Development of Catalytic Methods to Exploit Sulfur Dioxide in Organic Synthesis

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Trinity Term 2014

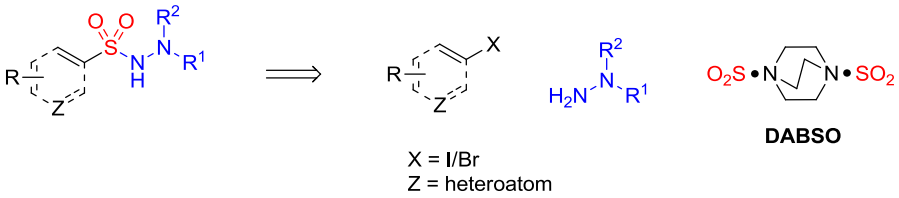
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

In the following thesis, new methodologies towards the synthesis of a range of sulfonyl (-SO_2-) containing functional groups are documented. These methods utilise easy-to-handle sulfur dioxide surrogates, such as DABSO (*vide infra*), and exploit palladium catalysis as a new mechanistic protocol for the incorporation of the -SO_2- unit.

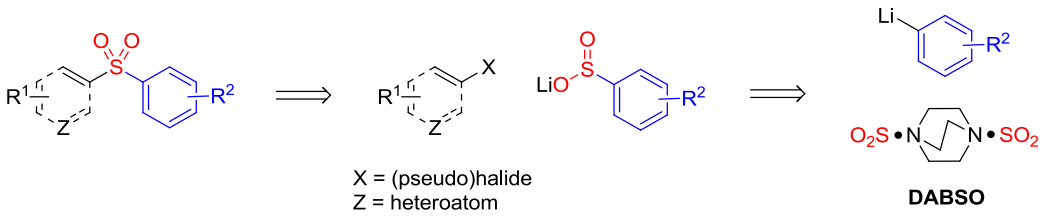
Chapter 1 is a literature review surveying sulfur dioxide in organic synthesis, the established uses of SO_2 surrogates and the importance of the sulfonyl moiety in chemistry. Palladium-catalysed (carbonylative) cross-couplings are also broadly discussed as they provide inspiration for, and mechanistic similarities with, the proposed chemistry.

Chapter 2 describes a *de novo* synthesis of the sulfonamide functional group; a three-component and convergent methodology coupling (hetero)aryl and alkenyl halides with sulfur dioxide (provided by easy-to-handle surrogates such as DABSO) and hydrazine nucleophiles, is documented. This is achieved through the action of a readily available palladium catalytic system and is the first example of a metal-catalysed *sulfonylative* cross-coupling of halide based electrophiles.[1–3]

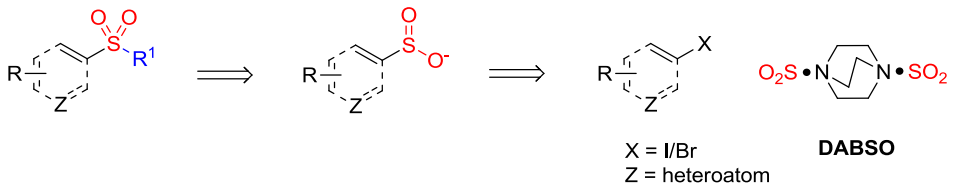


Chapter 3 presents a new method of generating (hetero)aryl and alkenyl sulfones. The ability of organometallic reagents to add to sulfur dioxide (supplied *via* DABSO) is applied to deliver the corresponding metal sulfinate salt. This *in situ* derived sulfinate is coupled with an (hetero)aryl or alkenyl (pseudo)halide using palladium catalysis to form

the desired sulfone. An electronically modified XantPhos-type ligand was designed for the reaction in order to suppress unwanted aryl-aryl exchange.[4]



Chapter 4 documents the generation of (hetero)aryl and alkenyl sulfinates from the corresponding halide and DABSO through a palladium-catalysed sulfination protocol, obviating the need for organometallic reagents. A mild set of conditions using IPA as both a solvent and reductant together with a low loading of palladium catalyst offers an attractive route to sulfonyl compounds thanks to the *in situ* derived sulfinates being converted into a broad variety of functional groups *via* established onwards reactivity.[5]



Chapter 5 discusses the conclusion of the research and the potential for future work.

Chapter 6 presents the experimental 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.

Edward Emmett

May 2014

Acknowledgements

First and foremost I would like to thank Prof. Michael Willis. He has been a fantastic supervisor and I am indebted to him for so many things. His enthusiasm for the project and intellectual input to help steer me in the right direction were invaluable; also for his trust and belief in me to take responsibility to develop and mould the project and for always having an open-door, being approachable, friendly and understanding especially in tough times. Thank you.

Thanks also go to Bao Nguyen, the grandfather of DABSO, to whom I owe a lot for my success. His willingness to host and help me in Leeds for a placement is also gratefully acknowledged. I would like to thank AstraZeneca and the EPSRC for funding, especially Barry Hayter my industrial supervisor. He has been prepared to help at any time and often at his own expense for which I am very grateful. In addition, thanks to everyone at AZ Macclesfield who made me feel so welcome during my CASE placement. I would like to particularly acknowledge Mike Nunn who spent considerable amounts of his time helping me and answering many questions through nothing other than kind-heartedness. I would also like to thank all the staff at Oxford University CRL and Colin Sparrow for running the GCMS experiments.

Big thanks go to all the past and present members of the Willis group of which there have been many! You have all been amazing to work with day-to-day and we have also shared some great times outside the lab. Rob, Paul, Carlos and Joel thanks for helping me get started when I first joined the group and answering all the associated ridiculous questions. Thanks to the twins, SJ and Jessie, for your unerring friendliness and sharing our mutual love of animals and football respectively. It was great to have a friendly face to turn to when chemistry was being frustrating. Thanks to team SO_2, especially Charlie and Alex, who have shared all the ups and downs. Most importantly, you have been great friends as

well as work colleagues and I hope you agree we have been a great team. Thanks to Matt, Manjeet, James, Manu, Alex, Cat, SJ, Tom, James, Fiona and Anais for proof reading – I owe you all. Finally, particular thanks go to two people: Alex for his great friendship, from football to Colorado to exquisite Alan Partridge quoting, it has been first class. Also to Cat for being my lab-rock from day one: for checking my Org. Syn. reactions, to always being there for a chat to keep each other going and to sharing some great times over MasterChef, Whole Foods Market and pronunciation. This journey would have been nowhere near as enjoyable without you both.

I would also like to thank my family and friends (especially my lunch duo Holly and Ness) for always being there for me. The gratitude to my parents for their support and the sacrifice that they have invested cannot be expressed in words. Thank you to Erin for being the constant in my life – your love, patience and strength has been eternally appreciated even if I have not always shown it as much as I should.

Finally I would like to dedicate this thesis to my Grandma who doted over her grandchildren and would have been so proud to see me finish.

Table of Contents

Abbreviations and Acronyms

Å	Angström (10^{-10} metres)
Ac	acetyl
Ad	adamantyl
app.	apparent
approx.	approximately
aq.	aqueous
Ar	aryl
AZ	AstraZeneca
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
Bt	benzotriazole
Bu	butyl
CAN	ceric ammonium nitrate
cat.	catalyst *or* catalytic
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CRL	Chemistry Research Laboratory
Cy	cyclohexyl
d	doublet *or* deuterated
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane-*bis*(sulfur dioxide) adduct
DBE	dibutyl ether
DCE	1,2-dichloroethane
DCM	dichloromethane
decomp.	decomposition
DEPT	distortionless enhancement by polarisation transfer
Dioxane	1,4-dioxane
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPhil	Doctor of Philosophy
DSC	differential scanning calorimetry
E	electrophile
E2	bimolecular elimination
EI	electron impact
EPSRC	Engineering and Physical Sciences Research Council
eq.	equation
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
FI	field ionisation
FT	Fourier transform
g	gram *or* gas
GC(MS)	gas chromatography (mass spectrometry)
GSK	GlaxoSmithKline
[H]	reductant
hept.	heptet
Het.	heteroaryl
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
hr(s)	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
i	iso
IPA	2-propanol (isopropyl alcohol)
IR	infrared
J	coupling constant
KF	Karl Fischer
l	liquid

L	ligand *or* litre
LCAP	liquid chromatography area percent
LC(MS)	liquid chromatography (mass spectrometry)
LDA	lithium diisopropylamide
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(s)	minute(s)
mol	mole
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Nuc	nucleophile
o	*ortho*
[O]	oxidant
Oct	octyl
p	*para*
PES	polyethersulfone
PG	protecting group
Ph	phenyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
Pr	propyl
q	quartet

quant.	quantitative
quin.	quintet
R	generic group/substituent
RaNi	Raney Nickel
RT	room temperature
s	singlet *or* solid
s	secondary
sat.	saturated
sec(s)	second(s)
S_NAr	nucleophilic aromatic substitution
t	triplet
t	tertiary
TBAB	tetrabutylammonium bromide
temp.	temperature
TCT	trichlorotriazine
Tf	triflyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl
Ts	tosyl
UV	ultraviolet
wt	weight
X	(pseudo)halide (unless stated otherwise)
Z	heteroatom (unless stated otherwise)
δ	chemical shift
η	hapticity
μ	micro (10^{-6})
ν	frequency
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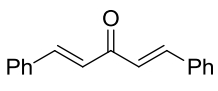
Ligand and Chemical Structures



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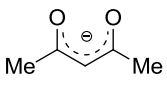

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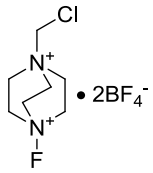

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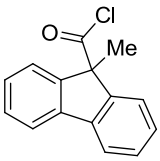

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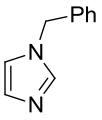

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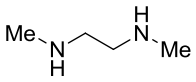

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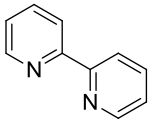

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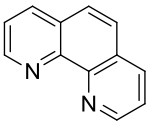

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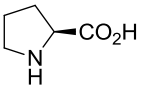

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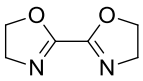

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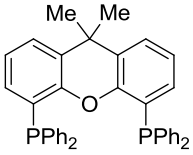

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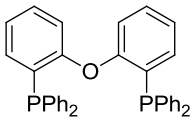

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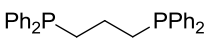

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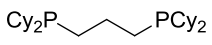

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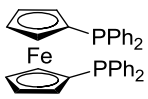

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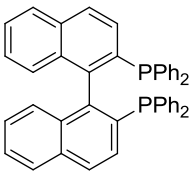

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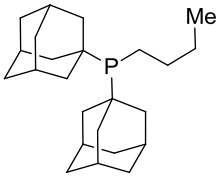

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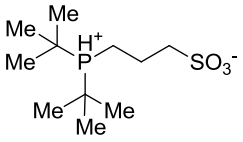

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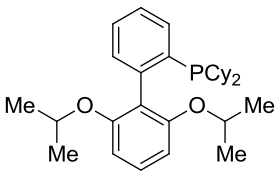

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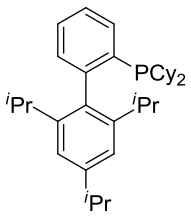

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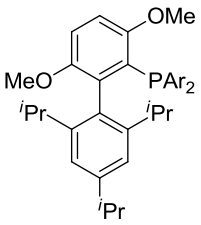

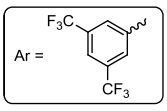

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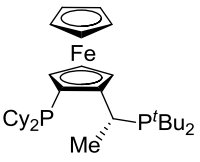

JosiPhos
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Chapter 1 – Introduction

1.1 The Sulfonyl (-SO_2-) Moiety in Organic Chemistry

Sulfonyl (-SO_2-) containing functional groups such as sulfonamides, sulfones and sulfonates are ubiquitous in organic chemistry (Figure 1.1).

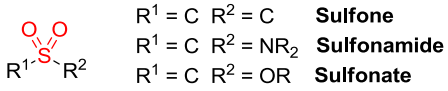


Figure 1.1 Examples of sulfonyl functional groups

From multi-billion dollar pharmaceutical products[6–8] and agrochemicals[9–11] to polymeric materials,[12] food additives[13] and intermediates in synthesis,[14–16] the -SO_2- moiety is encountered regularly by organic chemists (Figure 1.2). As a result, robust, versatile, efficient and practically simple methods for its introduction are required and in high demand.

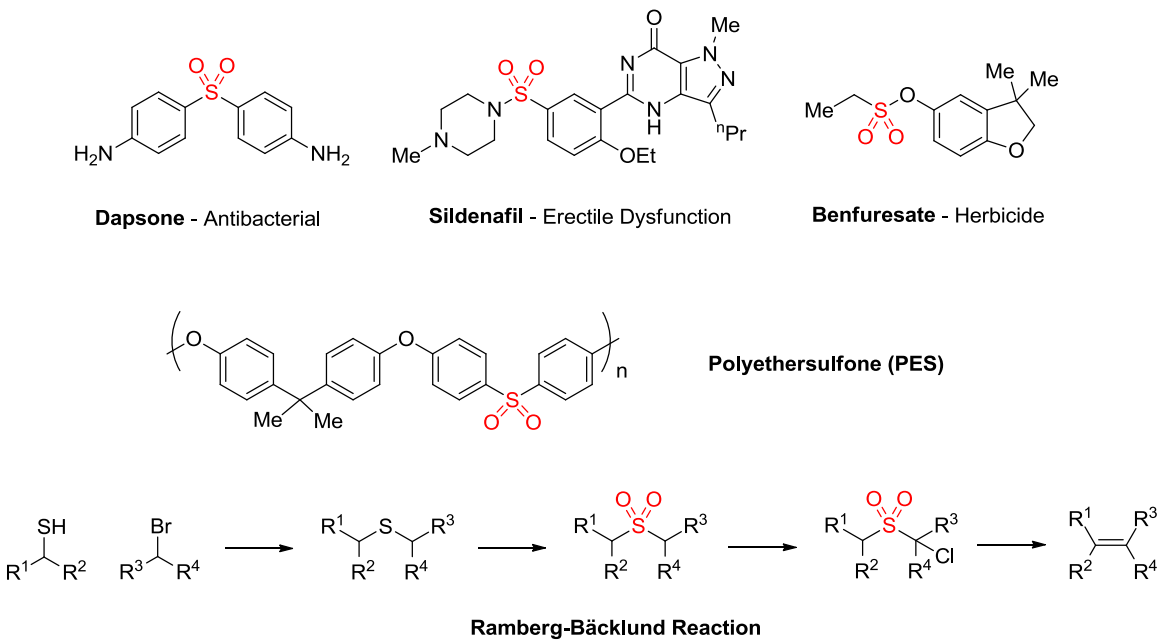


Figure 1.2 Sulfonyl containing functional groups in pharmaceuticals, agrochemicals, materials and synthesis

The nature of the methodology chosen to synthesise sulfonyl compounds is dependent on the precise functional group, and a more detailed discussion of methods will be presented at the beginning of each chapter as they are encountered in this thesis, however three principal techniques summarise the field.

Firstly, for aromatic compounds, (chloro)sulfuric acid are often the reagents of choice (eq. A, Figure 1.3).[17] However, the use of harsh acids creates problems with functional group tolerance, while the Friedel-Crafts-type mechanism leads to a significant lack of versatility due to the inherent regioselective bias imposed by the electronic and steric properties of the arene substrate.

Secondly, sulfur dioxide gas can be used in combination with organometallics (e.g. Grignard reagents or organolithiums),[18–22] or diazonium reagents (eq. B). [23–25] Once again this technique is not ideal because of the requirement of sensitive starting materials together with toxic and difficult-to-handle gaseous SO_2.

Finally, oxidation state manipulation from the corresponding sulfinyl or sulfenyl level is another popular procedure (eq. C).[14,26] However, strong oxidising agents affecting functional group tolerance can significantly limit the versatility of this method, while the starting material synthesis can be long, linear and not without its own problems (e.g. odorous thiols).

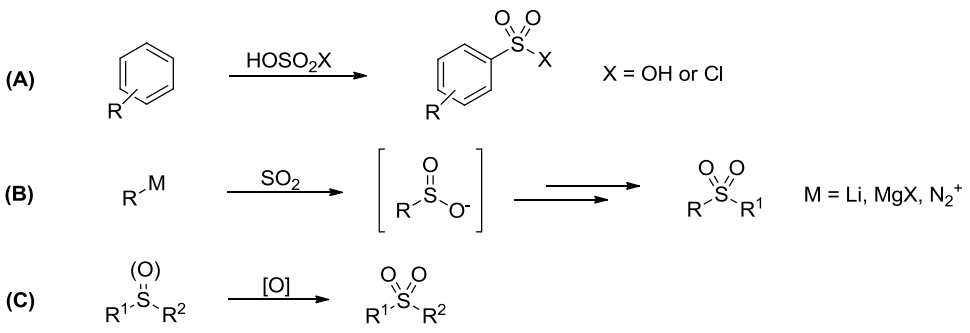


Figure 1.3 Principle strategies for sulfonyl moiety synthesis

Taking into consideration their widespread use and the limitations of current processes, there is a clear mandate for the development of milder methodologies for sulfonyl group synthesis, with improved versatility and selectivity.

1.2 Sulfur Dioxide

1.2.1 General and Organic Chemistry of SO_2

Sulfur dioxide, SO_2, is a toxic and pungent odorous gas present in the Earth's atmosphere at one part per billion by volume. It is produced naturally by volcanoes through the aerobic combustion of sulfur-containing ores. However, its presence is predominantly man-made due to industrial processes such as fossil fuel combustion at power plants; sulfur impurities present in coal, for example, release SO_2 upon aerobic combustion. Not only is it a potent greenhouse gas but in the presence of catalytic nitrogen oxides and water, it is oxidised to sulfuric acid, the principal component of acid rain.[27]

Sulfur dioxide is predominantly produced (*via* aerobic combustion of elemental sulfur) for use as a feedstock in the contact process (sulfuric acid manufacture),[27] however it is also extensively used as a food preservative (E220) for example acting as an antibiotic and antioxidant in wine and dried fruits.[28] Although its use in organic chemistry has been well documented,[29–31] its acceptance as a reagent in synthesis and widespread application still appears to be somewhat limited. The toxicity and issues associated with handling gaseous reagents may be significant factors but given the prevalence of other small gaseous building blocks such as carbon monoxide[32–34] and hydrogen, this cannot be the exclusive issue. Perhaps it is simply a result of a lack of versatile and synthetically useful transformations and therefore academic investigations into further uses would be more than justified.

The principal mechanisms of SO_2 integration into organic molecules have remained the same for decades: through stoichiometric organometallic addition to form metal sulfinate salts,[18–22] radical addition using diazonium salts[23–25] or pericyclic processes such as Alder-ene[35] and chelatropic cycloadditions (Figure 1.4).[36,37] The initial products from these reactions, however, are rarely useful in themselves; further synthetic transformations being required to convert them to more applicable -SO_2- containing functional groups. While the transformations of sulfinate salts are generally well-known and established (Chapter 4), the organometallic and diazonium methods are particularly limited (aside from the use of gas) by the sensitive nature of the starting materials.

The elaboration of sultines, sulfolenes and allyl sulfinic acids, the products from the pericyclic reactions, are certainly much less prevalent, although Vogel and co-workers have recently published a review highlighting advances in this area, including their application to sulfone, sulfonamide and sulfonate synthesis through C-C bond formation.[30] Nonetheless, the constraints of the pericyclic processes, in terms of molecular scaffold, severely limit the synthetic versatility of these reactions.

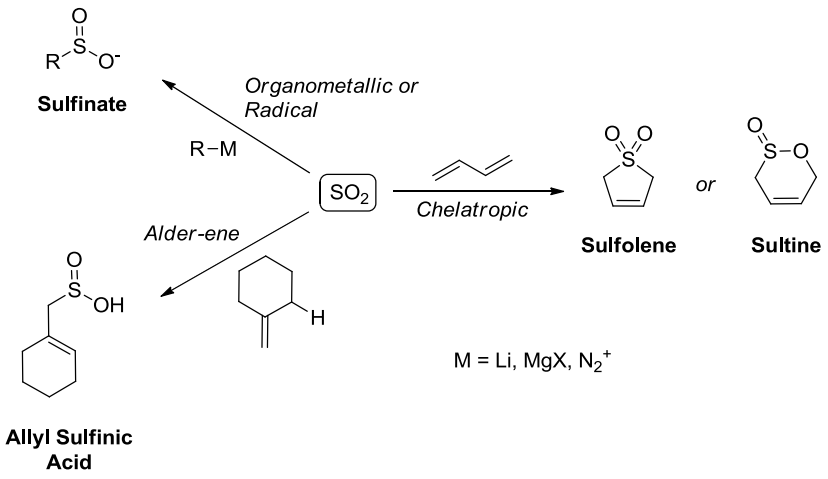


Figure 1.4 Mechanisms of SO_2 gas incorporation

This linear approach to sulfonyl group synthesis, with limited mechanistic routes and the problems of toxicity and handling a gas explains why Friedel-Crafts sulfonylation and

oxidation state manipulation are more frequently used methods of -SO_2- moiety formation (Figure 1.3). If new mild and convergent mechanistic pathways of sulfur dioxide incorporation could be developed, its popularity as a reagent may be improved.

1.2.2 Inorganic Organometallic Chemistry of SO_2

Sulfur dioxide has arguably received more prominent attention in inorganic organometallic chemistry, where its reactions with transition metal complexes have been widely studied.[38–44] Its behaviour as a ligand is particularly varied with at least five different binding modes to metal centres identified (Figure 1.5).[38]

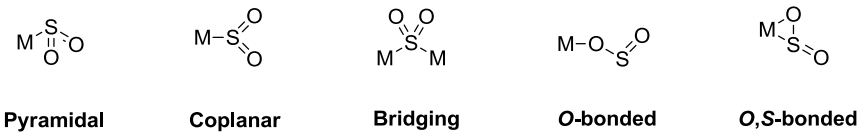


Figure 1.5 Varied modes of ligation of SO_2 to metals

Of particular relevance to this project is its similarity to carbon monoxide which is striking in organometallic chemistry. This can be explained by the identical symmetry of their frontier molecular orbitals (Figure 1.6).[45] In CO, the HOMO is a predominantly non-bonding σ orbital and the LUMO is a π^* orbital, each with their largest co-efficient on carbon. In sulfur dioxide, the HOMO is a predominantly non-bonding a_1 orbital in the plane of the S–O bonds and the LUMO is an antibonding b_1 orbital of π symmetry perpendicular to this plane; both with their largest co-efficient on the sulfur. This isolobal relationship suggests a paralleled reactivity and indeed, sulfur dioxide can insert into metal-carbon bonds in a 1,1 fashion to give metal-sulfinato complexes such as **1**,[42,46,47] just as CO inserts to give metal-acyl complexes like **2** (Figure 1.6).[33,46] These amphoteric, "carbene-like" properties are relatively rare and go some way to explain these molecules' comparable behaviour.

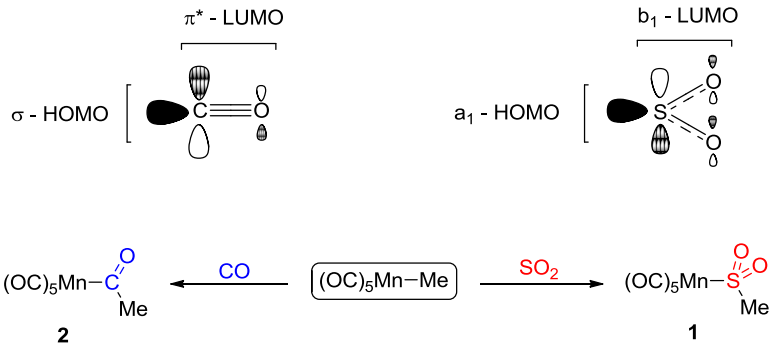


Figure 1.6 Isolobality of SO_2 and CO and an example of their 1,1 insertion into M-C bonds

Carbon monoxide is a well known and utilised reagent in organic chemistry. Its incorporation into molecules is usually achieved through the mediation of metal catalysis and its ability to act as a ligand for transition metals and insert into metal-carbon bonds are the key aspects of this chemistry (Section 1.3.2).[32–34] Sulfur dioxide's similar ability raises the intriguing possibility that transition metal catalysis could be exploited to harness SO_2.

1.2.3 Sulfur Dioxide Surrogates

The handling of sulfur dioxide gas is not a trivial procedure. As with any gas, the use of specialist equipment is required to contain the reagent and tolerate a system which may be under pressure. Alternatively a stream of gas can flow through the system; this is not only wasteful but if the gas is toxic (like SO_2), it presents a significant safety concern too. Therefore the use of an easy-to-handle surrogate for SO_2 is an attractive proposition. One historical practice is to create sulfur dioxide gas through the addition of Brønsted acid to benign inorganic salts like sulfites or metabisulfites (e.g. Na_2SO_3/$Na_2S_2O_5$), avoiding a pressurized gas cylinder.[48] However, this still requires the handling of the *ex situ* formed gas. During the course of this research, Wu *et al.*[49] and Shavnya *et al.*[50] published the use of potassium metabisulfite ($K_2S_2O_5$) as a solid source of *in situ* sulfur dioxide in

procedures which are adaptations of reactions presented during the course of this thesis. Neither group use acidic conditions but they do not elaborate as to how they believe SO_2 is being formed. These reactions are discussed further in the appropriate sections of this thesis (Chapters 2 and 4 respectively).

3-Sulfolene **3** is another such SO_2 surrogate; a chelatropic adduct of sulfur dioxide and butadiene **4** (Figure 1.7). This pericyclic reaction is reversible and although more commonly used as a masked source of **4** for Diels-Alder reactions,[51] sulfolene has also been shown to be a source of SO_2 for two precedented transformations: alkene isomerisation in steroids and *N*-oxide reduction to amines.[52] However, the stoichiometric by-product of reactive butadiene **4** and the high extrusion temperature required (>100 ^oC) is perhaps a reason why this surrogate has not been explored further.

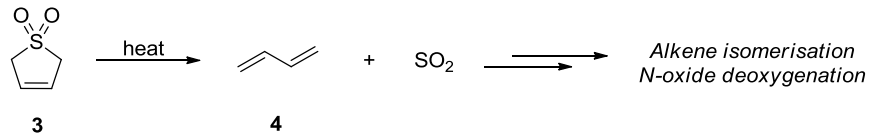


Figure 1.7 3-Sulfolene **3** as a surrogate for SO_2

Chakrapani and co-workers have also investigated the use of sulfur dioxide surrogates for biological systems (Figure 1.8).[53–55] They studied 2,4-dinitrobenzene sulfonamides **5** as SO_2 pro-drugs, which could "decompose" under the action of a thiol to release sulfur dioxide. Secondly they utilised 1-aryl-benzosultine derivatives **6**, which can undergo cycloreversion to generate sulfur dioxide, to probe the biological role of SO_2 in living systems.[56]

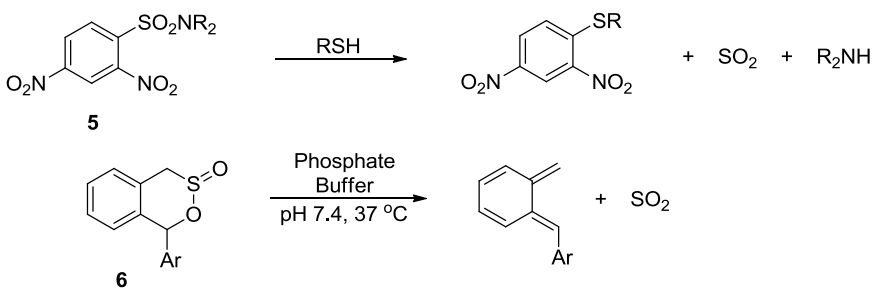
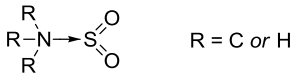


Figure 1.8 SO_2 surrogates **5** and **6** developed for biological applications

Amine-Sulfur Dioxide Complexes

Within our laboratory we proposed the use of amine-sulfur dioxide complexes **7** as surrogates for SO_2. These relatively little-known charge transfer adducts are formed between Lewis-basic amines and Lewis-acidic sulfur dioxide (Figure 1.9). Many of these are solid and surprisingly stable despite their unusual structure. Complexes of ammonia,[57] methylamine,[58] *N*-methylaniline[59] and quinuclidine[60] have all been identified demonstrating the range of amines capable of undergoing this complexation chemistry.



7

Figure 1.9 Amine-sulfur dioxide complexes **7**

These adducts have been known and studied for over 100 years, with a wealth of literature published investigating the nature of the S-N dative covalent bond. Raman and infrared spectroscopy have been used in conjunction with computational studies, X-ray crystallography and NMR spectroscopy to probe their structure. [61–67]

Despite this interest, practical uses for the complexes remain very limited. Olah and co-workers have demonstrated that the trimethylamine complex **7a** can achieve a range of dehydration and reductive transformations which are known with gaseous SO_2 (Figure 1.10).[68–72]

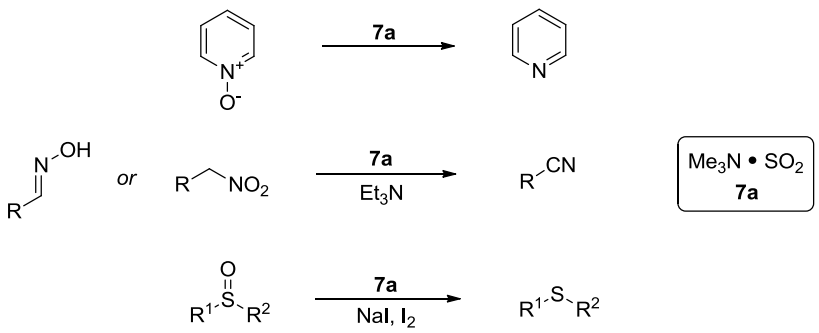


Figure 1.10 Examples of Olah's reduction reactions with trimethylamine-sulfur dioxide complex **7a**

This chemistry has also been indirectly used in several processes. Industrially, amine solutions are patented as gas scrubbers, removing sulfur dioxide from effluent;[73,74] while Rudkevich and co-workers used amine complexation as a method of determining the concentration of SO_2 in solution through a colourimetric metalloporphyrin assay.[75] Finally Olah *et al.* also discovered that the complex formed between poly(4-vinylpyridine) and sulfur dioxide acted as a mild acid catalyst in an α-aminonitrile synthesis *via* a Strecker-type reaction.[76] However in all of the presented uses, to the best of our knowledge, never has a complex been used as a source of SO_2 which ultimately becomes incorporated in the final product.

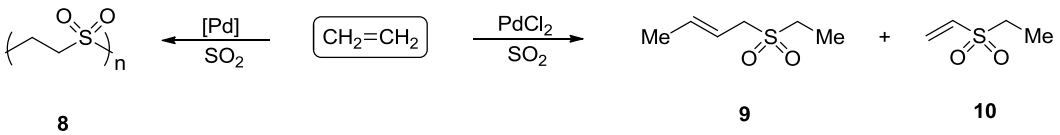
Within our group we have identified the adduct formed between the tertiary amine DABCO and two molecules of sulfur dioxide[60] (which we have named DABSO, **7b** Figure 1.11) to be a particularly relevant complex and subsequently exploited it in organic synthesis. As a bench-stable easy-to-handle white powder it has all the required attributes of a replacement for sulfur dioxide gas. It has excellent thermal (see experimental data) and vacuum stability while also being >50 wt% SO_2, minimising the waste associated with having a carrier molecule. In addition, as a tertiary amine, the released DABCO is less likely than a primary or secondary amine to cause unwanted side reactions following de-complexation. Finally, its precisely known composition allows sulfur dioxide to be added to the reaction medium in a controlled loading, in a much easier fashion than achievable with a gas. This last factor has proved essential for much of the chemistry presented in this thesis.

Figure 1.11 Crystal structure and physical form of DABSO **7b**

1.2.4 Use of SO_2 in Transition Metal Catalysis

The idea of using transition metal catalysis to incorporate sulfur dioxide into organic molecules is not a novel concept, however it has been very sparsely explored, with one review surveying the area.[31] To the best of our knowledge, only a small number of reactions have been reported which predominantly focus on the functionalisation of alkenes.

A variety of palladium species can catalyse the reaction of ethene and sulfur dioxide. Depending on the precise conditions, either perfectly alternating co-polymer **8** is formed[77] or a mixture of oligomeric sulfones **9** and **10** (Figure 1.12).[78] For the polymerisation, the catalyst has a very low catalytic turnover number and is consumed by precipitation of elemental palladium black, hinting at the difficulty of using sulfur dioxide with transition metal catalysts. In addition, the carbonylative analogue with CO occurs with a catalytic activity an order of magnitude higher[79] but this does however show the paralleled reactivity of CO and SO_2 (Section 1.2.2).



8 **9** **10**

Figure 1.12 Reactions of ethene and SO_2 under palladium catalysis

Another application is the synthesis of alkyl sulfinic acids from alkenes *via* a sulfonylative analogue of hydroformylation (eq. A, Figure 1.13).[80–82] Again palladium acts as the catalyst (in the form of cationic bidentate-phosphine-ligated Pd(II) species), although platinum is also active, providing a better *n*:*iso* selectivity albeit with lower activity. The fourth example is once again a functionalisation of an unsaturated molecule; 2,5-dialkenylsulfolane derivative **11** is formed from the palladium-mediated reaction of conjugated diene **12** and sulfur dioxide (eq. B, Figure 1.13).[83]

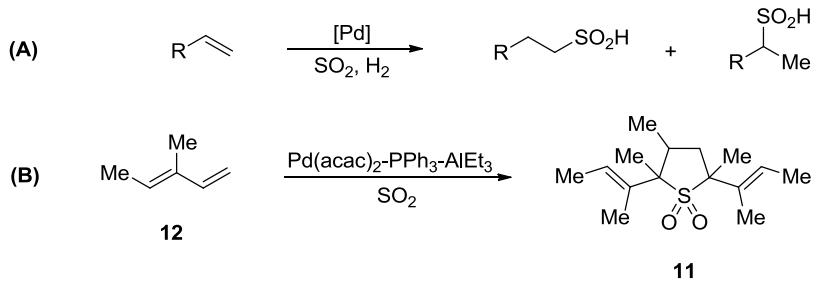


Figure 1.13 Further reactions incorporating sulfur dioxide with palladium catalysis

The final two examples concern the sulfonylation of aryl diazonium salts (Figure 1.14). Firstly this can be achieved through the reaction with SO_2 and H_2 gasses with a heterogeneous palladium on carbon catalyst to give aryl sulfinic acids **13**.[23] Only three examples are demonstrated with no mechanistic evidence provided as how this process occurs. This transformation is also known with over-stoichiometric copper.[24] Finally, aryl sulfonyl chlorides **14** can be formed from the corresponding diazonium salt *via* a copper-catalysed Sandmeyer-type process.[84] This reaction is certainly more widely known, thanks to the synthetic utility of the products; an Organic Syntheses publication[25] and a flow chemistry procedure recently published by Ley *et al.*[85] highlight this.

Figure 1.14 Sulfonylation of aryl diazonium salts using metal catalysis

To the best of our knowledge no reactions involving the sulfonylative functionalisation of aryl halides, arguably the most synthetically useful and celebrated of transition metal catalysis coupling partners, have been explored.

1.3 Palladium-Catalysed Cross-Couplings

1.3.1 General Introduction

The use of metal catalysis, as a method of bond construction in organic synthesis is one of the most important and powerful techniques in the synthetic toolbox. For palladium, from its initial development in the 1960s and 70s through the modern day and into the future, its role in chemistry is unparalleled.[86]

At the simplest level, a sub-stoichiometric amount of a palladium(0) containing species, mediates the coupling of an electrophilic and a nucleophilic component (Figure 1.15). The electrophilic species is usually an aryl/alkenyl/heteroaryl halide or pseudohalide. In other words, substrates with traditional "leaving groups" but that are generally unable to undergo typical nucleophilic substitution because the (pseudo)halide is attached to an sp^2 hybridised carbon. The ability to elaborate at these "unreactive" positions is one reason why this technique is so revered.

The nucleophilic component can be an extraordinarily wide variety of substrates; from heteroatomic nucleophiles such as amines,[87] alcohols[88] and thiols,[89] through hydride equivalents,[90] to carbon nucleophiles such as organometallics (organolithiums,[91] Grignard reagents,[92] organotin reagents,[93] organozinc reagents,[94] organoboron species),[95] enolates,[96] alkenes[97] and alkynes.[98] The variety of compounds which can be made through palladium-catalysed cross-coupling is extraordinary.

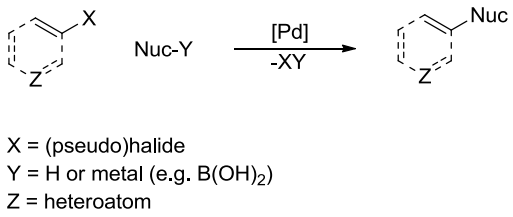


Figure 1.15 General schematic of palladium-catalysed cross-couplings

The nature of the catalyst itself clearly plays an integral role. The coupling mechanism is accepted to be mediated by a palladium species in the "zero" oxidation state. This can be introduced either through an organically soluble and semi-stabilised Pd(0) compound such as Pd_2dba_3 or $Pd(PPh_3)_4$ or often a more stable and easier-to-handle Pd(II) species such as $Pd(OAc)_2$ or $Pd(MeCN)_2Cl_2$. These Pd(II) compounds have to be reduced *in situ* to Pd(0) before being able to effect catalysis (mechanism, Section 1.3.2).

Together with the palladium source, another critical factor to a successful catalytic system is the identity of the ligand, which is most often an organophosphine. These bind to palladium and play several essential roles. Firstly, they render the Pd(0) soluble to allow homogeneous catalysis to take place. Secondly, they stabilise palladium(0) preventing formation of catalytically inactive and insoluble palladium black (metallic nanoparticles of elemental palladium). Finally, and most importantly, they modify the electronic properties of and the steric properties surrounding the palladium centre. This allows the kinetics of the reaction to be subtly controlled, leading to faster reactions under milder conditions, with lower catalyst loadings and greater selectivity (where applicable). The design and development of new specialised ligands across the decades has been one of the key driving forces for the progression of this chemistry to the status it holds today.[86]

Decades of research have led to the situation where the importance of palladium-catalysed cross-couplings cannot be overstated. This culminated in the awarding of the 2010 Nobel Prize in chemistry to Heck, Suzuki and Negishi for the discovery and development of this field.

1.3.2 Carbonylative Cross-Couplings

The domain of palladium-catalysed carbonylative cross-couplings provides the greatest inspiration to the chemistry presented in this thesis. It is also assumed that it provides the closest mechanistic parallel given the similarities observed between CO and SO_2 with respect to inorganic organometallic chemistry (Section 1.2.2). In carbonylative cross-couplings, a modification through having carbon monoxide as a third component in the reaction is made. The result is the insertion of CO in-between the electrophilic and nucleophilic components, to reveal a three-component convergent synthesis of carbonyl containing compounds (Figure 1.16).[32–34]

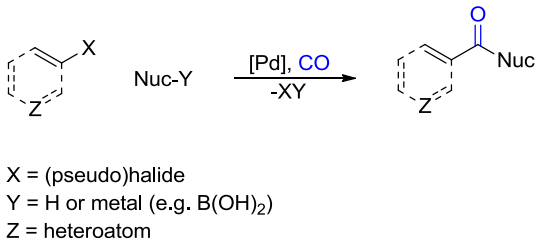


Figure 1.16 General schematic of palladium-catalysed carbonylative cross-couplings

There are some distinct advantages to the synthesis of carbonyl compounds by this method. Firstly, like traditional cross-coupling, the versatility of the electrophilic and nucleophilic components leads to the ability to make a varied array of carbonyl compounds using a single mechanistic scenario. Secondly, the convergent nature of the methodology allows a rapid increase in molecular complexity in one synthetic step. Finally, from an atom economy point of view, CO is the ideal building block for carbonyl compounds.

This methodology is becoming more widespread and popular, to extent that in a recent review, carbonylation was described as "a reaction come of age."[34] A full development of scope has certainly helped but also advances in operational procedures have significantly assisted. The safety concerns of using pressurised highly toxic gas may well have

hindered its utility in the past but the development of easy-to-use purpose-built pressure reactors has minimized these concerns.[99] In addition, the application of easy-to-handle CO surrogates[100] such as $Mo(CO)_6$,[101] DMF[102] and COgen[103] (see Chemical Structures, page xi) have further allayed these fears.

Mechanism[32,33,104,105]

Palladium-catalysed cross-couplings generally share key aspects to their mechanistic cycle. These shall be discussed in relation to carbonylations here, however broadly speaking, there are few differences to a traditional cross-coupling which proceeds without a CO insertion step. The catalytic cycle is presented diagrammatically in Figure 1.17 and the individual steps are discussed in detail below.

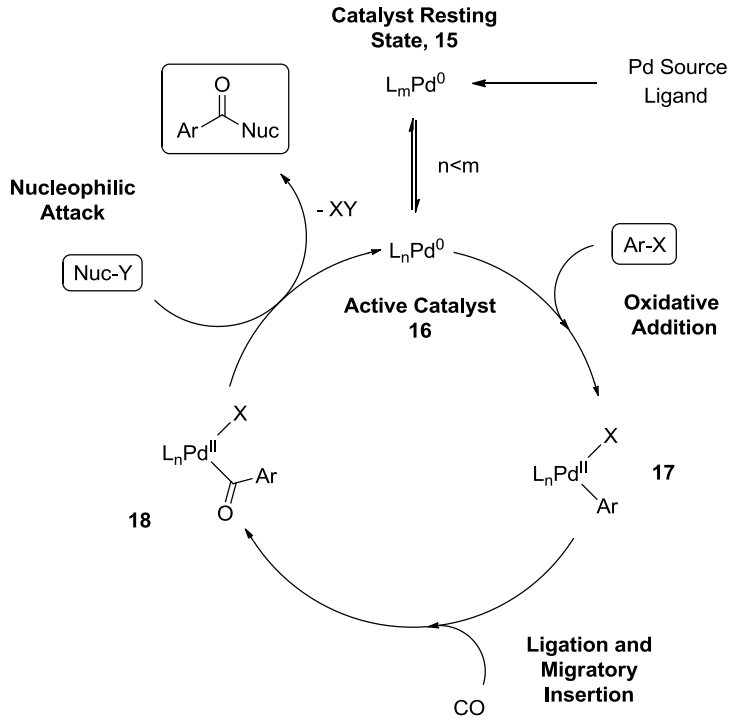


Figure 1.17 Mechanism of palladium-catalysed carbonylative cross-couplings

Active Catalyst Generation

It is very rare for a palladium containing compound added to the reaction to be the active catalyst. The predominant reason for this is that the active catalyst is normally a highly reactive species, which is simply too reactive and unstable to exist in a bottle and be weighed out on the bench. Therefore the first stage of the process requires reactions of the added pre-catalyst species to form the desired reactive species.

When a palladium(0) compound is used (e.g. Pd_2dba_3 or $Pd(PPh_3)_4$), the added specialised ligand simply displaces the dummy ligands (i.e. dba or PPh_3) to form a catalyst resting state **15**. This is still an off-cycle species, as it is often a relatively "unreactive" 16 or 18 (depending on the nature of the ligand) electron complex. Ligand dissociation is required as a final step to ultimately form the highly reactive 12 or 14 electron active catalyst **16**. There is a ligand association-dissociation equilibrium between this resting state and the active catalyst.

If a palladium(II) compound is used (e.g. $Pd(OAc)_2$), the situation is complicated slightly as an additional step of *in situ* reduction from Pd(II) to Pd(0) is required. The mechanism of this reduction is not always clear and indeed many different proposals have been suggested depending on the type of cross-coupling being performed.[106] Three such mechanisms are shown in Figure 1.18.

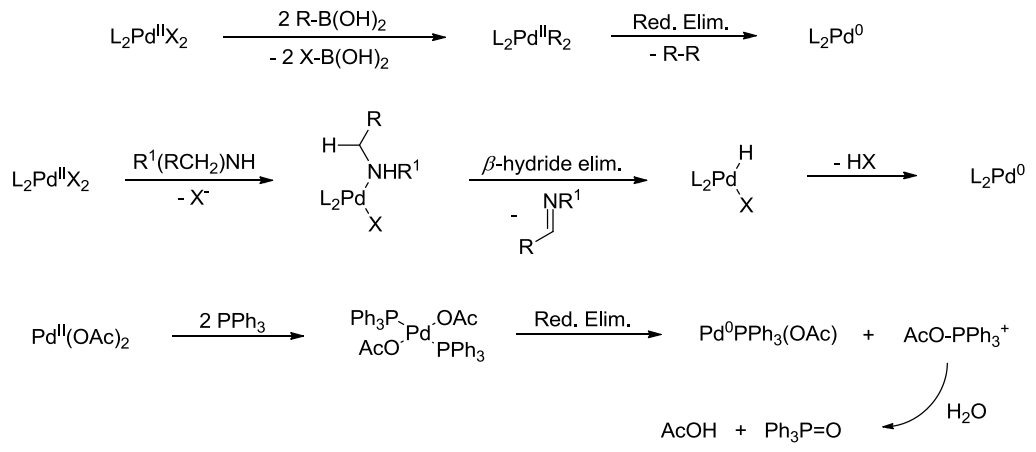


Figure 1.18 Selected mechanisms of *in situ* Pd(II) reduction to Pd(0)

Oxidative Addition

Following the formation of the active catalyst, the first step of the catalytic cycle is the oxidative addition of the electrophilic component to form the Pd(II) intermediate **17**. The rate of oxidative addition follows the trend of C-X bond strength with aryl iodides being faster than bromides, which are in turn faster than chlorides for example. The nature of the active catalyst also has an effect on rate, with sterically unencumbered electron-rich complexes reacting fastest (i.e. L is non-bulky, strong σ donor).

The mechanism of oxidative addition can be highly dependent on the metal centre, ligands and substrates, however it is generally thought for traditional palladium catalysis to be a concerted process of intramolecular C-X bond cleavage; the electrophilic component coordinates to a vacant coordination site (created by the ligand dissociation event of active catalyst formation from catalyst resting state) either through a three-centred MCX σ-complex, or a π-complex if nearby π bonds are present (as is the case for aryl halides), to allow this intramolecular cleavage to take place.

CO Coordination and Insertion

The next step of the catalytic cycle involves coordination of CO (once again through a vacant coordination site) to the metal centre in an η^1 mode. CO is an excellent ligand for transition metals due to its strong σ donor property (high energy HOMO) and strong π acceptor property (low energy LUMO). Following this coordination, CO inserts into the M-C bond to form the palladium(II) acyl complex **18**. This intramolecular migratory insertion reaction is arguably the most studied reaction in organometallic chemistry. Characteristics can vary considerably for each reaction but factors which influence the rate and which are relevant to this thesis include that the insertion is accelerated by catalysts containing bulky ligands and by having an accepting "Ar" group which is electron-rich.

Nucleophilic Attack

The final stage of the catalytic cycle is attack of the nucleophile on the acyl palladium(II) intermediate **18**. This not only yields the desired product but also regenerates the active catalyst **16** which is then ready to turnover the catalytic cycle again. The mechanism of nucleophilic attack depends on the nature of the nucleophile and even then has not always been unambiguously elucidated. For heteroatom nucleophiles such as amines and alcohols, it is thought that there is direct attack on the acyl carbon itself, expelling the palladium species in the process. In one-step this generates the product and following loss of X^- from the palladium, regenerates the active catalyst. Alternatively, the nucleophile attacks the palladium centre, displacing X^- in the process. Reductive elimination then takes place, forming the product and regenerating the active catalyst. This procedure is likely to occur for example in carbonylative Suzuki reactions, whereby transmetallation occurs to transfer the carbon nucleophile from boron to palladium.

1.4 Research Aims

1.4.1 Overview

The primary aims of this research encompass several aspects. Firstly, to develop new and improved routes to vital sulfonyl functional groups such as sulfonamides, sulfones and sulfinates and to achieve this by harnessing and exploiting the use of sulfur dioxide as a reactant in organic synthesis, a practice which we believe has been under-investigated. In addition, we wanted to use easy-to-handle surrogates for sulfur dioxide, such as DABSO, which would eliminate the safety concerns of working with a toxic gaseous reagent under pressure. Finally, our aim was to develop sulfonylative palladium-catalysed cross-couplings where possible to achieve the union of these aims, inspired by established carbonylations and the similarities of SO_2 to CO (Figure 1.19).

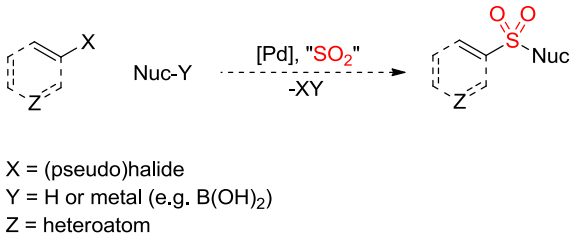


Figure 1.19 Proposed palladium-catalysed sulfonylative cross-couplings

1.4.2 Previous Work

It has been shown within our group (and now by others) that DABSO is an excellent surrogate for SO_2 in a range of transformations which were known to utilise and incorporate sulfur dioxide gas (Figure 1.20).[107–110] These have generally, but not exclusively, focussed on the generation of metal sulfinate salts **19** from the addition of organometallics to DABSO followed by their *in situ* functionalisation. However, a reaction to form sulfamides and one demonstrating a chelatropic reaction to generate sulfolene **20**, show additional versatility.

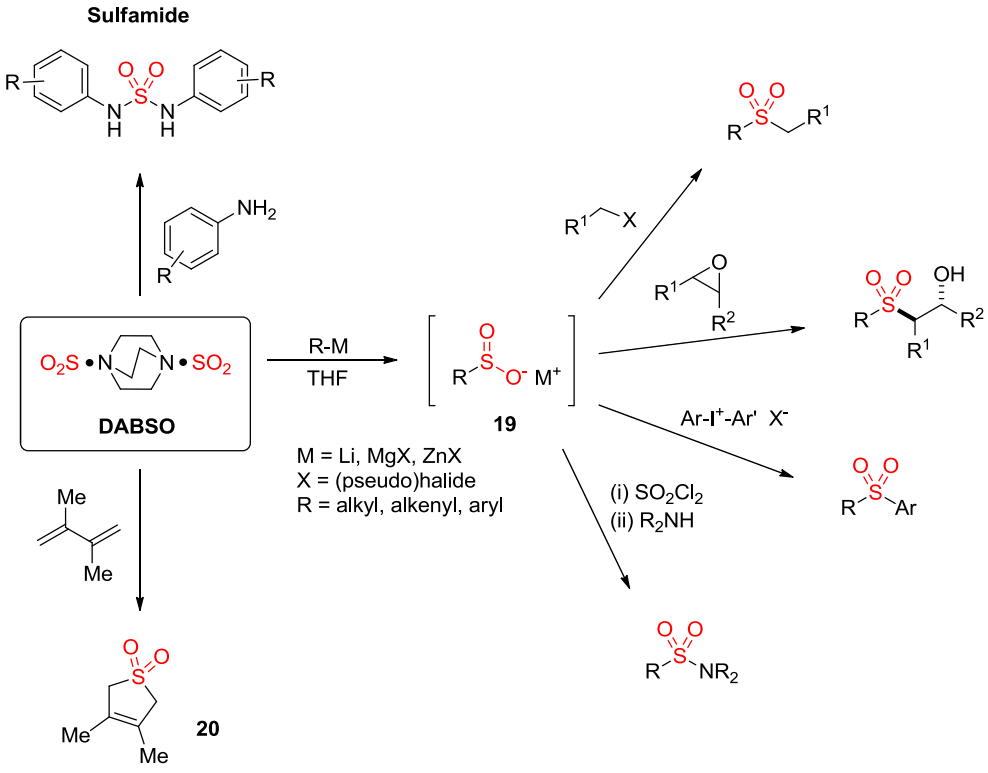


Figure 1.20 Reactions of DABSO developed in our group

In addition, as a Master's student, I co-developed the first -CSO_2N- linker to be synthesised *via* our proposed metal-catalysed cross-coupling procedure. Aryl iodides coupled with SO_2, provided by DABSO, and 1,1-disubstituted hydrazines **21** affording a range of *N*-aminosulfonamides. This aminosulfonylation process was mediated by a simple Pd-^{t}Bu$_3$P catalytic system (Figure 1.21).[1,111]

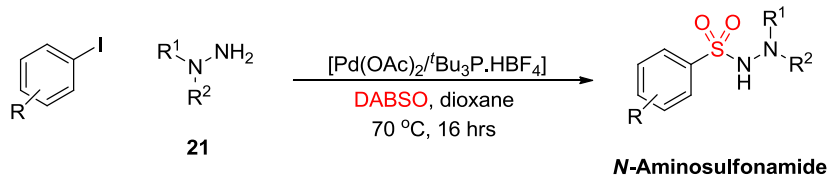


Figure 1.21 Aminosulfonylation of aryl iodides with DABSO and hydrazines

A detailed discussion of this reaction appears in Chapter 2 where full investigations into the development and extension of this aminosulfonylation protocol are documented.

Chapter 2 – Palladium-Catalysed Aminosulfonylation

2.1 Traditional Syntheses of Sulfonamides

The sulfonamide functional group is arguably the most important and most employed of the sulfonyl moieties. It is used in agrochemicals[10] and food additives[13] as well as an intermediate in organic synthesis where it can serve as a protecting group for nitrogen[15] and a directing group for *ortho*-functionalisation.[16] However, its most prominent use is in the pharmaceutical industry where sulfonamides are present in many blockbuster medicinal agents (Figure 2.1).[6–8] These encompass a wide range of treatments[112] from cholesterol regulation[113] to diuretics[114] and erectile dysfunction,[115] however they are historically best known as an important class of antibiotics.[116] This led to the umbrella term "sulfa drugs" being used to describe sulfonamide-containing medications.[8]

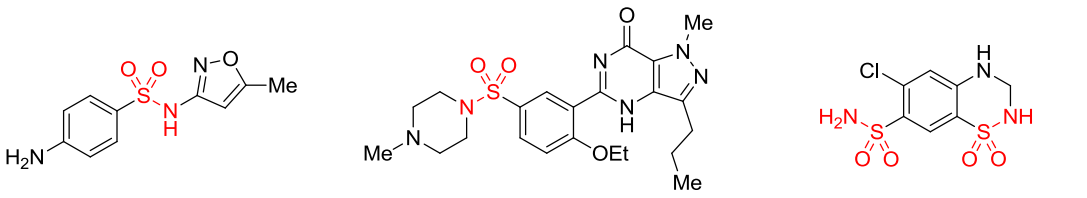


Figure 2.1 Pharmaceutical agents containing the sulfonamide functional group

Unsurprisingly, given their widespread use, there are many methods documented for the synthesis of sulfonamides. The most prevalent technique is the reaction of the corresponding amine and sulfonyl chloride under basic conditions. This amination is simple to carry out and reliable, although over-sulfonylation can occur with ammonia or primary amines (Figure 2.2).[117]

However, it is the access to the sulfonyl chloride starting material that represents this reaction's most significant limitation. Aromatic sulfonyl chlorides are normally made by

a Friedel-Crafts sulfonylation either directly with chlorosulfuric acid, or through a two-step procedure with sulfuric acid (forming the sulfonic acid **22**) and subsequent chlorination.[17] The chlorination can be achieved with agents such as thionyl chloride,[118] phosphorous pentachloride[119] or trichlorotriazine.[120] These are particularly harsh conditions which significantly limit the scope of the reaction. In addition, the very nature of the Friedel-Crafts mechanism results in a constraint in the accessible regioisomers due to the inherent electronic and steric bias of the arene substrate. An alternative route into sulfonyl chlorides is an oxidative chlorination methodology from the corresponding thiol **23**[121–123] or sulfinate **24**[18,124] (Figure 2.2). However, the odorous nature of thiols and the difficulty in accessing sulfinates (Chapter 4), and to a certain extent thiols, has limited the applicability of these methods.

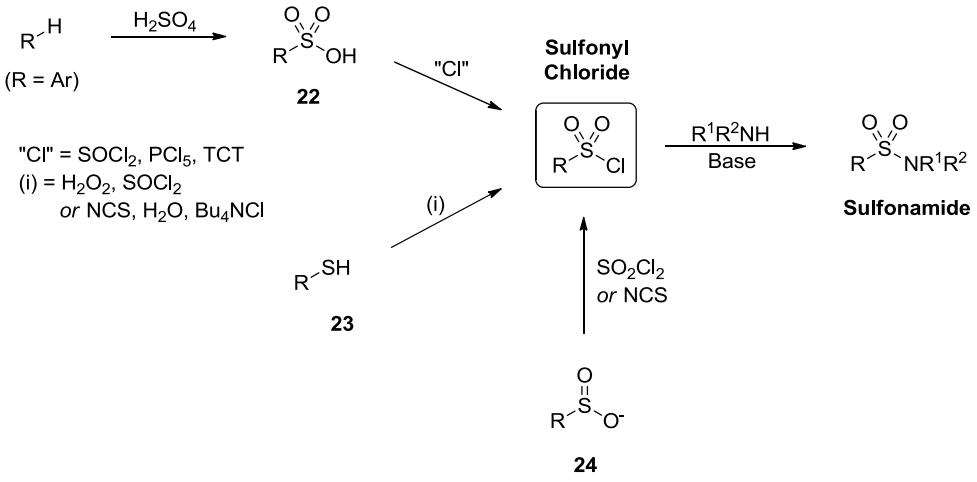


Figure 2.2 Synthesis of sulfonyl chlorides and their subsequent amination

Not only can sulfonyl chlorides be difficult to generate but they are also a sensitive functionality due to their moisture intolerance. Therefore several alternative methods have been developed whereby different intermediates to sulfonyl chlorides are exploited to form sulfonamides (Figure 2.3). These include the amination of a more stable benzotriazole sulfonyl-type intermediate **25** (eq. A),[125] the direct formation of the sulfonamide from the sulfonic acid **22** (*via* **26**)[126] or sulfinate **24**[127] (eq. B and D

respectively) or oxidative methods from sulfinate esters **27**, which avoid sulfonyl intermediates completely (eq. C).[26] Once again these methods are not without problems, predominantly in the synthesis of the starting materials (*vide supra*). They can also be highly atom uneconomic, use intolerant oxidants or require specialist, difficult-to-access reagents. Hence, these methods are generally overlooked in favour of the sulfonyl chloride method, despite its own limitations.

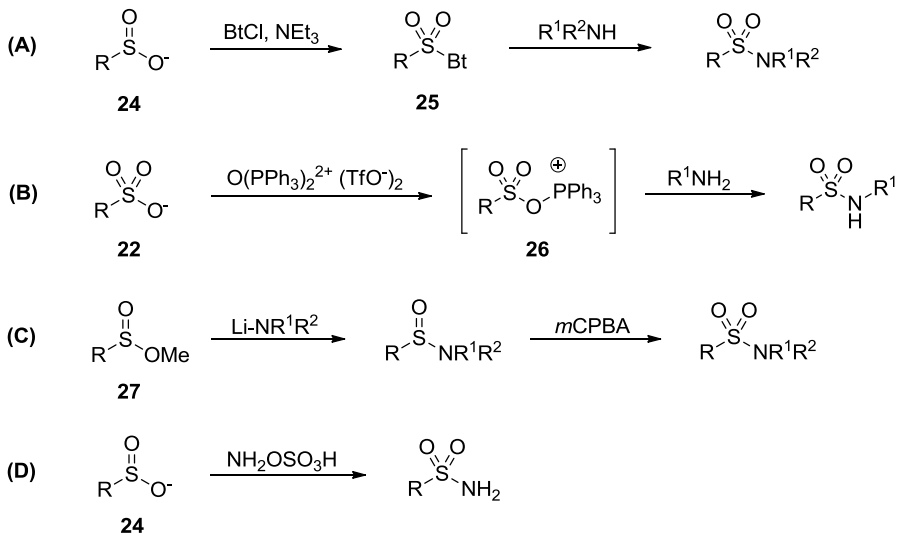
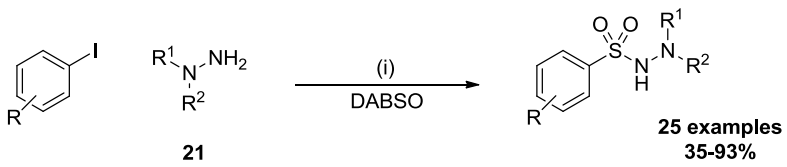


Figure 2.3 Alternative syntheses of sulfonamides avoiding sulfonyl chloride intermediates

Finally, once a sulfonamide has been synthesised, the latent reactivity of any unsubstituted nitrogen can be exploited to further functionalise the sulfonamide; for example Buchwald-Hartwig arylation[128] or nucleophilic substitution.[129] However, this technique, and indeed those described above, demonstrate that in general long and linear sequences of reactions are required to form sulfonamides. Therefore the development of a method of sulfonamide generation under mild conditions, using readily-available and easy-to-handle starting materials and through a convergent and low-step-count methodology, would mark a significant improvement over the existing literature.

2.2 Origin of Project and Previous Work

In order to effect these improvements, the proposal to develop sulfonylative palladium-catalysed cross-couplings as a method of forming sulfonyl functional groups was introduced in Chapter 1. Given the medicinal importance of sulfonamides, an aminosulfonylation protocol was investigated; a three-component and convergent union of aryl halides, sulfur dioxide and nitrogen nucleophiles. During the course of my Master's (Part II) project, I co-developed the first examples of this reaction, which could be achieved using aryl iodides, DABSO as an easy-to-handle sulfur dioxide source, and hydrazines, forming *N*-aminosulfonamides as products (Figure 2.4).[1,111]



(i) Aryl iodide (1 equiv., 0.23 mmol), hydrazine (1.5 equiv.), DABSO (1.1 equiv. *or* 0.6 equiv. + 0.5 equiv. DABCO), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), 1,4-dioxane [0.14 M], 70 °C, 16 hrs

Figure 2.4 First palladium-catalysed aminosulfonylation of aryl halides using hydrazines

Using the readily available $Pd(OAc)_2$ and $^tBu_3P.HBF_4$ as a catalytic system, a range of aryl iodides were successfully sulfonylated under relatively mild conditions, to include electron-rich and electron-poor substrates as well as *ortho*, *meta* and *para* substitution patterns. Unfortunately, only 1,1-disubstituted hydrazines **21** were capable of acting as the nucleophilic component. It was also found that a low loading of DABSO (and therefore sulfur dioxide) was a key aspect to this reaction (0.6–1.1 equivalents). Indeed, very poor conversion was achieved when using sulfur dioxide gas which suggested that it was acting as a metal-catalyst poison. This highlighted another benefit of using a sulfur dioxide surrogate – the measured delivery of SO_2.

Following these results, the first aim of this research project was to continue to pursue investigations into this reaction, to extend the scope and fully exploit the capability of the new methodology.

2.3 Synthesis of Alkenyl *N*-Aminosulfonamides

The original investigation of the scope had focused on the sulfonylation of *aryl* halides as a result of their ubiquity in palladium-catalysed cross-couplings. This allowed the synthesis of sulfonamides which could not be made *via* Friedel-Crafts chemistry due to steric or electronic restrictions, as well as those for which the corresponding sulfonyl chloride was inaccessible due to chemoselectivity issues (e.g. phenolic/anilinic sulfonyl chlorides). Heteroaromatic and alkenyl sulfonyl chlorides, unlike their aryl analogues, do not have an established commercial availability, reflecting the inadequacies in current methods of sulfonyl chloride formation and thereby leaving heteroaromatic and alkenyl *sulfonamides* an under-explored area of chemical space.[130] Hence, a primary aim for this chemistry was to access these interesting functional groups. The scope of the aminosulfonylation protocol with respect to heteroaromatic substrates was investigated by Charlotte Richards-Taylor, another member of the Willis group whose results demonstrated the ability of aminosulfonylation to be applied to a wide variety of nitrogen, sulfur and oxygen containing heterocycles. Her results are presented in the following paper[2] and her DPhil thesis.[131] I investigated the scope with respect to synthesising alkenyl sulfonamides **28**.

A range of alkenyl iodides, which had previously been synthesised by other members of our group for another project (see Section 6.2.2),[132] were subjected to the conditions previously optimised for aryl iodides (Figure 2.5). Using 4-aminomorpholine **29** as the hydrazine component, we were pleased to observe that alkenyl iodides were suitable substrates in this aminosulfonylation, although yields in the region of 50–65% were

significantly lower than those typically obtained for *aryl* iodides (75–90%). Both mono- and disubstituted alkenyl sulfonamides were generated equally well (cf. **28a** and **28b**) although the terminal alkenyl sulfonamide **28f** was not formed. A brief re-investigation of conditions yielded no improvement.

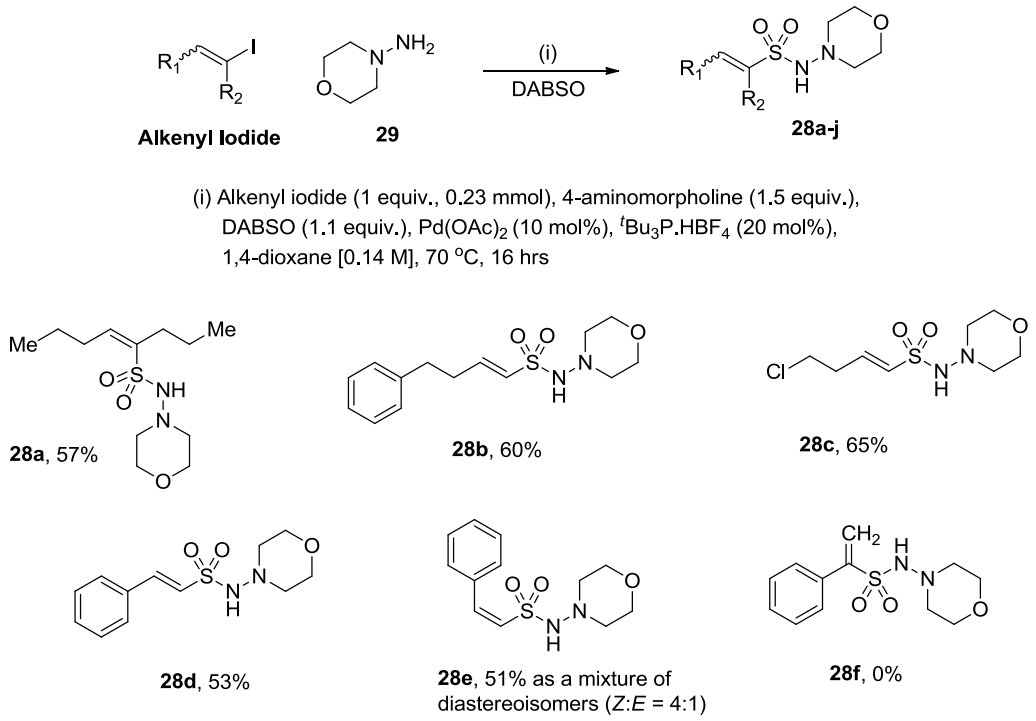


Figure 2.5 Aminosulfonylation of alkenyl iodides

It was postulated that the poor stability of either the starting material alkenyl iodide or product sulfonamide **28** was the likely origin of the lower yields, as mass balance was generally not recovered. For the alkenyl iodides, an elimination reaction to give the alkyne (either through base induced E2 or *β*-hydride elimination of the alkenyl-palladium species) was suggested as a decomposition pathway. For the product, a Michael addition (of DABCO for example) to the unsaturated sulfonamide was proposed. To investigate this, four alkenyl iodides **30**-**33** were synthesised which could not eliminate to form the alkyne either due to the constraints of ring size or through substitution pattern (Figure 2.6).[133–135] These were subjected to identical aminosulfonylation conditions to those documented in Figure 2.5.

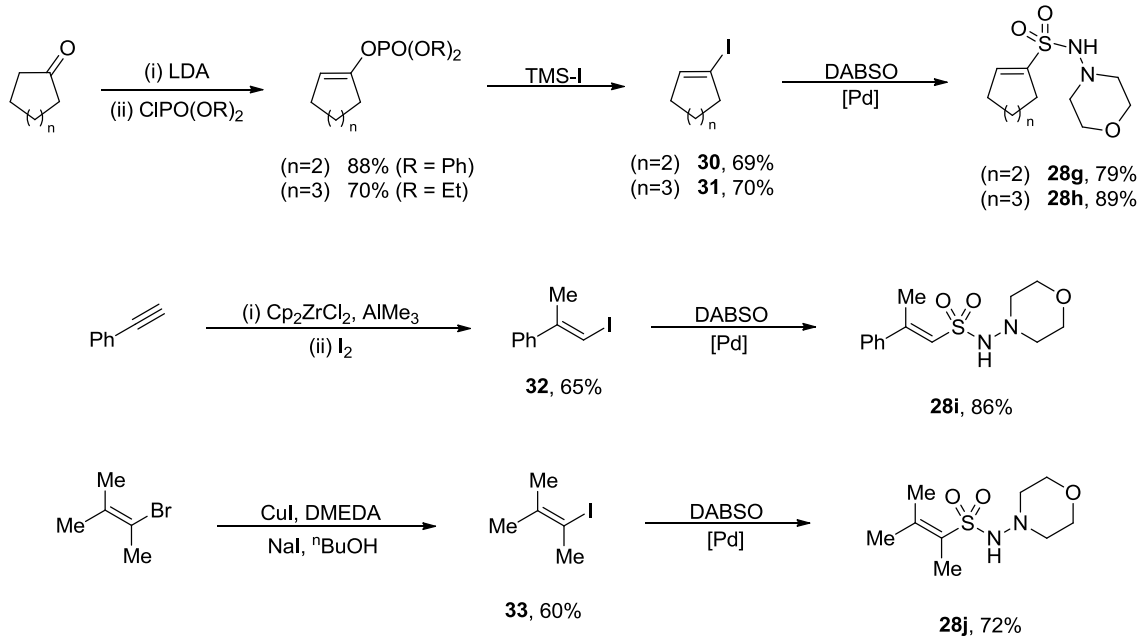


Figure 2.6 Aminosulfonylation (conditions as Figure 2.5) of alkenyl iodides **30**-**33** unable to form alkynes

Pleasingly these alkenyl iodides generated the corresponding *N*-aminosulfonamides in yields comparable to those obtained with *aryl* iodides. The good yields produced from cyclic substrates **28g** and **28h**, with relatively unhindered *β*-positions, perhaps suggest that it is the instability of the starting material, rather than Michael addition to the product, that is the primary reason behind the reduced yields observed in the original set of alkenyl iodides (Figure 2.5).

2.4 Hydrazine-Sulfur Dioxide Complexes

In the conception of this sulfonylative palladium catalysis project, the use of a carrier amine complex as the sulfur dioxide source was implemented. This allowed flexibility and easy variation in the identity of the coupling nucleophile. DABCO was chosen thanks to the complex's excellent physical properties, coupled to the fact that its tertiary nature meant that it was less likely to interfere in the coupling reaction than a primary or secondary amine. However, the resultant carrier molecule could in principle still hinder the coupling reaction, for instance by coordination to palladium. It had been suggested

that the presence of DABCO may be the reason behind hydrazines being the only compatible nucleophile (Section 2.7). Our attention therefore turned to a pre-complexation of the coupling nucleophile with sulfur dioxide, thus removing the need for a carrier species. 4-Aminomorpholine-SO_2 complex **34**,[136] once again an easy-to-handle white solid, was synthesised and shown to couple under almost identical conditions (Figure 2.7).

A complication of this reaction was that added base was required in order to effect catalytic turnover. In a DABSO aminosulfonylation, the released carrier species DABCO provided this role. In this reaction, DABCO was in fact demonstrated to be the optimal base revealing complete conversion of aryl iodide. However, 80% conversion was also achieved with Cs_2CO_3, demonstrating that these novel sulfonylations are not limited to the use (or formation *in situ*) of DABSO. A brief investigation of conditions revealed a similar behaviour with respect to variation in reaction parameters as the DABSO method, showing that this reaction was already operating in the optimum space. A small selection of aryl, heteroaryl and alkenyl iodides were chosen to demonstrate scope (Figure 2.7).

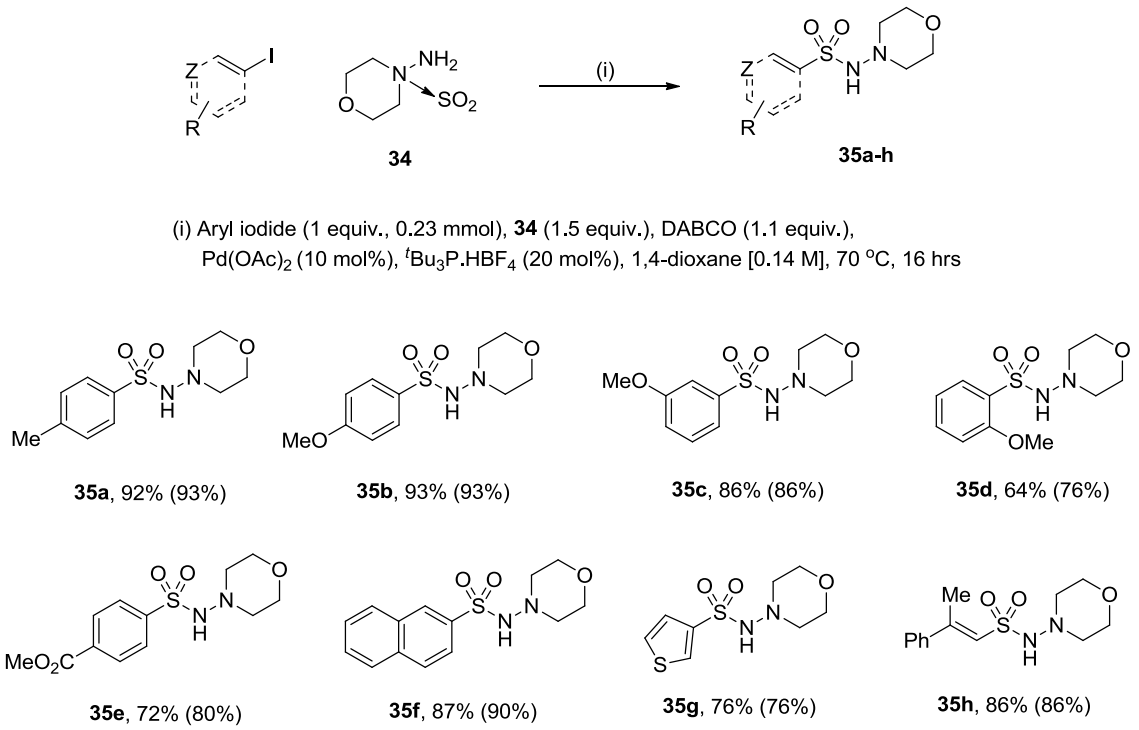


Figure 2.7 Aminosulfonylation using hydrazine-sulfur dioxide complex **34** – yield obtained using DABSO method shown in parentheses for comparison

Pleasingly, the yields for this reaction were almost identical to those obtained using the DABSO method. Only electron-withdrawing *p*-CO_2Me substrate **35e** and sterically demanding *o*-OMe substituted **35d** demonstrated a reduction in yield of about 10% (Figure 2.7). These aryl iodides had previously been observed to be more challenging in the DABSO procedure (perhaps due to a slower SO_2 insertion step (see CO insertion in Section 1.3.2)) in that an increase in DABSO loading from 0.6 equivalents (for sterically unencumbered electron-rich substrates) to 1.1 equivalents was required to produce good yields.[1] This loading (2.2 equivalents of SO_2) was higher than that provided by 1.5 equivalents of complex **34**, however increasing the loading of **34** in fact led to a reduction in yield. A high level of hydrazine had also been previously shown to be detrimental to the DABSO reaction and therefore it appeared that the inability to independently vary the loadings of SO_2 and hydrazine in this new procedure was likely to be the cause of the reduced yields.

2.5 N-N Bond Cleavage of *N*-Aminosulfonamides

With the inability to use simple amines as coupling partners in this novel sulfonylation methodology, procedures were sought to convert *N*-aminosulfonamides into the versatile unsubstituted sulfonamides **36**. This would be ideally achieved through direct N-N bond cleavage. However, during the course of my Master's project, a range of potential conditions were applied to *N*-aminosulfonamide **37** but were unsuccessful.[111] Either unreacted starting material was recovered, or most often, decomposition through S-N bond cleavage (cf. de-tosylation)[15] was observed. It was therefore proposed to use a hydrazine coupling partner where one (or both) of the substituents was a protecting group. The ensuing deprotection of the coupled product would allow access to *N*-aminosulfonamides **38** and **39** with substitution patterns for which there were literature precedented N-N bond cleavage conditions (Figure 2.8).[137,138]

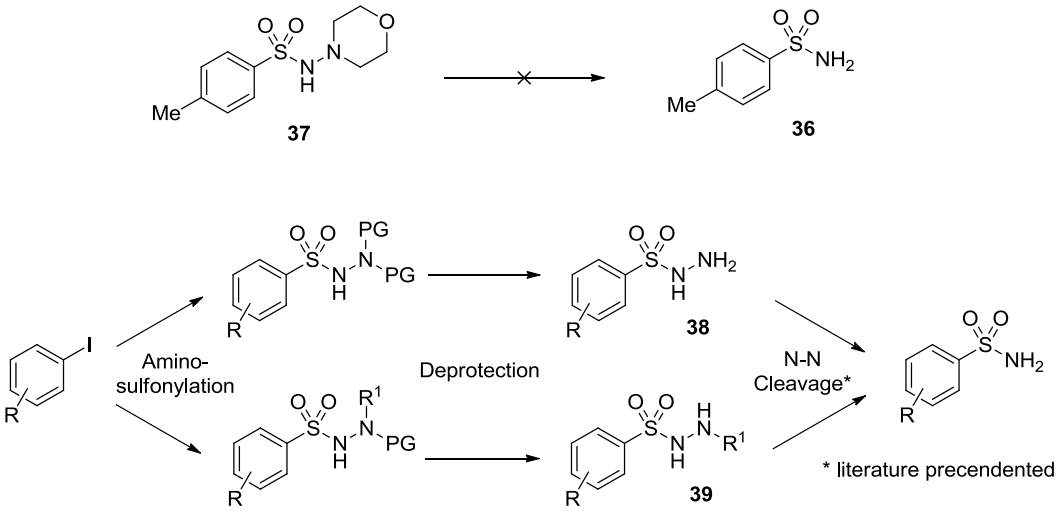
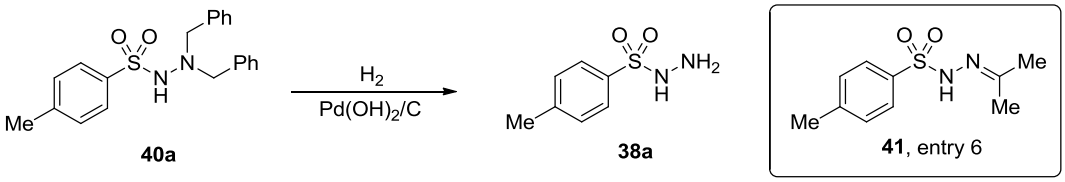


Figure 2.8 Unsuccessful direct N-N bond cleavage of **37** and proposed alternative route using protecting groups

The choice of protecting group was unfortunately limited due to the fact that hydrazines substituted with electron withdrawing groups (e.g. carbamates) gave a very poor yield in the coupling step (1,1-Me,Boc-hydrazine gave only 9% conversion of 4-iodotoluene). However, using the commercially available 1,1-dibenzylhydrazine, palladium-catalysed aminosulfonylation proceeded in a very good 85% yield to afford **40a**. A hydrogenation reaction was then investigated to reveal the unsubstituted hydrazine **38a**. Using $Pd(OH)_2/C$ as the heterogeneous catalyst, a range of solvents were screened to effect the hydrogenative deprotection under a balloon pressure of hydrogen (Table 2.1).

Table 2.1 Screen of solvents for benzyl group deprotection of **40a**[a]



Entry	Solvent	Yield[b]
1	MeOH	-
2	AcOH	-
3	DMF	-
4	EtOAc	50%
5	THF	50%
6	Acetone	100%[c]

[a] Reaction conditions: *N*-aminosulfonamide (1 equiv.), $Pd(OH)_2/C$ (10 mol% Pd), solvent [0.16 M], $H_{2(g)}$ balloon, 16 hrs, RT. [b] ^1H NMR spectroscopy conversion determined by integration to nearest 5%. [c] Isolated yield of hydrazone **41**.

Several solvents gave poor reactions, leaving mainly unreacted **40a** (Table 2.1, entries 1-5), however acetone proved excellent giving full conversion (entry 6). The reason for this highly specific solvent dependence became clear when it was observed that the product was in fact hydrazone **41** rather than hydrazine **38a**. It is suggested that **38a** poisons the heterogeneous catalyst and it is only through its removal *via* a condensation reaction with the acetone solvent, that the catalyst remains active. The *in situ* derived hydrazone pleasingly underwent a literature precedented N-N bond cleavage using zinc in acetic acid,[137] yielding the desired unsubstituted sulfonamide **36**, which was analytically pure and did not require further purification, in 83% yield across two-steps (Figure 2.9). Unfortunately, attempts to effect a direct palladium-catalysed sulfonylation of cyclohexyl hydrazone were unsuccessful.

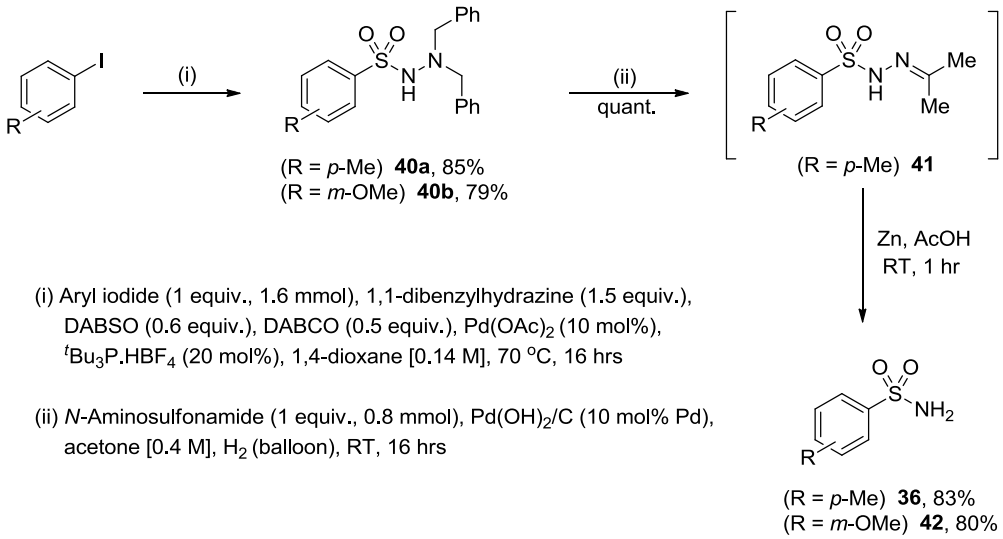


Figure 2.9 Synthesis of unsubstituted aryl sulfonamides from aryl iodides

These optimised conditions were also applied to 3-iodoanisole, revealing the corresponding sulfonamide **42** in 63% yield across the three steps. This substrate, as a result of the directing properties of the substituents, would require a long, challenging and low yielding synthesis *via* traditional aromatic chemistry.

It should also be mentioned that the use of 1,1-Me,Bn-hydrazine was investigated in this chemistry (following the sequence shown by the bottom pathway in Figure 2.8). Although the aminosulfonylation proved routine, the hydrogenation reaction was poor yielding, perhaps because of the inability to form the hydrazone. In addition, the proposed precedented cleavage conditions of **39** of refluxing RaNi[138] were less attractive than those already demonstrated with Zn/AcOH. Following the success presented above, no further work was carried out using monoprotected hydrazines.

2.6 Functionalisation of *N*-Aminosulfonamides

In order to further exploit these unusual *N*-aminosulfonamide products, functionalisation of the "free NH" was proposed; combining this functionalisation with the protecting group chemistry developed in Section 2.5 could also reveal a new route to primary sulfonamides **43** (Figure 2.10).

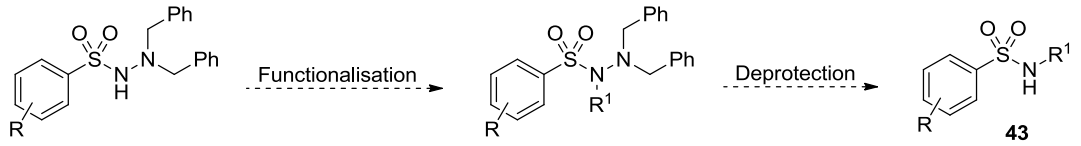


Figure 2.10 Proposed functionalisation of *N*-aminosulfonamides and subsequent deprotection

Unfortunately, attempted alkylations of two *N*-aminosulfonamides **44** and **40a** led to the unexpected isolation of hydrazone side products **45** and **46** respectively, which appeared to occur through S-N bond cleavage (Figure 2.11).[139] It was suggested that this arose through the base-promoted elimination of Ts-H after *N*-alkylation. From this it followed that *N*-aminosulfonamides could behave as protected or masked sulfinates **50** and this idea was fully investigated by Charlotte Richards-Taylor in the Willis group. As a result she developed a new methodology for the synthesis of sulfones (Figure 2.11).[131,140]

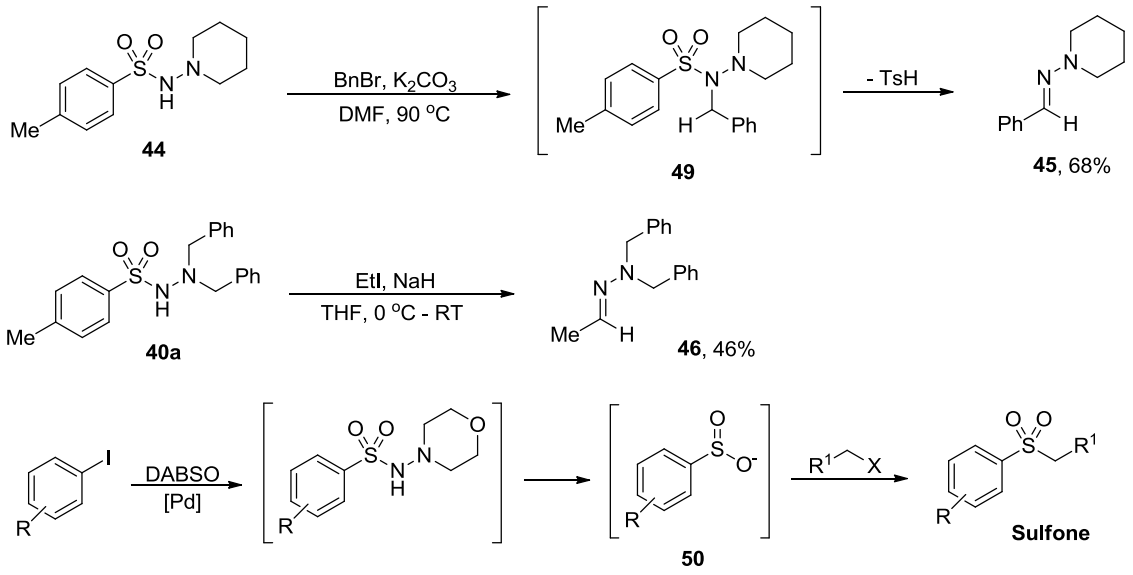


Figure 2.11 Attempted *N*-alkylations leading to the development of a new sulfone synthesis

In addition, an attempted *arylation* of **40a** using Buchwald's conditions for arylation of amides and sulfonamides,[141] led unexpectedly to the formation of diaryl sulfone **47** in very good yield (Figure 2.12). Again it was suggested that *N*-aminosulfonamide **40a** was behaving as a masked source of *p*-tolyl sulfinate **48**, with the hydrazine component decomposing into nitrogen gas and dibenzyl via a radical mechanism;[139,142,143] this clearly could not have occurred through the mechanism proposed for the alkylation procedures. Charlotte observed during the course of her studies that *N*-aminosulfonamides were unstable to decomposition to the sulfinate when heated under basic conditions in the absence of alkylation agent, thereby supporting the theory for this unusual arylation chemistry. Although she also observed intermediates corresponding to **49** in Figure 2.11, in the alkylation chemistry, thus substantiating the alternative alkylation mechanism too.[140]

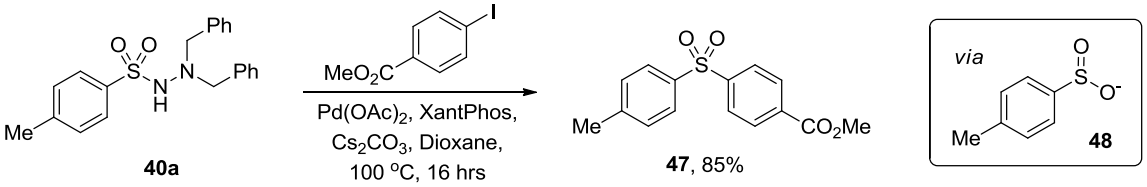


Figure 2.11 Attempted *N*-arylation of **40a** leading to unexpected diaryl sulfone **47** formation

No further work was carried out in this arylation area as it was felt that this was an indirect route to diaryl sulfones with the use of expensive hydrazines as "dummy groups" being wasteful. Instead, the idea of forming diaryl sulfones from sulfinates was investigated through an alternative methodology which is presented in Chapter 3.

These results also led us to propose a new method for transforming *N*-aminosulfonamides into unsubstituted sulfonamides (cf. Section 2.5). *N*-Aminosulfonamide **35c** was treated with aqueous NaOH to reveal sulfinate **51** which was then electrophilically aminated *in situ* using hydroxylamine-*O*-sulfonic acid.[127] Unsubstituted sulfonamide **42** was thereby generated in a good 78% yield (Figure 2.12).

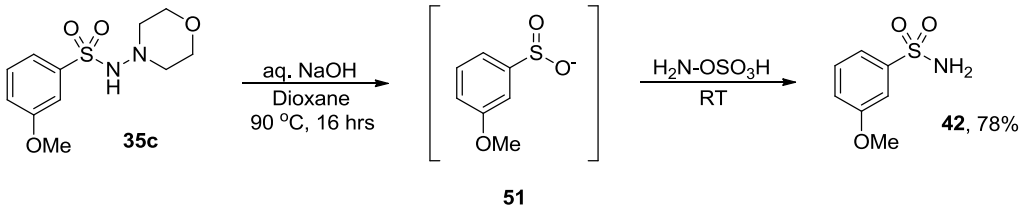


Figure 2.12 Unsubstituted sulfonamide **42** *via* electrophilic amination

2.7 Beyond Hydrazines

Attempts to couple alternative nucleophiles in this palladium-catalysed sulfonylation with DABSO other than 1,1-disubstituted hydrazines have unfortunately been unsuccessful. A range of theories have been put forward to explain this.

Firstly, the substitution pattern of the hydrazine appears to be key with 1,1-functionalisation essential. The resulting full substitution at the beta position when the nucleophile is coordinated to palladium, removes the potential for *β*-hydride elimination (**52**, Figure 2.13). This elimination in palladium-coordinated amines, for example, has been shown to be the origin of deleterious protodehalogenation in Buchwald-Hartwig couplings.[87] However, alternative nucleophiles such as anilines, tertiary amines, hydroxylamines and hydrazones which have no beta hydrogen atoms also proved to be ineffective in our system.

***52**, no β hydrogens* **53**

Figure 2.13 Proposed intermediates **52** and **53**

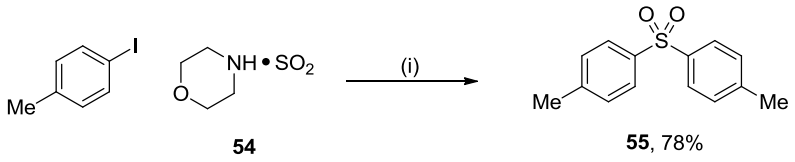
A second theory was that hydrazines are known reductants[144] and since a Pd(II) source was being added to the reaction, only hydrazines were able to effect the required

reduction to obtain an active Pd(0) species. A test for this theory was devised by proceeding with a reaction containing only 0.5 equivalents of hydrazine and then adding alternative nucleophiles after 30 mins while the reaction was still in progress. In all cases 50% conversion to the *N*-aminosulfonamide was achieved with no further products. This also suggests that the alternative nucleophiles are not suppressing the reaction but are simply unreactive.

A third theory is that hydrazines are known to be exceptionally nucleophilic due to the alpha effect.[145] The added nucleophilicity of having *bis* functionalisation on the neighbouring nitrogen may also contribute. The fact that monosubstituted hydrazines are incompatible and that 1,1-diphenylhydrazine and 1,1-Me,Boc-hydrazine were ineffective or low yielding respectively, is also suggestive that the electronics and therefore nucleophilicity is important. In addition, our working assumption is that the mechanism parallels that of carbonylation and so would lead to a palladium-sulfinato catalytic intermediate similar to **53** (Figure 2.13). **53** has been shown to be a very stable species, from which the sulfonyl group could not be displaced with a range of nucleophiles, other than hydrogen gas, under stoichiometric and forcing conditions.[31] Therefore, perhaps hydrazines are the only species nucleophilic enough to effect this displacement. However, other "enhanced-nucleophilic" species such as azides, hydroxylamines and deprotonated amines still did not couple.

A final proposal is that the released carrier amine DABCO, which is very nucleophilic due to its sterically un-crowded lone pair, is coordinating to palladium and thereby blocking coordination sites for the coupling nucleophile (with hydrazines being the only species nucleophilic enough to displace it). In order to investigate this, a screen of conditions was performed using the morpholine-sulfur dioxide complex **54**, anticipating that after sulfonylation the morpholine would go on to couple and form the sulfonamide (cf. Section 2.4). Although this proved unsuccessful in that the sulfonamide was never

observed, an unexpected side product, symmetrical diaryl sulfone **55** was observed in good yield (Figure 2.14).



54 **55**, 78%

(i) 4-Iodotoluene (1 equiv., 0.45 mmol), **54** (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), Et_3N (1.1 equiv.), ^tBuOH (1.5 mL), 85 °C, 16 hrs

Figure 2.14 Unexpected symmetrical diaryl sulfone **55** formation

Interestingly, if this reaction is carried out in the presence of 4-aminomorpholine, the corresponding *N*-aminosulfonamide **35a** is isolated as the only product, demonstrating the ability of complex **54** to act as a simple SO_2 source like DABSO.

An optimisation of conditions and scope was carried out by Ryan Norris, a Master's (Part II) student in the group and the full results are presented in his thesis.[146] He found that the conditions presented in Figure 2.14 were very close to optimal. The reaction worked well for electron-neutral and electron-rich aryl halides but that there was often additional products in the form of the corresponding symmetrical diaryl sulfide and biaryl. With electron-poor aryl halides, the symmetrical biaryl was the highest yielding product with no SO_2 insertion observed.

Although the synthetic utility of this reaction is limited due to the symmetric nature of the products, the results, together with those obtained from the hydrazine work, contribute to furthering our understanding of the mechanism of palladium catalysed sulfonylations. This will hopefully ultimately lead to a widening of the scope of compatible nucleophiles in the future.

2.8 Additional Versatility

As a final exploration of the utility of aminosulfonylation, three further variations are documented. Firstly, for situations where the use of gas is not problematic (e.g. pilot plant) we wanted to show that DABSO could be formed *in situ* by passing the gas through a DABCO solution (Figure 2.15). This was indeed achievable although following complex formation, the solution needed to be degassed in order to remove "free" dissolved SO_2. If this did not occur, a poor conversion of aryl iodide was observed, presumably due to catalyst sequestration.

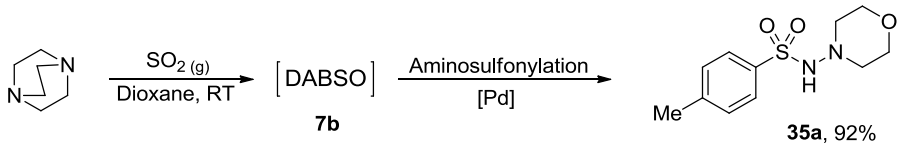


Figure 2.15 Aminosulfonylation using *in situ* derived DABSO

Secondly, the idea of having SO_2 attached to a carrier molecule led to the suggestion that this chemistry could be amenable to a solid-supported reagent system and perhaps ultimately flow chemistry. Merrifield resin **56** was functionalised with DABCO to give **57** to which sulfur dioxide was complexed forming **58** (Figure 2.16). This solid-supported sulfur dioxide source **58** was demonstrated to perform aminosulfonylation to generate **35a** in a pleasing (non-optimised) 70% yield.

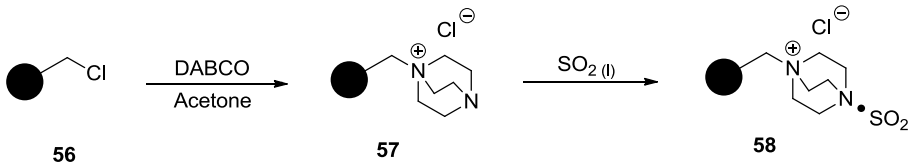
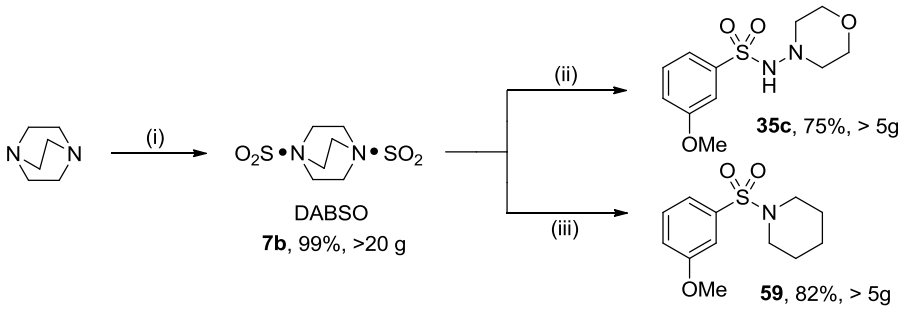


Figure 2.16 Synthesis of a solid-supported SO_2 surrogate

Finally, in order to demonstrate the easy-to-handle nature and applicability of DABSO on a large scale, the synthesis of DABSO (**7b**, >20 g) and an aminosulfonylation reaction

(**35c**, >5 g) were optimised for an Organic Synthesis publication.[3] The synthesis of DABSO was a simple scale-up of the current procedure, although it was not included in the final publication. For the aminosulfonylation, palladium, ligand and hydrazine loading could all be reduced and the reaction performed at a greater concentration without erosion of yield (Figure 2.17).

Also, an example of sulfonamide formation (**59**, >5 g) through Grignard chemistry developed by Holly Woolven in the Willis group[109] was re-optimised for the larger scale and documented (Figure 2.17). Once again the loading of reagents used in excess (DABSO and amine) could be significantly reduced.



(i) DABCO (1 equiv., 89 mmol), $SO_{2(l)}$ (excess), -30 °C - RT

(ii) DABSO (0.6 equiv.), DABCO (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), $^tBu_3P.HBF_4$ (7 mol%), 4-aminomorpholine (1.2 equiv.), 3-iodoanisole (1 equiv., 25 mmol), 1,4-dioxane [0.18 M], 70 °C, 16 hrs

(iii) DABSO (1.25 equiv.), $(3\text{-OMe})C_6H_4MgBr$ (1 equiv., 28 mmol (1M solution in THF)) THF [0.18 M], -40 °C, 1 hr *then* SO_2Cl_2 (1 equiv.), -40 °C - RT, 90 mins *then* piperidine (4 equiv.), RT, 16 hrs

Figure 2.17 Large scale syntheses of DABSO and sulfonamides

2.9 Summary

In summary, the full development of the palladium-catalysed aminosulfonylation of halides has been investigated.[1–3] Through my work and that of others, this reaction now allows access to aryl, heteroaryl and alkenyl sulfonamides with perfect regiocontrol, under mild conditions, using easy-to-handle and readily available substrates and in a one-step convergent manner. Although the reaction is currently limited to the use of hydrazines as the nucleophilic coupling component, the *N*-aminosulfonamide products have proved to be synthetically versatile materials and through onwards reactions can form unsubstituted sulfonamides and sulfones.

Following publication of this project, Wu *et al*. published three papers documenting variations of aminosulfonylations. In their first two papers, they describe an almost identical procedure with almost identical conditions either replacing DABSO with $K_2S_2O_5$[49] or aryl halides with aryl boronic acids (oxidative procedure).[147] In their final paper they replace aryl halides with aryl diazonium salts but under metal-free conditions.[148] In all three cases, no extension of scope is documented with the same *N*-aminosulfonamide products being formed, as hydrazines remain the only compatible coupling partners. In addition Beller and co-workers have recently published an identical aminosulfonylation procedure using Na_2SO_3 as an *ex-situ* sulfur dioxide source in a two-chamber reaction vessel, but once again there is no extension of scope.[48]

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Chapter 3 – A New Palladium-Catalysed Synthesis of Diaryl Sulfones

3.1 Traditional Syntheses of Sulfones

Aryl, heteroaryl and alkenyl sulfones play a very important role in organic chemistry. This includes prominence as polymeric plastic materials,[12] as intermediates in organic synthesis,[14] as agrochemicals[11,149] and an extensive pharmaceutical relevance (Figure 3.1).[150–153] Their particular importance in medicinal chemistry stems from their ability to display a wide range of biological activities from targeting HIV[154] to treating leprosy[155] and depression.[156]

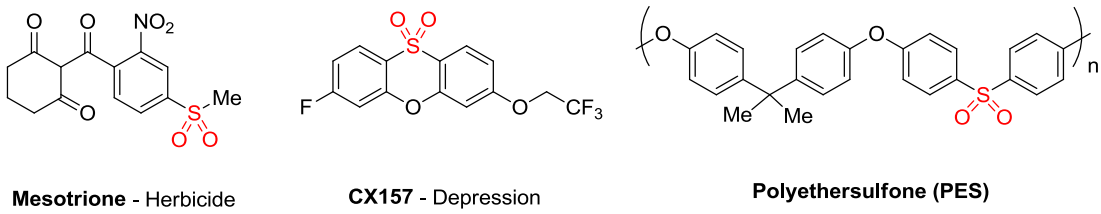


Figure 3.1 Examples of aryl sulfones in pharmaceuticals, agrochemicals and materials

Their established use has led to a significant amount of research being dedicated to developing methods for their synthesis and historically two methods have dominated the area. The first is a Friedel-Crafts sulfonylation whereby "unfunctionalised" arenes **60** react with aromatic sulfonyl chlorides **61** through the mediation of a Lewis-acid catalyst or additive. Many different conditions have been documented over the decades but three of the most modern procedures are shown in Figure 3.2.[157–159] One problem with this method is that the scope is often limited to electron-rich arenes and aromatic sulfonyl chlorides, although there are isolated examples of electron-poor arenes,[158] aliphatic sulfonyl chlorides[157] and aromatic sulfonic acids[160] being used. However, the most significant limitation is imposed by the very nature of the Friedel-Crafts mechanism; the substitution pattern of the sulfone is limited by the inherent electronic and steric bias of

the arene substrate. Often mixtures are obtained, and by their very regioisomeric nature, these can be difficult to separate.

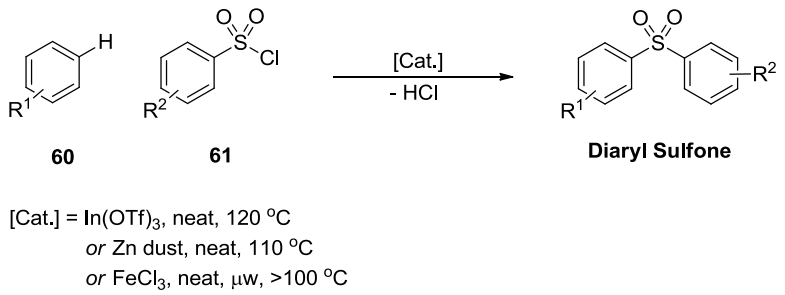


Figure 3.2 Modern methods of diaryl sulfone synthesis *via* Friedel-Crafts sulfonylation

The second and most commonly used method is the oxidation of the corresponding sulfide (or sulfoxide) **62**, often mediated by a catalyst (Figure 3.3). There is an extensive list of different oxidants and catalyst combinations reported to perform this transformation,[161–164] which demonstrates the lack of a general procedure, and is mainly down to two issues. The first is the inability to oxidise the corresponding sulfide fully to the sulfone, with many conditions giving undesired mixtures of partially oxidised sulfoxide and sulfone. In order to overcome this, more powerful oxidants and harsher conditions are required to push the substrate through the sulfoxide and up to the sulfone oxidation level. This then leads to the second issue, since such conditions are often functional group intolerant and suffer from a limited scope. In addition, there is also the implicit assumption that the corresponding starting material sulfide is easy to make but this often requires the use of odorous thiols which are themselves not always commonly available, leading to a long and linear synthetic sequence.

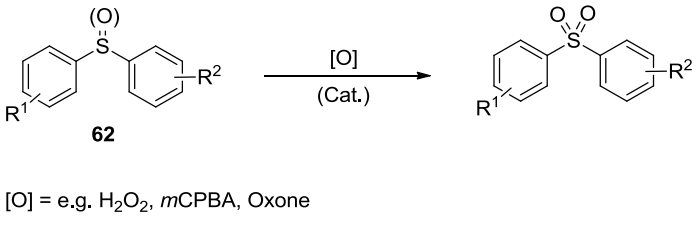


Figure 3.3 Diaryl sulfone synthesis *via* oxidation

In order to address some of the problems associated with these traditional procedures, the development of transition-metal-catalysed cross-coupling has been applied to the synthesis of sulfones. This is primarily effected through the coupling of a sodium sulfinate salt **63** with an activated partner. This partner can be electrophilic in the form of an (hetero)aryl or alkenyl (pseudo)halide **64**[142,143,165–168] or nucleophilic as a boronic acid **65** (oxidative conditions).[169–172] Copper catalysis has been the best documented but palladium has also been applied (Figure 3.4).

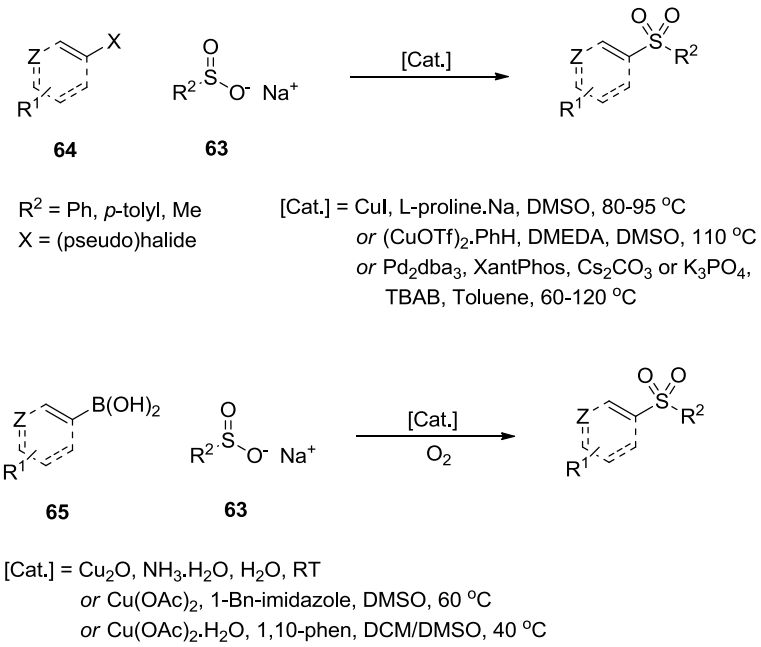


Figure 3.4 Examples of diaryl sulfone synthesis *via* metal-catalysed coupling with sodium sulfinates **63**

This technique of using transition metal catalysis is not exempt from problems, especially in the (pseudo)halide cases. Perhaps due to the poor nucleophilicity of sulfinates (pK_{aH} ~2), the conditions required are relatively harsh with high reaction temperatures and long reaction times being particularly prevalent (Figure 3.4). In addition the low solubility of the salt can lead to the requirement of undesirable solvents, specialised ionic liquids and/or stoichiometric (phase-transfer) additives. However, the most limiting factor in all cases is the poor scope documented with respect to the sodium sulfinate salt. Only three sulfinates are ever used in these metal catalysed examples (phenyl, *p*-tolyl and

methyl), reflecting the fact these are the only commonly commercially available substrates. This also suggests that sulfinates are not trivial to synthesise and methods are reviewed in Chapter 4, where a new mild and versatile route to sulfinate salts is described.

Two further routes to diaryl sulfone formation are important to mention (Figure 3.5). Bandgar and co-workers documented the palladium-catalysed coupling of sulfonyl chlorides **61** with boronic acids **65** under impressively mild conditions, although only tosyl and benzene sulfonyl chlorides were shown to couple.[173] Secondly, during the course of this project, Manolikakes *et al.* developed a metal-free protocol whereby sulfinate salts **63** react with diaryliodonium salts **66** to furnish the corresponding sulfones.[174,175] Although the metal-free conditions are attractive, the use of diaryliodonium salts is wasteful, producing stoichiometric aryl iodide as a byproduct, and so this method lacks versatility towards using non-trivial aryl groups.

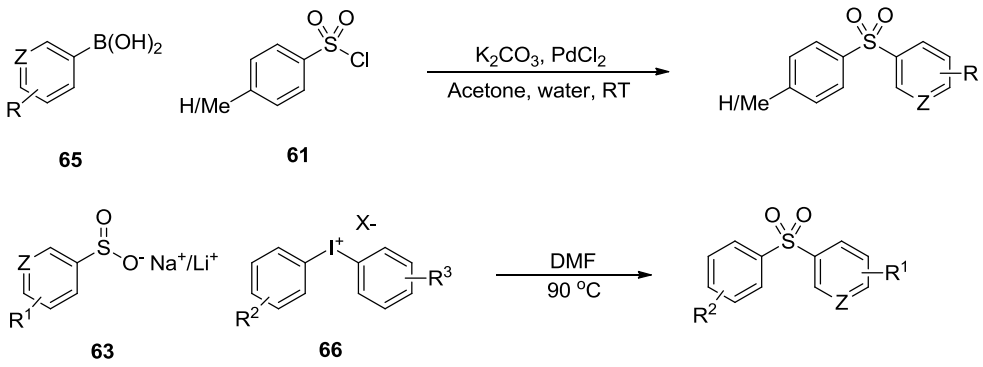


Figure 3.5 Further methods of diaryl sulfones synthesis

The methods described so far have primarily been applicable to the synthesis of (di)aryl and heteroaryl sulfones, although metal-catalysed cross-coupling has also been successfully demonstrated to produce alkenyl sulfones.[167,168,172] For completion, it should also be mentioned that a common route to alkenyl sulfones is through the addition of sulfinate salts **63** across alkenes or alkynes (Figure 3.6).[176–179] In much the same way, the scope of these transformations is entirely governed by the ability to access sulfinate salts.

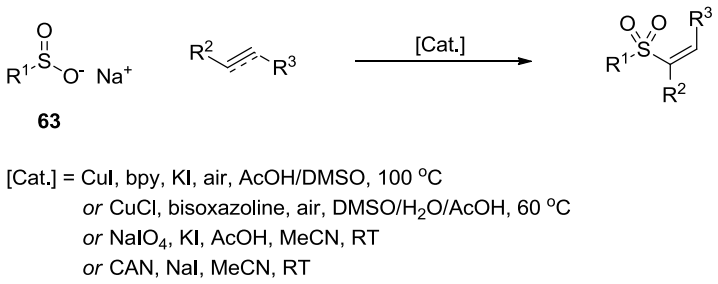


Figure 3.6 Alkenyl sulfones *via* addition of sulfinates across unsaturated C=C bonds

In summary, many different methods exist for the synthesis of aryl, heteroaryl and alkenyl sulfones but no single method is able to offer good versatility for both substituents of the -SO_2- moiety under mild and economic conditions. Therefore the need remains to develop new methodologies towards sulfones with improved flexibility.

3.2 Origin of Project

Following the unexpected formation of symmetrical diaryl sulfones (Section 2.6), we became interested in the more versatile unsymmetrical variant. Our development of the easy-to-handle sulfur dioxide surrogate DABSO, led a new disconnection of diaryl sulfones to be proposed, which had the potential to address some of the issues associated with current methodologies. A three-component metal-catalysed convergent synthesis using electrophilic and nucleophilic components together with SO_2 provided by DABSO was suggested. The electrophilic component would come from the readily available (pseudo)halide substrates, while the nucleophilic component could come in several forms and would be chosen through evaluation (Figure 3.7).

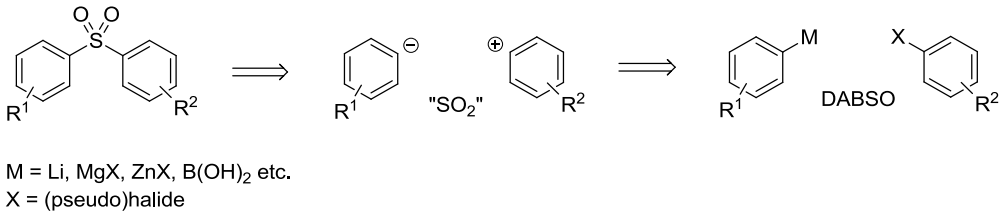


Figure 3.7 Proposed disconnection of diaryl sulfones exploiting DABSO

One possible scenario was a sulfonylative Suzuki coupling (i.e. using an aryl boron species as the nucleophilic component); unfortunately this proved unattainable, with reactions either returning unreacted starting material, or more often furnishing direct Suzuki coupling product. Since organotins,[180] organozincs,[108] organolithiums[18–20] and Grignard reagents[21,22,109,181] were all known to add rapidly to DABSO (or sulfur dioxide) to form the corresponding sulfinate, we did not believe that a one-step reaction akin to a carbonylative Stille, Negishi or Kumada cross-coupling would be possible. Instead a two-step, one-pot procedure was proposed, whereby initial addition of an aryl metal species **67** to DABSO would give the crude sulfinate salt **63**, which could then be taken directly through a metal-catalysed C-S bond formation to deliver the desired sulfone (Figure 3.8).

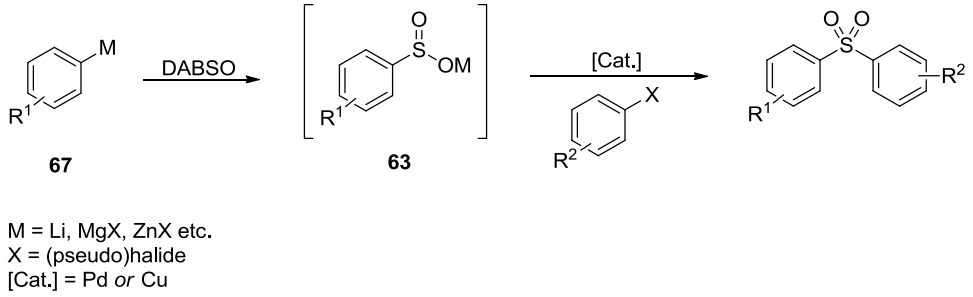


Figure 3.8 Proposed two-step one-pot synthesis of diaryl sulfones

There was excellent precedent for this reaction given our group has extensive experience on the addition of organometallics to DABSO.[107,109] In addition, it was known that C-S bond formation between an aryl halide and sulfinate could be achieved under similar conditions, following the unexpected isolation of diaryl sulfone from an attempted arylation of *N*-aminosulfonamides (Section 2.6). Furthermore, as detailed in Section 3.1, the metal-catalysed coupling of aryl (pseudo)halides with *sodium* sulfinates is very well documented although we believed that a sulfinate with a more strongly Lewis-acidic counter cation, such as lithium or magnesium halide, would require changes to the literature conditions.

3.3 Optimisation of Conditions

3.3.1 Initial Investigations

The starting point was the use of readily available Grignard reagents, for whose addition to DABSO conditions had already been developed within the group.[109] Using a commercial solution of *p*-tolyl magnesium bromide in THF, successful formation of the corresponding sulfinate salt **68** was achieved as expected. However, using similar metal catalysis conditions to those developed for sodium sulfinates (Figure 3.4), no sulfone was formed, with **68** remaining unreacted (Figure 3.9).

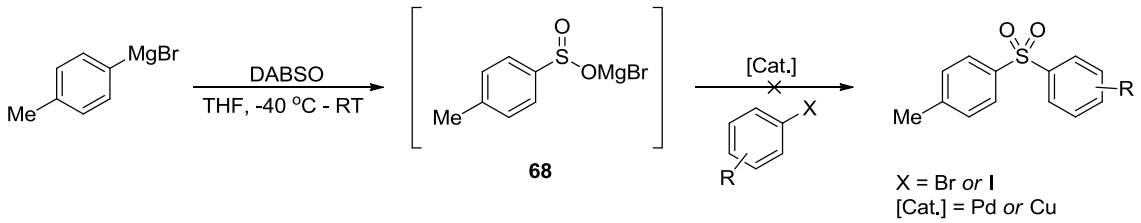
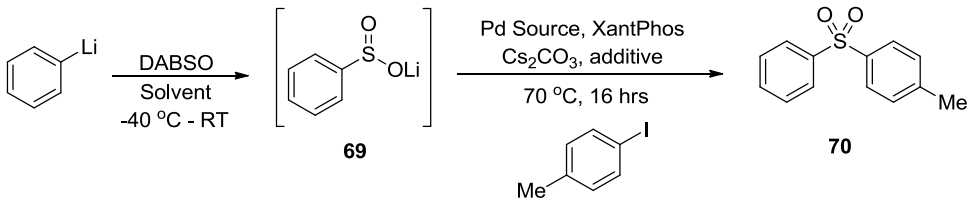


Figure 3.9 Unsuccessful attempts to couple magnesium bromide sulfinate **68**

Postulating that this was a result of having DABCO present in the reaction mixture, pure **68** was synthesised by adding the Grignard reagent directly to sulfur dioxide. However, cross-coupling was still not realised and, given the precedent with sodium salts, it was concluded that changing the identity of the counter cation must be having a significant effect. It was therefore decided to use organolithiums instead, forming a lithium sulfinate which we hoped would be more closely related (as a result of the group I cation) to sodium salts. Using a commercial solution of PhLi in $^{n}Bu_2O$, with identical conditions employing DABSO to those developed in our group for Grignard reagents,[109] we were pleased to observe by HPLC analysis full conversion to the lithium sulfinate **69**, with only traces of benzene from deleterious protonation. This crude suspension of **69** was combined with 4-iodotoluene under metal catalysis to attempt to effect C-S bond formation. Pleasingly, under the action of palladium catalysis (Pd_2dba_3, XantPhos, Cs_2CO_3 and $^{n}Bu_4NCl$, the conditions reported by Cacchi for sodium sulfinate

coupling),[142,143] the desired sulfone **70** was formed, albeit in low conversion (entry 1, Table 3.1).

Table 3.1 Initial reactions investigating palladium catalysed cross-coupling of lithium sulfinates[a]

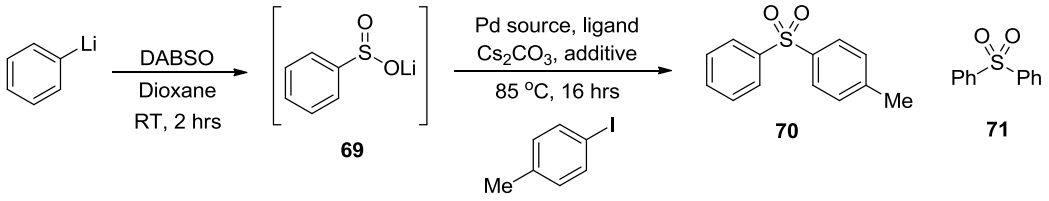


Entry	Solvent	Pd Source	Additive	Conversion[b]
1	THF	Pd_2dba_3	$^nBu_4NCl$	20
2	THF	$Pd(OAc)_2$	$^nBu_4NCl$	65
3	THF	$Pd(OAc)_2$	-	65
4[c]	1,4-Dioxane	$Pd(OAc)_2$	-	100

[a] Reaction conditions: PhLi (1.4 equiv.), DABSO (0.75 equiv.), [solvent] (0.18 M), 2 hrs; *then* 4-iodotoluene (1 equiv., 0.35 mmol), palladium source (10 mol% Pd), XantPhos (10 mol%), Cs_2CO_3 (1.5 equiv.), additive (1.4 equiv.). [b] Of aryl halide, determined by ^{1}H NMR spectrum integration, to nearest 5%. [c] 1st Step performed at RT; 2nd step at 85 °C.

By replacing Pd_2dba_3 with $Pd(OAc)_2$ conversion was increased further while it was realised that the $^nBu_4NCl$ additive was not required (entries 2 and 3, Table 3.1). Switching solvent to dioxane and thereby allowing the coupling step to be performed at a higher temperature of 85 °C achieved full conversion (entry 4). Unfortunately upon purification, two products were identified: desired sulfone **70** and diphenyl sulfone **71** as an inseparable 3:1 mixture (70% effective yield of **70**). It was initially suggested that this byproduct had been produced by the pseudo dimerisation of sulfinate **69** akin to boronic acid homocoupling, which is a common side reaction in Suzuki couplings.[182] Therefore a more extensive optimisation of the second step was undertaken, to probe the factors which influenced this side product formation (selected results, Table 3.2). A whole range of factors were investigated from palladium source to ligands, bases, additives, temperature and solvents but maintaining conversion while obtaining a substantial improvement in selectivity was not achieved.

Table 3.2 Attempted optimisation of palladium coupling to improve selectivity[a]



Entry	Pd Source	Ligand	Additive	Conversion[b]	70:71[b]
1	$Pd(OAc)_2$	XantPhos	-	100	3:1
2[c]	$Pd(OAc)_2$	XantPhos	-	35	-
3[d]	$Pd(OAc)_2$	XantPhos	-	100	3:1
4[e]	$Pd(OAc)_2$	XantPhos	-	100	7:2
5[f]	$Pd(OAc)_2$	XantPhos	-	25	-
6	$Pd_2(dba)_3$	XantPhos	-	10	-
7	$Pd_2(dba)_3$	XantPhos	$^{n}Bu_4NCl$[g]	100	2:1
8[h]	$Pd(OAc)_2$	XantPhos	-	15	-
9[i]	$Pd(OAc)_2$	XantPhos	-	10	-
10[j]	$Pd(OAc)_2$	XantPhos	-	0	-
11	$Pd(OAc)_2$	XantPhos	IPA[k]	100	3:1
12	$Pd(OAc)_2$	XantPhos	12-C-4[l]	40	-
13	$Pd(OAc)_2$	DPEPhos	-	20	-
14	$Pd(OAc)_2$	$^{t}Bu_3P.HBF_4$	-	15	-
15	$Pd(OAc)_2$	CatacXiumA	-	0	-
16	$Pd(OAc)_2$	XPhos	-	0	-
17	$Pd(OAc)_2$	JosiPhos	-	0	-
18	$Pd(OAc)_2$	JackiePhos	-	0	-
19	$Pd(TFA)_2$	XantPhos	-	30	-
20	$PdCl_2(MeCN)_2$	XantPhos	-	20	-
21	$Pd(PPh_3)_2Cl_2$	XantPhos	-	50	-
22	$(Pd(allyl)Cl)_2$	XantPhos	-	45	-

[a] Reaction conditions: PhLi (1.4 equiv.), DABSO (0.75 equiv.), 1,4-dioxane [0.18 M]; *then* 4-iodotoluene (1 equiv., 0.35 mmol), palladium source (10 mol% Pd), ligand (10 mol%), Cs_2CO_3 (1.5 equiv.), additive (as indicated). [b] Determined by integration of crude ^1H NMR spectrum, to nearest 5%. [c] With 1.2 equiv. PhLi. [d] At 95 °C. [e] At 70 °C. [f] At 60 °C. [g] 1.5 Equiv. [h] With K_2CO_3 in place of Cs_2CO_3. [i] With K_3PO_4. [j] With NaO^{t}Bu. [k] 0.3 mL. [l] 2 Equiv.

3.3.2 Application of XantPhos-type Ligands

Following this unsuccessful screen, the identity of the aryl lithium was investigated. Using *m*-tolyl lithium **72a**, we fully expected to see the corresponding symmetrical sulfone **76** as the undesired side product. Much to our surprise however, sulfone **75**, whereby a phenyl group had been incorporated where the aryl halide fragment should have been, was observed (Figure 3.10).

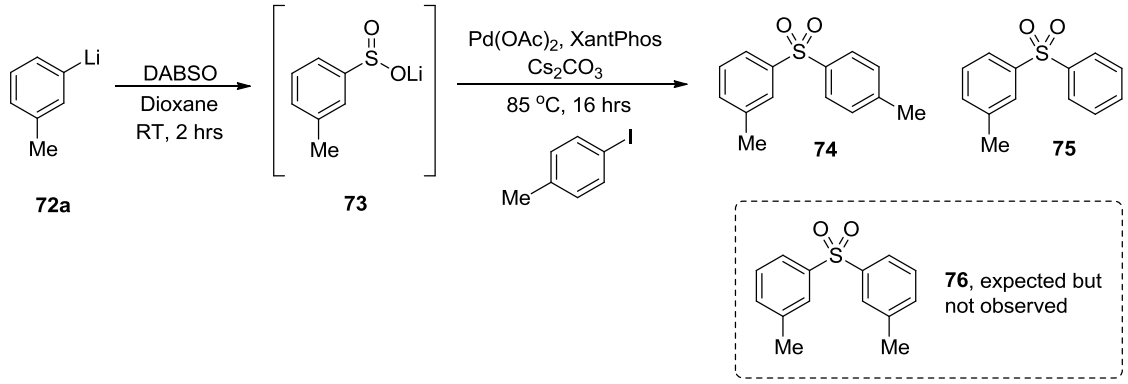


Figure 3.10 Use of *m*-tolyl lithium **72a** and the unexpected side product **75** formation

The only source of phenyl groups present in this reaction are those bonded to the phosphorous atom in the XantPhos ligand and therefore it appeared that the aryl halide fragment was exchanging for a phenyl group on the ligand. An examination of the literature revealed that this aryl-aryl exchange is a known process and is proposed to go through the mechanism detailed in Figure 3.11 (demonstrated with a representative bisphosphine).[183–188]

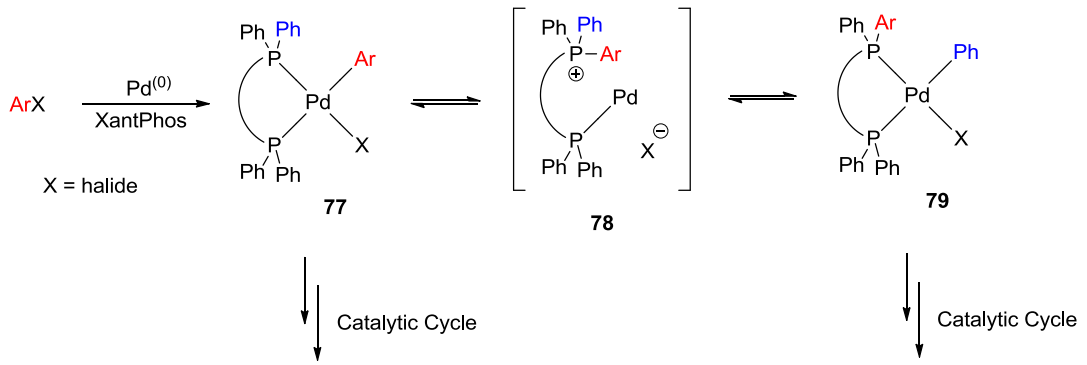


Figure 3.11 Proposed mechanism of aryl-aryl exchange

Following oxidative addition of an aryl halide to the ligated Pd(0) catalyst to give **77**, a $C_{(Ar)}$-P reductive elimination occurs to reveal phosphonium intermediate **78**. A C-P re-oxidative addition then occurs this time across the $C_{(Ph)}$-P bond to give **79**. This equilibrium process results in a mixture of "equivalent oxidative addition intermediates", **77** and **79**, which can both continue around the main catalytic cycle and hence produce a mixture of desired and phenylated sulfones.

The literature suggests this exchange process is especially common in two cases; firstly, with the use of electron-rich aryl halides (because the corresponding phosphonium intermediate is more stabilised) and secondly, where the nucleophilic coupling partner is a poor nucleophile (or insoluble). For the latter case, this leads to a build up of oxidative addition intermediate **77** because the subsequent nucleophilic coordination/transmetallation step is slow, resulting in the corresponding side-reaction equilibrium being driven towards the exchange "product" **79**. Examples where this exchange has occurred include the arylation of ureas (electron-poor nucleophiles) especially with electron-rich halides and Suzuki couplings (where transmetallation can be rate limiting).[184,187,188] The sulfinates' poor solubility and low nucleophilicity made clear why this byproduct was observed in our reaction. Although this side-reaction was not reported by Cacchi for the coupling of sodium sulfinates,[142,143] in our hands we did observe these side products albeit in a reduced quantity compared to the corresponding

lithium reaction. Perhaps the stronger Lewis-acidic character of lithium with respect to sodium, leads to a slower coordination of the sulfinate to palladium.

Following this discovery, there was now a potential avenue of investigation to improve selectivity in our reaction, since the identity of the ligand plays an essential role in this exchange process. From the results of the original screen (Table 3.2) it was clear that the identity of the ligand was particularly important, with the XantPhos backbone appearing to be the only scaffold to give good conversion. This is consistent with Cacchi's work on sodium sulfinates where Xantphos was found to be the only ligand to form sulfones.[142,143] It was therefore decided that a range of XantPhos derivatives **80** should be synthesised, varying the groups attached to the phosphorus, to include electron-rich and -poor aryl, alkyl and sterically hindered substituents. These were made *via* the bis *ortho*-lithiation of 9,9-dimethylxanthene **81** followed by trapping of the lithiated intermediate **82** with the appropriate chlorophosphine (Figure 3.12).[186–189]

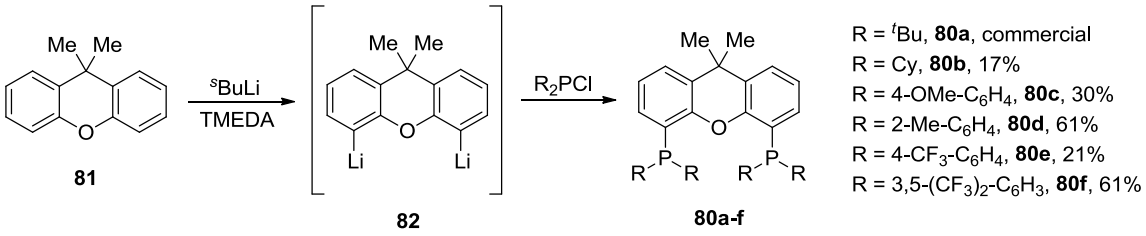
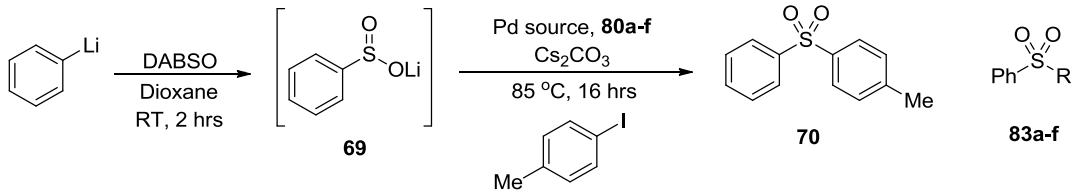


Figure 3.12 Synthesis of XantPhos derivatives **80**

These ligands were then screened using the best conditions obtained previously (Table 3.2, entry 1) and selected results are shown in Table 3.3. It can be seen that alkyl substituted XantPhos-type ligands **80a** and **80b** and the sterically hindered *o*-tolyl-XantPhos **80d** afforded no conversion of starting material (Table 3.3, entries 3–5 and 7). The electron rich *p*-anisyl substituted ligand **80c** gave a worse selectivity, as expected (entry 6). Pleasingly, the electron-poor bis(CF_3)-substituted XantPhos **80f**[187,188] did provide a small improvement in selectivity but gave low conversion (entry 10). By

switching to the corresponding aryl bromide and increasing the reaction temperature to 110 °C an excellent selectivity with full conversion was finally achieved (entry 13).

