Novel *S*-Based Chemotypes of Tunable Reactivity for Applications in Chemical Biology

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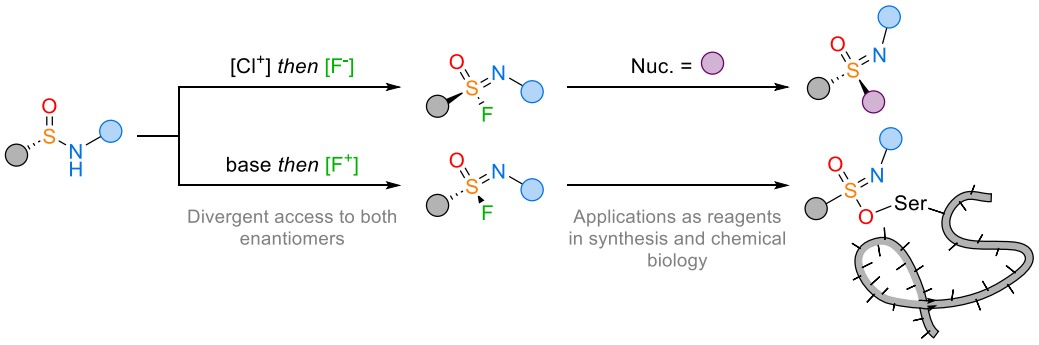
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

In this thesis, new methodologies towards the synthesis of aza-S(IV) and S(VI) functionalities are documented. These approaches include the development of sulfonimidoyl halides as chiral intermediates, bifunctional reagents and electrophilic warheads, and the application of alternative S(IV) nucleophiles in cross-coupling transformations.

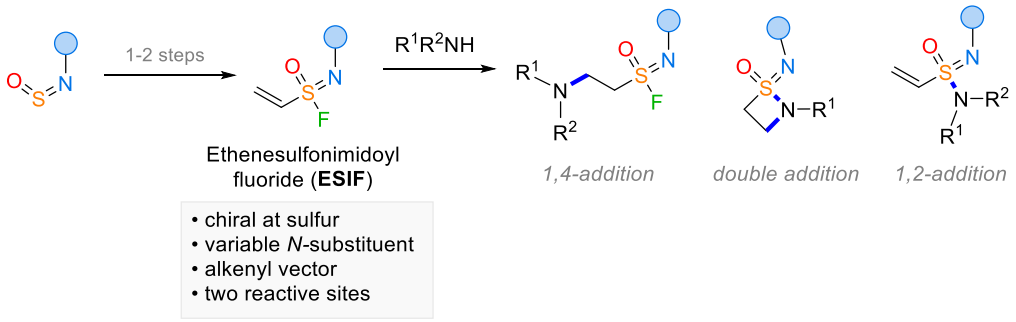
Chapter 1 is a literature review detailing the advances in the synthesis and application of sulfur halides in various oxidation states. The properties and rapidly expanding utility of S(VI)-fluorides is discussed, as this forms the groundwork for the research described in this thesis.

Chapter 2 describes the practical synthesis of sulfonimidoyl fluorides in both a racemic and an enantioenriched manner, utilising separate methodologies. A divergent approach is documented, permitting access to pairs of enantiomers of sulfonimidoyl fluorides. The robustness of this class of reagents, as well as their reactivity is examined. In particular, the utilisation of sulfonimidoyl fluorides as electrophilic warheads in chemical biology settings is explored, with additional new reactive functionalities described.

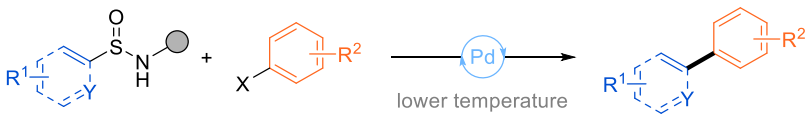


Chapter 3 presents the application of alkenyl sulfonimidoyl fluorides as bifunctional reagents for the first time, with selective reactivity demonstrated at the two distinct reactive sites. The development of a simple, scalable method for the synthesis of various *C*- and *N*-

substituted alkenyl sulfonimidoyl fluorides is detailed. Investigation of the reactivity of these functionalities is demonstrated, with the choice of nitrogen substituent proving key to achieving high levels of selectivity.



Chapter 4 discusses the investigation of sulfinamides as nucleophiles in cross-coupling procedures with aryl halides. The use of aryl primary sulfinamides facilitates reactions to occur at lower temperature than previously reported reaction of aryl sulfinates, with significant advances detailed in the use of 2-pyridyl substrates. Sulfinamides possess an additional vector for modulating reactivity through nitrogen substitution, with *N*-trityl substituted sulfinamides providing an attractive alternative. The expansion of this methodology to alkenylation and allylation transformations has been established.



Chapter 5 summarises the research in this thesis and suggests potential areas for future work.

Chapter 6 presents the experimental data and procedures for this research.

Declaration

I declare that the work in this thesis had not been previously submitted for a degree at the university of Oxford or any other higher education institution.

The experimental work in Chapter 2 was not carried out collaboratively. All results and characterisation data seen in this chapter are my own work.

The experimental work in Chapter 3 was carried out in collaboration with Erik Diepers, a former master's student in the Willis group. The experiments and procedures performed by Erik Diepers are clearly labelled within chapter 3 and the experimental section.

The experimental work in Chapter 4 was carried out in collaboration with Dr Xinlan Aloise Ford Cook and Dr Antoine de Gombert, former DPhil students in the Willis group. The experiments and procedures performed by Dr Xinlan Aloise Ford Cook and Dr Antoine de Gombert are clearly labelled within chapter 4 and the experimental section.

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May 2023

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Abbreviations and acronyms

1,2-DCE	1,2-dichloroethane
AAC	azide-alkyne cycloaddition
ABP	activity-based probe
ABPP	activity-based protein profiling
Ac	acetyl
Acr	acridinium
AEBSF	4-(2-aminoethyl)benzenesulfonyl fluoride
app.	apparent
aq.	aqueous
Ar	aromatic
BCB	bicyclo[1.1.0]butane
BDE	bond dissociation energy
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bn	benzyl
boc	*tert*-butyloxycarbonyl
br.	broad
Bu	butyl
Bz	benzoyl
Cbz	carboxybenzyl
CIP	Cahn-Ingold-Prelog
Cy	cyclo
d	doublet
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	DABCO-*Bis*(SO_2) adduct
Dan	1,8-diaminonaphthalene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
E	electrophile
e.e.	enantiomeric excess

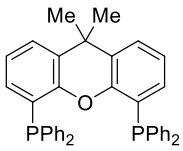
e.r.	enantiomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donating group
equiv.	equivalent
ESC	ethenesulfonyl chloride
ESF	ethenesulfonyl fluoride
ESI	electrospray ionisation
ESIF	ethenesulfonimidoyl fluoride
Et	ethyl
EWG	electron withdrawing group
FDA	food and drug administration
FSBA	5'-(4-fluorosulfonylbenzoyl)adenosine
g	gram(s)
h	hour(s)
HFIP	hexafluoro-2-propanol
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HWE	Horner-Wadsworth Emmons
Hz	hertz
i	*iso*
IC_{50}	half-maximal inhibitory concentration
Int.	intermediate
IR	infrared
isoDTB	isotopically labeled desthiobiotin azide
J	coupling constant
L	litre
LA	Lewis acid
LD	lethal dose

LRMS	low resolution mass spectrometry
m	milli or multiplet
M	metal *or* molar
m.p.	melting point
m/z	mass to charge ratio
MDSF	methanedisulfonyl fluoride
Me	methyl
Mes	mesityl
MIDA	*N*-methyliminodiacetic acid
min	minute
MISF	*N*-methylimidazolium sulfinyl fluoride hexafluorophosphate
moc	2-(methoxycarbonyl)
mol	mole
MRSA	methicillin-resistant *Staphylococcus aureus*
n	*normal*
n.r.	no reaction
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NHS	*N*-hydroxysuccinate
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*
O.A.	oxidative addition
Oct	octyl
p	*para*
Ph	phenyl
Phth	phthalimide
Piv	pivaloyl
PMB	*para*-methoxybenzyl

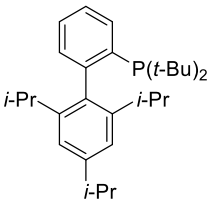
PMP	*para*-methoxyphenyl
PMSF	phenylmethylsulfonyl fluoride
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalysis
q	quartet
R	generic substituent/group
r.t.	room temperature
rac	racemic
R.E.	reductive elimination
s	singlet
SASF	2-substituted-alkynyl-1-sulfonyl fluoride
sat.	saturated
SIF	sulfonimidoyl fluoride
SMC	Suzuki-Miyaura cross-coupling
SMOPS	sodium 3-methoxy-3-oxopropane-1-sulfinate
SSF	styrenylsulfonyl fluoride
SuFEx	Sulfur(VI) Fluoride exchange
SuPhenEx	Sulfur-Phenolate exchange
SuTEx	Sulfur-Triazole exchange
t	tertiary
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCCA	trichloroisocyanuric acid
Tf	triflic
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TM	transmetalation
Tol	tolyl
TOP	tandem orthogonal proteolysis

Tr	trityl
Ts	tosyl
X	(pseudo)halide

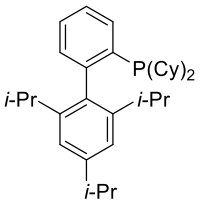
Ligands and Chemical Structures



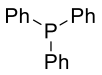
Xantphos



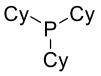
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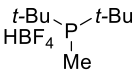
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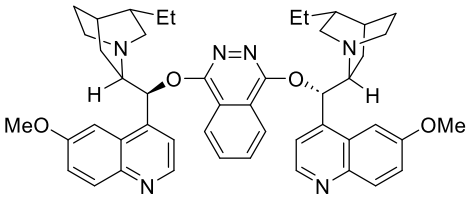
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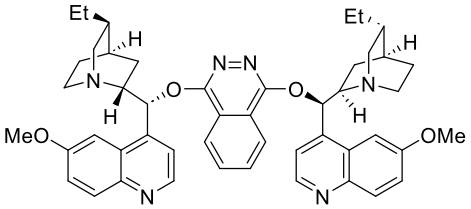
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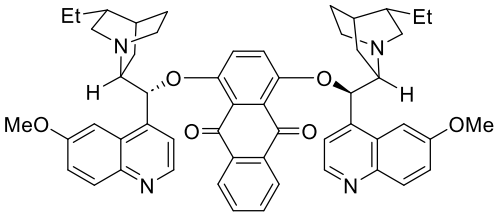
$P(t\text{-}Bu)_2Me{\cdot}HBF_4$



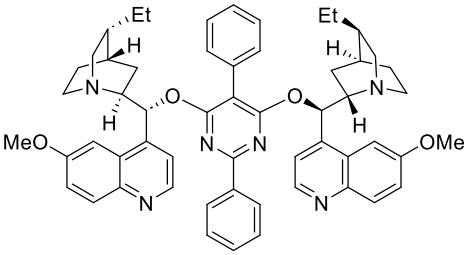
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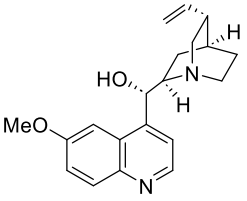
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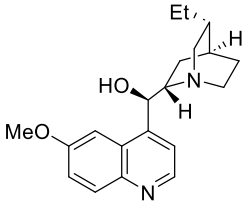
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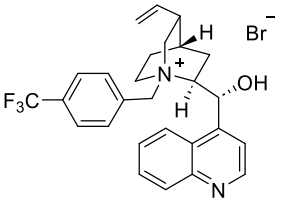
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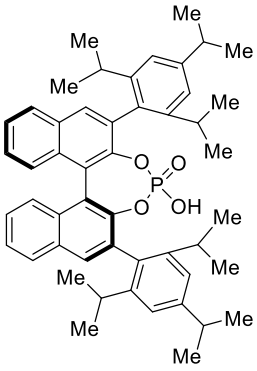
Quinidine



Hydroquinine



N-(4-Trifluoromethylbenzyl)cinchonium bromide



(*S*)-TRIP

1 Introduction

1.1 Sulfur(IV) and (VI)-functionalities in organic chemistry

Sulfur-containing compounds have a rich history in the field of organic synthesis; predominantly in either S(IV) or S(VI) oxidation states. Sulfoxides and sulfinamides are commonly used in asymmetric transformations as chiral ligands and catalysts.[1, 2] The use of sulfonamides, sulfones and sulfoxides is also prevalent in medicinal chemistry, with >20% of FDA approved drugs containing a sulfonyl -SO_2- motif (**Figure 1-1**).[3-5] The replacement of one oxygen atom for an imidic nitrogen substituent has been utilised in the mono-aza analogues of these compounds, sulfonimidamides,[6] sulfoximines,[7] and sulfilimines, respectively (**Figure 1-1**).[8, 9]

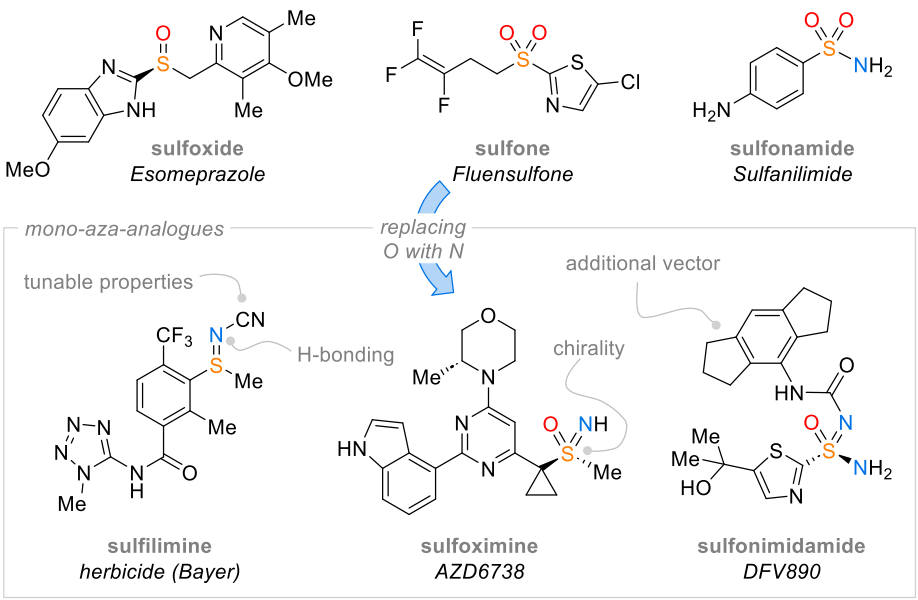


Figure 1-1 Sulfur-functionalities in pharmaceutical and agrochemical agents.

Compared to their sulfonyl counterparts, these reagents possess an additional functional handle to explore chemical space,[10] modulate their reactivity and physiochemical properties,[6] and participate as both hydrogen bond donors and acceptors. In addition to this, these compounds can also contain a chiral centre at sulfur, which plays a vital role in

selectivity in medicinal chemistry.[11] With new synthetic techniques becoming available for their synthesis, the increased versatility of sulfoximines and sulfonimidamides is becoming attractive, and pharmaceutical firms have started considering these functionalities for drug candidates.[11] For example, AZD6478, developed by AstraZeneca as an ataxia telangiectasia and Rad3 related (ATR) kinase inhibitor,[12] and sulfonimidamide, DFV890, recently disclosed by Novartis in phase II trials for COVID-19 and osteoarthritis.[13]

Within the class of S(VI)-functionalities, S(VI)-halides have received comparatively less attention. These compounds have primarily been utilised in organic synthesis as reagents and intermediates, although their use as final compounds has been more prominent in recent years.[14-16] This introductory chapter will outline some representative examples of S(VI)-halides and ultimately our motivation for investigating this class of compounds.

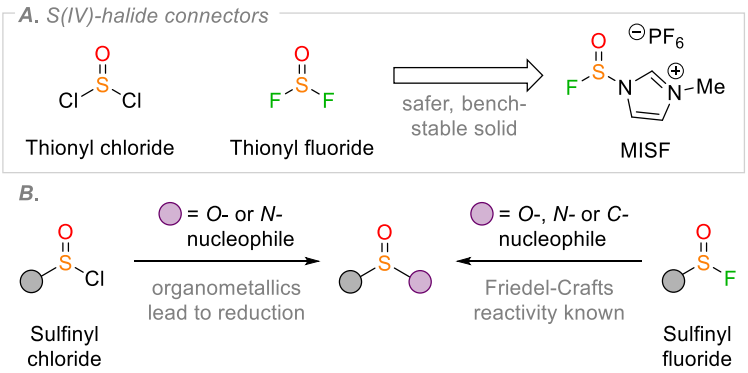
1.2 Overview of sulfur halide reagents

1.2.1 S(II) and S(IV) halides

The use of sulfur-halides spans across multiple oxidation states (II-VI), although S(II) halides are comparatively less frequently encountered.[17-20] Sulfenyl chlorides are the most prominent example of S(II) halides, providing utility as promoters for glycosylation reactions,[18] modifying reagents for tryptophan and cysteine residues,[19, 21, 22] and useful precursors for the synthesis of sulfenamides.[23] The advent and uptake of sulfenyl halides has been severely limited by the odorous nature of these compounds, which coupled with their volatility and limited shelf-life means handling is often challenging.[24] This increased reactivity at lower oxidation states of sulfur is a common feature, with a general trend of reactivity at sulfur of S(II)>S(IV)>S(VI).

The high reactivity of S(IV) halides gives rise to their proclivity as reagents and intermediates rather than final motifs. This is typified by the use of thionyl chloride as a

chlorinating agent and its use in formation of sulfinylamine reagents (**Scheme 1-1 A**).[25] Sulfinyl chlorides are commonly used as electrophilic sulfinyl equivalents formed *in situ*, that undergo reactions with oxygen and nitrogen nucleophiles (**Scheme 1-1 B**).[26-28] Reaction of sulfinyl chlorides with organometallic reagents leads to chlorination of the organometallic reagent, accompanied by formation of the reduced thiol product, a common undesired pathway for reaction of S-Cl containing motifs in all oxidation states.[27] The fluoride analogues of these compounds, thionyl fluoride and sulfinyl fluorides have been much less studied. As thionyl fluoride is a toxic gas its use has been limited due to a lack of safe, lab-scale methods for its generation. Recent advances have relied on its *ex situ* generation from thionyl chloride[29-31] or alternative non-gaseous S(IV)-fluoride exchange reagents such as *N*-methylimidazolium sulfinyl fluoride hexafluorophosphate (MISF), recently reported by Sammis and co-workers (**Scheme 1-1 A**).[32] The synthesis of sulfinyl fluorides is challenging, with limited examples of their isolation and characterisation.[33, 34] Their reactivity mirrors that of sulfinyl chlorides, with nucleophilic substitution reactions using alcohols and amines (**Scheme 1-1 B**).[33] Friedel-Crafts reactivity has been reported to form sulfoxides utilising antinomy fluoride or boron trifluoride as activators.[35] Sulfinyl bromides and iodides tend to disproportionate rapidly, so are usually avoided.[34]

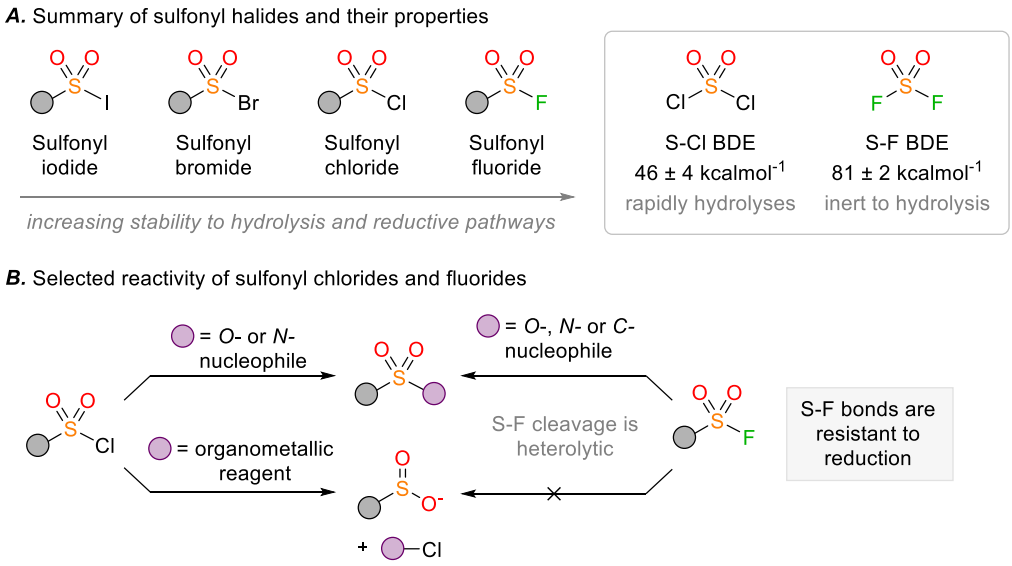


Scheme 1-1 Examples of S(IV)-halides and their utility to form S(IV)-functional groups.

1.2.2 Sulfonyl halides

The relative inertness of S(VI) compounds makes them better connectors. Sulfonyl chlorides are perhaps the most commonly used S(VI) electrophiles; commercially available arylsulfonyl chlorides, such as tosyl and nosyl chloride, are prominently used to functionalise amines and alcohols (**Scheme 1-2 B**). The desired halide substitution reaction is often plagued by reductive homolytic scission side processes to S(IV) compounds, such as sulfinates, in the attempted formation of heteroatom linked sulfonyl motifs such as sulfamide (*N*-linked) and sulfamates (*O*-linked), and the reaction of organometallic nucleophiles.[36, 37] Sulfonyl bromides and iodides are even more prone to reduction and radical reactions (**Scheme 1-2 A**).

As fluorine is the most electronegative element, the reaction of S(VI) fluorides results in only substitution pathways, with exclusive heterolytic cleavage of S-F bonds (**Scheme 1-2 B**). This privileged reactivity has been reviewed in great detail.[16, 36, 38-41] A key example of this divergent reactivity/stability is for the inorganic sulfuryl halides: sulfuryl chloride (SO_2Cl_2) rapidly reacts with water to give HCl and sulfuric acid at room temperature, whereas sulfuryl fluoride (SO_2F_2) is inert to hydrolysis even when heated at 150 °C in a sealed tube (**Scheme 1-2 A**).[42] This stability can be attributed in part to the measured bond strengths of S-F bonds relative to S-Cl bonds in S(VI) systems: the homolytic BDE of S-F bond in SO_2F_2 (81 ± 2 kcalmol^{-1}) is far larger than S-Cl bond in SO_2Cl_2 (46 ± 4 kcalmol^{-1}).[43] This resistance to reduction means carbon-based nucleophiles for example, silyl enol ethers react selectively at sulfur.[44]



Scheme 1-2 Summary of the properties and reactivities of sulfonyl halides.

Given the stability of S(VI)-F reagents, their reactivity requires stabilisation of the developing fluoride anion to transit from a strong covalent bond to a leaving group (**Figure 1-2**). This is achieved with assistance – traditionally with "H^+" (**Figure 1-2 A**), in particular in aqueous environments, or "R_3Si^+" due to the formation of one of the strongest single bonds in nature – Si-F.[36, 45, 46] More recently these processes have been accelerated by basic amines such as Et_3N, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO), hydroxybenzotriazole (HOBt) or phosphazine catalysts (e.g. BEMP).[47-49] Initial work using DBU was postulated to proceed by nucleophilic catalysis, displacing fluoride; hence activating the S(VI)-centre for further reaction.[48] Recent mechanistic and computational studies by Zuilhof and Ball groups have elucidated an alternative role of tertiary amines; they act as Brønsted bases, increasing the nucleophilicity of the amine or alcohol (**Figure 1-2 B**).[50, 51] The use of Lewis acids has also been used to promote reaction of S(VI)-F containing compounds; in recent years the Ball group have pioneered calcium triflimide for this reaction.[52] Mechanistic studies have revealed its role in stabilising developing charge at S=O functionality and departing fluoride (**Figure 1-2 C**).[50]

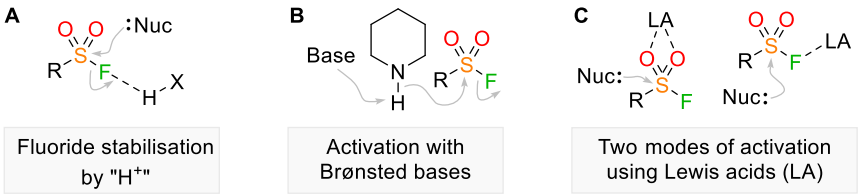
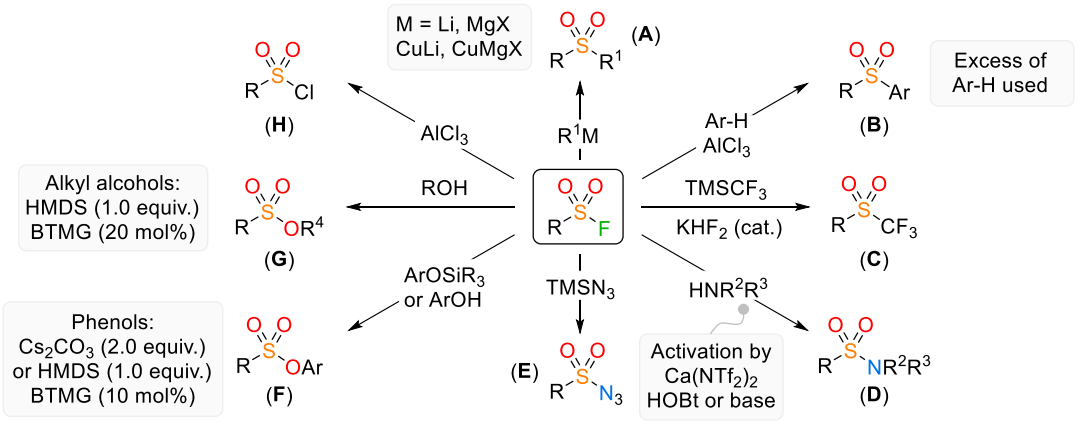


Figure 1-2 Selected methods of activation of S(VI)-fluorides.

In 2014, Sharpless proposed the remarkable stability of S(VI)-F reagents under typical acidic and basic conditions coupled with their special requirements for reactivity, was the hallmark of a candidate for click chemistry.[36] This so coined sulfur-fluoride exchange (SuFEx) reactivity is of particular significance in chemical biological and drug-discovery applications. Whereas other click chemistries typically utilise metals (e.g., copper accelerated azide-alkyne cycloaddition),[53] reactions of SuFEx reagents can occur in metal-free processes. The bonds formed can be more diverse compared to classical click-chemistries with a range of nucleophiles compatible such as amines and alcohols, which are ubiquitous starting materials. In combination with various molecular plugins (SuFExable hubs), this lends towards a more modular assembly of suites of reagents, with pre-installation of functional groups not required.

Sulfonyl fluorides are known to react with a range of nucleophiles under mild conditions (**Scheme 1-3**).[38] In contrast to sulfonyl chlorides, treatment with organometallic reagents (**A**),[54] arenes (**B**)[55] and Ruppert-Prakash reagent ($TMSCF_3$) affords the corresponding sulfones (**C**).[56] Reaction of nitrogen-nucleophiles such as amines and azides are efficient under specific conditions,[57] mediated by calcium triflimide,[52, 58] HOBt, or tertiary amine bases (**D** and **E**).[47, 59, 60] The combination of calcium triflimide with DABCO has allowed for room temperature SuFEx reactions to occur and the use of sub-stoichiometric quantities of calcium triflimide, albeit in lower yields.[50] Initial formation of S-O linkages was achieved using silyl ethers, but more recently has been achieved using free alcohols (**F**). Of note is

the use of alkyl alcohols in these transformations; Moses and co-workers developed conditions to combat issues of subsequent deoxyfluorination reported for these substrates (**G**).[61] The halogen exchange of sulfonyl fluorides is also possible using aluminium trichloride to access sulfonyl chlorides (**H**).[62]



Scheme 1-3 Selection of reactions of sulfonyl fluorides at sulfur with various nucleophilic reagents.

The stability of sulfonyl fluorides under a range of conditions has been exploited in a range of bifunctional reagents that undergo selective reactivity at an additional site (**Figure 1-3**). Arylsulfonyl fluorides containing halide and boronic acid handles have been used in palladium- and copper-catalysed cross-coupling reactions.[63-66] Other unsaturated systems such as ethenesulfonyl fluoride (ESF, **1**) and 2-substituted alkynylsulfonyl fluorides (SASF) have been established as SuFExable hubs for a wide number of reactions (discussed in more detail in chapter 3.1).[59, 67, 68]

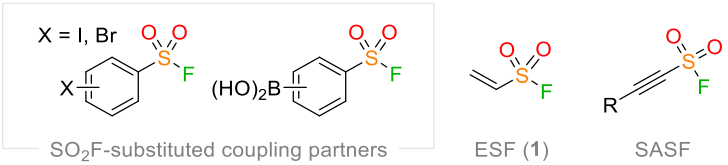


Figure 1-3 Examples of bifunctional sulfonyl fluorides. ESF = ethenesulfonyl fluoride, SASF = 2-substituted-alkynyl-1-sulfonyl fluorides.

The controllable reactivity of sulfonyl fluorides has also seen their application in various areas of organic synthesis (**Figure 1-4**). One of the most prominent examples is PyFluor, a commonly used deoxyfluorination reagent for the transformation of alkyl alcohols into the corresponding fluoride (**A**).[69] Modified ^{18}F labelled PyFluor is effective for incorporating radiolabels into molecules with short reaction times in highly efficient processes. Efficient reagents for *in situ* generation of difluorocarbenes (**B**)[70, 71] and amide coupling reactions (SuFExAmide (**C**)) have also been established.[72] SuFEx reactions between sulfonyl fluorides and silyl ethers have been used frequently in material chemistry, in both polysulfonate formation (**D**) and surface modification reactions.[49, 73, 74]

The rapid adoption of sulfonyl fluorides in chemical biology settings has been aided by the ease of synthesis, the unreactive nature of the fluoride leaving group, and the stability of the linkages formed with amino acids.[36] The relative inertness of sulfonyl fluorides ensures they remain unreactive until positioned in the active site with appropriate activation, for example through catalytic histidine or glutamate residues.[75, 76] Their use is now routine (**E**),[15] for example, pan-serine protease inhibitor, phenylmethylsulfonyl fluoride (PMSF)[77, 78] and 5′-fluorosulfonylbenzoyl 5′-adenosine (FSBA),[79] targeting various amino acid residues. The substituent effect of arylsulfonyl fluorides has been systematically evaluated recently by Bush, Burley and co-workers.[80] Significant differences in aqueous stability and intrinsic reactivity was observed across the spectrum of compounds tested. For further discussion of the use of S(VI)-fluorides as chemical probes see **chapter 2.4.1**.

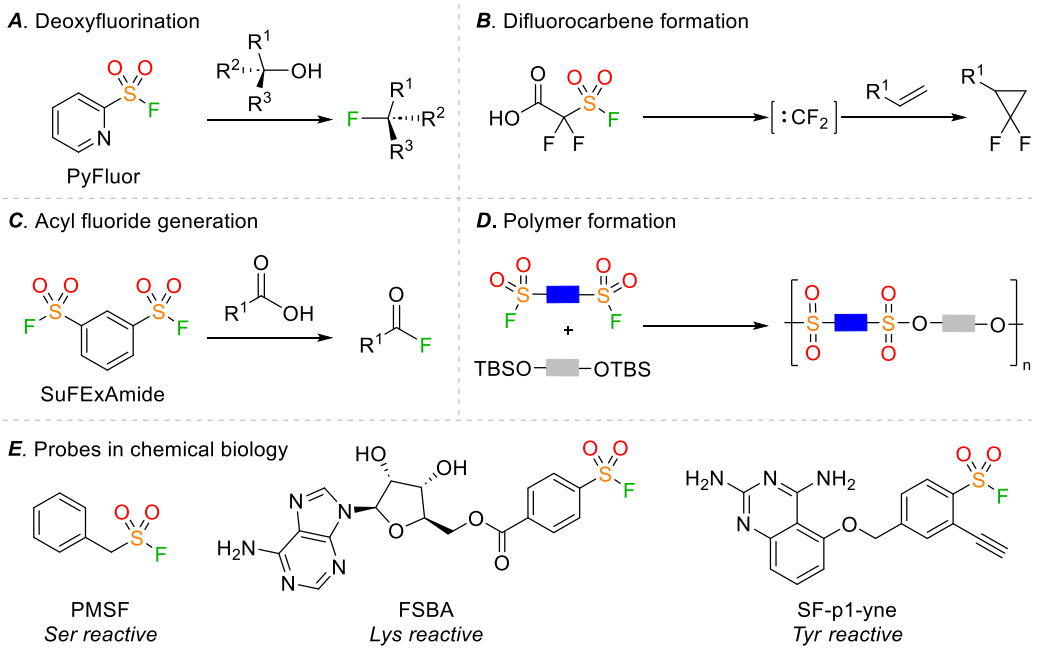


Figure 1-4 Selected applications of sulfonyl fluorides in organic synthesis and chemical biology.

Modulation of the native reactivity of sulfonyl fluorides is somewhat limited to varying the carbon-substituent. The vast majority of research has focussed on aryl sulfonyl fluorides, in part due to the enhanced stability of these compounds and the multitude of methods to access them.[36] A number of aliphatic sulfonyl fluorides have however been identified as highly selective inhibitors, in particular peptide-type inhibitors (**Figure 1-5**).[14, 15] Furthermore, their application in parallel synthesis of aliphatic sulfonamides for drug discovery has proved beneficial compared to less selective sulfonyl chlorides.[60] Sulfonyl fluorides bearing α-protons can participate in additional reactions compared to their aryl counterparts, including elimination pathways forming highly reactive sulfene intermediates.[81] Accordingly, the synthesis of aliphatic sulfonyl fluorides has gained increasing attention in recent years with several complementary methodologies reported.[82-88]

Like sulfonyl fluorides, fluorosulfates and sulfamoyl fluorides (*O*- and *N*-linked respectively) have been explored as covalent warheads, modifying similar amino acid residues (**Figure 1-5**).[15, 89] Fluorosulfates in particular have extensive applications, and in

recent years they have been utilised in molecular glues and inverse drug discovery strategies.[90, 91] However, both functionalities display reduced reactivity in biological systems compared to sulfonyl fluorides, as a result of resonance donation of the accompanying heteroatom, tempering the electrophilicity of sulfur. This has profound impact on the use of these functionalities in reaction with amines and alcohols, with often forcing conditions required.[58] Depending on the nature of the alcohol substituent, fluorosulfates can also act as pseudohalides in metal-mediated cross-coupling procedures.[92, 93]

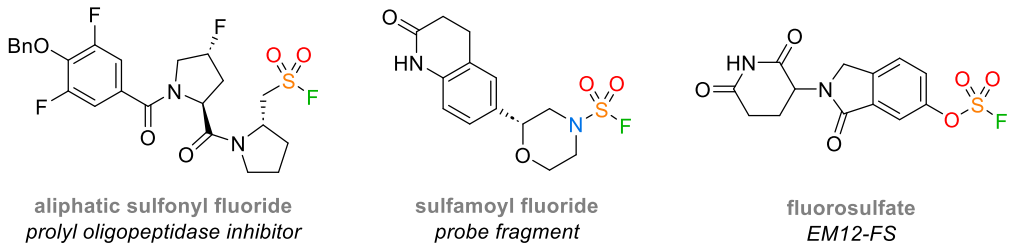
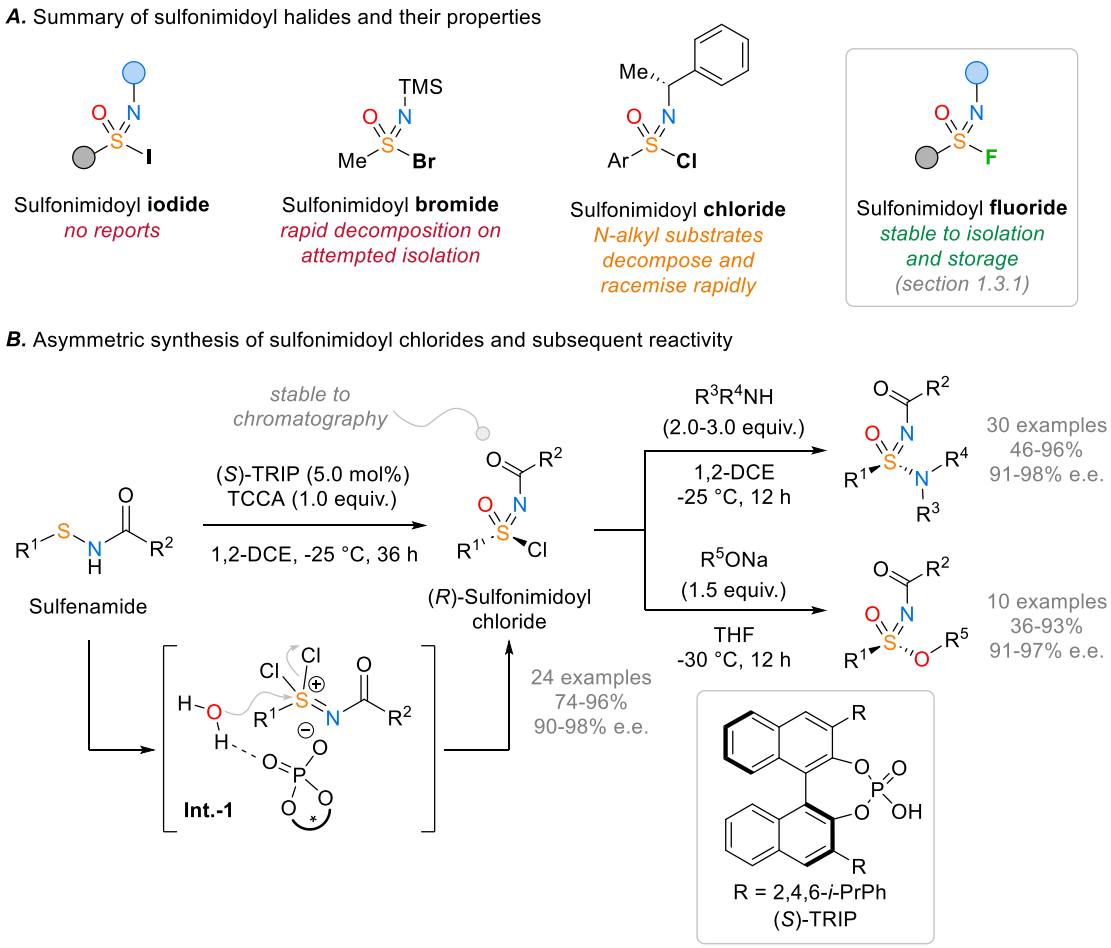


Figure 1-5 Variation of arylsulfonyl fluorides *via* replacement of *C*-aryl by *C*-alkyl, amine and alcohol substituents.

1.2.3 Sulfonimidoyl halides

An alternative vector for modulating reactivity of sulfonyl halides is replacing one of the oxygen atoms with a nitrogen atom in the form of sulfonimidoyl halides. This set of functionalities exhibit similar benefits to sulfoximines and sulfonimidamides discussed *vide infra*. Of significance is the ability of the nitrogen substituent to influence the reactivity and stability of sulfonimidoyl halides. This is particularly apparent for sulfonimidoyl chlorides, wherein their isolation is significantly restricted by the nitrogen substituent; *N*-alkyl substituted sulfonimidoyl chlorides decompose rapidly and significantly, enantiopure substrates racemise within minutes to hours even at low temperatures (**Scheme 1-4 A**).[94] Stabilisation can be achieved with electron-withdrawing groups on nitrogen such as carbamates, sulfonates and amides. This class of compounds have been reported to be stable

to column chromatography and storage for several months without decomposition or racemisation if prepared in optically pure form (**Scheme 1-4 B**).[95-97]



Scheme 1-4 An overview of sulfonimidoyl halides and their properties, including a recent example of asymmetric sulfonimidoyl chloride synthesis and application.

The synthesis of sulfonimidoyl chlorides was first established by Levchenko and co-workers in 1960, and in a similar vein to sulfonyl chlorides,[98-100] their use has since been dominated as intermediates generated *in situ*. Reaction with amines and alcohols provides access to sulfonimidamides and sulfonimidates, respectively. A notable contribution to the use of enantioenriched sulfonimidoyl chlorides was detailed by Tang, Li and co-workers recently.[97] The authors demonstrated their synthesis from sulfenamides *via* a chiral phosphoric acid mediated process (*via* postulated **Int.-1**) in high enantiomeric excess (e.e.) and impressive substrate scope (**Scheme 1-4 B**). Reactions with amines and alcohols

proceed in an enantiospecific manner, whereas use of organometallic reagents results in reduction to sulfinamides. Previously in the literature, stoichiometric quantities of Lewis acids have been used to address the challenging transformation of sulfonimidoyl chlorides to sulfoximines,[101-104] as well as visible light-mediated processes.[105, 106] In contrast to sulfonyl chlorides there are few examples of commercial sulfonimidoyl chlorides, which can be ascribed to their relative instability. This is reaffirmed by their transformation to more stable sulfonimidate ester and sulfonimidoyl fluoride analogues for formation of libraries of compounds.

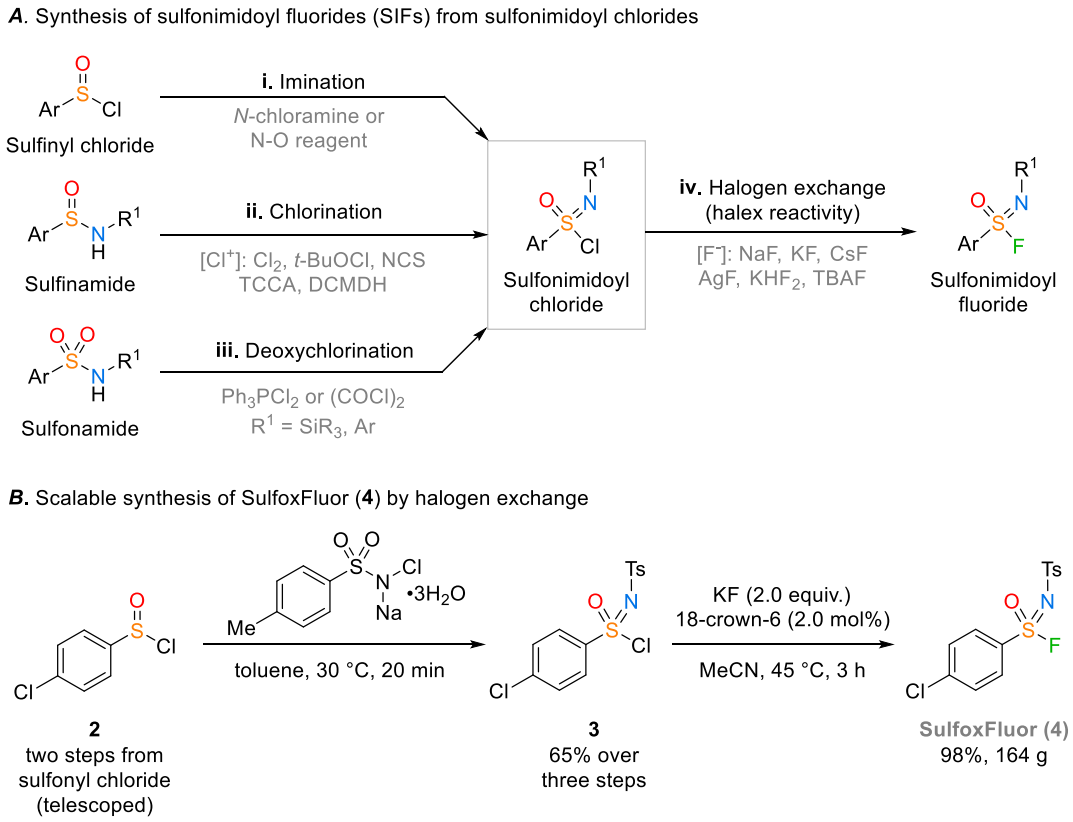
Sulfonimidoyl bromides have been implicated as intermediates in halogen exchange reaction with sulfonimidoyl chlorides en route to sulfonimidates.[107] Their synthesis *in situ* has also been achieved using electrophilic brominating source *N*-bromosuccinimide (NBS) (**Scheme 1-4 A**),[108] although in both cases sulfonimidoyl bromides were not isolated. Analogous sulfonimidoyl iodides have no reports in the scientific literature. This is perhaps surprising given the plethora of examples of sulfonyl bromides and iodides. As observed for sulfonyl halides, the most stable mono-aza analogues are sulfonimidoyl fluorides (**Scheme 1-4 A**). The stability of sulfonimidoyl fluorides to column chromatography and various reaction conditions make them amenable for the synthesis of libraries of S(VI)-functionalities through SuFEx reactions.[51, 109, 110] The following sections will discuss their synthesis and reactivity.

1.3 Synthesis of sulfonimidoyl fluorides

Early syntheses of sulfonimidoyl fluorides was pioneered by Johnson and co-workers, proceeding *via* halogen exchange reaction of sulfonimidoyl chlorides with fluoride sources (**Scheme 1-5 A**).[111] Sulfonimidoyl chlorides themselves can be accessed *via* oxidative chlorination of sulfinamides (**ii**). Although chlorine was the preferred reagent initially,[112]

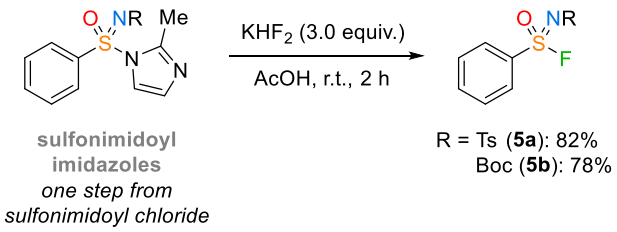
advances have seen its substitution for milder, more functional group tolerant chlorinating agents such as *N*-chlorosuccinimide (NCS) and trichloroisocyanuric acid (TCCA).[113-116] The use of metal-mediated processes for the formation of sulfinamides *in situ* and subsequent conversion to sulfonimidoyl chlorides has been reported from aryl diazonium and boroxine precursors.[115, 117] An alternative method to synthesise sulfonimidoyl chlorides is the imination of sulfinyl chlorides (**i**).[95] Although this is limited due to the instability of sulfinyl chloride starting materials, requiring their fresh preparation and the use of strong oxidants such as chloramine-T. Deoxychlorination of *N*-substitituted sulfonamides using triphenylphosphine dichloride is also a common route to these compounds, especially in industrial settings, although it produces stoichiometric phosphorous waste (**iii**).[108]

A range of fluoride sources can be utilised for the halogen exchange reaction, with often the choice dependent on the *N*-substituent and hence the electrophilicity at sulfur (**iv**).[111, 113, 118] These reactions are convenient to perform, with significant changes in polarity of the intermediates during the reaction.[111] Hence it is easy to monitor by thin layer chromatography (TLC) as sulfonimidoyl fluorides are considerably more mobile on silica gel than their chloride counterparts and can be assessed readily by analysis of ^{1}H and ^{19}F NMR spectra.[111] The direct application of this strategy is showcased by the scalable synthesis of SulfoxFluor (**4**),[119] a frequently used deoxyfluorination reagent developed by the Hu group.[120] Imination of 4-chlorobenzene sulfinyl chloride (**2**) with chloramine-T trihydrate, followed by halogen exchange of **3** using potassium fluoride in the presence of 18-crown-6 yielded 186 grams of the sulfonimidoyl fluoride product (**4**) in high yield (98%, **Scheme 1-5 B**).[119]



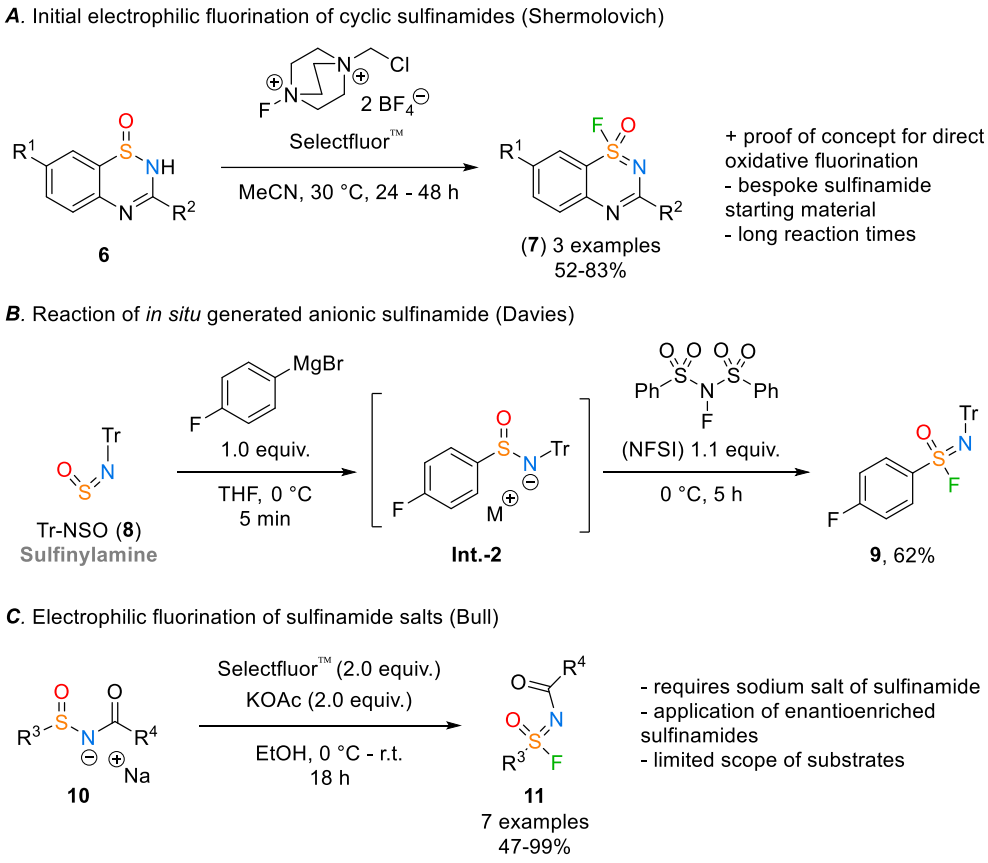
Scheme 1-5 Synthesis of sulfonimidoyl fluorides *via* sulfonimidoyl chlorides: (***A***) common routes to sulfonimidoyl chlorides and their conversion to sulfonimidoyl fluorides; (***B***) application of sulfonimidoyl chlorides to synthesise large quantities of SulfoxFluor (**4**).

In 2022, Bolm and co-workers offered an alternative precursor, sulfonimidoyl imidazoles, for exchange reactions to access sulfonimidoyl fluorides (**5a-b**, **Scheme 1-6**).[121] These reagents are bench-stable, crystalline solids meaning they are comparatively easy to use in contrast to sulfonimidoyl chlorides, especially at a late stage. This is somewhat negated by their synthesis which proceeds directly from sulfonimidoyl chlorides. Their strength is also their greatest weakness, with reactions carried out in AcOH as the solvent to achieve synthetically useful yields. Moreover, the combination of strong acid and fluoride raises the question as to whether this is a safe transformation with liberation of HF plausible.



Scheme 1-6 Conversion of sulfonimidoyl imidazoles to sulfonimidoyl fluorides.

A more direct disconnection to access sulfonimidoyl fluorides is through direction fluorination of sulfur from sulfinamide precursors. Despite the advance of oxidative chlorination occurring in the 1980s, the first electrophilic fluorination of a sulfinamide did not occur until 2013. Treatment of cyclic sulfinamide **6** with (chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) (Selectfluor™) provided access to sulfonimidoyl fluorides (**7**) directly in one step in moderate to good yields (**Scheme 1-7 A**).[122] Although few examples and bespoke starting materials, this work laid the foundations for later developments. The generation of sulfinamides *in situ* (**Int.-2**) from sulfinylamine Tr-NSO (**8**) and subsequent conversion to sulfonimidoyl fluoride **9** using *N*-fluorobenzenesulfonimide (NFSI) was first established by a previous DPhil student in the Willis group, Dr Thomas Davies (**Scheme 1-7 B**).[123] Later work published during the completion of this thesis, by Bull and co-workers showed this reaction is also efficient starting from sodium sulfinamide salts (**10**) using Selectfluor™ as the oxidant (**Scheme 1-7 C**).[110]



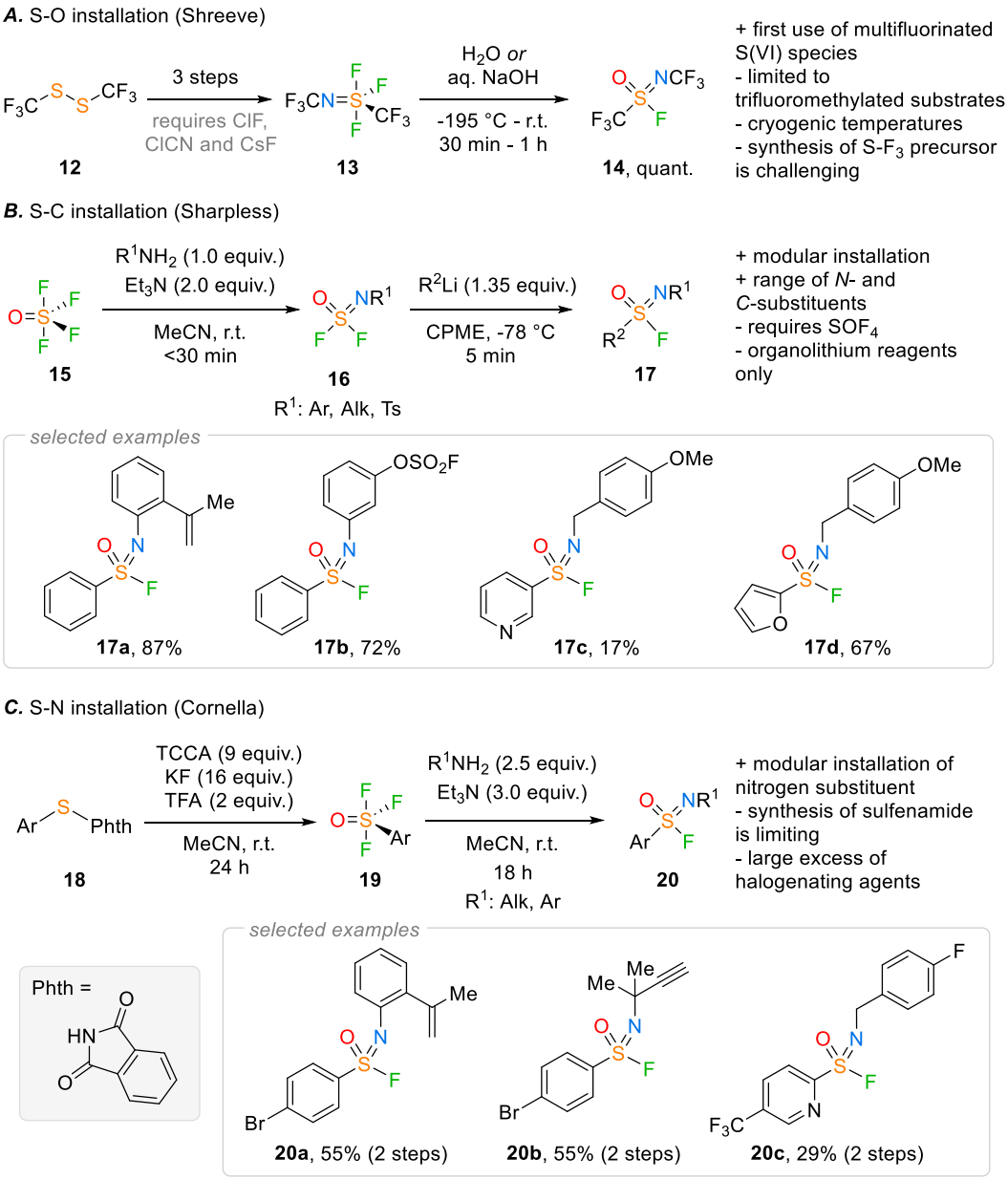
Scheme 1-7 Direction fluorination of sulfinamides: (***A***) Selectfluor™ as oxidant for cyclic sulfinamides; (***B***) *in situ* generation and conversion of anionic sulfinamides with *N*-fluorobenzenesulfonimide (NFSI); (***C***) oxidative fluorination of sodium sulfinamide salts.

Other methods for accessing sulfonimidoyl fluorides rely on the pre-installation of multi-fluorinated sulfur centres, reacting with either *O*-, *C*-, or *N*-based nucleophiles. The first reported synthesis of sulfonimidoyl fluorides was achieved using this approach in 1976. Shreeve and co-workers documented the hydrolysis of $CF_3S(NCF_3)F_3$ (**13**) to trifluoromethylsulfonimidoyl fluoride (**14**) (**Scheme 1-8 A**).[124] This approach is however severely limited by synthesis of starting material **13** requiring the use of chloromonofluoride, cyanogen chloride and disulfide **12** at cryogenic temperatures. Moreover, the carbon and nitrogen substituents are fixed at an early stage.

Iminosulfur oxydifluorides (**16**) are perhaps the most convenient intermediate to access a range of different carbon-substituted sulfonimidoyl fluorides (**17**) in a modular manner, with

the final step being formation of the S-C bond. The seminal example of these hub's synthesis and reactivity was reported by Cramer and Coffman in 1961 (reaction with amines).[125] Latter contributions from Seppelt and Sundermeyer (reaction with halogens),[126] followed by Sharp and Ross (reactions with arylsilyl ethers)[46] demonstrated the utility of these building blocks, although no carbon nucleophiles were reported. This strategy was only realised by Sharpless and co-workers in 2016 in a pioneering example of S-F chemistry (**Scheme 1-8 B**).[45] The reaction of S-F compounds with organometallics to form S-C bonds has proven to be somewhat capricious.[111] However, the authors found reaction with organolithium reagents at cryogenic temperatures generated a wide range of sulfonimidoyl fluorides (e.g. **17a-d**) in a modular manner. Of note, is the use of functional groups that might be liable to oxidative halogenation conditions in previously established route such as sulfides, olefins and ferrocenes. This methodology has been further applied to the use of heteroatom nucleophiles such as silylated alcohols, amines, and Ruppert-Prakash reagent ($TMSCF_3$).[38, 56] The challenge of this method is the synthesis of the key SuFExable hub **16**, achieved through reaction using gaseous thionyl tetrafluoride (SOF_4, **15**), which is generated in an autoclave. This has severely limited its uptake in industrial and academic settings.

In 2021, Cornella and co-workers reported the late-stage installation of the S-N bond through the reaction of amines with $RS(O)F_3$ reagents (**19**, **Scheme 1-8 C**) to give sulfonimidoyl fluorides (**20**).[127] Although complementary to the previously discussed methods, the synthesis of requisite starting materials from sulfenamide **18** using super-stoichiometric quantities of oxidant hinders the application of this methodology in a wider sense.



Scheme 1-8 Synthesis of sulfonimidoyl fluorides from higher fluorination level S(VI) reagents.

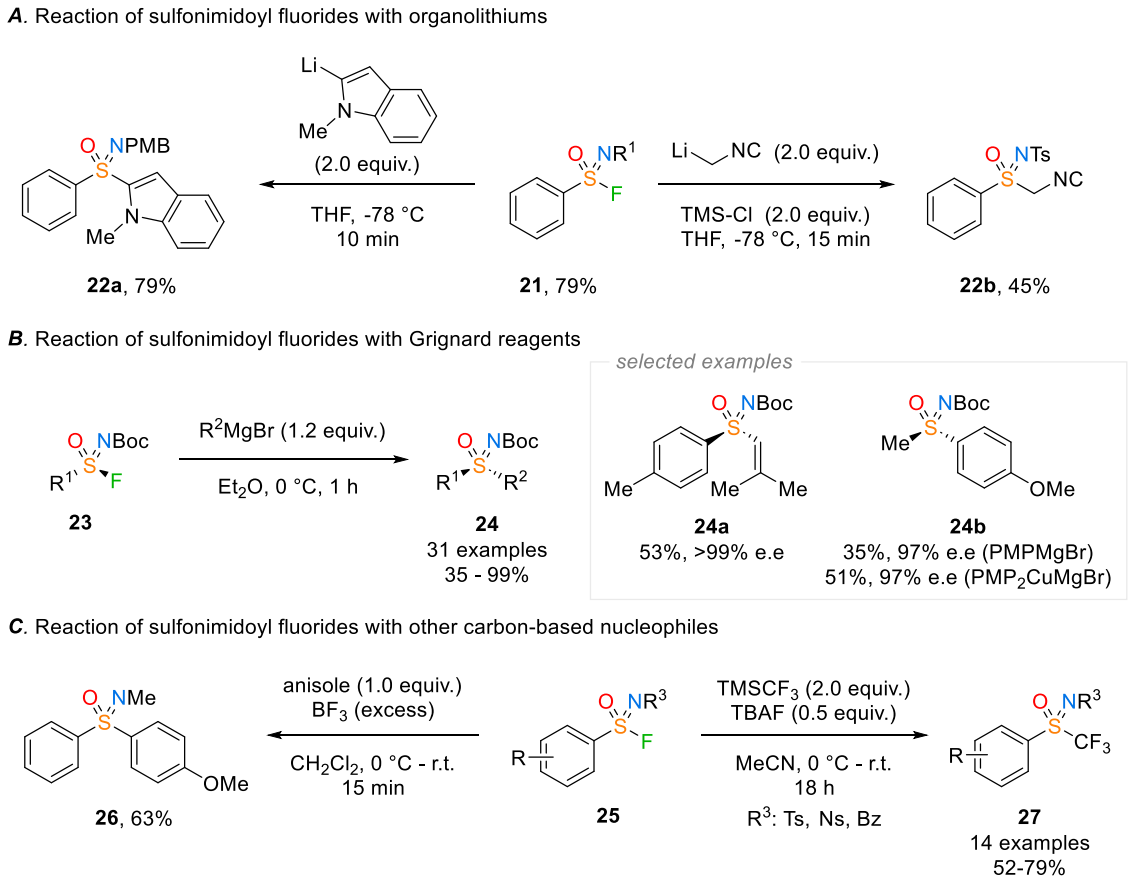
Alternative disconnections such as the imination of sulfinyl fluorides or oxidation of sulfinimidyl fluorides have yet to be realised. This is presumed to be due to the instability and reactivity of these S(IV)-fluorides.

1.4 Applications of sulfonimidoyl fluorides

The foundations for developing the reactivity of sulfonimidoyl fluorides has typically been based on reported reactions of their sulfonyl counterparts (**Scheme 1-3**). Reactivity differences and discussion of these functionalisations is discussed below.

1.4.1 Reactions with carbon-nucleophiles

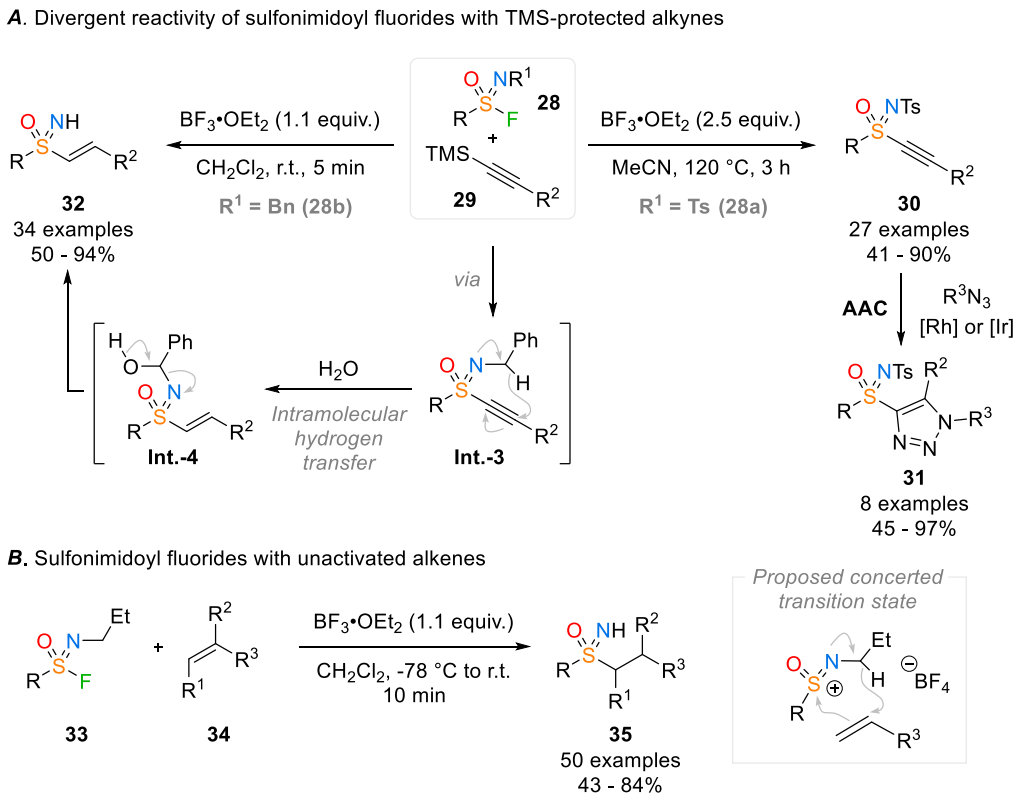
Perhaps the main limitation of sulfonimidoyl chlorides is their incompatibility in desired reactions with organometallic reagents to access sulfoximines, with reduction to the corresponding sulfinamide reported akin to the reaction of sulfonyl chlorides.[112] Sulfonimidoyl fluorides address this challenge in part through efficient reaction with alkyl- and aryl-lithium reagents selectively at sulfur, affording the corresponding sulfoximines (**Scheme 1-9 A**, **22a-b**).[45, 103, 111] A limited range of commercially available organolithiums have been successfully trialled, with exceptions of singular examples of more complex examples such as α-lithiated isocyanide reagents (**Scheme 1-9 A**).[103, 128] A recent report by Lopchuk and co-workers displayed the broadest substrate scope to date, with reactions of a wide range of functionality rich organolithiums.[129] In 2022, the Bull group utilised less basic and more commercially available Grignard reagents in combination with sulfonimidoyl fluorides (**Scheme 1-9 B**).[109] A wider range of nucleophiles were successfully incorporated yielding (hetero)aryl (**24b**), alkenyl (**24a**), allyl and alkyl sulfoximines. Moreover, a singular example of an organocuprate nucleophile was developed using extended reaction times (**24b**). Importantly, these transformations proceed in an enantiospecific manner, offering an alternative strategy to access enantioenriched sulfoximines. It also provides a complementary range of *N*-electron-withdrawing substituents to the previous work by Sharpless and Johnson, which had focussed on *N*-electron-donating substituents.[45, 111]



Scheme 1-9 Selected reactions of sulfonimidoyl fluorides with carbon-nucleophiles.

Furthermore, examples of less reactive carbon-based nucleophiles have been developed (**Scheme 1-9 C**). Johnson and co-workers reported the reaction of sulfonimidoyl fluorides with anisole and silylenol ethers in conjunction with Lewis acid additives (boron trifluoride and titanium(IV) chloride respectively) yielded the corresponding sulfoximines (e.g. **26**) in high yields.[111] A general synthesis of trifluoromethylated sulfoximines (**27**) was described by Bolm,[113] based on earlier work by Yagupolskii and co-workers,[130] using a combination of the Ruppert-Prakash reagent ($TMSCF_3$) and tetrabutyl ammonium fluoride (TBAF). Of note is the unsuccessful reaction of sulfonimidoyl chlorides under these reaction conditions. The authors attributed the unsuccessful use of aliphatic sulfonimidoyl fluorides in these transformations to deprotonation of acidic α-hydrogens by basic fluoride.

The use of activated alkynes in SuFEx reactions was recently disclosed by Jiang, Wang and co-workers.[131] The use of different nitrogen-protecting groups allowed for divergent reaction of sulfonimidoyl fluorides (**28**) with silicon-substituted alkynes (**29**) in the presence of boron trifluoride diethyl etherate (**Scheme 1-10 A**). *N*-Tosyl-protected sulfonimidoyl fluorides (**28a**) gave the corresponding alkynyl sulfoximines (**30**) at elevated temperatures, which could undergo azide-alkyne cycloaddition (AAC) reactions with alkynes, yielding the corresponding triazoles (**31**). Alkyl protecting groups such as benzyl (**28b**), contain α-hydrogens that undergo intramolecular proton transfer (**Int.-3**) during the reaction to give *N*-H alkenyl sulfoximines (**32**).



Scheme 1-10 Reaction of sulfonimidoyl fluorides with unactivated alkynes **29** and alkenes **34**. AAC = azide-alkyne cycloaddition.

The authors extended this strategy to the use of unactivated alkenyl substrates (**34**).[132] *N*-*n*-Propyl sulfonimidoyl fluorides (**33**) were converted to the corresponding *N*-H, *C*-alkyl sulfoximines (**35**) in short reaction times, again using boron trifluoride diethyl etherate

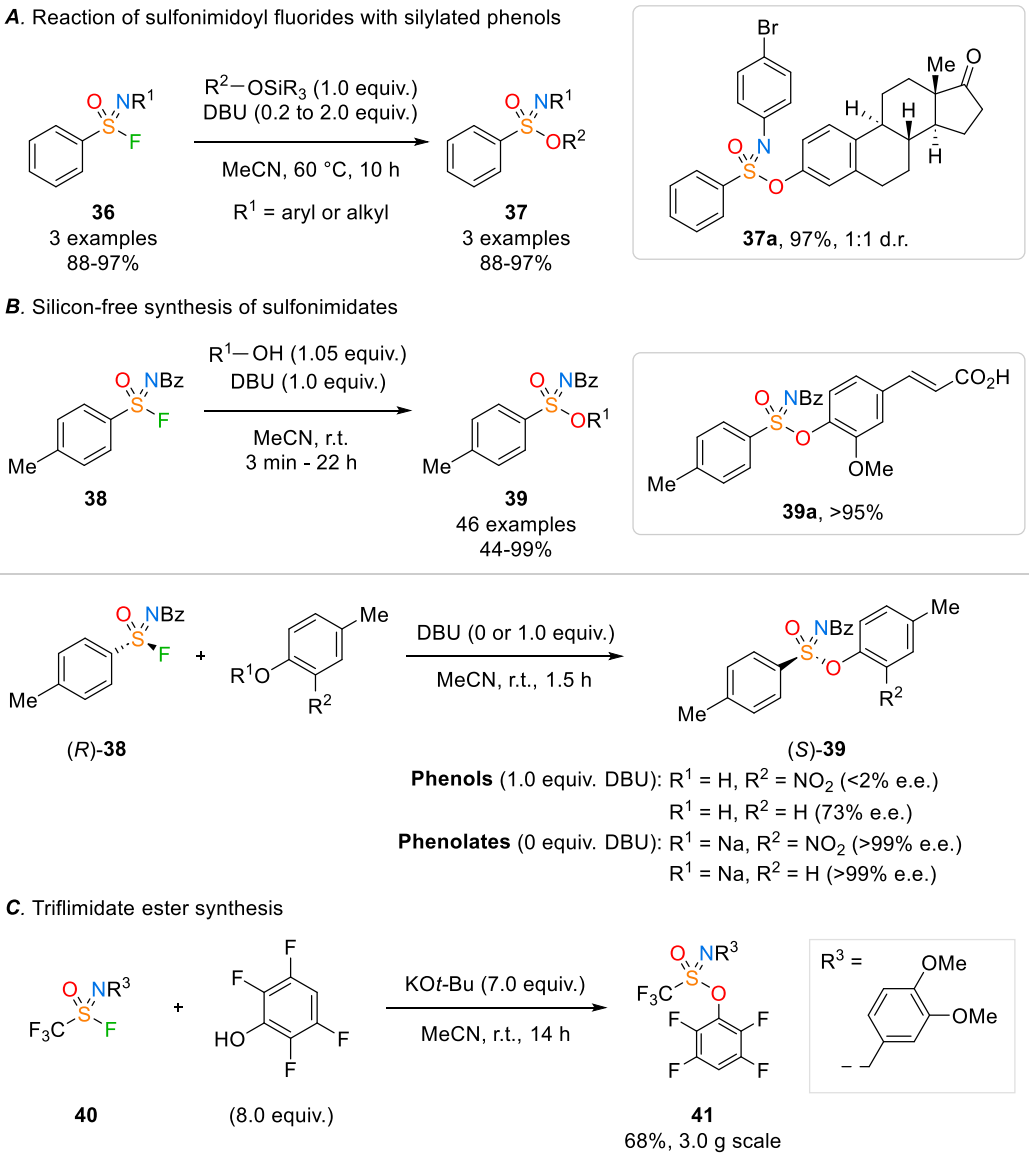
(**Scheme 1-10 B**). In the case of *N*-alkyl substituents, the authors propose the formation of a sulfonimidoyl cation; stabilised *via* interaction of the *p*-orbital of the nitrogen atom bearing an electron-rich group, which undergoes reaction with an alkene *via* a concerted transition state.

1.4.2 Reactions with oxygen-nucleophiles

Classically prepared from sulfonimidoyl chlorides in two-step procedures,[133] sulfonimidates have also been accessed from sulfonimidoyl fluoride analogues for more direct, modular access. Although sulfonimidates were first reported in the 1970s, they have seen a resurgence in recent years, most prominently as building blocks for the synthesis of sulfoximine and sulfonimidamides.[134] These reagents have also found uses as alkyl transfer reagents and as monomeric units in polymer chemistry.[135] Of note is the pioneering of sulfur-phenolate exchange (SuPhenEx) reactions by Zuilhof and co-workers, which provides a valuable addition to the toolbox of dynamic covalent chemistry.[136]

Sharpless and co-workers have demonstrated the DBU-promoted formation of S-O links from sulfonimidoyl fluorides and silicon-protected phenols, giving the corresponding sulfonimidates (**37**) at 60 °C (**Scheme 1-11 A**).[45] The driving force for this reactivity was thought to be derived from the strong silicon-fluorine bond formation during the course of the reaction. This class of reactions was later advanced by Zuilhof and co-workers in a silicon-free protocol (**Scheme 1-11 B**).[51] Unprotected phenols were found to be significantly more reactive than Si-protected counterparts, reacting in under 30 minutes for the majority of substrates at room temperature. It is of note that the sulfonimidoyl fluorides (**38**) used in this study possess an electron-withdrawing group on nitrogen, in contrast to *N*-aryl and -alkyl substrates used by Sharpless and co-workers.[45] Use of enantioenriched sulfonimidoyl fluoride (*R*)-**38** afforded sulfonimidates (*S*)-**39** enantiospecifically when using sodium

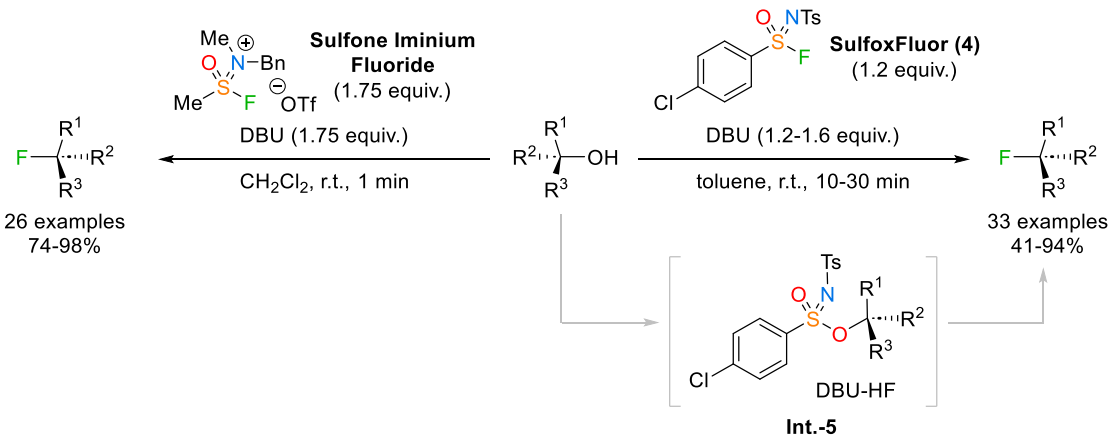
phenolates or an excess of electron-rich phenols, with the authors proposing an addition-elimination mechanism.[51] Less activated nucleophiles and treatment with DBU led to significant racemisation. This SuFEx reactivity has been exploited by the same laboratory for main-chain polymerisation of chiral di-sulfonimidoyl fluoride compounds with diphenol(ate)s.[137] The configurational chirality at sulfur of these compounds is an exciting advance; their optical activity might result in conformational effects on the polymer.



Scheme 1-11 Selected examples of formation of sulfonimidates from sulfonimidoyl fluorides.

Specific examples accessing triflimidates (**41**) have also been established (**Scheme 1-11 C**), initially using superstoichiometric quantities of tetrafluorophenol (8.0 equiv.) and potassium *tert*-butoxide (7.0 equiv.).[138] These products are bench-stable, precursors to sulfoximines and sulfonimidamides. An improved synthesis has since been devised, using phenols (1.5 equiv.) in combination with either DIPEA at room temperature (for *N*-aryl examples) or DBU at 50 °C (for *N*-alkyl examples).[139]

All of these reactions make use of phenol(ate)s as nucleophilic partners, with unsuccessful reports when aliphatic alcohols were used in their place.[51] As these compounds can be accessed in alternatives ways, their stability is presumably not the issue.[134] The products of these reactions, aliphatic sulfonimidates, may undergo further reaction with fluoride generated *in situ*. This is supported by the frequent use of SulfoxFluor, which rapidly converts alcohols into the corresponding alkyl fluorides at room temperature (**Scheme 1-12**), proceeding through the intermediate sulfonimidate ester (**Int.-5**).[120] Alternative sulfonimidoyl fluoride reagents that do not possess strong electron-withdrawing groups on nitrogen are less successful in these reactions. An alternative, highly reactive sulfone iminium fluoride has recently been disclosed by Melvin and co-workers.[140, 141] Reactions with alcohols, carboxylic acids and phosphinic acids are complete in one minute using this bench stable reagent.



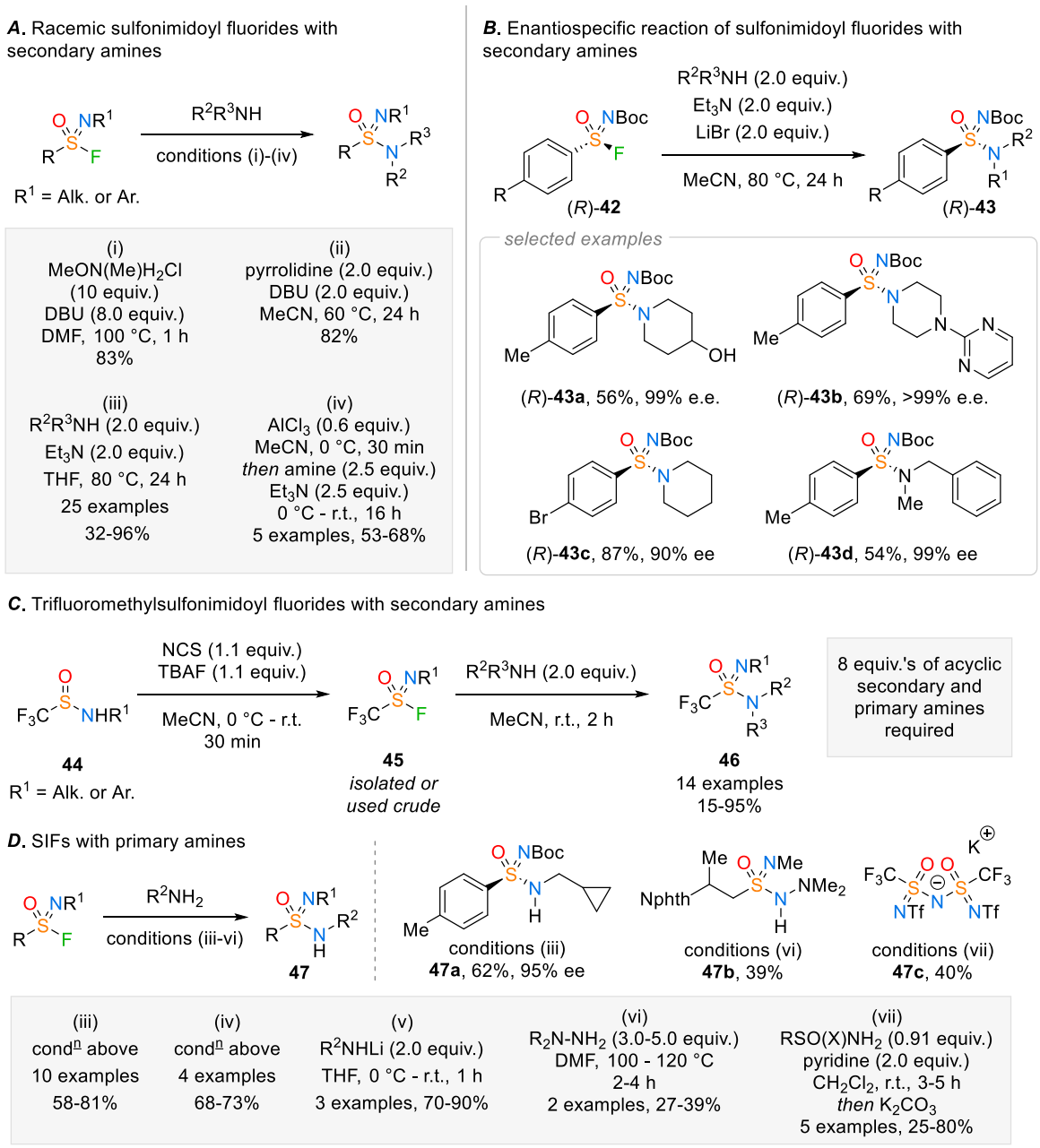
Scheme 1-12 Deoxyfluorination of aliphatic alcohols using sulfonimidoyl fluoride, SulfoxFluor (**4**) *via* sulfonimidate intermediate (**Int.-5**), and sulfone iminium fluoride.

1.4.3 Reactions with nitrogen-nucleophiles

Reaction of sulfonimidoyl fluorides with amine nucleophiles leads to the formation of sulfonimidamides. Akin to sulfonimidate esters, these compounds can be synthesised from sulfonimidoyl chlorides and sulfinamides, as well as sulfenamides. The products formed by the latter two, *N*-H sulfonimidamides,[142, 143] are complementary to those directly accessible from sulfonimidoyl halides (*N*-substituted).

The reaction of amines with sulfonimidoyl fluorides perhaps surprisingly requires harsher conditions than previously discussed nucleophiles and analogous reaction of sulfonyl fluorides (**Scheme 1-3**). For reaction of secondary amines, a range of conditions have been developed; excess amine and base (2.0 – 10 equivalents) can be employed at elevated temperatures (60 – 100 °C) (**Scheme 1-13 A**, conditions i-iii),[45, 110, 144] or the pre-treatment of the sulfonimidoyl fluoride with aluminium trichloride facilitates the subsequent nucleophilic addition of a secondary amine to occur at room temperature (**Scheme 1-13 A**, conditions iv).[117] Bull and co-workers demonstrated these reactions could be performed in an enantiospecific manner with a range of secondary amines ((*R*)-**43a-d**, **Scheme 1-13 B**), with lithium bromide used as a fluoride scavenger to prevent racemisation.[110] The one

exception to these conditions is the use of *C*-trifluoromethylsulfonimidoyl fluorides (**45**), which are significantly more reactive; reactions proceed at room temperature with amines, albeit significant excess of acyclic secondary amines is required (**Scheme 1-13 C**). These substrates are also efficient electrophiles when primary amine (8.0 equivalents) and ammonia (gas) nucleophiles are utilised. Primary amines have been used in a more general sense as their lithium amide form (**Scheme 1-13 D**, conditions v), at elevated temperatures (conditions iii and vi) and/or in large excess. Of note is the use of hydrazine (conditions vi, **47b**) and hydroxylamine (conditions i) analogues by the Crosswhaite group, with the sulfonimidamide products displaying interesting biological activity.[144] The use of *N*-triflylsubstituents has been exploited to enhance the reactivity of these compounds, with ammonia, lithium nitride and sulfon(imid)amide nucleophiles compatible under mild conditions.[145] The products of the latter two reactions (**47c**) are a class of superacids.



Scheme 1-13 Overview of the reactivity of sulfonimidoyl fluorides with primary, secondary and heteroatom-substituted amines utilising different reaction conditions.

1.4.4 Use as chemical probes

Despite the rich history of sulfonyl fluorides used as chemical probes, dating back to Fahrney and Gold's disclosure of PMSF,[78] the use of sulfonimidoyl fluorides in this context is limited to a singular publication by Grimster and co-workers.[146] In a study comparing the reactivity of S(VI)-F containing warheads, the authors found the choice of *N*-substituent of

sulfonimidoyl fluorides had a profound effect on the reactivity and stability of this class of compounds (**Figure 1-6**). Electron deficient sulfonimidoyl fluorides were found to label *N*-acetyltyrosine at a similar rate (*N*-boc (**48c**), relative rate = 0.98) or more rapidly (*N*-acetyl (**48a**) and *N*-pivaloyl (**48b**), relative rate = 2.5 and 1.22 respectively (**Figure 1-6 A**)) than the corresponding sulfonyl fluoride. Importantly, these compounds showed improved hydrolytic stability compared to sulfonyl fluoride **48d**. More electron rich analogues either showed little to no reactivity, with labelling using *N*-aryl substrate **48e** substantially reduced. *N*-Alkyl substrates (**48f**) were remarkably inert, with no reactivity or decomposition of these substrates observed, even at pH 5.[147] Similar trends in reactivity were observed with *N*-acetylcysteine (**49**), although this was more challenging to quantify as the reactions formed a mixture of disulfides **50a** and **50b** as the major components through a series of reduction reactions ((**Figure 1-6 B**).

The tuneable reactivity of sulfonimidoyl fluoride warheads clearly merits further investigation. The reduced electrophilicity of *N*-alkyl compounds is particularly promising in terms of designing selective chemical probes.

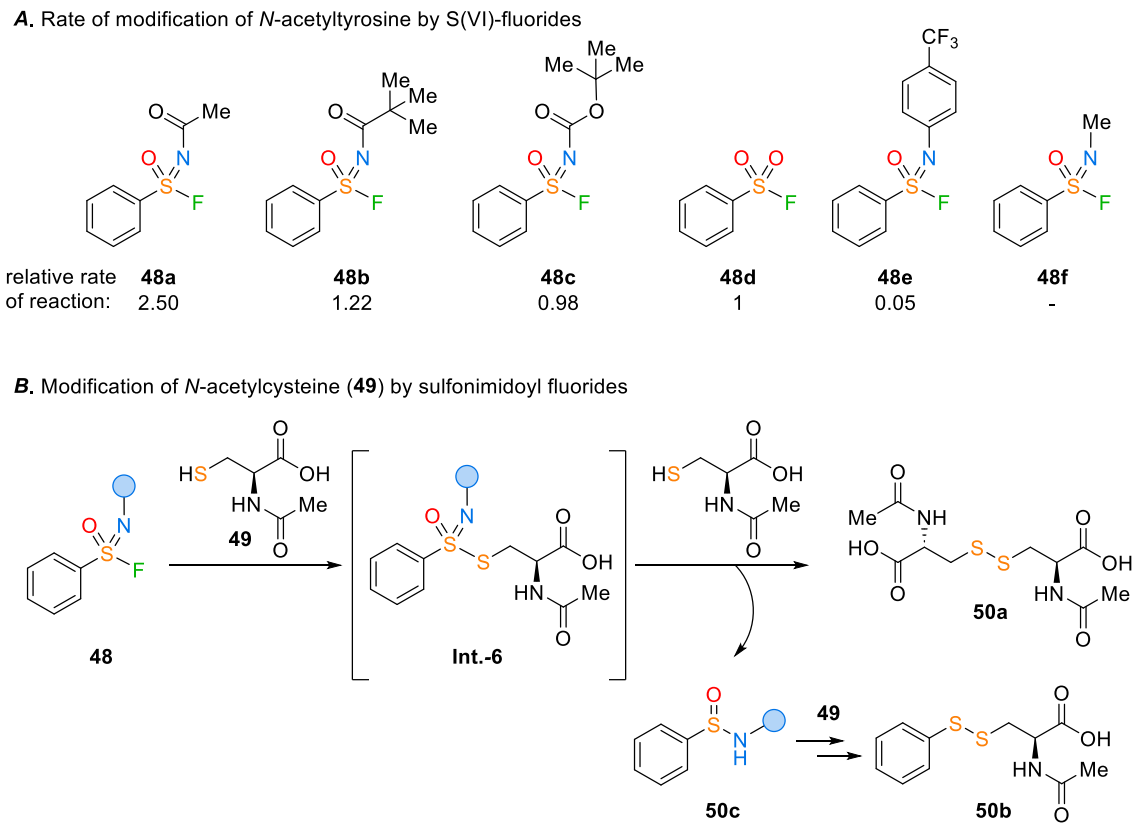


Figure 1-6 Evaluation of S(VI)-fluoride warheads with nucleophilic amino-acid side chains under physiological conditions (Grimster). All reactions performed at pH 7.5 and at 37 °C.

1.5 Summary and project objectives

This introduction has discussed the key advantages S(VI)-fluorides possess over other S(VI)-halides and common derivatisations of these reagents. The development of mono-aza-analogues, sulfonimidoyl fluorides, has led to advances in accessing aza-S(VI)-derivatives, such as sulfoximines and sulfonimidamides. The previous discussion has highlighted the benefits of sulfonimidoyl fluorides, with noticeable conditions towards their applications from Sharpless, Bolm and Bull laboratories. It is noticeable that the innate chirality of these compounds has not been fully utilised to date. Moreover, the systematic evaluation of the properties of sulfonimidoyl fluorides, such as their stereochemical stability, and their reactivity are yet to be studied.

One of the objectives of the research described in this thesis, was to develop methodologies for accessing optically pure sulfonimidoyl fluorides (**chapter 2.3**). These reagents are a privileged functional group in that they are chiral and reactive at sulfur, a property we endeavoured to explore in chemical biology settings (**chapter 2.4**). Building on this work, this research aimed to establish the utility of bifunctional sulfonimidoyl fluorides (chapter 3), where there are two reactive sites e.g., an additional alkene functionality. We envisaged that a new class of SuFExable hubs of this type would provide access to underrepresented aliphatic sulfonimidoyl fluorides and cyclic S(VI) systems. Thirdly, sulfinamide starting materials have been utilised to access S(VI)-functionalities but have yet to be evaluated for S-N bond cleavage reactions. Sulfinamides were investigated as alternative nucleophilic coupling partners in Pd-mediated processes (chapter 4), with the goal of improving cross-coupling conditions employed for sulfinate salts, such as lowering the reaction temperature.

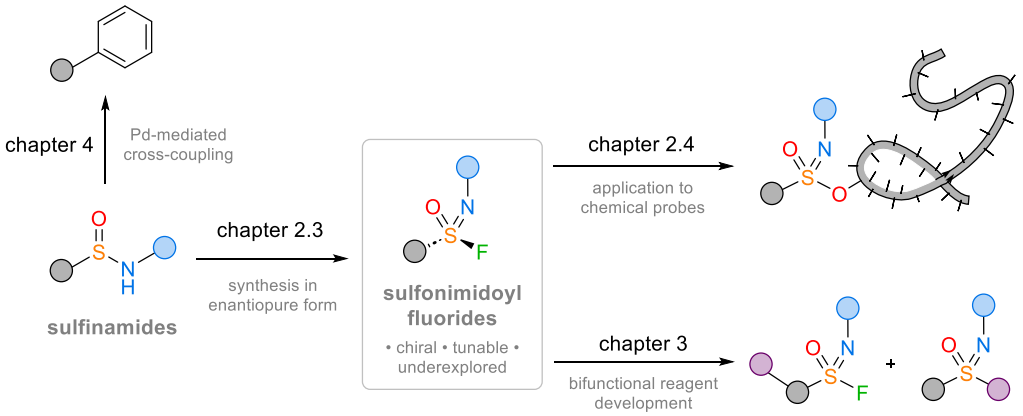


Figure 1-7 The key aims of this research.

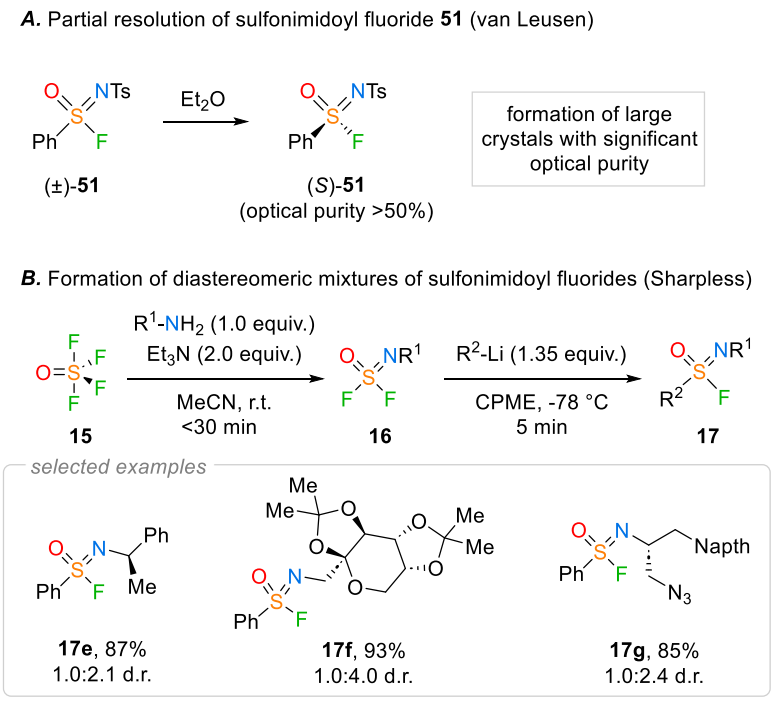
2 Enantioenriched sulfonimidoyl fluorides: synthesis and application

2.1 Introduction

The properties of sulfonimidoyl fluorides (SIFs) have been extensively discussed in chapter 1.3. In particular, their innate chirality is a significant benefit in comparison to their sulfonyl counterparts, provided that the stereocentre can be controlled. Accessing these motifs as single enantiomers is henceforth of significant interest, in particular for their use in the preparation of other chiral S(VI) functionalities, and as warheads in the context of chemical biology settings. Despite the substantial literature surrounding chiral S(IV) reagents, namely sulfinamides and sulfoxides,[1] chiral S(VI) reagents have been comparatively underexplored.[148, 149] We were encouraged by examples of the application of single enantiomers of other S(VI) substrates, namely sulfoximines[150] and sulfonimidamides,[114, 151] as chiral ligands and bioactive compounds.

2.1.1 Previous work on synthesis of enantioenriched sulfonimidoyl fluorides

A partial resolution of a single racemic sulfonimidoyl fluoride was the first foray into this area by Van Leusen in 1984 (**Scheme 2-1 A**).[128] Crystals of (*S*)-**51** were obtained from an ether solution of the racemic material (±)-**51**, with enrichment in the optical rotation achieved (>50% optical purity based on conversion to known sulfoximine). An alternative approach to access specific stereochemistry at sulfur is the formation of single diastereomers, through installation of additional stereocentre(s). The most prominent example of this strategy is from the Sharpless laboratory, wherein iminosulfur oxydifluorides (**16**), containing a chiral amine substituent, undergo reaction with organolithium reagents to generate sulfonimidoyl fluorides (**Scheme 2-1 B**).[45] This, however, results in formation of mixtures of inseparable diastereomers (**17e-g**, 1.1:1 to 4:1 d.r.), therefore, not providing a general strategy.



Scheme 2-1 Early efforts to access optically active sulfonimidoyl fluorides.

The lack of synthetic methods to access these compounds in high enantiomeric purity is highlighted by the separation of racemic sulfonimidoyl fluoride enantiomers using chiral preparative high-performance liquid chromatography (HPLC) reported by Zuilhof and co-workers.[51] This report did provide insightful information on the stereochemical fidelity of sulfonimidoyl fluorides, with single enantiomers stable in solution, but readily racemised in the presence of excess DBU at low temperatures.

2.1.2 Sulfinamides as precursors to S(VI) functional groups

We reasoned the ideal precursors to access enantioenriched sulfonimidoyl fluorides in an expedient manner are sulfinamides (**Figure 2-2**). Importantly, there are various methods reported for their stereoselective preparation, which have been reviewed in detail (Figure 2.1);[148, 152, 153] of note, chiral sulfinyl transfer agents that contain a pre-formed sulfur stereocentre (e.g., sulfinate esters or thiosulfinates), undergo nucleophilic displacement reactions with inversion of stereochemistry at sulfur (**Figure 2.1 A**). Although there have

been substantial developments in the asymmetric oxidation of sulfides and disulfides to sulfoxides and thiosulfinates respectively, the analogous conversion of sulfenamides to sulfinamides has been less well documented. There has been recent notable contribution from Tang, Li and co-workers wherein the first catalytic asymmetric oxidation of sulfenamides using chiral phosphoric acids was detailed (**Figure 2-1 B**).[154] Spontaneous crystallisation of diastereomeric mixtures of sulfinamides and resolution of sulfinamides have also been used, albeit to a lesser extent due to limited substrate scope.[155-157]

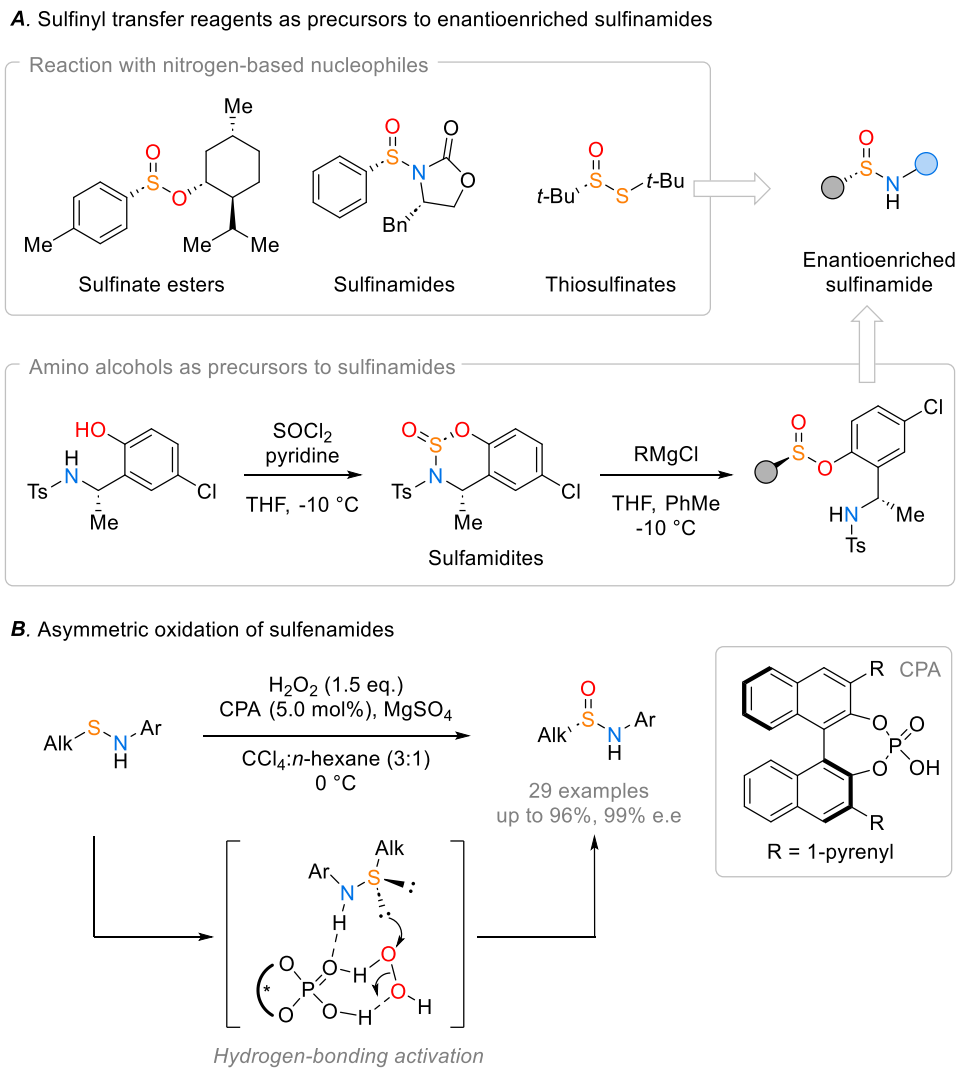


Figure 2-1 Examples of synthetic methods to access enantioenriched sulfinamides.

Sulfinamides are a unique class of S(IV) reagents, capable of both *N*-functionalisation and *S*-functionalisation *via* the respective lone pairs. The development of *tert*-butanesulfinamide as a chiral auxiliary catapulted the *N*-functionalisation of sulfinamides into the synthetic chemistry toolbox; namely for the synthesis of chiral amines (*via* condensation and reaction with an organometallic reagent, **Figure 2-2**, **52**).[158-161] *N*-Functionalised sulfinamides have since been used pre-eminently as ligands in asymmetric transformations (such as Ming-Phos, **53**, **Figure 2-2**).[1, 2, 162]

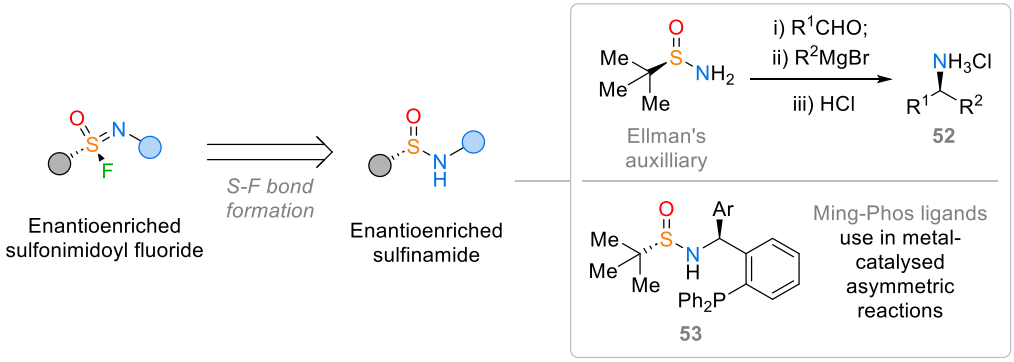
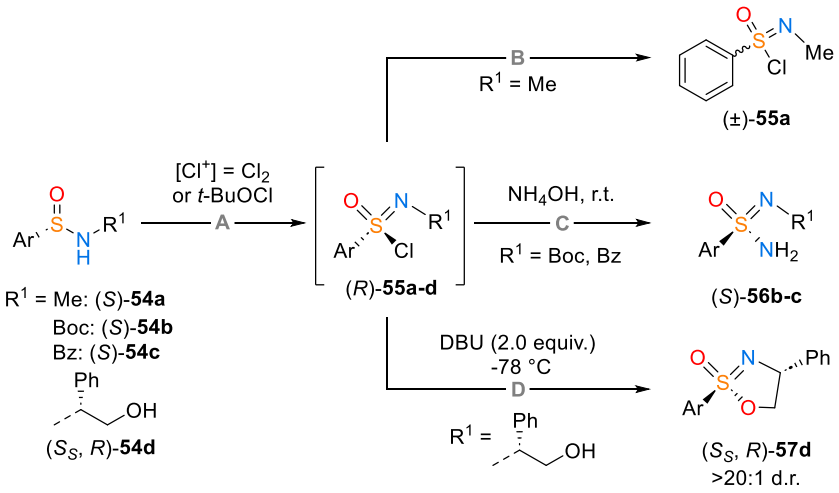


Figure 2-2 Sulfinamides as direct precursors to enantioenriched sulfonimidoyl fluorides *via* S-F fluorination and examples of their use for the synthesis of chiral amines (**52**) and as chiral ligands (**53**).

The requisite *S*-functionalisation of sulfinamides to S(VI) species is often accompanied by unwanted *N*-functionalisation, which would need to be controlled in our case. There have been various strategies for influencing this selectivity, including choice of *N*-substituent,[163, 164] electrophile[165] and base,[166] which are discussed in further detail below.

We were encouraged by precedent in the literature using enantioenriched sulfinamides as starting materials in stereospecific processes to access S(VI)-functionalities. Of note is the seminal work by Cram and Johnson, whereby the direct oxidation of sulfinamides to sulfonimidoyl chlorides was demonstrated (**Scheme 2-2**, **A**).[95, 167] When optically active *N*-alkylsulfinamide (*S*)-**54a** was subjected to oxidative halogenation, the reaction was found to proceed through the sulfur lone pair with retention of stereochemistry at sulfur ((*R*)-**55a**), although an inversion in the (Cahn-Ingold-Prelog) CIP nomenclature is noted (*S*) to (*R*). The

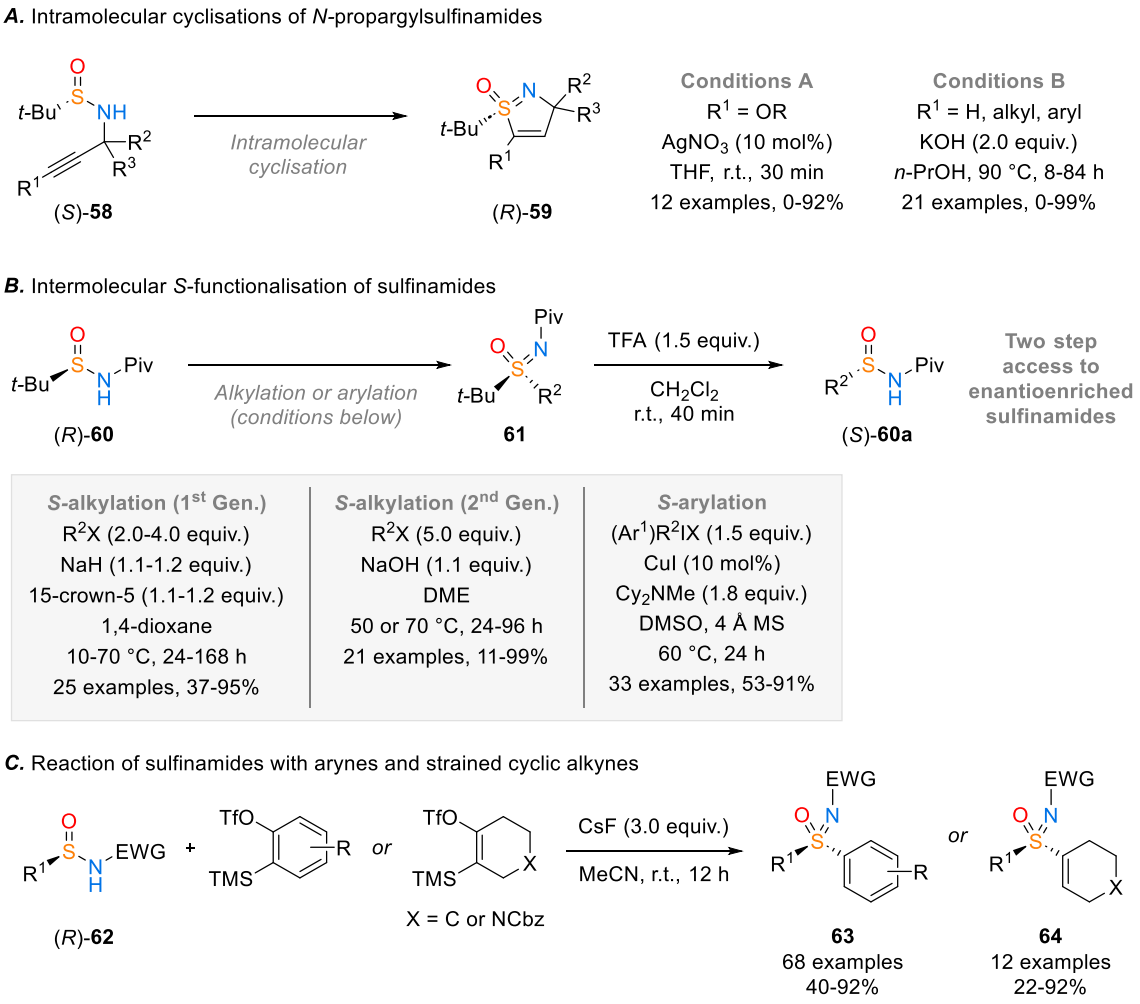
N-alkyl sulfonimidoyl chloride (**55a**) was found to be unstable, with racemisation occurring within few hours (**B**). The use of more stable *N*-EWG substituted analogues (**55b-c**) as intermediates was later explored by Bolm and co-workers (**Scheme 2-2**, **C**).[114] This gave independent proof of configuration of sulfonimidoyl chlorides, with absolute configurations of derived enantiopure sulfonimidamides, (*S*)-**56b-c**, assigned by X-ray structure determination and circular dichroism spectra. The Reggelin and Stockman laboratories have established a similar strategy for the stereocontrolled syntheses of cyclic sulfonimidates utilising enantioenriched sulfinamides as starting materials (**Scheme 2-2**, **D**).[107, 168] These products (**57d**) are convenient precursors to access enantioenriched sulfoximines through reaction with Grignard reagents.



Scheme 2-2 Stereospecific conversion of sulfinamides (**54**) to S(VI) reagents (**56-57**) *via* sulfonimidoyl chlorides (**55**).

The direct conversion of sulfinamides to sulfoximines has since been established, circumventing the intermediacy of sulfonimidates (**Scheme 2-3**). Intramolecular cyclisation of sulfinamides *via* the sulfur lone pair has been utilised for the synthesis of cyclic sulfoximines (**59**). For example, silver- and base-mediated 5-endo-dig cyclisations have been developed,[169, 170] proceeding with retention of stereochemistry at sulfur (**Scheme** 2-3 **A**). An even more diverse range of sulfoximines can be accessed *via* intermolecular C-

S bond formation. Recent studies from the Maruoka laboratory have shown that both *S*-alkylation (1st gen. and 2nd gen. conditions)[164,166] and *S*-arylation[163] of sulfinamides is possible in an enantiospecific manner (**Scheme 2-3 B**). The importance of the nitrogen-protecting group in these processes is highlighted, with the reactions limited to the use of specific electron-withdrawing groups (EWGs), namely pivaloyl (Piv), on nitrogen to avoid competing *N*- and *O*-functionalisation. One of the greatest utilities of this work is the reductive functionalisation of sulfoximine products (**61**) to the corresponding sulfinamides (*S*)-**60a** *via* de-*tert*-butylation reaction. Recent work has utilised enantioenriched *N*-EWG sulfinamides (*R*)-**62** in reactions with arynes and cyclic alkynes generated *in situ*, for the synthesis of sulfoximines (**63** and **64**, **Scheme 2-3 C**).[171]



Scheme 2-3 Stereospecific transformations of sulfinamides to sulfoximines.

2.1.3 Synthetic strategy

As the oxidative functionalisation of sulfinamides occurs with retention of the stereochemistry at sulfur, we rationalised a divergent approach could be envisaged to access both enantiomers of respective sulfonimidoyl fluorides (**Figure 2-3**). Reported oxidative chlorination followed by *in situ* halogen exchange (**A**) would give a net inversion process at sulfur (although (*S*)-sulfinamide to (*S*)-sulfonimidoyl fluoride by CIP nomenclature). Whereas the opposite enantiomer could be accessed *via* a direct oxidative fluorination approach (**B**, (*S*)-sulfinamide to (*R*)-sulfonimidoyl fluoride by CIP nomenclature). This strategy would be of particular use for the synthesis of pairs of enantiomers for use in chemical biology settings and for derivatisation to other S(VI)-functionalities through reaction at sulfur.

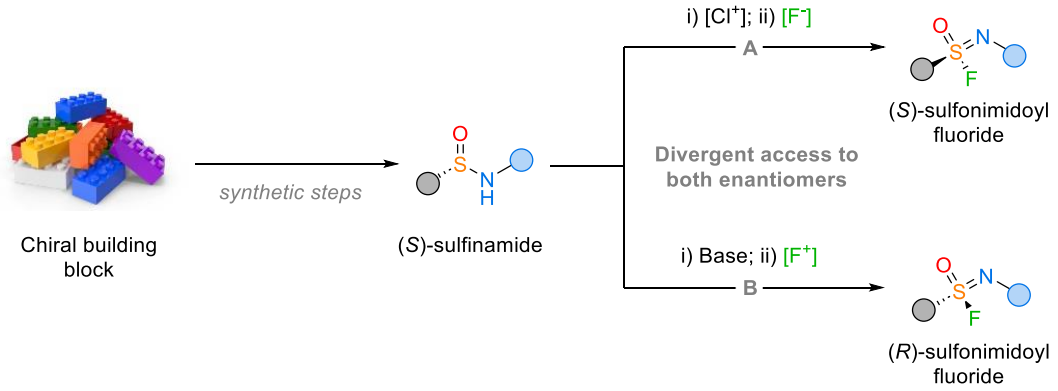
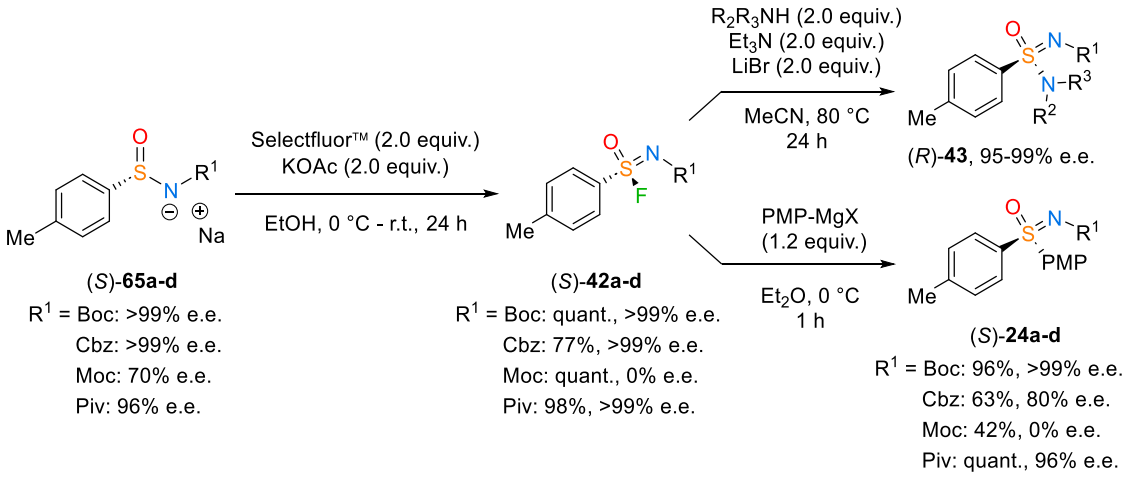


Figure 2-3 Synthetic strategy for accessing both enantiomers of sulfonimidoyl fluorides from a single enantiomer of sulfinamide.

During the course of this research, the oxidative fluorination of sulfinamide sodium salts (**65**) to form enantioenriched sulfonimidoyl fluorides was published by the Bull group (**Scheme 2-4**).[109, 110] The authors demonstrated Selectfluor™ was a competent electrophile for this process, with reactions proceeding enantiospecifically, with the exception of *N*-methyloxycarbonyl (moc) substrates (**65c**). The utility of enantiomerically pure sulfonimidoyl fluorides (**42**) was demonstrated by their reaction with amines and organometallic reagents to access enantioenriched sulfonimidamides (**43**) and sulfoximines

(**24**), respectively. The number of enantioenriched sulfonimidoyl fluorides accessed disclosed is limited and suffers from the requirement of formation of a sulfinamide salt (**65**) prior to reaction with an electrophilic fluorinating reagent.



Scheme 2-4 Synthesis of enantioenriched sulfonimidoyl fluorides (**42**) and their conversion to sulfonimidamides (**43**) and sulfoximines (**24**) in a series of enantiospecific transformations (Bull).

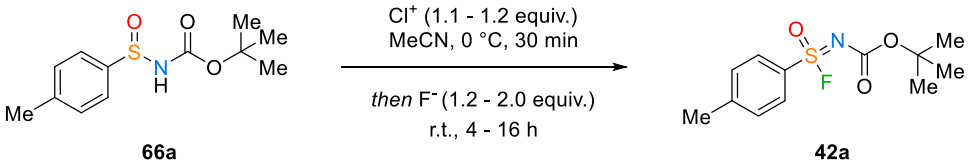
2.2 Racemic sulfonimidoyl fluorides

2.2.1 Optimisation of reaction conditions

The initial work on the project focused on the synthesis of racemic sulfonimidoyl fluorides from sulfinamides, as proof of concept for the desired transformation with enantioenriched materials. Racemic sulfinamides can be accessed in a straightforward manner from sulfinate, organometallic or thiol precursors.[28, 113, 161, 172, 173] Oxidative chlorination of sulfinamides followed by halogen exchange with a fluoride source is well precedented in the literature, with a variety of chlorinating agents and fluoride reagents suitable (**Scheme 1-5 A**).[111, 113, 118, 146] Literature conditions were initially trialled (**Table 2-1**, entry 1),[111] with moderate yield obtained (50%) using *tert*-butyl (*p*-tolylsulfinyl)carbamate (**66a**). Traditionally the halogen exchange reaction of sulfonimidoyl chlorides has required the addition of 18-crown-6 to solubilise the fluoride source.[111] Its use resulted in significant issues in terms of reproducibility for reactions in our hands, with varying quantities of hydrolysis products

observed; presumably due to the hygroscopicity of 18-crown-6. This is highlighted by the increase in yield observed when both KF and 18-crown-6 were dried under high-vacuum prior to use (50% to 74%, entry 1 *vs.* 2). We found that use of 18-crown-6 was not necessary, with comparable yield achieved (77%, entry 4). Furthermore, fewer equivalents (1.1 equiv.) of *tert*-butyl hypochlorite were well tolerated (entry 3). This is of significance given the associated toxicity of this chlorinating agent.[174] Accordingly, alternative chlorinating agents were trialled with NCS and TCCA proving optimal (84% and 83%, entries 5 and 6). These are both more user friendly as *tert*-butyl hypochlorite requires storage under an inert atmosphere at low temperature (<5 °C) and for reactions to be performed in a darkened fumehood.[174]

Table 2-1 Optimisation for conversion of sulfinamide **66a** to sulfonimidoyl fluoride **42a** *via* oxidative chlorination followed by halogen exchange. Isolated yields. [a] 18-crown-6 dried at 80 °C under high vacuum.



66a **42a**

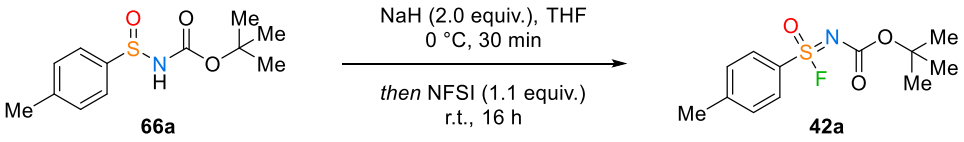
Entry	Cl^+ (equiv.)	F^- (equiv.)	Time (step 2)	Yield (%)
1	*t*-BuOCl (1.2)	KF (2.0), 18-crown-6 (0.1)	4 h	50
2	*t*-BuOCl (1.2)	KF (2.0), 18-crown-6 (0.1)[a]	16 h	74
3	*t*-BuOCl (1.1)	KF (2.0), 18-crown-6 (0.1)[a]	16 h	76
4	*t*-BuOCl (1.1)	KF (2.0)	16 h	77
5	TCICA (1.1)	KF (2.0)	16 h	84
6	NCS (1.1)	KF (2.0)	16 h	83
7	NCS (1.1)	AgF (2.0)	16 h	71
8	NCS (1.1)	CsF (2.0)	16 h	83
9	NCS (1.1)	TBAF (2.0)	16 h	<10
10	NCS (1.1)	KHF_2 (2.0)	16 h	85
11	NCS (1.1)	KHF_2 (1.5)	16 h	88
12	NCS (1.1)	KHF_2 (1.2)	16 h	95

Alternative fluoride sources were less successful (entries 7-9) with the exception of potassium bifluoride (KHF_2, 85%, entry 10). In particular, TBAF led to formation of an array of hydrolysis products (entry 9). Pleasingly, the stoichiometry of fluoride could be reduced to improve the atom economy, with isolated yield of 95% obtained with the optimised conditions (entry 12).

The more direct access to sulfonimidoyl fluorides, *via* oxidative fluorination, was modelled on the reactivity disclosed by Dr. Thomas Davies with an anionic sulfinamide, using NFSI as an oxidant (**Scheme 1-7 B**).[123] The yield for this transformation is moderate considering the formation of the sulfinamide intermediate is high yielding. In contrast to the formation of sulfonimidoyl chlorides (**Table 2-1**), use of a base to deprotonate the sulfinamide proved essential, with trace of the desired product obtained without (**Table 2-2**, entry 1). This may be due to the reduced electrophilicity of NFSI versus common chlorinating agents.[175, 176] Pleasingly, the initial hit for the reaction was high yielding (70%, entry 2). As the starting material was not fully consumed in 4 h at 0 °C (entry 2), longer reaction time and ambient temperatures were trialled to gain full conversion of the sulfinamide starting material (79%, entry 3). Sodium hydride presents multiple issues in relation to scale-up and use in industry, as well as often heterogeneous reaction mixtures.[177] Pleasingly, other bases were well tolerated (entries 4-6), including hydroxide and carbonate bases. The influence of the counterion in these examples was minimal (entry 5 *vs*. 6) even though its impact has been profound in other functionalisation reactions of sulfinamides.[110, 164] An increase in yield was observed on reducing the equivalents of both sodium hydride and potassium carbonate (entries 7, 8 and 10). From an atom economy and safety point of view this is advantageous. Addition of 15-crown-5 was found to be detrimental (<10%, entry 9), in contrast to its critical role in the *S*-alkylation methodology developed by Maruoka and co-workers (**Scheme 2-3 B**).[164] NFSI was found to be the optimum fluorinating agent, with alternative

fluorinating agents, such as Selectfluor™, unsuccessful with (entry 11) and without (entry 12) the presence of base. As NFSI has been found to be 4-6 orders less reactive than Selectfluor™ in reactions of enamines and stabilised anions,[175, 178, 179] the lack of reactivity can be ascribed to limited solubility in THF.

Table 2-2 Selected optimisation for conversion of sulfinamide **66a** to sulfonimidoyl fluoride **42a** *via* oxidative fluorination.



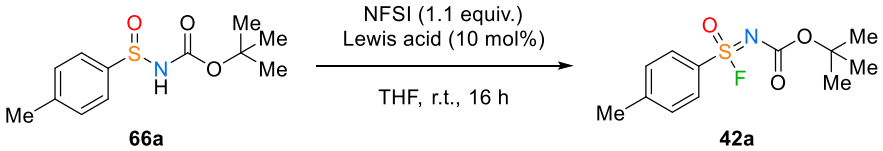
66a **42a**

Entry	Variation to above system	Yield (%)
1	no base	<10
2	2nd step: 0 °C, 4 h	70
3	-	79
4	Base: K_2CO_3 (2.0 equiv.)	78
5	Base: KOH (2.0 equiv.)	72
6	Base: NaOH (2.0 equiv.)	74
7	NaH (1.5 equiv.)	82
8	NaH (1.2 equiv.)	87
9	NaH (1.2 equiv.), 15-crown-5 (1.1 equiv.)	<10
10	K_2CO_3 (1.2 equiv.)	84
11	NaH (1.2 equiv.), Selectfluor™ (1.1 equiv.)	<10
12	no base, Selectfluor™ (1.1 equiv.)	<10

In an attempt to address the lack of reactivity in base-free reactions (**Table 2-2**, entry 1), we turned towards the evaluation of Lewis acid additives for the activation of NFSI (**Table 2-3**), a strategy previously employed to enhance the rate of fluorination of β-keto esters.[180] Use of copper and zinc triflate (44 and 33%, entries 1 and 2 respectively) resulted in significant enhancement of reactivity (*vs.* entry 1), albeit with significant quantities of sulfinamide **66a** starting material unreacted. The importance of the metal counterion is highlighted by the lack of reactivity observed using $Sc(OTf)_3$ (entry 3). Although addition of $TiCl_4$ resulted in complete consumption of starting material, none of the desired product was observed (entry

4). This may be a result of Lewis acid activation of the desired sulfonimidoyl fluoride resulting in hydrolysis products. These results are still encouraging, especially for the use of base-sensitive starting materials, and further investigation may be warranted.

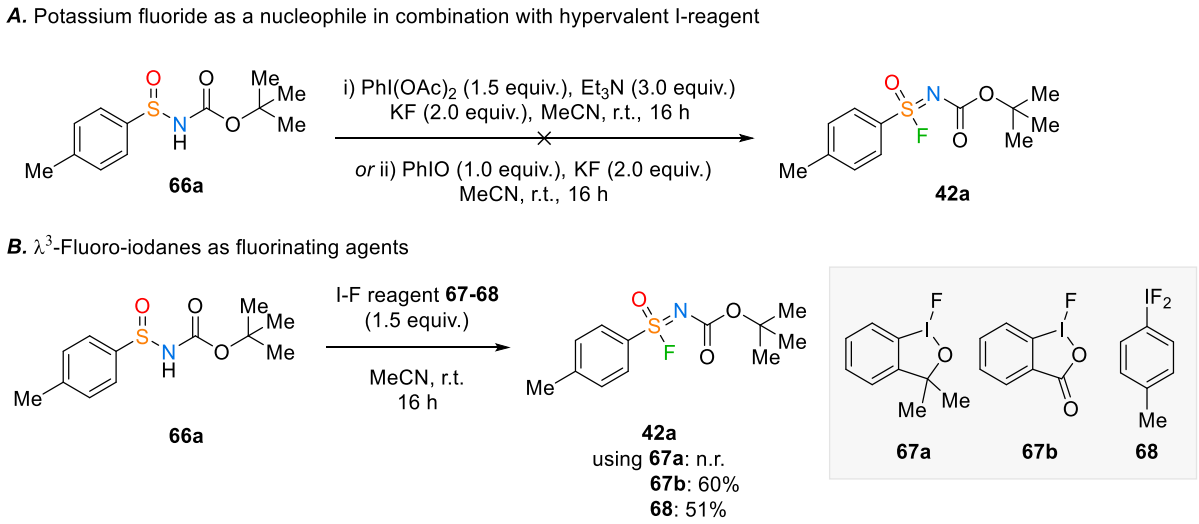
Table 2-3 Synthesis of sulfonimidoyl fluoride **42a** using Lewis acids.



Entry	Lewis acid	Yield (%)
1	$Cu(OTf)_2$	44
2	$Zn(OTf)_2$	33
3	$Sc(OTf)_3$	n.r.
4	$TiCl_4$	decomp.

To this end, the use of hypervalent iodine reagents was explored. We were encouraged by literature reactions of sulfinamides with hypervalent iodine reagents in combination with alcohol and amine nucleophiles to form sulfonimidates and sulfonimidamides, respectively.[143, 181] Employing KF (2.0 equiv.) as the nucleophile under the published conditions resulted in minimal conversion of the starting material and no product formation in both cases (**Scheme 2-5 A**). The use of pre-formed λ^3-fluoro-iodanes, a class of environmentally benign, cheap and tunable reagents was instead investigated (**Scheme 2-5 B**).[182, 183] The highly reactive nature of linear iodoarenes (such as **68**) initially limited their use,[182] until the introduction of bench stable cyclic fluorobenziodoxoles **67a** and **67b**.[183, 184] These reagents can be accessed in 1-3 steps from cheap, commercially available 2-iodomethylbenzoate and 2-iodobenzoic acid respectively.[29, 184, 185] Of note is the recent commercial availability of dimethyl analogue **67a**.[186] Their applications are widespread from accessing fluorinated heterocycles to metal-catalysed iodofluorination reactions,[187, 188] often complementary to alternative fluorinating agents.[189-191] To the best of our knowledge, their use for formation of heteroatom-fluorine bonds has yet to be disclosed.

No product was detected using dimethyl fluoro-iodane **67a** in combination with sulfinamide **66a** at room temperature (**Scheme 2-5 B**). Encouragingly, use of **67b** gave a 60% yield, with no remaining starting material observed in crude ^{1}H NMR spectra. Difluoroiodotoluene **68** was also found to be a competent electrophile (51%). However, this reagent was not investigated further due to its associated toxicity, hygroscopicity and propensity to liberate HF.[182]

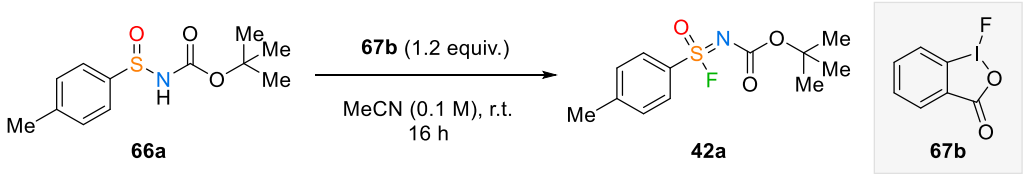


Scheme 2-5 Evaluation of the use of hypervalent iodine reagents (**67-68**) for accessing sulfonimidoyl fluoride **42a**.

Unlike the use of NFSI, there was no requirement for base to be used in these transformations with higher yields obtained in its absence (**Table 2-4**, entry 1). A short optimisation was carried out to achieve higher yields for this transformation using fluoro-iodane **67b**. Pleasingly, comparative yield (54%) was obtained using fewer equivalents of **67b** (entry 2), this was found to aid purification as excess **67b** was difficult to separate from sulfonimidoyl fluoride **42a** by column chromatography. Alternative solvents commonly used in combination with fluoro-iodanes had a significant impact on reactivity (entries 3-7); use of THF, $CHCl_3$ and hexafluoroisopropanol (HFIP) resulted in no reaction progression (entries 3-5), whereas α,α,α-trifluorotoluene resulted in similar conversion (49%, entry 6). The activation of hypervalent fluoroiodane reagents by hydrogen bonding to HFIP has been

reported, albeit at elevated temperatures.[192] Dichloromethane (entry 7) proved optimal with high yield obtained (81%). The use of fluoro-iodanes satisfies an important criterion for late-stage electrophilic fluorinating reagents, namely that their preparation from simple anionic fluoride salts can be modulated for the use of ^{18}F-labelling studies; a potential future application of the developed methodology.[193]

Table 2-4 Selected optimisation of oxidative fluorination of sulfinamide **66a** using **67b**.



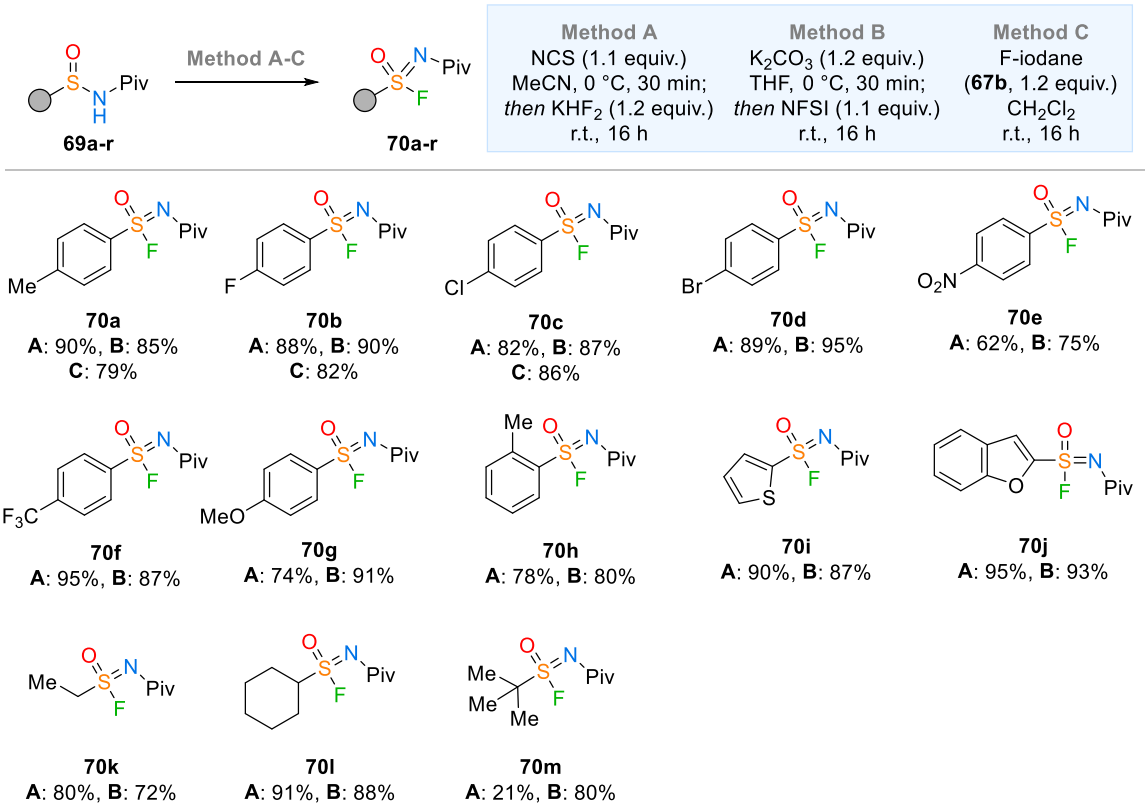
Entry	Variation to above system	Yield (%)
1	NaH (1.2 equiv.), **67b** (1.5 equiv.)	34
2	-	54
3	THF (0.1 M)	n.r.
4	$CHCl_3$ (0.1 M)	n.r.
5	HFIP (0.1 M)	n.r.
6	$PhCF_3$ (0.1 M)	49
7	CH_2Cl_2 (0.1 M)	81

2.2.2 Scope of reactions

Pleasingly, a variety of *C*-aryl, *N*-Piv substituted sulfinamides (**69**) were efficiently converted to their corresponding sulfonimidoyl fluorides (**70**) using the three discussed strategies (**Table 2-5**). Various *para*-substituted aromatics were well tolerated including functional handles, such as halides (**70b-7d**) and nitro functionality (**70e**), which could be potentially derivatised as bifunctional reagents. Importantly, all methods were high yielding for these transformations. Both electron-deficient (**70e** and **70f**) and electron-rich (**70g**) aromatic sulfonimidoyl fluorides were accessed in moderate to good yields. Steric hindrance at the sulfur centre was well tolerated, with *ortho*-methyl substituted sulfonimidoyl fluoride **70h** accessed in high yields (82% and 85%, respectively for method A and B). Pleasingly heteroaryl sulfinamides (**69i** and **69j**) performed analogously under oxidative chlorination

and fluorination conditions to give **70i** and **70j**. Aliphatic sulfinamides (**69k-69m**) in general were competent substrates, with the exception of *tert*-butyl sulfinamide (**69m**). This starting material resulted in poor conversion *via* oxidative chlorination (Method A), although high yields were achieved using direct fluorination (Method B). This diminished reactivity seems to be a consequence of steric hindrance at sulfur as other aliphatic sulfonimidoyl fluorides were isolated in good yields, with linear chains and cyclic systems being readily incorporated.

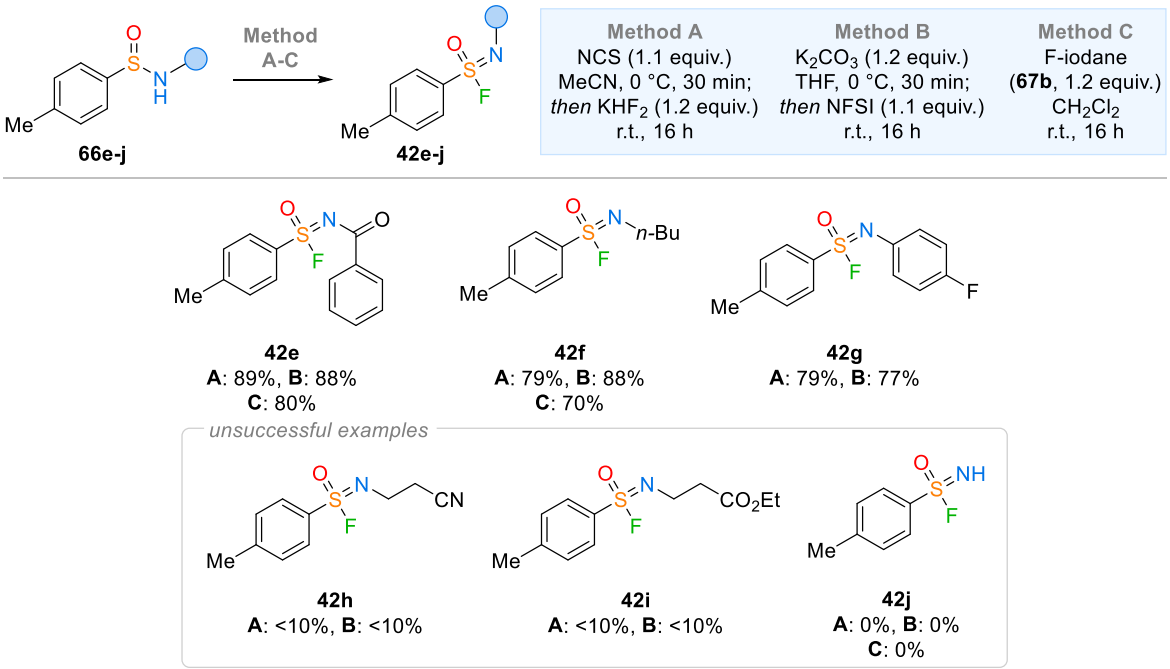
Table 2-5 Scope of the oxidative halogenation of sulfinamides **69** *via* oxidative chlorination (halogen exchange, method A), fluorination (methods B and C). Variation of the carbon substituent of the sulfinamide partner.



The compatibility of a variety of nitrogen functionalities was explored using *para*-toluene *N*-substituted sulfinamides (**66**). We were pleased to find various sulfonimidoyl fluorides (**42**) could be accessed, giving potential to tune the reactivity of these reagents based on the electronic and steric properties of the substituent (**Table 2-6**). Alternative

electron-withdrawing groups on nitrogen were efficient starting materials, including benzoyl protecting group (**66e**), yielding the corresponding sulfonimidoyl fluoride in excellent yields (**42e**). *N*-Butyl sulfonimidoyl fluoride (**42f**) was synthesised in high yields, showcasing the method's tolerance of aliphatic side-chains. Furthermore, aniline motifs yielded promising results (**42g**). Unfortunately, substrates containing β-EWG's on nitrogen were unsuccessful (**42h** and **42i**). The desired products would be useful precursors to form cyclic sulfonimidamides or sulfonimidates through reduction and concomitant cyclisation in a one-pot SuFEx reaction. Disappointingly, attempts to access *N*-H substrate (**42j**) were also unsuccessful, with only decomposition products observed, including sulfonyl fluorides. The sulfonimidoyl fluorides synthesised have shown remarkable stability with little to no degradation observed by ^{1}H NMR spectroscopy for all substrates stored on the benchtop for periods up to a year.

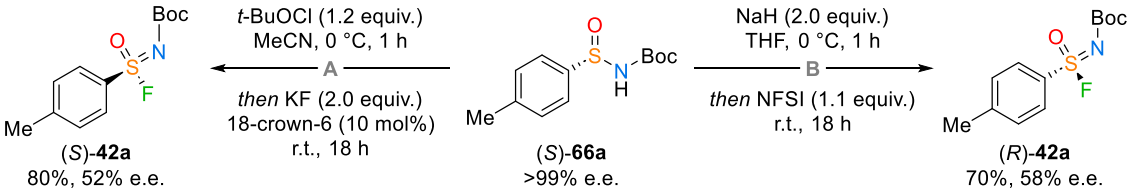
Table 2-6 Scope of the oxidative halogenation of sulfinamide **66** *via* oxidative chlorination (halogen exchange, method A), fluorination (methods B and C). Variation of the nitrogen substituent of the sulfinamide partner.



2.3 Enantiomerically pure sulfonimidoyl fluorides

2.3.1 Optimisation of conditions

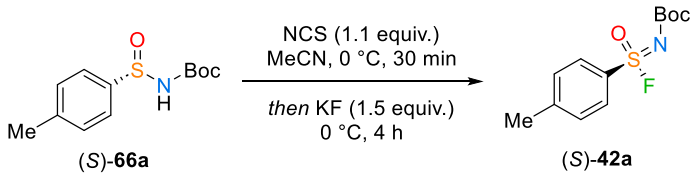
We planned to apply the reaction conditions and scope developed for the conversion of racemic sulfinamides to sulfonimidoyl fluorides for the synthesis of optically pure reagents. The synthesis of enantioenriched sulfinamides was achieved in 1-3 steps from commercially available starting materials following literature preparations (see the experimental section for full details). Reaction of enantioenriched (*S*)-*tert*-butyl (*p*-tolylsulfinyl)carbamate sulfinamide, (*S*)-**66a**, under initial halogenation conditions (methods A and B) proceeded in good yield (**Scheme 2-6**). Pleasingly, both enantiomers of **42a** were accessed using the two discussed methods, giving proof-of-concept for the enantiodivergent approach. To our disappointment both the reactions were not enantiospecific.



Scheme 2-6 Conversion of (*S*)-**66a** to both enantiomers of **42a** using initial reaction conditions.

The removal of 18-crown-6 proved to be crucial, again, with significant enhancement in enantiospecificity observed in its absence, in combination with shorter reaction time (**Table** 2-7, entry 1). Fewer equivalents of fluoride source resulted in improved retention of stereochemical information (entries 2-5), with use of both KF and KHF_2 (1.2 equiv.) affording (*S*)-**42a** in high enantiomeric excess (97 and >99% e.e., entries 5 and 6).

Table 2-7 Optimisation of enantiospecific oxidative halogenation sequence for (*S*)-**66a**. Isolated yields.

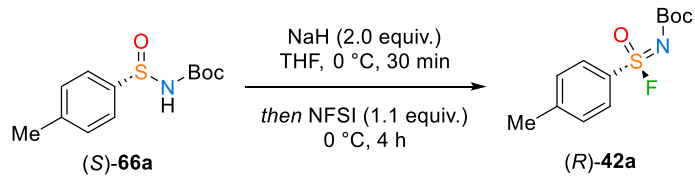


(*S*)-**66a** (*S*)-**42a**

Entry	Variation to above system	Yield (%)	e.e. (%)
1	*t*-BuOCl (1.2 equiv.), KF (2.0 equiv.)	80	79
2	-	91	91
3	KHF_2 (1.5 equiv.)	93	92
4	KF (1.2 equiv.)	88	97
5	KHF_2 (1.2 equiv.)	94	>99

Reducing the reaction time for both steps of the oxidative fluorination sequence (1st step: 30 min *vs.* 1 h, 2nd step: 8 h *vs.* 18 h) resulted in significantly improved enantiospecificity of the reaction (**Table 2-8**, entry 1 *vs.* **Scheme 2-6**, **B**). The non-stereospecificity can tentatively be ascribed to excess base in the reaction and/or elevated temperatures; an increase in the enantiomeric excess for *(R)*-**42a** was observed with reduction in the stoichiometry of the base (entries 2 *vs.* 3 and 4 *vs.* 5) at 0 °C. This led to the optimised conditions for oxidative fluorination (entries 3 and 5), with the reaction proceeding enantiospecifically in both cases.

Table 2-8 Optimisation of enantiospecific oxidative fluorination to (*R*)-**42a**. Isolated yields.

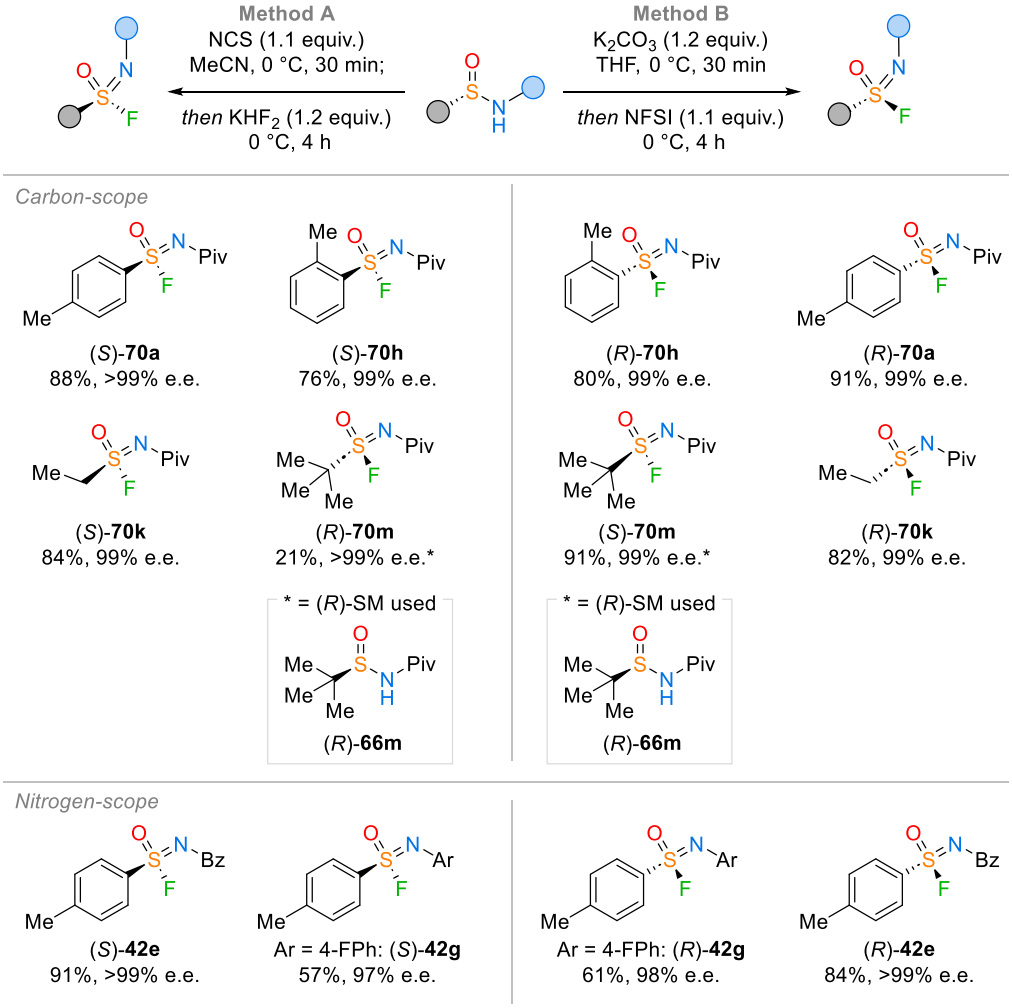


(*S*)-**66a** (*R*)-**42a**

Entry	Variation to above system	Yield (%)	e.e. (%)
1	2nd step: r.t., 8 h	72	82
2	NaH (1.5 equiv.)	74	91
3	NaH (1.2 equiv.)	87	>99
4	K_2CO_3 (1.5 equiv.)	73	95
5	K_2CO_3 (1.2 equiv.)	77	>99

2.3.2 Scope of enantioenriched sulfonimidoyl fluorides

A series of other enantioenriched sulfonimidoyl fluorides were synthesised (**Scheme 2-7**, Method A and B). It was found that *C*-aryl *N*-Piv sulfinamides ((*S*)-**69a** and **h**) were converted to both enantiomers of the corresponding sulfonimidoyl fluorides (**70a** and **h**) in high enantiomeric excess. Of note is that steric hindrance is well tolerated ((*S*)-**70h**). Pleasingly both enantiomers of *C*-ethyl sulfonimidoyl fluoride (**70k**) were accessed in high enantiomeric excess. Ellman-auxiliary analogue (*R*)-**69m** yielded the desired product (*R*)-**70m** in low yield (21%) using method A. The direct fluorination occurred with high yields and stereospecificity ((*S*)-**70m**, 91%, 99% e.e.). Other electron-withdrawing groups on nitrogen such as benzoyl (**42e**) were well tolerated with high yield and enantioselectivities obtained for both enantiomers. Difficulties encountered in the synthesis of enantioenriched *N*-alkyl and -aryl sulfinamides has limited progress in accessing other *N*-substituted substrates. However, a singular example of aniline derived sulfonimidoyl fluoride (**42g**) was prepared in high enantiomeric excess (97% and 98% e.e., respectively). This is importantly the first example of a non-EWG substituted enantioenriched sulfonimidoyl fluoride.

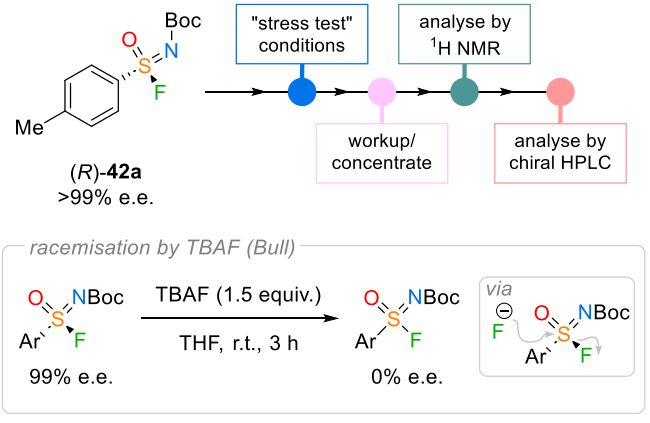


Scheme 2-7 Scope of enantioenriched sulfonimidoyl fluorides accessed using enantioenriched sulfinamides.

2.3.3 Stability tests of enantioenriched sulfonimidoyl fluorides

With plans to use sulfonimidoyl fluorides as linchpins for accessing other S(VI) functional groups and as chemical probes, their stability, tolerance to a variety of reaction conditions and stereochemical fidelity was of utmost importance. Therefore, optically pure *N*-boc sulfonimidoyl fluoride (*R*)-**42a** was employed in a series of 'stress test' conditions to see if any decomposition of the reagent or degradation of the stereochemical fidelity was observed (**Figure 2-4**). Stirring in a variety of solvents resulted in no detectable racemisation or degradation (entries 1-3), in particular, the use of DMSO and H_2O is promising for application in biological systems. However, the use

of isopropanol resulted in moderate levels of degradation and racemisation (entry 4). The sulfonimidoyl fluoride (*S*)-(**42a**) was resubjected to reaction conditions employed in its synthesis (entries 5-7), with only addition of excess fluoride proving detrimental (entry 7); this is in line with previous results during this project, whereby reduced equivalents of fluoride resulted in improved enantiospecificity (**Table 2-7**). Furthermore, the recent publication by the Bull group reaffirms this hypothesis.[110] The authors show that treatment with TBAF leads to significant racemisation (0% retention in e.e., **Figure 2-4**). The observed retention of stereochemical information on treatment with base (entry 5) suggests that the reduced enantiospecificity observed in optimisation of oxidative fluorination conditions for enantioenriched sulfinamide ((*S*)-**66a**, **Table 2-8)**, is not due to racemisation of the sulfonimidoyl fluoride product (**42a**). Subjection of (*R*)-(**42a**) to silica for 4 hours was also well tolerated with no degradation observed. Further exploration of the stability of these compounds is warranted, in particular, with differing *N*- and *C*-substituents, in the presence of buffer solutions and to different wavelengths of light.



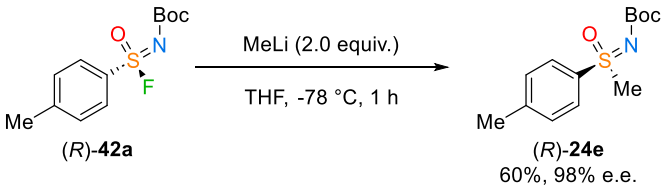
Entry	Conditions	Decomposition[a]	e.e.
1	DMSO	0%	>99%
2	H_2O	0%	>99%
3	$CDCl_3$	0%	>99%
4	IPA	25-30%	75%
5	NaH (1.5 equiv.)[b]	0%	98%
6	NFSI (1.1 equiv.)[b]	0%	98%
7	KHF_2 (1.5 equiv.)[c]	0%	93%
8	silica, 4 h	0%	98%

(*R*)-**42a** in solvent (0.1 M), r.t., 18 h. [a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]THF, 0 °C, 4h. [c]MeCN, 0 °C, 4 h.

Figure 2-4 Stability tests of (*R*)-**42a** under a range of conditions.

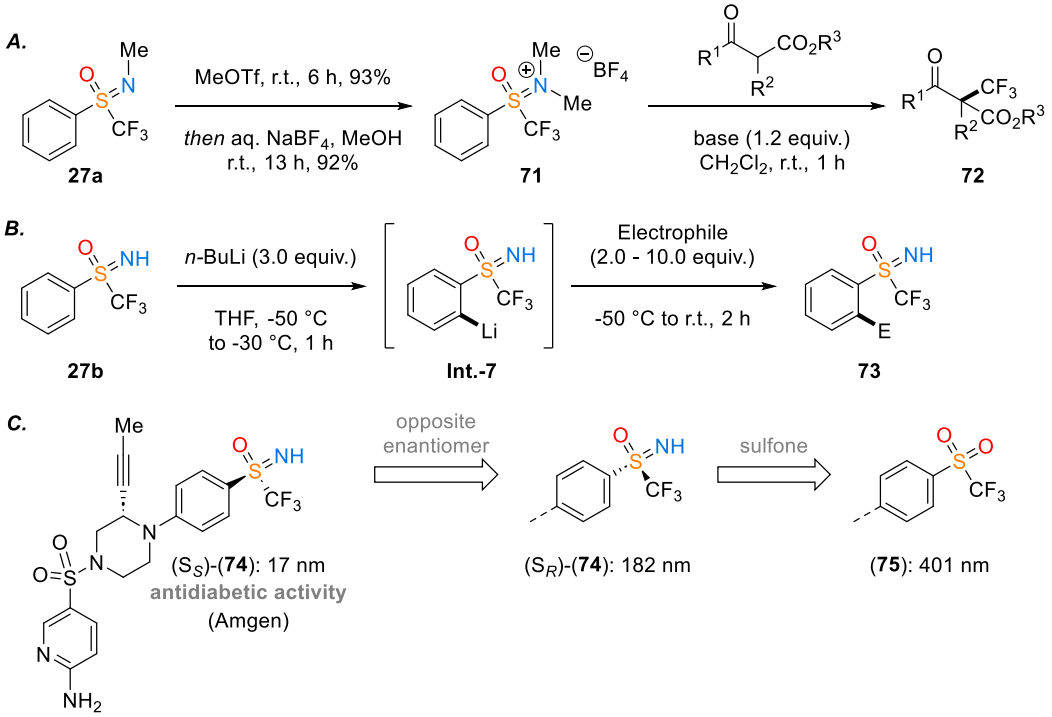
2.3.4 Derivatisations of sulfonimidoyl fluorides

The application of enantioenriched sulfonimidoyl fluorides as direct precursors to chiral sulfonimidamides and sulfonimidates has been demonstrated by the Bull and Zuilhof groups, respectively (chapter 1.4).[51, 110] As previously discussed, the Bull group were able to effectively combine Grignard reagents with enantioenriched sulfonimidoyl fluorides to access sulfoximines (**Scheme 1-9 B**). We were interested in developing a complementary methodology, wherein organolithium nucleophiles would be utilised to access chiral sulfoximines. Reaction of *N*-Boc sulfonimidoyl fluoride (*R*)-**42a** with methyl lithium proceeded in an enantiospecific manner (**24e**, 98% e.e.) in moderate yield (60%) using unoptimized conditions (**Scheme 2-8**). The expansion of this methodology to more complex substrates and further derivatisations would be of interest.



Scheme 2-8 Conversion of (*R*)-**42a** to the corresponding enantioenriched sulfoximine **24e**.

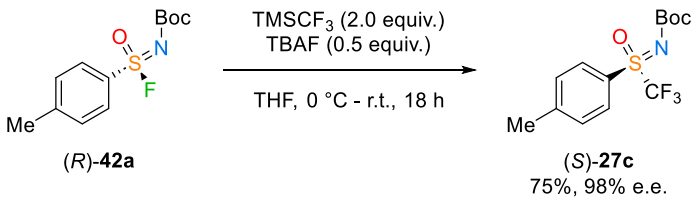
Moreover, the utility of enantiopure sulfonimidoyl fluorides has not been fully realised, in particular for accessing enantiopure *S*-trifluoromethyl sulfoximines. These reagents have been historically underexplored, with notable works from Magnier, Hu and Bolm groups reigniting interest in recent years.[194-196] They have varied applications (**Scheme 2-9**), for example, as precursors to fluoroalkylating agents (e.g. Shibata's reagent, **71**),[197] ortho-directing groups in directed metalation sequences (**27b**)[198], and importantly as bioactive substances with antidiabetic activity (**74**).[199] Notably, scientists at Amgen found trifluoromethylsulfoximine (S_S)-**74** was approximately 23 times more potent than the corresponding sulfone analogue (**75**).[199] Interestingly, the stereochemistry at sulfur for this compound could exhibit a 10-fold difference in reactivity (*vs.* (S_R)-**74**).



Scheme 2-9 Selected applications of *S*-trifluoromethyl sulfoximines: (***A***) Use as precursors to sulfone iminium reagent **71**, a trifluoromethylation reagent; (***B***) directing groups for ortho-lithiation and functionalisation; (***C***) application as antidiabetic reagents.

Despite these applications, the asymmetric synthesis of trifluoromethyl sulfoximines has yet to be reported. The preparation of these compounds in an enantiomerically pure manner has relied on separation by chiral semi-preparative HPLC or supercritical fluid chromatography of the product or of sulfilimine precursors respectively.[200, 201]

Encouragingly, we found that utilisation of the conditions reported by Bolm and co-workers to access these compounds racemically, using the Ruppert-Prakash reagent ($TMSCF_3$) with enantiopure sulfonimidoyl fluoride (*R*)-**42a**,[113] resulted in a stereospecific method for accessing trifluoromethylated sulfoximine **27c** in high yields (**Scheme 2-10**).



Scheme 2-10 Application of (*R*)-**42a** for accessing *S*-trifluoromethyl sulfoximine **27c**.

Application of this strategy to *tert*-butane substituted substrates, such as **70m**, with subsequent de-*tert*-butylation would potentially give access to enantioenriched trifluoromethyl sulfinamides.[202] This class of reagents are useful linchpins for accessing other *C*-trifluoromethyl aza-S(VI) species in an optically pure manner. Furthermore, use of difluoromethyl and monofluoromethyl substrates using analogous conditions may solve the limited methods to access these compounds.[203]

2.4 Application to synthesis of bifunctional probes

2.4.1 Chiral chemical probes

Community-wide efforts to expand the portfolio of validated small molecule probes have led to initiatives such as Target 2035, with the goal to develop a suite of chemical tools to modulate every protein in the proteome by 2035.[204] Chemical probes for investigating catalytic serine, threonine and cysteine residues have advanced considerably and are now widely implemented in an increasing number of academic and drug discovery programs.[205] Expanding the types of amino acid residues targetable is important for advancing protein function and chemical probe discovery.[206, 207] The use of S(VI)-fluorides in this regard is of particular interest, given their propensity to engage with serine, threonine, lysine, tyrosine, cysteine and histidine residues (**Chapter 1.2.2**).[208] The replacement of one S=O bond for an imidic S=N functionality has recently been shown to improve the selectivity of these somewhat promiscuous class of compound; sulfuramimidoyl fluorides were found to have attenuated reactivity *vs.* their fluorosulfate analogues by Kelly, Sharpless and co-workers (**Figure 2-5 A**).[209] This weaker electrophilicity was utilised for the application of these compounds in inverse drug discovery approaches. These results, in combination with Grimster's initial reports on sulfonimidoyl fluorides as warheads (**Chapter 1.4.4**),[146] inspired us to explore this unique class of reagents as chemical probes. The benefits of sulfonimidoyl fluorides have been extensively discussed *vide infra*, in the context of

chemical probes perhaps the most engaging property is that they are inherently chiral at sulfur. In combination with their unique reactivity, this places sulfonimidoyl fluorides in a privileged position for selective interactions as warheads (**Figure 2-5 B**).

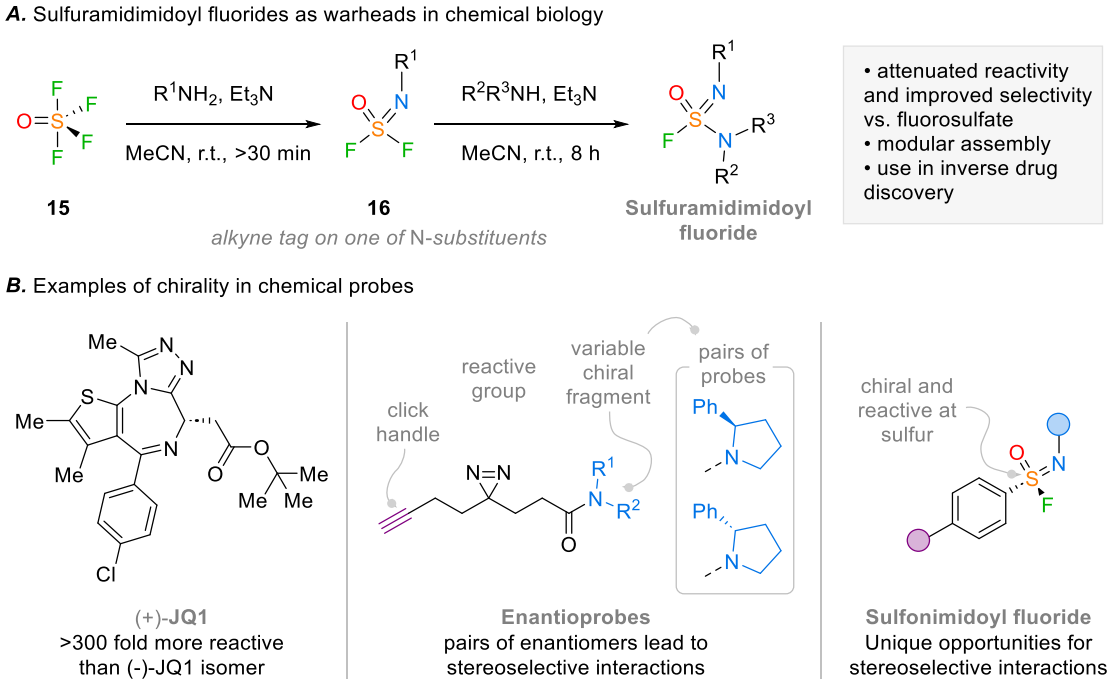


Figure 2-5 Examples of chiral warheads in chemical biology: (***A***) Disclosed synthesis and reactivity of sulfuramidimidoyl fluorides; (***B***) Prominent examples of chiral chemical probes, their utility and the rationale for sulfonimidoyl fluorides as chemical probes.

The fundamental role chirality plays in the interaction and selectivity between a small molecule and its target is important in the context of chemical biology and drug discovery. Indeed, greater than 60% of FDA-approved drugs approved between 1951 and 2021 contain one or more stereocentres.[210] Notably there has been a rise in compounds with a heteroatom stereocentre. Despite its pivotal role in medicinal chemistry programmes, the effect of chirality has only recently been described in the context of chemical probes. The most prominent example of this is the discovery of bromodomain inhibitors, such as (+)-JQ1 (**Figure 2-5 B**).[211] The determined X-ray crystal structures revealed only the (+)-JQ1 enantiomer bound directly into the binding site. More recently, the Cravatt laboratory have been at the forefront of the introduction of enantioprobes; pairs of functionalised probes that

differ only in their absolute configuration (**Figure 2-5 B**).[212] This provides direct evidence of specific stereochemistry-dependent small molecule/protein interactions in cells. The enantioprobes disclosed consist of a diazirine component (photoreactive group), alkyne tag (click chemistry handle to allow protein analysis) and a variable stereogenic element six atoms away from the reactive centre.

2.4.2 Activity-based protein profiling (ABPP)

Activity-based protein profiling (ABPP) is a chemical proteomic method that employs active site-directed probes to simultaneously visualise changes in the activity of many proteins in samples.[213, 214] This technology can be used to identify protein targets of small molecules; the vast utility of ABPP has been extensively reviewed.[213, 214] Activity based probes (ABPs) used in this context all share a similar fundamental design (**Figure 2-6**); a reactive group (also termed warhead), linker and a reporter tag. The latter functionality is used to enable visualisation and/or purification of labelled proteins, this can be in the form of a fluorophore (such as rhodamine), biotin or clickable functionalities (e.g., azide or alkyne).

Weerapana and co-workers adapted one of the most precedented and well documented pan-serine-protease inhibitors, 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF), to give the first example of a sulfonyl fluoride ABP, DAS1 (**Figure 2-6**).[215] This probe has been used to enrich and identify serine proteases and tyrosine residues from complex proteomes using tandem orthogonal proteolysis (TOP)-ABPP.[215, 216] Importantly, DAS1 displays similar efficacy to AEBSF. It has, however, been noted there are drawbacks of DAS1; it is promiscuous, labelling many other proteins, and labelled active site serine and cysteine residues undergo hydrolysis.[217] Therefore, we were interested in evaluating mono-aza-analogues of DAS1, in the form of sulfonimidoyl fluoride **76** in chemical biology settings

(**Figure 2-6**). This analogue was traced back to the corresponding aryl bromide **78**, with various methods to convert an aryl halide to the corresponding S(IV) and S(VI) reagents in the literature.[218-220] This would facilitate the late-stage introduction of the key S-C bond and crucially allow for modular installation of the nitrogen functionality in order to explore its effect on the selectivity and reactivity of the ABP.

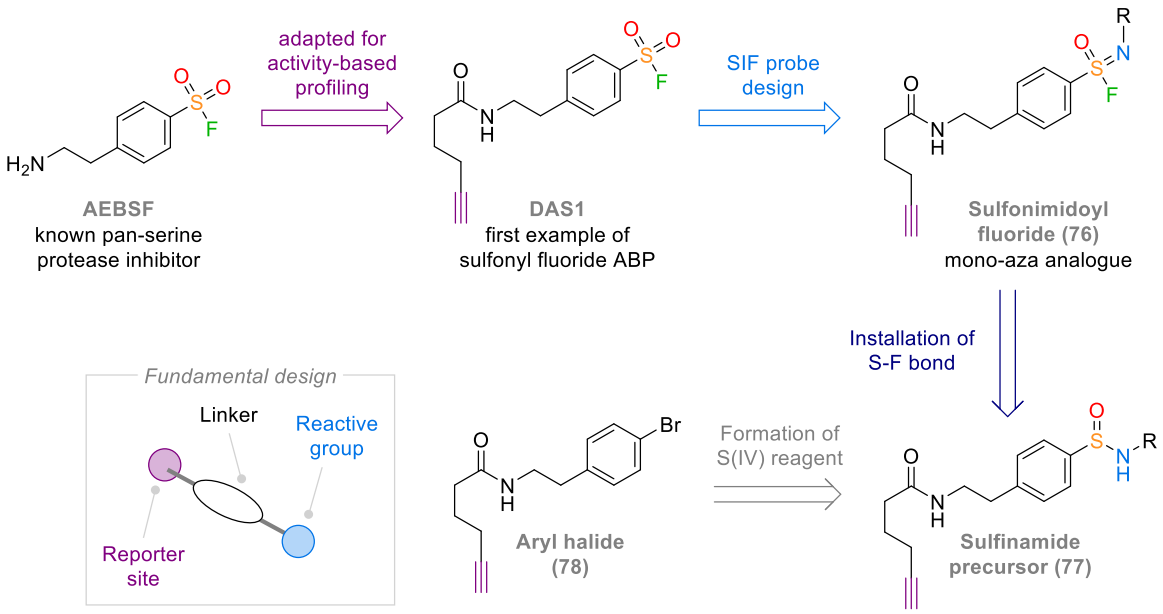
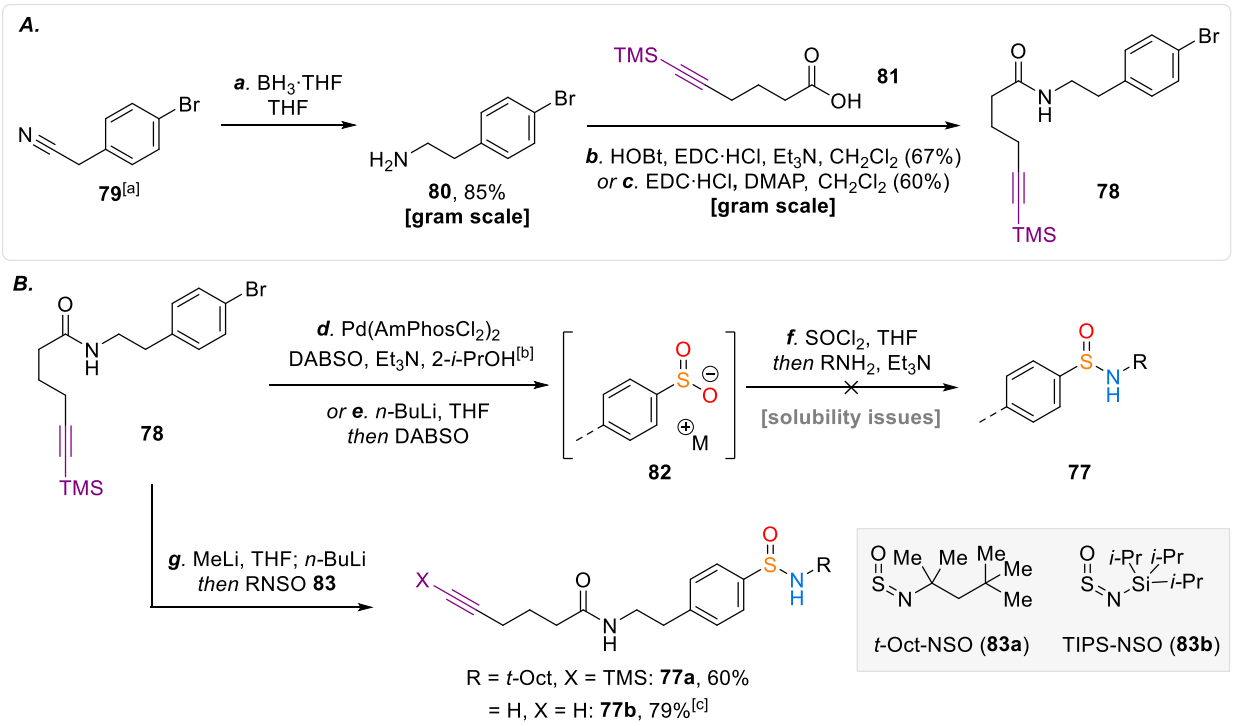


Figure 2-6 Design and proposed retrosynthesis of sulfonimidoyl fluoride activity-based probes (ABP) based on sulfonyl fluoride ABP DAS1.

2.4.3 Synthesis of aza-sulfur(VI) probe reagents

The synthesis of the key precursor **78** was achieved from commercially available 4-bromophenylacetonitrile (**79**) in two steps (**Scheme 2-11 A**). Reduction using BH_3·THF yielded the free amine (**80**) after basification of the generated HCl salt in the workup in 85% yield. This procedure could be performed on 25.5 mmol scale to generate over 4.3 g of the desired product. Subsequent amide coupling to TMS-protected alkyne **81** (prepared in one step), gave aryl bromide **78** in 67% yield using a combination of hydroxybenzotriazole (HOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (EDC·HCl) and Et_3N

(condition b). Although high yielding, the atom economy of the reaction was poor with excess of all reagents, aside from alkyne **81**, required; this is of particular note given the required synthesis of amine **80**. A simpler coupling procedure (condition c) using EDC·HCl (1.0 equiv.) and DMAP (0.25 equiv.) in combination with slight excess of amine (1.16 equiv.) resulted in comparative yield on 17.7 mmol scale (60%).

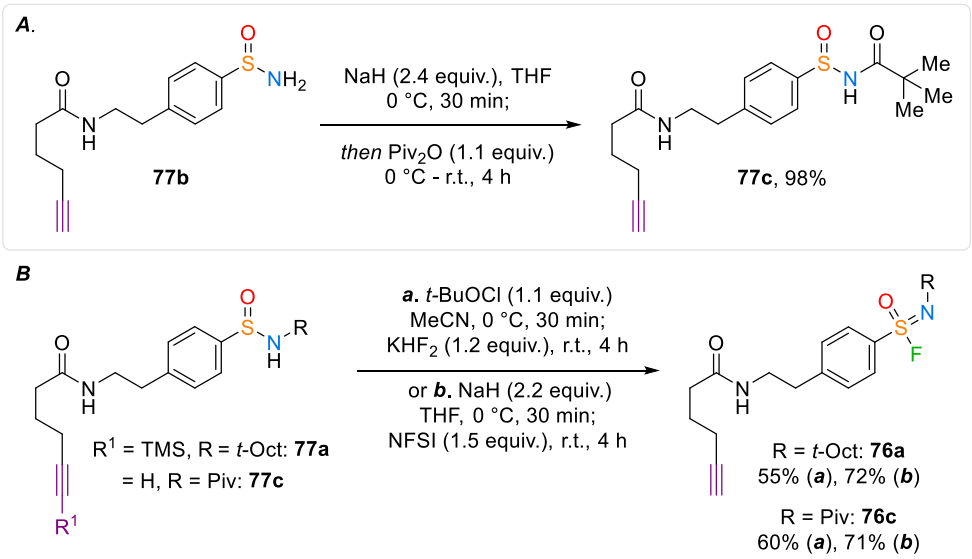


Scheme 2-11 Synthesis of probe precursors: (***A***) assembly of aryl bromide **78**; (***B***) synthesis of sulfinamides 77a and 77b. Reagents and conditions: (**a**) BH_3·THF (2.0 equiv.) THF, 0-70 °C, 24 h then HCl (6 M)/MeOH (1:1) 0-70 °C, 4 h; (**b**) **81** (1.2 equiv.), HOBt (1.4 equiv.), EDC·HCl (1.5 equiv.) CH_2Cl_2, r.t., 5 min; 80 (1.5 equiv.), Et_3N (3.0 equiv.), 0 °C - r.t, 18 h, 67%; (**c**) **81** (1.0 equiv.), EDC·HCl (1.0 equiv.), DMAP (0.25 equiv.), amine **80** (1.16 equiv.), CH_2Cl_2, r.t., 18 h, 60% (17.7 mmol); (**d**) $Pd(AmPhosCl_2)_2$ (5.0 mol%), DABSO (0.6 equiv.), Et_3N (3.0 equiv.), 2-*i*-PrOH, 75 °C, 48 h; (**e**) *n*-BuLi (2.50 equiv.), THF, -78 °C, 40 min then DABSO (0.6 equiv.), r.t., 1 h; (**f**) ii) $SOCl_2$ (1.5 equiv.), THF, r.t., 30 min then RNH_2 (1.5 equiv.), Et_3N (1.5 equiv.), r.t., 16 h; (**g**) MeLi (1.2 equiv.), THF, -78 °C, 10 min; *n*-BuLi (1.5 equiv.), -78 °C, 30 min then RNSO **83** (1.2 equiv.), -78 °C, 30 min; 0 °C, 30 min. [a]£35.80 / 25 g (Sigma Aldrich as of 15/04/23). [b]24 h = incomplete conversion. [c]Addition of TBAF (3.0 equiv.), r.t., 10 min.

Although a variety of methods for converting aryl bromides to S(IV) functionalities are known,[218, 221] there are few examples with other functionalities present.[143, 222, 223] The previously reported Pd-mediated reaction of aryl halides with SO_2-surrogate, DABCO-*bis*(sulfur dioxide) (DABSO), resulted in slow conversion to the desired sulfinate **82** (**Scheme 2-11 B**, condition d).[218] Full conversion could be achieved with longer reaction

time (48 h *vs.* 24 h), albeit accompanied by formation of the protodehalogenated des-bromoproduct. Further transformation of the crude sulfinate salt **82** to the corresponding sulfinamide **77** proved challenging, with reactions plagued by solubility issues.[28] Utilising lithium-halogen exchange before addition to DABSO (condition e) resulted in similar issues and significant formation of protodehalogenated product. Instead, an alternative strategy was pursued that bypassed the sulfinate intermediate (**82**); lithium-halogen exchange followed by addition of sulfinyl amine, *t*-Oct-NSO **83a** gave direct access to sulfinamide **77a** in moderate yield (condition f, 60%).[224] The use of MeLi (1.2 equiv.) to initially deprotonate the amide prior to addition of *n*-BuLi (1.5 equiv.) at -78 °C proved to be key for achieving high yields for this. During this work, a new silylsulfinylamine reagent, TIPS-NSO (**83b**), was developed by a DPhil student in the Willis group, Mingyan Ding.[143] This linchpin allows the rapid preparation of primary sulfinamides *via* fluoride-mediated removal of the silyl protecting group. Application of TIPS-NSO under the optimised conditions gave access to primary sulfinamide **77b**, with concomitant deprotection of the alkynyl-TMS group in high yield (79%).

This substrate provides a key building block for accessing various *N*-substituted sulfinamides through *N*-functionalisation reactions.[225] Pivalation of primary sulfinamide **77b** was achieved using an excess of sodium hydride and trimethylacetic anhydride (**77c**, 98%, **Scheme 2-12 A**). At this point we had sulfinamides with similar steric properties but contrasting electronic properties. Oxidative halogenation of these compounds under modified conditions from **chapter 2.2.2** gave the final desired probe compounds **76a** and **76c** in moderate to good yields (**Scheme 2-12 B**).



Scheme 2-12 Synthesis of sulfonimidoyl fluoride probes **76a** and **76c**: (***A***) functionalisation of primary sulfinamide 77b; (***B***) oxidative halogenation of sulfinamide precursors **77a** and **77c**.

These compounds have been submitted for biological evaluation in collaboration with Elisabeth Rothweiler and Dr Kilian Huber (at the Nuffield Department of Medicine, Oxford). Sulfonimidoyl fluorides (**76**) were tested in in-gel fluorescence experiments in human breast cancer cell line, MDA MB231,[226] at 100 μM with one hour incubation at room temperature. Initial results show labelling for both analogues, with weaker labelling for *N*-Piv analogue **76c** (see appendix 1.2). The above compounds will be used in an isotopically labelled Desthoibiotin Azide (isoDTB)-ABPP platform.[227]

2.5 Exploration of other warheads

2.5.1 Sulfur-triazole reagents

The reliance on fluorine as the leaving group is limiting in terms of modifications of a warhead's reactivity, specificity and binding affinity at protein sites across the proteome. The utility of triazoles as leaving groups in this regard has been explored for sulfonyl systems namely by the Hsu group.[228] Sulfonyl-triazole exchange (SuTEx) chemistry has emerged as a valuable tool for liganding tyrosine sites in protein domains. SuTEx probes

comprise of a sulfonyl triazole unit that can be varied at carbon or the triazole leaving group (**Figure 2-7 A**). Modification of the latter in structure activity relationship studies showed that 3-aryl-substituted 1,2,4-triazoles (**84c**) have enhanced reactivity (~4 fold *vs.* unsubstituted (**84b**)) and improved selectivity for tyrosine over lysine residues.[229, 230] The reactivity of SuTEx reagents was directly compared to SuFEx warheads (**84a**); SuTEx group augmented reactivity with *p*-cresol (tyrosine mimic) in solution reactivity studies (using HPLC analysis). This increased reactivity was in agreement with proteome reactivity studies (~1700 proteins labelled *vs.* 70-130 for sulfonyl fluoride analogues),[229] which can be ascribed to the stabilisation of the triazolide leaving group through hydrogen bonding and resonance. Notably, SuTEx functionalities are found to display high stability in organic and aqueous solvents, important features for their development into ABPs.

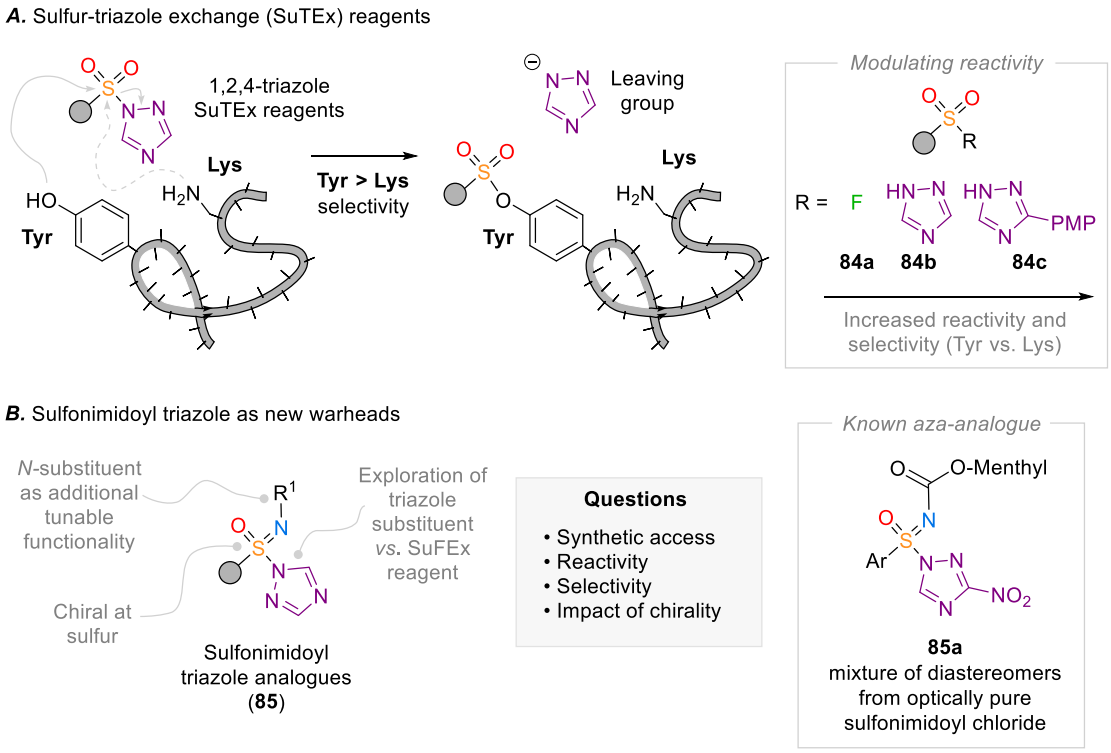
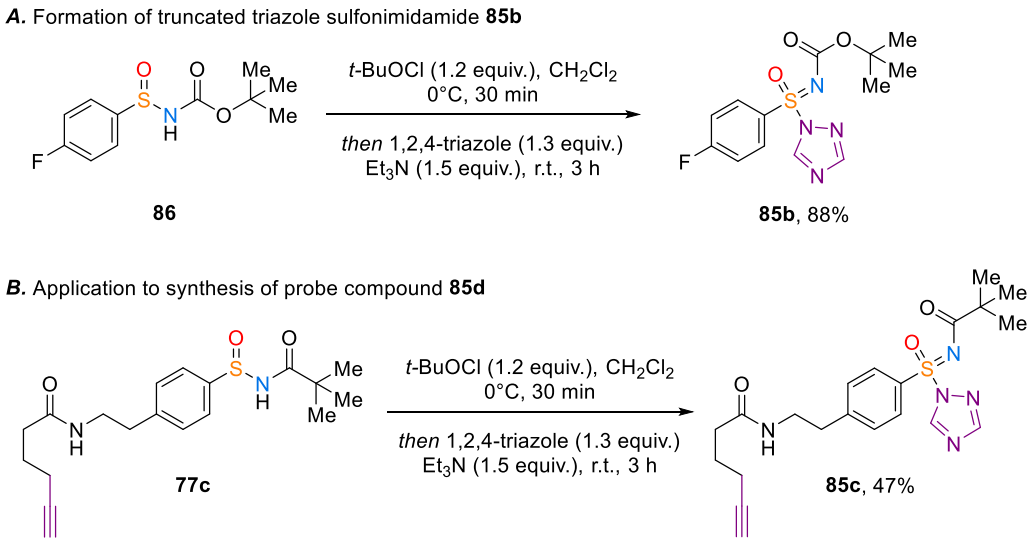


Figure 2-7 Summary of sulfur-triazole exchange (SuTEx) reagents.

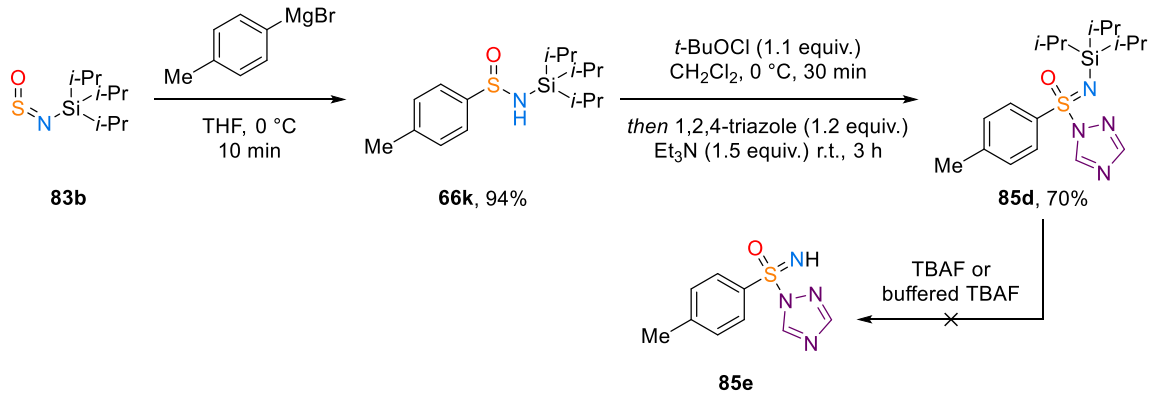
The exploration of sulfonimidoyl triazoles has been severely limited with only a singular example of aza-sulfur 1,2,4-triazole analogues (**85**), sulfonimidoyl nitrotriazole (**85a**)

disclosed by Kluge *et al.* (**Figure 2-7 B**).[96] We were encouraged by the use of sulfonimidoyl imidazoles by Bolm and co-workers as precursors to sulfonimidoyl fluorides (**Scheme 1-6**).[121] The modular synthesis of sulfonimidoyl triazoles would be a valuable addition to the SuTEx toolkit as chemical biology warheads and as precursors to other S(VI)-reagents. To evaluate the capability of these reagents, a model system was determined using truncated compound, 4-fluorobenzene *N*-substituted sulfinamide **86**. The one-pot chlorination and amination of the sulfinamide proceeded smoothly to generate the corresponding triazole sulfonimidamide (**85b**) in good yields (88%, **Scheme 2-13 A**). The product was found to be an easy to handle, crystalline white solid that is stable on the bench-top for over 6 months. Reaction on the probe sulfinamide **77c** progressed in a similar manner (**85c,** 47%, **Scheme 2-13 B**). Challenging purification of this compound resulted in the lower yield obtained. This compound has been submitted to our collaborators for biological testing in direct comparison with SuFEx reagents in cell studies. Preliminary results indicate enhanced reactivity of these compounds *vs.* sulfonimidoyl fluoride analogues **76a** and **76c** (see appendix 1.2).



Scheme 2-13 Synthesis of novel SuTEx warheads (**85**) *via* oxidative halogenation methods.

One of the issues of sulfonimidoyl fluorides is the inability to obtain *N*-H substrates; either due to synthetic challenges or the instability of the products to hydrolysis (**Chapter 2.2.2**). Compounds with a free *N*-H are of significant interest with additional hydrogen bonding capabilities, as well as providing a linchpin for accessing other *N*-functionalised S(VI)-reagents through reaction with appropriate electrophilic species. We hoped to exploit the difference in leaving group for SuTEx reagents to access the analogous *N*-H SuTEx reagent **85e**. The direct precursor, *N*-TIPS substrate **85d**, could be made in high yield in a two-pot process from TIPS-NSO **83b** (**Scheme 2-14**). Attempts thus far to remove the TIPS group have proved unsuccessful; treatment with TBAF solution (1.1 equiv.) or buffered TBAF solution (TBAF:AcOH 1:1, 1.1 equiv.) resulted in full consumption of the starting material, but none of the desired compound could be isolated by flash column chromatography. Alternative methods of purification and further investigations into other silyl deprotections and alternative precursors would be of interest.

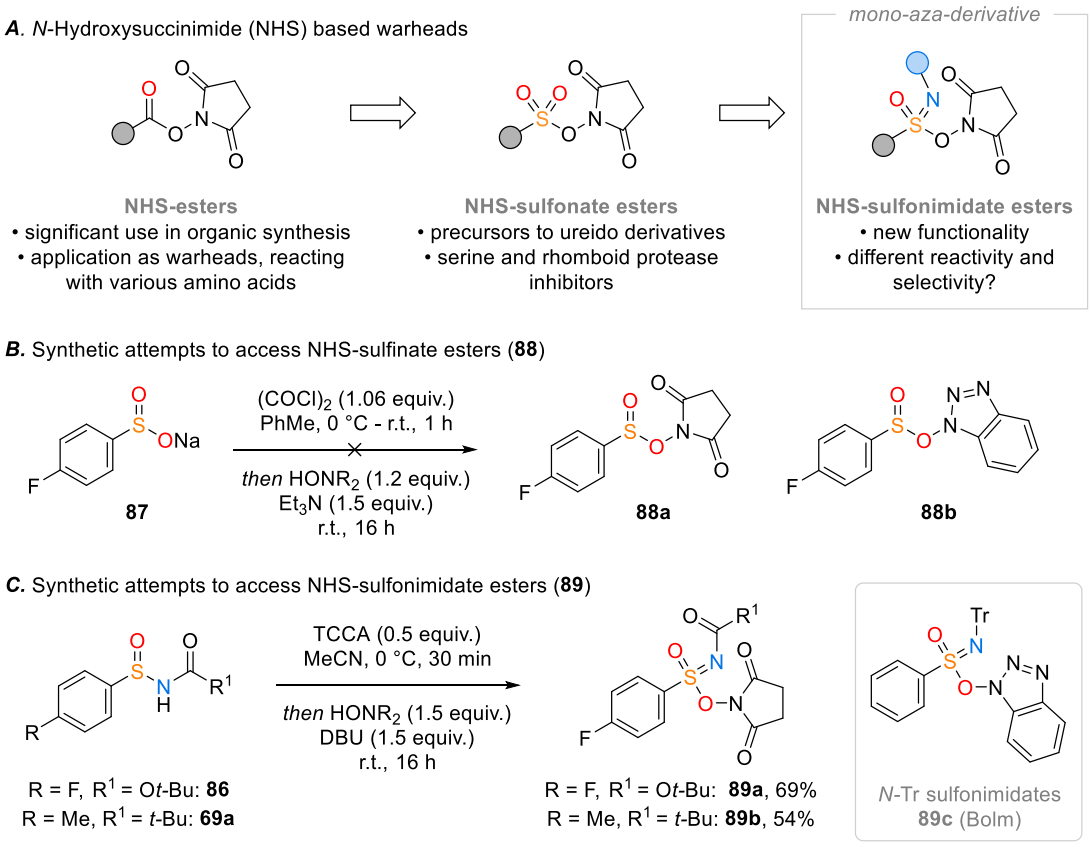


Scheme 2-14 Attempts to access *N*-H sulfonimidoyl triazole **85e** *via N*-TIPS precursor **85d**.

2.5.2 Sulfonimidate esters

N-Hydroxysuccinimide-esters (NHS-esters) have recently been employed as covalent warheads, reacting with various nucleophilic amino acids including lysines, serines, threonines and tyrosines (**Scheme 2-15 A**).[231] This often non-selective labelling of proteins

can be disadvantageous. We were encouraged by reports of the closely related *N*-hydroxysuccinimide sulfonate esters. These functionalities have also been explored as inhibitors of serine and rhomboid proteases,[232, 233] albeit reacting *via* a distinctly different pathway (**Scheme 2-15 A**).[234, 235] As the choice of substituent on the succinimide backbone and importantly the sulfonyl leaving group can alter selectivity and reactivity for this class of compounds, we were interested in exploring mono-aza S(IV) and S(VI) analogues (**Scheme 2-15 A**). To our knowledge the preparation of these compounds has not been reported. Related *N*-Tr,*O*-benzotriazolyl sulfonimidates (**89c**) have been reported by Bolm and co-workers as activated intermediates for accessing sulfonimidamides (**Scheme 2-15 C**), although no variation of the nitrogen substituent was explored.[236]



Scheme 2-15 Exploration of *N*-hydroxysuccinimide (NHS) S(IV) and S(VI) derivatives as warheads.

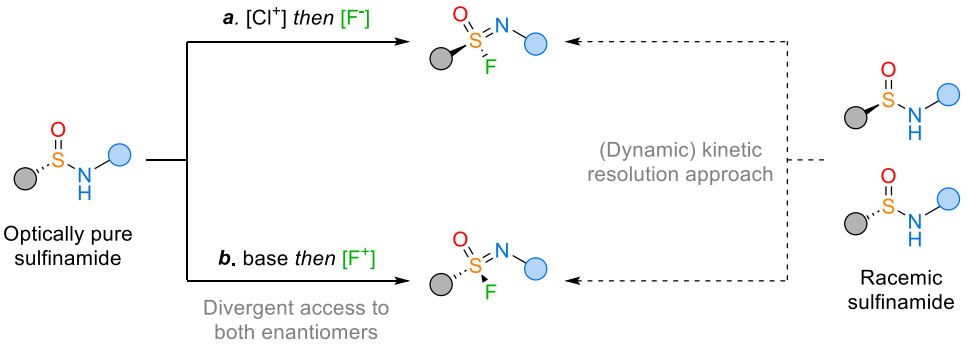
The synthesis of sulfinate ester analogues **88a** and **88b** *via* reaction of respective hydroxylamines with *in situ*-generated sulfinyl chloride was unsuccessful (**Scheme 2-15 B**).

In contrast, the S(VI)-sulfonimidate esters **89a-b** were accessed conveniently from sulfinamide precursors, **86** and **69a**, in encouraging yields for unoptimized processes (**Scheme 2-15 C**). Moreover, NHS-derivatives proved to be stable to column chromatography and could be stored on the bench-top for over 6 months. This in contrast to *N*-Tr *O*-benzotriazolyl sulfonimidates (**89c**); they are stored at -21°C under an inert atmosphere by Bolm and co-workers and the authors recommended to not expose them to silica for longer than necessary.[236] The desired application of these new reagents (**89a-b**) in solution-reactivity studies and subsequently as full ABPs was not performed due to time constraints.

2.6 Summary and future work

In summary, we have shown in this **Chapter 2** that sulfonimidoyl fluorides are configurationally stable functionalities with wide-spreading synthetic possibilities and applications. Optimisation of three different methods for installing a S-F bond from sulfinamides was carried out, with reactions performed under mild conditions using only a slight excess of oxidants. The scope of these transformations was examined on racemic substrates to gain insight into the functional group tolerance of these reactions, substantially with alkyl, aryl and electron-withdrawing substituents tolerated on nitrogen. Subjecting enantionenriched sulfinamides to either halogen transfer or direct fluorination conditions facilitated access to both enantiomers of sulfonimidoyl fluoride products from a single starting material (**Scheme 2-16**, methods ***a*** and ***b***). These useful synthetic handles could be derivatised to the corresponding sulfoximines in enantiospecific transformations. Of note for future endeavours is the further evaluation of trifluoromethylation and subsequent de-*tert*-butylation reactions to access enantiopure trifluoromethyl aza-S(IV) and -S(VI) functionalities.

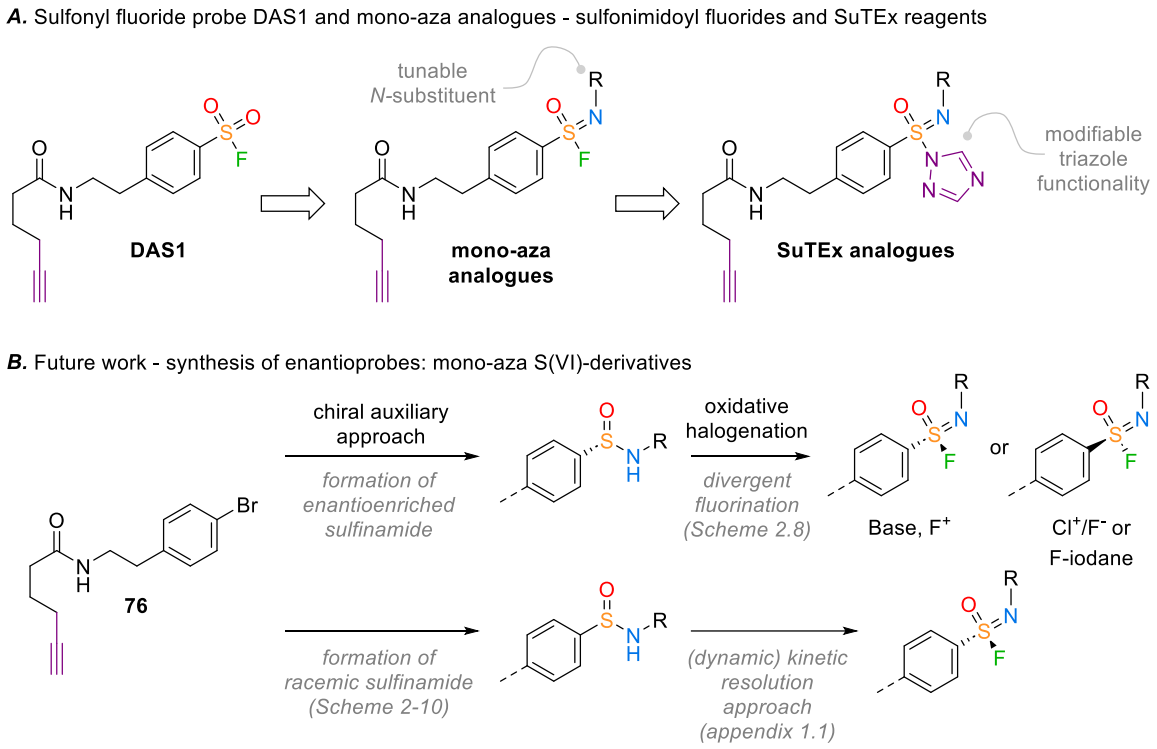
The bottleneck for synthesising enantioenriched sulfonimidoyl fluorides using the above methods is the synthesis of the requisite optically pure sulfinamides. A (dynamic) kinetic resolution approach that utilises abundant racemic sulfinamides to access enantioenriched sulfonimidoyl fluorides would be a significant advance in the field. Preliminary evaluations of this approach are detailed in appendix 1.1.



Scheme 2-16 Summary of methods developed to access enantioenriched sulfonimidoyl fluorides from enantioenriched sulfinamides (methods **a-b**) or from racemic sulfinamides using a (dynamic) kinetic resolution approach.

The application of oxidative halogenation to access sulfonimidoyl fluoride based ABPs was conducted, providing electronically differentiated mono-aza DAS1 analogues for biological testing (**Scheme 2-17 A**). Initial results for these compounds in fluorescence-based assays is encouraging, with differential reactivity dependent on the nitrogen functionality. Alternative leaving groups other than fluoride have been explored, in particular SuTEx and NHS-sulfonimidate reagents. These new classes of aza-S(VI)-reagents are exciting functionalities yet to be fully realised, with promising biological activity in preliminary studies. Their use as bench-stable precursors to other S(VI)-reagents and reactivity with various nucleophiles in solution-based studies would be an interesting avenue of research, in particular if these compounds can be accessed in an enantioenriched manner. Accessing aza-DAS1 analogues in an enantioenriched form could be envisaged to take place *via* a

resolution approach or by asymmetric synthesis utilising a chiral auxiliary to access enantioenriched sulfinamides (**Scheme 2-17 B**).

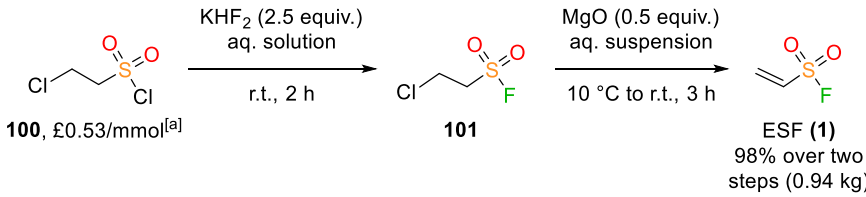


Scheme 2-17 Summary of work towards aza-S(VI) chemical probes: (***A***) application of above oxidative halogenation strategies to access sulfonimidoyl fluoride and sulfonimidoyl triazole analogues of DAS1; (***B***) proposed asymmetric synthesis of sulfonimidoyl fluoride derivatives *via* two approaches.

3 Alkenylsulfonimidoyl fluorides: synthesis and application

3.1 Introduction to ethenesulfonyl fluoride (ESF)

Ethenesulfonyl fluoride (ESF, **1**), a low molecular weight SuFExable hub, was first reported by Hedrick of the Monsanto Company in 1953.[237] Its synthesis is readily achieved through a two-step, on-water procedure starting from 2-chloroethanesulfonyl chloride **100**, a commercially available, cheap building block. This can be easily scaled up to kilogram scale using just liquid-liquid phase separation as means of purification, meaning large quantities can be accessed rapidly (**Scheme 3-1**).[238]



Scheme 3-1 Reported synthesis of ethenesulfonyl fluoride (ESF, **1**) on kilogram scale. [a] £80.70 / 25 g (Sigma Aldrich as of 24/03/23).

ESF is a clear, colourless liquid that is stable under most conditions, although on prolonged standing it is found to polymerise without the addition of hydroquinone.[237] It is a highly toxic substance, found to have an oral LD_{50} of just 10 mg/kg for mice, as well as being extremely toxic through contact with the skin.[59, 238] Furthermore, it has a pungent odor and is a severe lachrymator. This combined with its low flash and boiling points means it is challenging to use, especially on larger scale.[238] The acute toxicity and safety issues associated with ESF and its precursor 2-chlorosulfonyl chloride **100** requires its synthesis to be performed in a well-ventilated hood. Moreover, glassware used should be soaked with either aqueous ammonia or sodium hydroxide overnight.[238]

Despite the issues associated with ESF, its use has been widespread in synthetic chemistry settings in academia and industry as a unique modular clickable-hub, with two distinct

reactive sites.[68] In addition to the classical SuFEx reactivity discussed in **Chapter 1.4**, whereby nucleophilic reaction occurs at sulfur directly,[38-40] ESF offers further connections *via* its ability to react with nucleophiles at the 4-position. Accordingly, Sharpless has coined ESF "the most perfect Michael acceptor ever found", with a wide range of nucleophiles compatible to access highly functionalised sp^3-sulfonyl fluorides.[36] Mayr and co-workers have performed a series of reactions of ESF with sulfonium and pyridinium ylides to establish its electrophilicity.[239] The authors found that ESF is one of the most electrophilic monosubstituted ethylenes ever reported, with similar reactivity to that of maleic anhydride. The SO_2F functionality was found to activate C=C bonds up to 10^8 times more strongly than a vinyl sulfone (**Figure 3-1**).

The seminal report on the systematic evaluation on reactivity of ESF was published by Hyatt and co-workers in 1979,[59] with many subsequent reports in the following 40+ years.[38, 68, 84] Reaction of secondary amines is often quantitative in the literature; in general, no purification is needed as excess ESF can be simply distilled off under reduced pressure (**102a**).[59, 147] Less nucleophilic partners, such as secondary sulfonamides and anilines are also competent under similar reaction conditions (**102b-c**).[59, 240] The use of primary amines allows access to both mono- and di-substituted (excess of ESF in AcOH) aliphatic sulfonyl fluorides (**102d-e**).[59, 241] The latter are important monomer building blocks for SuFEx-based polysulfonates.[73] Of note is the high-throughput application of the aza-Michael addition using microdroplets, with significant rate acceleration observed.[242] Reaction of thiols, in particular in bioconjugation transformations is a rising area of interest (**103a-b**), of note is the utilisation of this methodology for radiolabelling.[243] Sulfinates and alcohols have also been combined with ESF (**103c** and **104a** respectively), although only few examples have been reported.[59] Recently a copper-mediated conjugate addition of carboxylic acids has been developed (**104b**), highlighting the electrophilicity of ESF.[244] The scope of carbon-based

nucleophiles is significantly broader, with dicarbonyls reacting selectively (**105a**).[240] Radical additions to ESF have also been reported, either starting from alkyl iodides with a Mn catalyst and Hantzsch ester (HE) combination (**105b**),[245] or from carboxylic acids *via* activated ester formation, using a Eosin Y-Na_2/HE catalytic system.[82] There are examples of asymmetric addition of nucleophiles to ESF, which proceed in excellent yields and enantioselectivity (**105c**) using quinine-derived thiourea and squaramide based catalysts (e.g. **106**).[246, 247]

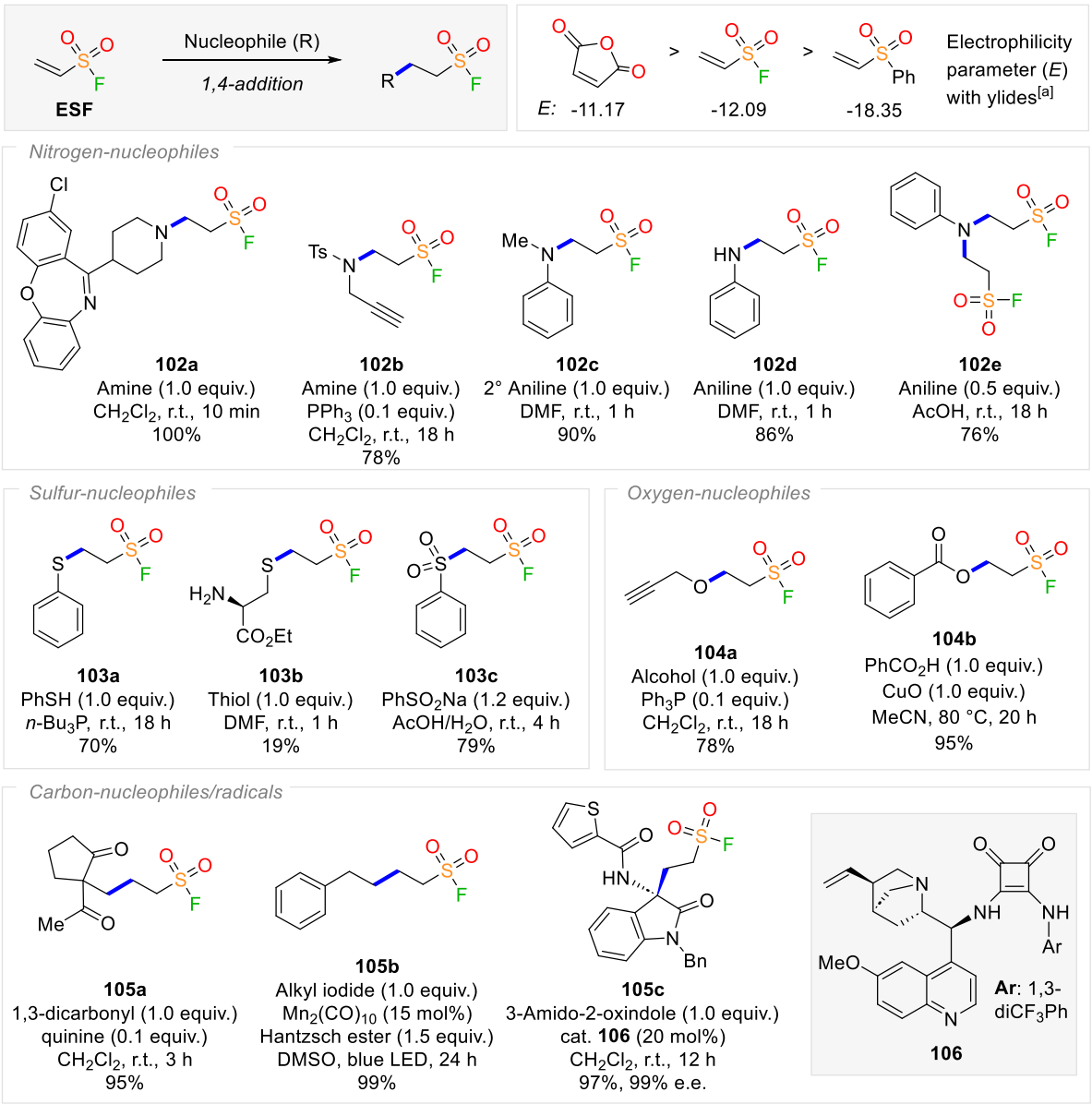
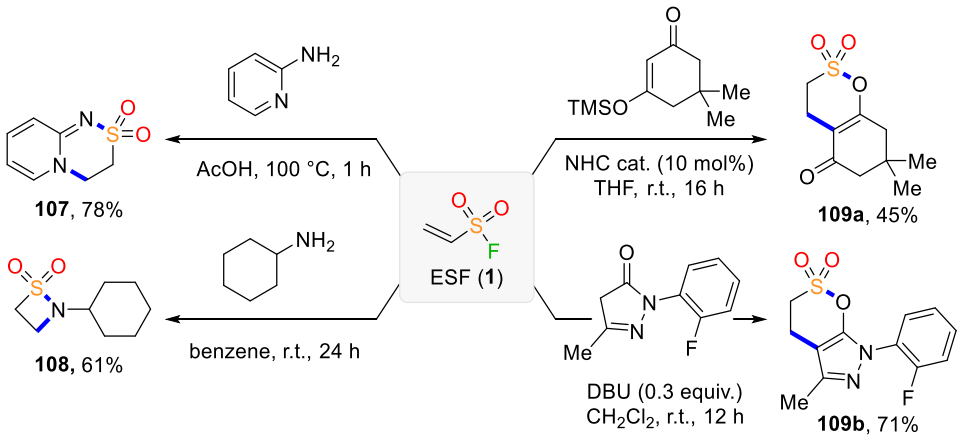


Figure 3-1 Examples of 1,4-addition of nucleophiles to ESF. [a] Electrophilicity parameter determined by Mayr and co-workers using sulfonium and pyridinium ylides.[239]

Despite the two electrophilic sites of ESF, there are only few reported methods utilising this property with a bis-nucleophile reacting at both reaction sites (**Scheme 3-2**). For example, reaction with heterocyclic amines such as 2-aminopyridines gives access to fused heterocycles incorporating the sulfonamide moiety (**107**).[59] When primary amines are used in excess the corresponding β-sultams can be accessed (**108**);[248, 249] a class of privileged molecules established as scaffolds in modern drug discovery with wide spectrum of biological activities.[250-254] Annulation of pyrazolones and enol ethers to form sultone-fused products (**109a-b**) has also been achieved under basic conditions and *N*-heterocyclic carbene (NHC) catalysis respectively.[255, 256] The products of the former, fused pyrazolones, are highly active pharmacophores.

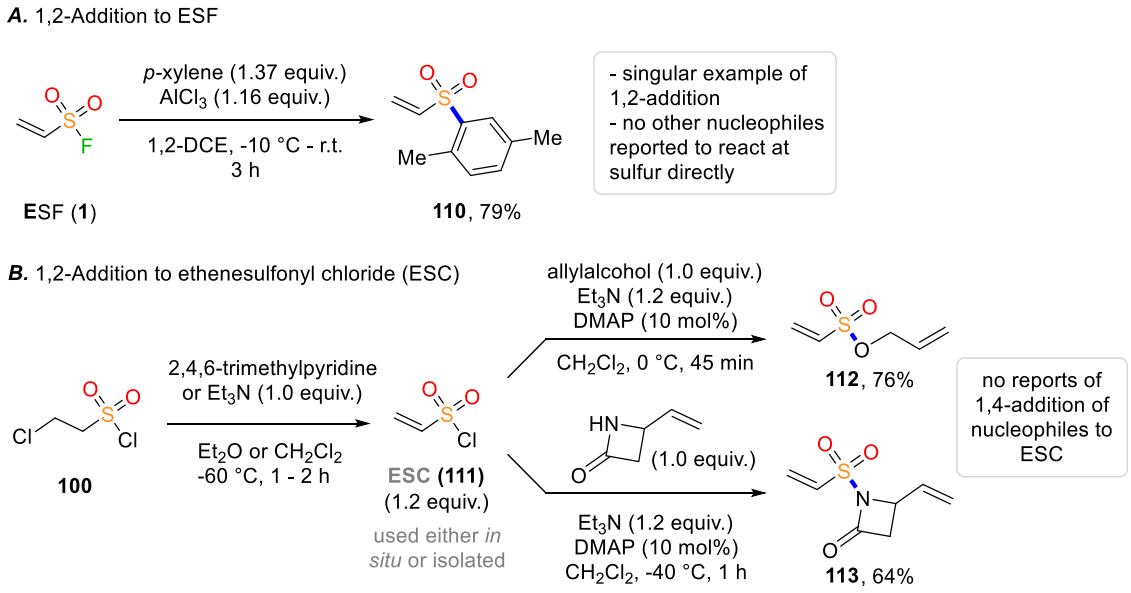


Scheme 3-2 Examples of reactions utilising dual-warhead nature of ESF.

Cycloadditions of ESF have also been reported, including Diels-Alder reactions,[59] [3+2]- and [2+2]-cycloaddition reactions.[257-260] These reactions all proceed under markedly mild conditions, with their application in photo-mediated processes of note.

All of the reactions discussed *vide supra* are highly selective, with minimal purification required. Given the vast array of SuFEx reactions developed,[38] it is surprising there is only a singular example of selective 1,2-addition to ESF; a Friedel-Crafts reaction of *p*-xylene mediated by stoichiometric $AlCl_3$ (**110**, **Scheme 3-3 A**).[55] Ethenesulfonyl chloride (ESC,

111) has been used instead to directly access medicinally relevant ethenesulfonamides (**113**) and sulfonate esters (**112**) in a selective manner (**Scheme 3-3 B**).[261, 262] These reactions typically proceed with an organic base, such as triethylamine, and an excess of ESC. There are no reports of 1,4-addition occurring, highlighting the importance of the S-F bond in both activating the β-position and providing a stable functionality. It is worth noting that the commercially available 2-chloroethanesulfonyl chloride precursor (**100**) can be used for a more expedient synthesis of ethenesulfonamides and sulfonate esters, with *in situ* formation of ESC.[263]

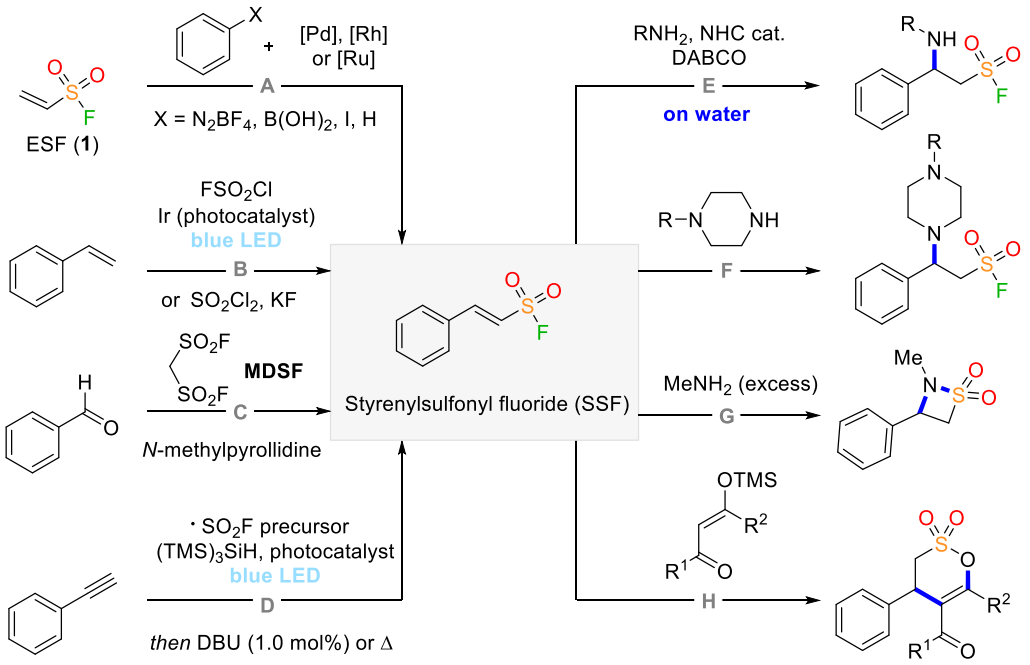


Scheme 3-3 1,2-Additions to vinylsulfonyl halides to form vinylsulfonate esters and vinyl sulfonamides.

3.2 Alternative alkenylsulfonyl fluorides

One of the limitations of ESF is the restricted diversity the molecule has, as there are no points of diversification. There are a number of alkenylsulfonyl fluorides established as SuFExable linkers that address this. Styrenylsulfonyl fluorides (SSFs), an intriguing class of compounds, are perhaps the most significant (**Scheme 3-4**). They can be synthesised from various starting materials, including ESF (metal-mediated processes, **A**),[248, 264-273] styrenes

(halosulfonylation reactions, **B**),[83, 257, 274] benzaldehydes (Knoevenagel-type condensations, **C**),[275] and alkynes (hydrofluorosulfonylation reactions, **D**).[86,276]



Scheme 3-4 Examples of the synthesis and application of styrenylsulfonyl fluorides (SSFs). MDSF = methanedisulfonyl fluoride.

SSFs are found to be competent Michael acceptors, reacting with a range of nucleophiles including primary and secondary amines (**Scheme 3-4**).[246] Conditions required for these transformations are typically harsher in comparison to those used for ESF (**Figure 3-1**); heating of reaction mixtures to 50 °C is often required for secondary amines and good yields are only achieved when EWG's are on the aromatic ring (**F**).[266] This reactivity difference is in agreement with Mayr's electrophilicity scale whereby cinnamoyl sulfonyl fluorides are calculated to be 4.5 orders of magnitude lower in the context of Michael additions with sulfonium and pyridinium ylides.[239] Recent developments utilising "on-water" reactivity has started to address this, allowing reactions to occur at room temperature (**E**).[277, 278] Similar to ESF these compounds may partake in double addition reactions such as the formation of substituted β-sultam derivatives using an excess of an alkyl amine (**G**),[248] as well as with

1,3-dicarbonyls and silyl enol ethers to generate sultones in a one pot process (**H**).[256, 279] Intriguingly, (*Z*)-2-styrenylsulfonyl fluorides do not react with amines to give the corresponding products.[276]

Given the attenuated reactivity of SSFs, selective 1,2-addition approaches are achievable using silyl-protected phenols under mild conditions, with no observed 1,4-addition (**Figure** 3-2 **A**).[266] $AlCl_3$ mediated Friedel-Crafts reactivity is also possible, as well as selective 1,2-addition of secondary amines.[266] These reactions are of particular importance given the number of bioactive compounds containing a styrenyl sulfonyl moiety (**Figure** 3-2 **B**).[280-283] Moreover, β-substituted ESF derivatives themselves have begun to find application in chemical biology, for example as reagents for overcoming multi-drug resistance of bacterial infections,[284] cancer therapy,[285] and proteasome inhibitors (**Figure** 3-2 **C**).[249]

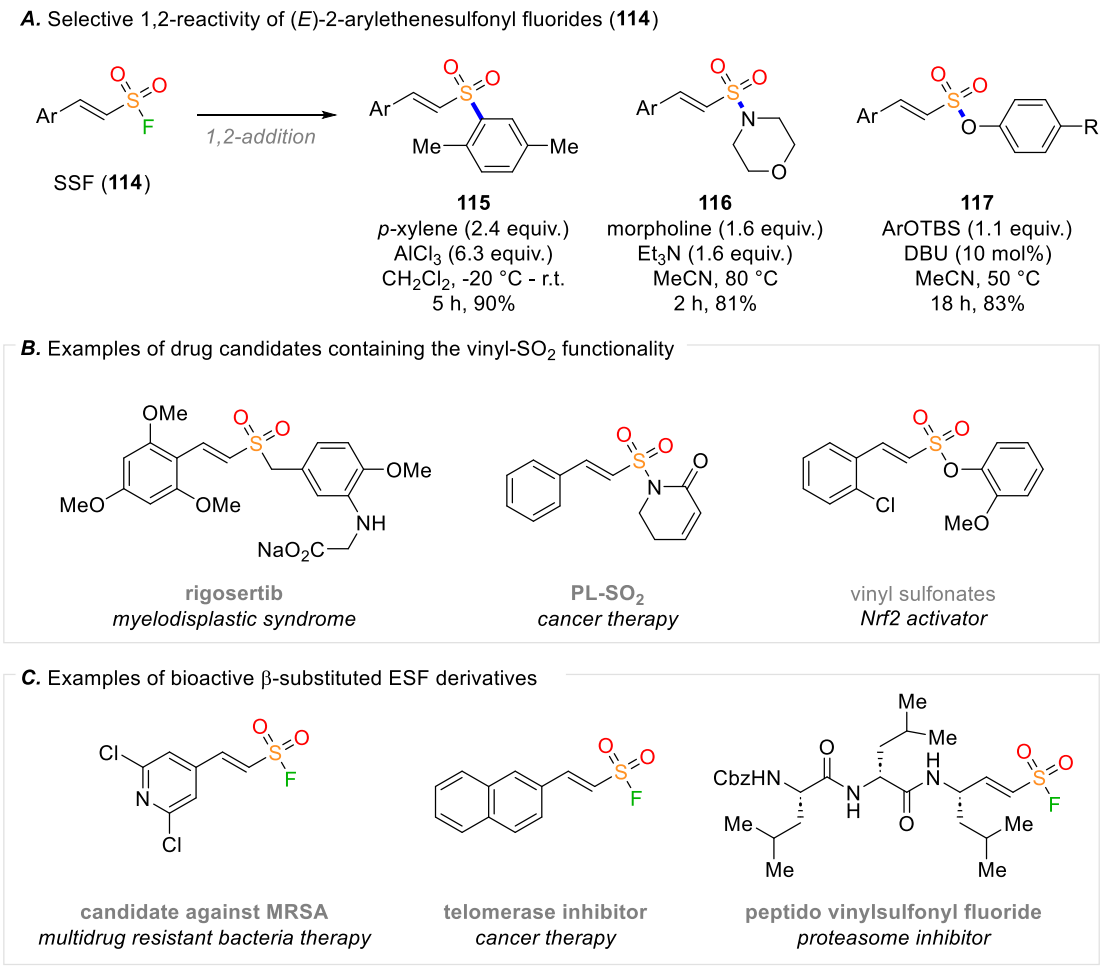


Figure 3-2 Synthesis of alkenylsubstituted S(VI)-substrates and their use in the pharmaceutical industry.

Alternative alkenylsulfonyl fluorides that possess different properties and offer different alternatives as small molecular weight SuFExable hubs have been developed. Of note is 1-bromoethenesulfonyl fluoride (Br-ESF, **118**),[251, 286] a multifunctional reagent synthesised from ESF in one-pot in simultaneous papers by Qin, Moses and Fokin laboratories.[287-289] This hub benefits from the additional bromo-functionality, providing a new dimension for reactivity. Br-ESF can undergo cycloaddition reactions with azides, nitrile oxides (generated *in situ*) and diazo reagents to access triazole (**119**),[287, 289] isoxazole (**120**)[287, 288] and pyrazole (**121**)[290] heterocyclic frameworks respectively. Moreover, the alkenyl bromide functionality can be utilised in cross-coupling reactions with aryl boronic acids to access α-aryl ESF derivatives (**122**).[291] The synthesis of medicinally relevant β-sultams (**123**) and fused

cyclobutanes (**124**) has also been established using Br-ESF in combination with primary amines and pyridones respectively.[251, 287, 292]

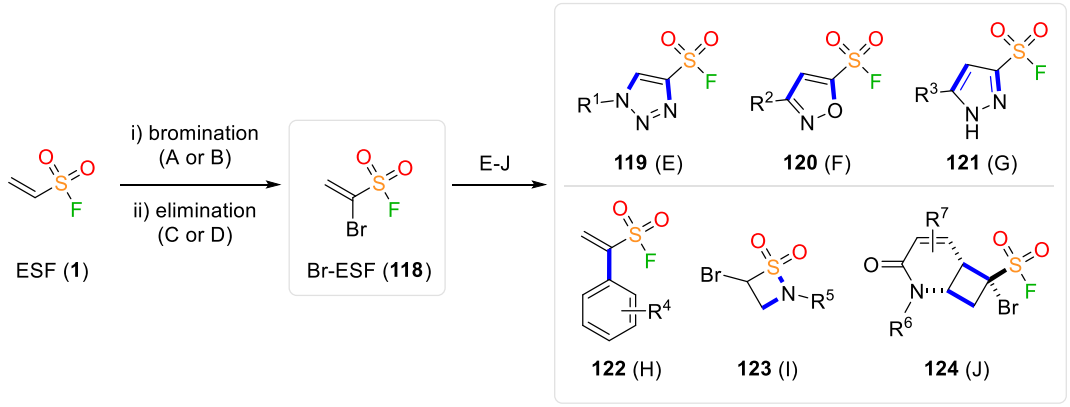


Figure 3-3 1-Bromoethenesulfonyl fluoride (Br-ESF, **118**) as an alternative SuFEx hub with additional functionality and reactivity compared to ESF (**1**). Conditions: (**A**) Br_2 (1.5 equiv.), 40 W white light, $CHCl_3$, r.t., 10 h, 91% (113 g); (**B**) Br_2 (3.0 equiv.), $CHCl_3$, reflux, 3 h, 87%; (**C**) *N*,*N*-diiospropylethylamine (1.0 equiv.), CH_2Cl_2, -78 °C – r.t., 2 h, 87%; (**D**) Et_3N (1.0-4.0 equiv.), THF or MeCN, 0 °C, 5 min (use *in situ*); (**E**) R^1N_3 (0.33-0.72 equiv.), MeCN or DMF, 90 or 50 °C, 3-14 h; (**F**) *N*-hydroxyimidoyl chloride (1.0 equiv.), THF, 0 °C – r.t., 1 h; (**G**) diazo reagent (1.0 equiv.), $CHCl_3$, r.t., 1 h; (**H**) $ArB(OH)_2$ (1.5 equiv.), $Pd_2(dba)_3$ (5.0 mol%), P(*o*-Tol)$_3$ (10 mol%), K_3PO_4 (2.0 equiv.), toluene, 50 °C, 24 h; (**I**) R^5NH_2 (1.0 equiv.), K_2CO_3 (1.0 equiv.), 0 – 50 °C, 30 min; (**J**) 2-pyridone (1.0 equiv.), thioxanthone (0.50 equiv.), MeCN, 365 nm UV light, 24 h.

3.3 Project aims

The high reactivity of ESF is clearly demonstrated by the sheer number of publications that cite its use, with over 600 papers utilising this compound.[68] There are however clear limitations of this hub, namely its toxicity and innate limitation of exploration of chemical space, with the alkene and sulfonyl fluoride unit fixed. The investigation of mono-aza analogues of ESF in the form of ethenesulfonimidoyl fluorides (ESIFs, **125**) provides a viable solution to this (**Figure 3-4**). This unique class of compounds has yet to be reported. The value of the additional nitrogen substituent would mirror those previously discussed in **chapter 1.1**, in particular the addition of a convenient handle to attach clickable functionalities such as alkynes and fluorophores to generate activity-based protein profiling probes is significant.

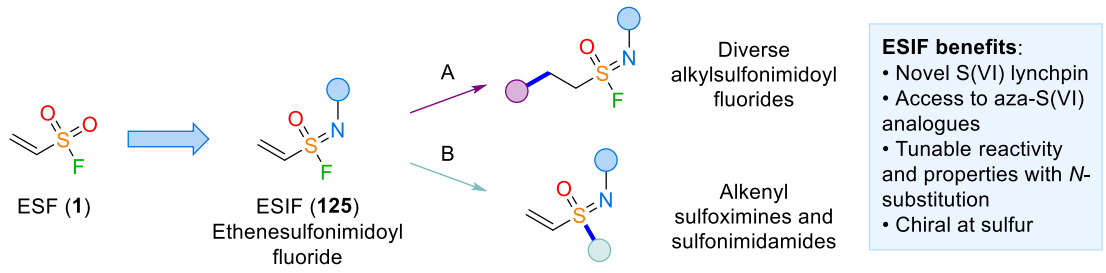


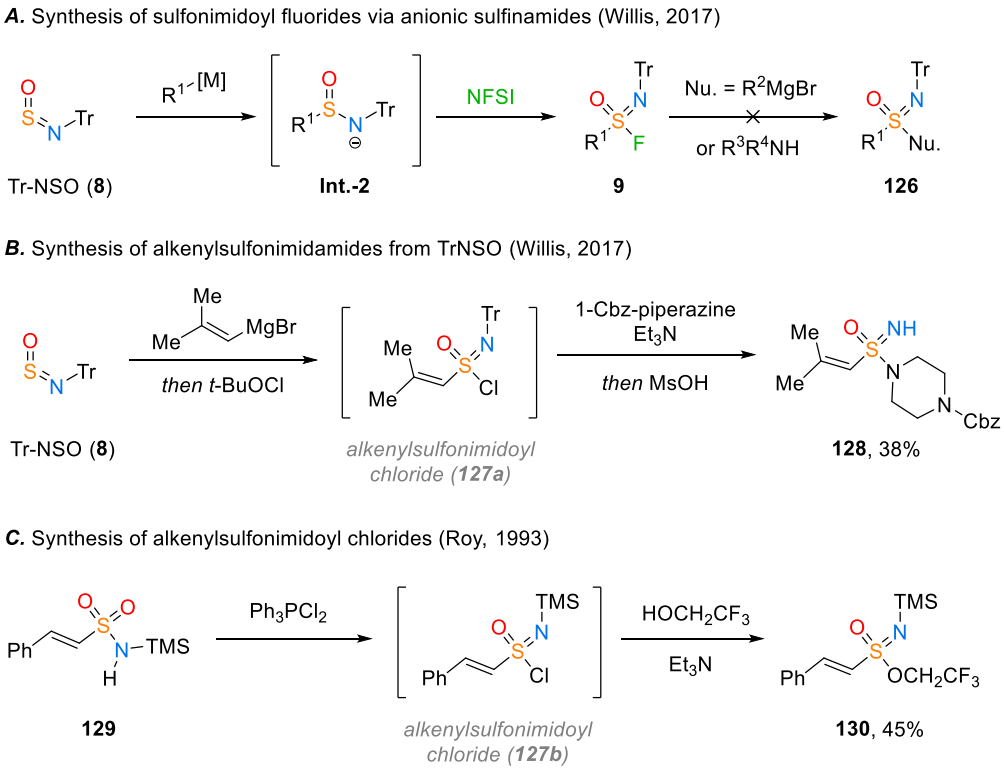
Figure 3-4 Ethenesulfonyl fluoride (ESF, **1**) and ethenesulfonimidoyl fluoride (ESIF, **125**) – potential modes of reactivity.

As discussed in **chapter 3.1**, ESF has a propensity to selectively participate in 1,4-additions with nucleophiles, with reaction *via* SuFEx pathways severely limited (**Scheme 3-3 A**).[55] Analogous 1,4-reactivity of ESIFs would give rise to functionalised sp^3-sulfonimidoyl fluorides; a class of underexplored S(VI)-reagents. Moreover, the nitrogen substituent of ESIFs could be utilised to tune the reactivity of these compounds to allow selective functionalisation at both the β-position (pathway A) and sulfur (pathway B). This could be particularly beneficial for the expedient syntheses of alternative alkenyl aza-sulfur(VI) functional groups such as sulfonimidamides and sulfoximines in a modular manner. Although their sulfonyl counterparts, vinyl sulfonamides and sulfones, are often utilised as warheads in chemical biology,[281, 282] there is only one reported paper of the biological activity of alkenyl sulfoximines and none for sulfonimidamides.[293-295] The variation of the nitrogen substituent of the former resulted in significant changes in their reactivity. The scarcity of exploration of these compounds is in part due to the lack of viable methods to synthesise these functionalities.[143, 296, 297] Recent progress from Bull and Armstrong groups detailed the synthesis of these compounds in non-modular, multi-step procedures.[298] Therefore, new methodologies to access libraries of this class of reagents in an expedient, modular manner would be beneficial.

In order to modulate physical properties of these compounds, such as volatility, the nitrogen-substituent may be tuned; with the ideal substrate being a bench-stable solid derivative. Once ESIFs have been established, their reactivity will be evaluated and directly compared to that of ESF.

