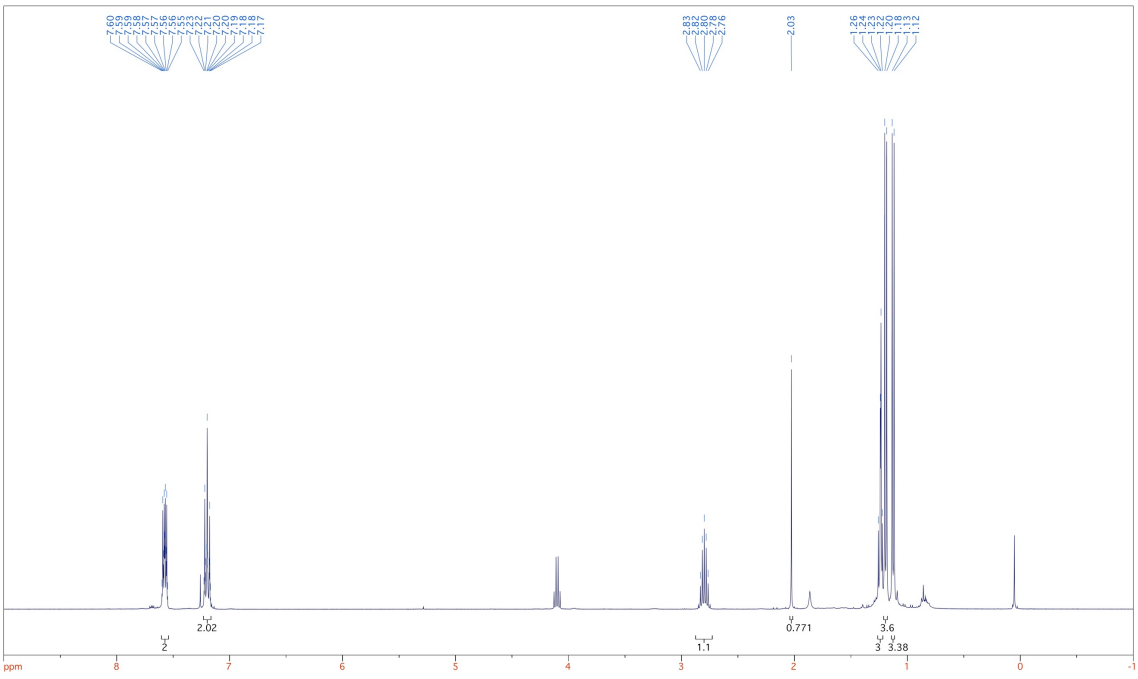


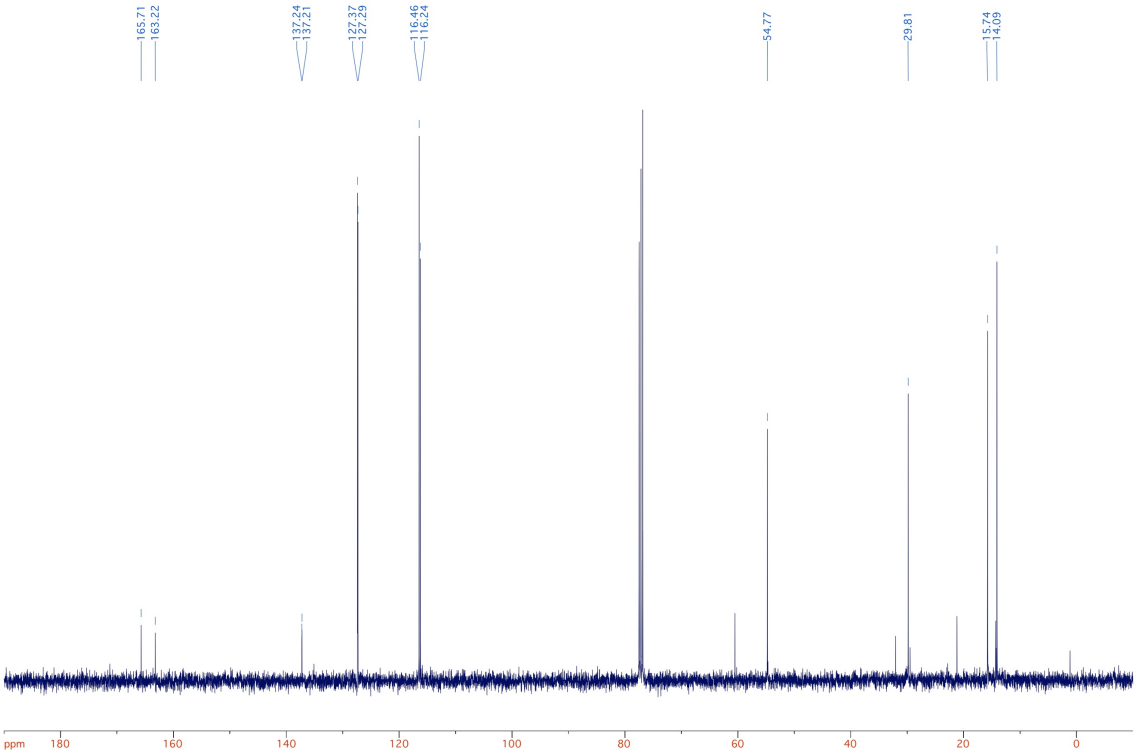
Compound **Table2.4, entry 7**



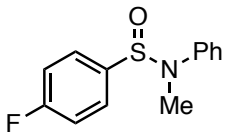
Compound **Table 2.4, entry 9**

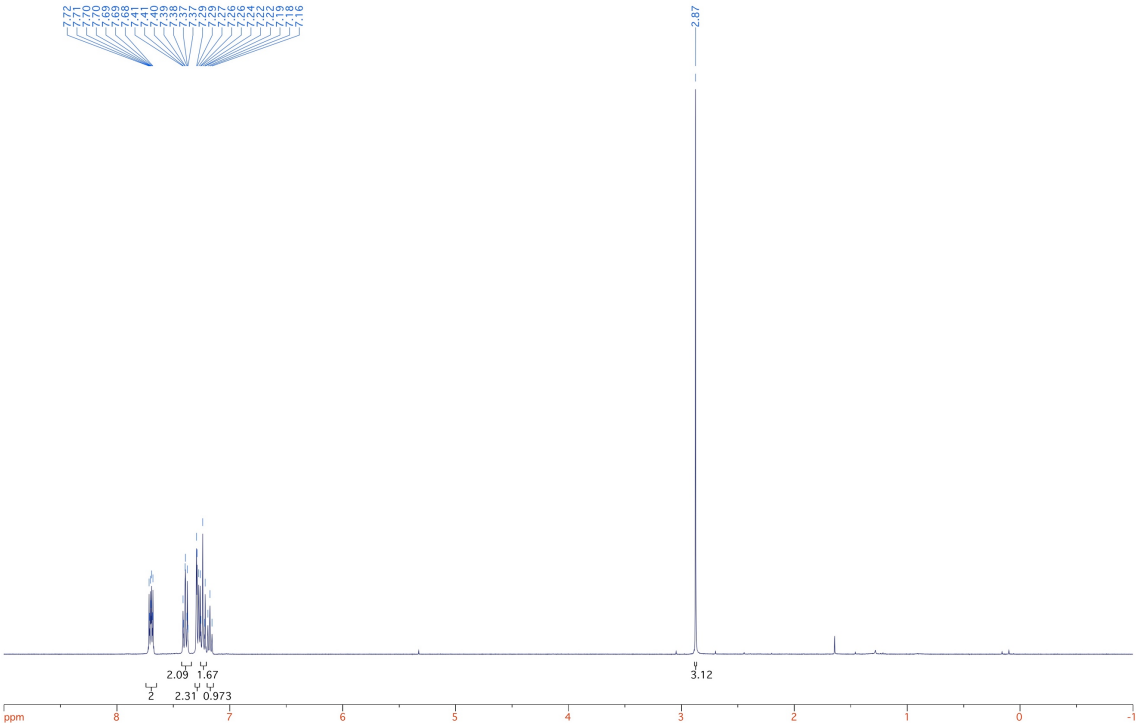


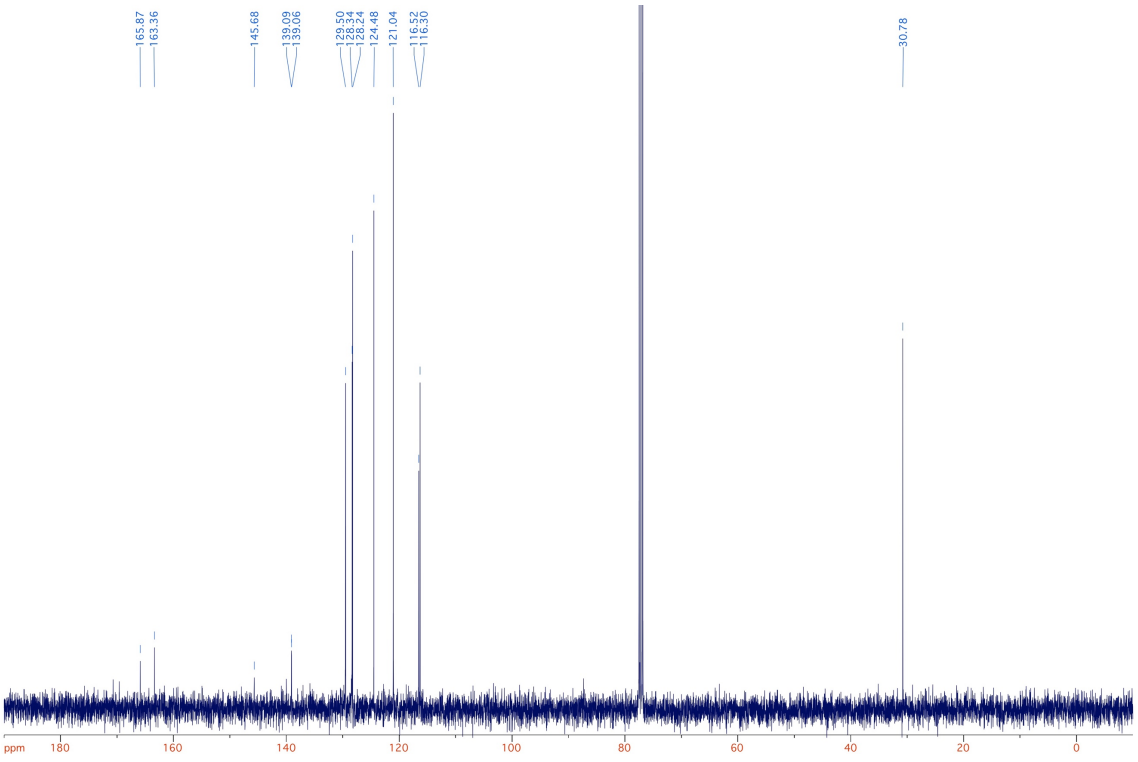




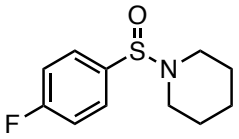
Compound **Table 2.4, entry 10**

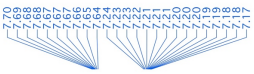




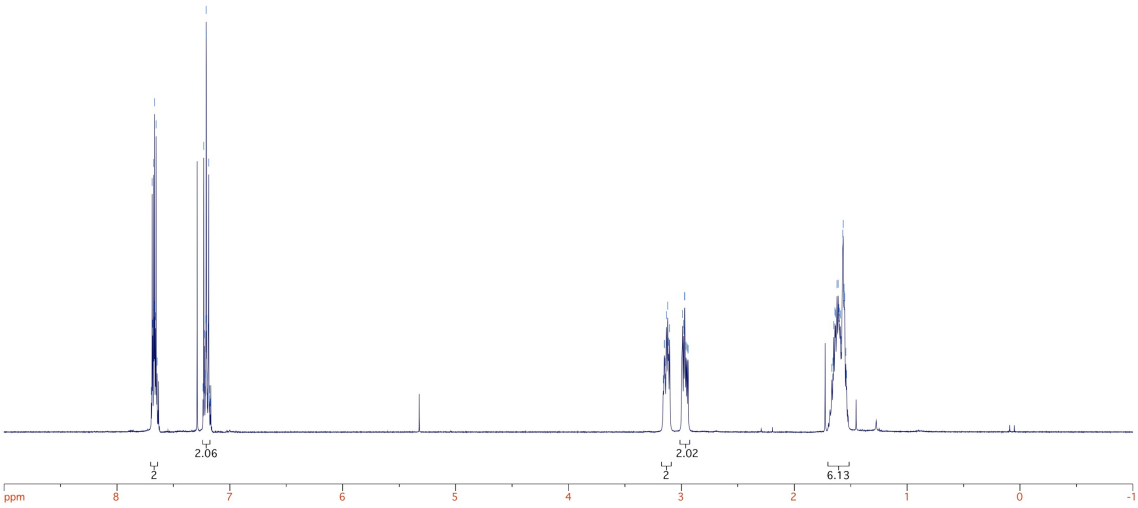


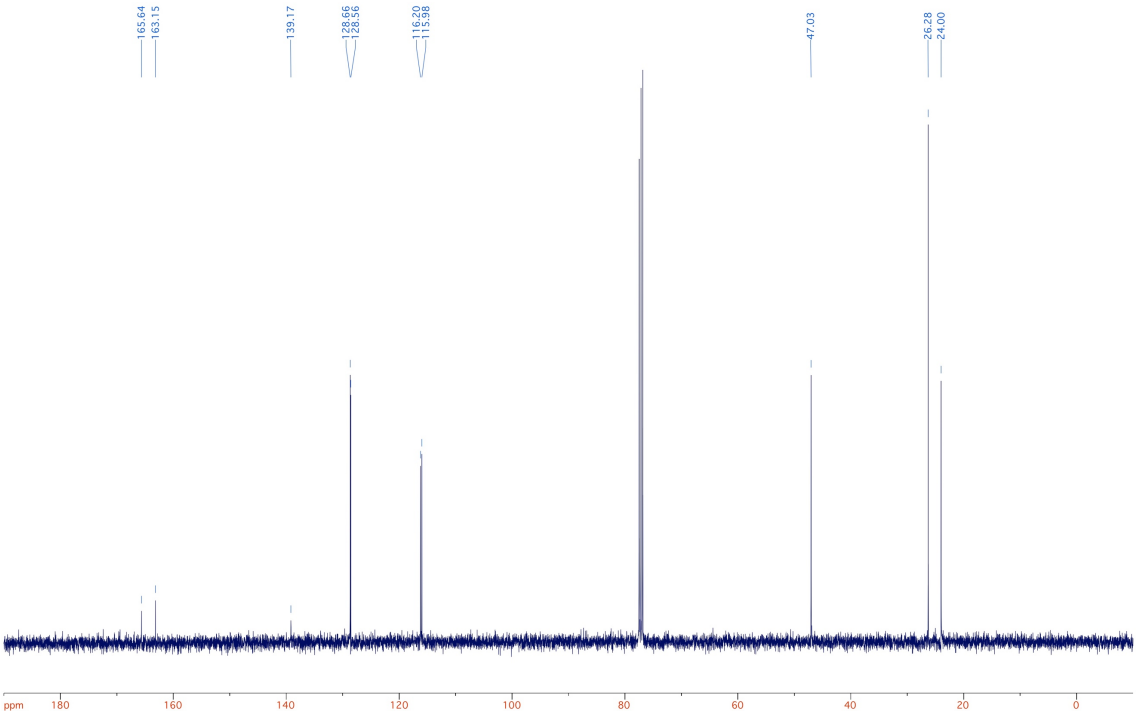
Compound **47**


O
S
N
F

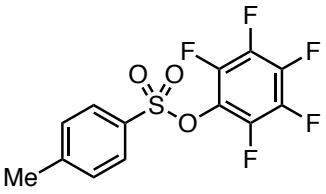


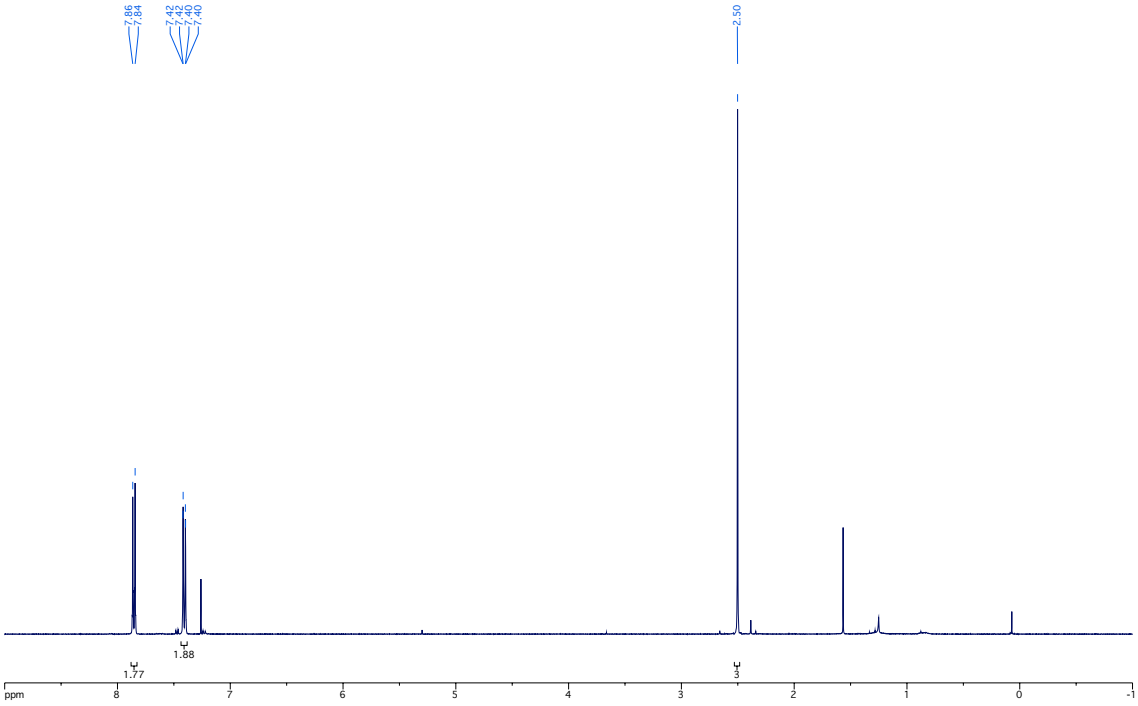


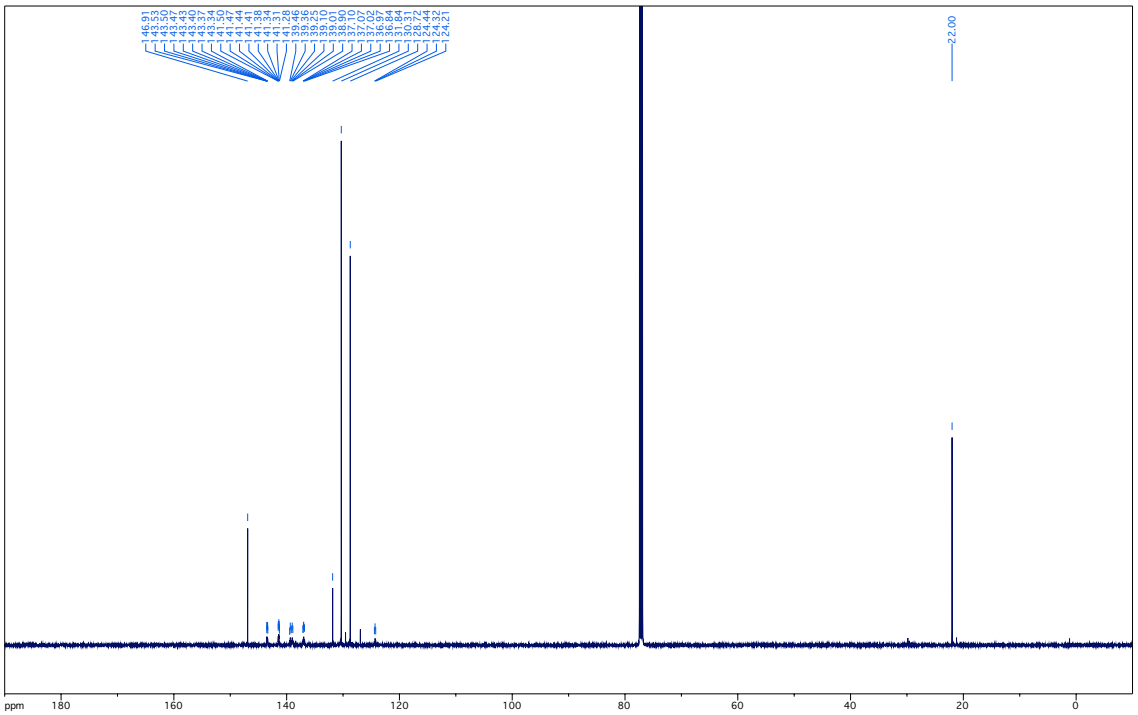

2.06
2
2.02
2
6.13
ppm
8
7
6
5
4
3
2
1
0
-1


165.64
163.15
139.17
128.66
128.56
116.20
115.98
47.03
26.28
24.00
ppm
180
160
140
120
100
80
60
40
20
0