Table 3.3 Screening of XantPhos-type ligands **80** for suppression of aryl-aryl exchange[a]



Entry	Pd Source	Ligand	Conversion[b]	70:83a-f[b]
1	$Pd(OAc)_2$	XantPhos	100%	3:1
2[c]	$Pd_2(dba)_3$	XantPhos	100%	2:1
3	$Pd(OAc)_2$	**80a**	-	-
4	$Pd(OAc)_2$	**80b**	-	-
5[c]	$Pd_2(dba)_3$	**80b**	-	-
6	$Pd(OAc)_2$	**80c**	40%	1:1
7	$Pd(OAc)_2$	**80d**	Trace	-
8	$Pd(OAc)_2$	**80e**	95%	3:1
9	$Pd(OAc)_2$	**80f**	-	-
10[c]	$Pd_2(dba)_3$	**80f**	50%	5:1
11[d]	$Pd(OAc)_2$	XantPhos	100%	7:2
12[c,d]	$Pd_2(dba)_3$	**80f**	100%	4:1
13[d]	$Pd(OAc)_2$	**80f**	100%	15:1

[a] Reaction conditions: PhLi (1.4 equiv.), DABSO (0.75 equiv.), 1,4-dioxane [0.18 M]; *then* 4-iodotoluene (1 equiv., 0.35 mmol), palladium source (10 mol% Pd), ligand (10 mol%), Cs_2CO_3 (1.5 equiv.). [b] Determined by ^1H NMR spectrum integration, to nearest 5%. [c] With $^nBu_4NCl$ additive (1.5 equiv.). [d] Performed with corresponding aryl bromide at 110 °C.

3.4 Scope of the Reaction

With the optimised conditions in hand, attention turned to the scope of this developed sulfonylation. First, a general route to aryl lithiums **72** was required, since phenyl lithium was the only commercially available substrate. We chose to use the lithium-halogen

exchange reaction between readily available aryl bromides and butyl lithium. Unfortunately, all experiments attempted (with *n*, *s* or *t*-BuLi in a variety of solvents) where the *in situ* formed aryl lithium was directly used without purification were either unsuccessful or capricious. It was postulated that the byproducts of the exchange, bromobutane or LiBr, were interfering in the palladium coupling step. Indeed, when the optimised reaction (Table 3.3, entry 13) was doped with LiBr (1.4 equiv.), a poor 20% conversion of 4-bromotoluene was obtained. We had previously observed that performing the lithium-halogen exchange in $^{n}Bu_2O$ using ^{t}BuLi lead to LiBr precipitating and thus it could be easily removed by filtration (Figure 3.13). Pleasingly, using this filtered solution restored reactivity in the palladium coupling step and the scope of the aryl bromide fragment was now able to be surveyed.

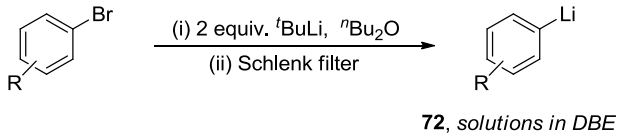
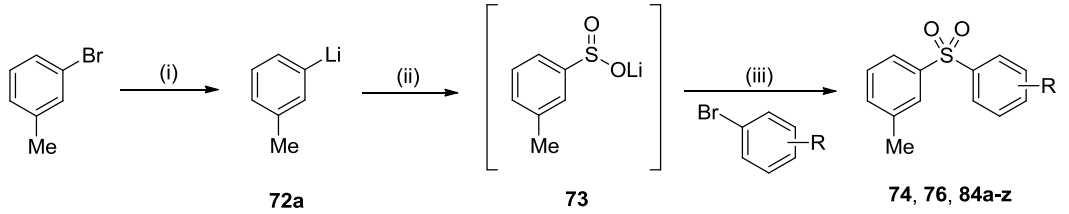


Figure 3.13 Synthesis of aryl lithium solutions **72**

The scope of the aryl halide fragment was investigated using *m*-tolyl lithium **72a**. This allowed access to diaryl sulfones which could not in general be made by Friedel-Crafts chemistry or had not been demonstrated *via* sodium sulfinate coupling (Section 3.1). We were pleased to observe that a wide variety of substrates were compatible in this sulfone formation (Figure 3.14). These included both electron-rich and -poor aryl bromides with substituents tolerated in the *meta* and *para* positions but unfortunately not the *ortho* position (**84u**,**v**). Useful and sensitive functionalities such as halides (**84l**, **m**), ester (**84h**) and unprotected aniline (**84f**) were compatible, as was starting from the corresponding aryl iodide (**84e**) or triflate (**74**). The incorporation of aldehyde and thioether groups (**84d**, **l**) was particularly pleasing as these sulfones could not be synthesised by traditional oxidation chemistry (Section 3.1) without the use of protecting groups. A range of heteroaromatic bromides were also tested and pyridyl, thiophene and benzofuryl sulfones

(**84n-r**) were successfully synthesised. In addition, alkenyl sulfones (**84s**, **t**) could be generated by using an alkenyl tosylate (with K_3PO_4 in place of Cs_2CO_3).[168]



(i) 3-Bromotoluene (29 mmol, 1 equiv.), ^{t}BuLi (2 equiv.), ^{n}Bu$_2$O (5 mL), 0 °C to RT, 1 hr, *then* filter and titrate
(ii) *m*-Tolyl lithium **72a** (0.49 mmol, 1.4 equiv.), DABSO (0.75 equiv.), 1,4-dioxane (2 mL), RT, 2 hrs
(iii) Aryl bromide (0.35 mmol, 1 equiv.), $Pd(OAc)_2$ (10 mol%), ligand **80f** (10 mol%), Cs_2CO_3 (1.5 equiv.), 110 °C, 16 hrs

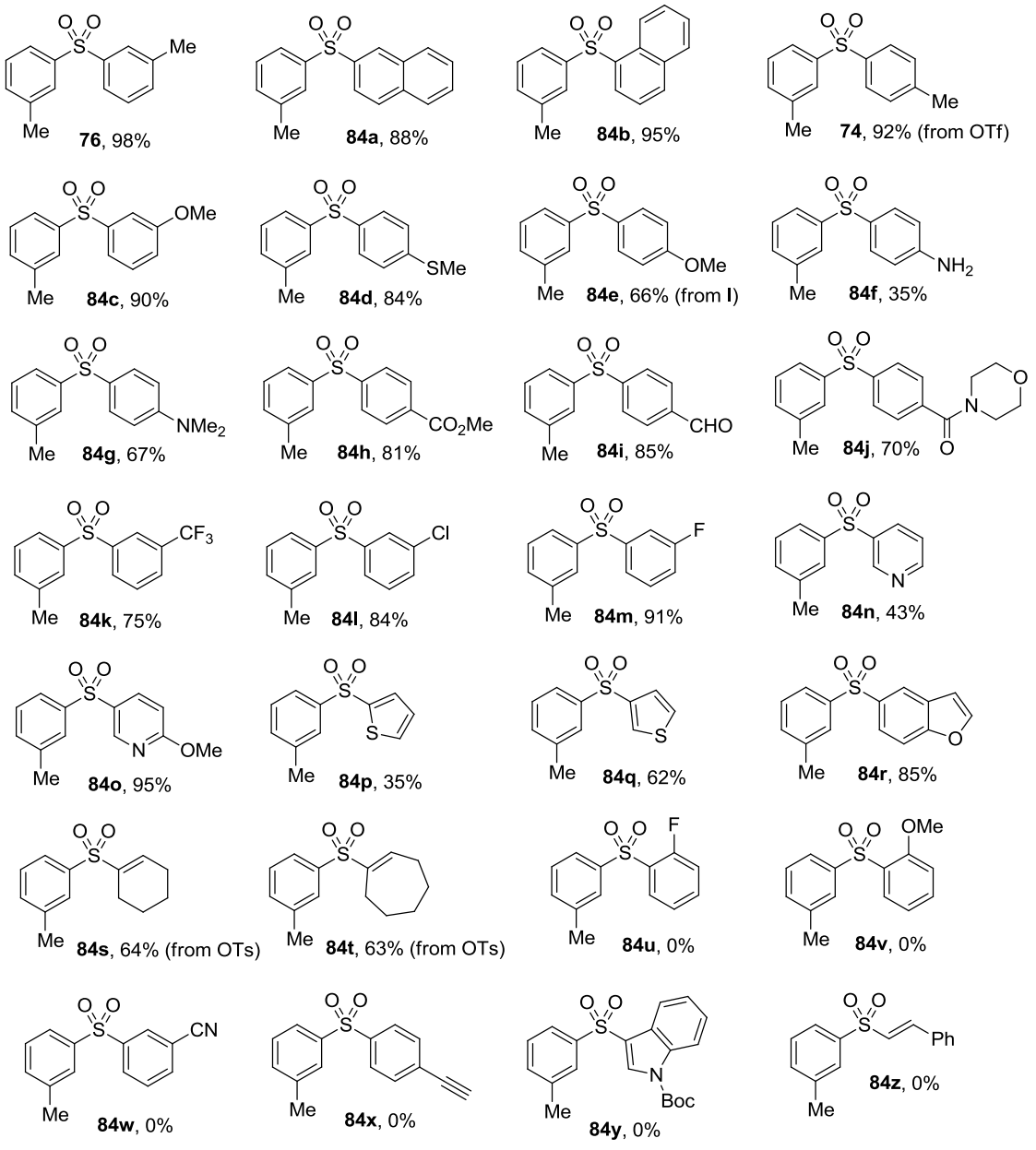


Figure 3.14 Scope of aryl halides in diaryl sulfone synthesis

Attention was then turned to the scope of the organolithium fragment with the use of 3-bromoanisole as the electrophilic coupling partner (Figure 3.15). A range of organolithiums were easily made by either lithium-halogen exchange (Figure 3.13) or directed deprotonation and subsequently added to DABSO to form the corresponding sulfinate. Many *aryl* lithium sulfinates, including those with electron-donating and -withdrawing substituents in the *meta* and *para* positions, were successfully coupled. Compatible functionality included trifluoromethyl (**85h**), chloro (**85g**) and silyl (**85f**) substrates. Unfortunately, *ortho* substituents were not tolerated (**85k**) and in addition, non-aryl sulfinates also proved to be incompatible (**85j**, **l-n**) perhaps due to the differing electronic properties of the corresponding sulfinate nucleophiles.

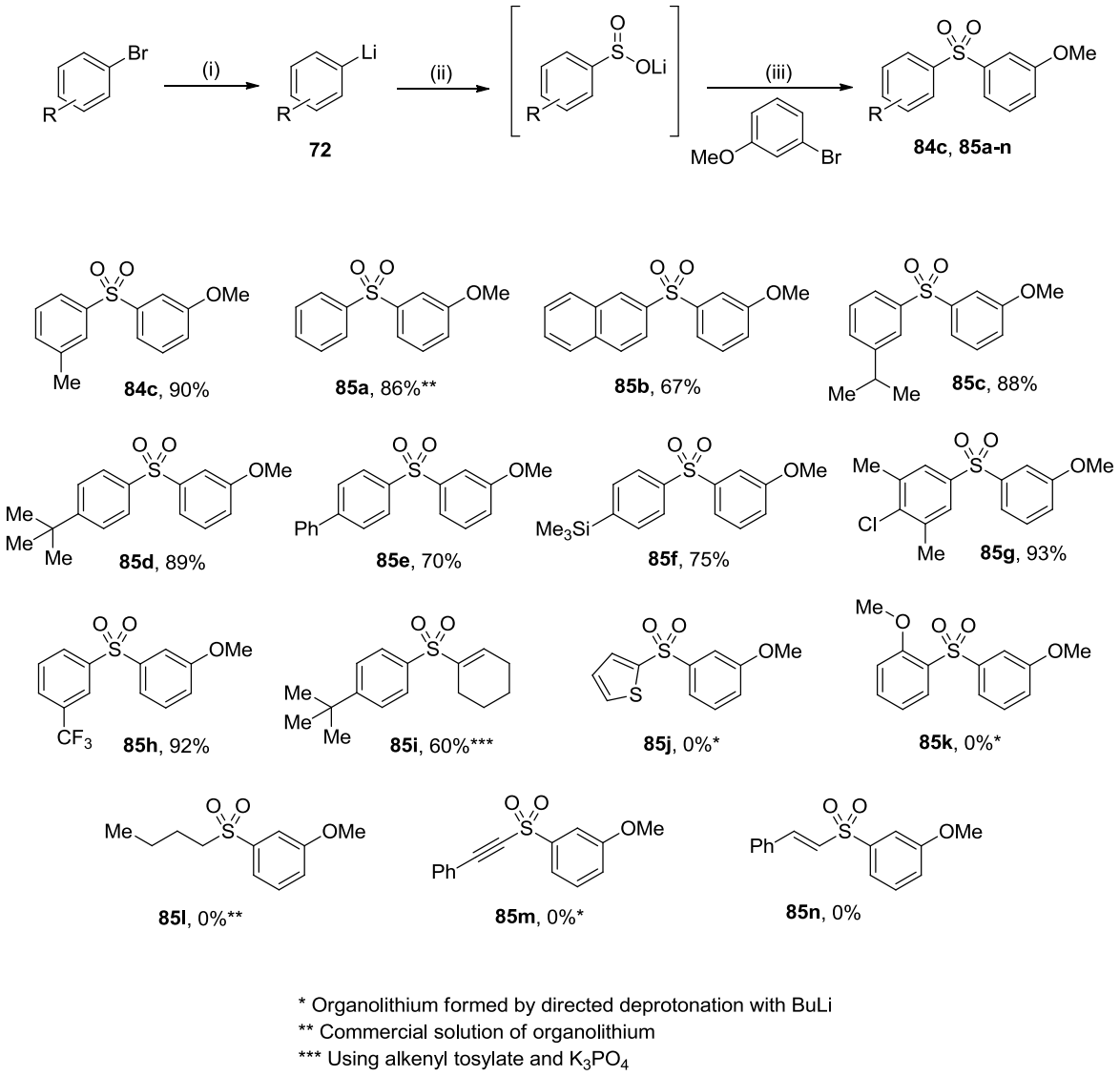


Figure 3.15 Scope of organolithium in diaryl sulfone synthesis (conditions as Figure 3.14)

3.5 Target Synthesis[190]

In order to fully demonstrate the value of the developed methodology, this reaction was applied to the synthesis of a target molecule. GSK 742457, **86**, is a pharmaceutical candidate for the treatment of Alzheimer's disease that has gone through Phase II clinical trials.[191] A disconnection back to a bis-halogenated quinoline was envisaged, for which the 3-iodo-8-chloro substrate **88** could be easily made *via* iodination of 8-chloroquinoline **89** (which can be synthesised by a classical Skraup quinoline synthesis) (Figure 3.16).

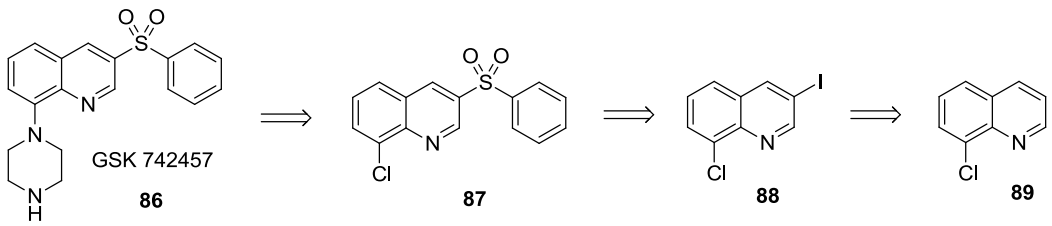
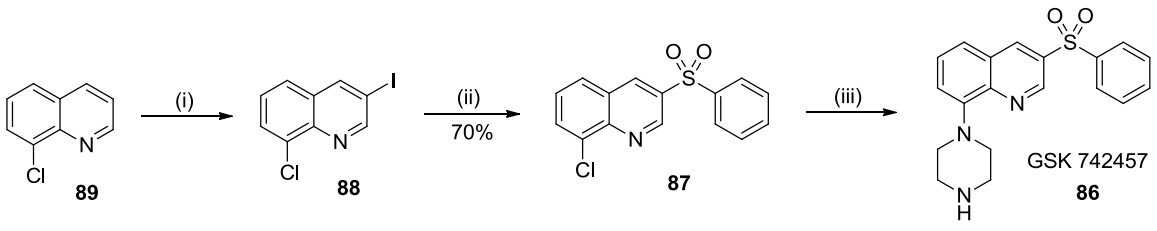


Figure 3.16 Proposed retrosynthesis of GSK 742457 **86** to exploit our new methodology

In the forward direction, **89** was successfully iodinated with NIS following a known literature procedure to afford **88**.[191] Sulfone formation using PhLi with our developed conditions was then performed to reveal **87** in a pleasing 70% yield. Finally a Buchwald-Hartwig coupling was carried out using piperazine[87] to yield the target molecule **86** in 68% yield (unoptimised) (Figure 3.17). This route through the bis-halogenated quinoline **88** would be attractive to discovery chemists as the ability to selectively sulfonylate at the iodide followed by amination at the chloride would allow the rapid synthesis of a diverse library of substituted quinoline products.



(i) NIS, AcOH, 70 °C, 18 hrs, 39%
(ii) Conditions as Figure 3.14 using PhLi
(iii) $Pd(OAc)_2$, RuPhos, NaO^{t}Bu, piperazine, 1,4-dioxane, 90 °C, 16 hrs, 68%

Figure 3.17 Forward synthesis of GSK 742457, **86**

3.6 Synthesis of *Ortho*-Substituted Sulfones

A significant limitation of the developed methodology is the fact that neither coupling partner can tolerate *ortho* substituents. However, this problem is significantly reduced when it is recognised that sulfones are well precedented to direct *ortho*-functionalisation.[192,193] It was decided to demonstrate this procedure using sulfone **85d**, whereby the 1,3-disposition of the sulfone and OMe groups (both *ortho* directing groups) was exploited to regioselectively *ortho* lithiate in one of four possible positions. The resultant lithiated intermediate **90** was trapped with two example electrophiles in MeI and I_2, forming the interesting 1,2,3 trisubstituted diaryl sulfones **91** and **92** (Figure 3.18).

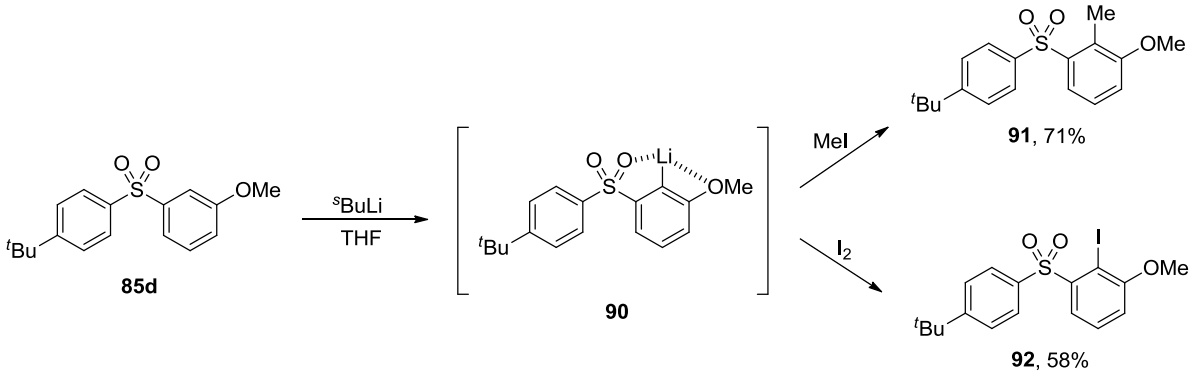


Figure 3.18 Accessing *ortho* substituted diaryl sulfones **91** and **92** *via* directed lithiation

3.7 Summary

In summary, a new disconnection and route to (di)aryl, heteroaryl and alkenyl sulfones has been developed through a convergent three-component palladium-catalysed coupling approach.[4] The reaction exploits the easy-to-handle sulfur dioxide surrogate DABSO, coupling SO_2 with easily accessible (hetero)aryl/alkenyl (pseudo)halides and aryl lithiums (themselves coming from the readily available aryl bromides). A modified XantPhos-type ligand was synthesised and applied in this reaction in order to achieve

selectivity over an unwanted aryl-aryl exchange side reaction. This new reaction allowed a wide variety of sulfones to be synthesised, and improved on some of the limitations of current methodologies. *Ortho*-substituted sulfones could also be accessed *via* an onwards directed lithiation procedure. In order to demonstrate the utility of the developed methodology, a synthesis of a pharmaceutical agent currently in development was successfully undertaken, exploiting an extremely versatile bis-halogenated quinoline. Finally, despite their relative simple structure, we were pleased to observe that over 90% of sulfones synthesised by this new methodology were novel, further highlighting the relevance of this new technique.

Chapter 4 – Palladium-Catalysed Sulfination

4.1 Traditional Syntheses and Utility of Sulfinate Salts

Sulfinate salts (deprotonated sulfinic acids) are extremely versatile intermediates in organic synthesis. Although they are rarely produced as a final product, they are excellent starting materials for a wide range of reactions.[194,195] Sulfinates can, for example, be alkylated (eq. D, Figure 4.1),[22,107,196,197] arylated (eq. G),[4,172,174] aminated (eq. C)[198] or chlorinated (eq. B),[18,124] thereby accessing almost any sulfonyl (-SO_2-) functional group required. To access the sulfinyl (-SO-) oxidation level, their reaction with thionyl chloride reveals the sulfinyl chloride (eq. E)[199] which, in turn, can be used to make sulfinamides **94**,[200] sulfinate esters **95**[201] and sulfoxides **93**.[202,203] In addition, sulfinates have been used to form disulfides *via* reduction (eq. H),[194] sulfonic acids by oxidation (eq. A)[204] and biaryls *via* desulfonylative metal-catalysed cross-couplings (eq. I, Figure 4.1).[205–207]

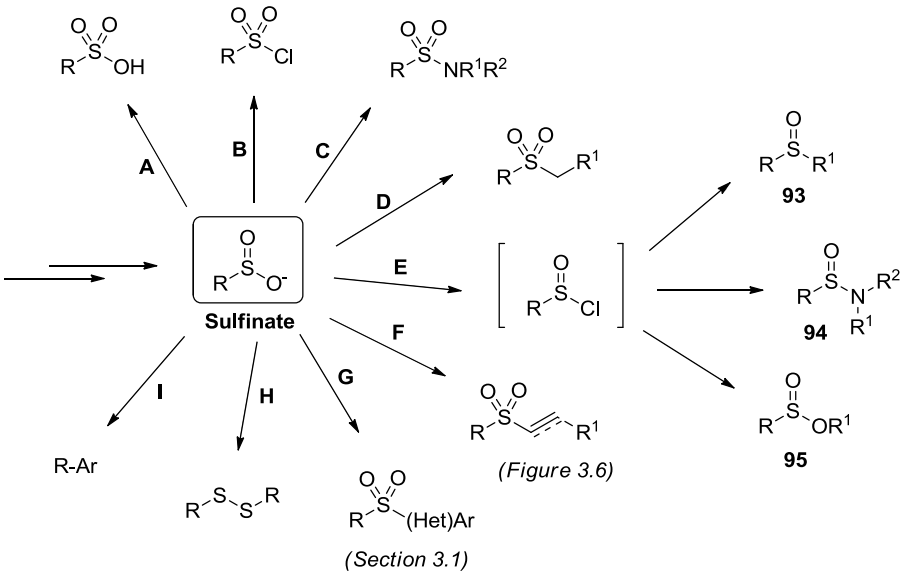


Figure 4.1 Sulfinate salts as versatile starting materials in organic synthesis

However, closer examination of the literature reveals that the scope with respect to sulfinates can be surprisingly limited, which could be for several reasons. Firstly, many

procedures have been developed around the use of *sodium* sulfinates as they have (albeit limited) commercial availability. The phenyl, *p*-tolyl and methyl sodium sulfinates are the only widely available substrates and therefore many papers detail a scope based solely on a selection of these three examples (e.g. Figure 3.4).

Where a more varied scope is used, the reduction of the corresponding sulfonyl chloride is often the route of choice (eq. B, Figure 4.2). This is most practically achieved, with the greatest generality, using sodium sulfite.[208,209] However many other reductants have been established,[194] for example zinc dust followed by cationic exchange with Na_2CO_3.[210] However, as documented in Section 2.1, the linear and harsh synthesis, and sensitive nature of, sulfonyl chlorides can be a hindrance to the scope and viability of any given procedure.

An alternative to using *sodium* sulfinates is the formation of other metal sulfinates *via* organometallic addition to sulfur dioxide gas or DABSO (eq. A, Figure 4.2). An application of this procedure, forming diaryl sulfones from lithium sulfinates, was presented in Chapter 3.[4] In addition, our group, and others, have demonstrated the synthetic utility of these *in situ* generated lithium, magnesium or zinc sulfinate salts in a range of methodologies (Section 1.4.2).[21,22,107–109] Despite the recent improvement in this method by replacing gaseous SO_2 with DABSO, a significant limitation remains in the use of sensitive, difficult-to-handle and pyrophoric organometallic reagents. This is not only from a safety point of view, but they also interfere substantially with functional group tolerance and therefore scope. In addition, reactions of sulfinates can be sensitive to the nature of the counter cation (Section 3.3.2) and so methods are not interchangeable.

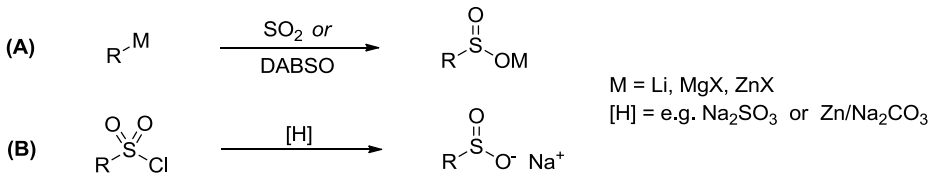


Figure 4.2 The two most common and versatile methods of sulfinate synthesis

Many other methods, for example the oxidation of the corresponding thiol derivative[211] or metal-catalysed diazonium sulfonylation with sulfur dioxide[23,24] have been documented to produce sulfinic acids and their salts, and these are excellently reviewed in a dedicated book chapter.[194] However, these methods often occur in highly specific systems or require the synthesis of a more complicated starting material than the sulfinate product warrants, and are therefore of limited use in organic synthesis.

4.2 Origin of Project

In Chapter 2, the development of the first sulfonylative palladium-catalysed cross-coupling was demonstrated.[1,2] In connection with the desire to further the synthetic reach of this method of SO_2 incorporation, a new route to form sulfinates *via* a sulfonylative analogue of the well precedented metal-catalysed formylation[32,33,104] of aryl halides was proposed (eq. A, Figure 4.3). We realised the benefits of the proposed mild and tolerant reaction conditions in comparison to the limitations of current procedures (*vide supra*).

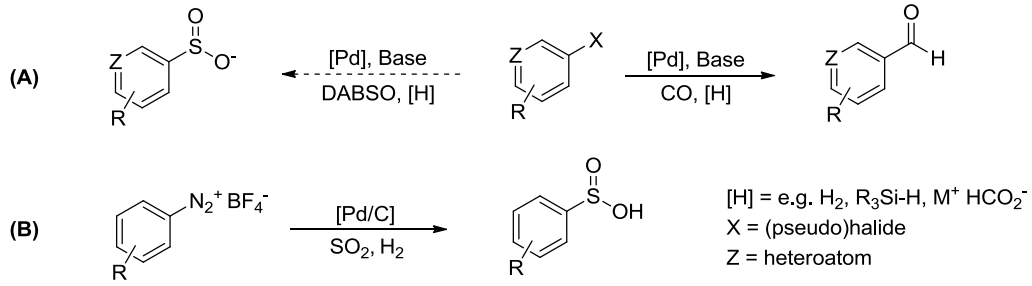


Figure 4.3 Proposed palladium-catalysed sulfination influenced by literature precedent

There was encouraging precedent for this reaction in that Keim and Pelzer had shown that aryl diazonium tetrafluoroborate salts could be transformed into sulfinic acids through the action of a palladium on carbon catalyst with a mixture of pressurised sulfur dioxide and hydrogen gasses, albeit only with three examples (eq. B, Figure 4.3).[23,31] We

proposed to firstly use the much more accessible and safe aryl (pseudo)halides while also removing the need for gaseous reagents by replacing SO_2 with DABSO and H_2 with an easy-to-handle reductant such as a silane or formate (both of which have been used successfully in formylations).[212–215] Finally, we intended to make the stable deprotonated sulfinate salt rather than the free sulfinic acid, which is prone to disproportionation.[216]

4.3 Optimisation of Conditions

The initial starting point was to take the conditions used in our aminosulfonylation methodology (Chapter 2)[1,2] and replace the hydrazine nucleophile with a "hydride equivalent." Trioctylsilane was chosen as it is established as an efficient reductant in the formylation of aryl halides with good selectivity over direct reduction (i.e. protodehalogenation).[215] Triethylamine was also added as a base since at least two equivalents were theoretically required to quench the hydrogen iodide produced from catalytic turnover and deprotonate the sulfinic acid product (Figure 4.4). In this initial reaction, pleasingly, full conversion of the 4-iodotoluene starting material was observed and the presence of the desired sulfinate **48** detected by LCMS. However, several other products were also detected, including toluene **96** from direct reduction, the symmetrical diaryl sulfone **55** and the major product, diarylsulfide **97**.

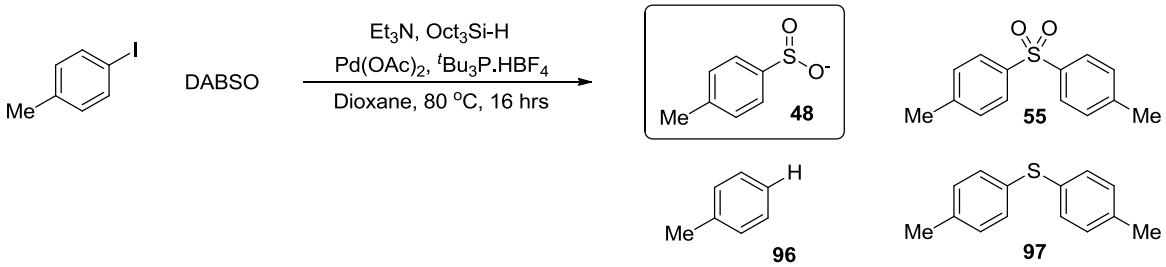
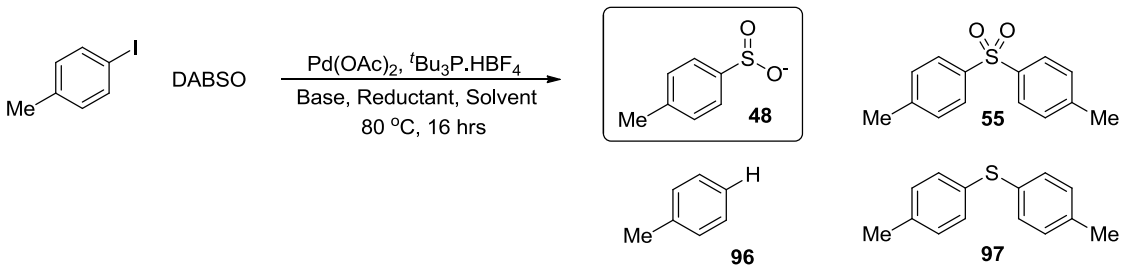


Figure 4.4 Initial reaction exploring palladium-catalysed sulfination

An initial evaluation of bases, reductants and solvents was then undertaken, in a semi-quantitative fashion (by HPLC area), to ascertain whether it was going to be viable to favour the sulfinate **48** (Table 4.1). It was found that nitrogenous bases performed better than traditional cross-coupling bases such as carbonates, phosphates and butoxides in terms of the ratio of desired sulfinate **48** to sulfide **97**. However, no great increase in **48** was observed through variation of the identity of the amine base (Table 4.1, entries 1–5, 12 and 13).

Table 4.1 Initial screen of conditions to favour sulfinate **48** formation[a]



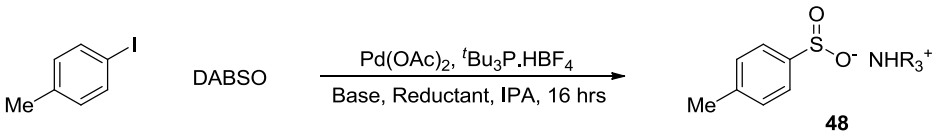
Entry	Base	Reductant	Solvent	48:97[f]	LCAP[b] (55 + 96)
1	Et_3N	Oct_3SiH	Dioxane	0.9 : 1	6%
2	DABCO	Oct_3SiH	Dioxane	0.6 : 1	15%
3	DIPEA	Oct_3SiH	Dioxane	0.5 : 1	6%
4	Cs_2CO_3	Oct_3SiH	Dioxane	trace	-[c]
5	K_2CO_3	Oct_3SiH	Dioxane	0.2 : 1	6%[c]
6	Et_3N	$Na^+HCO_2^-$	Dioxane	1.7 : 1	4%
7	Et_3N	$Na^+HCO_2^-$	NMP	trace	-[c]
8[d]	Et_3N	$Na^+HCO_2^-$	IPA	8.4 : 1[e]	4%
9	Et_3N	$Na^+HCO_2^-$	Toluene	-	-[c]
10	Et_3N	$Na^+HCO_2^-$	^{n}BuOH	10 : 1	11%[c]
11	Et_3N	$Na^+HCO_2^-$	^{t}BuOH	7.3 : 1	12%
12	K_3PO_4	$Na^+HCO_2^-$	IPA	**97** only	-[c]
13	NaO^tBu	$Na^+HCO_2^-$	IPA	-	100% (**96**)

[a] Reaction conditions: 4-iodotoluene (1 equiv., 0.3 mmol), DABSO (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), reductant (2.5 equiv.), base (3 equiv.), solvent [0.2 M]. [b] Liquid Chromatography Area Percent. [c] Unreacted 4-iodotoluene recovered. [d] 2.9 : 1 without formate reductant. [e] Corresponds to a 68% HPLC yield relative to an internal standard. [f] Ratio determined by HPLC area.

The identity of the reductant and solvent had a particularly strong effect. Only trioctylsilane and sodium formate returned desired sulfinate **48** (Table 4.1, entries 1 and 6) with other reductants (not shown in table) such as $NH_4^+HCO_2^-$, Et_3N-HCOOH mix, Et_3SiH, $(EtO)_3SiH$ and PMHS all returning starting material with traces of other side products. The switch to alcoholic solvents (with formate) gave a substantial increase of **48** such that it was now the major product, with IPA an optimal balance of selectivity and side product profile (entries 8, 10 and 11). Following the addition of an internal standard (4,4'-dimethylbiphenyl) (entry 8), an encouraging 68% HPLC yield was confirmed.

At this point, a more extensive and fully quantitative (relative to an internal standard) screen of conditions was undertaken investigating temperature, reaction time, palladium source, equivalents of reagents, more reductants and amine bases, additives and identity of the aryl halide. A selection of these results is displayed in Table 4.2. Unfortunately the sole improvement observed was a small increase in yield of **48** from 68% to 71% through replacing sodium formate with calcium formate (Table 4.2, entry 14).

Table 4.2 Further screen of conditions to optimise yield of sulfinate **48**[a]



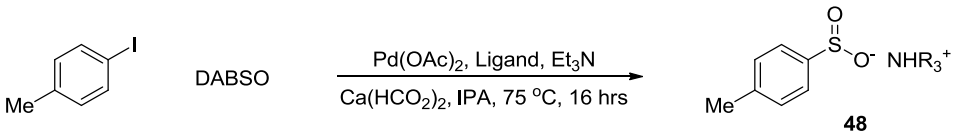
Entry	Base (equiv.)	Reductant (equiv.)	DABSO equiv.	Temp.	Yield (48)[b]
1	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	68%
2[c]	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	57%
3[d]	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	52%
4[e]	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	55%
5	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	90 °C	42%
6	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.1	60 °C	26%
7	Et_3N (4)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	64%
8	Et_3N (2)	$Na^+HCO_2^-$ (2.5)	1.1	75 °C	63%
9	Et_3N (3)	$Na^+HCO_2^-$ (1.2)	1.1	75 °C	58%
10	Et_3N (3)	$Na^+HCO_2^-$ (5)	1.1	75 °C	63%
11	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	0.6	75 °C	53%
12	Et_3N (3)	$Na^+HCO_2^-$ (2.5)	1.6	75 °C	43%
13	Et_3N (3)	$K^+HCO_2^-$ (2.5)	1.1	75 °C	38%
14	Et_3N (3)	$Ca(HCO_2)_2$ (1.5)	1.1	75 °C	71%
15	Et_3N (3)	$^iPr_3SiH$ (2.5)	1.1	75 °C	37%
16	Et_3N (3)	Ph_3SiH (2.5)	1.1	75 °C	47%

[a] Reaction conditions: 4-iodotoluene (1 equiv., 0.3 mmol), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO, reductant, base, solvent [0.2 M]. [b] HPLC yield relative to internal standard. [c] With Pd_2dba_3 (5 mol%). [d] With tetrabutylammonium bromide additive (1.2 equiv.). [e] At [0.3 M].

This left one major factor which had not been investigated; the identity of the ligand. It had been found in the early aminosulfonylation chemistry, that although in general extremely bulky, monodentate and electron-rich phosphines such as $^tBu_3P.HBF_4$ were best performing for sulfonylation, this ligand had outperformed all other ligands by over 30%.[2] In addition, in experiments using the morpholine-sulfur dioxide complex **54**, which

unexpectedly gave symmetrical diaryl sulfones, this ligand was the *only* one to produce sulfonylated products (Section 2.7).[146] We had therefore decided to initially keep this ligand constant. However, following the failure to obtain a yield beyond 71%, the identity of the ligand was explored and provided unexpected success. A selection of ligands was chosen to cover a range of common ligand classes (Table 4.3).

Table 4.3 Screen of ligands to optimise yield of sulfinate **48**[a]



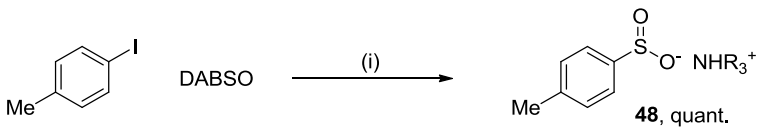
Entry	Ligand	Yield (48)[b]
1	$^{t}Bu_3P.HBF_4$	71%
2[c]	$^{t}Bu_3P.HBF_4$	59%
3	BINAP	23%
4	dppf	84%
5	$dcpp.2HBF_4$	25%
6	$PCy_3.HBF_4$	88%
7	$^{t}Bu_2MeP.HBF_4$	95%
8	CataCXium A	96%
9	dtbpps	89%

[a] Reaction conditions: 4-iodotoluene (1 equiv., 0.3 mmol), DABSO (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol% for monodentate, 12 mol% for bidentate), $Ca(HCO_2)_2$ (1.5 equiv.), Et_3N (3 equiv.), solvent [0.2 M]. [b] HPLC yield relative to internal standard. [c] With 12 mol% ligand.

From the initial set (Table 4.3, entries 1–7), $^{t}Bu_2MeP.HBF_4$ performed excellently giving a near perfect 95% yield (entry 7). This relatively subtle change (replacing one ^{t}Bu with a Me) resulted in a substantial increase in the yield of **48**, reducing the side products to all but traces. This reduction in steric parameter appeared to be key, as entries 8 and 9 show two further ligands in this class of monodentate ligand with two bulky tertiary alkyl groups and one primary alkyl group, which also demonstrated excellent yields.[217] The

improved yield also obtained with $PCy_3.HBF_4$ (entry 6) provided further suggestion that the reaction had been operating in a "too-bulky" environment which had led to the formation of significant quantities of side products. CataCXium A (entry 8) was carried forward as along with the best yield, it is a more stable ligand in that it does not require introduction as a salt. Beller and co-workers have also shown that CataCXium A is a superior ligand to $^tBu_3P.HBF_4$ in formylation chemistry, thanks to the increased stability of the catalytic intermediates.[104,218] Given the proposed parallel between CO and SO_2 in cross-coupling chemistry, this may be another reason behind the improved yields with non-$^tBu_3P$ ligands.

With the best performing CataCXium A ligand in hand, a final re-optimisation of conditions was undertaken. Although the identity of the reductant had been a significant factor with the $^tBu_3P.HBF_4$ ligand, we were aware of the ability of the solvent, IPA, to behave as a reductant in palladium catalysis.[90,219] Pleasingly, an identical yield was obtained in the absence of formate. Several other components of the reaction could also be improved, with palladium, ligand and DABSO loading being reduced to 5 mol%, 7.5 mol% and 0.6 equivalents respectively, with no erosion of yield. However, the use of three equivalents of Et_3N was still necessary despite only two equivalents appearing to be required in a proposed mechanism (Section 4.6), perhaps due to volatility. Nonetheless, combining these improvements still gave an excellent set of optimised conditions (Figure 4.5), generating the desired sulfinate **48** in quantitative HPLC yield.

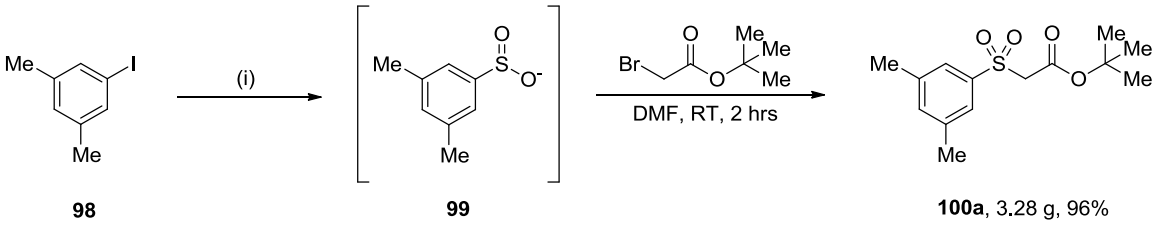


(i) 4-iodotoluene (1 equiv., 0.3 mmol), DABSO (0.6 equiv.), $Pd(OAc)_2$ (5 mol%), CataCXium A (7.5 mol%), Et_3N (3 equiv.), IPA [0.2 M], 75 °C, 16 hrs

Figure 4.5 Final optimised conditions for palladium-catalysed sulfination

As an additional study, we investigated whether conditions could be improved further when performing the reaction on a larger scale. On a 12 mmol scale, palladium and ligand loading could be reduced to 1 mol% and 1.5 mol% respectively, retaining quantitative yield. An excellent 91% conversion was even achieved at a 0.5 mol%/0.75 mol% catalytic loading. In addition, the reaction gave an identical yield at a process-suitable double concentration (11 volumes, 0.4 M) (Figure 4.6).

At the beginning of the chapter it was mentioned that sulfinates are excellent starting materials for a range of sulfur containing functional groups and are rarely produced as a desired final product. It was therefore decided not to attempt to purify and isolate the sulfinates (which had thus far been identified and quantified by HPLC relative to an internal standard) but instead react them onwards *in situ*. On a 12 mmol scale, using 3,5-dimethyliodobenzene **98** in order to demonstrate the formation of a non-commercially available sulfinate **99**, the crude reaction mixture in IPA was cooled to room temperature and a solution of *tert*-butyl bromoacetate in DMF added. After 2 hours stirring at room temperature, full conversion of **99** was achieved. The reaction was worked up and purified to reveal sulfone **100a** in an excellent 96% yield (3.28 g) (Figure 4.6).



98 **99** **100a**, 3.28 g, 96%

(i) Aryl Iodide **98** (1 equiv., 12 mmol), DABSO (0.6 equiv.), Et_3N (3 equiv.), $Pd(OAc)_2$ (1 mol%), CataCXium A (1.5 mol%), IPA [0.4 M], 75 °C, 16 hrs

Figure 4.6 Optimised sulfination procedure on a larger scale

Following the completion of the optimisation, Shavnya and co-workers from Pfizer published a related palladium-catalysed sulfination transformation, using $K_2S_2O_5$ as a surrogate sulfur dioxide source (Figure 4.7).[50] However, we believed our conditions to be superior for several reasons and therefore the project warranted continuation. Their use of

metabisulfite was in greater excess (2 equiv.) compared to our use of DABSO (0.6 equiv.) while they also added 30 mol% of a mixture of two ligands (PPh_3 and 1,10-phenanthroline) compared to our use of one (CataCXium A) in as low as 1.5 mol%. In addition, a sodium formate reductant was used in excess (2.2 equiv.) compared to our use of the benign solvent IPA as a dual solvent-reductant and they required 1.1 equiv. of an additional additive, TBAB. Also their use of DMSO as a solvent raised potential safety concerns due to its oxidising nature in the same pot as a formate reductant. But finally and most importantly, their yields were generally in the range of 50–70%. Our promising result of 96% yield on a large scale, encouraged us to believe that we could obtain much improved yields.

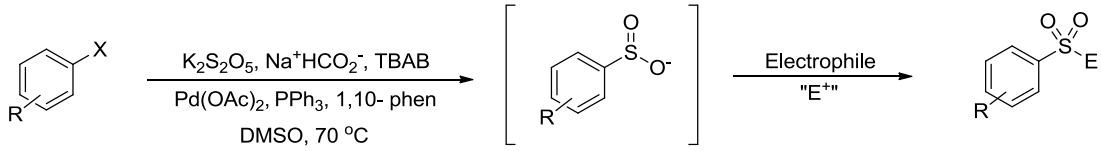
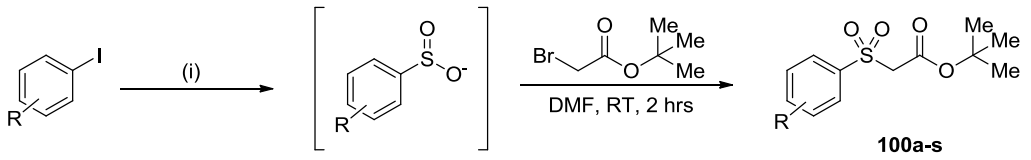


Figure 4.7 Shavnya's sulfination procedure

4.4 Scope of the Electrophilic Fragment

Following the successful demonstration of the developed reaction on a large scale, we returned to smaller scale work to investigate the scope of the procedure with respect to the aryl halide fragment. For practicality, in addition to wanting to achieve the best results for more challenging substrates, 5 mol% $Pd(OAc)_2$ and 7.5 mol% CataCXium A were used as standard catalyst conditions (Figure 4.8).



(i) Aryl iodide (1 equiv., 0.3 mmol), $Pd(OAc)_2$ (5 mol%), CataCXium A (7.5 mol%), DABSO (0.6 equiv.), Et_3N (3 equiv.), IPA [0.2 M], 75 °C, 16 hrs

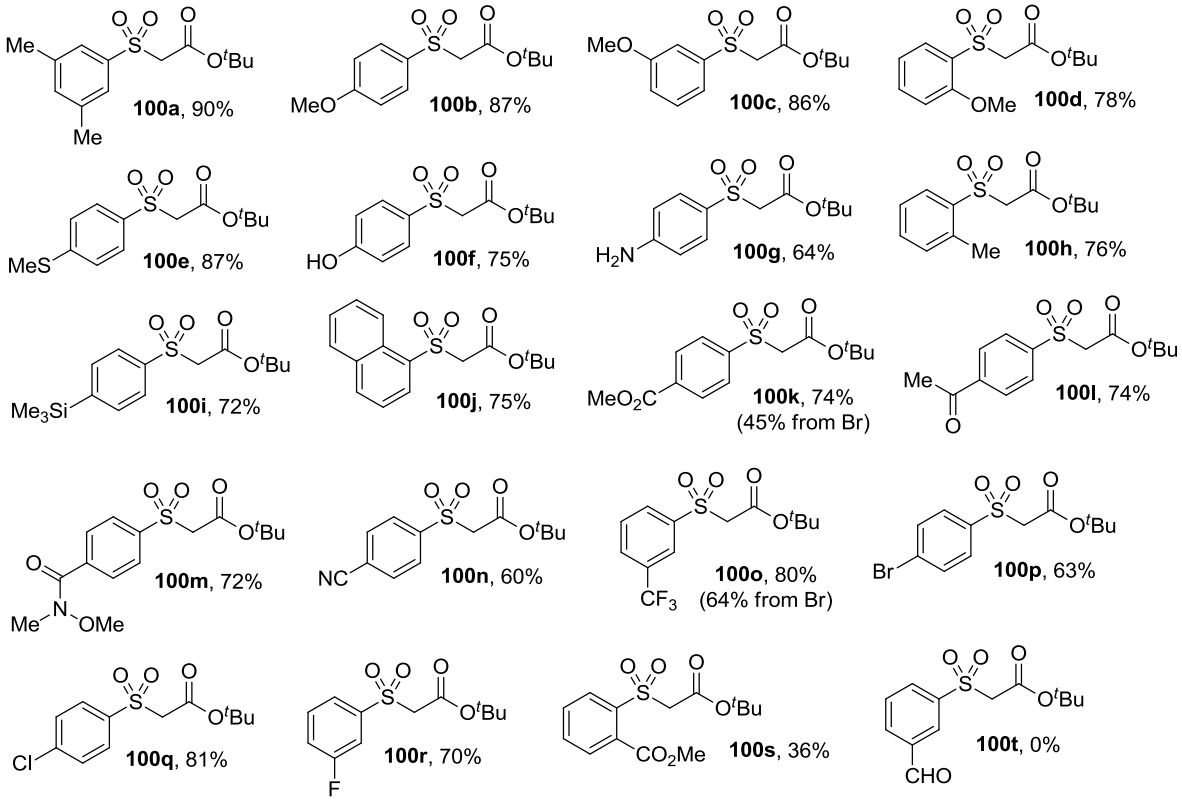


Figure 4.8 Scope of aryl halides in palladium-catalysed sulfination

We were pleased to observe an excellent scope, encompassing a broad range of functional groups and substitution patterns. This included both electron-rich and -poor substrates and *ortho*, *meta* and *para* substituted aryl iodides. Many sensitive and/or synthetically useful functional groups were tolerated such as halides (**100p-r**), ester (**100k**, **s**), Weinreb amide (**100m**), ketone (**100l**), silane (**100i**), nitrile (**100n**) and unprotected phenol and aniline functionalities (**100f**, **g**). Unfortunately, the aldehyde (**100t**) and nitro substrates returned no product. Using an aryl bromide as the electrophilic coupling component was also possible albeit in a reduced yield (**100k**, **o**). More forcing conditions of 100 °C were required and only electron-poor aryl bromides underwent this

transformation, with electron-neutral and -rich substrates giving only traces of desired product with returned halide starting material. The use of either an electron-rich or electron-poor aryl triflate under the conventional or more forcing conditions only returned unreacted triflate.

Our attention then turned to more challenging substrates in the form of heteroaryl and alkenyl iodides (Figure 4.9). Pleasingly, this was successful, with benzothiophene (**101c**), thiophene (**101d**), indole (**101b**), benzofuran (**101a**), quinoline (**101f**) and pyridine (**101e**) substrates performing well. Only the 2-substitued thiophene and pyrazole iodide (**101i**) failed to give products. Cycloheptenyl iodide gave a good yield of the desired alkenyl sulfone (**101g**), although limited generality was observed with differently substituted aliphatic alkenyl iodides giving poorer yields (**101h**).

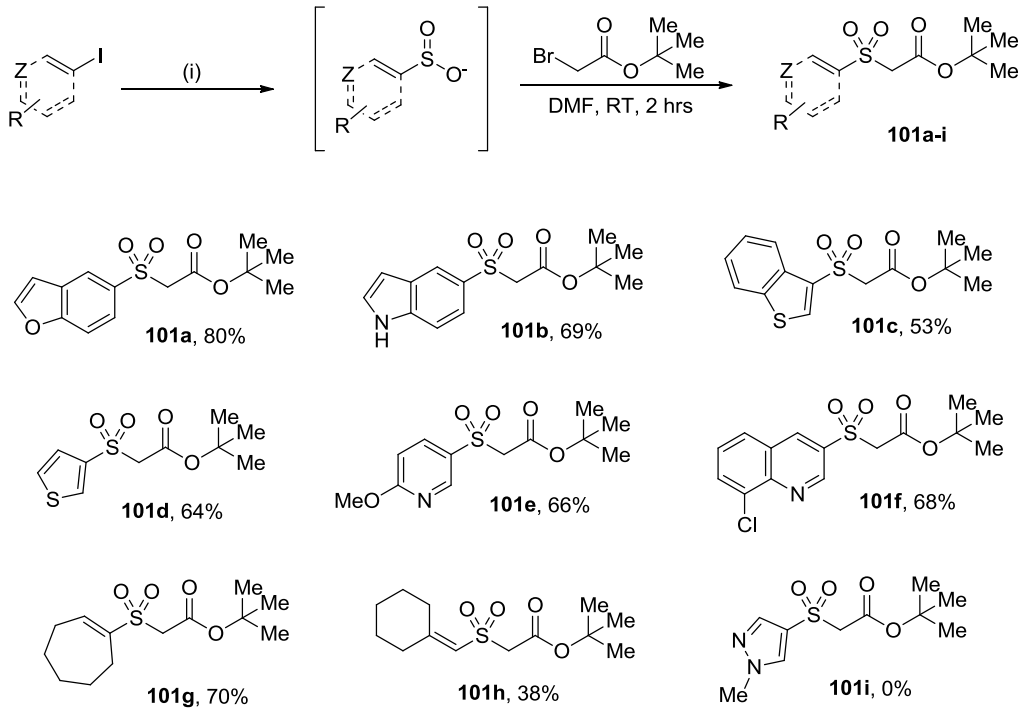


Figure 4.9 Scope of heterocyclic and alkenyl iodides in sulfination (conditions as Figure 4.8)

4.5 Reactivity of Sulfinates

As mentioned before, the synthesis of sulfinate salts is normally performed for their use as an intermediate rather than their isolation as a final compound. Therefore the synthetic utility of this developed palladium-catalysed sulfination relies on the ability of the sulfinate to undergo further synthetic transformations. Ideally a range of reactions could be applied to the crude sulfinate in a one-pot reaction with no work-up after the sulfination. This concept of applying onwards reactions *in situ* is especially important as the purification of sulfinates is difficult due to their instability towards disproportionation in the presence of acids.[31,216] We therefore attempted to apply known and synthetically useful transformations of sulfinate salts to the crude reaction mixture formed from the palladium-catalysed sulfination (Figure 4.10). Our intention was not to optimise the yield or conditions of every onwards reaction nor to cover every possible use of a sulfinate, rather it was to show the synthetic versatility this reaction could possess in one-pot procedures.

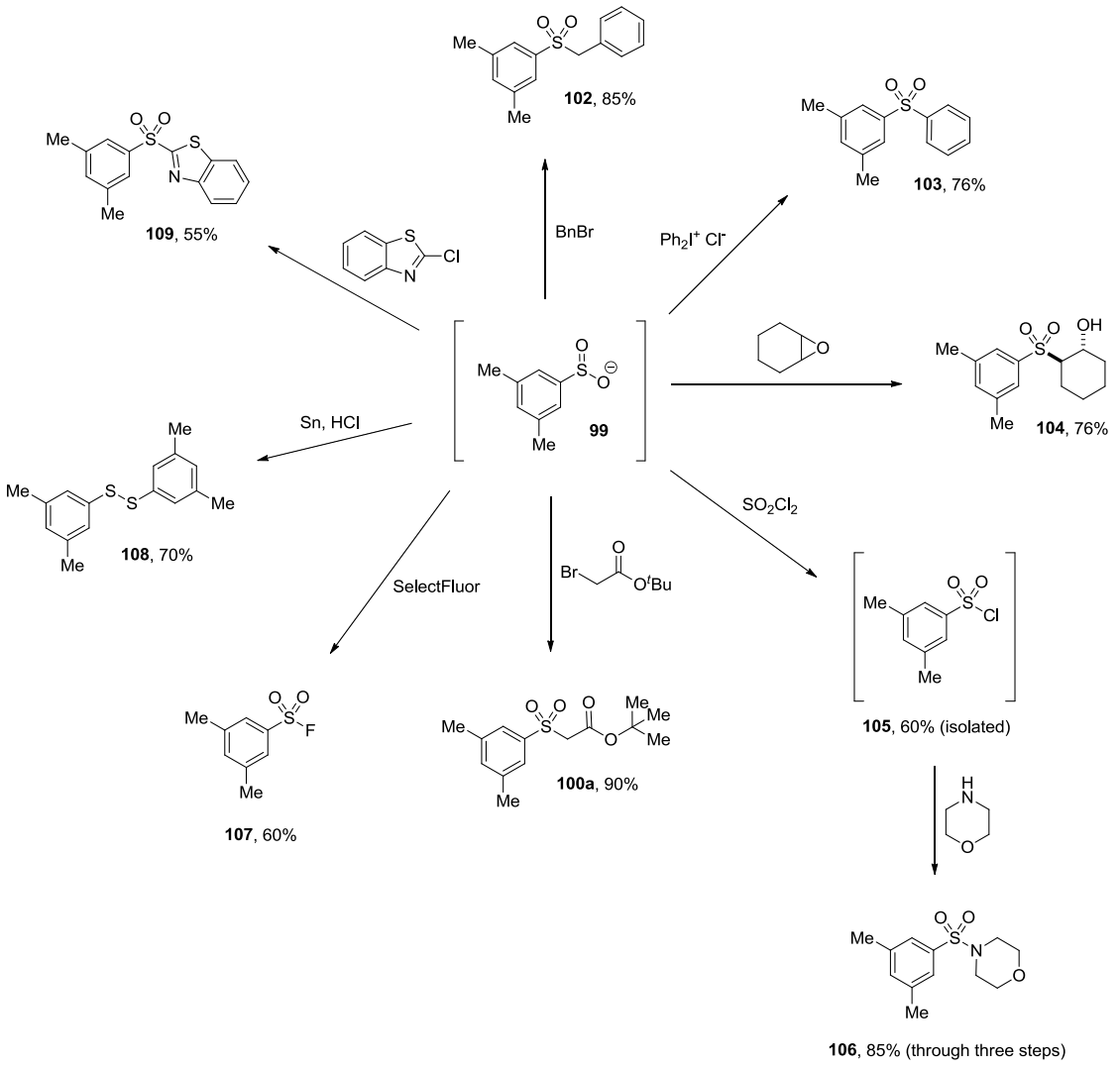


Figure 4.10 Reactions of *in situ* synthesised aryl sulfinate **99** (yields relative to aryl iodide across two steps)

Alkylation (100a and 102)[22]

Although an alkylation reaction with *tert*-butyl bromoacetate was used to exhibit the scope of the aryl halide component (**100a**), an additional reaction was demonstrated with a less activated electrophile in benzyl bromide. Following a similar procedure of adding a DMF solution of the electrophile direct to the crude IPA solution of sulfinate, heating at 75 ^{o}C for 6 hrs revealed the benzyl sulfone **102** in 85% yield.

Arylation with iodonium salts (103)

Manolikakes and Umierski have recently shown the metal free arylation of sodium and lithium sulfinates using diaryliodonium salts.[174,175] Our group has also applied this to sulfinates formed *in situ* using organometallics and DABSO (Section 1.4.2).[107] Following removal of the IPA solvent, reproduction of the conditions of heating in DMF at 90 ^{o}C for 24 hrs using our crude sulfinate and diphenyliodonium chloride gave 76% of the diaryl sulfone **103**.

***β*-Hydroxy sulfones *via* epoxide ring opening (104)**

Both Nageswar *et al.* and our group have demonstrated the capacity of metal sulfinates to open epoxide rings forming *β*-hydroxy sulfones.[107,121] Following removal of the IPA solvent, heating of the crude sulfinate with cyclohexene oxide in water at 90 ^{o}C for 6 hrs revealed the desired hydroxy sulfone **104** in 76% yield.

Chlorination (and in situ amination) (105 and 106)

Hamada, Barrett and our group have shown that the oxidative chlorination of sulfinates with SO_2Cl_2 in THF reveals the corresponding sulfonyl chlorides.[18,21,109] These can be aminated *in situ* to form sulfonamides. This chemistry was also successful with our crude sulfinate (following IPA removal) either yielding the isolated sulfonyl chloride **105** in 60% yield, or through *in situ* amination with morpholine, the sulfonamide **106** in 85% yield through three steps. The discrepancy in yield highlights the isolation difficulties of sulfonyl chlorides (Section 2.1).

Fluorination (107)

A relatively unknown procedure of fluorination of sodium sulfinates with SelectFluor® (an easy-to-handle source of "F^+", see Chemical Structures, page xi) in MeCN yields the biologically important sulfonyl fluoride.[220] This transformation was successfully applied to our crude sulfinate (following the solvent switch) to give a 60% yield of **107**.

Reduction (108)

Our initial intention was to access the thiophenol derivative. However, upon examination of the literature, it became apparent that this procedure was relative rare because typical reducing conditions revealed the "under-reduced" disulfide. One general procedure to the thiol was found using a Sn/HCl reduction[221] but in our hands this too gave the disulfide **108** in 70% yield. Nonetheless, these disulfides can be synthetically useful as "thiol-equivalent" starting materials.[222,223]

Heteorarylation *via* S_NAr with activated heterocycles (109)

Yu and co-workers have shown that sodium sulfinates can be heteorarylated using activated heterocycles *via* an S_NAr type process.[224] Following removal of the IPA solvent and applying Yu's conditions of heating the sulfinate with 2-chlorobenzothiazole in DMSO for 6 hrs at 110 ^oC, 55% of the desired heteroaryl sulfone **109** was isolated. Despite the low yield, this method is still important as it allows the synthesis of difficult-to-access and interesting sulfonyl containing heterocyclic scaffolds.

Summary of onwards reactions

There were also reactions which unfortunately failed. Attempts to use sulfinates to access the sulfinyl oxidation level (e.g. sulfinyl chloride) through a thionyl chloride reaction was unsuccessful (eq. E, Figure 4.1),[199] although given the sensitive nature of these species, their instability in a crude reaction mixture was perhaps unsurprising. In addition, a conjugate addition reaction of the sulfinate to a Michael acceptor proved inaccessible[225] as well as an electrophilic amination with hydroxylamine-*O*-sulfonic acid (Section 2.6).[127] In addition, although quantitative conversion by HPLC to the corresponding sulfonic acid was observed through oxidation with hypochlorite,[204] adequate purification proved impossible due to the water solubility of the acid. We have no doubt that this reaction would be viable for a less water soluble substrate. In general though, we have successfully demonstrated the synthetic utility of the developed palladium-catalysed sulfination reaction to access a wide variety of sulfur containing scaffolds. The *in situ*

derived ammonium sulfinates have also been observed to demonstrate reactivity at least comparable, and in many cases showing increased rates of reaction, to their metal counterparts. This could be as a result of their increased solubility profile in organic solvents.

4.6 Mechanistic Evidence

In keeping with our belief that sulfonylation parallels strongly with carbonylation (an assumption which acquires further weight when the observed ligand dependence of the sulfination is compared to formylation, Table 4.3),[104] the following mechanistic pathways are tentatively suggested (Figure 4.11):

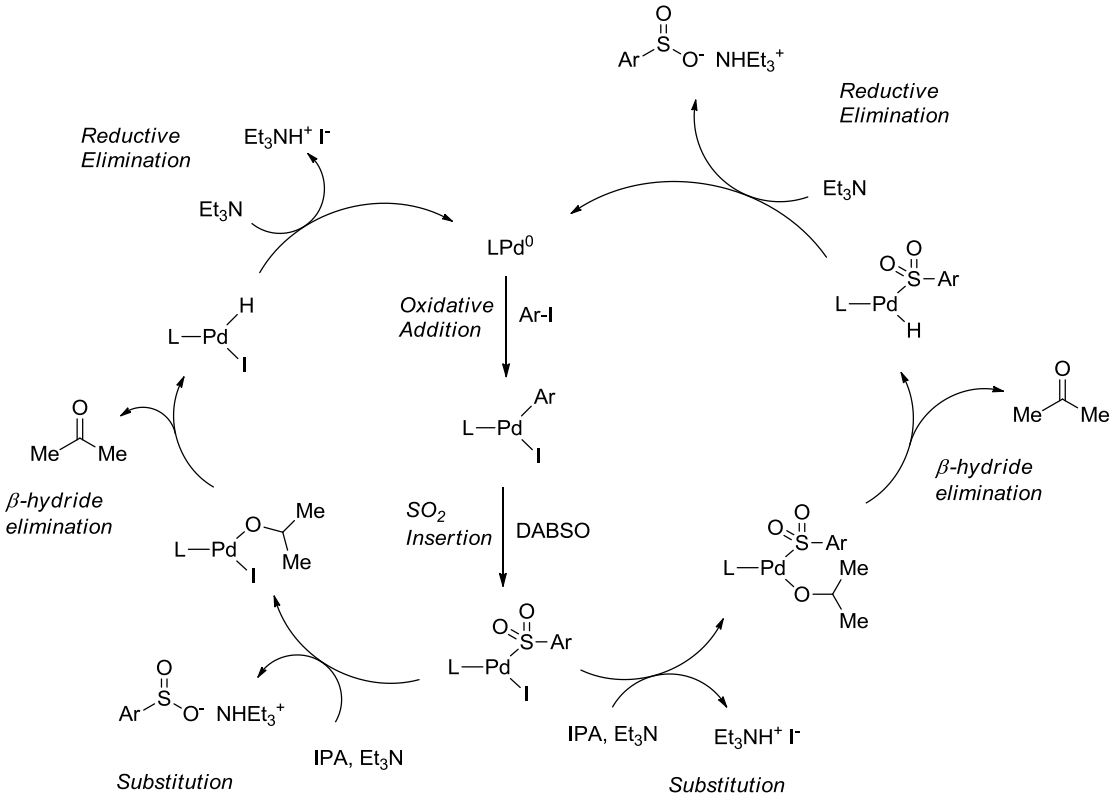
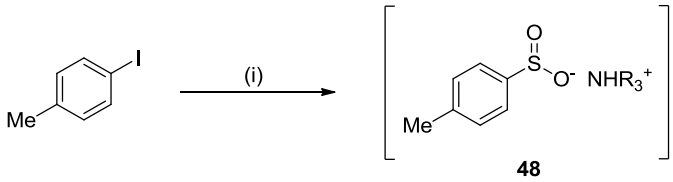


Figure 4.11 Proposed mechanistic catalytic cycle pathways for sulfination

With both iodide and aryl sulfinate (pK_{aH} ~2) good leaving groups, the two possible pathways are similar in nature. What is common to both routes is the requirement of a reductant, postulated to be the IPA solvent. If this is the case, one equivalent of acetone should be produced during the course of the reaction, although since acetone is volatile and the reaction temperature is above its boiling point, it is unlikely to be detectable. However, by switching to cyclohexanol as a solvent, a similar secondary alcohol, the detection of cyclohexanone could be easily quantified by GCMS relative to an internal standard. This very experiment was undertaken and a 76% yield (relative to aryl iodide) of cyclohexanone was obtained while the crude HPLC revealed identical behaviour in sulfinate formation to the IPA system. This is good evidence that the alcoholic solvent is behaving as a required reductant.

It was also postulated that no reaction (or at most 5% through one catalytic turnover) should occur when ^{t}BuOH, a non-reducing alcoholic solvent, was used in place of IPA. Therefore this modified reaction was monitored over the course of 6 hours in parallel with the conventional system in IPA (Figure 4.12).



48

(i) 4-iodotoluene (1 equiv., 0.3 mmol), DABSO (0.6 equiv.), Et_3N (3 equiv.), $Pd(OAc)_2$ (5 mol%), CataCXium A (7.5 mol%), solvent [0.2 M], 75 °C

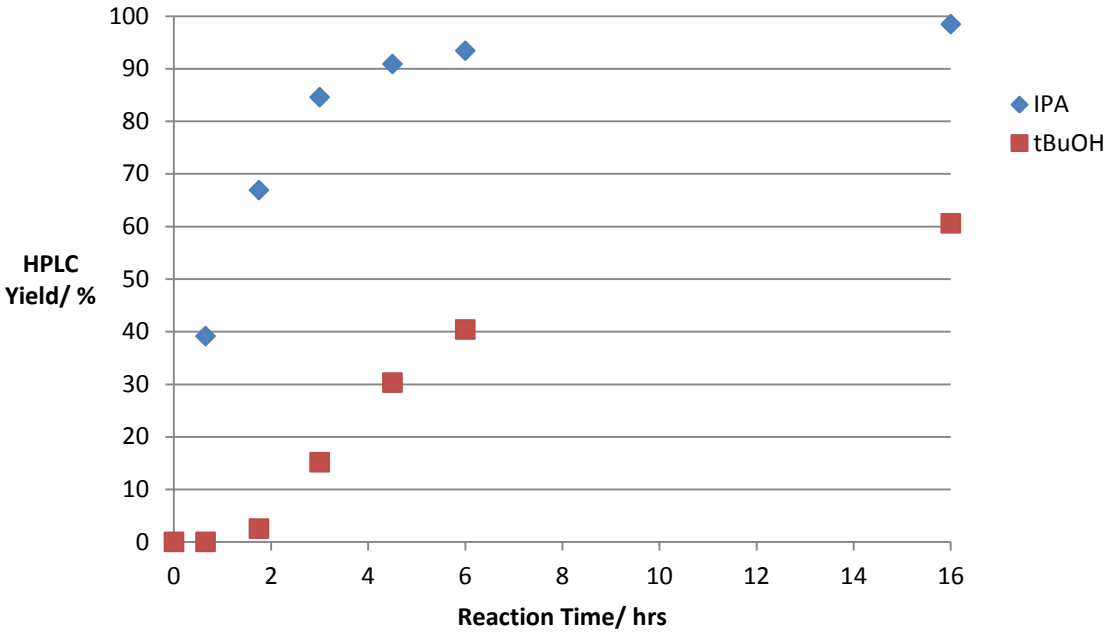


Figure 4.12 Progress of reaction in IPA and ^{t}BuOH

Surprisingly, the reaction did proceed in ^{t}BuOH to a yield of 60% after 16 hours. However, the reaction appears to progress differently in that there was 90 minute lag time observed before any product formed and the rate of reaction was significantly slower. This is suggestive of a different reductant operating in the ^{t}BuOH reaction. Postulating that this was triethylamine, a known reductant of Pd(II) to Pd(0), Et_3N was substituted with DABCO, a tertiary amine base unable to undergo the required *β*-hydride elimination to effect the reduction. This completely suppressed the formation of **48** in the ^{t}BuOH reaction while still producing sulfinate in the IPA reaction.

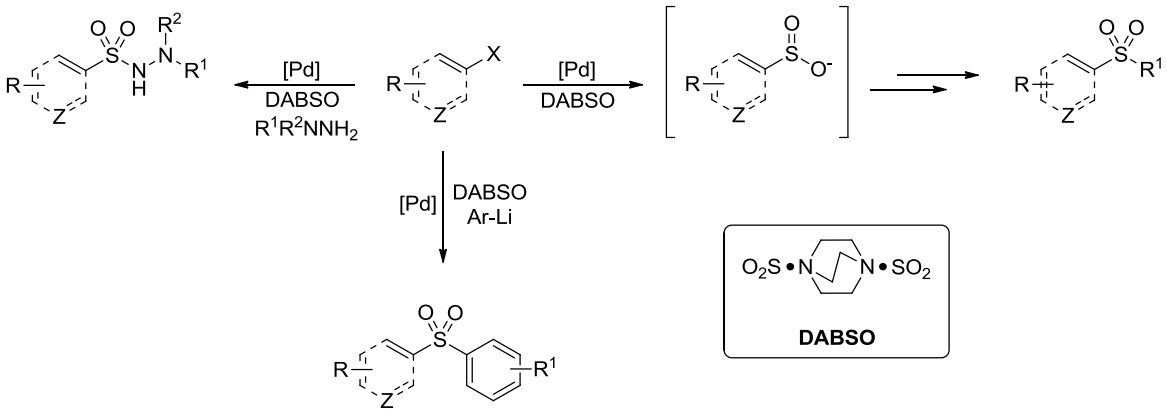
Although not conclusive proof, these mechanistic results are suggestive of the alcohol being the primary reductant in the case of reducing alcoholic solvents. When the solvent is non-reducing, like ^{t}BuOH, only a slow background reaction occurs with Et_3N acting as the reductant.

4.7 Summary

In summary, a novel route to aryl, heteroaryl and alkenyl sulfinates from the corresponding halide has been successfully developed.[5] This new palladium-catalysed methodology uses low catalyst loadings down to 1 mol% Pd and mild conditions with IPA acting as both a process friendly solvent[226] and an *in situ* reductant. In addition, the transformation uses readily available substrates and reagents only, and offers substantial improvements to current methodologies of sulfinate synthesis, avoiding organometallic reagents and harsh acids and oxidants. By not being limited to the synthesis of a particular sulfonyl functional group, this methodology allows the conversion of the *in situ* derived sulfinates into a multitude of different functional groups, through established onwards reactions. Some preliminary mechanistic studies support the theory that the IPA solvent has this dual role as the required equivalent of reductant and work is ongoing within our group to further elucidate the mechanism of this transformation.

Chapter 5 – Conclusion and Future Work

The discovery by our group that amine-sulfur dioxide complexes, such as DABSO, are suitable, easy-to-handle surrogates for sulfur dioxide has revitalised the disconnection of sulfonyl contain organic molecules back to sulfur dioxide. Not only have others in the group shown that it is an excellent replacement for the gas in known organic transformations,[107,109] this thesis has demonstrated that DABSO can be exploited in novel catalytic chemistry. This included a new palladium catalysed route to versatile diaryl sulfones from *in situ* derived lithium sulfinates, themselves coming from the reaction of aryl lithium and DABSO.[4] In addition, of particular significance was the development of the first palladium-catalysed sulfonylative cross-couplings of (hetero)aryl and alkenyl halides which were discovered thanks to the ability to add SO_2 in a controlled low loading.[1–3,5]



As a relatively young area, future work investigating the application of amine-sulfur dioxide complexes in organic chemistry has the potential to be very fruitful. It would be very interesting to continue the exploration of known reactions of sulfur dioxide gas, for example the isomerisation of alkenes,[35] through creating improved and more user friendly conditions. The recent work of Vogel demonstrates the synthetic utility of pericyclic reactions with sulfur dioxide and applying DABSO could improve this chemistry further.[30]

Also of great interest is the continued application of DABSO and amine-sulfur dioxide complexes in metal catalysis. To extend the scope of these sulfonylations, for instance to include aryl chlorides and other nucleophiles, elucidation of further mechanistic evidence will be important. The isolation of catalytic intermediates, kinetic studies, computational studies or ReactIR monitoring, for example, could reveal whether our proposed mechanistic parallel with carbonylative metal catalysis is correct. Following these investigations, clues may be provided as to how to extend these reactions beyond their current limitations e.g. by using alternative metals or ligands.

Chapter 6 – Experimental Data and Procedures

6.1 General Considerations

Chemicals were purchased from Sigma Aldrich, Alfa Aesar, Fluorochem, TCI, Strem, Acros Organics or BOC gasses and used without further purification with the exception of the following chemicals. (i) Amines used to make amine-sulfur dioxide complexes were purified by either vacuum sublimation (DABCO) or distillation (morpholine and 4-aminomorpholine) immediately prior to use. (ii) Solid cross-coupling bases such as Cs_2CO_3, K_2CO_3, K_3PO_4, NaO^tBu were dried in a vacuum drying pistol (130 ^oC, 10 mbar, 24 hrs) and stored under nitrogen in a dessicator. (iii) Aryl bromides used to make aryl lithium solutions were purified by distillation or recrystallisation, as appropriate. (iv) 9,9-Dimethylxanthene and trimethylsilyl chloride were purified by distillation. (v) Et_3N and TMEDA were purified by stirring over CaH_2 for 24 hrs before distilling.

Solvents were used, unless mentioned otherwise, without further purification as HPLC grade purchased from Sigma Aldrich or Fischer Scientific. Anhydrous (KF titration < 10 ppm) THF, DCM, MeCN, Et_2O, MeOH, pentane and toluene were obtained from an in-house Grubbs solvent drying system (Innovative Technology Inc. PS-400-7) having passed through dried alumina columns. 1,4-Dioxane, DME and $^nBu_2O$ were purified by stirring over CaH_2 for 24 hrs before distilling onto activated 4Å molecular sieves and stored under nitrogen. Other anhydrous solvents were used directly as the commercial anhydrous grade. Solvents used in metal catalysis or organometallic chemistry were thoroughly degassed by bubbling nitrogen prior to use. ‘Petrol’ refers to the fraction of light petroleum ether boiling in the range 40–60 ^oC.

Reactions were performed with continuous magnetic stirring, under an atmosphere of nitrogen, unless otherwise stated, using standard Schlenk techniques. Nitrogen and argon gases were obtained from in-house supplies and passed through a Manifold fitted with a

Drierite-filled drying tube. All glassware was dried in an oven (>200 ^{o}C, overnight) and cooled under high vacuum (0.1 mbar) prior to use. "Glass reaction tube" refers to a 10 mL CEM microwave reaction vial. Cooling between -10 ^{o}C and room temperature was achieved using a salt-ice-water slush bath. Cooling between -10 ^{o}C and -78 ^{o}C was achieved using a dry-ice-acetone bath. Flash column chromatography was performed using Apollo scientific silica gel 60 (particle size 0.040-0.063 nm) with the indicated eluents. Thin Layer Chromatography (TLC) analysis was carried out on Merck Kieselgel 60 PF254 pre-coated aluminium backed sheets and visualised either by UV fluorescence and/or by staining with potassium permanganate or vanillin.

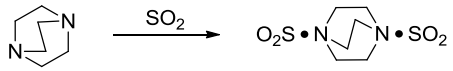
NMR spectra were recorded at ambient temperature, unless otherwise stated, on Brüker DPX200 (200 MHz), AVIII400 (400 MHz) or AVII500 (500 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, DEPT and comparison with spectra of related compounds. Signal multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br., broad; app., apparent.

Melting points were measured using a Leica Gallen III hot-stage microscope. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High resolution mass spectra were measured by the internal service at the University of Oxford using a Bruker Daltronics microTOF spectrometer. *m/z* ratio values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm. Infrared spectra were determined neat using a Bruker Tensor 27 FT spectrometer with an internal range of 600-4000 cm^{-1}. Elemental analyses were carried out through an external service managed by Stephen Boyer at London Metropolitan University. Differential Scanning Calorimetry was carried out by Stuart Wells at AstraZeneca, Macclesfield.

6.2 Chapter 2 Data

6.2.1 Amine-Sulfur Dioxide Complexes

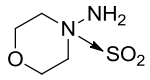
General procedure A for the formation of amine-sulfur dioxide complexes, exemplified by the preparation of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide), DABCO-$(SO_2)_2$, DABSO (7b)



7b

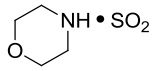
Method adapted from procedure documented by Santos and Mello.[60] A 250 mL round-bottom flask was fitted with a dried cold-finger condenser, attached to a Dreschel bottle oil bubbler system and cooled under a flow of argon. Sublimed 1,4-diazabicyclo[2.2.2]octane (DABCO) (10.0 g, 89.2 mmol) was added to the flask and the system flushed with argon for a further 3 mins. A flow of sulfur dioxide gas was introduced into the system (~2 bubbles/sec) for 3 mins. The reaction flask was cooled to -30 ^{o}C, the condenser to -78 ^{o}C and sulfur dioxide was condensed dropwise onto the DABCO with stirring until the solid was completely covered and a free flowing slurry was obtained. The gas flow was stopped and the flask warmed to -10 ^{o}C and left stirring at "reflux" for 1 hr. The flask was warmed to room temperature while the system was flushed with nitrogen allowing the excess sulfur dioxide to evaporate through the bubbler overnight, revealing DABSO **7b** as a white powder (21.3 g, 99%); DSC 200 ^{o}C (exothermic); ^{1}H NMR (400 MHz, MeOD-d_4) δ 3.22 (12H, s); ^{13}C NMR (100 MHz, MeOD-d_4) δ 45.4; IR υ_{max} (neat)/cm^{-1} 1474, 1459, 1335 (SO_2), 1225, 1100 (SO_2), 1053. Elemental analysis found 29.94% C, 4.95% H, 11.96% N; $C_6H_{12}N_2O_4S$ requires 29.99% C, 5.03% H, 11.66% N.

4-Aminomorpholine-sulfur dioxide complex (34)



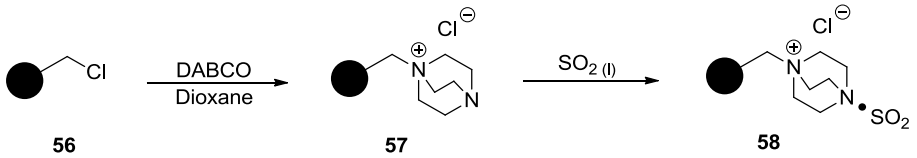
The general procedure **A** was followed with the use of distilled 4-aminomorpholine (1.00 mL, 10.4 mmol) affording *complex* **34** as a white powder (1.65 g, 96%); DSC 95 ^{o}C (endothermic); ^{1}H NMR (400 MHz, MeOD-d_4) δ 3.80 (4H, br. s, ($NCH_2CH_2O)_2$), 3.02 (4H, br. s, ($NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, MeOD-d_4) δ 66.5, 56.0; IR υ_{max} (neat)/cm^{-1} 2869, 2600 (br.), 2173, 1630, 1595, 1468, 1299 (SO_2), 1200, 1104 (SO_2); Elemental analysis found 29.01% C, 6.15% H, 16.82% N, 19.08% S; $C_4H_{10}N_2O_3S$ requires 28.91% C, 6.06% H, 16.86% N, 19.29% S.

Morpholine-sulfur dioxide complex (54)



The general procedure **A** was followed with the use of distilled morpholine (5.00 mL, 57.8 mmol) affording *complex* **54** as an off-white powder (8.52 g, 98%); mp 75–76 ^{o}C (decomp.); ^{1}H NMR (400 MHz, MeOD-d_4) δ 3.91–3.86 (4H, m, ($NCH_2CH_2O)_2$), 3.24–3.20 (4H, m, ($NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, MeOD-d_4) δ 64.9, 44.5; IR υ_{max} (neat)/cm^{-1} 2988, 2852, 2530, 1626, 1446, 1309 (SO_2), 1181, 1140, 1104 (SO_2), 1084, 1035.

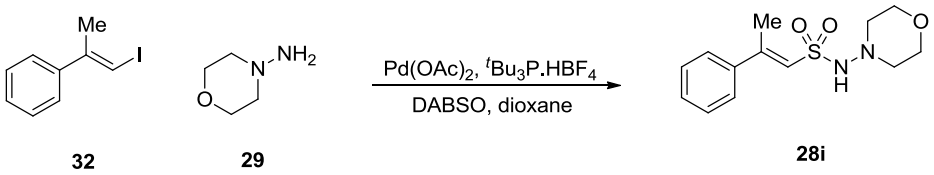
Polymer-supported sulfur dioxide complex (58)



A 100 mL round-bottom flask was charged with Merrifield resin **56** (2.0–2.2 mmol Cl/g, 5.0 g, 10-12 mmol), DABCO (1.5 g, 13 mmol) and acetone (20 mL). The resultant suspension was heated at reflux for 24 hrs. The reaction mixture was cooled to room temperature and filtered. The residue washed with further acetone (3 × 20 mL), and dried under high vacuum affording **57** as a white powder (6.30 g, ~quant.). General procedure **A** was then followed with **57** affording *complex* **58** as a white powder (7.10 g, ~quant.).

6.2.2 *N*-Aminosulfonamides *via* Aminosulfonylation

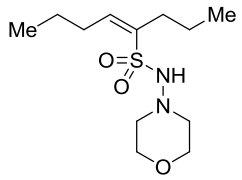
General procedure B for the formation of *N*-aminosulfonamides using DABSO, exemplified by the preparation of (*E*)-*N*-morpholino-2-phenylprop-1-ene-1-sulfonamide (28i)



A glass reaction tube was charged with (*E*)-(1-iodoprop-1-en-2-yl)benzene **32** (50 mg, 0.20 mmol), DABSO (54 mg, 0.23 mmol), palladium(II) acetate (5.0 mg, 20 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (12 mg, 40 μmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 4-Aminomorpholine **29** (30 μL, 0.31 mmol) and 1,4-dioxane (1.6 mL) were added through the septum and the reaction mixture heated at 70 °C for 16 hrs. After cooling to room temperature, the reaction mixture was filtered through Celite®. The Celite® pad was washed sequentially with

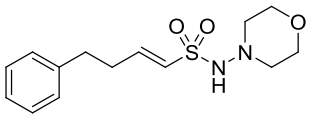
DCM (10 mL) and Et_2O (5 mL) and the combined organic filtrate concentrated *in vacuo*. Purification by flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28i** as an off-white microcrystalline solid (50 mg, 86%); mp 117–118 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (5H, m, Ar-*H*), 6.54 (1H, q, *J* 1.0, C*H*), 5.43 (1H, s, N*H*), 3.75 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.89 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.59 (3H, d, *J* 1.0, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 140.3, 129.8, 128.8, 126.3, 124.1, 66.7, 57.3, 17.9; IR υ_{max} (neat)/cm^{-1} 3226, 2830, 1608, 1309 (SO_2), 1263, 1140 (SO_2), 1106; LRMS (ESI) *m/z* 283 (10%, $[M+H]^+$), 305 (15%, $[M+Na]^+$), 587 (100%, $[2M+Na]^+$), 869 (30%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 305.0928 $[M+Na]^+$, $C_{13}H_{18}N_2O_3SNa$ requires *m/z* 305.0930.

(*Z*)-*N*-Morpholinooct-4-ene-4-sulfonamide (28a)



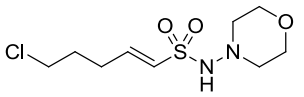
The general procedure **B** was followed with the use of (*Z*)-4-iodooct-4-ene (50 mg, 0.21 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28a** as an off-white microcrystalline solid (33 mg, 57%); mp 73–75°C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, t, *J* 7.5, C*H*), 5.09 (1H, br. s, N*H*), 3.70 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.81 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.34 (2H, t, *J* 8.0, $CHCCH_2$), 2.21 (2H, app. q, *J* 7.5, CH_2CHCCH_2), 1.67–1.46 (4H, m, 2 × CH_2Me), 0.97 (6H, 2 × t, 2 × *J* 7.5, 2 × *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.7, 66.7, 57.3, 30.5, 29.0, 22.8, 21.8, 14.1, 13.8; IR υ_{max} (neat)/cm^{-1} 3205, 2957, 2872, 1455, 1323 (SO_2), 1279, 1170, 1138 (SO_2), 1108, 1074; LRMS (ESI) *m/z* 277 (25%, $[M+H]^+$), 299 (85%, $[M+Na]^+$), 331 (20%, $[M+Na+MeOH]^+$), 575 (100%, $[2M+Na]^+$), 851 (15%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 299.1400 $[M+Na]^+$, $C_{12}H_{24}N_2O_3SNa$ requires *m/z* 299.1400.

(*E*)-*N*-Morpholino-4-phenylbut-1-ene-1-sulfonamide (28b)



The general procedure **B** was followed with the use of (*E*)-(4-iodobut-3-enyl)benzene (50 mg, 0.19 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28b** as an off-white microcrystalline solid (35 mg, 60%); mp 95–97°C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (2H, m, Ar-*H*), 7.24–7.17 (3H, m, Ar-*H*), 6.92 (1H, dt, *J* 15.0, 7.0, CH_2CHCH), 6.26 (1H, dt, *J* 15.0, 1.5, CH_2CHCH), 5.13 (1H, br. s, N*H*), 3.67 (4H, t, *J* 4.5, $(NCH_2CH_2O)_2$), 2.84 (2H, t, *J* 7.5, CCH_2CH_2CH), 2.72 (4H, t, *J* 4.5, $(NCH_2CH_2O)_2$), 2.63 (2H, app. q, *J* 7.0, CCH_2CH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 139.9, 128.6, 128.3, 127.2, 126.4, 66.6, 57.2, 33.7, 32.6; IR υ_{max} (neat)/cm^{-1} 3210, 3060, 2960, 2856, 2284, 1960, 1714, 1632, 1496, 1361 (SO_2), 1278, 1149 (SO_2), 1072, 1011; LRMS (ESI) *m/z* 297 (20%, $[M+H]^+$), 319 (80%, $[M+Na]^+$), 615 (100%, $[2M+Na]^+$), 911 (10%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 319.1091 $[M+Na]^+$, $C_{14}H_{20}N_2O_3SNa$ requires *m/z* 319.1087.

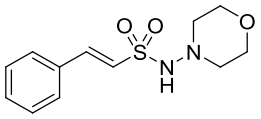
(*E*)-5-Chloro-*N*-morpholinopent-1-ene-1-sulfonamide (28c)



The general procedure **B** was followed with the use of (*E*)-5-chloro-1-iodopent-1-ene (50 mg, 0.22 mmol). Flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **28c** as a beige microcrystalline solid (38 mg, 65%); mp 102–103 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, dt, *J* 15.0, 7.0, $CHCHSO_2$), 6.33 (1H, dt, *J* 15.0, 1.5, $CHCHSO_2$), 5.29 (1H, br. s, N*H*), 3.74 (4H, t, *J* 4.5, $(NCH_2CH_2O)_2$), 3.58 (2H, t, *J* 6.5, $ClCH_2$), 2.86 (4H, t, *J* 4.5, $(NCH_2CH_2O)_2$), 2.48 (2H, app. q, *J* 7.0, $ClCH_2CH_2CH_2$), 2.02–1.94 (2H, app. quin., *J* 6.5, $ClCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 127.8, 66.6, 57.4, 43.6, 30.2, 28.4;

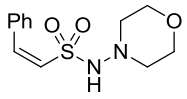
IR υ_{max} (neat)/cm^{-1} 3210, 2962, 2859, 1634, 1458, 1326 (SO_2), 1151 (SO_2), 1111; LRMS (ESI) *m/z* 269 (10%, $[M+H]^+$), 291 (60%, $[M(^{35}Cl)+Na]^+$), 293 (25%, $[M(^{37}Cl)+Na]^+$), 559 (100%, $[2M(^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 291.0538 $[M(^{35}Cl)+Na]^+$, $C_9H_{17}N_2O_3SNa(^{35}Cl)$ requires *m/z* 291.0541.

(*E*)-*N*-Morpholino-2-phenylethenesulfonamide (28d)



The general procedure **B** was followed with the use of (*E*)-(2-iodovinyl)benzene (50 mg, 0.22 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28d** as an off-white microcrystalline solid (31 mg, 53%); mp 159–161 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* 15.5, C*H*CHSO$_2$), 7.54–7.50 (2H, m, Ar-*H*), 7.47–7.41 (3H, m, Ar-*H*), 6.81 (1H, d, *J* 15.5, CHC*H*SO$_2$), 5.31 (1H, br. s, N*H*), 3.73 (4H, t, *J* 4.5, (NCH$_2$C*H*$_2$O)$_2$), 2.88 (4H, t, *J* 4.5, (NC*H*$_2$CH$_2$O)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 132.5, 131.1, 129.2, 128.3, 123.5, 66.6, 57.4; IR υ_{max} (neat)/cm^{-1} 3175, 2851, 1457, 1370, 1327 (SO_2), 1263, 1137 (SO_2), 1108; LRMS (ESI) *m/z* 269 (15%, $[M+H]^+$), 291 (55%, $[M+Na]^+$), 323 (15%, $[M+Na+MeOH]^+$), 559 (100%, $[2M+Na]^+$), 827 (20%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 291.0772 $[M+Na]^+$, $C_9H_{14}N_2O_2SNa$ requires *m/z* 291.0774.

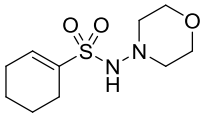
(*Z*)-*N*-Morpholino-2-phenylethenesulfonamide (28e)



The general procedure **B** was followed with the use of (*Z*)-(2-iodovinyl)benzene (50 mg, 0.22 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28e** as a 4:1 mixture with *E*-isomer **28d** as an off-white microcrystalline solid (30 mg, 51%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (2H, m,

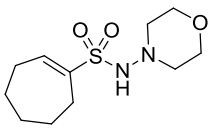
Ar-*H*), 7.43–7.39 (3H, m, Ar-*H*), 7.08 (1H, d, *J* 12.0, CHC*H*SO_2), 6.48 (1H, d, *J* 12.0, C*H*CHSO_2), 5.48 (1H, s, N*H*), 3.68 (4H, t, *J* 4.5, (NCH_2CH_2O)$_2$), 2.78 (4H, t, *J* 4.5, (NCH_2CH_2O)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 132.4, 130.4, 130.1, 128.2, 126.9, 66.5, 57.0; LRMS (ESI) *m/z* 269 (40%, $[M+H]^+$), 291 (100%, $[M+Na]^+$), 559 (20%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 291.0775 $[M+Na]^+$, $C_9H_{14}N_2O_2SNa$ requires *m/z* 291.0774.

_N_-Morpholinocyclohex-1-ene-1-sulfonamide (28g)



The general procedure **B** was followed with the use of 1-iodocyclohex-1-ene **30** (50 mg, 0.24 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28g** as an off-white microcrystalline solid (47 mg, 79%); mp 120–122 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98–6.94 (1H, m, C*H*), 5.13 (1H, br. s, N*H*), 3.72 (4H, t, *J* 4.5, (NCH_2CH_2O)$_2$), 2.82 (4H, t, *J* 4.5, (NCH_2CH_2O)$_2$), 2.40–2.34 (2H, m, CH_2), 2.32–2.25 (2H, m, CH_2), 1.76–1.69 (2H, m, CH_2), 1.67–1.60 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 136.5, 66.6, 57.3, 25.5, 23.7, 22.1, 20.9; IR υ_{max} (neat)/cm^{-1} 3196, 1438, 1319 (SO_2), 1263, 1143 (SO_2), 1108, 1052; LRMS (ESI) *m/z* 247 (10%, $[M+H]^+$), 269 (85%, $[M+Na]^+$), 301 (25%, $[M+Na+MeOH]^+$), 515 (100%, $[2M+Na]^+$), 761 (10%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 269.0930 $[M+Na]^+$, $C_{10}H_{18}N_2O_3SNa$ requires *m/z* 269.0930.

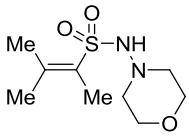
_N_-Morpholinocyclohept-1-ene-1-sulfonamide (28h)



The general procedure **B** was followed with the use of 1-iodocyclohept-1-ene **31** (50 mg, 0.23 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the

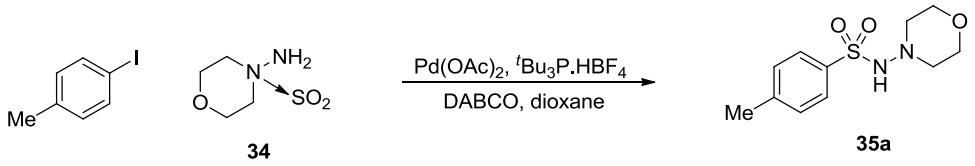
N-aminosulfonamide **28h** as an off-white microcrystalline solid (52 mg, 89%); mp 109–110 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, t, *J* 6.5, C*H*), 5.09 (1H, br. s, N*H*), 3.73 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.84 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.56 (2H, dd, *J* 5.5, 5.5, CH_2CSO_2), 2.37 (2H, app. q, *J* 6.5, CH_2CHC), 1.83–1.77 (2H, m, CH_2), 1.66–1.56 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 141.3, 66.6, 57.6, 31.4, 28.6, 28.0, 26.5, 25.5; IR υ_{max} (neat)/cm^{-1} 3168, 2919, 2849, 1645, 1455, 1299 (SO_2), 1157, 1140 (SO_2), 1114; LRMS (ESI) *m/z* 261 (15%, $[M+H]^+$), 283 (45%, $[M+Na]^+$), 543 (100%, $[2M+Na]^+$), 803 (25%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 283.1088 $[M+Na]^+$, $C_{11}H_{20}N_2O_3SNa$ requires *m/z* 283.1087.

3-Methyl-*N*-morpholinobut-2-ene-2-sulfonamide (28j)



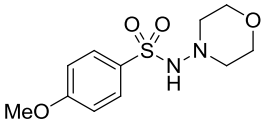
The general procedure **B** was followed with the use of 2-iodo-3-methylbut-2-ene **33** (50 mg, 0.26 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28j** as an off-white microcrystalline solid (43 mg, 72%); mp 132–133 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (1H, br. s, N*H*), 3.71 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.81 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.25 (3H, app. q, *J* 1.5, *Me*), 2.07 (3H, app. t, *J* 1.0, *Me*), 1.92 (3H, app. d, *J* 1.0, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 128.8, 66.8, 57.0, 24.3, 22.8, 16.6; IR υ_{max} (neat)/cm^{-1} 3174, 2960, 2920, 2863, 1653, 1457, 1319 (SO_2), 1260, 1151 (SO_2), 1106; LRMS (ESI) *m/z* 235 (5%, $[M+H]^+$), 257 (80%, $[M+Na]^+$), 289 (30%, $[M+Na+MeOH]^+$), 491 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 257.0932 $[M+Na]^+$, $C_9H_{18}N_2O_3SNa$ requires *m/z* 257.0930.

General procedure C for the formation of *N*-aminosulfonamides using 4-aminomorpholine-sulfur dioxide complex 34, exemplified by the preparation of 4-methyl-*N*-morpholinobenzenesulfonamide (35a)



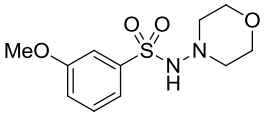
A glass reaction tube was charged with 4-iodotoluene (50 mg, 0.23 mmol), 4-aminomorpholine-sulfur dioxide complex **34** (57 mg, 0.34 mmol), DABCO (28 mg, 0.34 mmol), palladium(II) acetate (5.0 mg, 23 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (13 mg, 46 μmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1,4-Dioxane (1.6 mL) was added through the septum and the reaction mixture heated at 70 °C for 16 hrs. After cooling to room temperature, the reaction mixture was filtered through Celite®. The Celite® pad was washed sequentially with DCM (10 mL) and Et_2O (5 mL) and the combined organic filtrate concentrated *in vacuo*. Purification by flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **35a** as an off-white microcrystalline solid (54 mg, 92%); mp 154–155 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* 8.0, Ar-*H*), 7.31 (2H, d, *J* 8.0, Ar-*H*), 5.60 (1H, s, N*H*), 3.60 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.62 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.44 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 135.6, 129.5, 128.2, 66.6, 56.7, 21.6; IR υ_{max} (neat)/cm^{-1} 3188, 2968, 2923, 2868, 1459, 1334 (SO_2), 1165 (SO_2); LRMS (ESI) *m/z* 257 (20%, $[M+H]^+$), 279 (80%, $[M+Na]^+$), 311 (30%, $[M+Na+MeOH]^+$), 535 (100%, $[2M+Na]^+$), 791 (20%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 279.0776 $[M+Na]^+$, $C_{11}H_{16}N_2O_3SNa$ requires *m/z* 279.0774.

4-Methoxy-*N*-morpholinobenzenesulfonamide (35b)



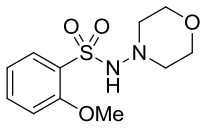
The general procedure **C** was followed with the use of 4-iodoanisole (50 mg, 0.21 mmol). Flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **35b** as an off-white microcrystalline solid (54 mg, 93%); mp 174–175 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* 9.0, Ar-*H*), 6.99 (2H, d, *J* 9.0, Ar-*H*), 5.36 (1H, s, N*H*), 3.89 (3H, s, O*Me*), 3.62 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.63 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 130.3, 130.1, 114.0, 66.7, 56.8, 55.6; IR υ_{max} (neat)/cm^{-1} 3212, 2961, 2923, 2853, 1497, 1327 (SO_2), 1262, 1111 (SO_2), 1094; LRMS (ESI) *m/z* 273 (20%, $[M+H]^+$), 295 (65%, $[M+Na]^+$), 327 (20%, $[M+Na+MeOH]^+$), 567 (100%, $[2M+Na]^+$), 839 (20%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 295.0723 $[M+Na]^+$, $C_{11}H_{16}N_2O_4SNa$ requires *m/z* 295.0724.

3-Methoxy-*N*-morpholinobenzenesulfonamide (35c)



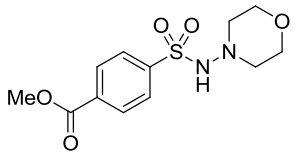
The general procedure **C** was followed with the use of 3-iodoanisole (50 mg, 0.20 mmol). Flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **35c** as a pale yellow microcrystalline solid (50 mg, 86%); mp 125–126 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* 7.5, Ar-*H*), 7.49 (1H, s, Ar-*H*), 7.43 (1H, app. t, *J* 8.0, Ar-*H*), 7.14–7.12 (1H, m, Ar-*H*), 5.62 (1H, s, N*H*), 3.87 (3H, s, O*Me*), 3.62 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.64 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.8, 130.0, 120.3, 119.7, 112.6, 66.7, 56.8, 55.7; IR υ_{max} (neat)/cm^{-1} 3215, 2963, 2923, 2857, 1479, 1362 (SO_2), 1245, 1161 (SO_2), 1111, 1036; LRMS (ESI) *m/z* 295 (35%, $[M+Na]^+$), 567 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 295.0723 $[M+Na]^+$, $C_{11}H_{16}N_2O_4SNa$ requires *m/z* 295.0724.

2-Methoxy-*N*-morpholinobenzenesulfonamide (35d)



The general procedure **C** was followed with the use of 2-iodoanisole (50 mg, 0.21 mmol). Flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **35d** as an off-white microcrystalline solid (37 mg, 64%); mp 150–151 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* 8.0, Ar-*H*), 7.60–7.56 (1H, m, Ar-*H*), 7.11 (1H, app. t, *J* 7.5, Ar-*H*), 7.04 (1H, d, *J* 8.5, Ar-*H*), 5.95 (1H, s, N*H*), 4.00 (3H, s, O*Me*), 3.58 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.67 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 135.1, 131.8, 126.9, 120.9, 112.1, 66.4, 56.6, 56.4; IR υ_{max} (neat)/cm^{-1} 3235, 2961, 2923, 2854, 1481, 1333 (SO_2), 1280, 1162 (SO_2), 1071; LRMS (ESI) *m/z* 295 (80%, $[M+Na]^+$), 567 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 295.0723 $[M+Na]^+$, $C_{11}H_{16}N_2O_4SNa$ requires *m/z* 295.0724.

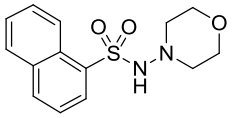
Methyl 4-(*N*-morpholinosulfamoyl)benzoate (35e)



The general procedure **C** was followed with the use of methyl 4-iodobenzoate (50 mg, 0.19 mmol). Flash column chromatography (50–100% Et_2O in petrol) afforded the *N-aminosulfonamide* **35e** as an off-white microcrystalline solid (41 mg, 72%); mp 183–184 °C (DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (2H, d, *J* 8.5, Ar-*H*), 8.06 (2H, d, *J* 8.5, Ar-*H*), 5.49 (1H, s, N*H*), 3.98 (3H, s, CO_2Me), 3.62 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$), 2.64 (4H, t, *J* 4.5, ($NCH_2CH_2O)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 142.6, 134.3, 130.0, 128.2, 66.6, 56.8, 52.7; IR υ_{max} (neat)/cm^{-1} 3170, 2960, 2922, 2852, 1696 (C=O), 1459, 1339 (SO_2), 1289, 1176 (SO_2), 1110, 1088; LRMS (ESI) *m/z* 301 (25%, $[M+H]^+$), 323 (40%, $[M+Na]^+$), 355 (10%, $[M+Na+MeOH]^+$), 623 (100%,

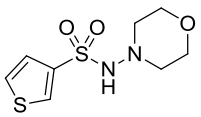
$[2M+Na]^+$), 923 (25%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 299.0707 $[M-H]^-$, $C_{12}H_{15}N_2O_5S$ requires *m/z* 299.0707.

_N_-Morpholinonaphthalene-1-sulfonamide (35f)



The general procedure **C** was followed with the use of 1-iodonaphthalene (50 mg, 0.20 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **35f** as a white microcrystalline solid (50 mg, 86%); mp 158–159 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (1H, d, *J* 8.5, Ar-*H*), 8.40 (1H, d, *J* 7.5, Ar-*H*), 8.11 (1H, d, *J* 8.5, Ar-*H*), 7.94 (1H, d, *J* 8.0 Ar-*H*), 7.69 (1H, app. t, *J* 8.0, Ar-*H*), 7.59 (2H, app. q, *J* 8.0, Ar-*H*), 5.76 (1H, s, N*H*), 3.48 (4H, t, *J* 5.0, $(NCH_2CH_2O)_2$), 2.54 (4H, t, *J* 5.0, $(NCH_2CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.1, 133.5, 131.4, 128.9, 128.5, 128.2, 126.9, 125.1, 124.2, 66.5, 56.8; IR υ_{max} (neat)/cm^{-1} 3215, 2964, 2858, 1457, 1325 (SO_2), 1266, 1163 (SO_2), 1134, 1111; LRMS (ESI) *m/z* 293 (10%, $[M+H]^+$), 315 (15%, $[M+Na]^+$), 607 (100%, $[2M+Na]^+$, 899 (30%, $[3M+Na]^+$); HRMS (ESI) found *m/z* 315.0774 $[M+Na]^+$, $C_{14}H_{16}N_2O_3SNa$ requires *m/z* 315.0774.

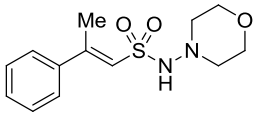
_N_-Morpholinothiophene-3-sulfonamide (35g)



The general procedure **C** was followed with the use of 3-iodothiophene (50 mg, 0.24 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **35g** as an off-white microcrystalline solid (45 mg, 76%); mp 157–158 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, d, *J* 2.0, Ar-*H*), 7.46–7.41 (2H, m, Ar-*H*), 5.67 (1H, s, N*H*), 3.65 (4H, t, *J* 4.5, $(NCH_2CH_2O)_2$), 2.66 (4H,

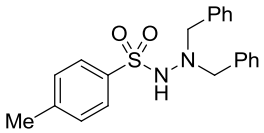
t, *J* 4.5, (NC*H*$_2$CH$_2$O)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 132.0, 127.6, 126.2, 66.6, 56.8; IR υ_{max} (neat)/cm^{-1} 3206, 3113, 2962, 2923, 2857, 1327 (SO_2), 1264, 1206, 1160 (SO_2), 1109, 1073; LRMS (ESI) *m/z* 271 (60%, $[M+Na]^+$), 303 (15%, $[M+Na+MeOH]^+$), 519 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 271.0182 $[M+Na]^+$, $C_8H_{12}N_2O_3SNa$ requires *m/z* 271.0182.

(*E*)-*N*-Morpholino-2-phenylprop-1-ene-1-sulfonamide (28i)



The general procedure **C** was followed with the use of (*E*)-(1-iodoprop-1-en-2-yl)benzene **32** (50 mg, 0.20 mmol). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **28i** as an off-white microcrystalline solid (50 mg, 86%). Data consistent with that reported above (obtained *via* general procedure **B**).

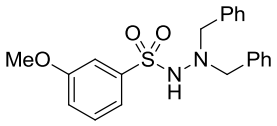
***N*',*N*'-Dibenzyl-4-methylbenzenesulfonohydrazide (40a)**



The general procedure **B** was followed with the use of 4-iodotoluene (350 mg, 1.6 mmol), 1,1-dibenzylhydrazine (510 mg, 2.4 mmol), DABSO (230 mg, 0.96 mmol), DABCO (90 mg, 0.80 mmol), palladium(II) acetate (36 mg, 0.16 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (93 mg, 0.32 mmol) and 1,4-dioxane (11 mL) in a 25 mL round-bottom flask. Flash column chromatography (13:6:1 petrol:Et_2O:Et_3N) afforded the *N-aminosulfonamide* **40a** as a pale yellow microcrystalline solid (499 mg, 85%); mp 123–124 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* 8.5, Ar-*H*), 7.28–7.26 (6H, m, Ar-*H*), 7.19–7.16 (6H, m, Ar-*H*), 5.53 (1H, s, N*H*), 3.73 (4H, s, N(C*H*$_2$Ph)$_2$), 2.41 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 135.4, 134.9, 129.8,

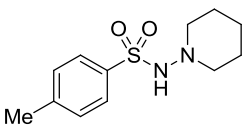
129.4, 128.4, 128.2, 127.6, 59.7, 21.6; IR υ_{max} (neat)/cm^{-1} 3203, 1738, 1598, 1427, 1325 (SO_2), 1157 (SO_2), 1091; LRMS (ESI) *m/z* 367 (80%, $[M+H]^+$), 389 (60%, $[M+Na]^+$), 755 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 389.1280 $[M+Na]^+$, $C_{21}H_{22}N_2O_2SNa$ requires *m/z* 389.1294.

_N'_,_N'_-Dibenzyl-3-methoxybenzenesulfonohydrazide (40b)



The general procedure **B** was followed with the use of 3-iodoanisole (350 mg, 1.50 mmol), 1,1-dibenzylhydrazine (475 mg, 2.25 mmol), DABSO (395 mg, 1.65 mmol), palladium(II) acetate (34 mg, 0.15 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (87 mg, 0.30 mmol) and 1,4-dioxane (10 mL) in a 25 mL round-bottom flask. Flash column chromatography (11:8:1 petrol:Et_2O:Et_3N) afforded the *N-aminosulfonamide* **40b** as a pale yellow oil (450 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* 8.0, Ar-*H*), 7.34–7.25 (8H, m, Ar-*H*), 7.20–7.18 (4H, m, Ar-*H*), 7.04 (1H, dd, *J* 8.0, 2.0, Ar-H), 5.59 (1H, s, N*H*), 3.80 (3H, s, O*Me*), 3.75 (4H, s, N(CH_2Ph)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 139.5, 134.9, 129.7, 129.6, 128.4, 127.7, 120.6, 119.7, 112.4, 59.9, 55.4; IR υ_{max} (neat)/cm^{-1} 1598, 1478, 1315 (SO_2), 1240, 1150 (SO_2), 1022; LRMS (ESI) *m/z* 405 (15%, $[M+Na]^+$), 787 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 405.1227 $[M+Na]^+$, $C_{21}H_{22}N_2O_3SNa$ requires *m/z* 405.1243.

4-Methyl-*N*-(piperidin-1-yl)benzenesulfonamide (44)

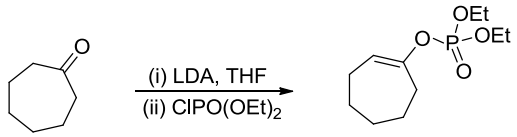


The general procedure **B** was followed with the use of 4-iodotoluene (50 mg, 0.23 mol), 1-aminopiperidine (34 µl, 0.35 mmol), DABSO (33 mg, 0.14 mmol), DABCO (13 mg, 0.11 mmol), palladium(II) acetate (5.0 mg, 20 µmol), tri-*tert*-butylphosphonium

tetrafluoroborate (12 mg, 40 μmol) and 1,4-dioxane (1.6 mL). Flash column chromatography (25–75% Et_2O in petrol) afforded the *N-aminosulfonamide* **44** as an off-white microcrystalline solid (51 mg, 87%); mp 128–129 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* 8.5, Ar-*H*), 7.30 (2H, d, *J* 8.5, Ar-*H*), 5.31 (1H, s, N*H*), 2.55 (4H, t, *J* 5.0, ($NCH_2CH_2CH)_2$), 2.44 (3H, s, *Me*), 1.52 (4H, app. quin., *J* 5.5, ($NCH_2CH_2CH)_2$), 1.27–1.35 (2H, m, ($NCH_2CH_2CH)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 135.8, 129.3, 128.1, 57.8, 25.6, 23.0, 21.6; IR υ_{max} (neat)/cm^{-1} 3205, 3178, 2956, 2854, 1330 (SO_2), 1164 (SO_2), 1096; LRMS (ESI) *m/z* 277 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 277.0982 $[M+Na]^+$, $C_{12}H_{18}N_2O_2SNa$ requires *m/z* 277.0981.

6.2.3 Starting Materials and Other Reactions

Cycloheptenyl diethylphosphate (A)

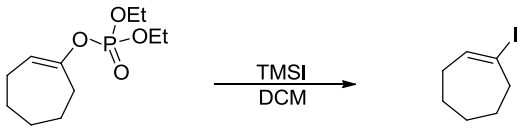


A

Method adapted from a procedure documented by Wiemer *et al.*[134] A solution of LDA in THF (1.8 M, 9.2 mL, 17 mmol) was added dropwise over 10 mins to a solution of cycloheptanone (1.8 mL, 15 mmol) in anhydrous THF (20 mL) cooled to -78 ^{o}C and the reaction mixture stirred for 30 mins. A solution of diethylphosphorochloridate (8.1 g, 30 mmol) in anhydrous THF (20 mL) was added dropwise at the same temperature and the resulting solution stirred for 30 mins, then for a further 1 hr at room temperature. The reaction mixture was cooled to 0 ^{o}C and quenched dropwise with aq. NH_4Cl (50 mL). The aqueous mixture was extracted with EtOAc (3 × 60 mL) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10–50% EtOAc in petrol) afforded the titled *alkenyl phosphate* **A** as a pale yellow oil (2.61 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (1H, td, *J* 6.5,

2.5, C*H*), 4.15 (4H, app. quin.d, *J* 7.5, 1.0, 2 × CH_2), 2.43–2.40 (2H, m, CH_2), 2.10–2.05 (2H, m, CH_2), 1.73–1.56 (6H, m, 3 × CH_2), 1.35 (6H, td, *J* 7.0, 1.0, 2 × *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2 (d, $J_{C\text{-}P}$ 9.5), 115.4 (d, $J_{C\text{-}P}$ 5.5), 64.0 (d, $J_{C\text{-}P}$ 6.0), 33.3 (d, $J_{C\text{-}P}$ 3.5), 30.6, 26.9, 25.0, 24.8, 16.1 (d, $J_{C\text{-}P}$ 7.0); IR υ_{max} (neat)/cm^{-1} 2926, 1678, 1445, 1369, 1268, 1158, 1104, 1019; LRMS (ESI) *m/z* 249 (5%, $[M+H]^+$), 520 (100%, $[2M+Na]^+$), 767 (90%, $[3M+Na]^+$). HRMS (ESI) found *m/z* 249.1247 $[M+H]^+$, $C_{11}H_{22}O_4P$ requires *m/z* 249.1250.

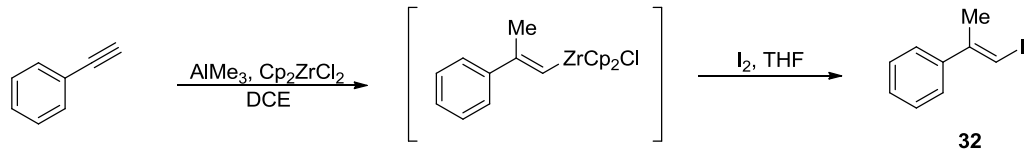
1-Iodocyclohept-1-ene (31)



A **31**

Method adapted from a procedure documented by Wiemer *et al.*[134] TMS-I (3.5 mL, 25 mmol) was added dropwise to a solution of cycloheptenyl diethylphosphate **A** (2.10 g, 8.46 mmol) in anhydrous DCM (20 mL), cooled to 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for 30 mins before being cooled to 0 ^{o}C and quenched with aq. NH_4Cl (20 mL). The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers washed with aq. $Na_2S_2O_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the alkenyl iodide **31** as a colourless oil (1.10 g, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (1H, t, *J* 6.5, C*H*), 2.78–2.75 (2H, m, CH_2), 2.06 (2H, app. q, *J* 6.0, CH_2), 1.76–1.70 (2H, m, CH_2), 1.58–1.52 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 100.7, 45.0, 31.4, 31.0, 26.6, 26.3; HRMS (FI) found *m/z* 221.9905 (100%, $[M^+]$), $C_7H_{11}I$ requires *m/z* 221.9906. Data consistent with the literature.[227]

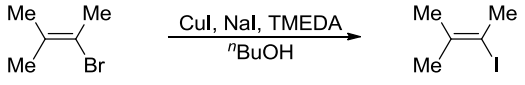
(*E*)-(1-Iodoprop-1-en-2-yl)benzene (32)



32

Method adapted from procedure documented by Charette *et al.*[133] $AlMe_3$ (2.0 M solution in hexanes, 10 mL, 20 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (2.9 g, 10 mmol) in anhydrous DCE (25 mL) under argon. Phenyl acetylene (1.0 g, 10 mmol) was added dropwise and the resultant solution stirred at room temperature for 16 hrs. The reaction mixture was then cooled to 0 ^oC and a solution of iodine (3.0 g, 12 mmol) in anhydrous THF (15 mL) was added dropwise and the resultant suspension warmed to room temperature and stirred for 2 hrs. The reaction mixture was cooled to 0 ^oC and simultaneously quenched with water (25 mL) and diluted with Et_2O (25 mL). The organic layer was separated, washed with aq. $Na_2S_2O_3$ (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the alkenyl iodide **32** as a colourless oil (1.59 g, 65%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (5H, m, Ar-*H*), 6.53 (1H, q, *J* 1.0, C*H*), 2.29 (3H, d, *J* 1.0, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.5, 128.4, 127.8, 126.0, 79.1, 24.4; HRMS (FI) found *m/z* 243.9741 (100%, $[M^+]$), C_9H_9I requires *m/z* 243.9749. Data consistent with the literature.[133]

2-Iodo-3-methylbut-2-ene (33)

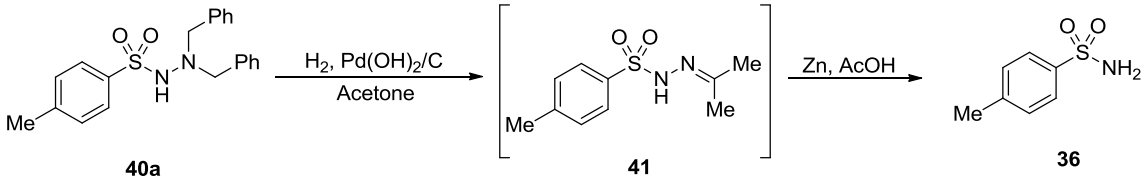


B **33**

Method adapted from a procedure documented by Buchwald *et al.*[135] A 50 mL Schlenk tube was charged with NaI (4.5 g, 30 mmol) and CuI (380 mg, 2.0 mmol), sealed with a rubber septum and evacuated and filled with argon four times. DMEDA (0.43 mL, 4.0 mmol), 2-bromo-3-methylbut-2-ene **B** (2.3 mL, 20 mmol) and anhydrous ^{n}BuOH

(10 mL) were added through the septum. The Schlenk tube was sealed and the reaction mixture heated at 120 ^{o}C for 24 hrs. The resulting suspension was cooled to room temperature, poured onto pentane (100 mL) and washed with a solution of 35% aq. NH_3 (5 mL) in water (100 mL) followed by water (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by distillation (fraction at 120–140 ^{o}C) affording the alkenyl iodide **33** as a colourless liquid (2.85 g, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (3H, app. t, *J* 1.0, *Me*), 1.94 (3H, app. q, *J* 1.5, *Me*), 1.82 (3H, app. d, *J* 1.0, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 93.2, 31.4, 30.3, 18.9; HRMS (FI) found *m/z* 195.9743 (100%, [M^+]), C_5H_9I requires *m/z* 195.9749. Data consistent with the literature.[135,228]

General procedure D for the formation of unsubstituted sulfonamides from the corresponding dibenzyl-*N*-aminosulfonamide, exemplified by the preparation of tosylamine (36)

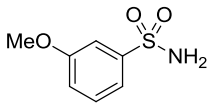


A glass reaction tube was charged with recrystallised *N*',*N*'-dibenzyl-4-methylbenzenesulfonohydrazide **40a** (290 mg, 0.80 mmol) and Pearlman's catalyst ($Pd(OH)_2$ on carbon, 20 wt% Pd, ~60% moisture, 140 mg, 0.08 mmol Pd). Acetone (2 mL) was added and the reaction mixture degassed with nitrogen. The tube was flushed with H_2 gas and left stirring under a balloon of H_2 atmosphere for 16 hrs. The reaction flask was purged with nitrogen, the suspension filtered through Celite® and the Celite® pad washed with DCM (5 mL). The filtrate was concentrated *in vacuo* affording analytically pure *tosyl hydrazone* **41** as white crystals (180 mg, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* 8.0, Ar-*H*), 7.31 (2H, d,

J 8.0, Ar-*H*), 2.43 (3H, s, Ar-*Me*), 1.94 (3H, s, NC*Me*), 1.80 (3H, s, NC*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 144.0, 135.4, 129.5, 128.0, 25.3, 21.6, 16.8; IR υ_{max} (neat)/cm^{-1} 3225, 1655, 1597, 1389, 1330 (SO_2), 1158 (SO_2), 1086; LRMS (ESI) *m/z* 227 (65%, $[M+H]^+$), 249 (95%, $[M+Na]^+$), 281 (40%, $[M+Na+MeOH]^+$), 475 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 249.0668 $[M+Na]^+$, $C_{10}H_{14}N_2O_2SNa$ requires *m/z* 249.0668.

The N-N bond cleavage was carried out in accordance with a similar literature procedure.[137] The crude sulfonyl hydrazone **41** (180 mg, 0.80 mmol) was dissolved in acetic acid (5 mL) and zinc dust (1.30 g, 25 mmol) added. The resulting suspension was stirred at room temperature for 1 hr. The reaction mixture was diluted with DCM (10mL), sonicated for 1 min and filtered through Celite®, the zinc residue being washed with further DCM (5 mL). The filtrate was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording analytically pure tosyl amine **36** as white crystals (114 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* 8.5, Ar-*H*), 7.31 (2H, d, *J* 8.5, Ar-*H*), 4.95 (2H, br. s, N*H*$_2$), 2.44 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.0, 129.7, 126.4, 21.5; LRMS (ESI) *m/z* 194 (100%, $[M+Na]^+$), 226 (80%, $[M+Na+MeOH]^+$). Data consistent with commercial sample.

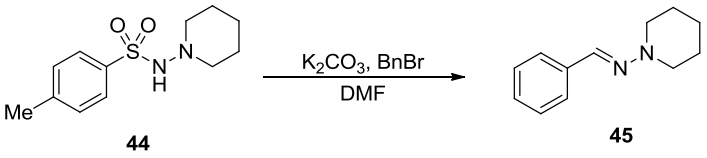
3-Methoxybenzenesulfonamide (42) (*via* dibenzyl-*N*-aminosulfonamide 40b)



The general procedure **D** was followed using re-crystallised *N*',*N*'-dibenzyl-3-methoxybenzenesulfonohydrazide **40b** (120 mg, 0.30 mmol) to first afford the corresponding hydrazone as a white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57–7.38 (3H, m, Ar-*H*), 7.16–7.10 (1H, m, Ar-*H*), 3.87 (3H, s, O*Me*), 1.96 (3H, s, NC*Me*), 1.80 (3H, s, NC*Me*); LRMS (ESI) *m/z* 210 (100%, $[M+Na]^+$). Zinc in acetic acid reduction afforded unsubstituted sulfonamide **42** as colourless crystals (46 mg, 80%); ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.48 (1H, app. t, *J* 8.0, Ar-*H*), 7.41–7.35 (4H, m, Ar-*H* incl. N*H*$_2$), 7.16 (1H, dd, *J* 8.0, 2.5, Ar-*H*), 3.82 (3H, s, O*Me*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 145.4, 130.1, 117.6 (2C), 110.8, 55.5; LRMS (ESI) *m/z* 186 (100%, $[M-H]^-$). HRMS (ESI) *m/z* 210.0192 $[M+Na]^+$, $C_7H_9NO_3SNa$ requires 210.0195. Data consistent with the literature.[229]

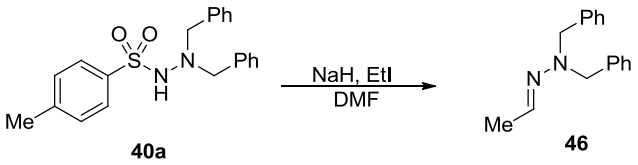
(*E*)-*N*-Benzylidenepiperidin-1-amine (45)



44 **45**

The *hydrazone* **45** was formed as an unexpected product from the attempted *N*-alkylation of *N*-aminosulfonamide **44**. A two-necked 50 mL round-bottom flask was charged with *N*-aminosulfonamide **44** (200 mg, 0.79 mmol) and potassium carbonate (1.1 g, 7.9 mmol). DMF (10 mL) and benzyl bromide (103 µL, 0.86 mmol) were added sequentially and the resultant suspension stirred at room temperature for 16 hrs. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (50 mL) and aq. LiCl (2 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O in petrol) afforded the *hydrazone* **45** as off-white crystals (95 mg, 64%); mp 60–61 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.59 (2H, m, Ar-*H*), 7.56 (1H, s, CC*H*NN), 7.37–7.32 (2H, m, Ar-*H*), 7.28–7.23 (1H, m, Ar-*H*), 3.18 (4H, t, *J* 5.5, N(C*H*$_2$CH$_2$)$_2$CH$_2$), 1.77 (4H, app. quin, *J* 6.0, N(CH$_2$C*H*$_2$)$_2$CH$_2$), 1.59–1.53 (2H, m, N(CH$_2$CH$_2$)$_2$C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.6, 128.5, 127.8, 125.9, 52.1, 25.2, 24.1; IR υ_{max} (neat)/cm^{-1} 2939, 1589, 1444, 1356, 1261, 1153, 1084, 1065; LRMS (ESI) *m/z* 189 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 189.1386 $[M+H]^+$, $C_{12}H_{17}N_2$ requires *m/z* 189.1386.

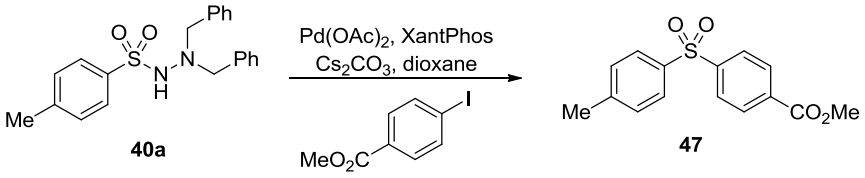
(*E*)-1,1-Dibenzyl-2-ethylidenehydrazine (46)



40a **46**

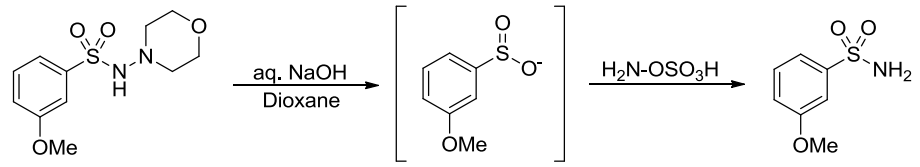
The *hydrazone* **46** was formed as an unexpected product from the attempted *N*-alkylation of *N*-aminosulfonamide **40a**. A solution of *N*-aminosulfonamide **40a** (1.5 g, 4.1 mmol) in anhydrous DMF (5 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.25 g, 6.1 mmol) in DMF (5 mL) cooled to 0 ^{o}C. After 10 mins the reaction was warmed to room temperature and stirred for 1 hr. Ethyl iodide (0.43 mL, 5.3 mmol) was added dropwise and the reaction stirred for a further 12 hrs at room temperature. The reaction mixture was quenched with aq. NH_4Cl (5 mL) and then poured onto water (40 mL). The aqueous mixture was extracted with EtOAc (3 × 40 mL) and the combined organic layers washed sequentially with water (100 mL), brine (100 mL) and 5% aq. LiCl (2 × 40 mL). The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (25% Et_2O in petrol) afforded the *hydrazone* **46** as a pale yellow oil (452 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (10H, m, Ar-*H*), 6.58 (1H, q, *J* 5.0 , MeC*H*NN), 4.24 (4H, s, N(C*H*$_2$Ph)$_2$), 1.81 (3H, d, *J* 5.0, *Me*CHNN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8, 128.3 128.2, 127.8, 127.0, 58.5, 18.8; IR υ_{max} (neat)/cm^{-1} 1603, 1494, 1453, 1384, 1117, 1072, 1028; LRMS (ESI) *m/z* 239 (80%, $[M+H]^+$), 477 (100%, $[2M+H]^+$); HRMS (ESI) found *m/z* 239.1545 $[M+H]^+$, $C_{16}H_{19}N_2$ requires *m/z* 239.1543.

Methyl 4-tosylbenzoate (47)



The diaryl sulfone **47** was formed as an unexpected side product from the attempted *N*-arylation of *N*-aminosulfonamide **40a**. A glass reaction tube was charged with *N*-aminosulfonamide **40a** (75 mg, 0.20 mmol), methyl 4-iodobenzoate (64 mg, 0.25 mmol), cesium carbonate (133 mg, 0.40 mmol), palladium(II) acetate (2.3 mg, 10 μmol) and XantPhos (8.9 mg, 15 μmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1,4-Dioxane (1.0 mL) was added through the septum and the reaction heated at 100 °C for 16 hrs. After cooling to room temperature, the reaction mixture was filtered through Celite®. The Celite® pad was washed sequentially with DCM (10 mL) and Et_2O (5 mL) and the combined organic extracts concentrated *in vacuo*. Purification by flash column chromatography (10–50% Et_2O in petrol) afforded the *diaryl sulfone* **47** as a pale yellow microcrystalline solid (51 mg, 86 %); mp 163–164 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* 9.0, Ar-*H*), 7.99 (2H, d, *J* 9.0, Ar-*H*), 7.84 (2H, d, *J* 8.0, Ar-*H*), 7.32 (2H, d, *J* 8.0, Ar-*H*), 3.94 (3H, s, CO_2*Me*), 2.41 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 145.9, 144.7, 137.8, 134.1, 130.4, 130.1, 127.9, 127.5, 52.6, 21.6; IR υ_{max} (neat)/cm^{-1} 1724, 1594, 1438, 1401, 1324 (SO_2), 1279, 1216, 1155 (SO_2), 1102, 1072, 1014; LRMS (ESI) *m/z* 313 (30%, $[M+Na]^+$), 603 (100%, $[2M+Na]^+$). HRMS (ESI) found *m/z* 313.0504 $[M+Na]^+$, $C_{15}H_{14}O_4SNa$ requires *m/z* 313.0505.

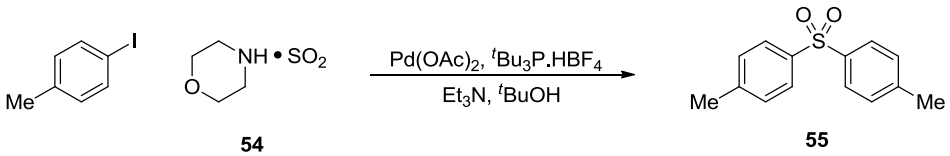
3-Methoxybenzenesulfonamide (42) (*via* sulfinate 51)



35c **51** **42**

A glass reaction tube was charged with *N*-aminosulfonamide **35c** (136 mg, 0.50 mmol), 1,4-dioxane (1 mL) and aq. 1M NaOH (1 mL, 1.0 mmol). The resultant solution was heated under nitrogen at 90 ^{o}C for 16 hrs. The reaction mixture was cooled to room temperature and hydroxylamine-*O*-sulfonic acid (170 mg, 1.5 mmol) added. The resultant solution was stirred under nitrogen at room temperature for 16 hrs. The reaction mixture was diluted with EtOAc (15 mL) and washed with aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (4 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10–40% EtOAc in petrol) afforded sulfonamide **42** as a white crystalline solid (73 mg, 78%). Data consistent with that reported above (obtained *via* general procedure **D**).