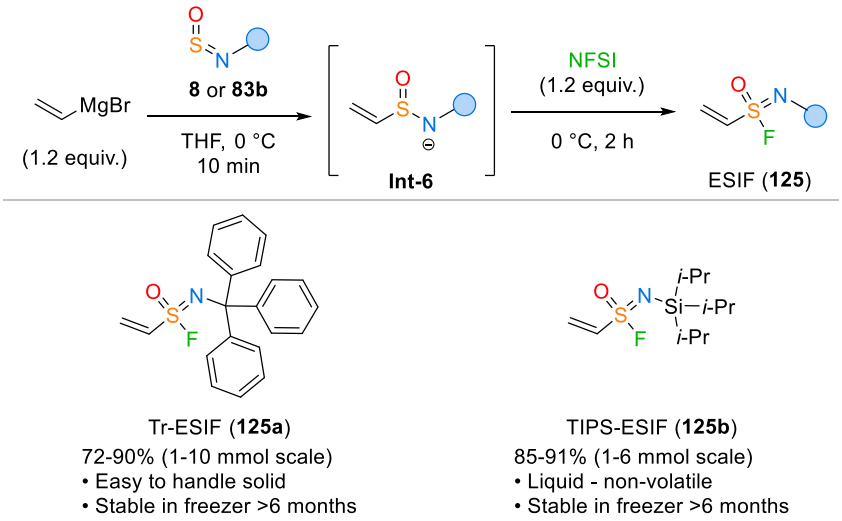
3.4 Synthetic route design

As previously discussed in **Chapter 1.3**, the Willis group reported the development of organometallic additions to a sulfinylamine (Tr-NSO, **8**) to form anionic sulfinamides that could undergo oxidative halogenation to form the corresponding sulfonimidoyl halide reagent.[123] The authors explored the use of NFSI to access *C*-aryl sulfonimidoyl fluorides, but these compounds did not give the desired reactivity with amines and organometallic reagents to generate sulfonimidamides and sulfoximines respectively (**126**, **Scheme 3-5 A**). Instead, sulfonimidoyl chlorides (**127a**) were used as intermediates. Their reaction with amines and triethylamine, followed by acidic deprotection of the trityl functionality gave the desired NH-sulfonimidamide compounds in a one-pot procedure (**Scheme 3-5 B**).[297] In this report the authors detailed the use of isopropenylmagnesium bromide as their starting organometallic reagent with the desired sulfonimidamide (**128**) accessed in moderate yield *via* an alkenylsulfonimidoyl chloride. The synthesis of alkenylsulfonimidoyl fluorides was however not reported. There is only one other example of the synthesis of an alkenylsulfonimidoyl halide (**127b**); Roy reported the deoxychlorination of *N*-silylsulfonamides (**129**) using stoichiometric quantities of dichlorotriphenylphosphorane (**Scheme 3-5 C**).[108] These crude products (**127b**) could then be functionalised through reaction with alcohols with selective reaction at sulfur observed (**130**), showcasing the utility of alkenylsulfonimidoyl chlorides.



Scheme 3-5 Examples of sulfonimidoyl halide synthesis and reactivity.

Encouraged by these literature findings, we proposed the synthesis of ESIFs (**125**) through reaction of an appropriate ethene organometallic reagent with a sulfinylamine reagent, followed by an electrophilic fluorinating agent. Using modified conditions to those described by Davies *et al.*,[297] the reaction of vinylmagnesium bromide with Tr-NSO, **8**, at 0 °C, was followed by addition of NFSI, resulting in smooth conversion to the desired sulfonimidoyl fluoride within 2 hours (**Scheme 3-6**). Isolation of Tr-ESIF, **125a**, could be achieved *via* simple filtration of the NHSI by-product formed in the reaction on addition of dichloromethane, or using flash column chromatography. The reaction can be performed on large scale with gram quantities accessed. Tr-ESIF was found to be an easy to handle, crystalline, white solid that is stable in the freezer for periods greater than 6 months. However, the compound did display some minimal degradation (5-10% impurity determined by ^{1}H NMR spectroscopy) when stored on the benchtop for several weeks. Therefore, storage is recommended in the freezer under an inert atmosphere.



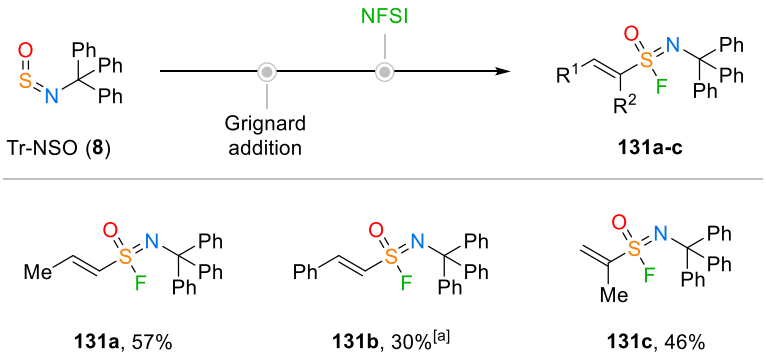
Scheme 3-6 Synthesis of *N*-substituted ESIF reagents (**125a-b**).

The procedure could be applied to other sulfinylamines developed in the Willis group including TIPS-NSO, **83b**,[143] to give the desired TIPS-ESIF (**125b**) in high yields on a range of scales. The resulting product is a non-volatile liquid and offers an orthogonal protecting group strategy, with removal of the TIPS-functionality using TBAF complementary to the acidic conditions required to remove a trityl group.[299] This compound is equally stable when stored in the freezer for periods greater than six months.

3.5 Substituted alkenylsulfonimidoyl fluorides

The effect of the carbon-substituent on reactivity is pronounced for alkenylsulfonyl fluorides (**chapter 3.2**). As the carbon component of ESIFs was attributed to the use of a vinyl organometallic reagent, by employing alternative organometallic reagents other substituted alkenylsulfonimidoyl fluorides could be accessed in a straightforward manner (**131a-c**, **Scheme 3-7**). A single geometric isomer, (*E*)- of *N*-tritylprop-1-ene-1-sulfonimidoyl fluoride (**131a**) was isolated in the one-pot process, with minimal quantities of the (*Z*)-isomer observed in the crude reaction mixture. Formation of cinnamoyl sulfonimidoyl fluoride (**131b**) occurred with lower yield (30%); this may be due to incomplete formation

of the corresponding organometallic reagent from the commercially available β-bromostyrene. Use of isopropenylmagnesium bromide gave access to α-Me-substituted alkenylsulfonimidoyl fluoride (**131c**) in moderate yield (46%), showcasing the tolerance to steric hindrance on carbon during the oxidative fluorination step.

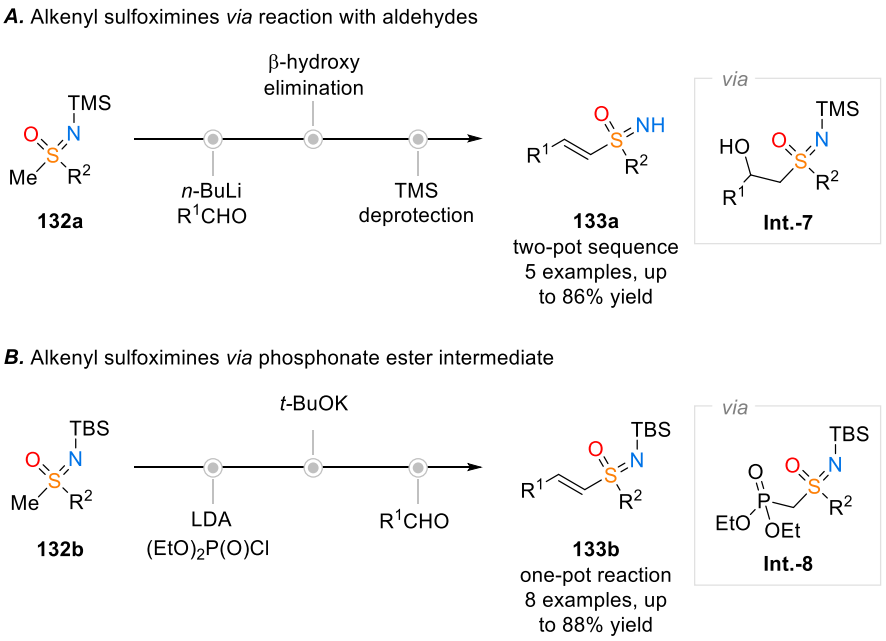


Scheme 3-7 Synthesis of α- and β-substituted alkenylsulfonimidoyl fluorides (**131**). [a] Starting from β-bromostyrene.

Although this provided an initial starting point for exploration of differing carbon-substituted ESIFs, the approach is limited by the commercial availability of Grignard reagents and their precursors. A complementary approach that would facilitate access to 1,1-disubstituted alkenyl substrates and alkenes containing functionalities incompatible with organometallic reagents, such as carbonyls and nitriles, was desired.

This led to the design of a synthetic route that would be modular in the attachment of carbon fragments at a late-stage in the synthesis. There are various methods reported for the transformation of methyl-substituted sulfoximines and sulfonamides into alkenyl substrates (**133a-b**) including the reaction of aldehydes, with sequential elimination of the alcohol (**Scheme 3-8 A**)[300, 301] or through formation of a phosphonate ester intermediate followed by a Horner-Wadsworth-Emmons (HWE) reaction with an appropriate aldehyde (**Scheme 3-8 B**).[298] These methods utilise the abundance of aldehydes and ketones as electrophilic

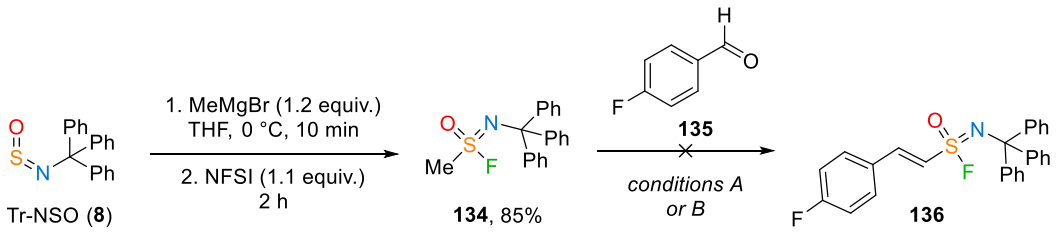
partners to establish a broad scope, often complementary to those generated from alkenylorganometallic reagents.



Scheme 3-8 Selected syntheses of alkenylsulfoximines (**133**) from methyl sulfoximines (**132**).

With this approach in mind, *C*-methyl-substituted sulfonimidoyl fluoride, **134**, is an ideal synthetic start point for the late-stage introduction of an alkenyl fragment. This reagent can be readily synthesised in one step from a sulfinylamine, such as Tr-NSO (**8**), using methylmagnesium bromide and NFSI in high yield, 85% (**Scheme 3-9**). When this compound was subjected to the conditions reported for functionalisation of sulfoximines by Bull and co-workers (conditions A),[298] no characteristic S-F peaks were observed by analysis of ^{19}F NMR spectra for the crude reaction mixture and no alkenyl proton environments were evident in ^{1}H NMR spectra. This indicates that during the reaction either elimination of fluoride *via* a sulfene-type intermediate or hydrolysis of the sulfonimidoyl fluoride occurs. Direct functionalisation with 4-fluorobenzaldehyde (**135**) with reduced equivalents of base (1.0 equiv.) was more promising (conditions B). Consumption of the starting material **134** resulted in a new S-F containing product. However, the corresponding

alkenyl product could not be isolated. These results are perhaps unsurprising as the functionalisation of the α-position of aza-S(VI)-fluorides has yet to be reported in the literature, although there are reports of α-functionalisation of sulfonyl fluorides.[302] These reactions typically employ organic bases, such as DBU, and highly reactive electrophiles such as iodomethane, with no reports of elimination or degradation products.[302] The formation of sulfene intermediates has been observed when an aqueous base is used in reactions of this type,[303] although this is more commonplace for aliphatic sulfonyl chlorides and sulfonimidoyl chlorides (iminosulfenes).[81, 112, 304] Encouragingly, there are reports of SuFEx reactions of *C*-alkyl,*N*-alkyl-sulfonimidoyl fluorides with amines under basic conditions, with reaction occurring selectively *via* a SuFEx reaction and no mention of a sulfene intermediate.[144] Hence, tailoring of the nitrogen-substituent and optimising the elimination of the alcohol generated under conditions B may be worth further investigation for these transformations.



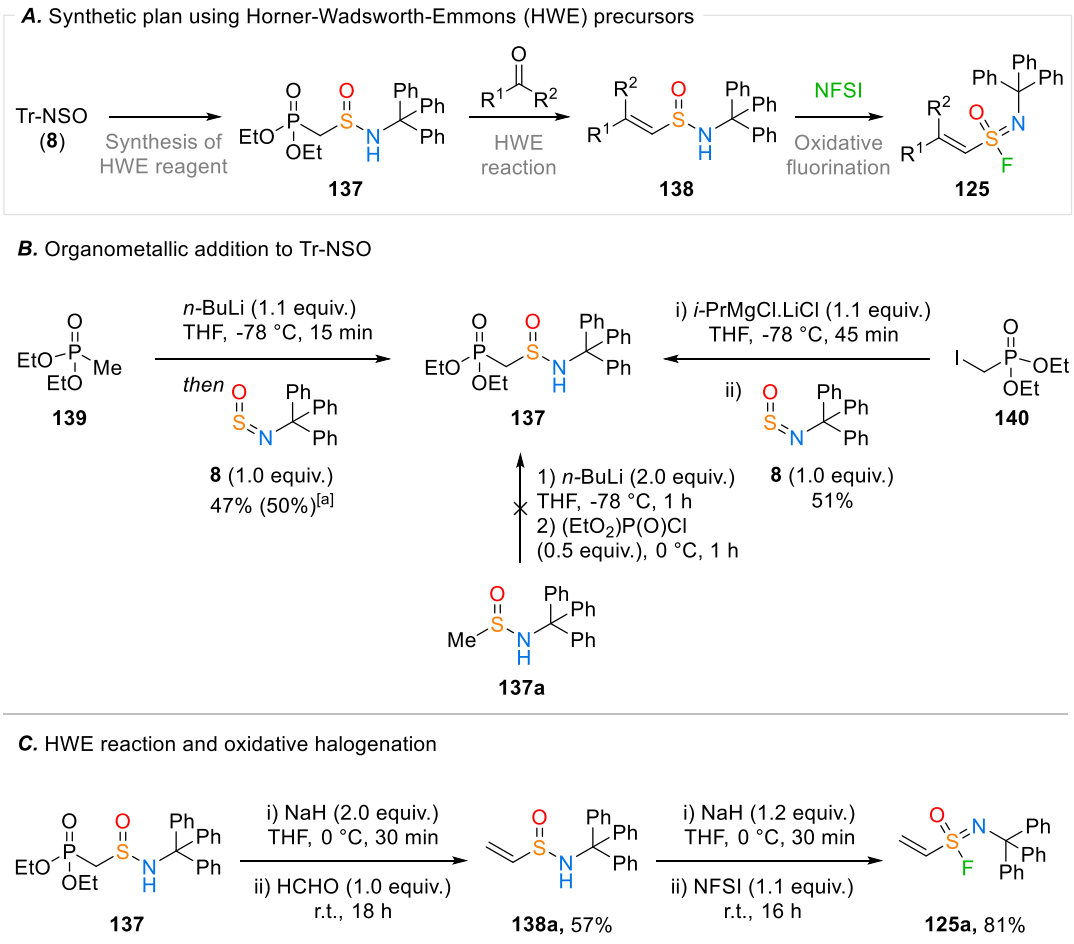
Conditions A:
i) *n*-BuLi (2.7 equiv.), diisopropylamine (1.5 equiv.) THF, -78 °C - r.t., 30 min
ii) **134** (1.0 equiv.), 1 h;
iii) $(EtO)_2P(O)Cl$ (1.3 equiv.), 5 min;
iii) t-BuOK (1.3 equiv.), 10 min;
iv) **135** (2.0 equiv.), 0 °C, 2 h

Conditions B:
i) *n*-BuLi (1.0 equiv.), Et_2O, -78 °C - 0 °C, 10 min;
ii) **135** (1.0 equiv.), -78 °C - r.t., 2 h;
iii) methyl chloroformate (1.0 equiv.), -78 °C - r.t. 30 min;
iv) *t*-BuOK (1.0 equiv.), THF, -78 °C - r.t., 1 h

Scheme 3-9 Synthetic routes trialled to access styrenylsulfonimidoyl fluoride **136** *via* methylsulfonimidoyl fluoride **134**.

Given the limitations of an anionic intermediate once the S-F bond is present, an alternative approach was devised relying on a three-step reaction sequence that commences *via* an α-phosphonate sulfinamide (**137**, **Scheme 3-10 A**). This functionalised intermediate could be formed by addition of lithiated phosphonate ester **(139)** to Tr-NSO (**8**) in moderate yield

(**Scheme 3-10 B**). In analogous reactions with other S(IV)-electrophiles, α-anions of phosphonate esters are typically used in excess (2.0-5.0 equiv.).[305-307] However, when two equivalents were used only a slight improvement in the yield was observed (50%). In order to monitor the formation of the α-anion in a qualitative manner, *in situ* generation of the Grignard reagent was accomplished using *iso*-propylmagnesium chloride lithium chloride complex (Turbo Grignard).[308] On full consumption of the α-iodo species (**140**, by analysis of TLC), Tr-NSO (**8**) was added and the reaction mixture quenched. Disappointingly, the yield stalled at 50%. It was proposed that reversion of the polarity may benefit the synthesis, starting from *C*-methylsulfinamide, **137a**. Reaction with diethylchlorophosphate was however unsuccessful, with substantial quantities of unreacted starting material remaining.



Scheme 3-10 Synthesis of alkenylsulfinamides and sulfonimidoyl fluorides using a Horner-Wadsworth-Emmons (HWE) type approach. [a] Using 2.0 equivalents of phosphonate ester.

With the desired phosphonate ester in hand, the HWE reaction with paraformaldehyde was achieved under standard conditions (**138a**, 57%, **Scheme 3-10 C**).[309] These preliminary, unoptimised results indicate that this may be an attractive, modular approach to alkenyl sulfinamides in one step from phosphonate ester **137** in combination with carbonyl electrophiles. Expansion of this to the use of substituted aldehydes and ketones to generate the corresponding alkenylsulfinamides (**138**) would be of interest. Literature routes to these compounds have relied on the use of Grignard reagents,[310, 311] unstable chlorosulfenamides and sulfinylamines,[311] or strong acids/oxidants.[312-314] The established route could be applied to accessing a range of aza-S(IV) and S(VI)-functionalities through subsequent known transformations of sulfinamides.[163, 164] Moreover, the sulfinamide products could be further explored as dienophiles,[313, 315] precursors to heterocycles[316] and as cross-coupling partners (see **Chapter 4.8**).

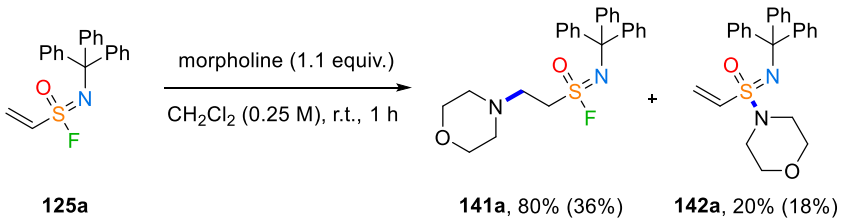
Generated alkenyl sulfinamide **138a** was readily converted to the desired sulfonimidoyl fluorides **125a** (81%) using modified conditions from **chapter 2.2** (**Scheme 3-10 C**). This route will be explored in further detail to generate a variety of alkenylsulfinamides, in particular those with functional groups that would be incompatible with organometallic reagents.

3.6 Reactions of *N*-alkyl ESIFs

3.6.1 1,4-Addition of amines to Tr-ESIF

Given the abundant examples of 1,4-additions of amines to ESF in operationally simple procedures, we commenced investigation into the conjugate addition of amines to ESIF compounds.[59] The initial reactions with amines and early screening of this system were performed by a previous master's student in the Willis group, Erik Diepers, and are fully reported in his thesis and indicated in the following text and schemes.[317] Reaction of Tr-ESIF

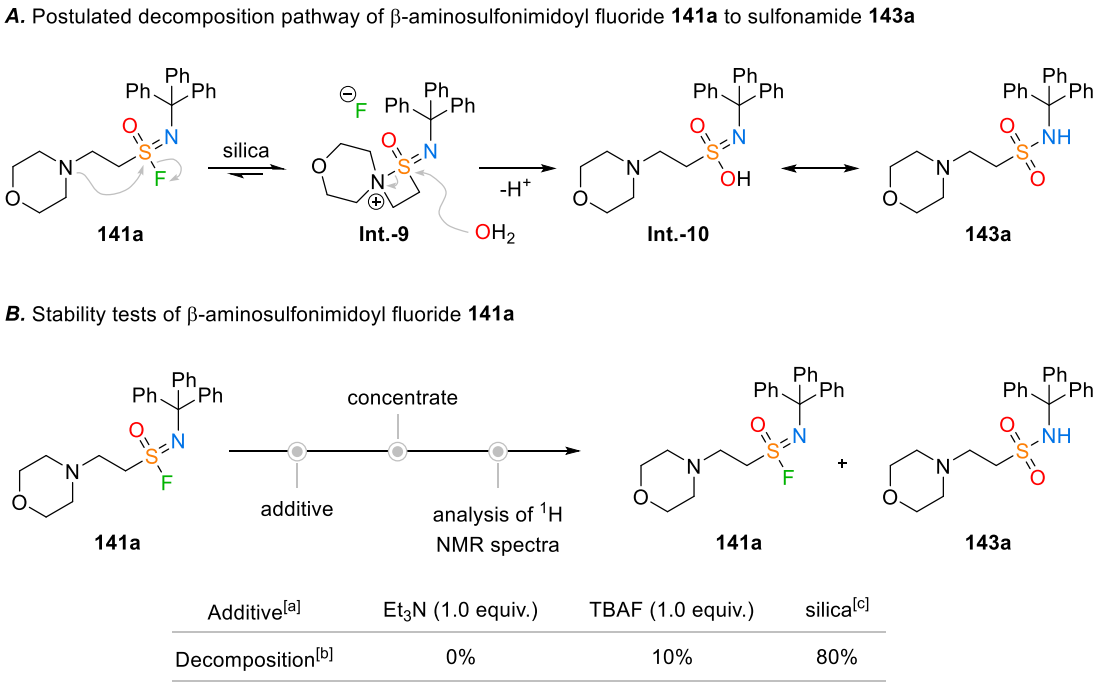
(**125a**) with morpholine was carried out by Diepers under the same conditions as reported in the literature for ESF (**Scheme 3-11**).[59, 147] The proof-of-concept reaction demonstrated a significant difference in reactivity for Tr-ESIF, with significant quantities of the 1,2-product (**142a**) observed in the crude ^{1}H NMR spectrum (ratio of 4:1 for 1,4- vs 1,2-addition). This is surprising given the selectivity of reactions using ESF, wherein near quantitative yields are achieved.



Scheme 3-11 Initial reaction of morpholine with Tr-ESIF **125a** (Diepers). NMR yields calculated using quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in parenthesis.

It was found that isolation of the β-aminosulfonimidoyl fluoride, **141a**, by column chromatography led to partial hydrolysis, forming 2-morpholino-*N*-tritylethane-1-sulfonamide (**143a**), which could be isolated cleanly. This decomposition was observed on silica-based TLC plates, as well as on basic and neutral aluminium oxide-based columns. Formation of the hydrolysis product was indifferent to the solvent system. As β-aminosulfonyl fluorides are typically purified by evaporation of the excess, unreacted ESF, there are few examples of column chromatography, with no reports of their decomposition. A potential pathway for the decomposition occurs *via* intramolecular cyclisation of the tertiary amine, displacing fluoride to form a bicyclic intermediate (**Int.-9**), which then undergoes hydrolysis (**Int.-10**). A series of stability studies were performed on the pure sulfonimidoyl fluoride, **141a**: treatment with soluble fluoride, TBAF, or triethylamine led to minimal decomposition, whereas stirring in dichloromethane with silica gel led to 80% decomposition within an hour. This neighbouring group participation is

supported by no decomposition being observed for other alkylsulfonimidoyl fluorides such as methyl Tr-sulfonimidoyl fluoride (**134**, **Scheme 3-9**). Intriguingly, **141a** is remarkably stable on the bench-top (>9 months), only decomposing on silica or related systems.



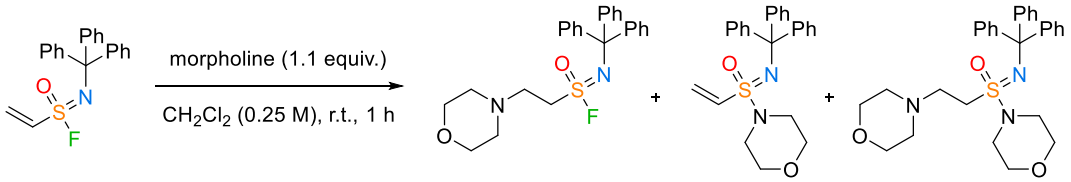
Additive[a]	Et_3N (1.0 equiv.)	TBAF (1.0 equiv.)	silica[c]
Decomposition[b]	0%	10%	80%

Figure 3-5 Decomposition of β-aminosulfonimidoyl fluoride (**141a**) to sulfonamide (**143a**). [a] Additive added to **141a** (0.1 mmol) in CH_2Cl_2 (0.4 mL, 0.25 M), r.t., 1 h. [b] Calculated using quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c] 2.0 g silica for 0.1 mmol **141a**.

To combat these purification issues, Diepers found filtration of the crude after stirring with Et_2O could give pure product, with additional quantities obtained by flash column chromatography (**Table 9**, entry 1). Although this procedure was acceptable and moderate yielding, a more general purification method would be required for the methods uptake or improvement of the reaction itself to obviate the necessity for column chromatography. After screening various stoichiometries of morpholine, Diepers found that using morpholine as the limiting reagent (entry 2, 0.5 equiv.) resulted in improved 1,4-selectivity for the reaction, with 5.2:1 ratio of 1,4- vs 1,2-addition observed in the crude ^{1}H NMR spectrum. Given the commercial availability of amines, this approach is less appealing as although

Tr-ESIF is simple to synthesise, the use of sub-stoichiometric quantities of morpholine renders purification by filtration not possible due to the insolubility of Tr-ESIF in Et_2O. Increasing the stoichiometry of morpholine resulted in disproportionately increased formation of the undesired 1,2-addition pathway (entry 3 and 4). Double addition was only observed when 1.5 equivalents or above were used (entry 3 and 4). The temperature the reaction was conducted at had little impact on the selectivity of the reaction (entry 5 and 6), with slightly attenuated rate of reaction at lower temperatures (entry 5). Increasing the duration of the reaction (entry 7-9) and changing the concentration (entry 10), resulted in minimal changes to the regioselectivity of the reaction. The choice of solvent had a pronounced effect on the reactivity: in particular, the use of DMSO resulted in the opposite selectivity observed (entry 11). The 1,4-addition product **142a** was found to be insoluble in acetonitrile and ethyl acetate (entry 12-13) and precipitated from the reaction mixture meaning the product could be partially isolated directly through filtration, albeit in low yields (25%). Addition of bases decreased the selectivity of addition (entry 14-15), with ethenesulfonimidamide (**143a**) the major product when stoichiometric triethylamine was used (entry 15). Lewis acids such as $Eu(OTf)_3$ were found to not be beneficial to the reaction (entry 16), with starting material **125a** remaining and reduction in regioselectivity. This is perhaps unsurprising given the utility of Lewis acids in SuFEx reactions.[50, 52] Addition of trifluoroacetic acid (TFA) and triphenylphosphine additives used in reactions with ESF were also not beneficial (entries 17-18).[73, 147, 288]

Table 9 Selected optimisation of 1,4-addition of morpholine to Tr-ESIF (**125a**).[a]



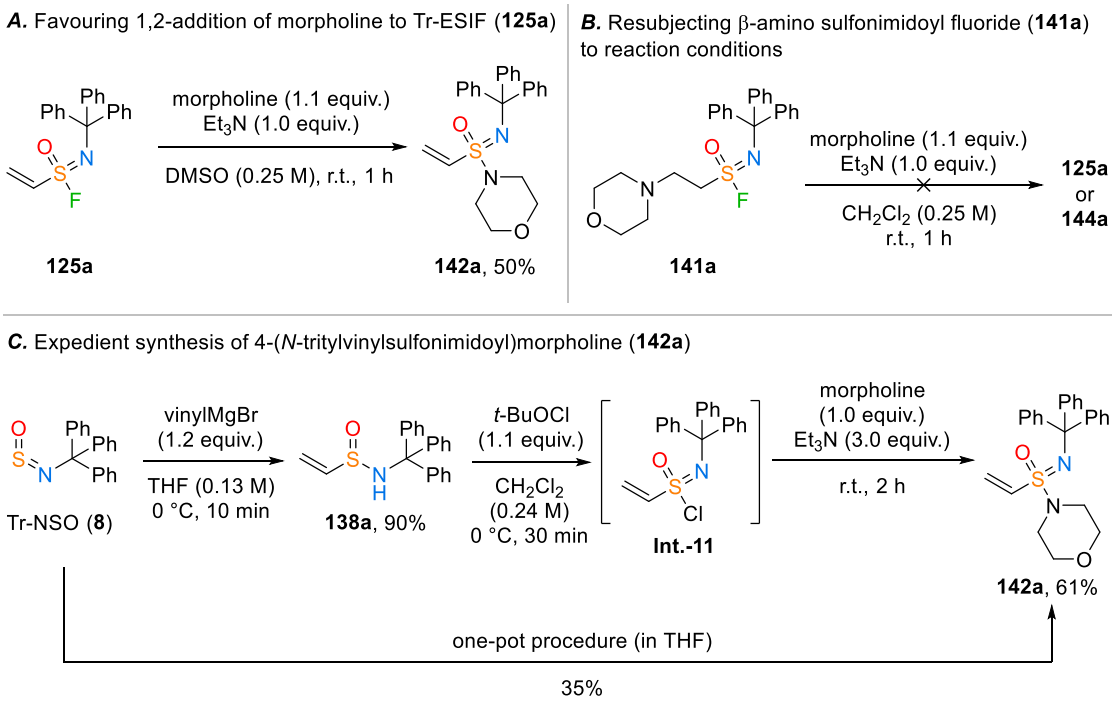
125a **141a** **142a** **144a**

Entry	Variation to above system	Yield 141a[a]	Yield 142a[a]	Yield 144a[a]
1	-[b]	81% (72%)	19% (18%)	0%
2	morpholine (0.5 equiv.)[b],[c]	81%	19%	0%
3	morpholine (1.5 equiv.)[b]	65%	29%	6%
4	morpholine (2.0 equiv.)[b]	53%	34%	13%
5	0 °C[b]	61%	27%	0%
6	40 °C[b]	79%	21%	0%
7	4 h	79%	21%	0%
8	8 h	75%	25%	0%
9	24 h	78%	22%	0%
10	0.1 M[b]	81%	19%	0%
11	DMSO (0.25 M)[b]	29%	64%	6%
12	EtOAc (0.25 M)[b]	41%	51%	8%
13	MeCN (0.25 M)[b]	53%	39%	8%
14	Et_3N (0.5 equiv.)	64%	36%	0%
15	Et_3N (1.0 equiv.)	41%	59%	0%
16	$Eu(OTf)_3$ (0.1 equiv.)[b]	60%	30%	0%
17	TFA (1.0 equiv.)[b]	0%	0%	0%
18	Ph_3P (0.1 equiv.)[b]	71%	29%	0%

[a] Calculated using quantitative ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard, remaining yield is SM (**125a**). [b] Reaction performed by Erik Diepers. [c] Yield base on morpholine being the limiting reagent (0.1 mmol).

In order to improve the yield obtained for the 1,2-addition product, **142a**, the reaction was carried out with two of the parameters that increased its formation during optimisation; Et_3N (1.0 equiv.) and DMSO (0.25 M). However, this just led to similar quantity of 1,2-addition product being formed (50%); increasing the equivalents of morpholine and base, and other parameters may be investigated to improve this (**Scheme 3-12 A**). Despite this process being unoptimized, the switch in selectivity is of marked difference to ESF and enables ESIFs to be used as a SuFExable hub capable of selective reaction at either site in a modular manner.

The 1,4-addition product (**141a**) was subjected to additional equivalents of morpholine in the presence of triethylamine to determine its stability under the reaction conditions and no reaction was found to occur (**Scheme 3-12 B**). This result implies that the increase in observed 1,2-addition product when using additional equivalents of morpholine is not due to the reversibility of the 1,4-addition. The previous findings wherein triethylamine (1.0 equiv.) did not cause any decomposition when added to β-aminosulfonimidoyl fluoride (**141a**) support this hypothesis (**Figure 3-5 B**).

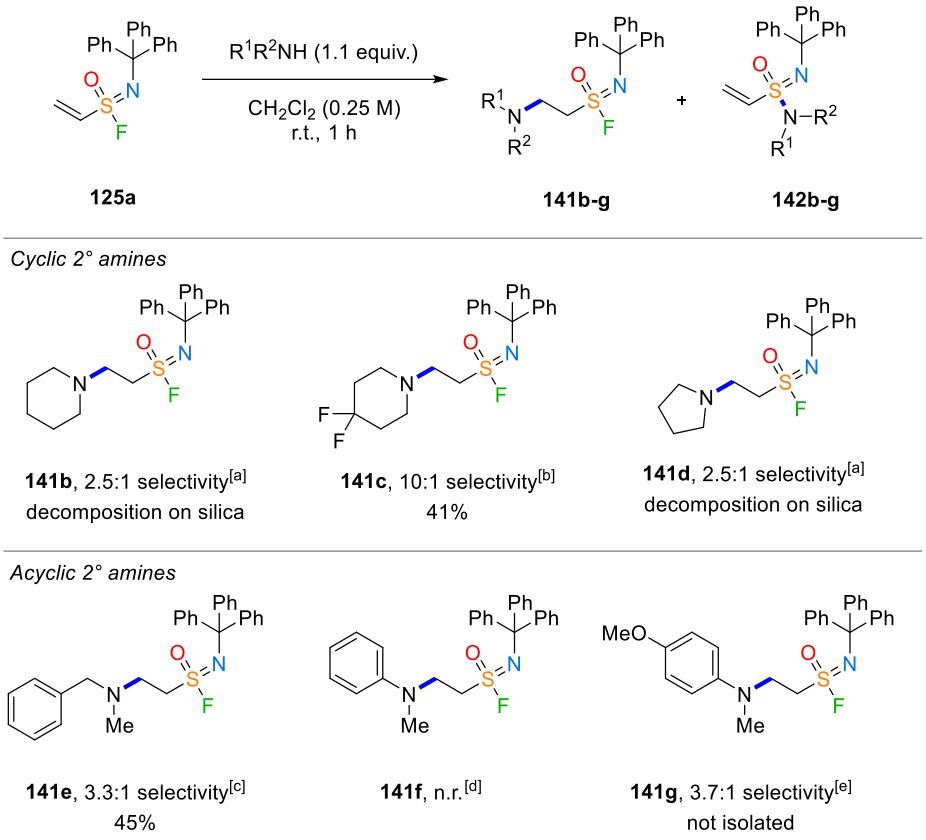


Scheme 3-12 Synthetic attempts to access 4-(*N*-tritylvinylsulfonimidoyl)morpholine (**142a**). Isolated yields.

In order to explore the utility of these transformations, the application of sulfonimidoyl chlorides to access these compounds was explored.[297] Vinylsulfonimidoyl chloride (**Int.-11**) was generated *in situ* from either isolated sulfinamide (**138a**) or anionic sulfinamide generated *in situ* and reacted with morpholine in the presence of triethylamine (**Scheme** 3-12 **C**). This gave the product **142a** in 55% yield over two steps or 35% in a one-pot

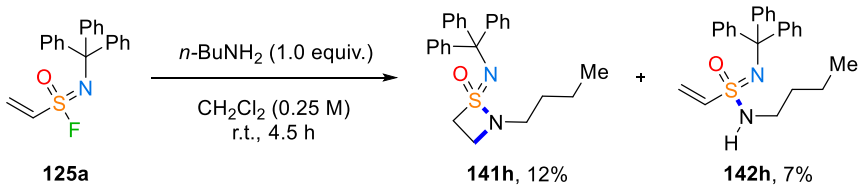
procedure (in THF). The lower yield for the one-pot process may be attributed to the oxidative chlorination and amination steps being less efficient in THF.

With the optimised conditions in hand, Diepers performed a preliminary substrate scope with Tr-ESIF (**Scheme 3-13**). Other cyclic secondary amines proved to be competent nucleophiles in the reaction, with varying degrees of regioselectivity. Increased nucleophilicity of the amine correlates with 1,2-addition being favoured to a greater degree (piperidine (**141b**) and pyrrolidine (**141d**), 2:1); this results in the best selectivity to date when 4,4-difluoropiperidine was employed (**141c**, 10:1), although the product could only be isolated in 41% yield, with some starting material remaining. The increased nucleophilicity of the amine may be responsible for the more significant decomposition of **141b** and **141d**, with none of the desired product obtained after column chromatography (**Figure 3-5 A**). The use of acyclic secondary amines was also attempted with the use of *N*-benzylmethylamine providing access to **141e** in 45% isolated yield and the corresponding sulfonamide decomposition product also isolated in 16% yield. Secondary anilines proved less reactive (**141f** and **141g**), although the desired product was observed for *N*-methyl-4-anisidine (**141g**) in crude ^{1}H NMR spectra, the product could not be isolated cleanly.



Scheme 3-13 Selected scope for the reaction of secondary amines with Tr-ESIF (**125a**) carried out by Erik Diepers. Selectivity's determined by analysis of crude ^{1}H NMR spectra (1,4- *vs.* 1,2-addition). [a] 16 h. [b] 6 h. [c] 2.5 h. [d] r.t., 3 h; 40 °C, 24 h. [e] 26 h.

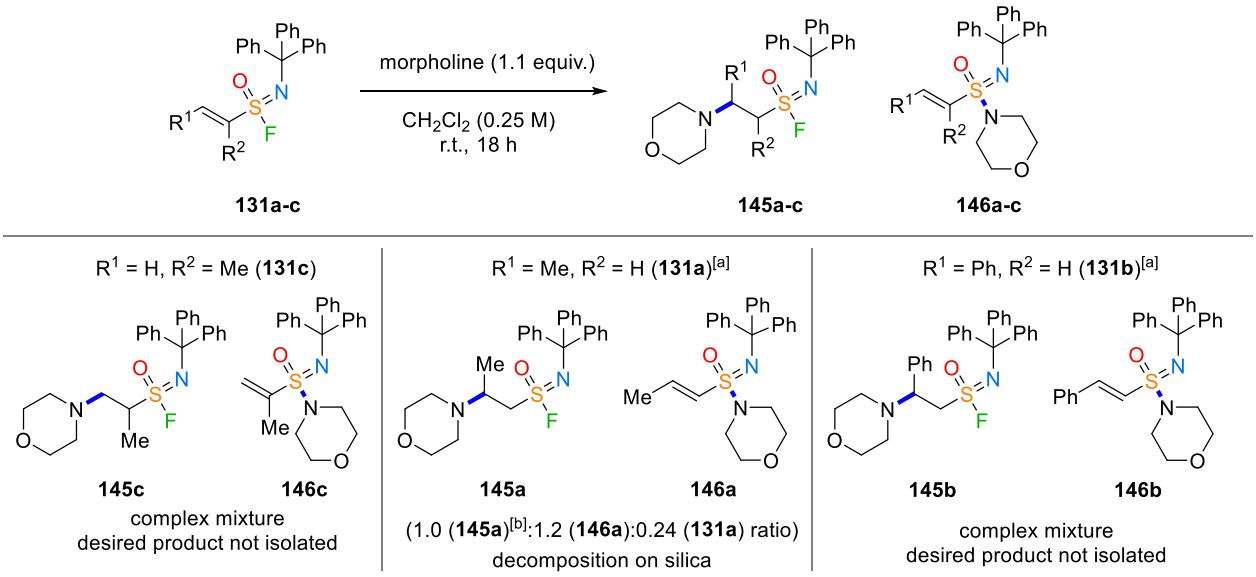
Diepers found the use of *n*-butylamine under modified conditions gave access to the bis-addition, β-sultam analogue, **141h**, in low yield (12%, **Scheme 3-14**), as well as the 1,2-addition product (**142h**, 7%). The low yields may be attributed to multiple purification attempts as well as reduced reactivity of primary amines. Despite the prevalence of β-sultams, this represents the first synthesis of a mono-aza analogue (**141h**). These are interesting motifs, especially given their potential application as bioisosteres of medicinally relevant β-lactams and -sultams.[250, 251, 318, 319]



Scheme 3-14 Reaction of *n*-butylamine to form β-sultam analogue **141h** (Diepers).

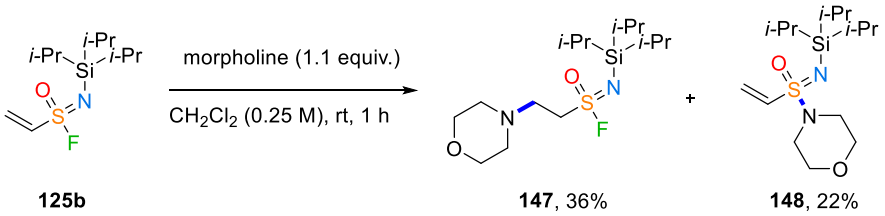
3.6.2 1,4-Addition of amines to alternative alkenylsulfonimidoyl fluorides

Given the striking effect substituents at the β-position of ESF on reactivity (**chapter 3.5**), we were interested in if a similar effect may be observed for ESIFs. The synthesised substituted alkenylsulfonimidoyl fluorides (**131a-c**, **Scheme 3-7**) were subjected to the optimised reaction conditions using morpholine as the nucleophilic partner (**Scheme 3-15**). Reaction times were considerably longer for these substrates with starting material remaining even after 18 h. An additional complication of these systems is the formation of diastereomers with an additional carbon stereocentre now present in the 1,4-addition products (**145a-c**). Reaction of α-Me Tr-ESIF (**131c**) led to a complex mixture of products with presence of two diastereomers of **145c**, remaining starting material and 1,2-addition products with overlapping signals meaning accurate ratios could not be determined. After column chromatography no clean product could be isolated. Reaction of β-Me Tr-ESIF (**131a**) also exhibited a complex reaction profile; it could be determined that there was significant formation of 1,2-product (**146a**) and remaining starting material (**131a**) in the crude reaction mixture. Unfortunately, the desired 1,4-addition product could not be isolated (**145a**). Cinnamoyl sulfonimidoyl fluoride (**131b**) resulted in similar complex reaction mixture with remaining starting material, 1,4-addition (**145b**) and 1,2-addition (**146b**) products present.



Scheme 3-15 Reaction of alkenyl Tr-SIFs with morpholine under the optimised conditions. [a] Selectivity determined by analysis of crude quantitative ^{1}H NMR spectra (1,4- *vs.* 1,2-addition vs SM). [b] 1.3:1 d.r.

The impact of the nitrogen-substituent was then explored, a key parameter ESF does not permit. TIPS-ESIF (**125b**) was used as the electrophilic partner by Diepers, resulting in a regioisomeric mixture of 1,4- and 1,2-addition products (**147** and **148** respectively, **Scheme** 3-16). Although the ratio of the products obtained (1.8:1) was less preferable than Tr-ESIF (**125a**, 4:1), it gives an indication that by fine tuning the steric and electronic properties the reactivity of this class of compounds may be altered.

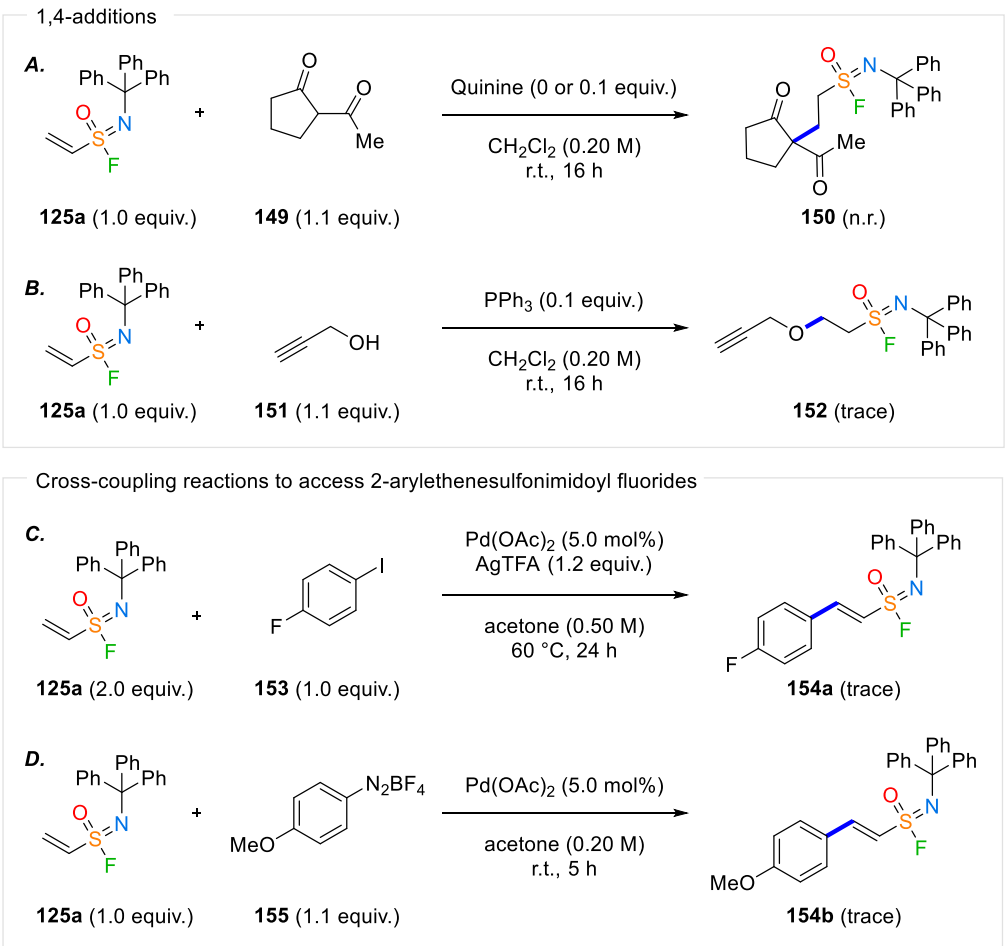


Scheme 3-16 Reaction of TIPS-ESIF (**125b**) with morpholine under the optimised conditions (Diepers).

3.6.3 Alternative reactions of Tr-ESIF

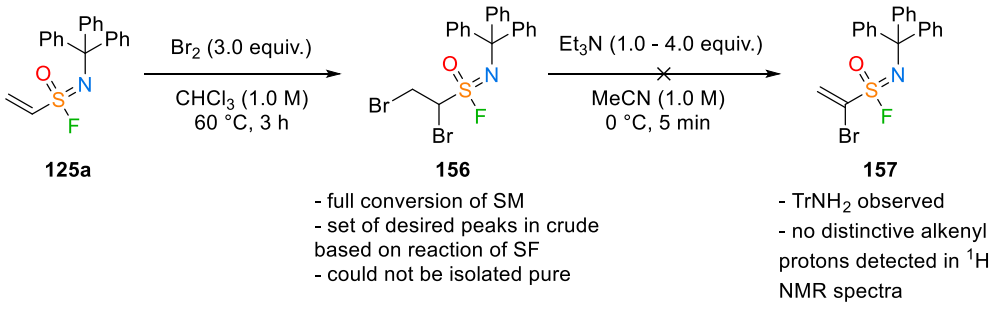
We were interested in probing the reactivity of Tr-ESIF (**125a**) further in a series of reactions known for ESF (**Scheme 3-17**). Nucleophiles that are reported to react with ESF, such as

2-acetylcyclopentan-1-one (**149**) were unreactive in the presence of Tr-ESIF (**125a**) with and without quinine as an additive (reaction A).[240] The use of propargyl alcohol (**151**) was more promising with some consumption of Tr-ESIF and new peaks in the crude ^{1}H NMR spectrum at similar chemical shift to those reported for the analogous sulfonyl fluoride (reaction B).[59] However, none of the desired product (**152**) was isolated after column chromatography. Reported reactions to access stryenylsulfonyl fluorides (SSFs) were trialled with Tr-ESIF as the starting material (reactions C and D). Use of 4-fluoroiodobenzene (**153**) and 4-methoxybenzenediazonium tetrafluoroborate (**155**) in Pd-catalysed reactions were unsuccessful, resulting in only trace amounts of product (**154a-b**).[271, 272]



Scheme 3-17 Additional reactions trialled on Tr-ESIF based on literature reactions of ESF.

The most promising reactivity was observed for the bromination of Tr-ESIF en route to the synthesis of mono-aza analogue of BESF (**157**, **Figure 3-3**). Using the conditions reported by Moses and co-workers, Tr-ESIF (**125a**) was treated with Br_2 and refluxed in chloroform for 3 h (**Scheme 3-18**).[287] After aqueous work-up, attempts to isolate the material (**156**) by column chromatography were unsuccessful. Therefore, attempts to unmask the desired BESIF analogue (**157**) were commenced, with triethylamine utilised as the base. However, the desired product was not observed and instead tritylamine was detected when using only 1.0 equivalents of triethylamine. Further investigations into this pathway are warranted especially given the diverse heterocyclic sulfonimidoyl fluorides that may be accessed from this precursor.



Scheme 3-18 Attempted synthesis of mono-aza analogue of BESF.

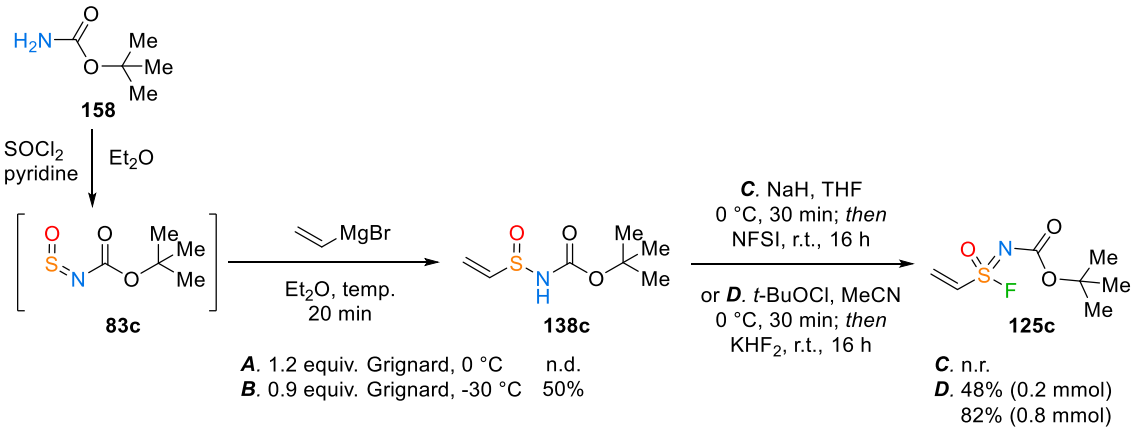
3.7 Electron-withdrawing substituents on nitrogen

3.7.1 Synthesis of reagents

Given the comparatively poor reactivity and regioselectivity for ESIFs we were intrigued to pursue alternative nitrogen substituents, namely electron neutral and withdrawing groups. We proposed their synthesis could be achieved from the corresponding sulfinylamine in an analogous manner. This class of compounds have been well studied with numerous reports detailing their synthesis and reactivity.[25, 320] However, they are more challenging to handle,

typically decomposing rapidly when in contact with moisture or air and thus are less user friendly.[25]

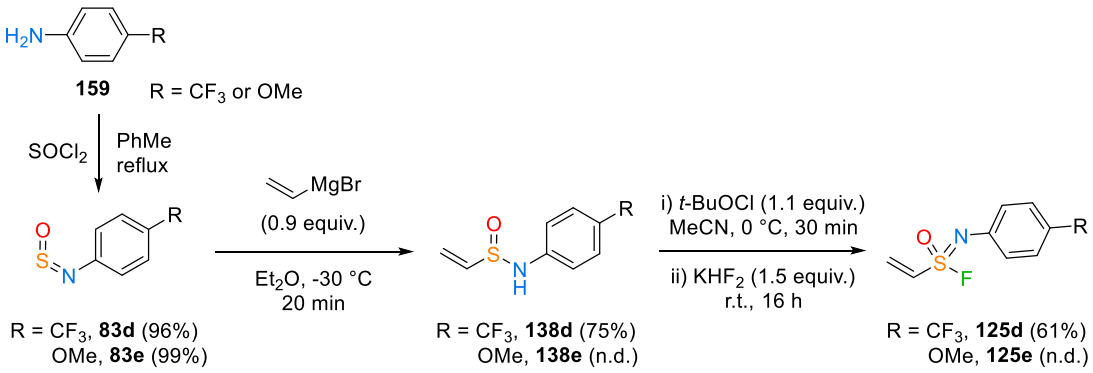
In order to access initial quantities of *N*-EWG ESIFs for reactivity testing this route was pursued. Reaction of excess vinylmagnesium bromide with boc-NSO (**83c**) led to the formation of a viscous oil and none of the desired product was observed after work-up (**Scheme 3-19** A). Reducing the equivalents of the Grignard reagent (0.9 equiv.) and the temperature (-30 °C) resulted in conversion to the desired *N*-boc sulfinamide (**138c**) in moderate yields (B). Although oxidative chlorination followed by halogen exchange (D) gave access to the desired boc-ESIF (**125c**) in high yield, oxidative fluorination under basic conditions gave none of the desired product (C).



Scheme 3-19 Synthesis of boc-ESIF (**125c**) in a two-step process.

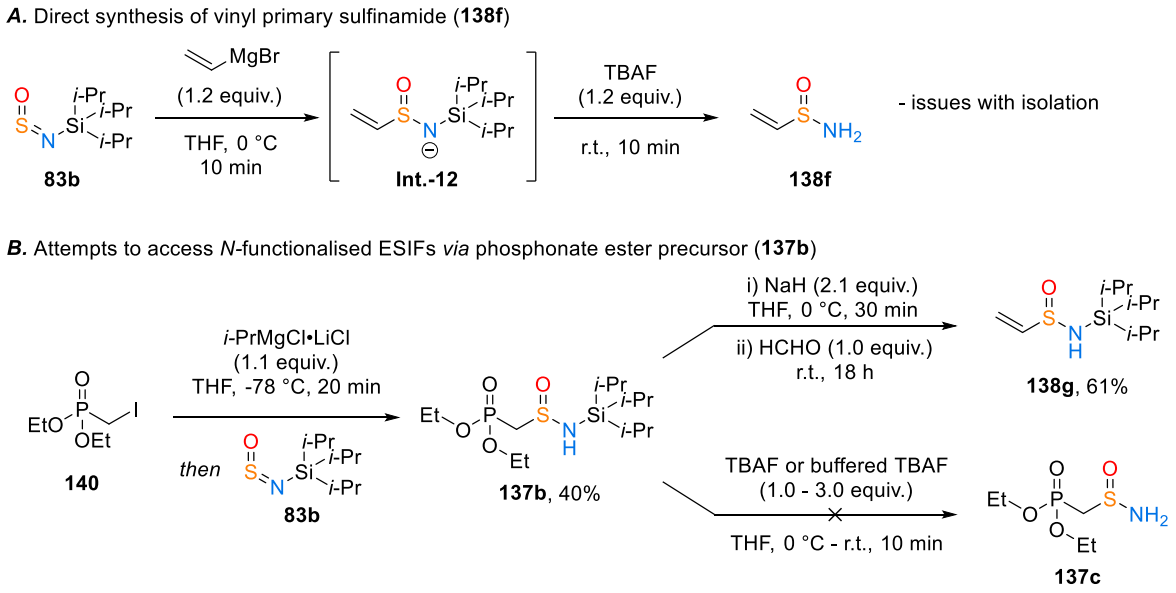
The same two-step approach was applied to aniline-derived sulfinylamine reagents (**83d** and **83e**), which can be formed by refluxing the respective aniline with thionyl chloride in toluene (**Scheme 3-20**).[25] Reaction with vinylmagnesium bromide (0.90 equiv.) resulted in clean formation of the desired sulfinamides (**138d** and **138e**) and could be performed on moderate scale (5.0 mmol). As described by Baudin and co-workers,[316] anisidine derived compound, **138e**, was found to be unstable to column chromatography and storage, so was

used without further purification in subsequent reactions. Oxidative chlorination followed by halogen exchange again proceeded smoothly to give access to the desired CF_3-substituted sulfonimidoyl fluoride (**125d**). 4-Methoxybenzene analogue (**125e**) was formed but could not be isolated, with significant decomposition occurring rapidly.



Scheme 3-20 Synthesis of *N*-aryl ESIF analogues (**125d-e**).

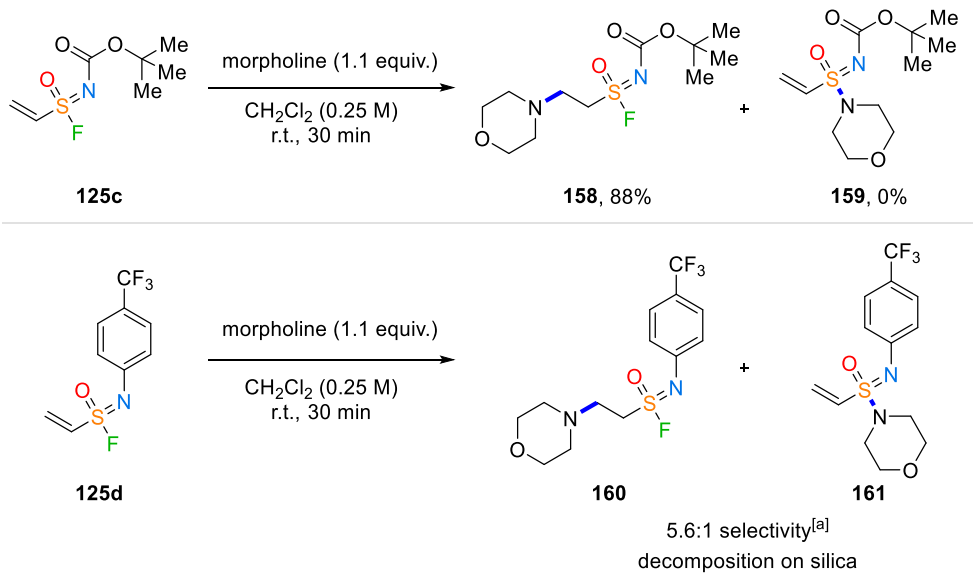
Although this approach can generate quantities of the desired sulfinamides and sulfonimidoyl fluorides, the use of unstable sulfinylamines is challenging and would potentially limit the uptake of these methods within industry. Therefore, an alternative approach was devised wherein a primary vinyl sulfinamide, **138f**, would be the key building block. Installation of substituents on nitrogen using an umpolung strategy, relying on electrophilic fragments, could provide access to a complementary set of compounds. Unfortunately, the primary sulfinamide (**138f**) was found to be volatile, with issues associated with its isolation (**Scheme 3-21 A**). Instead, the phosphonate ester route (**Scheme 3-10**) was utilised to form TIPS-protected sulfinamide **137b**, a higher molecular weight precursor (**Scheme 3-21 B**). This reagent can undergo the desired HWE reaction itself to access alkenyl TIPS-protected sulfinamide (**138g**). However, attempts to remove the TIPS functionality and form primary sulfinamide (**137c**) in order to functionalise nitrogen were unsuccessful (TBAF or buffered TBAF), with only decomposition products observed.



Scheme 3-21 Synthetic attempts to access *N*-functionalised ESIFs *via* alkenyl and phosphonate ester substituted primary sulfinamides.

3.7.2 Reactivity with amines

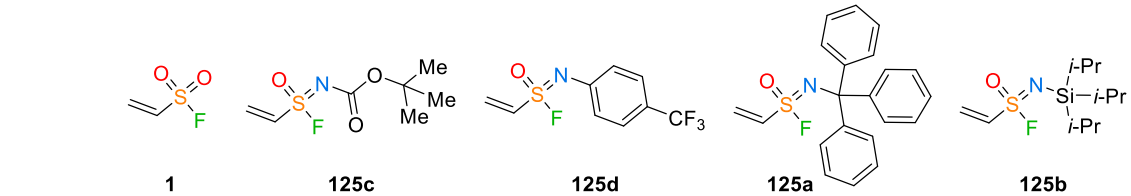
With requisite sulfonimidoyl fluorides in hand the influence of the EWG on nitrogen was explored under the optimised conditions (**Scheme 3-22**). The reaction of boc-ESIF (**125c**) proceeded with exquisite regioselectivity with none of the 1,2-addition product (**159**) observed in crude ^{1}H NMR spectra. Encouragingly, the desired product **158** could be isolated in the highest yield to date, 88%. This shows significant promise therefore as a SuFEx hub with further investigations into this compounds reactivity with other nucleophiles warranted. Interestingly, the product appears to be stable to silica. This is perhaps surprising given the enhanced reactivity of EWG substituted SIFs compared to EDG counterparts in a study by Grimster and co-workers.[146] The aniline derived SIF (**125d**) showcased improved regioselectivity (5.6:1) compared to Tr-ESIF (**125a**). However, the pure product (**160**) could not be isolated by column chromatography. In both cases the overall reactions proceeded at a markedly faster rate, with no starting material remaining after only 30 minutes.



Scheme 3-22 Reaction of *N*-substituted ESIF analogues with morpholine. [a] Calculated using quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

^{13}C and ^{1}H NMR chemical shifts have been used to predict and correlate electrophilicity patterns of α,β-unsaturated systems in the context of Michael addition reactions, with varying degrees of success.[321, 322] A series of one- and two-dimensional NMR spectroscopic experiments [i.e., NOESY, HMBC, HSQC] were performed to assign the proton and carbon resonances of compounds **125a-d**. As expected in the context of ESIF analogues, the presence of more electron-withdrawing substituents on nitrogen resulted in a substantial downfield shift (by up to 5.0 ppm) for the β-vinyl carbon (C_β) (**Figure 3-6**). Similar deshielding was observed in the ^{1}H NMR spectrum of these compounds. Both sets of data indicate a significant decrease in electron density at this position, in agreement with the observed increased reactivity; for example, the regioselectivity of boc-ESIF (**125c**) is >20:1 *vs.* 2:1 for TIPS-ESIF (**125b**). This trend is bolstered by the inclusion of ESF (**1**), which shows immaculate 1,4-selectivity, in line with the decreased electron density observed in both ^{1}H and ^{13}C NMR spectra. The inclusion of more data points in this study and the reaction of other nucleophiles would be valuable to confirm this hypothesis. Moreover, analysis of rate data for these compounds would also be of interest in addition to

regioselectivity. An important factor unique to these bis-electrophiles is the impact the change in electronics may have on reactivity at sulfur, with *N*-EWG substituted SIFs proving more reactive in biological systems in a study by Grimster and co-workers.[146] However, in these cases, it appears the increase in reactivity at the β-position is greater than that at sulfur.



	1	**125c**	**125d**	**125a**	**125b**
			^{1}H NMR (ppm)		
$C_\alpha H$ (δ):	6.82	6.87	6.87	6.81	6.71
$C_\beta H_2$ (δ):	6.76, 6.47	6.70, 6.38	6.71, 6.34	6.50, 6.11	6.43, 6.04
			^{13}C NMR (ppm)		
C_α (δ):	130.2	131.2	132.4	134.8	135.7
C_β (δ):	134.5	133.3	131.7	128.4	128.3
			1,4- vs 1,2-add[n]:		
Selectivity:[a]	1:0	>20:1	5.6:1	4:1	1.8:1

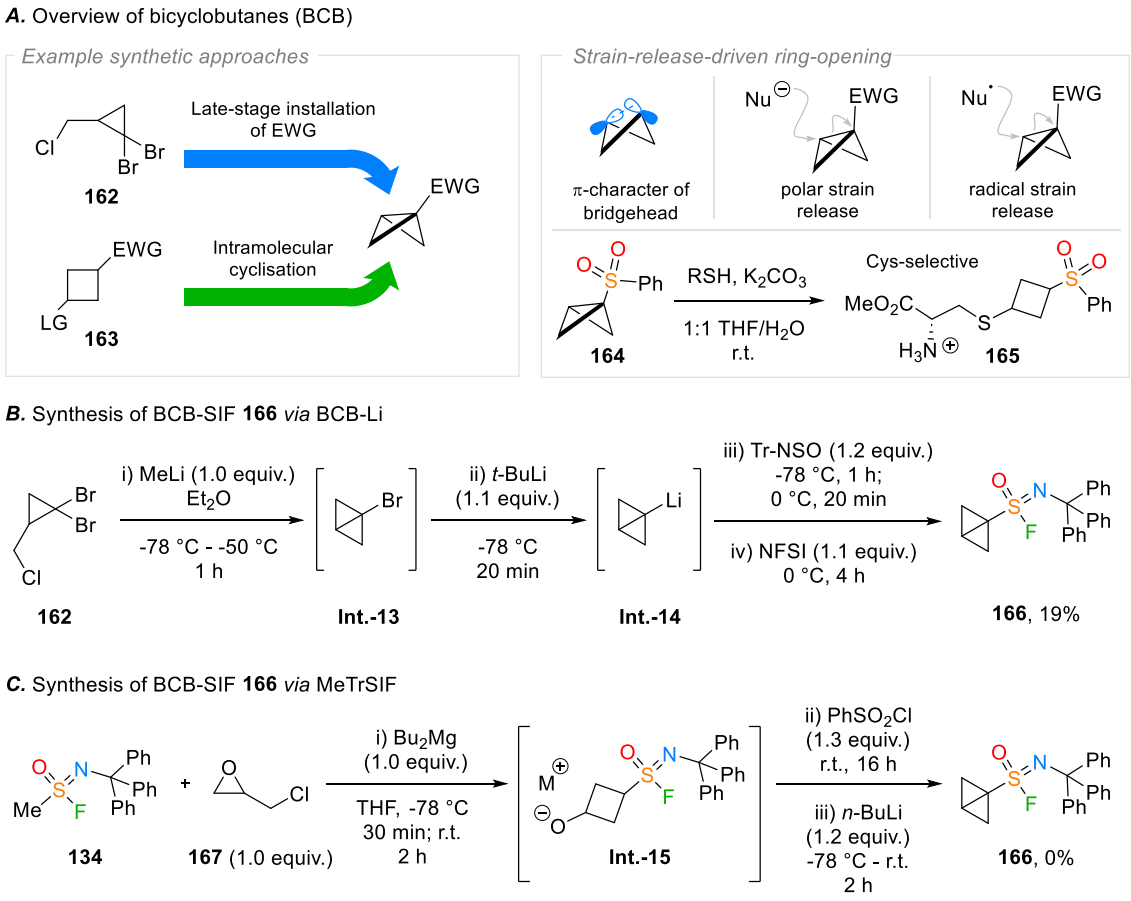
C_β ^{13}C and ^{1}H NMR shift = greater 1,4-addition selectivity

Figure 3-6 ^{1}H and ^{13}C NMR chemical shifts of β-carbon (C_β) and α-carbon (C_α) for ESF (**1**) and ESIF (**125**) analogues, and the observed selectivity in reactions with morpholine (1.1 equiv.), CH_2Cl_2 (0.25 M), r.t., 30 min - 1 h. [a] Selectivity ratio determined by analysis of quantitative ^{1}H NMR spectra of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

3.8 Bicyclo[1.1.0]butane sulfonimidoyl fluorides

Bicyclo[1.1.0]butanes (BCBs) are a class of highly strained isolable building blocks, making them interesting precursors and reagents (**Scheme 3-23**).[323-327] Their use as strain-release reagents is typified by addition of nucleophilic reagents across the weak central C-C bond, as well as rearrangement and radical reactions providing access to complex sp^3-rich scaffolds (**Scheme 3-23 A**). The former reactivity is akin to Michael acceptors, thus exploration of mimics of ethene functionalities with BCB's has led to a significant field of research, including their use as covalent warheads.[328, 329] Henceforth, we were interested in

the synthesis and application of BCB-SIFs (**166**). We desired to make a series of *N*-substituted ESIF analogues and ESF counterparts in a modular manner. Therefore, the late-stage installation of substituents was highly desirable. Amongst the various strategies utilised to access substituted BCBs, derivatisation of BCB-Li (**Int.-14**) was appealing due to the wide range of electrophiles compatible in the final step (**Scheme 3-23 A**).[330,331] Dibromocyclopropane, **162**, was converted to BCB-Li (**Int.-14**) following literature procedures (**Scheme 3-23 B**).[330] Trapping of this intermediate with Tr-NSO (**8**) and *in situ* fluorination delivered the desired sulfonimidoyl fluoride (**166**), albeit in poor yield (19% from cyclopropane **162**). This is the first example of either a BCB-SuFEx reagent or an aza-sulfur derivative of a BCB.[331] The product proved to be stable to long-term storage in the freezer under an inert atmosphere (>6 months). The optimisation of this procedure would be particularly beneficial to access greater quantities of material and to trial with other sulfinylamine reagents. We envision that this organolithium species could also be used to intercept other sulfur-electrophiles to generate ESF, ESIF and other aza-S(VI) analogues.



Scheme 3-23 Bicyclobutanes (BCBs) in the context of sulfonimidoyl fluorides.

Side-chain cyclisation is one of the most well-established routes to mono-substituted BCBs containing an electron-withdrawing substituent on the bridgehead (**Scheme 3-23 A**). Recent developments for this strategy by Jung and Lindsay permit the synthesis of BCB-sulfones in one-pot from methyl sulfones.[331] This transformation would offer significant benefits in terms of safety and complementary ability to synthesise substituted BCB derivatives. Based on this, methylsulfonimidoyl fluoride (**134**) was again applied as the precursor, disappointingly with no success (**Scheme 3-23 C**).

3.9 Summary and future work

In summary, we have shown in this **chapter 3**, that ethenesulfonimidoyl fluorides (ESIFs, **125**) are a promising new class of SuFExable hubs (**Figure 3-7**). This unique class of molecules offer several benefits compared to their sulfonyl counterpart, ESF (**1**), a widely

explored reagent in organic synthesis: tunable reactivity, exploration of chemical space, ease of use (non-volatile reagents). An expedient synthesis of these new reagents has been developed either in a one or two-step process depending on the nitrogen substituent. The synthetic routes allow for varying both the carbon and nitrogen substituent in a modular manner. Initial reactivity of amines with Tr-ESIF (**125a**) showed surprising difference in reactivity compared to its sulfonyl counterpart, ESF (**1**); a significant quantity of the 1,2-addition product was observed. Optimisation studies were carried out on a model system with an isolated yield of 72% achieved. A range of amines were explored using the optimised reaction conditions by Erik Diepers. Of note is the reaction of primary amines to form β-sultam analogue **141h**. The selectivity could also be switched by changing the reaction solvent and addition of base, facilitating access to highly sought-after vinyl sulfonimidamides.[298] The primary issue with this class of aza-Michael addition reactions is the instability of the products on silica, which severely limits the ease of purification of this class of compounds.

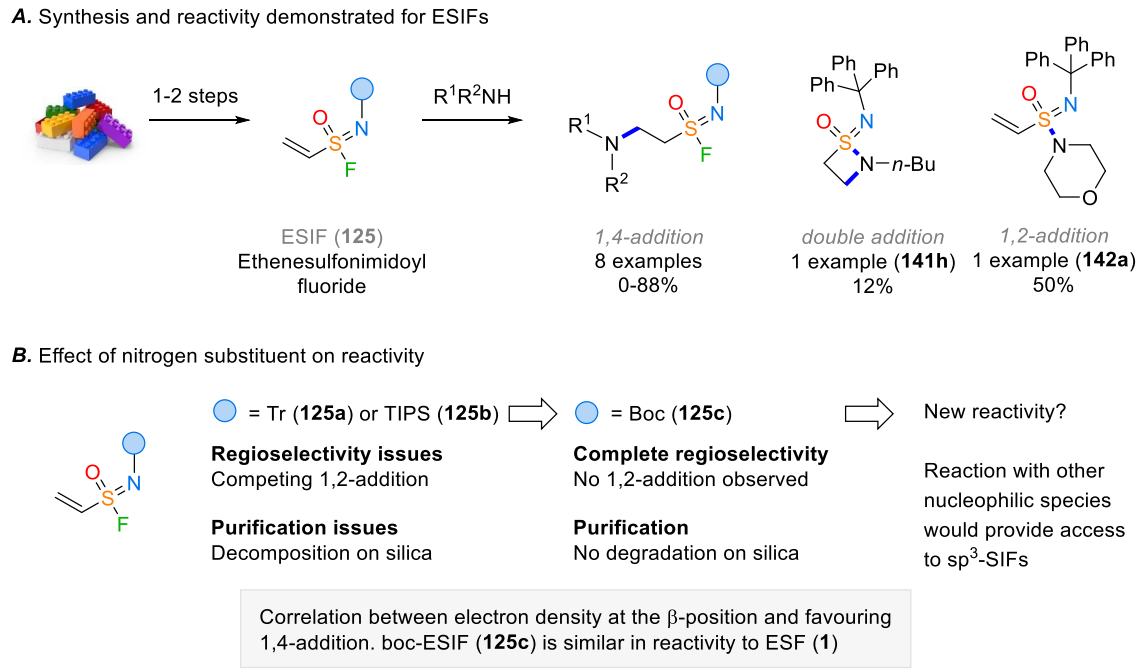


Figure 3-7 Summary of the use of ethenesulfonimidoyl fluorides (ESIFs).

In order to combat these issues, alternative nitrogen substituents were explored. Given the well documented reports of instability of sulfinylamines,[25] a new class of reagents, phosphonate ester sulfinamides (**137**), was developed. These compounds are competent pro-nucleophiles in HWE reactions with aldehydes to form alkenyl sulfinamides (**138**), precursors to ESIF analogues and compounds with potential application to form alkenyl S(VI)-substrates and as cross-coupling partners. The desired primary sulfinamide analogue (**138f**) could not be accessed due to isolation issues, although further efforts to access this compound are ongoing. Instead, unstable sulfinylamines were used for the synthesis of aniline derived ESIF (**125d**) and boc-ESIF (**125c**). The use of **125c** in particular resulted in excellent regioselectivity for reaction with morpholine, with the desired product isolated in 88% yield. Further exploration of boc-ESIF (**125c**) with additional nucleophiles will be carried out in the future as well as reaction with other nucleophiles known to react with ESF (**Figure 3-1**). Reaction of substituted alkenyl substrates was hindered by decomposition of the 1,4-addition products on silica (**145a-c**). Alternative reaction classes were trialled with Tr-ESIF; however, minimal conversion was observed in all cases. Radical additions and cycloadditions may be amenable reaction classes with diminished propensity to react at sulfur directly in unwanted side-reactions.

An alternative class of new potential Michael acceptor reagents has been developed in the form of BCB-S(VI)-fluorides. The unoptimized conversion of cyclopropane **162** to **166** is encouraging, with the sulfonimidoyl fluoride product proving stable for periods longer than 6 months. The synthesis and evaluation of further S(VI)- and S(IV)-analogues of this design will be investigated in a range of reactions with nucleophiles and as warheads in chemical biology settings.

4 Sulfinamides as nucleophiles in Pd-catalyzed cross-coupling reactions

4.1 Introduction to cross-couplings to form biaryls

In recent decades the advancement of metal-catalysed carbon-carbon bond-forming reactions has revolutionised the construction of biaryl motifs, used widely in biologically active compounds and materials chemistry. These processes utilise an organometallic nucleophilic partner, which typically undergoes transmetalation with a metal complex, and a (hetero)aryl halide as the electrophilic partner that undergoes oxidative addition. The "gold standard" for biaryl construction is the Suzuki-Miyaura cross-coupling (SMC), a transition-metal-catalysed reaction between an organoboron reagent and a halide or pseudohalide (**Figure 4-1 A**).[332, 333] Its broad application in academia and industry arises from the mild, functional group tolerant reaction conditions, allowing for late-stage incorporation of aromatic motifs in drug-discovery programs.[334]

Despite the widespread use of the SMC, poor reaction success is observed with certain classes of boronic acids, due to their instability under typical reaction conditions. Two key examples are heteroaromatic (particularly 2-heteroaryl) and polyfluorinated aryl boronic acids (**Figure 4-1 B**), which undergo rapid protodeboronation side-reactions.[335-337] Reports using 2-pyridyl boronic acid reagents typically suffer from poor yields and limited scope of electrophilic coupling partners.[338] This long-standing issue was coined the 2-pyridyl organometallic cross-coupling problem by Fagnou and co-workers,[339] and more recently reviewed in detail by the Willis group in 2021.[338] Given the crucial role of heteroaromatic scaffolds, significant research efforts have been conducted to improve their reactivity under SMC conditions, namely the development of bulky, electron-rich monophosphines (e.g.,

Xphos), alternative stable boronate derivatives, and the use of copper salts (**Figure 4-1 C**).[335, 336, 340]

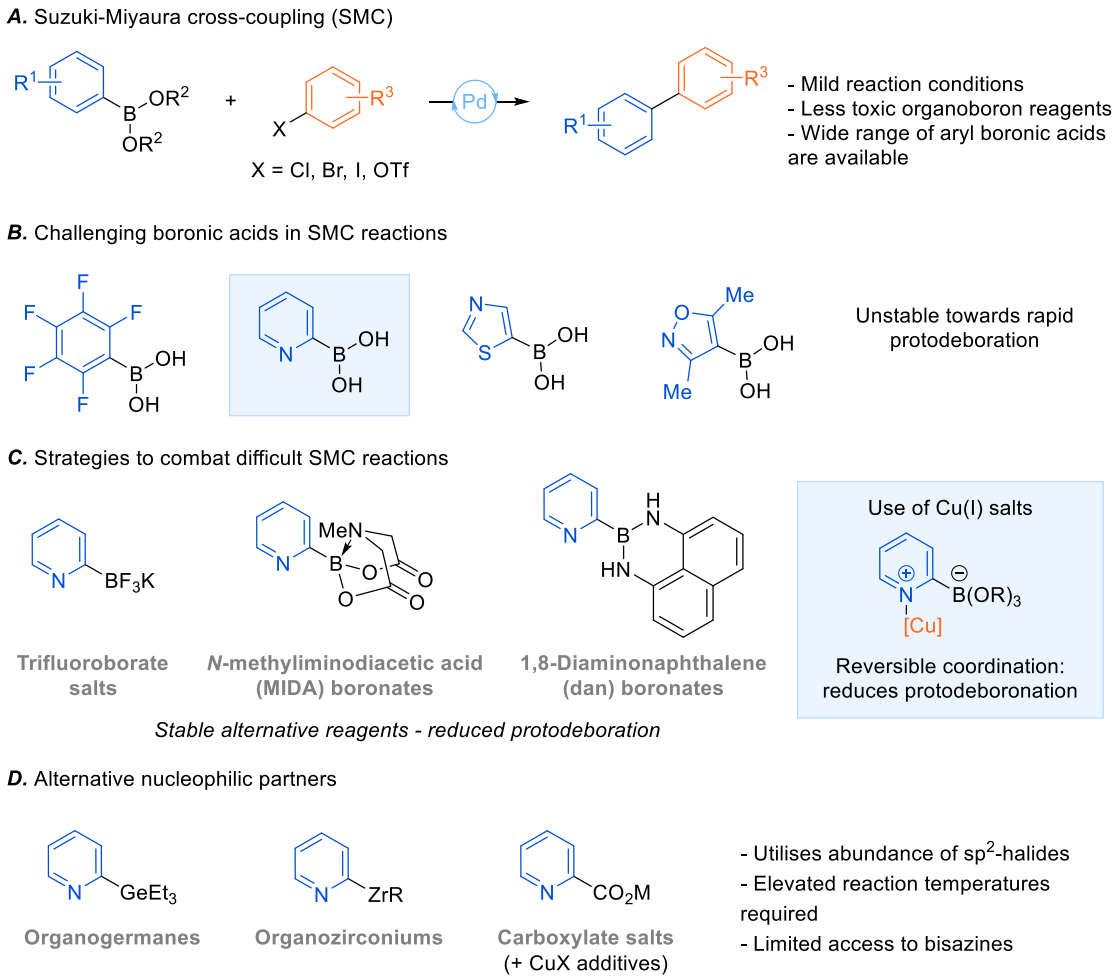


Figure 4-1 Summary of Suzuki-Miyaura cross-coupling (SMC) reactions.

Strategies for the construction of 2-arylpyridines have been developed that circumvent the requirement of 2-pyridyl nucleophilic fragments, for example inverting the polarity of the partners. However, this does not utilise the respective abundance of sp^2-halides versus boronic acids and is therefore less attractive. Therefore, the use of alternative nucleophilic coupling partners in combination with sp^2-halides has been the key strategy for providing a solution to challenging SMC substrates. Huo (zirconium)[341], Schoenebeck (germanium)[342] and Gooβen (carboxylates)[343,344] have made significant progress in this area (**Figure 4-1 D**). These approaches still suffer significant shortcomings, with elevated temperatures required

and limited use of heteroaromatic electrophiles to form bisazines, often proceeding in low yields.

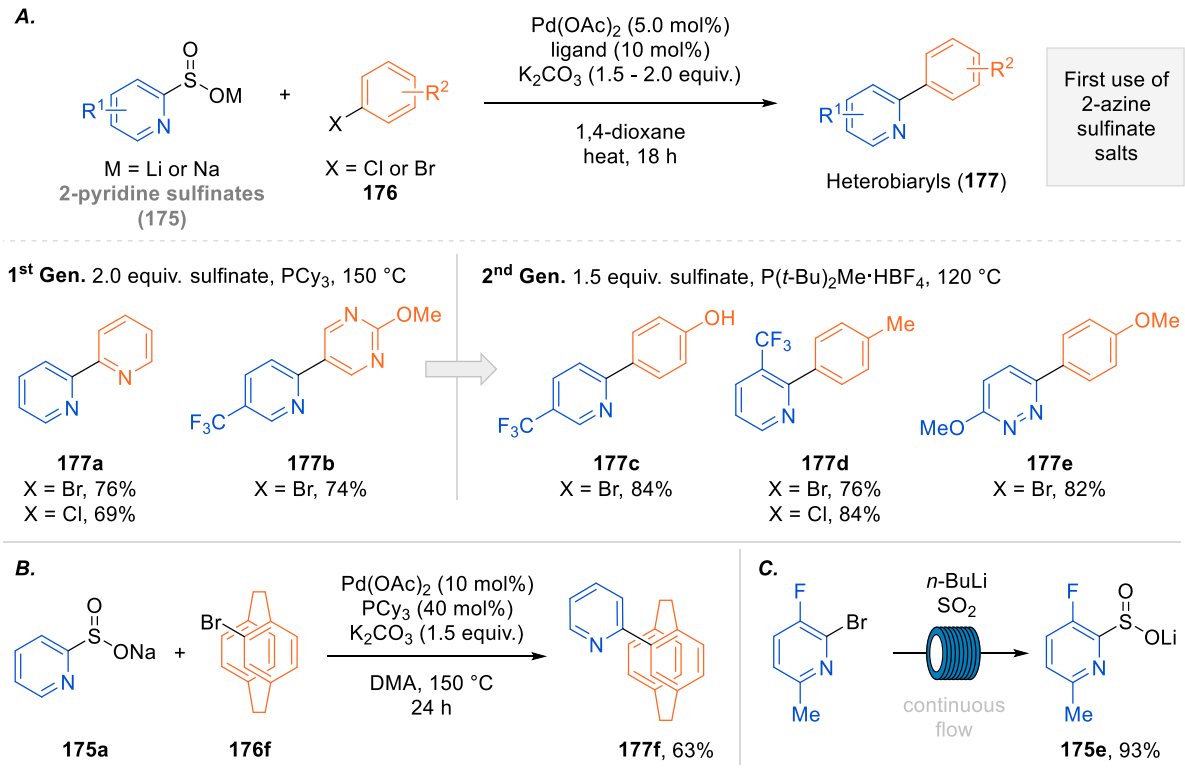
4.2 Desulfinative cross-couplings to form biaryls

Aryl sulfinate salts have attracted significant attention as alternative coupling partners for the construction of carbon-carbon and carbon-heteroatom bonds.[345] In comparison to other organometallic nucleophilic coupling partners, aryl sulfinates offer several advantages; they are bench stable, low-cost starting materials and SO_2 is the primary by-product. Moreover, sulfinate salts are generally odourless, non-toxic, easy to handle solids, with a number of protocols developed for their synthesis from various starting materials.[346, 347]

4.2.1 Sulfinate salts in Pd-catalysed desulfinative cross-couplings

The use of sulfinate salts as nucleophilic partners in cross-coupling reactions was first published by Sato and Okoski in 1992.[348] Their application was explored further by Duan, Forgione,[349-351-352] Billard and Nagarkar groups in combination with (pseudo)halides.[353, 354] This was extended to heteroaromatic ((benzo)furan and thiophene) sulfinate salts by Forgione and co-workers in the following years, using microwave irradiation at elevated temperatures (150-170 °C).[355-357] Although showcasing the utility of sulfinate precursors for cross-coupling procedures, it was not until 2017 that heteroarenesulfinates containing azine nitrogens were utilised. The Willis group pioneered the use of sodium and lithium 2-pyridyl sulfinate salts (**175**) as efficient nucleophilic coupling partners in combination with aryl chlorides and bromides (**176**, **Scheme 4-1 A – 1st Gen.**).[358] The generality of this methodology was highlighted by the application of these conditions for the synthesis of previously inaccessible pyridyl[2.2]paracyclophanes (**177f**), useful building blocks in materials science (**Scheme 4-1 B**).[359] A second-generation method was developed by the Willis group, wherein the use of $P(t\text{-Bu})_2Me{\cdot}HBF_4$ enabled the cross-couplings to be

performed at lower reaction temperatures (120-130 °C, (**Scheme 4-1 A – 2nd Gen.**)).[360] These milder conditions allowed a wider range of heteroaromatic sulfinate salts to be tolerated, including pyridazines (**177e**). The synthesis of pharmaceutically relevant heteroaromatic sulfinates has recently been realised using a continuous flow setup on a range of scales, with up to 31 grams of sulfinate (**175e**) generated over 35 minutes (**Scheme 4-1 C**). Isolated lithium salts were then subjected to the Willis group protocols (at 140 °C) to give bis-heteroaryls.[361]

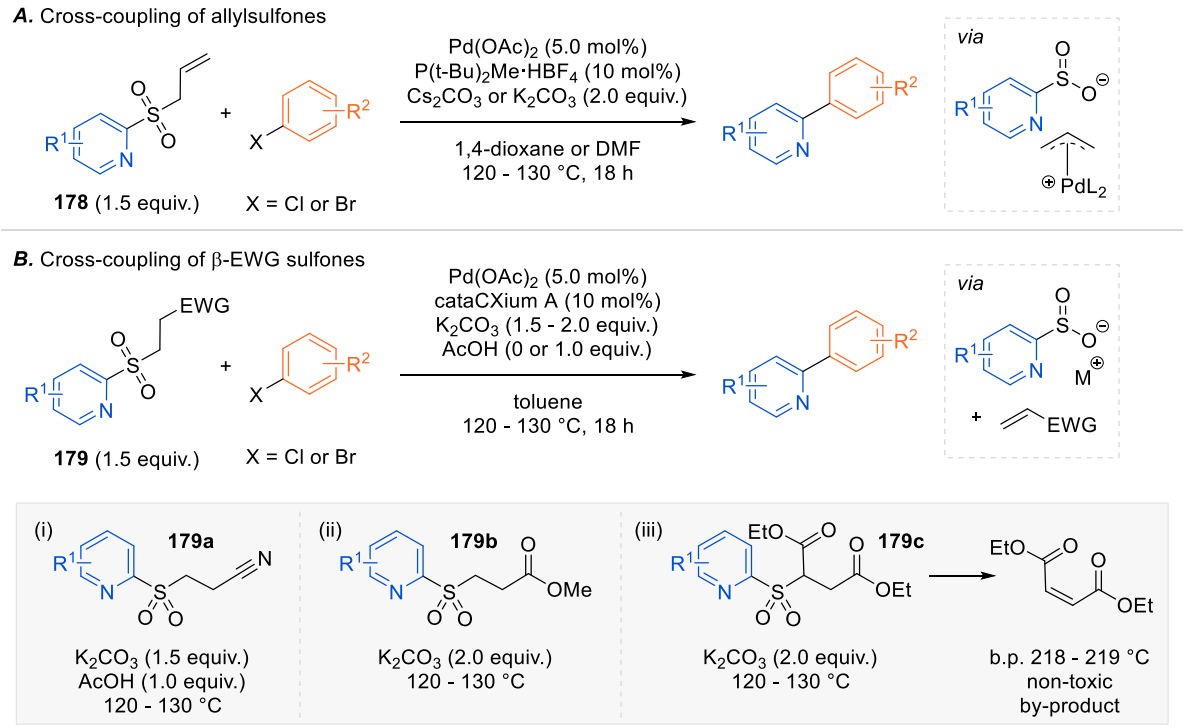


Scheme 4-1 Heteroaryl sulfinate salts as nucleophilic cross-coupling partners: (***A***) use of 2-heteroaryl sulfinate salts in desulfinative cross-coupling arylations (Willis, 2017); (***B***) application of sulfinate salts for the synthesis of 2-pyridylpara(cyclophanes) (Rowlands, 2021); (***C***) continuous flow synthesis of lithium sulfinates (Sedelmeier, 2020).

4.2.2 Use of latent sulfinates in desulfinative cross-couplings

Although heteroaromatic sulfinates are efficient coupling partners, their isolation and preparation are non-ideal due to their anionic nature. This leads to poor solubility in organic solvents and incompatibility with multi-step synthetic procedures. The Willis group has

recently pioneered the use of latent sulfinate reagents, in the form of sulfones, wherein the active sulfinate salt is unmasked *in situ* under reaction conditions (**Scheme 4-2**). Allylsulfones (**178**) were first established, providing an alternative synthetic building block that is neutral and simpler to purify (**Scheme 4-2 A**).[362] In 2021, a new generation of base-labile latent sulfinates was reported by the Willis group: β-nitrile and β-ester sulfones (**179a-c**, **Scheme 4-2 C**).[363] This method addresses issues associated with sulfinates and allylsulfones, namely the reagents are compatible in multi-step elaborations, including metal-catalysed processes and alkene functionalisation reactions. The β-EWG reagents are comparatively more straightforward to access, in particular, the methyl ester analogues (**179b**) can be synthesised in one-step protocols using sodium 1-methyl 3-sulfinopropanoate (SMOPS), a commercially available precursor, in combination with aryl halides.[364] The release of toxic acrylonitrile and methyl acrylate by-products can be circumvented through the use of diethyl succinate sulfones (**179c**). This alternative masking group releases non-toxic, non-volatile diethyl fumarate making this system more amenable to scale-up.



Scheme 4-2 Use of latent sulfinates in cross-coupling reactions: (***A***) Allylsulfones as sulfinate precursors (Willis, 2019); (***B***) β-EWG sulfones as base-activated (hetero)aryl cross-coupling partners (Willis, 2021).

4.2.3 Lowering reaction temperatures of desulfinative cross-couplings

Despite the advances of desulfinative cross-coupling methodologies, all of the reactions to date require temperatures of 120 °C or higher. Dr. Antoine de Gombert, a former DPhil student in the Willis group, investigated the mechanism of these transformations to elucidate strategies for lowering reaction temperatures.[221] The general catalytic cycle for these reactions first proceeds *via* reduction of the Pd(II) precatalyst to the Pd(0) active catalyst, followed by oxidative addition with an aryl halide (**Figure 4-2**). Subsequent transmetalation of the metal sulfinate salt with the oxidative addition complex is the rate limiting step for carbocyclic substrates, such as 4-methylbenzene sulfinate. Extrusion of SO_2, followed by reductive elimination results in formation of the product and regenerates the active Pd(0) catalyst.

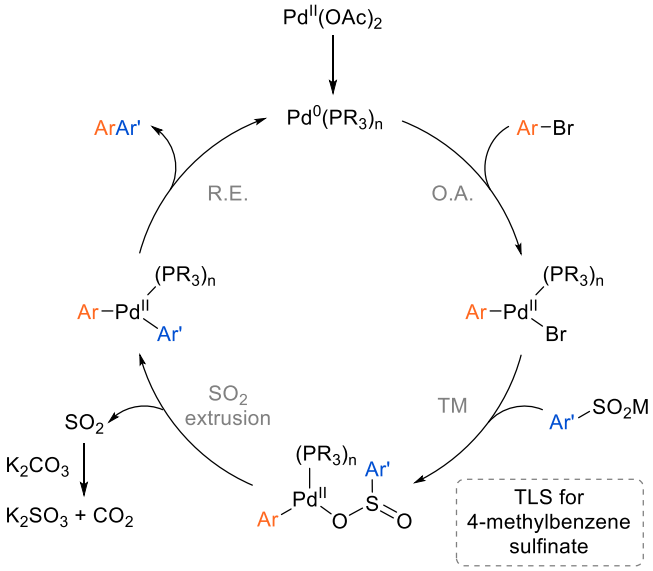
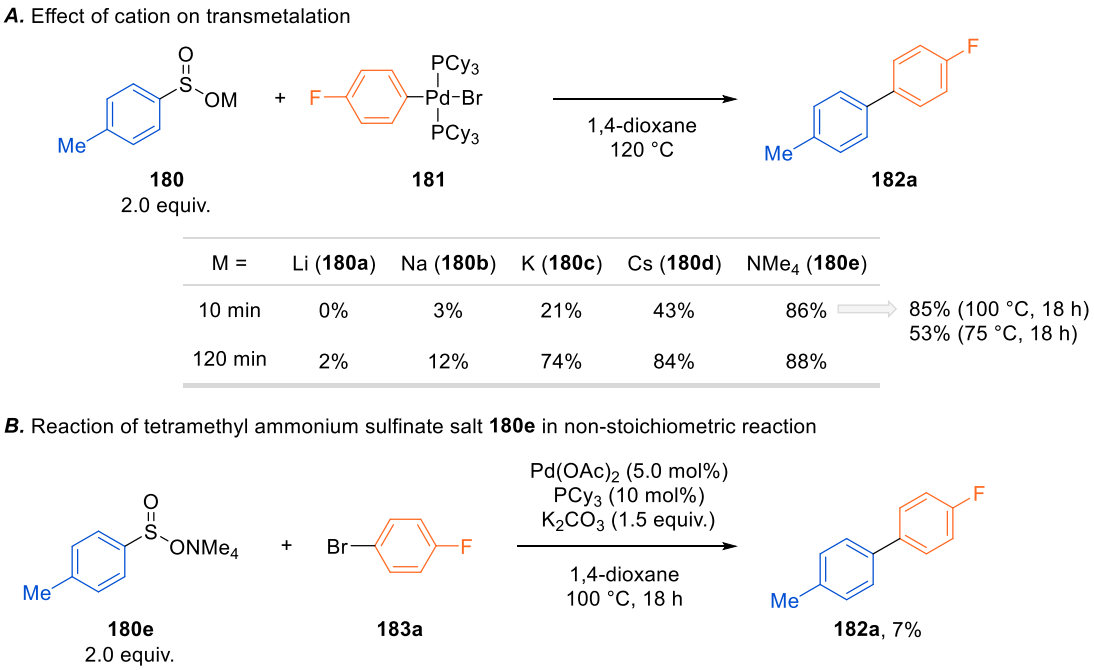


Figure 4-2 General mechanism for palladium-catalysed cross-coupling reactions between aryl halides and aryl sulfinate salts. O.A. = oxidative addition, TM = transmetalation, R.E. = reductive elimination.

As transmetalation of the sulfinate salt (**180**) with oxidative addition complex **181** is the turnover limiting step for carbocyclic substrates,[221] de Gombert studied the influence of the sulfinate cation for the reaction at 120 °C (**Scheme 4-3 A**). Moving down group 1 of the periodic table increased the rate significantly, with cesium sulfinate **180d** giving 84% product formation *vs.* only 2% formation with lithium sulfinate **180a**. The tetramethylammonium sulfinate (TMA) salt **180e** led to a dramatic increase in rate with 86% yield within the first 10 min. When TMA sulfinate salt (**180e**) was employed in stoichiometric reactions with oxidative addition complex **181** at lower temperatures for 18 hours, the biaryl product (**182a**) was obtained in encouraging yields (100 °C: 85%, 75 °C: 53%).[365] In contrast, the use of the TMA sulfinate salt **180e** under reported reaction conditions at 100 °C,[358] only yielded 7% of biaryl **182a** after 18 h (**Scheme 4-3 B**).



Scheme 4-3 Effect of counterion on lowering the temperature of desulfinative cross-couplings (de Gombert).

4.3 Sulfinamides as coupling partners

4.3.1 Project aims

The findings of de Gombert indicate that increasing the softness of the metal counterion led to faster rates of transmetalation with oxidative addition complexes (**Scheme 4-3 A**).[221, 365] We envisioned that replacing the hard anionic oxygen atom of sulfinate salts with a neutral nitrogen, in the case of the sulfinamide functional group, may improve the transmetalation process by increasing the affinity of the nucleophile for the soft palladium metal centre. In this chapter, the use of sulfinamides as alternative sulfur(IV) nucleophilic coupling partners in Pd-catalysed cross-coupling reactions is investigated (**Figure 4-3**). The key aim of this research is to explore alternative S(IV)-based nucleophiles at lower temperatures (<120 °C) and to extend this to important 2-(hetero)arylpyridine motifs (Y=N).

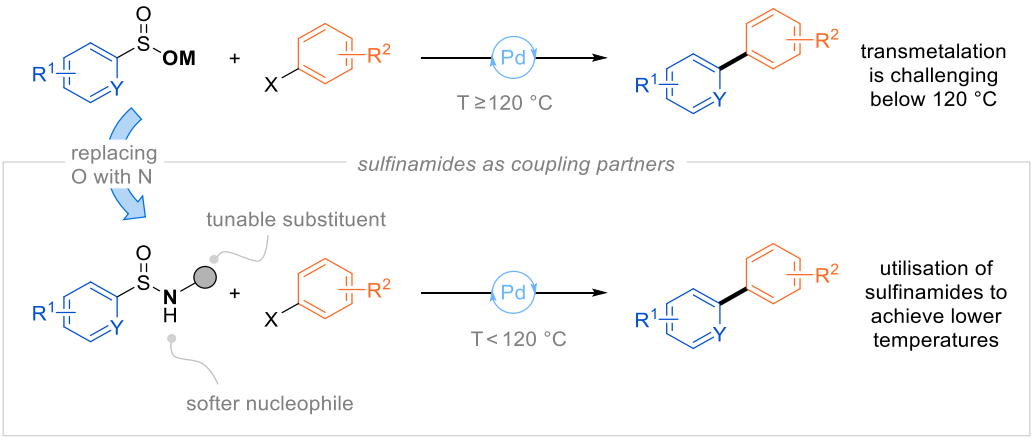
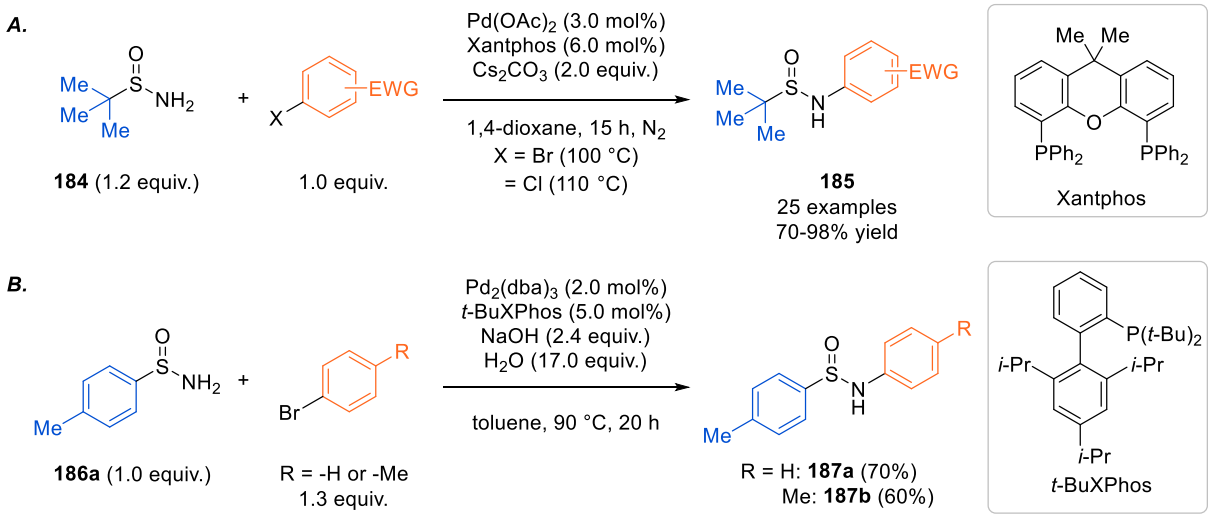


Figure 4-3 Rational design of sulfinamides as alternative softer nucleophilic coupling partners in Pd-mediated processes to access (hetero)biaryls.

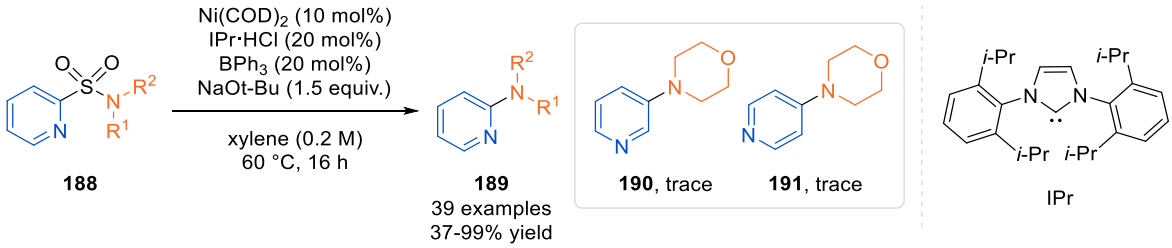
4.3.2 Precedent for sulfinamides in cross-coupling reactions

Sulfinamides have been employed previously in transition metal-catalysed processes, forming S-N appendages (**Scheme 4-4**). The Pd-catalysed coupling of primary sulfinamides (**184**) and aryl halides to form *N*-arylated sulfinamides (**185**) was first reported by Sivakumar and co-workers in 2011 (**Scheme 4-4 A**).[366] Zeng and co-workers reported a similar transformation using aryl sulfinamides under markedly different conditions (**Scheme 4-4 B**).[367] The authors reported two examples using racemic 4-methylbenzenesulfinamide **186a** as a coupling partner in good yields, with the addition of water and KOH essential for high yields in this methodology. The procedure is carried out at 90 °C, demonstrating that transmetalation of sulfinamides can occur at lower temperatures. Additional *N*-arylation of sulfinamide processes that are mediated by other metal catalysts have since been reported; nickel-catalysed coupling with aryl chlorides (Stradiotto, 2022)[368] and arylboronic acids (Yang and Yan, 2022),[369] as well as copper(I) (Cai, 2016)[370] and iron/copper co-catalytic systems with aryl iodides (Yang and Yan, 2019).[371] Although these pathways are unproductive for our desired S-N bond cleavage transformation, these reactions indicate that transmetalation of primary sulfinamides can occur with various metal centres.



Scheme 4-4 Use of sulfinamides as nucleophilic coupling partners in Pd-catalysed processes.

To date, the breaking of S-N bonds in cross-coupling processes is limited to contractive nickel-catalysed intramolecular desulfitative coupling of 2-pyridylsulfonamides **188** to form 2-aminopyridines **189** (**Scheme 4-5**).[372] Although an intramolecular reaction, this process occurs at significantly lower temperatures than those needed for desulfinative C-C cross-coupling procedures.



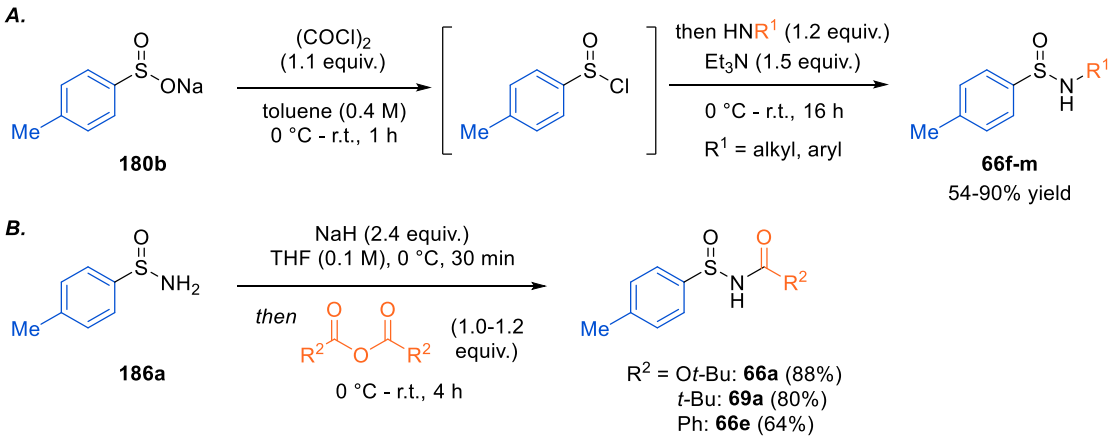
Scheme 4-5 Ni-catalysed desulfitative synthesis of 2-aminopyridines.

4.4 Optimisation of aryl sulfinamides in cross-coupling reactions

The optimisation of this system was investigated by Dr. Antoine de Gombert and latterly by Dr Xinlan Cook, previous DPhil students in the group, and are fully reported in their DPhil theses with the key findings detailed herein.[365, 373]

4.4.1 Initial exploration of *N*-substituted sulfinamides

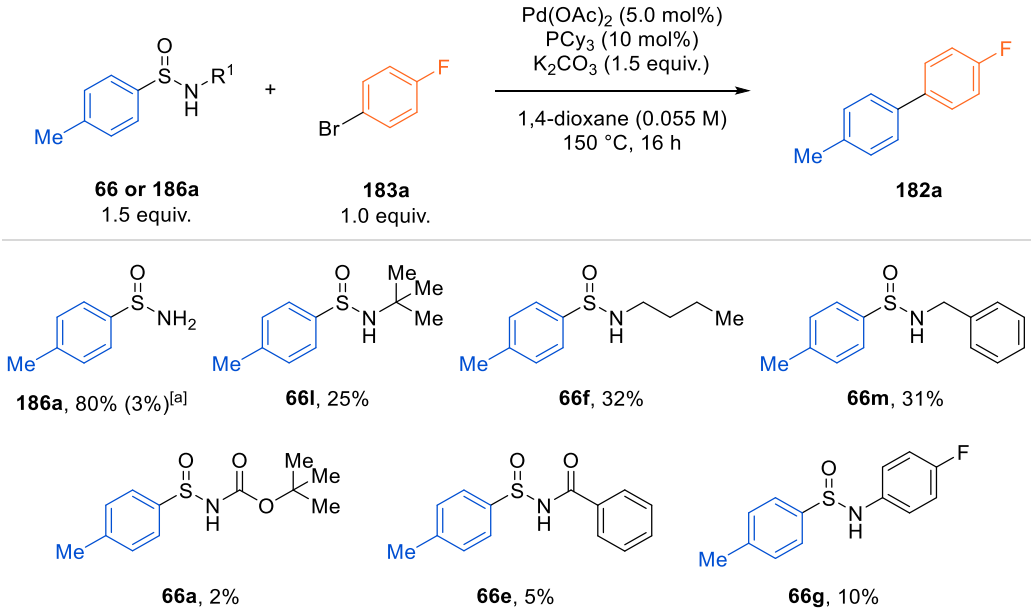
Sulfinamides offer several synthetic benefits over sulfinate salts, in the form of more straightforward purification and preparation. There are numerous methods for accessing these compounds as already discussed in **Chapter 2.1.2**. Furthermore, sulfinamides are typically bench stable, easy-to-handle solids.[225] In comparison to their sulfinate counterparts, sulfinamides possess a significant, additional vector, a *N*-substituent, that can be modified in order to alter reactivity in cross-couplings. To evaluate this parameter, several *N*-substituted 4-methylbenzene sulfinamides **66f-m** were synthesised from sodium 4-methylbenzene sulfinate **180b** *via* chlorination followed by treatment with the respective amine in the presence of triethylamine (**Scheme 4-6 A**).[374] To access electron-withdrawing groups on nitrogen, the deprotonated primary sulfinamide **186a** was functionalised with either an anhydride or ester derivative (**Scheme 4-6 B**).[114]



Scheme 4-6 Synthesis of *N*-substituted sulfinamides: (***A***) from sodium sulfinate salt **180b**; (***B***) from primary sulfinamide **186a**.

Various *N*-substituted sulfinamides were then evaluated as coupling partners in Pd-catalysed arylations by de Gombert,[365] using the previously developed conditions for arylsulfinates (**Scheme 4-7**).[358] The cross-coupling product **182a** was obtained in 80% HPLC yield when primary sulfinamide **186a** was used. Lower yields were observed for *N*-alkyl substituted

sulfinamides, for example, *t*-Bu (**66l**, 25%), *n*-Bu (**66f**, 32%) and benzyl (**66m**, 31%) sulfinamides. The use of electron-withdrawing substituents on nitrogen such as, boc (**66a**, 2%) or benzoyl (**66e**, 5%) group or aniline derived sulfinamides such as **66g** (10%), resulted in poor conversion, with significant quantities of sulfinamide starting material remaining (for additional nucleophiles see de Gombert thesis).[365] On lowering the reaction temperature to 100 °C, a significant reduction in reactivity was observed for primary sulfinamide **186a** (3% HPLC yield). This was the starting point for investigations into using primary sulfinamides as nucleophilic coupling partners at lower reaction temperatures.



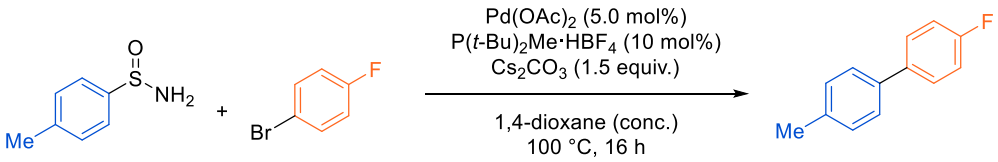
Scheme 4-7 Selected *N*-substituted sulfinamides trialled in cross-coupling reactions with 4-bromo-1-fluorobenzene **183** (de Gombert). All HPLC yields calculated using 1,3,5-trimethoxybenzene as an internal standard. [a] Reaction performed at 100 °C.

4.4.2 Optimisation of reaction of aryl primary sulfinamides

De Gombert found a significant improvement in the yield was achieved using cesium carbonate as the base instead of potassium carbonate (22% HPLC yield, **Table 4-1** entry 1).[365] The improved solubility of cesium carbonate in organic solvents is well reported, whereas the effect of the counterion present in reactions of sulfinamides is often neglected,

although discussed briefly in texts by Maruoka and Bull groups.[110, 164] Similar to the reported desulfinative procedures, de Gombert found the use of monodentate, electron-rich trialkyl phosphine ligands was optimum, with the ligand used in allylsulfone and aryl sulfinate processes, P(*t*-Bu)$_2$Me·HBF$_4$, giving the highest yield (35% HPLC yield, entry 2). Increasing the reaction concentration (entry 2 vs entry 3) and using a larger excess of base (entry 4) gave improved yields. The use of additives, such as tetra-alkyl ammonium halides, and bases typically used for sulfinamide transformations, such as sodium hydride and triethylamine, did not improve conversion (entry 5 and 6). In contrast to the results reported by Zeng and co-workers (**Scheme 4-4 B**),[367] addition of water was detrimental to the reaction (entry 7).

Table 4-1 Selected key results from the initial optimisation performed by Dr. Antoine de Gombert.



186a (1.3 equiv.) **183a** **182a**

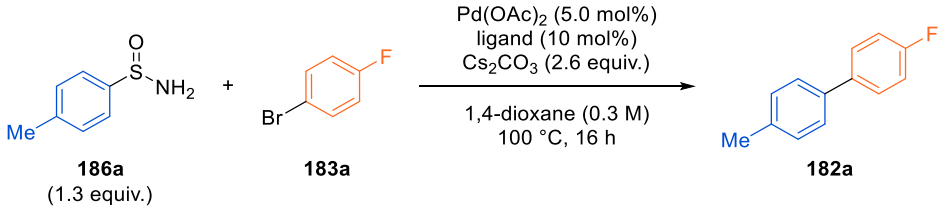
Entry	Variation to above system	Conc. (M)	Yield (%)
1	PCy_3	0.055	22
2	-	0.055	35
3	1,4-dioxane (0.11 M)	0.11	40
4	Cs_2CO_3 (3.0 equiv.)	0.11	49
5	Me_4NCl additive (1.5 equiv.)	0.11	24
6	NaH/Et_3N additive (1.5 equiv.)	0.11	38/35
7	H_2O (15 equiv.)	0.11	15

All HPLC yields calculated using 1,3,5-trimethoxybenzene as an internal standard.

On moving to a preparative scale and increasing the concentration of the reaction to 0.3 M, Cook found the best conditions to date with an isolated yield of 66% (**Table 4-2** entry 1).[373] Entry 2 illustrates the superior activity of the primary sulfinamide versus its sodium sulfinate counterpart, with only 4% yield obtained of the product at 100 °C. Given the hygroscopicity

and cost of cesium carbonate, other bases were trialled, with potassium phosphate and rubidium phosphate giving slightly reduced yields (entry 3 and 4). Increasing the equivalents of base gave a significant increase in yield (entry 5), with concurrently increasing the equivalents of sulfinamide to give a 2:1 ratio of (base:sulfinamide) proved to be the optimal conditions (entry 6). Performing the reaction at 90 °C, resulted in 53% HPLC yield of **182a** (entry 7). All the reactions were performed in pressurised systems in sealed microwave vials on 0.3 mmol scale. When Cook ran the reaction in a round bottom flask with condenser attached (entry 8), the reaction yield significantly dropped to 4%, with further investigation needed to optimise this non-pressurised system.

Table 4-2 Selected results from further optimisation of desulfinamidative cross-coupling performed by Dr. Xinlan Cook.



186a (1.3 equiv.) **183a** **182a**

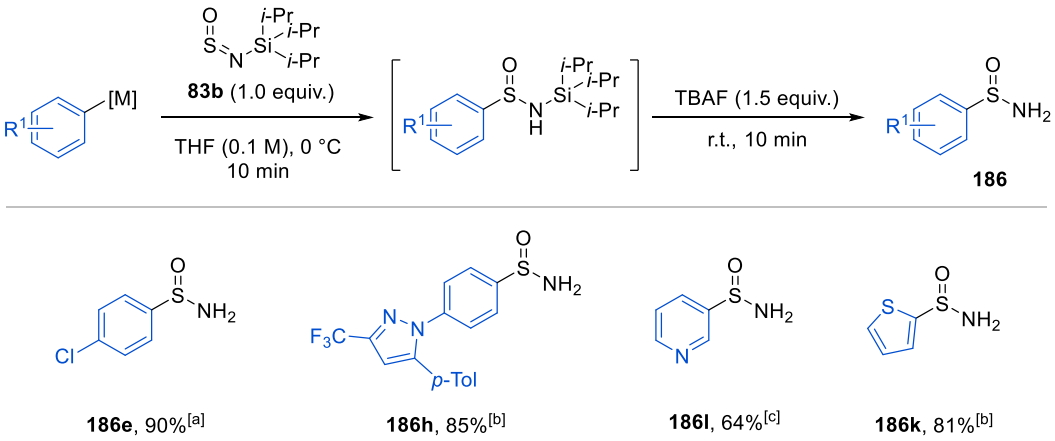
Entry	Variation to above conditions	Yield / %
1	-	69% (66%)
2	sodium sulfinate **180b** (1.3 equiv.)	4%
3	K_3PO_4	60%
4	Rb_2CO_3	55%
5	Cs_2CO_3 (3.0 equiv.)	74% (74%)
6	Cs_2CO_3 (3.0 equiv.)[a]	77% (77%)
7	Cs_2CO_3 (3.0 equiv.)[a][b]	53%
8	Cs_2CO_3 (3.0 equiv.)[a][c]	4%

HPLC yields using 1,3,5-trimethoxybenzene and *p*-ditolylether as internal standards. Isolated yields are in parenthesis. [a] = 1.5 equiv. of sulfinamide, [b] = 90 °C, [c] = non-pressurised flask and condenser.

4.5 Establishing the reaction scope of desulfinamidative cross-coupling

4.5.1 Synthesis of starting materials

An array of primary sulfinamides were synthesised to explore the substrate scope of the reaction (**Scheme 4-8**). Synthesis of primary sulfinamides (**186**) was achieved using the sulfinylamine reagent, TIPS-NSO (**83b**), in combination with an organometallic reagent and TBAF (**Scheme 4-8 A**).[143] The majority of organometallic reagents were used as commercial Grignard reagents, with more complex aryl bromides converted to the corresponding organometallic reagent *in situ*.



Scheme 4-8 Synthetic methods used to access arylprimary sulfinamides. [a] Commercial Grignard reagent. [b] Organolithium reagent. [c] Grignard reagent formed *in situ* using *i*-PrMgCl·LiCl.

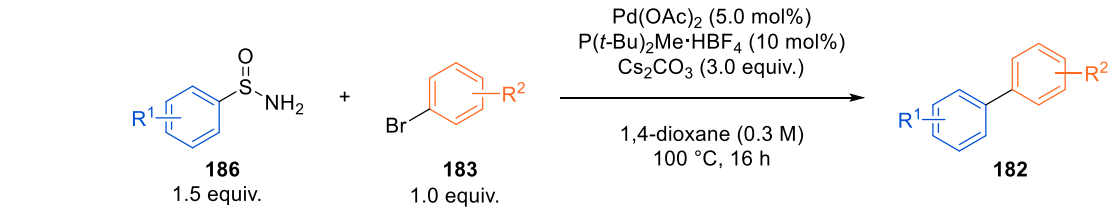
4.5.2 (Hetero)aryl sulfinamide cross-coupling

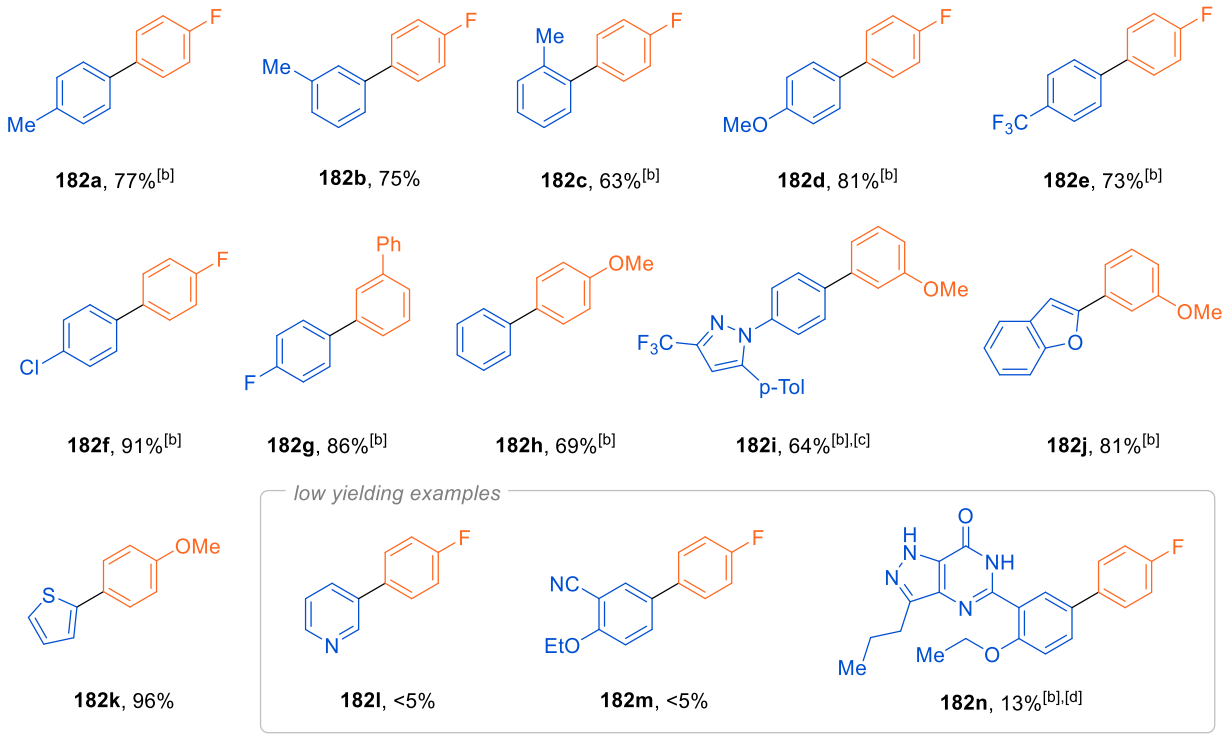
The scope of this reaction was explored in collaboration with my colleague Dr. Xinlan Cook; the compounds synthesised by Dr. Xinlan Cook are indicated in the table below (**Table 4-3**). With the optimised reaction conditions and a small library of aryl sulfinamides to hand, investigation of the scope of (hetero)aryl sulfinamides was explored.

Varying the substitution pattern on the aromatic ring was well tolerated with *para*-, *meta*- and *ortho*-tolyl sulfinamides reacting in moderate to good yields (**182a-c**, 63-77%). The decrease in yield for *ortho*-substituted sulfinamide **186c** is likely to be due to increased steric hindrance and is common across desulfinative cross coupling procedures, with typically elevated temperatures (+10 °C) required for high yields.[362, 363] Encouragingly, electron-rich

aromatic **182d** and electron-poor **182e** substrates were well tolerated. The use of 4-chlorobenzenesulfinamide **186f** demonstrated the chemoselectivity of the reaction conditions with 91% yield of the desired biaryl product (**182f**) obtained, which could undergo further cross-coupling reactions if desired. Incorporation of fragments of drug molecules was amenable to this methodology, with the core of COX-2 inhibitor, Celecoxib,[375] subjected to the reaction conditions, with the functionalised scaffold **182i** obtained in 64% yield. Notably, this reaction showcased lower equivalents of the sulfinamide coupling partner could be used (1.3 equiv. versus typical 1.5 equiv.) if it is a complex structure or difficult to access. Pleasingly, the reaction was tolerant of heteroaromatic sulfinamides, giving access to benzofuran **182j** in 81% yield. As discussed earlier in **chapter 4.1**, the instability of various heteroarylboronic acids, such as 2-thiophene, 3-pyridyl and 4-pyridyl substrates, due to moderate protodeboronation has been observed by Lloyd-Jones and co-workers.[335] Notably, thiophene sulfinamide analogue (**186k**) used in this reaction gave high yields of the corresponding heterobiaryl **182k** (96%), showcasing this class of compounds as alternative coupling partners for challenging SMC substrates. Disappointingly, use of 3-pyridine sulfinamide **186l** resulted in no product formation; the poor reactivity of this substrate can be ascribed to limited solubility under the reaction conditions. Further low yielding examples include functionalised arene **182m**, with significant quantities of decomposition products observed and the core of marketed drug sildenafil **182n**. The latter result can be attributed to the presence of additional free *N*-H moieties in the molecules and this substrate may require specific optimisation and finetuning of the stoichiometry of the base.

Table 4-3. Reaction scope of the desulfinamidative cross-coupling of primary aryl sulfinamides and aryl halides.[a]



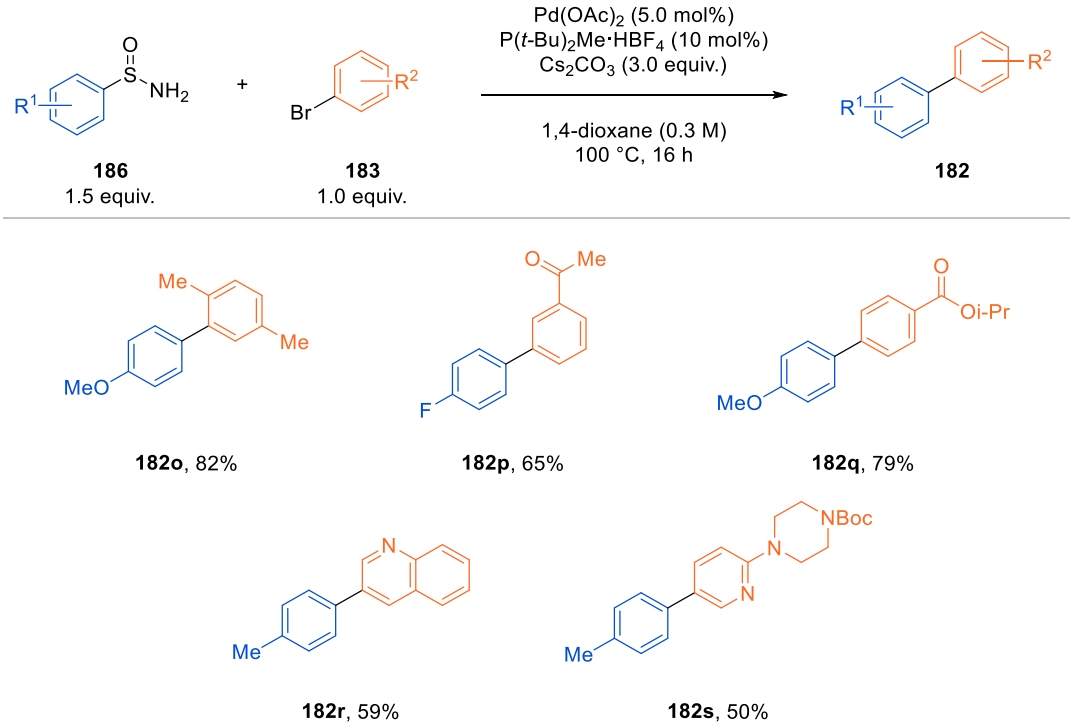


[a] Reaction conditions: sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (0.030 mmol, 10 mol%), Cs_2CO_3 (0.90 mmol, 3.0 equiv.), 1,4-dioxane (1.0 mL, 0.3 M), 100 °C, 16 h. [b] Compound synthesised by Dr. X. Cook. [c] Reaction run with sulfinamide (0.39 mmol, 1.3 equiv.). [d] Reaction run on 0.15 mmol scale.

Following variation of the sulfinamide coupling partner, the aryl halide component was explored by Cook (**Table 4-4**). Sterically encumbered, o*rtho*-substituted electrophiles were compatible with the reaction, giving 82% of biaryl **182o**. The reaction conditions were well tolerated by a range of functional groups including ketones (**182p**), esters (**182q**), amines

(**182r**) and sulfones (**182s**). Moreover, heterocyclic products (**182r-s**) were obtained in moderate yields from the corresponding heteroaryl bromides (59% and 50% respectively).

Table 4-4 Reaction scope of (hetero)aryl bromides in desulfinamidative cross-coupling reactions (Cook).[a]

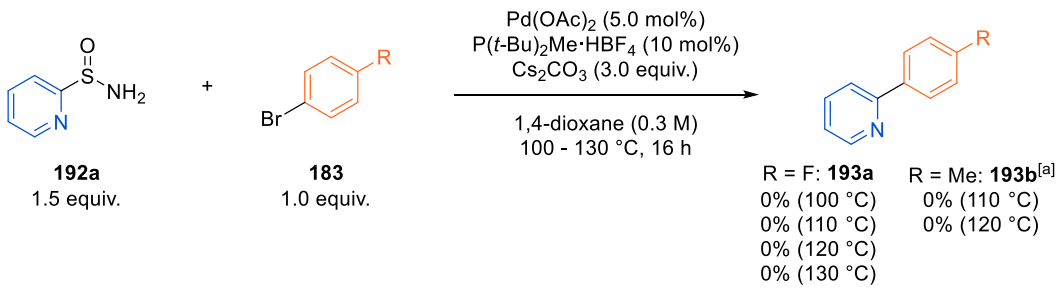


[a] Reaction conditions: sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.015 mmol, 5.0 mol%), P(*t*-Bu)$_2$Me·HBF_4 (0.030 mmol, 10 mol%), Cs_2CO_3 (0.90 mmol, 3.0 equiv.), 1,4-dioxane (1.0 mL, 0.3 M), 100 °C.

4.6 Tackling the 2-pyridyl problem

4.6.1 Unsubstituted 2-pyridyl sulfinamides

A noticeable missing element in the reaction scope discussed are 2-pyridines. Attempts to couple 2-pyridyl sulfinamide **192a** under the optimised reaction conditions were unsuccessful (**Scheme 4-9**). After 16 hours, both 2-pyridylsulfinamides (**192a**) and arylbromides **183a** and **183b** starting materials were observed, with none of the desired product **193a** or **193b** respectively. Even at elevated temperatures (110-130 °C), no reaction progression was observed. This lack of reactivity of 2-pyridyl substrates is in stark contrast to the nickel-catalysed desulfitative C-N coupling reaction reported by Lian and co-workers, which is limited to 2-pyridyl sulfonamides (**Scheme 4-5**).[372]



Scheme 4-9 Investigation into the reaction of 2-pyridyl sulfinamide **192a** with aryl halide **183a** or **183b**. Reaction at given temperature, yield determined by quantitative ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [a] Reaction carried out by Dr. Xinlan Cook, yield determined by HPLC analysis with *p*-ditolylether as the internal standard.

In the case of 2-pyridyl sulfinate salts, de Gombert and co-workers showed they strongly chelate the palladium metal centre in a $K^2_{N,O}$-mode, giving palladacycle **194-H** (**Figure** 4-4 **A**).[221] The extrusion of SO_2 from this intermediate to **195** was found to be the turnover-limiting step. The lack of reaction of 2-pyridine sulfinamides can be tentatively attributed to a similar, unproductive, $K^2_{N\text{-}N}$-chelation to the palladium centre (**196**, **Figure** 4-4 **B**). Attempts to isolate this intermediate in a similar manner to **194-H** by de Gombert proved unsuccessful. Further investigation into this may be beneficial to enhance understanding of the reactivity of these substrates and subsequently lead to lower temperature reactivity.

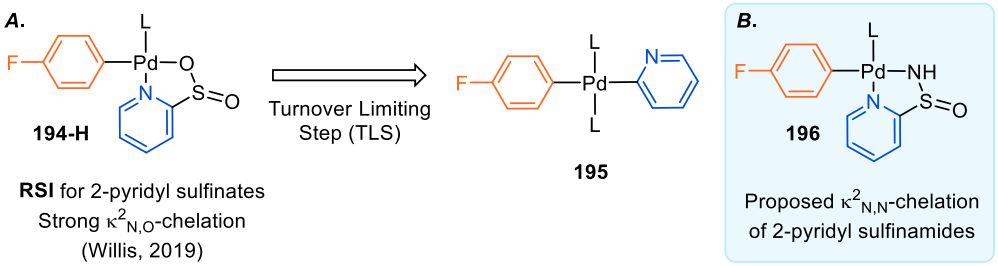


Figure 4-4 $K^2_{N\text{-}X}$-chelation of S(IV) nucleophiles to palladium centre.

This strong chelation of sulfinamides is perhaps unsurprising given their utility as ligands in metal-catalysed (namely rhodium[1, 376, 377] and gold[162]), often asymmetric, transformations. Of note for this work, is the effective use of sulfinamides as ligands in Pd-catalysed

reactions.[378] The optimal ligands for these transformations have an azine nitrogen proximal to the sulfinamide.[378]

4.6.2 Disrupting $K^2_{N,N}$-binding mode

Based on observations for (latent) sulfinates,[358, 362, 363] de Gombert evaluated two strategies to form less thermodynamically stable chelates of sulfinates:[221, 365] (1) weakening of the Pd-N bond by addition of an electron-withdrawing substituent to the pyridyl ring. This significantly increased the rate of extrusion of SO_2 from palladacycle **194-CF₃** versus the unsubstituted pyridine substrate **194-H** (**Figure 4-5 A**); (2) substitution at the 6-position, providing steric hindrance to the chelate (**Figure 4-5 B**). Although, the monomeric palladium sulfinate complex **194-H** was obtained for 2-pyridinesulfinate **175a**, when sodium 6-*tert*-butylpyridine sulfinate was reacted with oxidative addition complex **181**, de Gombert observed a dimeric solid-state structure.[221] This resembles that of the carbocyclic 4-methylbenzenesulfinate, with prevention of the $K^2_{N,O}$-binding mode. Analogous to the carbocyclic substrate, 6-substituted 2-pyridine lithium sulfinate **175f** was able to undergo a lower temperature coupling with oxidative addition complex **181** in the presence of $AgNO_3$ to give the desired product (**193d**) at only 75 °C.

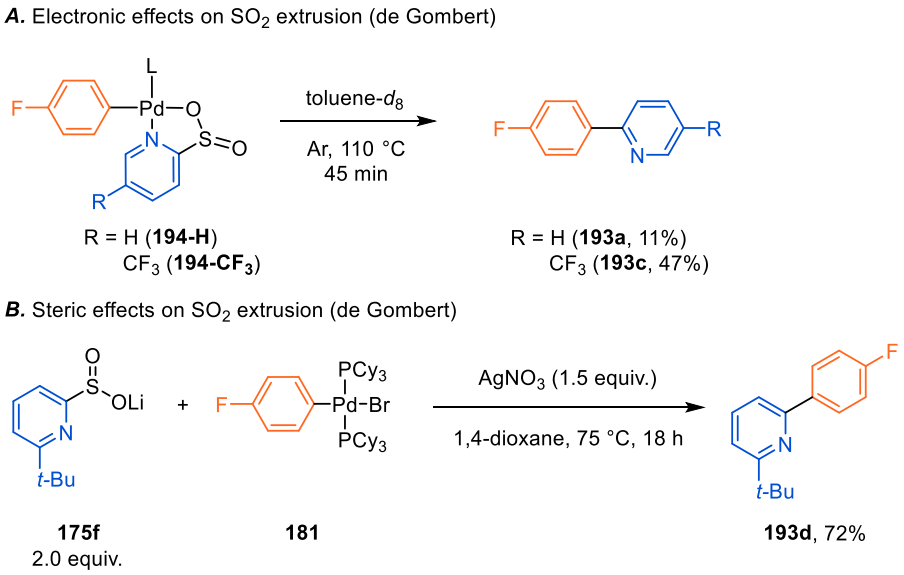
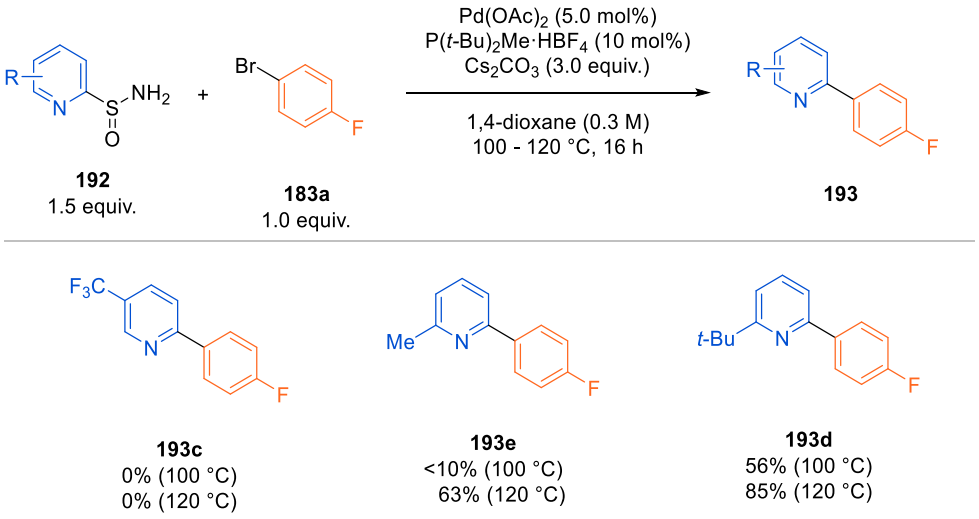


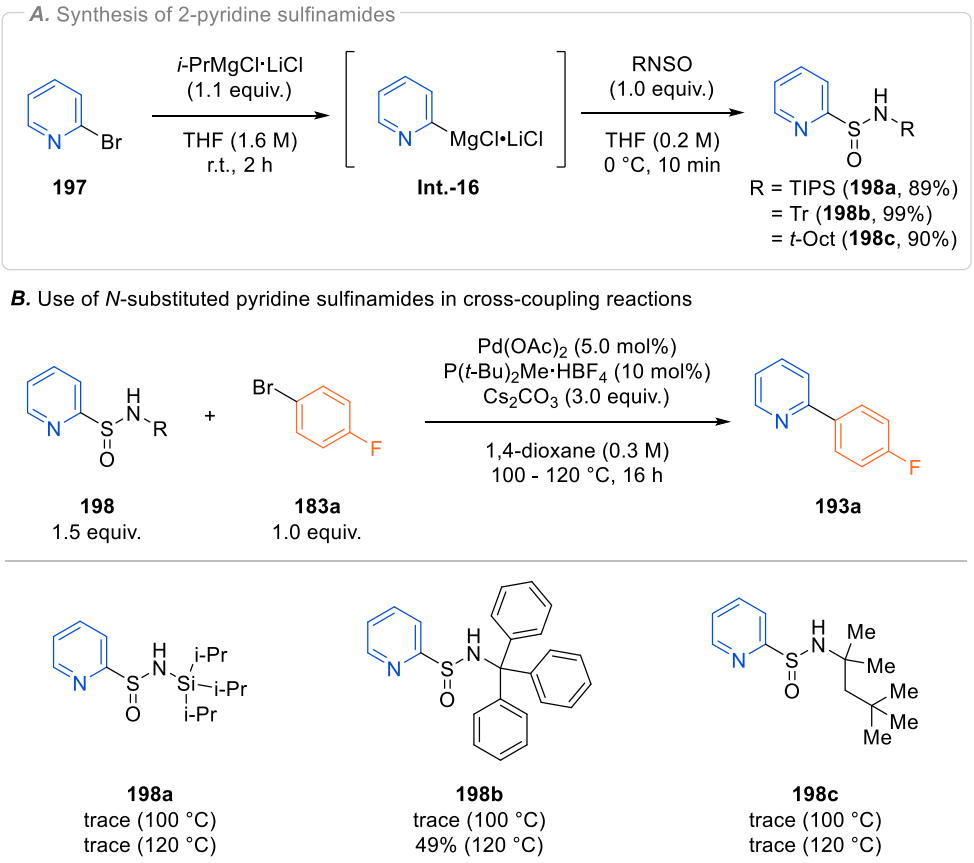
Figure 4-5 Effect of substituents on pyridine substrate on rate of SO_2 extrusion.

Given the success of these strategies with related sulfinates, the effect of the substituent on the 2-pyridinesulfinamide was evaluated (**Scheme 4-10**). Subjection of 5-trifluoromethylpyridine sulfinamide **192c** under the optimised reaction conditions did not result in the formation of the desired product, even at elevated temperatures (120 °C). When 6-Me substituted compound **192e** was subjected to the reaction conditions at 100 °C, low yields were obtained (<10%). Encouragingly, performing the reaction at 120 °C resulted in a significant increase in the yield of **193e** obtained (63%). This result indicates that elevated temperature is required to overcome the putative $K^2_{N,N}$-chelation. When 6-*tert*-butyl 2-pyridine sulfinamide **192d** was subjected to the optimal reaction conditions, the desired 2-arylpyridine **193d** was isolated in 56% yield. At elevated temperature (120 °C), higher yields (85%) were obtained with a clean reaction profile.



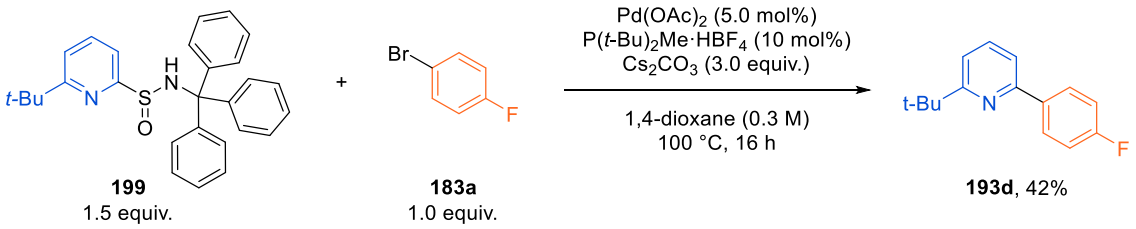
Scheme 4-10 Effect of pyridine substitution on desulfinamiditive cross-coupling transformations.

Given the desire to develop a general cross-coupling procedure for 2-pyridyl systems, further investigation into alternative reagents was carried out, focussing on the modification of the nitrogen substituent of the sulfinamide. The addition of 2-pyridyl Grignard reagent **Int.-16** to pre-formed sulfinylamines allowed access to a series of *N*-substituted 2-pyridyl sulfinamides (**198**) in one step in high yields (**Scheme 4-11 A**). When reacted under the optimised reaction conditions for carbocyclic substrates at 100 °C, all of these substrates performed poorly with none of the desired product (**193a**) observed (**Scheme 4-11 B**). When elevated temperature (120 °C) was trialled, a significant increase in yield was observed for the *N*-trityl substituted compound **198b** (49%), with remaining starting material accounting for the mass balance. Both *tert*-octyl and TIPS substituted sulfinamides (**198a** and **198c**) were inefficient coupling partners even at 120 °C. Of note is the commercial availability of the Tr-NSO precursor (**8**) and that **198b** can be purified readily through filtration. It is worth noting that unsubstituted 2-pyridyl reagents in desulfinative cross-coupling procedures often require additional heating to achieve a comparable efficacy to their substituted counterparts (+10 to 20 °C).[362, 363]



Scheme 4-11 Cross-coupling of *N*-substituted 2-pyridine sulfinamides.

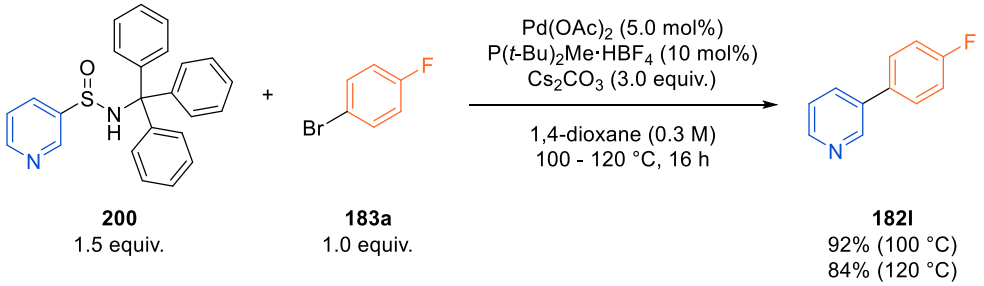
Given the improved yield obtained by increasing steric bulk at both the 6-position of the pyridine ring and on the sulfinamide nitrogen, a combination of both parameters was investigated to evaluate if the effects were additive (**Scheme 4-12**). Disappointingly the yield was substantially lower with both sterically hindered functionalities (**199**, 42%) *vs.* the corresponding primary sulfinamide (**192d**, 56%) under the same reaction conditions (**Scheme 4-10**). The presence of excessive steric bulk on the sulfinamide coupled with a sterically hindered phosphine ligand may lead to incompatibilities, hence less bulky ligands may be worth investigating in this regard.



Scheme 4-12 Combining steric substituents on 2-pyridine substrates.

4.6.3 3-Pyridyl *N*-trityl sulfinamides

Given the success of 2-pyridyl *N*-trityl analogue (**198b**), we were interested in expanding this methodology to other heterocyclic *N*-trityl sulfinamides, in particular those that the primary sulfinamide analogues were inefficient coupling partners. The use of 3-pyridine *N*-trityl sulfinamide **200** under the optimised reaction conditions was evaluated (**Scheme 4-13**). At 100 °C the corresponding biaryl product was obtained in high yield (92%); in comparison the primary analogue (**186l**) gave no desired product (**Table 4-3**). There was no increase in yield observed on increasing the reaction temperature to 120 °C (84%). These results give initial indication that *N*-trityl substituted sulfinamides may be viable coupling partners for challenging SMC substrates.



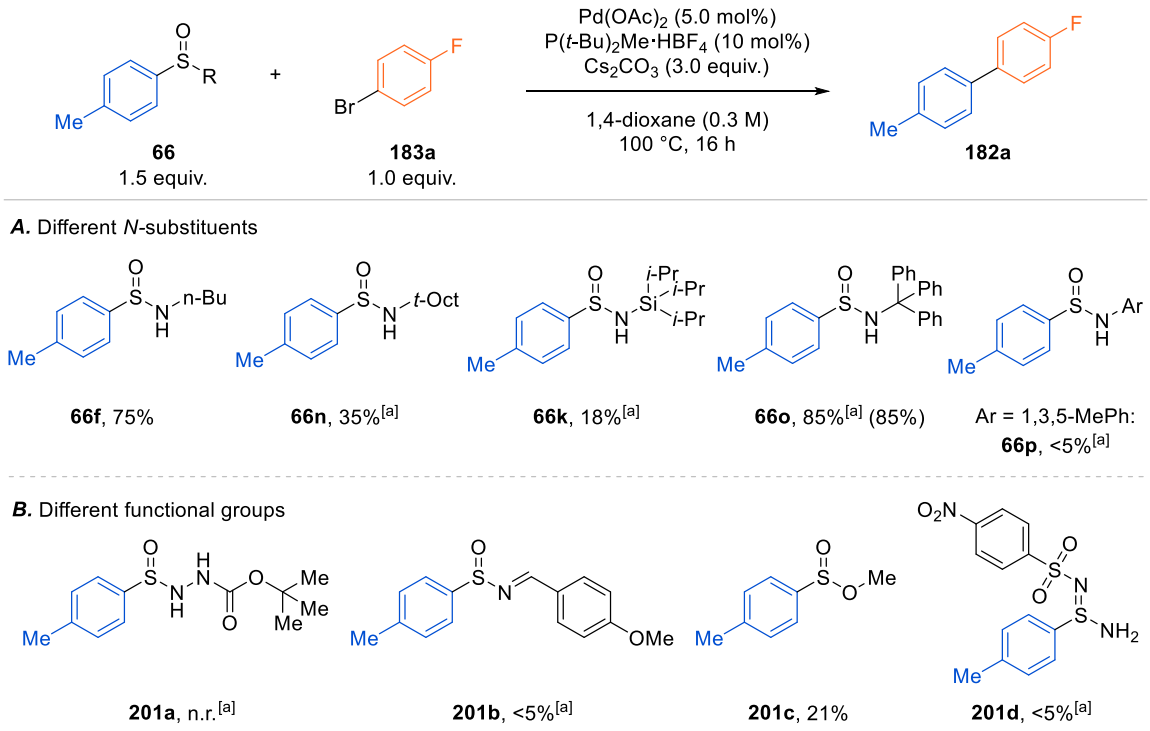
Scheme 4-13 Use of 3-pyridine *N*-trityl sulfinamide **200**. Isolated yields.

4.7 Investigation of other coupling partners

4.7.1 Nitrogen substituents

Given the significant increase in reactivity observed for *N*-trityl sulfinamides for heteroaryl substrates, we were intrigued to see if this phenomenon was solely due to disrupting the deleterious nitrogen interaction with the palladium centre or if it could be applied in a more general sense. Encouragingly, in de Gombert's initial optimisation, electron-rich *N*-alkyl sulfinamides were competent coupling partners (**Scheme 4-7**). However, primary sulfinamide **186a** performed substantially better. Given this privileged reactivity of primary sulfinamides, a variety of other S(IV)-nucleophiles were evaluated (**Scheme 4-14**). Under the now optimised conditions, *N*-*n*-butyl sulfinamide, **66f**, afforded the biaryl product **182a** in similar yield to the primary sulfinamide **186a** (75% *vs*. 77%), in stark contrast to the initial hits (32% *vs.* 81%) at 150 °C (**Scheme 4-7**). Although an interesting result, this compound is less favourable in terms of atom economy and is more challenging to synthesise than the primary sulfinamide as the requisite *n*-butyl sulfinylamine is unstable, decomposing even under inert atmosphere.[320, 379] In a similar manner to 2-pyridyl substrates (**Scheme** 4-11), the corresponding *tert*-octyl and triisopropylsilyl substituted sulfinamides (**66n** and **66k**) can be isolated directly from the respective sulfinylamine in one-step. However, these substrates both performed poorly, with low conversion of the sulfinamide starting material. To our delight, when using *N*-trityl sulfinamide **66o**, the yield was higher than obtained using primary sulfinamide **186a** (85% *vs*. 77%). Although from an atom economy perspective, the use of a trityl substituent is unfavourable, the use of *N*-trityl sulfinamides offers significant advantages over primary sulfinamides: isolation can be achieved by filtration in contrast to primary sulfinamides, which typically require purification by column chromatography. Methods for accessing these reagents are also complementary to those developed for primary sulfinamides, with recent processes developed from boroxine and diazonium precursors.[115, 236] Furthermore, the use of TBAF precludes fluoride sensitive functionalities such as other

silicon protecting groups and acidic sites. Increasing the steric bulk of *N*-aryl sulfinamides that were unsuccessful in initial optimisation e.g., substrate **66p** did not aid the reactivity.



Scheme 4-14 Evaluation of other S(IV) nucleophiles. Isolated yields. [a] Quantitative ^{19}F NMR yields determined using α,α,α-trifluorotoluene as an internal standard, isolated yields in parenthesis.

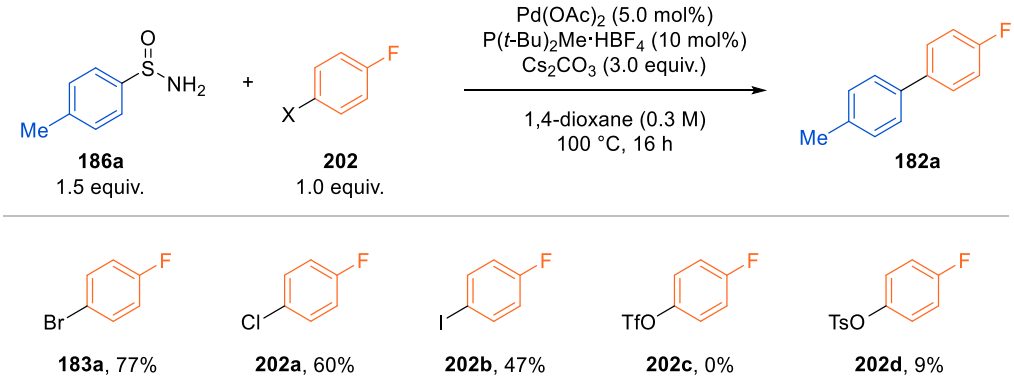
Various other S(IV)-nucleophiles (**201**) were evaluated based on these findings to investigate the effect of differing the electronic and steric factors of the nucleophile (**Scheme 4-14 B**). Hydrazidosulfinamide **201a** was ineffective in the cross-coupling reaction under the optimised conditions with none of the desired product observed. Although these starting materials have seen limited use in the literature,[380] their sulfonyl counterparts have been used sporadically in cross-coupling transformations,[381] with a singular report of reaction with aryl halides to form biaryl motifs from the Bo group in 2019.[382] Sulfinimine **201b** also proved to not be a competent nucleophile under these reaction conditions, with minimal reaction progression observed. The use of sulfinate esters was more promising (**201c**, 21%). However, given they are typically unstable liquids and the synthesis of these compounds is

usually achieved from thiols or sulfinates, they offer no obvious advantages compared to sulfinamides. The use of sulfinamidine nucleophiles (**201d**) would present an interesting alternative to sulfinamides, with an additional imidic functionality that can be finetuned to modulate the reactivity and selectivity. Given the recent advancements in the synthesis of *N*-EWG primary sulfinamidines from di-silylatedsulfurdiimides formed *in situ*, these substrates also benefit from a straightforward synthesis, albeit not as robust to different disconnections as sulfinamides to date.[383] Only unreacted starting materials were observed for *N*-Ns primary sulfinamidine **201d**. This highlights this class of compounds stability but also their reduced nucleophilicity in these systems. The use of electron donating groups on the imidic nitrogen may improve the nucleophilicity of this class of compounds, with recent advances for the synthesis of compounds of this type, *N*-Tr primary sulfinamidines, using flow chemistry reported by Luisi and co-workers.[384]

4.7.2 Use of alternative (pseudo)halides

Aryl bromides have typically been the sp^2-electrophile of choice in desulfinative cross-coupling procedures, although, there are examples using aryl iodides, chlorides and triflates.[349, 350] Of note is the use of aryl chlorides reported at elevated temperatures under markedly similar condition within the Willis group. The ability to routinely employ chloro-derivatives would be advantageous from both cost and availability of starting materials. Markovic *et al.* reported similar yields when using aryl bromides or chlorides in conjunction with aryl sulfinate salts.[360] In later work by Cook *et al.* more efficient coupling of aryl bromides versus chlorides with masked sulfinate nucleophiles was reported, exemplified when using 4-bromoanisole (88%) compared to the reduced yield when using 4-chloroanisole (61%).[363] In the exploration of the scope of sulfinamide coupling partners (**Table 4-3**) the selectivity for bromides could be leveraged to incorporate aryl chloride (**182f**). In alignment with the desulfinative procedures, the reaction worked less efficiently

with 1-chloro-4-fluorobenzene **202a**, although moderate yield could still be obtained (60%, **Scheme 4-15**). This could potentially be further optimised for a complementary procedure utilising the relative abundance of aryl chlorides. Despite the more reactive nature of aryl iodide **202b**, the yield was reduced in the desulfinamidative cross-coupling (47%). The use of pseudohalides such as triflate **202c** and tosylate **202d** was ultimately unsuccessful under the optimised reaction conditions (0 and 9% yield respectively). Given the difference in reactivity across the class of aryl halides this approach could be utilised for the coupling of polyhalogenated aryl halides, with elegant examples of this strategy in the literature.[385] Of note is the recent work of So and co-workers wherein the use of alkyl-indole-based phosphine ligand (*t*-BuPhSelectPhos) in desulfinative cross-couplings allowed for inversion of convential reactitivity of aryl halides, forming biaryl motifs with a triflate moiety still intact for further functionalisation.[386]



Scheme 4-15 Evaluation of alternative (pseudo)halides in desulfinamidative cross-coupling transformations. Quantitative ^{19}F NMR yields using α,α,α-trifluorotoluene as an internal standard.

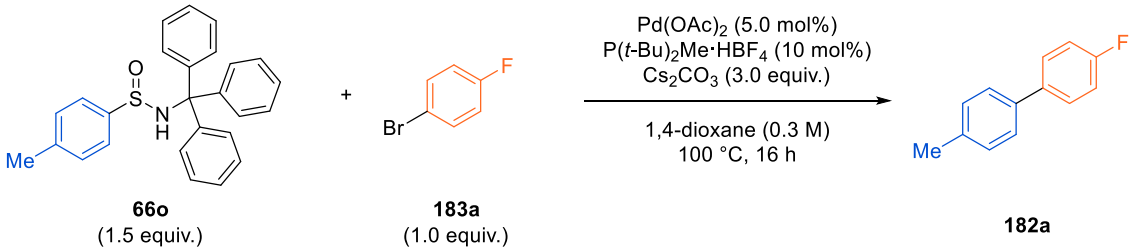
4.8 Utility of *N*-trityl sulfinamides

4.8.1 Optimisation for reaction of aryl *N*-trityl sulfinamides

With encouraging initial results, a short optimisation was carried out on the carbocyclic substrate, 4-methylbenzene *N*-trityl sulfinamide (**66o**). Increasing the temperature to 120 °C resulted in a slight increase in yield to 89% (**Table 4-5** entry 1). At 90 °C a markedly

increased yield (69%, entry 2) versus the primary analogue (53%, **Table 4-2** entry 7) was observed.[373] Reducing the temperature further to 80 °C yielded 27% of biaryl **182a** (**Table** 4-5 entry 3) compared to just 9% using primary sulfinamide **186a** (entry 4). This improved reactivity at lower reaction temperatures could be in part attributed to enhanced nucleophilicity of the sulfinamide nitrogen. The relative stoichiometry of the base and sulfinamide proved to be crucial for primary sulfinamides, with the optimum ratio of 2:1 determined by Cook (**Chapter 4.4**). As one of the acidic protons of the sulfinamide is now removed, lower stoichiometry of the base is well tolerated (entry 5). This may also be a consequence of the by-product of the reaction being a substituted sulfinylamine, Tr-NSO **8**, in comparison to the proposed thionylimide (HNSO) by-product. Thionylimide may be deprotonated under basic conditions or in a similar manner to extrusion of SO_2 react with carbonate/phosphate bases, thus consuming one equivalent of base per liberation of HNSO.[221] This reduction in stoichiometry of base is significant when using Cs_2CO_3 given its high molecular weight and relative cost in these cross-coupling reactions. Pleasingly, 1.5 equiv. of cesium carbonate gave comparable yields of the biaryl product **182a** (83%). Base was required for the transformation with none of the desired product observed in its absence.

Table 4-5 Optimisation of reaction temperature and bases (stoichiometry). Quantitative ^{19}F NMR yields determined using α,α,α-trifluorotoluene as an internal standard, isolated yields in parenthesis.



Entry	Variation to above system	Yield (%)
1	120 °C	91 (89)
2	90 °C	72 (73)
3	80 °C	27
4	80 °C, 4-methylbenzene sulfinamide **186a**	9
5	Cs_2CO_3 (1.5 equiv.)	82 (83)
6	no base	0
7	DBU (1.5 equiv.)	0
8	Et_3N (1.5 equiv.)	1
9	LiHMDS (1.5 equiv.)	55
10	KO*t*-Bu (1.5 equiv.)	95 (90)

As these reactions liberate Tr-NSO not HNSO or SO_2, the choice of base is not limited to those that can sequester liberated SO_2. Moving away from the use of inorganic bases such as K_3PO_4 and Cs_2CO_3 would be highly desirable as the use of these bases under heterogeneous conditions frequently leads to inadequate suspensions, often resulting in irreproducible observations.[387] This is of particular concern for large-scale applications, for example, the particle size of potassium phosphate had dramatic effect on yields achieved for the synthesis of Dasabuvir, an HCV-Polymerase Inhibitor drug.[388] When using soluble bases in the early stages of optimisation, de Gombert had observed significant reduction in formation of biaryl **182a** when using KO*t*-Bu either as the base (1.5 equiv.) or as an additive (1.5 equiv. with Cs_2CO_3 (1.5 equiv.), DBU (1.5 equiv.) was also inefficient.[365] Homogeneous reaction mixtures were observed using *N*-trityl sulfinamide **66m** in combination with DBU, Et_3N or LiHMDS (entries 7-9). However, in the cases of DBU and

Et_3N, the desired reactivity was not obtained, with substantial quantities of unreacted 1-bromo-4-fluorobenzene **183a** remaining (51-72%). Pleasingly, moderate yield was obtained using LiHMDS (55%), showcasing the potential of homogeneous bases. In contrast to the discussed results with primary sulfinamide **186a**, the use of KO*t*-Bu (entry 10) proved beneficial, with higher yields obtained (90%). Although the reaction mixture was still heterogeneous in nature, exploring this base at lower temperatures may be warranted.

Due to time constraints, the optimisation of ligand and solvent parameters was not carried out to date, but would be of interest given the significant impact on yield for primary sulfinamides. Although 1,4-dioxane is a go-to solvent for many cross-coupling procedures, it is considered a "substance of very high concern" (SVHC), in part due to its carcinogenic properties and probable serious effects to the environment and human health.[389, 390] Moreover, it is often being used above its boiling point in desulfinative cross-couplings. Therefore, credible alternatives would be warranted, such as CPME and anisole.[391]

4.8.2 Alkenyl *N*-trityl sulfinamides as nucleophilic coupling partners

Given the success of sp^2-sp^2 coupling of aryl sulfinamides with aryl halides, we were interested in expanding this methodology to other sp^2-centres, namely vinyl sulfinamides. For a discussion of the synthesis of these substrates see **Chapter 3.5**. The products of these reactions, functionalised styrenes are extremely useful building blocks for organic synthesis and have tremendous applications in polymer chemistry.[392-395] The analogous transformation of vinyl sulfinates has remained elusive, perhaps due to the difficulty synthesising these compounds.[396-398] It is worth noting the formation of dienyl sulfinates *in situ via* ring-opening of sulfolenes and subsequent Pd-mediated desulfinative cross-coupling reaction with aryl halides has been reported by Larionov and co-workers.[399, 400] Although this is limited to dienylation and polyenylation transformations, it provides proof-of-concept that alkene-arene bond formation can occur *via* a C-S cleavage pathway.[401]

One of the most general syntheses of styrenes involves the combination of aryl halides with a vinyl organometallic reagent using either Pd- or Ni-catalysis.[402] Specific challenges for cross-coupling of vinyl donors include their ability to undergo two different reaction pathways, either in the desired cross-coupling or in a Heck reaction that leaves the nucleophilic organometallic intact (**Figure 4-6 A**). Styrenyl products, by definition, also contain a terminal vinyl group that can serve as a substrate for subsequent Heck process. Therefore, vinylation reactions must display high selectivity for vinylation over primary Heck and secondary Heck processes, as well as avoiding polymerisation of the products. The reversal in roles of the reactive partners has been demonstrated, namely the combination of a vinyl (pseudo)halide with an aryl organometallic donor (**Figure 4-6 B**). This approach is used infrequently as it is hampered by the toxicity and low boiling point of vinyl halides, their instability under a range of conditions, as well as not utilising the vast abundance of aryl halide counterparts.[403]

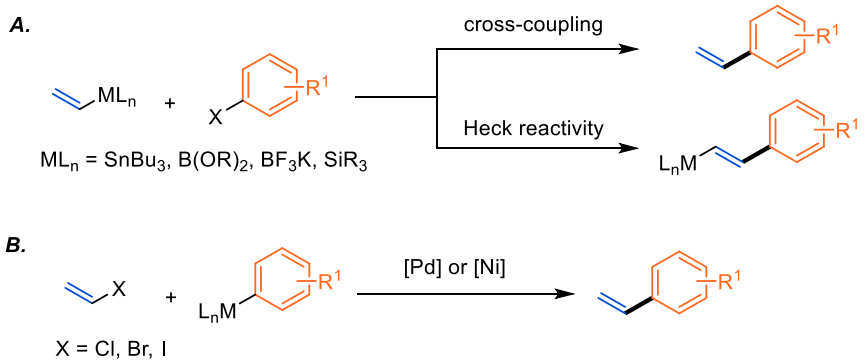
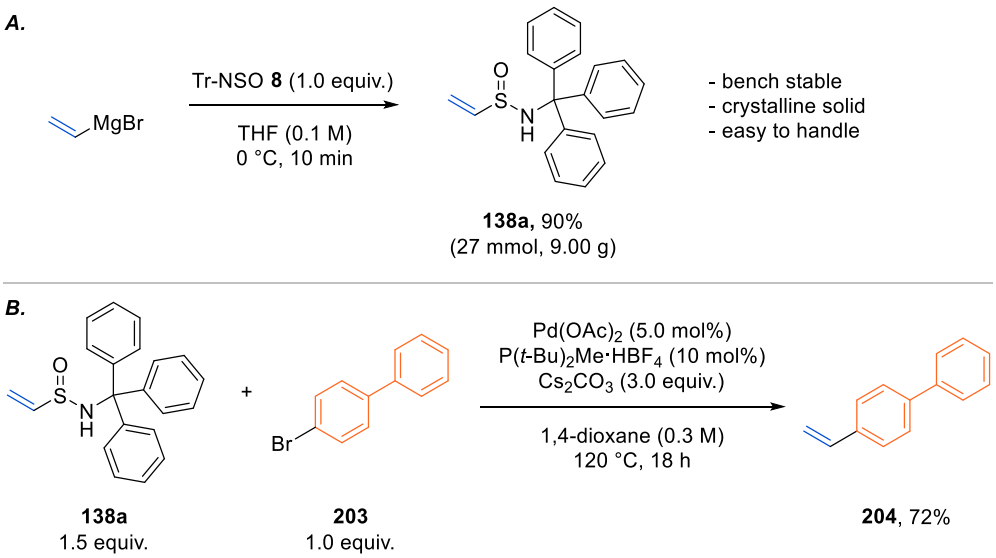


Figure 4-6 Formation of styrenes in cross-coupling reactions.

Akin to the 2-pyridyl problem, the use of traditional SMC reaction conditions is not applicable for vinylation reactions. This is in part due to the volatility and instability of vinylboronic acid, with methodologies requiring fresh preparation of this reagent before use and large excesses required.[404-406] Moreover these substrates require long reaction times and elevated temperatures.[406, 407] To circumvent the instability of vinylboronic acid, a variety of

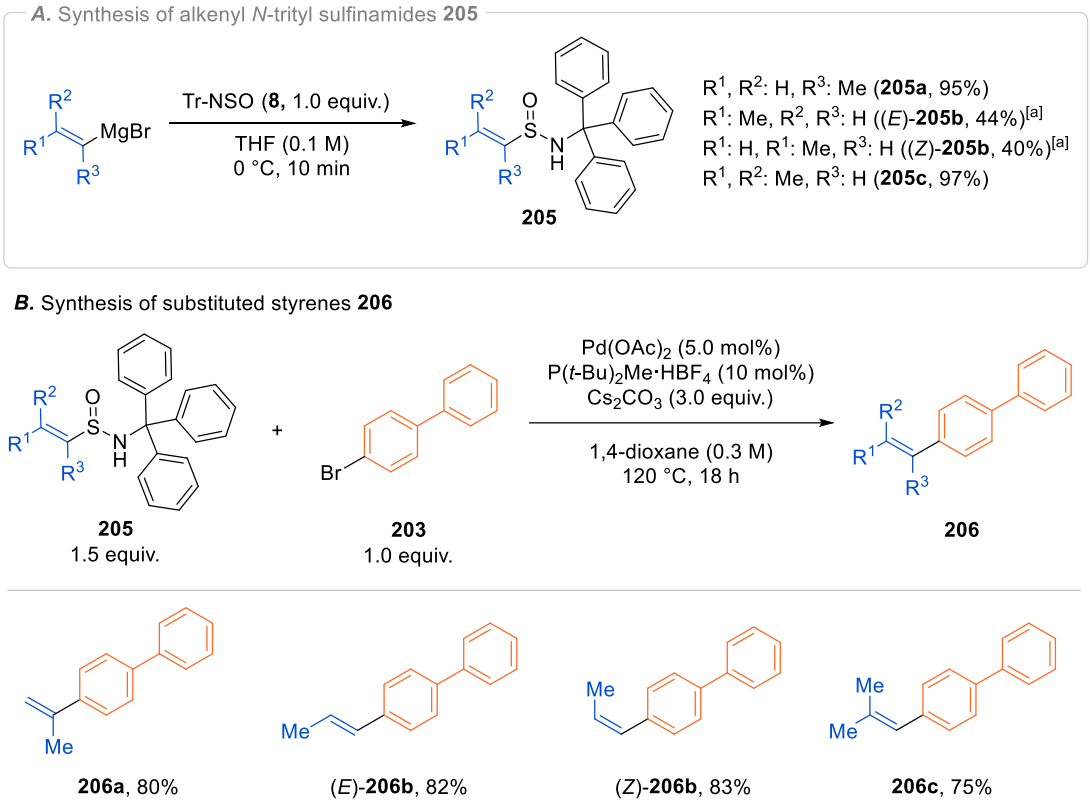
boronate derivatives have been explored.[407] The most notable of these is potassium vinyltrifluoroborate salt, a bench stable, crystalline solid.[408-410] There are however issues with this compound in terms of its cost and the requirement of highly toxic trimethylborate in its synthesis.[411] Moreover, significant exothermic events have been observed in the coupling of potassium vinyltrifluoroborate with aryl bromides, posing potential safety hazards especially for large-scale application.[412] Henceforth, an alternative set of vinyl nucleophilic partners would be of great interest and utility in both industry and academia.

Given the previous challenges discussed in **Chapter 3.7.1** for the synthesis of primary ethenesulfinamide **138f** as an isolable reagent, we were encouraged by the straightforward synthesis of *N*-tritylethenesulfinamide **138a** in high yield from Tr-NSO (**Scheme 4-16 A**). This reaction could be performed on upwards of 30 mmol scale to generate gram-scale quantities of the reagent with just filtration required to obtain pure product (**Scheme 4-16 A**). This reagent is bench stable for periods longer than 6 months under an inert atmosphere on the bench. In order to gain initial insight into its reactivity, *N*-tritylethenesulfinamide (**138a**) was subjected to the previously established conditions at elevated temperatures (120 °C), with 4-bromobiphenyl **203** chosen as the electrophilic coupling partner (**Scheme 4-16 B**). Pleasingly, the desired reactivity was observed with 72% yield of the desired product **204a** isolated. None of the aforementioned Heck-type product of either the starting material or product was observed.



Scheme 4-16 Synthesis of *N*-trityl vinylsulfinamide and its application in a cross-coupling transformation.

One of the additional benefits of *N*-tritylsubstituted sulfinamides is the modular one-step procedure to access the starting materials from Tr-NSO (**8**). Addition of different Grignard reagents gave access to the desired alkenyl sulfinamides (**205**) in high yields (**Scheme** 4-17 **A**). The *E*- and *Z*-isomers of compound **205b** could be separated at this stage from 1-propenylmagnesium bromide (mixture of isomers). At 120 °C, a small scope of substituted alkenes was demonstrated (**Scheme 4-17 B**). The presence of steric bulk at the α-position was well tolerated with high yield obtained for styrene **206a** (80%). Both *E*- and *Z*-β-substituted styrenes were accessed in high yields with retention of geometry observed for both substrates ((*E*)-**206b** and (*Z*)-**206b**, 82% and 83% respectively). Pleasingly, disubstituted substrate **205c**, afford styrene **206c** in 75% yield. As 2-methyl-1-propenyl primary sulfinamide is a known non-volatile compound,[143] its use as a direct comparison to **205c** would be a useful evaluation.

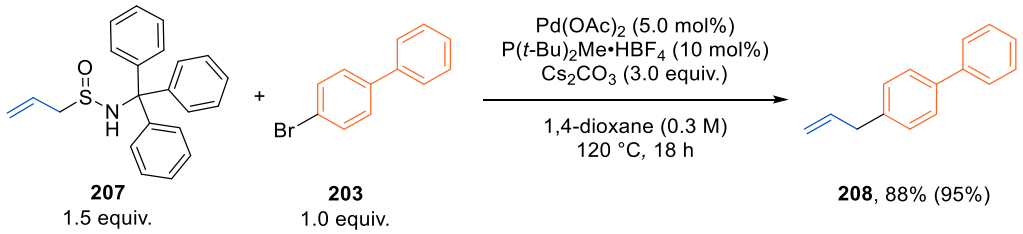


Scheme 4-17 Synthesis of alkenyl sulfinamides and their application in cross-coupling procedures. [a] 1-propenylmagnesium bromide solution (mixture of isomers) used, both isomers isolated in one reaction.

4.8.3 Allyl *N*-trityl sulfinamides as nucleophilic coupling partners

Allyl sulfinamide **207** was accessed in high yield (95%) from Tr-NSO and allylmagnesium bromide. This showcases an additional benefit of *N*-trityl sulfinamides, as the primary sulfinamide analogue of **207** undergoes dimerization readily.[413] *N*-Trityl sulfinamide **207** was subjected to the reaction conditions at 120 °C. The desired product **208** was obtained in high yield (88%, **Scheme 4-18**), showcasing the utility and generality of these reaction conditions and *N*-tritylsulfinamides as a class of nucleophile in cross-coupling procedures. Allylated arenes themselves are an important class of compounds, having found application as reagents for a variety of synthetically useful transformations, in the perfume and pharmaceutical industries.[414] These structures also form the cores of many natural products. Given that allyl boronic esters typically require high temperatures (>80 °C) in SMC reactions, further investigation into the utility of this methodology may be warranted.[415, 416]

The extension of this methodology to substituted allyl motifs is of great interest given the range of products that can be formed; this would require selectivity for clean product to be formed with linear and branched products possible.[417-419]



Scheme 4-18 Formation of allylarene **208** from allyl *N*-Tr sulfinamide **207**. Yield in parantheses for synthesis of allyl *N*-Tr sulfinamide **207**.

4.9 Summary and future work

In summary, we have shown in this **Chapter 4** that sulfinamides can be employed as efficient nucleophilic coupling partners in palladium-catalysed formation of sp^2-sp^2 and sp^2-sp^3 bonds (**Figure 4-7 A**). Reaction of primary sulfinamides with aryl bromides has been developed, with a range of aryl sulfinamide partners employed at 100 °C. These are lower reaction temperatures than those previously used in desulfinative cross-couplings using metal sulfinate salts. Notably, heterocyclic sulfinamides were successfully employed as nucleophilic reagents. The use of 2-pyridine sulfinamide was unsuccessful using the optimised conditions, even at elevated temperatures. The synthesis of 2-pyridylarenes was achieved drawing inspiration from sulfinate salts, with substitution at the 6-position enabling reactions to proceed at 100 °C, with higher yields obtained with elevated reaction temperatures.

A significant advantage of sulfinamides is the ability to tune the nitrogen substituent to enhance reactivity, enabling a more general solution for 2-pyridyl substrates through substitution on nitrogen with the trityl group (**Figure 4-7 B**). The yields for this reaction are not as desired, with optimisation required to fully realise the utility of this reagent. This

could be extended to troublesome 3-pyridyl substrates with the use of *N*-Tr analogue **200** vastly superior to its primary sulfinamide counterpart.

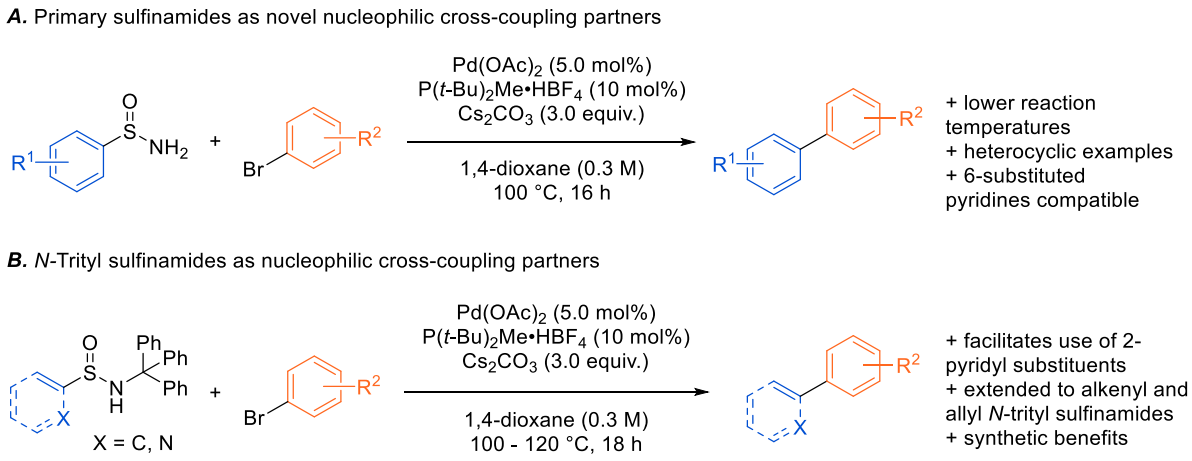
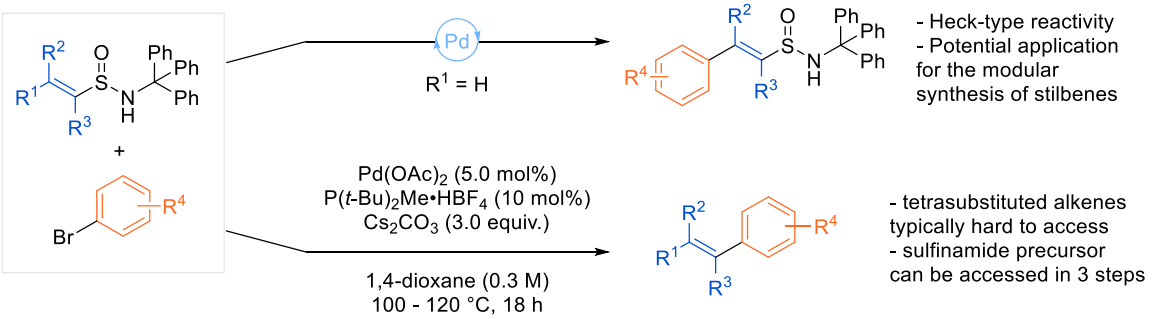


Figure 4-7 Summary of the use of sulfinamides as nucleophilic cross-coupling partners.

Alternative S(IV) reagents were examined based on the success of the sulfinamide analogues, however, *N*-trityl sulfinamide **66m** proved to be most competent (**Figure 4-7 B**). The use of *N*-trityl sulfinamides allows for lower temperature reactions to be performed with alternative set of conditions with high yielding reactions achieved at 90 °C. Moreover, use of *N*-trityl sulfinamides has expanded the coupling partners that can be accessed and reacted; alkenyl and allyl sulfinamides were able to be coupled in high yields under unoptimised conditions giving access to styrenes and allylbenzenes respectively, albeit at 120 °C. Optimisation of these conditions to facilitate lower temperatures would enhance the utility of this methodology. Development of conditions that facilitate the Heck reaction of substrates, followed by subsequent alkenylation reactions would be of great interest, in particular if these reactions could be performed in tandem (**Scheme 4-19**). The future extension of this methodology to the use and synthesis of tetrasubstituted alkenes would also be highly beneficial. These motifs are challenging to access *via* SMC reactions or Hiyama-Denmark protocols, with synthetic routes to these starting materials inefficient and

linear. Mechanistic insights into the benefits of the *N*-Tr substituent are ongoing and may elucidate strategies to further lower the reaction temperature.



Scheme 4-19 Proposed future directions for alkenyl sulfinamide coupling partners.

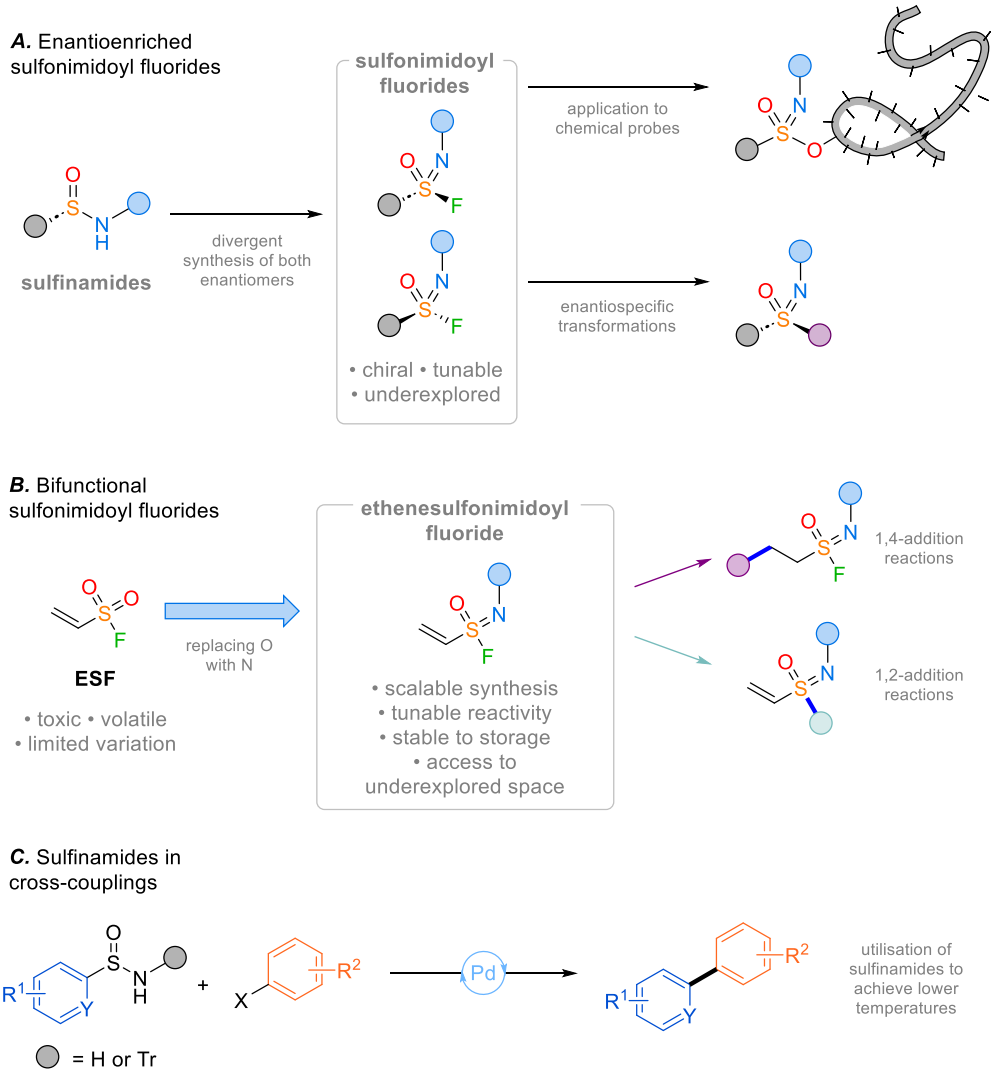
5 Conclusions and future work

In this thesis, the successful synthesis and application of sulfinamides and sulfonimidoyl fluorides has been described. This research contributes to the rapidly growing body of work on aza-sulfur(IV) and sulfur(VI) chemistry, with significant benefits of this class of reagents *vs.* their oxygen counterparts.

Of particular importance with aza-sulfur(VI) functional groups is their innate chirality if substituted accordingly with four distinct groups. In the case of sulfonimidoyl fluorides, this offers significant benefits; their application in accessing other chiral S(VI) moieties, such as sulfoximines and sulfonimidamides, and the unique position they occupy as covalent warheads in chemical biology settings. To this end, distinct methods were established to synthesise racemic sulfonimidoyl fluorides, with a broad substrate scope. Application to enantioenriched systems was optimised allowing for various enantioenriched sulfonimidoyl fluorides to be accessed (**Scheme 5-1 A)**. These could be derivatised to corresponding sulfoximines in an enantiospecific manner. As previously discussed, application of Ellman auxiliary derived trifluoromethylsulfoximines *via* this route, would allow a three step-access to enantioenriched trifluoromethyl sulfinamides *via* de-*tert*-butylation sequence. The utility and robustness of sulfonimidoyl fluorides has begun to be established with initial stress-tests and with further studies, these compounds will likely find wide application in academic and industrial settings.

Encouraged by the benefits sulfonimidoyl fluorides offer, a series of alkyne-tagged ABPs were developed. The reactive and chiral nature of the sulfur stereocentre is an untapped avenue of research, the racemic substrates have shown promising initial reactivity and the synthesis and subsequent application of single enantiomers of these compounds would be of significant interest. This work led to the investigation of alternative electrophilic

S(VI)-species including SuTEx and NHS-sulfonimidate analogues. These bench-stable reagents are ideal precursors for further exploration with various nucleophiles and in chemical biology settings. Future work should aim to systematically evaluate a range of S(VI)-species as electrophilic partners in solution-based assays with amino acid mimics. This could be accompanied by analytical data, rate studies, solubility and stability tests to determine the true utility of these findings.



Scheme 5-1 Overview of work in this thesis.

The utility of sulfonimidoyl fluorides was furthered by their application as bifunctional reagents in the form of alkenylsulfonimidoyl fluorides (**Scheme 5-1 B**). These mono-aza

analogues of ESF have significant benefits in terms of their handling and accessing chemical space. A series of *C*- and *N*-substituted alkenylsulfonimidoyl fluorides were synthesised and evaluated in reactions with amines. The most promising substrates to date are those with EWGs on nitrogen with improved selectivity in reactions and ease of purification. Further studies on the stability and reactivity of these compounds will facilitate their utility as widespread SuFExable hubs. In order to access challenging substrates, a new methodology for accessing alkenyl sulfinamides is disclosed. This class of compounds are a useful building block themselves with reported cycloaddition reactions for example, but with no general synthesis. Further extension of this work to more complex carbonyl electrophiles in HWE reactions of α-phosphonate sulfinamides would help to fully utilise their potential.

Inspired by the ongoing field of bicyclobutane chemistry, the first synthesis of an aza-sulfur BCB was developed, albeit in low yield. Optimisation of this process and application of this approach to other sulfur-based electrophiles would be an interesting avenue to explore. A direct comparison of this class of compounds against their ethene counterparts would provide proof of concept for the utilisation of this scaffold in strain-release chemistry and potentially as chemical warheads.

Throughout this research, sulfinamides have been at the forefront as intermediates and precursors to other S(VI) functionalities. Their application in desulfinamidative cross-coupling processes has been detailed (**Scheme 5-1 C**); the use of sulfinamides in place of sulfinate salts and latent sulfones has begun to address some of the issues regarding high temperatures in these reactions. The reactions of primary sulfinamides occurs at ≥20 °C lower temperature than analogous sulfinates and sulfones, with this improved reactivity ascribed to enhanced transmetalation. Utilisation of the addition parameter of nitrogen substitution has allowed the extension of this work to challenging 2-pyridyl, 3-pyridyl, alkenyl and allyl substrates in cross-coupling transformations. Although the yields for these

reactions are unoptimized, initial results are encouraging. Further optimisation of the latter substrates would be of particular interest given the associated challenges with nucleophilic vinyl coupling partners. In combination with the discussed HWE chemistry to access alkenyl sulfinamides, a two-step procedure could be envisaged from phosphonate ester sulfinamides to di-, tri- or tetra-substituted alkenes in a modular manner.

Initial mechanistic insights into the benefits of *N*-trityl substituents in this process are ongoing, and further optimisation of this functionality may be possible through a structure-activity relationship approach, varying the steric and electronic parameters.

6 Experimental data and procedures

6.1 General considerations

Handling techniques: Unless otherwise stated, all reactions were performed under an inert nitrogen atmosphere with anhydrous solvent and constant magnetic stirring, using standard Schlenk techniques. All reactions were run using glassware that was oven dried at 200 °C for at least 2 hours and allowed to cool to room temperature (r.t.) under a positive pressure of nitrogen. All inert gases were sourced from the University of Oxford's internal supplies and dried through $CaCl_2$ drying columns. Reaction temperatures refer to the temperature of the aluminium heating block or cooling bath. This was measured using a mercury thermometer for reactions heated above room temperature (20 – 200 °C), or with an ethanol low-temperature thermometer when reactions were cooled below room temperature (-80 – 19 °C). Cooling of reaction mixtures to -78 °C was achieved using an acetone-dry ice bath. Room temperature refers to an ambient temperature of 21 ± 2 °C.

Reagents: All reagents used were obtained from commercial sources and used without further purification, unless otherwise stated; commercial sources include Sigma Aldrich Chemical Co. Ltd., Fluorochem Ltd., Alfa Aesar, Insight Biotechnology Ltd., Acros Organics Ltd. and Strem Chemicals Inc. Phosphine ligands and salts (K_2CO_3, Cs_2CO_3) were all stored under inert atmosphere and inside a desiccator. Salts were dried by heating at 200 °C with stirring under high vacuum (< 1 mbar) for 18 h. All Grignard reagents were titrated in duplicate before use according to a modified procedure of Love and Jones using salicylaldehyde phenylhydrazone as an indicator.[420] All organolithiums were either titrated in duplicate using the same method or using commercial titration solution (2-propanol 1.0M in toluene with 0.2% of 1,10-phenanthroline, Aldrich). Fluoro-iodanes **67**-**68**[421, 422] were prepared according to the literature precedent and stored under an inert atmosphere at -20 °C. Anhydrous solvents were purified by filtration through dried alumina columns using the University of Oxford internal solvent drying system (Innovative Technology Inc. PS-400-7) and sparged with nitrogen before use. Solvents used in the desulfinamidative cross-coupling were degassed thoroughly by vigorously bubbling a stream of N_2 through the solvent for a minimum of 15 mins prior to use. Reagent grade solvents were used for purification. Use of 'Petrol' as a solvent, refers to the fraction of petroleum ether, which boils within the range 40 – 60 °C. 'Brine' refers to a saturated aqueous solution of sodium chloride.

Chromatography: Reactions were monitored by thin-layer chromatography (TLC) until deemed to be complete. TLC was performed on Merck silica gel 60 PF254 pre-coated aluminium backed TLC sheets and visualized by UV lamp ($\lambda_{max.}$ = 254 nm) and/or TLC staining by dipping in $KMnO_4$, Dragendorff or vanillin solutions Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) with the solvent system indicated in parenthesis. For cross-coupling products in chapter 4 the crude mixture was adsorbed onto celite and dry loaded onto a silica column. Retention factors (R_F) are reported with the solvent system used in parentheses.

NMR Spectroscopy: ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AVIII400 Ultrashield spectrometer in deuterated solvent at the stated operating frequency. ^{13}C NMR spectra were recorded with ^{1}H broadband decoupling. Chemical shifts (δ) are referenced relative to the residual solvent peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; $(CD_3)_2SO$: δ_H = 2.50 ppm, δ_C = 39.52 ppm; C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm). ^{19}F NMR was referenced externally to $CFCl_3$ (δ_F = 0.0 ppm). Chemical shifts (δ) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR, and 0.1 ppm for ^{13}C, ^{19}F and ^{31}P NMR spectrometry. Resonance multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br.), apparent (app.), doublet of doublet (dd), etc. Coupling constants (*J*) are given in Hertz (Hz) Spectra assignments were deduced using chemical shifts, coupling constants, 2D-NMR spectra (COSY and HSQC) and/or by comparison to spectra of related compounds.

Mass Spectrometry: Low-resolution mass spectra were recorded on an Agilent 6120 Quadruple spectrometer (ESI) using methanol:water:formic acid (90:10:0.1). High resolution mass spectra were obtained *via* the in-house service at the Chemistry Research Laboratory, University of Oxford, utilizing a Bruker Daltronics MicroTOF spectrometer. Mass spectra samples were prepared as 1 mg/mL solutions in MeOH/MeCN. The m/z values are all recorded in Daltons to one decimal place for the low resolution spectrum and to four decimal places on the high resolution. For high resolution mass spectra, the mass found was compared to the mass calculated from the monoisotopic molecular formula, and all results were found to be within a tolerance of 5 ppm of the calculated values.

IR Spectroscopy: Infrared spectra were determined neat using a Bruker Tensor 27 Fourier Transform spectrometer with an internal range of 600-4000 cm^{-1} and all absorptions are given in wavenumbers (ν_{max}) to the nearest whole number (cm^{-1}).

Compound names are generated by PerkinElmer ChemDraw Professional. Internal reaction temperatures were measured using a HANNA K-type thermometer (resolution of 0.1 °C, range: -149.9 – 999.9 °C) equipped with a customized K-type thermocouple probe coated in PTFE (2mm diameter X 150 mm length).

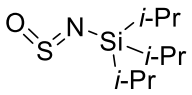
Melting point: Melting points were recorded in degrees Celsius (°C) using a STUART scientific hotstage microscope apparatus SMP1 or a Reichert melting point apparatus and are reported uncorrected.

Chiral analysis: optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^{25}$ is expressed in deg cm^3 g^{-1} dm^{-1} and c is expressed in g 100 cm^{-3}. The enantiomeric ratio (*e.r.*) and enantiomeric excess (*e.e.*) was determined by chiral stationary phase HPLC in a Dionex P680 chromatogram with a Dionex UVD170U detector (λ_{max} = 225 – 275 nm) using a flow rate of 1.0 mL min^{-1} with the Daicel Chiralpack column stated in the compound assignment. The eluent used and retention times ($\mathbf{T}_{major}$ and $\mathbf{T}_{minor}$) are described in the compound assignment.

6.2 Data for chapter 2

6.2.1 Synthetic procedures

6.2.1.1 Synthesis of sulfinylamines



((Triisopropylsilyl)imino)-λ^4-sulfanone (TIPS-NSO, 83b)

Synthesis of triisopropylsiyl amine, TIPS-NH_2 (S1):

According to a procedure by Ding *et al.*,[143] triisopropylsilyl chloride (32.85 g, 170.4 mmol, 1.00 equiv.) was dissolved in anhydrous diethyl ether (340 mL, 0.5 M). The solution was cooled to -78 °C and anhydrous ammonia was bubbled through the solution for 2 h. The reaction was then warmed to 0 °C and stirred for another 3 h with adequate venting to remove excess ammonia. When bubbling ceased, the reaction slurry was filtered through a pad of anhydrous Na_2SO_4 (twice), washing with Et_2O (20 mL) and concentrated *in vacuo* to afford TIPS-NH_2 **S1** as a colourless oil (29.1 g, 168.2 mmol, 99%). The material was sufficiently pure to use in the following step.

^{1}H NMR (400 MHz, C_6D_6) δ 1.02 (d, *J* = 7.2 Hz, 18H, C*H*$_3$), 0.95 – 0.83 (m, 3H, C*H*), -0.09 – -0.14 (m, 2H, N-*H*$_2$); **^{13}C NMR** (101 MHz, C_6D_6) δ 18.4, 12.5.

Notes

1) The solvent is removed on the rotary evaporator at room temperature (21 ± 2 °C).
2) TIPS-NH_2 is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months.
3) Adequate venting for the reaction is essential with wide exit needles to ensure rapid condensation of liquid ammonia does not occur.

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T.Q. Davies, M.C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]

Synthesis of triisopropylsiyl amine, TIPS-NSO (83b):

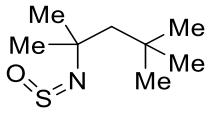
According to a procedure by Ding *et al.*,[143] to an oven-dried round-bottom flask was added triisopropylsilyl amine **S1** (5.23 g, 30.2 mmol, 1.00 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous diethyl ether (300 mL, 0.1 M) was added. The solution was cooled to 0 °C and anhydrous triethylamine (8.67 mL, 62.2 mmol, 2.06 equiv.) was added. Thionyl chloride (2.27 mL, 31.1 mmol, 1.03 equiv.) was then added dropwise and the reaction mixture was stirred vigorously at 0 °C for 2 h. Filtration through a pad of anhydrous Na_2SO_4 and concentration *in vacuo* afforded TIPS-NSO **83b** as a light-yellow oil (6.59 g, 30.0 mmol, 99%).

Notes

1) The solvent is removed on the rotary evaporator at room temperature (21 ± 2 °C).
2) TIPS-NSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months.

^{1}H NMR (400 MHz, C_6D_6) δ 1.13 – 1.04 (m, 3H, C*H*), 1.01 (d, *J* = 6.2 Hz, 18H, CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ 18.0, 12.4.

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T.Q. Davies, M.C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



((2,4,4-Trimethylpentan-2-yl)imino)-λ^4-sulfanone (*t*-Oct-NSO, 83a)

According to a procedure by Zhang *et al.*,[224] to an oven-dried round-bottom flask was added *tert*-octylamine (5.11 g, 39.6 mmol, 1.0 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous diethyl ether (100 mL, 0.4 M) and anhydrous triethylamine (11.6 mL, 83.2 mmol, 2.1 equiv.) were added. The solution was cooled to 0 °C and thionyl chloride (3.00 mL, 41.3 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was stirred vigorously at 0 °C for 2 h. Filtration through a pad of anhydrous Na_2SO_4 and concentration *in vacuo* afforded *t*-Oct-NSO **83a** as a light-yellow oil (6.94 g, 39.6 mmol, 99%).

Notes

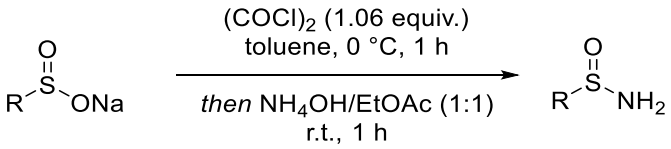
1) The solvent is removed on the rotary evaporator at room temperature (21 ± 2 °C).
2) *t*-Oct-NSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 2H, CH_2), 1.61 (s, 6H, (CH_3)$_2$), 1.02 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 67.7, 55.5, 32.2, 31.5, 31.3.

Data is consistent with the literature: Z.-X. Zhang, T. Q. Davies, M. C. Willis, *J. Am. Chem. Soc.* **2019**, *141*, 13022–13027.[224]

6.2.1.2 Synthesis of primary sulfinamides

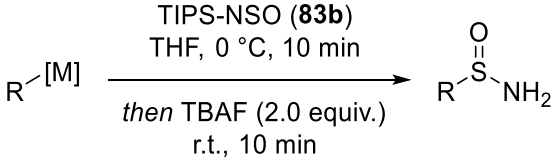
General Procedure A



Following a modified procedure reported by R. J. Kazlauskas and C. K. Savile:[172]

Oxalyl chloride (1.06 equiv.) was added dropwise to a solution of sodium sulfinate salt (1.0 equiv.) in PhMe (0.5 M) at 0 ℃. The resultant solution was stirred at room temperature for 1 h and then added to a biphasic mixture of NH_4OH (1 ml/1 mmol of sulfinate) and EtOAc (1 ml/1 mmol of sulfinate) at 0 ℃. The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 ml) and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined EtOAc layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Primary sulfinamide **186** was then purified by flash chromatography with the appropriate solvent system.

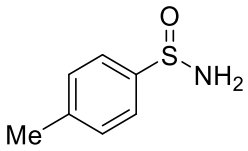
General Procedure B



Following a modified procedure reported by M. Ding, Z.-X. Zhang, T. Q. Davies and M. C. Willis.[143]

An oven-dried round-bottom flask containing TIPS-NSO **83b** (1.0 equiv.) was sealed and subjected to three N_2 evacuation/refill cycles before pre-sparged, anhydrous THF (TIPS-NSO conc. 0.1 M) was added. The solution was cooled to 0 °C and then the corresponding Grignard or organolithium reagent (1.2 equiv.) was added dropwise. The reaction was stirred at 0 °C for 10 minutes prior to the addition of tetrabutylammonium fluoride (TBAF) solution (1.0 M in THF, 2.0 equiv.) at the same temperature. The reaction was warmed to room temperature and stirred for another 10 minutes before being diluted with EtOAc (10 mL) and quenched with saturated aqueous solution of EDTA tetrasodium salt (10 mL). The

aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Primary sulfinamide **186** was then purified by flash column chromatography with the appropriate solvent system.



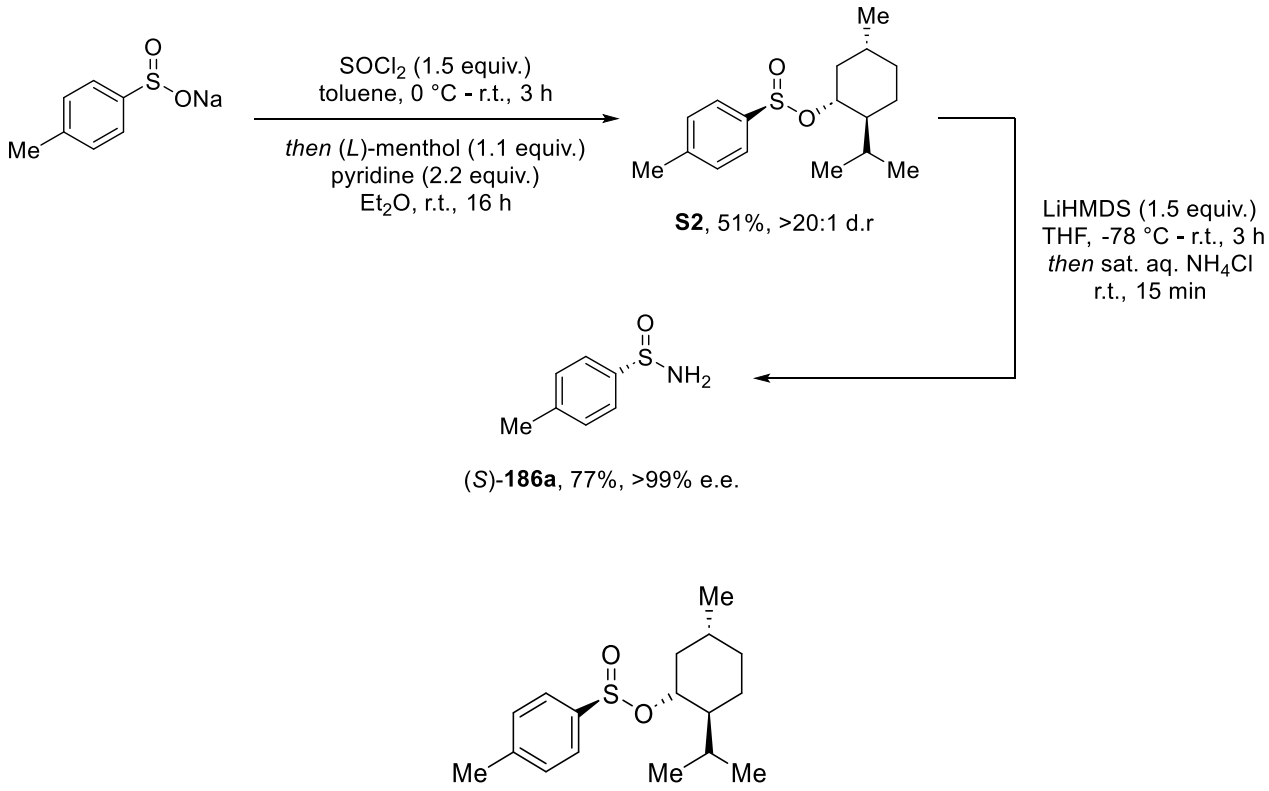
4-Methylbenzenesulfinamide (186a)

Following General Procedure A, oxalyl chloride (4.55 mL, 53.0 mmol, 1.06 equiv.), sodium *para*-toluenesulfinate **180b** (8.90 g, 50.0 mmol, 1.0 equiv.), PhMe (100 mL), NH_4OH (50 mL) and EtOAc (50 mL) were used. Flash column chromatography (SiO_2, Petrol:EtOAc = 1:3) afforded the desired sulfinamide **186a** as a white crystalline solid (5.90 g, 38.1 mmol, 76%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.54 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.33 (d, *J* = 8.0Hz, 2H, Ar-*H*), 6.21 (s, 2H, N-H_2), 2.36 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 145.2, 140.0, 129.2, 125.4, 20.8; **HRMS** (ESI^+, m/z) calculated for $[C_7H_9NOSNa]^+$ $[M+Na]^+$ 178.0297, found 178.0298 (Δ0.5 ppm); **IR** υ_{max} (neat)/cm^{-1} 3282, 3164, 3071, 1089, 1024, 1010, 811, 732, 670; **R_F:** 0.23 (Petrol:EtOAc 1:3); **Chiral HPLC:** [Chiralpak IA3, hexane:*i*PrOH 85:15, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*R*)-**186a**, τ_R = 8.2 min; (*S*)-**186a**, τ_R = 9.9 min.].

Data is consistent with the literature: G. Zhang, Y. Xing, S. Xu, C. Ding, S. Shan, *Synlett* **2018**, *29*, 1232-1238.[423]

Synthesis of enantioenriched analogue:



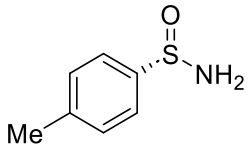
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (S2)

According to a modified procedure by O'Brien *et al.*,[424] to a cooled solution of thionyl chloride (3.05 mL, 42.1 mmol, 1.5 equiv.) in PhMe (17 mL, 1.7 M) at 0 °C, was added sodium *para*-toluene sulfinate **180b** (5.00 g, 28.1 mmol, 1.0 equiv.) portion-wise over 20 min [*Note*: liberation of SO_2]. The resulting solution was warmed to room temperature and stirred for 2 h. The solution was fitted with a distillation apparatus and under reduced pressure, excess thionyl chloride was distilled off as a toluene azeotrope (45 °C, 30 mbar). The residue was diluted with anhydrous Et_2O (25 mL) and cooled to 0 °C, with formation of white precipitate (NaCl) observed. A solution of *L*-(-)-menthol (4.82 g, 30.9 mmol, 1.1 equiv.) in pyridine (5.00 mL, 61.7 mmol, 2.2 equiv.) was then added dropwise over 30 min. The resulting suspension was warmed to room temperature and stirred for 16 h. The reaction was poured onto H_2O (20 mL), with the layers separated. The aqueous layer was extracted with Et_2O (2 × 8 mL) and the combined organic layers were washed sequentially with 1 M HCl (3 × 8 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless gummy solid. The residue was dissolved in acetone (20 mL) and treated with conc. HCl (1 drop), the solution was cooled

to -20 °C resulting in formation of crystals, which were filtered and washed with cold acetone. The mother liquor was then concentrated to half its volume, and conc. HCl (1 drop) was added and the process repeated 5 times. The combined crystal crops were crystallised from hot acetone to yield a spindly crystalline white solid (3.56 g, 12.1 mmol, 43%, >20:1 d.r.). [*Note:* the reaction was scaled to 112.4 mmol with the product accessed in 51% yield]

^{1}H NMR (400 MHz, $CDCl_3$) 7.62 – 7.57 (m, 2H, *m*-C_6H_4Me), 7.35 – 7.30 (m, 2H, *o*-C_6H_4Me), 4.12 (td, *J* = 10.7, 4.5 Hz, 1H, R_2CH-OS(O)R), 2.42 (s, 3H, Ar-CH_3), 2.33 – 2.24 (m, 1H, AlkC*H*), 2.12 (qd, *J* = 6.9, 2.6 Hz, 1H, AlkC*H*), 1.75 – 1.64 (m, 2H, AlkCH_2), 1.56 (s, 2H, AlkC*H*), 1.48 (dddq, *J* = 12.9, 9.8, 6.6, 3.3 Hz, 1H, AlkC*H*), 1.40 – 1.31 (m, 1H, AlkC*H*), 1.22 (td, *J* = 12.2, 10.9 Hz, 1H, AlkC*H*), 1.11 – 0.99 (m, 1H, AlkC*H*), 0.96 (d, *J* = 6.5 Hz, 3H, AlkCH_3), 0.86 (d, *J* = 7.1 Hz, 3H, $C(CH_3)_a$-$(CH_3)_b$), 0.72 (d, *J* = 7.0 Hz, 3H, $C(CH_3)_a(CH_3)_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 142.6, 129.8, 125.2, 80.4, 48.0, 43.1, 34.2, 31.9, 25.4, 23.3, 22.2, 21.7, 21.0, 15.6; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 317.2; **R_F** 0.65 (Petrol:EtOAc 5:1).

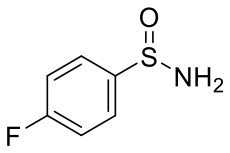
The spectra and data matched those previously reported in the literature: P. J. Rayner, P. O'Brien, R. A. J. Horan, *J. Am. Chem. Soc.* **2013**, *135*, 8071–8077.[424]



(*S*)-4-Methylbenzenesulfinamide ((*S*)-186a)

According to a procedure by Bolm *et al.*,[114] to a cooled solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate **S2** (6.00 g, 20.4 mmol, 1.0 equiv.) in THF (100 mL, 0.20 M) at -78 °C, was added LiHMDS (30.6 mL, 30.6 mmol, 1.0 M in THF, 1.5 equiv.) dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to -78 °C, and quenched with sat. NH_4Cl (50 mL), warmed to room temperature and stirred for 1 h. The reaction mixture was diluted by EtOAc (100 mL), the organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a light brown solid. This crude residue was purified by recrystallization from hexane:EtOAc (2:1, 90 °C to r.t.) to afford the title compound as colourless crystals in 3 batches (2.45 g, 15.8 mmol, 77%, >99% e.e.).

The data were consistent with 4-methylbenzenesulfinamide (**186a**). [Chiralpak IA3, hexane:*i*PrOH 85:15, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*S*)-**186a**, τ_R = 9.9 min.]; $[\alpha]_D^{25}$= +75.1° (*c* = 1.0, $CHCl_3$).

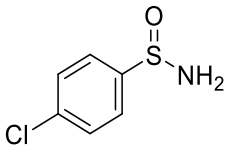


4-Fluorobenzenesulfinamide (186g)

Following General Procedure A, oxalyl chloride (499 μL, 5.82 mmol, 1.06 equiv.), 4-fluorobenzenesulfinic acid sodium salt (1.00 g, 5.49 mmol, 1.0 equiv.), PhMe (11 mL), NH_4OH (5.5 mL) and EtOAc (5.5 mL) were used. Flash column chromatography (SiO_2, Petrol:EtOAc = 1:3) afforded the desired sulfinamide **186g** as a white crystalline solid (680 mg, 4.28 mmol, 78%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.71 – 7.67 (m, 2H, Ar-*H*), 7.39 – 7.34 (m, 2H, Ar-*H*), 6.32 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 163.3 (d, $^1J_{F-C}$ = 247.1 Hz), 144.2 (d, $^4J_{F-C}$ = 2.8 Hz), 128.0 (d, $^3J_{F-C}$ = 9.0 Hz), 115.7 (d, $^2J_{F-C}$ = 22.3 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ -111.40 (tt, *J* = 9.0, 5.3 Hz); **LRMS** (ESI^+, m/z) $[M+H]^+$: 159.9; **IR** υ_{max} (neat)/cm^{-1} 3277, 3166, 3072, 1562, 1494, 1397, 1244, 1168, 1089, 1020, 1010, 836, 671; **R_F:** 0.23 (Petrol:EtOAc 1:3).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



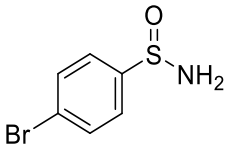
4-Chlorobenzenesulfinamide (186f)

Following General Procedure B, TIPS-NSO **83b** (658.3 mg, 3.00 mmol, 1.0 equiv.), THF (30 mL), 4-chlorophenylmagnesium bromide solution (3.60 mL, 3.60 mmol, 1.00 M in THF, 1.2 equiv.) and TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash

column chromatography (SiO_2, Petrol:EtOAc = 1:3 to 1:5) afforded the desired sulfinamide **186f** as a white solid (502.1 mg, 2.86 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.48 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.42 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 137.7, 129.3, 127.2; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 198.0; **R_F:** 0.26 (Petrol:EtOAc 1:3).

Data is consistent with the literature: S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *60*, 758-765.[413]

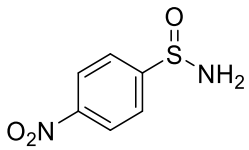


4-Bromobenzenesulfinamide (S3)

Following modified General Procedure A, oxalyl chloride (696 µL, 8.11 mmol, 1.06 equiv.), sodium 4-bromobenzenesulfinate (1.86 g, 7.65 mmol, 1.0 equiv.), PhMe (7.7 mL), NH_4OH (7.7 mL) and EtOAc (7.7 mL) were used. Filtration, washing with hexane afforded the desired sulfinamide **S3** as a white solid (1.26 g, 5.74 mmol, 75%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) 7.75 – 7.71 (m, 2H, Ar-*H*), 7.61 – 7.56 (m, 2H, Ar-*H*), 6.37 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) 147.6, 131.6, 127.7, 123.9; **HRMS** (ESI^+, m/z) calculated for $[C_6H_7BrNOS]^+$ $[M+H]^+$ 219.9426, found 219.9423 (Δ-1.5 ppm); **R_F:** 0.25 (Petrol:EtOAc 1:3).

Data is consistent with the literature: S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *60*, 758-765.[413]



4-Nitrobenzenesulfinamide (S4)

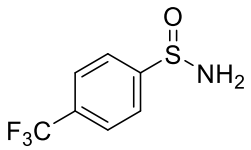
According to a modified procedure by Liang *et al.*,[425] to a solution of commercially available 4-nitrothiophenol (2.5 g, 16.1 mmol, 1.0 equiv.) and AcOH (0.93 mL, 16.1 mmol, 1.0 equiv.)

at -40 °C, was added sulfuryl chloride (2.73 mL, 38.8 mmol, 2.4 equiv.) dropwise. The reaction mixture was stirred for 30 min at -40 °C, warmed to room temperature and stirred for 2 h. The reaction mixture was then stirred at 30 °C for 16 h, cooled to room temperature and concentrated under a flow of N_2 to remove acetyl chloride, affording the intermediate sulfinyl chloride as a brown solid. This solid was dissolved in THF (20 mL) and cooled to 0 °C. To this was added a mixture of NH_4OH (16 mL) and EtOAc (16 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with brine (100 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, Petrol:EtOAc = 1:2 to 0:1) afforded the desired sulfinamide **S4** as a yellow solid (1.22 g, 6.56 mmol, 41%).

[*Note:* significant gas evolution observed on addition of sulfuryl chloride, slow addition required to prevent solidification of reaction mixture. After heating overnight, gas evolution ceased]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.33 (m, 2H, Ar-*H*), 8.02 – 7.92 (m, 2H, Ar-*H*), 4.43 (br. s, 2H, N-H_2); **LRMS** (ESI$^+$, m/z) [M+Na]$^+$: 209.2; **IR** υ_{max} (neat)/cm^{-1} 3324, 3215, 3097, 1583, 1521, 1351, 1340, 1085, 1056, 863, 853, 747, 722, 686; **R_F:** 0.21 (Petrol:EtOAc 1:3).

Data is consistent with the literature: J. L. G. Ruano, J. Aleman, C. Fajardo, A. Parra. *Org. Lett.*, **2005**, *7*, 5493 – 5496.[426]



4-(Trifluoromethyl)benzenesulfinamide (186e)

Preparation of organometallic reagent:

(4-(Trifluoromethyl)phenyl)magnesium bromide solution was prepared according to the following procedure. An oven-dried round bottom flask was charged with magnesium turnings (193 mg, 7.92 mmol, 1.32 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous THF (7.2 mL, Ar-Br conc. 1.0 M) was added. 1-Bromo-4-(trifluoromethyl)benzene (1.01 mL, 7.20 mmol, 1.2 equiv.) was added dropwise

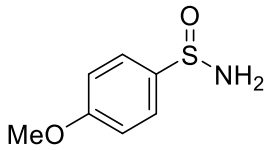
to this suspension at a rate to maintain a gentle reflux. The resulting solution was refluxed for a further 2 h before cooling to room temperature.

Preparation of sulfinamide:

186e was then prepared following General Procedure B, using TIPS-NSO **83b** (1.316 g, 6.00 mmol, 1.0 equiv.), THF (60 mL), (4-(trifluoromethyl)phenyl)magnesium bromide solution (7.2 mmol, 1.2 equiv.) and TBAF solution (12.0 mL, 12.0 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, Petrol:EtOAc = 1:1 to 1:6) afforded the desired sulfinamide **186e** as a white solid (443.1 mg, 2.11 mmol, 35%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.92 – 7.85 (m, 4H, Ar-*H*), 6.51 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 152.8, 130.7 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 126.6, 125.7 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 272.6 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ -61.3 (s); **R_F:** 0.41 (Petrol:EtOAc 1:3).

Data is consistent with the literature: F. Saito, *Angew. Chem. Int. Ed.* **2022**, *61*, e202213872.[427]

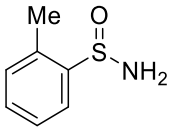


4-Methoxybenzenesulfinamide (186d)

Following General Procedure B, TIPS-NSO **83b** (438.8 mg, 2.00 mmol, 1.0 equiv.), THF (20 mL), 4-methoxyphenylmagnesium bromide solution (4.90 mL, 2.40 mmol, 0.49 M in THF, 1.2 equiv.) and TBAF solution (4.00 mL, 4.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:2 to 1:4) afforded the desired sulfinamide **186d** as a white solid (242.8 mg, 1.42 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.99 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.40 (s, 2H), 3.84 (s, 3H, C-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.0, 137.9, 127.2, 114.4, 55.6; **LRMS** (ESI^+, m/z) $[M+Na]^+$ 194.0; **R_F:** 0.30 (Petrol:EtOAc 1:3).

Data is consistent with the literature: R. R. Groleau, R. S. L. Chapman, H. Ley-Smith, L. Liu, T. D. James, S. D. Bull. *J. Org. Chem.* **2020**, *85*, 1208−1215.[428]

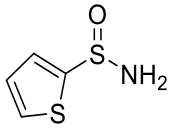


2-Methylbenzenesulfinamide (186c)

Following General Procedure B, TIPS-NSO **83b** (658.3 mg, 3.00 mmol, 1.0 equiv.), THF (30 mL), 2-methylphenylmagnesium bromide solution (1.83 mL, 3.60 mmol, 1.97 M in Et_2O, 1.2 equiv.) and TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:2 to 1:5) afforded the desired sulfinamide **186c** as a white solid (410.7 mg, 2.65 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.6, 3.7 Hz, 1H, Ar-*H*), 7.39 (dd, *J* = 5.7, 3.4 Hz, 2H, Ar-*H*), 7.24-7.18 (m, 1H, Ar-*H*), 4.23 (s, 2H, N-H_2), 2.46 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 136.0, 131.3, 131.1, 126.8, 122.9, 18.8; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 178.0; **IR** υ_{max} (neat)/cm^{-1} 3286, 3187, 2983, 1470, 1427, 1064, 1022, 875, 756, 713; **R_F:** 0.26 (Petrol:EtOAc 1:3).

Data is consistent with the literature: L. Ma, G. Li, J. Huang, J. Zhua, Z. Tang, *Tetrahedron Lett.* **2018**, *59*, 4255–4258.[429]

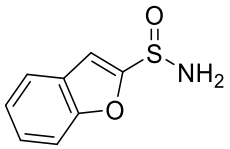


Thiophene-2-sulfinamide (186k)

Following General Procedure B, TIPS-NSO **83b** (658.3 mg, 3.00 mmol, 1.0 equiv.), THF (30 mL), 2-thienylmagnesium bromide solution (3.13 mL, 3.60 mmol, 1.15 M in THF, 1.2 equiv.) and TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:1 to 1:8) afforded the desired sulfinamide **186k** as an off-white solid (333.9 mg, 2.27 mmol, 76%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.83 (dd, *J* = 5.1, 1.4 Hz, 1H, Ar-*H*), 7.31 (dd, *J* = 3.6, 1.4 Hz, 1H, Ar-*H*), 7.17 (dd, *J* = 5.0, 3.6 Hz, 1H, Ar-*H*), 6.60 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 151.2, 131.2, 128.8, 128.0; **LRMS** (ESI^+, m/z) $[M+H]^+$: 148.0; **R_F:** 0.30 (Petrol:EtOAc 1:3).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



Benzofuran-2-sulfinamide (186j)

Preparation of organometallic reagent:

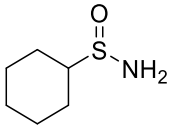
2-Lithiobenzofuran solution was prepared according to the following procedure. To a cooled solution of benzofuran (283.6 mg, 2.40 mmol, 1.2 equiv.) in THF (4.8 mL, benzofuran conc. 0.5 M) at -78 °C, was added *n*-butyllithium solution (1.00 mL, 2.40 mmol, 2.39 M in hexanes, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 10 minutes.

Preparation of sulfinamide:

182j was then prepared following General Procedure B, using TIPS-NSO **83b** (438.8 mg, 2.00 mmol, 1.0 equiv.), THF (10 mL), 2-lithiobenzofuran solution (2.40 mmol, 1.2 equiv.) and TBAF solution (4.00 mL, 4.00 mmol, 1.0 M in THF, 2.0 equiv.). Flash column chromatography (SiO_2, Petrol/EtOAc = 1:3 to 1:5) afforded the desired sulfinamide **186j** as a white solid (297.9 mg, 1.64 mmol, 82%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H, Ar-*H*), 7.67 (dq, *J* = 8.3, 0.9 Hz, 1H, Ar-*H*), 7.42 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H, Ar-*H*), 7.33 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H, Ar-*H*), 7.27 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 6.85 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 159.4, 155.7, 126.9, 126.1, 123.7, 122.3, 111.8, 108.2; **LRMS** (ESI^+, m/z) $[M+H]^+$: 182.0; **R_F:** 0.33 (Petrol:EtOAc 1:3).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



Cyclohexanesulfinamide (S5)

According to a modified procedure by Lo *et al.*,[28] an oven-dried round-bottom flask containing pre-dried DABSO (600 mg, 2.50 mmol, 0.5 equiv.) was sealed and subjected to three N_2 evacuation/refill cycles before pre-sparged, anhydrous THF (20 mL, Grignard conc. 0.25 M) was added. Cyclohexanemagnesium bromide (5.26 mL, 5.00 mmol, 0.95 M in THF, 1.0 equiv.) was added dropwise to the resulting suspension at room temperature and the reaction mixture was stirred for 30 min. $SOCl_2$ (400 μL, 5.50 mmol, 1.1 equiv.) was then added dropwise, and the mixture was stirred at room temperature for 30 min. The reaction mixture was transferred *via* a syringe and added dropwise to a stirred solution of NH_4OH (5 mL) and EtOAc (10 mL) at 0 °C. Anhydrous THF (20 mL) was added to the reaction mixture to ensure a quantitative transfer of the sulfinyl chloride. After addition, the mixture was stirred at room temperature for 30 min, quenched with brine (100 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, Petrol:EtOAc = 1:2 to 0:1) afforded the desired sulfinamide **S5** as an off-white solid (401 mg, 2.72 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 2H, N-*H*$_2$), 2.47 (tt, *J* = 11.3, 3.7 Hz, 1H, $R_2CHS(=O)$), 2.10 – 1.99 (m, 2H, AlkC-*H*), 1.88 (app. dddd, *J* = 17.1, 10.3, 3.8, 1.9 Hz, 2H, AlkC-*H*), 1.74 – 1.63 (m, 1H, AlkC-*H*), 1.53 – 1.15 (m, 5H, AlkC-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) 63.7, 25.9, 25.7, 25.4, 25.3, 25.2 [note: due to chirality at sulfur centre, six ^{13}C NMR environments are observed for cyclohexane group]; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 170.0; **IR** υ_{max} (neat)/cm^{-1} 3269, 3197, 3103, 2928, 2853, 1451, 1042, 1018, 893, 853, 681; **R_F** 0.15 (Petrol:EtOAc 1:5).

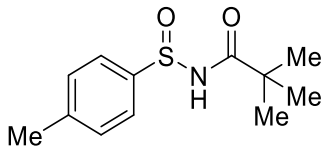
Data is consistent with the literature: F. Xue, F. Wang, J. Liu, J. Di, Q. Liao, H. Lu, M. Zhu, L. He, H. He, D. Zhang, H. Song, X. Liu, Y. Qin, *Angew. Chem. Int. Ed.* **2018**, *57*, 6667 – 6671.[430]

6.2.1.3 Synthesis of *N*-Piv sulfinamides

General Procedure C

According to a modified procedure by Maruoka *et al.*:[164]

NaH (60% dispersion in mineral oil, 2.5 equiv.) was added to a cooled solution of respective primary sulfinamide **186** (1.1 equiv.) in anhydrous THF (sulfinamide conc. 0.11 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 10 min, before a solution of pivalic anhydride (1.0 equiv.) in anhydrous THF (anhydride conc. 0.17 M) was added dropwise. The reaction mixture was stirred vigorously for a further 1 h, cooled to 0 °C and quenched with MeOH (10 mL), then brine (10 mL) and sat. NH_4Cl (10 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL), and combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. *N*-Piv sulfinamide **69** was then purified by flash column chromatography with the appropriate solvent system.

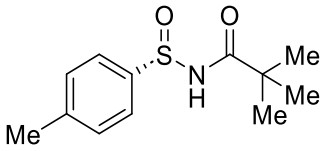


***N*-(*p*-Tolylsulfinyl)pivalamide (69a)**

Following General Procedure C, 4-methylbenzenesulfinamide **186a** (427.0 mg, 2.75 mmol), NaH (60% dispersion in mineral oil, 250 mg, 6.25 mmol) in THF (25 mL) and pivalic anhydride (507 µL, 2.50 mmol) in THF (15 mL). Flash chromatography (SiO_2, CH_2Cl_2:EtOAc = 5:1) afforded the desired sulfinamide **69a** as an off-white solid (481.1 mg, 2.01 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H, Ar-*H*), 7.41 – 7.38 (m, 1H, N-*H*), 7.39 – 7.33 (m, 2H, Ar-*H*), 2.44 (s, 3H, Ar-C*H*$_3$), 1.22 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.8, 142.7, 141.2, 130.3, 124.8, 39.8, 27.3, 21.6; **LRMS** (ESI$^+$, m/z) $[M+Na]^+$: 262.0; **IR** υ_{max} (neat)/cm^{-1} 3343, 2980, 2365, 1658, 1596, 1229, 1179, 1034, 1010, 812, 683; **R_F:** 0.58 (Petrol:EtOAc 2:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 µL injection, (*R*)-**69a**, τ_R = 13.08 min; (*S*)-**69a**, τ_R = 11.57 min.].

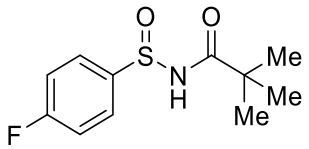
Data is consistent with the literature: D. Leca, K. Song, M. Amatore, L. Fensterbank, E. Lacôte and M. Malacria, *Chem. Eur. J.*, **2004**, *10*, 906–916.[181]



(S)-*N*-(*p*-Tolylsulfinyl)pivalamide ((*S*)-69a)

Following General Procedure C, (*S*)-4-methylbenzenesulfinamide (*S*)-**186a** (427.0 mg, 2.75 mmol), NaH (60% dispersion in mineral oil, 250 mg, 6.25 mmol) in THF (25 mL) and pivalic anhydride (507 µL, 2.50 mmol) in THF (15 mL) added over 2 h. Flash column chromatography (SiO_2, CH_2Cl_2:EtOAc = 5:1) afforded the desired sulfinamide (*S*)-**69a** as an off-white solid (490 mg, 2.01 mmol, 84%, >99% e.e.).

The data were consistent with *N*-(*p*-tolylsulfinyl)pivalamide **(69a)**. **Chiral HPLC:** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 µL injection, (*S*)-**69a**, τ_R = 11.17 min.]; $[\alpha]_D^{25}$= +51.3° (*c* = 1.0, $CHCl_3$).

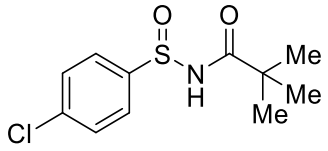


***N*-((4-Fluorophenyl)sulfinyl)pivalamide (69b)**

Following General Procedure C, 4-fluorobenzenesulfinamide **186g** (500.8 mg, 3.15 mmol), NaH (60% dispersion in mineral oil, 286 mg, 7.15 mmol) in THF (28.5 mL) and pivalic anhydride (578 µL, 2.86 mmol) in THF (17 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfinamide **69b** as a white solid (550.1 mg, 2.26 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H, Ar-*H*), 7.57 (s, 1H, N-*H*), 7.30 – 7.20 (m, 2H, Ar-*H*), 1.22 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.8, 165.0 (d, $^1J_{F\text{-}C}$ = 253.1 Hz), 139.9, 127.3 (d, $^3J_{F\text{-}C}$ = 9.1 Hz), 117.0 (d, $^2J_{F\text{-}C}$ = 22.7 Hz), 39.8, 27.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -107.0 (tt, *J* = 8.4, 5.0 Hz); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 266.0; **HRMS** (ESI^+, m/z)

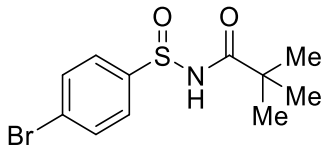
calculated for $[C_{11}H_{14}FNO_2SNa]^+$ 266.0621 $[M+Na]^+$, found 266.0621 (Δ -0.34 ppm); **M.p.** 140-142 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3203, 2972, 1691, 1667, 1588, 1492, 1476, 1399, 1220, 1144, 1092, 1070, 773, 733, 706, 647; **R_F:** 0.21 (Petrol:EtOAc 2:1).



***N*-((4-Chlorophenyl)sulfinyl)pivalamide (69c)**

Following General Procedure C, 4-chlorobenzenesulfinamide **186f** (386.4 mg, 2.20 mmol), NaH (60% dispersion in mineral oil, 200 mg, 5.00 mmol) in THF (20 mL) and pivalic anhydride (406 µL, 2.00 mmol) in THF (12 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfinamide **69c** as a white solid (419.5 mg, 1.62 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, N-*H*), 7.54 – 7.47 (m, 2H, Ar-*H*), 7.47 – 7.40 (m, 2H, Ar-*H*), 1.20 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.2, 142.2, 137.9, 129.4, 126.4, 39.7, 26.8; **HRMS** (ESI^+, m/z) calculated for $[C_{11}H_{14}ClNO_2SNa]^+$ $[M+Na]^+$ 282.0326, found 282.0338 (Δ 4.24 ppm); **M.p.** 142-144 °C ($CHCl_3$); **IR** υ_{max} (neat)/cm^{-1} 3204, 2973, 1694, 1664, 1477, 1398, 1082. 1025, 756, 743; **R_F:** 0.20 (Petrol:EtOAc 2:1).

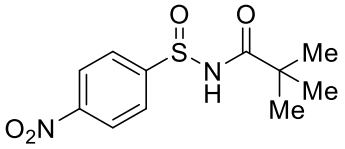


***N*-((4-Bromophenyl)sulfinyl)pivalamide (69d)**

Following General Procedure C, 4-bromobenzenesulfinamide **S3** (484.2 mg, 2.20 mmol), NaH (60% dispersion in mineral oil, 200 mg, 5.00 mmol) in THF (20 mL) and pivalic anhydride (406 µL, 2.00 mmol) in THF (12 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **69d** as a white solid (550.4 mg, 1.81 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, N-*H*), 7.69 – 7.63 (m, 2H, Ar-*H*), 7.53 – 7.48 (m, 2H, Ar-*H*), 1.22 (s, 9H, (C*H*$_3$)$_3$)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.2, 143.2, 132.6, 131.7,

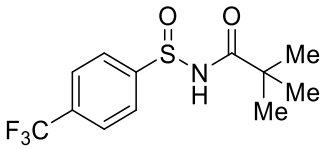
126.6, 39.8, 27.1; **LRMS** (ESI$^+$, m/z) [M+H]$^+$: 304.0; **M.p.** 140-142 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3301, 2974, 1659, 1474, 1225, 1068, 1003, 794, 742; **R_F:** 0.21 (Petrol:EtOAc 2:1).



***N*-((4-Nitrophenyl)sulfinyl)pivalamide (69e)**

Following General Procedure C, 4-nitrobenzenesulfinamide **S4** (1.024 g, 5.50 mmol), NaH (60% dispersion in mineral oil, 500 mg, 12.5 mmol) in THF (50 mL) and pivalic anhydride (1.014 mL, 5.00 mmol) in THF (30 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **69e** as a yellow solid (1.10 g, 4.05 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.39 (m, 2H, Ar-*H*), 7.95 – 7.91 (m, 2H, Ar-*H*), 7.60 (s, 1H, N-*H*), 1.24 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.6, 151.2, 150.2, 126.3, 124.7, 40.0, 27.2; **LRMS (ESI)** m/z (ESI+) [M+Na]$^+$: 293.0; **M.p.** 127-129 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3220, 2933, 1700, 1605, 1526, 1477, 1398, 1345, 1132, 1093, 1067, 854, 833, 743, 724; **R_F:** 0.21 (Petrol:EtOAc 2:1).



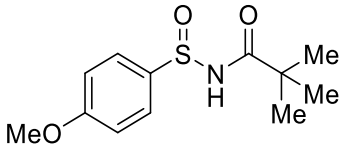
***N*-((4-Trifluoromethyl)phenyl)sulfinyl)pivalamide (69f)**

Following General Procedure C, 4-trifluoromethylbenzenesulfinamide **186e** (460.2 mg, 2.20 mmol), NaH (60% dispersion in mineral oil, 200 mg, 5.00 mmol) in THF (20 mL) and pivalic anhydride (406 µL, 2.00 mmol) in THF (12 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfinamide **69f** as a white solid (447.6 mg, 1.53 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, N-*H*), 7.77 (s, 4H, Ar-*H*), 1.22 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.1, 148.3, 133.9 (q, $^2J_{F\text{-}C}$ = 33.1 Hz), 126.5 (q, $^3J_{F\text{-}C}$ = 3.8 Hz),

125.7, 124.8 (q, $^{1}J_{F\text{-}C}$ = 272.7 Hz), 40.0, 27.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.9 (s); **HRMS** (ESI^+, m/z) calculated for $[C_{12}H_{15}F_3NO_2S]^+$ $[M+H]^+$ 294.0770, found 294.0776 (Δ 1.99 ppm); **R_F:** 0.25 (Petrol:EtOAc 2:1).

Data is consistent with the literature: Y. Aota, T. Kano, K. Maruoka, *J. Am. Chem. Soc.* **2019**, *141*, 19263 – 19268.[163]

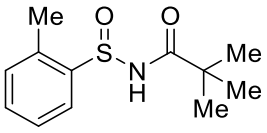


***N*-((4-Methoxyphenyl)sulfinyl)pivalamide (69g)**

Following General Procedure C, 4-methoxybenzenesulfinamide **186d** (106.2 mg, 0.62 mmol), NaH (60% dispersion in mineral oil, 56.0 mg, 1.40 mmol) in THF (5.6 mL) and pivalic anhydride (114 µL, 0.56 mmol) in THF (3.3 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **69g** as a white solid (61.8 mg, 0.24 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, s, N*H*), 7.64 – 7.59 (m, 2H, Ar-*H*), 7.06 – 6.98 (m, 2H, Ar-*H*), 3.86 (s, 3H, Ar-OCH_3), 1.20 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.9, 162.6, 135.3, 126.6, 115.0, 55.7, 39.7, 27.2; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 278.0; **IR** υ_{max} (neat)/cm^{-1} 3221, 2972, 1694, 1595, 1496, 1478, 1398, 1230, 1133, 1093, 1069, 827, 771, 754; **R_F** 0.30 (Petrol:EtOAc 1:1).