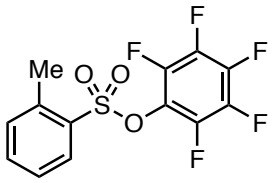
Compound **50a**

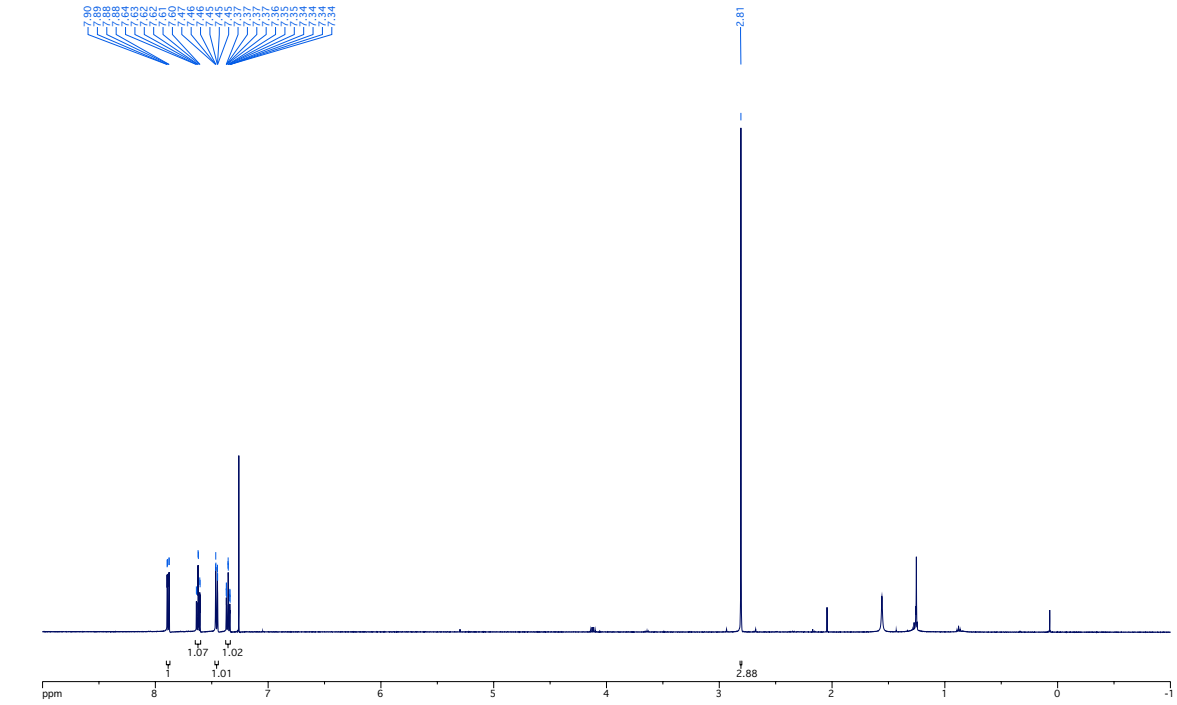


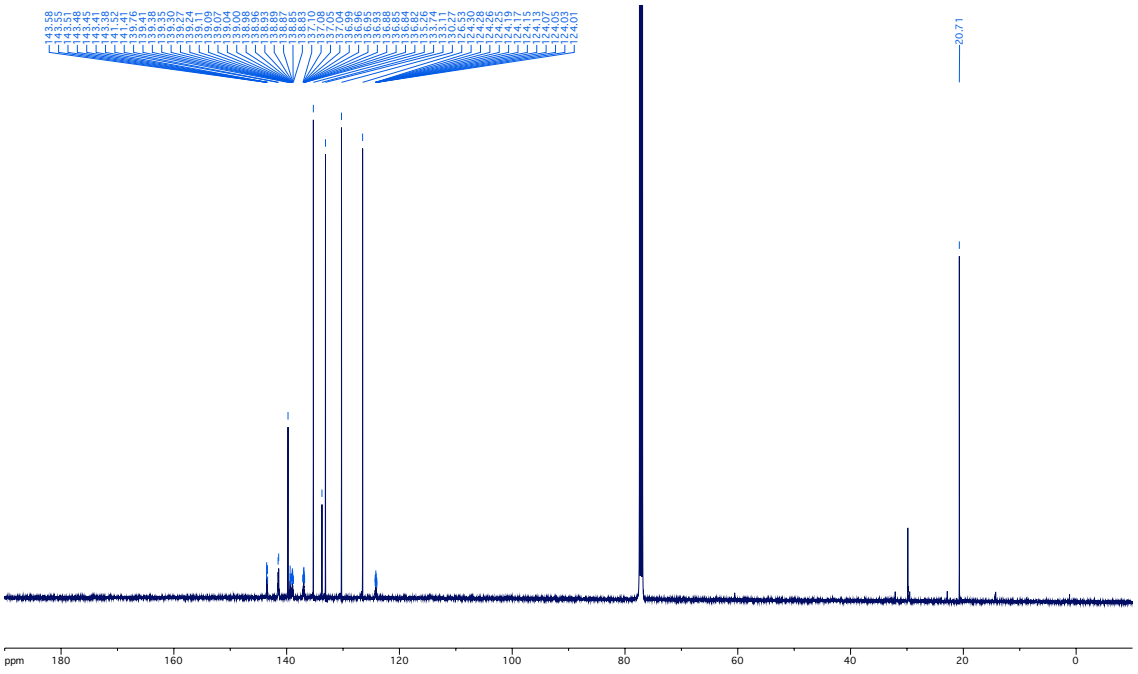




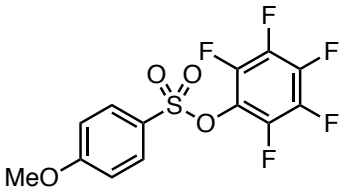
Compound **50b**

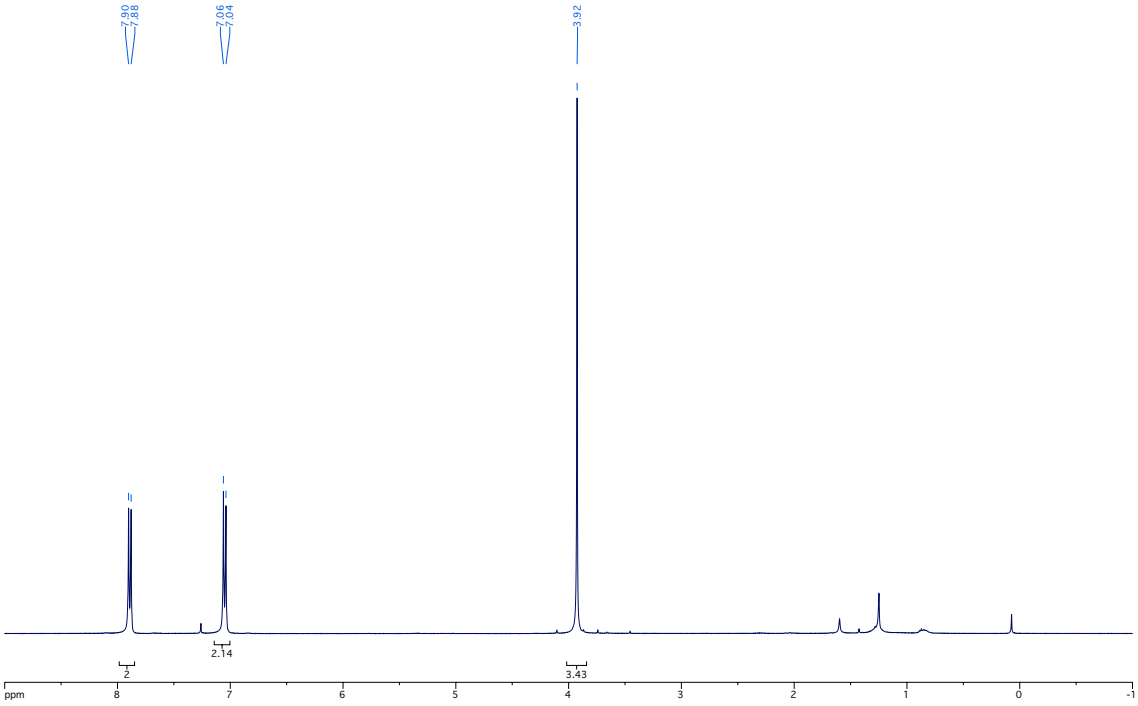


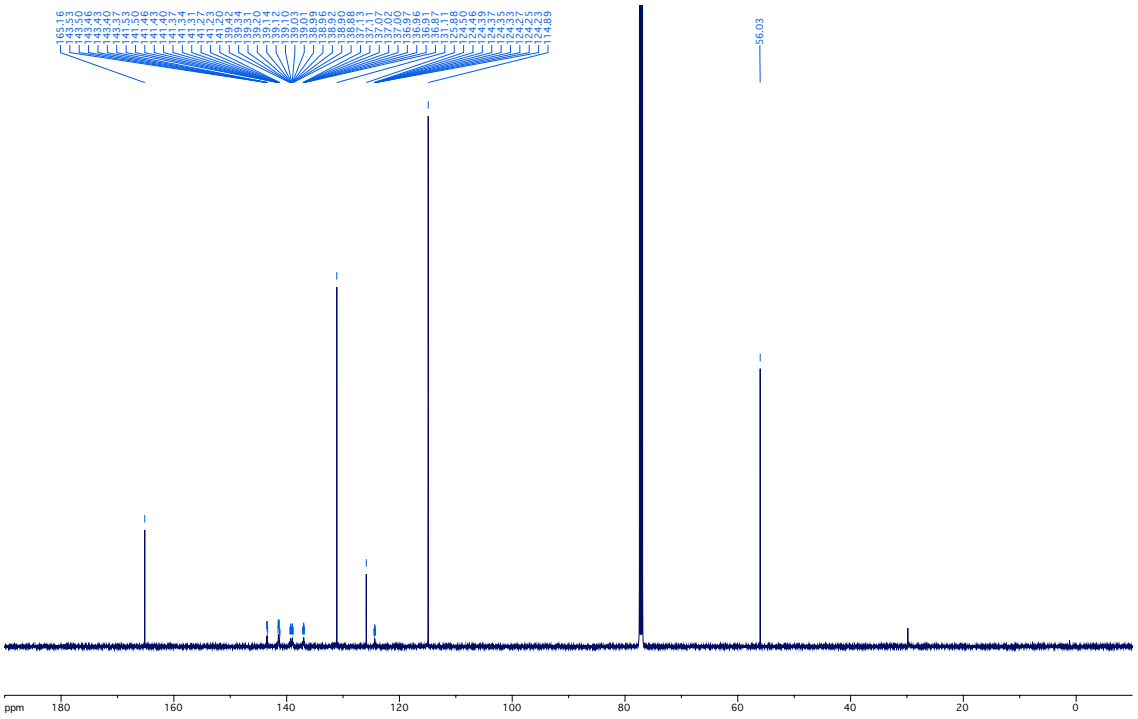




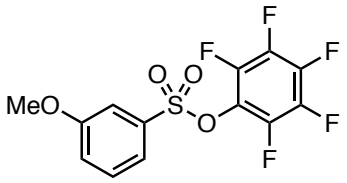
Compound **50c**

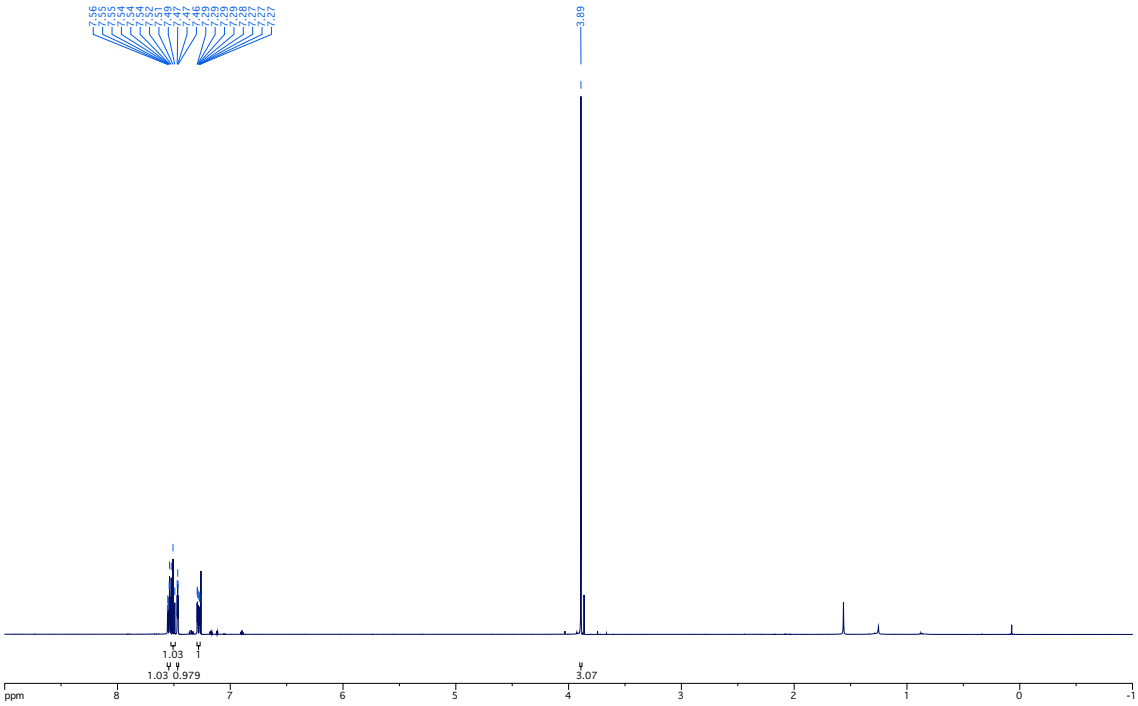


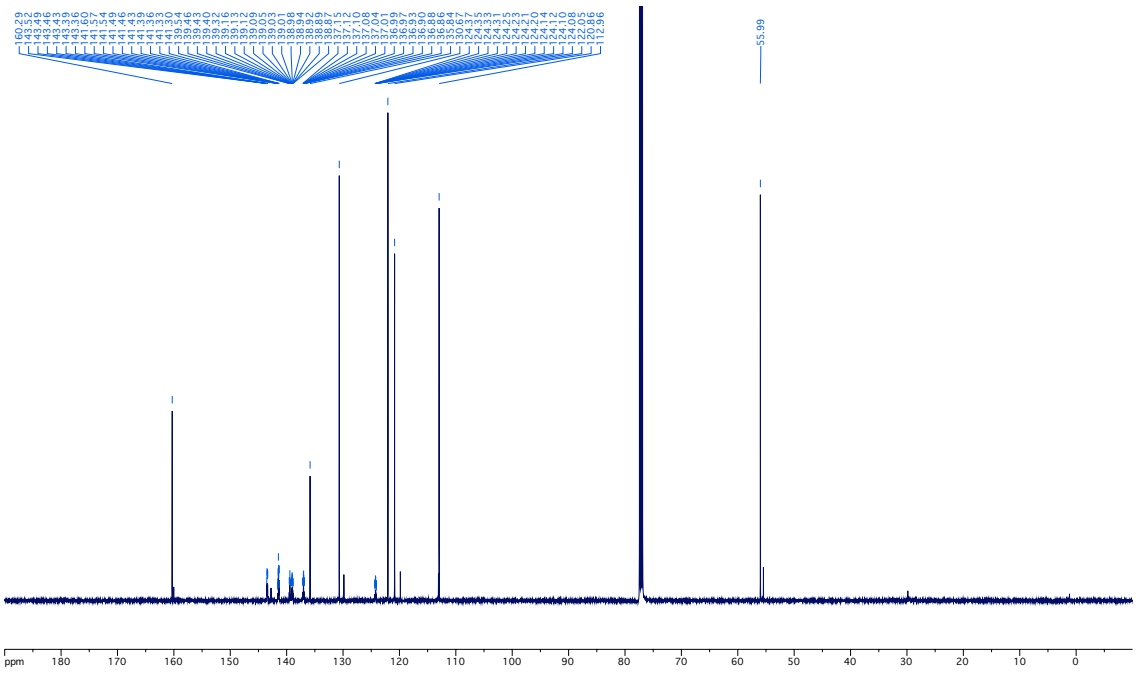




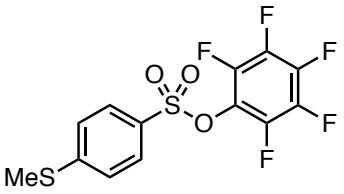
Compound **50d**

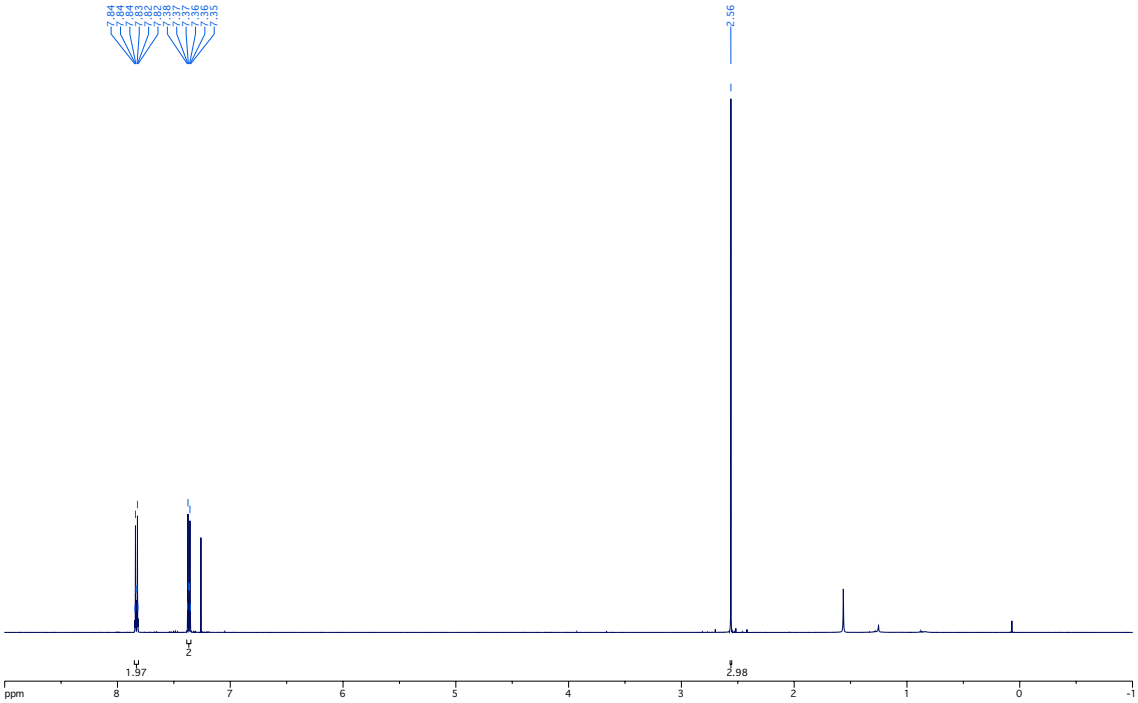


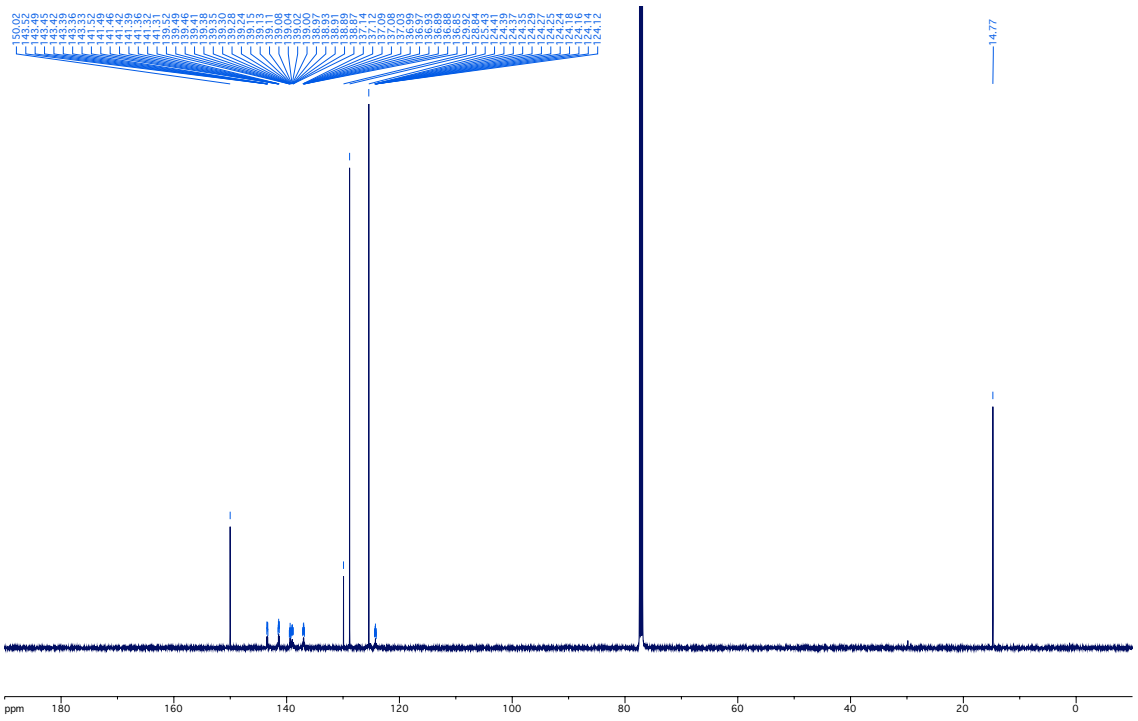




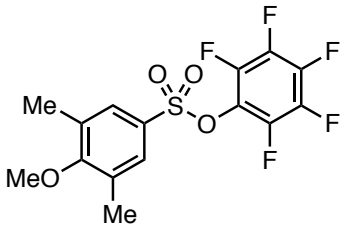
Compound **5e**

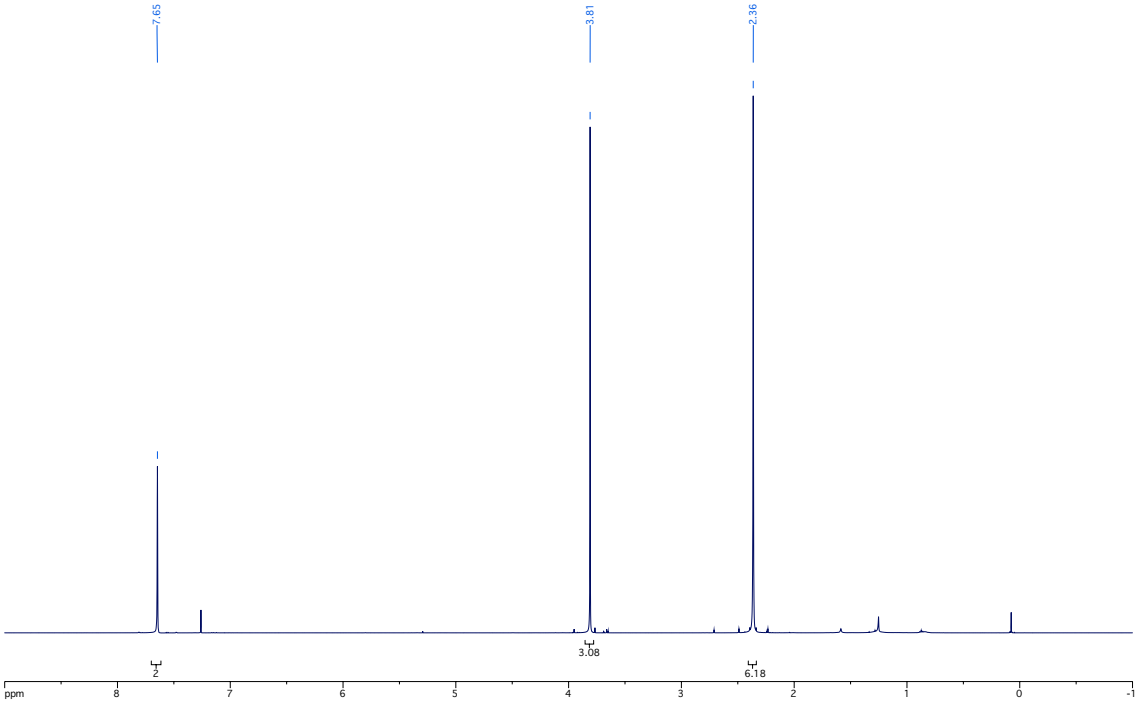

F
F
F
F
F
O
O
S
O
MeS

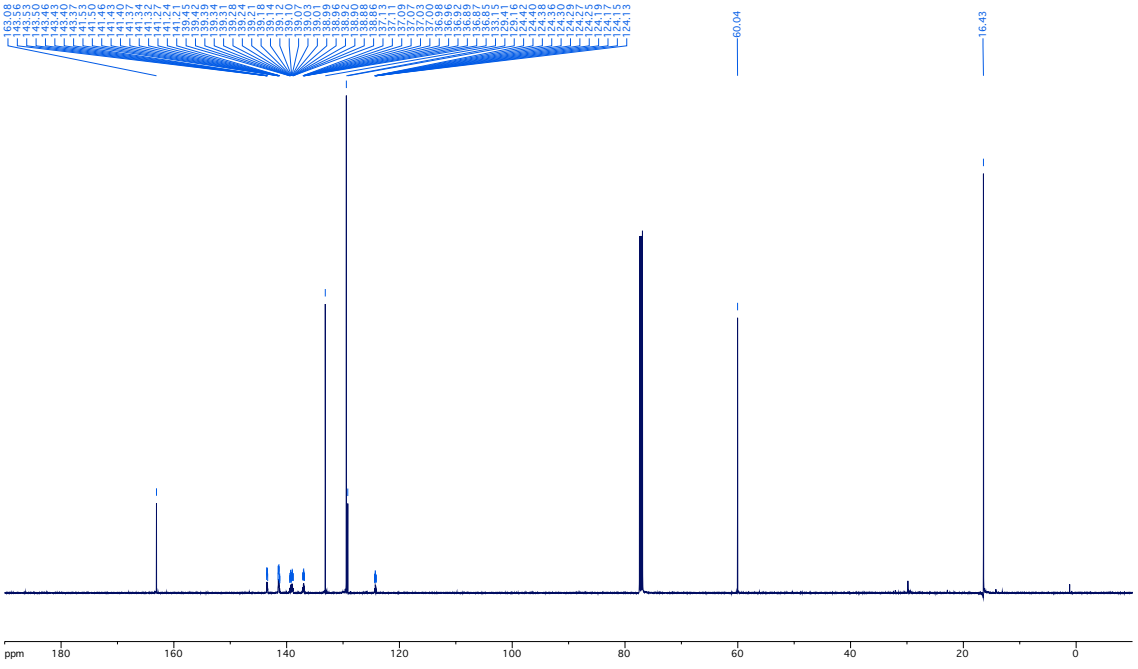

7.84
7.84
7.84
7.83
7.83
7.82
7.82
7.39
7.37
7.36
7.36
7.35
2.56
1.97
2
2.98
ppm
8
7
6
5
4
3
2
1
0
-1