4,4'-Sulfonylbis(methylbenzene) (55)



54 **55**

A glass reaction tube was charged with 4-iodotoluene (100 mg, 0.46 mmol), morpholine-sulfur dioxide complex **54** (76 mg, 0.50 mmol), palladium(II) acetate (10 mg, 46 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (27 mg, 92 μmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. Triethylamine (70 μL, 0.50 mmol) and anhydrous *tert*-butanol (1.5 mL) were added and the reaction mixture heated at 85 °C for 16 hrs. After cooling to room temperature, DCM (2 mL) was added and the diluted reaction mixture filtered through Celite®. The Celite® pad was washed

sequentially with DCM (10 mL) and Et_2O (5 mL) and the combined organic filtrate concentrated *in vacuo*. Purification by flash column chromatography (0–25% Et_2O in petrol) afforded the diaryl sulfone **55** as an off-white microcrystalline solid (45 mg, 80%); mp 156–157 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (4H, d, *J* 8.0, Ar-*H*), 7.29 (4H, d, *J* 8.0, Ar-*H*), 2.40 (6H, s, 2 × *Me*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 139.1, 129.9, 127.6, 21.6; IR υ_{max} (neat)/cm^{-1} 2914, 2850, 1734, 1596, 1317 (SO_2), 1288, 1152 (SO_2), 1104, 1071, 1016; LRMS (ESI) *m/z* 247 (30%, $[M+H]^+$), 269 (45%, $[M+Na]^+$), 301 (10%, $[M+Na+MeOH]^+$), 515 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 269.0604 $[M+Na]^+$, $C_{14}H_{14}O_2SNa$ requires *m/z* 269.0607. Data consistent with the literature.[142]

Procedure for forming DABSO *in situ*

A glass reaction tube was charged with 1,4-diazabicyclo[2.2.2]octane (DABCO) (15 mg, 0.14 mmol), sealed with a rubber septum and evacuated and filled with argon four times. 1,4-Dioxane (1.5 mL) was added and the resulting suspension stirred for 5 mins until fully dissolved. A balloon of sulfur dioxide gas was bubbled through the solution with vigorous stirring, resulting in the precipitation of a fine white powder. The resulting fine suspension was thoroughly degassed with argon for 4 hrs, adding further dioxane as required to maintain a total volume of 1–1.5 mL. Under argon gas, 4-iodotoluene (50 mg, 0.23 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO) (13 mg, 0.11 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (13 mg, 46 μmol), palladium(II) acetate (5.0 mg, 23μmol) and 4-aminomorpholine (33 μL, 0.34 mmol) were charged and the reaction mixture heated at 70 ^{o}C for 16 hrs. The product was purified in accordance with general procedure **B** affording the *N-aminosulfonamide* **35a** as a white microcrystalline solid (54 mg, 92%). Data consistent with that reported above (obtained *via* general procedure **B**).

Use of polymer-supported sulfur dioxide surrogate 58

The general procedure **B** was followed with the use of 4-iodotoluene (50 mg, 0.23 mmol) and **58** (172 mg, 0.34 mmol) (in place of DABSO). Following an identical work-up procedure, a crude ^{1}H NMR spectrum was taken which showed 70% conversion of 4-iodotoluene to *N*-aminosulfonamide **35a**.

Organic Syntheses reactions (Figure 2.17)

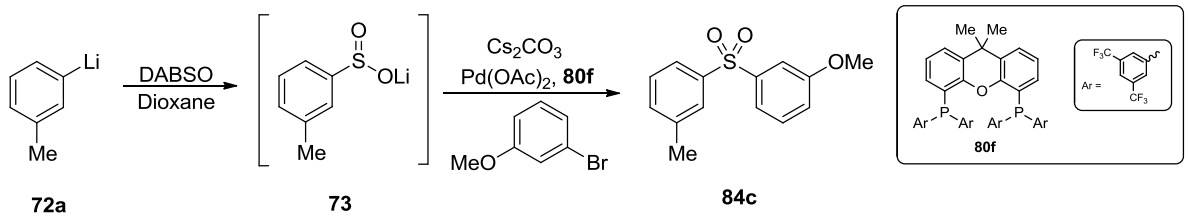
Detailed experimental procedures are documented within the publication.[3]

Thanks to Maria Gerelle and Fiona Truscott for the synthesis of the following alkenyl iodides: (*Z*)-4-iodooct-4-ene (for synthesis of **28a**),[230] (*E*)-(4-iodobut-3-enyl)benzene (for synthesis of **28b**),[132] (*E*)-5-chloro-1-iodopent-1-ene (for synthesis of **28c**),[132] (*E*)-(2-iodovinyl)benzene (for synthesis of **28d**),[231] (*Z*)-(2-iodovinyl)benzene (for synthesis of **28e**)[133] and 1-iodocyclohex-1-ene **30** (for synthesis of **28g**).[132]

6.3 Chapter 3 Data

6.3.1 Diaryl Sulfones *via* Sulfinate Coupling

General procedure E for the formation of diaryl sulfones exemplified by the preparation of 1-methoxy-3-(*m*-tolylsulfonyl)benzene (84c)

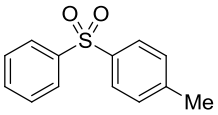


72a **73** **84c**

A glass reaction tube was charged with DABSO (63 mg, 0.26 mmol) and evacuated and filled with nitrogen twice. 1,4-Dioxane (2 mL) was added and the resultant suspension stirred while the tube was flushed with nitrogen gas for 3 mins. 3-Tolyl lithium **72a** (1.09 M solution in DBE/heptane, 0.45 mL, 0.49 mmol) was added dropwise to the vigorously stirred suspension at room temperature. The resulting suspension was stirred at room temperature for 2 hrs. Another glass reaction tube was charged with 3-bromoanisole (45 µL, 0.35 mmol), cesium carbonate (171 mg, 0.53 mmol), ligand **80f** (39 mg, 35 µmol) and palladium(II) acetate (8.0 mg, 35 µmol), sealed with a crimped cap and evacuated and filled with nitrogen three times. The lithium sulfinate slurry in dioxane was transferred by syringe and the reaction heated at 110 ^{o}C with vigorous stirring for 16 hrs under sealed tube conditions. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a Celite® pad which was washed with further DCM (20 mL). The filtrate was concentrated *in vacuo*. Flash column chromatography (10–25% Et_2O in petrol) afforded the *diaryl sulfone* **84c** as a pale yellow microcrystalline solid (83 mg, 90%); mp 59–60 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.73 (2H, m, Ar-*H*), 7.51 (1H, br. d, *J* 7.5, Ar-*H*), 7.46 (1H, app. t, *J* 2.0, Ar-*H*), 7.43–7.35 (3H, m, Ar-*H*), 7.08 (1H, dd, *J* 8.0, 2.5, Ar-*H*), 3.85 (3H, s, O*Me*), 2.41 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 142.8, 141.3, 139.5, 134.0, 130.3, 129.1,

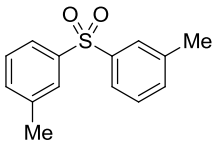
127.9, 124.8, 119.8, 119.4, 112.2, 55.6, 21.3; IR υ_{max} (neat)/cm^{-1} 3064, 2837, 1596, 1478, 1435, 1289 (SO_2), 1246, 1145 (SO_2), 1099, 1046; LRMS (ESI) *m/z* 280 (30%, $[M+NH_4]^+$), 285 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 285.0556 $[M+Na]^+$, $C_{14}H_{14}O_3SNa^+$ requires *m/z* 285.0557.

1-Methyl-4-(phenylsulfonyl)benzene (70)



The general procedure **E** was followed with the use of phenyl lithium (1.80 M solution in DBE, 270 µL, 0.49 mmol) and 4-bromotoluene (60 mg, 0.35 mmol). Flash column chromatography (0–25% Et_2O in petrol) afforded the *diaryl sulfone* **70** as a pale yellow microcrystalline solid (68 mg, 84%); mp 124–125 ^oC (DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* 7.0, Ar-*H*), 7.83 (2H, d, *J* 8.0, Ar-*H*), 7.57–7.46 (3H, m, Ar-*H*), 7.29 (2H, d, *J* 8.0, Ar-*H*), 2.39 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) 144.1, 141.9, 138.6, 132.9, 129.8, 129.2, 127.6, 127.4, 21.5; IR υ_{max} (neat)/cm^{-1} 1593, 1447, 1307 (SO_2), 1151 (SO_2), 1106, 1070 ; LRMS (ESI) *m/z* 250 (50%, $[M+NH_4]^+$), 255 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 255.0443 $[M+Na]^+$, $C_{13}H_{12}O_2SNa^+$ requires *m/z* 255.0450. Data consistent with the literature.[175]

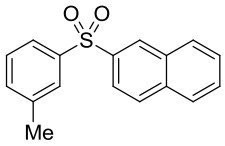
3,3'-Sulfonylbis(methylbenzene) (76)



The general procedure **E** was followed with the use of 3-bromotoluene (43 µL, 0.35 mmol). Flash column chromatography (5–15% Et_2O in petrol) afforded the *diaryl sulfone* **76** as a white microcrystalline solid (84 mg, 98%); mp 96–97 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.73 (4H, m, Ar-*H*), 7.41–7.34 (4H, m, Ar-*H*), 2.40 (6H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.5, 133.9, 129.1, 127.8, 124.7,

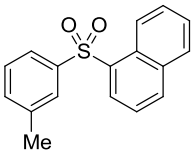
21.3; IR υ_{max} (neat)/cm^{-1} 2926, 1475, 1410, 1362, 1294 (SO_2), 1221, 1143 (SO_2), 1097, 1072 ; LRMS (ESI) *m/z* 264 (40%, $[M+NH_4]^+$), 269 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 269.0606 $[M+Na]^+$, $C_{14}H_{14}O_2SNa^+$ requires *m/z* 269.0607.

2-(*m*-Tolylsulfonyl)naphthalene (84a)



The general procedure **E** was followed with the use 2-bromonaphthalene (72 mg, 0.35 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *diaryl sulfone* **84a** as a pale orange crystalline solid (87 mg, 88%); mp 132–133 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, s, Ar-*H*), 8.01–7.80 (6H, m, Ar-*H*), 7.67–7.58 (2H, m, Ar-*H*), 7.42–7.33 (2H, m, Ar-*H*), 2.40 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.5, 138.5, 134.9, 134.0, 132.1, 129.6, 129.3, 129.1, 129.0, 128.9, 127.93, 127.86, 127.5, 124.8, 122.6, 21.3; IR υ_{max} (neat)/cm^{-1} 3059, 1410, 1314, 1301 (SO_2), 1149 (SO_2), 1130, 1095, 1067; HRMS (FI) found *m/z* 282.0726 ($[M]^+$), $C_{17}H_{14}O_2S^+$ requires *m/z* 282.0714.

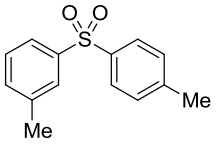
1-(*m*-Tolylsulfonyl)naphthalene (84b)



The general procedure **E** was followed with the use 1-bromonaphthalene (49 µL, 0.35 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *diaryl sulfone* **84b** as a white microcrystalline solid (94 mg, 95%); mp 99–100 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* 8.5, Ar-*H*), 8.52 (1H, d, *J* 7.5, Ar-*H*), 8.09 (1H, d, *J* 8.0, Ar-*H*), 7.90 (1H, d, *J* 8.0, Ar-*H*), 7.79 (1H, d, *J* 7.5, Ar-*H*), 7.77 (1H, s, Ar-*H*), 7.65–7.51 (3H, m, Ar-*H*), 7.39–7.30 (2H, m, Ar-*H*), 2.36 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 139.3, 135.8, 135.0, 134.2, 133.9, 129.9, 129.0,

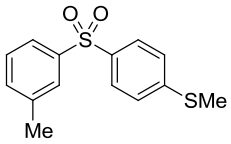
128.9, 128.4, 128.3, 127.6, 126.8, 124.5, 124.3 (2C), 21.3; IR υ_{max} (neat)/cm^{-1} 3066, 1505, 1314, 1299 (SO_2), 1220, 1155 (SO_2), 1128, 1084; HRMS (FI) found *m/z* 282.0712 ($[M]^+$), $C_{17}H_{14}O_2S^+$ requires *m/z* 282.0714.

1-Methyl-3-tosylbenzene (74)



The general procedure **E** was followed with the use 4-tolyl trifluoromethanesulfonate **D** (84 mg, 0.35 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *diaryl sulfone* **74**, co-eluting with an unknown impurity (~5% by ^1H NMR spectroscopy integration) and **76** (10% by ^1H NMR spectroscopy integration) as a beige microcrystalline solid (90 mg, ~equivalent to 90% of **74**); mp 115–116 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* 8.0, Ar-*H*), 7.75–7.71 (2H, m, Ar-*H*), 7.40–7.32 (2H, m, Ar-*H*), 7.30 (2H, d, *J* 8.0, Ar-*H*), 2.39 (6H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 141.7, 139.4, 138.7, 133.8, 129.8, 129.0, 127.7, 127.6, 124.6, 21.5, 21.3; IR υ_{max} (neat)/cm^{-1} 1595, 1410, 1360, 1319, 1287 (SO_2), 1147 (SO_2), 1102, 1074; LRMS (ESI) *m/z* 264 (15%, $[M+NH_4]^+$), 269 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 269.0606 $[M+Na]^+$, $C_{14}H_{14}O_2SNa^+$ requires *m/z* 269.0607. Data consistent with literature.[142]

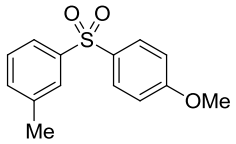
Methyl(4-(*m*-tolylsulfonyl)phenyl)sulfane (84d)



The general procedure **E** was followed with the use 4-bromothioanisole (71 mg, 0.35 mmol). Flash column chromatography (10–35% Et_2O in petrol) afforded the *diaryl sulfone* **84d** as a yellow crystalline solid (82 mg, 84%); mp 89–90 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* 8.5, Ar-*H*), 7.74–7.71 (2H, m, Ar-*H*), 7.40–7.33 (2H,

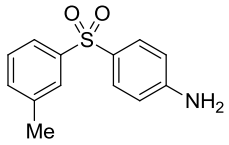
m, Ar-*H*), 7.28 (2H, d, *J* 8.5, Ar-*H*), 2.49 (3H, s, Ar-S*Me*), 2.40 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 141.6, 139.5, 137.3, 133.8, 129.1, 127.9, 127.7, 125.4, 124.6, 21.3, 14.7; IR υ_{max} (neat)/cm^{-1} 1578, 1476, 1395, 1300 (SO_2), 1154 (SO_2), 1106, 1082; HRMS (FI) found *m/z* 278.0436 ([M]$^+$), $C_{14}H_{14}O_2S_2^+$ requires *m/z* 278.0435.

1-((4-Methoxyphenyl)sulfonyl)-3-methylbenzene (84e)



The general procedure **E** was followed with the use 4-iodoanisole (82 mg, 0.35 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *diaryl sulfone* **84e** as a colourless crystalline solid (61 mg, 66%); mp 82–83 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* 9.0, Ar-*H*), 7.74–7.70 (2H, m, Ar-*H*), 7.39–7.31 (2H, m, Ar-*H*), 6.96 (2H, d, *J* 9.0, Ar-*H*), 3.84 (3H, s, Ar-O*Me*), 2.39 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 142.1, 139.4, 133.6, 133.2, 129.8, 129.0, 127.5, 124.4, 114.4, 55.6, 21.3; IR υ_{max} (neat)/cm^{-1} 1593, 1496, 1466, 1292 (SO_2), 1262, 1140 (SO_2), 1100, 1072, 1019; HRMS (FI) found *m/z* 262.0667 ([M]$^+$), $C_{14}H_{14}O_3S^+$ requires *m/z* 262.0664.

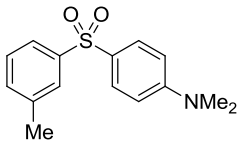
4-(*m*-Tolylsulfonyl)aniline (84f)



The general procedure **E** was followed with the use 4-bromoaniline (60 mg, 0.35 mmol). Flash column chromatography (30–70% Et_2O in petrol) afforded the *diaryl sulfone* **84f** as a pale yellow microcrystalline solid (30 mg, 35%); mp 180–181 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$:DMSO-d_6 3:1) δ 7.05–7.01 (2H, m, Ar-*H*), 6.96 (2H, d, *J* 8.5, Ar-*H*), 6.81–6.72 (2H, m, Ar-*H*), 6.07 (2H, d, *J* 8.5, Ar-*H*), 5.02 (2H, br. s, N*H*$_2$), 1.80 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 3:1) δ 151.8, 141.9, 137.7, 131.7, 128.1, 127.6, 125.5, 125.1, 122.5, 112.1, 19.9; IR υ_{max} (neat)/cm^{-1} 3434, 3379, 3357, 3250,

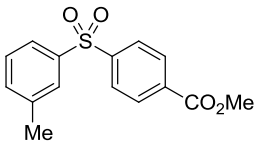
1638, 1588, 1501, 1476, 1313, 1291 (SO_2), 1219, 1141 (SO_2), 1102, 1073; LRMS (ESI) *m/z* 270 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 270.0560 $[M+Na]^+$, $C_{13}H_{13}NO_2SNa^+$ requires *m/z* 270.0559.

_N_,_N_-Dimethyl-4-(_m_-tolylsulfonyl)aniline (84g)



The general procedure **E** was followed with the use 4-bromo-*N*,*N*-dimethylaniline (70 mg, 0.35 mmol). Flash column chromatography (20–60% Et_2O in petrol) afforded the *diaryl sulfone* **84g** as a pale yellow crystalline solid (65 mg, 67%); mp 174–175 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* 9.0, Ar-*H*), 7.72–7.67 (2H, m, Ar-*H*), 7.36–7.27 (2H, m, Ar-*H*), 6.65 (2H, d, *J* 9.0, Ar-*H*), 3.02 (6H, s, N*Me*$_2$), 2.38 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 143.1, 139.1, 133.0, 129.4, 128.8, 127.2, 126.5, 124.0, 111.0, 40.0, 21.3; IR υ_{max} (neat)/cm^{-1} 2914, 1596, 1519, 1443, 1374, 1296 (SO_2), 1229, 1139 (SO_2), 1101; LRMS (ESI) *m/z* 276 (10%, $[M+H]^+$), 298 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 298.0866 $[M+Na]^+$, $C_{15}H_{17}NO_2SNa^+$ requires *m/z* 298.0872.

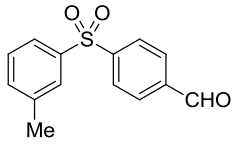
Methyl 4-(_m_-tolylsulfonyl)benzoate (84h)



The general procedure **E** was followed with the use of methyl 4-bromobenzoate (75 mg, 0.35 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *diaryl sulfone* **84h** as a white crystalline solid (82 mg, 81%); mp 112–113 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (2H, d, *J* 8.5, Ar-*H*), 8.01 (2H, d, *J* 8.5, Ar-*H*), 7.77–7.74 (2H, m, Ar-*H*), 7.43–7.37 (2H, m, Ar-*H*), 3.93 (3H, s, CO_2*Me*), 2.40 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 145.6, 140.5, 139.7, 134.4, 134.1, 130.4, 129.3, 128.0, 127.6,

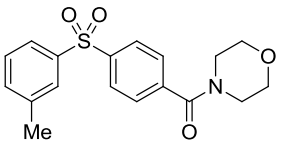
125.0, 52.6, 21.3; IR υ_{max} (neat)/cm^{-1} 3062, 2958, 1725 (C=O), 1437, 1396, 1274 (SO_2), 1155 (SO_2), 1095, 1012; LRMS (ESI) *m/z* 308 (25%, $[M+NH_4]^+$), 313 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 313.0493 $[M+Na]^+$, $C_{15}H_{14}O_4SNa^+$ requires *m/z* 313.0505.

4-(*m*-Tolylsulfonyl)benzaldehyde (84i)



The general procedure **E** was followed with the use 4-bromobenzaldehyde (65 mg, 0.35 mmol). Flash column chromatography (25–40% Et_2O in petrol) afforded the *diaryl sulfone* **84i** as a beige microcrystalline solid (77 mg, 85%); mp 117–118 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 10.08 (1H, s, C*H*O), 8.11 (2H, d, *J* 8.5, Ar-*H*), 8.00 (2H, d, *J* 8.5, Ar-*H*), 7.79–7.75 (2H, m, Ar-*H*), 7.45–7.40 (2H, m, Ar-*H*), 2.42 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 146.8, 140.3, 139.9, 139.0, 134.6, 130.2, 129.4, 128.3, 128.1, 125.1, 21.3; IR υ_{max} (neat)/cm^{-1} 1696 (C=O), 1386, 1320, 1291 (SO_2), 1197, 1146 (SO_2), 1098, 1071; LRMS (ESI) *m/z* 283 (20%, $[M+Na]^+$), 315 (100%, $[M+Na+MeOH]^+$); HRMS (ESI) found *m/z* 283.0400 $[M+Na]^+$, $C_{14}H_{12}O_3SNa^+$ requires *m/z* 283.0399.

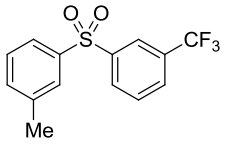
Morpholino(4-(*m*-tolylsulfonyl)phenyl)methanone (84j)



The general procedure **E** was followed with the use (4-bromophenyl)(morpholino)methanone **E** (95 mg, 0.35 mmol). Flash column chromatography (35–75% EtOAc in petrol) afforded the *diaryl sulfone* **84j** as a white powder (85 mg, 70%); mp 191–192 ^oC (DCM); ^1H NMR (500 MHz, DMSO-d_6, 363K) δ 7.99 (2H, d, *J* 8.5, Ar-*H*), 7.80–7.74 (2H, m, Ar-*H*), 7.62 (2H, d, *J* 8.5, Ar-*H*), 7.54–7.50 (2H, m, Ar-*H*), 3.62–3.58 (4H, m, $N(CH_2CH_2)_2O$), 3.45 (4H, br. s, $N(CH_2CH_2)_2O$), 2.41

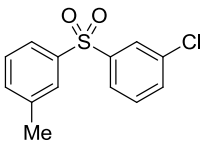
(3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, DMSO-d_6, 298K) δ 167.4, 141.9, 140.6, 140.5, 139.8, 134.6, 129.7, 128.2, 127.64, 127.61, 124.8, 66.0, 65.9, 47.4, 41.9, 20.8; IR υ_{max} (neat)/cm^{-1} 2859, 1628 (C=O), 1440, 1320, 1299 (SO_2), 1279, 1256, 1157 (SO_2), 1146, 1113, 1101, 1071, 1030, 1010; HRMS (FI) found *m/z* 345.1026 ([M]$^+$), $C_{18}H_{19}NO_4S^+$ requires *m/z* 345.1035.

1-Methyl-3-((3-(trifluoromethyl)phenyl)sulfonyl)benzene (84k)



The general procedure **E** was followed with the use 1-bromo-3-(trifluoromethyl)benzene (49 µL, 0.35 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *diaryl sulfone* **84k** as a white microcrystalline solid (82 mg, 78%); mp 74–75 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, br. s, Ar-*H*), 8.13 (1H, br. d, *J* 8.0, Ar-*H*), 7.84–7.75 (3H, m, Ar-*H*), 7.67 (1H, app. t, *J* 8.0, Ar-*H*), 7.46–7.39 (2H, m, Ar-*H*), 2.43 (3H, s, Ar-*Me*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 140.4, 139.9, 134.6, 131.9 (q, J_{C-F} 34), 130.9, 130.1, 129.8 (q, J_{C-F} 3), 129.4, 128.1, 125.0, 124.6 (q, J_{C-F} 4), 123.1 (q, J_{C-F} 273), 21.3; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.8 (s); IR υ_{max} (neat)/cm^{-1} 3067, 1324, 1302 (SO_2), 1180, 1153 (SO_2), 1127, 1105, 1068; HRMS (FI) found *m/z* 300.0442 ([M]$^+$), $C_{14}H_{11}F_3O_2S^+$ requires *m/z* 300.0432.

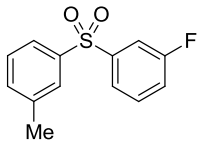
1-Chloro-3-(*m*-tolylsulfonyl)benzene (84l)



The general procedure **E** was followed with the use 1-bromo-3-chlorobenzene (41 µL, 0.35 mmol). Flash column chromatography (5–15% Et_2O in petrol) afforded the titled *diaryl sulfone* **84l** as a 11:1 co-eluting mixture with **76** as a white microcrystalline solid (85 mg, equivalent to 84% of **84l**); mp 84–85 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ

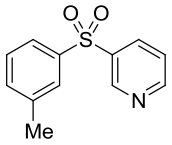
7.94–7.91 (1H, m, Ar-*H*), 7.85–7.81 (1H, m, Ar-*H*), 7.77–7.73 (2H, m, Ar-*H*), 7.55–7.51 (1H, m Ar-*H*), 7.48–7.36 (3H, m, Ar-*H*), 2.42 (3H, s, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.6, 139.8, 135.4, 134.4, 133.2, 130.5, 129.3, 128.0, 127.6, 125.7, 124.9, 21.3; IR υ_{max} (neat)/cm^{-1} 1576, 1457, 1411, 1324, 1288 (SO_2), 1154 (SO_2), 1121, 1071; LRMS (ESI) *m/z* 289 (100%, [M(^{35}Cl)+Na]$^+$), 291 (30%, [M(^{37}Cl)+Na]$^+$); HRMS (ESI) found *m/z* 289.0057 [M(^{35}Cl)+Na]$^+$, $C_{13}H_{11}{}^{35}ClO_2SNa^+$ requires *m/z* 289.0060.

1-Fluoro-3-(*m*-tolylsulfonyl)benzene (84m)



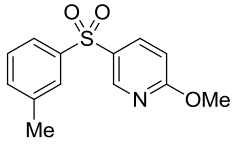
The general procedure **E** was followed with the use 1-bromo-3-fluorobenzene (39 µL, 0.35 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *diaryl sulfone* **84m** as a 7:1 co-eluting mixture with **76** as a white microcrystalline solid (91 mg, equivalent to 91% of **84m**); mp 65–66 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (3H, m, Ar-*H*), 7.64 (1H, app. dt, *J* 8.0, 2.0, Ar-*H*), 7.50 (1H, app. td, *J* 8.0, 5.0, Ar-*H*), 7.44–7.36 (2H, m, Ar-*H*), 7.26 (1H, app. td, *J* 8.0, 2.5, Ar-*H*), 2.42 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J_{C-F} 252), 143.8 (d, J_{C-F} 7), 140.7, 139.7, 134.4, 131.1 (d, J_{C-F} 8), 129.3, 128.0, 124.9, 123.4 (d, J_{C-F} 3), 120.3 (d, J_{C-F} 21), 114.9 (d, J_{C-F} 24), 21.3; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -109.3 (s); IR υ_{max} (neat)/cm^{-1} 3085, 1590, 1472, 1432, 1411, 1326, 1289 (SO_2), 1223, 1148 (SO_2), 1090; LRMS (ESI) *m/z* 273 (100%, [M+Na]$^+$); HRMS (ESI) found *m/z* 273.0352 [M+Na]$^+$, $C_{13}H_{11}FO_2SNa^+$ requires *m/z* 273.0356.

3-(*m*-Tolylsulfonyl)pyridine (84n)



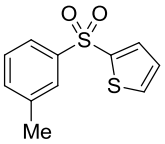
The general procedure **E** was followed with the use of 3-bromopyridine (34 µL, 0.35 mmol). Flash column chromatography (30–50% EtOAc in petrol) afforded the *diaryl sulfone* **84n** as a white microcrystalline solid (35 mg, 43%); mp 84–85 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (1H, s, Ar-*H*), 8.79 (1H, s, Ar-*H*), 8.22 (1H, br. d, *J* 8.0, Ar-*H*), 7.77 (2H, br. s, Ar-*H*), 7.49–7.40 (3H, m, Ar-*H*), 2.42 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.6, 140.5, 139.9, 138.4, 135.2, 134.6, 129.4, 128.0, 124.9, 123.8, 21.3; IR υ_{max} (neat)/cm^{-1} 3051, 1599, 1470, 1417, 1305 (SO_2), 1227, 1157 (SO_2), 1111, 1080, 1021; LRMS (ESI) *m/z* 234 (10%, $[M+H]^+$), 256 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 256.0401 $[M+Na]^+$, $C_{12}H_{11}NO_2SNa^+$ requires *m/z* 256.0403.

2-Methoxy-5-(*m*-tolylsulfonyl)pyridine (84o)



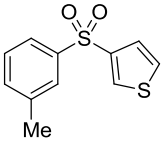
The general procedure **E** was followed with the use 5-bromo-2-methoxypyridine (45 µL, 0.35 mmol). Flash column chromatography (5–15% EtOAc in petrol) afforded the *diaryl sulfone* **84o** as a white crystalline solid (88 mg, 95%); mp 98–99 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, dd, *J* 2.5, 0.5, Ar-*H*), 7.99 (1H, dd, *J* 9.0, 2.5, Ar-*H*), 7.75–7.71 (2H, m, Ar-*H*), 7.42–7.35 (2H, m, Ar-*H*), 6.79 (1H, dd, *J* 9.0, 0.5, Ar-*H*), 3.97 (3H, s, Ar-O*Me*), 2.40 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 148.0, 141.5, 139.7, 137.5, 134.1, 131.0, 129.2, 127.6, 124.5, 111.6, 54.3, 21.3; IR υ_{max} (neat)/cm^{-1} 1588, 1562, 1487, 1443, 1411, 1374, 1287 (SO_2), 1219, 1160 (SO_2), 1130, 1107, 1078, 1007; HRMS (FI) found *m/z* 263.0622 ($[M]^+$), $C_{13}H_{13}NO_3S^+$ requires *m/z* 263.0616.

2-(*m*-Tolylsulfonyl)thiophene (84p)



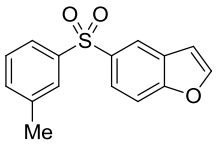
The general procedure **E** was followed with the use of 2-bromothiophene (34 µL, 0.35 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *diaryl sulfone* **84p** as a 10:1 co-eluting mixture with **76** as a beige microcrystalline solid (31 mg, equivalent to 35% of **84p**); mp 145–146 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (2H, m, Ar-*H*), 7.70 (1H, dd, *J* 4.0, 1.5, Ar-*H*), 7.64 (1H, dd, *J* 5.0, 1.5, Ar-*H*), 7.43–7.36 (2H, m, Ar-*H*), 7.09 (1H, dd, *J* 5.0, 4.0, Ar-*H*), 2.42 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.8, 139.6, 134.1, 133.7, 133.2, 129.2, 127.8, 127.6, 124.5, 21.3; IR υ_{max} (neat)/cm^{-1} 3099, 1473, 1346, 1317 (SO_2), 1248, 1227, 1142 (SO_2), 1103, 1085, 1013; LRMS (ESI) *m/z* 261 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 261.0017 $[M+Na]^+$, $C_{11}H_{10}O_2S_2Na^+$ requires *m/z* 261.0014.

3-(*m*-Tolylsulfonyl)thiophene (84q)



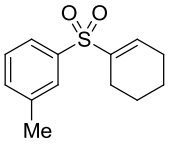
The general procedure **E** was followed with the use of 3-bromothiophene (33 µL, 0.35 mmol). Flash column chromatography (5–25% Et_2O in petrol) afforded the *diaryl sulfone* **84q** as a white microcrystalline solid (52 mg, 62%); mp 96–97 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.09 (1H, m, Ar-*H*), 7.79–7.75 (2H, m, Ar-*H*), 7.44–7.37 (3H, m, Ar-*H*), 7.36–7.32 (1H, m, Ar-*H*), 2.42 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.4, 139.6, 134.1, 131.4, 129.1, 128.3, 127.7, 125.8, 124.6, 21.3; IR υ_{max} (neat)/cm^{-1} 3102, 1492, 1317, 1300 (SO_2), 1208, 1149 (SO_2), 1107, 1082; LRMS (ESI) *m/z* 256 (10%, $[M+NH_4]^+$), 261 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 261.0019 $[M+Na]^+$, $C_{11}H_{10}O_2S_2Na^+$ requires *m/z* 261.0014.

5-(*m*-Tolylsulfonyl)benzofuran (84r)



The general procedure **E** was followed with the use of 5-bromobenzofuran (69 mg, 0.35 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *diaryl sulfone* **84r** as a beige crystalline solid (81 mg, 85%); mp 94–95 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, d, *J* 2.0, Ar-*H*), 7.88 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 7.79–7.75 (2H, m, Ar-*H*), 7.73 (1H, d, *J* 2.0, Ar-*H*), 7.59 (1H, d, *J* 8.5, Ar-*H*), 7.40–7.32 (2H, m, Ar-*H*), 6.87 (1H, dd, *J* 2.0, 1.0, Ar-*H*), 2.39 (3H, s, Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 147.2, 141.9, 139.5, 136.4, 133.8, 129.1, 127.9, 127.7, 124.6, 123.9, 122.0, 112.3, 107.1, 21.3; IR υ_{max} (neat)/cm^{-1} 3093, 1536, 1452, 1437, 1312, 1299 (SO_2), 1263, 1250, 1143 (SO_2), 1118, 1092, 1057, 1017; LRMS (ESI) *m/z* 290 (25%, $[M+NH_4]^+$), 295 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 295.0394 $[M+Na]^+$, $C_{15}H_{12}O_3SNa^+$ requires *m/z* 295.0399.

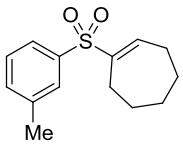
1-(Cyclohex-1-en-1-ylsulfonyl)-3-methylbenzene (84s)



The general procedure **E** was followed with the use of cyclohex-1-en-1-yl 4-methylbenzenesulfonate **F** (88 mg, 0.35 mmol) and K_3PO_4 (111 mg, 0.53 mmol) (in place of Cs_2CO_3). Flash column chromatography (10–20% Et_2O in petrol) afforded the *sulfone* **84s** as a white crystalline solid (53 mg, 64%); mp 76–77 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (2H, m, Ar-*H*), 7.42–7.39 (2H, m, Ar-*H*), 7.08–7.03 (1H, m, C=C*H*), 2.43 (3H, s, Ar-*Me*), 2.31–2.24 (2H, m, CH_2), 2.20–2.14 (2H, m, CH_2), 1.69–1.61 (2H, m, CH_2), 1.61–1.54 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 139.2 (2C), 138.2, 133.9, 128.9, 128.2, 125.2, 25.4, 22.8, 21.8, 21.3, 20.8; IR υ_{max} (neat)/cm^{-1} 2946, 1643, 1473, 1417, 1289 (SO_2), 1143 (SO_2), 1086, 1049; LRMS (ESI) *m/z* 237

(35%, $[M+H]^+$), 254 (100%, $[M+NH_4]^+$), 259 (90%, $[M+Na]^+$), 495 (25%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 259.0764 $[M+Na]^+$, $C_{13}H_{16}O_2SNa^+$ requires *m/z* 259.0763.

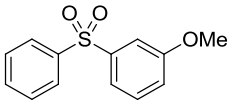
1-(Cyclohept-1-en-1-ylsulfonyl)-3-methylbenzene (84t)



The general procedure **E** was followed with the use of cyclohept-1-en-1-yl 4-methylbenzenesulfonate **G** (93 mg, 0.35 mmol) and K_3PO_4 (111 mg, 0.53 mmol) (in place of Cs_2CO_3). Flash column chromatography (10–20% Et_2O in petrol) afforded the titled *sulfone* **84t** as a white crystalline solid (55 mg, 63%); mp 65–66 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (2H, m, Ar-*H*), 7.43–7.37 (2H, m, Ar-*H*), 7.29 (1H, t,

J 6.5, C=C*H*), 2.43 (3H, s, Ar-*Me*), 2.40–2.34 (4H, m, 2 × CH_2), 1.76–1.68 (2H, m, CH_2), 1.59–1.52 (2H, m, CH_2), 1.45–1.37 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 142.8, 139.4, 132.2, 133.8, 128.9, 128.2, 125.1, 31.2, 28.5, 27.6, 26.1, 25.4, 21.3; IR υ_{max} (neat)/cm^{-1} 2934, 2850, 1644, 1478, 1447, 1411, 1362, 1292 (SO_2), 1218, 1150 (SO_2), 1133, 1083; LRMS (ESI) *m/z* 251 (80%, $[M+H]^+$), 268 (100%, $[M+NH_4]^+$), 273 (45%, $[M+Na]^+$), 523 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 273.0916 $[M+Na]^+$, $C_{14}H_{18}O_2SNa^+$ requires *m/z* 273.0920.

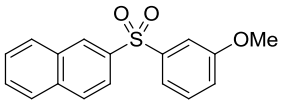
1-Methoxy-3-(phenylsulfonyl)benzene (85a)



The general procedure **E** was followed with the use of phenyl lithium (1.68 M solution in DBE, 290 µL, 0.49 mmol) and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (20–35% Et_2O in petrol) afforded the *diaryl sulfone* **85a** as a colourless crystalline solid (75 mg, 86%); mp 90–91 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ

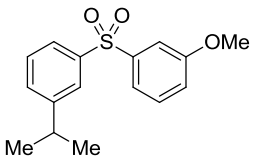
7.97–7.93 (2H, m, Ar-*H*), 7.60–7.38 (6H, m, Ar-*H*), 7.08 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 3.84 (3H, s, Ar-O*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 142.6, 141.5, 133.2, 130.3, 129.2, 127.6, 119.9, 119.5, 112.2, 55.6; IR υ_{max} (neat)/cm^{-1} 1597, 1472, 1448, 1421, 1361, 1301 (SO_2), 1246, 1149 (SO_2), 1099, 1069, 1026; HRMS (FI) found *m/z* 248.0502 ($[M]^+$), $C_{13}H_{12}O_3S^+$ requires *m/z* 248.0507. Data consistent with the literature.[175]

2-((3-Methoxyphenyl)sulfonyl)naphthalene (85b)



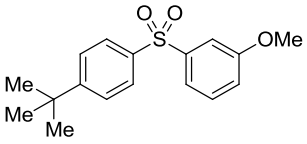
The general procedure **E** was followed with the use of 2-naphthyllithium (0.74 M solution in heptane/DBE, 0.66 mL, 0.49 mmol), and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (15–30% Et_2O in petrol) afforded the *diaryl sulfone* **85b** as a white crystalline solid (70 mg, 67%); mp 81–82 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, s, Ar-*H*), 7.99 (1H, d, *J* 8.0, Ar-*H*), 7.94 (1H, d, *J* 8.5, Ar-*H*), 7.90–7.85 (2H, m, Ar-*H*), 7.67–7.56 (3H, m, Ar-*H*), 7.52 (1H, app. t, *J* 2.0, Ar-*H*), 7.41 (1H, app. t, *J* 8.0, Ar-*H*), 7.07 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 3.85 (3H, s, Ar-O*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 142.7, 138.3, 135.0, 132.2, 130.4, 129.6, 129.4, 129.1, 129.0, 127.9, 127.6, 122.6, 120.0, 119.5, 112.3, 55.7; IR υ_{max} (neat)/cm^{-1} 1578, 1477, 1425, 1315, 1282 (SO_2), 1239, 1151 (SO_2), 1126, 1079, 1036; LRMS (ESI) *m/z* 299 (55%, $[M+H]^+$), 316 (20%, $[M+NH_4]^+$), 321 (25%, $[M+Na]^+$), 619 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 321.0542 $[M+Na]^+$, $C_{17}H_{14}O_3SNa^+$ requires *m/z* 321.0556.

1-*iso*-Propyl-3-((3-methoxyphenyl)sulfonyl)benzene (85c)



The general procedure **E** was followed with the use of 3-*iso*propyl-phenyllithium (0.68 M solution in heptane/DBE, 0.72 mL, 0.49 mmol) and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *diaryl sulfone* **85c** as an off-white microcrystalline solid (89 mg, 88%); mp 55–56 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (1H, m, Ar-*H*), 7.76–7.71(1H, m, Ar-*H*), 7.52 (1H, dt, *J* 7.5, 1.5, Ar-*H*), 7.47–7.38 (4H, m, Ar-*H*), 7.08 (1H, ddd, *J* 8.0, 2.5, 1.0, Ar-*H*), 3.85 (3H, s, Ar-O*Me*), 2.98 (1H, hept., *J* 7.0, Me_2CHAr), 1.26 (6H, d, *J* 7.0, Me_2CHAr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.4, 142.9, 141.3, 131.4, 130.3, 129.2, 125.5, 125.2, 119.8, 119.4, 112.2, 55.6, 34.1, 23.7; IR υ_{max} (neat)/cm^{-1} 2963, 1597, 1477, 1432, 1302 (SO_2), 1286, 1240, 1154 (SO_2), 1099, 1037; LRMS (ESI) *m/z* 291 (60%, $[M+H]^+$), 308 (100%, $[M+NH_4]^+$), 313 (30%, $[M+Na]^+$); HRMS (ESI) found *m/z* 313.0860 $[M+Na]^+$, $C_{16}H_{18}O_3SNa^+$ requires *m/z* 313.0869.

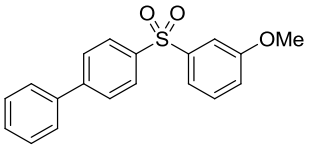
1-((4-(*tert*-Butyl)phenyl)sulfonyl)-3-methoxybenzene (85d)



The general procedure **E** was followed with the use of 4-*tert*-butyl-phenyllithium (0.76 M solution in heptane/DBE, 0.65 mL, 0.49 mmol) and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *diaryl sulfone* **85d** as a white crystalline solid (95 mg, 89%); mp 109–110 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* 8.5, Ar-*H*), 7.54–7.49 (3H, m, Ar-*H*), 7.46 (1H, app. t, *J* 2.0, Ar-*H*), 7.40 (1H, app. t, *J* 8.0, Ar-*H*), 7.07 (1H, ddd, *J* 8.0, 2.5, 1.0, Ar-*H*), 3.84 (3H, s, Ar-O*Me*), 1.31 (9H, s, Ar-C*(Me)$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.0, 143.0,

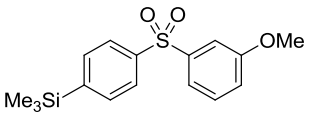
138.4, 130.3, 127.5, 126.3, 119.8, 119.3, 112.2, 55.6, 35.1, 31.0; IR υ_{max} (neat)/cm^{-1} 2970, 1593, 1480, 1285 (SO_2), 1241, 1152 (SO_2), 1112, 1093, 1037; LRMS (ESI) *m/z* 305 (85%, $[M+H]^+$), 322 (100%, $[M+NH_4]^+$), 327 (25%, $[M+Na]^+$); HRMS (ESI) found *m/z* 327.1017 $[M+Na]^+$, $C_{17}H_{20}O_3SNa^+$ requires *m/z* 327.1025.

4-((3-Methoxyphenyl)sulfonyl)-1,1'-biphenyl (85e)



The general procedure **E** was followed with the use of 4-biphenyllithium (0.67 M solution in heptane/DBE, 0.73 mL, 0.49 mmol) and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (20–30% Et_2O in petrol) afforded the *diaryl sulfone* **85e** as a white crystalline solid (80 mg, 70%); mp 123–124 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* 8.5, Ar-*H*), 7.71 (2H, d, *J* 8.5, Ar-*H*), 7.59–7.55 (3H, m, Ar-*H*), 7.51–7.39 (5H, m, Ar-*H*), 7.10 (1H, ddd, *J* 8.0, 2.5, 0.5, Ar-*H*), 3.86 (3H, s, Ar-O*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 146.1, 142.8, 140.0, 139.1, 130.4, 129.0, 128.5, 128.1, 127.9, 127.3, 119.9, 119.5, 112.2, 55.7; IR υ_{max} (neat)/cm^{-1} 1592, 1478, 1429, 1396, 1305, 1291 (SO_2), 1255, 1242, 1148 (SO_2), 1102, 1040; HRMS (FI) found *m/z* 324.0826 ($[M]^+$), $C_{19}H_{16}O_3S^+$ requires *m/z* 324.0820.

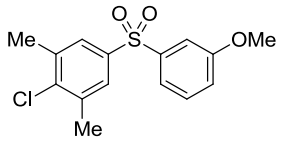
(4-((3-Methoxyphenyl)sulfonyl)phenyl)trimethylsilane (85f)



The general procedure **E** was followed with the use of (4-(trimethylsilyl)phenyl)lithium (from (4-bromophenyl)trimethylsilane **I**) (0.71 M solution in heptane/DBE, 0.69 mL, 0.49 mmol), and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (15–30% Et_2O in petrol) afforded the *diaryl sulfone* **85f** as a white crystalline solid (84 mg, 75%); mp 92–93 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* 8.5,

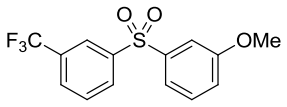
Ar-*H*), 7.65 (2H, d, *J* 8.5, Ar-*H*), 7.53 (1H, app. dq, *J* 8.0, 1.0, Ar-*H*), 7.46 (1H, app. t, *J* 2.0, Ar-*H*), 7.40 (1H, app. t, *J* 8.0, Ar-*H*), 7.08 (1H, ddd, *J* 8.5, 2.5, 1.0, Ar-*H*), 3.85 (3H, s, Ar-O*Me*), 0.28 (9H, s, Si*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 147.7, 142.8, 141.6, 134.1, 130.3, 126.4, 119.9, 119.5, 112.2, 55.7, -1.4; IR υ_{max} (neat)/cm^{-1} 2951, 1598, 1581, 1479, 1434, 1320, 1287 (SO_2), 1243, 1149 (SO_2), 1107, 1042; LRMS (ESI) *m/z* 321 (100%, $[M+H]^+$), 338 (50%, $[M+NH_4]^+$), 343 (25%, $[M+Na]^+$), 663 (20%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 343.0789 $[M+Na]^+$, $C_{16}H_{20}O_3SSiNa^+$ requires *m/z* 343.0795.

2-Chloro-5-((3-methoxyphenyl)sulfonyl)-1,3-dimethylbenzene (85g)



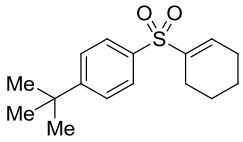
The general procedure **E** was followed with the use of (4-chloro-3,5-dimethylphenyl)lithium (0.71 M solution in heptane/DBE, 0.69 mL, 0.49 mmol), and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (15–25% Et_2O in petrol) afforded the *diaryl sulfone* **85g** as a white crystalline solid (101 mg, 93%); mp 124–125 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (2H, s, Ar-*H*), 7.50 (1H, app. dt, *J* 8.0, 2.5, Ar-*H*), 7.45–7.39 (2H, m, Ar-*H*), 7.09 (1H, ddd, *J* 8.0, 2.5, 1.0, Ar-*H*), 3.86 (3H, s, Ar-O*Me*), 2.42 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 142.6, 140.3, 138.8, 137.9, 130.4, 127.1, 119.8, 119.4, 112.3, 55.7, 20.9; IR υ_{max} (neat)/cm^{-1} 3075, 1597, 1481, 1418, 1307 (SO_2), 1285, 1253, 1152 (SO_2), 1120, 1090, 1034; LRMS (ESI) *m/z* 311 (100%, $[M(^{35}Cl)+H]^+$), 313 (35%, $[M(^{37}Cl)+H]^+$), 328 (35%, $[M(^{35}Cl)+NH_4]^+$), 333 (60%, $[M(^{35}Cl)+Na]^+$), 643 (30%, $[2M(^{35}Cl,^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 333.0323 $[M(^{35}Cl)+Na]^+$, $C_{15}H_{15}{}^{35}ClO_3SNa^+$ requires *m/z* 333.0323.

1-Methoxy-3-((3-(trifluoromethyl)phenyl)sulfonyl)benzene (85h)



The general procedure **E** was followed with the use of (3-(trifluoromethyl)phenyl)lithium (0.85 M solution in heptane/DBE, 0.58 mL, 0.49 mmol), and 3-bromoanisole (45 µL, 0.35 mmol). Flash column chromatography (15–30% Et_2O in petrol) afforded the *diaryl sulfone* **85h** as a white crystalline solid (102 mg, 92%); mp 72–73 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s, Ar-*H*), 8.13 (1H, d, *J* 8.0, Ar-*H*), 7.83 (1H, d, *J* 8.0, Ar-*H*), 7.67 (1H, app. t, *J* 8.0, Ar-*H*), 7.56–7.52 (1H, m, Ar-*H*), 7.48–7.43 (2H, m, Ar-*H*), 7.13 (1H, ddd, *J* 8.5, 2.5, 1.0, Ar-*H*), 3.87 (3H, s, Ar-O*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 142.9, 141.7, 131.9 (q, J_{C-F} 34), 130.9, 130.7, 130.1, 129.9 (q, J_{C-F} 3), 124.6 (q, J_{C-F} 4), 123.0 (q, J_{C-F} 273), 120.00, 119.96, 112.4, 55.7; ^{19}F {^1H} NMR (376 MHz, $CDCl_3$) δ -62.8 (s); IR υ_{max} (neat)/cm^{-1} 1599, 1480, 1419, 1324, 1301 (SO_2), 1252, 1132 (SO_2), 1105, 1070, 1028; LRMS (ESI) *m/z* 317 (30%, $[M+H]^+$), 334 (90%, $[M+NH_4]^+$), 339 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 339.0267 $[M+Na]^+$, $C_{14}H_{11}F_3O_3SNa^+$ requires *m/z* 339.0273.

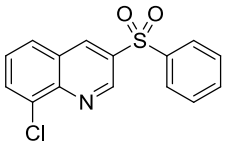
1-(*tert*-Butyl)-4-(cyclohex-1-en-1-ylsulfonyl)benzene (85i)



The general procedure **E** was followed with the use of 4-*tert*-butyl-phenyllithium (0.70 M solution in heptane/DBE, 0.70 mL, 0.49 mmol), cyclohex-1-en-1-yl 4-methylbenzenesulfonate **F** (88 mg, 0.35 mmol) and K_3PO_4 (111 mg, 0.53 mmol) (in place of Cs_2CO_3). Flash column chromatography (5–15% Et_2O in petrol) afforded the *sulfone* **85i** as a white crystalline solid (58 mg, 60%); mp 114–115 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* 8.5, Ar-*H*), 7.53 (2H, d, *J* 8.5, Ar-*H*), 7.05 (1H, app. hept., *J* 1.5, C=C*H*), 2.30–2.24 (2H, m, CH_2), 2.22–2.16 (2H, m, CH_2), 1.69–1.62 (2H, m,

C*H*$_2$), 1.61–1.54 (2H, m, C*H*$_2$), 1.35 (9H, s, Ar-C*(Me)*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 140.0, 137.9, 136.4, 127.8, 126.0, 35.2, 31.1, 25.4, 22.8, 21.8, 20.8; IR υ_{max} (neat)/cm^{-1} 2957, 1644 (C=C), 1592, 1401, 1364, 1307, 1288 (SO_2), 1150 (SO_2), 1110, 1087; LRMS (ESI) *m/z* 279 (85%, $[M+H]^+$), 296 (20%, $[M+NH_4]^+$), 301 (25%, $[M+Na]^+$), 579 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 301.1230 $[M+Na]^+$, $C_{16}H_{22}O_2SNa^+$ requires *m/z* 301.1233.

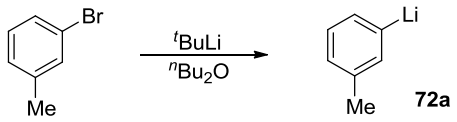
8-Chloro-3-(phenylsulfonyl)quinoline (87)



The general procedure **E** was followed with the use of phenyl lithium (1.93 M solution in DBE, 255 µL, 0.49 mmol) and 8-chloro-3-iodoquinoline **88** (101 mg, 0.35 mmol). Flash column chromatography (0–40% acetone in petrol) afforded the *diaryl sulfone* **87** as an off-white crystalline solid (74 mg, 70%); mp 226–227 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (1H, d, *J* 2.0, Ar-*H*), 8.86 (1H, d, *J* 2.0, Ar-*H*), 8.06–8.02 (2H, m, Ar-*H*), 8.00 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.92 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.62 (2H, app. t, *J* 7.5, Ar-*H*), 7.58–7.53 (2H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.5, 140.6, 137.2, 135.8, 134.1, 134.0, 132.7, 129.7, 128.4, 128.2, 127.9, 127.8; IR υ_{max} (neat)/cm^{-1} 1587, 1482, 1444, 1360, 1326, 1309 (SO_2), 1152 (SO_2), 1097, 1075; LRMS (ESI) *m/z* 304 (100%, $[M(^{35}Cl)+H]^+$), 306 (30%, $[M(^{37}Cl)+H]^+$), 326 (40%, $[M(^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 326.0000 $[M(^{35}Cl)+Na]^+$, $C_{15}H_{10}{}^{35}ClNO_2SNa^+$ requires *m/z* 326.0013.

6.3.2 Starting Materials and Other Reactions

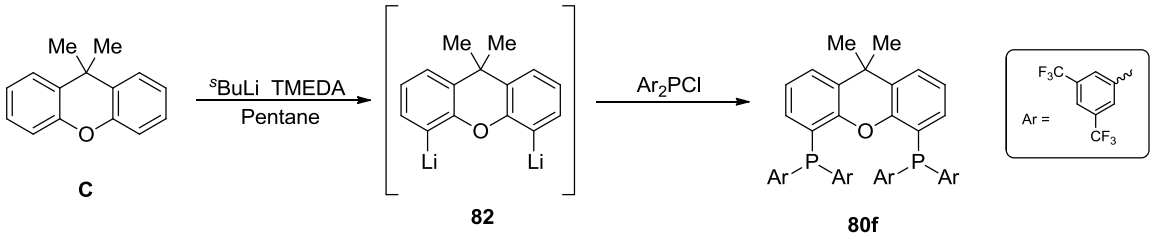
Preparation of aryl lithium solutions, exemplified by the formation of *m*-tolyl lithium solution (72a)



A stirred solution of 3-bromotoluene (3.5 mL, 28.9 mmol) in DBE (5 mL) in a 100 mL two-necked round-bottom flask was cooled to -10 ^{o}C and ^{t}BuLi solution in heptane (27.5 mL, titrated to 2.10 M, 57.7 mmol) was added dropwise *via* syringe pump (0.25 mL/min) maintaining the external temperature between 0 and -10 ^{o}C. At the end of the addition the cooling bath was removed and the resultant suspension warmed to room temperature and stirred for a further 1 hr. The reaction mixture was filtered through a Schlenk-sinter into a 100 mL round-bottom Schlenk-flask and the filtrate stored in the freezer (-25 ^{o}C) thus under N_2 as a solution of *m*-tolyl lithium **72a** in heptane/DBE.

All other aryl lithiums were prepared using the same procedure but on a reduced scale of aryl bromide (7 mmol), DBE (3 mL) and ^{t}BuLi in heptane (14 mmol) – the resulting solution being stored in a 25 mL round-bottom Schlenk-flask. All aryl lithiums were titrated against a 1.0 M solution of 2-propanol in toluene with 0.2% 1,10-phenanthroline as the indicator prior to use.

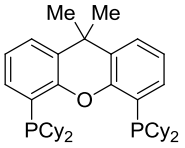
General procedure F for the formation of XantPhos-type ligands, exemplified by the formation of (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphine) (80f)



Method adapted from procedure documented by Beletskaya *et al.*[187,188] ^{s}BuLi solution in cyclohexane/hexane (titrated to 1.45 M, 4.7 mL, 6.9 mmol) was added dropwise to a solution of 9,9-dimethylxanthene **C** (600 mg, 2.85 mmol) and TMEDA (1.0 mL, 6.9 mmol) in anhydrous pentane (15 mL) in a 50 mL two-necked flask fitted with a condenser cooled to 0 ^{o}C. The resultant orange solution was heated at reflux for 90 mins. The flask was cooled to -78 ^{o}C and a solution of bis(3,5-bis(trifluoromethyl)phenyl)chlorophosphine (3.37 g, 6.90 mmol) in THF (3 mL) was added dropwise *via* syringe pump (0.2 mL/min). The resultant suspension was stirred at the same temperature for 10 mins then warmed to room temperature and stirred for a further 16 hrs. The reaction mixture was diluted with EtOAc (60 mL) and washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a thick yellow oil. Purification by flash column chromatography (0–20% EtOAc in petrol) gave a partially solidified yellow gum. This was dissolved in $CHCl_3$ (3 mL), filtered and MeOH (15 mL) added dropwise with stirring. An off-white solid precipitated and was collected by filtration. The solid was re-precipitated by the same method affording the ligand **80f** as a white powder (1.95 g, 61%); mp 144–145 ^{o}C ($CHCl_3$/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (4H, s, Ar-*H*), 7.62 (8H, s, Ar-*H*), 7.58 (2H, dd, *J* 7.5,1.5, Ar-*H*), 7.14 (2H, t, *J* 7.5, Ar-*H*), 6.41 (2H, app. dq, *J* 7.5, 1.5, Ar-*H*), 1.68 (6H, s, 2 × *Me*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (t, *J* 9.5), 138.9–138.4 (m), 133.8–133.1 (m), 132.1 (qt, *J* 33.5, 3.0), 131.1, 131.0, 128.2, 125.0, 123.4 (br.), 122.9 (q, *J* 273), 121.3–121.1 (m), 34.7, 31.0; ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ -14.6

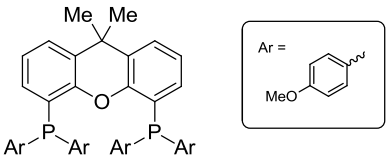
(s); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -63.1 (s); IR υ_{max} (neat)/cm^{-1} 1405, 1354, 1277, 1232, 1119; HRMS (EI) found *m/z* 1107.0573 (100%, $[M\text{-}Me]^+$), 1122.0767 (40%, $[M]^+$), $C_{47}H_{24}F_{24}OP_2^+$ (M^+) requires *m/z* 1122.0919. Elemental analysis found 50.38% C, 2.28% H; $C_{47}H_{24}F_{24}OP_2$ requires 50.29% C, 2.15% H. Data consistent with the literature.[187,188]

(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(dicyclohexylphosphine) (80b)



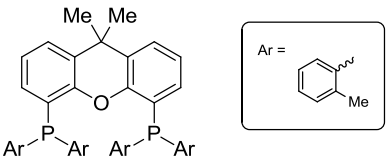
Method adapted from procedure documented by Kuwano and Kusano.[189] The general procedure **F** was followed with the use of ^{s}BuLi (2.4 mL), 9,9-dimethylxanthene (300 mg, 1.43 mmol), TMEDA (0.47 mL) and pentane (8 mL). Chlorodicyclohexylphosphine (0.76 mL, 3.43 mmol) in pentane (3 mL) was added dropwise at 0 ^{o}C and the resultant suspension heated at reflux for 16 hrs. No purification by flash column chromatography was necessary. The crude solid after work-up was precipitated from $CHCl_3$/MeOH (as per the general procedure) affording the ligand **80b** as a white powder (150 mg, 17%); mp 237–238 ^{o}C ($CHCl_3$/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.32 (4H, m, Ar-*H*), 7.06 (2H, app. t, *J* 7.5, Ar-*H*), 2.09–2.01 (4H, m, C*H*P),1.82–1.55 (23H, m, *Cy* (incl. 2 x *Me*)), 1.40–1.05 (23H, m, *Cy*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.0, 126.3, 123.9, 123.7, 122.3, 122.2, 34.5, 31.9, 30.8 (br.), 29.9, 27.0 (d, *J* 7.5), 26.5; ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ -21.2 (s); IR υ_{max} (neat)/cm^{-1} 2918, 2848, 1444, 1394, 1216, 1195, 1108; LRMS (ESI) *m/z* 603 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 603.3871 $[M+H]^+$, $C_{39}H_{56}OP_2$ requires *m/z* 603.3879. Data consistent with the literature.[189]

(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(bis(4-methoxyphenyl)phosphine) (80c)



Method adapted from procedure documented by Beletskaya *et al.*[187] The general procedure **F** was followed with the use of ^{s}BuLi (2.4 mL), 9,9-dimethylxanthene (300 mg, 1.43 mmol), TMEDA (0.47 mL), pentane (8 mL). Chlorobis(4-methoxyphenyl)phosphine (1.00 g, 3.43 mmol) in THF (3 mL) was added dropwise at -20 ^{o}C and the resultant suspension stirred at room temperature for 16 hrs. Purification by flash column chromatography (25–100% DCM in petrol) gave a white solid which was precipitated from $CHCl_3$/MeOH (as per the general procedure) affording the ligand **80c** as a white powder (300 mg, 30%); mp 212–213 ^{o}C ($CHCl_3$/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* 7.5, Ar-*H*), 7.14–7.07 (8H, m, Ar-*H*), 7.00–6.94 (2H, m, Ar-*H*), 6.76 (8H, d, *J* 8.5, Ar-*H*), 6.58 (2H, s, Ar-*H*), 3.79 (12H, s, 4 × O*Me*), 1.65 (6H, s, 2 × *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 152.4 (t, *J* 9.5), 135.1 (t, *J* 11.0), 131.8, 129.8, 128.5, 126.7 (t, *J* 9.5), 126.0, 123.2, 113.7, 54.9, 34.4, 31.7; ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ -19.9 (s); IR υ_{max} (neat)/cm^{-1} 1593, 1496, 1402, 1284, 1237, 1175, 1094, 1028; HRMS (EI) found *m/z* 683.2049 (30%, $[M\text{-}Me]^+$), 698.2084 (100%, $[M]^+$), $C_{47}H_{24}F_{24}OP_2$ (M^+) requires *m/z* 698.2351. Data consistent with the literature.[187]

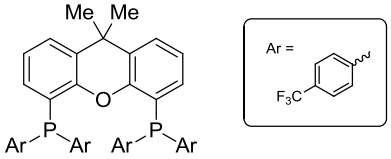
(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(di-*o*-tolylphosphine) (80d)



Method adapted from procedure documented by Hartwig *et al.*[186] The general procedure **F** was followed with the use of ^{s}BuLi (2.4 mL), 9,9-dimethylxanthene (300 mg,

1.43 mmol), TMEDA (0.47 mL), pentane (8 mL). Chlorodi-*o*-tolylphosphine (850 mg, 3.43 mmol) in THF (3 mL) was added dropwise at 0 ^{o}C and the resultant suspension stirred at room temperature for 16 hrs. Purification by flash column chromatography (0–20% EtOAc in petrol) gave a white solid which was precipitated from $CHCl_3$/MeOH (as per the general procedure) affording the ligand **80d** as a white powder (550 mg, 61%); mp 227–228 ^{o}C ($CHCl_3$/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* 7.5, Ar-*H*), 7.19–7.10 (8H, m, Ar-*H*), 7.00–6.92 (6H, m, Ar-*H*), 6.68 (4H, d, *J* 7.5, Ar-*H*), 6.48 (2H, d, *J* 7.5, Ar-*H*), 2.27 (12H, s, 4 × Ar-*Me*),1.69 (6H, s, 2 × *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (t, *J* 10), 142.5 (t, *J* 13.5), 135.6 (t, 6.5), 132.7, 132.4, 129.8, 129.7 (t, *J* 2.5), 128.1, 126.3, 125.7, 124.2 (t, *J* 9.0), 123.4, 34.5, 31.9, 21.2 (t, *J* 11.5); ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ -32.5 (s); IR υ_{max} (neat)/cm^{-1} 1404, 1378, 1238, 1202, 1131; LRMS (ESI) *m/z* 635 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 635.2625 $[M+H]^+$, $C_{43}H_{40}OP_2$ requires *m/z* 635.2627. Data consistent with the literature.[186]

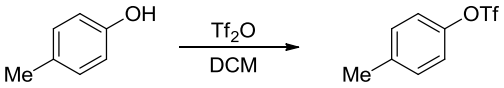
(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(bis(4-(trifluoromethyl)phenyl)phosphine (80e)



The general procedure **F** was followed with the use of ^{s}BuLi (2.4 mL), 9,9-dimethylxanthene (300 mg, 1.43 mmol), TMEDA (0.47 mL), pentane (8 mL). Chlorobis(4-(trifluoromethyl)phenyl)phosphine (1.00 g, 2.86 mmol) in THF (3 mL) was added dropwise at -78 ^{o}C and the resultant suspension stirred at room temperature for 16 hrs. Purification by flash column chromatography (0–30% EtOAc in petrol) gave a yellow oil which was precipitated from $CHCl_3$/MeOH (as per the general procedure) affording the ligand **80e** as a white powder (210 mg, 21%); mp 172–173 ^{o}C ($CHCl_3$/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.48 (11H, m, Ar-*H*), 7.30–7.23 (7H, m, Ar-*H*), 7.04 (2H, app. t, *J* 7.5, Ar-*H*), 6.48 (2H, d, *J* 7.0, Ar-*H*), 1.69 (6H, s,

2 × *Me*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (t, *J* 10), 141.3 (t, *J* 7.5), 134.0 (t, *J* 10.5), 131.8, 130.8 (q, *J* 33), 130.4, 127.4, 125.1 (q, *J* 3.5), 124.1, 124.0 (q, *J* 272), 123.3 (t, *J* 8.5), 34.6, 31.7; ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ -17.5 (s); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.8 (s); IR υ_{max} (neat)/cm^{-1} 1608, 1407, 1322, 1236, 1166, 1119, 1105, 1059, 1015; HRMS (EI) found *m/z* 835.1169 (60%, $[M\text{-}Me]^+$), 850.1389 (100%, $[M]^+$), $C_{47}H_{24}F_{24}OP_2$ (M^+) requires *m/z* 850.1424.

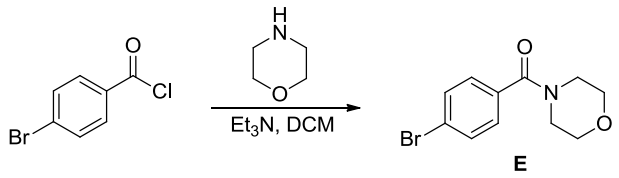
p-Tolyl trifluoromethanesulfonate (D)



D

A solution of triflic anhydride (2.00 mL, 12.0 mmol) in anhydrous DCM (5 mL) was added dropwise to a solution of pyridine (1.62 mL, 20.0 mmol) and *p*-cresol (1.08 g, 10.0 mmol) in anhydrous DCM (10 mL) at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for 1 hr. The solution was diluted with DCM (15 ml) and quenched with aq. 1M HCl (15 mL). The layers were separated and the organic layer was washed with aq. $NaHCO_3$ (2 × 30 mL) and brine (1 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation affording the titled aryl triflate **D** as a colourless liquid (2.04 g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* 8.5, Ar-*H*), 7.16 (2H, d, *J* 8.5, Ar-*H*), 2.39 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 138.5, 130.7, 121.0, 118.8 (q, *J* 320), 20.9; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -72.9 (s); LRMS (ESI) *m/z* 263 (100%, $[M+Na]^+$). Data consistent with the literature.[232]

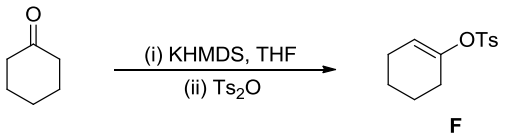
(4-Bromophenyl)(morpholino)methanone (E)



E

To a solution of morpholine (0.47 mL, 5.5 mmol) and Et_3N (0.76 mL, 5.5 mmol) in DCM (10 mL) cooled to 0 ^oC was added 4-bromobenzoyl chloride (1.0 g, 4.6 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 24 hrs until the acid chloride was consumed by TLC. The reaction was diluted with DCM (15 mL) and quenched with water (25 mL). The layers were separated and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were washed with aq. $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (35–50% EtOAc in petrol) afforded the titled amide **E** as a pale yellow oil (0.57 g, 93%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* 8.5, Ar-*H*), 7.29 (2H, d, *J* 8.5, Ar-*H*), 3.98–3.27 (8H, m, N(CH_2CH_2)$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 134.0, 131.8, 128.8, 124.2, 66.8, 48.1, 42.6; LRMS (ESI^+) found *m/z* 270 (10%, $[M(^{79}Br)+H]^+$), 272 (10%, $[M(^{81}Br)+H]^+$), 292 (100%, $[M(^{79}Br)+Na]^+$), 294 (90%, $[M(^{81}Br)+Na]^+$). Data consistent with the literature.[233]

Cyclohex-1-en-1-yl 4-methylbenzenesulfonate (F)

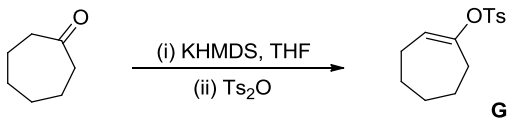


F

Method adapted from procedure documented by Reeves *et al.*[168] To a stirred solution of cyclohexanone (0.73 mL, 7.0 mmol) in anhydrous THF (20 mL) cooled to -15 ^oC in a 50 mL two-necked round-bottom flask, was added KHMDS (15% w/w solution in toluene, 14 mL, 9.1 mmol). The reaction mixture was stirred for 1 hr at the same temperature before tosic anhydride (2.97g, 9.1 mmol) was added. The resultant suspension was stirred for a further 30 mins at -15 ^oC before being warmed to room

temperature and stirred overnight. The reaction was quenched with aq. $NaHCO_3$ (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10–30% EtOAc in petrol) afforded the titled alkenyl tosylate **F** as a pale yellow oil (1.25 g, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* 8.0, Ar-*H*), 7.33 (2H, d, *J* 8.0, Ar-*H*), 5.38–5.32 (1H, m, C*H*=C(OTs)), 2.46 (3H, s, Ar-*Me*), 2.14–1.96 (4H, m, 2 × CH_2), 1.71–1.57 (2H, m, CH_2), 1.56–1.42 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.8, 133.5, 129.5, 128.2, 117.1, 27.5, 23.8, 22.6, 21.6, 21.2; LRMS (ESI) *m/z* 253 (30%, $[M+H]^+$), 270 (100%, $[M+NH_4]^+$), 275 (95%, $[M+Na]^+$). Data consistent with the literature.[168]

Cyclohept-1-en-1-yl 4-methylbenzenesulfonate (G)

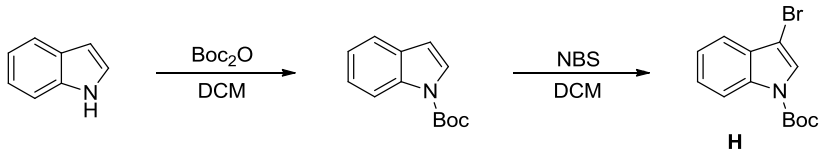


G

Method adapted from procedure documented by Reeves *et al.*[168] To a stirred solution of cycloheptanone (0.83 mL, 7.0 mmol) in anhydrous THF (20 mL) cooled to -15 ^{o}C in a 50 mL two-necked round-bottom flask, was added KHMDS (15% w/w solution in toluene, 14 mL, 9.1 mmol). The reaction mixture was stirred for 1 hr at the same temperature before tosic anhydride (2.97g, 9.1 mmol) was added. The resultant suspension was stirred for a further 30 mins at -15 ^{o}C before being warmed to room temperature and stirred overnight. The reaction was quenched with aq. $NaHCO_3$ (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10–30% EtOAc in petrol) afforded the titled alkenyl tosylate **G** as a colourless oil (1.14 g, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* 8.0, Ar-*H*), 7.33 (2H, d, *J* 8.0, Ar-*H*), 5.40 (1H, t, *J* 6.5, C*H*=C(OTs)), 2.45 (3H, s, Ar-*Me*), 2.34–2.29 (2H, m, CH_2), 1.98 (2H, app. q, *J* 6.5, CH_2), 1.67–1.60 (2H, m, CH_2), 1.56–1.46 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 152.3, 144.7, 133.3, 129.5, 128.3, 122.1, 33.2, 30.3, 26.5, 24.9, 24.8, 21.6; LRMS (ESI) *m/z* 267 (70%, $[M+H]^+$), 284 (40%, $[M+NH_4]^+$), 289 (80%, $[M+Na]^+$), 555 (100%, $[2M+Na]^+$). Data consistent with the literature.[168]

tert-Butyl 3-bromo-1H-indole-1-carboxylate (H)



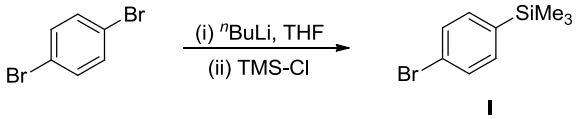
H

Boc_2O (2.42 g, 11.0 mmol) was added portionwise to a solution of indole (1.00 g, 8.5 mmol), DMAP (100 mg, 0.9 mmol) and triethylamine (1.5 mL, 11.0 mmol) in DCM (20 mL) cooled to 0 ^oC in a 100 mL two-necked round-bottom flask. The reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was diluted with DCM (30 mL) and washed with water (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was dissolved in petrol and filtered through a plug of silica using 3:1 Et_2O:petrol as the eluent. The filtrate was concentrated *in vacuo* affording Boc-indole as a white microcrystalline solid (1.80 g, 97%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, d, *J* 7.5, Ar-*H*), 7.61 (1H, d, *J* 3.5, Ar-*H*), 7.57 (1H, d, *J* 7.5, Ar-*H*), 7.32 (1H, app. t, *J* 7.5, Ar-*H*), 7.24 (1H, app. t, *J* 7.5, Ar-*H*), 6.58 (1H, d, *J* 3.5, Ar-*H*), 1.69 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 135.1, 130.5, 125.8, 124.1, 122.6, 120.9, 115.1, 107.2, 83.5, 28.1 HRMS (FI^+) found *m/z* 217.1109 (100%, $[M]^+$), $C_{13}H_{15}NO_2$ requires 217.1103. Data consistent with the literature.[234]

Boc-indole (1.00 g, 4.6 mmol) and NBS (0.90 g, 5.1 mmol) were charged in a 50 mL round-bottom flask, fitted with a condenser and DCM (20mL) added. The reaction mixture was strired at reflux for 2 hrs. The reaction mixture cooled to room temperature, diluted with DCM (30 mL) and quenched with water (30 mL). The layers were separated and the organic layer washed sequentially with 1M aq. NaOH (30 mL) and water

(50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O in petrol) afforded the titled bromoindole **H** as a colourless microcrystalline solid (1.32 g, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, br. d, *J* 7.5, Ar-*H*), 7.67 (1H, s, Ar-*H*), 7.57–7.53 (1H, m, Ar-*H*), 7.42–7.31 (2H, m, Ar-*H*), 1.69 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 134.6, 129.4, 125.4, 124.8, 123.2, 119.5, 115.1, 97.9, 84.3, 28.1; HRMS (FI$^+$) found *m/z* 297.0201 (100%, [M]$^+$), $C_{13}H_{14}{}^{79}BrNO_2$ requires 297.0208. Data consistent with the literature.[235]

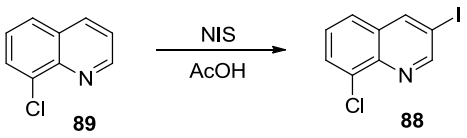
(4-Bromophenyl)Trimethylsilane (I)



I

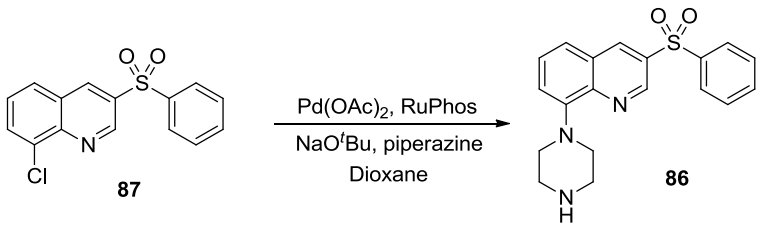
Method adapted from procedure documented by Itami *et al.*[236] To a stirred solution of 1,4-dibromobenzene (3.54 g, 15.0 mmol) in anhydrous Et_2O (30 mL) cooled to -78 ^{o}C in a 100 mL two-necked round-bottom flask was added ^{n}BuLi (1.78 M solution in hexane, 8.5 mL, 15.5 mmol) dropwise over the course of 15 mins. The reaction mixture was stirred at this temperature for 4 hrs. Distilled trimethylsilylchloride (2.3 mL, 18.0 mmol) was then added dropwise over the course of 10 mins. The reaction mixture was stirred at this same temperature for 10 mins before being warmed to room temperature and stirred for a further 2 hrs. The reaction was quenched with water (50 mL), the layers separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by Kugelrohr distillation affording the titled aryl silane **I** as a colourless oil (3.12 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* 8.0, Ar-*H*), 7.40 (2H, d, *J* 8.0, Ar-*H*), 0.28 (9H, s, Si*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 134.9, 130.8, 123.5, -1.2; HRMS (FI$^+$) found *m/z* 227.9977 (100%, [M]$^+$), $C_9H_{13}{}^{79}BrSi$ requires 227.9970. Data consistent with the literature.[237]

8-Chloro-3-iodoquinoline (88)



Method adapted from procedure documented by Gladwin *et al.*[191] *N*-Iodosuccinimide (7.6 g, 34 mmol) was added portionwise to a stirred solution of 8-chloroquinoline **89** (5.0 g, 31 mmol) in acetic acid (35 mL) at 70 ^{o}C. The reaction mixture was stirred at the same temperature for 18 hrs and then cooled to room temperature before being concentrated *in vacuo.* The resultant brown solid was dissolved in DCM (100 mL) and washed sequentially with aq. $Na_2S_2O_3$ (100 mL) and aq. $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised twice from hot EtOAc affording the quinoline **88** as an off-white crystalline solid (3.48 g, 39%); mp 98–99 ^{o}C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (1H, d, *J* 2.0, Ar-*H*), 8.57 (1H, d, *J* 2.0, Ar-*H*), 7.85 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.65 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.49 (1H, app. t, *J* 8.0, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 144.1, 142.7, 133.8, 131.0, 130.2, 127.5, 125.9, 91.0; IR υ_{max} (neat)/cm^{-1} 3029, 1572, 1474, 1354, 1307, 1080; LRMS (ESI) *m/z* 290 (100%, $[M(^{35}Cl)+H]^+$), 292 (100%, $[M(^{37}Cl)+H]^+$); HRMS (ESI) found *m/z* 311.9055 $[M+Na]^+$, $C_9H_5N^{35}ClINa^+$ requires *m/z* 311.9047. Data consistent with the literature.[191]

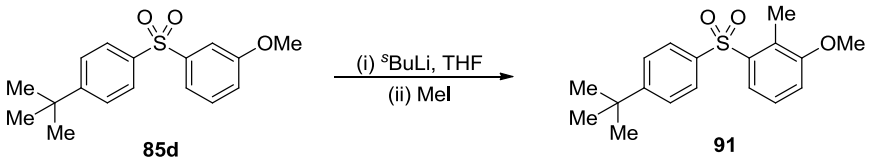
3-(Phenylsulfonyl)-8-(piperazin-1-yl)quinoline, GSK-742457 (86)



A glass reaction tube was charged with 8-chloro-3-(phenylsulfonyl)quinoline **87** (76 mg, 0.25 mmol), sodium *tert*-butoxide (31 mg, 0.33 mmol), piperazine (65 mg, 0.75 mmol), palladium acetate (3.0 mg, 13 μmol) and RuPhos (9.0 mg, 19 μmol). The tube was sealed

with a rubber septum and evacuated and filled with nitrogen four times. 1,4-Dioxane (1 mL) was added through the septum and the reaction was heated at 90 ^{o}C for 16 hrs. The reaction mixture was cooled to room temperature, diluted with DCM (10 mL) and filtered through a Celite® pad, washing the pad with further DCM (5 mL). The filtrate was washed with water (3 × 15 mL) and the combined aqueous layers extracted with DCM (30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100:5:2 DCM:MeOH:35% aq. NH_3) afforded the quinoline **86** as a pale brown microcrystalline solid (60 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (1H, d, *J* 2.5, Ar-*H*), 8.76 (1H, d, *J* 2.5, Ar-*H*), 8.03–7.99 (2H, m, Ar-*H*), 7.60–7.49 (5H, m, Ar-*H*), 7.28–7.25 (1H, m, Ar-*H*), 3.38–3.32 (4H, m, 2 × C*H*$_2$), 3.19 (4H, t, *J* 4.5, 2 × C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 144.8, 143.6, 141.1, 137.2, 134.3, 133.7, 129.5, 128.8, 127.9, 127.8, 122.5, 119.2, 53.2, 46.2; IR υ_{max} (neat)/cm^{-1} 1566, 1447, 1377, 1322 (SO_2), 1246, 1156 (SO_2), 1093, 1023, 908, 761, 722; LRMS (ESI) *m/z* 354 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 354.1263 $[M+H]^+$, $C_{19}H_{20}O_2N_3S^+$ requires *m/z* 354.1271. Data consistent with the literature.[191]

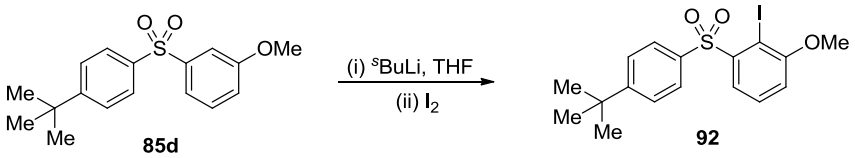
1-((4-(*tert*-Butyl)phenyl)sulfonyl)-3-methoxy-2-methylbenzene (91)



In a glass reaction tube, ^{s}BuLi solution in cyclohexane/hexane (titrated to 1.40 M, 0.37 mL, 0.52 mmol) was added dropwise to a stirred solution of 1-((4-(*tert*-Butyl)phenyl)sulfonyl)-3-methoxybenzene **85d** (122 mg, 0.40 mmol) in anhydrous THF (1.5 mL) cooled to -78 ^{o}C. The resultant solution was stirred for 10 mins at the same temperature before being warmed to 0 ^{o}C and stirred for a further 1 hr at this temperature. The reaction mixture was re-cooled to -78 ^{o}C, MeI (38 µL, 0.60 mmol) added dropwise and stirred for 10 mins at the same temperature before being warmed to

room temperature and stirred for a further 2 hrs. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15–35% Et_2O in petrol) afforded the *sulfone* **91** as a white crystalline solid (90 mg, 71%); mp 158–159 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.78 (2H, d, *J* 8.5, Ar-*H*), 7.49 (2H, d, *J* 8.5, Ar-*H*), 7.35 (1H, app. t, *J* 8.0, Ar-*H*), 7.07 (1H, d, *J* 8.0, Ar-*H*), 3.83 (3H, s, Ar-O*Me*), 2.33 (3H, s, Ar-*Me*), 1.32 (9H, s, Ar-C*(Me)*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.7, 140.3, 138.5, 127.4, 126.9, 126.5, 126.0, 121.0, 114.9, 56.0, 35.1, 31.0, 11.9; IR υ_{max} (neat)/cm^{-1} 2960, 1591, 1468, 1443, 1399, 1304 (SO_2), 1260, 1198, 1146 (SO_2), 1109, 1088, 1043; LRMS (ESI) *m/z* 319 (80%, $[M+H]^+$), 336 (100%, $[M+NH_4]^+$), 341 (100%, $[M+Na]^+$), 659 (50%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 341.1185 $[M+Na]^+$, $C_{18}H_{22}O_3SNa^+$ requires *m/z* 341.1182.

1-((4-(*tert*-Butyl)phenyl)sulfonyl)-2-iodo-3-methoxybenzene (92)



In a glass reaction tube, ^{s}BuLi solution in cyclohexane/hexane (titrated to 1.40 M, 0.37 mL, 0.52 mmol) was added dropwise to a stirred solution of 1-((4-(*tert*-Butyl)phenyl)sulfonyl)-3-methoxybenzene **85d** (122 mg, 0.40 mmol) in anhydrous THF (1.5 mL) cooled to -78 ^oC. The resultant solution was stirred for 10 mins at the same temperature before being warmed to 0 ^oC and stirred for a further 1 hr at this temperature. The reaction mixture was re-cooled to -78 ^oC, a solution of iodine (152 mg, 0.60 mmol) in anhydrous THF (0.5 mL) added dropwise and stirred for 10 mins at the same temperature before being warmed to room temperature and stirred for a further 2 hrs. The reaction was quenched with aq. $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in*

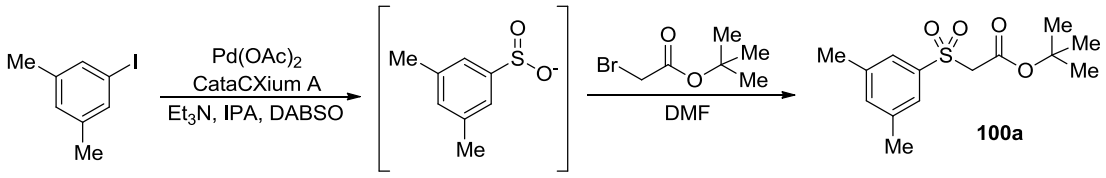
vacuo. Purification by flash column chromatography (15–35% Et_2O in petrol) afforded the *sulfone* **92** as a white crystalline solid (100 mg, 58%); mp 189–190 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.88 (2H, d, *J* 8.5, Ar-*H*), 7.52 (1H, app. t, *J* 8.0, Ar-*H*) with overlapping 7.49 (2H, d, *J* 8.5, Ar-*H*), 7.01 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 3.90 (3H, s, Ar-O*Me*), 1.32 (9H, s, Ar-C*(Me)$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.1, 144.5, 136.4, 129.5, 128.8, 125.7, 123.5, 114.7, 87.0, 57.1, 35.2, 31.0; IR υ_{max} (neat)/cm^{-1} 2961, 1593, 1566, 1464, 1434, 1399, 1306 (SO_2), 1290, 1267, 1187, 1161, 1144 (SO_2), 1107, 1084, 1038, 1010; LRMS (ESI) *m/z* 431 (60%, $[M+H]^+$), 448 (70%, $[M+NH_4]^+$), 453 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 452.9971 $[M+Na]^+$, $C_{17}H_{19}IO_3SNa^+$ requires *m/z* 452.9992.

Diphenylsulfone **71** was analysed relative to a commercial sample.

6.4 Chapter 4 Data

6.4.1 Compounds from Palladium-Catalysed Sulfination

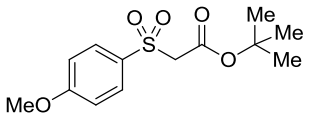
General procedure G for the formation of *β-tert*-butylacetate sulfones exemplified by the preparation of *tert*-butyl 2-((3,5-dimethylphenyl)sulfonyl)acetate (100a)



A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4.0 mg, 15 µmol) and CataCXium A (8.0 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, a solution of *tert*-butyl bromoacetate (89 µL, 0.60 mmol) in anhydrous DMF (0.5 mL) was added dropwise and the resultant solution stirred at the same temperature for 2 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was poured onto water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5–20% Et_2O in petrol) afforded the *sulfone* **100a** as a pale yellow microcrystalline solid (77 mg, 90%); mp 56–57 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, s, Ar-*H*), 7.29 (1H, s, Ar-*H*), 4.01 (2H, s, CH_2), 2.40 (6H, s, 2 × Ar-*Me*), 1.37 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 139.2, 138.6, 135.7, 125.9, 83.4, 62.2, 27.6, 21.2; IR υ_{max} (neat)/cm^{-1} 2978, 1727 (C=O), 1610, 1457, 1371, 1323 (SO_2), 1287, 1133 (SO_2), 1102; LRMS (ESI) *m/z* 307 (60%, $[M+Na]^+$), 591 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 307.0978 $[M+Na]^+$, $C_{14}H_{20}O_4SNa^+$ requires *m/z* 307.0975.

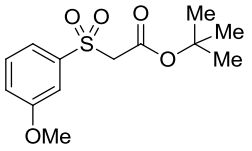
Procedure as follows for large-scale reaction; a 100 mL round-bottom flask was charged with DABSO (1.73 g, 7.2 mmol), palladium(II) acetate (27 mg, 0.12 mmol) and CataCXium A (65 mg, 0.18 mmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (1.7 mL, 12 mmol), triethylamine (5.0 mL, 36 mmol) and anhydrous 2-propanol (30 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, a solution of *tert*-butyl bromoacetate (3.5 mL, 24 mmol) in anhydrous DMF (10 mL) was added dropwise over 20 mins and the resultant solution stirred at the same temperature for 2 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was poured onto water (150 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Automated flash column chromatography (0–20% EtOAc in petrol) afforded the *sulfone* **100a** as a pale yellow oil which crystallised to an off-white microcrystalline solid with standing (3.28 g, 96%).

***tert*-Butyl 2-((4-methoxyphenyl)sulfonyl)acetate (100b)**



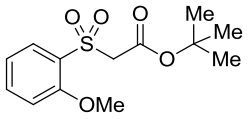
The general procedure **G** was followed with the use of 4-iodoanisole (70 mg, 0.30 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **100b** as a pale yellow oil (75 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* 9.0, Ar-*H*), 7.02 (2H, d, *J* 9.0, Ar-*H*), 4.01 (2H, s, C*H*$_2$), 3.89 (3H, s, O*Me*), 1.39 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.5, 130.8, 130.4, 114.2, 83.4, 62.3, 55.7, 27.7; IR υ_{max} (neat)/cm^{-1} 2980, 1729 (C=O), 1595, 1499, 1370, 1326 (SO_2), 1299, 1259, 1140 (SO_2), 1085, 1022; LRMS (ESI) *m/z* 304 (40%, $[M+NH_4]^+$), 309 (35%, $[M+Na]^+$), 595 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 309.0773 $[M+Na]^+$, $C_{13}H_{18}O_5SNa^+$ requires *m/z* 309.0767.

tert-Butyl 2-((3-methoxyphenyl)sulfonyl)acetate (100c)



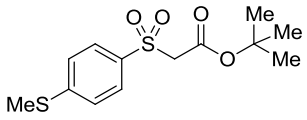
The general procedure **G** was followed with the use of 3-iodoanisole (36 µL, 0.30 mmol). Flash column chromatography (15–40% Et_2O in petrol) afforded the *sulfone* **100c** as a pale yellow oil (74 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.45 (2H, m, Ar-*H*), 7.43 (1H, app. t, *J* 2.0, Ar-*H*), 7.19 (1H, ddd, *J* 8.0, 2.5, 1.0, Ar-*H*), 4.03 (2H, s, C*H*$_2$), 3.87 (3H, s, O*Me*), 1.37 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.8, 139.9, 130.2, 120.54, 120.51, 112.9, 83.5, 62.0, 55.7, 27.6; IR υ_{max} (neat)/cm^{-1} 2980, 1730 (C=O), 1598, 1482, 1316 (SO_2), 1288, 1247, 1140 (SO_2), 1091, 1035; LRMS (ESI) *m/z* 304 (35%, $[M+NH_4]^+$), 309 (30%, $[M+Na]^+$), 595 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 309.0765 $[M+Na]^+$, $C_{13}H_{18}O_5SNa^+$ requires *m/z* 309.0767.

tert-Butyl 2-((2-methoxyphenyl)sulfonyl)acetate (100d)



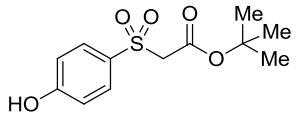
The general procedure **G** was followed with the use of 2-iodoanisole (39 µL, 0.30 mmol). Flash column chromatography (25–50% Et_2O in petrol) afforded the *sulfone* **100d** as an off-white microcrystalline solid (67 mg, 78%); mp 89–90 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.62 (1H, ddd, *J* 7.5, 1.5, 1.0, Ar-*H*), 7.12 (1H, app. t, *J* 7.5, Ar-*H*), 7.07 (1H, d, *J* 8.5, Ar-*H*), 4.30 (3H, s, O*Me*), 4.01 (2H, s, C*H*$_2$), 1.24 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 157.3, 135.8, 130.6, 126.8, 120.6, 112.2, 83.1, 60.3, 56.3, 27.5; IR υ_{max} (neat)/cm^{-1} 2944, 1721 (C=O), 1590, 1479, 1434, 1323 (SO_2), 1304, 1276, 1220, 1153 (SO_2), 1099, 1016; LRMS (ESI) *m/z* 304 (40%, $[M+NH_4]^+$), 309 (35%, $[M+Na]^+$), 595 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 309.0775 $[M+Na]^+$, $C_{13}H_{18}O_5SNa^+$ requires *m/z* 309.0767.

tert-Butyl 2-((4-(methylthio)phenyl)sulfonyl)acetate (100e)



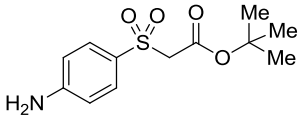
The general procedure **G** was followed with the use of 4-iodothioanisole (75 mg, 0.30 mmol). Flash column chromatography (15–35% Et_2O in petrol) afforded the *sulfone* **100e** as a yellow oil (79 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.34 (2H, d, *J* 8.5, Ar-*H*), 4.01 (2H, s, C*H*$_2$), 2.52 (3H, s, S*Me*), 1.38 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 147.8, 134.3, 128.7, 125.1, 83.5, 62.1, 27.6, 14.6; IR υ_{max} (neat)/cm^{-1} 2980, 1728 (C=O), 1579, 1395, 1322 (SO_2), 1292, 1146 (SO_2), 1095, 1078; LRMS (ESI) *m/z* 320 (50%, $[M+NH_4]^+$), 325 (50%, $[M+Na]^+$), 627 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 325.0543 $[M+Na]^+$, $C_{13}H_{18}O_4S_2Na^+$ requires *m/z* 325.0539.

tert-Butyl 2-((4-hydroxyphenyl)sulfonyl)acetate (100f)



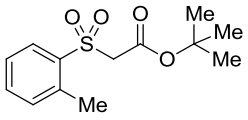
The general procedure **G** was followed with the use of 4-iodophenol (66 mg, 0.30 mmol). Flash column chromatography (40–70% Et_2O in petrol) afforded the *sulfone* **100f** as a pale yellow oil (61 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* 9.0, Ar-*H*), 6.94 (2H, d, *J* 9.0, Ar-*H*), 4.05 (2H, s, C*H*$_2$), 1.40 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.6, 130.9, 129.3, 116.0, 84.2, 62.4, 27.7; IR υ_{max} (neat)/cm^{-1} 3383 br. (OH), 2981, 1728 (C=O), 1586, 1502, 1370, 1312 (SO_2), 1288, 1136 (SO_2), 1083; LRMS (ESI) *m/z* 290 (45%, $[M+NH_4]^+$), 295 (45%, $[M+Na]^+$), 567 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 295.0613 $[M+Na]^+$, $C_{12}H_{16}O_5SNa^+$ requires *m/z* 295.0611.

tert-Butyl 2-((4-aminophenyl)sulfonyl)acetate (100g)



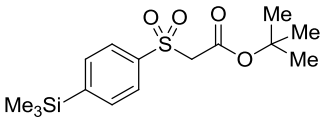
The general procedure **G** was followed with the use of 4-iodoaniline (66 mg, 0.30 mmol). Flash column chromatography (60–75% Et_2O in petrol) afforded the *sulfone* **100g** as an off-white microcrystalline solid (52 mg, 64%); mp 105–107 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* 9.0, Ar-*H*), 6.71 (2H, d, *J* 9.0, Ar-*H*), 3.98 (2H, s, C*H*$_2$), 1.39 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 151.7, 130.7, 126.7, 113.9, 83.2, 62.5, 27.7; IR υ_{max} (neat)/cm^{-1} 3486, 3379 (NH_2), 2945, 1732 (C=O), 1627, 1596, 1508, 1372, 1317 (SO_2), 1287, 1129 (SO_2), 1084; LRMS (ESI) *m/z* 289 (45%, $[M+NH_4]^+$), 294 (40%, $[M+Na]^+$), 565 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 294.0777 $[M+Na]^+$, $C_{12}H_{17}O_4SNNa^+$ requires *m/z* 294.0770.

tert-Butyl 2-(*o*-tolylsulfonyl)acetate (100h)



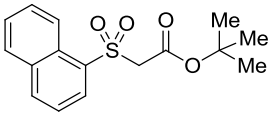
The general procedure **G** was followed with the use of 2-iodotoluene (38 µL, 0.30 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *sulfone* **100h** as a pale yellow microcrystalline solid (62 mg, 76%); mp 66–67 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.55 (1H, app. td, *J* 7.5, 1.5, Ar-*H*), 7.41–7.34 (2H, m, Ar-*H*), 4.09 (2H, s, C*H*$_2$), 2.72 (3H, s, Ar-*Me*), 1.29 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 138.1, 137.0, 134.1, 132.6, 130.7, 126.4, 83.5, 61.5, 27.5, 20.3; IR υ_{max} (neat)/cm^{-1} 2945, 1720 (C=O), 1470, 1365, 1317 (SO_2), 1224, 1156 (SO_2), 1097, 1060; LRMS (ESI) *m/z* 288 (85%, $[M+NH_4]^+$), 293 (50%, $[M+Na]^+$), 563 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 293.0822 $[M+Na]^+$, $C_{13}H_{18}O_4SNa^+$ requires *m/z* 293.0818.

tert-Butyl 2-((4-(trimethylsilyl)phenyl)sulfonyl)acetate (100i)



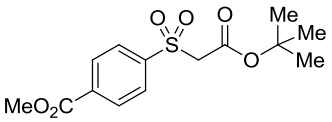
The general procedure **G** was followed with the use of (4-iodophenyl)Trimethylsilane **J** (83 mg, 0.30 mmol). Flash column chromatography (5–25% Et_2O in petrol) afforded the *sulfone* **100i** as a colourless oil (71 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* 8.0, Ar-*H*), 7.71 (2H, d, *J* 8.0, Ar-*H*), 4.03 (2H, s, C*H*$_2$), 1.35 (9H, s, C*Me*$_3$), 0.30 (9H, s, Si*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 148.9, 139.0, 133.8, 127.2, 83.5, 62.1, 27.6, -1.5; IR υ_{max} (neat)/cm^{-1} 2956, 1732 (C=O), 1370, 1327 (SO_2), 1291, 1251, 1145 (SO_2), 1103, 1080; LRMS (ESI) *m/z* 346 (100%, $[M+NH_4]^+$), 351 (75%, $[M+Na]^+$), 679 (85%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 351.1059 $[M+Na]^+$, $C_{15}H_{24}O_4SSiNa^+$ requires *m/z* 351.1057.

tert-Butyl 2-(naphthalen-1-ylsulfonyl)acetate (100j)



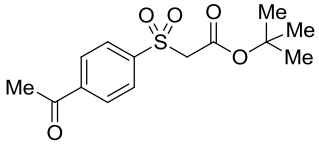
The general procedure **G** was followed with the use of 1-iodonaphthalene (44 µL, 0.30 mmol). Flash column chromatography (10–25% Et_2O in petrol) afforded the *sulfone* **100j** as an off-white microcrystalline solid (69 mg, 75%); mp 85–87 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, dd, *J* 8.5, 0.5, Ar-*H*), 8.34 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 8.17 (1H, d, *J* 8.0, Ar-*H*), 8.00 (1H, d, *J* 8.0, Ar-*H*), 7.77–7.71 (1H, m, Ar-*H*), 7.67–7.60 (2H, m, Ar-*H*), 4.25 (2H, s, C*H*$_2$), 1.25 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 135.6, 134.1, 133.8, 131.3, 129.4, 128.9, 128.7, 127.0, 124.2, 123.7, 83.4, 61.8, 27.5; IR υ_{max} (neat)/cm^{-1} 2944, 1724 (C=O), 1506, 1370, 1319 (SO_2), 1290, 1150 (SO_2), 1119; LRMS (ESI) *m/z* 324 (80%, $[M+NH_4]^+$), 329 (50%, $[M+Na]^+$), 635 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 329.0827 $[M+Na]^+$, $C_{16}H_{18}O_4SNa^+$ requires *m/z* 329.0818.

Methyl 4-((2-(*tert*-butoxy)-2-oxoethyl)sulfonyl)benzoate (100k)



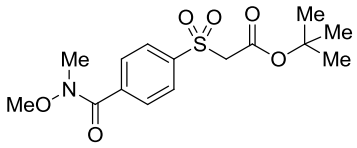
The general procedure **G** was followed with the use of methyl 4-iodobenzoate (79 mg, 0.30 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **100k** as a pale yellow microcrystalline solid (70 mg, 74%); mp 89–90 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (2H, d, *J* 8.5, Ar-*H*), 8.03 (2H, d, *J* 8.5, Ar-*H*), 4.07 (2H, s, C*H*$_2$), 3.97 (3H, s, CO_2*Me*), 1.37 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 161.0, 142.6, 135.1, 130.2, 128.6, 83.9, 61.8, 52.7, 27.7; IR υ_{max} (neat)/cm^{-1} 1723 (C=O), 1401, 1329 (SO_2), 1303, 1272, 1159 (SO_2), 1102, 1082, 1017; LRMS (ESI) *m/z* 332 (90%, $[M+NH_4]^+$), 337 (80%, $[M+Na]^+$), 651 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 337.0724 $[M+Na]^+$, $C_{14}H_{18}O_6SNa^+$ requires *m/z* 337.0716.

***tert*-Butyl 2-((4-acetylphenyl)sulfonyl)acetate (100l)**



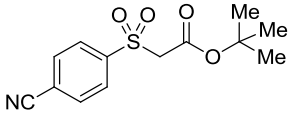
The general procedure **G** was followed with the use of 4'-iodoacetophenone (74 mg, 0.30 mmol). Flash column chromatography (25–60% Et_2O in petrol) afforded the *sulfone* **100l** as an off-white microcrystalline solid (66 mg, 74%); mp 81–82 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* 8.5, Ar-*H*), 8.05 (2H, d, *J* 8.5, Ar-*H*), 4.07 (2H, s, C*H*$_2$), 2.68 (3H, s, CO*Me*), 1.38 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 161.0, 142.5, 141.0, 129.0, 128.8, 84.0, 61.8, 27.7, 26.9; IR υ_{max} (neat)/cm^{-1} 2927, 1725 (C=O ester), 1685 (C=O ketone), 1402, 1371, 1331 (SO_2), 1305, 1262, 1143 (SO_2), 1122, 1090, 1019; LRMS (ESI) *m/z* 316 (85%, $[M+NH_4]^+$), 321 (80%, $[M+Na]^+$), 619 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 321.0771 $[M+Na]^+$, $C_{14}H_{18}O_5SNa^+$ requires *m/z* 321.0767.

tert-Butyl 2-((4-(methoxy(methyl)carbamoyl)phenyl)sulfonyl)acetate (100m)



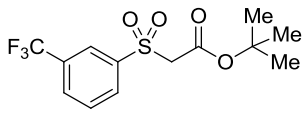
The general procedure **G** was followed with the use of 4-iodo-*N*-methoxy-*N*-methylbenzamide **K** (87 mg, 0.30 mmol). Flash column chromatography (40–60% EtOAc in petrol) afforded the *sulfone* **100m** as a pale yellow oil (74 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, d, *J* 8.5, Ar-*H*), 7.84 (2H, d, *J* 8.5, Ar-*H*), 4.06 (2H, s, C*H*$_2$), 3.51 (3H, s, N*Me*), 3.37 (3H, s, O*Me*), 1.36 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 160.9, 140.4, 139.6, 128.8, 128.2, 83.8, 61.8, 61.3, 33.1, 27.6; IR υ_{max} (neat)/cm^{-1} 2980, 2938, 1731 (C=O), 1643 (C=O), 1370, 1327 (SO_2), 1290, 1143 (SO_2), 1084; LRMS (ESI) *m/z* 344 (90%, $[M+H]^+$), 361 (30%, $[M+NH_4]^+$), 366 (100%, $[M+Na]^+$), 709 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 366.0988 $[M+Na]^+$, $C_{15}H_{21}O_6SNNa^+$ requires *m/z* 366.0982.

tert-Butyl 2-((4-cyanophenyl)sulfonyl)acetate (100n)



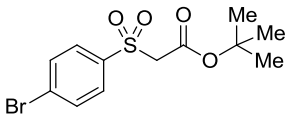
The general procedure **G** was followed with the use of 4-iodobenzonitrile (69 mg, 0.30 mmol). Flash column chromatography (20–35% Et_2O in petrol) afforded the *sulfone* **100n** as an off-white microcrystalline solid (51 mg, 60%); mp 95–96 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, d, *J* 8.5, Ar-*H*), 7.89 (2H, d, *J* 8.5, Ar-*H*), 4.09 (2H, s, C*H*$_2$), 1.40 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 142.8, 132.8, 129.4, 117.9, 117.0, 84.3, 61.6, 27.7; IR υ_{max} (neat)/cm^{-1} 2231 (CN), 1731 (C=O), 1371, 1327 (SO_2), 1287, 1252, 1141 (SO_2), 1082; LRMS (ESI) *m/z* 299 (45%, $[M+NH_4]^+$), 304 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 304.0619 $[M+Na]^+$, $C_{13}H_{15}O_4NSNa^+$ requires *m/z* 304.0614.

tert-Butyl 2-((3-(trifluoromethyl)phenyl)sulfonyl)acetate (100o)



The general procedure **G** was followed with the use of 3-iodobenzotrifluoride (44 µL, 0.30 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *sulfone* **100o** as a pale yellow microcrystalline solid (78 mg, 80%); mp 60–61 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s, Ar-*H*), 8.16 (1H, d, *J* 8.0, Ar-*H*), 7.95 (1H, d, *J* 8.0, Ar-*H*), 7.76 (1H, app. t, *J* 8.0, Ar-*H*), 4.09 (2H, s, C*H*$_2$), 1.37 (9H, s, C*Me*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 140.0, 131.9, 131.8 (q, $J_{C\text{-}F}$ 34), 130.8 (q, $J_{C\text{-}F}$ 3.5), 130.0, 125.8 (q, $J_{C\text{-}F}$ 3.5), 123.0 (q, $J_{C\text{-}F}$ 273), 84.1, 61.9, 27.6; ^{19}F {^1H} NMR (376 MHz, $CDCl_3$) δ -62.8 (s); IR υ_{max} (neat)/cm^{-1} 1734 (C=O), 1610, 1373, 1327 (SO_2), 1303, 1290, 1143, 1120 (SO_2), 1102, 1072; LRMS (ESI) *m/z* 342 (100%, $[M+NH_4]^+$), 347 (95%, $[M+Na]^+$), 671 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 347.0541 $[M+Na]^+$, $C_{13}H_{15}O_4SF_3Na^+$ requires *m/z* 347.0535.

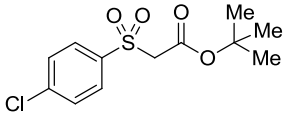
tert-Butyl 2-((4-bromophenyl)sulfonyl)acetate (100p)



The general procedure **G** was followed with the use of 1-bromo-4-iodobenzene (85 mg, 0.30 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *sulfone* **100p** as a pale yellow microcrystalline solid (63 mg, 63%); mp 73–74 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* 8.5, Ar-*H*), 7.73 (2H, d, *J* 8.5, Ar-*H*), 4.04 (2H, s, C*H*$_2$), 1.39 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 137.8, 132.4, 130.1, 129.5, 83.9, 61.9, 27.7; IR υ_{max} (neat)/cm^{-1} 2996, 2937, 1717 (C=O), 1573, 1470, 1392, 1330 (SO_2), 1297, 1249, 1157 (SO_2), 1111, 1082, 1067, 1011; LRMS (ESI) *m/z* 352 (95%, $[M(^{79}Br)+NH_4]^+$), 354 (95%, $[M(^{81}Br)+NH_4]^+$), 357 (100%, $[M(^{79}Br)+Na]^+$),

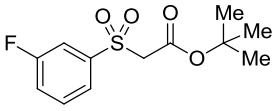
359 (100%, $[M(^{81}Br)+Na]^+$), 693 (100%, $[2M(^{79}Br,^{81}Br)+Na]^+$); HRMS (ESI) found *m/z* 356.9771 $[M(^{79}Br)+Na]^+$, $C_{12}H_{15}O_4S^{79}BrNa^+$ requires *m/z* 356.9767.

tert-Butyl 2-((4-chlorophenyl)sulfonyl)acetate (100q)



The general procedure **G** was followed with the use of 1-chloro-4-iodobenzene (72 mg, 0.30 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *sulfone* **100q** as a pale yellow microcrystalline solid (71 mg, 81%); mp 49–51 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* 8.5, Ar-*H*), 7.56 (2H, d, *J* 8.5, Ar-*H*), 4.04 (2H, s, C*H*$_2$), 1.40 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 141.0, 137.3, 130.1, 129.4, 83.9, 62.0, 27.7; IR υ_{max} (neat)/cm^{-1} 2981, 1730 (C=O), 1583, 1476, 1395, 1370, 1328 (SO_2), 1292, 1145 (SO_2), 1084, 1014; LRMS (ESI) *m/z* 308 (100%, $[M(^{35}Cl)+NH_4]^+$), 310 (40%, $[M(^{37}Cl)+NH_4]^+$), 313 (95%, $[M(^{35}Cl)+Na]^+$), 315 (35%, $[M(^{37}Cl)+Na]^+$), 603 (90%, $[2M(^{35}Cl,^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 313.0278 $[M(^{35}Cl)+Na]^+$, $C_{12}H_{15}O_4S^{35}ClNa^+$ requires *m/z* 313.0272.

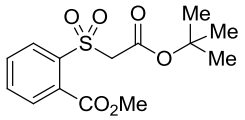
tert-Butyl 2-((3-fluorophenyl)sulfonyl)acetate (100r)



The general procedure **G** was followed with the use of 1-fluoro-3-iodobenzene (35 µL, 0.30 mmol). Flash column chromatography (10–30% Et_2O in petrol) afforded the *sulfone* **100r** as a pale yellow oil (58 mg, 70%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, ddd, *J* 8.0, 1.5, 1.0, Ar-*H*), 7.66 (1H, app. dt, *J* 8.0, 2.0, Ar-*H*), 7.59 (1H, app. td, *J* 8.0, 5.0, Ar-*H*), 7.39 (1H, app. tdd, *J* 8.0, 2.5, 1.0, Ar-*H*), 4.05 (2H, s, C*H*$_2$), 1.38 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ 253), 160.9, 140.8 (d, $J_{C\text{-}F}$ 7), 131.0 (d, $J_{C\text{-}F}$ 8), 124.3 (d, $J_{C\text{-}F}$ 3), 121.4 (d, $J_{C\text{-}F}$ 21), 116.0 (d, $J_{C\text{-}F}$ 25), 83.9, 61.9, 27.6;

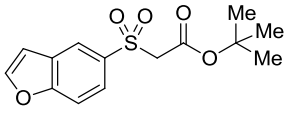
^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -109.1 (s); IR υ_{max} (neat)/cm^{-1} 2982, 1731 (C=O), 1594, 1478, 1371, 1331 (SO_2), 1304, 1225, 1138 (SO_2), 1083; LRMS (ESI) *m/z* 292 (55%, $[M+NH_4]^+$), 297 (80%, $[M+Na]^+$), 571 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 297.0565 $[M+Na]^+$, $C_{12}H_{15}O_4SFNa^+$ requires *m/z* 297.0567.

Methyl 2-((2-(*tert*-butoxy)-2-oxoethyl)sulfonyl)benzoate (100s)



The general procedure **G** was followed with the use of methyl 2-iodobenzoate (45 µL, 0.30 mmol). Flash column chromatography (30–40% Et_2O in petrol) afforded the *sulfone* **100s** as a pale yellow oil (34 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.79–7.65 (3H, m, Ar-*H*), 4.55 (2H, s, C*H*$_2$), 3.98 (3H, s, CO_2*Me*), 1.39 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 161.6, 137.9, 133.8, 132.8, 131.7, 131.0, 130.0, 83.5, 62.2, 53.2, 27.7; IR υ_{max} (neat)/cm^{-1} 2981, 1728 (C=O), 1435, 1370, 1328 (SO_2), 1288, 1259, 1148 (SO_2), 1112, 1056; LRMS (ESI) *m/z* 332 (75%, $[M+NH_4]^+$), 337 (80%, $[M+Na]^+$), 651 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 337.0719 $[M+Na]^+$, $C_{14}H_{18}O_6SNa^+$ requires *m/z* 337.0716.

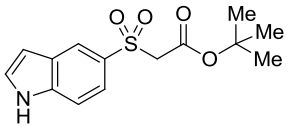
***tert*-Butyl 2-(benzofuran-5-ylsulfonyl)acetate (101a)**



The general procedure **G** was followed with the use of 5-iodobenzofuran **L** (73 mg, 0.30 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **101a** as a pale yellow oil (71 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* 2.0, Ar-*H*), 7.89 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 7.79 (1H, d, *J* 2.0, Ar-*H*), 7.67 (1H, d, *J* 8.5), 6.91 (1H, dd, *J* 2.0, 1.0, Ar-*H*), 4.08 (2H, s, C*H*$_2$), 1.35 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 157.4, 147.5, 133.6, 127.8, 124.6, 123.1, 112.1, 107.1, 83.5, 62.5, 27.6;

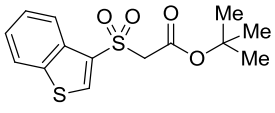
IR υ_{max} (neat)/cm^{-1} 2981, 1728 (C=O), 1453, 1370, 1318 (SO_2), 1292, 1261, 1125 (SO_2), 1110, 1061, 1027; LRMS (ESI) *m/z* 314 (40%, $[M+NH_4]^+$), 319 (35%, $[M+Na]^+$), 615 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 319.0619 $[M+Na]^+$, $C_{14}H_{16}O_5SNa^+$ requires *m/z* 319.0611.

tert-Butyl 2-((1H-indol-5-yl)sulfonyl)acetate (101b)



The general procedure **G** was followed with the use of 5-iodoindole (73 mg, 0.30 mmol). Flash column chromatography (30–60% Et_2O in petrol) afforded the *sulfone* **101b** as an off-white microcrystalline solid (61 mg, 69%); mp 104–105 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (1H, br. s, N*H*), 8.27 (1H, d, *J* 2.0, Ar-*H*), 7.70 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 7.52 (1H, d, *J* 8.5, Ar-*H*), 7.38 (1H, app. t, *J* 3.0, Ar-*H*), 6.68–6.66 (1H, m, Ar-*H*), 4.09 (2H, s, C*H*$_2$), 1.33 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 138.4, 129.5, 127.4, 127.1, 122.8, 121.1, 111.7, 104.0, 83.4, 62.8, 27.6; IR υ_{max} (neat)/cm^{-1} 3339 (NH), 2983, 1731 (C=O), 1311 (SO_2), 1293, 1140 (SO_2), 1119, 1059; LRMS (ESI) *m/z* 313 (55%, $[M+NH_4]^+$), 318 (30%, $[M+Na]^+$), 613 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 318.0774 $[M+Na]^+$, $C_{14}H_{17}O_4SNNa^+$ requires *m/z* 318.0770.

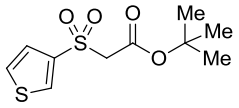
tert-Butyl 2-(benzo[b]thiophen-3-ylsulfonyl)acetate (101c)



The general procedure **G** was followed with the use of 3-iodobenzothiophene **M** (78 mg, 0.30 mmol). Flash column chromatography (15–30% Et_2O in petrol) afforded the *sulfone* **101c** as an off-white microcrystalline solid (50 mg, 53%); mp 116–117 ^oC (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, s, Ar-*H*), 8.24 (1H, d, *J* 8.0, Ar-*H*), 7.94 (1H, d,

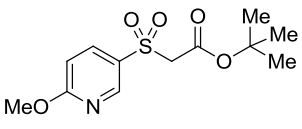
J 8.0, Ar-*H*), 7.59–7.48 (2H, m, Ar-*H*), 4.15 (2H, s, CH_2), 1.32 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 140.3, 138.0, 133.8, 132.7, 126.1, 126.0, 123.1, 122.8, 83.6, 61.8, 27.6; IR υ_{max} (neat)/cm^{-1} 3081, 1715 (C=O), 1457, 1420, 1367, 1332, 1322 (SO_2), 1310, 1231, 1158 (SO_2), 1104; LRMS (ESI) *m/z* 335 (100%, $[M+Na]^+$), 650 (95%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 335.0390 $[M+Na]^+$, $C_{14}H_{16}O_4S_2Na^+$ requires *m/z* 335.0382.

tert-Butyl 2-(thiophen-3-ylsulfonyl)acetate (101d)



The general procedure **G** was followed with the use of 3-iodothiophene (31 µL, 0.30 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **101d** as a pale yellow oil (50 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, dd, *J* 3.0, 1.5, Ar-*H*), 7.48 (1H, dd, *J* 5.0, 3.0, Ar-*H*), 7.44 (1H, dd, *J* 5.0, 1.5, Ar-*H*), 4.05 (2H, s, CH_2), 1.40 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 139.2, 133.6, 128.0, 126.4, 83.7, 62.2, 27.7; IR υ_{max} (neat)/cm^{-1} 2980, 1728 (C=O), 1370, 1322 (SO_2), 1293, 1208, 1139 (SO_2), 1095; LRMS (ESI) *m/z* 280 (50%, $[M+NH_4]^+$), 285 (45%, $[M+Na]^+$), 547 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 285.0228 $[M+Na]^+$, $C_{10}H_{14}O_4S_2Na^+$ requires *m/z* 285.0226.

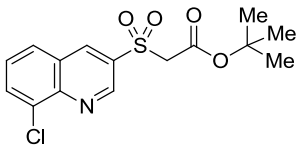
tert-Butyl 2-((6-methoxypyridin-3-yl)sulfonyl)acetate (101e)



The general procedure **G** was followed with the use of 5-iodo-2-methoxypyridine (71 mg, 0.30 mmol). Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **101e** as a yellow oil (57 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, d, *J* 2.5, Ar-*H*), 8.03, (1H, dd, *J* 9.0, 2.5, Ar-*H*), 6.87 (1H, d, *J* 9.0, Ar-*H*), 4.03 (5H,

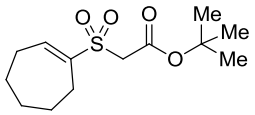
2 × overlapping s, OMe and C*H*$_2$), 1.42 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 161.4, 149.5, 138.6, 128.1, 111.3, 83.9, 62.4, 54.5, 27.7; IR υ_{max} (neat)/cm^{-1} 2981, 2946, 1730 (C=O), 1590, 1564, 1483, 1372, 1330 (SO_2), 1287, 1151 (SO_2), 1127, 1094, 1010; LRMS (ESI) *m/z* 288 (100%, $[M+H]^+$), 310 (70%, $[M+Na]^+$), 597 (90%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 310.0728 $[M+Na]^+$, $C_{12}H_{17}O_5SNNa^+$ requires *m/z* 310.0720.

tert-Butyl 2-((8-chloroquinolin-3-yl)sulfonyl)acetate (101f)



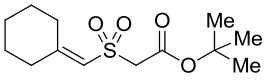
The general procedure **G** was followed with the use of 8-chloro-3-iodoquinoline **88** (87 mg, 0.30 mmol), palladium(II) acetate (7 mg, 30 μmol), CataCXium A (16 mg, 45 μmol), DABSO (79 mg, 0.33 mmol), triethylamine (125 μL, 0.9 mmol) and 2-propanol (1.5 mL). Flash column chromatography (0–60% acetone in petrol) afforded the *sulfone* **101f** as an off-white microcrystalline solid (70 mg, 68%); mp 124–125 °C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (1H, d, *J* 2.0, Ar-*H*), 8.83 (1H, d, *J* 2.0, Ar-*H*), 8.05 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.94 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.66 (1H, app. t, *J* 8.0, Ar-*H*), 4.18 (2H, s, C*H*$_2$), 1.37 (9H, s, C*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 148.0, 146.0, 139.3, 134.2, 133.1, 132.9, 128.5, 128.3, 127.5, 84.3, 62.1, 27.7; IR υ_{max} (neat)/cm^{-1} 1728 (C=O), 1336 (SO_2), 1308, 1215, 1165, 1121 (SO_2), 1083; LRMS (ESI) *m/z* 342 (100%, $[M(^{35}Cl)+H]^+$), 344 (30%, $[M(^{37}Cl)+H]^+$), 364 (30%, $[M(^{35}Cl)+Na]^+$), 366 (10%, $[M(^{37}Cl)+Na]^+$), 705 (45%, $[2M(^{35}Cl,^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 364.0390 $[M(^{35}Cl)+Na]^+$, $C_{15}H_{16}O_4SN^{35}ClNa^+$ requires *m/z* 364.0381.

tert-Butyl 2-(cyclohept-1-en-1-ylsulfonyl)acetate (101g)



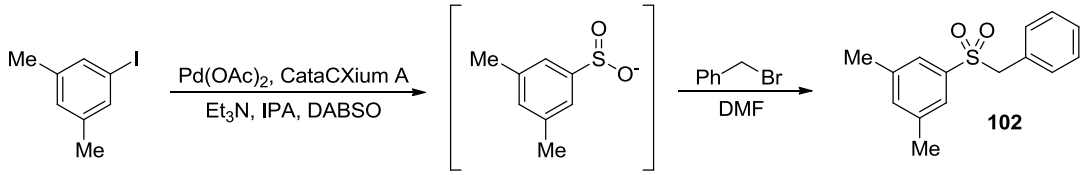
The general procedure **G** was followed with the use of 1-iodocyclohept-1-ene **31** (67 mg, 0.30 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *sulfone* **101g** as a yellow oil (58 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, t, *J* 6.5, C=C*H*), 3.83 (2H, s, $SO_2CH_2CO_2$), 2.61–2.56 (2H, m, CH_2), 2.38 (2H, app. q, *J* 6.5, CH_2), 1.84–1.78 (2H, m, CH_2), 1.72–1.65 (2H, m, CH_2), 1.64–1.57 (2H, m, CH_2), 1.46 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 145.9, 142.6, 83.3, 58.5, 31.1, 28.7, 27.9, 27.8, 25.9, 25.2; IR υ_{max} (neat)/cm^{-1} 2929, 1730 (C=O), 1449, 1395, 1369, 1307 (SO_2), 1132 (SO_2); LRMS (ESI) *m/z* 297 (80%, $[M+Na]^+$), 571 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 297.1133 $[M+Na]^+$, $C_{13}H_{22}O_4SNa^+$ requires *m/z* 297.1131.

tert-Butyl 2-((cyclohexylidenemethyl)sulfonyl)acetate (101h)



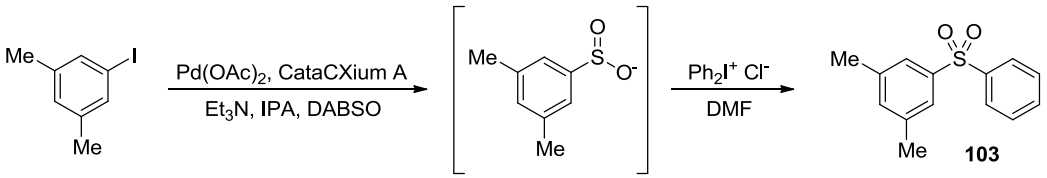
The general procedure **G** was followed with the use of (iodomethylene)cyclohexene **N** (67 mg, 0.30 mmol). Flash column chromatography (5–20% Et_2O in petrol) afforded the *sulfone* **101h** as a yellow oil (31 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (1H, s, CC*H*SO_2), 3.88 (2H, s, $SO_2CH_2CO_2$), 2.73 (2H, t, *J* 6.0, CH_2CCH), 2.25 (2H, t, *J* 6.0, CH_2CCH), 1.75–1.65 (4H, m, 2 × CH_2), 1.65–1.58 (2H, m, CH_2), 1.49 (9H, s, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.9, 121.0, 83.5, 62.0, 37.6, 29.5, 28.3, 27.8, 27.5, 25.7; IR υ_{max} (neat)/cm^{-1} 2938, 1731, 1624, 1540, 1371, 1312 (SO_2), 1133 (SO_2); LRMS (ESI) *m/z* 297 (100%, $[M+Na]^+$), 571 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 297.1126 $[M+Na]^+$, $C_{13}H_{22}O_4SNa^+$ requires *m/z* 297.1131.

1-(Benzylsulfonyl)-3,5-dimethylbenzene (102)



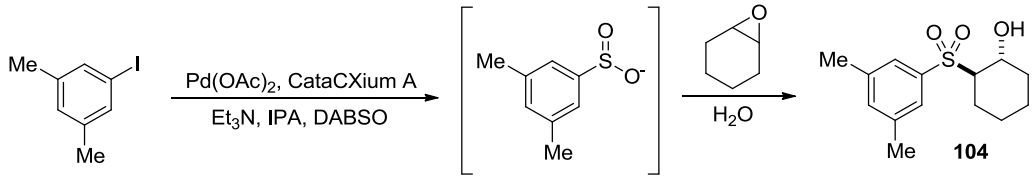
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, a solution of benzyl bromide (106 µL, 0.90 mmol) in anhydrous DMF (0.5 mL) was added and the resultant solution heated at 75 ^{o}C for 6 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was cooled to room temperature, poured onto water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (5–25% Et_2O in petrol) afforded the *sulfone* **102** as an off-white microcrystalline solid (66 mg, 85%); mp 75–76 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (6H, m, Ar-*H*), 7.13–7.09 (2H, m, Ar-*H*), 4.28 (2H, s, C*H*$_2$), 2.31 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.5, 135.2, 130.8, 128.6, 128.4, 128.2, 126.1, 62.8, 21.0; IR υ_{max} (neat)/cm^{-1} 2922, 1457, 1291 (SO_2), 1260, 1155 (SO_2), 1128, 1105; LRMS (ESI) *m/z* 278 (90%, $[M+NH_4]^+$), 283 (30%, $[M+Na]^+$), 543 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 283.0764 $[M+Na]^+$, $C_{15}H_{16}O_2SNa^+$ requires *m/z* 283.0763.

1,3-Dimethyl-5-(phenylsulfonyl)benzene (103)



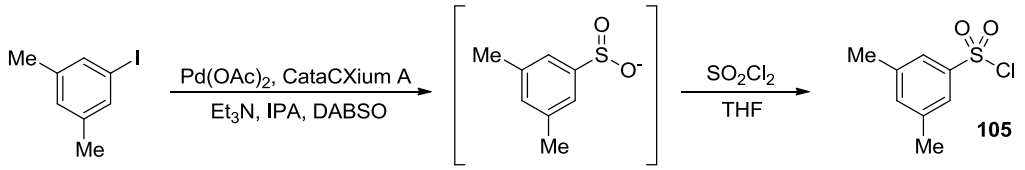
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Diphenyl iodonium chloride (190 mg, 0.60 mmol) and DMF (1.5 mL) were added and the resultant suspension heated at 90 ^{o}C for 24 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was cooled to room temperature, poured onto water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (5–20% Et_2O in petrol) afforded the *sulfone* **103** as an off-white microcrystalline solid (56 mg, 76%); mp 87–88 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (2H, m, Ar-*H*), 7.59–7.47 (5H, m, Ar-*H*), 7.17 (1H, s, Ar-*H*), 2.36 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.2, 139.3, 134.9, 133.0, 129.2, 127.5, 125.1, 21.2; IR υ_{max} (neat)/cm^{-1} 1608, 1447, 1299 (SO_2), 1149 (SO_2), 1112, 1082; LRMS (ESI) *m/z* 247 (35%, $[M+H]^+$), 264 (95%, $[M+NH_4]^+$), 269 (55%, $[M+Na]^+$), 515 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 269.0606 $[M+Na]^+$, $C_{14}H_{14}O_2SNa^+$ requires *m/z* 269.0607.

1,3-Dimethyl-5-(phenylsulfonyl)benzene (104)



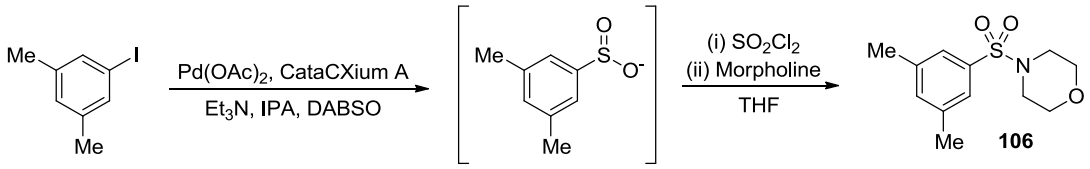
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Water (1.5 mL) and cyclohexene oxide (300 µL, 3.0 mmol) were added sequentially and the resultant suspension heated at 90 ^{o}C for 6 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was cooled to room temperature, poured onto aq. NH_4Cl (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (20–40% Et_2O in petrol) afforded the *sulfone* **104** as an off-white microcrystalline solid (61 mg, 76%); mp 126–127 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, s, Ar-*H*), 7.30 (1H, s, Ar-*H*), 4.37 (1H, br. s, O*H*), 3.93 (1H, app. td, *J* 10.0, 5.0, C*H*OH), 2.96 (1H, ddd, *J* 12.5, 9.5, 4.0, C*H*SO_2), 2.41 (6H, s, 2 × Ar-*Me*), 2.17–2.10 (1H, m, CHOHC*H*H'), 1.92–1.85 (1H, m, $CHSO_2CHH$'), 1.76–1.67 (2H, m, CH_2), 1.40–1.10 (4H, m, CHOHCH*H'*, $CHSO_2CHH'$ and CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.4, 135.8, 126.4, 68.8, 68.1, 34.1, 25.7, 24.5, 23.5, 21.2; IR υ_{max} (neat)/cm^{-1} 3513 (OH), 2944, 2867, 1609, 1445, 1271 (SO_2), 1133 (SO_2), 1104, 1065, 1041; LRMS (ESI) *m/z* 269 (40%, $[M+H]^+$), 286 (75%, $[M+NH_4]^+$), 291 (35%, $[M+Na]^+$), 559 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 291.1023 $[M+Na]^+$, $C_{14}H_{20}O_3SNa^+$ requires *m/z* 291.1025.

3,5-Dimethylbenzene-1-sulfonyl chloride (105)



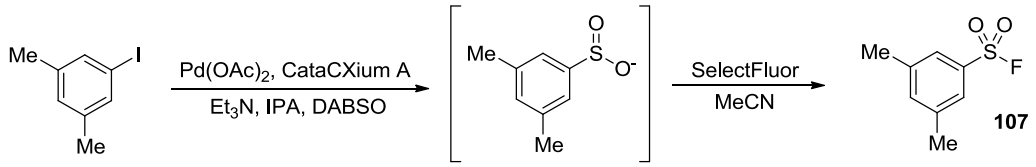
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. THF (1.5 mL) was added, the resultant suspension cooled to 0 ^{o}C and sulfuryl chloride (73 µL, 0.90 mmol) added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was poured onto aq. NH_4Cl (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (0–5% Et_2O in petrol) afforded the *sulfonyl chloride* **105** as a white microcrystalline solid (37 mg, 60%); mp 89–90 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, s, Ar-*H*), 7.36 (1H, s, Ar-*H*), 2.45 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 140.0, 136.9, 124.4, 21.2; IR υ_{max} (neat)/cm^{-1} 1608, 1445, 1364 (SO_2), 1309, 1267, 1165 (SO_2), 1106; HRMS (FI) found *m/z* 204.0009 [M(^{35}Cl)]$^{+}$, $C_8H_9O_2S^{35}Cl^{+}$ requires *m/z* 204.0012.

4-((3,5-Dimethylphenyl)sulfonyl)morpholine (106)



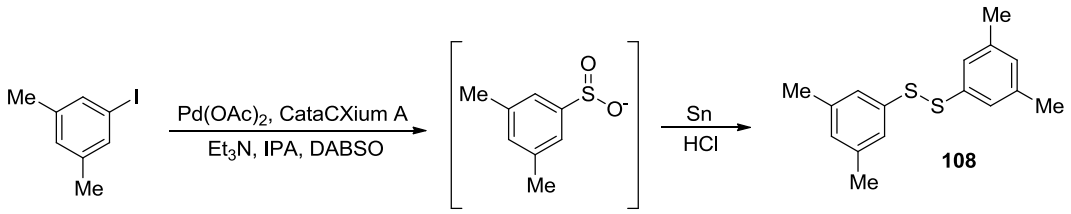
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. THF (1.5 mL) was added, the resultant suspension cooled to 0 ^{o}C and sulfuryl chloride (73 µL, 0.90 mmol) added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 hrs until consumption of the sulfinate was observed by HPLC. Morpholine (175 µL, 2.0 mmol) was then added dropwise and the reaction mixture stirred for a further 2 hrs at room temperature until consumption of the sulfonyl chloride was observed by HPLC. Upon completion, the reaction mixture was poured onto water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (20–60% Et_2O in petrol) afforded the *sulfonamide* **106** as an off-white microcrystalline solid (65 mg, 85%); mp 144–145 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, s, Ar-*H*), 7.24 (1H, s, Ar-*H*), 3.75 (4H, t, *J* 4.5, $N(CH_2C\mathit{H}_2)_2O$), 2.99 (4H, t, *J* 4.5, $N(C\mathit{H}_2CH_2)_2O$), 2.40 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 134.74, 134.65, 125.3, 66.1, 46.0, 21.2; IR υ_{max} (neat)/cm^{-1} 2857, 1607, 1455, 1343 (SO_2), 1328, 1296, 1261, 1158 (SO_2), 1112, 1066; LRMS (ESI) *m/z* 256 (100%, $[M+H]^+$), 278 (80%, $[M+Na]^+$), 533 (45%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 278.0824 $[M+Na]^+$, $C_{12}H_{17}O_3SNNa^+$ requires *m/z* 278.0821.