Data is consistent with the literature: Y. Aota, T. Kano, K. Maruoka. *J. Am. Chem. Soc.* **2019**, *141*, 19263 – 19268.[163]

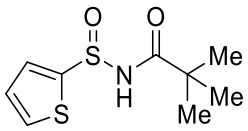


***N*-(*o*-Tolylsulfinyl)pivalamide (69h)**

Following General Procedure C, using 2-methylbenzenesulfinamide **186c** (500.3 mg, 3.22 mmol), NaH (60% dispersion in mineral oil, 293.0 mg, 7.33 mmol) in THF (29 mL) and pivalic

anhydride (578 µL, 2.93 mmol) in THF (17 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfinamide **69** as a white solid (593.5 mg, 2.48 mmol, 85%).

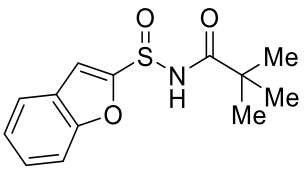
^{1}H NMR (400 MHz, $CDCl_3$) 7.99 – 7.95 (m, 1H, Ar-*H*), 7.42 – 7.38 (m, 2H, Ar-*H*), 7.31 (br. s, 1H, N-*H*), 7.23 – 7.19 (m, 1H, Ar-*H*), 2.32 (d, *J* = 0.6 Hz, 3H, C*H*$_3$), 1.15 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.5, 141.8, 135.7, 132.0, 131.4, 127.2, 124.1, 39.9, 27.3, 18.3; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 262.0; **HRMS** (ESI^+, m/z) calculated for $[C_{12}H_{17}NO_2SNa]^+$ $[M+Na]^+$ 262.0872, found 262.0872 (Δ -0.12 ppm); **M.p.** 136-137 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3057, 2974, 1691, 1477, 1399, 1132, 1077, 1046, 1023, 9045, 834, 755; **R_F** 0.21 (Petrol:EtOAc 2:1).



***N*-(Thiophen-2-ylsulfinyl)pivalamide (69i)**

Following General Procedure C, thiophene-2-sulfinamide **186k** (323.9 mg, 2.20 mmol), NaH (60% dispersion in mineral oil, 200 mg, 5.00 mmol) in THF (20 mL) and pivalic anhydride (406 µL, 2.00 mmol) in THF (12 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfinamide **69i** as a white solid (227.8 mg, 0.98 mmol, 49%).

^{1}H NMR 8.23 (s, 1H, N-*H*), 7.64 (dd, *J* = 5.0, 1.3 Hz, 1H, Ar-*H*), 7.49 (dd, *J* = 3.7, 1.3 Hz, 1H, Ar-*H*), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H, Ar-*H*), 1.24 (s, 9H, (CH$_3$)$_3$); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 254.0; **M.p.** 131-133 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3245, 2956, 1675, 1397, 1215, 1075, 821, 734; **R_F:** 0.22 (Petrol:EtOAc 2:1).

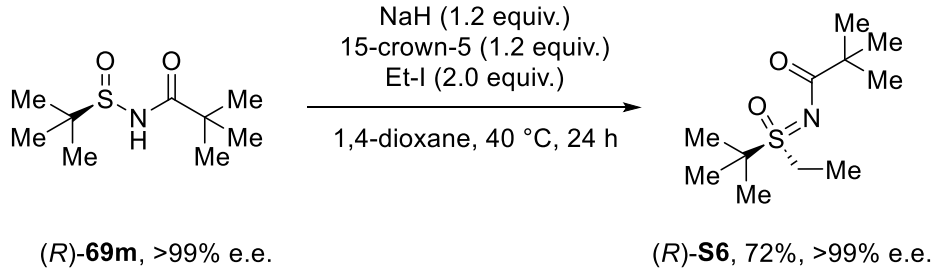


***N*-(Benzofuran-2-ylsulfinyl)pivalamide (69j)**

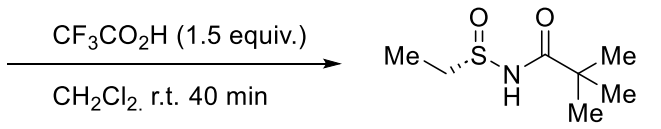
Following General Procedure C, benzofuran-2-sulfinamide **186j** (398.7 mg, 2.20 mmol), NaH (60% dispersion in mineral oil, 200 mg, 5.00 mmol) in THF (20 mL) and pivalic anhydride (406 µL, 2.00 mmol) in THF (12 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **69j** as a white solid (398.7 mg, 1.50 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br. s, 1H, N-*H*), 7.68 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H, Ar-*H*), 7.57 (dq, *J* = 8.4, 0.9 Hz, 1H, Ar-*H*), 7.46 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H, Ar-*H*), 7.38 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 7.35 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H, Ar-*H*), 1.29 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.6, 156.6, 154.7, 127.4, 126.6, 124.4, 122.8, 112.3, 111.7, 40.0, 27.3; **HRMS** (ESI^+, m/z) calculated for $[C_{13}H_{16}NO_3S]^+$ $[M+H]^+$ 266.0845, found 266.0852 (Δ 2.46 ppm); **M.p.** 126-128 °C (DCM); **R_F:** 0.21 (Petrol:EtOAc 2:1).

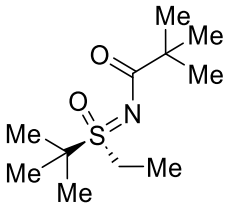
Synthesis *via* de-*tert*-butylation sequence:



(*R*)-**69m**, >99% e.e. (*R*)-**S6**, 72%, >99% e.e.



(*S*)-**69k**, 54%, >99% e.e.



(*R*)-*N*-(*tert*-Butyl(ethyl)(oxo)-λ^6-sulfaneylidene)pivalamide ((*R*)-S6)

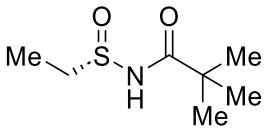
According to a modified procedure by Maruoka *et al.*,[164] to a solution of (*R*)-*N*-(*tert*-butylsulfinyl)pivalamide (*R*)-**69m** (205 mg, 1.00 mmol, 1.0 equiv.) in 1,4-dioxane (6.0 mL,

0.17 M) was added NaH (60% in mineral oil, 48.0 mg, 1.20 mmol, 1.2 equiv.) and 15-crown-5 (237 µL, 1.20 mmol, 1.2 equiv.) at room temperature. After stirring for 10 min, ethyl iodide (161 µL, 2.00 mmol, 2.0 equiv.) was added. After stirring for 24 h at 40 °C, the reaction mixture was cooled to room temperature and quenched with sat. NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, CH_2Cl_2:EtOAc = 10:1 to 5:1) afforded the desired sulfoximine as a white solid (168.0 mg, 0.72 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) 3.59 (dq, *J* = 13.8, 7.4 Hz, 1H, CH_aCH_bCH_3), 3.36 (dq, *J* = 13.8, 7.4 Hz, 1H, CH_aCH_bCH_3), 1.44 (s, 9H, C(=O)C(CH_3)$_3$), 1.40 (t, *J* = 7.4 Hz, 3H, CH_aCH_bCH_3), 1.16 (s, 9H, SC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 187.9, 62.1, 41.7, 41.3, 28.0, 23.5, 8.4; **LRMS** (ESI$^+$, m/z) $[M+Na]^+$: 256.1; **R_F** 0.35 (CH_2Cl_2:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 µL injection, (*R*)-**S6**, τ_R = 8.81 min]; $[\alpha]_D^{25}$= +79.9° (*c* = 1.0, $CHCl_3$).

Data is consistent with the literature: Y. Aota, T. Kano, K. Maruoka. *Angew. Chem. Int. Ed.* **2019**, *58*, 17661 – 17665.[164]

The racemic sample was prepared using *N*-(*tert*-butylsulfinyl)pivalamide on the same scale (1.00 mmol), affording the desired sulfoximine **S6** as a white solid (150.2 mg, 0.65 mmol, 65%). The data were consistent with (*R*)-*N*-(*tert*-butyl(ethyl)(oxo)-λ^6-sulfaneylidene)pivalamide ((*R*)-**S6**): **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 µL injection, (*R*)-**S6**, τ_R = 8.85 min; (*S*)-**S6**, τ_R = 10.42 min.].



(*S*)-*N*-(Ethylsulfinyl)pivalamide (*S*)-69k

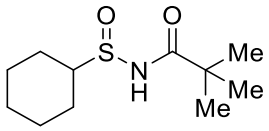
According to a modified procedure from Maruoka *et al.*,[164] to a solution of (*R*)-*N*-(*tert*-butyl(ethyl)(oxo)-λ^6-sulfaneylidene)pivalamide **S6** (130 mg, 0.56 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (2.0 mL, 0.28 M) was added TFA (65 µL, 0.84 mmol, 1.5 equiv.) at room temperature over 5 min. After stirring for 40 min, the reaction mixture was diluted with

CH_2Cl_2 (5 mL) and brine (5 mL) was added. The organic layer was separated and washed with sat. $NaHCO_3$ (5 mL). The aqueous layers were washed with CH_2Cl_2 (3 × 5 mL). Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (SiO_2, EtOAc:acetone = 4:1) afforded the desired sulfinamide (*S*)-**69k** as a white solid (54.1 mg, 0.30 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (app. d, *J* = 5.5 Hz, 1H, N-*H*), 2.98 (q, *J* = 7.8 Hz, 2H, C*H*$_2$), 1.32 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.24 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.1, 49.3, 39.9, 27.3, 6.3.; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 200.0; **IR** υ_{max} (neat)/cm^{-1} 3184, 2973, 1696, 1479, 1400, 1366, 1137, 1077, 900, 836, 780, 760; **R$_F$** 0.18 (Petrol:EtOAc 2:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**69k**, τ_R = 13.90 min.]; $[\alpha]_D^{25}$ = +14.3° (*c* = 1.0, $CHCl_3$).

Data is consistent with the literature: Y. Aota, T. Kano, K. Maruoka. *Angew. Chem. Int. Ed.* **2019**, *58*, 17661 – 17665.[164]

The racemic sample was prepared using *N*-(*tert*-butyl(ethyl)(oxo)-λ^6-sulfaneylidene)pivalamide **S6** on the same scale (0.56 mmol), affording the desired sulfinamide **69k** as a white solid (72.2 mg, 0.41 mmol, 73%). The data were consistent with (*S*)-*N*-(ethylsulfinyl)pivalamide ((*S*)-**69k**): **Chiral HPLC [**Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**69k**, τ_R = 11.61 min; (*S*)-**69k**, τ_R = 13.84 min.].

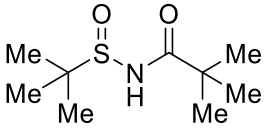


***N*-(Cyclohexylsulfinyl)pivalamide (69l)**

Following General Procedure C, cyclohexanesulfinamide **S5** (202 mg, 1.38 mmol), NaH (60% dispersion in mineral oil, 125 mg, 3.22 mmol) in THF (12.5 mL) and pivalic anhydride (254 μL, 1.25 mmol) in THF (8.5 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:3) afforded the desired sulfinamide **69l** as a white solid (280.1 mg, 1.21 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H, N-*H*), 2.98 (tt, *J* = 11.2, 3.8 Hz, 1H, C*H*S(=O)), 2.05 – 1.96 (m, 1H, AlkC-*H*), 1.82 (dt, *J* = 12.1, 3.5 Hz, 1H, AlkC-*H*), 1.77 – 1.69 (m, 2H, AlkC-*H*$_2$),

1.63 – 1.55 (m, 1H, AlkC-*H*), 1.37 (dd, *J* = 12.6, 3.3 Hz, 1H, AlkC-*H*), 1.28 – 1.14 (m, 4H, AlkC-*H*), 1.11 (app. d, *J* = 0.7 Hz, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.4, 61.7, 39.8, 27.0, 25.7, 25.6, 25.3, 24.94, 24.86 [*note*: due to chiral centre at sulfur, carbon environments of the cyclohexane ring are all distinct]; **LRMS** (ESI$^+$, m/z) [M+Na]$^+$: 254.0; **HRMS** (ESI$^+$, m/z) calculated for $[C_{11}H_{21}NO_2SNa]^+$ [M+Na]$^+$ 254.1185, found 254.1185 (Δ -0.08 ppm); **M.p.** 160 °C (CH_2Cl_2); **IR** υ_{max} (neat)/cm^{-1} 3201, 2932, 2856, 1696, 1478, 1450, 13670, 1134, 1063, 907, 836, 773, 646; **R_F:** 0.32 (Petrol:EtOAc 1:3).



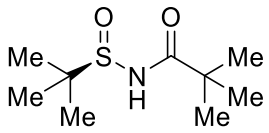
***N*-(*tert*-Butylsulfinyl)pivalamide (69m)**

According to a modified procedure by Maruoka *et al.*,[164] to a cooled solution of *tert*-butanesulfinamide (605 mg, 5.00 mmol, 1.0 equiv.) in anhydrous THF (50 mL, 0.10 M) at 0 °C, was added NaH (60% dispersion in mineral oil, 480 mg, 12.0 mmol, 2.4 equiv.). The reaction mixture was warmed to room temperature and stirred for 10 min, before pivalic anhydride (1.20 mL, 6.00 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred vigorously for a further 1 h, cooled to 0 °C before quenching with MeOH (10 mL), then brine (10 mL) and sat. NH_4Cl (10 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL), and combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, CH_2Cl_2:EtOAc = 5:1) afforded the desired sulfinamide **69m** as a white solid (802 mg, 3.91 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 1H, N-*H*), 1.26 (s, 9H, (C(C*H*$_3$)$_3$S(=O)), 1.25 (s, 9H, (C(C*H*$_3$)$_3$C(=O)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.8, 57.4, 40.1, 27.4, 22.1; **LRMS** (ESI$^+$, m/z) [M+Na]$^+$: 228.0; **IR** υ_{max} (neat)/cm^{-1} 3180, 2970, 1700, 1686, 1476, 1397, 1366, 1131, 1067, 902, 835, 765, 648; **R_F:** 0.17 (Petrol:EtOAc 2:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**69m**, τ_R = 7.56 min; (*S*)-**69m**, τ_R = 11.65 min.].

Data is consistent with the literature: Y. Aota, T. Kano, K. Maruoka. *Angew. Chem. Int. Ed.* **2019**, *58*, 17661 – 17665.[164]

Preparation of enantionenriched material:



(*R*)-*N*-(*tert*-Butylsulfinyl)pivalamide ((*R*)-(69m))

According to a modified procedure by Maruoka *et al.*,[164] to a cooled solution of (*R*)-*tert*-butanesulfinamide (666.0 mg, 5.50 mmol, 1.1 equiv.) in anhydrous THF (55 mL, 0.10 M) at 0 °C, was added NaH (60% dispersion in mineral oil, 500 mg, 12.5 mmol, 2.5 equiv.). The reaction mixture was warmed to room temperature and stirred for 10 min, before a solution of pivalic anhydride (1.0 mL, 5.00 mmol, 1.0 equiv.) in THF (30 mL) was added over 2 h. The reaction mixture was stirred vigorously for a further 10 min, cooled to 0 °C before quenching with MeOH (10 mL), then brine (10 mL) and sat. NH_4Cl (10 mL) were added. The mixture was extracted with EtOAc (3 × 20 mL), and combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, CH_2Cl_2:EtOAc = 5:1) afforded sulfinamide (*R*)-**69m** as a white solid (750 mg, 3.66 mmol, 73%, >99% e.e.).

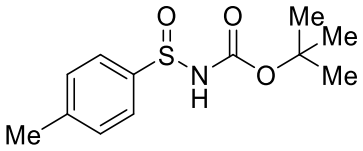
The data were consistent with *N*-*tert*-butylsulfinyl)pivalamide (**69m**). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**69m**, τ_R = 7.57 min. $[\alpha]_D^{25}$ = +32.0° (*c* = 1.0, $CHCl_3$).

6.2.1.4 Synthesis of *N*-substituted sulfinamides

General Procedure D

Following a modified procedure by Y. Z. Ji, J. Y. Zhang, H. J. Li, C. G. Han, Y. K. Yang and Y. C. Wu:[374]

A cooled solution of sodium 4-methylbenzene sulfinate (1.0 equiv.) in PhMe (0.4 M) at 0 °C, was purged with N_2. To this, oxalyl chloride (1.1 equiv.) was added dropwise, and the reaction mixture was slowly warmed to room temperature and stirred for 1 h, to generate the corresponding sulfinyl chloride. This solution was added dropwise to a mixture of respective amine 1.2 equiv.) and triethylamine (1.5 equiv.) in PhMe (1.4 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h, before diluting with EtOAc (50 mL) and H_2O (50 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed sequentially with HCl (0.1 M, 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Sulfinamide **66** was then purified by flash chromatography with the appropriate solvent system. [*Note*: slow addition of oxalyl chloride and adequate venting is essential with significant gas release on addition].



***tert*-Butyl (*p*-tolylsulfinyl)carbamate (66a)**

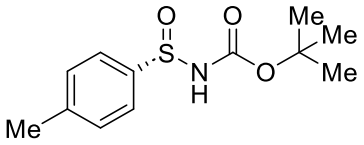
According to a modified procedure by Bolm *et al.*,[114] to a cooled solution of 4-methylbenzenesulfinamide **186a** (249.9 mg, 1.61 mmol, 1.0 equiv.) in anhydrous THF (7.0 mL, 0.2 M) at -78 °C, was added *n*-BuLi (1.88 mL, 4.03 mmol, 2.15 M in hexanes, 2.5 equiv.) dropwise. The reaction mixture was stirred at - 78 °C for 10 min, before addition of di-*tert*-butyl dicarbonate (527 mg, 2.42 mmol, 1.5 equiv.). The reaction mixture was stirred for a further 10 min at this temperature, before slowly warming to room temperature and stirred for 4 h. The solution was quenched with sat. $NaHCO_3$ (8 mL), and diluted with CH_2Cl_2 (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over anhydrous MgSO4, filtered and concentrated *in vacuo* to give an

off-white solid. Flash column chromatography (SiO_2, Pentane:EtOAc = 2:1) afforded the desired sulfinamide **66a** as a white solid (361 mg, 1.42 mmol, 88%). [*Note:* reaction gave comparable yield (84%) when performed on 5.15 mmol scale].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H, Ar-*H*), 7.37 – 7.32 (m, 2H, Ar-*H*), 6.62 (s,1H, N-*H*), 2.42 (s, 3H, Ar-C*H*$_3$), 1.51 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6, 142.6, 140.8, 130.2, 124.8, 83.7, 28.2, 21.6; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 278.0; **IR** υ_{max} (neat)/cm^{-1} 3375, 2981, 1729, 1706, 1394, 1369, 1336, 1261, 1157, 1095, 1073, 897, 778, 669; **R_F:** 0.26 (Petrol:EtOAc 2:1); **Chiral HPLC:** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**66a**, τ_R = 27.21 min; (*S*)-**66a**, τ_R = 20.55 min.].

Data is consistent with the literature: C. Worch, I. Atodiresei, G. Raabe, C. Bolm. *Chem. Eur. J.* **2010**, *16*, 677 – 683. [114]

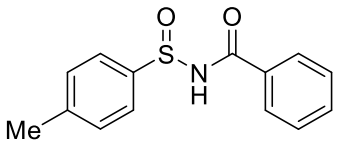
Preparation of enantionenriched material:



(*S*)-*tert*-Butyl (*p*-tolylsulfinyl)carbamate ((*S*)-(66a))

According to a procedure by Bolm *et al*.,[114] to a cooled solution of (*S*)-4-methylbenzenesulfinamide **(*S*)-186a** (799.4 mg, 5.15 mmol, 1.0 equiv.) in anhydrous THF (23 mL, 0.2 M) at -78 °C, was added *n*-BuLi (5.36 mL, 12.9 mmol, 2.40 M in hexanes, 2.5 equiv.) dropwise. The reaction mixture was stirred at -78 °C for 10 min, before addition of di-*tert*-butyl dicarbonate (1.35 g, 6.18 mmol, 1.2 equiv.) in one portion. The reaction mixture was stirred for a further 10 min at this temperature, before slowly warming to room temperature and stirred for 4 h. The solution was quenched with sat. $NaHCO_3$ (23 mL), and diluted with CH_2Cl_2 (45 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried over anhydrous MgSO4, filtered and concentrated *in vacuo* to give an off-white solid. Recrystallization from hexane/EtOAc (3:1, 90 °C to room temperature) afforded the desired sulfinamide (*S*)-**66a** as a white solid (800.2 mg, 3.13 mmol, 63%, >99% e.e.).

The data were consistent with *tert*-butyl-(*p*-tolylsulfinyl)carbamate (**66a**). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)- **66a**, τ_R = 20.57 min.]. $[\alpha]_D^{25}$= +100.6° (*c* = 1.0, $CHCl_3$).



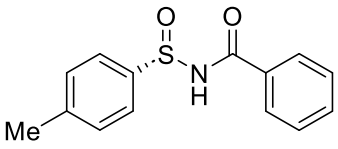
_N_-(_p_-Tolylsulfinyl)benzamide (66e)

According to a modified procedure by Bolm *et al.*,[114] to a cooled solution of 4-methylbenzenesulfinamide **186a** (250 mg, 1.61 mmol, 1.0 equiv.) in anhydrous THF (7.0 mL, 0.2 M) at -78 °C, was added *n*-BuLi (2.15 M in hexanes, 1.88 mL, 4.03 mmol, 2.5 equiv.) dropwise. The reaction mixture was stirred at -78 °C for 10 min, before addition of benzoic anhydride (437 mg, 1.93 mmol, 1.2 equiv.). The reaction mixture was stirred for a further 10 min at this temperature, before slowly warming to room temperature and stirred for 4 h. The solution was quenched with saturated $NaHCO_3$ (8 mL), and diluted with CH_2Cl_2 (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give an off-white solid. Flash column chromatography (SiO_2, Pentane:EtOAc = 7:3) afforded sulfinamide **66e** as an off-white solid (267 mg, 1.03 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, N-*H*), 7.82 – 7.75 (m, 2H, Ar-*H*), 7.71 (dd, *J* = 8.5, 2.0 Hz, 2H, Ar-*H*), 7.62 – 7.54 (m, 1H, Ar-*H*), 7.50 – 7.43 (m, 2H, Ar-*H*), 7.39 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 2.45 (s, 3H, Ar-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 167.5, 142.3, 141.4, 133.3, 131.7, 130.4, 129.0, 127.9, 124.9, 24.7; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 282.0; **IR** υ_{max} (neat)/cm^{-1} 3222, 3171, 1674, 1599, 1580, 1452, 1401, 1243, 1091, 1060, 808, 780, 706; **R_F** 0.21 (Petrol:EtOAc 2:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*R*)-**66e**, τ_R = 14.23 min; (*S*)-**66e**, τ_R = 16.21 min.].

Data is consistent with the literature: C. Worch, I. Atodiresei, G. Raabe, C. Bolm. *Chem. Eur. J.* **2010**, *16*, 677 – 683.[114]

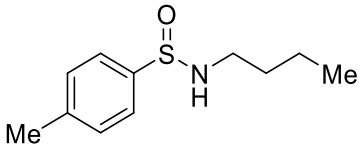
Preparation of enantionenriched material:



(*S*)-*N*-(*p*-Tolylsulfinyl)Benzamide (*S*)-66e

According to a modified procedure by Bolm *et al.*,[114] to a cooled solution of (*S*)-4-methylbenzenesulfinamide (*S*)-**186a** (125.7 mg, 0.81 mmol, 1.0 equiv.) in anhydrous THF (3.5 mL, 0.2 M) at -78 °C, was added *n*-BuLi (0.837 mL, 2.03 mmol, 2.42 M in hexanes, 2.5 equiv.) dropwise. The reaction mixture was stirred at -78 °C for 10 min, before addition of benzoic anhydride (219 mg, 0.97 mmol, 1.2 equiv.). The reaction mixture was stirred for a further 10 min at this temperature, before slowly warming to room temperature and stirred for 4 h. The solution was quenched with saturated $NaHCO_3$ (8 mL), and diluted with CH_2Cl_2 (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give an off-white solid. Flash column chromatography (SiO_2, Pentane:EtOAc = 7:3) afforded sulfinamide (*S*)-**66e** as an off-white solid (132.2 mg, 0.50 mmol, 63%, >99% e.e.).

The data were consistent with *N*-(*p*-tolylsulfinyl)benzamide (**66e**). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*S*)-**66e**, τ_R = 16.31 min.]. $[\alpha]_D^{25}$= +112° (*c* = 1.0, $CHCl_3$).



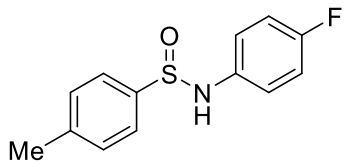
***N*-Butyl-4-methylbenzenesulfinamide (66f)**

Following General Procedure D, sodium 4-methylbenzene sulfinate **180b** (5.00 g, 28.1 mmol) in PhMe (70 mL), oxalyl chloride (2.65 mL, 30.9 mmol) and *n*-butyl amine (3.30 mL, 33.7 mmol) and triethylamine (5.87 mL, 42.1 mmol) in PhMe (20 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfinamide **66f** as a colourless oil (4.86 g, 23.0 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.30 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 3.94 (s, N*H*, 1H), 3.11 (dtd, *J* = 12.6, 7.0, 5.5 Hz, 1H, $NHC\mathit{H_A}H_B$), 2.82 (dq, *J* = 12.3, 7.1 Hz, 1H, $NHCH_A\mathit{H_B}$), 2.41 (s, Ar-C$\mathit{H_3}$, 3H), 1.48 (app. p, *J* = 7.4 Hz, 2H, $NHCH_2C\mathit{H_2}CH_2CH_3$), 1.32 (ddt, *J* = 14.2, 7.2, 6.0 Hz, 2H, $NHCH_2CH_2C\mathit{H_2}CH_3$), 0.87 (t, *J* = 7.3 Hz, 3H, $CH_2C\mathit{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.6, 141.3, 129.6, 126.0, 41.1, 32.8, 21.5, 20.1, 13.8; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 234.0; **IR** υ_{max} (neat)/ cm^{-1} 3221, 2968, 2931, 2871, 1492, 1465, 1087, 1051, 811, 622; **R_F** 0.27 (Petrol:EtOAc 2:1)

Data is consistent with the literature: Y. Z. Ji, J. Y. Zhang, H. J. Li, C. Han, Y. K. Yang and Y. C. Wu, *Org. Biomol. Chem.*, **2019**, *17*, 4789 – 4800.[374]

[*Note*: over time the sulfinamide changes colour to a yellow oil, however, no observed degradation by analytical techniques.]

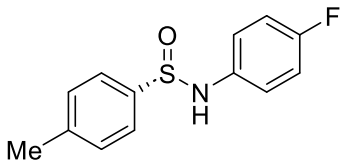


***N*-(4-Fluorophenyl)-4-methylbenzenesulfinamide (66g)**

Following General Procedure D, sodium 4-methylbenzene sulfinate **180b** (5.00 g, 28.1 mmol) in PhMe (70 mL), oxalyl chloride (2.65 mL, 30.9 mmol), 4-fluoroaniline (3.19 mL, 33.7 mmol) and triethylamine (5.87 mL, 42.1 mmol) in PhMe (20 mL). Purification by trituration with hexane:EtOAc (1:1) thrice, to remove excess aniline, afforded the desired sulfinamide **66g** as an off-white solid (5.53 g, 22.2 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.29 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.06 – 7.01 (m, 2H, Ar-*H*), 6.93 (dd, *J* = 9.7, 7.5 Hz, 2H, Ar-*H*), 6.39 (s, 1H, N-*H*), 2.41 (s, 3H, C$\mathit{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7 (d, $^1\mathit{J_{F\text{-}C}}$ = 242.8 Hz), 142.0, 141.3, 136.4 (d, $^4\mathit{J_{F\text{-}C}}$ = 2.8 Hz), 129.9, 125.7, 121.9 (d, $^3\mathit{J_{F\text{-}C}}$ = 8.0 Hz), 116.2 (d, $^2\mathit{J_{F\text{-}C}}$ = 22.8 Hz), 21.5; **^{19}F NMR** (377 MHz, $CDCl_3$) -119.2 (tt, *J* = 8.5, 4.7 Hz); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 272.0; **IR** υ_{max} (neat)/ cm^{-1} 3046, 3030, 1509, 1210, 1099, 1052, 1015, 812, 777, 691; **R_F** 0.30 (Petrol:EtOAc 2:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 85:15, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*R*)-**66g**, τ_R = 12.71 min; (*S*)-**66g**, τ_R = 15.24 min.].

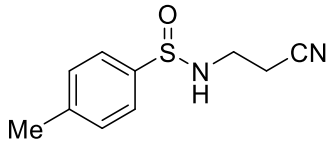
Data is consistent with the literature: R. Chakravarti, A. Mano, H. Iwai, S. S. Aldeyab, R. P. Kumar, M. L. Kantam, A. Vinu. *Chem. Eur. J.*, **2011**, *17*, 6673 – 6682.[431]



(*S*)-*N*-(4-Fluorophenyl)-4-methylbenzenesulfinamide (*S*)-(66g)

According to a modified procedure by Carreño *et al.*,[432] *n*-BuLi (730 μL, 1.56 mmol, 2.15 M in hexanes, 1.1 equiv) was added dropwise to a solution of 4-fluoroaniline (135 μL, 1.42 mmol, 1.0 equiv) in THF (10 mL, 0.14 M) at −78 °C. After 15 min of stirring at this temperature, the resulting mixture was added to a solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate **S2** (500 mg, 1.70 mmol, 1.2 equiv) in THF (1.0 mL) at −78 °C. After 1 h stirring at the same temperature, sat. aq. solution of NH_4Cl was added (5 mL), the solution transferred to a separating funnel and the layers separated. The organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crystallisation on addition of an ether/hexane mixture afforded the desired sulfinamide **66g** as a light brown solid (138.4 mg, 0.55 mmol, 39% yield, 98% e.e.).

The data were consistent with *N*-(*p*-tolylsulfinyl)benzamide (**66e**). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, 10 μL injection, (*R*)-**66g**, τ_R = 13.12 min; (*S*)-**66g**, τ_R = 16.09 min.]. $[\alpha]_D^{25}$ = +151° (*c* = 1.0, $CHCl_3$).

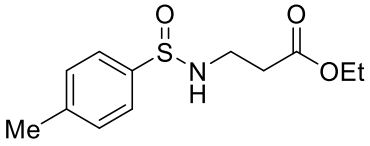


***N*-(2-Cyanoethyl)-4-methylbenzenesulfinamide (66h)**

Following General Procedure D, sodium 4-methylbenzene sulfinate **180b** (1.922 g, 10.0 mmol) in PhMe (25 mL), oxalyl chloride (944 μL, 11.0 mmol) and 3-aminopropanenitrile (878 μL, 12.0 mmol) and triethylamine (2.09 mL, 15.0 mmol) in PhMe (7.1 mL). Flash column

chromatography (SiO_2, Petrol:EtOAc = 8:1 to 2:1) afforded the desired sulfinamide **66h** as an orange solid (1.21 g, 5.81 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7.33 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 4.58 (d, *J* = 8.5 Hz, 1H, N-*H*), 3.32 (app. dp, *J* = 13.8, 6.7 Hz, 1H, C*H*), 3.23 (app. tt, *J* = 13.8, 6.8 Hz, 1H, C*H*), 2.55 (dd, *J* = 6.9, 6.1 Hz, 1H, C*H*), 2.48 (dd, *J* = 7.0, 6.1 Hz, 1H, C*H*), 2.42 (s, 3H, Ar-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 140.4, 130.0, 126.0, 117.8, 37.5, 21.5, 20.4.; **HRMS** (ESI^+, m/z) calculated for $[C_{10}H_{12}N_2OSNa]^+$ $[M+Na]^+$ 231.0563, found 231.0565 (Δ 1.04 ppm); **IR** υ_{max} (neat)/ cm^{-1} 3227, 3189, 2262, 1456, 1089, 1069, 897; **M.p.** 83-84 °C ($CHCl_3$); **R_F** 0.17 (Petrol:EtOAc 2:1).



Ethyl 3-((*p*-tolylsulfinyl)amino)propanoate (66i)

Following General Procedure D, sodium 4-methylbenzene sulfinate **180b** (1.922 g, 10.0 mmol) in PhMe (25 mL), oxalyl chloride (944 μL, 11.0 mmol) and ethyl 3-aminopropanoate (900 μL, 12.0 mmol) and triethylamine (2.09 mL, 15.0 mmol) in PhMe (7.1 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 8:1 to 2:1) afforded the desired sulfinamide **66i** as a yellow oil (0.724 g, 2.84 mmol, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.3, 1.9 Hz, 2H, Ar-*H*), 7.32 – 7.25 (m, 2H, Ar-*H*), 4.73 (t, *J* = 6.6 Hz, 1H, N-*H*), 4.19 – 4.07 (m, 2H, OCH_2), 3.39 – 3.26 (m, 1H, C*H*), 3.11 (dtdd, *J* = 13.7, 7.1, 5.3, 2.3 Hz, 1H, C*H*), 2.62 – 2.41 (m, 2H, CH_2), 2.40 (s, 3H, Ar-CH_3), 1.28 – 1.20 (m, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2, 141.4, 141.2, 129.7, 126.1, 60.9, 37.4, 35.6, 21.4, 14.3.; **HRMS** (ESI^+, m/z) calculated for $[C_{12}H_{17}NO_3SNa]^+$ $[M+Na]^+$ 278.0821, found 278.0828 (Δ 2.37 ppm); **IR** υ_{max} (neat)/ cm^{-1} 3229, 2986, 1734, 1187, 1053, 1036, 815, 656; **R_F** 0.10 (Petrol:EtOAc 2:1).

6.2.1.5 Synthesis of sulfonimidoyl fluorides

General Procedure E

To a cooled solution of respective sulfinamide (1.0 equiv.) in MeCN (0.1 M) at 0 °C, was added NCS (1.1 equiv.). The resultant reaction mixture was stirred at 0 °C for 30 min, before addition of KHF_2 (1.2 equiv.). The resulting solution was stirred for 18 h at room temperature, then diluted with EtOAc (5 mL) and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Sulfonimidoyl fluoride (**42e-j** and **70a-m**) was then purified by flash chromatography with the appropriate solvent system.

General Procedure F

To a cooled solution of respective sulfinamide (1.0 equiv.) in THF (0.1 M) at 0 °C, was added NaH (60% dispersion in mineral oil, 1.2 equiv.) or K_2CO_3 (1.2 equiv.). The resultant reaction mixture was stirred at 0 °C for 30 min, before addition of NFSI (1.1 equiv.). The resulting solution was stirred for 18 h at room temperature, then diluted with EtOAc (5 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Sulfonimidoyl fluoride (**42e-j** and **70a-m**) was then purified by flash chromatography with the appropriate solvent system.

General Procedure G

To a solution of respective sulfinamide (1.0 equiv.) in CH_2Cl_2 (0.1 M), was added 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b**(1.2 equiv.). The resultant solution was stirred at room temperature for 18 h, then diluted with CH_2Cl_2 (5 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Sulfonimidoyl fluoride (**42** and **70**) was then purified by flash chromatography with the appropriate solvent system.

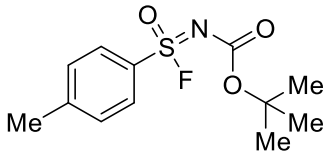
General Procedure H

To a cooled solution of respective sulfinamide (1.0 equiv.) in MeCN (0.1 M) at 0 °C, was added NCS (1.1 equiv.). The resultant reaction mixture was stirred at 0 °C for 30 min, before addition

of KHF_2 (1.2 equiv.). The resulting solution was stirred at 0 °C for 4 h, then diluted with EtOAc (5 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Sulfonimidoyl fluoride (**42** and **70**) was then purified by flash chromatography with the appropriate solvent system.

General Procedure I

To a cooled solution of respective sulfinamide (1.0 equiv.) in THF (0.1 M) at 0 °C, was added NaH (60% dispersion in mineral oil, 1.2 equiv.) or K_2CO_3 (1.2 equiv.). The resultant reaction mixture was stirred at 0 °C for 30 min, before addition of NFSI (1.1 equiv.). The resulting solution was stirred at 0 °C for 4 h, then diluted with EtOAc (5 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Sulfonimidoyl fluoride (**42** and **70**) was then purified by flash chromatography with the appropriate solvent system.



***tert*-Butyl (fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (42a)**

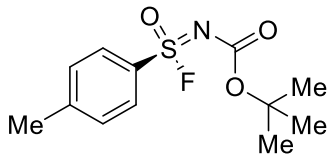
Oxidative chlorination/halogen exchange: Following General Procedure E, *tert*-butyl-(*p*-tolylsulfinyl)carbamate **66a** (25.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **42a** as an off-white oil (25.8 mg, 0.095 mmol, 95%).

Oxidative fluorination (NFSI): Following General Procedure F, *tert*-butyl-(*p*-tolylsulfinyl)carbamate **66a** (25.5 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **42a** as an off-white oil (23.8 mg, 0.087 mmol, 87%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, *tert*-butyl-(*p*-tolylsulfinyl)carbamate **66a** (25.5 mg, 0.10 mmol), 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **42a** as an off-white oil (22.0 mg, 0.080 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.97 (m, 2H, Ar-*H*), 7.42 – 7.38 (m, 2H, Ar-*H*), 2.48 (s, 3H, C*H*$_3$), 1.53 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.7 (d, $^3J_{C\text{-}F}$ = 3.1 Hz), 147.1, 130.8 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 130.2, 128.2, 82.7, 28.0, 21.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 68.8 (s); **LRMS** (ESI$^+$, m/z) [M+Na]$^+$: 296.0; **HRMS** (ESI$^+$, m/z) calculated for [$C_{12}H_{16}FNO_3SNa$]$^+$ [M+Na]$^+$ 296.0727, found 296.0278 (Δ 0.14 ppm); **IR** υ_{max} (neat)/cm^{-1} 2980, 2930, 1726, 1703 (C=O), 1595, 1272, 1253, 1151, 814; **R$_F$** 0.46 (Petrol:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**42a**, τ_R = 14.54 min, (*S*)-**42a**, τ_R = 15.90 min.].

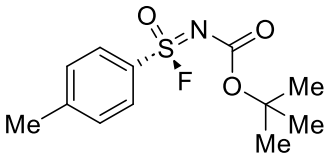
Data is consistent with the literature: R. Kowalczyk, A. J. F. Edmunds, R. G. Hall, C. Bolm, *Org. Lett.* **2011**, *13*, 4, 768–771.[113]



(*S*)-*tert*-Butyl (fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate ((*S*)-42a)

Following General Procedure H**,** (*S*)-*tert*-butyl-(*p*-tolylsulfinyl)carbamate (*S*)-**66a** (25.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*S*)-**42a** as a light brown oil (25.7 mg, 0.094 mmol, 94%, >99% e.e.).

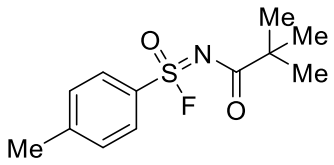
The data were consistent with *tert*-butyl (fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (**42a**). [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**42a**, τ_R = 15.95 min.]. $[\alpha]_D^{25}$= +4.4° (*c* = 1.0, $CHCl_3$).



(*R*)-*tert*-Butyl (fluoro(oxo)(*p*-tolyl)- λ^6-sulfaneylidene)carbamate ((*R*)-42a)

Following General Procedure I**,** (*S*)-*tert*-butyl-(*p*-tolylsulfinyl)carbamate (*S*)-**66a** (25.5 mg, 0.10 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*R*)-**42a** as an off-white oil (24.0 mg, 0.087 mmol, 87%, >99% e.e.).

The data were consistent with *tert*-butyl (fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (**42a**). [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 µL injection, (*R*)-**42a**, τ_R = 14.42 min.]. $[\alpha]_D^{25}$= -2.1° (*c* = 1.0, $CHCl_3$).



4-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (70a)

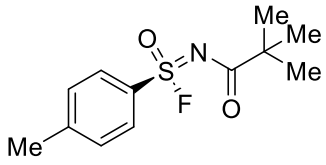
Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(*p*-tolylsulfinyl)pivalamide **69a** (23.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **70a** as an off-white oil (23.2 mg, 0.090 mmol, 90%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(*p*-tolylsulfinyl)pivalamide **69a** (23.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **70a** as an off-white oil (22.1 mg, 0.085 mmol, 85%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, *N*-(*p*-tolylsulfinyl)pivalamide **69a** (23.9 mg, 0.10 mmol), 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **70a** as an off-white oil (20.4 mg, 0.079 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.41 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 2.49 (s, 3H, ArC*H*$_3$), 1.24 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.0, 147.0, 131.8 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 130.3, 128.1, 27.3, 22.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 65.8 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 280.0; **HRMS** (ESI^+, m/z) calculated for $[C_{12}H_{16}FNO_2SNa]^+$ $[M+Na]^+$ 280.0778, found 280.0779 (Δ 0.48 ppm); **IR** υ_{max} (neat)/cm^{-1} 2977, 2925, 1713, 1658, 1595, 1478, 1423, 1375, 1308, 1190, 1084, 861, 814, 655; **R$_F$** 0.44 (Petrol:EtOAc 5:1). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 80:20, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70a**, τ_R = 7.69 min, (*S*)-**70a**, τ_R = 13.0 min].

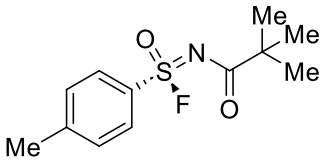
Data is consistent with the literature: S. Greed, O. Symes, J. A. Bull, *Chem. Commun.*,**2022**, *58*, 5387-5390.[109]



(*S*)-4-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride ((*S*)-70a)

Following General Procedure H, (*S*)-*N*-(*p*-tolylsulfinyl)pivalamide (*S*)-**69a** (23.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*S*)-**70a** as an off-white oil (23.0 mg, 0.088 mmol, 88%, >99% e.e.).

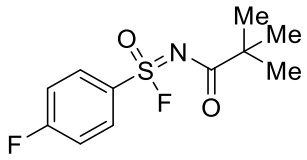
The data were consistent with 4-methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (**70a**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**70a**, τ_R = 12.85 min.]; $[\alpha]_D^{25}$ = -2.1° (*c* = 1.0, $CHCl_3$).



(*R*)-4-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride ((*R*)-70a)

Following General Procedure I**,** (*S*)-*N*-(*p*-tolylsulfinyl)pivalamide (*S*)-**69a** (23.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*R*)-**70a** as an off-white oil (23.4 mg, 0.091 mmol, 88%, 99% e.e.).

The data were consistent with 4-methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (**70a**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**70a**, τ_R = 7.68 min.].



4-Fluoro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70b)

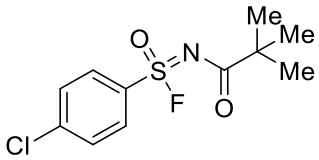
Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-fluorophenyl)sulfinyl)pivalamide **69b** (24.3 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70b** as an off-white oil (22.9 mg, 0.088 mmol, 88%).

Oxidative fluorination (NFSI): Following General Procedure F, using *N*-((4-fluorophenyl)sulfinyl)pivalamide **69b** (24.3 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70b** as an off-white oil (23.6 mg, 0.090 mmol, 90%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, *N*-((4-fluorophenyl)sulfinyl)pivalamide **69b** (24.3 mg, 0.10 mmol), 1-fluoro-1λ^3-

benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70b** as an off-white oil (21.4 mg, 0.082 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 2H, Ar-*H*), 7.35 – 7.28 (m, 2H, Ar-*H*), 1.25 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.7, 166.9 (d, $^1J_{F-C}$ = 259.7 Hz), 131.1 (d, $^3J_{F-C}$ = 10.0 Hz), 117.2 (d, $^2J_{F-C}$ = 23.1 Hz), 42.4, 27.2 [note: missing quaternary C]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.9 (d, *J* = 1.6 Hz, S*F*), -99.7 (tt, *J* = 7.5, 2.3 Hz, Ar-*F*); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 284.0; **HRMS** (ESI^+, m/z) calculated for $[C_{11}H_{13}F_2NO_2SNa]^+$ $[M+Na]^+$ 284.0527, found 284.0526 (Δ -0.30 ppm); **IR** υ_{max} (neat)/cm^{-1} 2977, 1688, 1591, 1460, 1306, 1277, 1244, 1178, 1152, 1012, 839, 703, 666; **R_F** 0.53 (Petrol:EtOAc 5:1).



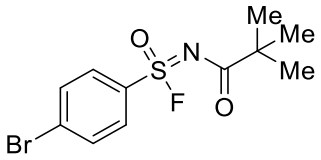
4-Chloro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70c)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-chlorophenyl)sulfinyl)pivalamide **69c** (26.0 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70c** as an off-white oil (22.8 mg, 0.082 mmol, 82%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-((4-chlorophenyl)sulfinyl)pivalamide **69c** (26.0 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70c** as an off-white oil (24.0 mg, 0.087 mmol, 87%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, *N*-((4-chlorophenyl)sulfinyl)pivalamide **69c** (26.0 mg, 0.10 mmol), 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70c** as an off-white oil (23.8 mg, 0.082 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.98 (m, 2H, Ar-*H*), 7.66 – 7.56 (m, 2H, Ar-*H*), 1.24 (app. d, *J* = 8.2 Hz, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.4, 142.1, 130.1, 129.4, 128.6, 42.5, 27.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.5 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 300.0; **HRMS** (ESI^+, m/z) calculated for $[C_{11}H_{13}ClFNO_2SNa]^+$ 300.0232, found 300.0233 (Δ 0.62 ppm); **IR** υ_{max} (neat)/cm^{-1} 2977, 1685, 1576, 1476, 1276, 1157, 1123, 1090; **R_F** 0.45 (Petrol:EtOAc 5:1).

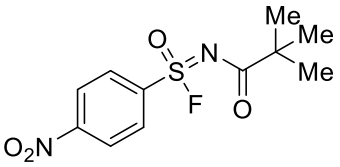


4-Bromo-*N*-pivaloylbenzenesulfonimidoyl fluoride (70d)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-bromophenyl)sulfinyl)pivalamide **69d** (30.4 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70d** as a white solid (28.6 mg, 0.089 mmol, 89%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-((4-bromophenyl)sulfinyl)pivalamide **69d** (30.4 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70d** as a white solid (30.5 mg, 0.095 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H, Ar-*H*), 7.83 – 7.72 (m, 2H, Ar-*H*), 1.24 (app. d, *J* = 8.2 Hz, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.3, 142.1, 133.1, 129.4, 128.6, 42.5, 27.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.4 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 344.0; **IR** υ_{max} (neat)/cm^{-1} 2975, 1685, 1572, 1478, 1275, 1160, 1069, 1010, 749; **R_F** 0.47 (Petrol:EtOAc 5:1).

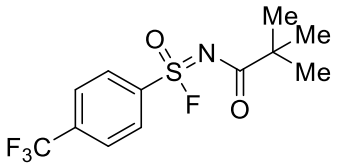


4-Nitro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70e)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-nitrophenyl)sulfinyl)pivalamide **69e** (27.3 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70e** as a yellow oil (18.0 mg, 0.062 mmol, 62%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-((4-nitrophenyl)sulfinyl)pivalamide **69e** (27.3 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70e** as a white solid (21.6 mg, 0.075 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.45 (m, 2H, Ar-*H*), 8.37 – 8.27 (m, 2H, Ar-*H*), 1.26 (d, J = 9.8 Hz, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.1, 148.0, 129.5, 128.7, 125.0 (d, $^2J_{CF}$ = 18.8 Hz), 42.6, 27.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.3 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 311.1; **R_F** 0.43 (Petrol:EtOAc 5:1).

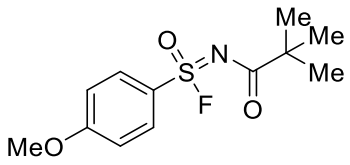


***N*-Pivaloyl-4-(trifluoromethyl)benzenesulfonimidoyl fluoride (70f)**

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-(trifluoromethyl)phenyl)sulfinyl)pivalamide **69f** (29.3 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70f** as a white solid (29.5 mg, 0.095 mmol, 95%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-((4-(trifluoromethyl)phenyl)sulfinyl)pivalamide **69f** (29.3 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70f** as a white solid (27.2 mg, 0.087 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 2H, Ar-*H*), 7.96 – 7.87 (m, 2H, Ar-*H*), 1.26 (d, *J* = 8.7 Hz, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.3, 146.4, 136.6 (q, $^2J_{C\text{-}F}$ = 33.6 Hz), 127.1 (q, $^4J_{C\text{-}F}$ = 3.9 Hz), 122.9 (q, $^1J_{C\text{-}F}$ = 273.4 Hz), 42.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 27.2.; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.0 (s, S*F*), -63.4 (s, C*F*$_3$); **LRMS (ESI)** m/z (ESI+) $[M+H]^+$: 312.3; **IR** υ_{max} (neat)/cm^{-1} 2980, 1689, 1407, 1325, 1179, 1144, 1064; **R_F** 0.44 (Petrol:EtOAc 5:1).



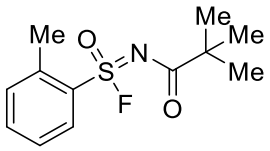
4-Methoxy-*N*-pivaloylbenzenesulfonimidoyl fluoride (70g)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-((4-methoxyphenyl)sulfinyl)pivalamide **69g** (25.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70g** as a white solid (20.1 mg, 0.074 mmol, 74%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-((4-methoxyphenyl)sulfinyl)pivalamide **69g** (25.5 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70g** as a white solid (25.0 mg, 0.091 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H, Ar-*H*), 7.09 – 7.04 (m, 2H, Ar-*H*), 3.92 (s, 3H, OC*H*$_3$), 1.24 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.0, 165.2, 130.5, 125.8, 114.9, 56.1, 27.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 67.0; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 296.0; **R_F** 0.41 (Petrol:EtOAc 5:1).

Data is consistent with the literature: S. Greed, O. Symes, J. A. Bull, *Chem. Commun.*,**2022**, *58*, 5387-5390.[109]

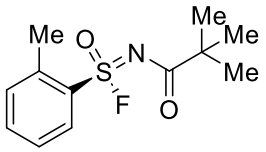


2-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (70h)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(*o*-tolylsulfinyl)pivalamide **69h** (23.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70h** as an off-white oil (20.1 mg, 0.078 mmol, 78%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(*o*-tolylsulfinyl)pivalamide **69h** (23.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70h** as a white solid (20.6 mg, 0.080 mmol, 80%).

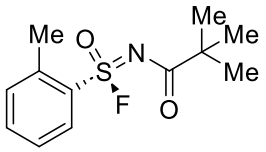
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.61 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-*H*), 7.45 – 7.39 (m, 2H, Ar-*H*), 2.77 – 2.69 (app. m, 3H, Ar-CH_3), 1.23 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.9, 138.7, 135.1, 133.9 (d, $^2J_{CF}$ = 19.1 Hz), 133.1, 129.5, 126.7, 42.3, 27.2, 20.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 58.6 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 280.0; **HRMS** (ESI^+, m/z) calculated for $[C_{12}H_{17}FNO_2S]^+$ $[M+H]^+$ 258.0959, found 258.0959 (Δ 0.01 ppm); **IR** υ_{max} (neat)/cm^{-1} 2976, 1680, 1459, 1310, 1275, 1176, 1158, 845, 720, 703, 684; **R_F** 0.45 (Petrol:EtOAc 5:1). **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70h**, τ_R = 12.1 min, (*S*)-**70h**, τ_R = 13.75 min.].



(*S*)-2-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride ((*S*)-70h)

Following General Procedure H, (*S*)-*N*-(*o*-tolylsulfinyl)pivalamide (*S*)-**69h** (23.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*S*)-**70h** as an off-white oil (19.5 mg, 0.076 mmol, 76%, 99% e.e.).

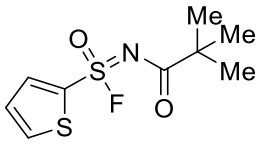
The data were consistent with 2-methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (**70h**) [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**70h**, τ_R = 14.09 min.].



(*R*)-2-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride ((*R*)-70h)

Following General Procedure I, (*S*)-*N*-(*o*-tolylsulfinyl)pivalamide (*S*)-**69h** (23.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride (*R*)-**70h** as an off-white oil (22.3 mg, 0.080 mmol, 80%, 99% e.e.).

The data were consistent with 4-methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (**70h**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70h**, τ_R = 12.32 min.].

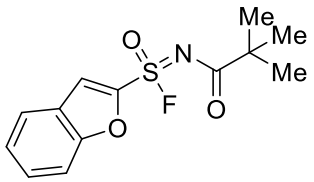


_N_-Pivaloylthiophene-2-sulfonimidoyl fluoride (70i)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(thiophen-2-ylsulfinyl)pivalamide **69i** (23.1 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70i** as a crystalline off-white solid (22.4 mg, 0.090 mmol, 90%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(thiophen-2-ylsulfinyl)pivalamide **69i** (23.1 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70i** as a crystalline off-white solid (21.8 mg, 0.087 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 4.0, 1.5, 0.7 Hz, 1H, Ar-*H*), 7.82 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar-*H*), 7.21 (dd, *J* = 5.1, 3.9 Hz, 1H, Ar-*H*), 1.25 (d, *J* = 0.7 Hz, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.3, 142.9, 136.2, 135.1, 128.3, 42.3, 27.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 74.0 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 272.0; **IR** υ_{max} (neat)/cm^{-1} 3302, 1702, 1479, 1421, 138, 1178,1122, 1097, 1026, 869,797, 737; **M.p.** 109-110 °C ($CHCl_3$); **R_F** 0.30 (Petrol:EtOAc 9:1).



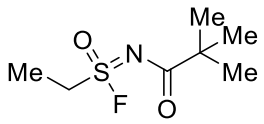
_N_-Pivaloylbenzofuran-2-sulfonimidoyl fluoride (70j)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(benzofuran-2-sulfinyl)pivalamide **69j** (26.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2,

Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70j** as an off-white oil (27.0 mg, 0.095 mmol, 95%).

Oxidative fluorination (NFSI): Following General Procedure F, using *N*-(benzofuran-2-sulfinyl)pivalamide **69j** (26.5 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (Petrol:EtOAc 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70j** as an off-white oil (26.2 mg, 0.093 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.73 (dd, *J* = 1.5, 0.9 Hz, 1H, Ar-*H*), 7.67 – 7.56 (m, 2H, Ar-*H*), 7.43 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, Ar-*H*), 1.27 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.1, 156.7, 144.0 (d, *J* = 34.2 Hz), 129.7, 125.4, 125.2, 123.7, 117.4 (d, *J* = 2.5 Hz), 112.9, 42.5, 27.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 65.8 (d, *J* = 1.5 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{13}H_{15}FNO_3S]^+$ $[M+H]^+$ 284.0751, found 284.0751 (Δ 0.02 ppm); **IR** υ_{max} (neat)/cm^{-1} 2977. 1695. 1336. 1278, 1194, 1176, 785, 728; **R$_F$** 0.35 (Petrol:EtOAc 9:1).



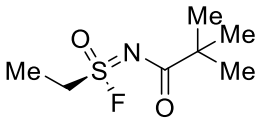
***N*-Pivaloylethanesulfonimidoyl fluoride (70k)**

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(ethylsulfinyl)pivalamide **69k** (17.7 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70k** as an off-white oil (15.6 mg, 0.080 mmol, 80%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(ethylsulfinyl)pivalamide **69k** (17.7 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70k** as an off-white oil (14.0 mg, 0.072 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 – 3.70 (m, 2H, C*H*$_2$), 1.62 (t, *J* = 7.3 Hz, 3H, C*H*$_3$), 1.20 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.2 (C=O), 49.1 (*C*H$_2$), 39.9 (*C*(CH$_3$)$_3$), 29.7

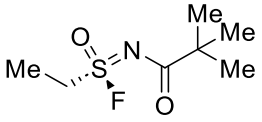
($C(CH_3)_3$), 6.6 (CH_2CH_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ 49.4 (d, *J* = 4.0 Hz); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 218.0; **IR** υ_{max} (neat)/cm^{-1} 3283, 2980, 2931, 2873, 1710, 1522, 1479, 1401, 1330, 1166, 1107, 862, 798, 712; **R_F** 0.50 (Petrol:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 70:30, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70k**, τ_R = 9.12 min, (*S*)-**70k**, τ_R = 14.15 min.].



(*S*)-*N*-Pivaloylpropane-2-sulfonimidoyl fluoride ((*S*)-70k)

Following General Procedure H, (*S*)-*N*-(ethylsulfinyl)pivalamide (*S*)-**69k** (17.7 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (Petrol:EtOAc 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*S*)-**70k** as an off-white oil (16.4 mg, 0.084 mmol, 84%, >99% e.e.).

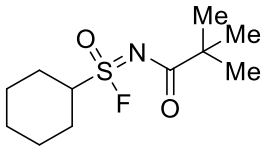
The data were consistent with *N*-pivaloylethanesulfonimidoyl fluoride (**70k**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**70k**, τ_R = 14.40 min.].



(*R*)-*N*-Pivaloylethanesulfonimidoyl fluoride ((*R*)-70k)

Following General Procedure I**,** (*S*)-*N*-(ethylsulfinyl)pivalamide (*S*)-**69k** (17.7 mg, 0.10 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Purification by flash column chromatography (Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*R*)-**70k** as an off-white oil (15.9 mg, 0.082 mmol, 82%, 99% e.e.).

The data were consistent with *N*-pivaloylethanesulfonimidoyl fluoride (**70k**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70k**, τ_R = 9.90 min.].

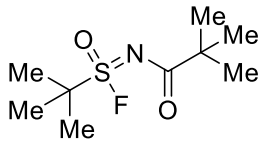


_N_-Pivaloylcyclohexanesulfonimidoyl fluoride (70l)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(cyclohexylsulfinyl)pivalamide **69l** (23.1 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70l** as an off-white oil (22.8 mg, 0.091 mmol, 91%).

Oxidative fluorination (NFSI): Following General Procedure F, using *N*-(cyclohexylsulfinyl)pivalamide **69l** (23.1 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70l** as an off-white oil (21.9 mg, 0.088 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, tt, *J* = 12.1, 3.5 Hz, AlkC*H*), 2.35 – 2.16 (2H, m, AlkCH_2), 2.01 – 1.90 (2H, m, AlkCH_2), 1.79 – 1.70 (2H, m, AlkCH_2), 1.70 – 1.61 (1H, m, AlkC*H*), 1.44 – 1.22 (3H, m, 3 x AlkC*H*), 1.19 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.6, 62.7, 42.3, 27.3, 26.4, 26.2, 25.0, 24.9, 24.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 40.6 (d, *J* = 2.0 Hz); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 272.1; **HRMS** (ESI^+, m/z) calculated for $[C_{10}H_{22}FNO_2SNa]^+$ $[M+Na]^+$ 272.1091, found 272.1090 (Δ-0.33 ppm); **IR** υ_{max} (neat)/cm^{-1} 2977, 2863, 1686, 1480, 1453, 1308, 1284, 1229, 1193, 843, 824, 795, 711; **R_F** 0.55 (Petrol:EtOAc 5:1).



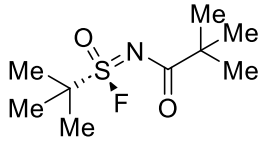
2-Methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride (70m)

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(*tert*-butylsulfinyl)pivalamide **69m** (20.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc

10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70m** as an off-white oil (4.7 mg, 0.021 mmol, 21%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(*tert*-butylsulfinyl)pivalamide **69m** (20.5 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **70m** as an off-white oil (18.1 mg, 0.080 mmol, 80%).

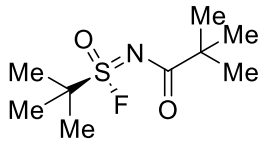
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H, C(C*H*$_3$)$_3$S), 1.19 (s, 9H, C(C*H*$_3$)$_3$C(=O)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.2 (d, $^2J_{FC}$ = 10.7 Hz), 42.3, 27.2, 24.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 29.6 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 246.0; **R_F** 0.31 (Petrol:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 85:15, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70m**, τ_R = 6.22 min, (*S*)-**70m**, τ_R = 7.18 min.].



(*R*)-2-Methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride ((*R*)-70m)

Following General Procedure H, (*R*)-*N*-(*tert*-Butylsulfinyl)pivalamide (*R*)-**69m** (20.5 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*R*)-**70m** as an off-white oil (4.7 mg, 0.021 mmol, 21%, >99% e.e.).

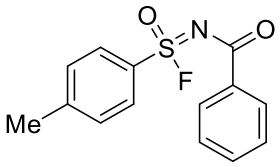
The data were consistent with 2-methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride (**70m**) [Chiralpak IC, hexane:*i*PrOH 85:15, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**70m**, τ_R = 6.25 min.]. $[\alpha]_D^{25}$= -1.4° (*c* = 1.0, $CHCl_3$).



(*S*)-2-Methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride ((*S*)-70m)

Following General Procedure I**,** (*R*)-*N*-(*tert*-Butylsulfinyl)pivalamide (*R*)-**69m** (20.5 mg, 0.10 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*S*)-**70m** as an off-white oil (18.0 mg, 0.080 mmol, 91%, 99% e.e.).

The data were consistent with 2-methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride (**70m**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**70m**, τ_R = 7.18 min.]. $[\alpha]_D^{25}$= +2.2° (*c* = 1.0, $CHCl_3$).



***N*-Benzoyl-4-methylbenzenesulfonimidoyl fluoride 42e**

Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(*p*-tolylsulfinyl)benzamide **66e** (25.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42e** as an off-white oil (24.6 mg, 0.089 mmol, 89%).

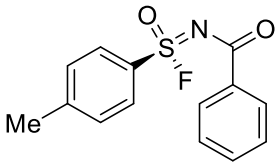
Oxidative fluorination (NFSI): Following General Procedure F, using *N*-(*p*-tolylsulfinyl)benzamide **66e** (25.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42e** as an off-white oil (24.4 mg, 0.088 mmol, 88%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, using *N*-(*p*-tolylsulfinyl)benzamide **66e** (25.9 mg, 0.10 mmol), 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-

3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **42e** as an off-white oil (22.2 mg, 0.080 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 8.3, 1.1 Hz, 2H, Ar-*H*), 8.09 – 8.04 (m, 2H, Ar-*H*), 7.62 – 7.54 (m, 1H, Ar-*H*), 7.51 – 7.41 (m, 4H, Ar-*H*), 2.51 (d, *J* = 0.9 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 147.3, 133.3, 130.4, 130.1, 129.9, 128.5, 128.2, 127.3, 22.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 65.3 (s); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 300.0; **HRMS** (ESI^+, m/z) calculated for $[C_{10}H_{22}FNO_2SNa]^+$ $[M+Na]^+$ 300.0465, found 300.0465 (Δ 0.08 ppm); **IR** υ_{max} (neat)/cm^{-1} 3066, 2976, 2929, 1688, 1597, 1378, 1284, 1272, 1174, 762, 684, 655; **R_F** 0.53 (Petrol:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**42e**, τ_R = 32.40 min, (*S*)-**42e**, τ_R = 15.20 min.].

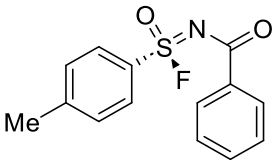
Data is consistent with the literature: R. Kowalczyk, A. J. F. Edmunds, R. G. Hall, C. Bolm. *Org. Lett.* **2011**, *13*, 768-771.[113]



(*S*)-*N*-Benzoyl-4-methylbenzenesulfonimidoyl fluoride (*S*)-42e

Following General Procedure H, (*S*)-*N*-(*p*-tolylsulfinyl)benzamide (*S*)-**66e** (25.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*S*)-**42e** as an off-white oil (25.1 mg, 0.091 mmol, 91%, >99% e.e.).

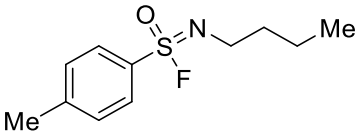
The data were consistent with *N*-benzoyl-4-methylbenzenesulfonimidoyl fluoride (**42e**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*S*)-**42e**, τ_R = 15.52 min.].



(*R*)-*N*-Benzoyl-4-methylbenzenesulfonimidoyl fluoride (*R*)-42e

Following General Procedure I, (*S*)-*N*-(*p*-tolylsulfinyl)benzamide (*S*)-**66e** (25.9 mg, 0.10 mmol), K_2CO_3 (16.6 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride (*R*)-**42e** as an off-white oil (23.3 mg, 0.084 mmol, 84%, >99% e.e.).

The data were consistent with *N*-benzoyl-4-methylbenzenesulfonimidoyl fluoride (**42e**) [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**42e**, τ_R = 32.1 min.].



***N*-Butyl-4-methylbenzenesulfonimidoyl fluoride (42f)**

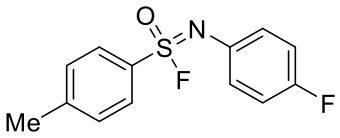
Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-butyl-4-methylbenzenesulfinamide **66f** (21.1 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42f** as an off-white oil (18.1 mg, 0.079 mmol, 79%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-butyl-4-methylbenzenesulfinamide **66f** (21.1 mg, 0.10 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42f** as an off-white oil (20.2 mg, 0.088 mmol, 88%).

Oxidative fluorination (fluoro-iodane 67b): Following General Procedure G, *N*-butyl-4-methylbenzenesulfinamide **66f** (21.1 mg, 0.10 mmol), 1-fluoro-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one **67b** (31.9 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL). Flash

column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **42f** as an off-white oil (16.2 mg, 0.070 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H, Ar-*H*), 7.36 – 7.30 (m, 2H, Ar-*H*), 3.52 – 3.40 (m, 2H, AlkC*H*$_2$), 2.45 (s, 3H, Ar-C*H*$_3$), 1.71 – 1.59 (m, 2H, AlkC*H*$_2$), 1.51 – 1.38 (m, 2H, AlkC*H*$_2$), 0.95 (t, *J* = 7.3 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 129.8, 127.7, 127.3, 43.1, 34.0, 31.8, 20.2, 13.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 85.6 (t, *J* = 8.0 Hz); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 252.0; **IR** υ_{max} (neat)/cm^{-1} 3290, 2960, 2932, 2873, 1599, 1424, 1401, 1160, 1093, 892, 814, 659; **R_F** 0.27 (Petrol:EtOAc 5:1).



***N*-(4-Fluorophenyl)-4-methylbenzenesulfonimidoyl fluoride (42g)**

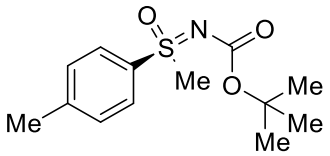
Oxidative chlorination/halogen exchange: Following General Procedure E, *N*-(4-fluorophenyl)-4-methylbenzenesulfinamide **66g** (24.9 mg, 0.10 mmol), NCS (14.7 mg, 0.11 mmol) and KHF_2 (7.97 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42g** as an off-white oil (21.0 mg, 0.079 mmol, 79%).

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(4-fluorophenyl)-4-methylbenzenesulfinamide **66g** (24.9 mg, 0.10 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol) and NFSI (34.7 mg, 0.11 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc 10:1 to 5:1) afforded the desired sulfonimidoyl fluoride **42g** as an off-white oil (20.7 mg, 0.077 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H, Ar-*H*), 7.42 – 7.38 (m, 2H, Ar-*H*), 7.24 – 7.18 (m, 2H, Ar-*H*), 7.05 – 6.96 (m, 2H, Ar-*H*), 2.48 (s, 3H, Ar-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.0, 130.1, 128.0, 125.3, 116.2, 116.0, 21.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ 81.5 (S*F*, d, *J* = 16.0 Hz), -119.0 (tt, *J* = 8.0, 4.5, 2.5 Hz, Ar*F*); **LRMS** (ESI^+, m/z) $[M+Na]^+$: 268.0; **HRMS** (ESI^+, m/z) calculated for $[C_{13}H_{12}F_2NOS]^+$ $[M+H]^+$ 268.0602, found 268.0605 (Δ 1.23 ppm); **IR** υ_{max} (neat)/cm^{-1} 2925, 1505, 1448, 1362, 1306, 1257, 1218, 1120, 836, 730; **R_F** 0.57

(Petrol:EtOAc 5:1); **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 95:5, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**42g**, τ_R = 32.40 min, (*S*)-**42g**, τ_R = 15.20 min.].

6.2.1.6 Derivatisations of sulfonimidoyl fluorides



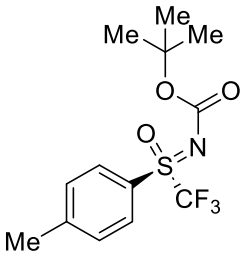
***tert*-Butyl (*R*)-(methyl(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate ((*R*)-(24e))**

According to a modified procedure by Johnson *et al.*,[111] *tert*-butyl (*R*)-(fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (*R*)-**42a** (27.3 mg, 0.10 mmol, 1.0 equiv.) was dissolved in THF (0.5 mL, 0.2 M) and cooled to -78 °C. MeLi (125 μL, 0.20 mmol, 1.60 M in Et_2O, 2.0 equiv.) was added dropwise and the resultant solution stirred at the same temperature for 15 min. The reaction mixture was diluted with EtOAc (5 mL) and quenched with saturated aqueous solution of EDTA tetrasodium salt (5mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 5:1 to 1:1) afforded the desired sulfoximine (*R*)-**24e** as a white solid (16.2 mg, 0.60 mmol, 60%, 98% e.e.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H, Ar-*H*), 7.41 – 7.35 (m, 2H, Ar-*H*), 3.21 (s, 3H, C*H*$_3$), 2.45 (s, 3H, Ar-C*H*$_3$), 1.38 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 145.0, 135.9, 130.4, 127.6, 80.7, 45.2, 28.2, 21.7; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 292.1; **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**24e**, τ_R = 15.1 min.].

Data is consistent with the literature: S. Greed, O. Symes, J. A. Bull, *Chem. Commun.*,**2022**, *58*, 5387-5390.[109]

The racemic sample was prepared using *tert*-butyl-(fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate **42a** on the same scale (0.10 mmol), affording the desired sulfoximine **24e** as a white solid (16.3 mg, 0.61 mmol, 61%). The data were consistent with *tert*-butyl (*R*)-(fluoro(oxo)(*p*-tolyl)- λ^6-sulfaneylidene)carbamate **24e**: **Chiral HPLC [**Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**24e** τ_R = 15.23 min; (*S*)-**24e**, τ_R = 9.05 min.].



tert-Butyl (_R_)-(methyl(oxo)(_p_-tolyl)-λ^6-sulfaneylidene)carbamate ((_R_)-(27c))

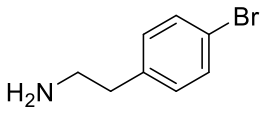
According to a modified procedure by Kowalczyk *et al.*,[113] $TMSCF_3$ (2 M solution in THF, 2.0 equiv) was added to *tert*-butyl (*R*)-(fluoro(oxo)(*p*-tolyl)- λ^6-sulfaneylidene)carbamate (*R*)-**42a** (27.3 mg, 0.10 mmol, 1.0 equiv.) under argon at room temperature. The mixture was stirred for 10 min, cooled to 0 °C and stirred for 10 min. TBAF (0.050 mL, 0.05 mmol, 1.0 M solution in THF, 0.5 equiv.) was added slowly by syringe resulting in a rapid reaction with bubbling. The reaction was stirred at the same temperature for 30 min before warming to room temperature. After stirring for a further 18 h at room temperature, the reaction mixture was subjected directly to flash column chromatography (SiO_2, CH_2Cl_2:pentane = 1:1) affording the desired sulfoximine (*R*)-**27c** as a white solid (24.1 mg, 0.075 mmol, 75%, 98% e.e.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.8, 2.2 Hz, 2H, Ar-*H*), 7.50 – 7.44 (m, 2H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$), 1.43 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 148.0, 130.8, 130.5, 128.3, 120.5 (q, $^1J_{C\text{-}F}$ = 322.4 Hz), 82.5, 27.9, 22.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.8 (s); **LRMS** (ESI$^+$, m/z) [M+Na]$^+$: 346.1; **Chiral HPLC** [Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**27c**, τ_R = 15.1 min, (*S*)-**27c**, τ_R = 9.55 min].

The racemic sample was prepared using *tert*-butyl-(fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate **42a** on the same scale (0.10 mmol), affording the desired sulfoximine **27c** as a white solid (16.3 mg, 0.61 mmol, 61%). The data were consistent with *tert*-butyl (*R*)-(fluoro(oxo)(*p*-tolyl)- λ^6-sulfaneylidene)carbamate (*R*)-**27c**: **Chiral HPLC [**Chiralpak IC, hexane:*i*PrOH 90:10, flow rate 1.0 mL/min, 25 °C, λ = 250 nm, 10 μL injection, (*R*)-**27c**, τ_R = 15.23 min; (*S*)-**27c**, τ_R = 9.05 min].

Data is consistent with the literature: R. Kowalczyk, A. J. F. Edmunds, R. G. Hall, C. Bolm. *Org. Lett.* **2011**, *13*, 768-771.[113]

6.2.1.7 Preparation of probe compounds



2-(4-Bromophenyl)ethan-1-amine (80)

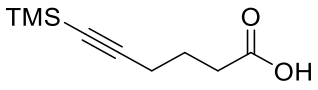
Following a modified procedure by Runyon *et al.*,[433] to a cooled solution of 4-bromophenylacetonitrile **79** (5.00 g, 25.5 mmol, 1.0 equiv.) in THF (26 mL, 1.0 M) at 0 °C, was added borane tetrahydrofuran complex solution (1 M solution, 51.0 mL, 2.0 equiv.) dropwise over 30 min. The reaction mixture was warmed to room temperature and then heated to 70 °C for 24 h. The reaction mixture was cooled to 0 °C, and quenched by slow addition of MeOH (12.5 mL) and 6 M HCl (12.5 mL). The reaction mixture was then heated at 70 °C for another 4 h, cooled to room temperature and concentrated *in vacuo*. This residue was diluted with H_2O (75 mL) and washed with EtOAc (2 × 18 mL), with the EtOAc layers discarded. The aqueous layer was basified with 1 M NaOH and extracted with EtOAc (3 × 18 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil that required no further purification (4.31 g, 21.7 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.07 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 2.94 (t, *J* = 6.7 Hz, 2H, $ArCH_2CH_2NH_2$), 2.69 (t, *J* = 6.8 Hz, 2H, $ArCH_2CH_2NH_2$), 1.27 (2H, br. s, NH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.0, 131.6, 130.7, 120.1, 43.5, 39.6; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 200.0; **R_F** 0.34 (Petrol:EtOAc 1:1).

Data is consistent with the literature: M. Szostak, B. Sautier, M. Spain, D. J. Procter. *Org. Lett.* **2014**, *16*, 1092–1095.[434]

Notes

1) Slow addition of MeOH/6 M HCl essential as strongly exothermic reaction with significant effervescence.
2) Basification of aqueous layer is essential with significant drop in yield if pH <8.
3) Drying over Na_2SO_4 is much more preferable than $MgSO_4$, which resulted in white suspension and decrease in yield.

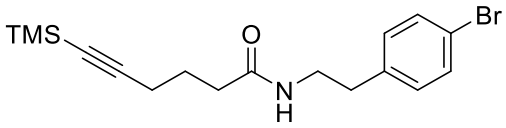


6-(Trimethylsilyl)hex-5-ynoic acid (81)

Following a procedure by Buckl *et al.*,[435] a solution of hex-5-ynoic acid **S7** (1.10 mL, 10.0 mmol, 1.0 equiv.) in THF (100 mL, 0.1 M) was cooled to -78 °C. To the colourless solution *n*-BuLi (8.40 mL, 21.0 mmol, 2.1 equiv., 2.50 M in hexanes,) was added dropwise over 15 min. The resulting yellow mixture was stirred for 30 min before chlorotrimethylsilane (2.90 mL, 22.8 mmol, 2.28 equiv.) was added dropwise at -78 °C and stirred for 90 min at this temperature. The colourless solution was warmed to room temperature and stirred for 4 h. To this was added AcOH (10%, 30 mL) and the mixture was stirred vigorously for 20 min. The reaction mixture was transferred to a separating funnel and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1) afforded the desired acid **81** as a colourless oil (1.75 g, 9.50 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (t, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 2.32 (t, *J* = 6.9 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 1.85 (app. h, *J* = 7.1 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 0.14 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.4, 105.8, 85.9, 32.8, 23.5, 19.3, 0.2; **LRMS** (ESI^+, m/z) $[M+H]^+$: 185.0; **IR** υ_{max} (neat)/cm^{-1} 2959, 2175, 1708, 1413, 1249, 1047, 841, 760, 638; **R_F** 0.46 (Petrol:EtOAc 4:1).

Data is consistent with the literature: B. M. Trost, K. Lehr, D. J. Michaelis, J. Xu, A. K. Buckl. *J. Am. Chem. Soc.* **2010**, *132*, 8915 – 8917.[435]



***N*-(4-Bromophenethyl)-6-(trimethylsilyl)hex-5-ynamide (78)**

Using HOBt procedure (step B): Following a modified procedure by Liu *et al.*,[436] to a solution of EDC·HCl (1.38 g, 7.18 mmol, 1.5 equiv.) and HOBt (0.906 g, 6.70 mmol, 1.4 equiv.) in CH_2Cl_2 (12 mL, 0.4 M conc. of acid), was added a solution of 6-(trimethylsilyl)hex-5-ynoic acid **81** (881 mg, 4.78 mmol, 1.0 equiv.) in DCM (6.0 mL, 0.8 M conc. of acid), followed by a solution of 2-(4-bromophenyl)ethan-1-amine **80** (1.437 g, 7.18 mmol, 1.5 equiv.) in CH_2Cl_2 (6.0 mL, 0.8 M). On cooling to 0 °C, Et_3N (2.00 mL, 14.4 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 16 h at this temperature. The reaction mixture was transferred to a separating funnel, diluted with DCM (30 mL) and the layers were separated. The organic layer was washed successively with H_2O (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as an off-white solid. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1 to 1:1) afforded amide **78** as a white solid (1.17 g, 3.20 mmol, 67%).

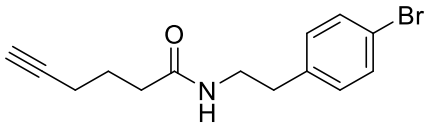
[*Note:* reaction performed on 2x scale (14.36 mmol) with comparable yield obtained (69%)]

Using DMAP procedure (step C): To a solution of 6-(trimethylsilyl)hex-5-ynoic acid **81** (3.26 g, 17.7 mmol, 1.0 equiv.) in CH_2Cl_2 (88 mL, 0.2 M), was added 2-(4-bromophenyl)ethan-1-amine **80** (4.092 g, 20. 5 mmol, 1.1 equiv.), EDC·HCl (3.387 g, 17.7 mmol, 1.0 equiv.) and DMAP (540 mg, 4.42 mmol, 0.25 equiv.) at room temperature. The resultant reaction mixture was stirred for 16 h at the same temperature. The reaction mixture was transferred to a separating funnel, diluted with DCM (30 mL) and the layers were separated. The organic layer was washed successively with H_2O (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1 to 1:1) afforded amide **78** as a white solid (3.88 g, 10.6 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.05 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 5.62 (t, *J* = 6.0 Hz, 1H, N-*H*), 3.46 (td, *J* = 7.0, 5.9 Hz, 2H, $CH_2CH_2CH_2CONHR$), 2.75 (t,

J = 7.0 Hz, 2H, $ArCH_2CH_2NH_2$), 2.23 (t, J = 7.1 Hz, 4H, $ArCH_2CH_2NH_2$ + $CH_2CH_2CH_2CONHR$), 1.80 (dt, J = 7.9, 6.9 Hz, 2H, $CH_2CH_2CH_2CONHR$), 0.12 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 137.9, 131.8, 130.6, 120.5, 106.3, 85.6, 40.5, 35.3, 35.2, 24.4, 19.3, 0.2; **HRMS** (ESI^+, m/z) calculated for $[C_{17}H_{26}NO_2{}^{79}BrSi]^+$ $[M+H]^+$ 366.0883, found 366.0885 (Δ 0.38 ppm), calculated for $[C_{17}H_{26}NO_2{}^{81}BrSi]^+$ $[M+H]^+$ 368.0863, found 368.0863; **M.p.** 84-85 °C (CH_2Cl_2); **IR** υ_{max} (neat)/cm^{-1} 3273, 2960, 2902, 2174, 1643, 1555, 1489, 1249, 1012, 842, 760, 636; **R_F** 0.40 (Petrol:EtOAc 1:1).

Des-TMS product isolated from above procedure or through analogous reaction with hex-5-ynoic acid (detailed below):



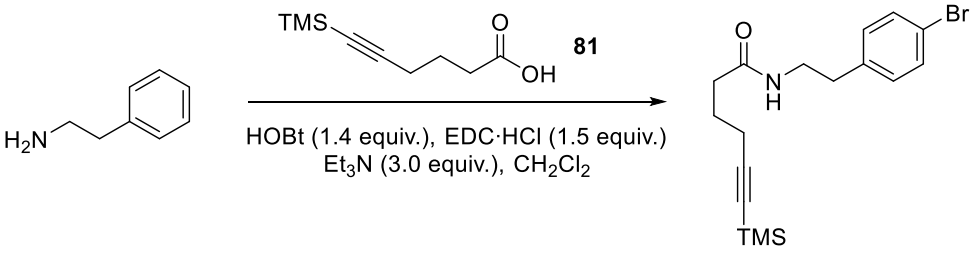
***N*-(4-Bromophenethyl)hex-5-ynamide (S8)**

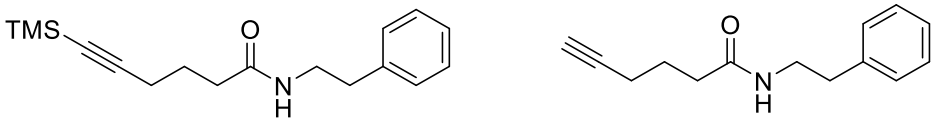
Using reaction conditions above (HOBt procedure, step B, 4.78 mmol scale): Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1 to 1:1) afforded amide **S8** as a white solid (284.3 mg, 0.97 mmol, 20%).

Using HOBt procedure (step B) with hex-5-ynoic acid: Following a modified procedure by Liu *et al.*,[436] to a solution of EDC·HCl (688 mg, 3.59 mmol, 1.5 equiv.) and HOBt (453 mg, 3.35 mmol, 1.4 equiv.) in CH_2Cl_2 (6.0 mL, 0.4 M conc. of acid), was added a solution of hex-5-ynoic acid **S7** (264 μL, 2.39 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL, 0.8 M conc. of acid), followed by a solution of 2-(4-bromophenyl)ethan-1-amine **80** (713 mg, 3.58 mmol, 1.5 equiv.) in CH_2Cl_2 (3 mL, 0.8 M). On cooling to 0 °C, Et_3N (1.00 mL, 7.18 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 16 h at this temperature. The reaction mixture was transferred to a separating funnel, diluted with DCM (15 mL) and the layers were separated. The organic layer was washed successively with H_2O (10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as an off-white solid. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1 to 1:1) afforded amide **S8** as a white solid (190.2 mg, 0.65 mmol, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H, Ar-*H*), 7.04 – 7.00 (m, 2H, Ar-*H*), 6.00 (t, *J* = 6.0 Hz, 1H, N-*H*), 3.42 (td, *J* = 7.1, 5.9 Hz, 2H, Alk-H_2), 2.73 (t, *J* = 7.1 Hz, 2H, Alk-H_2), 2.23 (t, *J* = 7.4 Hz, 2H, Alk-H_2), 2.17 (td, *J* = 6.9, 2.7 Hz, 2H, Alk-H_2), 1.93 (t, *J* = 2.6 Hz, 1H, C-*H*), 1.83 – 1.71 (m, 2H, Alk-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 137.9, 131.6, 130.5, 120.3, 83.5, 69.3, 40.4, 35.1, 34.9, 24.2, 17.8; **HRMS** (ESI^+, m/z) calculated for $[C_{14}H_{16}NO^{79}BrNa]^+$ $[M+Na]^+$ 316.0308, found 316.0312 (Δ 1.42 ppm), calculated for $[C_{14}H_{16}NO^{81}BrNa]^+$ $[M+Na]^+$ 318.0287, found 318.0288(Δ 0.10 ppm); **M.p.** 97 - 99 °C (DCM); **IR** υ_{max} (neat)/cm^{-1} 3276, 3246, 2960, 2250, 1636, 1591, 1488, 1253, 1037, 911, 736.

Related products from reaction of des-bromo starting material for comparative purposes and analysis of crude reaction mixtures:

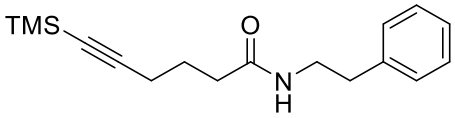




***N*-Phenethyl-6-(trimethylsilyl)hex-5-ynamide (S9)** and ***N*-Phenethylhex-5-ynamide (S10)**

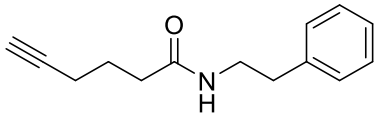
Using HOBt procedure (step B): Following a modified procedure by Liu *et al.*,[436] to a solution of EDC·HCl (1.38 g, 7.18 mmol, 1.5 equiv.) and HOBt (0.906 g, 6.70 mmol, 1.4 equiv.) in CH_2Cl_2 (12 mL, 0.4 M conc. of acid), was added a solution of 6-(trimethylsilyl)hex-5-ynoic acid **81** (881 mg, 4.78 mmol, 1.0 equiv.) in CH_2Cl_2 (6.0 mL, 0.8 M conc. of acid), followed by a solution of 2-phenylethan-1-amine (870.1 mg, 7.18 mmol, 1.5 equiv.) in CH_2Cl_2 (6.0 mL, 0.8 M). On cooling to 0 °C, Et_3N (2.00 mL, 14.36 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for 16 h at this temperature. The reaction mixture was transferred to a separating funnel, diluted with CH_2Cl_2 (30 mL) and the layers were

separated. The organic layer was washed successively with H_2O (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as an off-white solid. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1 to 1:1) afforded *N*-phenethyl-6-(trimethylsilyl)hex-5-ynamide **(S9)** as a white solid (801.0 mg, 2.79 mmol, 58%) and *N*-Phenethylhex-5-ynamide **(S10)** as a white solid (251.4 mg, 1.17 mmol, 24%).



***N*-Phenethyl-6-(trimethylsilyl)hex-5-ynamide (S9)**

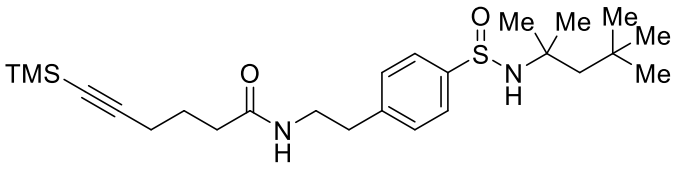
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H, Ar-*H*), 7.25 – 7.22 (m, 1H, Ar-*H*), 7.21 – 7.17 (m, 2H, Ar-*H*), 5.65 (br. s, 1H, N-*H*), 3.52 (q, *J* = 6.6 Hz, 2H, Alk-H_2), 2.81 (t, *J* = 7.0 Hz, 2H, Alk-H_2), 2.25 (td, *J* = 7.2, 2.4 Hz, 4H, Alk-H_2), 1.86 – 1.75 (m, 2H, Alk-H_2), 0.13 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 138.9, 128.8, 126.6, 106.3, 85.6, 40.7, 35.8, 35.3, 24.5, 19.4, 0.3; **HRMS** (ESI^+, m/z) calculated for $[C_{17}H_{25}NO_2SiNa]^+$ $[M+Na]^+$ 310.1598, found 310.1605 (Δ 2.36 ppm); **M.p.** 61-63 °C (CH_2Cl_2); **IR** υ_{max} (neat)/cm^{-1} 3292, 2960, 2175, 1645, 1553, 1249, 842, 760, 669.



***N*-Phenethylhex-5-ynamide (S10)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (tt, *J* = 7.0, 1.1 Hz, 2H, Ar-*H*), 7.10 – 7.03 (m, 1H, Ar-*H*), 7.05 – 7.01 (m, 2H, Ar-*H*), 6.22 (t, *J* = 5.9 Hz, 1H, N-*H*), 3.33 (td, *J* = 7.2, 5.8 Hz, 2H, Alk-H_2), 2.66 (t, *J* = 7.2 Hz, 2H, Alk-H_2), 2.11 (t, *J* = 7.3 Hz, 2H, Alk-H_2), 2.04 (td, *J* = 6.9, 2.7 Hz, 2H, Alk-H_2), 1.81 (t, *J* = 2.6 Hz, 1H, C-*H*), 1.66 (pd, *J* = 7.2, 3.7 Hz, 2H, Alk-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 138.8, 128.6, 128.4, 126.3, 83.4, 69.1, 40.6, 35.6, 34.9, 24.2, 17.7; **HRMS** (ESI^+, m/z) calculated for $[C_{14}H_{17}NONa]^+$ $[M+Na]^+$ 238.1202, found 238.1205 (Δ 1.09 ppm); **IR** υ_{max} (neat)/cm^{-1} 3299, 2939, 2174, 1645, 1552, 1455, 1250, 844, 700.

Data is consistent with the literature: X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* **2009**, *48*, 2367 – 2371.[436]



_N_-(4-(((2,4,4-Trimethylpentan-2-yl)amino)sulfinyl)phenethyl)-6-(trimethylsilyl)hex-5-ynamide (77a)

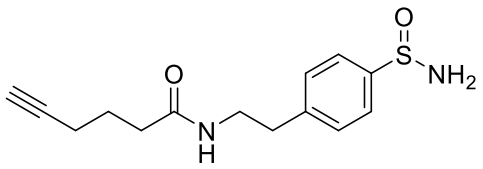
Preparation of organolithium: MeLi (170 µL, 0.264 mmol, 1.60 M in Et_2O, 1.2 equiv.) was added dropwise to a cooled solution of *N*-(4-bromophenethyl)-6-(trimethylsilyl)hex-5-ynamide **78** (80.6 mg, 0.22 mmol, 1.0 equiv.) in THF (1.1 mL, amide conc. 0.2 M) at -78 °C. The reaction mixture was stirred for 10 min at the same temperature before dropwise addition of *n*-BuLi (110 µL, 0.33 mmol, 2.35 M in hexanes, 1.5 equiv.). The reaction mixture was stirred for a further 30 min at the same temperature.

Preparation of sulfinamide: A solution of *tert*-Oct-NSO **83a** (46.5 mg, 0.264 mmol, 1.2 equiv.) in THF (0.56 mL, amide conc. 0.4 M) was added dropwise to the organolithium solution at -78 °C. After stirring for 30 min at -78 °C, the reaction mixture was warmed to 0 °C and stirred for a further 30 min. The reaction mixture was then quenched with saturated aqueous solution of EDTA tetrasodium salt (10 mL), followed by addition of EtOAc (10 mL). The resultant mixture was transferred to a separating funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vauco*. Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 1:5) afforded the desired sulfinamide **77a** as a colourless oil (60.9 mg, 0.13 mmol, 60%).

Notes

1) Aqueous workup can also be performed using saturated aqueous NH_4Cl, with slightly lower yield obtained (50%).
2) Performing the reaction with only *n*-BuLi (2.5 equiv.) resulted in substantially lower yields (25-34%), with significant quantities of des-bromo product **S9**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H, Ar-*H*), 7.31 – 7.28 (m, 2H, Ar-*H*), 5.66 (d, *J* = 6.5 Hz, 1H, N-*H*), 3.84 (s, 1H, N-*H*), 3.50 (dtd, *J* = 11.1, 7.9, 4.5 Hz, 2H, AlkCH_2), 2.86 (t, *J* = 7.0 Hz, 2H, AlkCH_2), 2.34 (tdd, *J* = 13.2, 8.0, 4.9 Hz, 1H, AlkC*H*), 2.24 (td, *J* = 7.2, 3.2 Hz, 3H, AlkC*H*), 2.06 – 1.98 (m, 1H, AlkC*H*), 1.91 – 1.75 (m, 1H, AlkCH_2), 1.66 (d, *J* = 14.9 Hz, 1H, AlkCH_aH$_b$), 1.59 (d, *J* = 14.9 Hz, 1H, AlkCH$_a$$H_b$), 1.51 (s, 3H, C$H_3$), 1.46 (s, 3H, C$H_3$), 1.01 (s, 9H, (C$H_3$)$_3$), 0.88 (t, *J* = 7.2 Hz, 2H, AlkCH_2), 0.12 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.5, 145.0, 142.0, 129.4, 126.1, 106.3, 85.7, 58.5, 56.4, 40.6, 35.5, 35.1, 32.5, 31.94, 31.92, 30.6, 29.5, 24.4, 19.4, 0.3 [note: for gem-dimethyl carbons in *tert*-octyl group, NC(CH_3)$_2$CH$_2$C(CH$_3$)$_3$, 2 peaks were found instead of 1 due to the loss of symmetry caused by chiral sulfur atom]; **LRMS (ESI)** m/z (ESI+) $[M+Na]^+$: 485.2; **HRMS** (ESI^+, m/z) calculated for $[C_{25}H_{44}N_2O_2SSi]^+$ $[M+H]^+$ 463.2809, found 463.2816 (Δ 1.54 ppm); **IR** υ_{max} (neat)/cm^{-1} 3287, 2956, 2873, 2174, 1642, 1539, 1467, 1381, 1248, 1188, 1123, 1035, 1010, 843, 760, 698, 677, 638; **R_F** 0.20 (Petrol:EtOAc 1:5).



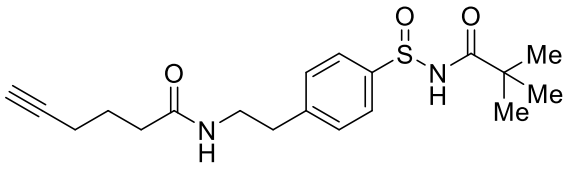
***N*-(4-(Aminosulfinyl)phenethyl)hex-5-ynamide (77b)**

Preparation of organolithium: MeLi (600 µL, 0.96 mmol, 1.60 M in Et_2O, 1.2 equiv.) was added dropwise to a cooled solution of *N*-(4-bromophenethyl)-6-(trimethylsilyl)hex-5-ynamide **78** (293.1 mg, 0.80 mmol, 1.0 equiv.) in THF (4.0 mL, amide conc. 0.2 M) at -78 °C. The reaction mixture was stirred for 10 min at the same temperature before dropwise addition of *n*-BuLi (511 µL, 1.20 mmol, 2.35 M in hexanes, 1.5 equiv.). The reaction mixture was stirred for a further 30 min at the same temperature.

Preparation of sulfinamide: A solution of TIPS-NSO **83b** (210.6 mg, 0.264 mmol, 1.2 equiv.) in THF (2.0 mL, amide conc. 0.4 M) was added dropwise to the organolithium solution at -78 °C. After stirring for 30 min at -78 °C, the reaction mixture was warmed to 0 °C and stirred for a further 30 min. TBAF (2.4 mL, 2.4 mmol, 1.0 M in THF, 3.0 equiv.) was added, then the reaction mixture was warmed to room temperature and stirred for a

further 10 min. The reaction mixture was then quenched with saturated aqueous solution of EDTA tetrasodium salt (30 mL), followed by addition of EtOAc (30 mL). The resultant mixture was transferred to a separating funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vauco*. Flash column chromatography (SiO_2, Petrol:EtOAc:MeOH = 1:1:0 to 1:5:0 to 0:10:1) afforded the desired sulfinamide **77b** as a colourless oil (176.4 mg, 0.63 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 2H, Ar-*H*), 7.36 – 7.31 (m, 2H, Ar-*H*), 5.59 (s, 1H, N-*H*), 4.37 (s, 2H, N-H_2), 3.53 (td, *J* = 7.0, 5.9 Hz, 2H, AlkCH_2), 2.88 (t, *J* = 7.0 Hz, 2H, AlkCH_2), 2.27 (t, *J* = 7.3 Hz, 2H, AlkCH_2), 2.21 (td, *J* = 6.8, 2.7 Hz, 2H, AlkCH_2), 1.95 (t, *J* = 2.7 Hz, 1H, C*H*), 1.82 (p, *J* = 7.1 Hz, 2H, AlkCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.4, 144.9, 142.6, 129.5, 125.9, 83.7, 69.4, 40.5, 35.7, 35.1, 25.3, 24.2, 20.3, 17.9, 13.7; **LRMS** (ESI^+, m/z) $[M+Na]^+$: 301.1; **HRMS** (ESI^+, m/z) calculated for $[C_{14}H_{18}N_2O_2SNa]^+$ $[M+Na]^+$ 278.1099, found 278.1101 (Δ 2.12 ppm); **IR** υ_{max} (neat)/cm^{-1} 3294, 3095, 2312, 1642, 1549, 1222, 1030, 1005, 696; **R_F** 0.31 (EtOAc:MeOH 10:1).

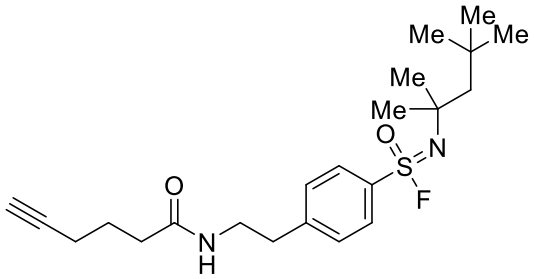


***N*-(4-(Pivalamidosulfinyl)phenethyl)hex-5-ynamide (77c)**

Following modified General Procedure C, using *N*-(4-(aminosulfinyl)phenethyl)hex-5-ynamide **77b** (55.6 mg, 0.20 mmol), NaH (60% dispersion in mineral oil, 19.2 mg, 0.48 mmol, 2.4 equiv.) in THF (2.0 mL) and pivalic anhydride (48.0 µL, 0.24 mmol, 1.2 equiv.) in THF (1.0 mL). Flash chromatography (SiO_2, EtOAc:MeOH = 20:1 to 10:1) afforded the desired sulfinamide **77c** as an off-white oil (71.0 mg, 0.20 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 1H, N-*H*), 7.67 – 7.61 (m, 2H, Ar-*H*), 7.40 – 7.35 (m, 2H, Ar-*H*), 5.70 (t, *J* = 6.1 Hz, 1H, N-*H*), 3.61 – 3.43 (m, 2H), 2.89 (t, *J* = 7.1 Hz, 2H), 2.41 – 2.22 (m, 2H), 2.05 (d, *J* = 2.4 Hz, 1H, C-*H*), 1.96 – 1.76 (m, 2H), 1.61 (dddd, *J* = 13.6, 10.3, 8.6, 5.3 Hz, 1H), 1.39 – 1.28 (m, 1H), 1.22 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101

MHz, $CDCl_3$) 178.9, 172.9, 143.7, 142.3, 130.0, 125.2, 87.2, 70.3, 40.5, 35.8, 34.8, 34.4, 30.6, 27.7, 27.2; **HRMS** (ESI^+, m/z) calculated for $[C_{19}H_{26}N_2O_3SNa]^+$ $[M+Na]^+$ 385.1556, found 385.1558 (Δ 0.20 ppm); $\mathbf{R_F}$ 0.15 (EtOAc:MeOH 10:1).



4-(2-(Hex-5-ynamido)ethyl)-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfonimidoyl fluoride (76a)

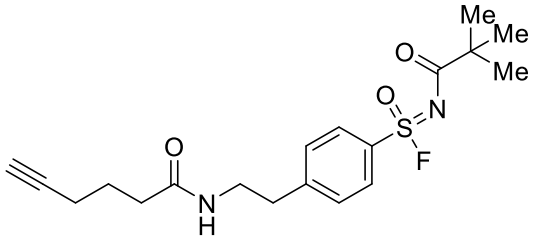
Oxidative chlorination/halogen exchange: Following modified General Procedure E, *N*-(4-(((2,4,4-trimethylpentan-2-yl)amino)sulfinyl)phenethyl)-6-(trimethylsilyl)hex-5-ynamide (**77a**) (48.5 mg, 0.10 mmol), *tert*-butyl hypochlorite (12.5 μL, 0.11 mmol, 1.1 equiv.) and KHF_2 (15.9 mg, 0.30 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **76a** as an off-white oil (22.5 mg, 0.055 mmol, 55%).

[*Note:* reaction carried out in a darkened fumehood due to use of *tert*-butyl hypochlorite]

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(4-(((2,4,4-trimethylpentan-2-yl)amino)sulfinyl)phenethyl)-6-(trimethylsilyl)hex-5-ynamide (**77a**) (45.5 mg, 0.10 mmol), NaH (8.0 mg, 0.20 mmol, 2.0 equiv.) and NFSI (47.3 mg, 0.15 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **76a** as an off-white oil (29.4 mg, 0.072 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H, Ar-*H*), 7.34 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 5.51 (s, 1H, N-*H*), 3.61 – 3.48 (m, 2H, Alk-*H*), 2.91 (t, *J* = 7.0 Hz, 2H, Alk-*H*), 2.35 (dd, *J* = 8.8, 5.4 Hz, 1H, Alk-*H*) 2.26 (td, *J* = 7.2, 3.1 Hz, 2H, Alk-*H*), 1.93 – 1.76 (m, 1H, Alk-*H*), 1.73 – 1.55 (m, 3H, Alk-*H*), 1.57 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.49 – 1.41 (m, 1H, Alk-*H*), 1.33 (dddd, *J* = 13.1, 10.2, 7.0, 4.7 Hz, 1H, Alk-*H*), 1.04 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.0, 143.8, 129.3, 127.5, 70.3, 58.8, 55.8, 46.1, 35.7, 34.8, 31.2, 29.6, 24.4, 22.6, 19.4 [*note*: missing C peaks]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 95.58 – 93.11 (m);

HRMS (ESI$^+$, m/z) could not find accurate mass; **IR** υ_{max} (neat)/cm^{-1} 2981, 1653, 1475, 1277, 1155, 1026, 974, 846, 734, 683; $\mathbf{R_F}$ 0.21 (Petrol:EtOAc 5:1).



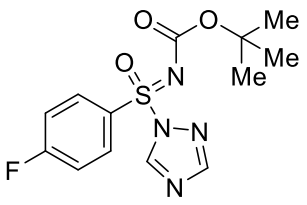
4-(2-(Hex-5-ynamido)ethyl)-*N*-pivaloylbenzenesulfonimidoyl fluoride (76c)

Oxidative chlorination/halogen exchange: Following modified General Procedure E, *N*-(4-(pivalamidosulfinyl)phenethyl)hex-5-ynamide **77c** (36.2 mg, 0.10 mmol), *tert*-butyl hypochlorite (12.5 μL, 0.11 mmol, 1.1 equiv.) and KHF_2 (7.8 mg, 0.12 mmol) in MeCN (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **76c** as an off-white oil (17.7 mg, 0.060 mmol, 60%).

[*Note:* reaction carried out in a darkened fumehood due to use of *tert*-butyl hypochlorite]

Oxidative fluorination (NFSI): Following General Procedure F, *N*-(4-(((2,4,4-trimethylpentan-2-yl)amino)sulfinyl)phenethyl)-6-(trimethylsilyl)hex-5-ynamide (**77a**) (45.5 mg, 0.10 mmol), NaH (8.0 mg, 0.20 mmol, 2.0 equiv.) and NFSI (47.3 mg, 0.15 mmol) in THF (1.0 mL). Flash column chromatography (SiO_2, Petrol:EtOAc = 10:1 to 2:1) afforded the desired sulfonimidoyl fluoride **76c** as an off-white oil (27.2 mg, 0.072 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H, Ar-*H*), 7.40 – 7.34 (m, 2H, Ar-*H*), 5.53 (s, 1H, N-*H*), 3.54 (q, *J* = 6.8 Hz, 2H, Alk-*H*), 2.90 (q, *J* = 7.1 Hz, 4H, Alk-*H*), 2.20 (t, *J* = 7.2 Hz, 2H, Alk-*H*), 2.04 – 1.93 (m, 2H, Alk-*H*), 1.16 (s, 9H, $(CH_3)_3$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 65.9 (s); **HRMS** (ESI$^+$, m/z) calculated for $[C_{19}H_{25}N_2O_3FSNa]^+$ $[M+Na]^+$ 403.1462, found 403.1464; **IR** υ_{max} (neat)/cm^{-1} 3386, 2929, 1740, 1707, 1174, 951, 863, 650; $\mathbf{R_F}$ 0.14 (Petrol:EtOAc 5:1).



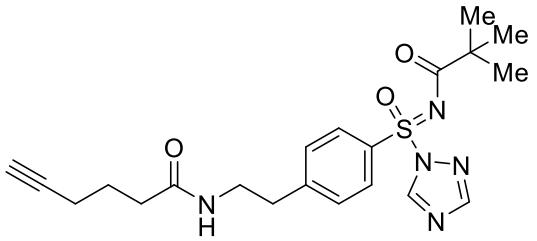
tert-Butyl ((4-fluorophenyl)(oxo)(1*H*-1,2,4-triazol-1-yl)-λ^6-sulfaneylidene)carbamate (85b)

To a cooled solution of *tert*-butyl ((4-fluorophenyl)sulfinyl)carbamate **S11** (259.2 mg, 1.00 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL, 0.2 M) at 0 °C, was added *tert*-butyl hypochlorite (150 μL, 1.20 mmol, 1.2 equiv.). The resultant solution was stirred at the same temperature for 30 min. 1,2,4-Triazole (90.0 mg, 1.30 mmol, 1.3 equiv.) and Et_3N (210 μL, 1.5 mmol, 1.5 equiv.) were added and the reaction mixture warmed to room temperature and stirred for 3 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), transferred to a separating funnel and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfonimidamide **85b** as a white crystalline solid (287.8 mg, 0.88 mmol, 88%).

[*Note:* reaction carried out in a darkened fumehood due to use of *tert*-butyl hypochlorite]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H, triazole-*H*), 8.31 – 8.23 (m, 2H, Ar-*H*), 8.04 (s, 1H, , triazole-*H*), 7.34 – 7.25 (m, 2H, Ar-*H*), 1.38 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{F-C}$ = 260.5 Hz), 154.1, 152.8, 145.7, 132.2 (d, $^3J_{F-C}$ = 10.2 Hz), 130.4 (d, $^4J_{F-C}$ = 3.2 Hz), 117.3 (d, $^2J_{F-C}$ = 23.2 Hz), 83.0, 27.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -99.3 (tt, *J* = 7.9, 4.8 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{13}H_{16}FN_4O_3S]^+$ $[M+H]^+$ 327.0922, found 327.0928 (Δ 1.92 ppm); **IR** υ_{max} (neat)/cm^{-1} 2981, 1725, 1696, 1589, 1450, 1271, 1149, 1097; **R_F:** 0.56 (Petrol:EtOAc 1:1).

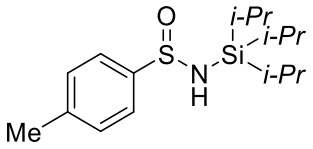
[*Note:* sulfinamide **S11** prepared by Artem Naumenko]



***N*-(4-(*N*-pivaloyl-1H-1,2,4-triazole-1-sulfonimidoyl)phenethyl)hex-5-ynamide (85c)**

To a cooled solution of *N*-(4-(pivalamidosulfinyl)phenethyl)hex-5-ynamide **77c** (36.2 mg, 0.10 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL, 0.2 M) at 0 °C, was added *tert*-butyl hypochlorite (14.9 μL, 0.12 mmol, 1.2 equiv.). The resultant solution was stirred at the same temperature for 30 min. 1,2,4-Triazole (8.97 mg, 0.13 mmol, 1.3 equiv.) and Et_3N (21 μL, 0.15 mmol, 2 equiv.) were added and the reaction mixture warmed to room temperature and stirred for 3 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), transferred to a separating funnel and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 4:1) afforded the desired sulfonimidamide **85c** as an off white oil (20.2 mg, 0.047 mmol, 47%).

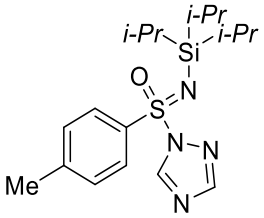
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, triazole-*H*), 8.12 (dd, *J* = 8.7, 3.2 Hz, 2H, Ar-*H*), 7.98 (s, 1H, triazole-*H*), 7.49 – 7.43 (m, 2H, Ar-*H*), 5.55 (s, 1H, N-*H*), 3.63 – 3.45 (m, 2H, Alk-*H*), 2.93 (dt, *J* = 12.6, 6.8 Hz, 2H, Alk-*H*), 2.42 – 2.22 (m, 1H, Alk-*H*), 2.09 – 2.02 (m, 1H, Alk-*H*), 1.68 – 1.56 (m, 3H, Alk-*H*), 1.45 (q, *J* = 5.9 Hz, 2H), 1.26 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.7, 172.9, 148.1, 133.4, 130.3, 129.3, 128.9, 127.6, 87.1, 70.3, 42.6, 41.1, 36.0, 34.9, 34.4, 30.5, 29.5, 27.3; **IR** υ_{max} (neat)/cm^{-1} 3294, 1931, 1670, 1548, 1207, 1138, 1097, 1027; **R_F:** 0.23 (Petrol:EtOAc 4:1).



4-Methyl-*N*-(triisopropylsilyl)benzenesulfinamide (66k)

Following modified General Procedure B TIPS-NSO **83b** (438.2 mg, 2.00 mmol), 4-methylphenylmagnesium bromide solution (2.40 mL, 2.40 mmol, 1.00 M in THF, 1.2 equiv.) and THF (10 mL, 0.20 M). Flash column chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **66k** as an off-white solid (501.3 mg, 1.87 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.59 (m, 2H, Ar-*H*), 7.30 – 7.26 (m, 2H, Ar-*H*), 3.66 (s, 1H, N-*H*), 2.39 (s, 3H, Ar-C*H*$_3$), 1.31 – 1.20 (m, 3H, C*H*$(CH_3)_2$), 1.13 (dd, *J* = 7.3, 5.9 Hz, 18H, CH(C*H*$_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.3, 141.0, 129.7, 125.0, 21.4, 18.1, 18.0, 11.9 [note: for dimethyl carbons in tri-isopropylsilyl group, NSi $(CH(CH_3)_2)_3$, 2 peaks were found instead of 1 due to the loss of symmetry caused by chiral sulfur atom]; **HRMS** (ESI^+, m/z) calculated for $[C_{16}H_{29}NOSNa]^+$ $[M+Na]^+$ 334.1631, found 334.1634 (Δ0.78 ppm); **IR** υ_{max} (neat)/cm^{-1} 2961. 2865, 1463, 1055, 881; **M.p.** 97-99 °C ($CHCl_3$); **R_F:** 0.50 (Petrol:EtOAc 1:1).

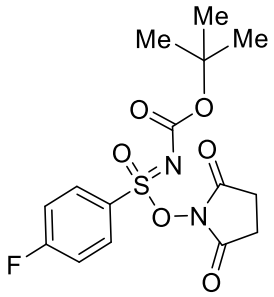


1-(4-Methyl-*N*-(triisopropylsilyl)phenylsulfonimidoyl)-1H-1,2,4-triazole (85d)

To a cooled solution of 4-methyl-*N*-(triisopropylsilyl)benzenesulfinamide **Int.-TIPS** (311.6 mg, 1.00 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL, 0.1 M) at 0 °C, was added *tert*-butyl hypochlorite (125 μL, 1.10 mmol, 1.1 equiv.). The resultant solution was stirred at the same temperature for 30 min. 1,2,4-Triazole (82.9 mg, 1.20 mmol, 1.2 equiv.) and Et_3N (209 μL, 1.50 mmol, 1.5 equiv.) were added and the reaction mixture warmed to room temperature and stirred for 3 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), transferred to a separating funnel and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column

chromatography (SiO_2, Petrol:EtOAc = 4:1) afforded the desired sulfonimidamide **85d** as an off white oil (20.2 mg, 0.047 mmol, 47%).

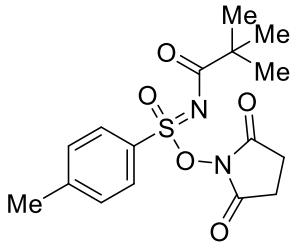
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, triazole-*H*), 7.90 – 7.85 (m, 2H, Ar-*H*), 7.81 (s, 1H, triazole-*H*), 7.23 – 7.19 (m, 2H, Ar-*H*), 2.30 (s, 3H, CH_3), 1.12 – 1.01 (m, 3H, C*H*), 0.97 (dd, *J* = 7.0, 4.2 Hz, 18H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.8, 144.8, 143.7, 137.9, 129.8, 128.1, 21.6, 18.00, 17.96, 12.8 [note: for dimethyl carbons in tri-isopropylsilyl group, NSi $(CH(CH_3)_2)_3$, 2 peaks were found instead of 1 due to the loss of symmetry caused by chiral sulfur atom]; **HRMS** (ESI^+, m/z) calculated for $[C_{18}H_{30}N_4OSSi]^+$ $[M+Na]^+$ 401.1802, found 401.1820 (Δ 4.52 ppm); **IR** υ_{max} (neat)/cm^{-1} 2945, 2867, 1400, 1193, 1094, 989, 883, 659; **M.p.** 120 – 122 °C ($CHCl_3$)**.**



2,5-Dioxopyrrolidin-1-yl *N*-(*tert*-butoxycarbonyl)-4-fluorobenzenesulfonimidate (89a)

Trichloroisocyanuric acid (284.1 mg, 1.10 mmol, 90% purity, 1.1 equiv.) was added to a solution of *tert*-butyl ((4-fluorophenyl)sulfinyl)carbamate **S11** (259.2 mg, 1.00 mmol, 1.0 equiv.) in MeCN (10 mL, 0.1 M) at 0 °C. The resultant solution was stirred at the same temperature for 30 min. *N*-Hydroxysuccinimide (172.6 mg, 1.50 mmol, 1.5 equiv.) and DBU (224 μL, 1.50 mmol, 1.5 equiv.) were added and the reaction mixture warmed to room temperature and stirred for a further 18 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), transferred to a separating funnel and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 8:1) afforded the desired sulfonimidate **89a** as a white crystalline solid (257.7 mg, 0.69 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 2H, Ar-*H*), 7.31 – 7.21 (m, 2H, Ar-*H*), 2.79 – 2.74 (m, 4H, AlkC*H*$_2$), 1.52 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7, 167.0 (d, $^{1}J_{C\text{-}F}$ = 259.6 Hz), 152.3, 132.5 (d, $^{3}J_{C\text{-}F}$ = 10.0 Hz), 130.1 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 116.8 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz), 83.0, 27.9, 25.6; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -99.8 (tt, *J* = 8.1, 4.9 Hz); **HRMS** (ESI^+, m/z) accurate mass not found; **IR** υ_{max} (neat)/cm^{-1} 1748, 1713, 1590, 1242, 1149, 1093, 708.



2,5-Dioxopyrrolidin-1-yl 4-methyl-*N*-pivaloylbenzenesulfonimidate (89b)

Trichloroisocyanuric acid (56.8 mg, 0.22 mmol, 90% purity, 1.1 equiv.) was added to a solution of *N*-(*p*-tolylsulfinyl)pivalamide **69a** (47.9 mg, 0.20 mmol, 1.0 equiv.) in MeCN (2.0 mL, 0.1 M) at 0 °C. The resultant solution was stirred at the same temperature for 30 min. *N*-Hydroxysuccinimide (34.5 mg, 0.30 mmol, 1.5 equiv.) and DBU (44.8 μL, 0.30 mmol, 1.5 equiv.) were added and the reaction mixture warmed to room temperature and stirred for a further 18 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), transferred to a separating funnel and the layers separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 8:1) afforded the desired sulfonimidate **89b** as a white crystalline solid (41.9 mg, 0.12 mmol, 54%).

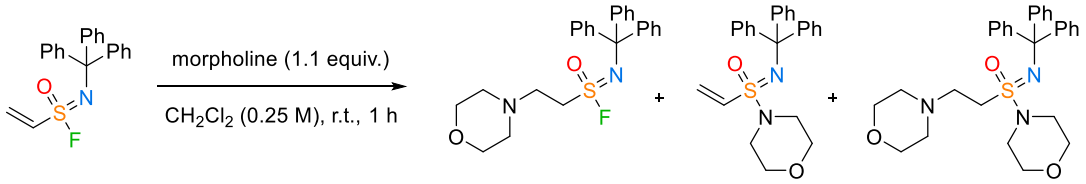
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H, Ar-*H*), 7.43 – 7.37 (m, 2H, Ar-*H*), 2.78 (s, 4H, AlkC*H*$_2$), 2.48 (s, 3H, Ar-C*H*$_3$), 1.21 (s, 9H, (C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.7, 168.9, 147.1, 131.4, 130.1, 129.2, 42.4, 27.3, 25.6, 22.0; **HRMS** (ESI^+, m/z) calculated for $[C_{16}H_{21}N_2O_5S]^+$ $[M+H]^+$ 353.1166, found 353.1160 (Δ -1.63 ppm); **IR** υ_{max} (neat)/cm^{-1} 1757, 1683, 1290, 1121, 700; **R_F:** 0.23 (Petrol:EtOAc 8:1).

6.3 Data for chapter 3

6.3.1 Additional optimisation for the 1,4-addition of morpholine to Tr-ESIF (125a) on a screening scale (0.20 mmol)

Additional reaction conditions screened by Erik Diepers during the initial optimisation of the 1,4-addition of morpholine to Tr-ESIF (**125a**) are documented in **Table** .

Table 6.3-1 Additional optimisation of 1,4-addition of morpholine to Tr-ESIF (**125a**) by Erik Diepers.



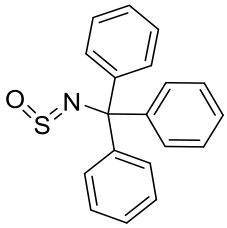
125a **141a** **142a** **144a**

Entry	Variation to above system	Yield 141a[a] / %	Yield 142a[a] / %	Yield 144a[a] / %
1	-	81 (72)	19 (18)	0
2	morpholine (0.7 equiv.)	54	12	0
3	morpholine (1.0 equiv.)	79	21	0
4	morpholine (1.2 equiv.)	74	26	0
5	CH_2Cl_2 (0.50 M)	80	20	0
6	30°C	81	19	0
7	$CHCl_3$ (0.25 M)	72	20	8
8	DMF (0.25 M)	52	48	0
9	THF (0.25 M)	67	28	5
10	Et_2O (0.25 M)	53	39	8
11	Et_3N (1.5 equiv.)	73	21	6
12	NEt(*i*-Pr)$_2$ (0.5 equiv.)	37	63	0
13	Ca(OTf)$_2$ (0.2 equiv.)	70	24	0
14	Cu(OTf)$_2$ (0.1 equiv.)	63	18	0
15	Sc(OTf)$_3$ (0.1 equiv.)	62	22	0

[a] Ratios calculated using quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Remaining percentages are Tr-ESIF (**125a**).

6.3.2 Synthetic procedures

6.3.2.1 Synthesis of sulfinylamines



(Tritylimino)-λ^4-sulfanone (Tr-NSO, 8)

According to a procedure by Davies *et al.*,[143] to an oven-dried round-bottom flask was added tritylamine (10.0 g, 38.6 mmol, 1.0 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous diethyl ether (145 mL, 0.27 M) and anhydrous triethylamine (10.8 mL, 77.1 mmol, 2.0 equiv.) were added. The solution was cooled to 0 °C and thionyl chloride (2.80 mL, 38.6 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred vigorously at 0 °C for 2 h. Filtration through a pad of celite and concentration *in vacuo* afforded Tr-NSO **8** as a white solid (11.6 g, 38.6 mmol, quant.).

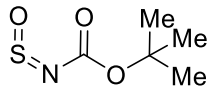
Notes

1) The solvent is removed on the rotary evaporator at room temperature (21 ± 2 °C).
2) TrNSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 15H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.5, 128.8, 128.3, 127.8, 81.3;

Data is consistent with the literature: T. Q. Davies, A. Hall, M. C. Willis, *Angew. Chem. Int. Ed.* **2017**, *56*, 14937-14941.[297]

*Synthesis of TIPS-NSO (**83b**) and all relevant data is included in chapter 6.2 data for chapter 2.*



tert-Butyl (oxo-λ⁴-sulfaneylidene)carbamate (boc-NSO, 83c)

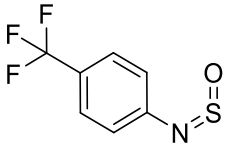
According to a modified procedure by Davies *et al.*,[123] thionyl chloride (1.0 mL, 13.8 mmol, 1.05 equiv.) was added to a solution of *tert*-butyl carbamate (1.5 g, 12.8 mmol, 1.0 equiv.) in Et_2O (30 mL, 0.43 M), and the resultant mixture was cooled to 0 °C. Pyridine (2.2 mL, 27.3 mmol, 2.1 equiv.) was then added dropwise. The reaction was allowed to warm to room temperature and stirred for 48 h. Precipitated pyridine hydrochloride was removed using a filter stick under an inert atmosphere and the filtrate was concentrated *in vacuo* to give sulfinylamine **83c** as a yellow oil (1.78 g, 85%, 92% purity determined by ^{1}H NMR).

Notes

1) The solvent is removed on the rotary evaporator at room temperature under an inert atmosphere (21 ± 2 °C).
2) Boc-NSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >1 month.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 9H, C*H*$_3$);

Data is consistent with the literature: T. Q. Davies, Thesis.[123]



((4-(Trifluoromethyl)phenyl)imino)-λ⁴-sulfanone (4-CF_3Ph-NSO, 83d)

According to a procedure by Davies *et al.*,[123] thionyl chloride (832 μL, 11.5 mmol, 1.2 equiv.) was added to a cooled solution of 4-(trifluoromethyl)aniline (1.20 mL, 9.56 mmol, 1.0 equiv.) in toluene (27 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h, before refluxing for 5 h. Concentration *in vacuo* gave sulfinylamine **83d** as a dark brown oil (1.90 g, 96%).

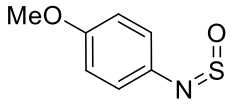
Notes

1) The solvent is removed on the rotary evaporator at 50 °C.

2) 4-CF_3Ph-NSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.69 (d, *J* = 8.3 Hz, 2H, Ar-*H*); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.9 (s);

Data is consistent with the literature: D. M. Chemes, E. H. Cutin, R. M. S. Alvarez, N. L. Robles, H. Oberhammer, *J. Fluor. Chem.* **2018**, *210*, 94-101.[437]



((4-Methoxyphenyl)imino)-λ^4-sulfanone (4-OMePh-NSO, 83e)

According to a procedure by Davies *et al.*,[123] thionyl chloride (832 μL, 11.5 mmol, 1.2 equiv.) was added to a cooled solution of *para*-anisidine (1.18 g, 9.56 mmol, 1.0 equiv.) in toluene (27 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h, before refluxing for 5 h. Concentration *in vacuo* gave sulfinylamine **83e** as a dark brown oil (1.60 g, 99%).

Notes

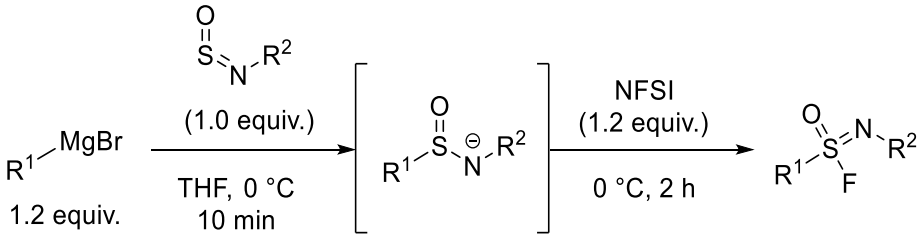
1) The solvent is removed on the rotary evaporator at 50 °C.
2) 4-OMePh-NSO is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 9.0 Hz, Ar-*H*), 6.89 (2H, d, *J* = 9.0 Hz, Ar-*H*), 3.85 (3H, s, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 137.4, 129.6, 114.3, 55.7;

Data is consistent with the literature: G. Kresze, M. Berger, *Orgn. Magn. Reson.*, **1976**, *8*, 170-172.[438]

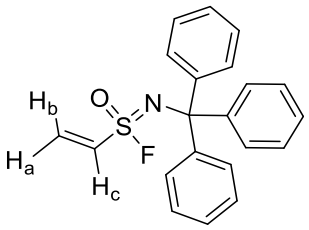
6.3.2.2 Synthesis of sulfonimidoyl fluorides

General Procedure J



Following a modified procedure reported by T. Q. Davies:[123]

The respective organometallic reagent (1.2 equiv.) was added dropwise to a solution of respective sulfinylamine (1.0 equiv.) in anhydrous THF (0.1 M) at 0 °C. The resultant solution was stirred at 0 °C for 10 min. Then NFSI (1.2 equiv.) was added and the reaction mixture was stirred at 0 °C for another 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography using the appropriate solvent system or filtration (CH_2Cl_2).



***N*-Tritylethenesulfonimidoyl fluoride (Tr-ESIF, 125a)**

Following General Procedure J, Tr-NSO **8** (3.05 g, 10.0 mmol), vinylmagnesium bromide solution (12.5 mL, 12.0 mmol, 0.96 M in THF), NFSI (3.78 g, 12.0 mmol) and THF (100 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 8:1) afforded the desired sulfonimidoyl fluoride **125a** as a white crystalline solid (3.16 g, 9.00 mmol, 90%).

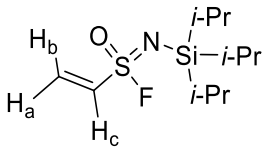
Notes

1) Reaction was performed on range of scales from 1 mmol to 10 mmol (72-90%).
2) Tr-ESIF is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months. Storage

at room temperature led to decomposition in 2 weeks (5-10% impurity determined by ^{1}H NMR).

3) The product can also be isolated by addition to CH_2Cl_2 to the crude mixture (10 mmol scale reaction, filtering off the NHSI by-product and concentrating the filtrate to give sufficiently pure Tr-ESIF (2.98 g, 8.50 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 6H, Ar-*H*), 7.33 – 7.22 (m, 9H, Ar-*H*), 6.81 (ddd, *J* = 16.5, 9.7, 2.5 Hz, 1H, H_c), 6.50 (dd, *J* = 16.5, 1.0 Hz, 1H, H_b), 6.11 (ddd, *J* = 9.7, 4.9, 1.0 Hz, 1H, H_a); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2, 146.2, 134.8 (d, $^{2}J_{C\text{-}F}$ = 33.6 Hz), 128.8, 128.4, 127.9, 127.2, 74.0 (d, $^{3}J_{C\text{-}F}$ = 4.7 Hz) [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for substituted carbon in trityl groups]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 85.4 (dd, *J* = 5.0, 2.5 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{21}H_{18}FNOSNa]^+$ $[M+Na]^+$ 374.0985, found 374.0996 (Δ2.8 ppm); **IR** υ_{max} (neat)/cm^{-1} 3060, 1492, 1364, 1209, 975, 749, 700, 673; **M.p.** 103-105 °C ($CHCl_3$); **R_F:** 0.29 (Petrol:EtOAc = 8:1).



_N_-(Triisopropylsilyl)ethenesulfonimidoyl fluoride (TIPS-ESIF, 125b)

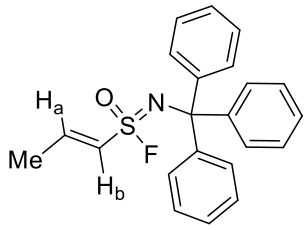
Following General Procedure J, TIPS-NSO **83b** (1.31 g, 6.00 mmol), vinylmagnesium bromide solution (7.5 mL, 7.20 mmol, 0.96 M in THF), NFSI (2.27 g, 7.20 mmol) and THF (60 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 8:1) afforded the desired sulfonimidoyl fluoride **125b** as a yellow oil (1.45 g, 5.46 mmol, 91%).

Notes

1) Reaction was performed on range of scales from 1.0 mmol to 6.0 mmol (85-91%).
2) TIPS-ESIF is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >6 months.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (ddd, *J* = 16.4, 9.6, 3.1 Hz, 1H, H_c), 6.43 (d, *J* = 16.4 Hz, 1H, H_b), 6.04 (1H, dd, *J* = 9.6, 5.3 Hz, H_a), 1.19 – 1.07 (m, 3H, C*H*$(CH_3)_2$), 1.09 – 1.04 (m, 18H, CH(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7 (d, $^{2}J_{C\text{-}F}$ = 38.2 Hz), 128.3 (d, $^{3}J_{C\text{-}F}$ = 1.6 Hz,), 18.00, 17.98, 12.7 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz) [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for methyl groups in TIPS]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 83.9 (dd,

J = 5.5, 3.1 Hz); **HRMS** (ESI$^+$, m/z) calculated for $[C_{11}H_{25}FNOSSi]^+$ $[M+H]^+$ 266.1405, found 266.1406 (Δ 0.48 ppm); **IR** υ_{max} (neat)/cm^{-1} 3035, 2892, 1422, 1074, 884, 750, 702, 666; **R_F:** 0.30 (Petrol:EtOAc = 8:1).



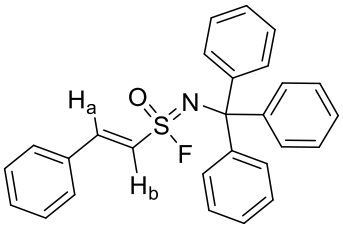
***(E)-N*-Tritylprop-1-ene-1-sulfonimidoyl fluoride (131a)**

Following General Procedure J, Tr-NSO **8** (610.8 mg, 2.00 mmol), 1-propenylmagnesium bromide solution (4.8 mL, 2.40 mmol, 0.50 M in THF), NFSI (757 mg, 2.40 mmol) and THF (20 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 8:1 to 4:1) afforded the desired sulfonimidoyl fluoride **131a** as an off-white solid (416.6 mg, 1.14 mmol, 57%).

Note

(*E*)-*N*-Tritylprop-1-ene-1-sulfonimidoyl fluoride is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 6H, Ar-*H*), 7.39 – 7.27 (m, 9H, Ar-*H*), 7.06 (dq, *J* = 14.1, 7.0 Hz, 1H, H_b), 6.58 (app. ddt, *J* = 13.0, 2.7, 1.6 Hz, 1H, H_a), 2.01 (app. dt, *J* = 7.0, 1.6 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.40, 146.36, 143.2, 128.8, 128.0, 127.8, 127.1, 73.7 (d, $^3J_{C\text{-}F}$ = 4.7 Hz), 17.1 [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for substituted carbon in trityl groups]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 86.1 (s); **HRMS** (ESI$^+$, m/z) calculated for $[C_{22}H_{20}FNOSNa]^+$ $[M+Na]^+$ 388.1142, found 388.1140 (Δ -0.5 ppm); **IR** υ_{max} (neat)/cm^{-1} 3060, 1492, 1447, 1359, 1202, 947, 754, 701, 665; **M.p.** 110-112 °C; **R_F:** 0.30 (Petrol:EtOAc = 8:1).



(*E*)-2-Phenyl-*N*-tritylethene-1-sulfonimidoyl fluoride (131b)

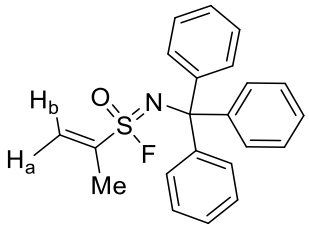
Preparation of organometallic reagent:

(*E*)-Styrylmagnesium bromide was prepared according to the following procedure. An oven-dried round bottom flask was charged with magnesium turnings (96.3 mg, 3.96 mmol, 1.32 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous THF (3.6 mL, 1.0 M) was added. β-Bromostyrene (462 μL, 3.60 mmol, 1.2 equiv.) was added dropwise to this suspension at a rate to maintain a gentle reflux. The resulting solution was refluxed for a further 2 h before cooling to room temperature.

Preparation of sulfonimidoyl fluoride:

131b was then prepared following General Procedure J, Tr-NSO **8** (916.2 mg, 3.00 mmol, 1.0 equiv.), (*E*)-styrylmagnesium bromide solution (3.60 mmol, 1.2 equiv.), NFSI (1.13 g, 3.60 mmol, 1.2 equiv.) and THF (20 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 50:1) afforded the desired sulfonimidoyl fluoride **131b** as a white solid (386 mg, 0.90 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.4 Hz, 1H, *H$_a$*), 7.55 (dd, *J* = 7.7, 2.0 Hz, 2H, Ar-*H*), 7.52 – 7.43 (m, 9H, Ar-*H*), 7.39 – 7.26 (m, 9H, Ar-*H*), 7.04 (dd, *J* = 15.4, 2.5 Hz, 1H, *H$_b$*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.4, 146.3, 143.2, 131.9, 131.6, 129.3, 128.9, 128.8, 127.9, 127.2, 123.9 (d, $^2J_{C\text{-}F}$ = 33.0 Hz), 74.1 (d, $^3J_{C\text{-}F}$ = 4.4 Hz) [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for substituted carbon in trityl groups]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 89.2 (d, *J* = 2.8 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{27}H_{22}FNOSNa]^+$ $[M+Na]^+$ 450.1298, found 450.1298 (Δ -0.05 ppm); **IR** υ_{max} (neat)/cm^{-1} 3064, 1615, 1492, 1449, 1357, 972, 704, 663, 644; **R_F:** 0.30 (Petrol:EtOAc = 8:1).



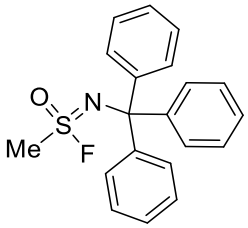
_N_-Tritylprop-1-ene-2-sulfonimidoyl fluoride (131c)

Following General Procedure J, Tr-NSO **8** (1.832 g, 6.00 mmol), isopropenylmagnesium bromide solution (14.4 mL, 7.20 mmol, 0.50 M in THF), NFSI (2.27 g, 7.20 mmol) and THF (60 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 8:1) afforded the desired sulfonimidoyl fluoride **131c** as a white solid (1.01 g, 2.79 mmol, 46%).

Note

> *N*-Tritylprop-1-ene-2-sulfonimidoyl fluoride is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance.

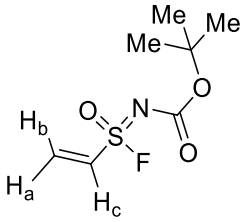
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (app. dq, *J* = 7.2, 1.4 Hz, 6H, Ar-*H*), 7.36 – 7.21 (m, 9H, Ar-*H*), 6.28 (q, *J* = 0.9 Hz, 1H, H_b), 5.78 (app. dp, *J* = 5.5, 1.4 Hz, 1H, H_a), 2.37 (dd, J = 1.6, 0.9 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.43, 146.39, 143.8 (d, $^{2}J_{C-F}$ = 28.7 Hz), 128.9, 128.1, 127.9, 127.1, 124.2, 73.8 (d, $^{3}J_{C-F}$ = 4.3 Hz), 18.1 [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for substituted carbon in trityl groups]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 75.5 (d, *J* = 5.9 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{22}H_{20}FNOSNa]^+$ $[M+Na]^+$ 388.1142, found 388.1158 (Δ4.2 ppm); **IR** υ_{max} (neat)/cm^{-1} 3059, 1492, 1447, 1379, 1354, 848, 758, 699; **M.p.** 115 – 117 °C; **R_F:** 0.36 (Petrol:EtOAc = 8:1).



_N_-tritylmethanesulfonimidoyl fluoride (134)

Following General Procedure J, Tr-NSO **8** (1.527 g, 5.00 mmol), methylmagnesium bromide solution (2.0 mL, 6.00 mmol, 3.0 M in Et_2O), NFSI (1.89 g, 6.00 mmol) and THF (50 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 6:1) afforded the desired sulfonimidoyl fluoride **134** as a white solid (1.44 g, 4.25 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (app. dt, *J* = 8.1, 1.3 Hz, 6H, Ar-*H*), 7.36 – 7.27 (m, 9H, Ar-*H*), 3.36 (d, *J* = 2.6 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.27, 146.22, 128.8, 127.9, 127.1, 74.0 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 42.6 (d, $^2J_{C\text{-}F}$ = 28.3 Hz) [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for substituted carbon in trityl groups]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 85.0 (q, *J* = 2.8 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{20}H_{18}FNOSNa]^+$ $[M+Na]^+$ 362.0985, found 362.0998 (Δ3.5 ppm); **IR** υ_{max} (neat)/cm^{-1} 1491, 1358, 910, 750, 701, 662; **M.p.** 141-143 °C; **R_F:** 0.16 (Petrol:EtOAc = 8:1).



***tert*-Butyl (fluoro(oxo)(vinyl)-λ^6-sulfaneylidene)carbamate, boc-ESIF (125c)**

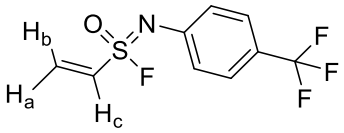
Following modified General Procedure E, *tert*-butyl (vinylsulfinyl)carbamate **138c** (153 mg, 0.80 mmol, 1.0 equiv.), *tert*-butyl hypochlorite (100 μL, 0.88 mmol, 1.1 equiv.), KHF_2 (93.7 mg, 1.20 mmol, 1.5 equiv.) and MeCN (8.0 mL mL) at room temperature for 16 h. Flash chromatography (SiO_2, Petrol:EtOAc = 20:1 to 10:1 to 4:1) afforded the desired sulfonimidoyl fluoride **125c** as a colourless oil (138.1 mg, 0.66 mmol, 82%).

Note

1) *tert*-Butyl (fluoro(oxo)(vinyl)-λ^6-sulfaneylidene)carbamate is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance.
2) Reaction also performed on 0.2 mmol scale (48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 16.6, 9.8, 1.7 Hz, 1H, *H$_c$*), 6.70 (app. dt, *J* = 16.6, 1.1 Hz, 1H, *H$_b$*), 6.38 (ddd, *J* = 9.8, 4.2, 1.3 Hz, 1H, *H$_a$*), 1.49 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.5 (d, $^3J_{C\text{-}F}$ = 3.5 Hz), 133.3 (d, $^3J_{C\text{-}F}$ = 1.8 Hz), 131.2 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 82.9,

27.9; **^{19}F NMR** (377MHz, $CDCl_3$) δ 62.3 (d, *J* = 4.0 Hz); **HRMS** (ESI^+, m/z) could not be obtained for boc-ESIF (**125c**), alternative MS methods will be evaluated; **IR** υ_{max} (neat)/cm^{-1} 2939, 1708, 1371, 1290, 1158, 765; **R_F:** 0.35 (Petrol:EtOAc = 8:1).



***N*-(4-(Trifluoromethyl)phenyl)ethenesulfonimidoyl fluoride (125d)**

Following modified General Procedure E, *N*-(4-(trifluoromethyl)phenyl)ethenesulfinamide **138d** (188 mg, 0.80 mmol, 1.0 equiv.), *tert*-butyl hypochlorite (100 μL, 0.88 mmol, 1.1 equiv.), KHF_2 (93.7 mg, 1.2 mmol, 1.5 equiv.) and MeCN (8.0 mL) at room temperature for 16 h. Flash chromatography (SiO_2, Petrol:EtOAc = 20:1 to 10:1 to 4:1) afforded the desired sulfonimidoyl fluoride **125d** as a colourless oil (124 mg, 0.49 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.27 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.87 (ddd, *J* = 16.6, 9.8, 2.0 Hz, 1H, H_c), 6.71 (dd, *J* = 16.6, 1.1 Hz, 1H, H_b), 6.34 (ddt, *J* = 9.8, 4.6, 1.1 Hz, 1H, H_a); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7 (d, $^3J_{C\text{-}SF}$ = 5.5 Hz), 132.3 (d, $^2J_{C\text{-}SF}$ = 28.8 Hz), 131.7, 126.6 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 126.5 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 124.1 (d, $^4J_{C\text{-}SF}$ = 4.6 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 77.0 (d, *J* = 4.8 Hz, S*F*), -62.2 (s, CF_3); **HRMS** (ESI^+, m/z) could not be obtained for *N*-(4-(trifluoromethyl)phenyl)ethenesulfonimidoyl fluoride (**125d**), alternative MS methods will be evaluated; **IR** υ_{max} (neat)/cm^{-1} 1616, 1517, 1364, 1324, 1279, 1123, 1062, 845, 740, 688; **R_F:** 0.25 (Petrol:EtOAc = 8:1).

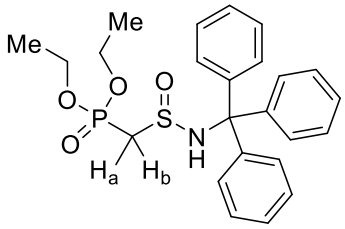
6.3.3 Synthesis of sulfinamides

General Procedure K

The respective organometallic reagent (1.0 – 2.0 equiv.) was added dropwise to a solution of respective sulfinylamine (1.0 equiv.) in anhydrous THF (0.1 M) at 0 °C. The resultant solution was stirred at 0 °C for 10 minutes. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography using the appropriate solvent system.

General Procedure L

Vinylmagnesium bromide solution (0.9 equiv.) was added dropwise to a solution of respective sulfinylamine (1.0 equiv.) in anhydrous Et_2O (0.1 M) at -30 °C. The resultant solution was stirred at -30 °C for 20 minutes. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography using the appropriate solvent system.



Diethyl (((tritylamino)sulfinyl)methyl)phosphonate (137)

1) Preparation of **137** using organolithium reagent

Preparation of organometallic reagent:

((Diethoxyphosphoryl)methyl)lithium solution was prepared according to the following procedure. *n*-BuLi (1.45 mL, 3.30 mmol, 2.27 M in hexane, 1.1 equiv.) was added dropwise to a cooled solution of diethylmethylphosphonate **139** (438 µL, 3.00 mmol, 1.0 equiv.) in THF (4.6 mL, diethylmethylphosphonate conc. 0.65 M) at -78 °C. The resulting solution was stirred at the same temperature for 10 minutes.

Preparation of sulfinamide:

137 was then prepared following General Procedure K, Tr-NSO **8** (916.2 mg, 3.00 mmol, 1.0 equiv.), ((diethoxyphosphoryl)methyl)lithium solution (3.00 mmol, 1.0 equiv.) and THF (11.4 mL, 0.26 M). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **137** as a white solid (640 mg, 1.40 mmol, 47%).

Note

The reaction was performed under the same conditions with excess organolithium reagent: diethylmethylphosphonate **139** (876 µL, 6.0 mmol, 2.0 equiv.) and *n*-BuLi (3.91 mL, 6.60 mmol, 2.27 M in hexane, 2.2 equiv.) in THF (9.2 mL, diethylmethylphosphonate conc. 0.65 M). Flash chromatography (SiO_2, Petrol:EtOAc = 2:1 to 1:1) afforded the desired sulfinamide **137** as a white solid (686 mg, 1.50 mmol, 50%).

2) Preparation of **137** using Turbo Grignard reagent

Preparation of organometallic reagent:

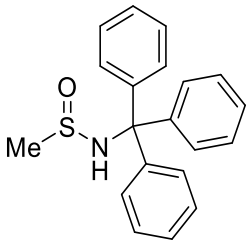
((Diethoxyphosphoryl)methyl)magnesium chloride lithium chloride complex solution was prepared according to the following procedure. Diethyliodomethane phosphonate **140** (278 mg, 1.00 mmol, 1.0 equiv.) in THF (1.0 mL, 1.0 M) was added to a solution of isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent,

0.90 mL, 1.10 mmol, 1.22 M in THF, 1.1 equiv.) at -78 °C. The resultant solution was stirred at the same temperature for 45 minutes.

Preparation of sulfinamide:

137 was then prepared following General Procedure K, Tr-NSO **8** (305.4 mg, 1.00 mmol, 1.0 equiv.), ((diethoxyphosphoryl)methyl)magnesium chloride lithium chloride complex solution (1.00 mmol, 1.0 equiv.) and THF (1.0 mL, 1.0 M). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **137** as a white solid (233 mg, 0.51 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H, N-*H*), 7.45 – 7.40 (m, 6H, Ar-*H*), 7.37 – 7.30 (m, 6H, Ar-*H*), 7.29 – 7.24 (m, 3H, Ar-*H*), 4.43 – 4.27 (m, 2H, C*H*$_2$CH$_3$), 4.09 (dq, *J* = 8.2, 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.15 (dd, *J* = 16.2, 14.6 Hz, 1H, CH$_a$*H*$_b$), 2.64 (app. t, *J* = 14.7 Hz, 1H, C*H*$_a$H$_b$), 1.35 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 129.1, 128.2, 127.4, 72.7, 63.3 (d, $^2J_{C\text{-}P}$ = 5.6 Hz), 62.2 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 49.4, 48.1, 16.4 (d, $^3J_{CP}$ = 6.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.3 (s); **HRMS** (ESI^+, m/z) calculated for $[C_{24}H_{28}NO_4PS]^+$ $[M+Na]^+$ 480.1369, found 480.1367 (Δ-0.5 ppm); **IR** υ_{max} (neat)/cm^{-1} 1447, 1237, 1023, 973, 733, 702; **M.p.** 140-142 °C ($CHCl_3$); **R_F:** 0.32 (Petrol:EtOAc = 1:1).



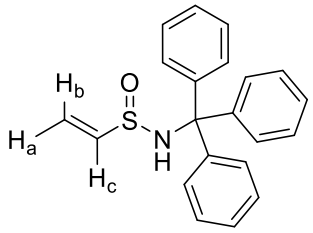
***N*-tritylmethanesulfinamide (137a)**

Following General Procedure K, Tr-NSO **8** (610.8 mg, 2.00 mmol), methylmagnesium bromide solution (0.80 mL, 2.40 mmol, 3.0 M in Et_2O) and THF (20 mL). Filtration (washing with hexane/Et_2O) afforded the desired sulfinamide **137a** as a white solid (611 mg, 1.90 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 15H, Ar-*H*), 5.14 (s, 1H, N-*H*), 2.59 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 129.2, 128.2, 127.5, 73.0, 44.2; **LRMS** (ESI^+,

m/z) $[M+Na]^+$ 344.1; **IR** υ_{max} (neat)/cm^{-1} 3187, 1493, 1447, 1002, 909, 732, 701; **R_F:** 0.31 (Petrol:EtOAc = 1:1);

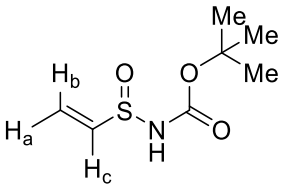
Data is consistent with the literature: P. M. Matos, W. Lewis, J. C. Moore, R. A. Stockman, *Org. Lett.* **2018**, *20*, 3674–3677.[439]



***N*-Tritylethenesulfinamide (138a)**

Diethyl (((tritylamino)sulfinyl)methyl)phosphonate **137** (91.4 mg, 0.20 mmol, 1.0 equiv.) was dissolved in THF (1.0 mL, 0.2 M) and cooled to 0 °C. NaH (16.0 mg, 0.40 mmol, 2.0 equiv., 60% in mineral oil) was added and the resultant suspension was stirred for 30 minutes at the same temperature. Paraformaldehyde (6.01 mg, 0.20 mmol, 1.0 equiv.) was added and the reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL). The aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 5:1 to 1:1) afforded the desired sulfinamide **138a** as a white solid (38.0 mg, 0.11 mmol, 57%).

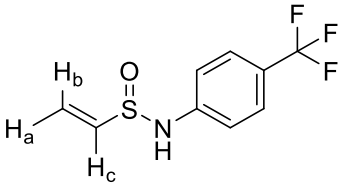
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 6H, Ar-*H*), 7.35 – 7.24 (m, 9H, Ar-*H*), 6.56 (dd, *J* = 16.3, 9.4 Hz, 1H, H_c), 6.11 (d, *J* = 16.3 Hz, 1H, H_a), 5.81 (d, *J* = 9.4 Hz, 1H, H_b), 5.15 (s, 1H, N-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 142.8, 129.2, 128.0, 127.4, 122.1, 72.9; **HRMS** (ESI^+, m/z) calculated for $[C_{21}H_{19}NOS]^+$ $[M+Na]^+$ 356.1080, found 356.1077 (Δ-0.7 ppm); **IR** υ_{max} (neat)/cm^{-1} 3201, 3059, 1597, 1493, 1447, 1038, 754, 700; **M.p.** 173 – 175 °C ($CHCl_3$); **R_F:** 0.25 (Petrol:EtOAc = 1:1).



***tert*-Butyl (vinylsulfinyl)carbamate (138c)**

Following General Procedure L, *tert*-butyl (oxo-λ^4-sulfaneylidene)carbamate (boc-NSO, **83c**, 1.70 g, 10.4 mmol, 92% purity by ^{1}H NMR), vinylmagnesium bromide solution (9.36 mL, 9.36 mmol, 1.0 M in THF) and Et_2O (104 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **138c** as a white solid (914.9 mg, 4.78 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, N*H*), 6.70 (1H, dd, *J* = 16.4, 9.6 Hz, H_c), 6.24 (1H, dd, *J* = 16.4, 0.6 Hz, H_b), 6.02 (1H, dd, *J* = 9.6, 0.6 Hz, H_a), 1.48 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6, 140.4, 124.5, 83.6, 28.1; **LRMS** (ESI$^+$, m/z) $[M+H]^+$ 192.1; **IR** υ_{max} (neat)/cm^{-1} 2983, 1731, 1423, 1395, 129, 1160, 1084, 964, 822, 721; **R_F:** 0.16 (Petrol:EtOAc = 1:1).

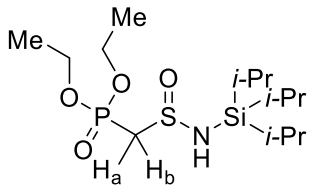


***N*-(4-(Trifluoromethyl)phenyl)ethenesulfinamide (138d)**

Following General Procedure L, using ((4-(trifluoromethyl)phenyl)imino)-λ^4-sulfanone (4-F_3CPh-NSO, **83d**, 1.04 g, 5.00 mmol), vinylmagnesium bromide solution (4.5 mL, 4.50 mmol, 1.0 M in THF) and Et_2O (50 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **138d** as an off-white solid (882 mg, 3.75 mmol, 75%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.63 (s, 1H, N-*H*), 7.62 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.24 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.04 (dd, *J* = 16.4, 9.5 Hz, 1H, H_c), 6.14 (d, *J* = 9.5 Hz, 1H, H_a), 6.12 (d, *J* = 16.5 Hz, 1H, H_b); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 145.9, 141.7, 126.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.5 (q, $^1J_{C\text{-}F}$ = 271.2 Hz), 123.9, 121.8 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 116.6; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ -60.1 (s); **HRMS** (ESI$^+$, m/z) calculated for $[C_9H_9F_3NOS]^+$ $[M+H]^+$

236.0352, found 236.0345 (Δ-2.76 ppm); **IR** υ_{max} (neat)/cm^{-1} 3173, 1705, 1620, 1292, 1163, 1114, 1070, 931; **M.p.** 115-117 °C; **R_F:** 0.13 (Petrol:EtOAc = 1:1).



Diethyl ((((triisopropylsilyl)amino)sulfinyl)methyl)phosphonate (137b)

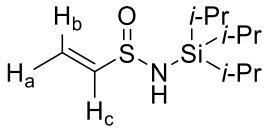
Preparation of organometallic reagent:

((Diethoxyphosphoryl)methyl)magnesium chloride lithium chloride complex solution was prepared according to the following procedure. Diethyliodomethane phosphonate **140** (1.67 g, 6.00 mmol, 2.0 equiv.) in THF (6.0 mL, 1.0 M) was added to a solution of isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 5.4 mL, 6.60 mmol, 1.22 M in THF, 2.2 equiv.) at -78 °C. The resultant solution was stirred at the same temperature for 45 minutes.

Preparation of sulfinamide:

137b was then prepared following General Procedure K, TIPS-NSO (**83b**, 658.2 mg, 3.00 mmol, 1.0 equiv.), ((diethoxyphosphoryl)methyl)magnesium chloride lithium chloride complex solution (6.00 mmol, 6.0 equiv.) and THF (10.0 mL, 0.33 M). Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfinamide **137b** as a brown oil (440 mg, 1.18 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H, N-*H*), 4.24 – 4.07 (m, 2H, CH_2CH$_3$), 4.06 – 3.93 (m, 2H, CH_2CH$_3$), 3.22 (dd, *J* = 16.1, 14.5 Hz, 1H, CH_aH$_b$), 2.94 (t, *J* = 14.8 Hz, 1H, CH$_a$$H_b$), 1.19 (t, *J* = 7.1, 6H, CH$_2$CH_3), 1.13 – 0.97 (m, 3H, C*H*(CH$_3$)$_2$), 0.97-0.88 (m, 18 H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.5 (s); **R_F:** 0.30 (Petrol:EtOAc 1:1). [*Note:* further data unable to be collected as the product decomposed rapidly in $CDCl_3$, other deuterated solvents will be evaluated in due course]



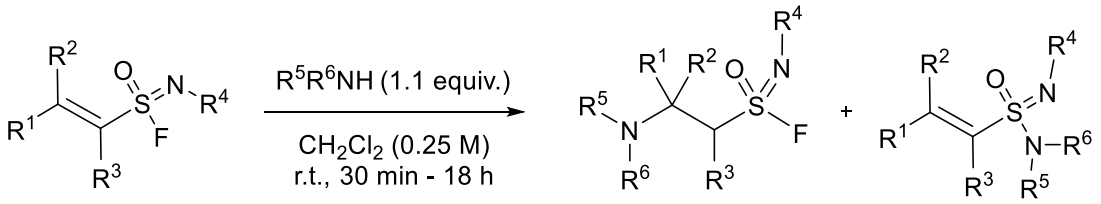
N-(Triisopropylsilyl)ethenesulfinamide (138g)

Diethyl ((((triisopropylsilyl)amino)sulfinyl)methyl)phosphonate **137b** (74.3 mg, 0.20 mmol, 1.0 equiv.) was dissolved in THF (1.0 mL, 0.1 M) and cooled to -78 °C. NaH (16.0 mg, 0.40 mmol, 2.0 equiv., 60% in mineral oil) was added and the resultant suspension was stirred for 30 min at the same temperature. Paraformaldehyde (6.0 mg, 0.20 mmol, 1.0 equiv.) was added and the reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL). The aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 5:1 to 1:1) afforded the desired sulfinamide **138g** as a colourless oil (30.2 mg, 0.12 mmol, 61%).

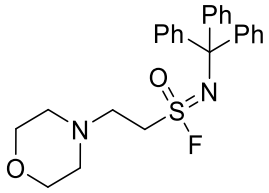
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 16.5, 9.5 Hz, 1H, H_c), 5.87 (dd, *J* = 16.5, 0.7 Hz, 1H, H_b), 5.64 (d, *J* = 9.5 Hz, 1H, H_a), 3.86 (s, 1H, N-*H*), 1.13-1.01 (m, 3H, C*H*), 1.00-0.91 (m, 18H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2, 120.2, 17.70, 17.65, 11.5 [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for methyl groups in TIPS]; **HRMS** (ESI^+, m/z) calculated for $[C_{11}H_{25}NOSSiNa]^+$ $[M+Na]^+$ 270.1318, found 270.1329 (Δ 3.93 ppm); **IR** υ_{max} (neat)/cm^{-1} 2944, 2867, 1464, 1306, 1065, 929, 703; **R_F:** 0.20 (Petrol:EtOAc = 1:1).

6.3.4 Reactions of sulfonimidoyl fluorides

General Procedure M



The respective amine (1.1 equiv.) was added to a solution of respective alkenylsulfonimidoyl fluoride (1.0 equiv.) in anhydrous CH_2Cl_2 (0.25 M) at room temperature. The resultant solution was stirred at room temperature for the indicated time (30 min – 18 h) and concentrated *in vacuo*. The crude product was purified by flash column chromatography using the appropriate solvent system.



2-Morpholino-*N*-tritylethane-1-sulfonimidoyl fluoride (141a)

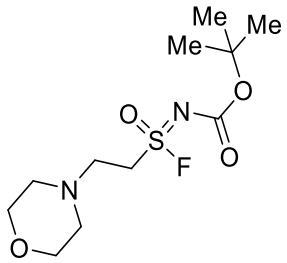
Following General Procedure M, *N*-tritylethenesulfonimidoyl fluoride **125a** (70.5 mg, 0.20 mmol), morpholine (19 μL, 0.22 mmol) and CH_2Cl_2 (0.80 mL) for 1 h. Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfonimidoyl fluoride **141a** as a white solid (61.4 mg, 0.14 mmol, 65%).

Note

Isolated yield of 72% can be achieved by stirring the crude mixture with Et_2O (1.7 ml) for 30 min. Filtration afforded the desired product as an off-white solid (50.5 mg, 0.12 mmol, 58%). Purification of the filtrate by column chromatography (Petrol:EtOAc, 1:1) yielded a further batch of pure product (12.2 mg, 0.03 mmol, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 6H, Ar-*H*), 7.35 – 7.24 (m, 9H, Ar-*H*), 3.74 (t, *J* = 4.7 Hz, 4H, OC*H*$_2$), 3.74 – 3.54 (m, 2H, SC*H*$_2$), 3.06 (app. tdd, *J* = 15.1, 10.7, 6.8 Hz,

2H, C*H*$_2$CH$_2$S), 2.59 – 2.52 (m, 4H, NC*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.30, 143.26, 128.8, 127.8, 127.1, 73.9 (d, $^3J_{C\text{-}F}$ = 4.8 Hz), 66.9, 53.3, 52.9, 52.5 (d, $^2J_{C\text{-}F}$ = 20.9 Hz) [note: due to chirality at sulfur centre, two ^{13}C NMR environments are observed for quarternary carbon in trityl group]; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 82.0 (s); **HRMS** (ESI^+, m/z) calculated for $[C_{25}H_{27}F_2N_2O_2SNa]^+$ $[M+Na]^+$ 461.1669, found 461.1670; **IR** υ_{max} (neat)/cm^{-1} 3173, 1705, 1620, 1292, 1163, 1114, 1070, 931; **M.p.** 140 °C (CH_2Cl_2); **R_F:** 0.13 (Petrol:EtOAc = 1:1).

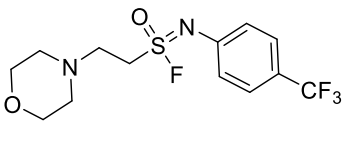


***tert*-Butyl (fluoro(2-morpholinoethyl)(oxo)-λ^6-sulfaneylidene)carbamate (158)**

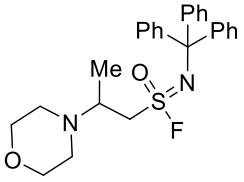
Following General Procedure M, *tert*-butyl (fluoro(oxo)(vinyl)-λ^6-sulfaneylidene)carbamate **125c** (41.9 mg, 0.20 mmol), morpholine (19 μL, 0.22 mmol) and CH_2Cl_2 (0.80 mL) for 30 min. Flash chromatography (SiO_2, Petrol:EtOAc = 1:1) afforded the desired sulfonimidoyl fluoride **158** as a colourless oil (52.0 mg, 0.18 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 – 3.63 (m, 6H, O(CH_2)$_2$ and SCH_2), 2.97 (t, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$S), 2.52 (dd, *J* = 5.6, 3.6 Hz, 4H, morph-NC*H*$_2$), 1.47 (s, 9H, OC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.8 (d, $^3J_{C\text{-}F}$ = 3.1 Hz), 82.8, 66.7, 53.2, 51.6, 49.9 (d, $^2J_{C\text{-}F}$ = 12.4 Hz), 27.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 59.3 (d, *J* = 3.1 Hz); **HRMS** (ESI^+, m/z) calculated for $[C_{11}H_{22}FN_2O_4S]^+$ $[M+H]^+$ 297.1279, found 297.1273 (Δ-2.0 ppm); **IR** υ_{max} (neat)/cm^{-1} 2980, 1701, 1369, 1292, 1155, 1118, 914, 763, 706; **R_F:** 0.13 (Petrol:EtOAc = 1:1).

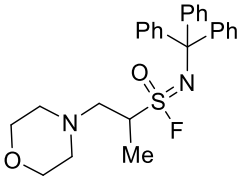
6.3.4.1 Unsuccessfully isolated 1,4-adducts



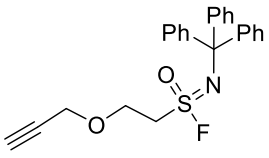
160, unable to separate by column chromatography



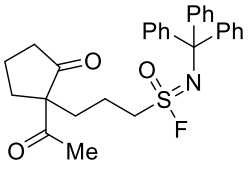
145c, decomposition during column chromatography



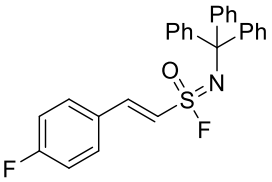
145a, decomposition during column chromatography



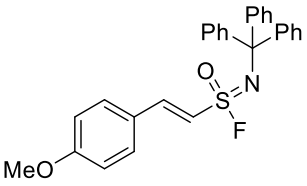
152, trace



150, n.r.

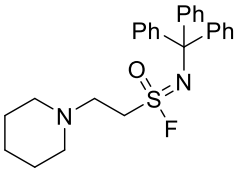


154a, trace

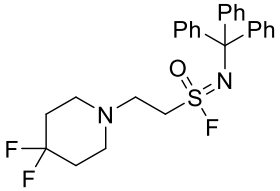


154b, trace

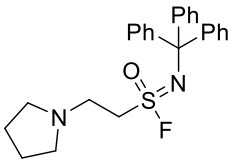
6.3.4.2 1,4-Addition products included in the thesis that were synthesised by E. Diepers[317]



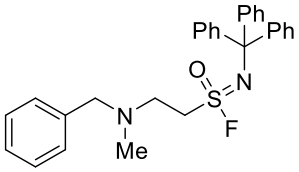
141b, decomposition during column chromatography



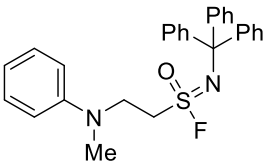
141c, 41%



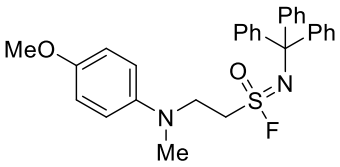
141d, decomposition during column chromatography



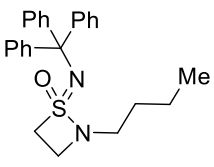
141e, 45%



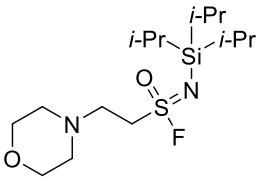
141f, n.r.



141g, decomposition during column chromatography

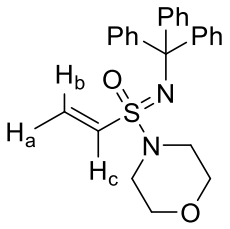


141h, 12%



147, 36%

6.3.4.3 Synthesis of sulfonimidamides



4-(*N*-Tritylvinylsulfonimidoyl)morpholine (142a)

1) Preparation of **142a** from Tr-ESIF (**125a**)

Following modified General Procedure M, *N*-tritylethenesulfonimidoyl fluoride **125a** (70.5 mg, 0.20 mmol, 1.0 equiv.), morpholine (19 µL, 0.22 mmol, 1.1 equiv.), Et_3N (28 µL, 0.20 mmol, 1.0 equiv.) and DMSO (0.80 mL) for 1 h. Flash chromatography (SiO_2, Petrol:EtOAc = 2:1) afforded the desired sulfonimidamide **142a** as a white solid (41.7 mg, 0.10 mmol, 50%).

2) Preparation of **142a** from *N*-tritylethenesulfinamide (**138a**)

In a darkened fume-hood, *tert*-butyl hypochlorite (150 µL, 1.32 mmol, 1.32 equiv.) was added to o a stirred solution of *N*-tritylethenesulfinamide **138a** (400.1 mg, 1.20 mmol, 1.2 equiv.) in CH_2Cl_2 (12 mL, 0.1 M) at 0 °C. The resultant solution was stirred at 0 °C for 30 min. Morpholine (88 µL, 1.00 mmol, 1.0 equiv.) and Et_3N (418 µL, 3.00 mmol, 3.0 equiv.) were then sequentially added. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with brine (10 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, Petrol:EtOAc = 8:1 to 2:1) afforded the desired sulfonimidamide **142a** as a white solid (257.4 mg, 0.61 mmol, 61%).

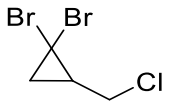
3) Preparation of **142a** in one-pot from Tr-NSO (**8**)

According to a modified procedure by Davies *et al.*,[297] in a darkened fume-hood, vinylmagnesium bromide solution (1.10 mL, 1.10 mmol, 1.0 M in THF, 1.1 equiv.) was added dropwise to a solution of Tr-NSO **8** (305.4 mg, 1.00 mmol, 1.0 equiv.) in anhydrous THF (10 mL, 0.1 M) at 0 °C. The resultant solution was stirred at 0 °C for 10 min. Then *tert*-butylhypochlorite (125 µL, 1.10 mmol, 1.1 equiv.) was added and the reaction mixture was stirred at 0 °C for another 30 min. Morpholine (88 µL, 1.00 mmol, 1.0 equiv.) and Et_3N

(418 μL, 3.00 mmol, 3.0 equiv.) were then sequentially added. The reaction mixture was warmed to room temperature and stirred for 45 minutes. The reaction mixture was quenched with brine (10 mL). The aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, Petrol:EtOAc = 4:1 to 2:1) afforded the desired sulfonimidamide **142a** as a white solid (146.0 mg, 0.35 mmol, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 6H, Ar-*H*), 7.30 – 7.21 (m, 6H, Ar-*H*), 7.22 – 7.17 (m, 3H, Ar-*H*), 6.51 (dd, *J* = 16.5, 9.8 Hz, 1H, H_c), 6.15 (d, *J* = 16.5 Hz, 1H, H_b), 5.87 (d, *J* = 9.8 Hz, 1H, H_a), 3.23 (ddd, *J* = 11.4, 6.0, 3.5 Hz, 2H, OCH_2), 3.13 (ddd, *J* = 11.4, 6.0, 3.5 Hz, 2H, OCH_2), 2.85 – 2.71 (m, 4H, NCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.0, 134.3, 129.2, 127.5, 126.5, 124.8, 66.2, 46.1; **HRMS** (ESI^+, m/z) calculated for $[C_{25}H_{26}N_2O_2SNa]^+$ $[M+Na]^+$ 441.1607, found 441.1608 (Δ0.10 ppm); **IR** υ_{max} (neat)/cm^{-1} 3173, 1705, 1620, 1292, 1163, 1114, 1070, 931; **M.p.** 147-149 °C; **R_F:** 0.13 (Petrol:EtOAc = 1:1).

6.3.5 Synthesis of bicyclobutane analogues



1,1-Dibromo-2-(chloromethyl)cyclopropane (162)

Cyclopropane **162** was prepared following a modified procedure by Bennett *et al.*[440] An oven-dried 100 mL round-bottom-flask was charged with dibenzo-18-crown-6 (465 mg, 1.29 mmol, 5.0 mol%), pinacol (122 mg, 1.03 mmol, 4.0 mol%) under a N_2 atmosphere. CH_2Cl_2 (15 mL) was added to the solids, followed by allyl chloride (3.15 mL, 38.7 mmol, 2.0 equiv.) and bromoform (2.26 mL, 25.8 mmol, 1.0 equiv.). To the resulting solution, a solution of sodium hydroxide (9.80 g, 245.1 mmol, 9.5 equiv.) in water (9.8 mL) was added in one go. The flask was equipped with a reflux condenser and a N_2 balloon, and the reaction was stirred for 16 h at 40 °C. The reaction mixture was allowed to cool down to room temperature and poured into a beaker containing 50 mL of pentane. The mixture was gently stirred with a glass stick and sonicated for five minutes. The mixture was let to sediment for 20 minutes and the supernatant pentane was passed through a celite plug. [**Note**: extra attention should be paid to avoid pouring the black precipitate or the water phase over the filter]. The black precipitate was washed twice more with 50 mL of pentane repeating the stirring-sonication-plug procedure. The solvent was then concentrated *in vacuo* and the resulting residue was redissolved in pentane (60 mL). The mixture was filtered through a thin layer of silica and the silica filter was washed with further pentane (40 mL). Concentration *in vacuo* resulted in a turbid liquid, which was passed through a Pasteur pipette containing a small amount of $MgSO_4$ to afford the pure intermediate **162** as a colourless liquid (900 mg, 3.62 mmol, 15%).

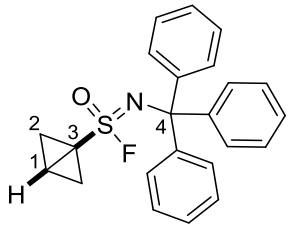
Notes

1) Aqueous solution of sodium hydroxide was made according to the following procedure. Sodium hydroxide pellets was ground to a fine powder and then added to vigorously stirred water at 0 °C. The solution was stirred at room temperature until the sodium hydroxide has fully dissolved.
2) The solvent is removed on the rotary evaporator at room temperature (21 ± 2 °C).

3) 1,1-Dibromo-2-(chloromethyl)cyclopropane is stored in the freezer (-20 °C) under an inert atmosphere and can be taken out and used regularly without loss of performance for periods >1 year.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (dd, *J* = 7.5, 1.4 Hz, 2H, C*H*$_2$Cl), 2.04 (app. dq, *J* = 10.3, 7.5 Hz, 1H, C*H*), 1.93 (dd, *J* = 10.3, 7.5 Hz, 1H, C*H*$_a$H$_b$), 1.48 (t, *J* = 7.5 Hz, 1H, CH$_a$*H*$_b$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 46.3, 32.3, 29.0, 25.8; **R_F**: 0.63 (hexane).

Data is consistent with the literature: S. H. Bennett, A. Fawcett, E. H. Denton, T. Biberger, V. Fasano, N. Winter, V. K. Aggarwal, *J. Am. Chem. Soc.* **2020**, *142*, 16766–16775.[440]



***N*-Tritylbicyclo[1.1.0]butane-1-sulfonimidoyl fluoride (166)**

Preparation of organolithium:

Bicyclo[1.1.0]butan-1-yllithium solution was prepared according to the following modified procedure by Bennett *et al.*[440] An oven-dried 25 mL round-bottom-flask was charged with 1,1-dibromo-2-(chloromethyl)cyclopropane **162** (248.3 mg, 1.00 mmol, 1.0 equiv.) and anhydrous Et_2O (5.0 mL, 0.2 M). The solution was cooled to –78 °C, then methyl lithium (0.63 mL, 1.00 mmol, 1.60 M in Et_2O, 1.0 equiv.) was added dropwise. The reaction mixture was stirred for 30 min at –78 °C, followed by 1 h at –50 °C. The solution was then cooled back to –78 °C and a high vacuum was applied for 2 min to remove volatile MeBr liberated. *t*-BuLi (0.65 mL, 1.10 mmol, 1.70 M in pentane, 1.1 equiv.) was then added dropwise and the resultant reaction mixture stirred for 1 h at –78 °C.

Preparation of sulfonimidoyl fluoride:

Bicyclo[1.1.0]butan-1-yllithium solution was added dropwise to a suspension of Tr-NSO **8** (305.4 mg, 1.00 mmol, 1.0 equiv.) in Et_2O (1.2 mL, Tr-NSO conc. 0.1 M) at -78 °C and stirred for 1 h. The reaction mixture was warmed to 0 °C and stirred for a further 20 min before addition of NFSI (378 mg, 1.20 mmol, 1.2 equiv.). The reaction mixture was warmed to room temperature and stirred for 1 h, before quenching with sat. aq. NH_4Cl solution (20

mL). The aqueous phase was then extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc = 20:1 to 10:1 to 5:1) afforded sulfonimidoyl fluoride **166** as an off-white solid (72.5 mg, 0.19 mmol, 19%).

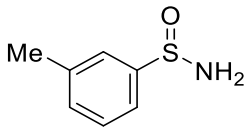
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (5H, m, Ar-*H*), 7.24 – 7.11 (10H, m, Ar-*H*), 2.67 (1H, ddd, *J* = 5.8, 3.8, 1.9 Hz, C_2-*H*), 2.51 (1H, ddd, *J* = 6.1, 3.8, 1.9 Hz, C_2-*H*), 2.37 (1H, ddt, *J* = 3.8, 2.3, 1.3 Hz, C_1-*H*), 1.49 (1H, app. dq, *J* = 2.6, 1.3 Hz, C_2-*H*), 1.40 (1H, ddt, *J* = 3.0, 2.0, 1.0 Hz, C_2-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.51, 146.46, 128.7, 127.8, 127.1, 73.7 (d, $^3J_{C\text{-}F}$ = 4.6 Hz), 39.1, 37.9, 23.6 (d, $^2J_{C\text{-}F}$ = 57.0 Hz), 14.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 87.8 (s); **HRMS** (ESI^+, m/z) calculated for $[C_{23}H_{20}FNOSNa]^+$ $[M+Na]^+$ 400.1142, found 400.1159 (Δ4.3 ppm); **IR** υ_{max} (neat)/cm^{-1} 1492, 1448, 1363, 1211, 826, 760, 704; **M.p.** 130 °C ($CHCl_3$); **R_F:** 0.28 (Petrol:EtOAc = 8:1).

6.4 Data for chapter 4

6.4.1 Synthetic procedures and date

6.4.1.1 Synthesis of primary sulfinamides

[*Note:* Primary sulfinamides used in chapter 2 are included in **Chapter 6.2**]

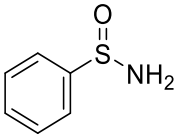


3-Methylbenzenesulfinamide (186b)

Following General Procedure B, using TIPS-NSO **83b** (658.3 mg, 3.00 mmol, 1.0 equiv.), THF (30 mL), 3-methylphenylmagnesium bromide solution (3.67 mL, 3.60 mmol, 0.98 M in THF, 1.2 equiv.) and TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, Petrol:EtOAc 1:2 to 1:5) afforded the desired sulfinamide **186b** as a white solid (394.4 mg, 2.54 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.55 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.54 – 7.50 (m, 1H, Ar-*H*), 7.37 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.28 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 5.01 (s, 2H, N-H_2), 2.42 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.3, 138.8, 131.5, 128.6, 125.8, 122.5, 21.3; **LRMS** m/z (ESI^+) $[M+Na]^+$: 178.0; **R_F:** 0.25 (Petrol:EtOAc 1:3).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]

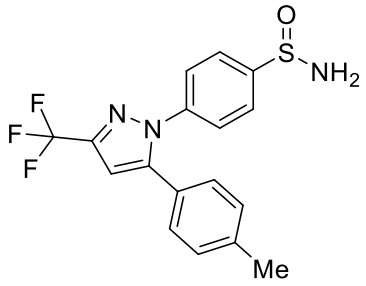


Benzenesulfinamide (186h)

Following General Procedure A, using oxalyl chloride (499 µL, 5.82 mmol, 1.06 equiv.), benzenesulfinic acid sodium salt (901 mg, 5.49 mmol, 1.0 equiv.), PhMe (11 mL), NH_4OH (5.5 mL) and EtOAc (5.5 mL) were used. Flash column chromatography (SiO_2, Petrol:EtOAc 1:3) afforded the desired sulfinamide **186h** as a white solid (567 mg, 4.02 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H, Ar-*H*), 7.50 – 7.46 (m, 3H, Ar-*H*), 4.56 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5, 131.1, 129.0, 125.6; **LRMS** m/z (ESI^+) $[M+Na]^+$: 164.0; **R_F:** 0.24 (Petrol:EtOAc 1:3).

Data is consistent with the literature: S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *60*, 758-765.[413]



4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfinamide (186i)

Preparation of organometallic reagent:

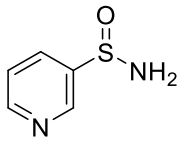
(4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)lithium solution was prepared according to the following procedure. To a cooled solution of 1-(4-bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazole (914.9 mg, 2.40 mmol, 1.2 equiv.) in THF (2.4 mL, Ar-Br conc. 1.0 M) at -78 °C, was added *n*-butyllithium solution (1.05 mL, 2.52 mmol, 2.39 M in hexanes, 1.26 equiv.) dropwise. The reaction was stirred at the same temperature for 40 minutes.

Preparation of sulfinamide:

186i was then prepared following General Procedure B, using TIPS-NSO **83b** (658.3 mg, 2.00 mmol, 1.0 equiv.), THF (20 mL), (4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)lithium solution (2.4 mmol, 1.2 equiv.) and TBAF solution (4.0 mL, 4.0 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, CH_2Cl_2:EtOAc 1:1 to 1:2) afforded the desired sulfinamide **186i** as a colourless oil (541.5 mg, 2.11 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 7.42 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 7.15 – 7.07 (m, 4H, Ar-*H*), 6.72 (s, 1H, Pyr-*H*), 4.77 (s, 2H, N-H_2), 2.33 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.3, 145.2, 143.8 (q, $^2J_{C-F}$ = 38.4 Hz), 141.5, 139.6, 129.7, 128.8, 126.7, 125.9, 125.6, 121.2 (d, $^1J_{C-F}$ = 269.0 Hz), 106.0 (d, $^4J_{C-F}$ = 2.0 Hz), 21.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.3 (s); **R_F:** 0.25 (Petrol:EtOAc 1:3).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



Pyridine-3-sulfinamide (186l)

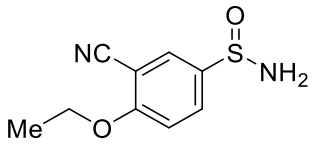
Preparation of organometallic reagent:

3-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 3-bromopyridine (231 μL, 2.40 mmol, 1.2 equiv.) in THF (1.3 mL, Ar-Br conc. 1.8 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.97 mL, 2.42 mmol, 1.25 M in THF, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 1 h.

Preparation of sulfinamide:

186l was then prepared following General Procedure B, using TIPS-NSO **83b** (438.8 mg, 2.00 mmol, 1.0 equiv.), THF (10 mL), 3-pyridylmagnesium chloride lithium chloride complex solution (2.20 mmol, 1.1 equiv.) and TBAF solution (4.00 mL, 4.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, EtOAc:MeOH 0:1 to 10:1) afforded the desired sulfinamide **186l** as an off-white solid (114.2 mg, 0.80 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H, Ar-*H*), 8.05 (dt, *J* = 8.0, 1.9 Hz, 1H, Ar-*H*), 7.43 (dd, *J* = 8.0, 4.8 Hz, 1H, Ar-*H*), 4.80 (s, 2H, N-*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 147.6, 142.8, 133.9, 123.8; **LRMS** m/z (ESI^+) $[M+H]^+$: 165.0; **IR** υ_{max} (neat)/cm^{-1} 3213, 3086, 1578, 1415, 1052, 1020, 703; **R_F:** 0.30 (Petrol:EtOAc 1:3).



3-Cyano-4-ethoxybenzenesulfinamide (186m)

Preparation of organometallic reagent:

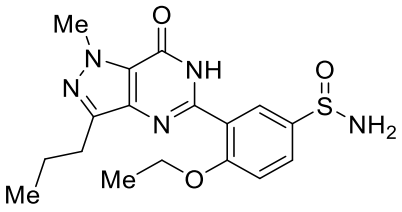
(3-Cyano-4-ethoxyphenyl)lithium solution was prepared according to the following procedure. To a solution of 5-bromo-2-ethoxybenzonitrile (542.6 mg, 2.40 mmol, 1.2 equiv.) in THF (4.8 mL) in an oven-dried 25 mL round-bottom flask was added *n*-butyllithium solution (1.07 mL, 2.40 mmol, 2.25 M in hexanes, 1.2 equiv.) dropwise at -78 °C. The reaction was stirred at the same temperature for 1 h.

Preparation of sulfinamide:

186m was then prepared following General Procedure B, using TIPS-NSO **83b** (438.8 mg, 2.00 mmol, 1.0 equiv.), THF (20 mL), (3-cyano-4-ethoxyphenyl)lithium solution (2.40 mmol, 1.2 equiv.) and TBAF solution (4.00 mL, 4.00 mmol, 1.0 M in THF, 2.0 equiv.). Flash column chromatography (SiO_2, CH_2Cl_2/EtOAc = 1:2 to 1:4) afforded the desired sulfinamide **186m** as a white solid (306.9 mg, 1.46 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 7.87 (dd, *J* = 8.8, 2.3 Hz, 1H, Ar-*H*), 7.07 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 4.46 (s, 2H, N-H_2), 4.22 (qd, *J* = 7.0, 1.0 Hz, 2H, CH_2), 1.52 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7, 138.5, 132.1, 131.8, 115.5, 112.5, 102.9, 65.5, 14.5; **LRMS** m/z (ESI$^+$) $[M+H]^+$: 211.0.

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzenesulfinamide (186n)

Preparation of organometallic reagent:

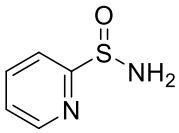
(4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)phenyl)lithium was prepared according to the following procedure. To a solution of 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one (1.174 g, 3.00 mmol, 1.0 equiv.) in THF (15 mL, 0.2 M) in an oven-dried 50 mL round-bottom flask, was added methyllithium solution (2.25 mL, 3.60 mmol, 1.60 M in Et_2O, 1.2 equiv.) at -78 °C. The reaction mixture was stirred at the same temperature for 10 min before addition of *n*-butyllithium solution (1.80 mL, 4.50 mmol, 1.80 M in hexanes, 1.5 equiv.) dropwise at -78 °C. The reaction was stirred at the same temperature for 50 minutes.

Preparation of sulfinamide:

186n was then prepared following modified General Procedure B, using TIPS-NSO **83b** (986.0 mg, 4.50 mmol, 1.5 equiv.), THF (7.5 mL), (4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)phenyl)lithium (2.00 mmol, 1.0 equiv.) with stirring at -78 °C for 20 min, then warmed to 0 °C and stirring for 30 min. TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.) was then added and the reaction mixture stirred at 0 °C for 10 min. Flash column chromatography (Silica, Petrol:EtOAc:MeOH 1:2:0 to 0:1:0 to 0:10:1) afforded the desired sulfinamide **186n** as an off-white solid (1.00 g, 2.67 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 7.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 4.46 (s, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 4.27 (s, 3H), 2.97 – 2.89 (m, 2H), 1.93 – 1.79 (m, 2H), 1.63 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 158.0, 153.7, 149.0, 144.9, 139.4, 137.9, 129.1, 127.6, 124.3, 122.8, 112.9, 64.5, 37.8, 27.1, 21.7, 14.4, 13.8; **LRMS** m/z (ESI^+) $[M+H]^+$: 376.1; **R_F:** 0.15 (EtOAc).

Data is consistent with the literature: M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**, *24*, 1711–1715.[143]



Pyridine-2-sulfinamide (192a)

Preparation of organometallic reagent:

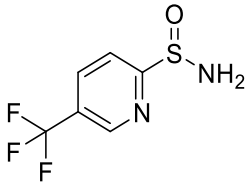
2-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 2-bromopyridine (210 μL, 2.20 mmol, 1.1 equiv.) in THF (1.3 mL, Ar-Br conc. 1.7 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.94 mL, 2.42 mmol, 1.25 M in THF, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 2 h.

Preparation of sulfinamide:

192a was then prepared following General Procedure B, using TIPS-NSO **83b** (438.8 mg, 2.00 mmol, 1.0 equiv.), THF (10 mL), 2-pyridylmagnesium chloride lithium chloride complex (2.20 mmol, 1.1 equiv.) and TBAF solution (4.00 mL, 4.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, EtOAc:MeOH 0:1 to 10:1) afforded the desired sulfinamide **192a** as an off-white solid (250.1 mg, 1.76 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dt, *J* = 4.7, 1.3 Hz, 1H, Ar-*H*), 8.00 – 7.88 (m, 2H, Ar-*H*), 7.44 (ddd, *J* = 7.3, 4.7, 1.5 Hz, 1H, Ar-*H*), 4.69 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5, 150.2, 138.2, 125.8, 120.7; **LRMS** m/z (ESI$^+$) $[M+Na]^+$: 165.0.

Data is consistent with the literature: R. R. Groleau, R. S. L. Chapman, H. Ley-Smith, L. Liu, T. D. James, S. D. Bull. *J. Org. Chem.* **2020**, *85*, 1208−1215.[428]



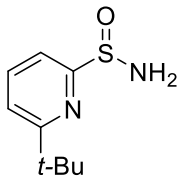
5-(Trifluoromethyl)pyridine-2-sulfinamide (192c)

Following modified General Procedure A, using oxalyl chloride (380 μL, 4.40 mmol, 1.1 equiv.), sodium 5-(trifluoromethyl)pyridine-2-sulfinate (932.6 mg, 4.00 mmol, 1.0 equiv.), PhMe (8 mL), NH_4OH (4 mL) and EtOAc (4 mL) were used. Filtration, washing with hexane afforded the desired sulfinamide **192c** as a white solid (520.1 mg, 2.47 mmol, 62%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.08 – 9.06 (m, 1H, Ar-*H*), 8.47 (dd, *J* = 8.3, 2.3 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 6.56 (s, 2H, N-H_2); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 170.9, 146.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 135.7 (q, $^4J_{C\text{-}F}$ = 3.6 Hz), 126.1 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 123.4 (q, $^1J_{C\text{-}F}$ = 273.1 Hz), 119.7; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ -60.9 (s); **LRMS** m/z (ESI^+) $[M+Na]^+$: 233.0; **IR** υ_{max} (neat)/cm^{-1} 2954, 2881, 1642, 1588, 1435, 1091, 987; **R_F:** 0.15 (Petrol:EtOAc 1:3).

Note

Sodium 5-(trifluoromethyl)pyridine-2-sulfinate starting material was kindly prepared by Dr. Xinlan Cook. 897 mg, 77%



6-(*tert*-Butyl)pyridine-2-sulfinamide (192d)

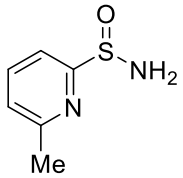
Preparation of organometallic reagent:

(6-(*tert*-Butyl)pyridin-2-yl)lithium solution was prepared according to the following procedure. To a cooled solution of 2-bromo-6-*tert*-butyl pyridine (650 mg, 3.04 mmol, 1.2 equiv.) in THF (15.2 mL, Ar-Br conc. 0.2 M) at -78 °C, was added *n*-butyllithium solution (1.35 mL, 3.04 mmol, 2.27 M in hexanes, 1.2 equiv.) dropwise. The reaction mixture was stirred at the same temperature for 40 minutes.

Preparation of sulfinamide:

192d was then prepared following General Procedure B, using TIPS-NSO **83b** (555.8 mg, 2.53 mmol, 1.0 equiv.), THF (25 mL), (6-(*tert*-butyl)pyridin-2-yl)lithium solution (3.04 mmol, 1.2 equiv.) and TBAF solution (5.06 mL, 5.06 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, CH_2Cl_2:EtOAc 1:2 to 1:4) afforded the desired sulfinamide **192d** as an off-white solid (265 mg, 1.87 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.70 (dd, *J* = 7.7, 1.0 Hz, 1H, Ar-*H*), 7.48 (dd, *J* = 7.9, 1.0 Hz, 1H, Ar-*H*), 4.82 (s, 2H, N-H_2), 1.40 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2, 162.2, 138.4, 121.8, 118.2, 38.0, 30.2; **LRMS** m/z (ESI$^+$) $[M+Na]^+$: 221.1; **IR** υ_{max} (neat)/cm^{-1} 2960, 2934, 2873, 1655, 1588, 1467, 1086, 1067, 799; **R_F:** 0.23 (Petrol:EtOAc 1:3).



6-Methylpyridine-2-sulfinamide (192e)

Preparation of organometallic reagent:

(6-(Methyl)pyridin-2-yl)lithium solution was prepared according to the following procedure. To a cooled solution of 2-bromo-6-methyl pyridine (430 μL, 3.60 mmol, 1.2 equiv.) in THF (9.0 mL, Ar-Br conc. 0.4 M) at -78 °C, was added *n*-butyllithium solution (1.59 mL, 3.60 mmol, 2.27 M in hexanes, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 40 minutes.

Preparation of sulfinamide:

192e was then prepared following General Procedure B, using TIPS-NSO **83b** (658.3 mg, 3.00 mmol, 1.0 equiv.), THF (21 mL), (6-(methyl)pyridin-2-yl)lithium solution (3.6 mmol, 1.2 equiv.) and TBAF solution (6.00 mL, 6.00 mmol, 1.00 M in THF, 2.0 equiv.). Flash column chromatography (Silica, EtOAc:MeOH 0:1 to 10:1) afforded the desired sulfinamide **192e** as an off-white solid (142.0 mg, 0.91 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.73 (ddd, *J* = 7.7, 1.2, 0.6 Hz, 1H, Ar-*H*), 7.28 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 4.71 (s, 2H, N-H_2), 2.63 (s, 3H, CH_3);

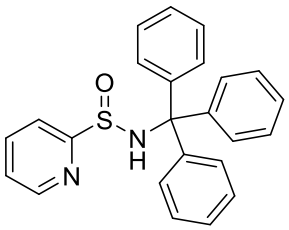
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 159.8, 138.2, 125.7, 117.6, 24.5; **LRMS** m/z (ESI^+) $[M+Na]^+$: 179.0; **R_F:** 0.22 (Petrol:EtOAc 1:3).

Data is consistent with the literature: S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *60*, 758-765.[413]

6.4.1.2 Synthesis of *N*-trityl sulfinamides

General Procedure N

An oven-dried round-bottom flask containing Tr-NSO **8** (1.0 equiv.) was sealed and subjected to three N_2 evacuation/refill cycles before pre-sparged anhydrous THF (Tr-NSO conc. 0.17 M) was added. The solution was cooled to 0 °C and then the corresponding Grignard or organolithium reagent (1.2 equiv.) was added dropwise. The reaction was stirred at 0 °C for 10 minutes before being diluted with EtOAc (30 mL) and quenched with saturated aqueous solution of EDTA tetrasodium salt (30 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. *N*-Trityl sulfinamide was then purified by flash column chromatography with the appropriate solvent system or by filtration, washing with hexane and Et_2O.



***N*-Tritylpyridine-2-sulfinamide (198b)**

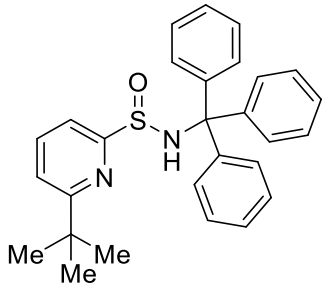
Preparation of organometallic reagent:

2-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 2-bromopyridine (210 μL, 2.20 mmol, 1.1 equiv.) in THF (1.3 mL, Ar-Br conc. 1.7 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.25 M in THF, 1.94 mL, 2.42 mmol, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 2 h.

Preparation of sulfinamide:

198b was then prepared according to General Procedure N, using Tr-NSO **8** (610.8 mg, 2.00 mmol, 1.0 equiv.), 2-pyridylmagnesium chloride lithium chloride complex solution (2.20 mmol, 1.1 equiv.) and THF (10 mL, 0.2 M). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **198b** as a white solid (761 mg, 1.98 mmol, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, Pyr-*H*), 7.82 (td, *J* = 7.6, 1.8 Hz, 1H, Pyr-*H*), 7.72 (dt, *J* = 7.8, 1.0 Hz, 1H, Pyr-*H*), 7.45 – 7.41 (m, 6H, Ar-*H*), 7.38 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, Pyr-*H*), 7.35 – 7.24 (m, 9H, Ar-*H*), 6.33 (s, 1H, N-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 149.8, 144.9, 138.1, 129.4, 128.0, 127.4, 125.5, 121.6, 72.8; **HRMS** (ESI^+, m/z) calculated for $[C_{24}H_{20}N_2OSNa]^+$ $[M+Na]^+$ 407.1189, found 407.1196 (Δ 1.82 ppm); **IR** υ_{max} (neat)/cm^{-1} 3057, 3002, 1448, 1037, 754, 701; **M.p.** 195 °C; **R_F:** 0.13 (Petrol:EtOAc 1:1).



6-(*tert*-Butyl)-*N*-tritylpyridine-2-sulfinamide (193d)

Preparation of organometallic reagent:

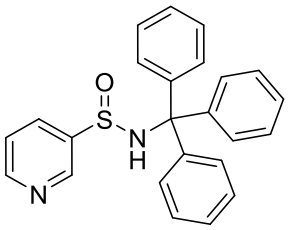
6-(*tert*-Butyl)pyridin-2-yl)lithium solution was prepared according to the following procedure. To a cooled solution of 2-bromo-6-*tert*-butyl pyridine (650 mg, 3.04 mmol, 1.2 equiv.) in THF (15.2 mL, Ar-Br conc. 0.2 M) at -78 °C, was added *n*-butyllithium solution (1.35 mL, 3.04 mmol, 2.27 M in hexanes, 1.2 equiv.) dropwise. The reaction mixture was stirred at the same temperature for 40 minutes.

Preparation of sulfinamide:

193d was then prepared following General Procedure N, using Tr-NSO **8** (610.8 mg, 2.00 mmol, 1.0 equiv.), (6-(*tert*-butyl)pyridin-2-yl)lithium solution (3.04 mmol, 1.2 equiv.), THF (10 mL, 0.2 M). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **193d** as a white solid (809 mg, 1.84 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.8 Hz, 1H, Pyr-*H*), 7.63 (dd, *J* = 7.7, 0.9 Hz, 1H, Pyr-*H*), 7.49 – 7.45 (m, 6H, Ar-*H*), 7.43 (dd, *J* = 7.9, 0.9 Hz, 1H, Pyr-*H*), 7.34 – 7.25 (m, 9H, Ar-*H*), 1.35 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 162.4, 145.3, 138.6, 129.4, 128.0, 127.3, 121.2, 119.5, 72.8, 37.9, 30.1; **HRMS** (ESI^+, m/z) calculated for

$[C_{28}H_{28}N_2OSNa]^+$ $[M+Na]^+$ 463.1815, found 463.1815 (Δ 0.09 ppm); **M.p.** 176 °C; **R_F:** 0.35 (Petrol:EtOAc 1:1).



***N*-Tritylpyridine-3-sulfinamide (200)**

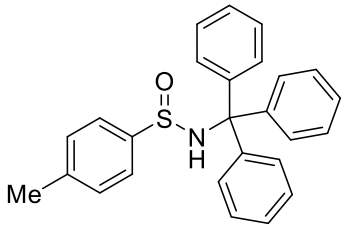
Preparation of organometallic reagent:

3-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 3-bromopyridine (231 μL, 2.40 mmol, 1.2 equiv.) in THF (1.3 mL, Ar-Br conc. 1.8 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.97 mL, 2.42 mmol, 1.25 M in THF, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 1 h.

Preparation of sulfinamide:

200 was then prepared following General Procedure **B**N, using Tr-NSO **8** (610.8 mg, 2.00 mmol, 1.0 equiv.), THF (10 mL) and 3-pyridylmagnesium chloride lithium chloride complex solution (2.40 mmol, 1.2 equiv.). Flash column chromatography (Silica, Petrol:EtOAc 1:1 to 0:1) afforded the desired sulfinamide **200** as a white solid (610.2 mg, 1.59 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 2.4, 0.8 Hz, 1H, Pyr-*H*), 8.67 (dd, *J* = 4.8, 1.6 Hz, 1H, Pyr-*H*), 8.06 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H, Pyr-*H*), 7.42 (ddd, *J* = 8.1, 4.8, 0.8 Hz, 1H, Pyr-*H*), 7.39 – 7.28 (m, 15H, Ar-*H*), 5.48 (s, 1H, N-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7, 147.7, 144.3, 143.7, 134.1, 129.6, 128.3, 127.8, 123.9, 74.0; **HRMS** (ESI^+, m/z) calculated for $[C_{24}H_{20}N_2OSNa]^+$ $[M+Na]^+$ 407.1189, found 407.1194 (Δ 1.33 ppm); **IR** υ_{max} (neat)/cm^{-1} 3059, 3004, 1494, 1447, 1413, 1017, 755, 700; **M.p.** 178-179 °C; **R_F:** 0.31 (EtOAc).

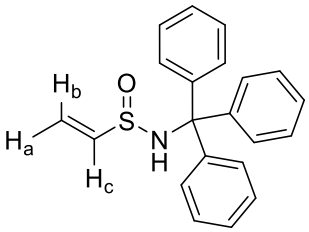


4-Methyl-*N*-tritylbenzenesulfinamide (66m)

Prepared according to General Procedure N, using Tr-NSO **8** (916.2 mg, 3.00 mmol), 4-methylphenylmagnesium bromide solution (3.60 mL, 3.60 mmol, 1.00 M in THF) and THF (15 mL). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **66m** as a white solid (1.13 g, 2.84 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H, Ar-*H*), 7.47 – 7.42 (m, 6H, Ar-*H*), 7.41 – 7.36 (m, 6H, Ar-*H*), 7.38 – 7.28 (m, 5H, Ar-*H*), 5.23 (s, 1H, N-*H*), 2.45 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.8, 144.3, 141.3, 129.8, 129.7, 128.1, 127.6, 125.7, 73.6, 21.4; **HRMS** (ESI^+, m/z) calculated for $[C_{26}H_{23}NOSNa]^+$ $[M+Na]^+$ 420.1393, found 420.1393 (Δ 0.57 ppm); **IR** υ_{max} (neat)/cm^{-1} 3059, 2243, 1397, 1326,1088, 1015, 960, 701; **M.p.** 162 – 164 °C; **R_F:** 0.55 (Petrol:EtOAc 1:1).

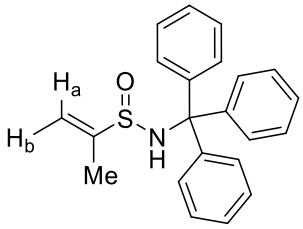
[Note: When scaled up to a 15 mmol scale, gave a 94% yield]



***N*-Tritylethenesulfinamide (138a)**

Prepared according to General Procedure N, using Tr-NSO **8** (9.16 mg, 30.0 mmol), 4-methylphenylmagnesium bromide solution (36.0 mL, 36.0 mmol, 1.00 M in THF) and THF (150 mL). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **138a** as a white solid (9.00 g, 27.0 mmol, 90%).

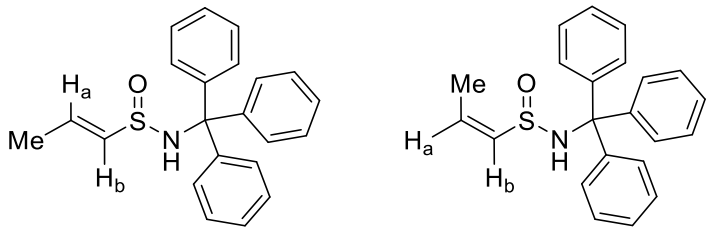
Data consistent with synthesis in **Chapter 6.3.3**.



***N*-Tritylprop-1-ene-2-sulfinamide (205a)**

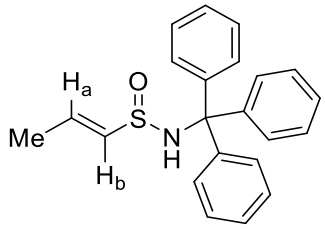
Prepared according to General Procedure N, using Tr-NSO **8** (916.2 mg, 3.00 mmol), isopropenylmagnesium bromide solution (7.20 mL, 3.6 mmol, 0.50 M in THF) and THF (15 mL). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **205a** as a white solid (987.2 mg, 2.84 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 15H, Ar-*H*), 5.89 (d, *J* = 1.0 Hz, 1H, H_a), 5.52 (q, *J* = 1.5 Hz, 1H, H_b), 4.85 (s, 1H, N-*H*), 2.03 (t, *J* = 1.2 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 144.8, 129.6, 128.1, 127.5, 117.5, 73.3, 16.4; **HRMS** (ESI^+, m/z) calculated for $[C_{22}H_{21}NOSNa]^+$ $[M+Na]^+$ 370.1236, found 370.1236 (Δ -0.03 ppm); **IR** υ_{max} (neat)/cm^{-1} 3304.8, 2980, 1651, 1550, 1489, 1446, 1072, 1012, 756, 702; **M.p.** 140 – 142 °C ($CHCl_3$); **R_F:** 0.36 (Petrol:EtOAc 1:1).



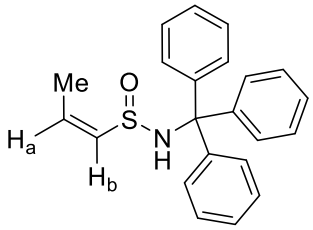
(*E*)-*N*-Tritylprop-1-ene-1-sulfinamide (*E*)-205b and **(*Z*)-*N*-Tritylprop-1-ene-1-sulfinamide (*Z*)-205b**

Prepared according to General Procedure N, using Tr-NSO **8** (610.8 mg, 2.00 mmol), 1-propenylmagnesium bromide solution (4.80 mL, 2.4 mmol, 0.50 M in THF, mixture of isomers) and THF (10 mL). Flash chromatography (SiO_2, Petrol:EtOAc = 3:1 to 1:1) afforded the desired sulfinamide (*E*)-**205b** as a white solid (305.6 mg, 0.88 mmol, 44%) and sulfinamide (*Z*)-**205b** as a white solid (280.2 mg, 0.81 mmol, 40%).



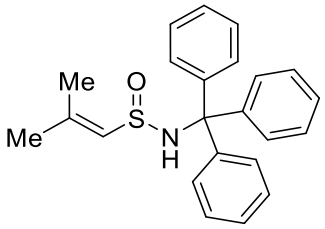
(*E*)-*N*-Tritylprop-1-ene-1-sulfinamide (*E*)-205b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 15H, Ar-*H*), 6.44 (dq, *J* = 13.8, 6.8 Hz, 1H, H_b), 6.20 (dd, *J* = 14.9, 1.7 Hz, 1H, H_a), 5.05 (s, 1H, N-*H*), 1.87 (dd, *J* = 6.9, 1.6 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.8, 135.5, 135.2, 129.2, 128.0, 127.4, 72.8, 17.3; **HRMS** (ESI^+, m/z) calculated for $[C_{22}H_{21}NOSNa]^+$ $[M+Na]^+$ 370.1236, found 370.1242 (Δ -1.59 ppm); **IR** υ_{max} (neat)/cm^{-1} 3060, 1492, 1447, 1092, 1063, 1038, 1019, 754, 701; **M.p.** 179 – 181 °C; **R_F:** 0.29 (Petrol:EtOAc 1:1).



(*Z*)-*N*-Tritylprop-1-ene-1-sulfinamide (*Z*)-205b

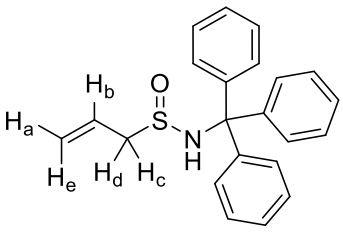
^{1}H NMR (400 MHz, $CDCl_3$) 7.39 – 7.26 (m, 15H, Ar-*H*), 6.38 (dq, *J* = 9.8, 1.6 Hz, 1H, H_a), 5.94 (dq, *J* = 9.9, 7.1 Hz, 1H, H_b), 5.36 (s, 1H, N-*H*), 1.75 (dd, *J* = 7.1, 1.6 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 138.6, 132.1, 129.3, 128.1, 127.4, 73.1, 15.0; **HRMS** (ESI^+, m/z) calculated for $[C_{22}H_{21}NOSNa]^+$ $[M+Na]^+$ 370.1236, found 370.1251 (Δ 4.02 ppm); **IR** υ_{max} (neat)/cm^{-1} 3060, 1597, 1494, 1447, 1038, 1021, 755, 700; **M.p.** 172 – 174 °C; **R_F:** 0.15 (Petrol:EtOAc 1:1).



2-Methyl-*N*-tritylprop-1-ene-1-sulfinamide (205c)

Prepared according to General Procedure N, using Tr-NSO **8** (610.8 mg, 2.00 mmol), 2-methyl-1- propenylmagnesium bromide solution (5.22 mL, 2.40 mmol, 0.46 M in THF) and THF (10 mL). Filtration twice, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **205c** as a white solid (703.3 mg, 1.95 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 15H, Ar-*H*), 6.14 (app. p, *J* = 1.3 Hz, 1H, C*H*), 5.20 (s, 1H, N-*H*), 1.76 (d, *J* = 1.4 Hz, 3H, C*H*$_3$), 1.69 (d, *J* = 1.1 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 142.9, 133.4, 129.2, 128.0, 127.3, 72.9, 25.2, 20.0; **HRMS** (ESI^+, m/z) calculated for $[C_{23}H_{24}NOS]^+$ $[M+H]^+$ 362.1573, found 362.1585 (Δ 3.27 ppm); **M.p.** 184 - 186 °C; **R_F:** 0.12 (Petrol:EtOAc 1:1).



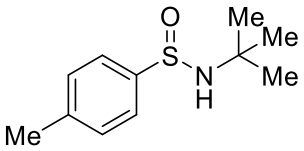
***N*-Tritylprop-2-ene-1-sulfinamide (207)**

Prepared according to General Procedure N, using Tr-NSO **8** (916.2 mg, 3.00 mmol), allylmagnesium bromide solution (3.60 mL, 3.60 mmol, 1.00 M in Et_2O) and THF (15 mL). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **207** as a white solid (987.7 mg, 2.84 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 15H, Ar-*H*), 6.02 (dddd, *J* = 17.2, 10.2, 9.0, 6.0 Hz, 1H, *H*$_b$), 5.52 (dd, *J* = 10.1, 1.7 Hz, 1H, *H*$_a$), 5.30 (dq, *J* = 17.1, 1.3 Hz, 1H, *H*$_e$), 5.22 (s, 1H. N-*H*), 3.55 (ddt, *J* = 12.6, 6.0, 1.2 Hz, 1H, *H*$_d$), 3.03 (dd, *J* = 12.7, 9.0 Hz, 1H, *H*$_c$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 129.1, 128.1, 127.4, 125.9, 124.1, 72.6, 59.6; **HRMS** (ESI^+, m/z) calculated for $[C_{22}H_{21}NOSNa]^+$ $[M+Na]^+$ 370.1236, found 370.1245 (Δ

2.40 ppm); **IR** υ_{max} (neat)/cm^{-1} 3158, 1494, 1000, 756, 700; **M.p.** 120 – 122 °C; **R_F:** 0.30 (Petrol:EtOAc 1:1).

6.4.1.3 Synthesis of *N*-substituted sulfinamides

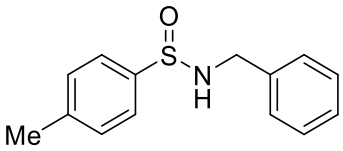


***N*-(*tert*-Butyl)-4-methylbenzenesulfinamide (66l)**

Prepared according to General Procedure D, using sodium 4-methylbenzene sulfinate **180b** (2.50 g, 14.0 mmol) in PhMe (35 mL), oxalyl chloride (1.33 mL, 15.5 mmol) and *tert*-butyl amine (1.80 mL, 16.8 mmol) and triethylamine (2.94 mL, 21.1 mmol) in PhMe (10 mL). Flash column chromatography (SiO_2, Petrol:EtOAc 10:1 to 1:1) afforded the desired sulfinamide **66l** (1.82 g, 8.62 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.29 – 7.26 (m, 2H, Ar-*H*), 3.81 (s, 1H, N-*H*), 2.40 (3H, s, Ar-CH_3), 1.40 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 141.1, 129.6, 125.7, 54.4, 31.3, 21.4; **LRMS (ESI)** m/z (ESI$^+$) [M+Na]$^+$: 234.0; **IR:** υ_{max} (neat)/ cm^{-1} 3169, 2970, 2923, 1493, 1475, 1366, 1228, 1205, 1177, 1088, 1055, 1035, 950, 925, 811, 708, 625; **R_F** 0.38 (Petrol:EtOAc 2:1).

The spectra and data matched those previously reported in the literature: H. Yu, Z. Li, C. Bolm, *Angew. Chem. Int. Ed.*, **2018**, *57*, 15602 – 15605.[441]



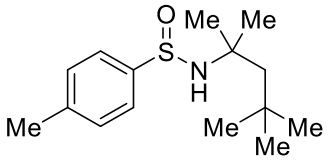
***N*-benzyl-4-methylbenzenesulfinamide (66m)**

Prepared according to General Procedure D, using sodium 4-methylbenzene sulfinate **180b** (1.922 g, 10.0 mmol) in PhMe (25 mL), oxalyl chloride (944 µL, 11.0 mmol) and benzylamine (1.31 mL, 12.0 mmol) and triethylamine (2.09 mL, 15.0 mmol) in PhMe (7.1 mL). Flash column chromatography (SiO_2, Petrol:EtOAc 8:1 to 1:1) afforded the desired sulfinamide **66m** as a white solid (2.07 g, 8.44 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.36 – 7.23 (m, 7H), 4.60 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.23 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.89 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.43 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 140.8, 137.9, 129.6, 128.6, 128.3, 127.6, 126.1, 44.5, 21.4; **LRMS (ESI)** m/z (ESI^+) $[M+H]^+$: 246.1.

The spectra and data matched those previously reported in the literature: H. Yu; Z. Li; C. Bolm, *Angew. Chem. Int. Ed.* **2018,** *57*, 15602 – 15605.[441]

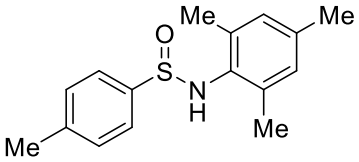


4-Methyl-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfinamide (66n)

Prepared according to General Procedure B, using *t*-Oct-NSO **83a** (350.6 mg, 2.00 mmol), 4-methylphenylmagnesium bromide solution (2.40 mL, 2.40 mmol, 1.00 M in THF) and THF (10 mL, 0.20 M). Flash column chromatography (Petrol:EtOAc 1:1) afforded the desired sulfinamide **66n** as an off-white solid (501.3 mg, 1.87 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.20 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 3.83 (s, 1H, N-*H*), 2.32 (s, 3H, Ar-CH_3), 1.61 (d, *J* = 14.9 Hz, 1H, AlkCH_aH$_b$)), 1.54 (d, *J* = 14.9 Hz, 1H, AlkCH$_a$$H_b$), 1.46 (s, 3H, C$H_3$), 1.40 (s, 3H, C$H_3$), 0.96 (s, 9H, (C$H_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 140.7, 129.3, 125.5, 58.1, 56.1, 32.4, 31.75, 31.73, 29.1, 21.2 [note: for gem-dimethyl carbons in *tert*-octyl group, NC(CH_3)$_2$CH$_2$C(CH$_3$)$_3$, 2 peaks were found instead of 1 due to the loss of symmetry caused by chiral sulfur atom]; **LRMS (ESI)** m/z (ESI^+) $[M+H]^+$: 268.2; **M.p.** 90-92 °C; **R_F:** 0.43 (Petrol:EtOAc 1:1).

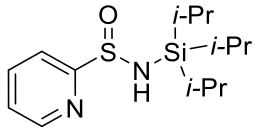
The spectra and data matched those previously reported in the literature: H. Yu; Z. Li; C. Bolm, *Angew. Chem. Int. Ed.* **2018,** *57*, 15602 – 15605.[441]



***N*-mesityl-4-methylbenzenesulfinamide (66p)**

Prepared according to General Procedure B, using (mesitylimino)-λ^4-sulfanone (362.5 mg, 2.00 mmol), 4-methylphenylmagnesium bromide solution (2.40 mL, 2.40 mmol, 1.00 M in THF) and THF (20 mL, 0.10 M). Flash column chromatography (Petrol:EtOAc 1:1) afforded the desired sulfinamide **66p** as an off-white solid (491.1 mg, 1.80 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H, Ar-*H*), 7.40 – 7.32 (m, 2H, Ar-*H*), 6.91 (s, 2H, Ar-*H*), 5.49 (s, 1H, N-*H*), 2.45 (s, 3H, C*H*$_3$), 2.39 (s, 6H, C*H*$_3$), 2.28 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4, 141.9, 135.9, 134.4, 133.9, 129.9, 129.7, 125.5, 21.5, 21.0, 19.3; **LRMS (ESI)** m/z (ESI^+) $[M+H]^+$: 274.1; **IR** υ_{max} (neat)/ cm^{-1} 2979, 2925, 1492, 1164, 1156, 1011, 885.



***N*-(Triisopropylsilyl)pyridine-2-sulfinamide (198a)**

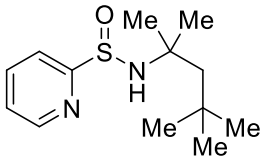
Preparation of organometallic reagent:

2-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 2-bromopyridine (210 μL, 2.20 mmol, 1.1 equiv.) in THF (1.3 mL, Ar-Br conc. 1.7 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.25 M in THF, 1.94 mL, 2.42 mmol, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 2 h.

Preparation of sulfinamide:

198a was then prepared according to General Procedure B, using TIPS-NSO **83b** (438.2 mg, 2.00 mmol), 2-pyridylmagnesium chloride lithium chloride complex solution (2.20 mmol, 1.1 equiv.) and THF (10 mL, 0.2 M). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **198a** as an off-white solid (532.2 mg, 1.78 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.64 (m, 1H, Ar-*H*), 7.90 – 7.83 (m, 2H, Ar-*H*), 7.39 (ddd, *J* = 6.6, 4.7, 2.1 Hz, 1H, Ar-*H*), 4.75 (s, 1H, N-*H*), 1.25 (ddt, *J* = 13.6, 8.4, 6.5 Hz, 3H, C*H*), 1.11 (t, *J* = 7.4 Hz, 18H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 149.8, 138.1, 125.5, 120.4, 17.98, 17.94, 12.0 [for dimethyl carbons in tri-*iso*propylsilyl group, NSi (CH(*C*H_3)$_2$)$_3$, 2 peaks were found instead of 1 due to the loss of symmetry caused by chiral sulfur atom]; **HRMS** (ESI^+, m/z) calculated for $[C_{14}H_{26}N_2OSSiNa]^+$ $[M+Na]^+$ 321.1427, found 312.1427(Δ -0.05 ppm); **R_F:** 0.17 (Petrol:EtOAc 1:1).



***N*-(2,4,4-trimethylpentan-2-yl)Pyridine-2-sulfinamide (198c)**

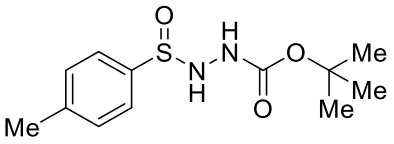
Preparation of organometallic reagent:

2-Pyridylmagnesium chloride lithium chloride complex solution was prepared according to the following procedure. To a solution of 2-bromopyridine (210 μL, 2.20 mmol, 1.1 equiv.) in THF (1.3 mL, Ar-Br conc. 1.7 M) was added isopropylmagnesium chloride lithium chloride complex solution (Turbo Grignard Reagent, 1.25 M in THF, 1.94 mL, 2.42 mmol, 1.2 equiv.) dropwise. The reaction was stirred at the same temperature for 2 h.

Preparation of sulfinamide:

198c was then prepared according to General Procedure B, using *t*-Oct-NSO **83a** (350.6 mg, 2.00 mmol), 2-pyridylmagnesium chloride lithium chloride complex solution (2.20 mmol, 1.1 equiv.) and THF (10 mL, 0.20 M). Filtration, washing with hexane and small amounts of Et_2O afforded the desired sulfinamide **198c** as a white solid (459.6 mg, 1.81 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dt, *J* = 4.7, 1.4 Hz, 1H, Ar-*H*), 7.86 – 7.84 (m, 2H, Ar-*H*), 7.36 (td, *J* = 4.8, 3.7 Hz, 1H, Ar-*H*), 4.50 (s, 1H, N-*H*), 1.66 (d, *J* = 14.8 Hz, 1H, CH_aCH$_b$), 1.61 (d, *J* = 14.9 Hz, 1H, CH$_a$CH_b), 1.50 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 0.98 (s, 9H, (CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 150.0, 138.0, 125.3, 120.6, 58.3, 56.3, 32.2, 31.9, 31.8, 29.8; **HRMS** (ESI^+, m/z) calculated for $[C_{13}H_{22}N_2OSNa]^+$ $[M+Na]^+$ 277.1345, found 277.1356 (Δ 3.93 ppm); **M.p.** 110-112 °C ($CHCl_3$); **IR** υ_{max} (neat)/ cm^{-1} 3198, 2960, 2904, 1452, 1049, 759; **R_F:** 0.25(Petrol:EtOAc 1:3).



tert-Butyl 2-(_p_-tolylsulfinyl)hydrazine-1-carboxylate (201a)

4-Methylbenzenesulfinic acid:

Following a modified procedure by Arroyo *et al.*:[442]

To a solution of sodium 4-methylbenzenesulfinate **180b** (356.4 mg, 2.0 mmol) in Et_2O:H_2O (50 mL, 1:1) was added conc. HCl (180 μL) and the resultant mixture stirred at room temperature for 1 h. The reaction mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude 4-methylbenzenesulfinic acid (297.4 mg, 1.90 mmol, 95%), which was used directly in the next step.

tert-Butyl 2-(_p_-tolylsulfinyl)hydrazine-1-carboxylate

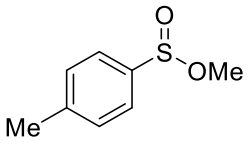
Following a modified procedure by Gafur *et al.*:[380]

To a solution of 4-methylbenzenesulfinic acid (297.4 mg, 1.90 mmol, 1.2 equiv.), DMAP (39.1 mg, 0.32 mmol, 0.20 equiv.) in CH_2Cl_2 (8 mL, 0.20 M) was added *tert*-butyl carbazate (211.5 mg, 1.6 mmol, 1.0 equiv.) followed by EDC · HCl (364.2 mg, 1.90 mmol, 1.2 equiv.) and stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with aq. HCl (1 M, 20 mL) and brine (20 mL) sequentially. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc 1:1) afforded the desired sulfinamide **201a** as a white semi-solid (397.5 mg, 1.47 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H, Ar-*H*), 7.32 – 7.28 (m, 2H, Ar-*H*), 6.91 (s, 1H, N-*H*), 6.43 (s, 1H, N-*H*), 2.39 (s, 3H, Ar-CH_3), 1.35 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 142.4, 138.2, 129.7, 126.1, 81.6, 28.1, 21.5;

The spectra and data matched those previously reported in the literature: S. H. Gafur, S. L. Waggoner, E. Jacobsen, C. G. Hamaker, S. R. Hitchcock, *Synthesis* **2018**, *50*, 4855-4866.[380]

Compound 201b was synthesised by Dr Michael Tilby



Methyl 4-methylbenzenesulfinate (201c)

Following a modified procedure by Fawcett *et al.*:[443]

Freshly recrystallised *N*-bromosuccinimide (7.12 g, 40.0 mmol, 2.0 equiv.) was added in one portion to a vigorously stirring solution of 4-methylbenzenethiol (2.484 g, 20.0 mmol, 1.0 equiv.) in DCM:MeOH (200 mL, 1:1) at 0 °C. The resultant solution was warmed to room temperature and stirred for 1 h at the same temperature. The mixture was poured into sat. aq. $NaHCO_3$ (20 mL) at 0 °C and shaken until discoloration. The organic phase was collected, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, Petrol:EtOAc 2:1) afforded the desired sulfinate ester **201c** as a colourless oil (2.69 g, 15.8 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.1, 2.2 Hz, 2H), 7.35 – 7.29 (m, 2H), 3.44 (dd, *J* = 2.2, 1.1 Hz, 3H), 2.40 (d, *J* = 2.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 141.0, 129.8, 125.4, 49.4, 21.6; **LRMS** (ESI^+) *m/z* $[M+Na]^+$ 193.0.

The spectra and data matched those previously reported in the literature:[443] A. Fawcett, A. Murtaza, C. H. U. Gregson, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 4573-4578.

[*Note:* the product should be stored under an inert atmosphere at -21 °C to prevent decomposition]

Compound 201d was synthesised by Mingyan Ding

6.4.1.4 Synthesis of cross-coupling products

General procedure O

Aryl primary sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (if it is a solid) (0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in an oven-dried microwave vial and sealed with a microwave cap. The reaction vial was evacuated and filled with N_2 (× 6). Anhydrous, degassed 1,4-dioxane (1.0 mL, 0.3 M) was then added, followed by the addition of aryl bromide (if it is a liquid) (0.30 mmol, 1.0 equiv.). The reaction was then heated at the indicated temperature (100 or 120 °C) for the time indicated (16 to 18 h) with fast magnetic stirring (>800 rpm), before being cooled to room temperature. The reaction solvent was concentrated *in vacuo* and the crude residue adsorbed onto celite and purified by flash column chromatography with the appropriate solvent system.

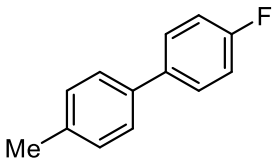
[*Note:* Biaryl substrates synthesised by Dr. Xinlan Cook who collaborated on the desulfinamidative cross-coupling are indicated in the relevant scope tables in **Chapter 4**, and as such are not included in this experimental.]

General procedure P

Aryl *N*-trityl sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (if it is a solid) (0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in an oven-dried microwave vial and sealed with a microwave cap. The reaction vial was evacuated and filled with N_2 (× 6). Anhydrous, degassed 1,4-dioxane (1.0 mL, 0.3 M) was then added, followed by the addition of aryl bromide (if it is a liquid) (0.30 mmol, 1.0 equiv.). The reaction was then heated at the indicated temperature (100 or 120 °C) for the time indicated (16 to 18 h) with fast magnetic stirring (>800 rpm), before being cooled to room temperature. The reaction solvent was concentrated *in vacuo* and the crude residue adsorbed onto celite and purified by flash column chromatography with the appropriate solvent system.

General procedure Q

Alkenyl sulfinamide (0.45 mmol, 1.5 equiv.), 4-bromobiphenyl (0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in an oven-dried microwave vial and sealed with a microwave cap. The reaction vial was evacuated and filled with N_2 (× 6). Anhydrous, degassed 1,4-dioxane (1.0 mL, 0.3 M) was then added. The reaction was then heated at 100 °C for 16 h with fast magnetic stirring (>800 rpm), before being cooled to room temperature. The reaction solvent was concentrated *in vacuo* and the crude residue adsorbed onto celite and purified by flash column chromatography with the appropriate solvent system.



4-Fluoro-4'-methyl-1,1'-biphenyl (182a)

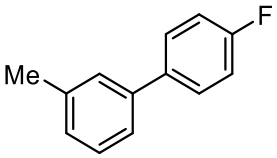
Following General Procedure O, using 4-methylbenzenesulfinamide **186a** (69.8 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **182a** as a white solid (43.4 mg, 0.23 mmol, 77%).

Following General Procedure P, using 4-methyl-*N*-tritylbenzenesulfinamide **66o** (178.7 mg, 0.45 mmol, 1.5 equiv.) 1-bromo-4-fluorobenzene (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **182a** as a white solid (47.5 mg, 0.26 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H, Ar-*H*), 7.47 – 7.43 (m, 2H, Ar-*H*), 7.27 – 7.23 (m, 2H, Ar-*H*), 7.14 – 7.08 (m, 2H, Ar-*H*), 2.40 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{CF}$ = 245.8 Hz), 137.5, 137.4 (d, $^4J_{CF}$ = 3.4 Hz), 137.2, 129.7, 128.6 (d, $^3J_{CF}$ = 8.0 Hz), 127.0, 115.7 (d, $^2J_{CF}$ = 21.4 Hz), 21.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -

116.28 (tt, J = 8.6, 5.3 Hz); **HRMS** (GC EI$^+$, m/z) calculated for $[C_{13}H_{11}F]^+$ $[M]^+$ 186.0845, found 186.0839; $\mathbf{R_F}$ = 0.59 (100% Petrol).

Data consistent with the literature: A. d. Gombert, A. I. McKay, C. J. Davis, K. M. Wheelhouse, M. C. Willis, *J. Am. Chem. Soc.* **2020**, *142*, 3564–3576.[221]

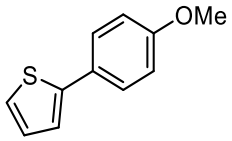


4-Fluoro-3'-methyl-1,1'-biphenyl (182b)

Following General Procedure O, using 3-methylbenzenesulfinamide **186b** (69.8 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **182b** as a white solid (41.8 mg, 0.22 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H, Ar-*H*), 7.39 – 7.29 (m, 3H, Ar-*H*), 7.20 – 7.15 (m, 1H, Ar-*H*), 7.12 (t, J = 8.8 Hz, 2H, Ar-*H*), 2.43 (d, J = 0.9 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (d, $^1J_{C\text{-}F}$ = 246.0 Hz), 140.4, 138.6, 137.6 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 128.8 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 128.7, 128.1, 128.0, 124.3, 115.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 21.7.; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -116.0 (tt, J = 8.8, 5.3 Hz).; $\mathbf{R_F}$ = 0.51 (100% Petrol).

Data consistent with the literature: S. K. Kariofillis, S. Jiang, A. M. Zuranski, S. S. Gandhi, J. I. Martinez Alvarado, A. G. Doyle, *J. Am. Chem. Soc.* **2022**, *144*, 2, 1045–1055.[444]



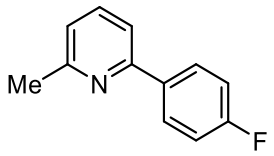
2-(4-Methoxyphenyl)thiophene (182k)

Following General Procedure O, using 2-thiophene sulfinamide **186k** (66.2 mg, 0.45 mmol, 1.5 equiv.), 4-bromoanisole (37.7 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015

mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF$_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **182k** as a white solid (54.9 mg, 0.29 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H, Ar-*H*), 7.24 – 7.20 (m, 2H, Ar-*H*), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1H, Ar-*H*), 6.95 – 6.90 (m, 2H, Ar-*H*), 3.84 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 144.5, 128.0, 127.4, 127.4, 124.0, 122.2, 114.4, 55.5; **R_F** = 0.47 (100% Petrol).

Data consistent with the literature: D. Liu, K. Yang, D. Fang, S.-J. Li, Y. Lan, Y. Chen, *Angew. Chem. Int. Ed.* **2023**, *62*, e202213686.[445]

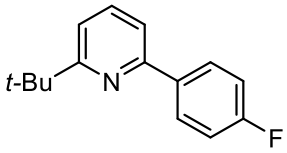


2-(4-Fluorophenyl)-6-methylpyridine (193e)

Following General Procedure O, using 6-methylpyridine-2-sulfinamide **192e** (70.3 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF$_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) at 120 °C were used. Flash column chromatography (SiO_2, hexanes:EtOAc 10:1) afforded the desired biaryl **193e** as a colourless oil (35.4 mg, 0.22 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H, Ar-*H*), 7.63 (t, *J* = 7.7 Hz, 1H, Pyr-*H*), 7.46 (d, *J* = 7.8 Hz, 1H, Pyr-*H*), 7.17 – 7.11 (m, 2H, Ar-*H*), 7.09 (d, *J* = 7.6 Hz, 1H, Pyr-*H*), 2.62 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.5 (d, $^1J_{CF}$ = 247.9 Hz), 158.5, 156.0, 137.2, 135.9 (d, $^4J_{CF}$ = 3.2 Hz), 128.9 (d, $^3J_{CF}$ = 8.3 Hz), 121.7, 117.5, 115.7 (d, $^2J_{CF}$ = 21.5 Hz), 24.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.5 (tt, *J* = 9.1, 5.4 Hz).

Data consistent with the literature: P. Chatelain, C. Muller, A. Sau, D. Brykczyńska, M. Bahadori, C. N. Rowley, J. Moran, *Angew. Chem. Int. Ed.* **2021**, *60*, 25307-25312.[446]



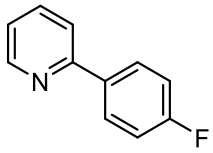
2-(*tert*-Butyl)-6-(4-fluorophenyl)pyridine (193d)

Following General Procedure O, using 6-(*tert*-butyl)pyridine-2-sulfinamide **192d** (69.8 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), $P(t\text{-Bu})_2Me{\cdot}HBF_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) at 120 °C were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **193d** as a white solid (59.4 mg, 0.25 mmol, 85%).

Following General Procedure P, using 4-methyl-*N*-tritylbenzenesulfinamide **199** (198.1mg, 0.45 mmol, 1.5 equiv.) 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), $P(t\text{-Bu})_2Me{\cdot}HBF_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **193d** as a white solid (47.5 mg, 0.26 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 2H, Ar-*H*), 7.68 (t, *J* = 7.8 Hz, 1H, Pyr-*H*), 7.51 (dd, *J* = 7.8, 0.9 Hz, 1H, Pyr-*H*), 7.28 (dd, *J* = 7.9, 0.9 Hz, 1H, Pyr-*H*), 7.19 – 7.10 (m, 2H, Ar-*H*), 1.44 (s, 9H, $(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 163.5 (d, $^1J_{CF}$ = 247.7 Hz), 154.5, 137.0, 136.1 (d, $^4J_{CF}$ = 3.2 Hz), 128.7 (d, $^3J_{CF}$ = 8.2 Hz), 117.4, 116.7, 115.6 (d, $^2J_{CF}$ = 21.5 Hz), 37.9, 30.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.6 (s).

Data consistent with the literature: A. d. Gombert, A. I. McKay, C. J. Davis, K. M. Wheelhouse, M. C. Willis, *J. Am. Chem. Soc.* **2020**, *142*, 3564–3576.[221]

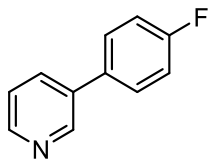


2-(4-Fluorophenyl)pyridine (193a)

Following General Procedure P, using *N*-tritylpyridine-2-sulfinamide **198b** (173.0 mg, 0.45 mmol, 1.5 equiv.) 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **193a** as a white solid (25.6 mg, 0.15 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H, Ar-*H*), 8.00 – 7.94 (m, 2H, Ar-*H*), 7.72 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H, Ar-*H*), 7.66 (dt, *J* = 8.0, 1.1 Hz, 1H, Ar-*H*), 7.31 – 7.17 (m, 1H, Ar-*H*), 7.16 – 7.11 (m, 2H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C\text{-}F}$ = 248.1 Hz), 156.6, 149.8, 136.9, 135.7 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 128.8 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 122.2, 120.3, 115.8 (d, $^2J_{C\text{-}F}$ = 21.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -113.2 (tt, *J* = 8.6, 5.4 Hz); **R_F:** 0.31 (EtOAc).

Data consistent with the literature: A. d. Gombert, A. I. McKay, C. J. Davis, K. M. Wheelhouse, M. C. Willis, *J. Am. Chem. Soc.* **2020**, *142*, 3564–3576.[221]

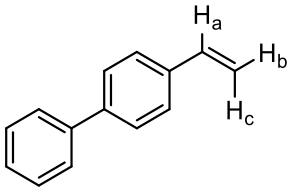


3-(4-Fluorophenyl)pyridine (182l)

Following General Procedure P, using *N*-tritylpyridine-3-sulfinamide **200** (173.0 mg, 0.45 mmol, 1.5 equiv.) 1-bromo-4-fluorobenzene **183a** (33.0 µL, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired biaryl **182l** as a white solid (47.7 mg, 0.28 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 – 8.79 (m, 1H, Pyr-*H*), 8.62 – 8.56 (m, 1H, Pyr-*H*), 7.82 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H, Pyr-*H*), 7.57 – 7.49 (m, 2H, Ar-*H*), 7.36 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H, Pyr-*H*), 7.20 – 7.12 (m, 2H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (d, $^{1}J_{C\text{-}F}$ = 247.8 Hz), 148.5, 148.1, 135.9, 134.4, 134.0 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 128.9 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 123.7, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) -114.1 (tt, *J* = 8.5, 5.3 Hz); **R_F:** 0.31 (EtOAc).

Data consistent with the literature: V. Salamanca, A. Toledo, A. C. Albeniz, *J. Am. Chem. Soc.*, **2018**, *140*, 17851-17856.[447]

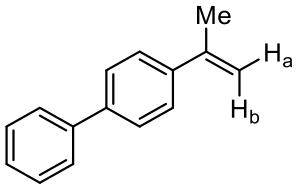


4-Vinyl-1,1'-biphenyl (204)

Following General Procedure Q, using *N*-tritylethenesulfinamide **138a** (150.0 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene **204** as a white solid (38.9 mg, 0.22 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 4H, Ar-*H*), 7.53 – 7.49 (m, 2H, Ar-*H*), 7.49 – 7.44 (m, 2H, Ar-*H*), 7.39 – 7.34 (m, 1H, Ar-*H*), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1H, H_a), 5.82 (dd, *J* = 17.6, 0.9 Hz, 1H, H_c), 5.30 (dd, *J* = 10.9, 0.9 Hz, 1H, H_b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 140.7, 136.7, 136.5, 128.9, 127.5, 127.4, 127.1, 126.8, 114.0; **R_F:** 0.31 (Petrol).