14.77
ppm
180
160
140
120
100
80
60
40
20
0

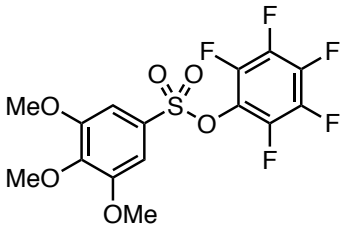
Compound **50f**

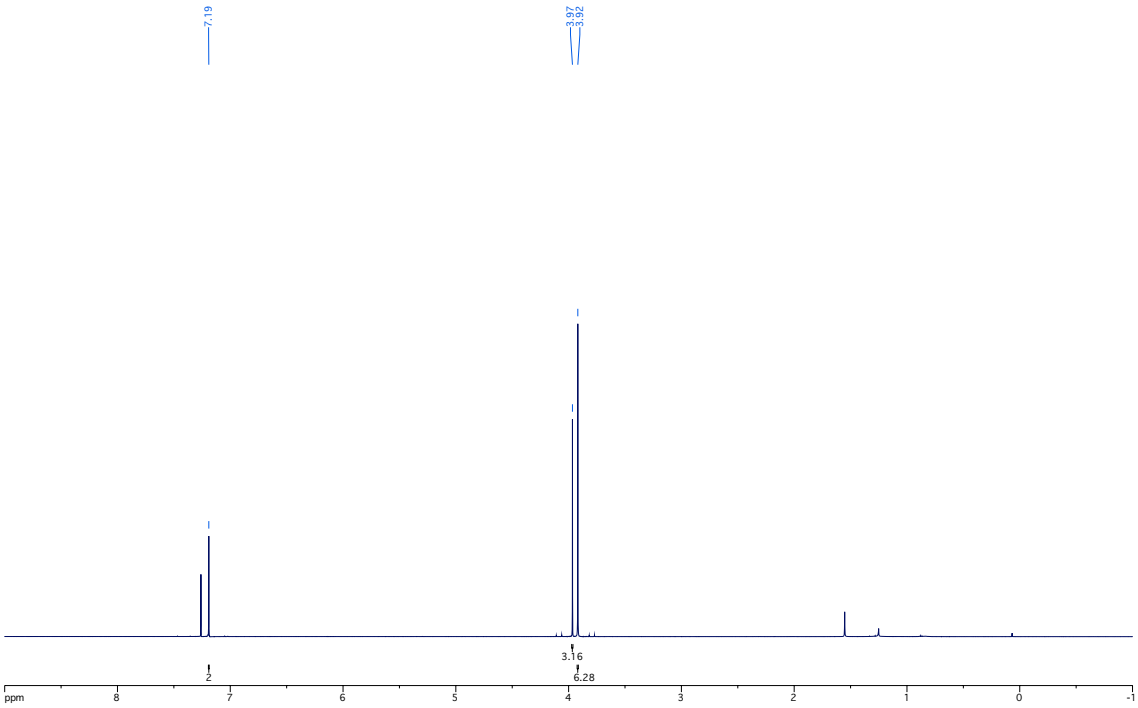


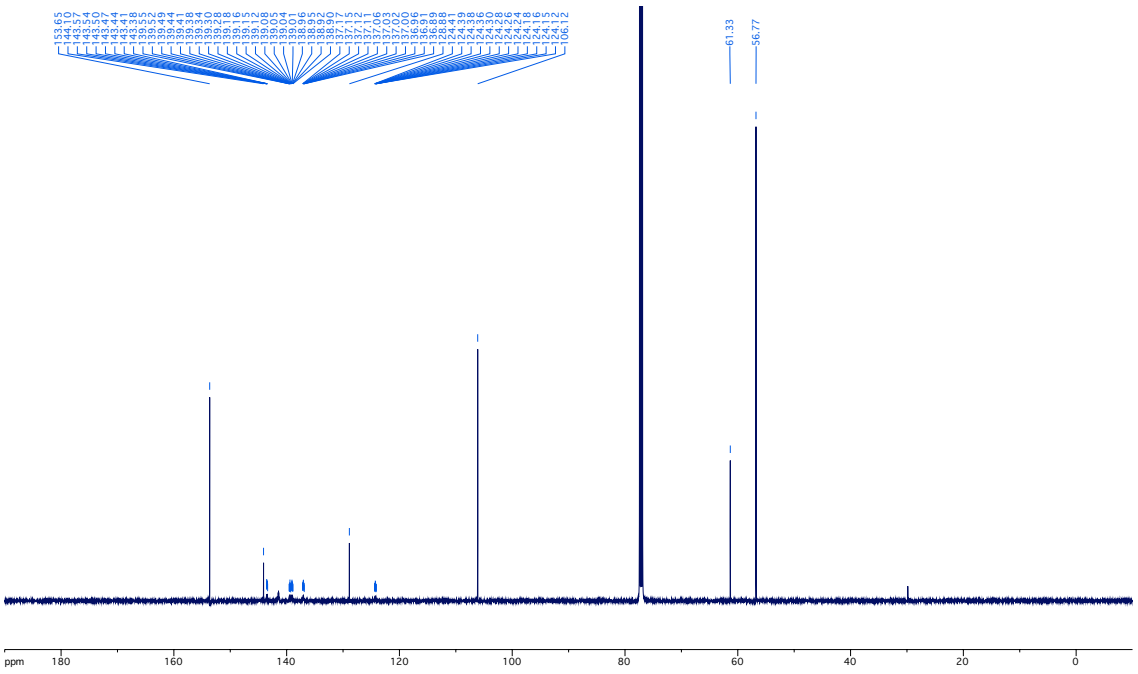




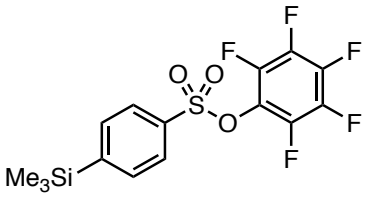
Compound **50g**

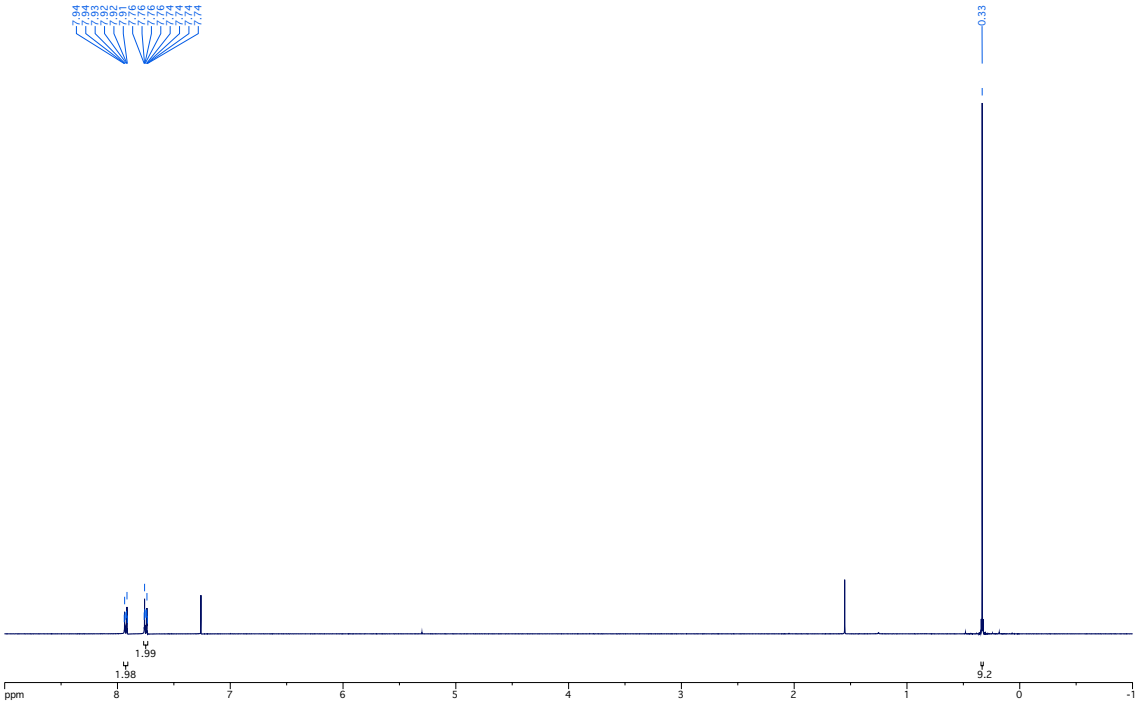


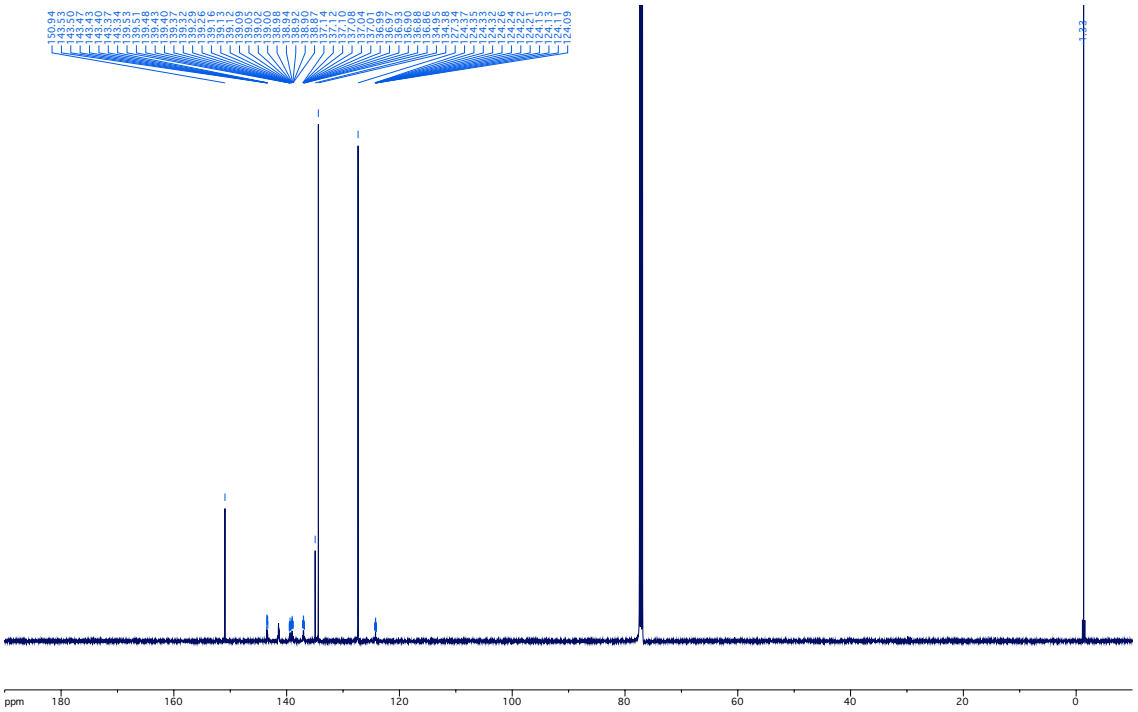




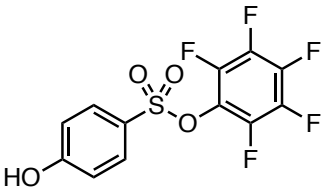
Compound **50h**

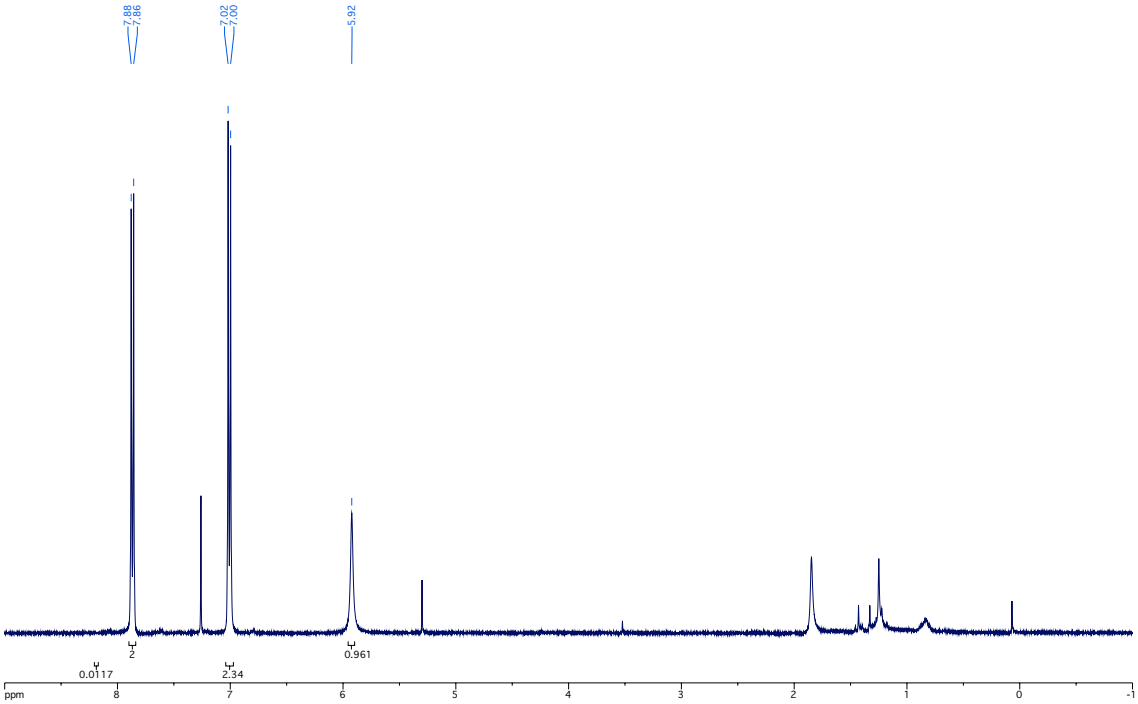


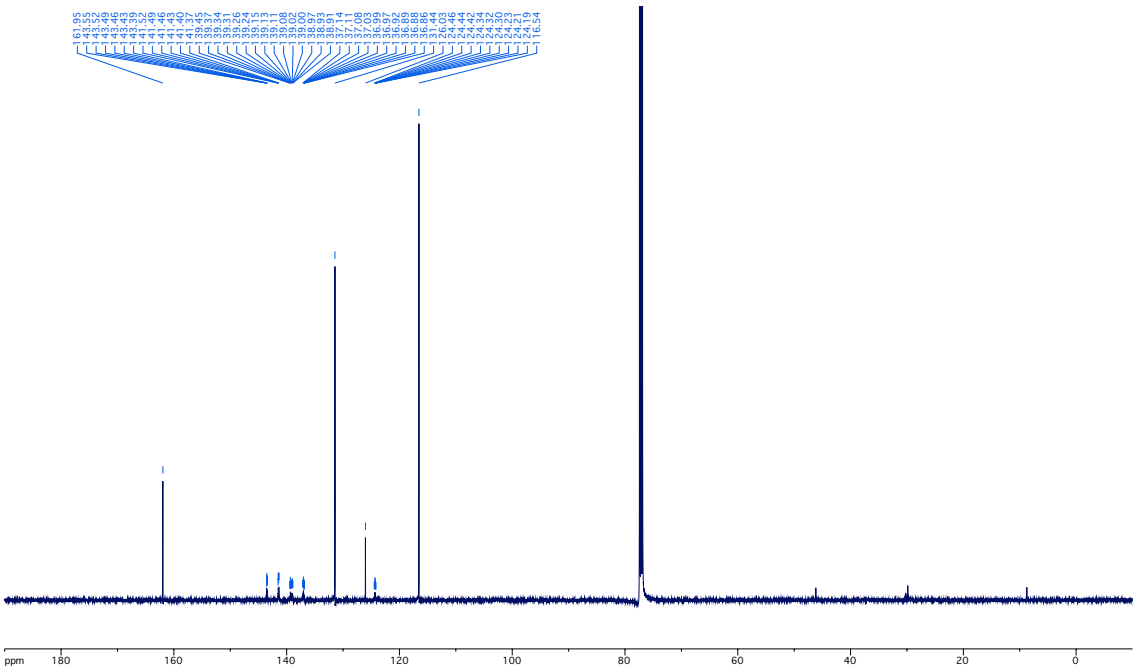




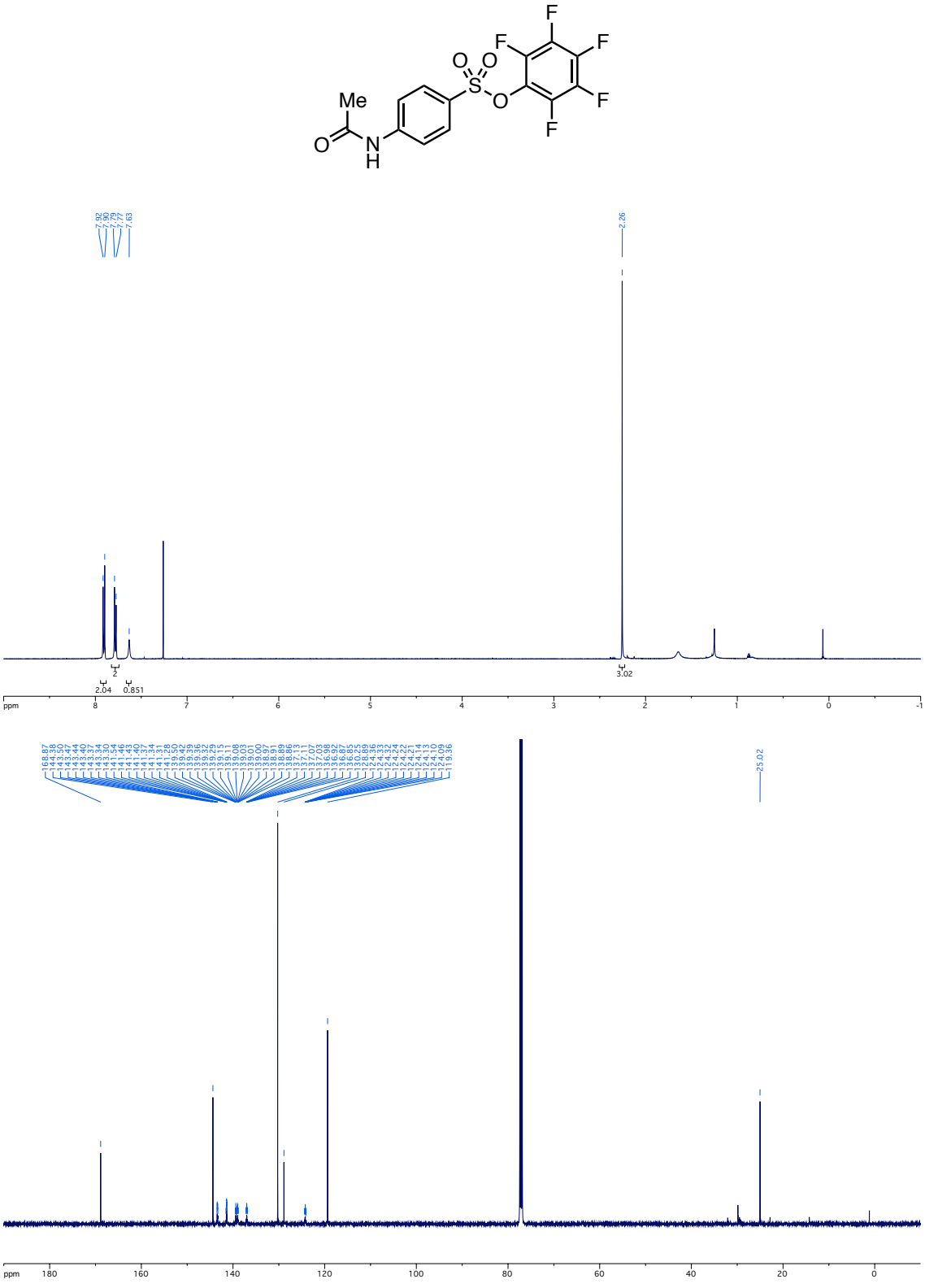
Compound **50i**



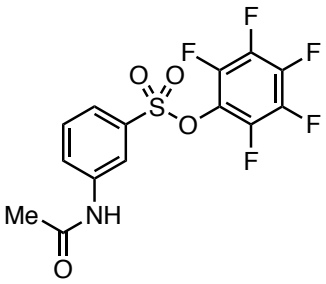


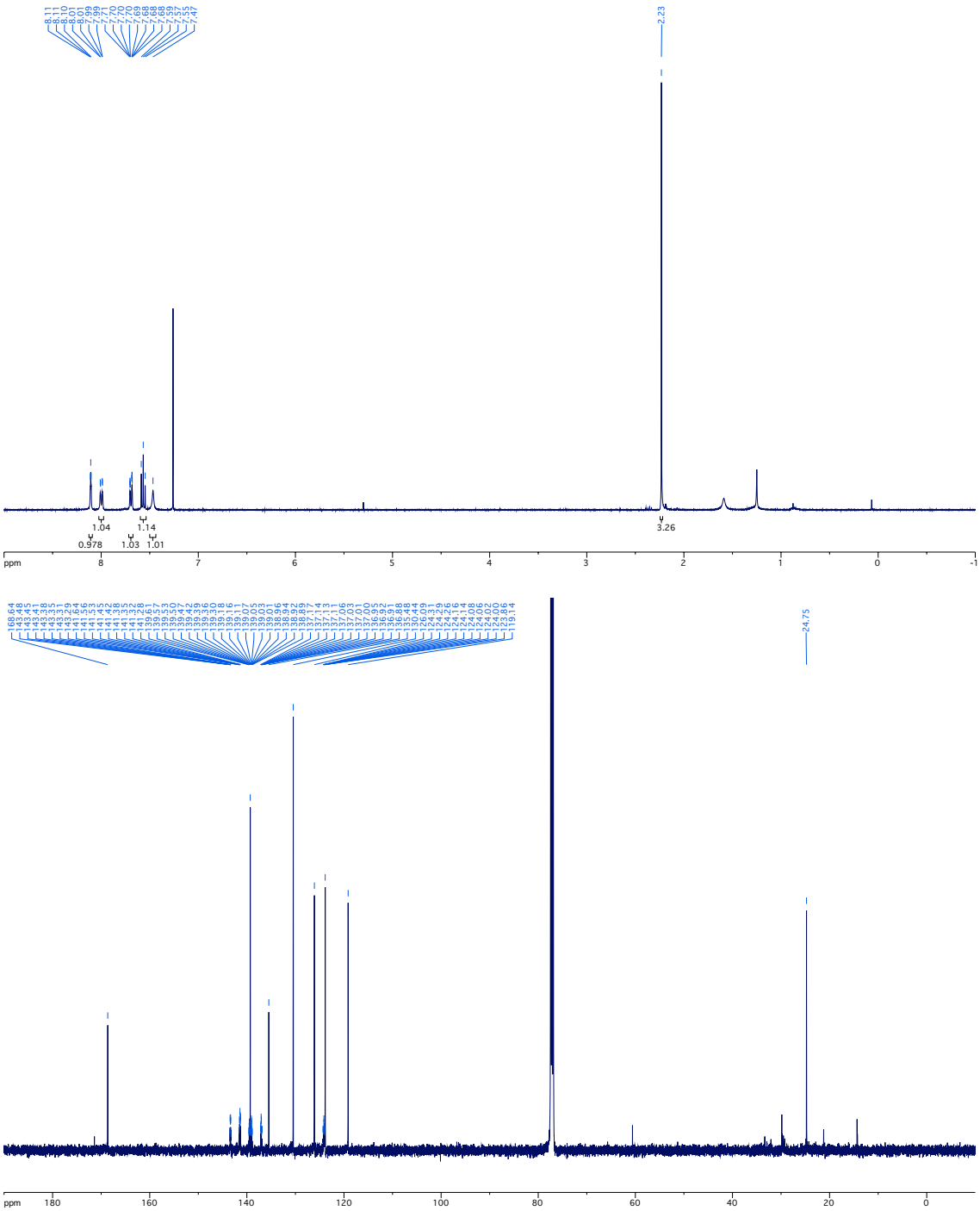


Compound **50j**

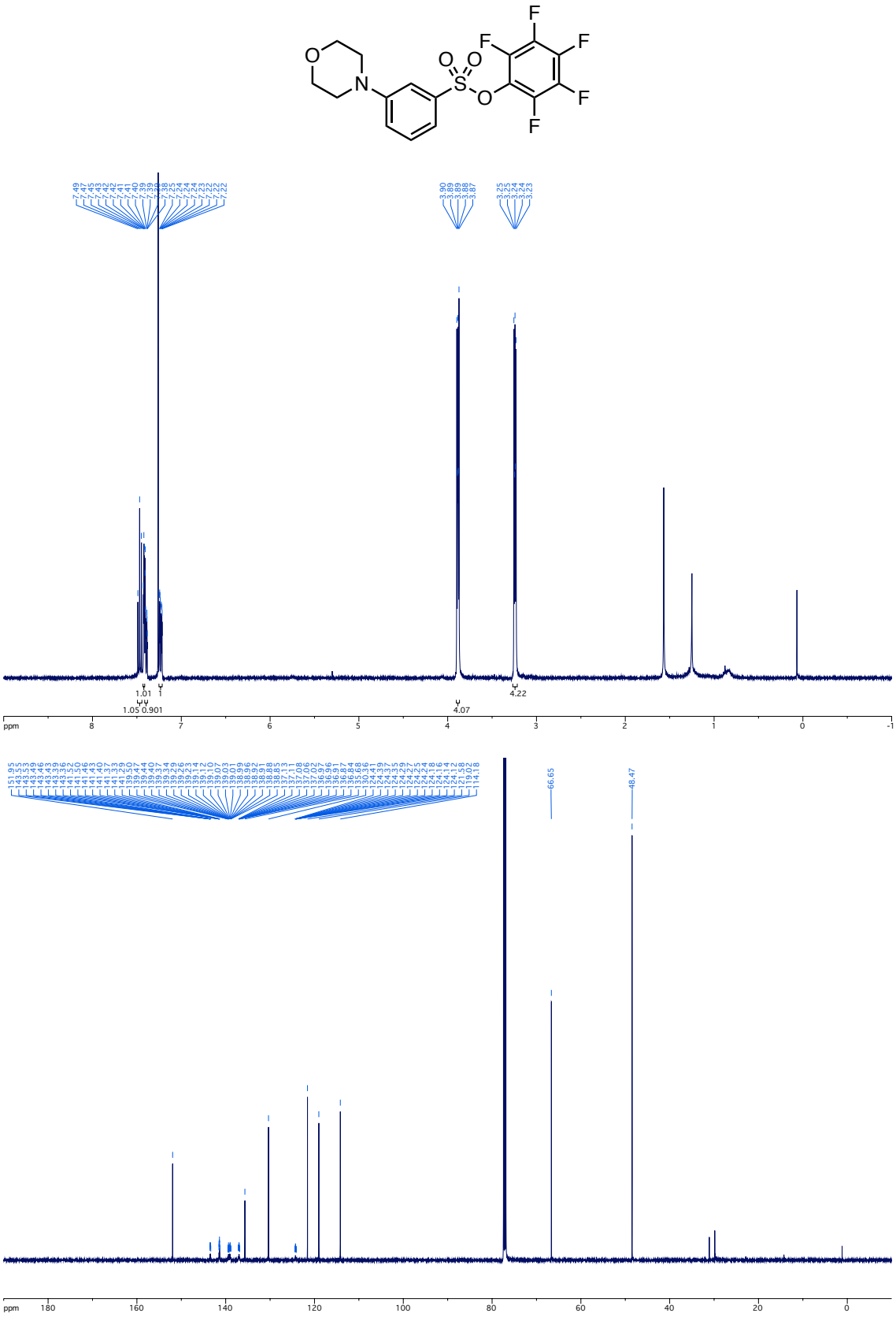


Compound **50k**

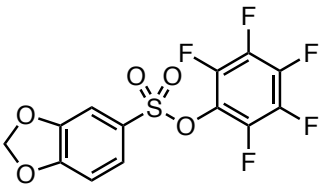

F
F
F
F
F
O
O
S
O
Me
NH
O

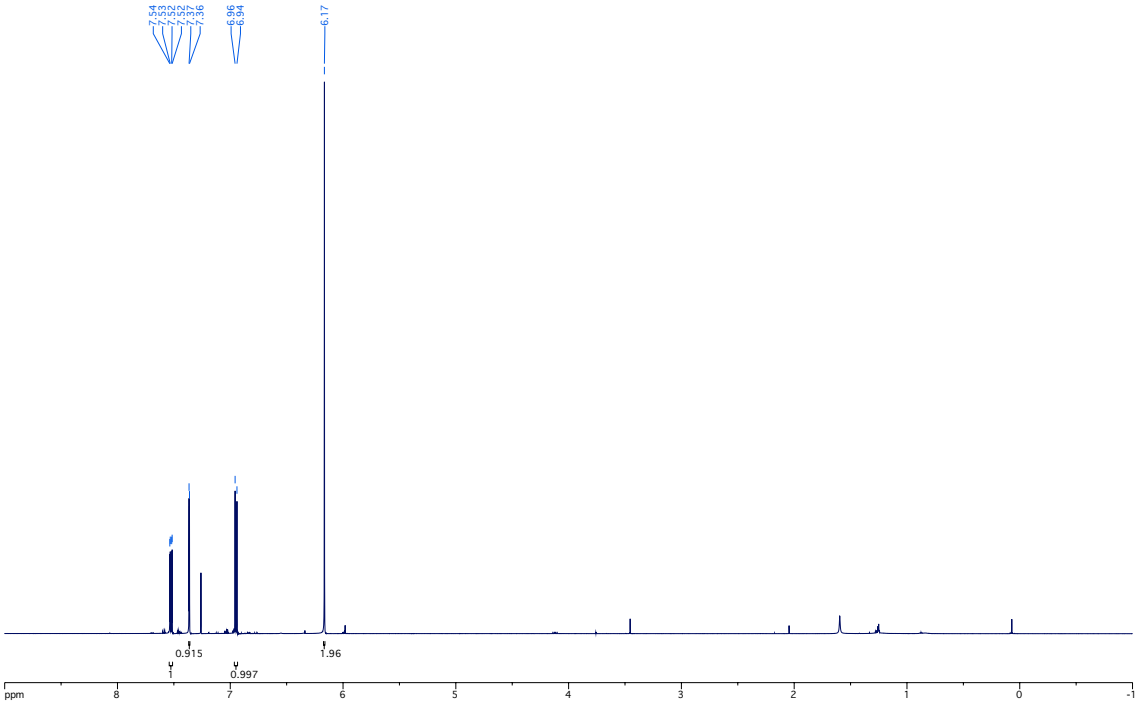

8.11
8.11
8.10
8.10
8.01
8.01
7.99
7.99
7.77
7.77
7.70
7.70
7.70
7.70
7.69
7.69
7.68
7.68
7.59
7.59
7.57
7.57
7.55
7.47
2.23
1.04
1.14
0.978
1.03
1.01
3.26
ppm
8
7
6
5
4
3
2
1
0
-1
168.64
143.48
143.45
143.41
143.38
143.35
143.32
143.29
141.64
141.55
141.45
141.38
141.35
141.28
139.61
139.57
139.50
139.47
139.43
139.39
139.36
139.30
139.18
139.11
139.07
139.05
139.01
138.96
138.92
138.89
137.77
137.14
137.13
137.06
137.03
137.00
136.93
136.91
136.88
136.44
130.44
126.09
124.29
124.26
124.14
124.08
124.06
124.02
124.00
123.96
119.14
24.75
ppm
180
160
140
120
100
80
60
40
20
0