3,5-Dimethylbenzene-1-sulfonyl fluoride (107)



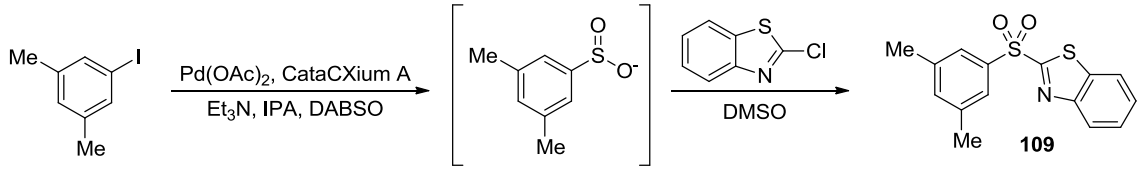
A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. MeCN (1.5 mL) and SelectFluor® (530 mg, 1.50 mmol) were added sequentially and the reaction mixture was stirred at room temperature for 2 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was poured onto water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (0–5% Et_2O in petrol) afforded the *sulfonyl fluoride* **107** as a yellow microcrystalline solid (34 mg, 60%); mp 34–35 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, s, Ar-*H*), 7.39 (1H, s, Ar-*H*), 2.44 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 137.2, 132.7 (d, $J_{C\text{-}F}$ 23), 125.8, 21.1; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ 65.7 (s); IR υ_{max} (neat)/cm^{-1} 2925, 1610, 1456, 1399 (SO_2), 1313, 1272, 1198 (SO_2), 1112; HRMS (FI) found *m/z* 188.0304 $[M]^+$, $C_8H_9O_2SF^+$ requires *m/z* 188.0307.

1,2-Bis(3,5-dimethylphenyl)disulfane (108)



A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Powdered elemental tin (1.0 g, 8.5 mmol) and water (1 mL) were added, then conc. aq. HCl was added dropwise. The resultant suspension was heated at 90 ^{o}C for 16 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (25 mL) and DCM (25 mL), and filtered through Celite®. The organic layer was separated and the aqueous layer extracted with further DCM (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (100% petrol) afforded the *disulfide* **108** as a colourless oil (29 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (4H, s, Ar-*H*), 6.87 (2H, s, Ar-*H*), 2.30 (12H, s, 4 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.8, 129.0, 125.1, 21.2; HRMS (FI) found *m/z* 274.0854 $[M]^+$, $C_{16}H_{18}S_2^+$ requires *m/z* 274.0850. Data consistent with the literature.[238]

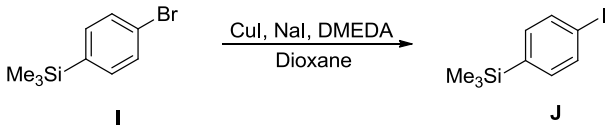
2-((3,5-Dimethylphenyl)sulfonyl)benzo[d]thiazole (109)



A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 µmol) and CataCXium A (8 mg, 23 µmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 µL, 0.30 mmol), triethylamine (125 µL, 0.90 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially through the septum and the reaction mixture heated at 75 ^{o}C for 16 hrs. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. DMSO (1.5 mL) and 2-chlorobenzothiazole (117 µL, 0.90 mmol) were added and the resultant solution heated at 100 ^{o}C for 6 hrs until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL) and washed with brine (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (15–50% Et_2O in petrol) afforded the *sulfone* **109** as an off-white microcrystalline solid (50 mg, 55%); mp 175–176 ^{o}C (DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* 8.0, Ar-*H*), 7.96 (1H, d, *J* 8.0, Ar-*H*), 7.77 (2H, s, Ar-*H*), 7.56 (2H, td, *J* 7.0, 1.5, Ar-*H*), 7.27 (1H, s, Ar-*H*), 2.40 (6H, s, 2 × Ar-*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 152.9, 139.7, 138.1, 137.1, 136.3, 127.8, 127.4, 126.4, 125.5, 122.2, 21.2; IR υ_{max} (neat)/cm^{-1} 1468, 1334 (SO_2), 1305, 1270, 1152 (SO_2), 1107, 1023; LRMS (ESI) *m/z* 304 (90%, $[M+H]^+$), 326 (80%, $[M+Na]^+$), 629 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 326.0285 $[M+Na]^+$, $C_{15}H_{13}O_2S_2NNa^+$ requires *m/z* 326.0280.

6.4.2 Starting Materials

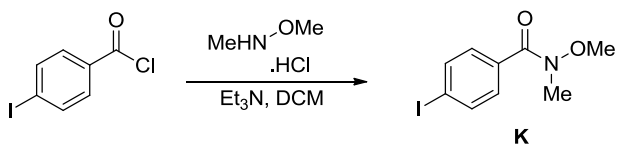
(4-Iodophenyl)Trimethylsilane (J)



I J

Method adapted from a procedure documented by Buchwald *et al.*[135] A glass reaction tube was charged with CuI (16 mg, 0.08 mmol) and NaI (0.30 g, 2.0 mmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. (4-Bromophenyl)Trimethylsilane **I** (0.23 g, 1.0 mmol), DMEDA (18 µL, 0.16 mmol) and 1,4-dioxane (1.2 mL) were added sequentially through the septum and the reaction heated at 100 ^{o}C for 24 hrs. The reaction mixture was cooled to room temperature and poured onto a solution of 35% aq. NH_3 (5 mL) in water (20 mL). The mixture was extracted with DCM (3 × 20 mL) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the titled *aryl iodide* **J** as a colourless liquid (270 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* 8.0, Ar-*H*), 7.10 (2H, d, *J* 8.0, Ar-*H*), 0.11 (9H, s, Si*Me*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 136.8, 135.0, 95.7, -1.3; IR υ_{max} (neat)/cm^{-1} 2954, 1568, 1373, 1248, 1105, 1057, 1006; HRMS (EI) found *m/z* 260.9591 (100%, $[M\text{-}Me]^+$), 275.9821 (20%, $[M]^+$), $C_9H_{13}SiI^+$ (M^+) requires *m/z* 275.9826.

4-Iodo-*N*-methoxy-*N*-methylbenzamide (K)

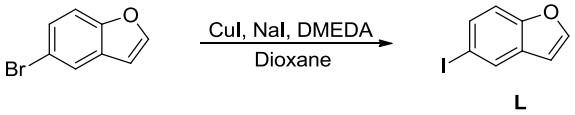


K

Triethylamine (0.60 mL, 4.3 mmol) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (200 mg, 2.1 mmol) in DCM (5 mL) cooled to 0 ^{o}C. A solution of 4-iodobenzoyl chloride (0.50 g, 1.9 mmol) in DCM (5 mL) was

added dropwise at the same temperature and the resultant suspension warmed to room temperature and stirred for 1 hr until the acid chloride was consumed as observed by TLC. The reaction mixture was quenched with aq. $NaHCO_3$ (20 mL), the layers separated and the aqueous layer extracted with DCM (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10–50% EtOAc in petrol) afforded the titled *amide* **K** as a thick colourless oil (0.48 g, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* 8.5, Ar-*H*), 7.42 (2H, d, *J* 8.5, Ar-*H*), 3.52 (3H, s, N*Me*), 3.34 (3H, s, O*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 137.1, 133.3, 129.9, 97.3, 61.1, 33.4; IR υ_{max} (neat)/cm^{-1} 2933, 1636 (C=O), 1584, 1414, 1376, 1212, 1181, 1110, 1065, 1007; LRMS (ESI) *m/z* 292 (35%, $[M+H]^+$), 314 (10%, $[M+Na]^+$), 605 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 313.9647 $[M+Na]^+$, $C_9H_{10}O_2NINa^+$ requires *m/z* 313.9648.

5-Iodobenzofuran (L)

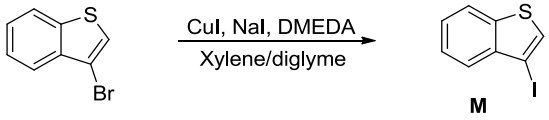


L

Method adapted from a procedure documented by Buchwald *et al.*[135] A glass reaction tube was charged with CuI (16 mg, 0.08 mmol) and NaI (0.30 g, 2.0 mmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 5-Bromobenzofuran (125 µL, 1.00 mmol), DMEDA (18 µL, 0.16 mmol) and 1,4-dioxane (1.2 mL) were added sequentially through the septum and the reaction heated at 100 ^{o}C for 24 hrs. The reaction mixture was cooled to room temperature and poured onto a solution of 35% aq. NH_3 (5 mL) in water (20 mL). The mixture was extracted with DCM (3 × 20 mL) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the titled aryl iodide **L** as a colourless liquid (232 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* 2.0, Ar-*H*), 7.60 (1H, d, *J* 2.0, Ar-*H*), 7.57 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 7.30 (1H, d, *J* 8.5, Ar-*H*), 6.72 (1H, dd, *J* 2.0, 1.0, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 145.8,

132.8, 130.1, 130.0, 113.4, 105.8, 86.2; HRMS (FI) found *m/z* 243.9387, $C_8H_5OI^+$ (M^+) requires *m/z* 243.9385.

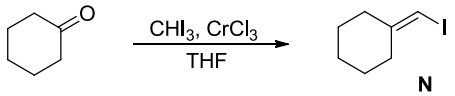
3-Iodobenzo[*b*]thiophene (M)



M

Method adapted from a procedure documented by Buchwald *et al.*[135] A glass reaction tube was charged with CuI (20 mg, 0.10 mmol) and NaI (0.30 g, 2.0 mmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 3-Bromobenzo[*b*]thiophene (131 µL, 1.00 mmol), DMEDA (22 µL, 0.20 mmol), *m*-xylene (0.8 mL) and diglyme (0.2 mL) were added sequentially through the septum and the reaction heated at 130 ^oC for 24 hrs. The reaction mixture was cooled to room temperature and poured onto a solution of 35% aq. NH_3 (5 mL) in water (20 mL). The mixture was extracted with DCM (3 × 20 mL) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the titled heteroaryl iodide **M** as a colourless liquid (230 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* 8.0, Ar-*H*), 7.78 (1H, d, *J* 8.0, Ar-*H*), 7.62 (1H, s, Ar-*H*), 7.51–7.46 (1H, m, Ar-*H*), 7.43–7.38 (1H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.3, 129.1, 125.21, 125.15 (2C), 122.4, 78.2; HRMS (FI) found *m/z* 259.9156, $C_8H_5SI^+$ (M^+) requires *m/z* 259.9157. Data consistent with the literature.[135]

(Iodomethylene)cyclohexene (N)



N

Method adapted from a procedure documented by Lee *et al.*[239] A solution of cyclohexanone (0.62 mL, 6.0 mmol) and iodoform (4.74 g, 12 mmol) in anhydrous THF

(15 mL) was added dropwise to a suspension of anhydrous $CrCl_3$ (2.96 g, 24 mmol) in anhydrous THF (30 mL) under nitrogen at room temperature. The resultant suspension was stirred for 48 hrs at the same temperature. Water (200 mL) was added and the reaction mixture extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (100% hexane) afforded the titled alkenyl iodide **N** as a colourless liquid (0.44 g, 33%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, s, C*H*I), 2.29 (4H, app. q, *J* 5.5, 2 × C*H*$_2$), 1.61–1.48 (6H, m, 3 × C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 71.1, 37.2, 35.8, 28.0, 26.9, 26.0; HRMS (FI) found *m/z* 221.9907, $C_7H_{11}I^+$ (M^+) requires *m/z* 221.9906. Data consistent with the literature.[239]

Thanks to Charlotte Richards-Taylor for the synthesis of 5-iodo-2-methoxypyridine.

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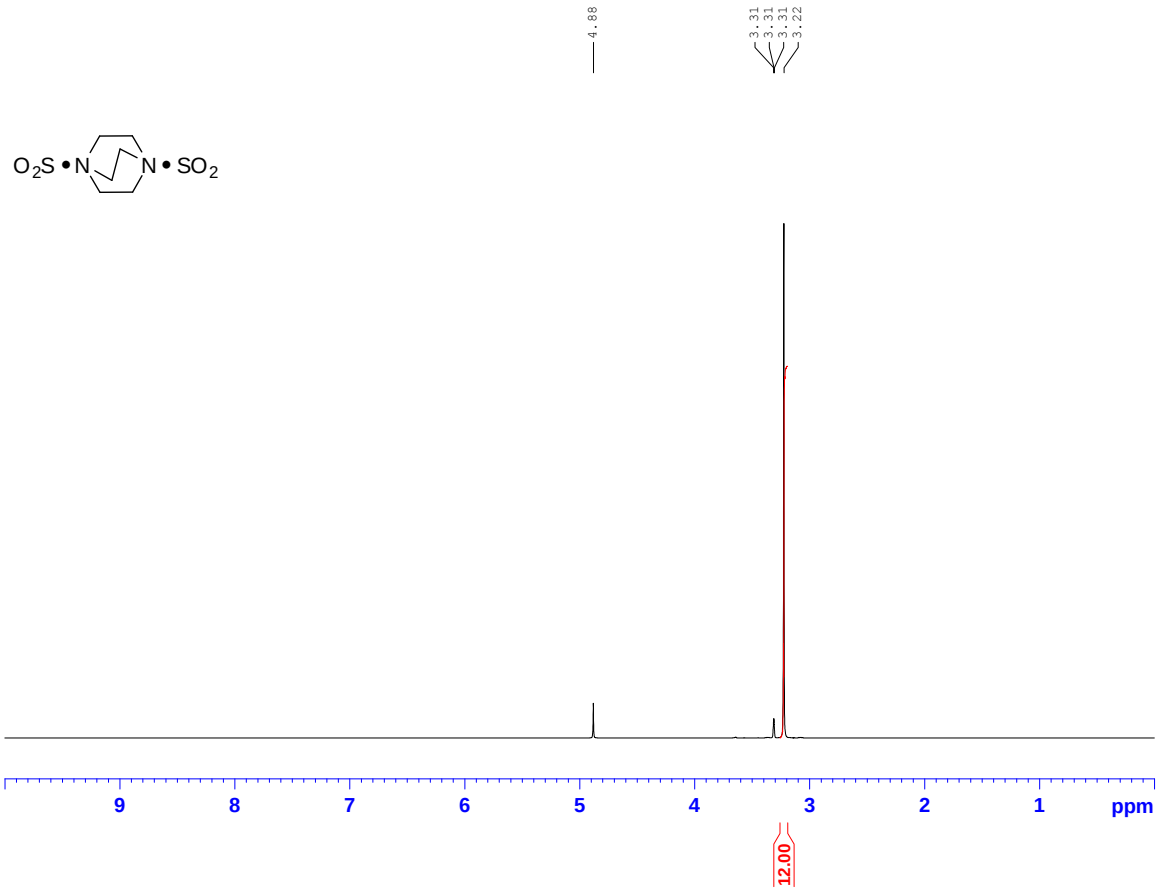
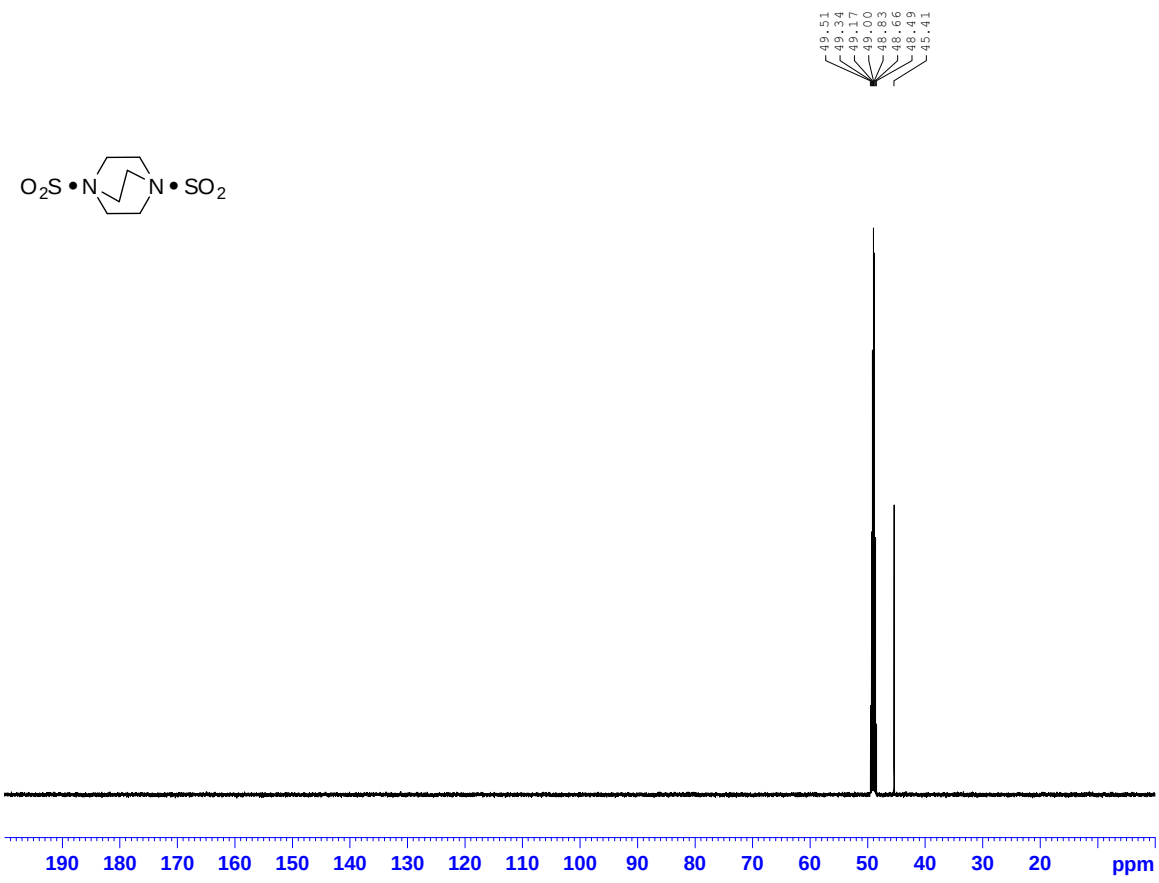
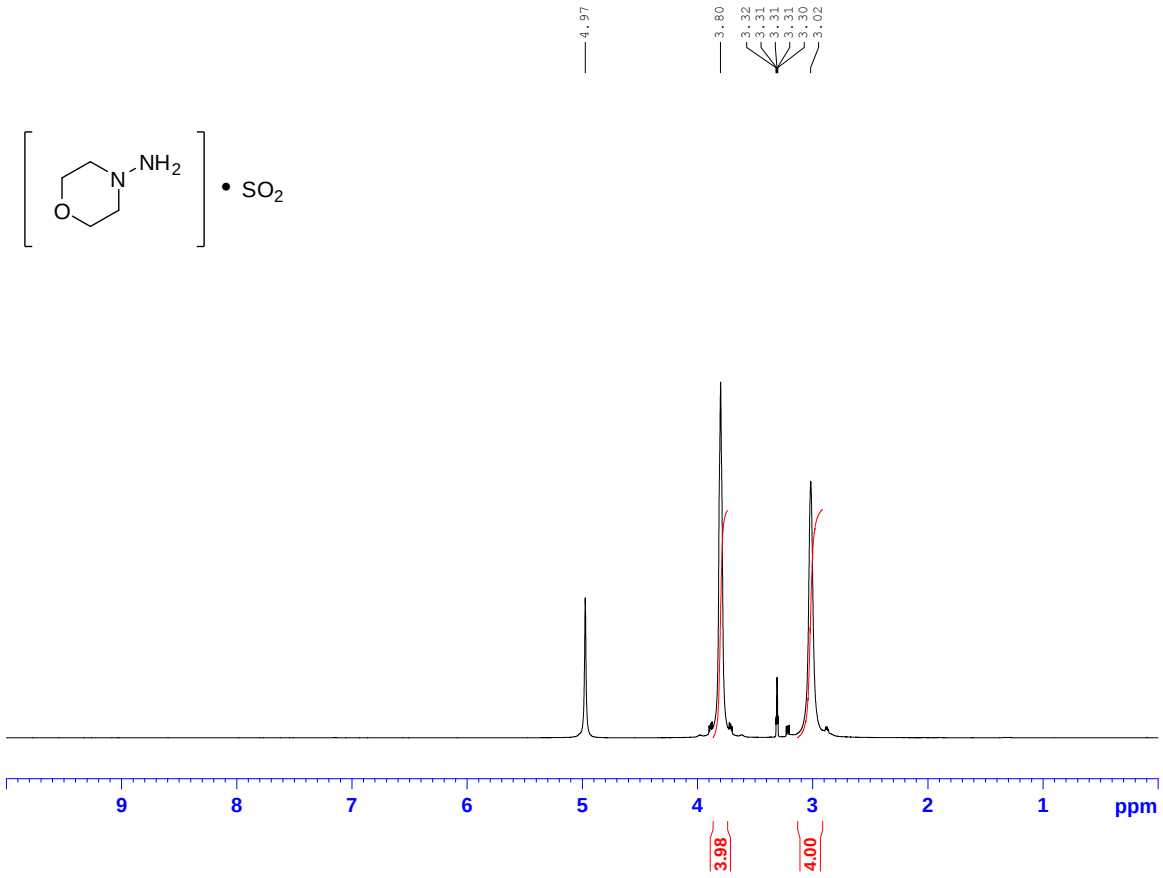
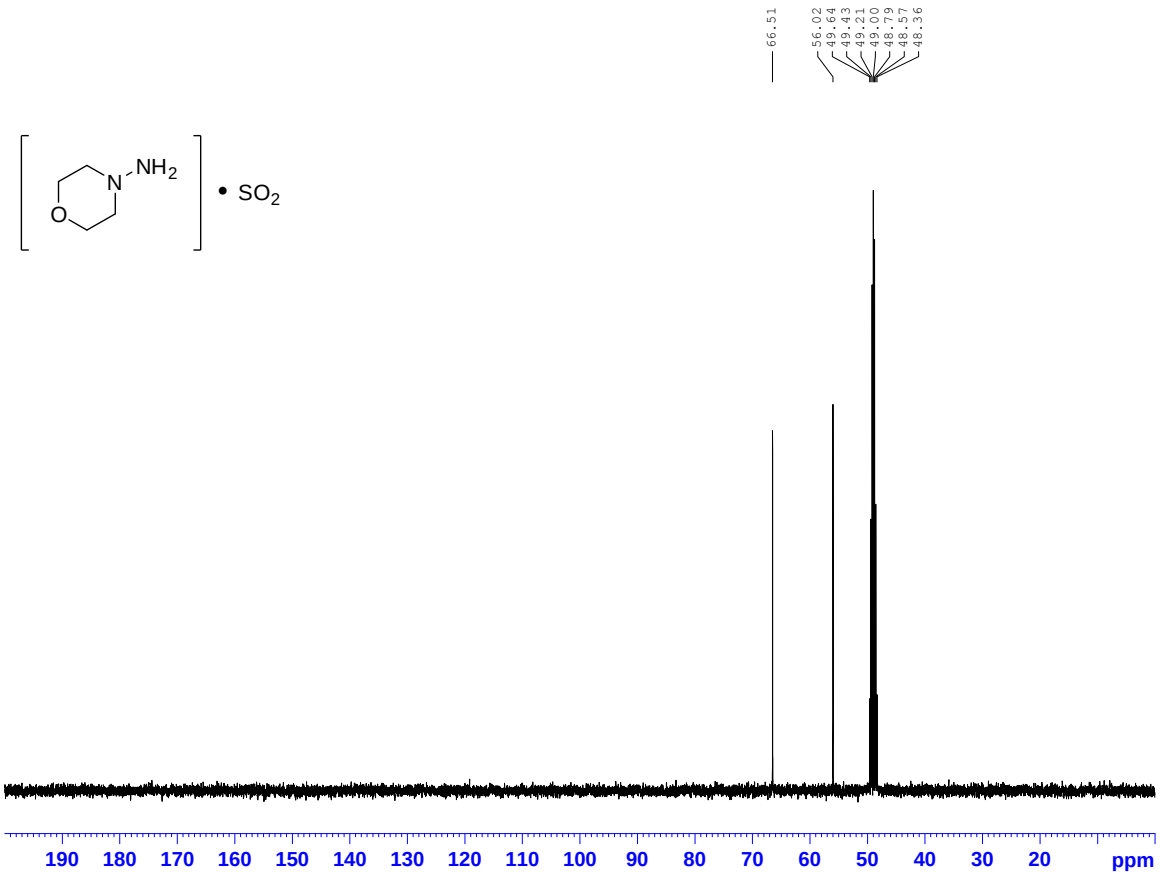

4.88
3.31
3.31
3.31
3.22
O2S • N
N • SO2
9
8
7
6
5
4
3
2
1
ppm
12.00


49.51
49.34
49.17
49.00
48.83
48.66
48.49
45.41
O2S • N
N • SO2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


4.97
3.80
3.32
3.31
3.31
3.31
3.30
3.02
NH2
N
O
• SO2
9
8
7
6
5
4
3
2
1
ppm
3.98
4.00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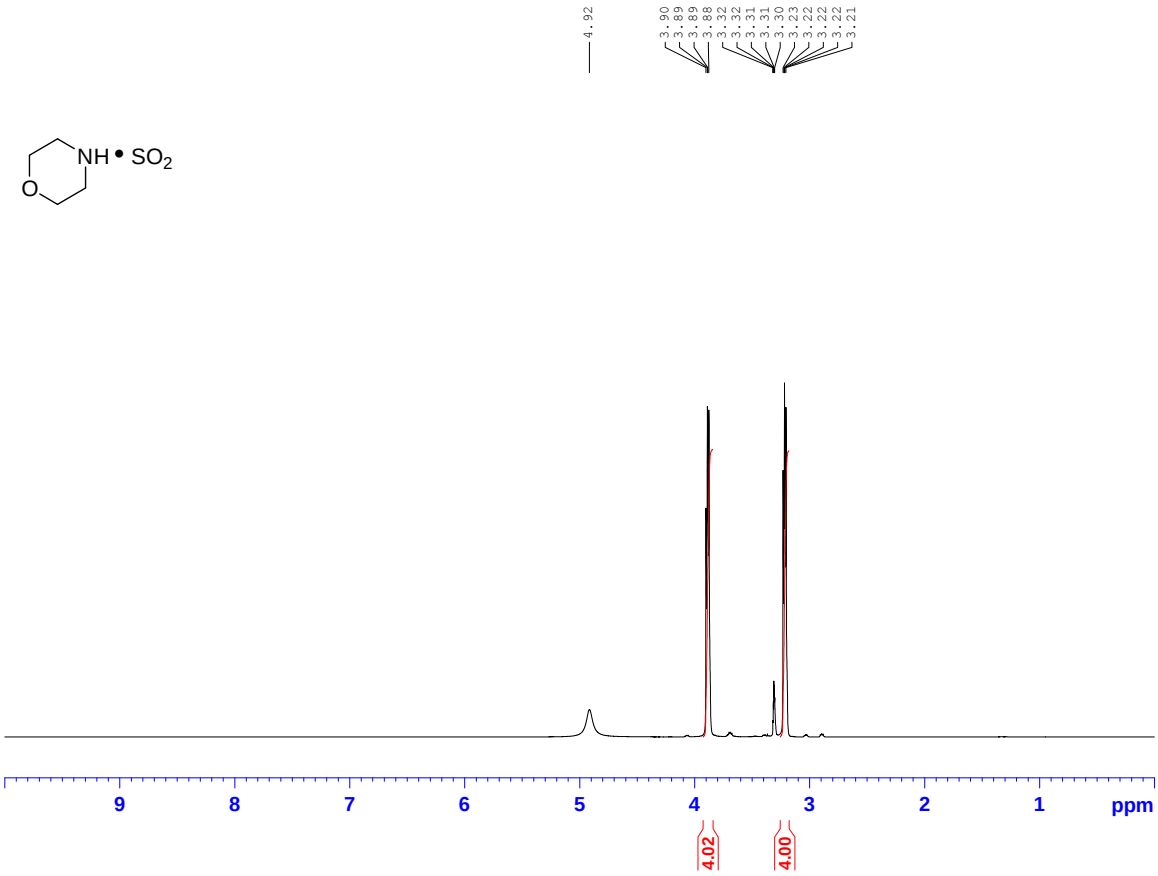
56.02
49.64
49.43
49.21
49.00
48.79
48.57
48.36
NH2
N
O
• SO2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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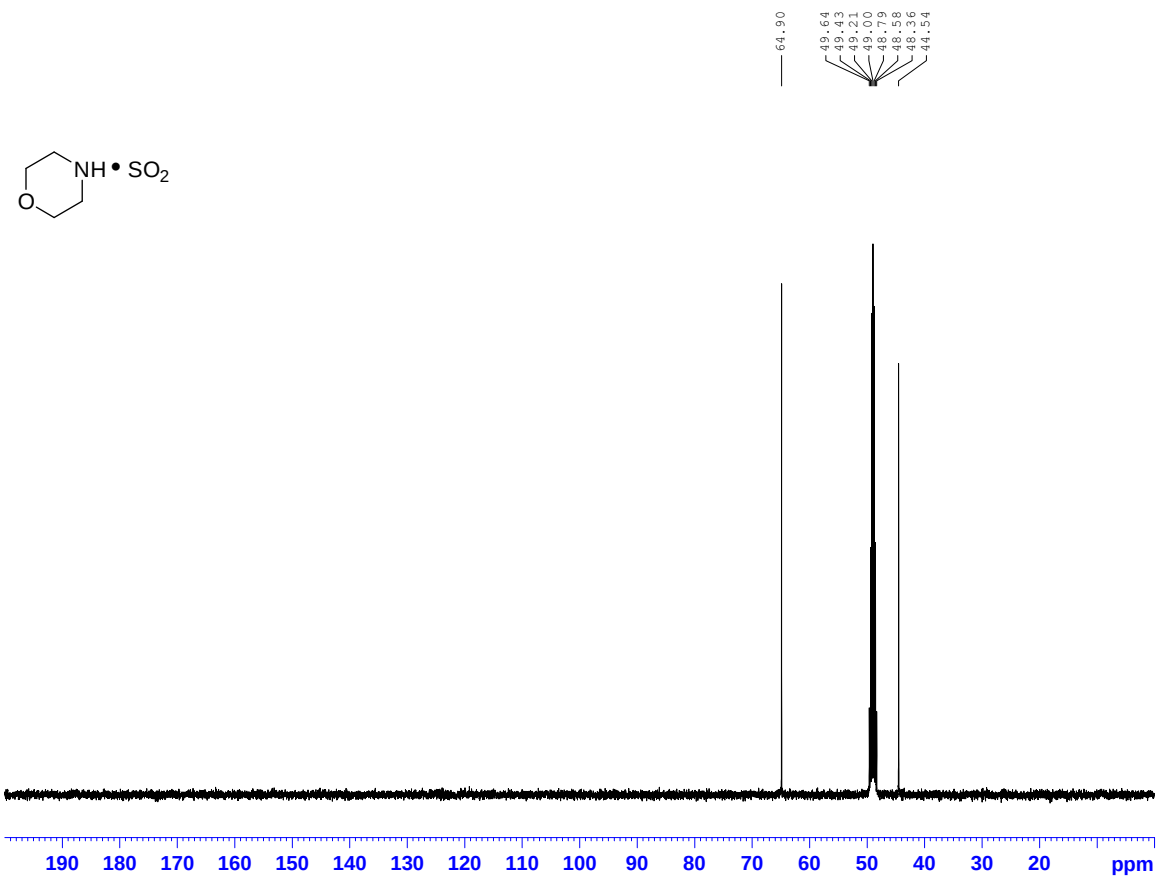
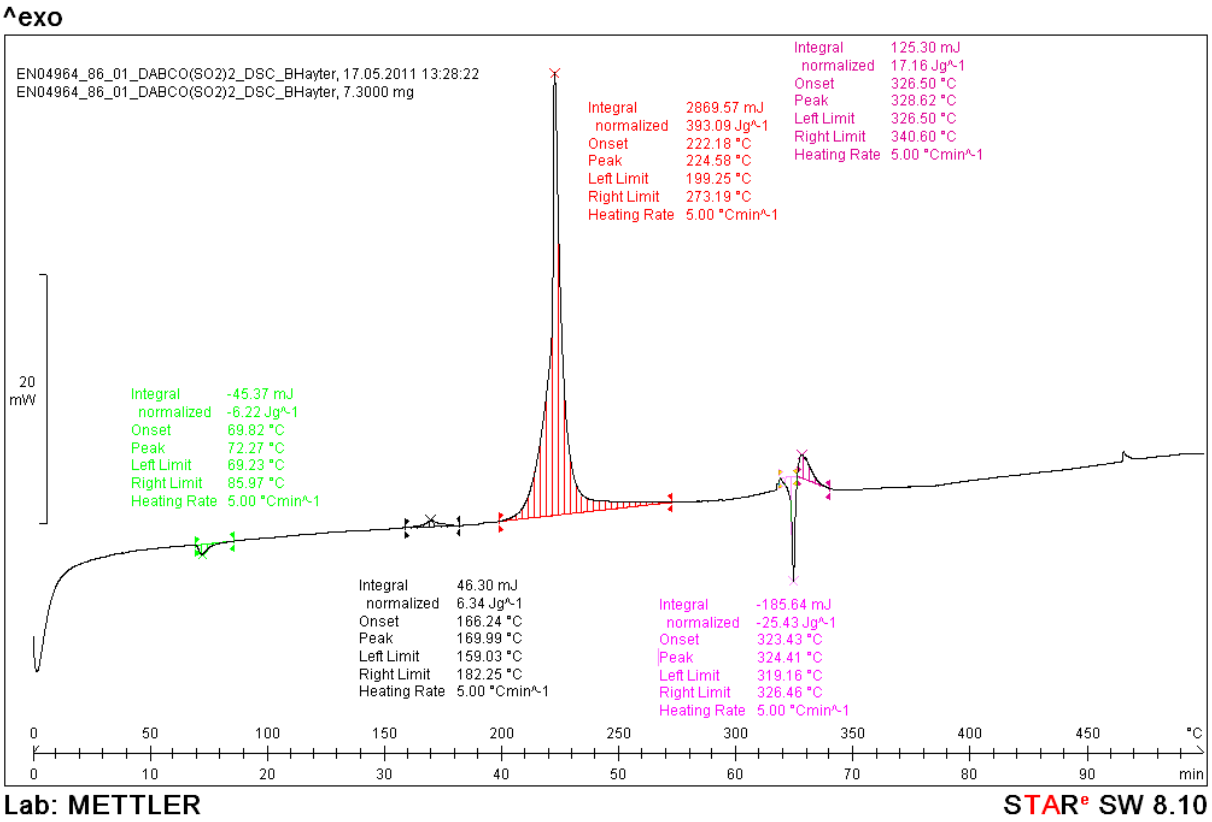
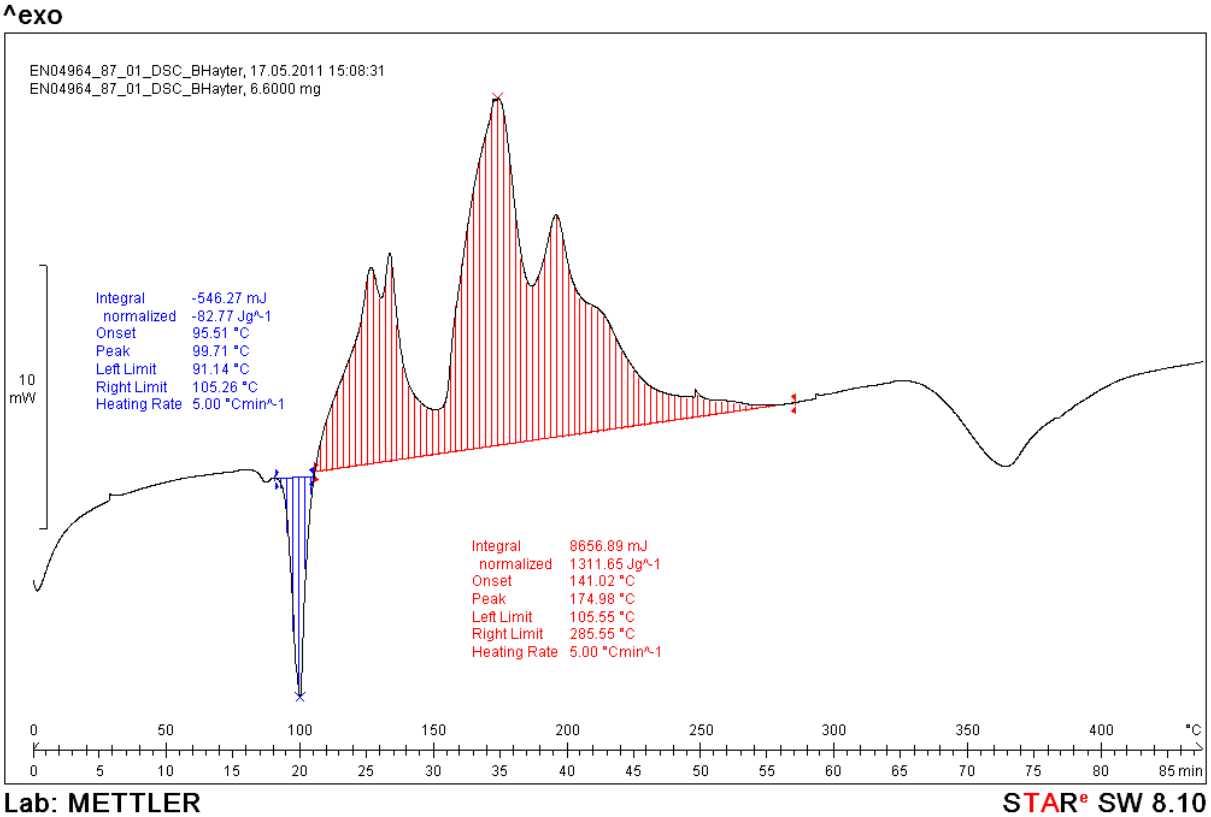
3.90
3.89
3.89
3.88
3.32
3.32
3.31
3.31
3.30
3.23
3.22
3.22
3.22
3.21
NH • SO2
O
9
8
7
6
5
4
3
2
1
ppm
4.02
4.00

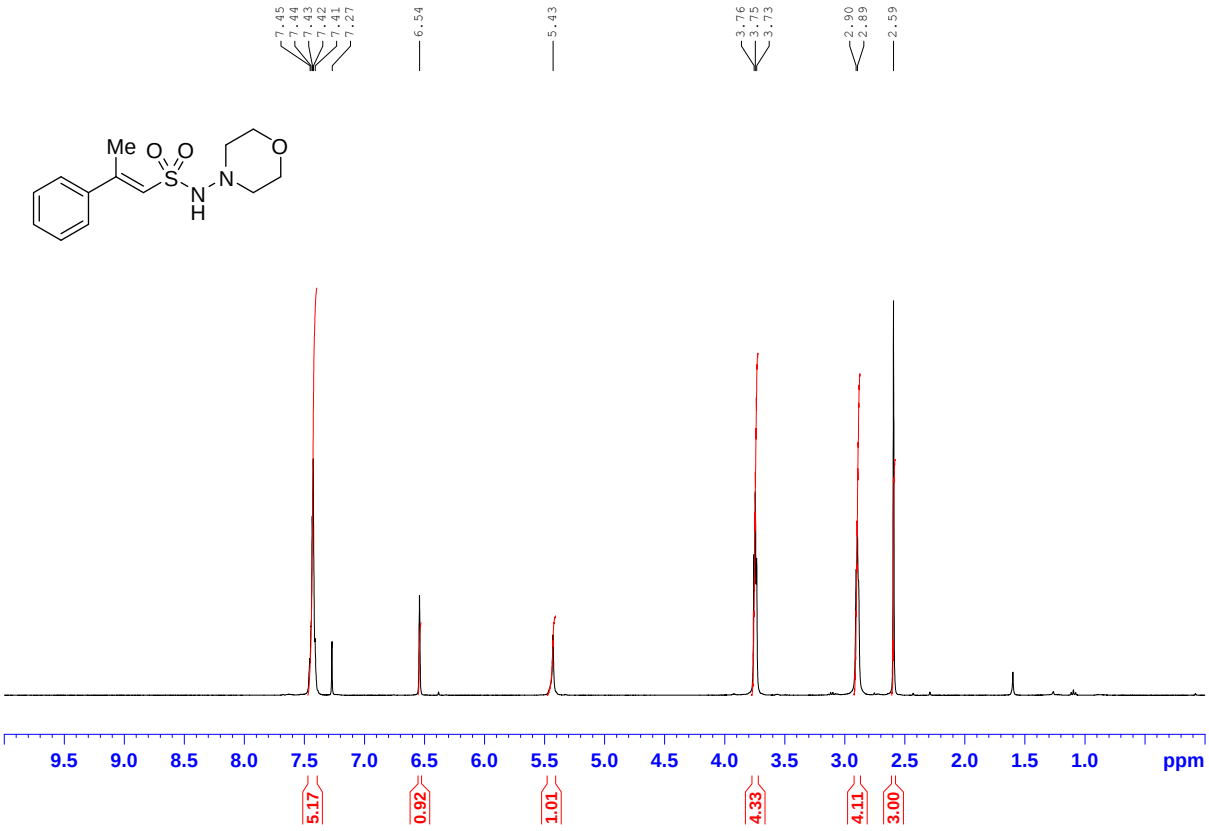

64.90
49.64
49.43
49.21
49.00
48.79
48.58
48.36
44.54
NH • SO2
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

DABSO (7b) DSC



4-Aminomorpholine sulfur dioxide complex (34) DSC

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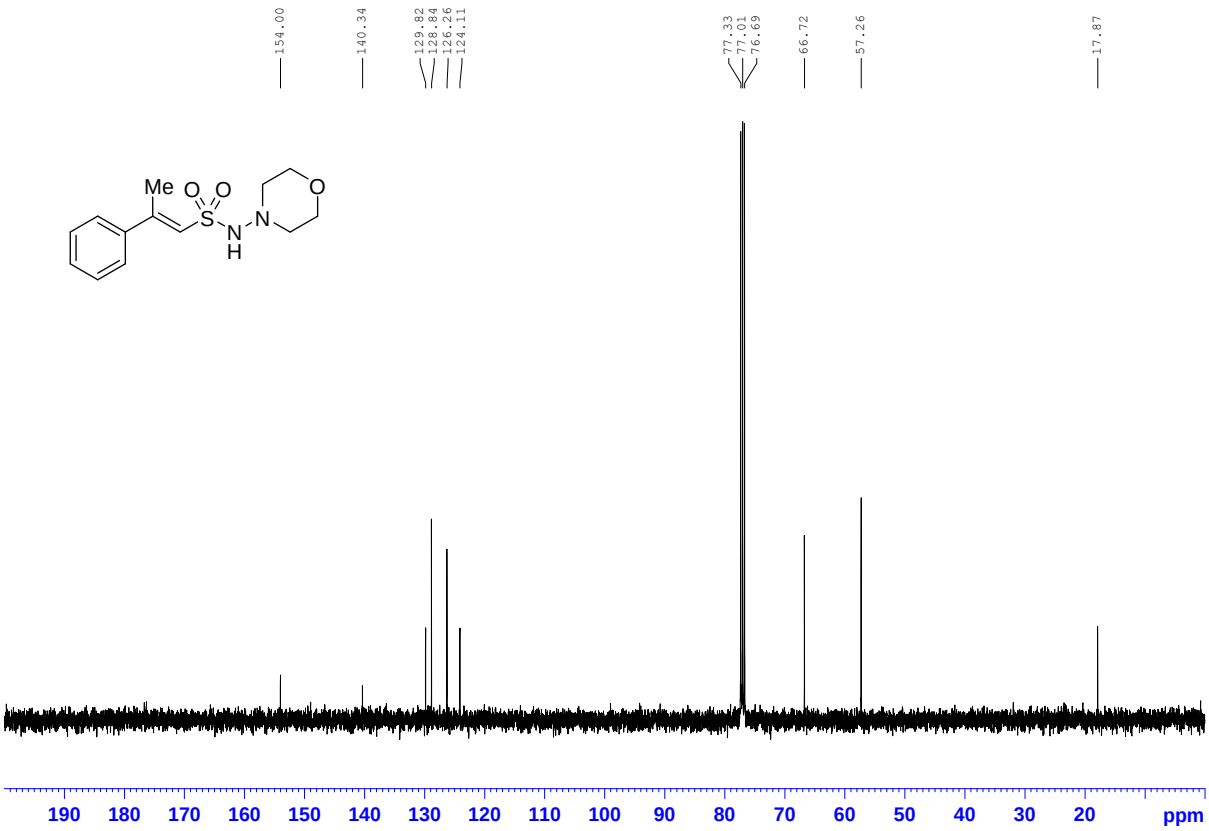
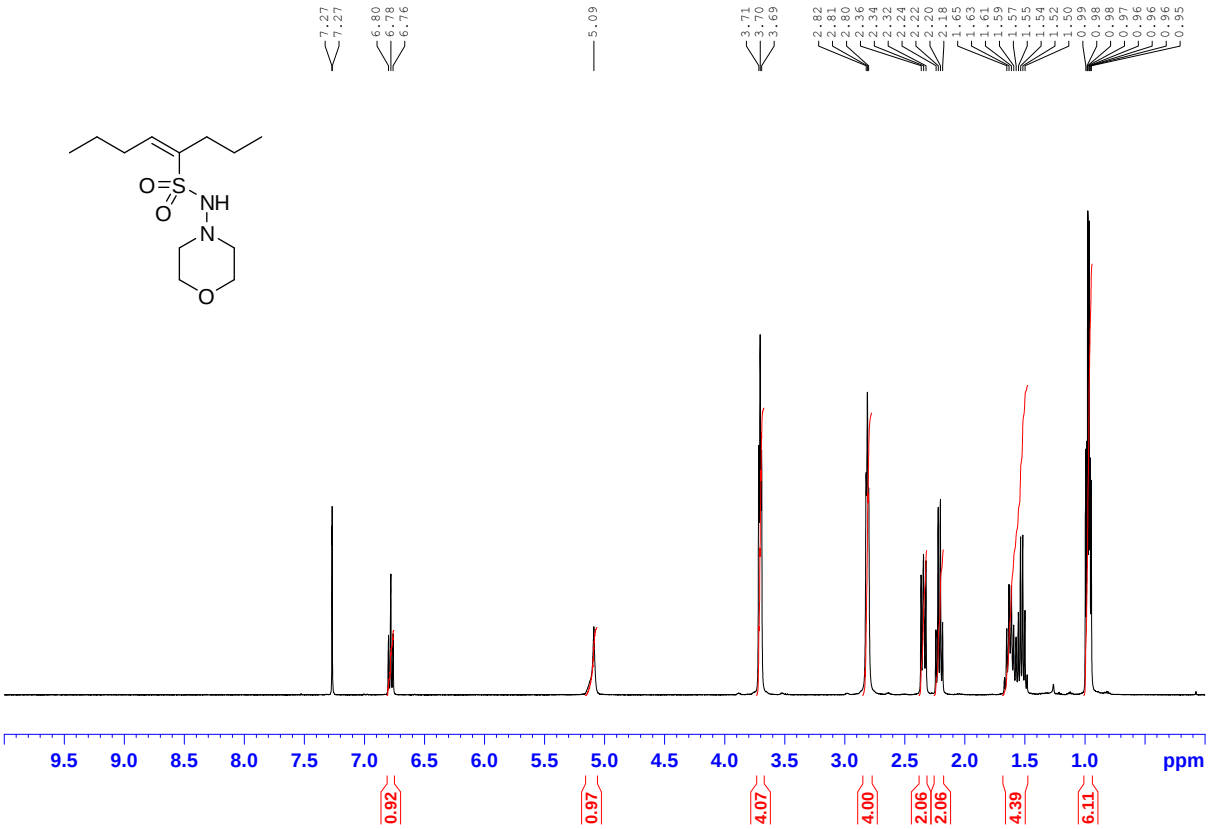
7.44
7.43
7.42
7.41
7.27
6.54
5.43
3.76
3.75
3.73
2.90
2.89
2.59
Me
O
O
S
N
H
N
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.17
0.92
1.01
4.33
4.11
3.00


154.00
140.34
129.82
128.84
126.26
124.11
77.33
77.01
76.69
66.72
57.26
17.87
Me
O
O
S
N
H
N
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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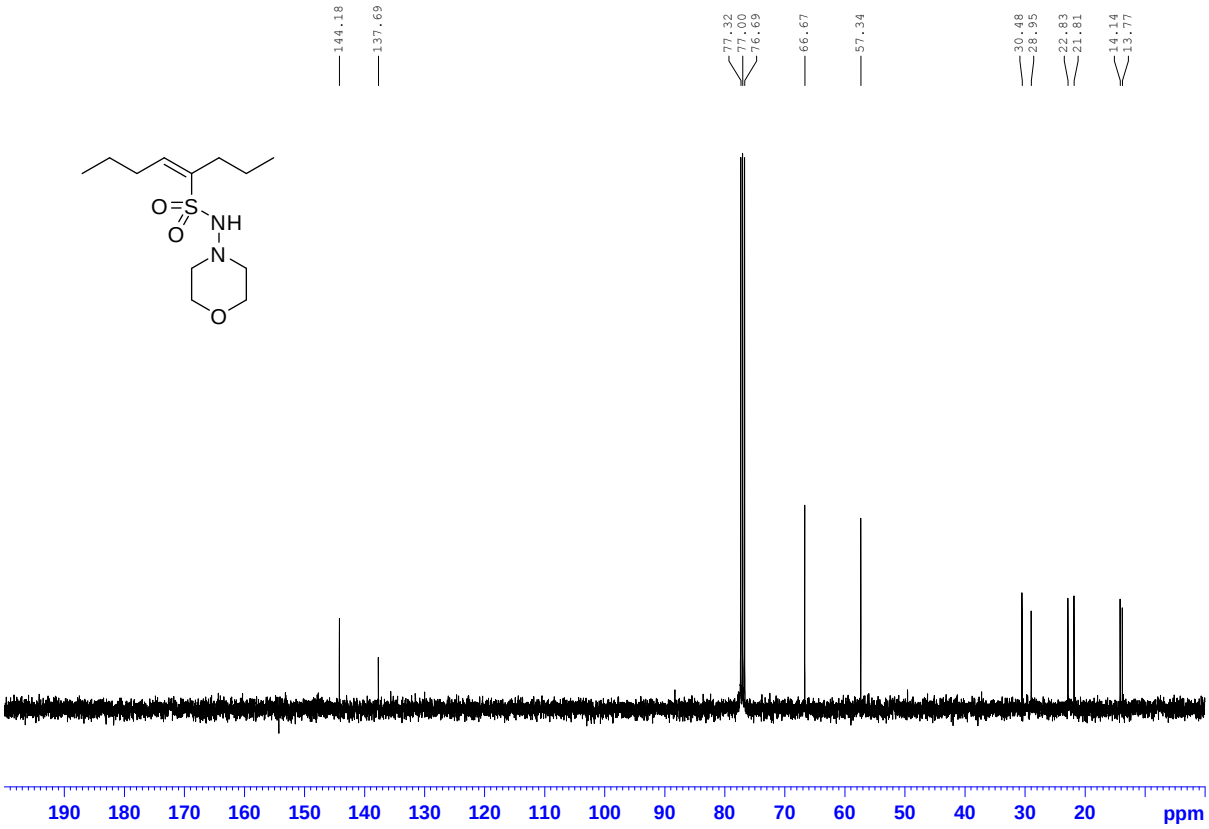
7.27
6.80
6.78
6.76
5.09
3.71
3.70
3.69
2.82
2.81
2.80
2.36
2.34
2.32
2.24
2.22
2.20
2.18
1.65
1.63
1.61
1.59
1.57
1.55
1.54
1.52
1.50
0.99
0.98
0.98
0.97
0.96
0.96
0.96
0.95
O=S
O
NH
N
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.92
0.97
4.07
4.00
2.06
2.06
4.39
6.11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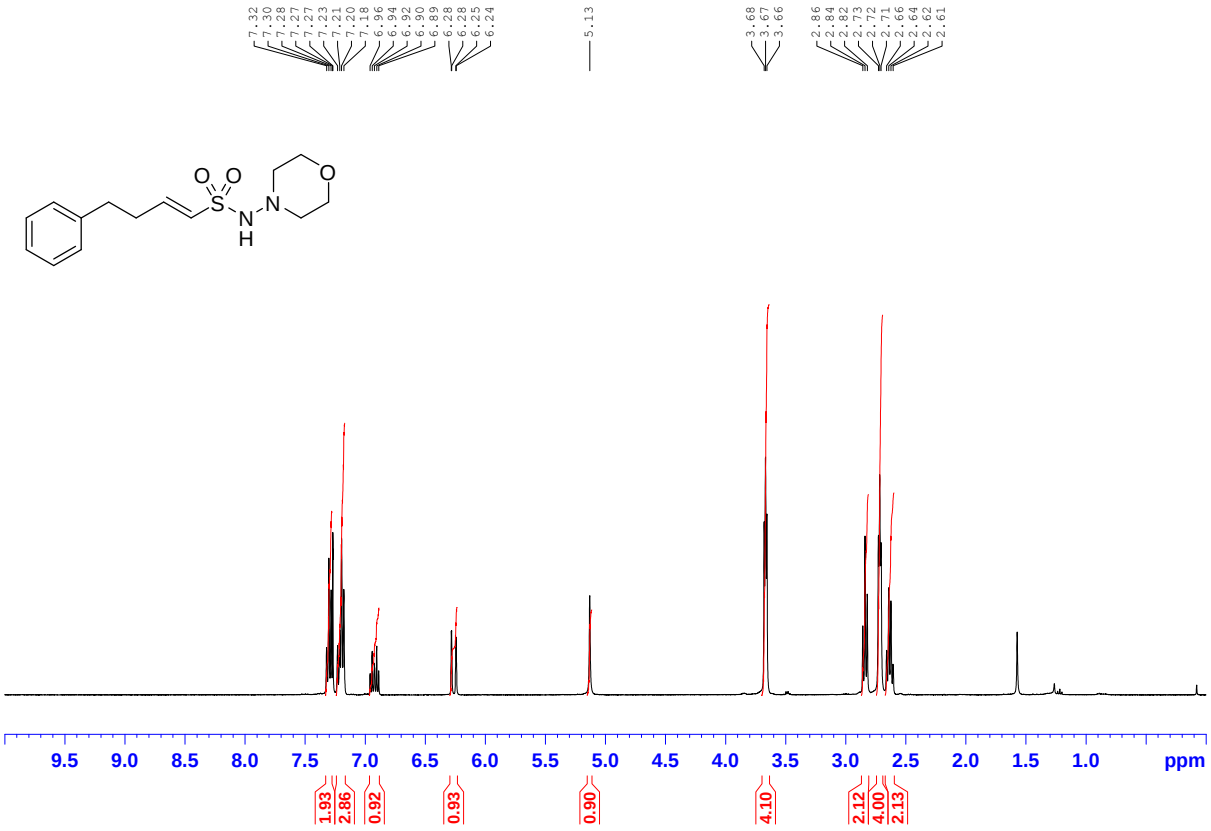
137.69
77.32
77.00
76.69
66.67
57.34
30.48
28.95
22.83
21.81
14.14
13.77
O=S
O
NH
N
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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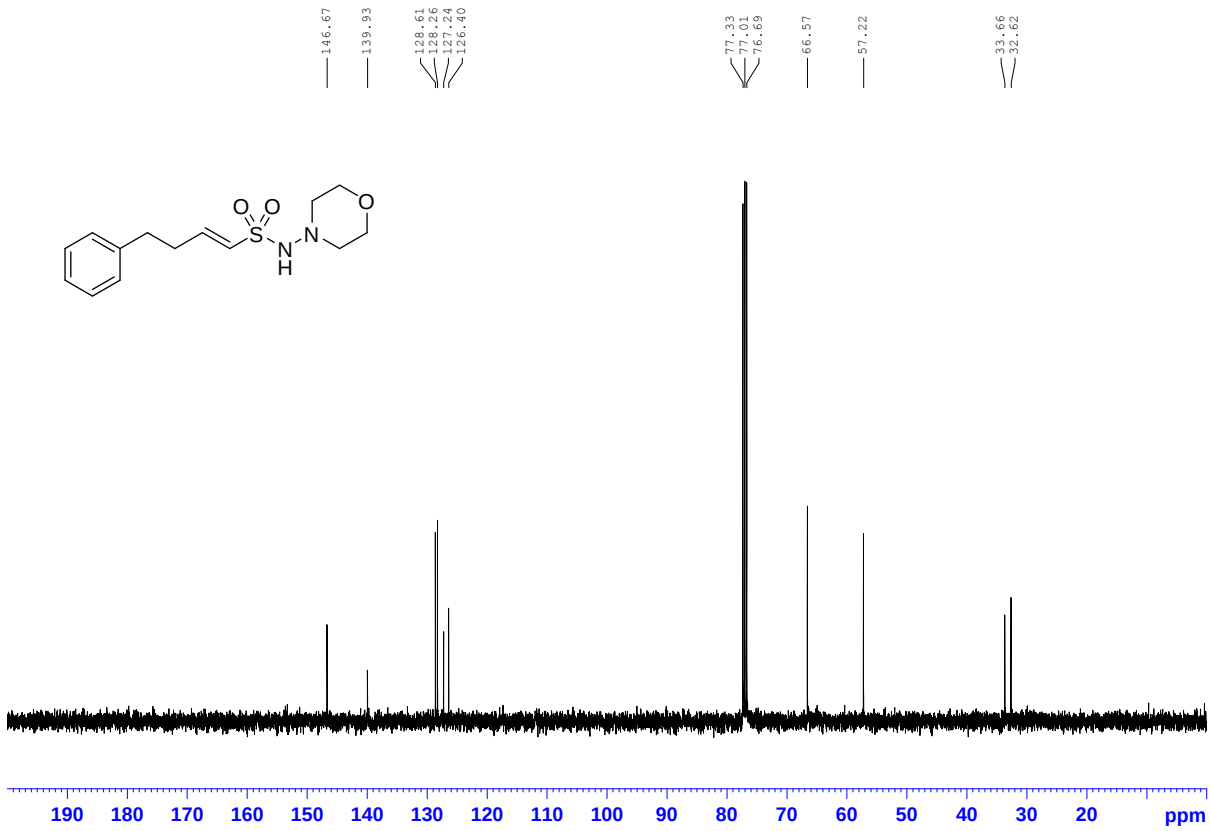
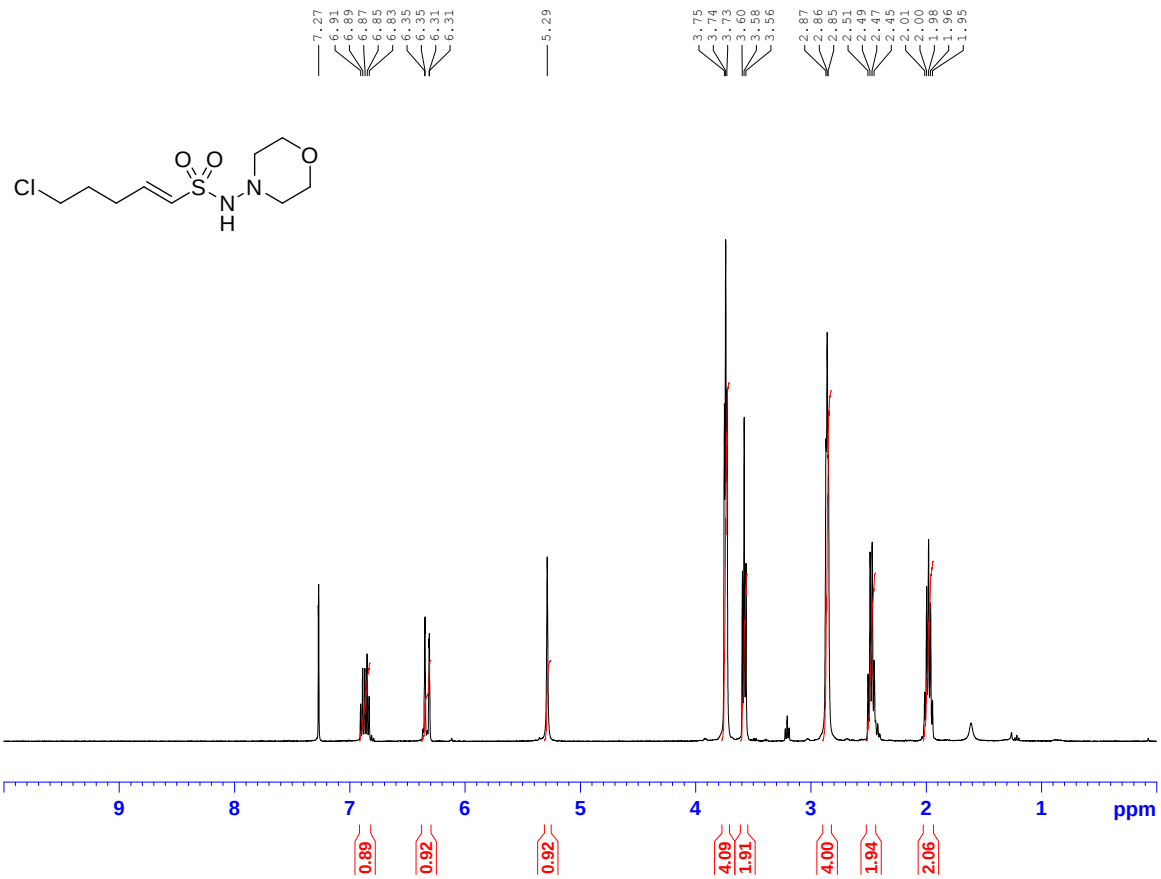
7.30
7.28
7.27
7.27
7.23
7.21
7.20
7.18
6.96
6.94
6.92
6.90
6.89
6.28
6.28
6.25
6.24
5.13
3.68
3.67
3.66
2.86
2.84
2.82
2.73
2.72
2.71
2.66
2.64
2.62
2.61
O
O
S
N
H
N
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.93
2.86
0.92
0.93
0.90
4.10
2.12
4.00
2.13


146.67
139.93
128.61
128.26
127.24
126.40
77.33
77.01
76.69
66.57
57.22
33.66
32.62
O
O
S
N
H
N
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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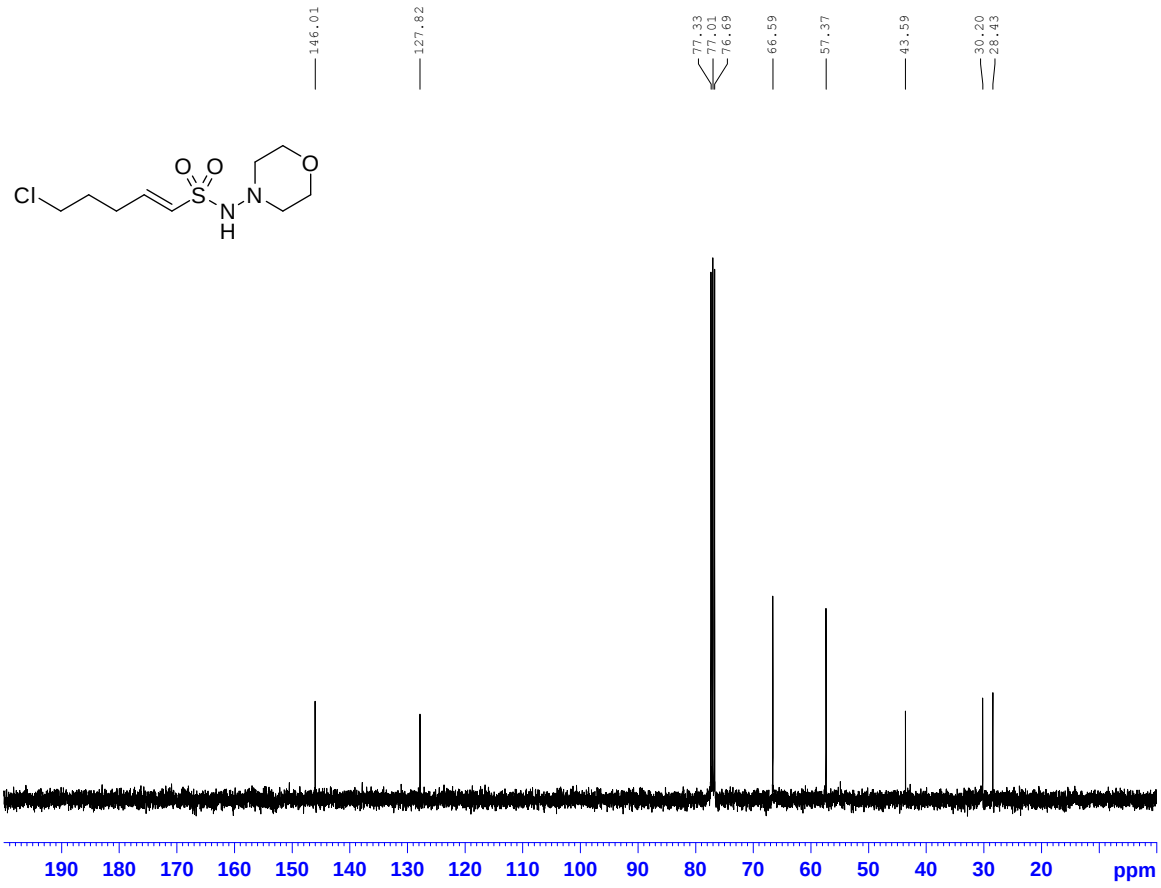
6.91
6.89
6.87
6.85
6.83
6.35
6.31
5.29
3.75
3.74
3.73
3.60
3.58
3.56
2.87
2.86
2.85
2.51
2.49
2.47
2.45
2.01
2.00
1.98
1.96
1.95
Cl
O
O
S
N
H
O
N
9
8
7
6
5
4
3
2
1
ppm
0.89
0.92
0.92
4.09
1.91
4.00
1.94
2.06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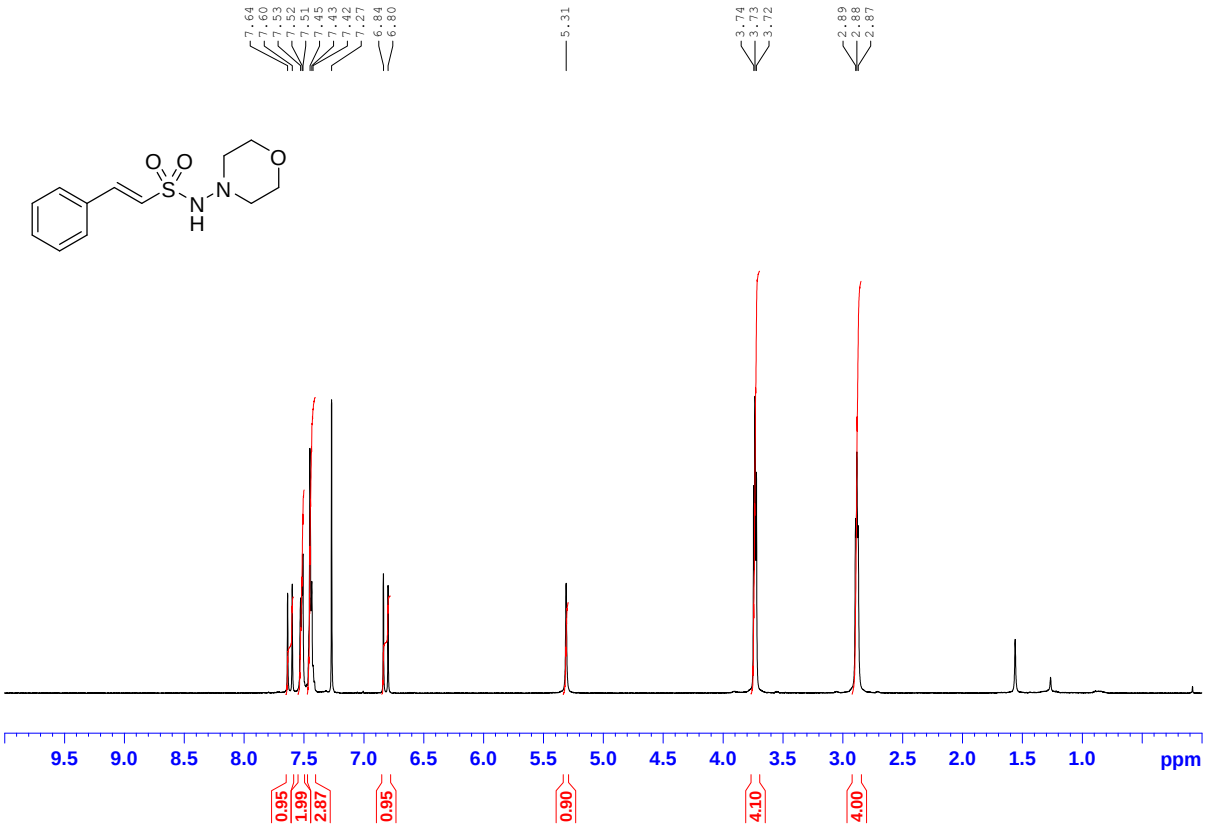
127.82
77.33
77.01
76.69
66.59
57.37
43.59
30.20
28.43
Cl
O
O
S
N
H
O
N
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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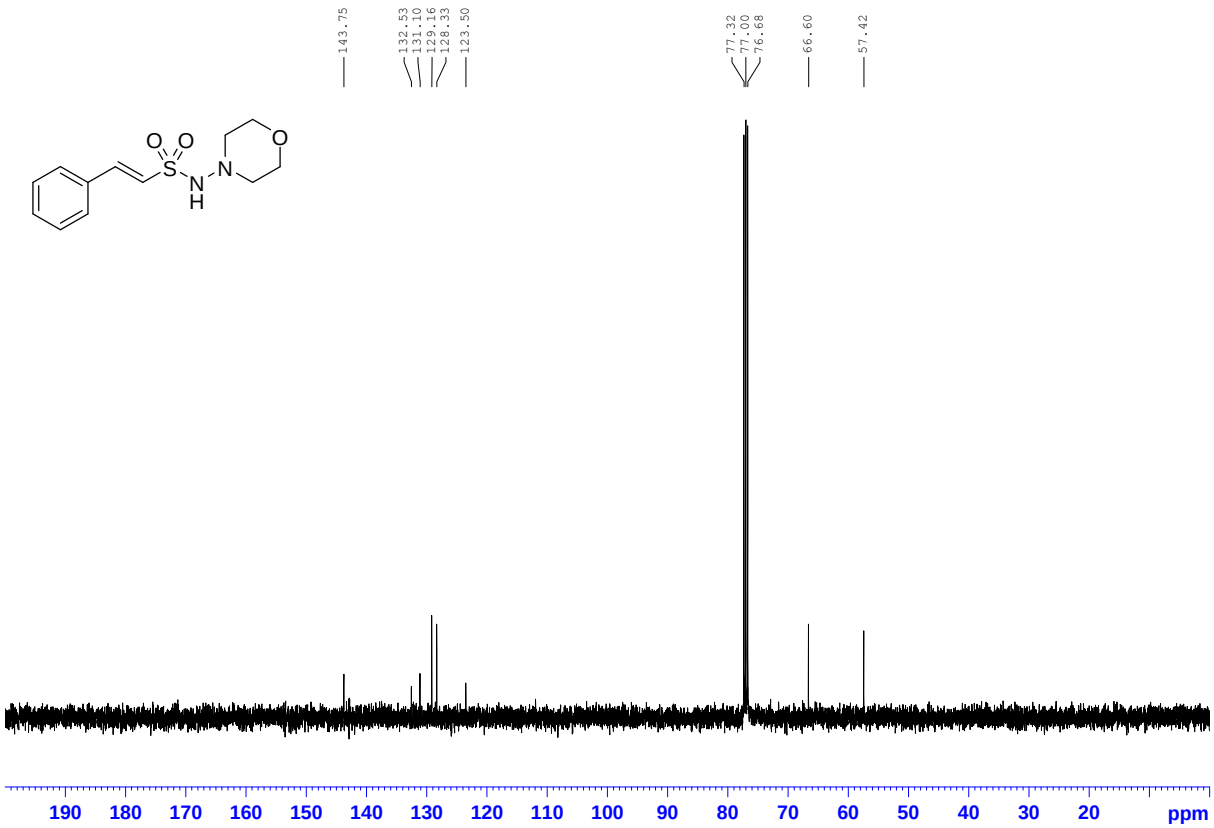
7.60
7.53
7.52
7.51
7.45
7.43
7.42
7.27
6.84
6.80
5.31
3.74
3.73
3.72
2.89
2.88
2.87
O
O
S
N
H
N
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.95
1.99
2.87
0.95
0.90
4.10
4.00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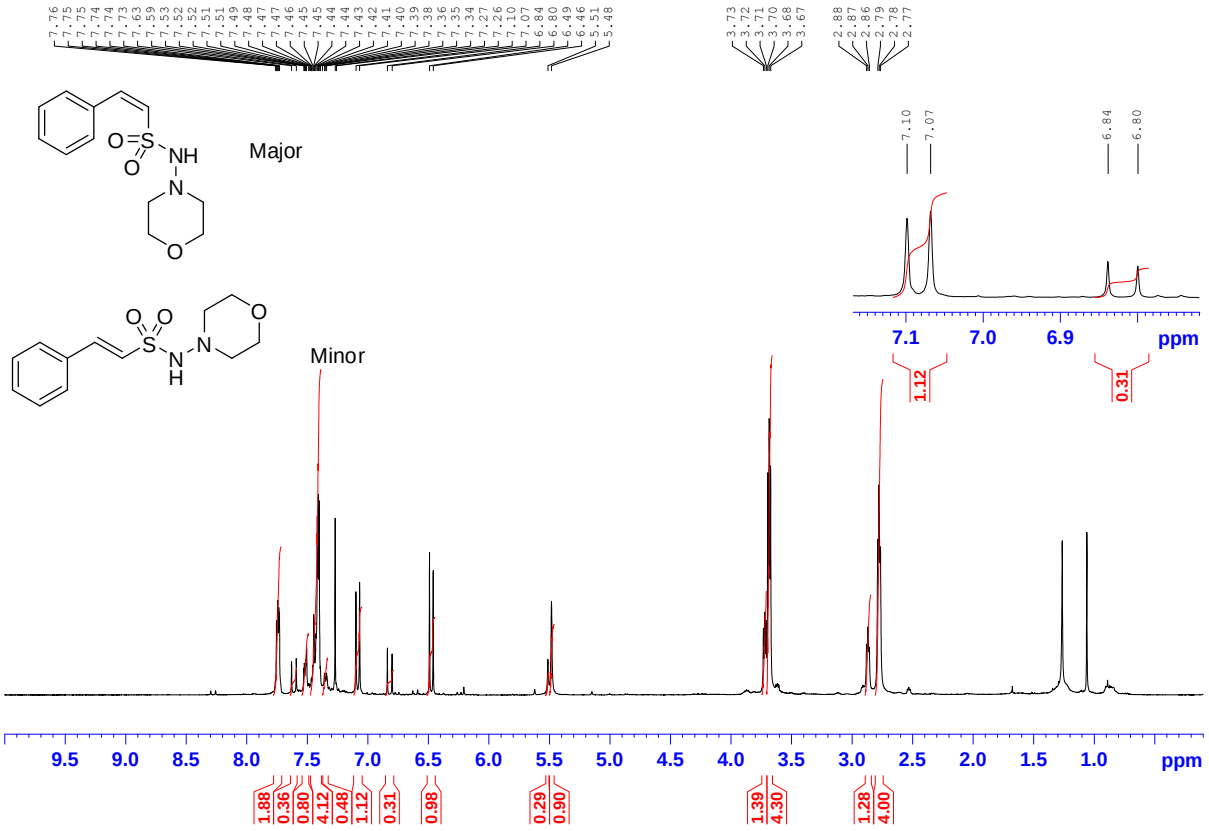
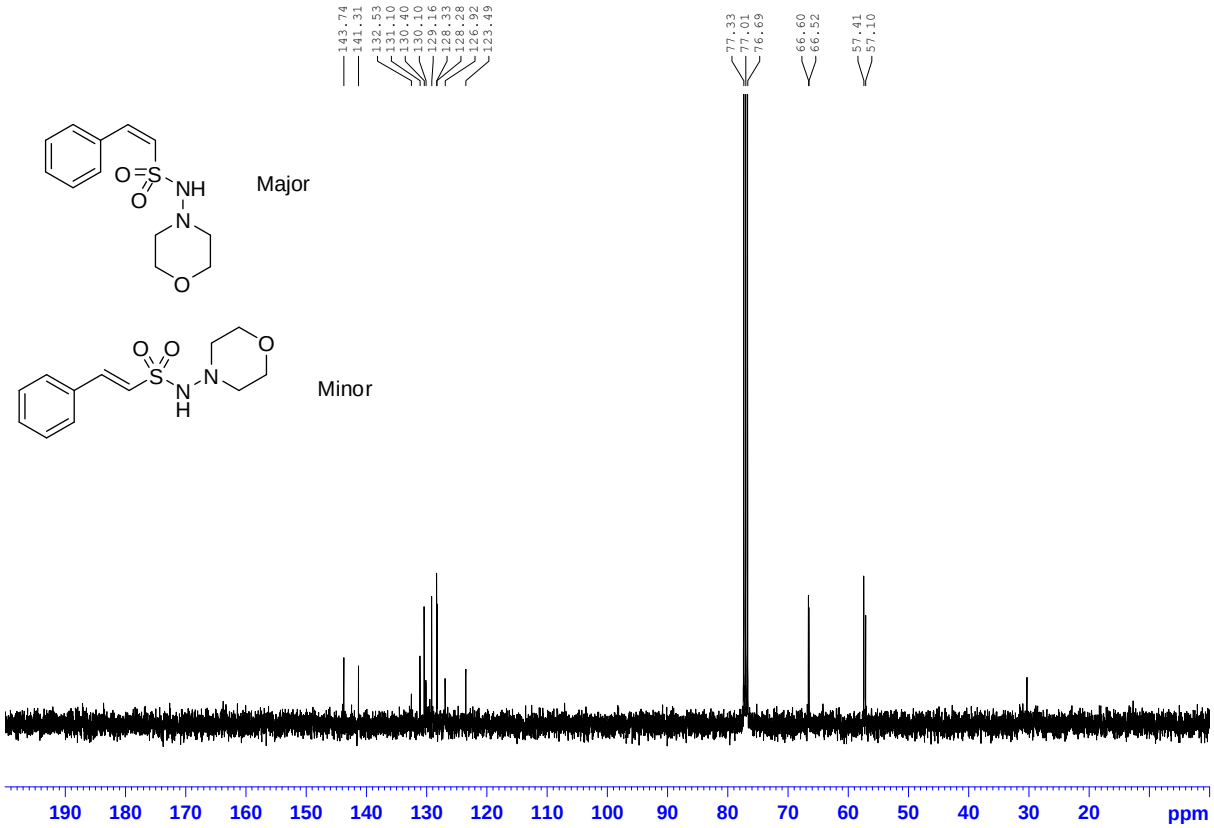
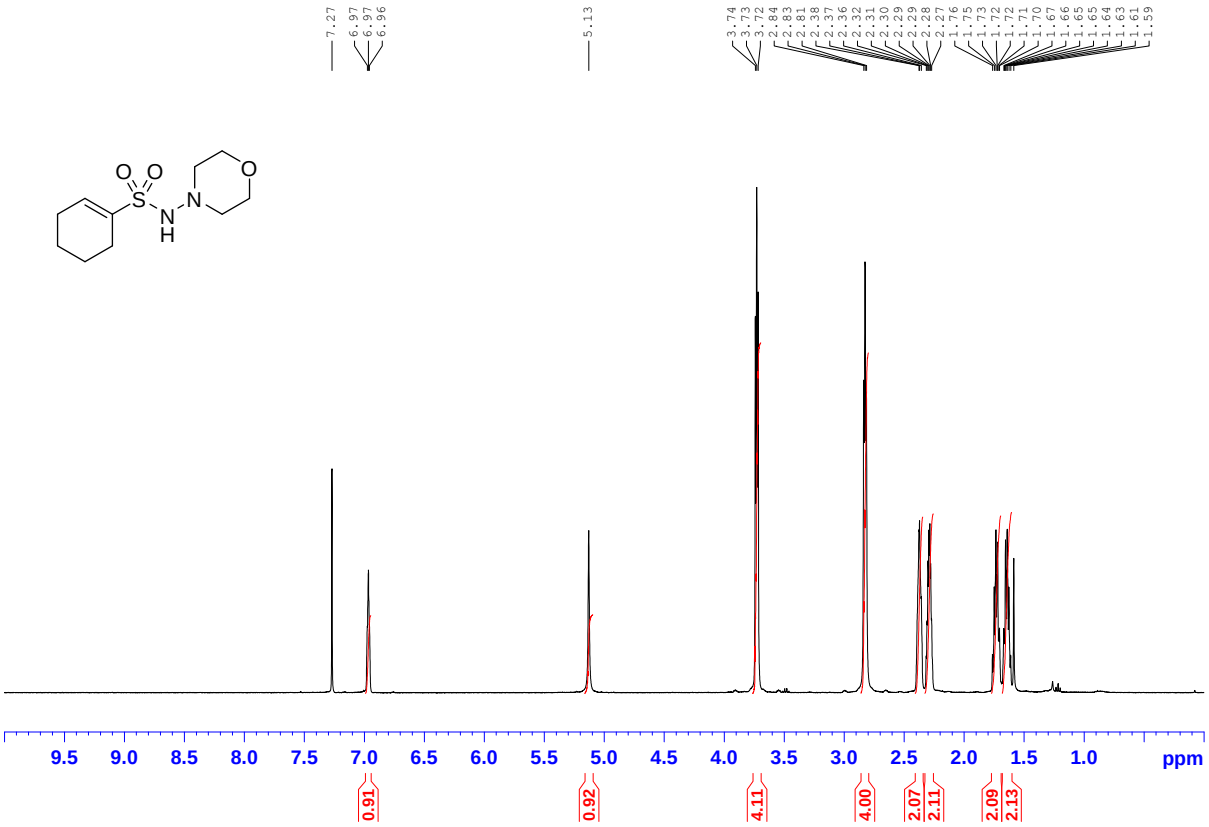
131.10
129.16
128.33
123.50
77.32
77.00
76.68
66.60
57.42
O
O
S
N
H
N
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Major
Minor
ppm


Major
Minor
ppm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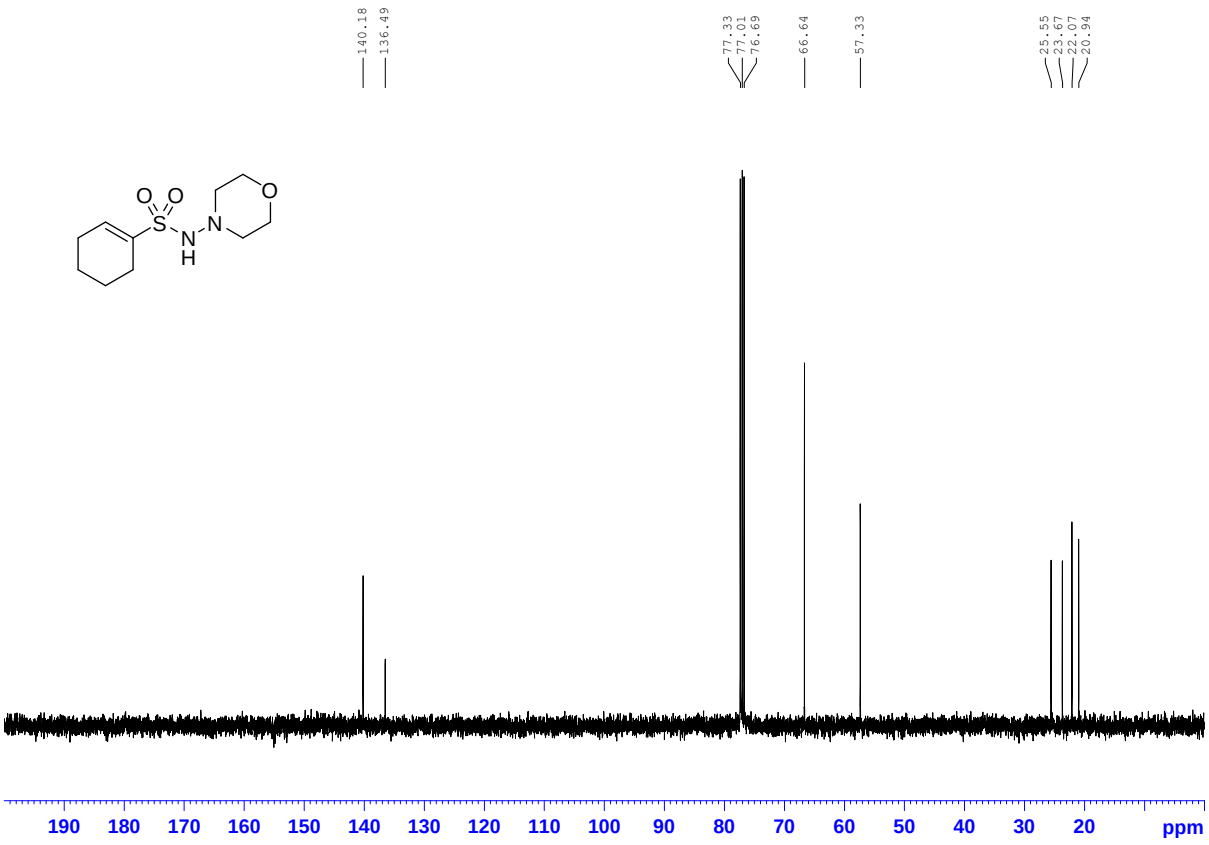
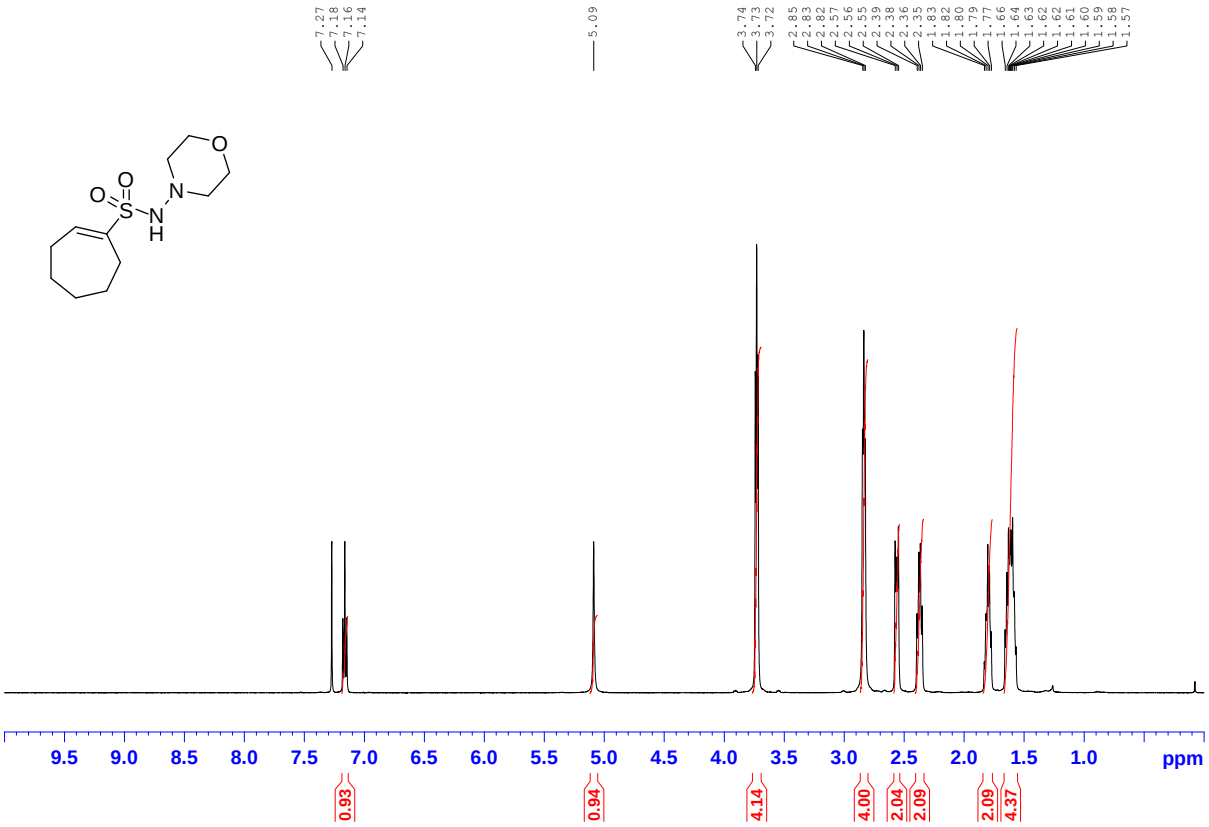
6.97
6.97
6.96
5.13
3.74
3.73
3.72
2.84
2.83
2.81
2.38
2.37
2.36
2.32
2.31
2.30
2.29
2.29
2.28
2.27
1.76
1.75
1.73
1.72
1.72
1.71
1.70
1.67
1.66
1.65
1.65
1.64
1.63
1.61
1.59
O
O
S
N
N
H
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.91
0.92
4.11
4.00
2.07
2.11
2.09
2.13