Data consistent with the literature: X. Zhou, Y. Xu, G. Dong, *J. Am. Chem. Soc.*, **2021**, *143*, 20042-20048.[448]

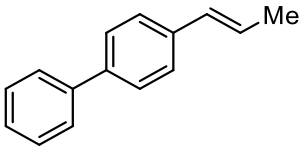


4-(Prop-1-en-2-yl)-1,1'-biphenyl (206a)

Following General Procedure Q, using *N*-tritylprop-1-ene-2sulfinamide **205a** (156.4 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene **206a** as a white solid (46.5 mg, 0.24 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 6H, Ar-*H*), 7.51 – 7.46 (m, 2H, Ar-*H*), 7.41 – 7.36 (m, 1H, Ar-*H*), 5.49 (dd, *J* = 1.5, 0.8 Hz, 1H, vinyl-C*H*$_a$), 5.16 (t, *J* = 1.5 Hz, 1H, vinyl-C*H*$_b$), 2.24 (dd, *J* = 1.4, 0.8 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.8, 140.8, 140.2, 140.1, 128.8, 127.3, 127.0, 127.0, 126.0, 112.5, 21.9; **R_F:** 0.31 (Petrol).

Data consistent with the literature: J. Li, J. Li, R. He, J. Liu, L. Chen, Y. Huang, Y. Li, *Org. Lett.*, **2022**, *24*, 1620-1625.[449]



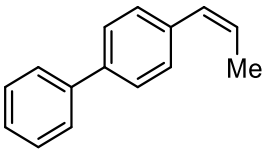
(*E*)-4-(Prop-1-en-1-yl)-1,1'-biphenyl (*E*)-206b

Following General Procedure Q, using (*E*)-*N*-tritylprop-1-ene-1sulfinamide (*E*)-**205b** (156.4 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene (*E*)-**206b** as a white solid (48.0 mg, 0.25 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H, Ar-*H*), 7.60 – 7.55 (m, 2H, Ar-*H*), 7.50 – 7.41 (m, 4H, Ar-*H*), 7.40 – 7.34 (m, 1H, Ar-*H*), 6.48 (dd, *J* = 15.8, 1.8 Hz, 1H, C=C*H*Me),

6.32 (dq, *J* = 15.7, 6.5 Hz, 1H, ArC*H*=CHMe), 1.95 (dd, *J* = 6.5, 1.6 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 139.6, 137.1, 130.7, 128.9, 127.3, 127.3, 127.0, 126.4, 126.0, 18.7; **R_F:** 0.24 (Petrol).

Data is consistent with the literature: K. E. Kawamura, A. S.-M. Chang, D. J. Martin, H. M. Smith, P. T. Morris, A. K. Cook, *Organometallics* **2022**, *41*, 4, 486-496.[450]

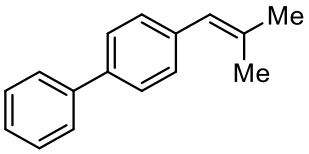


(*Z*)-4-(Prop-1-en-1-yl)-1,1'-biphenyl (*Z*)-206b

Following General Procedure Q, using (*Z*)-*N*-tritylprop-1-ene-1sulfinamide (*Z*)-**205b** (156.4 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene (*Z*)-**206b** as a white solid (48.4 mg, 0.25 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar-*H*), 7.51 – 7.45 (m, 2H, Ar-*H*), 7.45 – 7.41 (m, 2H, Ar-*H*), 7.41 – 7.35 (m, 1H, Ar-*H*), 6.52 (dq, *J* = 11.6, 1.9 Hz, 1H, C=C*H*Me), 5.87 (dq, *J* = 11.6, 7.2 Hz, 1H, ArC*H*=CHMe), 2.00 (dd, *J* = 7.2, 1.8 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 139.3, 136.8, 129.6, 129.4, 128.9, 127.3, 127.2, 127.1, 127.0, 14.9; **R_F:** 0.31 (Petrol).

Data is consistent with the literature: H. Liu, M. Xu, J. Chen, Y. Gu, Y. Xia, *Org. Lett.* **2020**, *22*, 3, 1193-1198.[451]

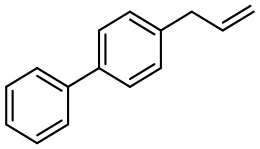


4-(2-Methylprop-1-en-1-yl)-1,1'-biphenyl (206c)

Following General Procedure Q, using 2-methyl-*N*-tritylprop-1-ene-1sulfinamide **205c** (162.7 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene **206c** as a white solid (47.1 mg, 0.25 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H, Ar-*H*), 7.60 – 7.57 (m, 2H, Ar-*H*), 7.49 – 7.43 (m, 2H, Ar-*H*), 7.38 – 7.32 (m, 3H, Ar-*H*), 6.35 – 6.33 (m, 1H, alkenyl-C*H*), 1.96 (d, *J* = 1.5 Hz, 3H, C*H*$_3$), 1.95 (d, *J* = 1.3 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 139.6, 137.1, 130.7, 128.9, 127.3, 127.3, 127.0, 126.4, 126.0, 18.7; **R_F:** 0.41 (Petrol).

Data is consistent with the literature: T. Dalton, S. Greβies, M. Das, M. Niehues, M. L. Schrader, C. Gutheil, B. J. Ravoo, F. Glorius, *Angew. Chem. Int. Ed.* **2021**, *60*, 8537-8541.[452]



4-Allyl-1,1'-biphenyl (208)

Following General Procedure Q, using *N*-tritylprop-2-ene-1-sulfinamide **207** (162.7 mg, 0.45 mmol, 1.5 equiv.), 4-bromobiphenyl **203** (69.9 mg, 0.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), P(t-Bu)$_2$Me·HBF_4 (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) and 1,4-dioxane (1.0 mL, 0.3 M) were used. Flash column chromatography (SiO_2, hexanes) afforded the desired styrene **208** as a white solid (51.4 mg, 0.26 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H, Ar-*H*), 7.58 – 7.54 (m, 2H, Ar-*H*), 7.48 – 7.43 (m, 2H, Ar-*H*), 7.38 – 7.33 (m, 1H, Ar-*H*), 7.32 – 7.28 (m, 2H, Ar-*H*), 6.04 (ddt, *J* =

16.8, 10.0, 6.7 Hz, 1H), 5.19 – 5.11 (m, 2H, vinylCH_2), 3.46 (dd, J = 6.7, 1.5 Hz, 2H, PhCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 139.3, 139.2, 137.5, 129.1, 128.9, 127.3, 127.2, 127.2, 116.1, 40.0; **R_F:** 0.42 (Petrol).

Data is consistent with the literature: L. Qin, M. Sharique, U. K. Tambar, *J. Am. Chem. Soc.* 2019, *141*, 43, 17305–17313.[453]

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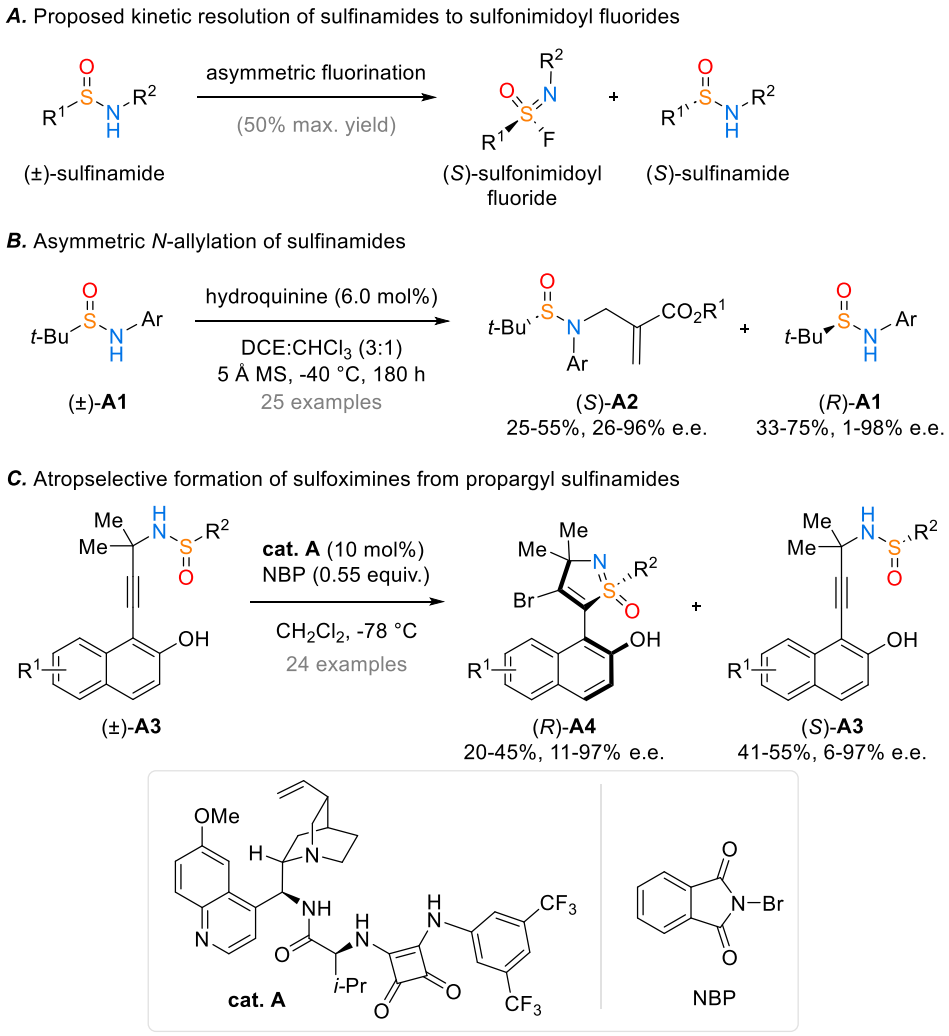
Appendix

A. 1.1 Towards the (dynamic) kinetic resolution of sulfinamides

A. 1.1.1 Kinetic resolution of sulfinamides

Despite the recent advances for the synthesis of chiral sulfinamides, methods are limited to multistep approaches, the use of chiral auxiliaries or odorous S(II) reagents.[148, 149, 155, 163, 164, 225, 454] Moreover, the application of structurally complex starting materials is challenging and there are limited commercially available reagents.[454] This led to a proposed kinetic resolution approach to access enantioenriched sulfonimidoyl fluorides from racemic sulfinamides (**Scheme A-1**).

The kinetic resolution of sulfinamides is an unexplored area, with few examples and until recently limited to *N*-functionalisation reactions. Kazlauskas group detailed an enzymatic resolution of acyl sulfinamides in high enantiomeric excess and moderate yields, although this is not a general process.[156] An asymmetric Cu(I)-catalysed *N*-arylation of sulfinamides has also been reported by Cai and co-workers.[370] However, this methodology is limited by moderate enantioselectivities and harsh reaction conditions. Encouragingly, during the course of this research the kinetic resolution of *N*-aryl sulfinamides (**A1**) *via* asymmetric *N*-allylation using hydroquinine was reported by Li and co-workers (**Scheme A-1 B**).[155] This process is highly enantioselective, with selectivity factors often greater than 50, but again the products are limited in their functionality and application (**A2**), and the reaction times are exceedingly long (7.5 days). The *S*-functionalisation of racemic *N*-propargylic sulfinamides (**A3**) has recently been reported by Yan, Qin and co-workers, in a kinetic resolution process to access sulfoximines ((*R*)-**A4**, **Scheme A-1 C**).[455] Cinchona alkaloid-derived urea **cat. A** was used to induce asymmetry.

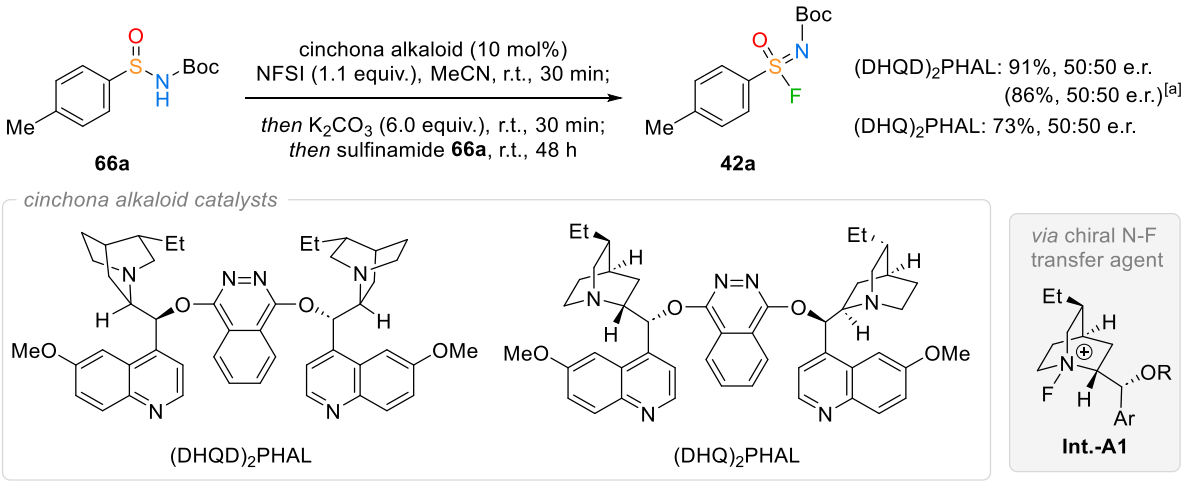


Scheme A-1 Proposed and selected kinetic resolutions of sulfinamides in the literature.

Although, there are no examples of asymmetric fluorination of heteroatoms reported, there is ample literature precedent for the stoichiometric and catalytic asymmetric fluorination of carbon stereocentres, with extensive reviews on the topic.[456] Example approaches focus on chiral Lewis acid complexes,[457] anionic (phosphoric acids)[458] and cationic (quaternary ammonium salts)[459, 460] phase-transfer catalysis (PTC). The use of chiral tertiary amines (cinchona alkaloids)[461-463] is perhaps the most well established, with significant mechanistic insights into this process.[463] The application of these strategies for the kinetic resolution of sulfinamides is discussed in the following section.

A-1.1.2 Cinchona alkaloids - reaction optimisation

At the outset of our investigations, we trialled bis-cinchona alkaloid derivatives, such as $(DHQD)_2PHAL$, as catalysts for asymmetric S-F bond formation, in part due to their commercial availability (**Scheme A-2**). The availability of *pseudo*-enantiomer $(DHQ)_2PHAL$ provides additional motivation in order to access either enantiomer of sulfonimidoyl fluorides products. This approach relies on the use of fluorinating agents, such as NFSI, that are insoluble in non-polar solvents. On stirring with an alkaloid, they form a chiral quinuclidine fluorine-transfer agent (**Int.-A1**), which is soluble under the reaction conditions. This solubility difference and enhanced reactivity of *N*-fluoroquinucludinium salts *vs.* NFSI facilitates high levels of enantioselectivity through diminishment of the background reaction.[178, 179]



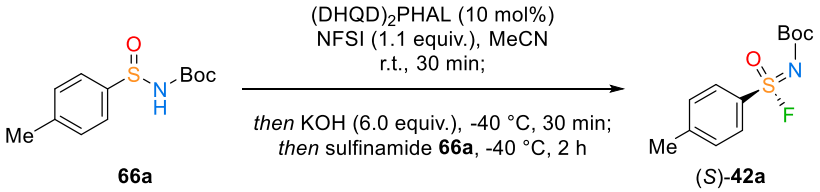
Scheme A-2 Initial attempt at an asymmetric fluorination of a sulfinamide **66a** with a bis-cinchona alkaloid derived catalyst. Isolated yields. [a] Reaction performed for 8 h.

NFSI was premixed with the organocatalyst, before base and nucleophile were added, in order to allow for initial fluorine transfer to the quinuclidine nitrogen of cinchona alkaloids. Initial subjection of *N*-Boc substituted sulfinamide **66a** to conditions from Shibata and co-workers resulted in high conversion to the desired product **42a** using both bis-cinchona alkaloid derivatives (**Scheme A-2,** 91% and 73% respectively).[463] Unfortunately, in both

cases the product was racemic. The reaction was found to proceed in shorter reaction times compared to C-F bond forming transformations (12 to 60 h), with comparable yield achieved in 8 hours (73%).

Encouraged by this initial reactivity, the reaction was performed at lower temperature (-40 °C, **Table A-1**, entry 2), where it was found that moderate conversion (68%) was obtained with shorter reaction time (2 h). Pleasingly, the product was obtained with a low level of enantioinduction (59.5:40.5 e.r.), providing proof-of-concept for this approach. The nature of the base had a significant impact on conversion for the transformation, without improving the enantioinduction (entries 1-4). The nature of the counterion was not investigated, although this may be worth additional investigation. Reducing the stoichiometry of NFSI led to negligible increase in enantiomeric ratio (entry 5). In contrast, lowering the equivalents of base had a profound impact on the conversion and a slight improvement in enantioselectivity (entries 6-7). The highest enantiomeric ratio (69.5:30.5 e.r.) to date was obtained by performing the reaction at lower temperature (-78 °C, entry 8), which required changing the solvent to acetone, with K_2CO_3 used as the base. Control reactions were evaluated to gain understanding to the low enantioenduction (entries 9-10). Background reaction without $(DHQD)_2PHAL$ or base led to minimal conversion of the starting sulfinamide **66a**.

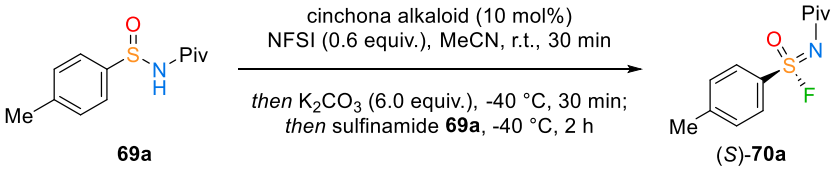
Table A-1 Selected optimisation for the asymmetric fluorination of sulfinamide **66a**. Conversions determined by analysis of the crude ^{1}H NMR spectra.



Entry	Variation to above system	Conversion (%)	e.r.
1	-	83	59:41
2	K_2CO_3 (6.0 equiv.)	69	59.5:40.5
3	K_3PO_4 (6.0 equiv.)	58	58.5:41.5
4	KH_2PO_4 (6.0 equiv.)	trace	n.d.
5	NFSI (0.6 equiv.)	60	60.5:39.5
6	NFSI (0.6 equiv.), KOH (2.0 equiv.)	31	65:35
7	NFSI (0.6 equiv.), KOH (1.0 equiv.)	30	66.5:33.5
8	Acetone, -78 °C, K_2CO_3 (6.0 equiv.)	43	69.5:30.5
9	no $(DHQD)_2PHAL$	<5	n.d.
10	no base	<5	n.d.

For further screening, a K_2CO_3/MeCN system was evaluated at -40 °C, with reduced equivalents of NFSI (0.6 equiv.). Alternative bis-cinchona alkaloid derivatives were trialled with an alternative *N*-protecting group, pivaloyl (**Table A-2**). Use of sulfinamide **69a** resulted in similar conversion (entry 1) but significantly reduced enantioinduction. Although disappointing, this suggests that tuning of the *N*-substituent may be a parameter to modulate selectivity. Performing the reaction with *pseudo*-enantiomer $(DHQ)_2$-alkaloids yielded similar results, encouragingly with the opposite enantiomer of sulfonimidoyl fluoride **69a** obtained (entries 2-4). Monomeric cinchona alkaloids such as hydroquinine and quinidine led to a reduction in conversion with negligible effects on the enantioinduction (entries 5 and 6). Singularly-quaternised cinchona alkaloid derived phase-transfer catalysts have been used frequently for asymmetric fluorination and benefit from their highly modular nature.[459] However, use of *N*-benzylated cinchonium bromide disappointingly led to racemic sulfonimidoyl product **70a** in lower yields (entry 9).

Table A-2 Selected optimisation for asymmetric fluorination of **69a**. Conversions determined by analysis of the crude ^{1}H NMR spectra. [a] (*R*)-**69a** isolated (40%, 59:41 e.r.).

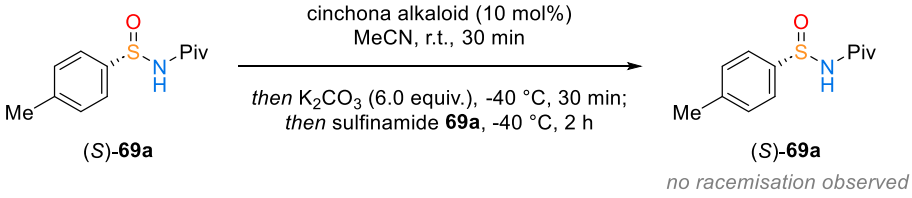


69a (*S*)-**70a**

Entry	Cinchona alkaloid	Conversion (%)	e.r.
1	$(DHQD)_2PHAL$	55	54:46
2	$(DHQ)_2PHAL$	55	44.5:55.5
3	$(DHQ)_2PYR$	58	45.5:54.5
4	$(DHQ)_2AQN$	51	44.5:55.5[a]
5	Hydroquinine	39	45.5:54.5
6	Quinidine	30	51.5:48.5
7	*N*-(4-trifluoromethylbenzyl) cinchonium bromide	30	50:50

Of note, the unreacted sulfinamide **69a** was isolated and its enantiomeric ratio (59:41 e.r., entry 4) of the opposite stereoisomer (*R*)-**69a**, showcases that the process does not undergo racemisation of the sulfinamide.

This was further supported by subjecting the optically pure starting material to the reaction conditions without the presence of NFSI, with no racemisation observed (**Scheme A-3**). Moreover, the sulfonimidoyl fluoride product (**70a**) also did not undergo stereochemical degradation when resubjected to the reaction conditions. These results in combination with minimal background reaction (**Table A-2**, entry 9-10) imply that the key S-F bond formation proceeds with only moderate asymmetric induction. This could be probed further by use of stoichiometric *N*-F transfer reagent in these transformations. The moderate enantioselectivity coupled with stepwise, time-consuming set-up of reactions resulted in this approach not being explored any further.



Scheme A-3 Subjection of enantioenriched starting material under reaction conditions without NFSI.

Due to the rapid S-F formation observed for these transformations at low temperatures. The non-asymmetric variant of this approach was investigated, the use of which may be beneficial for problematic S-F transformations of sulfinamides or related S(IV) analogues. Quinuclidine and DABCO were selected as non-chiral transfer-fluorine reagents, due to their presence as cores in cinchona alkaloid and Selectfluor™ systems respectively. The use of both tertiary amine bases in sub-stoichiometric and stoichiometric quantities was found to mediate the desired transformation in short reaction times (**Scheme A-4**). The use of 10 mol% of the reagents is particularly encouraging at an un-optimised stage. The improved reactivity *vs.* NFSI (no tertiary amine) can be ascribed to the formed *N*-fluoroquinucludinium salts being stronger fluorinating reagents.[178]



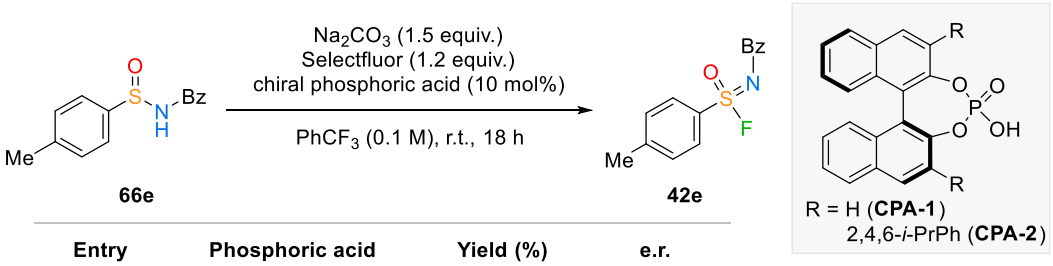
Scheme A-4 Utilisation of tertiary amine phase transfer catalysts in stoichiometric and sub-stoichiometric quantities for the transformation of sulfinamide **69a** to sulfonimidoyl fluoride **70a**.

A-1.1.3 Alternative asymmetric fluorination strategies

The Toste laboratory has pioneered the concept of utilizing chiral phosphate catalysts in combination with insoluble fluorinating agent, Selectfluor™, to effect asymmetric fluorination under phase-transfer conditions.[458] The use of chiral phosphoric acids is

beneficial as they are modular functionalities that can be readily tuned both electronically and sterically. Utilising conditions developed by the Toste laboratory,[458] sulfinamide **66e** was treated with Na_2CO_3 and Selectfluor™, with chiral phosphoric acids (**CPA-1** and **CPA-2** ((*S*)-TRIP)). Although high conversions were observed, the product obtained (**42e**) was racemic (**Table** , entries 1 and 2). This is perhaps unsurprising given the background reaction without the chiral phosphoric acid (entry 3) proceeded at a similar rate. Performing these reactions at lower temperatures and in different solvent systems may help to diminish the background reaction and achieve asymmetric induction for this process.

Table A-3 Initial attempt at an asymmetric fluorination of sulfinamide **66e** with chiral phosphoric acids.



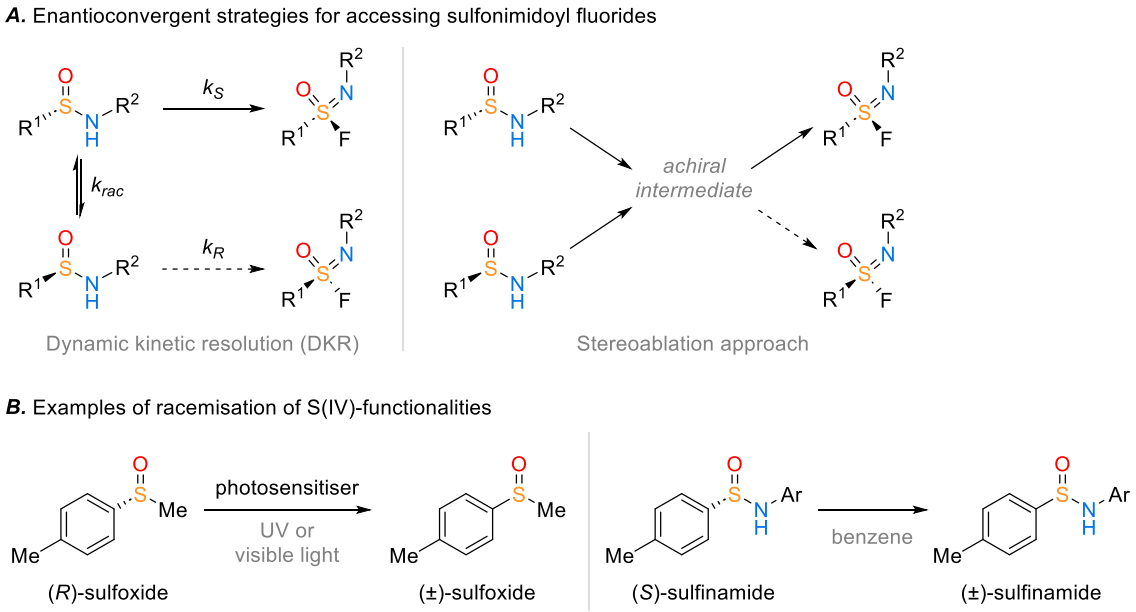
Entry	Phosphoric acid	Yield (%)	e.r.
1	**CPA-1**	79	50:50
2	(*S*)-TRIP (**CPA-2**)	85	50:50
3	-	80	50:50

As discussed *vide infra* (**Scheme 2-5**), difluoroiodane reagent **67b** is a competent electrophilic fluorinating agent in combination with sulfinamides. Aryl-IF_2 species with chiral substituents on the arene ring is an alternative approach for future exploration. These reagents have been used stoichiometrically[464] or in sub-stoichiometric quantities (10-20 mol%) generated *in situ* to form carbon-fluorine bonds in an asymmetric manner.[465-468] [467, 469, 470]

A-1.1.4 Racemisation of sulfinamides

The above strategies are limited by the maximum achievable yield of 50%, innate to kinetic resolution approaches. This is somewhat mediated by the possible transformation of

unreacted enantioenriched sulfinamide starting materials in an enantiospecific manner to access SIFs (**Scheme 2-7**); plausibly in a two-step enantiodivergent manner. We envisaged that a dynamic kinetic resolution (stereomutation) or enantioconvergent (stereoablation) approach would be beneficial (**Scheme A-5**). For this process to occur, racemisation at sulfur must occur either at the sulfinamide state or *via* an achiral, potentially planar intermediate.

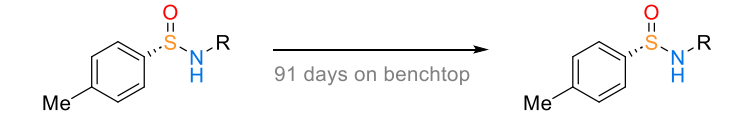


Scheme A-5 **(*A*)** Proposed strategies for accessing single enantiomers of sulfonimidoyl fluorides from racemic sulfinamides. (***B***) Examples of racemisations of sulfoxides and sulfinamides in the literature.

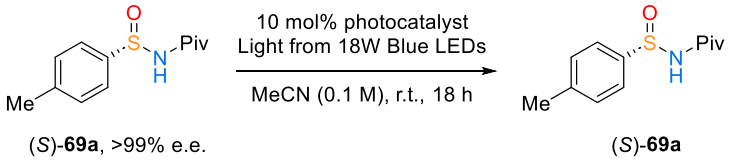
In a series of (un)fortunate events, primary and *N*-Boc substituted sulfinamides (**186a** and **66a**) were positioned on the benchtop during the COVID-19 pandemic, unattended for over 3 months. On return, substantial racemisation (35% and 29% reduction in enantiomeric excess respectively) was observed for both substrates in this time period (**Scheme A-5**). We hoped to utilise and enhance this observed racemisation for DKR processes using light sources. Dissolution of both *N*-boc (**66a**) and primary (**186a**) sulfinamide, followed by subjection to a 40 W white light (λ = 450 nm) for 18 h resulted in no stereochemical degradation (**Scheme A-6**, entry 1). We therefore evaluated the use of photosensitisers for the racemisation of *N*-piv sulfinamide **69a**, instead of direct excitation. Upon irradiation of

a 100 mM solution of (*S*)-**69a** in MeCN using an 18 W blue light-emitting diode (LED) (λ = 420 nm) for 18 h, no reaction was observed without a photosensitiser (entry 2). Commercial photosensitisers used in racemisation processes of sulfoxides,[471, 472] Ru(II)(bpy)$_3$, xanthone and thioxanthone (at 10 mol%) gave initial indication of racemisation although less than 10% change in enantiomeric ratio (entries 3-5). In contrast, the addition of Mes-Acr-Me$^+$ and (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ resulted in multiple decomposition products that were unidentifiable (entries 6 and 7).

A. Observed racemisation of *p*-tolyl sulfinamides during COVID-19 lockdown

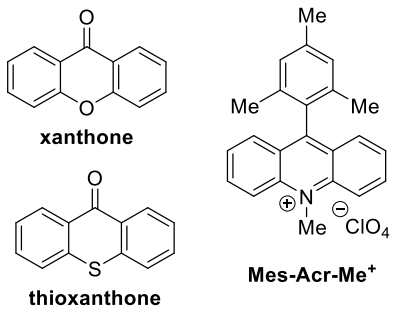


B. Attempted racemisations of sulfinamide **69a** using light-mediated processes



Entry	catalyst	e.e.
1	-[a]	>99%
2	-	>99%
3	Ru(bpy)$_3$(PF$_6$)$_2$	92%
4	xanthone	92%
5	thioxanthone	92%
6	Mes-Acr-Me$^+$	n.d.[b]
7	(Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$	n.d.[b]

photocatalyst structures



Scheme A-6 Investigation of the racemisation of sulfinamides *via* light-mediated processes. [a] *N*-Boc sulfinamide (*S*)-**66a** or primary sulfinamide (*S*)-**186a**, white light. [b] Decomposition observed of sulfinamide so enantiomeric e.e. not determined.

Of note, during the course of this work additional photocatalysts such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 2,4,6-triphenylpyrylium

tetrafluoroborate (TPT^+) were shown to racemise sulfoxides rapidly and hence may be worth further investigation.[473] The use of different wavelengths of light is a crucial parameter not yet explored, in particular thioxanthone and xanthone reagents were not used at their maximum absorption wavelength (380 nm and 366 nm respectively). As Cram and Booms' racemisation of sulfinamides exhibited a large solvent dependence,[474] with nonpolar solvents (benzene) giving rates several orders of magnitude faster than polar solvents (HMPA), performing the reactions in different solvents may aid racemisation processes. Moreover, investigation of *N*-substituents is paramount with the racemisation of sulfoxides dependent on the substituents attached to sulfur.[473] If optimised the utilisation of a photocatalysed racemisation in combination an effective asymmetric fluorination method may be applicable to achieve a dynamic kinetic resolution approach to sulfonimidoyl fluorides.

A-1.2 Biological testing of S(VI)-warheads

Compounds **76a**, **76c** and **85c** were tested in in-gel fluorescence experiments at 100 μM with 1 h of incubation at room temperature. Compounds **76a** and **76c** resulted in regular labelling, with very strong labelling for **85c** in MDA MB231 with 10 μL and 20 μL loading. Identification of binding sites and labelled proteins with isoDTB ABPP workflow is ongoing for SuTEx probe **85c**.

A-2 Synthetic Procedures

Procedure for cinchona alkaloid mediated process using K_2CO_3 in acetone:

$(DHQD)_2PHAL$ (10 mol%) and NFSI (1.1 equiv.) in acetone (0.1 M) were stirred under nitrogen atmosphere at room temperature for 30 min. K_2CO_3 (6.0 equiv.) was then added to the solution, and the reaction mixture stirred for 30 min at –78 °C. A solution of sulfinamide (1.0 equiv.) in acetone (0.1 M) was added to the catalyst solution. The reaction was stirred at the same temperature for 2 h with monitoring by TLC. The reaction mixture was diluted with EtOAc (10 mL) and brine (5 mL) and transferred to a separating funnel. The layers were separated and the aqueous layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography afforded the desired sulfonimidoyl fluoride.

[*Note:* the same procedure was utilised with achiral tertiary amines DABCO and quinuclidine with either 10 mol% or 1.0 equiv.]

Procedure for chiral phosphoric acid approach:

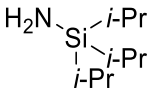
To a solution of sulfinamide (1.0 equiv.) in $PhCF_3$ (0.1 M) was added anhydrous Na_2CO_3 (1.5 equiv.), Selectfluor (1.2 equiv.) and respective phosphoric acid (10 mol%) under N_2. The reaction mixture was stirred for 18 h at room temperature, diluted with EtOAc (10 mL) and brine (5 mL), and transferred to a separating funnel. The layers were separated and the aqueous layer extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatrography afforded the desired sulfonimidoyl fluoride.

Procedure for photo-catalysed racemisation approach:

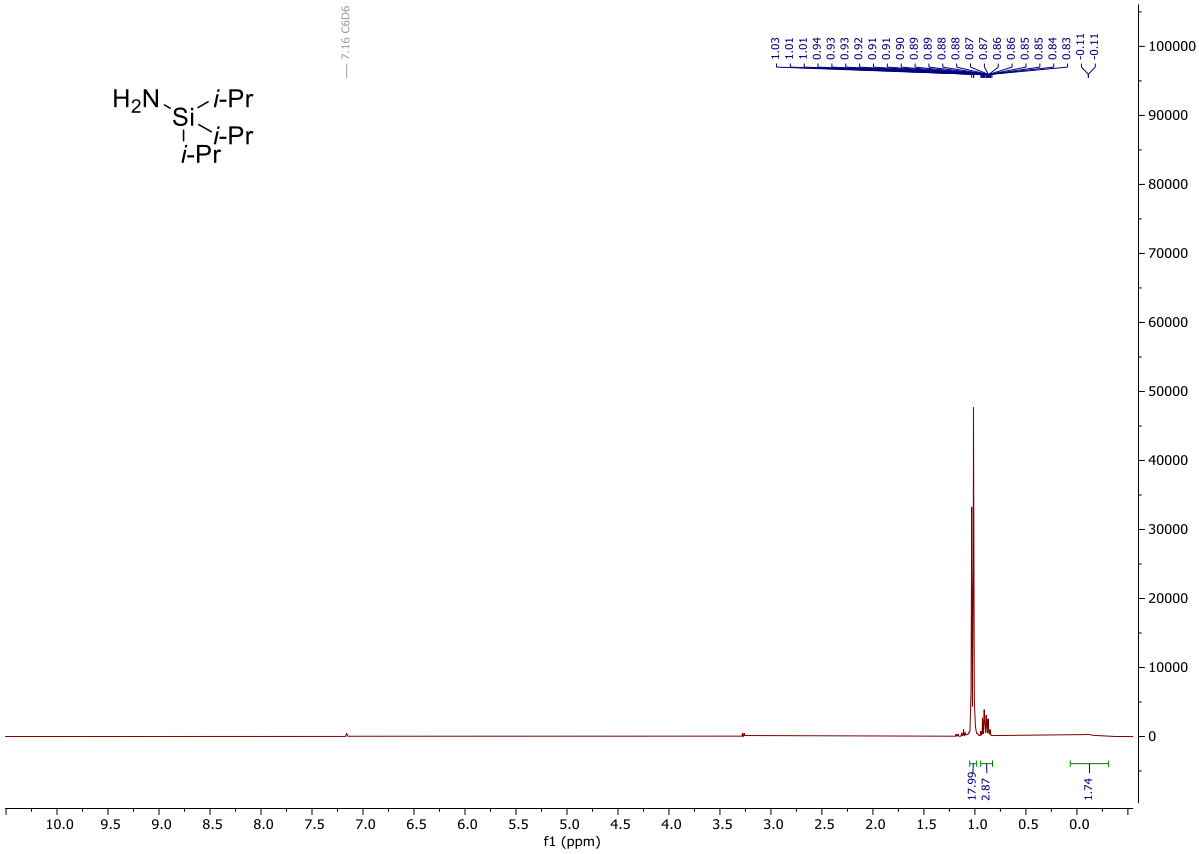
The respective sulfinamide was dissolved in MeCN (0.1 M) and respective photosensitiser was added (10 mol%). The resultant solution was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the sulfinamide re-isolated by flash column chromatography.

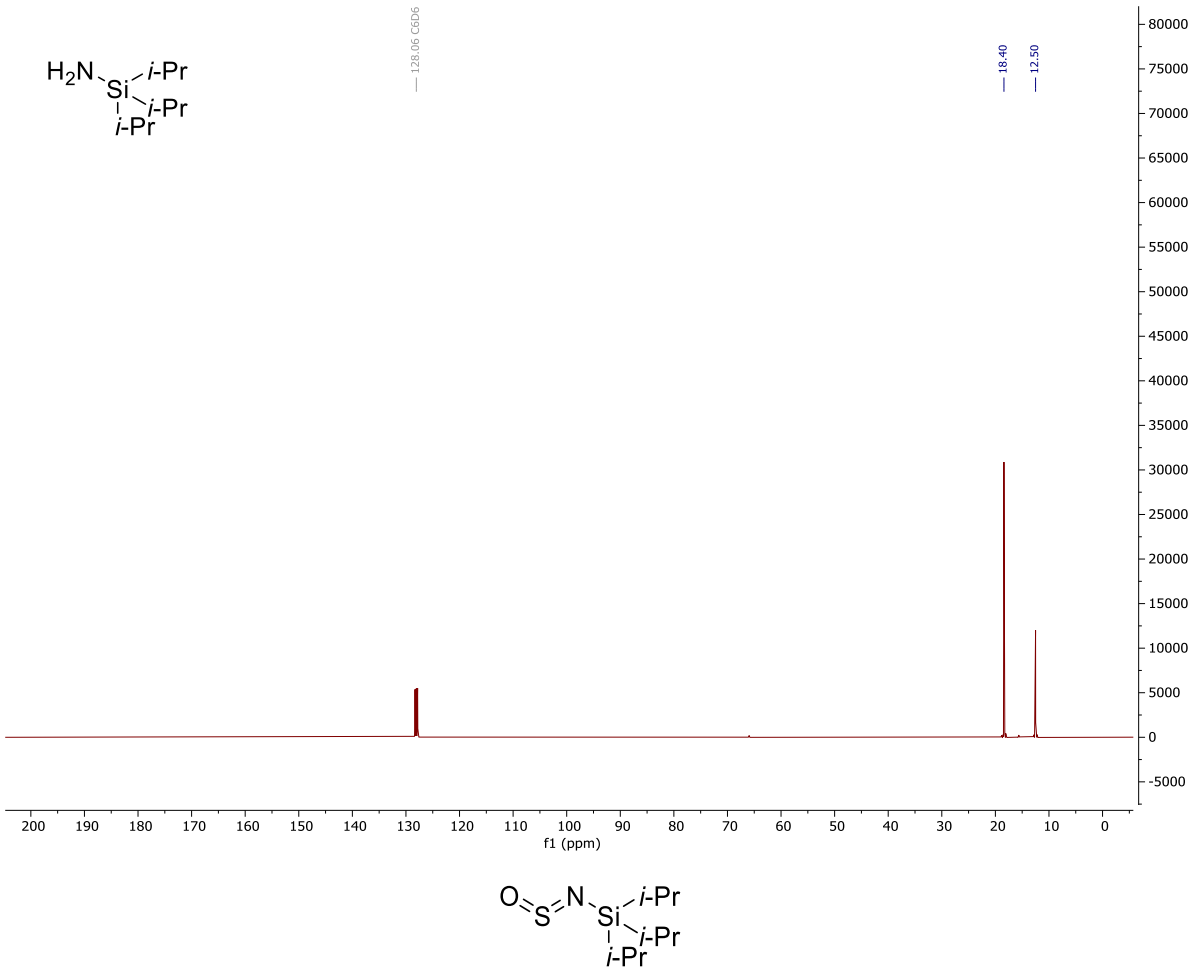
8.1 Spectra from Chapter 2

8.1.1 Sulfinylamines



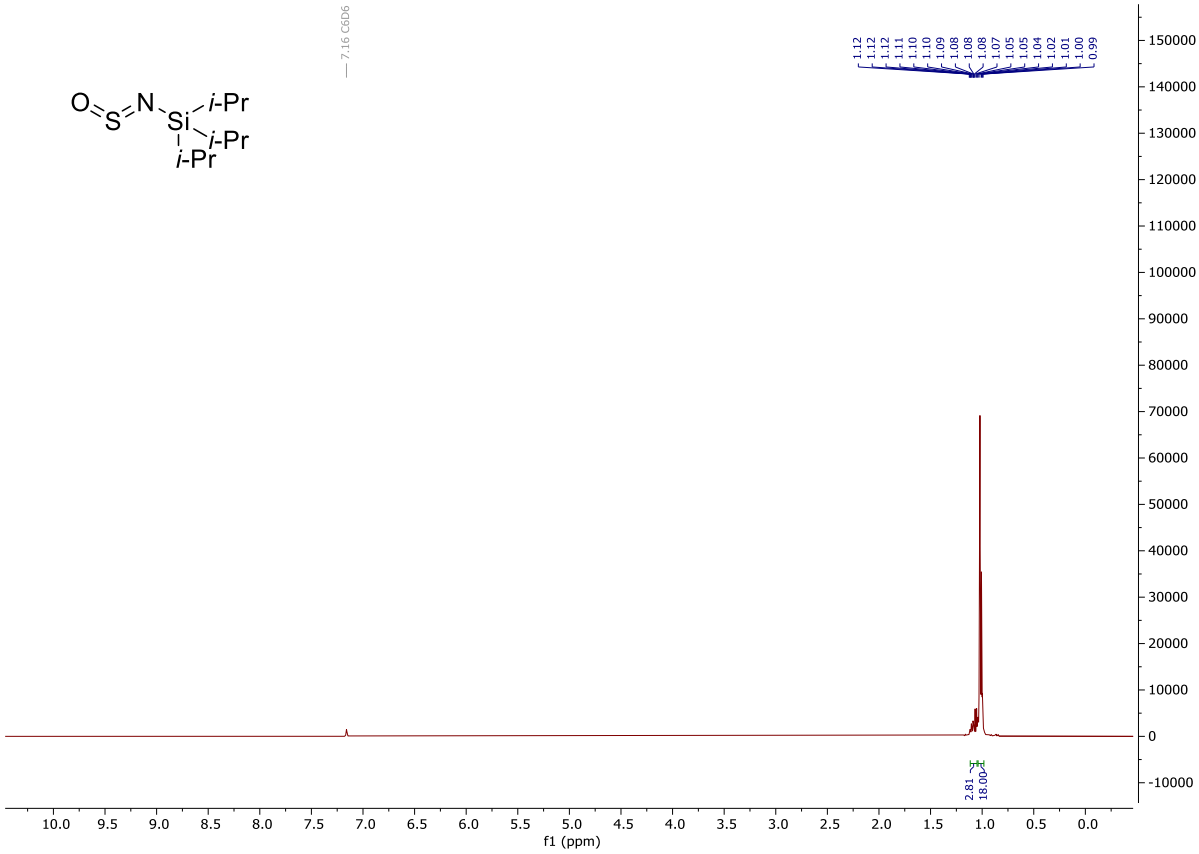
Triisopropylsiyl amine, TIPS-NH_2 (S1)

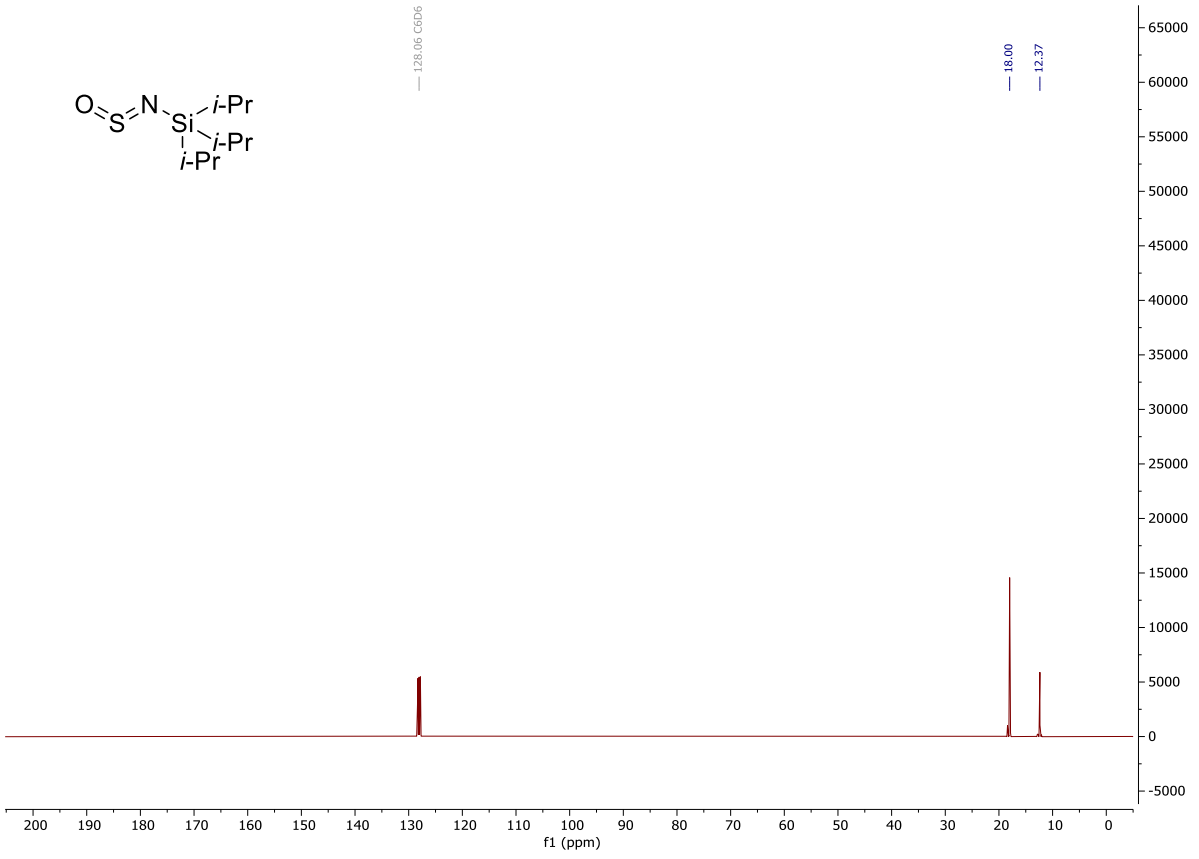


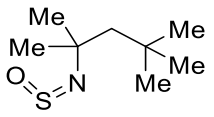

H2N
Si
i-Pr
i-Pr
i-Pr
128.06 C6D6
18.40
12.50
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

O
S
N
Si
i-Pr
i-Pr
i-Pr

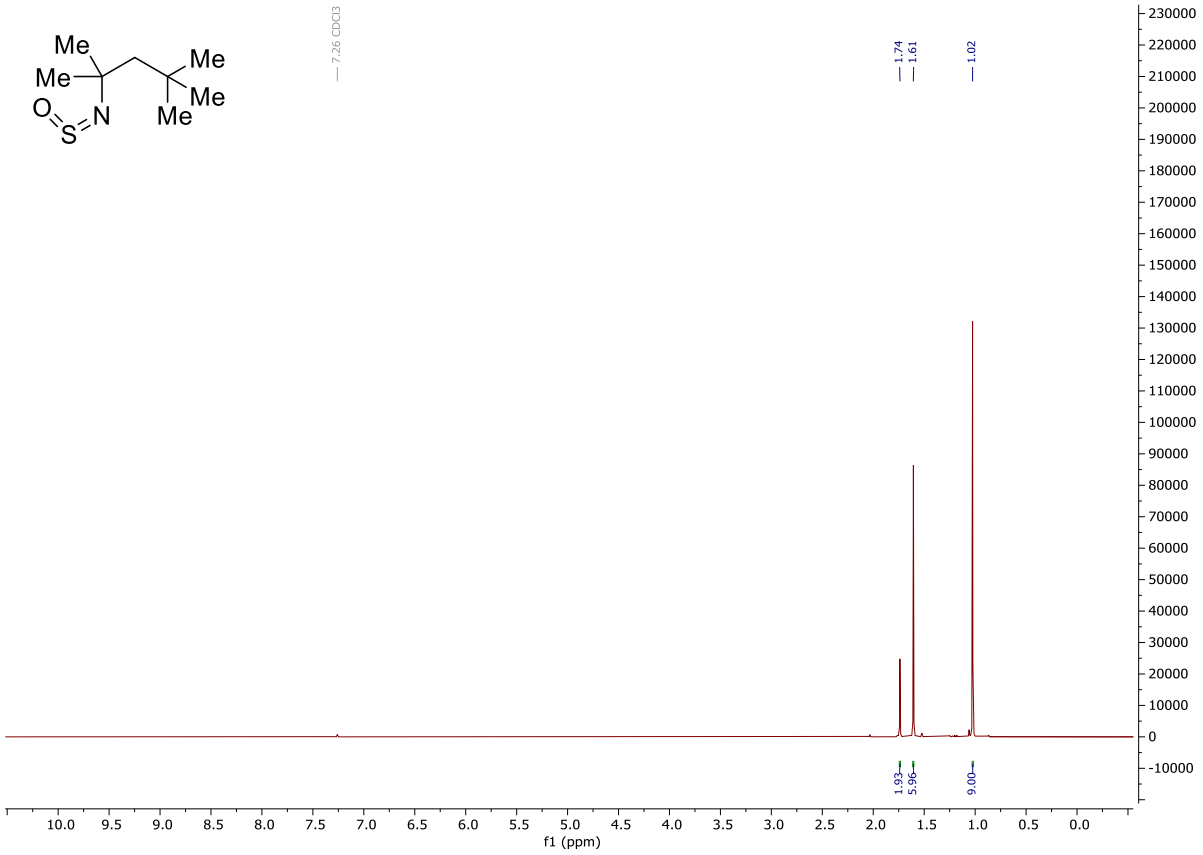
TIPS-NSO (83b)

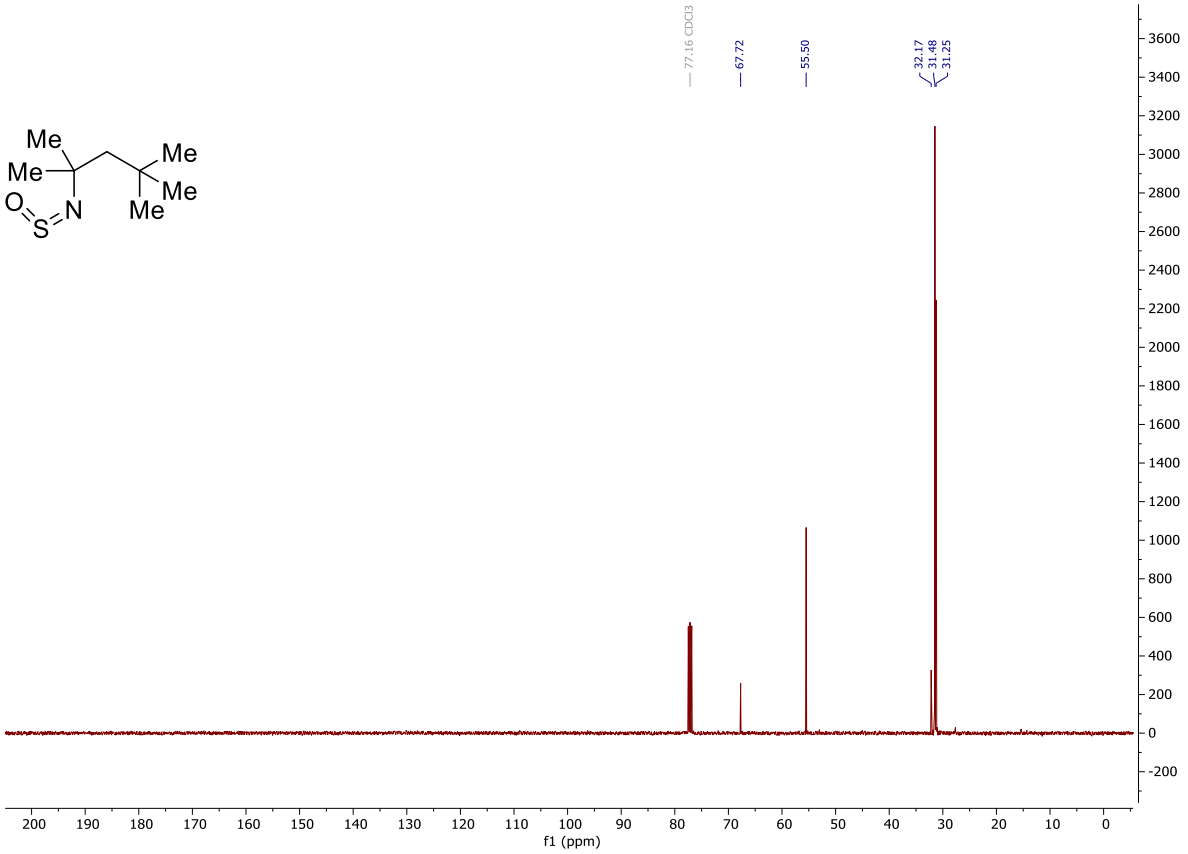

7.16 C6D6
1.12
1.12
1.12
1.11
1.10
1.10
1.09
1.08
1.08
1.08
1.07
1.05
1.05
1.04
1.02
1.01
1.00
0.99
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18.00
f1 (ppm)


128.06 C6D6
18.00
12.37
f1 (ppm)

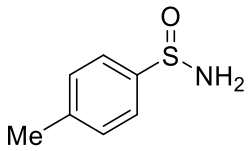

Me
Me
Me
Me
Me
O
S
N

_t_-Oct-NSO (83a)

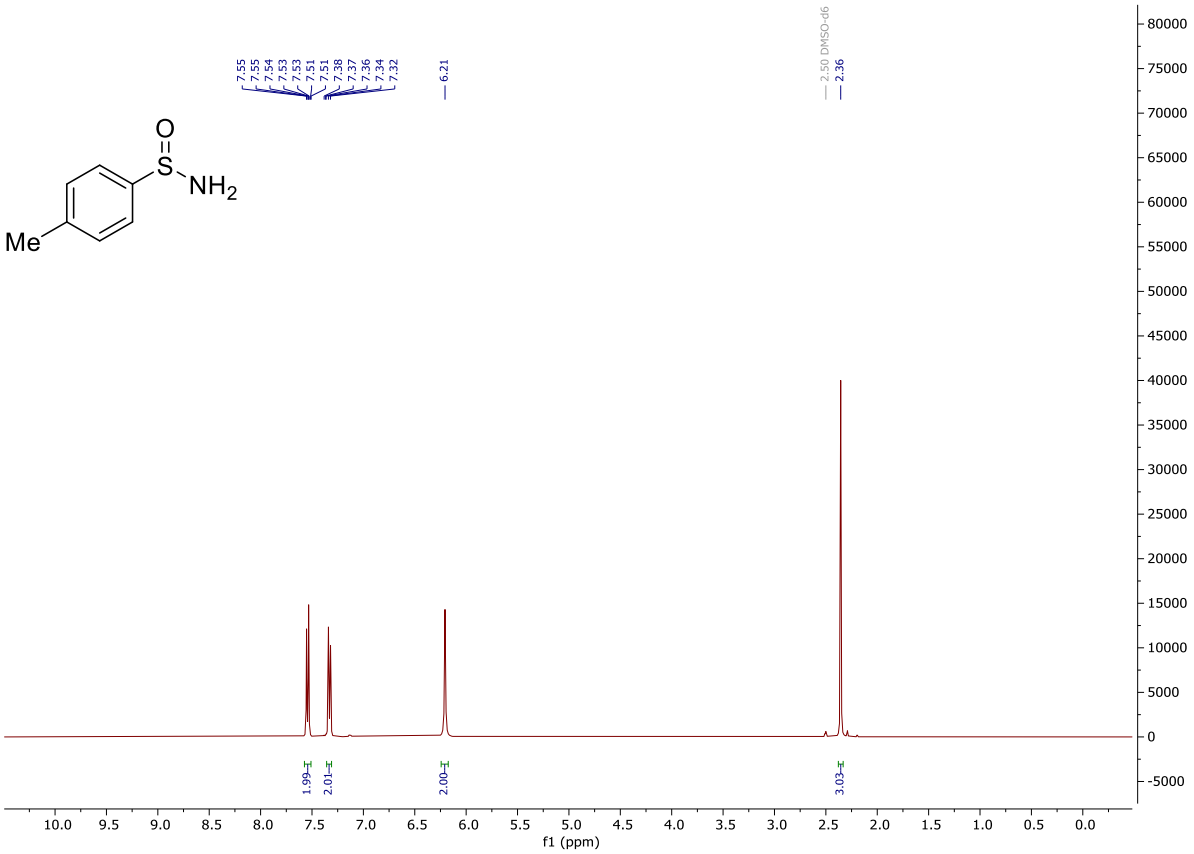

Me
Me
Me
Me
Me
O
S
N
7.26 CDCl3
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1.61
1.02
1.93
5.96
9.00
f1 (ppm)

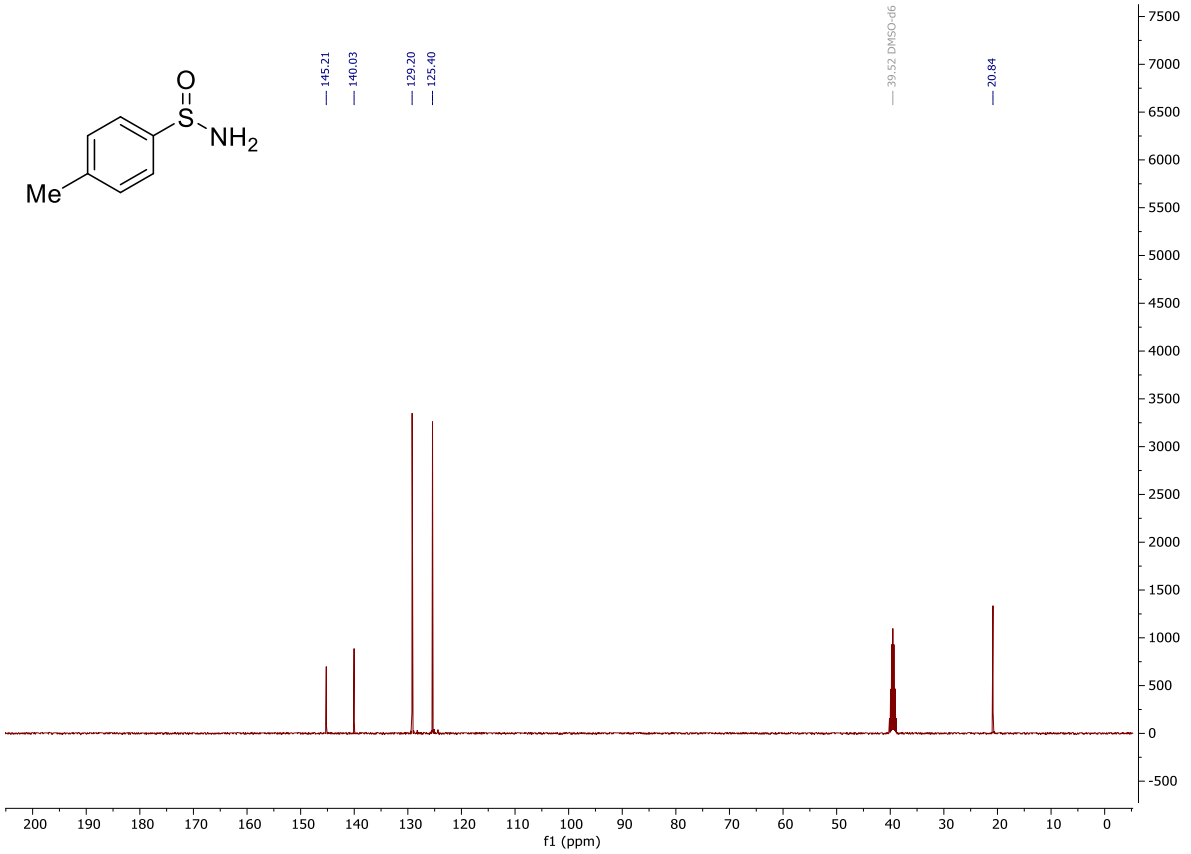

Me
Me
Me
Me
Me
O
S
N
77.16 CDCl3
67.72
55.50
32.17
31.48
31.25
f1 (ppm)

8.1.2 Primary sulfinamides

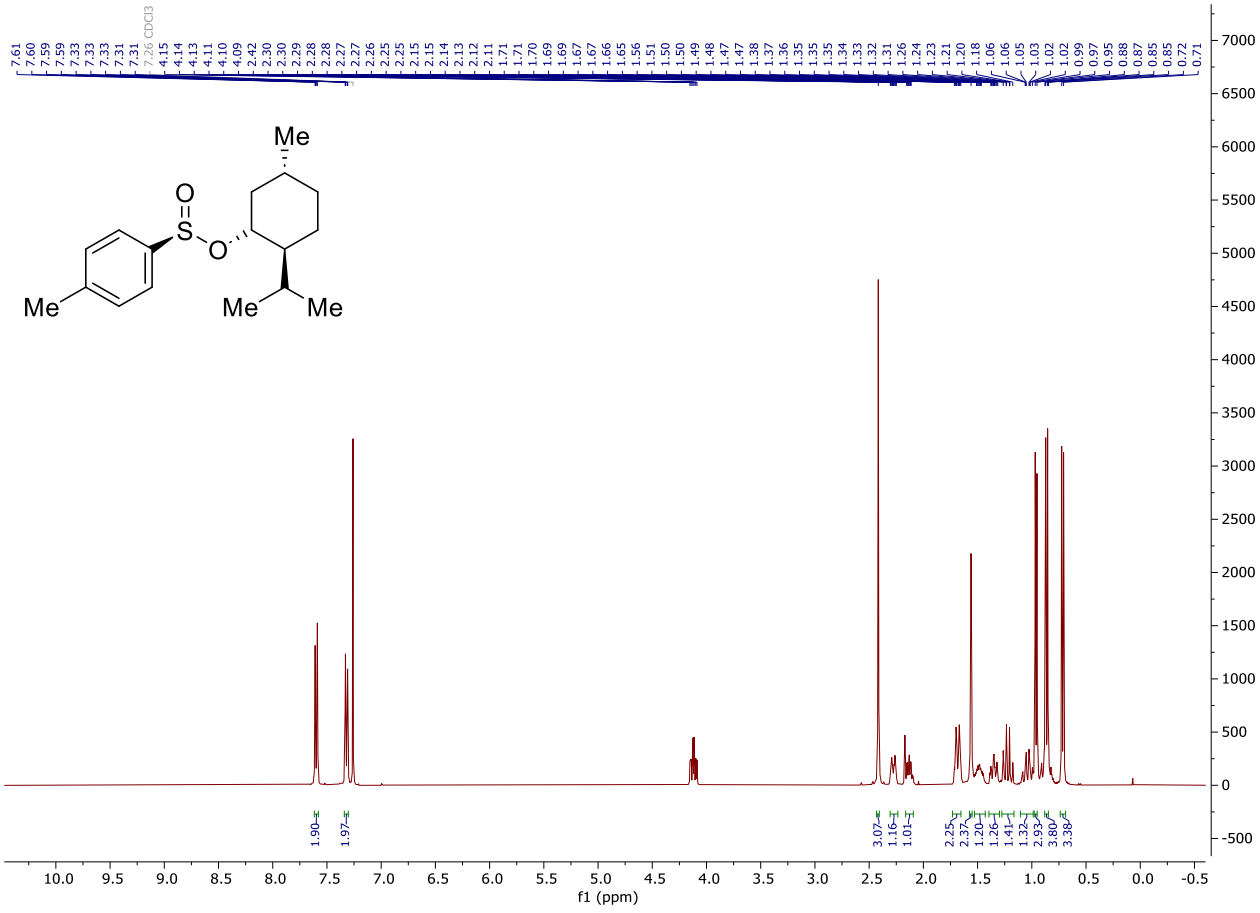


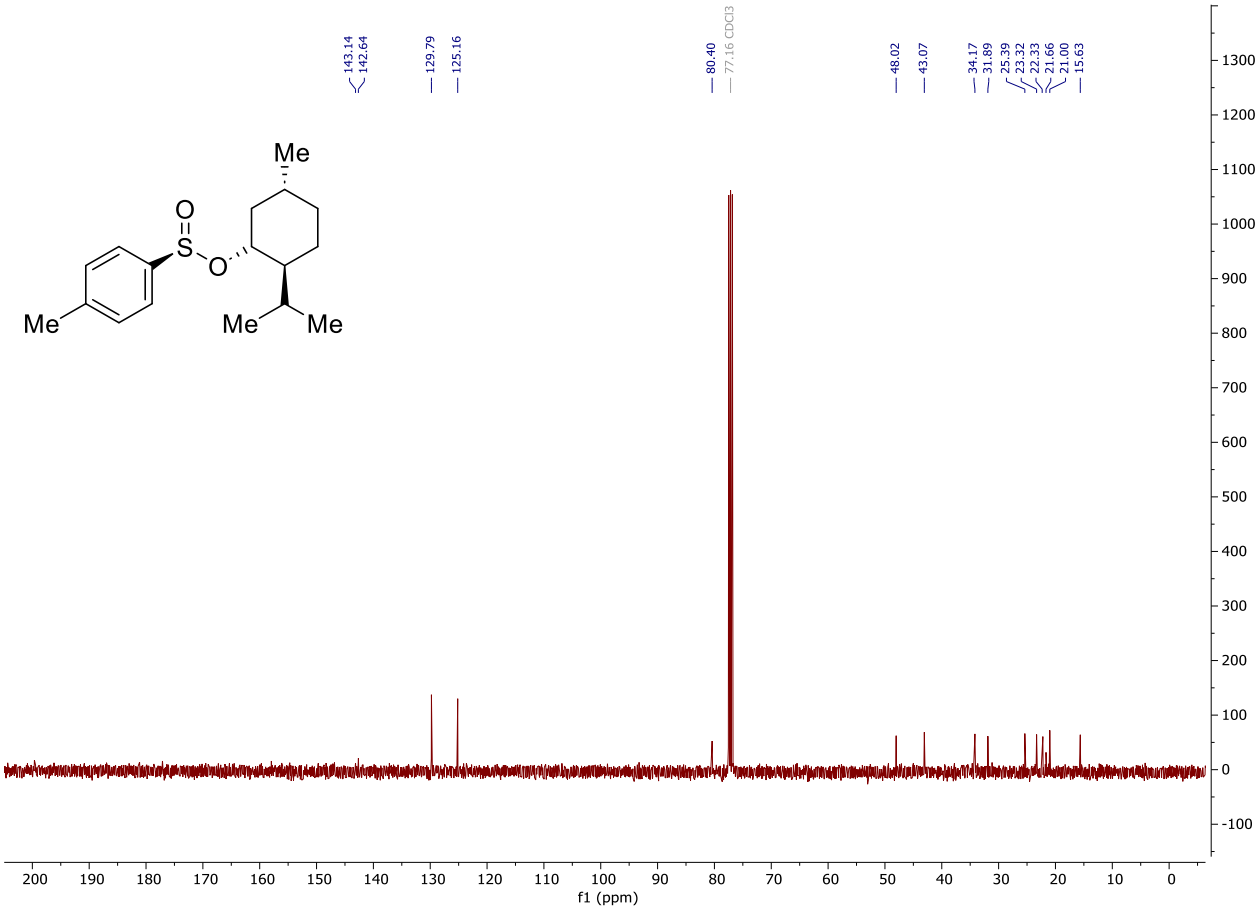
4-Methylbenzenesulfinamide (186a)

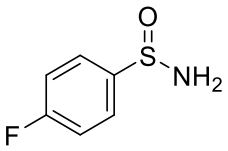




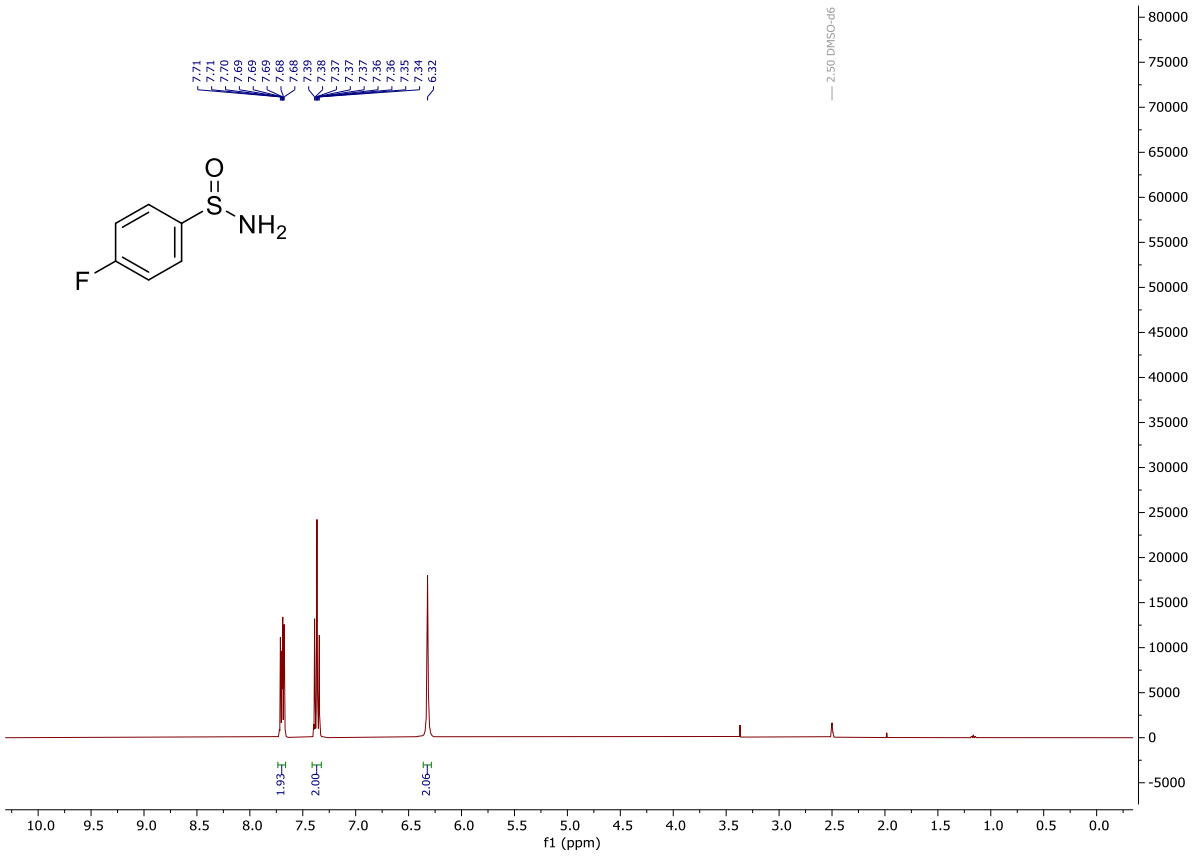
(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (S2)

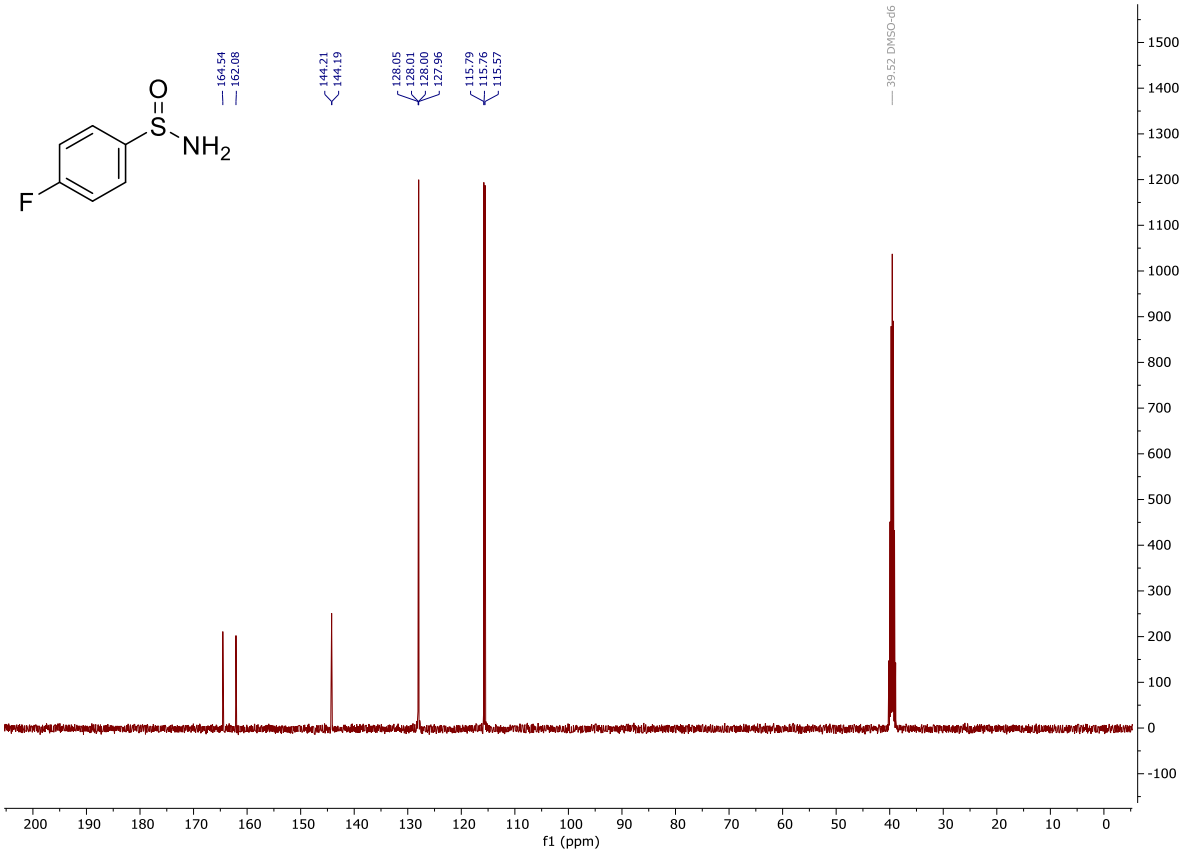

Me
O
S
O
Me
Me
Me
f1 (ppm)

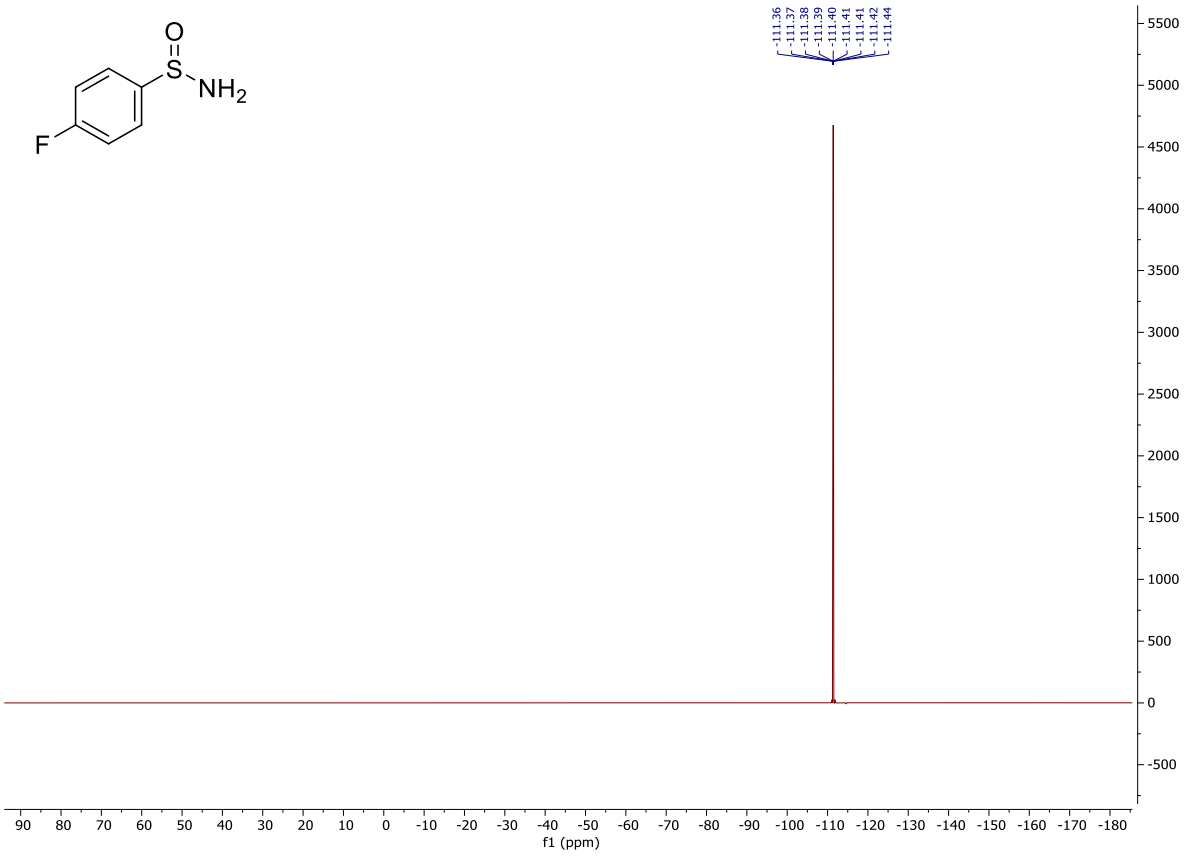

Me
O
S
O
Me
Me
Me
f1 (ppm)

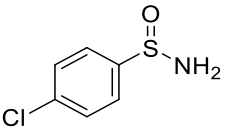


4-Fluorobenzenesulfinamide (186g)

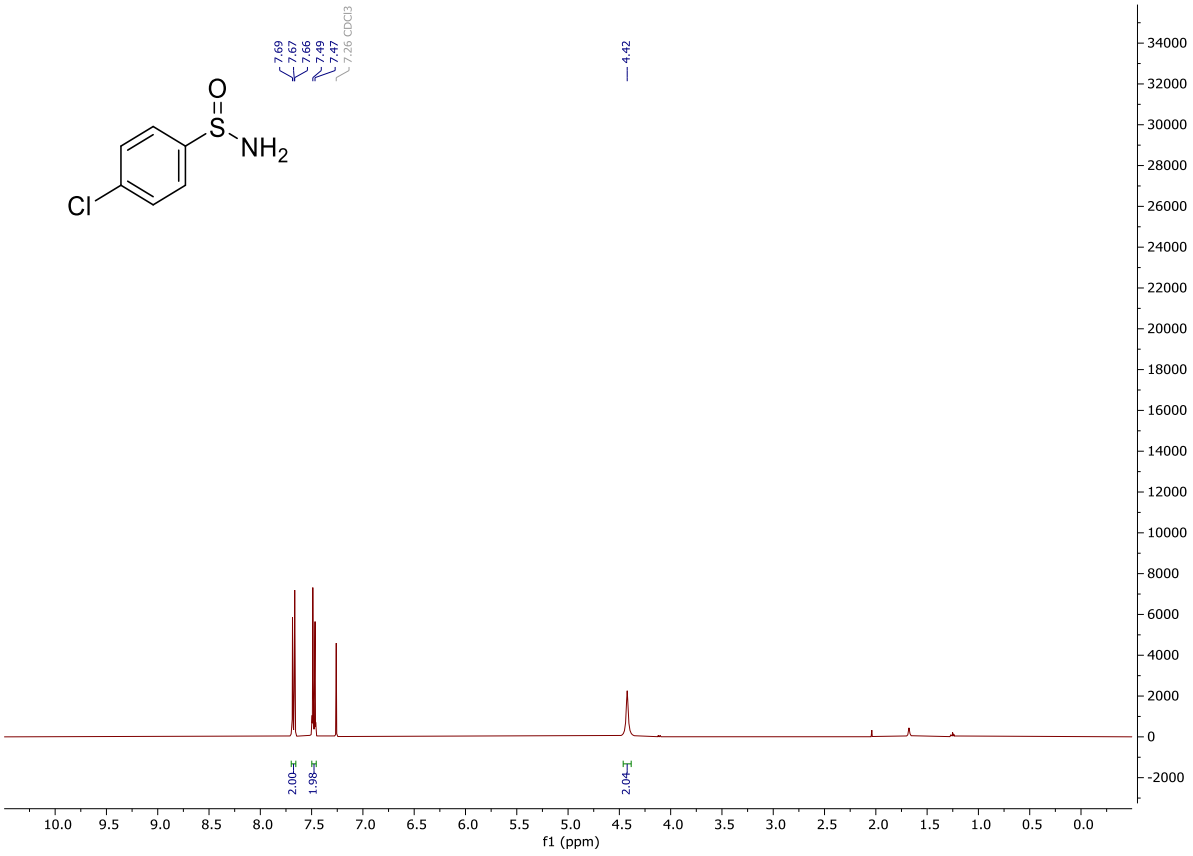


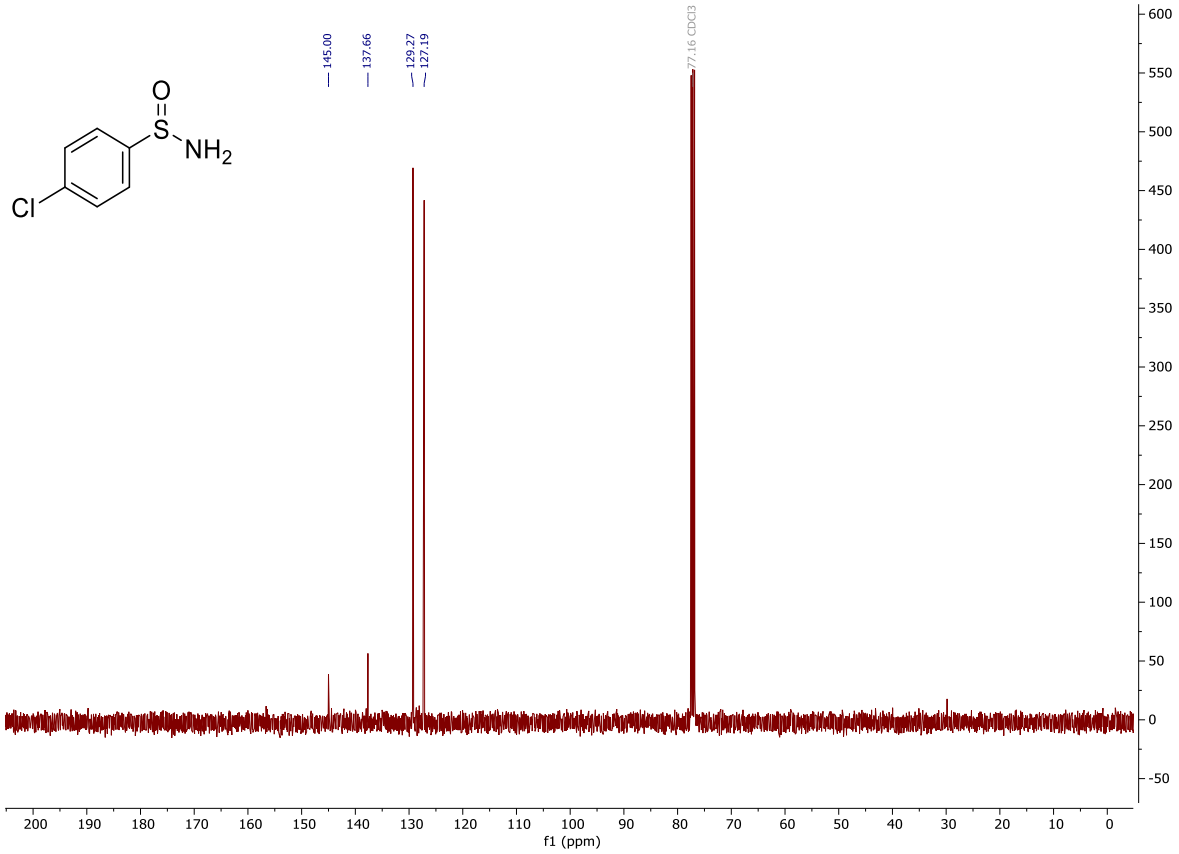

O
S
NH2
F
164.54
162.08
144.21
144.19
128.05
128.01
128.00
127.96
115.79
115.76
115.57
39.52 DMSO-d6
f1 (ppm)

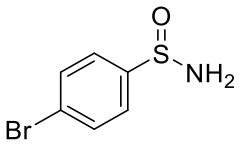

O
S
NH2
F
-111.36
-111.37
-111.38
-111.39
-111.40
-111.41
-111.41
-111.42
-111.44
f1 (ppm)



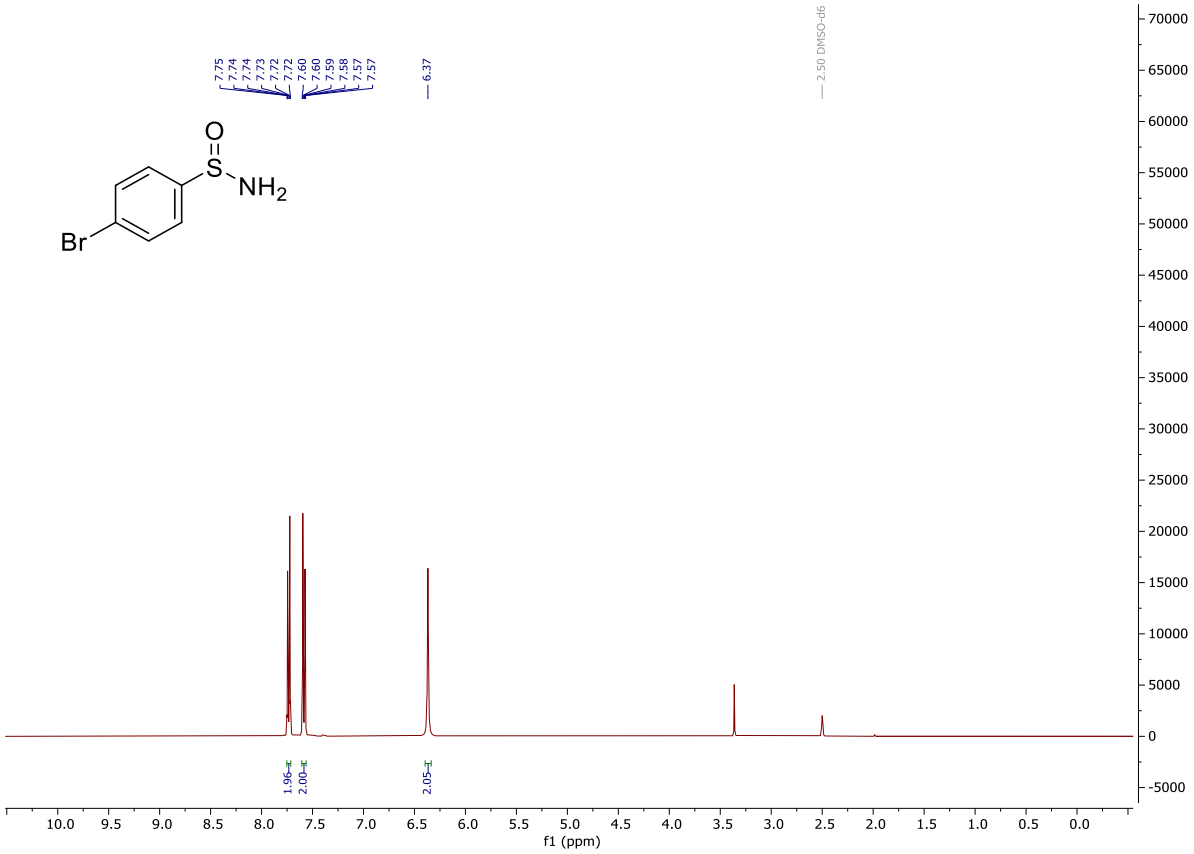
4-Chlorobenzenesulfinamide (186f)

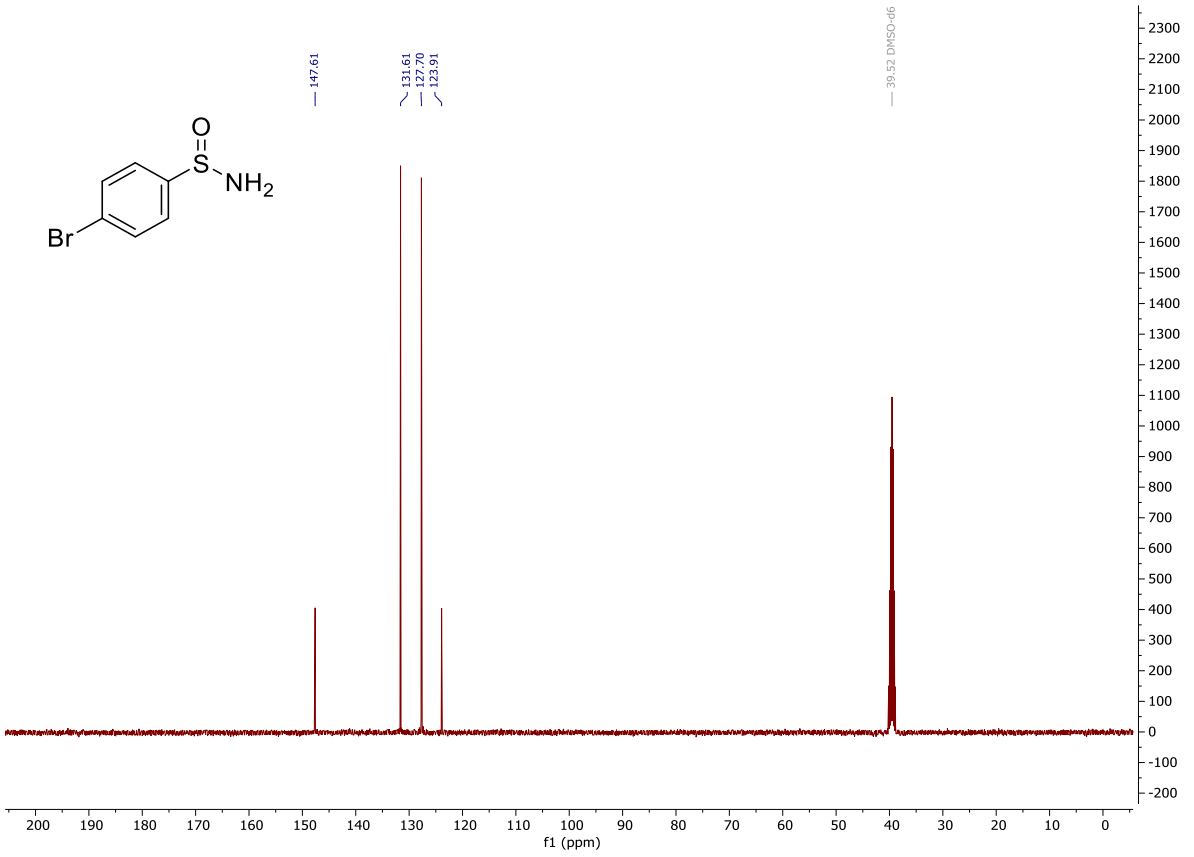


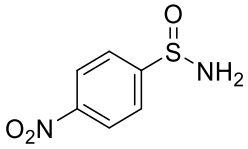




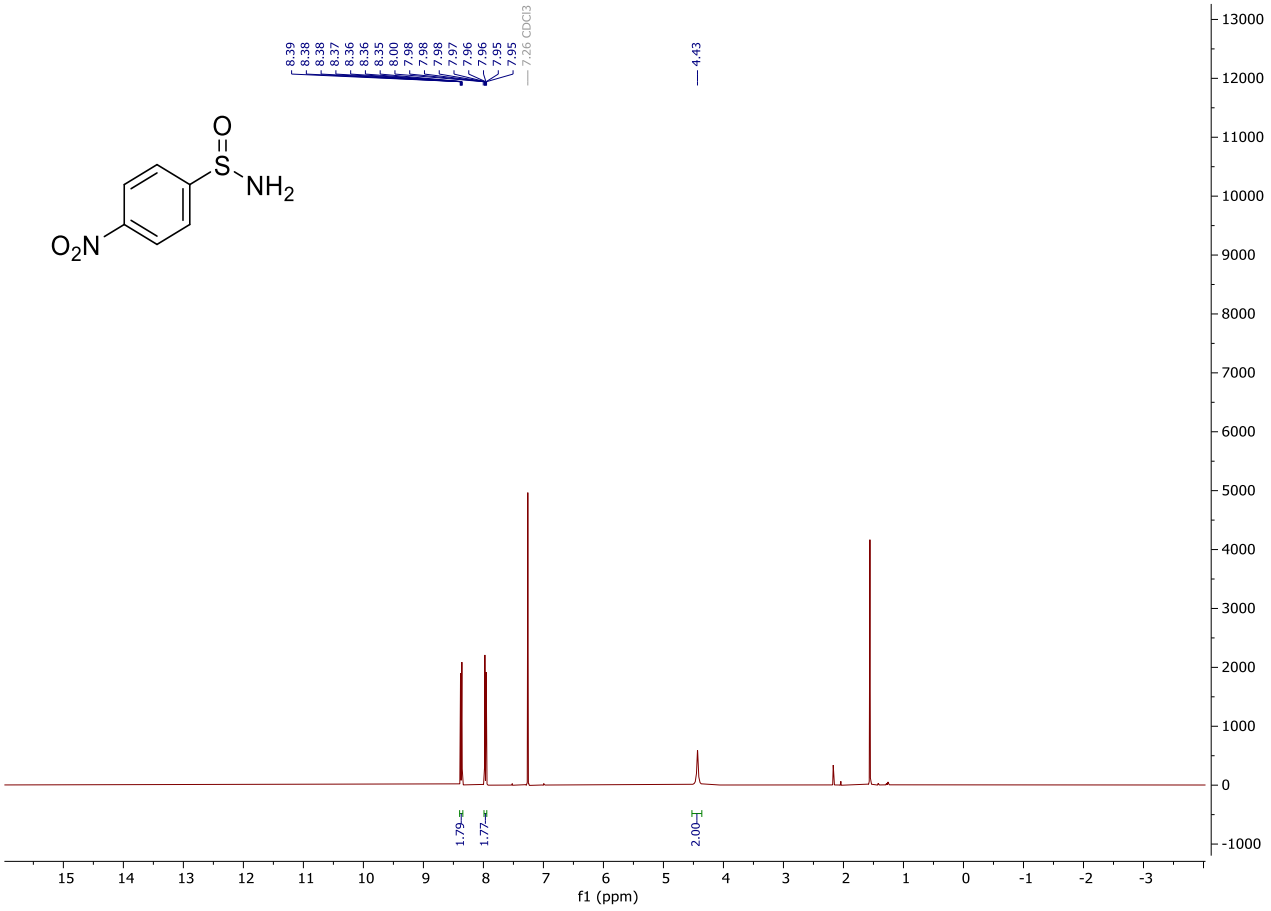
4-Bromobenzenesulfinamide (S3)

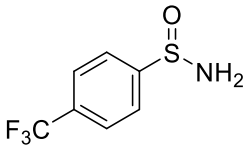

7.75
7.74
7.74
7.73
7.72
7.72
7.60
7.59
7.58
7.57
7.57
6.37
2.50 DMSO-d6
O
S
NH2
Br
1.96
2.00
2.05
f1 (ppm)


147.61
131.61
127.70
123.91
39.52 DMSO-d6
O
S
NH2
Br
f1 (ppm)

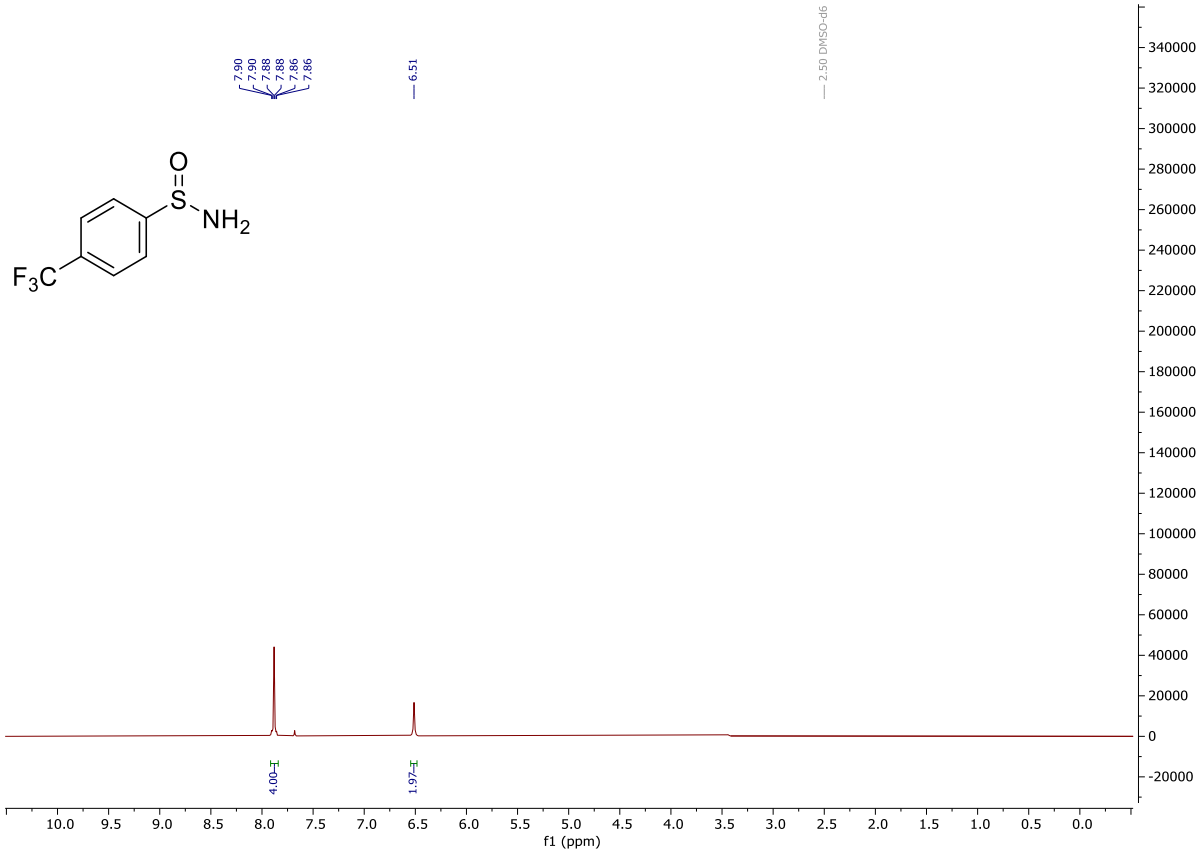


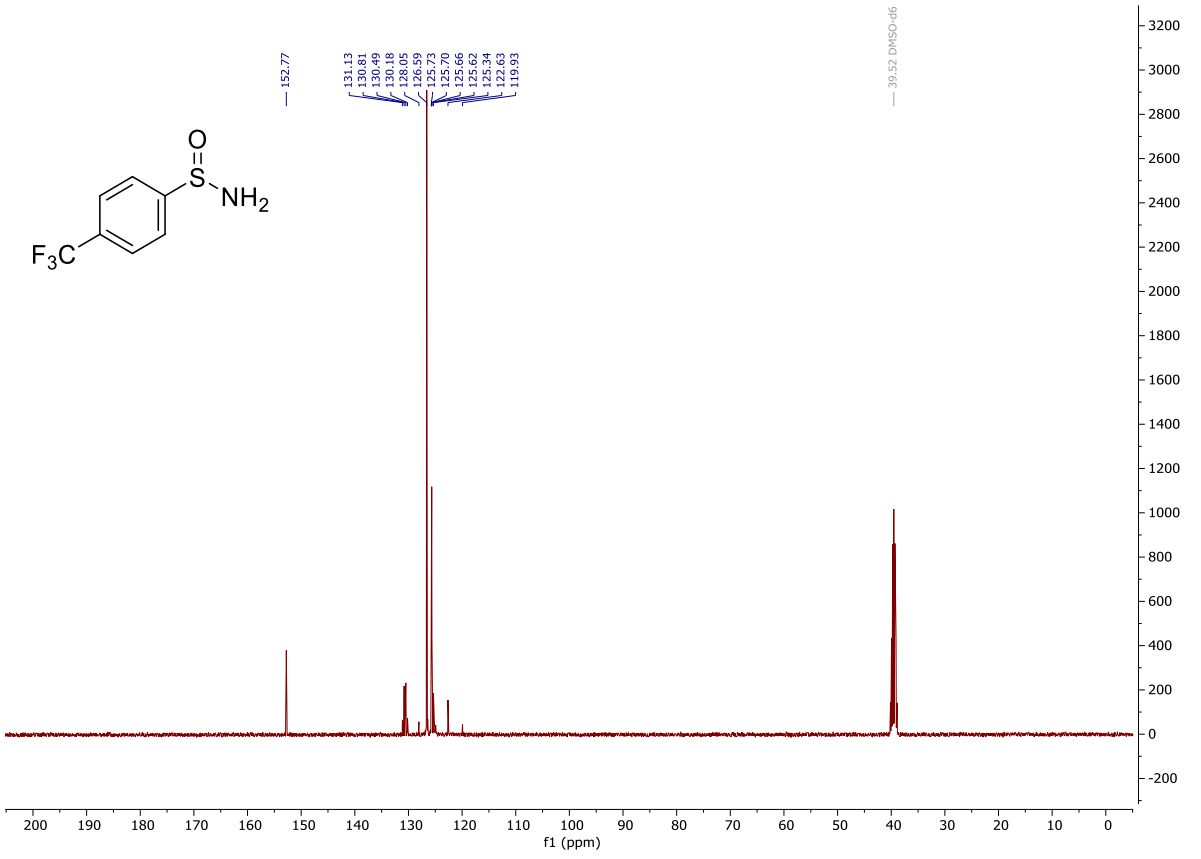
4-Nitrobenzenesulfinamide (S4)

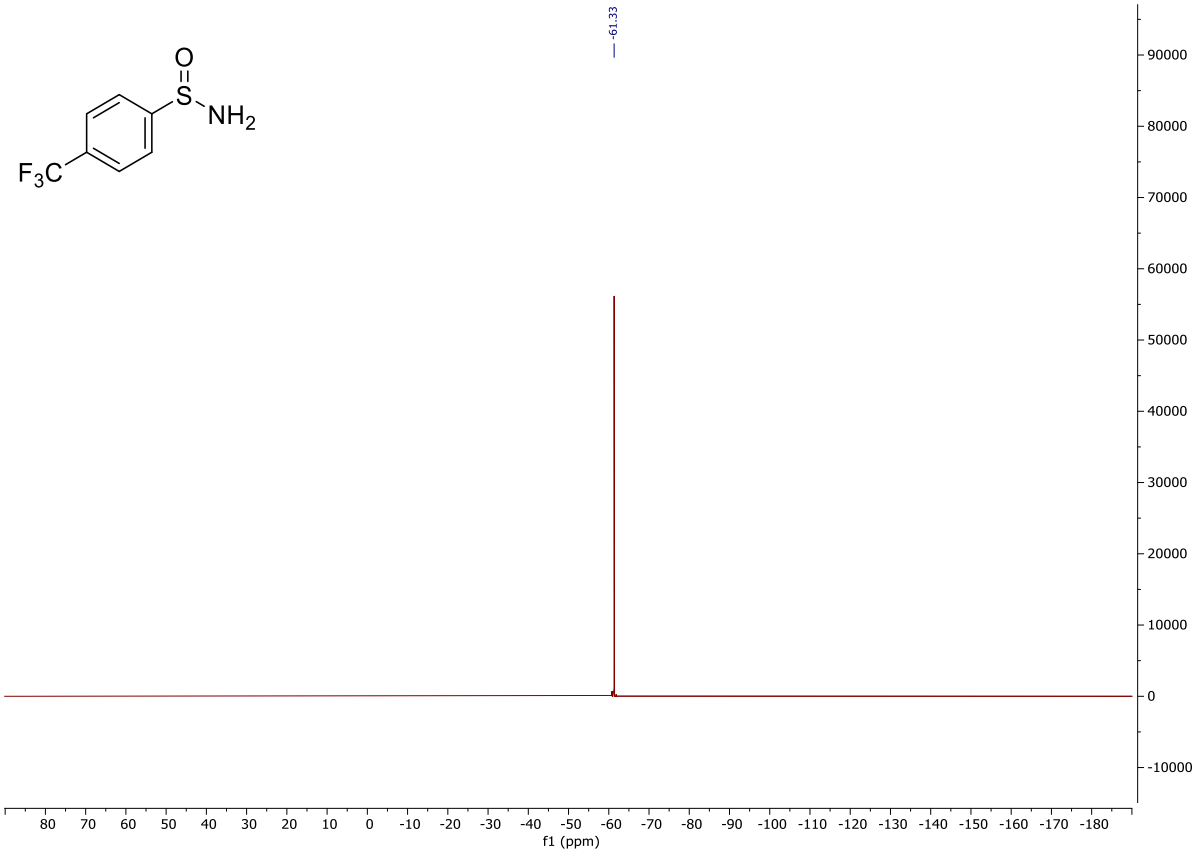


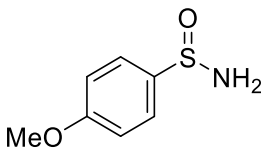


4-(Trifluoromethyl)benzenesulfinamide (186e)

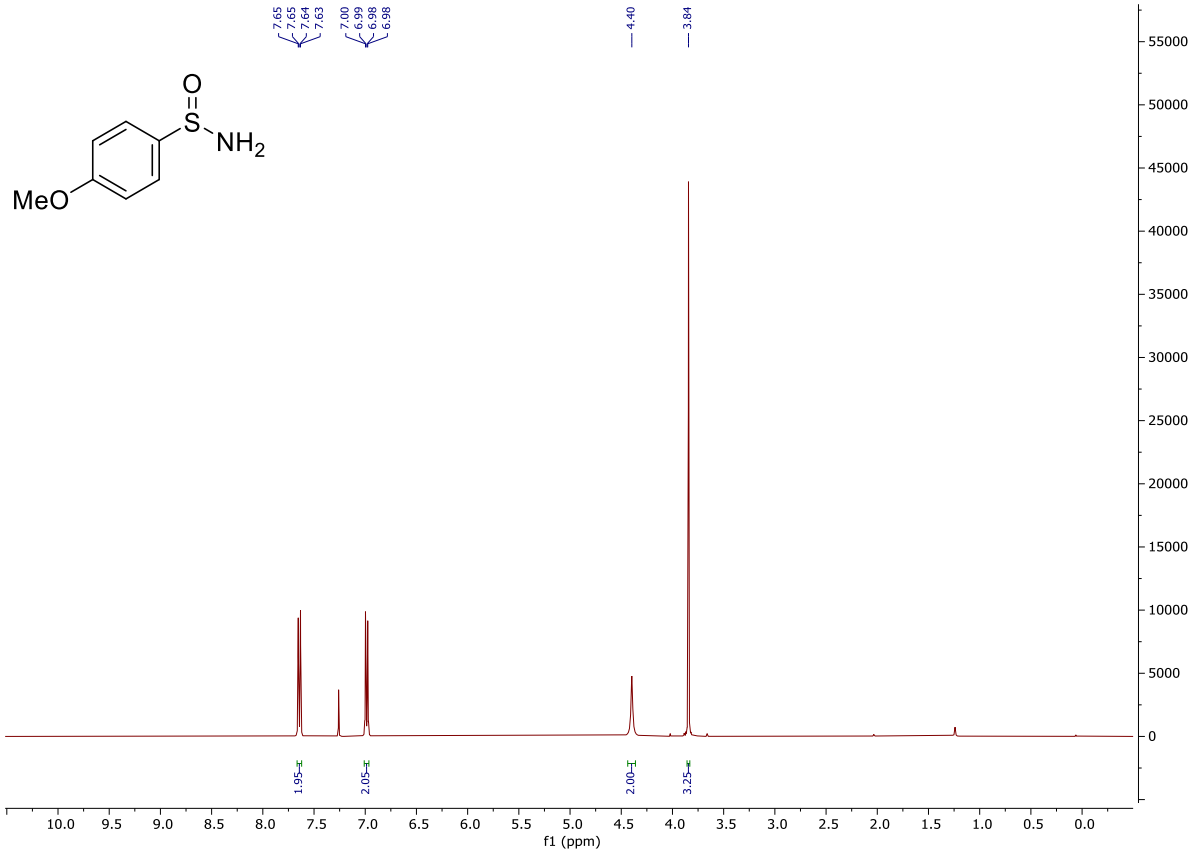

7.90
7.90
7.88
7.88
7.86
7.86
6.51
2.50 DMSO-d6
O
S
NH2
F3C
4.00
1.97
f1 (ppm)

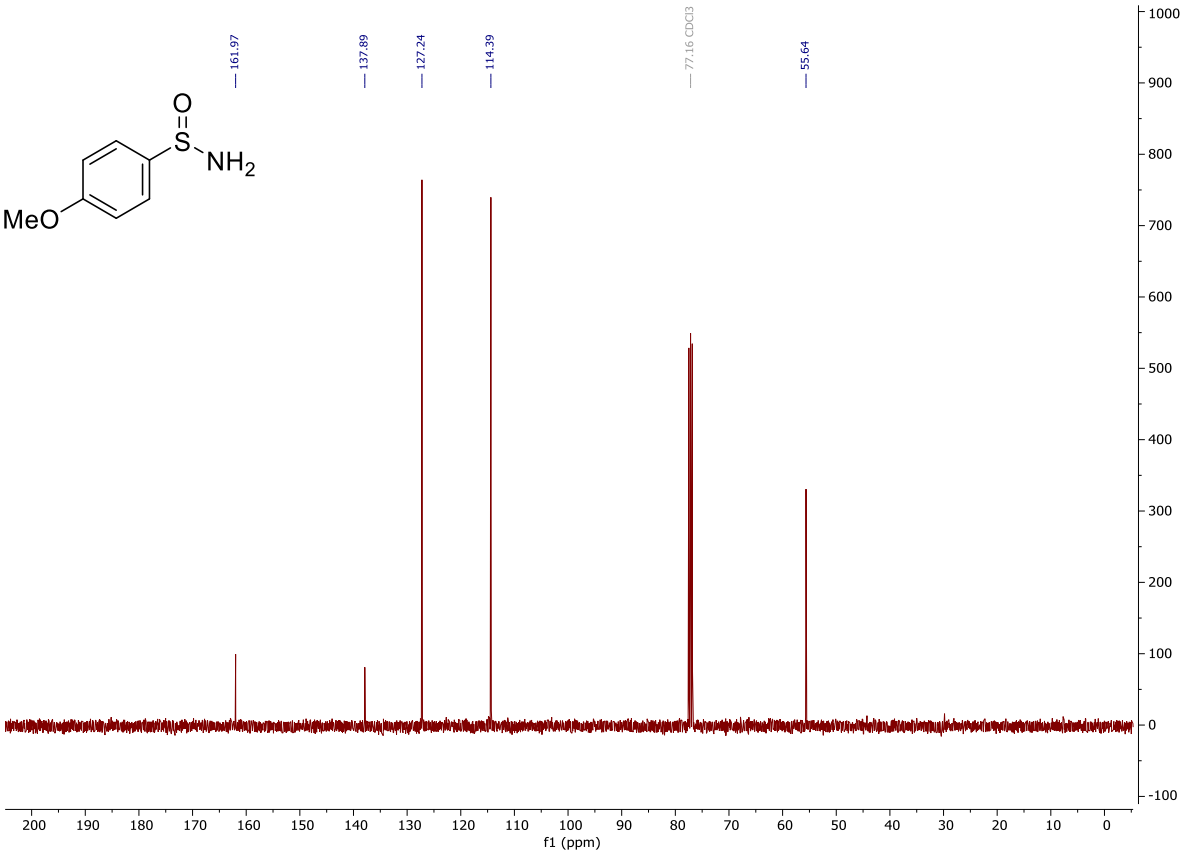

152.77
131.13
130.81
130.49
130.18
128.05
126.59
125.73
125.70
125.66
125.62
125.34
122.63
119.93
39.52 DMSO-d6
O
S
NH2
F3C
f1 (ppm)

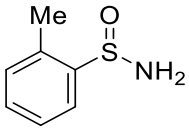




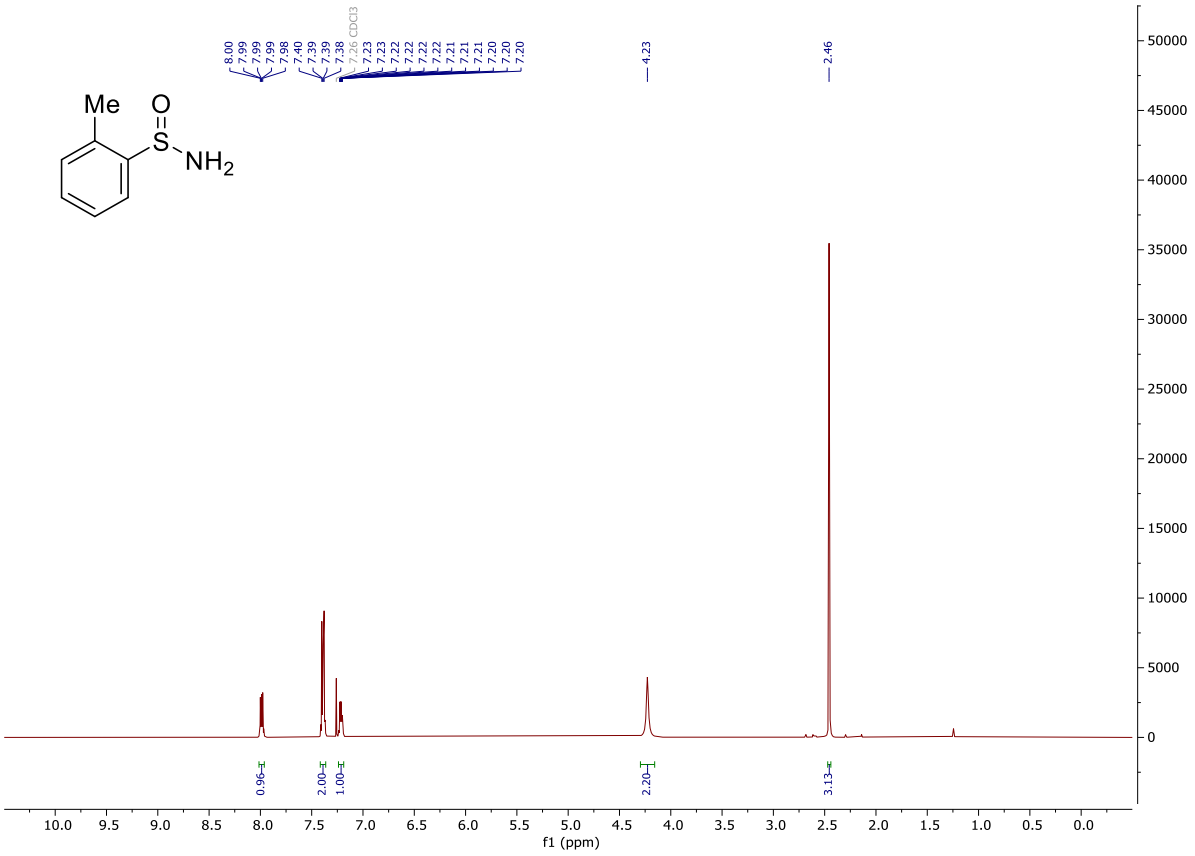
4-Methoxybenzenesulfinamide (186d)

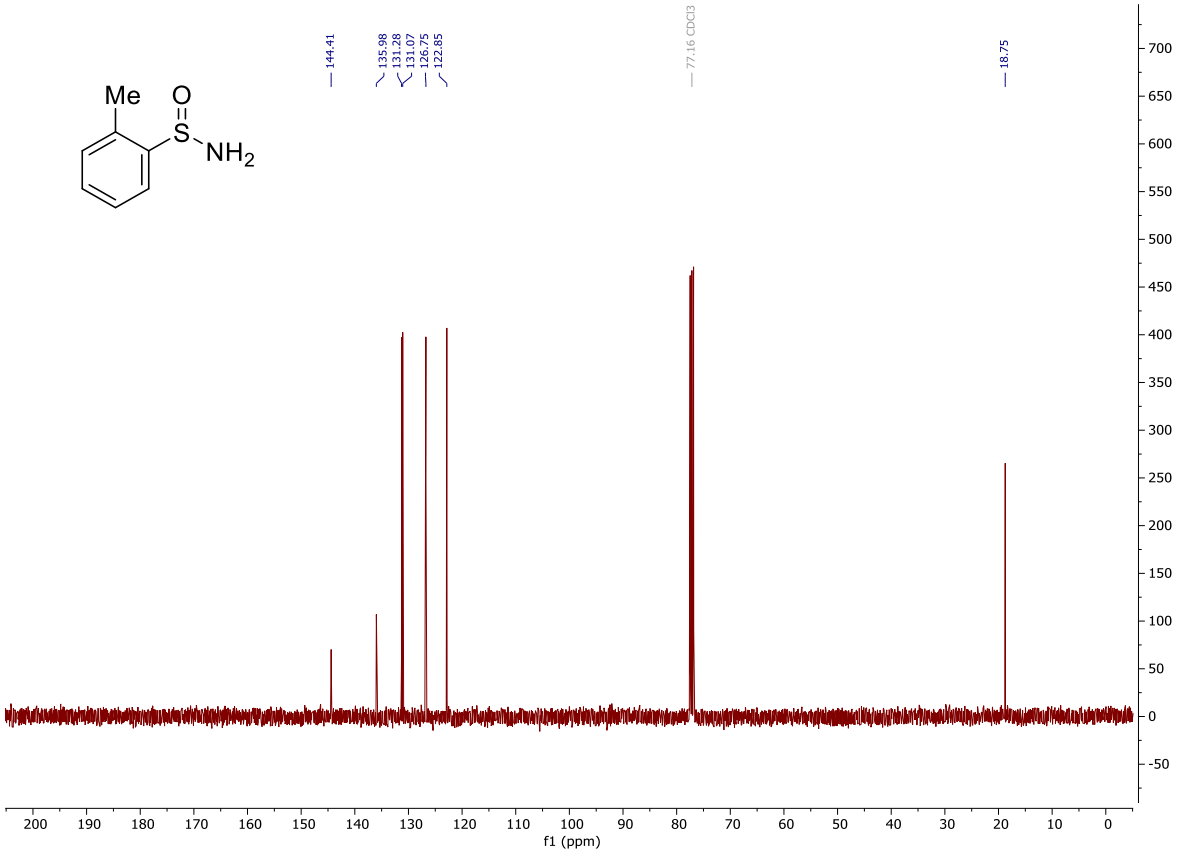

7.65
7.65
7.64
7.63
7.00
6.99
6.98
6.98
4.40
3.84
O
S
NH2
MeO
1.95
2.05
2.00
3.25
f1 (ppm)

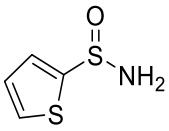

161.97
137.89
127.24
114.39
77.16 CDCl3
55.64
O
S
NH2
MeO
f1 (ppm)



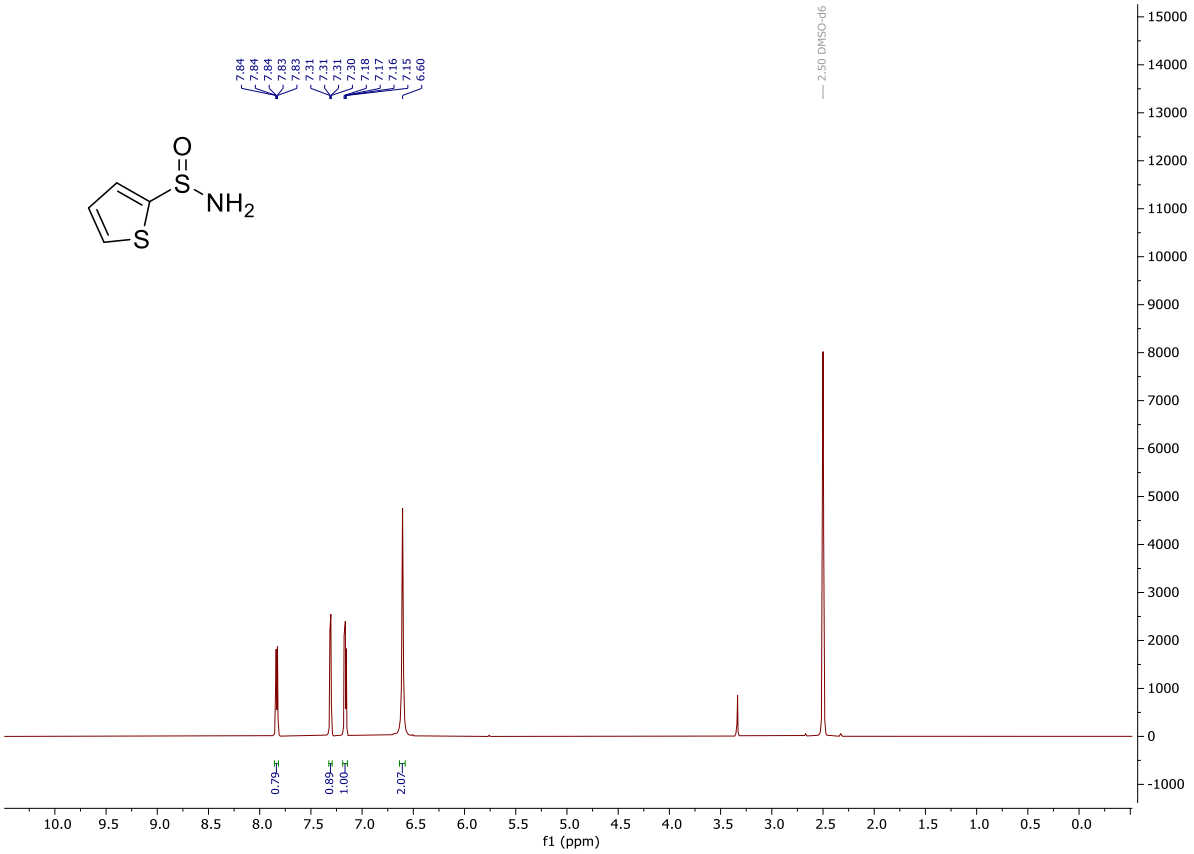
2-Methylbenzenesulfinamide (186c)

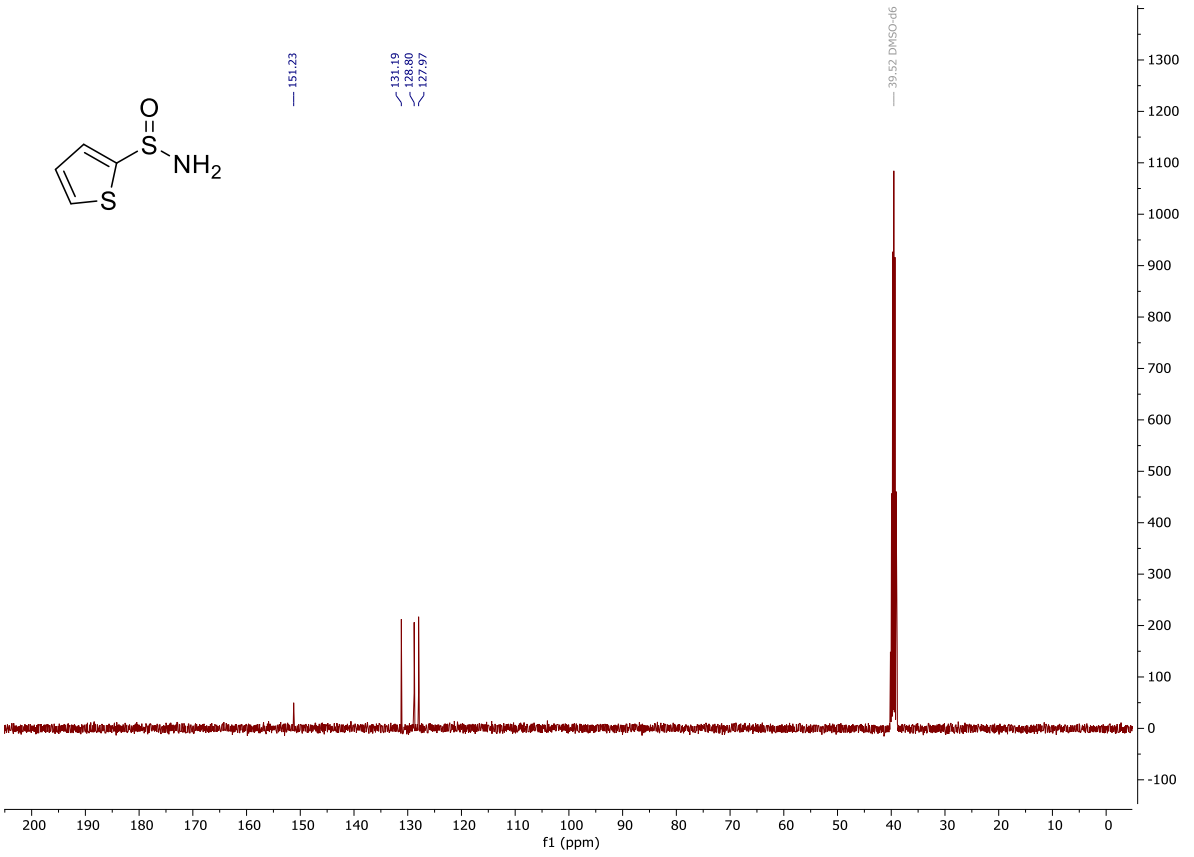


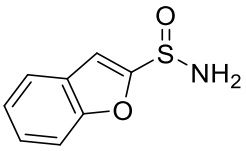




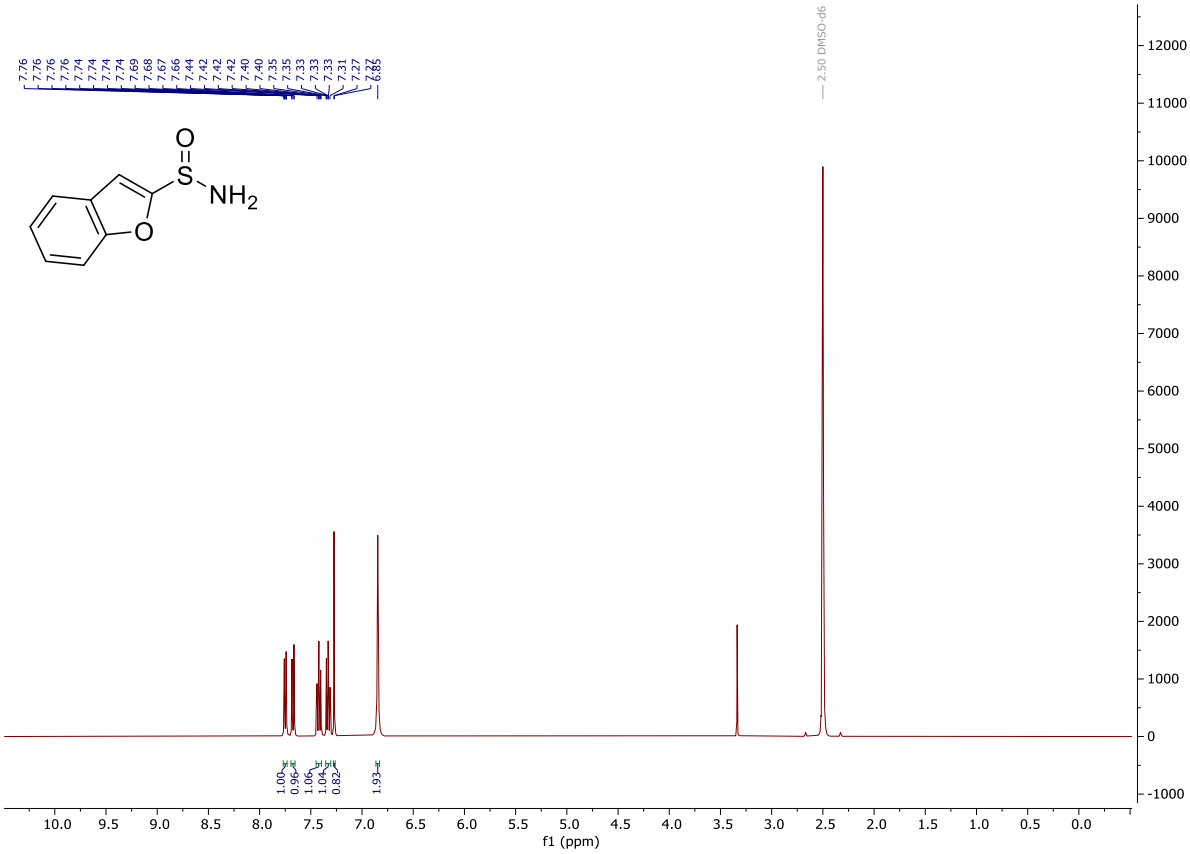
Thiophene-2-sulfinamide (186k)

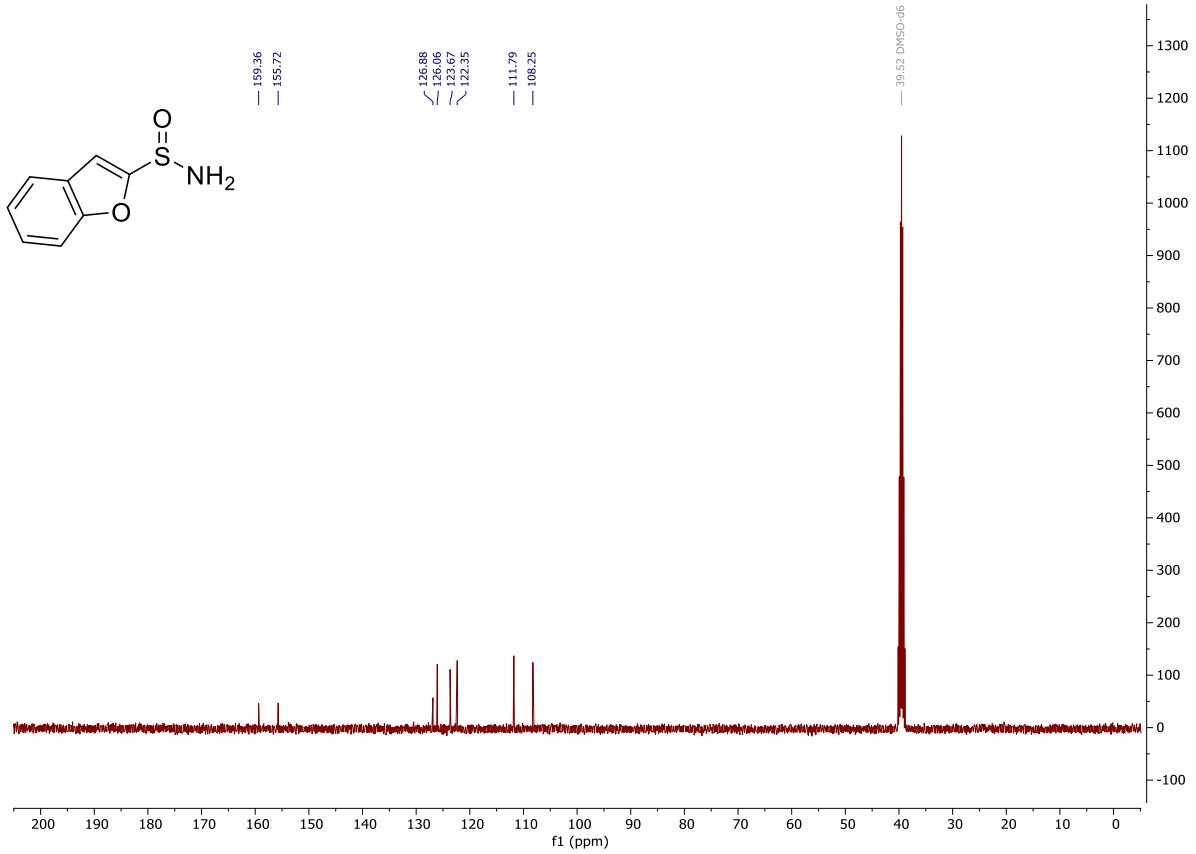

7.84
7.84
7.84
7.83
7.83
7.31
7.31
7.31
7.30
7.18
7.17
7.16
7.15
6.60
2.50 DMSO-d6
O
S
NH2
S
0.79
0.89
1.00
2.07
f1 (ppm)

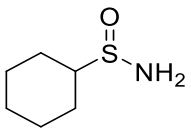

151.23
131.19
128.80
127.97
39.52 DMSO-d6
O
S
NH2
S
f1 (ppm)



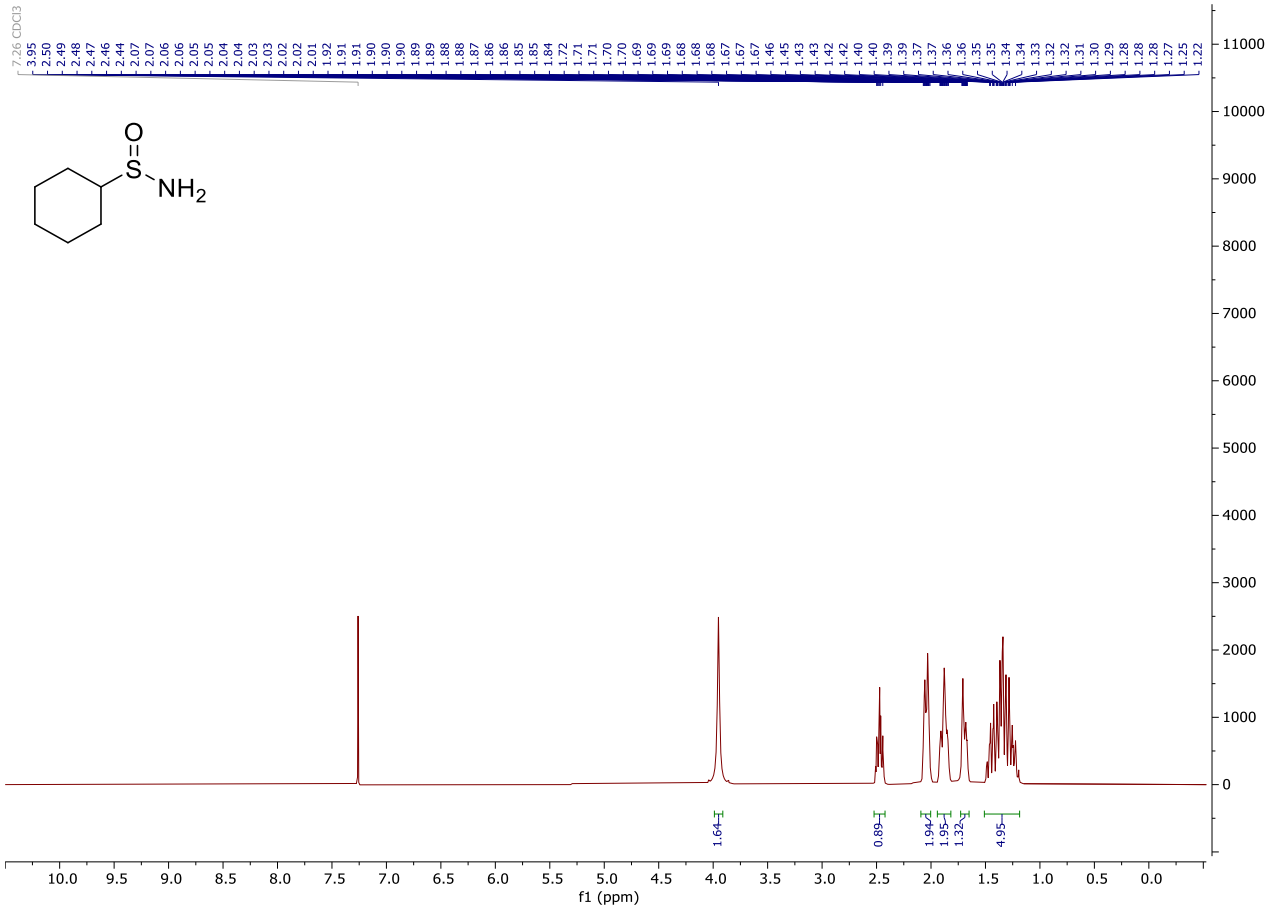
Benzofuran-2-sulfinamide (186j)

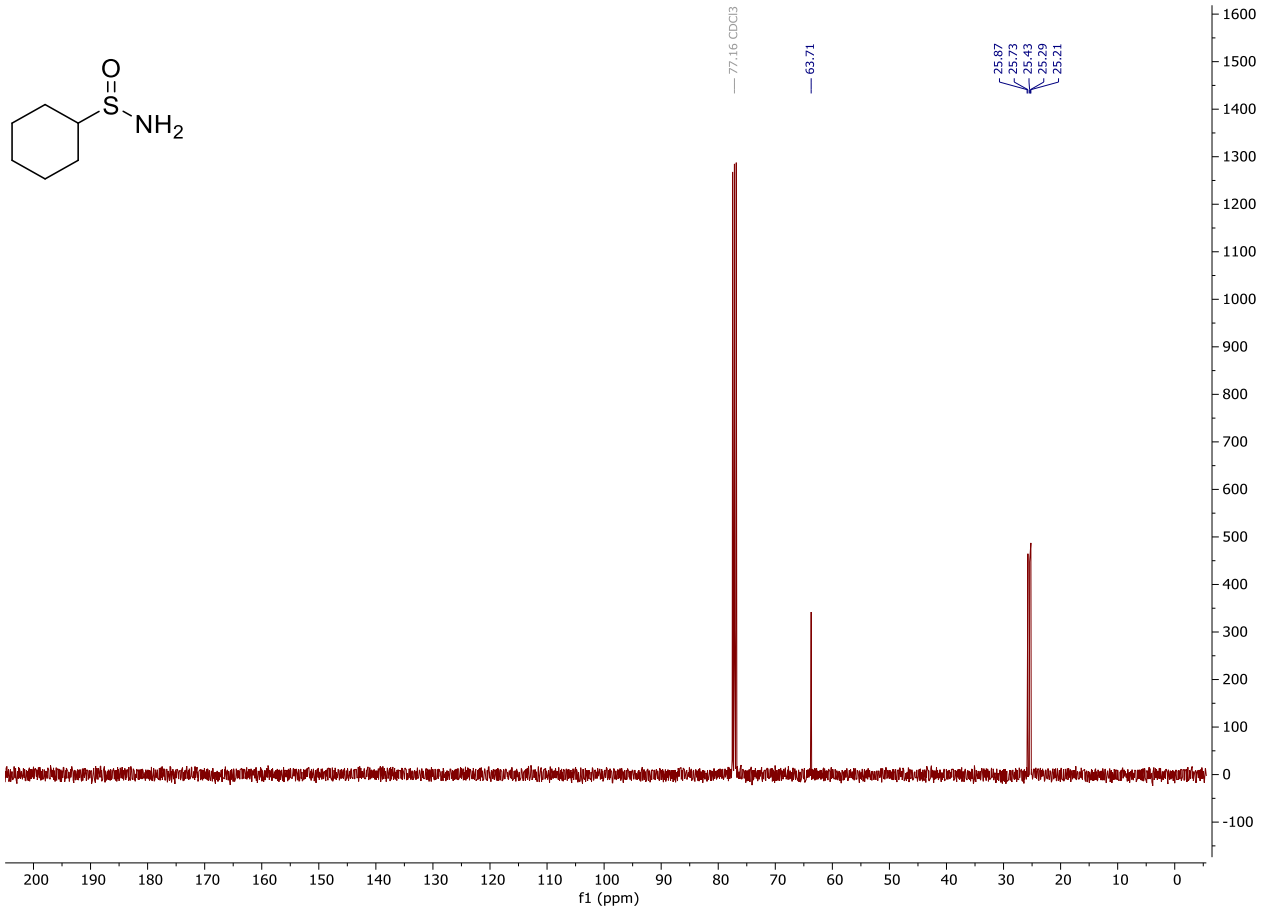




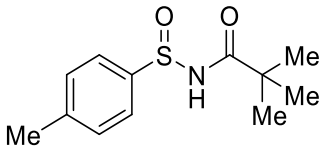


Cyclohexanesulfinamide (S5)

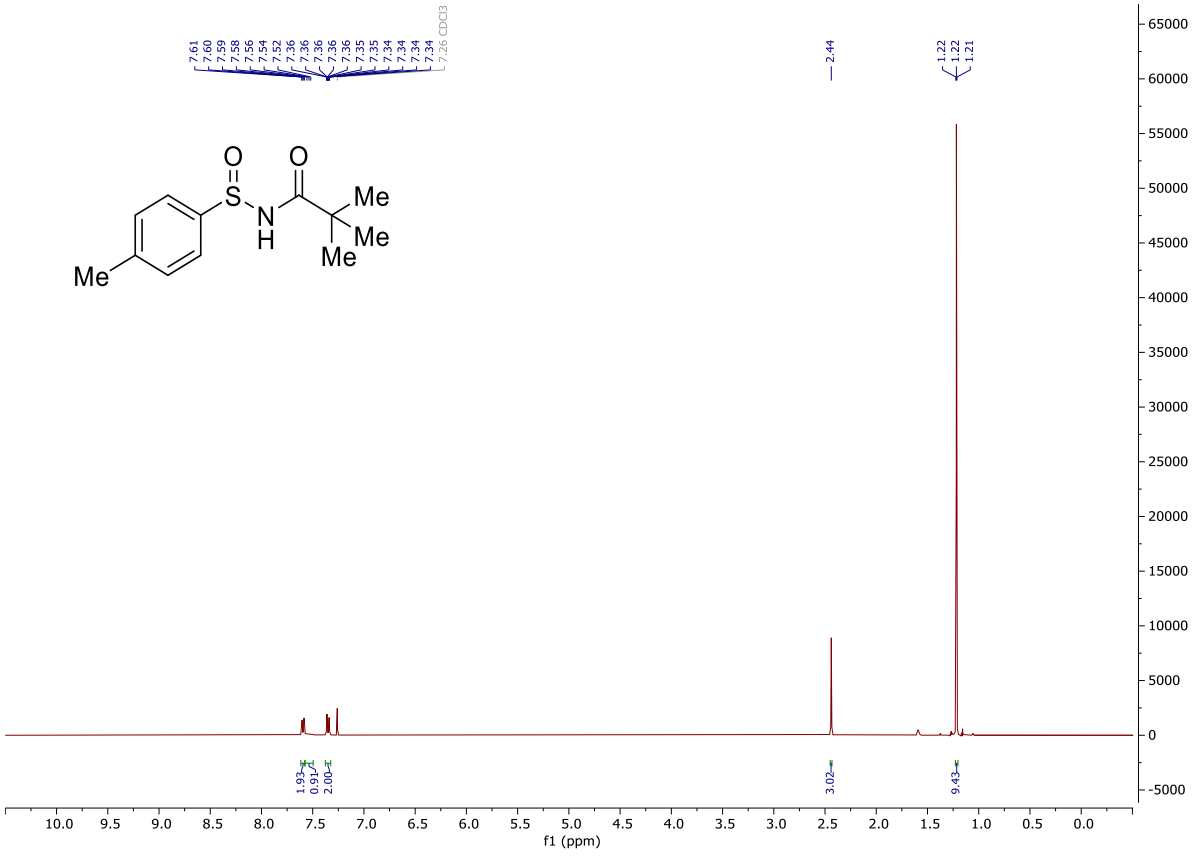

7.26 CDCl3
O
S
NH2
1.64
0.89
1.94
1.95
1.32
4.95
f1 (ppm)

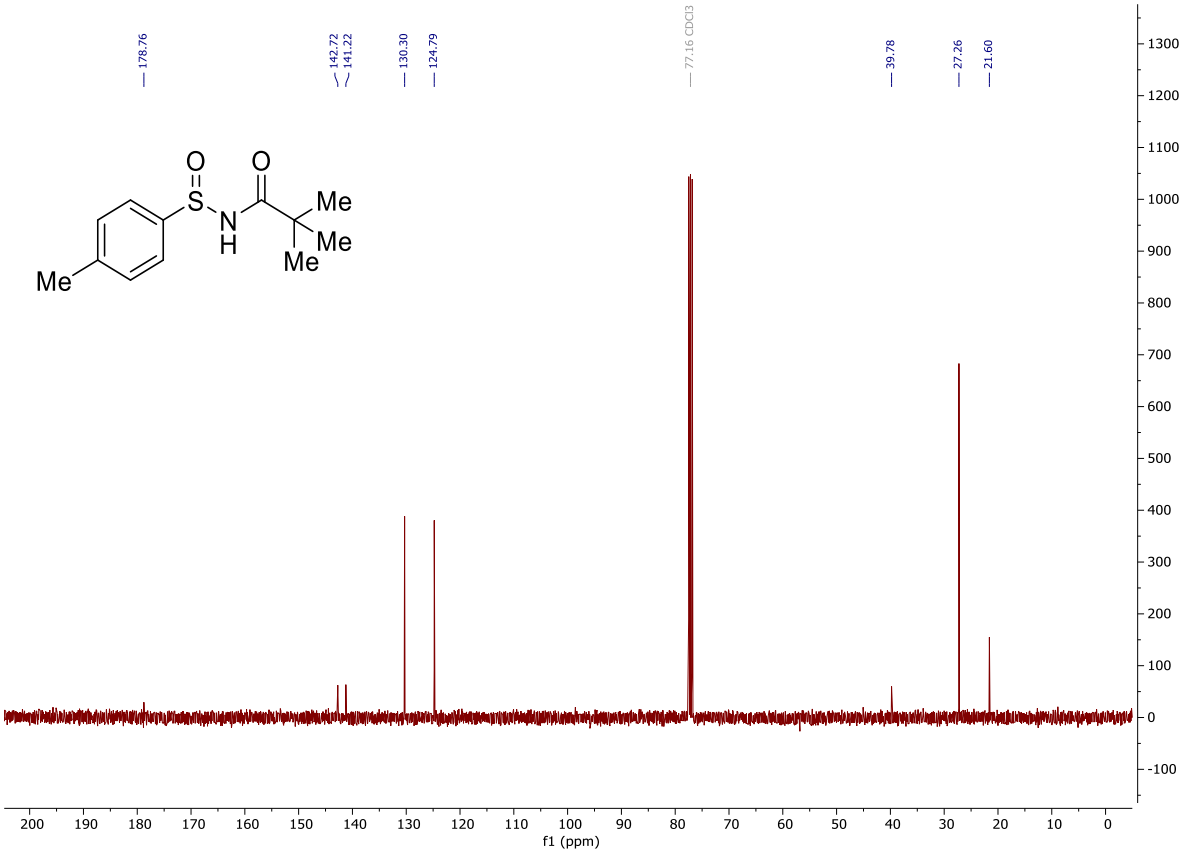

77.16 CDCl3
63.71
25.87
25.73
25.43
25.29
25.21
O
S
NH2
f1 (ppm)

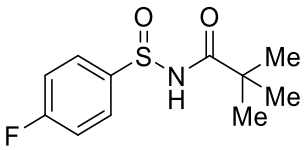
8.1.3 *N*-Piv sulfinamides



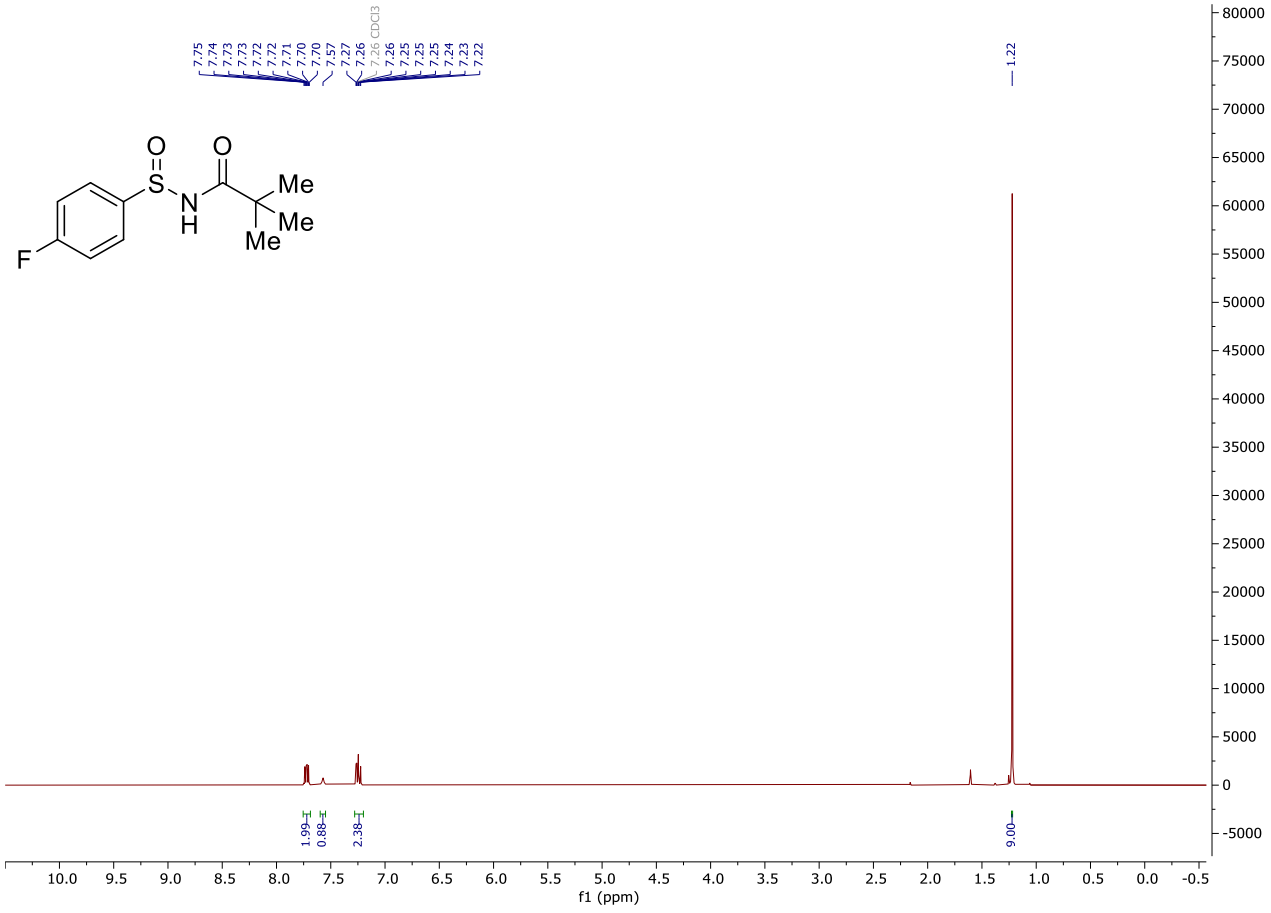
***N*-(*p*-Tolylsulfinyl)pivalamide (69a)**

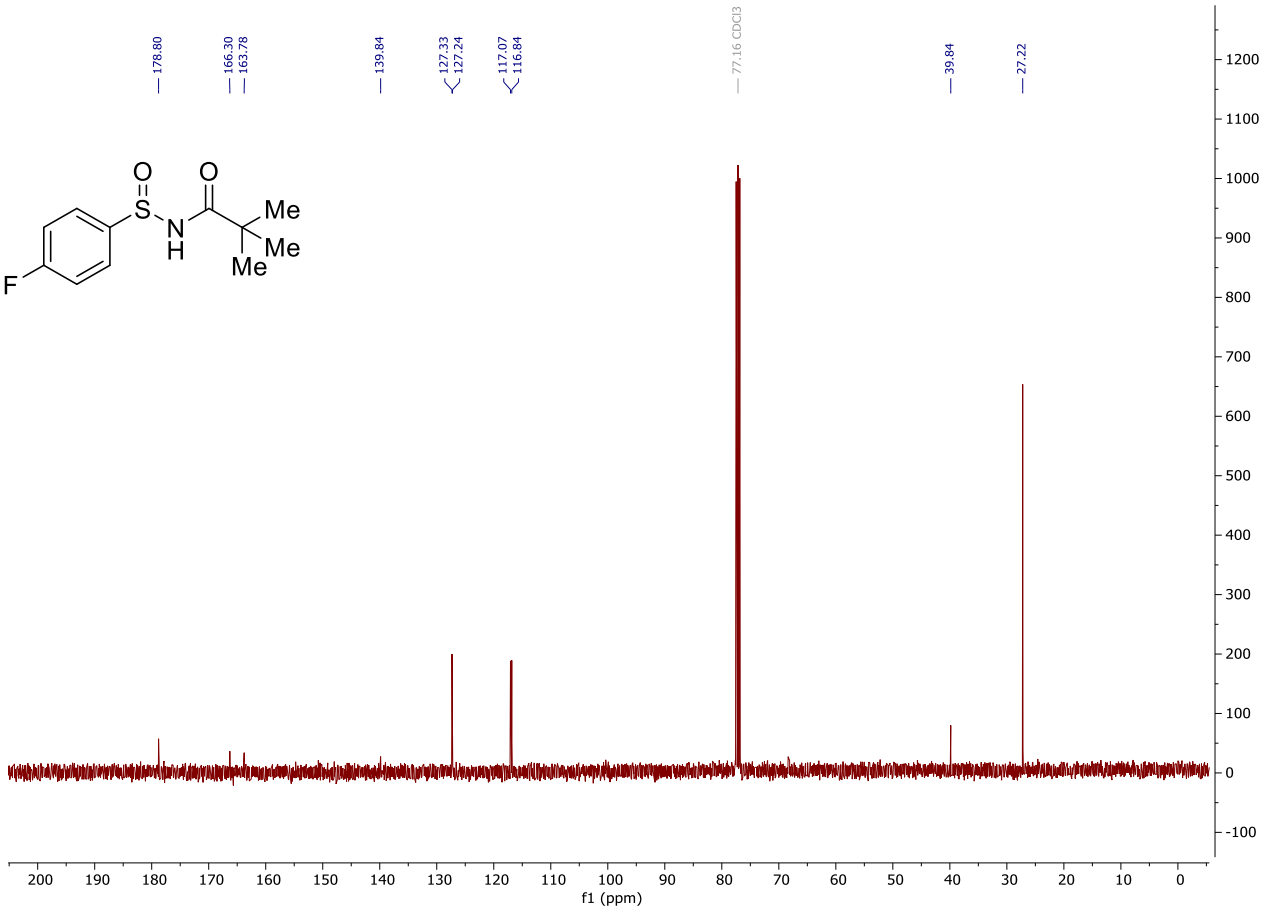


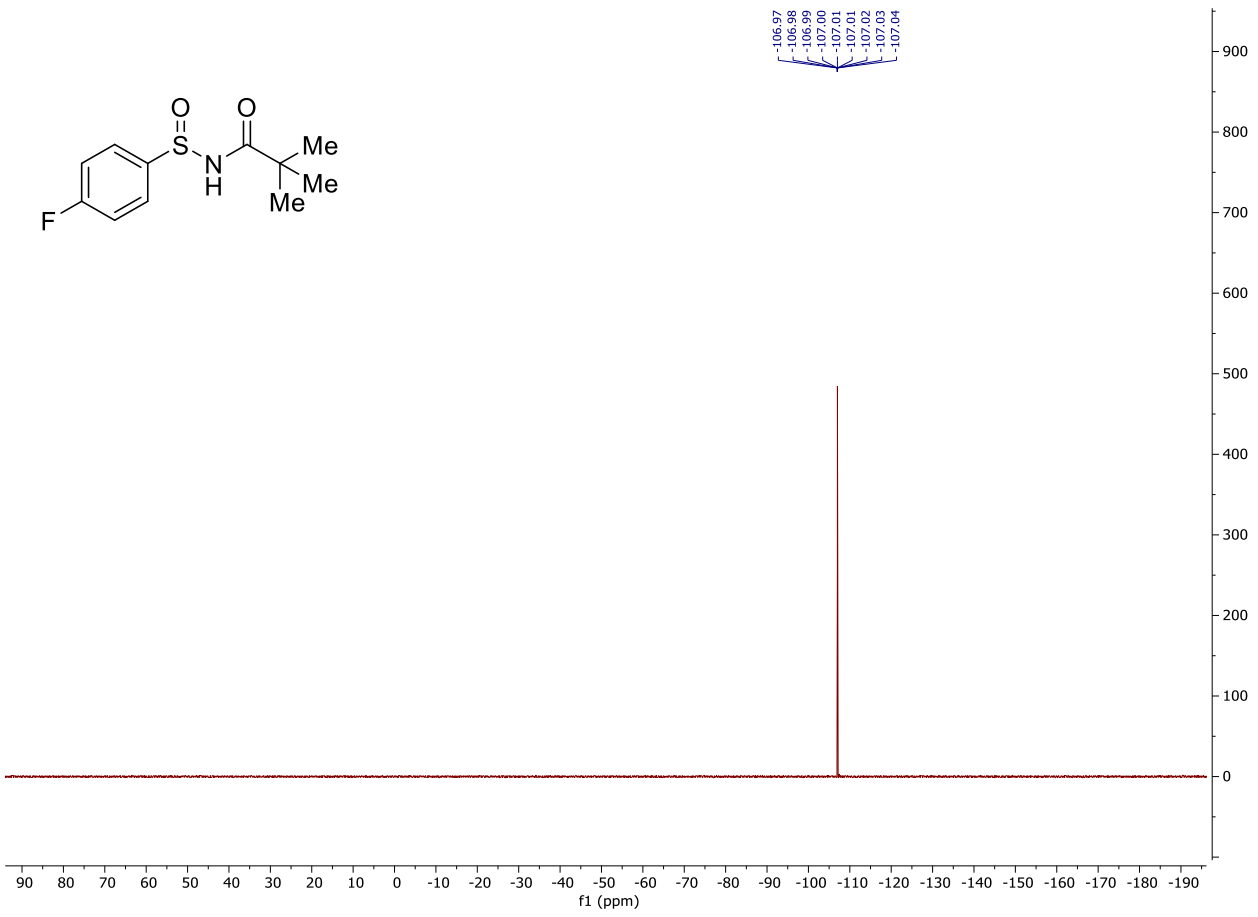


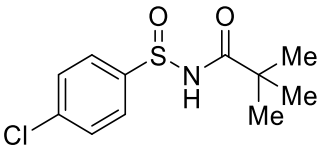


_N_-((4-Fluorophenyl)sulfinyl)pivalamide (69b)

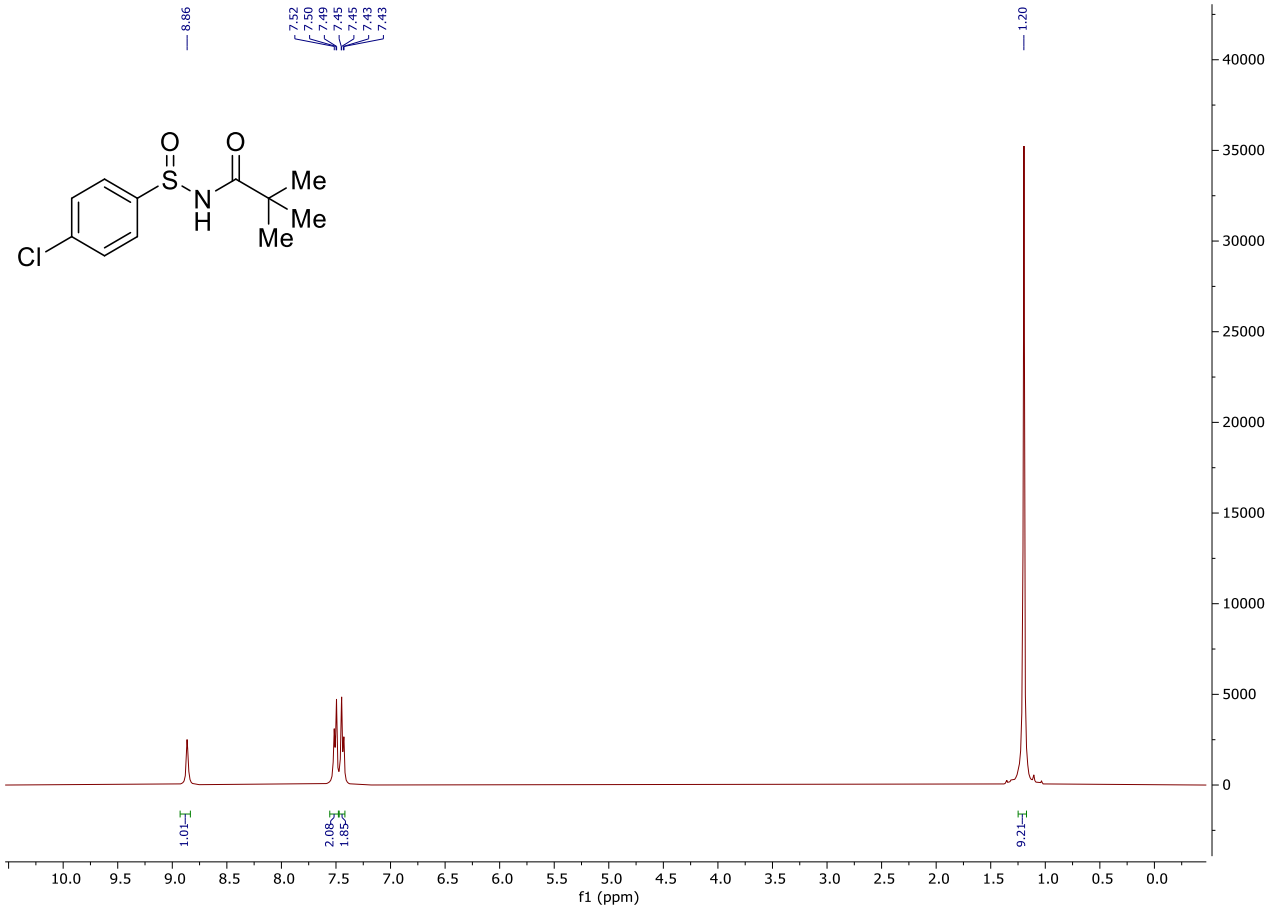

7.75
7.74
7.73
7.73
7.72
7.72
7.71
7.70
7.70
7.57
7.27
7.26
7.26 CDCl3
7.26
7.25
7.25
7.25
7.24
7.23
7.22
1.22
O
S
N
H
O
Me
Me
Me
F
1.99
0.88
2.38
9.00
f1 (ppm)

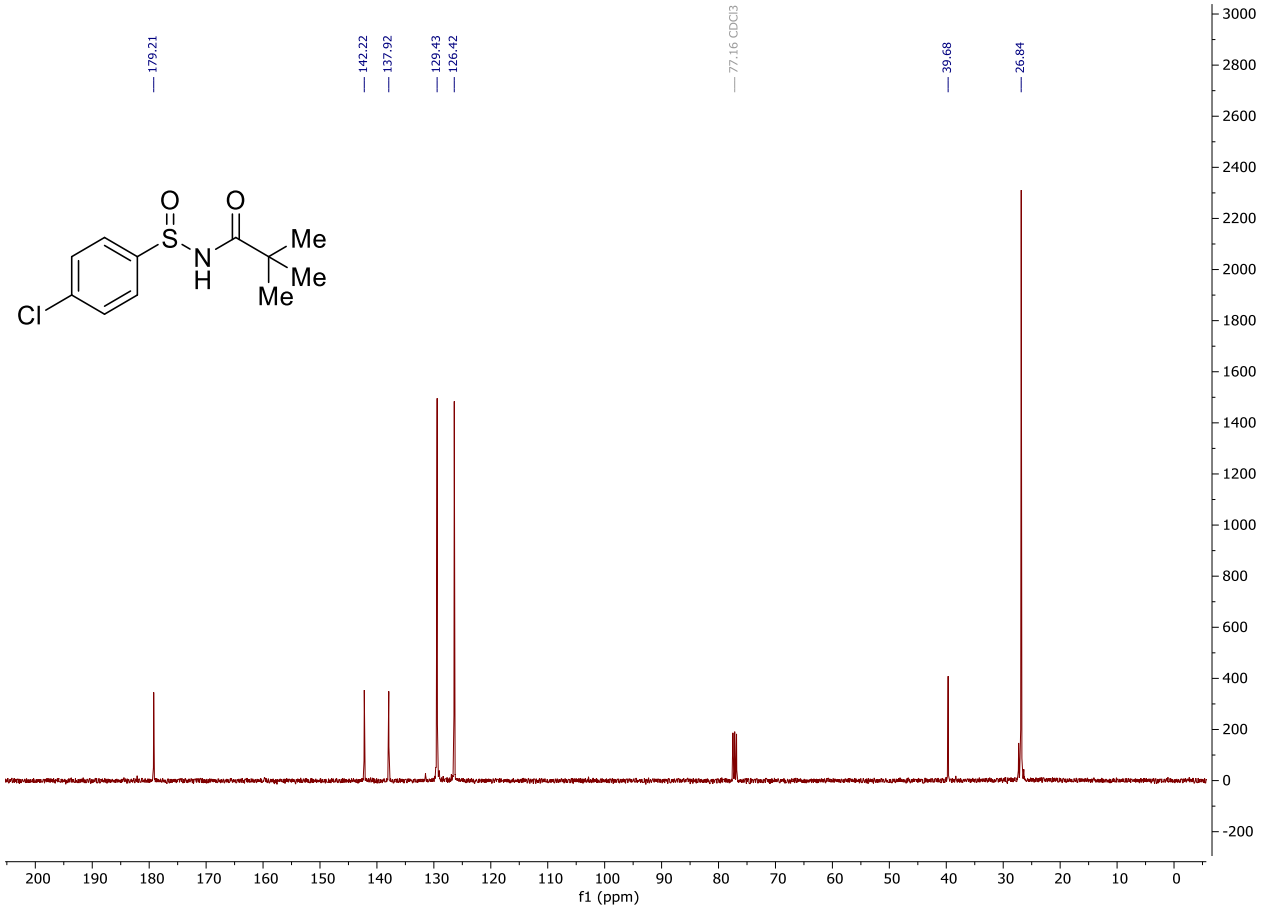

178.80
166.30
163.78
139.84
127.33
127.24
117.07
116.84
77.16 CDCl3
39.84
27.22
O
S
N
H
O
Me
Me
Me
F
f1 (ppm)

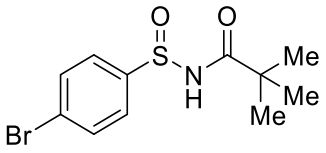




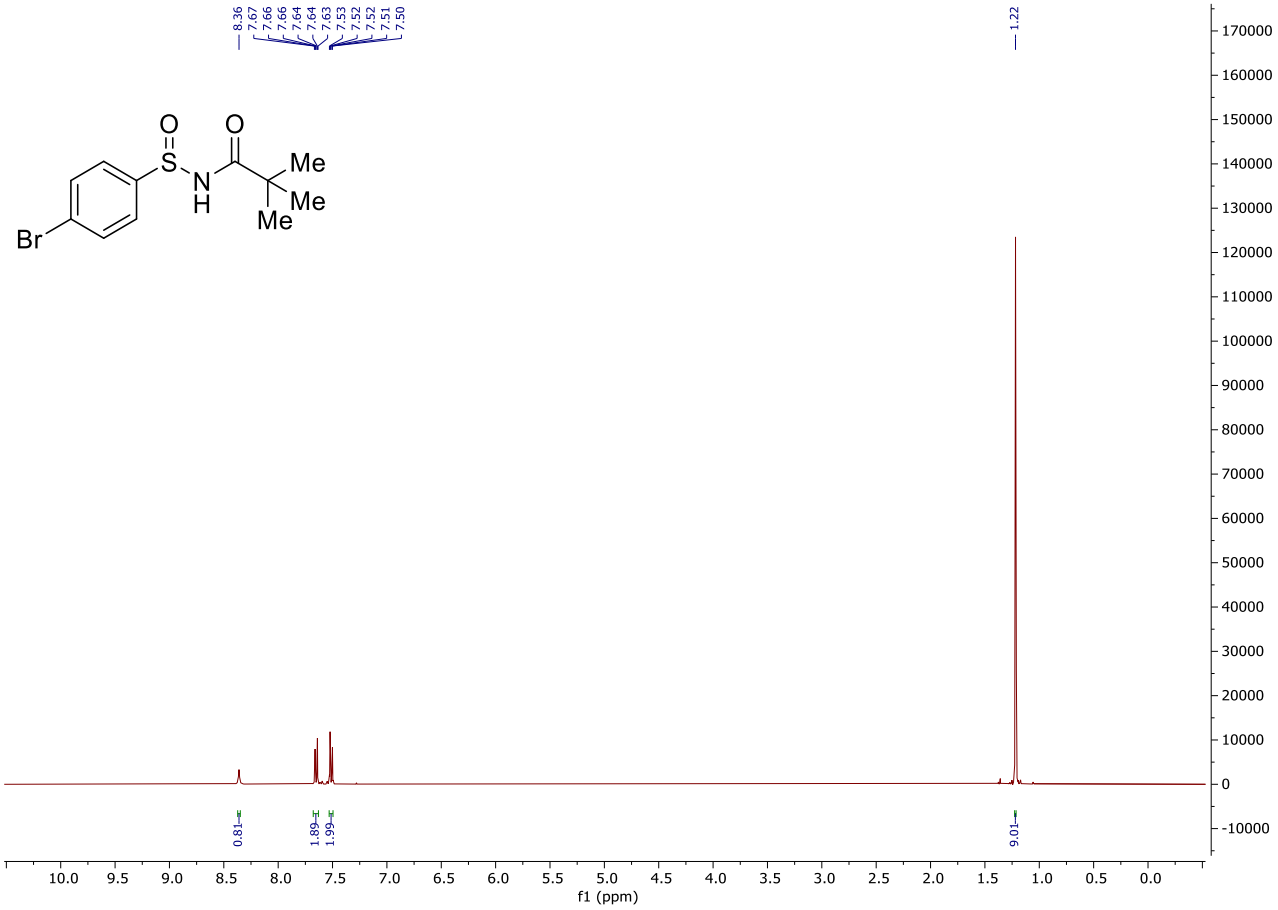
***N*-((4-Chlorophenyl)sulfinyl)pivalamide (69c)**

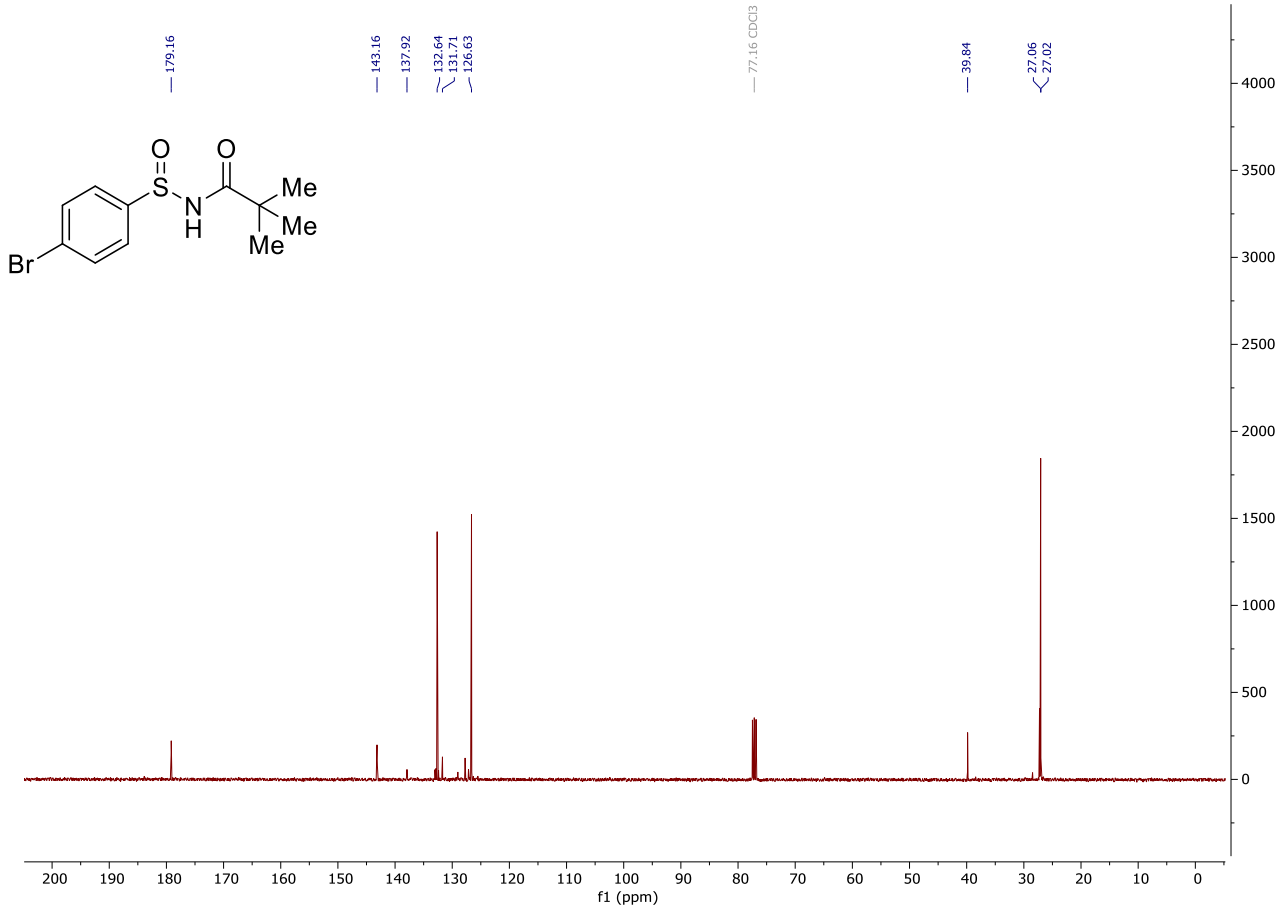

8.86
7.52
7.50
7.49
7.45
7.45
7.43
7.43
1.20
O
O
S
N
H
Me
Me
Me
Cl
1.01
2.08
1.85
9.21
f1 (ppm)

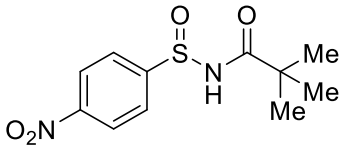

179.21
142.22
137.92
129.43
126.42
77.16 CDCl3
39.68
26.84
O
O
S
N
H
Me
Me
Me
Cl
f1 (ppm)



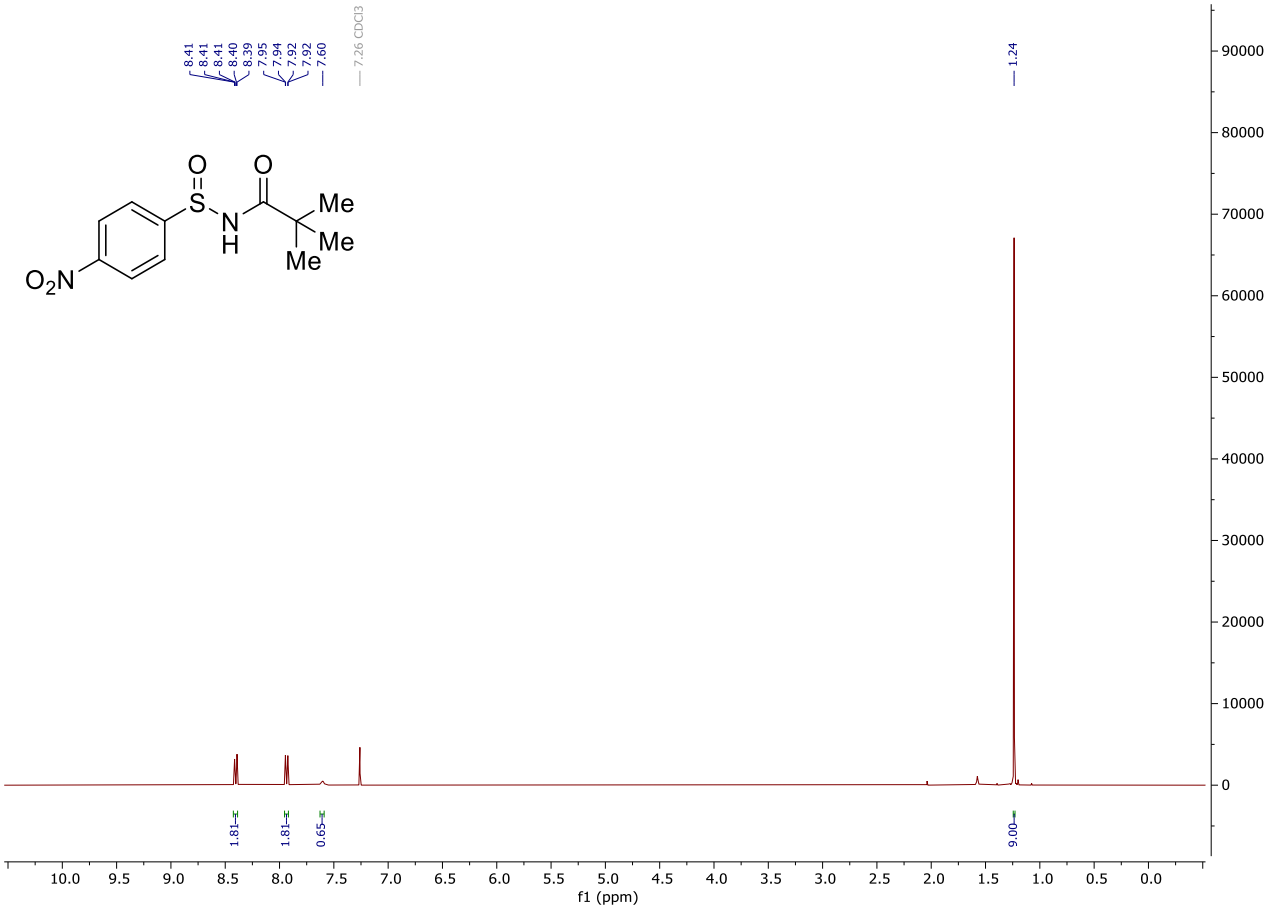
_N_-((4-Bromophenyl)sulfinyl)pivalamide (69d)

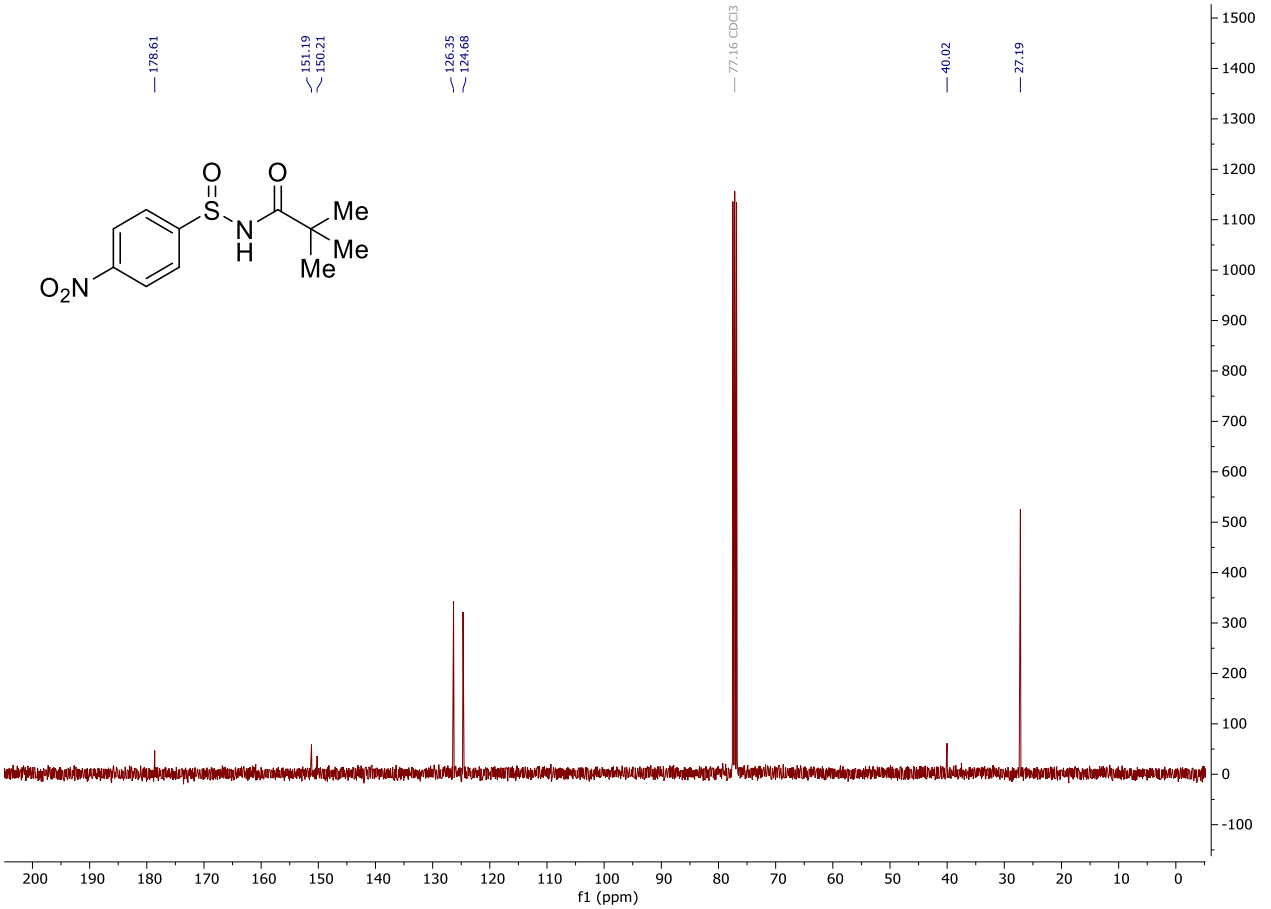


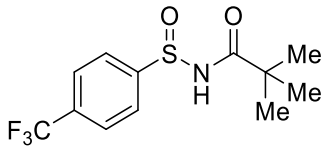




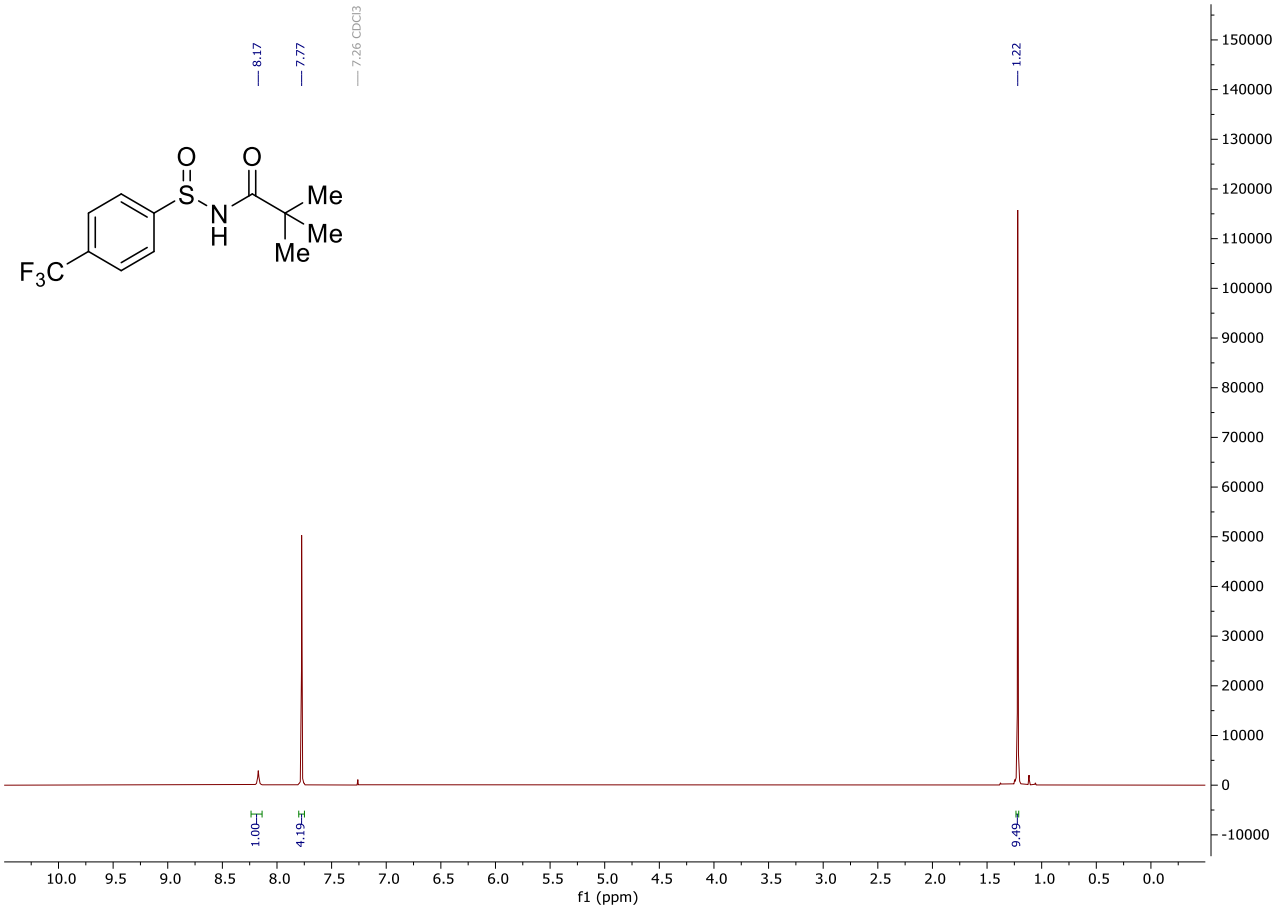
_N_-((4-Nitrophenyl)sulfinyl)pivalamide (69e)

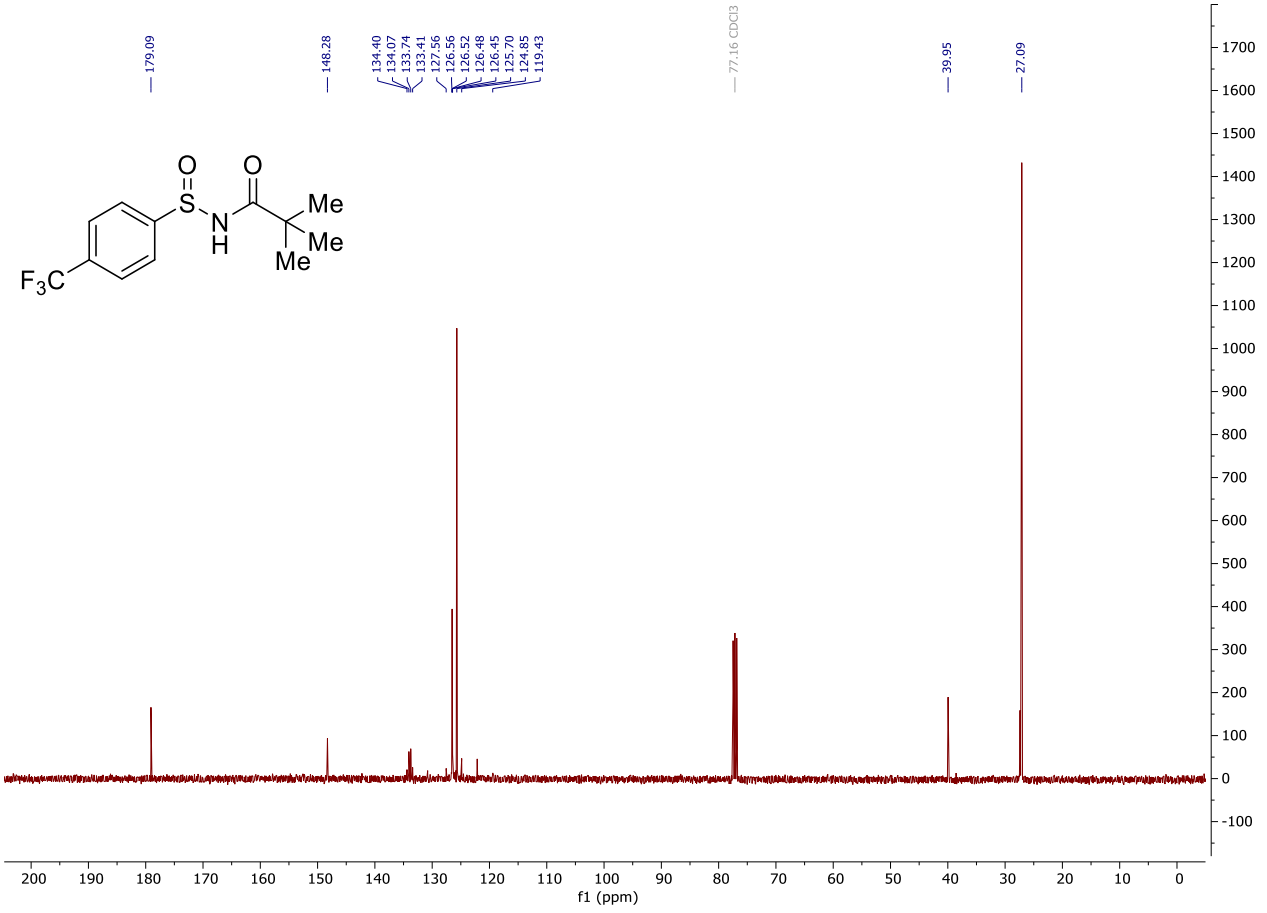

8.41
8.41
8.41
8.40
8.39
7.95
7.94
7.92
7.92
7.60
7.26 CDCl3
1.24
O
S
N
H
O
Me
Me
Me
O2N
1.81
1.81
0.65
9.00
f1 (ppm)

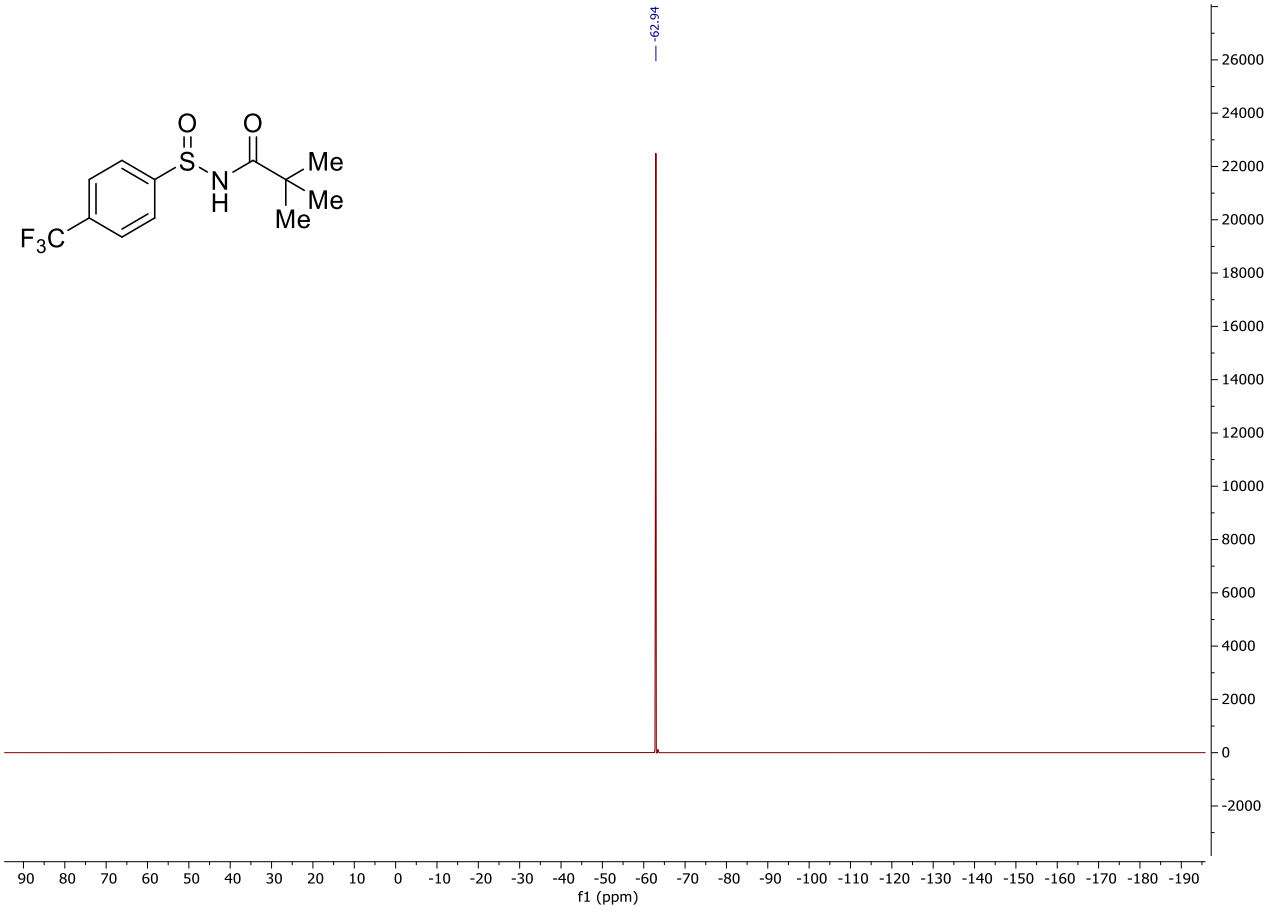

178.61
151.19
150.21
126.35
124.68
77.16 CDCl3
40.02
27.19
O
S
N
H
O
Me
Me
Me
O2N
f1 (ppm)

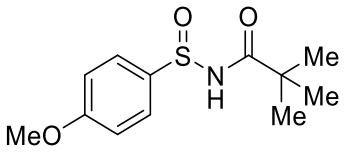


_N_-((4-Trifluoromethyl)phenyl)sulfinyl)pivalamide (69f)

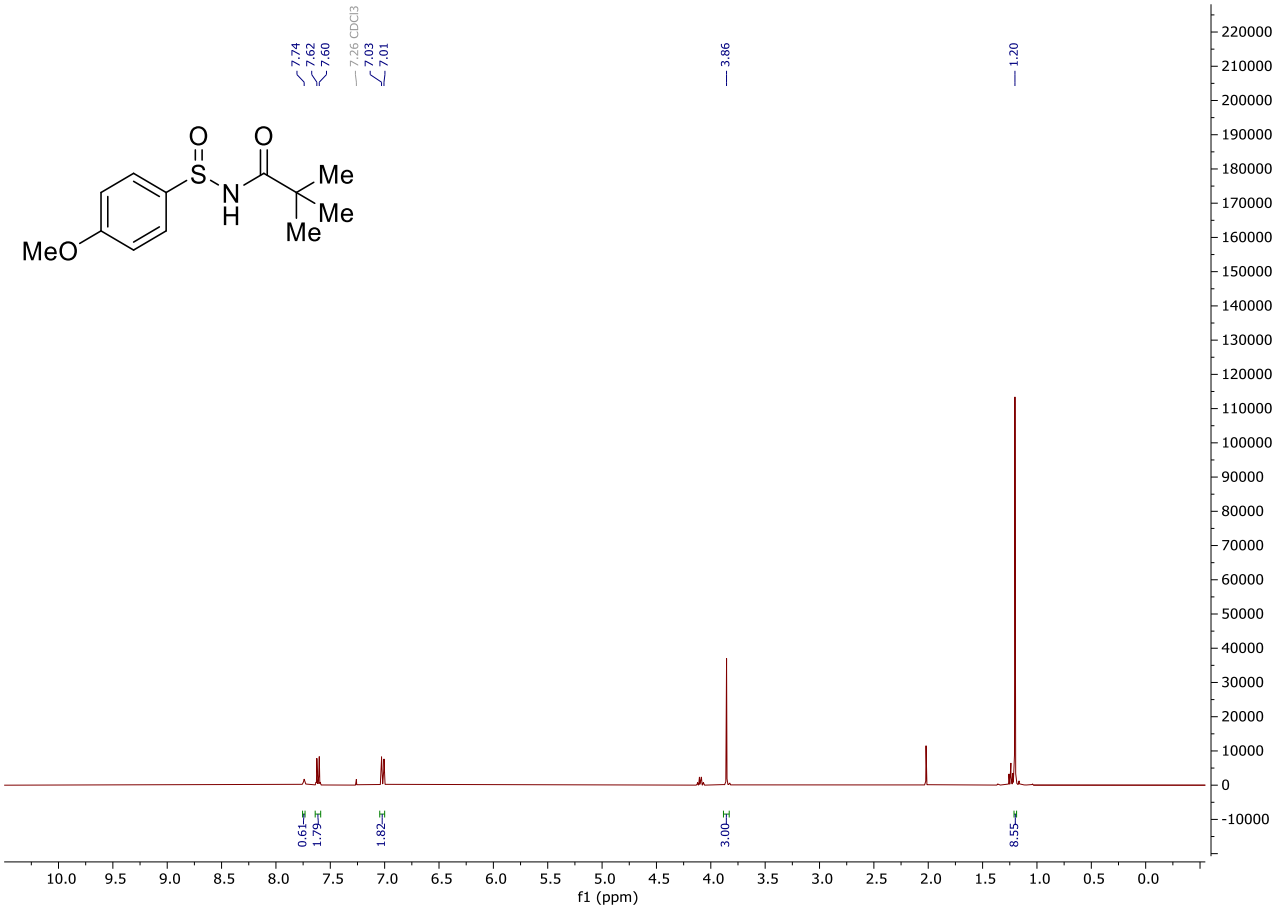


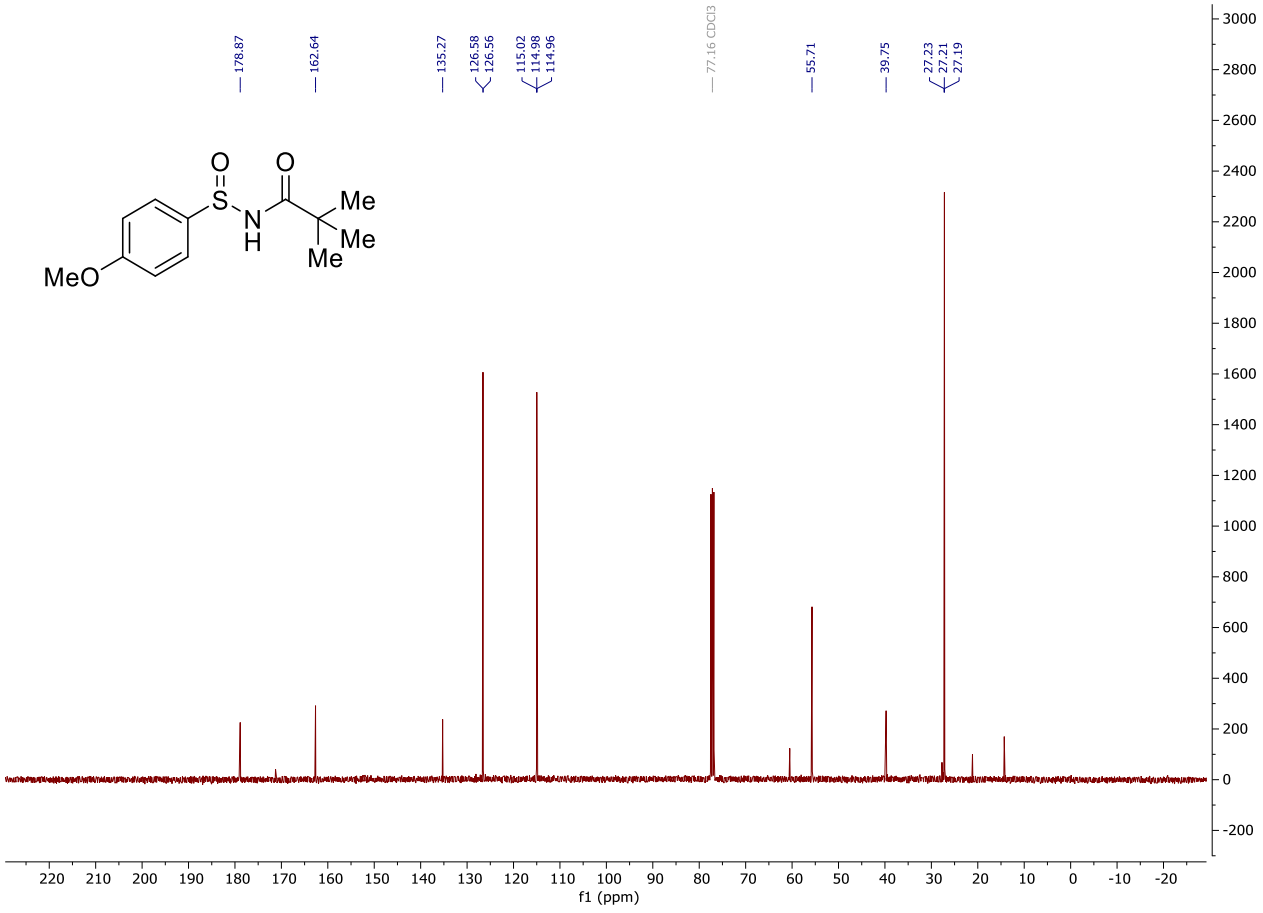

179.09
148.28
134.40
134.07
133.74
133.41
127.56
126.56
126.52
126.48
126.45
125.70
124.85
119.43
77.16 CDCl3
39.95
27.09
O
S
N
H
O
Me
Me
Me
F3C
f1 (ppm)

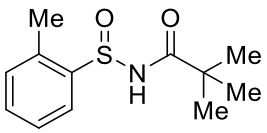

-62.94
O
S
N
H
O
Me
Me
Me
F3C
f1 (ppm)



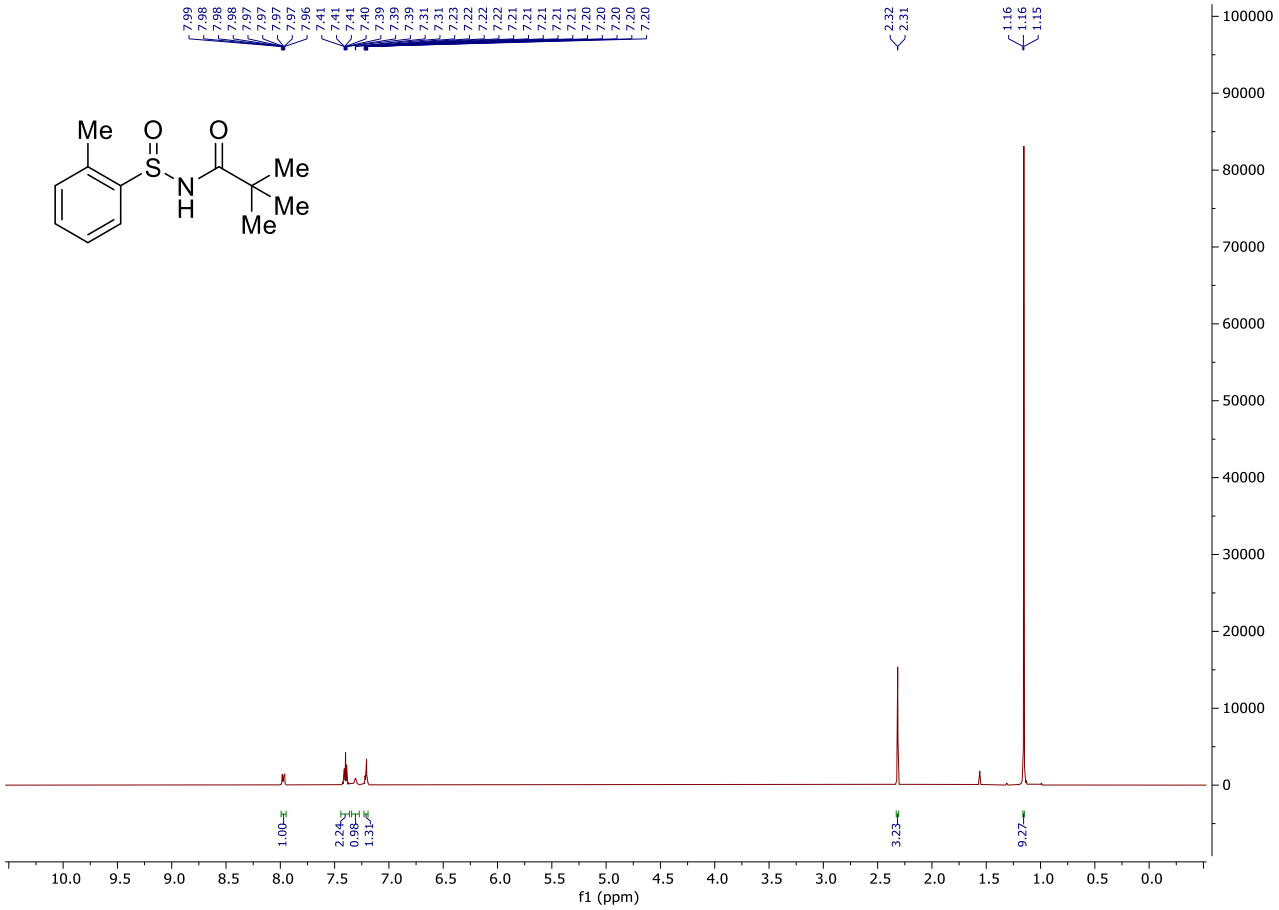
_N_-((4-Methoxyphenyl)sulfinyl)pivalamide (69g)

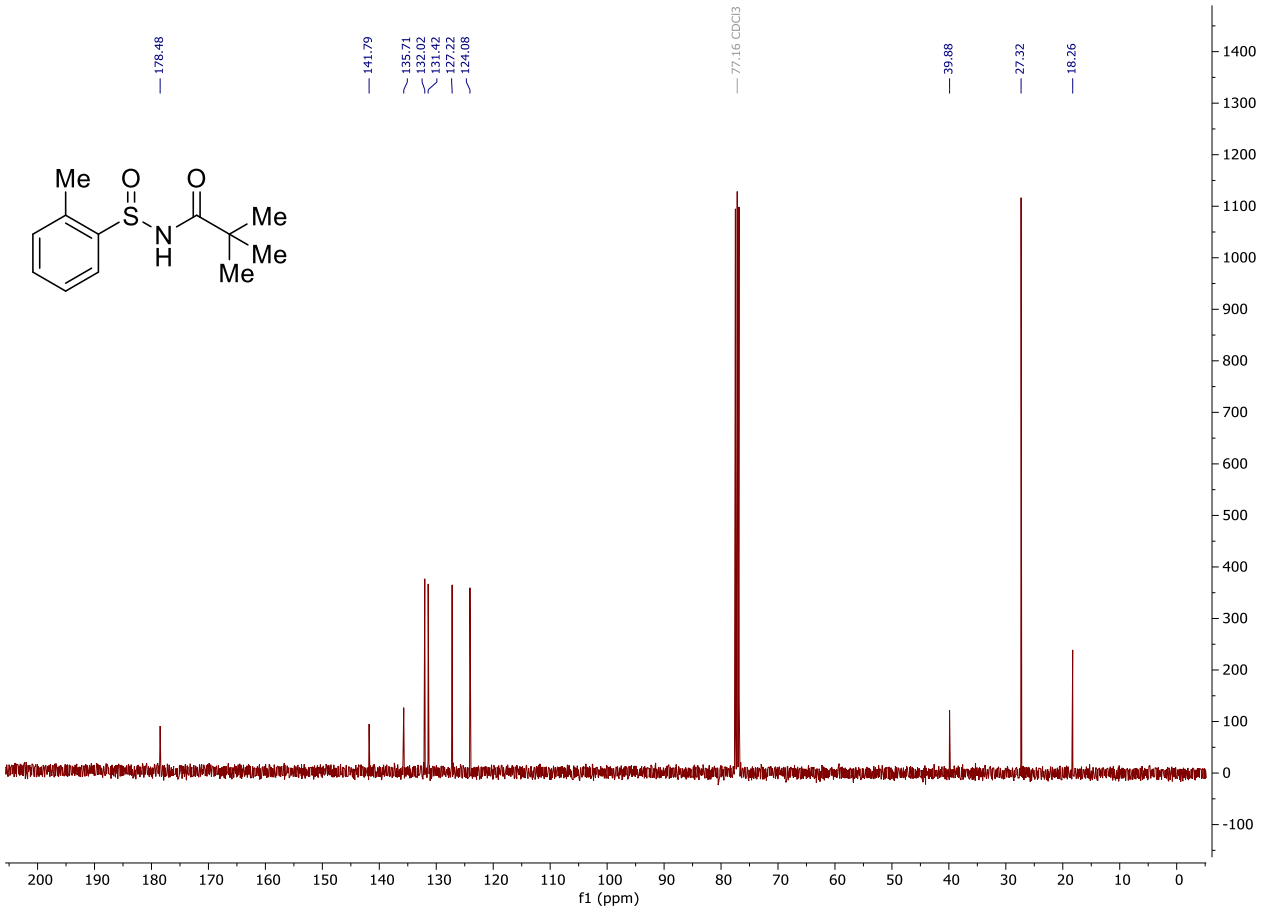


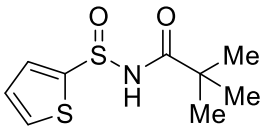




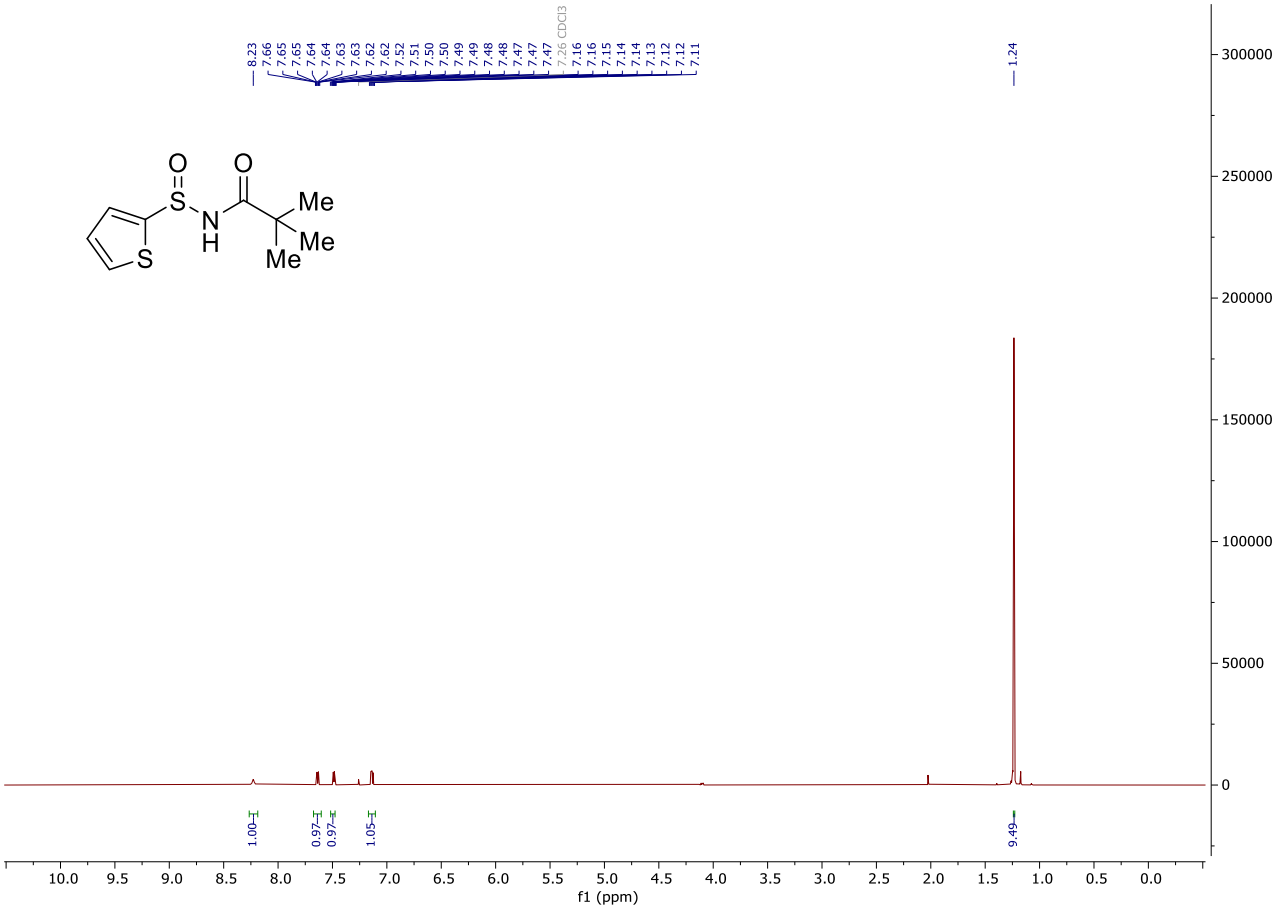
_N_-(_o_-Tolylsulfinyl)pivalamide (69h)

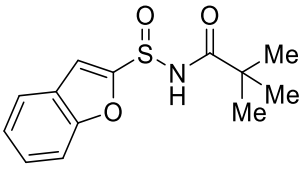

7.99
7.98
7.98
7.98
7.97
7.97
7.97
7.97
7.96
7.41
7.41
7.41
7.40
7.39
7.39
7.39
7.31
7.31
7.23
7.22
7.22
7.21
7.21
7.21
7.21
7.20
7.20
7.20
7.20
2.32
2.31
1.16
1.16
1.15
Me
O
S
N
H
O
Me
Me
Me
1.00
2.24
0.98
1.31
3.23
9.27
f1 (ppm)


178.48
141.79
135.71
132.02
131.42
127.22
124.08
77.16 CDCl3
39.88
27.32
18.26
Me
O
S
N
H
O
Me
Me
Me
f1 (ppm)

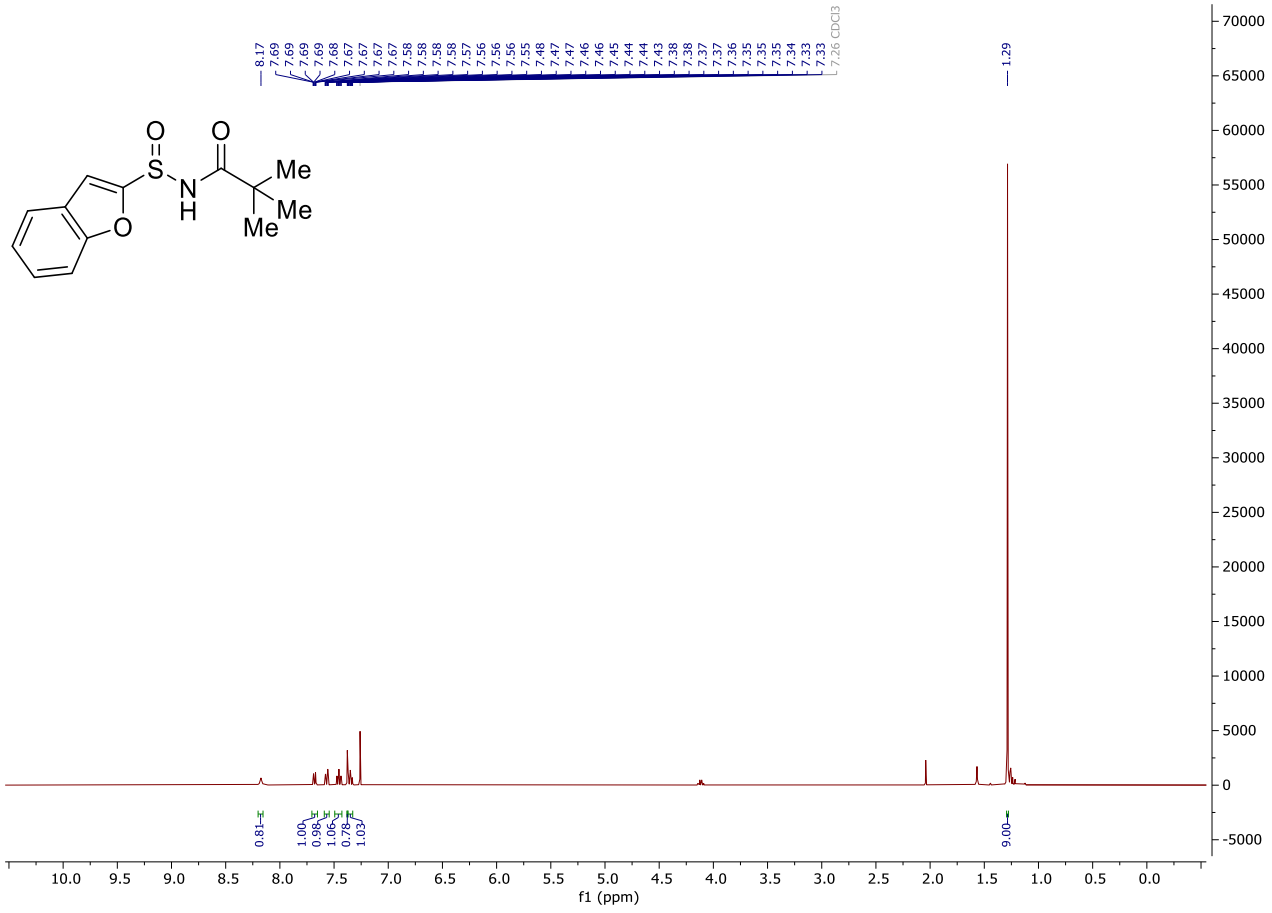


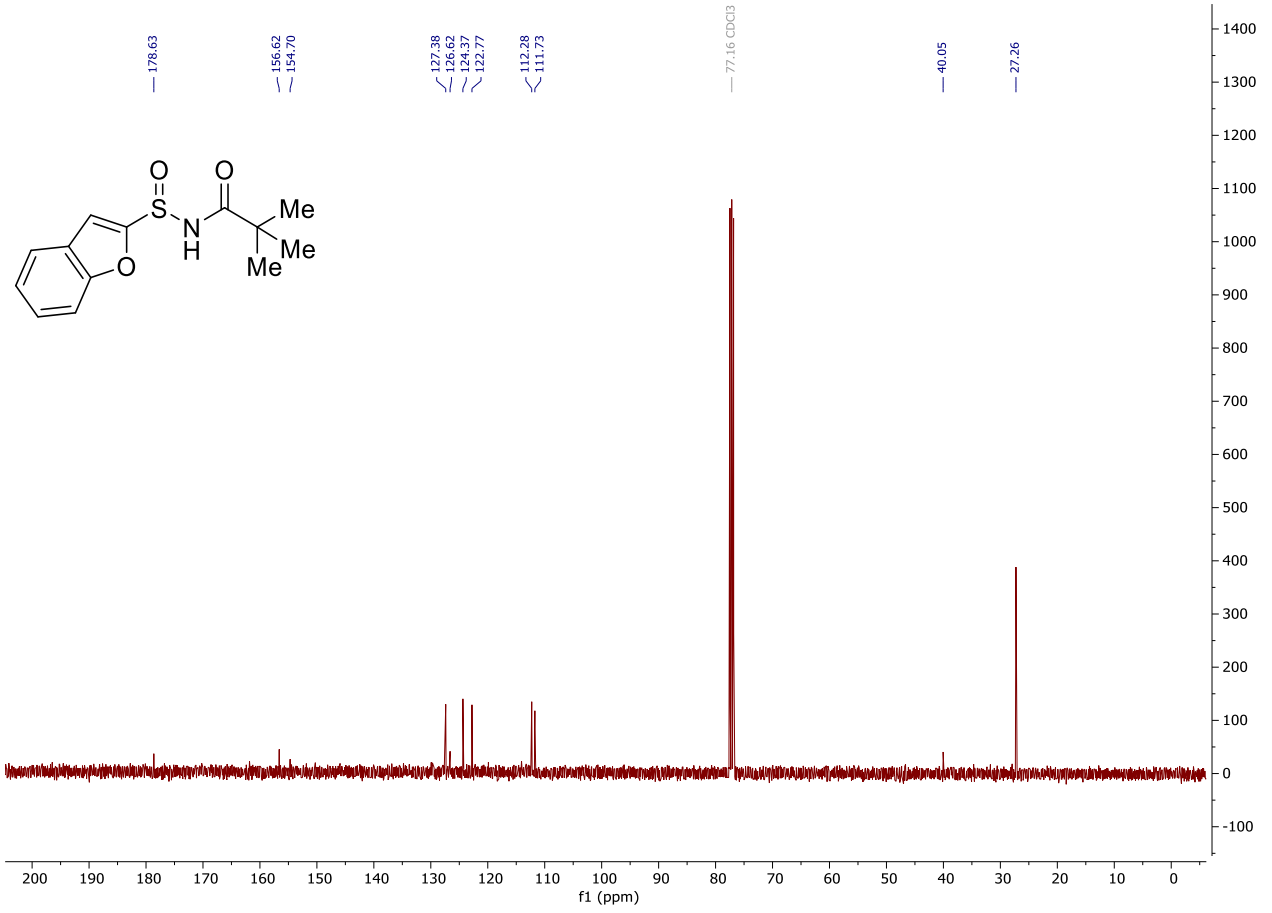
***N*-(Thiophen-2-ylsulfinyl)pivalamide (69i)**

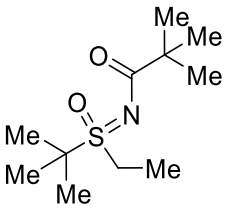




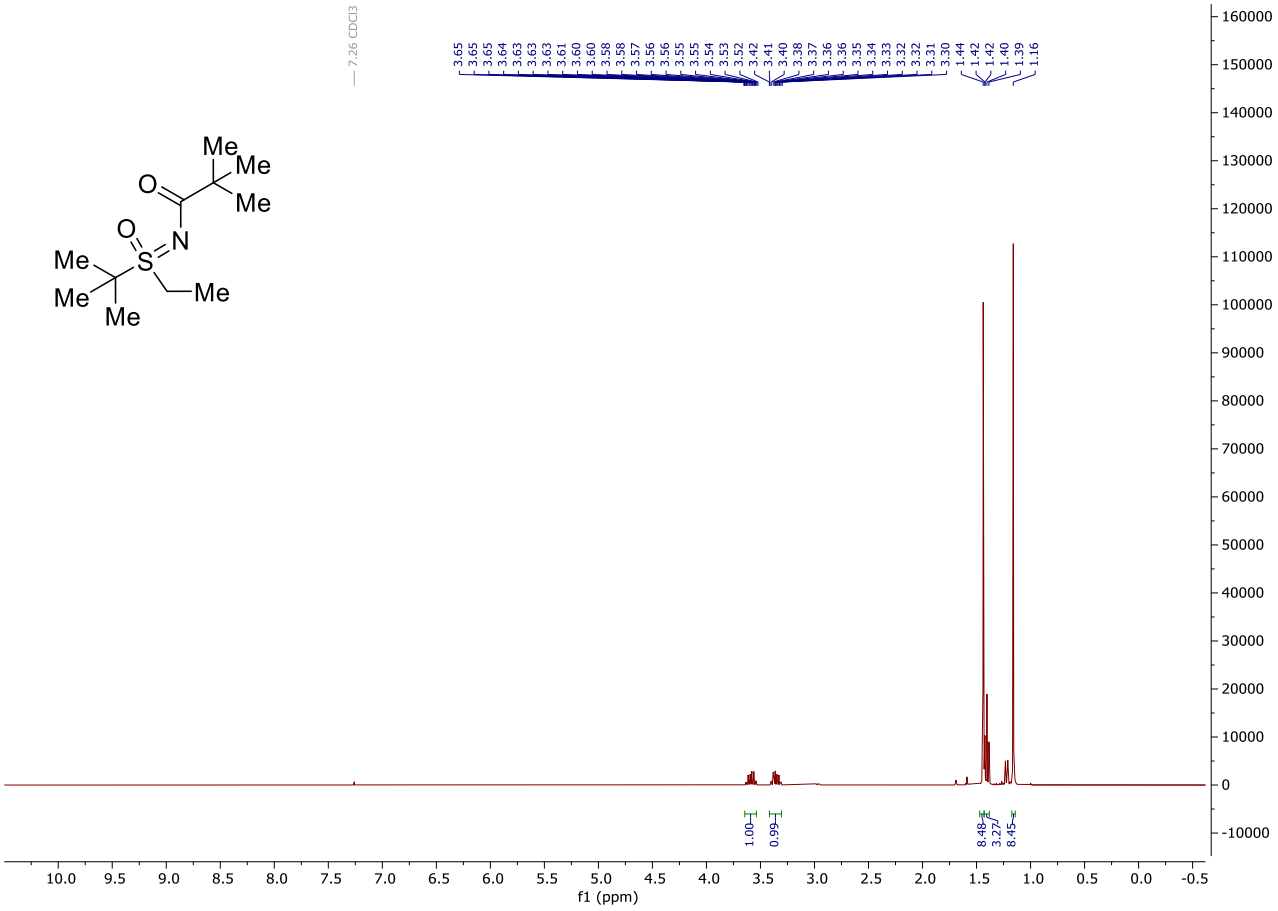
***N*-(Benzofuran-2-ylsulfinyl)pivalamide (69j)**

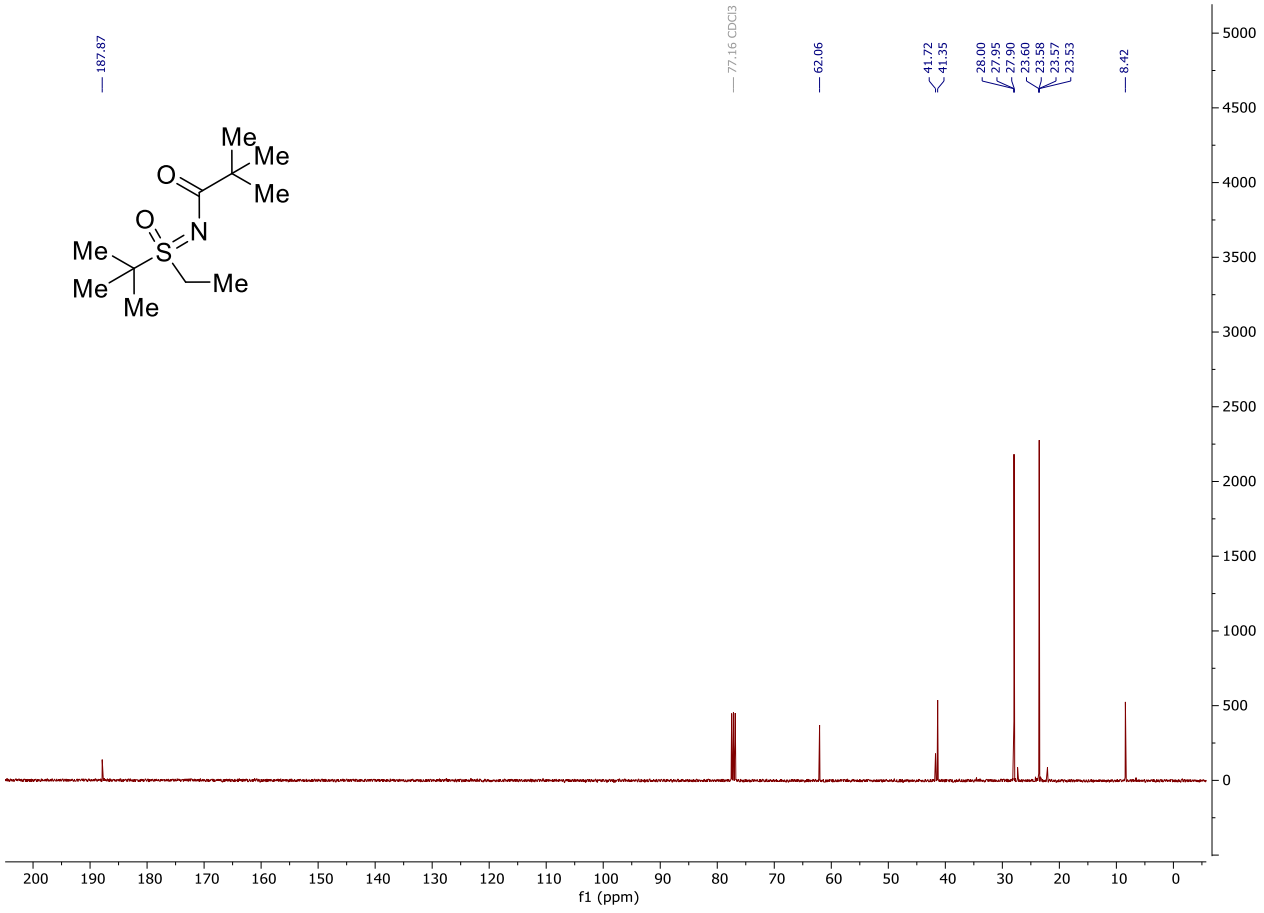

8.17
7.69
7.69
7.69
7.69
7.68
7.67
7.67
7.67
7.67
7.58
7.58
7.58
7.58
7.57
7.56
7.56
7.56
7.55
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.26 CDCl3
1.29
O
O
S
N
H
O
Me
Me
Me
0.81
1.00
0.98
1.06
0.78
1.03
9.00
f1 (ppm)

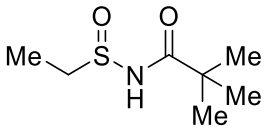

178.63
156.62
154.70
127.38
126.62
124.37
122.77
112.28
111.73
77.16 CDCl3
40.05
27.26
O
O
S
N
H
O
Me
Me
Me
f1 (ppm)



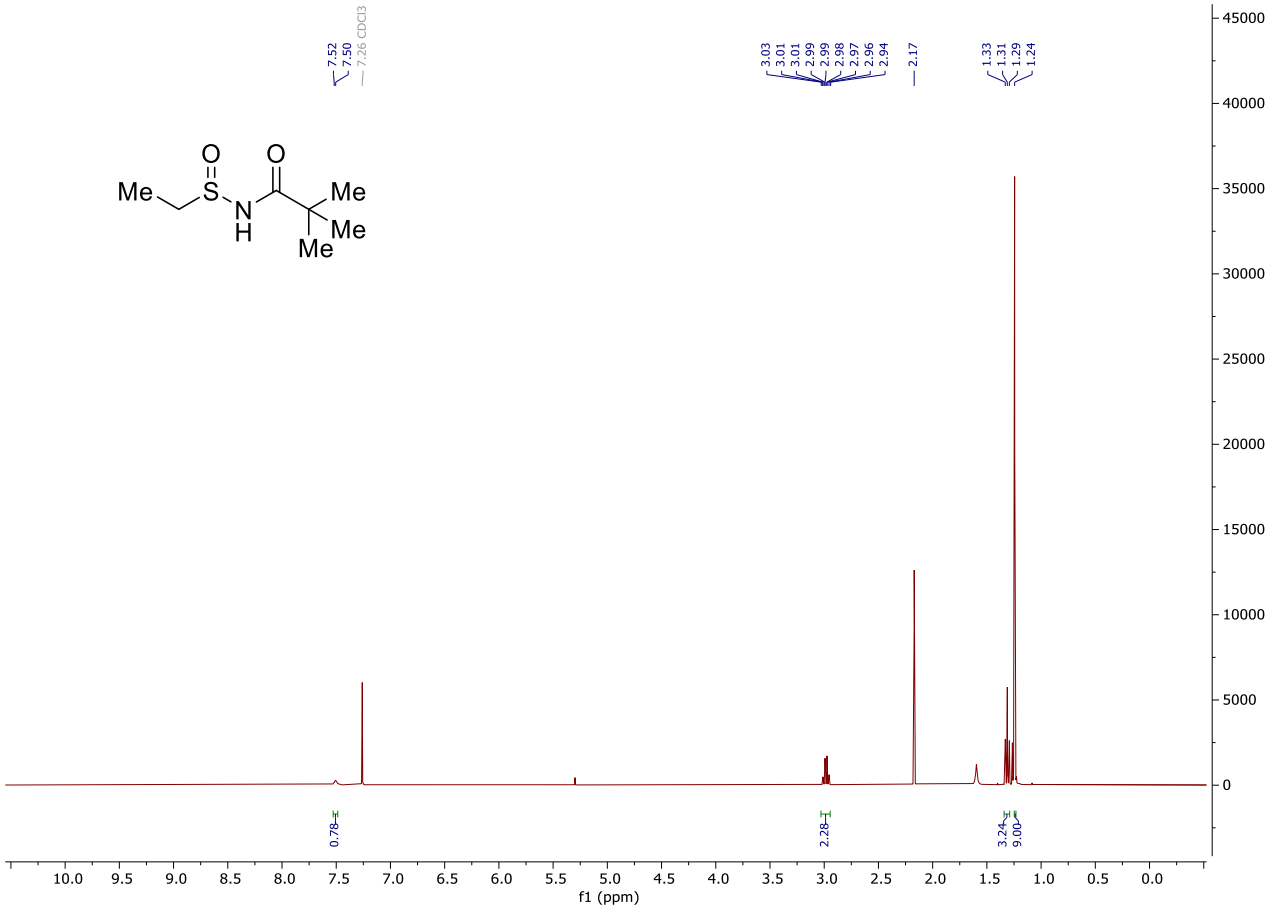
_N_-(_tert_-Butyl(ethyl)(oxo)-λ^6-sulfaneylidene)pivalamide (S6)