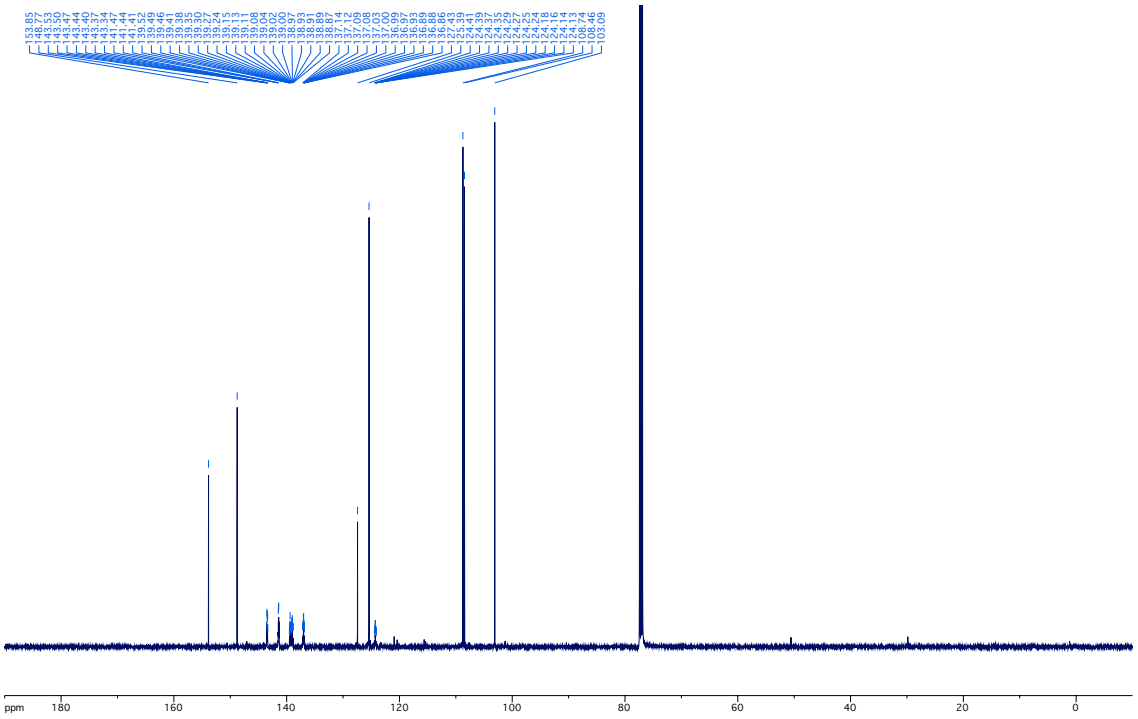
Compound **2l**



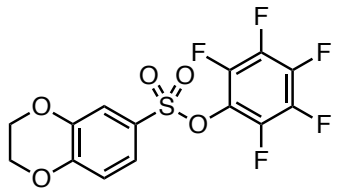
Compound **50m**

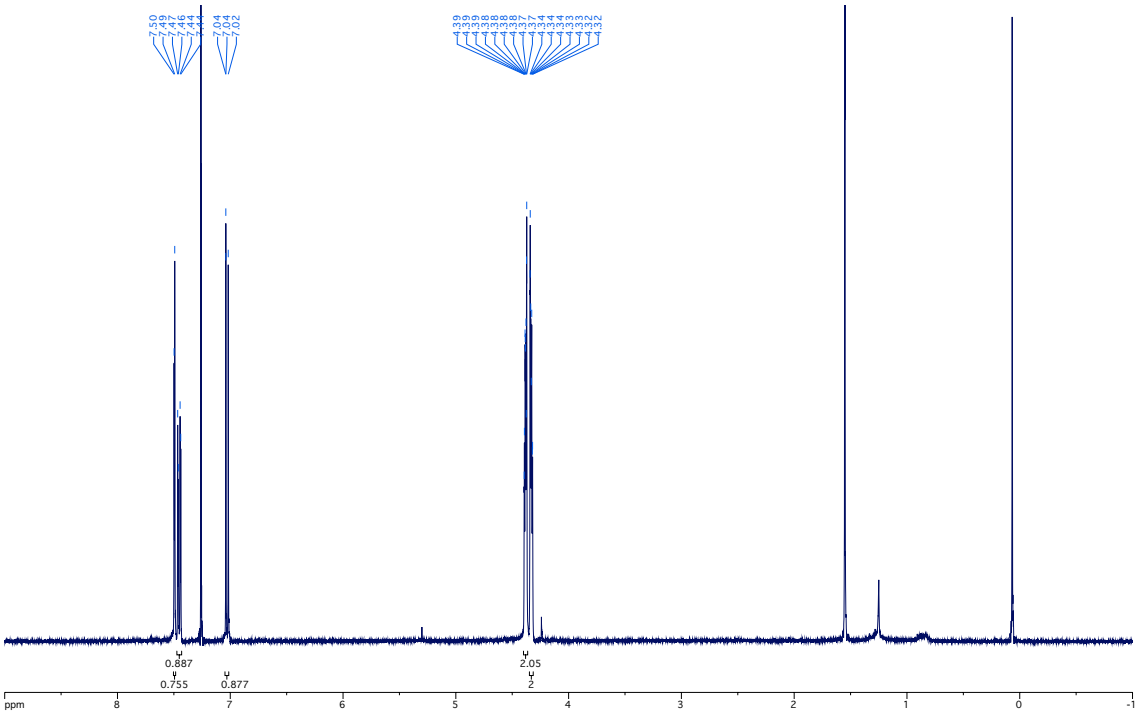

F
F
F
F
F
O
O
S
O
O
O

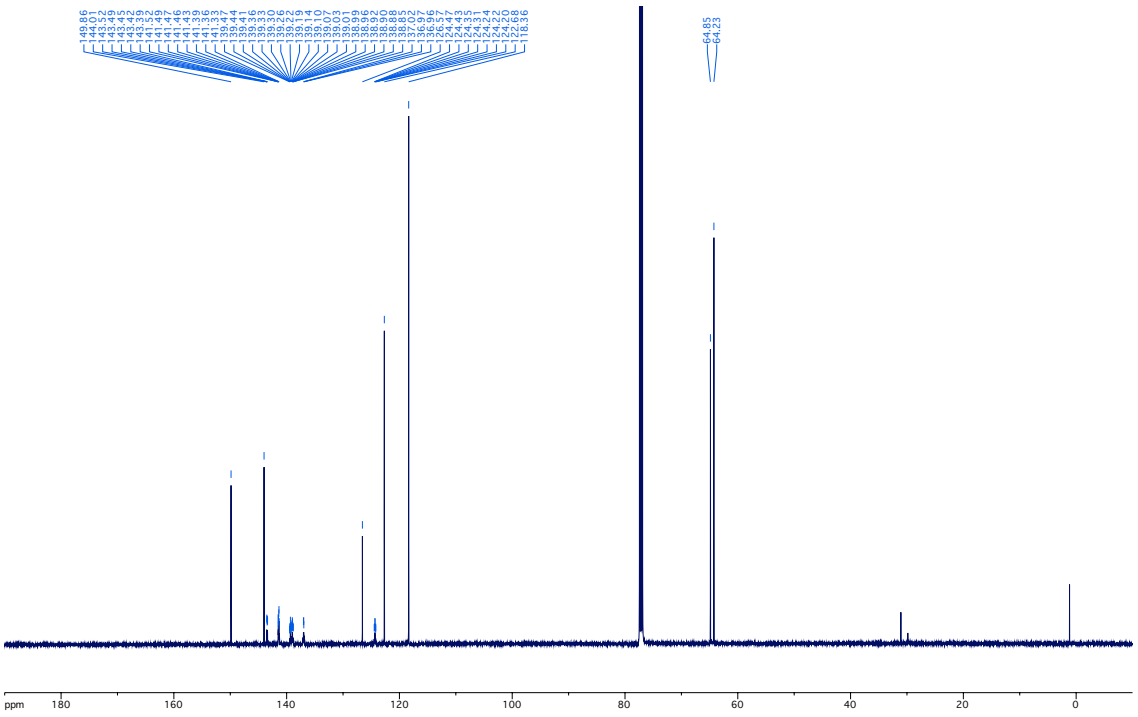

7.54
7.53
7.52
7.52
7.37
7.36
6.96
6.94
6.17
0.915
0.997
1.96
ppm


ppm

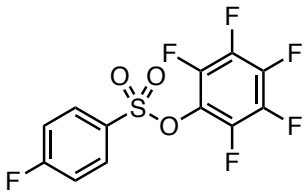
Compound **2n**

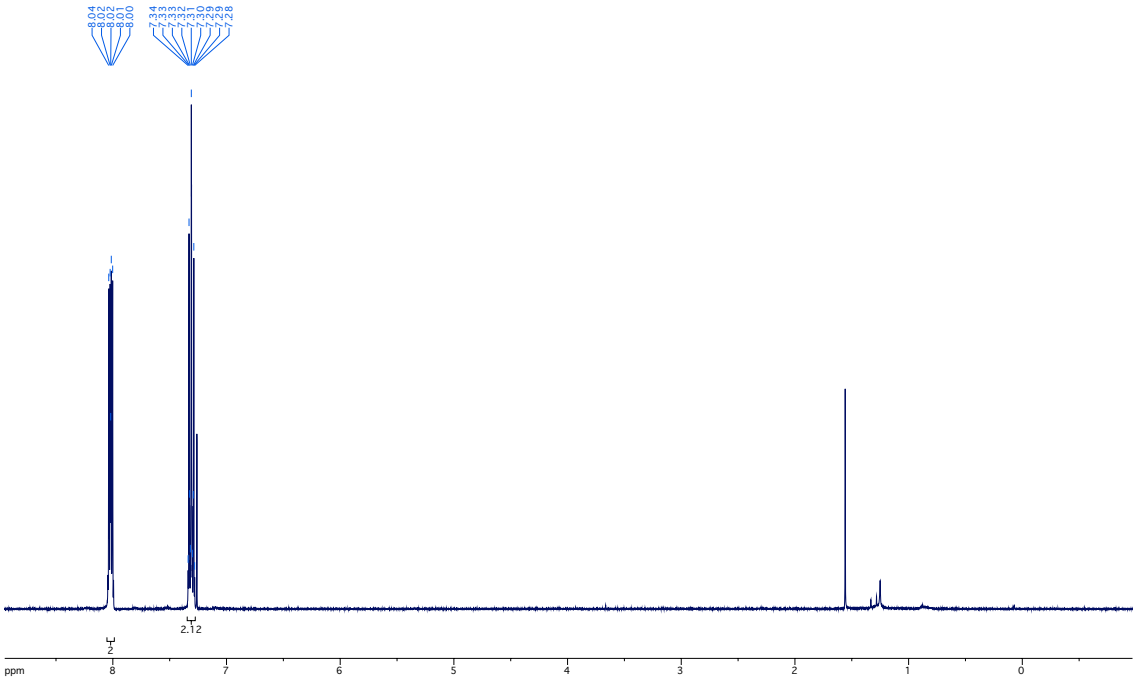






Compound **50o**


F
F
F
F
F
O
O
S
O
F


8.04
8.02
8.01
8.01
8.00
7.34
7.33
7.33
7.32
7.31
7.30
7.29
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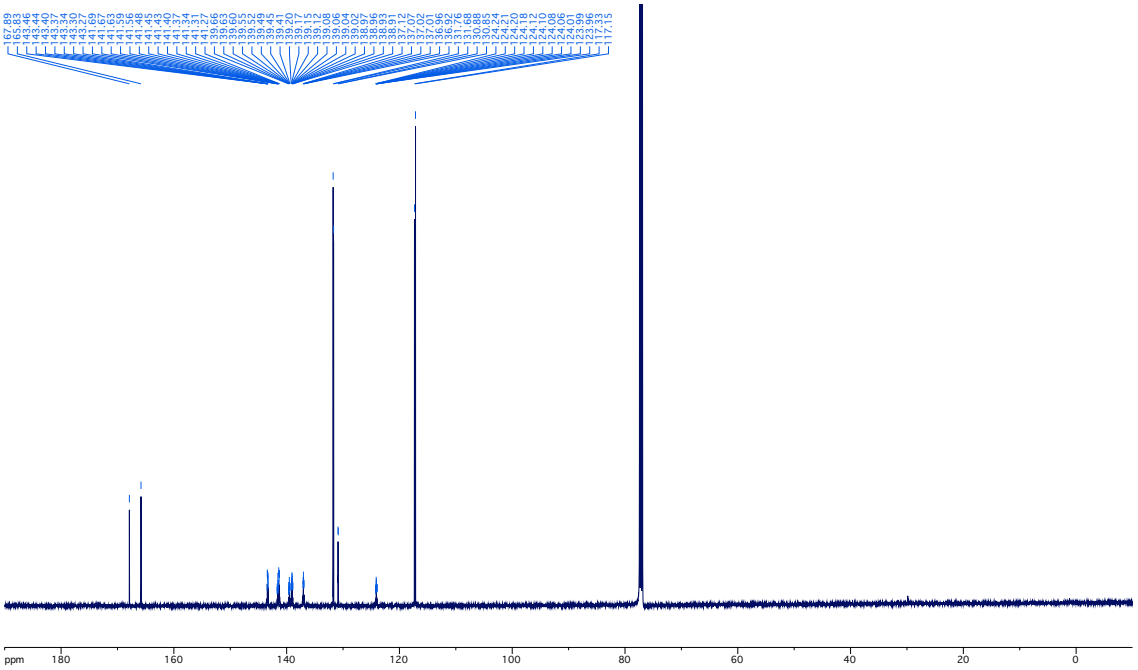
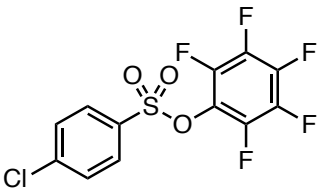
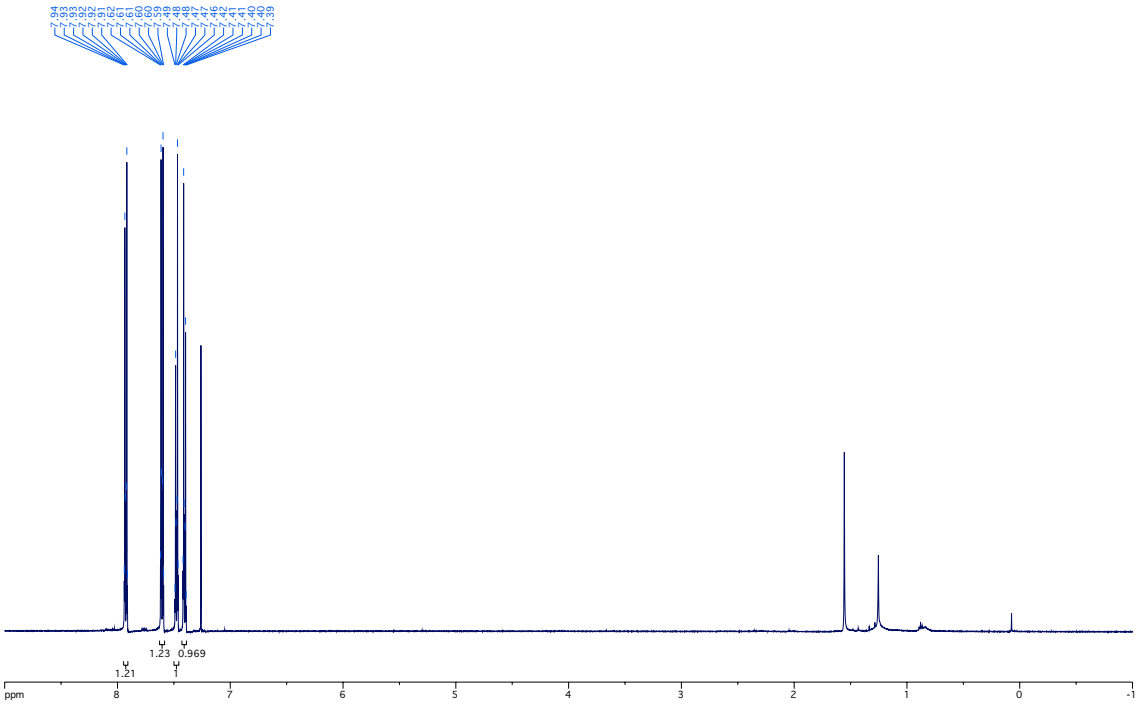
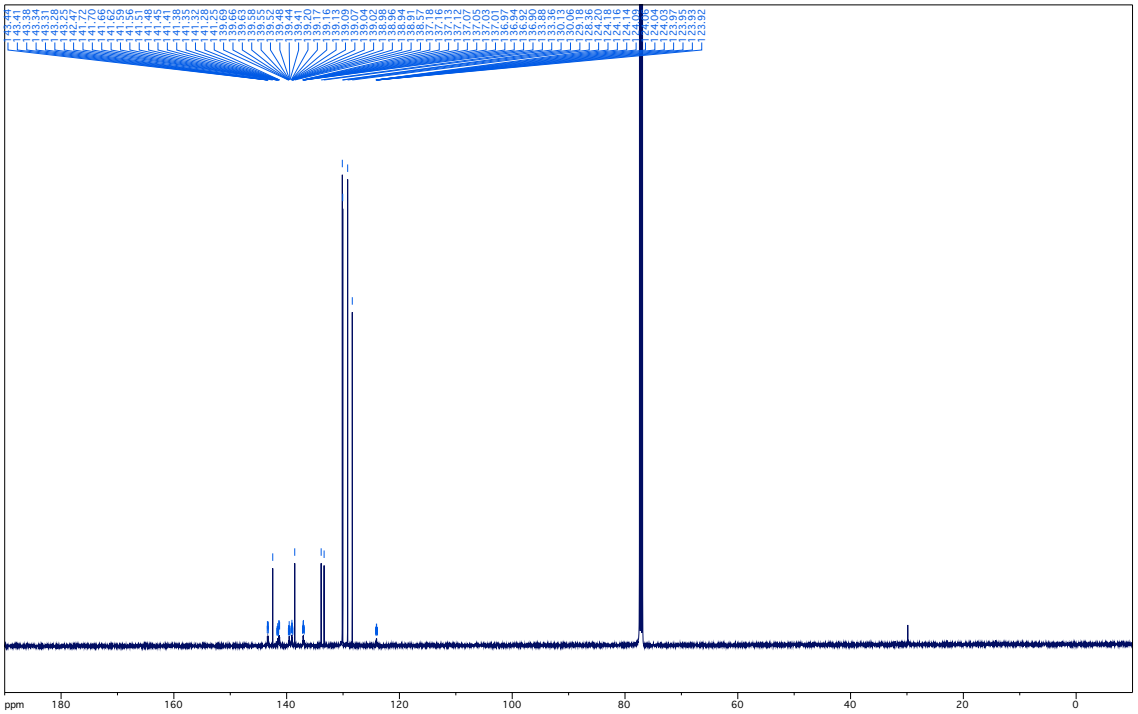
5
4
3
2
1
0