140.18
136.49
77.33
77.01
76.69
66.64
57.33
25.55
23.67
22.07
20.94
O
O
S
N
N
H
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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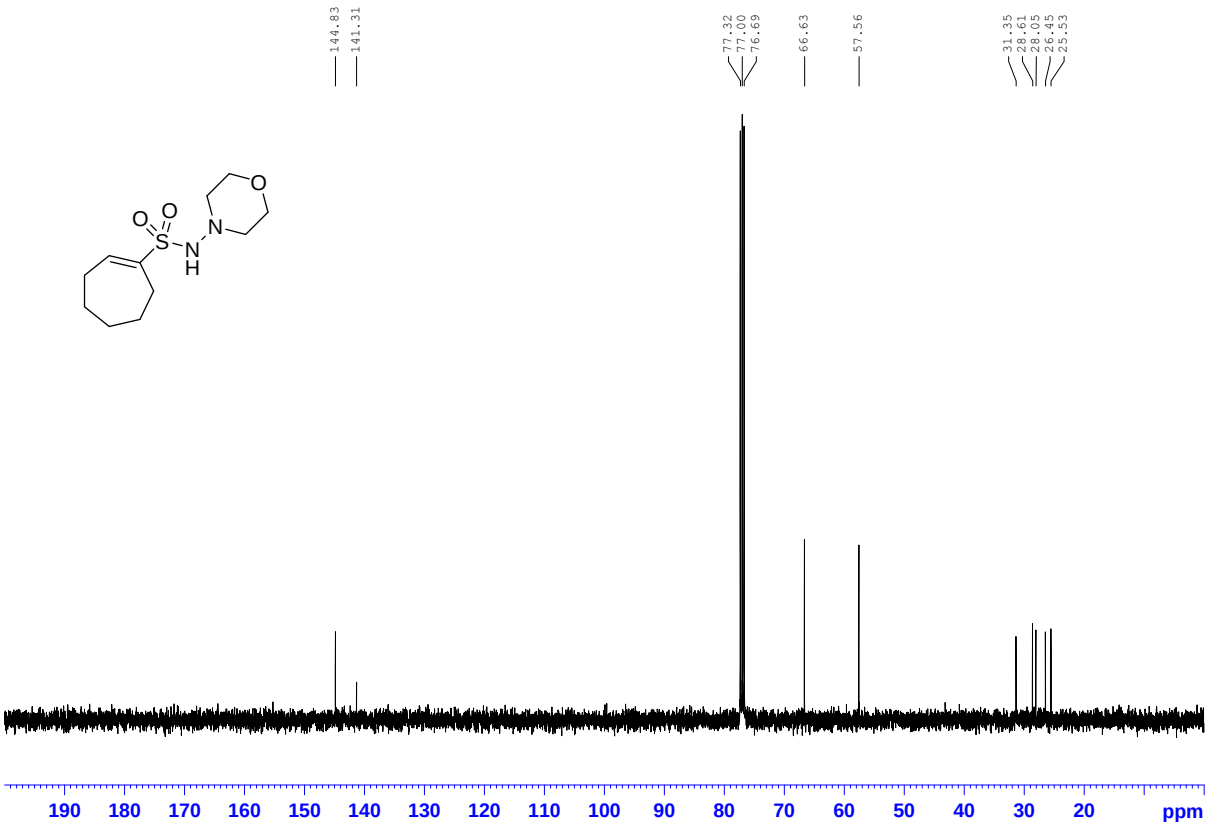
7.18
7.16
7.14
5.09
3.74
3.73
3.72
2.85
2.83
2.82
2.57
2.56
2.55
2.39
2.38
2.36
2.35
1.83
1.82
1.80
1.79
1.77
1.66
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.58
1.57
O
O
S
N
H
N
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.93
0.94
4.14
4.00
2.04
2.09
2.09
4.37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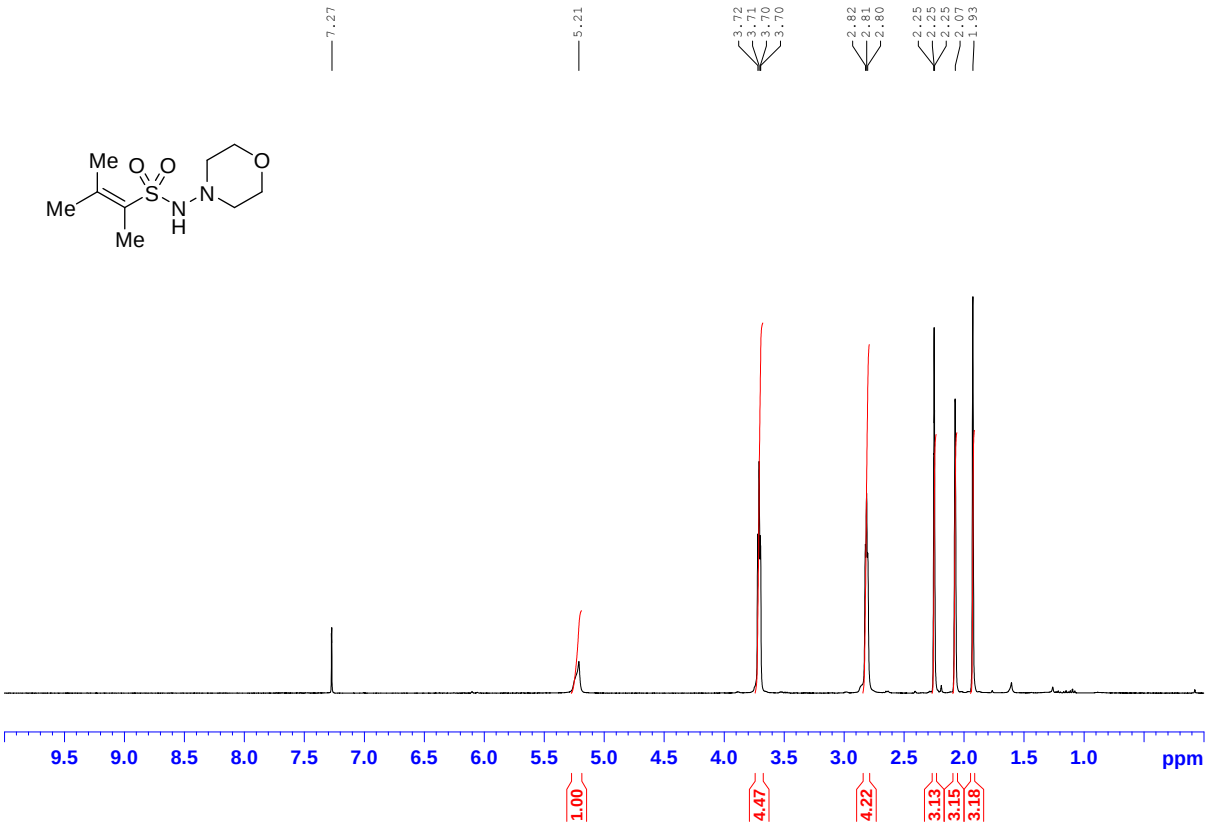
77.32
77.00
76.69
66.63
57.56
31.35
28.61
28.05
26.45
25.53
O
O
S
N
H
N
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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5.21
3.72
3.71
3.70
3.70
2.82
2.81
2.80
2.25
2.25
2.25
2.07
1.93
Me
O
O
S
N
O
Me
N
H
Me
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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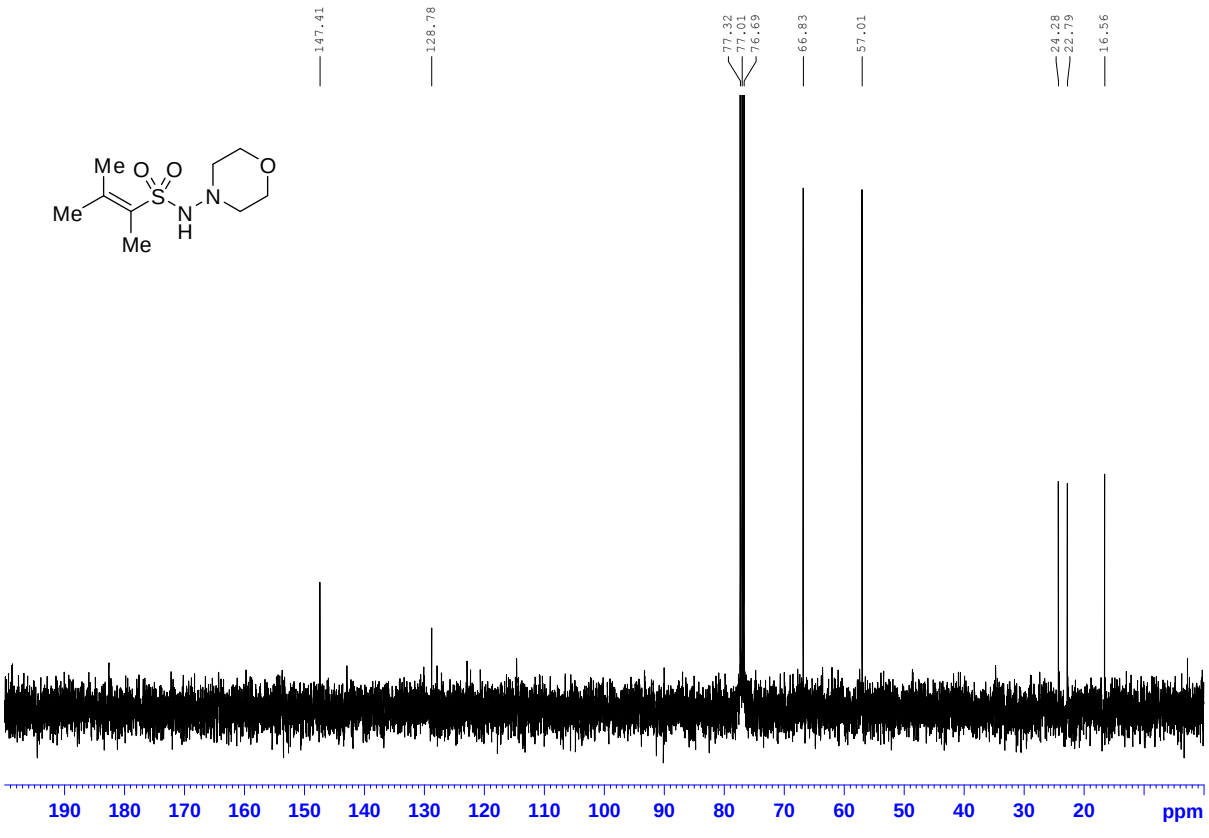
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S
N
O
Me
N
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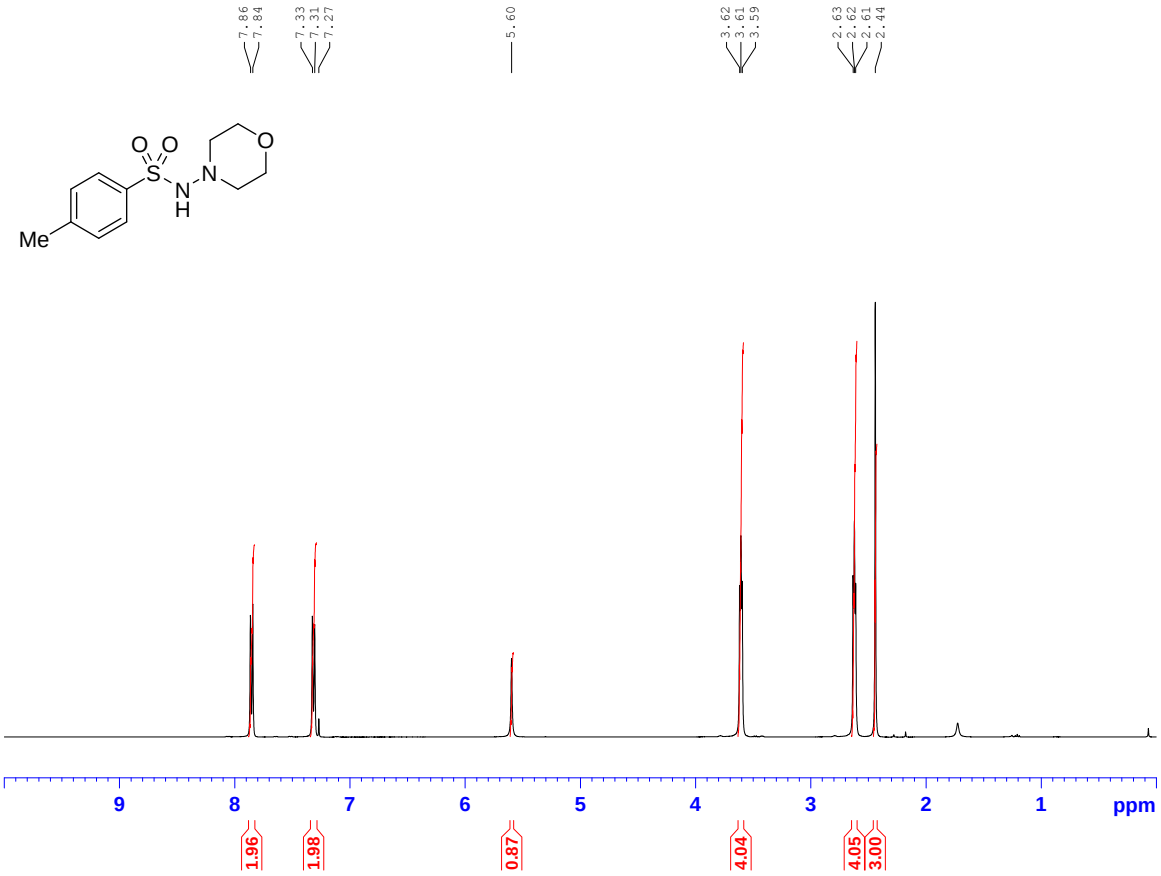
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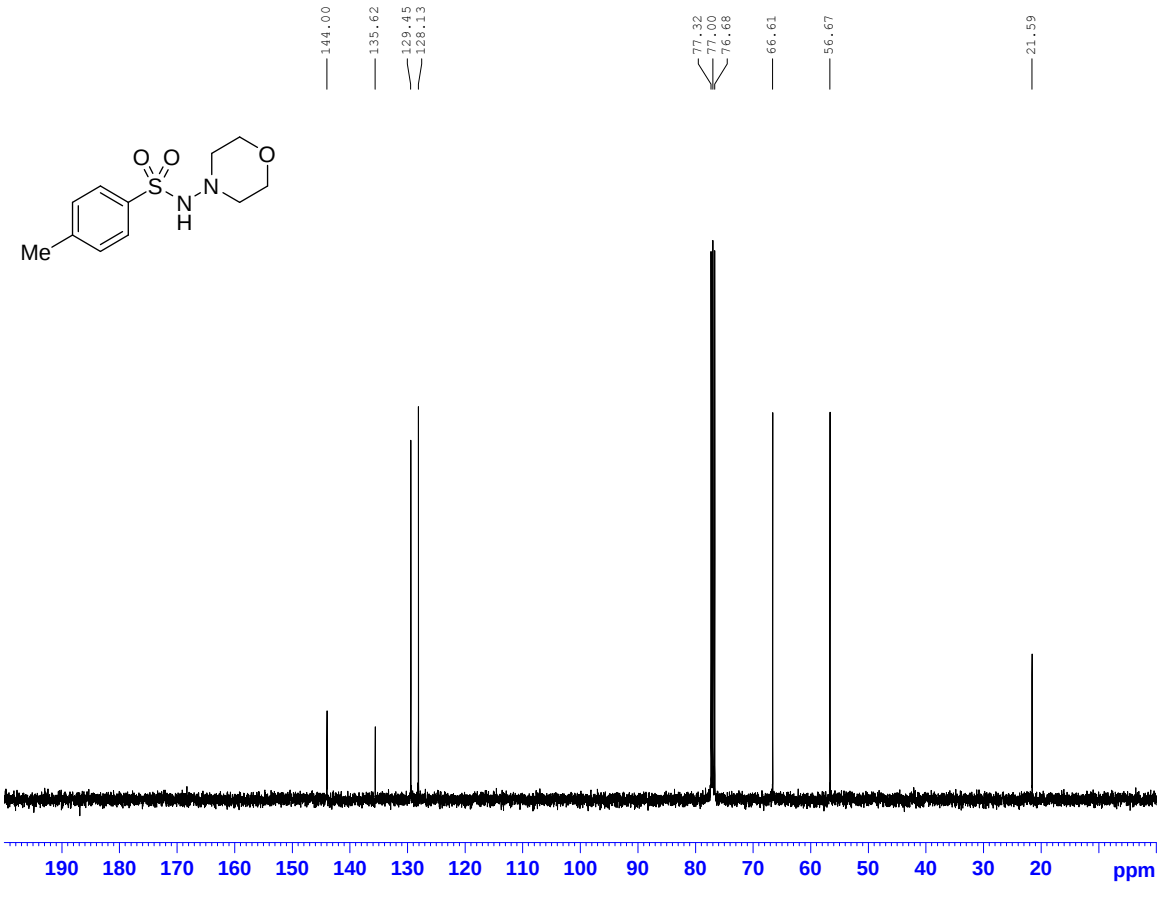
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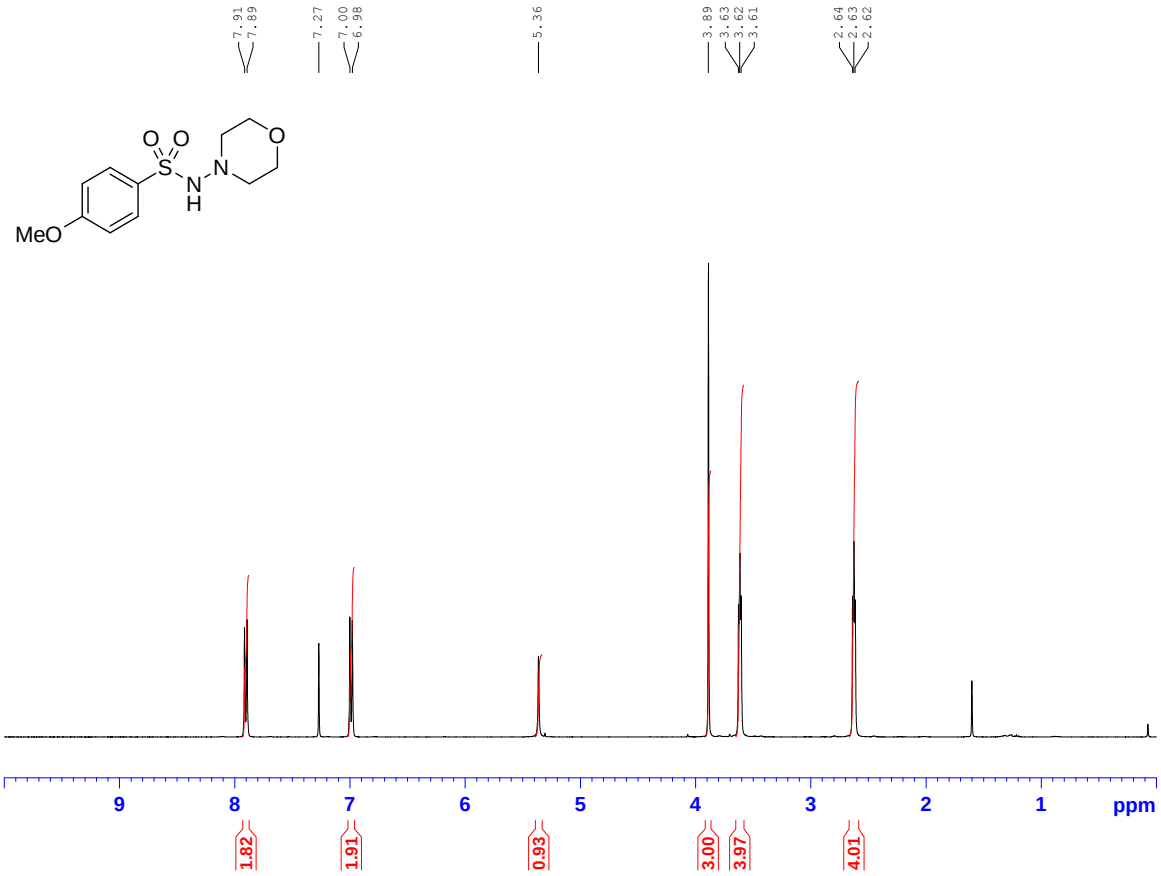
ppm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MeO
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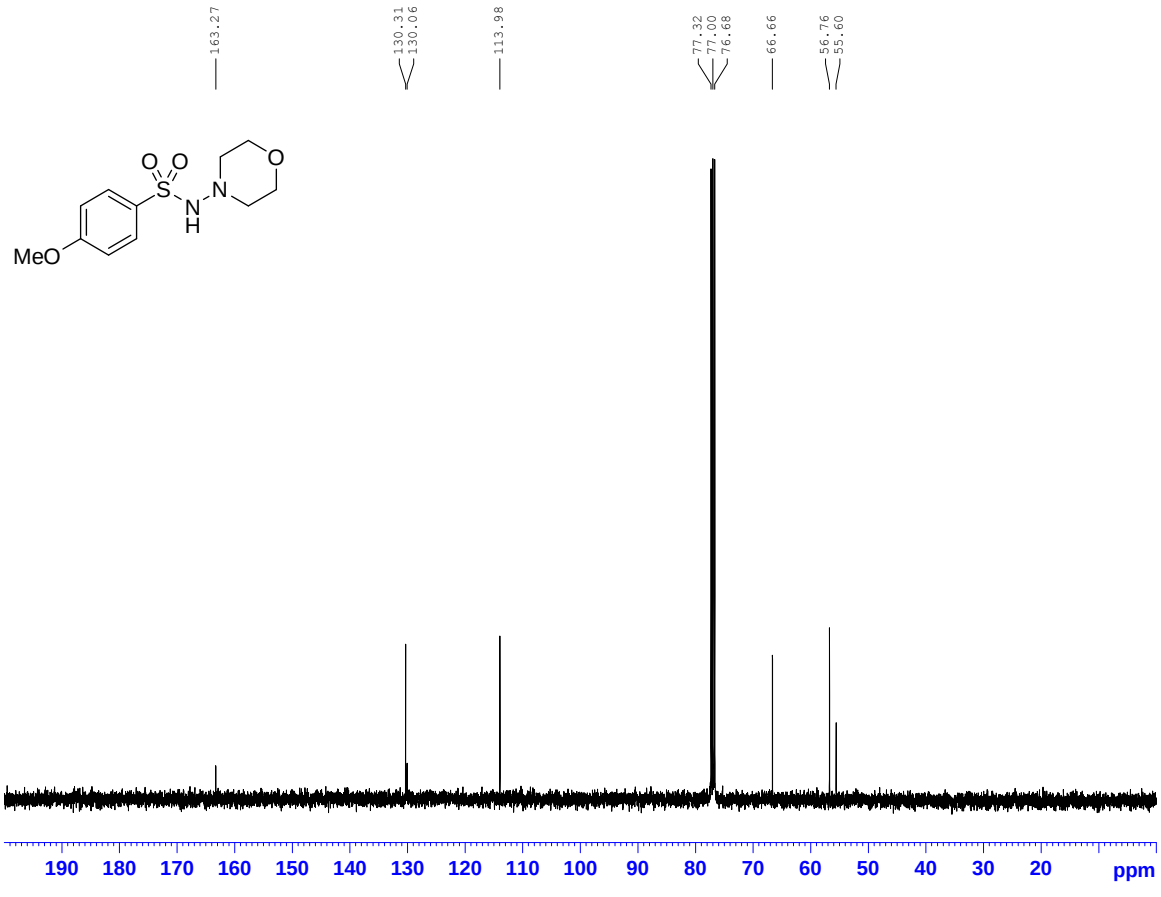
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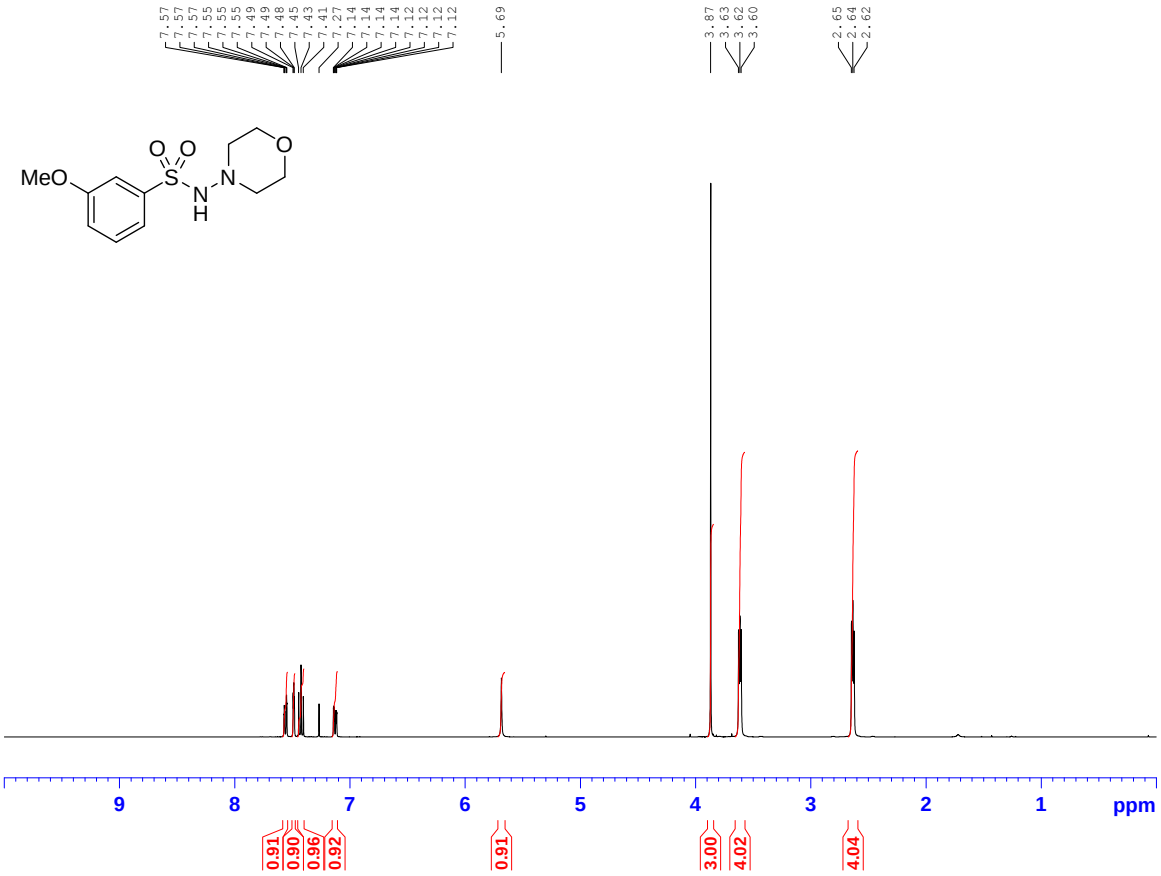
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O
O
S
N
H
N
O
9
8
7
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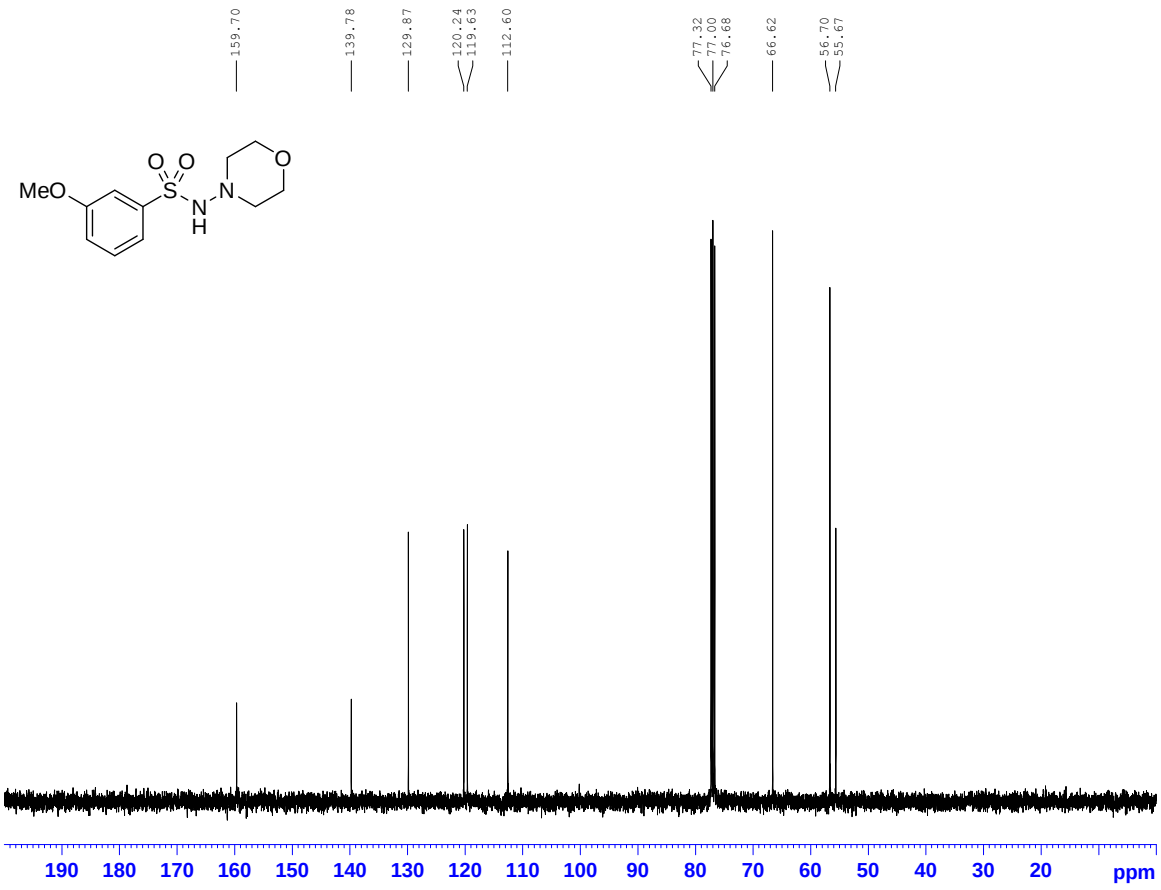
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O
S
N
H
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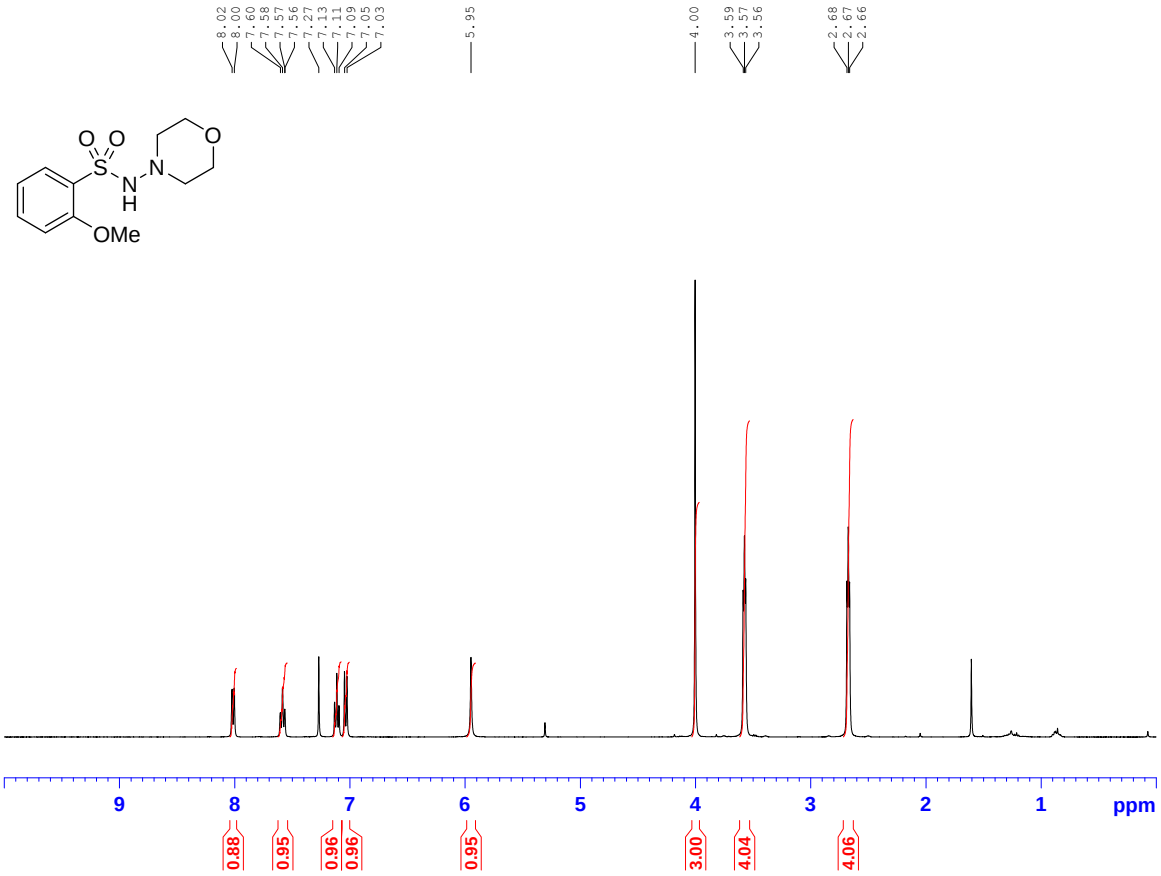
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7.27
7.13
7.11
7.09
7.05
7.03
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4.00
3.59
3.57
3.56
2.68
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O
O
S
N
H
O
N
OMe
9
8
7
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0.96
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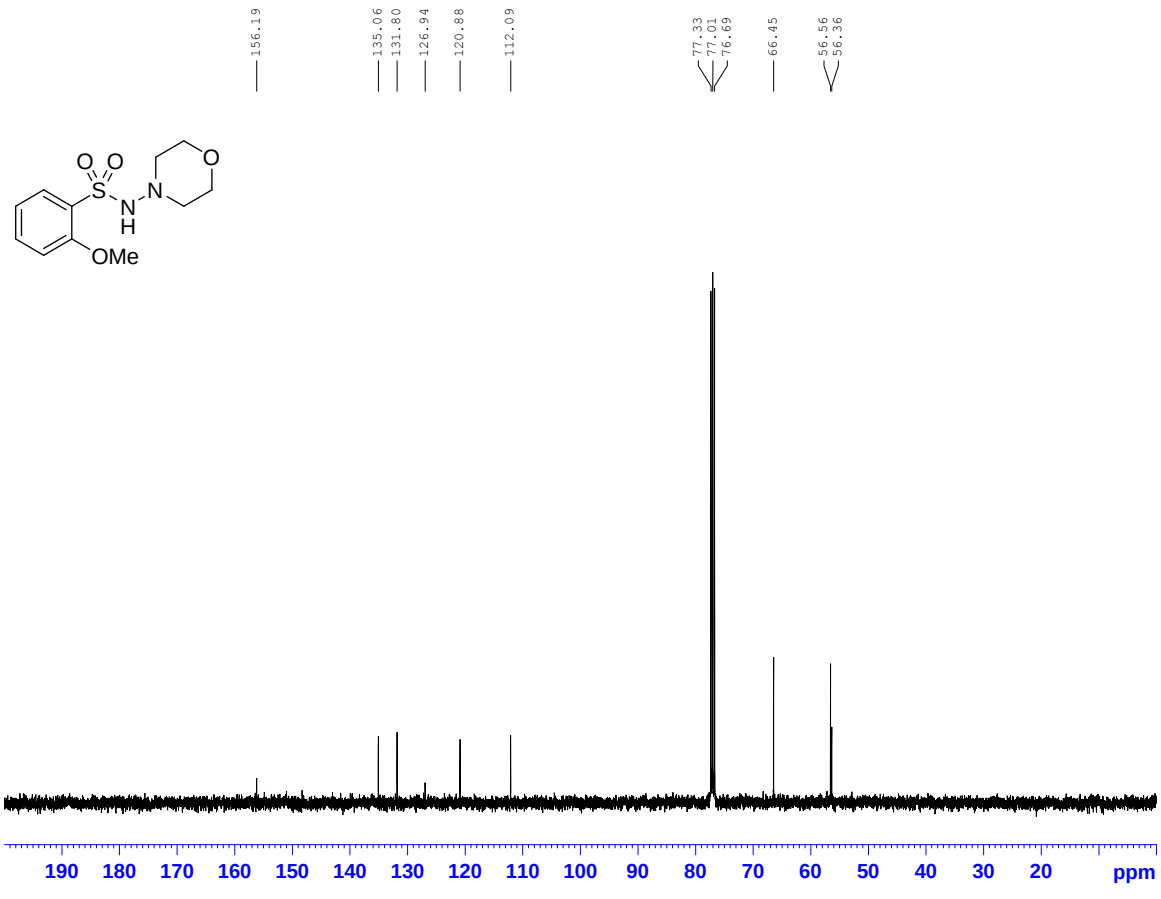
4.06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66.45
56.56
56.36
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S
N
H
O
N
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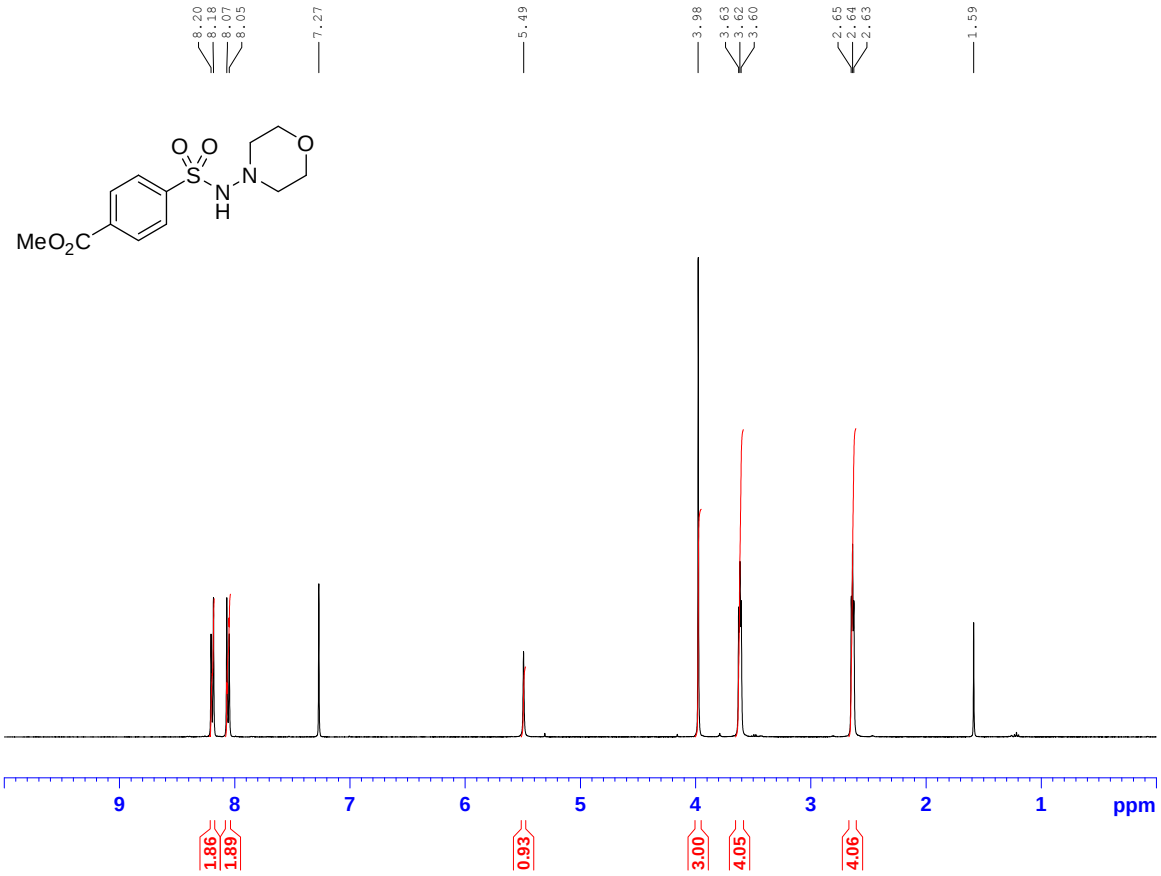
ppm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2.65
2.64
2.63
1.59
MeO2C
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8
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5
4
3
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ppm
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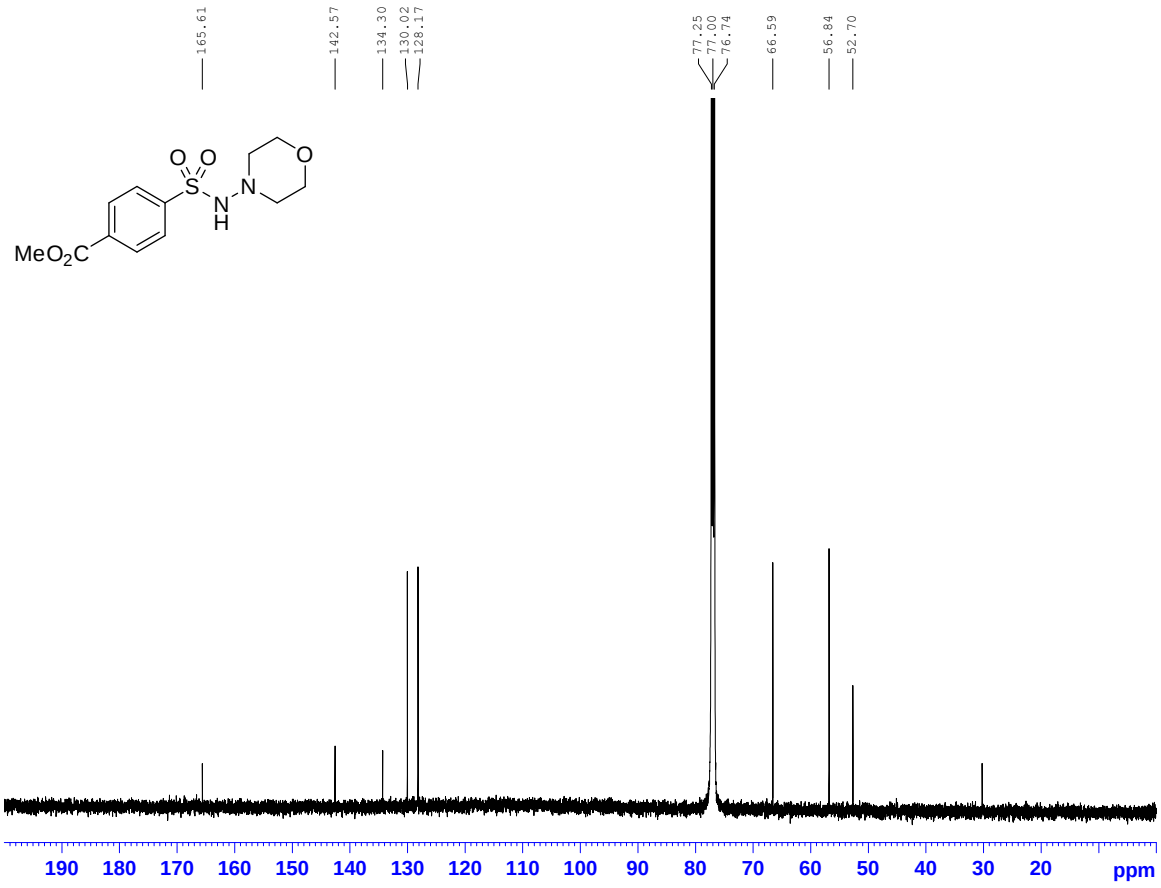
3.00
4.05
4.06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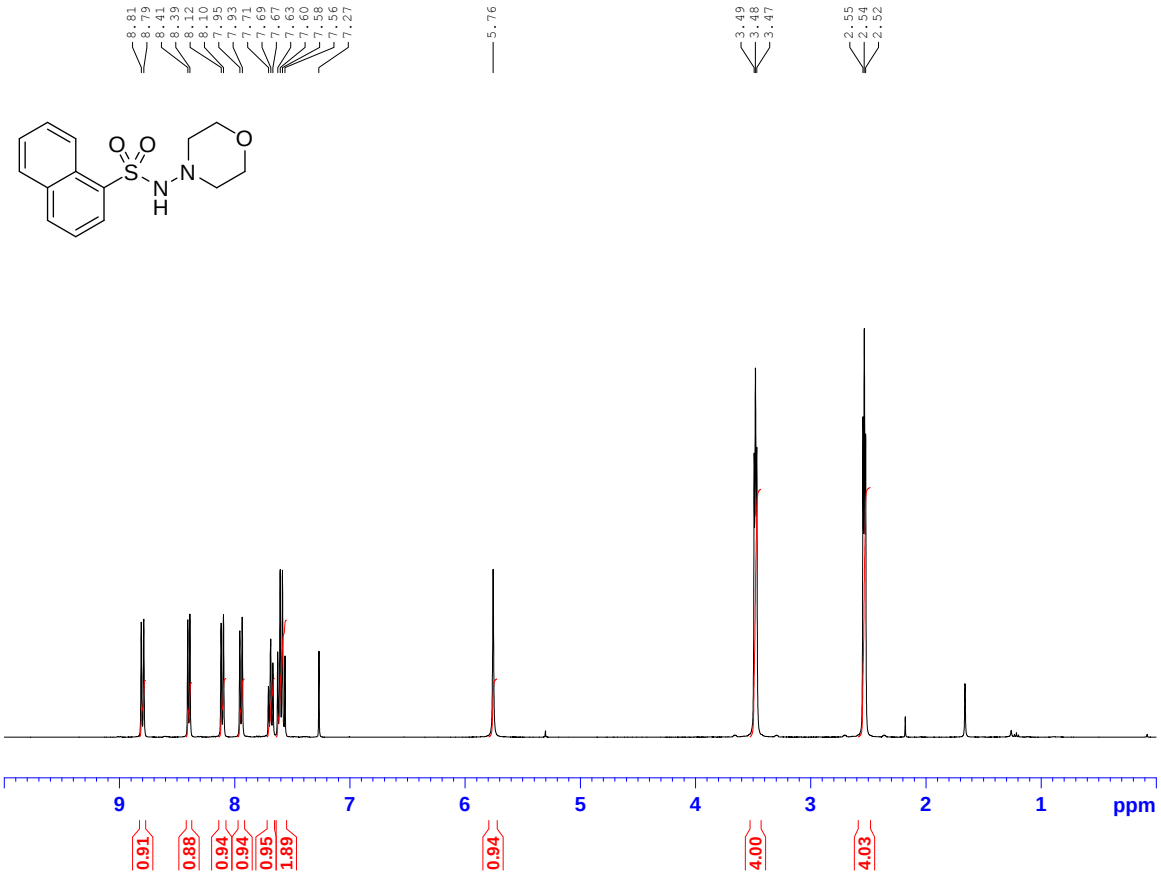
20
ppm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7.60
7.58
7.56
7.27
5.76
3.49
3.48
3.47
2.55
2.54
2.52
O
O
S
N
H
N
O
9
8
7
6
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ppm
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0.95
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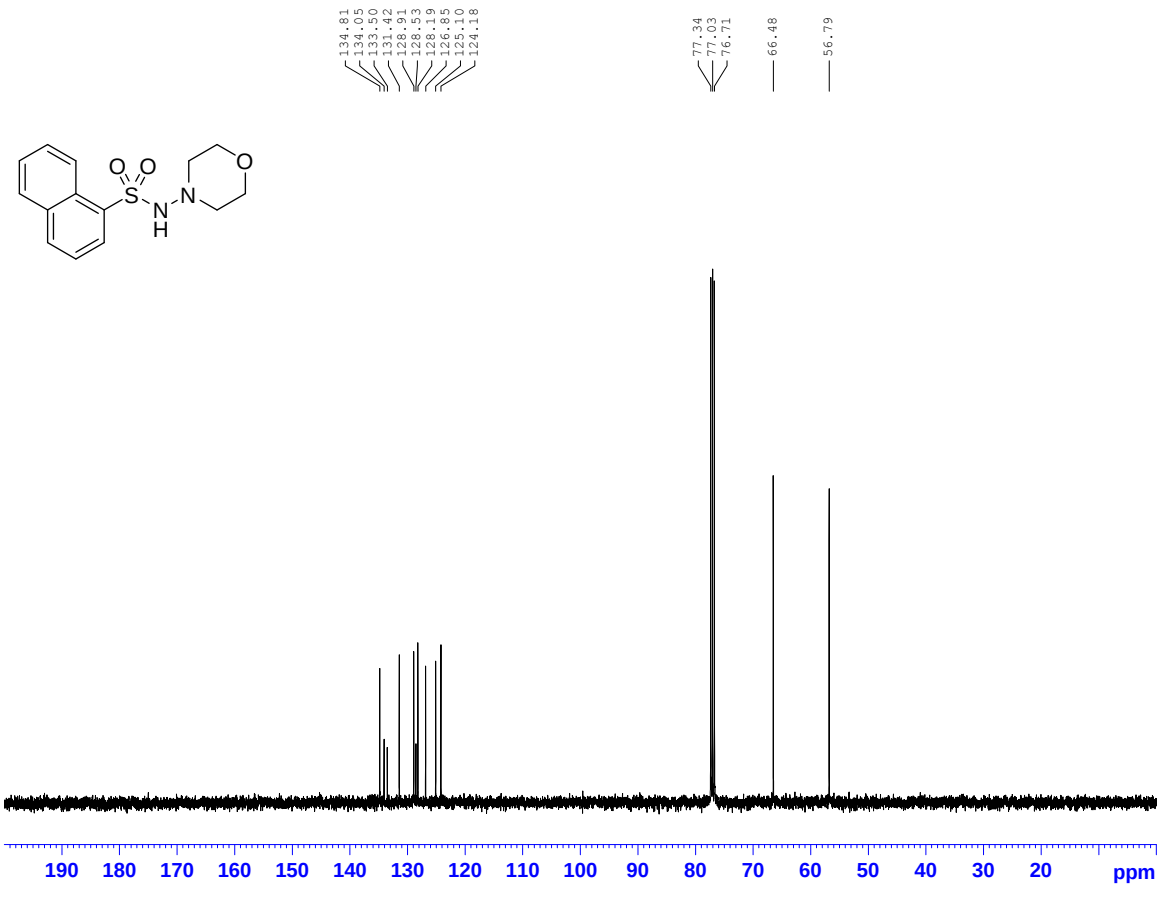
4.03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77.34
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56.79
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O
S
N
H
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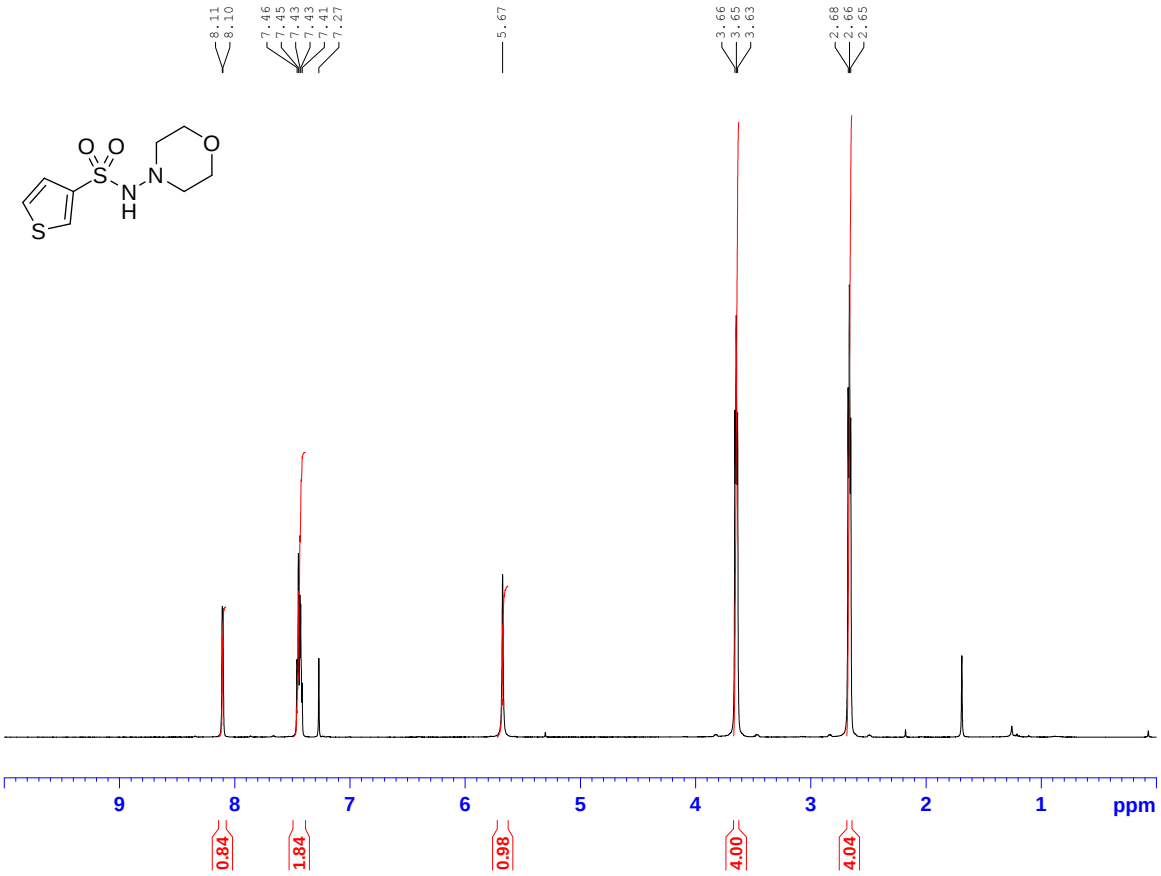
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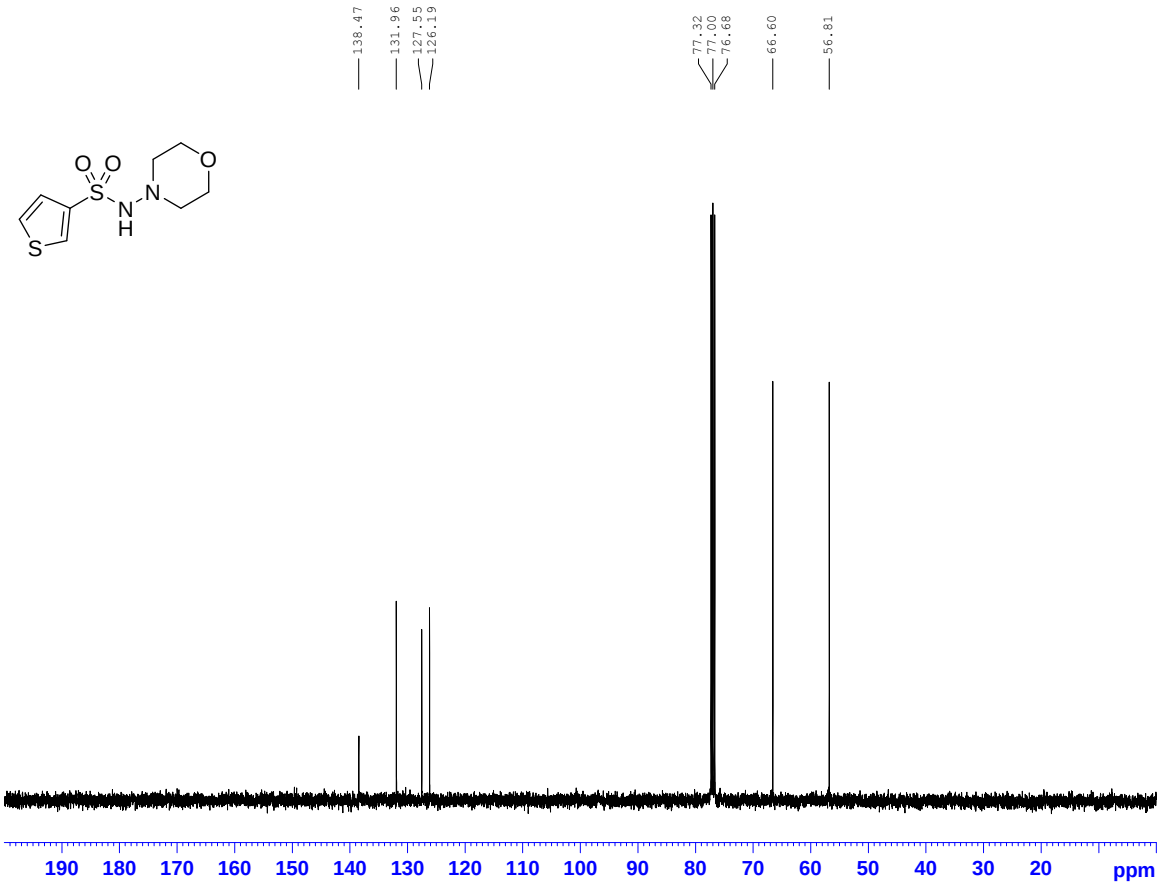
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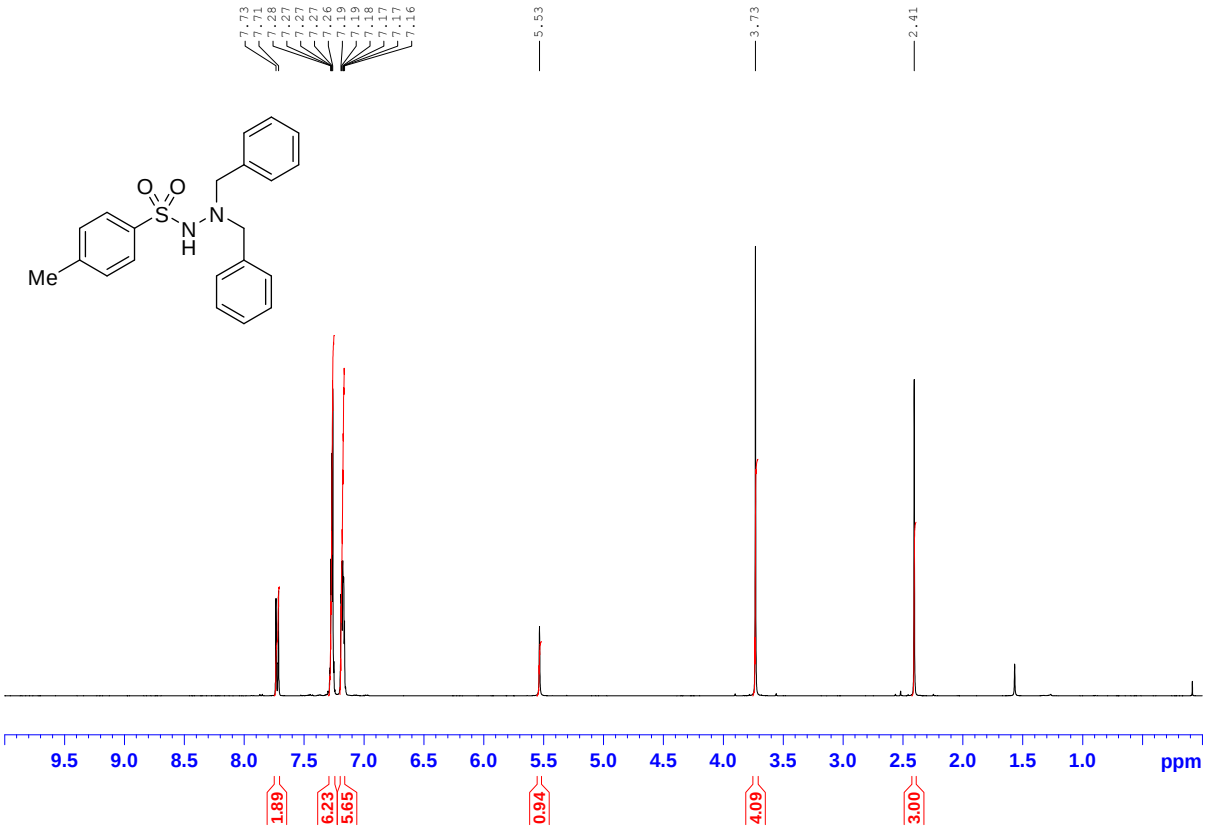
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3.73
2.41
O
O
S
N
N
H
Me
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7.0
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6.0
5.5
5.0
4.5
4.0
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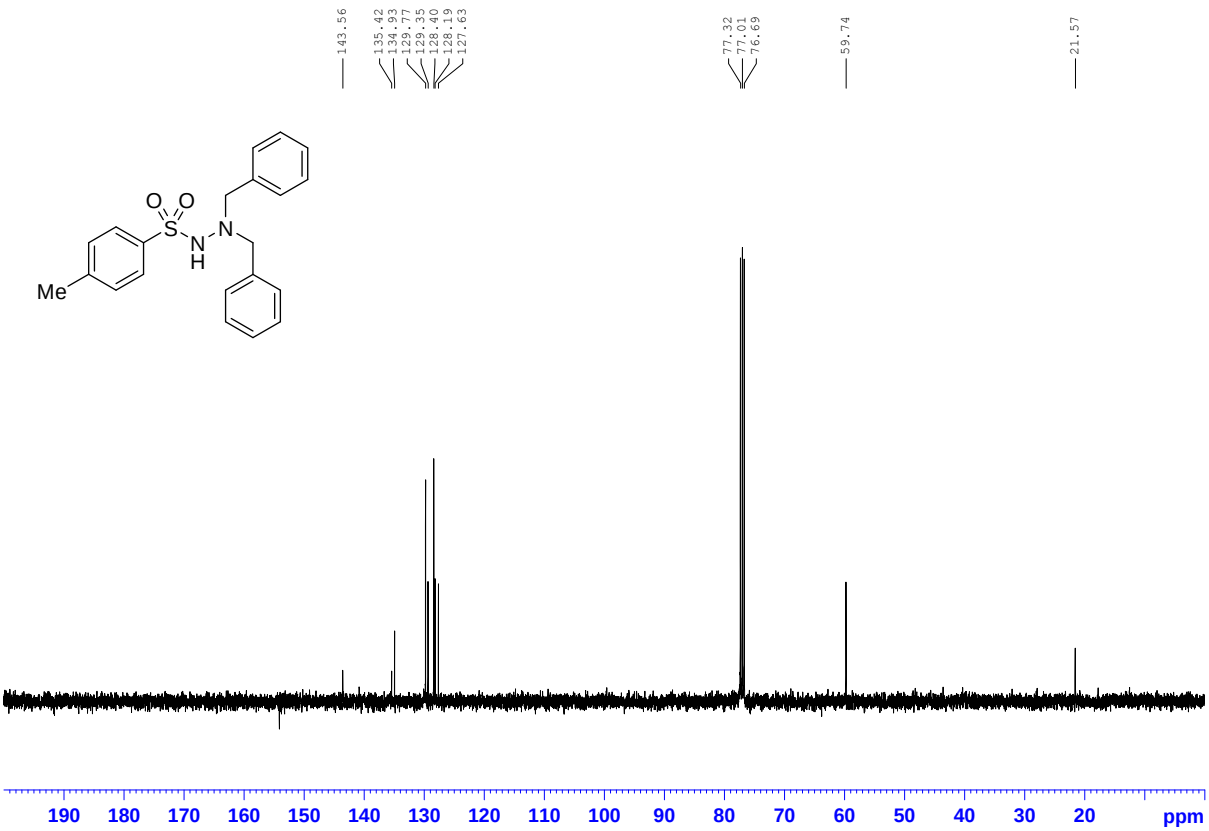
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76.69
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S
N
N
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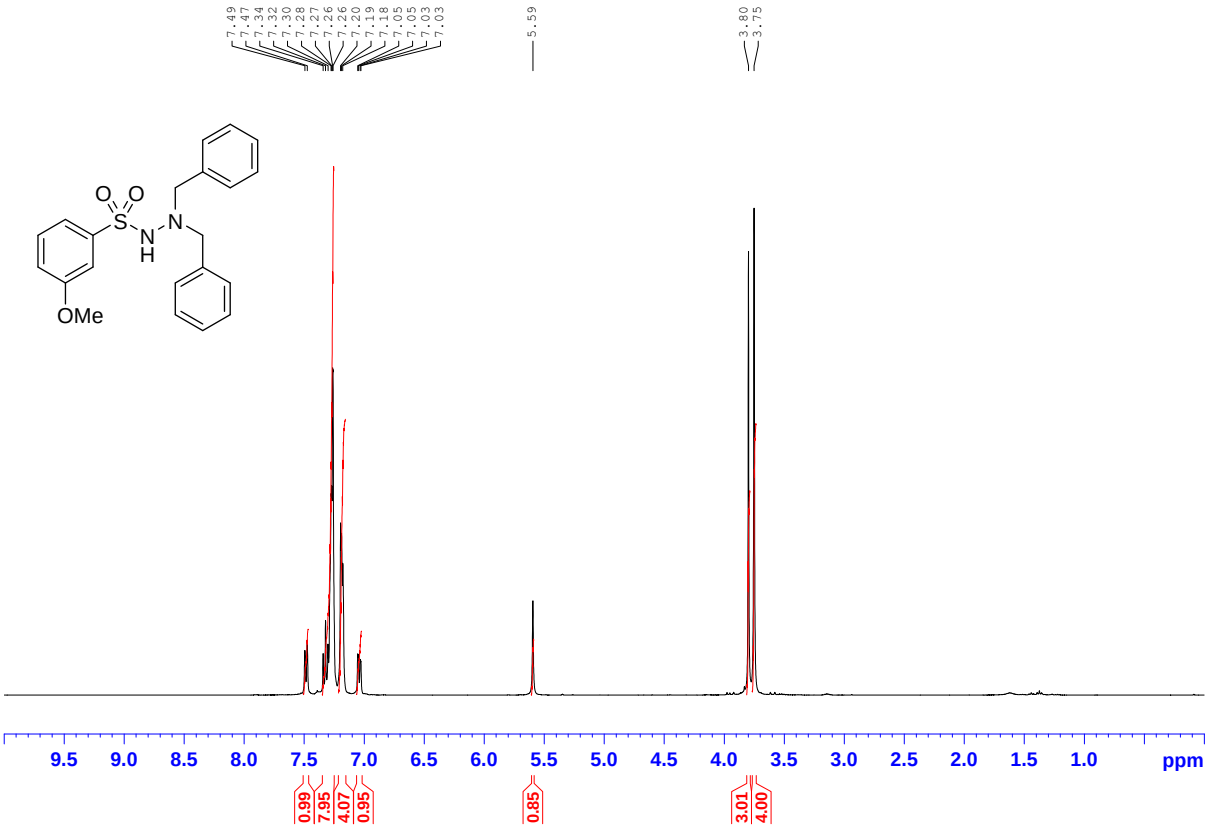
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7.05
7.03
7.03
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3.80
3.75
O
O
S
N
N
H
OMe
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9.0
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8.0
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6.0
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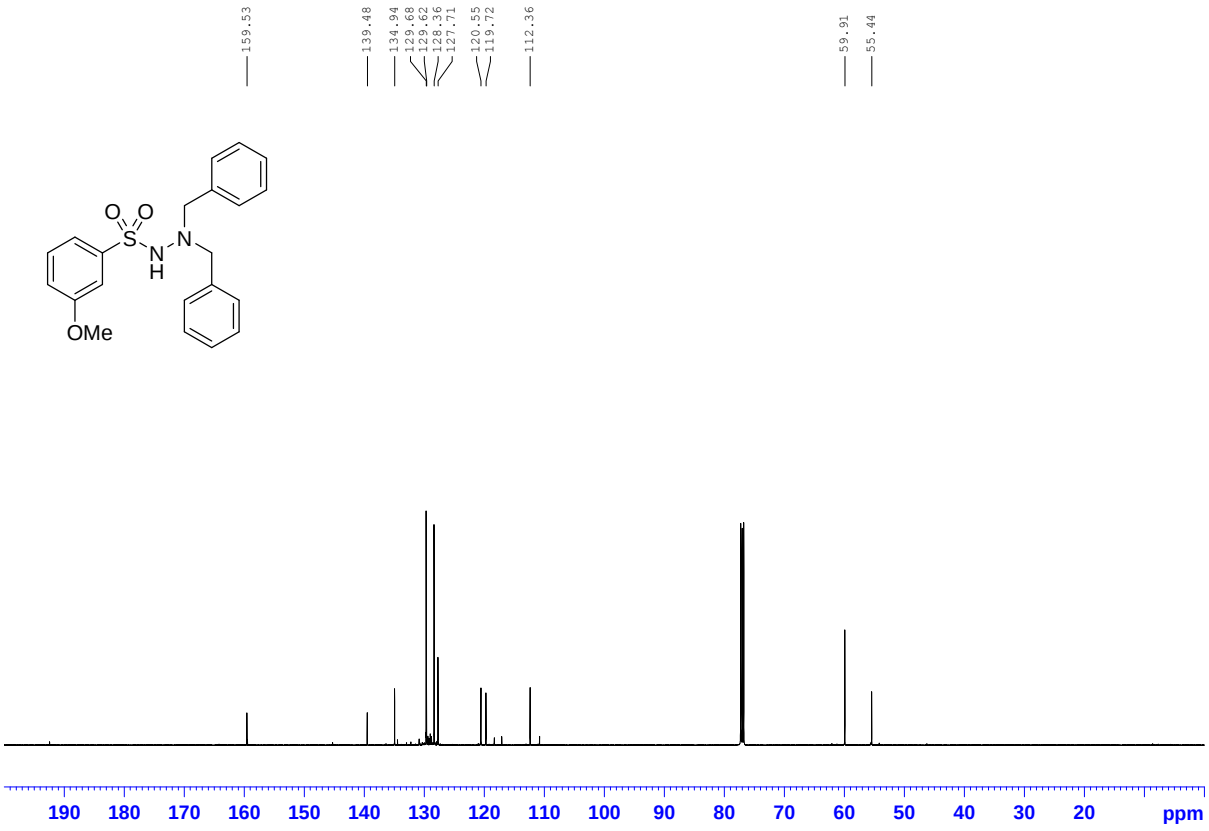
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55.44
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O
S
N
N
H
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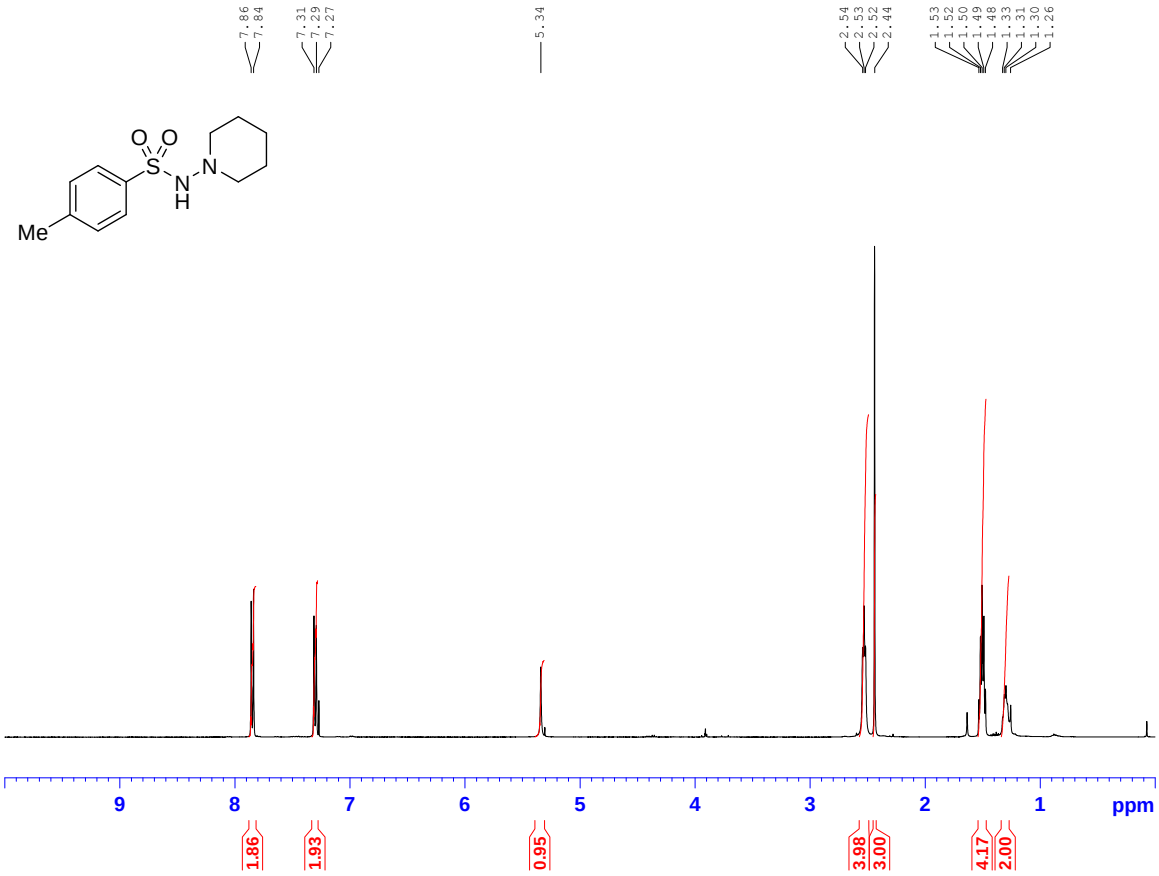
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1.48
1.33
1.31
1.30
1.26
O
O
S
N
N
H
Me
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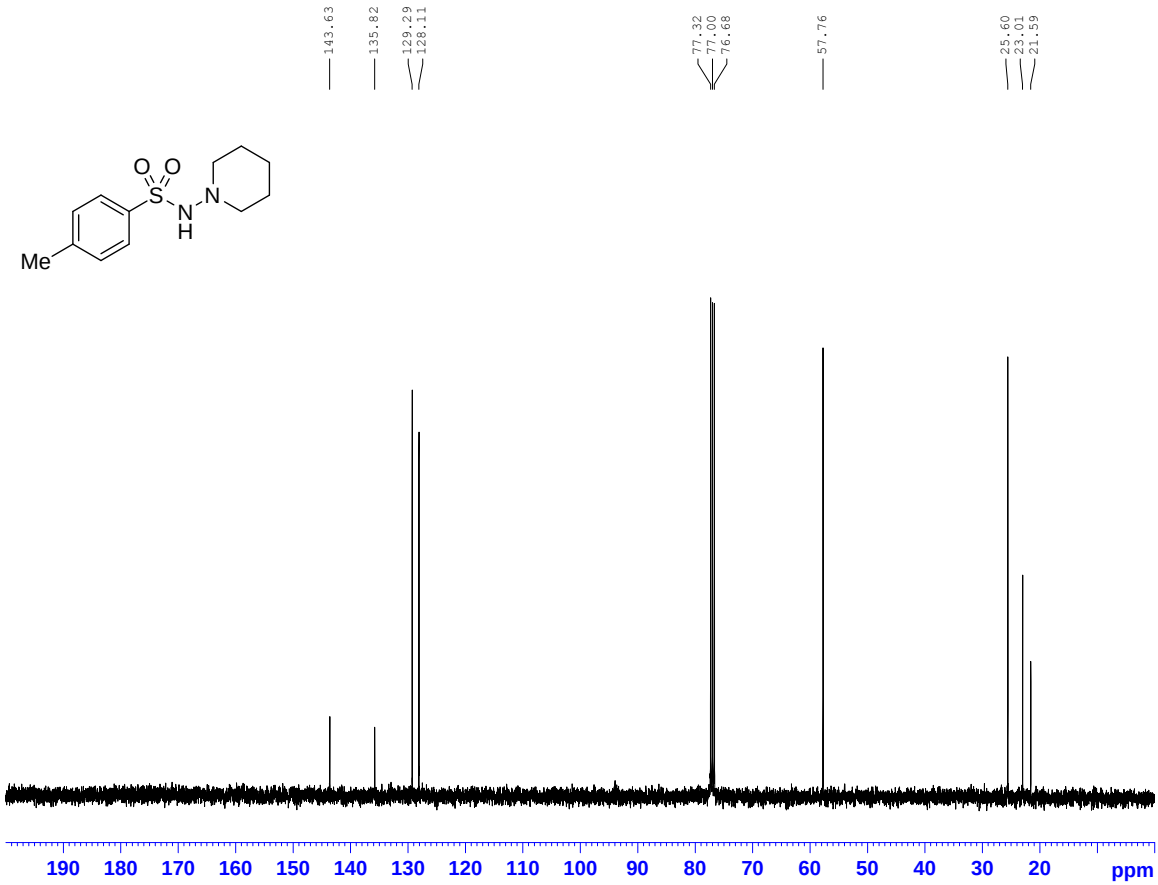
2.00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21.59
O
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N
N
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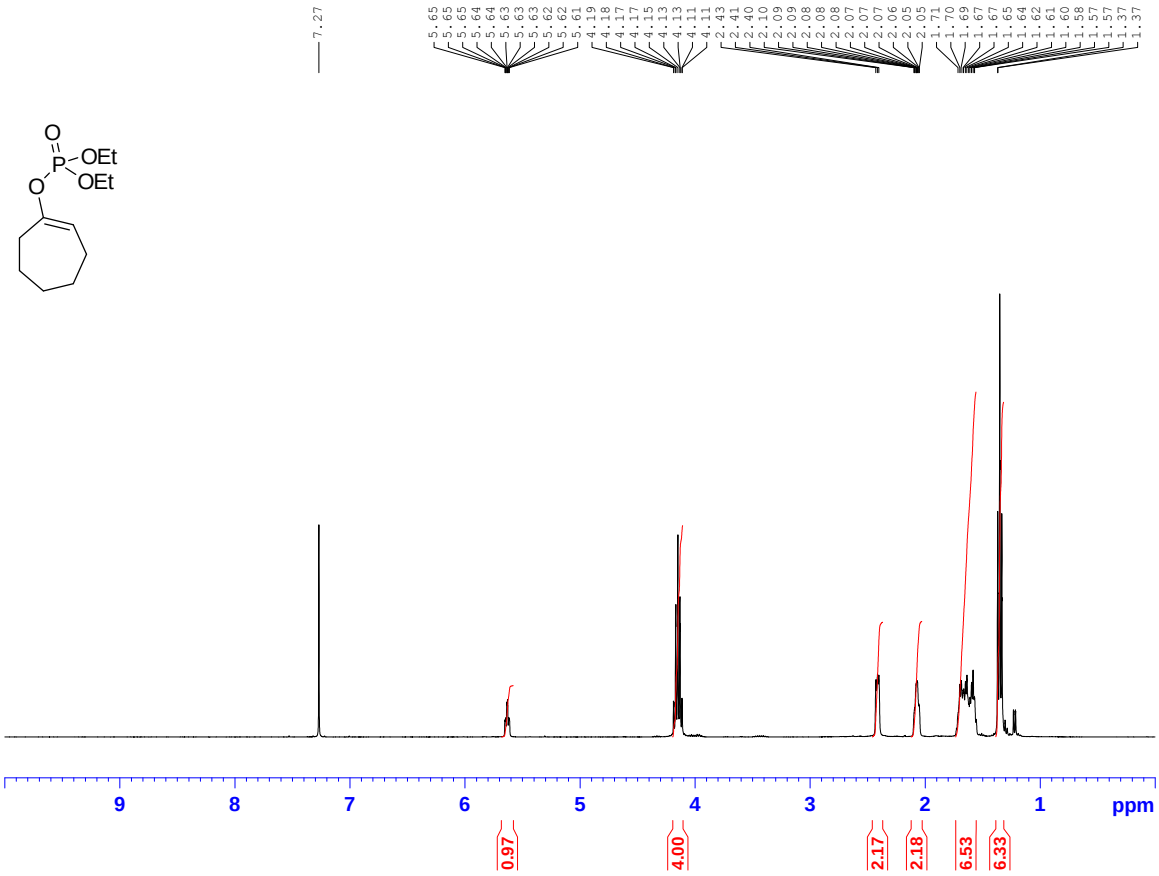
ppm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4.18
4.17
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4.13
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4.11
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2.09
2.08
2.08
2.08
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1.57
1.37
1.37
O
P
OEt
OEt
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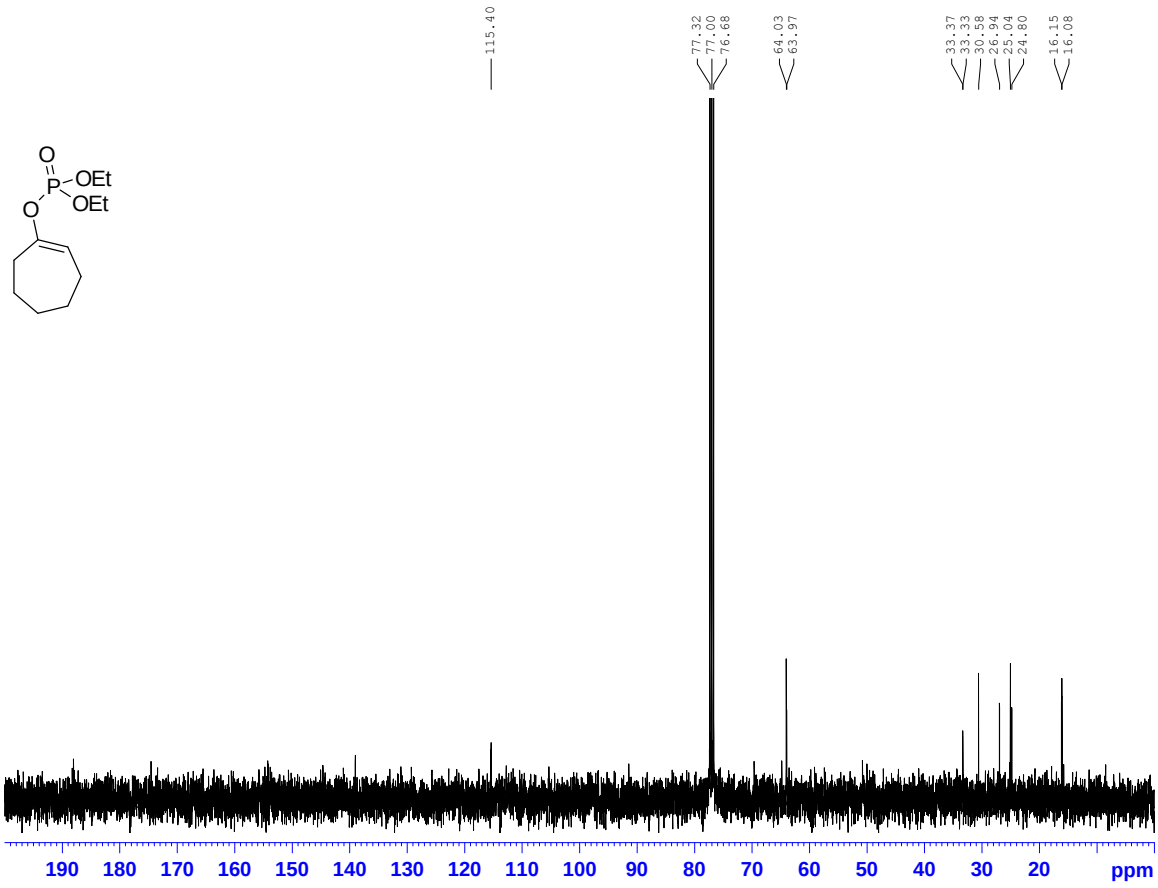
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24.80
16.15
16.08
O
P
OEt
OEt
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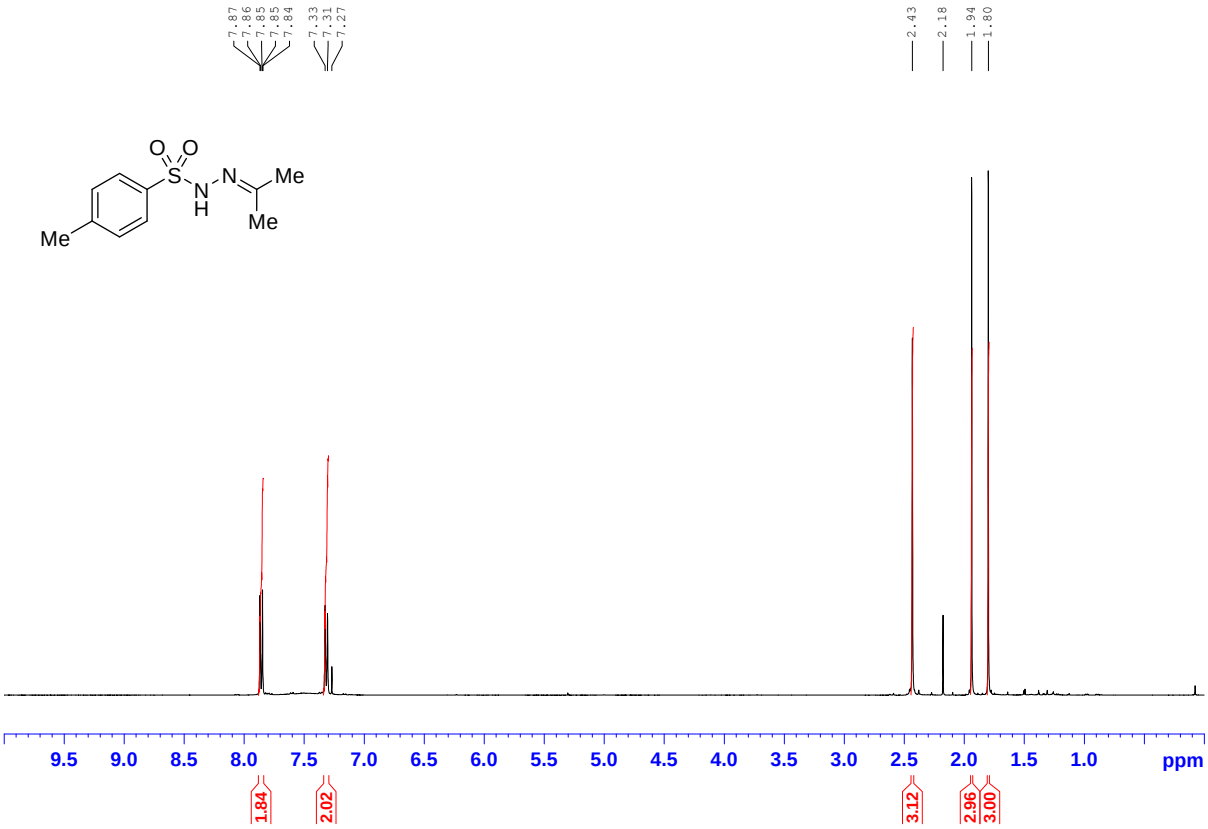
20
ppm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2.18
1.94
1.80
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O
S
N
H
N
Me
Me
Me
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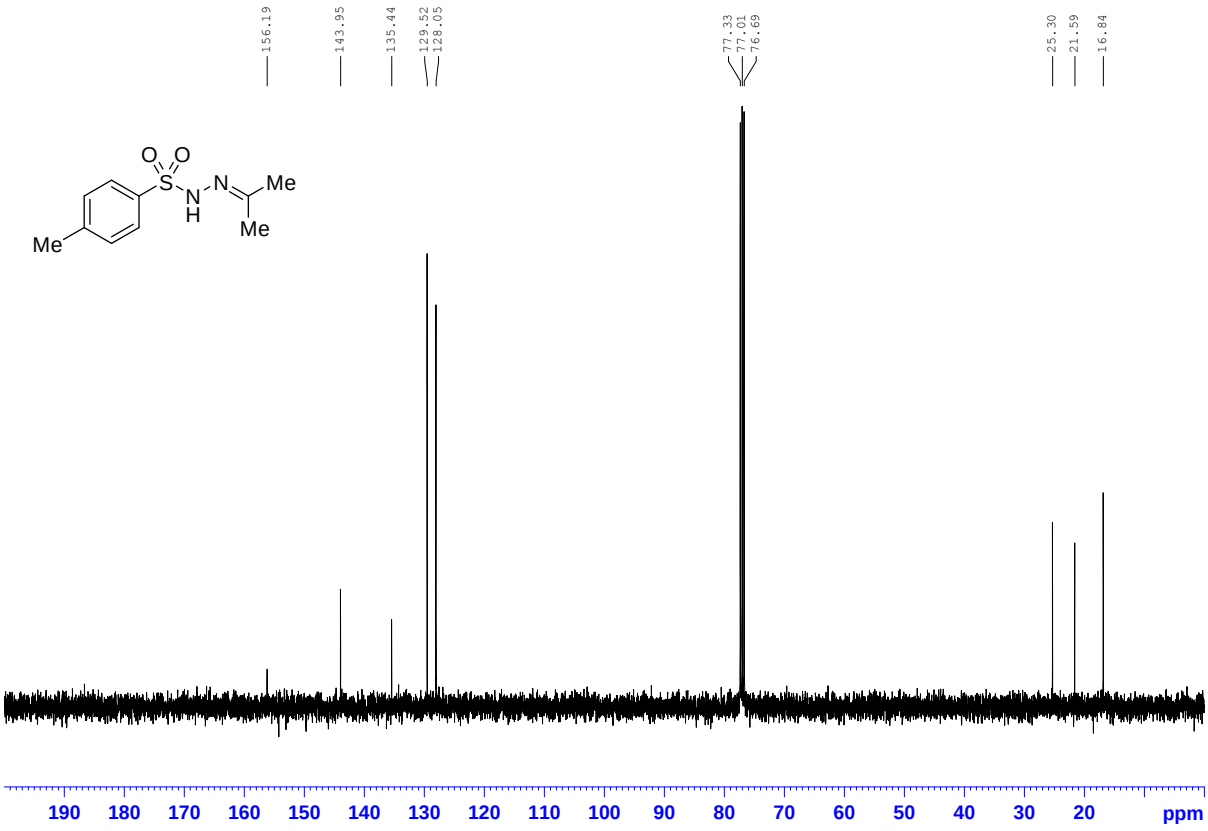
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N
Me
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Me
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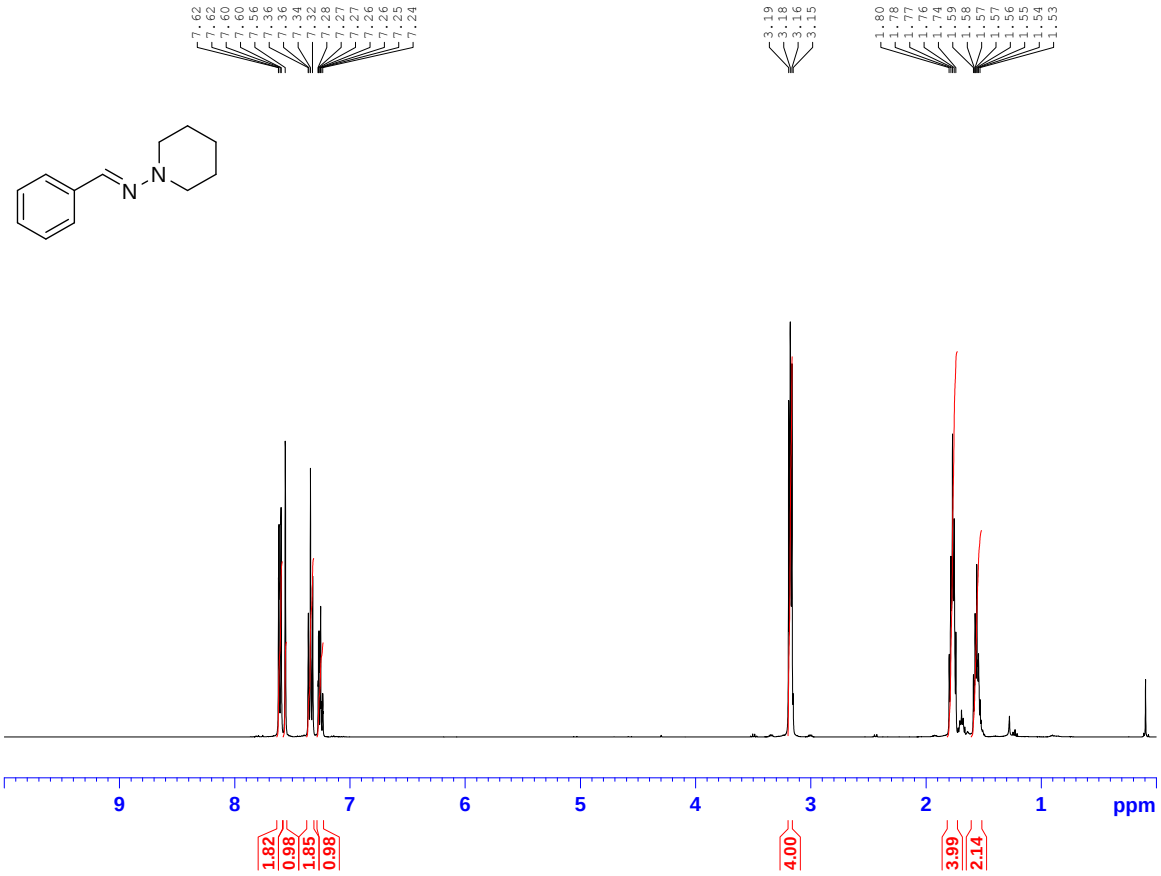
ppm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7.24
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3.18
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3.15
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1.77
1.76
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1.58
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1.54
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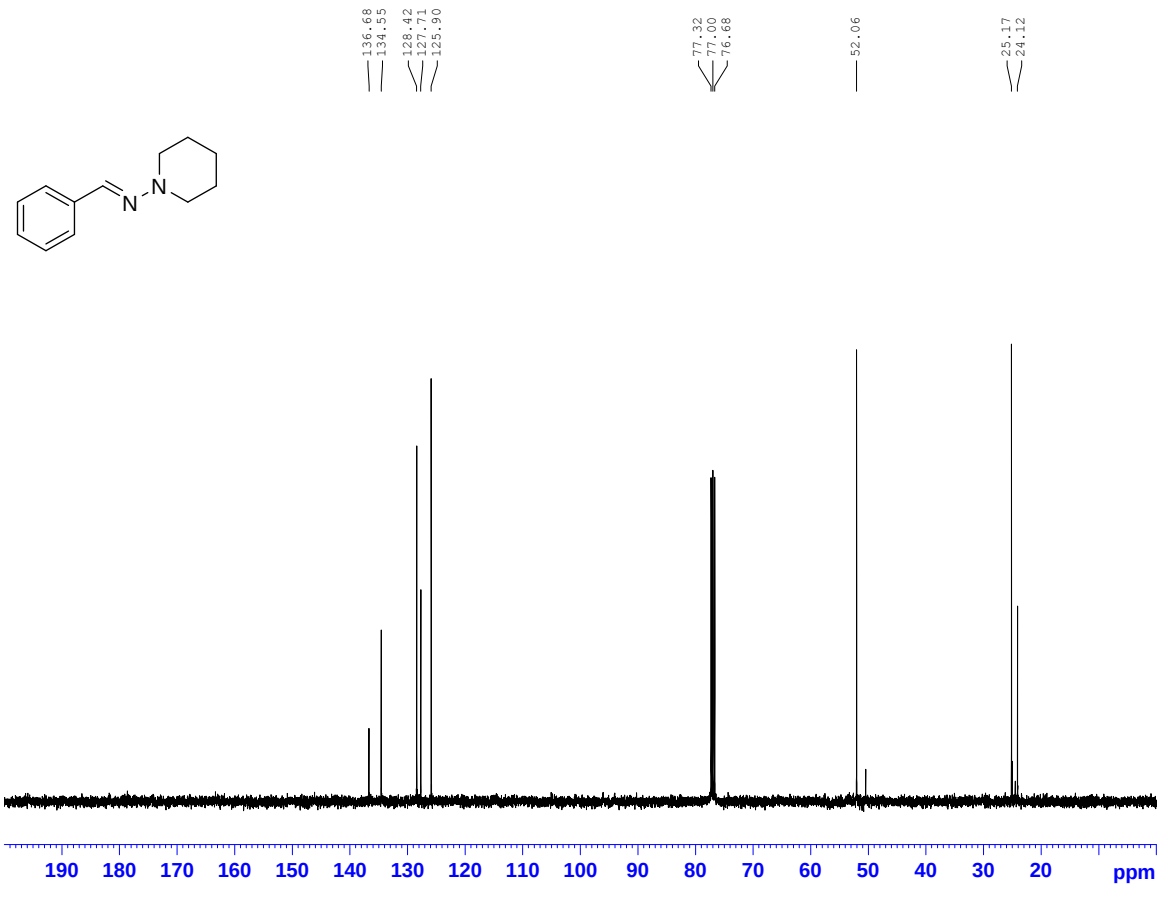
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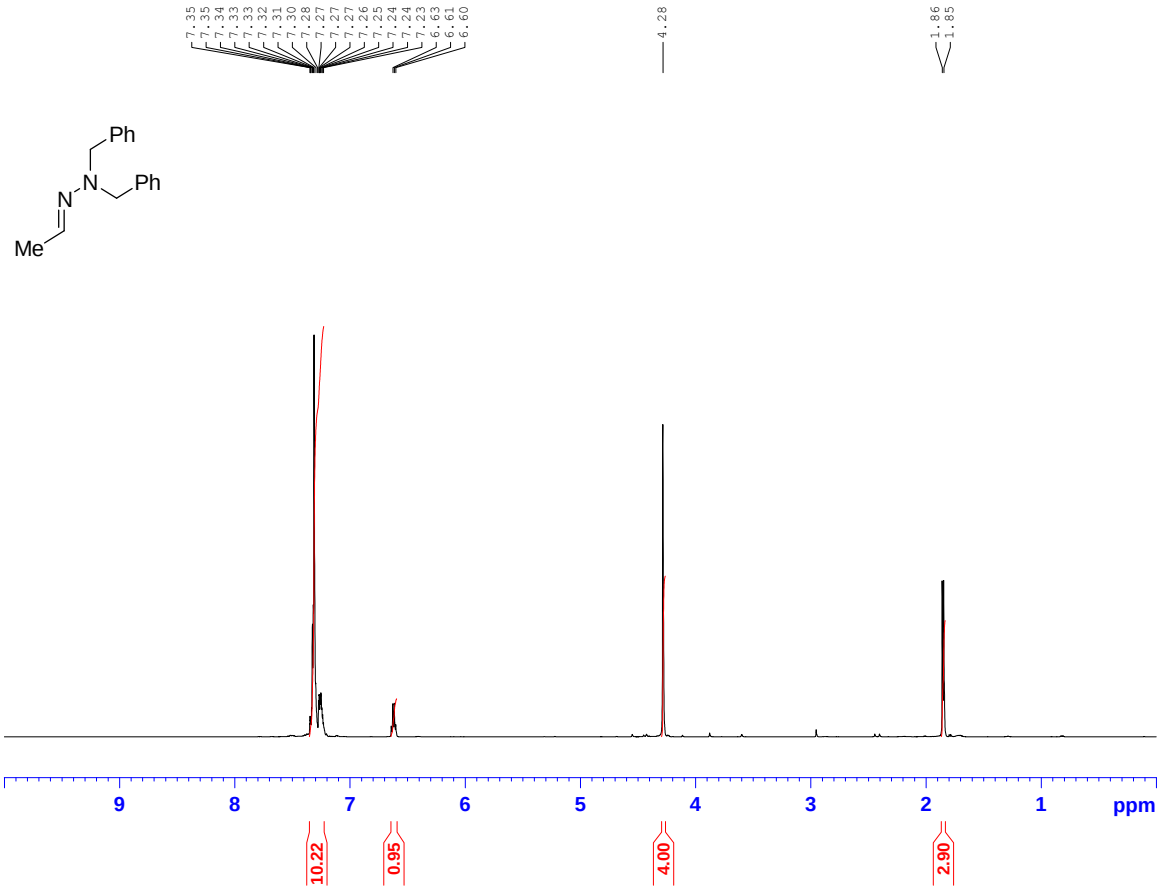
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7.24
7.23
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1.85
Ph
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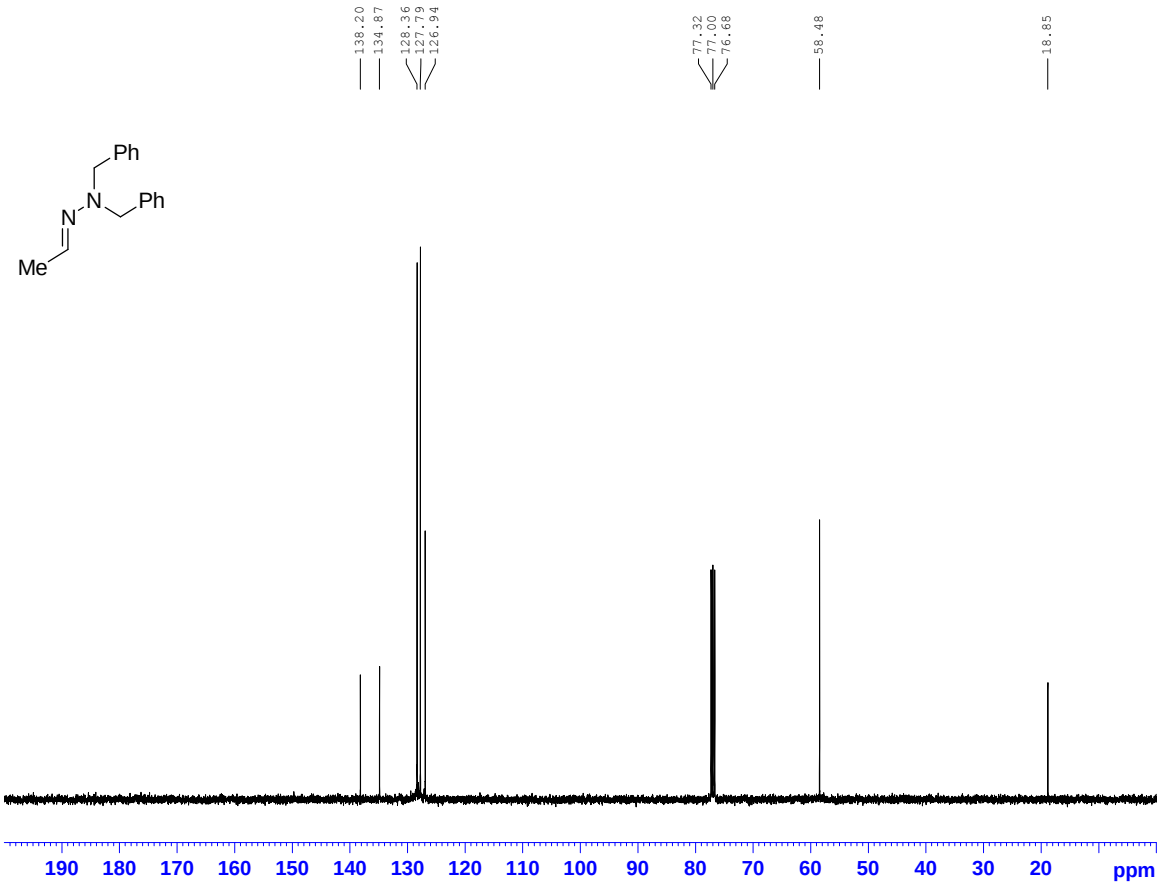
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Ph
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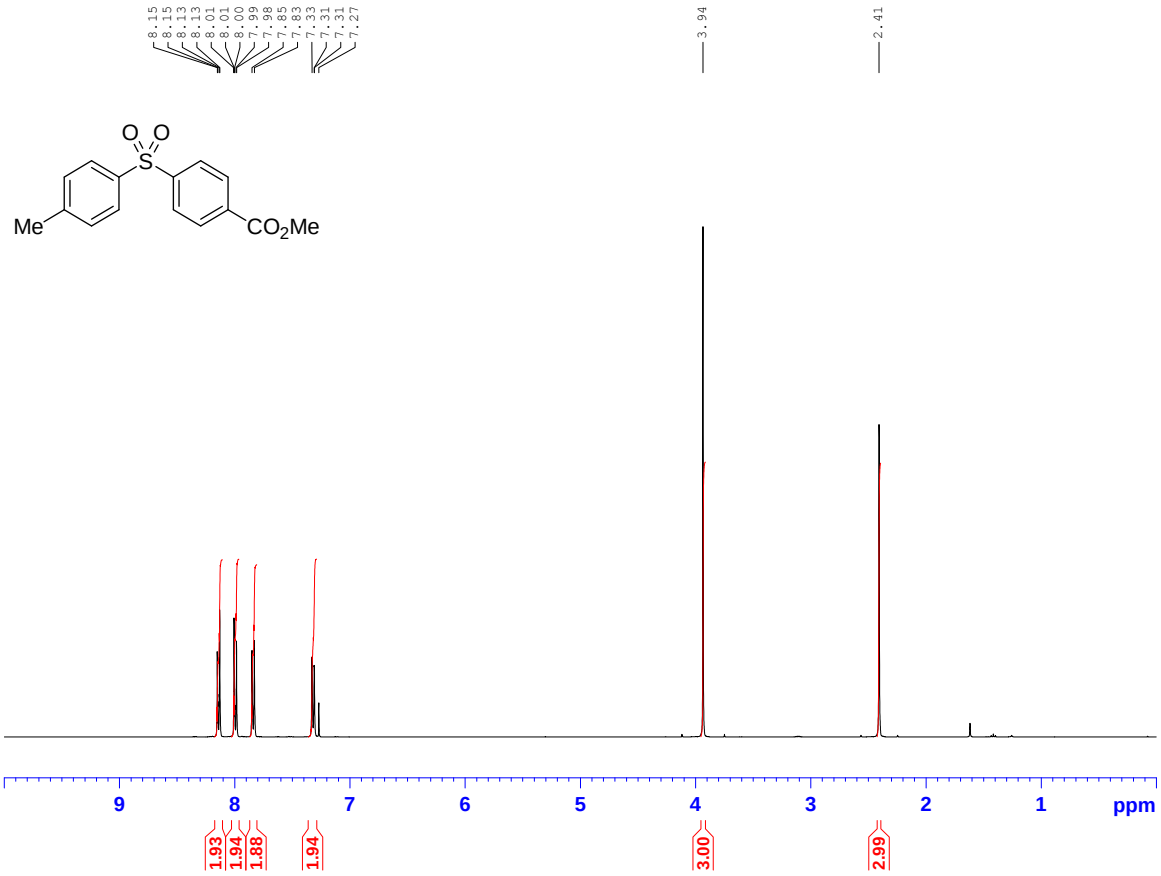
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7.31
7.27
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O
S
Me
CO2Me
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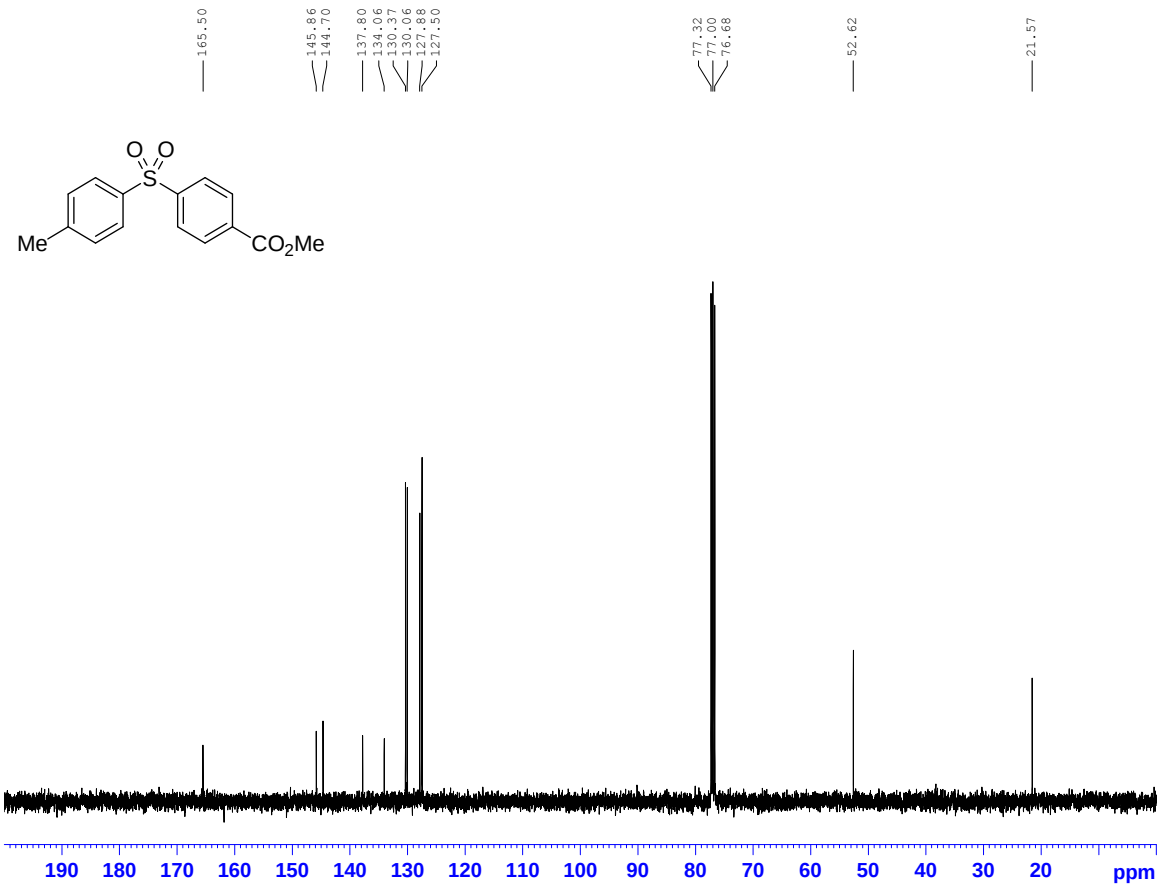
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S
Me
CO2Me
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180
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150
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110
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90
80
70
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50
40
30
20
ppm