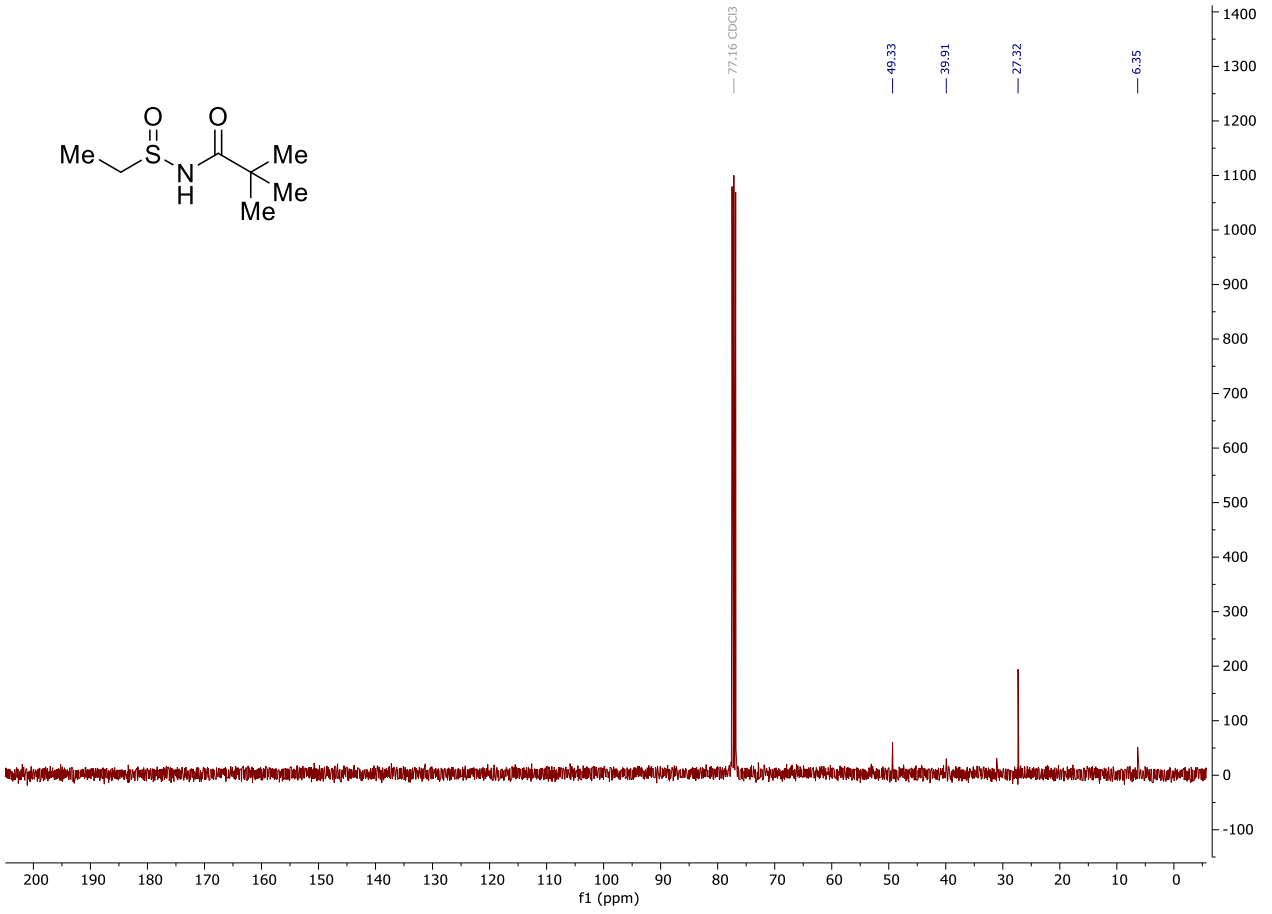


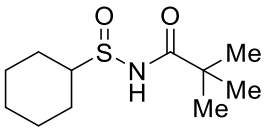




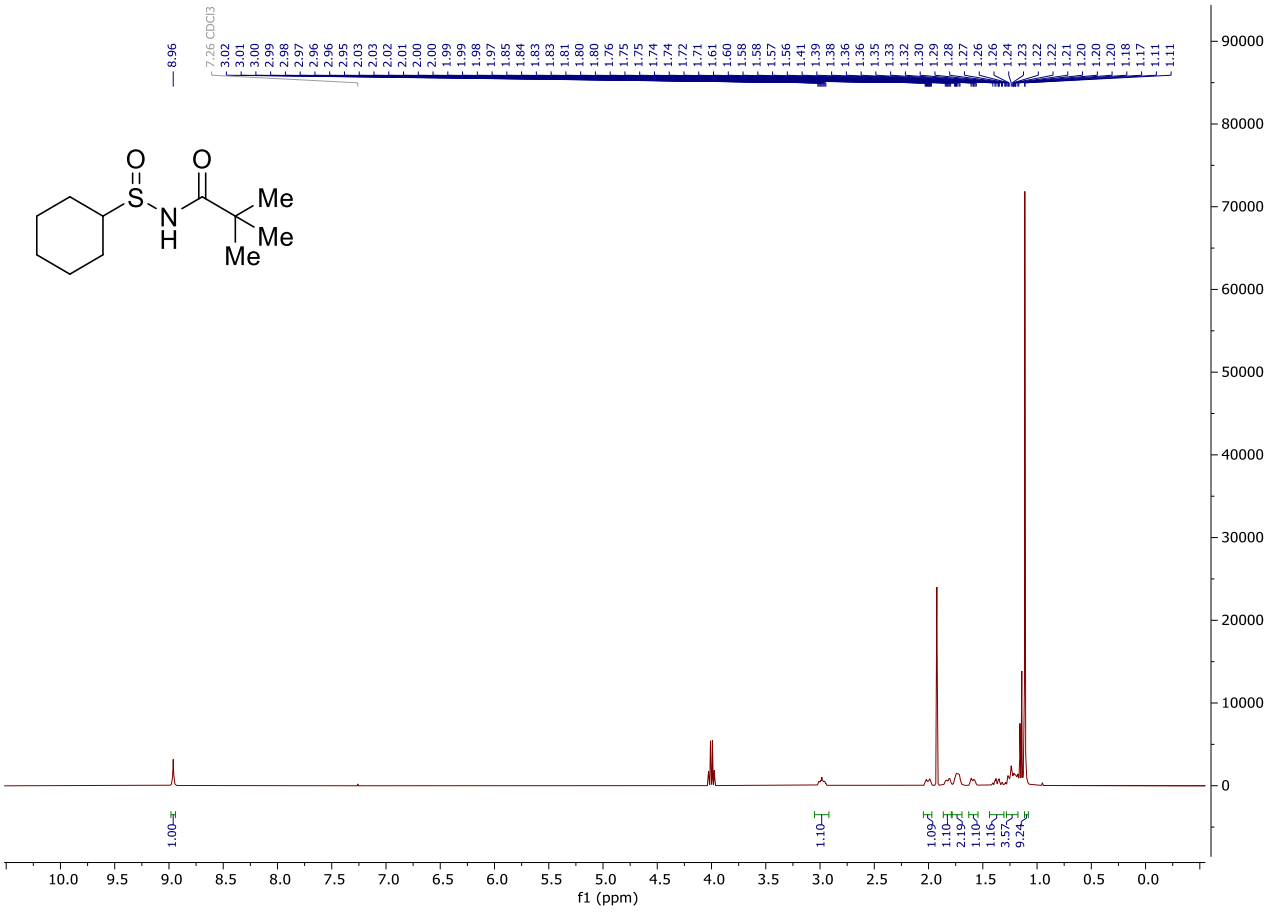
_N_-(Ethylsulfinyl)pivalamide (69k)

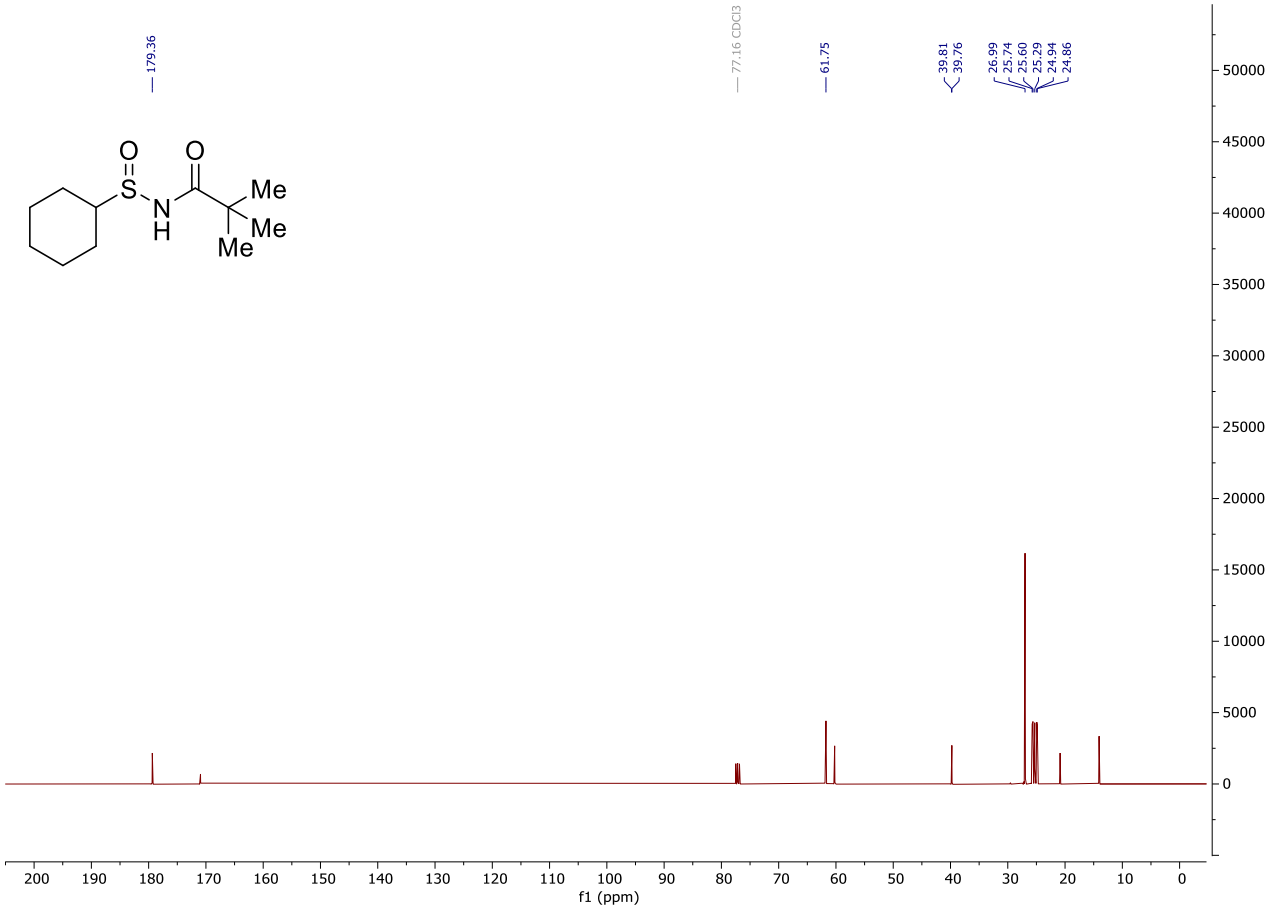

7.52
7.50
7.26 CDCl3
3.03
3.01
3.01
2.99
2.99
2.98
2.97
2.96
2.94
2.17
1.33
1.31
1.29
1.24
Me
O
S
N
H
O
Me
Me
Me
0.78
2.28
3.24
9.00
f1 (ppm)

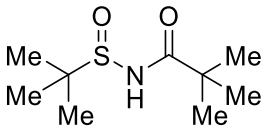

77.16 CDCl3
49.33
39.91
27.32
6.35
Me
O
S
N
H
O
Me
Me
Me
f1 (ppm)



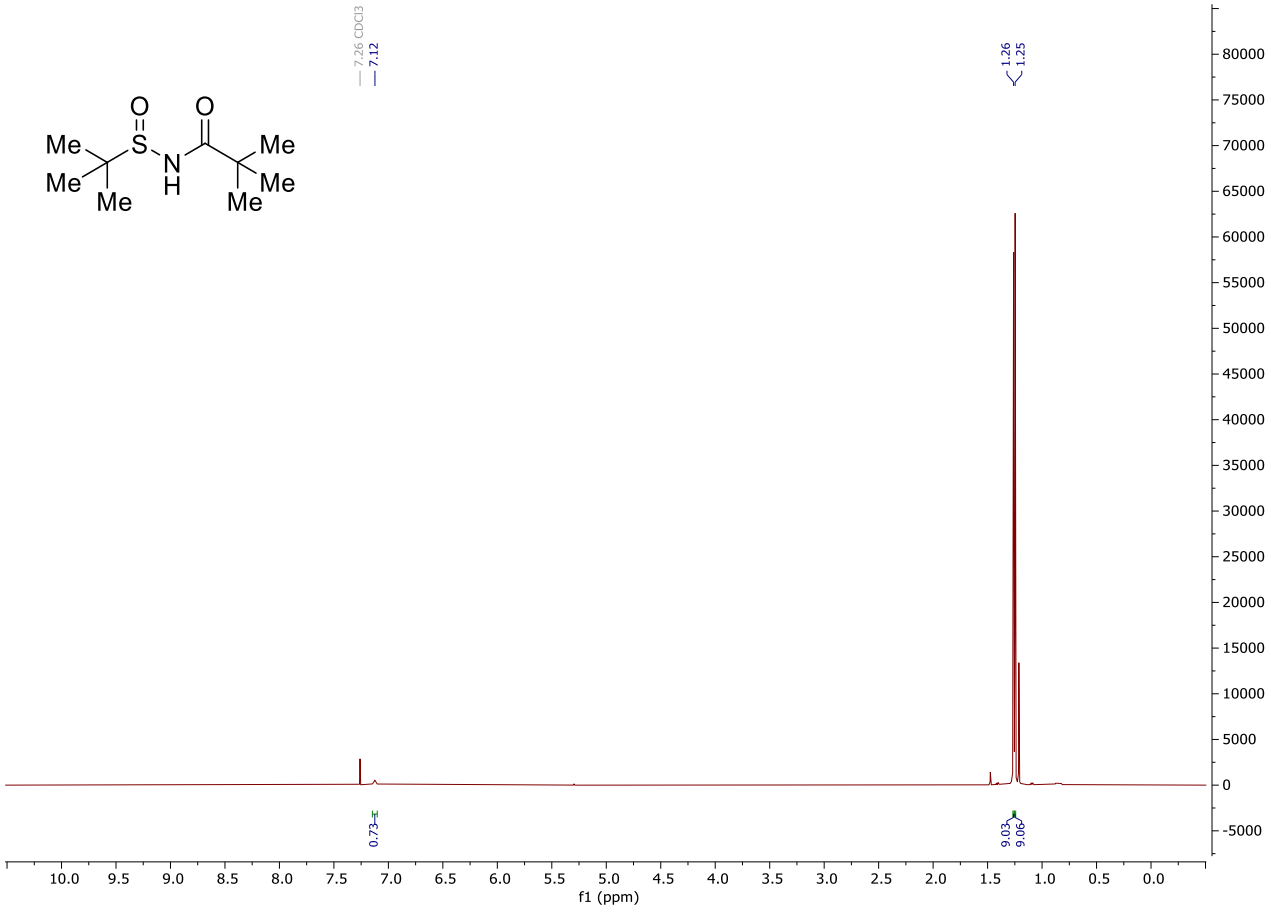
_N_-(Cyclohexylsulfinyl)pivalamide (69l)

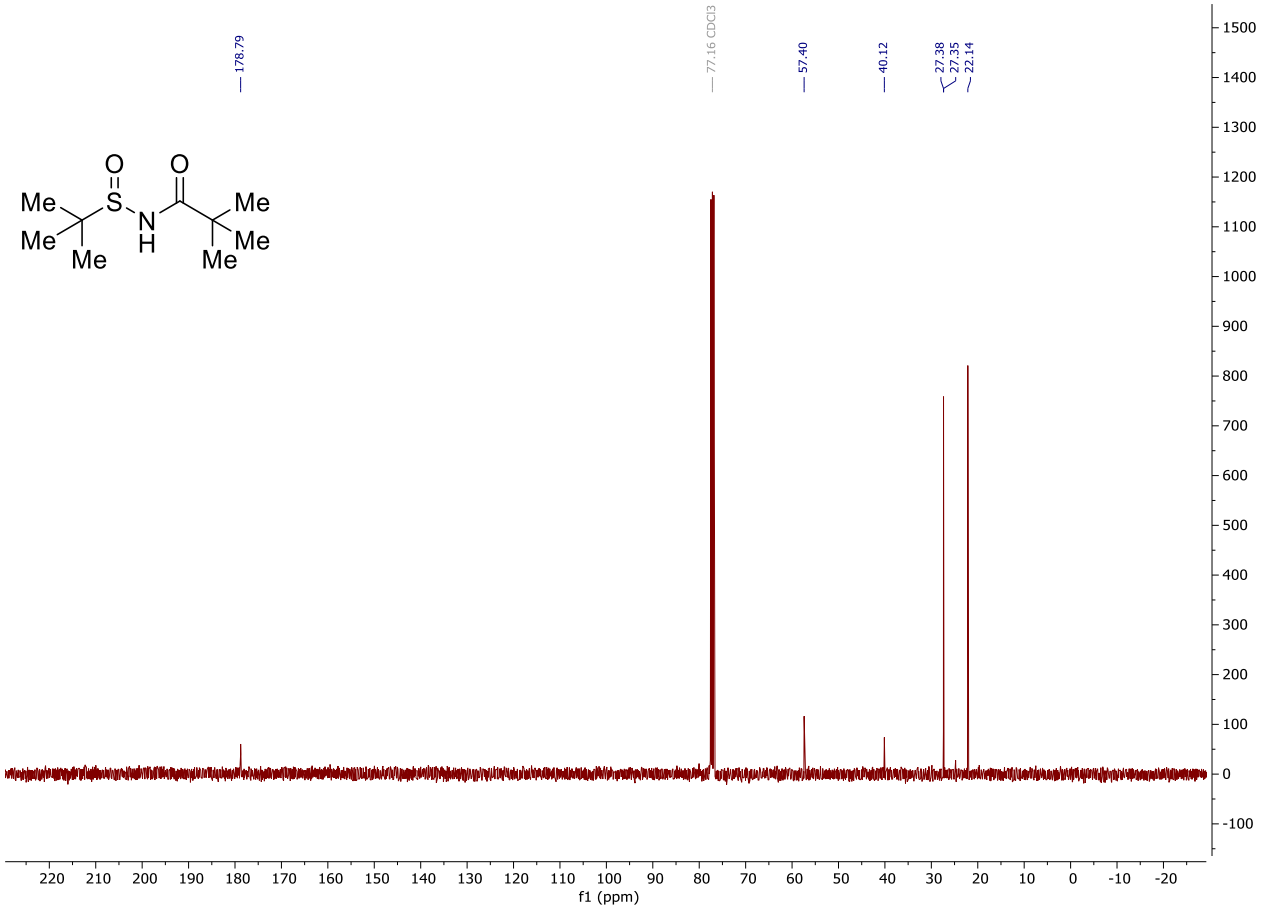




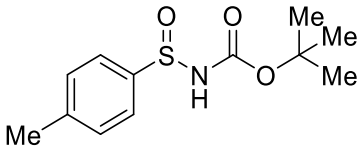


***N*-(*tert*-butylsulfinyl)pivalamide (69m)**

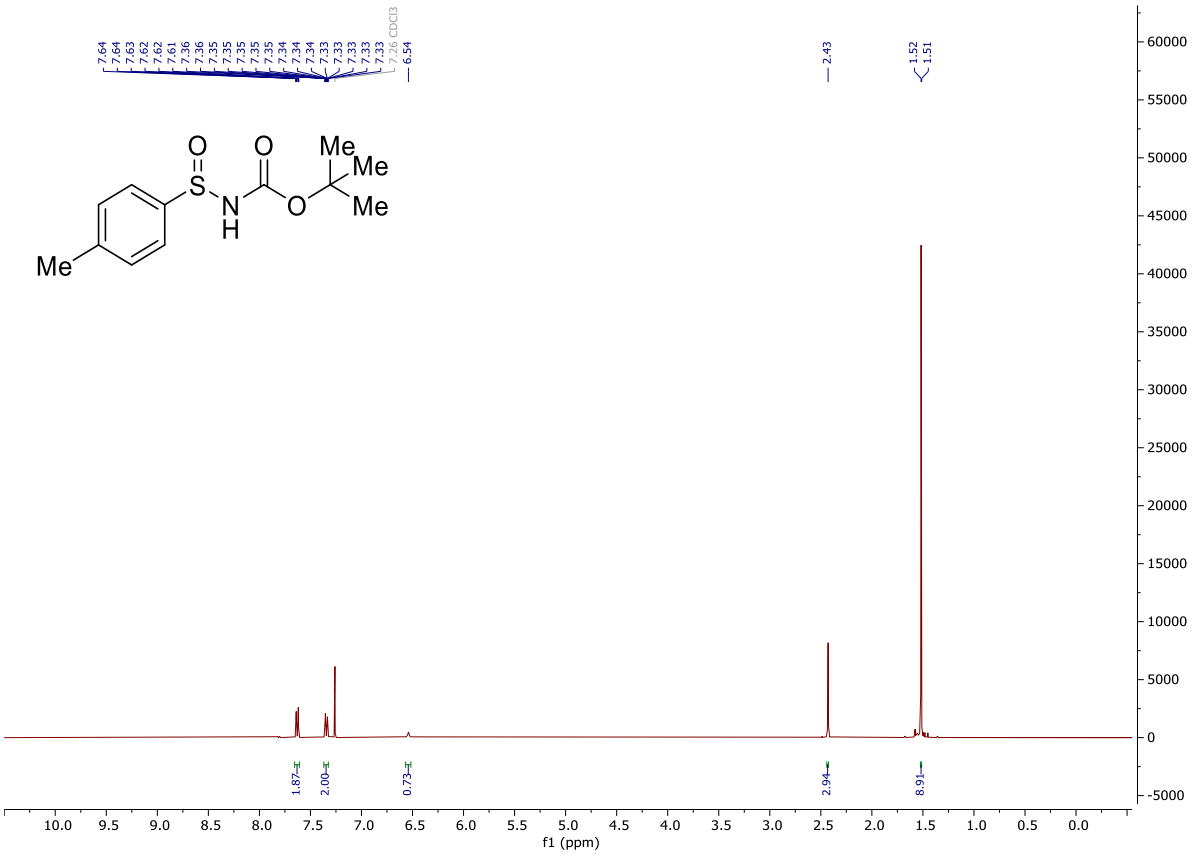

7.26 CDCl3
7.12
1.26
1.25
0.73
9.03
9.06
f1 (ppm)

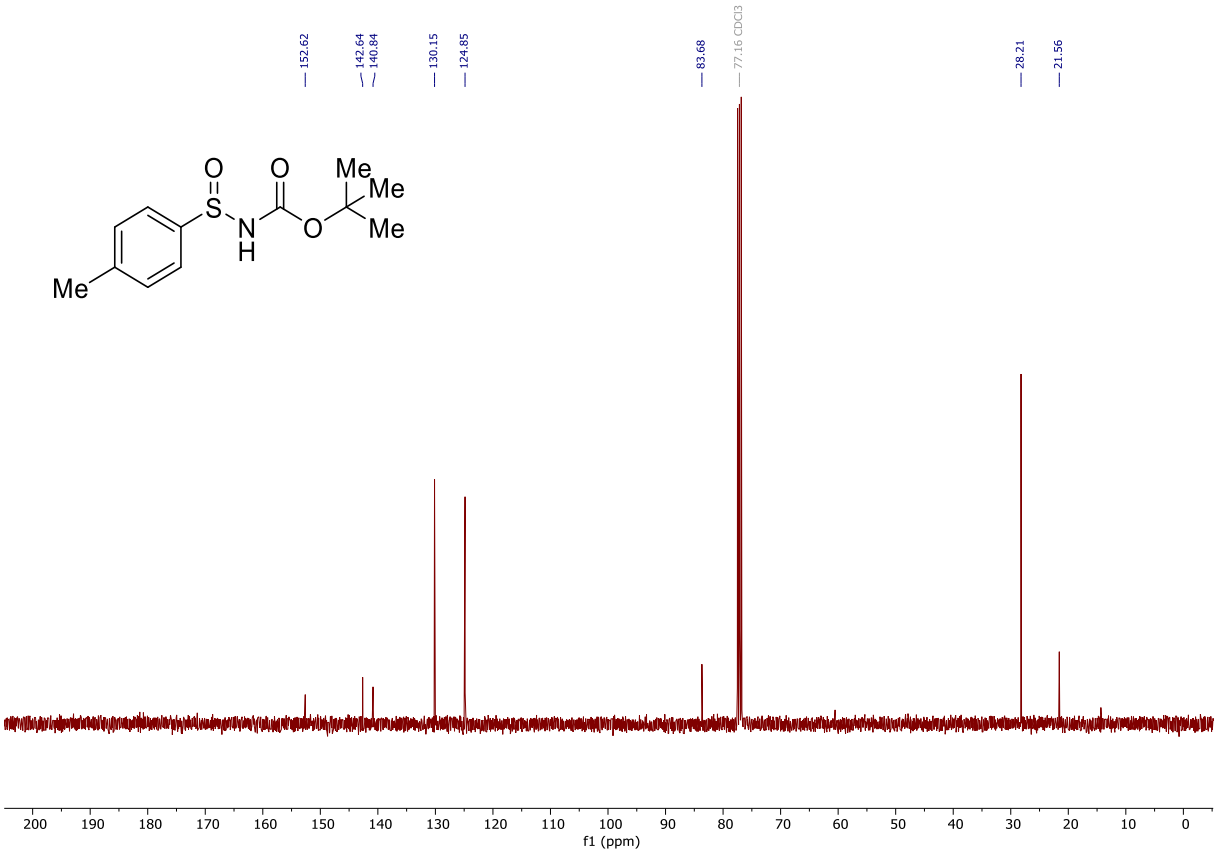

178.79
77.16 CDCl3
57.40
40.12
27.38
27.35
22.14
f1 (ppm)

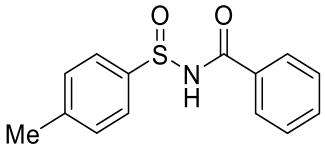
8.1.4 *N*-substituted sulfinamides



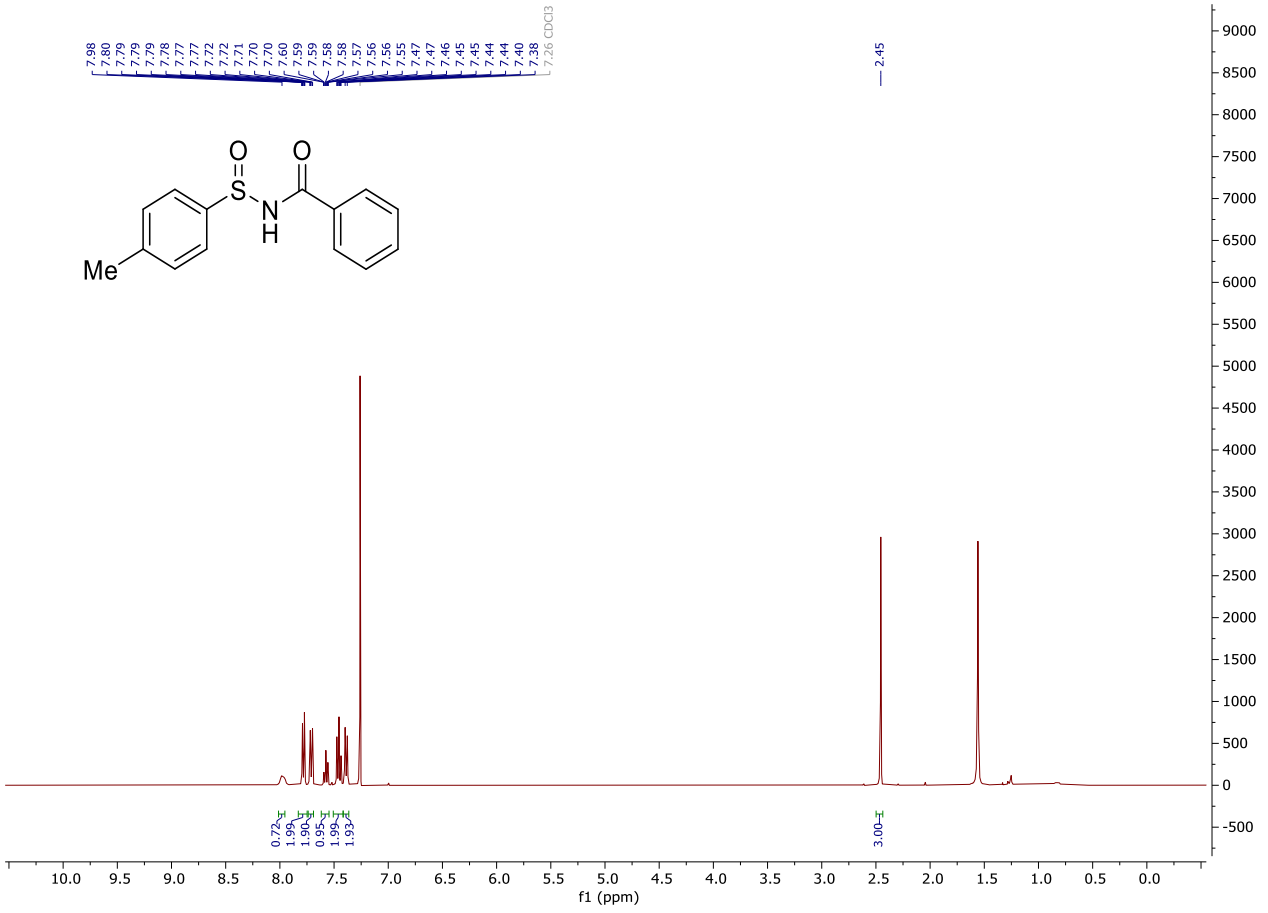
***tert*-Butyl (*p*-tolylsulfinyl)carbamate (66a)**

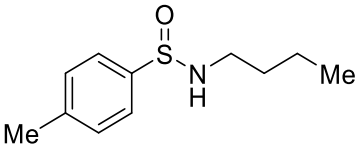




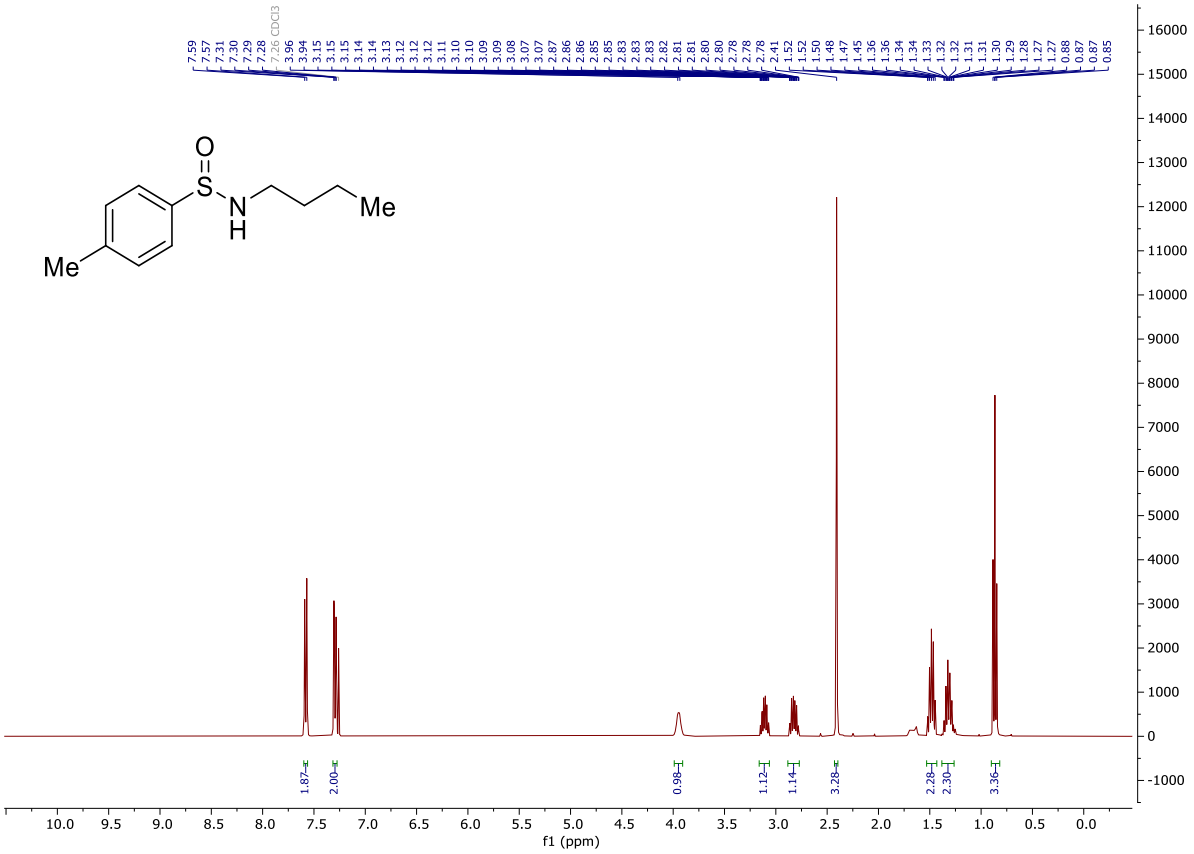


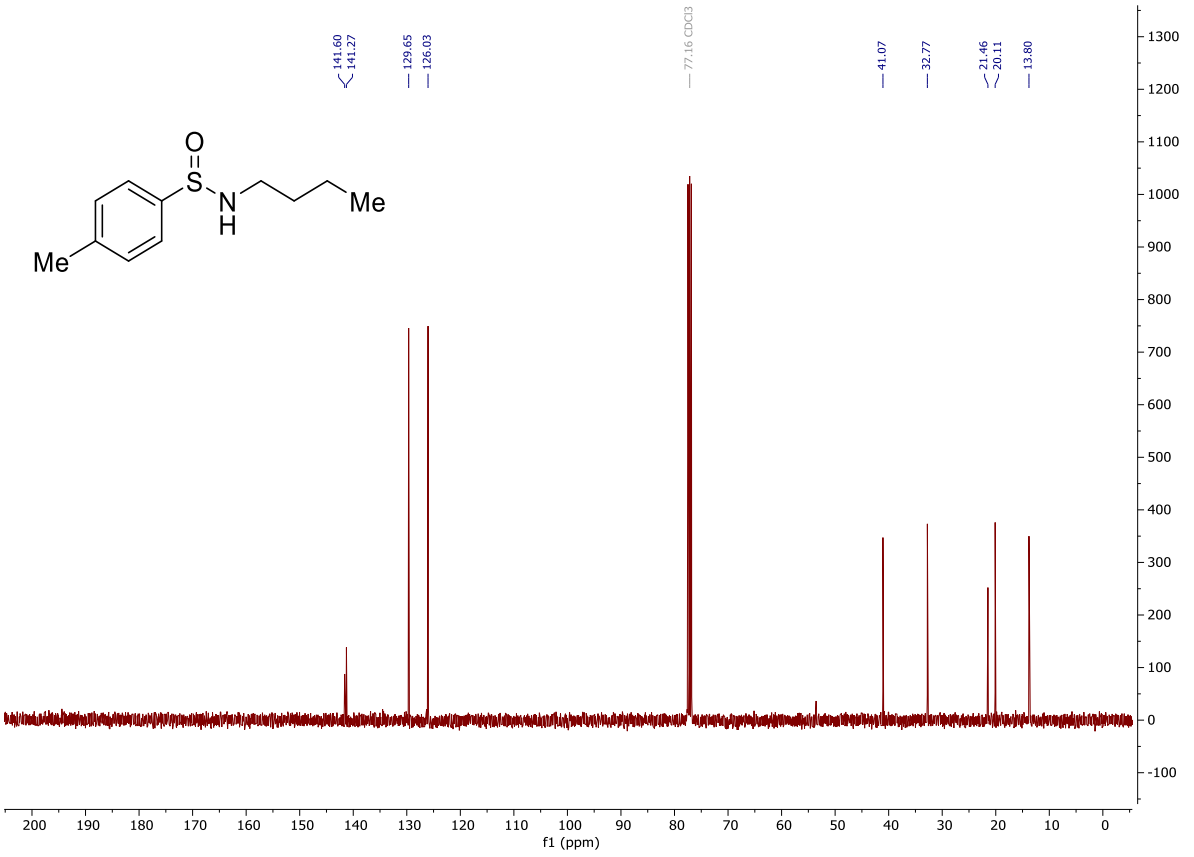
_N_-(_p_-Tolylsulfinyl)benzamide (66e)

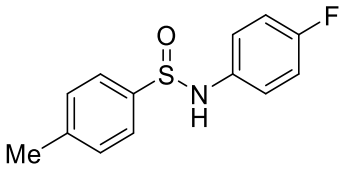




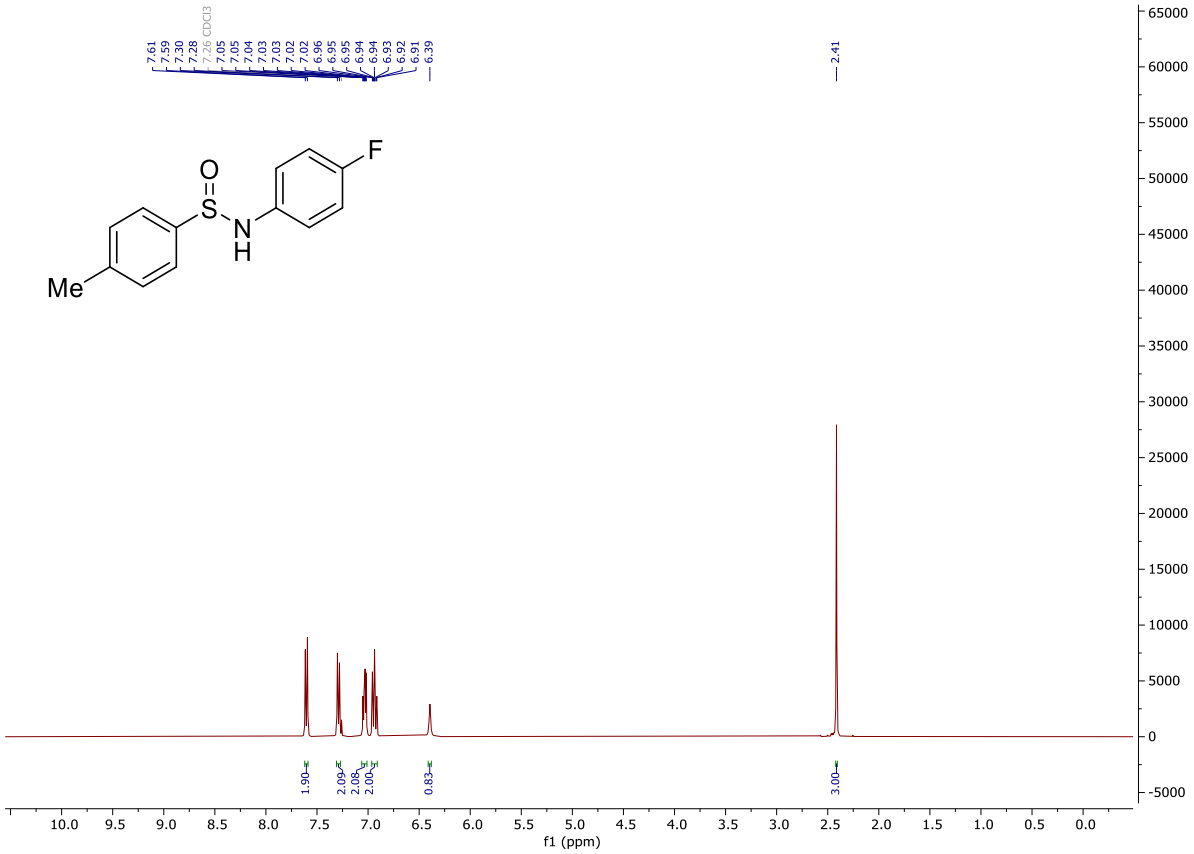
***N*-Butyl-4-methylbenzenesulfinamide (66f)**

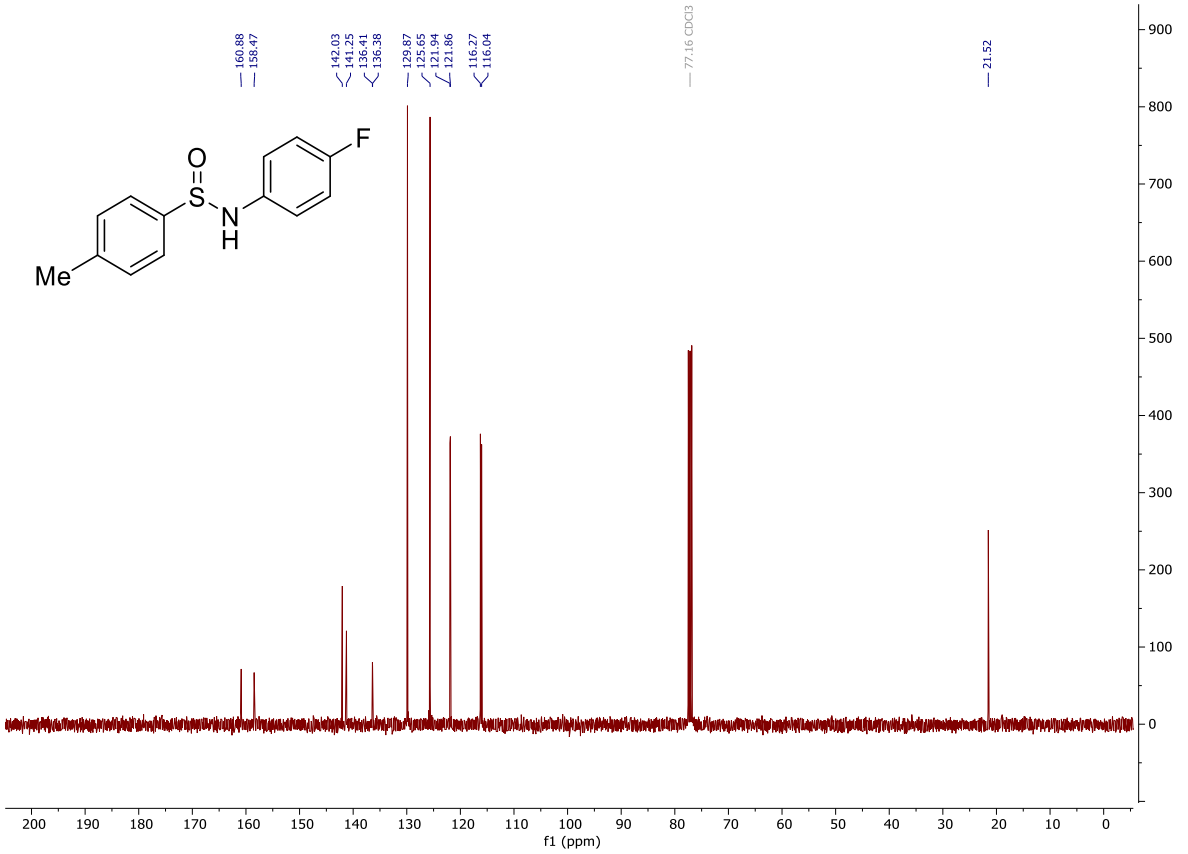

7.59 7.57 7.31 7.30 7.29 7.28 7.26 CDCl3 3.96 3.94 3.15 3.15 3.15 3.14 3.14 3.13 3.12 3.12 3.12 3.11 3.11 3.10 3.09 3.09 3.08 3.07 3.07 2.87 2.86 2.86 2.85 2.85 2.83 2.83 2.83 2.82 2.81 2.81 2.80 2.80 2.78 2.78 2.78 2.41 1.52 1.52 1.50 1.48 1.47 1.45 1.36 1.36 1.34 1.34 1.33 1.32 1.32 1.31 1.31 1.30 1.29 1.28 1.27 1.27 0.88 0.87 0.87 0.85
O
S
N
H
Me
Me
1.87 2.00 0.98 1.12 1.14 3.28 2.28 2.30 3.36
f1 (ppm)

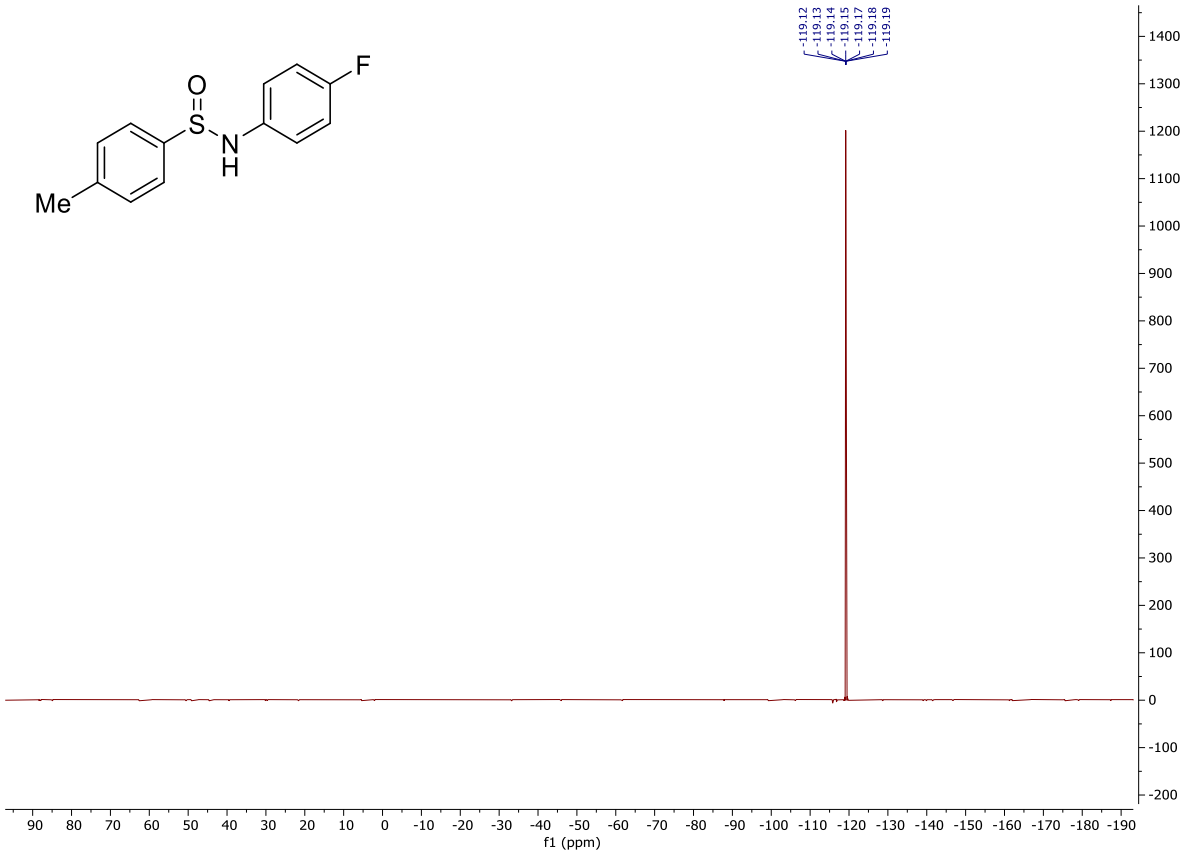

141.60 141.27 129.65 126.03 77.16 CDCl3 41.07 32.77 21.46 20.11 13.80
O
S
N
H
Me
Me
f1 (ppm)

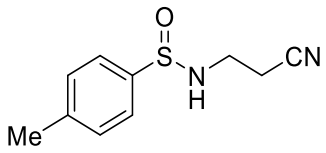


_N_-(4-Fluorophenyl)-4-methylbenzenesulfinamide (66g)

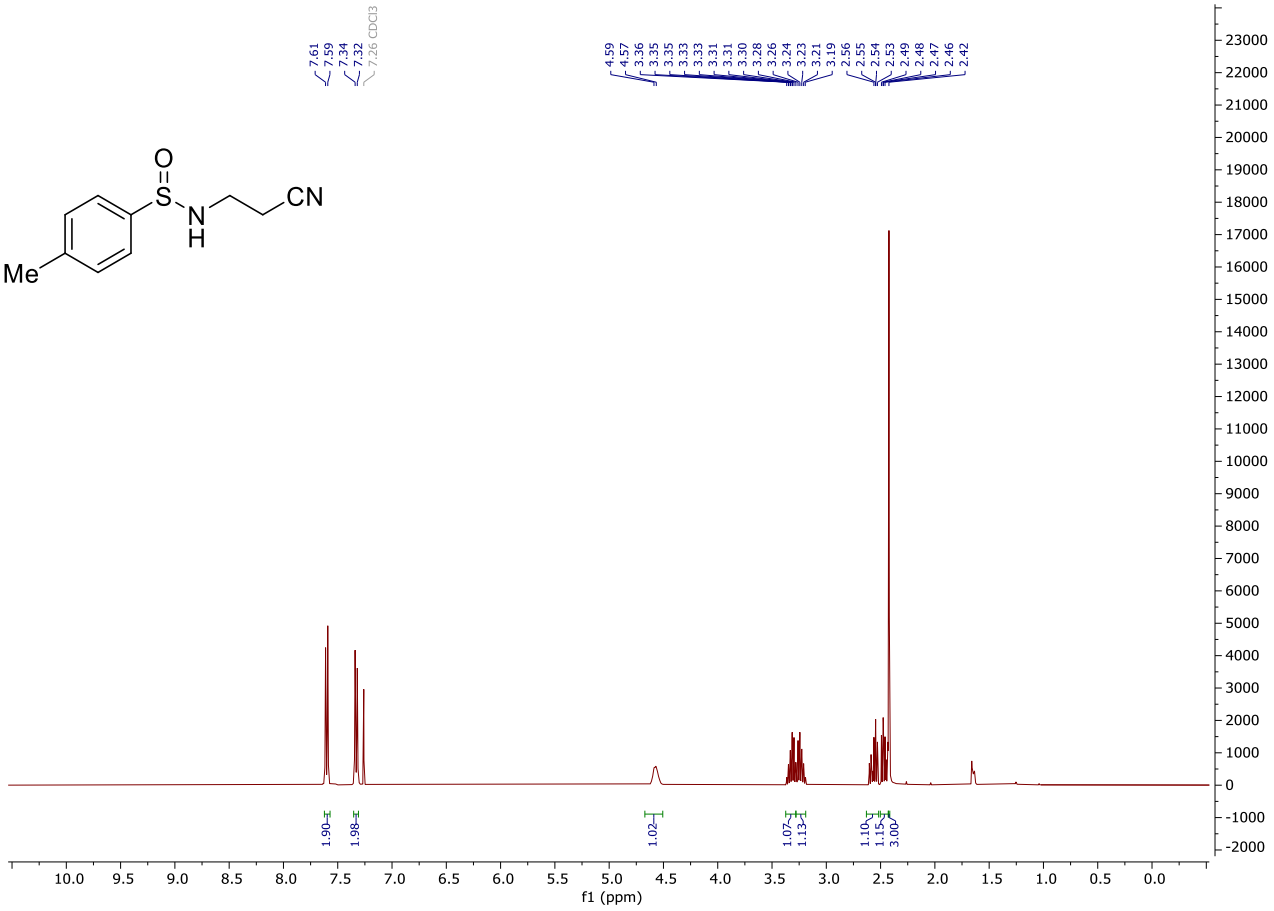


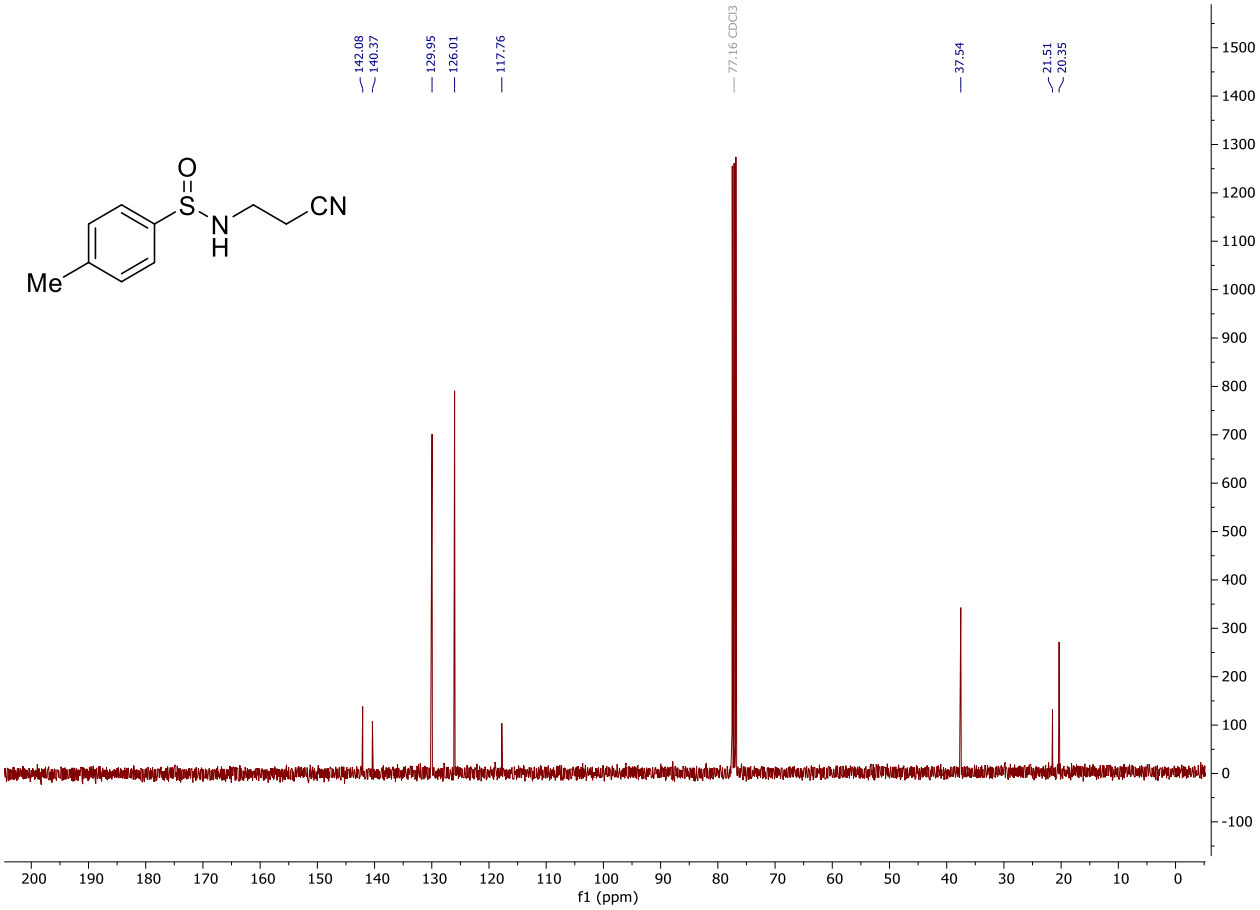

160.88
158.47
142.03
141.25
136.41
136.38
129.87
125.65
121.94
121.86
116.27
116.04
77.16 CDCl3
21.52
O
S
N
H
F
Me
f1 (ppm)

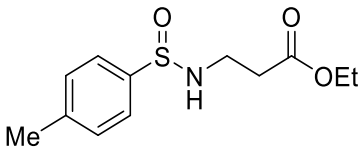

-119.12
-119.13
-119.14
-119.15
-119.17
-119.18
-119.19
O
S
N
H
F
Me
f1 (ppm)



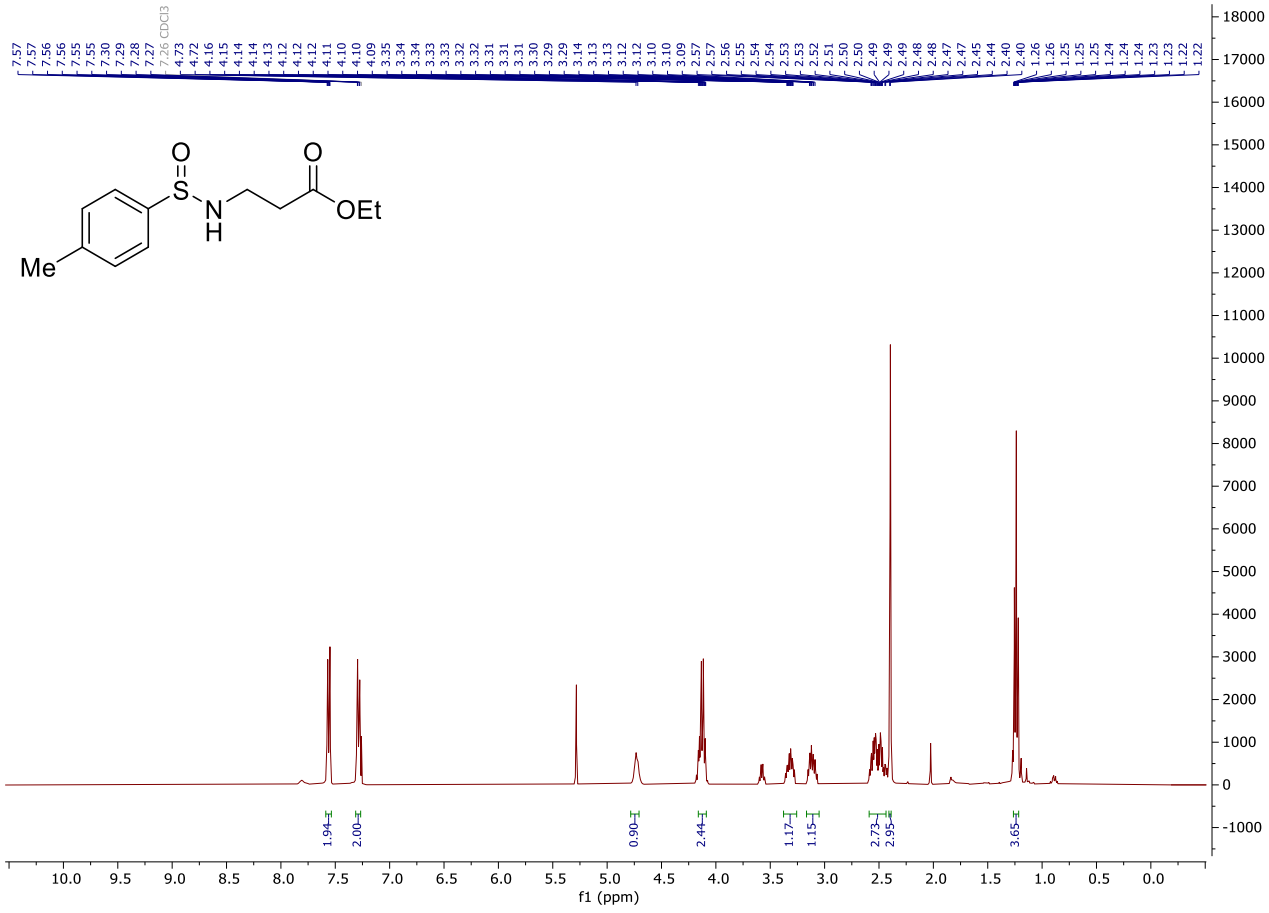
_N_-(2-Cyanoethyl)-4-methylbenzenesulfinamide (66h)

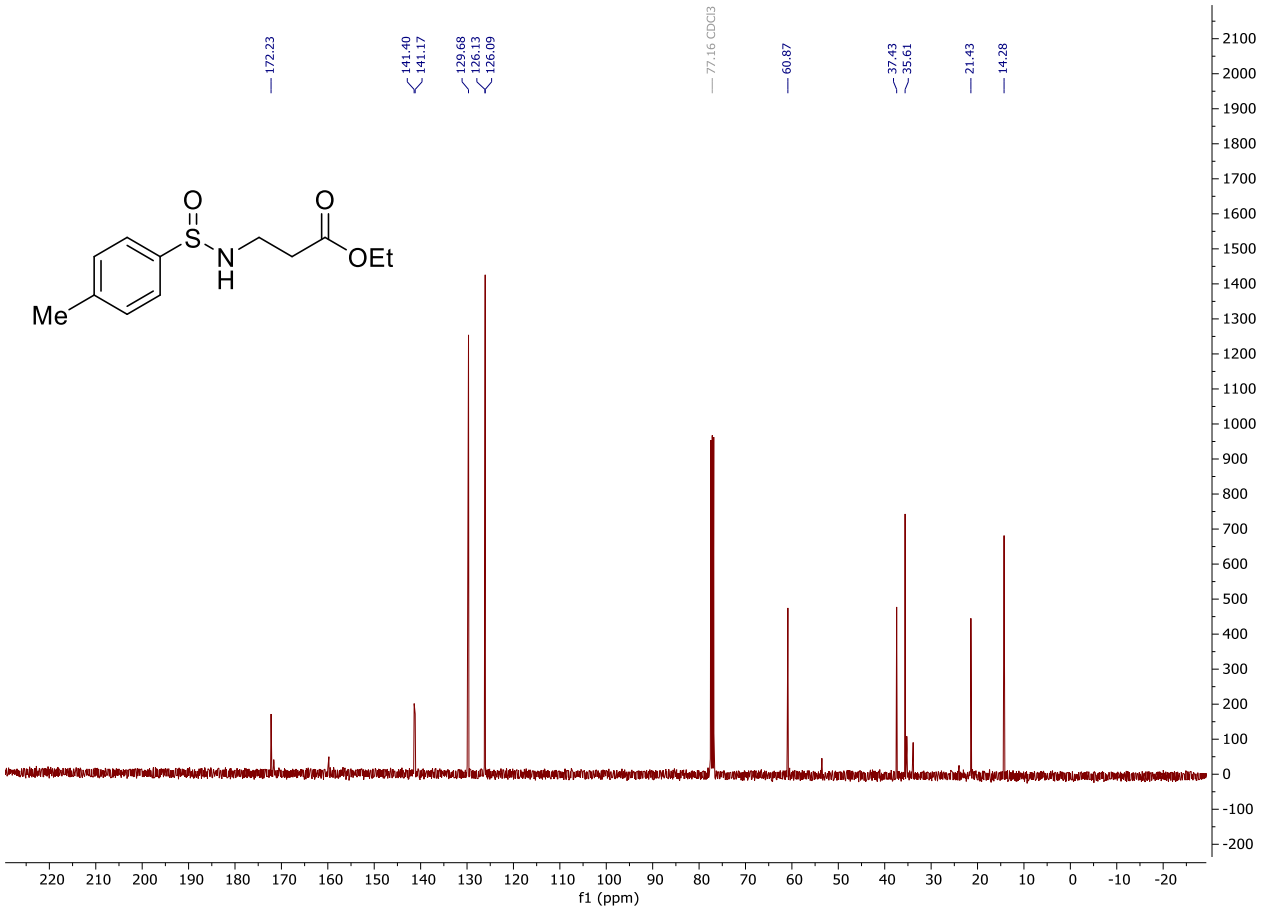




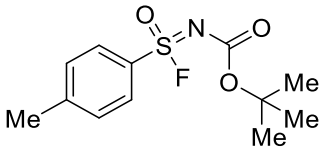


Ethyl 3-((*p*-tolylsulfinyl)amino)propanoate (66i)

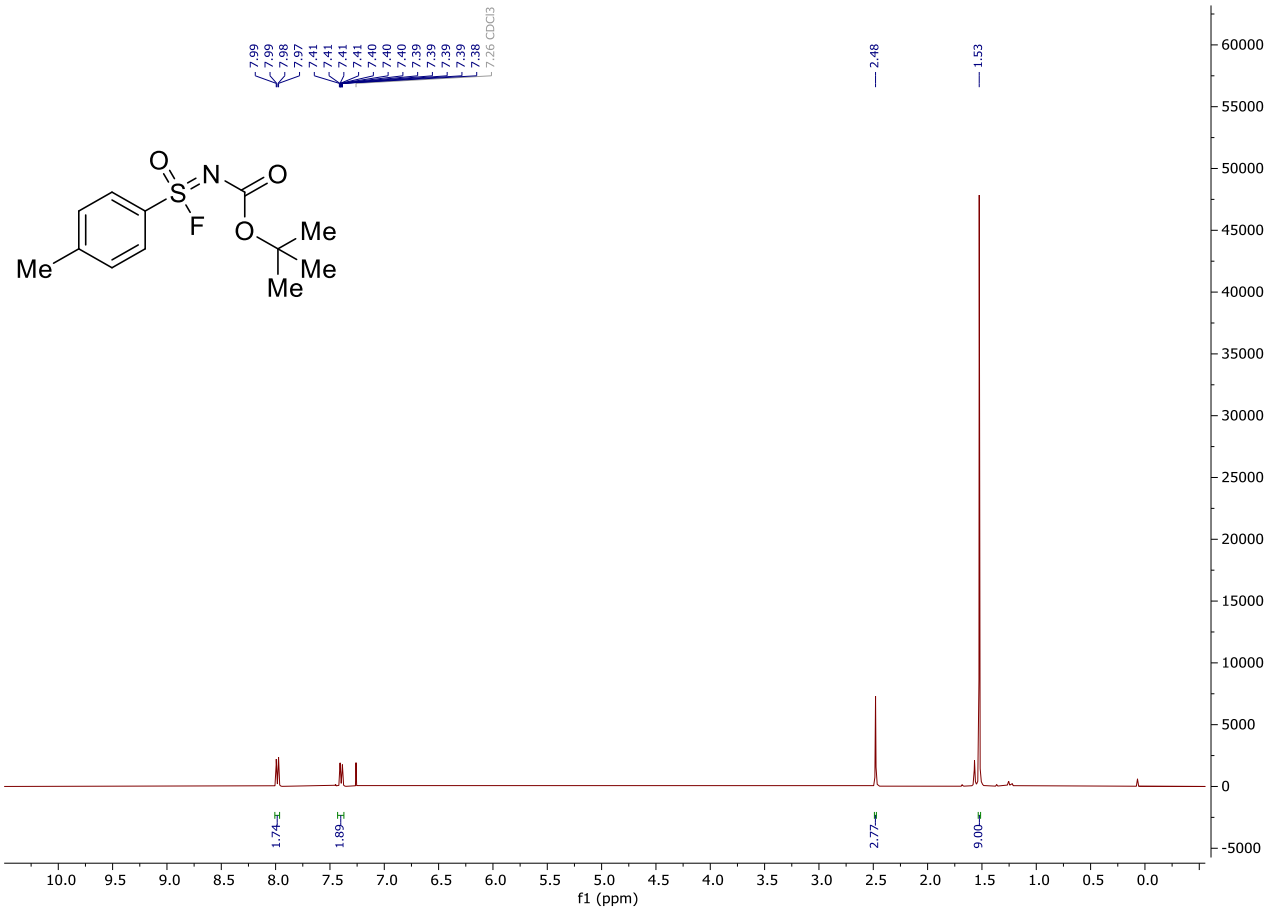

Me
O
S
N
H
O
OEt
f1 (ppm)

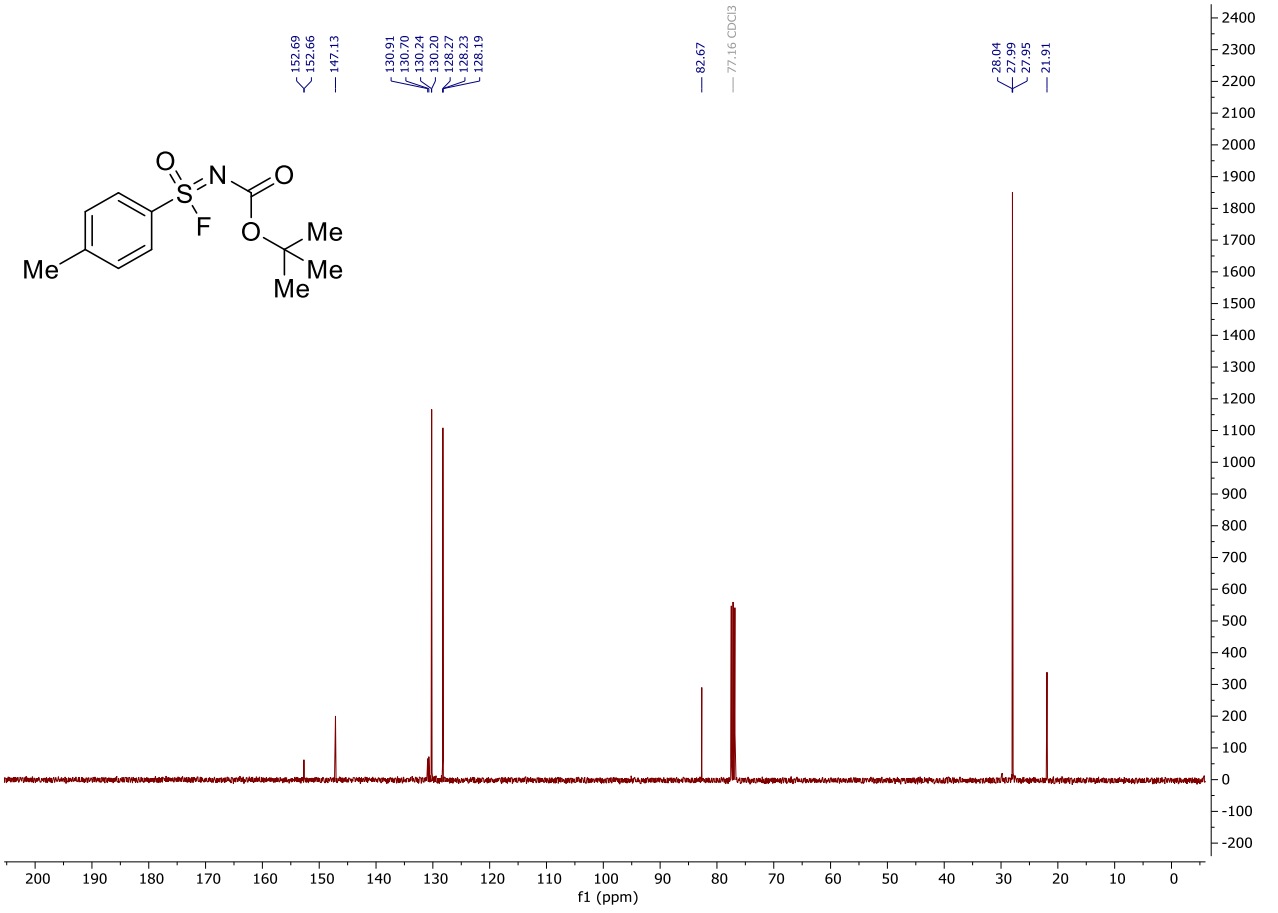

Me
O
S
N
H
O
OEt
172.23
141.40
141.17
129.68
126.13
126.09
77.16 CDCl3
60.87
37.43
35.61
21.43
14.28
f1 (ppm)

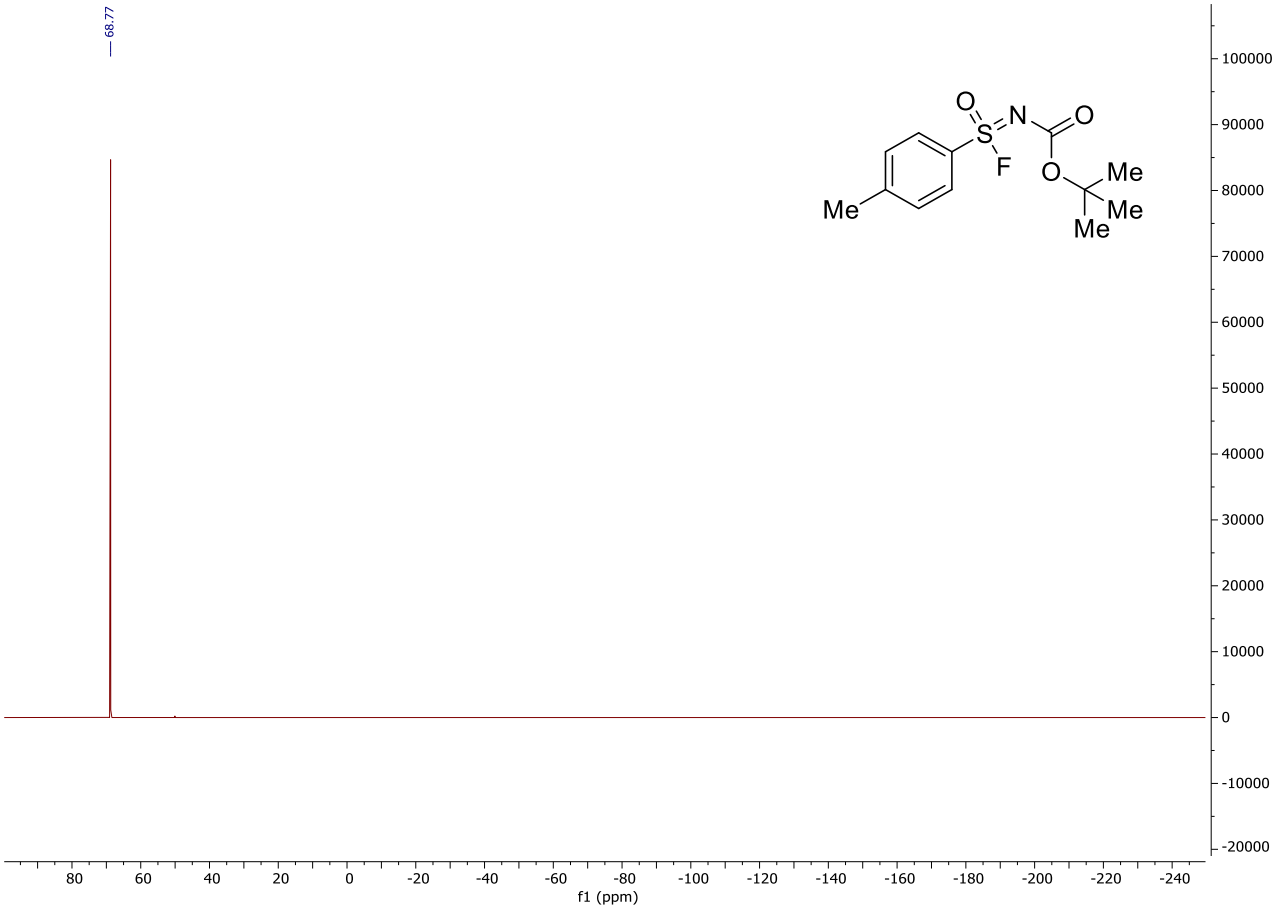
8.1.5 Sulfonimidoyl fluorides

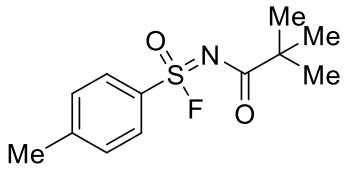


***tert*-Butyl (fluoro(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate (42a)**

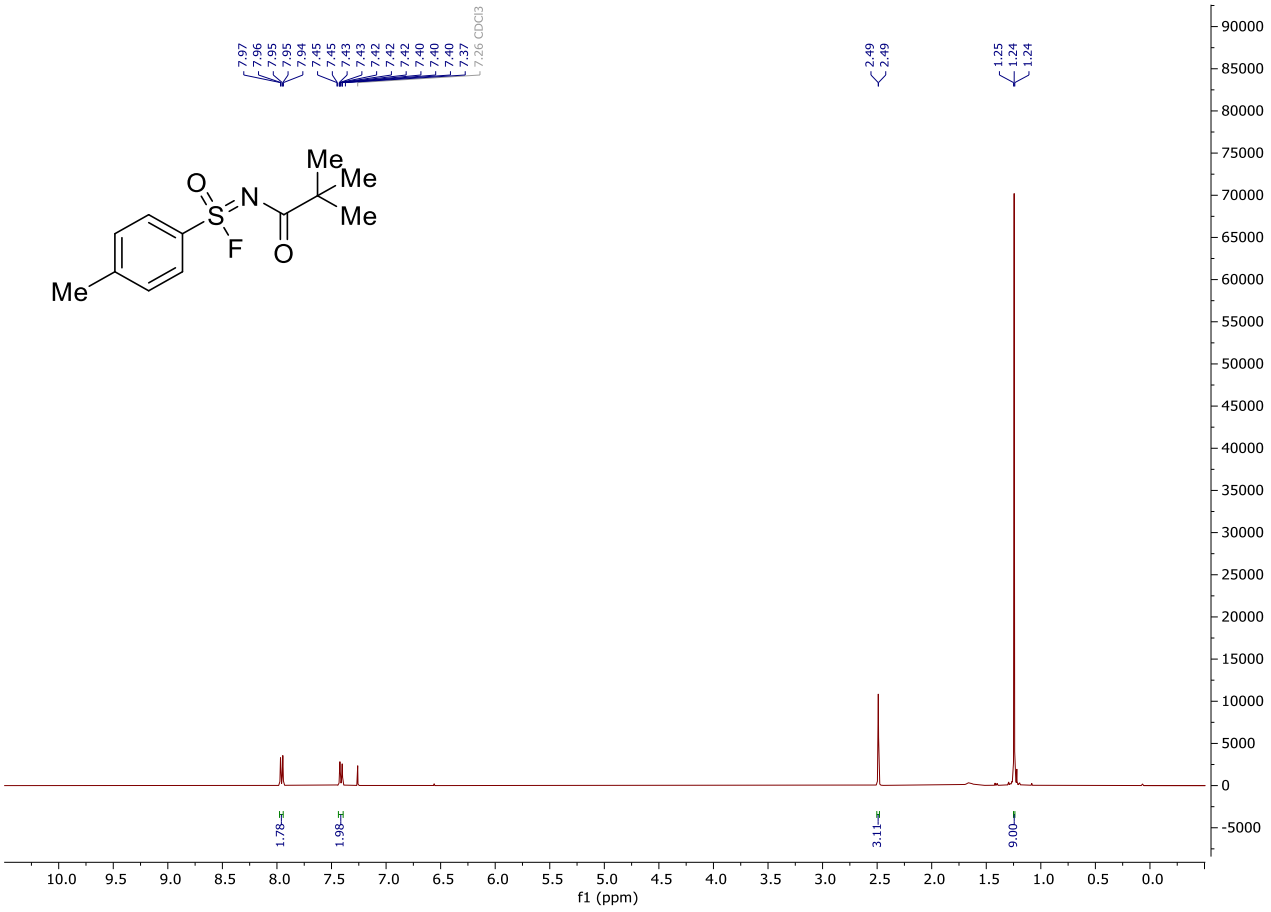


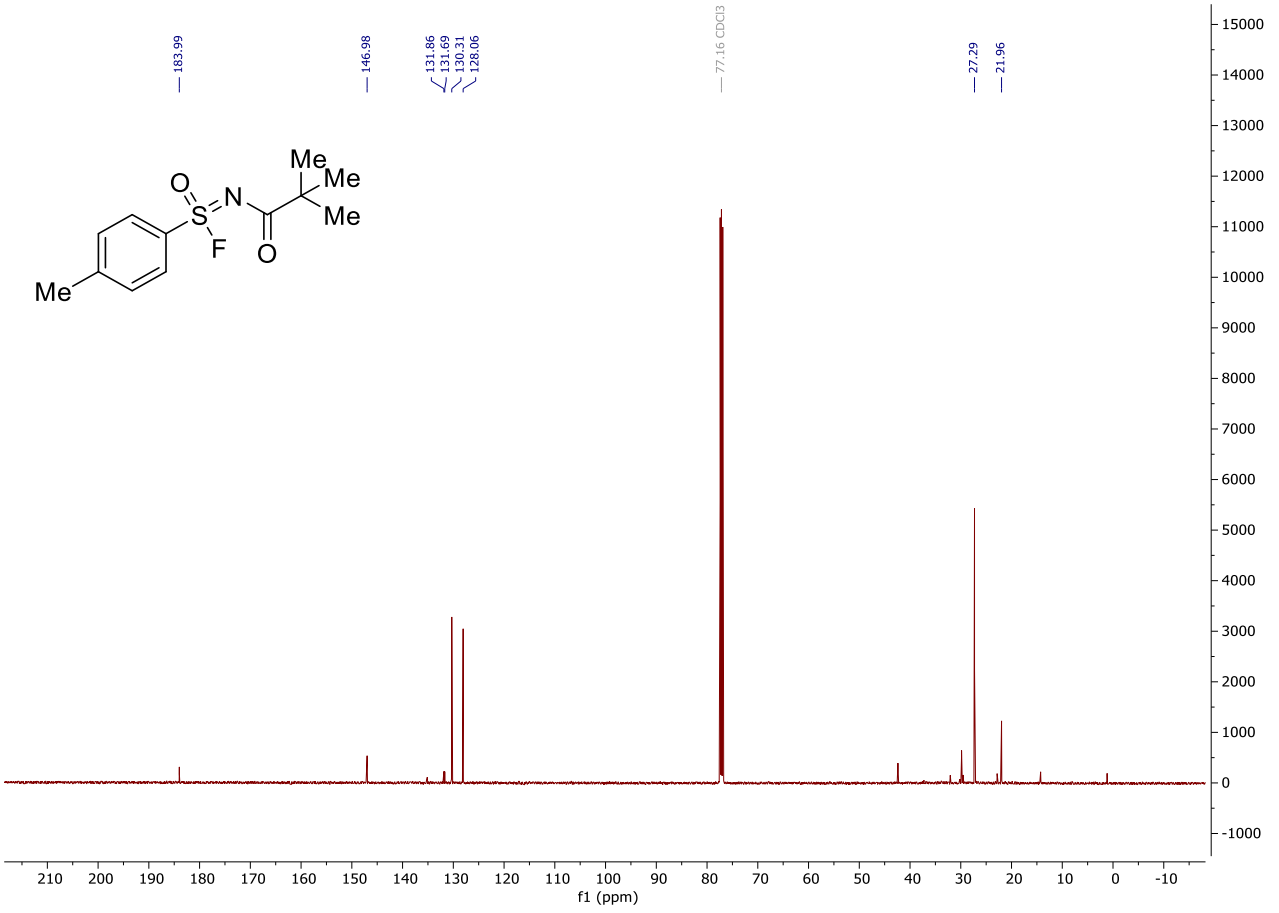

152.69
152.66
147.13
130.91
130.70
130.24
130.20
128.27
128.23
128.19
82.67
77.16 CDCl3
28.04
27.99
27.95
21.91
O
S
N
O
F
O
Me
Me
Me
Me
f1 (ppm)

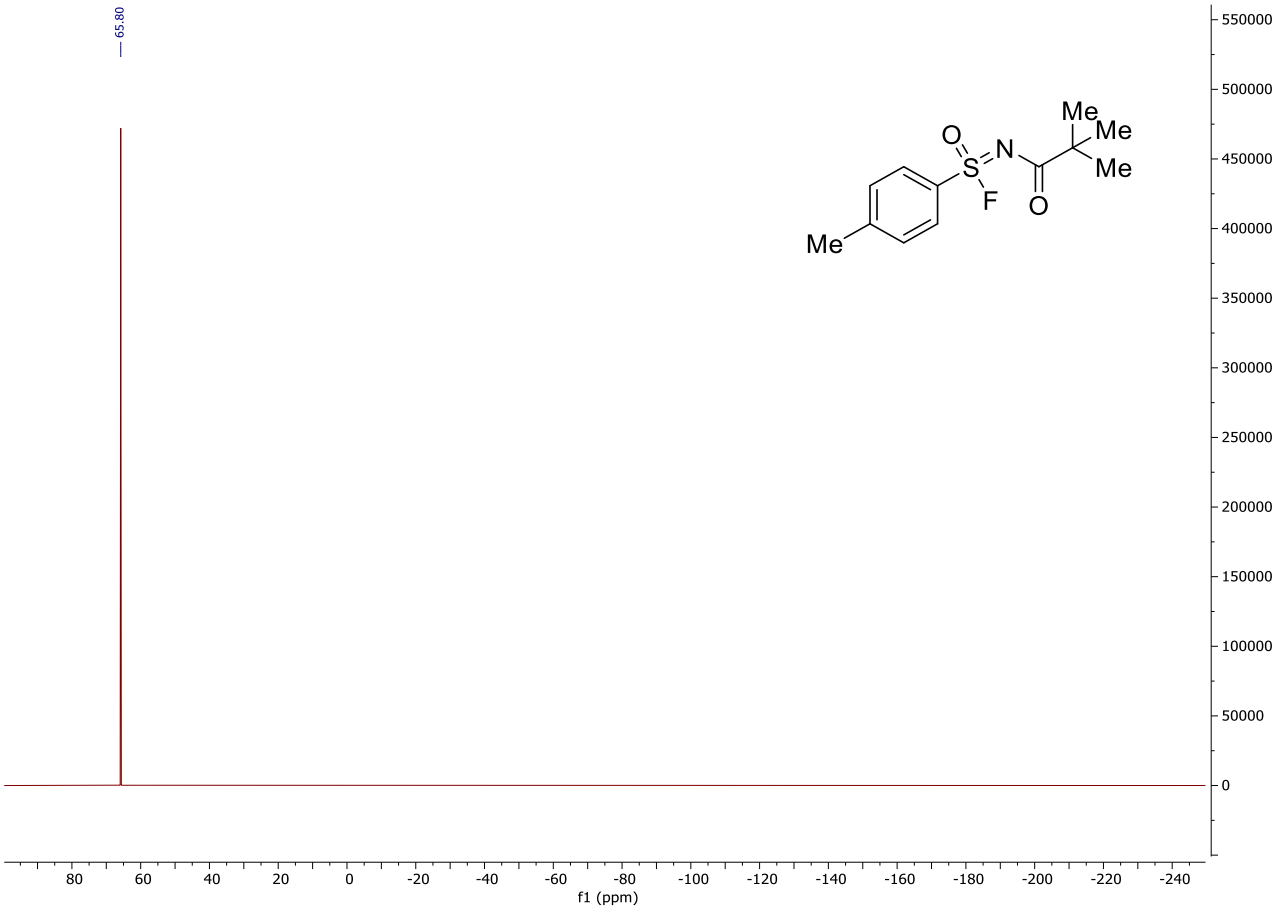

68.77
O
S
N
O
F
O
Me
Me
Me
Me
f1 (ppm)

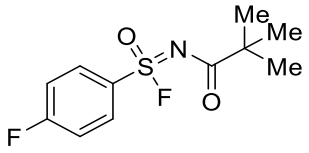


4-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (70a)

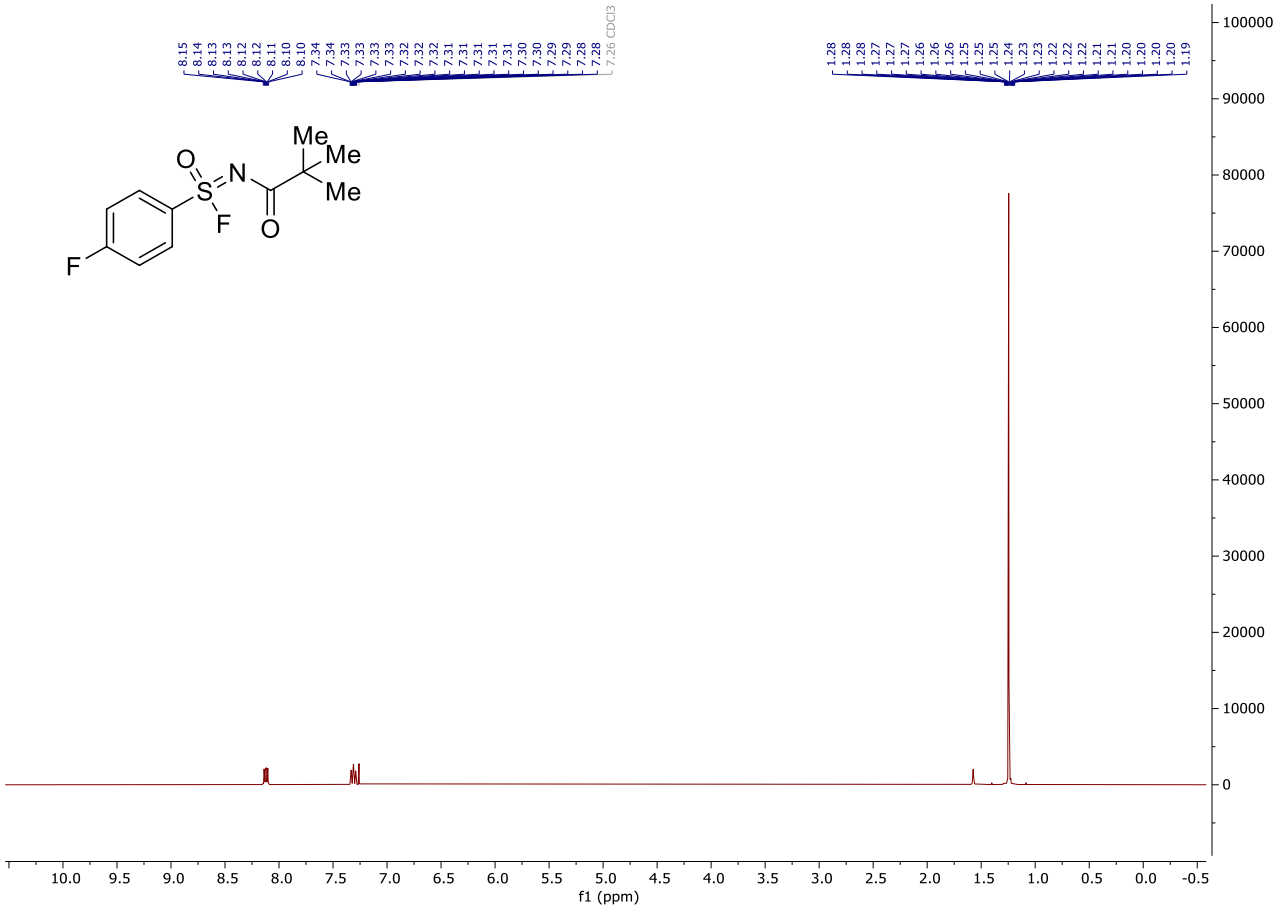


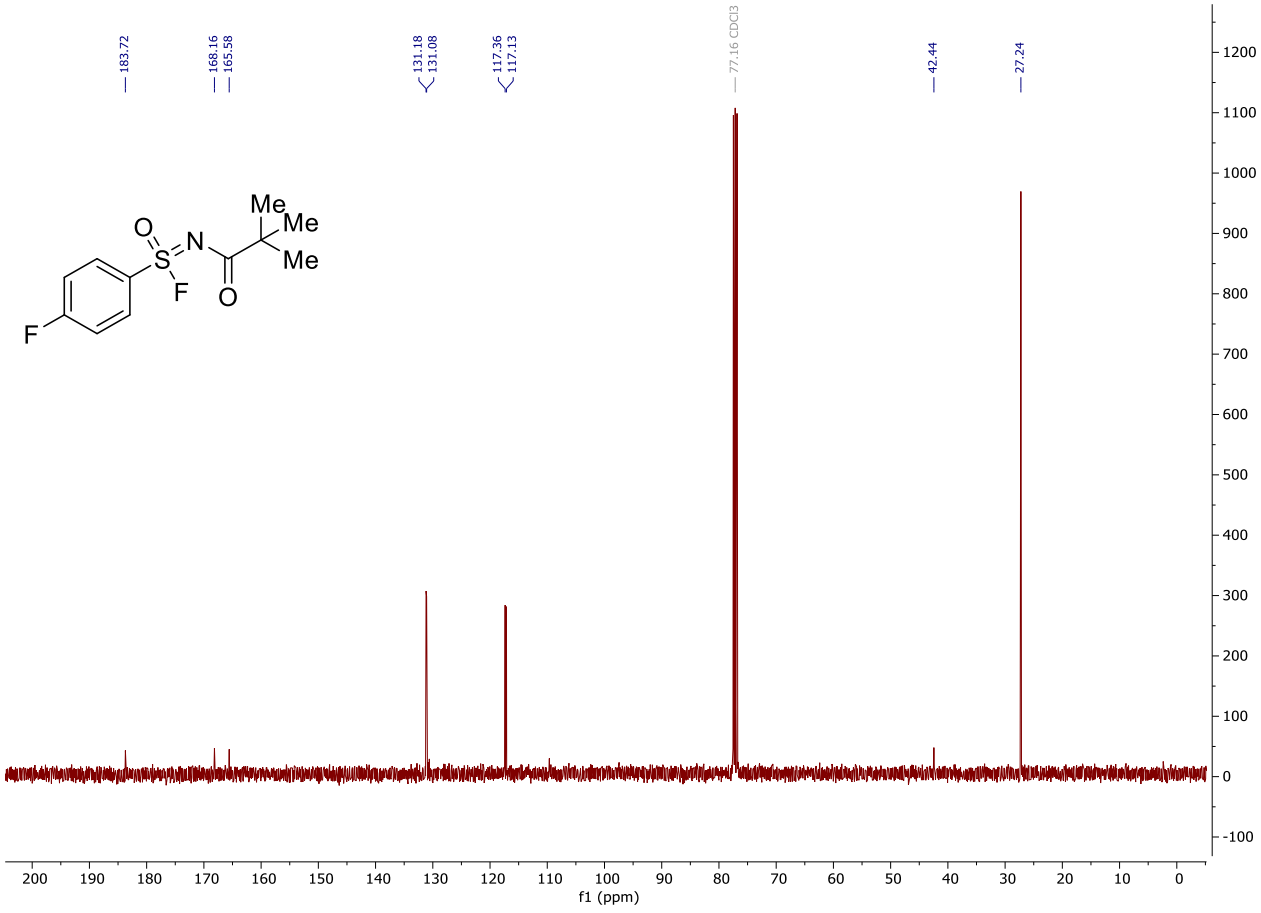

183.99
146.98
131.86
131.69
130.31
128.06
77.16 CDCl3
27.29
21.96
f1 (ppm)

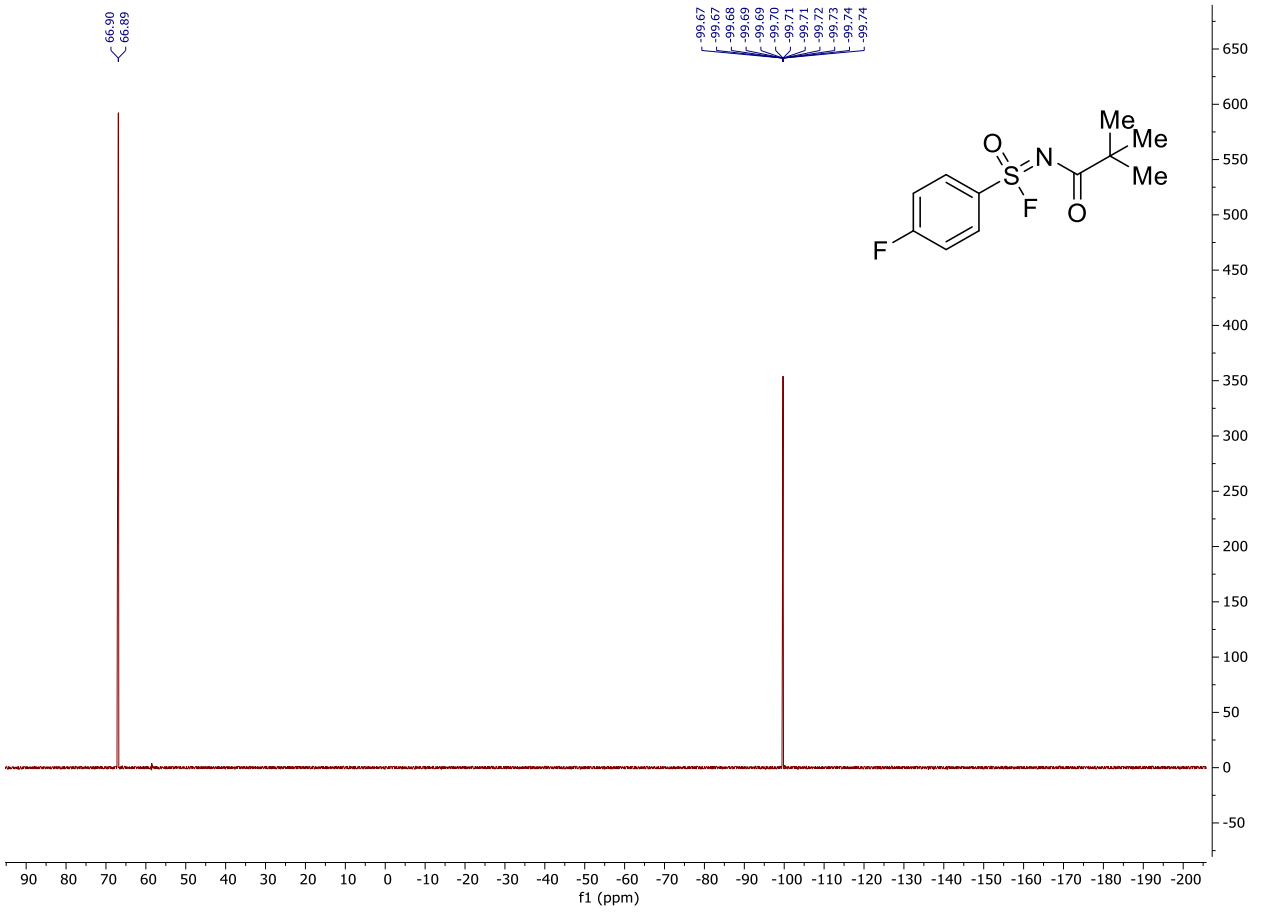

65.80
f1 (ppm)

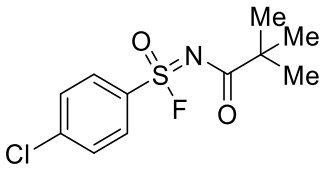


4-Fluoro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70b)

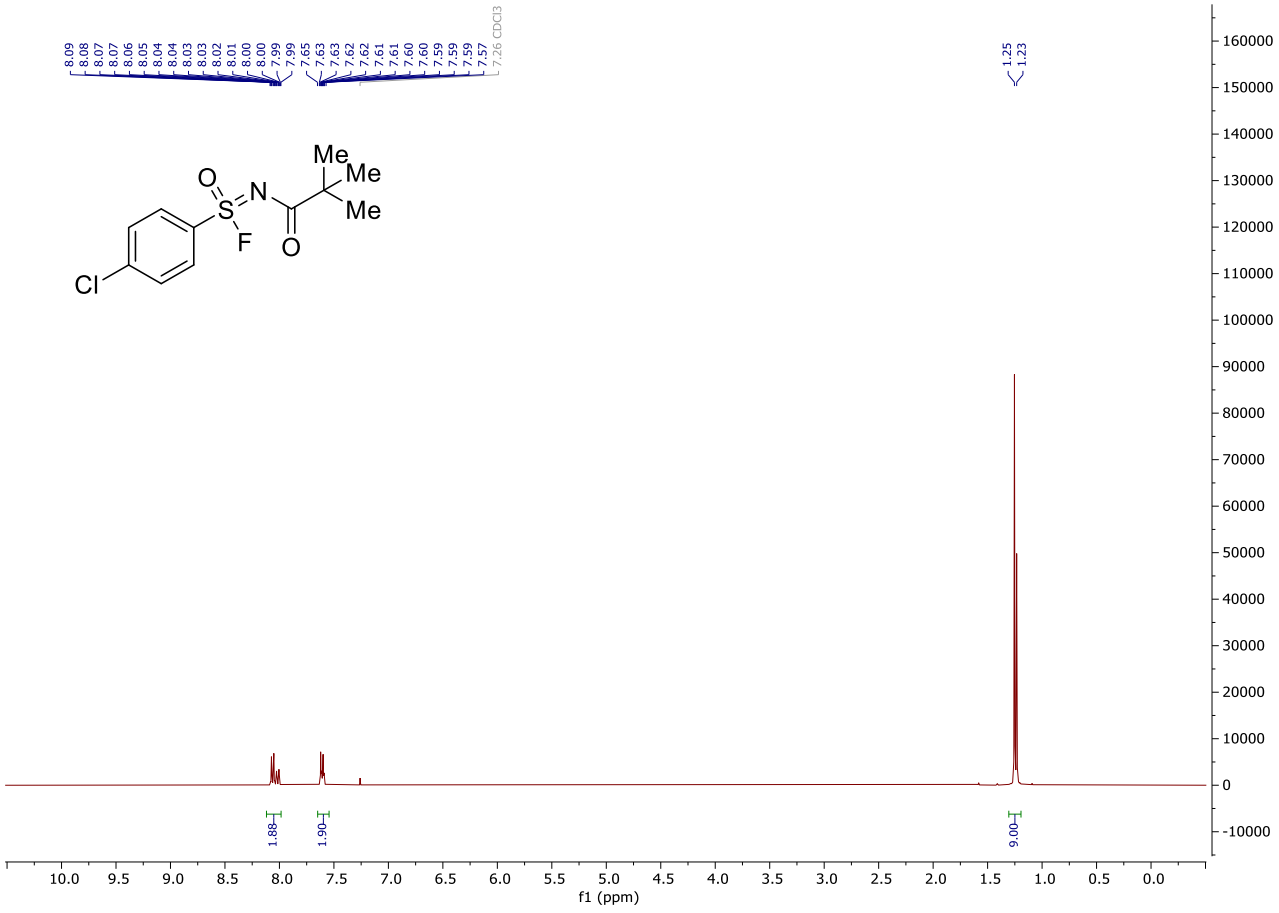


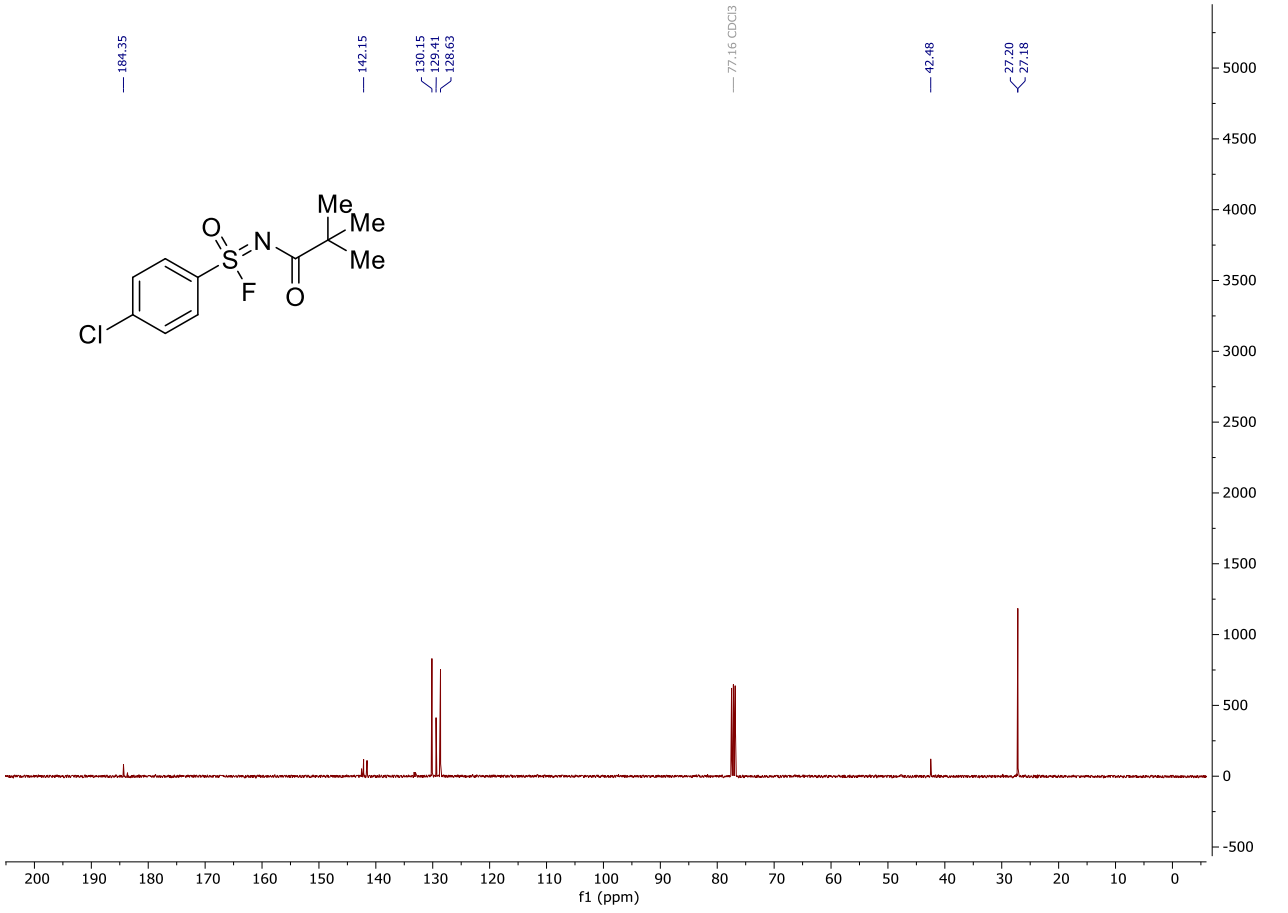

183.72
168.16
165.58
131.18
131.08
117.36
117.13
77.16 CDCl3
42.44
27.24
f1 (ppm)

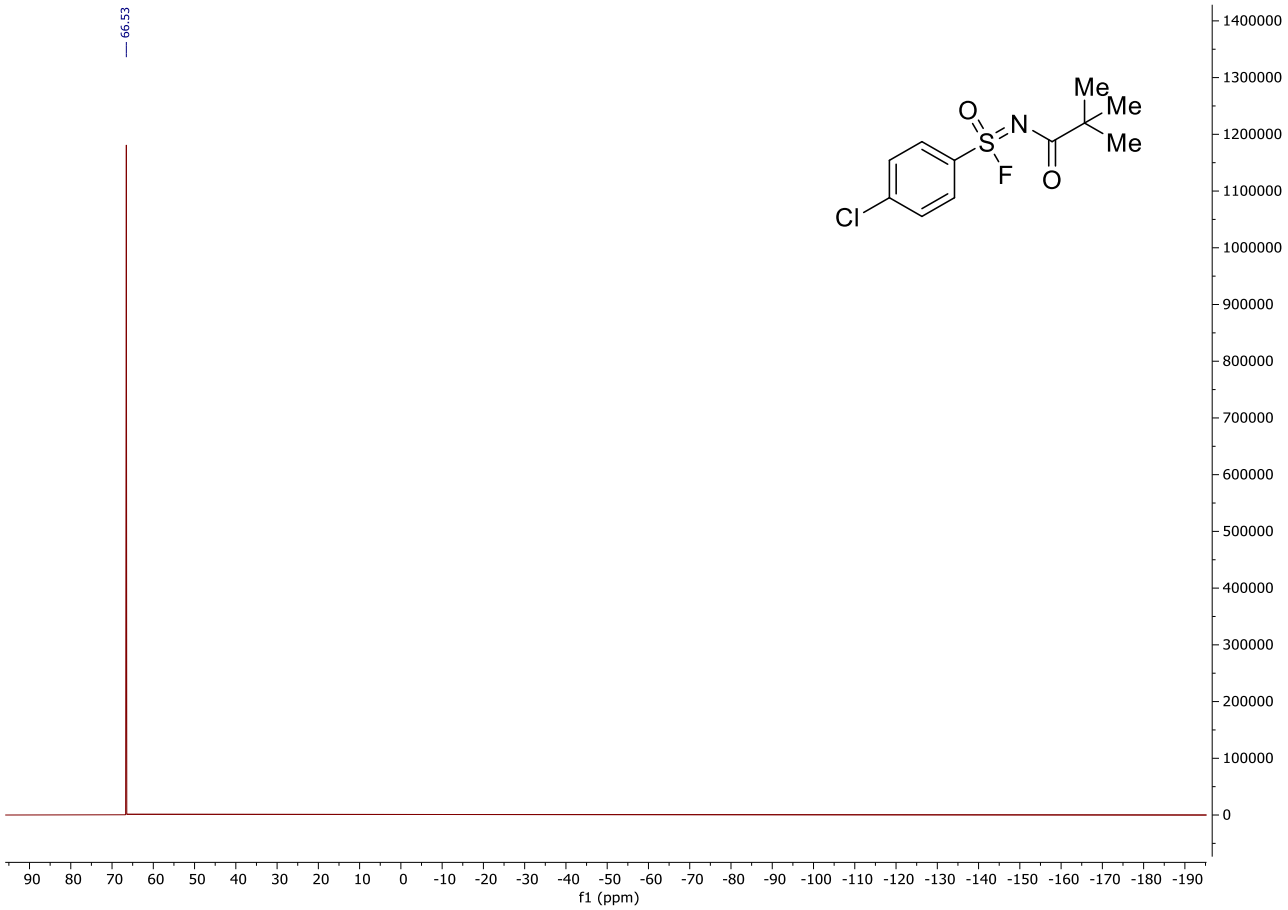

66.90
66.89
-99.67
-99.67
-99.68
-99.69
-99.69
-99.70
-99.71
-99.71
-99.72
-99.73
-99.74
-99.74
f1 (ppm)

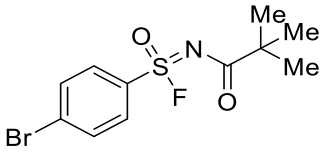


4-Chloro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70c)

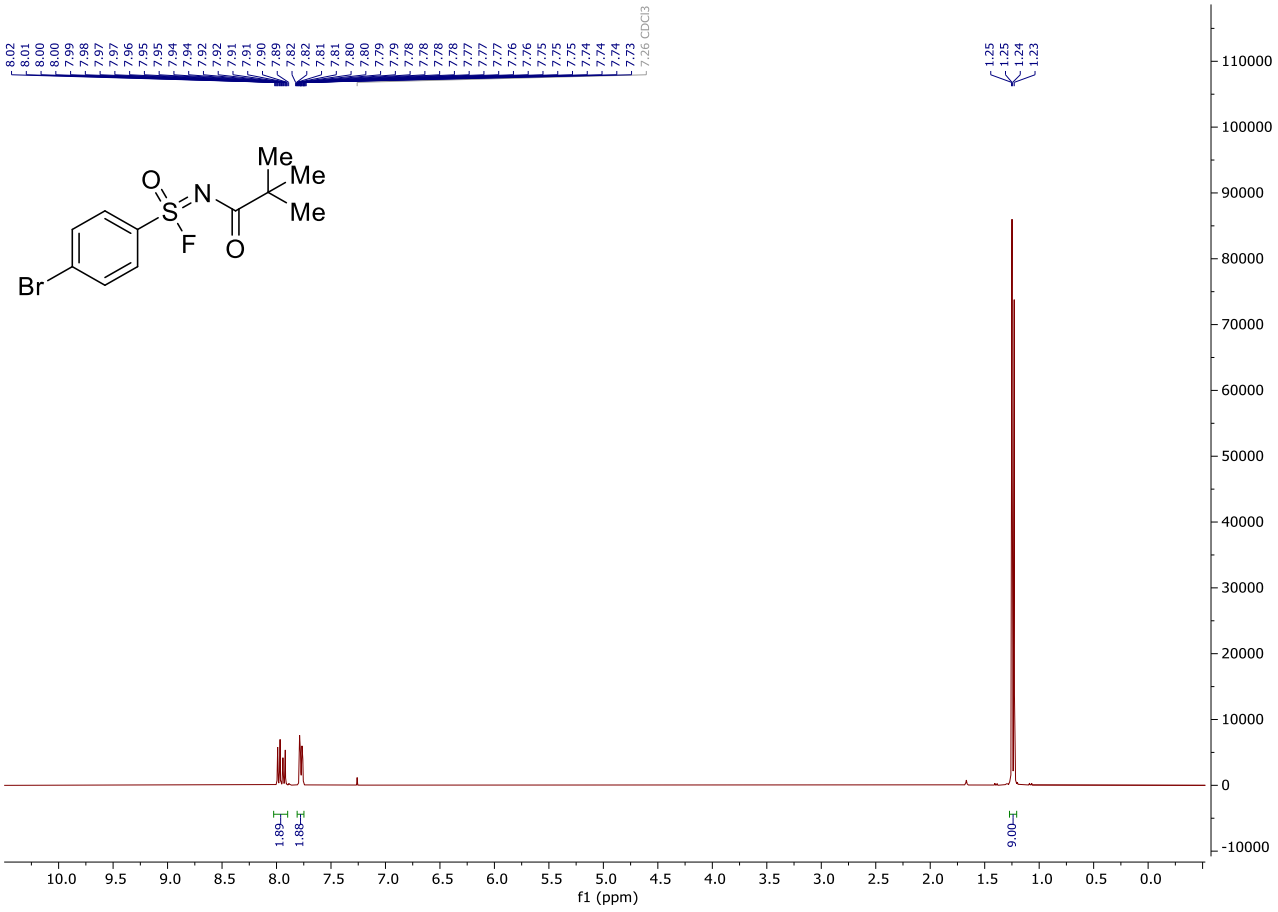


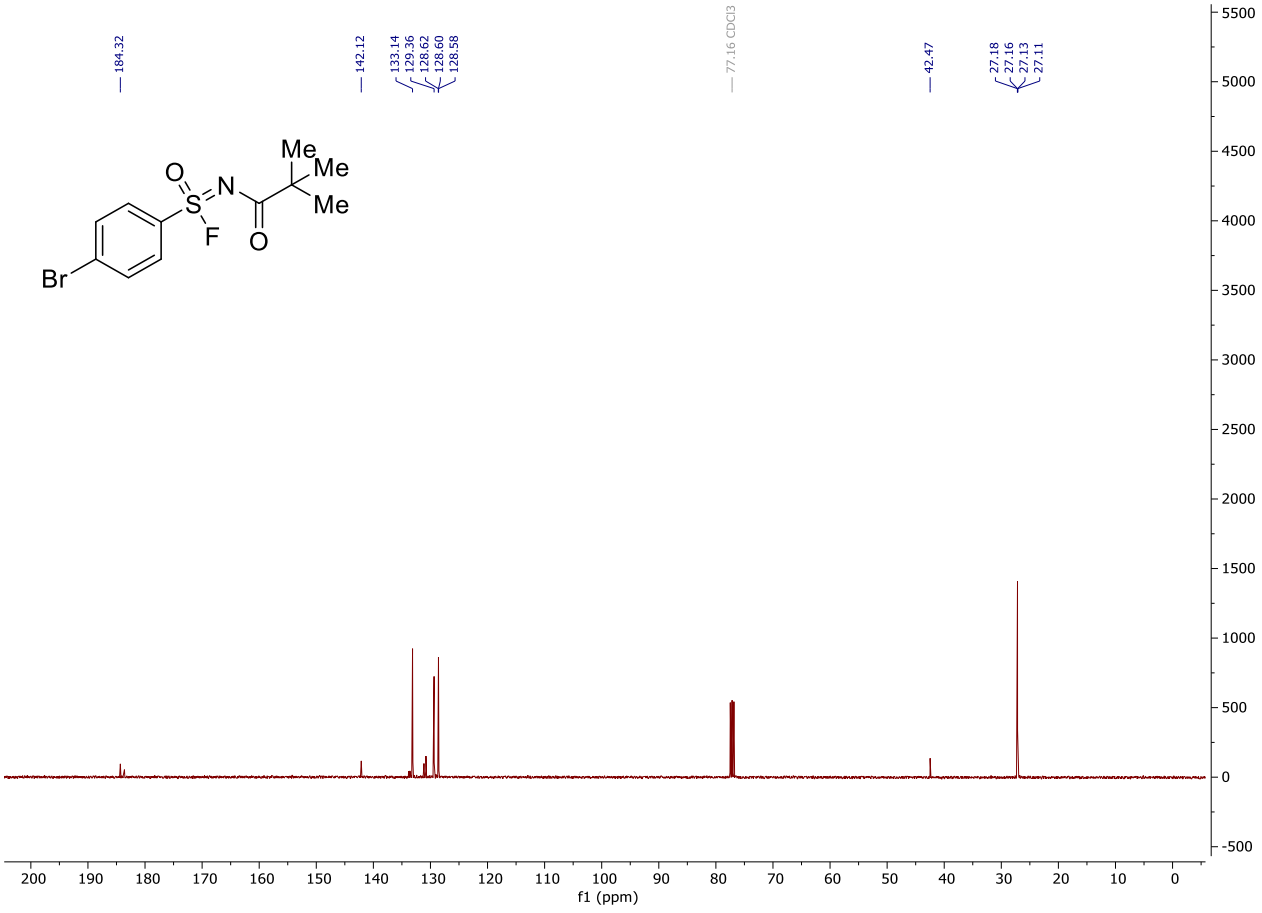

184.35
142.15
130.15
129.41
128.63
77.16 CDCl3
42.48
27.20
27.18
Me
Me
Me
O
S
N
F
O
Cl
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

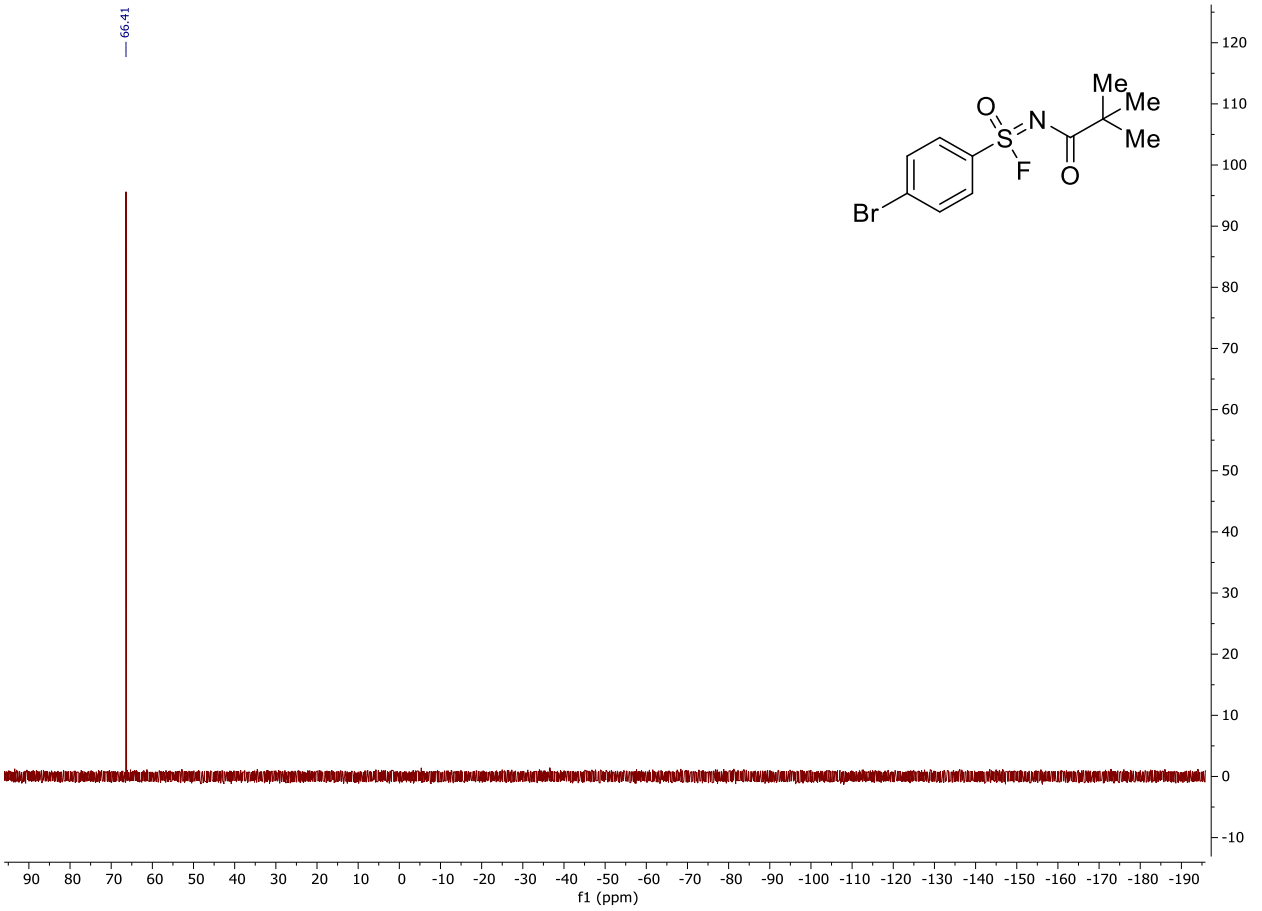

66.53
Me
Me
Me
O
S
N
F
O
Cl
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

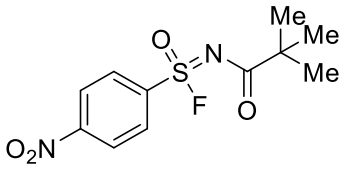


4-Bromo-*N*-pivaloylbenzenesulfonimidoyl fluoride (70d)

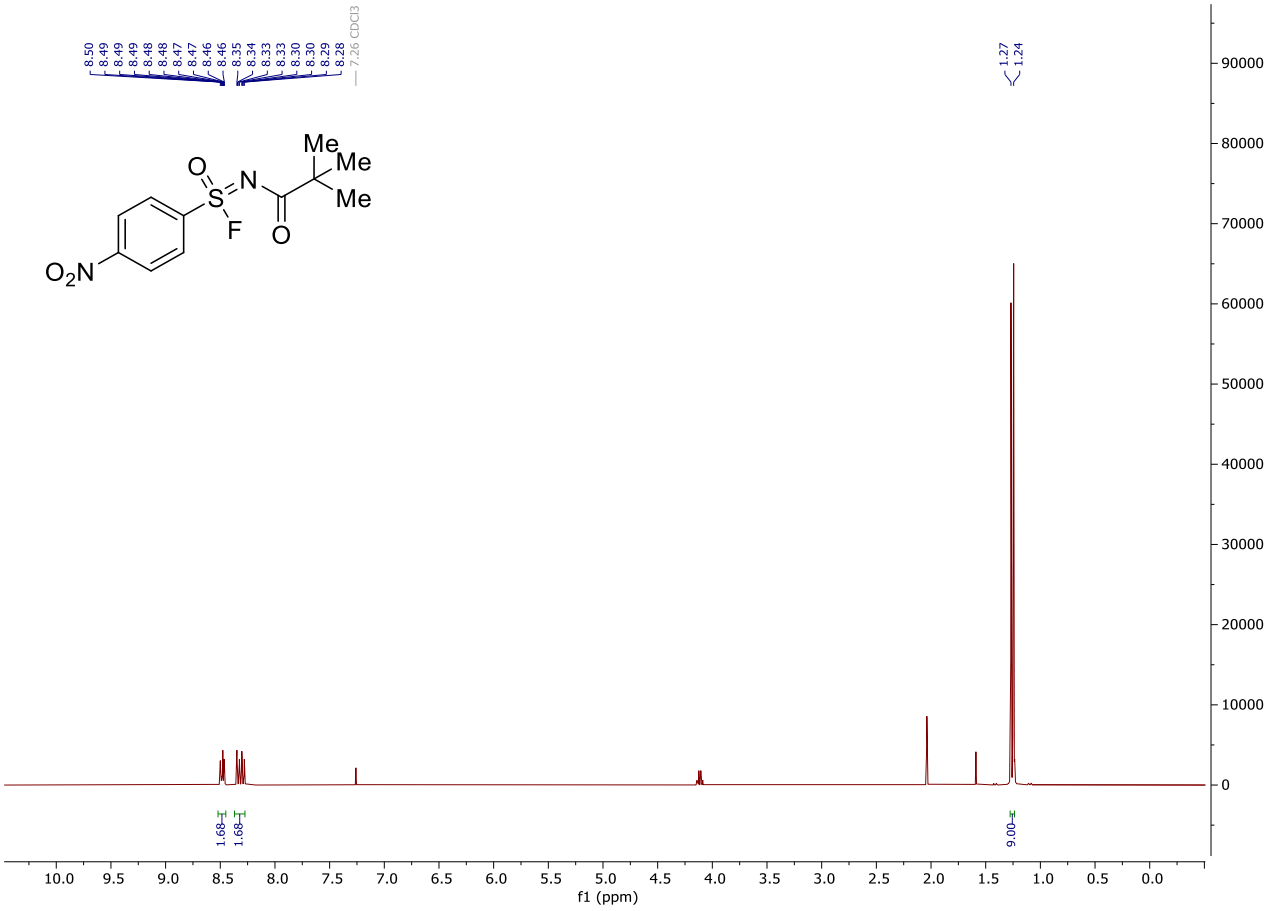


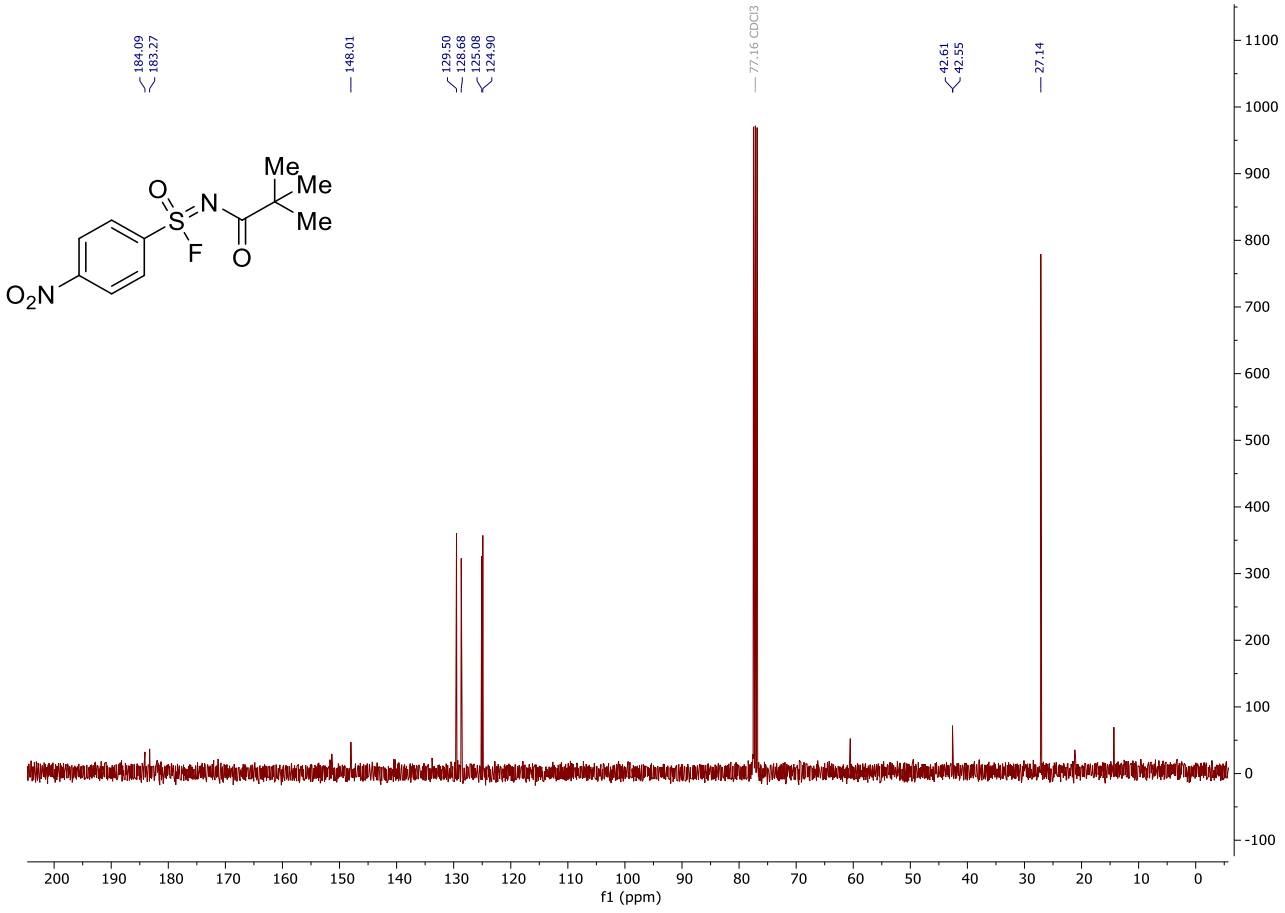

184.32
142.12
133.14
129.36
128.62
128.60
128.58
77.16 CDCl3
42.47
27.18
27.16
27.13
27.11
Me
Me
Me
O
S
N
F
O
Br
f1 (ppm)

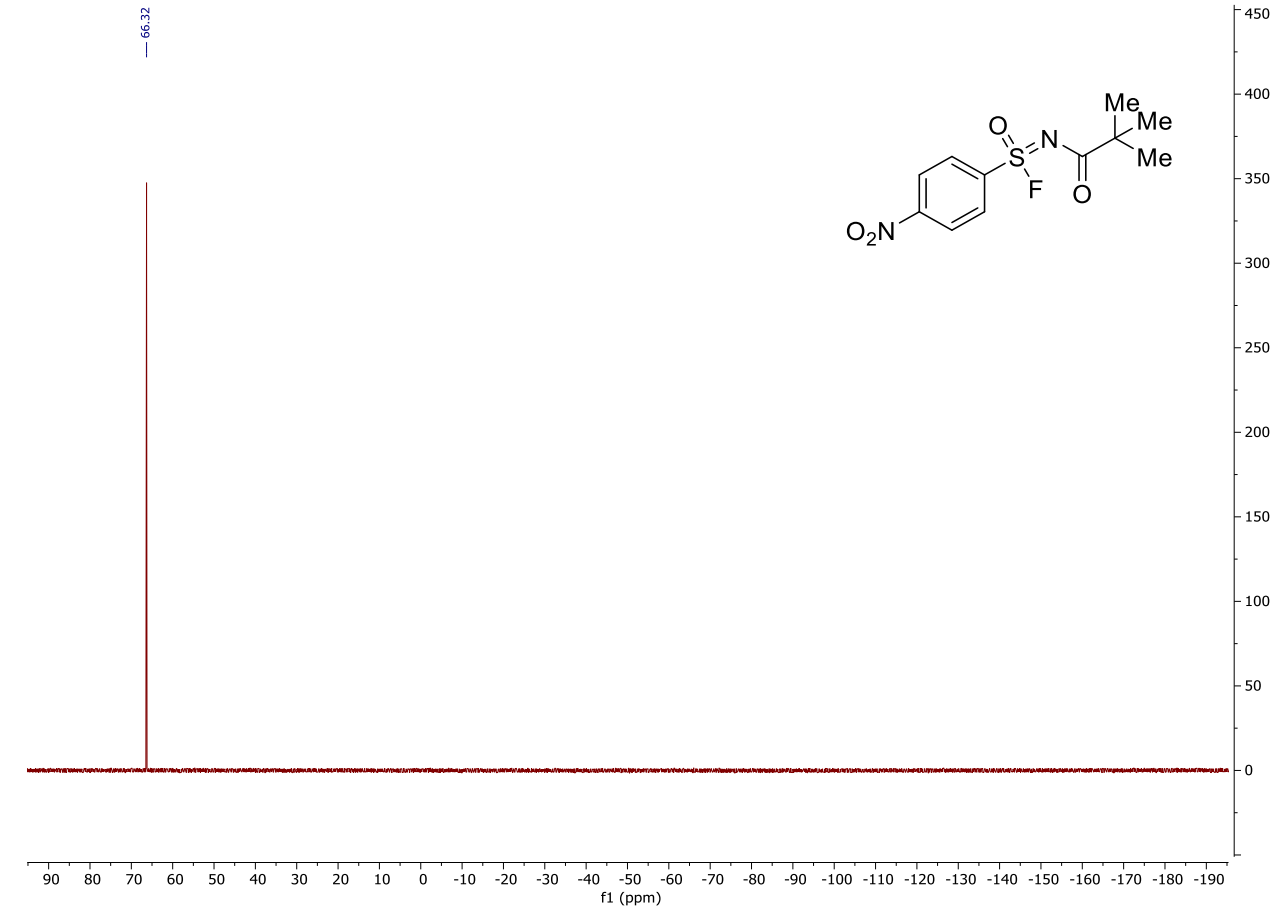

66.41
Me
Me
Me
O
S
N
F
O
Br
f1 (ppm)

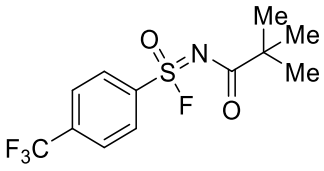


4-Nitro-*N*-pivaloylbenzenesulfonimidoyl fluoride (70e)

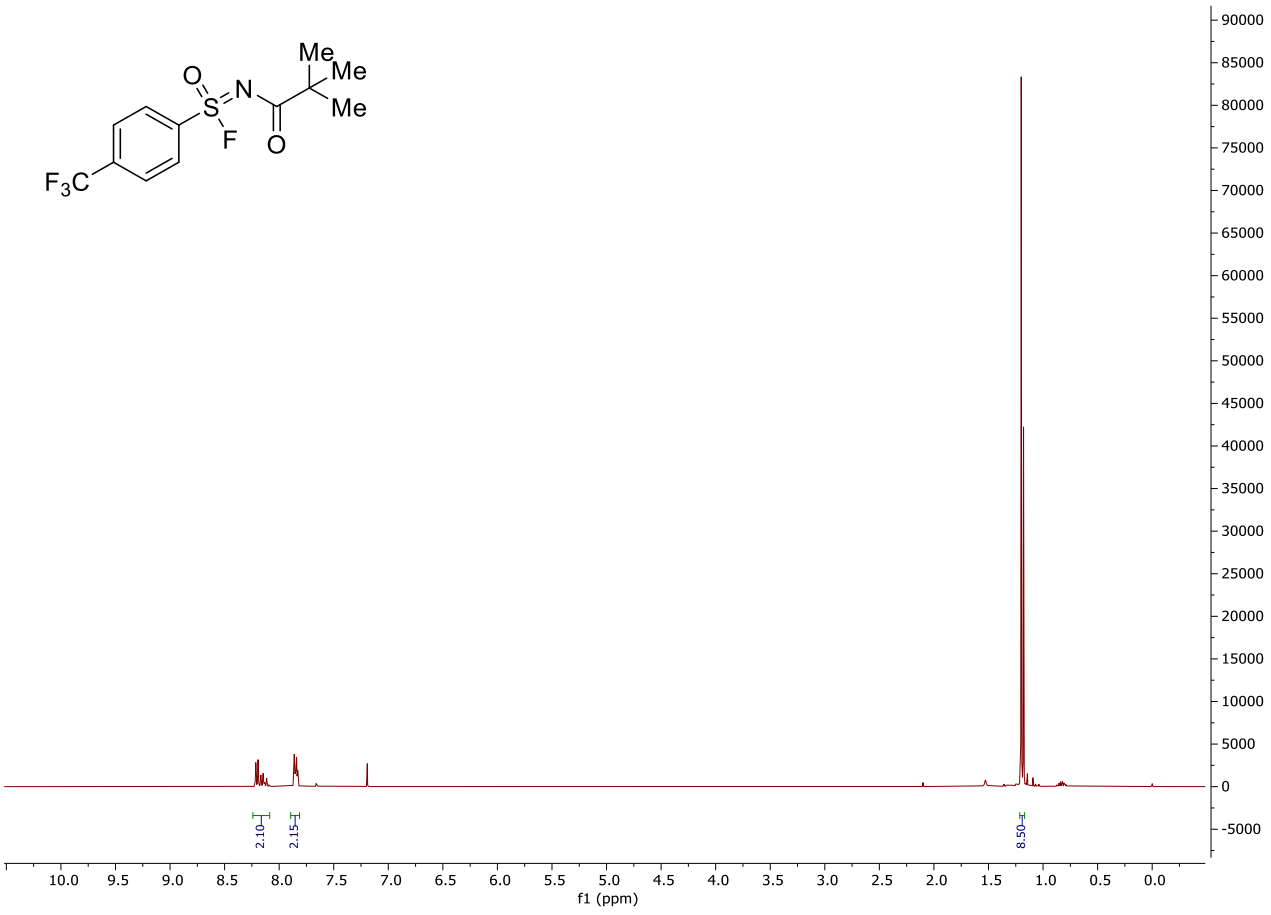


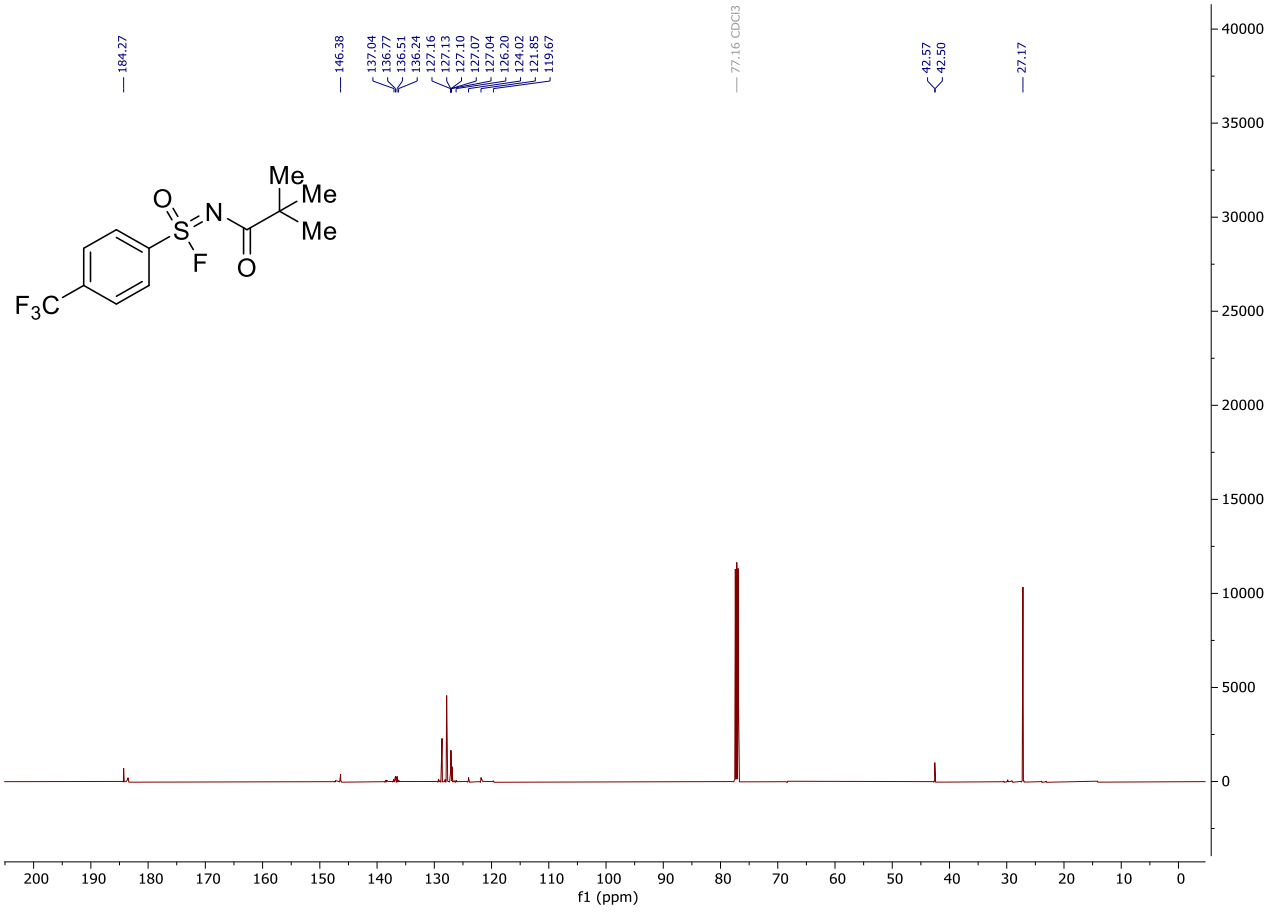

184.09
183.27
148.01
129.50
128.68
125.08
124.90
77.16 CDCl3
42.61
42.55
27.14
f1 (ppm)

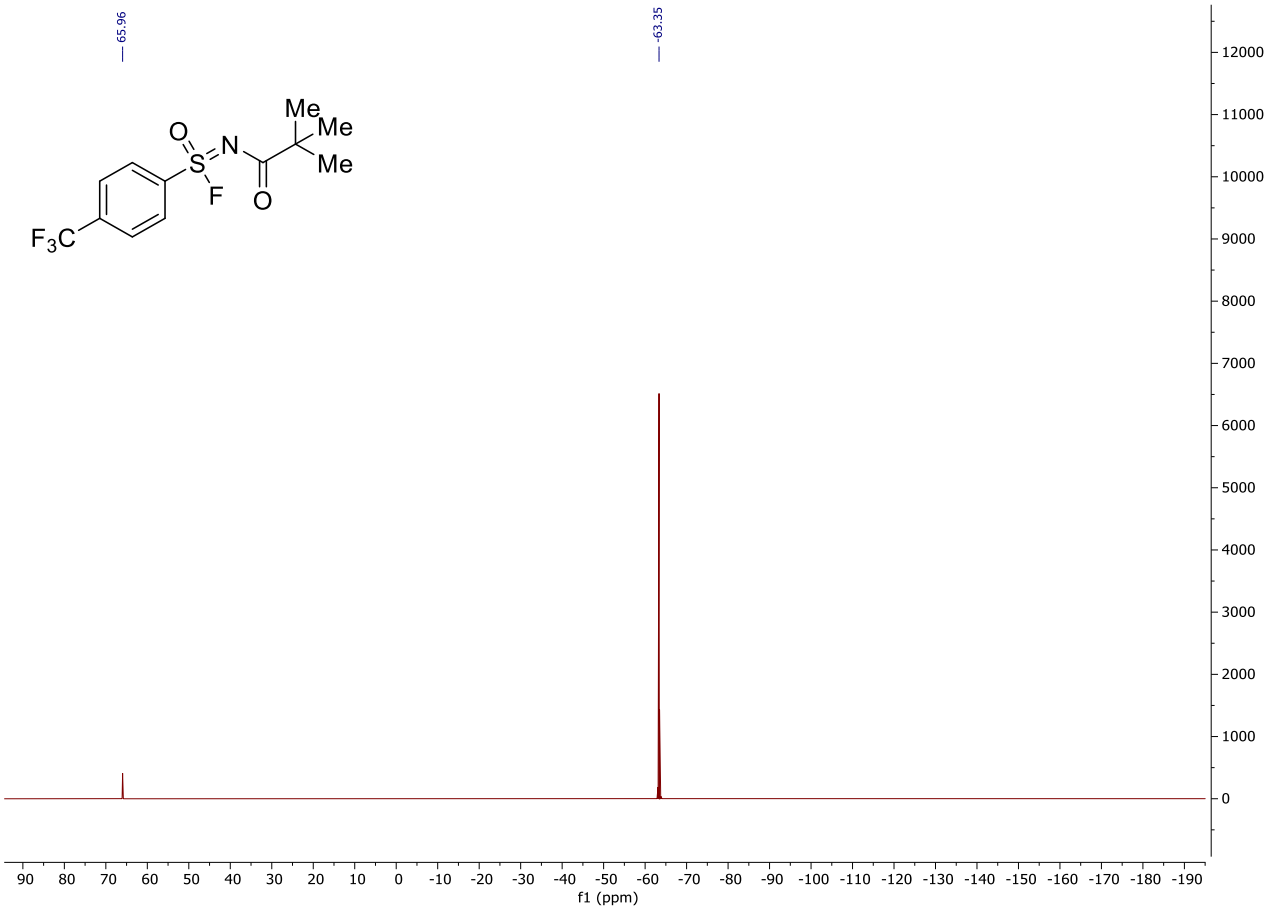

66.32
f1 (ppm)

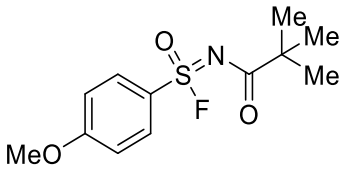


_N_-Pivaloyl-4-(trifluoromethyl)benzenesulfonimidoyl fluoride (70f)

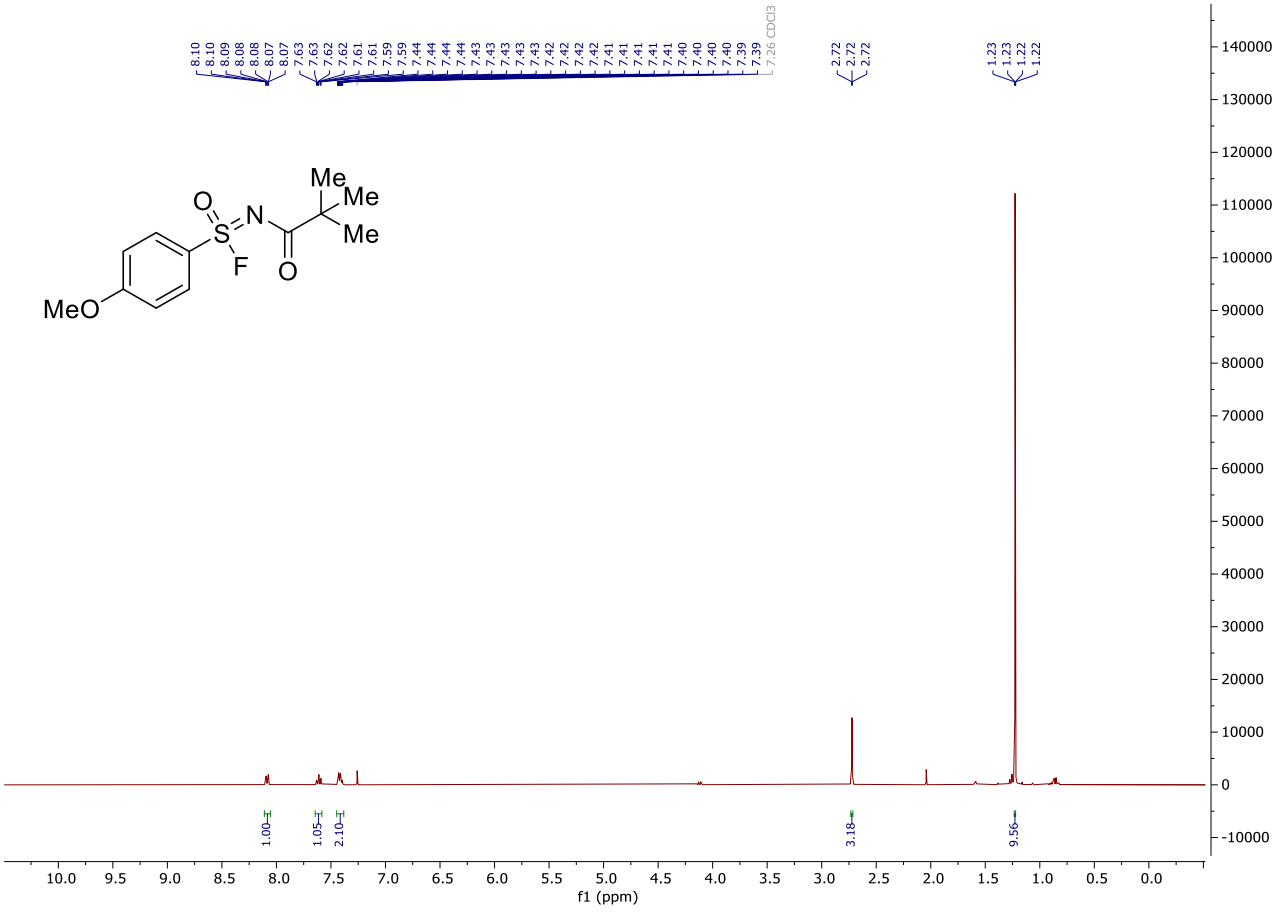


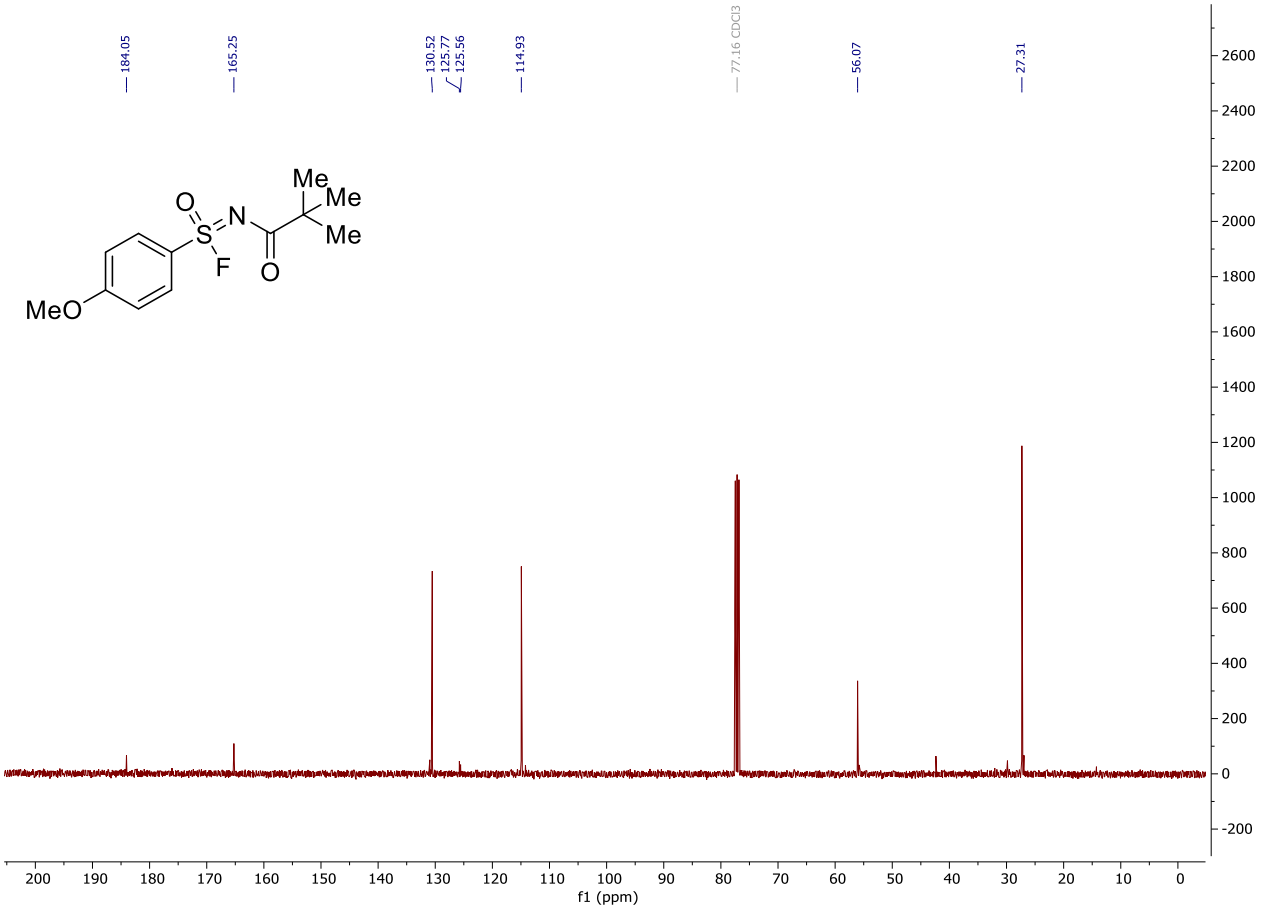

184.27
146.38
137.04
136.77
136.51
136.24
127.16
127.13
127.10
127.07
127.04
126.20
124.02
121.85
119.67
77.16 CDCl3
42.57
42.50
27.17
Me
Me
Me
O
S
N
F
O
F3C
40000
35000
30000
25000
20000
15000
10000
5000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

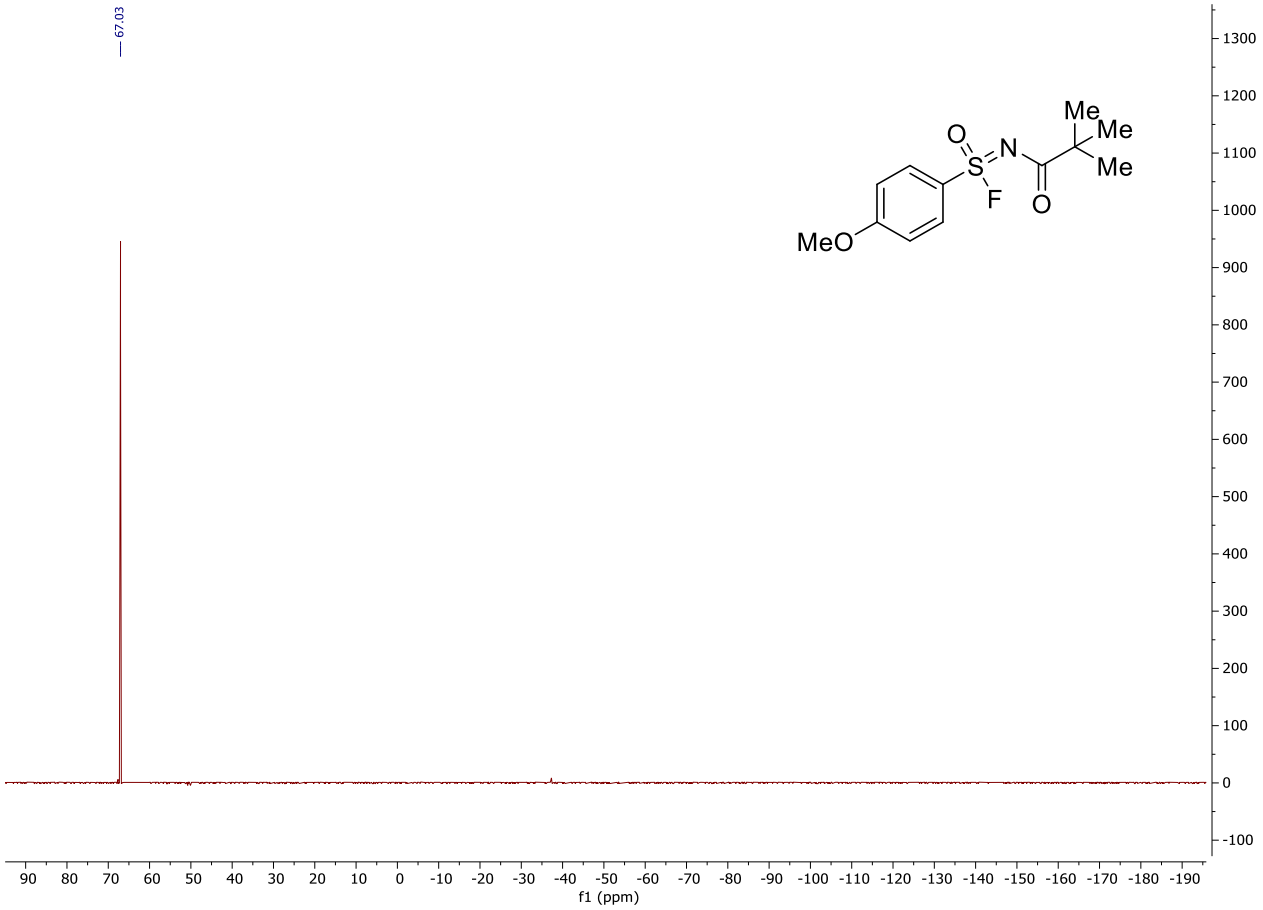

65.96
-63.35
Me
Me
Me
O
S
N
F
O
F3C
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

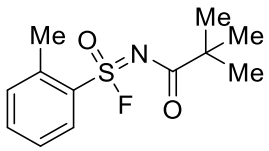


4-Methoxy-*N*-pivaloylbenzenesulfonimidoyl fluoride (70g)

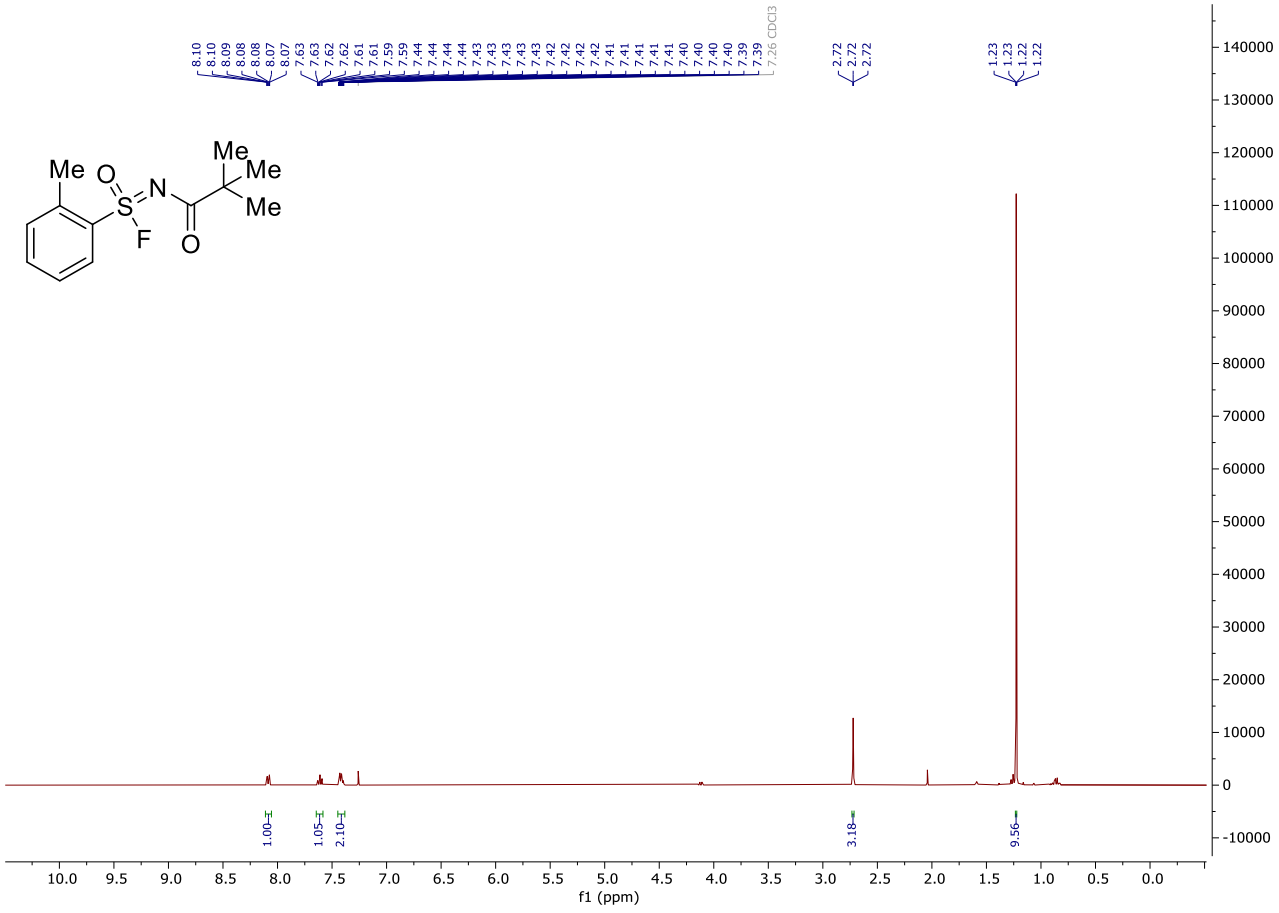


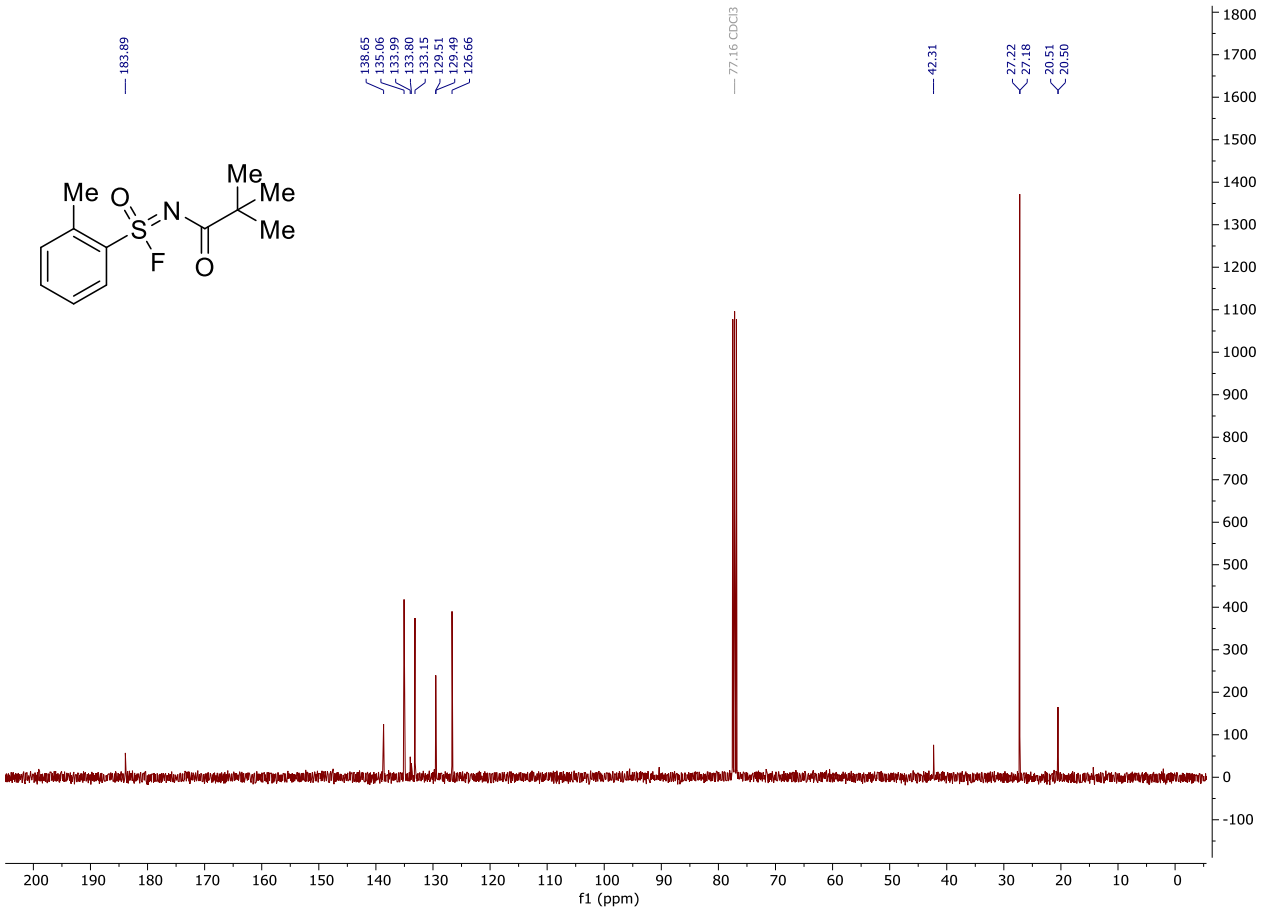

184.05
165.25
130.52
125.77
125.56
114.93
77.16 CDCl3
56.07
27.31
Me
Me
Me
O
S
N
F
O
MeO
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

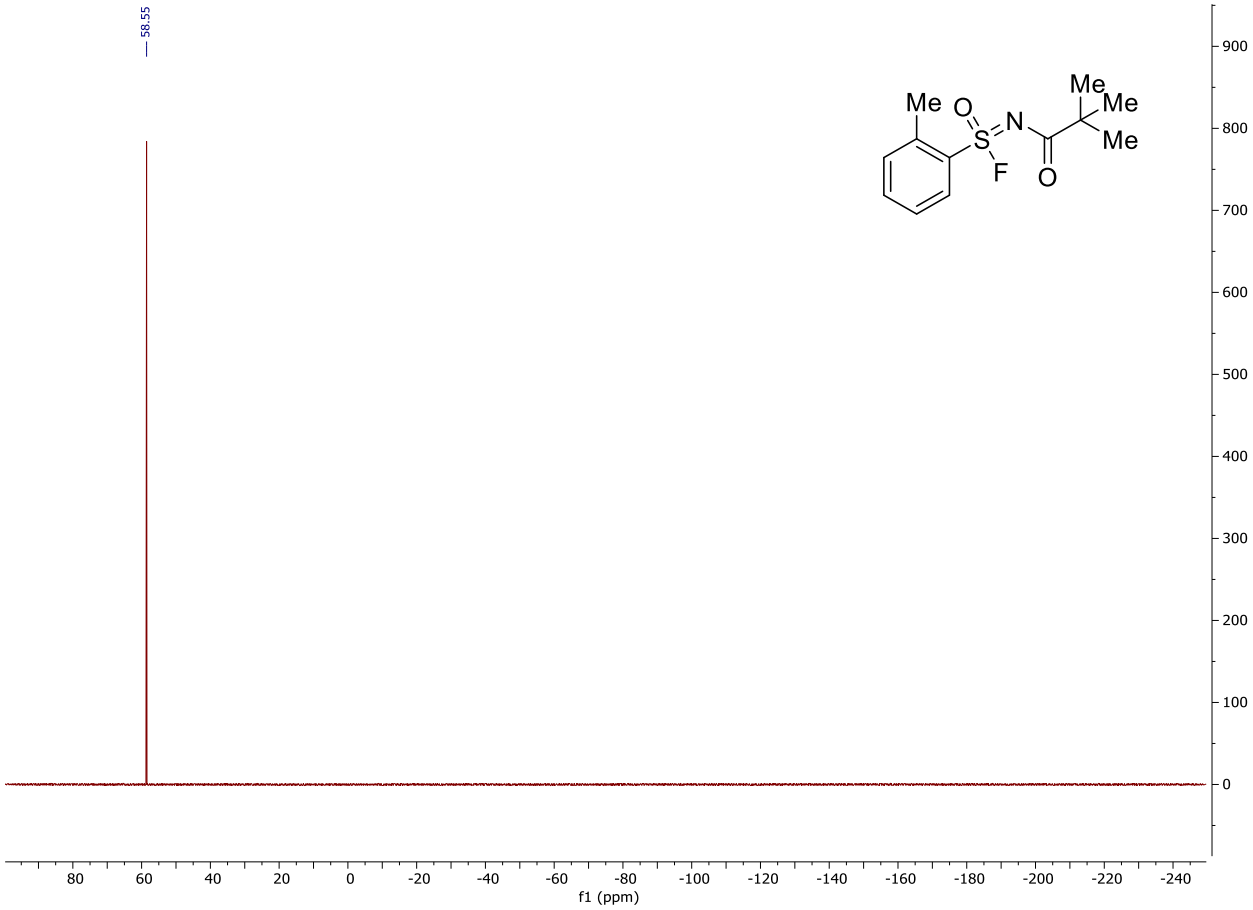


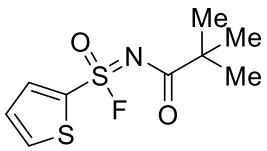


2-Methyl-*N*-pivaloylbenzenesulfonimidoyl fluoride (70h)

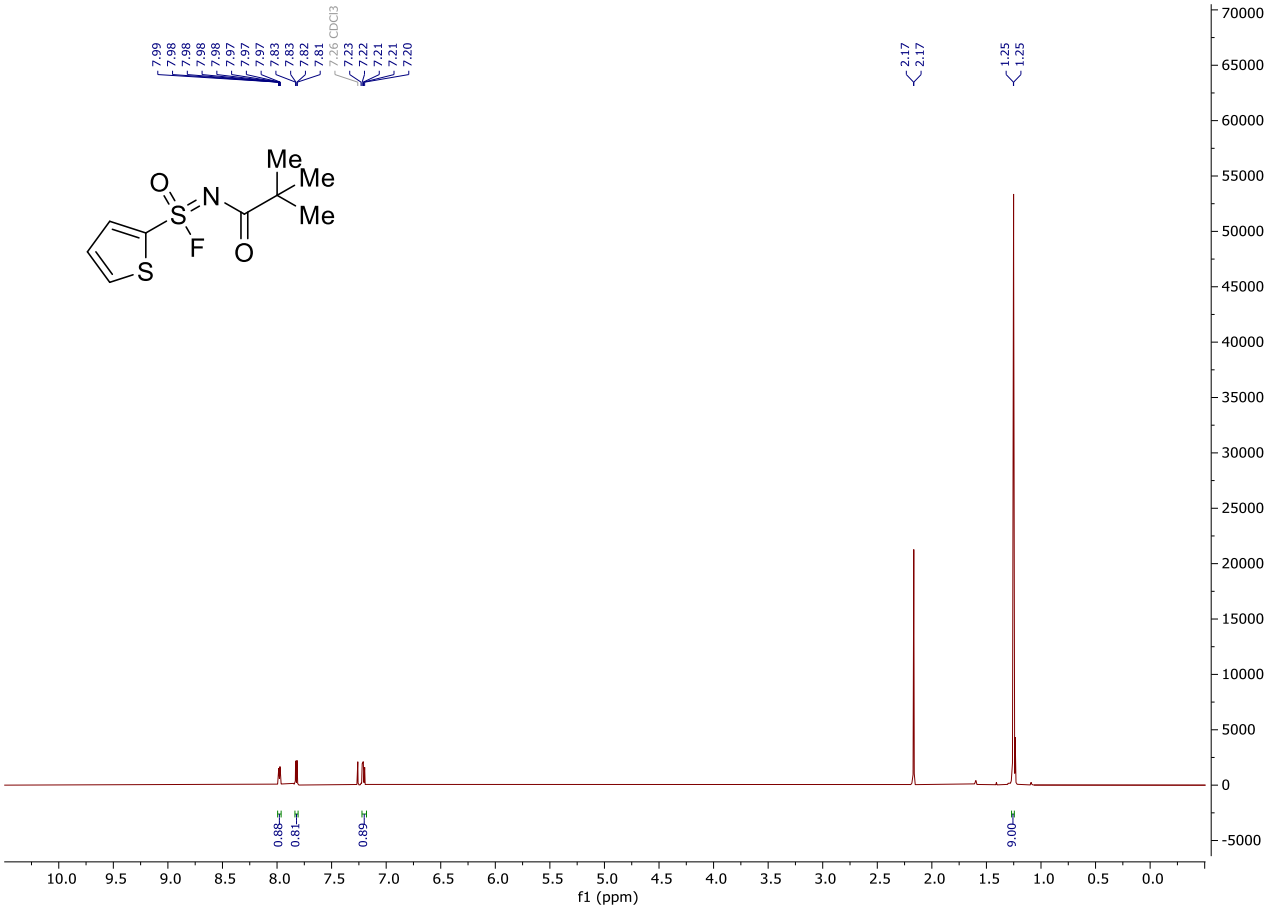

Me
O
S
N
F
O
Me
Me
Me
8.10
8.09
8.08
8.07
7.63
7.62
7.61
7.59
7.44
7.43
7.42
7.41
7.40
7.39
7.26 CDCl3
2.72
1.23
1.22
1.00
1.05
2.10
3.18
9.56
f1 (ppm)

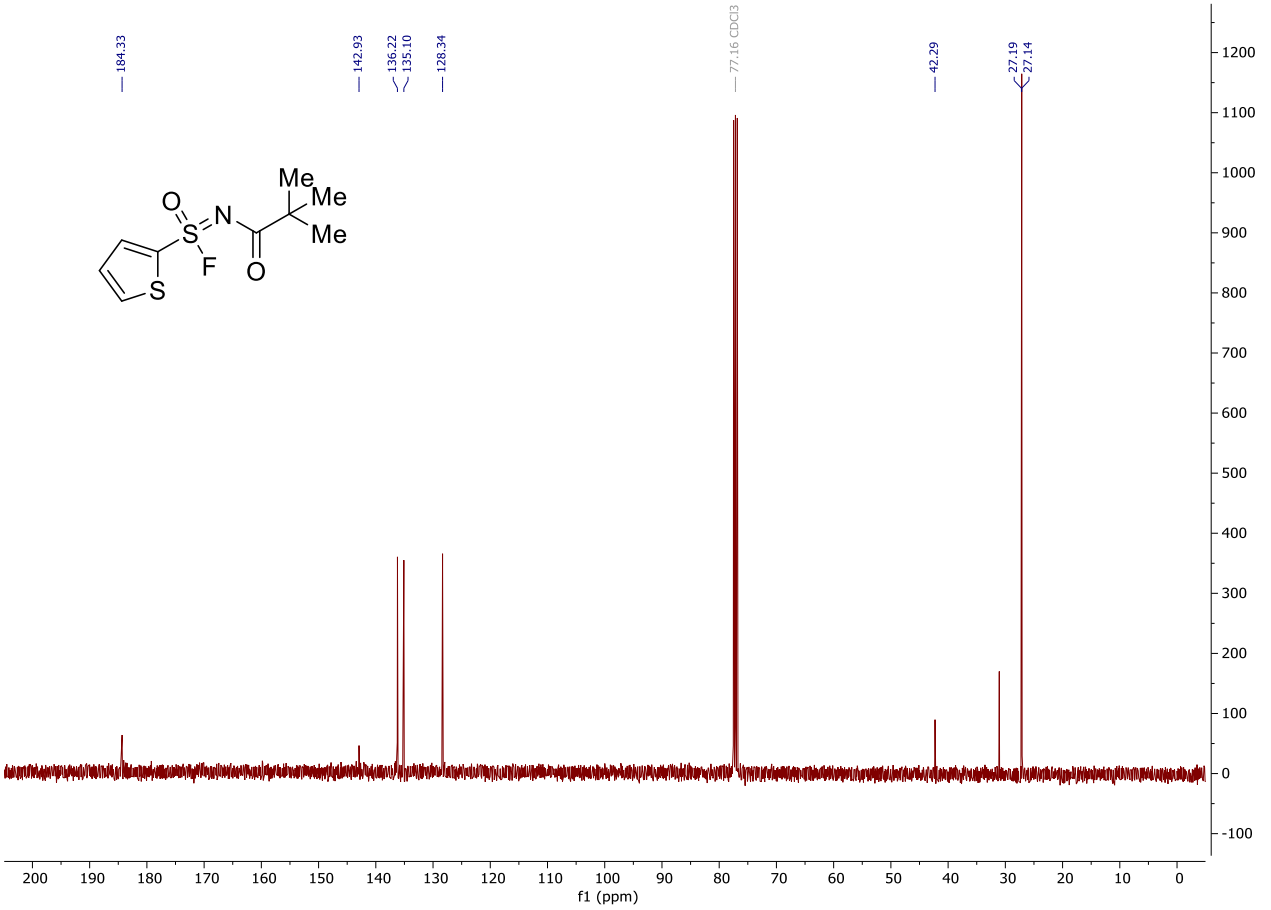

Me
O
S
N
F
O
Me
Me
Me
183.89
138.65
135.06
133.99
133.80
133.15
129.51
129.49
126.66
77.16 CDCl3
42.31
27.22
27.18
20.51
20.50
f1 (ppm)

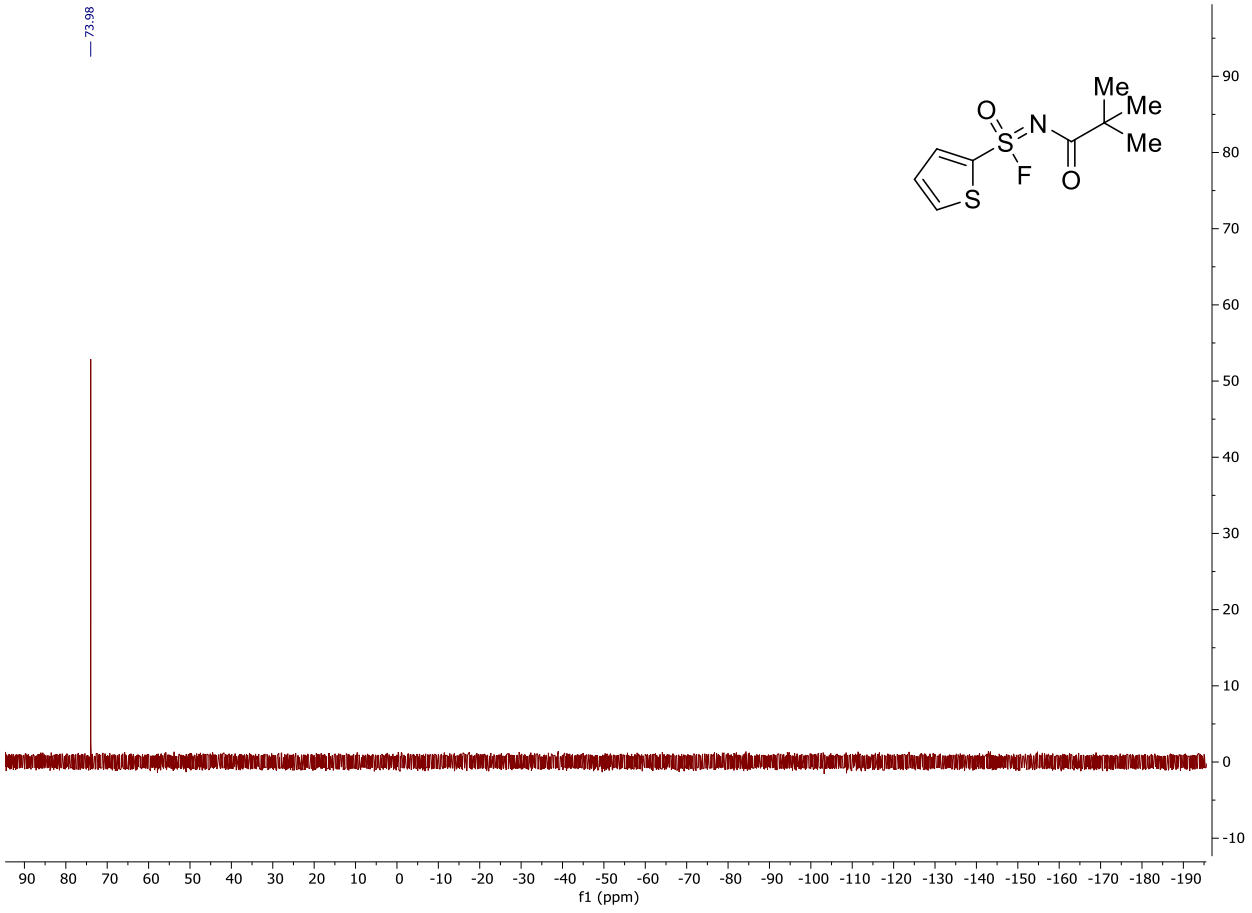


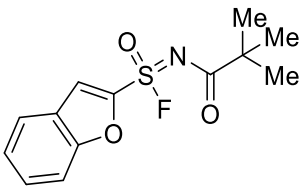


***N*-Pivaloylthiophene-2-sulfonimidoyl fluoride (70i)**

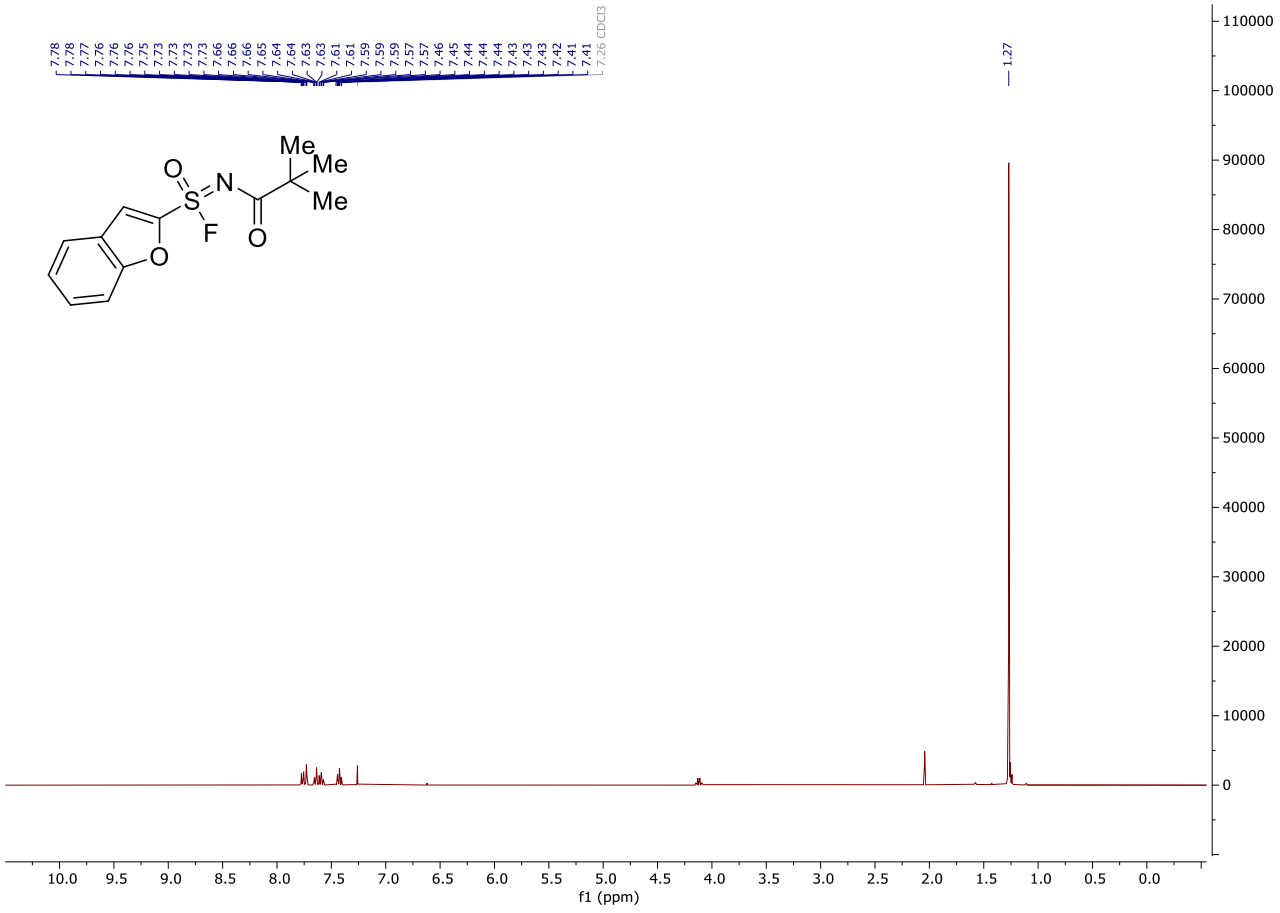

7.99
7.98
7.98
7.98
7.98
7.97
7.97
7.97
7.83
7.82
7.81
7.26 CDCl3
7.23
7.22
7.21
7.21
7.20
2.17
2.17
1.25
1.25
Me
Me
Me
O
N
S
F
O
S
0.88
0.81
0.89
9.00
f1 (ppm)

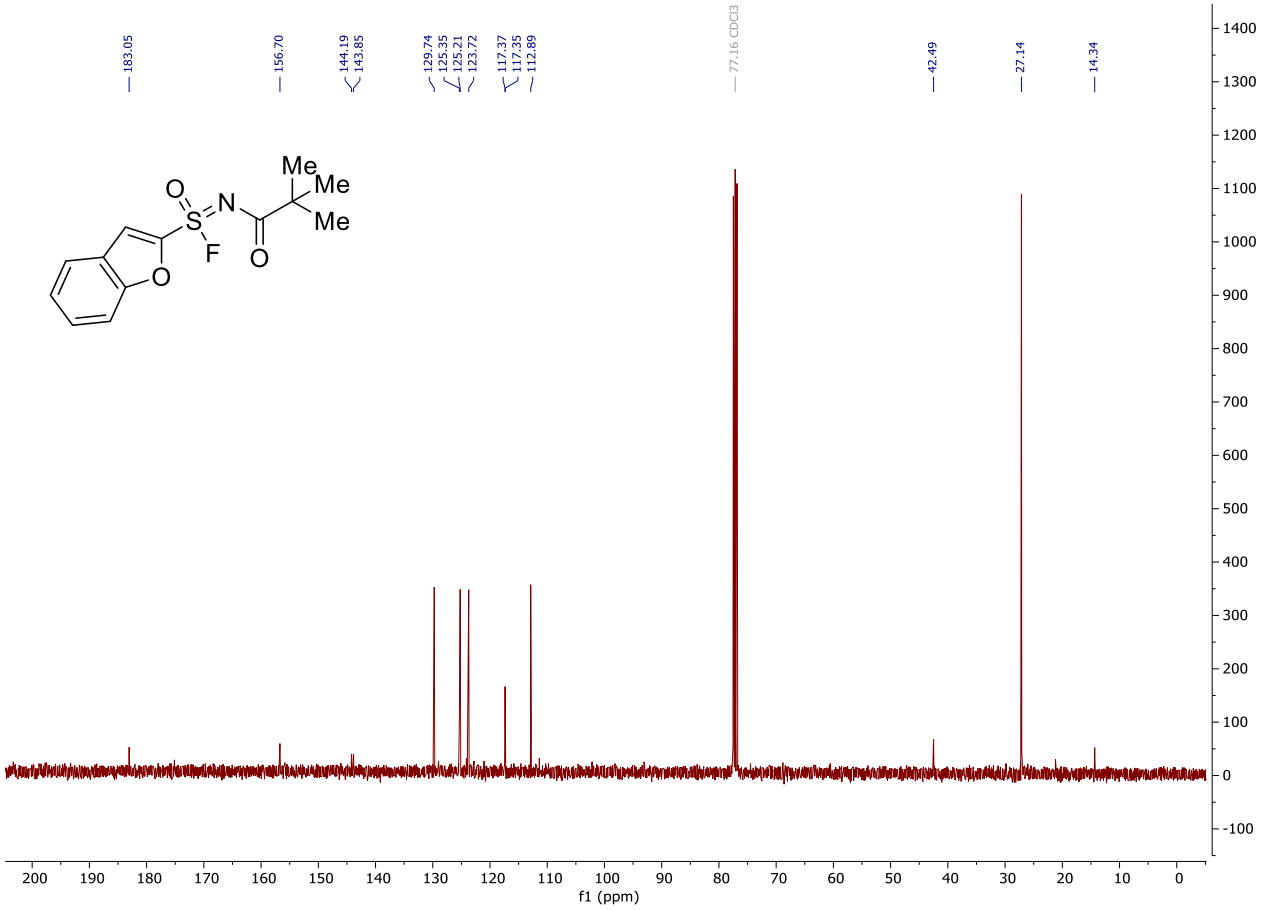

184.33
142.93
136.22
135.10
128.34
77.16 CDCl3
42.29
27.19
27.14
Me
Me
Me
O
N
S
F
O
S
f1 (ppm)

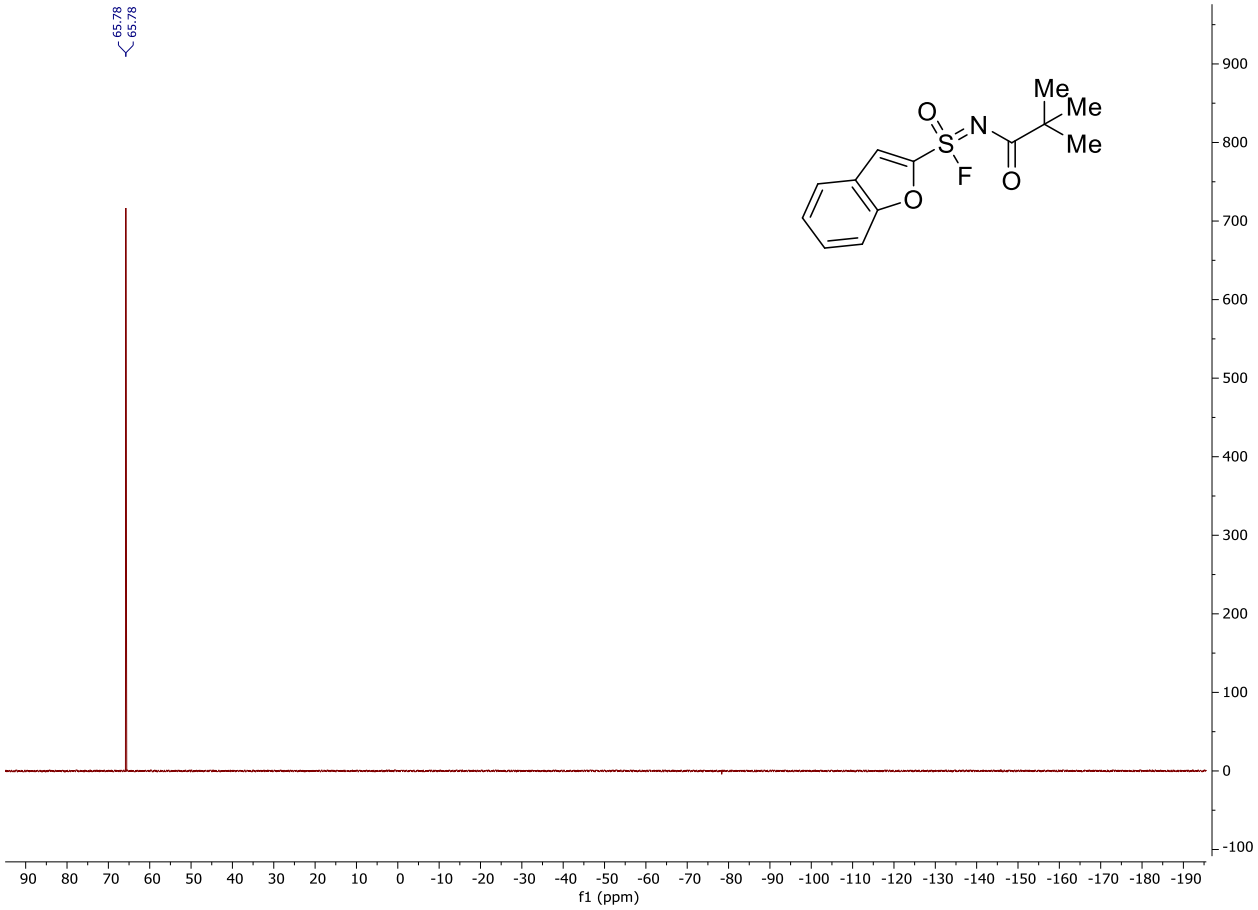


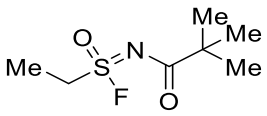


_N_-Pivaloylbenzofuran-2-sulfonimidoyl fluoride (70j)

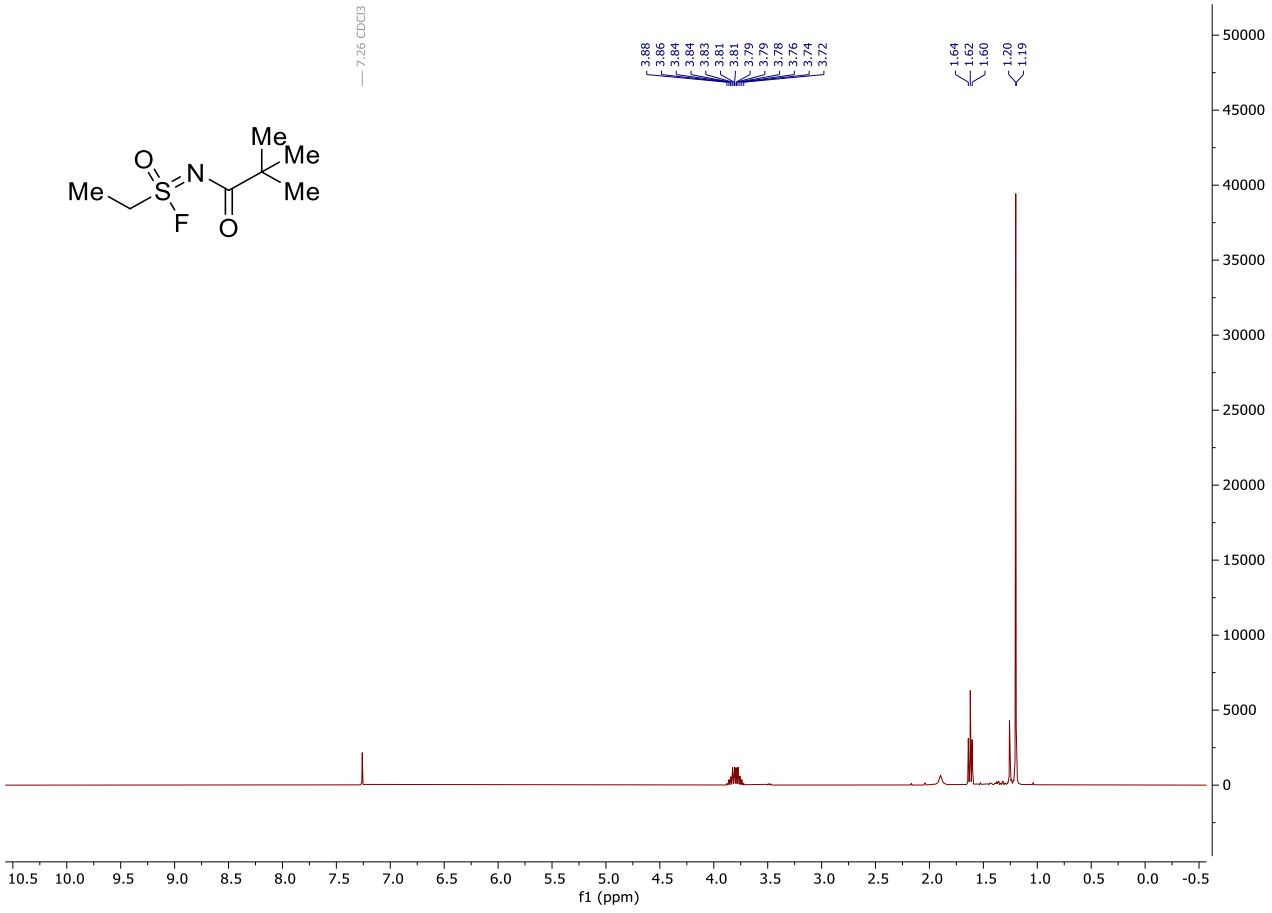

7.78
7.78
7.77
7.76
7.76
7.76
7.75
7.73
7.73
7.73
7.73
7.66
7.66
7.66
7.65
7.64
7.64
7.63
7.63
7.61
7.61
7.59
7.59
7.59
7.59
7.57
7.57
7.46
7.45
7.44
7.44
7.44
7.43
7.43
7.43
7.42
7.41
7.41
7.26 CDCl3
1.27
Me
Me
Me
O
S
N
F
O
O
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
10.0
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
0.5
0.0
f1 (ppm)

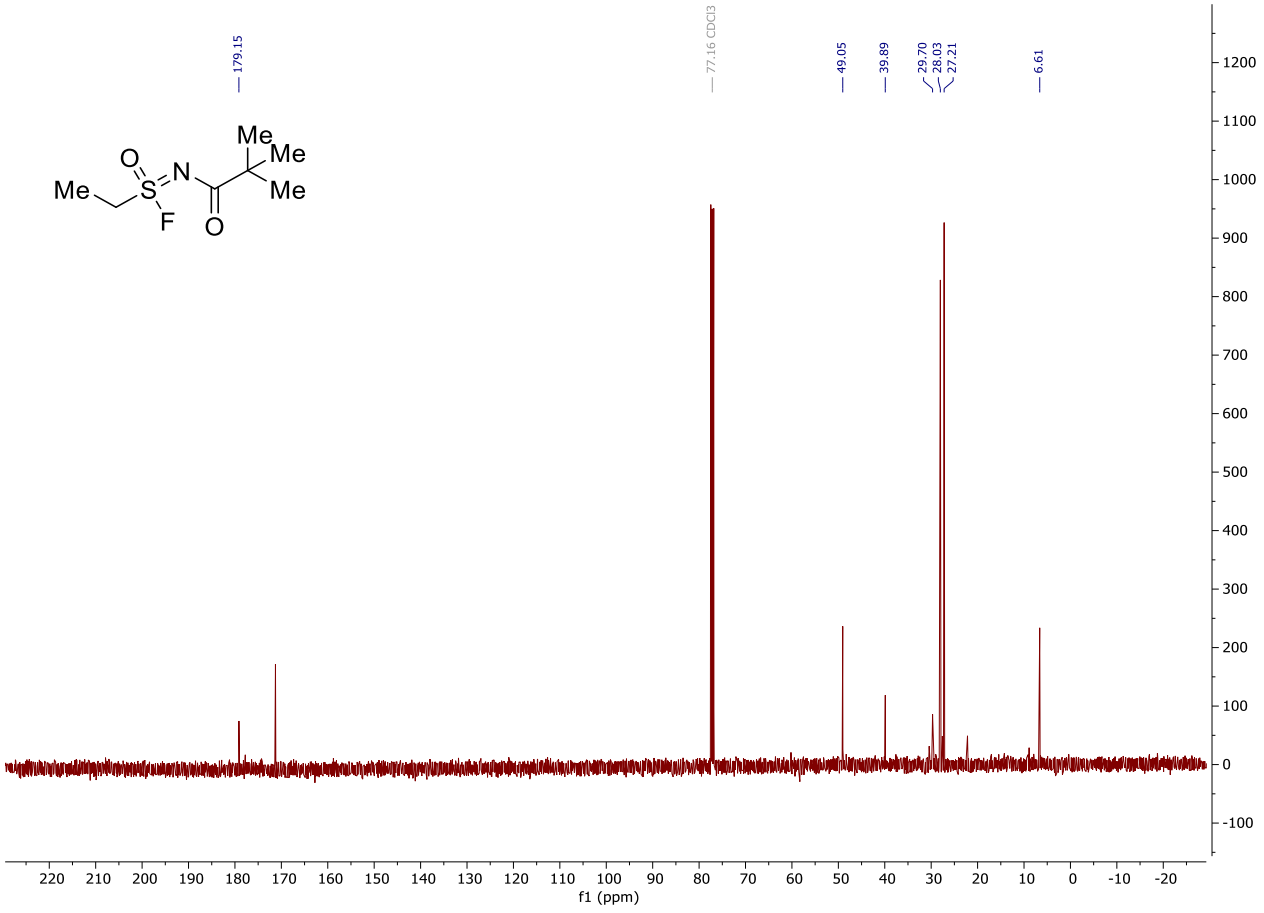

183.05
156.70
144.19
143.85
129.74
125.35
125.21
123.72
117.37
117.35
112.89
77.16 CDCl3
42.49
27.14
14.34
Me
Me
Me
O
S
N
F
O
O
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

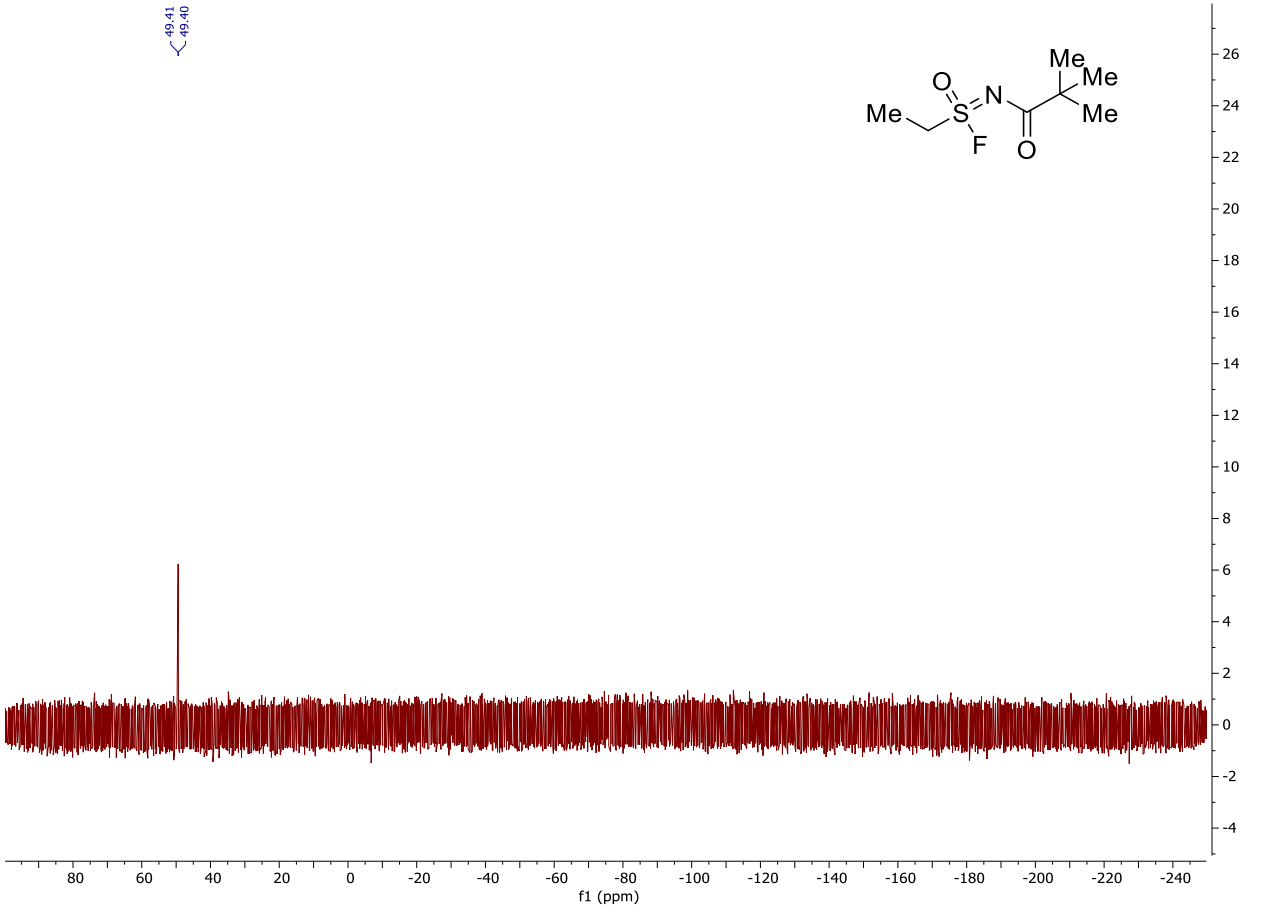


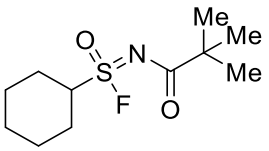


_N_-Pivaloylethanesulfonimidoyl fluoride (70k)

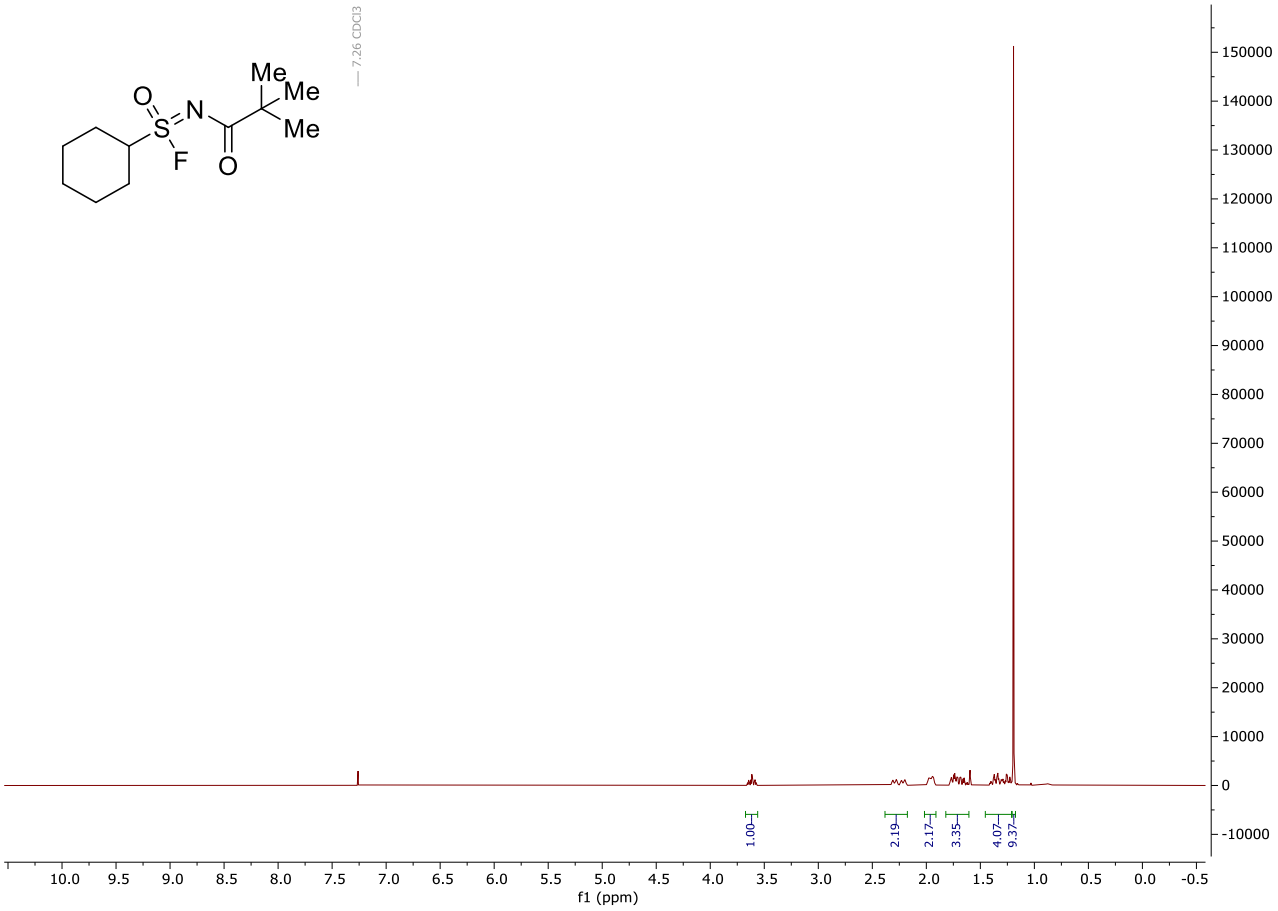

7.26 CDCl3
3.88
3.86
3.84
3.84
3.83
3.81
3.81
3.79
3.79
3.78
3.76
3.74
3.72
1.64
1.62
1.60
1.20
1.19
Me
Me
Me
O
N
S
Me
F
O
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

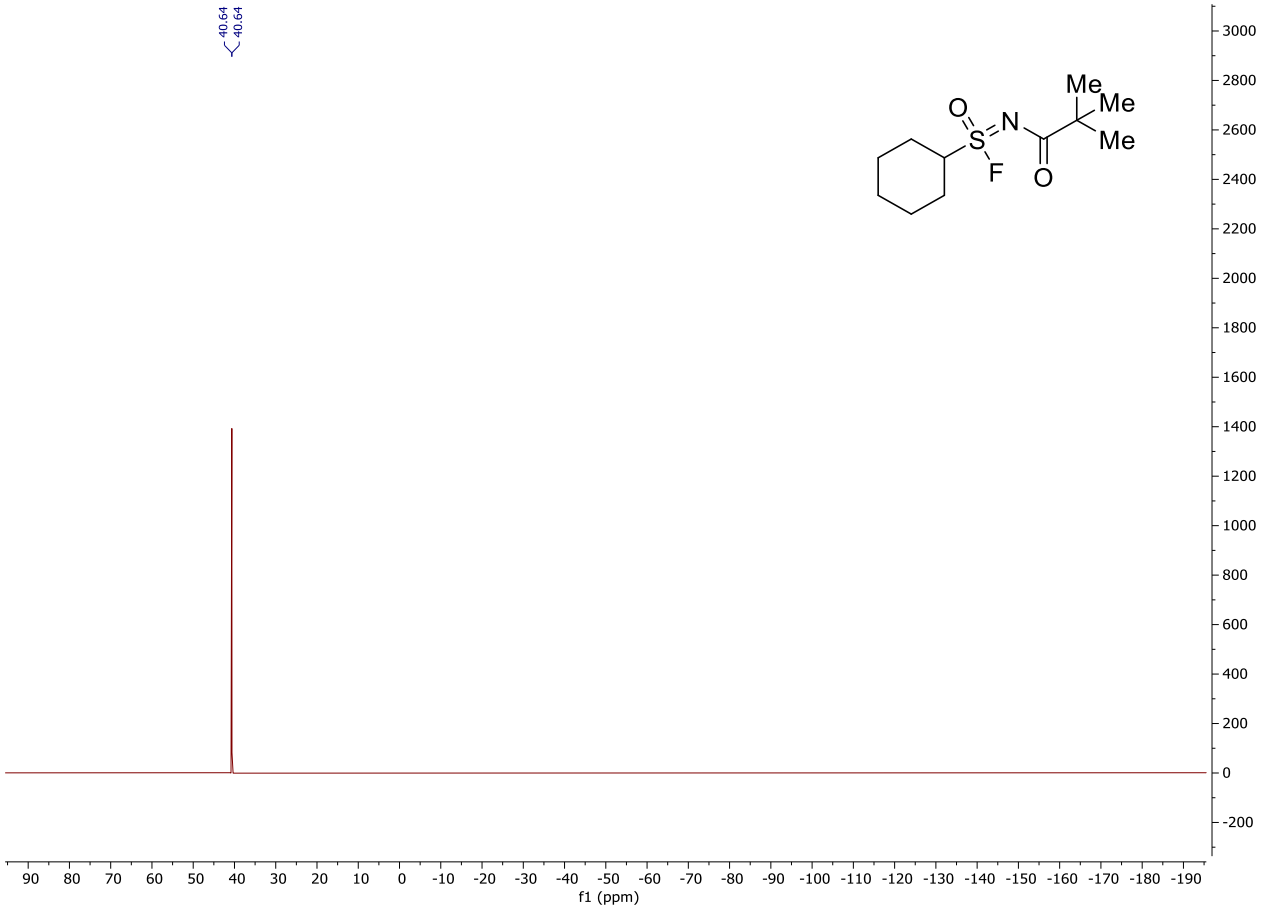

179.15
77.16 CDCl3
49.05
39.89
29.70
28.03
27.21
6.61
f1 (ppm)

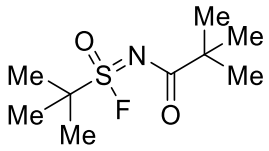

49.41
49.40
f1 (ppm)



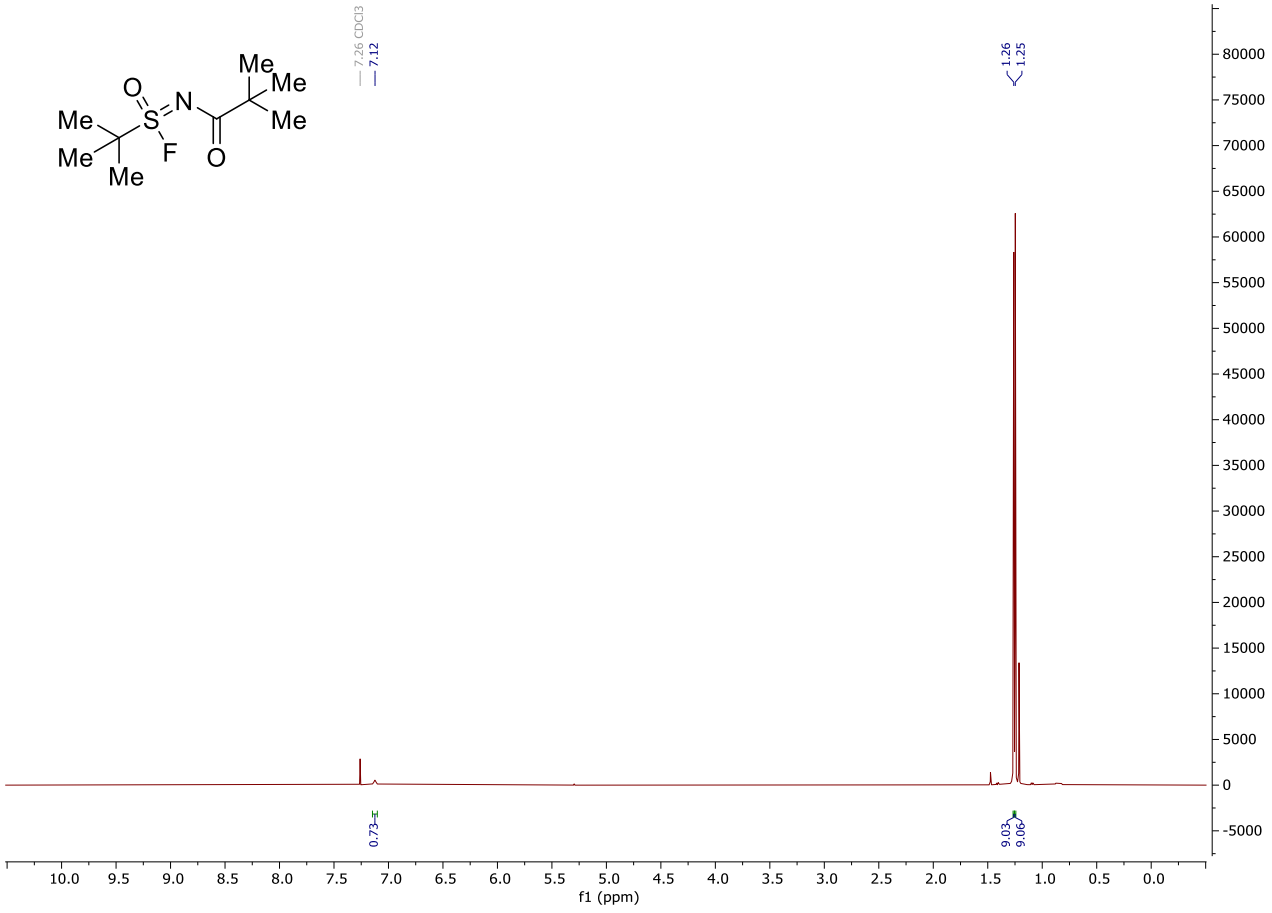
_N_-Pivaloylcyclohexanesulfonimidoyl fluoride (70l)

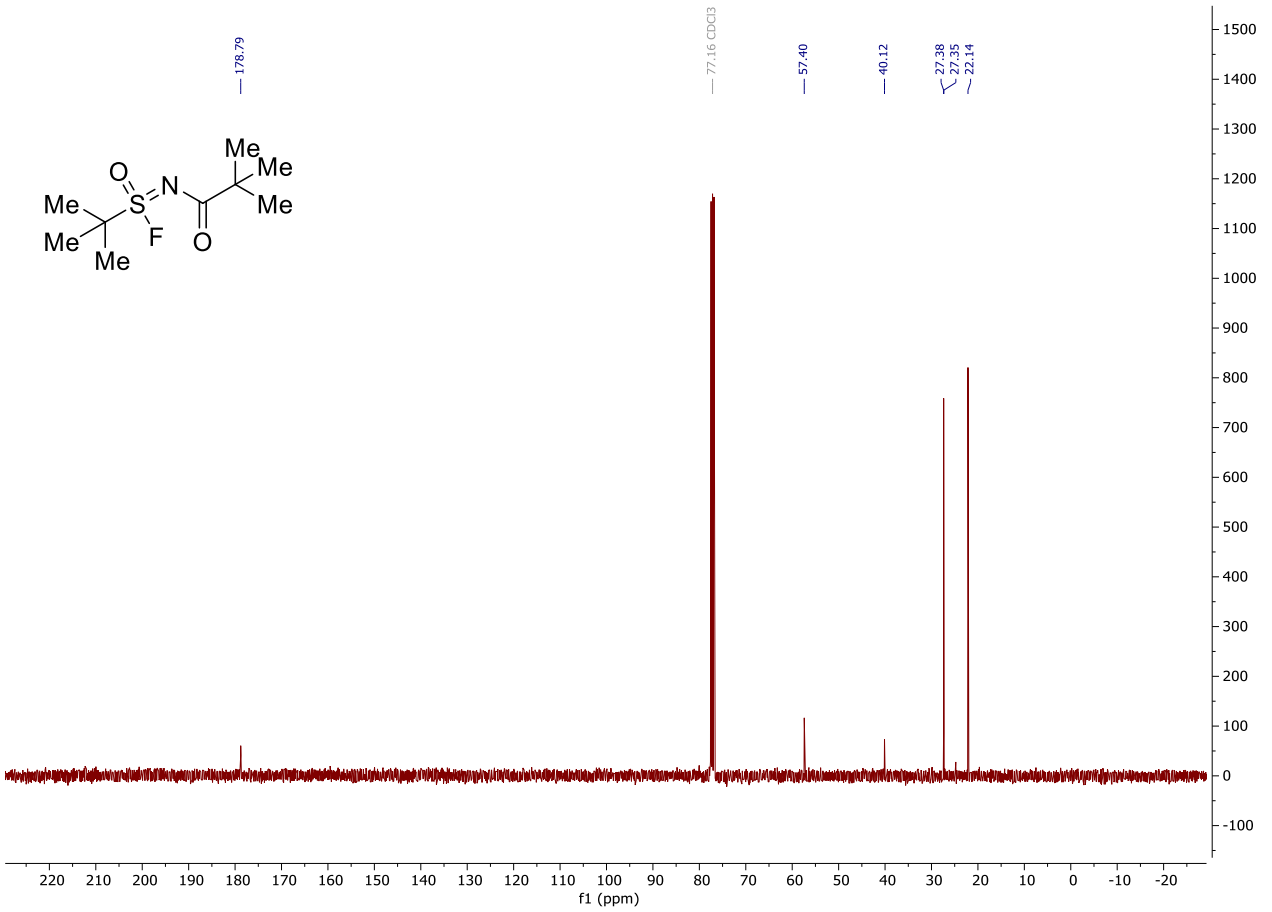


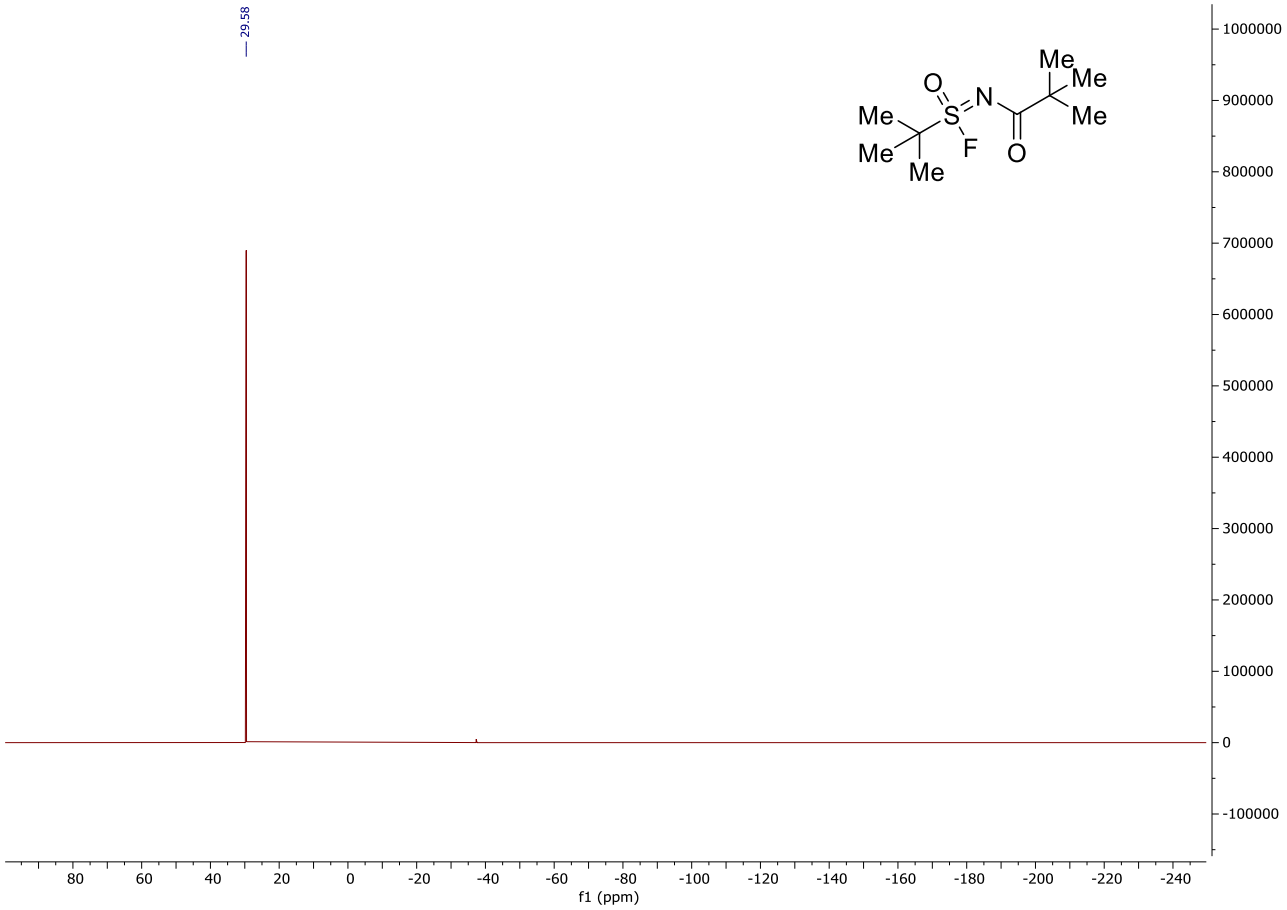


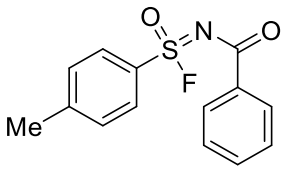


2-Methyl-*N*-pivaloylpropane-2-sulfonimidoyl fluoride (70m)

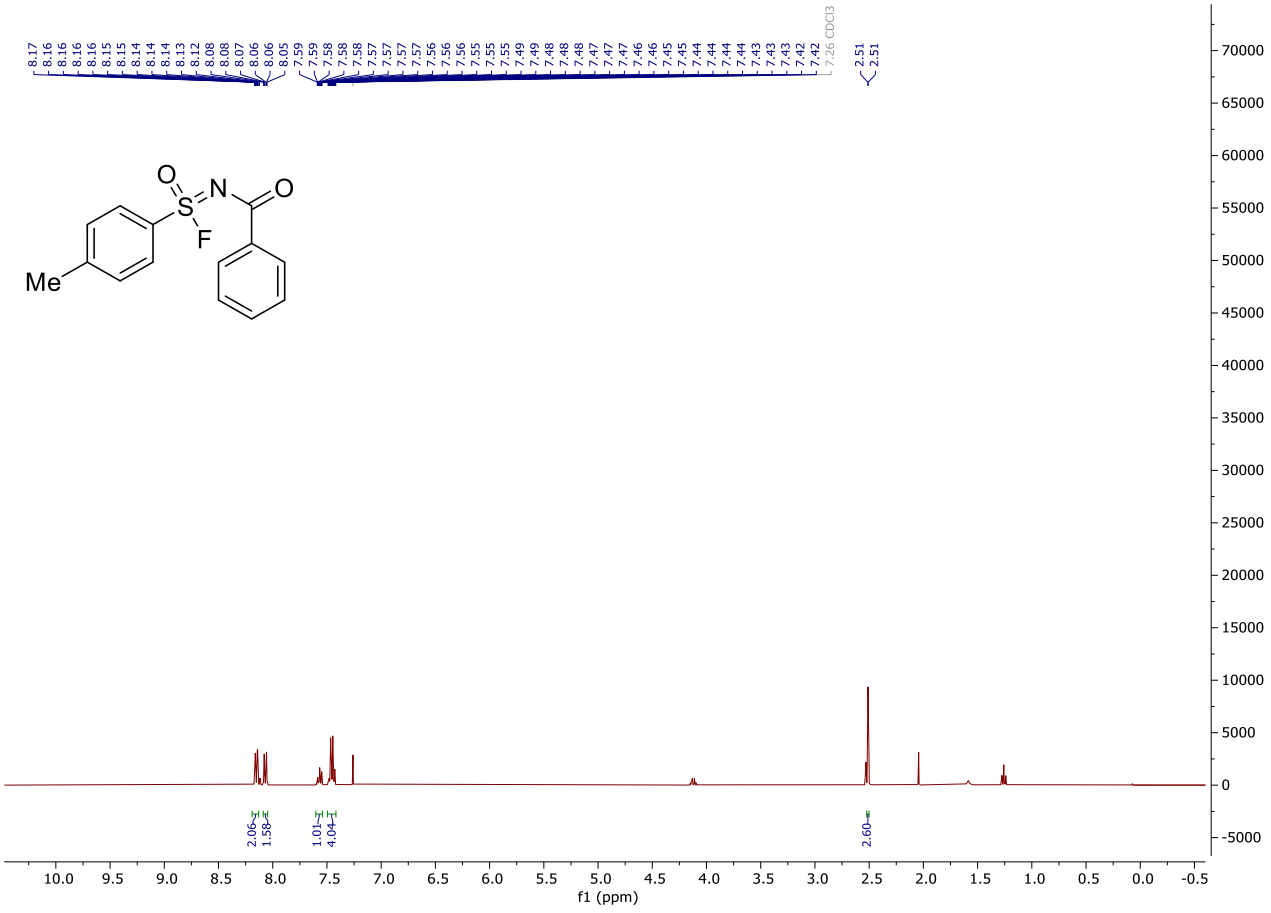

Me
Me
O
N
S
F
Me
Me
Me
O
7.26 CDCl3
7.12
1.26
1.25
0.73
9.03
9.06
f1 (ppm)

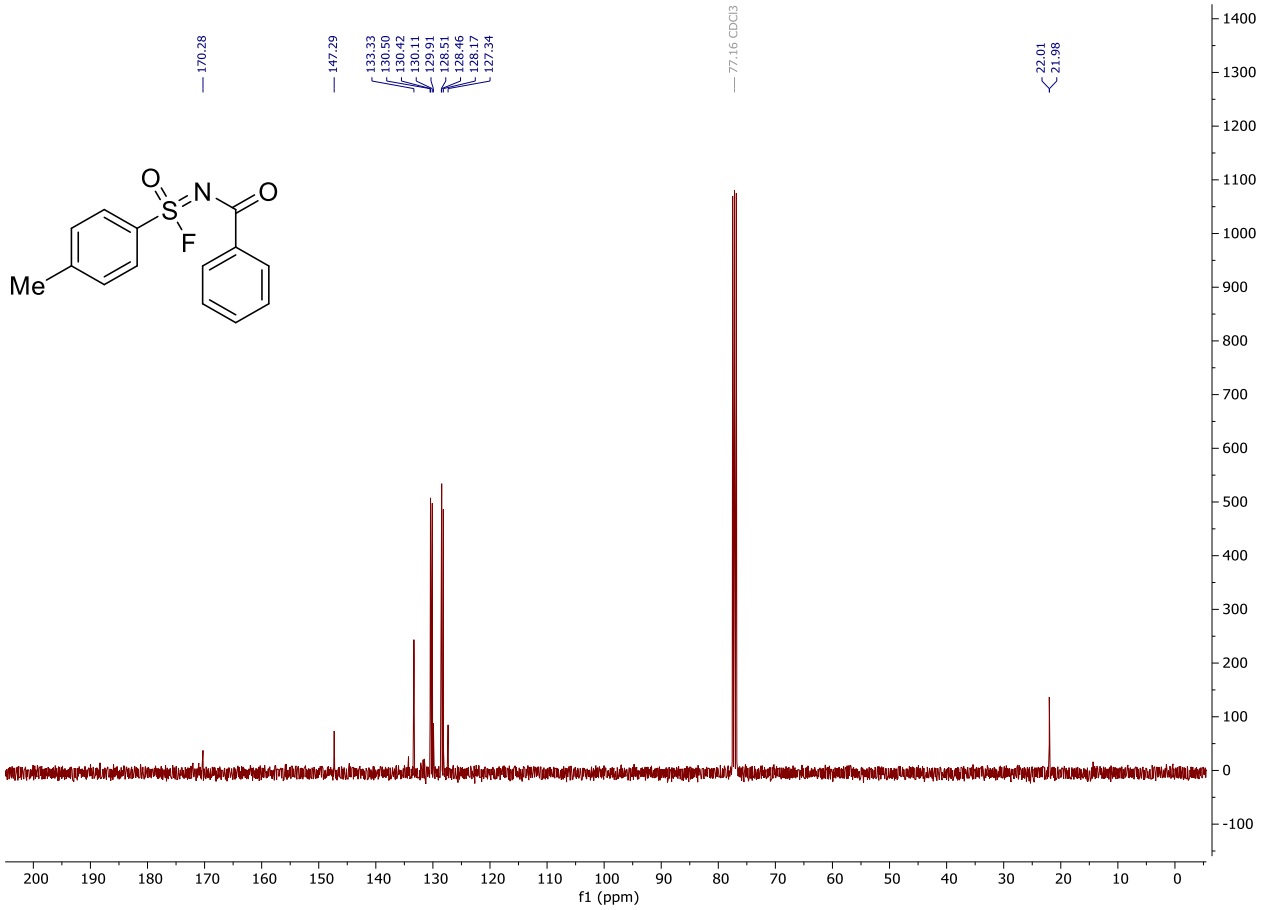

Me
Me
O
N
S
F
Me
Me
Me
O
178.79
77.16 CDCl3
57.40
40.12
27.38
27.35
22.14
f1 (ppm)

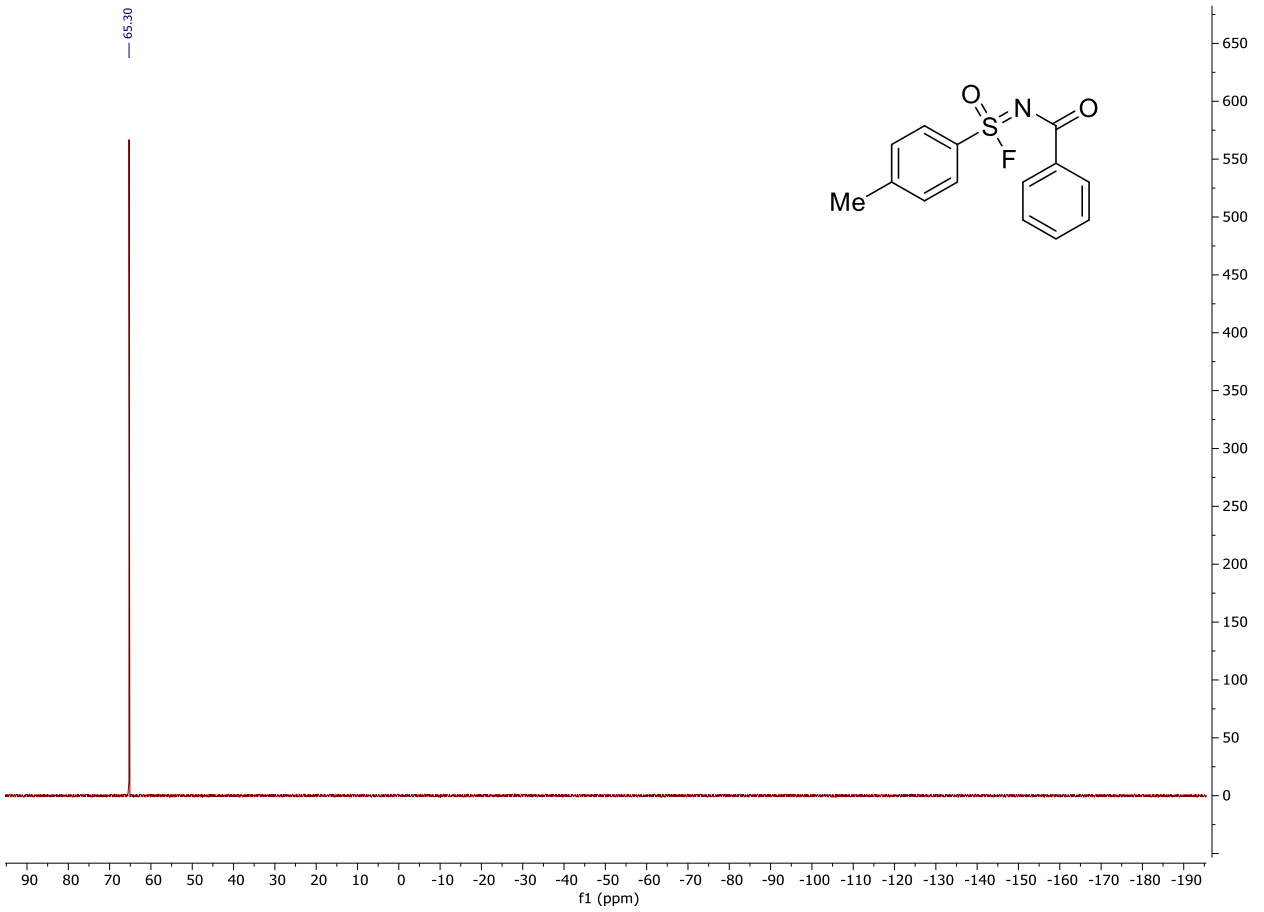


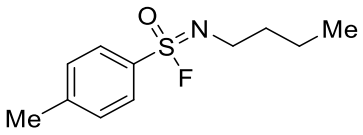


_N_-Benzoyl-4-methylbenzenesulfonimidoyl fluoride (42e)