ppm
180
160
140
120
100
80
60
40
20
0

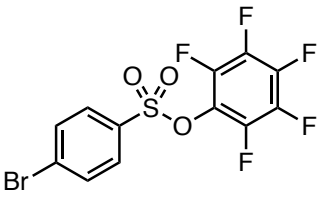
Compound **2p**

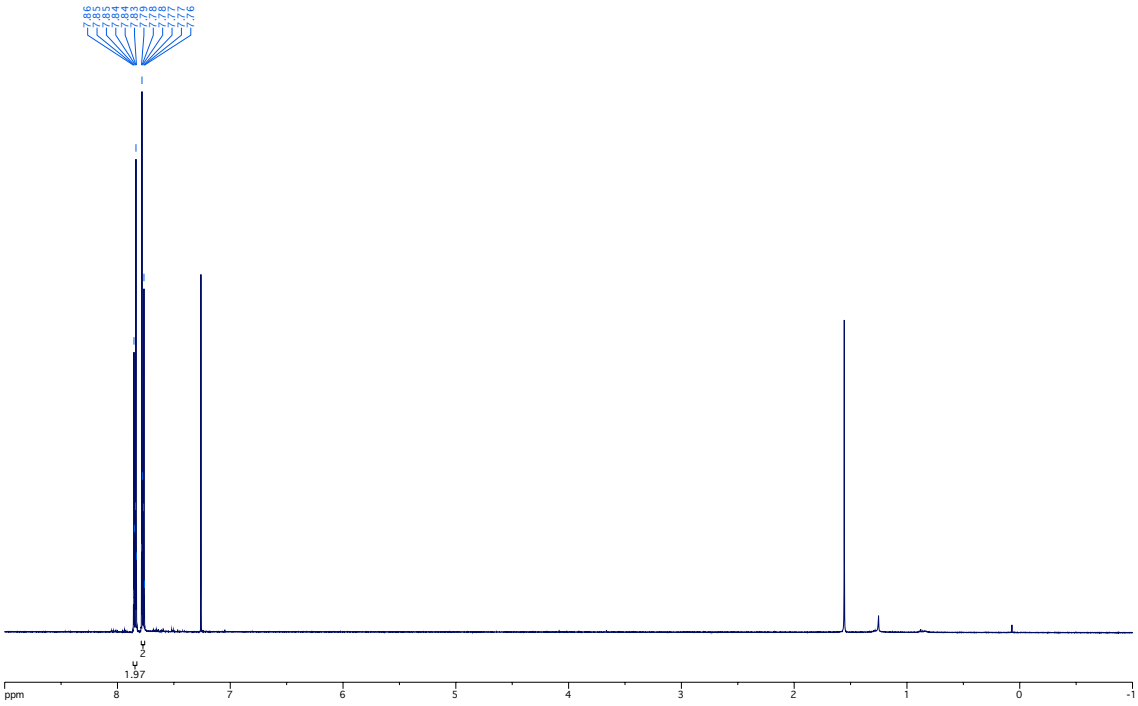


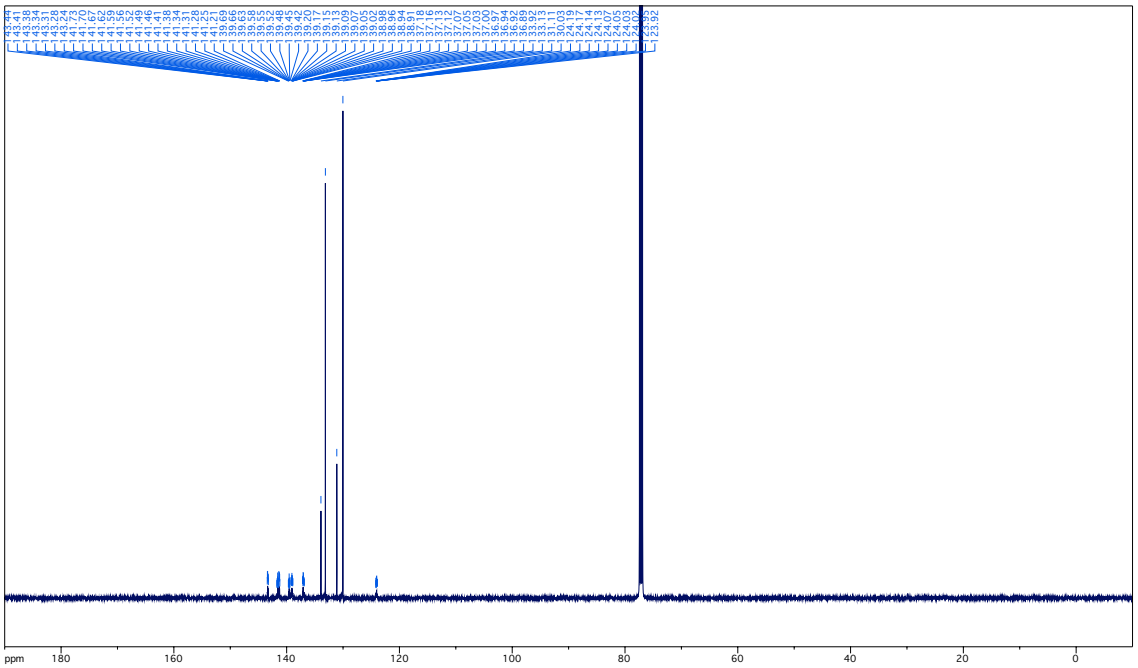




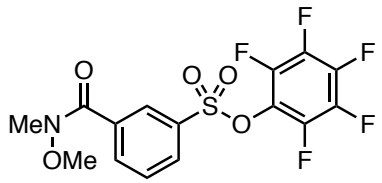
Compound **50q**

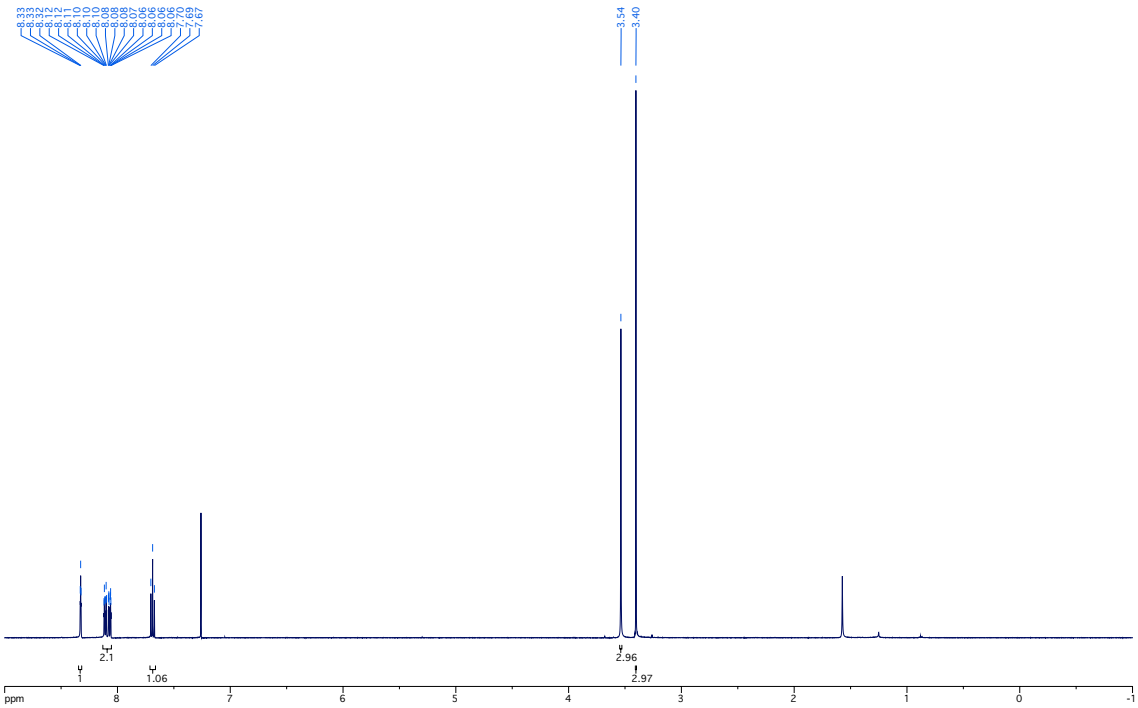


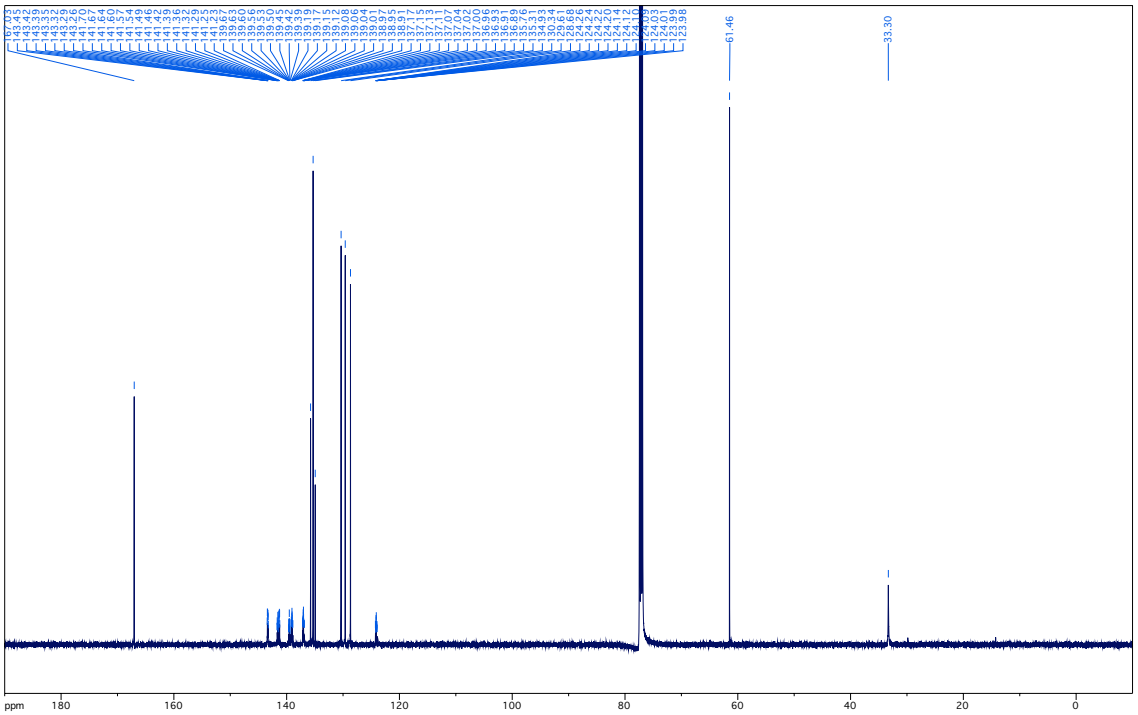




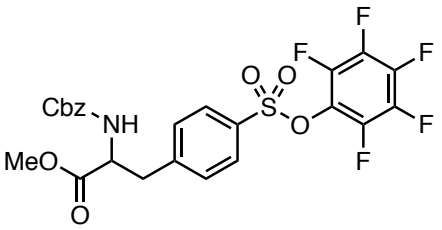
Compound **50r**

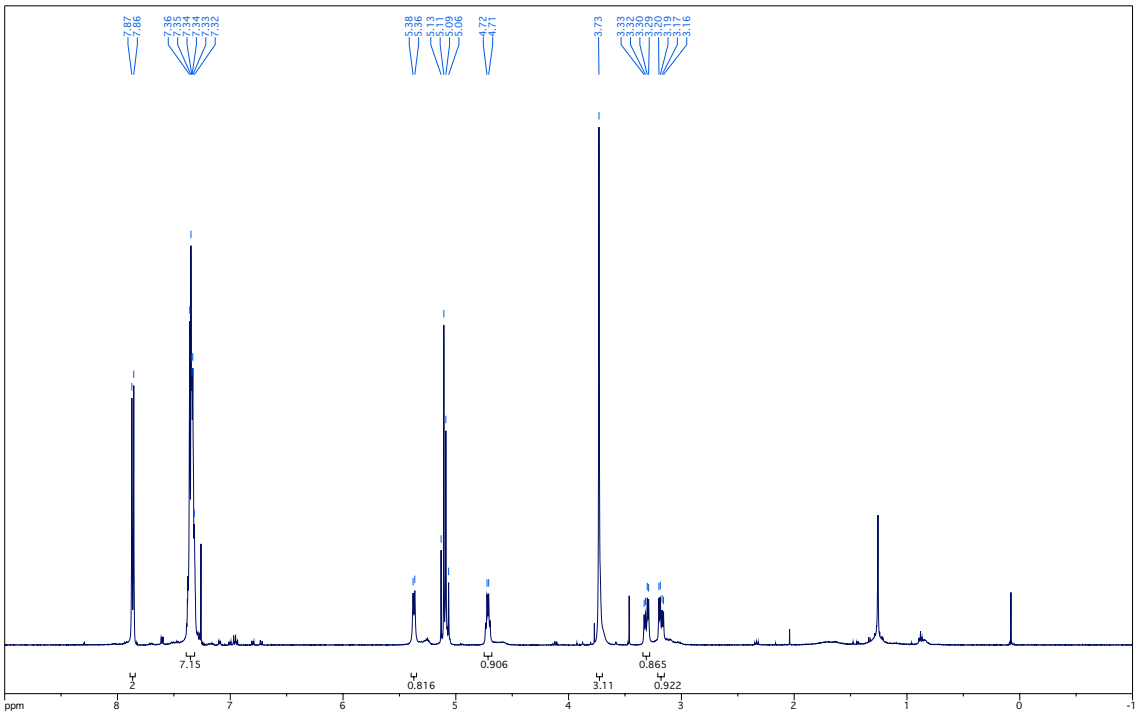


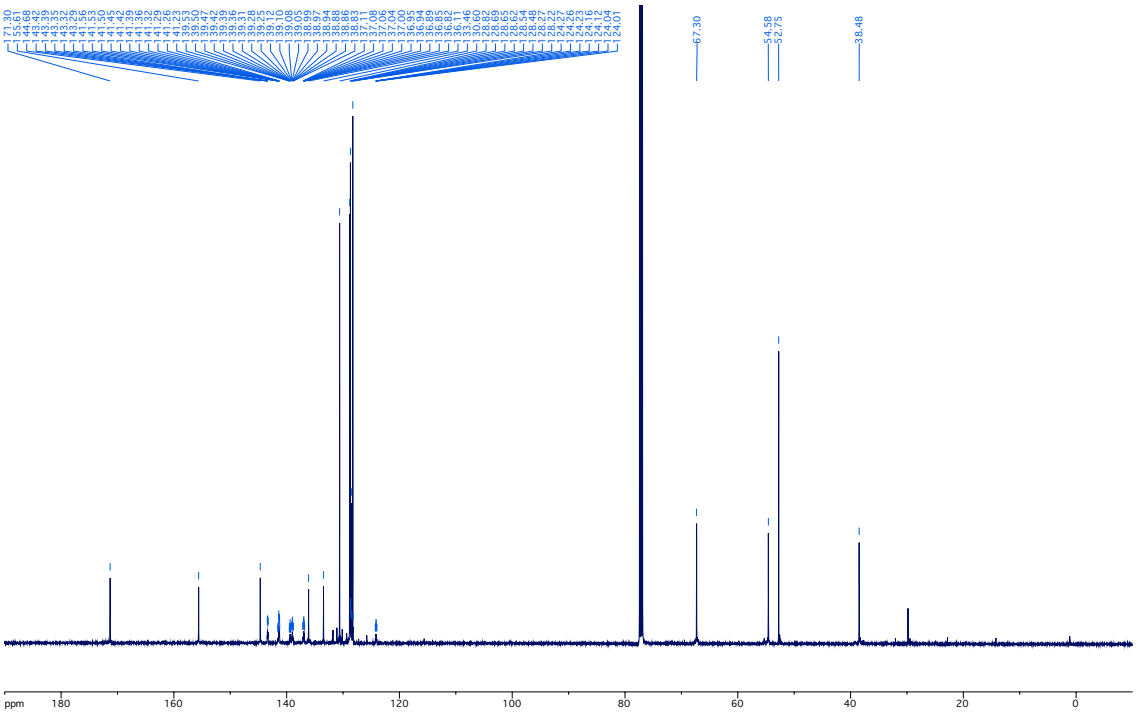




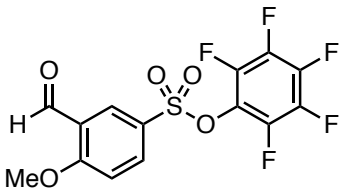
Compound **50s**

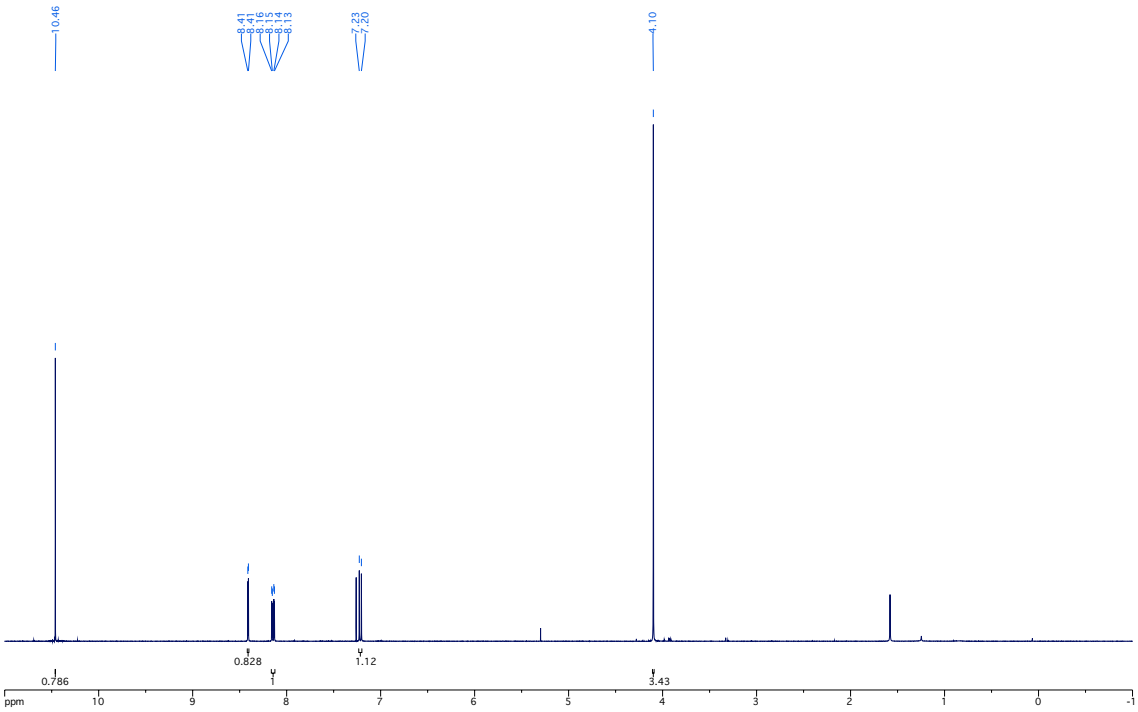


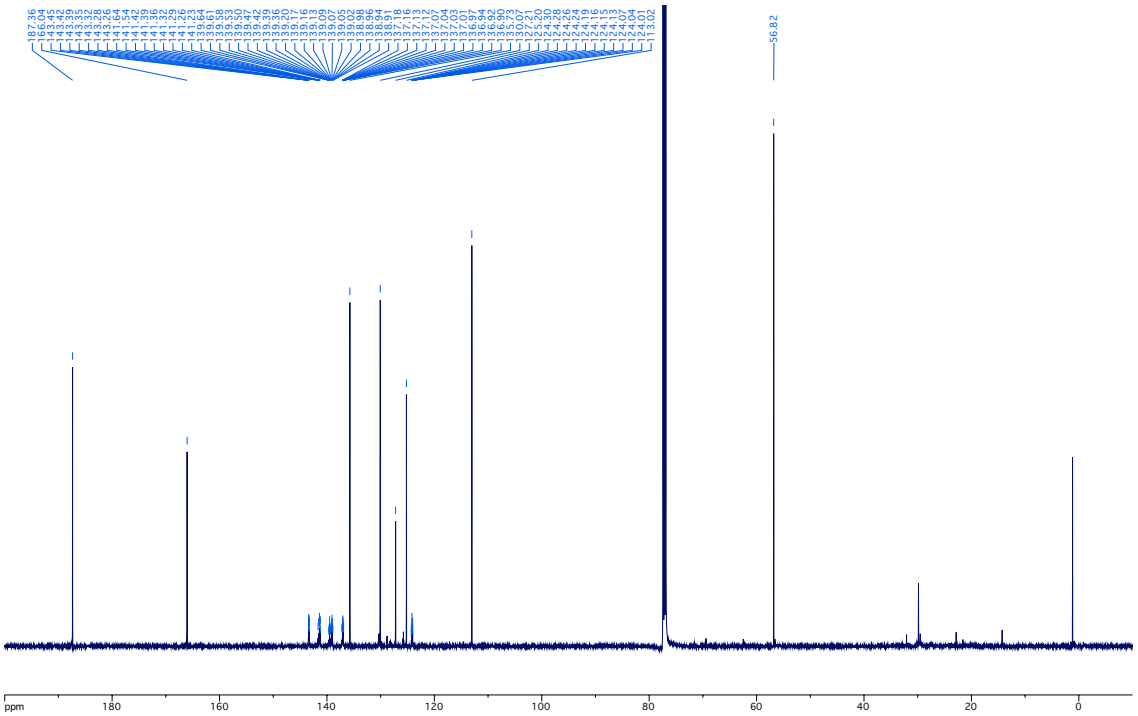




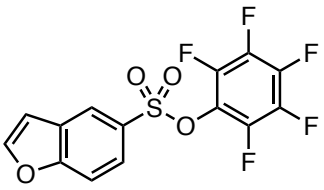
Compound **50t**

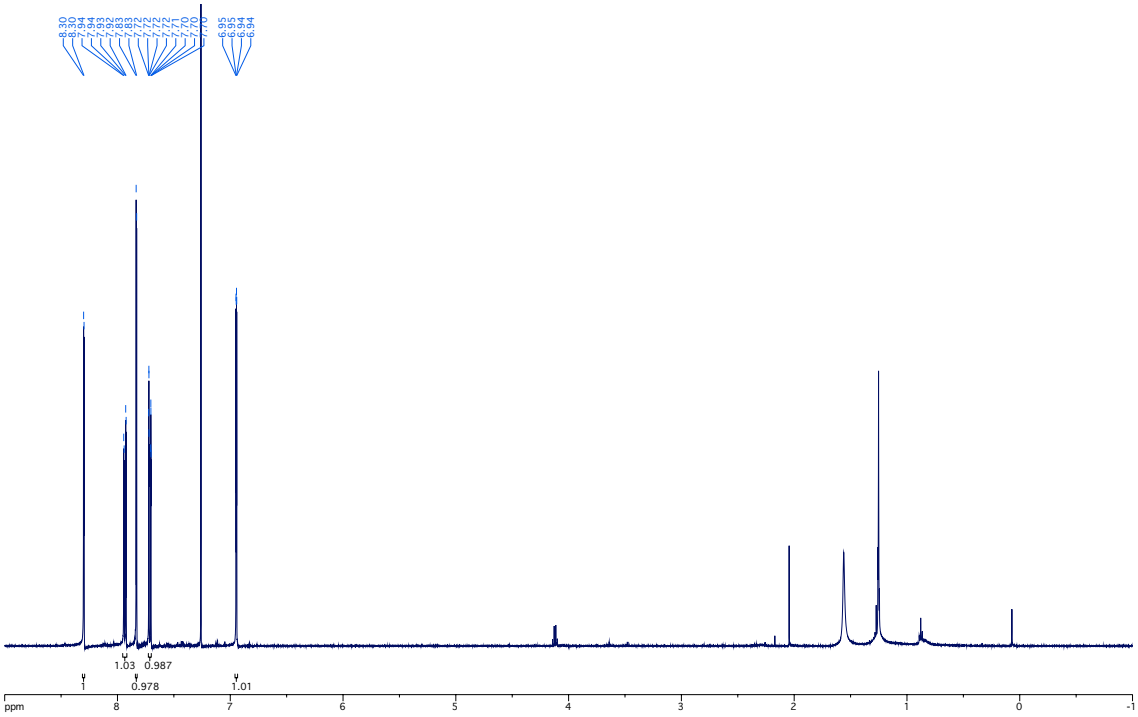


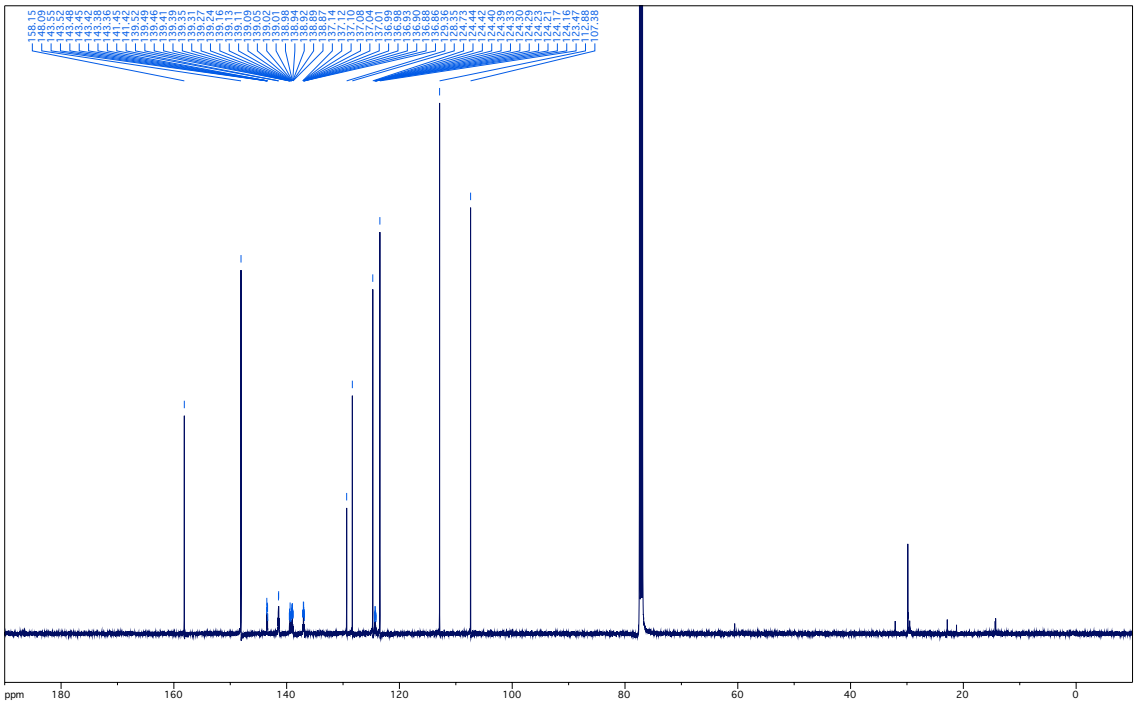




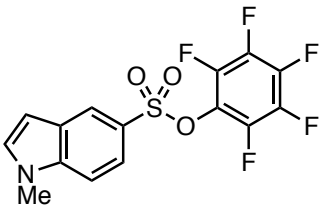
Compound **50u**

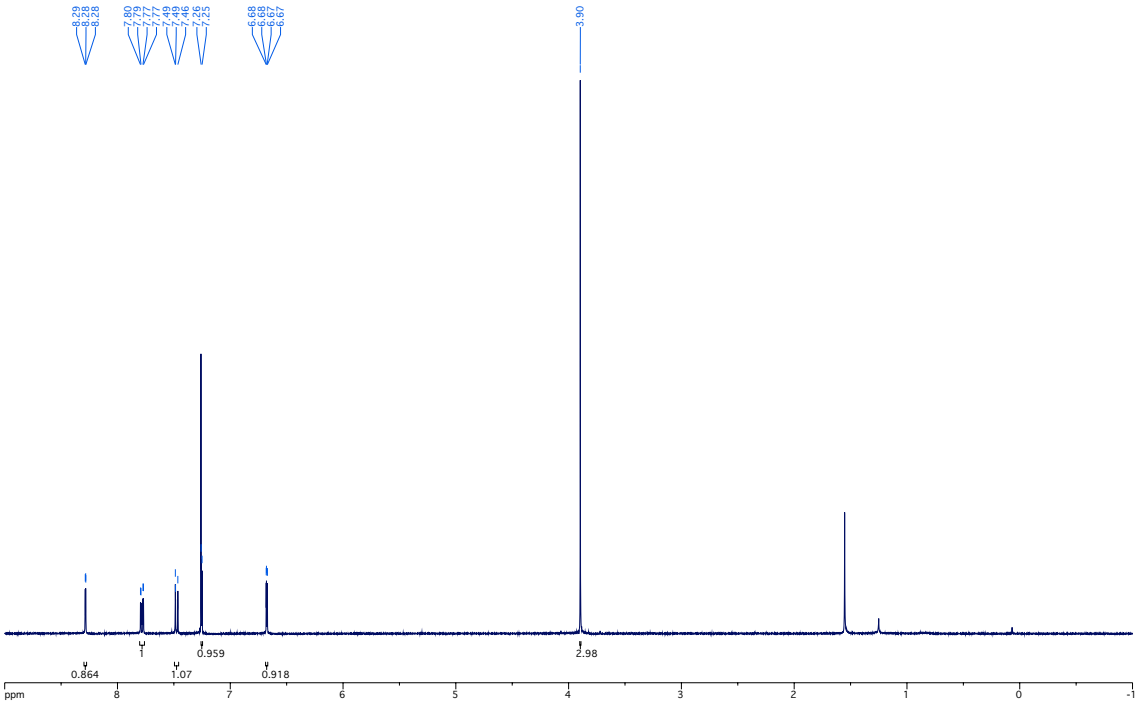


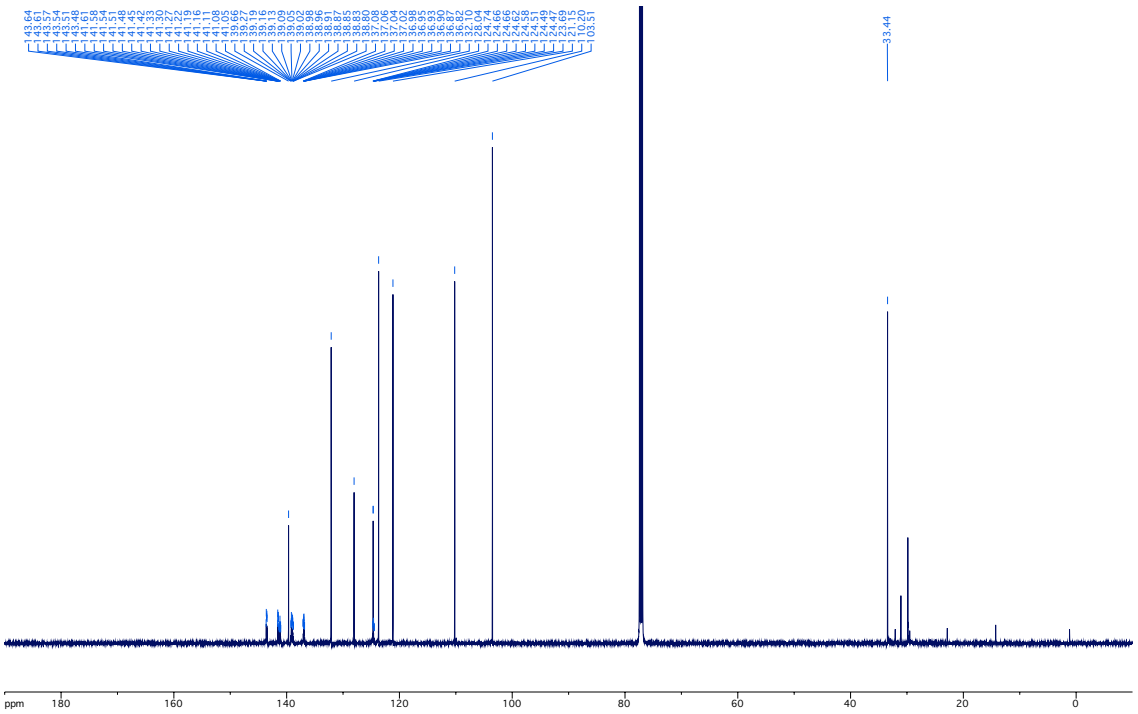




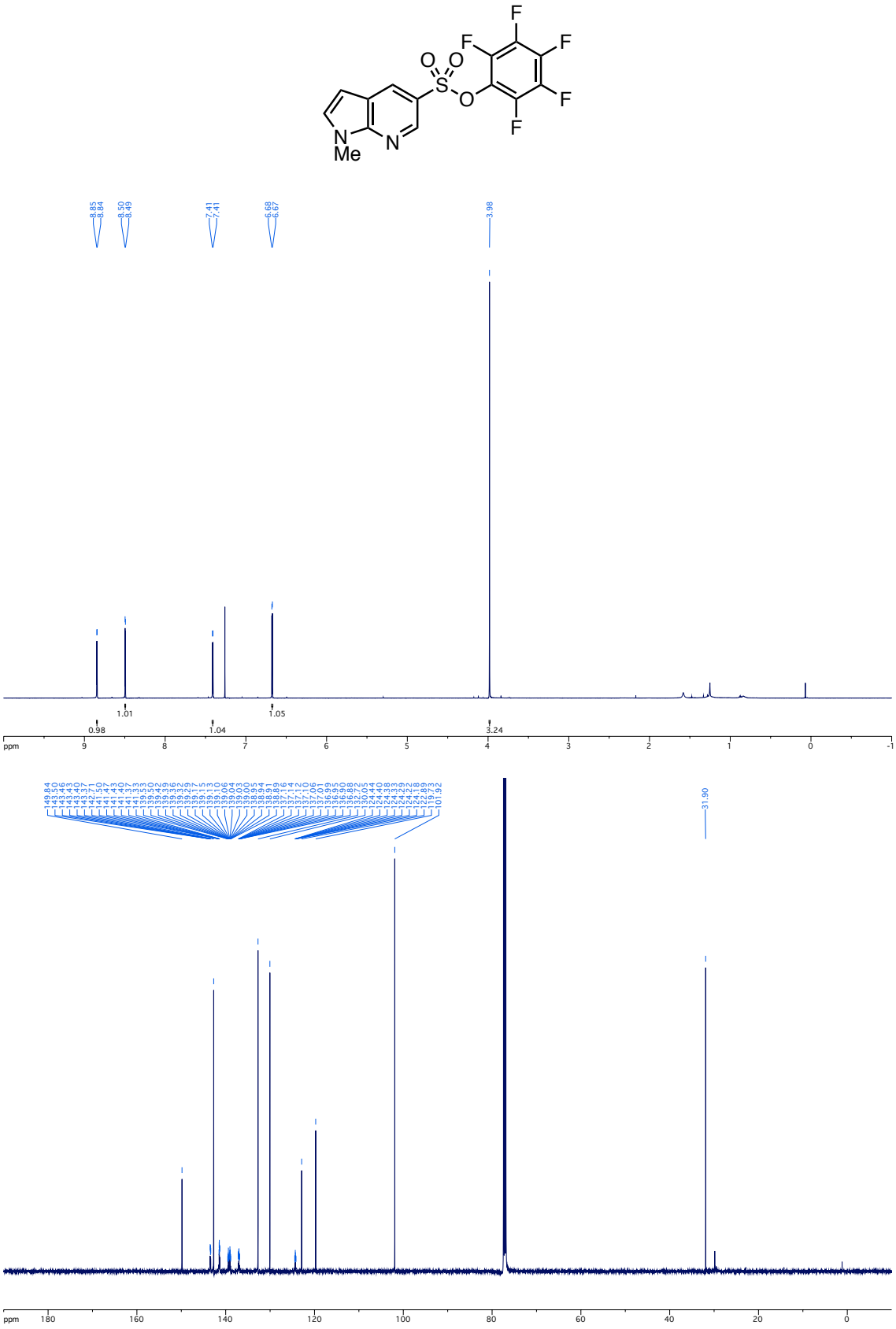
Compound **50v**


F
F
F
F
F
O
O
S
O
N
Me

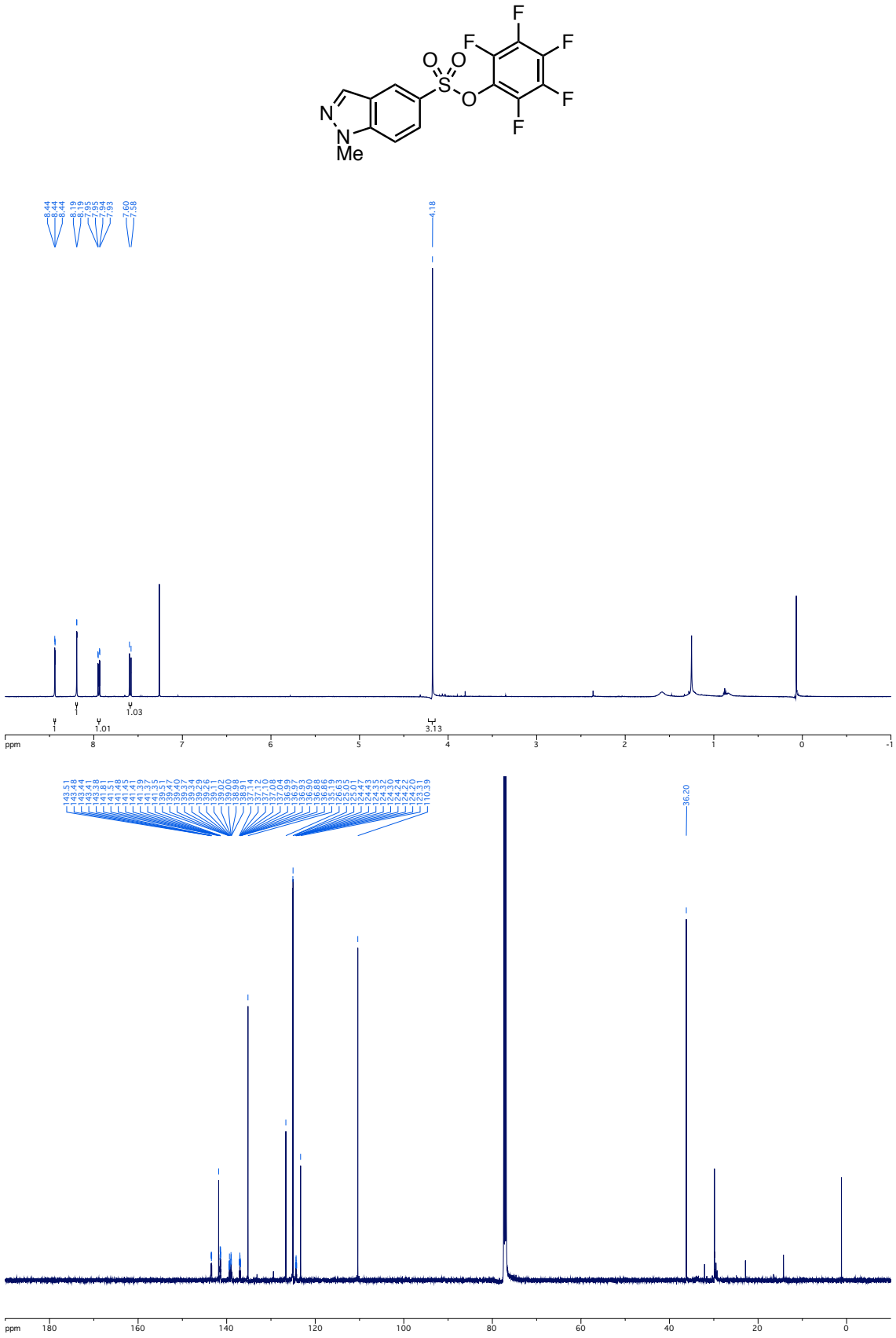

8.29
8.28
8.28
8.28
7.80
7.79
7.77
7.77
7.49
7.49
7.46
7.26
7.25
6.68
6.68
6.67
6.67
3.90
0.864
1
1.07
0.959
0.918
2.98
ppm