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7.74
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7.50
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7.41
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7.39
7.38
7.37
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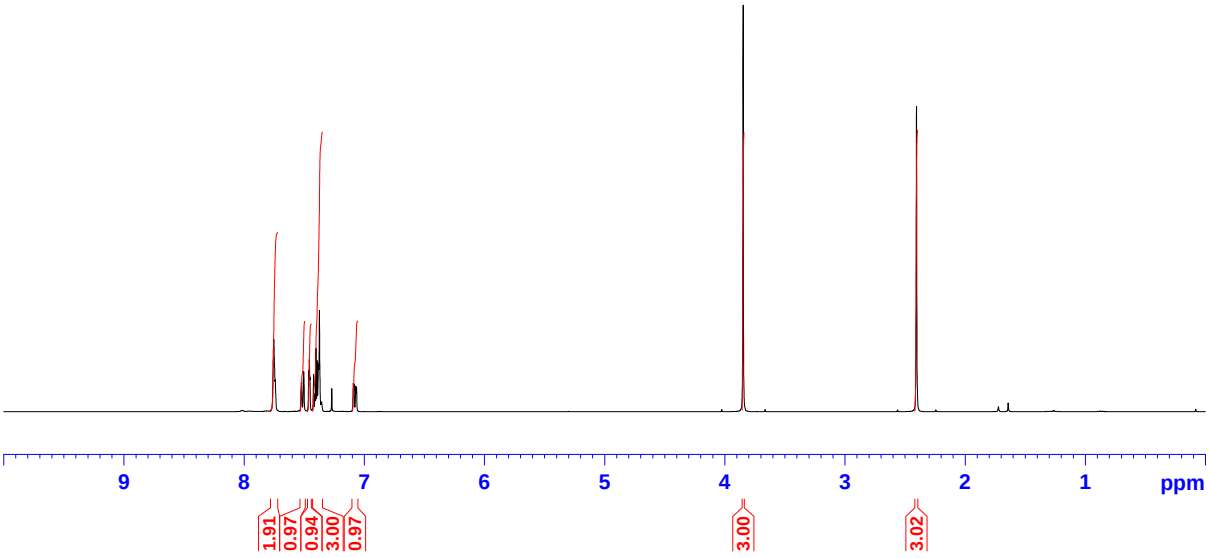
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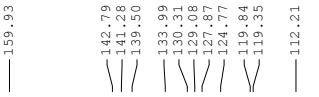
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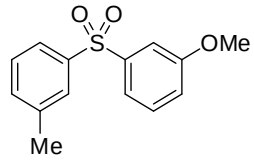
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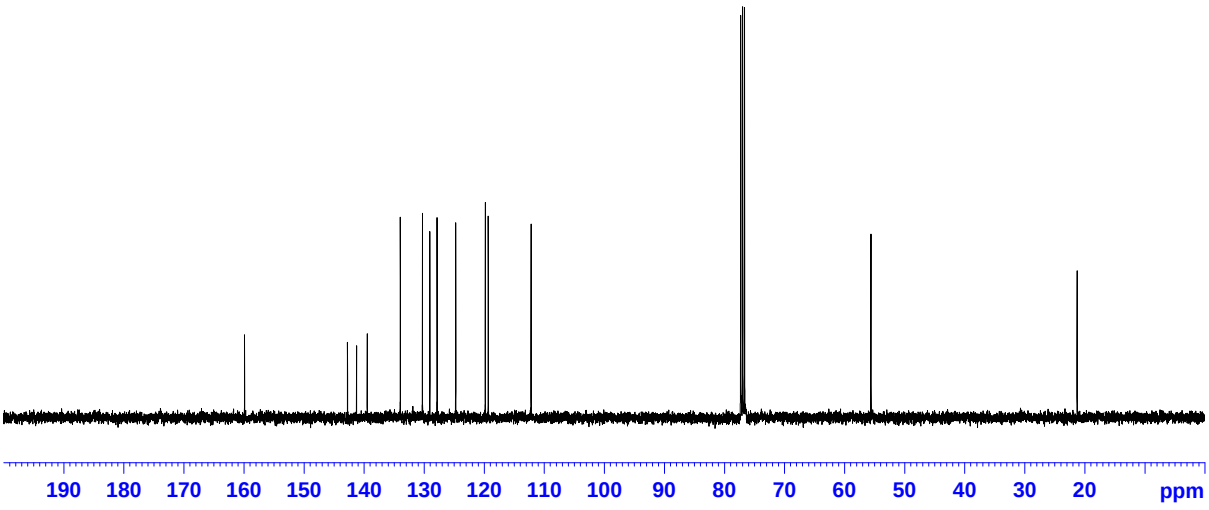
S
OMe
Me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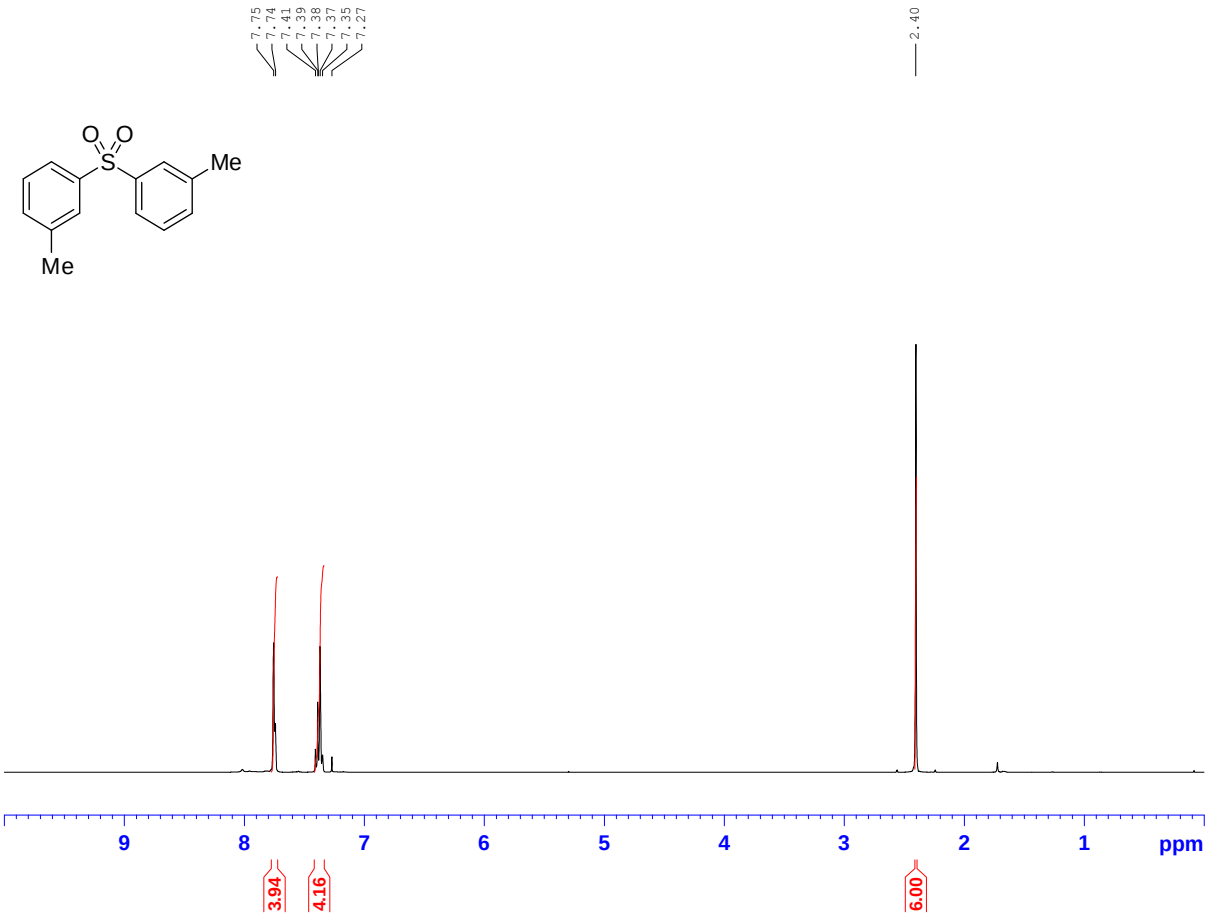
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7.27
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Me
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8
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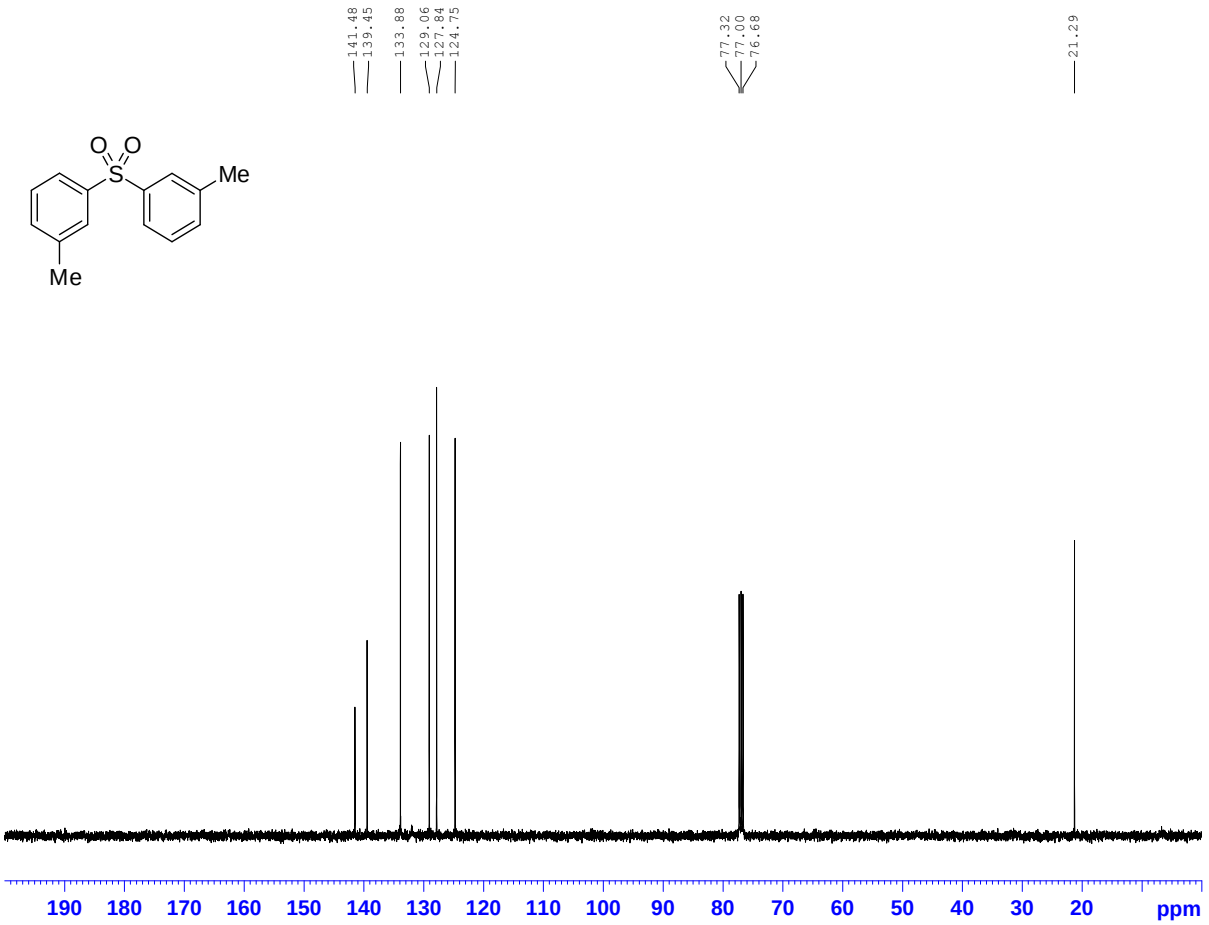
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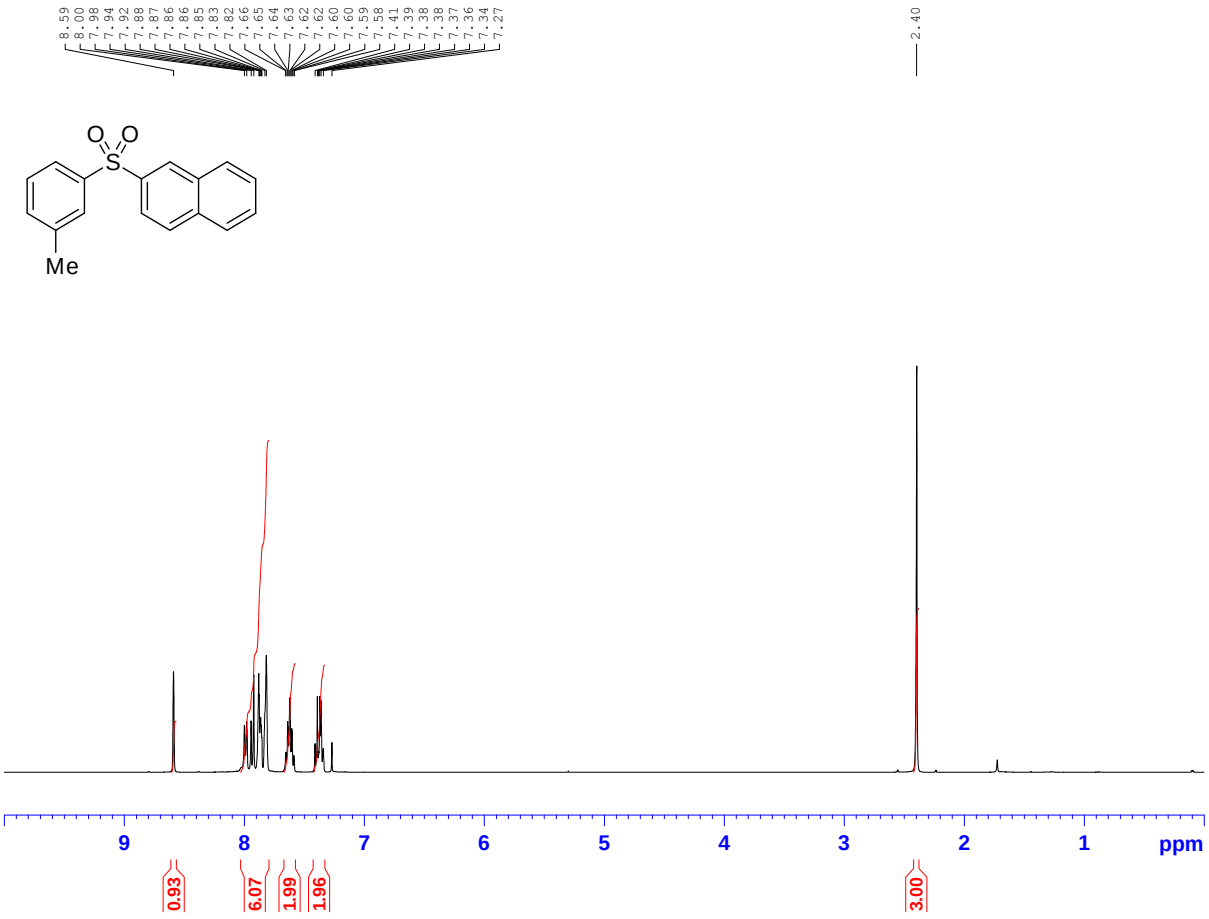
ppm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7.63
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7.62
7.60
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7.59
7.58
7.41
7.39
7.38
7.38
7.37
7.36
7.34
7.27
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O
O
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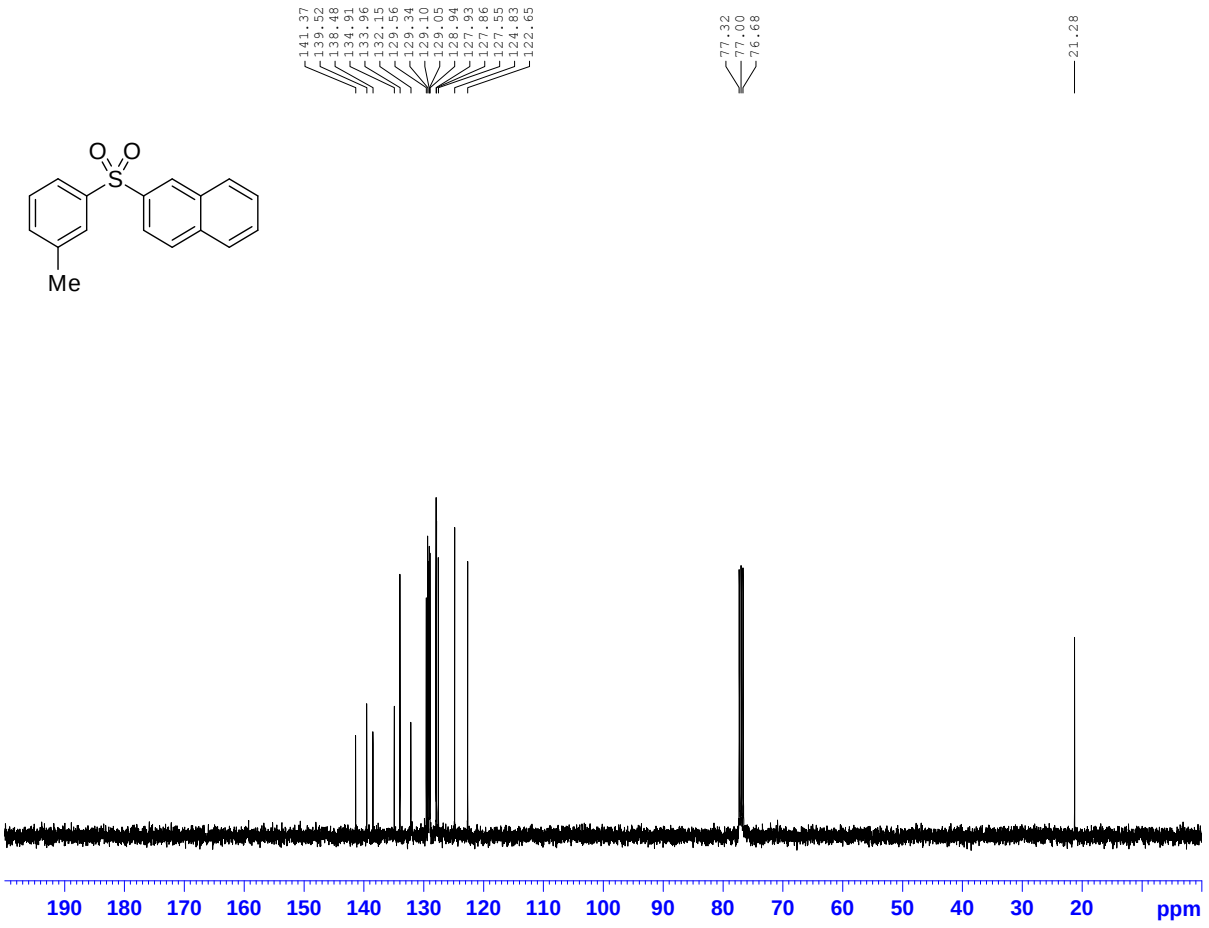
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124.83
122.65
77.32
77.00
76.68
21.28
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O
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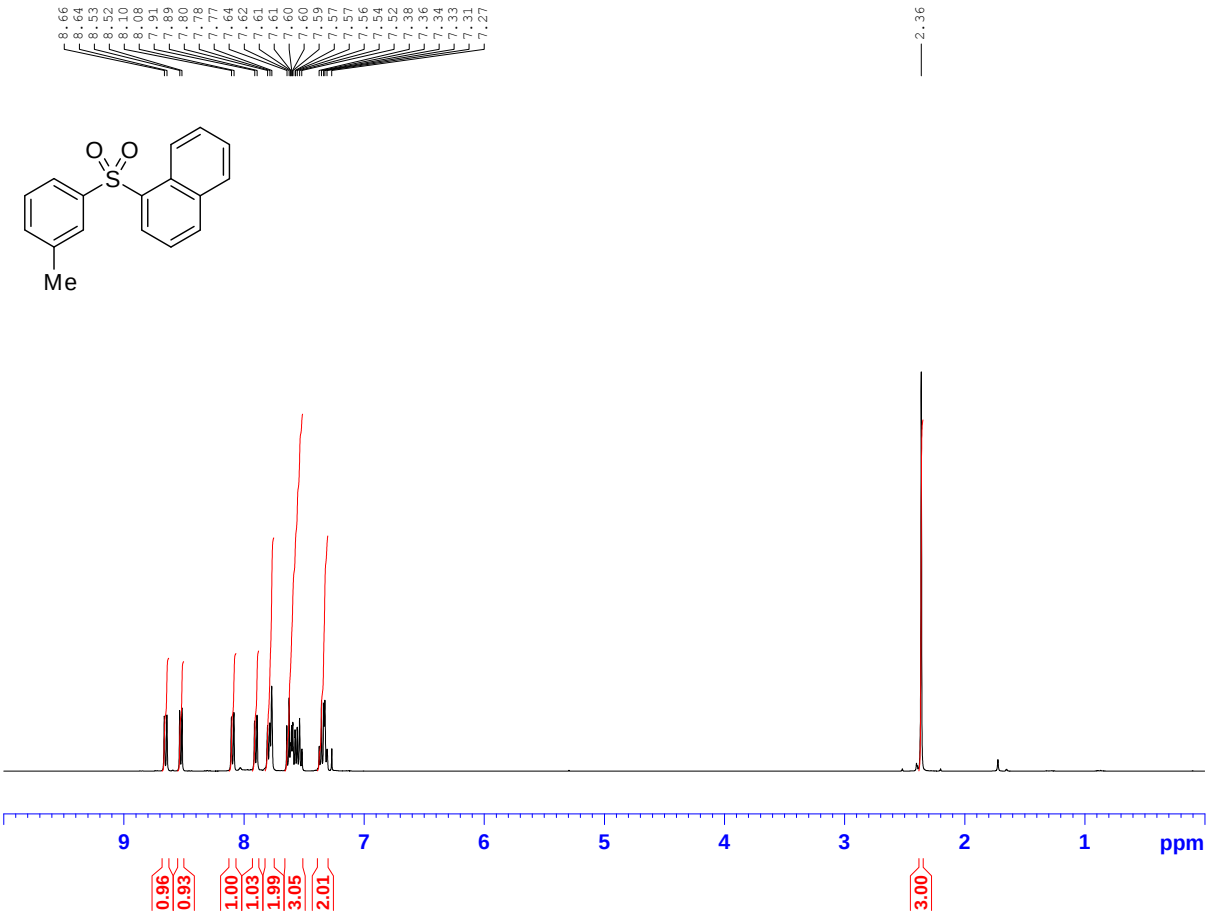
ppm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7.31
7.27
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O
S
Me
9
8
7
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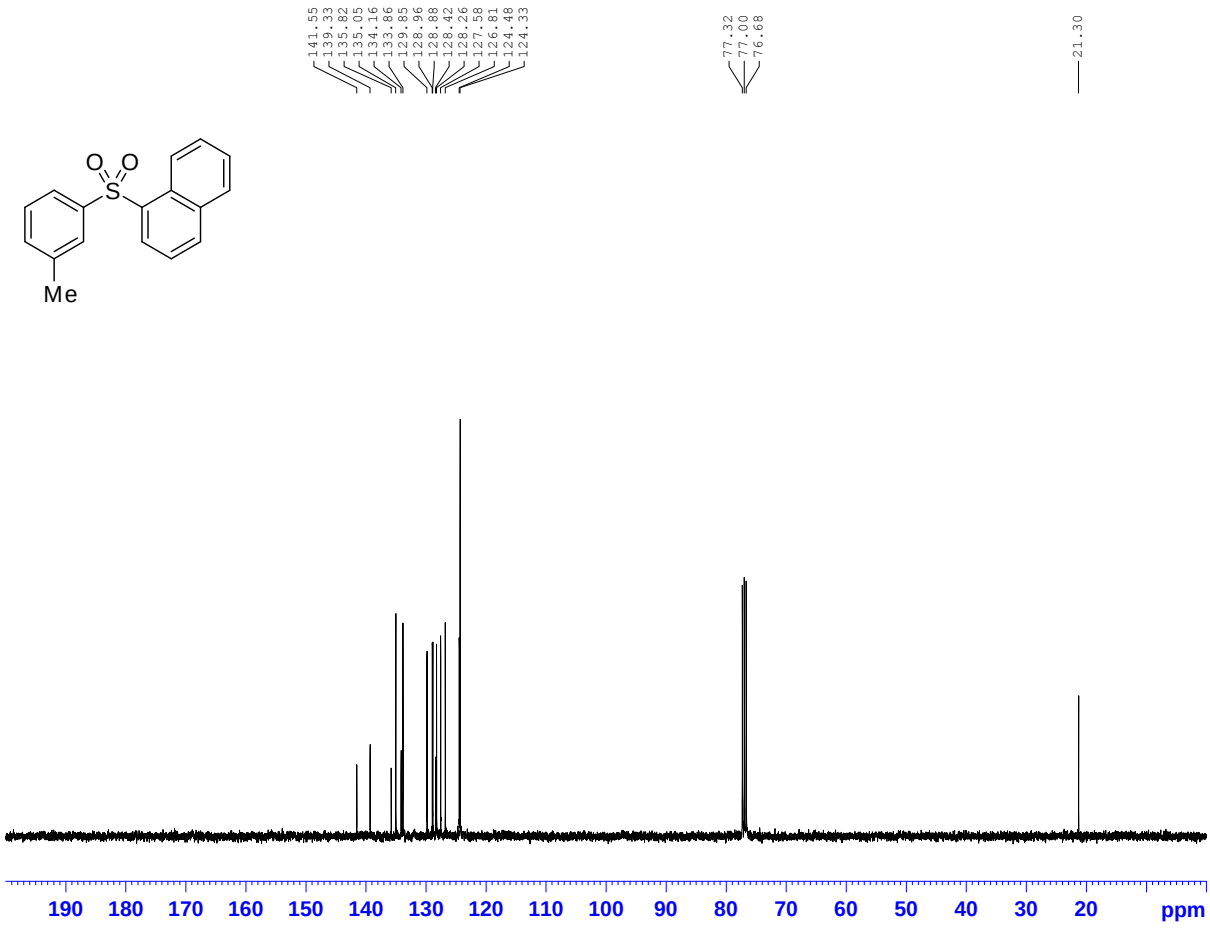
3.00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124.48
124.33
77.32
77.00
76.68
21.30
O
O
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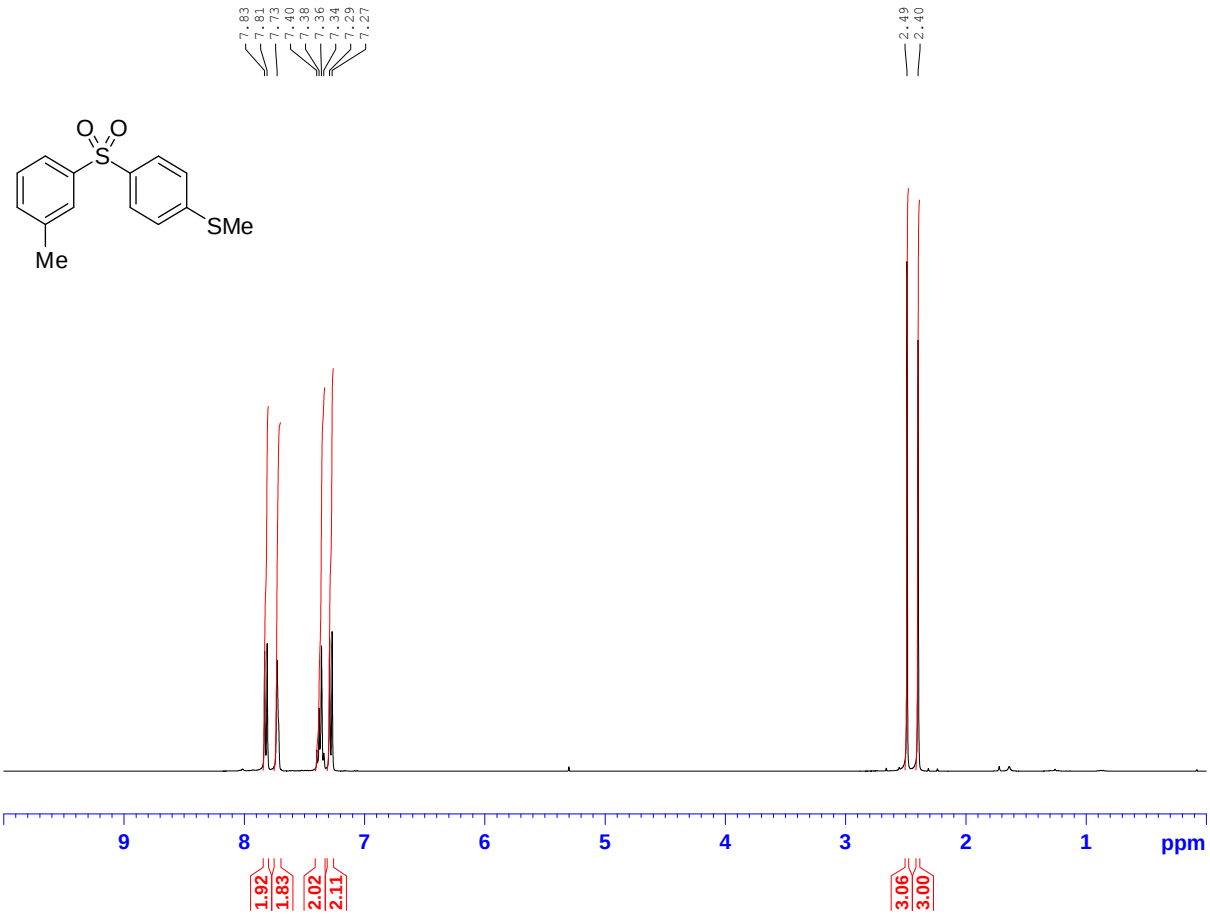
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2.40
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O
S
SMe
Me
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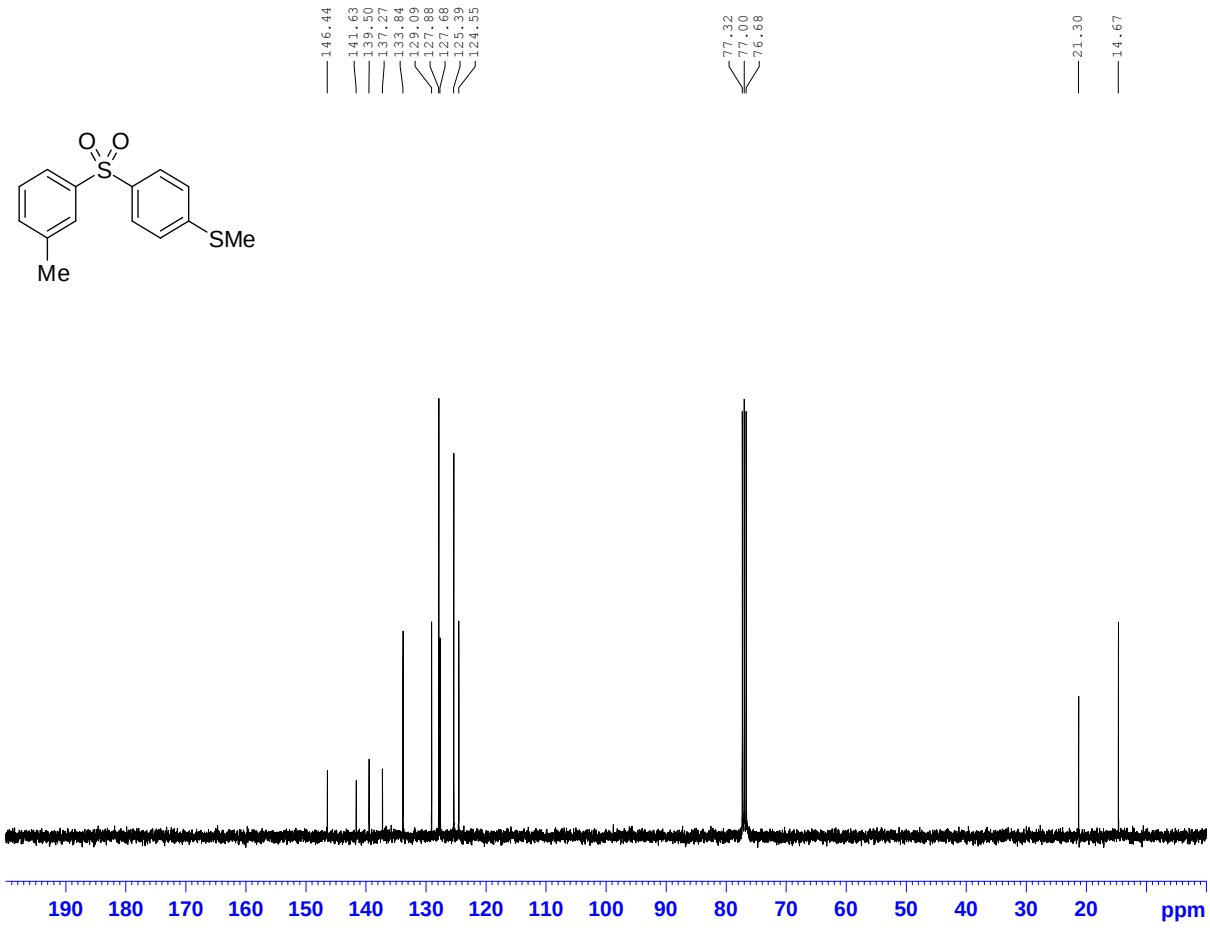
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O
S
SMe
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20
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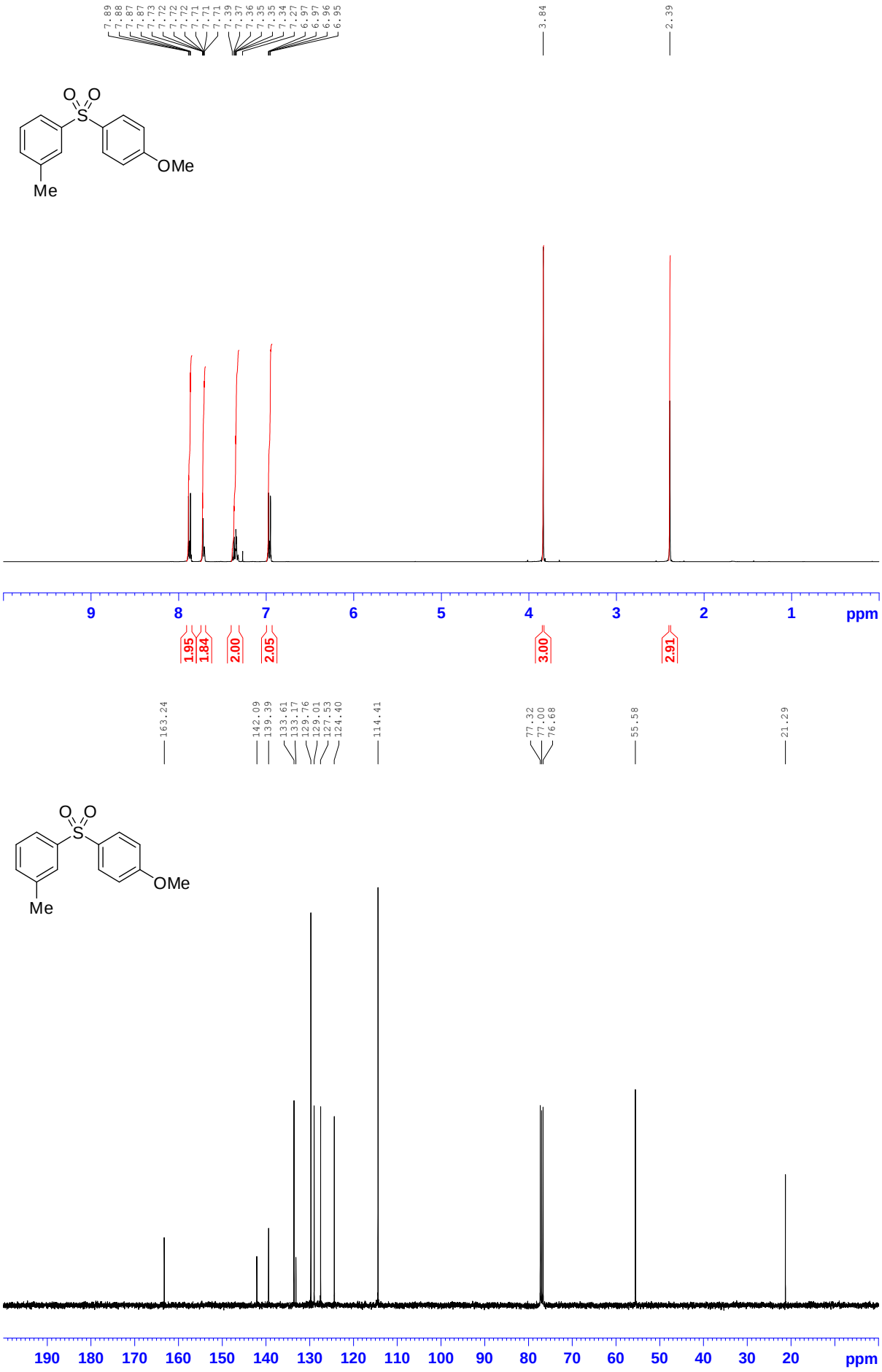
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2.39
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O
S
OMe
Me
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6
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4
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ppm
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3.00
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O
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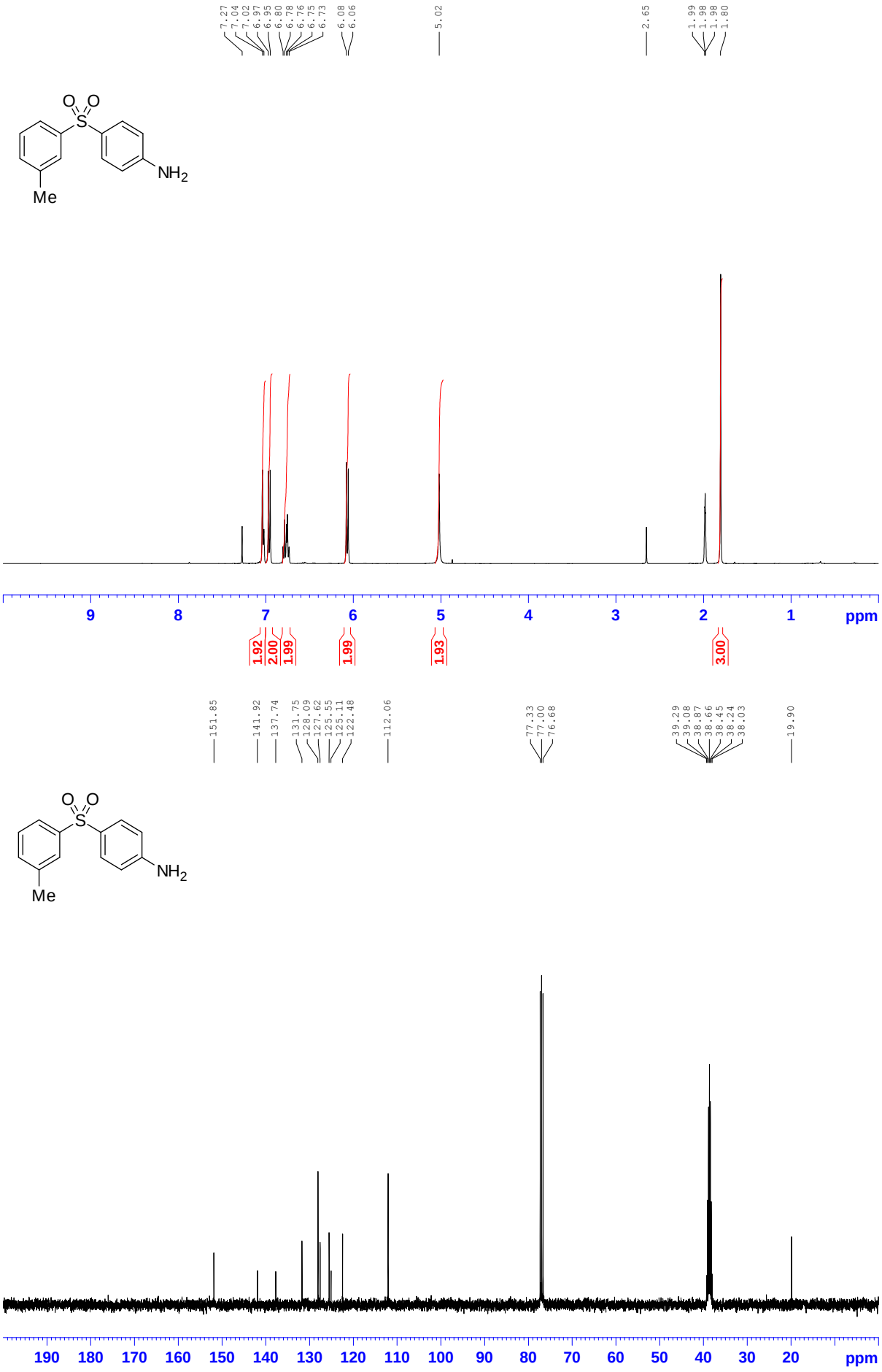
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127.62
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77.00
76.68
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38.03
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S
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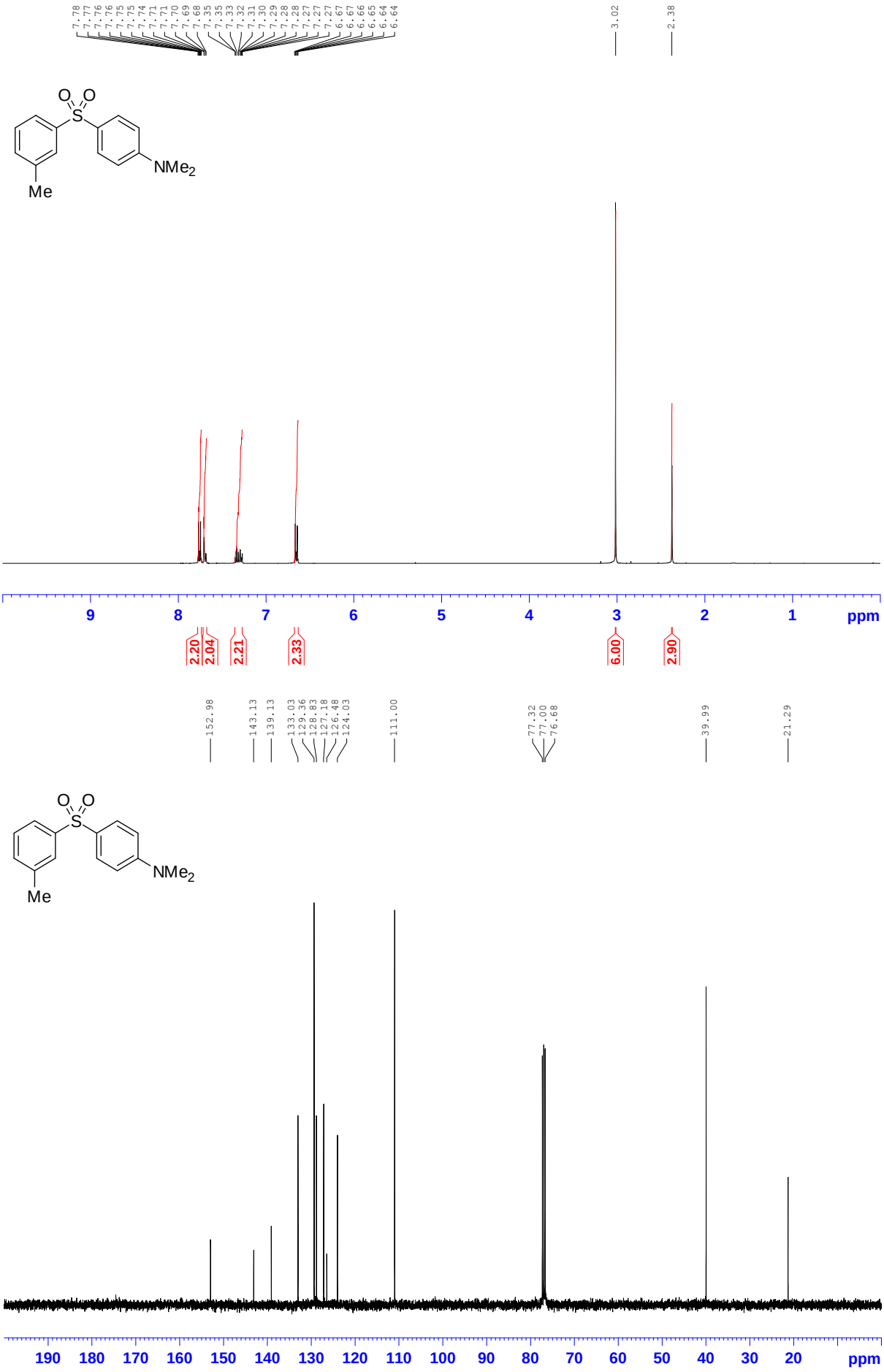
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6.64
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O
S
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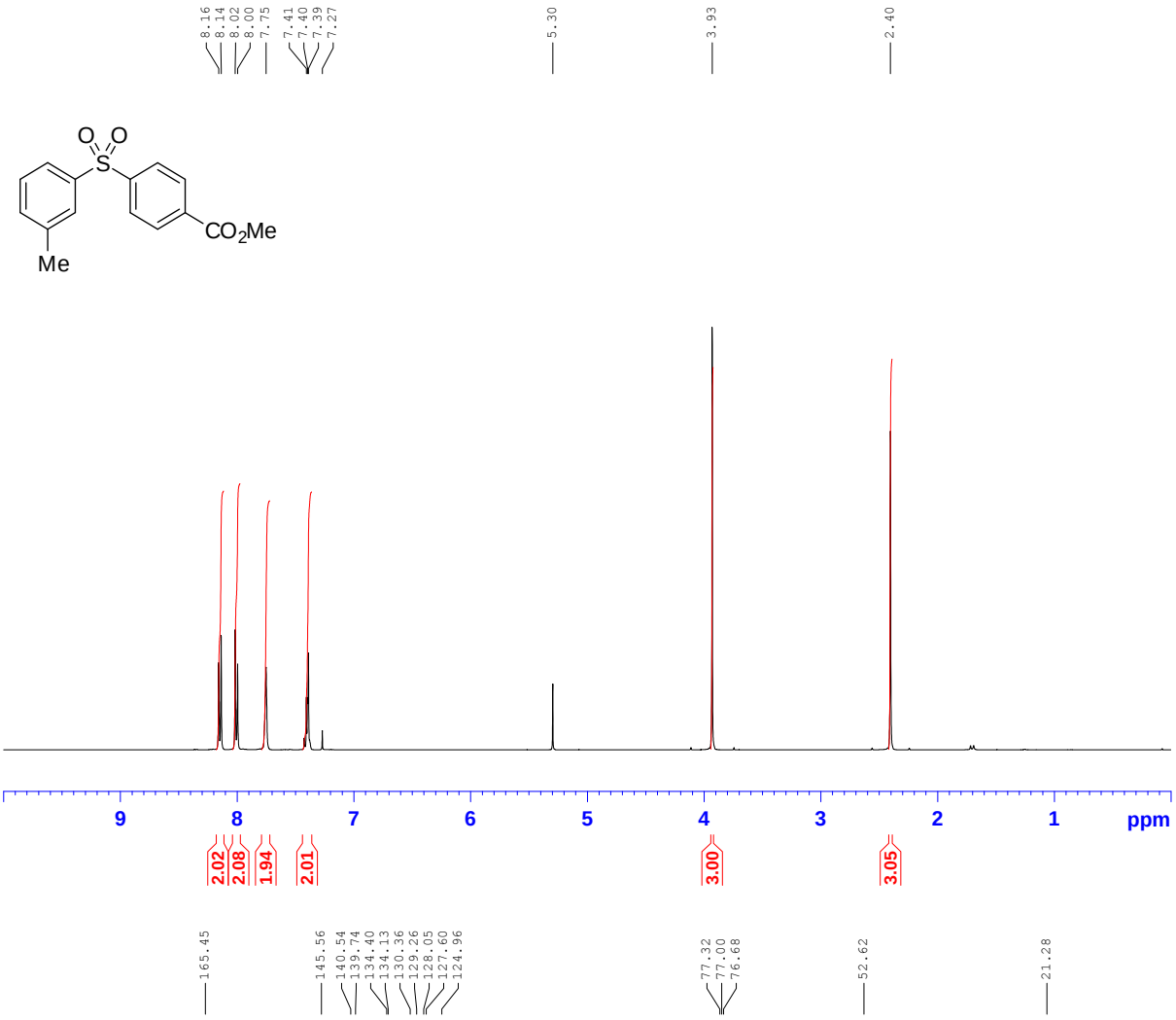
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O
S
CO2Me
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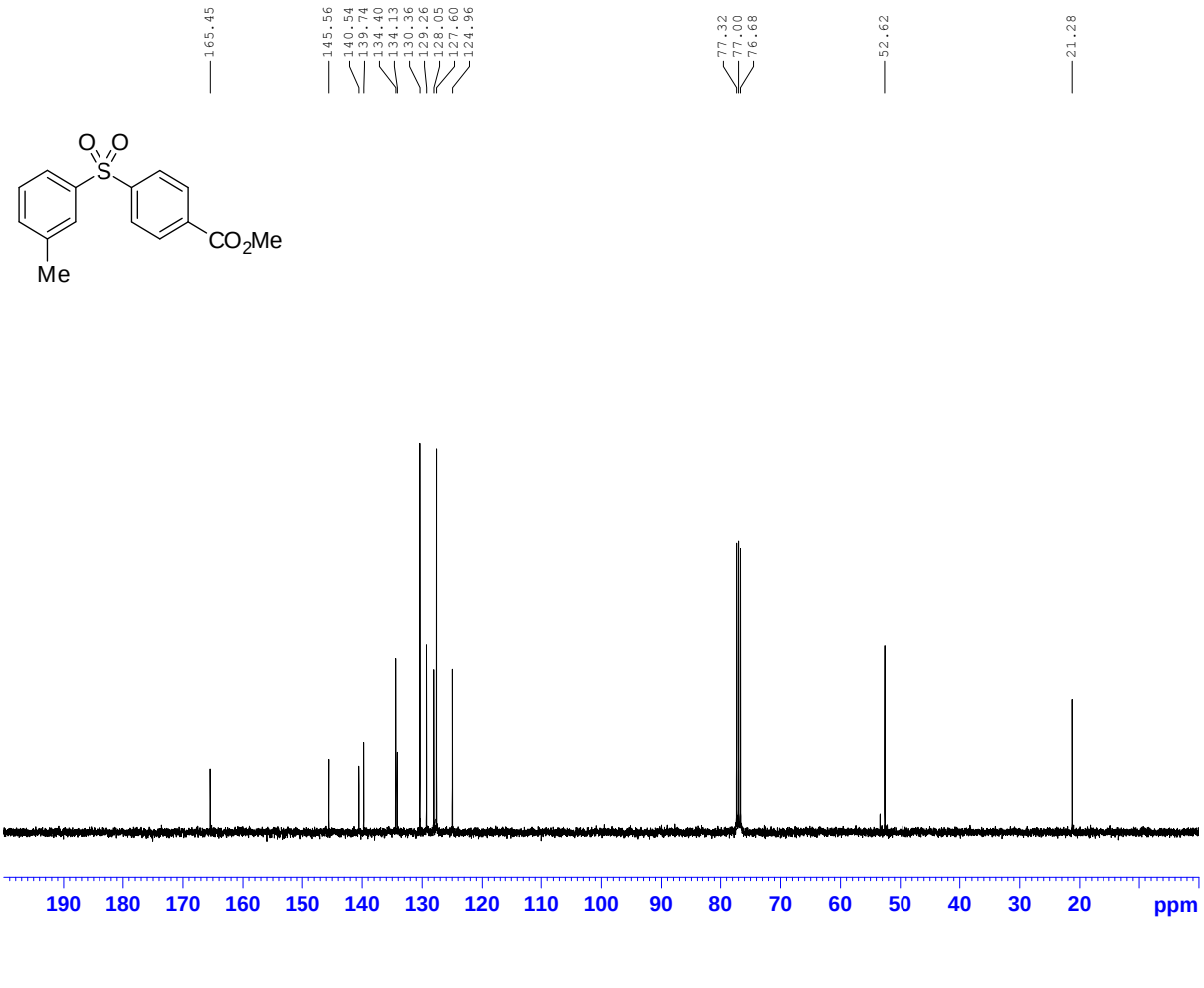
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O
S
CO2Me
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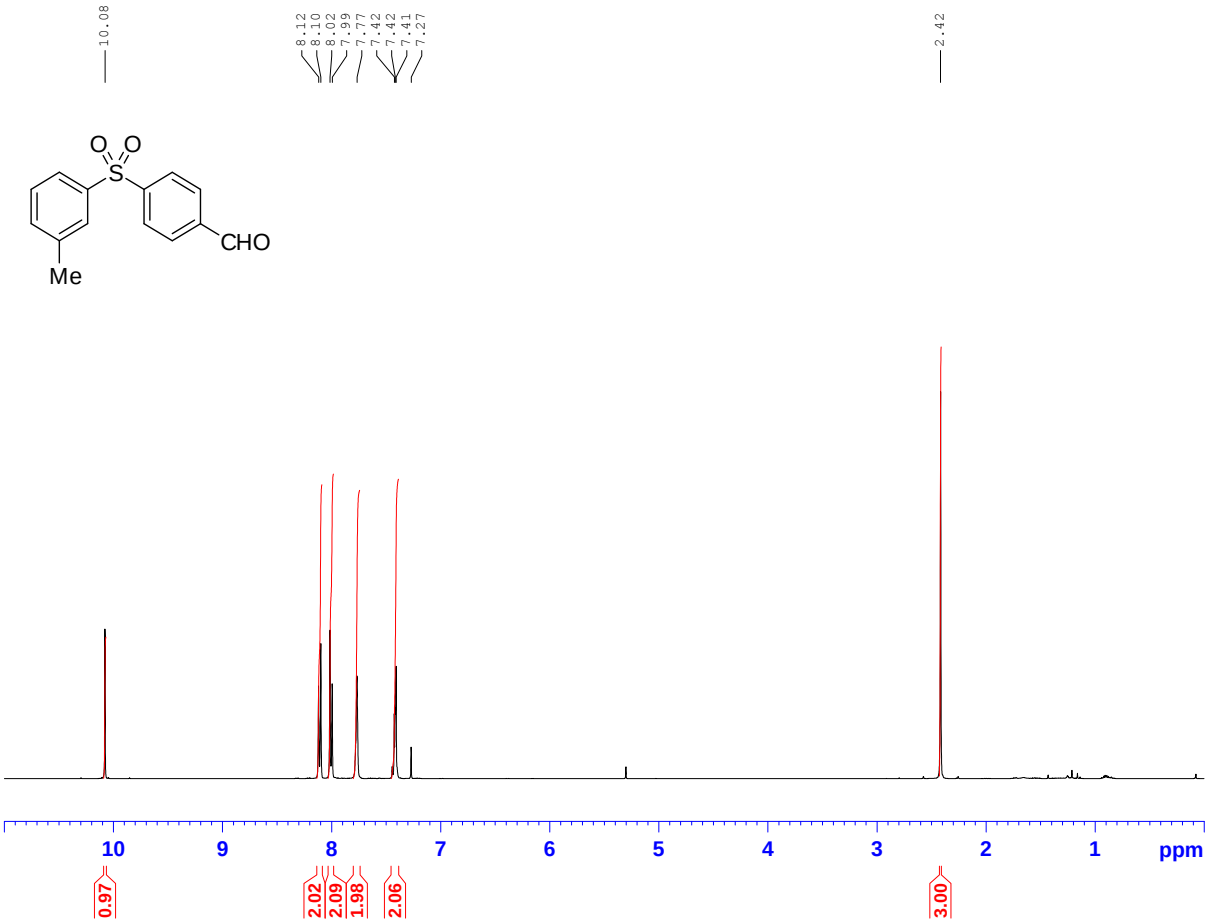
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O
S
CHO
Me
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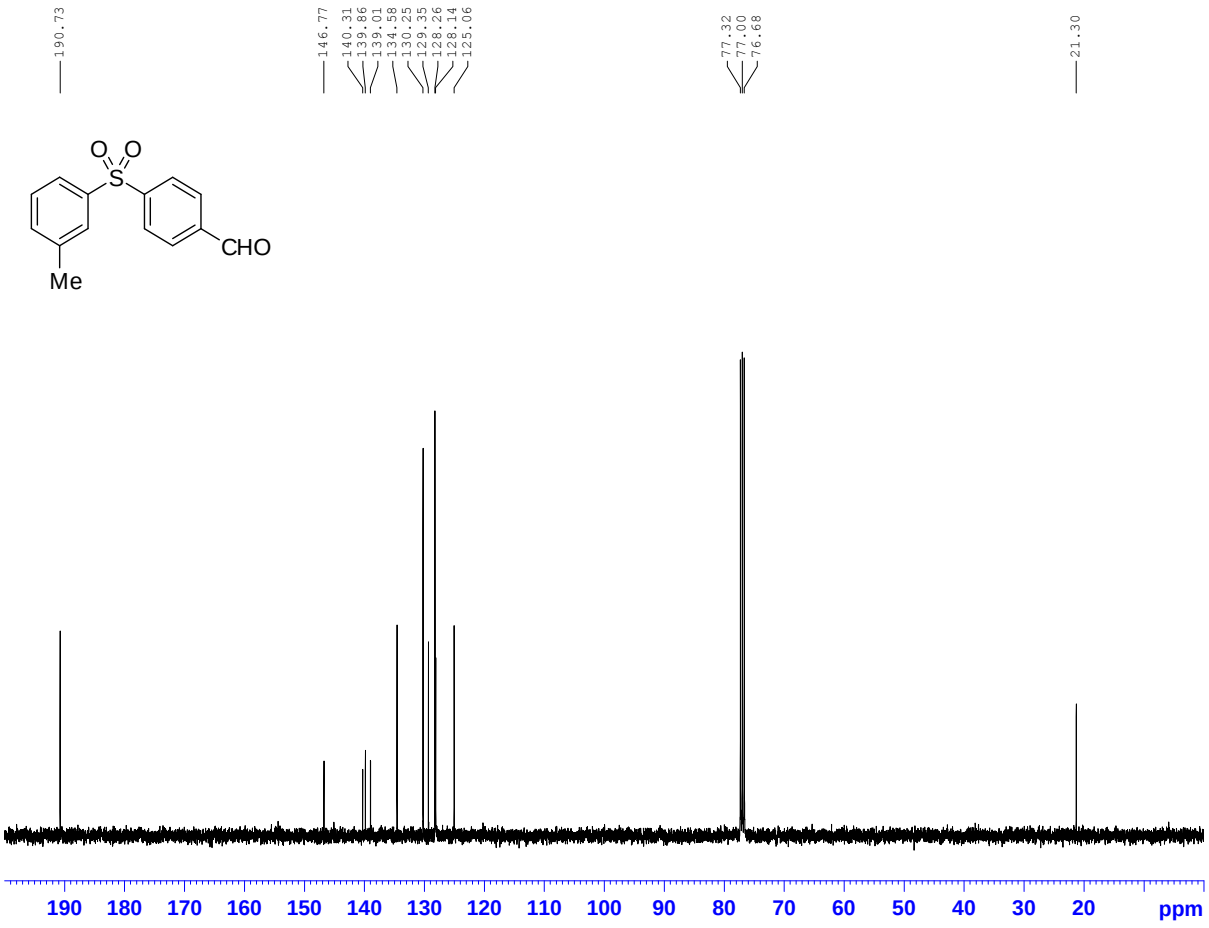
3.00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76.68
21.30
O
O
S
CHO
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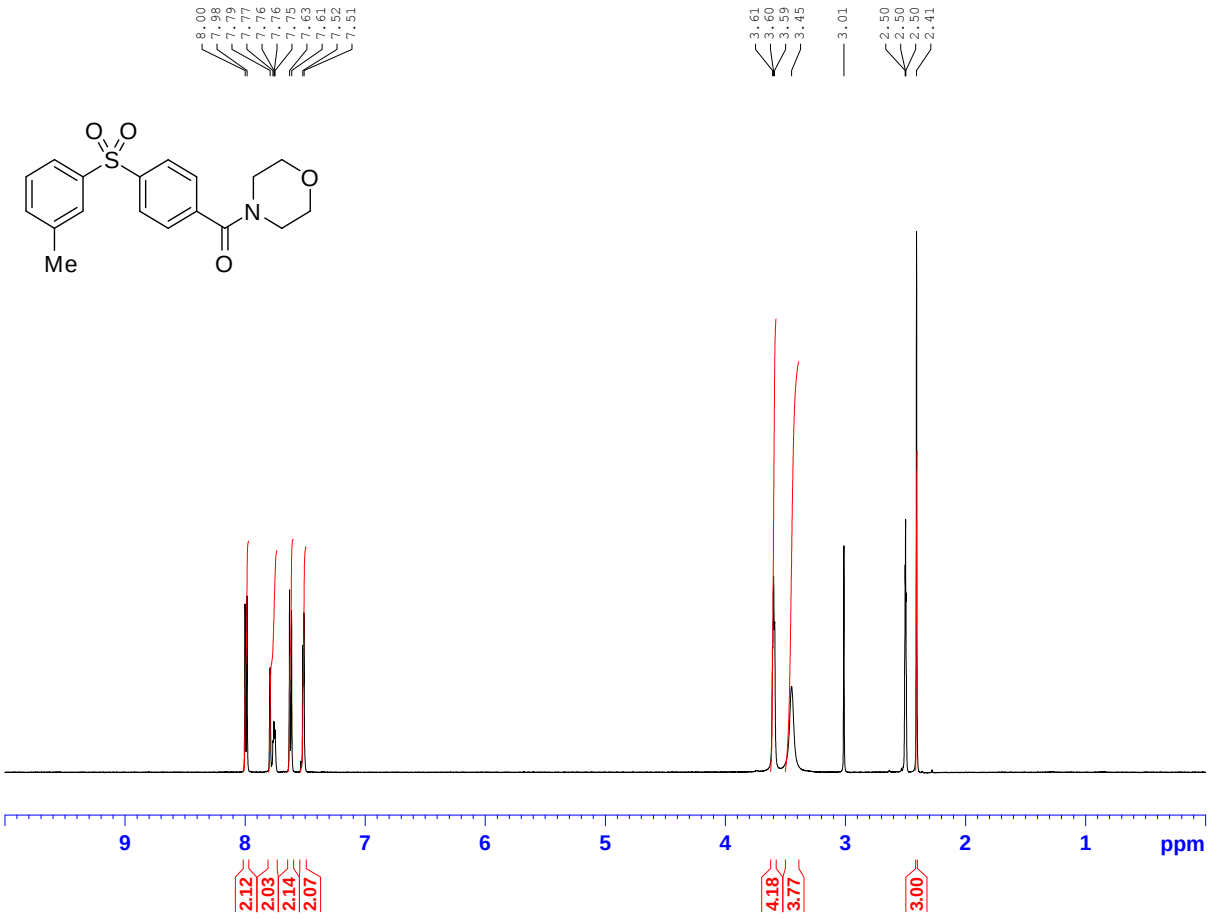
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S
O
N
Me
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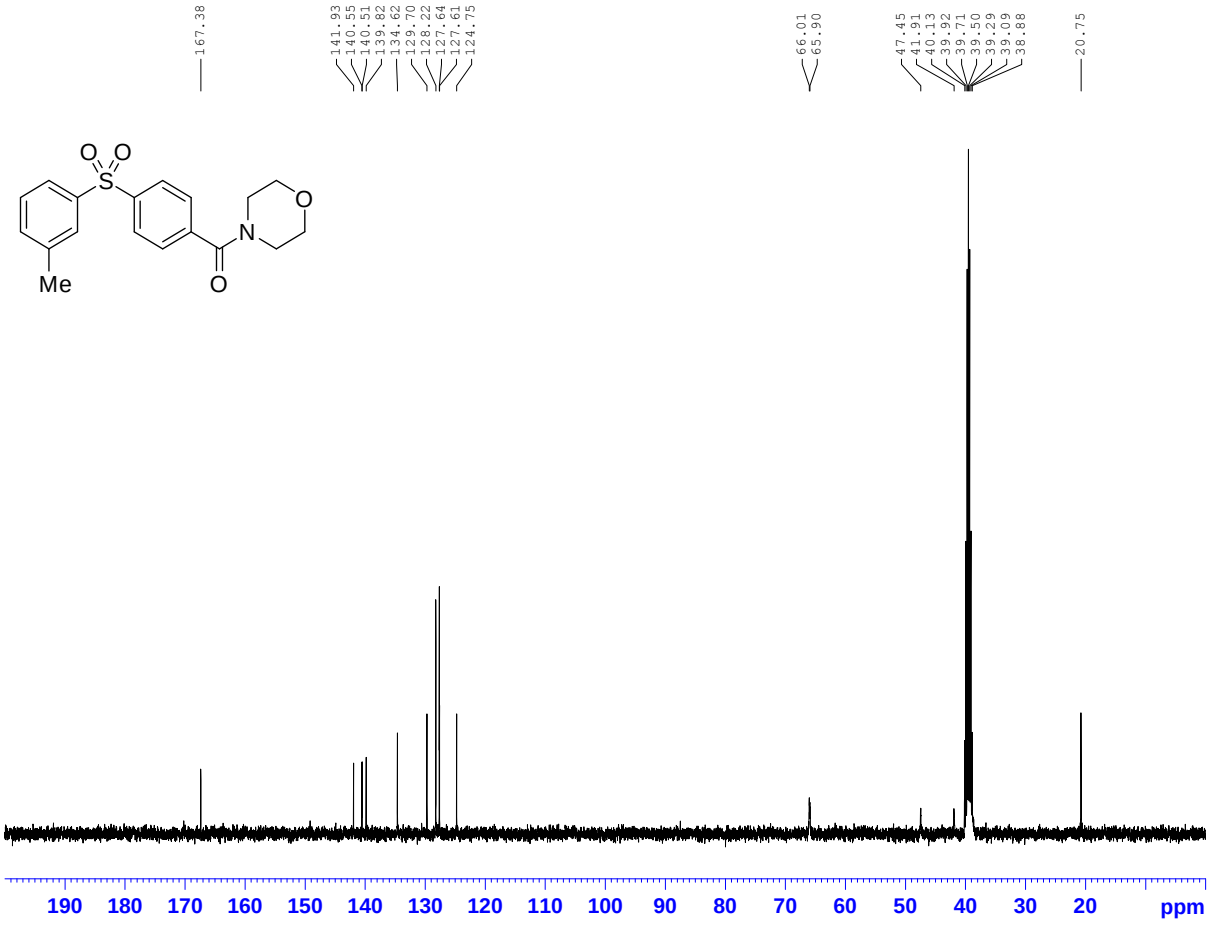
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S
O
N
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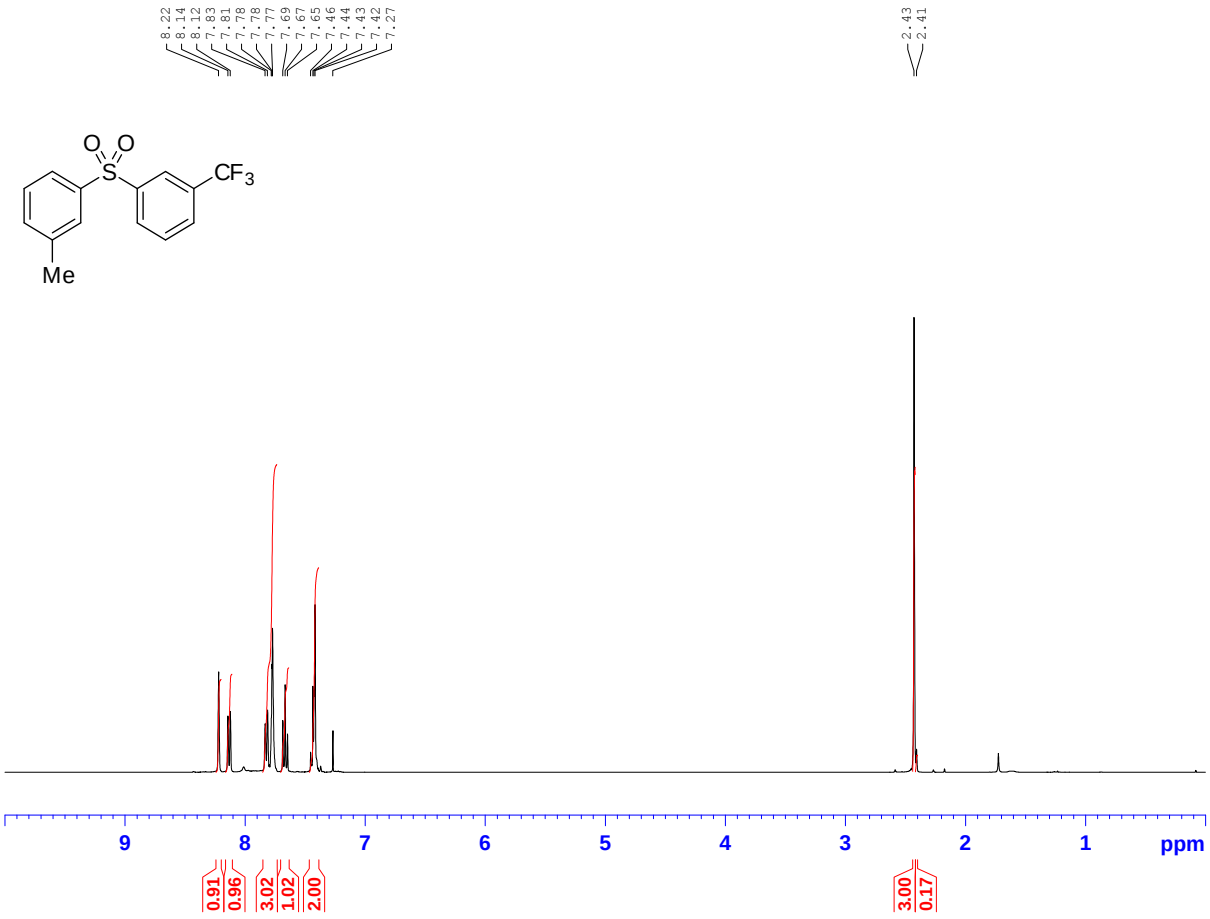
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7.42
7.27
2.43
2.41
O
O
S
CF3
Me
9
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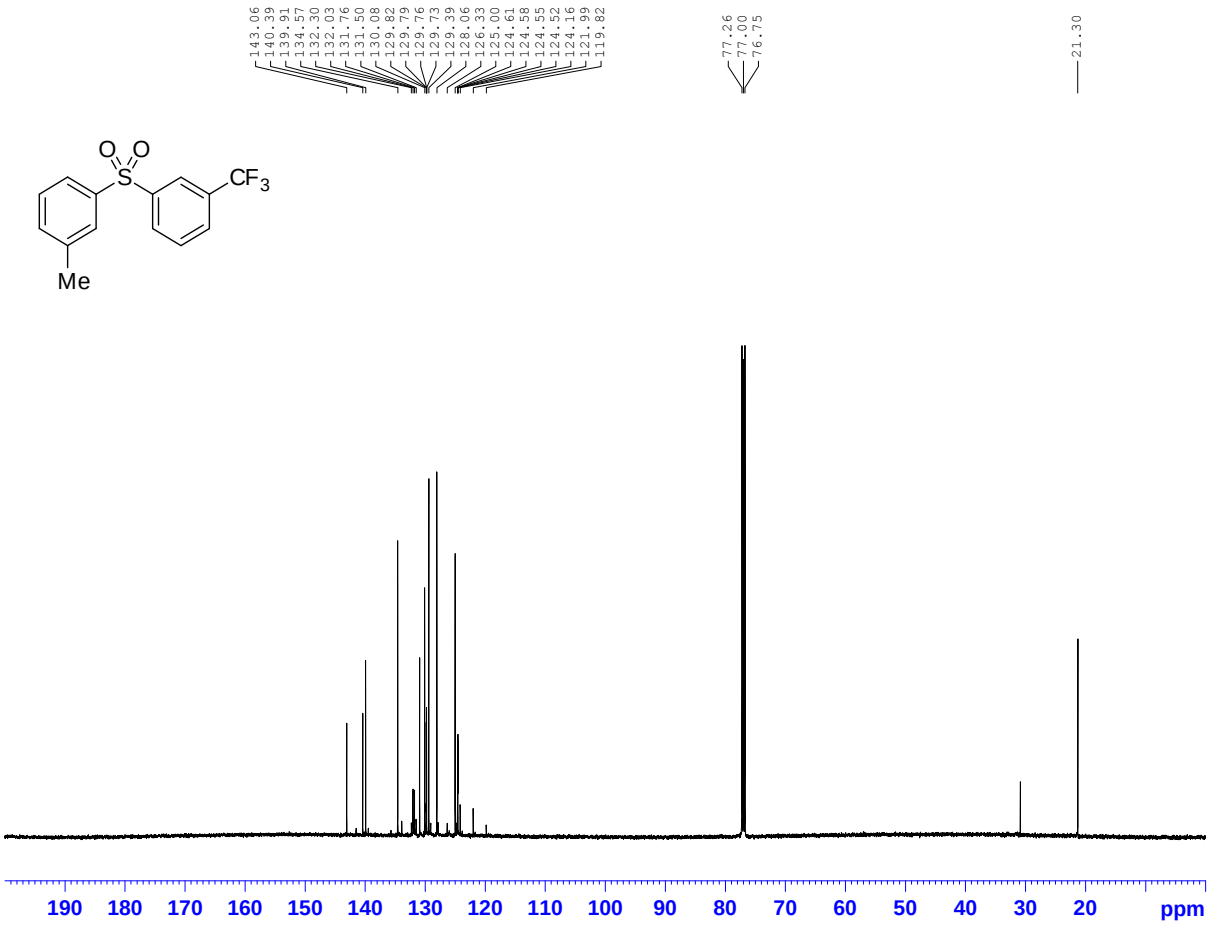
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O
S
CF3
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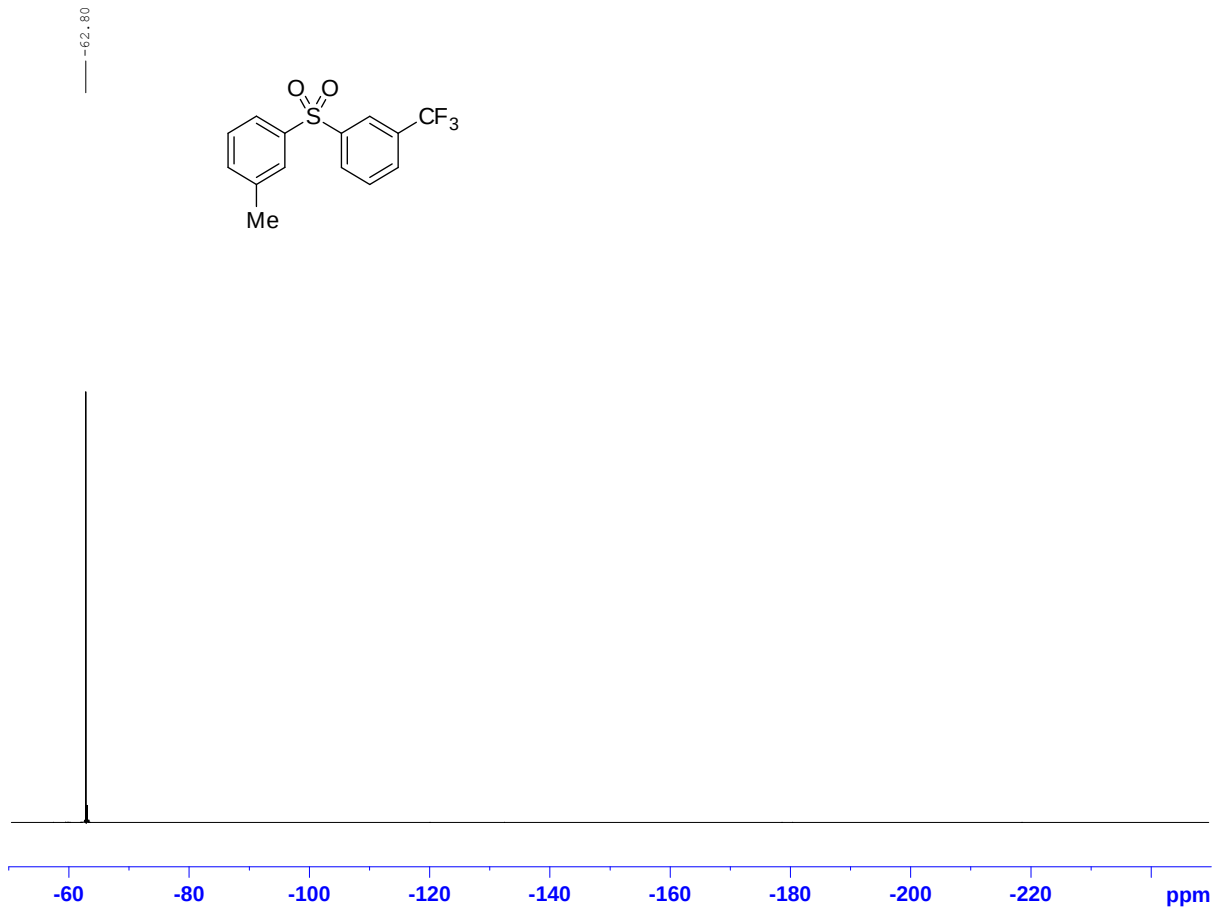
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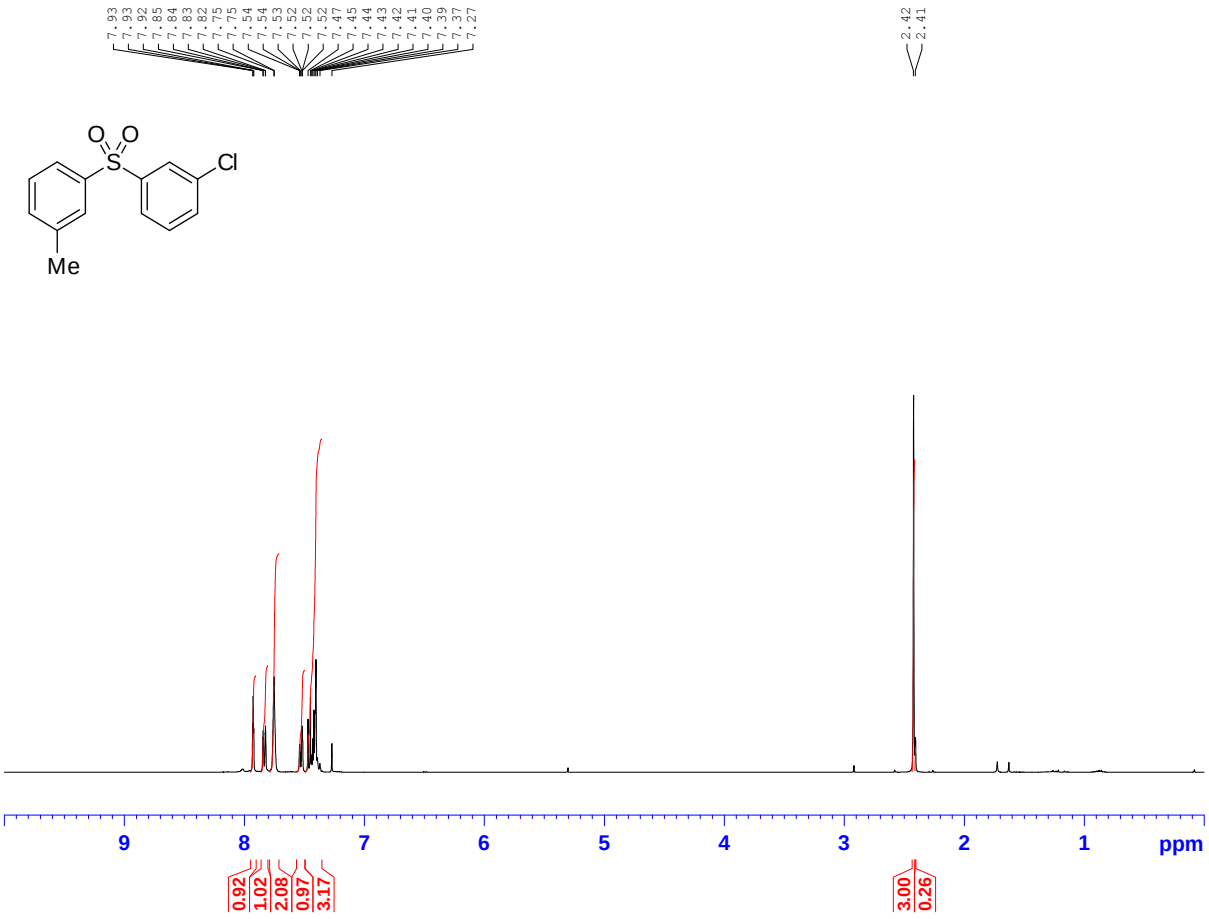
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7.45
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7.27
2.42
2.41
O
O
S
Cl
Me
9
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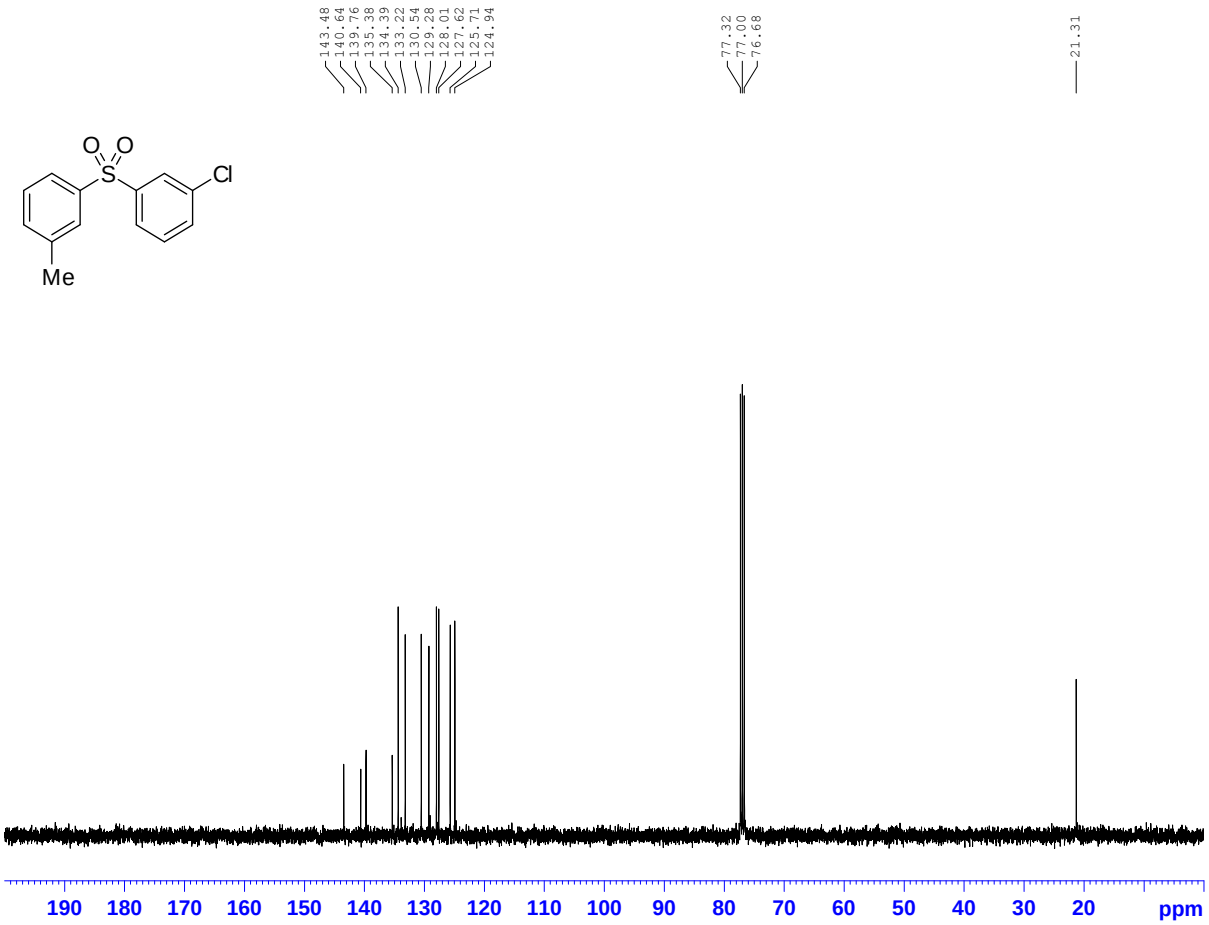
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S
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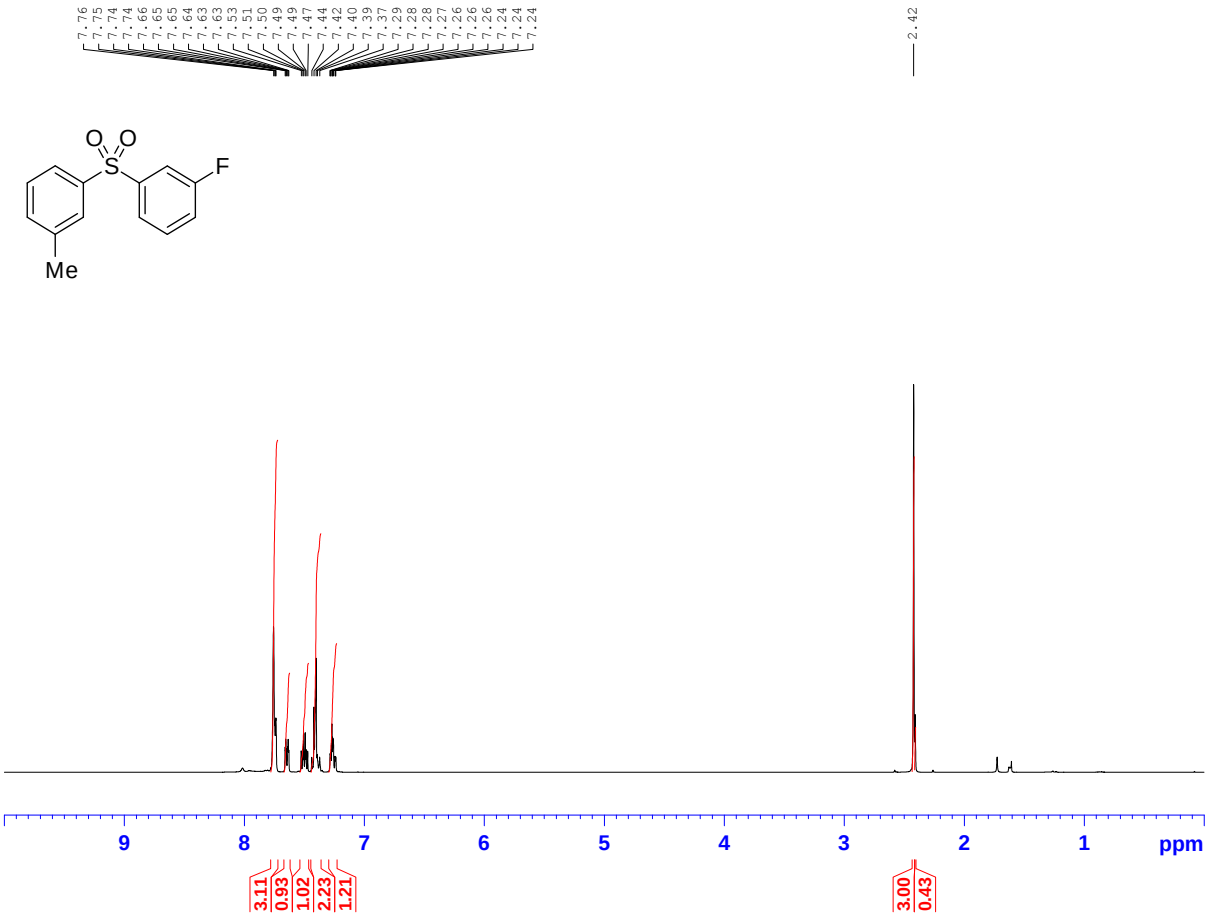
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7.28
7.28
7.27
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7.26
7.26
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7.24
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O
S
F
Me
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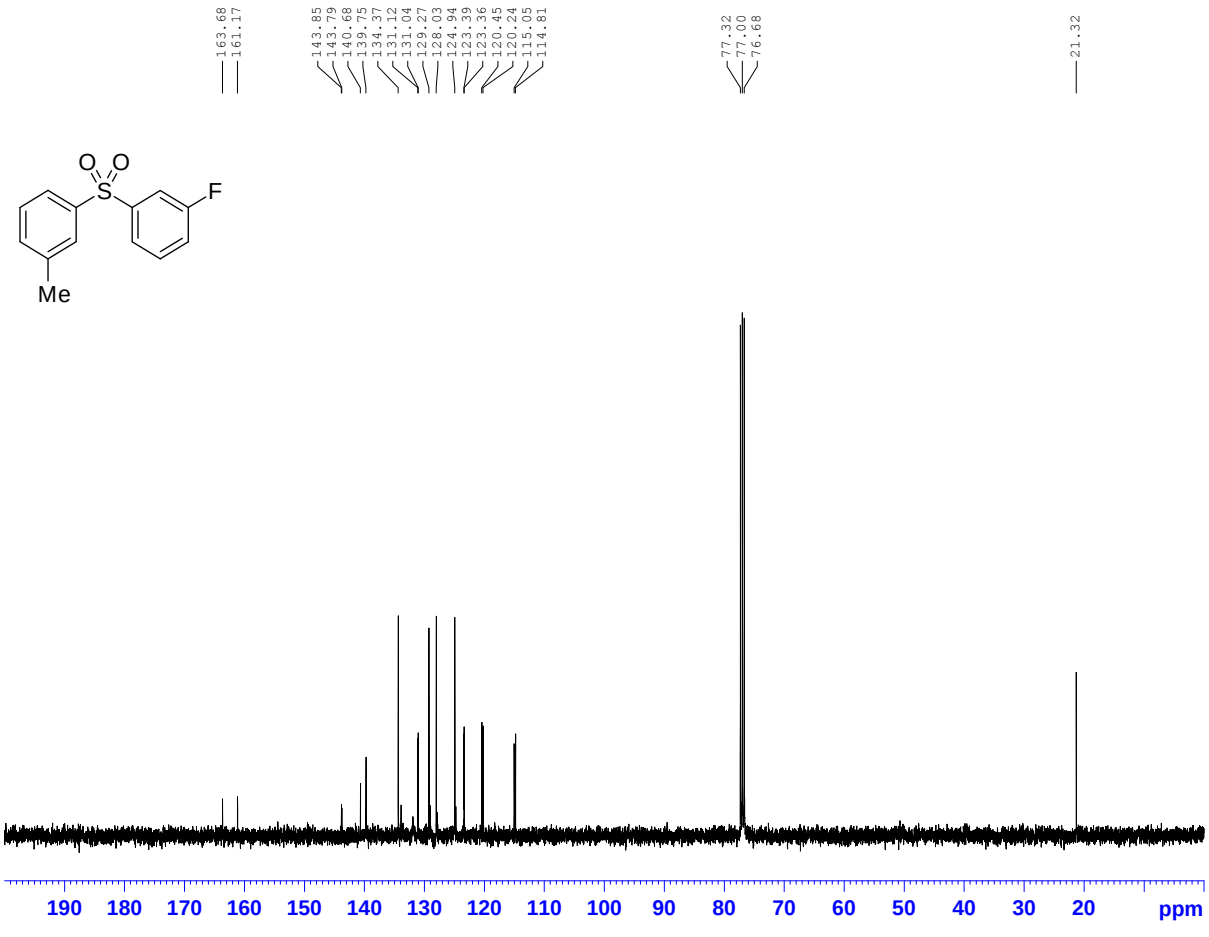
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123.36
120.45
120.24
115.05
114.81
77.32
77.00
76.68
21.32
O
O
S
F
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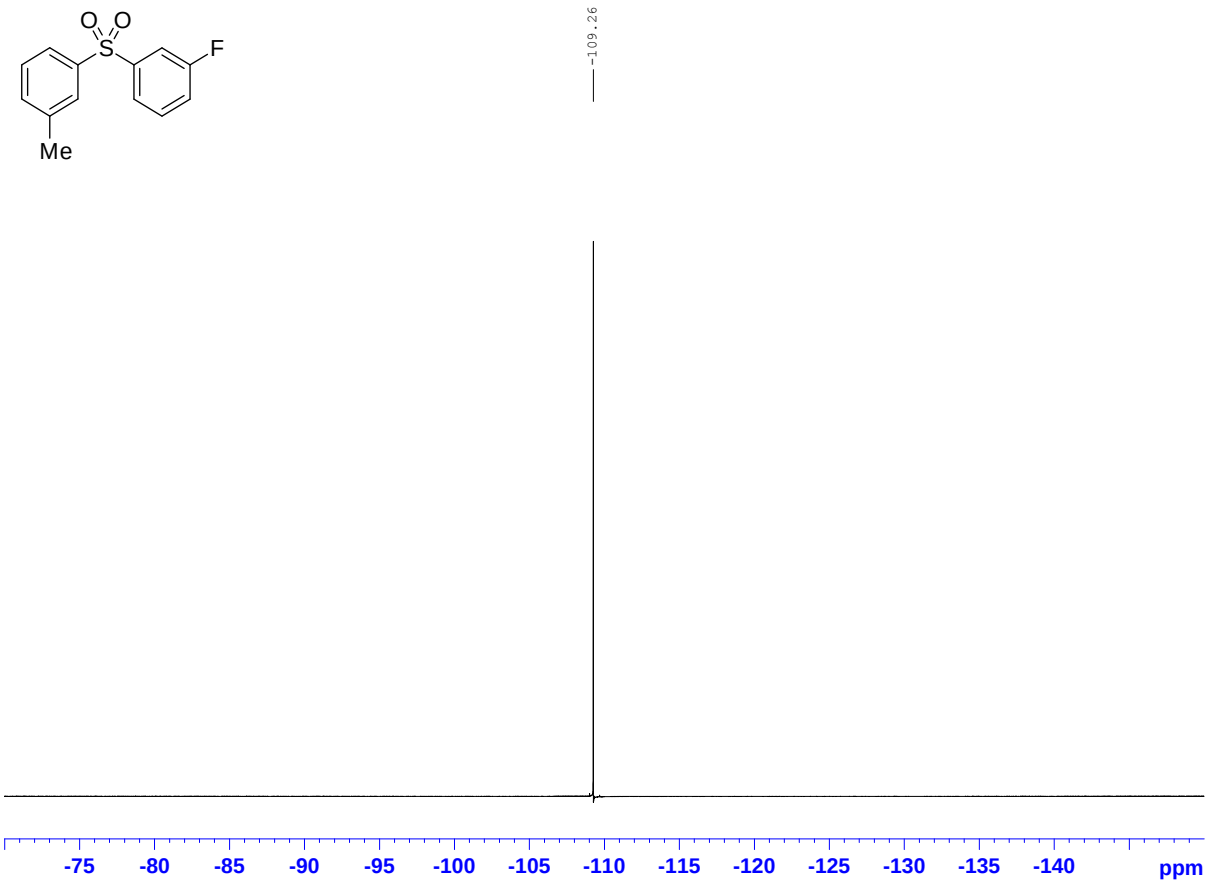
ppm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O
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Me
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-135
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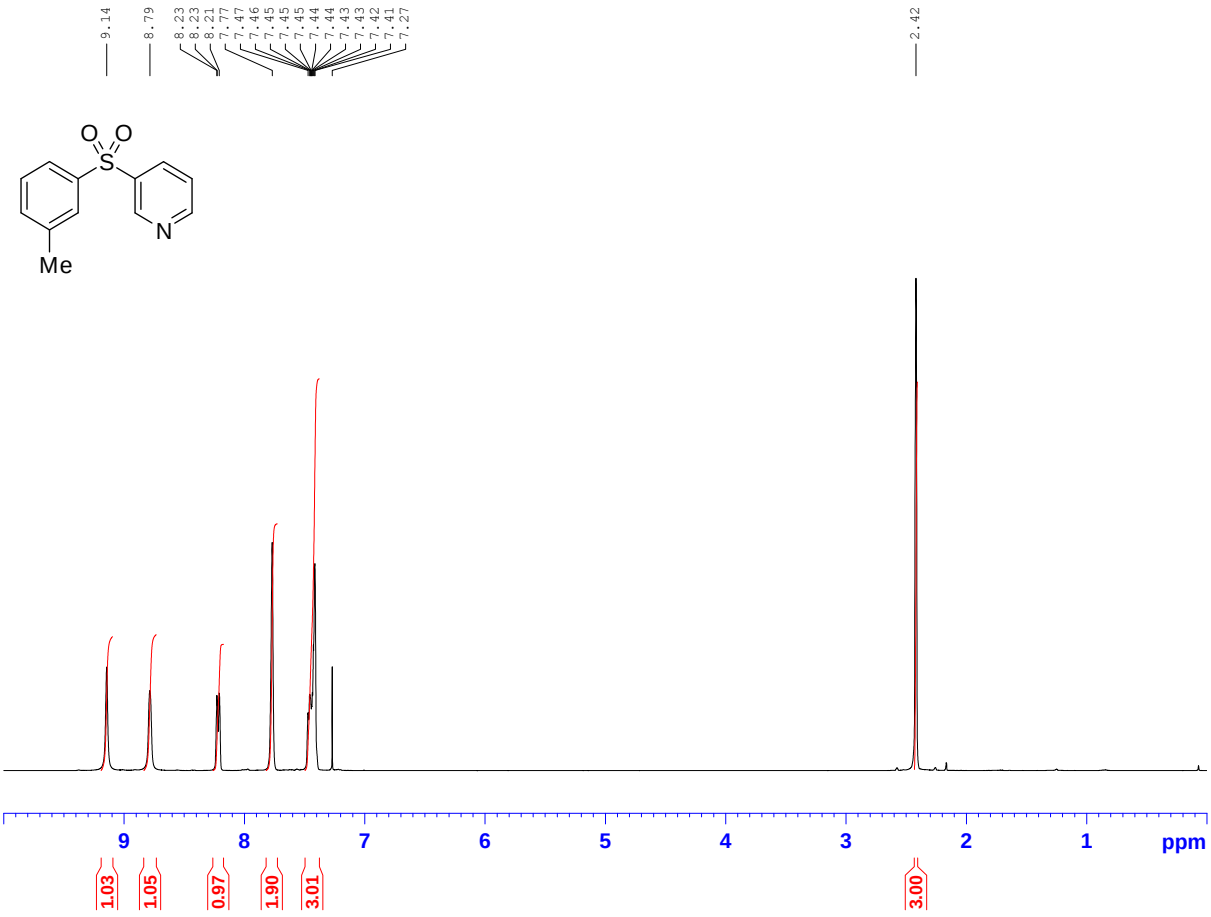
ppm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7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.27
2.42
O
O
S
N
Me
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5
4
3
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1
ppm
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1.05
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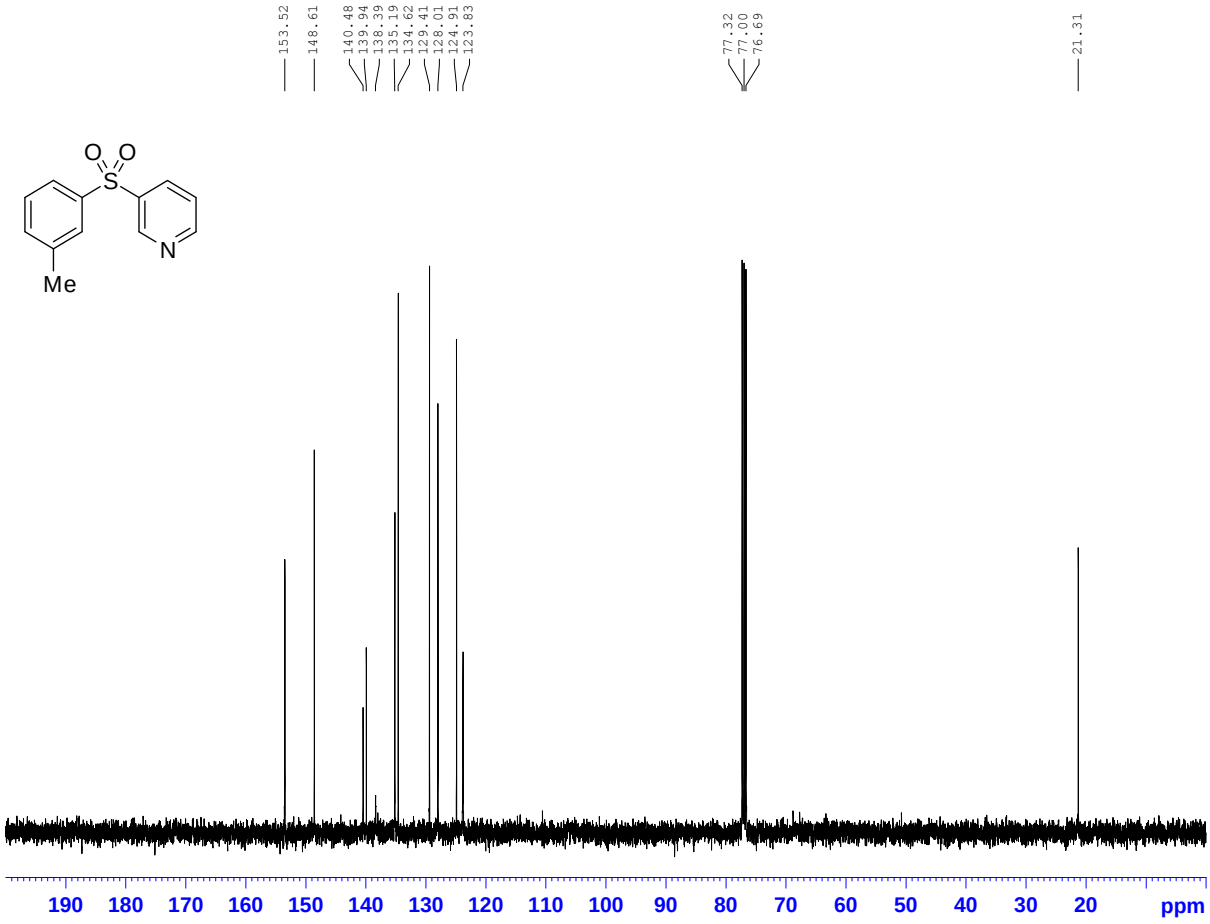
1.90
3.01
3.00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123.83
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77.00
76.69
21.31
O
O
S
N
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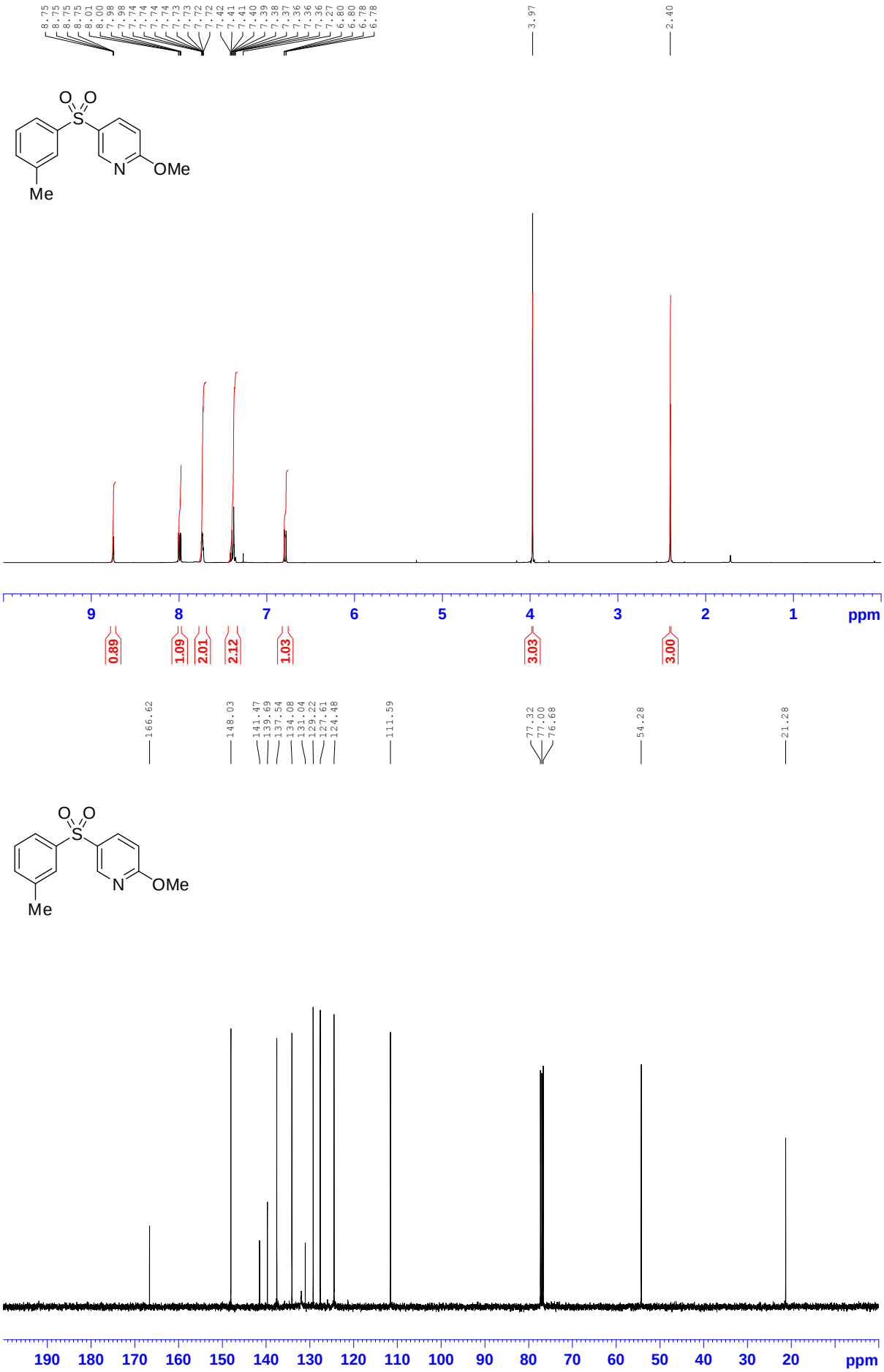
20
ppm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7.73
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7.72
7.42
7.41
7.41
7.40
7.39
7.38
7.37
7.36
7.36
7.27
6.80
6.78
6.78
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O
S
N
OMe
Me
9
8
7
6
5
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2
1
ppm
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O
S
N
OMe
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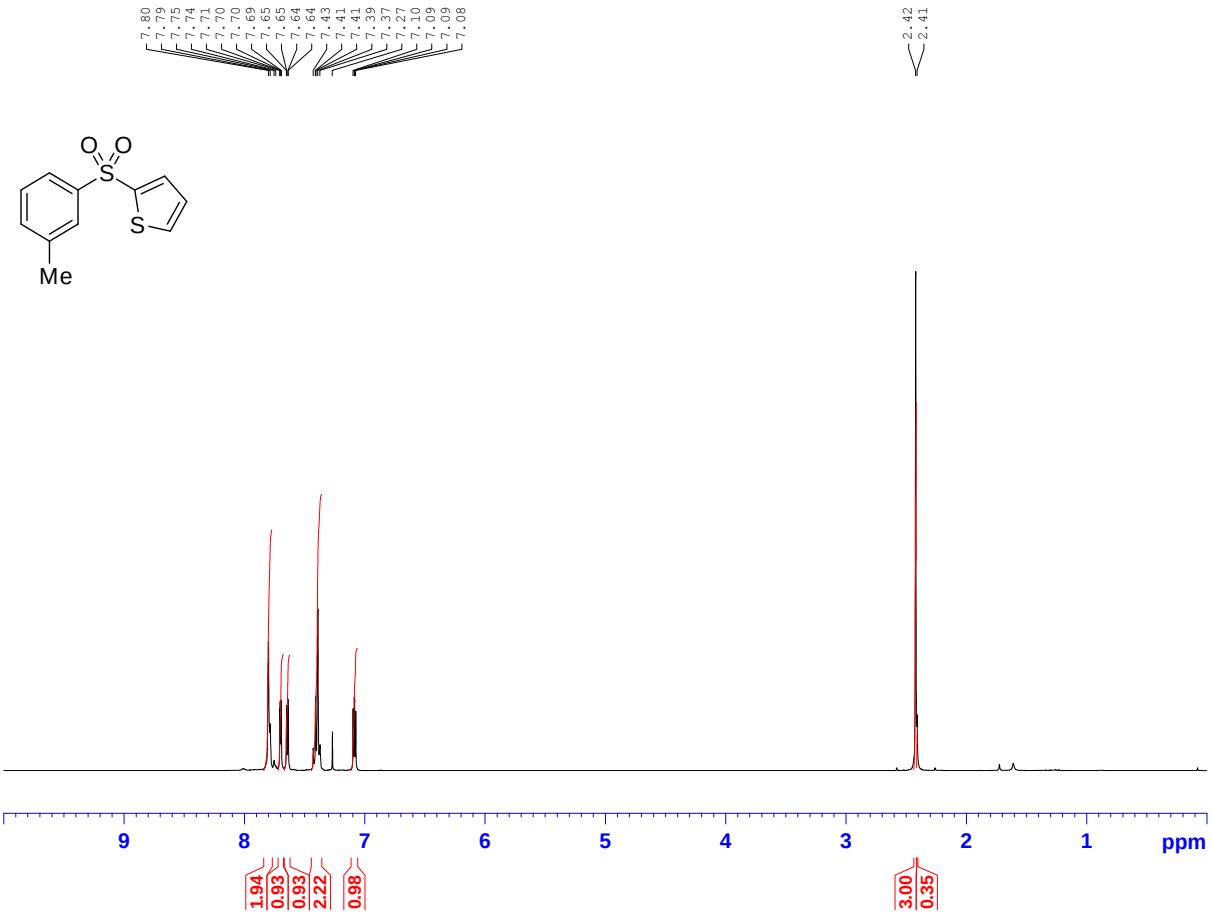
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7.37
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2.41
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O
S
S
Me
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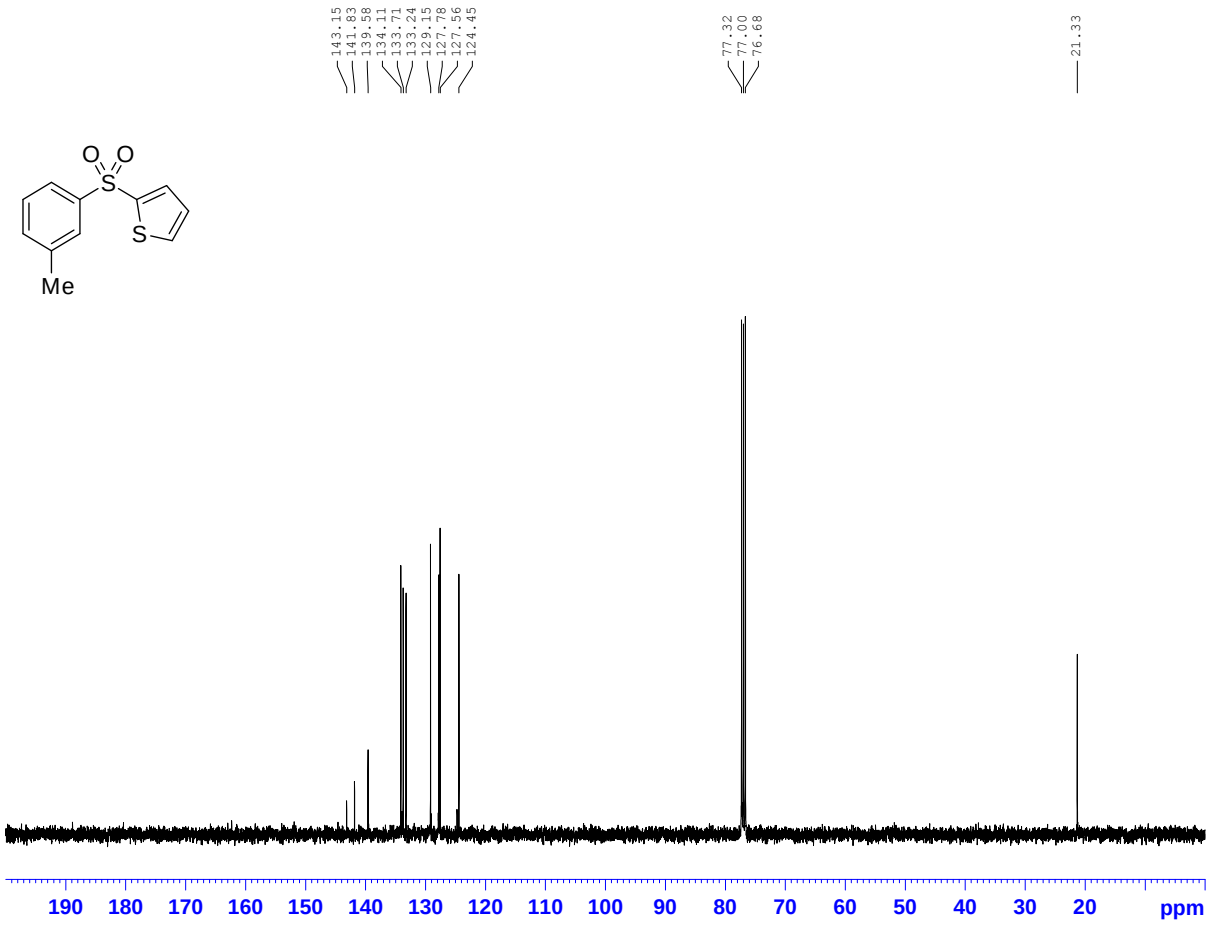
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77.00
76.68
21.33
O
O
S
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Me
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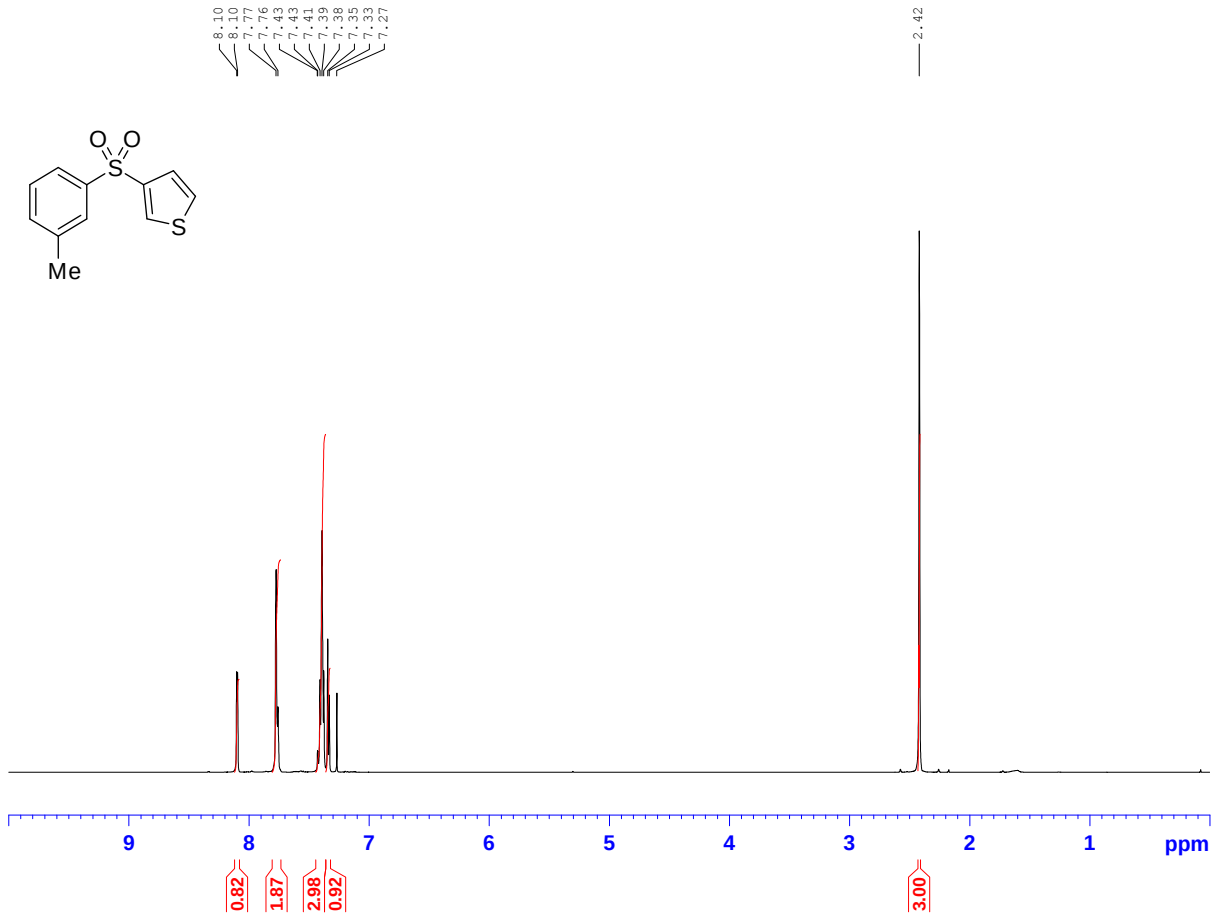
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7.27
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O
O
S
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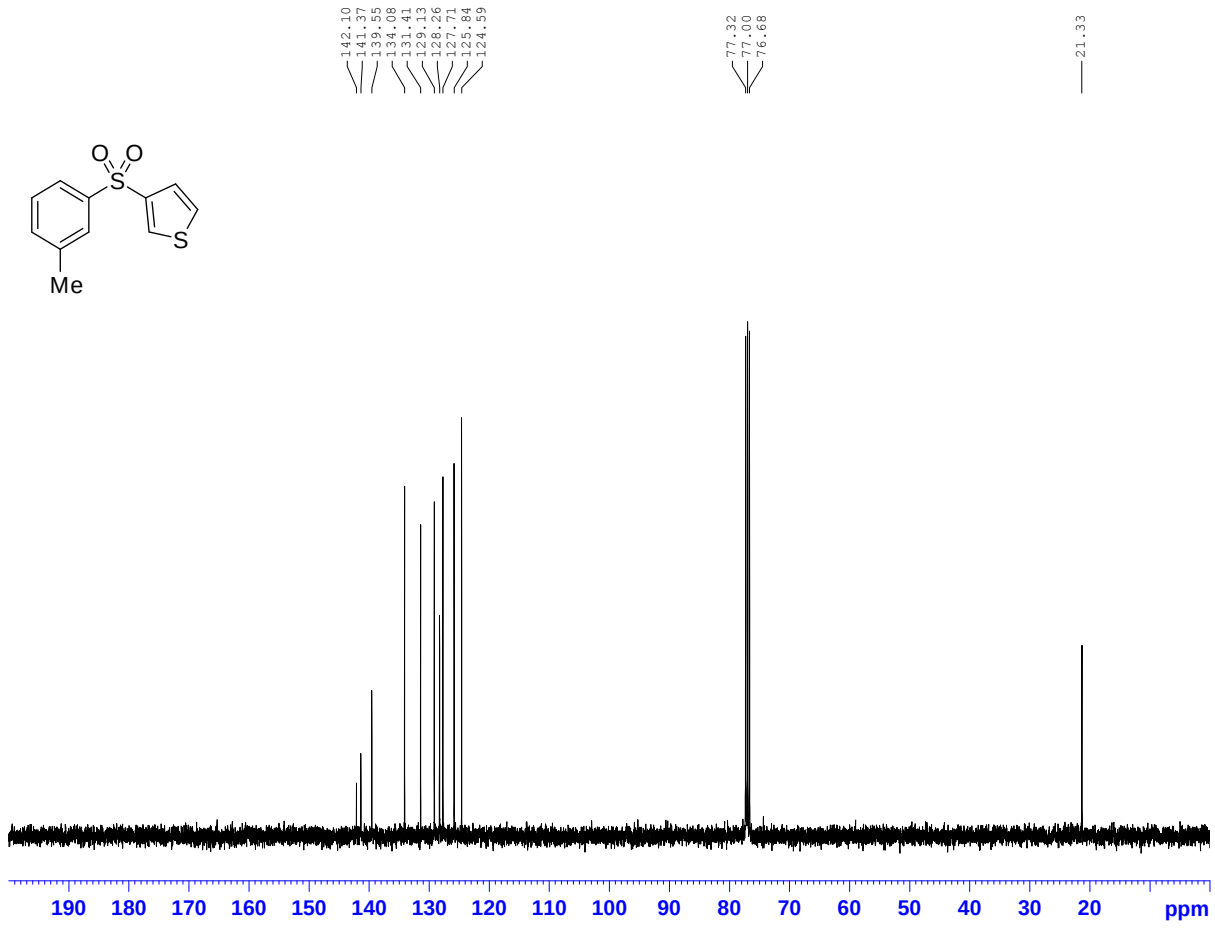
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77.00
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21.33
O
O
S
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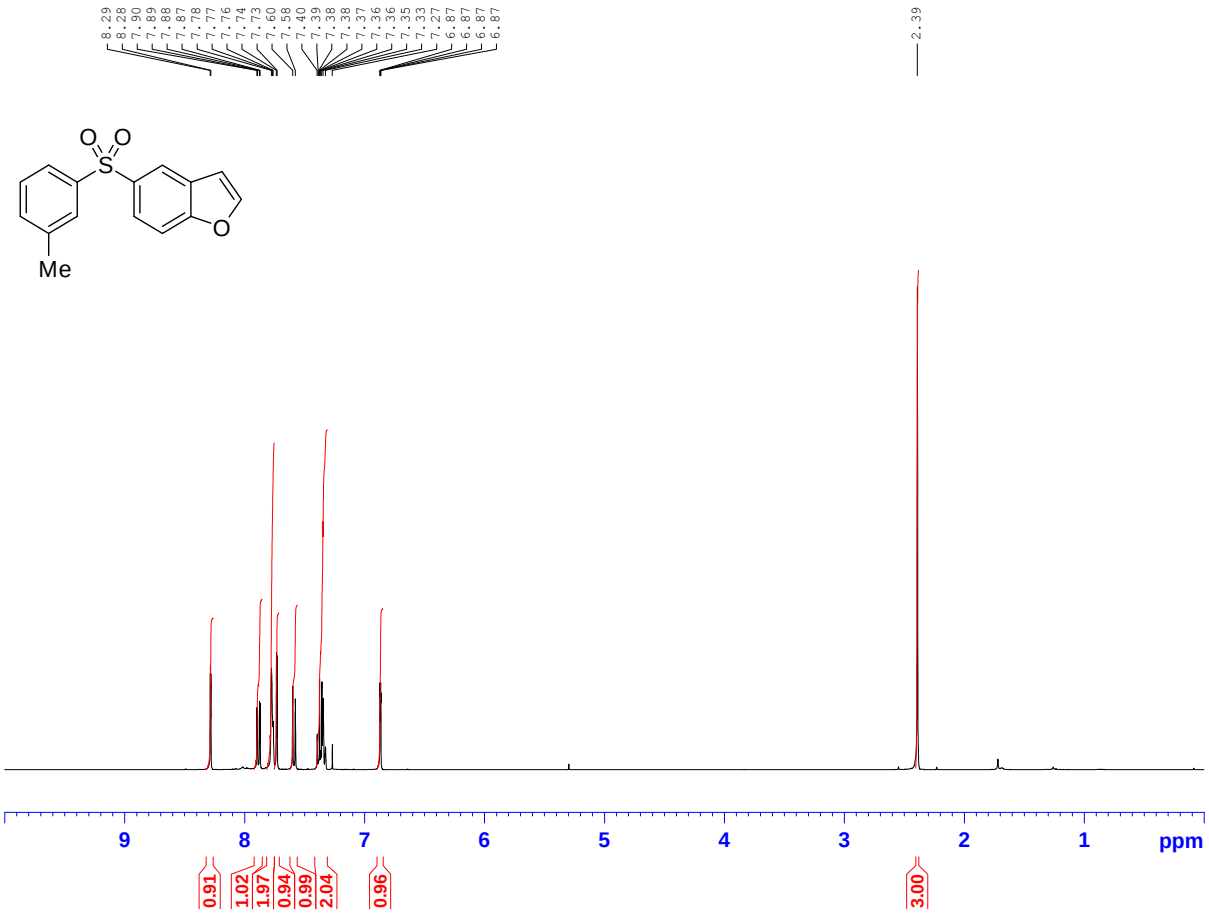
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7.38
7.37
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6.87
6.87
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Me
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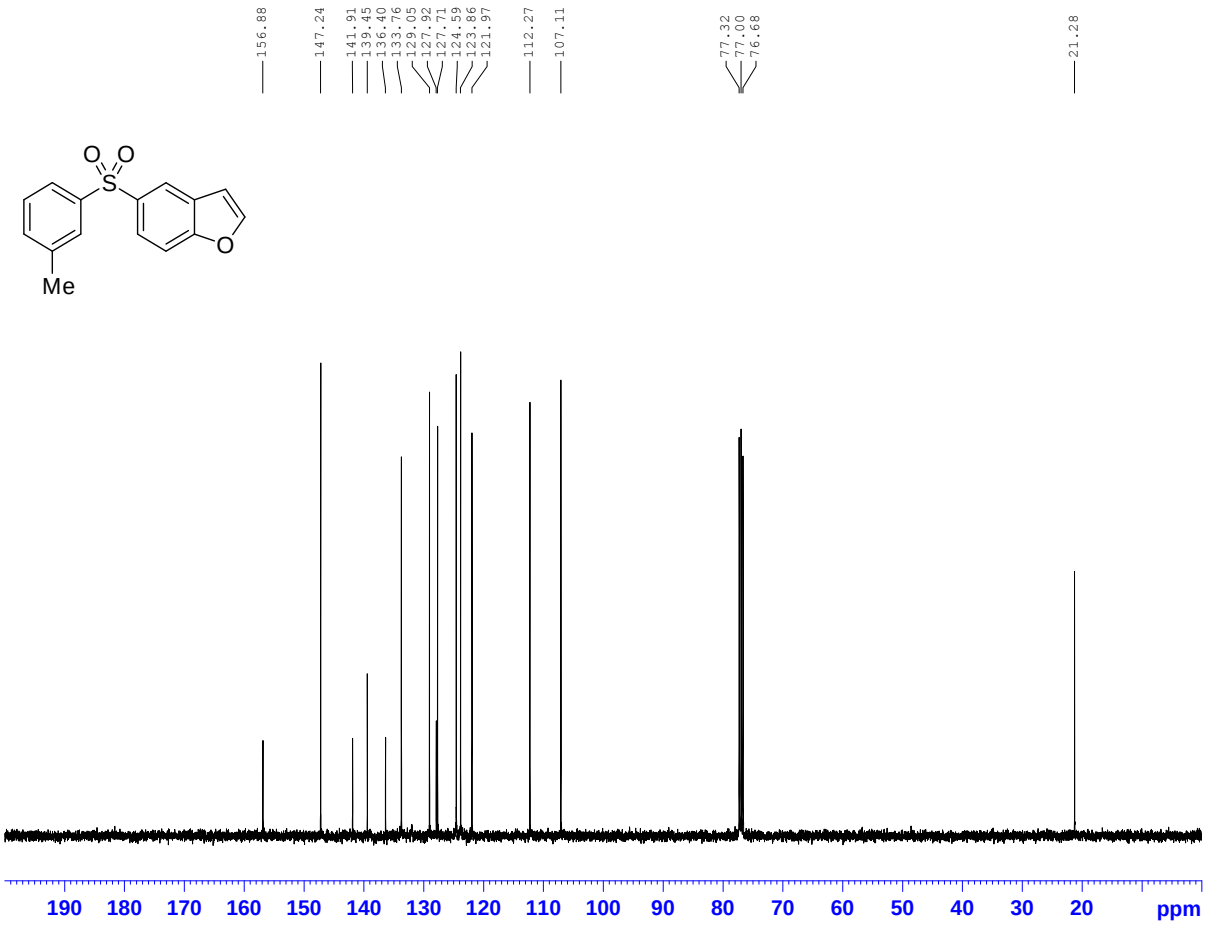
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77.00
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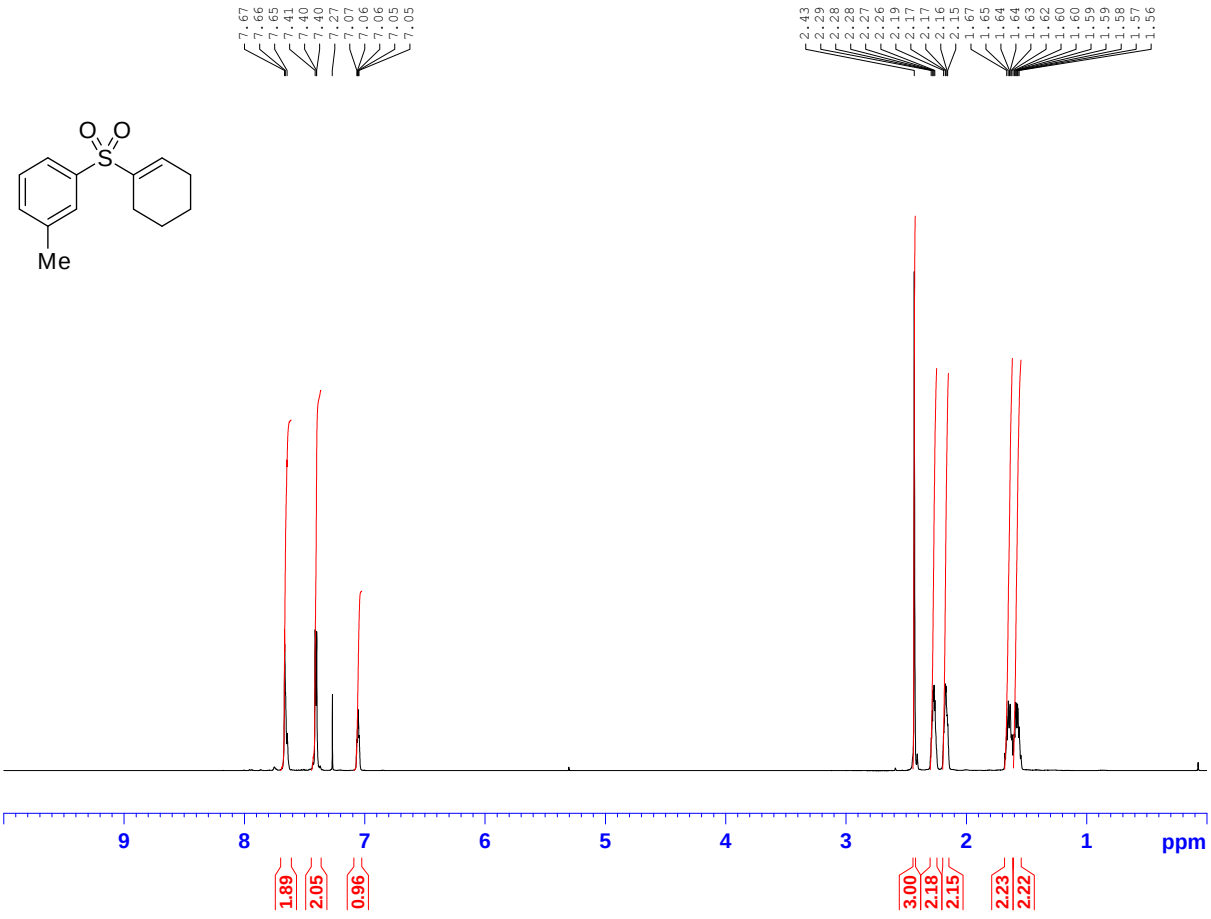
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7.05
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2.27
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2.19
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2.16
2.15
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1.65
1.64
1.64
1.63
1.62
1.60
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1.57
1.56
O
O
S
Me
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8
7
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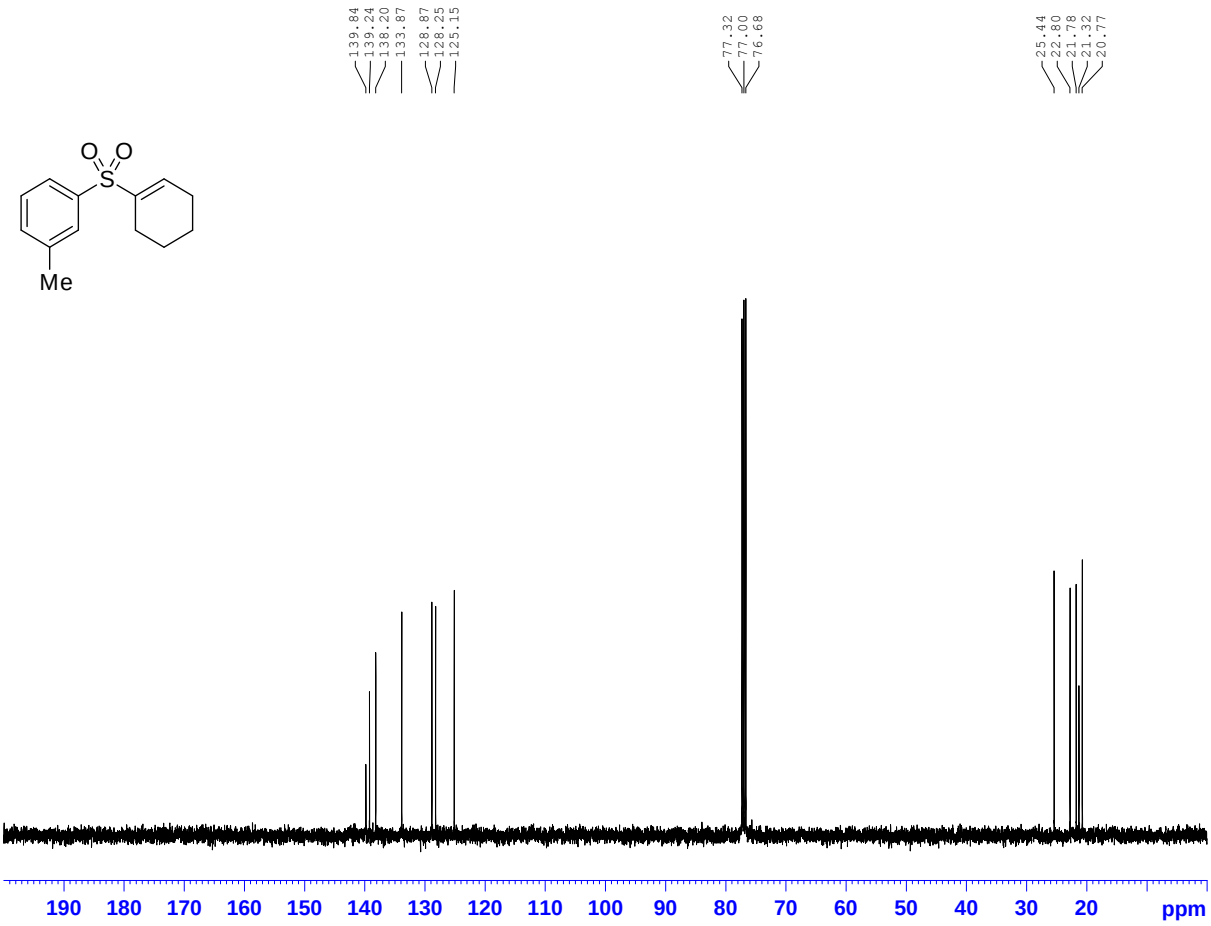
2.22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O
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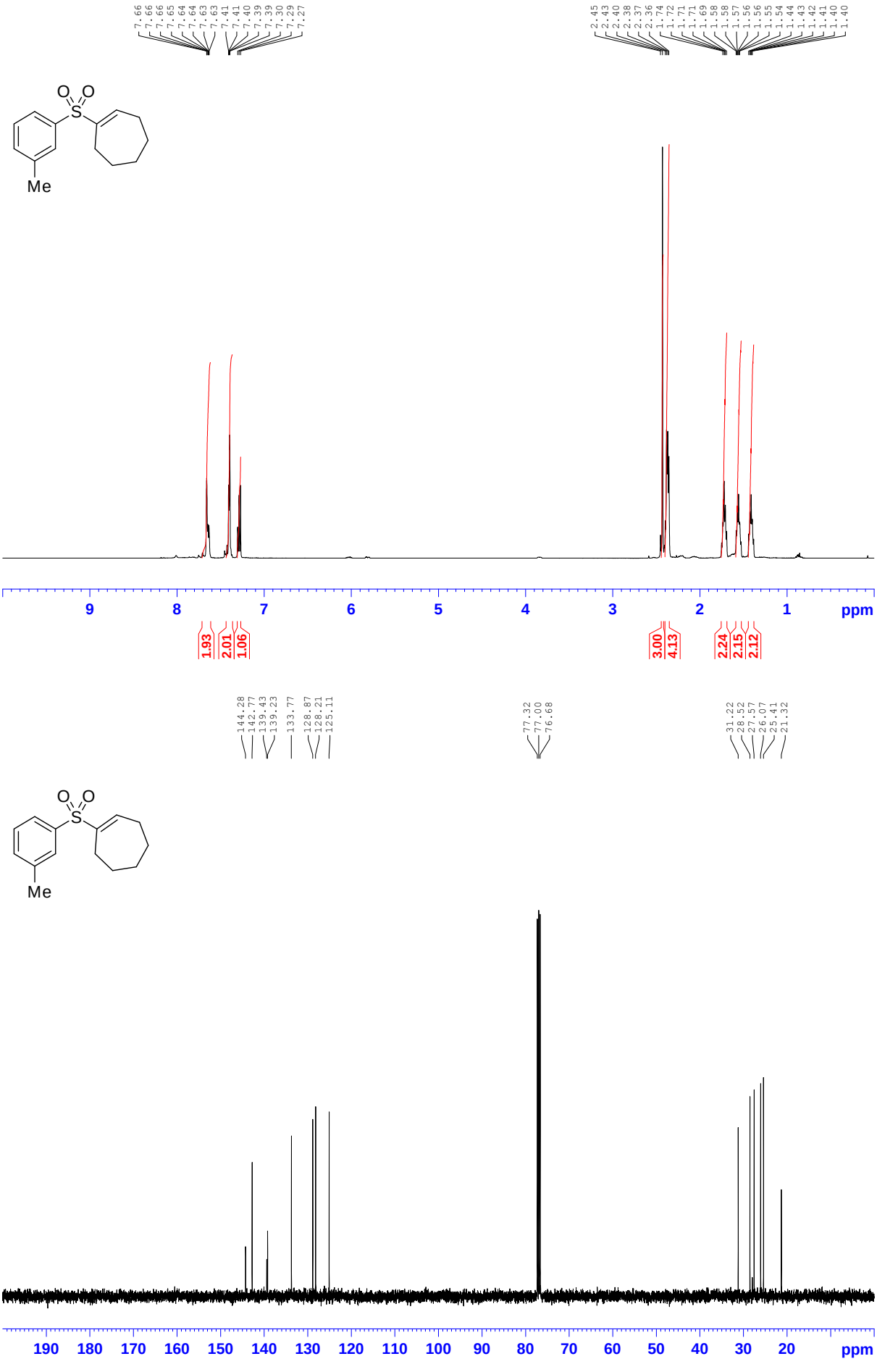
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1.57
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1.43
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1.41
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O
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Me
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ppm
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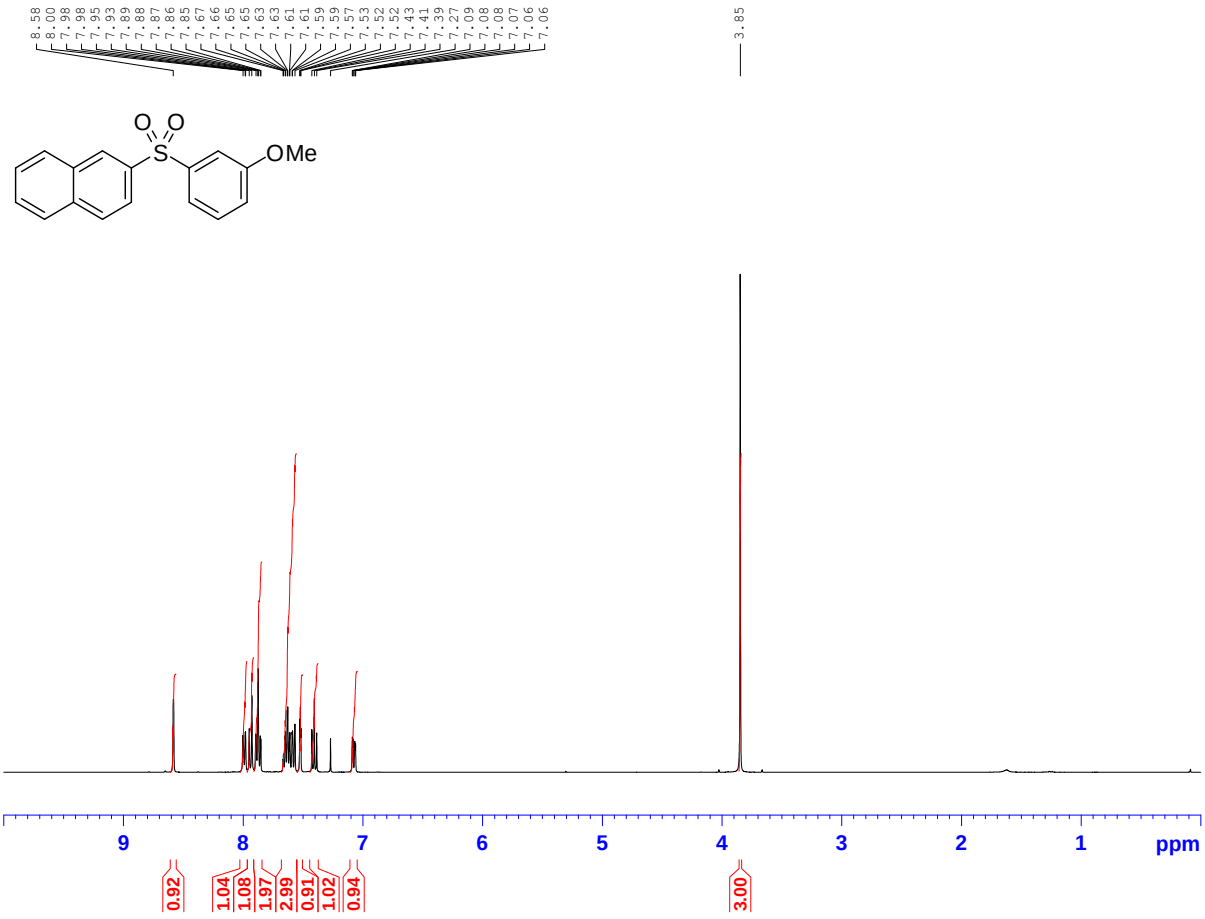
ppm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7.63
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7.59
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7.41
7.39
7.27
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7.08
7.08
7.07
7.06
7.06
3.85
O
O
S
OMe
9
8
7
6
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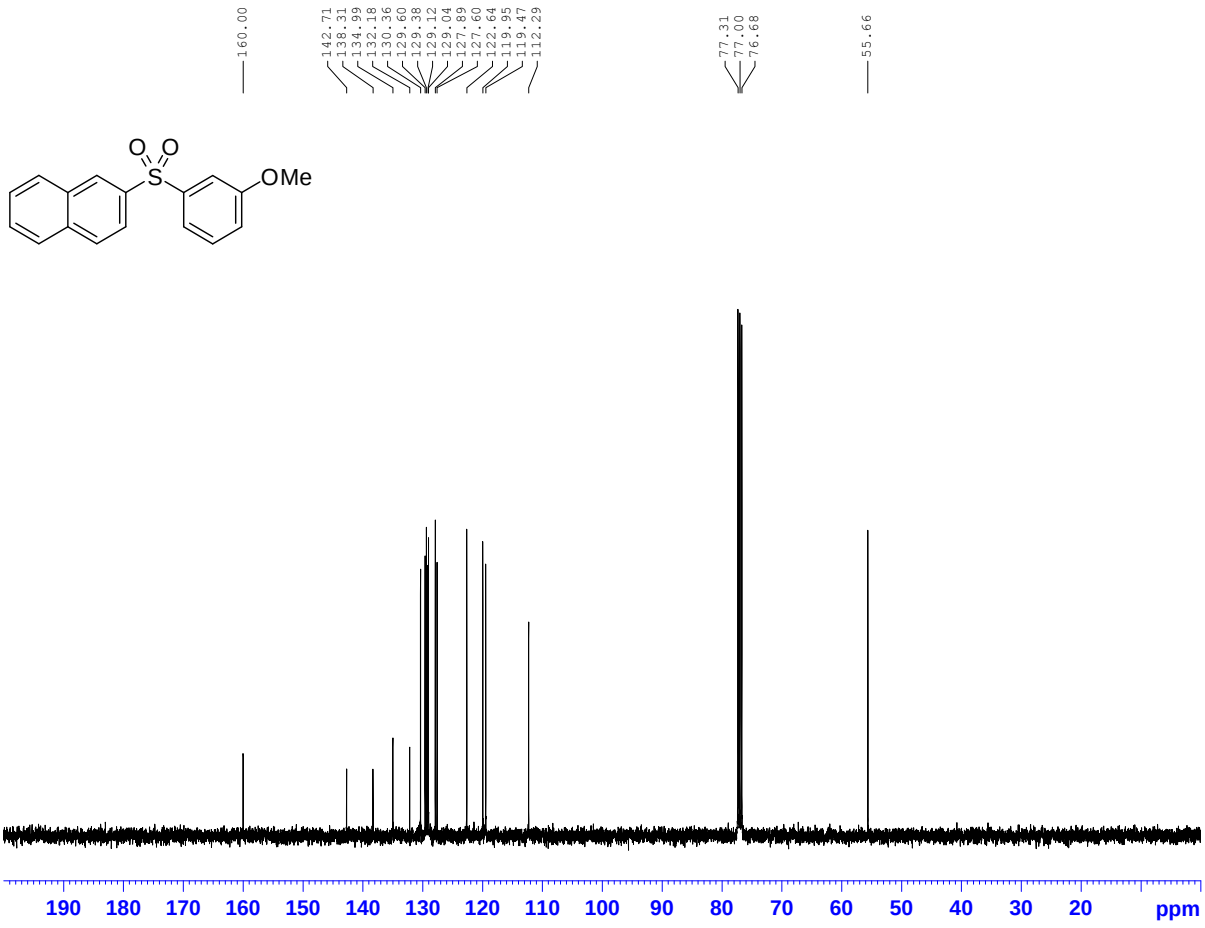
3.00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O
S
OMe
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30
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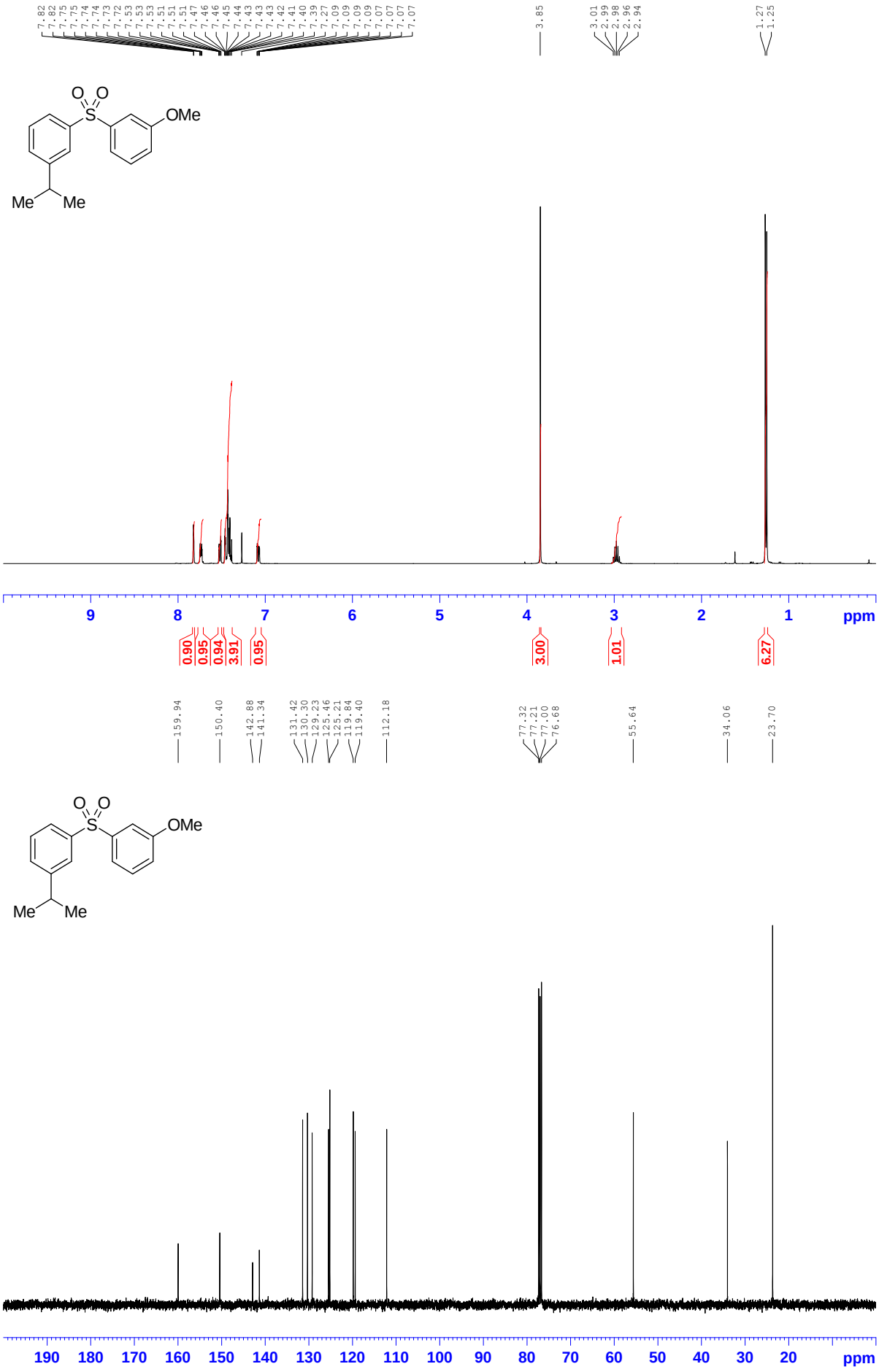
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7.51
7.47
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7.46
7.45
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7.43
7.43
7.42
7.41
7.40
7.39
7.27
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7.09
7.09
7.09
7.07
7.07
7.07
7.07
3.85
3.01
2.99
2.98
2.96
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1.27
1.25
O
O
S
OMe
Me
Me
9
8
7
6
5
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119.40
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77.21
77.00
76.68
55.64
34.06
23.70
O
O
S
OMe
Me
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20
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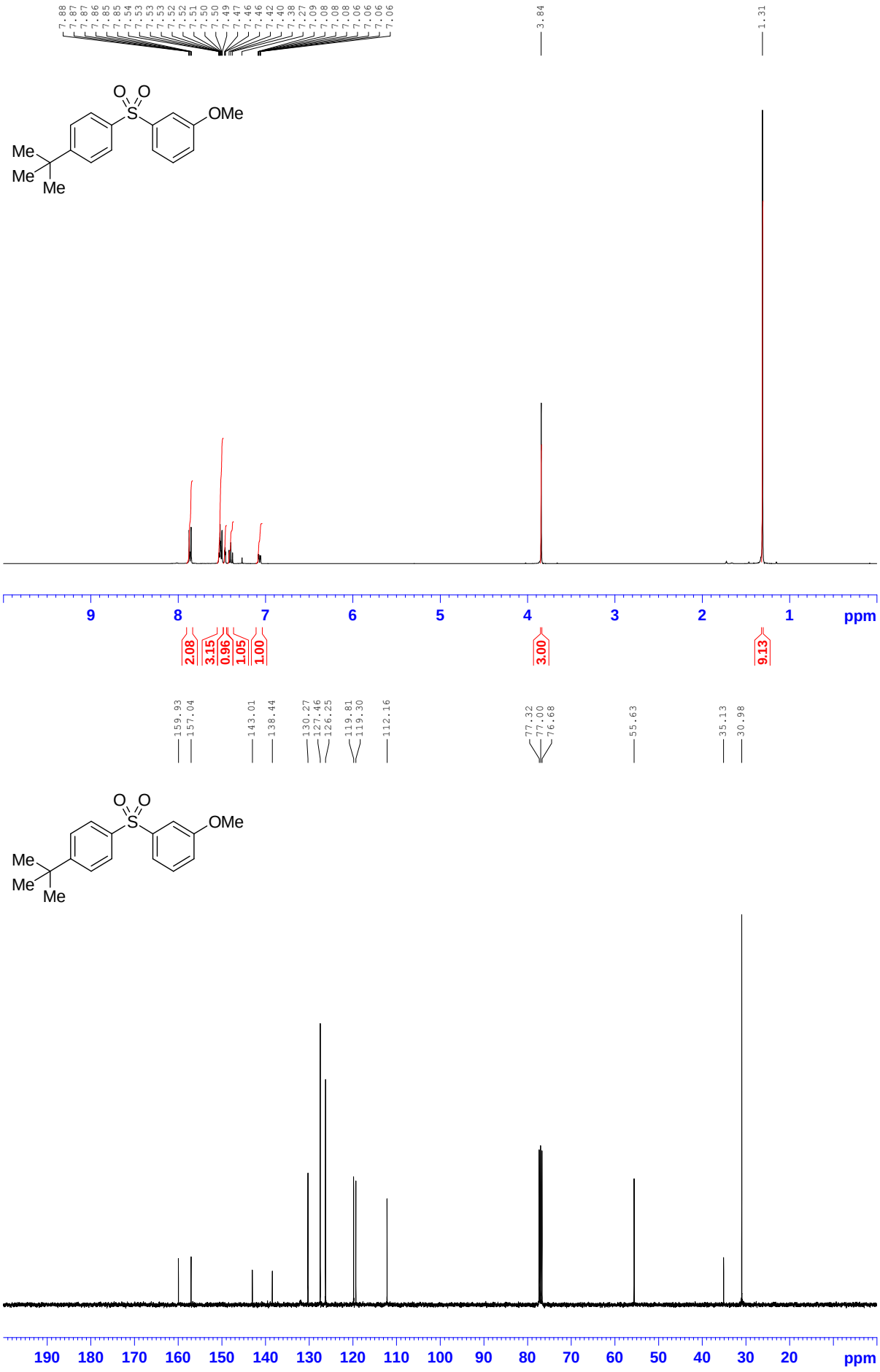
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7.27
7.09
7.08
7.08
7.06
7.06
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1.31
O
O
S
OMe
Me
Me
Me
9
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6
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4
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ppm
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OMe
Me
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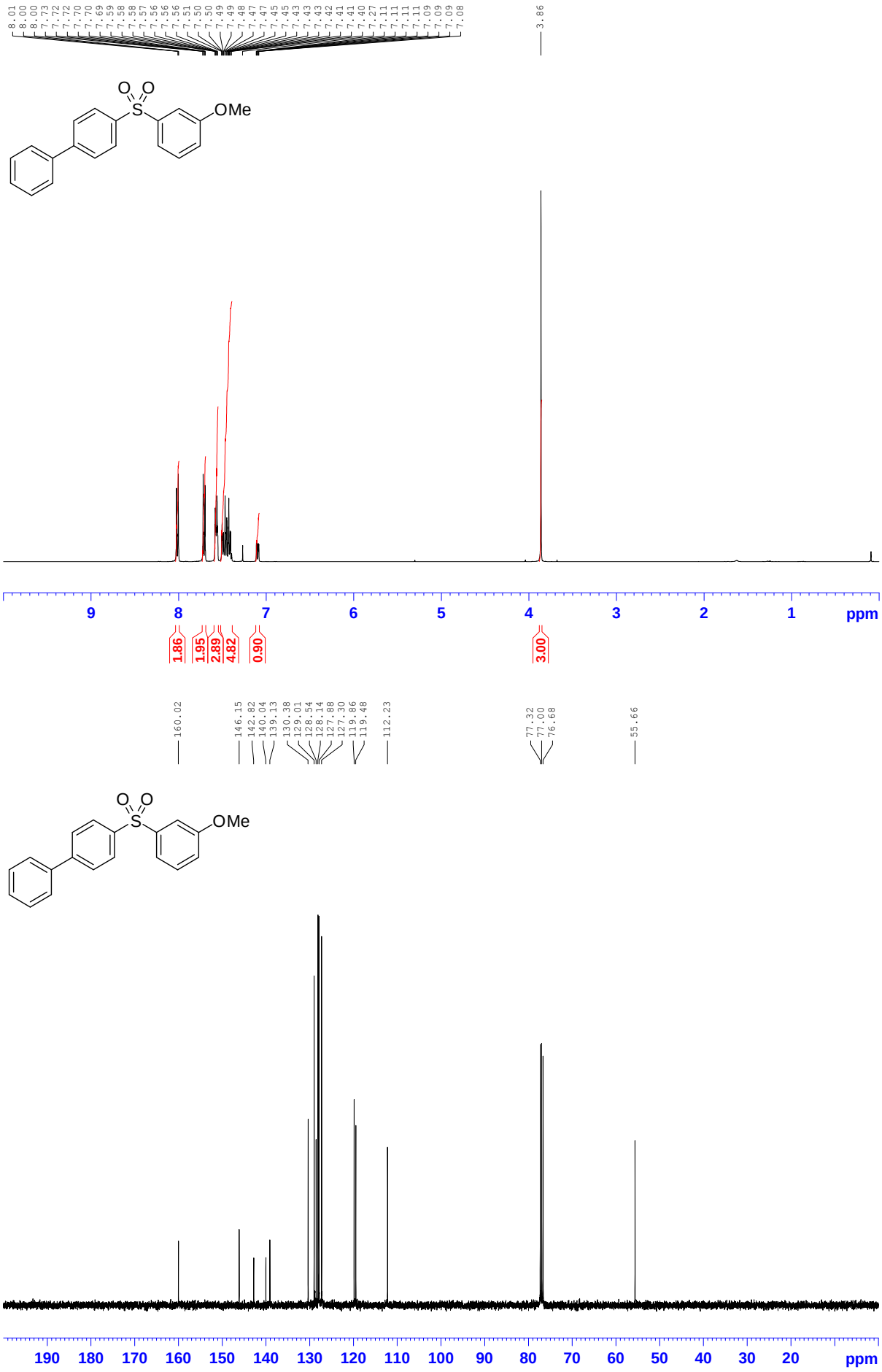
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7.56
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7.51
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7.48
7.47
7.47
7.45
7.45
7.43
7.43
7.43
7.42
7.41
7.41
7.40
7.27
7.11
7.11
7.11
7.09
7.09
7.09
7.08
3.86
O
O
S
OMe
9
8
7
6
5
4
3
2
1
ppm
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1.95
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0.90
3.00
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146.15
142.82
140.04
139.13
130.38
129.01
128.54
128.14
127.88
127.30
119.86
119.48
112.23
77.32
77.00
76.68
55.66
O
O
S
OMe
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160
150
140
130
120
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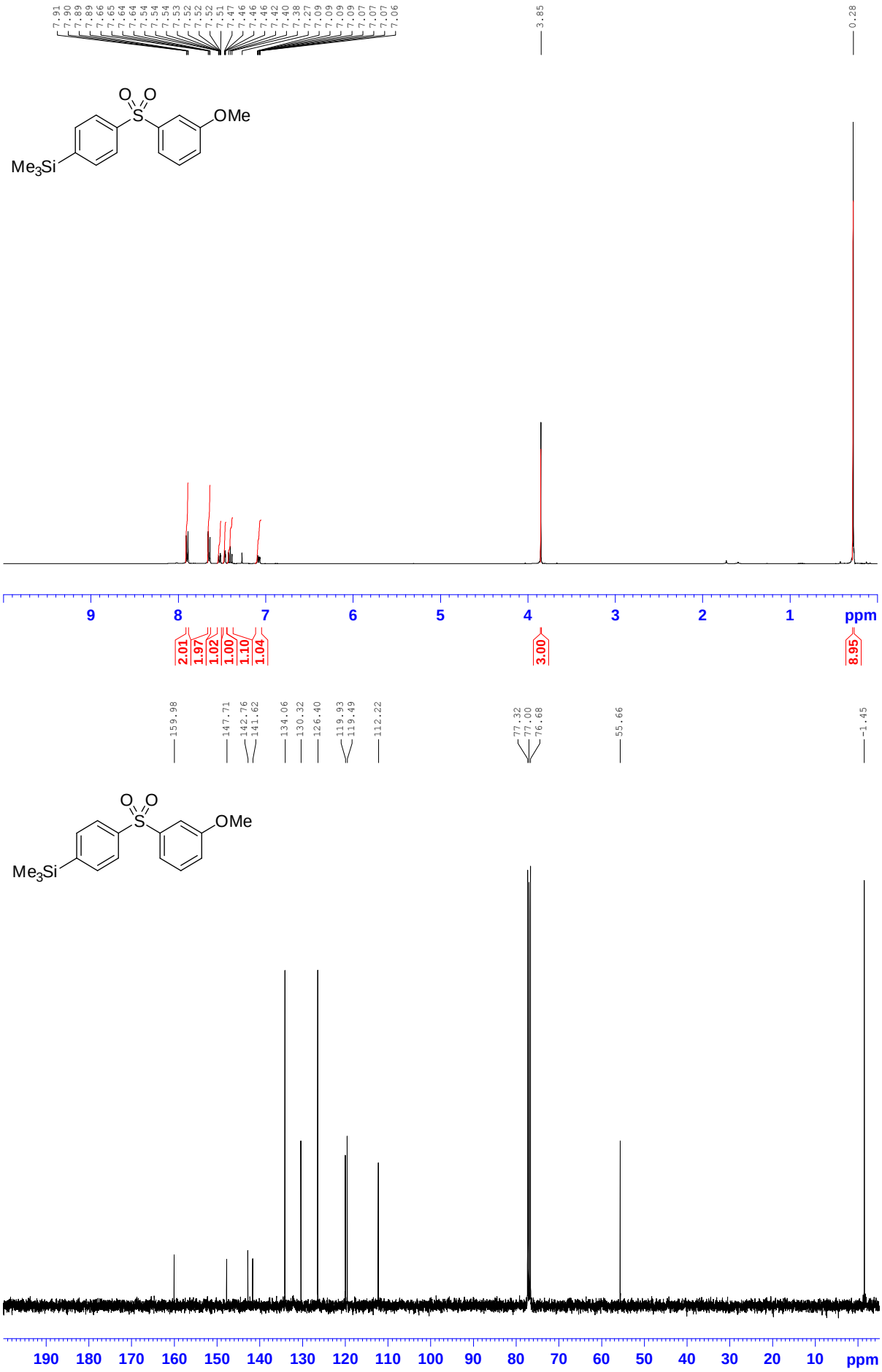
40
30
20
ppm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7.54
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7.53
7.52
7.52
7.52
7.51
7.47
7.46
7.46
7.46
7.42
7.40
7.38
7.27
7.09
7.09
7.09
7.07
7.07
7.07
7.06
3.85
0.28
O
O
S
OMe
Me3Si
9
8
7
6
5
4
3
2
1
ppm
2.01
1.97
1.02
1.00
1.10
1.04
3.00
8.95
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142.76
141.62
134.06
130.32
126.40
119.93
119.49
112.22
77.32
77.00
76.68
55.66
-1.45
O
O
S
OMe
Me3Si
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150
140
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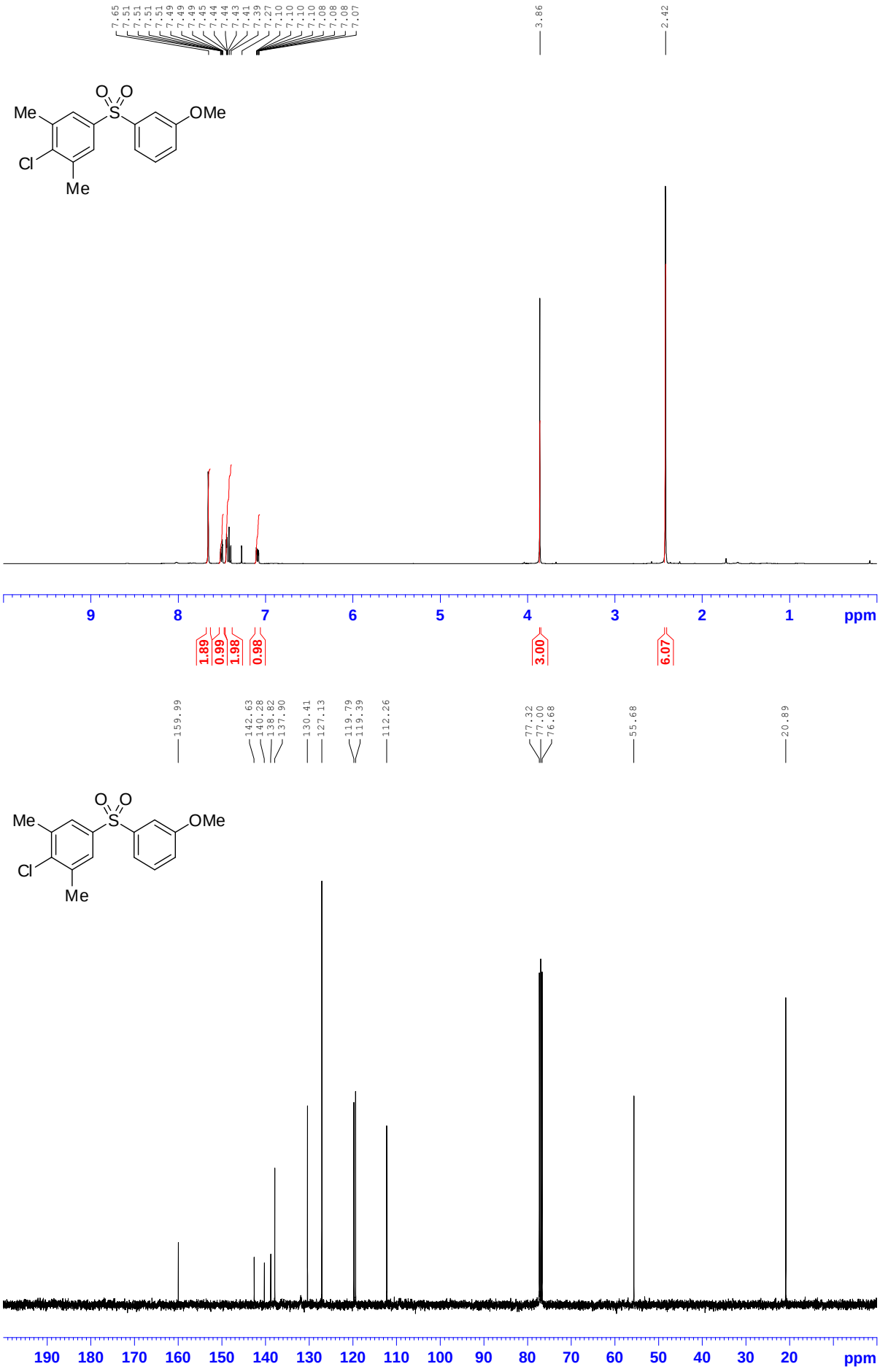
ppm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7.49
7.45
7.44
7.44
7.43
7.41
7.39
7.27
7.10
7.10
7.10
7.08
7.08
7.08
7.07
3.86
2.42
O
O
S
Me
OMe
Cl
Me
9
8
7
6
5
4
3
2
1
ppm
1.89
0.99
1.98
0.98
3.00
6.07
159.99
142.63
140.28
138.82
137.90
130.41
127.13
119.79
119.39
112.26
77.32
77.00
76.68
55.68
20.89
O
O
S
Me
OMe
Cl
Me
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160
150
140
130
120
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100
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80
70
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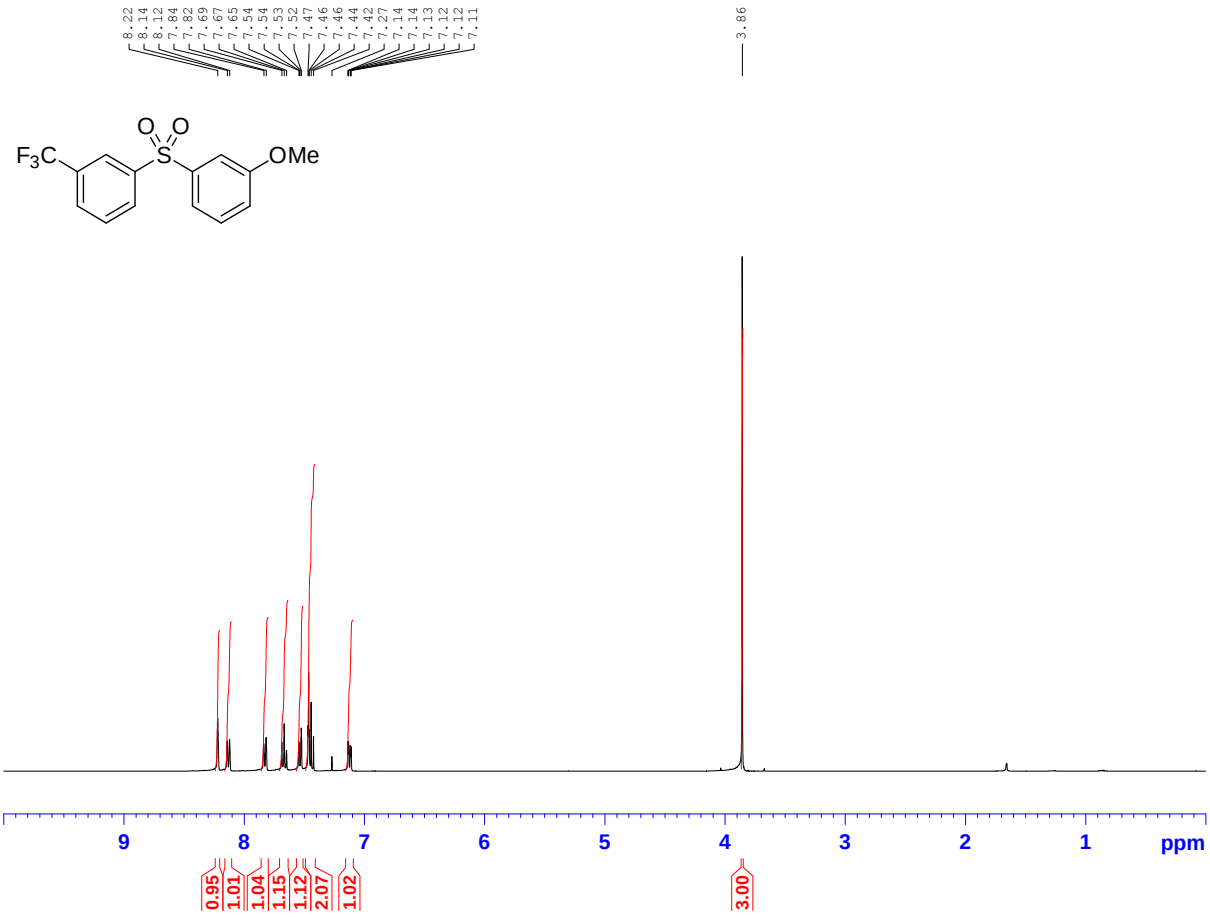
50
40
30
20
ppm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7.52
7.47
7.46
7.46
7.44
7.42
7.27
7.14
7.14
7.13
7.12
7.12
7.11
3.86
O
O
S
F3C
OMe
9
8
7
6
5
4
3
2
1
ppm
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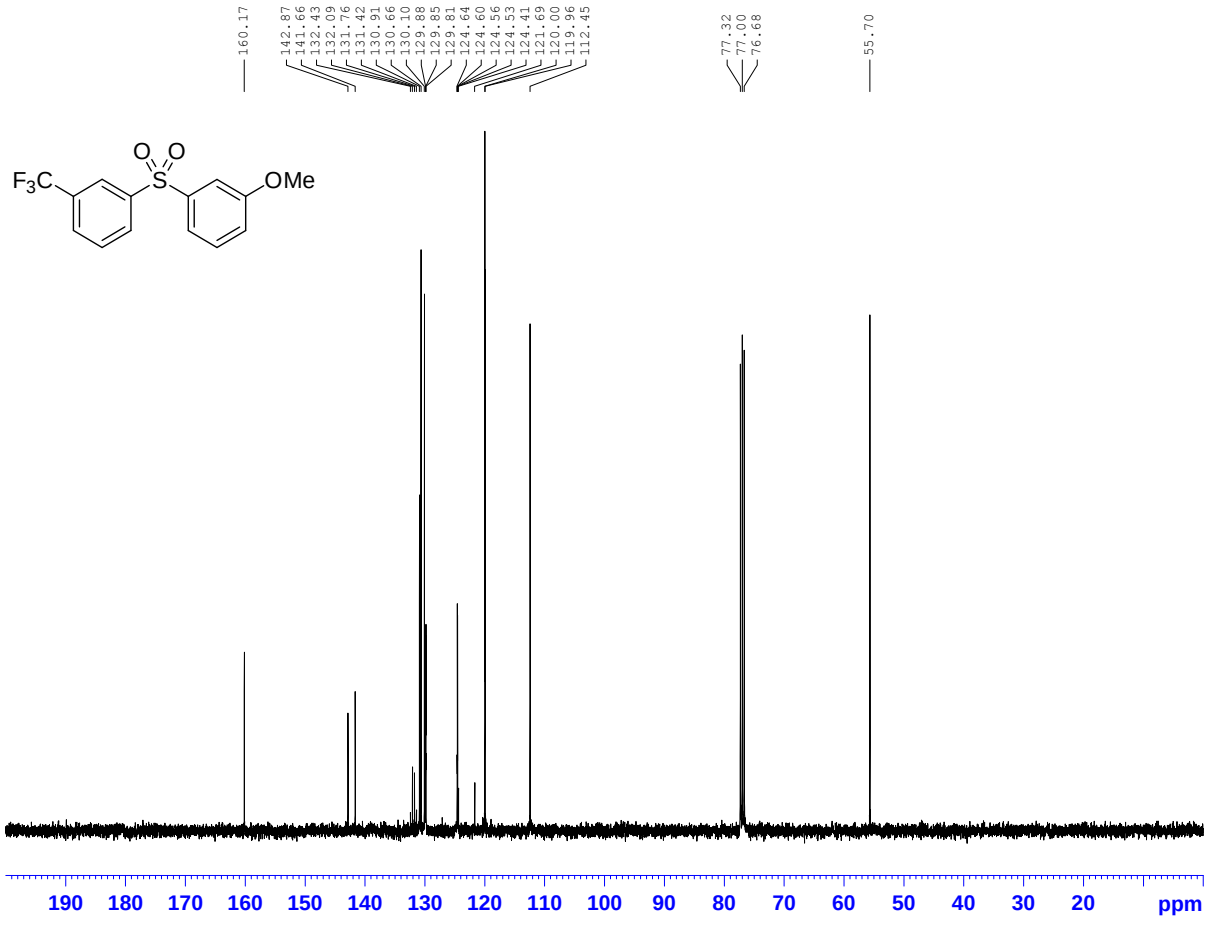
1.04
1.15
1.12
2.07
1.02
3.00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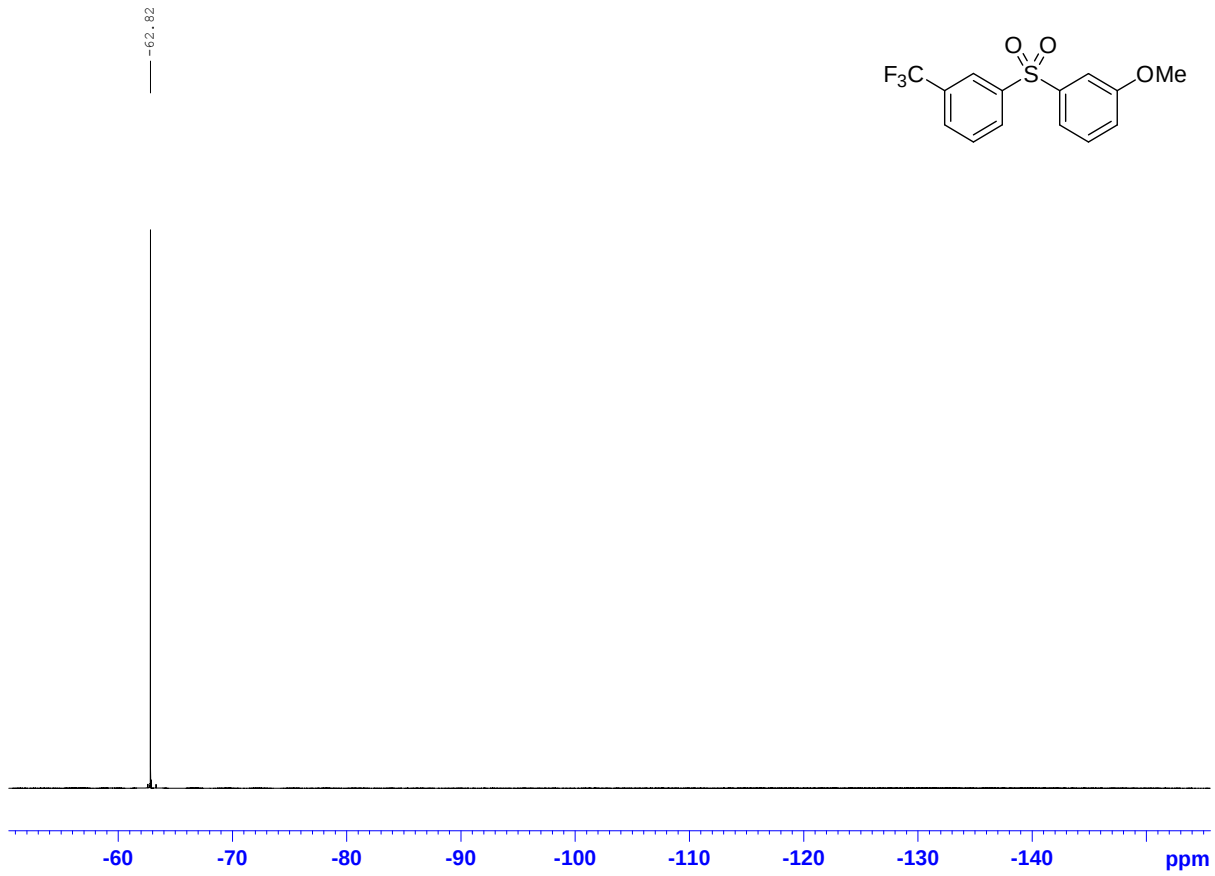
129.81
124.64
124.60
124.56
124.53
124.41
121.69
120.00
119.96
112.45
77.32
77.00
76.68
55.70
O
O
S
F3C
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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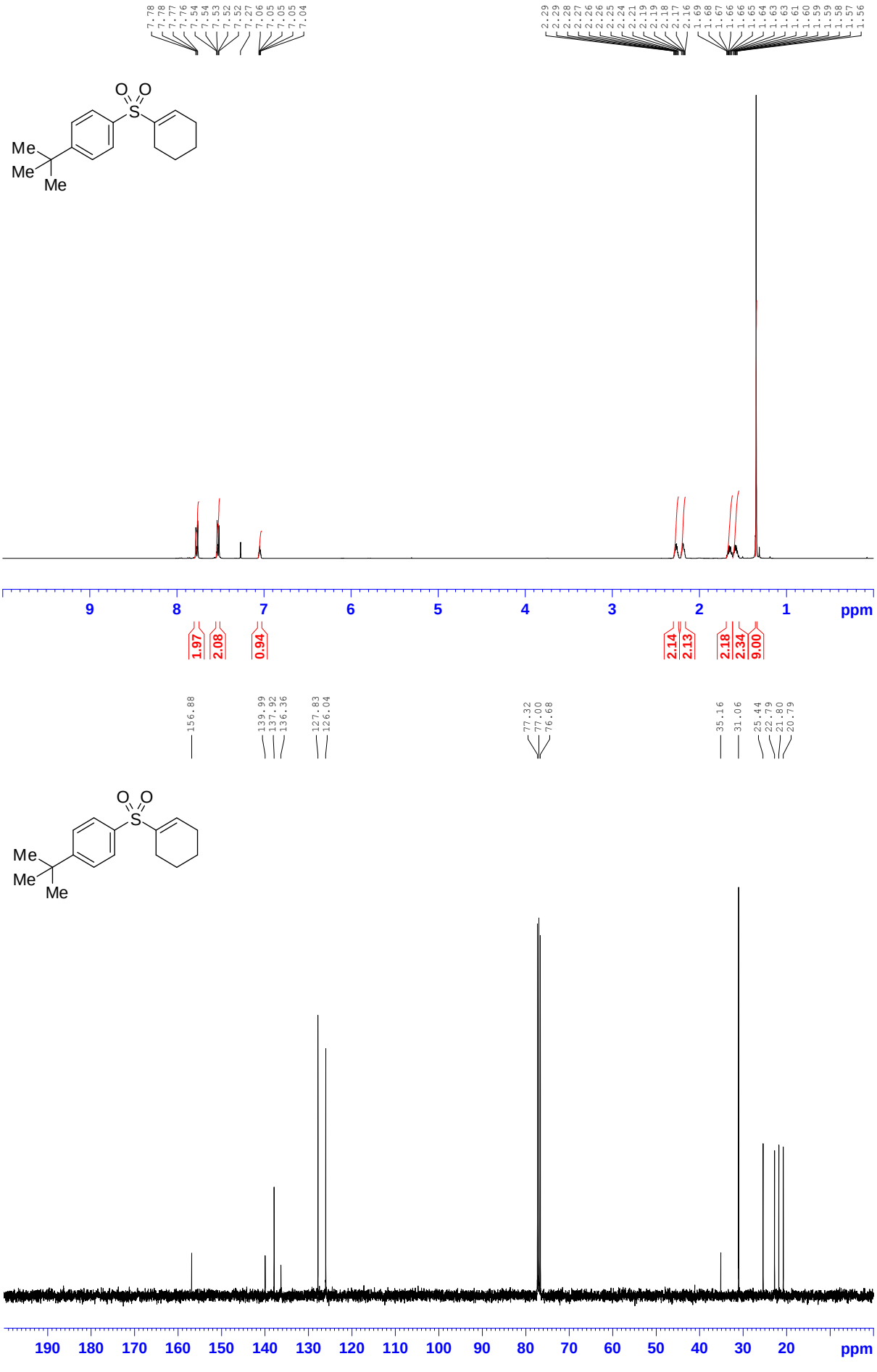
O
O
S
F3C
OMe
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm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7.53
7.52
7.52
7.27
7.06
7.05
7.05
7.04
2.29
2.29
2.28
2.27
2.26
2.26
2.25
2.24
2.21
2.19
2.19
2.18
2.17
2.16
1.69
1.68
1.67
1.66
1.66
1.65
1.64
1.63
1.63
1.61
1.60
1.59
1.59
1.58
1.57
1.56
O
O
S
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
1.97
2.08
0.94
2.14
2.13
2.18
2.34
9.00
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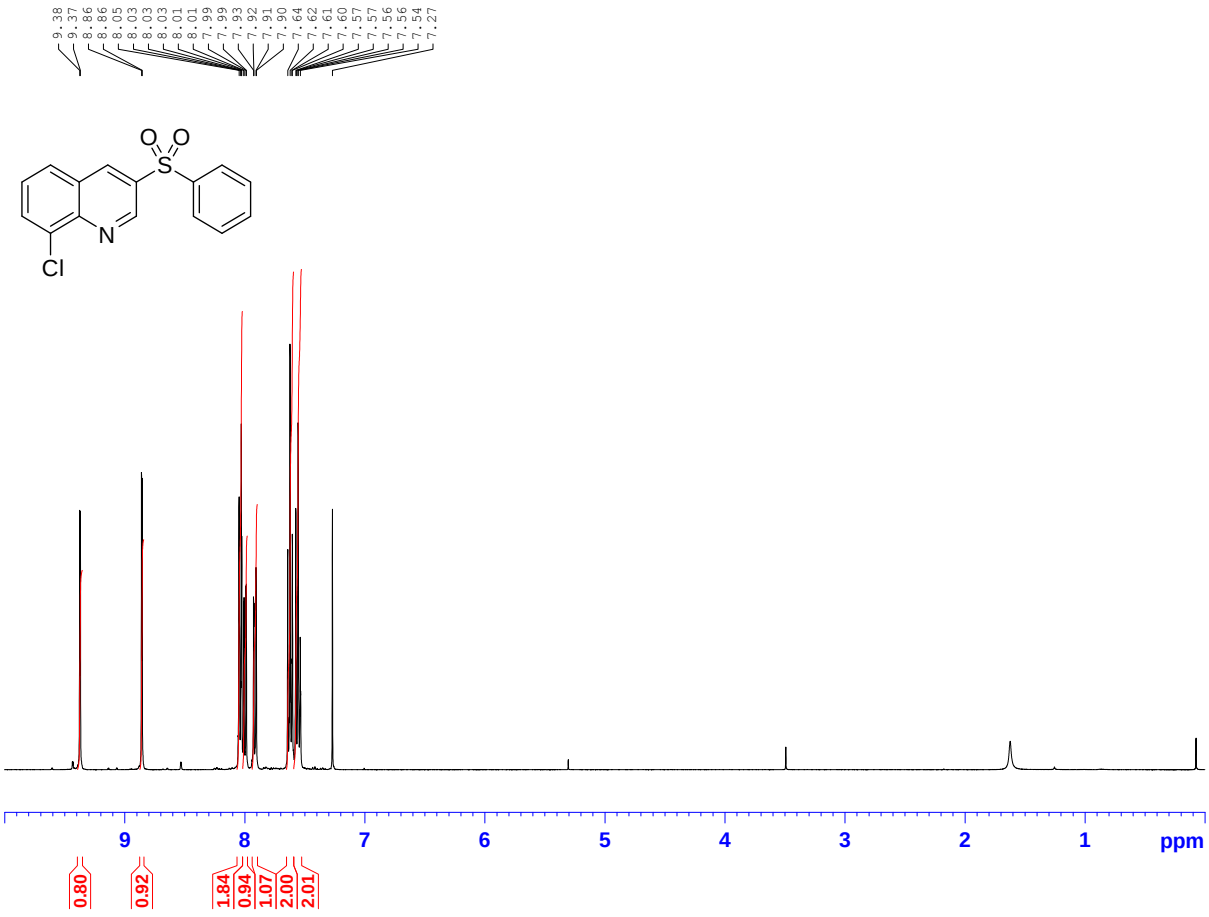
139.99
137.92
136.36
127.83
126.04
77.32
77.00
76.68
35.16
31.06
25.44
22.79
21.80
20.79
O
O
S
Me
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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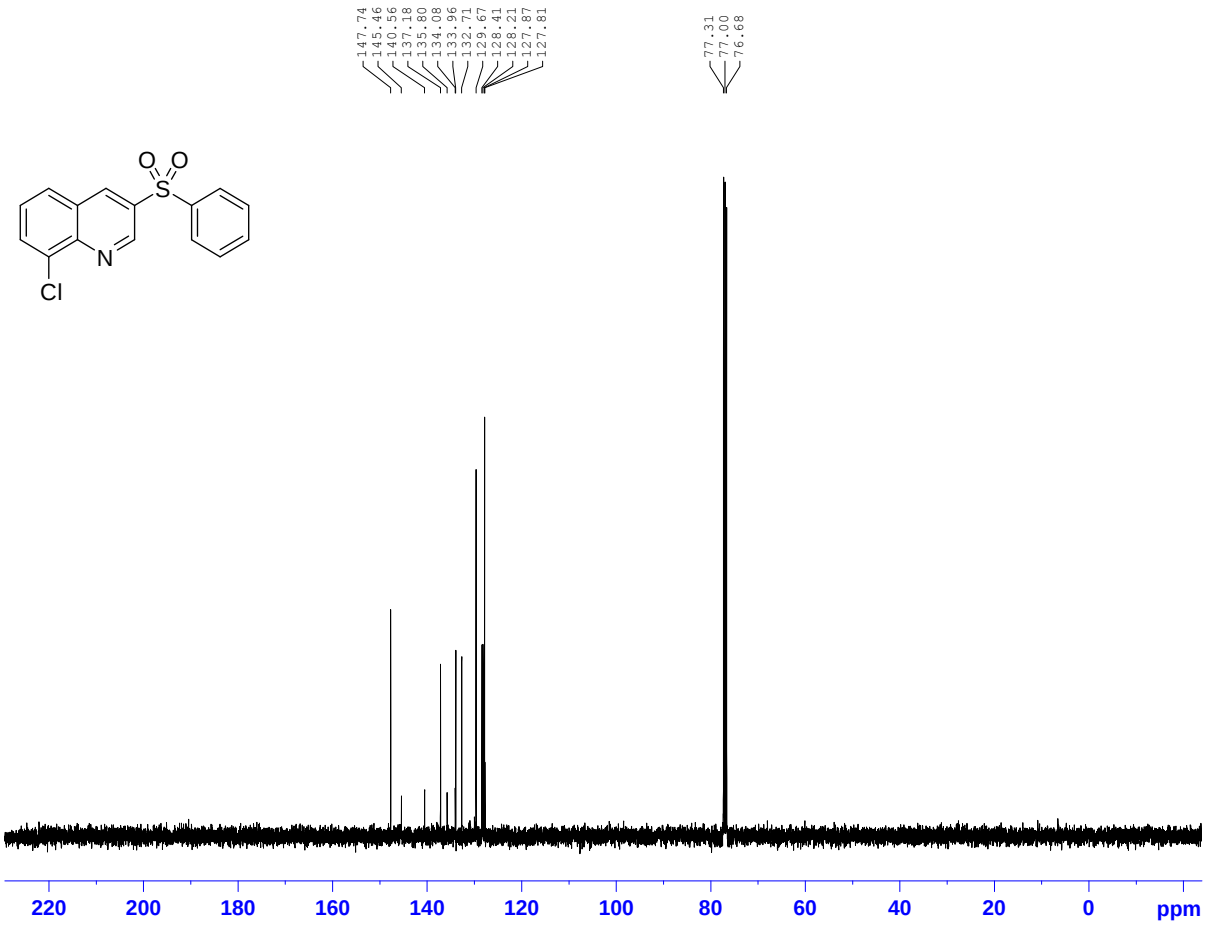
8.86
8.05
8.03
8.03
8.01
8.01
7.99
7.99
7.93
7.92
7.91
7.90
7.64
7.62
7.61
7.60
7.57
7.57
7.56
7.56
7.54
7.27
O
O
S
N
Cl
9
8
7
6
5
4
3
2
1
ppm
0.80
0.92
1.84
0.94
1.07
2.00
2.01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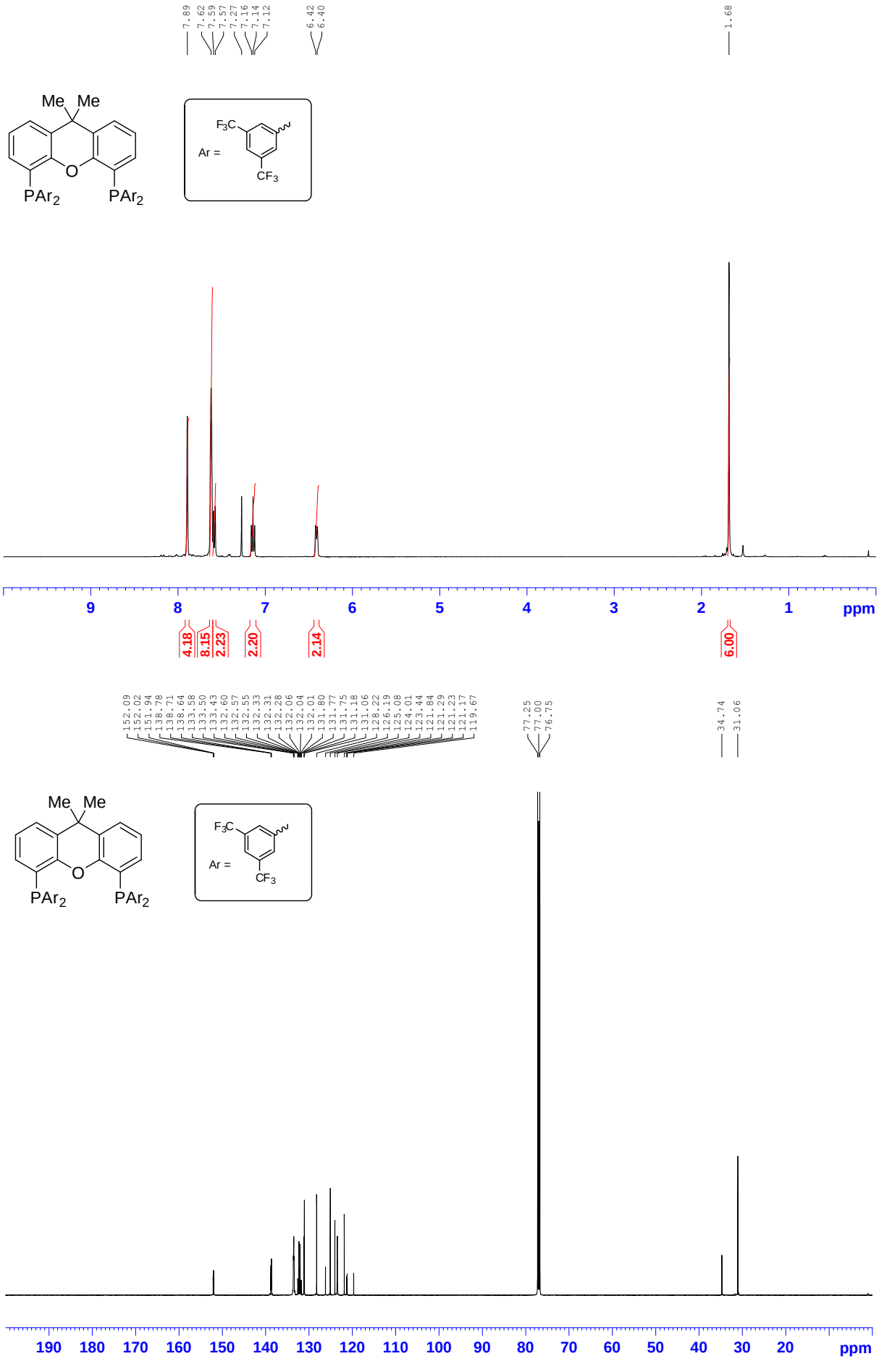
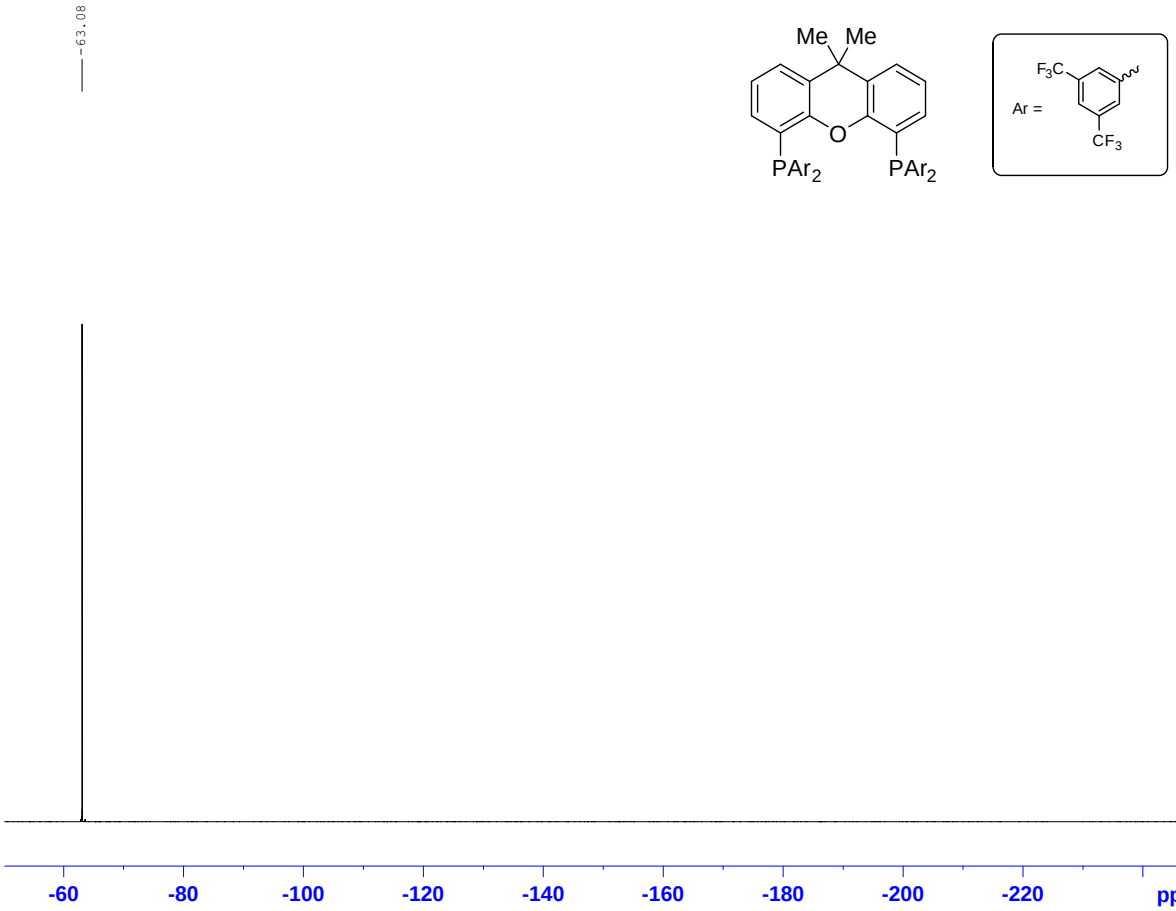
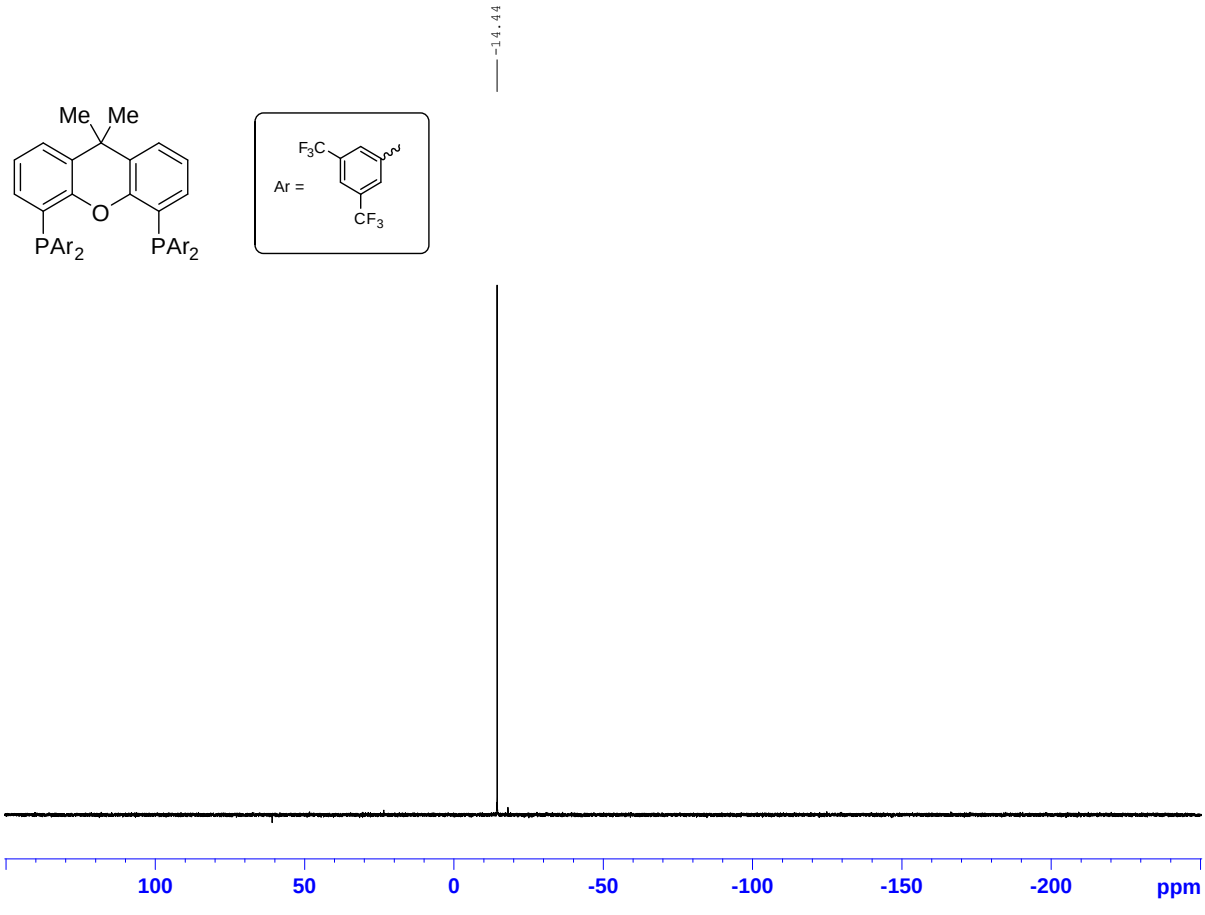
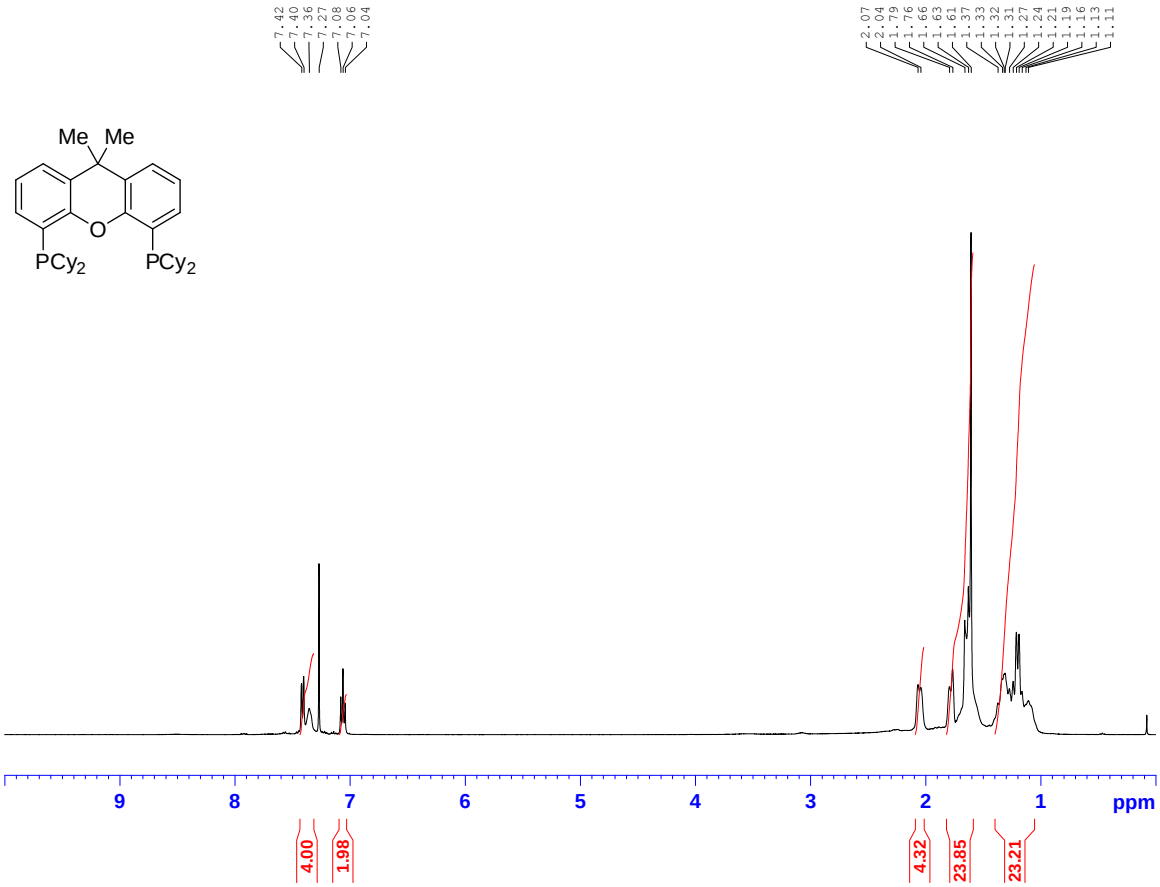
135.80
134.08
133.96
132.71
129.67
128.41
128.21
127.87
127.81
77.31
77.00
76.68
O
O
S
N
Cl
220
200
180
160
140
120
100
80
60
40
20
0
ppm