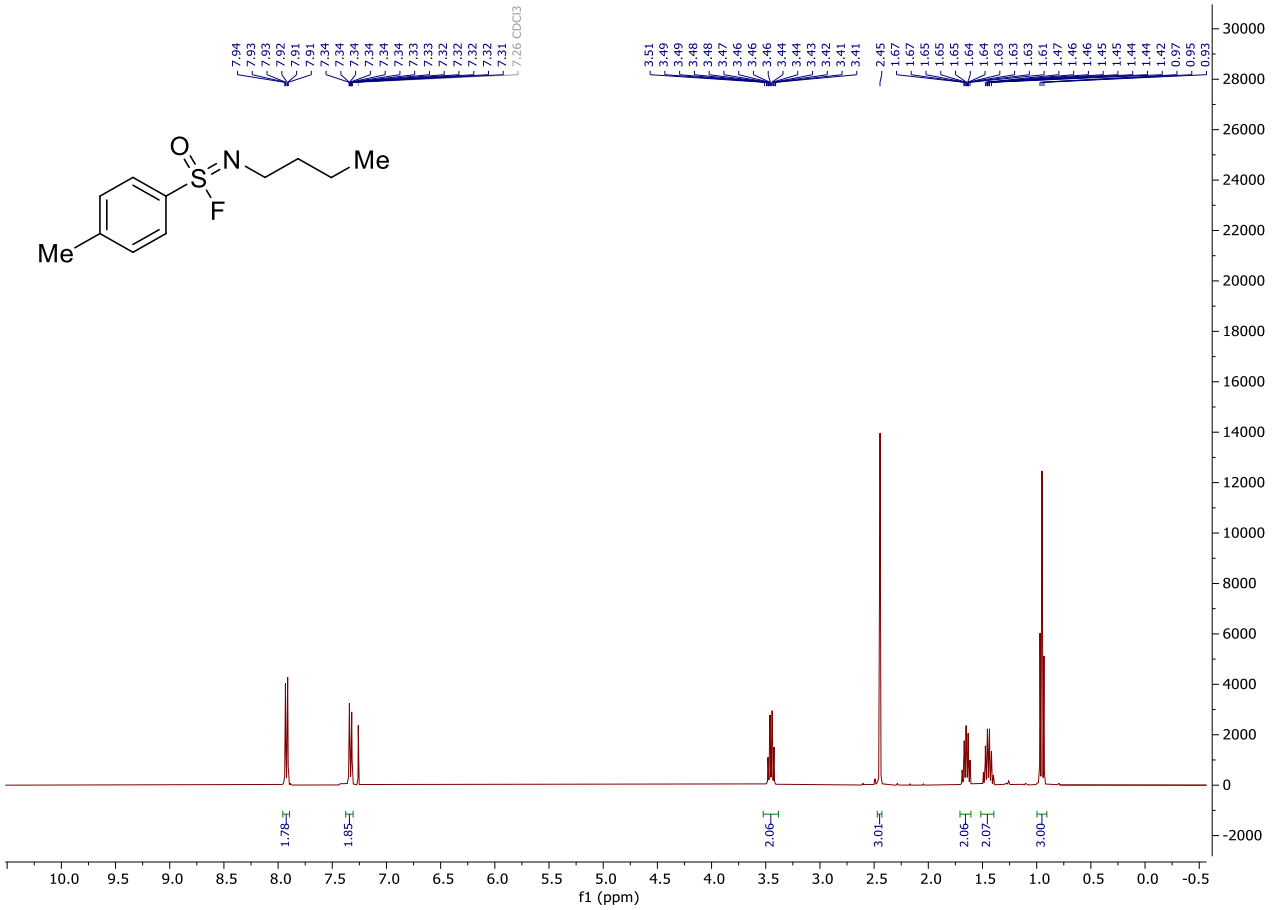

8.17 8.16 8.16 8.16 8.16 8.15 8.15 8.14 8.14 8.14 8.13 8.12 8.08 8.08 8.07 8.06 8.06 8.05
7.59 7.59 7.58 7.58 7.58 7.57 7.57 7.57 7.57 7.56 7.56 7.56 7.55 7.55 7.55 7.49 7.49 7.48 7.48 7.48 7.47 7.47 7.47 7.46 7.46 7.45 7.45 7.44 7.44 7.44 7.43 7.43 7.43 7.42 7.42
7.26 CDCl3
2.51 2.51
O
S
N
O
F
Me
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
2.06
1.58
1.01
4.04
2.60
10.0 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 0.5 0.0 -0.5
f1 (ppm)

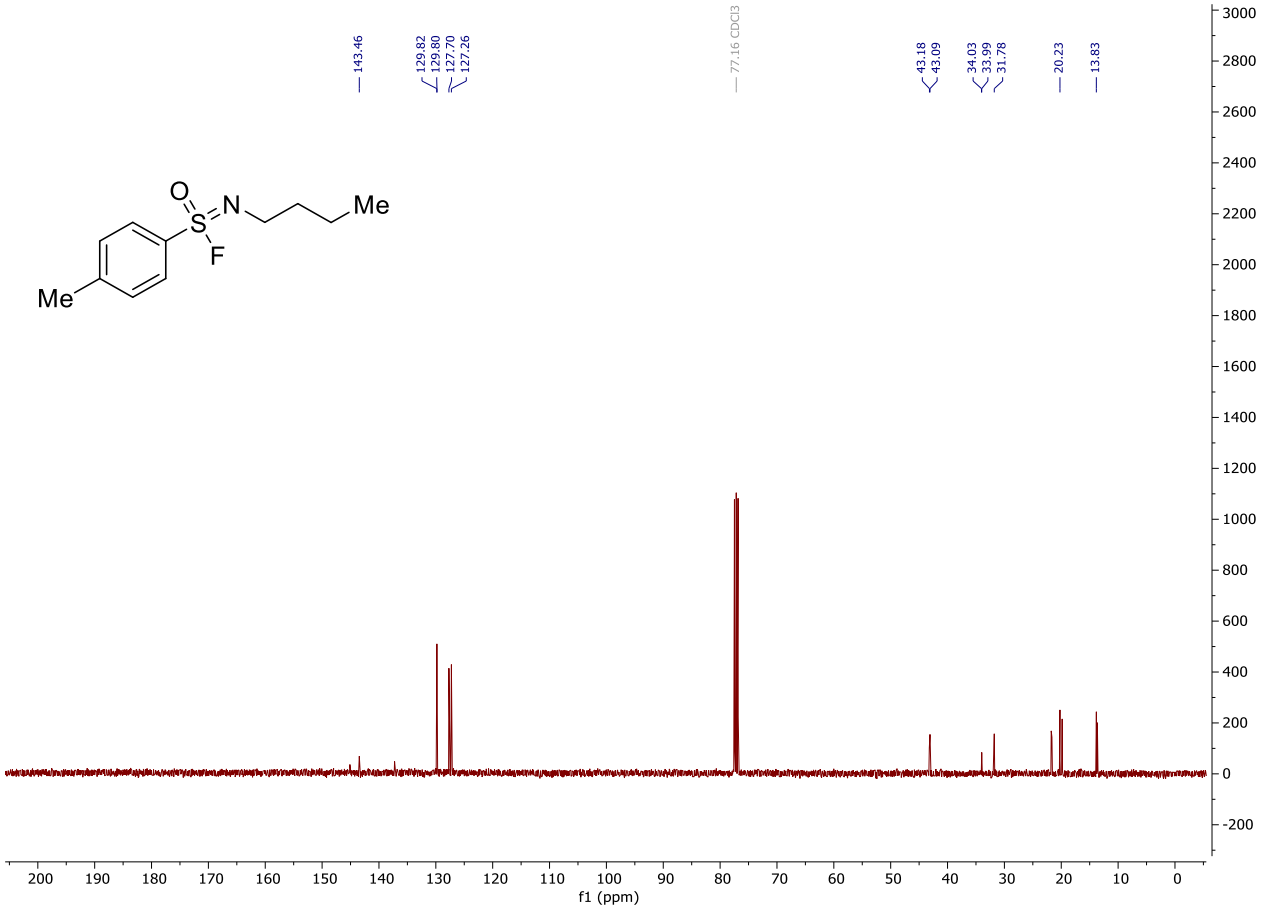

170.28
147.29
133.33
130.50
130.42
130.11
129.91
128.51
128.46
128.17
127.34
77.16 CDCl3
22.01
21.98
O
N
O
S
F
Me
f1 (ppm)

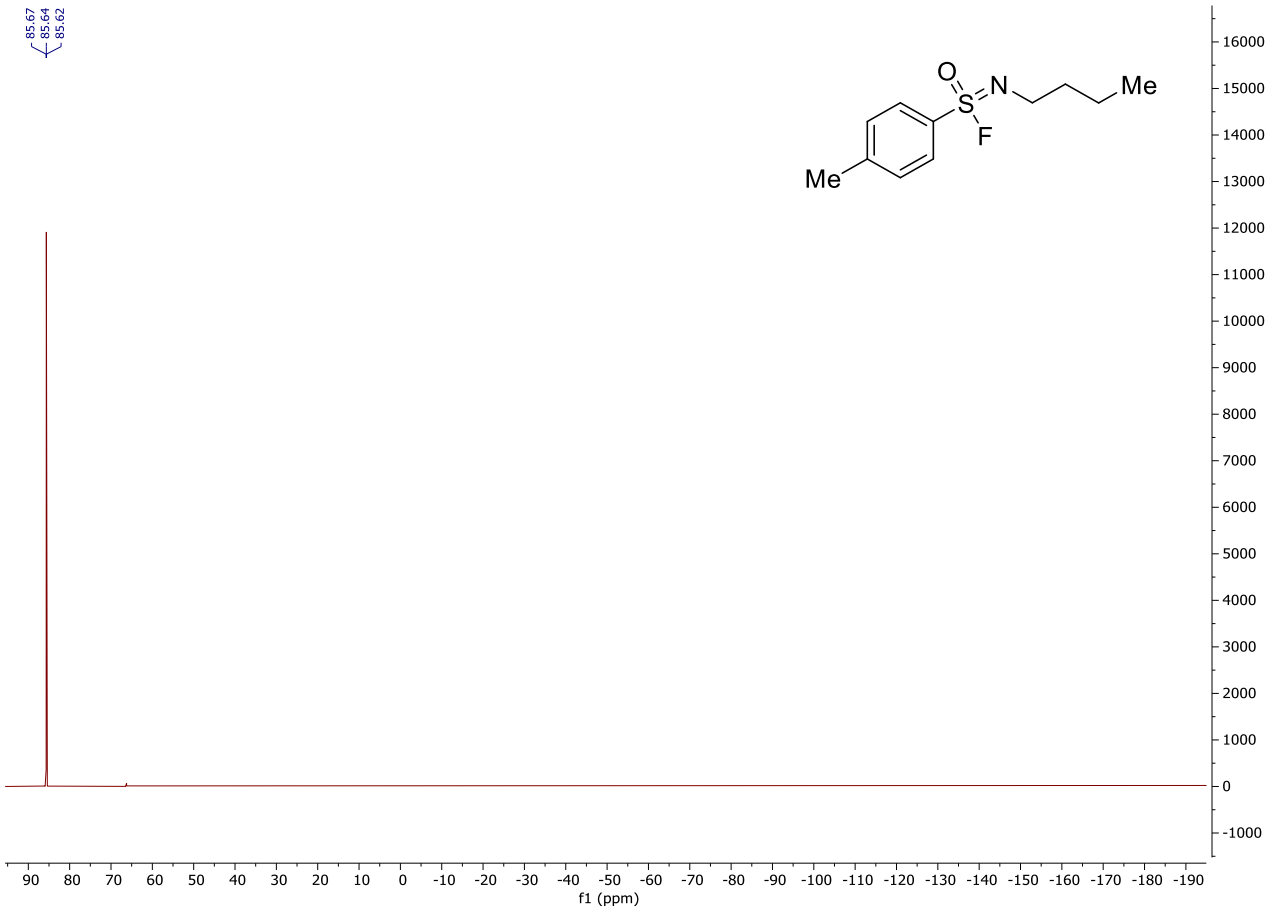

65.30
O
N
O
S
F
Me
f1 (ppm)

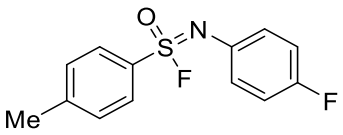


_N_-Butyl-4-methylbenzenesulfonimidoyl fluoride (42f)

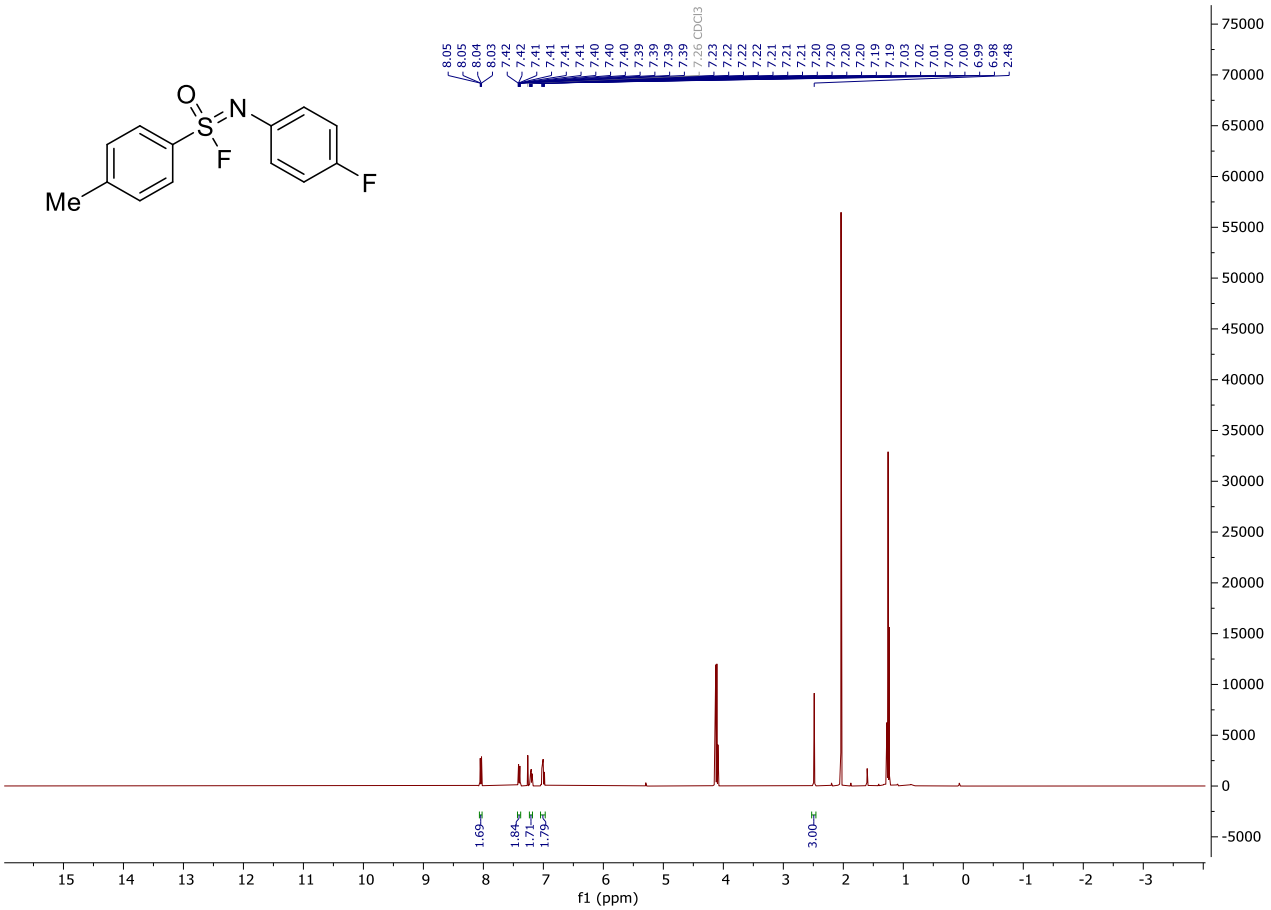


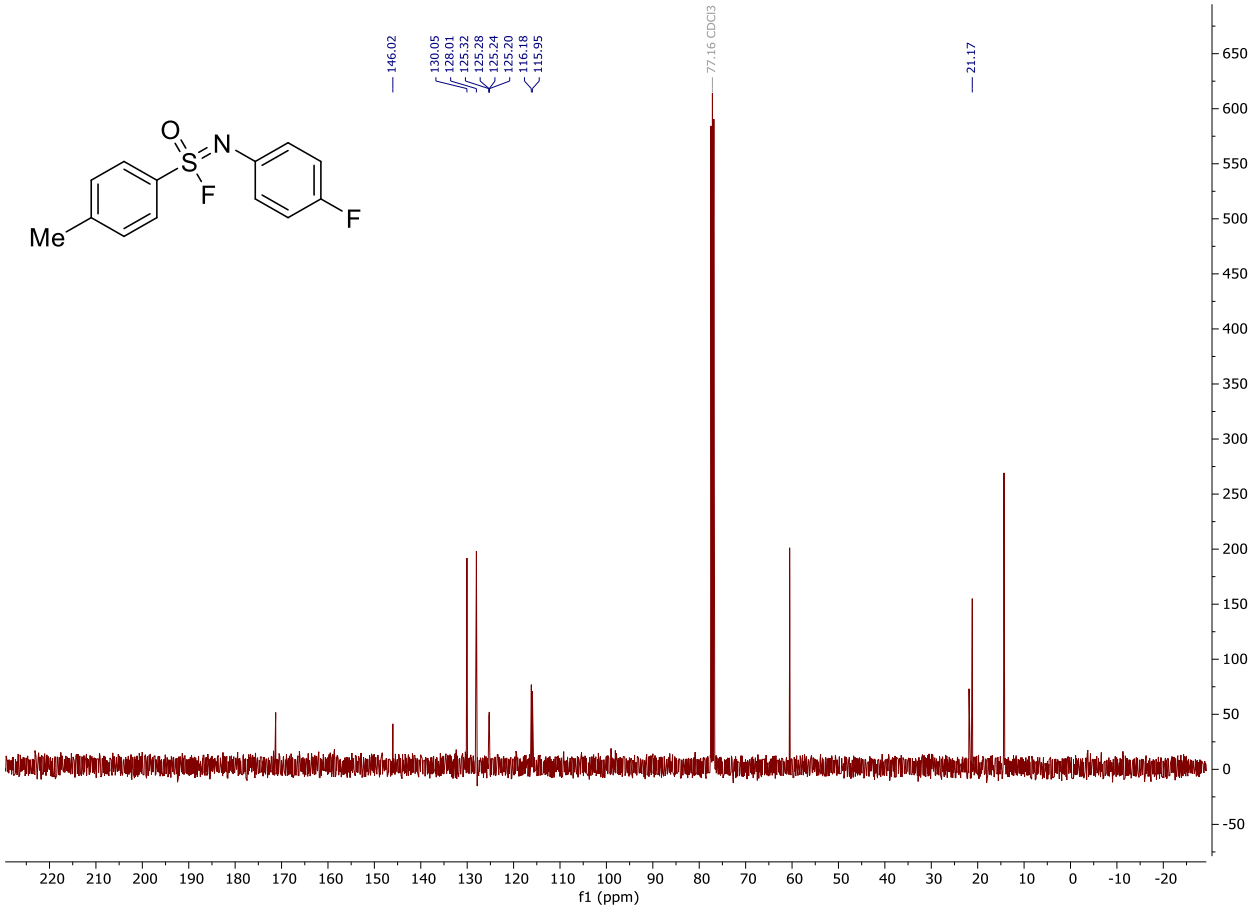

143.46
129.82
129.80
127.70
127.26
77.16 CDCl3
43.18
43.09
34.03
33.99
31.78
20.23
13.83
O
S
N
F
Me
Me
f1 (ppm)

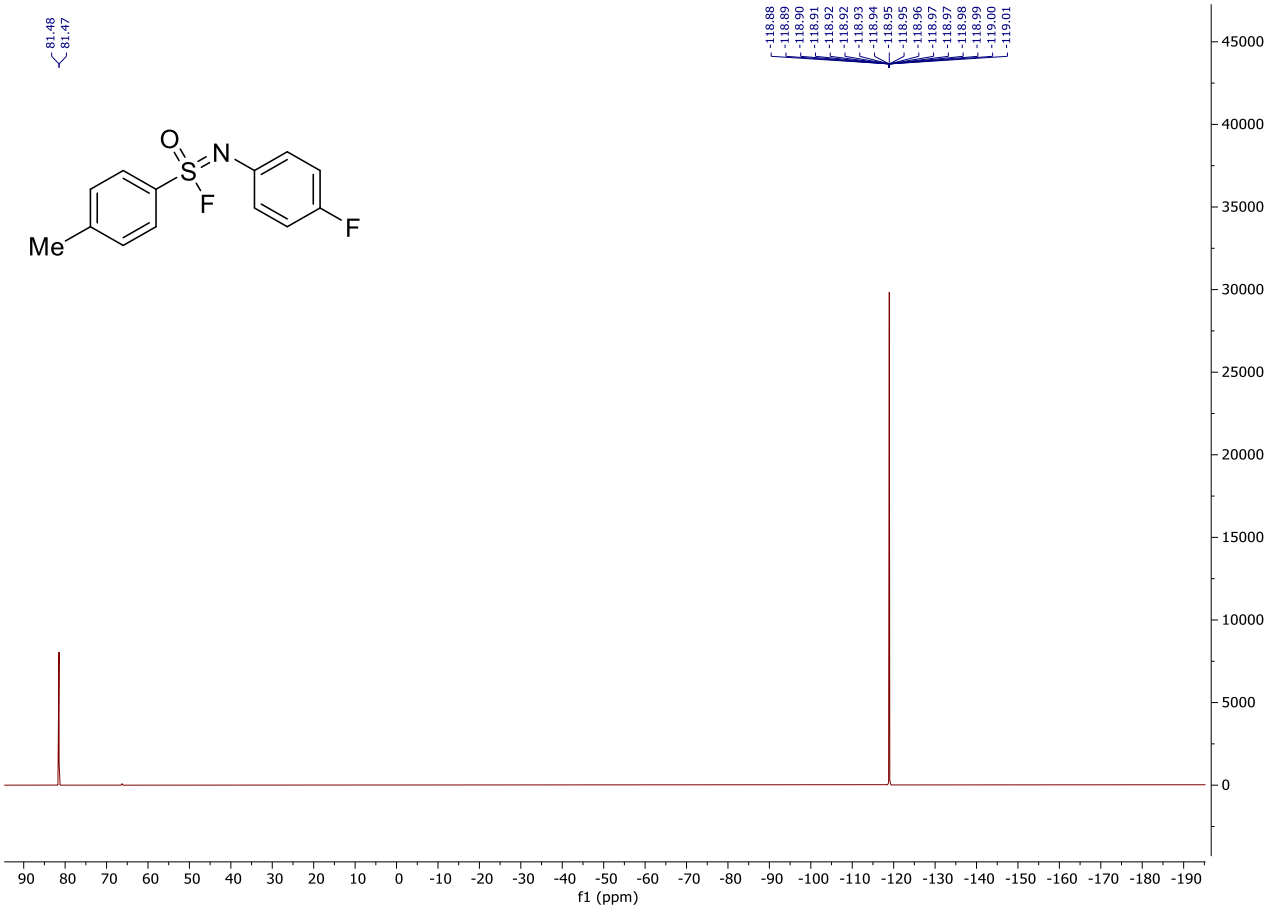

85.67
85.64
85.62
O
S
N
F
Me
Me
f1 (ppm)



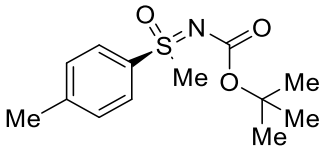
_N_-(4-Fluorophenyl)-4-methylbenzenesulfonimidoyl fluoride (42g)



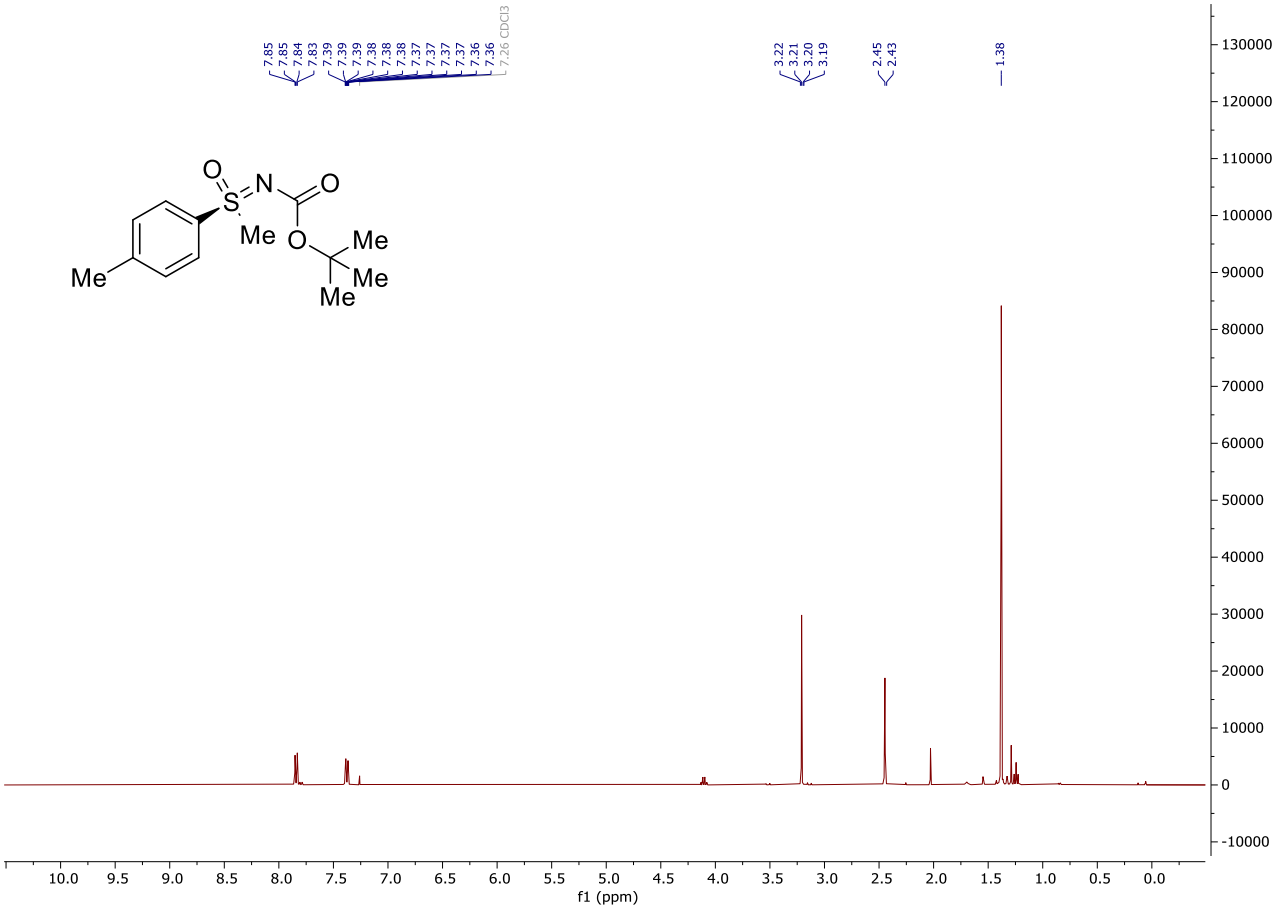

146.02
130.05
128.01
125.32
125.28
125.24
125.20
116.18
115.95
77.16 CDCl3
21.17
O
S
N
F
Me
F
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

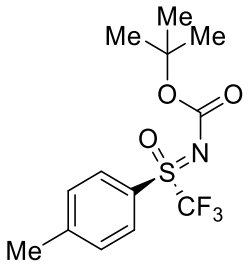

81.48
81.47
-118.88
-118.89
-118.90
-118.91
-118.92
-118.92
-118.93
-118.94
-118.95
-118.95
-118.96
-118.97
-118.97
-118.98
-118.99
-119.00
-119.01
O
S
N
F
F
Me
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

8.1.6 Derivatisations of sulfonimidoyl fluorides

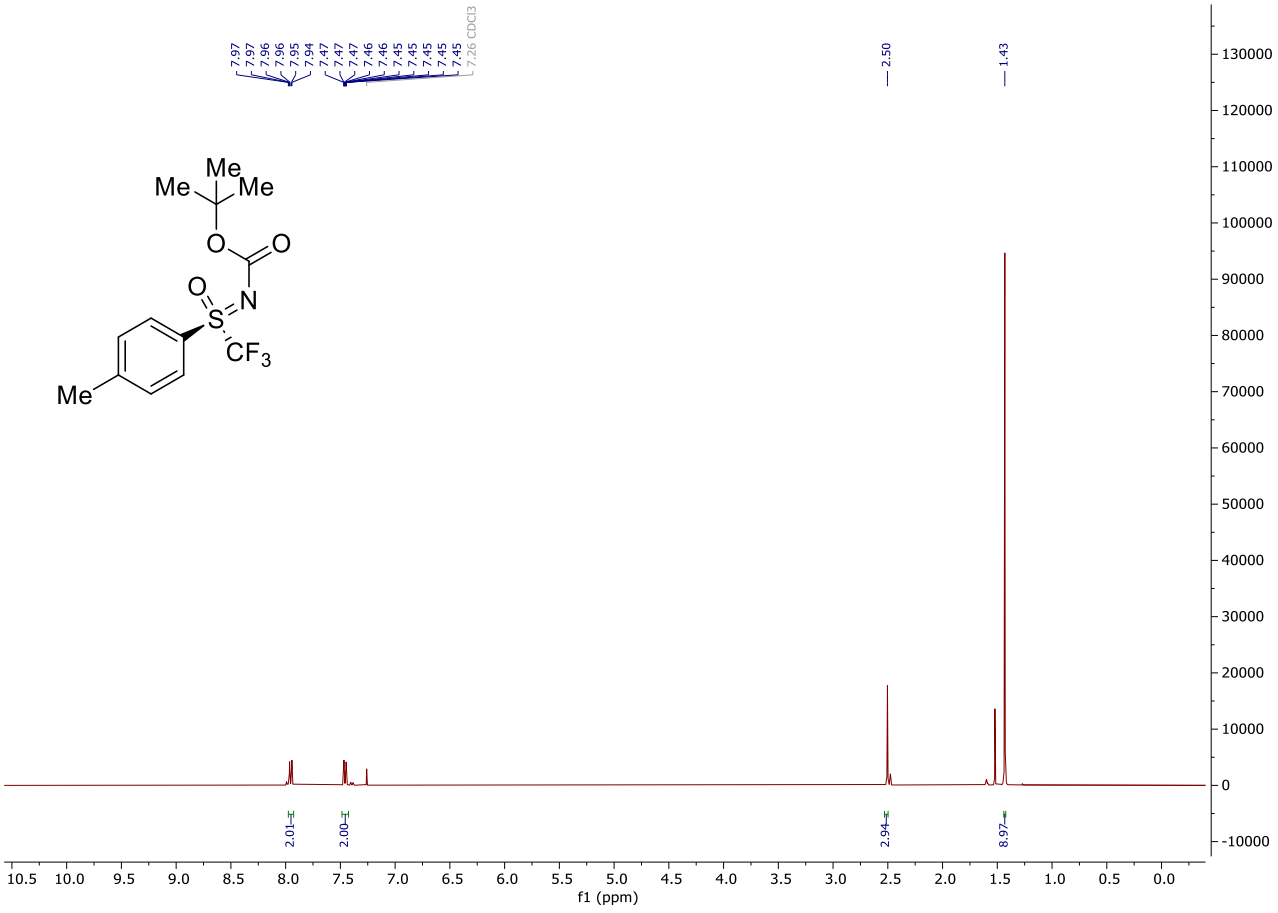


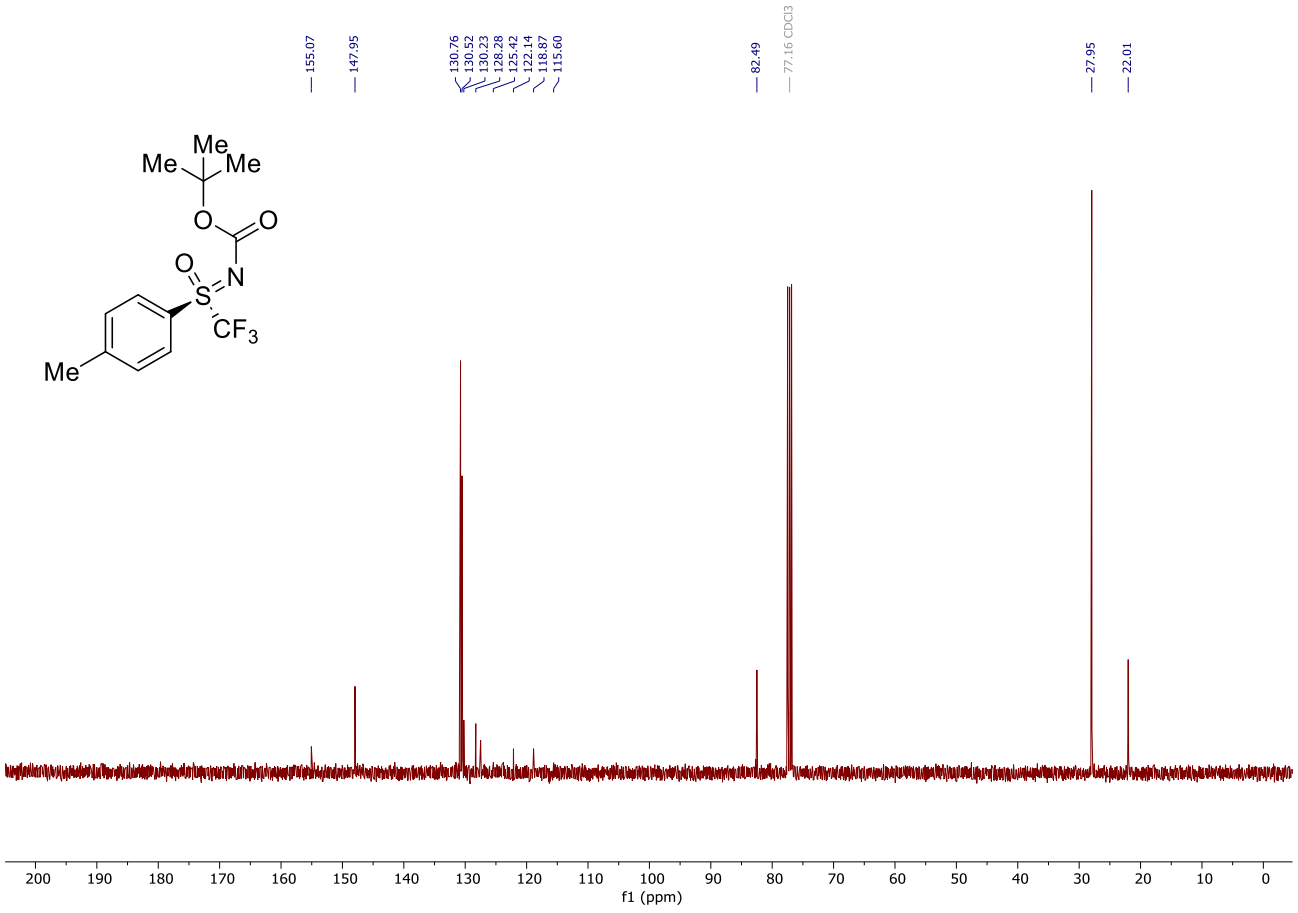
***tert*-Butyl (*R*)-(methyl(oxo)(*p*-tolyl)-λ^6-sulfaneylidene)carbamate ((*R*)-(24e))**

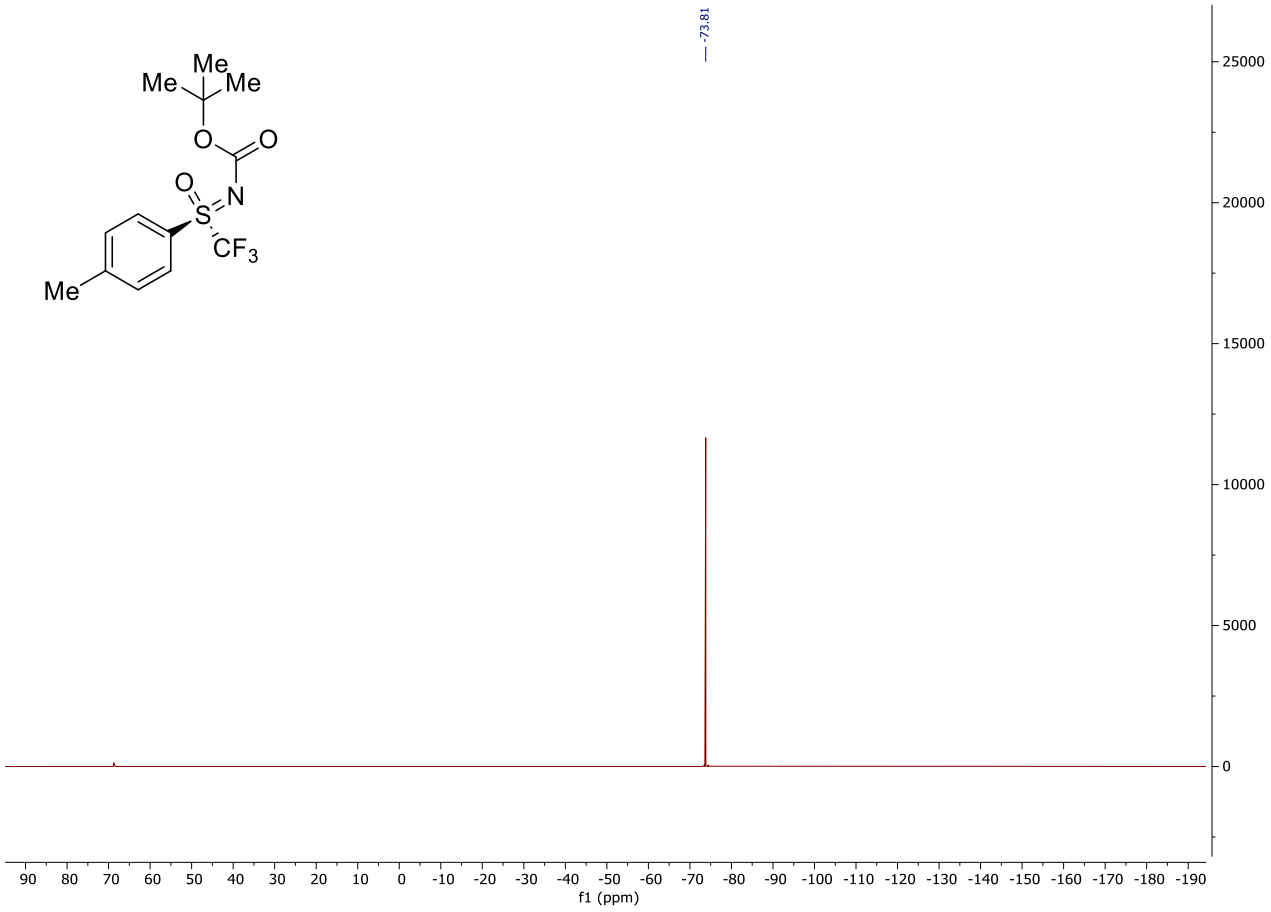




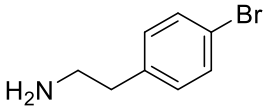
tert-Butyl (_R_)-(methyl(oxo)(_p_-tolyl)-λ^6-sulfaneylidene)carbamate ((_R_)-(27c))



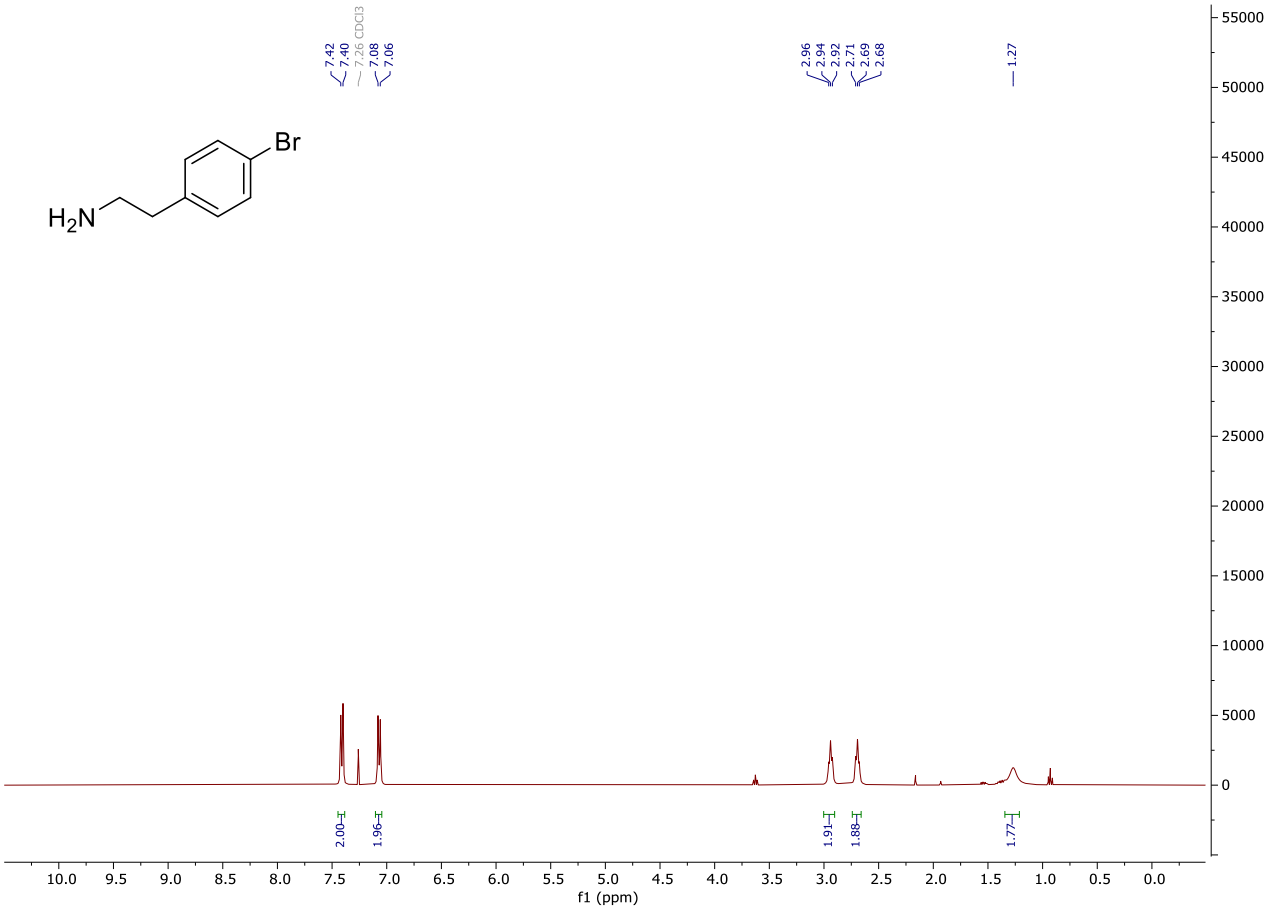

155.07
147.95
130.76
130.52
130.23
128.28
125.42
122.14
118.87
115.60
82.49
77.16 CDCl3
27.95
22.01
Me
Me
Me
O
O
O
N
S
CF3
Me
f1 (ppm)

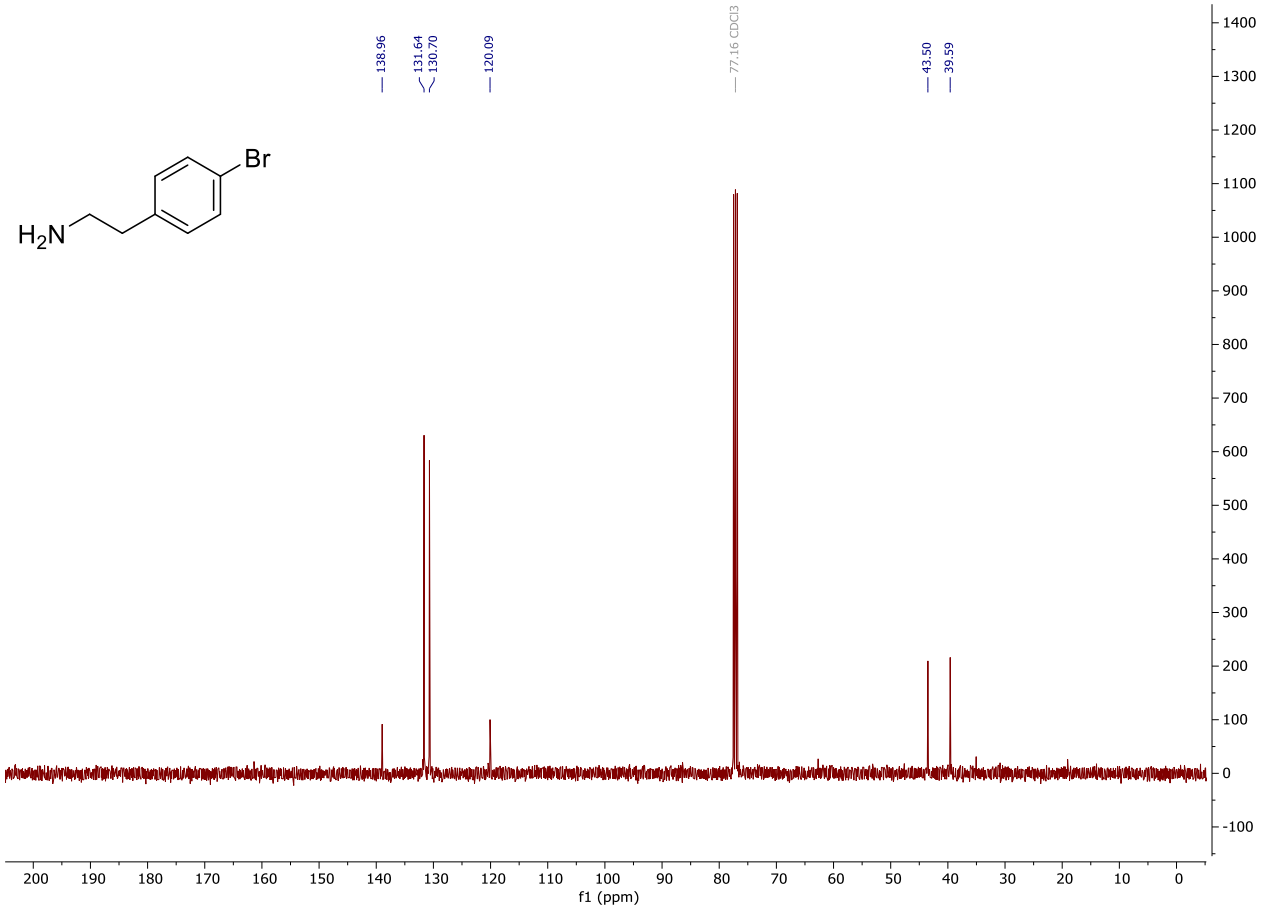

-73.81
Me
Me
Me
O
O
O
N
S
CF3
Me
f1 (ppm)

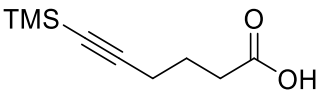
8.1.7 Preparation of probe compounds



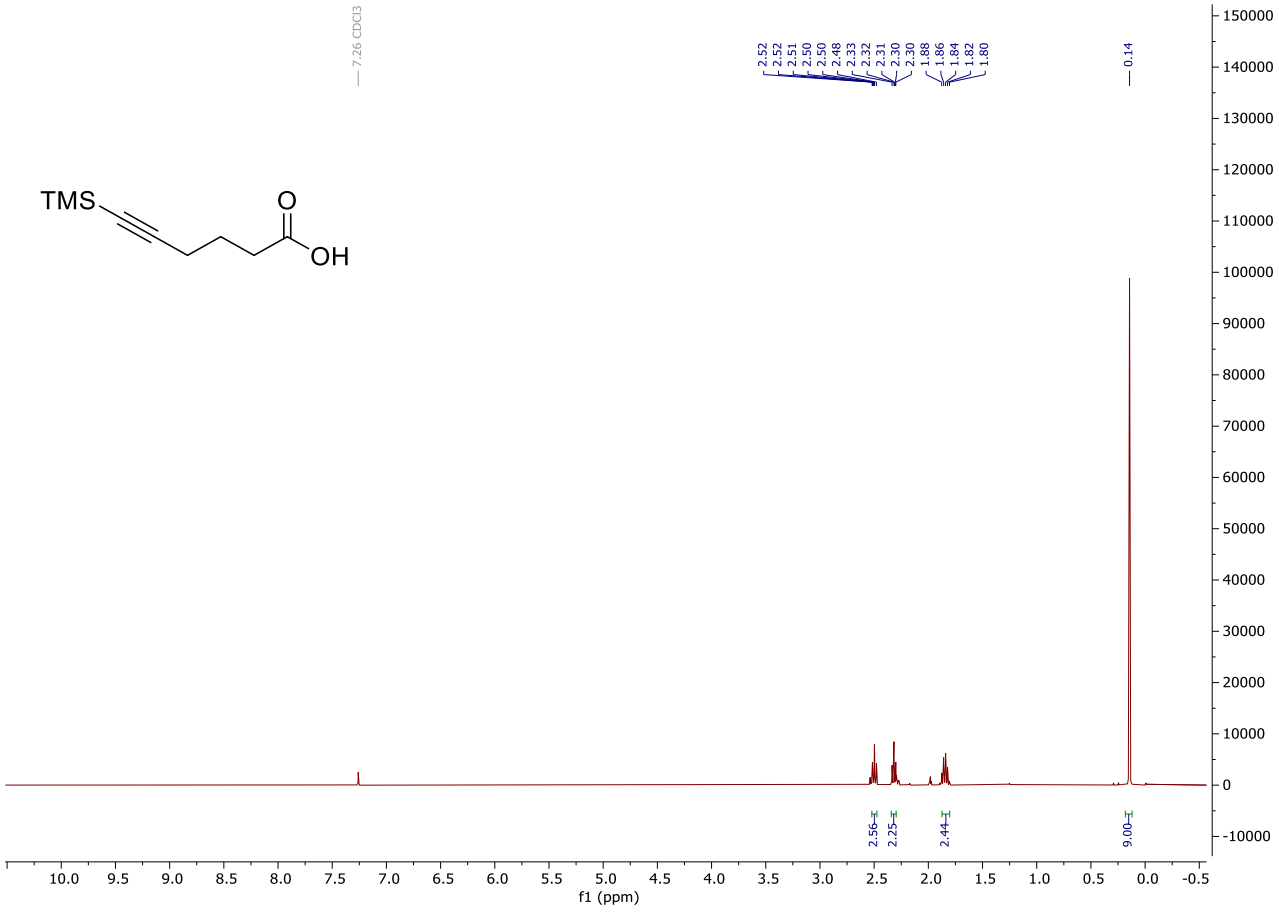
2-(4-Bromophenyl)ethan-1-amine (80)

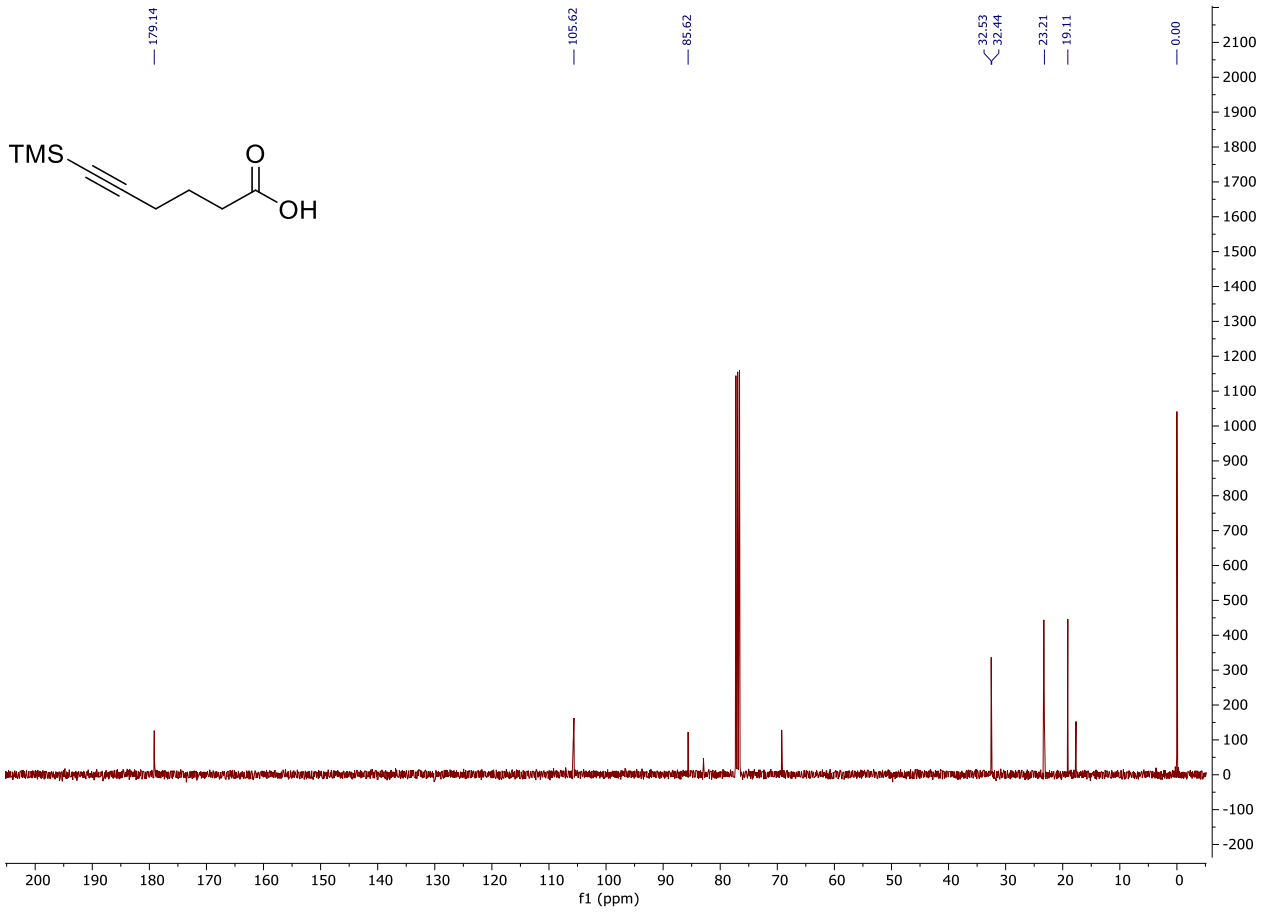


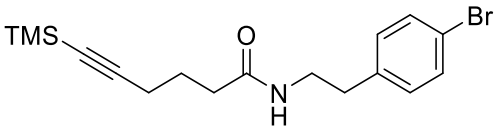




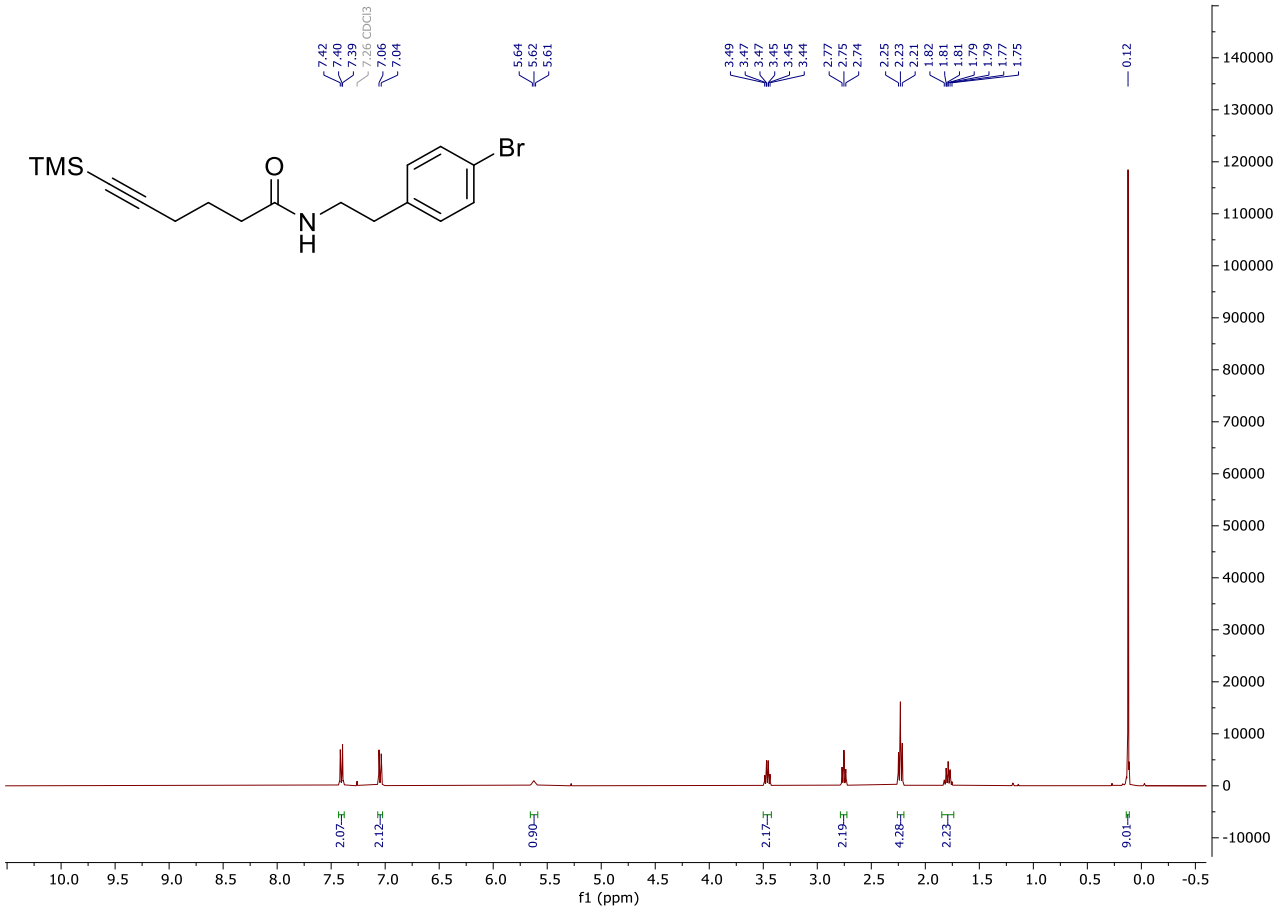
6-(Trimethylsilyl)hex-5-ynoic acid (81)

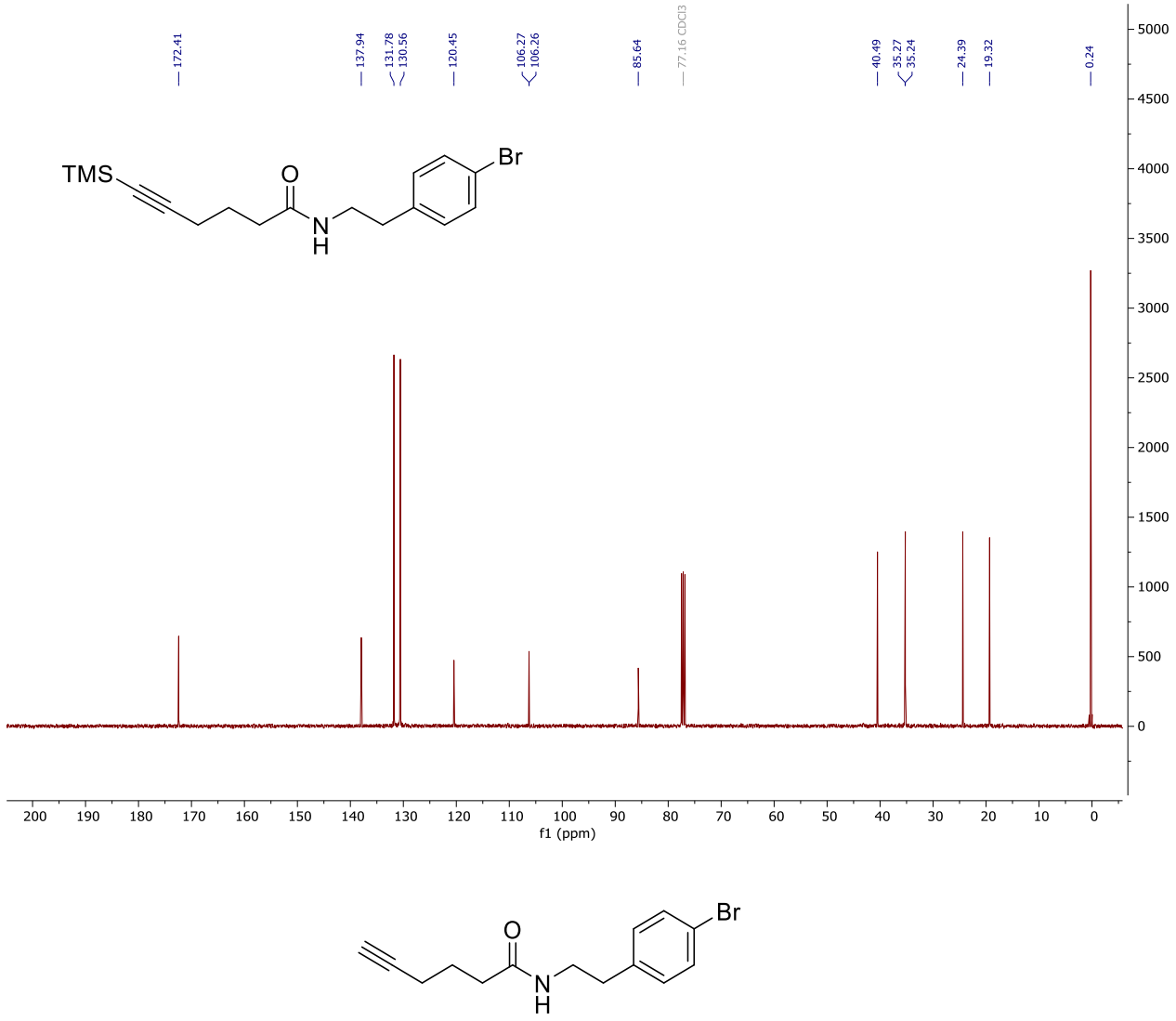

TMS
O
OH
7.26 CDCl3
2.52
2.52
2.51
2.50
2.50
2.48
2.33
2.32
2.31
2.30
2.30
1.88
1.86
1.84
1.82
1.80
0.14
2.56
2.25
2.44
9.00
f1 (ppm)


TMS
O
OH
179.14
105.62
85.62
32.53
32.44
23.21
19.11
0.00
f1 (ppm)

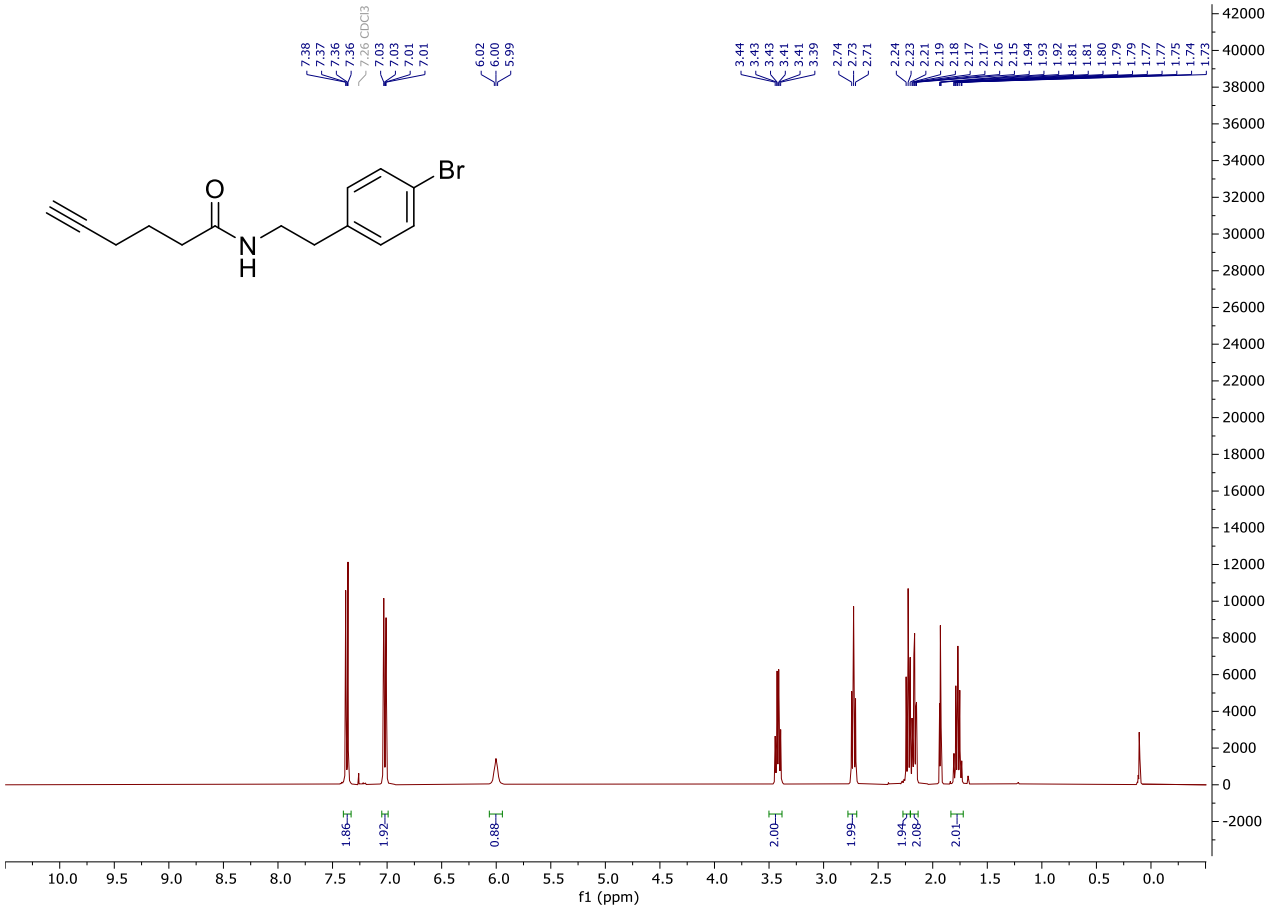


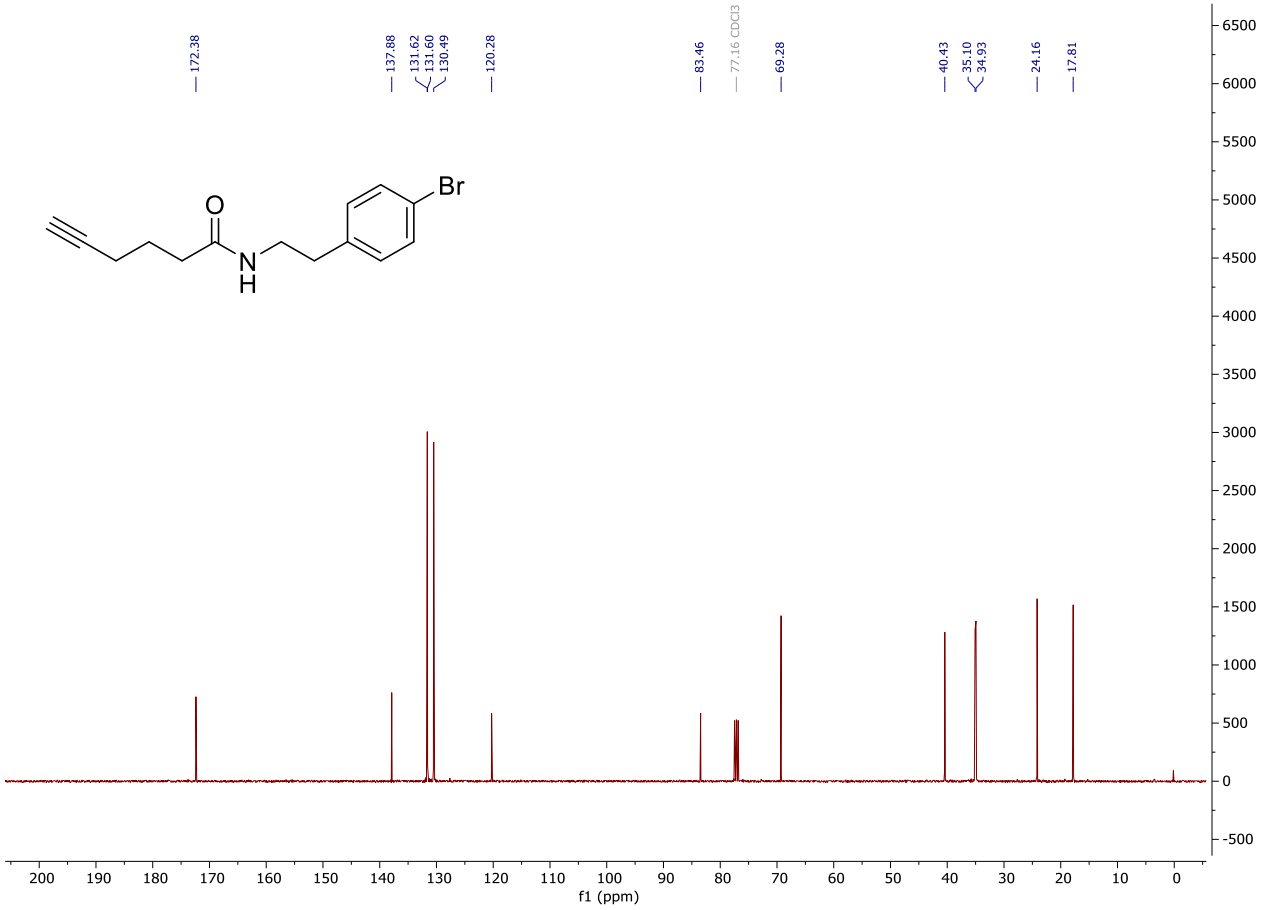
_N_-(4-Bromophenethyl)-6-(trimethylsilyl)hex-5-ynamide (78)

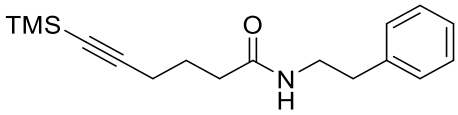




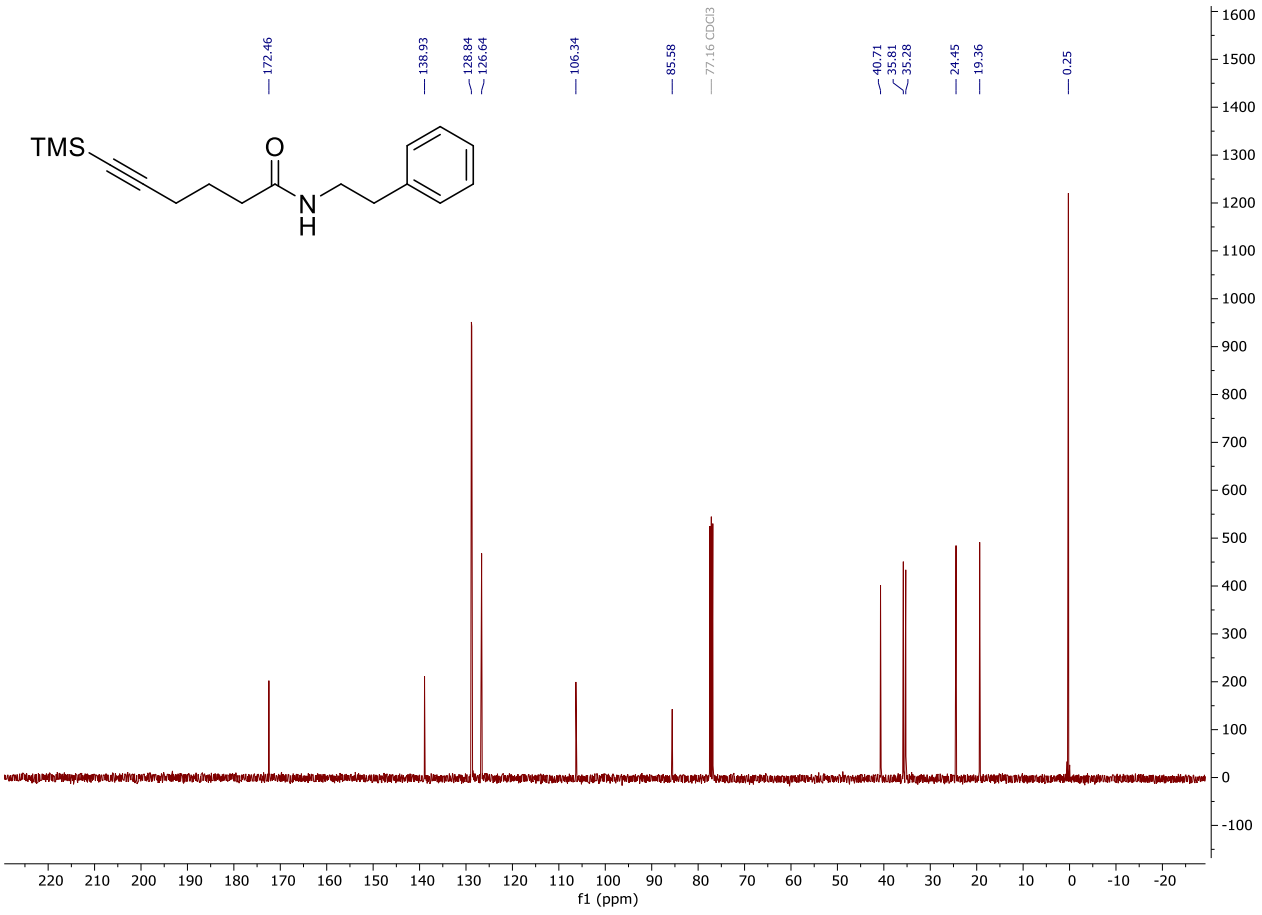
***N*-(4-Bromophenethyl)hex-5-ynamide (S8)**

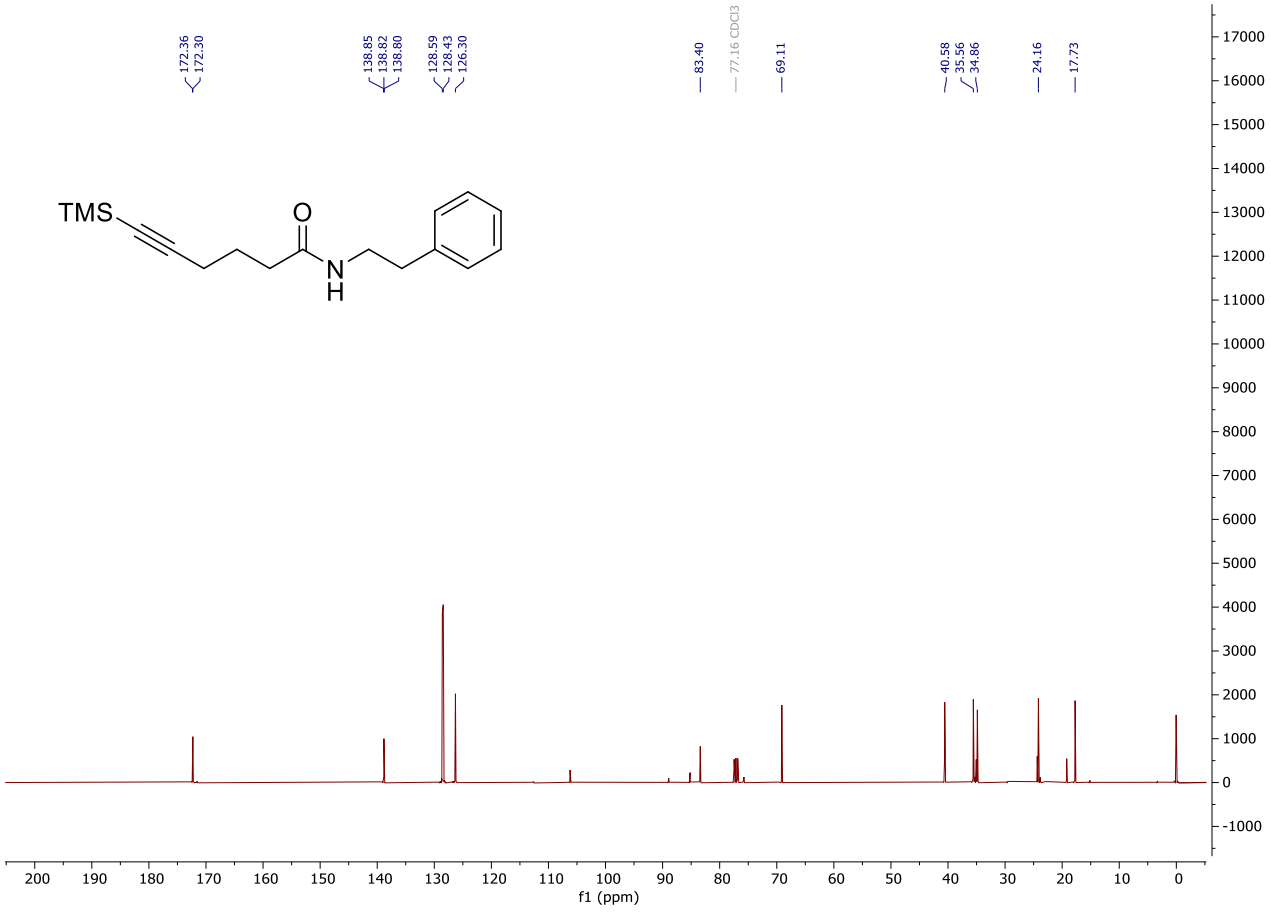

7.38
7.37
7.36
7.36
7.26 CDCl3
7.03
7.03
7.01
7.01
6.02
6.00
5.99
3.44
3.43
3.43
3.41
3.41
3.39
2.74
2.73
2.71
2.24
2.23
2.21
2.19
2.18
2.17
2.17
2.16
2.15
1.94
1.93
1.92
1.81
1.81
1.80
1.79
1.79
1.77
1.77
1.75
1.74
1.73
Br
O
N
H
1.86
1.92
0.88
2.00
1.99
1.94
2.08
2.01
f1 (ppm)

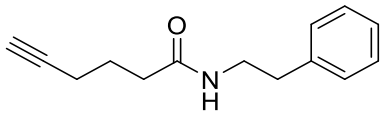

172.38
137.88
131.62
131.60
130.49
120.28
83.46
77.16 CDCl3
69.28
40.43
35.10
34.93
24.16
17.81
Br
O
N
H
f1 (ppm)



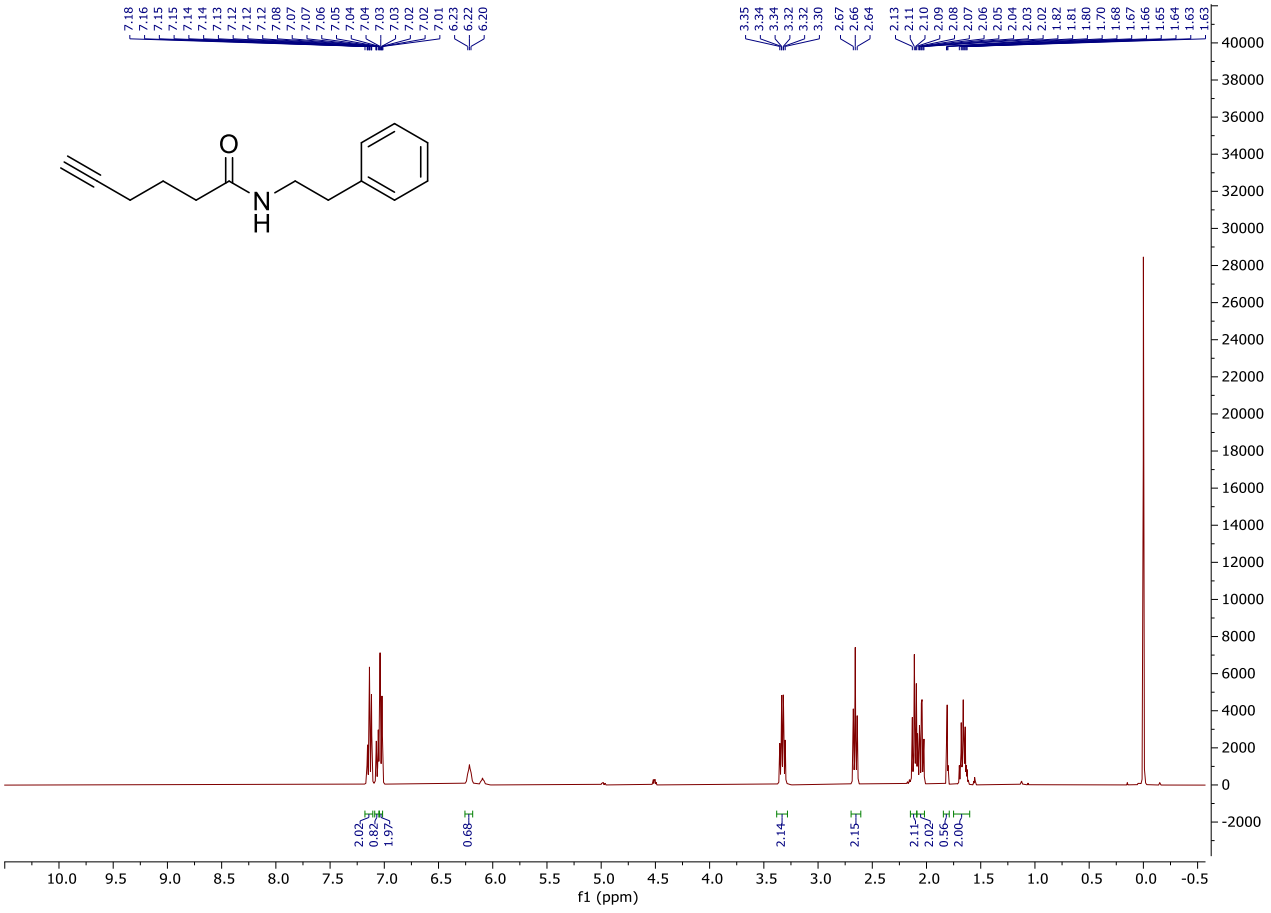
_N_-Phenethyl-6-(trimethylsilyl)hex-5-ynamide (S9)

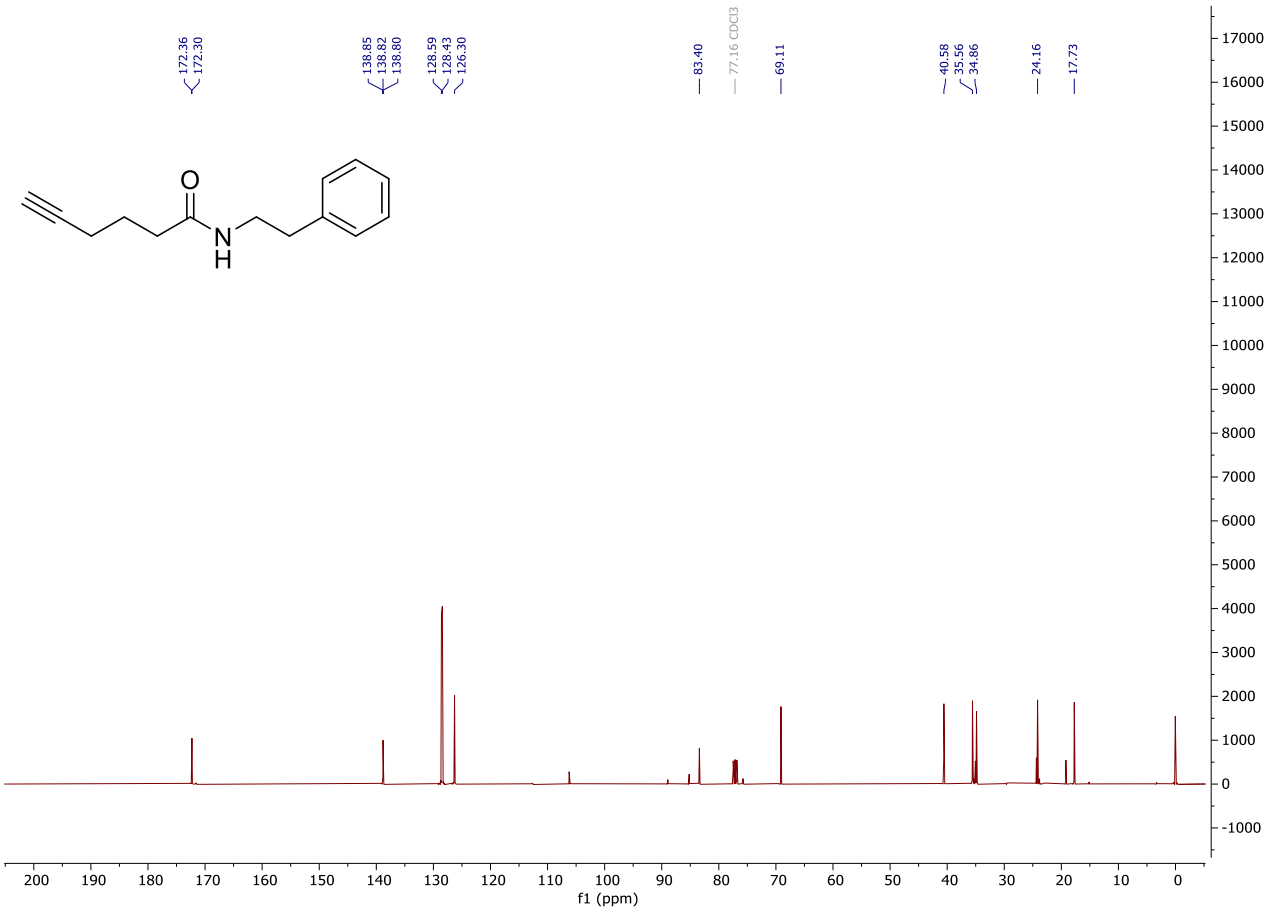


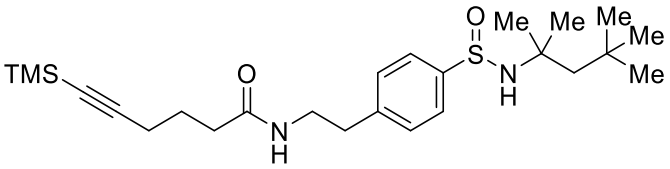




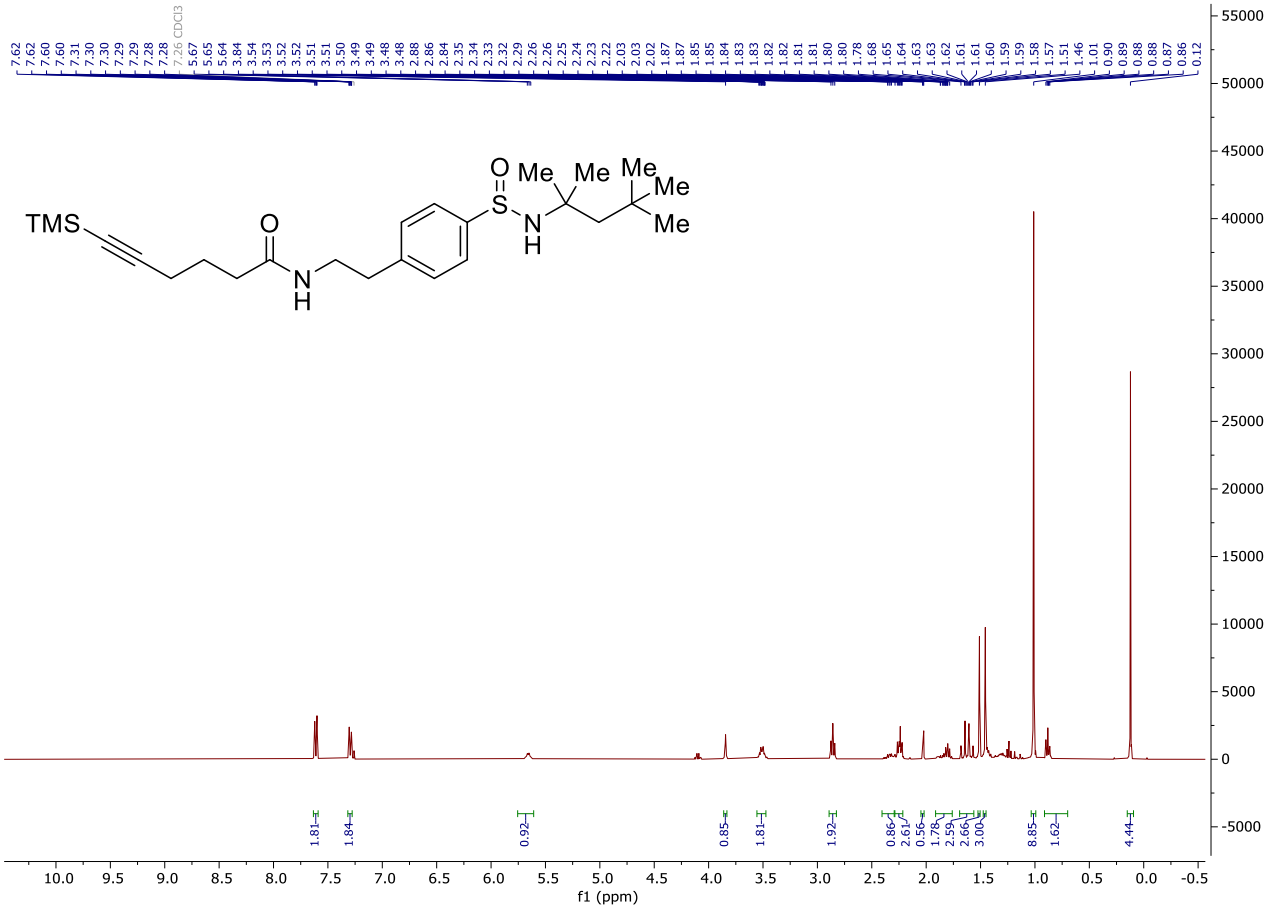
***N*-Phenethylhex-5-ynamide (S10)**

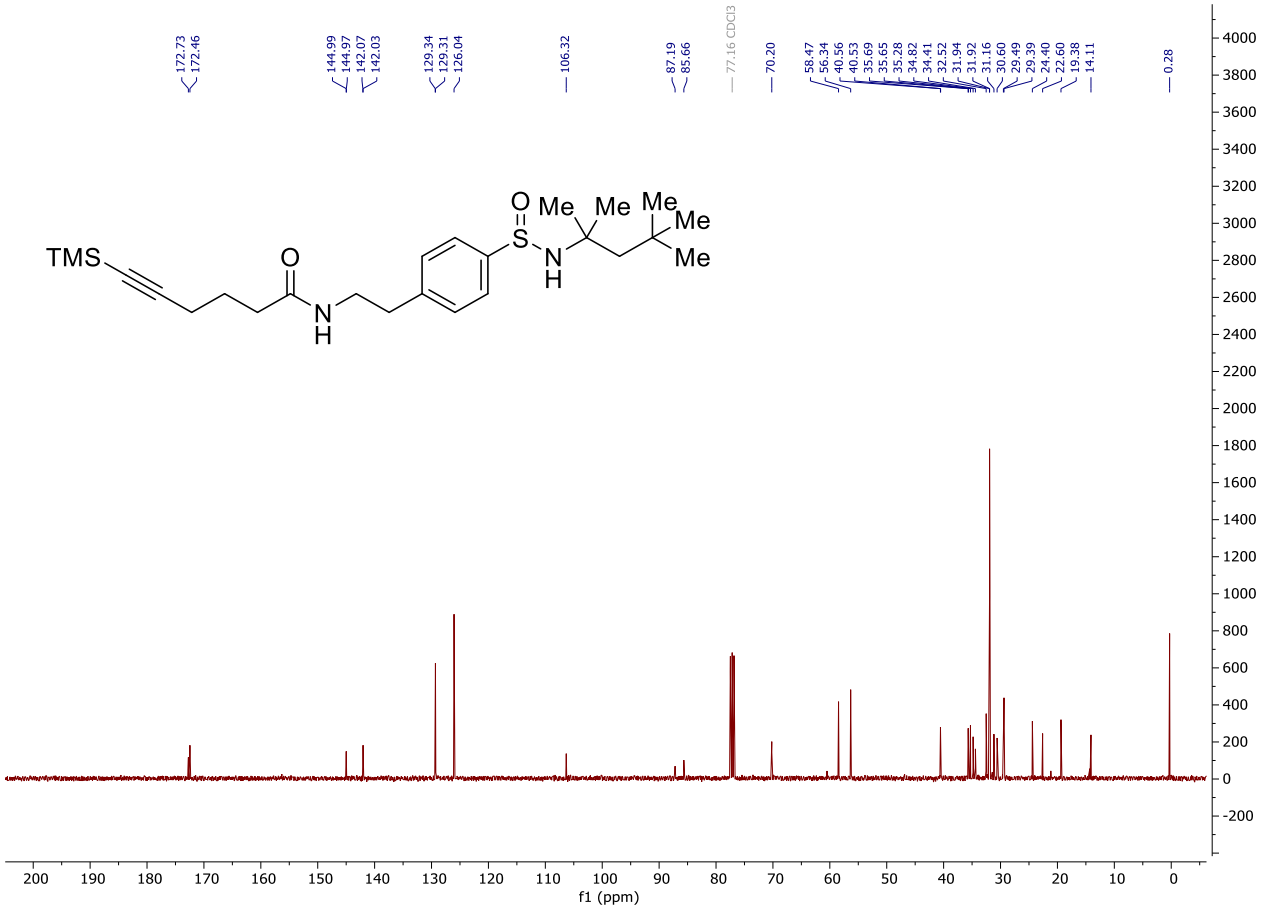

7.18 7.16 7.15 7.15 7.14 7.14 7.13 7.12 7.12 7.12 7.08 7.07 7.07 7.06 7.05 7.04 7.04 7.03 7.03 7.02 7.02 7.01 6.23 6.22 6.20
3.35 3.34 3.34 3.32 3.32 3.30 2.67 2.66 2.64 2.13 2.11 2.10 2.09 2.08 2.07 2.06 2.05 2.04 2.03 2.02 1.82 1.81 1.80 1.70 1.68 1.67 1.66 1.65 1.64 1.63 1.63
O
N
H
2.02 0.82 1.97 0.68 2.14 2.15 2.11 2.02 0.56 2.00
f1 (ppm)

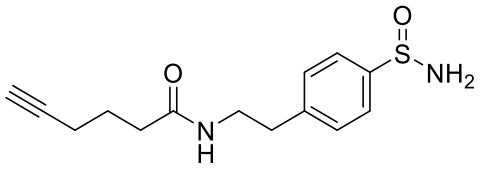

172.36 172.30 138.85 138.82 138.80 128.59 128.43 126.30 83.40 77.16 CDCl3 69.11 40.58 35.56 34.86 24.16 17.73
O
N
H
f1 (ppm)



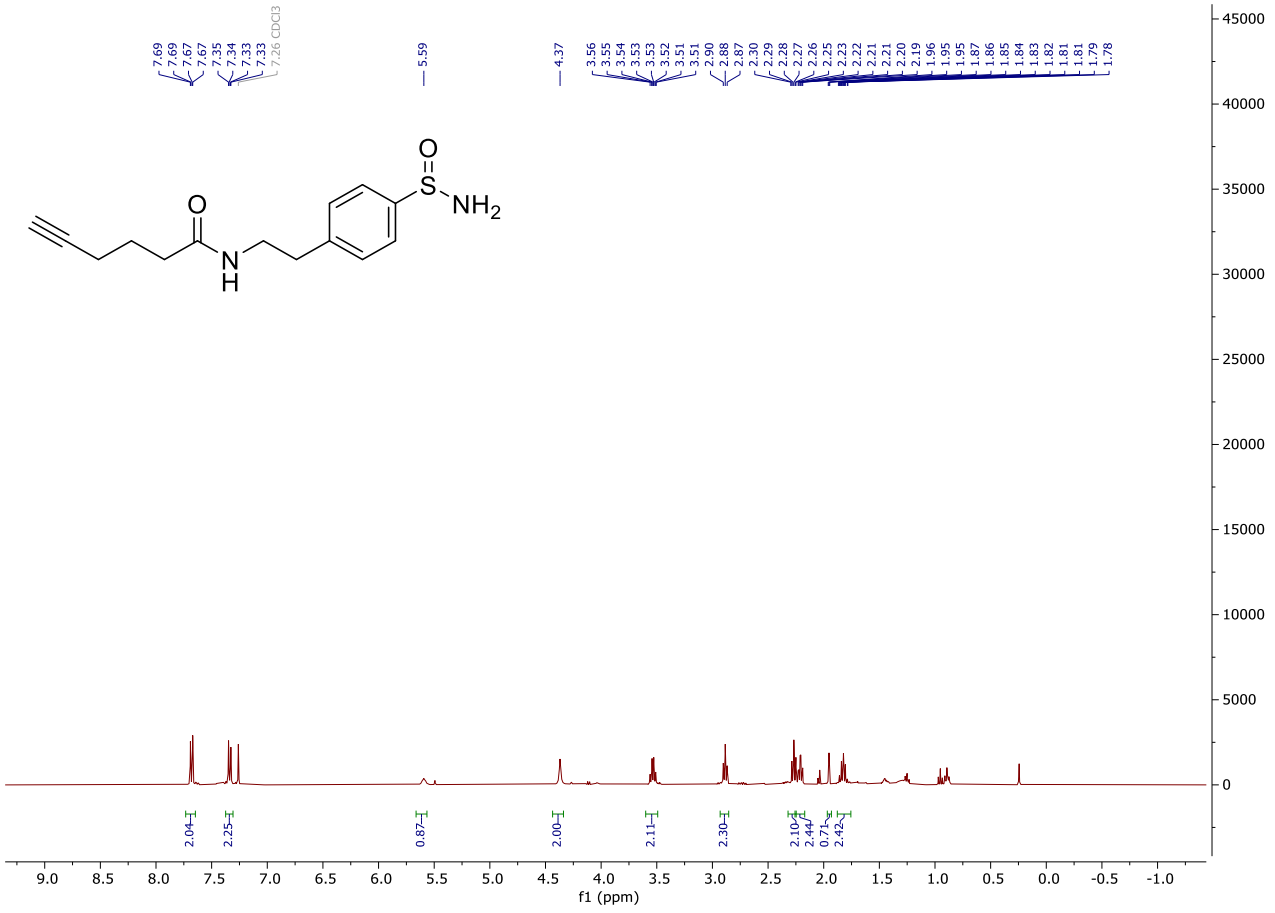
_N_-(4-(((2,4,4-Trimethylpentan-2-yl)amino)sulfinyl)phenethyl)-6-(trimethylsilyl)hex-5-ynamide (77a)

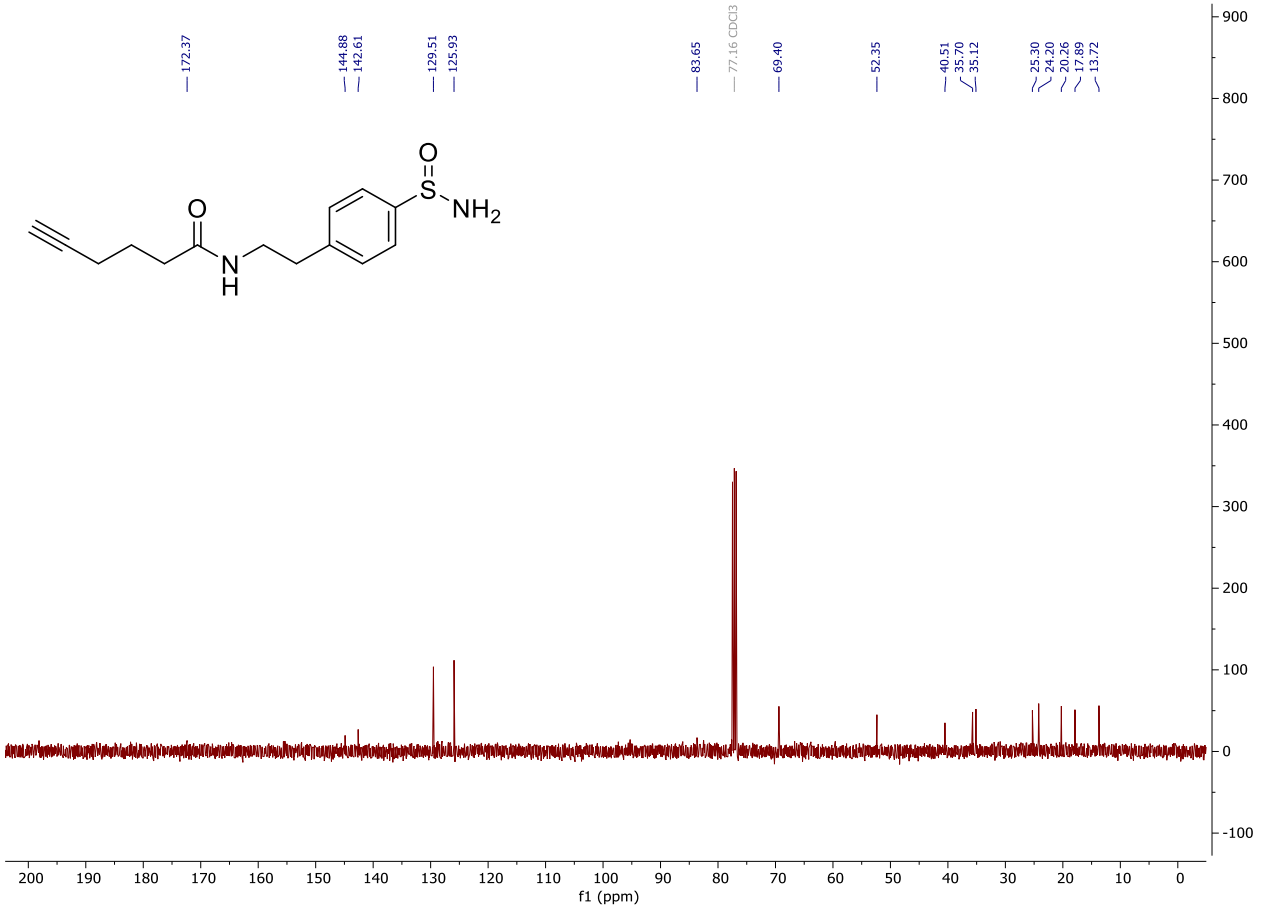


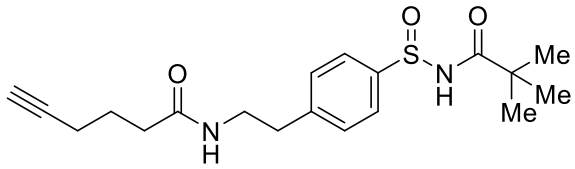




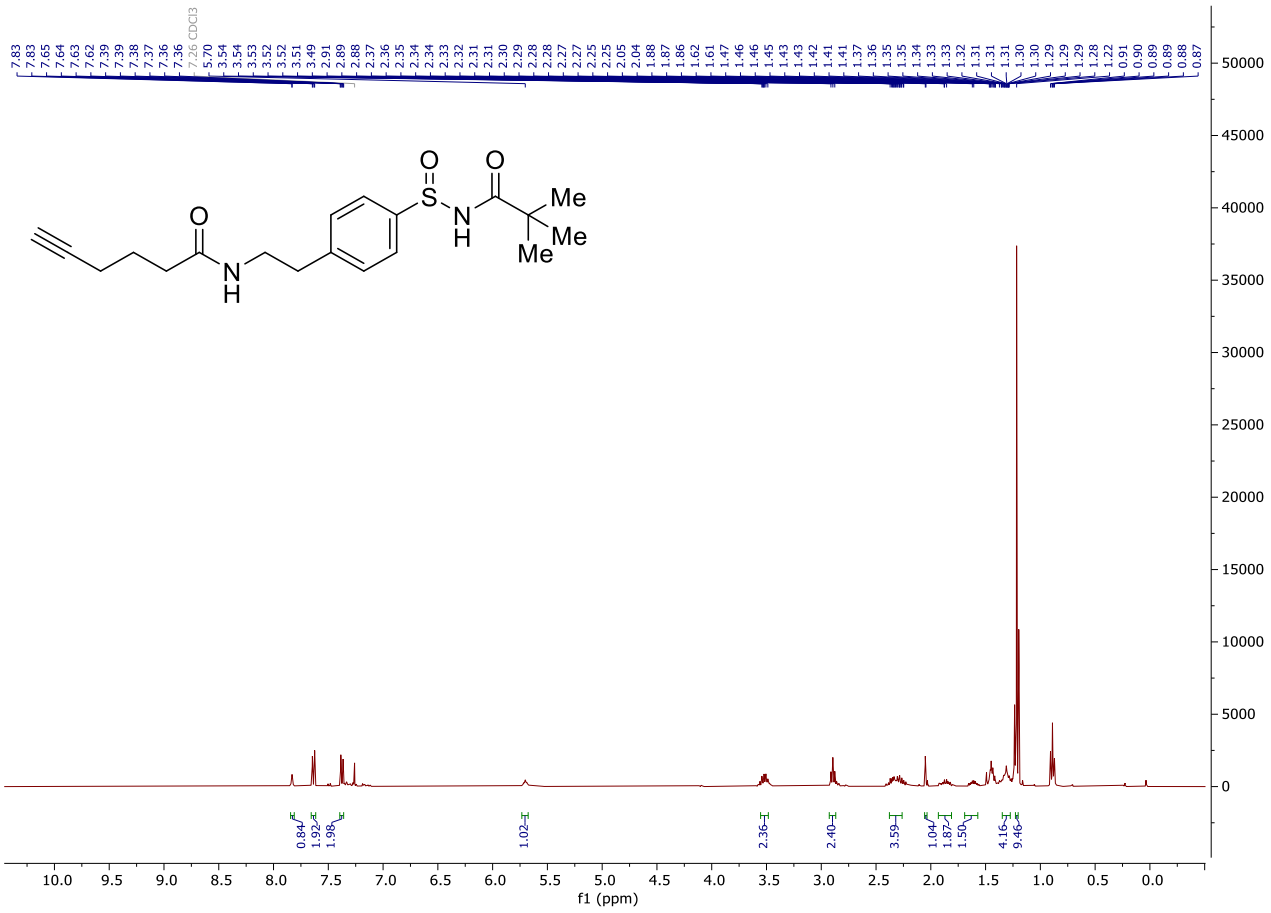
***N*-(4-(Aminosulfinyl)phenethyl)hex-5-ynamide (77b)**

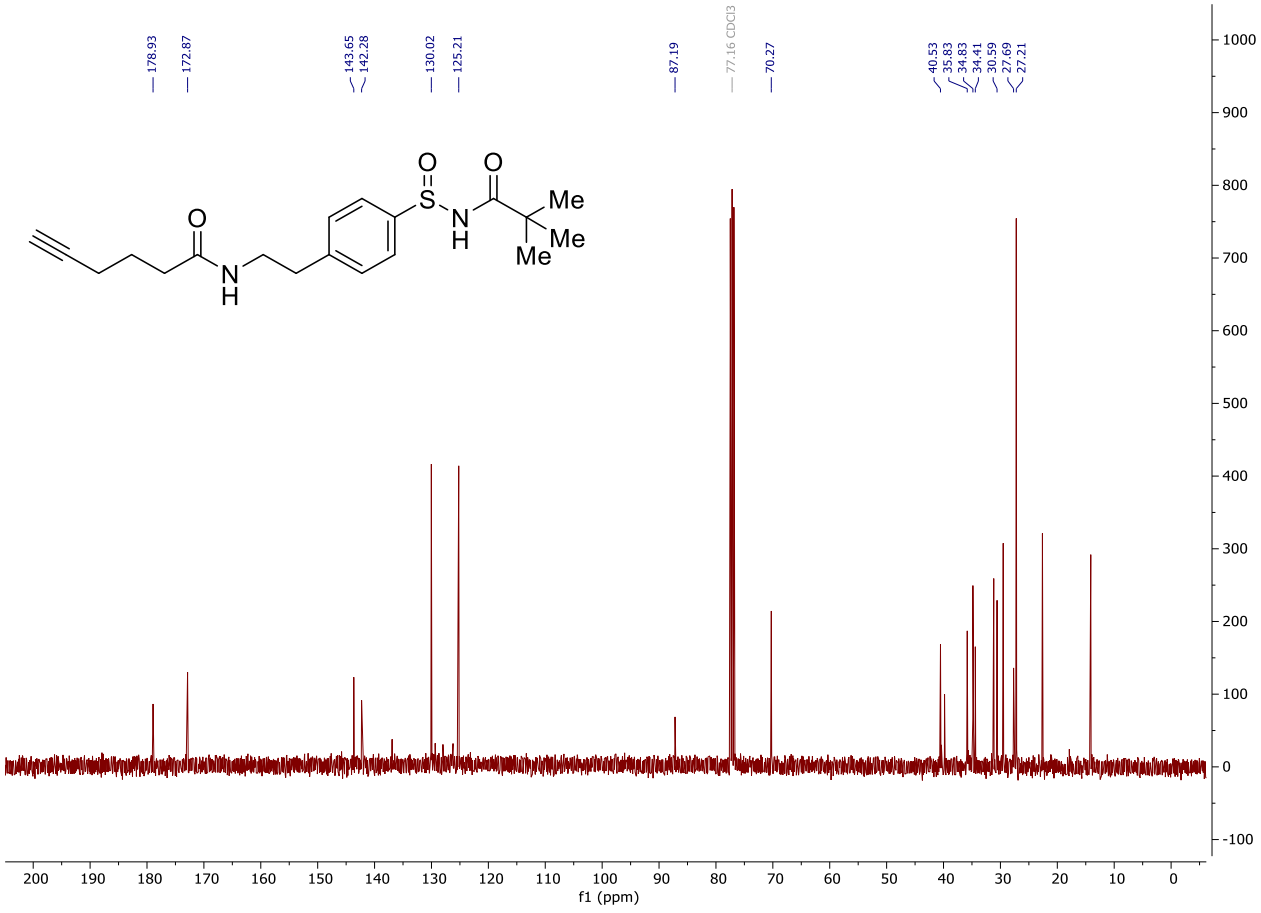

7.69
7.69
7.67
7.67
7.35
7.34
7.33
7.33
7.26 CDCl3
5.59
4.37
3.56
3.55
3.54
3.53
3.53
3.52
3.51
3.51
2.90
2.88
2.87
2.30
2.29
2.28
2.27
2.26
2.25
2.23
2.22
2.21
2.21
2.20
2.19
1.96
1.95
1.95
1.87
1.86
1.85
1.84
1.83
1.82
1.81
1.81
1.79
1.78
O
S
NH2
O
N
H
2.04
2.25
0.87
2.00
2.11
2.30
2.10
2.44
0.71
2.42
f1 (ppm)

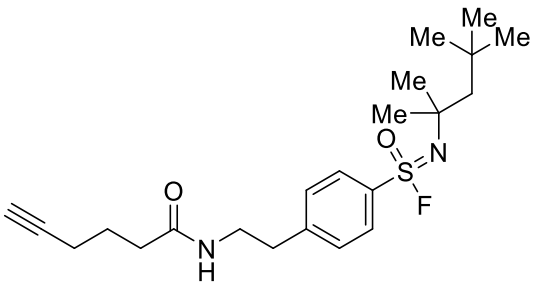

172.37
144.88
142.61
129.51
125.93
83.65
77.16 CDCl3
69.40
52.35
40.51
35.70
35.12
25.30
24.20
20.26
17.89
13.72
O
S
NH2
O
N
H
f1 (ppm)



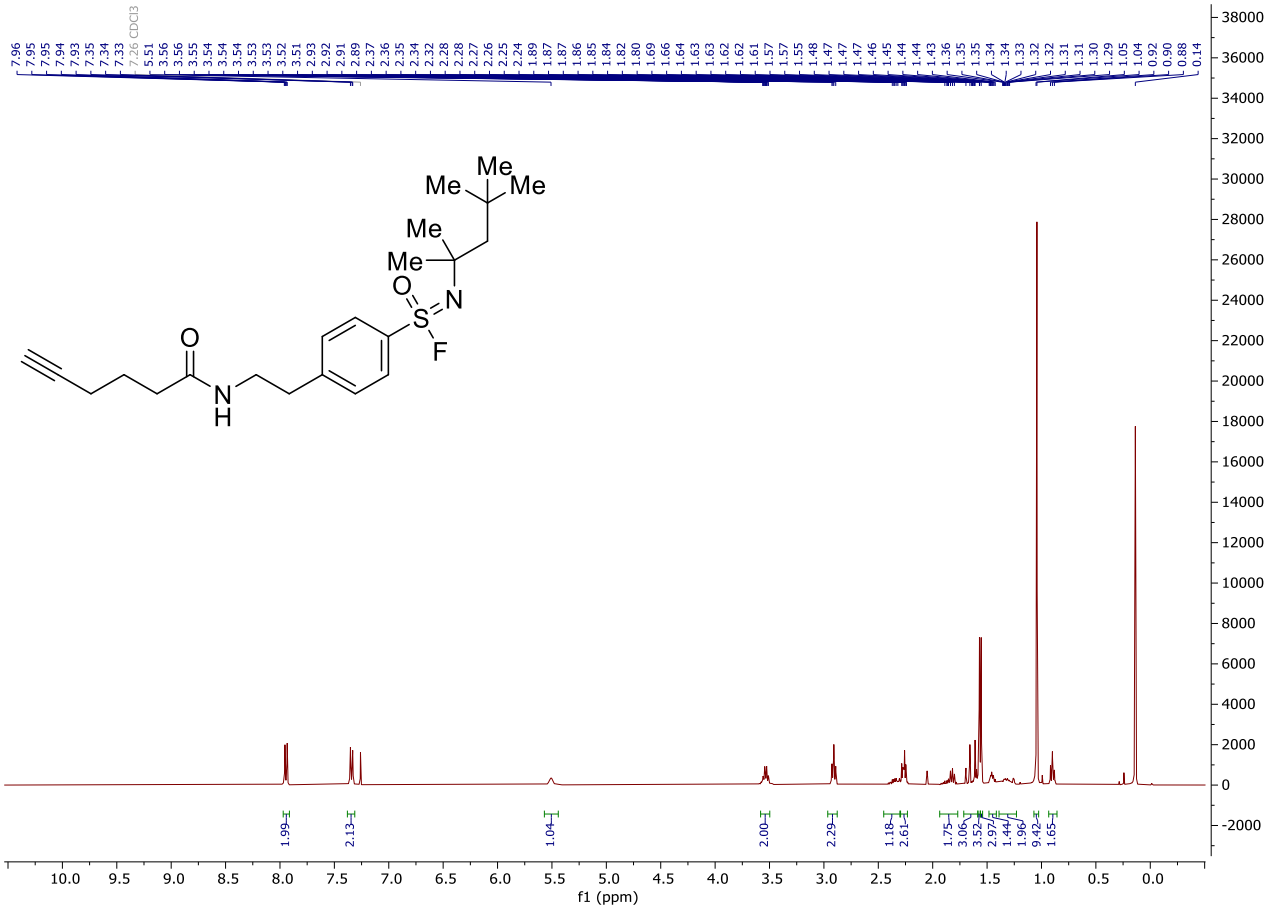
_N_-(4-(Pivalamidosulfinyl)phenethyl)hex-5-ynamide (77c)

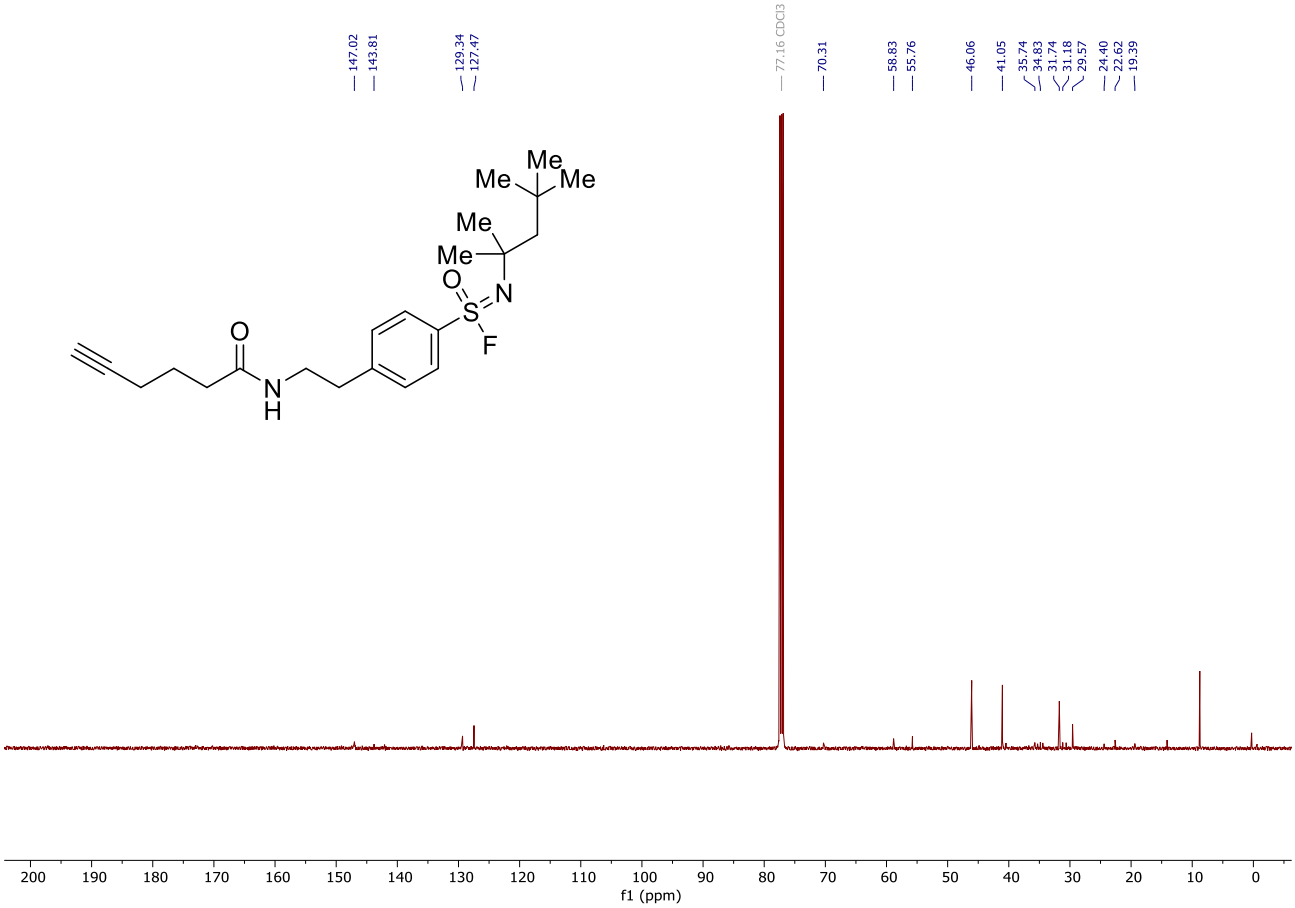


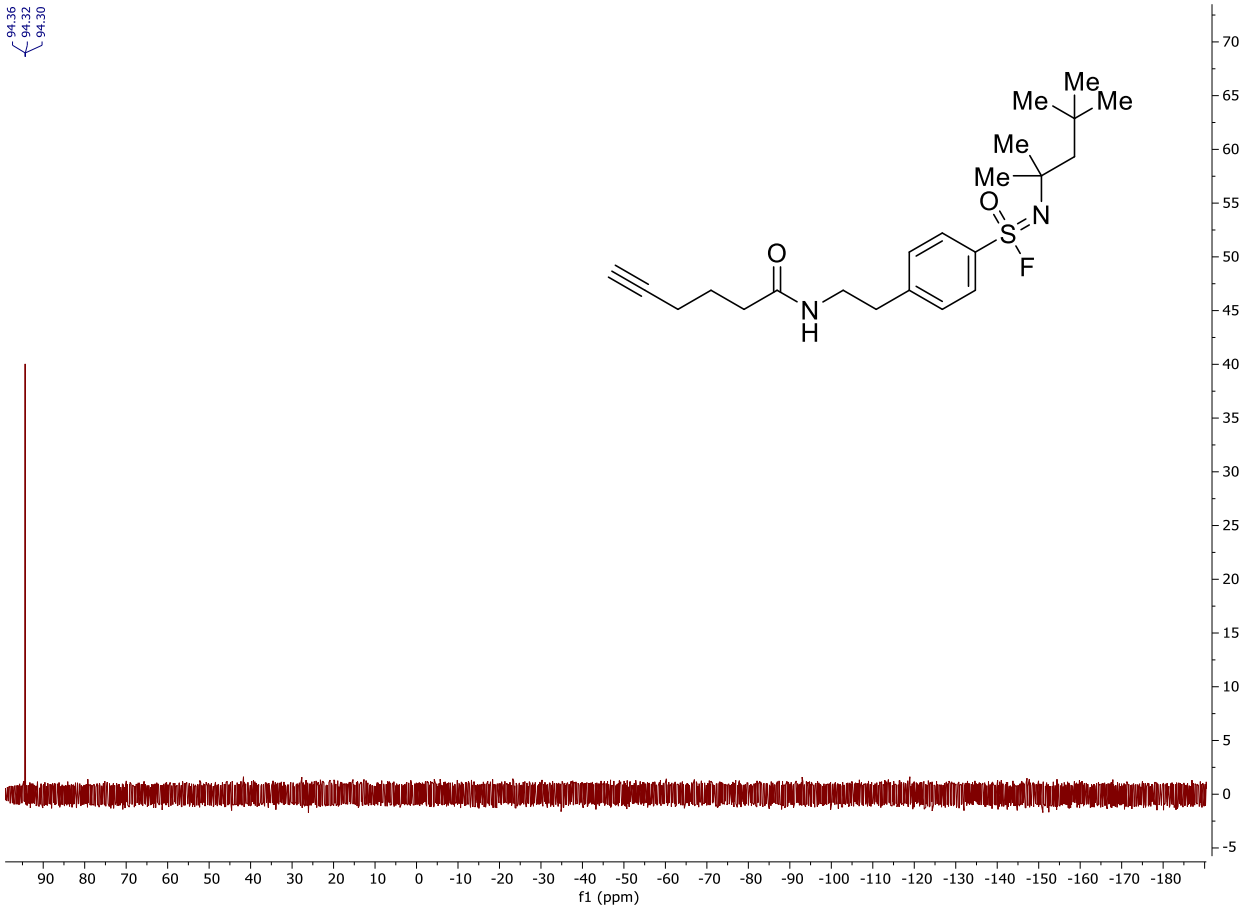


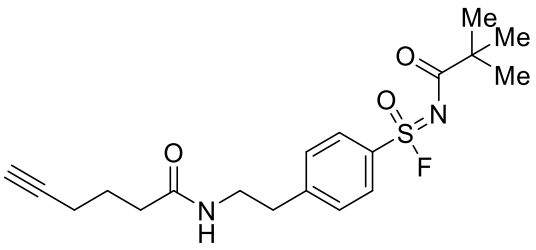


4-(2-(Hex-5-ynamido)ethyl)-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfonimidoyl fluoride (76a)

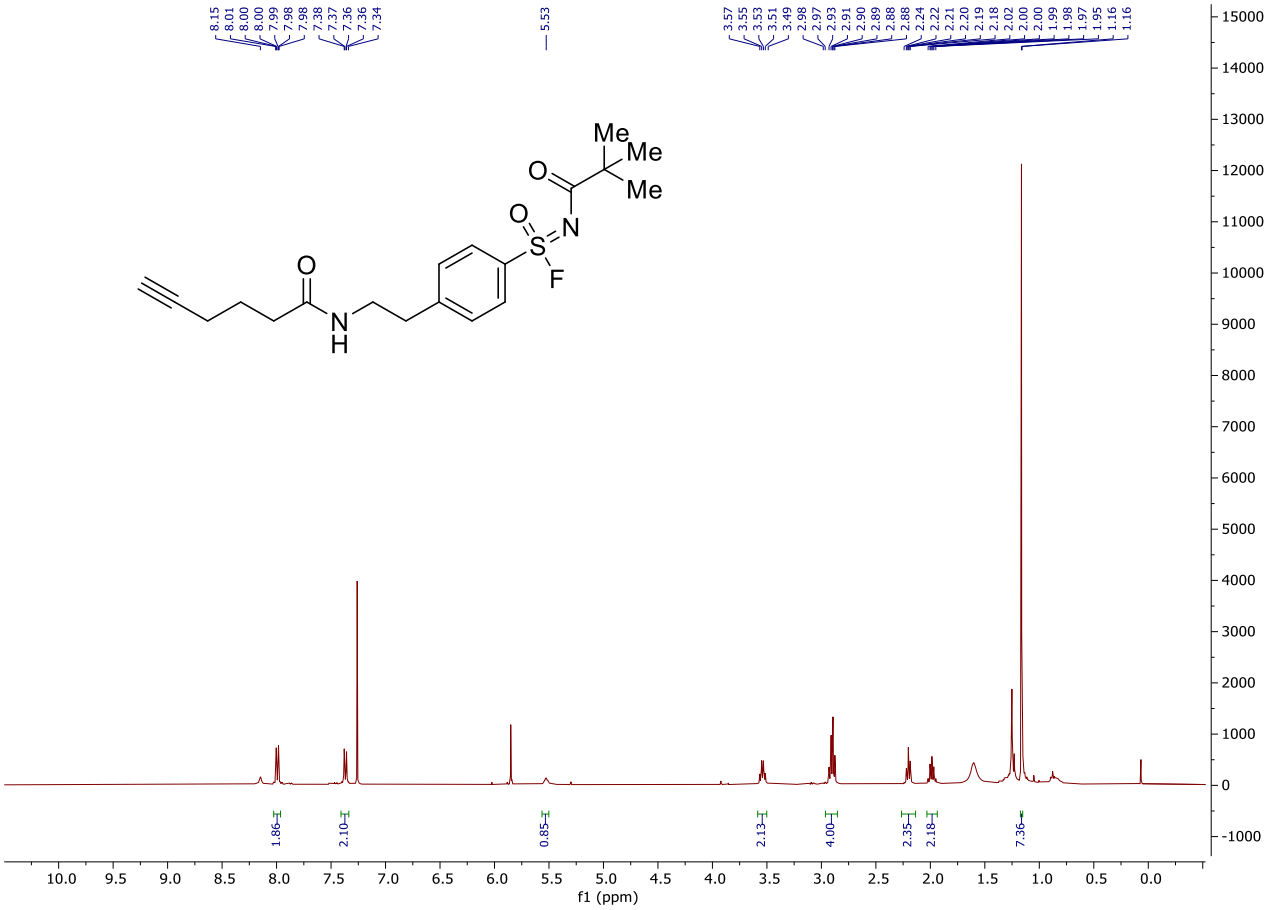

Me
Me
Me
Me
Me
O
S
N
F
O
N
H
f1 (ppm)

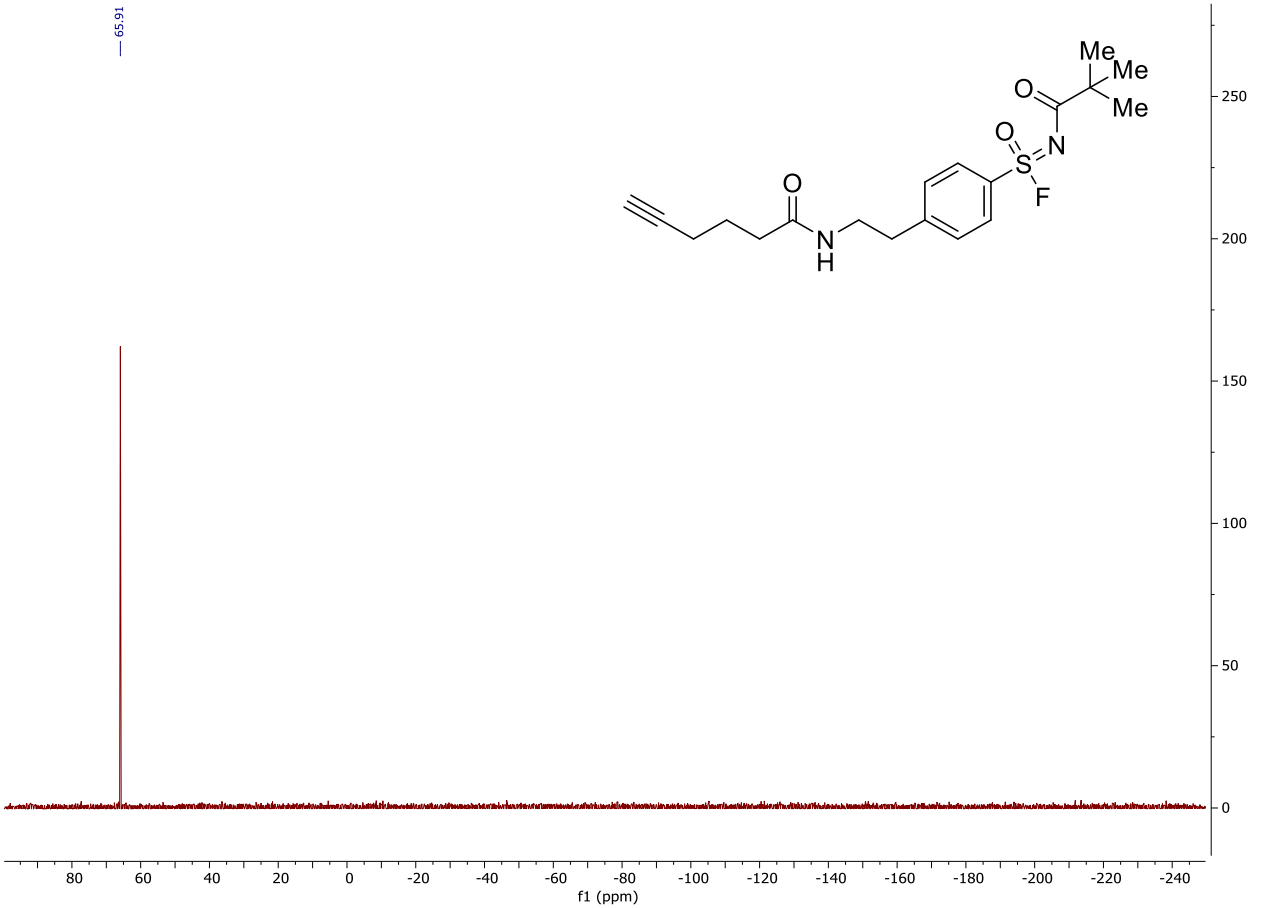

Me
Me
Me
Me
Me
O
S
N
F
O
N
H
f1 (ppm)

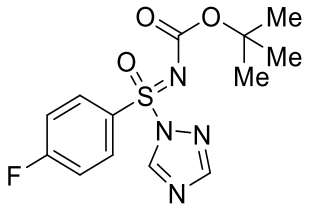




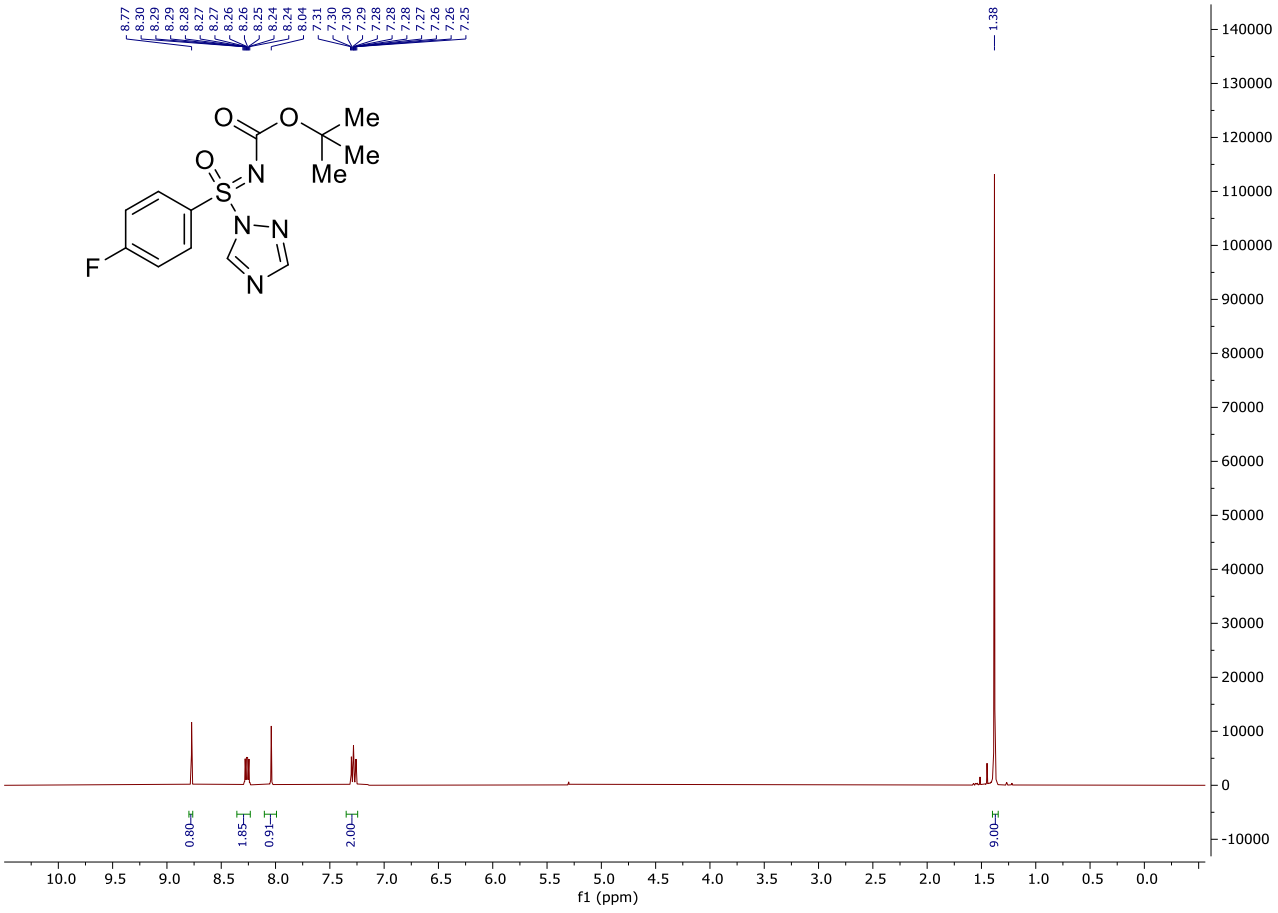
4-(2-(Hex-5-ynamido)ethyl)-*N*-pivaloylbenzenesulfonimidoyl fluoride (76c)

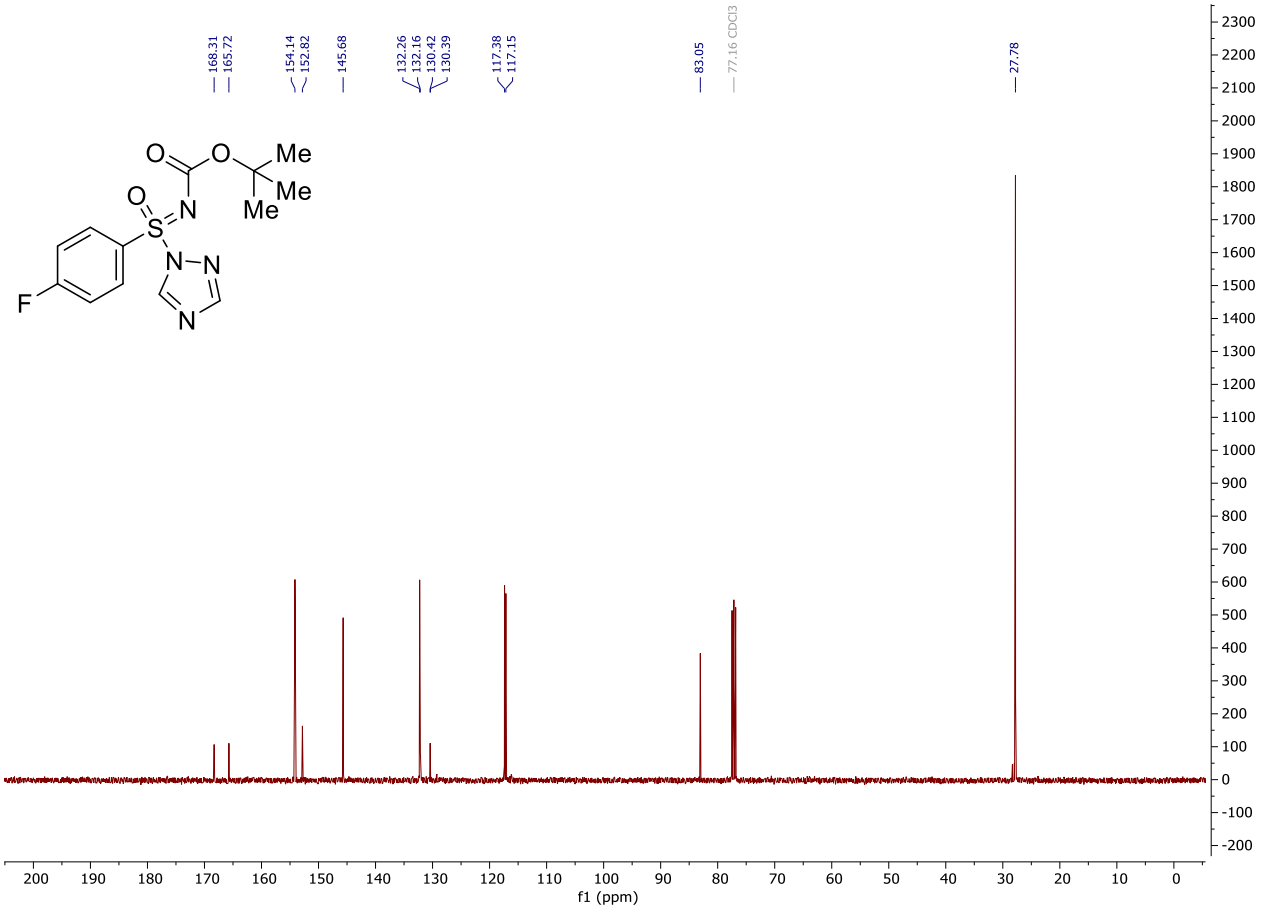

8.15
8.01
8.00
8.00
7.99
7.98
7.98
7.38
7.37
7.36
7.36
7.34
5.53
3.57
3.55
3.53
3.51
3.49
2.98
2.97
2.93
2.91
2.90
2.89
2.88
2.88
2.24
2.22
2.21
2.20
2.19
2.18
2.02
2.00
2.00
1.99
1.98
1.97
1.95
1.16
1.16
Me
Me
Me
O
O
N
S
F
O
N
H
1.86
2.10
0.85
2.13
4.00
2.35
2.18
7.36
f1 (ppm)

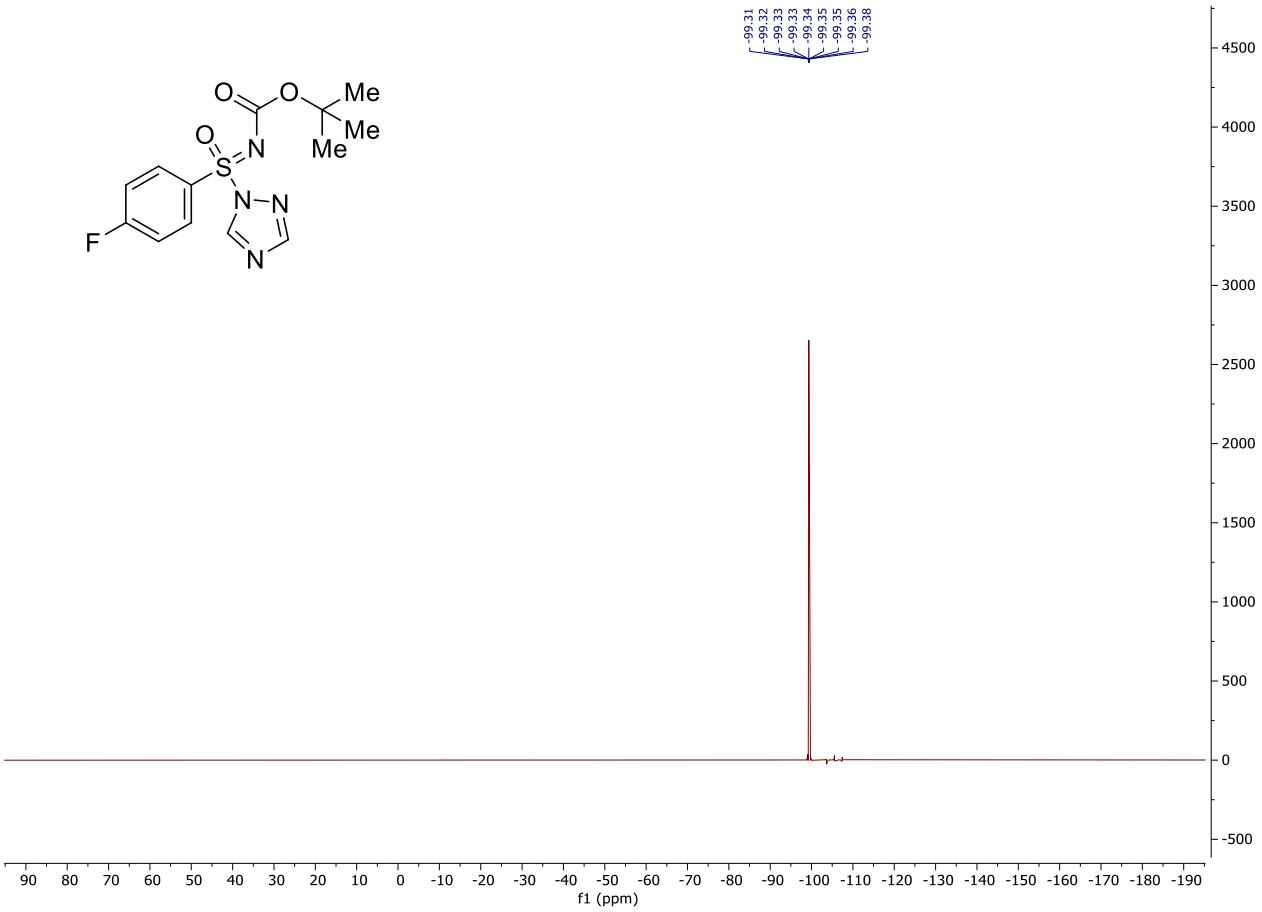

65.91
Me
Me
Me
O
O
N
S
F
O
N
H
f1 (ppm)

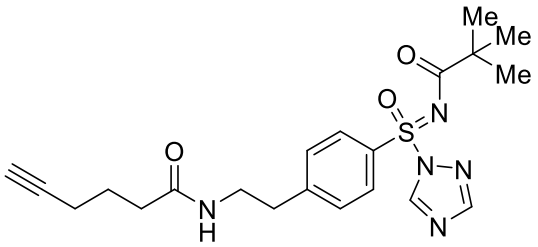


tert-Butyl ((4-fluorophenyl)(oxo)(1*H*-1,2,4-triazol-1-yl)-λ^6-sulfaneylidene)carbamate (85b)

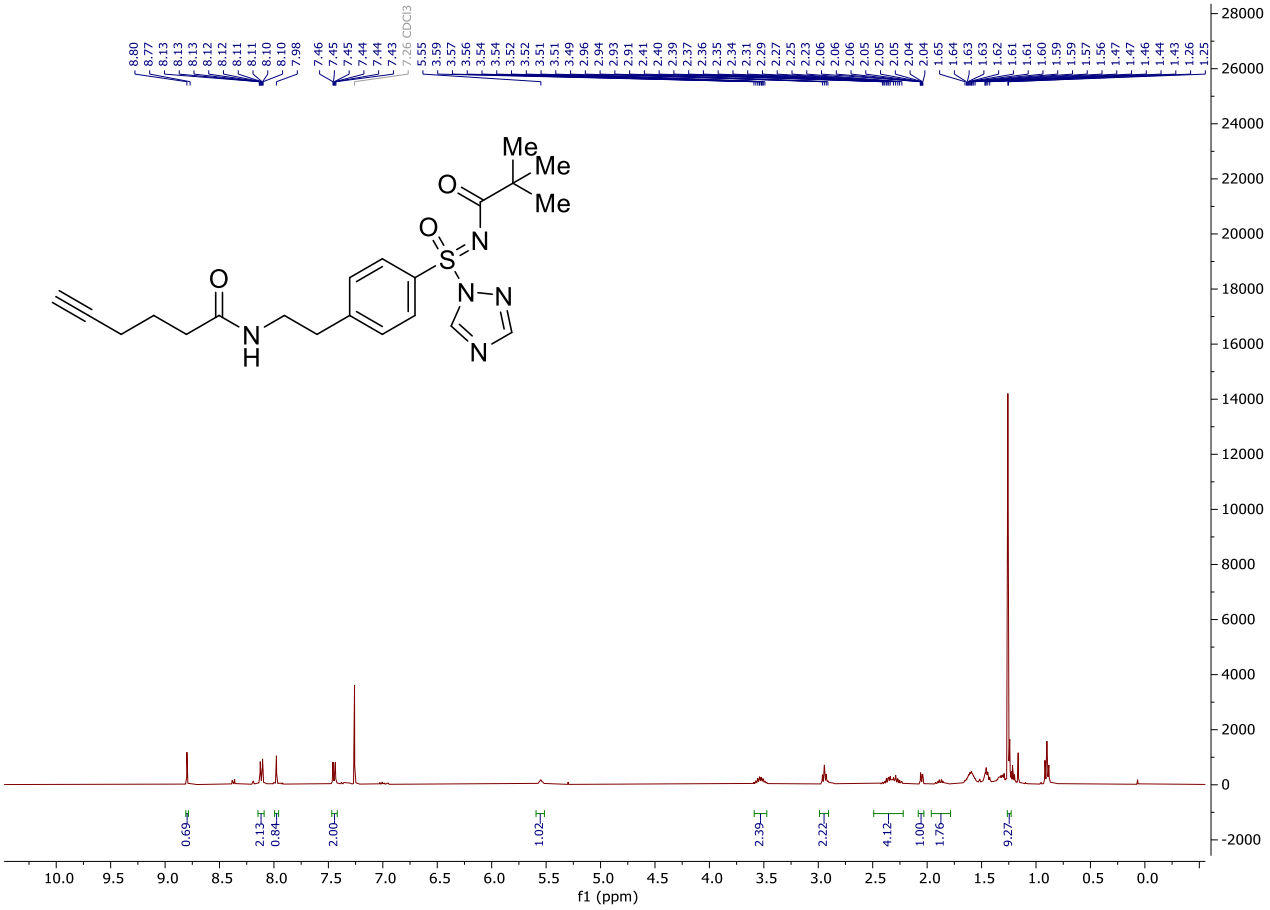


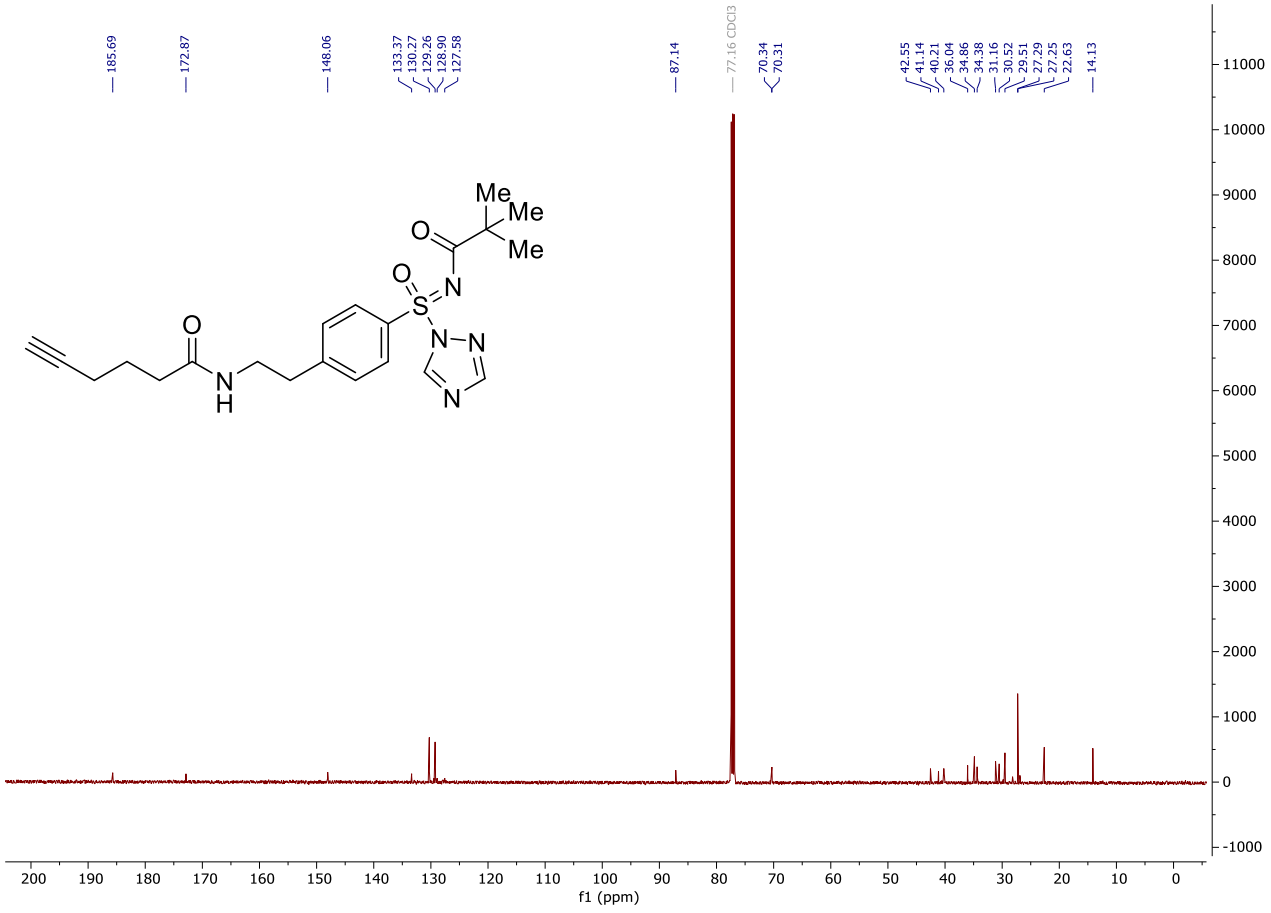

168.31
165.72
154.14
152.82
145.68
132.26
132.16
130.42
130.39
117.38
117.15
83.05
77.16 CDCl3
27.78
f1 (ppm)

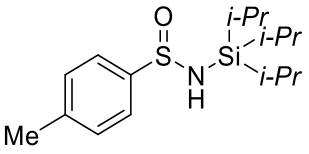

-99.31
-99.32
-99.33
-99.33
-99.34
-99.35
-99.35
-99.36
-99.38
f1 (ppm)



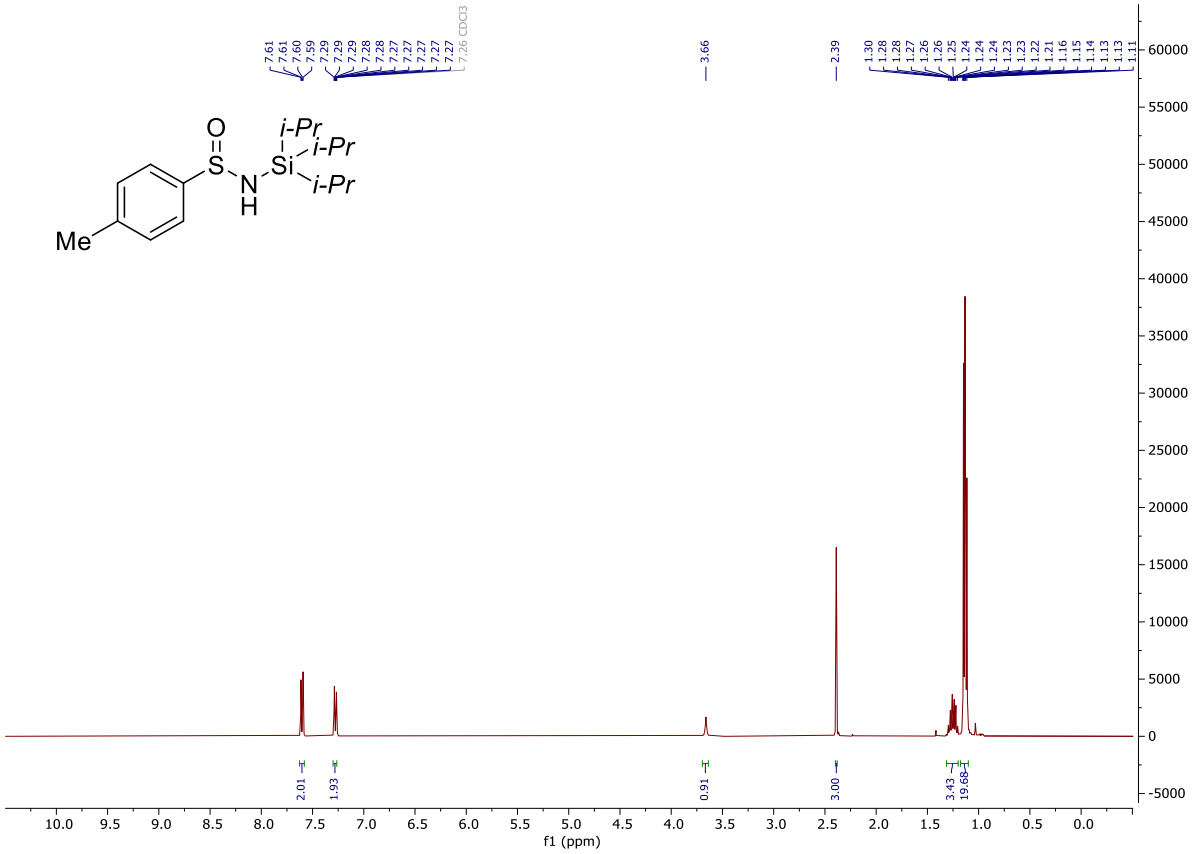
_N_-(4-(_N_-pivaloyl-1H-1,2,4-triazole-1-sulfonimidoyl)phenethyl)hex-5-ynamide (85c)

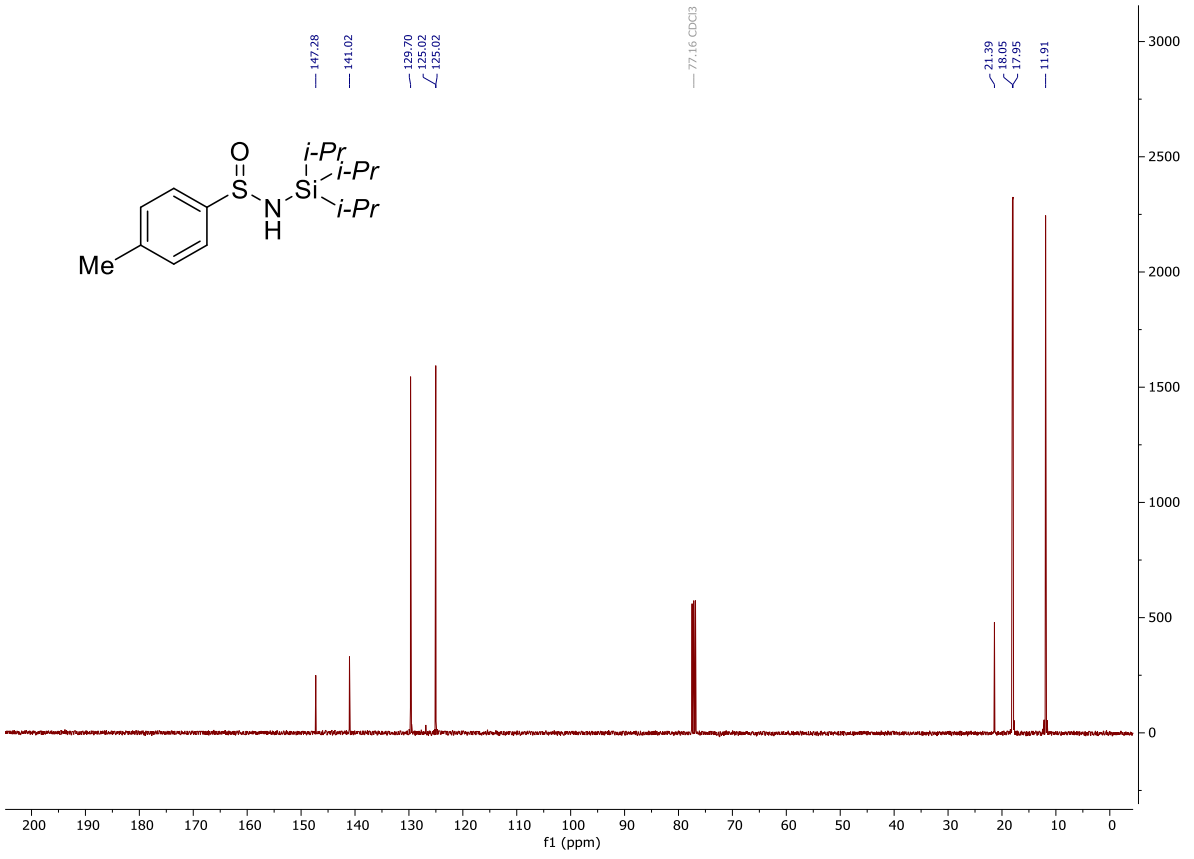


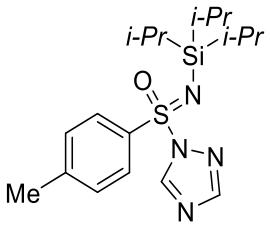




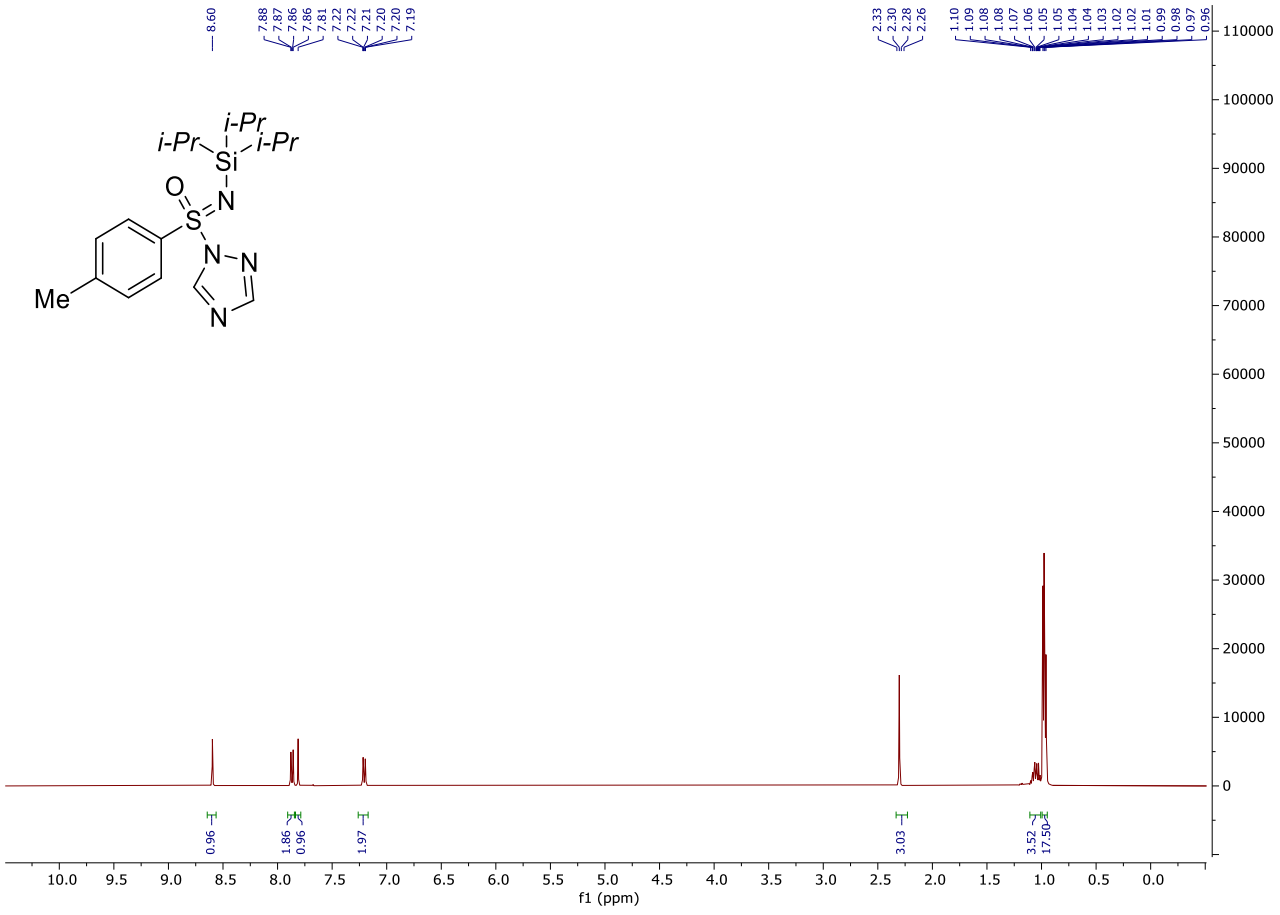
4-Methyl-*N*-(triisopropylsilyl)benzenesulfinamide (66k)

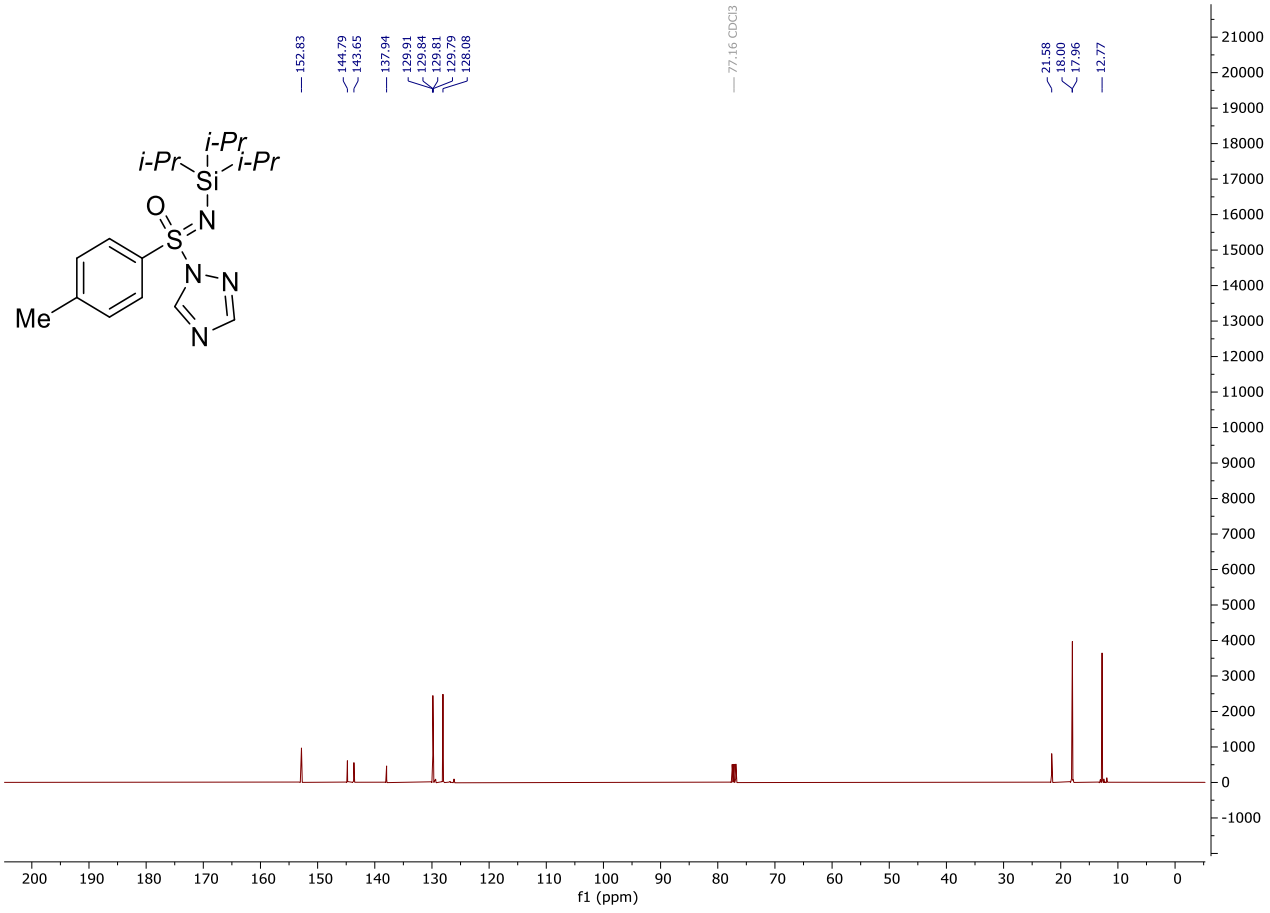

7.61
7.61
7.60
7.59
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.27
7.27
7.26 CDCl3
3.66
2.39
1.30
1.28
1.28
1.27
1.26
1.26
1.25
1.24
1.24
1.24
1.23
1.23
1.22
1.21
1.16
1.15
1.14
1.13
1.13
1.11
O
S
N
H
Si
i-Pr
i-Pr
i-Pr
Me
2.01
1.93
0.91
3.00
3.43
19.68
f1 (ppm)

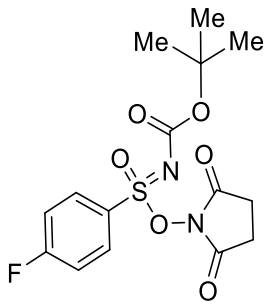

147.28
141.02
129.70
125.02
125.02
77.16 CDCl3
21.39
18.05
17.95
11.91
O
S
N
H
Si
i-Pr
i-Pr
i-Pr
Me
f1 (ppm)



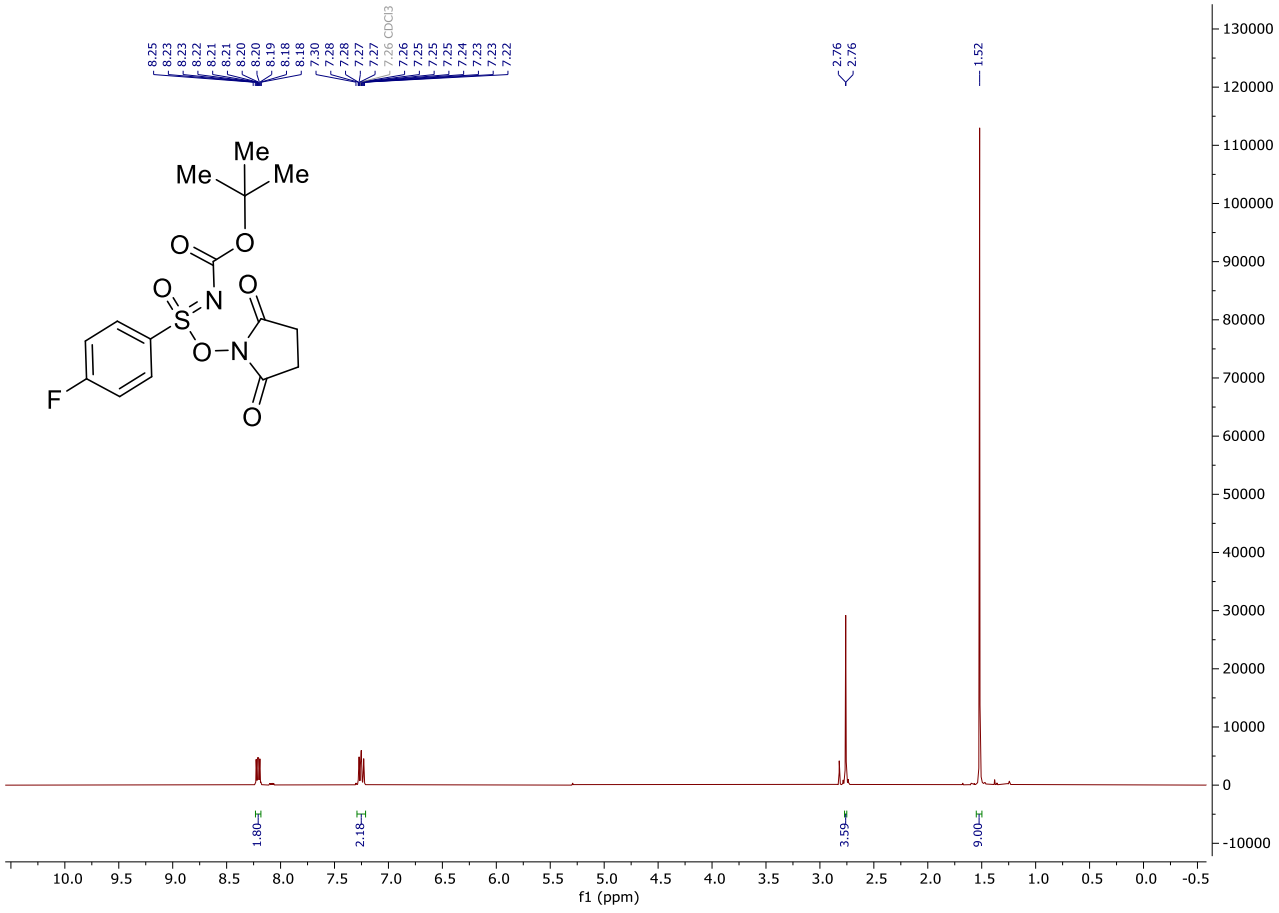
1-(4-Methyl-*N*-(triisopropylsilyl)phenylsulfonimidoyl)-1H-1,2,4-triazole (85d)

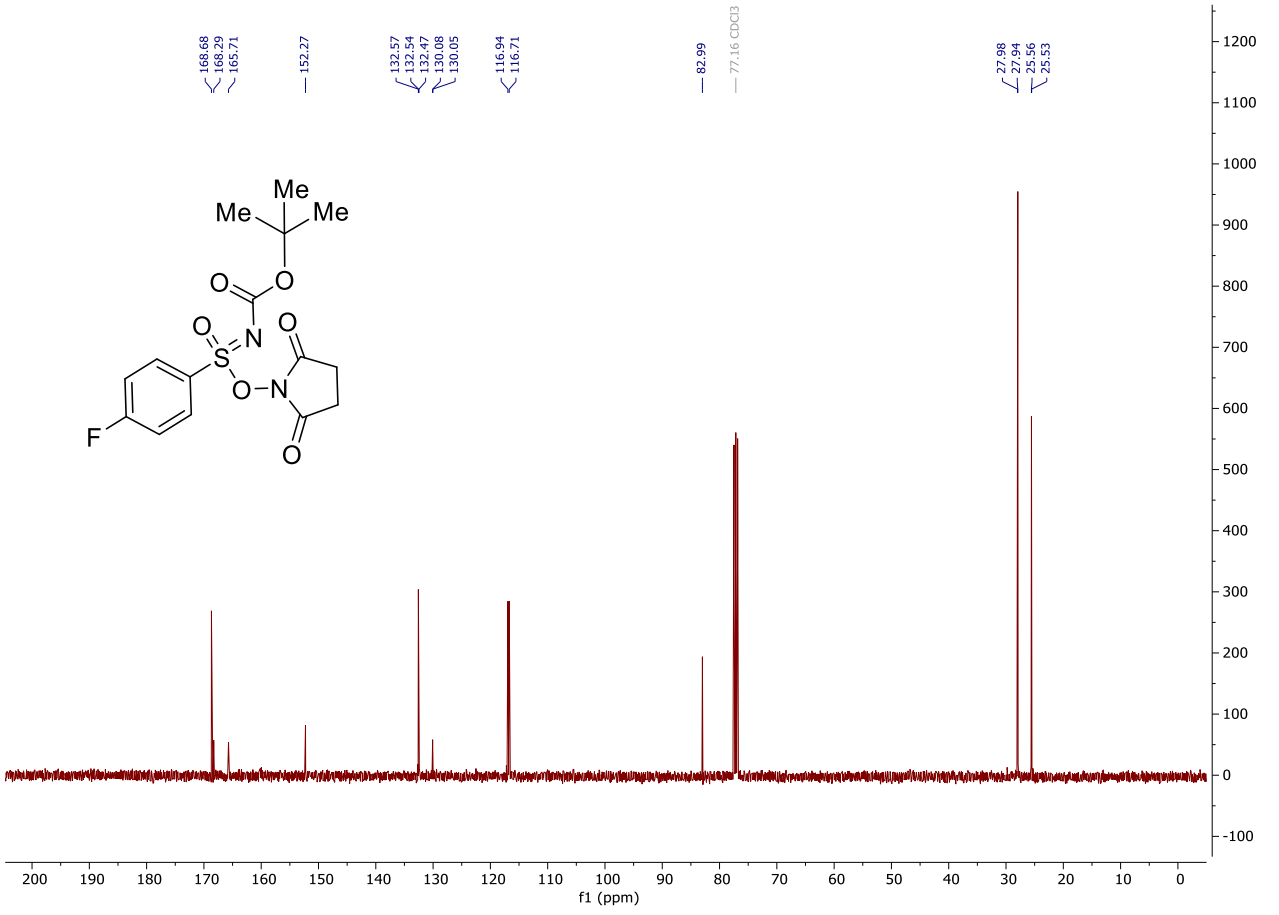


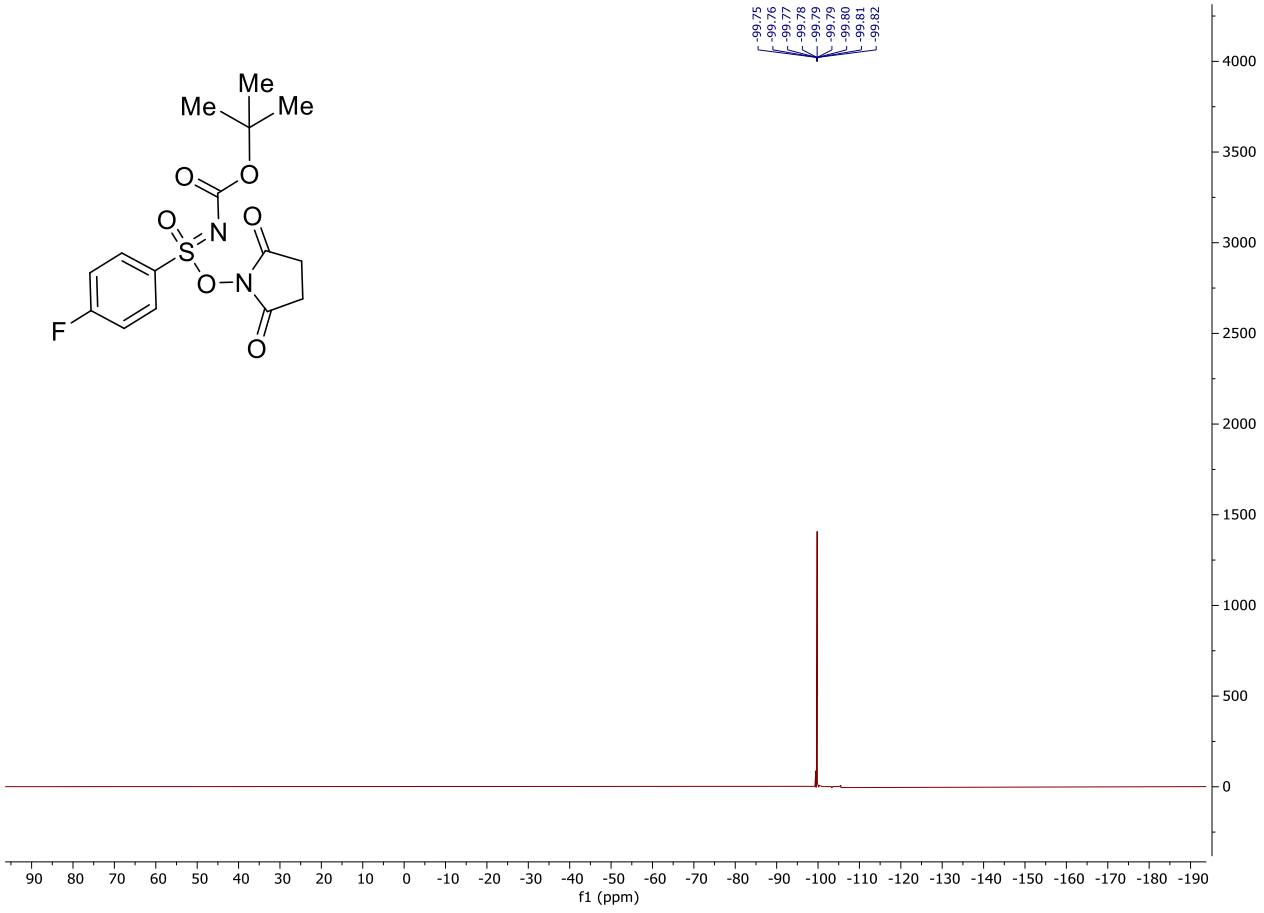


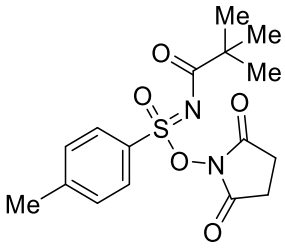


2,5-Dioxopyrrolidin-1-yl *N*-(*tert*-butoxycarbonyl)-4-fluorobenzenesulfonimidate (89a)

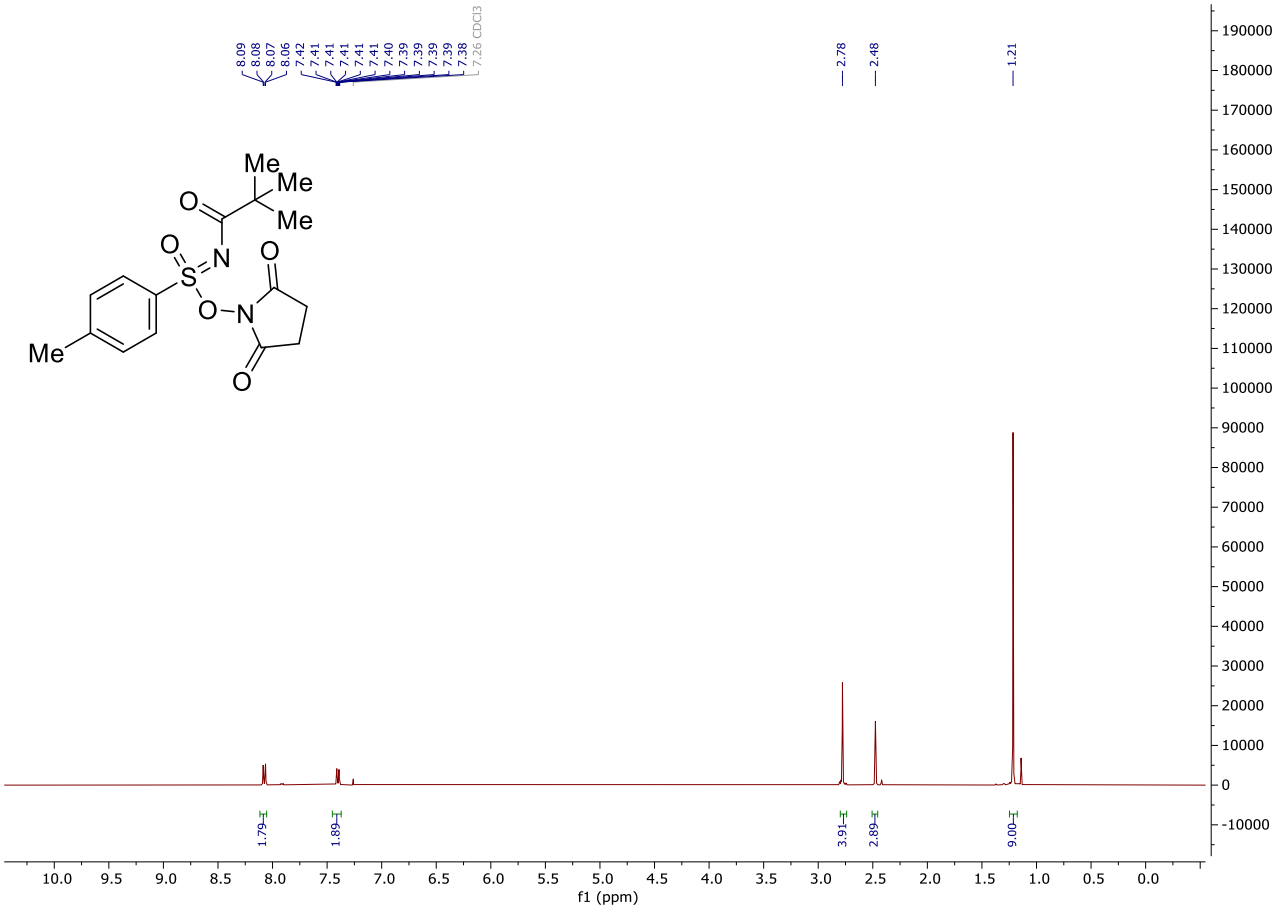

8.25
8.23
8.23
8.22
8.21
8.21
8.20
8.20
8.19
8.18
8.18
7.30
7.28
7.28
7.27
7.27
7.26 CDCl3
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.22
2.76
2.76
1.52
Me
Me
Me
O
O
O
N
O
S
O
O–N
O
F
1.80
2.18
3.59
9.00
f1 (ppm)

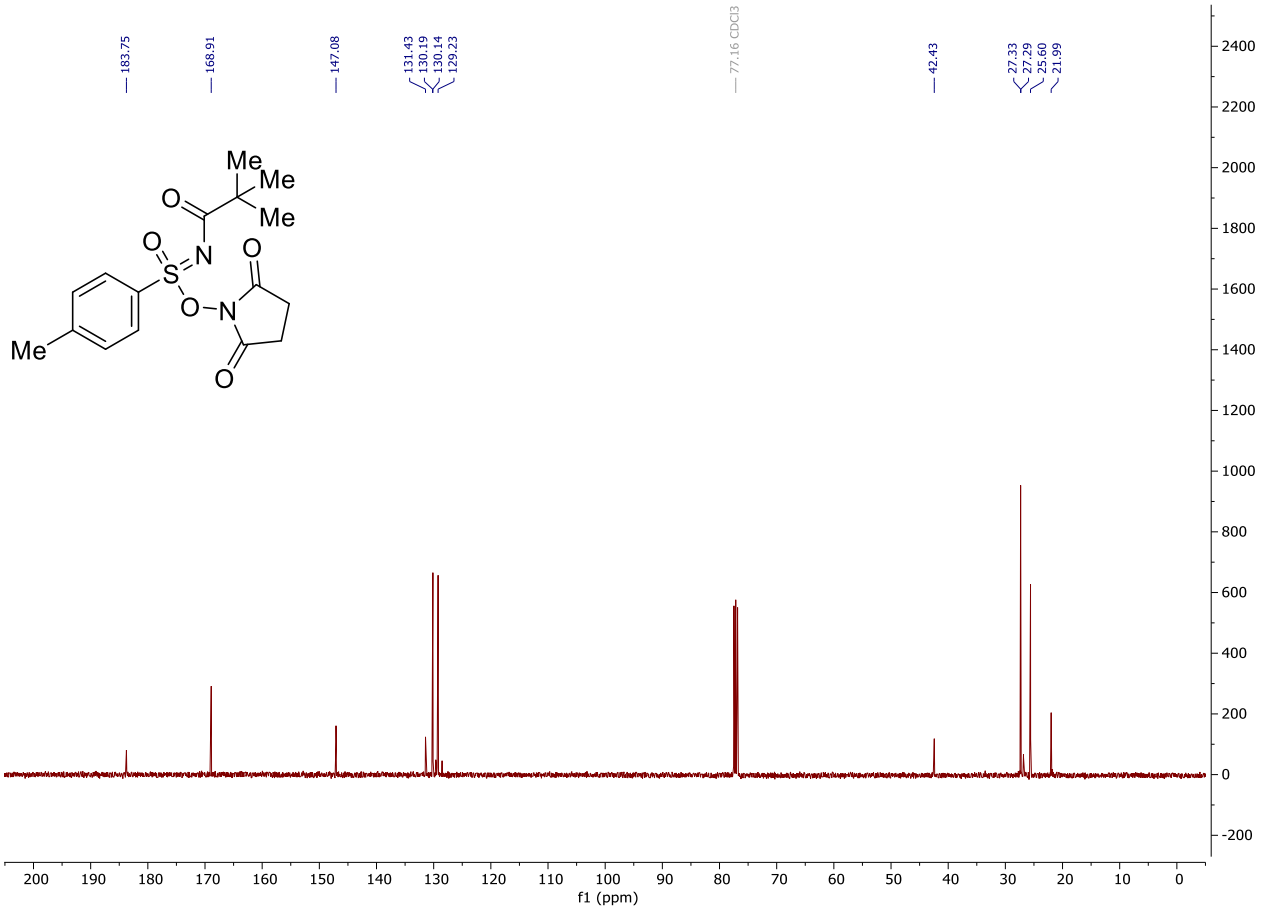

168.68
168.29
165.71
152.27
132.57
132.54
132.47
130.08
130.05
116.94
116.71
82.99
77.16 CDCl3
27.98
27.94
25.56
25.53
Me
Me
Me
O
O
O
N
O
S
O
O–N
O
F
f1 (ppm)





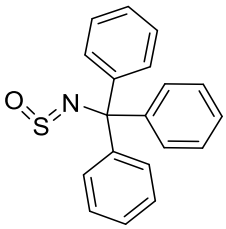
2,5-Dioxopyrrolidin-1-yl 4-methyl-*N*-pivaloylbenzenesulfonimidate (89b)


8.09
8.08
8.07
8.06
7.42
7.41
7.41
7.41
7.41
7.41
7.40
7.39
7.39
7.39
7.39
7.38
7.26 CDCl3
2.78
2.48
1.21
Me
Me
Me
O
N
S
O
O
O
N
O
Me
O
1.79
1.89
3.91
2.89
9.00
f1 (ppm)

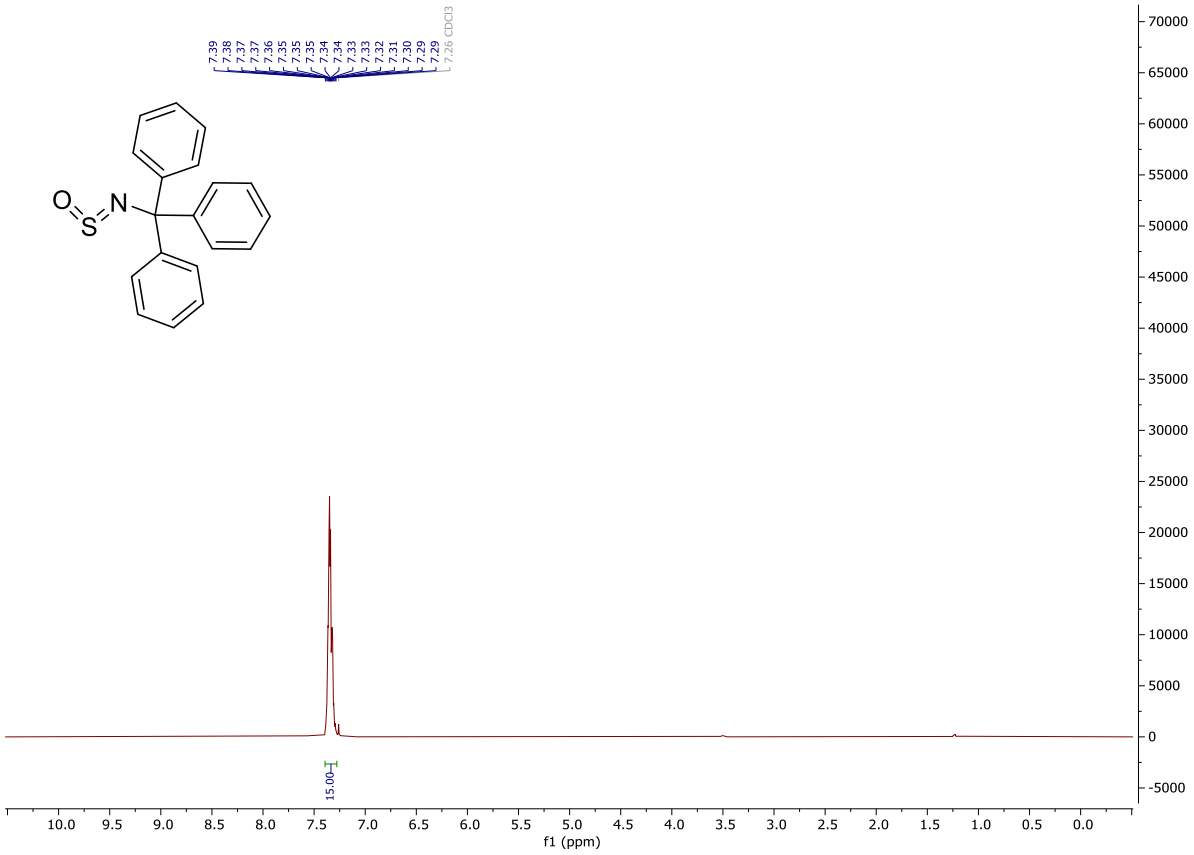

183.75
168.91
147.08
131.43
130.19
130.14
129.23
77.16 CDCl3
42.43
27.33
27.29
25.60
21.99
Me
Me
Me
O
N
S
O
O
O
N
O
Me
O
f1 (ppm)

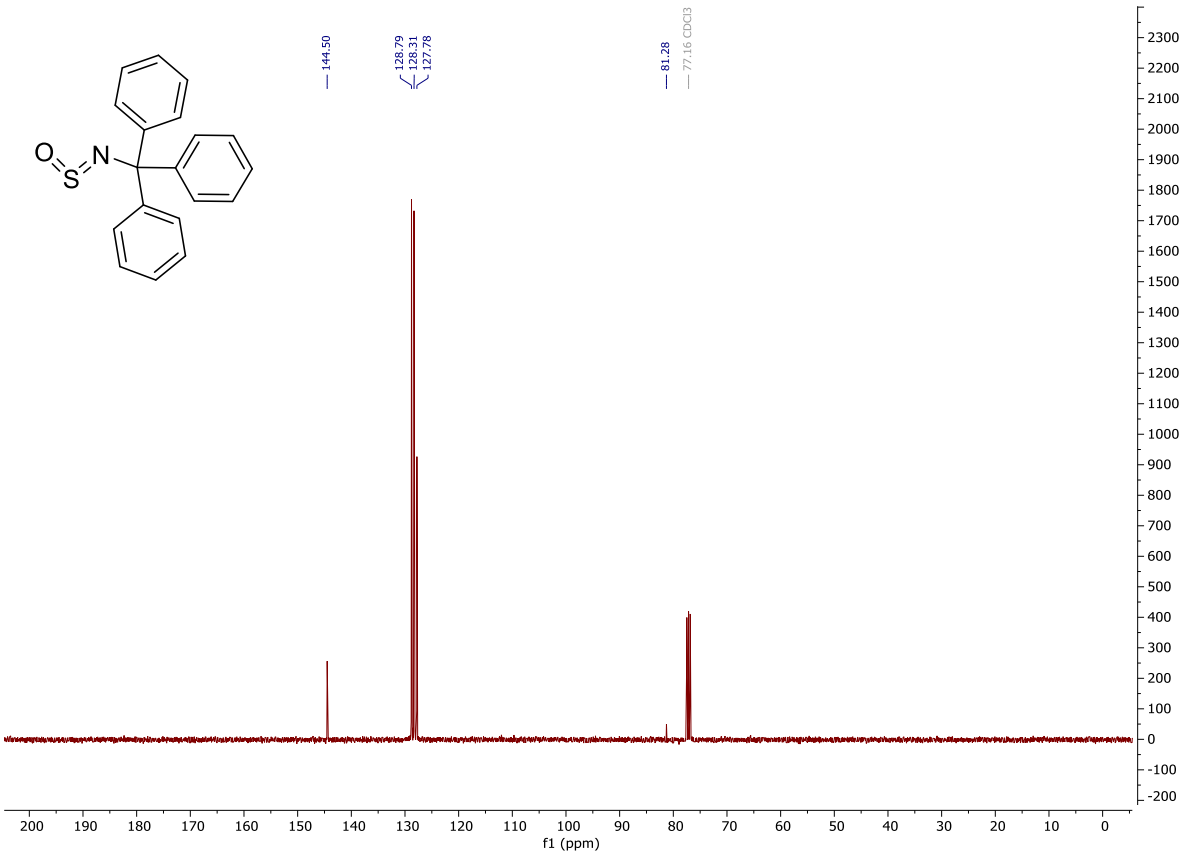
8.3. Spectra from Chapter 3

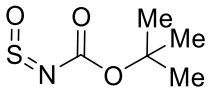
8.3.1 Sulfinyl amines



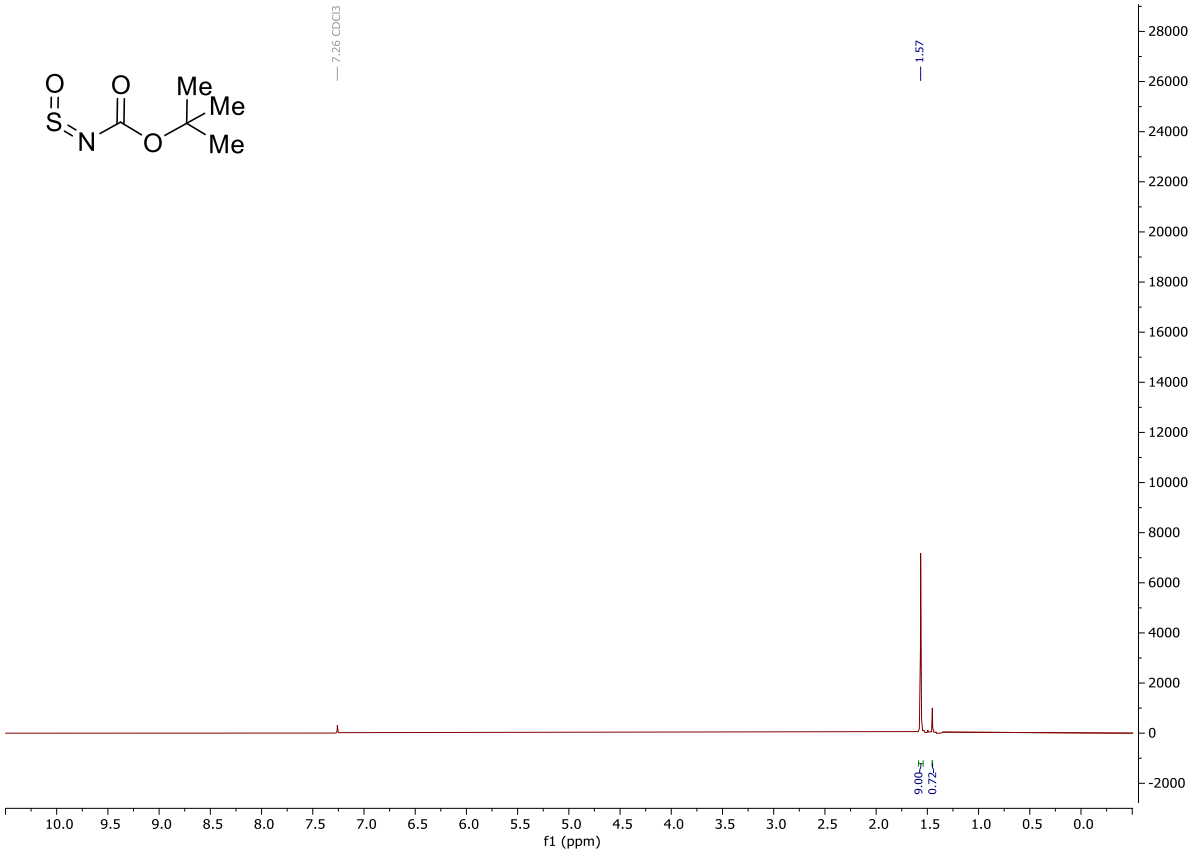
Tr-NSO (8)

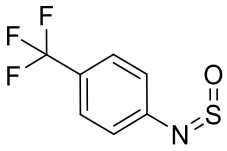




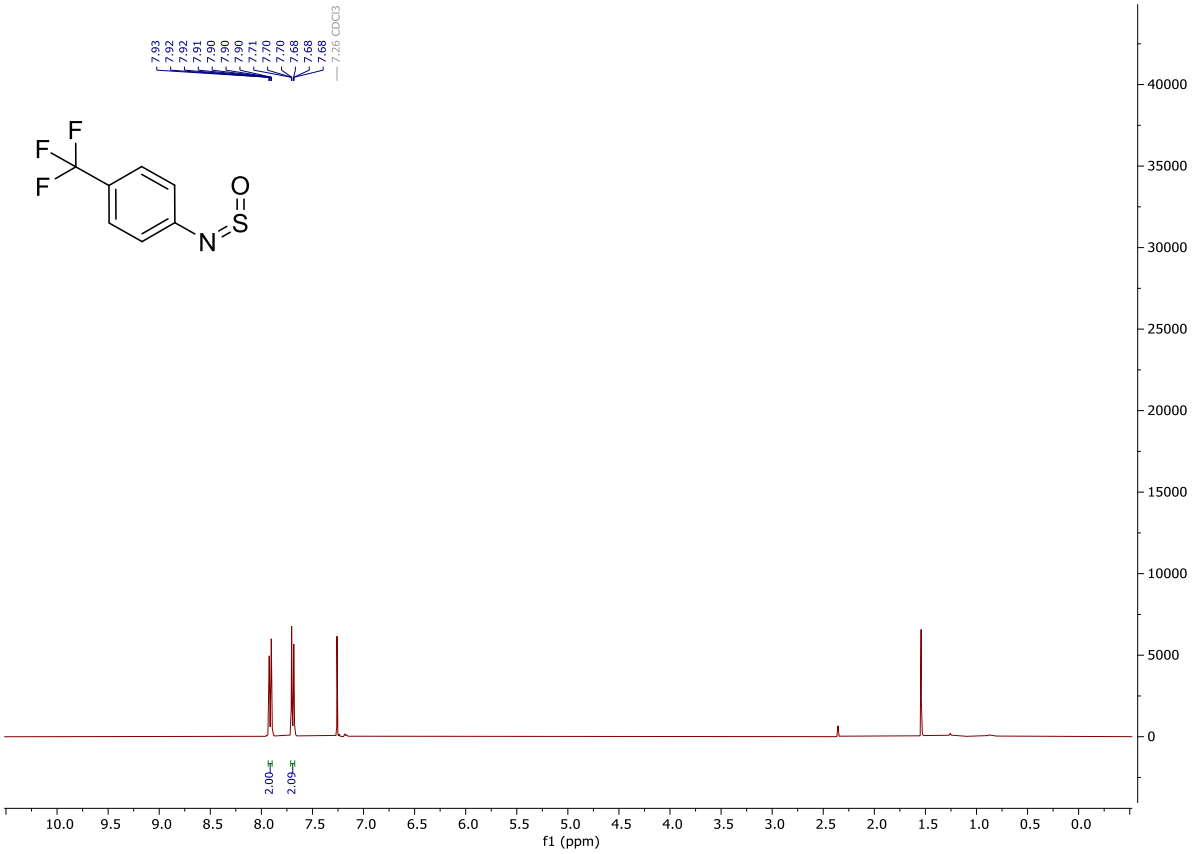


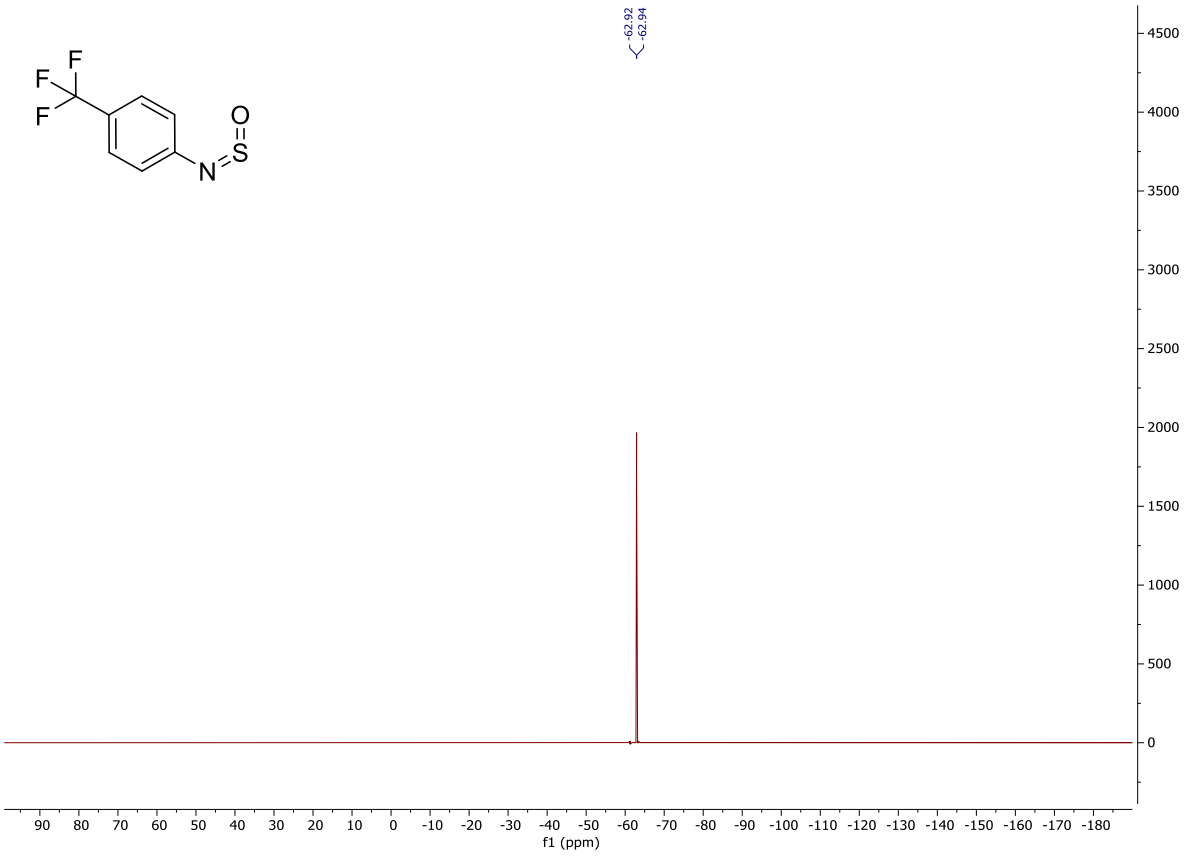
tert-Butyl (oxo-λ^4-sulfaneylidene)carbamate (boc-NSO, 83c)

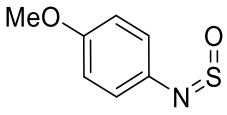




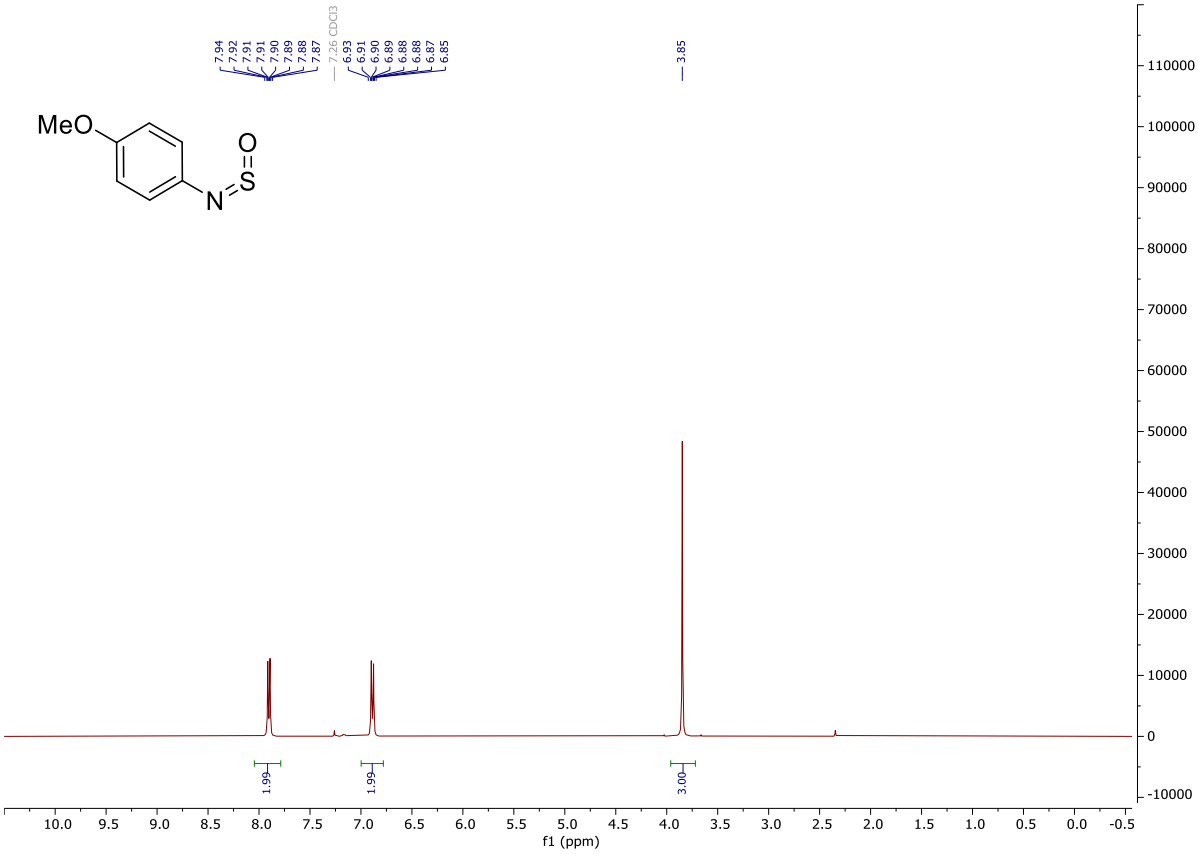
((4-(Trifluoromethyl)phenyl)imino)-λ^4-sulfanone (4-CF_3Ph-NSO, 83d)

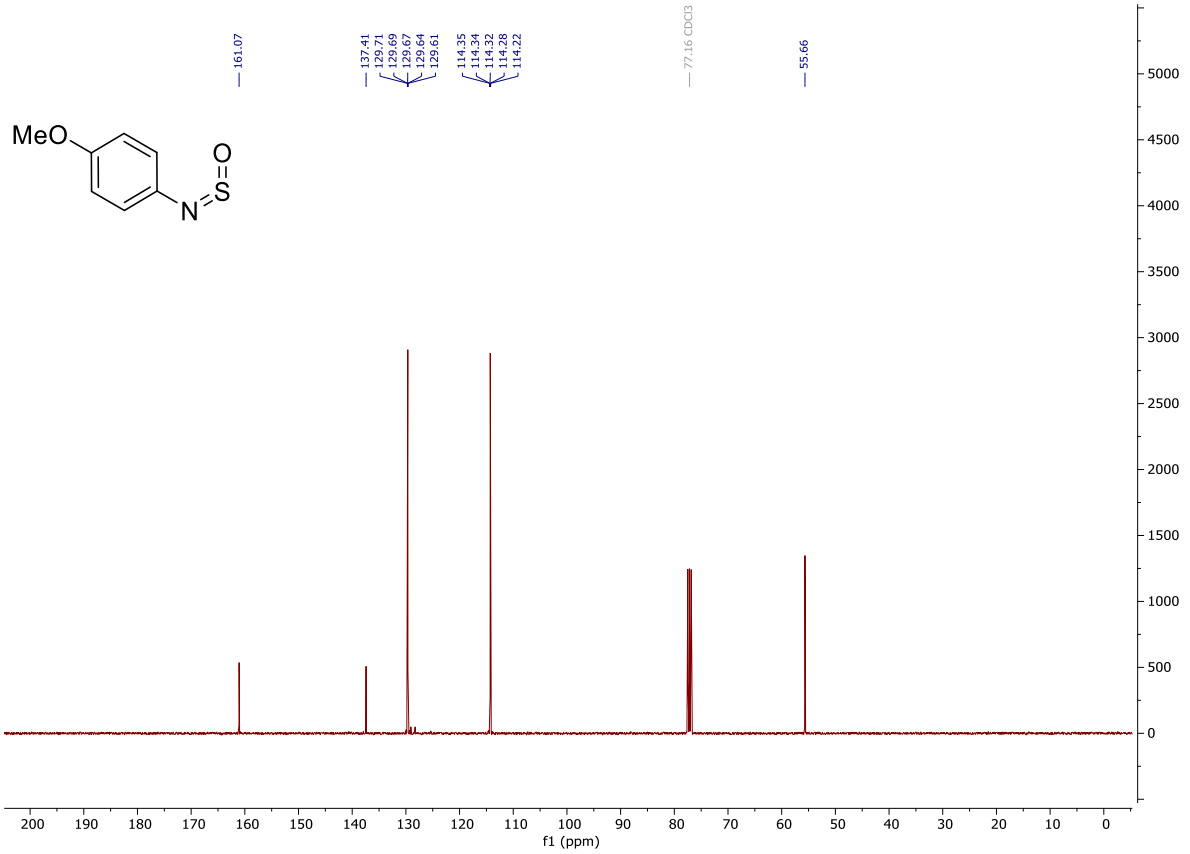

7.93
7.92
7.92
7.91
7.90
7.90
7.90
7.90
7.71
7.70
7.70
7.68
7.68
7.68
7.26 CDCl3
F
F
F
O
S
N
40000
35000
30000
25000
20000
15000
10000
5000
0
2.00
2.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


-62.92
-62.94
F
F
F
O
S
N
4500
4000
3500
3000
2500
2000
1500
1000
500
0
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180
f1 (ppm)

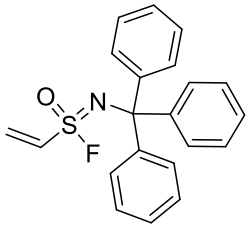


((4-Methoxyphenyl)imino)-λ^4-sulfanone (4-OMePh-NSO, 83e)

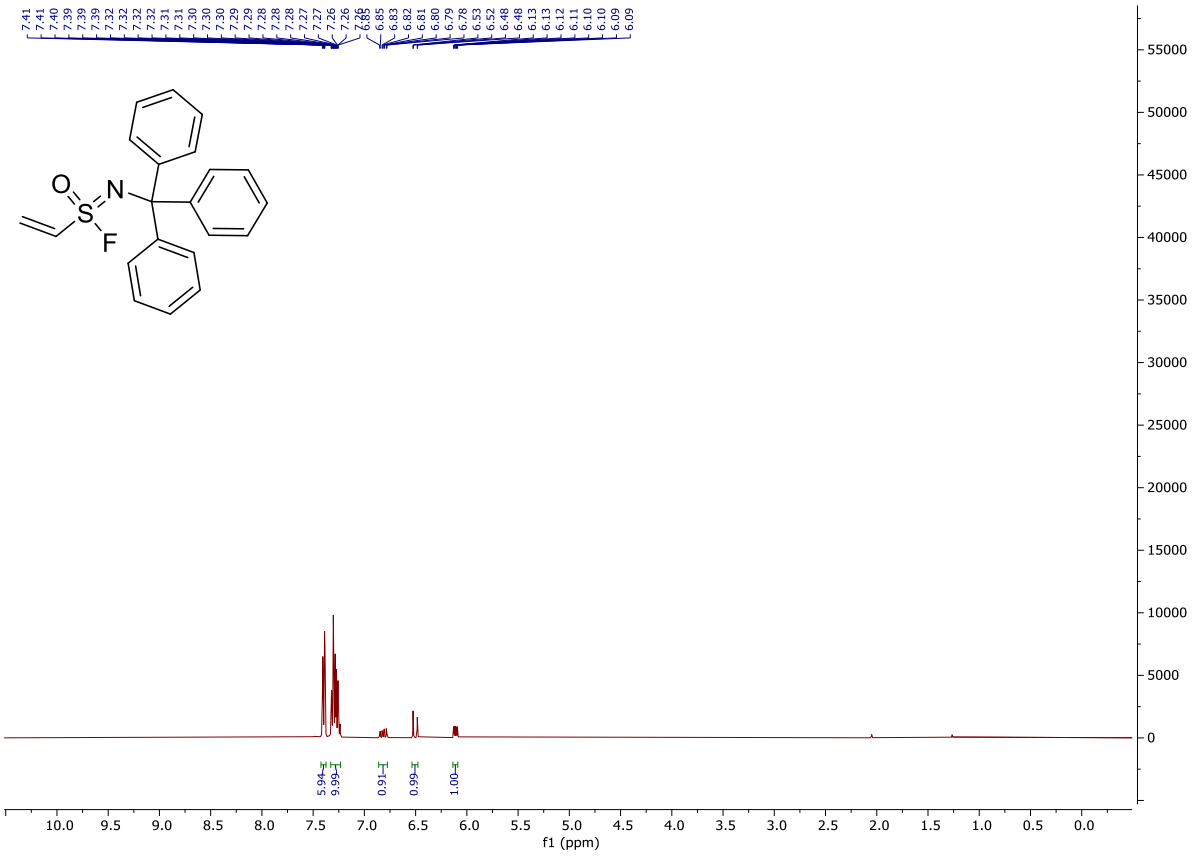


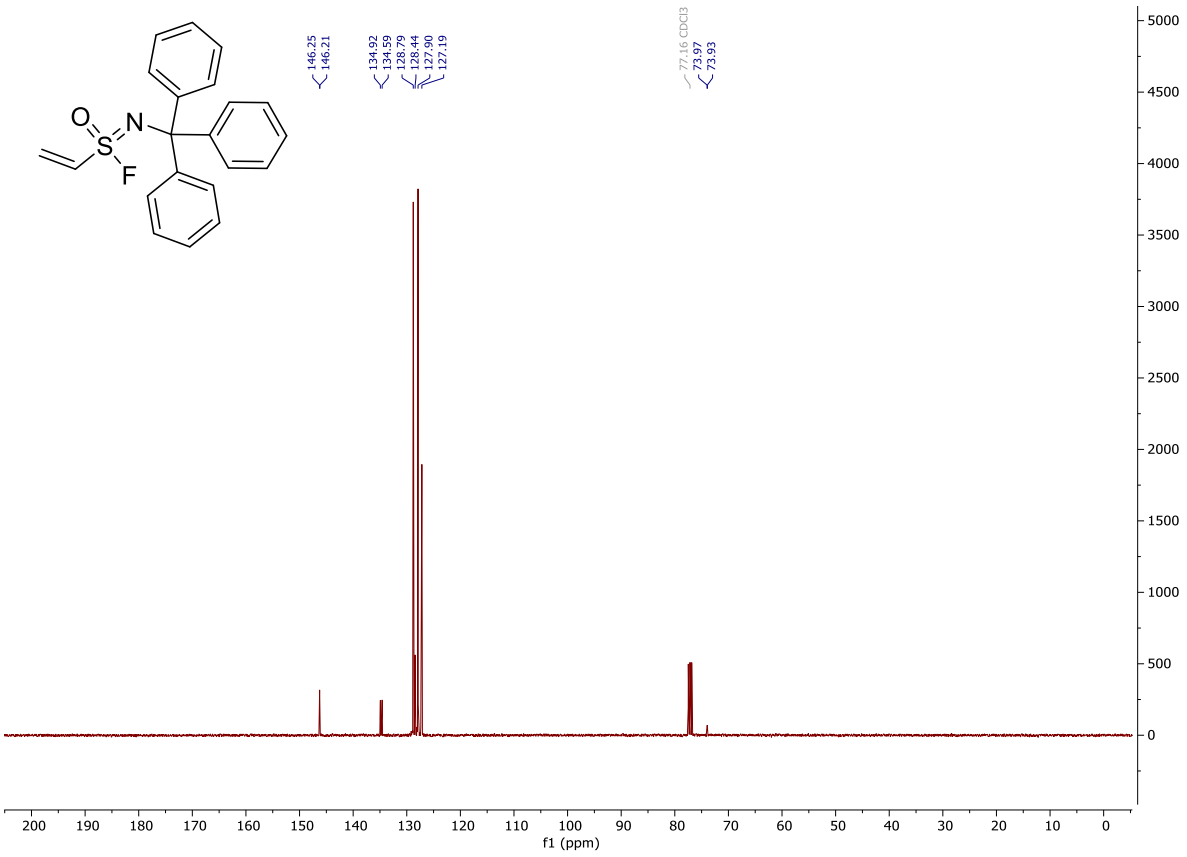

161.07
137.41
129.71
129.69
129.67
129.64
129.61
114.35
114.34
114.32
114.28
114.22
77.16 CDCl3
55.66
MeO
O
S
N
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

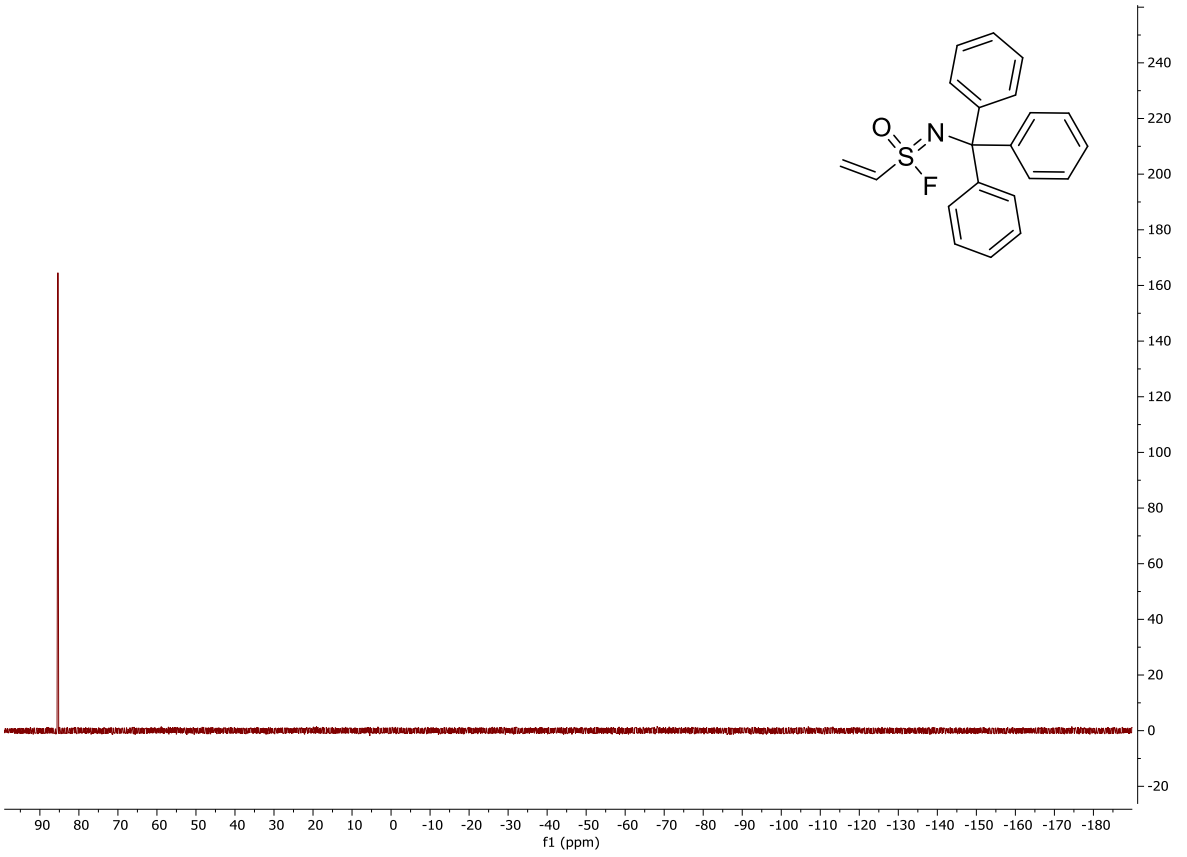
8.3.3 Sulfonimidoyl fluorides

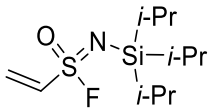


_N_-Tritylethenesulfonimidoyl fluoride (125a)

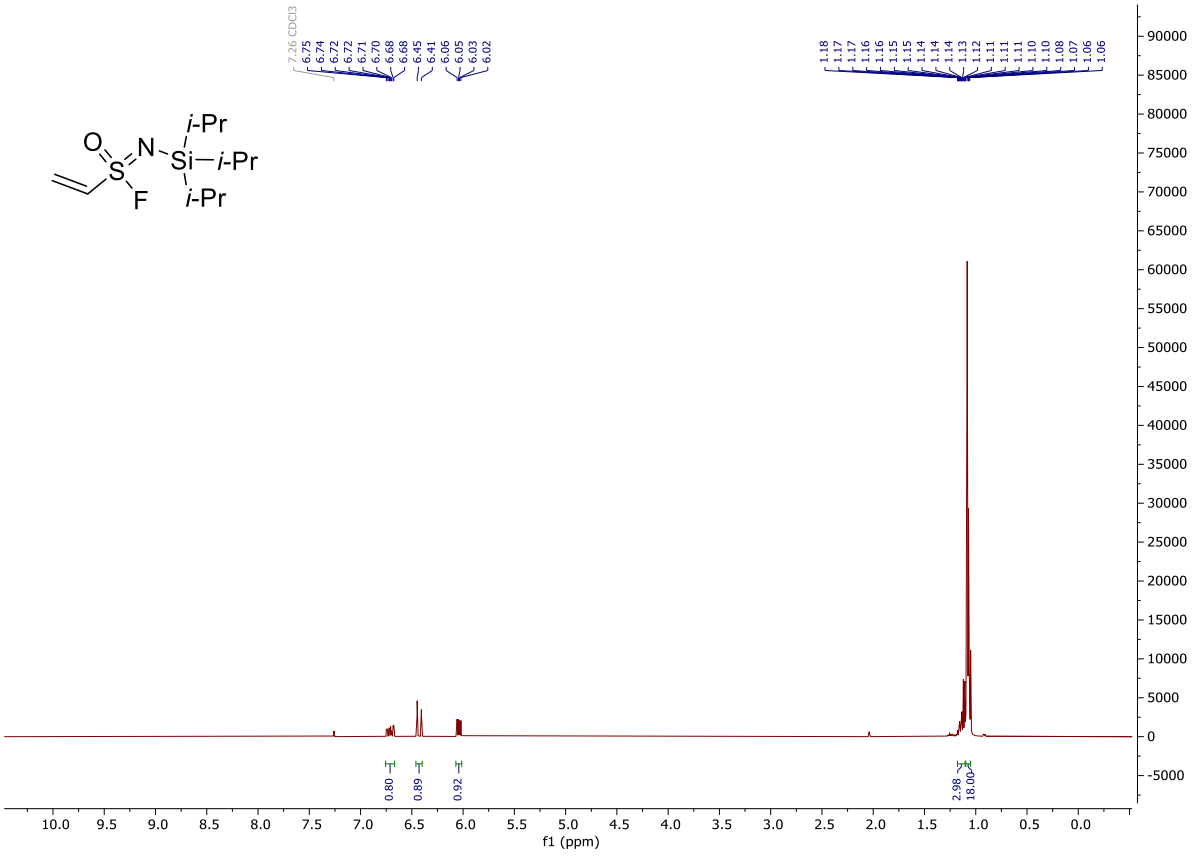


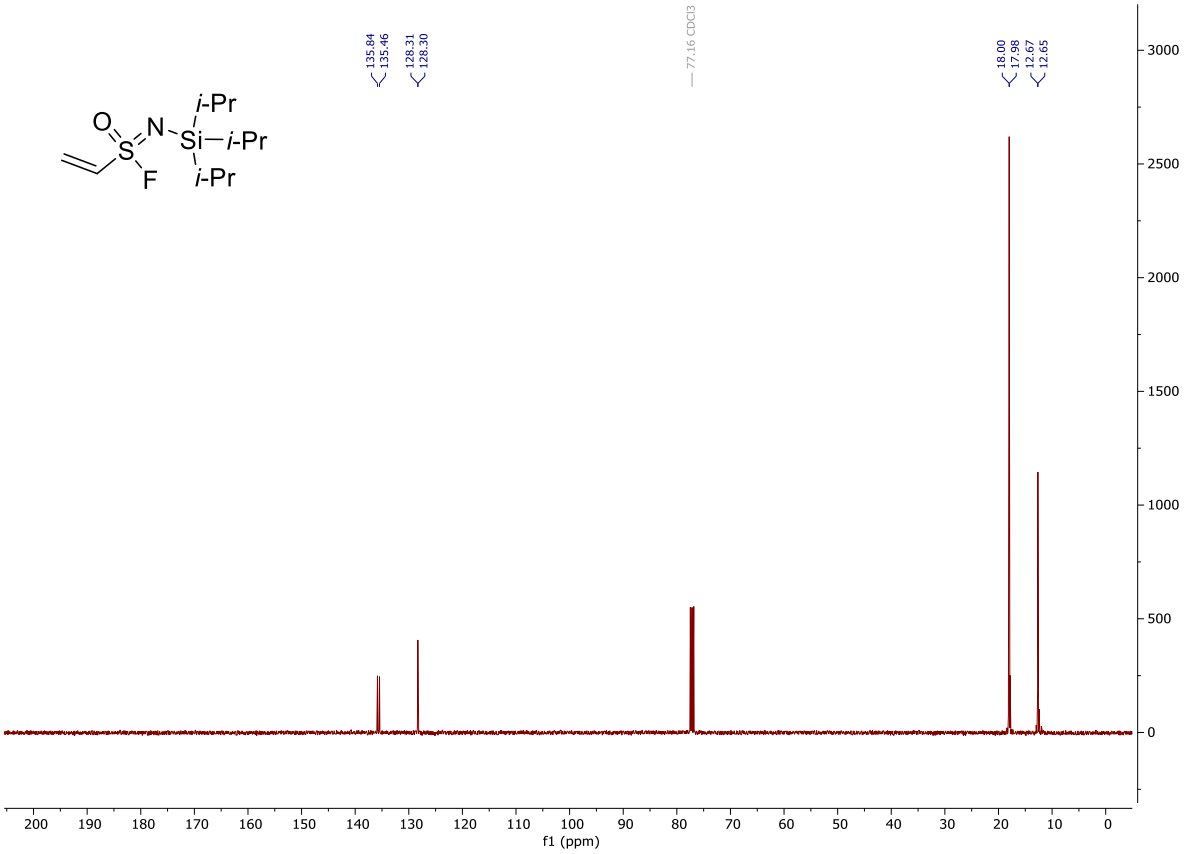

146.25
146.21
134.92
134.59
128.79
128.44
127.90
127.19
77.16 CDCl3
73.97
73.93
O
N
S
F
f1 (ppm)

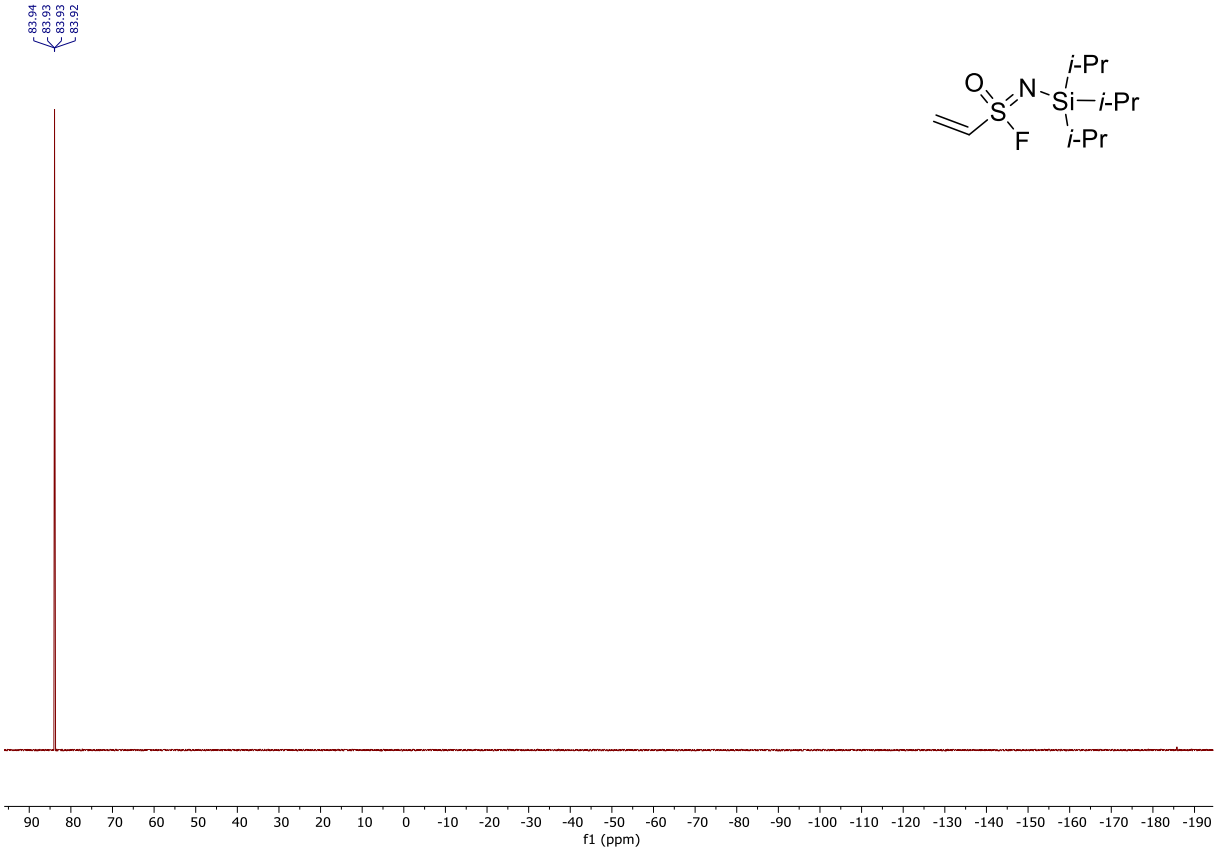

O
N
S
F
f1 (ppm)

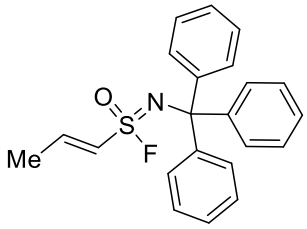


_N_-(Triisopropylsilyl)ethenesulfonimidoyl fluoride (TIPS-ESIF, 125b)