33.44
ppm

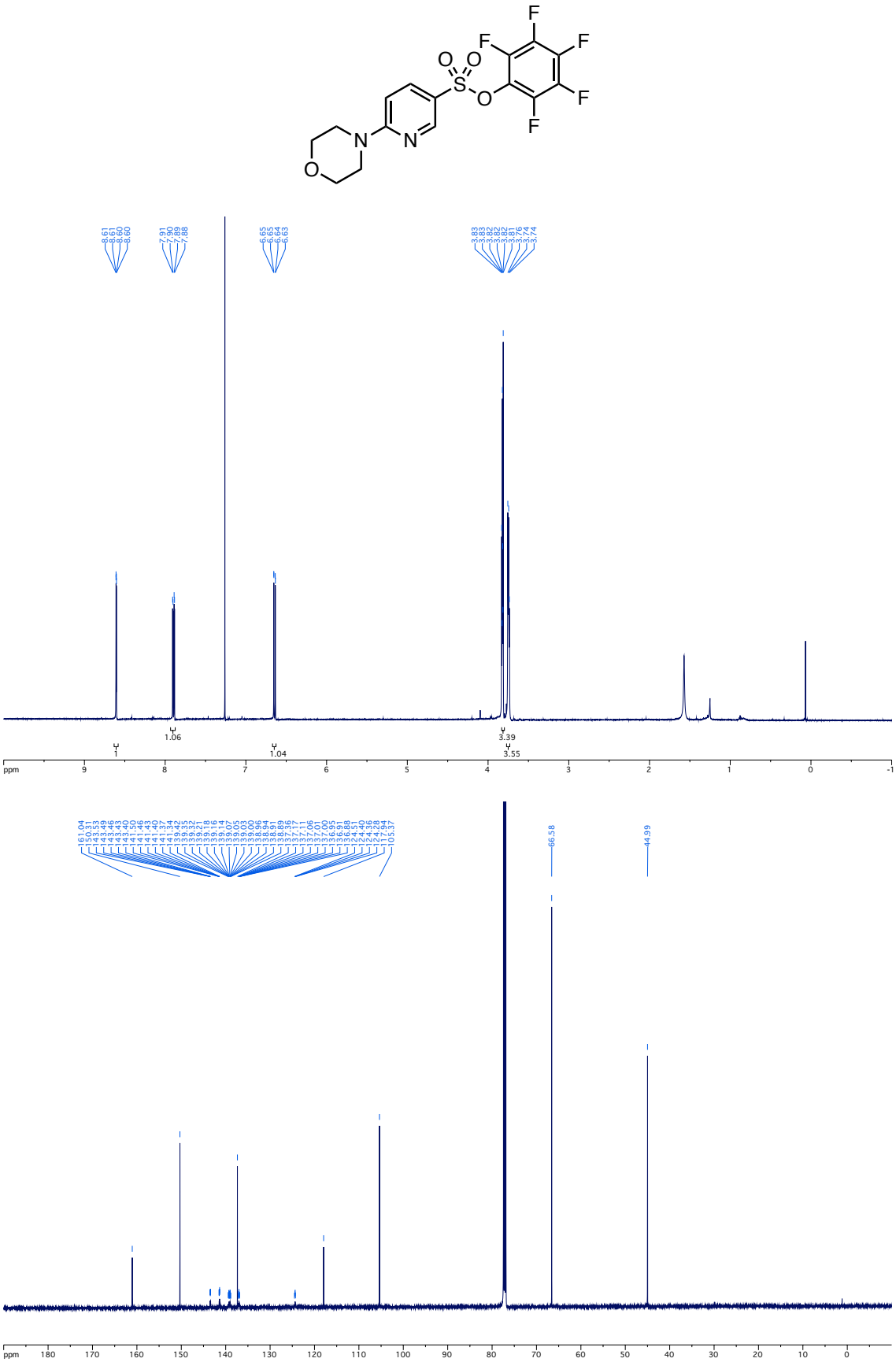
Compound **2w**



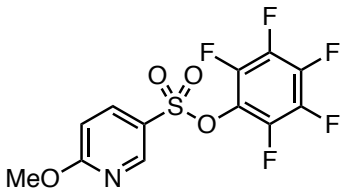
Compound **50x**

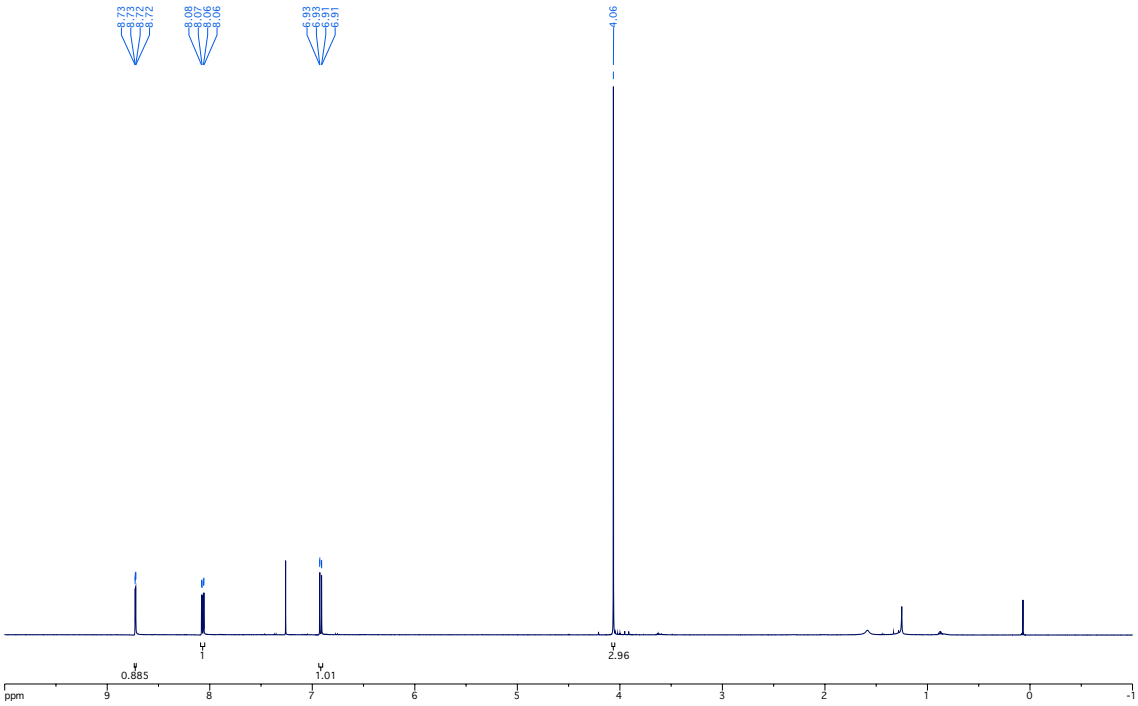


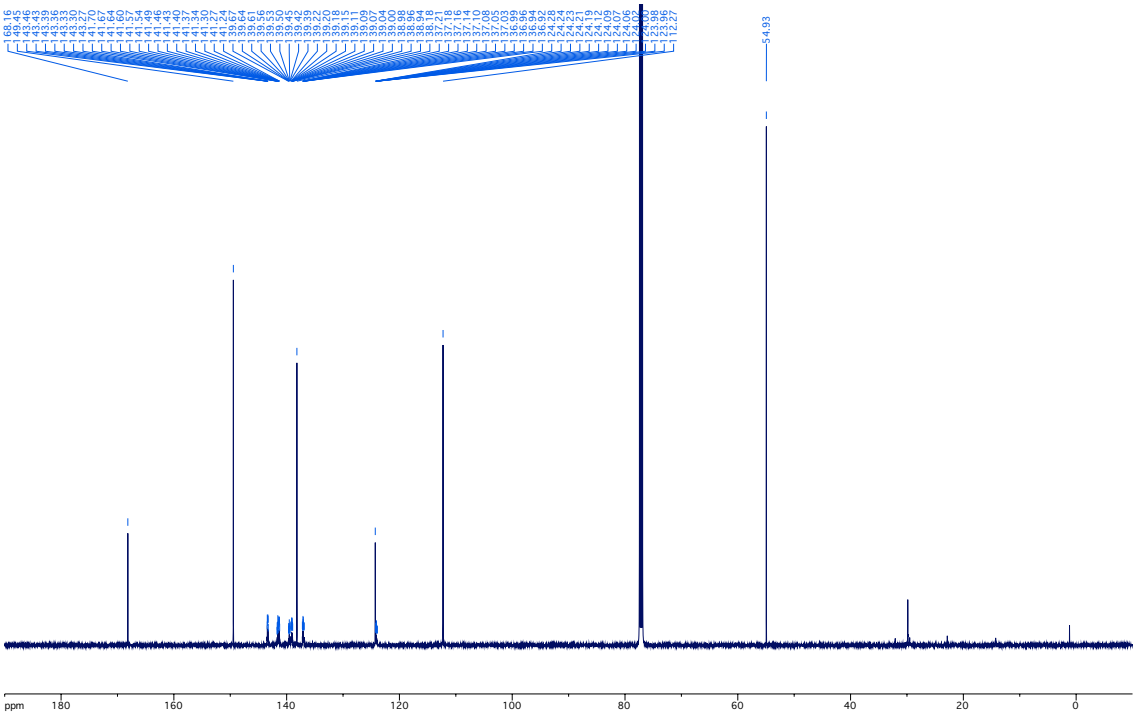
Compound **50y**



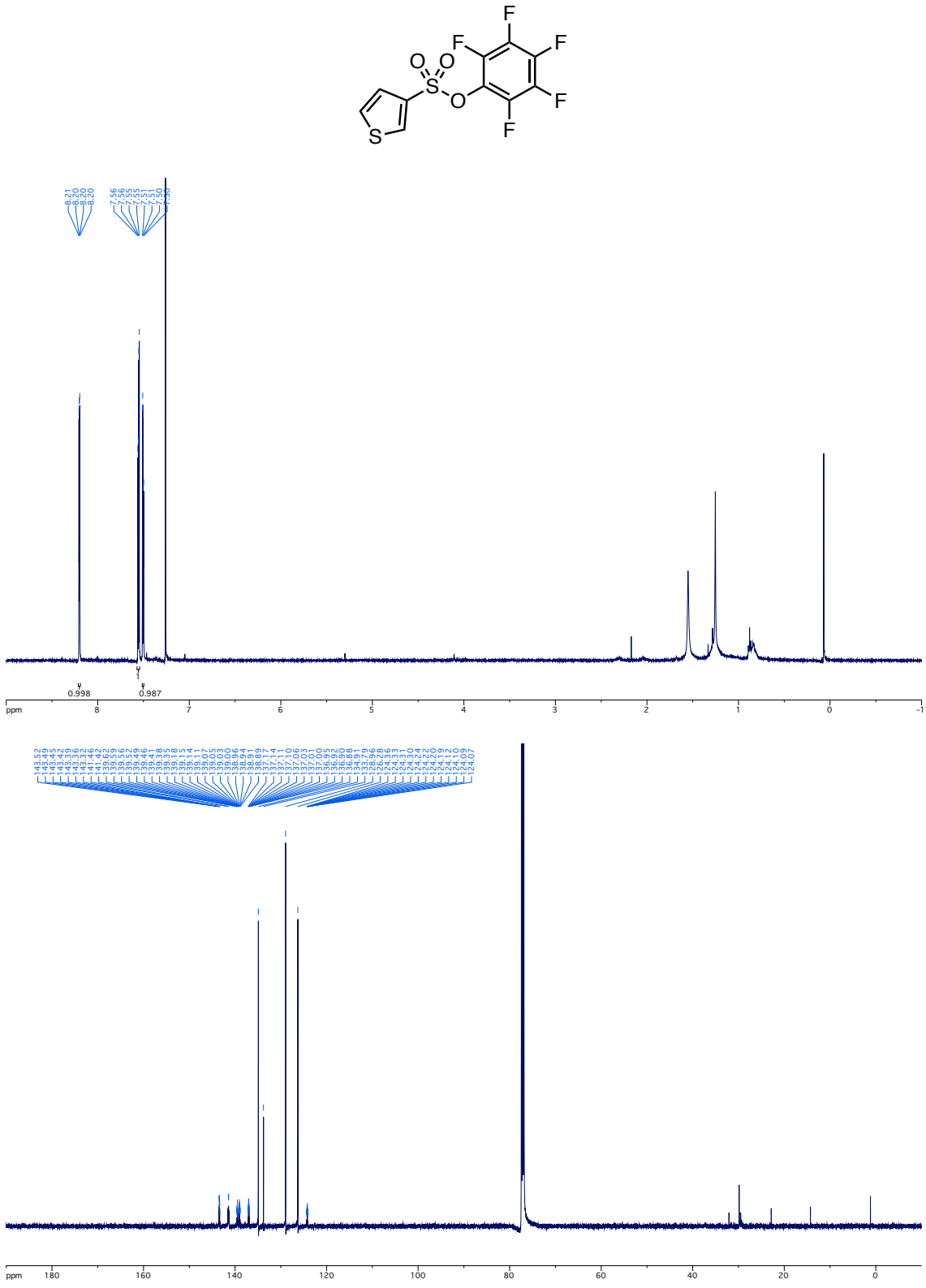
Compound **50z**



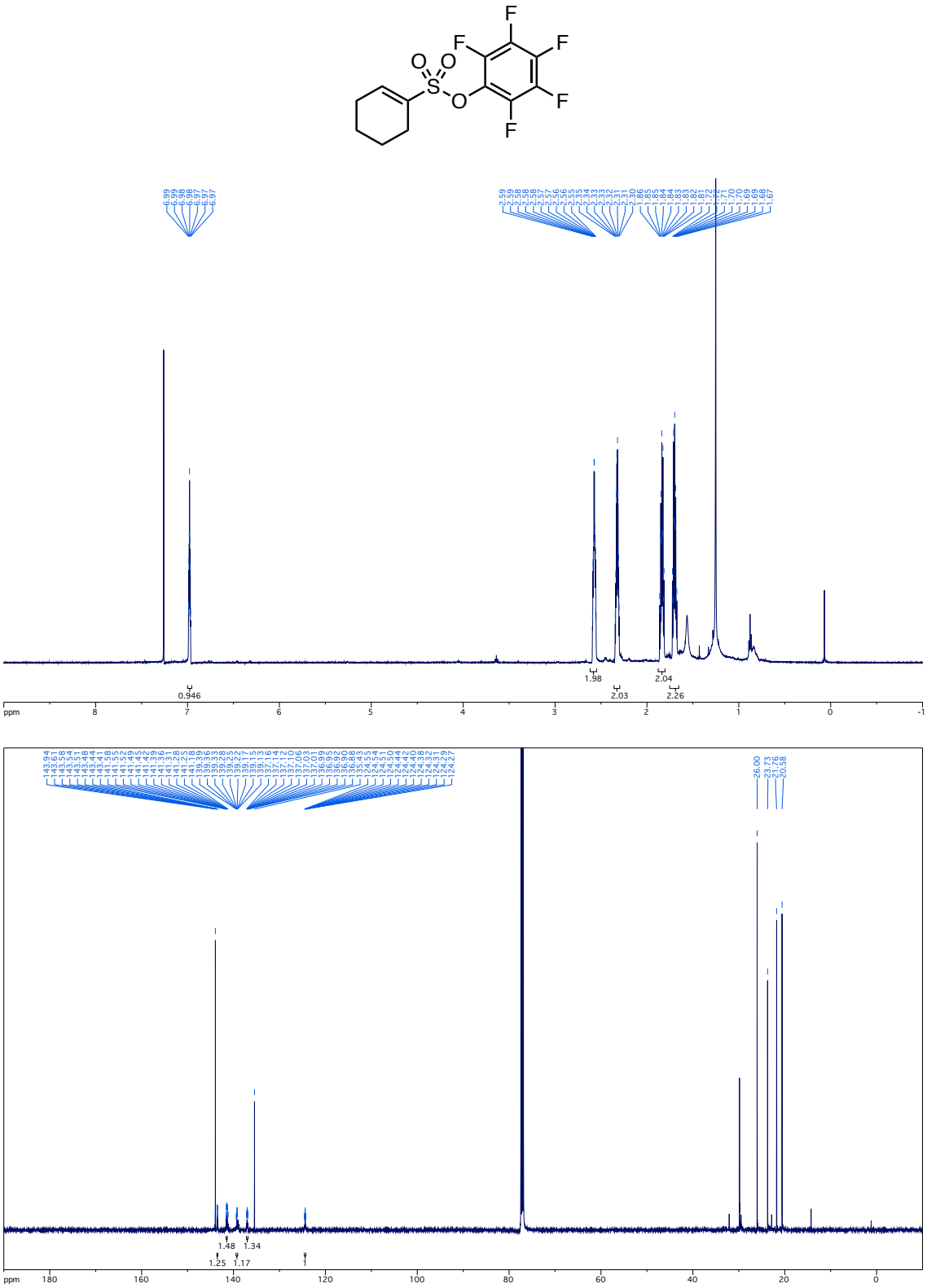




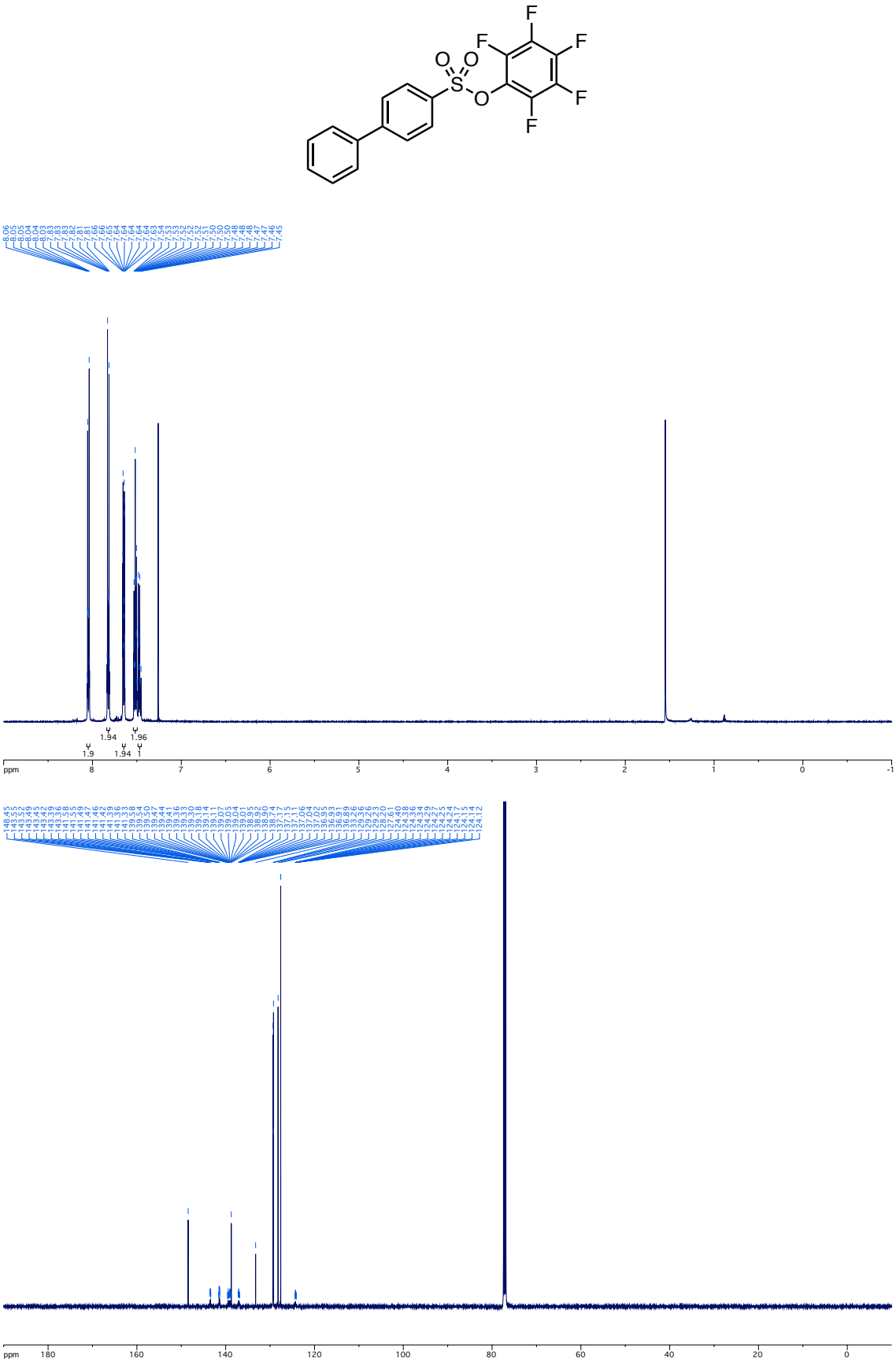
Compound **50aa**



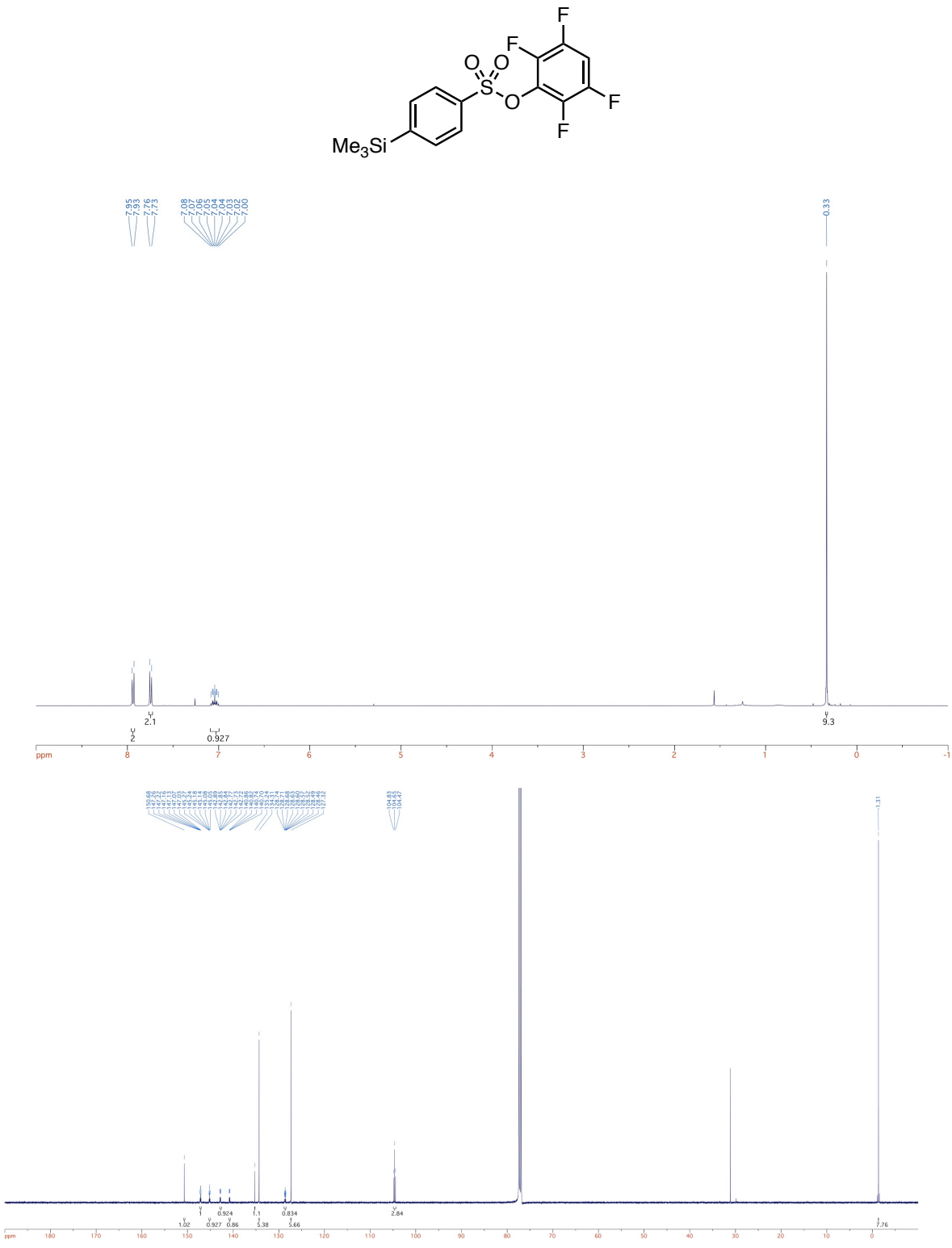
Compound **50ab**



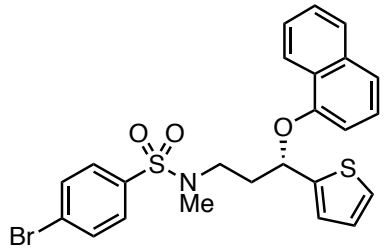
Compound **50ac**

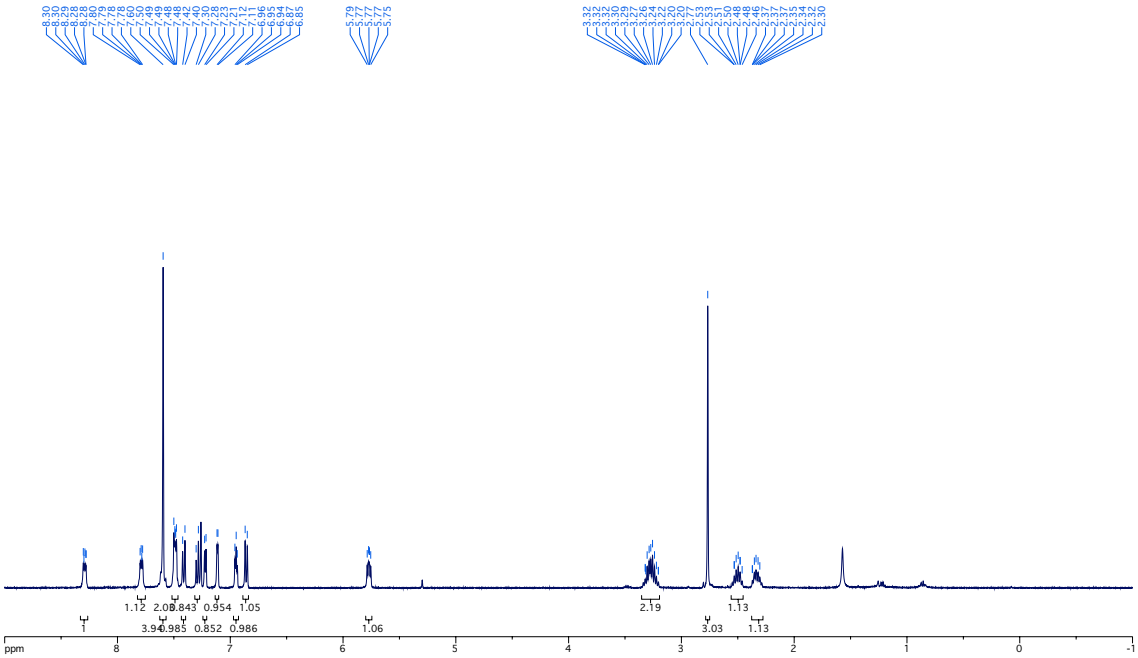


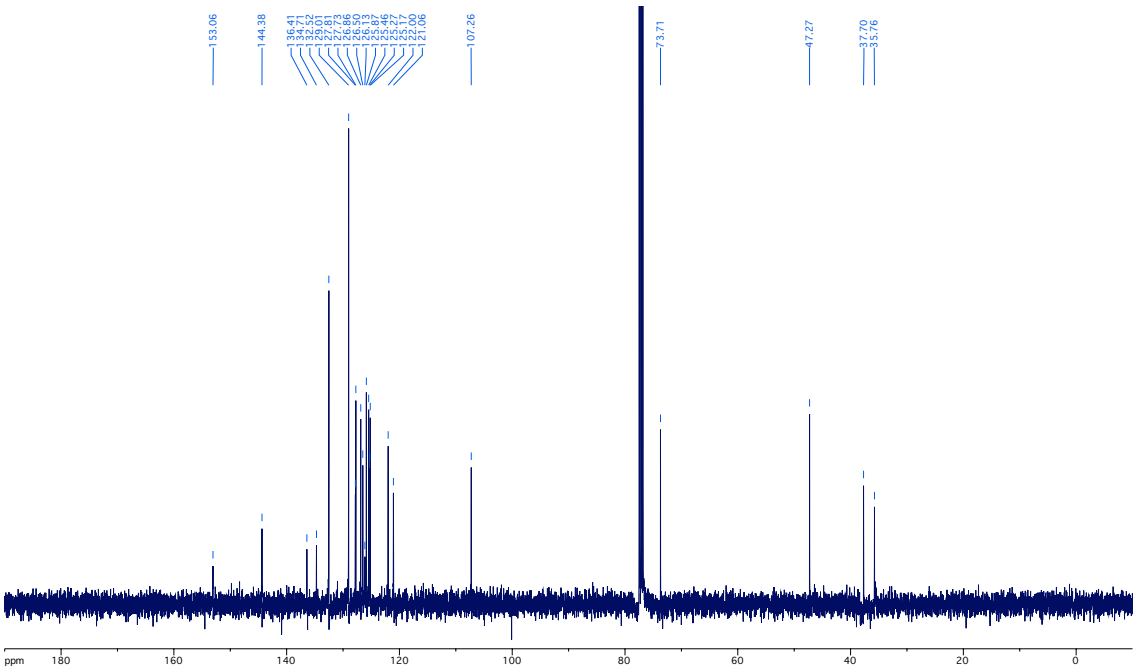
Compound **51b**


F
F
O
O
S
O
F
F
Me3Si
7.95
7.93
7.76
7.73
7.08
7.07
7.06
7.05
7.04
7.04
7.03
7.02
7.00
0.33
2.1
2
0.927
9.3
ppm
8
7
6
5
4
3
2
1
0
-1
104.83
104.67
104.47
1.31
1.02
0.927
0.924
0.86
1.1
5.38
0.834
5.66
2.84
7.76
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

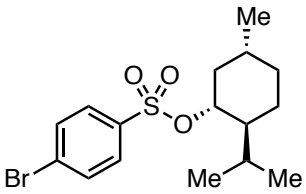
Compound **52**

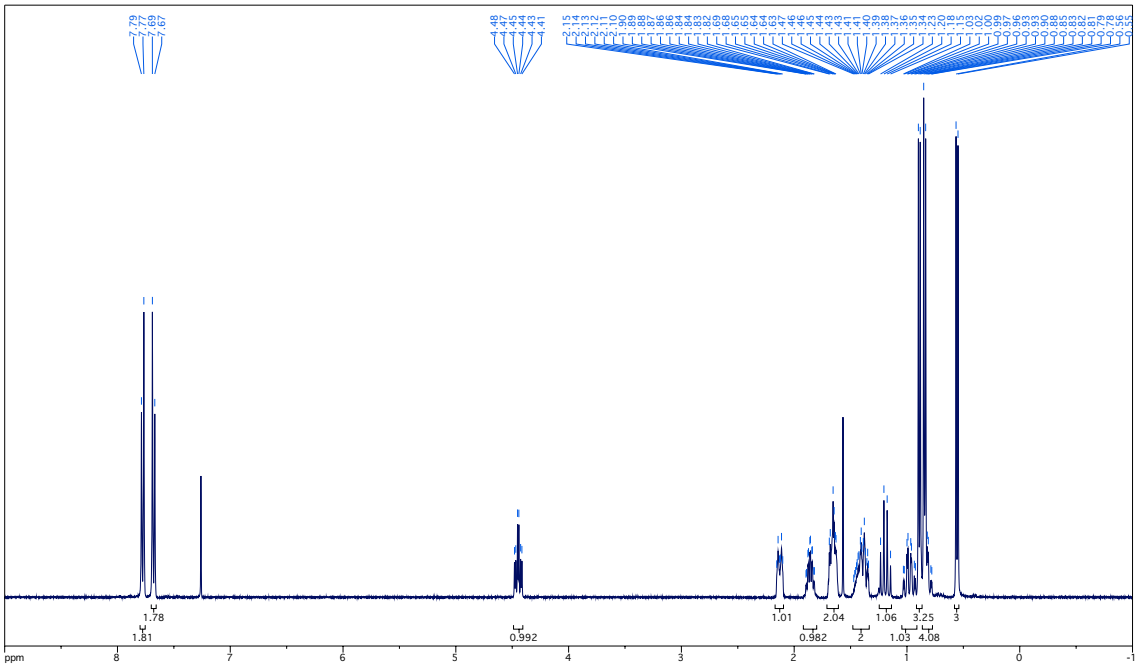

O
O
S
N
Me
O
S
Br

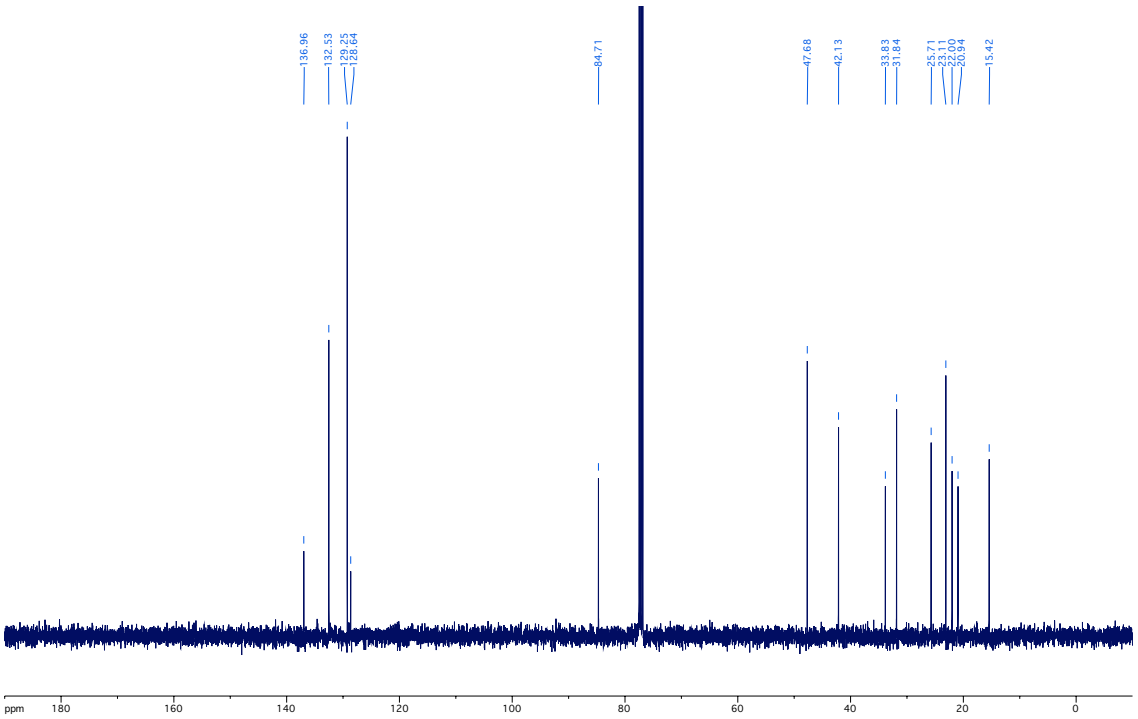

1.12
2.08
0.843
0.954
1.05
3.94
0.985
0.852
0.986
1.06
2.19
1.13
3.03
1.13
ppm


153.06
144.38
136.41
134.71
134.52
130.01
127.81
127.73
126.66
126.50
126.13
125.46
125.27
123.17
122.00
121.06
107.26
73.71
47.27
37.70
35.76
ppm

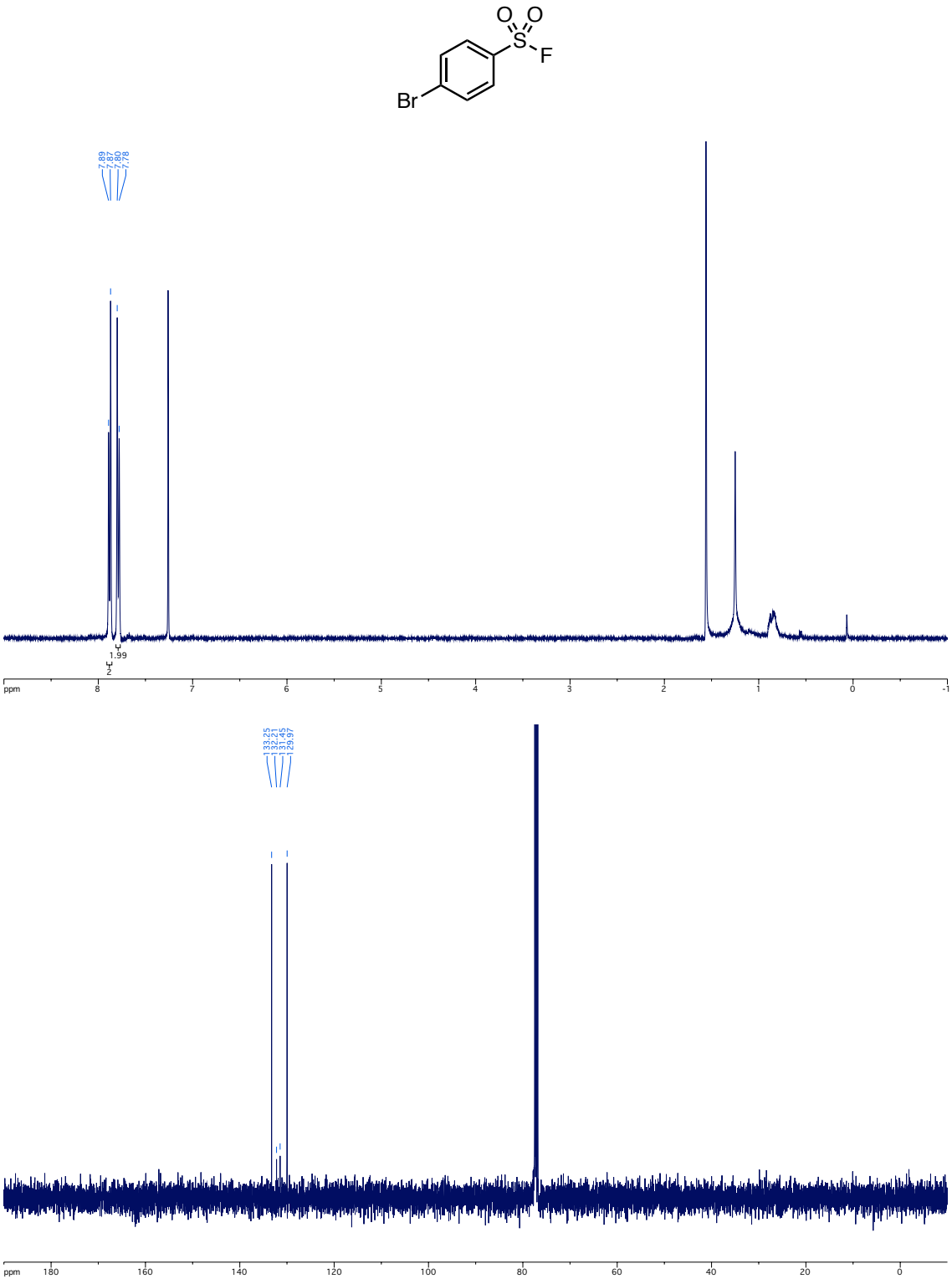
Compound **53**


Me
O
O
S
O
Br
Me
Me