7.89
7.62
7.59
7.57
7.27
7.16
7.14
7.12
6.42
6.40
1.68
Me Me
O
PAr2
PAr2
F3C
Ar =
CF3
9
8
7
6
5
4
3
2
1
ppm
4.18
8.15
2.23
2.20
2.14
6.00
152.09
152.02
151.94
138.78
138.71
138.64
133.58
133.50
133.43
132.60
132.57
132.55
132.33
132.31
132.28
132.06
132.04
132.01
131.80
131.77
131.75
131.18
131.06
128.22
126.19
125.08
124.01
123.44
121.84
121.29
121.23
121.17
119.67
77.25
77.00
76.75
34.74
31.06
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


-63.08
Me Me
O
PAr2
PAr2
F3C
Ar =
CF3
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm


-14.44
Me Me
O
PAr2
PAr2
F3C
Ar =
CF3
100
50
0
-50
-100
-150
-200
ppm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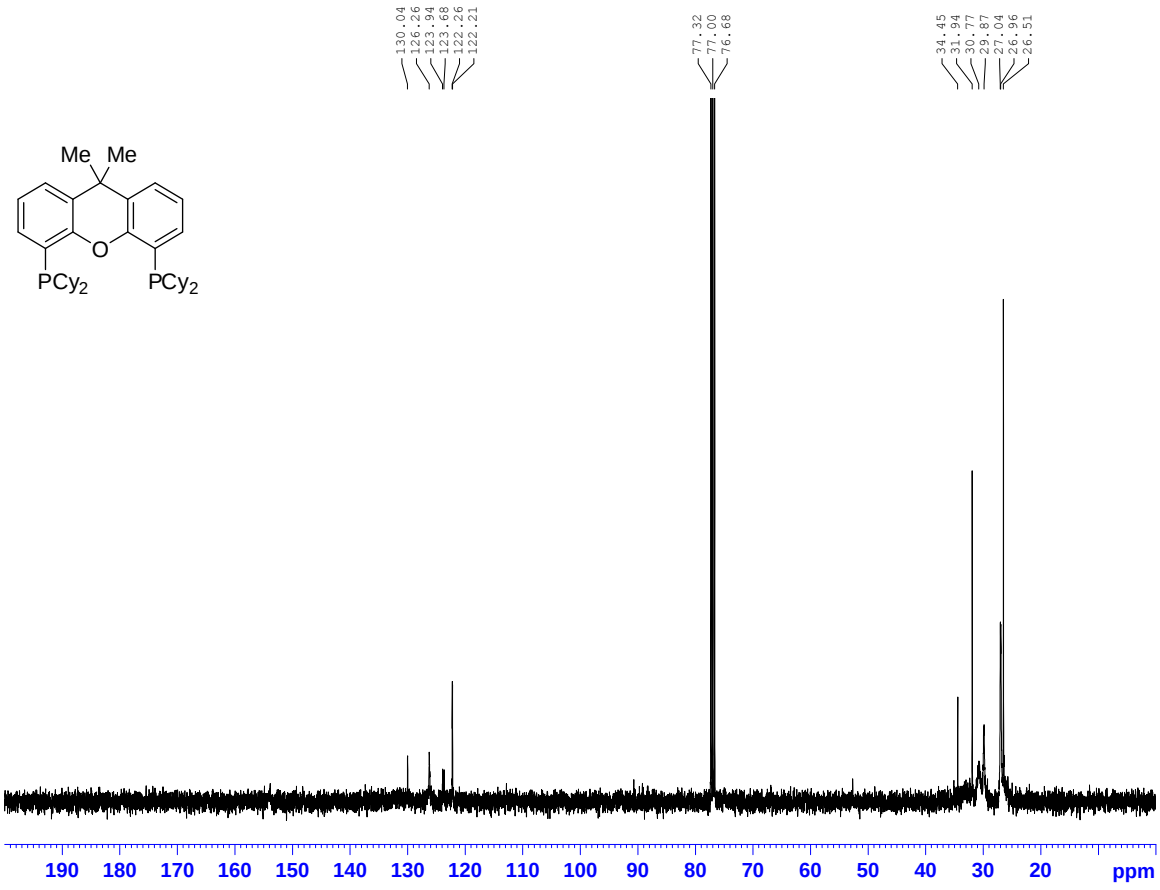
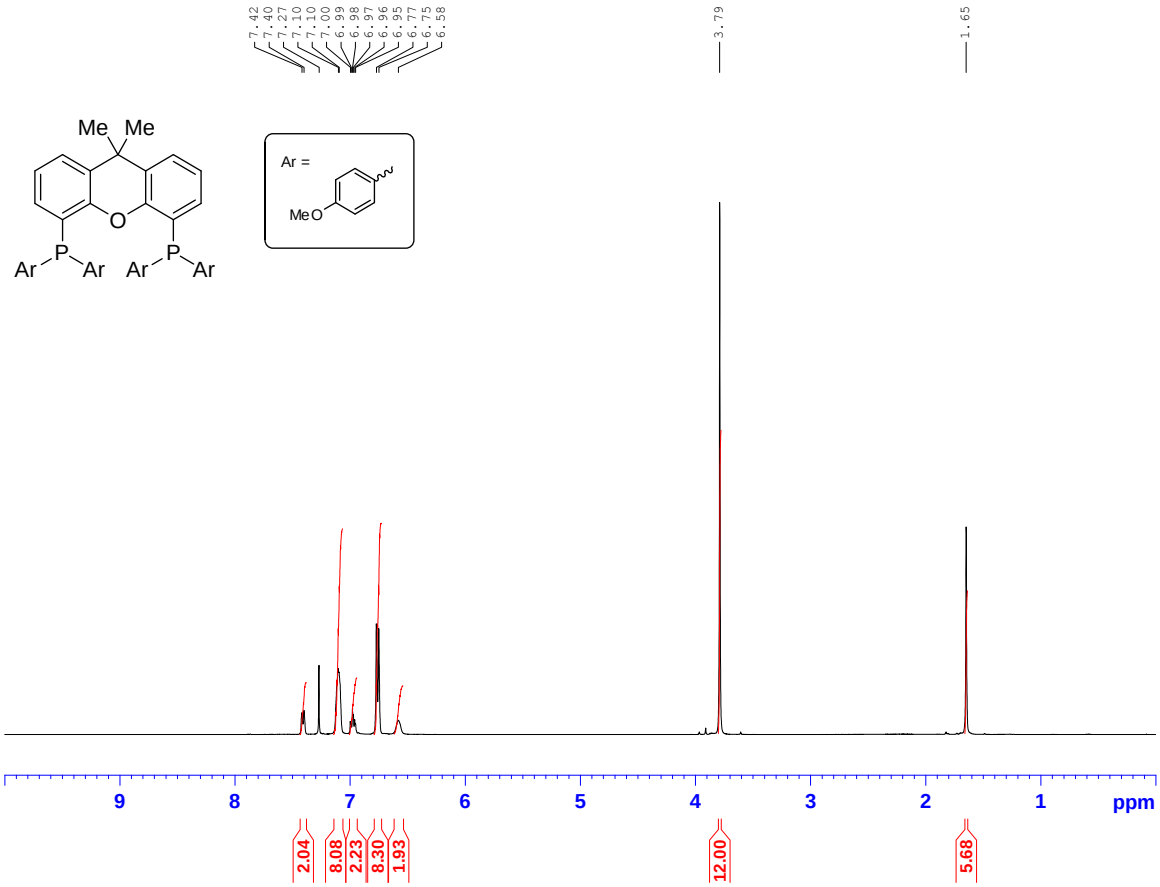
7.40
7.36
7.27
7.08
7.06
7.04
2.07
2.04
1.79
1.76
1.66
1.63
1.61
1.37
1.33
1.32
1.31
1.27
1.24
1.21
1.19
1.16
1.13
1.11
Me Me
O
PCy2
PCy2
9
8
7
6
5
4
3
2
1
ppm
4.00
1.98
4.32
23.85
23.21


130.04
126.26
123.94
123.68
122.26
122.21
77.32
77.00
76.68
34.45
31.94
30.77
29.87
27.04
26.96
26.51
Me Me
O
PCy2
PCy2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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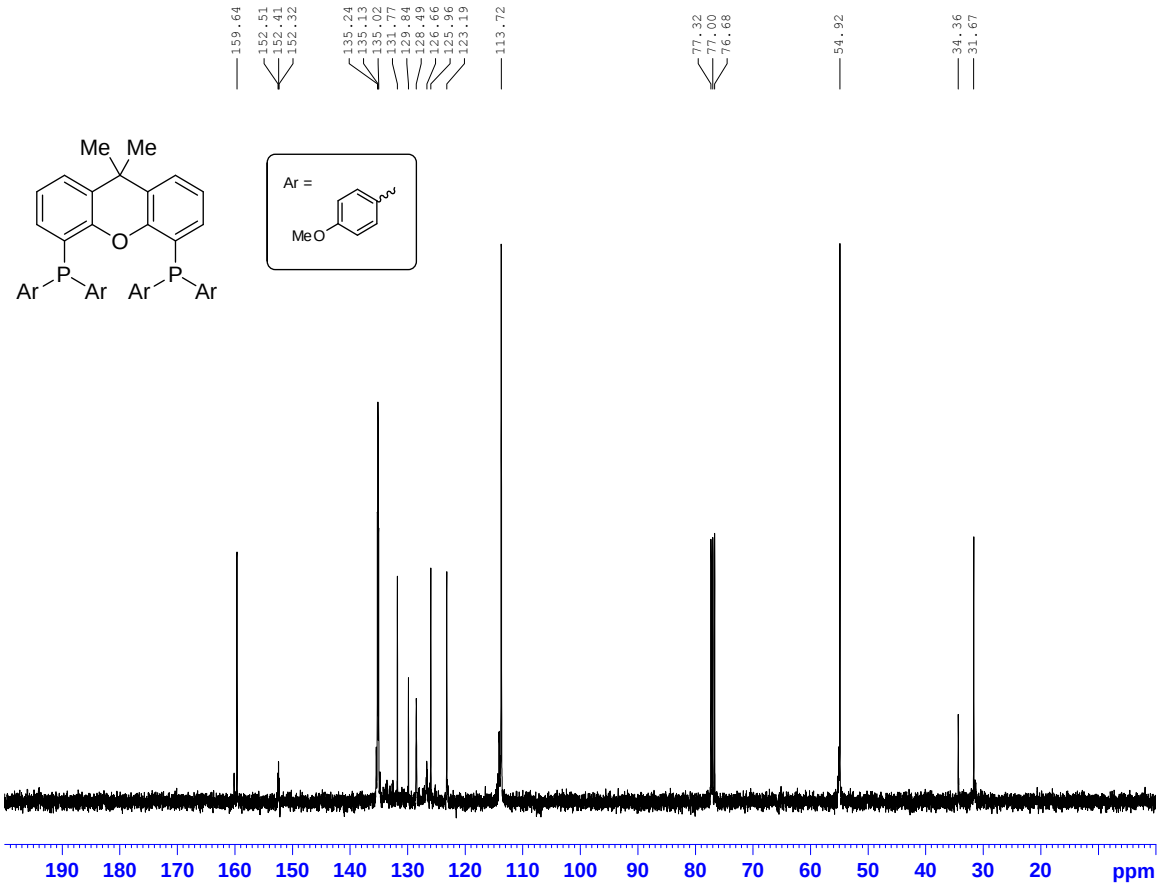
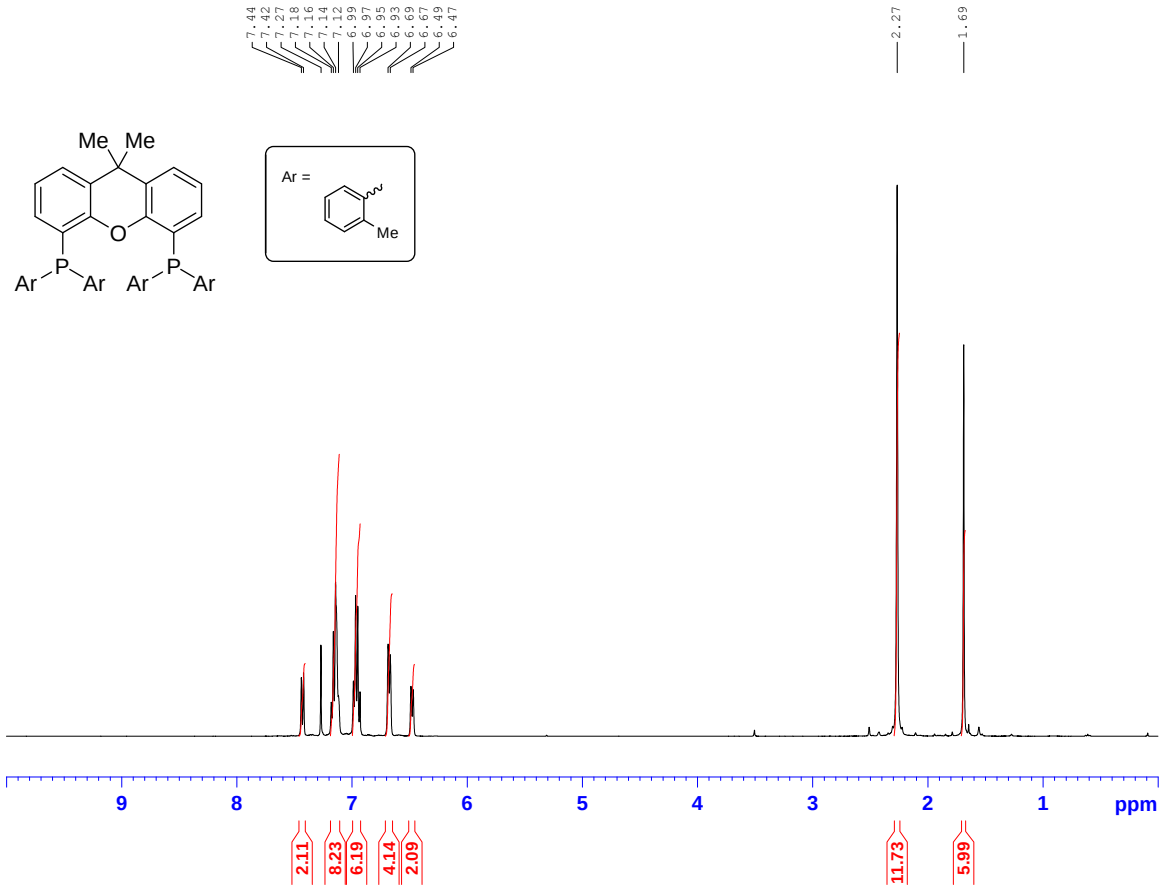
7.40
7.27
7.10
7.10
7.00
6.99
6.98
6.97
6.96
6.95
6.77
6.75
6.58
3.79
1.65
Me Me
O
Ar P Ar
Ar P Ar
Ar =
MeO
9 8 7 6 5 4 3 2 1 ppm
2.04
8.08
2.23
8.30
1.93
12.00
5.68


159.64
152.51
152.41
152.32
135.24
135.13
135.02
131.77
129.84
128.49
126.66
125.96
123.19
113.72
77.32
77.00
76.68
54.92
34.36
31.67
Me Me
O
Ar P Ar
Ar P Ar
Ar =
MeO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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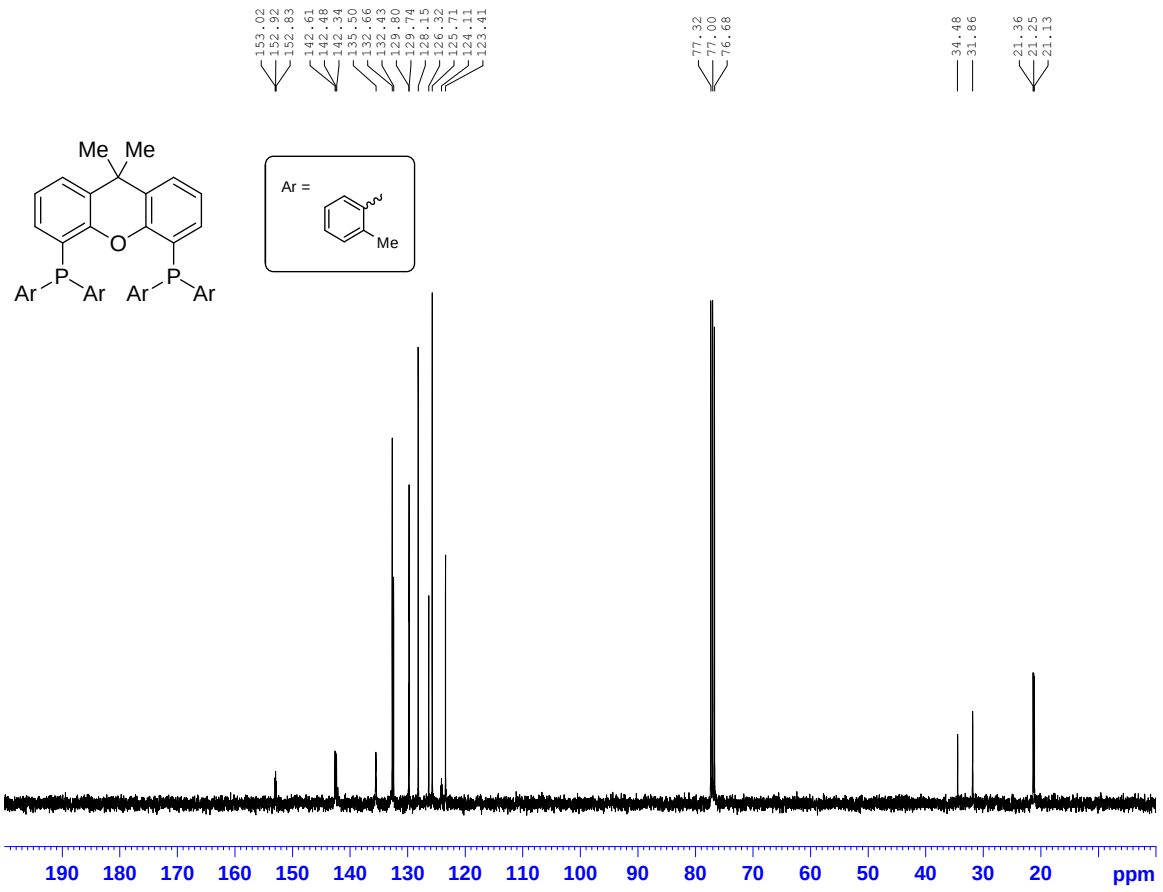
7.27
7.18
7.16
7.14
7.12
6.99
6.97
6.95
6.93
6.69
6.67
6.49
6.47
2.27
1.69
Me Me
O
Ar P Ar Ar P Ar
Ar =
Me
9 8 7 6 5 4 3 2 1 ppm
2.11
8.23
6.19
4.14
2.09
11.73
5.99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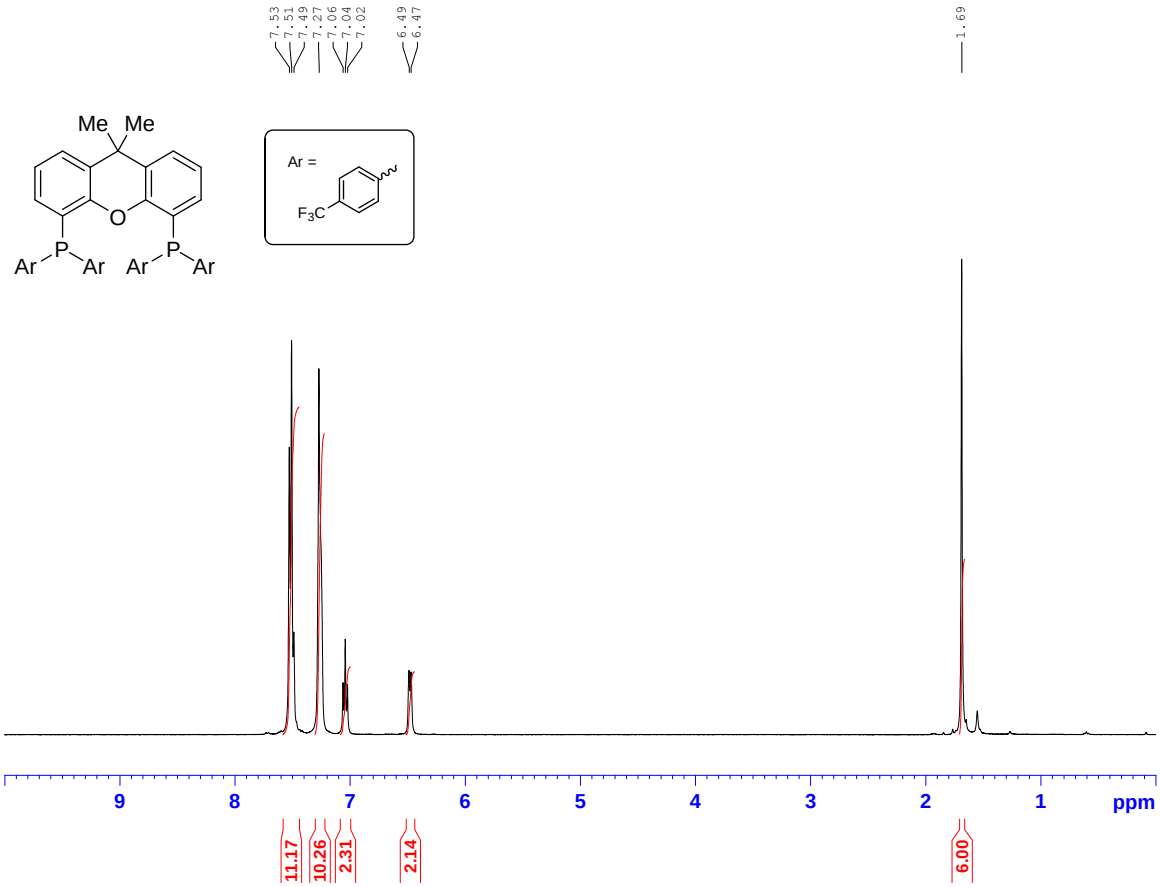
152.92
152.83
142.61
142.48
142.34
135.50
132.66
132.43
129.80
129.74
128.15
126.32
125.71
124.11
123.41
77.32
77.00
76.68
34.48
31.86
21.36
21.25
21.13
Me Me
O
Ar P Ar Ar P Ar
Ar =
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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7.51
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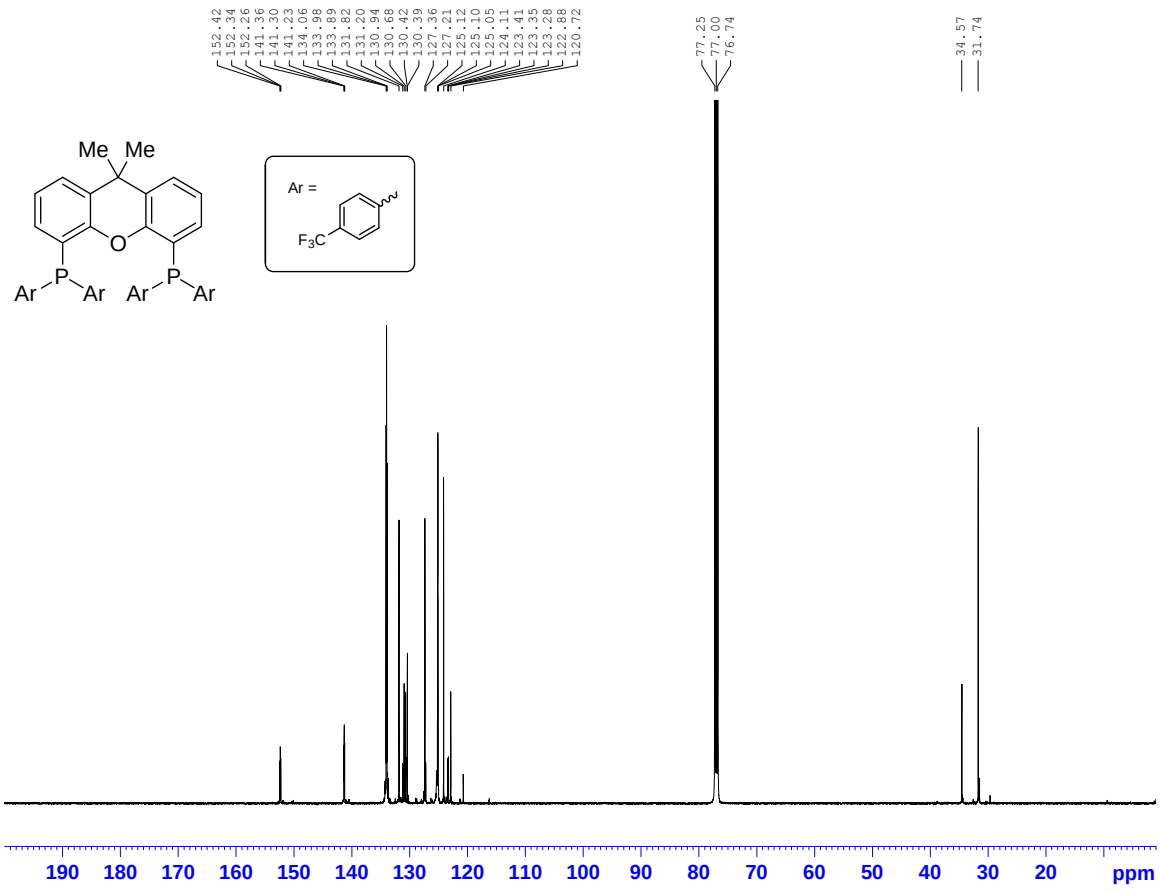
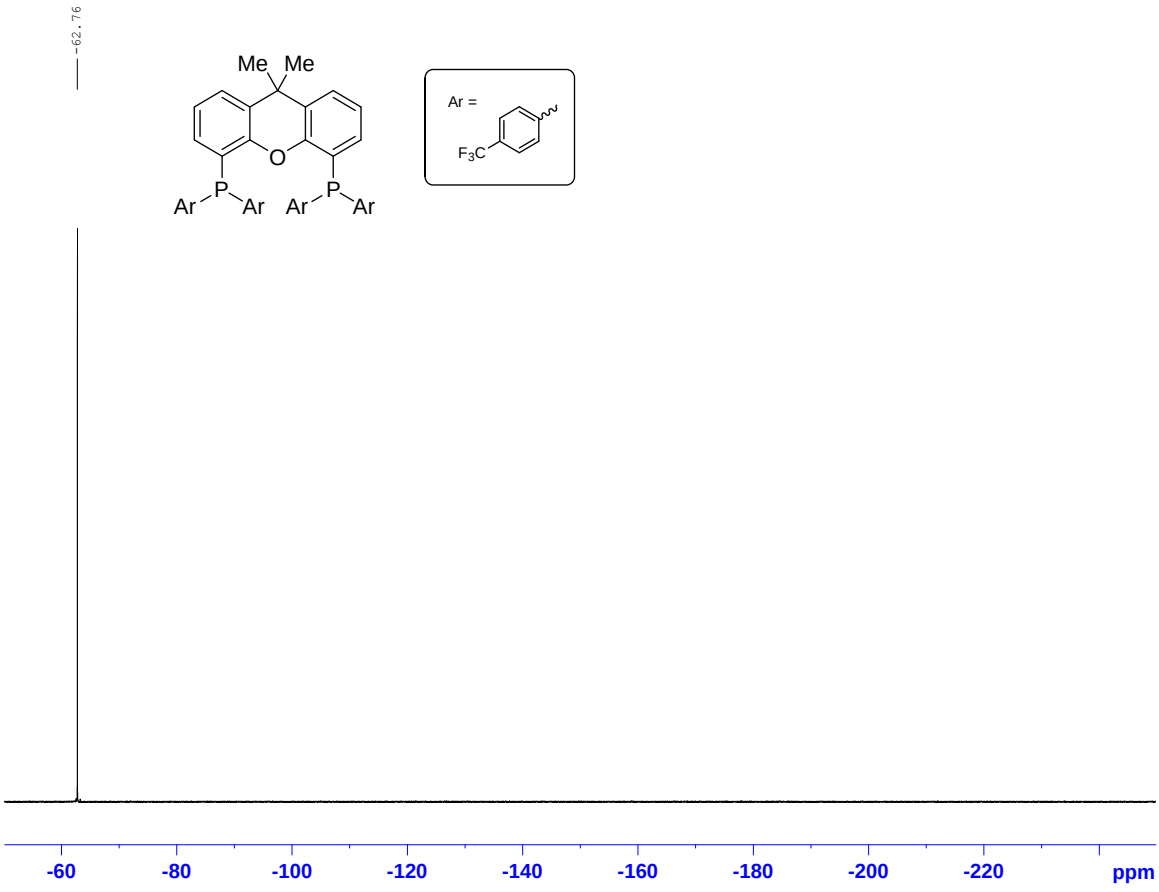
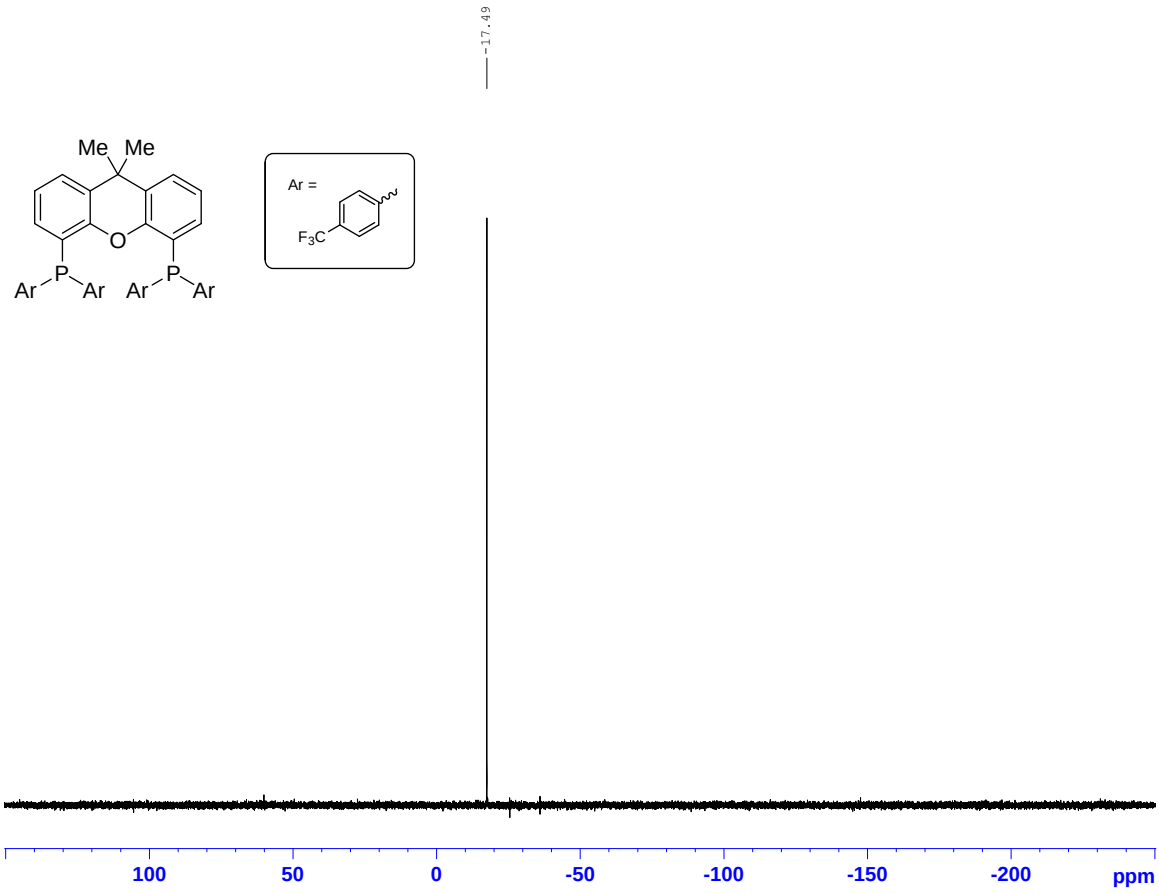
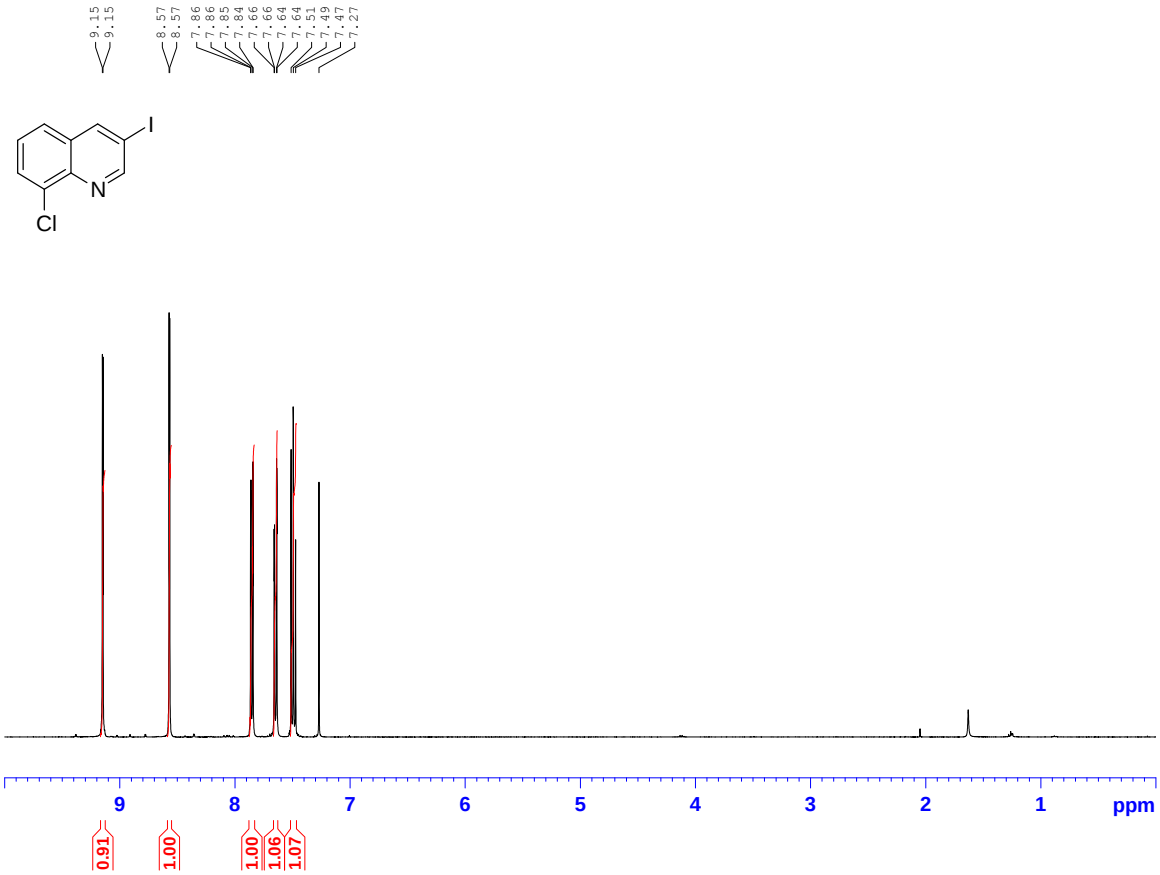
7.27
7.06
7.04
7.02
6.49
6.47
1.69
Me Me
O
Ar P Ar Ar P Ar
Ar =
F3C
9 8 7 6 5 4 3 2 1 ppm
11.17
10.26
2.31
2.14
6.00


152.42
152.34
152.26
141.36
141.30
141.23
134.06
133.98
133.89
131.82
131.20
130.94
130.68
130.42
130.39
127.36
127.21
125.12
125.10
125.05
124.11
123.41
123.35
123.28
122.88
120.72
77.25
77.00
76.74
34.57
31.74
Me Me
O
Ar P Ar Ar P Ar
Ar =
F3C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


-62.76
Me Me
O
Ar P Ar Ar P Ar
Ar =
F3C
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm


-17.49
Me Me
O
Ar P Ar Ar P Ar
Ar =
F3C
100
50
0
-50
-100
-150
-200
ppm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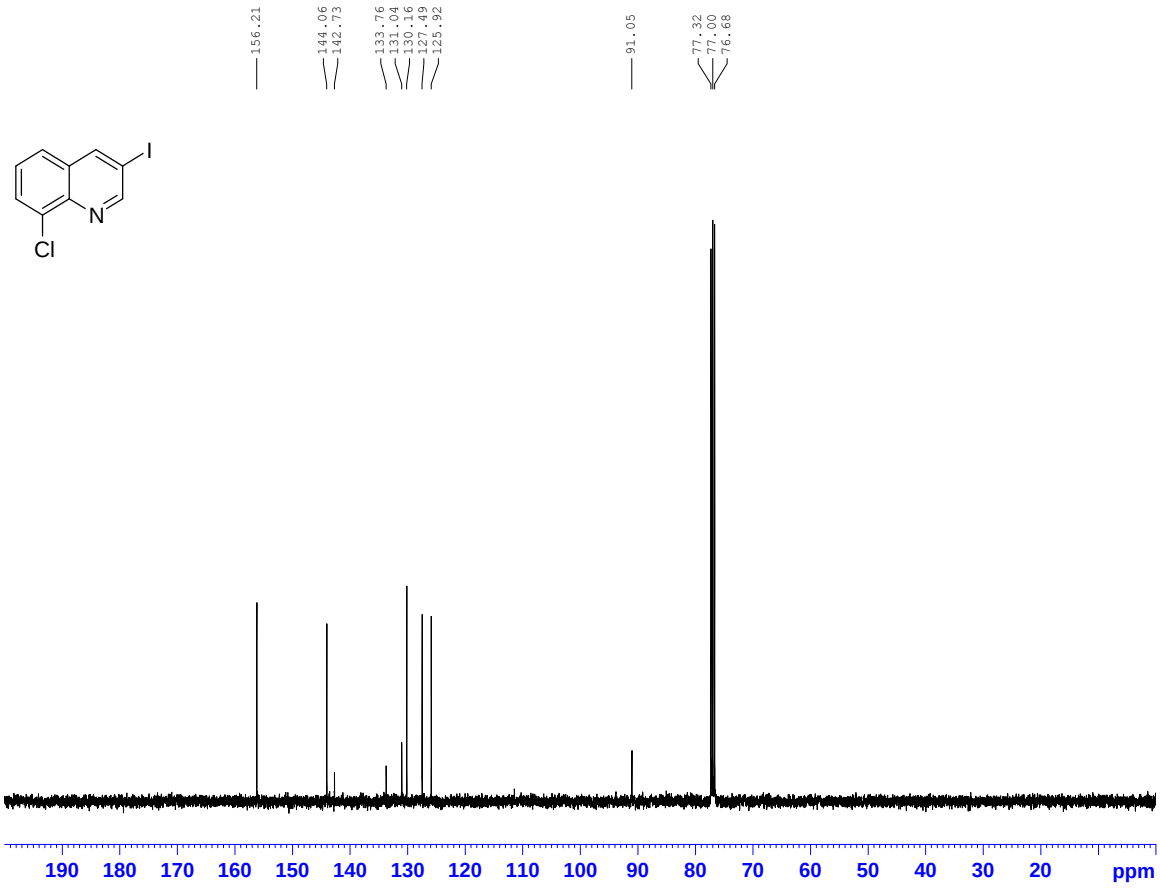
9.15
8.57
8.57
7.86
7.86
7.85
7.84
7.66
7.64
7.64
7.51
7.49
7.47
7.27
I
N
Cl
9
8
7
6
5
4
3
2
1
ppm
0.91
1.00
1.00
1.06
1.07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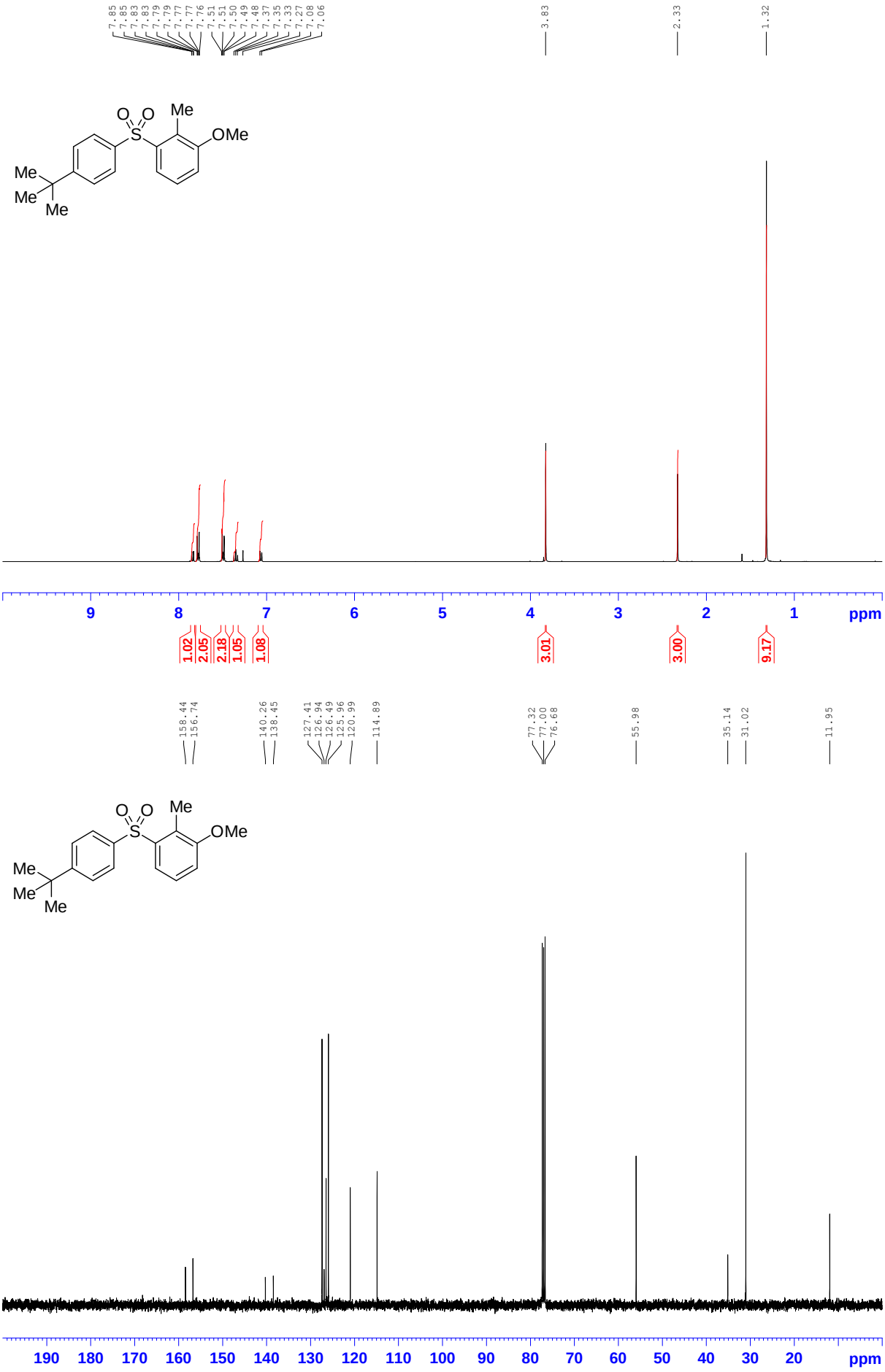
144.06
142.73
133.76
131.04
130.16
127.49
125.92
91.05
77.32
77.00
76.68
I
N
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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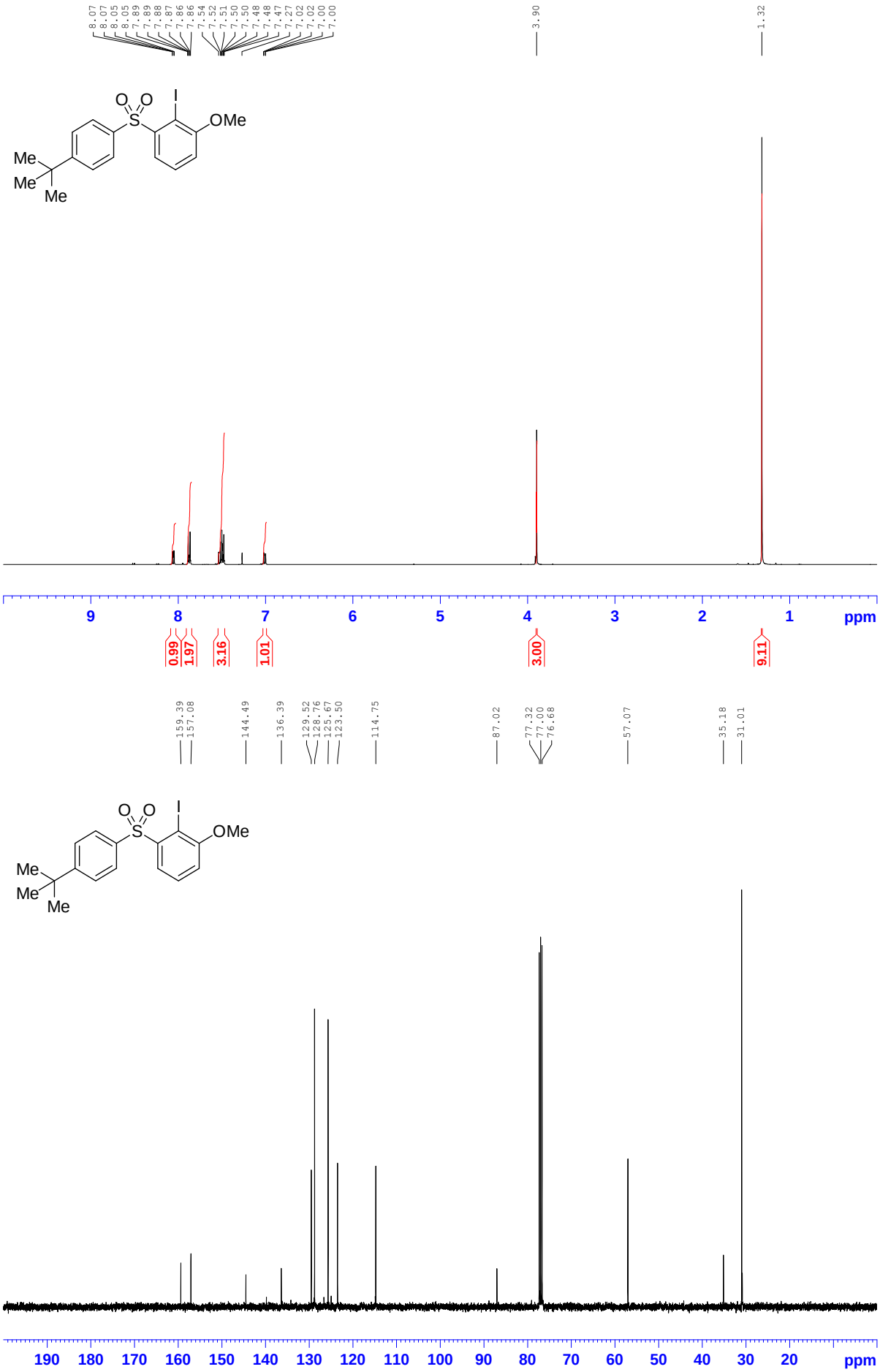
7.85
7.83
7.83
7.79
7.79
7.77
7.77
7.76
7.51
7.51
7.50
7.49
7.48
7.37
7.35
7.33
7.27
7.08
7.06
3.83
2.33
1.32
O
O
S
Me
OMe
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
1.02
2.05
2.18
1.05
1.08
3.01
3.00
9.17
158.44
156.74
140.26
138.45
127.41
126.94
126.49
125.96
120.99
114.89
77.32
77.00
76.68
55.98
35.14
31.02
11.95
O
O
S
Me
OMe
Me
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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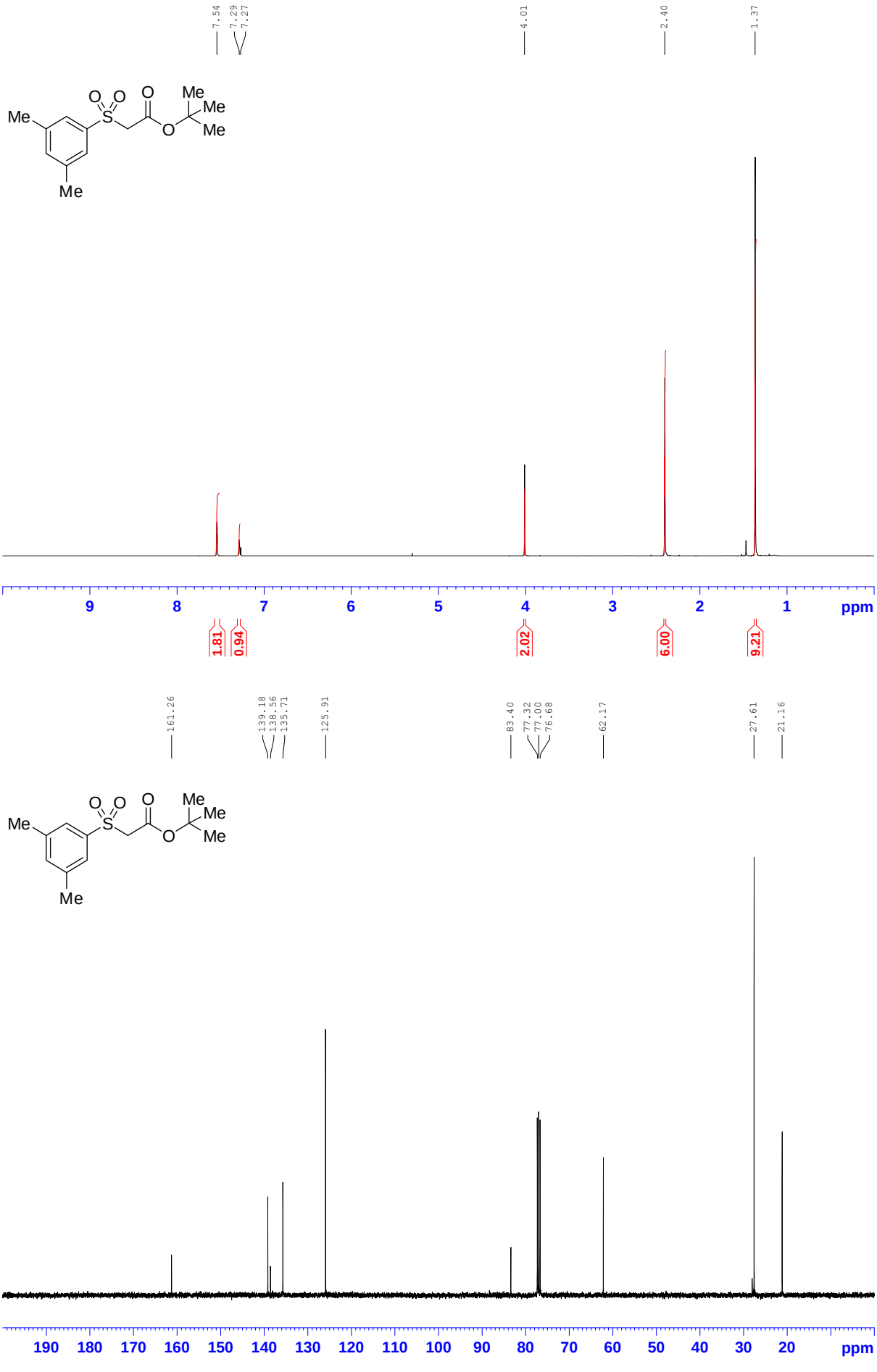
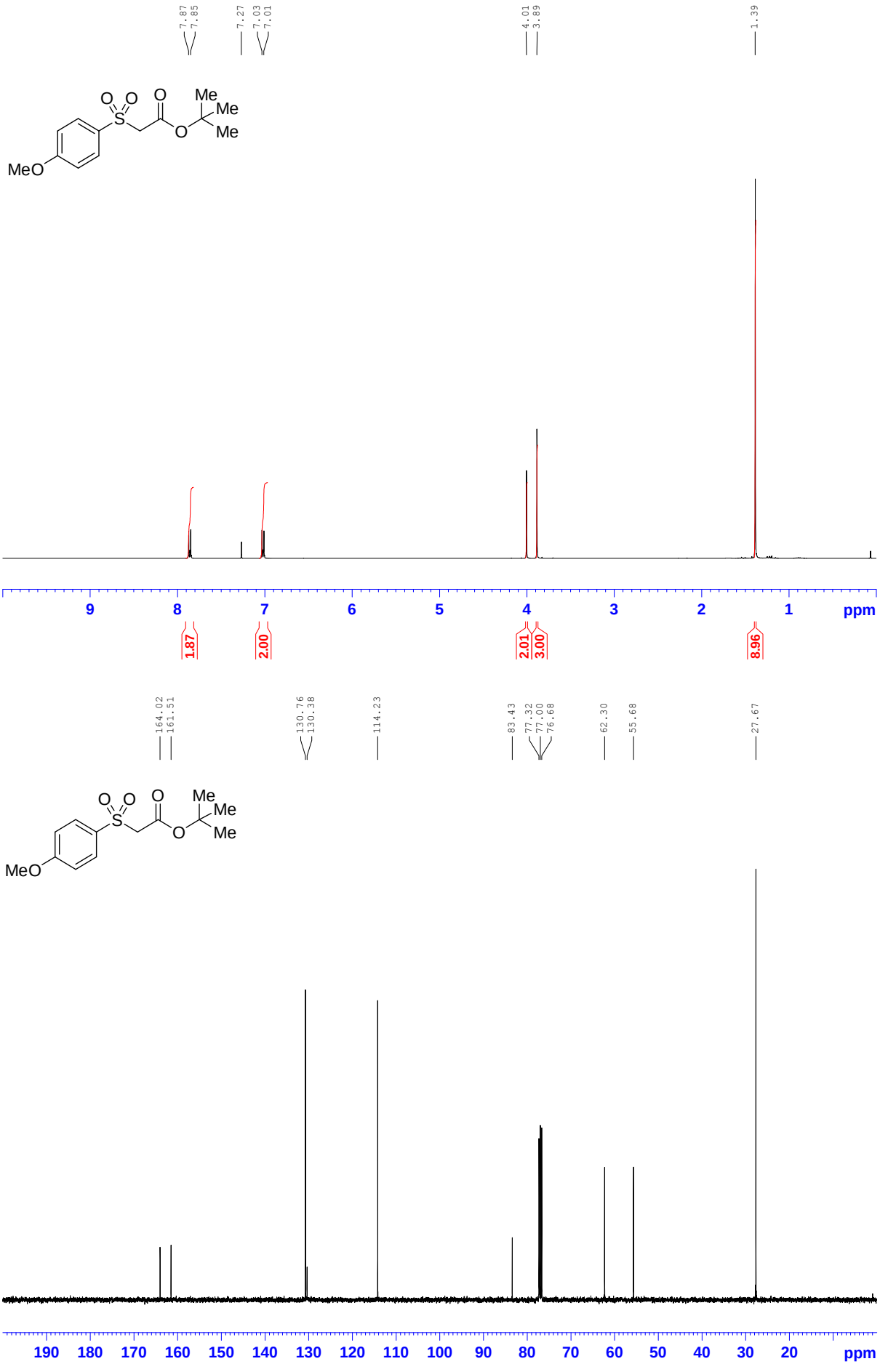
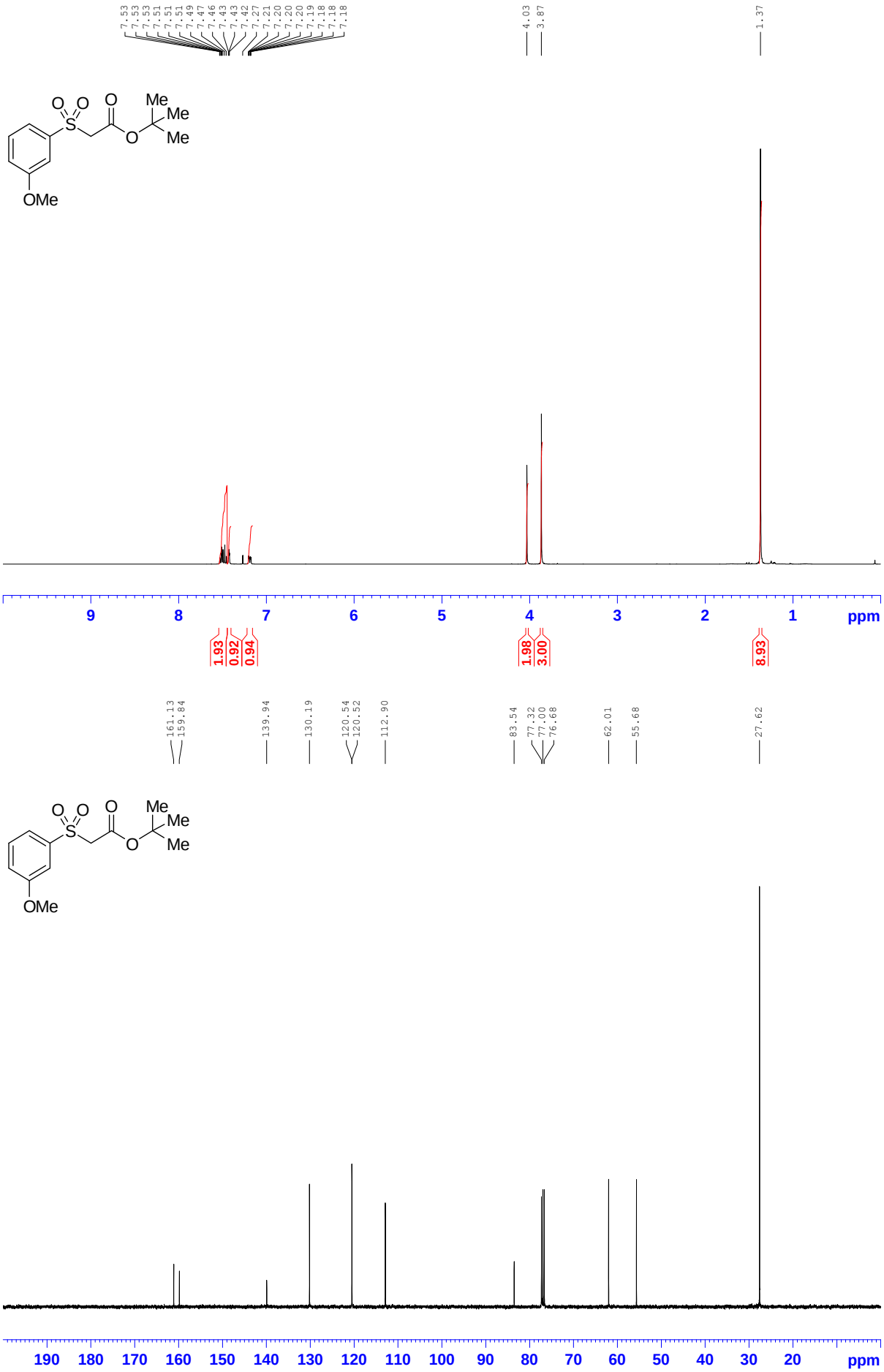
8.07
8.05
8.05
7.89
7.89
7.88
7.87
7.86
7.86
7.54
7.52
7.51
7.50
7.50
7.48
7.47
7.27
7.02
7.00
7.00
3.90
1.32
O
O
S
I
OMe
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.99
1.97
3.16
1.01
3.00
9.11
159.39
157.08
144.49
136.39
129.52
128.76
125.67
123.50
114.75
87.02
77.32
77.00
76.68
57.07
35.18
31.01
O
O
S
I
OMe
Me
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.54
7.29
7.27
4.01
2.40
1.37
Me
Me
Me
Me
O
O
O
O
S
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
1.81
0.94
2.02
6.00
9.21
161.26
139.18
138.56
135.71
125.91
83.40
77.32
77.00
76.68
62.17
27.61
21.16
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.87
7.85
7.27
7.03
7.01
4.01
3.89
1.39
O
O
S
O
O
Me
Me
Me
MeO
9
8
7
6
5
4
3
2
1
ppm
1.87
2.00
2.01
3.00
8.96
164.02
161.51
130.76
130.38
114.23
83.43
77.32
77.00
76.68
62.30
55.68
27.67
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.53
7.53
7.53
7.51
7.51
7.49
7.47
7.46
7.43
7.43
7.42
7.27
7.21
7.20
7.20
7.19
7.18
7.18
4.03
3.87
1.37
O
O
S
O
O
Me
Me
Me
OMe
9
8
7
6
5
4
3
2
1
ppm
1.93
0.92
0.94
1.98
3.00
8.93
161.13
159.84
139.94
130.19
120.54
120.52
112.90
83.54
77.32
77.00
76.68
62.01
55.68
27.62
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160
150
140
130
120
110
100
90
80
70
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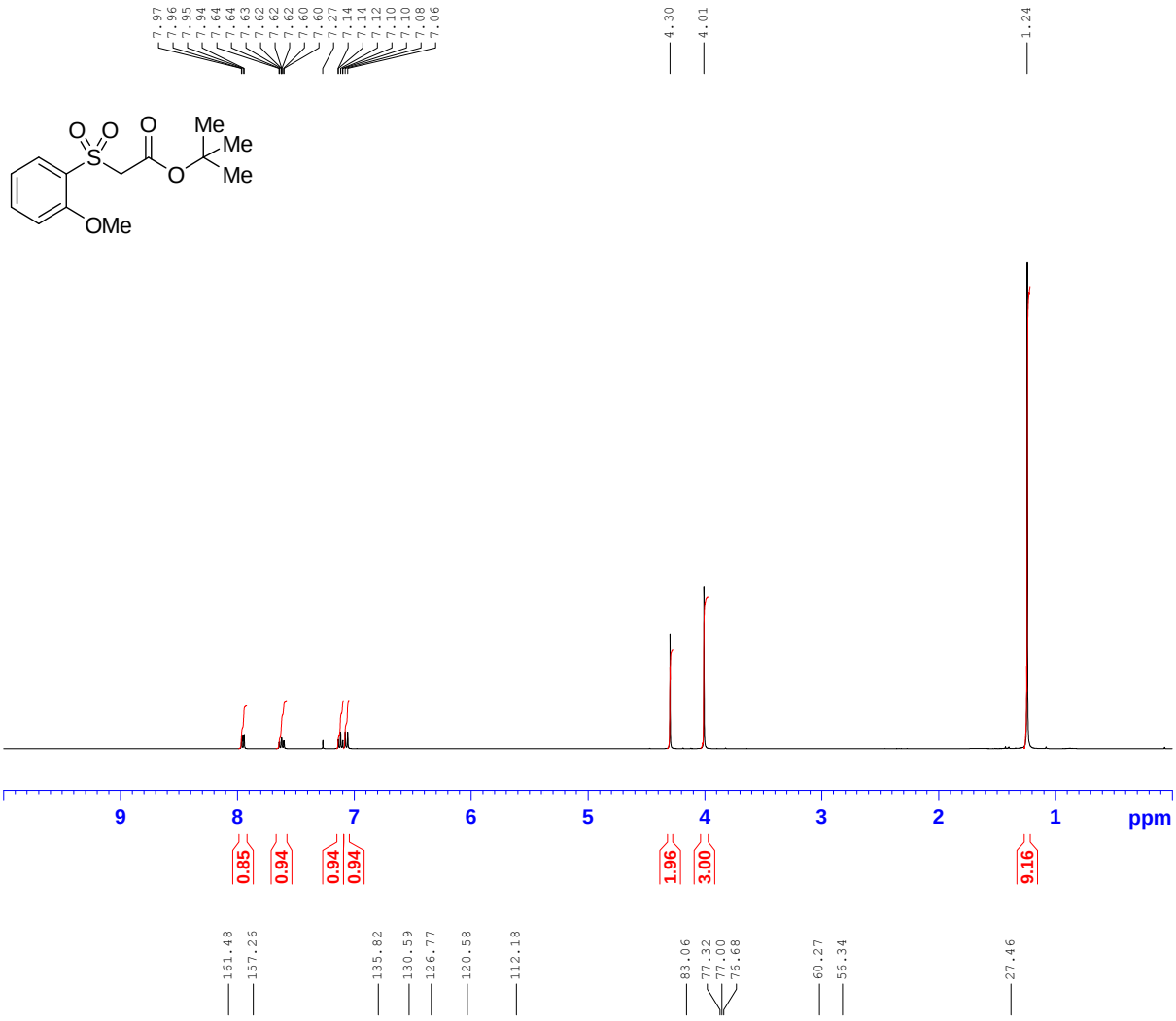
50
40
30
20
ppm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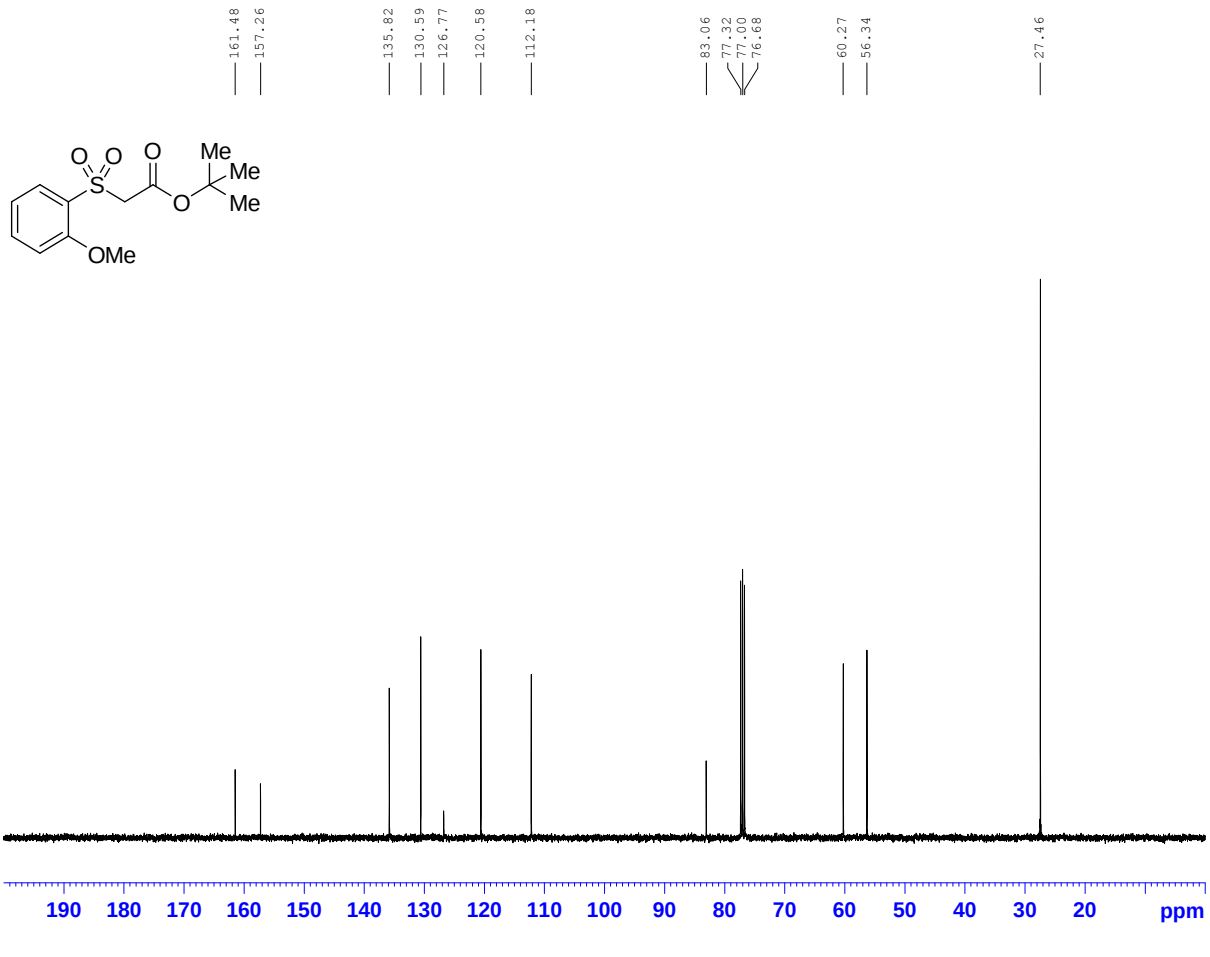
7.96
7.95
7.94
7.64
7.64
7.63
7.62
7.62
7.62
7.60
7.60
7.27
7.14
7.14
7.12
7.10
7.10
7.08
7.06
4.30
4.01
1.24
O
O
S
O
O
Me
Me
Me
OMe
9
8
7
6
5
4
3
2
1
ppm
0.85
0.94
0.94
0.94
1.96
3.00
9.16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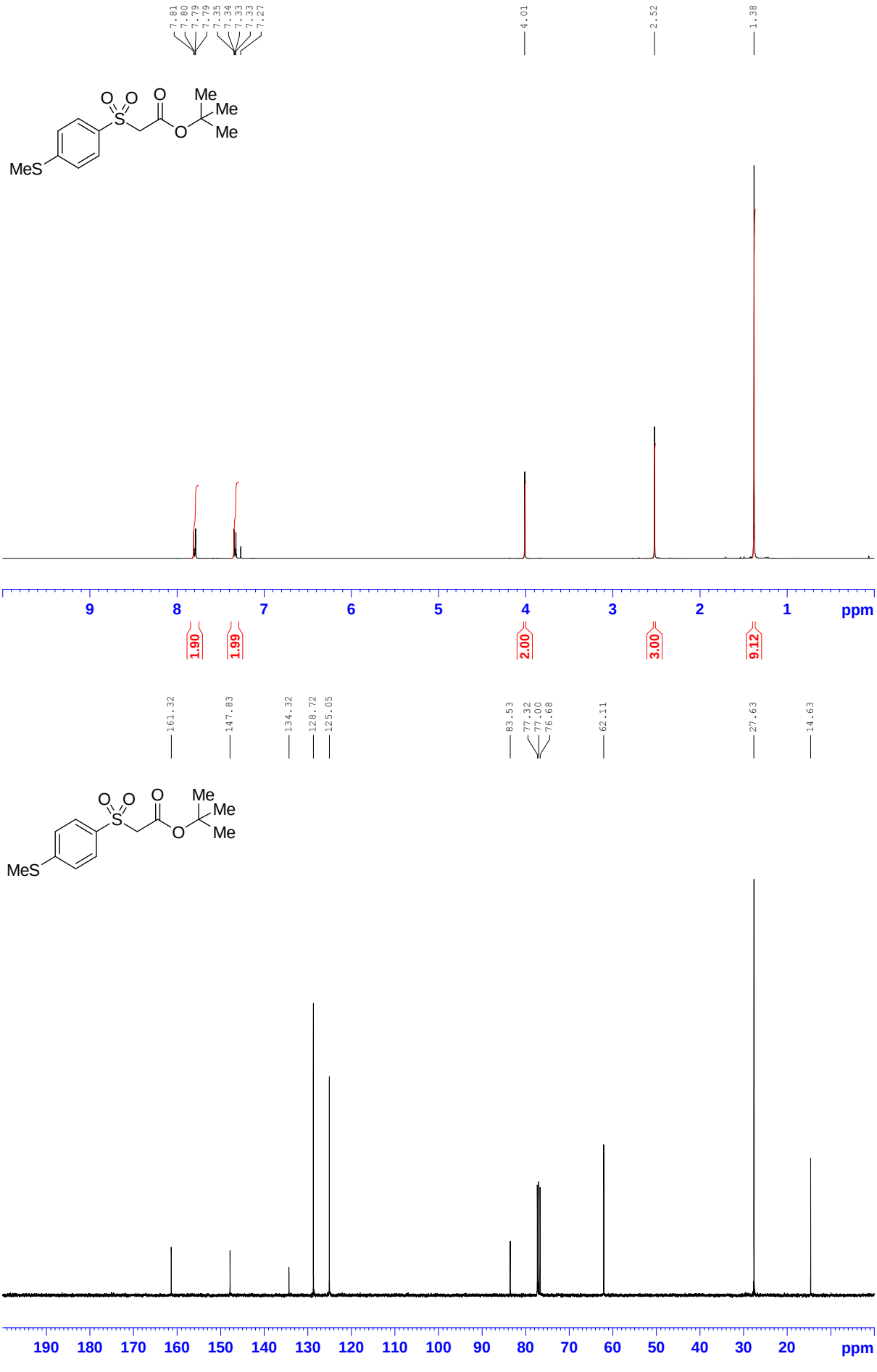
157.26
135.82
130.59
126.77
120.58
112.18
83.06
77.32
77.00
76.68
60.27
56.34
27.46
O
O
S
O
O
Me
Me
Me
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.79
7.79
7.35
7.34
7.33
7.33
7.27
4.01
2.52
1.38
O
O
S
O
O
Me
Me
Me
MeS
9
8
7
6
5
4
3
2
1
ppm
1.90
1.99
2.00
3.00
9.12
161.32
147.83
134.32
128.72
125.05
83.53
77.32
77.00
76.68
62.11
27.63
14.63
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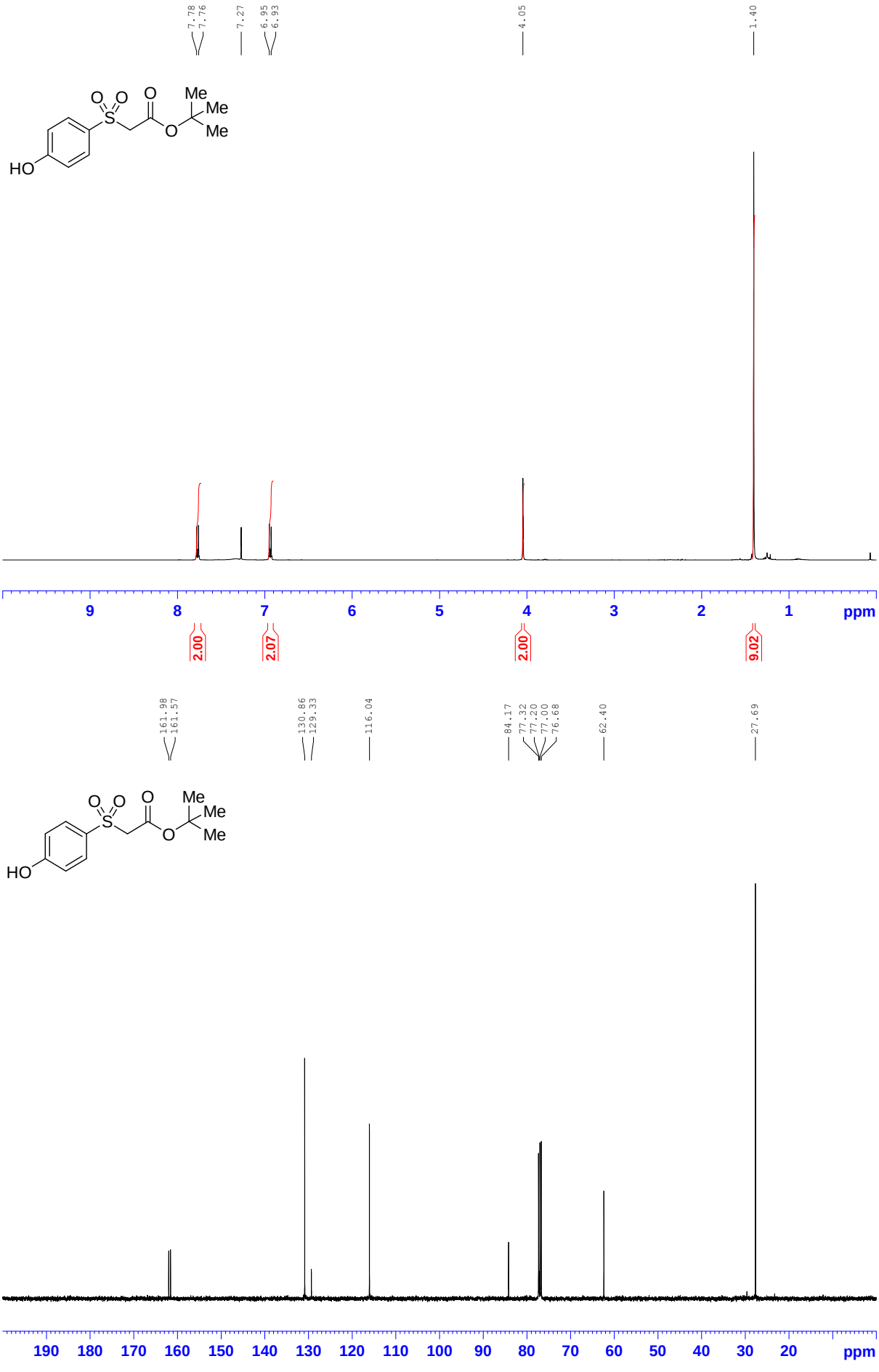
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.78
7.76
7.27
6.95
6.93
4.05
1.40
O
O
S
O
O
Me
Me
Me
HO
9
8
7
6
5
4
3
2
1
ppm
2.00
2.07
2.00
9.02
161.98
161.57
130.86
129.33
116.04
84.17
77.32
77.20
77.00
76.68
62.40
27.69
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180
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150
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130
120
110
100
90
80
70
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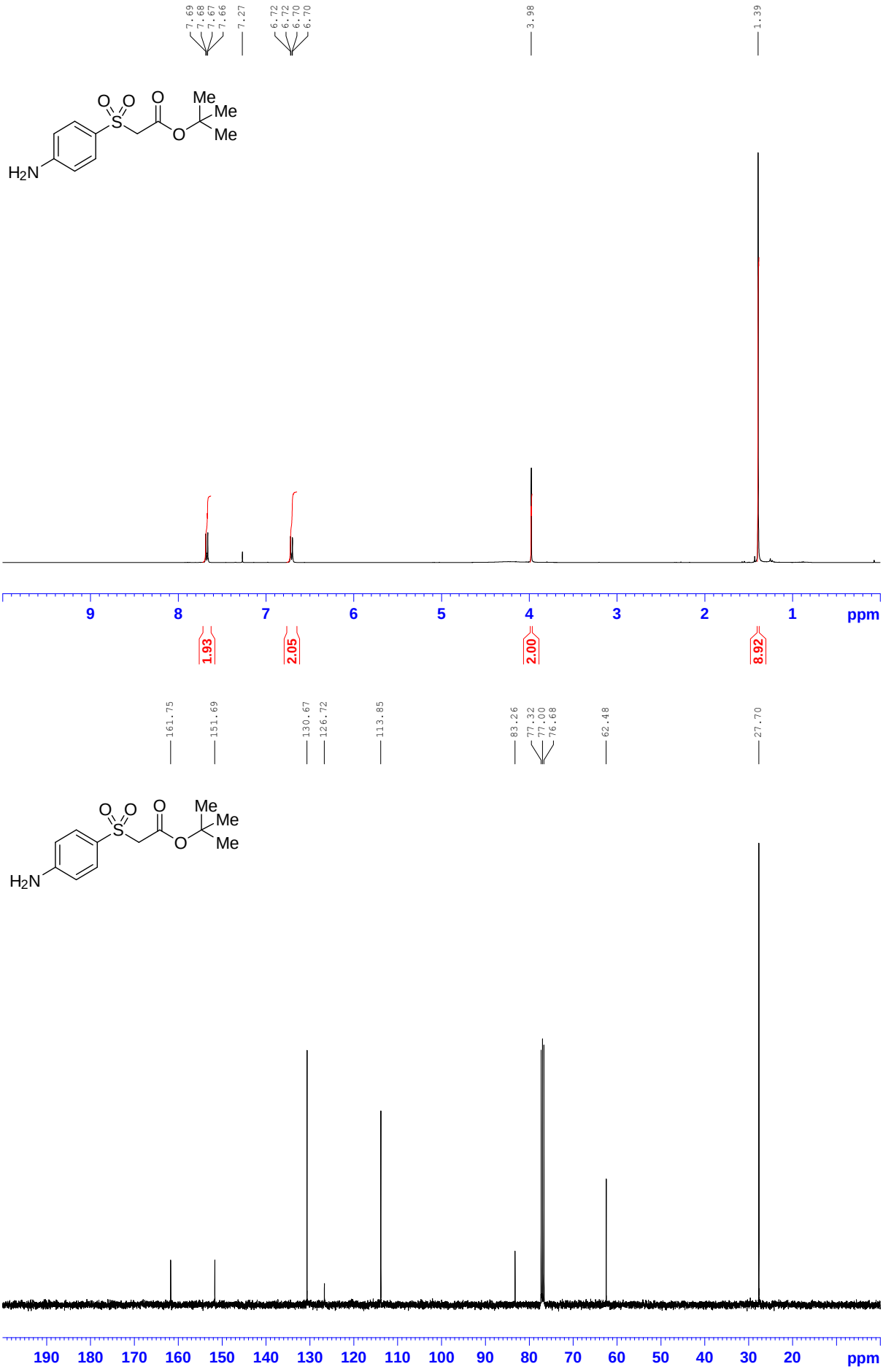
50
40
30
20
ppm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7.68
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7.66
7.27
6.72
6.72
6.70
6.70
3.98
1.39
O
O
S
O
O
Me
Me
Me
H2N
9
8
7
6
5
4
3
2
1
ppm
1.93
2.05
2.00
8.92
161.75
151.69
130.67
126.72
113.85
83.26
77.32
77.00
76.68
62.48
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160
150
140
130
120
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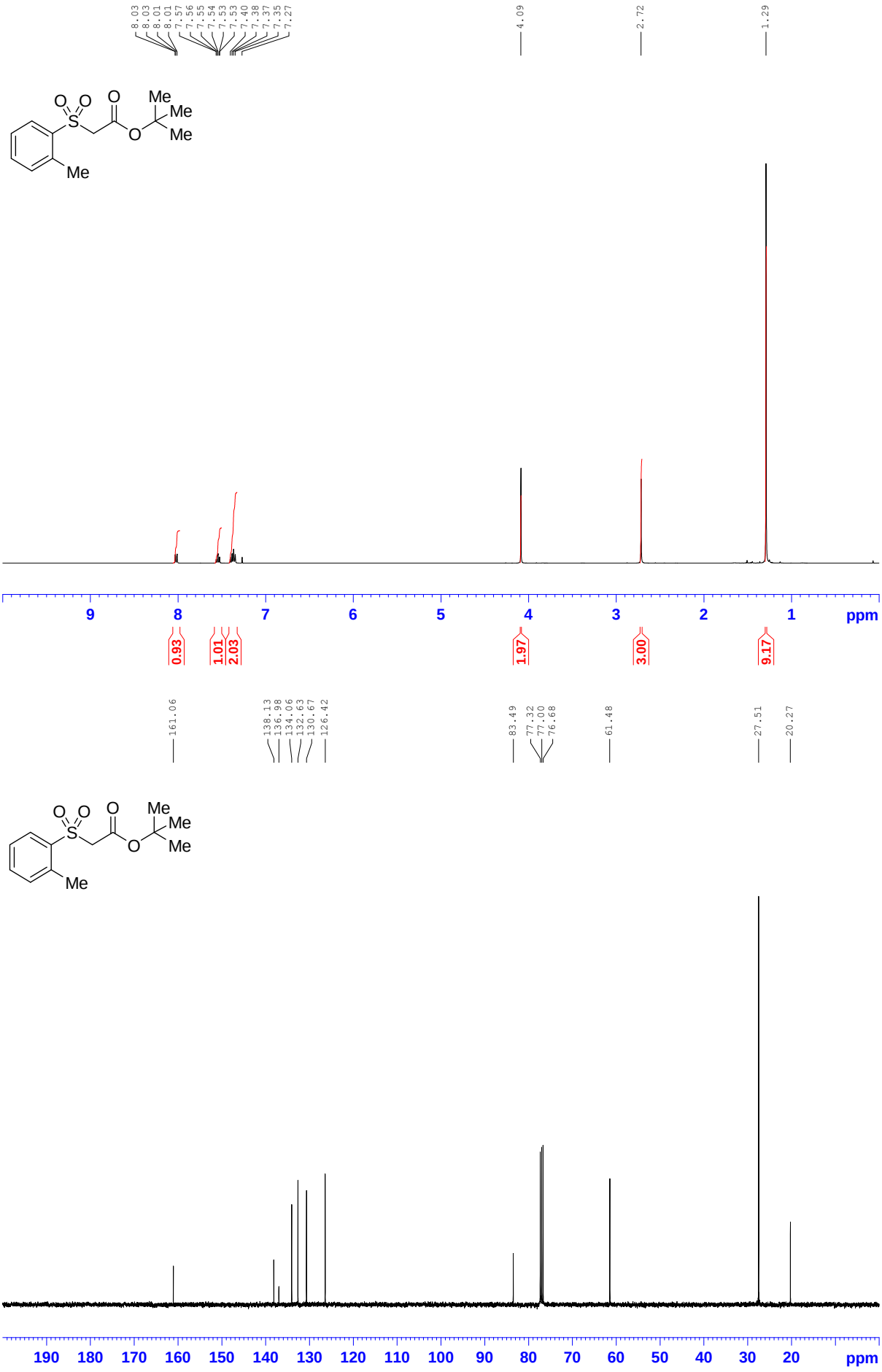
100
90
80
70
60
50
40
30
20
ppm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8.03
8.01
8.01
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7.56
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7.54
7.53
7.53
7.40
7.38
7.37
7.35
7.27
4.09
2.72
1.29
O
O
S
O
O
Me
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.93
1.01
2.03
1.97
3.00
9.17
161.06
138.13
136.98
134.06
132.63
130.67
126.42
83.49
77.32
77.00
76.68
61.48
27.51
20.27
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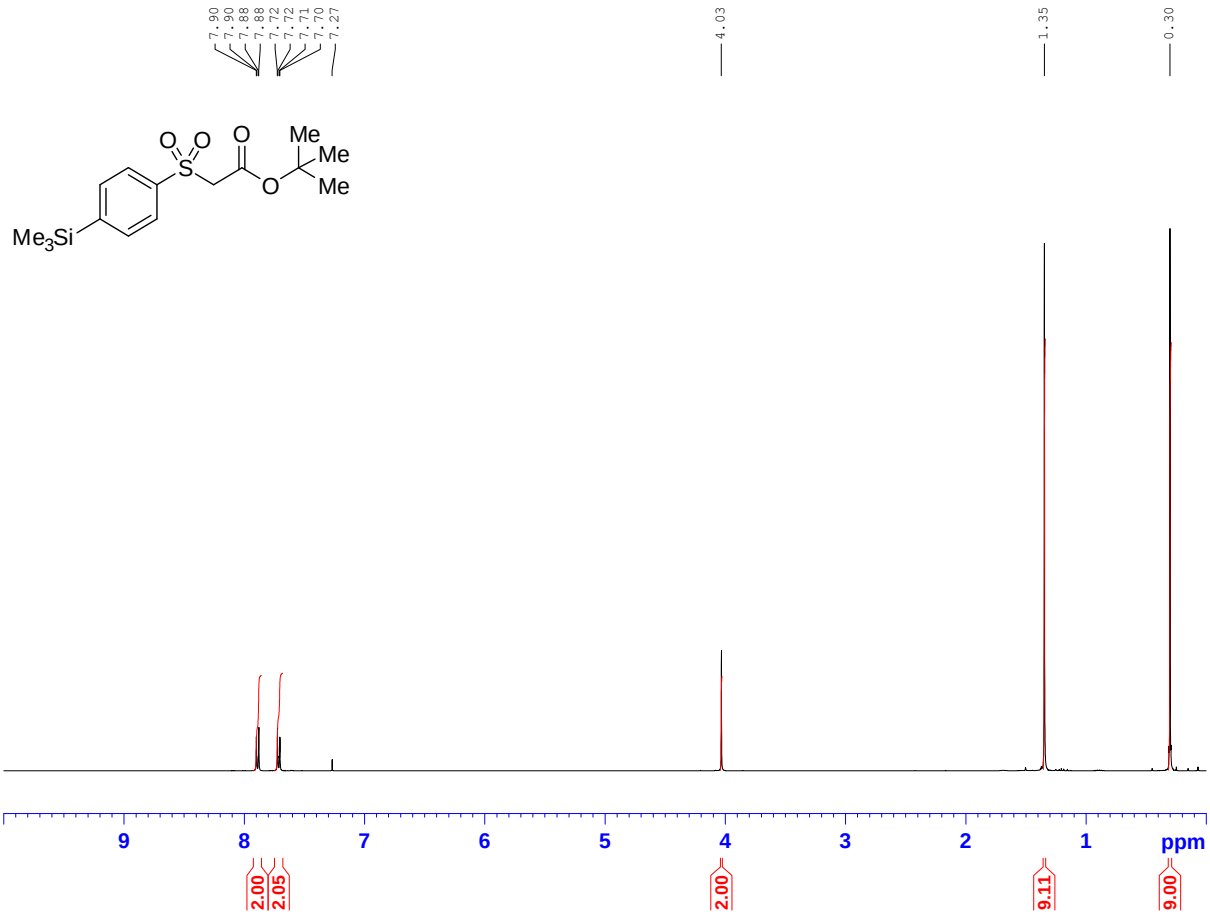
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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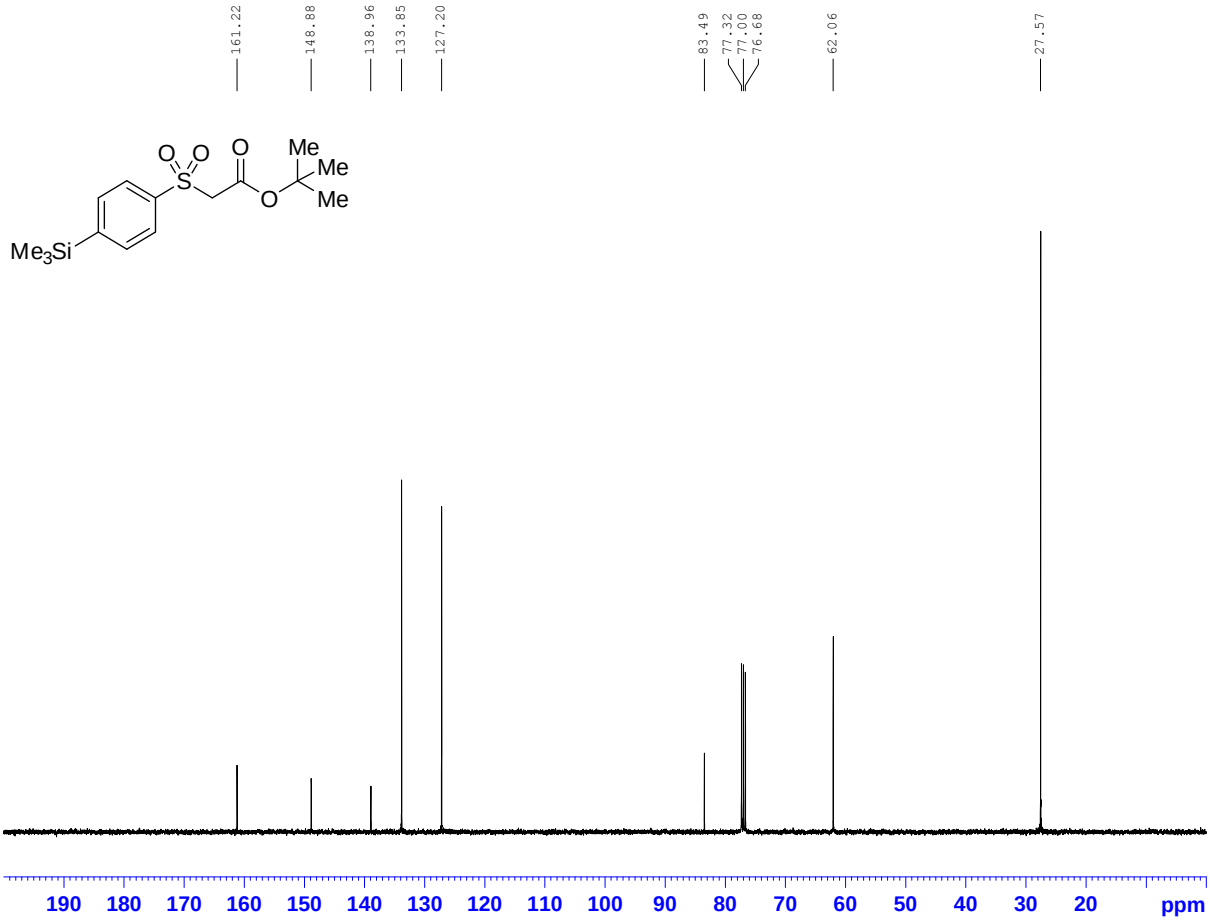
7.70
7.27
4.03
1.35
0.30
O
O
S
O
O
Me
Me
Me
Me3Si
9
8
7
6
5
4
3
2
1
ppm
2.00
2.05
2.00
9.11
9.00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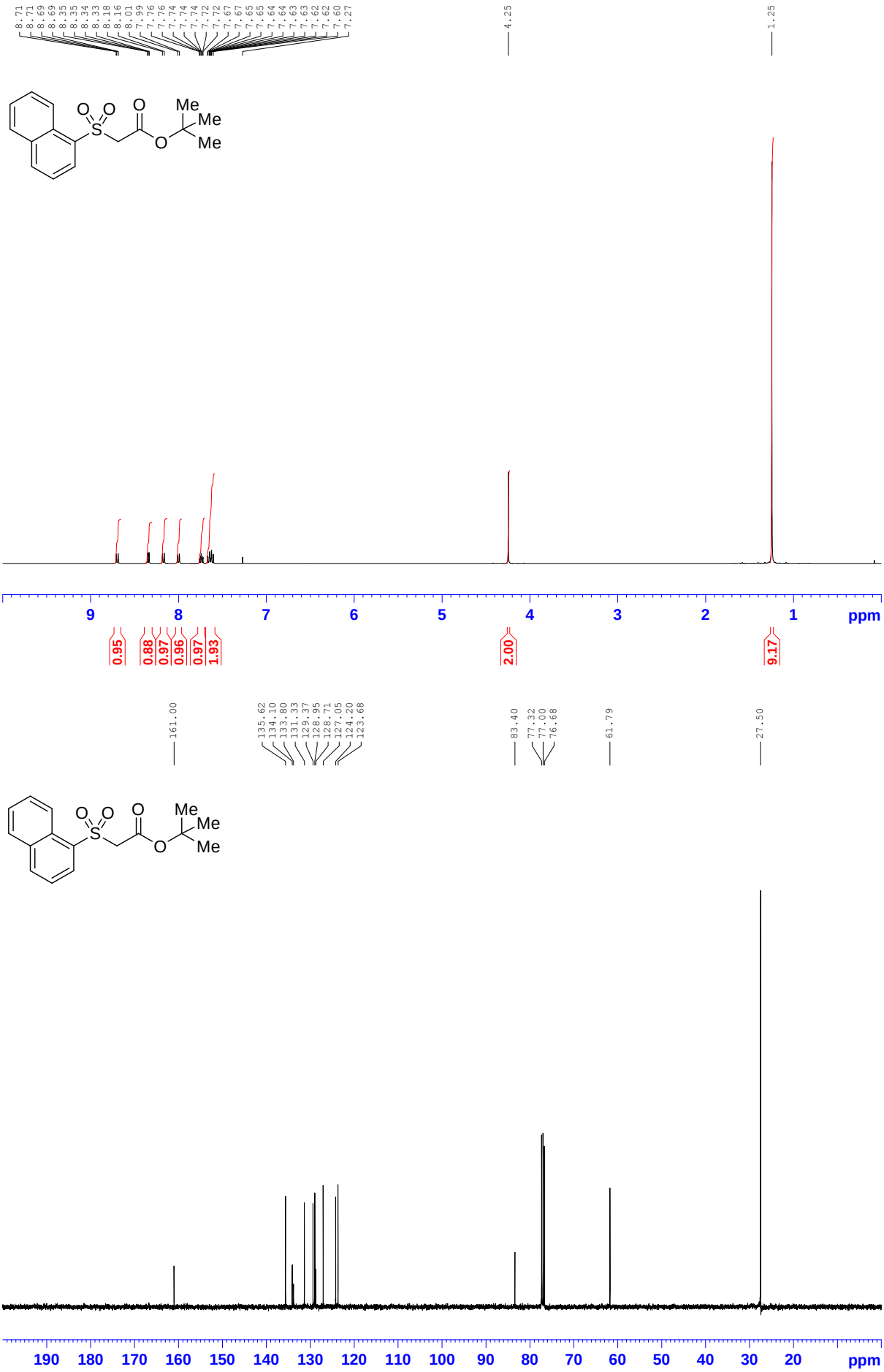
77.32
77.00
76.68
62.06
27.57
O
O
S
O
O
Me
Me
Me
Me3Si
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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8.71
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8.69
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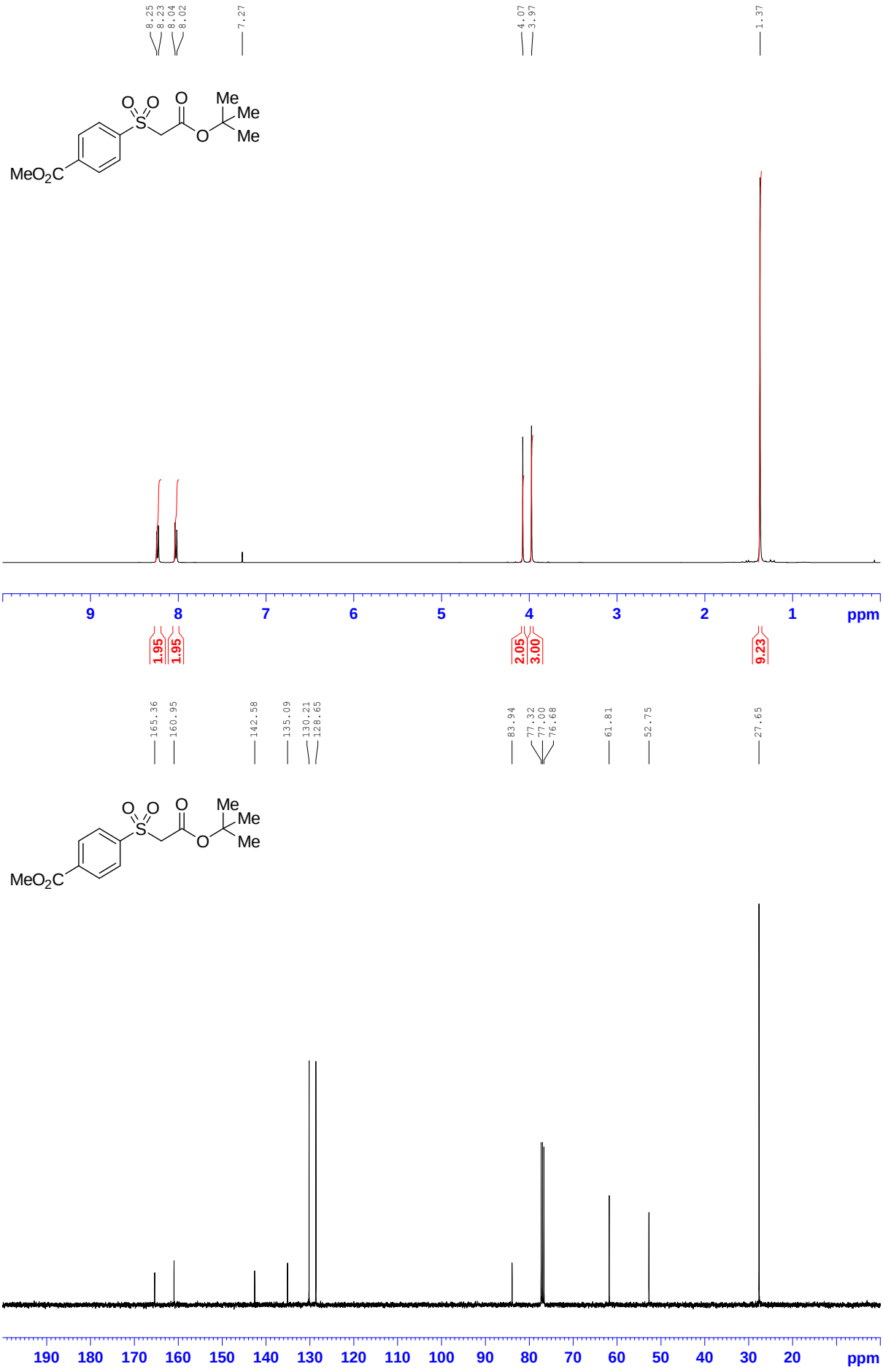
8.35
8.34
8.33
8.18
8.16
8.01
7.99
7.76
7.76
7.74
7.74
7.72
7.72
7.67
7.67
7.65
7.65
7.64
7.64
7.63
7.63
7.62
7.62
7.60
7.27
4.25
1.25
O
O
O
S
O
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.95
0.88
0.97
0.96
0.97
1.93
2.00
9.17
161.00
135.62
134.10
133.80
131.33
129.37
128.95
128.71
127.05
124.20
123.68
83.40
77.32
77.00
76.68
61.79
27.50
O
O
O
S
O
Me
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


8.25
8.23
8.04
8.02
7.27
4.07
3.97
1.37
O
O
S
O
O
Me
Me
Me
MeO2C
9
8
7
6
5
4
3
2
1
ppm
1.95
1.95
2.05
3.00
9.23
165.36
160.95
142.58
135.09
130.21
128.65
83.94
77.32
77.00
76.68
61.81
52.75
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150
140
130
120
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100
90
80
70
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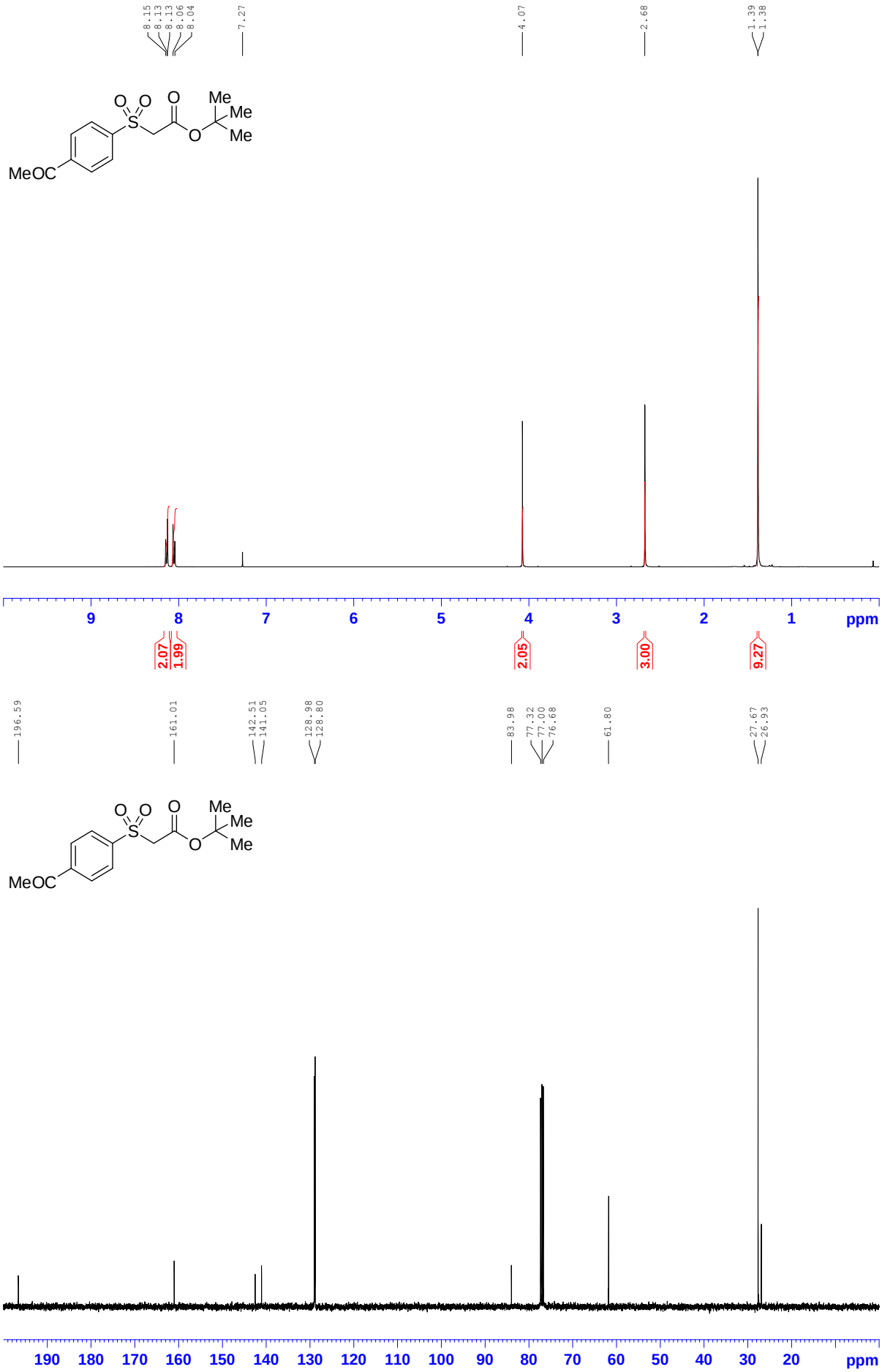
50
40
30
20
ppm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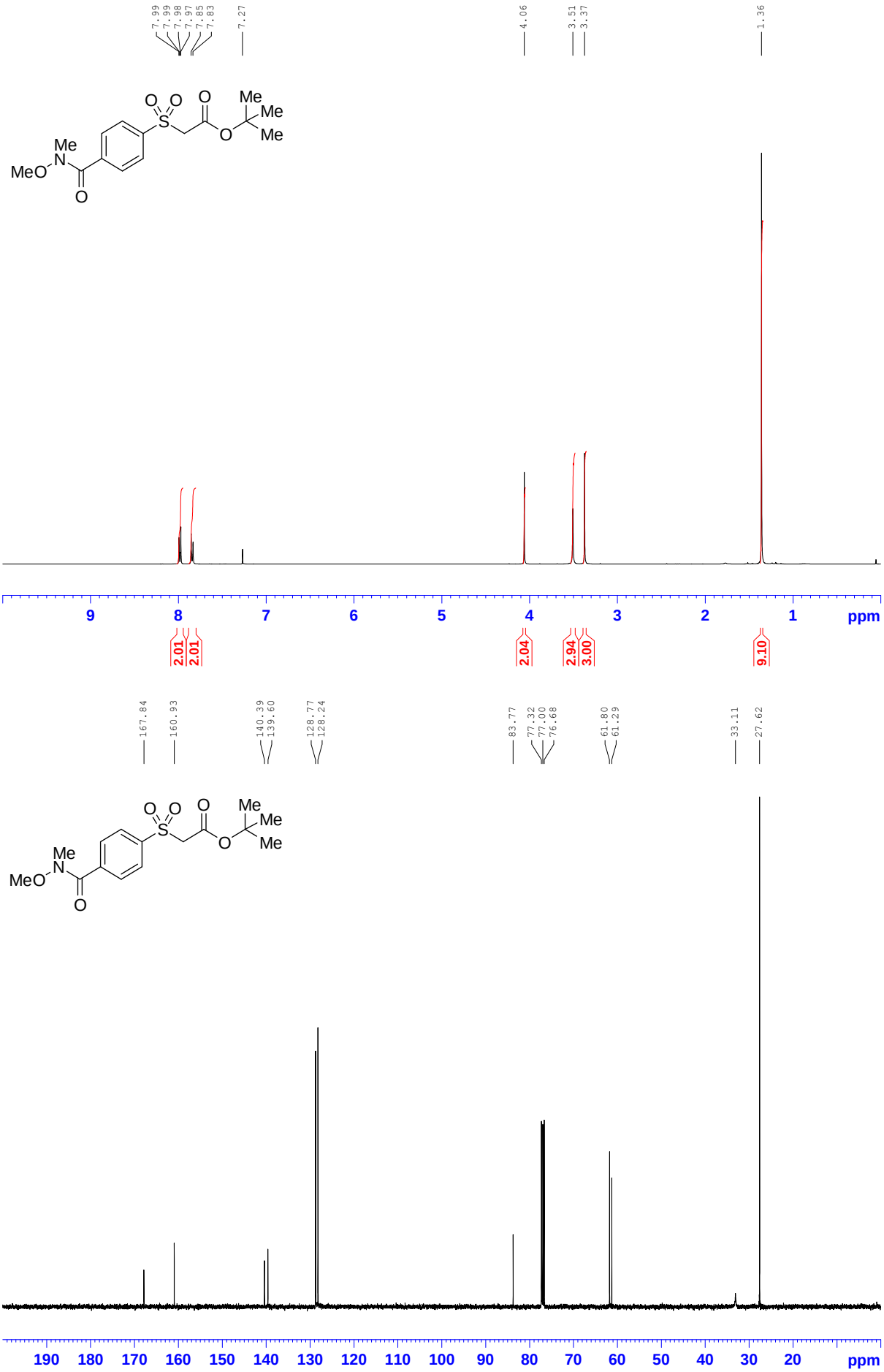
8.13
8.13
8.06
8.04
7.27
4.07
2.68
1.39
1.38
O
O
S
O
O
Me
Me
Me
MeOC
9
8
7
6
5
4
3
2
1
ppm
2.07
1.99
2.05
3.00
9.27
196.59
161.01
142.51
141.05
128.98
128.80
83.98
77.32
77.00
76.68
61.80
27.67
26.93
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.98
7.97
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7.83
7.27
4.06
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3.37
1.36
Me
Me
Me
O
O
O
S
O
Me
N
MeO
O
9
8
7
6
5
4
3
2
1
ppm
2.01
2.01
2.04
2.94
3.00
9.10
167.84
160.93
140.39
139.60
128.77
128.24
83.77
77.32
77.00
76.68
61.80
61.29
33.11
27.62
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120
110
100
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80
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40
30
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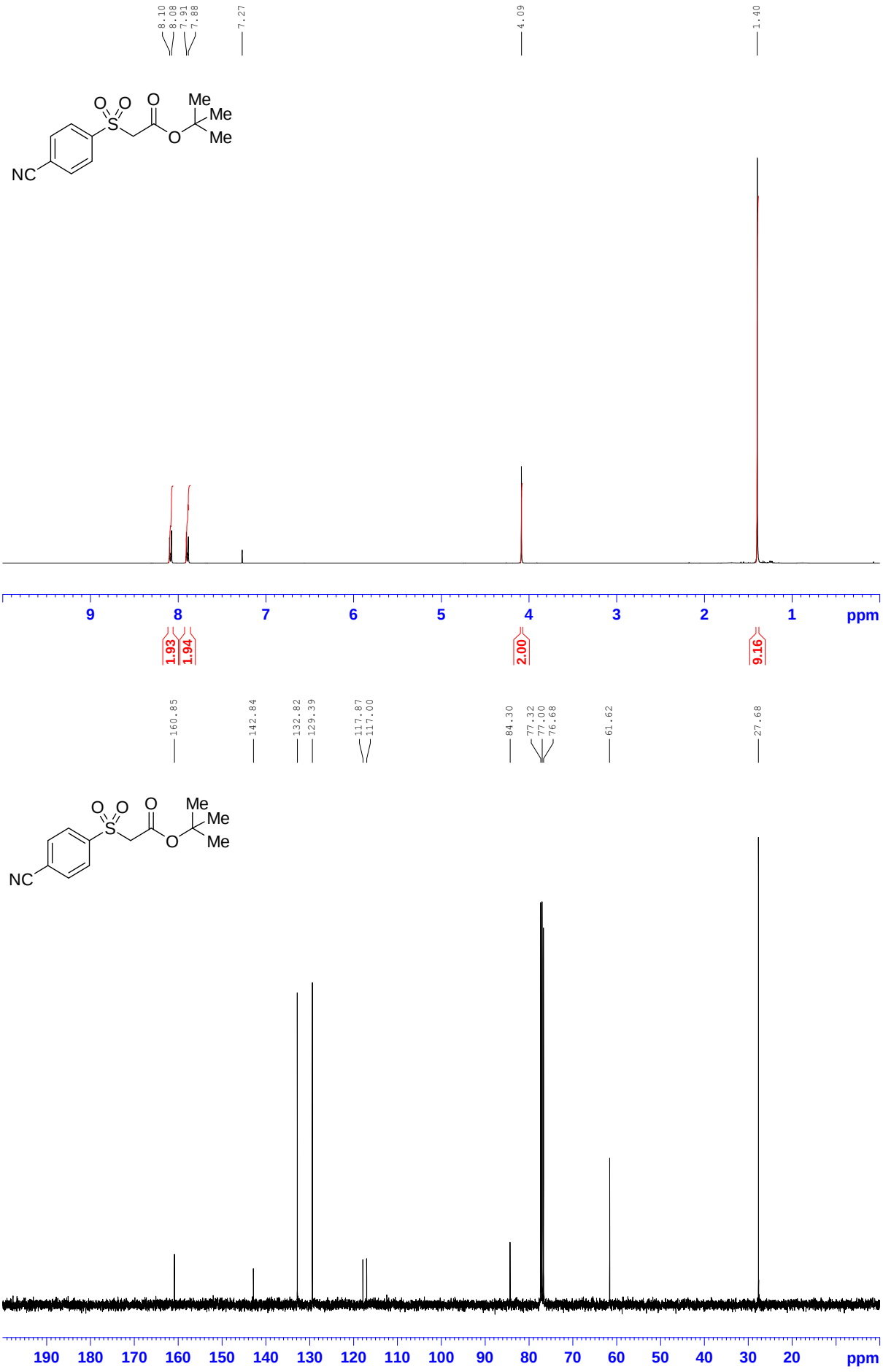
ppm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7.91
7.88
7.27
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1.40
O
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S
O
O
Me
Me
Me
NC
9
8
7
6
5
4
3
2
1
ppm
1.93
1.94
2.00
9.16
160.85
142.84
132.82
129.39
117.87
117.00
84.30
77.32
77.00
76.68
61.62
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160
150
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120
110
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80
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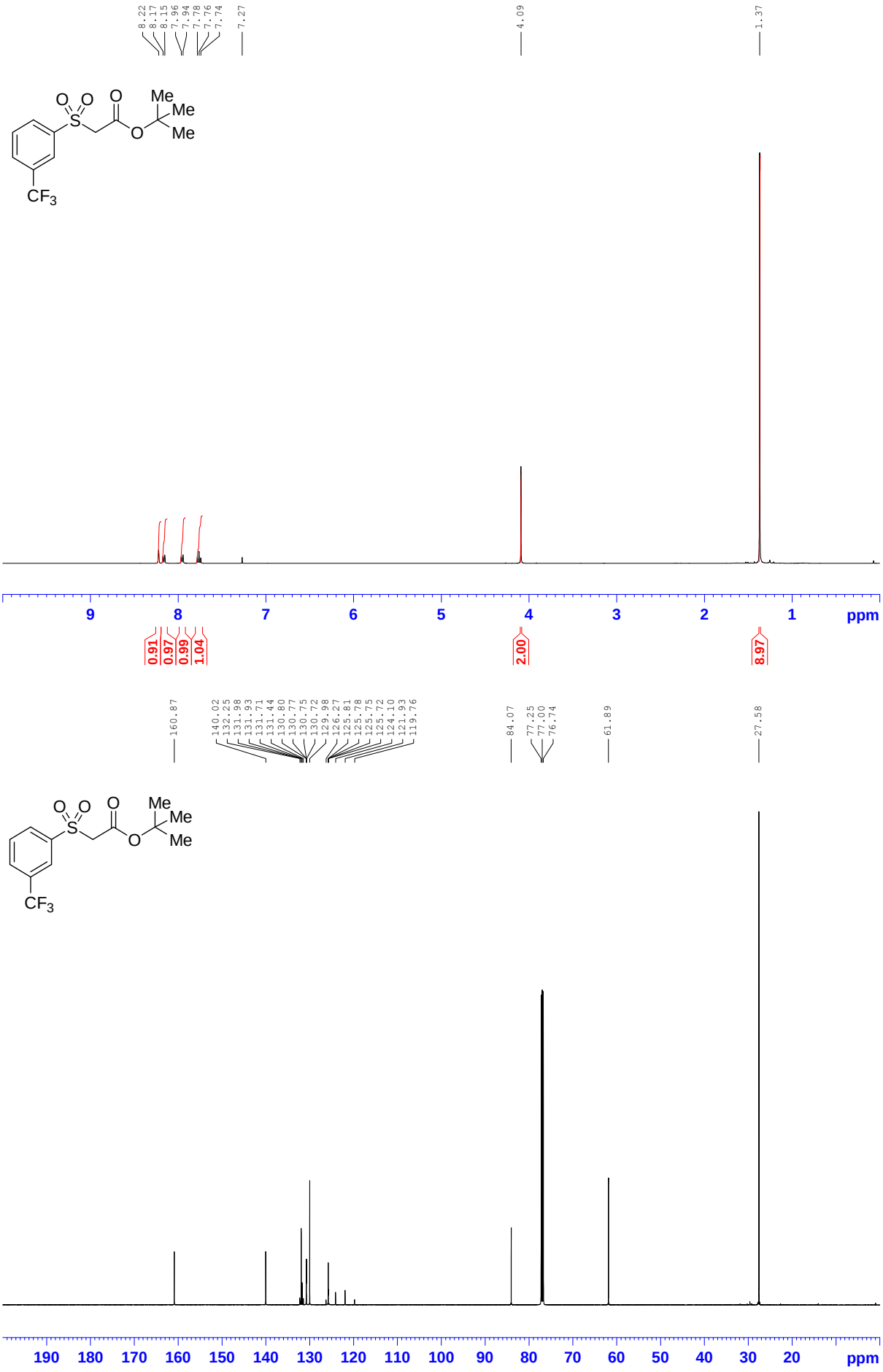
50
40
30
20
ppm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7.76
7.74
7.27
4.09
1.37
O
O
S
O
O
Me
Me
Me
CF3
9
8
7
6
5
4
3
2
1
ppm
0.91
0.97
0.99
1.04
2.00
8.97
160.87
140.02
132.25
131.98
131.93
131.71
131.44
130.80
130.77
130.75
130.72
129.98
126.27
125.81
125.78
125.75
125.72
124.10
121.93
119.76
84.07
77.25
77.00
76.74
61.89
27.58
O
O
S
O
O
Me
Me
Me
CF3
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160
150
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120
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80
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40
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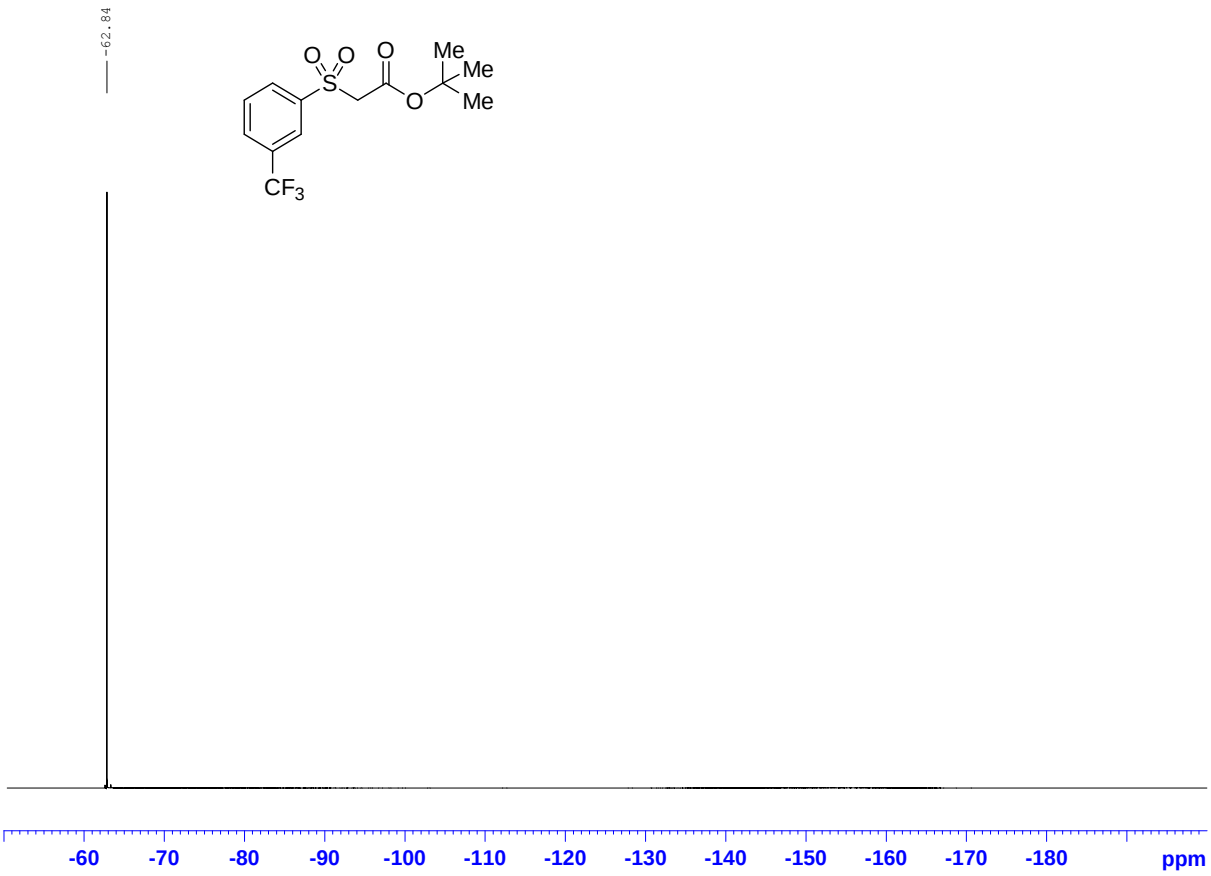
20
ppm