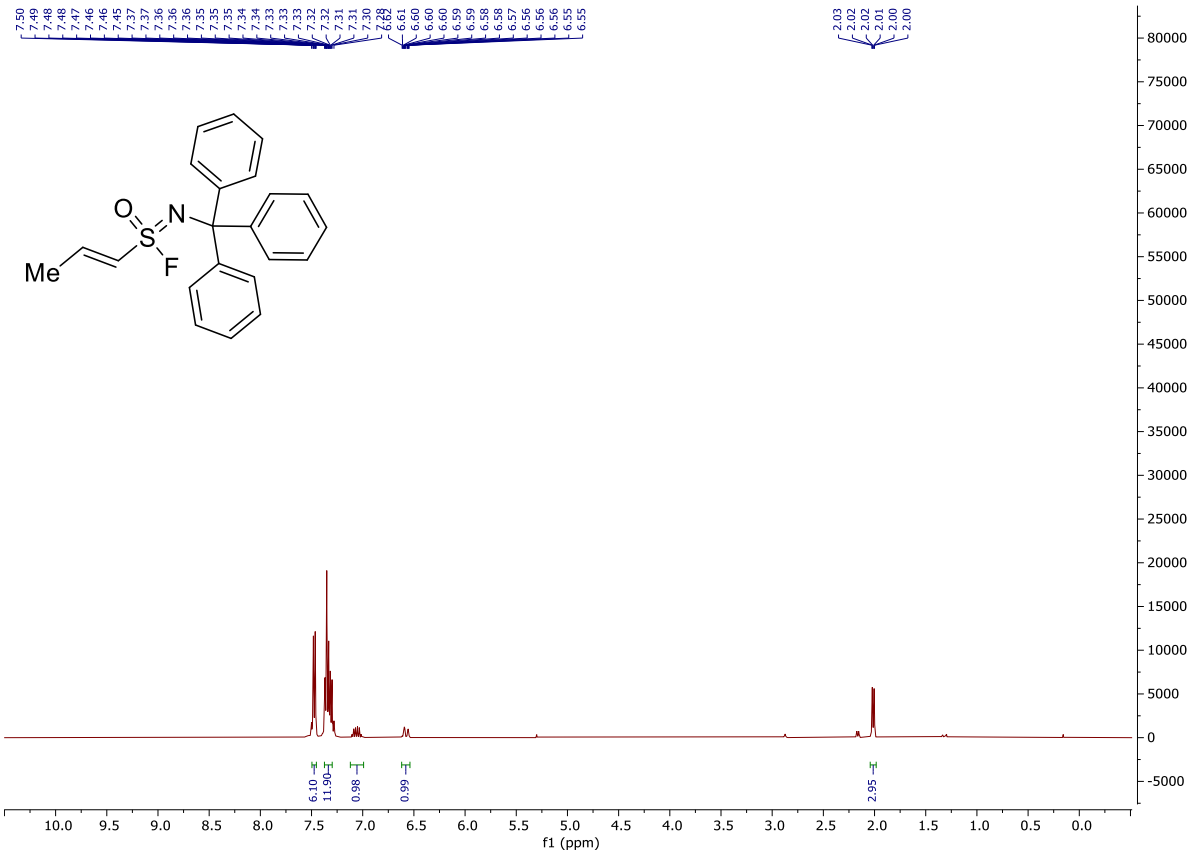


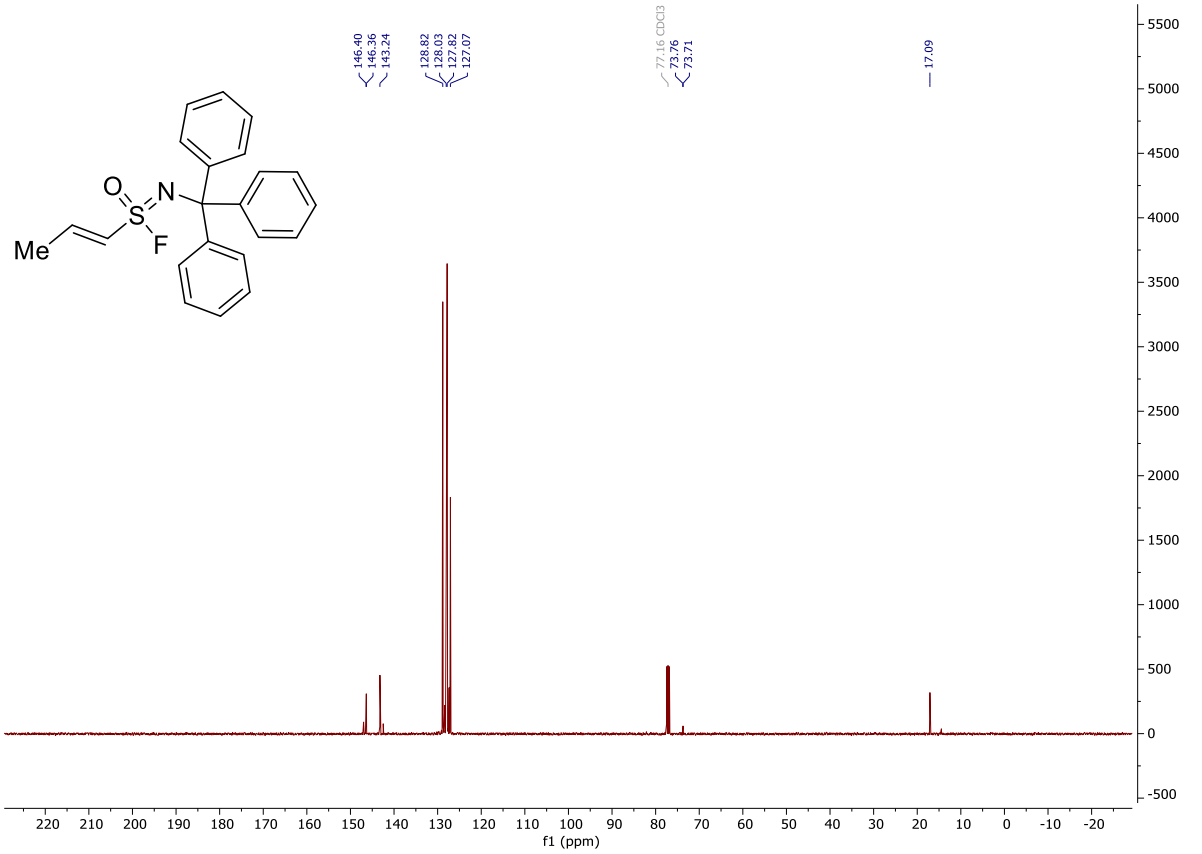

135.84
135.46
128.31
128.30
77.16 CDCl3
18.00
17.98
12.67
12.65
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
i-Pr
i-Pr
i-Pr
O
N
Si
S
F

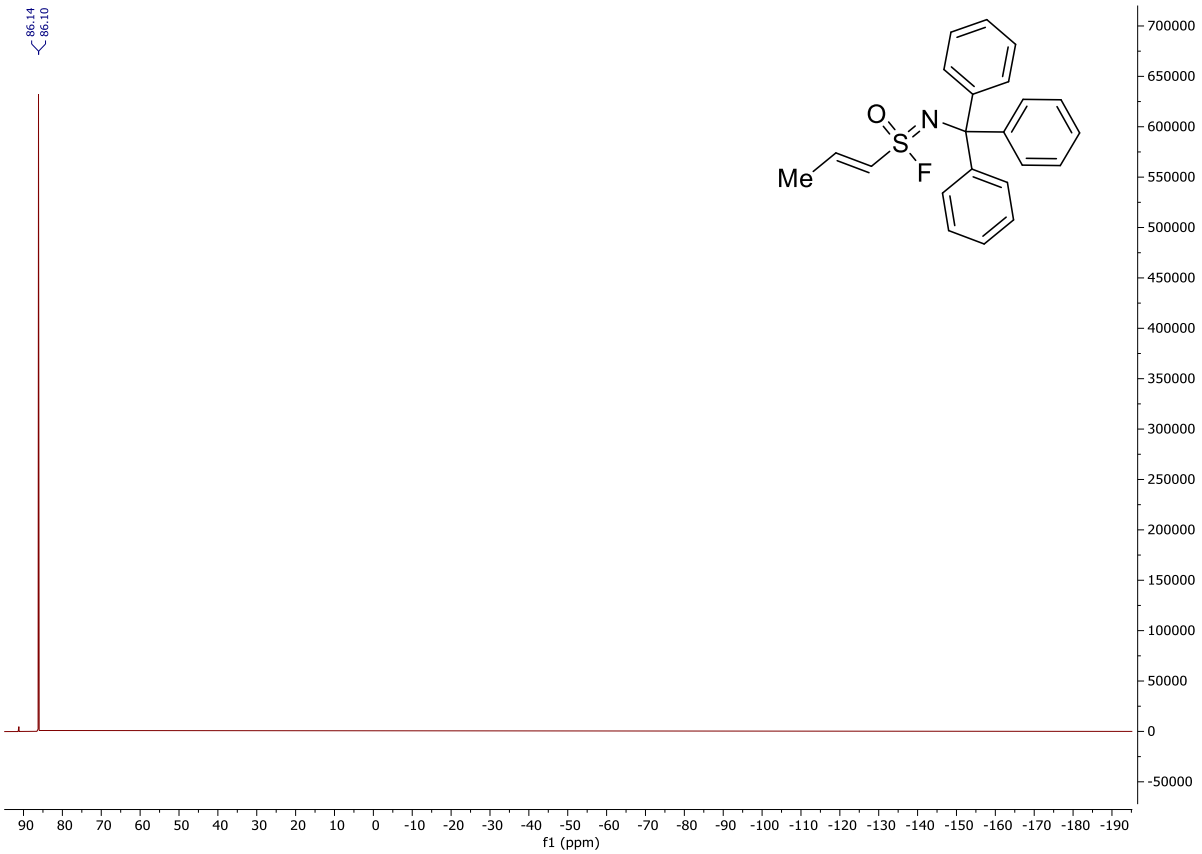

83.94
83.93
83.93
83.92
i-Pr
i-Pr
i-Pr
O
N
Si
S
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

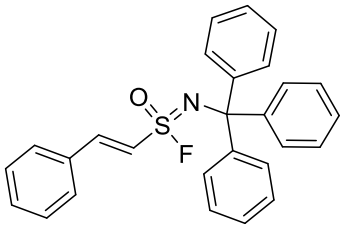


_(E)-N_-Tritylprop-1-ene-1-sulfonimidoyl fluoride (131a)

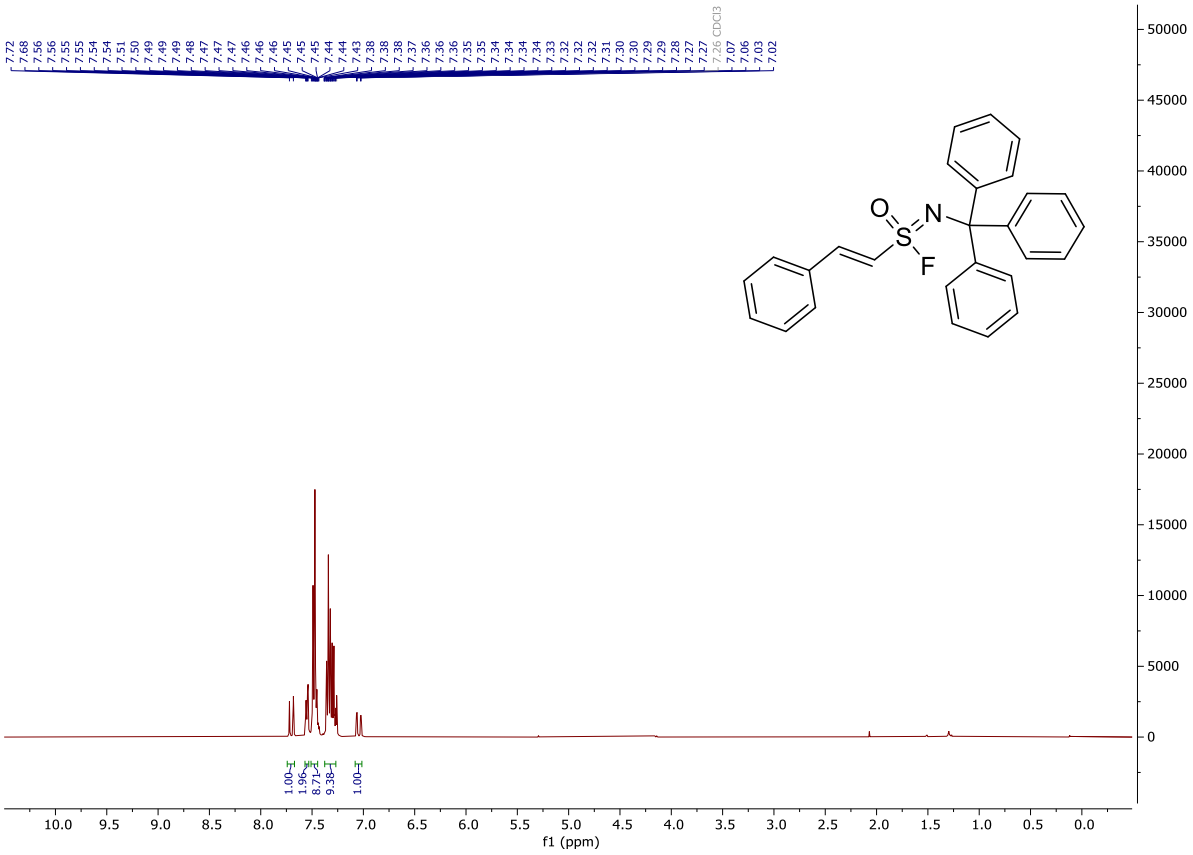


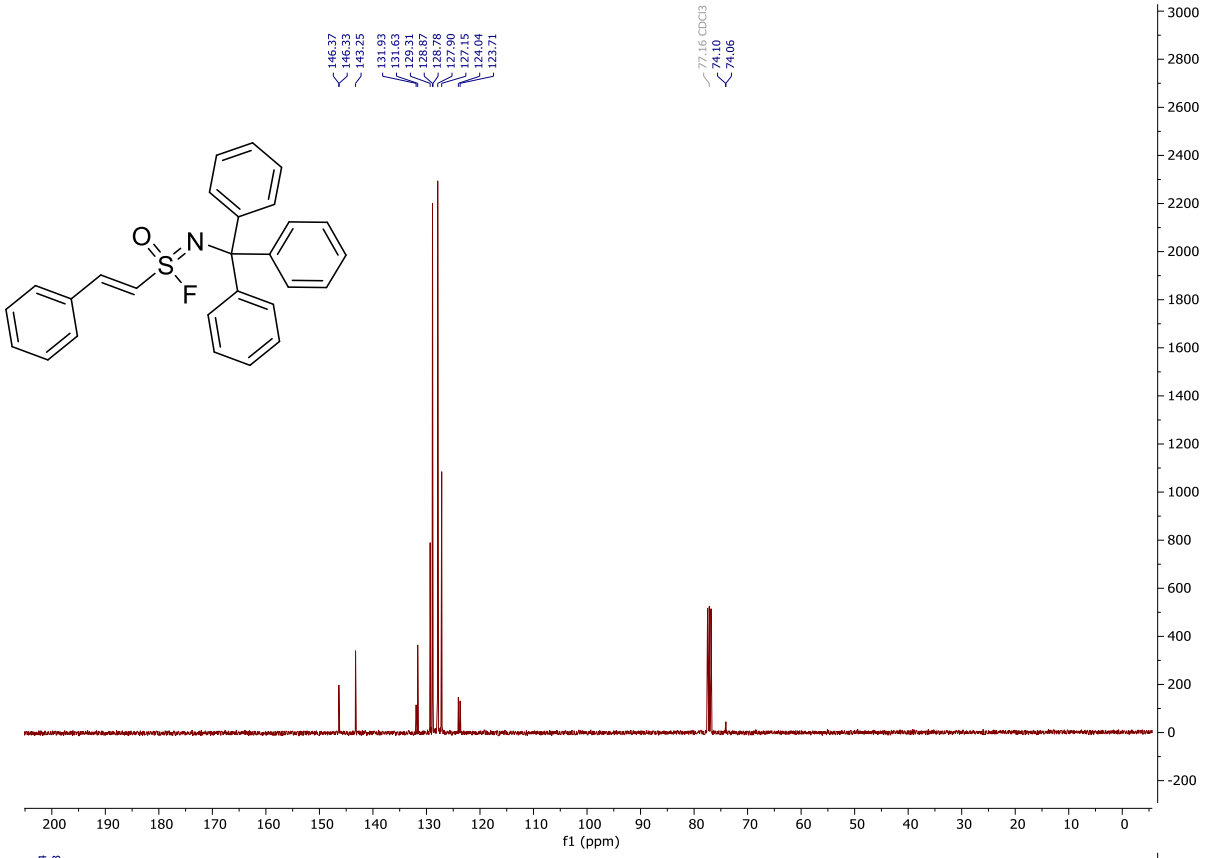

146.40
146.36
143.24
128.82
128.03
127.82
127.07
77.16 CDCl3
73.76
73.71
17.09
O
N
S
F
Me
f1 (ppm)

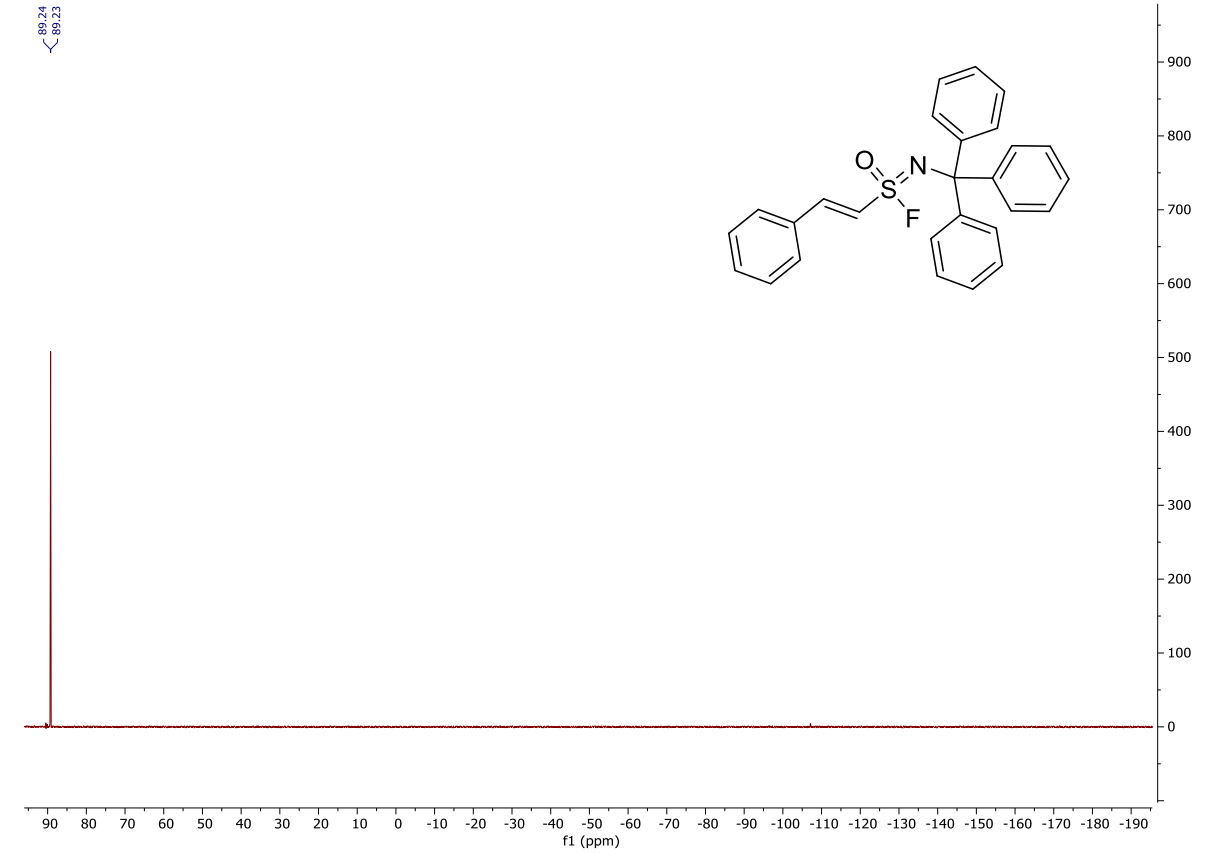

86.14
86.10
O
N
S
F
Me
f1 (ppm)

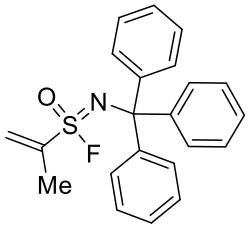


(*E*)-2-Phenyl-*N*-tritylethene-1-sulfonimidoyl fluoride (131b)

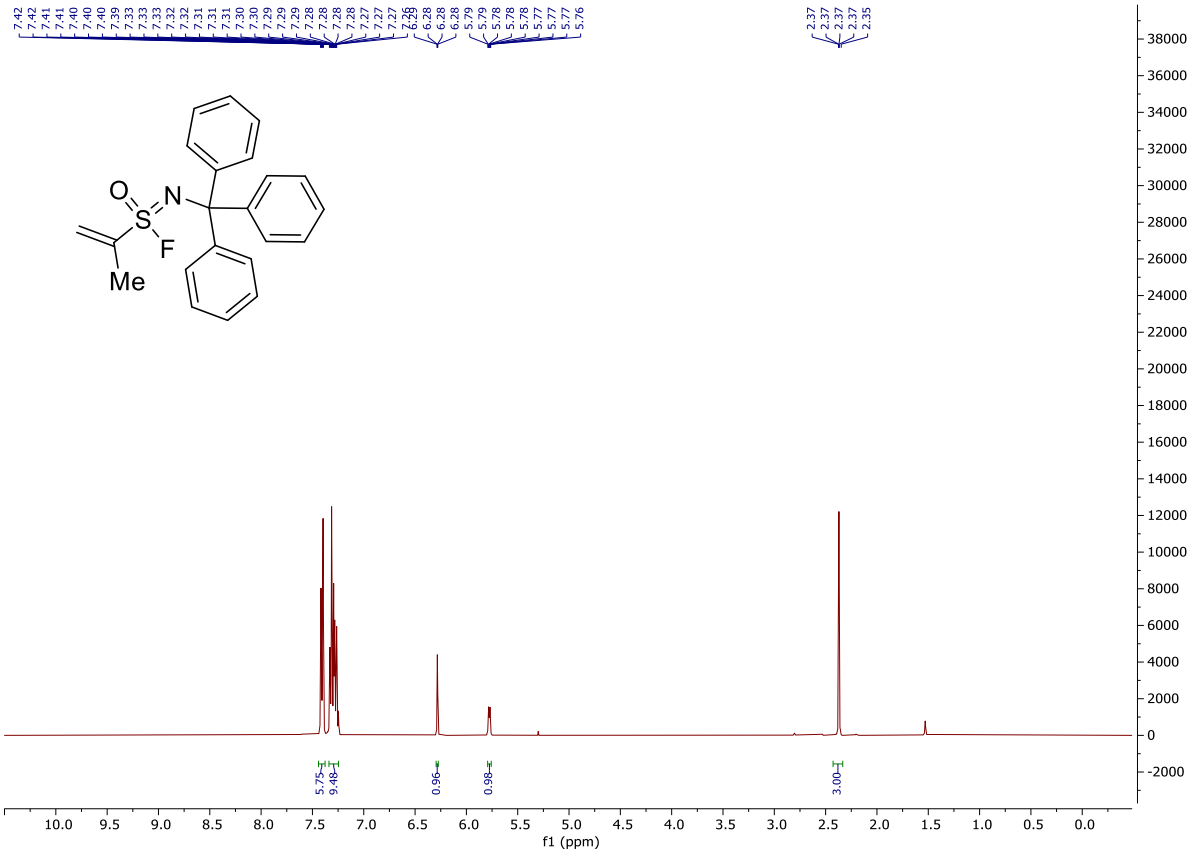


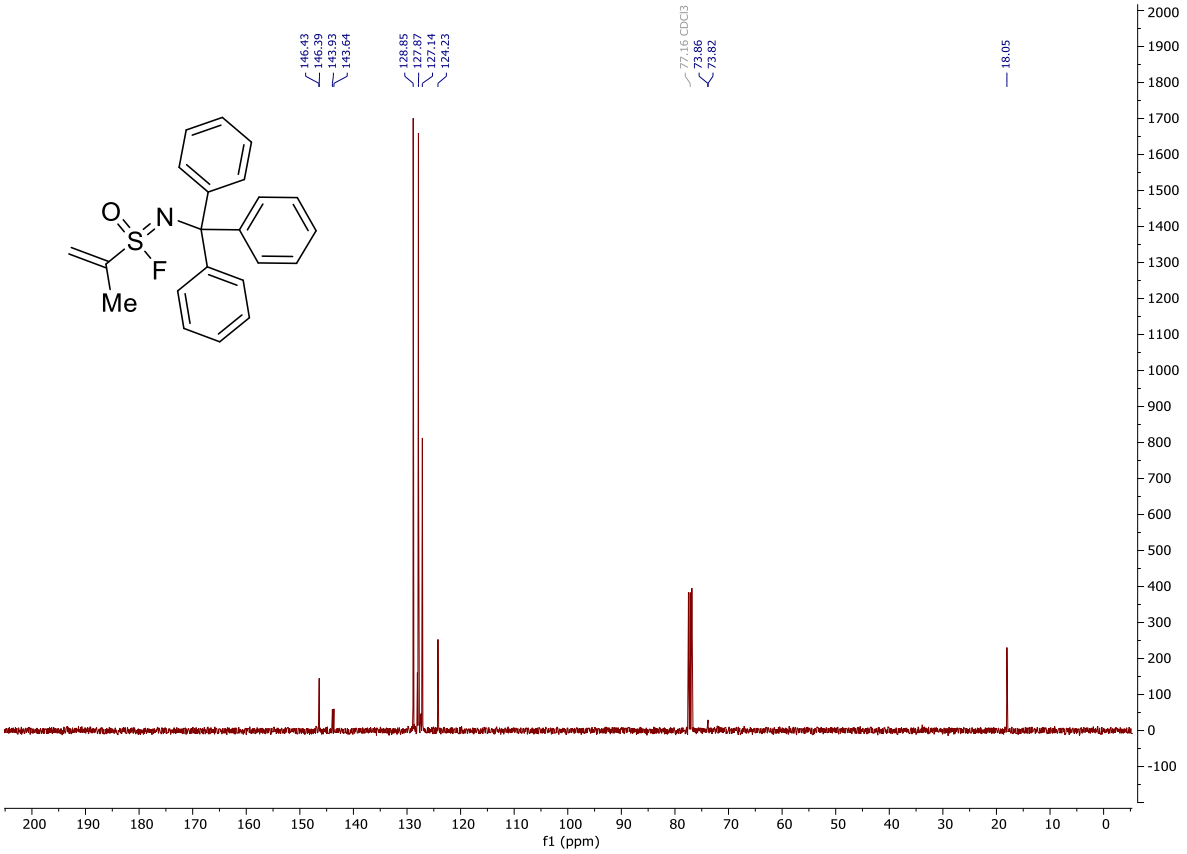

146.37
146.33
143.25
131.93
131.63
129.31
128.87
128.78
127.90
127.15
124.04
123.71
77.16 CDCl3
74.10
74.06
O
N
S
F
f1 (ppm)

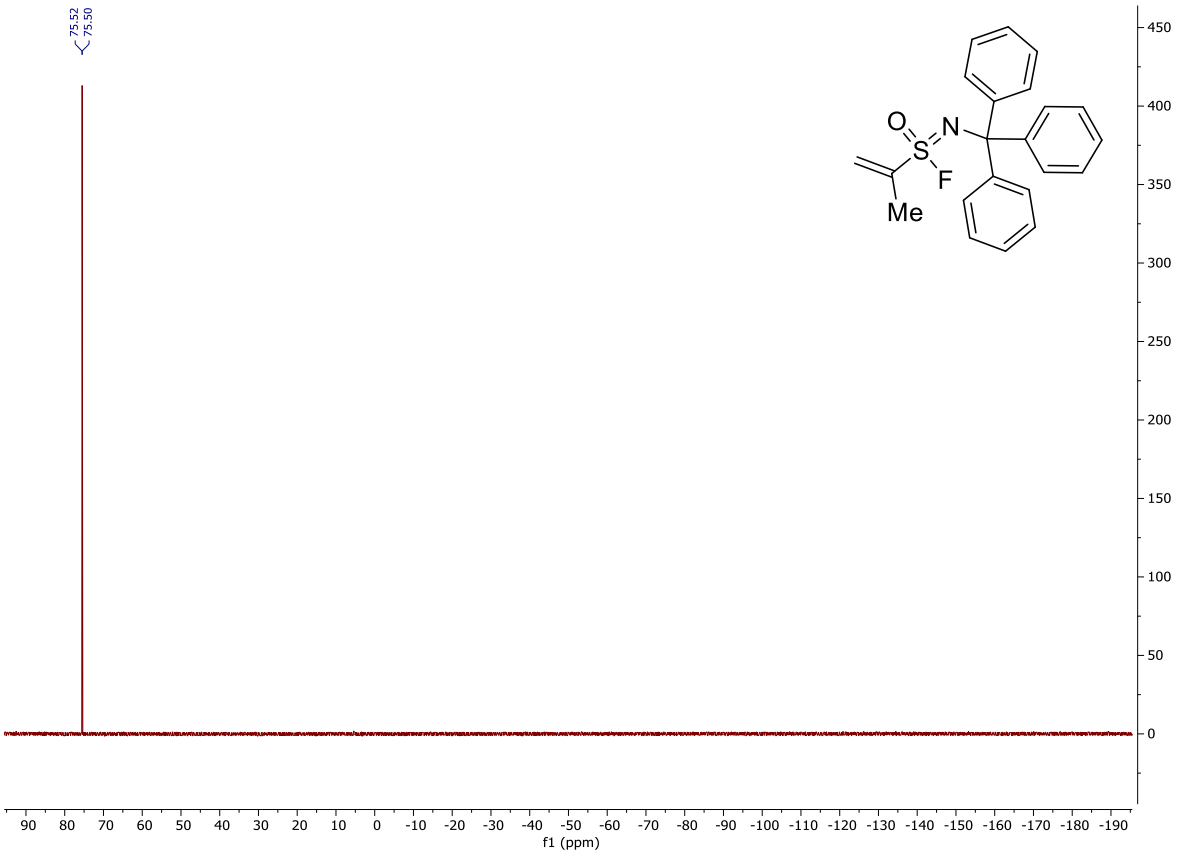

89.24
89.23
O
N
S
F
f1 (ppm)

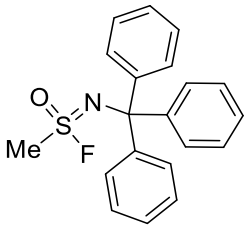


_N_-Tritylprop-1-ene-2-sulfonimidoyl fluoride (131c)

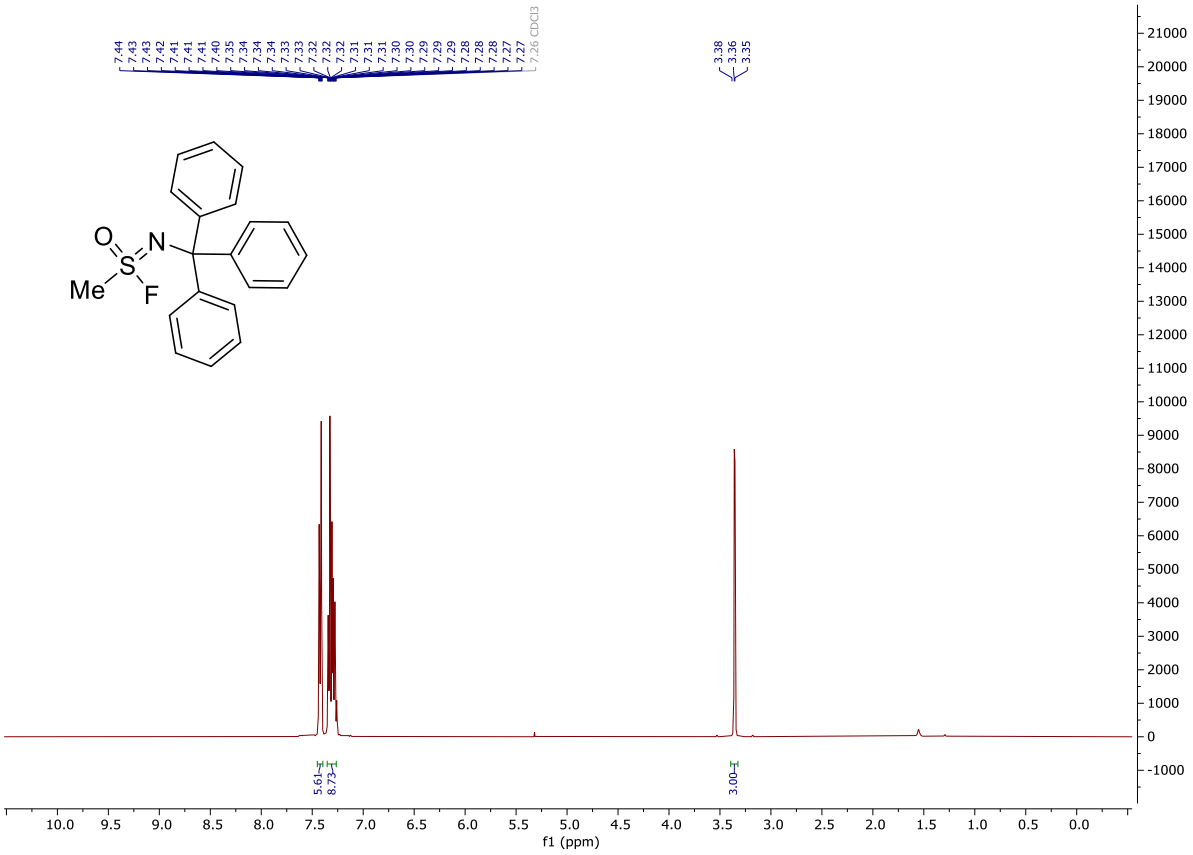


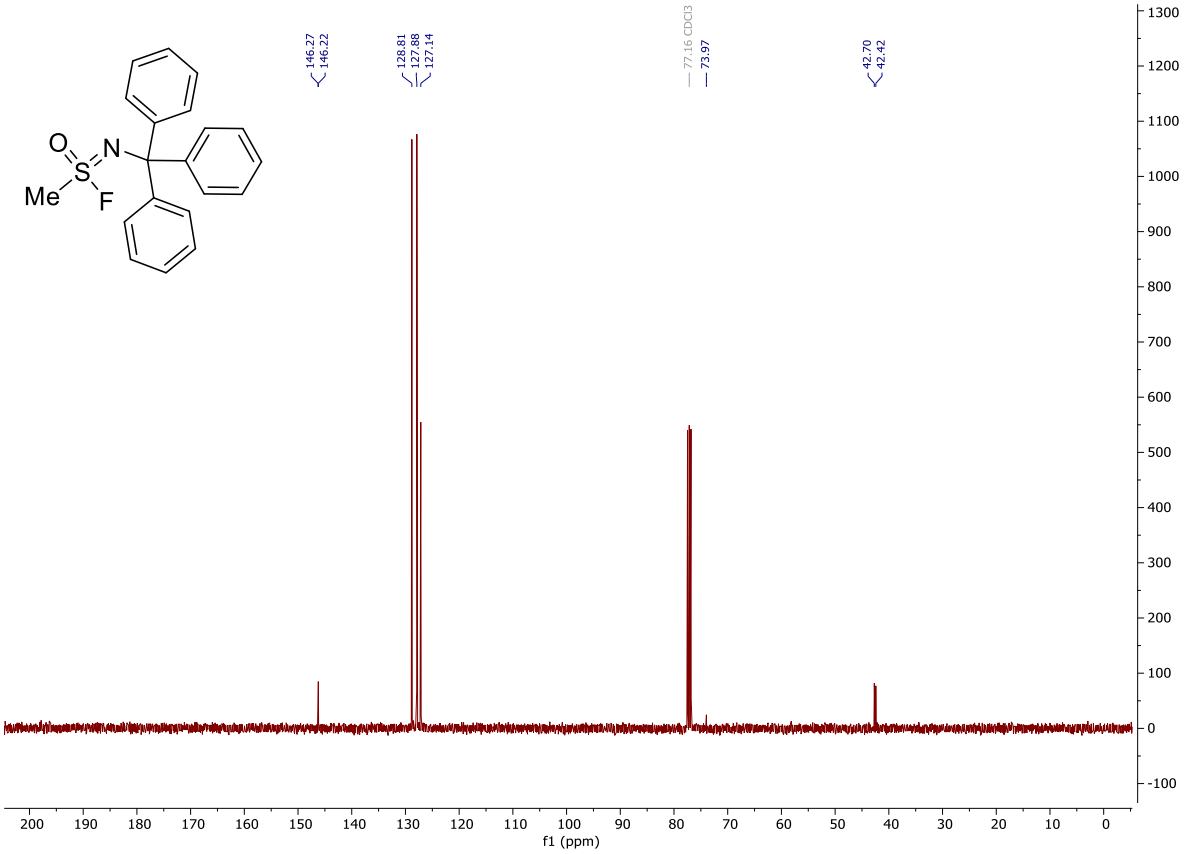

146.43
146.39
143.93
143.64
128.85
127.87
127.14
124.23
77.16 CDCl3
73.86
73.82
18.05
O
S
N
F
Me
f1 (ppm)

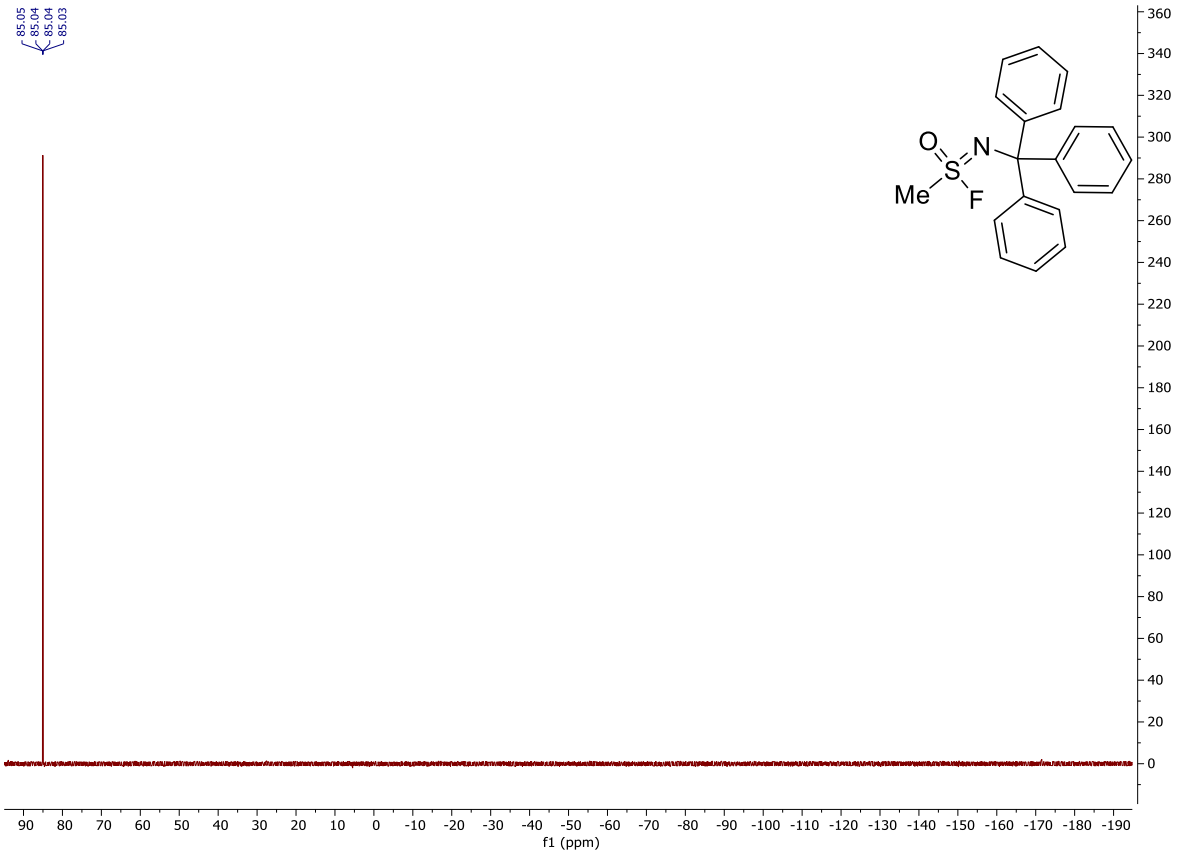

75.52
75.50
O
S
N
F
Me
f1 (ppm)

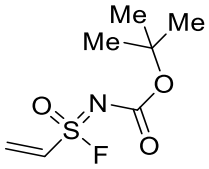


_N_-tritylmethanesulfonimidoyl fluoride (134)

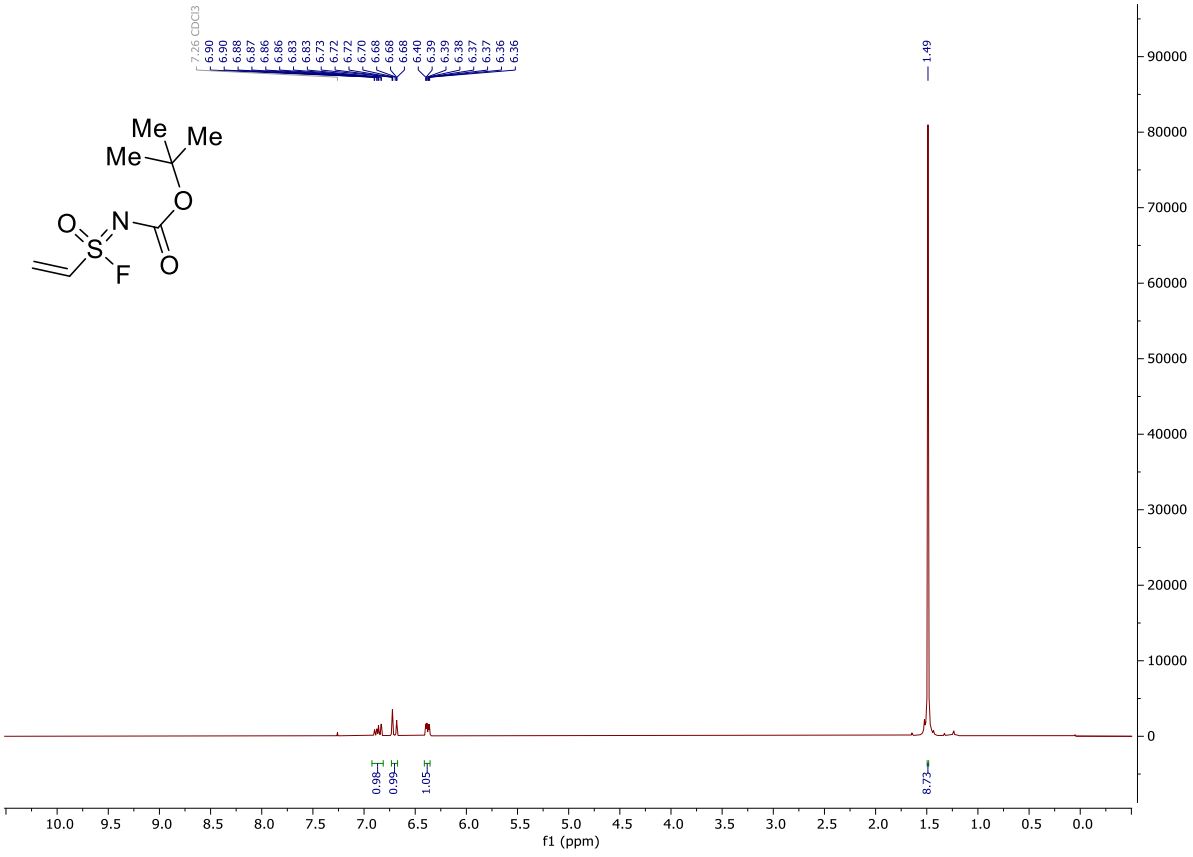


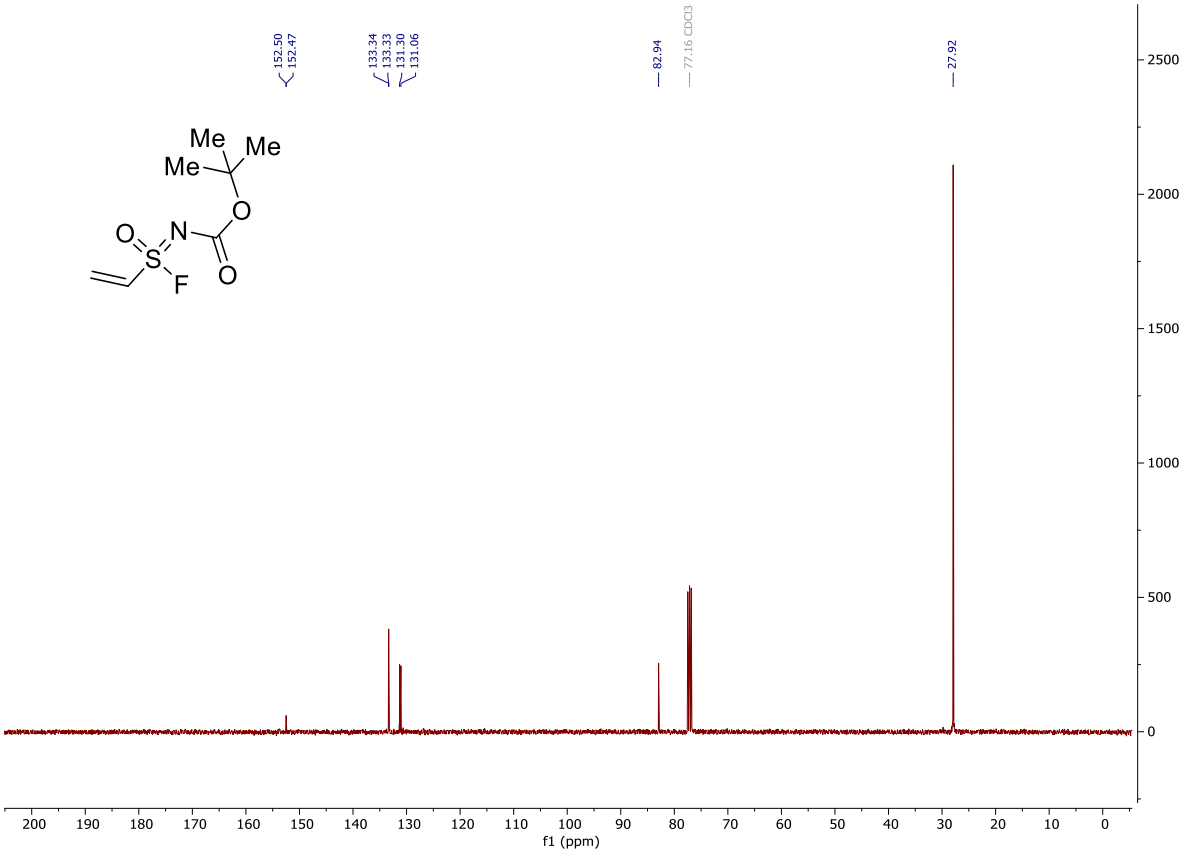

O
N
S
Me
F
146.27
146.22
128.81
127.88
127.14
77.16 CDCl3
73.97
42.70
42.42
f1 (ppm)

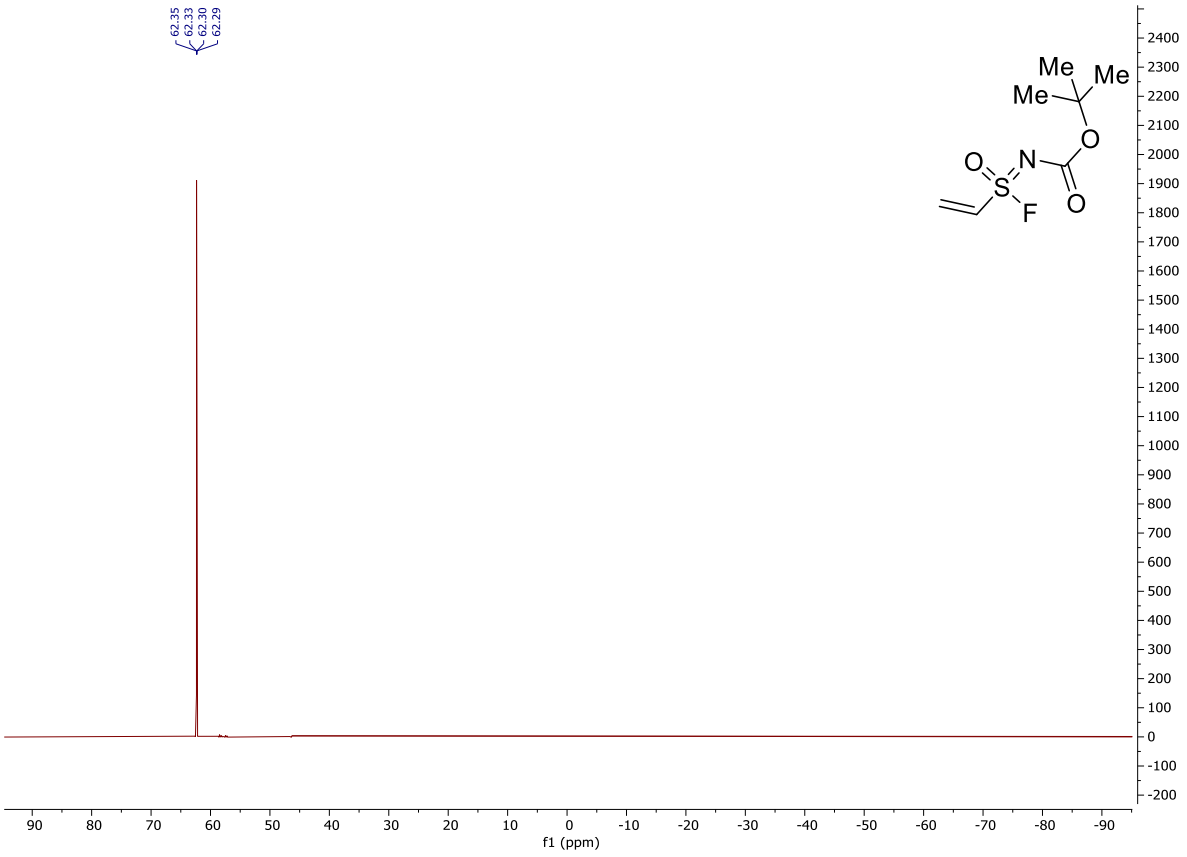

85.05
85.04
85.04
85.03
O
N
S
Me
F
f1 (ppm)

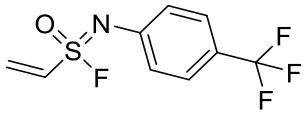


tert-Butyl (fluoro(oxo)(vinyl)-λ^6-sulfaneylidene)carbamate (125c)

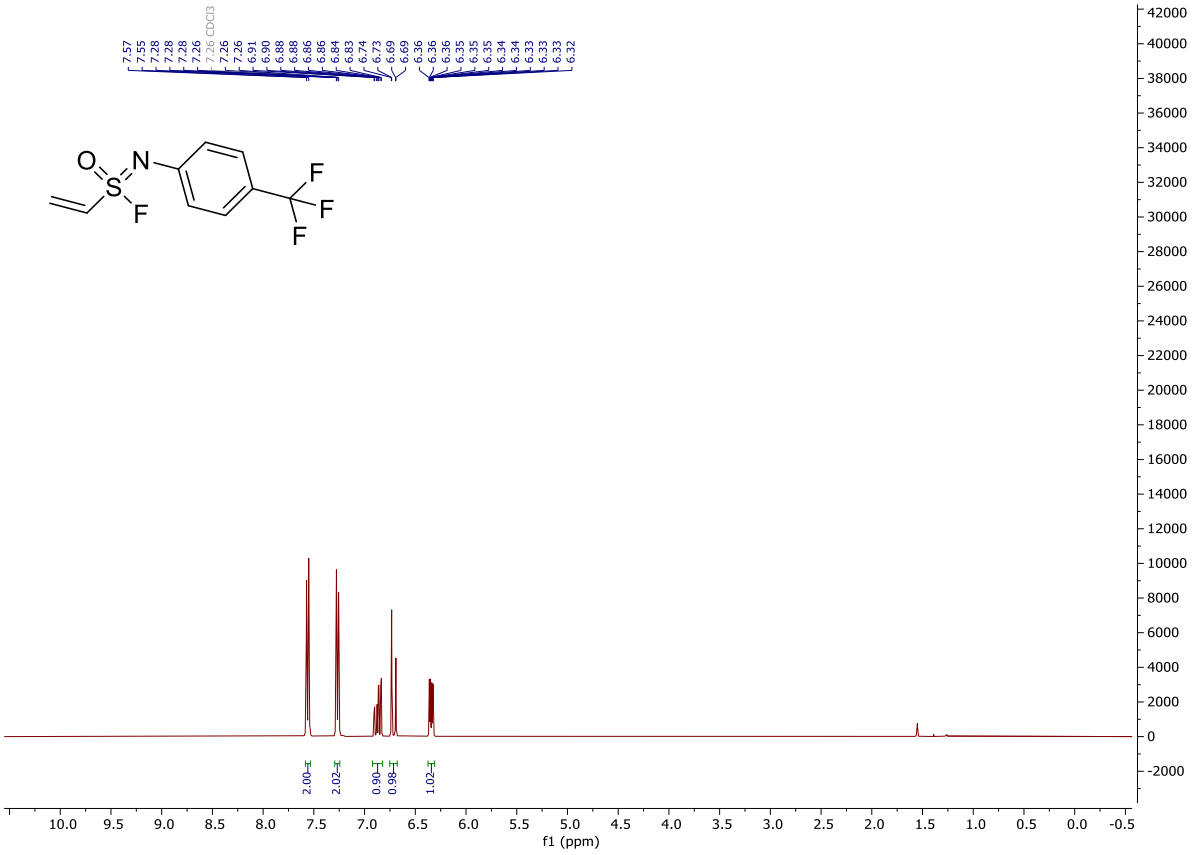


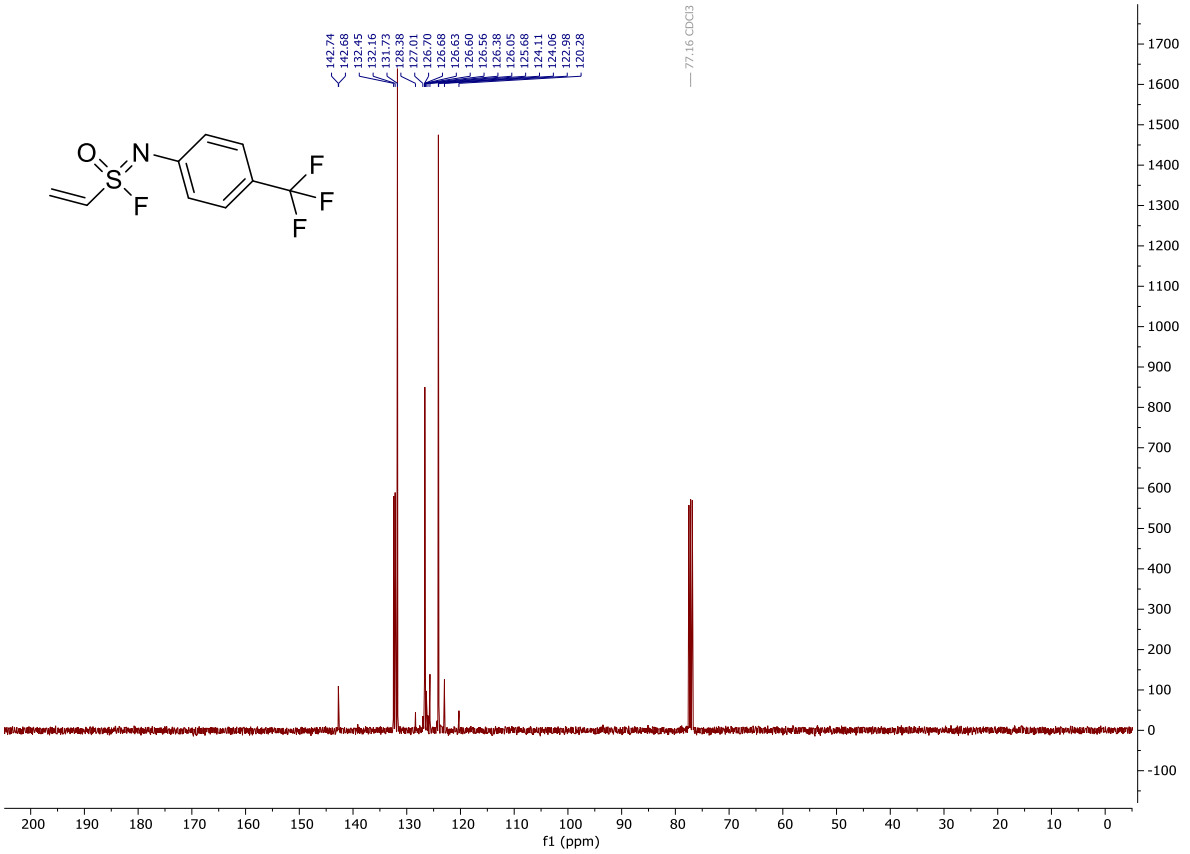

152.50
152.47
133.34
133.33
131.30
131.06
82.94
77.16 CDCl3
27.92
Me
Me
Me
O
N
O
S
F
O
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

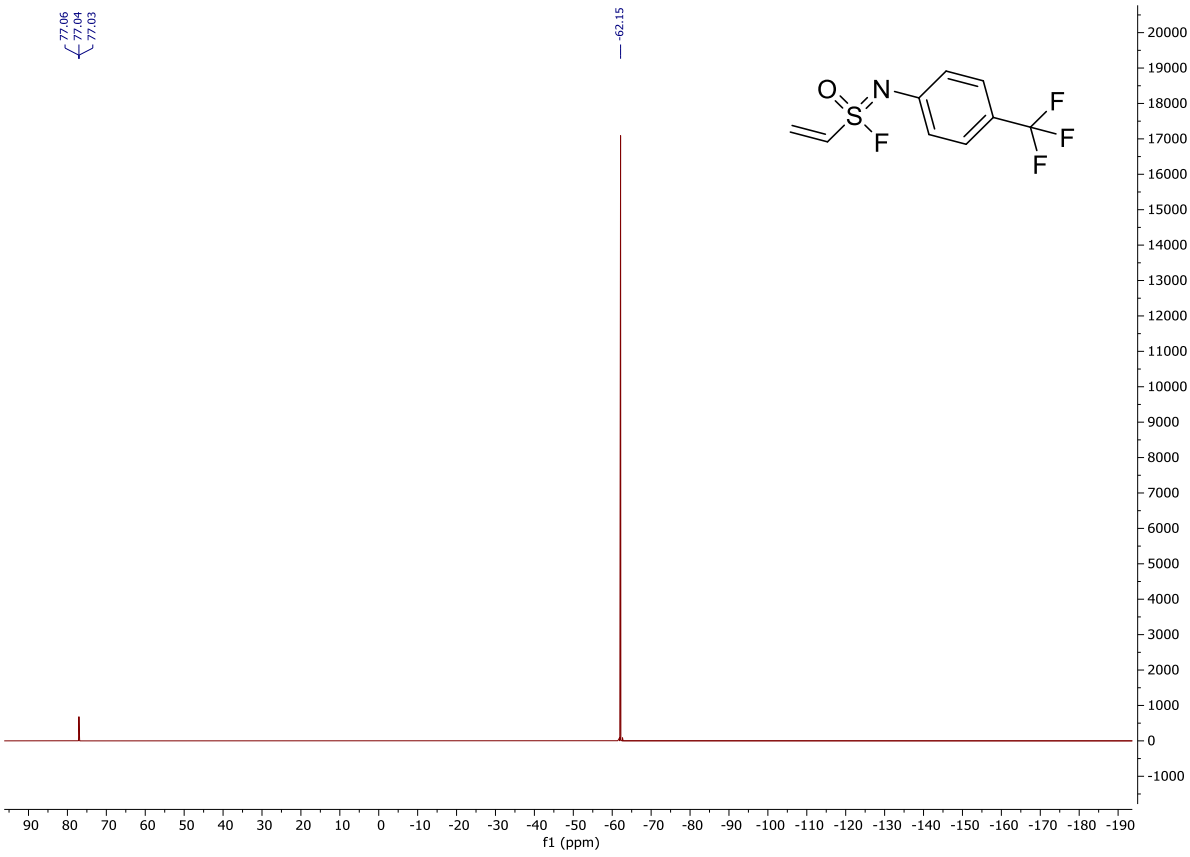

62.35
62.33
62.30
62.29
Me
Me
Me
O
N
O
S
F
O
2400 2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)



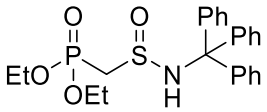
_N_-(4-(Trifluoromethyl)phenyl)ethenesulfonimidoyl fluoride (125d)



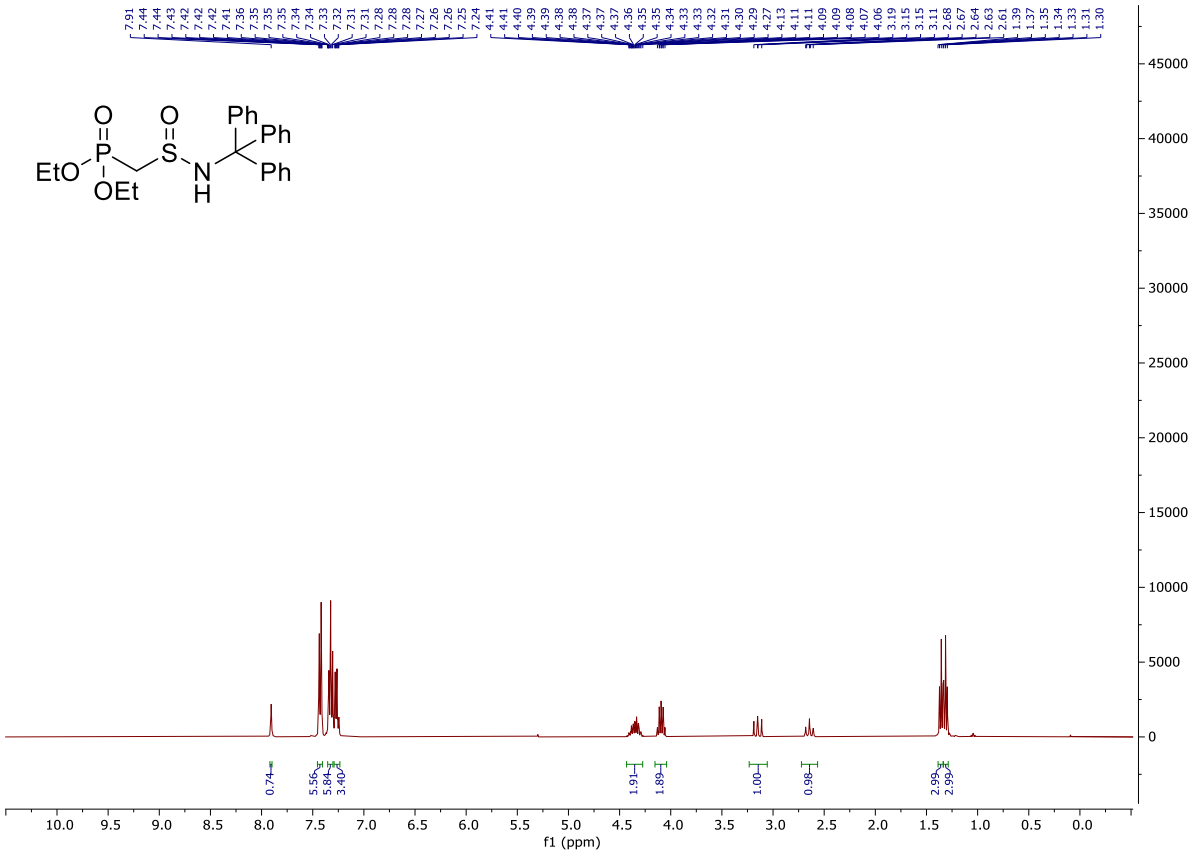

142.74
142.68
132.45
132.16
131.73
131.38
127.01
126.70
126.68
126.63
126.60
126.56
126.38
126.05
125.68
124.11
124.06
122.98
120.28
77.16 CDCl3
O
N
S
F
F
F
F
f1 (ppm)

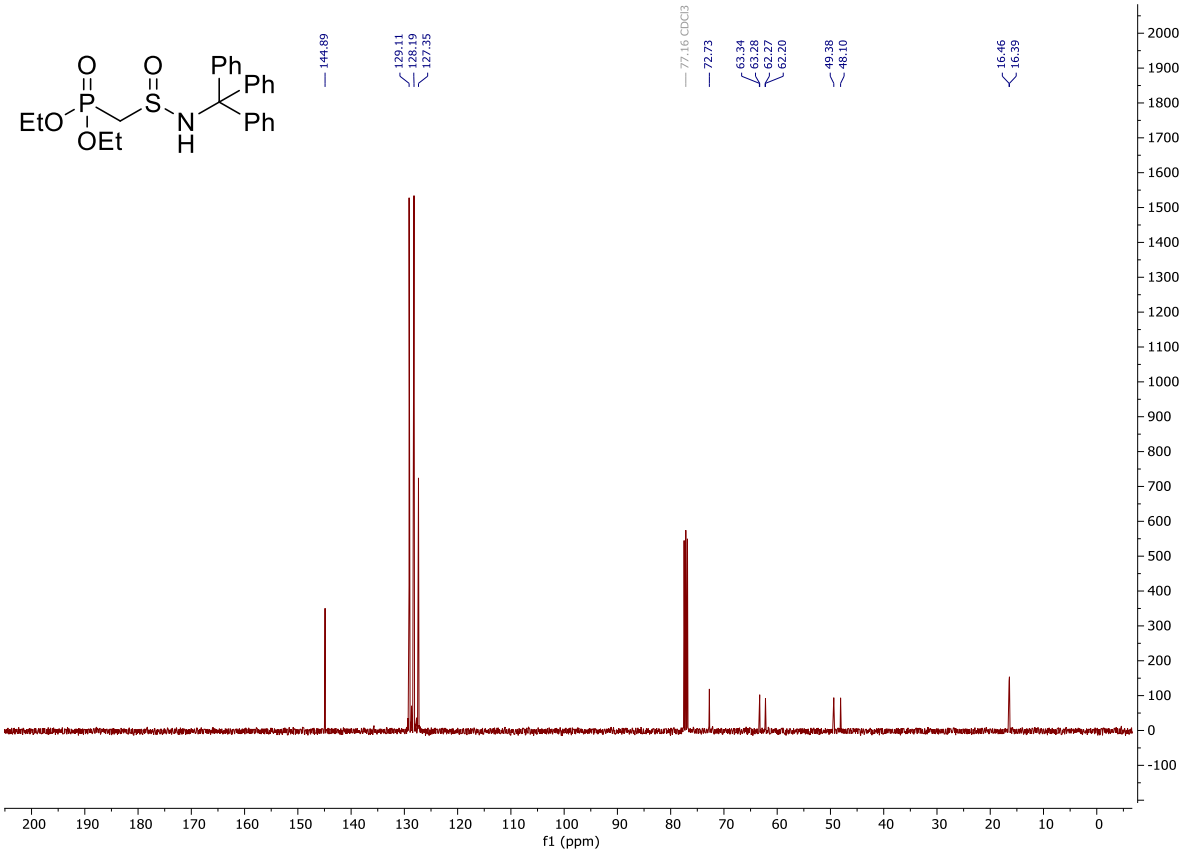

77.06
77.04
77.03
-62.15
O
N
S
F
F
F
F
f1 (ppm)

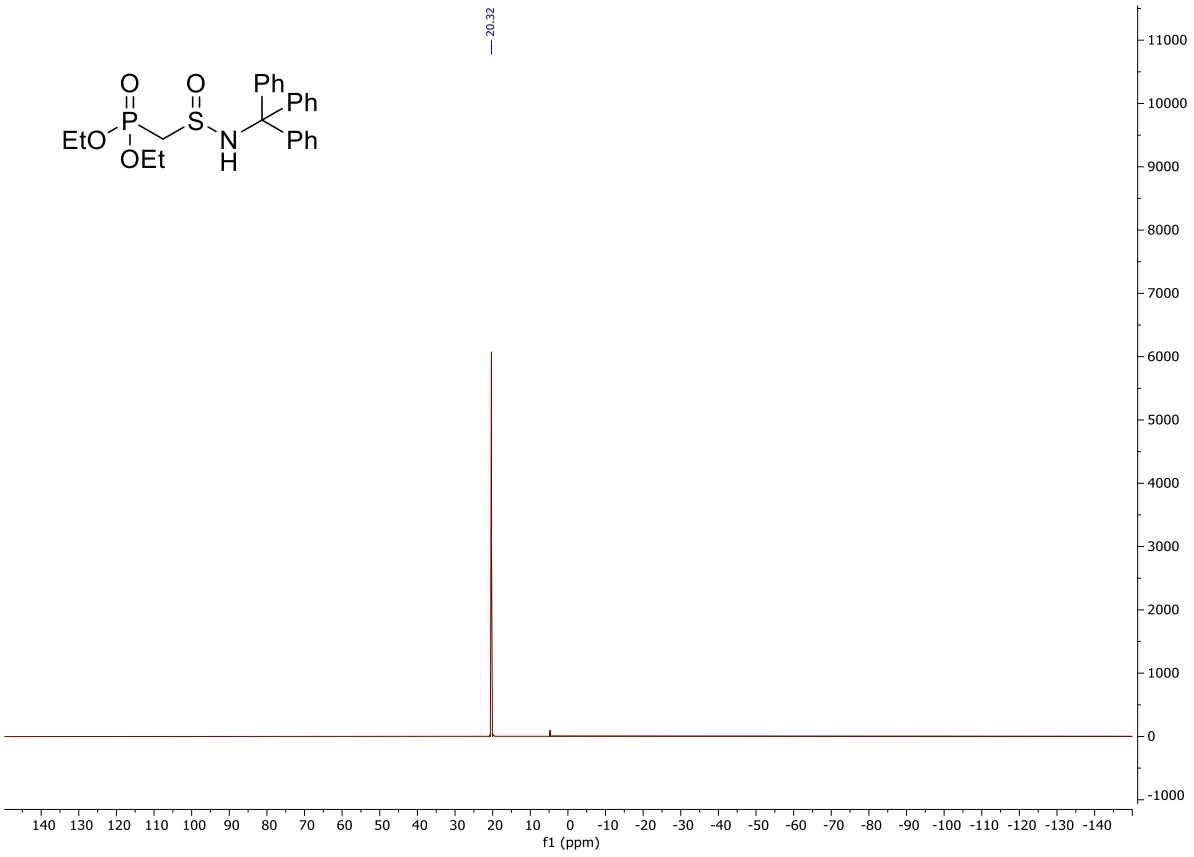
8.3.2 Sulfinamides

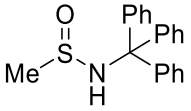


Diethyl (((tritylamino)sulfinyl)methyl)phosphonate (137)

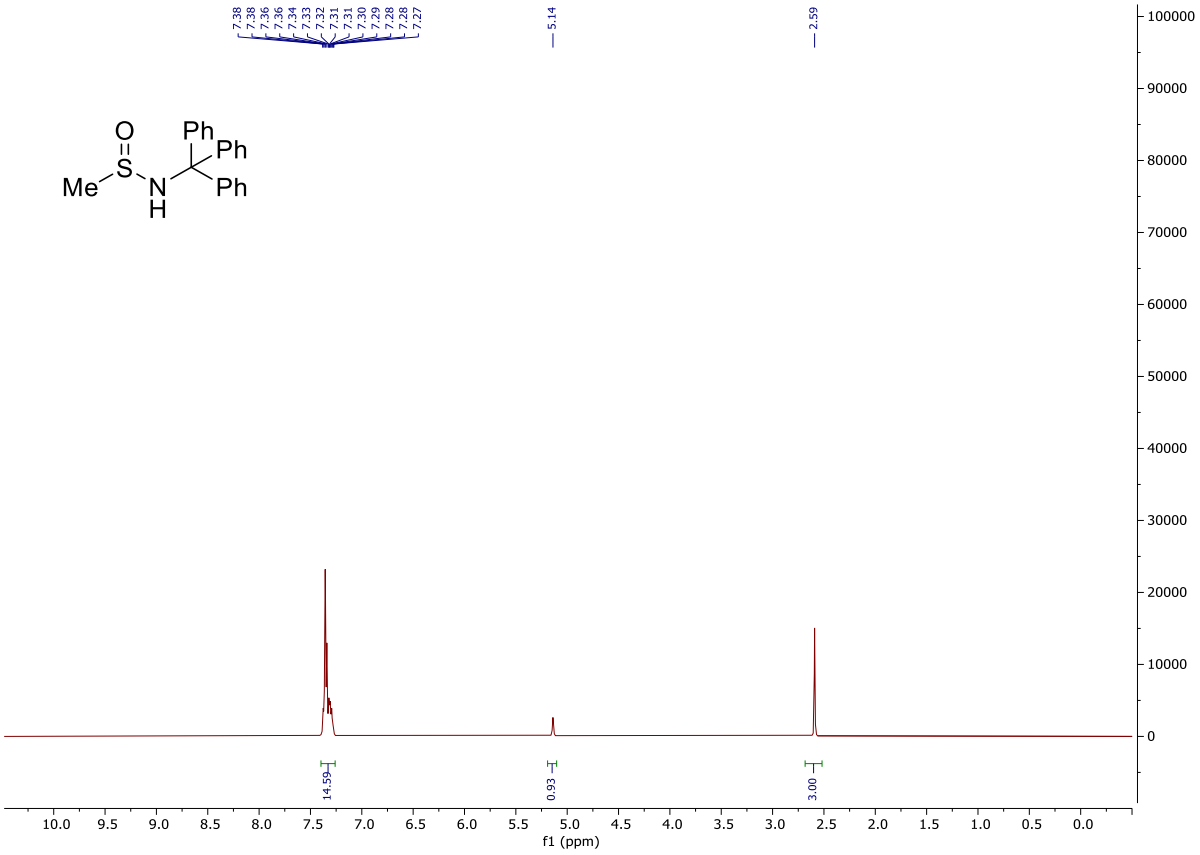


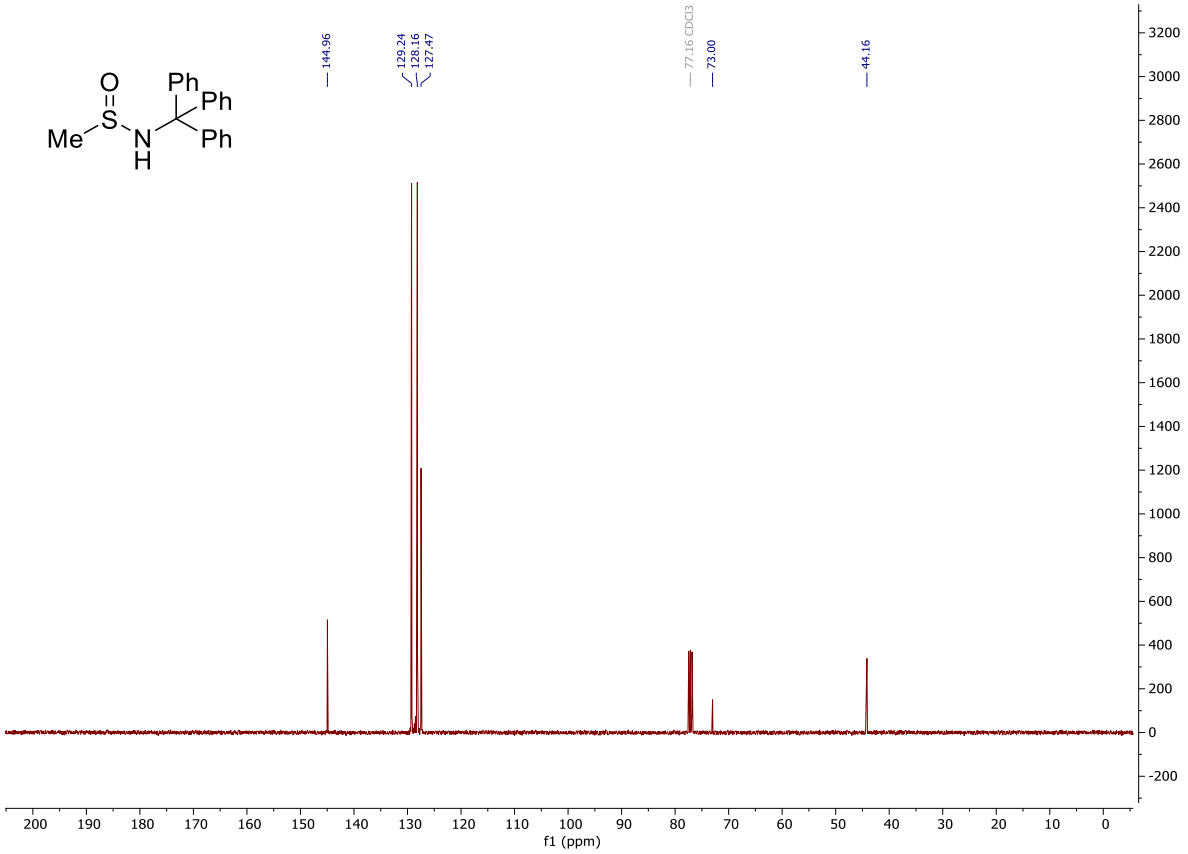

144.89
129.11
128.19
127.35
77.16 CDCl3
72.73
63.34
63.28
62.27
62.20
49.38
48.10
16.46
16.39
f1 (ppm)

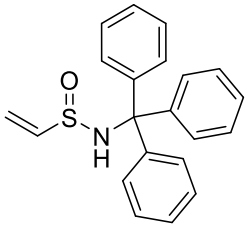

20.32
f1 (ppm)



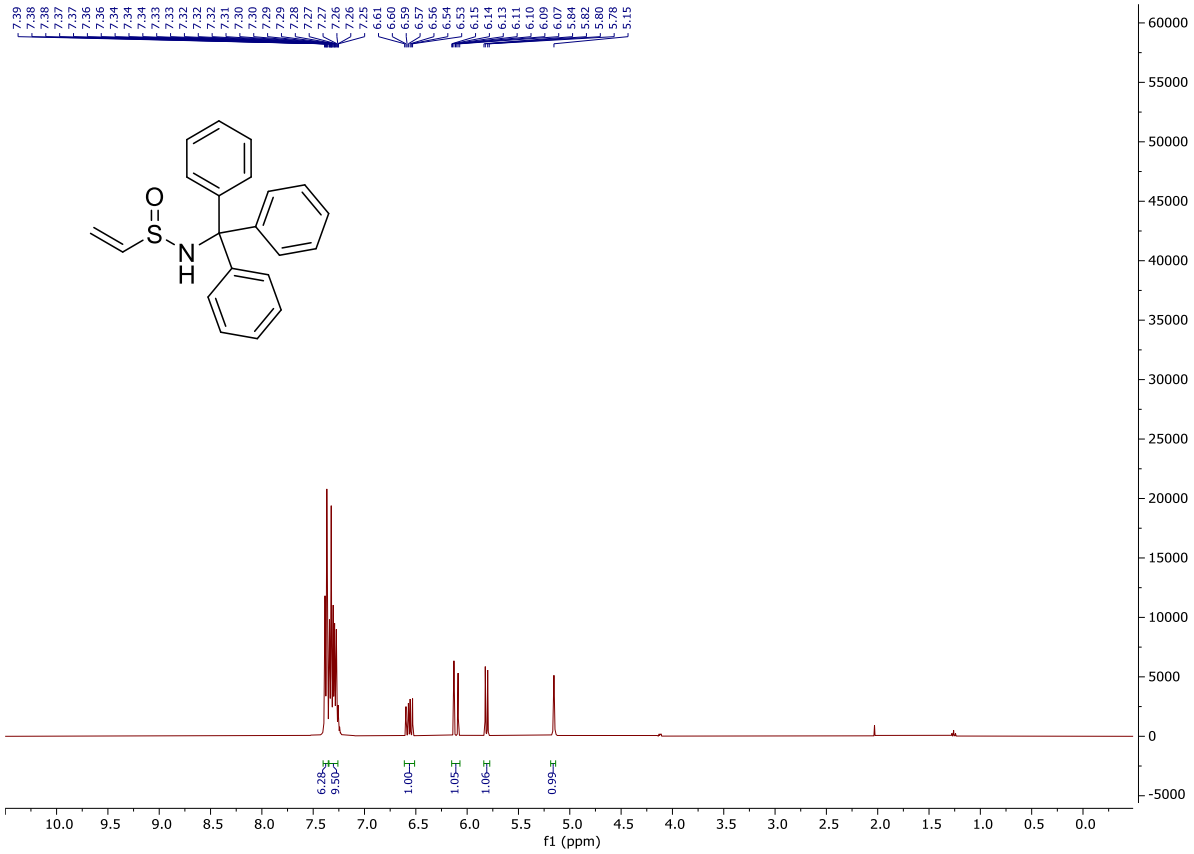
_N_-tritylmethanesulfinamide (137a)

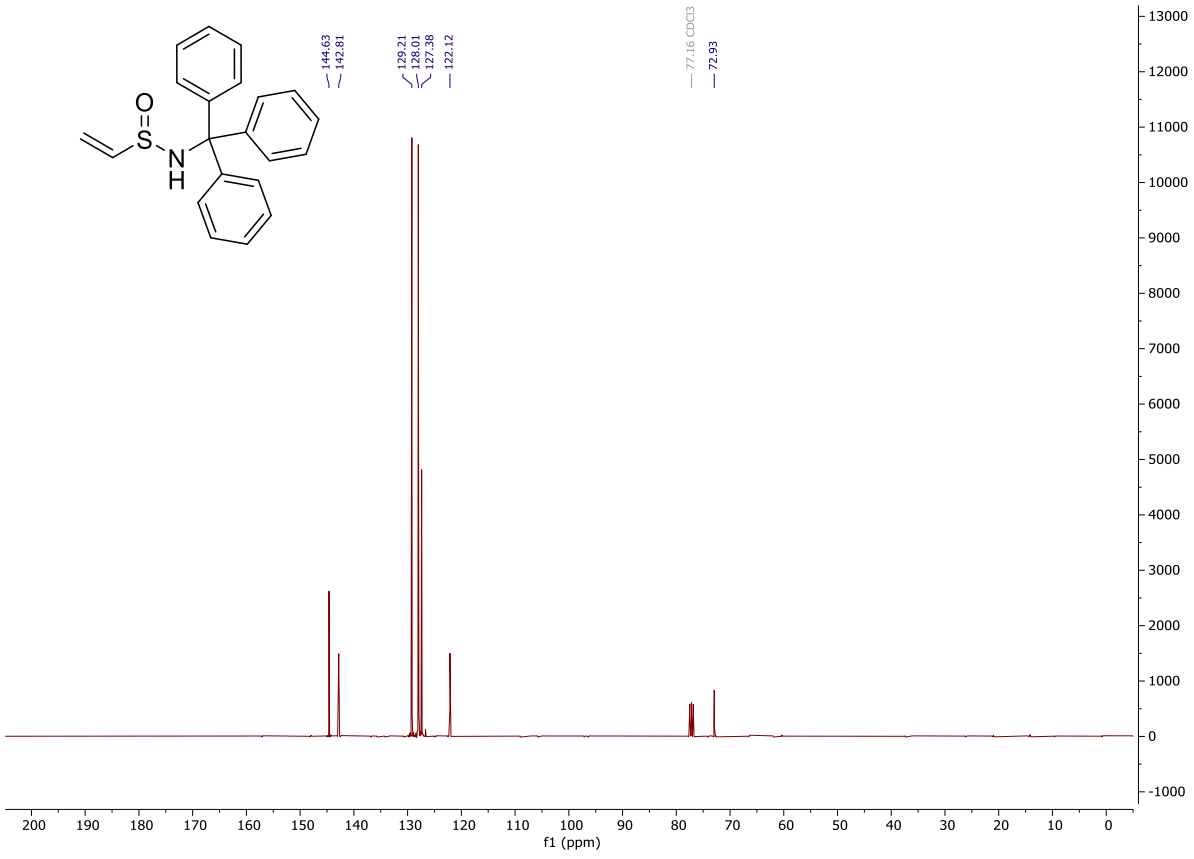


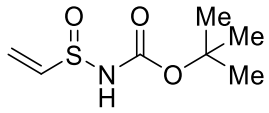




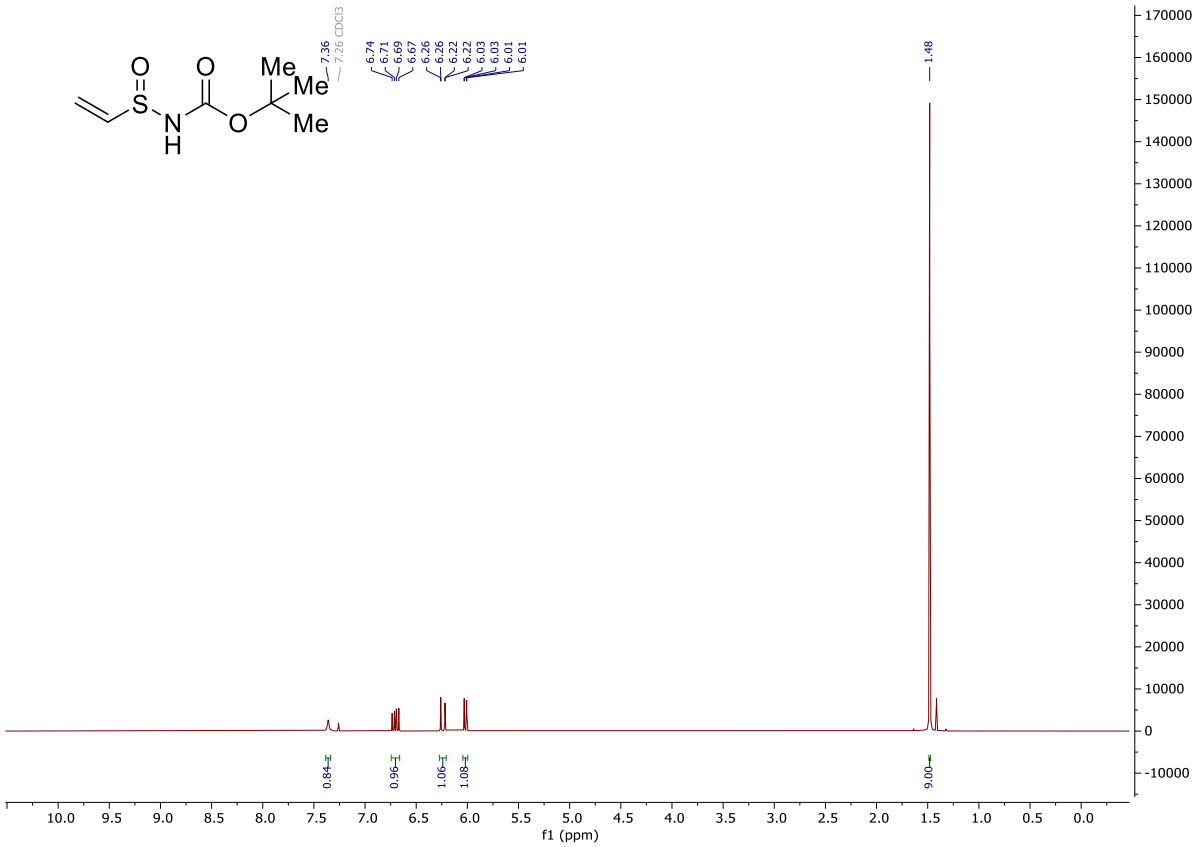
***N*-Tritylethenesulfinamide (138a)**

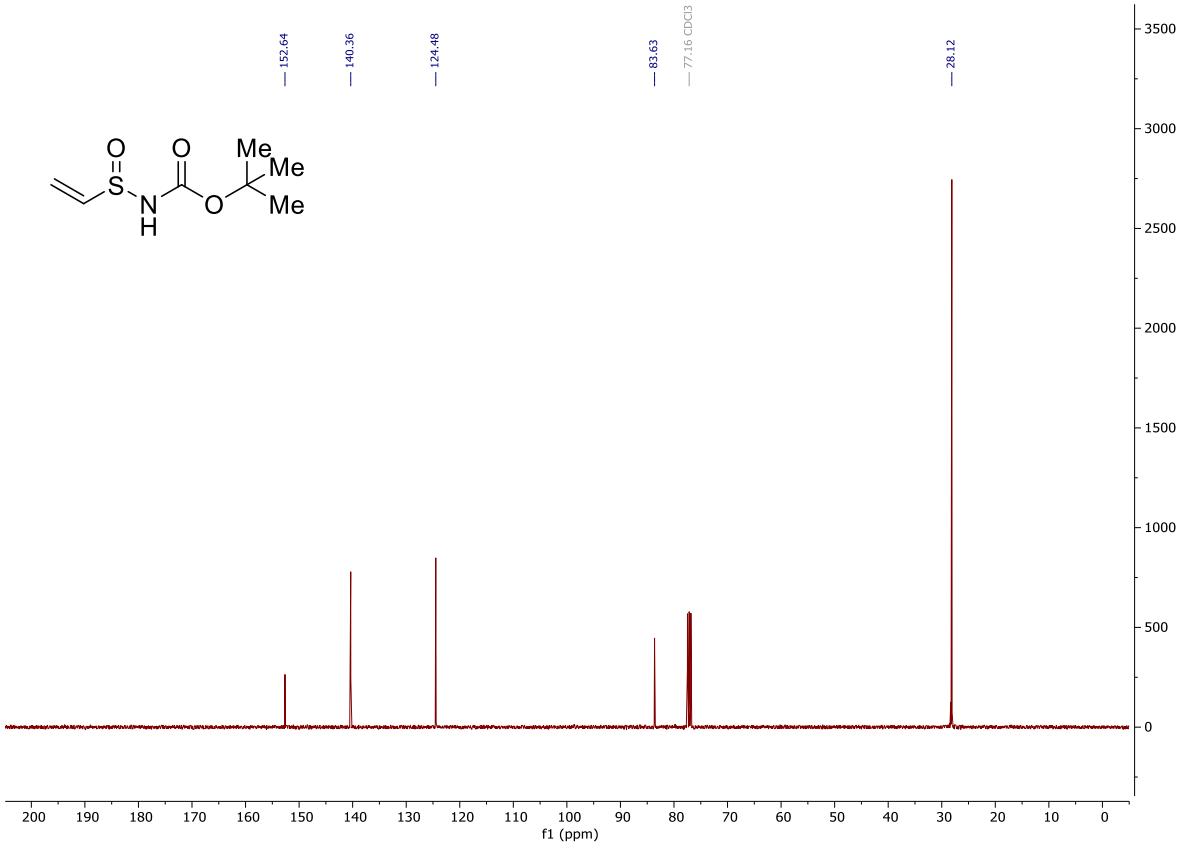

7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.28 7.27 7.27 7.26 7.26 7.25
6.61 6.60 6.59 6.57 6.56 6.54 6.53 6.15 6.14 6.13 6.11 6.10 6.09 6.07 5.84 5.82 5.80 5.78 5.15
O
S
N
H
6.28
9.50
1.00
1.05
1.06
0.99
f1 (ppm)

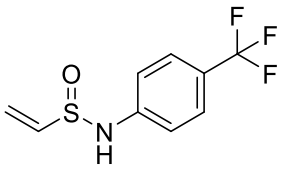

144.63
142.81
129.21
128.01
127.38
122.12
77.16 CDCl3
72.93
O
S
N
H
f1 (ppm)



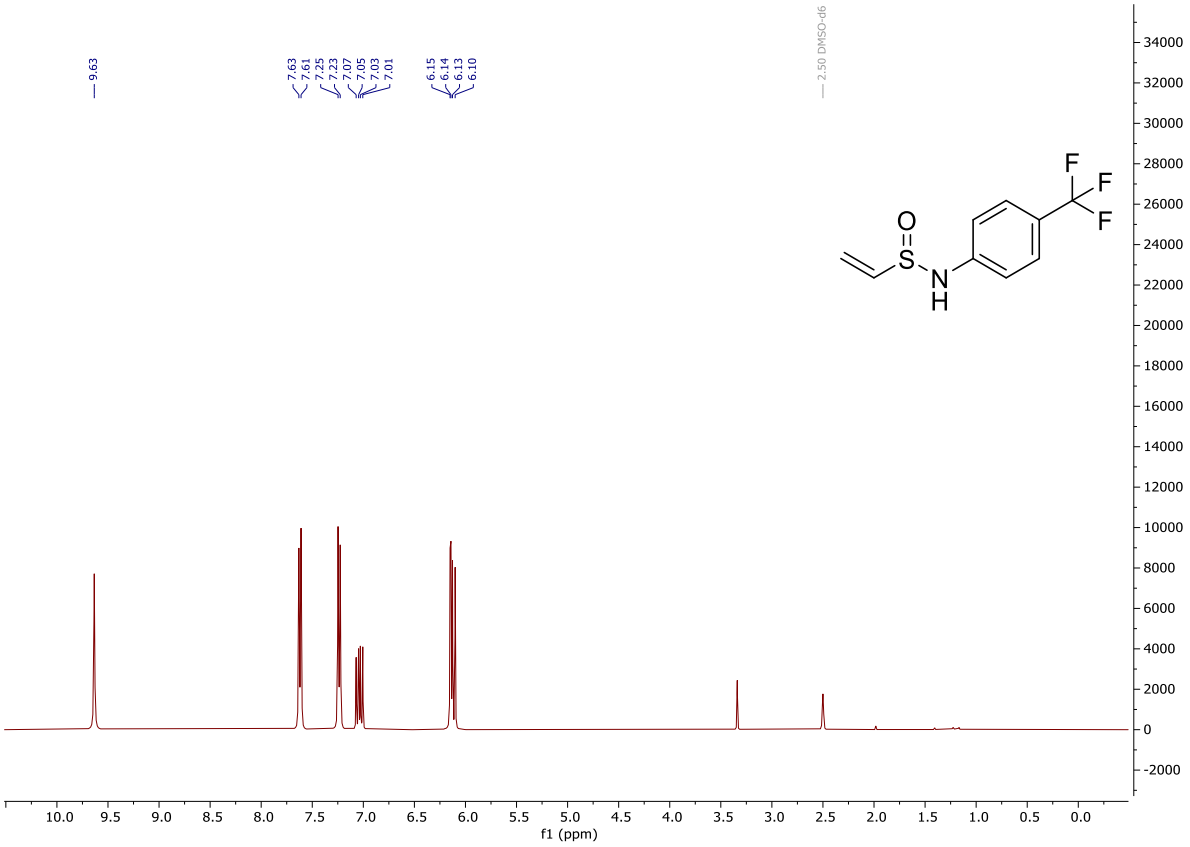
tert-Butyl (vinylsulfinyl)carbamate (138c)

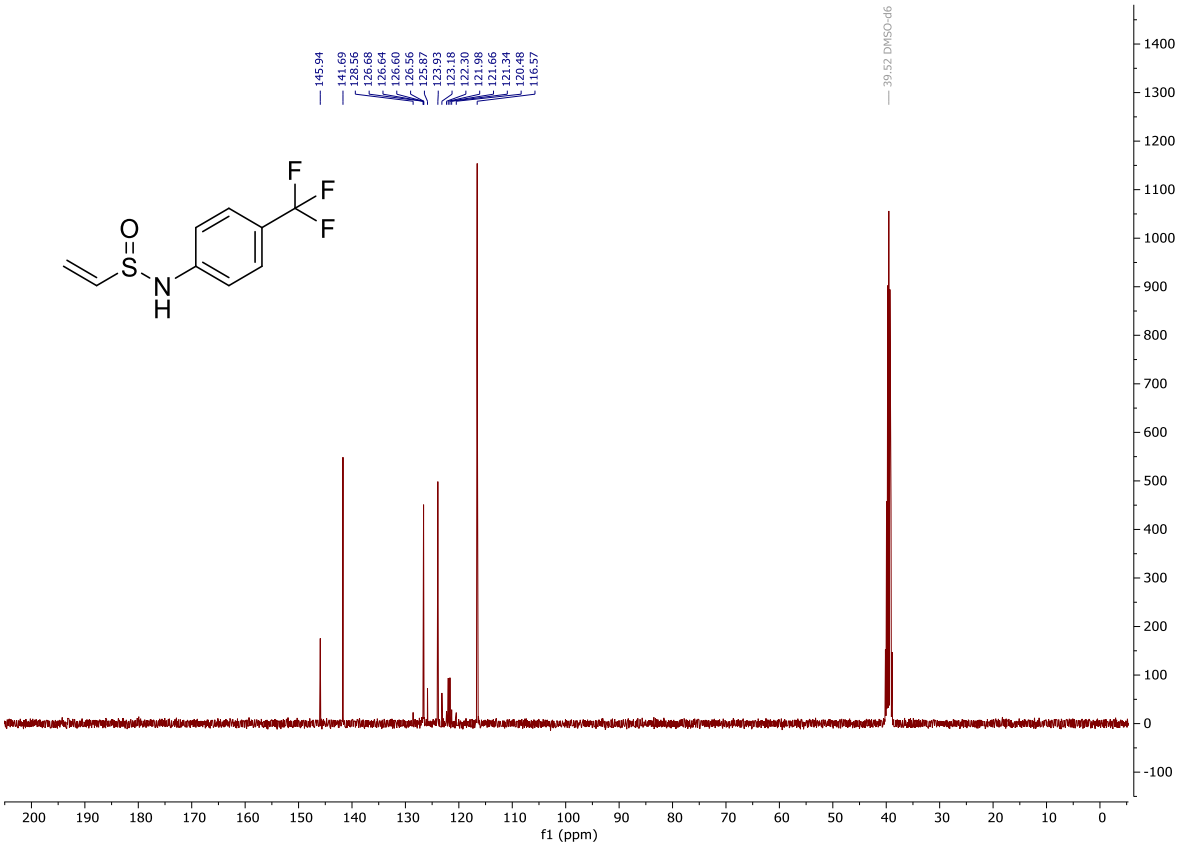


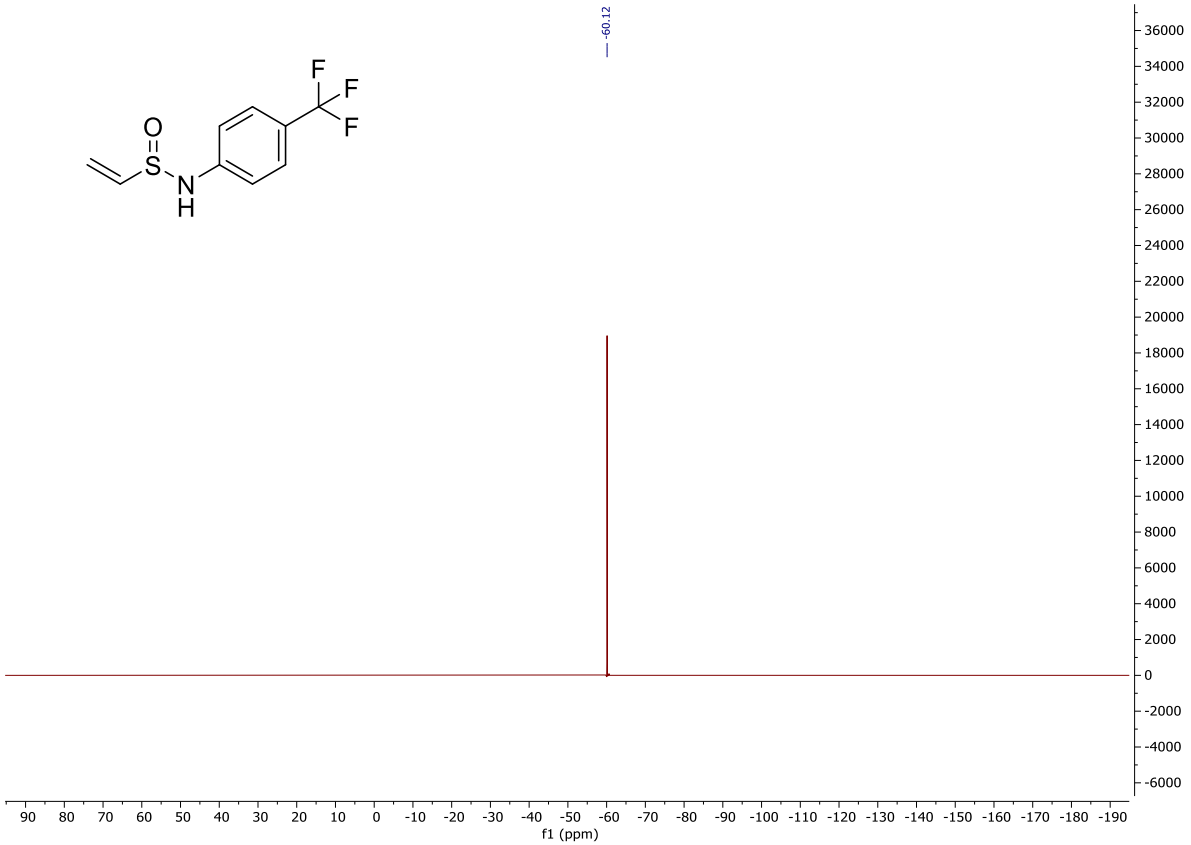


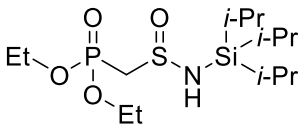


_N_-(4-(Trifluoromethyl)phenyl)ethenesulfinamide (13d)

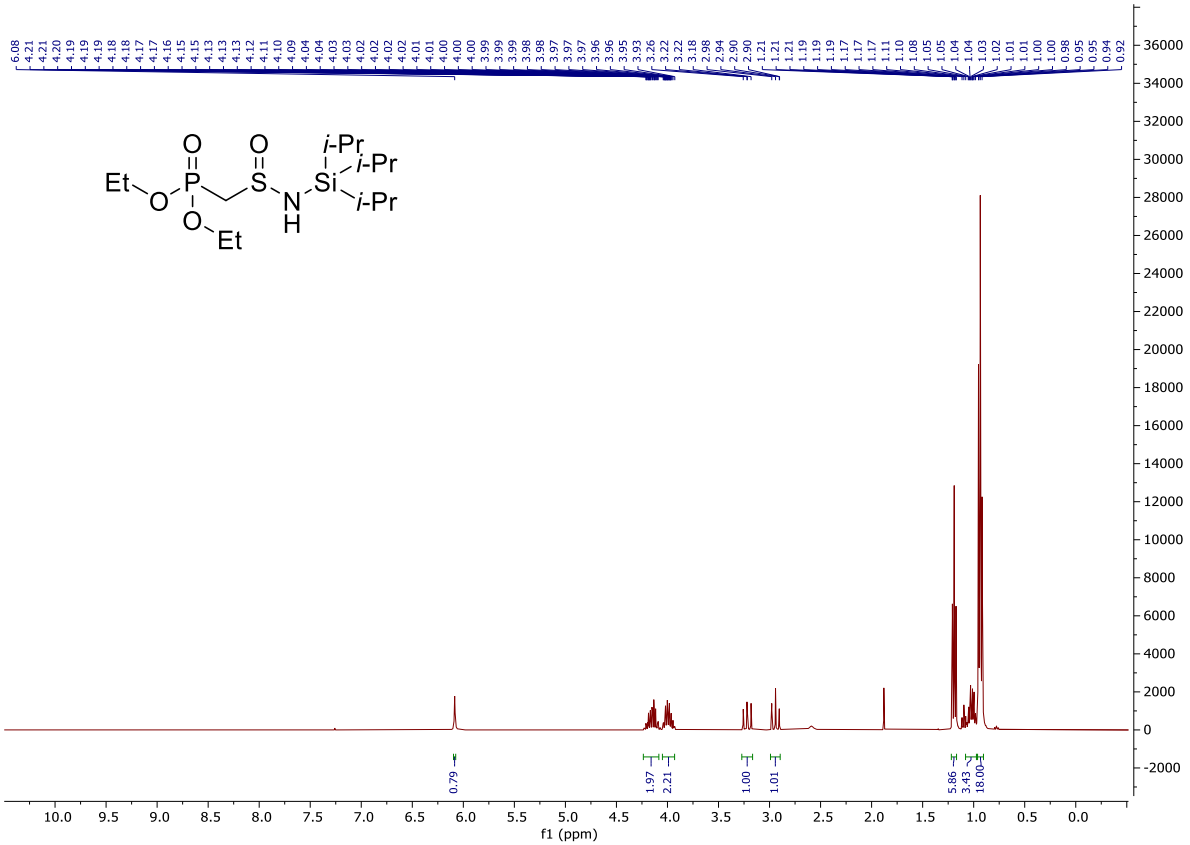

9.63
7.63
7.61
7.25
7.23
7.07
7.05
7.03
7.01
6.15
6.14
6.13
6.10
2.50 DMSO-d6
F
F
F
O
S
N
H
f1 (ppm)

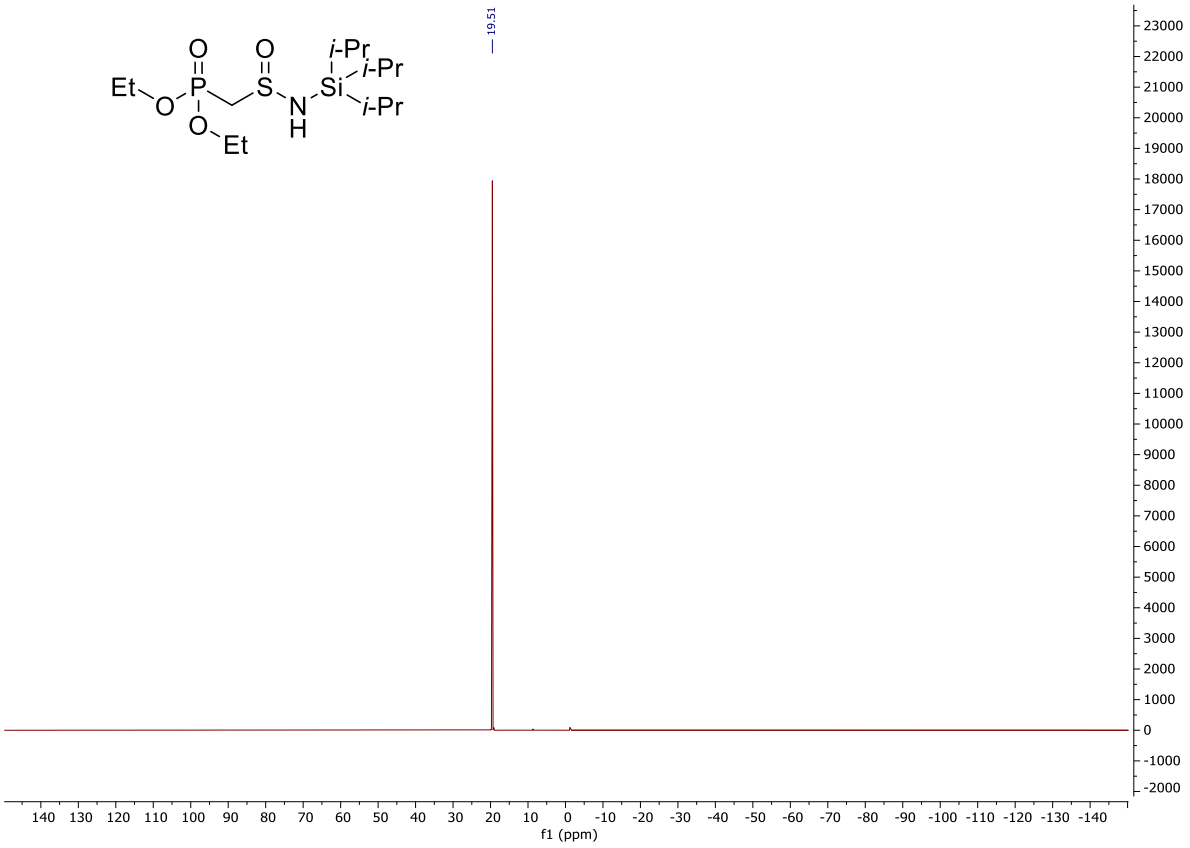

145.94
141.69
128.56
126.68
126.64
126.60
126.56
125.87
123.93
123.18
122.30
121.98
121.66
121.34
120.48
116.57
39.52 DMSO-d6
F
F
F
O
S
N
H
f1 (ppm)

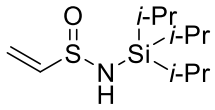




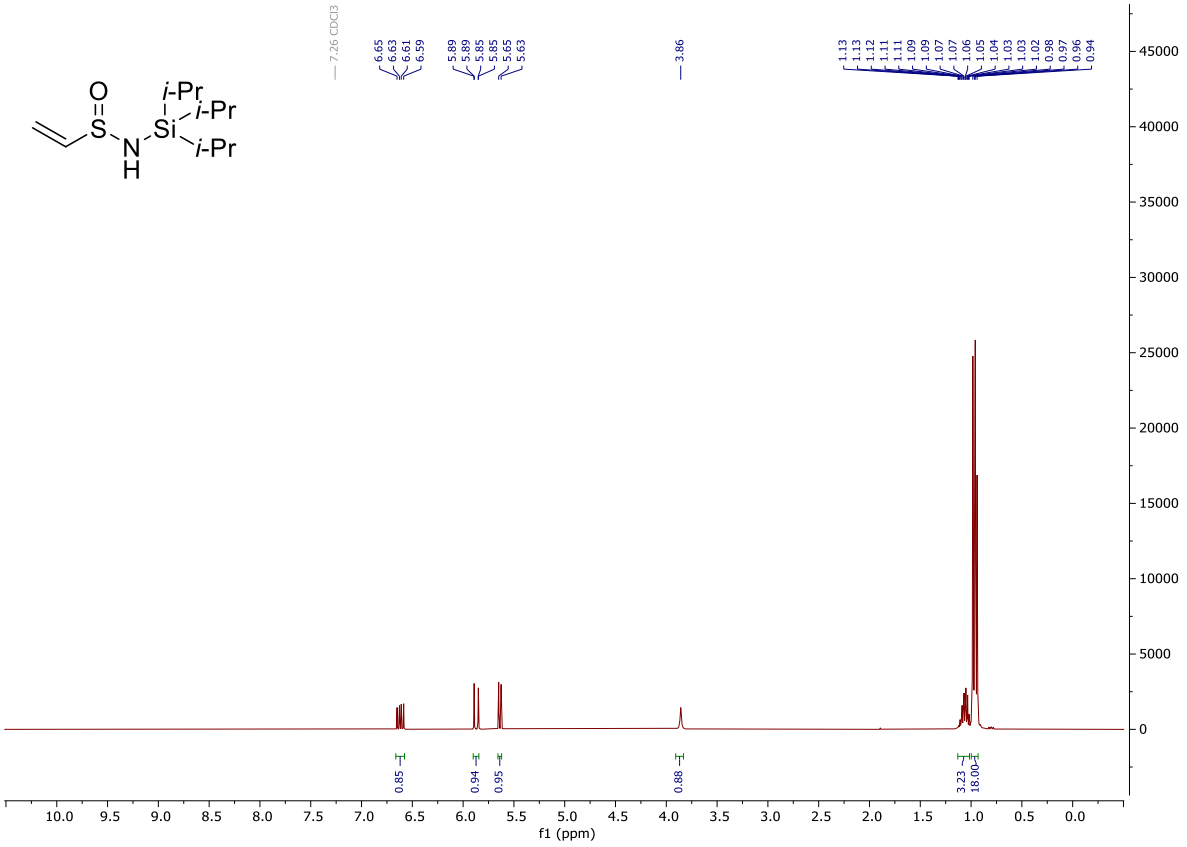
Diethyl ((((triisopropylsilyl)amino)sulfinyl)methyl)phosphonate (137b)

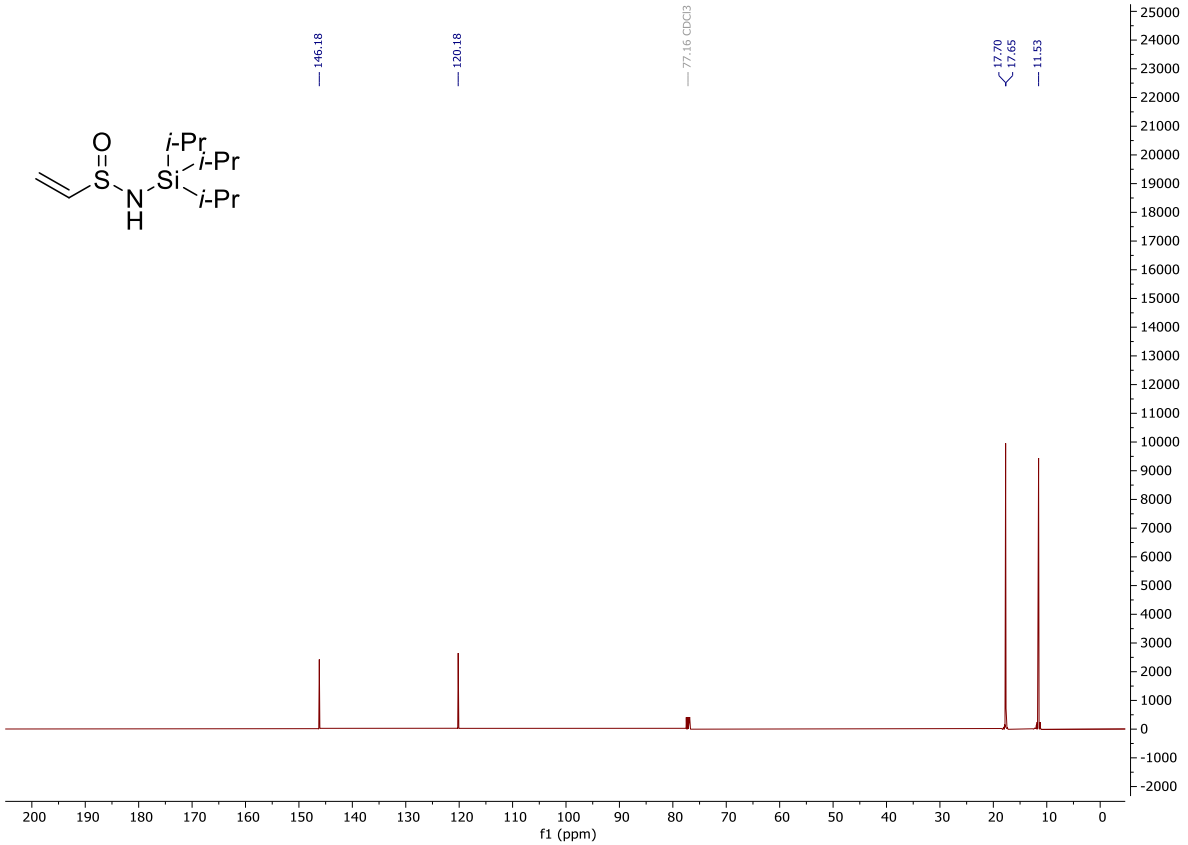

f1 (ppm)


19.51
f1 (ppm)

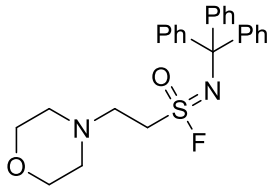


_N_-(Triisopropylsilyl)ethenesulfinamide (138g)

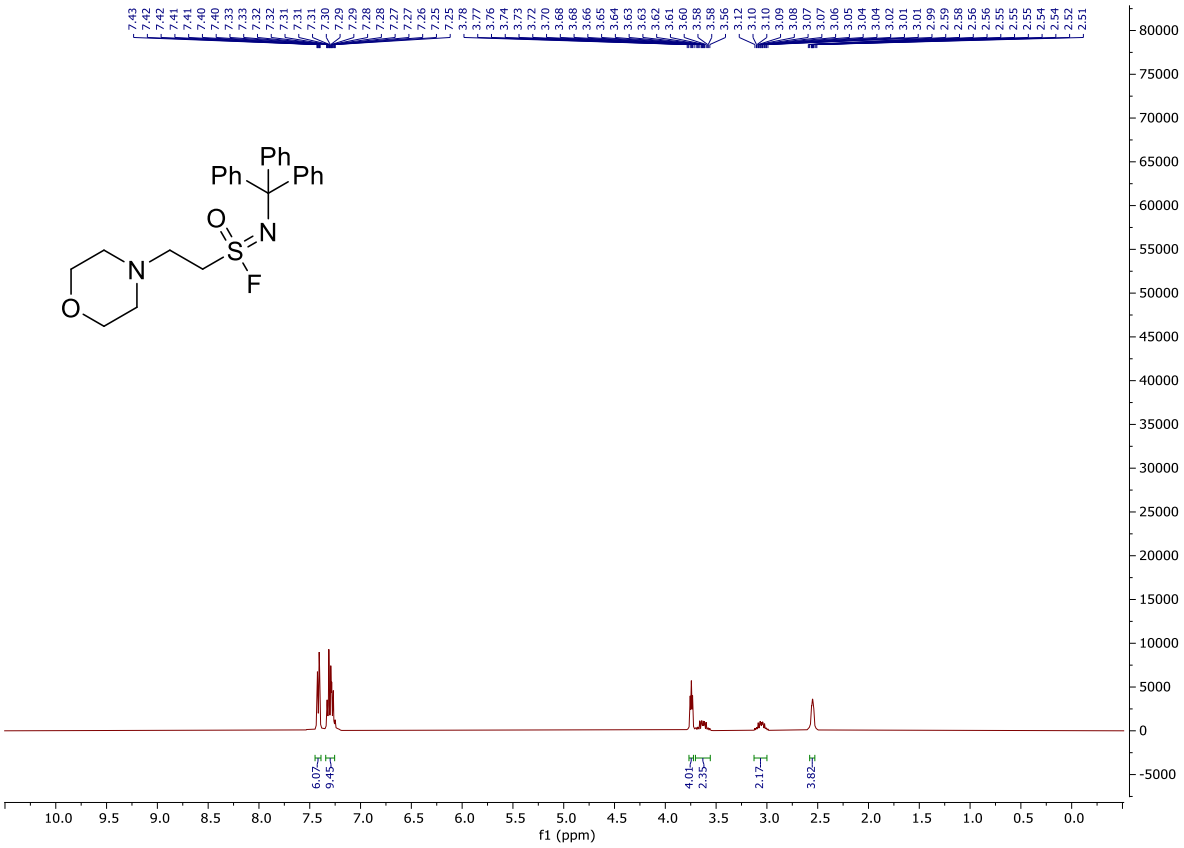


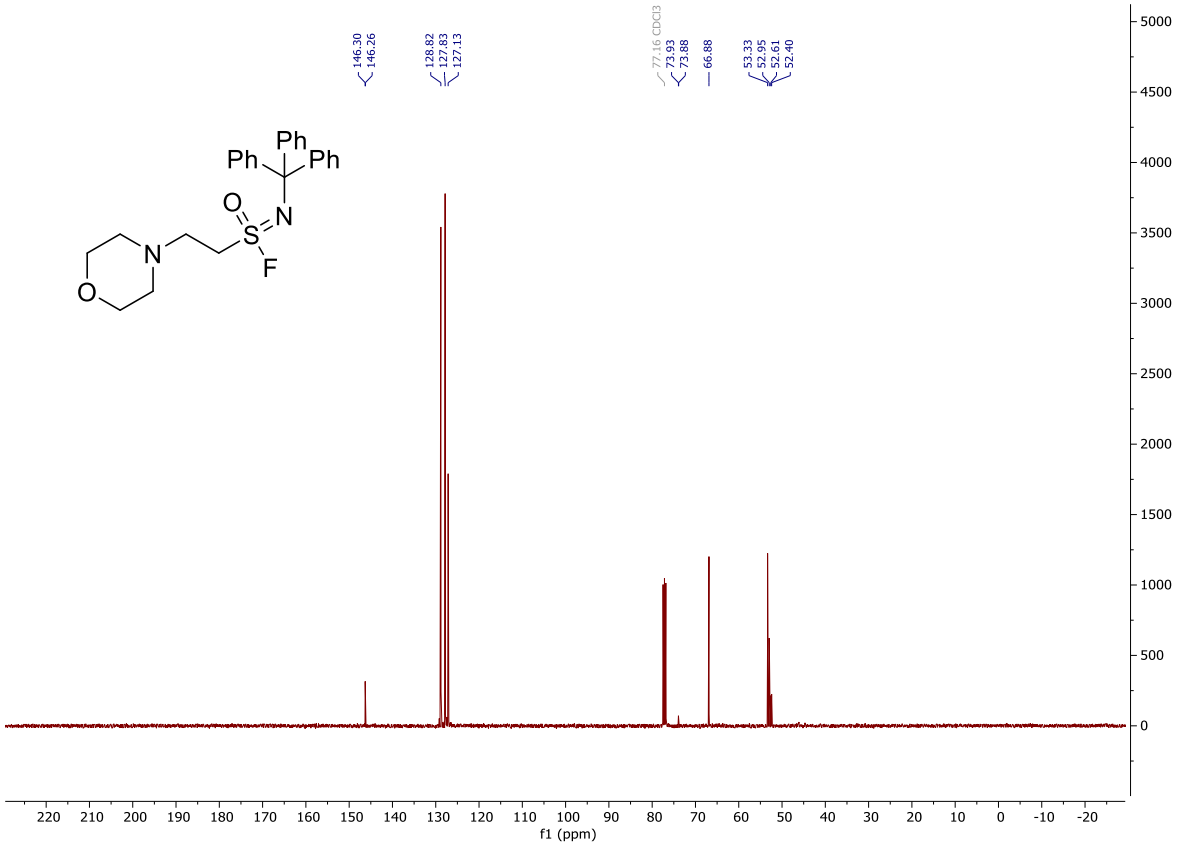

146.18
120.18
77.16 CDCl3
17.70
17.65
11.53
i-Pr
i-Pr
i-Pr
O
S
N
H
Si
f1 (ppm)

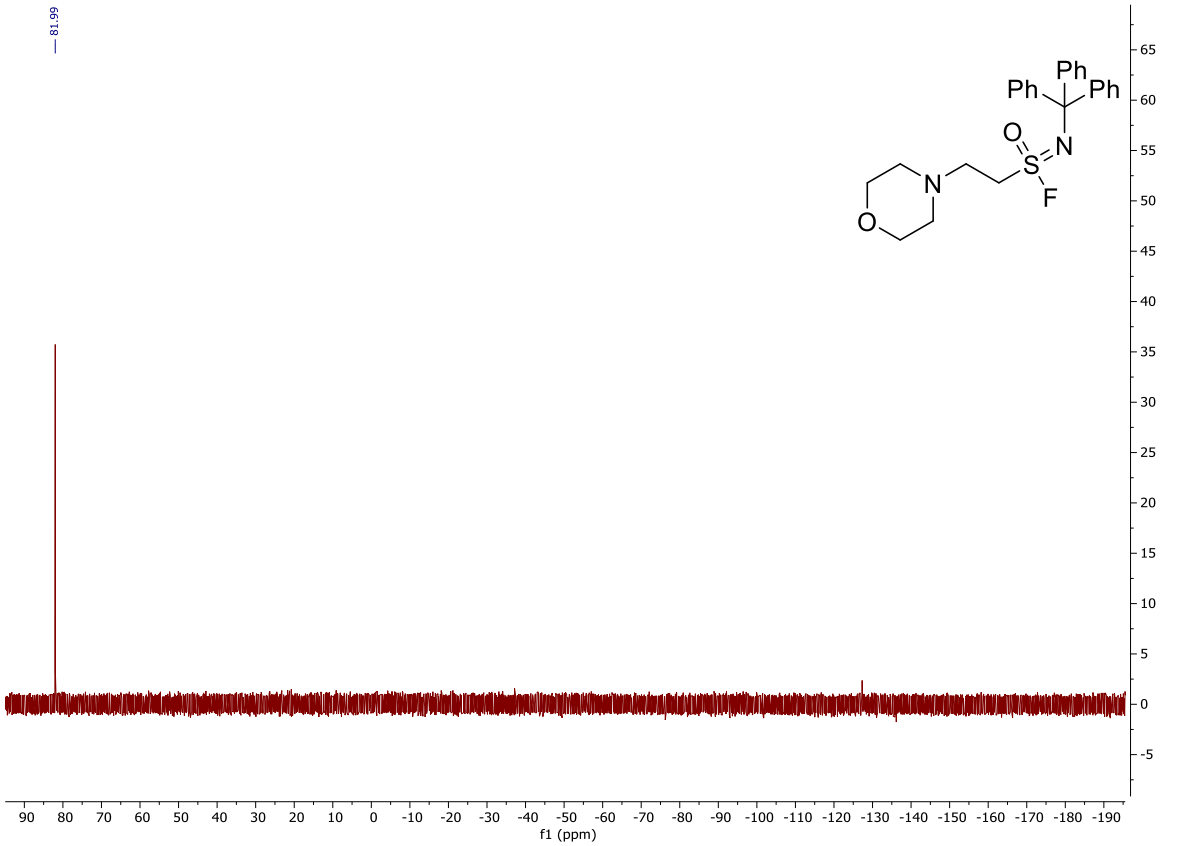
8.3.4 Reaction of sulfonimidoyl fluoride products

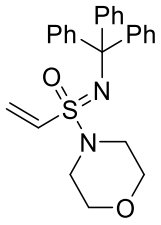


2-Morpholino-*N*-tritylethane-1-sulfonimidoyl fluoride (141a)

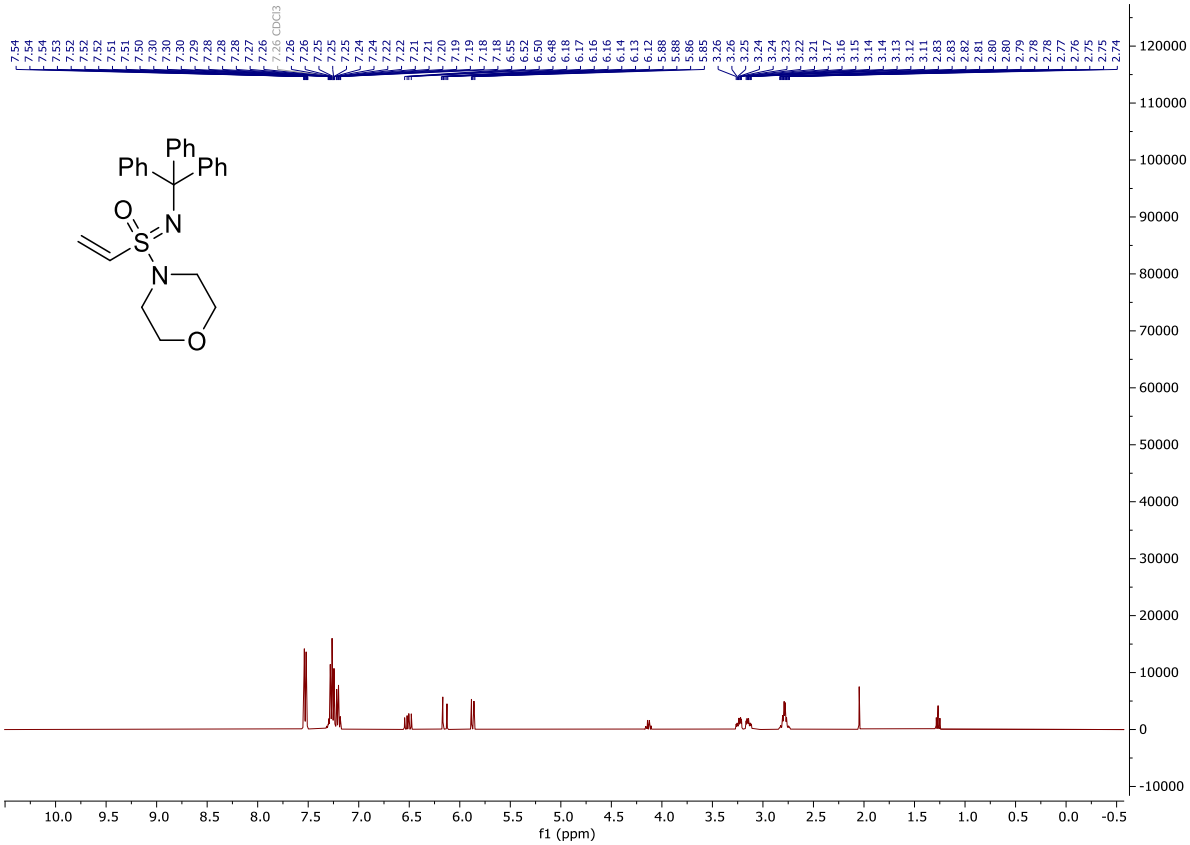


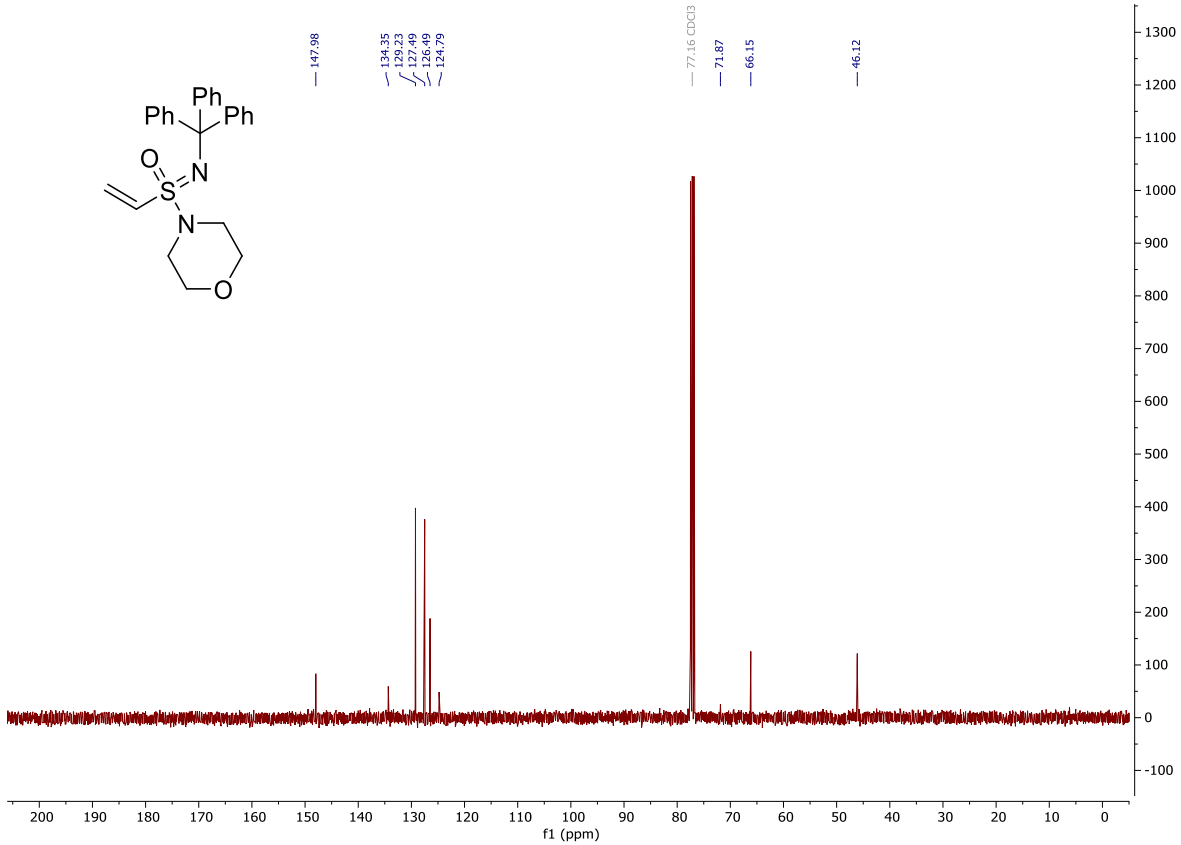

146.30
146.26
128.82
127.83
127.13
77.16 CDCl3
73.93
73.88
66.88
53.33
52.95
52.61
52.40
Ph
Ph
Ph
O
S
N
F
N
O
f1 (ppm)

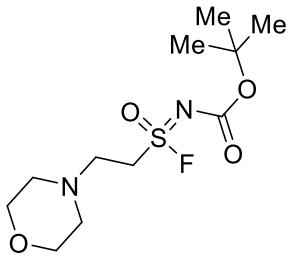

81.99
Ph
Ph
Ph
O
S
N
F
N
O
f1 (ppm)



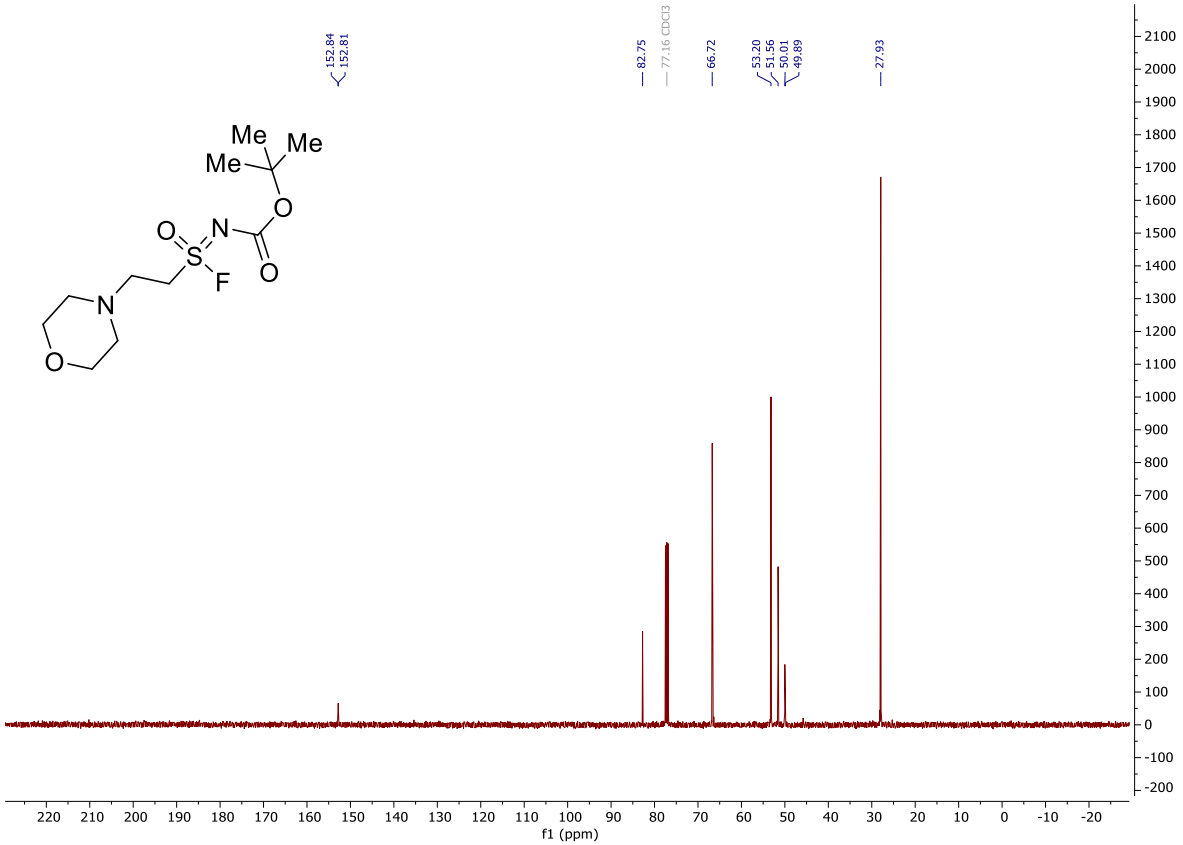
4-(*N*-Tritylvinylsulfonimidoyl)morpholine (142a)

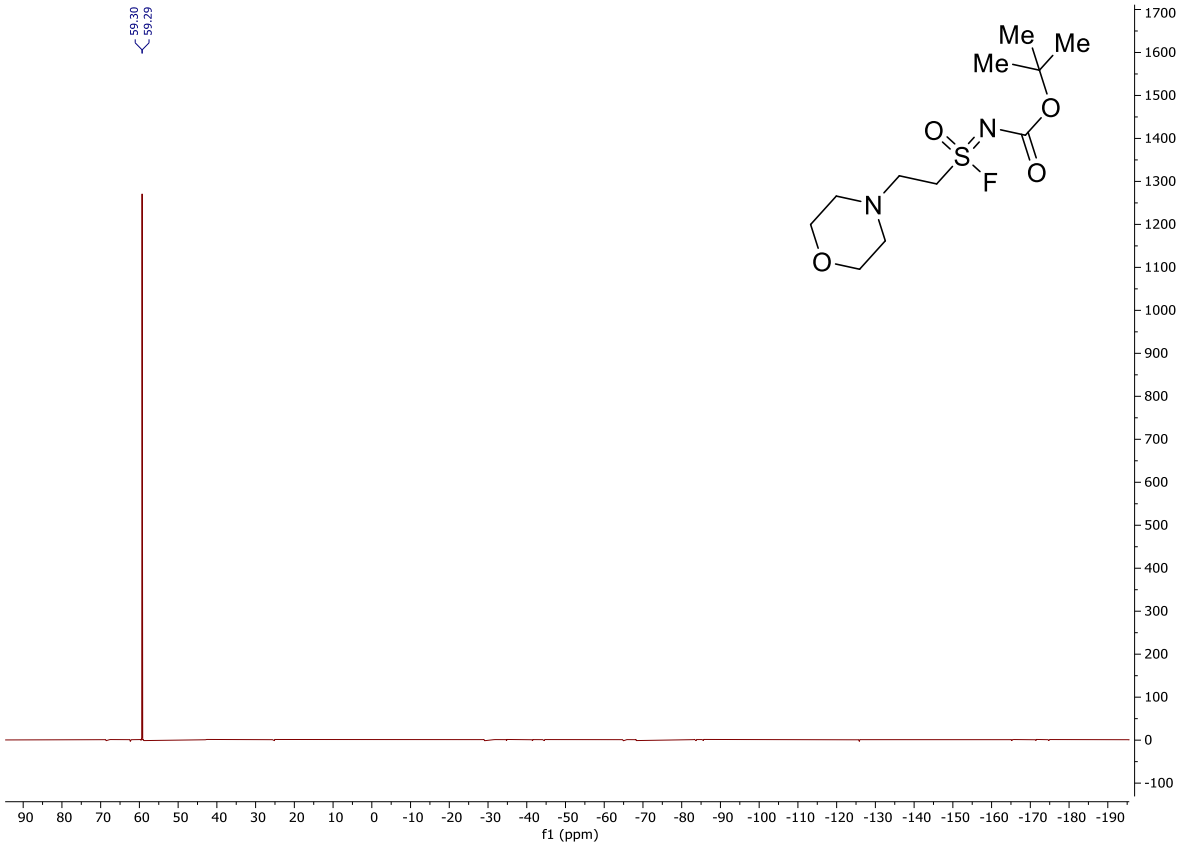




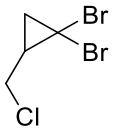


***tert*-Butyl (fluoro(2-morpholinoethyl)(oxo)-λ^6-sulfaneylidene)carbamate (158)**

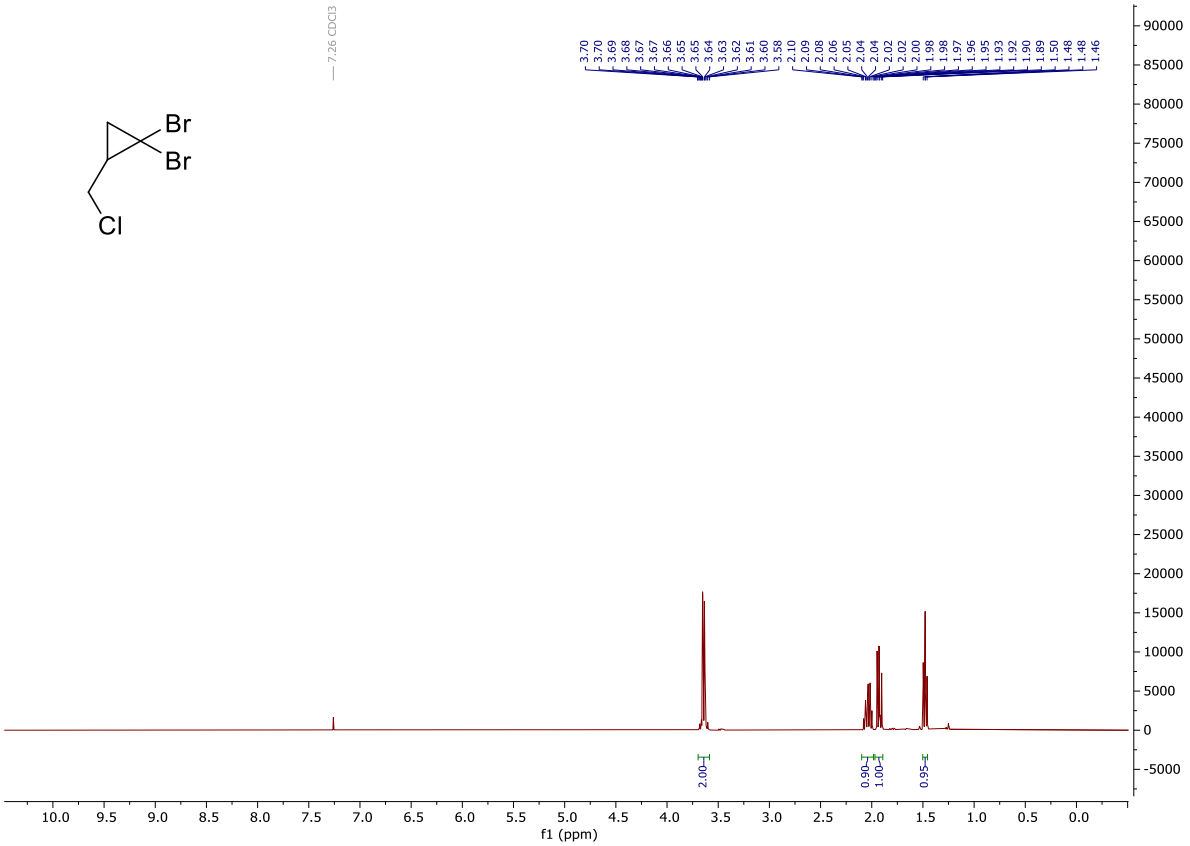

152.84
152.81
82.75
77.16 CDCl3
66.72
53.20
51.56
50.01
49.89
27.93
Me
Me
Me
O
N
O
S
F
O
N
O
f1 (ppm)

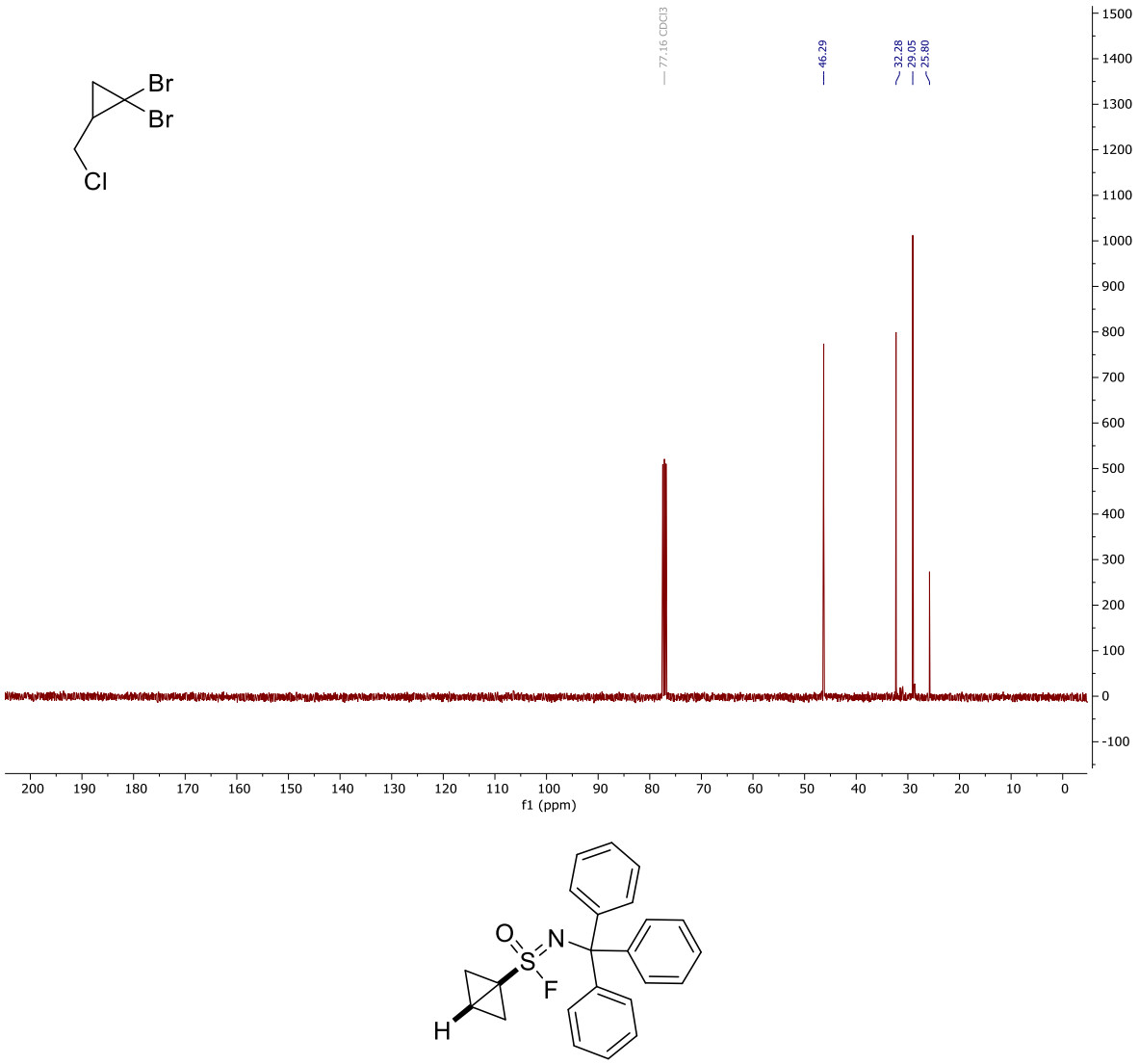

59.30
59.29
Me
Me
Me
O
N
O
S
F
O
N
O
f1 (ppm)

8.3.4 Synthesis of bicyclobutane analogues

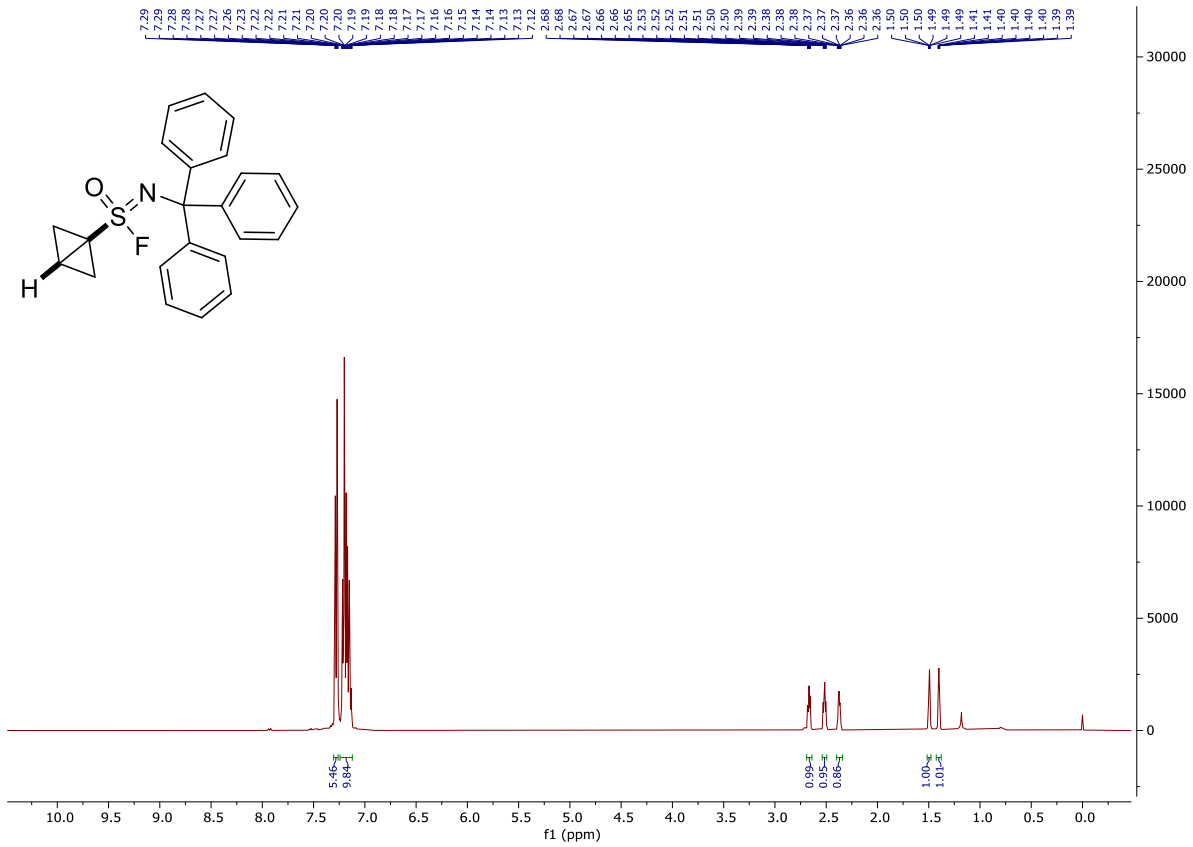


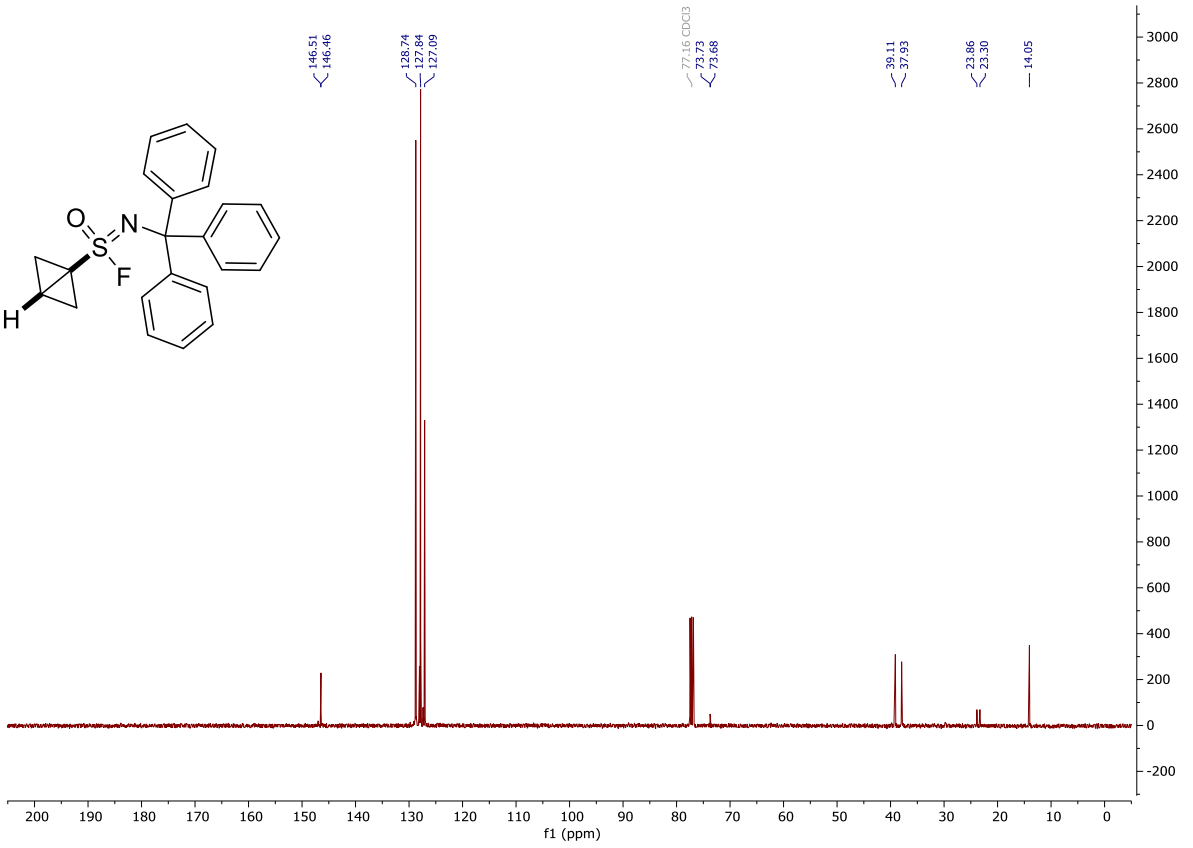
1,1-Dibromo-2-(chloromethyl)cyclopropane (162)

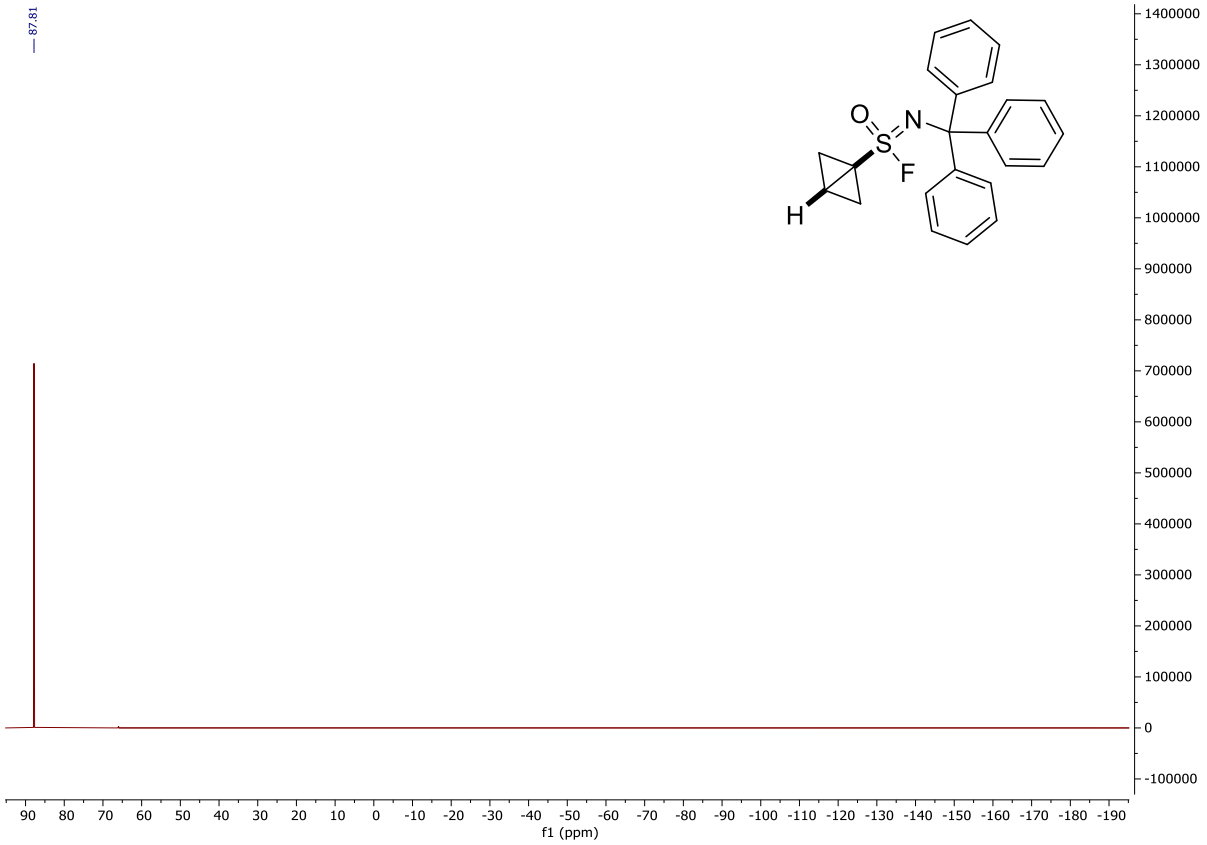




_N_-Tritylbicyclo[1.1.0]butane-1-sulfonimidoyl fluoride (166)

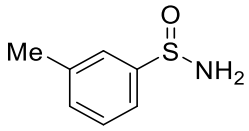

O
N
S
F
H
f1 (ppm)


O
N
S
F
H
77.16 CDCl3
f1 (ppm)

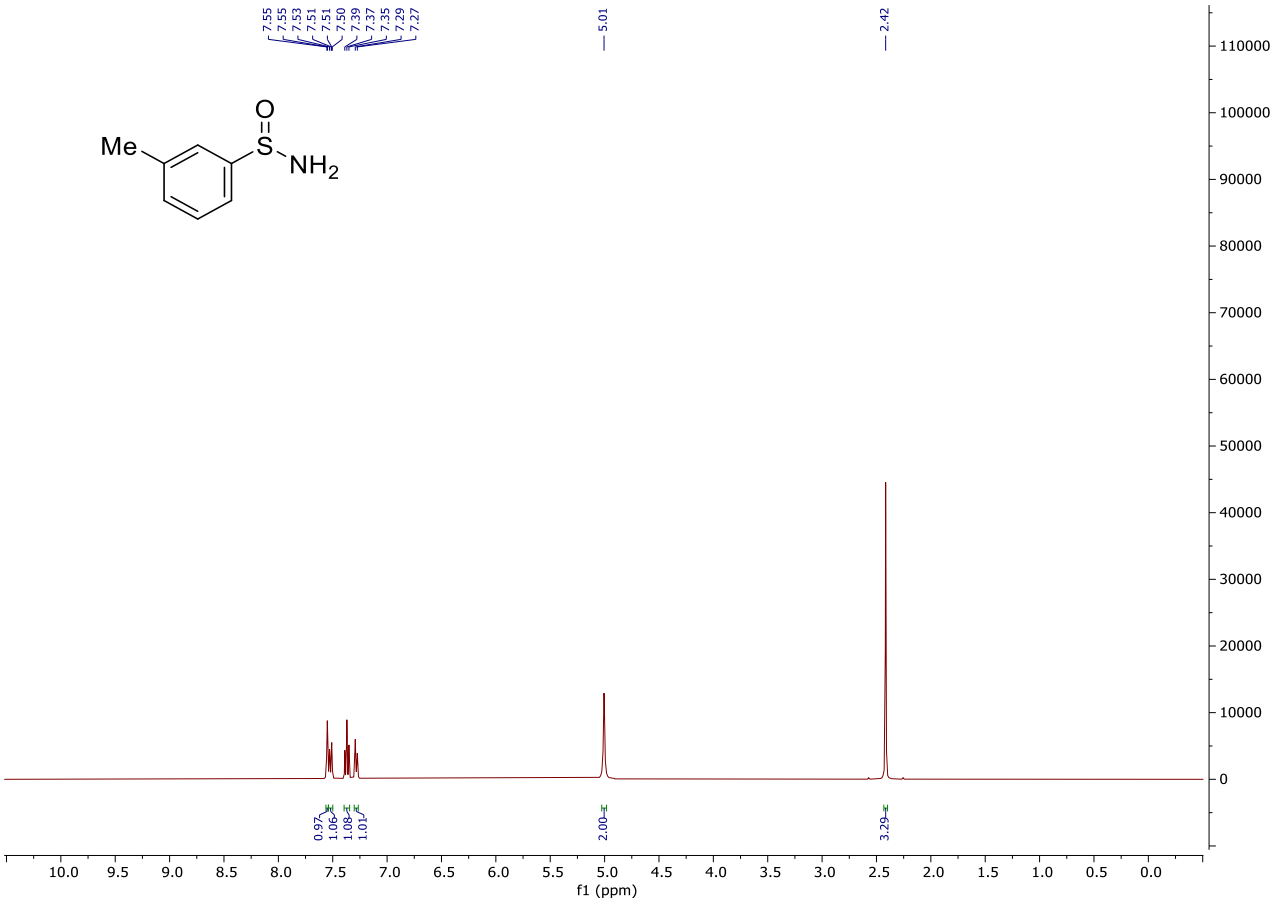

87.81
O
N
S
F
H
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

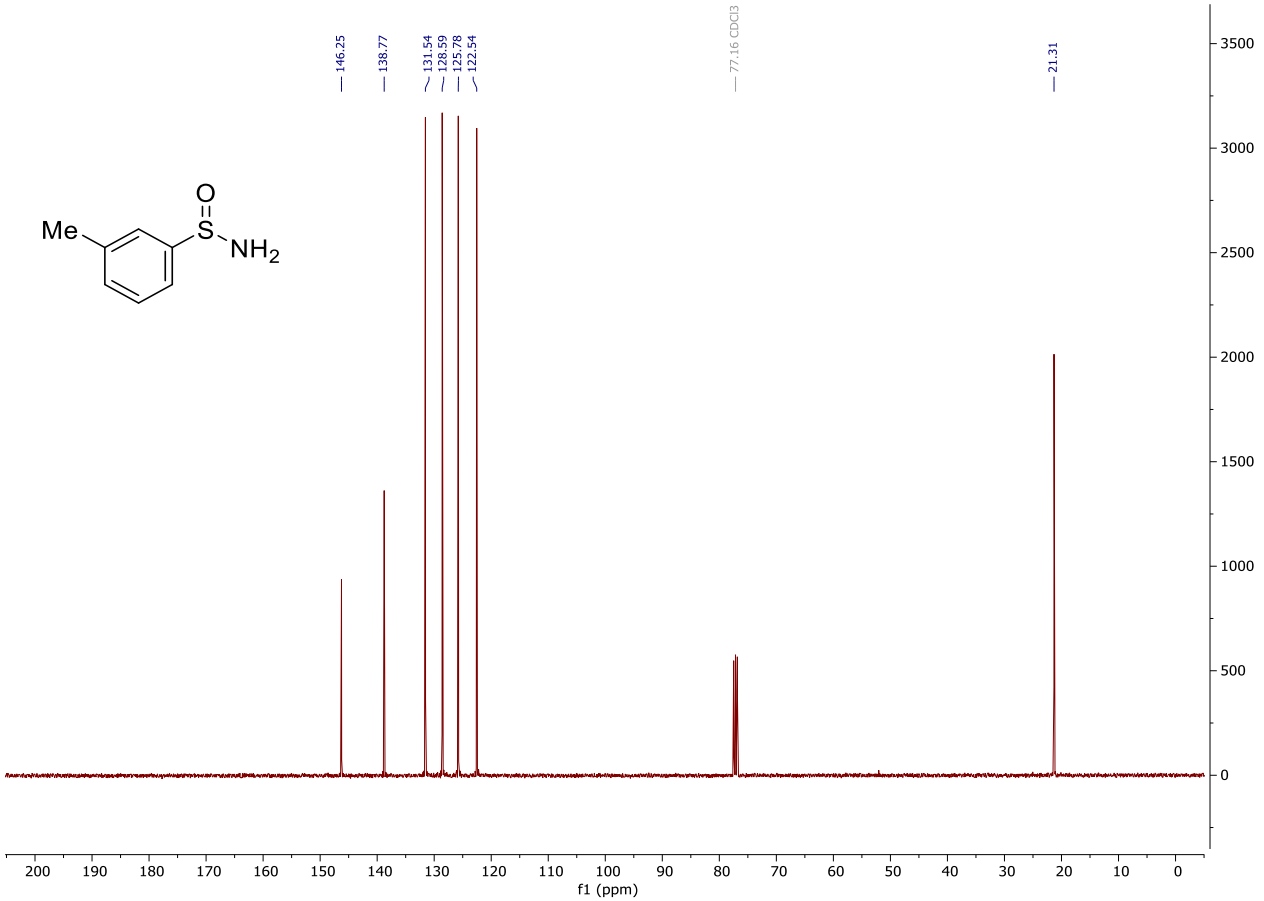
8.3. Spectra from Chapter 4

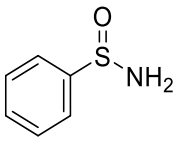
8.3.1 Primary Sulfinamides



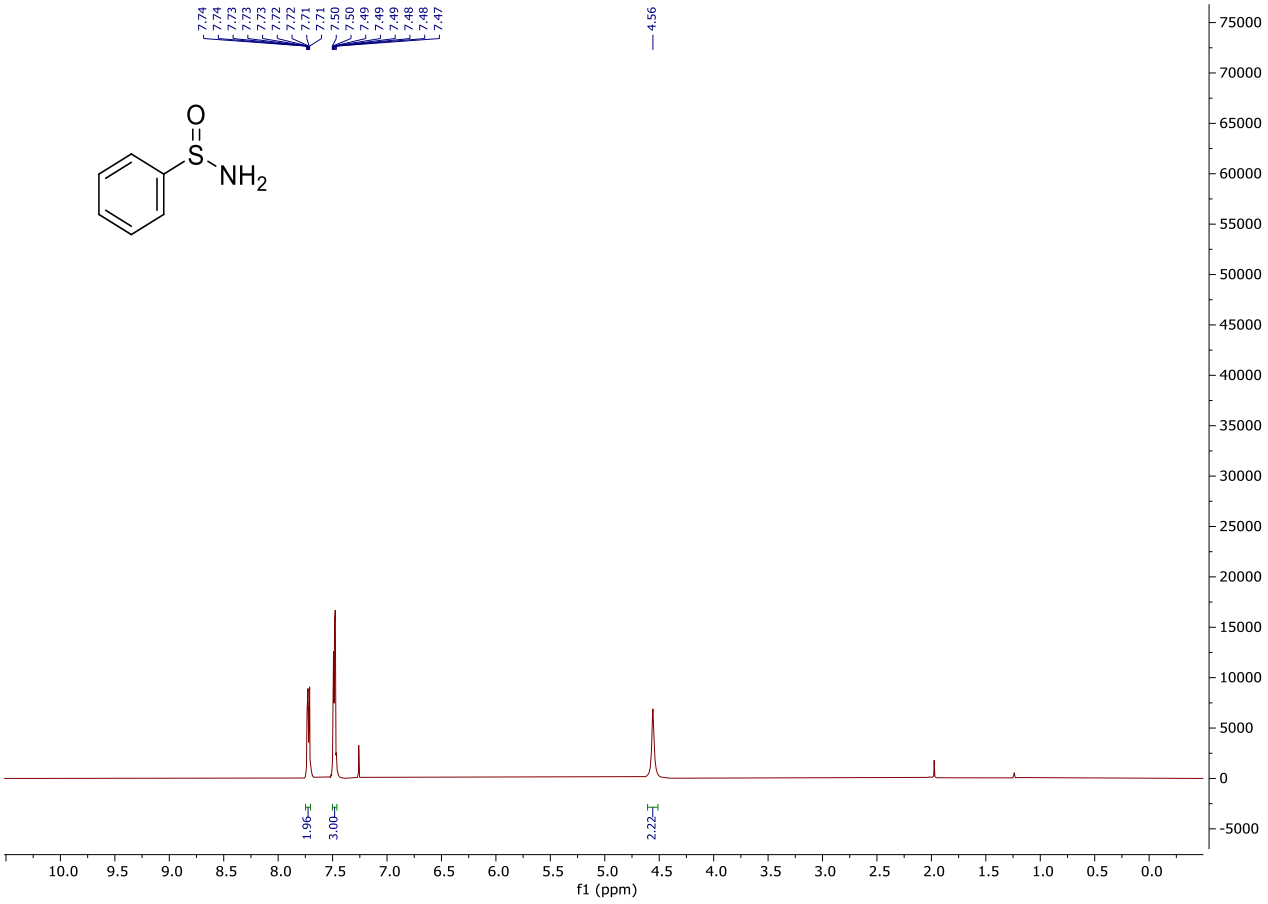
3-Methylbenzenesulfinamide (186b)

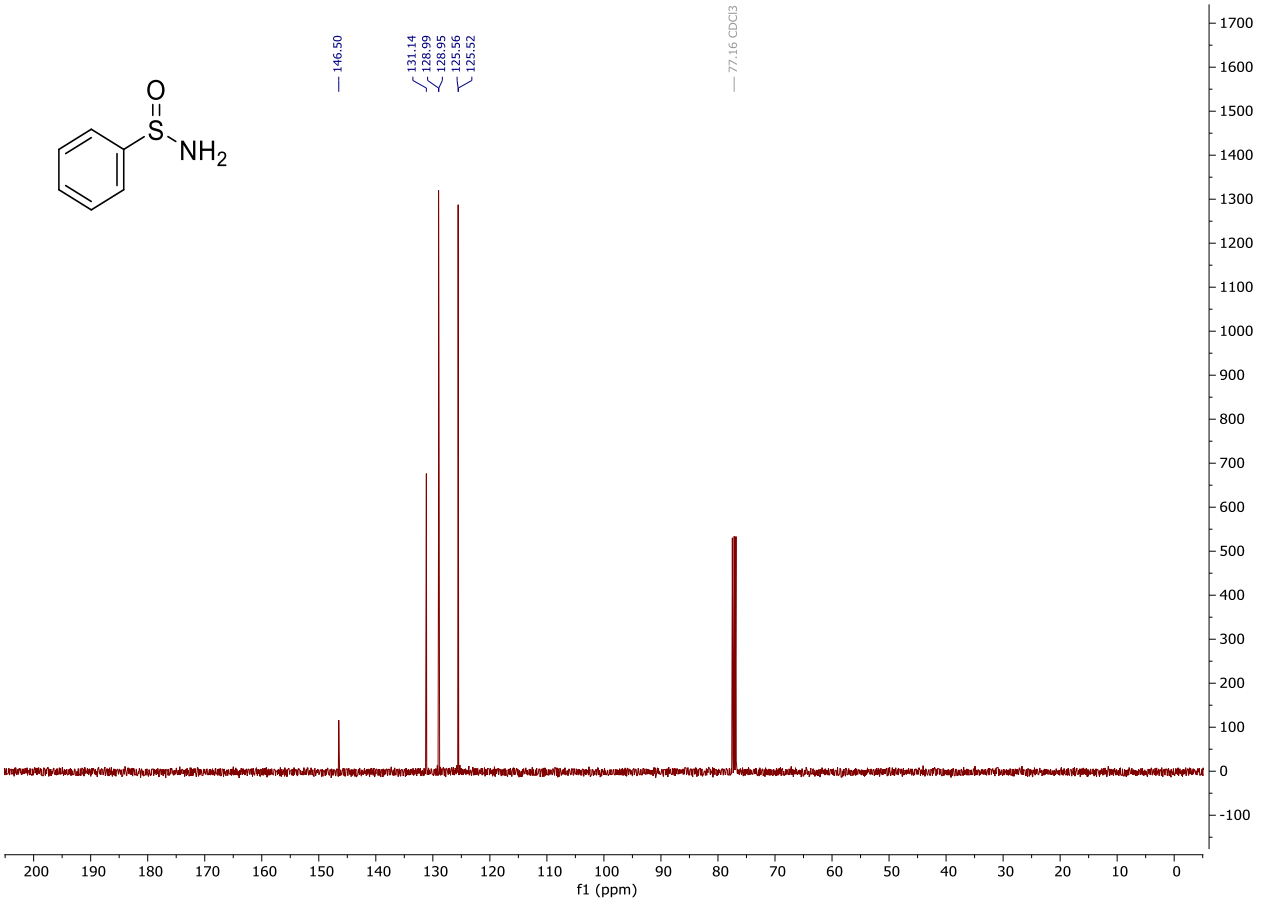


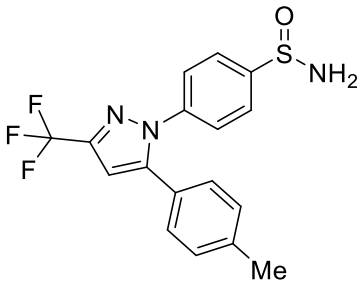




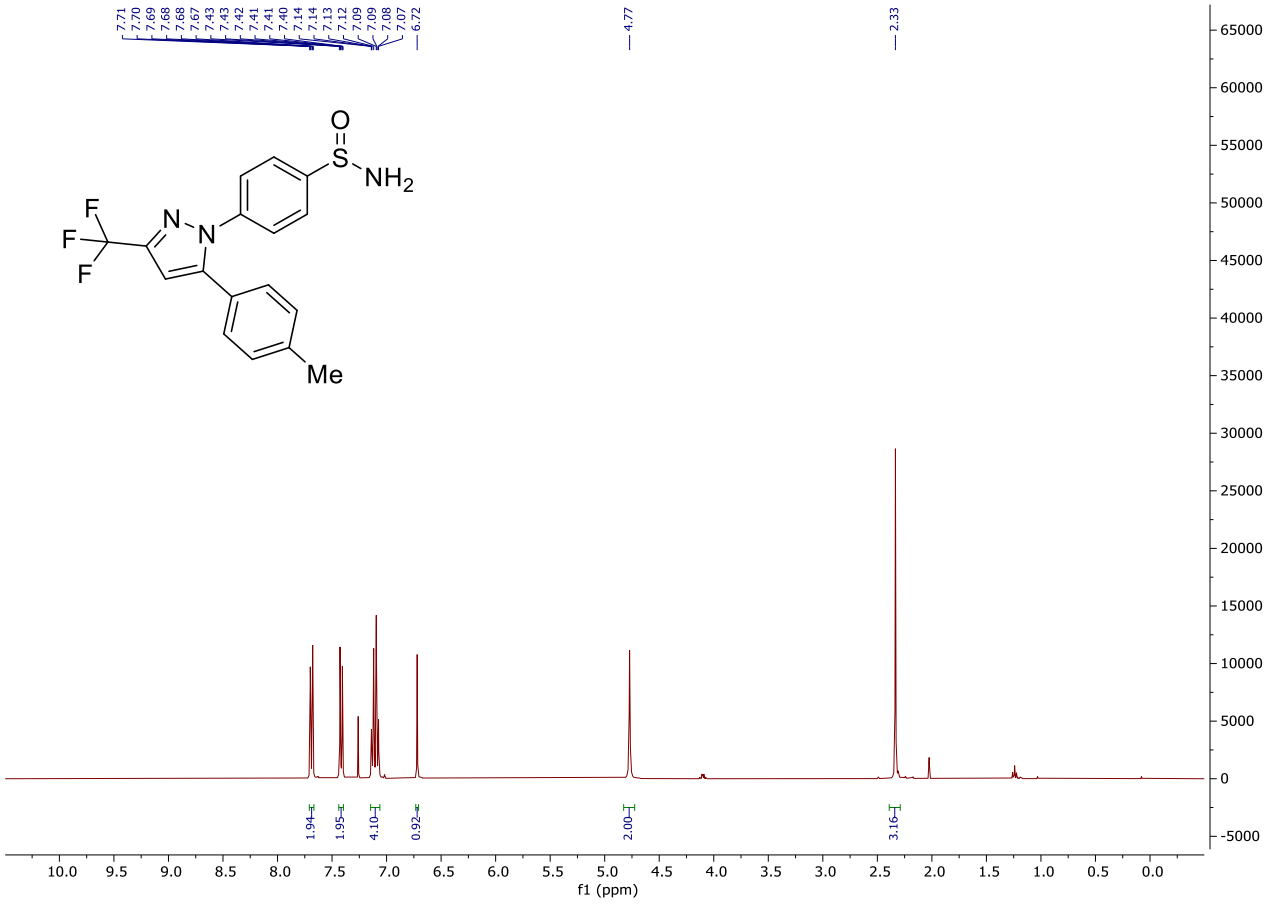
Benzenesulfinamide (186h)

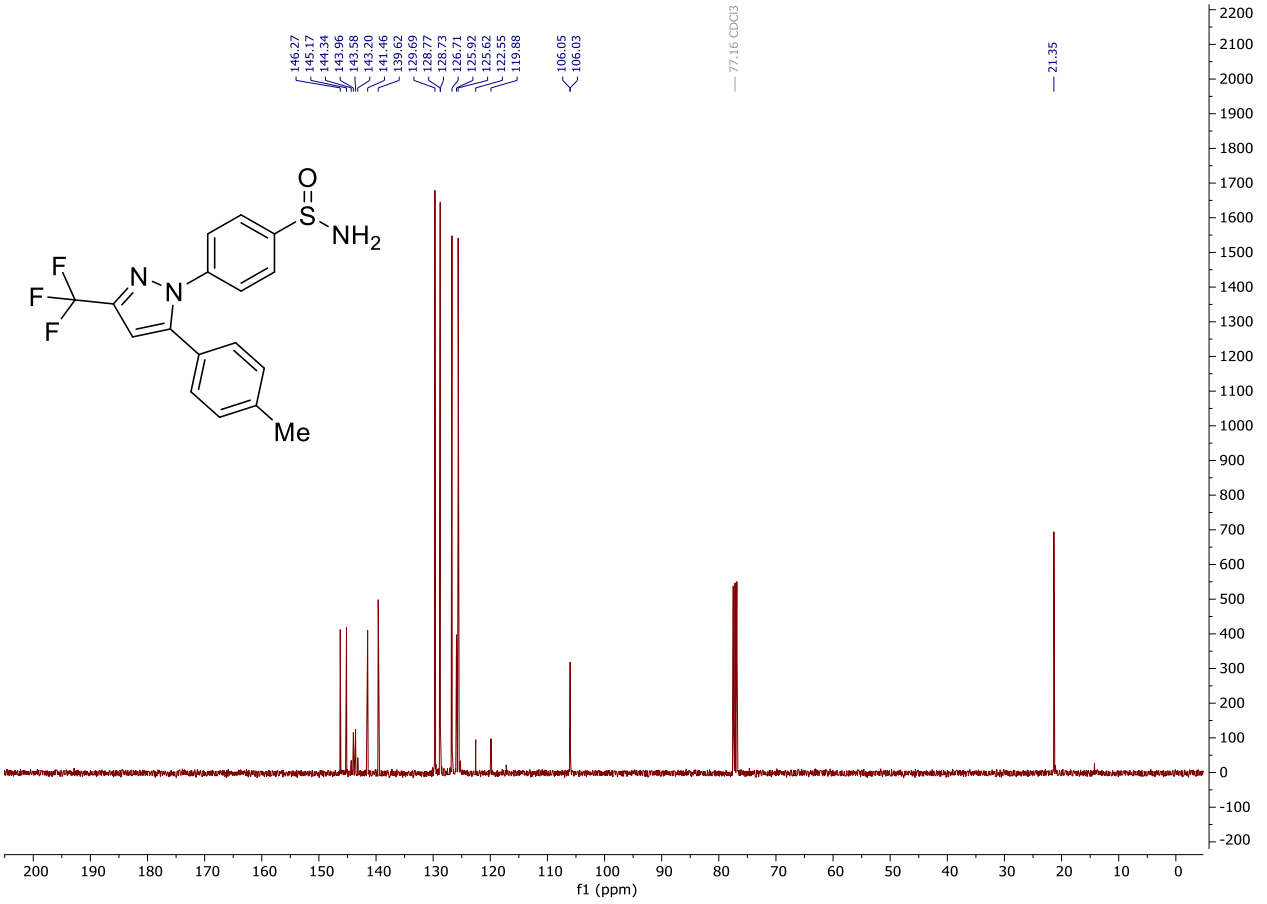

7.74
7.74
7.73
7.73
7.73
7.72
7.72
7.71
7.71
7.50
7.50
7.49
7.49
7.49
7.48
7.48
7.47
4.56
O
S
NH2
1.96
3.00
2.22
f1 (ppm)

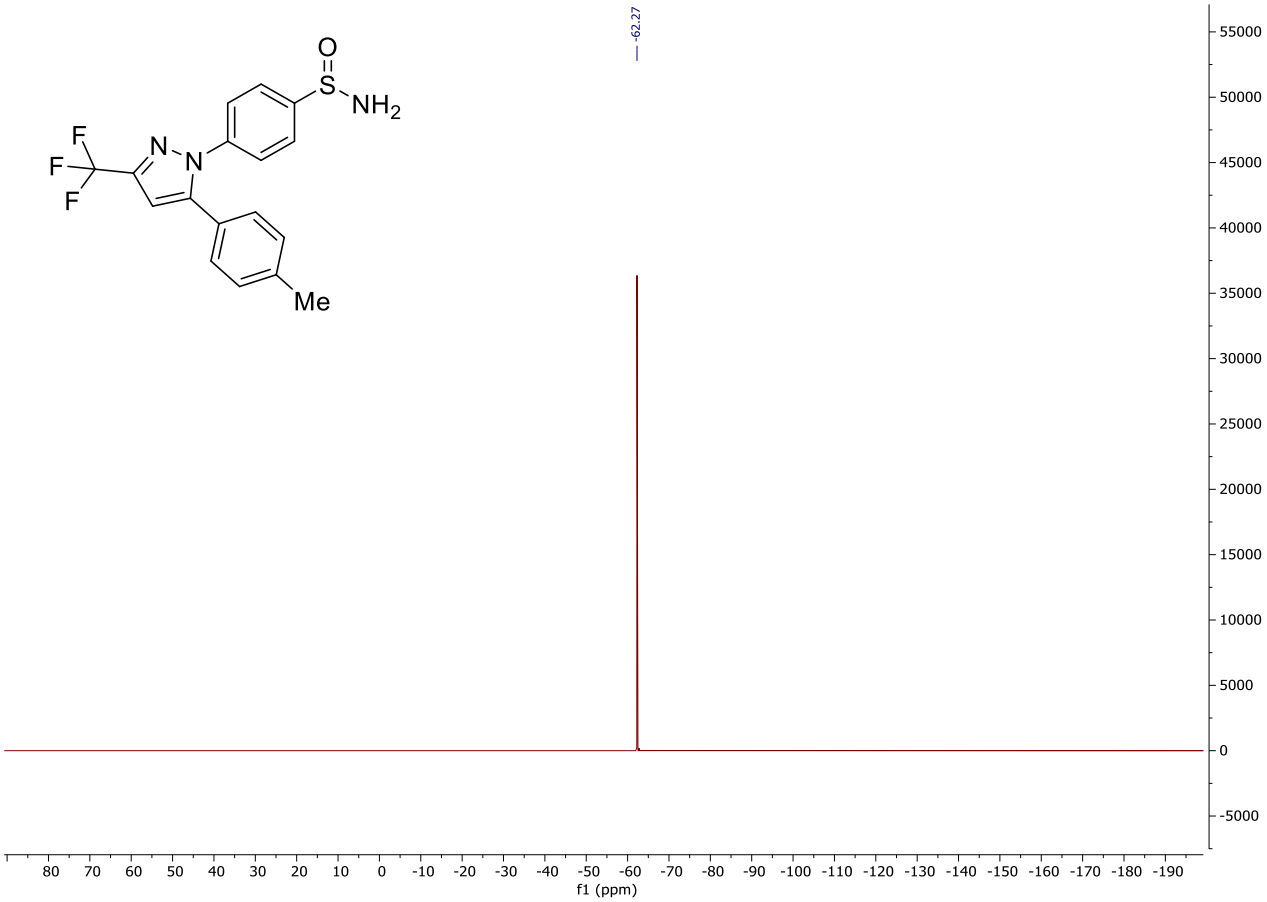

146.50
131.14
128.99
128.95
125.56
125.52
77.16 CDCl3
O
S
NH2
f1 (ppm)

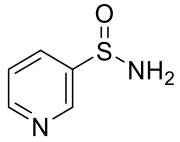


4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfinamide (186i)

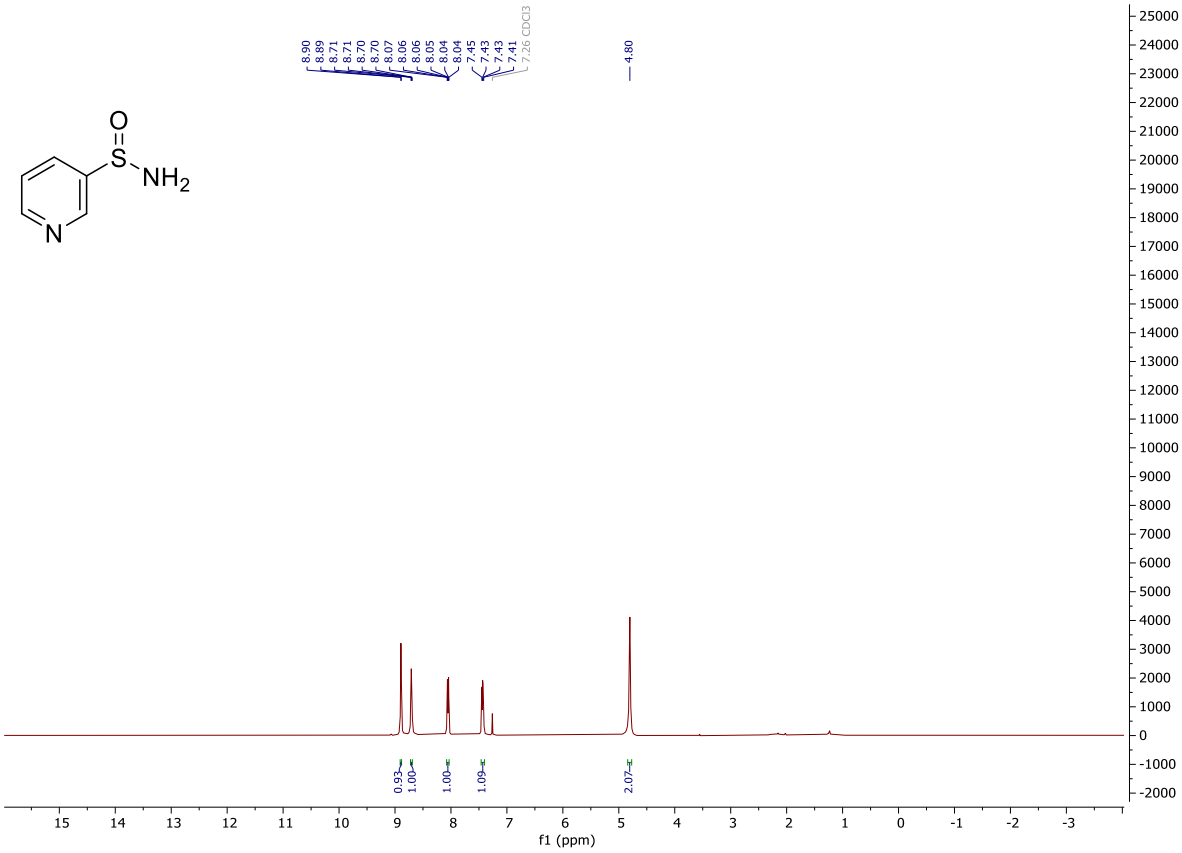


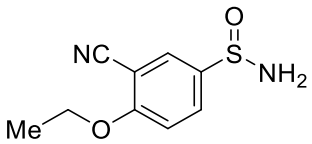

146.27
145.17
144.34
143.96
143.58
143.20
141.46
139.62
129.69
128.77
128.73
126.71
125.92
125.62
122.55
119.88
106.05
106.03
77.16 CDCl3
21.35
O
S
NH2
F
F
F
N
N
Me
f1 (ppm)


-62.27
O
S
NH2
F
F
F
N
N
Me
f1 (ppm)

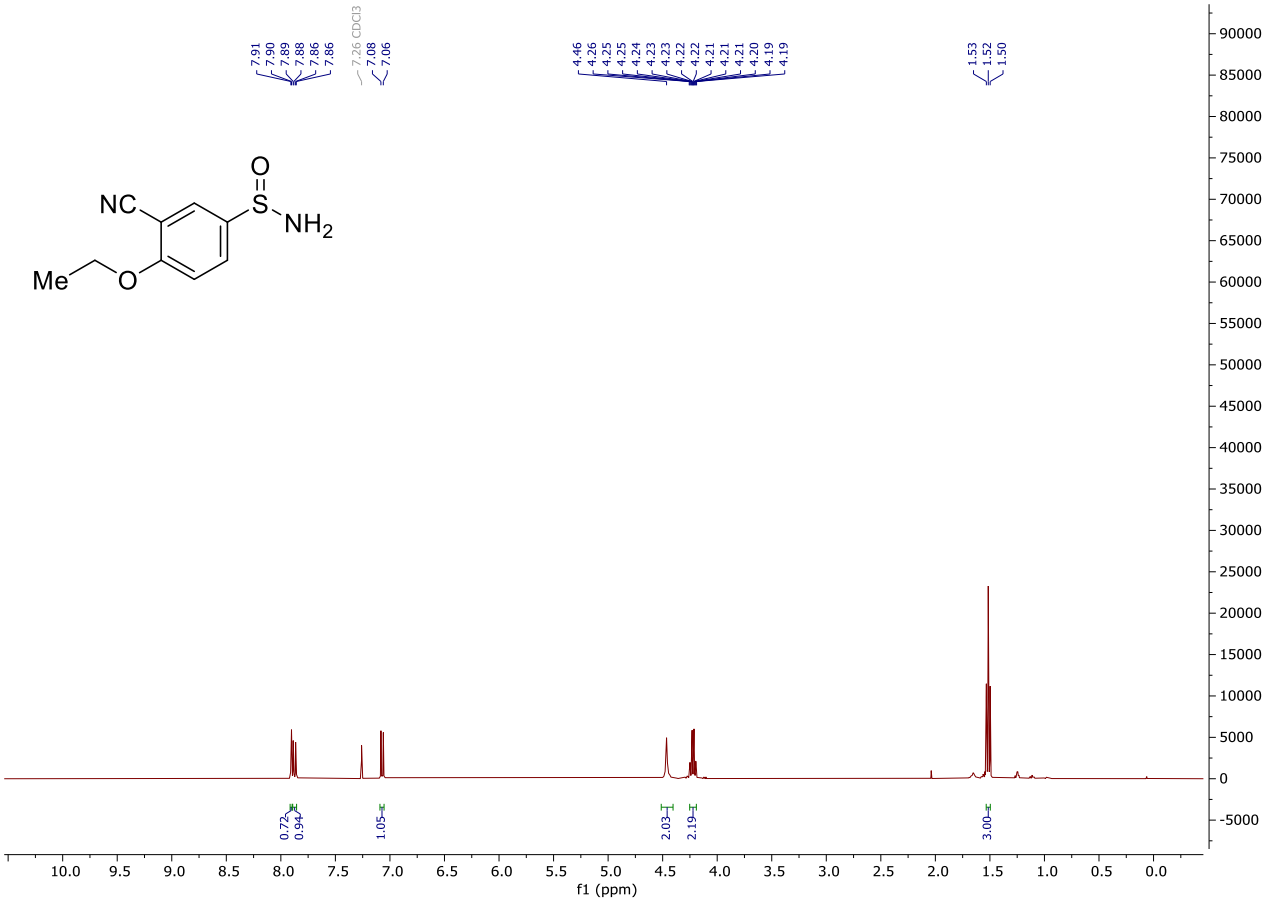


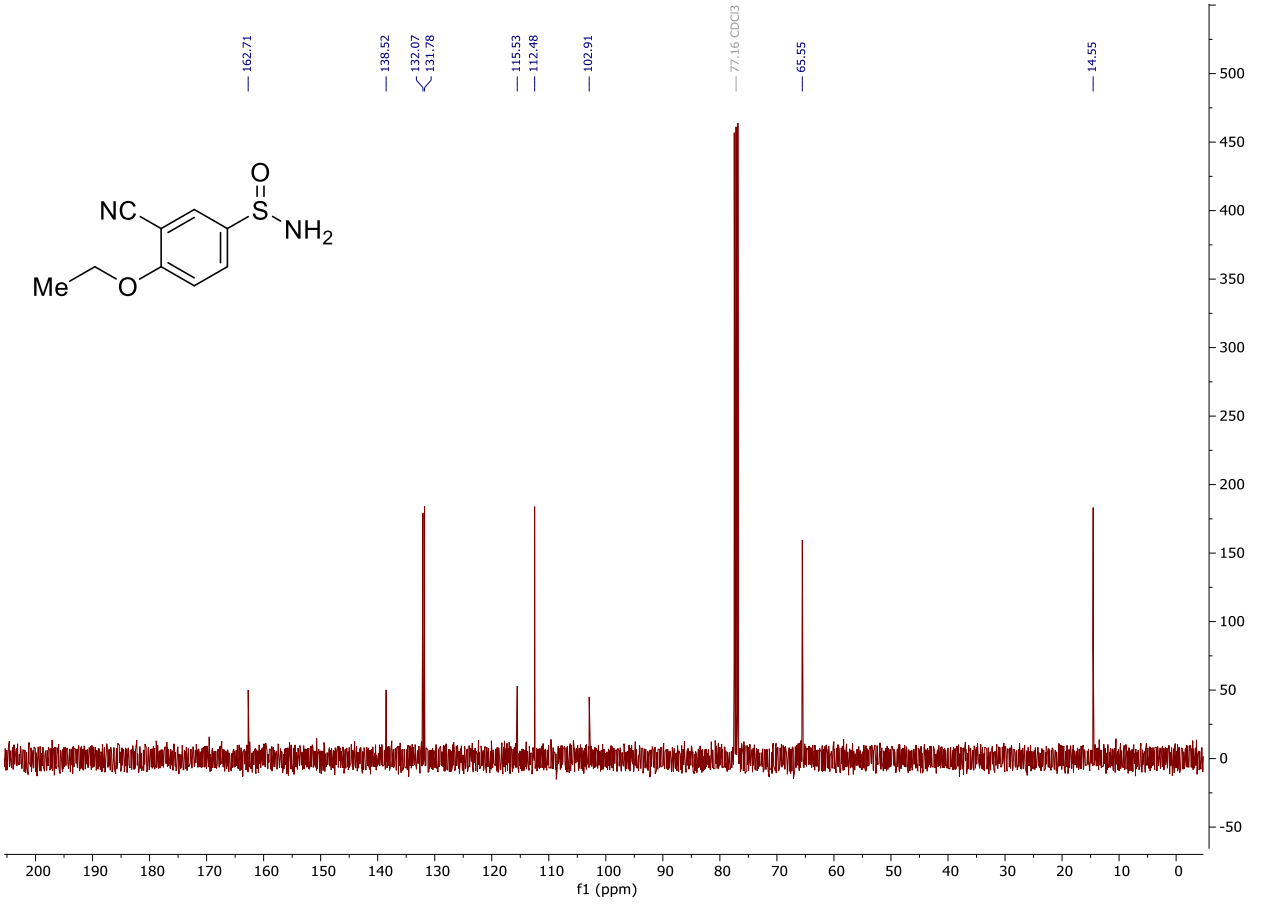
Pyridine-3-sulfinamide (186l)

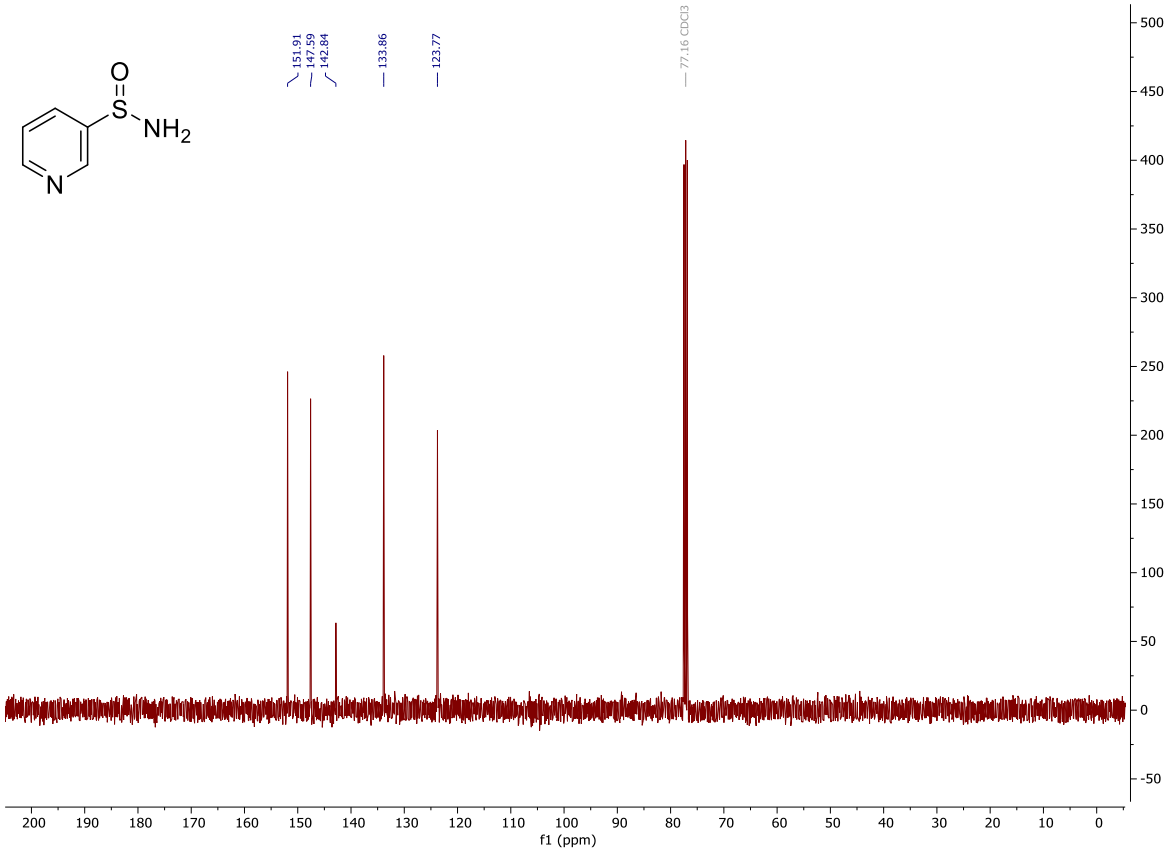


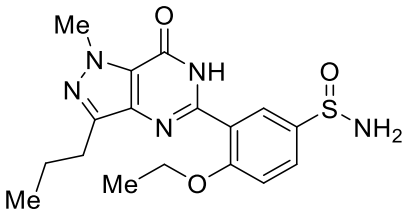


3-Cyano-4-ethoxybenzenesulfinamide (186m)

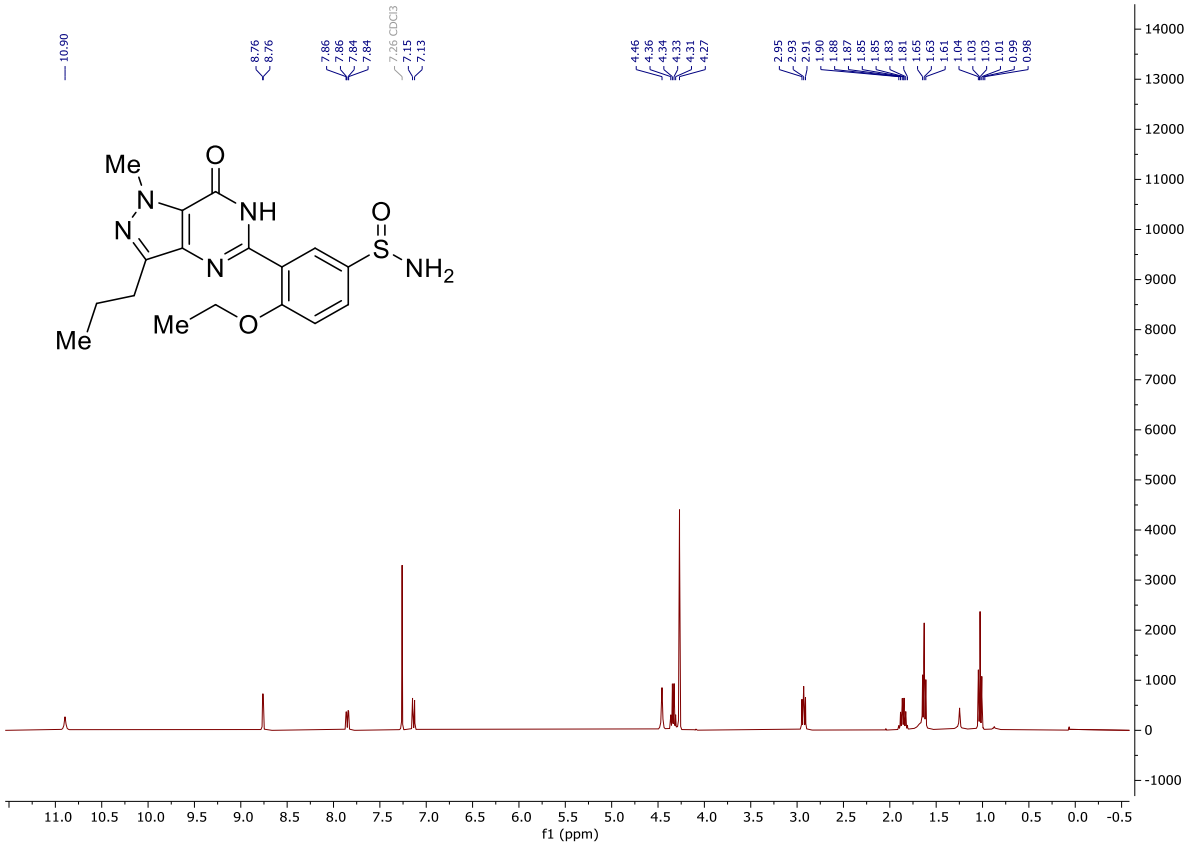

7.91
7.90
7.89
7.88
7.86
7.86
7.26 CDCl3
7.08
7.06
4.46
4.26
4.25
4.25
4.24
4.23
4.23
4.22
4.22
4.21
4.21
4.21
4.20
4.19
4.19
1.53
1.52
1.50
NC
O
S
NH2
Me
O
0.72
0.94
1.05
2.03
2.19
3.00
f1 (ppm)

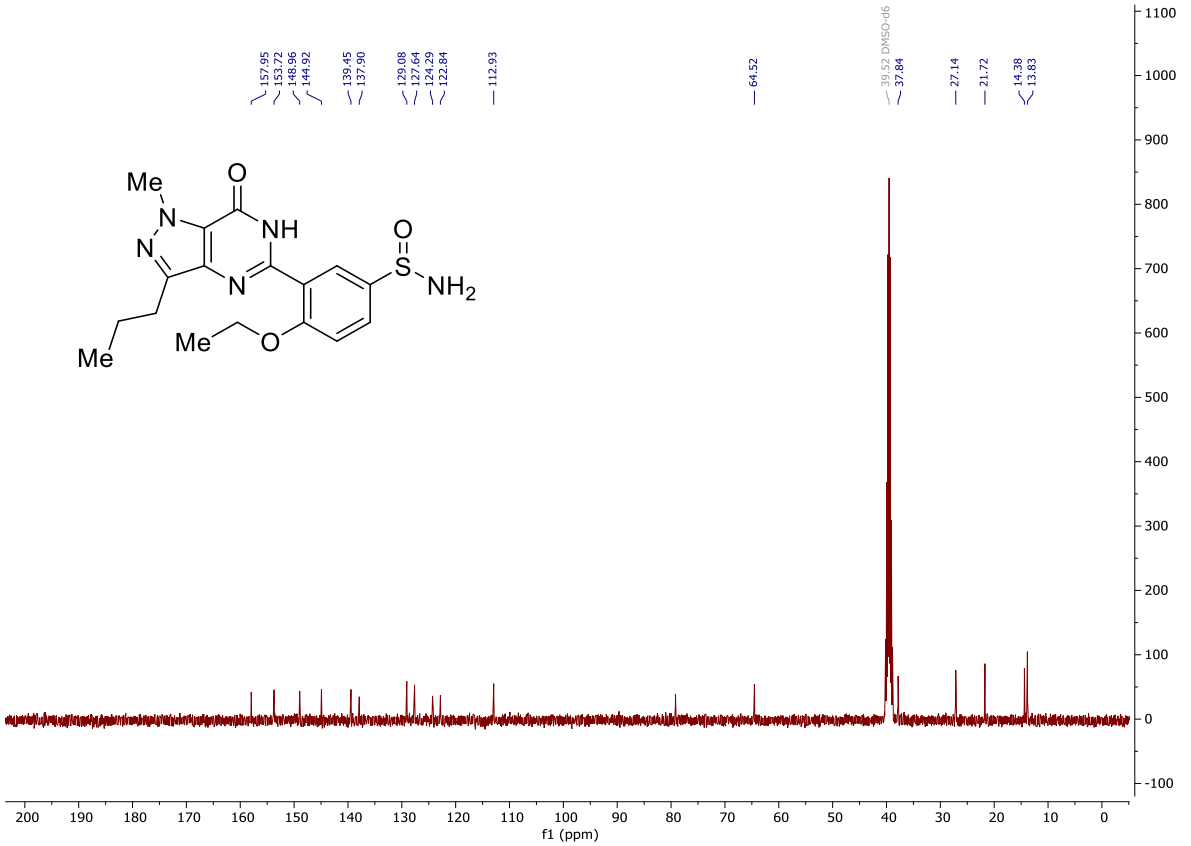

162.71
138.52
132.07
131.78
115.53
112.48
102.91
77.16 CDCl3
65.55
14.55
NC
O
S
NH2
Me
O
f1 (ppm)

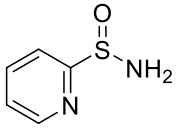




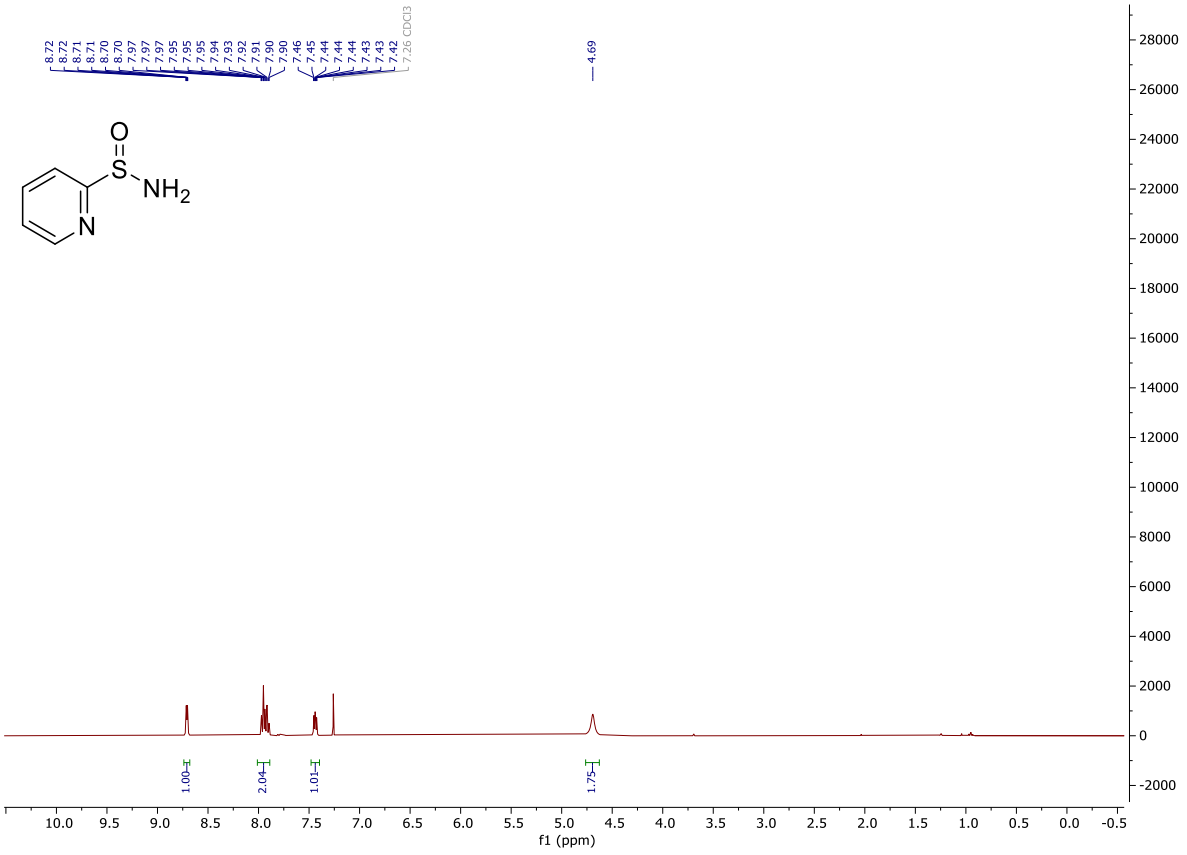
4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzenesulfinamide (186n)

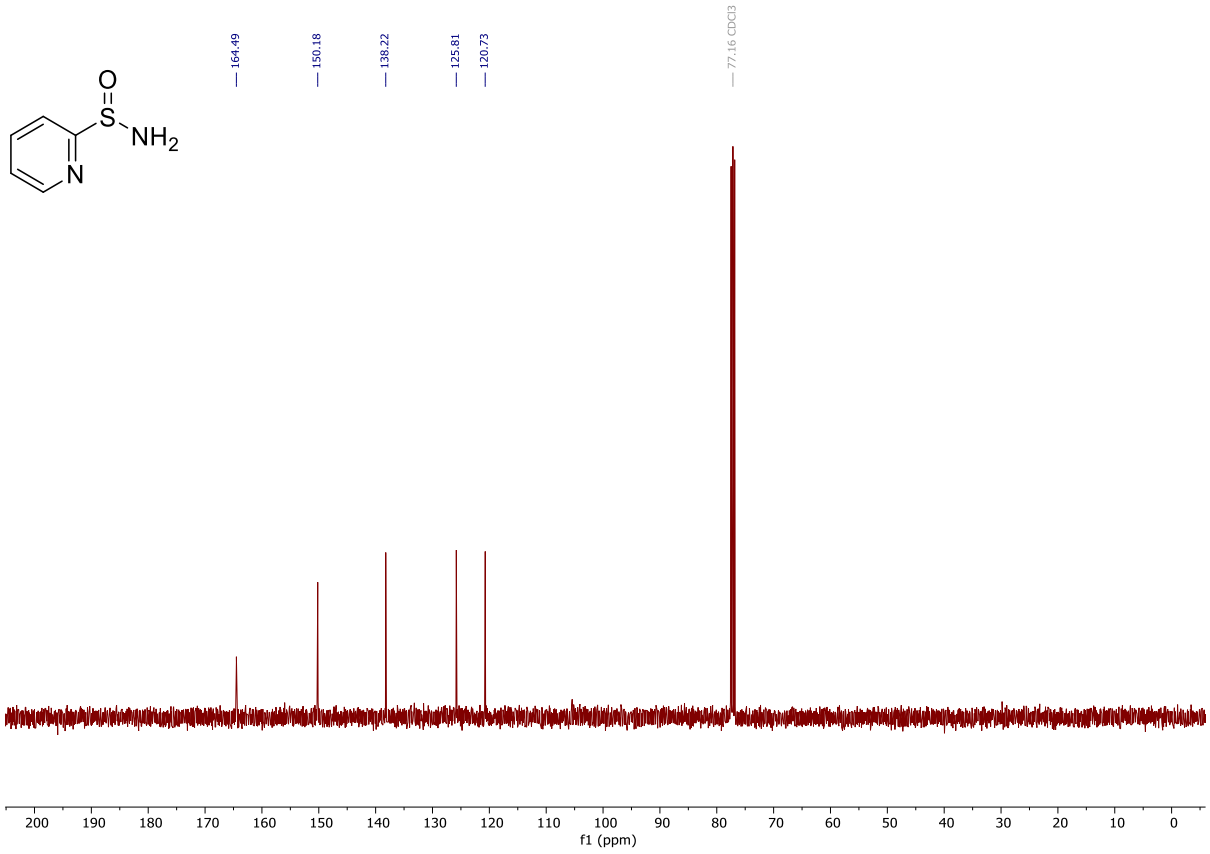

10.90
8.76
8.76
7.86
7.86
7.84
7.84
7.26 CDCl3
7.15
7.13
4.46
4.36
4.34
4.33
4.31
4.27
2.95
2.93
2.91
1.90
1.88
1.87
1.85
1.85
1.83
1.81
1.65
1.63
1.61
1.04
1.03
1.03
1.01
0.99
0.98
Me
N
N
O
NH
O
S
NH2
N
Me
O
Me
f1 (ppm)

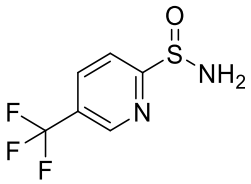

157.95
153.72
148.96
144.92
139.45
137.90
129.08
127.64
124.29
122.84
112.93
64.52
39.52 DMSO-d6
37.84
27.14
21.72
14.38
13.83
Me
N
N
O
NH
O
S
NH2
N
Me
O
Me
f1 (ppm)



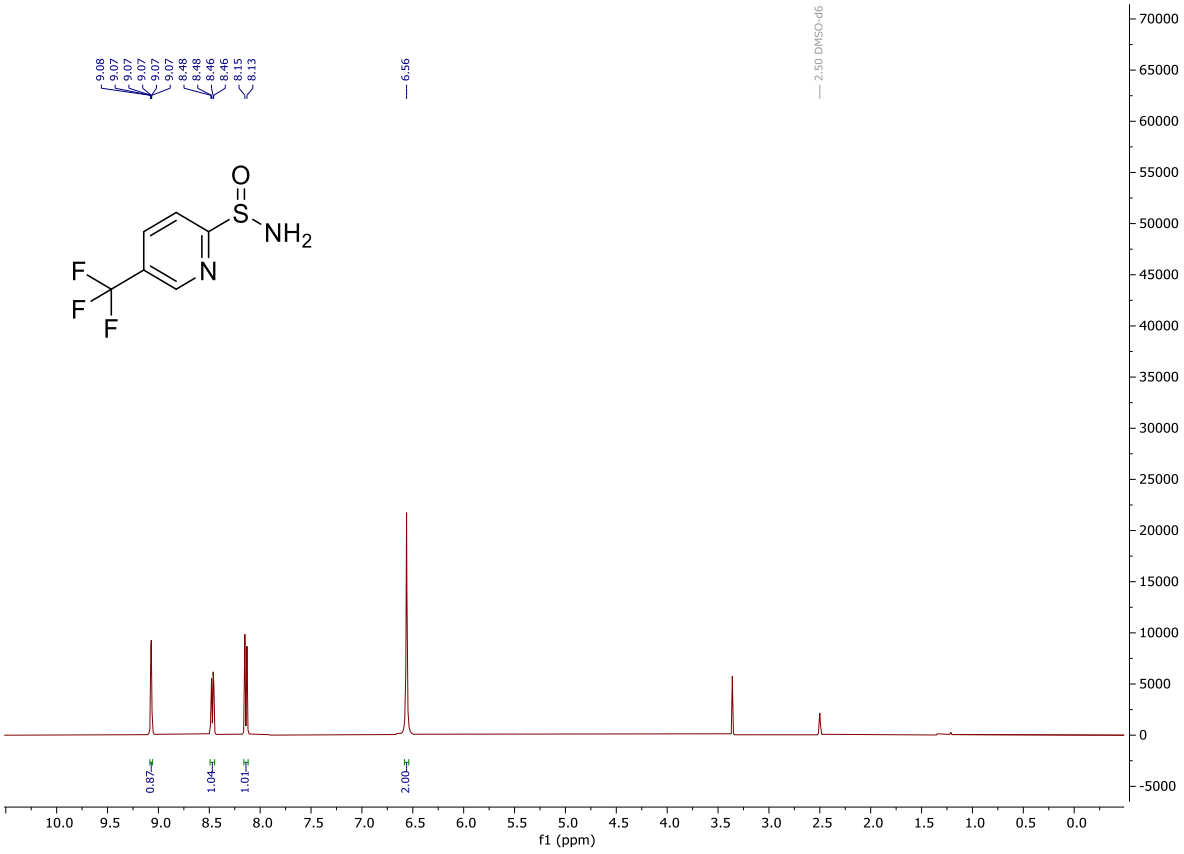
Pyridine-2-sulfinamide (XX)

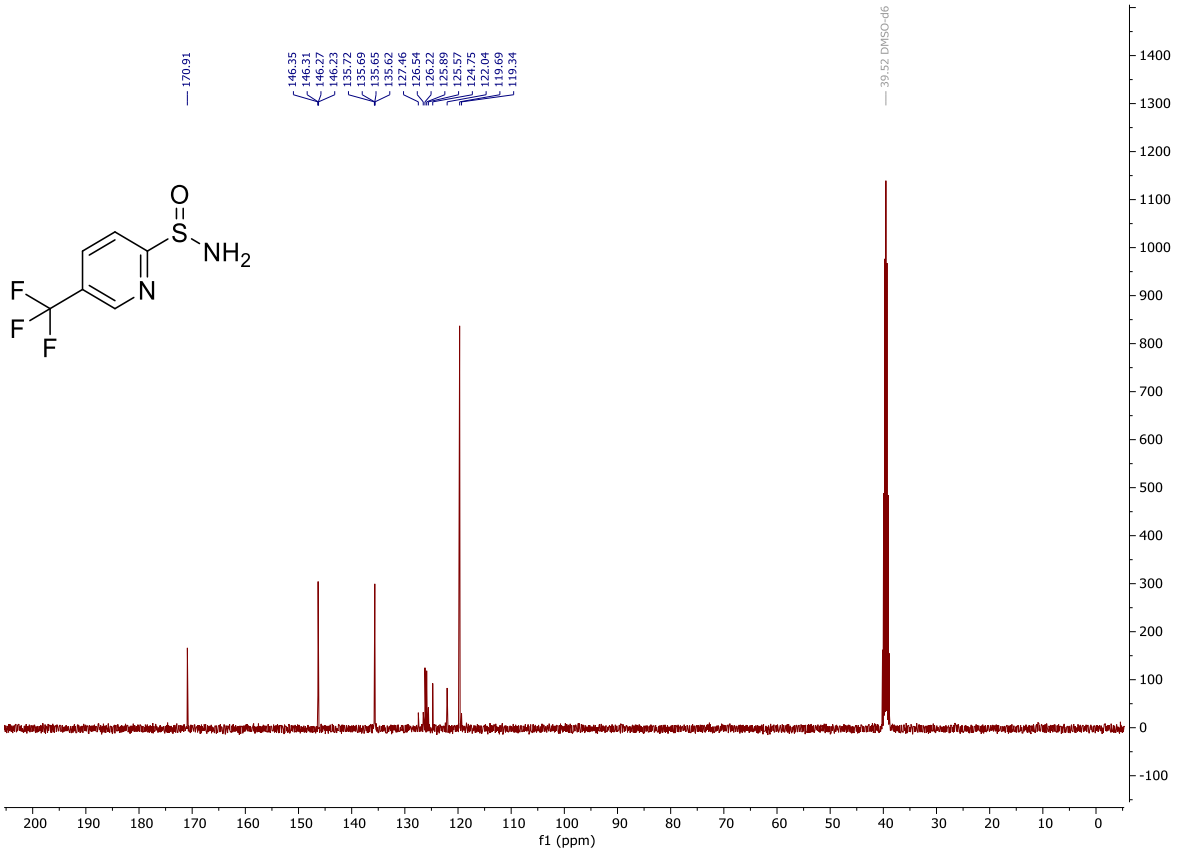


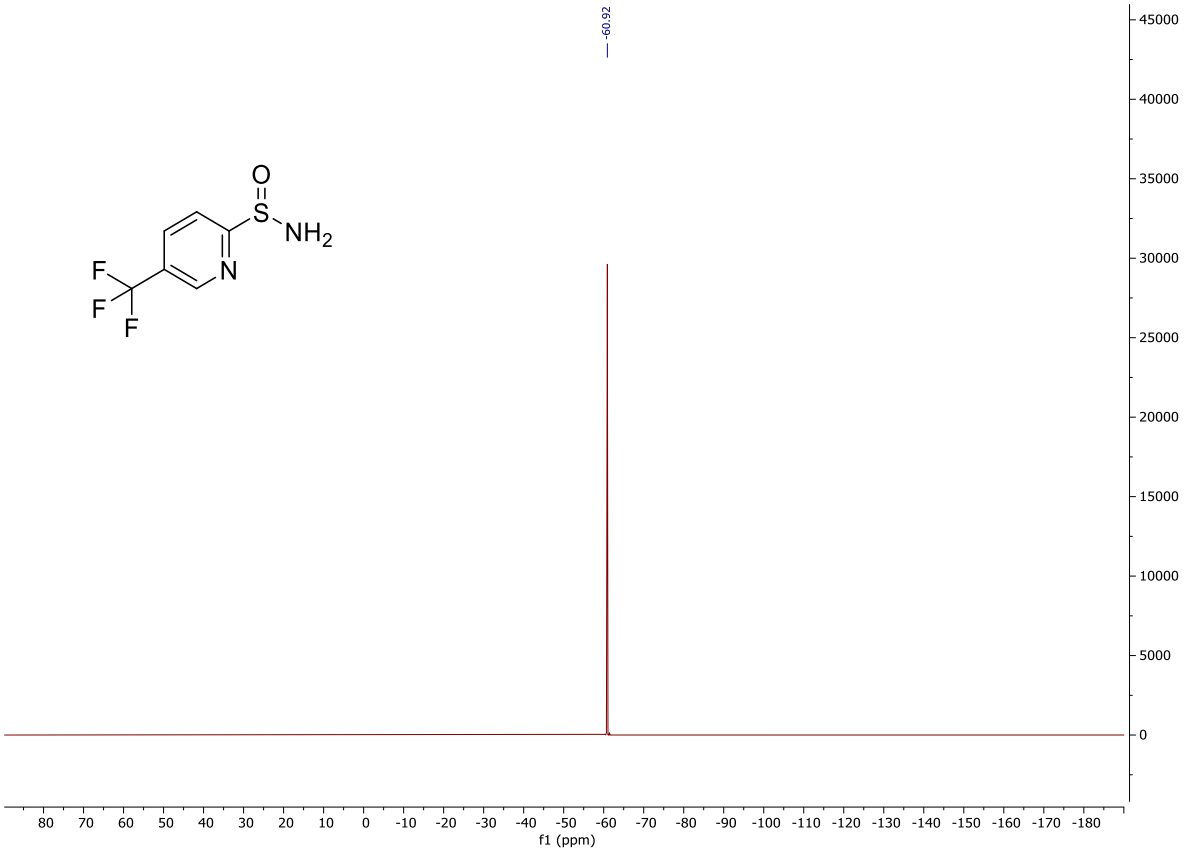


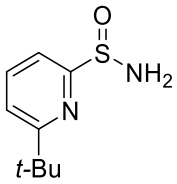


5-(Trifluoromethyl)pyridine-2-sulfinamide (192c)

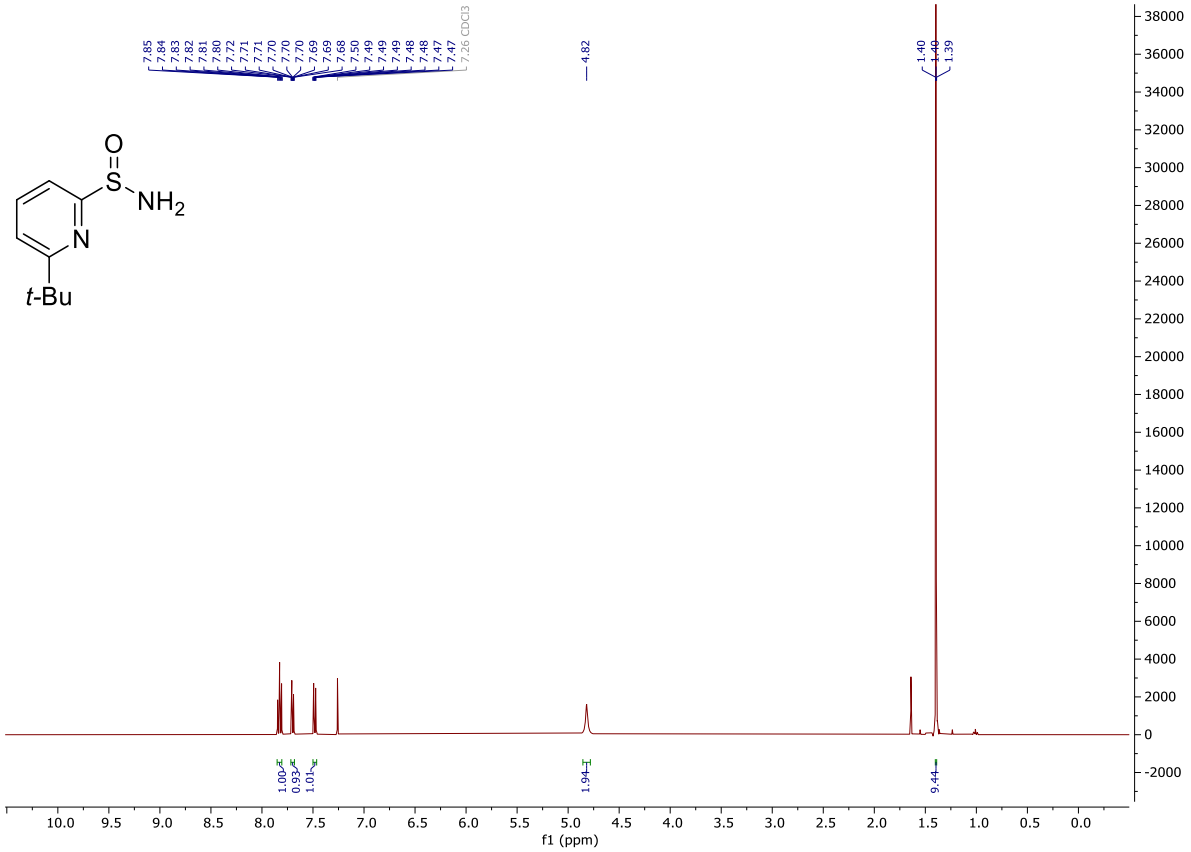

9.08
9.07
9.07
9.07
9.07
9.07
8.48
8.46
8.46
8.15
8.13
6.56
2.50 DMSO-d6
O
S
NH2
N
F
F
F
0.87
1.04
1.01
2.00
f1 (ppm)

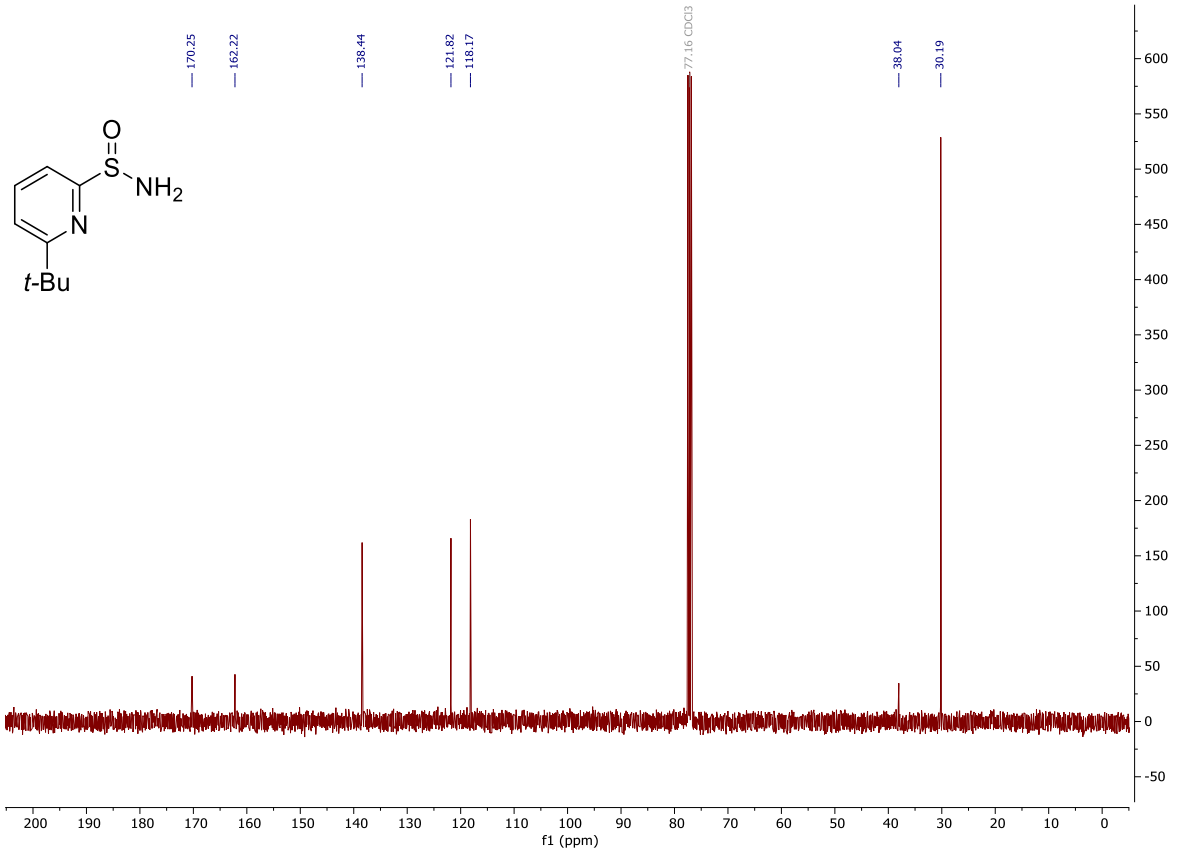

170.91
146.35
146.31
146.27
146.23
135.72
135.69
135.65
135.62
127.46
126.54
126.22
125.89
125.57
124.75
122.04
119.69
119.34
39.52 DMSO-d6
O
S
NH2
N
F
F
F
f1 (ppm)

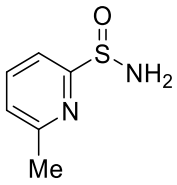




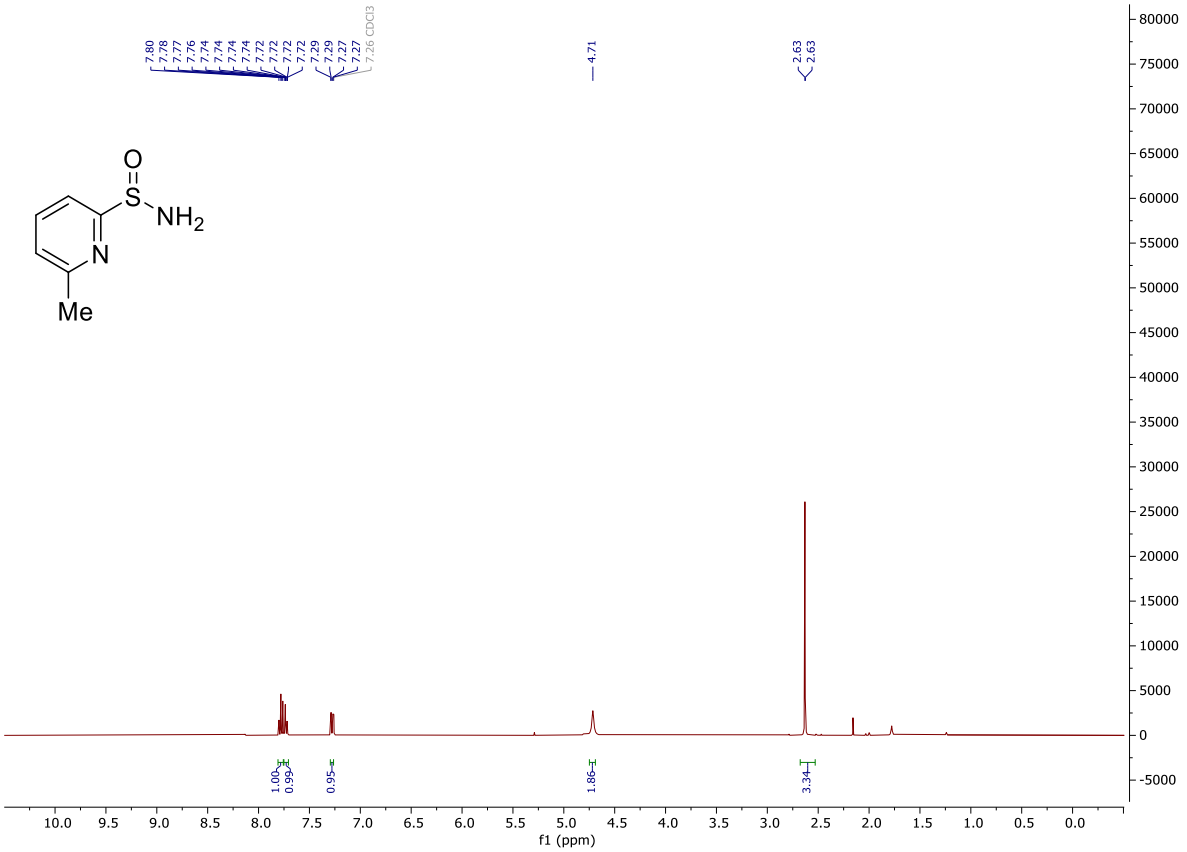
6-(*tert*-Butyl)pyridine-2-sulfinamide (192d)

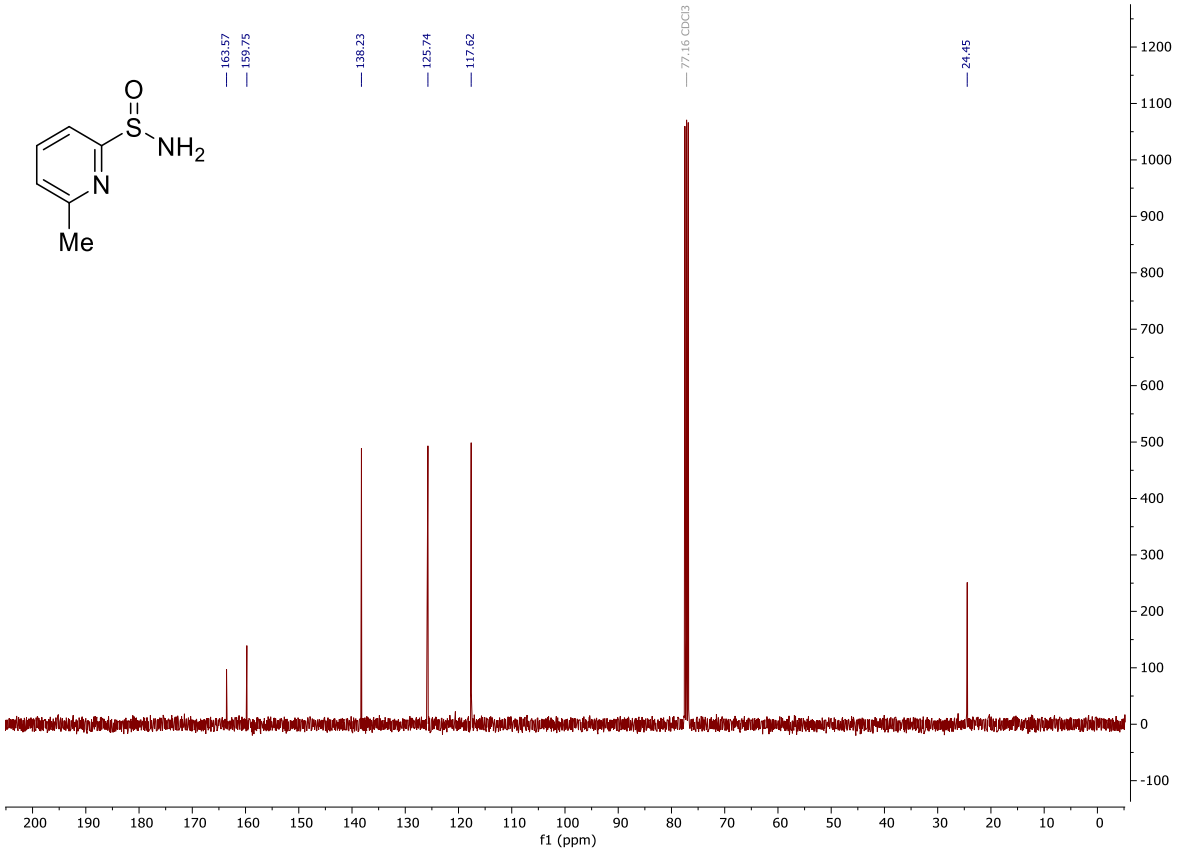

7.85
7.84
7.83
7.82
7.81
7.80
7.72
7.71
7.71
7.70
7.70
7.70
7.69
7.69
7.68
7.50
7.49
7.49
7.49
7.48
7.48
7.47
7.47
7.26 CDCl3
4.82
1.40
1.40
1.39
O
S
NH2
N
t-Bu
1.00
0.93
1.01
1.94
9.44
f1 (ppm)


170.25
162.22
138.44
121.82
118.17
77.16 CDCl3
38.04
30.19
O
S
NH2
N
t-Bu
f1 (ppm)

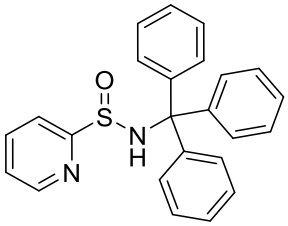


6-Methylpyridine-2-sulfinamide (192e)

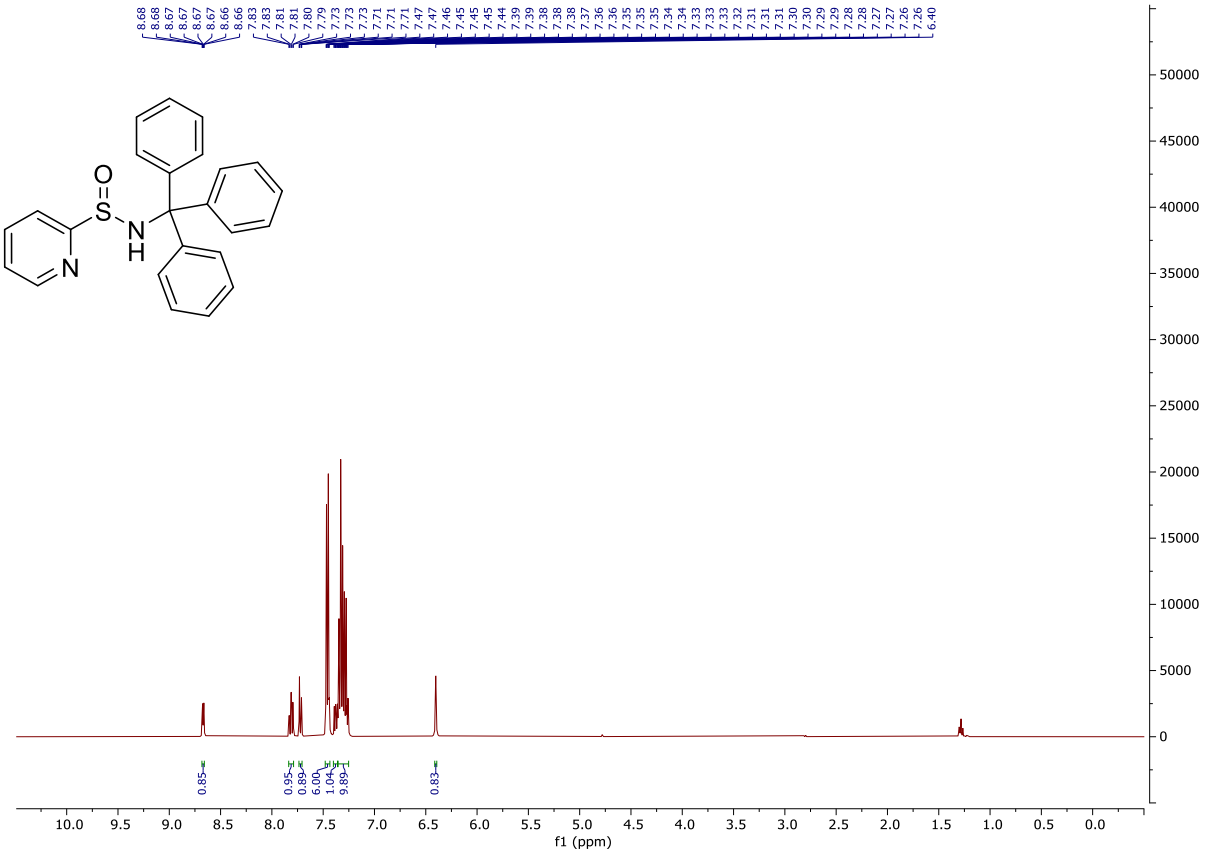


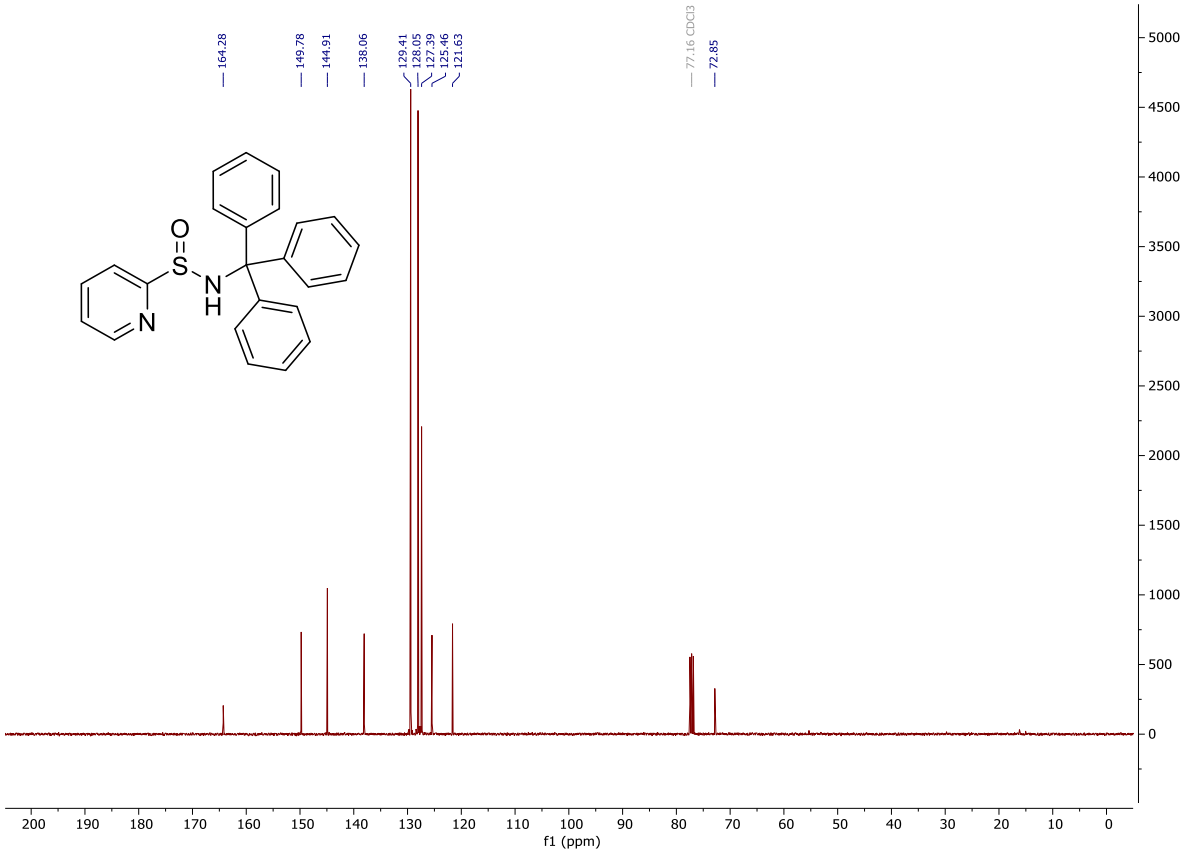

163.57
159.75
138.23
125.74
117.62
77.16 CDCl3
24.45
O
S
NH2
N
Me
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

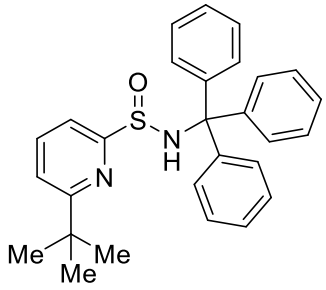
8.3.2 *N*-Trityl Sulfinamides



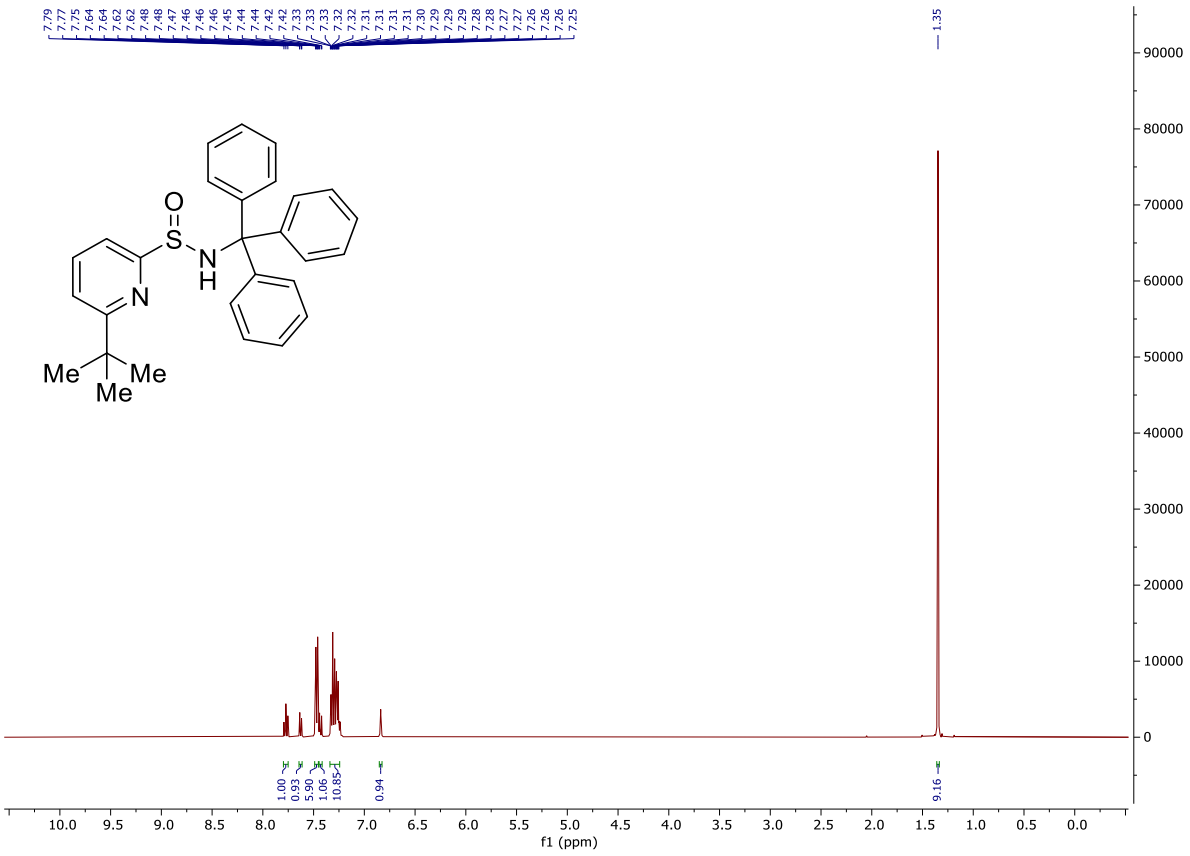
***N*-Tritylpyridine-2-sulfinamide (198b)**

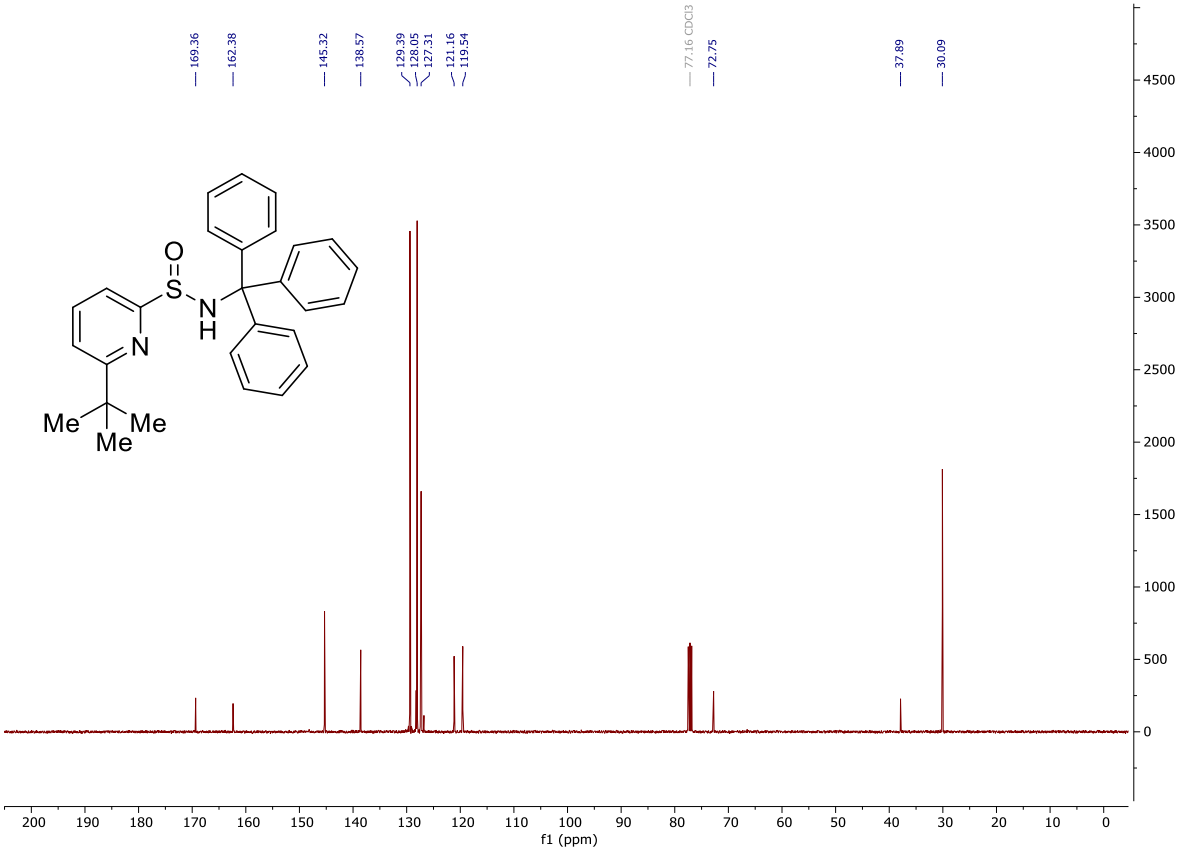


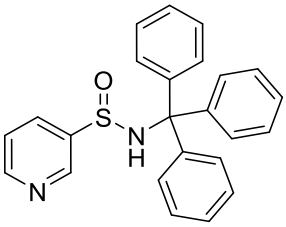




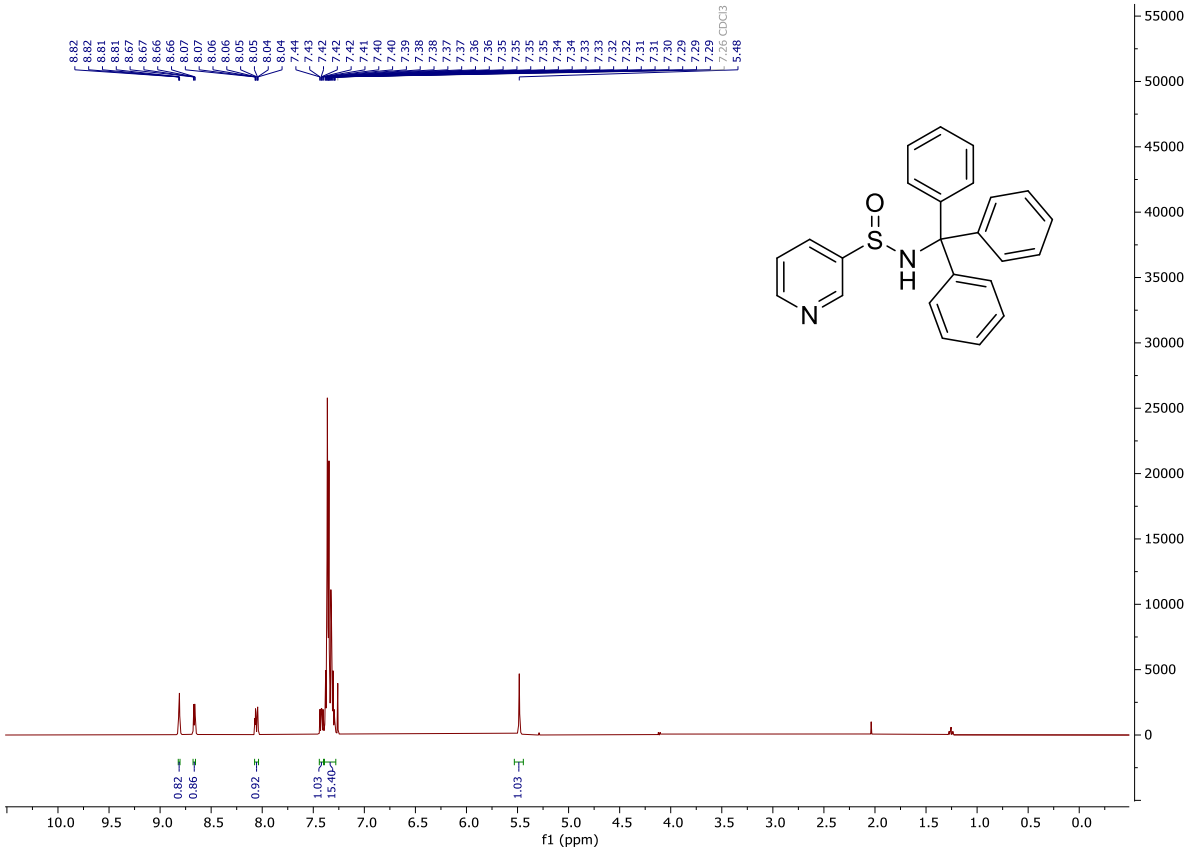
6-(*tert*-Butyl)-*N*-tritylpyridine-2-sulfinamide (193d)

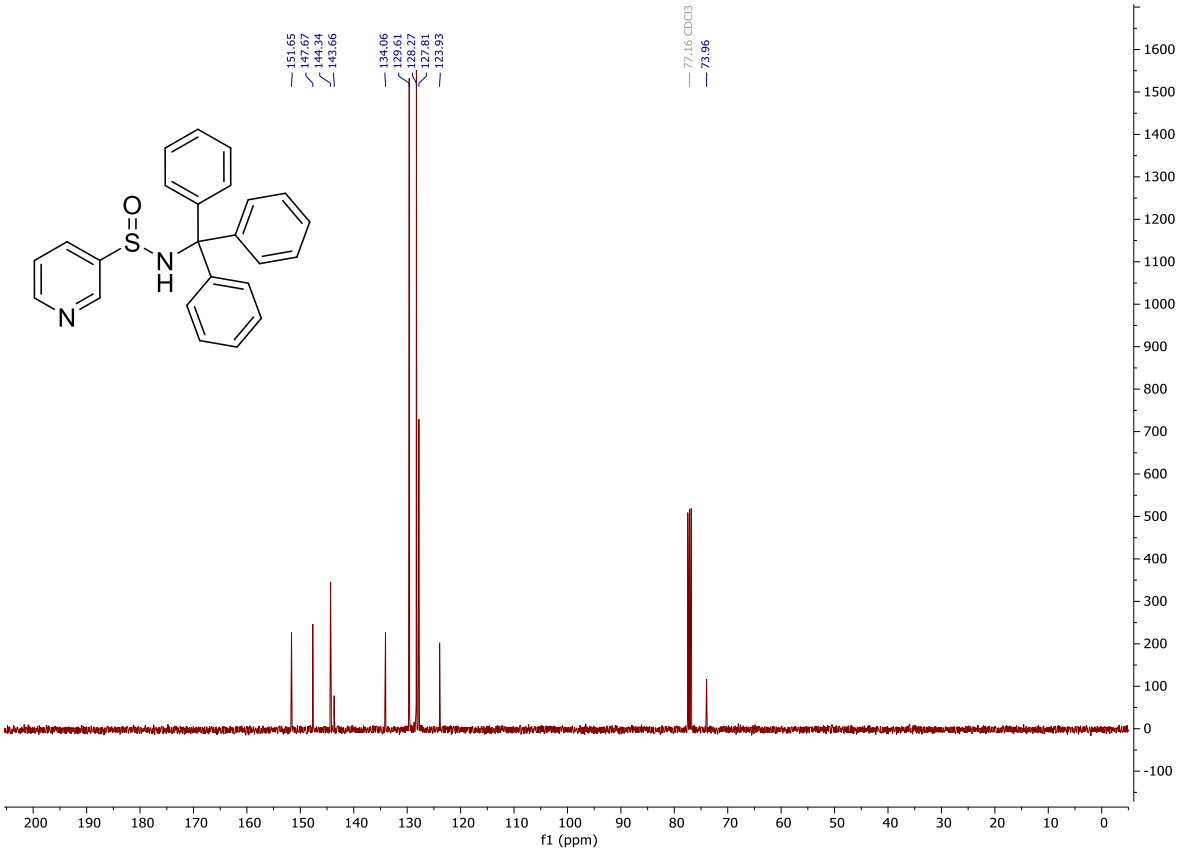

7.79 7.77 7.75 7.64 7.62 7.62 7.48 7.47 7.46 7.46 7.45 7.44 7.44 7.42 7.42 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.31 7.30 7.29 7.29 7.29 7.28 7.28 7.27 7.27 7.26 7.26 7.26 7.25
1.35
O
S
N
H
N
Me
Me
Me
1.00 0.93 5.90 1.06 10.85 0.94 9.16
f1 (ppm)

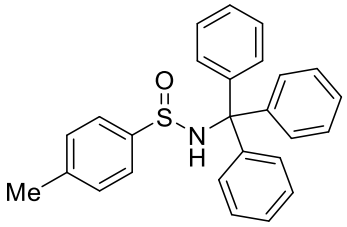

169.36 162.38 145.32 138.57 129.39 128.05 127.31 121.16 119.54
77.16 CDCl3 72.75
37.89 30.09
O
S
N
H
N
Me
Me
Me
f1 (ppm)



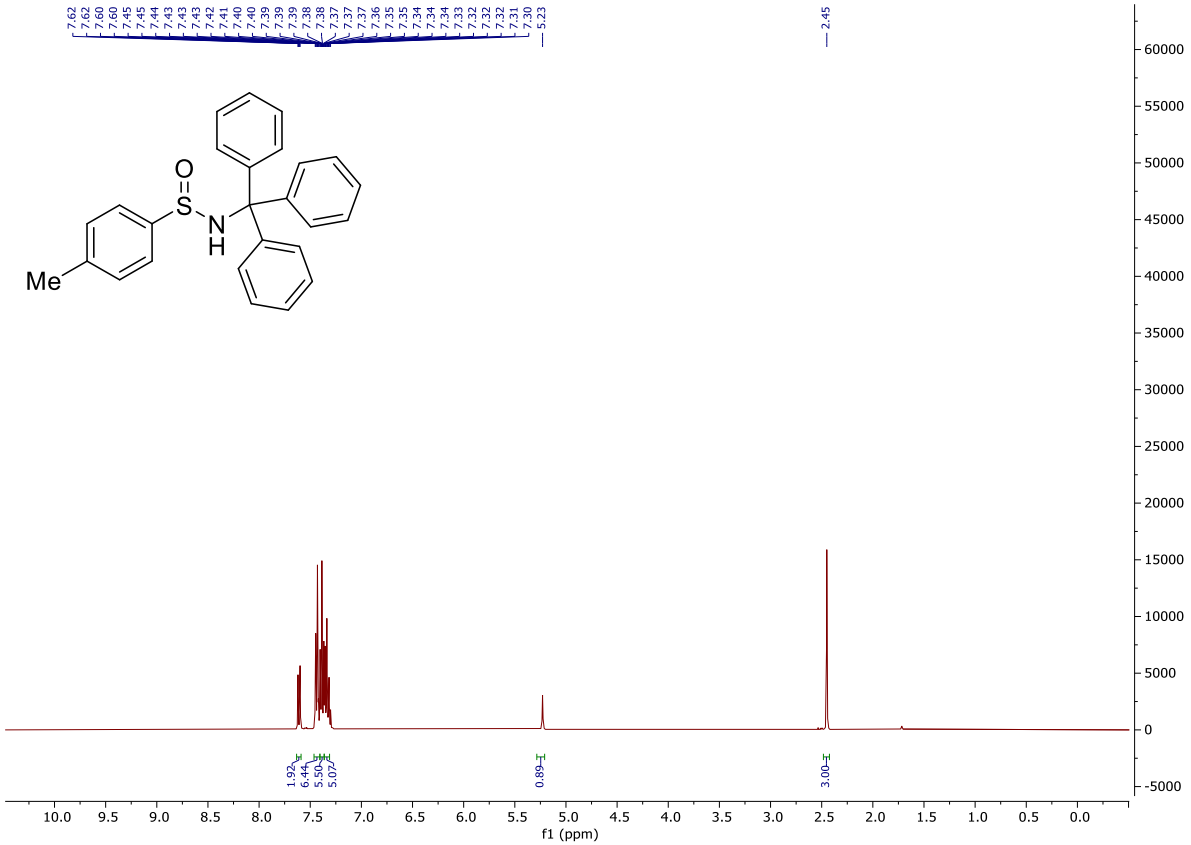
_N_-Tritylpyridine-3-sulfinamide (200)

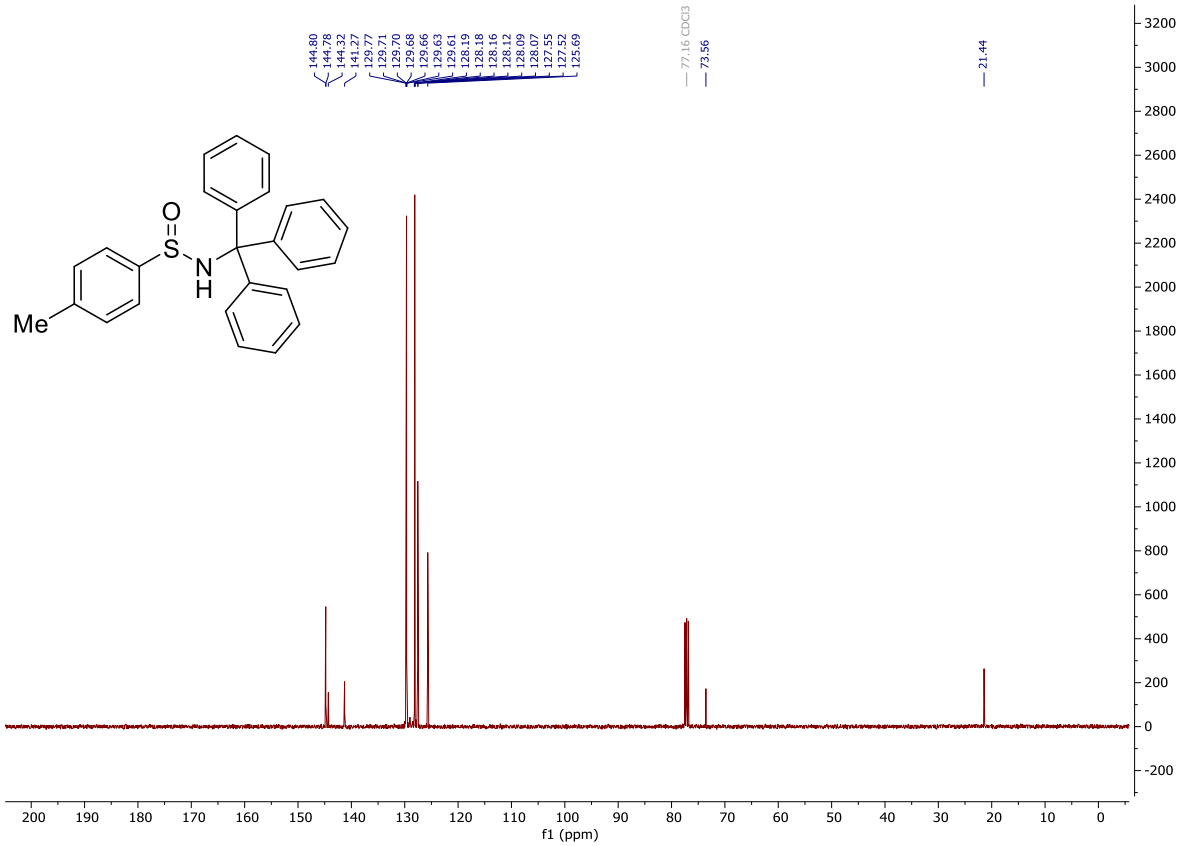


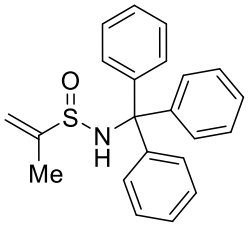




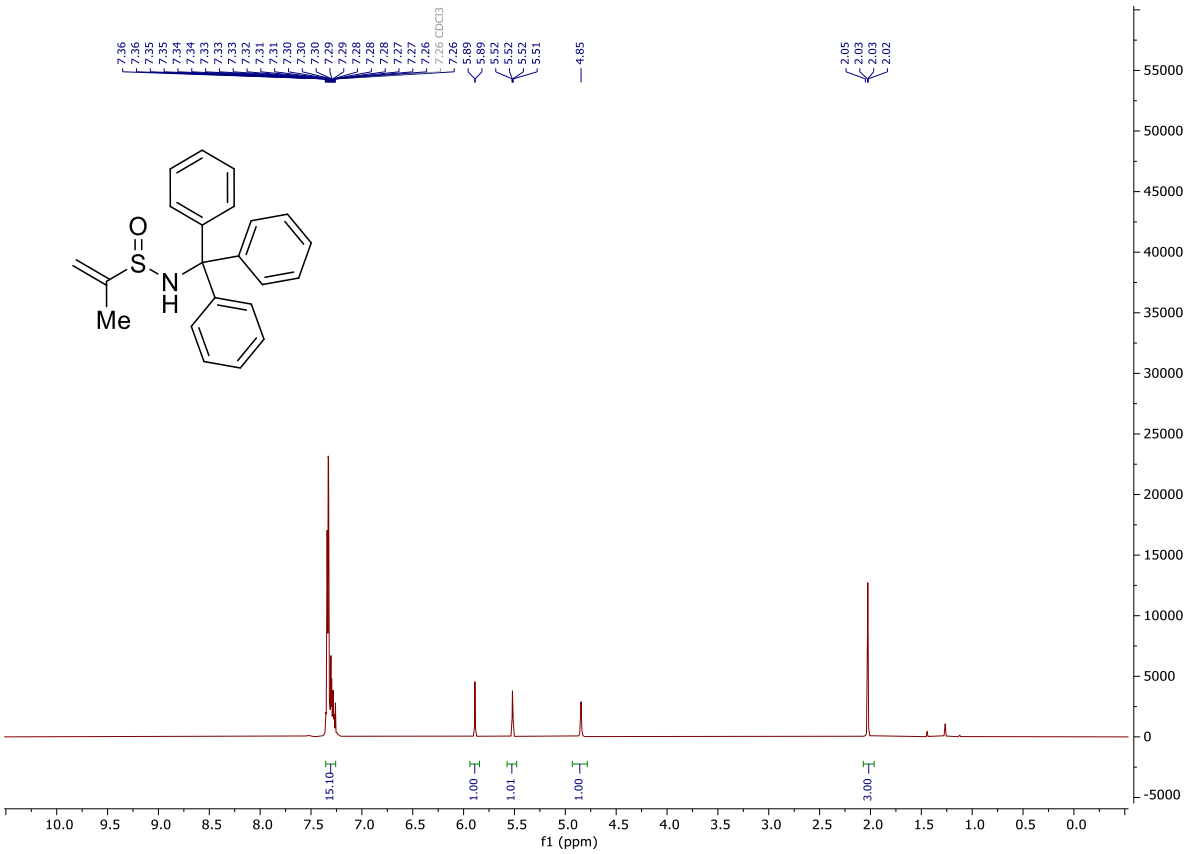
4-Methyl-*N*-tritylbenzenesulfinamide (66m)

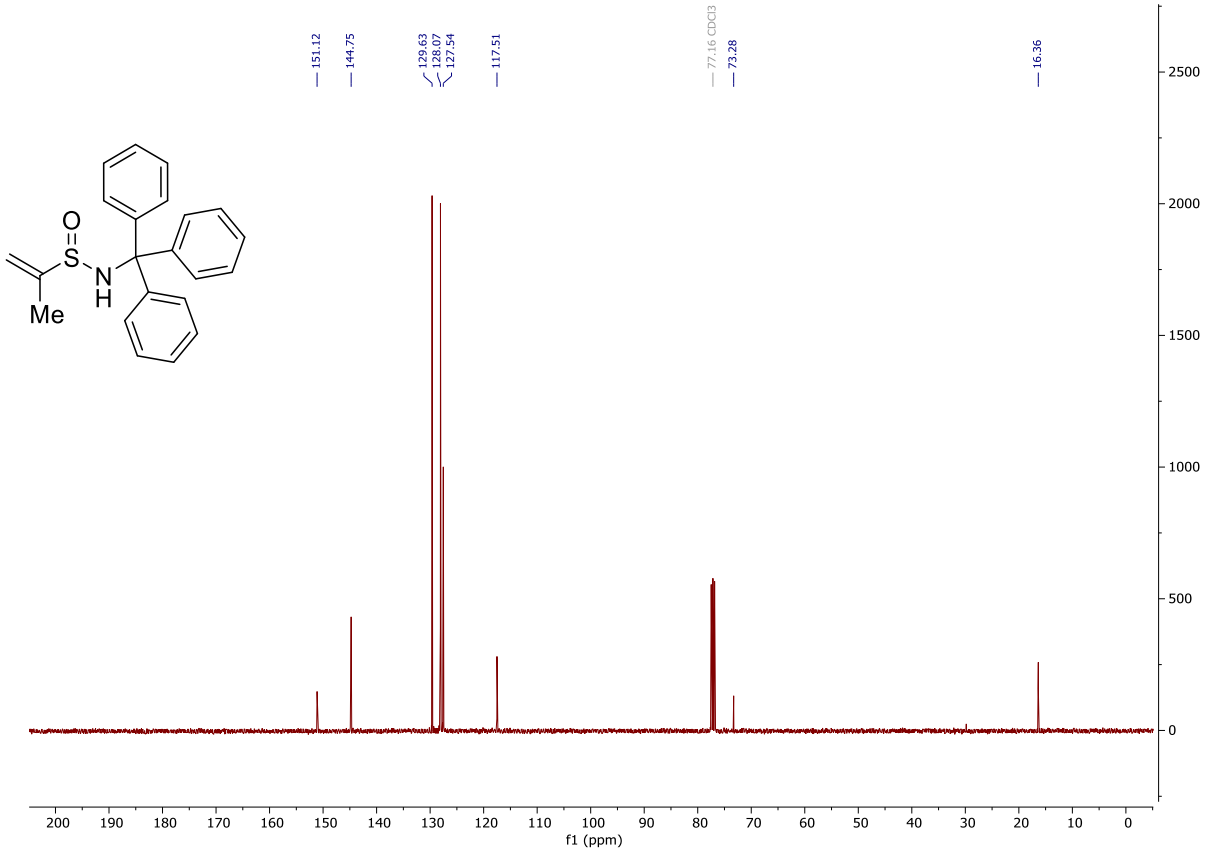

7.62 7.62 7.60 7.60 7.45 7.45 7.44 7.43 7.43 7.43 7.42 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.37 7.37 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.32 7.32 7.32 7.31 7.30 5.23
2.45
O
S
N
H
Me
1.92
6.44
5.50
5.07
0.89
3.00
f1 (ppm)

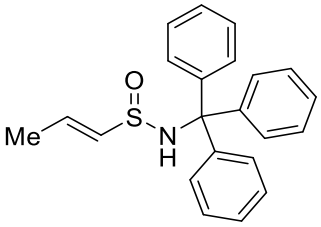

144.80 144.78 144.32 141.27 129.77 129.71 129.70 129.68 129.66 129.63 129.61 128.19 128.18 128.16 128.12 128.09 128.07 127.55 127.52 125.69
77.16 CDCl3
73.56
21.44
O
S
N
H
Me
f1 (ppm)



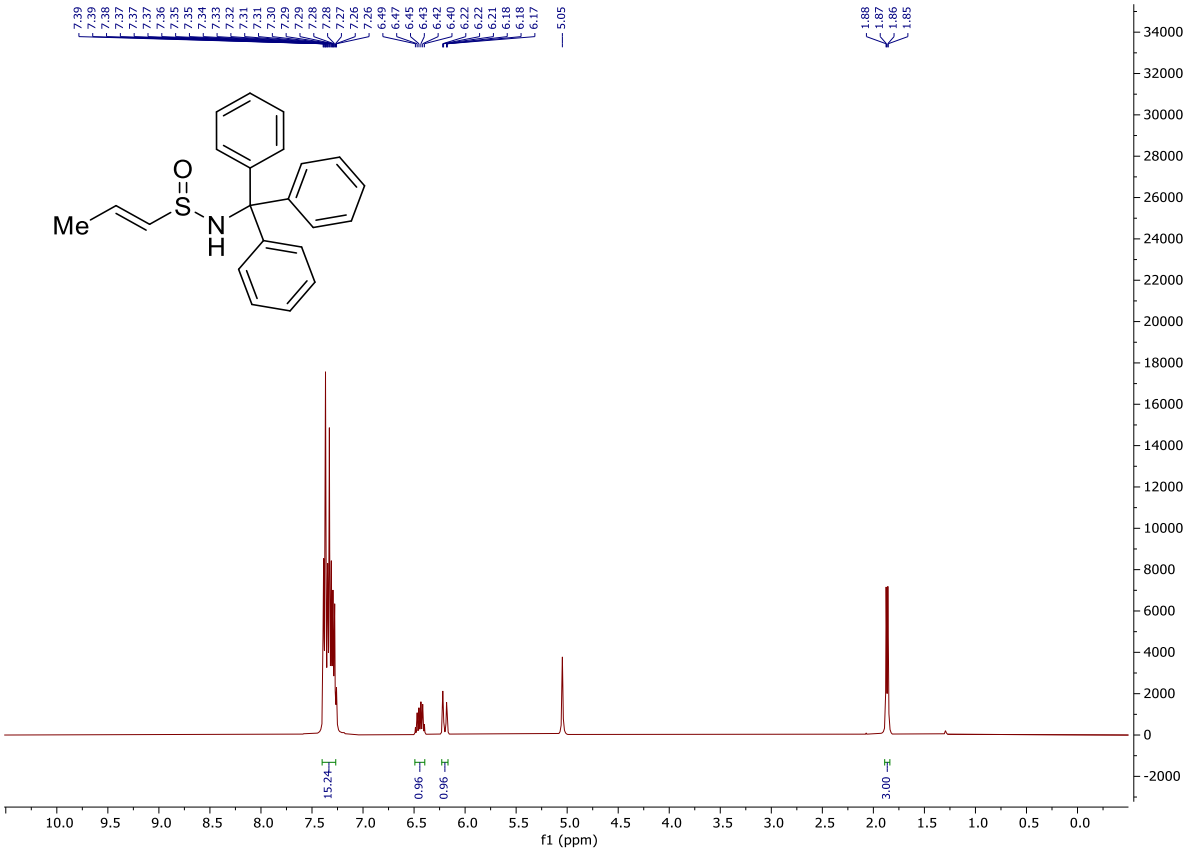
_N_-Tritylprop-1-ene-2-sulfinamide (205a)

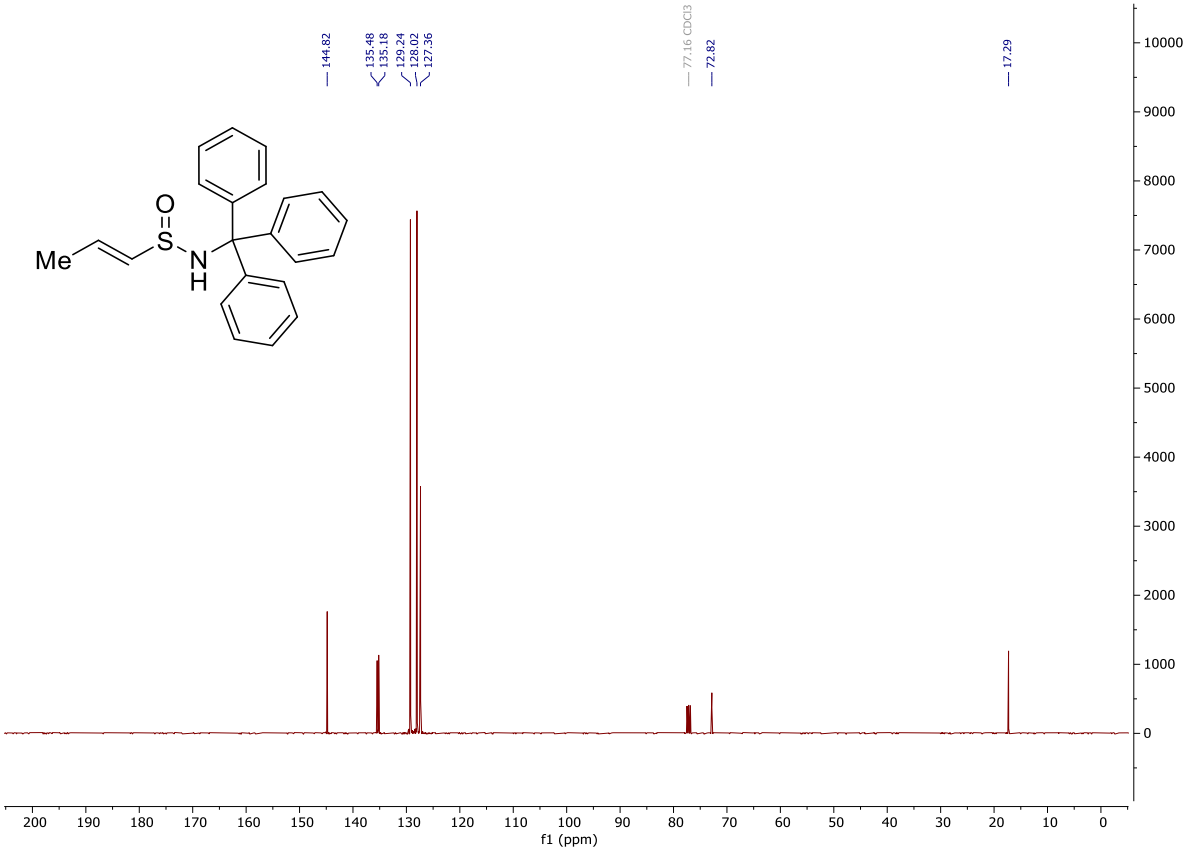


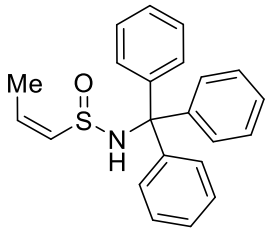




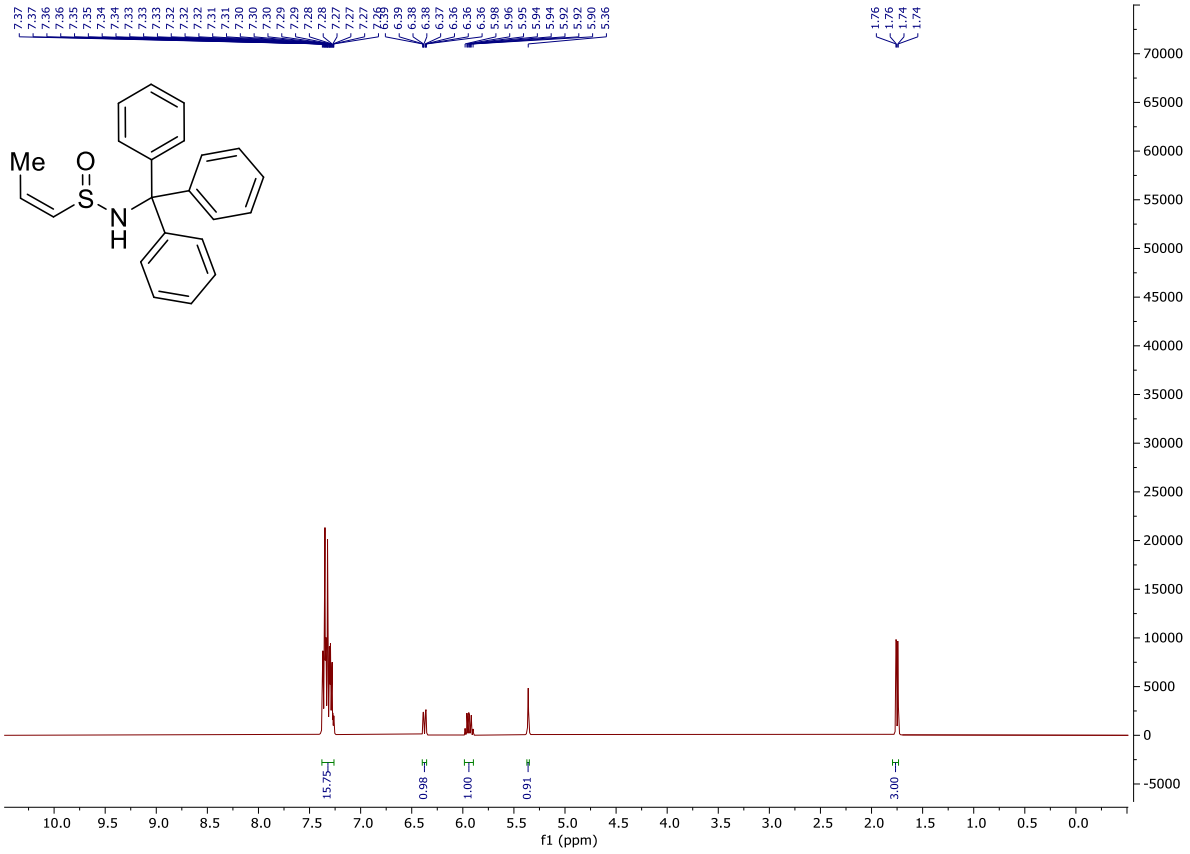
(*E*)-*N*-Tritylprop-1-ene-1-sulfinamide (*E*)-(205b)

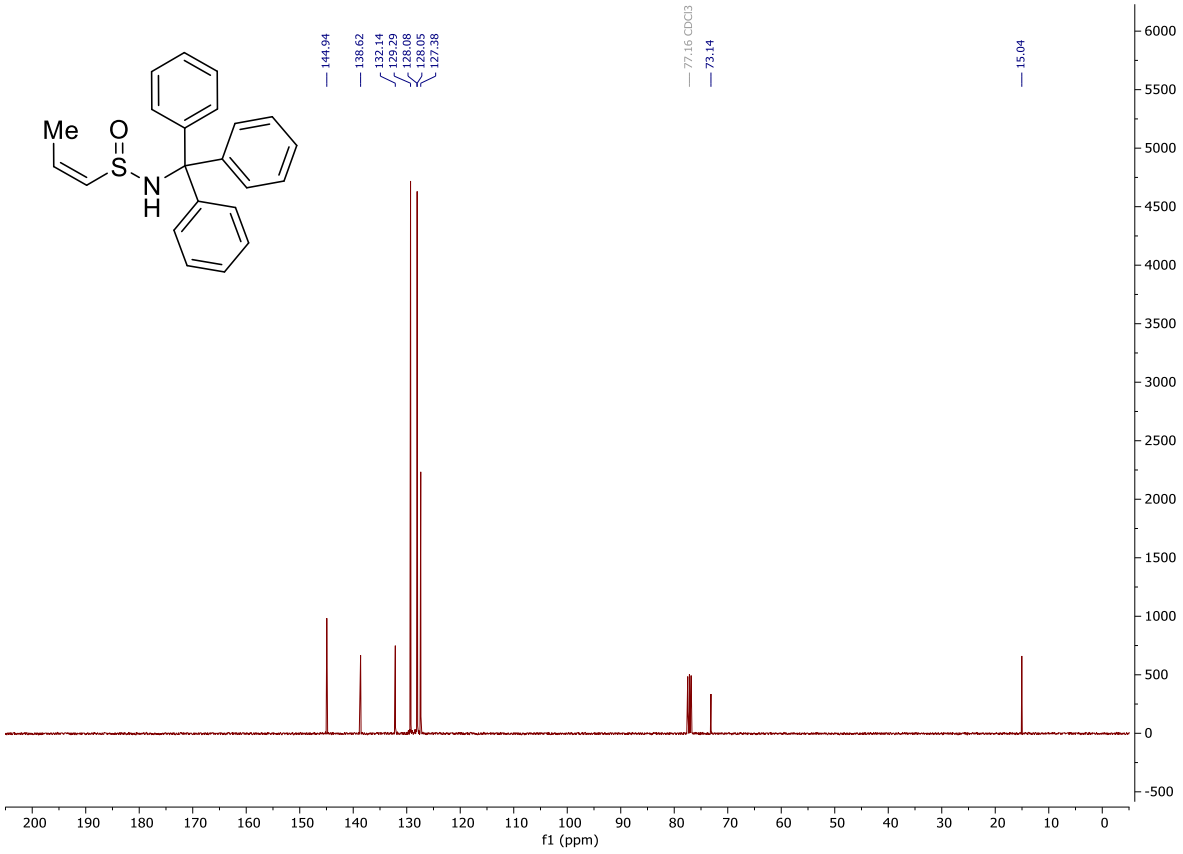

7.39
7.39
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.26
6.49
6.47
6.45
6.43
6.42
6.40
6.22
6.22
6.21
6.18
6.18
6.17
5.05
1.88
1.87
1.86
1.85
O
S
N
H
Me
15.24
0.96
0.96
3.00
f1 (ppm)

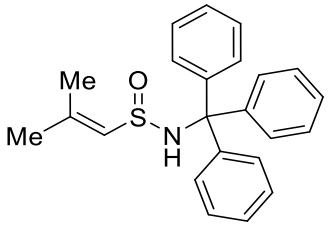

144.82
135.48
135.18
129.24
128.02
127.36
77.16 CDCl3
72.82
17.29
O
S
N
H
Me
f1 (ppm)



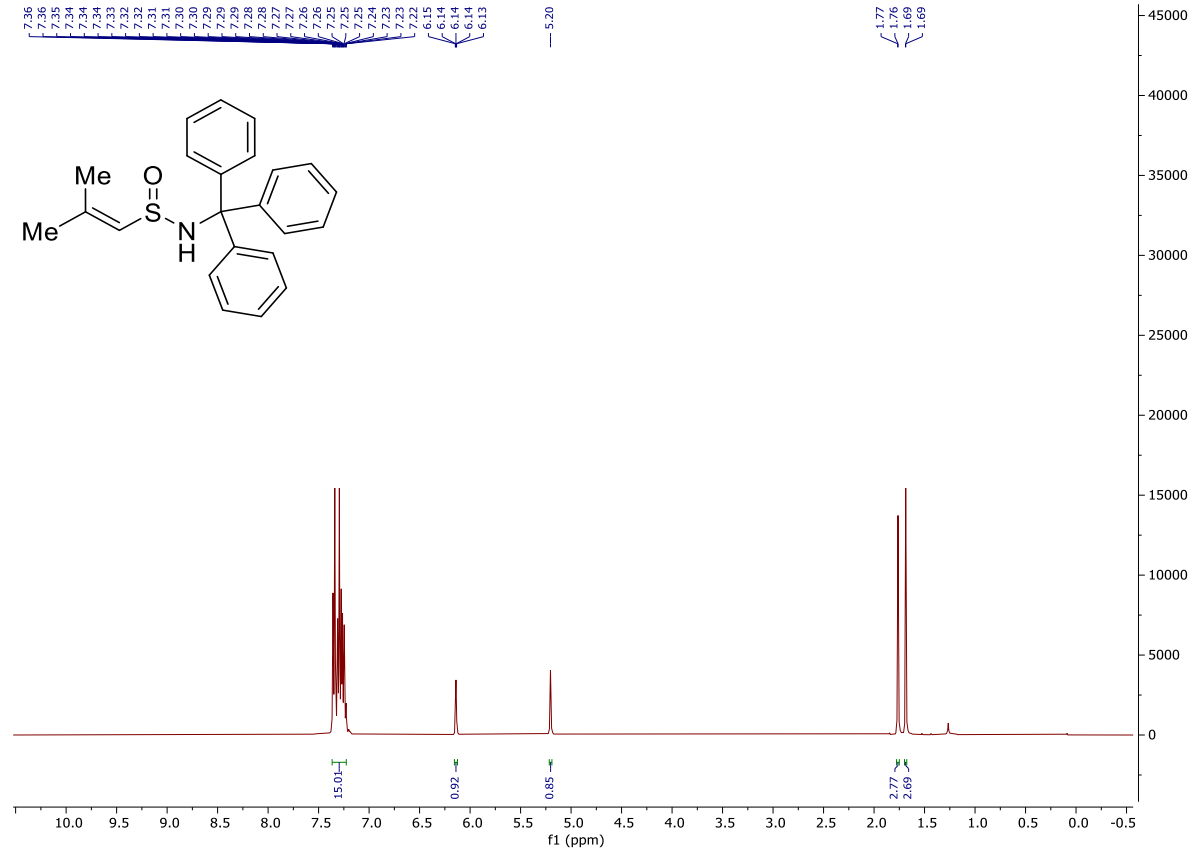
(*Z*)-*N*-Tritylprop-1-ene-1-sulfinamide (*Z*)-(205b)

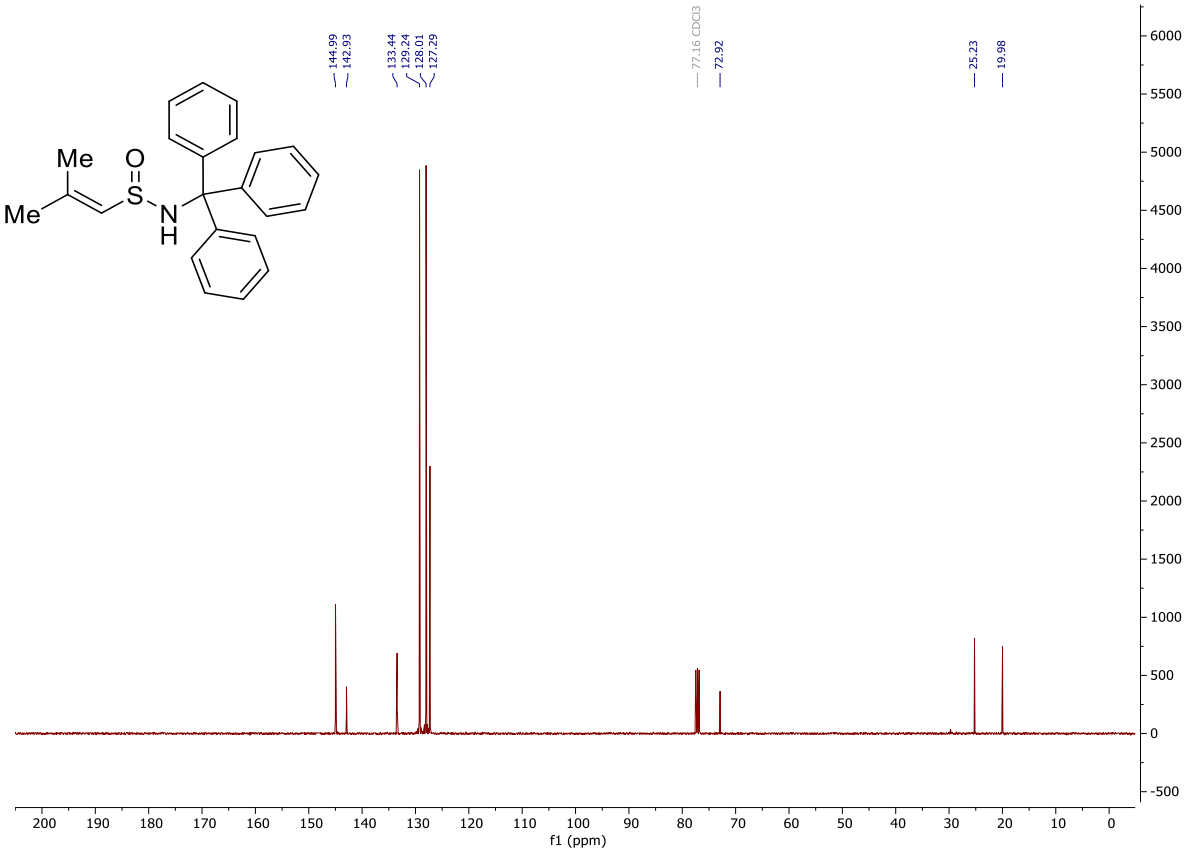


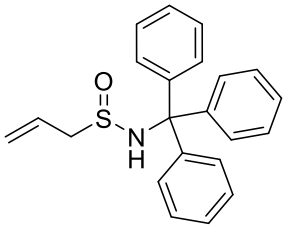




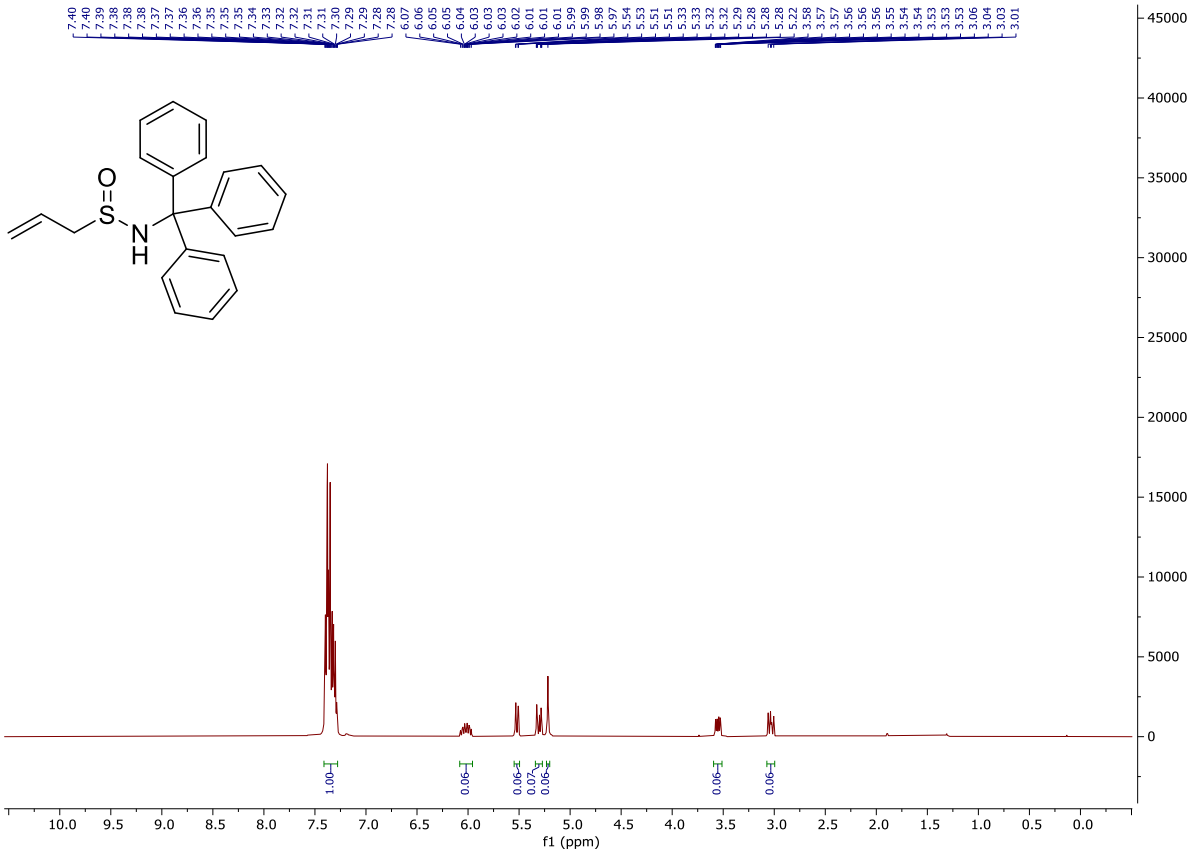
2-Methyl-*N*-tritylprop-1-ene-1-sulfinamide (205c)

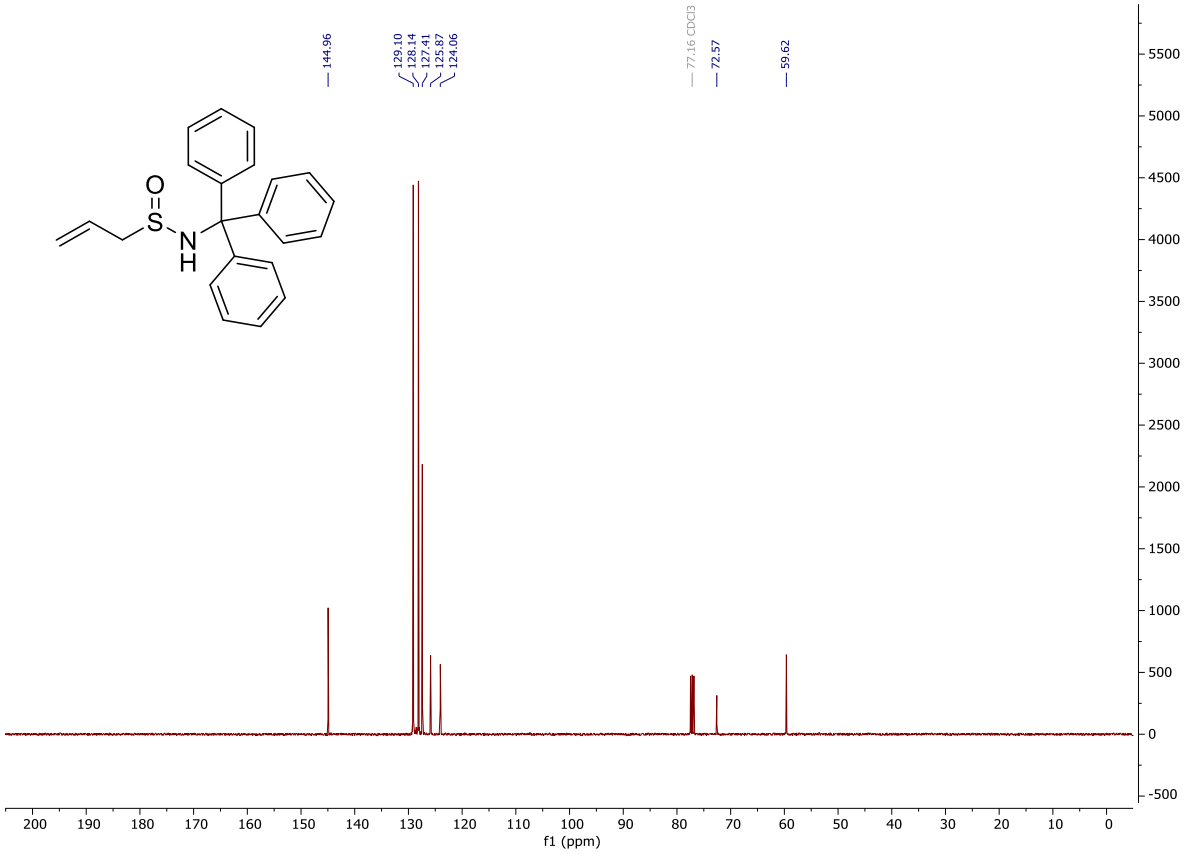

7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.22
6.15
6.14
6.14
6.14
6.13
5.20
1.77
1.76
1.69
1.69
Me
O
S
N
H
Me
15.01
0.92
0.85
2.77
2.69
f1 (ppm)


144.99
142.93
133.44
129.24
128.01
127.29
77.16 CDCl3
72.92
25.23
19.98
Me
O
S
N
H
Me
f1 (ppm)

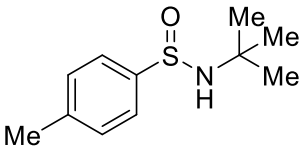


_N_-Tritylprop-2-ene-1-sulfinamide (207)

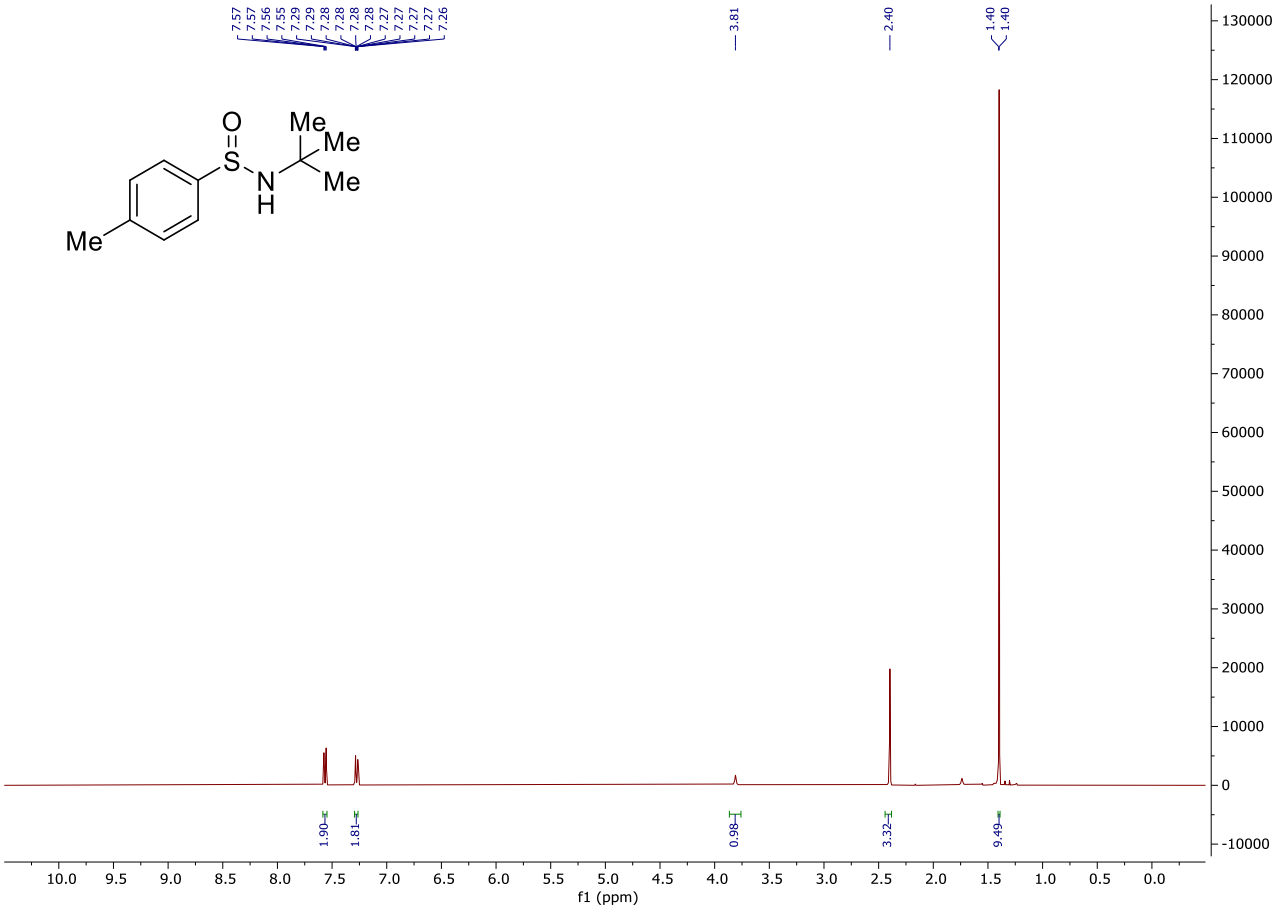


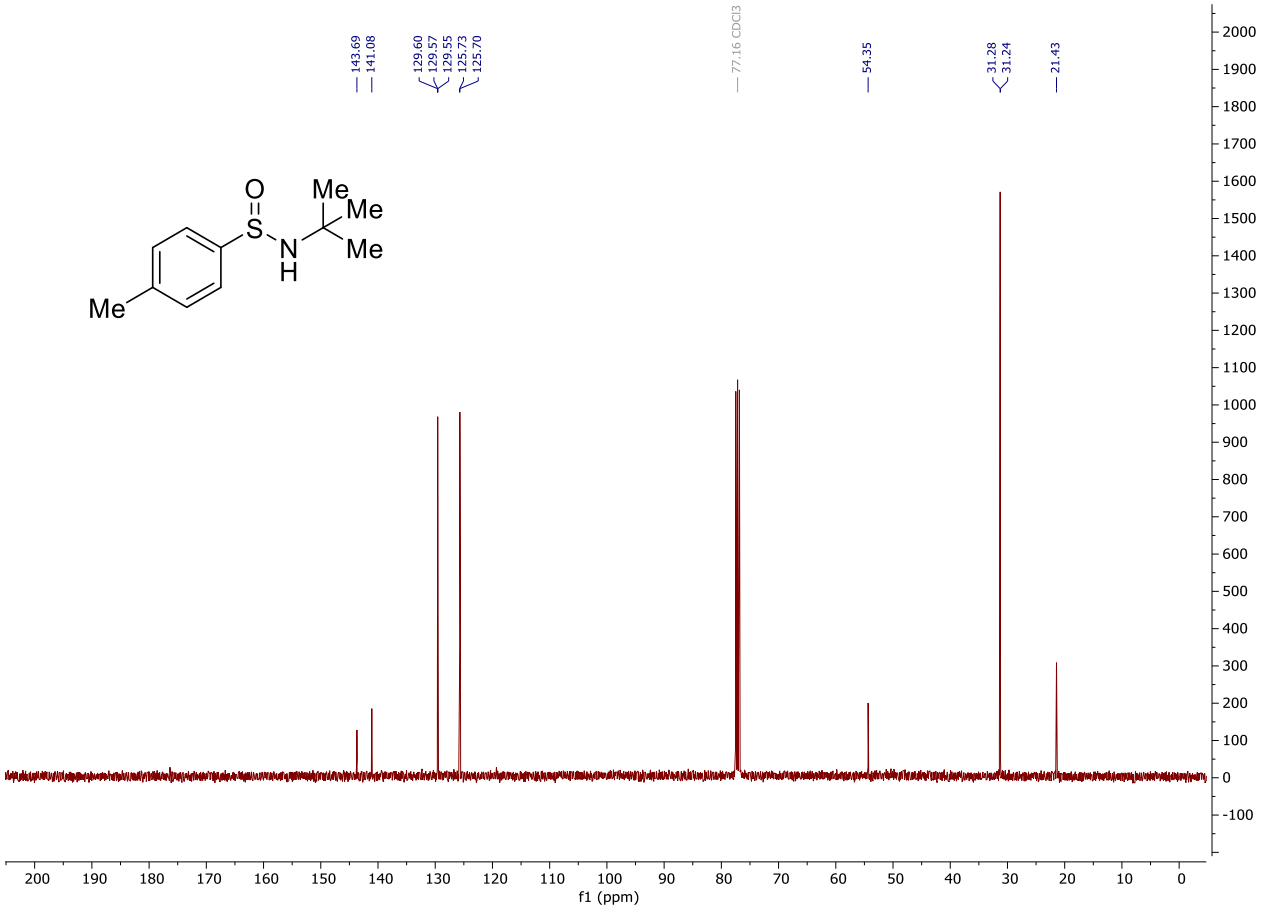

144.96
129.10
128.14
127.41
125.87
124.06
77.16 CDCl3
72.57
59.62
O
S
N
H
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

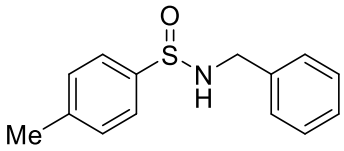
8.3.3 *N*-substituted Sulfinamides



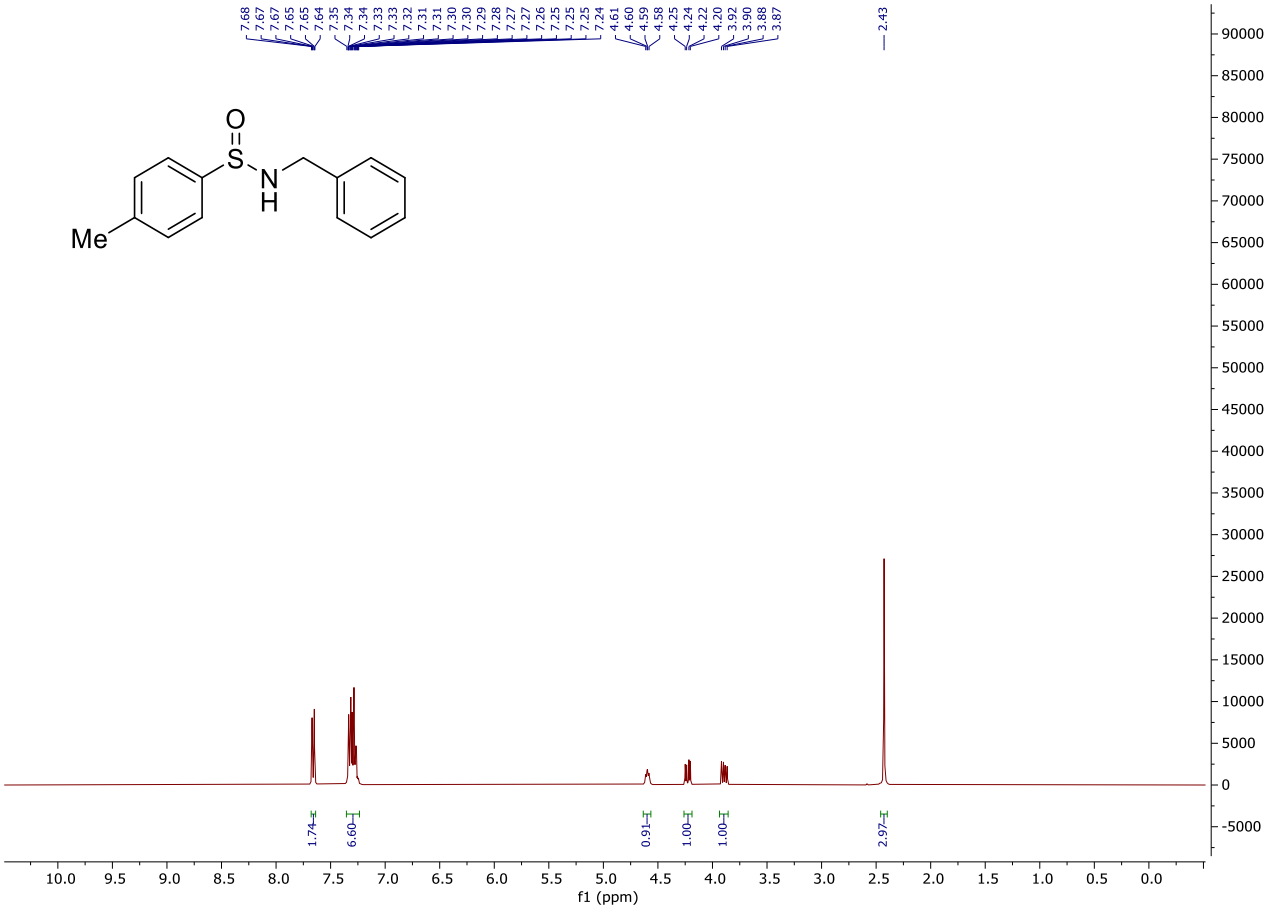
***N*-(*tert*-Butyl)-4-methylbenzenesulfinamide (66l)**

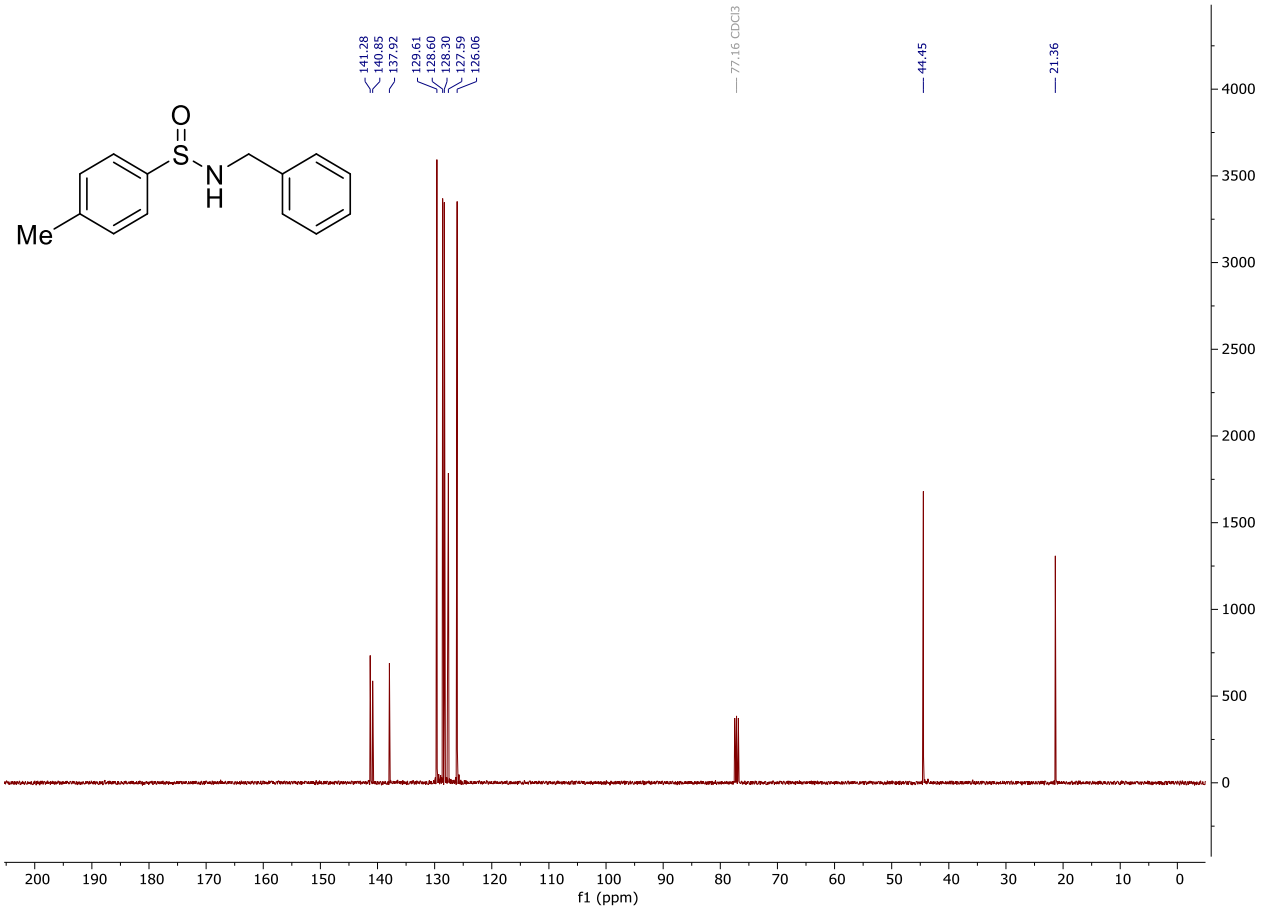


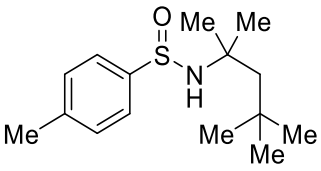




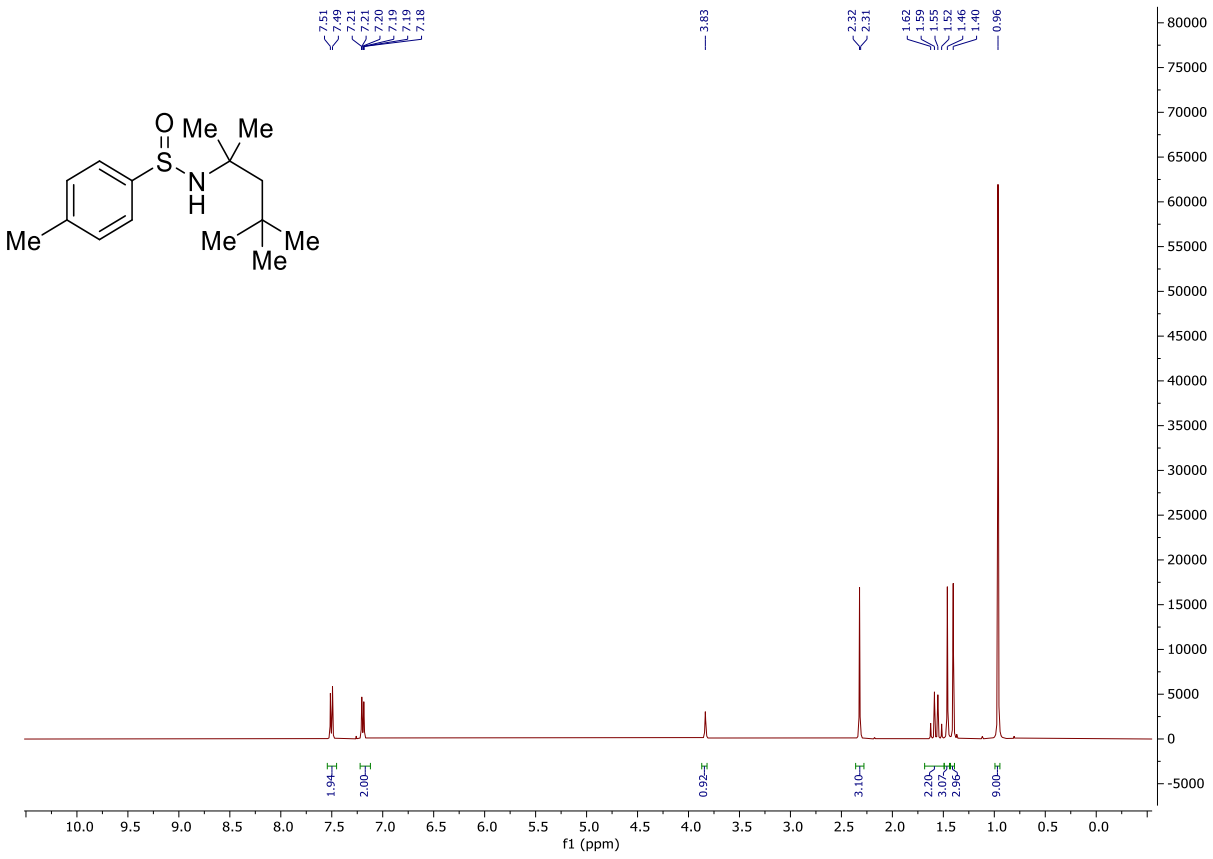
***N*-benzyl-4-methylbenzenesulfinamide (66m)**

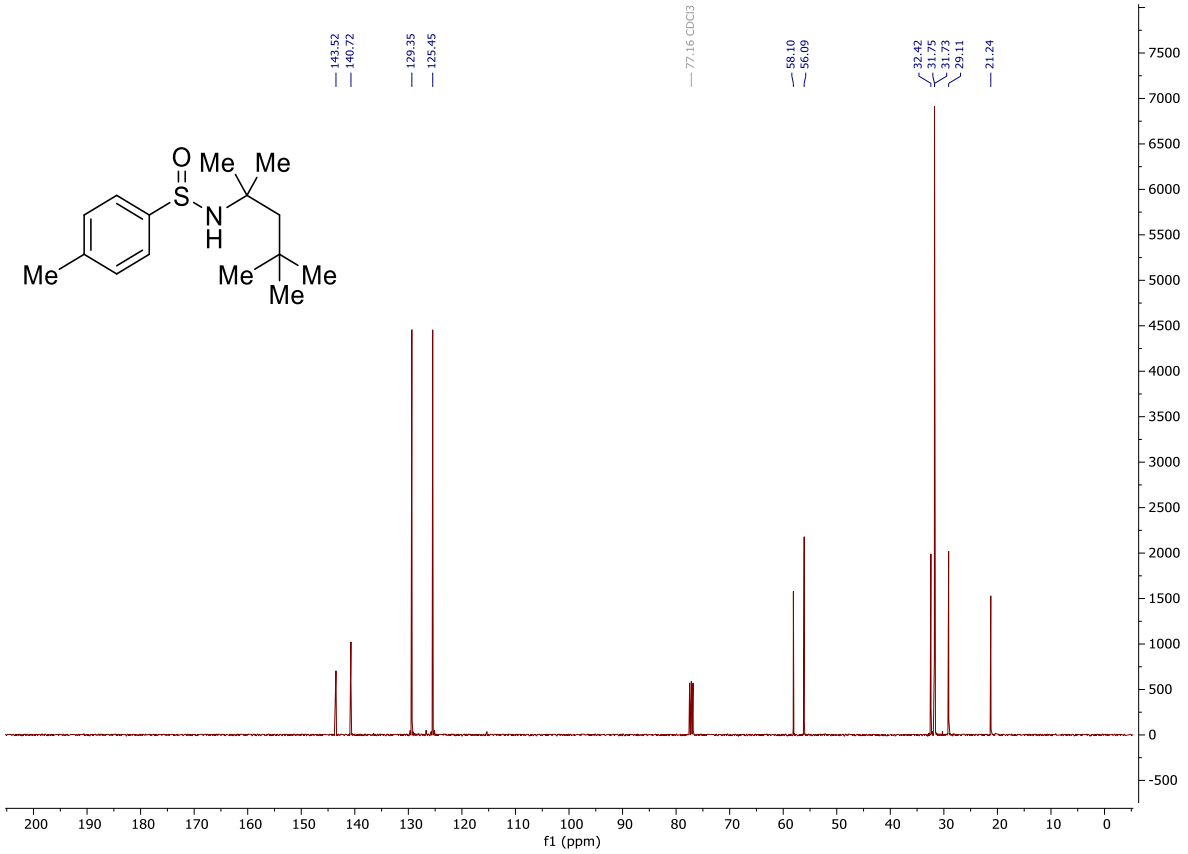

7.68
7.67
7.67
7.65
7.65
7.64
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.26
7.25
7.25
7.25
7.24
4.61
4.60
4.59
4.58
4.25
4.24
4.22
4.20
3.92
3.90
3.88
3.87
2.43
O
S
N
H
Me
1.74
6.60
0.91
1.00
1.00
2.97
f1 (ppm)

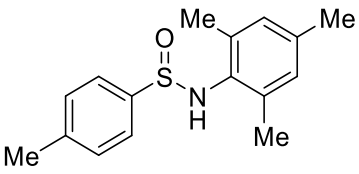

141.28
140.85
137.92
129.61
128.60
128.30
127.59
126.06
77.16 CDCl3
44.45
21.36
O
S
N
H
Me
f1 (ppm)



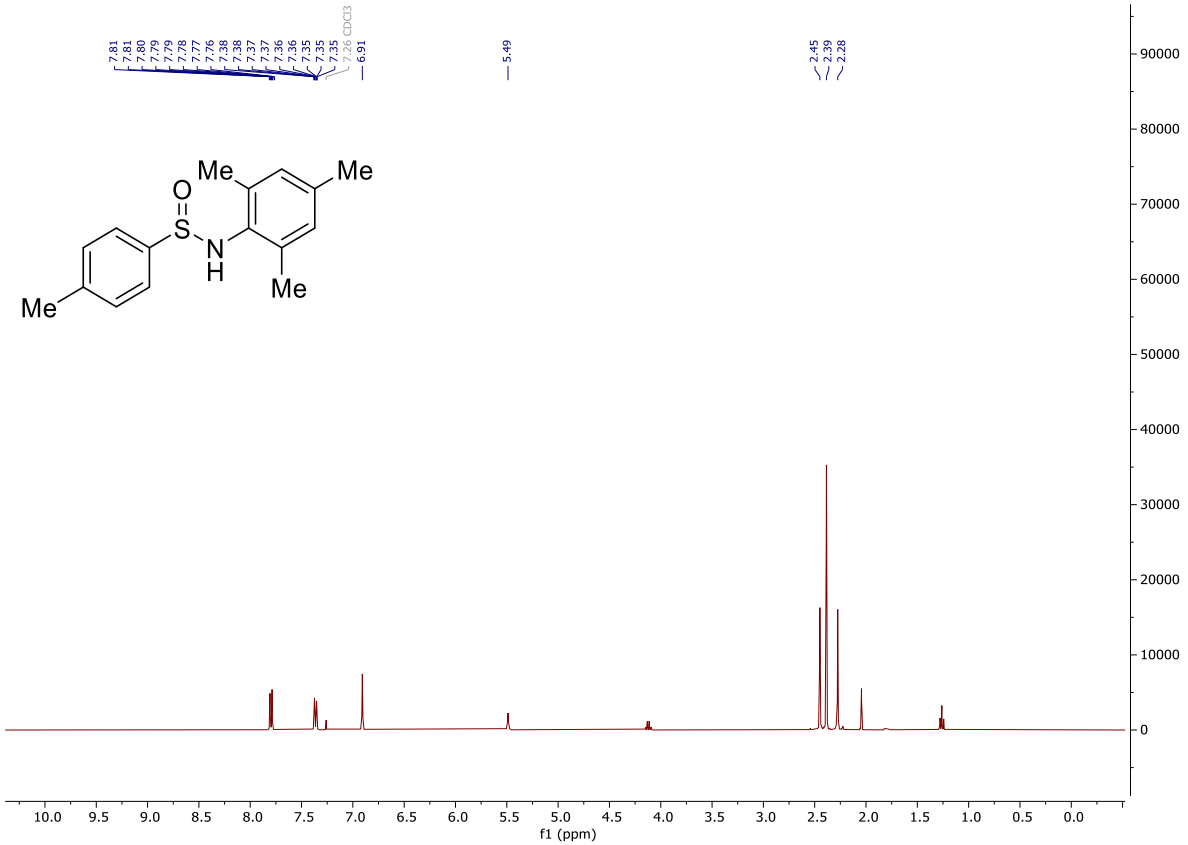
4-Methyl-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfinamide (66n)

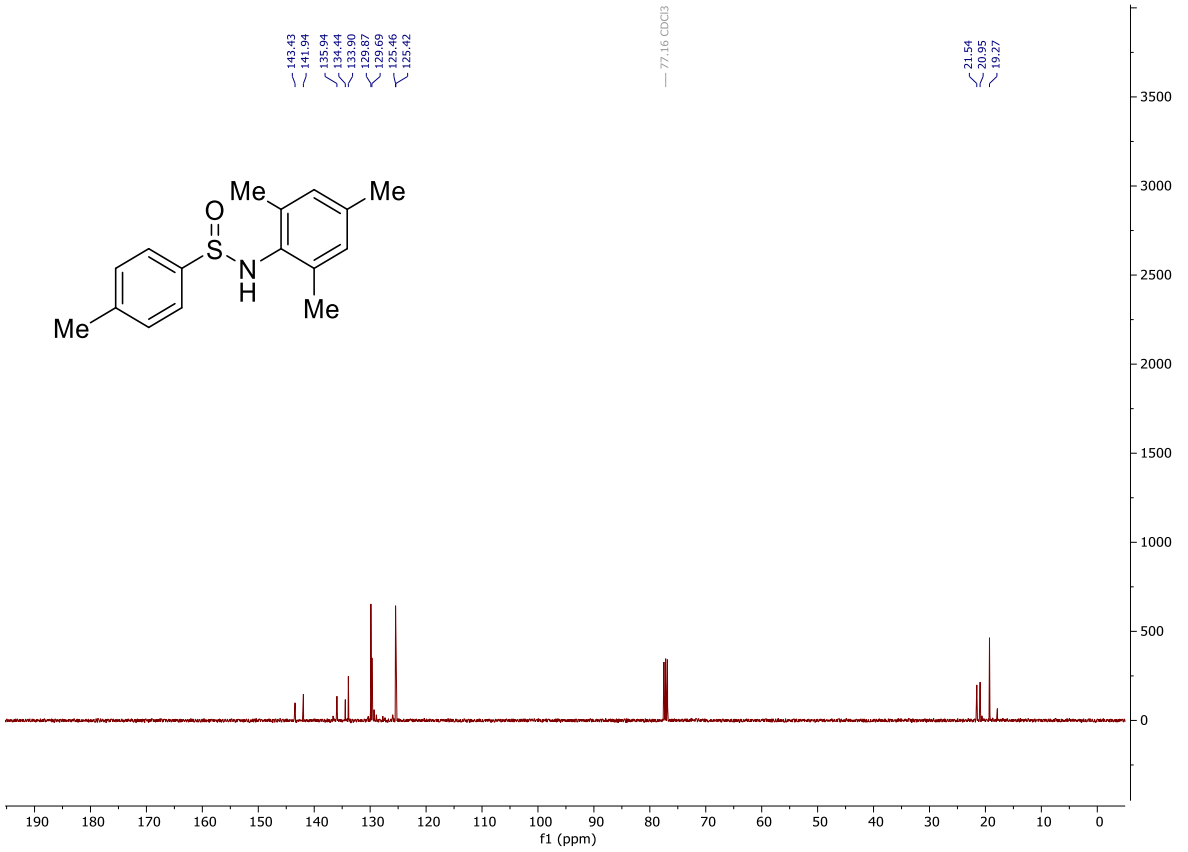


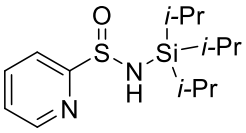




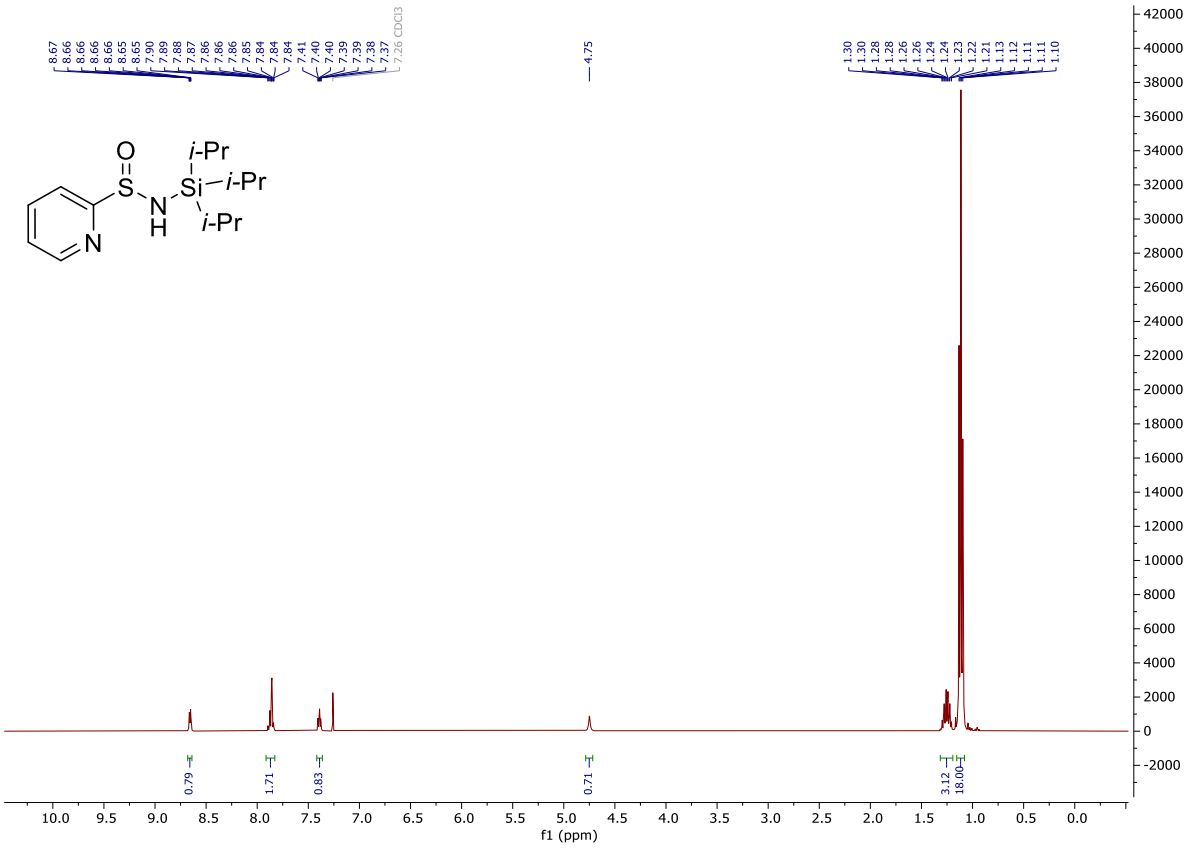
***N*-mesityl-4-methylbenzenesulfinamide (66p)**

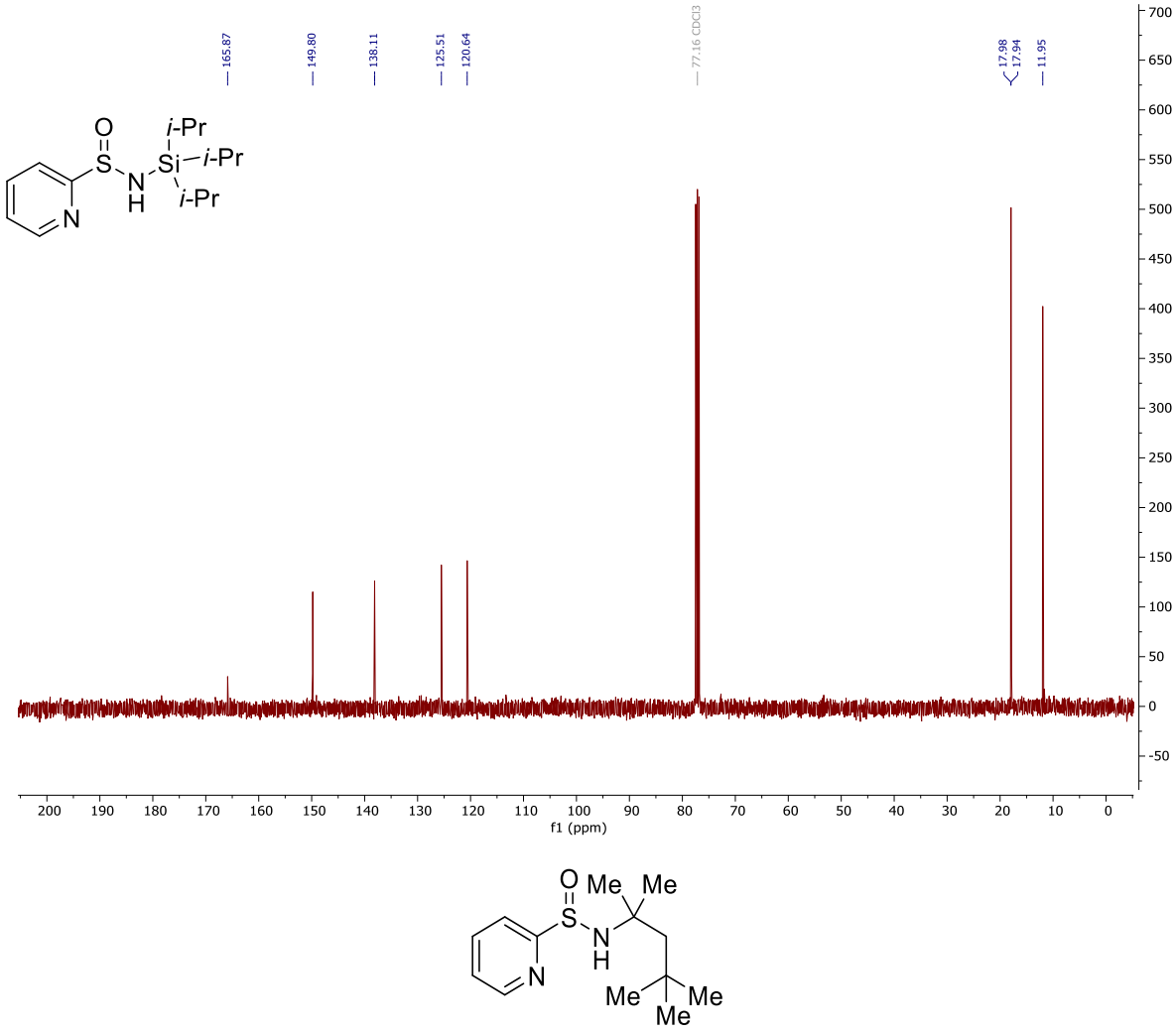

7.81
7.81
7.80
7.79
7.79
7.78
7.77
7.76
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.35
7.26 CDCl3
6.91
5.49
2.45
2.39
2.28
Me
Me
O
S
N
H
Me
Me
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


143.43
141.94
135.94
134.44
133.90
129.87
129.69
125.46
125.42
77.16 CDCl3
21.54
20.95
19.27
Me
Me
O
S
N
H
Me
Me
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

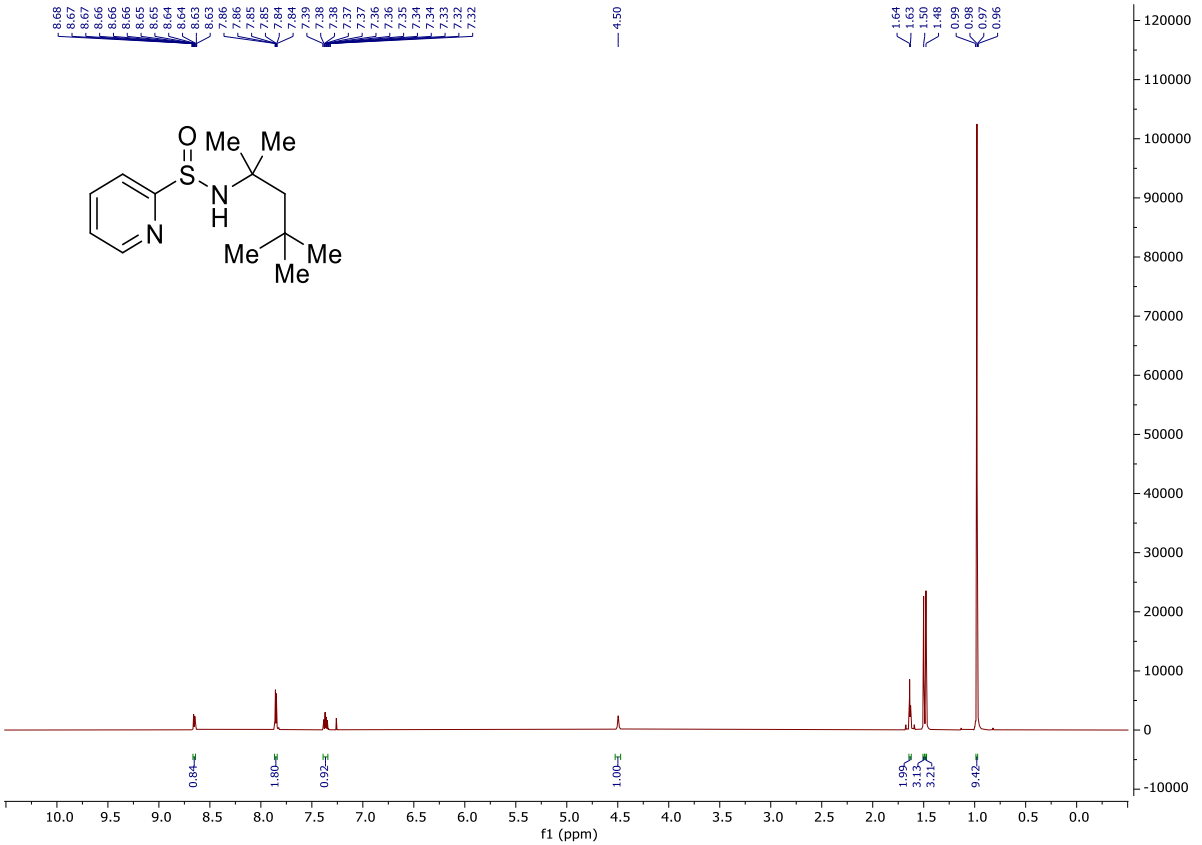


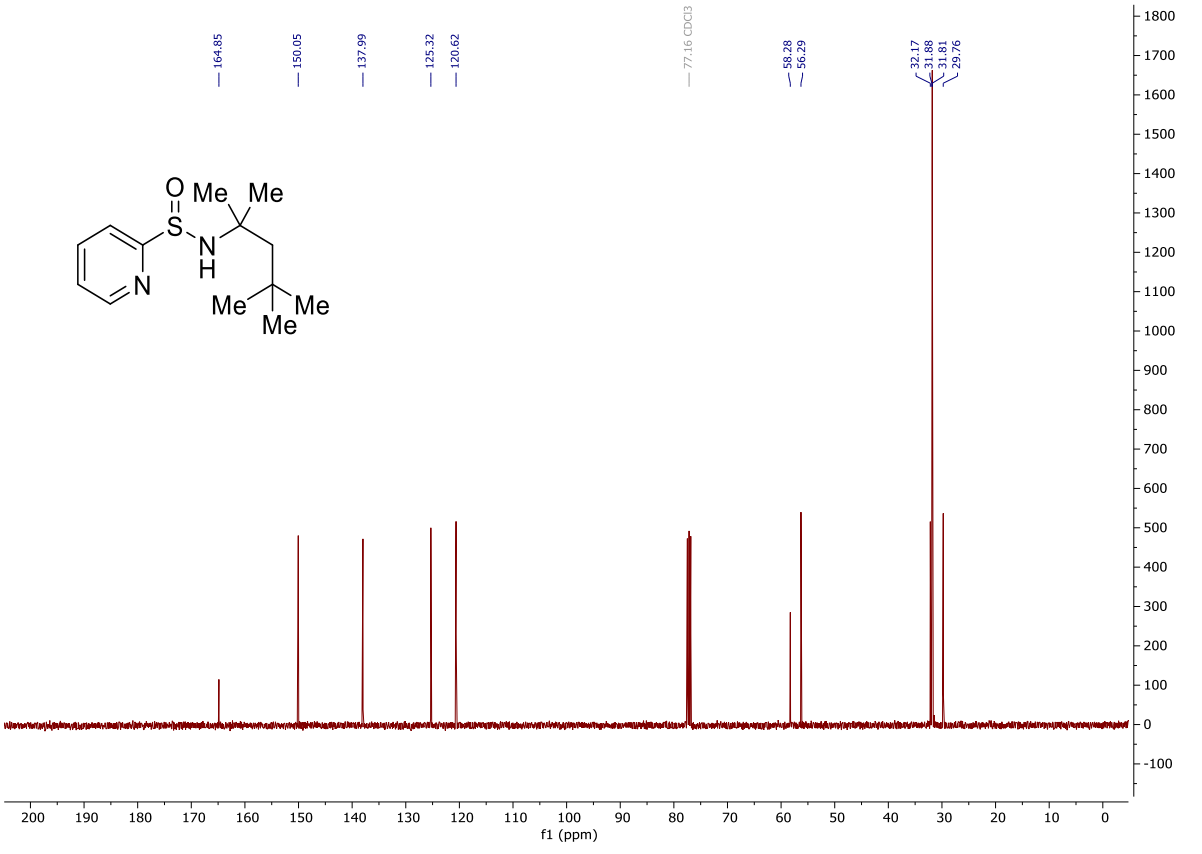
_N_-(Triisopropylsilyl)pyridine-2-sulfinamide (198a)

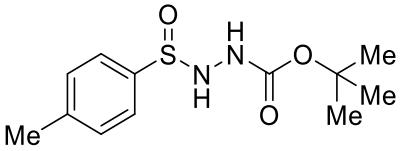




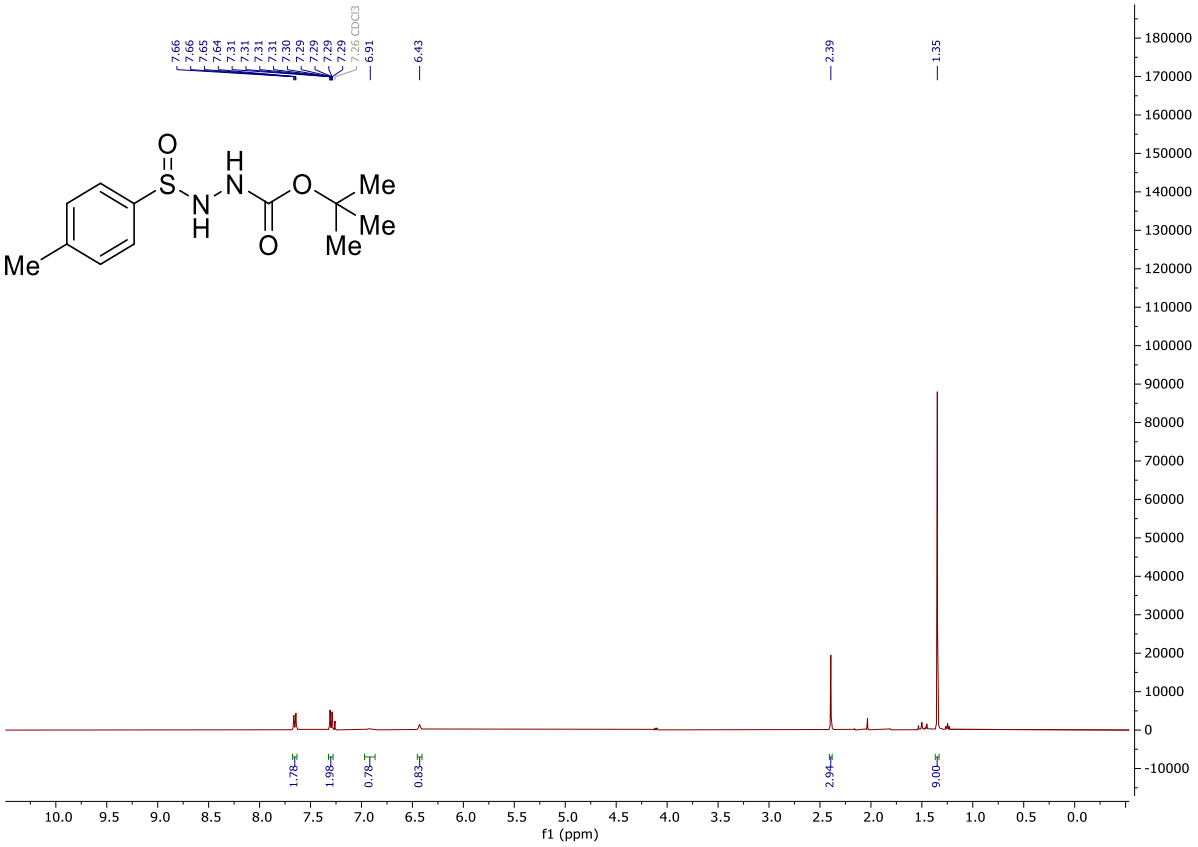
_N_-(2,4,4-trimethylpentan-2-yl)Pyridine-2-sulfinamide (198c)

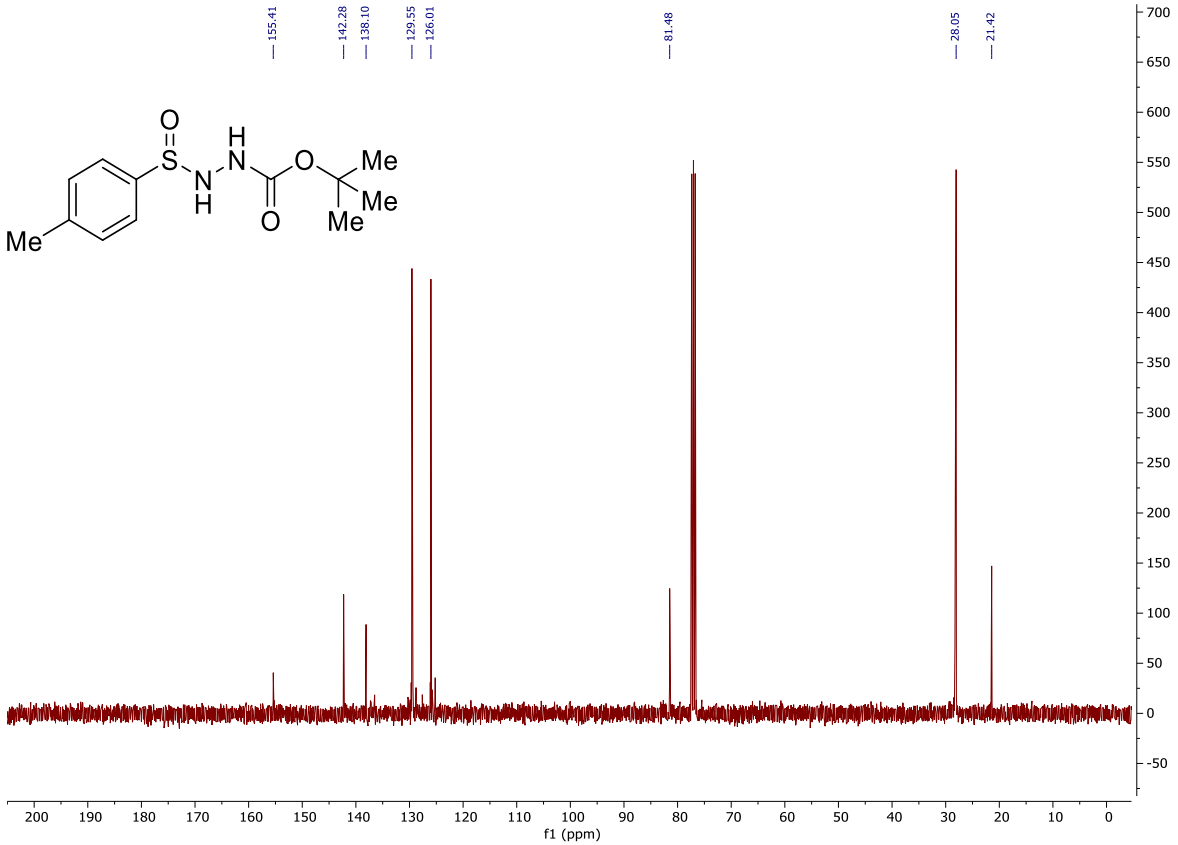

8.68
8.67
8.67
8.66
8.66
8.66
8.65
8.65
8.64
8.64
8.63
8.63
7.86
7.86
7.85
7.85
7.84
7.84
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.33
7.32
7.32
4.50
1.64
1.63
1.50
1.48
0.99
0.98
0.97
0.96
O
Me
Me
S
N
H
N
Me
Me
Me
0.84
1.80
0.92
1.00
1.99
3.13
3.21
9.42
f1 (ppm)

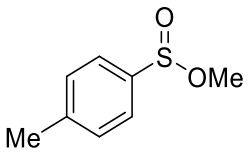

164.85
150.05
137.99
125.32
120.62
77.16 CDCl3
58.28
56.29
32.17
31.88
31.81
29.76
O
Me
Me
S
N
H
N
Me
Me
Me
f1 (ppm)



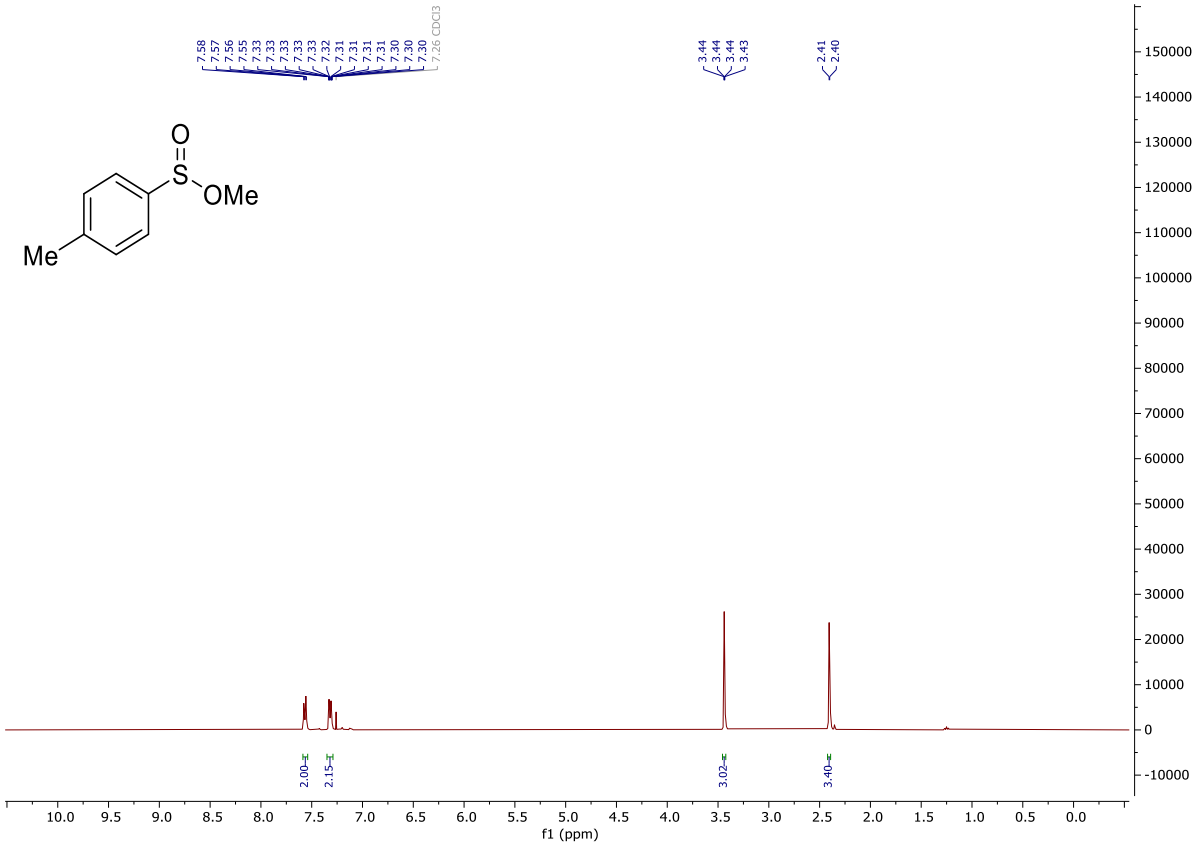
tert-Butyl 2-(_p_-tolylsulfinyl)hydrazine-1-carboxylate (201a)

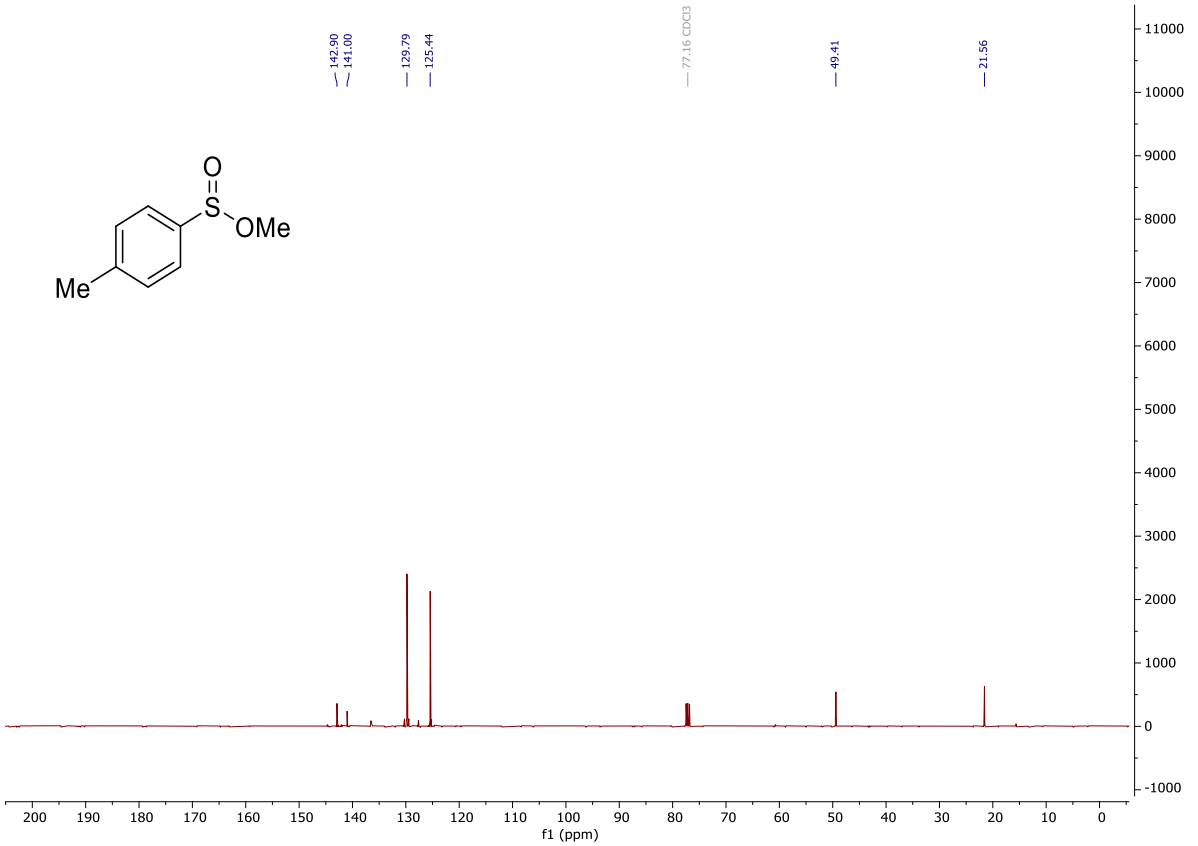




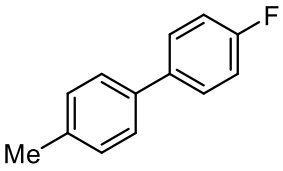


Methyl 4-methylbenzenesulfinate (201c)

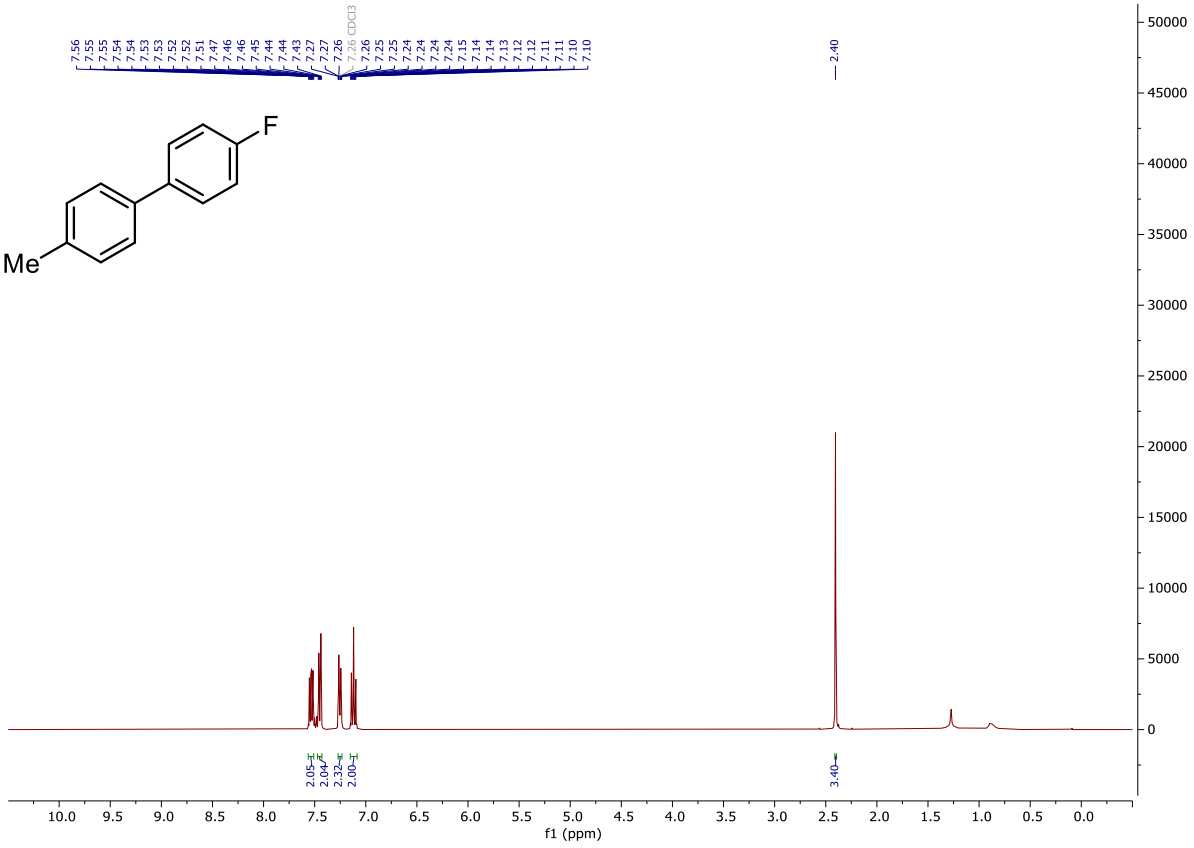

7.58
7.57
7.56
7.55
7.33
7.33
7.33
7.33
7.32
7.31
7.31
7.31
7.31
7.30
7.30
7.30
7.26 CDCl3
3.44
3.44
3.44
3.43
2.41
2.40
O
S
OMe
Me
2.00
2.15
3.02
3.40
f1 (ppm)

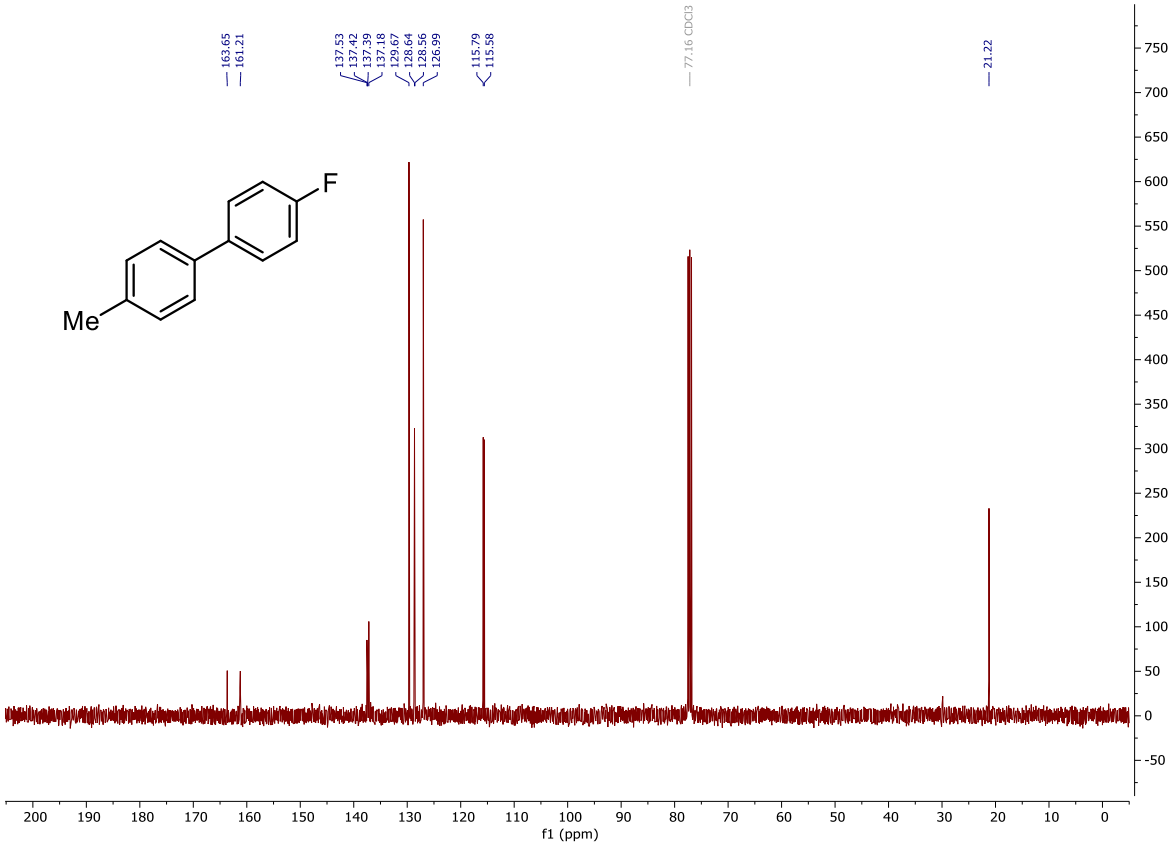

142.90
141.00
129.79
125.44
77.16 CDCl3
49.41
21.56
O
S
OMe
Me
f1 (ppm)

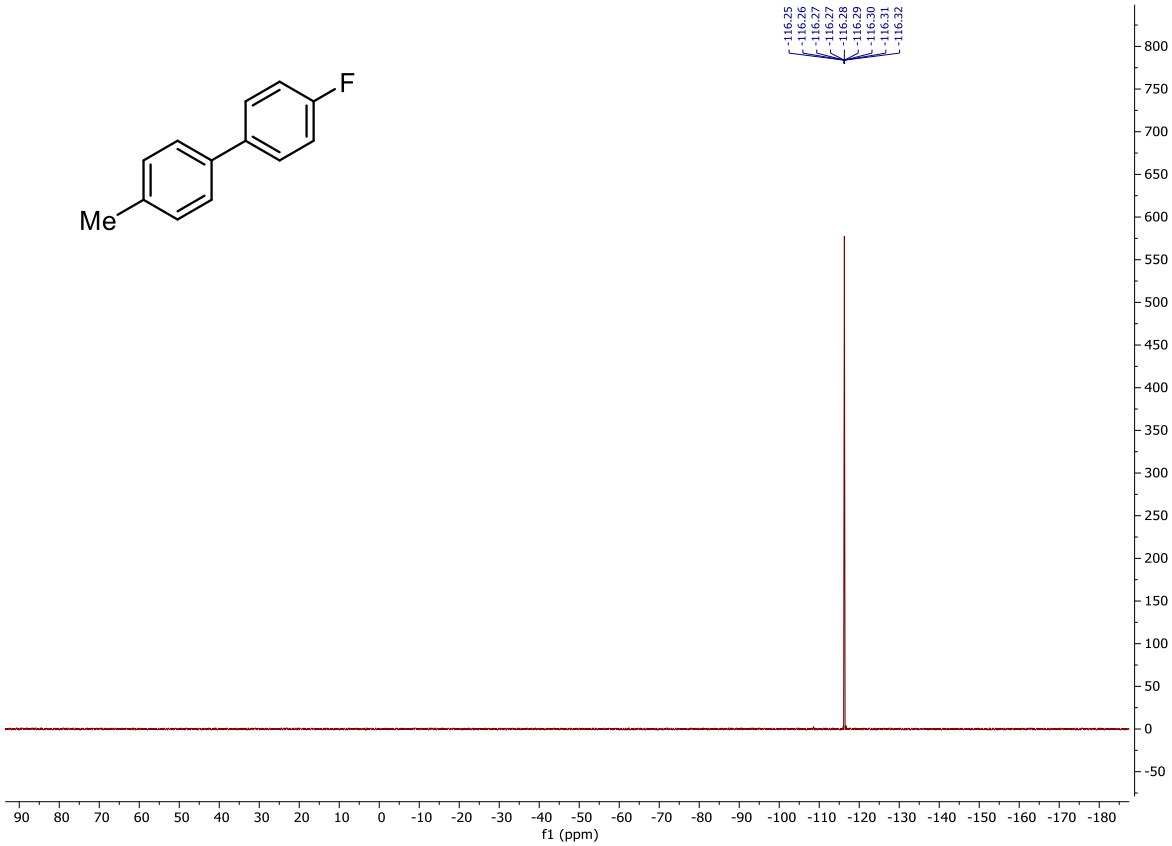
8.3.4 Biaryl products

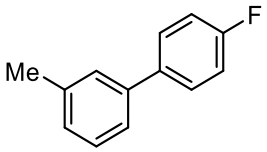


4-Fluoro-4'-methyl-1,1'-biphenyl (182a)

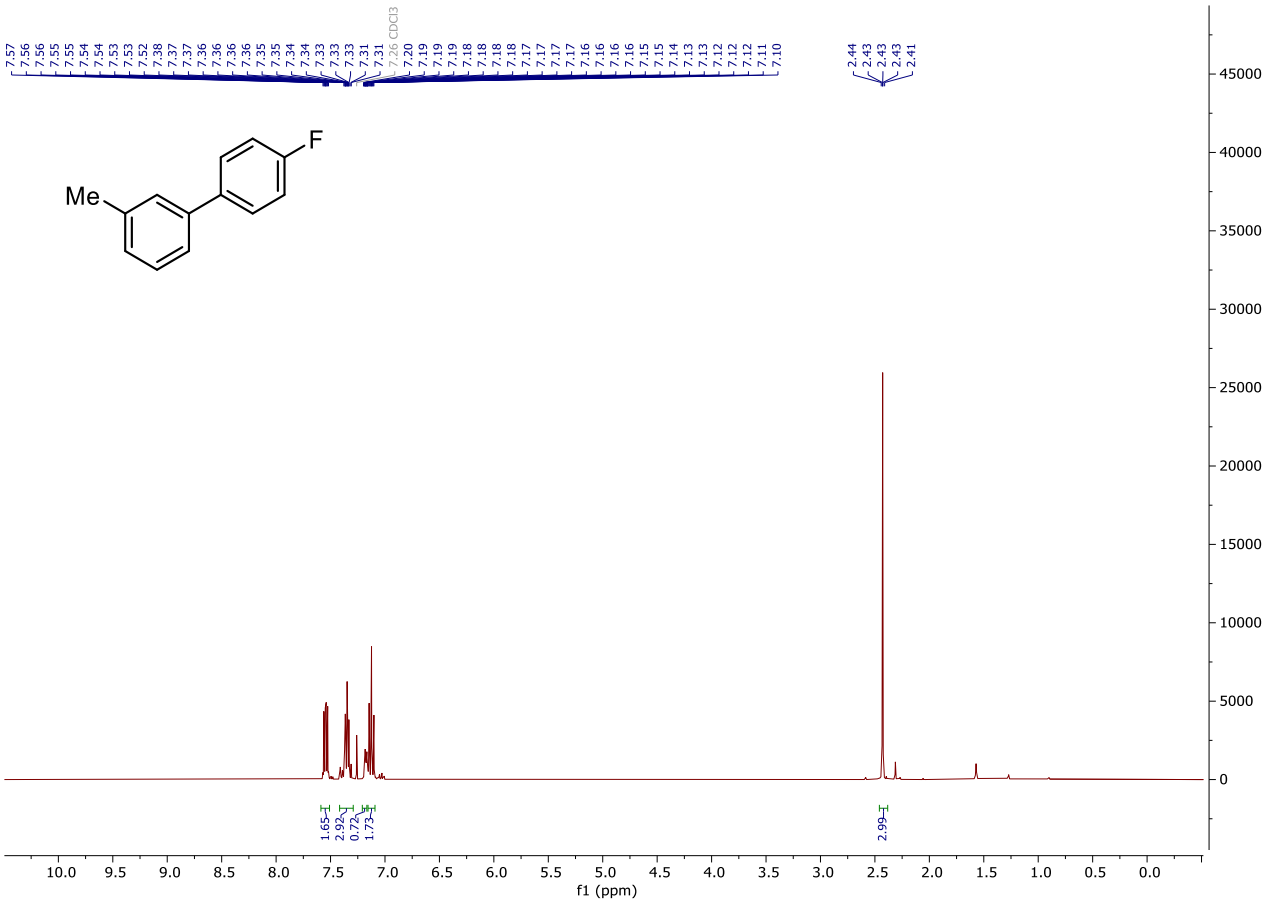


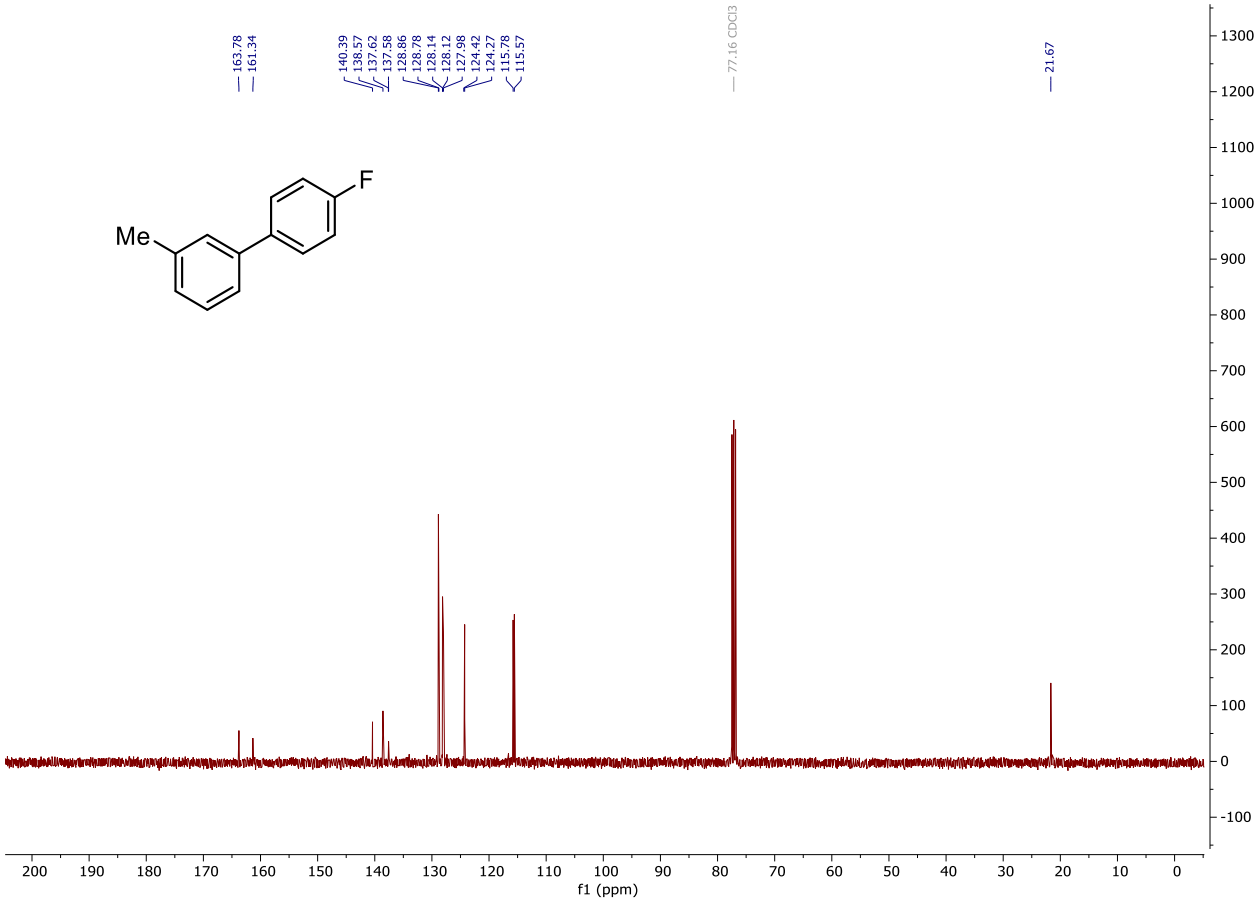

163.65
161.21
137.53
137.42
137.39
137.18
129.67
128.64
128.56
126.99
115.79
115.58
77.16 CDCl3
21.22
F
Me
f1 (ppm)

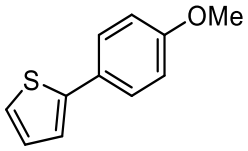

-116.25
-116.26
-116.27
-116.27
-116.28
-116.29
-116.30
-116.31
-116.32
F
Me
f1 (ppm)



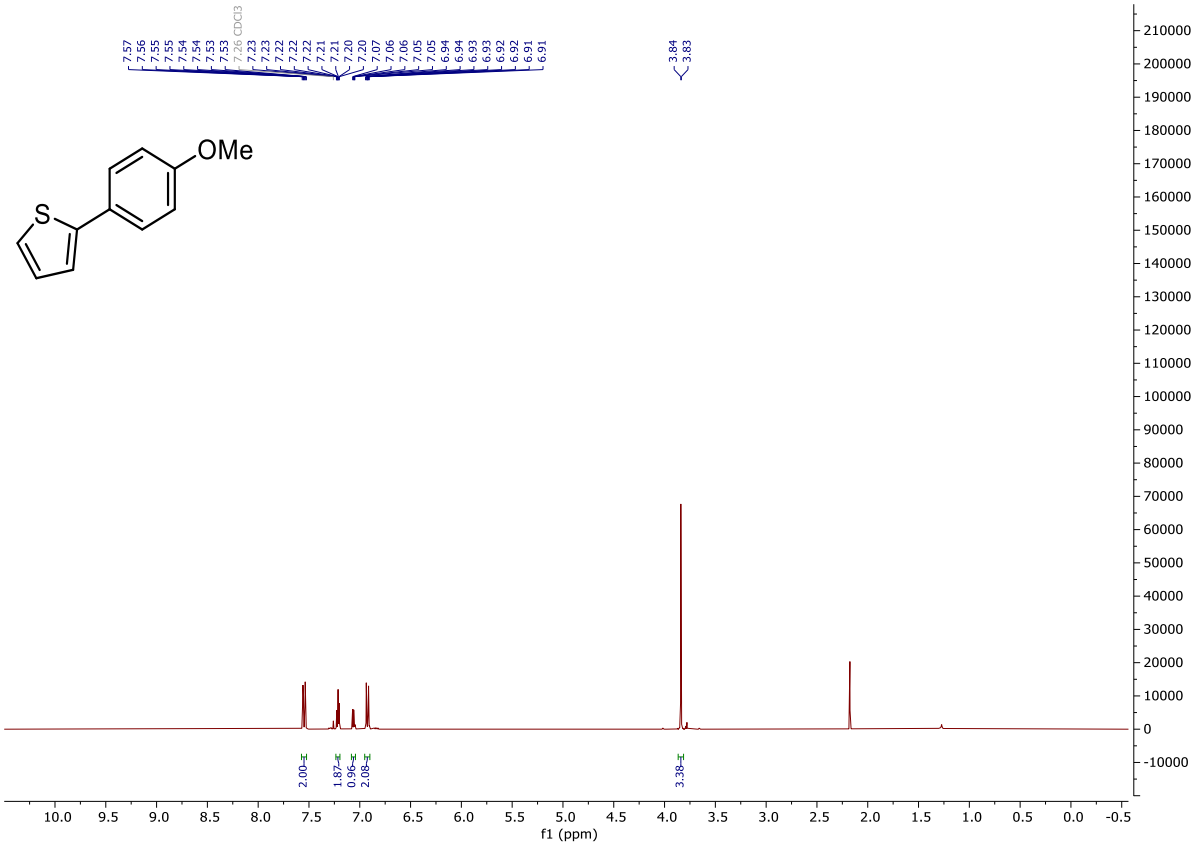
4-Fluoro-3'-methyl-1,1'-biphenyl (182b)

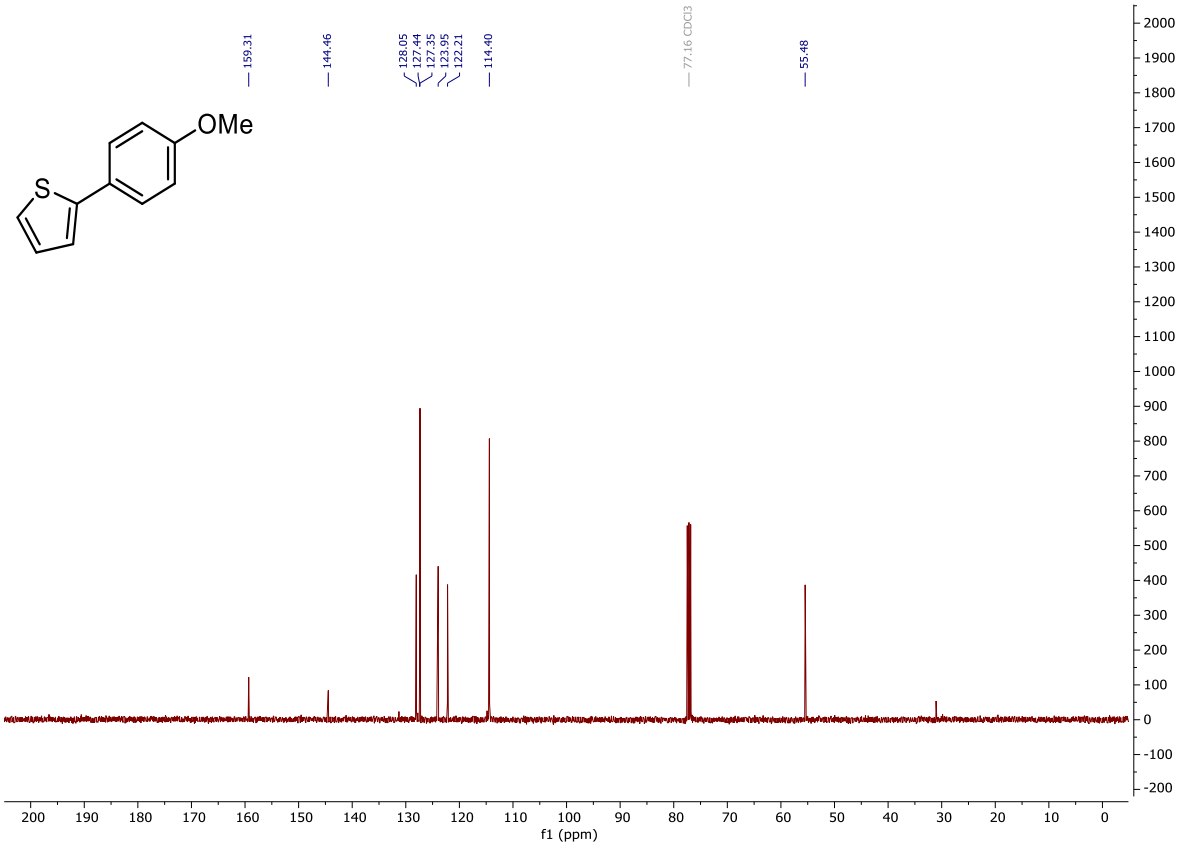


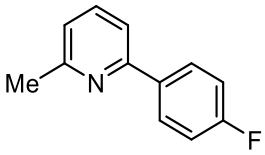




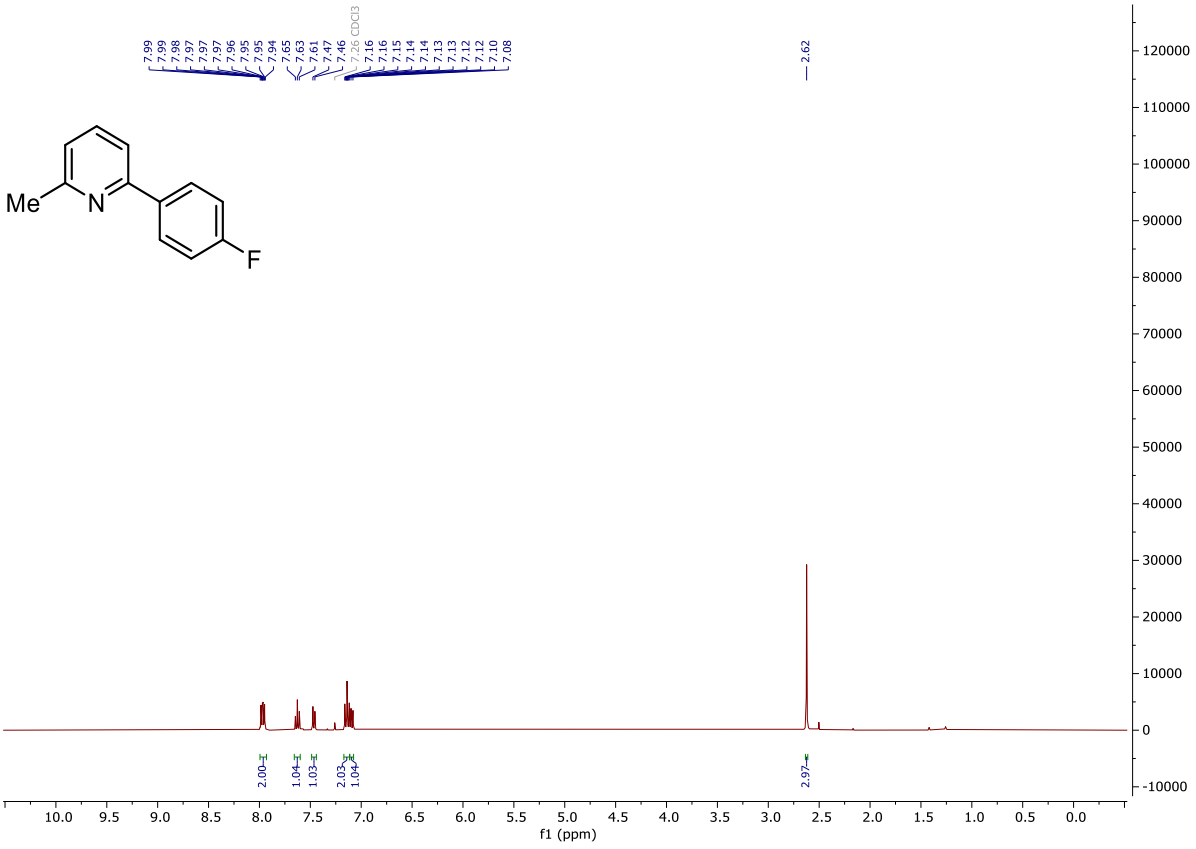
2-(4-Methoxyphenyl)thiophene (182k)

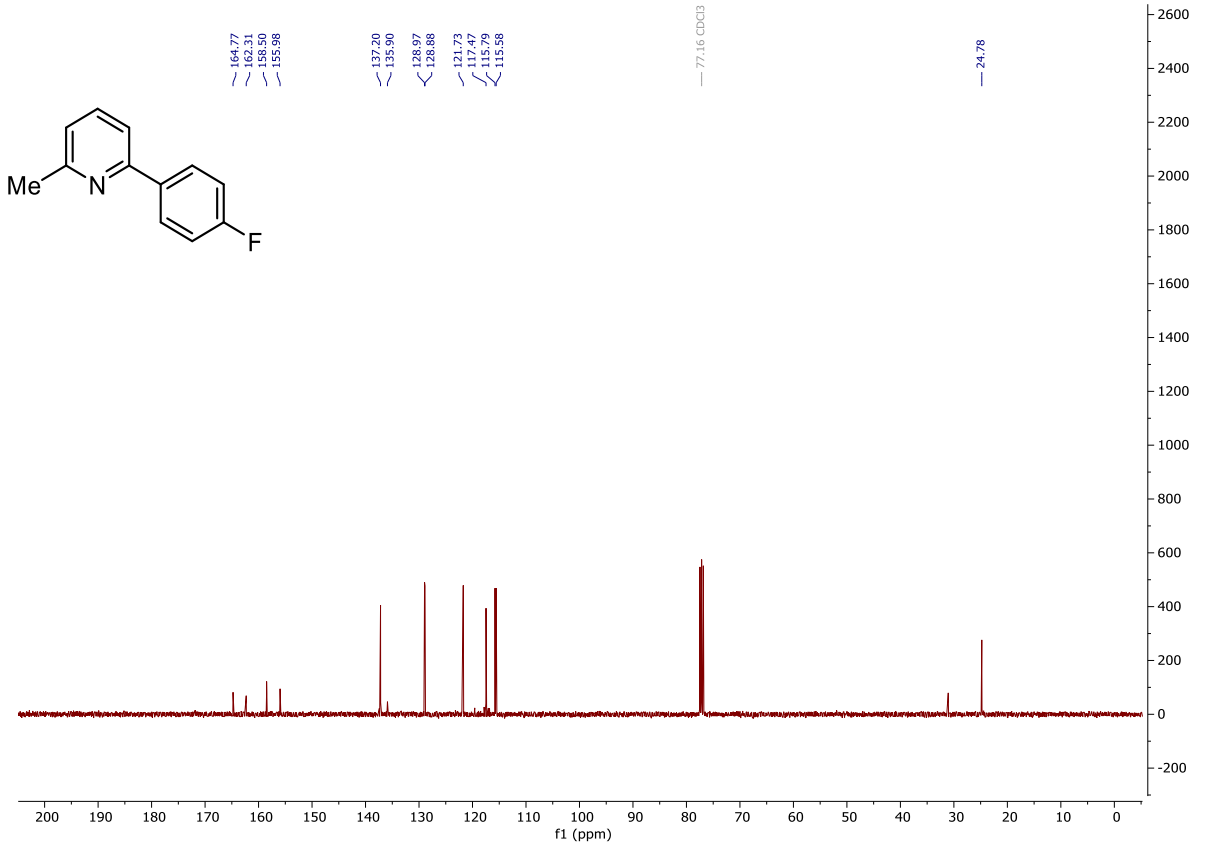

7.57
7.56
7.55
7.55
7.55
7.54
7.54
7.53
7.53
7.26 CDCl3
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.07
7.06
7.06
7.05
7.05
6.94
6.94
6.93
6.93
6.92
6.92
6.91
6.91
3.84
3.83
OMe
S
2.00
1.87
0.96
2.08
3.38
f1 (ppm)

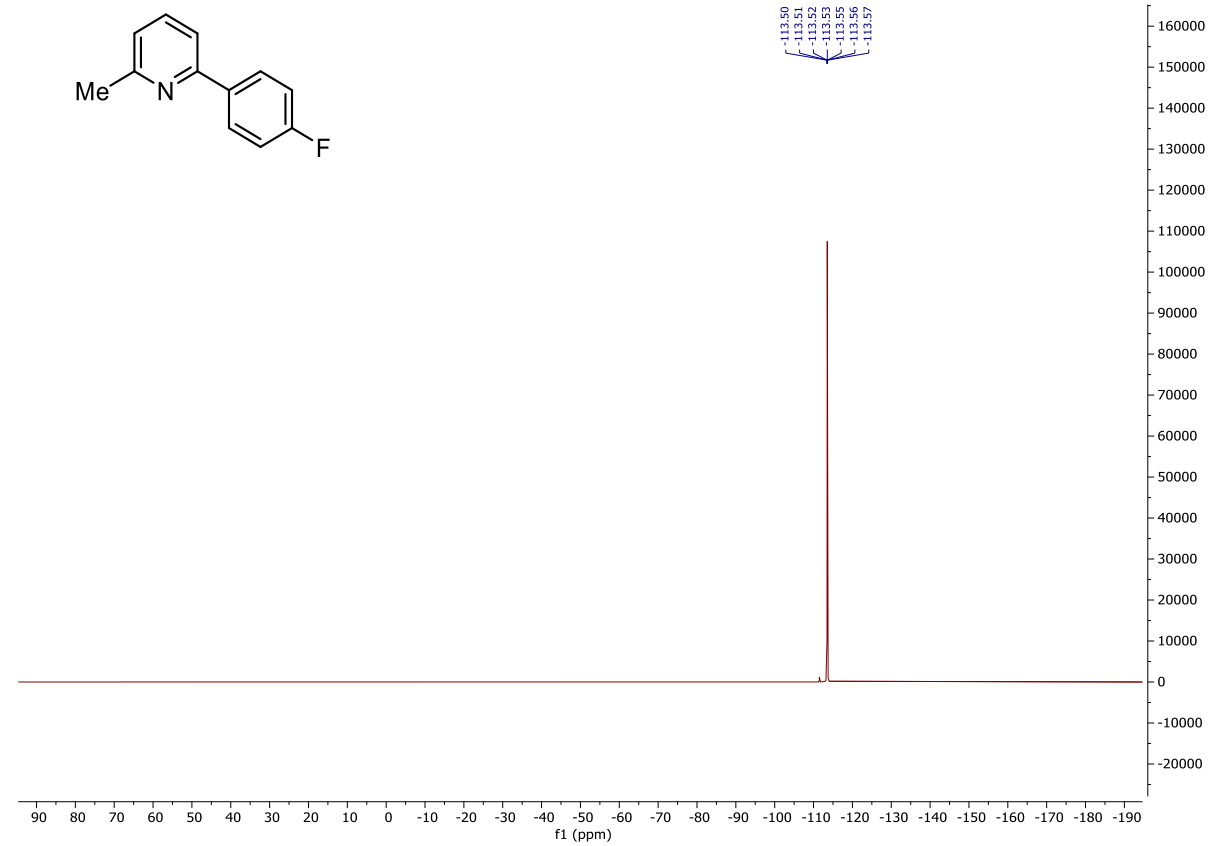

159.31
144.46
128.05
127.44
127.35
123.95
122.21
114.40
77.16 CDCl3
55.48
OMe
S
f1 (ppm)

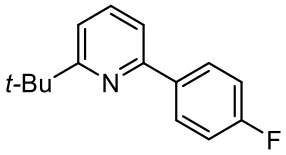


2-(4-Fluorophenyl)-6-methylpyridine (193e)

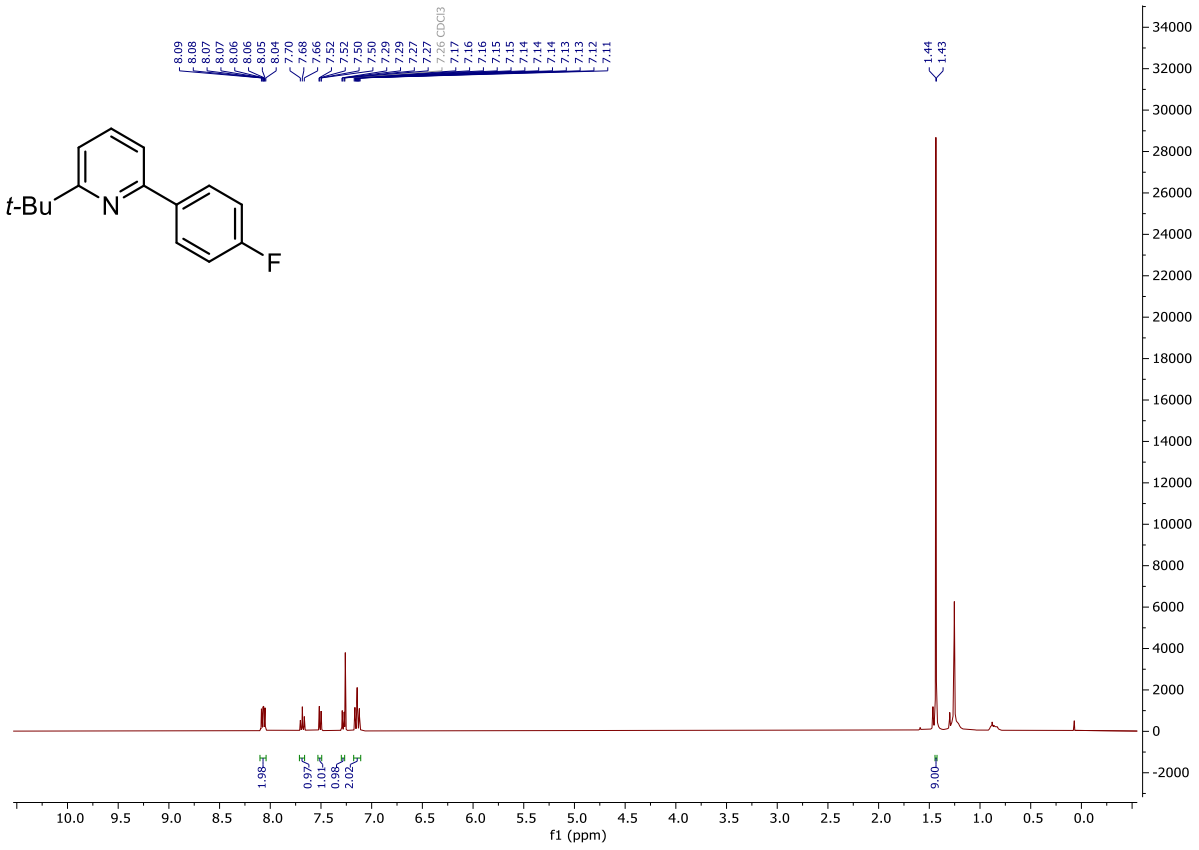


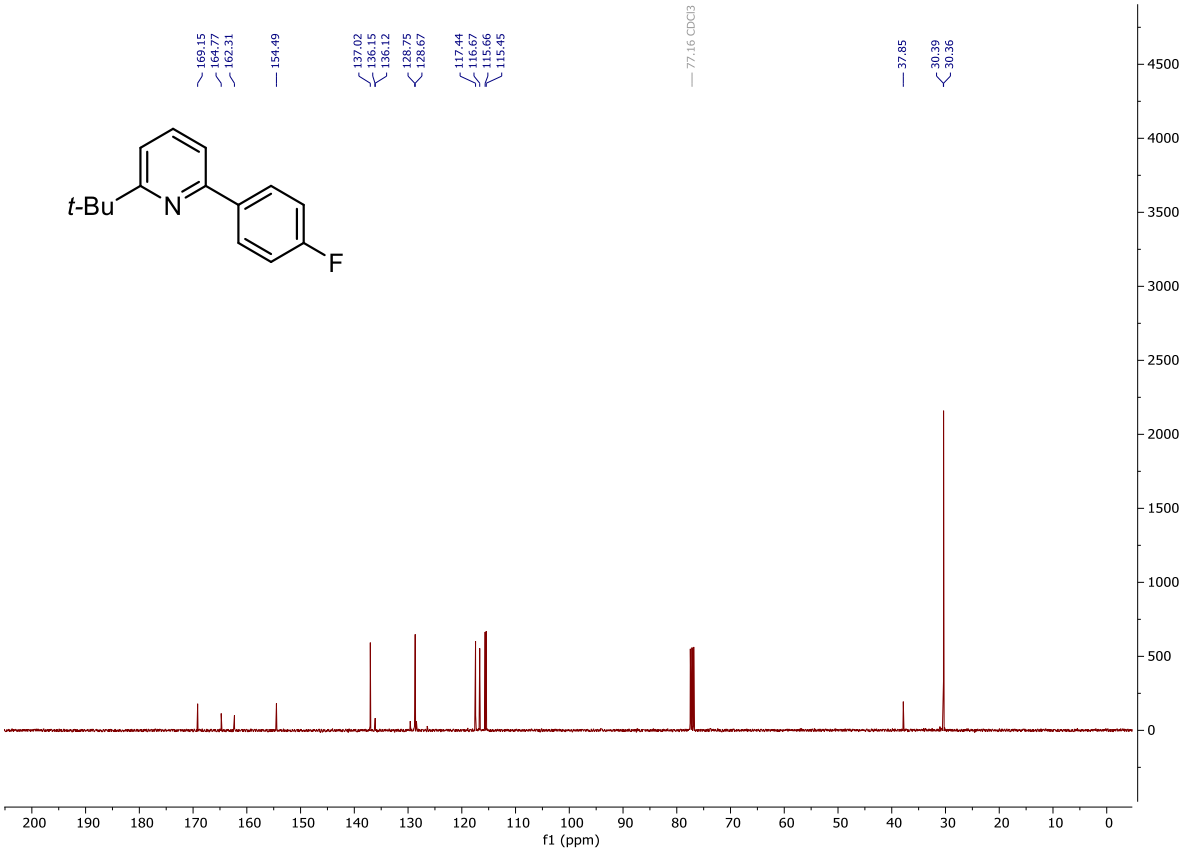

164.77
162.31
158.50
155.98
137.20
135.90
128.97
128.88
121.73
117.47
115.79
115.58
77.16 CDCl3
24.78
Me
N
F
f1 (ppm)

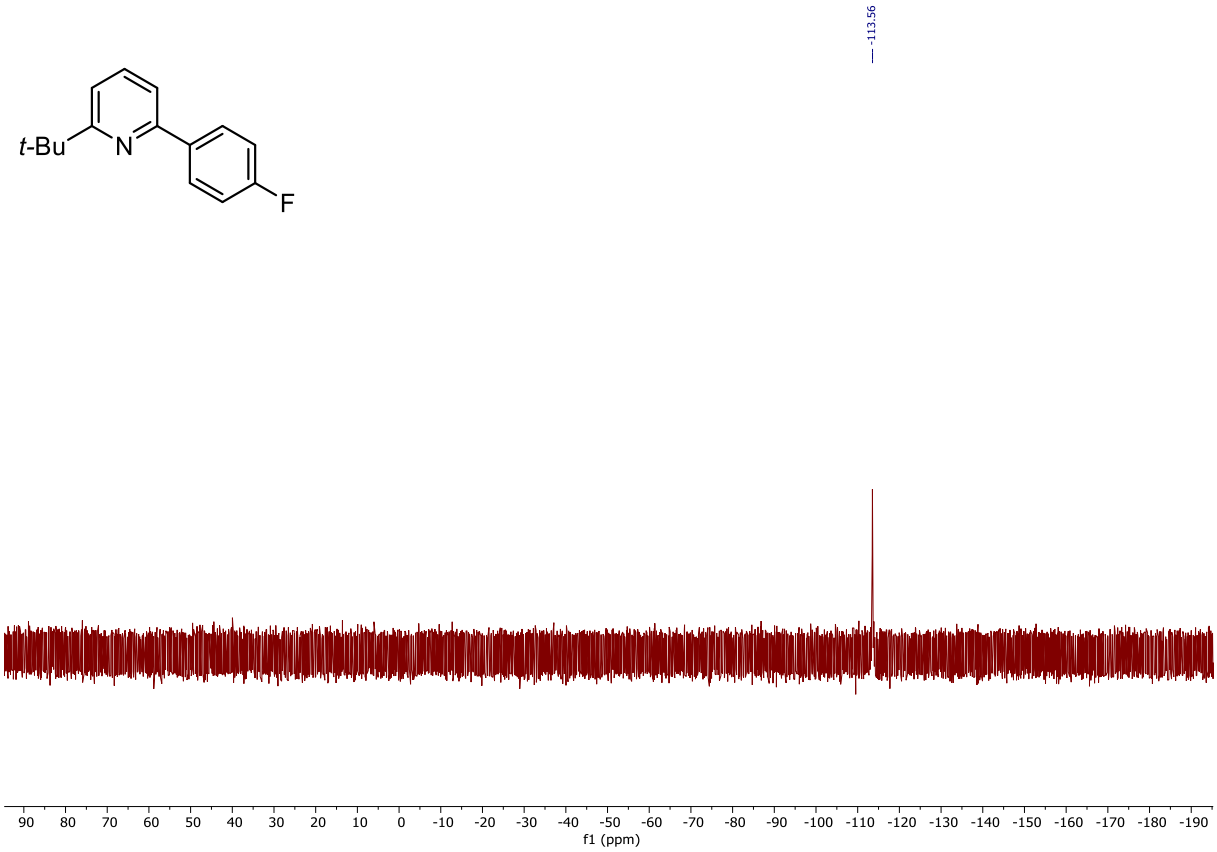

-113.50
-113.51
-113.52
-113.53
-113.55
-113.56
-113.57
Me
N
F
f1 (ppm)

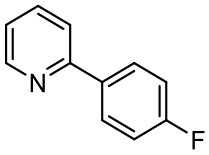


2-(*tert*-Butyl)-6-(4-fluorophenyl)pyridine (193d)

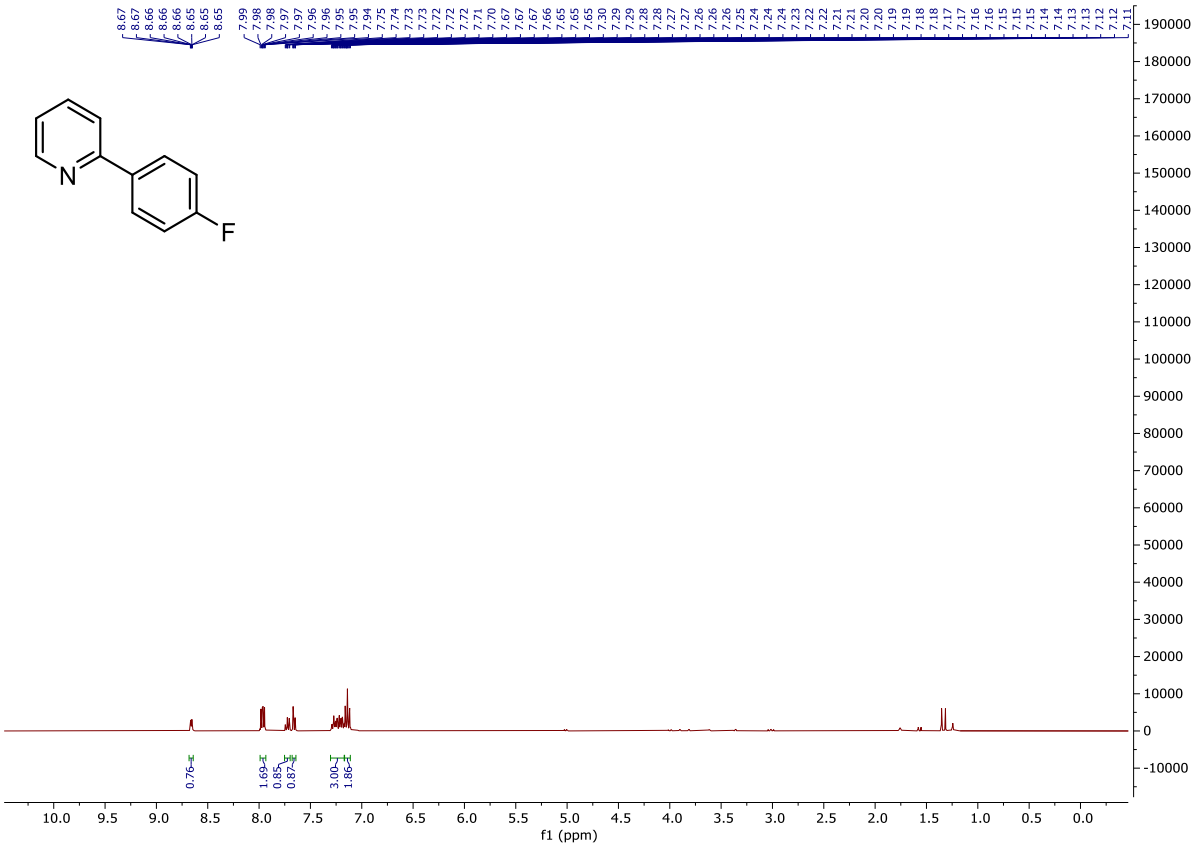


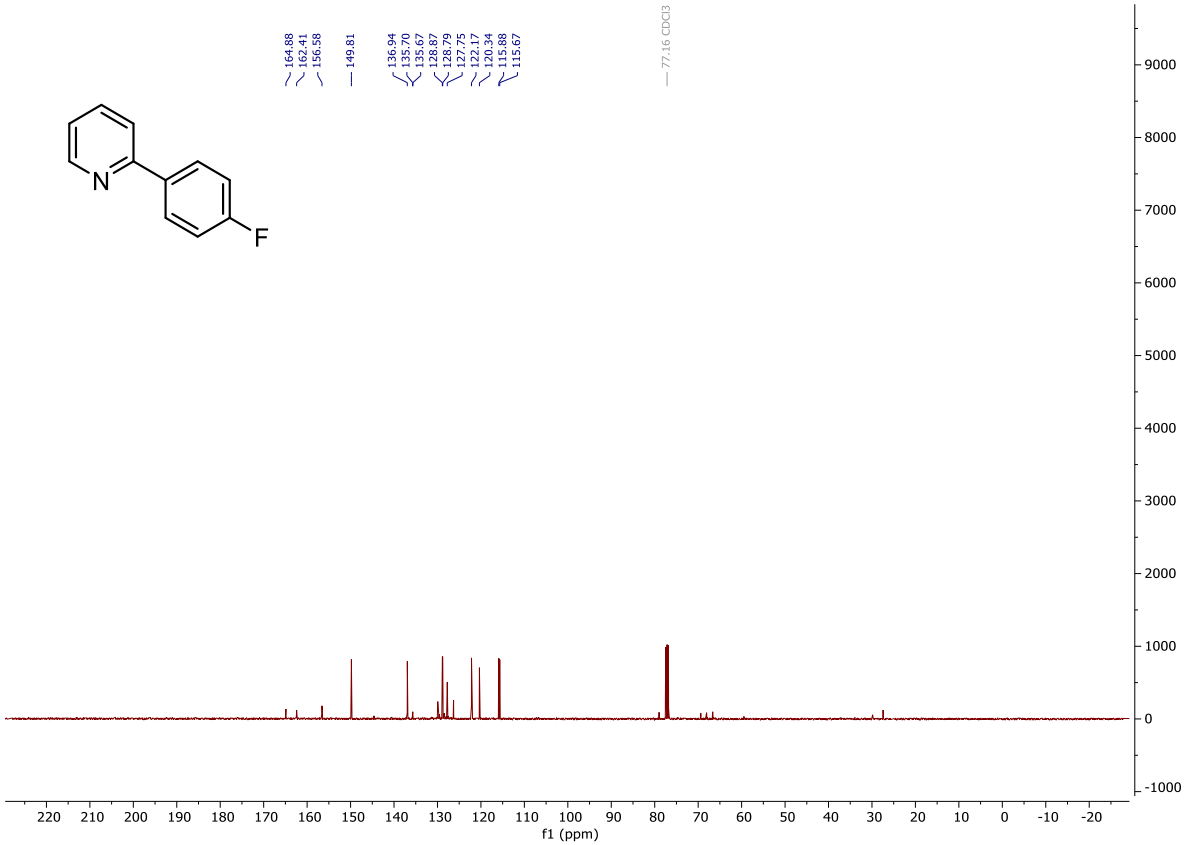

169.15
164.77
162.31
154.49
137.02
136.15
136.12
128.75
128.67
117.44
116.67
115.66
115.45
77.16 CDCl3
37.85
30.39
30.36
t-Bu
N
F
f1 (ppm)

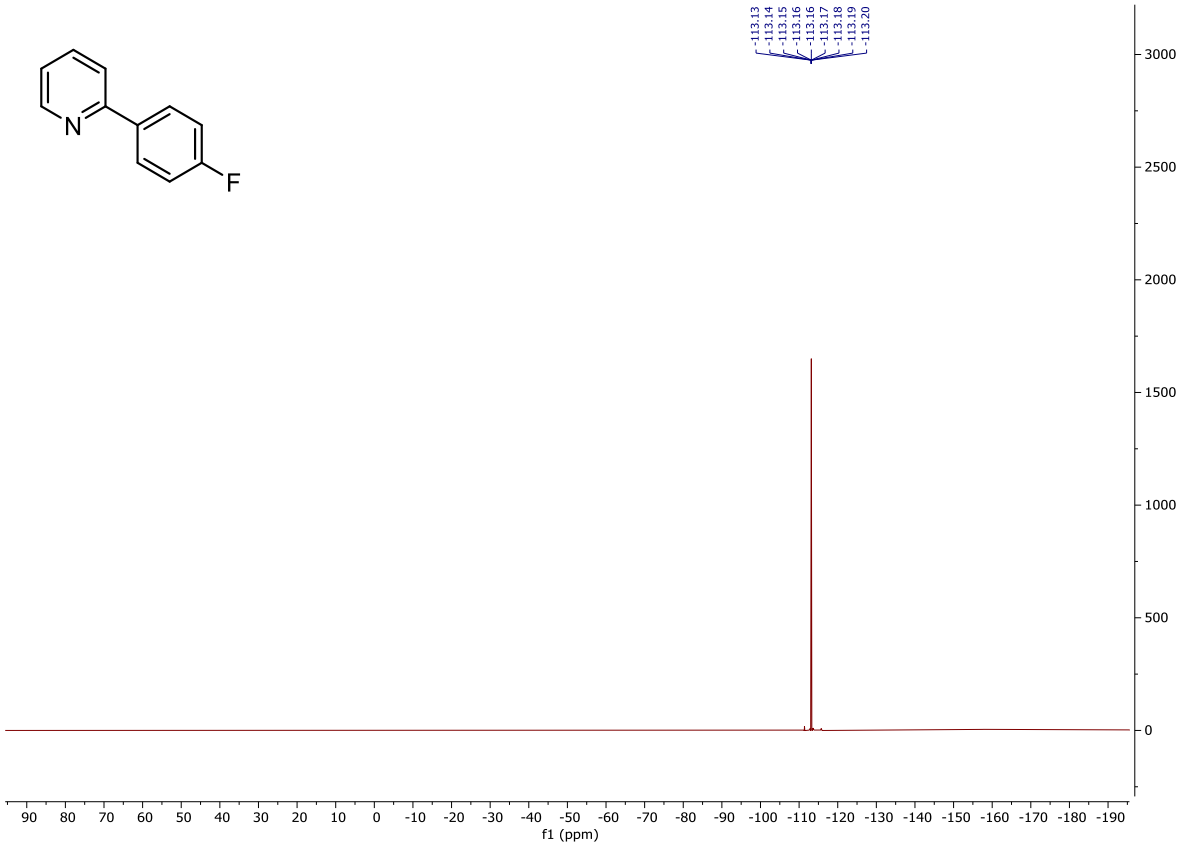

-113.56
t-Bu
N
F
f1 (ppm)

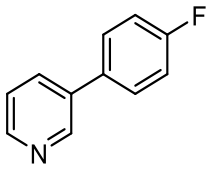


2-(4-Fluorophenyl)pyridine (193a)

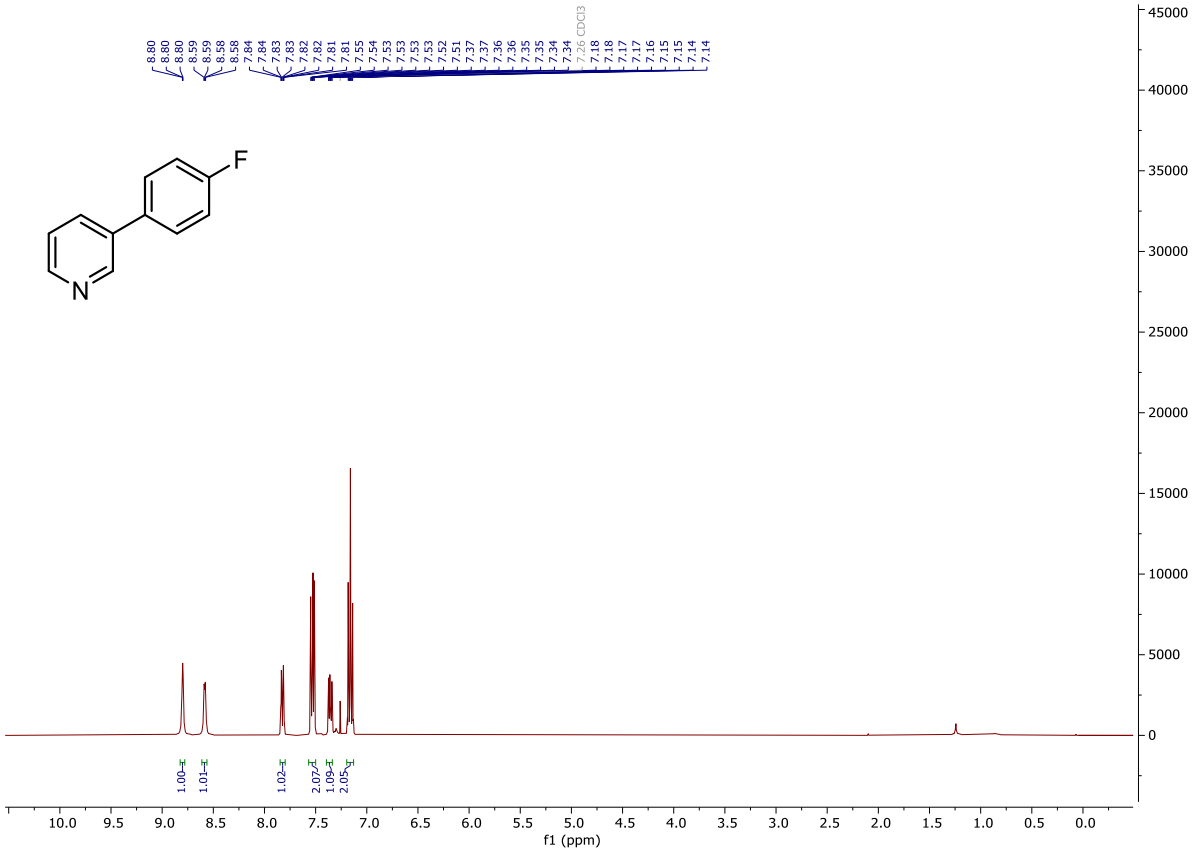


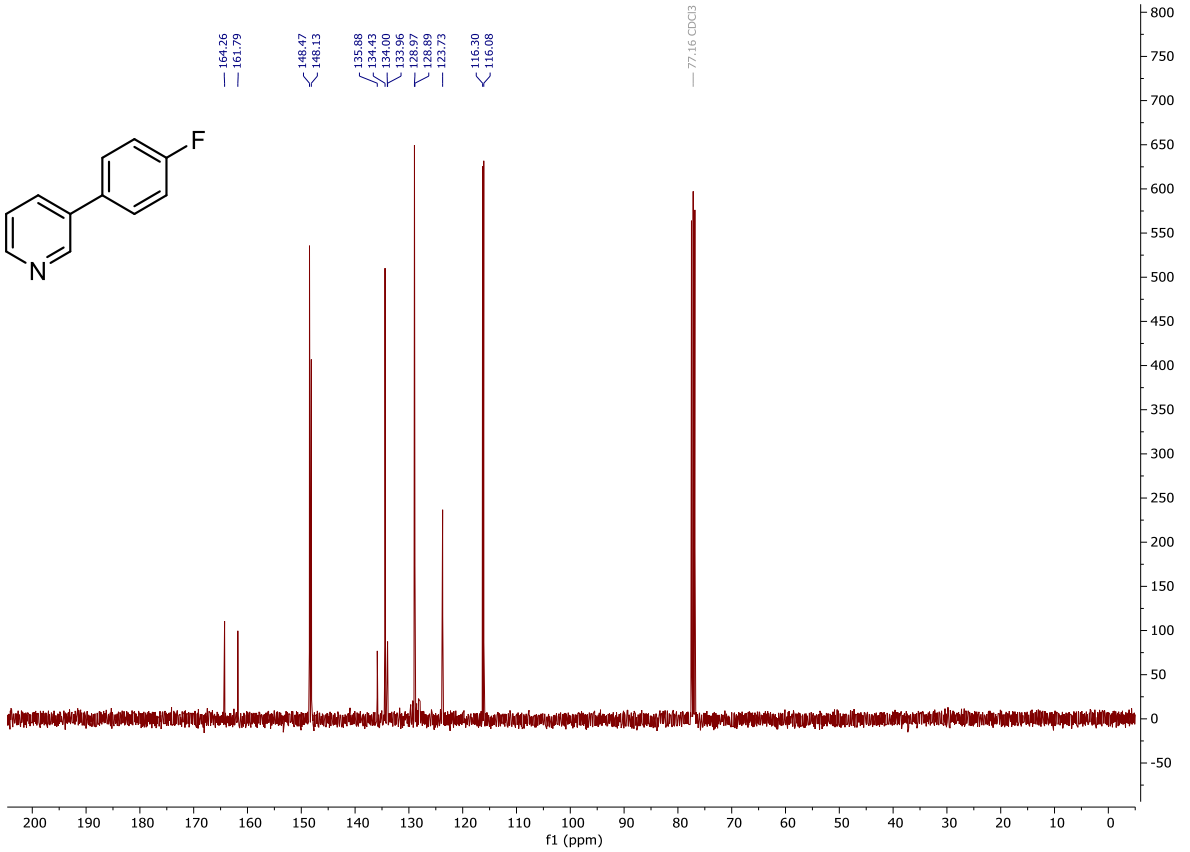

164.88
162.41
156.58
149.81
136.94
135.70
135.67
128.87
128.79
127.75
122.17
120.34
115.88
115.67
77.16 CDCl3
N
F
f1 (ppm)

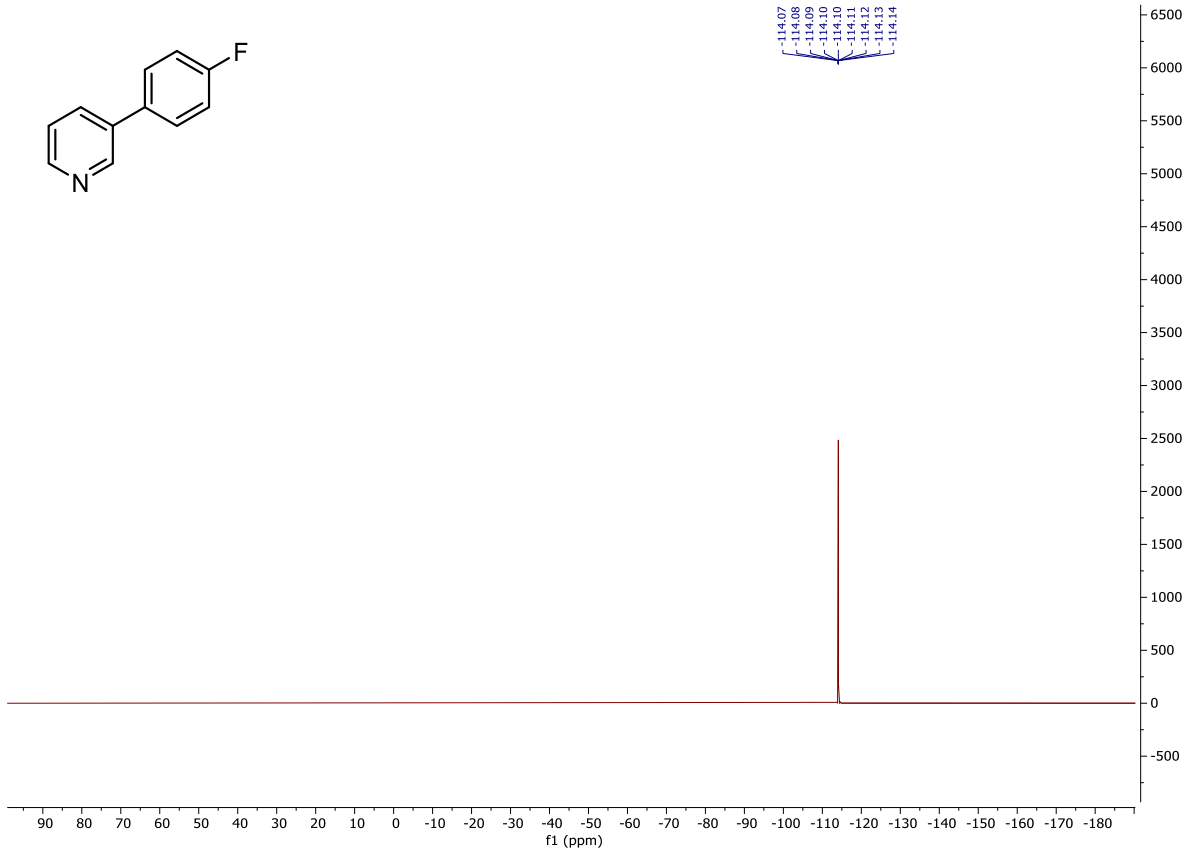

-113.13
-113.14
-113.15
-113.16
-113.16
-113.17
-113.18
-113.19
-113.20
N
F
f1 (ppm)



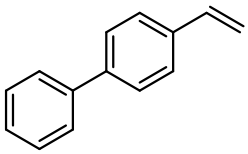
3-(4-Fluorophenyl)pyridine (182l)



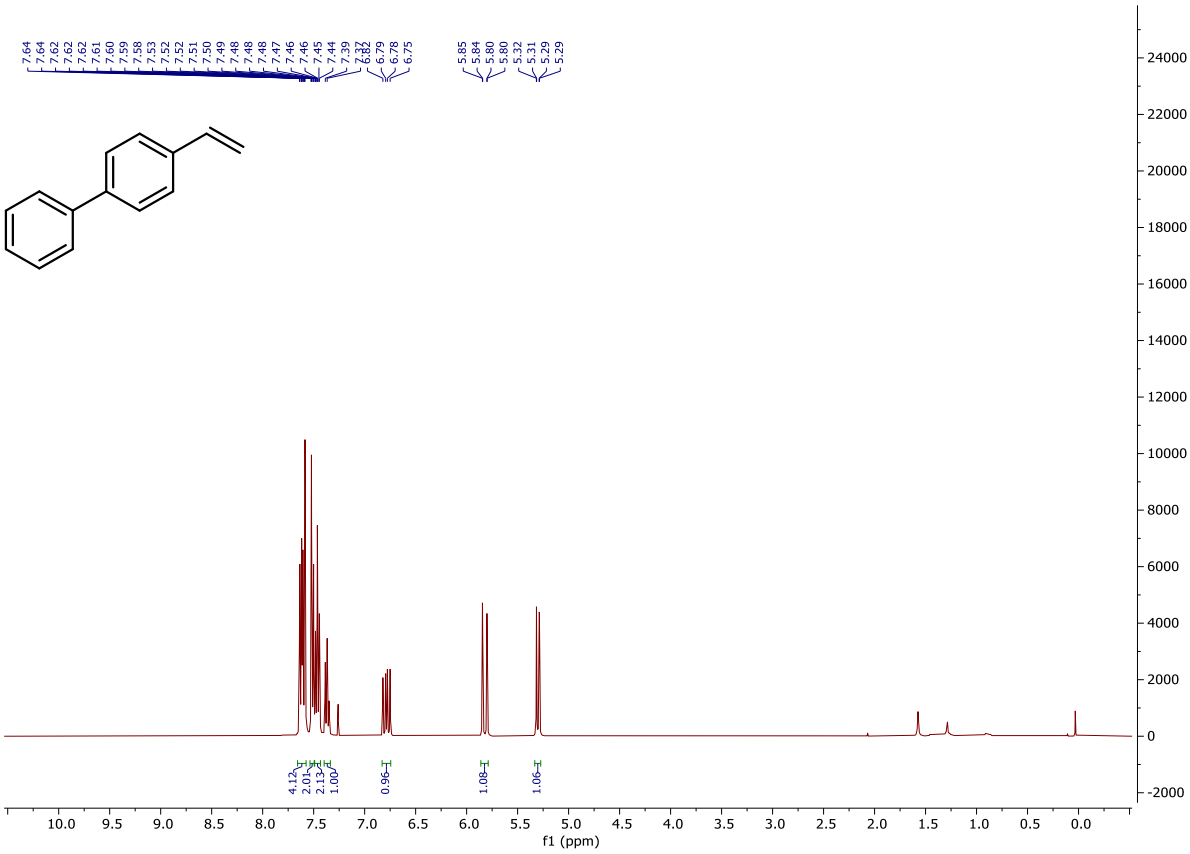

164.26
161.79
148.47
148.13
135.88
134.43
134.00
133.96
128.97
128.89
123.73
116.30
116.08
77.16 CDCl3
F
N
f1 (ppm)

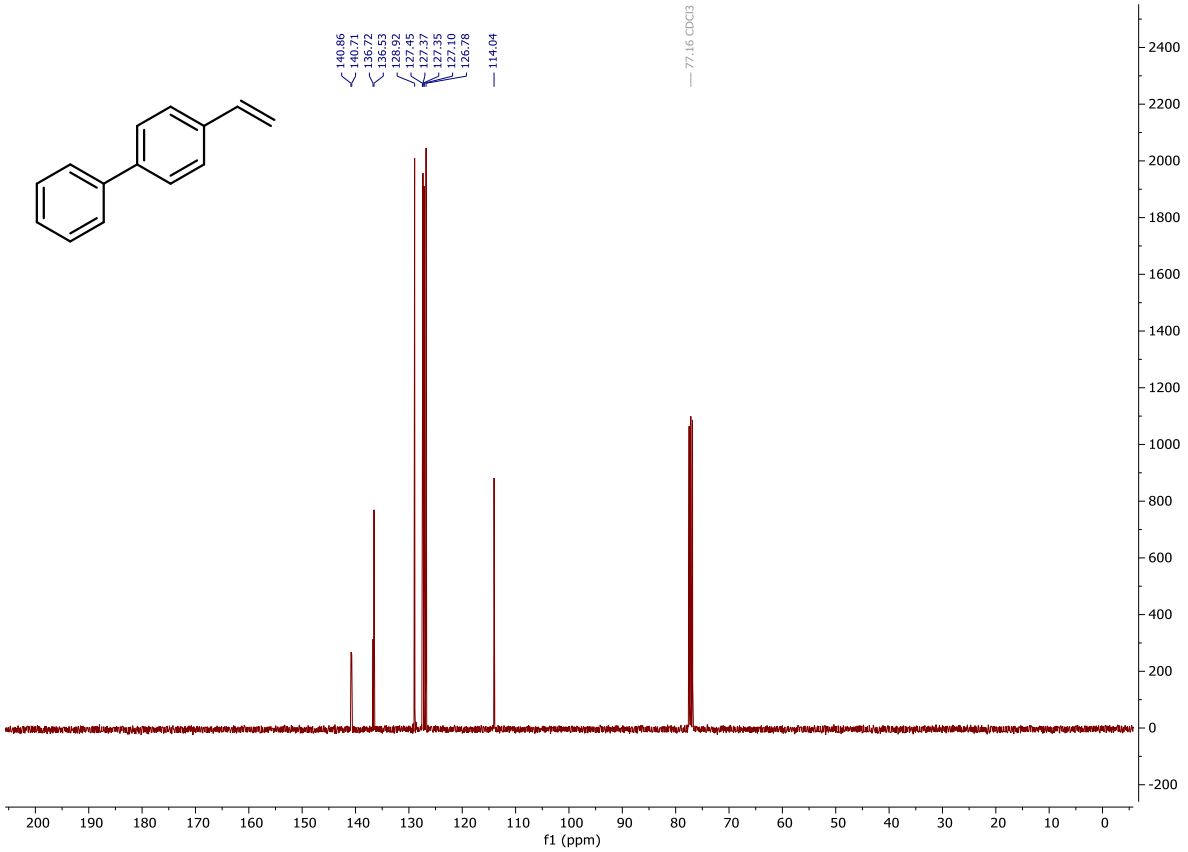

-114.07
-114.08
-114.09
-114.10
-114.10
-114.11
-114.12
-114.13
-114.14
F
N
f1 (ppm)

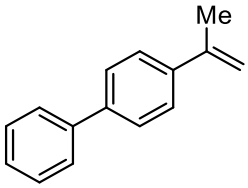
8.3.5 Styrene products



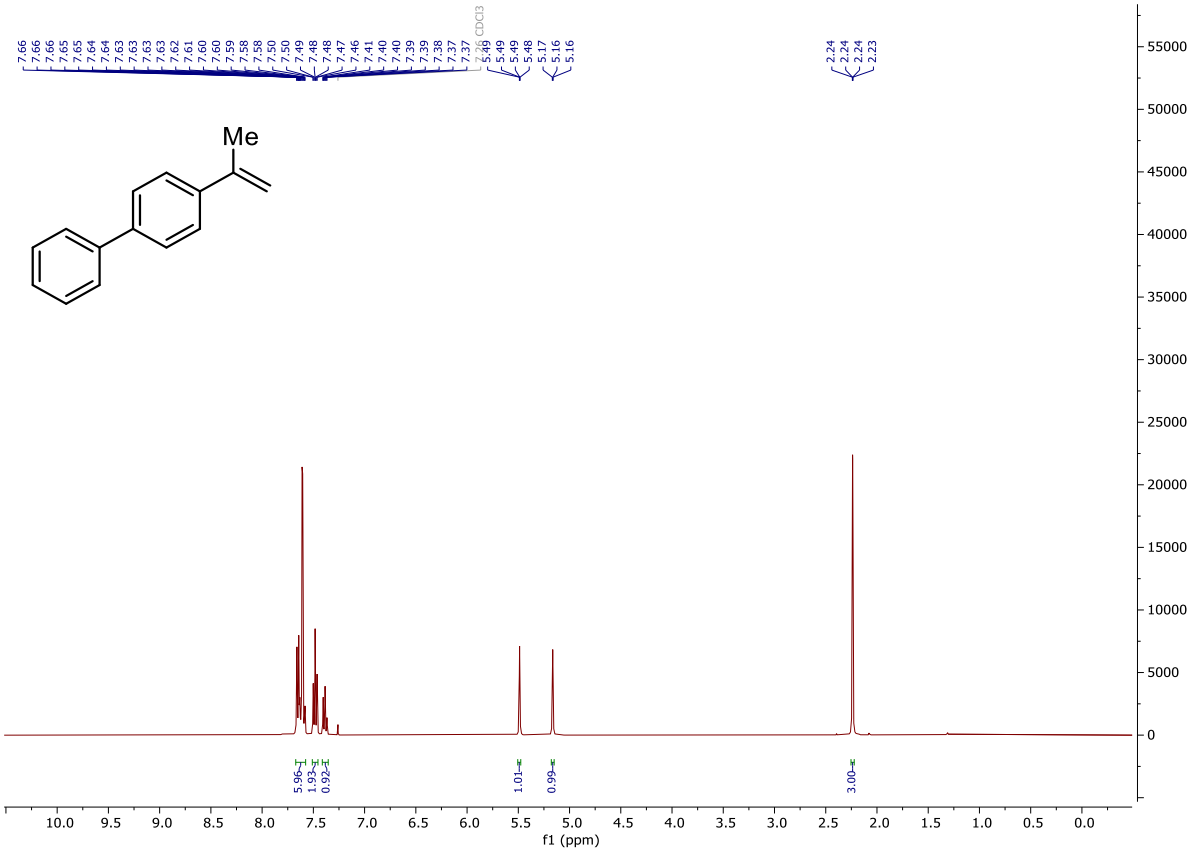
4-vinyl-1,1'-biphenyl (204)

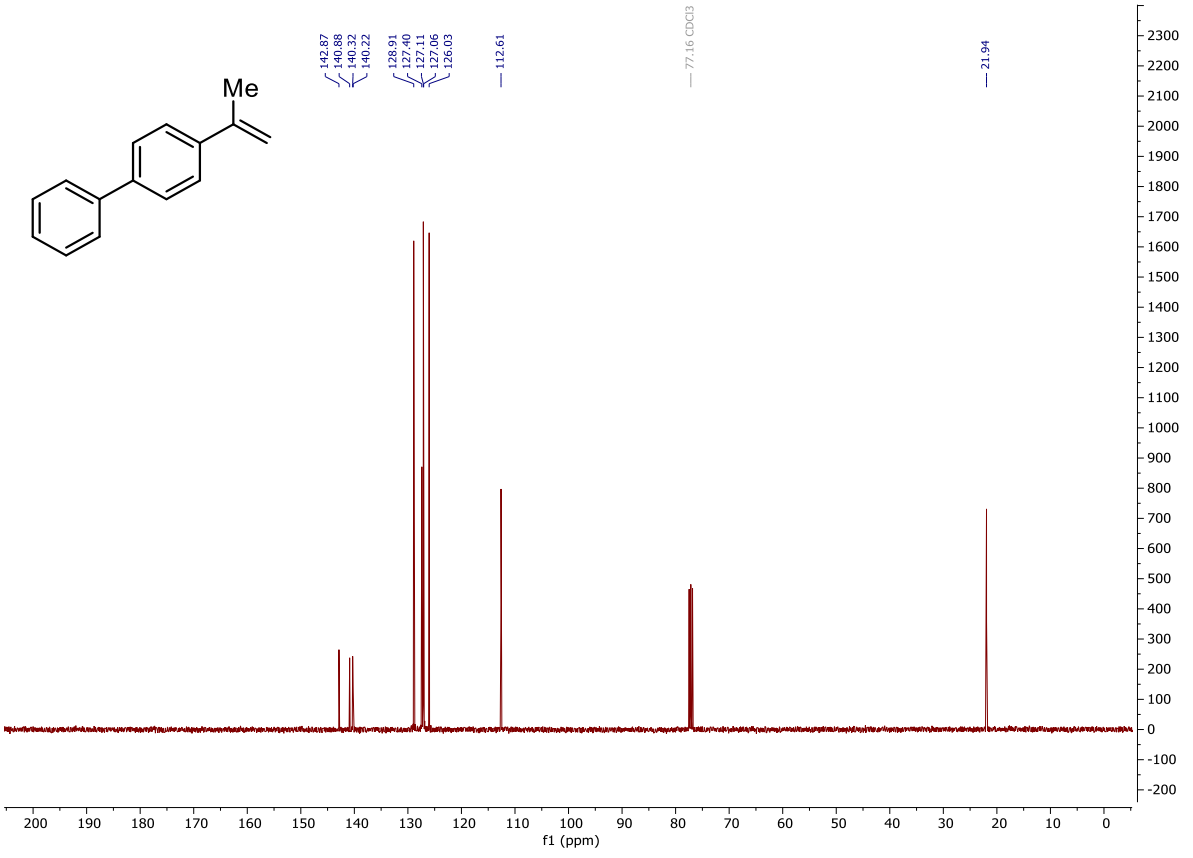


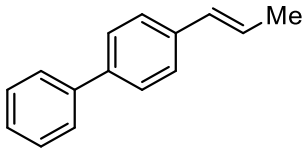




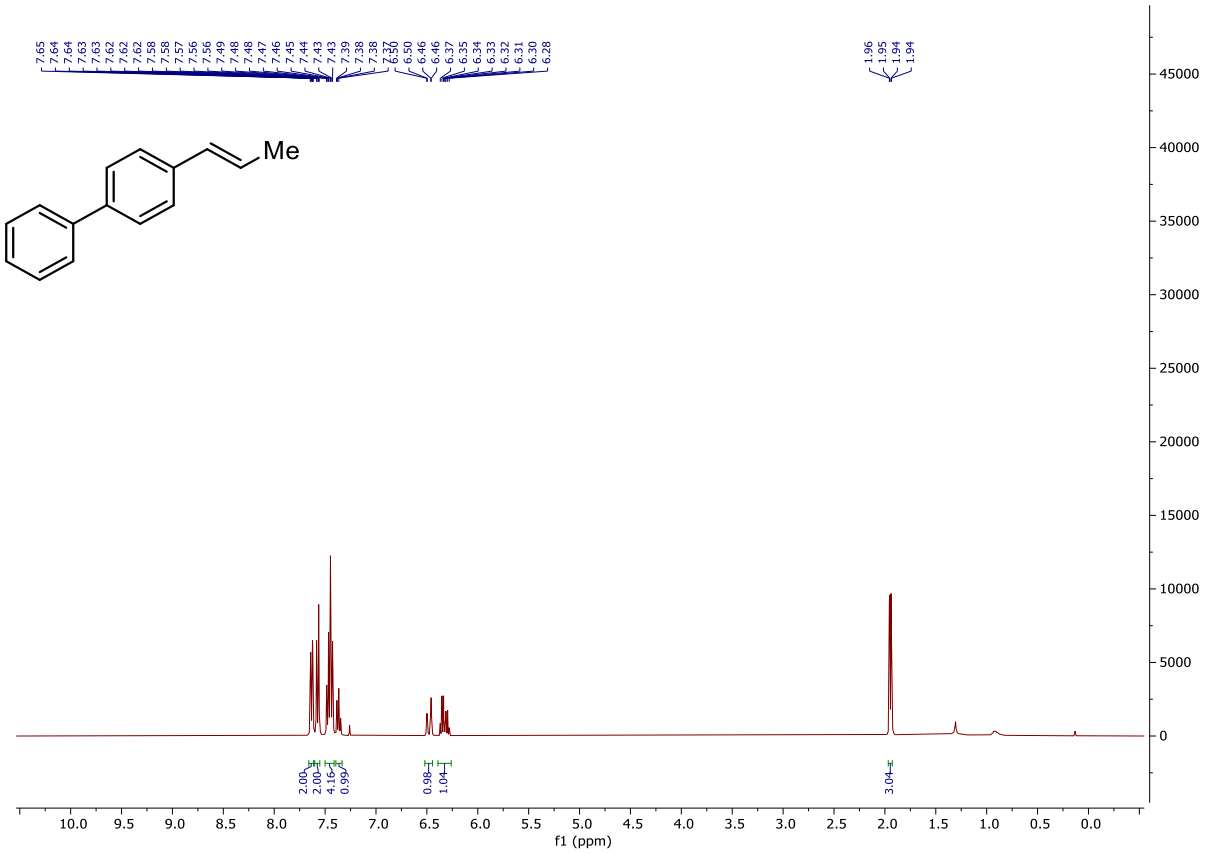
4-(prop-1-en-2-yl)-1,1'-biphenyl (206a)

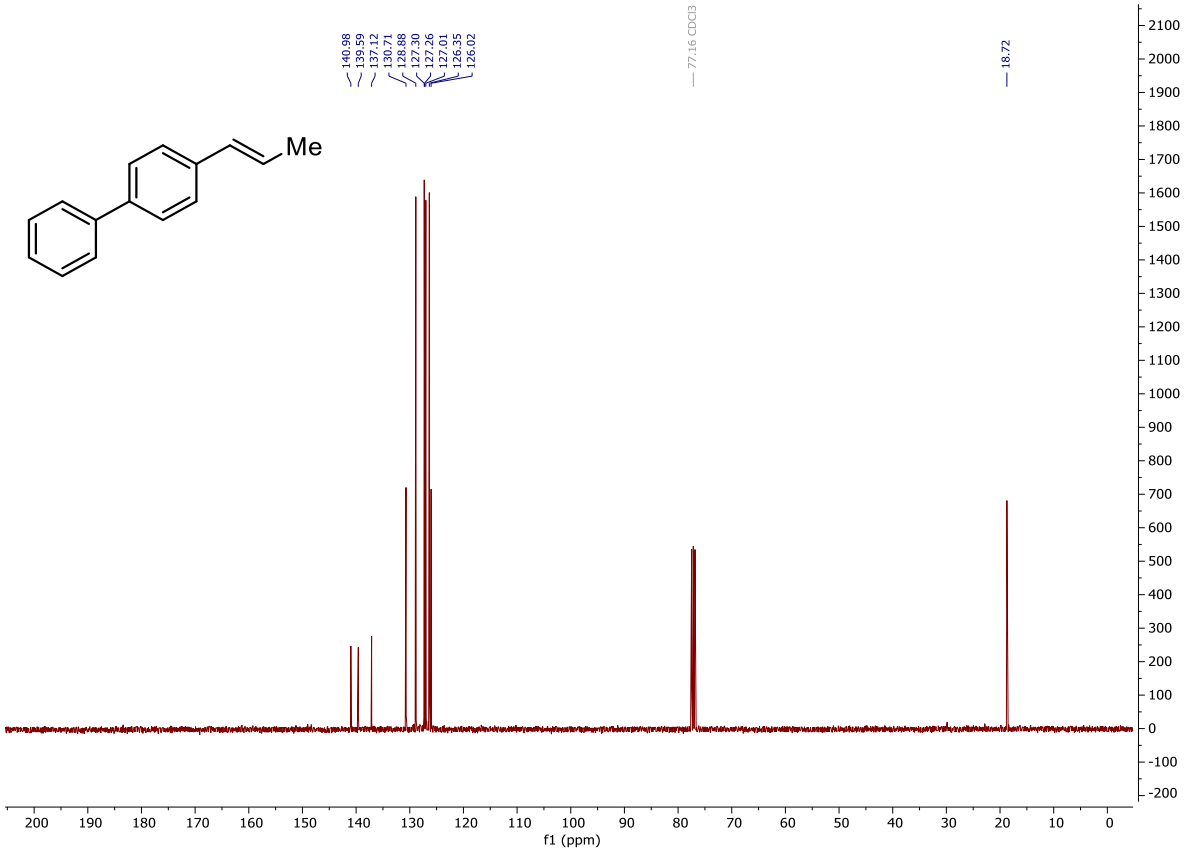

Me
7.66 7.66 7.66 7.65 7.65 7.64 7.64 7.63 7.63 7.63 7.63 7.62 7.61 7.60 7.60 7.59 7.58 7.58 7.50 7.50 7.49 7.48 7.48 7.47 7.46 7.41 7.40 7.40 7.39 7.39 7.38 7.37 7.37
CDCl3
5.49 5.49 5.49 5.48 5.17 5.16 5.16
2.24 2.24 2.24 2.23
5.96 1.93 0.92 1.01 0.99 3.00
f1 (ppm)

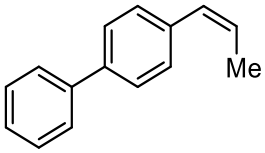

Me
142.87 140.88 140.32 140.22 128.91 127.40 127.11 127.06 126.03
112.61
77.16 CDCl3
21.94
f1 (ppm)



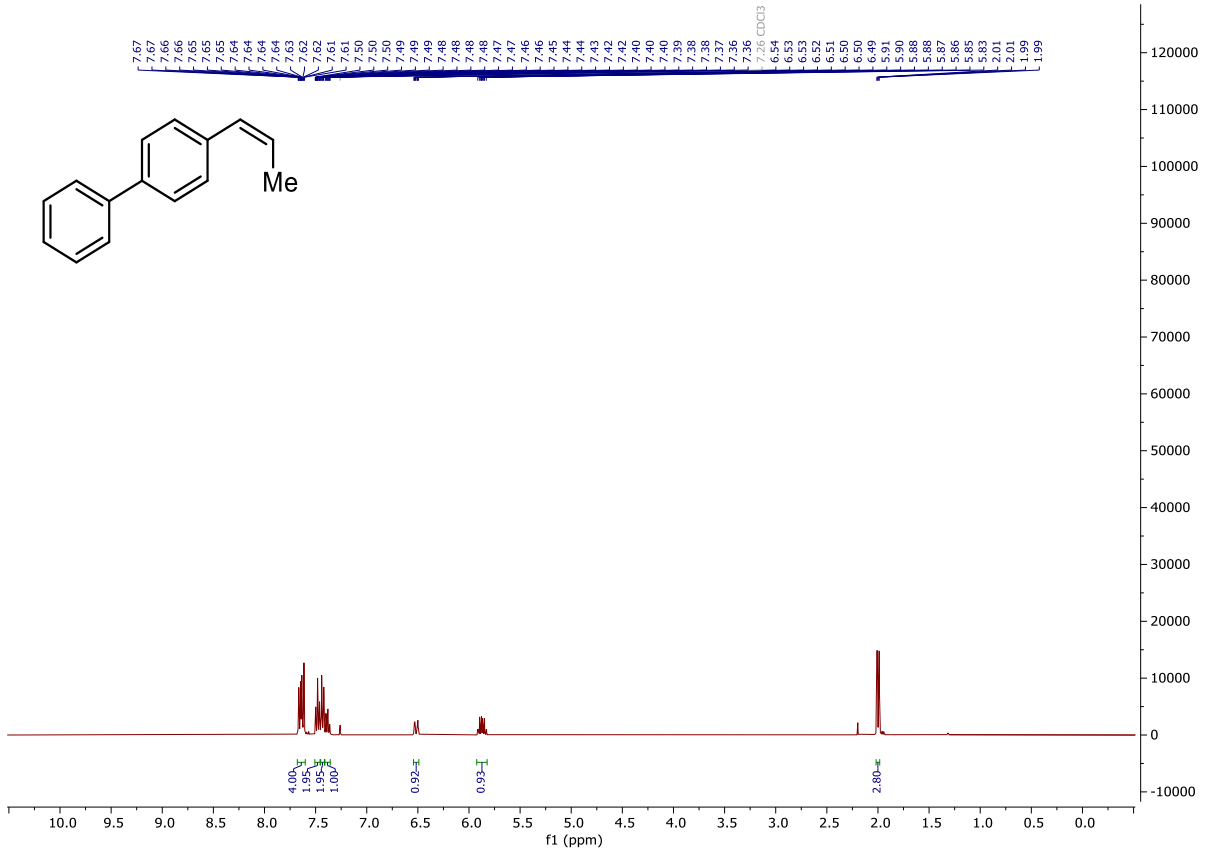
(*E*)-4-(prop-1-en-1-yl)-1,1'-biphenyl (*E*)-(206a)

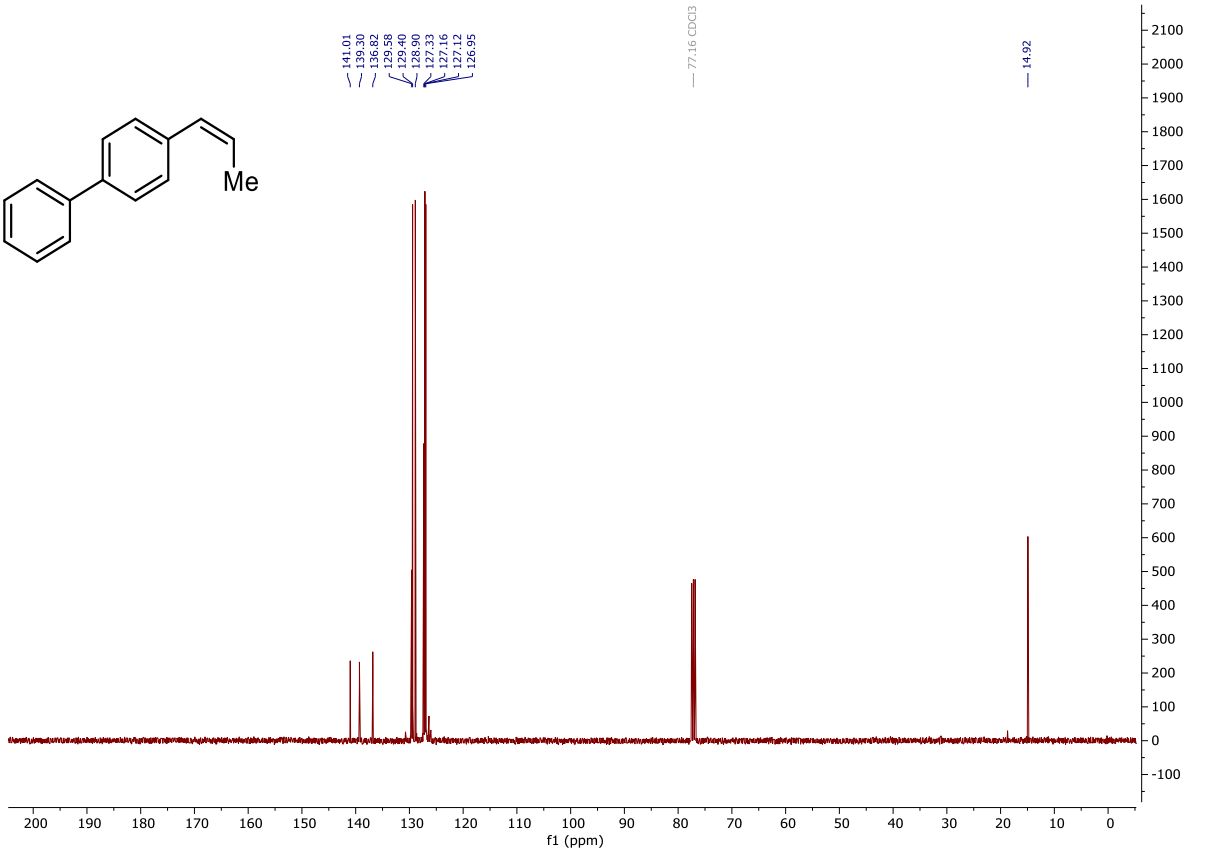


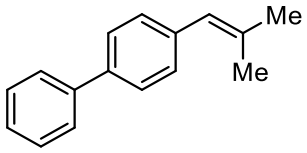




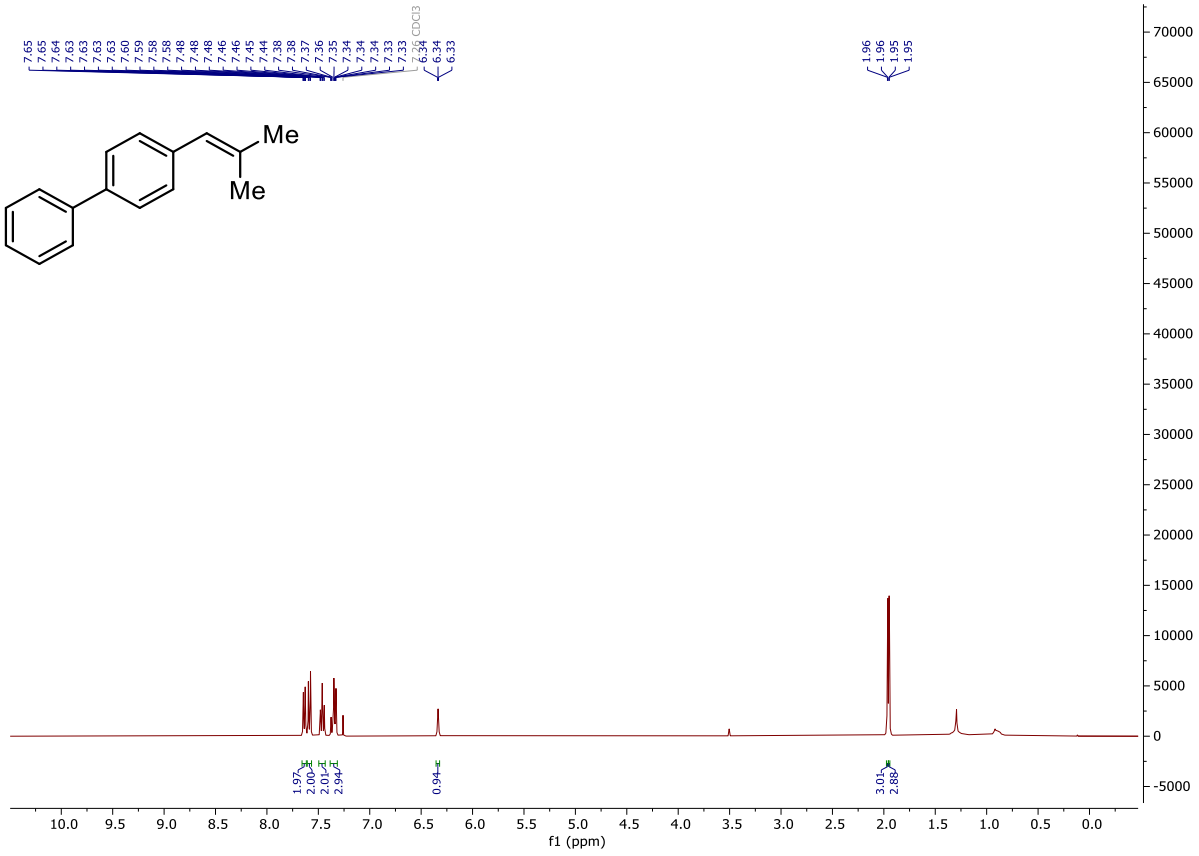
(Z)-4-(prop-1-en-1-yl)-1,1'-biphenyl (*Z*)-(206a)

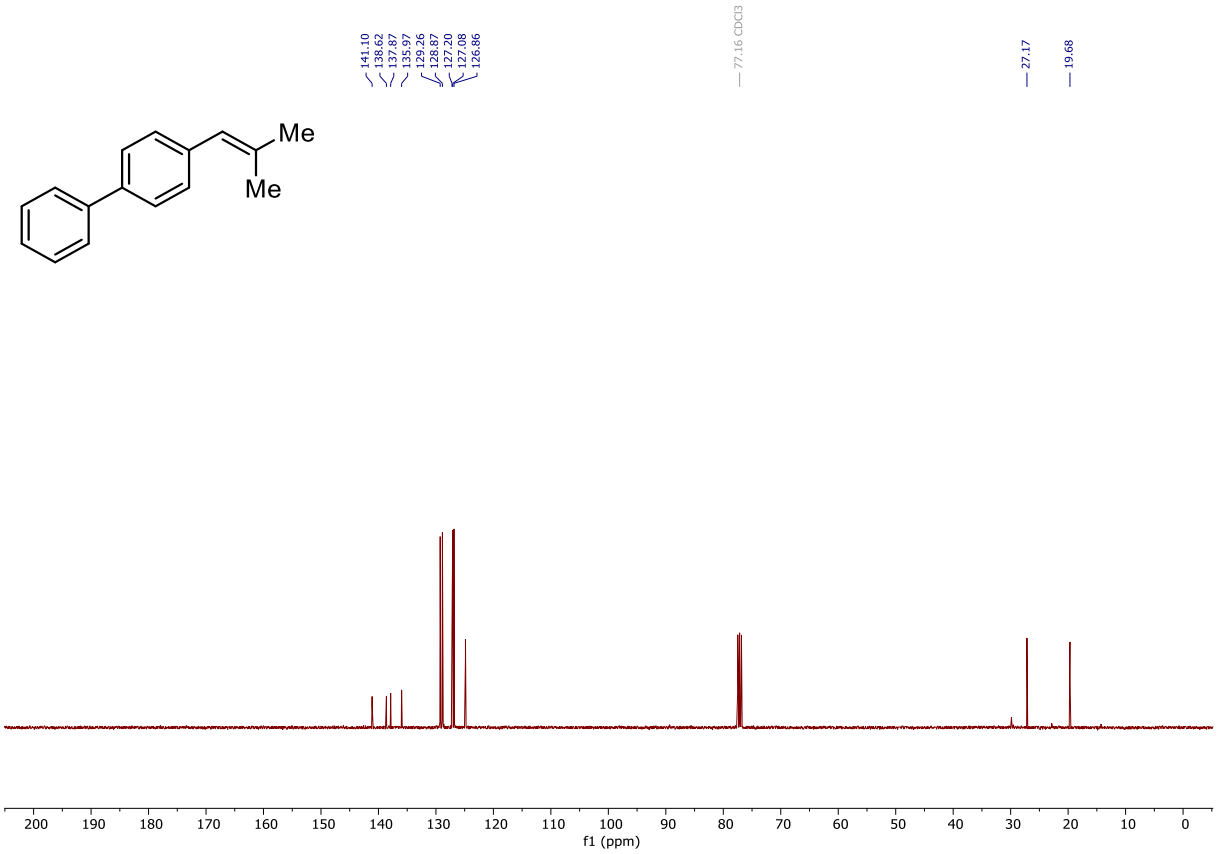

Me
7.67 7.67 7.66 7.66 7.65 7.65 7.64 7.64 7.64 7.64 7.63 7.62 7.62 7.61 7.61 7.50 7.50 7.50 7.49 7.49 7.49 7.48 7.48 7.48 7.48 7.47 7.47 7.46 7.46 7.45 7.44 7.44 7.43 7.42 7.42 7.40 7.40 7.40 7.39 7.38 7.38 7.37 7.36 7.36 7.26 CDCl3 6.54 6.53 6.53 6.52 6.51 6.50 6.50 6.49 5.91 5.90 5.88 5.88 5.87 5.86 5.85 5.83 2.01 2.01 1.99 1.99
4.00 1.95 1.95 1.00 0.92 0.93 2.80
f1 (ppm)

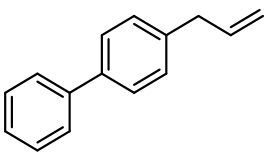

Me
141.01 139.30 136.82 129.58 129.40 128.90 127.33 127.16 127.12 126.95
77.16 CDCl3
14.92
f1 (ppm)



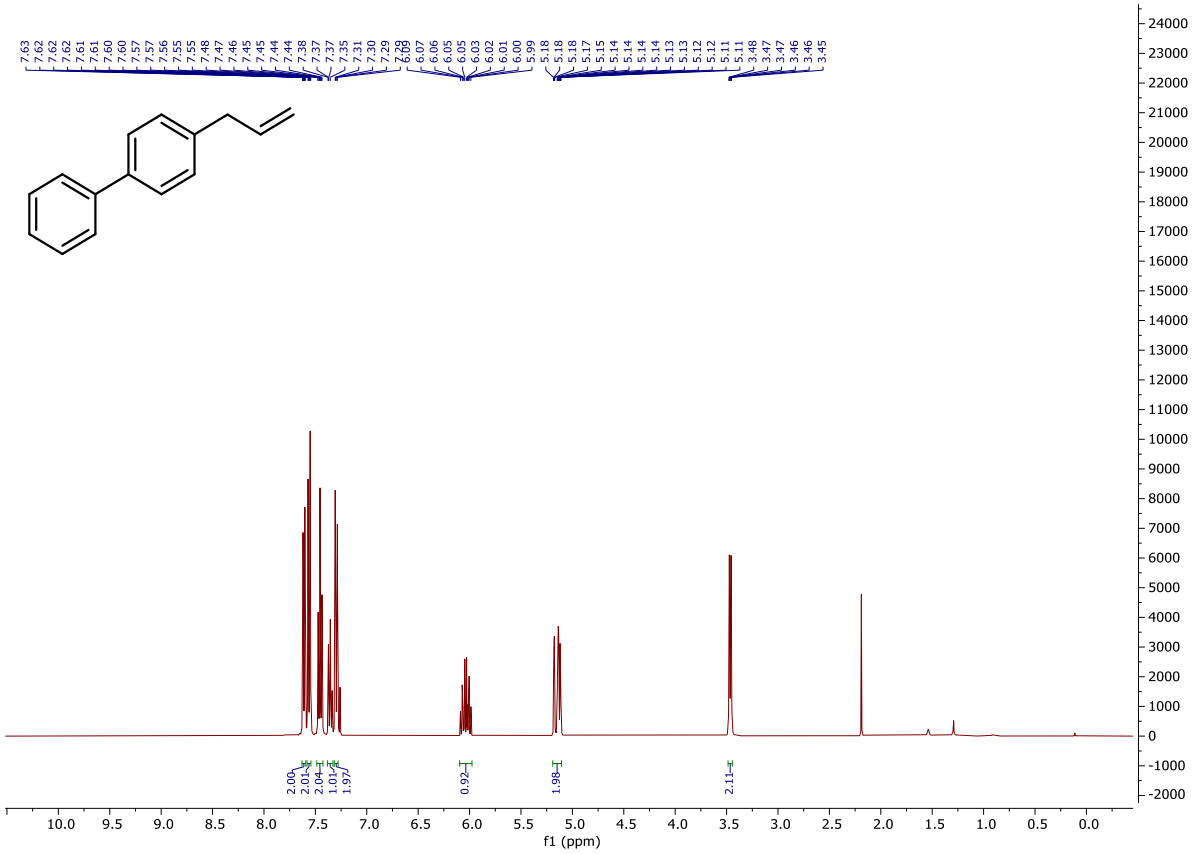
4-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (206c)

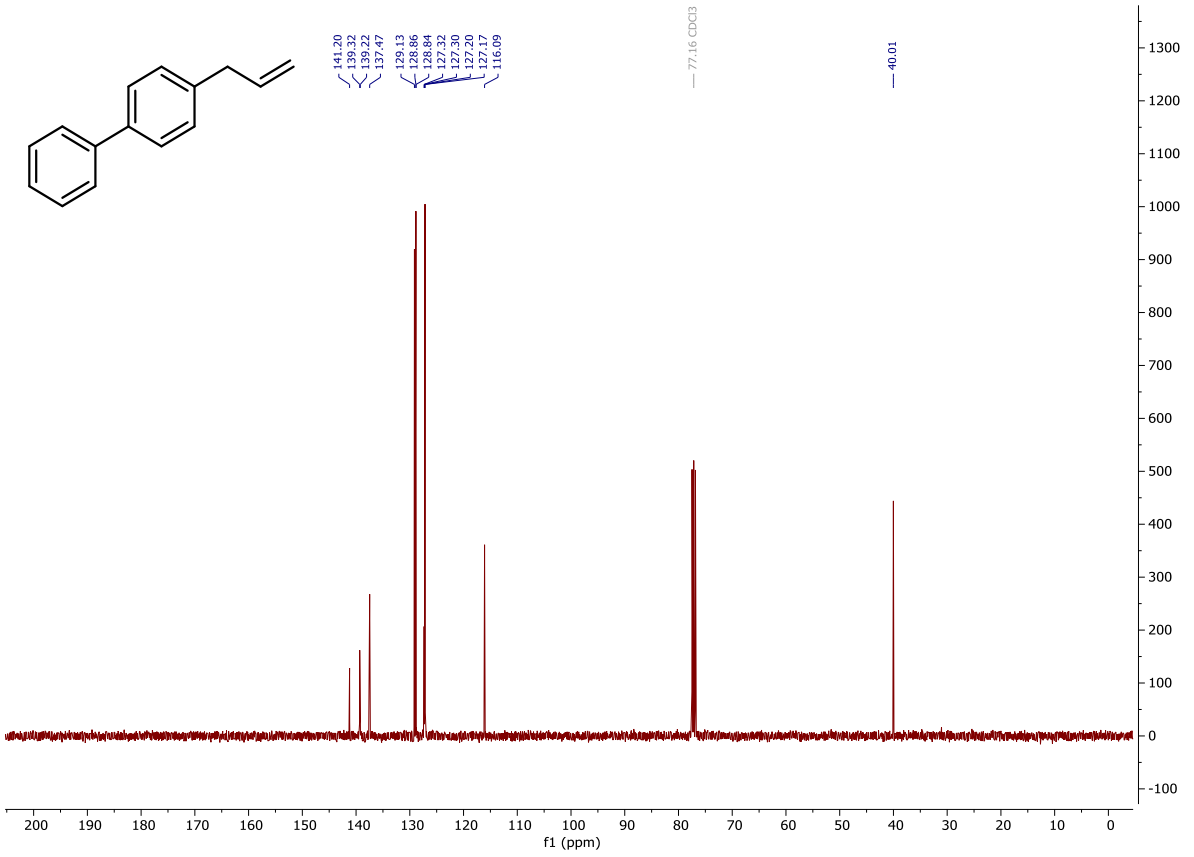






4-Allyl-1,1'-biphenyl (208)


7.63 7.62 7.62 7.62 7.61 7.61 7.60 7.60 7.57 7.57 7.56 7.55 7.55 7.48 7.47 7.46 7.45 7.45 7.44 7.44 7.38 7.37 7.37 7.35 7.31 7.30 7.29 7.09
6.07 6.06 6.05 6.05 6.03 6.02 6.01 6.00 5.99
5.18 5.18 5.18 5.17 5.15 5.14 5.14 5.14 5.14 5.13 5.13 5.12 5.12 5.11 5.11
3.48 3.47 3.47 3.46 3.46 3.45
2.00 2.01 2.04 1.01 1.97 0.92 1.98 2.11
f1 (ppm)


141.20 139.32 139.22 137.47 129.13 128.86 128.84 127.32 127.30 127.20 127.17 116.09
77.16 CDCl3
40.01
f1 (ppm)