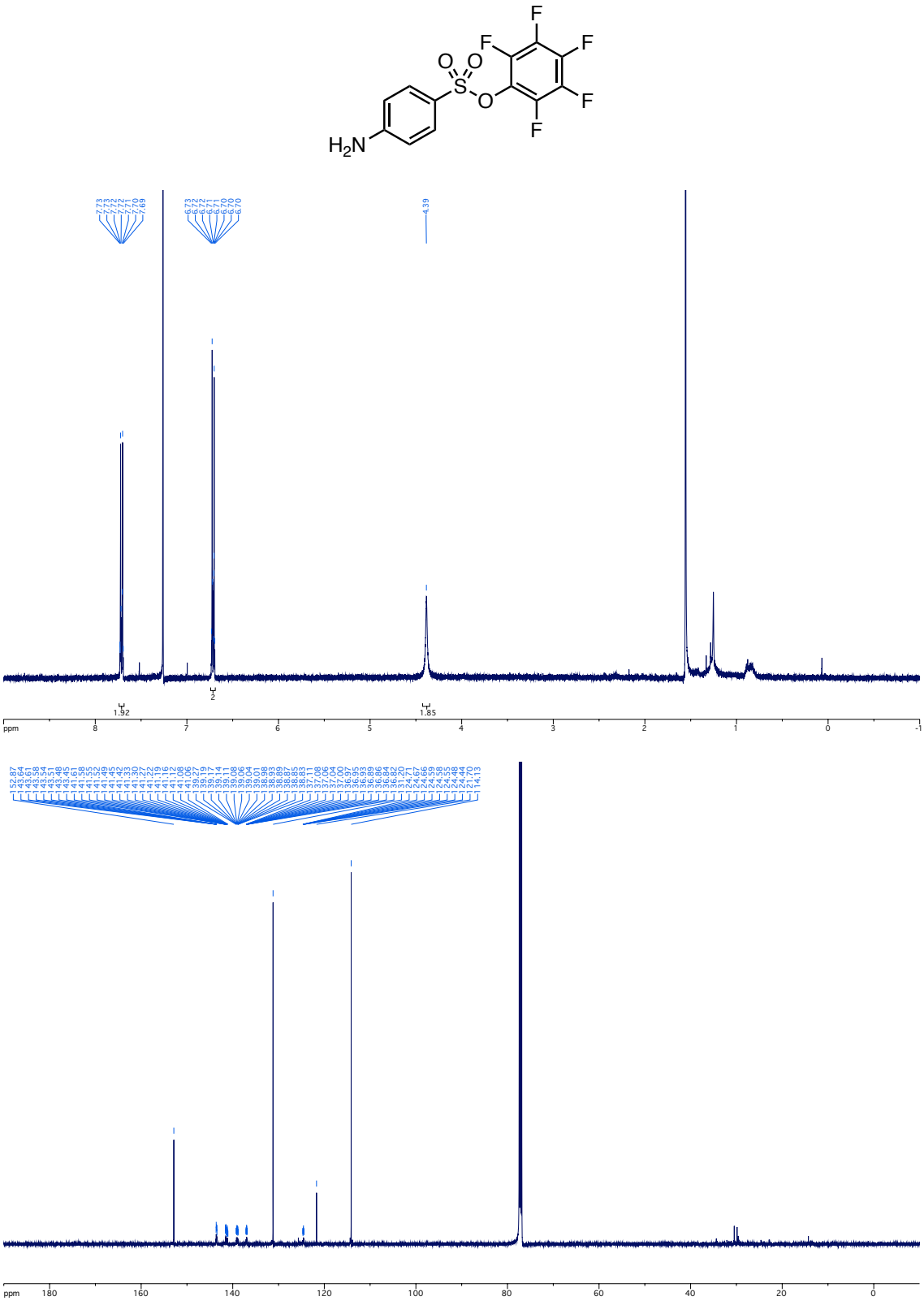

7.79
7.77
7.69
7.67
4.48
4.47
4.45
4.44
4.43
4.41
2.15
2.14
2.13
2.12
2.11
2.10
2.09
2.08
2.07
2.06
2.05
2.04
2.03
2.02
2.01
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.93
1.92
1.91
1.90
1.89
1.88
1.87
1.86
1.85
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.61
1.60
1.59
1.58
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.41
1.40
1.39
1.38
1.37
1.36
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.28
1.27
1.26
1.25
1.24
1.23
1.22
1.21
1.20
1.19
1.18
1.17
1.16
1.15
1.14
1.13
1.12
1.11
1.10
1.09
1.08
1.07
1.06
1.05
1.04
1.03
1.02
1.01
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
0.89
0.88
0.87
0.86
0.85
0.84
0.83
0.82
0.81
0.80
0.79
0.78
0.77
0.76
1.78
1.81
0.992
1.01
2.04
0.982
1.06
2
1.03
3.25
4.08
3
ppm
8
7
6
5
4
3
2
1
0
-1


136.96
132.53
129.25
128.64
84.71
47.68
42.13
33.83
31.84
25.71
23.11
21.10
20.94
15.42
ppm
180
160
140
120
100
80
60
40
20
0

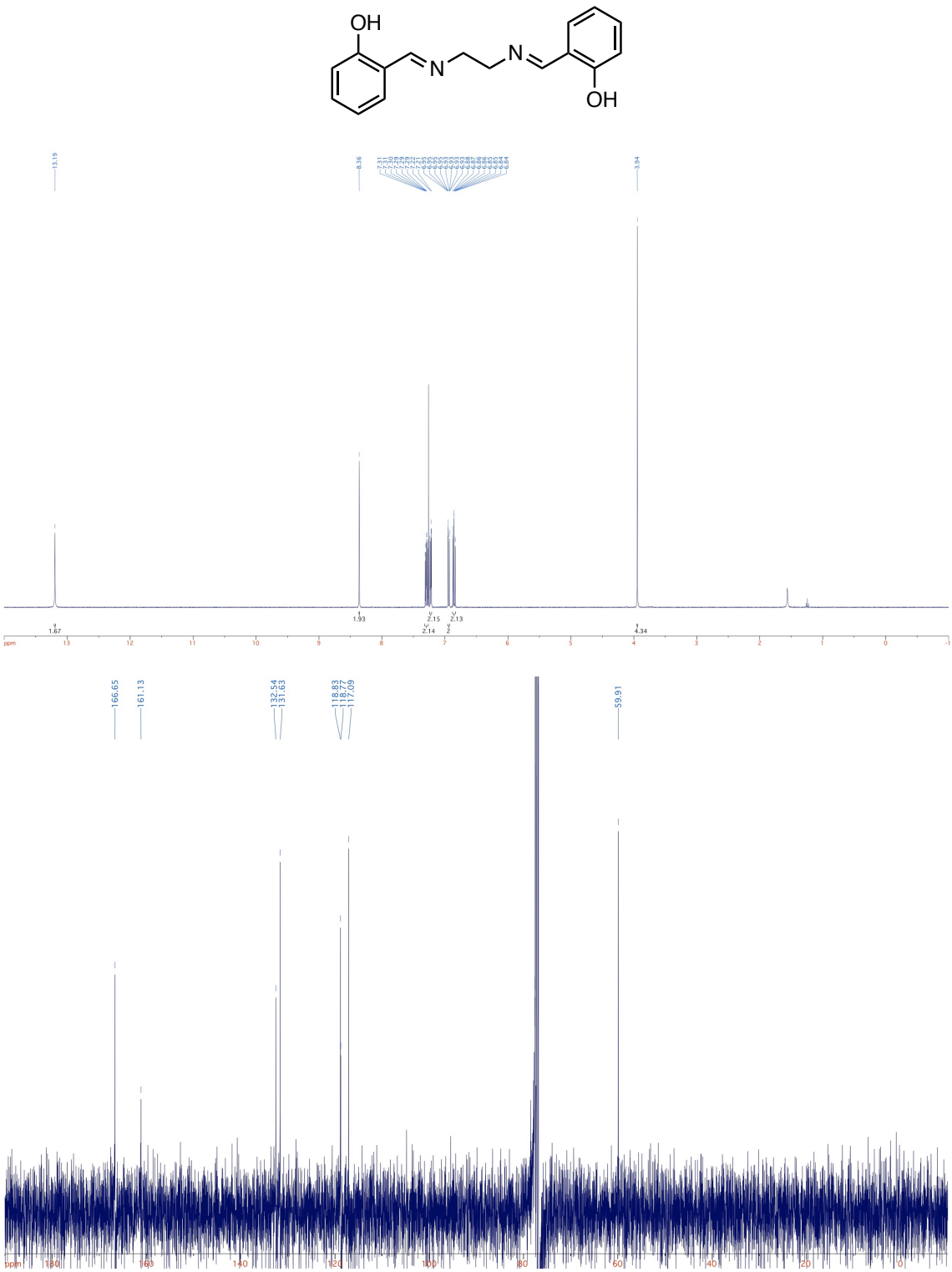
Compound **54**


O
O
S
F
Br
7.89
7.87
7.80
7.78
1.99
2
ppm
8
7
6
5
4
3
2
1
0
-1
133.25
132.21
131.45
129.97
ppm
180
160
140
120
100
80
60
40
20
0

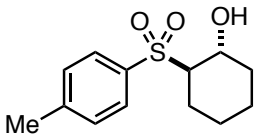
Compound **55**

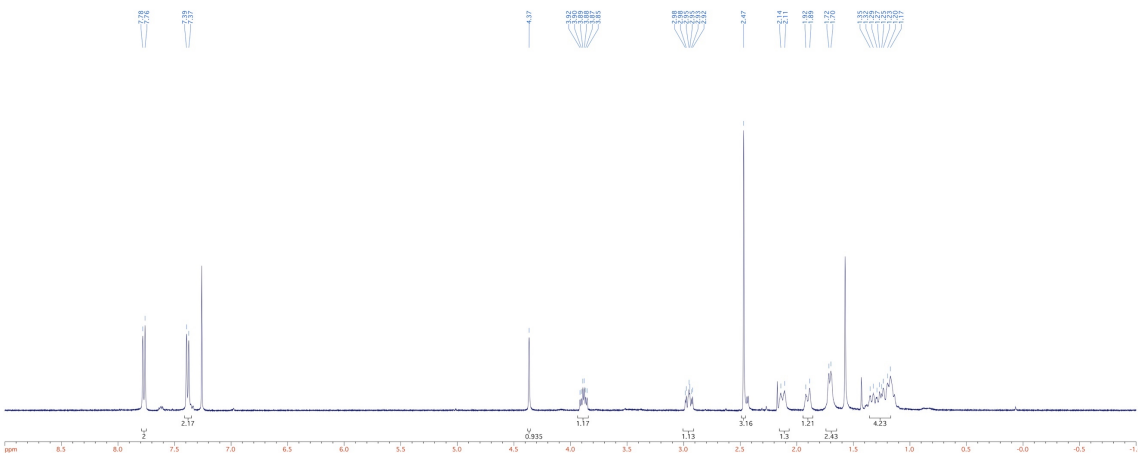

F
F
F
F
F
O
O
S
O
H_2N
7.73
7.72
7.71
7.70
7.69
6.73
6.72
6.71
6.70
4.39
1.92
2
1.85
ppm
8
7
6
5
4
3
2
1
0
-1
ppm
180
160
140
120
100
80
60
40
20
0

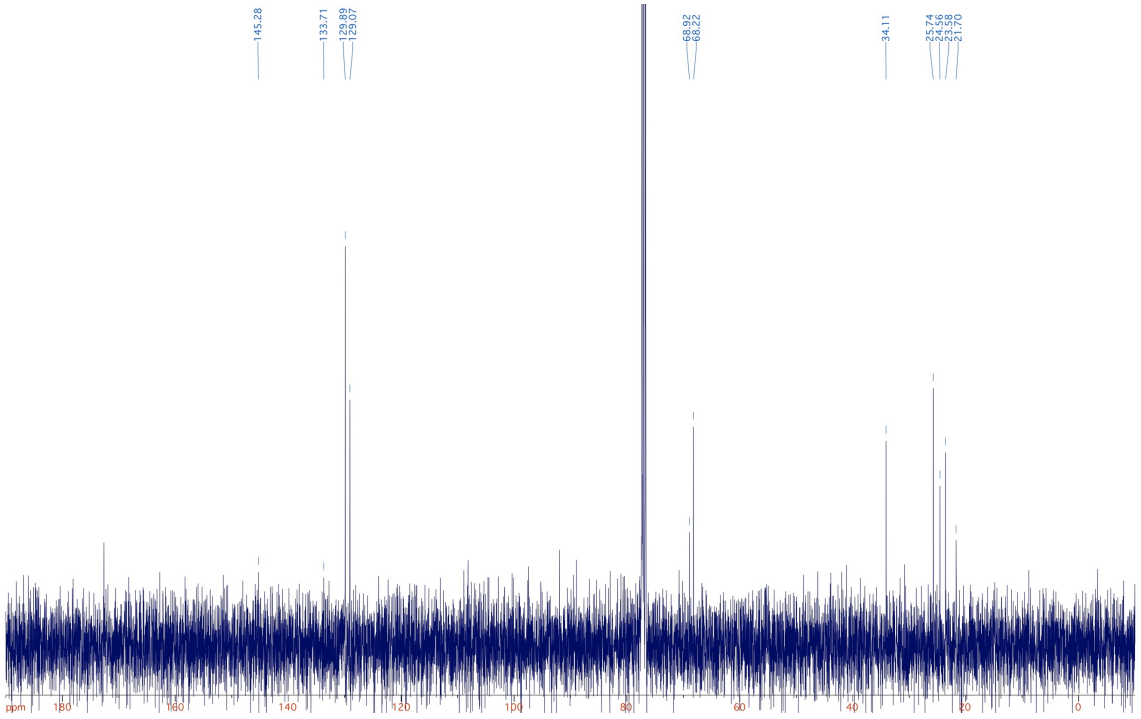
Compound **58**


OH
N
N
OH
13.19
8.36
7.31
7.30
7.29
7.28
7.27
7.22
6.96
6.95
6.94
6.93
6.92
6.91
6.90
6.89
6.88
6.87
6.86
6.85
6.84
3.94
1.67
1.93
2.15
2.14
2.13
2
4.34
ppm
166.65
161.13
132.54
131.63
118.83
118.77
117.69
117.09
59.91

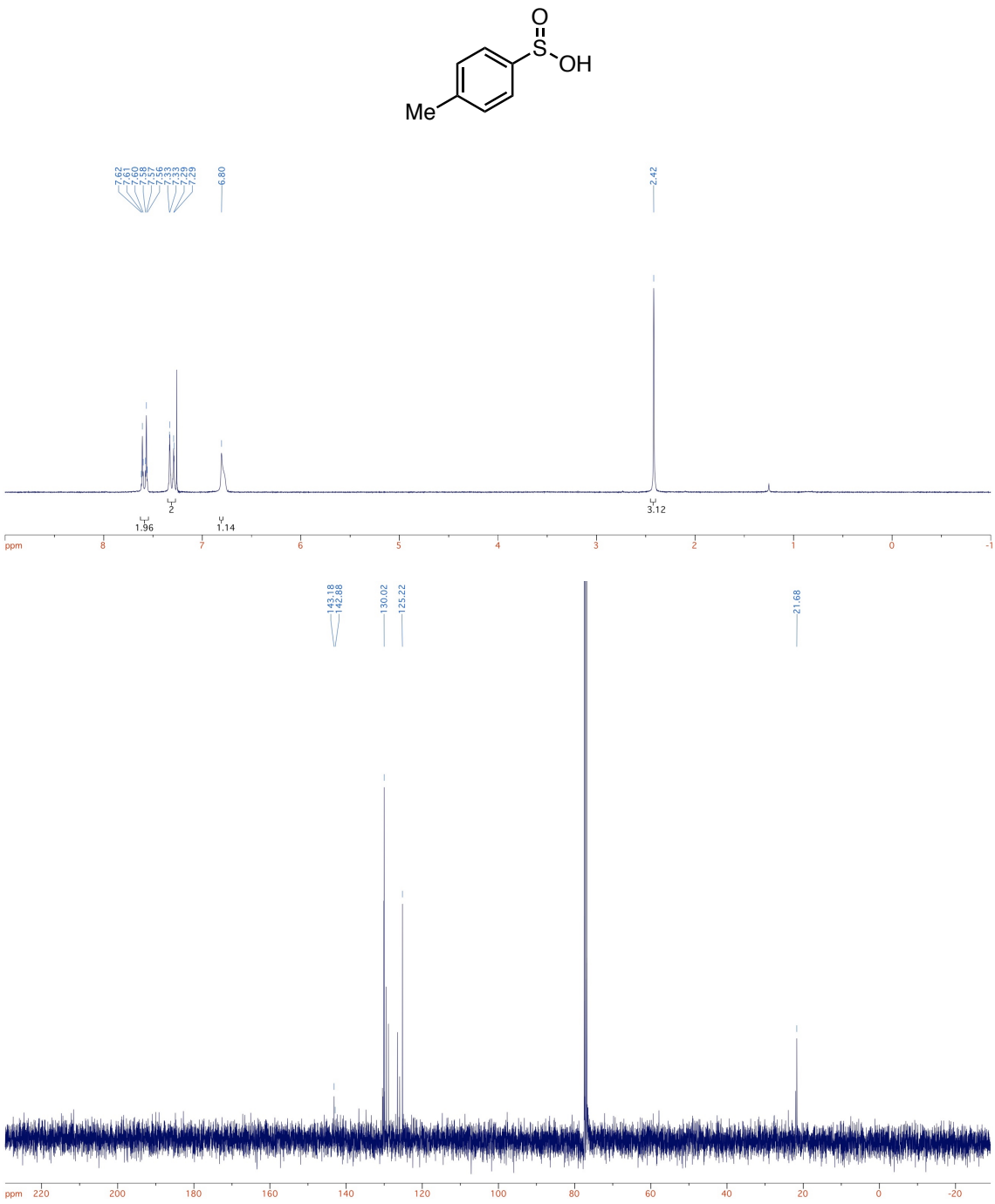
Compound **60**


O
O
S
OH
Me

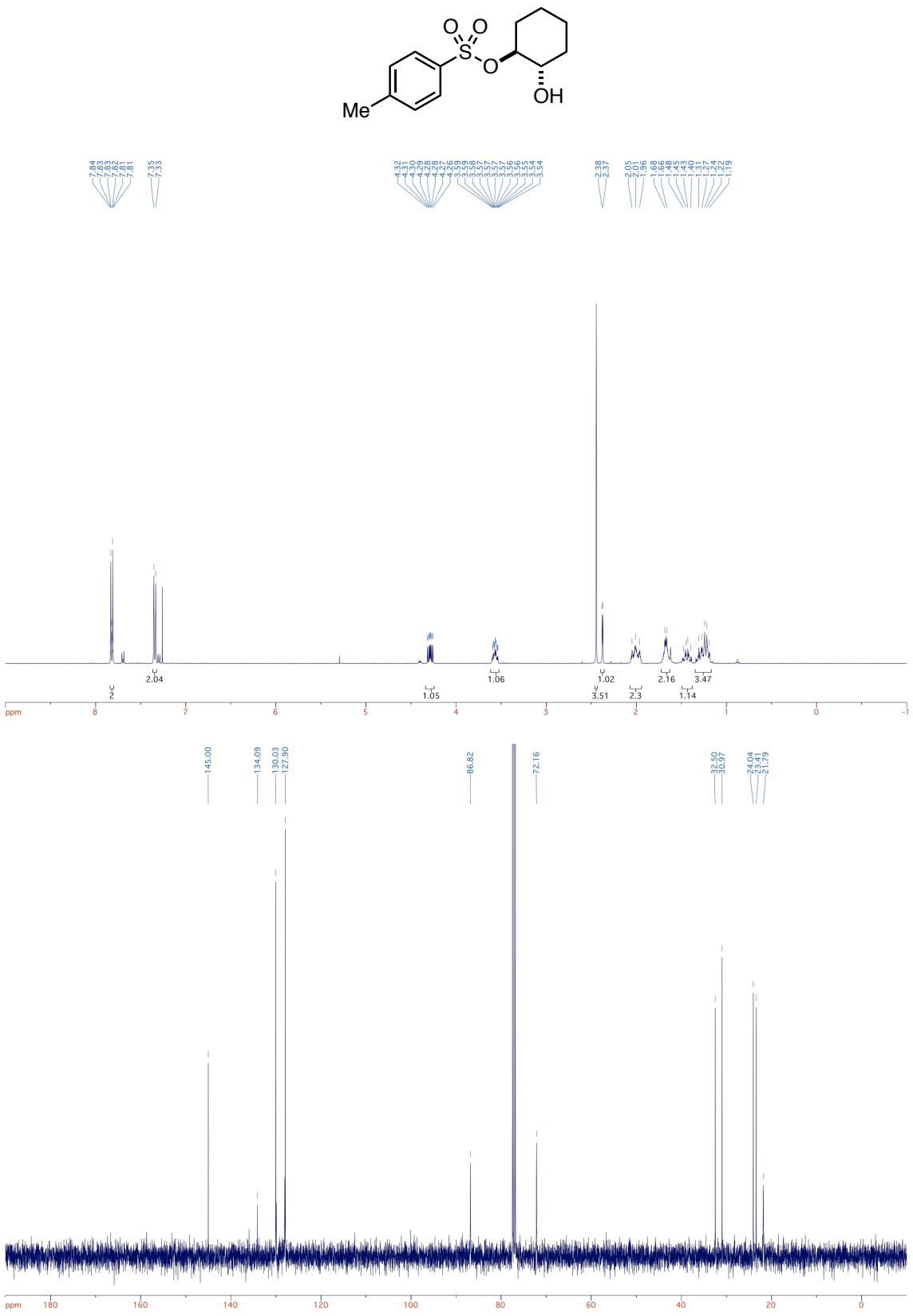



145.28
133.71
129.89
129.07
68.92
68.22
34.11
25.74
24.46
23.58
21.70

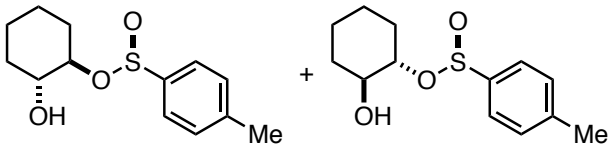
Compound **61**

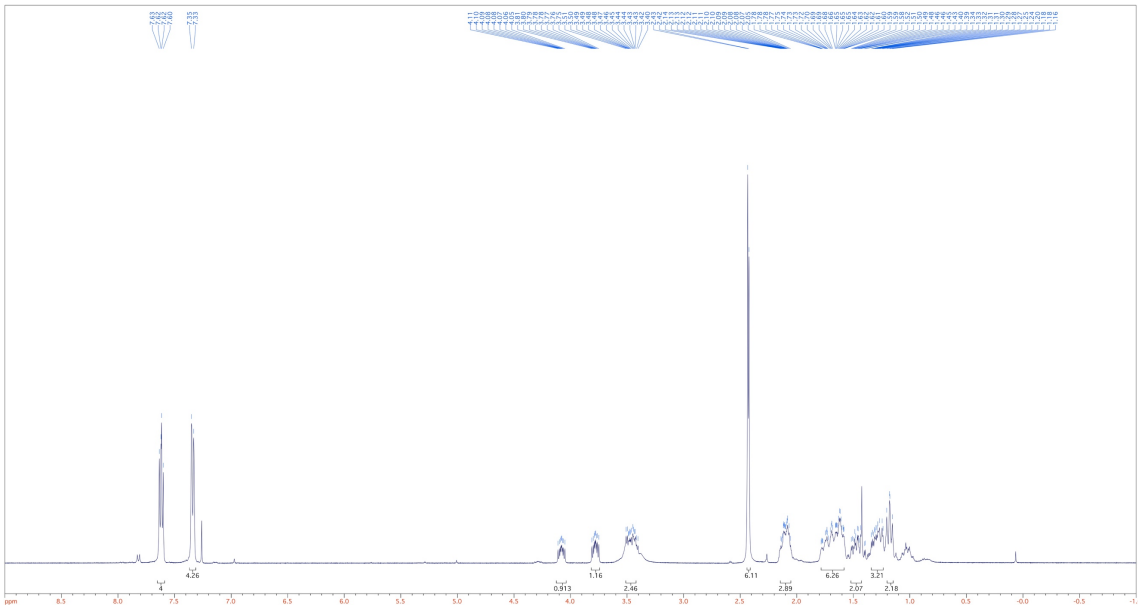

O
S
OH
Me
7.62
7.61
7.60
7.58
7.57
7.56
7.35
7.33
7.30
7.29
6.80
2.42
1.96
2
1.14
3.12
ppm
143.18
142.88
130.02
125.22
21.68

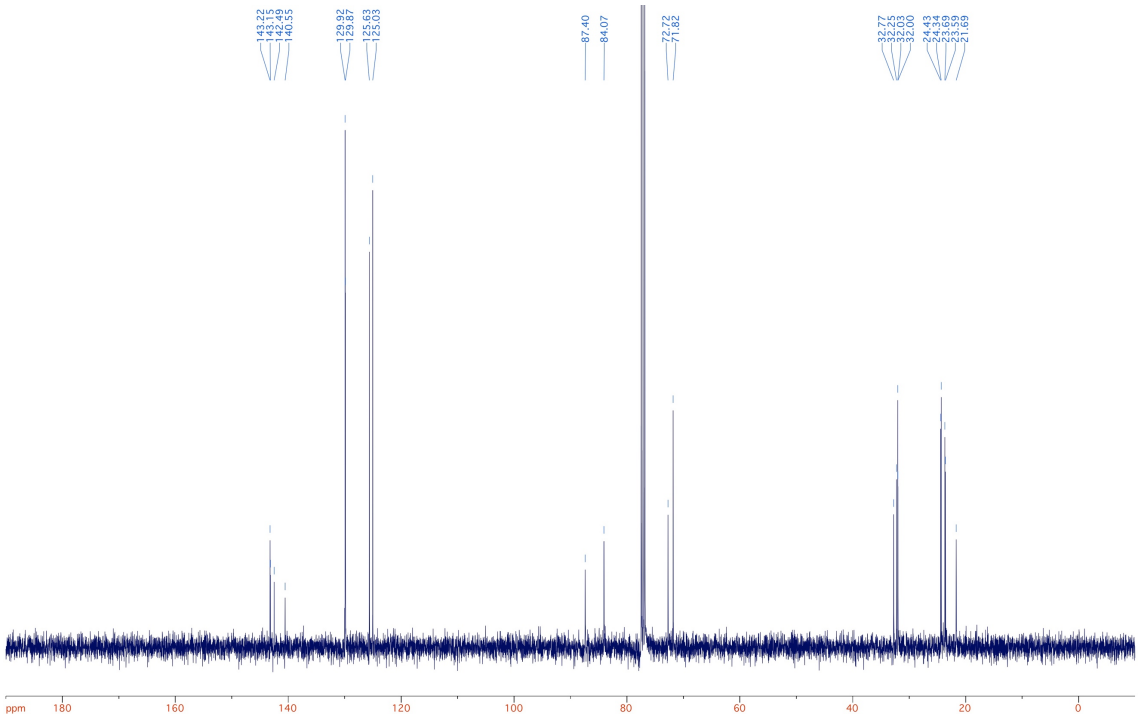
Compound **62**


Me
O
O
S
O
OH
2.04
1.05
1.06
1.02
3.51
2.3
2.16
3.47
1.14
ppm
145.00
134.09
130.03
127.90
86.82
72.16
32.50
30.97
24.04
23.41
21.79

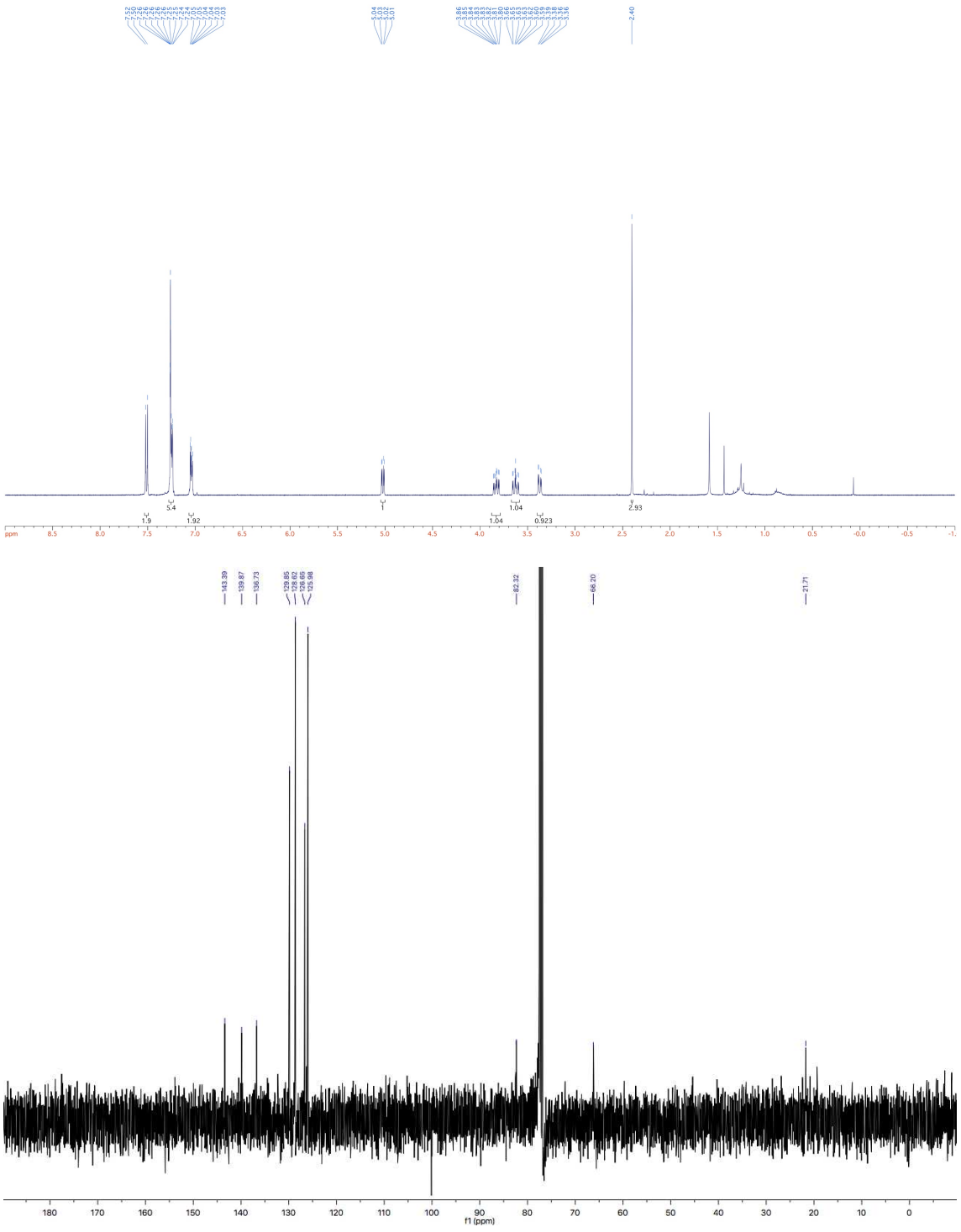
Compound **69**


O
S
O
OH
Me
+
O
S
O
OH
Me

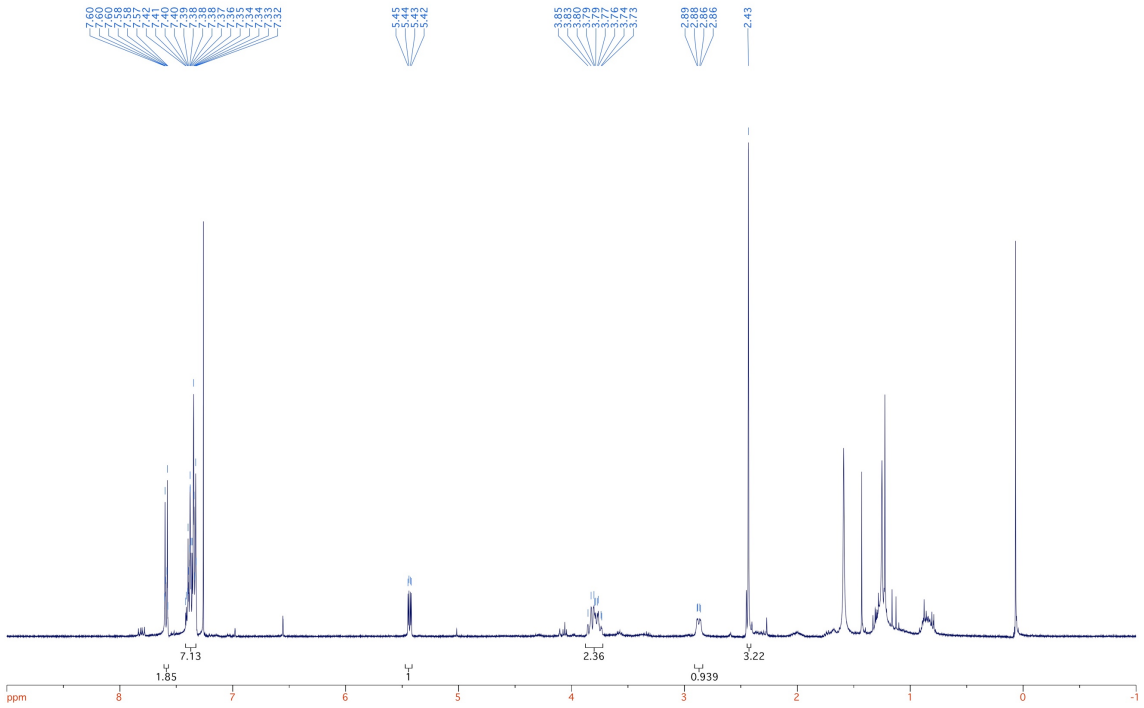


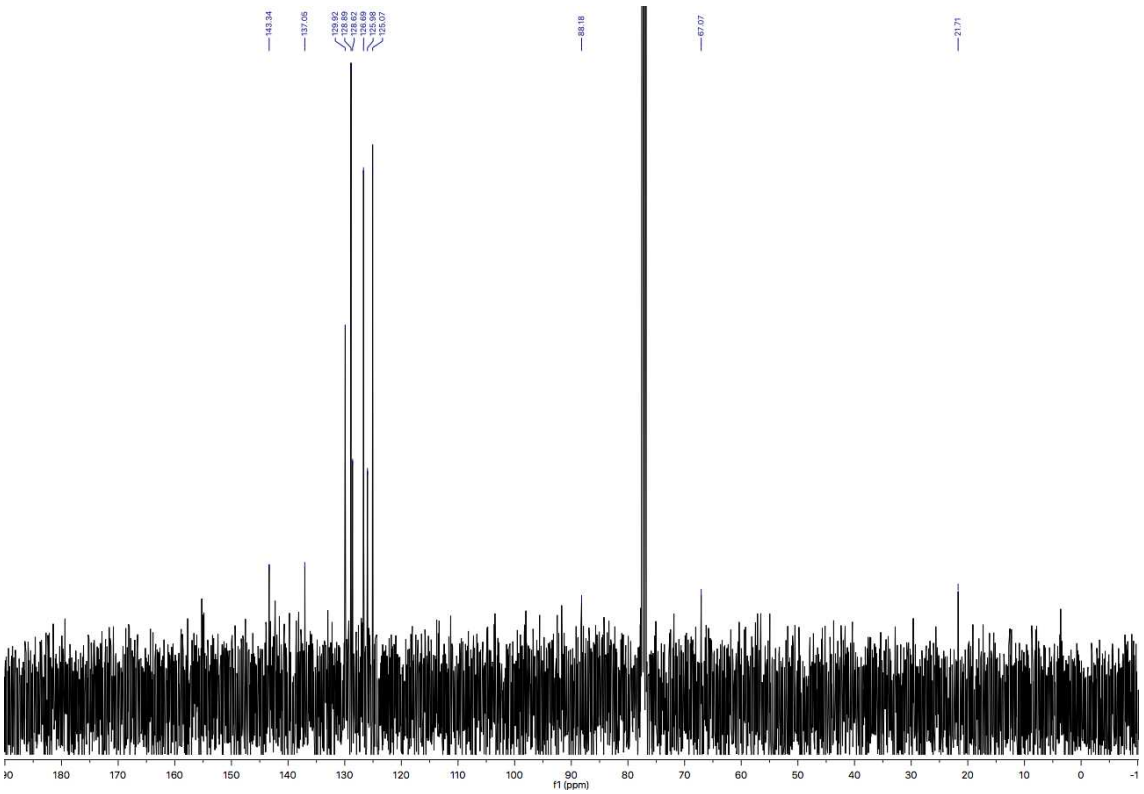

143.22
143.15
142.49
140.55
129.92
129.87
125.63
125.03
87.40
84.07
72.72
71.82
32.77
32.25
32.03
32.00
24.43
24.34
23.69
23.59
21.69
ppm
180
160
140
120
100
80
60
40
20
0

Isomer 1



Isomer 2


7.60
7.60
7.60
7.58
7.58
7.57
7.42
7.41
7.40
7.40
7.38
7.38
7.37
7.37
7.36
7.35
7.34
7.34
7.33
7.32
5.45
5.44
5.43
5.42
3.85
3.83
3.80
3.79
3.79
3.77
3.76
3.74
3.73
2.89
2.88
2.86
2.86
2.43
7.13
1.85
1
2.36
0.939
3.22
ppm


143.94
137.06
129.92
128.89
128.62
126.69
125.98
125.07
88.18
67.07
21.71
f1 (ppm)