-62.84
O
O
S
O
O
Me
Me
Me
CF3
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-70
-80
-90
-100
-110
-120
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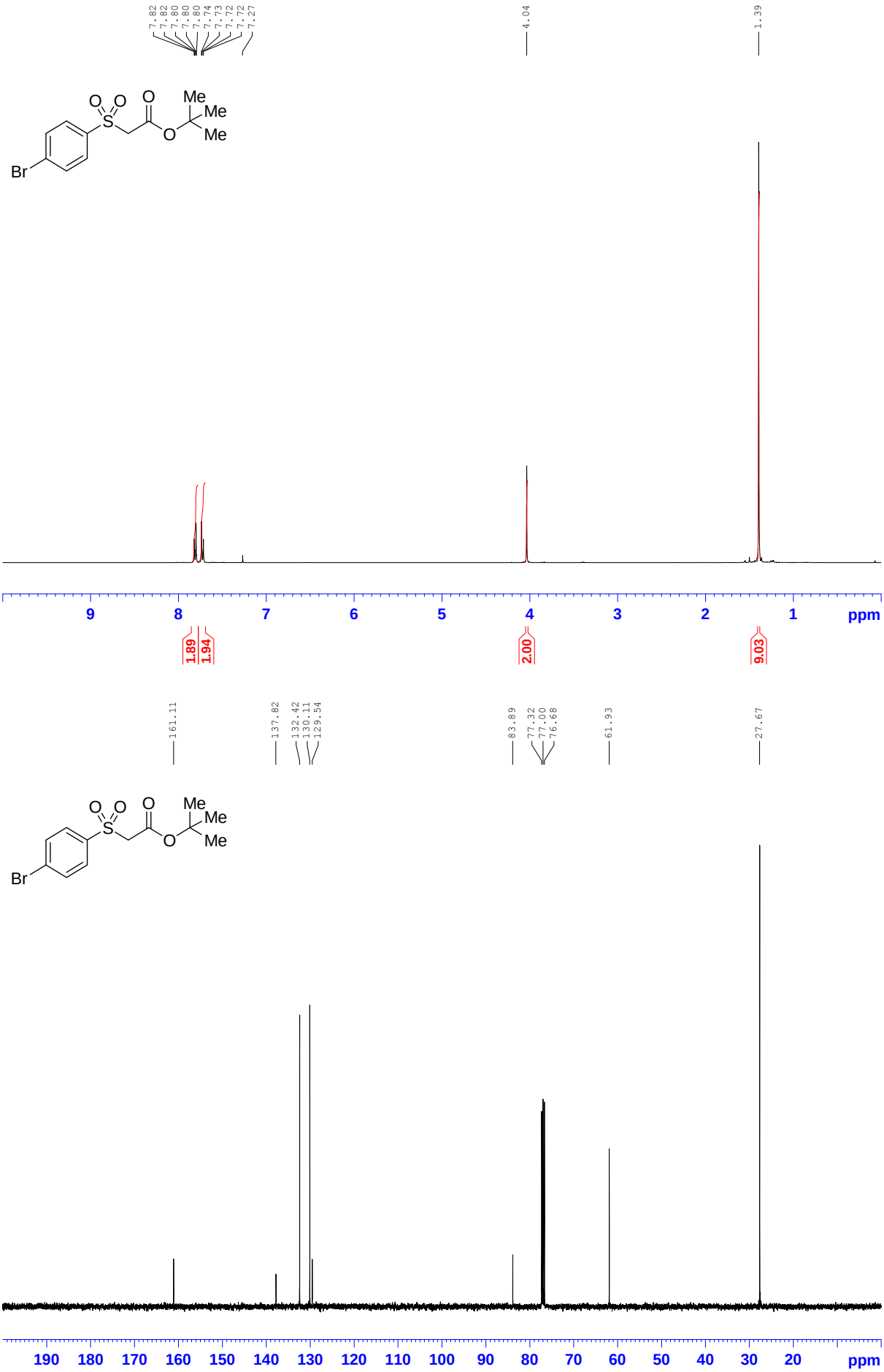
-140
-150
-160
-170
-180
ppm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7.80
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7.73
7.72
7.72
7.27
4.04
1.39
O
O
S
O
O
Me
Me
Me
Br
9
8
7
6
5
4
3
2
1
ppm
1.89
1.94
2.00
9.03
161.11
137.82
132.42
130.11
129.54
83.89
77.32
77.00
76.68
61.93
27.67
O
O
S
O
O
Me
Me
Me
Br
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180
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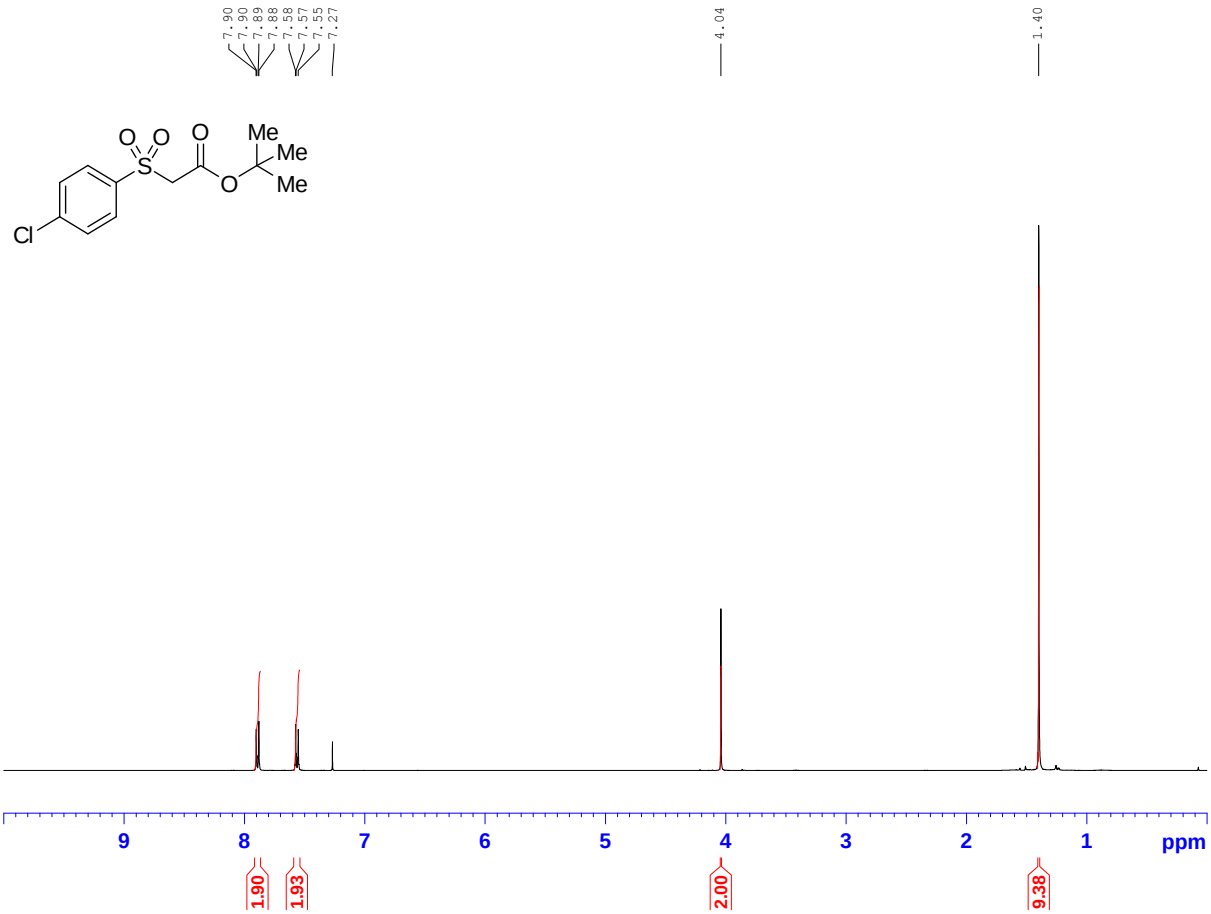
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.90
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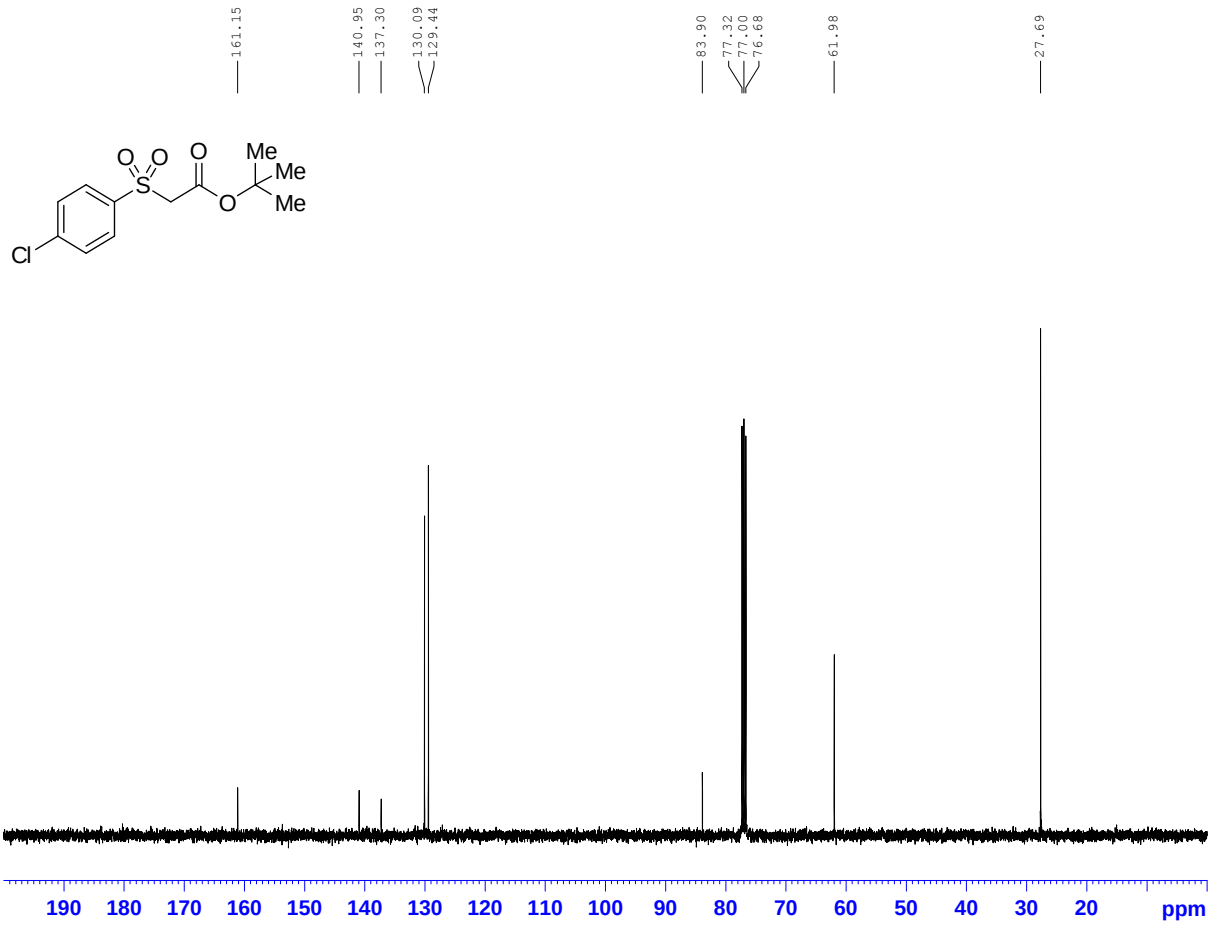
7.88
7.58
7.57
7.55
7.27
4.04
1.40
O
O
S
O
O
Me
Me
Me
Cl
9
8
7
6
5
4
3
2
1
ppm
1.90
1.93
2.00
9.38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77.00
76.68
61.98
27.69
O
O
S
O
O
Me
Me
Me
Cl
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180
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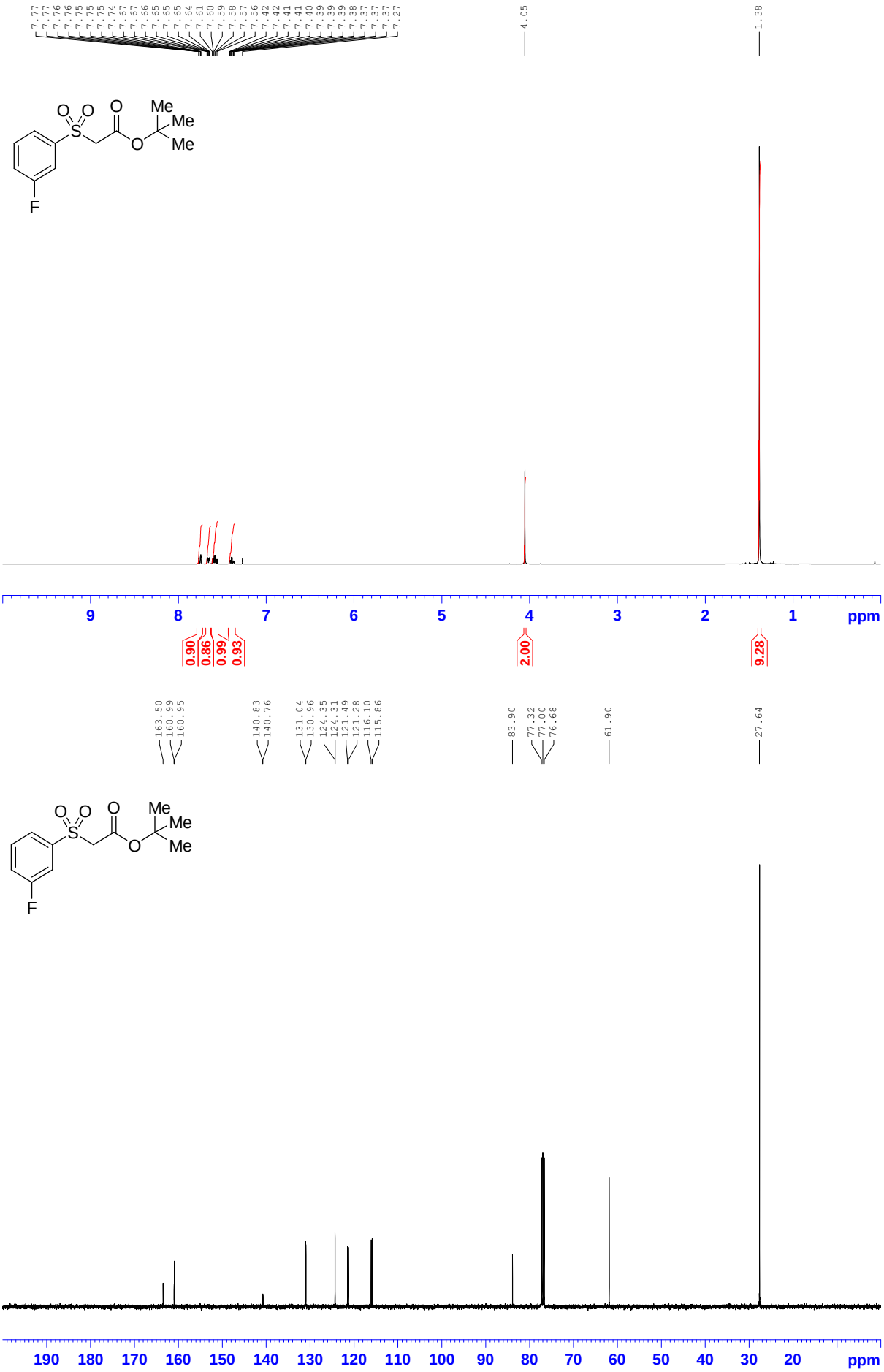
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.75
7.75
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7.67
7.66
7.65
7.65
7.64
7.61
7.60
7.59
7.58
7.57
7.56
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.39
7.38
7.37
7.37
7.37
7.27
4.05
1.38
O
O
S
O
O
Me
Me
Me
F
9
8
7
6
5
4
3
2
1
ppm
0.90
0.86
0.99
0.93
2.00
9.28
163.50
160.99
160.95
140.83
140.76
131.04
130.96
124.35
124.31
121.49
121.28
116.10
115.86
83.90
77.32
77.00
76.68
61.90
27.64
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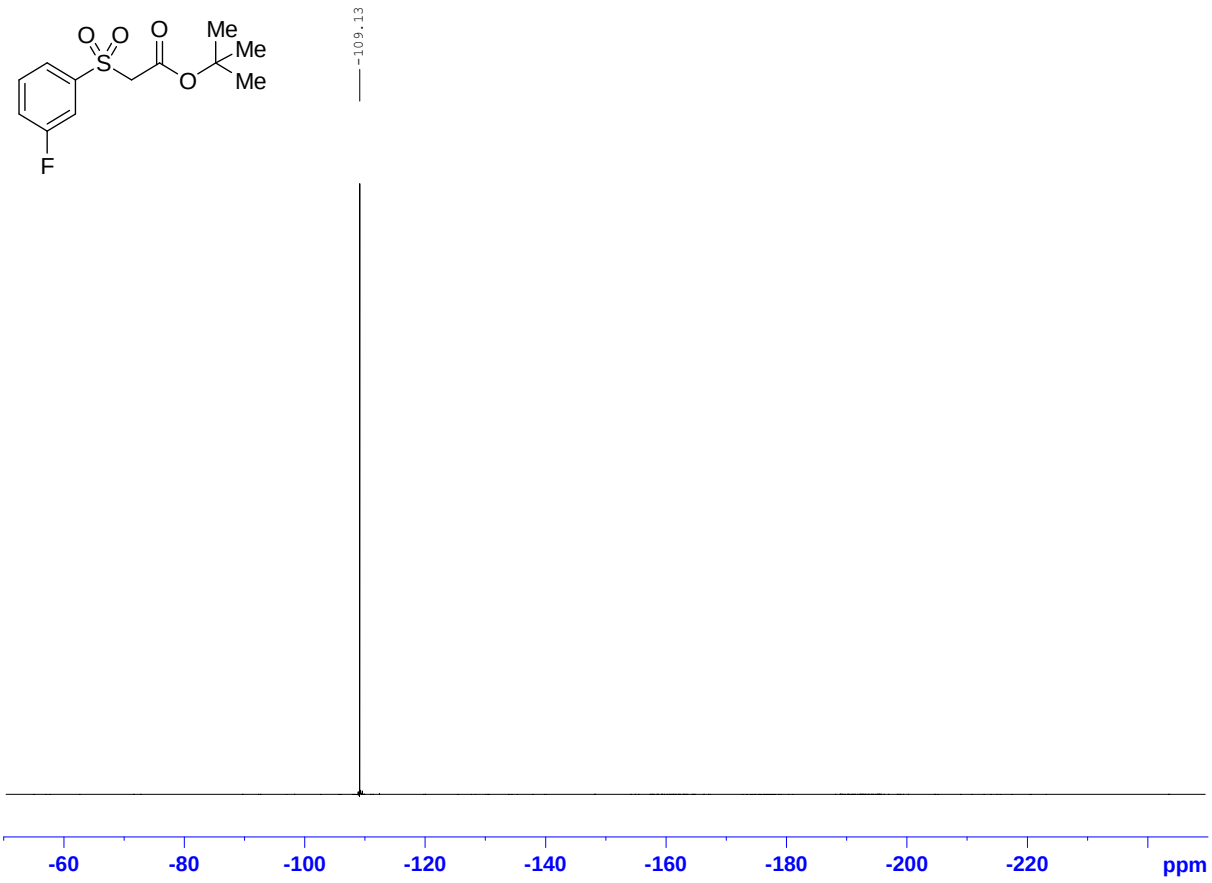
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
O
O
Me
Me
Me
F
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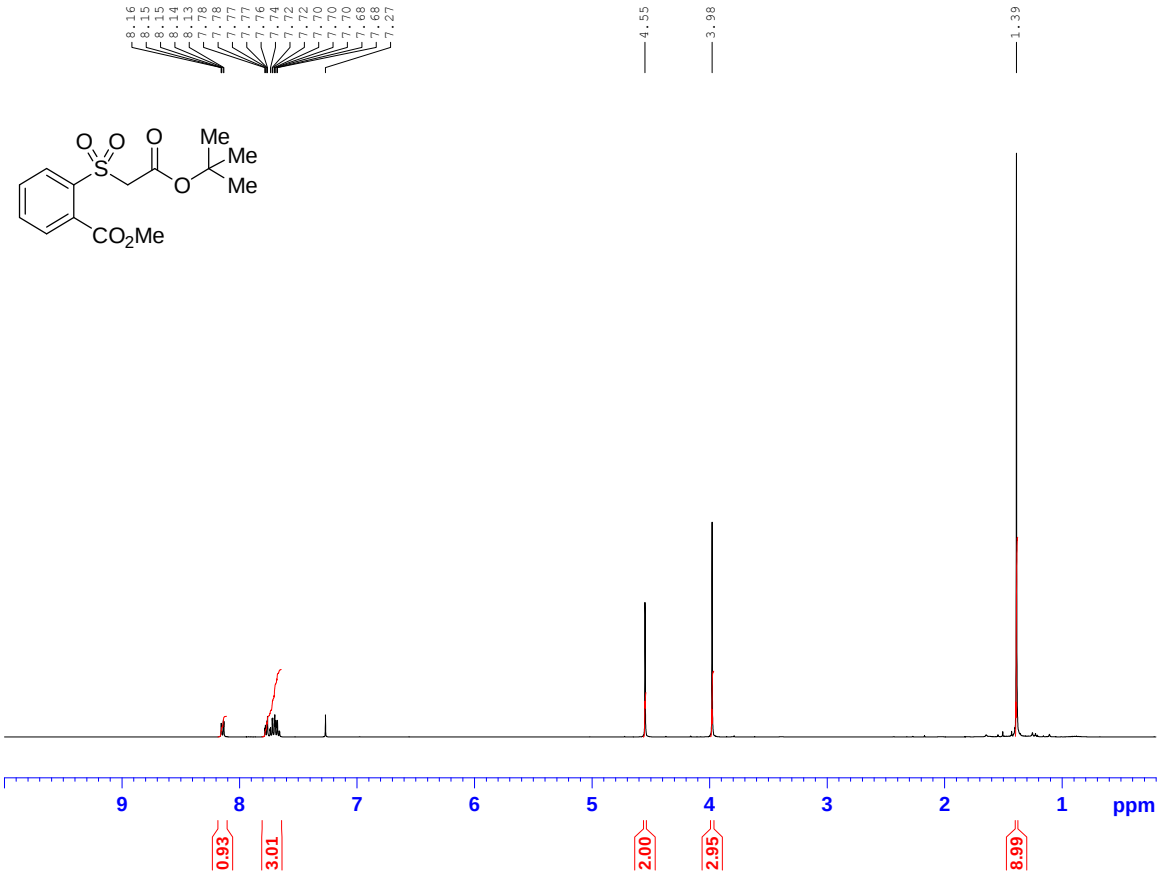
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm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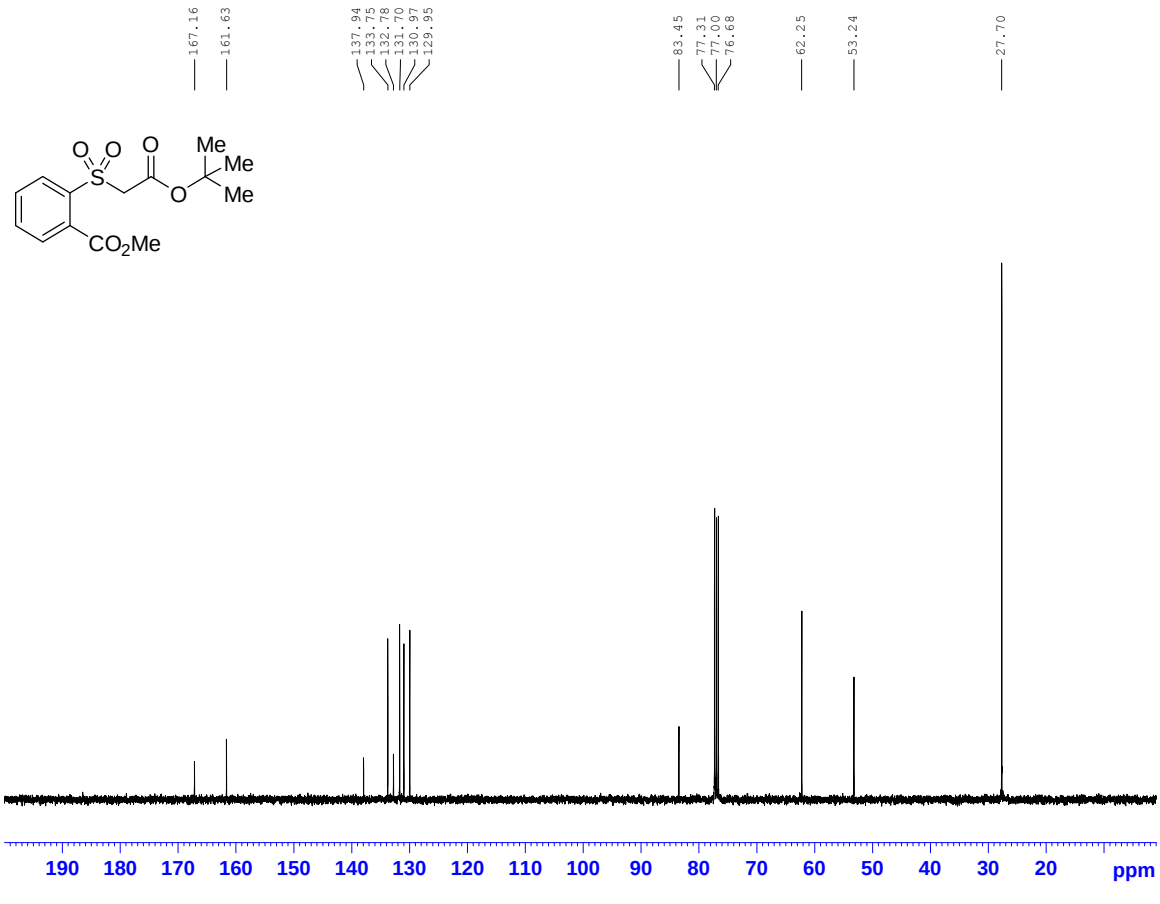
8.15
8.15
8.14
8.13
7.78
7.78
7.77
7.76
7.74
7.72
7.72
7.70
7.70
7.70
7.68
7.27
4.55
3.98
1.39
O
O
S
O
O
Me
Me
Me
CO2Me
9
8
7
6
5
4
3
2
1
ppm
0.93
3.01
2.00
2.95
8.99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161.63
137.94
133.75
132.78
131.70
130.97
129.95
83.45
77.31
77.00
76.68
62.25
53.24
27.70
O
O
S
O
O
Me
Me
Me
CO2Me
190
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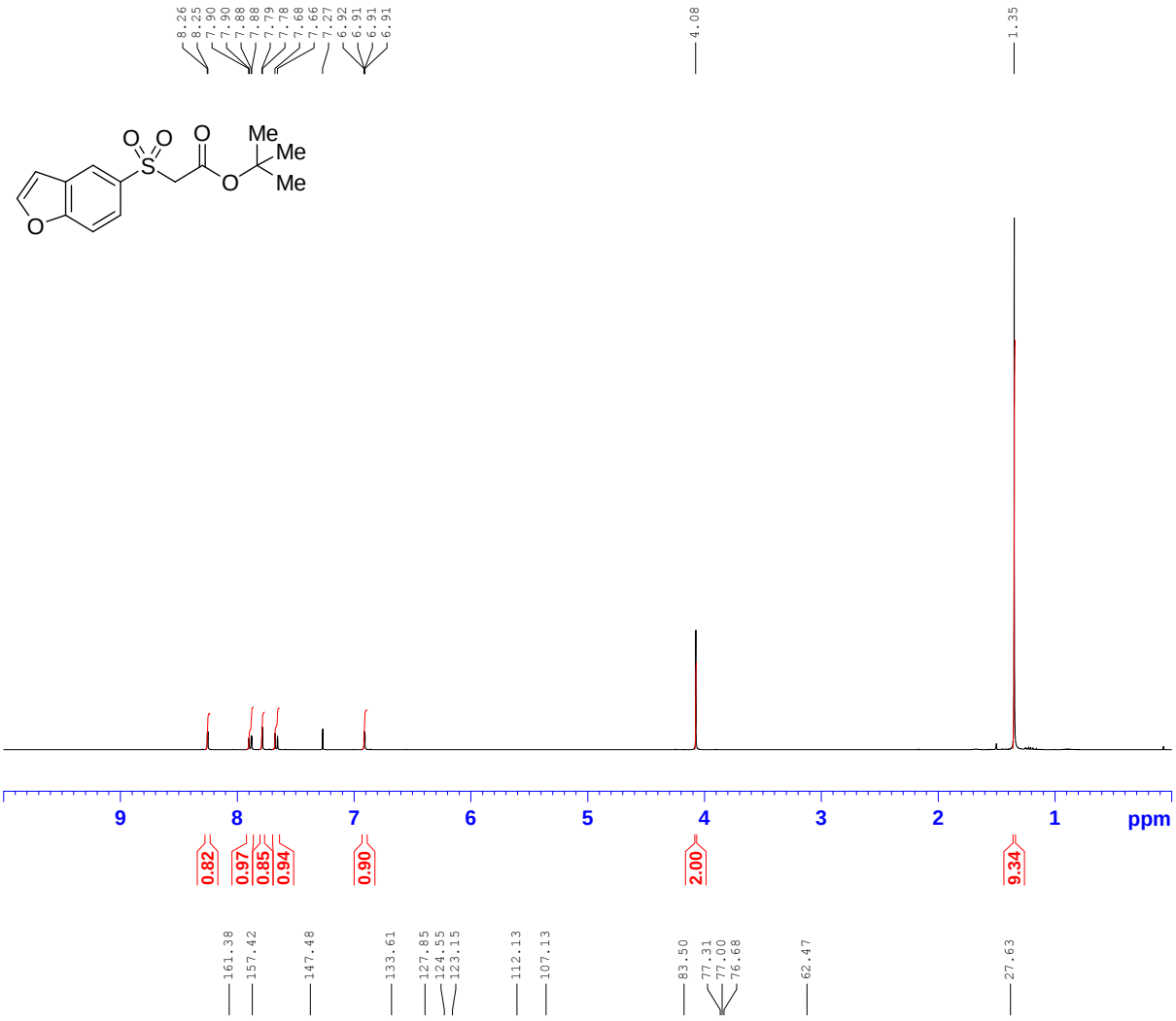
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.88
7.88
7.79
7.78
7.68
7.66
7.27
6.92
6.91
6.91
6.91
4.08
1.35
O
O
S
O
O
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
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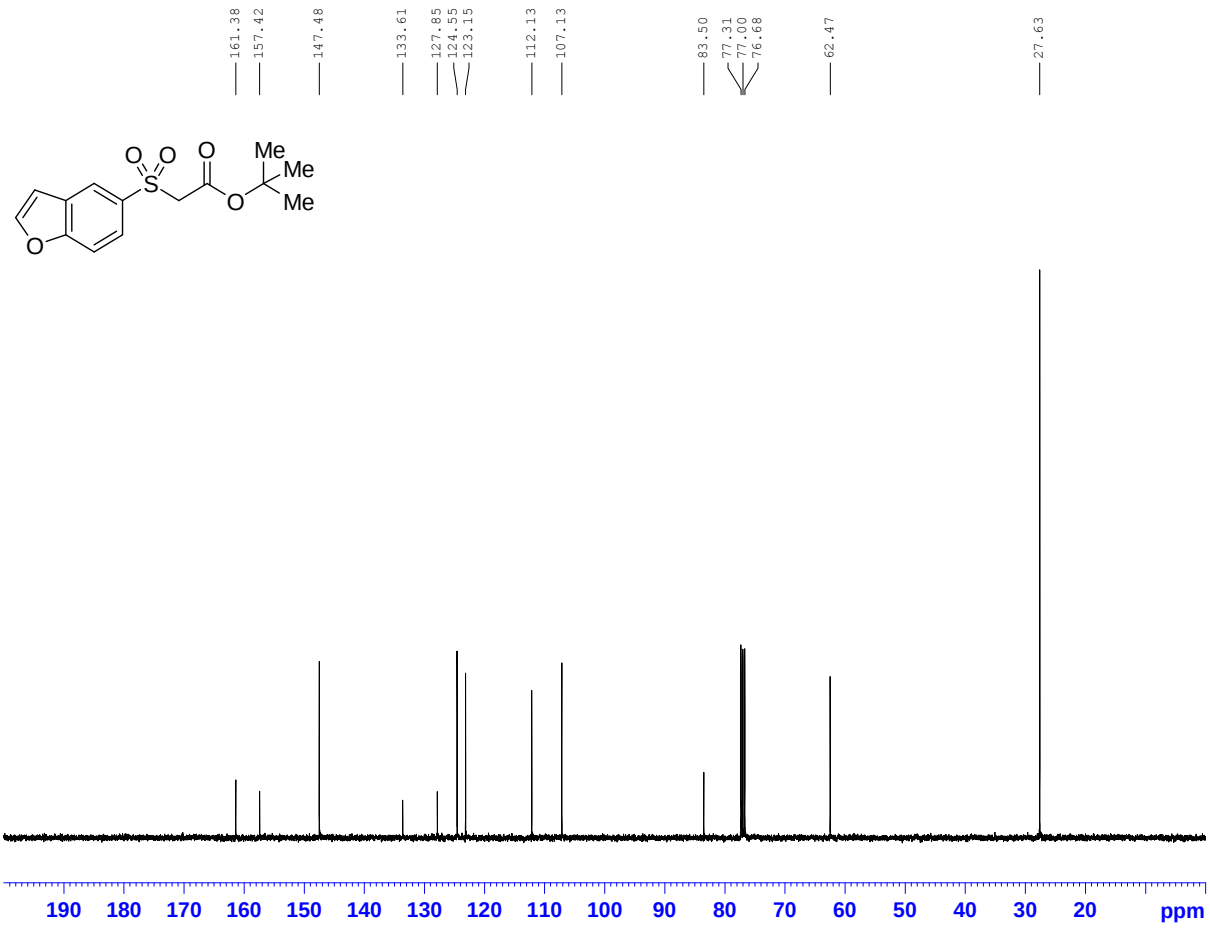
0.97
0.85
0.94
0.90
2.00
9.34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157.42
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133.61
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124.55
123.15
112.13
107.13
83.50
77.31
77.00
76.68
62.47
27.63
O
O
S
O
O
Me
Me
Me
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170
160
150
140
130
120
110
100
90
80
70
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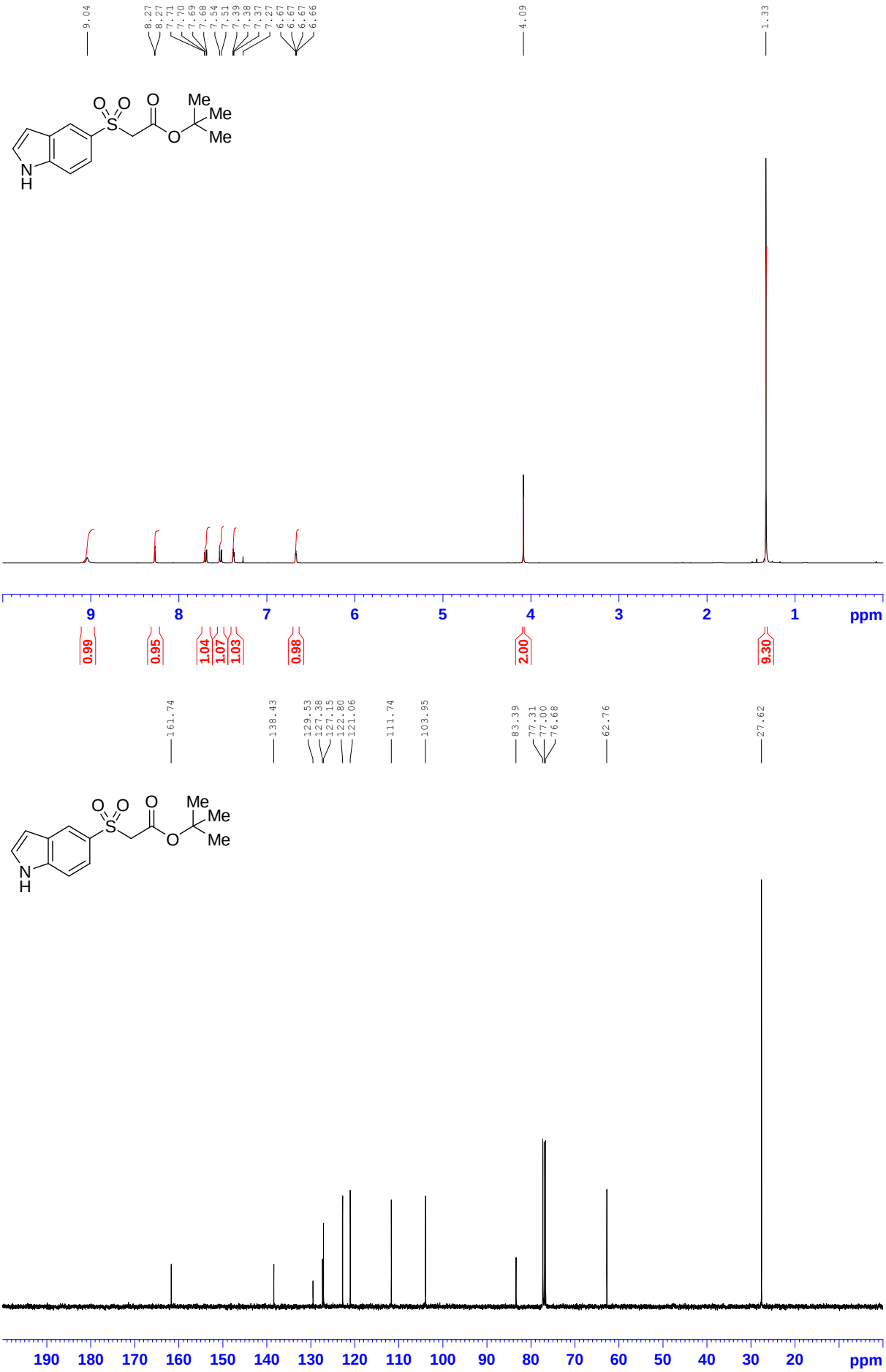
50
40
30
20
ppm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7.39
7.38
7.37
7.27
6.67
6.67
6.67
6.66
4.09
1.33
O
O
S
O
O
Me
Me
Me
N
H
9
8
7
6
5
4
3
2
1
ppm
0.99
0.95
1.04
1.07
1.03
0.98
2.00
9.30
161.74
138.43
129.53
127.38
127.15
122.80
121.06
111.74
103.95
83.39
77.31
77.00
76.68
62.76
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160
150
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120
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80
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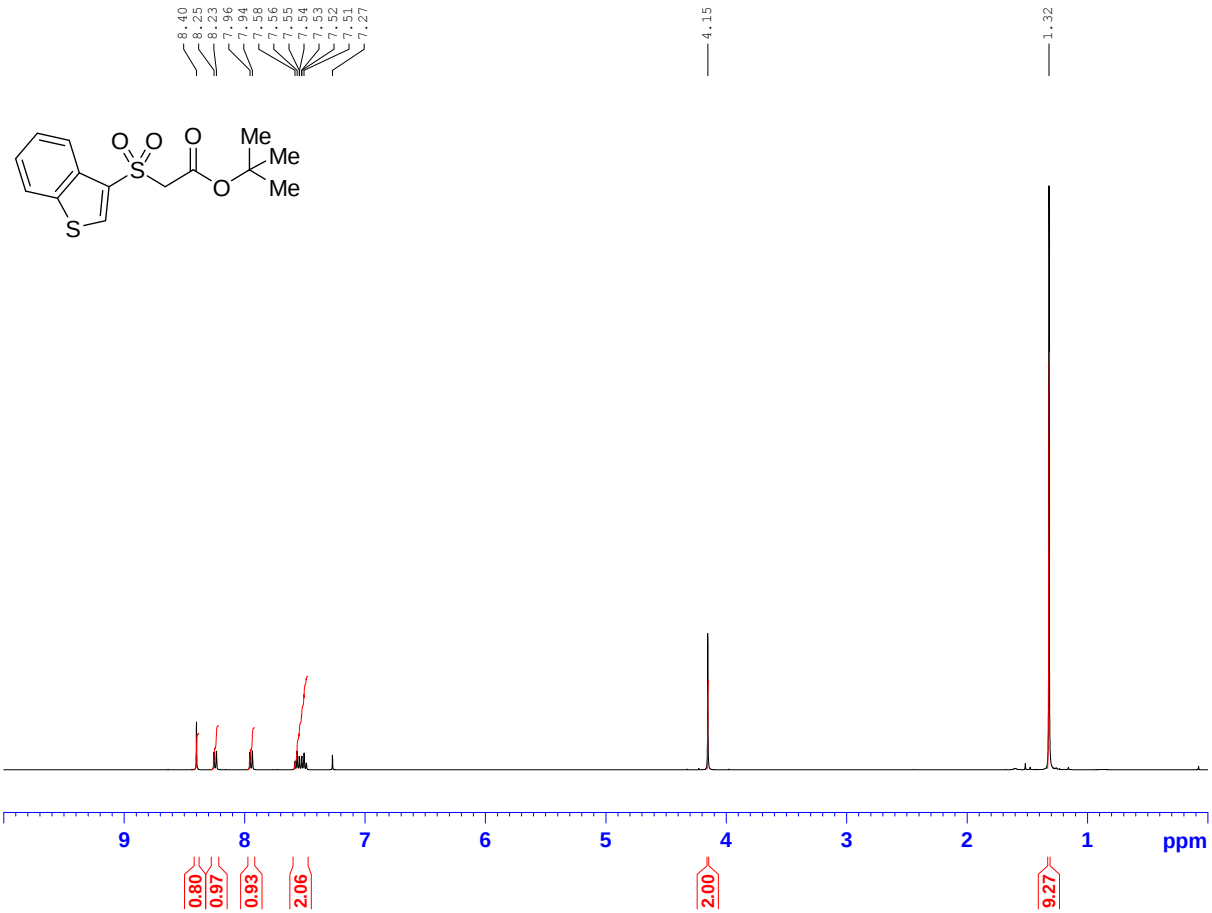
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7.55
7.54
7.53
7.52
7.51
7.27
4.15
1.32
O
O
S
O
O
Me
Me
Me
S
9
8
7
6
5
4
3
2
1
ppm
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0.97
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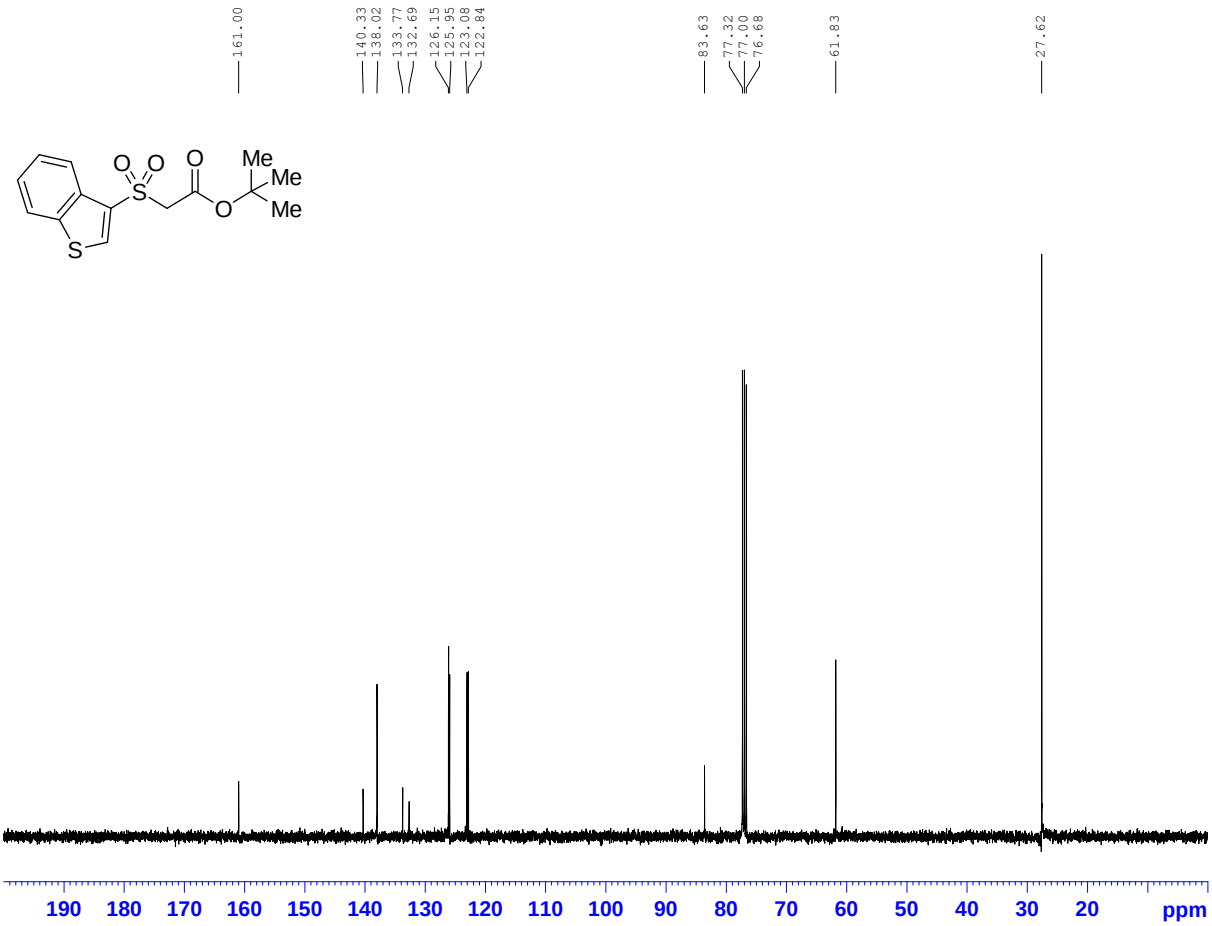
2.06
2.00
9.27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123.08
122.84
83.63
77.32
77.00
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61.83
27.62
O
O
S
O
O
Me
Me
Me
S
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160
150
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130
120
110
100
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80
70
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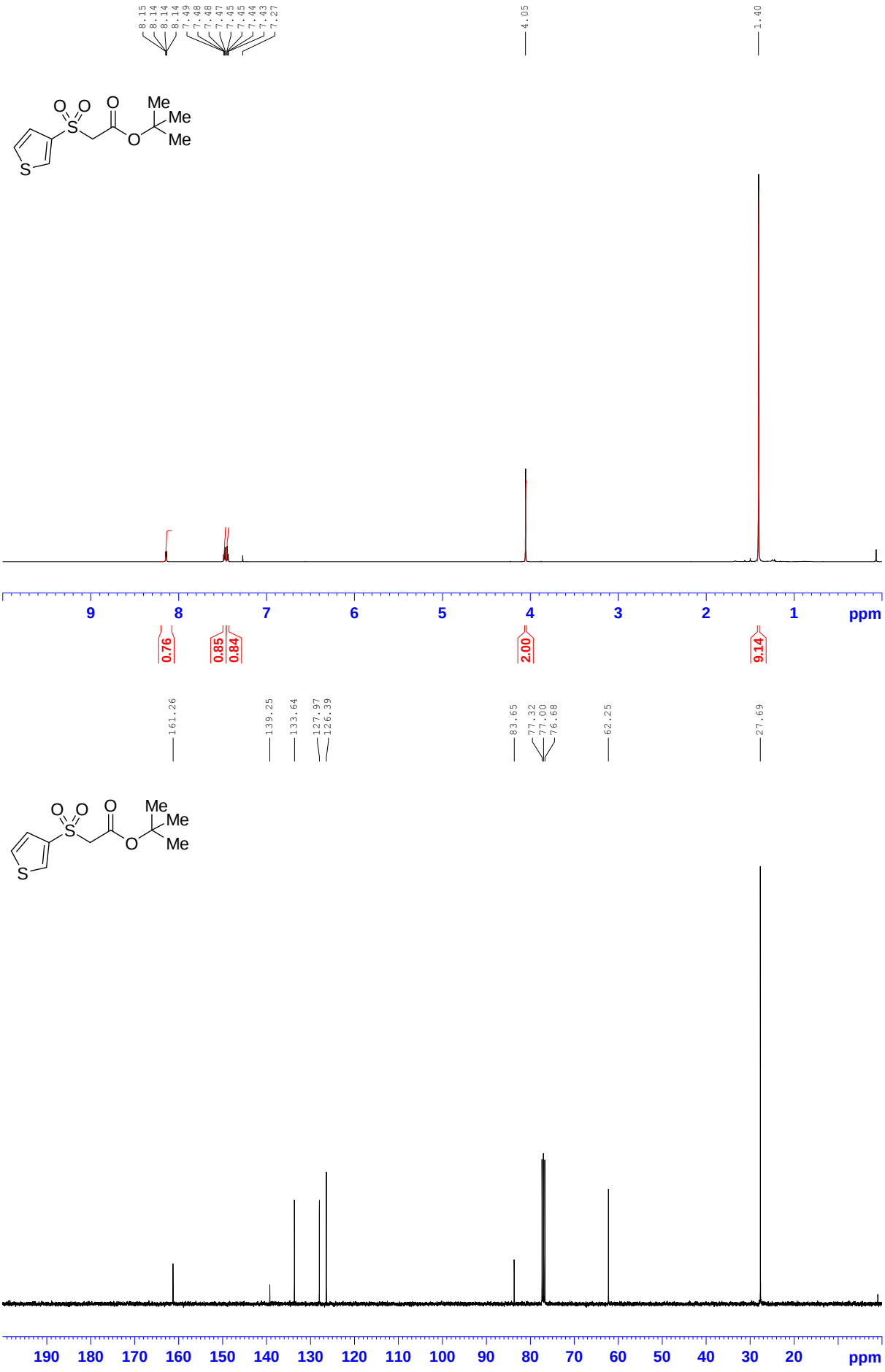
40
30
20
ppm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7.47
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7.45
7.44
7.43
7.27
4.05
1.40
O
O
S
O
O
Me
Me
Me
S
9
8
7
6
5
4
3
2
1
ppm
0.76
0.85
0.84
2.00
9.14
161.26
139.25
133.64
127.97
126.39
83.65
77.32
77.00
76.68
62.25
27.69
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160
150
140
130
120
110
100
90
80
70
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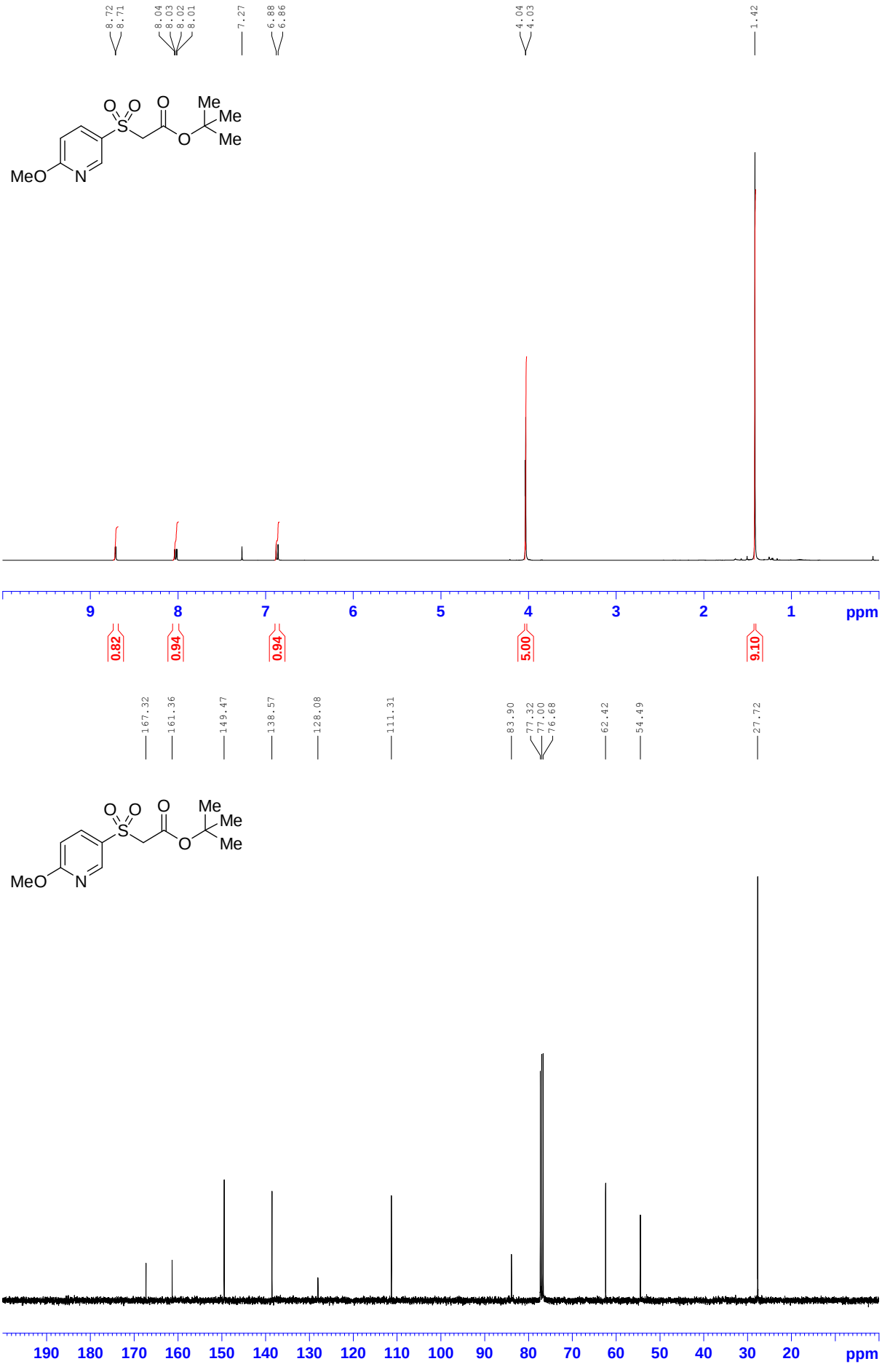
50
40
30
20
ppm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6.86
4.04
4.03
1.42
O
O
S
O
O
Me
Me
Me
MeO
N
9
8
7
6
5
4
3
2
1
ppm
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0.94
0.94
5.00
9.10
167.32
161.36
149.47
138.57
128.08
111.31
83.90
77.32
77.00
76.68
62.42
54.49
27.72
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


9.41
9.41
8.83
8.83
8.06
8.06
8.04
8.04
7.95
7.93
7.68
7.66
7.64
7.27
4.18
1.37
O
O
S
O
O
Me
Me
Me
N
Cl
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7
6
5
4
3
2
1
ppm
0.86
1.00
0.98
1.11
1.09
2.00
9.02
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148.02
145.95
139.31
134.16
133.14
132.86
128.50
128.33
127.52
84.33
77.32
77.00
76.68
62.15
27.68
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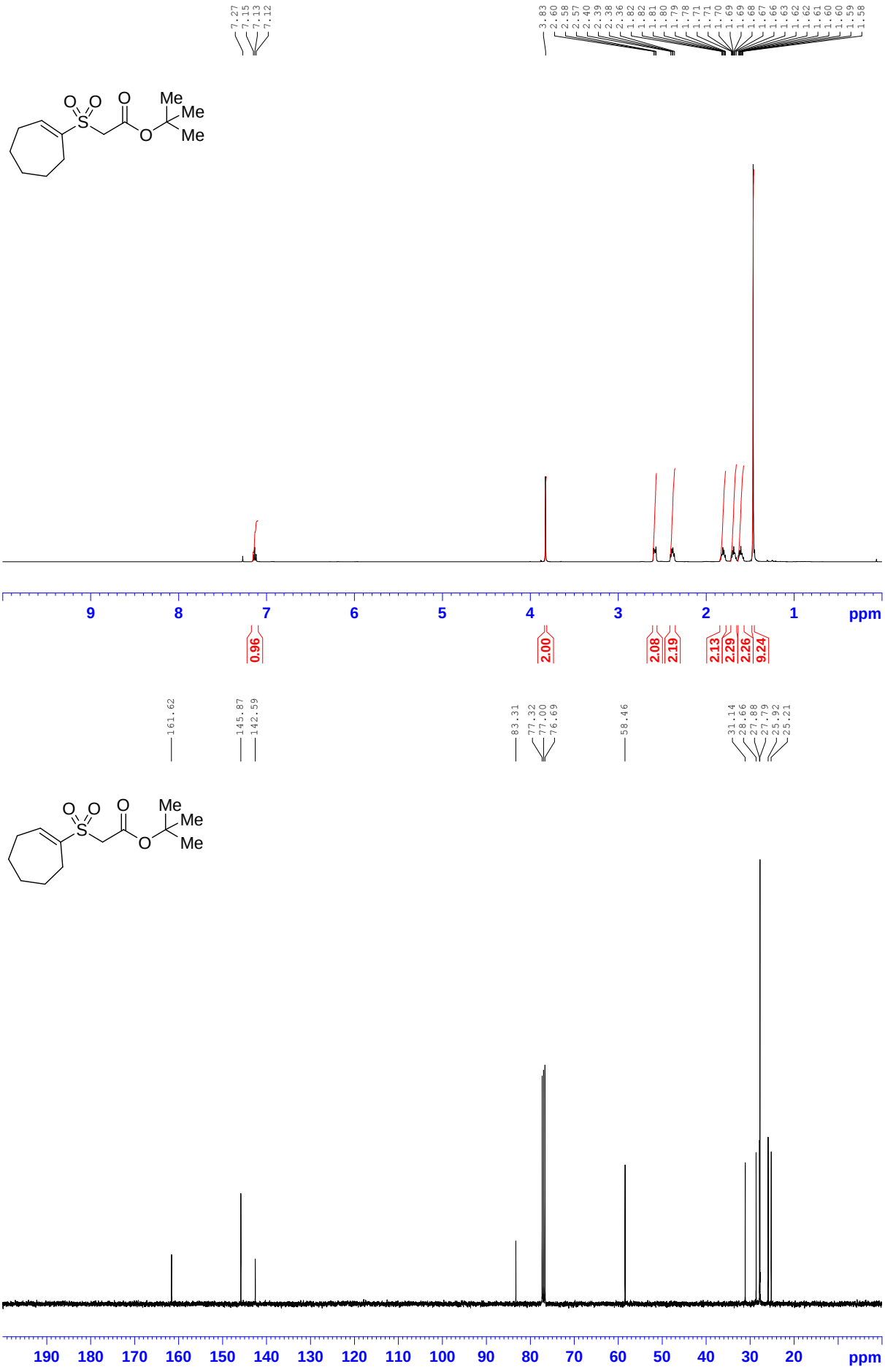
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.12
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2.57
2.40
2.39
2.38
2.36
1.82
1.81
1.80
1.79
1.78
1.71
1.71
1.70
1.69
1.69
1.68
1.67
1.66
1.63
1.62
1.62
1.61
1.60
1.60
1.59
1.58
O
O
S
O
O
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.96
2.00
2.08
2.19
2.13
2.29
2.26
9.24
161.62
145.87
142.59
83.31
77.32
77.00
76.69
58.46
31.14
28.66
27.88
27.79
25.92
25.21
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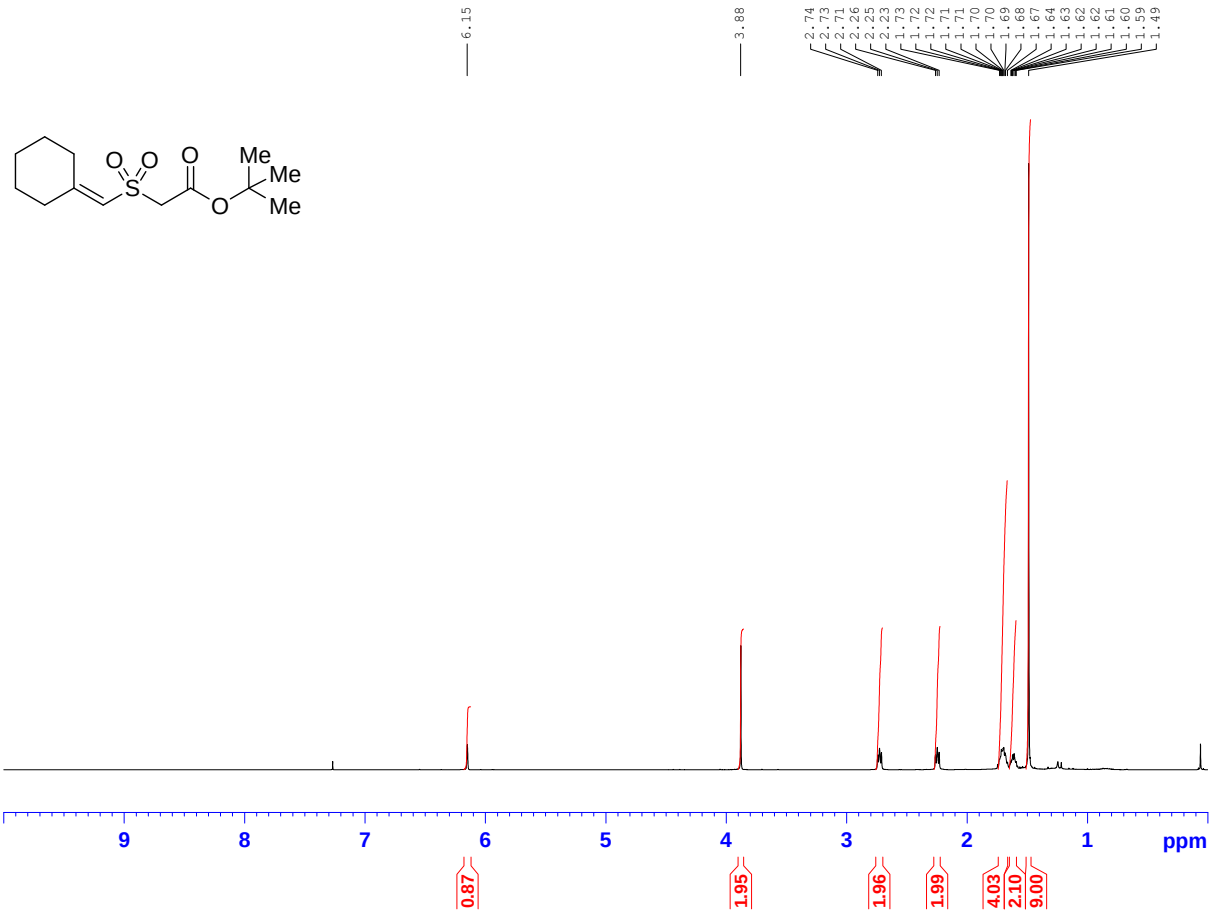
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


6.15
3.88
2.74
2.73
2.71
2.26
2.25
2.23
1.73
1.72
1.71
1.71
1.70
1.70
1.69
1.68
1.67
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.49
O
O
S
O
O
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
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1.96
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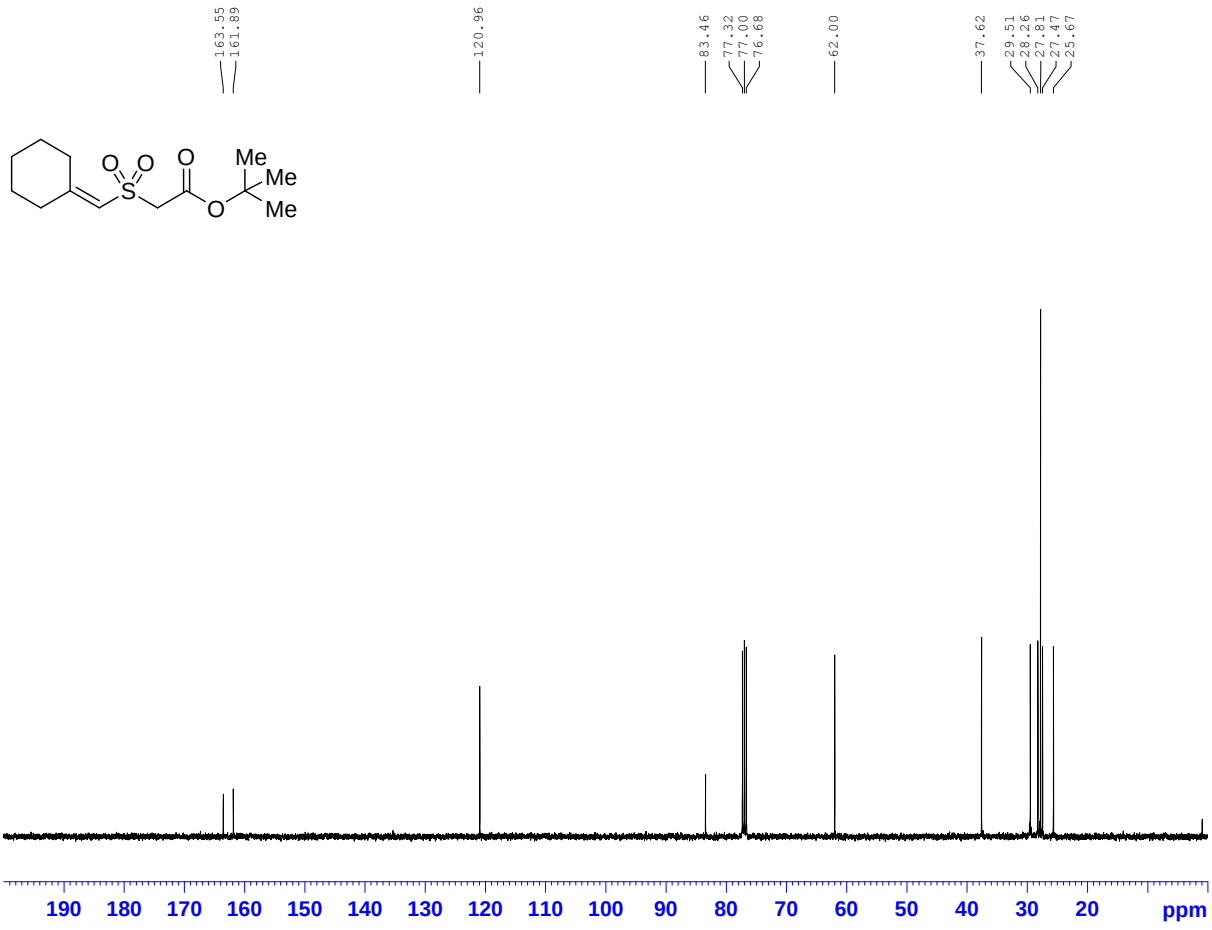
4.03
2.10
9.00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76.68
62.00
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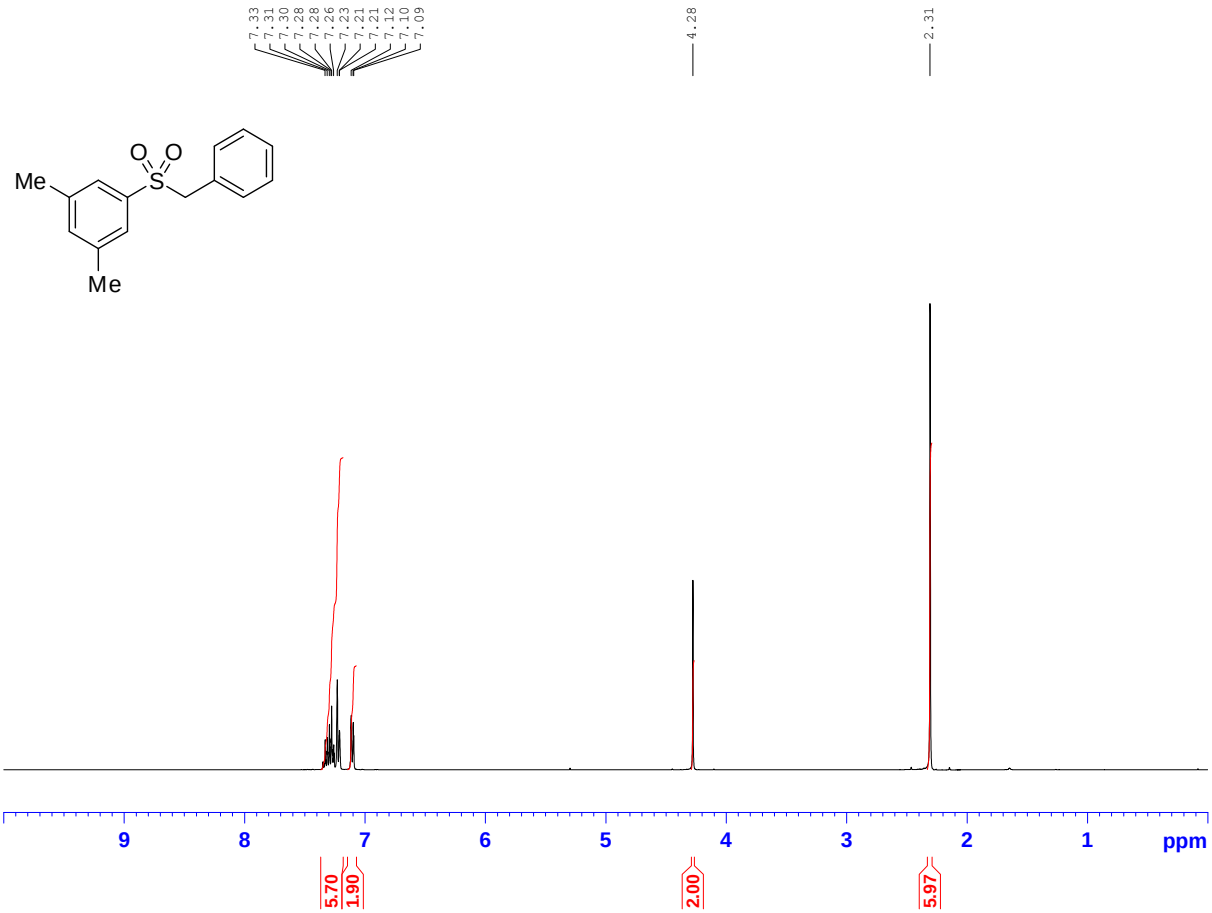
29.51
28.26
27.81
27.47
25.67
O
O
S
O
O
Me
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.26
7.23
7.21
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7.12
7.10
7.09
4.28
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Me
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8
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5
4
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ppm
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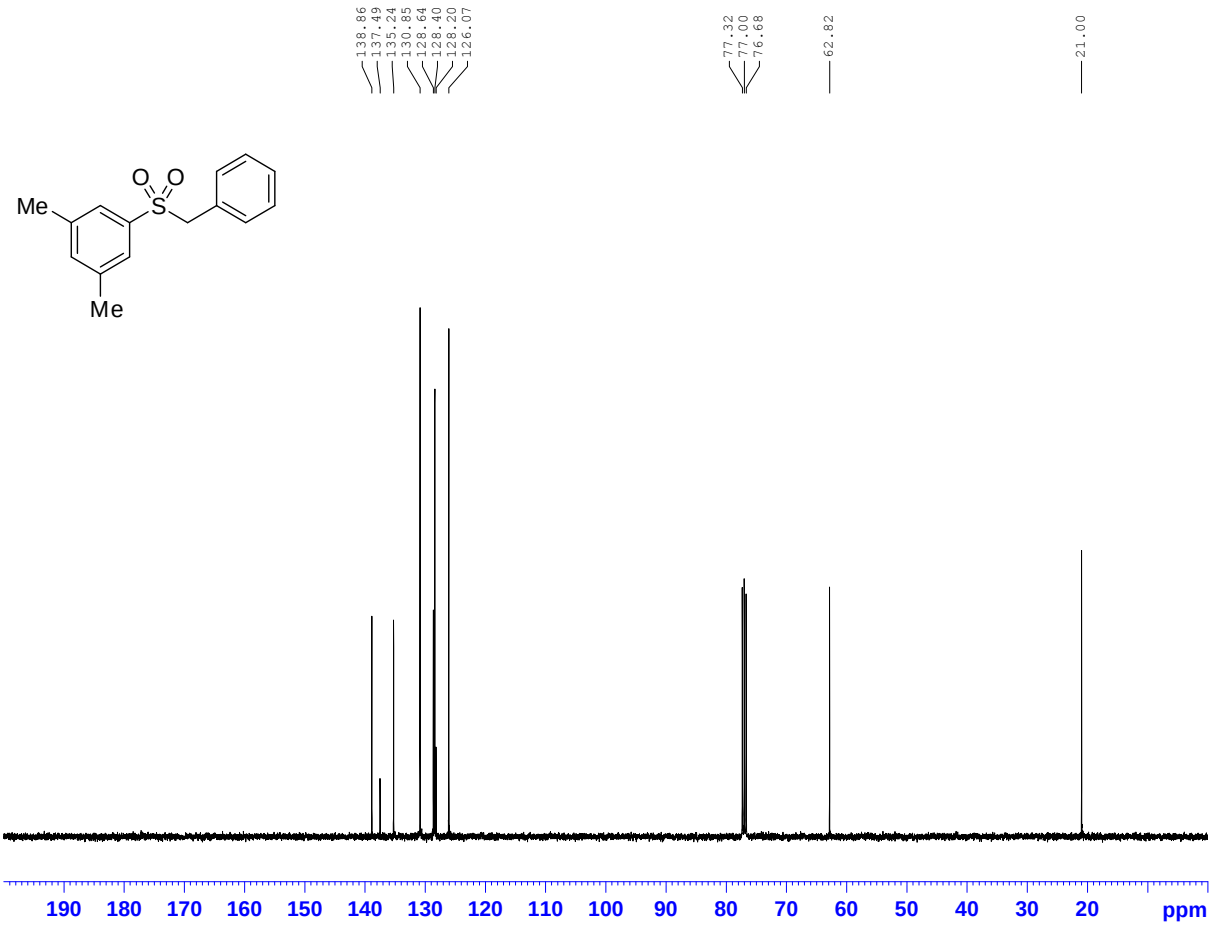
2.00
5.97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128.20
126.07
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77.00
76.68
62.82
21.00
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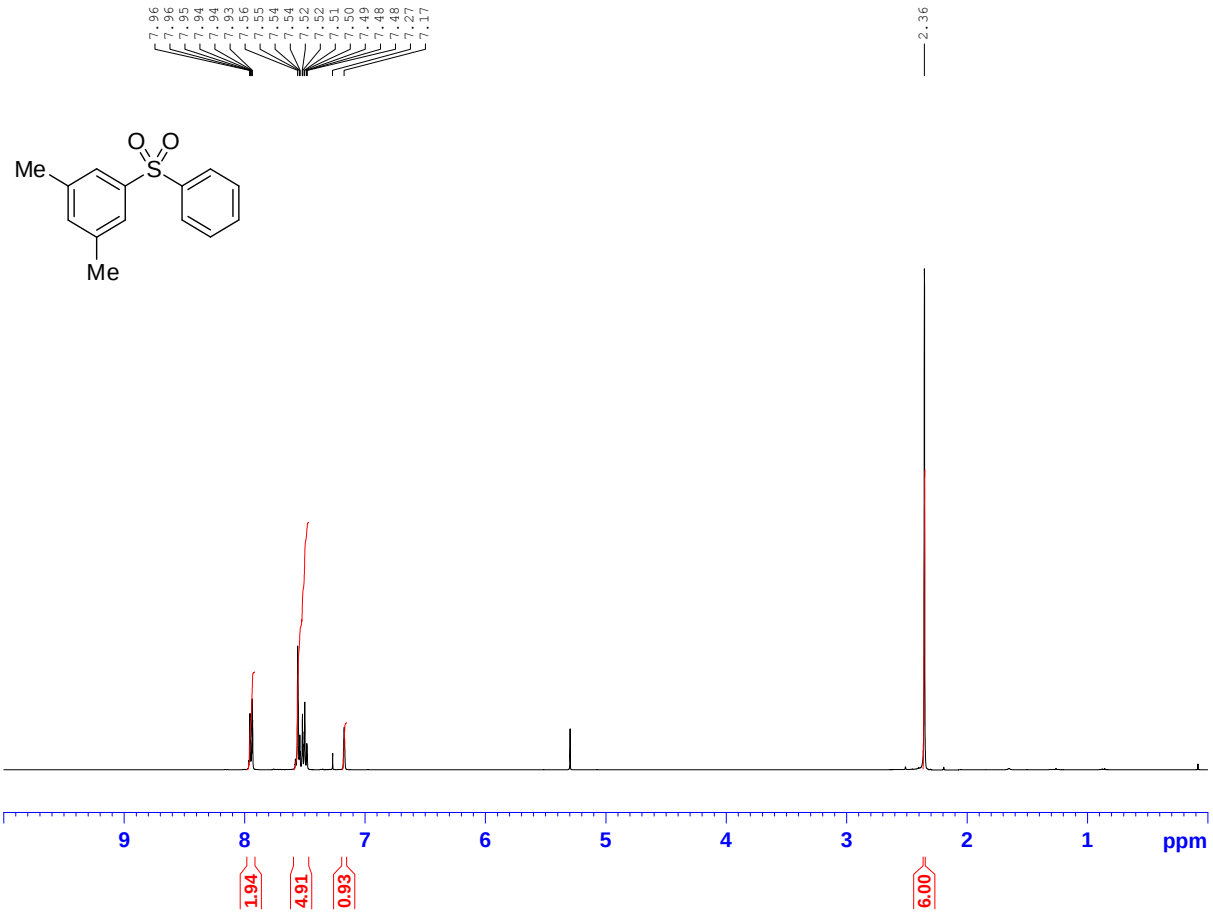
20
ppm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7.56
7.55
7.54
7.54
7.52
7.52
7.51
7.50
7.49
7.48
7.48
7.27
7.17
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8
7
6
5
4
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1
ppm
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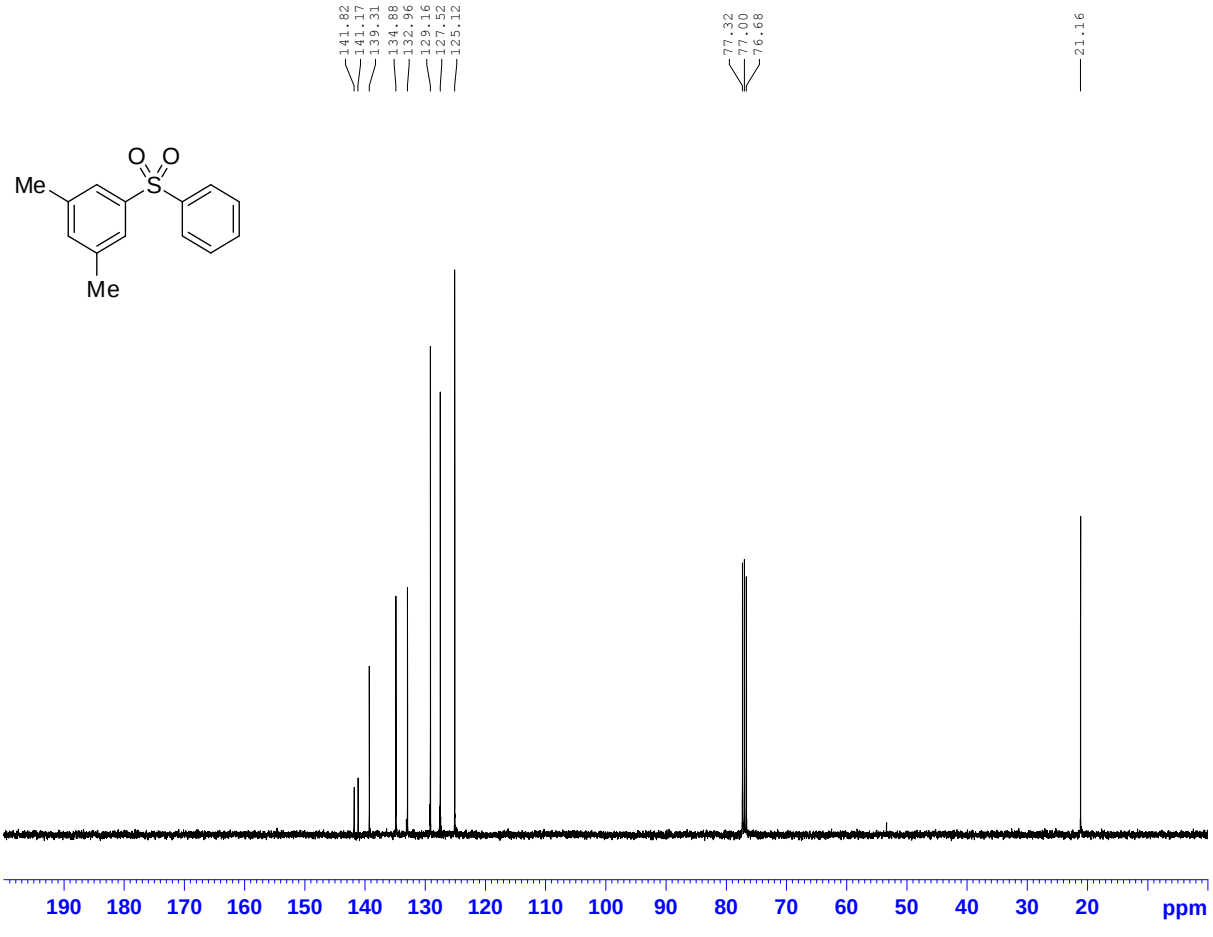
4.91
0.93
6.00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129.16
127.52
125.12
77.32
77.00
76.68
21.16
Me
Me
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160
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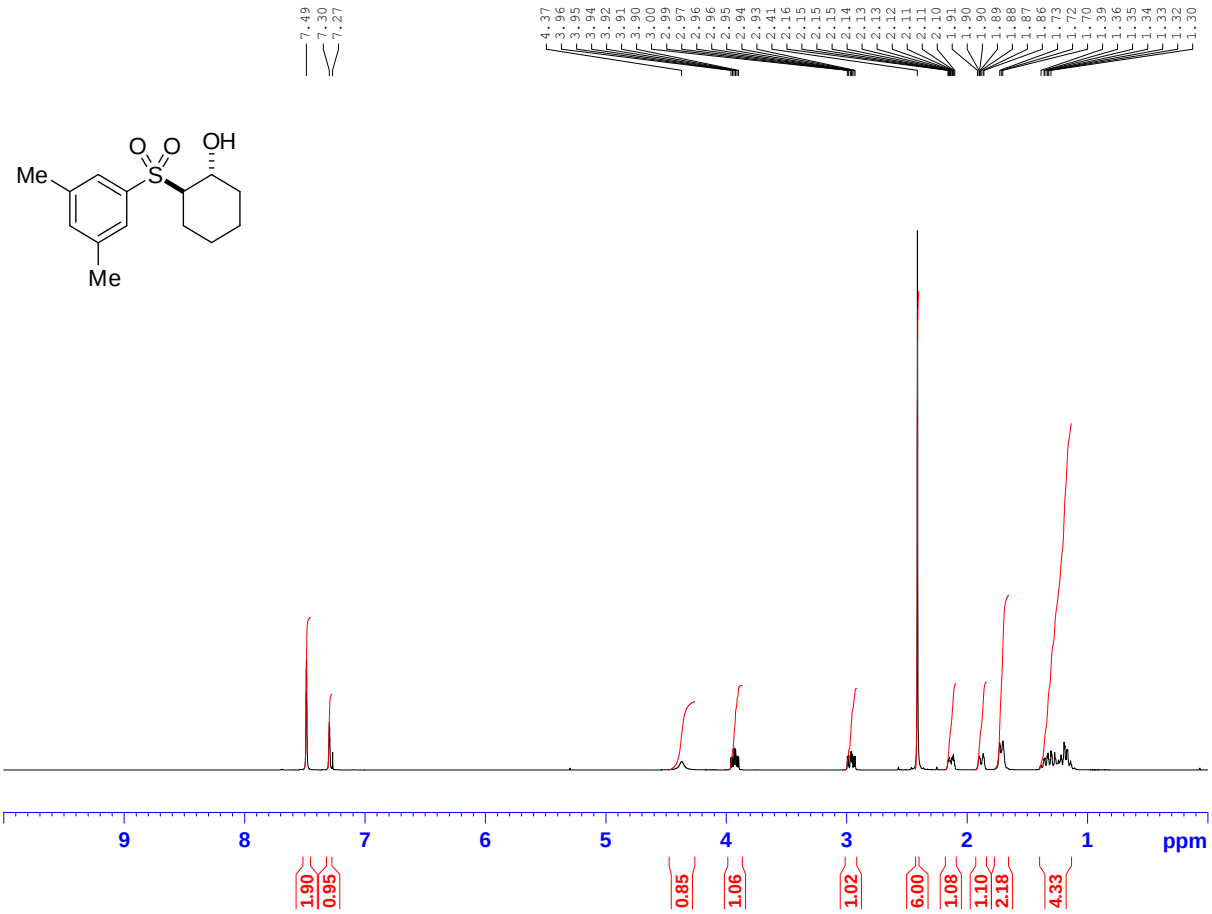
ppm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7.30
7.27
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3.95
3.94
3.92
3.91
3.90
3.00
2.99
2.97
2.96
2.96
2.95
2.94
2.93
2.41
2.16
2.15
2.15
2.15
2.14
2.13
2.13
2.12
2.11
2.11
2.10
1.91
1.90
1.90
1.89
1.88
1.87
1.86
1.73
1.72
1.70
1.39
1.36
1.35
1.34
1.33
1.32
1.30
O
O
OH
S
Me
Me
9
8
7
6
5
4
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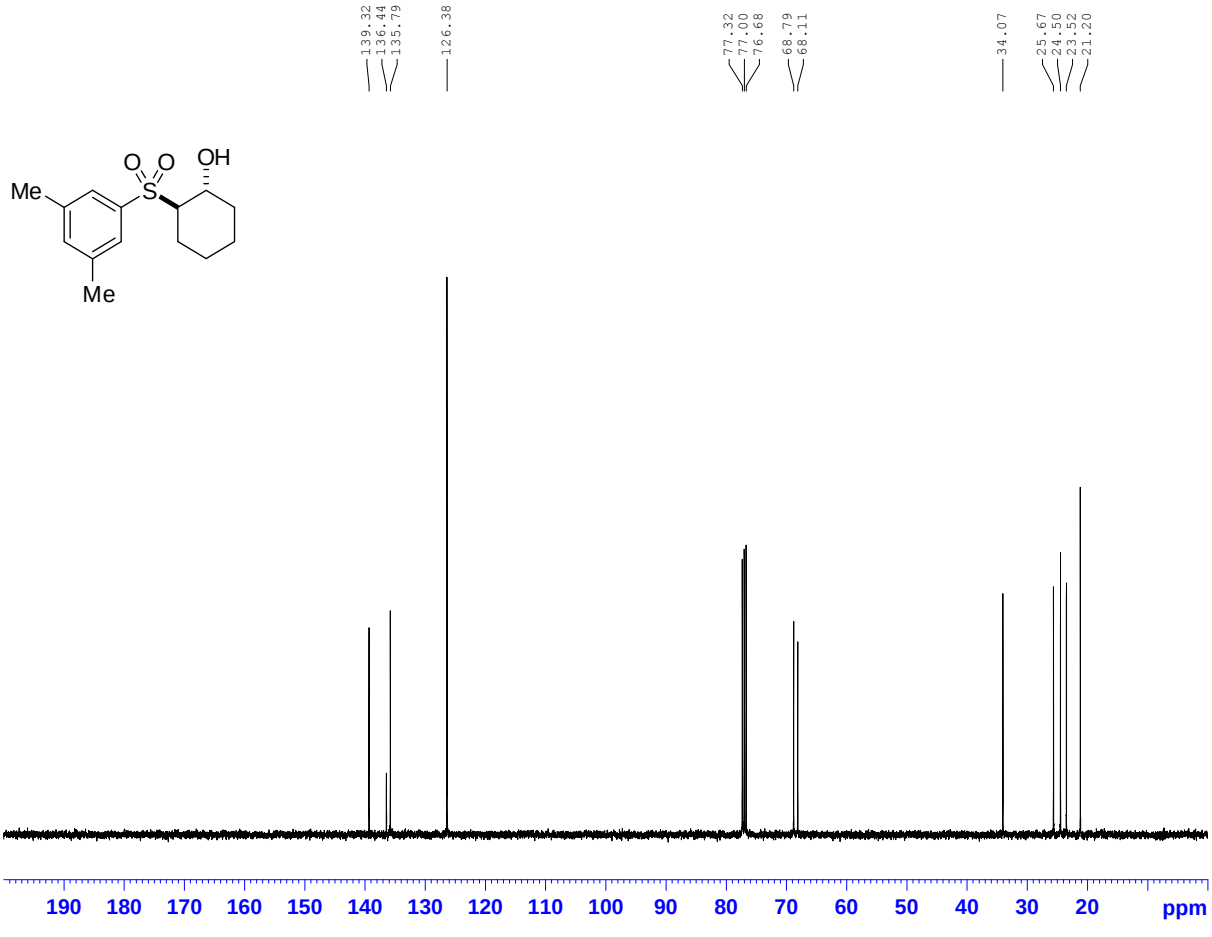
1.06
1.02
6.00
1.08
1.10
2.18
4.33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68.79
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34.07
25.67
24.50
23.52
21.20
O
O
OH
S
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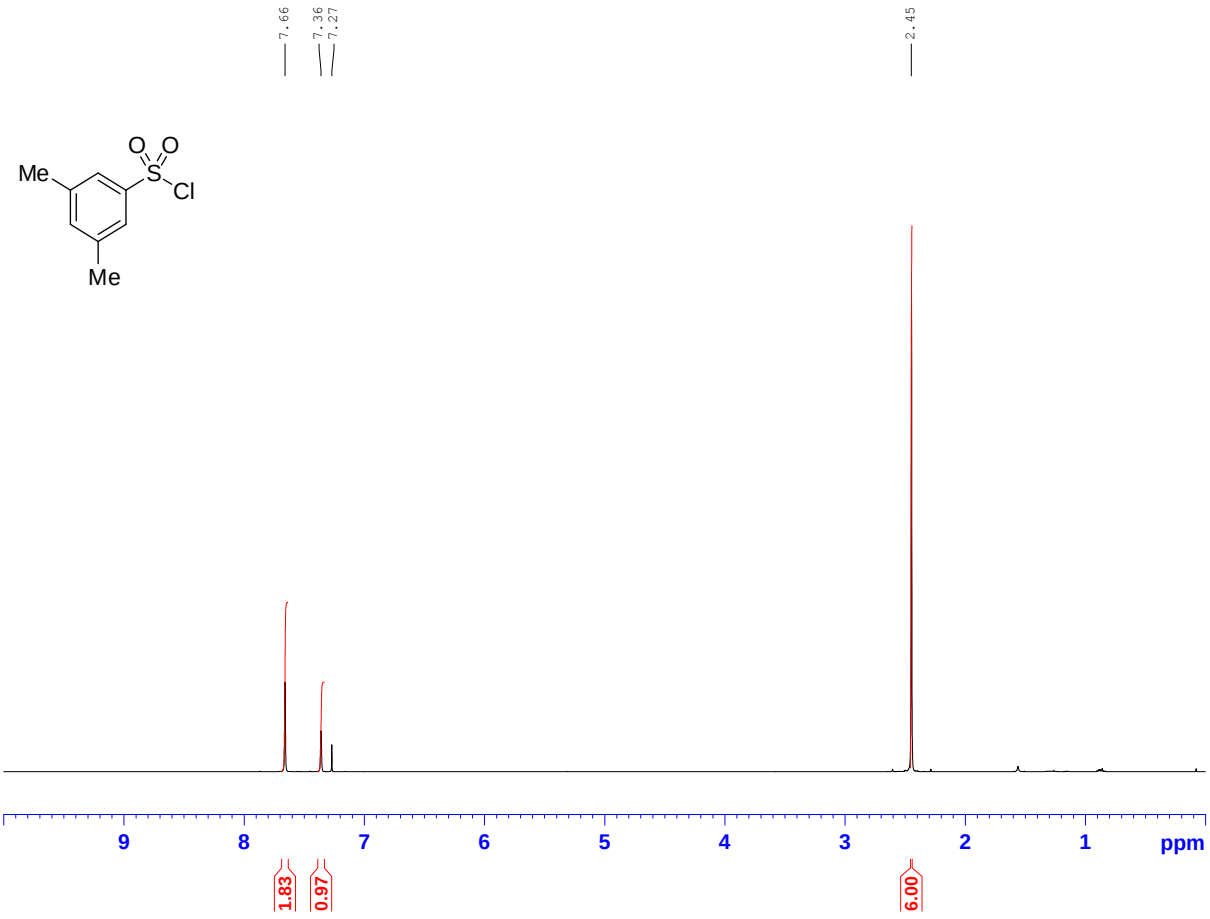
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7.36
7.27
2.45
Me
Me
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O
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Cl
9
8
7
6
5
4
3
2
1
ppm
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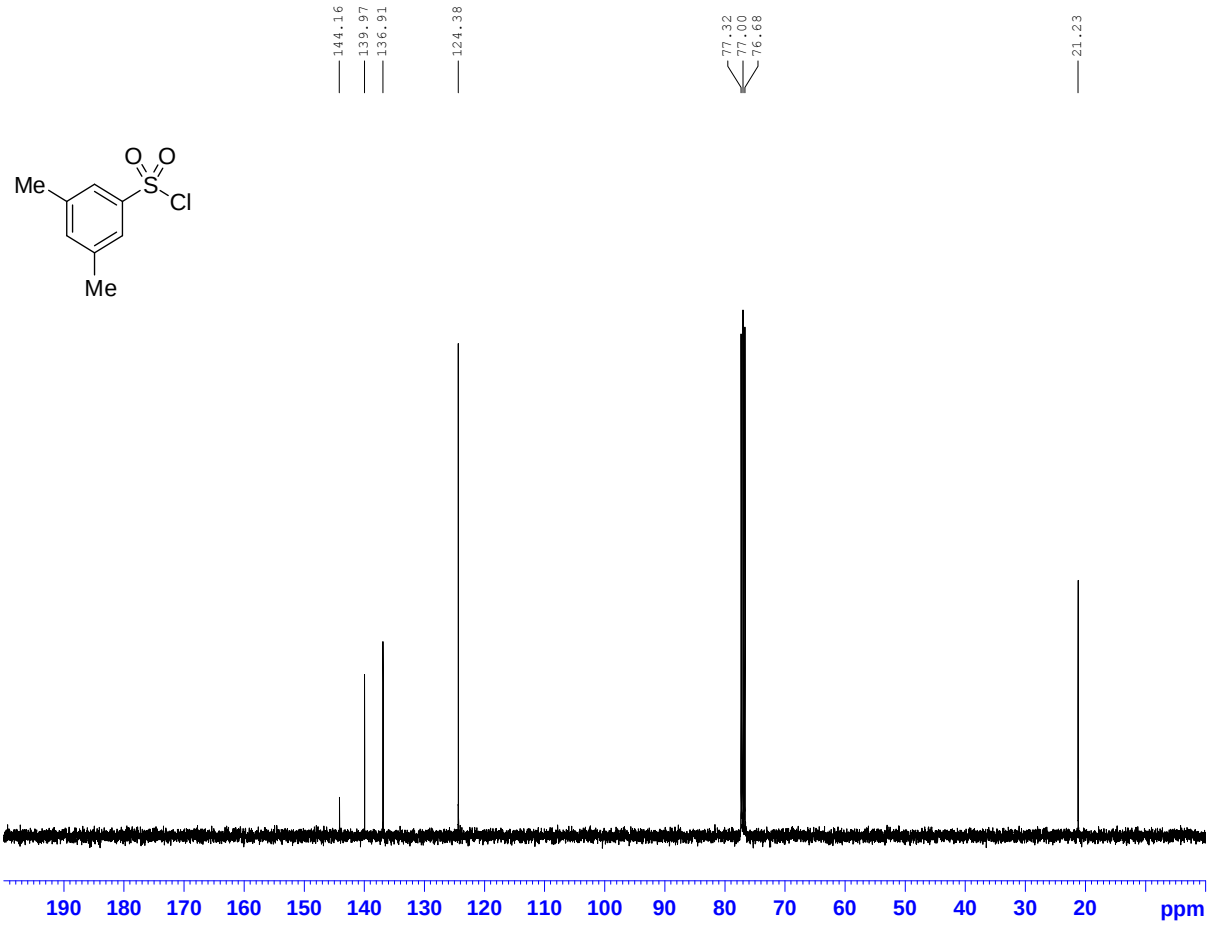
0.97
6.00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136.91
124.38
77.32
77.00
76.68
21.23
Me
Me
O
O
S
Cl
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160
150
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130
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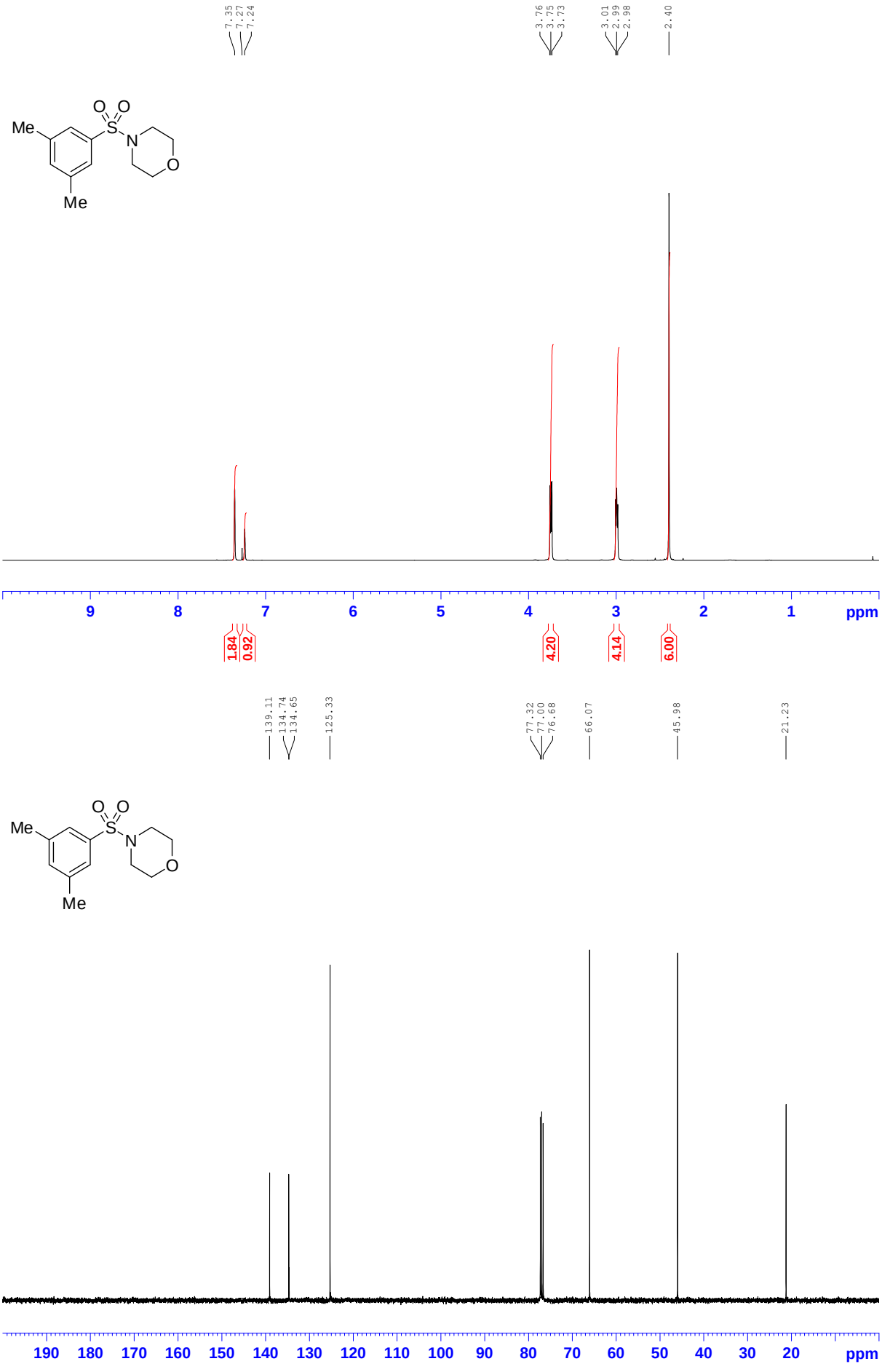
30
20
ppm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7.27
7.24
3.76
3.75
3.73
3.01
2.99
2.98
2.40
Me
Me
O
O
S
N
O
9
8
7
6
5
4
3
2
1
ppm
1.84
0.92
4.20
4.14
6.00
139.11
134.74
134.65
125.33
77.32
77.00
76.68
66.07
45.98
21.23
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170
160
150
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130
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110
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30
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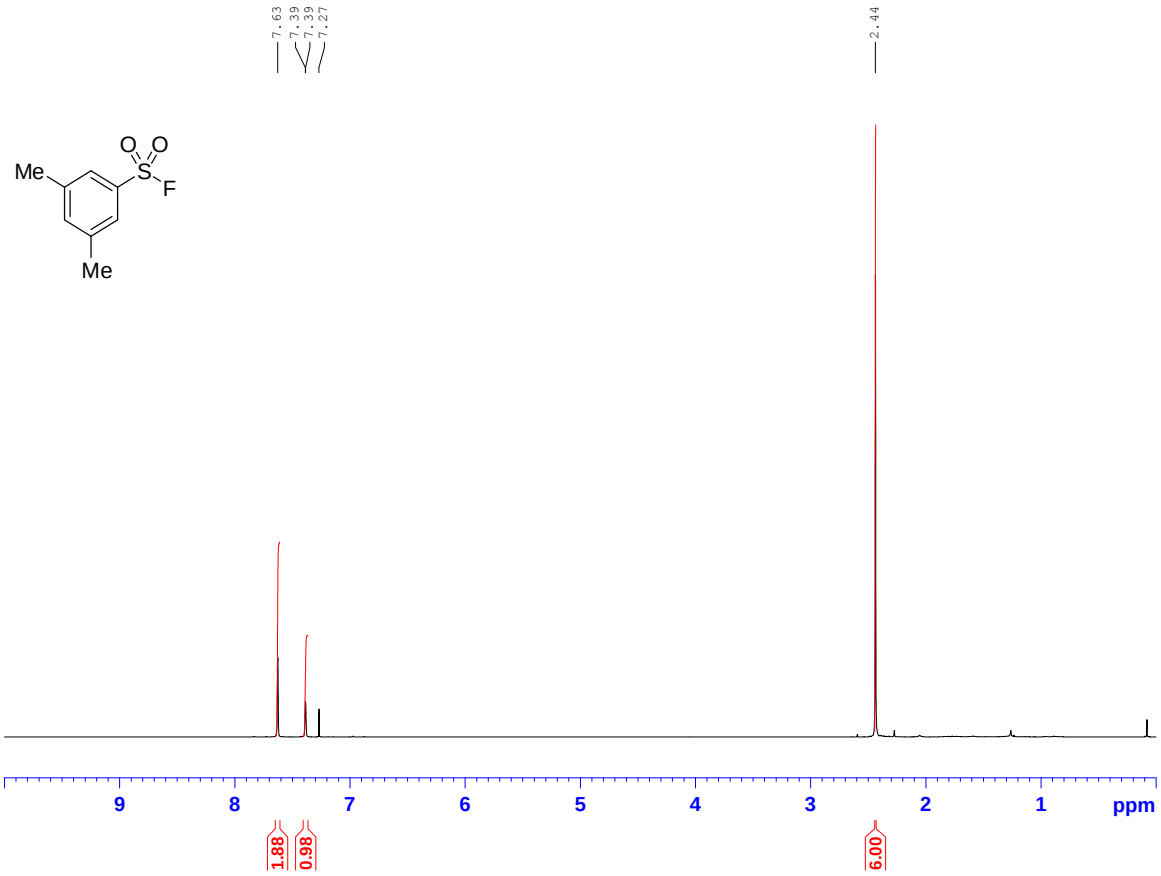
ppm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7.39
7.39
7.27
2.44
Me
Me
O
O
S
F
9
8
7
6
5
4
3
2
1
ppm
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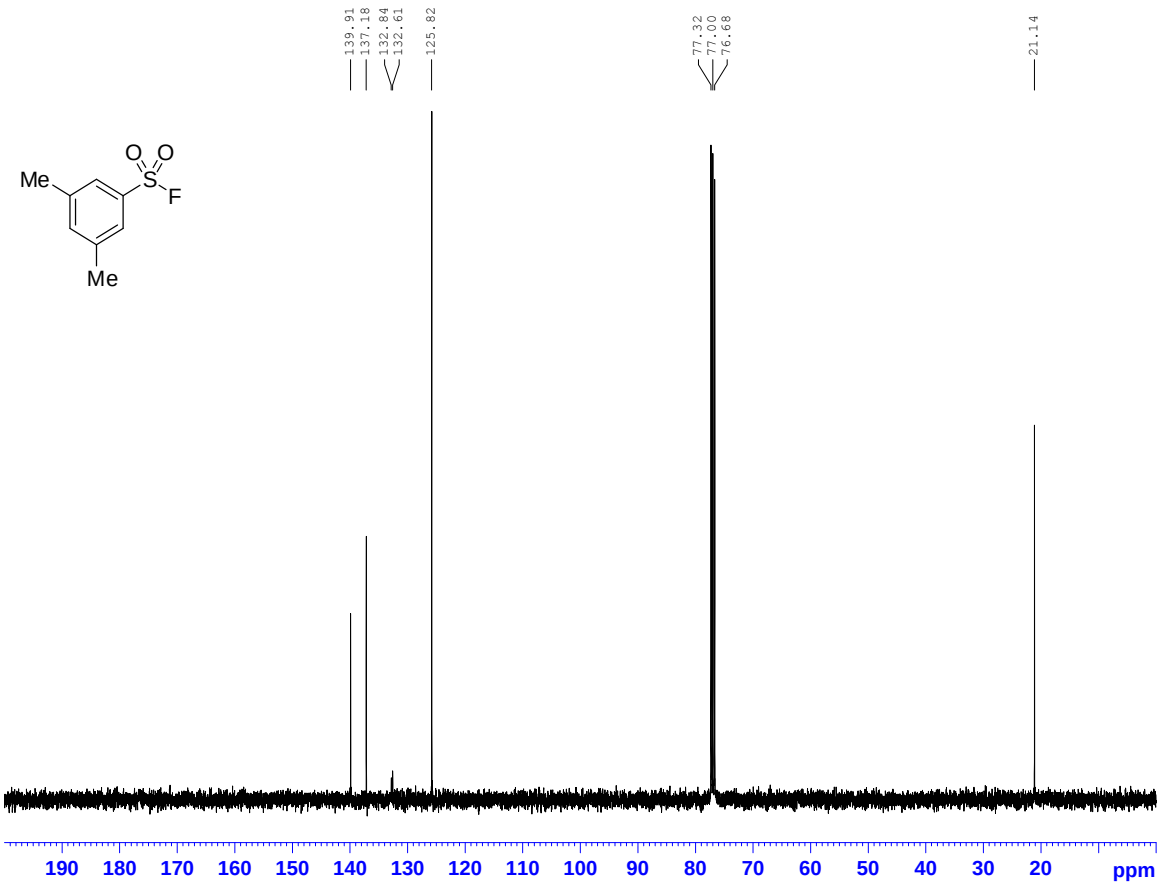
6.00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132.61
125.82
77.32
77.00
76.68
21.14
Me
Me
O
O
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170
160
150
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130
120
110
100
90
80
70
60
50
40
30
20
ppm


65.73
O
O
S
F
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40
20
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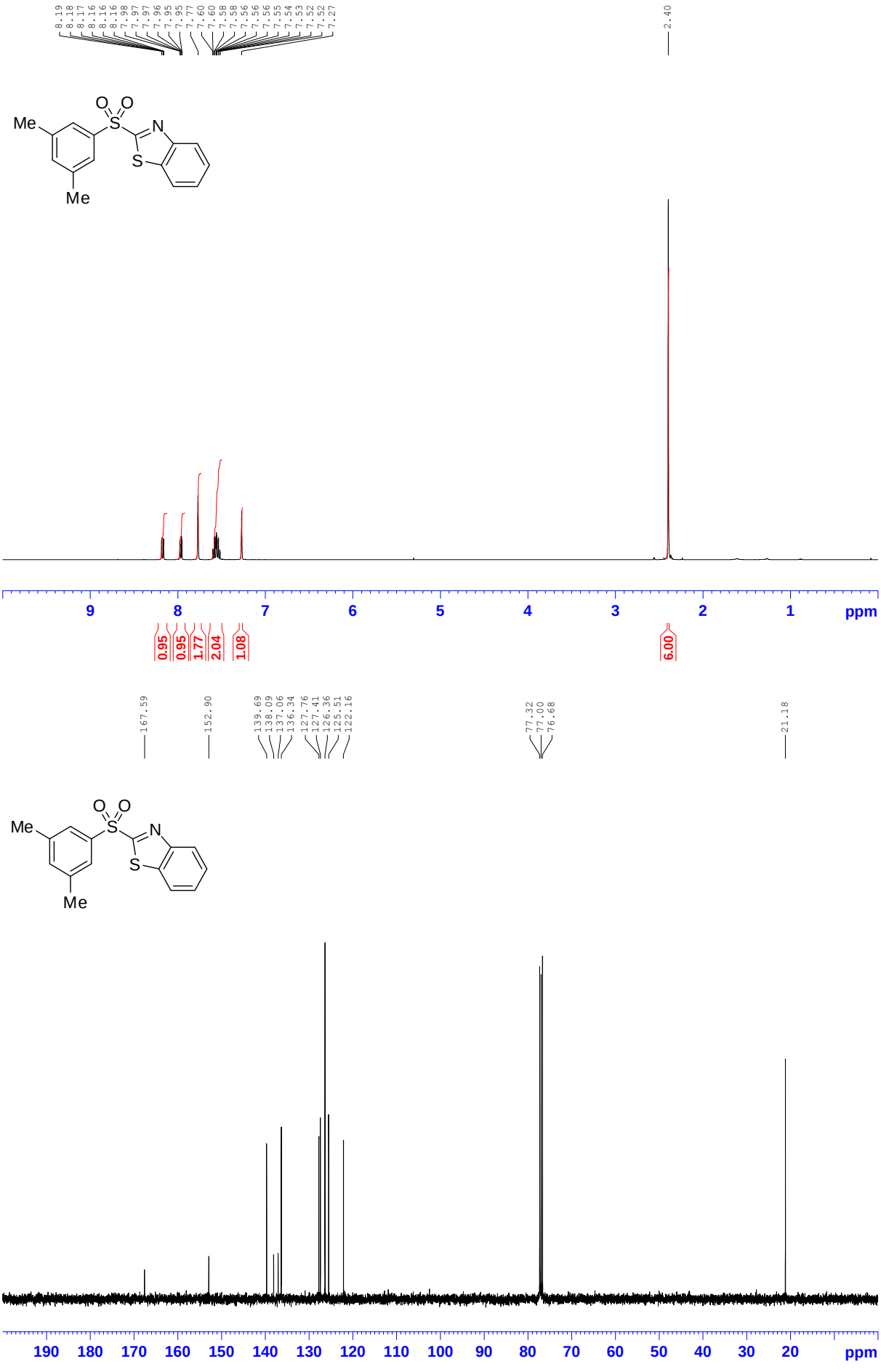
-80
-100
-120
-140
-160
-180
ppm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7.98
7.97
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7.96
7.95
7.95
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7.60
7.58
7.58
7.56
7.56
7.56
7.55
7.54
7.53
7.52
7.52
7.27
2.40
Me
Me
O
O
S
N
S
9
8
7
6
5
4
3
2
1
ppm
0.95
0.95
1.77
2.04
1.08
6.00
167.59
152.90
139.69
138.09
137.06
136.34
127.76
127.41
126.36
125.51
122.16
77.32
77.00
76.68
21.18
Me
Me
O
O
S
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S
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160
150
140
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120
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80
70
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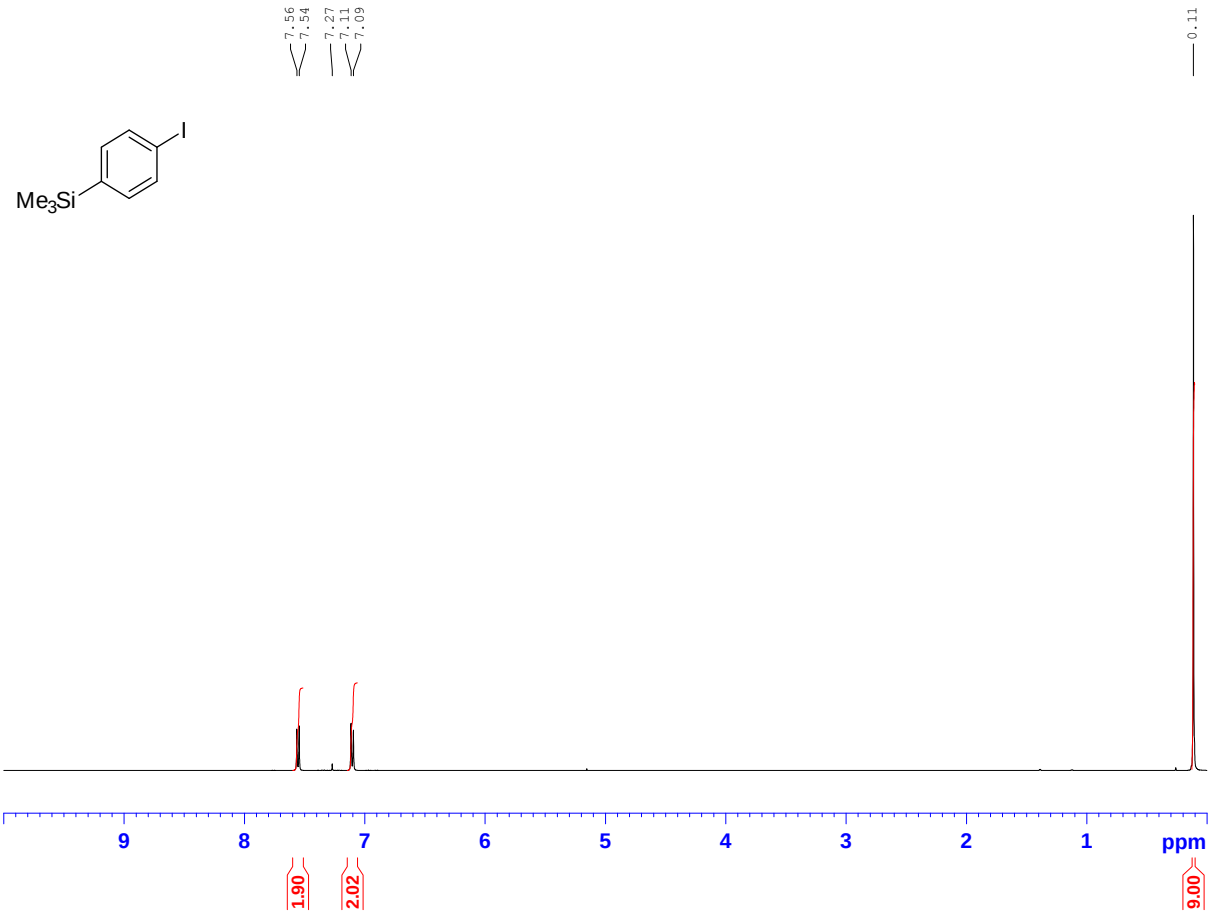
20
ppm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Me3Si
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7
6
5
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2
1
ppm
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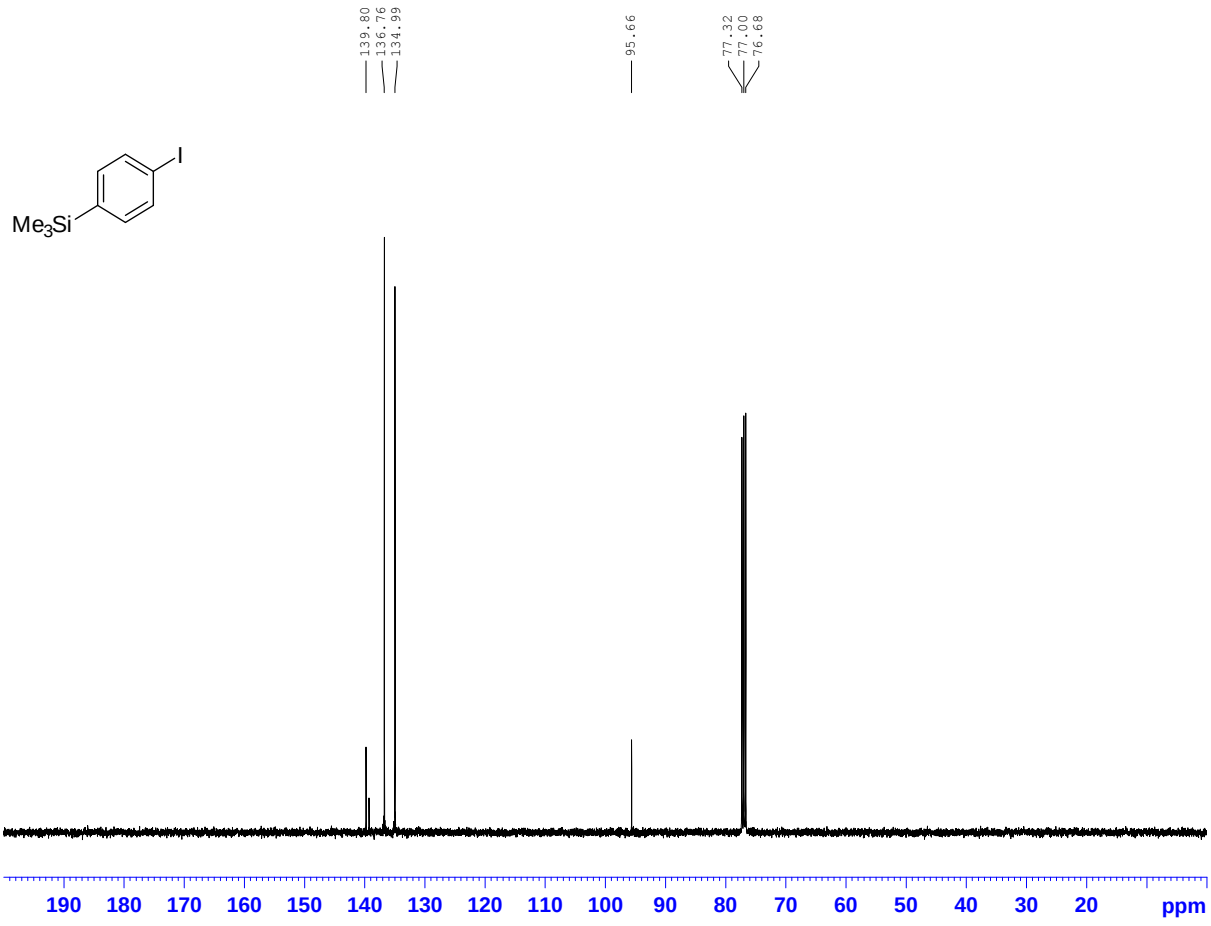
2.02
9.00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77.00
76.68
I
Me3Si
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160
150
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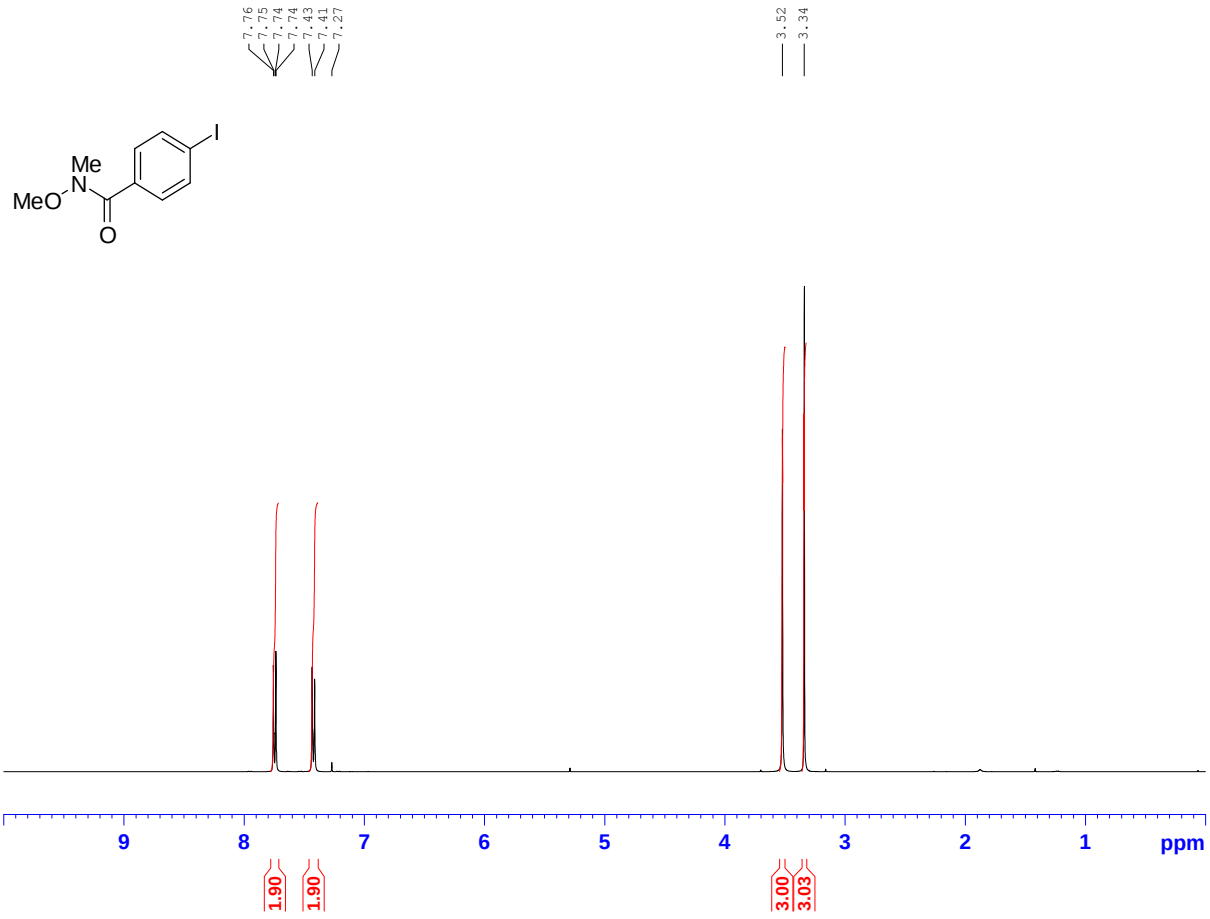
130
120
110
100
90
80
70
60
50
40
30
20
ppm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7.75
7.74
7.74
7.43
7.41
7.27
3.52
3.34
Me
N
MeO
O
I
9
8
7
6
5
4
3
2
1
ppm
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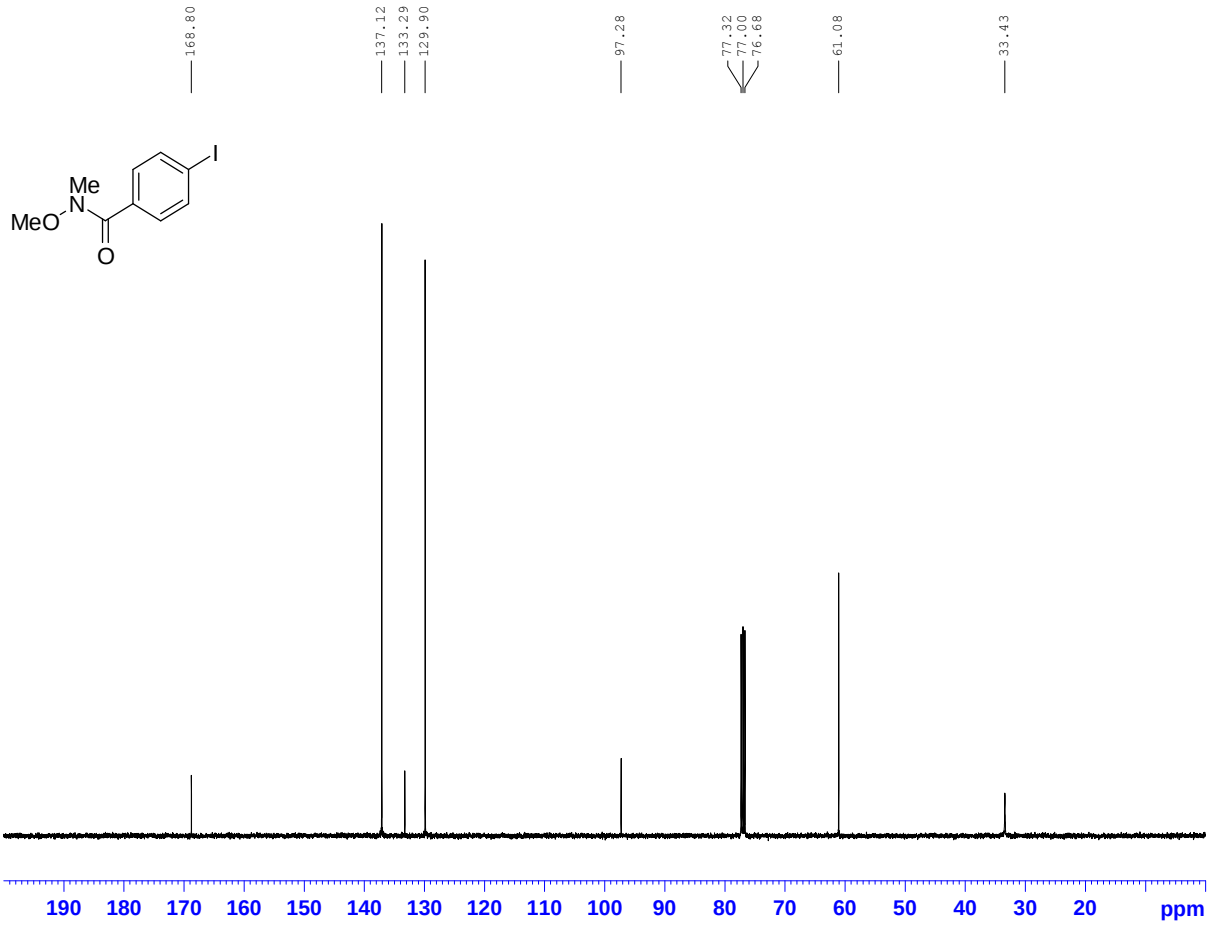
1.90
3.00
3.03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129.90
97.28
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77.00
76.68
61.08
33.43
Me
N
MeO
O
I
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160
150
140
130
120
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80
70
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50
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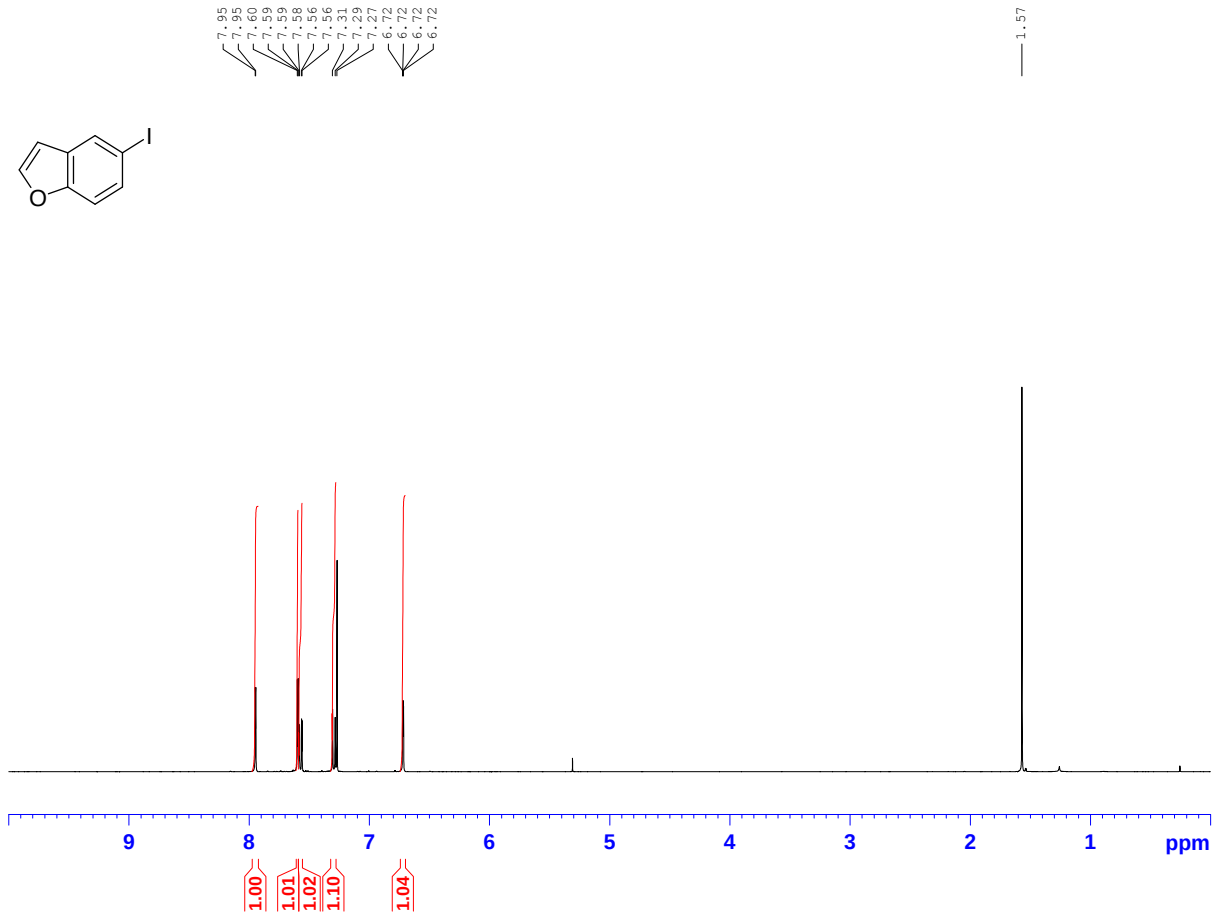
30
20
ppm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7.56
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7.29
7.27
7.72
6.72
6.72
6.72
1.57
I
O
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7
6
5
4
3
2
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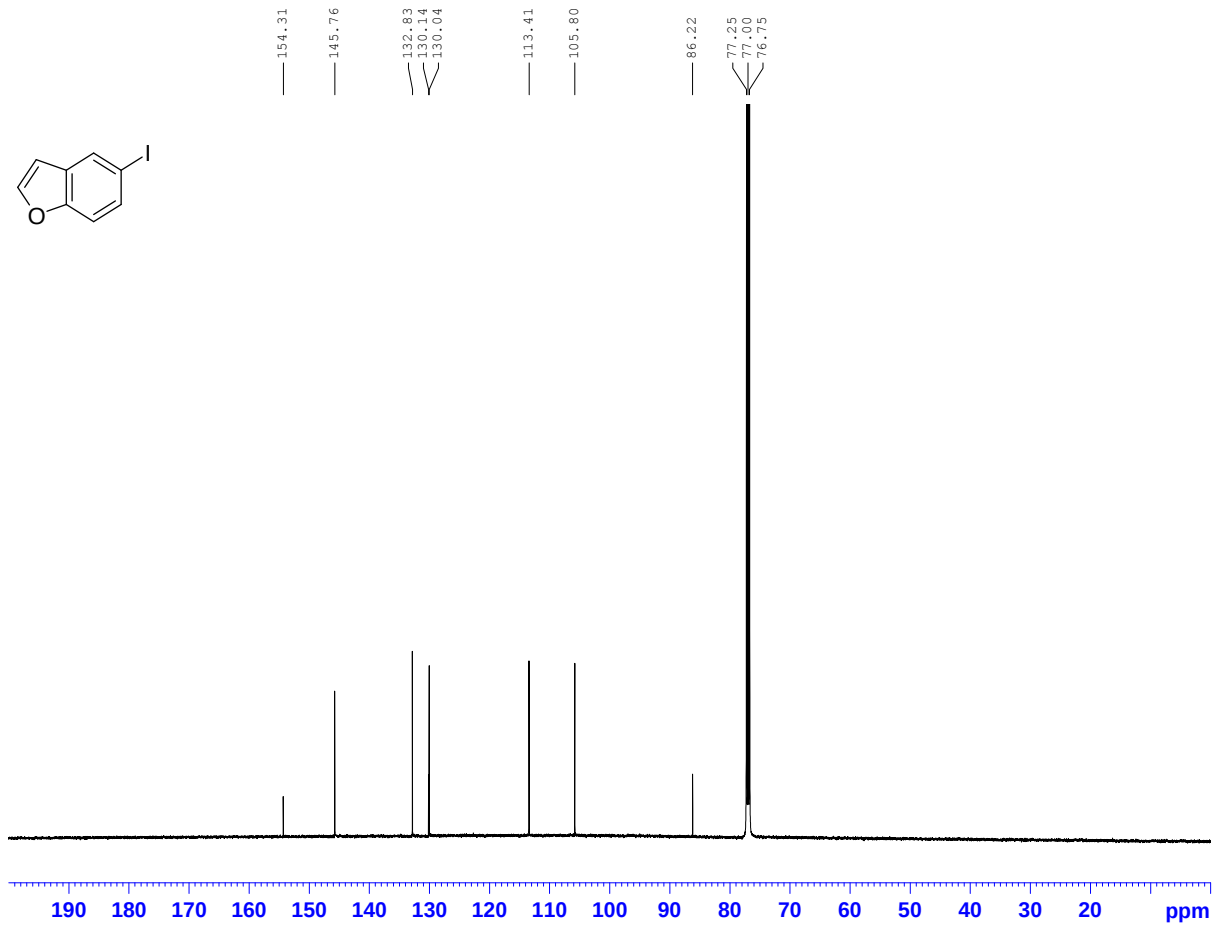
ppm
1.00
1.01
1.02
1.10
1.04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77.00
76.75
I
O
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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm